Turkish Computational and Theoretical Chemistry

Turkish Comp Theo Chem (TC&TC)

Volume(Issue): 8(2) – Year: 2024 – Pages: 1-11

e-ISSN: 2602-3237

https://doi.org/10.33435/tcandtc.1224592

Received: 28.12.2022 ***Accepted:*** 28.04.2023 *Research Article*

Identification of Selisistat Derivatives as SIRT1-3 Inhibitors by in Silico Virtual Screening.

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Abstract: Sirtuins family are a Nicotinamide Adenine Dinucleotide (NAD+) dependent histone deacetylase enzyme. Sirtuins have been implicated in the pathogenesis of various diseases including cancer, neurological disorders and metabolic syndromes, hence sirtuins appointed as a promising therapeutic target for diseases, by regulating of its activity by small molecules modulators. The indole containing selisistat (EX-527) and its derivatives set as the most potent and selective SIRT1 inhibitors. Selisistat showed an effective sirtuin inhibition on various cancer cell line, and has reached the clinical trials for endometriosis and Huntington's disease. In this study a set of selisistat derivatives were designed and virtually studied by means of molecular docking, ADMET, and molecular dynamics (MD) simulations. Two molecules were showed promising virtual binding affinity on the SIRT1-3 proteins. Compound 1 exhibits stronger in silico SIRT1 and SIRT2 affinities than EX-527, whereas compound 8 prefers SIRT3 binding. The ADMET analysis of the virtually active molecules demonstrated an acceptable drug-like profile and desirable pharmacokinetics properties. The MD simulation analysis revealed that compound 1 had significantly better alignment with SIRT1 and SIRT2 proteins than EX-527 according to Root Mean Square Deviation (RMSD) and Root Mean Square Fluctuation (RMSF) data, while compound 8 had a perfect alignment and fitting with SIRT3 protein than EX-527.

Keywords: Sirtuins, Selisistat, Molecular dynamic, RMSD, RMSF, Compound 1, 8.

1. Introduction

The seven members of the sirtuin family (SIRTs) are belong to class III of histone deacetylases (HDACs) which involving NAD+ as a cofactor. Sirtuins function as either mono-ADP-ribosyltransferase or deacylase activity which act as regulators of transcriptional progression [1,2]. Sirtuins share homology to protein of yeast silent information regulator 2 (SIR2) [3]. SIRT1 is the first enzyme discovered and most studied one. It is mainly localized in the nucleus but occasionally translocate to the cytoplasm[4,5]. SIRT2 generally exist in the cytoplasm and associated with microtubules and deacetylation of □-tubulin. SIRT3-5 are mitochondrial, while SIRT6-7 are nuclear enzymes [6]. As sirtuins are involving in the pathogenesis of diseases, therefore the developing of a potent and selective SIRT inhibitors molecule is the field of interest [7]. Selisistat is a potent and selective inhibitor for SIRT1 compared to SIRT2-3 while it exhibits no inhibition against SIRT4-7. Selisistat is an indole-based inhibitor were discovered by high-throughput screening (HTS) [8]. The (S) isomer of selisistat is more active than (R) isomer. A clinical trial of selisistat for the treatment of Huntington's disease is underway, while a clinical trial of using selisistat for the treatment of endometriosis is caried[9,10]. The crystal structure revealed that selisistat is complexed to different sirtuins through the occupation of nicotinamide binding site. A kinetic study showing that selisistat is uncompetitive inhibitor with the NAD or the substrate [11]. The SAR studies for selisistat revealed the necessity of carboxamide moiety and its position for the inhibitory activity, since changing the carboxamide from 1-position to 2-position led to a 350-fold loss in potency[11].A potent analogue compound 35 for

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selisistat was obtained by expansion of the carbon 6-membered ring to a 7-membered ring which retained the selectivity to SIRT1 (Fig. 1) [12]. AC-93253 is a molecule with modified indole ring favored SIRT2 inhibition. Inauhzin is another molecule with indole ring discovered via virtual screening for compounds has cytotoxic effect on H460 and HCT116 cancer cells derived from xenograft tumors [13].

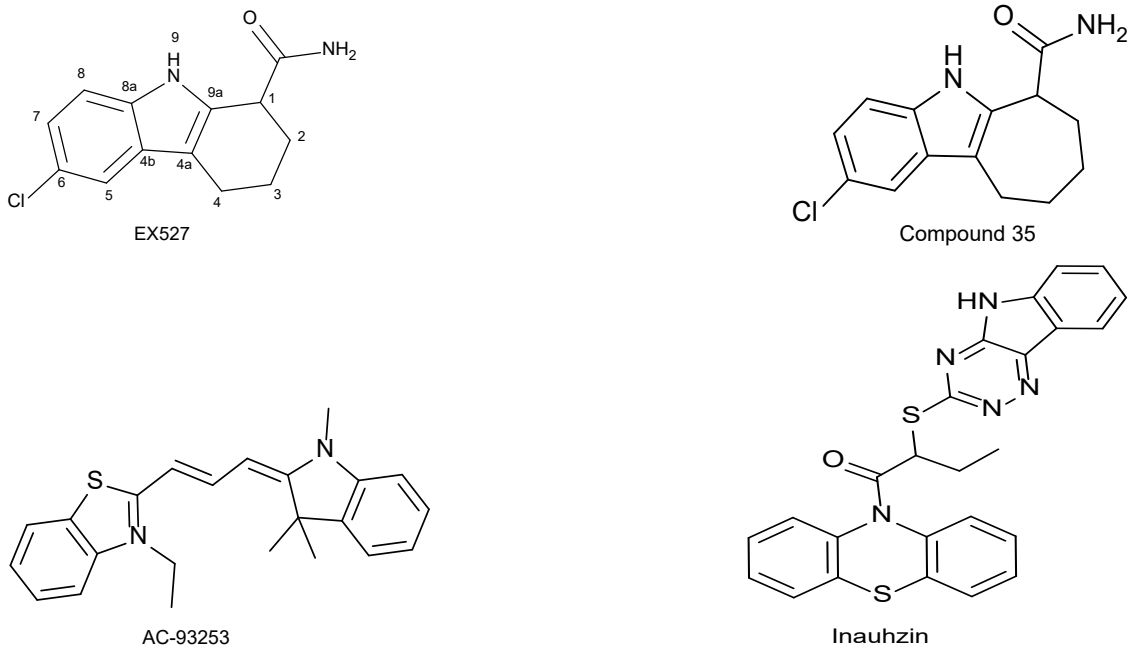


Figure 1. chemical structure of selisistat, compound 35, AC-93253, and inuahzin.

Developing new EX-527 analogues with superior pharmacokinetic and pharmacodynamic properties, increased activity, and selectivity for SIRT1, may lead to results that are even more promising biologically active molecule[13,14] Therefore, in this study we design a modified molecules that showed a higher binding affinity and more accepted kinetic stability than EX-527.

2. Computational Method

2.1 Protein Preparation and Grid Generation

Crystal structure of Homosapien SIRT1-3 proteins was downloaded from protein data bank (PDB) [12,15,16]. Proteins processed using protein preparation wizard in Schrodinger, New York, NY, 2021 to remove water molecules and non-essential atoms, then the missed atoms in protein residue was added and finally hydrogen was added and the hydrogen bonds were optimized by OLPS 2005 [16,17]. All the proteins conserve NAD in the core as co factor and co-crystalized with a ligand. The receptor grid prepared using the co crystalized ligand as center for the boundary box when the prepared ligands docked in binding site of protein. The dimension of boundary box used was 12 A^0.

2.2 Ligand Preparation

All ligands were sketched in chemdraw version 18.0.0.231 (4029) and entered as input files into the prepare ligand module. The structures were optimized for the lowest energy after the force fields applied to the ligands using LigPrep [17,18].

2.3 Molecular Docking

Docking performed using Grid-based Ligand Docking with Energetics (Glide) for receptor-ligand interaction and ligand ranked according to glide scoring function (G score). The ligands were also evaluated based on potential energy predictions and ligand binding geometries with SIRT proteins [19,20]. All compounds docking poses were sorted according to their dock score function and visualized using the Maestro v 13.0.135 interface (Schrodinger, New York, NY, 2021). The extra precision (XP) docking investigation was used to determine the compounds binding poses and binding energies[17].

2.4 ADMET Study

The top-ranked compounds were subjected to drug-like property prediction using Lipinski's rule of five and the ADME Descriptors calculation using Qikprobe software in Schrodinger maestro. Different molecular properties, such as the number of hydrogen bond acceptors and donors, are considered in Lipinski's rule of five [21]. The aim of study to get knowledge of the main pharmacokinetic properties of compounds, such as aqueous solubility, intestinal absorption, systemic distribution, metabolism, excretion, and hepatotoxicity, among many other descriptors for ADMET.

2.5 Molecular Dynamics Simulation

We choose and exposed three optimal complexes for MD simulation using the Desmond module version 2.0 (academic version) according to docking study [22,23].The system was designed by inserting a SPC water model in an orthorhombic periodic box of dimension 10 A^0 with OPLS_2005 force field, then neutralize it with counter ions (Na^+ and Cl) at neutral pH. In various constrained steps, the built protein-ligand complex with the solvent system was maintained for energy minimization and pre-equilibration. MD simulations were inspected for 20 ns at a constant temperature of 300 K with a relaxation time of 2 ps in NPT ensemble with Nose-Hoover thermostat. Electrostatic interactions were treated using Particle Mesh Ewald method for long and short range (cut-off distance of 9.0 Å), (with a 10–9 tolerance limit). The RMSF and RMSD from the Molecules were also plotted versus time to examine the dynamic stability of the complexes.

3 Results and discussion

3.1 Molecular Docking Study

In this study, selisistat was selected to serve as a reference structure for the development of a new group of compounds. A ligand library of 100 small molecules was created and subjected to multi-targeted molecular docking against SIRT proteins, including SIRT1 (PDB: 4I5I), SIRT2 (PDB: 5D7P), SIRT3 (PDB: 4JT8). The data obtained from molecular docking revealed the binding energies of ligands binding to receptors, as evidenced by varied G Scores. According to the evidence of substitution on the modified EX-527 structure (**Fig. 2**), no significant effect on the binding affinity and docking score occur by replacing the chloride in R1 with a small group such as methyl, bromine, or with methoxy group. Substitution of R2 with small polar groups like hydroxy or amine exerts a significant increment on the binding affinity and docking score due to the formation of extra hydrogen bonds to the molecule with proteins of the three enzymes. The inclusion of a five-member ring in R2 that has the ability to exchange hydrogen bonds such as pyrrole, imidazole can increase the binding affinity for SIRT3 but has no impact on the binding of the other enzymes. The addition of a polar hydrophilic group to R3, such as amine or hydroxyl, has a more favorable effect than R2 in the formation of hydrogen bond. The carboxamide group in the position one in the ring retained in S isomer without any change since, it essential for the activity of molecule [11]. Extending the aliphatic six-member ring to a seven-member ring maximize the binding affinity and docking score of molecules with the enzymes. Finally, the addition of small groups to the R4 position in molecules that act on SIRT1 and SIRT2, such as methyl or methoxy, was increased the virtual affinity and docking score. However, the addition of a larger group, such as a five-or six-member ring, was flipped the molecule in the enzyme active site, which decreased the binding probability. SIRT3 docked molecules exhibit a good binding affinity when a small group, such as hydroxyl, methyl is added to R2 or R3 and larger groups are added to R4, like formamide, acetamide or five-member rings. All of these findings are resulting in increasing of the docking score and binding affinity for molecules as compared to EX-527, as well as the increasing in the e-model energy, which is dependent on columbous, Van der Waals, and hydrogen bond energy. Interestingly, compounds **1** and **8** showed superior docking affinities in comparison to EX-527. The results were demonstrated that compound **1** has greater binding affinity than EX527 in the binding with SIRT1 and SIRT2, while compound **8** showed a high preference for SIRT3 (**Table 1 and Figure 3**).

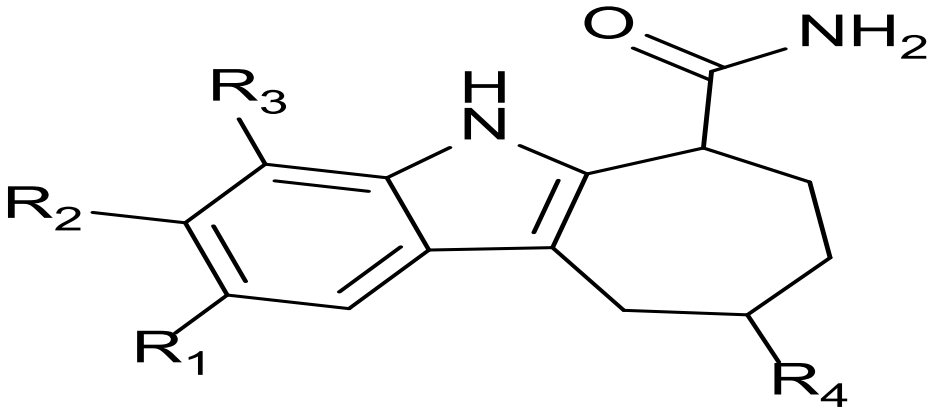


Figure 2. Site of substitution on the modified EX-527 structure.

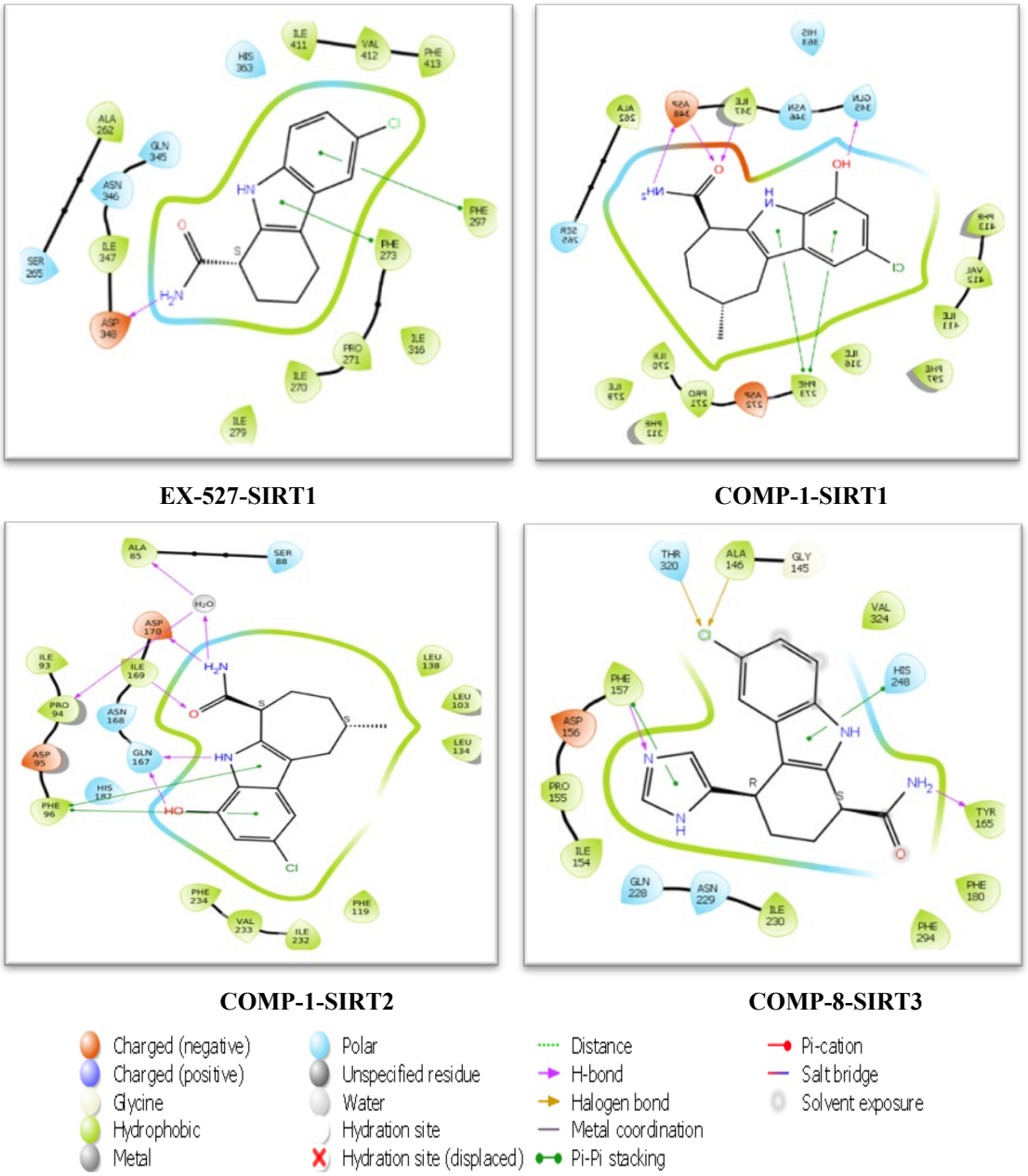


Figure 3. Top docked ligands with SIRT1-3 enzymes.

Table 1 chemical structure of top ranked compounds and their XP docking score with SIRT1-3

Comp ID	R1	R2	R3	R4	XP docking score in (kcal/mol)		
					SIRT1	SIRT2	SIRT3
EX-527					**-8.5**	**-9.7**	**-7**
Compound 1	**Cl**	**H**	**OH**	**S-CH3**	**-11.28**	**-12.12**	**-8.26**
Compound 2	**Cl**	**H**	**OH**	**S-OCH3**	**-11.3**	**-12.15**	**-7.83**
Compound 3	**Br**	**H**	**OH**	**H**	**-9. 26**	**-10.34**	**-7.67**
Compound 4	**Cl**	**H**	**H**	**S-Furan**	**-7.3**	**-11.53**	**-7.68**
Compound 5	**Cl**	**NH2**	**H**	**H**	**-10.1**	**-12.77**	**-7.2**
Compound 6	**Cl**	**H**	**OH**	**S-formamide**	**-8.52**	**-13.2**	**-8.86**
Compound 7	**Cl**	**H**	**NH2**	**S-formamide**	**-8.98**	**-11**	**-7.54**
Compound 8	**Cl**	**H**	**OH**	**R-imidazole**	**-6.6**	**-6.67**	**-8.8**

3.2 Drug-likeness Properties

Lipinski's rule of five and ADMET studies were used to further refine the compounds. We assessed the hit compounds for drug-likeness by assessing their various physicochemical properties, which are required for drug development. Compared to EX-527, all compounds fall within the acceptable range of the Lipinski rule and violate Jorgensen's criterion. Intriguingly, all of the aforementioned compounds exhibited a favorable profile for human oral absorption and good CNS penetration in comparison to EX-527 (Table 2). CNS penetration is crucial because EX-527 is proposed to treat neurological diseases such as Huntington's disease [9].

Table 2. Drug likeness properties of promising compounds

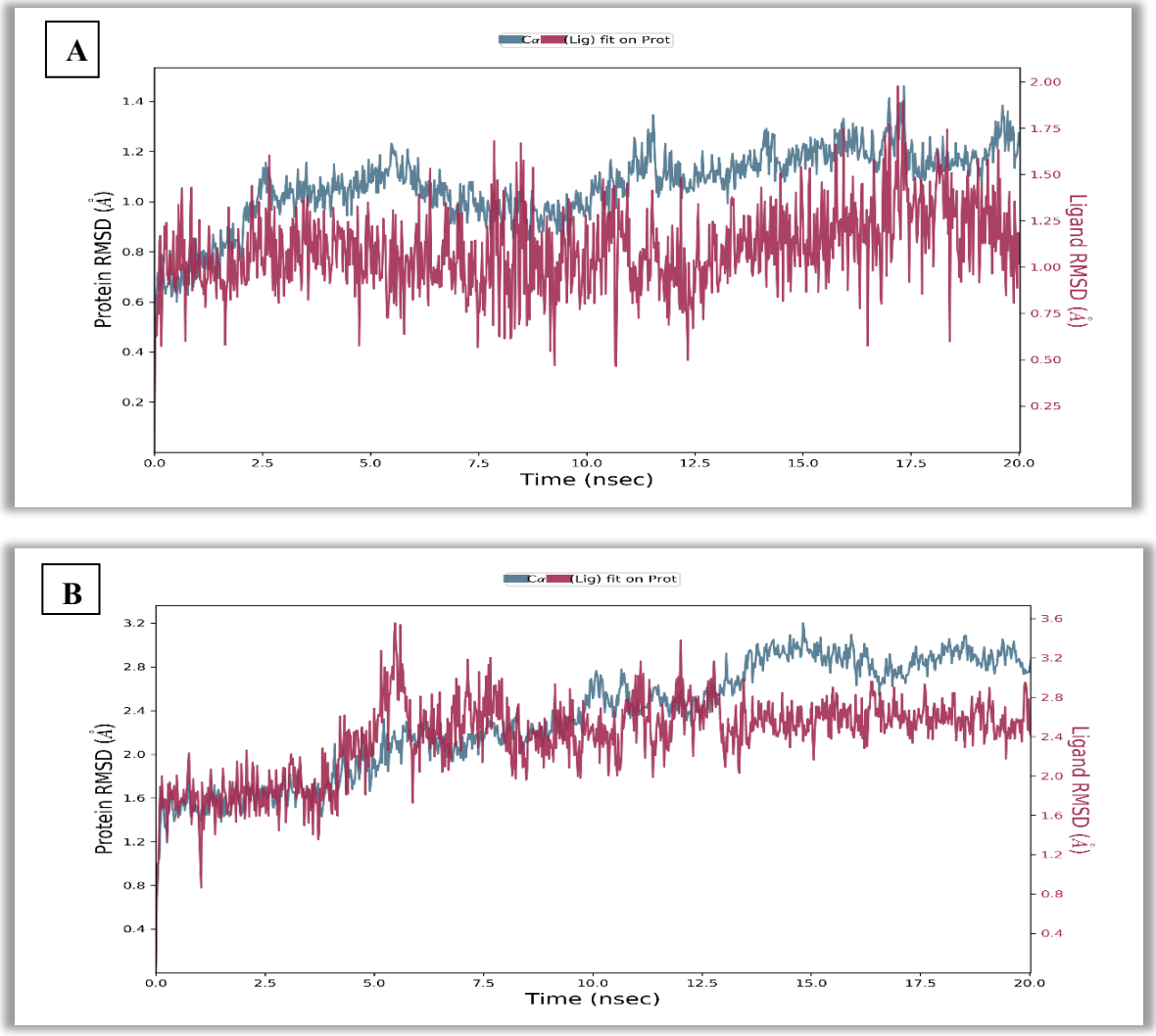
Comp ID	Rule of 5	Rule of 3	Oral absorption	CNS
EX-527	0	0	3	0
Compound 1	0	0	3	0
Compound 2	0	0	3	0
Compound 3	0	0	3	0
Compound 4	0	0	3	-1
Compound 5	0	0	3	0
Compound 6	1	0	2	-1
Compound 7	0	0	3	0
Compound 8	0	0	2	0

Rule Of Five Number of violations of Lipinski's rule of five. The rules are: mol_MW < 500, QPlogPo/w < 5, donorHB ≤ 5, accptHB ≤ 10. Compounds that satisfy these rules are considered drug like. (The "five" refers to the limits, which are multiples of 5.) maximum is 4 **Of Three** Number of violations of Jorgensen's rule of three. The three rules are: QPlogS > -5.7, QP PCaco > 22 nm/s, Primary Metabolites < 7. Compounds with fewer (and preferably no) violations of these rules are more likely to be orally available. maximum is 3 **Human Oral Absorption** Predicted qualitative human oral absorption: 1, 2, or 3 for low, medium, or high, respectively. **CNS** Predicted central nervous system activity on a –2 (inactive) to +2 (active) scale.

3.3 Molecular Dynamics Investigation

Simulations of molecular dynamics (MD) are now an established technique that can be applied effectively to comprehend macromolecular ligand-receptor bindings. Simulation results are comparable to biologically relevant ones. Also, unlike the more static molecular docking method, MD modelling does not ignore the fact that proteins change over time [24]. Therefore, the highest-scoring ligands with the most significant drug-like properties were subjected to MD simulations to understand the evolution of receptor binding ability over time and to compare it with MD result of EX-527. Specifically, we looked at the ligand's dynamic interaction profile with key residues that can influence their activity and occupancy in the binding pocket of the protein. The

dynamic behavior of EX-527-SIRT1 and Comp 1-SIRT1 was studied and recorded for 20 ns. The stability of the protein-ligand complex was assessed by comparing RMSD and RMSF values to the unbound protein structure. Comparing the Comp 1-SIRT1 complex to the EX-527-SIRT1 complex, we found that Comp 1-SIRT1 complex is much more stable with only minimal fluctuations as the simulation runs with RMSD value (2.4-2.8 A^0) (**Fig. 4B**), which indicate that the ligand aligned with protein and undergo similar conformation variation along the simulation time. The MD result also showed the stability of interactions Comp 1-SIRT1 complex. The main amino acids make the hydrophobic interactions are PHE-273, PHE-297, ILE-347 and HIS-363 the same with both compounds. The hydrogen bond forming amino acids with EX-527 are GLN-345 and ASP-348, While GLN-345 binds with compound 1 with 17% with the amine group at position 9, ASP-348 forms two hydrogen bonds with 72% and 32% with amine of carboxamide group and C8 hydroxyl group, respectively, and GLU-315 with 36% with amine of carboxamide group (**Fig. 4C**). It is possible to describe variations in the locations of the ligand atoms using the Ligand Root Mean Square Fluctuation (L-RMSF). Compound 1's RMSF value demonstrates how well it fits with the protein (**Fig. 4D**).



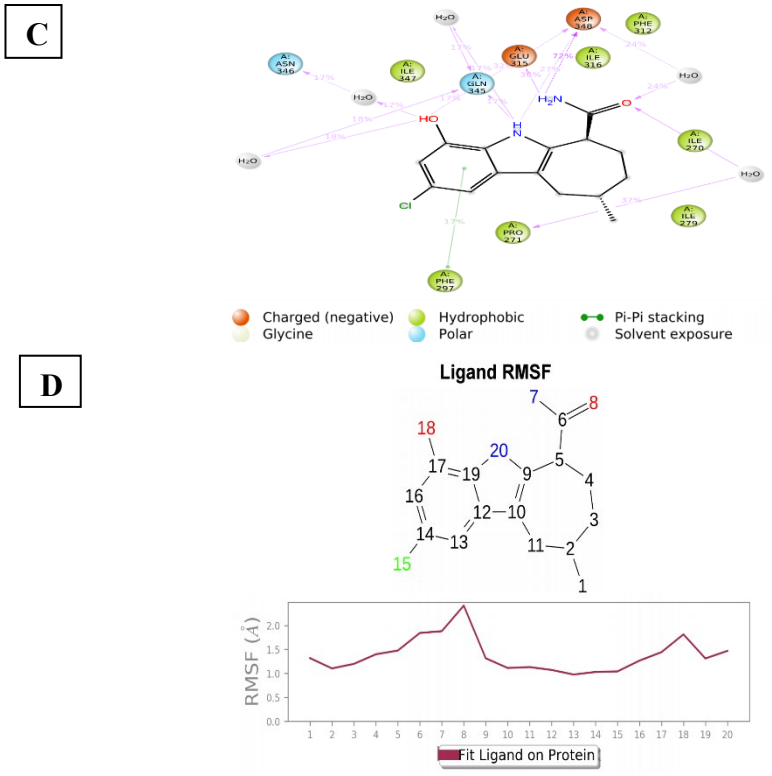
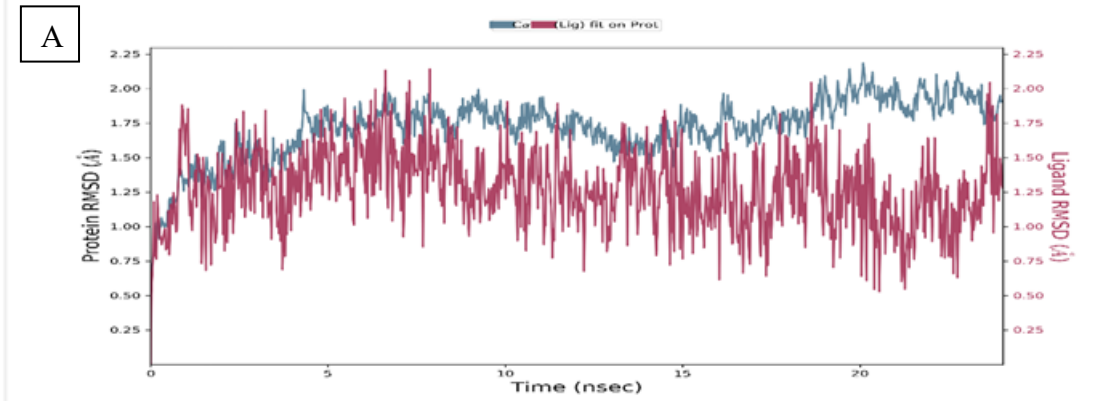


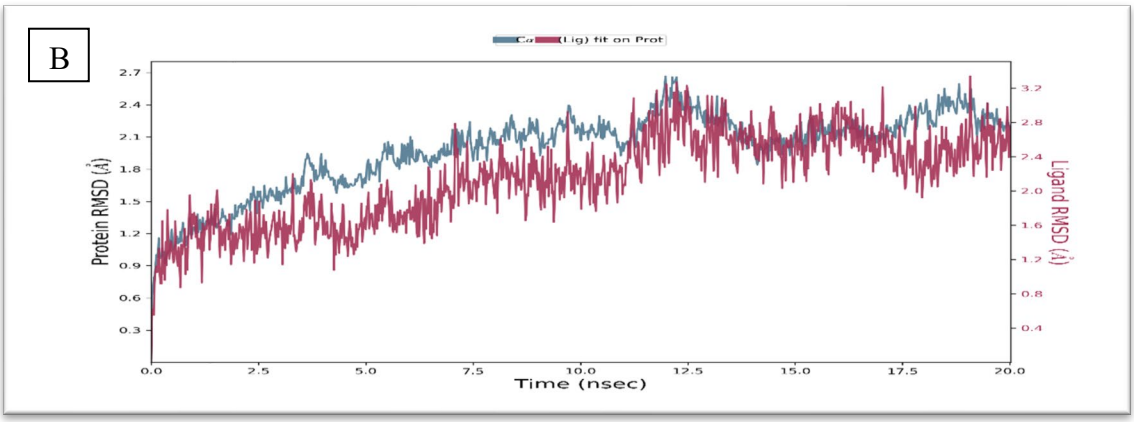
Figure 4. The molecular dynamic simulation results (A) RMSD plots of the receptor-ligand complex in MD simulation study EX-527-SIRT1. (B) RMSD of Comp **1**-SIRT1 complex, (C) Compound **1** contact with SIRT1 protein, (D) Compound **1** RMSF with SIRT1 protein

The dynamic study of EX-527-SIRT2 complex and Comp **1**-SIRT2 complex were showed that Comp **1** has more sharp fluctuation as the simulation run with SIRT2 than EX-527 with RMSD value (2.0 -2.8 A^0) (**Fig. 5B**). The major amino acids of SIRT2 makes the hydrophobic interactions are PHE-96, PHE-119 and ILE169 with EX-527, while ALA85, PHE-96 and PHE-119 for Comp **1**. The hydrogen bond forming amino acids GLN-167, ASN-168 and ASP-170 with EX-525, while GLN-167 forming two hydrogen bonds with C8 hydroxyl group 96% and with amine group at position 9 99% respectively, ILE-169 with 96% with oxygen of carbonyl group, ASP-168 with 42% with amine of carboxamide group and HIS-187 with 99% with C8 hydroxyl group for Comp **1**(**Fig. 5C**). The RMSF value demonstrates how well Comp **1** fits with the protein (**Fig. 5D**).Finally, the molecular dynamic study of the EX-527-SIRT3 complex and the Comp **8**-SIRT3 complex revealed that the binding of the EX-527-SIRT3 complex is unstable due to a high RMSD value above the acceptable range for a ligand therefore, when the value observed of a ligand is significantly larger than the RMSD of the protein, the ligand has most likely diffused away from its initial binding site. In the other side the MD study of Comp **8**-SIRT3 complex observe the stability of binding in the acceptable range of RMSD value (1.2-2.0 A^0) and the ligand aligned with protein and undergo similar conformation variation along the simulation time (**Fig. 6B**). The major amino acids involve in the hydrogen bonds formation are VAL-292 forming two hydrogen bonds with C8 hydroxyl group 98% and with amine group at position 9 99% respectively, GLY-295 with the oxygen of carbonyl group 95%, GLU-296 with amine of carboxamide group 86%, and ARG 158 with the nitrogen of the imidazole ring 24%, while those involve in hydrophobic interactions are PHE-180 HIS-248 and PHE-294 (**Fig. 6C**). The RMSF value provides an indication of how tightly the Comp 8 aligns on the SIRT3 protein (**Fig. 6D**).

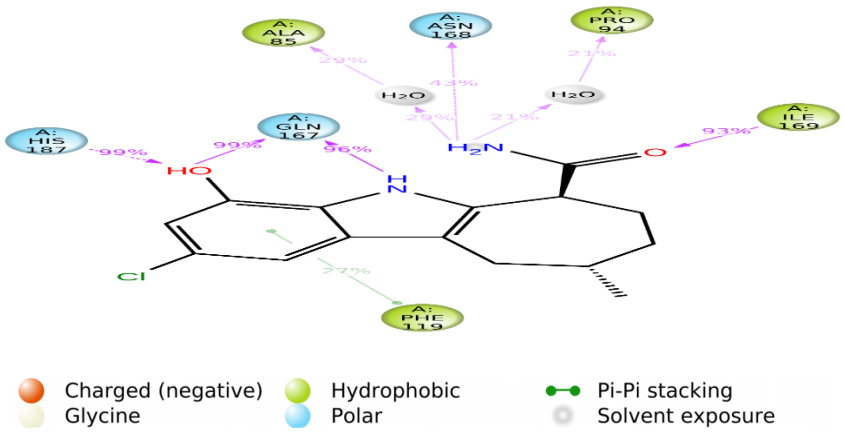
A


Cα (Lig) fit on Prot
Protein RMSD (Å)
Ligand RMSD (Å)
Time (nsec)

B


Cα (Lig) fit on Prot
Protein RMSD (Å)
Ligand RMSD (Å)
Time (nsec)

C


A: ALA 85
A: ASN 168
A: PRO 94
H2O
H2O
A: HIS 187
A: GLN 167
A: ILE 169
H2N
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A: PHE 119
Charged (negative)
Glycine
Hydrophobic
Polar
Pi-Pi stacking
Solvent exposure

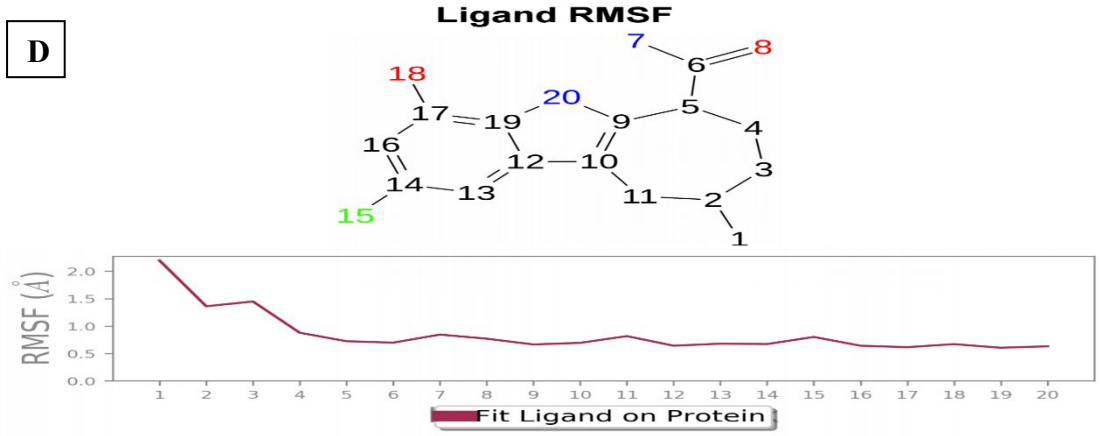
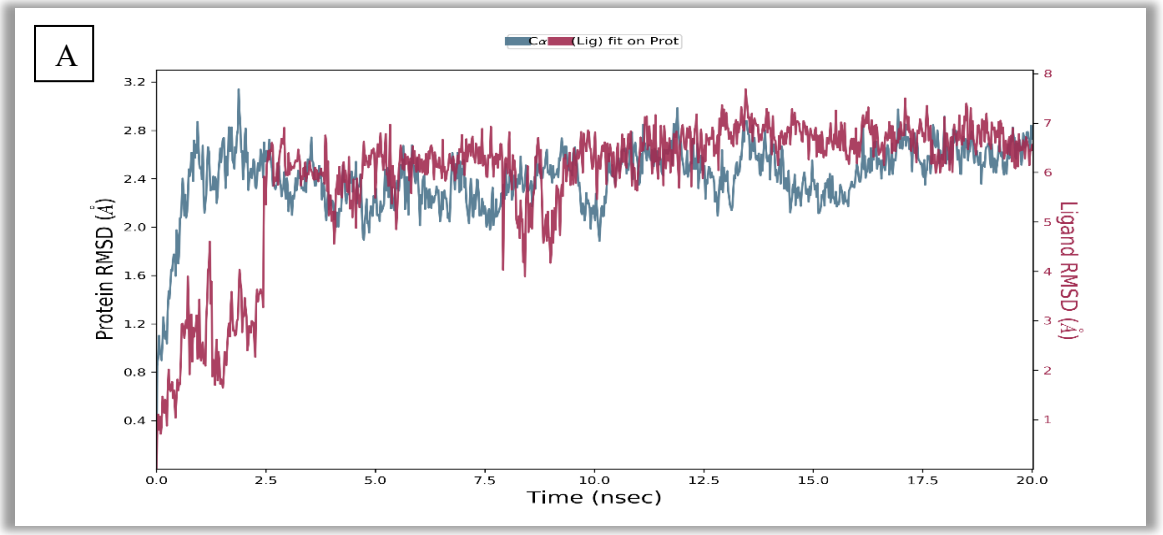


Fig. 5 The molecular dynamic simulation results (A) RMSD plots of the receptor-ligand complex in MD simulation study EX-527-SIRT2, (B) RMSD of Comp **1**-SIRT2 complex, (C) Compound **1** contact with SIRT2 protein, (D) Compound **1** RMSF with SIRT2 protein.



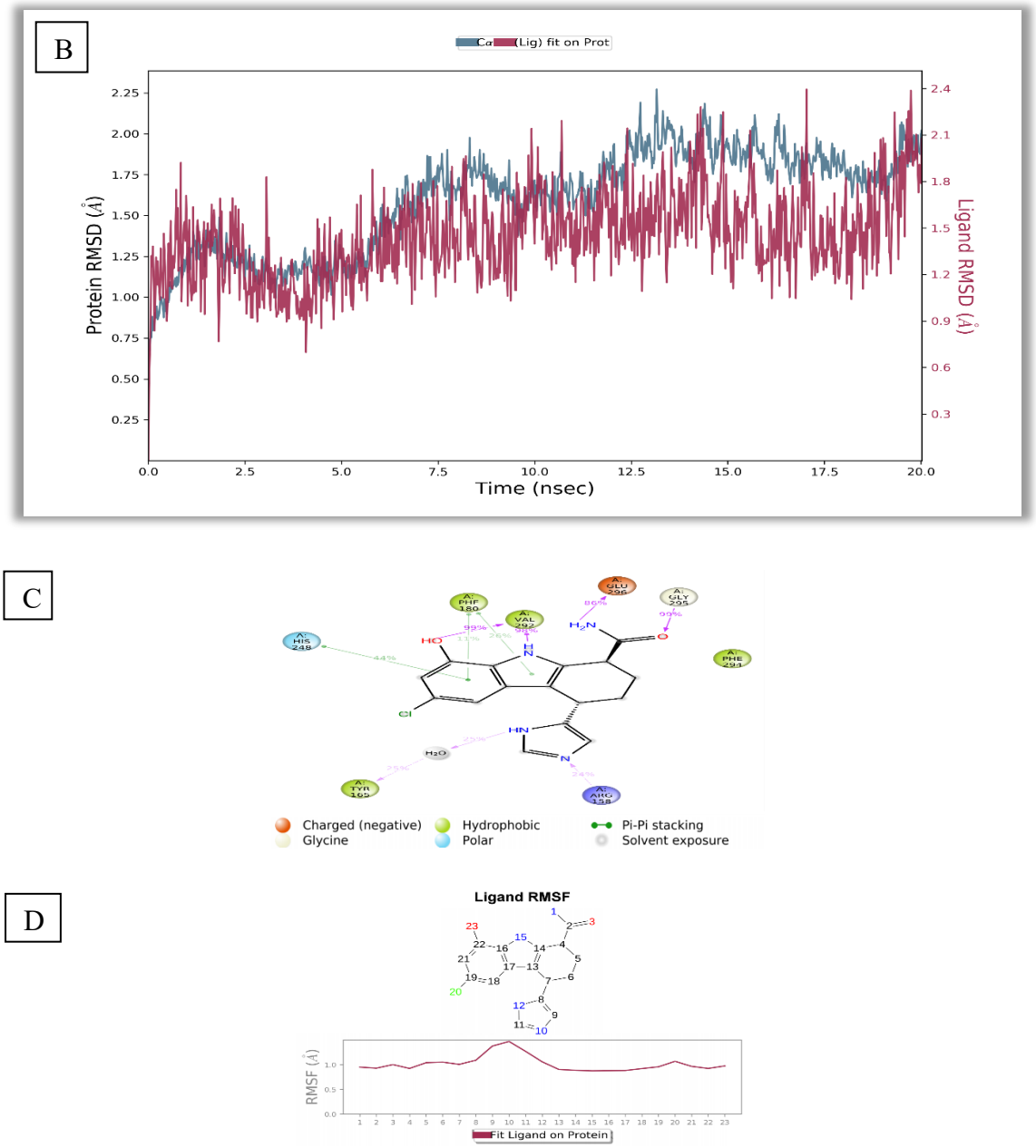


Figure 6. The molecular dynamic simulation results (A) RMSD plots of the receptor-ligand complex in MD simulation study EX-527-SIRT3, (B) RMSD of Comp **8**-SIRT3 complex, (C) Compound **8** contact with SIRT3 protein, (D) Compound **8** RMSF with SIRT3 protein.

4 Conclusions

Selisistat is a prospective therapeutic target for endometriosis and Huntington's disease. Developing novel derivatives is critical for treating both conditions. Our docking analysis results from a library of one hundred compounds show that Comp 1 and 8 have the highest binding affinity docking score among the others. The ADMET analysis demonstrates that these compounds are drug-like molecules and have a decent pharmacokinetic profile. The MD data revealed that the Comp 1-SIRT1, Comp 2-SIRT2, and Comp 8-SIRT3 complexes were stable and that the critical protein-ligand interactions were preserved throughout the simulation time. These results demonstrated that these compounds had lower RMSD and RMSF values than EX-527, as well as good ligand interaction with SIRT enzymes. The next step is to synthesize these compounds chemically and test how they work on the target tissue in vitro.

Declaration of Competing Interest

There are no conflicts to declare

Acknowledgement

The authors would like to express their gratitude to Baghdad College of Pharmacy for providing us with a purchased Schrodinger license in order to perform this in silico investigation.

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