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Homology Modeling, Molecular Dynamic Simulation and in Silico Screening of Activator for the Intensification of Human Sirtuin Type 1 (SIRT1) by novel 1, 3, 4-Thiadiazole Derivatives-A Potential Antiaging Approach

Sudipta Saha, Amit Rai, Mahendra Singh, Vinit Raj *, Durgesh Kumar and Anil Kumar Sahdev
Department of Pharmaceutical Sciences, Babasaheb Bhimrao Ambedkar University, Vidya Vihar, Rai Bareli Road, Lucknow 226025
* Author to whom correspondence should be addressed; E-Mail: raj.vinit24@gmail.com; Tel.: +918859383897.

Published: 4 December 2015

Abstract: Sirtuin type-1(SIRT1) is a regulator of various biosynthetic pathways via activation of peroxisome proliferator-activated receptor-γ and interacting with adenosine-mono-phosphate kinase. SIRT1 is the important target for various neurodegenerative, cancer and metabolic disorders as well as aging medicine. Keeping in view of the above fact, we considered novel 1,3,4-thiadiazole derivatives series for SIRT1 screening, which was performed through virtual screening, homological modeling, docking and computational studies. On the basis of available molecular structure in protein data bank of SIRT1 protein, we calculated the interaction energy designed molecules. The interaction energy of designed compound VR3 closely better than resveratrol (~ 6.4 kcal/mol). Among of them the VR 3 shown the best conformation fitting stability in the binding site of SIRT1 predicted by MD (Molecular dynamics) simulation for 2.5ns. Therefore, the designed compounds have good binding affinities to SIRT1 target, would serve better lead compound for antiaging screening for future drug design perspective.
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Keywords Homology modeling, Molecular docking, ADMET prediction, actives substrate binding domain of SIRT1, Antiaging

1. Introduction

In the last few years, sirtuin (SIRT) has become a large attention to scientific communities for developing lead optimization. Interesting in this protein family is to its crucial role in genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing and mitochondrial dysfunction (López-Otín, Blasco, Partridge, Serrano, & Kroemer, 2013). SIRT1 downregulates pro-inflammatory factors like p53[2-3] and nuclear factor-kappa B (NF-κB), whereas upregulates peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1α)(Amat et al., 2009; Wareski et al., 2009) and forkhead box class O transcription factors (FOXOs). SIRT 1 is the main target for diverse pharmacological properties including neurodegenerative disorders, cancer and metabolic disorders as well as aging medicine (Pallàs et al., 2009).

Because of that, the discovery of SIRT1 activator is an important target for drug discovery. In this study, we focused on developing a new scaffold which can be able to have potent activation effect. During searching of new lead for SIRT1 target, we used 1, 3, 4-thiadiazole moiety as it has one hydrogen binding domain and two-electron donor system. The previous literature survey suggested that 1, 3, 4-thiadiazole is the important pharmacophore than other isomers for binding to the receptor and it has multiple pharmacological actions as well. This ring exhibited antimicrobial (Demirbas, Karaoglu, Demirbas, & Sancak, 2004; Karegoudar et al., 2008), anticancer (Chou et al., 2003), antanxiety, anti-depressant (Clerici et al., 2001), anti-oxidant properties (Martinez et al., 1999), anticonvulsant activity (Yusuf, Khan, Khan, & Ahmed, 2013) and antitubercular activities (Alegaon et al., 2012). Thiadiazole ring expressed diverse biological activities, might be due to the presence of =N-C-S moiety (Oruç, Rollas, Kandemirli, Shvets, & Dimoglo, 2004).

In view of the above fact, the question arose whether 1, 3, 4-thiadiazole might be an important activator for SIRT1 target. To prove this hypothesis, homology modeling was performed using one or more known protein structures that are resembling to the structural sequence of SIRT1. Later, all these sequences collapsed together to reach the desired template sequence. Finally, docking studies was carried out between newly designed protein and prepared ligand to get interaction energy.

After that, the pharmacokinetics parameters (ADME, BBB and toxicity) were also measured with that designed compound to rule out whether these compounds might be suitable for *in vivo* biological system. We hypothesized that these compounds may be a lead target for antiaging as a SIRT1 agonist and also suitable for *in vivo* screening in the future.

Material and methods

In this present study, National Centre for Biotechnology Information (NCBI) (http://www.ncbi.nlm.nih.gov) and Protein Data Bank (PDB) (http://www.rcsb.org) were used as chemical sources. The software which was used to experiment, tabulated in table (1). Resveratrol, VR1, VR2, and VR3 structures were drawn through Chemdraw Ultra 10.0 figure (1) and their geometry was optimized six times with Gauss view 5.0. However, these structures represent a minimum energy optimization, selected for *in-silico* study and 3-D structure of sirtuin type-1 Protein structure was not available in the PDB and NCBI Protein database. The 3-D structure of the protein was prepared through the run blast of protein on the database of PDB that had shown the description of sequences

producing significant alignments of query cover and identity (37 and 97%, respectively). Finally, prepared 3-D protein structure was used for homological modeling figure (2).

Table 1 Softwares used for modeling and their Purposes

Softwares	**Purposes**
Chemdraw Ultra 10.0 and open babel GUI	For drawing the chemical structure and convert into PDB format
Argus Lab software,Gauss view 5.0	For optimizing the geometry of derivatives
1: 3-D pssm sever, phyre 2.0 server, easy moduller 2.0, swiss pdb viewer (spdbv 4.1.0), Modbase server and saves server plot.	For the homological modeling of Sirtuin type 1
Autodock 4.0,Discovery studio and autodock vina	For docking studies
Molinspiron software toolkit, Med Chem Designer and Lasar toxicity prediction service	For characterization of the derivatives

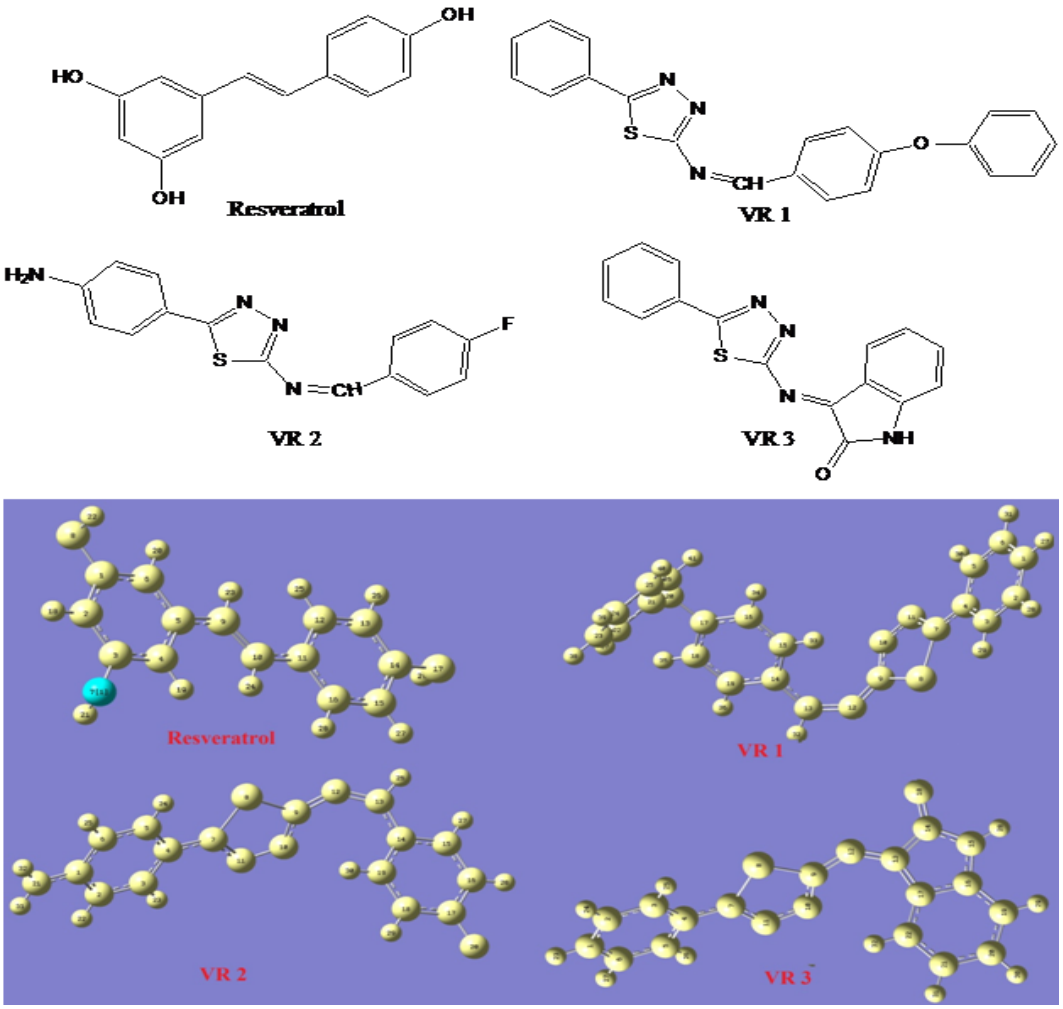

Figure 1: Structures of standard and designed compounds with optimized geometry

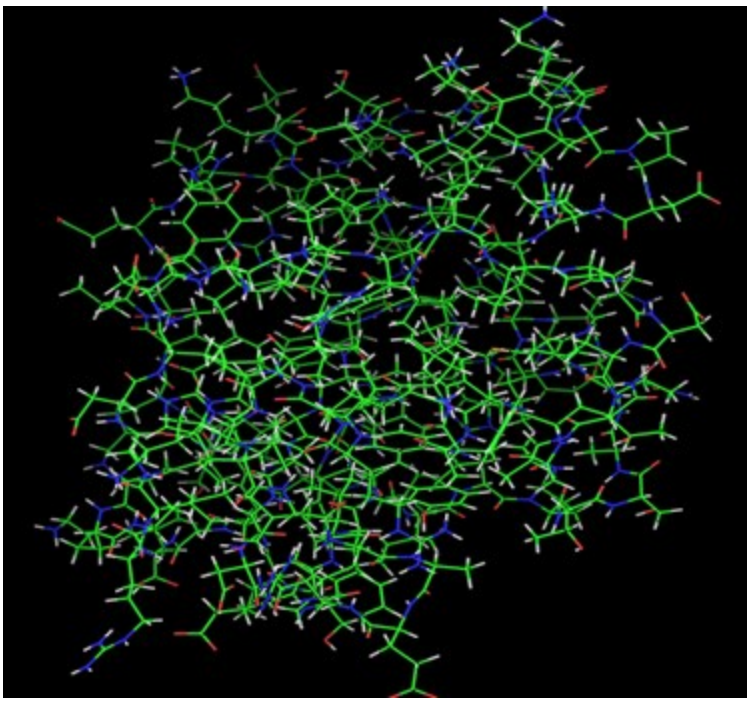

Figure 2: 3-Dimensional Structure Prediction of Sirtuin type 1 Protein of Homo sapiens

Amino acid sequences of Sirtuin type 1 Protein

GenBank: AAD40849.2

GenPept Graphics

>gi|7555471|gb|AAD40849.2|AF083106_1

sirtuin type 1 [Homo sapiens]

MADEAALALQPGGSPSAAGADREAASSPA
GEPLRKRPRRDGPGLERSPGEPGGAAPERE
VPAAARGCPGAAAAALWREAEAEAAAAG
GEQEAQATAAAGEGDNGPGLQGPSREPPL
ADNLYDEDDDDEGEEEEEAAAAAIGYRDN
LLFGDEIITNGFHSCESDEEDRASHASSSDW
TPRPRIGPYTFVQQHLMIGTDPRTILKDLLP
ETIPPPELDDMTLWQIVINILSEPPKRKKRK
DINTIEDAVKLLQECKKIIVLTGAGVSVSCG
IPDFRSRDGIYARLAVDFPDLPDPQAMFDIE
YFRKDPRPFFKFAKEIYPGQFQPSLCHKFIA
LSDKEGKLLRNYTQNIDTLEQVAGIQRIIQC
HGSFATASCLICKYKVDCEAVRGDIFNQVV
PRCPRCPADEPLAIMKPEIVFFGENLPEQFH
RAMKYDKDEVDLLIVIGSSLKVRPVALIPSS
IPHEVPQILINREPLPHLHFDVELLGDCDVII
NELCHRLGGEYAKLCCNPVKLSEITEKPPR
TQKELAYLSELPPTPLHVSEDSSSPERTSPPD
SSVIVTLLDQAAKSNDDLDVSESKGCMEEK
PQEVQTSRNVESIAEQMENPDLKNVGSSTG
EKNERTSVAGTVRKCWPNRVAKEQISRRL
DGNQYLFLPPNRYIFHGAEVYSDSEDDVLS
SSSCGSNSDSGTCQSPSLEEPMEDESEIEEFY
NGLEDEPDVPERAGGAGFGTDGDDQEAIN
EAISVKQEVTDMNYPSNKS

Homology modeling

SIRT1 was modeled by using Easy Modeler software and self-developed commends. The amino acid sequence of human SIRT1 was retrieved from Gen Bank (accession number: AF083106.2) in NCBI (Frye, 1999). It consists of 747 amino acids, among which residues 250-500 belong to SIRT1. The SIRT1 was then subjected to a PSI-BLAST search in order to identify the homologous proteins. 3-D pssm and phyre 2.0 servers were shown to produce a number of potential templates and identify better templates for sequences, were observed through distant relationships to any solved structure. Easy modeler software and self-developed command was used to generate the nine probabilities of query. Ramachandran plot checked and viewed in the swiss pdb reviewer 4.1.0.

Validation of the modeled structure

The backbone conformation of the modeled structure was calculated by analyzing the phi (Φ) and psi (ψ) torsion angles using Saves server and evaluations of the modeled 3-D structure of sirtuin was performed using PROCHECK by calculating the Ramachandran plot. This plot represented the distribution of the Φ and ψ angles for the amino acid residues.

Docking studies

Docking study of desiged compounds were performed with anti aging, molecular targets, namely SIRT1 by using Autodock 4.0 along with Autodock Vina. Before the docking study, we identified the active site domain with the help of Dog P/Castp active Site recognizer server of protein, wherein the legend showed the best configuration figure (3). Keeping in view active site amino acid sequence, Grid box was set. Their binding affinity (kcal/mol) and count of probable hydrogen bonds also evaluated in the similar experiment.

Prediction of pharmacokinetic properties

The designed compounds assessed for pharmacokinetic properties through medchem

designer software. Later, the pharmacokinetic parameters of the lead molecules analyzed, including their absorption, distribution, metabolism and excretion (ADME), using Molinspiration property online calculator (Bratislava). The percentage of absorption (%ABS) was calculated using TPSA by the following formula: % ABS = 109-(0.345×TPSA) (Zhao et al., 2002). Oral bioavailability and blood brain barrier (BBB) penetration of all compounds have performed by the ACD/ Lab-I online server.

Bioactivity prediction and Toxological comparative studies

For prediction of bioactivity and toxicological properties of titles compounds evaluated by Molinspiration property online calculator and the Lasar toxicity prediction server. The designed derivatives and original drug bioactivity predictions had been compared along with some selected activity GPCR (G-Protein coupled receptor).

MD Simulation study

Molecular dynamics simulation has been performed for the higher affinity complex with the help of Yasara tools. Hence, the complex placed in a cubic box and filled with solvent (HOH) by applying AMBER 99 force field, temperature 298 K that controlled through rescale velocities and pressure reached 1.000 bar these parameters were applied in order to check the stability of their complex. figure (4) shows the solvated structure when visualized in MD. After energy minimization of the solvated and electroneutral system its Potential Energy had been analyzed and plotted by using Sigma Plot 11.0 tools. MD simulation was run for 2.5ns. The following parameter evaluated, including: (i) Complex binding energy vs time which indicated that complex stability under the MD simulation figure(5), (ii) Potential energy of complex with respective time figure (6) and (iii) Average RMSD (Root Mean Square Deviation) graph which indicated convergence of the simulated structure towards an equilibrium state with respect to a reference structure (starting structure) figure (7).

Results and discussion

Homology modeling of SIRT1 and its evaluation

Before going to interaction energy analysis through docking studies, it is necessary to prepare an amino acid sequence of targeted SIRT1 in our experiment. Homology modeling and database searching are the key essential part for lead optimization. Total three molecules were used for this study and resveratrol were used as positive control.

For homology modeling, 3-D pssm and phyre 2.0 produced a larger number of potential templates. The selected templates were LJ8F, LMA3, LS5P, 2RCR, LQ2W, LICI, UEK, LRIA, LETP and LOGY with identity 39, 31, 28, 21, 18, 18, 17, 19, 16 and 16%, respectively. These best identical templates were downloaded from the protein data bank (PDB) with consideration of the x-ray diffraction and resolution (R). R value was within the range (not more than 3.0 A^0, and 0.5 obs). Again, Easy modeler software and self-developed commend were used to generate the nine probabilities of query or model. The best dope score was selected which resided with phi\psi out of core regions. Later these data were checked through Ramachandran plot and viewed

in the swiss pdb reviewer 4.1.0. Very few numbers of amino acid laid outside the core region. Therefore, loop modeling was done by the mod loop server and checked the output through the Ramachandran plot.

Validation of the modeled structure

The modeled structure of SIRT1 was calculated by analyzing the phi (Φ) and psi (ψ) torsion angles using the Saves server software and evaluations of the modeled 3D structure of certain were performed using PROCHECK by calculating the Ramachandran plot figure (8) and table (2). The percentage Φ and ψ angles were 92.3% of core residues, whereas this percentage was 0.2% for the disallowed residues.

Docking studies

Docking study of designing compounds was performed with antaging molecular targets SIRT1. We detected the active site domain with the help of DogP active Site recognizer server of protein where the legend showed the best configuration. Later, Grid box was set according to an active site sequence of amino acid. Their binding affinity (kcal/mol) and count of probable hydrogen bonds were evaluated table (3) through docking studies. Docking images of resveratrol, VR1, VR2 and VR3 with the target receptors was shown in figure (9). All Compounds exhibited good binding properties with SIRT1 receptor (affinity value -6.4, -7.0, -7.3 and -7.7 kcal/mol and 1, 0, 0, and 0, H-bonds, respectively for resveratrol, VR1, VR2, and VR3). Addition, the interaction of ligand to the receptor has concluded that PRO 419, GLU410 and VAL 412 common essential amino acids, which may be involved in enhancing the efficacy of SIRT1. Hence, this observation could be attributed as potential antigens with SIRT1 mimetic/facilitator mode of action.

Prediction of ADME properties

The ADME properties of the designed compounds were assessed by evaluating their physicochemical properties using the medchem designer software. Their molecular weights were <500 Da; they had <5 hydrogen bond donors and <10 hydrogen bond acceptors, and logP values of <5 table (4). These properties are within the acceptable range of Lipinski's rule of five. Furthermore, the pharmacokinetic parameters of the lead molecules were analyzed, including their ADME using Molinspiration property online calculator and Lasar toxicity prediction server. For the designed compounds, the partition coefficient (QPlogPo/w) and water solubility (QPlogS) values, the %ABS for the compounds ranged from approximately 80 to 95%. These pharmacokinetic parameters are well within the acceptable range defined for human use, thereby indicating their potential as drug-like molecules.

All designed compounds had shown the better BBB penetration power table (5) and the CNS active properties of all compounds were shown in the graph figure (10). Oral bioavailability of all designed compounds were calculated theoretically which lied in accepting a range (more than 70%). BBB penetration and oral bioavailability essential key for the pharmacokinetic profile of the compound to enhance the pharmacological activity. These all theoretically parameter of the designed compounds supported our hypothesis.

MlogP, Moriguchi estimation of logP. S+ log P logP calculated using Simulations Plus' highly accurate internal model; S+logD, logD at user-specified pH (default 7.4), based on S+logP;n-OHNH donor, Number of Hydrogen bond donor

protons; M_NO, Total number of Nitrogen and Oxygen atoms; T_PSA, Topological polar surface area in square angstroms; Rule Of Five, Lipinski's Rule of Five: a score indicating the number of potential problems a structure might have with passive oral absorption;miLog P, logarithm of compound partition coefficient between n-octanol and water; log D, logarithm of compound distribution coefficient; n-ROTB, number of rotatable bonds; MV, molecular volume; n-ON acceptor, number of Hydrogen bond acceptor protons.

Bioactivity prediction and Toxological comparative studies

In this study, for prediction of bioactivity and toxicological properties of titled compounds was also determined in our study. From all calculated parameters, it can be observed that all titled compounds expressed less affinity to GPCR (G-Protein coupled receptor) ligand, ion channel modulator, kinase inhibitor, nuclear receptor ligand, protease enzyme inhibitor and the toxicological as compared to resveratrol. All this investigation suggested that activation of SIRT1 through our compounds has great importance for providing neuroprotection in various neurodegenerative disorders including the temporal lobe epilepsy (TLE) (Shetty, 2011). The Bioactivity and Toxological data are given in table (6) and (7).

Computational details

A computational study for prediction of docking, energy minimization and ADMET properties of title compounds was performed. From all these parameters, it can be observed that all titled compounds exhibited a good ADMET and BBB properties. None of the compounds violated Lipinski,[s] parameters, making them potentially promising agents for antiaging durg. From the MD simulation study of compound VR 3 shown the stability of complex at 2.3ns with average energy -388.981 kcal/mol. In addition, the complex didn't show more fluctuation in potential energy in respectively with time. Whereas, binding energy of compound at 0 ps time was founded -189.469 Kcal/mol which increased -645.930 kcal/mol at 700 ps under MD simulation, whereas in the figure (5) the complex exhibited the fluctuation before the 800ps. Later, the complex shows the stability near 800 ps with -400(kcal/mol) compound binding energy. However, the RMSD of the backbone structure shown the stability near 200 ps. These findings suggested that the complex structure of VR 3 with SIRT1 shown the best stable fitting (affinity) in the MD simulation study.

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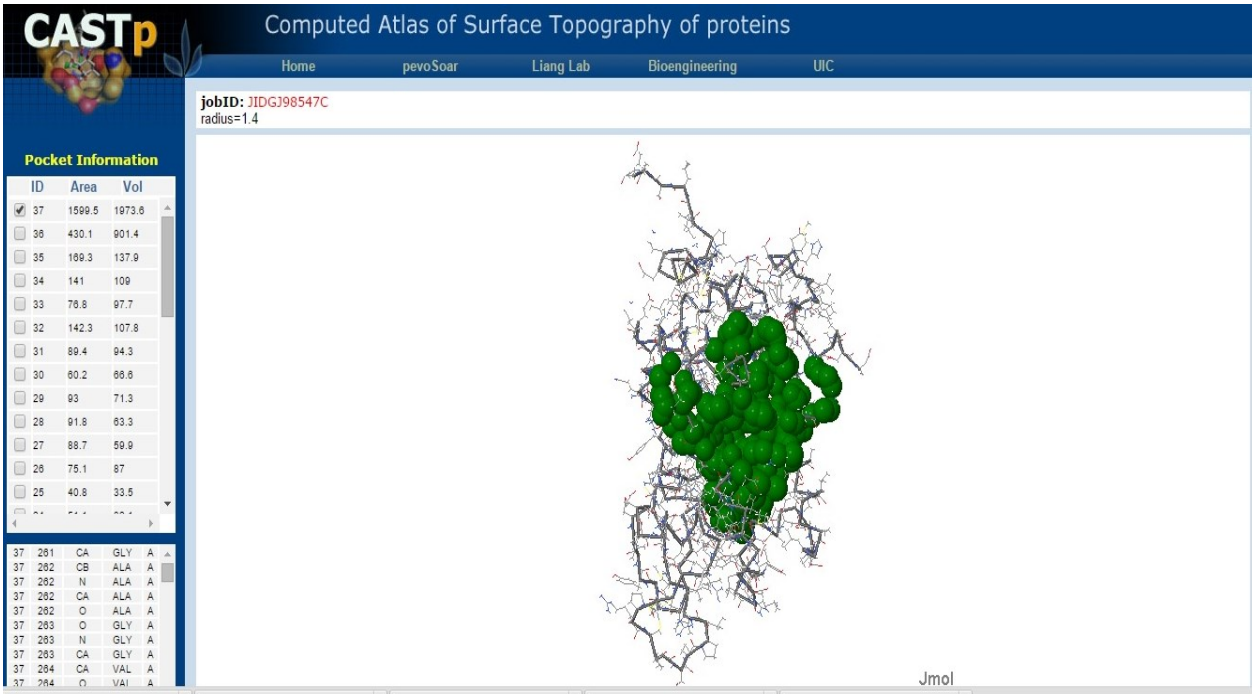

Figure 3: Amino acid present in the active site are labeled with green

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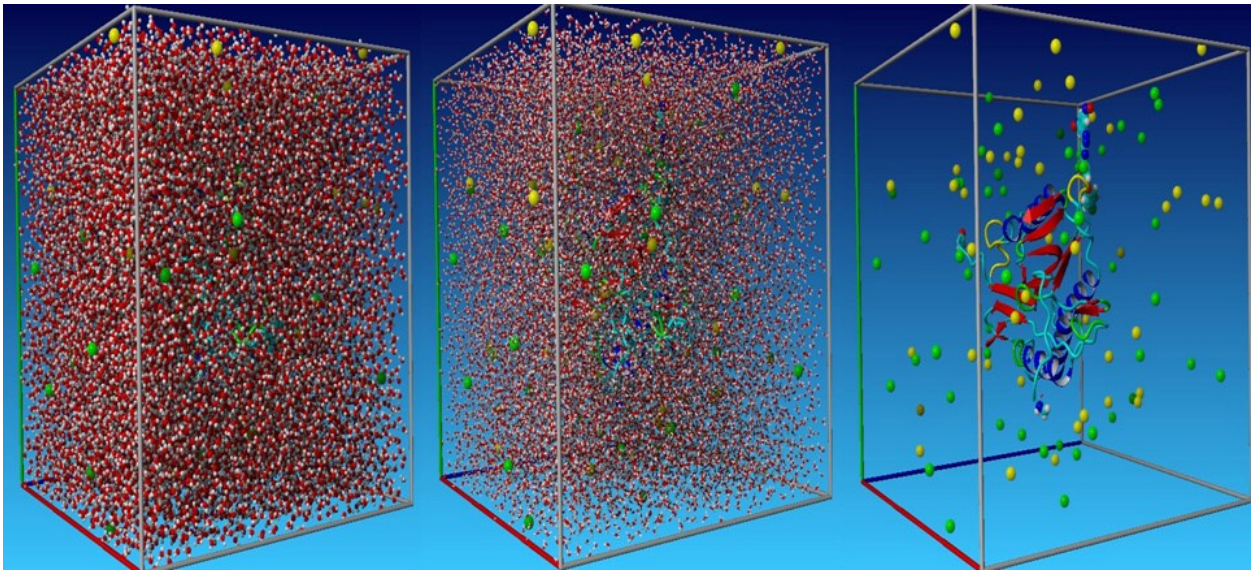

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Figure 4: Shows solvated structure visualized in MD simulation. Here red color represents the solvent. graph after Energy minimization step.Protein shown in greenish-yellow-red-blue color and ligand shown as white-sky in blue color.

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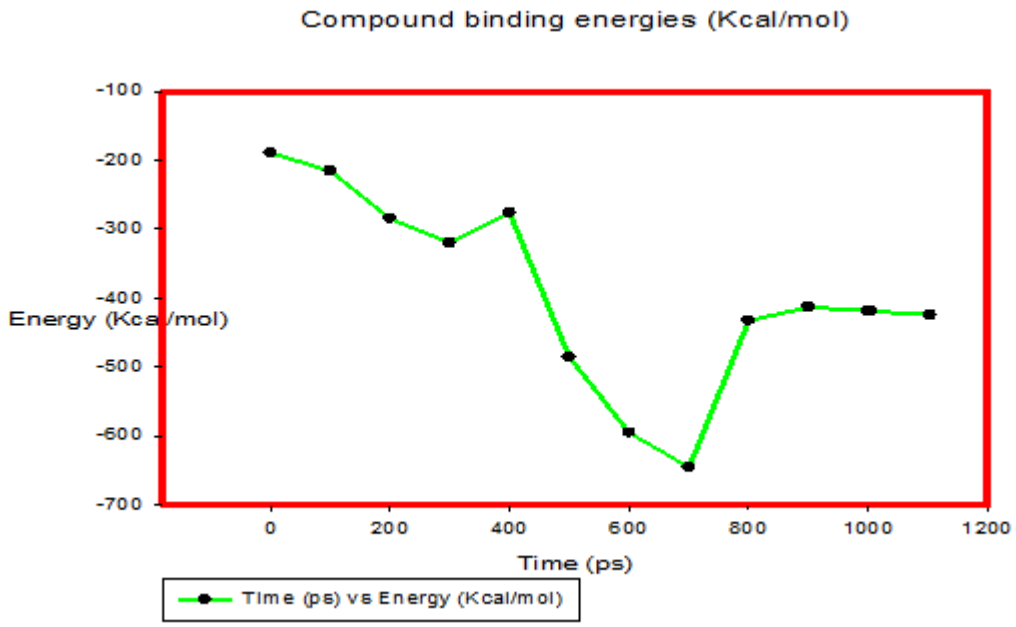


Figure 5: Shown the Time vs compound binding energy, which indicated that the energy stabilized at 1000 ps

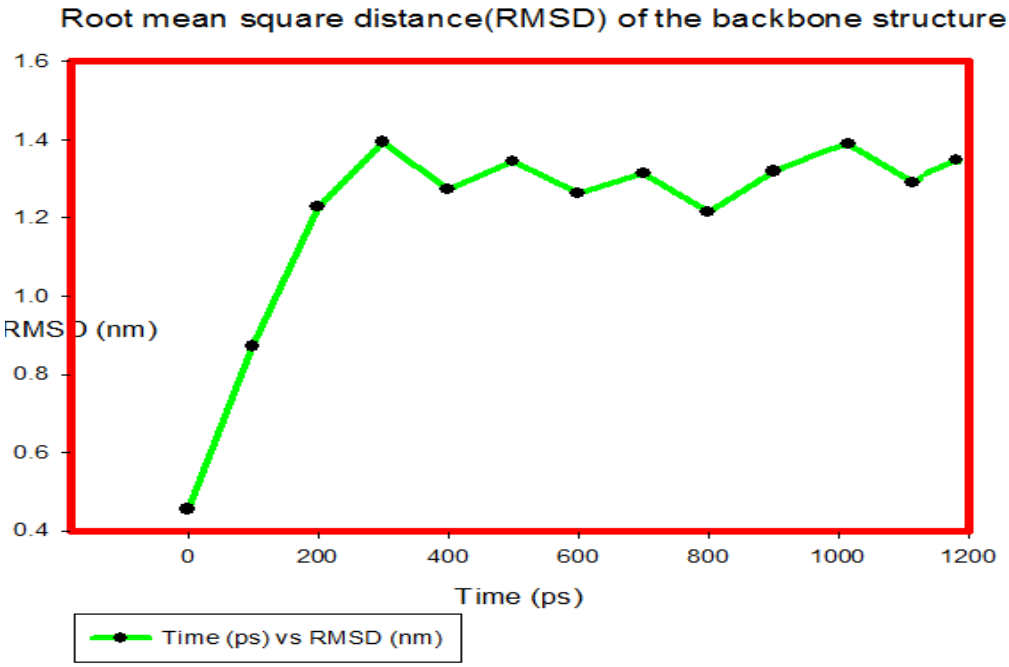


Figure 6: Root mean square distance (RMSD) of the backbone of the structure simulated over 2.5 nanoseconds.

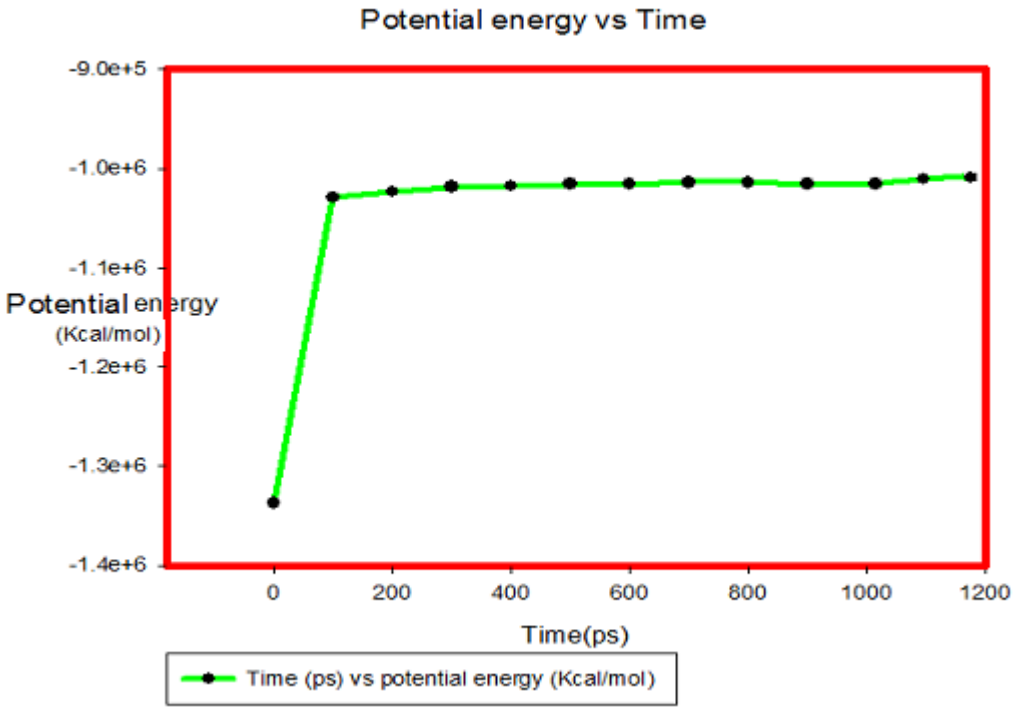


Figure 7: Shows Time (1200ps) Vs Potential Energy which indicated that very small fluctuation observed

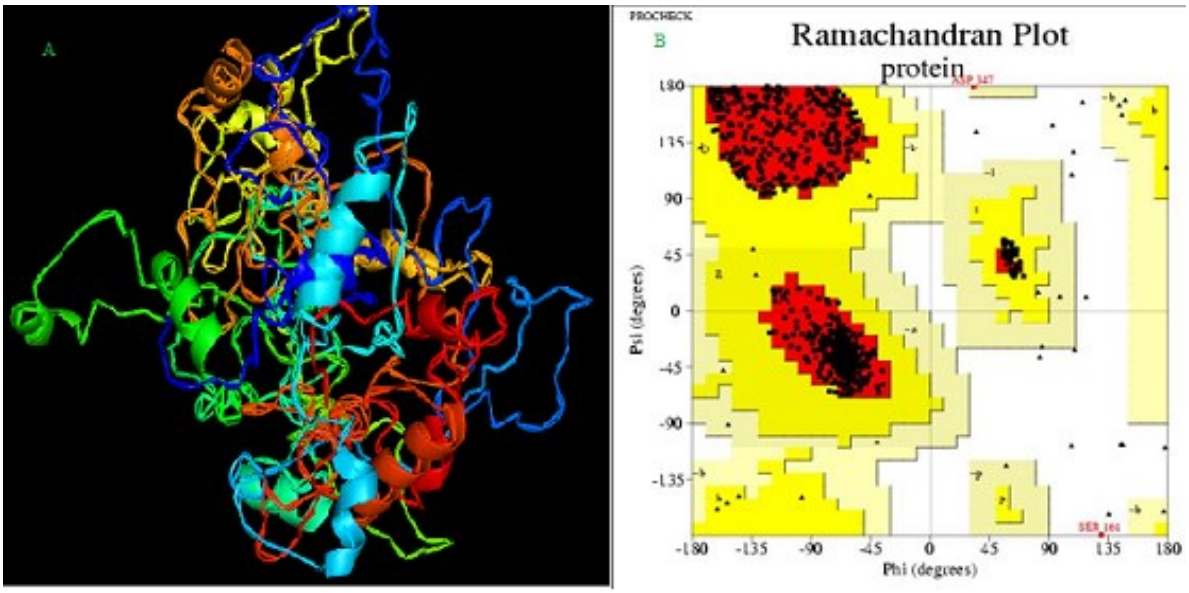


Figure 8: Protein structure validation: (A) Modeled structure of the SIRT1obtained from Easy Modeler. The structure is shown in secondary structure mode using Pymol. **(B)** Ramachandran plot for the modeled SIRT1. The most favored regions are colored red; additional allowed, generously allowed and disallowed regions are shown as yellow, light yellow and white fields, respectively.

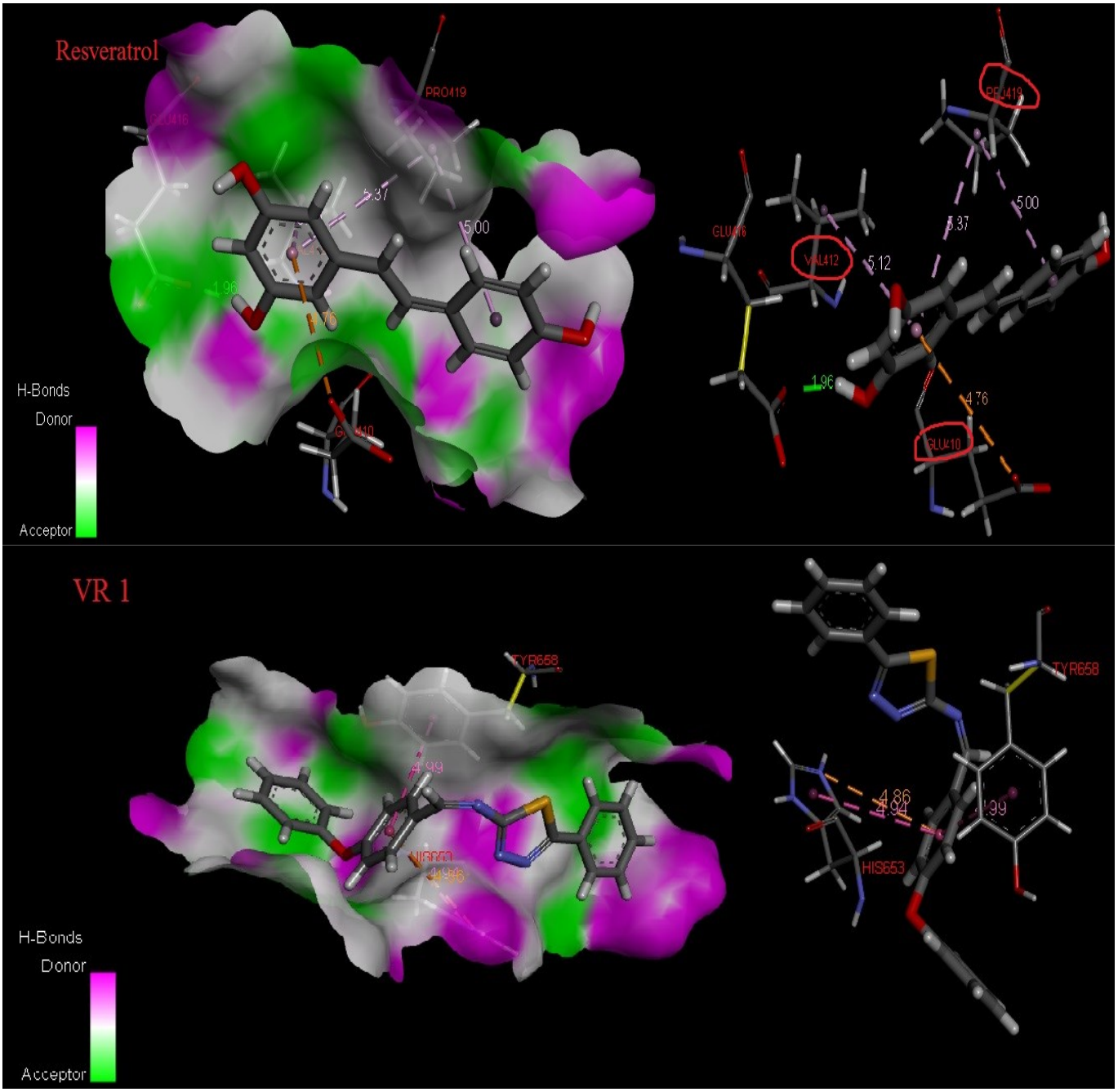
Table 2: Ramachandran plot statistics for the 3D model of SIRT1, calculated using PROCHECK

Parameter	Value
Core %	92.3
Allowed %	7.4
Disallowed %	0.2
General %	0.2

.

Table 3: Binding affinities of standard and designed compounds

Ligand	Receptor	Affinity(Kcal/Mol)	Amino acids involved in interactions	H- bonds	Pi bonds
Resveratrol	Sirtuin type1 (SIRT1)	-6.4	GLN A 361, GLY A 364, SER A 365, ALA A 367, LYS A 408, GLU A 410, ILE A 411, VAL A 412, PHE A 413, GLU A 416, ASN A 417, LEU A 418, PRO A 419, GLN A 421	1	4
VR1	Sirtuin type1 (SIRT1)	-7.0	ARG A 466, ASP A 481, GLN B 641, TYR B 642, LEU B 643, ILE B 651, PHE B 652, HIS B 653, GLY B 654, ALA B 655, GLU B 656,TYR B 658, SER B 659	0	3
VR2	Sirtuin type1 (SIRT1)	-7.3	ILE A 360, GLN A 361, GLY A 364, LYS A 408, GLU A 410, ILE A 411, VAL A 412, GLU A 416, ASN A 417, PRO A 419, GLN A 421	0	7
VR3	Sirtuin type1 (SIRT1)	-7.7	ILE A 359, ILE A 360, GLN A 361, GLY A 364, LYS A 408, GLU A 410, ILE A 411, VAL A 412, GLU A 416, ASN A 417, PRO A 419, GLN A 421, PHE A 422	0	7


Resveratrol
PRO419
5.37
5.00
1.96
4.76
H-Bonds
Donor
Acceptor
GLU410
VAL412
5.12
VR 1
TYR658
4.99
4.86
4.94
HIS653
H-Bonds
Donor
Acceptor

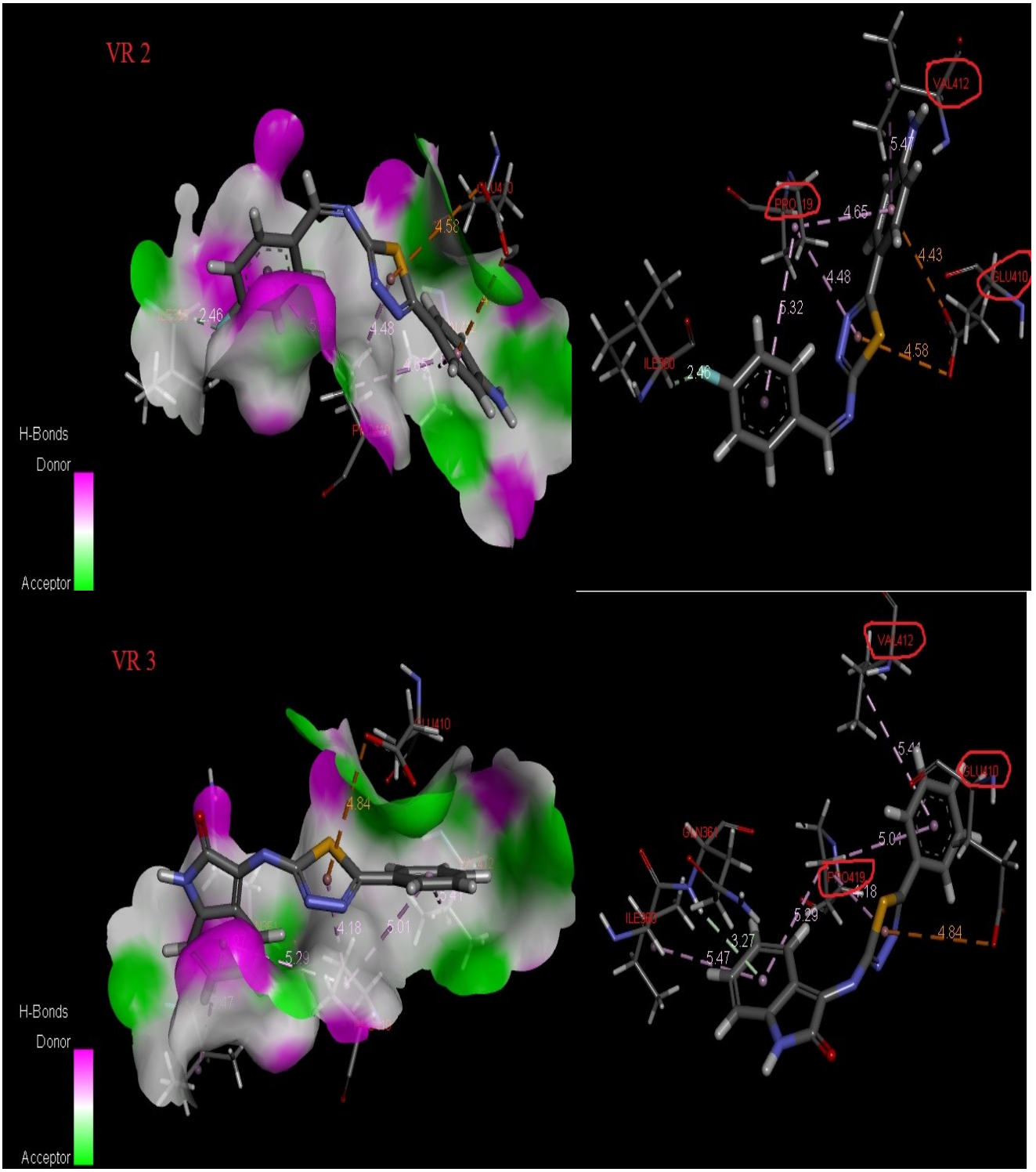


Figure 9: Docking images (a) Resveratrol, (b) VR 1, (c) VR 2 and (d) VR 3 with SIRT1, the green color dotted line shows hydrogen bonding and yellowish, light blue or whitish dotted line show Pi Donor, Acceptor and Alkyl bond respectively with amino acids involved in binding poses.

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Table 4. The theoretical ADME properties of resveratrol and all designed 1,3,4-thiadiazole derivatives.

S. No.		Rule	Resveratrol	VR 1	VR 2	VR 3
1.	S+ log P	−2.0 to 6.5)	2.907	4.679	2.892	2.454
2.	S +log D	−	2.897	4.679	2.892	2.454
3.	M log P	−	2.402	3.987	2.917	2.585
4.	T_PSA	−	60.690	47.370	64.160	67.240
5.	n-OHNH donor	<5	3.000	0.000	2.000	1.000
6.	M_NO.	−	3.000	4.000	4.000	5.000
7.	Rule of 5	≤ 1	0.000	0.000	0.000	0.000
8.	%ABS (% of absorption)	_	88.07	92.66	86.87	85.81
9.	MV	−	206.922	329.474	265.301	253.064
10.	n-ON acceptor	<10	3	4	4	5
11.	n-ROTB	−	2	5	3	2
12.	M. Wt.	< 500	228.249	371.465	298.343	306.347

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Table 5: BBB penetration of Resveratrol, VR1, VR2 and VR3

Parameter	Resveratrol	VR1	VR2	VR3
Rate of blood penetration Log PS	-1.6	-1.1	-1.1	-1.1
Extent of brain penetration Log PB	0.37	-0.15	-0.15	-0.15
Brain/plasma equilibration rate Log (PS*FU brain)	-2.5	-2.9	-3.0	-3.0

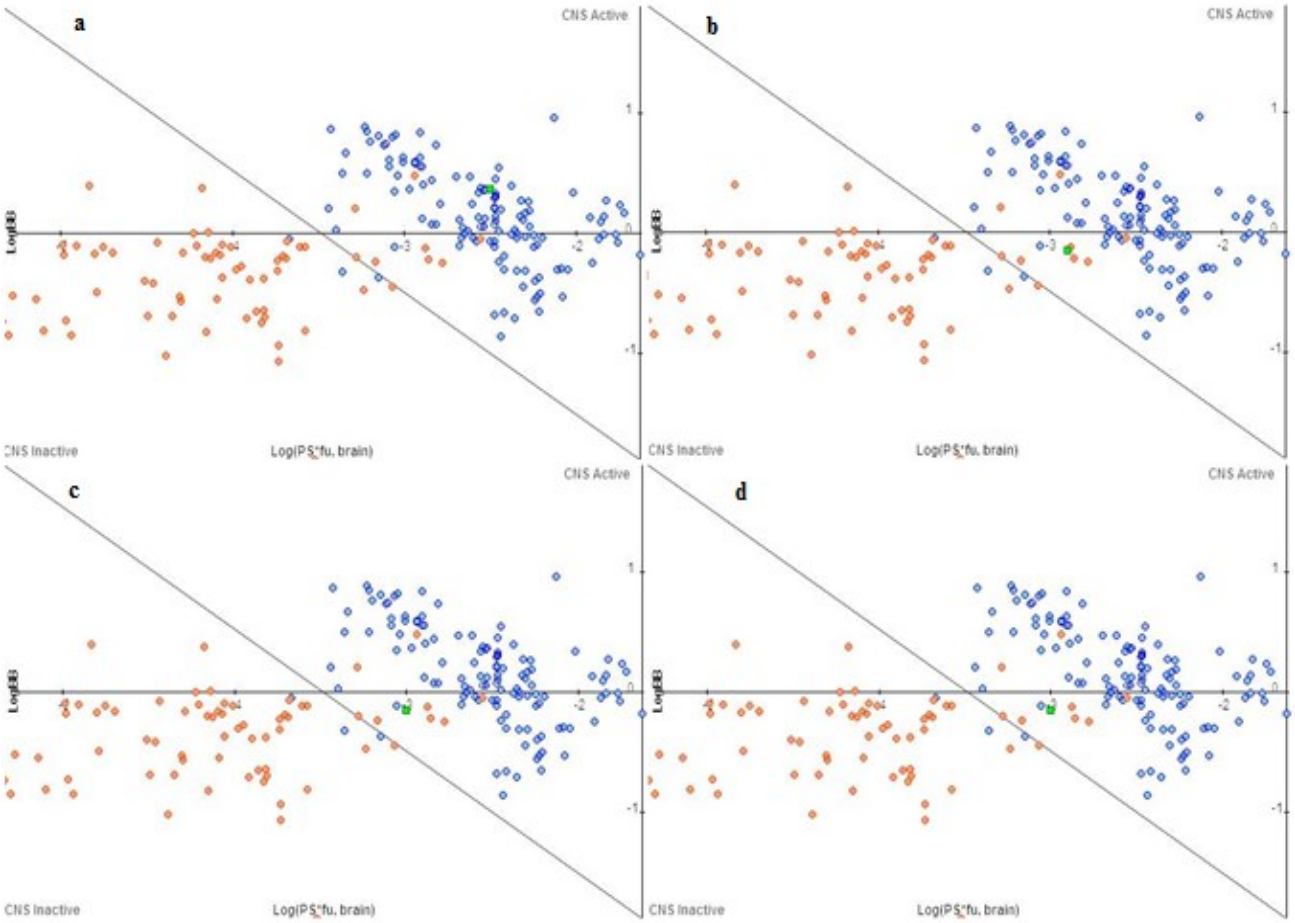

Figure 10: The BBB penetration power of the all active compounds (a, b, c, d, represents the following drug profile graph as resveratrol, VR1, VR2 and VR3 respectively). All graphs represent two region 1.CNS inactive 2.CNS active

Table 6: Score of bioactivity prediction of resveratrol and thiadiazole derivatives

S.No.	Receptors	Resveratrol	VR 1	VR 2	VR 3
1.	GPCR ligand	-0.20	-0.37	-0.46	-0.48
2.	Ion channel Modulator	0.02	-0.68	-0.79	-0.90
3.	Kinase inhibitor	-0.20	-0.11	-0.09	0.04
4.	Nuclear receptor ligand	0.01	-0.16	-0.39	-0.74
5.	Protease inhibitor	-0.42	-0.39	-0.55	-0.94
6.	Enzyme inhibitor	0.02	-0.24	-0.25	-0.32

Table 7: Topological comparative studies of resveratrol and thiadiazole derivatives

S.No.	DSSTox toxicity origin	Resveratrol	VR 1	VR 2	VR 3
1.	DSSTox Carcinogenic Potency DBS MultiCellCall: non-carcinogen	0.0127	0.0136	0.0123	0.00723
2.	DSSTox Carcinogenic Potency DBS Mutagenicity: non-mutagenic	0.162	0.101	0.00678	0.00723
3.	DSSTox Carcinogenic Potency DBS Rat: non-carcinogen	0.0517	0.0614	0.0417	0.0495
4.	Kazius-Bursi Salmonella mutagenicity: non-mutagenic	0.089	0.0335	0.0534	0.0419
5.	FDA v3b Maximum Recommended Daily Dose mmol: 0.0152722115276765	0.136	0.106	0.0834	0.0884
6.	DSSTox Carcinogenic Potency DBS SingleCellCall: non-carcinogen	0.011	0.0463	0.0126	0.0131
7.	EPA v4b Fathead Minnow Acute Toxicity LC50_mmol: 0.00359162218026281	0.207	0.184	0.203	0.19
8.	DSSTox ISSCAN v3a Canc: carcinogen	0.121	0.0869	0.243	0.000
9.	DSSTox Carcinogenic Potency DBS Hamster: non-carcinogen	0.137	0.237	0.179	0.131
10.	DSSTox Carcinogenic Potency DBS Mouse: non-carcinogen	0.0661	0.0146	0.105	0.0692

Animals **2015**, *5*, 1-x manuscripts; doi:10.3390/ani50x000x

Conclusion

Homology modeling approach was used in our study to developed 3D structure of SIRT1. According to exist literature and analysis of the results from the our research of the homology modeling, docking and computational study indicated that the designed novel 1,3,4-thiadiazole derivatives has a potent activation effect on SIRT1 receptor at potential antigen target as well as treatment of a number of life threading diseases. All compounds displayed significant binding affinity compared with resveratrol. Among of them compound VR 3 has shown significant efficacy as well as the complex stability in the MD simulation. The other parameters like toxicity, ADME, oral bioavailability and BBB penetration of all designed compounds showed similar trends. The docking study data strongly support the

assumption that SIRT1 may be involved in antiaging activity of 1, 3, 4-thiadiazole derivatives. However, the interaction of compounds with the receptor has concluded that PRO 419, GLU410 and VAL 412 common essential amino acids those may be involved in enhancing the efficacy of SIRT1. Thus, all data compared with the Resveratrol drug supported our antiaging hypothesis as a SIRT1 agonist (Kelly, 2010) .Hence, this observation could be attributed that the compound VR3 among of them as potential antiaging with SIRT1 mimetic/facilitator mode of action.

However, further studies, like synthesis, *in-vivo* evaluation and mechanism of action of these compounds are necessary to support this hypothesis. These titled compounds emerged as a lead for SIRT1 drug screening for future.

Conflict of interest statement
We wish to confirm that there are no known conflicts of interest associated with this publication.

Acknowledgements

The authors would like to express their gratitude to Babasaheb Bhimrao Ambedkar University (a Central University) Lucknow for providing the software and research data facilities.

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