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Identification of Sirtuin 1-targeted anti-Alzheimer agents using structure-based drug design and multi-database screening

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Sirtuin 1 (Sirt1) is a critical enzyme involved in cellular stress responses and neuroprotection, making it a significant target in Alzheimer's disease (AD) research. Dysregulation of Sirt1 contributes to amyloid-beta accumulation, tau hyperphosphorylation, and neuroinflammation—hallmarks of AD pathology. Structure-based drug design (SBDD) aims to develop small molecules that enhance Sirt1 activity, offering a novel therapeutic approach. By targeting Sirt1, these molecules can potentially mitigate AD progression, providing a promising strategy for developing effective treatments. In this present work, a pharmacophore containing six features has been designed using the Sirt1 macromolecule crystal structure using the Discovery Studio 2.0 software and validated by the Gunery-Henery (GH) Scoring method. The GH scores have been found in the acceptable range. Further, validated pharmacophores have been used for exploring the plant-derived database to retrieve the novel hits employing various parameters *viz* fit value, Lipinski rule of five violation, feature mapping, *in silico* pharmacokinetics and toxicological studies. After the virtual screening process, 24-24 molecules from the ZINC and FDA-approved database have been retrieved which have been further subjected to molecular docking to determine the binding interactions with the Sirt1 enzyme's active binding sites using the LibDock module in DS 2.0 software. Based on binding energy and binding interactions 2-2 molecules from the ZINC database and FDA-approved database have been selected for the molecular dynamic simulation. The knowledge obtained in this study may help reveal commercially available compounds that can become potent activators of Sirt1.

Keywords: Sirtuin 1, Alzheimer's disease, Structure-based drug design, Pharmacophore modeling, Molecular docking

Alzheimer's disease (AD) is a devastating neurodegenerative disorder characterised by progressive cognitive decline, memory impairment, and behavioural changes[1,2]. It is marked by the pathological accumulation of amyloid-beta (Aβ) plaques and neurofibrillary tangles composed of hyperphosphorylated tau protein in the brain[3]. Despite extensive research, there is still no cure for AD, and current treatments only offer limited symptomatic relief. Consequently, there is a pressing need for novel therapeutic approaches to address the disease's underlying causes and halt its progression[4,5]. Sirtuin1 (SIRT1) is a member of the Sirtuin family of NAD+-dependent deacetylases and has garnered significant attention due to its involvement in regulating various cellular processes, including ageing, metabolism, and stress responses[6]. In the context of neurodegeneration, SIRT1 is particularly noteworthy for its potential neuroprotective effects[7]. SIRT1 exerts its beneficial effects by deacetylating and modulating the activity of several key proteins and transcription factors involved in neuronal survival, inflammation, and metabolic regulation. These properties make SIRT1 an attractive target for therapeutic intervention in AD[8].

Research has demonstrated that SIRT1 activation can positively influence several pathological processes associated with AD[9]. For instance, SIRT1 activation has been shown to reduce the production of Aβ peptides, one of the primary culprits in AD pathology[10]. This is achieved through the deacetylation and activation of retinoic acid receptor beta (RARβ), which subsequently increases the expression of ADAM10, an enzyme that promotes the non-amyloidogenic processing of amyloid precursor

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protein (APP)[11]. Additionally, SIRT1 can modulate tau pathology by deacetylating and stabilizing microtubules, thus reducing tau hyperphosphorylation and aggregation. These findings suggest that SIRT1 activation could mitigate key pathological features of AD and confer neuroprotection[11].

Structure-based drug design (SBDD) is a powerful strategy in modern medicinal chemistry that involves designing molecules with specific interactions based on the three-dimensional structure of a target protein[12]. The resolved crystal structure of SIRT1 provides critical insights into its active site and binding pockets, facilitating the design of small molecules that can specifically bind to and modulate SIRT1 activity[13]. This rational approach allows for the identification and optimization of compounds that enhance SIRT1 activity, offering a promising pathway for developing new therapeutic agents for AD.

In the SBDD process, computational techniques such as molecular docking and virtual screening are employed to identify potential SIRT1 activators from extensive libraries of compounds[13]. These initial hits are then subject to medicinal chemistry efforts to optimize their binding affinity, specificity, and pharmacokinetic properties. The goal is to create molecules that are not only potent SIRT1 activators but also possess favourable characteristics for brain delivery and stability.

We intended to find novel modulators using online available databases as prospective therapies targeted to SIRT1 in AD based on the views discussed above. By using the sirt1 structural protein with nicotinamide-adenine-dinucleotide (NAD) interaction as a template structure, we conducted *in silico* research that considered the construction of a receptor-based pharmacophore model for virtual screening. Following using the created pharmacophore model to virtually screen from the database, the obtained compounds were further filtered for their drug-likeness using Lipinski's Veber's and ADMET filters. An investigation was conducted to determine the binding relationship between the drug-like compounds that were obtained and the sirt1 structural protein with NAD domain pocket residues. In addition, the compounds that were acquired from docking research with the tubulin structural protein were put through significant molecular dynamics (MD) simulations to determine whether or not they remained stable for a period of fifty nanoseconds. In addition, the compounds that exhibited binding interactions with critical residues of the tubulin structural protein, which were comparable to those shown in the crystallographic structure of the sirt1 structural protein –NAD, were docked with the mutant structure that was produced.

Material and methodology

Development of structure-based pharmacophore

Finding the precise location of the catalytic interaction between the protein and its bound co-crystallized ligand is accomplished using the structure-based pharmacophore model. The essential pharmacophoric properties that hinder protein activity may be identified by analysing this model's data. A structure-based pharmacophore was created using the 3D structure of sirt1 (4i4i) and its co-crystallized modulator NAD. Discovery Studio 2.0 was used to build six structure-based pharmacophore characteristics. HBA, HY, HBD, and aromatic rings were these properties[14].

Validation of Receptor-Ligand Pharmacophore Model

The Guner-Henry (GH) technique, also known as the decoy set validation method, is used in computational chemistry and cheminformatics to evaluate the developed pharmacophore model robustness[15]. This technique involves the following steps:

$$GH = \frac{3A}{4NH}\left(1 + \frac{A - R}{NA}\right)$$

Where: A is the number of active compounds

N_H is the number of hits (compounds predicted as active).

N_A is the total number of active compounds in the dataset.

R is the number of hits that are active compounds.

Virtual Screening

There are 1,64,919 compounds in the Zinc and 1,168 in FDA FDA-approved database were downloaded. The verified pharmacophore was used as a 3D query using the ligand Pharmacophore Mapping module in Discovery Studio 2.0 to identify chemicals that potentially affect Sirt1. Additionally, the possible compounds were sorted by feature mapping, fit value, and the Lipinski rule of five. Using the pkCSM web tool, the discovered chemicals underwent a further *in silico* pharmacokinetic and toxicological study to

further refine the mixture. Following the filtering procedure, the drug-like compounds were extracted and subjected to molecular docking with the sirt1 macromolecule[16].

Molecular Docking of Drug-Like Compounds with Sirt1

Molecular docking was used to build bioactive binding poses within the Sirt1 protein enzyme's catalytic site from the drug-like chemicals obtained *via* filtering. The protein structure (4i5i) was retrieved from PDB. The protein structure was built using SWISPDB viewer and used to determine binding score and chemical binding interactions using the Pyrx virtual screening tool and Autodock Vina module. Pymol and Discovery Studio Visualizer analysed protein-ligand binding[17].

Molecular dynamic simulation

Molecular dynamics (MD) simulation is a computational technique used to study the physical movements of atoms and molecules over time, providing insights into molecular structure and behaviour (The Desmond 2020.1 from Schrödinger, LLC). This process begins with the selection and preparation of the molecular system, including the choice of an appropriate force field to define the potential energy. The system is then solvated, typically in a water box, and ionized to mimic physiological conditions. Energy minimization is performed to remove any steric clashes, followed by equilibration under controlled temperature and pressure conditions. During the production run (100 ns), Newton's equations of motion are integrated over time to simulate atom movements, with trajectories recorded for subsequent analysis. Post-simulation, the trajectory data is analysed to assess molecular properties such as stability, conformational changes, and interactions, often visualized using specialized software. Advanced analyses may further refine the insights gained from the simulation[18].

Result and Discussion

Generation and validation of receptor-ligand pharmacophore model

Using Discovery Studio 2.0 software, six feature pharmacophore were developed which included two hydrogen bond acceptors, two hydrophobic and two hydrogen donors as shown in Fig. 1.

This six-feature-based pharmacophore was validated using the Gunery Henery scoring method. The database included 90 decoy compounds and 13 inhibitors that were known to have sirt1. To assess the model's capability to differentiate between active and decoy compounds, the pharmacophore model was used as a 3D query to explore the internal decoy database. The following metrics were computed: total hits (Ht), active hits (Ha), percentage yield of actives, percentage ratio of actives, and GH score. A GH score between 0.7 - 0.8 implies a very commendable model. The observed value for the pharmacophore model was 0.752, as seen in Table 1. The verified findings demonstrate that the model was very effective for database screening.

Drug-like compounds retrieved from virtual screening

A highly reliable pharmacophore was employed to explore the test compounds database and 1,64,919 compounds from the Zinc database and 1,168 in the FDA-approved database were retrieved. Afterwards, using various filtration parameters including fit values, and feature mapping 167 and 1128 compounds were separated respectively. In addition,

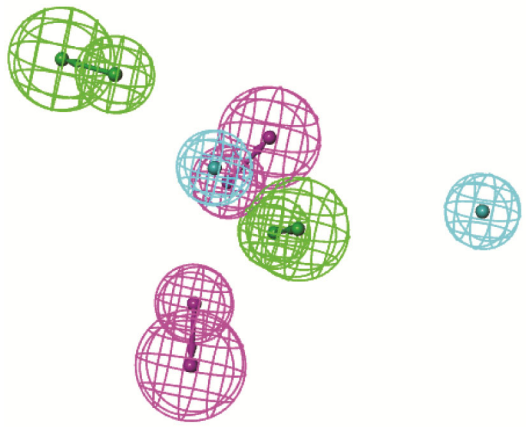

Fig. 1 — Six feature pharmacophore developed using the Sirt1 macromolecule crystallographic structure

Table 1 — GH scoring

Serial No.	Parameter	Pharmacophore model
1	Total molecules in database (D)	90
2	Total number of actives in the database (A)	13
3	Total hits (Ht)	16
4	Active hits (Ha)	12
5	% Yield of actives[(Ha/Ht) × 100]	75
6	% Ratio of actives [(Ha/A) × 100]	92.30769231
8	False negatives [A − Ha]	1
9	False positives [Ht − Ha]	4
10	Goodness of hit score (GH)	0.75206044

Table 2 — Compounds retrieved from the ZINC database using the virtual screening

Compd	Feature mapping	Fit value	Pharmaprint	RMSD
ZINC000096305829	5	1.53895	'111011'	0.78679
ZINC000001761773	4	0.913347	'110011'	0.730013
ZINC000004051748	4	0.418103	'110011'	0.59624
ZINC000029531980		1.37659	'101011'	0.876012
ZINC000061721897	4	0.0055947	'101011'	0.607984
ZINC000010385344	4	2.2263	'101011'	0.642002
ZINC001704324595	4	2.03028	'111010'	0.661957
ZINC000072310938	4	0.22949	'110011'	0.683539
ZINC000012633961	4	1.45456	'110011'	0.783514
ZINC000004902971	4	0.619084	'110011'	0.960868
ZINC000072403507	4	1.28423	'110011'	0.701416
ZINC000004280063	4	0.774454	'110011'	0.590432
ZINC000089702267	4	0.975683	'110011'	0.620019
ZINC000101465017	4	1.39425	'110011'	0.795978
ZINC000072405659	4	1.47417	'111010'	0.702612
ZINC000006581968	4	0.742085	'101011'	0.703027
ZINC000012947980	4	0.816387	'110011'	0.717542
ZINC000061721465	4	0.90965	'101011'	0.71698
ZINC000005258344	4	1.33655	'101011'	0.905207
ZINC001857703352	4	0.0803832	'110011'	0.521082
ZINC000000864920	4	0.959451	'110011'	0.387595
ZINC000019593876	4	2.45019	'110011'	0.767137
ZINC000012528461	4	2.18306	'110011'	0.444501
ZINC000096361335	4	0.711884	'110011'	0.508208
ZINC000096361333	4	0.771853	'111010'	0.473336

Ro5, veber's filters, and *in silico* pharmacokinetic and toxicological parameters also sorted the compounds (Table S1 and S2) and found 24-24 compounds from the ZINC and FDA-approved databases as shown in Table 2 and Table 3.

Molecular docking

Following the retrieval of compounds from the ZINC and FDA-approved databases, the molecular docking technique was used to investigate the binding interactions of the compounds that were recovered with the active binding sites of the Sirt1 enzyme domain. The efficiency of the AutoDock Vina technique was assessed before docking these compounds. This was accomplished by re-docking the co-crystallized ligand, NAD, into the Sirt1-binding pocket. Pyrx software was used for this evaluation. The purpose of this re-docking procedure is to act as a validation phase, which ensures that the docking algorithm properly reproduces the known binding mode of the co-crystallized ligand. This, in turn, confirms the dependability of the docking methodology for the following study of the flavonoid compounds. For this reason, we carried out docking of 24-24 compounds derived from ZINC and FDA-

Table 3 — Compounds retrieved from the FDA-approved database using the virtual screening

Compd	Feature mapping	Fit value	Pharmaprint
Octreotide	5	0.278623	'101111'
Erythromycin	5	0.90498	'101111'
Azithromycin	5	0.233393	'111110'
Bleomycin	5	0.269106	'011111'
Anidulafungin	5	1.79671	'011111'
Mupirocin	5	0.071551	'111110'
Carboprost Tromethamine	5	0.05182	'111110'
Teicoplanin	5	0.801434	'111110'
Hyperoside	5	0.149155	'111110'
Loganin	5	0.091427	'111110'
Acarbose	5	1.71839	'111110'
Sennoside A	5	0.580643	'111110'
Dirithromycin	5	0.202533	'111110'
Bicalutamide	5	0.04608	'111011'
Glutathione	4	0.121314	'111100'
Folic Acid	4	0.597669	'011110'
Adenosine triphosphate	4	0.456684	'111100'
Pravastatin	4	1.31799	'011110'
Valsartan	4	0.450008	'100111'
Masoprocol	4	0.508436	'101110'
Flunisolide	4	1.27205	'101110'
Pentagastrin	4	2.29931	'111100'
Bortezomib	4	2.2592	'101110'
Desmopressin	4	2.01664	'011110'

approved databases to evaluate the manner in which these compounds interact with the particular residues that are located in the catalytic site of the Sirt1 enzyme. All of the compounds that were retrieved were able to bind themselves to the Sirt1 enzyme with a high docking score, which was higher than the score for the reference compound. It was shown that these chemicals interact with the essential amino acid residues that are found in the Sirt1 protein. The amino acid residues Gln294, Phe297, Tyr280, His363, Gln345, Glu467, Asn465, Asp272, and Asp471 are shown in the Sirt1 crystal structure. For effective binding interactions, it is essential to have Phe273, Ala262, Ser441, Ser442, Arg466, Cys482, Phe414, Val266, and Arg274. The compounds that were recovered showed evidence of binding to the required amino acids, which indicates that they have the qualities needed to interact with the Sirt1 enzyme[19,20]. This is supported by Table 4, Table 5, Fig. 2 and Fig. 3.

Molecular dynamic simulation

MD simulation is used to explore the binding stability of protein-ligand docking complexes. The MD simulation also provides information regarding intermolecular interaction within a reference time. Herein, the complexes docking file of selected two NCI and two plant-based compounds with Sirt1 protein were analysed by utilising MD simulation approaches to confirm the stability and intermolecular interactions between protein and molecules against 100 ns time intervals[21]. In MD modelling, RMSD was evaluated between the initial and final simulated trajectories, and crucial features including binding interactions and conformation characteristics of the complex were also evaluated. For the enzyme-ligand complex (4i5i) involving ZINC000000864920, ZINC000096361333, Folic acid and Bicalutamide, the average RMSD values were found as 2.87, 3.08, 3.03 and 3.10 Å respectively as shown in Fig. 4. These values suggest efficient binding of the ligands with the sirt1 enzyme[22,23]. The lower RMSD values indicate a relatively stable and consistent binding of these ligands within the enzyme's active site across the simulation time frame.

Root Mean Square Fluctuation (RMSF), is an important feature that has to be considered when evaluating the structural flexibility of proteins during

Table 4 — Molecular docking analysis of ZINC database retrieved compounds with Sirt1 macromolecule

S. No.	Compd	Docking score	Hydrogen bond amino acids	Hydrophobic bond amino acid
1.	ZINC000000864920	–11.9	O-Ile347 (3.028), O-Gln320 (3.047)	Phe414, Val445, Phe297, Phe273, Ile316, Ile270
2.	ZINC000096361333	–11.2	H-Gln345 (2.367), O-Arg274 (3.195)	Ile411, Ile347, Phe273, Ala262, Ser442, Glu467, Asp272
3.	ZINC000096361335	–11.0	O-Arg274 (3.222), H-Val412 (1.839)	Glu467, Ser442, Ala262, Phe297, Phe273, Ile347, Ile411
4.	ZINC000004706789	–10.7	O-Gln345 (3.007), O-Val445 (3.278), O-Lys444 (3.239), O-Lys444 (3.088), O-Ser442 (2.744), H-Ser442 (2.841), H-Asp272 (2.841)	Ser275, Gly440, Ala262, Phe297, Ile411, Phe413
5.	ZINC000010385344	–10.5	H-Asn346 (2.445), O-Ser441 (3.107), O-Ser442 (3.084), O-Ser442 (3.182), O-Ser275 (3.016)	Phe297, Phe414, Tyr280, Val445, Phe273, Arg274, Ala262, Asp272, Glu467
6.	ZINC000089702267	–10.5	O-Gln345 (2.892), O-Ser441 (2.729), O-His363 (2.981), O-Ser442 (2.969), O-Lys444 (3.179), O-Gly263 (3.285)	Phe273, Val445, Ala262, Arg466, Glu467
7.	ZINC000012528461	–10.4	O-Ser441 (2.685), O-Ser442 (3.097), O-Ser442 (2.822), O-Arg274 (3.012), O-Lys444 (3.103),	Ile316, Ile347, Phe297, Ile411, Phe273, His363, Ala262
8.	ZINC000072405659	–10.4	H-His363 (2.478), O-His363 (3.007), O-Val412 (2.799), O-G;n345 (3.048), O-Ser441 (3.036), H-Ser441 (2.189)	Val445, Phe273, Ile316, Ile347
9.	ZINC000004051748	–10.2	O-His363 (3.101), O-Ser441 (3.095), O-Lys444 (3.289), O-Lys444 (3.139), O-Gln345 (3.101), H-Gln345 (1.965), O-Ser442 (2.722), H-Ser442 (2.317), S-Asn465 (3.689)	Ala262, Cys482, Arg466, Val266, Asp272
10.	ZINC000012947980	–10.1	O-Gln345 (3.252), O-Gln345 (2.996), O-Ser441 (3.051), O-Gly263 (3.148), O-Ser442 (3.123), O-Arg274 (3.320), O-Lys444 (2.882)	Ile347, Ile411, Phe297, Ile316, Phe273, Val445, His363, Ala262

Table 5 — Molecular docking analysis of FDA-approved database retrieved compounds with Sirt1 macromolecule

	Compd	Docking score	Hydrogen bond amino acids	Hydrophobic bond amino acid
1.	Folic acid	–11.5	H-Asn346 (2.375), O-Ala262 (3.140), H-Asp481 (2.400), O-Arg466 (2.975), H-Asn465 (2.543), O-Ser441 (2.776), H-Ser442 (2.146), O-Ser442 (2.983), O-Leu443 (3.055), O-Arg274 (2.868), O-Arg274 (3.071), H-Asp272 (2.648)	Val266, Cys482, Leu443
2.	Bicalutamide	–10.9	O-Gln345 (2.801), O-His363 (3.682), O-Gly261 (3.793), O-Ala262 (3.291), O-Asp272 (3.172), F-Tyr280 (3.044)	Phe414, Glu467, Asp272
3.	Valsartan	–9.8	O-Asp348 (3.243), C-Gln345 (3.515)	Arg274, Val445, Phe414, Ala262, Ile411, Phe273, Ile347
4.	Carboprost Tromethamine	–9.6	O-Lys444 (3.032), O-Val445 (3.123), O-Gln345 (3.164), O-Ser441 (2.946), O-Ser441 (3.044), O-Ser442 (2.826), O-Lys444 (3.032), H-Phe297 (2.383), H-Tyr280 (2.256)	Phe414, His363, Phe273, Ile411, Ile347, Ile316
5.	Masoprocol	–9.2	O-Arg274 (3.052)	Val445, Ile411, Phe413, Phe273, Phe297, Ile347
6.	Mupirocin	–9.0	H-Asn346 (2.965), O-Ser441 (2.786), O-Ser442 (3.086), O-Tyr280 (3.211), O-Arg274 (2.613)	Val445, Phe414, His363, Phe297, Phe173, Ile411, Ile347, Ala262
7.	Pravastatin	–8.9	H-Asp348 (3.041), C-Asn346 (3.561), H-Asn346 (2.312), H-Gln345 (2.550), O-Arg274 (2.978), O-Arg274 (3.079), H-Phe273 (3.313)	Val445, His363, Phe297, Ile411, Ile347
8.	Loganin	–8.5	O-Gln345 (2.888), O-Ser442 (2.824), O-Phe273 (3.129), O-Phe414 (2.951), C-Tyr280 (3.748)	Phe297, His363, Ile347
9.	Flunisolide	–8.4	O-Phe413 (3.751), H-Phe414 (2.736)	Ile316, His363, Phe273, Val445
10.	Glutathione	–8.2	O-Leu443 (3.384), O-Ser442 (2.835), O-Ser442 (2.847), H-Ser442 (2.740), O-Gly263 (3.071), H-Asn465 (2.374), O-Cys482 (3.153), O-Arg466 (3.702), H-Asp272 (2.275)	

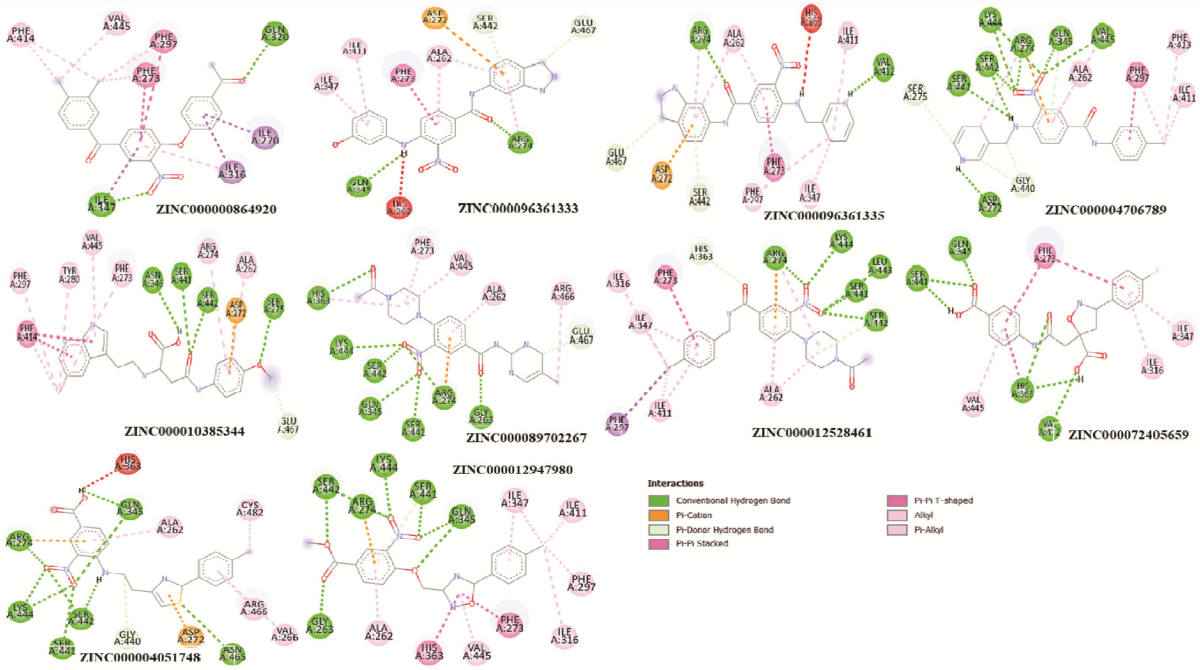

Fig. 2 — Molecular docking analysis of ZINC database retrieved compounds with Sirt1 macromolecule

MD. In addition to assisting in the evaluation of the influence that ligand binding has on the stability of proteins, it offers knowledge on the fluctuations of certain amino acid residues. For this investigation, we compute RMSF values to investigate the fluctuations that occur within the protein residues when they are attached to ligands. The protein's structural stability might be disrupted if the RMSF value is more than three angstroms, which indicates that there is a possibility of higher amino acid fluctuations

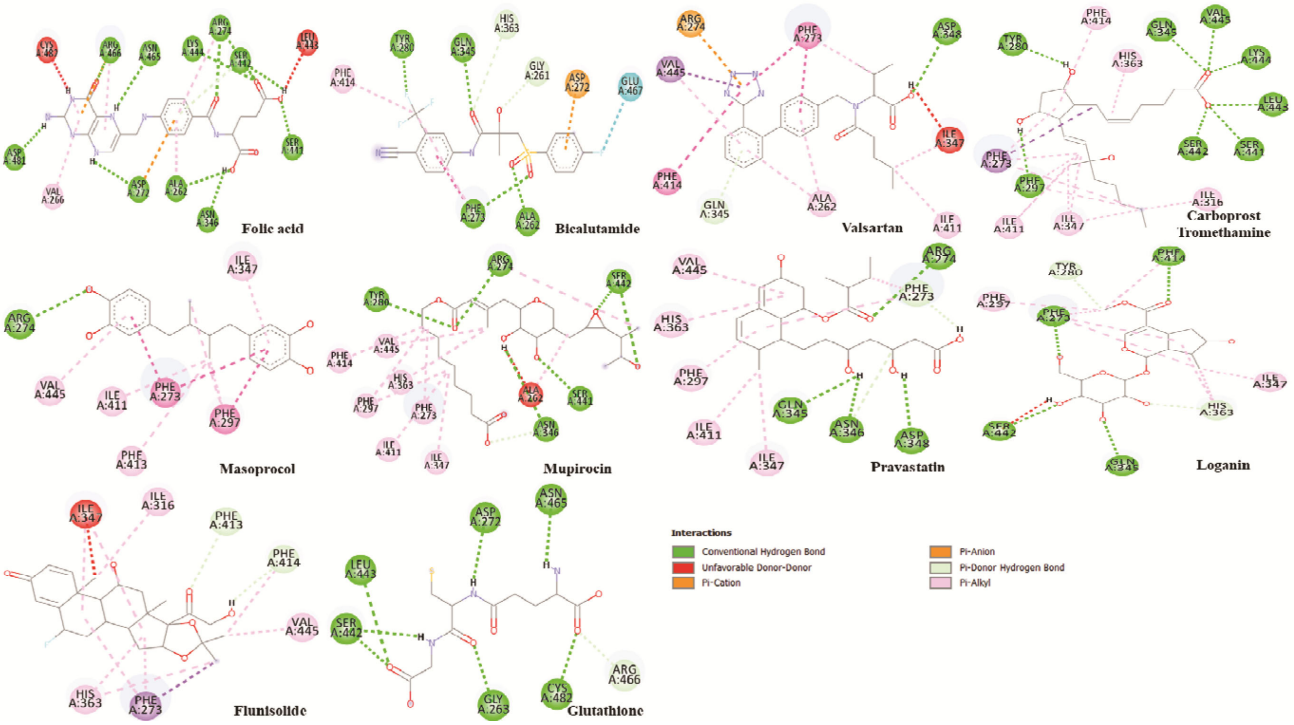

Fig. 3 — Molecular docking analysis of FDA approved database retrieved compounds with Sirt1 macromolecule

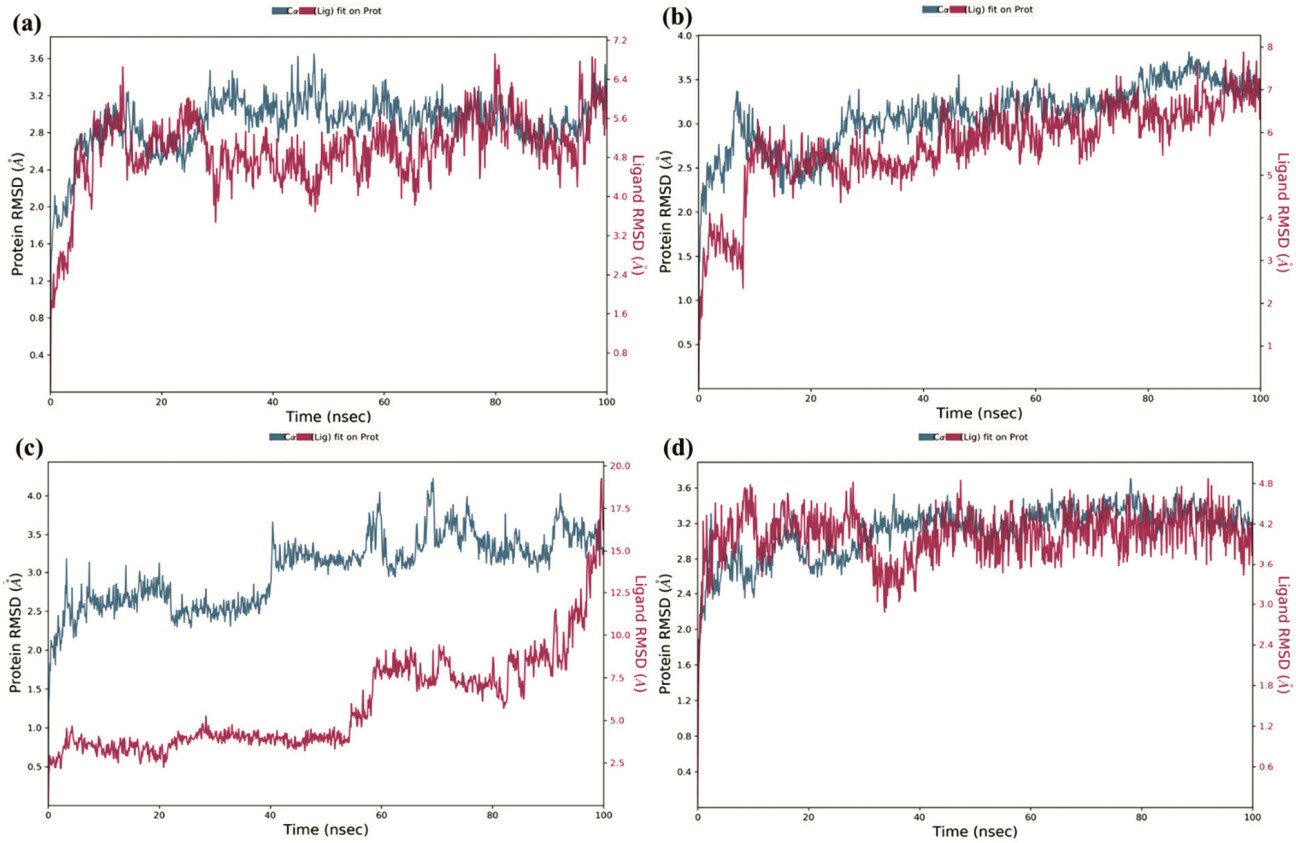

Fig. 4 — RMSD analysis of (a) ZINC000000864920 (b) ZINC000096361333 (c) Folic acid (d) Bicalutamide

following ligand binding. On the other hand, a value of RMSF that is less than three angstroms indicates that there are fewer variations in amino acids, which indicates that the protein is more stable and resistant to structural alterations. The values of the RMSF for the complexes that were chosen for this investigation varied from 0.4 to 3 Å, which indicates that there were moderate variations in the amino acid residues. In terms of the ligands that the protein bound, the average RMSF values were as follows: 1.78, 1.49, 1.70, and 1.60 Å for ZINC000000864920, ZINC000096361333, Folic acid and Bicalutamide correspondingly as shown in Fig. 5. Collectively, these RMSF values provide an indication of the complexes' stability as well as their flexibility while the MD simulations were being performed.

Compound ZINC000000864920 showed hydrogen bonding interactions with Tyr280, Arg282, Asp286, Gln294, Glu315, Gln345 and Asp348, hydrophobic interactions with Asp286, Glu315, Gln320, Asn346 and Asp348 amino acid residues with active binding active sites of sirt1 enzyme. Similarly, ZINC000096361333 showed hydrogen bonding interactions with Gly261, Ala262, Gly263, Ser266, Phe273, Tyr280, Gln294, Gln345, Asn346, His363, Phe414, Ser442 and Glu467; hydrophobic interactions with Arg274 and Lys444 amino acid residues of sirt1 macromolecules as shown in Fig. 6.

Interestingly, Folic acid compound showed hydrogen bond interactions with Ala262, Gly263, Val266, Ser267, Arg274, Asp292, Gln294, Gln345, Gly440, Ser441, Ser442, Leu443, Lys444, Asn465, Arg466, Asp481 and Cyt482 and Bicalutamide showed hydrogen bond interactions with Ala262, Gly263, Val266, Asp272, Phe273, Arg274, Tyr280, His363, Val412, Gly440 and Asn465 amino acid residues of sirt1 active binding sites. Folic acid and Bicalutamide compounds also formed hydrophobic interactions with Ala262, Phe273, Phe297 and Phe414 amino acid residues of sir1 enzyme active binding cavities as shown in Fig. 6.

Moreover, to evaluate the protein complexes to solvent molecules and their structural stability, several surface area measurements, such as SASA and rGyr, were analysed. The results revealed that the SASA values for ZINC000000864920, ZINC000096361333, Folic acid and Bicalutamide were 13282-14624 Å, 13575-15578 Å, 13523-14792 Å, and 13271-14791 Å, respectively. Additionally, the rGyr values for ZINC000000864920, ZINC000096361333, Folic acid and Bicalutamide were 20.09, 19.81, 19.9, and 22.85 Å, respectively.

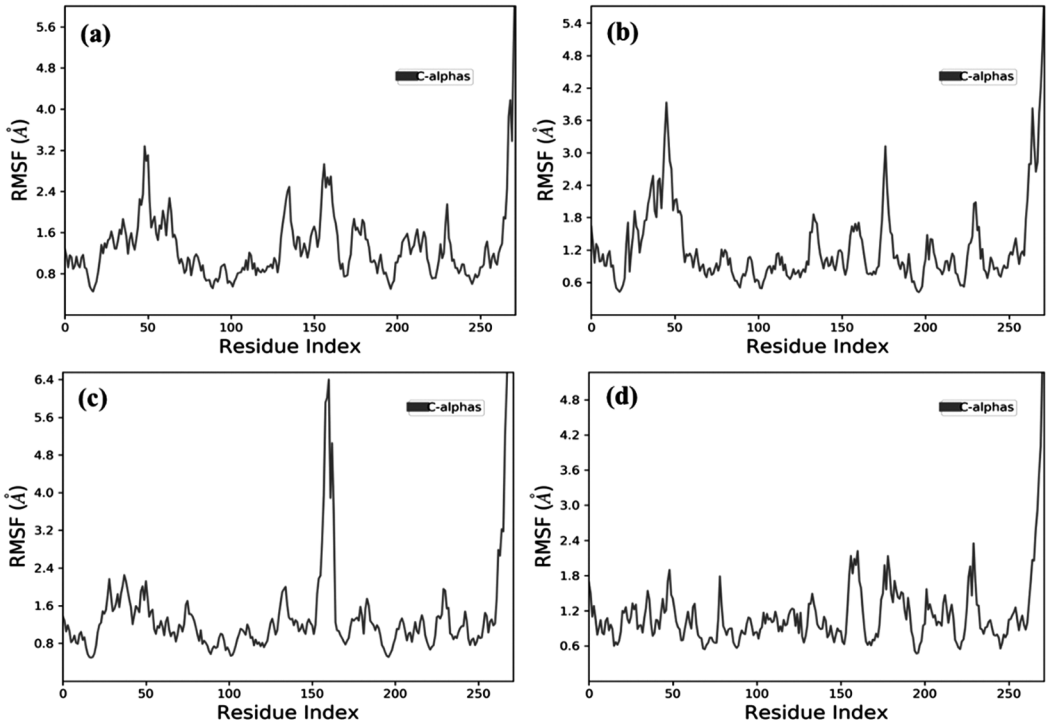

Fig. 5 — RMSF analysis of (a) ZINC000000864920 (b) ZINC000096361333 (c) Folic acid (d) Bicalutamide

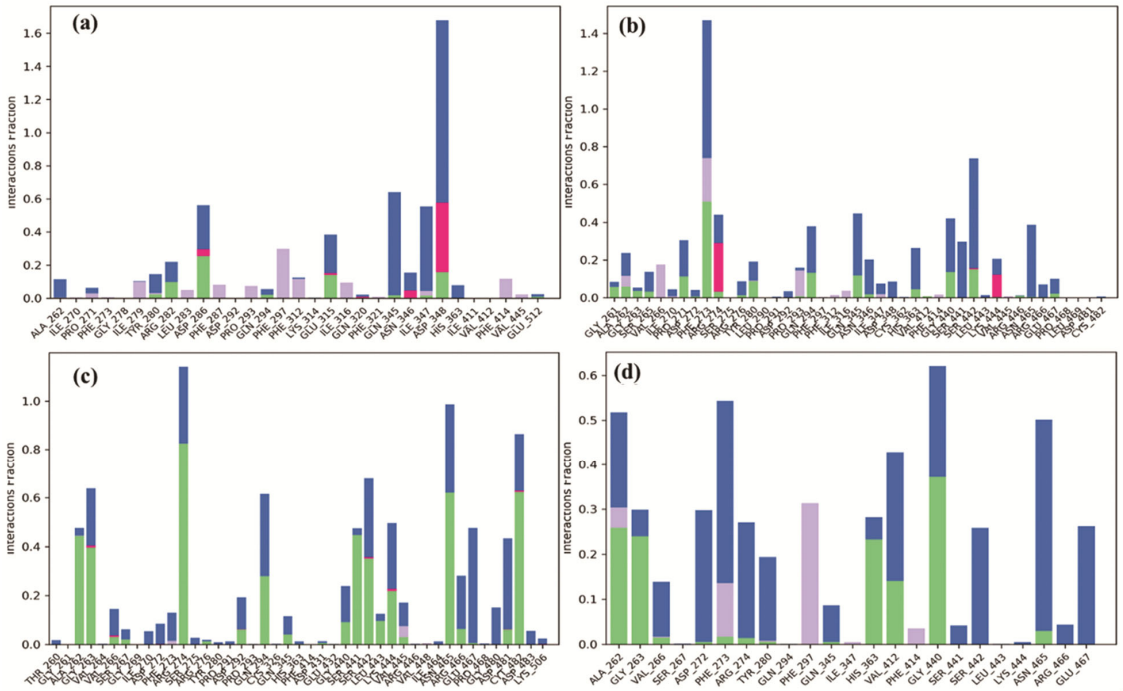

Fig. 6 — Binding interactions of (a) ZINC000000864920 (b) ZINC000096361333 (c) Folic acid (d) Bicalutamide with Sirt1 macromolecule

In the field of drug discovery research, the use of Computer-Aided Drug Design (CADD) techniques has resulted in the establishment of new standards for the identification of promising chemical compounds that target particular receptors. There is no denying the fact that CADD techniques make a major contribution to the improvement of the drug development pipeline. Through molecular docking, MM-GBSA calculations, and MD simulation investigations, it has been shown that the four compounds that have been offered have a promising affinity for Sirt1 [20]. At the same time, to evaluate the potential of these compounds against sirt1, multiple experimental verifications must be carried out. An efficient way to determine whether or not the molecules have a strong affinity for one another is the Surface Plasmon Resonance (SPR) test. A kinetic study is an appropriate method to investigate the processes that are responsible for the binding and unbinding of these molecules. Based on the results of the experiments, more optimization of the molecules may be required to enhance their therapeutic potential and maximize their effectiveness.

Conclusion

This study targeted sirt1, which elevates the metabolism of amyloid-beta (Aβ) peptides, which are central to the pathology of AD. The research screened NCI and plant-based databases using an *in silico* structure-based pharmacophore model. LOR5, Weber's filter, and fit value enhanced the screening procedure, giving 24 (ZINC database) and 24 (FDA-approved database) lead compounds with better binding affinity than the co-crystalized modulator. A further refinement utilizing Prime/MM-GBSA simulations led to the discovery of seven molecules that had binding energies that were higher than those of the reference ligand. The sirt1 modulator potential and stability of the lead compounds were validated by the use of MD simulations, which demonstrated that the lead compounds showed stable binding interactions with the sirt1protein. There was a significant sirt1 protein affinity shown by four different compounds: ZINC000000864920, ZINC000096361333, Folic acid and Bicalutamide.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

References

1 Spinelli M, Fusco S & Grassi C, *Front Neurosci*, 10 (2019) 469184.

2 Jain S, Chauhan N, Sharma S, Reddy K.R, Sadhu V & Kulkarni R. V, *Nanomat Diag Tools Devices*, (2020) 331. (https://doi.org/10.1016/b978-0-12-817923-9.00012-2).

3 Jain S, Bisht A, Verma K, Negi S, Paliwal S & Sharma S, *Cell Biochem Fun*, 40 (2022) 106.
4 Cortés N, Andrade V, Guzmán-Martínez L, Estrella M & Maccioni R. B, *Int J Mol Sci*, 19 (2018) 956.
5 Jain S, Singh R, Paliwal S & Sharma S, *Mini-Rev Med Chem*, 23 (2023) 2097.
6 Lefranc C, Friederich-Persson M, Braud L, Palacios-Ramirez R, Karlsson S, Boujardine N, Motterlini R, Jaisser F & Cat A N D, *Hypertension*, 73 (2019) 458.
7 Ibi D, Kondo S, Ohmi A, Kojima Y, Nakasai G, Takaba R & Hiramatsu M, *Neurochem Res*, 47 (2022) 2333.
8 Lei Y, Wang J, Wang D, Li C, Liu B, Fang X, You J, Guo M & Lu X.Y, *Mol Psychiatry*, 25 (2019) 1094.
9 Zhang M & Tang Z, *Biomed Pharm*, 161 (2023) 114474.
10 Roda A, Serra-Mir G, Montoliu-Gaya L, Tiessler L & Villegas S, *Neural Regen Res*, 17 (2022) 1666.
11 Khatib T, Chisholm D R, Whiting A, Platt B & McCaffery P, *J Alzheimer's Dis*, 73 (2020) 935.
12 Mortier J, Dhakal P & Volkamer A, 23 (2018) 1959.
13 Pulla V.K, Alvala M, Sriram D S, Viswanadha S, Sriram D & Yogeeswari P, *J Mol Graph Model*, 52 (2014) 46.
14 Jain S, Bhole D R & Labhade D S D, *Indian J Chem*, 63 (2024) 473.
15 Moussa N, Hassan A & Gharaghani S, *Heliyon*, 7 (2021) e06605.
16 Gentile D, Floresta G, Patamia V, Chiaramonte R, Mauro G L, Rescifina A & Vecchio M, *Int J Mol Sci*, 21 (2020) 1.
17 Patel S, Gururani R, Jain S, Paliwal V, Paliwal S, Paliwal S, Dwivedi J, Sharma A, Lee H & Sharma S, *J Bio Reg Hom Age*, 38 (2024) 5343.
18 Jain S, Sharma S, Paliwal A, Dwivedi J, Paliwal S, Paliwal V, Paliwal S & Sharma J, *Med Chem Res*, 33 (2024) 136.
19 Azminah A, Erlina L, Radji M, Mun'im A, Syahdi R R & Yanuar A, *Comp Bio Chem*, 83 (2019) 107096.
20 Alrouji M, Alhumaydhi F A, Alsayari A, Sharaf S E, Shafi S, Anwar S, Shahwan M, Atiya A & Shamsi A, *PLoS One*, 18 (2023) e0293185.
21 Liu F, Pang N, Xu R-M & Yang N, *Protein Cell*, 14 (2023) 387.
22 Karaman B, Alhalabi Z, Swyter S R, Mihigo S O, Andrae-Marobela K, Jung M, Sippl W & Ntie-Kang F, *Molecules*, 23 (2018) 416.
23 Abbotto E, Scarano N, Piacente F, Millo E, Cichero E & Bruzzone S, *Molecules*,. 27 (2022) 5641.