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Molecular docking studies of some new benzylidene, Naphthylidene base of benzoic acid and pyrazole derivatives for anticancer activity

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Abstract

Histone deacetylases 2, Class 1 HDAC family are emerged as an important therapeutic target for the treatment of various cancers. HDAC8 inhibitors are potent anti-cancer agents. Molecular docking studies were carried out on benzylidene base of benzoic acid,Naphthylidene base of benzoic acid and one heterocyclic (pyrazole) derivatives. Two type of benzoic acid and one heterocyclic (pyrazole) derivatives were designed virtually considering the basic pharmacophore of 4-[(2-Hydroxy-benzylidene)-amino]-benzoic acid, 4-{(E)-[(2-Hydroxy-1-naphthyl)methylene]amino}benzoic acid and 2-Phenyl-1,2-dihydro-3H-pyrazol-3-one. 53 ligands docked with Histone deacetylase 8 Human HDAC8 (PDB ID: 1T69) using GLIDE program (Version 5.0, Schrodinger, LLC, New York, 2008). Most of the compounds showed good binding interaction with the receptor. Based on the docking score 4-(5-Bromo-2-hydroxybenzylideneamino)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one (50), 4-((2-hydroxynaphthalen-1-yl)methyleneamino) benzoic acid (37), 4-(4-Bromobenzylideneamino)benzoic acid (1) showed highest docking score of -6.4061, -5.8214 and -4.8465 respectively, which are important for HDAC8 inhibition. In this present investigation, molecular docking studies were used to identify novel compounds targeting the HDAC8 protein. The designed pyrazole derivative showed good docking score. These prove to be potential inhibitors of HDCA8.

Keywords: Cancer, Histone deacetylase 8, Molecular Docking, Pyrazole derivatives.

Introduction

Cancer is one of the most fearful diseases of the 20th century and scattering more with continuance and increasing incidence in 21st century. It is thought about as a challenger of modernization and superior pattern of socio-cultural life conquered by western medicine. Multidisciplinary systematic investigations are making greatest efforts to fight this disease, but the sure-shot, perfect cure is yet to be brought into world medicine.

Molecular docking is defined as an optimization predicament, which would explain the "best-fit" direction of a ligand that binds to the exact protein that is used to forecast the structure of the inter-molecular complex formed between two or additional molecules.

The most remarkable case is the protein ligand interaction, because of its uses in medicines. Ligand is a tiny molecule, which interacts with protein's binding sites. There are numerous possible reciprocated conformations in which binding may occur. These are usually called binding modes (Sharma *et al*., 2010). In contemporary drug scheming, molecular docking is regularly used for understanding drug-receptor interaction. Molecular docking provides helpful information regarding drug receptor interactions and is commonly used to forecast the binding orientation of tiny molecule drug molecules to their protein targets in order to predict the attraction and activity of the tiny molecule.

Human beings have been in steady exposure to pathogens for several decades. Insidious microbial infections are chief problems around the world, particularly in immuno compromised patients. The recent development of antimicrobial drug research has occurred for the reason that there is a significant need for new antimicrobial agents to treat these life threatening insidious infections. The progress of antimicrobial resistance has greater than before in this century and there is a need for budding new antimicrobial agents which will be more selective, potent and not as much of toxic compared to the existing drugs in clinical treatment. Heterocycles possessing an azole ring system are found to demonstrate a wide spectrum of biological activities, as well as antibacterial and antifungal properties. Imidazole and its derivatives have gained notable significance due to their widespread biological activities and their use in synthetic chemistry. Imidazole derivatives hold a broad spectrum of pharmacological activities such as, antiinflammatory (Suzuki *et al*., 1992), analgesic, anticonvulsant (Pinza *et al*., 1993), antitubercular (Pandey *et al*., 2009), antimicrobial, anticancer and antiParkinson (Miyachi *et al*., 1998) activities. Imidazole and its derivatives are of immense importance due to their significant roles in biological systems, chiefly in, enzymes as proton donors and/or acceptors, harmonization system ligands and the base of charge–transfer processes. The imidazole nucleus appears in a numeral of naturally happening products like, histidine, amino acids and purines that encompass many of the most essential bases in nucleic acids. Likewise pyrazole derivatives have showed important biological activities, such as antimicrobial (Isloor *et al*., 2009), analgesic (Isloor *et al*., 2000), anti-inflammatory (Bekhita and Abdel Aziem, 2004) and anticancer (Dhanya *et al*., 2009) activities. This gave a great forward motion to the search for prospective pharmacologically active drugs carrying pyrazole substituent. The present investigation involves molecular docking studies of virtually designed benzylidene , naphthylidene base of benzoic acid and pyrazole derivatives and the docking scores are potential HDAC8 inhibitors.

Materials and Methods

Computational Design to choose best novel heterocyclic compound derivatives based on target based drug discovery:

Total 53 compounds are designed virtually based on the QSAR and pharmacophore model (Naresh Kandakatla *et al*., 2012). Two benzylidene , naphthylidene base of benzoic acid derivatives 4-[(2-Hydroxy-benzylidene)-amino]-benzoic acid, 4-{(E)-[(2-Hydroxy-1-naphthyl)methylene]amino}benzoic acid (Figure 1 and 2) and one heterocyclic derivative (Pyrazole) 2-Phenyl-1,2-dihydro-3H-pyrazol-3-one (Figure 3) are optimized using aromatic and acceptor groups and the ligands are listed in Table 1, 2 and 3. The ligands are sketched using ISIS Draw and these are given as input to prepare ligand module in Glide. 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.

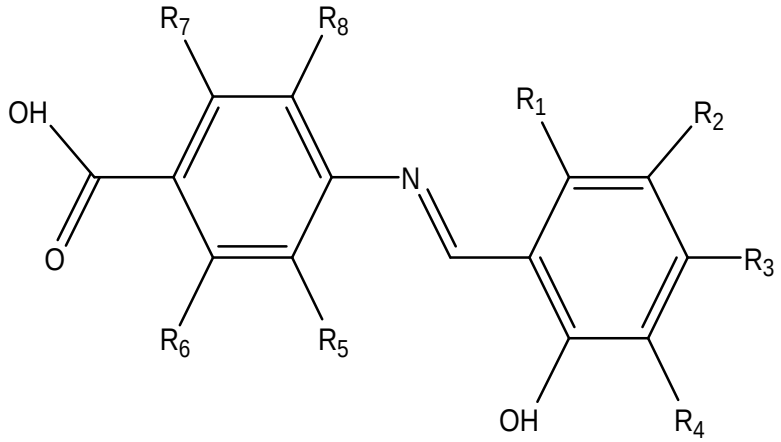

Figure 1: Parent nucleus of benzylidene base of benzoic acid derivative - Type 1

Table 1: benzylidene base of Benzoic acid derivatives - Type 1 (A1-A18)

Compound	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
A1	H	Br	H	H	H	H	H	H
A2	H	Br	Br	Br	H	H	H	H
A3	H	Br	Br	CH_3	H	H	H	H
A4	CH_3	Br	Br	CH_3	H	H	H	H
A5	CH_3	Br	Br	CH_3	H	CH_3	H	H
A6	CH_3	Br	Br	CH_3	H	CH_3	CH_3	H
A7	CH_3	Br	Br	CH_3	CH_3	CH_3	CH_3	H
A8	CH_3	Br	Br	CH_3	CH_3	CH_3	CH_3	CH_3
A9	CH_3	Br	Br	CH_3	Cl	CH_3	CH_3	CH_3
A10	CH_3	Br	Br	CH_3	CH_3	Cl	Cl	CH_3
A11	CH_3	Br	Br	Br	CH_3	Cl	Cl	CH_3
A12	CH_3	Br	Cl	Br	CH_3	Cl	Cl	CH_3
A13	CH_3	H	Cl	Br	CH_3	Cl	Cl	CH_3
A14	CH_3	H	Cl	H	CH_3	Cl	Cl	CH_3
A15	Cl	H	Cl	H	CH_3	Cl	Cl	CH_3
A16	Cl	H	Cl	OH	CH_3	Cl	Cl	CH_3
A17	Cl	H	Cl	OH	CH_3	Cl	OH	CH_3
A18	H	Br	Br	H	H	H	H	H

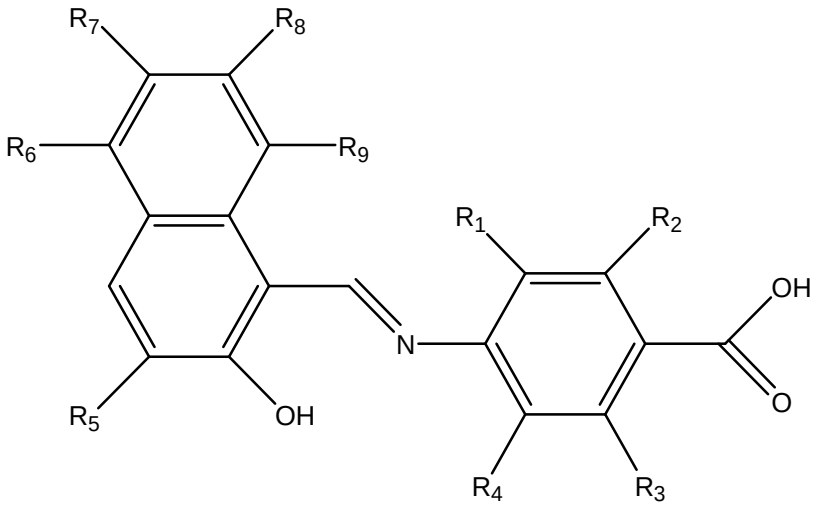

Figure 1: Parent nucleus of Naphthylidene base benzoic acid derivative - Type 2

Table 2: Naphthylidene base of Benzoic acid derivatives - Type 2 (A19-A36)

Compound	R1	R2	R3	R4	R5	R6	R7	R8	R9
A19	H	H	H	H	OH	H	OH	H	H
A20	H	H	H	H	OH	H	OH	H	CH_3
A21	H	H	H	H	OH	CH_3	OH	H	CH_3
A22	H	H	H	H	OH	CH_3	OH	OH	CH_3
A23	H	CH_3	H	H	OH	CH_3	OH	OH	CH_3
A24	H	CH_3	CH_3	H	OH	CH_3	OH	OH	CH_3
A25	H	OH	OH	H	OH	CH_3	OH	OH	CH_3
A26	CH_3	OH	OH	H	OH	CH_3	OH	OH	CH_3
A27	CH_3	OH	OH	H	OH	CH_3	OH	OH	CH_3
A28	CH_3	OH	OH	OH	OH	CH_3	OH	OH	CH_3
A29	OH	OH	OH	OH	OH	CH_3	OH	OH	CH_3

Table 2: contd

A30	OH	OH	OH	OH	OH	CH_3	OH	OH	OH
A31	OH	Cl	OH	OH	OH	CH_3	OH	OH	OH
A32	OH	Cl	Cl	OH	OH	CH_3	OH	OH	OH
A33	OH	Cl	Cl	OH	CH_2CH_3	CH_3	OH	OH	OH
A34	OH	H	H	OH	CH_2CH_3	CH_3	OH	OH	OH
A35	OH	H	H	OH	CH_2CH_3	H	OH	H	H
A36	H	H	H	H	H	H	OH	H	H
A37	H	H	H	H	H	H	H	H	H

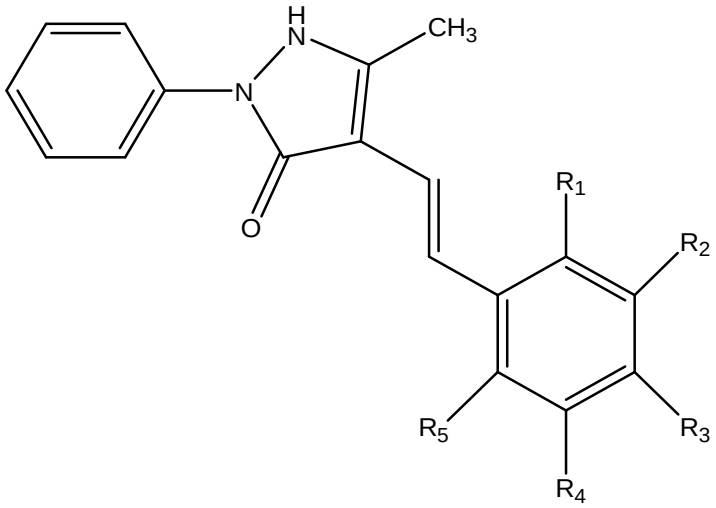

Figure 1: Parent nucleus of Pyrazole derivative

Table 3: Pyrazole derivatives (A38-A53)

Compound	R1	R2	R3	R4	R5
A38	H	CH_3	H	H	OH
A39	H	OH	H	H	OH
A40	H	OH	CH_3	H	OH
A41	H	OH	OH	H	OH
A42	H	OH	OH	CH_3	OH
A43	H	H	H	H	OH
A44	H	OH	OH	OH	OH
A45	H	Cl	H	OH	OH
A46	H	Cl	H	OH	OH
A47	H	Cl	H	H	OH
A48	H	Cl	H	H	NH2
A49	H	Cl	NH_2	H	NH2
A50	H	Br	H	H	OH
A51	NH_2	Cl	NH_2	H	NH_2
A52	NH_2	Cl	$NHNH_2$	H	NH_2
A53	NH_2	Br	$N(NH_2)_2$	H	NH_2

Docking Methodology

The steps involved in docking are as follows:
Ligand structure: The chemical structure of each ligand was drawn using build module**.**

Ligand preparation: In order to prepare elevated quality, all-atom 3D structures for huge numbers of drug-like molecules, starting with the 3D structures in SD Maestro format, LigPrep was used. LigPrep produced a single, low energy and 3D structure for each successfully processed input structure.

Preparation of protein: Molecular docking were performed for 53 compounds using the Glide program (Version 5.0, Schrodinger, LLC, New York, 2008) to be aware of the interaction of 3k with HDAC8. The Maestro user interface (version8.5, Schrodinger, LLC, New York, 2008) was engaged to set up and execute the docking protocol and also for analysis of the docking results. Human HDAC8 (PDB ID: 1T69) was selected for docking studies and was geared up for docking through protein research wizard, energy minimization has been conceded out using OPLS2001 force field. Structures of 1-3 were sketched using built panel. Maestro and prepared for docking through Ligprep module (energy minimized using MMFF force field). Glide grid generation wizard has been used to define the docking space. Docking was performed using SP (Standard Precision mode) docking protocol.

Receptor Grid Generation: Receptor grid generation requires a "prepared" structure: an all atom structure with appropriate bond orders and formal charges. Glide searches for constructive interactions between one or more ligand molecules and a receptor molecule, usually a protein. The shape and properties of the receptor are represented on a grid by several different sets of fields that provide progressively more accurate scoring of the ligand poses. The options in each tab of the Receptor Grid Generation panel allow defining the receptor structure by excluding any co-crystallized ligand that may be present, determine the position and size of the active site as it will be represented by receptor grids, and set up Glide constraints. A grid area was generated around the binding site of the receptor.

Ligand Docking: This is carried out using Glide Dock. Glide searches for positive interactions between one or more ligand molecules and a receptor molecule, usually a protein. Each ligand acts as sole molecule, while the receptor may comprise more than one molecule, e.g., a protein and a cofactor. Glide was run in rigid or flexible docking modes; the latter involuntarily generated conformations for each contributed ligand. The blend of position and direction of a ligand relative to the receptor, all along with its conformation in flexible docking, is referred to as a ligand pose. The ligand poses that Glide creates pass all the way through a series of hierarchical filters that evaluate the ligand's interface with the receptor. The first filters test the spatial fit of the ligand to the specified active site, and inspect the complementarity of ligand-receptor interactions using a grid-based method patterned after the empirical ChemScore role. Poses that conceded these initial screens entered the last stage of the algorithm that involve in the evaluation and minimization of a grid rough calculation to the OPLS-AA non bonded ligand-receptor interaction energy. Final scoring is then carried out on the energy-minimized poses.

Glide Extra-Precision Mode (XP): The extra-precision (XP) mode of Glide combines a powerful sampling procedure with the use of a tradition scoring function intended to identify ligand poses that would be accepted to have unfavourable energies, based on a well known ideology of physical chemistry. The presumption is that only active compounds will have available poses that avoid these penalties and also receive favourable scores for appropriate hydrophobic contact between the protein and the ligand, hydrogen-bonding interactions, and so on. The chief purposes of the XP method are to weed out false positives and to provide a better correlation between good poses and good scores. Extra-precision mode is a refinement tool designed for use only on good ligand poses. Finally, the minimized poses are re-scored using Schrödinger's proprietary GlideScore scoring function. GlideScore is based on ChemScore, but includes a steric-clash term and adds buried polar terms devised by Schrodinger to penalize electrostatic mismatches: Glide Score = 0.065*vdW + 0.130*Coul + Lipo + Hbond + Metal + BuryP + RotB + Site

Results and Discussion

All the 53 ligands were docked in the active site of Human HDAC8 (PDB ID: 1T69) using Glide Dock. Compounds were ranked based on the docking score. The docking score of all ligands are presented in Table 4. Heterocyclic functional group of all the molecules were found to be close to Zn^{2+} atom in the active site, and establishes a hydrogen bond with (50) ASP331, (37) SER329 and (1) THR68 which shows the major and favourable interaction of the ligands with HDAC8 .Amongst the53 molecules docked, compound 50, 37 and 1 was the one with the best Glide and E model score of (-40.88,-41.47,-39.46) respectively. It exhibited one hydrogen bonding interaction with active site amino acids. The hydroxamate group is placed near the Zn^{2+} atom.

Glide module of Schrodinger was used to carry out Molecular docking interaction studies in which, through blind docking approach using 53 heterocyclic derivatives were docked against HDAC8 protein of 1T69.

53 Set of ligand structures with receptor grid has used for flexible docking based on Monte Carlo based simulated algorithm in Glide v5.7 (Friesner *et al*., 2004) in which Glide standard precision (SP) and extra precision (XP) were performed. To screen large number of small molecules (lignad) first, ligands were docked by SP docking interaction analysis. Then 10–30% of final ligand poses was selected for 82 subsequent re-docking using XP. Ligand poses, which have high score in SP docking interaction analysis, were further used in XP docking. XP mode is more accurate than SP mode because it can screen out the false positive. XP docking was more efficient and accurate as its run time is longer than standard precision docking (SP). In grid-based docking technique, the receptor is basically rigid. XP was developed to place the ligands that bind to the receptor in particular conformation. The best posse of each ligand was ranked based on Glide XPG (Haider *et al*., 2014). In each XP docking more than 10,000 ligand poses were generated which pass through initial screening are further subjected to evaluation and minimization of grid approximation. Scoring is then carried on energy minimized poses of ligand-protein complex to generate Glide score (Frienser *et al*., 2006). From the docking results revealed that among the 53 chemical derivative best of three molecules was selected to taken for further analysis. The selected compound number and docking score was given in the table 4. Based on the docking score 4-(5-Bromo-2-hydroxybenzylideneamino)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one (50), 4-((2-hydroxynaphthalen-1-yl)methyleneamino) benzoic acid (37), 4-(4-Bromobenzylideneamino)benzoic acid (1) showed highest docking score of -6.4061, -5.8214 and -4.8465 respectively, which are important for HDAC8 inhibition.

Table 4: Docking scores and interactions with HDAC8

Mol ID	Molecule name	Docking score	Glide score	Glide energy	Glide model	No. of H-bond	Bond length
A1 (III)	4-(4-Bromobenzylideneamino)benzoic acid	-4.8465	-4.8465	-33.669353	-39.462967	N-H-O O-H-O	1.862 2.135
A2	4-[(*E*)-(3,4,5-tribromo-2-hydroxybenzylidene) amino]benzoic acid	-3.164221	-3.164221	-27.290464	-36.469875	C-O-H O-H-O C-O-H	1.640 1.930 2.024
A3	4-[(*E*)-(4,5-dibromo-2-hydroxy-3-methylbenzylidene) amino]benzoic acid	-2.939032	-2.939032	-49.362856	-64.532487	C-O-H	2.46
A4	4-[(*E*)-(3,4-dibromo-6-hydroxy-2,5-dimethylbenzylidene) amino]benzoic acid	-2.264928	-2.264928	-38.807655	-53.695961	C-N-H	2.440
A5	4-[(*E*)-(3,4-dibromo-6-hydroxy-2,5-dimethylbenzylidene) amino]-2-methylbenzoic acid	-2.730258	-2.730258	-39.742957	-57.039903	N-H-O O-H-O	2.355 2.308
A6	4-[(*E*)-(3,4-dibromo-6-hydroxy-2,5-dimethylbenzylidene) amino]-2,6-dimethylbenzoic acid	-2.255269	-2.255269	-36.235806	-38.531617	O-H-O C-O-H	2.029 2.017

A7	4-[(*E*)-(3,4-dibromo-6-hydroxy-2,5-dimethylbenzylidene) amino]-2,3,6-trimethylbenzoic acid	-4.587830	-4.587830	-47.575857	-50.852867	N-H-O N-H-O C-N-H O-H-O O-H-O	1.545 2.276 2.094 2.140 1.701
A8	4-[(*E*)-(3,4-dibromo-6-hydroxy-2,5-dimethylbenzylidene) amino]-2,3,5,6-tetramethylbenzoic acid	-2.936770	-2.936770	-41.812590	-60.298363	C-O-H O-H-O	2.105 1.693
A9	2-chloro-4-[(*E*)-(3,4-dibromo-6-hydroxy-2,5-dimethylbenzylidene) amino]-3,5,6-trimethylbenzoic acid	-2.123588	-2.123588	-41.591481	-46.321632	C-O-H C-O-H	2.810 2.448
A10	2,6-dichloro-4-[(*E*)-(3,4-dibromo-6-hydroxy-2,5-dimethylbenzylidene) amino]-3,5-dimethylbenzoic acid	-2.117479	-2.117479	-41.662735	-52.804038	C-O-H N-H-O	1.780 2.238
A11	2,6-dichloro-3,5-dimethyl-4-[(*E*)-(3,4,5-tribromo-2-hydroxy-6-methylbenzylidene) amino]benzoic acid	-2.166459	-2.166459	-37.143287	-53.683982	C-O-H N-H-O	2.167 2.403
A12	2,6-dichloro-4-[(*E*)-(3,5-dibromo-4-chloro-2-hydroxy-6-methylbenzylidene) amino]-3,5-dimethylbenzoic acid	-3.185619	-3.185619	-43.416501	-50.582968	O-H-O N-H-O	1.775 1.686
A13	4-[(*E*)-(3-bromo-4-chloro-2-hydroxy-6-methylbenzylidene) amino]-2,6-dichloro-3,5-dimethylbenzoic acid	-2.148987	-2.148987	-33.17045	-21.650323	C-O-H H-O-H	1.844 2.440
A14	2,6-dichloro-4-[(E)-(4-chloro-2-hydroxy-6-methylbenzylidene) amino]-3,5-dimethylbenzoic acid	-4.473058	-4.473058	-41.993950	-49.395259	O-H-O N-H-O	1.717 2.358

A15	2,6-dichloro-4-[(*E*)-(2,4-dichloro-6-hydroxybenzylidene) amino]-3,5-dimethylbenzoic acid	-2.033855	-2.033855	-37.613518	-44.281396	N-H-O C-O-H O-H-O	2.094 1.612 1.836
A16	2,6-dichloro-4-[(*E*)-(4,6-dichloro-2,3-dihydroxybenzylidene) amino]-3,5-dimethylbenzoic acid	-2.189321	-2.189321	-33.269384	-40.041605	O-H-O O-H-O	2.057 1.755
A17	2-chloro-4-[(*E*)-(4,6-dichloro-2,3-dihydroxybenzylidene) amino]-6-hydroxy-3,5-dimethylbenzoic acid	-1.93678	--1.93678	-33.29456	-38.03567	C-O-H	0.328
A18	4-[(*E*)-(4,5-dibromo-2-hydroxybenzylidene) amino]benzoic acid	-4.650567	-4.650567	-52.781501	-66.678982	O-H-O O-H-O N-H-O C-N-H	1.755 1.952 1.546 2.320
A19	4-{(*E*)-[(2,3,6-trihydroxynaphthalen-1-yl) methylidene] amino}benzoic acid	-2.212328	-2.212328	-43.729263	-40.726697	N-H-O N-H-O C-N-O O-H-O	2.368 1.563 2.182 1.672
A20	4-{(*E*)-[(2,3,6-trihydroxy-8-methylnaphthalen-1-yl)methylidene]amino} benzoic acid	-2.023633	-2.023633	-30.276024	-39.756890	C-O-H O-H-O	1.874 1.938
A21	4-{(E)-[(2,3,6-trihydroxy-5,8-dimethylnaphthalen-1-yl)methylidene]amino} benzoic acid	-2.308604	-2.308604	-36.287597	-37.249867	O-H-O C-O-H	2.210 2.072
A22	4-{(E)-[(2,3,6,7-tetrahydroxy-5,8-dimethylnaphthalen-1-yl)methylidene]amino} benzoic acid	-2.323585	-2.323585	-41.318823	-55.172305	C-O-H N-H-O O-H-O	1.659 2.058 2.000
A23	2-methyl-4-{(E)-[(2,3,6,7-tetrahydroxy-5,8-dimethylnaphthalen-1-yl)methylidene]amino} benzoic acid	-4.444613	-4.444613	-38.484663	-44.290012	O-H-O C-O-H C-O-H	1.853 1.615 1.704

A24	2,6-dimethyl-4-{(*E*)-[(2,3,6,7-tetrahydroxy-5,8-dimethylnaphthalen-1-yl)methylidene]amino}benzoic acid	-3.162943	-3.162943	-41.352284	-54.486199	O-H-O C-O-H N-H-O N-H-O	2.202 2.216 2.424 2.842
A25	2-hydroxy-6-methyl-4-{(*E*)-[(2,3,6,7-tetrahydroxy-5,8-dimethylnaphthalen-1-yl)methylidene]amino}benzoic acid	-2.505397	-2.505397	-35.245564	-35.982231	C-O-H O-H-O	1.958 1.941
A26	2,6-dihydroxy-4-{(*E*)-[(2,3,6,7-tetrahydroxy-5,8-dimethylnaphthalen-1-yl)methylidene]amino}benzoic acid	-2.353524	-2.353524	-48.727078	-56.265615	C-O-H	2.170
A27	2,6-dihydroxy-3-methyl-4-{(*E*)-[(2,3,6,7-tetrahydroxy-5,8-dimethylnaphthalen-1-yl)methylidene]amino}benzoic acid	-3.219405	-3.219405	-51.169111	-70.666239	O-H-O O-H-O N-H-O	1.779 1.948 1.623
A28	2,3,6-trihydroxy-5-methyl-4-{(E)-[(2,3,6,7-tetrahydroxy-5,8-dimethylnaphthalen-1-yl)methylidene]amino}benzoic acid	-3.510818	-5.510818	-39.571076	-60.355644	N-H-O O-H-O	2.104 1.773
A29	2,3,5,6-tetrahydroxy-4-{(E)-[(2,3,6,7-tetrahydroxy-5,8-dimethylnaphthalen-1-yl)methylidene]amino}benzoic acid	-3.153896	-3.153896	-41.426024	-54.763907	O-H-O C-O-H N-H-O	2.199 2.253 1.822
A30	2,3,5,6-tetrahydroxy-4-{(E)-[(2,3,6,7,8-pentahydroxy-5-methylnaphthalen-1-yl)methylidene]amino}benzoic acid	-2.505397	-2.505397	-35.245564	-35.982231	C-O-H O-H-O	1.958 1.941

A31	2-chloro-3,5,6-trihydroxy-4-{(*E*)-[(2,3,6,7,8-pentahydroxy-5-methylnaphthalen-1-yl)methylidene] amino}benzoic acid	-3.917370	-5.917370	-47.36213	-66.467397	N-H-O N-H-O	2.231 1.951
A32	2,6-dichloro-3,5-dihydroxy-4-{(*E*)-[(2,3,6,7,8-pentahydroxy-5-methylnaphthalen-1-yl)methylidene] amino}benzoic acid	-2.472200	-2.472200	-33.36132	-46.132863	O-H-O C-O-H	1.981 1.878
A33	2,6-dichloro-4-{(*E*)-[(3-ethyl-2,6,7,8-tetrahydroxy-5-methylnaphthalen-1-yl)methylidene] amino}-3,5-dihydroxybenzoic acid	-4.270046	-4.270046	-38.675576	-47.413979	N-H-O N-H-O C-O-H O-H-O	1.755 2.280 2.176 2.126
A34	4-{(E)-[(3-ethyl-2,6,7,8-tetrahydroxy-5-methylnaphthalen-1-yl)methylidene] amino}-3,5-dihydroxybenzoic acid	-2.47286	-2.47286	-26.790622	-39.358011	C-O-H O-H-O	2.124 1.783
A35	4-{(E)-[(3-ethyl-2,6-dihydroxynaphthalen-1-yl) methylidene] amino}-3,5-dihydroxybenzoic acid	-3.140616	-3.140616	-40.099602	-61.288927	O-H-O N-H-O N-H-O C-O-H	1.789 2.373 2.075 2.330
A36	4-{(E)-[(2,6-dihydroxynaphthalen-1-yl) methylidene] amino}benzoic acid	-2.613561	-2.613561	-44.488139	-64.738192	C-O-H	2.118
A37 (II)	4-((2-hydroxynaphthalen-1-yl)methyleneamino) benzoic acid	-5.82147	-5.82147	-31.447825	-41.478937	N-H-O N-H-O	1.871 2.303
A38	4-[(E)-2-(2-hydroxy-5-methylphenyl) ethenyl]-5-methyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one	-0.9642	-0.9642	-29.5901	-31.4921	C-O-H	0.932

A39	4-[(*E*)-2-(2,5-dihydroxyphenyl)ethenyl]-5-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one	-4.764335	-4.764335	-35.964177	-46.735914	O-H-O O-H-O	1.932 1.936
A40	4-[(*E*)-2-(2,5-dihydroxy-4-methylphenyl)ethenyl]-5-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one	-2.217575	-2.217575	-41.648260	-47.475469	N-H-O O-H-O	1.913 1.753
A41	5-methyl-2-phenyl-4-[(*E*)-2-(2,4,5-trihydroxyphenyl)ethenyl]-1,2-dihydro-3*H*-pyrazol-3-one	-3.139465	-3.139465	-33.690914	-40.199541	O-H-O O-H-O	2.068 1.939
A42	5-methyl-2-phenyl-4-[(*E*)-2-(2,4,5-trihydroxy-3-methylphenyl)ethenyl]-1,2-dihydro-3*H*-pyrazol-3-one	-3.135078	-3.135078	-44.861495	-61.572393	N-H-O O-H-O	2.109 1.970
A43	4-[(*E*)-2-(2-hydroxyphenyl)ethenyl]-5-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one	-1.7854	-1.7854	-36.2487	-40.09542	C-O-H O-H-O	1.261 1.073
A44	5-methyl-2-phenyl-4-[(*E*)-2-(2,3,4,5-tetrahydroxyphenyl) ethenyl]-1,2-dihydro-3*H*-pyrazol-3-one	-0.8932	-0.8932	-36.4676	-39.19027	N-H-O O-H-O	1.232 1.763
A45	4-[(*E*)-2-(5-chloro-2,3,4-trihydroxyphenyl)ethenyl]-5-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one	-4.736547	-4.736547	-35.960246	-46.925867	O-H-O C-O-H	1.967 1.975
A46	4-[(*E*)-2-(5-chloro-2,3-dihydroxyphenyl)ethenyl]-5-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one	-2.253741	-2.253741	-43.144163	-56.534353	C-O-H N-H-O O-H-O	1.797 2.020 2.024
A47	4-[(*E*)-2-(5-chloro-2-hydroxyphenyl)ethenyl]-5-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one	-3.020174	-3.020174	-32.083400	-47.160399	O-H-O C-O-H	2.040 2.114

A48	4-[(*E*)-2-(2-amino-5-chlorophenyl)ethenyl]-5-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one	-3.060281	-3.060281	-30.413624	-34.555194	C-O-H O-H-O	1.716 1.981
A49	4-[(*E*)-2-(2,4-diamino-5-chlorophenyl)ethenyl]-5-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one	-3.126877	-3.126877	-27.596933	-38.159567	C-O-H C-O-H O-H-O C-O-H	2.268 2.023 2.045 1.620
A50 (I)	4-(5-Bromo-2-hydroxybenzylideneamino)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one	-6.40613	-6.40613	-29.779523	-40.882543	C-O-H	2.063
A51	5-methyl-2-phenyl-4-[(*E*)-2-(2,4,6-triamino-3-chlorophenyl)ethenyl]-1,2-dihydro-3*H*-pyrazol-3-one	-4.650567	-4.650567	-52.781501	-66.678982	O-H-O O-H-O N-H-O C-N-H N-H-O	1.755 1.952 1.546 2.320 2.344
A52	4-[(*E*)-2-(2,6-diamino-3-chloro-4-hydrazinylphenyl) ethenyl]-5-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one	-4.435440	-4.435440	-19.462871	-22.337554	O-H-O O-H-O C-O-H C-O-H	1.914 2.149 2.171 1.677
A53	4-{(E)-2-[2,6-diamino-3-bromo-4-(triazan-2-yl)phenyl]ethenyl}-5-methyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one	-4.347846	-4.347846	-36.082372	-45.192319	O-H-O N-H-O N-H-O N-H-O	2.152 2.276 2.171 1.635

Conclusion

In the present study molecular docking studies conducted on Benzylidene, naphthylidene base of benzoic acid and one heterocyclic derivative (pyrazole). The docking method describes the binding interaction with the ligand and receptor HDAC8. Most of the compounds showed good binding interaction with the receptor. Based on the docking score 4-(5-Bromo-2-hydroxybenzylideneamino)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one (50), 4-((2-hydroxynaphthalen-1-yl) methyleneamino) benzoic acid (37), 4-(4-Bromobenzylideneamino)benzoic acid (1) showed highest docking score of -6.4061, -5.8214 and -4.8465 respectively, which are important for HDAC8 inhibition. The designed pyrazole derivative (4 - (5 - Bromo-2-hydroxybenzylideneamino)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one) showed good docking score. These prove to be potential inhibitors of HDCA8.

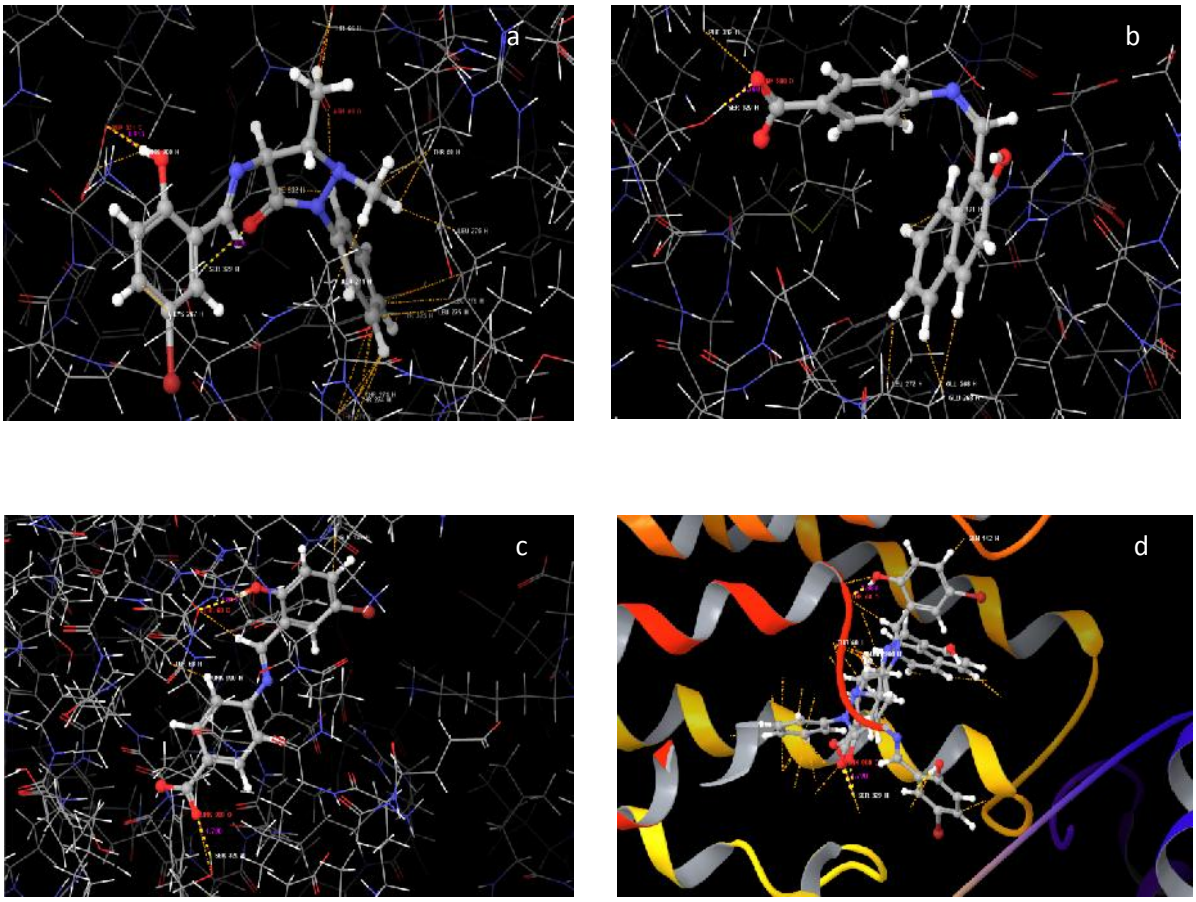

Figure 4: HDAC8 molecular interaction with compound a: 50; b: 37; c: 1 and d: Molecular interaction complex ribbon model with ranked compounds: I, II, III.

References

Bekhita, A.A., and Abdel Aziem, T. 2004. Design, synthesis and biological evaluation of some pyrazole derivatives as anti-inflammatory-antimicrobial agents. Bioorg. Med. Chem. 12: 1935–1945.

Dhanya, S., A.M. Isloor and Shetty, P. 2009. Synthesis, characterization and anticancer activity of 1,2,4-Triazolo[3,4-*b*]-1,3,4-thiadiazoles on Hep G2 cell lines. Der Pharma Chem. 1: 19–26.

Friesner Richard A., Jay L. Banks, Robert B. Murphy, Thomas A. Halgren, Jasna J. Klicic, Daniel T. Mainz, Matthew Repasky, P. 2004. Glide: a new approach for rapid, accurate docking and scoring. 1. Method and assessment of docking accuracy. J Med Chem. 47(7): 1739-1749.

Friesner, R.A., R.B. Murphy, M.P.Repasky, L.L.Frye, J.R.Greenwood, T.A.Halgren, P.C. Sanschagrin and Mainz, D.T. 2006. Extra Precision Glide: Docking and Scoring Incorporating a Model of Hydrophobic Enclosure for Protein-Ligand Complexes. J Med Chem. 49(21): 6177-6196.

Haider, S., M.S.Alam, H.Hamid, S.Shafi, A.Dhulap, F.Hussain, P.Alam, S.Umar, M.A.Pasha, S.Bano, S.Nazreen, Y.Ali and Kharbanda. C. 2014. Synthesis of novel 2-mercaptobenzoxazole based 1,2,3-triazoles as inhibitors of proinflammatory cytokines and suppressors of COX-2 gene expression. Eur J Med Chem. 81: 204-217.

Isloor, A.M., B. Kalluraya, Rao, M. 2000. Sydnone Derivatives: Part IV: Synthesis of 3-aryl-4-(substituted pyrazolidene hydrazine-4-thiazolyl) sydnones as possible analgesic and anticonvulsant agents. J. Saudi Chem. Soc. 4: 265–270.

Isloor, A.M., B. Kalluraya, Shetty, P. 2009. Regioselective reaction: Synthesis, characterization and pharmacological studies of some new Mannich bases derived from 1, 2, 4-triazoles. Eur. J. Med. Chem. 44: 3784–3787.

Miyachi, H., H. Kiyota and Segawa, M. 1998. Novel imidazole derivatives with subtype-selective antimuscarinic activity. Bioorg. Med. Chem. Lett. 8: 1807–1812.

Naresh, K., V. Geetha Ramakrishnan, and Sarma Jagarlapudi, S. 2012. QSAR Studies of N-(2-Aminophenyl)- Benzamide derivatives as Histone deacetylase2 Inhibitors. Int J PharmTech Res. 4: 1110-1121.

Pandey, J., V.K. Tiwari, S.S. Verma, V. Chaturvedi, S. Bhatnagar, S. Sinha, A.N. Gaikwad and Tripathi, R.P. 2009. Synthesis and antitubercular screening of imidazole derivatives. Eur J Med Chem. 44: 3350–3355.

Pinza, M., Z. Farina, A. Cerri, U. Pfeiffer, M.T. Riccaboni, S. Banfi, R. Biagetti, O. Pozzi, M. Magnani and Dorigotti, L. 1993. Synthesis and pharmacological activity of a series of dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-diones, a novel class of potent cognition enhancers. J Med Chem. 36: 4214–4220.

Sharma, N.K. and Jha Priyanka, K.K. 2010. Molecular docking: an overview. J Adv Sci Res. 1:67–72.

Suzuki, F., T. Kuroda, T. Tamura, S. Sato, K. Ohmori, Ichikawa, S. 1992. New anti inflammatory agents 2. 5-Phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-ones: a new class of nonsteroidal anti-inflammatory agents with potent activity like glucocorticoids. J. Med. chem. 35:2863–2870.

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