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In-silico screening, molecular docking, pharmacokinetics studies and design of histone deacetylase inhibitors as anti-Alzheimer agents

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ABSTRACT

Alzheimer's Disease (AD) is a complex illness mechanism and an untreatable ailment that presently brings huge sorrow to patients and their relatives. Presently, the cure for this disease is zero. The existing drugs have several side effects. Therapeutic Chemistry, a vital field of research, has been working tirelessly to develop new treatments that can be effective in curing this disease. Design, molecular docking, and pharmacokinetic assessment (ADMET) methods are used to determine and confirm the sturdy configuration of the receptor pocket. 16 Histone Deacetylase inhibitors have been docked with the acetylcholinesterase target for protein-ligand interaction. Compound 2 was found to possess the highest binding scores of 19.758 kcal/mol. This was used as a template to design several HDAC derivatives, but seven of the designed compounds had higher binding scores and better interaction than the template; 1: -20.031 kcal/mol, 2:-20.583 kcal/mol, 3:-19.925 kcal/mol, 4:-21.639 kcal/mol, **5**:-21.950 kcal/mol, 6:-19.917 kcal/mol, and **7**:-23.289 kcal/mol. The pharmacokinetics evaluation of these designed compounds (ADMET) results showed good drug-likeness and oral bioavailability scores. Based on the binding affinity scores of the designed compounds against AD, the designed compounds have superior pharmacological characteristics and can be used as neuro-therapeutic candidates after rigorous in-silico investigation.

1. Introduction

Alzheimer's disease (AD) is a central nervous system problem involving environmental and genetic factors and is characterized by anomalous actions, a reduction in thinking ability, neuronal loss, confusion, difficulty in communicating, and an inability to reason well. It is one of the key public health challenges that is most problematic to treat, mostly due to the increasing elderly population in the universe today [1-2]. In the onset and progression of AD, some features have been implicated, like membrane structure and lipid production disruption, metal ion dyshomeostasis [3]. Recent research has proposed that some of these characteristics could be twined together with other facets (i.e., protein aggregation) of the illness [4]. As such, quick and immediate medicinal approaches need to be developed for the cure of this disease.Histone deacetylases (HDACs) are residues in histone and non-histone substrates with epigenetic receptor modulators that diacetylated lysine. They can be divided into four classes (class I, class IIa, class IIb, and class IV) [5-6]. An equilibrium between histone-acetylation and deacetylation in normal cells is achieved by the activities of HDACs and HATs, respectively [7]. Some diseases can emerge as a result of an imbalance in the activities of HDACs and HATs in normal cells [8]. For instance, a serious part in oncogenesis via the development of complexes with other proteins is being played by class 1 HDSCs. Also, in AD memory-related dysfunction, class 1 HDACs and HDAC6 are implicated [9-10]. Therefore, treatment of neurodegenerative disorders has been given attention because of the usage of HDACs as inhibitors [11]. In the cortex and hippocampus of AD patients, HDAC2 and HDAC6 are over-expressed. This was shown by research [12–13]. An indication of neurodegenerative diseases, including AD, is an accumulation deviation of insoluble hyperphosphorylated tau (ptau) [14]. Ptau aggregation can be promoted and prevented from being degraded by acetylation of tau at Lys280, leading to reduced cognitive ability [15]. Tau is caused by neurological disorders

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caused by tau. Tau levels can be lost by the loss of HDAC6 or inhibition of its activity (HDAC6) [16-17]. Balance in aging and AD models can exert an anti-inflammatory effect and reinstate epigenetics. This can be achieved through a Food and Drug Administration-approved (FDA) HDAC inhibitor, which can improve synaptic roles and flexibility.

Selenium (Se), which is essentially a trace mineral in the human system, decreases with age, and this decrease may play different roles in the progression of Alzheimer's disease [18,19]. In former research reported by some researchers, multi target-directed ligands (MTDLs) were synthesized from selenium-containing compounds via design strategy [20–22], including "selenpezil" compounds [23], clioquinol–ebselen hybrids [24,25]. The enzymatic properties of glutathione peroxidase-like (GPx) were mimicked using a remarkable skill, as evidenced by those molecules scavenging hydrogen peroxide. Damaged cells from free radicals, which is a protection offered by selenium, and the treatment of AD make advancements in the use of HDAC6 inhibitors.

Computer-based techniques, including protein-ligand interaction, ADMET, and drug likeness studies, are relevant steps applied in drug development and discovery operations. The interactions between the binding molecules are a field of study called molecular docking. ADMET evaluation provides suitable information on properties that influence its characteristics. The characteristic of chemicals known in a substance or material is the sum of the physicochemical molecular properties identified, and this is termed drugs [26-27]. Some past research by researchers included the catalytic activity of the histone deacetylase (HDAC) enzymes, which is directly relevant to the pathogenesis of Alzheimer's Disease as well as several other diseases, and the important role of molecular modeling in the development of HDAC inhibitors with improved efficacy and selectivity [28]. Also, HDAC inhibitors and activators have been explored and identified as therapeutic agents for many diseases, such as neurogenerative disorders, osteodystrophy, cardiomyopathy, cancer, and diabetes [29].

The present study is aimed at identifying possible ligands that are derivatives of HDACs that can act as suitable drug candidates, using structure-based screening, design, drug properties, molecular docking, and pharmacokinetics evaluation to finalize suitable ligands for the treatment of Alzheimer's disease.

2. Materials and methods

2.1.Data Collection

2.1.1.Ligands

Sixteen carefully chosen HDAC inhibitors were used in this research, as indicated in supplementary file (Table 1), and structures were drawn with the aid of Chemdraw V 16.0, obtained from the literature [29]. The molecules were evaluated for their effects on human protein targets. These molecules were docked into the binding pose of a human receptor with ID 4EY7. Spartan'14 software was used for DFT calculation at the B3LYP theory level [30, 31] and a basis set of 6-311G* for optimization of drawn structures [32, 33]

2.1.2.Receptor and the Treatment

The target with an x-ray crystal structure and ID 4EY7 as shown in Figure 2, retrieved from the site www.rcsb.org. Its properties are displayed in table 2. Discovery Studio was used to treat the enzyme by removing water molecules and cofactors and saving the treated enzyme in a PDB.

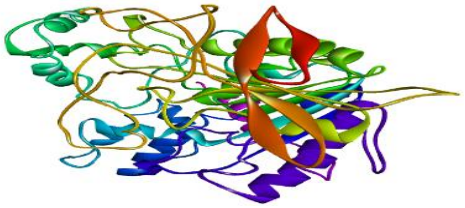


Figure 1: Prepared Protein target

2.2.Molecular Docking

The Human Acetylcholinesterase was docked with the ligands after pretreatment. The receptor pocket has five (5) interaction abilities. The solvation free energy and entropic contribution are an atom's vacuum-based energy in a force field ECEPP/3. The Monte Carlo (BPMC) procedure was used in the ICM space.

General procedures for molecular docking are shown in Figure 2. Molecular docking is frequently used to identify the type of interaction between the ligand and the receptor

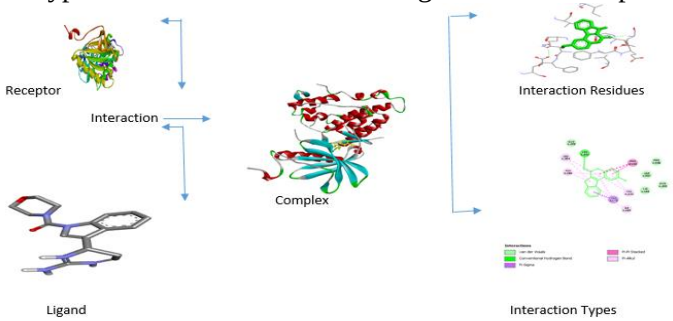


Figure 2. Molecular Docking Procedures

2.3. Druggability Studies and Pharmacokinetic Evaluation

Molecular properties and drug-likeness parameters have been calculated theoretically for all the designed molecules (1 to 7) using the swissadmet web server and www.molinspiration.com/cgi-bin/properties with the goal of identifying the ligands that satisfy the best requirements to display as drug-like ligands, based on the Lipinski's Ro5 [34], the Ghose rule [35], the Veber rule

[36], the Egan rule [37], the Muegge rule [38] and the bioavailability score [39]. ADMET has been calculated using biosig.unimelb.edu.au/pkcsm/ [40]. Some steps are taken in drug evaluation to advance the value of drug control; absorption of the molecule, distribution in the body, metabolism, excretion, and toxicity have been used to predict pharmacokinetic properties [41]. The ultimate function of ADMET is to control pharmacokinetic characteristics.

Table 2. Crystallographic properties of protein used in our study

a	b	c	d	e	f	g
4EY7	Hydrolase	2.35 Å	0.211	X-ray diffraction	A	No

[a]Protein,[b]Classification,[c]Resolution,[d]R-valuefree,[e]Method, [f]Chain,[g]Mutation

3. **Results and discussion**

3.1 Molecular Docking

This is carried out to find the most favorable pocket of interaction for a compound within a protein therapeutic target, which aids in the prediction of molecules in a short time. Sixteen HDAC derivatives from the literature were docked, as shown in Supplementary file (Table 3), with human acetylcholinesterase. Ligand two (2) had the best binding scores, and it was used as a template to design seven HDAC derivatives, as shown in Supplementary file (Table 4). The most potent inhibitors against this enzyme were obvious after the molecular docking of these structures to the HDAC energetic site

Based on the outcome obtained from the docking molecular, the compounds 1, 2, 3, 4, 5, 6, and 7 have lower energies of interaction with the human Acetylcholinesterase receptor than the reference inhibitor. Therefore, these molecules could be potential inhibitors of the studied receptor. The nature of interactions observed in newly liganded molecules is discussed below.

The interaction results between Ligand 1B and the receptor in Figure 3 show conventional hydrogen bond interactions with HIE212, SER218 and LEU308 residues, two carbon hydrogen bond interactions with ASP310 and ARG177 residues, one Amide-π stacked LEU214, and

one π-Alkyl interaction with PRO 216.

Figure 3 shows conventional hydrogen bond interactions with LEU308, HIE212, and SER 218 residues, two carbon hydrogen bond interactions with MET211 and SER215 residues, one amide-π stacked with interaction LEU214, and two π-Alkyl interactions with ALA318 and PRO216.

The interaction results between Ligand 3B and the receptor in Figure 3 show conventional hydrogen bond interactions with SER218, HIE212, and LEU308 residues, two carbon hydrogen bond interactions with ASP310 and SER215 residues, one Amide-π stacked LEU214, and three π-Alkyl interactions with ALA318, LEU315, and PRO225.

The interaction results between Ligand 4B and the receptor in Supplementary file (Figure 3) show conventional hydrogen bond interactions with LEU308, SER218, and HIE212 residues, two carbon hydrogen bond interactions with SER309 and SER215 residues, one Amide-π stacked LEU214 residue, and two π-Alkyl interactions with ALA318 and PRO218.

The interaction results between Ligand 5B and the receptor in Supplementary file (Figure 3) show conventional hydrogen bond interactions with HIE212, SER218, and LEU308 residues, two halogen interactions with MET211 and ASP310 residues, one Amide-π stacked LEU214, and two π-Alkyl interactions with PRO 216 and ALA318.

The interaction results between Ligand 6B and the receptor in Supplementary file (Figure 3) show conventional hydrogen bond interactions with LEU308, and SER218 residues, one carbon hydrogen bond interactions with MET211, HIE212, and SER215 residues, one Amide-π stacked PHE307 and five π-Alkyl interactions with ARG177, LEU173, LEU315, PRO216, and ALA318.

The interaction results between Ligand 7B and the receptor in Supplementary file (Figure 3) show conventional hydrogen bond interactions with SER218 and LEU308 residues, two carbon hydrogen bond interactions with ASP310 and MET211 residues, one Amide-π stacked LEU214, and four π-Alkyl interactions with ALA318, PRO 216, ARG177, and LEU173.

Poses of the docked seven compounds (1B, 2B, 3B, 4B, 5B, 6B, and 7B), when visually inspected, clearly indicate connections between binding modes and interactions of these molecules compared to the template (ligand 2 in table 3) with the human target receptor 4E7Y. All the designed compounds form hydrogen bonds with LEU308, residual SER218 hydrogen bonds, carbon hydrogen bonds with SER215, amide-bonds with LEU214, and -alkyl bonds with PRO216. Furthermore, similarities between the interactions of the designed HDAC derivatives confirm that these molecules can be certified as inhibitors against AD.

3.2 Druggability Studies and Pharmacokinetic Evaluation

The newly designed compounds in this research *in-silico* approach show excellent oral bioavailability. Good results in docking of the designed molecules means all (1–7) possess valid drug-like properties. The predicted LogP 5, HBA 10, HBD 5, TPAS 140, and MW 500 are all within the threshold boundary, which means they agree with Lipinski's Ro5 as indicated in Table 5. The values of GI absorption, TPSA, and nRB for the designed compounds indicate that they have excellent intestinal absorption and bioavailability. The designed compounds are assessed for their synthetic availability. Therefore, the compounds are easy to synthesize. In addition, Lipinski's Ro5 of drug-likeness as shown in Table 6, Ghose, Veber, Egan, and Muegge are contemporarily satisfied for the ligand compounds. This is a common misunderstanding.

Table 5.Lipinski's Ro5 potential inhibitors and the most potent inhibitor in the dataset.

a	b	c	d	e	f	g	h	i
1	0.41	313.21	71.33	2	3	6	0	High
2	1.01	341.26	71.33	2	3	8	0	High
3	0.33	355.25	88.4	2	4	8	0	High
4	0.06	341.22	88.4	2	4	7	0	High
5	0.83	345.23	71.33	2	4	7	0	High
6	0.61	391.28	97.11	2	5	7	0	High
7	1.32	415.3	88.4	2	4	7	0	High

[a]Molecule, [b]Logp(<5), [c]MW(≤500), [d]TPSA(≤140),[e]HBD(<5), [f]HBA(≤10), [g]NRB(<10), [h]Lipinski's Violation(≤1), [i]GI absorption

Table 6. Drug likeness prediction of the designed ligands

A	B	C	D	E	F	G	H
1	0	0	0	0	2.99	0	0
2	0	0	0	0	3.21	0	1
3	0	0	0	0	3.29	0	2
4	1	0	0	0	3.19	0	0
5	0	0	0	0	3.7	0	0
6	0	0	0	0	3.16	0	1
7	0	0	0	0	3.48	0	1

A=Molecule, B=Ghose Violation, C=Veber Violation, D=Egan Violation, E=Mugge Violation, F=Synthetic Accessibility, G=PAINS alert, H=Leadlieness Violation

Several medicines failed due to BBB permeation during the drug discovery process, harmfulness, and poor effectiveness. The aim of preclinical pharmacokinetics studies (ADMET) is to screen fragile drug candidates. This allows the drug-development process to pay attention to fewer but more likely-to-succeed drug contenders. Here, all our designed compounds are subjected to pharmacokinetics prediction (ADMET) and these predicted values are found within the threshold range as presented in Table 7. The pharmacokinetic parameters were calculated using Swissadme.ch and pKcsm predictors.

Adsorption and distribution models are contained in Supplementary file (Table 7). HIA and BBB are respectively relative to the absorption and distribution parameters and represented by an image called BOILED-egg as presented in Figure 4, permeation predictive model. Figure 4 shows that all designed compounds were predicted to be passively absorbed by the gastrointestinal tract, and all were done with the help of the P-gp.

Metabolism, excretion, and toxicity models are presented in Supplementary file (Table 7). The VDss and unbound fraction values indicate that the compounds will be distributed in tissue and plasma, respectively, thus becoming accessible to interact with the pharmacological target. These values indicate that the designed molecules can be well distributed and present a significant unbound fraction in the plasma, thus becoming available to interact with the pharmacological target. Fortunately, the newly designed compounds have no toxic end product.

In Supplementary file (Table 7), the predicted values of the total clearance, which is a measure of the competence of the body in removing a drug, indicate that all designed compounds have good renal elimination and are not substrates of the renal OCT2. Finally, all the designed compounds passed the AMES and Minnow toxicity tests. In general, Supplementary file (Table 7) shows that all the designed compounds could be excellent candidates for further studies or as superb drug candidates.

Oral availability of our designed bioactive compounds is shown in Figure 5, which is called bioavailability radar plots, which provide a graphic picture of the drug-likeness parameters of the designed molecules. The pink zone is a precise physicochemical space for oral bioavailability. Orally bioavailable designed predicted compounds are 1, 2, 3, 4, and 5, whereas compounds six (6) and seven (7) present only one off-shoot relative to INSATU (unsaturation) vertexes, leading to sub-optimal physico-chemical properties for their oral bioavailability.

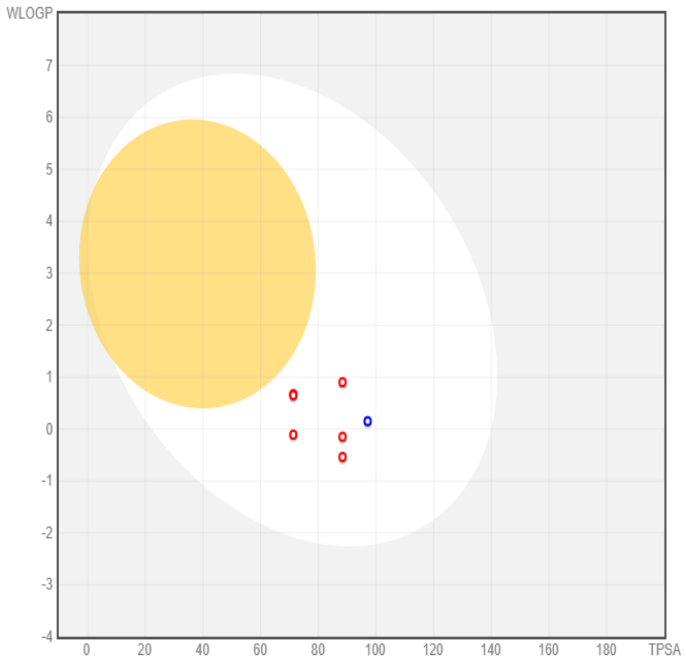
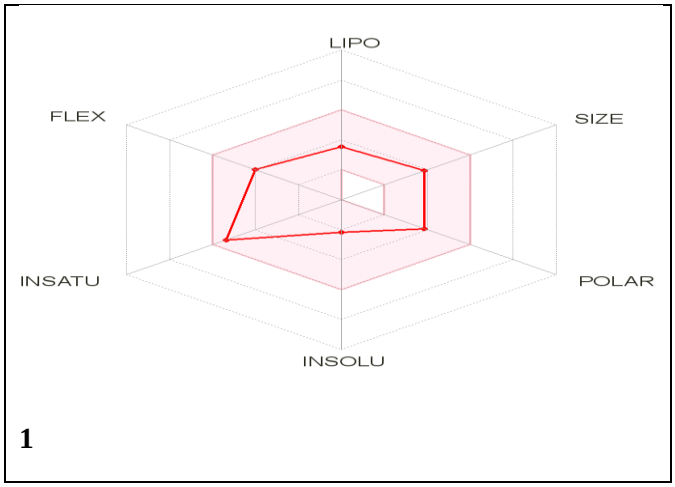
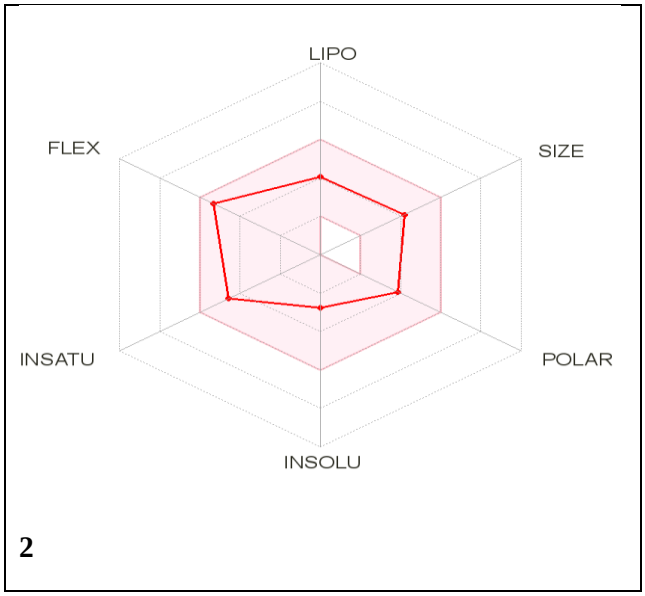
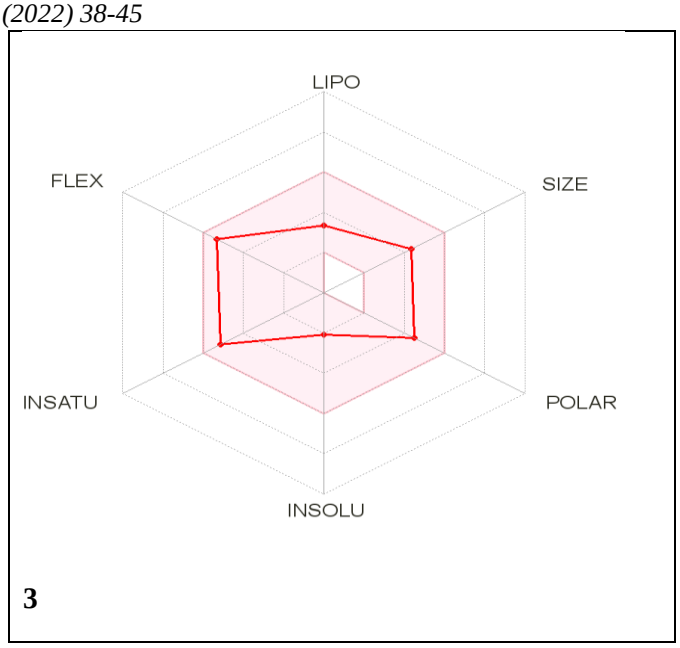
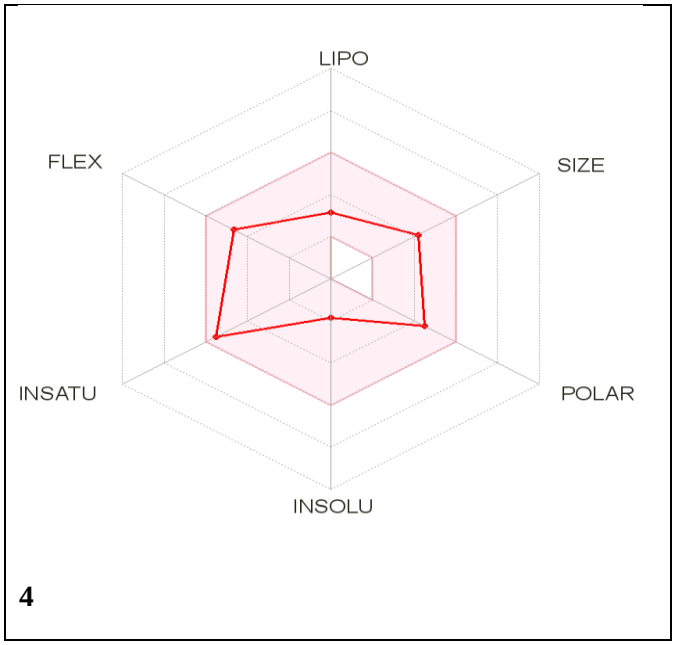


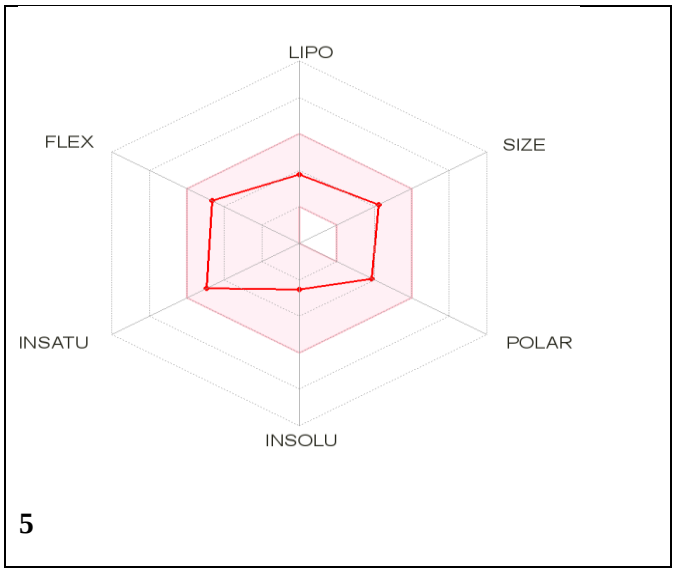
Figure 4: The BIOLED-egg











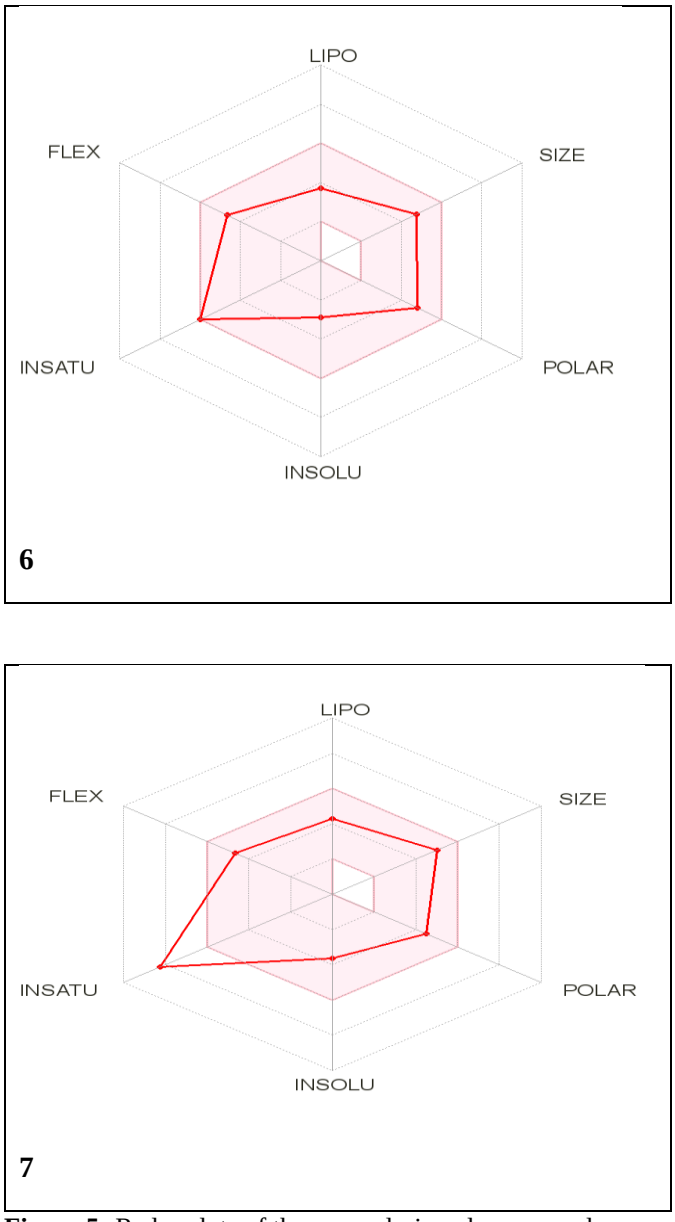


Figure 5: Radar plots of the seven designed compounds

4. Conclusion

Several HDAC derivatives were identified as theoretically effective AD ligands via a series of CADD processes and molecular docking. Meanwhile, the possible binding mode of inhibitors was established by molecular docking at the energetic site pose of the protein target. The main residues that were responsive to interactions are LEU308, SER218, SER215, LEU214, and PRO216. Hydrogen bonding and electrostatics were the primary forces that responded to bioactive interactions. Also, docking, drug-likeness, and ADMET studies confirm the potential and drug-likeness of the seven compounds 1, 2, 3, 4, 5, 6, and 7 as novel inhibitors of the HDAC receptor. In summary, these results indicate that the molecular docking, optimal, ADMET, and drug-likeness properties indicate the ability to be used to predict potent, non-toxic HDAC ligands and guide the discovery of new potential analogs.

Abbreviation

AD: Alzheimer Disease, Human gastrointestinal absorption: HIA and blood–brain barrier: BBB, Brain or IntestinaL EstimateD: BOILED, volume of distribution: VDss, central nervous system: CNS, P-glycoprotein; P-gp, organic cation transporter 2: OCT2, MF: Molecular formula, MW: Molecular weight, HBD: Hydrogen bond donor, HBA: Hydrogen bond acceptor, NRB: Number of rotatable bond, AS: Synthetic accessibility, GIA: Gastrointestinal Absorption, MR: Molar refractivity, PGP: Permeability glycoprotein, Histone acetyltransferases: HATs, GPx: glutathione peroxidase-like, HDACs: Histone Deacetylases, N_{flex}:- Number of Rotatable torsions, H_{bond}:- Hydrogen Bond energy, H_{phob}:- Hydrophobic Energy , CADD: Computer aided drug design

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Authors' contributions

AA designed and wrote the manuscript, UA, GAS and AES supervised and carried out the statistical analysis. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests

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