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Original Article

MOLECULAR DOCKING STUDIES OF DESIGNED BENZAMIDE DERIVATIVES AS HISTONE DEACETYLASE2 INHIBITORS

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ABSTRACT

Objective: Histone deacetylase2 is a promising target for cancer disease. Histone deacetylase2 belongs to class I family of HDAC's. Molecular docking studies were carried out on series of N (2-aminophenyl)-benzamide derivatives.

Methods: Benzamide derivatives were designed virtually considering the basic pharmacophore of N (2-aminophenyl)-benzamide. 54 ligands docked with Histone deacetylase2 PDB id: 3MAX using LigandFit (Discovery Studio 2.1). Most of the compounds showed good binding interaction with the receptor and the results are compared with the test compounds SAHA and MS-275 to find potentional HDAC2 inhibitors.

Results: Based on the docking score N-(2-amino-5-(1H-imidazol-2-yl)phenyl)benzamide (B2), N-(2-amino-5-(1H-imidazol-2-yl)phenyl)-4-vinylbenzamide (B18), N-(2-amino-5-(1H-imidazol-2-yl)phenyl)-4-methylbenzamide (B10) showed highest binding energy of 83.7 kcal/mol, 81.6 kcal/mol and 76.7 kcal/mol respectively in comparison with test compounds (SAHA 42.5 kcal/mol and MS-275 40.4 kcal/mol). The results showed hydrogen bond interaction with the Cys156, His146, Gly154 amino acids which are important for HDAC2 inhibition.

Conclusion: In this study, molecular docking studies were used to identify novel compounds targeting the HDAC2 protein. The designed benzamide derivatives of type 1 showed good docking score and interaction in competition with SAHA and MS-275. These prove to be potential inhibitors of HDCA2.

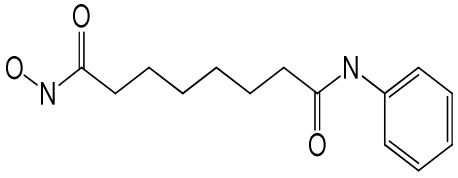
Keywords: Cancer, Histone deacetylase 2, Molecular Docking, Discovery studio.

INTRODUCTION

Histone deacetylase is one of the main targets for cancer disease. Chromatin structure of histone has two forms as Histone acetylases and Histone deacetylases [1]. The function of the Histone deacetylase is deacetylation of the epsilon N-acetyl-lysine group on histone tail of the protein. [2]. HDAC family is found in animals, plants, fungi, archaebacteria and eubacteria [3]. HDAC has been classified into three classes. Class 1 and 2 classified on the basis of sequence similarity Class 1 includes HDAC 1-3 and 8, which are homologus to yeast RPD3 found in nucleoplasm, Class 2 includes HDAC 4-7, 9-10, which are homologus to yeast Hda1 found in nucleus and cytoplasm and Class 3 includes HDAC11. Class 1 and 2 operated by zinc dependent and class 3 by NAD mechanism [4-8]. HDACs are involved in cell-cycle progression and differentiation, and their deregulation is associated with several cancers [9]. Development of HDAC inhibitors as anti cancer drugs has been initiated recently.

Four types of HDAC inhibitors are hydroxamates, cyclic peptides, aliphatic acids and benzamide are in clinical trials [10]. The compound SAHA (Suberoylanilide hydroxamic acid or Vorinostat) is a first HDAC inhibitor approved by FDA for treating Cutaneous T-cell Lymphoma [11].

The Benzamide derivative, which is in phase II clinical trials, is Entinostat (MS-275) for Hodgkin lymphoma [12]. The present study involves molecular docking studies of virtually designed benzamide derivatives and the docking scores are compared with the SAHA and Entinostat to find potential HDAC2 inhibitors.



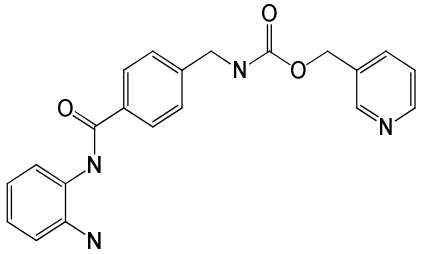


Fig. 1: Chemical structures of HDAC2 inhibitors, SAHA (Vorinostat) and Entinostat (MS-275)

MATERIALS AND METHODS

Data set

Total 54 compounds are designed virtually based on the QSAR and pharmacophore model [13]. Two types of benzamide derivatives are optimized using aromatic and acceptor groups and the ligands are listed in Table 1 and 2. The ligands are sketched using ISIS Draw and these are given as input to prepare ligand module in discovery studio. This generates 3D structures, tautomers, isomers and filters the ligands by Lipinski rule of five. After applying the force fields on ligands the structures are minimized for lowest energy.

Protein preparation

The crystal structure of the HDAC2 (PDB ID: 3MAX) was obtained from protein database from the PDB structural database site (http://www.rcsb.org/pdb). The receptor protein is prepared in Discovery studio by deleting water molecules and adding hydrogens. After applying CHARMm force field macromolecule 3MAX was assigned as receptor. The receptor cavity was searched using flood filling algorithm and partition site was adjusted for the better fitment of molecule in the partition site of receptor.

Docking

The docking method used in this study was LigandFit (Discovery studio) [14]. The crystal structure of the HDAC2 receptor with three chains as A, B and C and chain A was selected for docking and active sites were created and total 54 ligands were docked in the active site of 3MAX and docking score were compared with the SAHA and Entinostat.

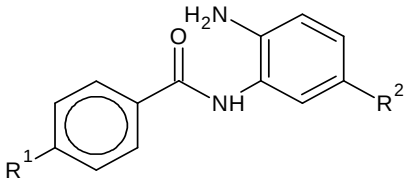


Table 1: Type1 Benzamide derivatives (1-24)

Compound No.	R1	R2
B1	H	2-Pyrrole
B2	H	2-Imidazole
B3	H	2-Oxazole
B4	H	3-Isooxazole
B5	H	3-hydroxyphenyl
B6	H	4-hydroxyphenyl
B7	H	3-formylphenyl
B8	H	4-formylphenyl
B9	Methyl	2-Pyrrole
B10	Methyl	2-Imidazole
B11	Methyl	2-Oxazole
B12	Methyl	3-Isooxazole
B13	Methyl	3-hydroxyphenyl
B14	Methyl	4-hydroxyphenyl
B15	Methyl	3-formylphenyl
B16	Methyl	4-formylphenyl
B17	Vinyl	2-Pyrrole
B18	Vinyl	2-Imidazole
B19	Vinyl	2-Oxazole
B20	Vinyl	3-Isooxazole
B21	Vinyl	3-hydroxyphenyl
B22	Vinyl	4-hydroxyphenyl
B23	Vinyl	3-formylphenyl
B24	Vinyl	4-formylphenyl

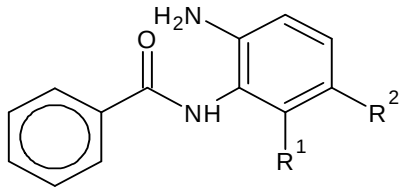


Table 2: Type 2 Benzamide derivatives (1-30)

Compound No.	R1 (Acceptors)	R2
BA1	NO2	2-Pyrrole
BA2	COOEt	2-Pyrrole
BA3	CHO	2-Pyrrole
BA4	COPh	2-Pyrrole
BA5	COCH3	2-Pyrrole
BA6	NO2	2-Imidazole
BA7	COOEt	2-Imidazole
BA8	CHO	2-Imidazole
BA9	COPh	2-Imidazole
BA10	COCH3	2-Imidazole
BA11	NO2	2-Oxazole
BA12	COOEt	2-Oxazole
BA13	CHO	2-Oxazole
BA14	COPh	2-Oxazole
BA15	COCH3	2-Oxazole
BA16	NO2	3-IsoOxazole
BA17	COOEt	3-IsoOxazole
BA18	CHO	3-IsoOxazole
BA19	COPh	3-IsoOxazole
BA20	COCH3	3-IsoOxazole
BA21	NO2	4-Hydroxyphenyl
BA22	COOEt	4-Hydroxyphenyl
BA23	CHO	4-Hydroxyphenyl
BA24	COPh	4-Hydroxyphenyl

BA25	COCH3	4-Hydroxyphenyl
BA26	NO2	3-Hydroxyphenyl
BA27	COOEt	3-Hydroxyphenyl
BA28	CHO	3-Hydroxyphenyl
BA29	COPh	3-Hydroxyphenyl
BA30	COCH3	3-Hydroxyphenyl

Table 3: Docking scores and interactions of type 1 benzamide derivatives

Compound No.	Docking Score (kcal/mol)	Hydrogen bond Interactions	Internal Energy
B1	45.917	Cys156, Gly154	-2.96
B2	83.742	His146, Cys156, Gly143, Gly305, Tyr308	-2.664
B3	47.075	Asp181, Cys156	0.037
B4	46.909	Gly305	-1.529
B5	54.609	His145, Asp181, His146, Arg39, Tyr308, Gly154	-1.548
B6	50.692	His145, Asp269, His146, Tyr308	-3.287
B7	56.546	His146, Asp181, Tyr308, Gly154, His145, Arg39	-1.086
B8	43.36	Cys156, Gly305	-4.181
B9	45.544	Tyr308, His146, His145	-2.917
B10	76.727	Asp181, Cys156	-2.253
B11	48.711	Cys156, Asp181	-1.428
B12	46.166	Asp181, Cys156	-1.536
B13	56.496	Arg39, His145, His146, Tyr308	-2.942
B14	54.657	His146, His145, Asp181	-1.287
B15	62.295	Asp181, Arg39	2.853
B16	45.612	Asp181, Cys156	-3.687
B17	52.643	Cys156,Asp181	-0.548
B18	81.609	Cys156, Gly154, Asp181, Gly306	-3.59
B19	55.943	Gly154, Cys156, Gly306, Asp181	-0.424
B20	55.897	Cys156, Asp181, Gly306	0.112
B21	58.339	His146, His145, Ala141, Arg39, Tyr308	-2.847
B22	53.288	His145, Asp181, His146	-1.629
B23	61.685	His145,Tyr308,Asp269	-2.611
B24	46.211	His145, His146, Tyr308	-1.544

Table 4: Docking scores and interactions of type 2 benzamide derivatives

Compound No.	Docking Score (kcal/mol)	Hydrogen bond Interactions	Internal Energy
BA1	3.112	Gly305, Gly154	-0.651
BA3	11.209	Gly143, Gly305, Gly154, Cys156	-2.248
BA6	45.926	Gly154, Gly143,	-1.924
BA8	61.43	His146, Gly143, Tyr308	-2.835
BA11	5.62	Cys156, Gly143	-1.54
BA13	19.755	Gly143	-2.696
BA16	6.009	Gly143	-2.406
BA18	16.601	Gly143	-2.171
BA21	2.793	Gly143, Gly305	3.673
BA23	9.303	Gly143	-5.132
BA26	2.354	Gly143, Cys156	3.31
BA28	8.701	Gly143	-5.157

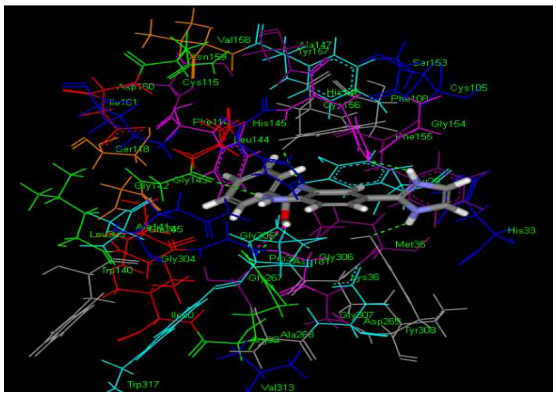
RESULTS AND DISCUSSIONS

All 54 ligands were docked in the active site of 3MAXA using Discovery studio. Compounds were ranked based on the docking score and compared with SAHA and MS-275. The Docking score of all ligands are listed in Table 3 and 4. The docking score of the SAHA is 42. 5 kcal/mol has three hydrogen bond interactions with Gly153, Cys156, Tyr308 and docking score of MS-275 is 40.4 kcal/mol has two hydrogen bond interactions with Tyr29, Phe155. The docking result shows most of the ligands from Table 3 has good binding interaction with the receptor. Table 4 ligands did not show interaction. The Ligand B2 N-(2-amino-5-(1H-imidazol-2-yl)phenyl)benzamide as docking score of 83.7 kcal/mol has five hydrogen bond interactions with the His146, Cys156, Gly143, Gly305, Tyr308 shown in Figure 2a. It shows nitrogen and oxygen of amide, nitrogen on aminophenyl group and imidazole ring has hydrogen bond interaction; Ligand B18 N-(2-amino-5-(1H-imidazol-2-yl)phenyl)-4-vinylbenzamide as docking score of 81.6 kcal/mol has four hydrogen bond interactions with Cys156, Gly154, Asp181, Gly306 shown in Figure 2b. It shows oxygen of amide, nitrogen on aminophenyl group and imidazole ring has hydrogen bond interaction; Ligand B10 N-(2-amino-5-(1H-imidazol-2-yl)phenyl)-4-methylbenzamide has docking score of 76.7 kcal/mol has two hydrogen bond interactions with Asp181, Cys156 shown in figure 2c. It shows oxygen of amide, nitrogen on aminophenyl group has hydrogen bond interactions.

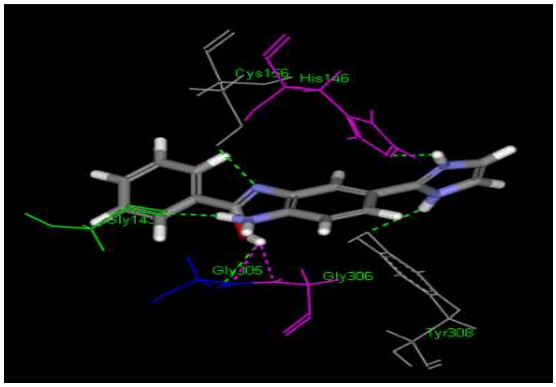
The result explains Cys156, Gly154 and His146 are common amino acids in the active site to interact with the ligand. Type 2 benzamide derivatives have not shown good interaction with the receptor. The docking score of Ligand BA6 N-(6-amino-3-(1H-imidazol-2-yl)-2-nitrophenyl) benzamide has 45.9 kcal/mol having two hydrogen bond interactions with Gly154, Gly143 shown in Figure 3a. Ligand BA8 N-(6-amino-2-formyl-3-(1H-imidazol-2-yl)phenyl)benzamide has docking score of 61.4 kcal/mol having three hydrogen bond interactions with His146, Gly143, Tyr308 shown in figure 3b. The

figure shows nitrogen on aminophenyl group and imidazole has hydrogen bond interactions. The result shows ligands with imidazole ring have good interaction with the receptor, because of its biological important chemical feature. Docking score of type 1 benzamide derivatives are higher than the reference compounds SAHA and MS-275 and type 2 benzamide derivatives have low scores and few ligands not shown interaction with the receptor, because the acceptor group near the amide is not allowing the compounds to interact with the receptor. Hence these compounds show low docking scores and Ligands BA2, BA4, BA5, BA7, BA9, BA10, BA12, BA14, BA15, BA17, BA19-20, BA22, BA24, BA25, BA27, BA29 and BA30 not shown interactions with the active site of the HDAC2. The docking result illustrates derivatives of N (2-aminophenyl)-benzamide shows the amide group and amino group on aminophenyl ring are important in interaction with the receptor. So type 1 benzamide derivatives are suggested as novel HDAC2 inhibitors.

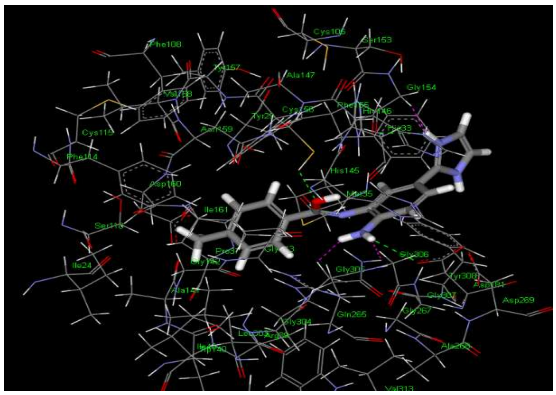
a)



B)



c).



d).

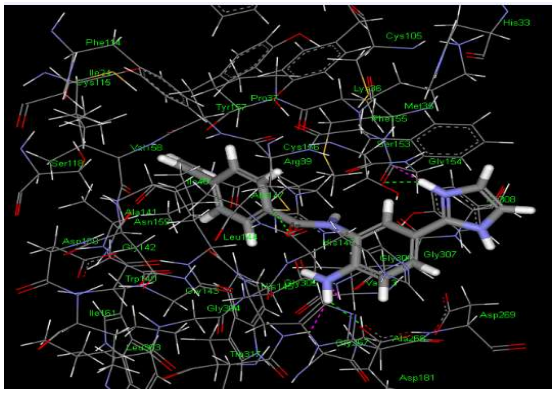
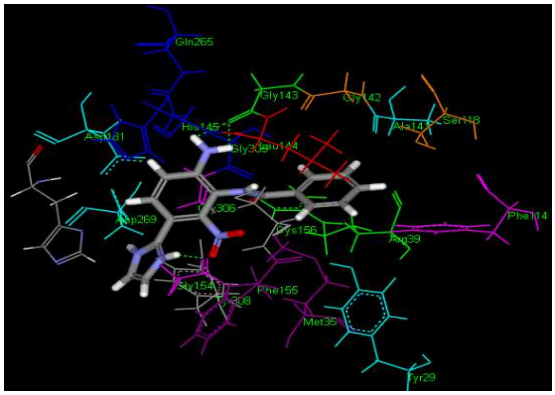


Fig. 2: The binding mode of the docked type1 benzamide derivatives (a &b) ligand B2 (c) ligand B18 and (d) ligand B10

a)



b)

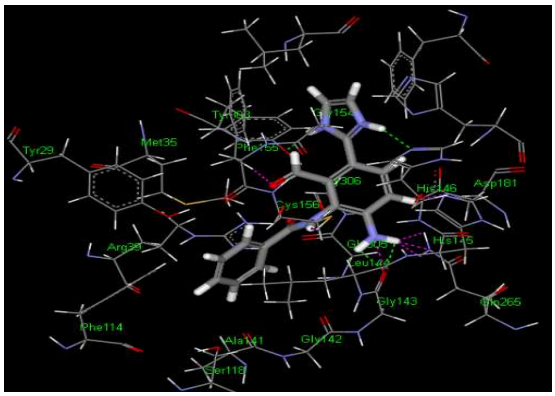


Fig. 3: The binding mode of the docked type2 benzamide derivatives a) ligand BA6 b) ligand BA8

CONCLUSION

In the present study molecular docking studies conducted on two types benzamide derivatives. The docking method describes the binding interaction with the ligand and receptor HDAC2. The result shows Cys156, Gly154 and His146 are important amino acids in the active site to bind with the ligands. Based on docking studies type 1 benzamide derivatives are best HDAC2 inhibitors.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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