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Analysis of polypeptide derivatilves targeting the melanocortin-4 receptor for treating hypoactive sexual desire disorder

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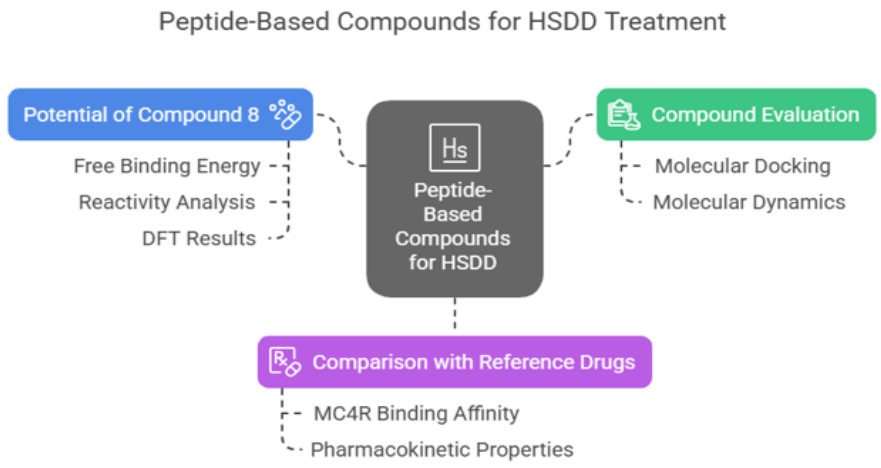
Abstract

Hypoactive sexual desire disorder (HSDD) affects over 13% of individuals globally, significantly impacting emotional well-being and relationships. Current pharmacological treatments for HSDD often have side effects. This study explored 14 peptide-based compounds as potential treatments for HSDD using *in silico* methods. Molecular docking results identified four compounds with promising potential as alternatives to existing medications. Molecular dynamics (MD) simulations compared the leading compound's binding affinity to the reference drug's affinity with the melanocortin-4 receptor (MC4R), showing a greater binding affinity (ΔG_{GBSA} = −76.23 kJ/mol) for the leading compound. Compound 8 also exhibited pharmacokinetic properties like the reference drugs. Density functional theory (DFT) analysis revealed that compound 8 had higher reactivity than the reference drug, indicated by a lower HOMO-LUMO value. These findings highlight the potential of compound 8 as a therapeutic agent for HSDD and its promise in developing a new class of peptide-based treatments.



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Highlights

- Hypoactive Sexual Desire Disorder (HSDD) affects over 13% of individuals worldwide.
- Current treatments of HSDD are associated with significant side effects.
- The study explored fourteen peptide-based compounds through silico methods.
- It identified four viable alternatives to existing HSDD medications.
- Compound 8 showed better binding, stability, & pharmacokinetics for HSDD treatment.

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1. Introduction

The physiological processes of sexual arousal and desire are key motivators of sexual behavior and are integral to reproduction (Thurston *et al.*, 2022). These processes involve complex interactions between hormones, neural pathways, and psychological factors (Calabrò *et al.*, 2019). Arousal triggers physiological responses such as increased heart rate and sensitivity, while desire is influenced by hormones such as testosterone and estrogen (Bogacki-Rychlik *et al.*, 2024). The brain's role in releasing neurotransmitters like dopamine is crucial for generating pleasure and motivation (Lorenz, 2019). While these processes are essential for reproduction at the population level, human sexuality also fulfills emotional, social, and relational functions beyond mere reproductive purposes, reflecting the multifaceted nature of sexual behavior.

Hypoactive sexual desire disorder (HSDD) is a prevalent condition, especially among women, affecting their overall quality of life (Ronghe *et al.*, 2023). It is characterized by a significant reduction or absence of sexual interest or desire, which leads to distress or interpersonal issues (Graziottin *et al.*, 2022). This condition can stem from various factors, including hormonal changes, psychological stress, relationship issues, medical conditions, or medications (Graziottin *et al.*, 2022; Ronghe *et al.*, 2023). The condition can lead to diminished self-worth, frustration, and tension within relationships. When left untreated, these emotional consequences can further compound the problem, creating a cycle of desire suppression and dissatisfaction (Akbari *et al*, 2018; Ronghe *et al.*, 2023). The effectiveness and associated side effects of existing therapeutic alternatives are limited, highlighting a significant gap in the availability of more potent treatment options (Thurston *et al.*, 2022).

Melanocortin receptors (MCRs) are part of the prototypic class A family of G protein-coupled receptors and play key roles in various physiological processes. MC1R regulates pigmentation, MC2R controls cortisol release, MC3R and MC4R regulate energy balance and appetite, and MC5R influences exocrine gland function and immune responses (Baldini and Phelan, 2019; Zhang *et al.*, 2024). Furthermore, research by Kühnen *et al.* (2019) suggested that these receptors could serve as valuable therapeutic targets for conditions such as HSDD, obesity, and other metabolic disorders. The diverse functions of melanocortin receptors highlight their potential significance in developing treatments for both metabolic and sexual health issues.

Bremelanotide is an interesting agent primarily targeting MC4R within the melanocortin receptor system (Thurston *et al.*, 2022). The activation of MC4R is linked to various physiological effects, including the modulation of sexual arousal and desire (Leone *et al.*, 2015). In studies focusing on HSDD in women, bremelanotide has shown promise as a treatment option (Safarinejad, 2008). Clinical trials have demonstrated that this approach is effective, with significant improvements reported in sexual desire and satisfaction among participants (Edinoff *et al.*, 2022; Mayer and Lynch 2020). The mechanism by which bremelanotide works is thought to involve increasing levels of libido and reducing anxiety associated with sexual experiences, potentially through its effects on neurochemical pathways in the brain (Ronghe *et al.*, 2023). However, it may also lead to side effects such as nausea, headache, flushing, injection site reactions, dizziness, and increased blood pressure (Al Musaimi 2024; Edinoff *et al.*, 2022). This highlights the necessity of developing alternative medications to improve the quality of life in individuals experiencing HSDD.

In the field of medicine, both synthetic and natural peptides have garnered significant attention from scientists due to their remarkable therapeutic potential and wide range of biological activities (Nhàn *et al.*, 2023). According to Siegel *et al.* (2020), peptides and their derivatives with healing properties have been shown to possess diverse bioactive effects, including anticancer, antifungal, and antimicrobial effects, making them valuable candidates for developing new treatments. Further research by Blanco-Miguez *et al.* (2016) and Wang *et al.* (2022) demonstrated that peptides exhibit a high level of affinity and specificity in their binding processes to target molecules. This precise binding can trigger specific intracellular effects, crucial for their effectiveness in therapeutic applications. The ability of peptides to interact selectively with target cells or proteins underscores their potential as powerful tools in precision medicine, enabling targeted therapeutic strategies with minimal side effects.

Bremelanotide is a synthetic analogue of the naturally occurring peptide melanotan II, which operates through its connection with alpha-melanocyte-stimulating hormone (α-MSH) receptors, particularly influencing melanocortin receptors involved in sexual arousal pathways (Böhm *et al.*, 2024; Yuan, 2022). To enhance the efficacy of these materials, improve their safety profiles, or increase patient compliance, scientists have explored structural modifications. By introducing electron-donating and electron-withdrawing groups, these derivatives can fine-tune the molecule's interactions with its biological targets. Electron-donating groups typically increase electron density, potentially enhancing receptor binding or selectivity, while electron-withdrawing groups could affect how the molecule is metabolized or reduce off-target effects (Ko *et al.*, 2024).

The field of drug design has undergone a significant transformation with the advent of computational techniques, which have greatly enhanced the efficiency and accuracy of developing new pharmaceuticals (Akash *et al.*, 2024; Sabe *et al.*, 2021). These methods utilize cutting-edge computer technology to model, simulate, and predict the interactions and behaviors of drug molecules, leading to a more efficient drug discovery process (Wang *et al.*, 2021). The use of docking, pharmacophore modeling, and virtual screening, combined with advancements in artificial intelligence and machine learning, has notably accelerated drug discovery (Parvatikar *et al.*, 2023). These innovations reduce the time and financial investments required for new medication development, increasing the likelihood of successfully finding effective and safe therapeutics (Parvathaneni *et al.*, 2019). Therefore, employing a computational approach is one of the crucial tools for assessing new pharmaceuticals.

This research is utilized *in silico* methodologies to identify novel potential therapeutics for HSDD. This study involved various computational techniques, such as molecular modeling, molecular dynamics simulations, pharmacokinetic analyses, and DFT. These methodologies facilitated the assessment of binding affinities, verification of binding stability, exploration of potential therapeutic effects, and evaluation of the reactivity of polypeptide derivatives with the MC4R receptor. The outcomes of this investigation are promising and may pave the way for the development of new pharmacological treatments for HSDD.

2. Methodology

2.1. Molecular docking approaches

To verify the reliability of the engaged docking technique, the ligand obtained from the crystal structure of 6w25 was redocked into the active site of the same structure to assess how closely the top conformation of the redocked ligand (i.e., the one with the lowest energy) aligned with the position of the original ligand (**Fig. 1**). As a result, the similarity index between the native drug-like compound fetched from the receptor and the redocked drug compound was comparable, and the calculated RMSD was nearly 1. Thus, the docking method applied in this study appears to be reliable.

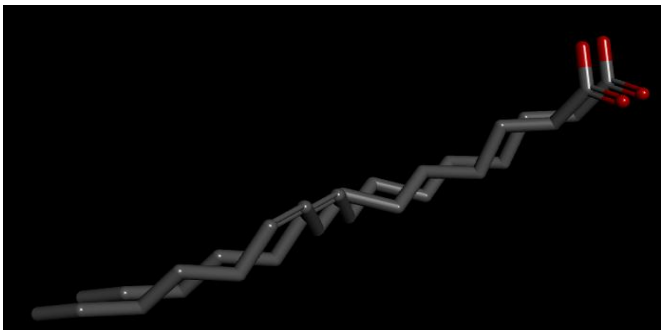

Figure 1. Superimposition of native drug-like molecules onto redocked drug compounds.
Source: Elaborated by the authors.

The biochemical activities of fourteen bremelanotide polypeptide derivatives (**Fig. 2**) and a reference drug (bremelanotide) were initially modeled in two dimensions using the Mavinsketch program (Oyebamiji *et al.*, 2024). The studied compounds were generated by adding electron-withdrawing and electron-donating groups to the parent compounds, which thereby alter (enhance or decrease) the activities of the parent compound. These structures were Oke optimized using the QuickPrep tool in Molecular Operating Environment (MOE) software (Oke *et al.*, 2022; Omotayo *et al.*, 2023), which refines molecular structures to ensure they are energetically favorable. The optimized compounds were saved in the molecular operating environment (MOE) format for further computational analysis. Concurrently, the melanocortin-4 receptor, crucial for various physiological functions, was retrieved from the Protein Data Bank (PDB ID: 6w25) and optimized using the QuickPrep tool in the MOE. This optimization ensured that the receptor's conformation was ideal for further studies.

The receptor binding sites were subsequently identified, and the most suitable site was chosen for docking studies. The optimized receptor was saved in MOE format, maintaining all necessary structural refinements for accurate modeling. Docking calculations were performed using the induced fit docking method, which allows the receptor to adapt flexibly to the ligand, to provide a potential simulation of binding interactions. The protein–ligand complex was saved in .pdb format for further study. 2D and 3D interactions were viewed through Biovia Discovery Studio and PyMOL, respectively.

2.2. MD simulation procedures

This research utilized the Amber field from the Amber software suite (Jakalian *et al.*, 2002; Showalter and Brüschweiler, 2007) to investigate the dynamics of intricate biological systems, focusing specifically on interactions involving MC4R, compound **8**, and a reference medication. The selection of the Amber force field was based on its exceptional precision in simulating molecular interactions, which allows for a comprehensive understanding of the structural and dynamic characteristics of biomolecules that are challenging to observe through experimental methods (Nerenberg and Head-Gordon, 2018). Before the simulations, the ligands and targets were solvated in water to stabilize the system and maintain proper charge distribution. Sodium (Na^+) and chloride (Cl^-) ions were added to neutralize the system and mimic physiological conditions, ensuring accurate modeling of electrostatic interactions.

The simulations began under NVT (constant number of particles, volume, and temperature) conditions at 310 K to stabilize the system. This was followed by an NPT (constant number of particles, pressure, and temperature) phase to stabilize further the pressure and temperature (Kakhar *et al.*, 2023). Finally, a 100-nanosecond (ns) production run was conducted to calculate the binding energies, and key parameters such as the root mean square deviation (RMSD), root mean square fluctuation (RMSF), radius of gyration (Rg) and molecular mechanics generalized Boltzmann solvation area (MMGBSA) were calculated. These metrics are essential for assessing the stability and flexibility of the protein–ligand complex, providing deeper insights into the dynamic behavior and binding characteristics of MC4R and its ligands.

2.3. Density functional theory procedures

In this study, compound **8** and a reference compound were built within the graphical user interface of Spartan 14. The 3D models were optimized using Beckes three Lee yang Parr (B3LYP) with the 6-31G** basis set (Oostenbrink *et al.*, 2007), a method that provides accurate predictions of molecular properties by investigating electronic structures (Olowosaga *et al.*, 2026). Following optimization, molecular descriptors were computed, including the energy gap between the HOMO and LUMO, which indicates the reactivity and stability of the compounds.

2.4. Methods of studying pharmacokinetic properties

In our efforts to develop effective antimicrobial agents, we investigated the physicochemical properties of the selected compounds using various web-based tools for predicting molecular properties. Compound **8** and a reference compound were first uploaded to the SwissADME server (www.swissadme.ch) to convert their chemical structures into the SMILES format. Next, the SMILES files were entered into the AdmetSAR tool (http://lmmd.ecust.edu.cn/admetsar2/) to predict the compounds' absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles. This analysis helped assess these compounds' pharmacokinetic behavior and potential toxicological risks.

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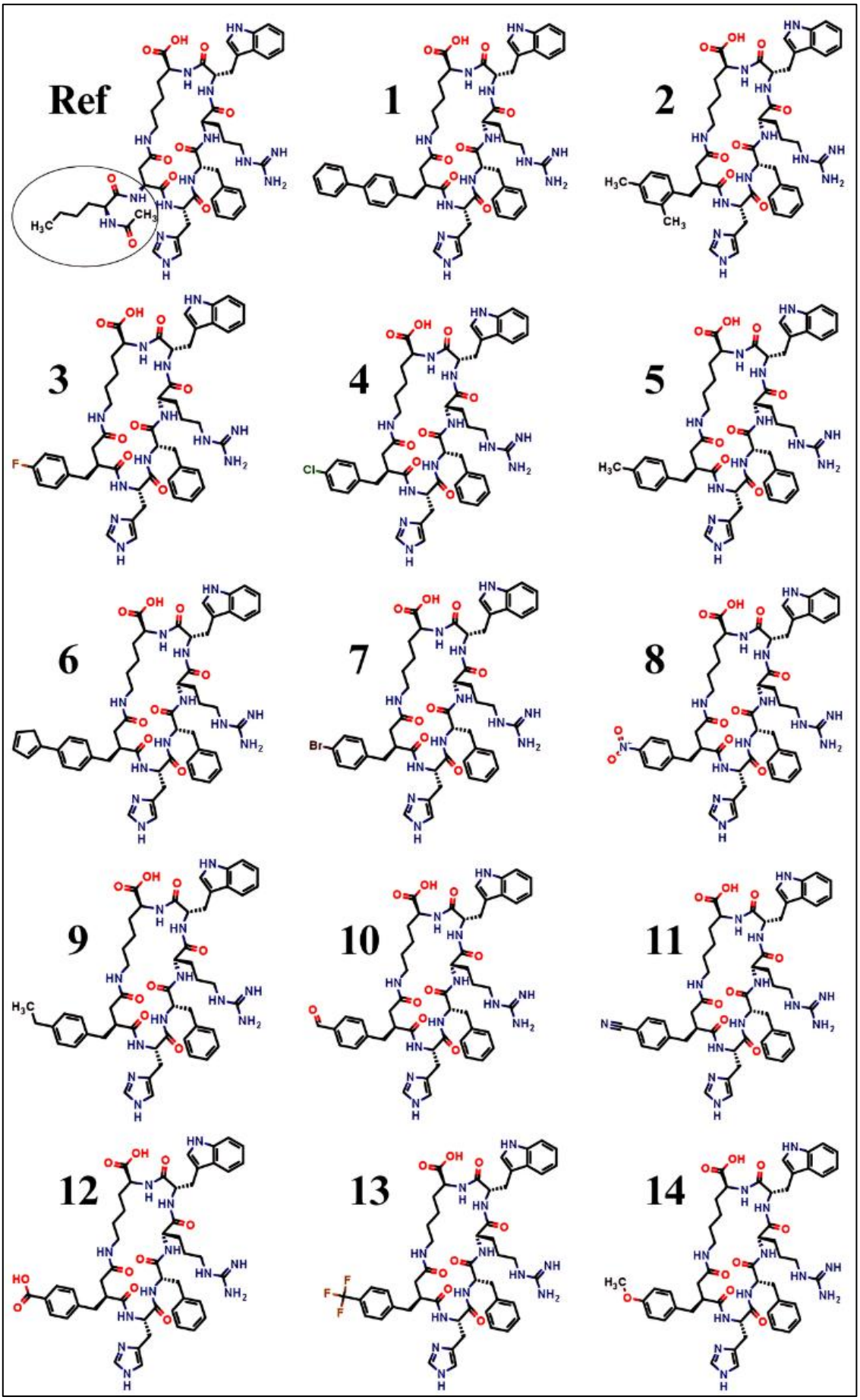

Figure 2. The chemical structures of bremelanotide (Ref: reference drug) and its derivatives (**1-14**).
Source: Elaborated by the authors.

3. Results and discussion

3.1. Calculated scorings for the studied compounds

The anti-hypoactive sexual desire disorder activities of the fourteen selected ligands were assessed through docking studies against MC4R. This investigation aimed at evaluating the potential of these ligands to inhibit the receptor by analyzing the interactions between the atoms in each ligand and the amino acid residues of the receptor protein. The activity of each compound was compared to that of bremelanotide, a well-known reference compound, to establish a benchmark for its inhibitory activities.

The binding affinities of the compounds (**Table 1**), which reflect their strength of interaction with MC4R, were assessed and revealed notable variations. Compound **8** exhibited the highest binding affinity among the compounds at –40.50 kJ/mol, followed closely by compound **4** at –38.57 kJ/mol. In contrast, compound **11** demonstrated the weakest interaction, with a binding affinity of –32.92 kJ/mol. Most compounds fell within the binding affinity range of –8.0 to –37.65 kJ/mol. For reference, bremelanotide displayed a binding affinity of –36.31 kJ/mol.

Table 1. Binding affinities (kJ/mol) of the polypeptides studied (**1-14**) and one reference drug.

Compound	Binding Affinity (kJ/mol)
1	–34.56
2	–34.38
3	–34.83
4	–38.60
5	–36.78
6	–35.11
7	–35.36
8	–40.51
9	–36.71
10	–33.75
11	–32.94
12	–35.54
13	–33.24
14	–33.69
Ref	–36.32

Source: Elaborated by the authors.

All fourteen compounds showed considerable potential to inhibit MC4R, suggesting that most of the ligands studied possess the ability to influence the target receptor. Notably, compounds **4**, **5**, **8**, and **9** exhibited stronger inhibitory effects than bremelanotide, a difference that can be attributed to the specific substituent groups present in these compounds, which modify their binding efficiency by affecting electron density and interaction dynamics with the receptor. The correlation between the configuration of the docked compounds **4**, **5**, **8**, and **9** and the structure of the reference compound showed that fair correlation between the selected structures was observed.

A comprehensive analysis of the protein–ligand interactions (**Fig. 3**) for the identified drugs underscores the pivotal role of structural and dynamic factors in biological molecules and processes (Saidj *et al.*, 2023).

Notably, hydrogen bonds and hydrophobic interactions emerge as critical forces that significantly influence the stability and functionality of these complexes (Vikhar *et al.*, 2024). These interactions are integral in promoting robust ligand binding to the active site residues within the receptor, thereby enhancing the overall stability and efficacy of the protein–ligand complexes (Ferenczy and Kellermayer 2022). For instance, compound 4 exhibited a series of hydrogen bond interactions, particularly with residues THR80 and THR246. These interactions are crucial in stabilizing the complex, ensuring the studied ligand binds very well to the binding site. Moreover, the hydrophobic interactions in Compound 4 were characterized by pi-bonds involving residues PRO78, ALA154, LEU155, and LYS242, which further contributed to the stabilization by providing additional nonpolar interactions that reinforce the binding. Additionally, compound 4 formed a pi-sigma bond with HIS158 and THR150, while other amino acid residues participated in van der Waals forces and carbon–hydrogen bond interactions, highlighting the multifaceted nature of these stabilizing forces.

The structural characteristics of compounds **5**, **8**, and **9**, as illustrated in **Fig. 3a**, reveal interaction patterns that closely resemble those observed for the referenced compound. For Compound **5**, a network of conventional hydrogen bonds was established with residues LYS73, ASN74, HIS76, and TRP80, with THR80 mirroring the interactions seen in compounds **4** and **5**, further solidifying the complex. The hydrophobic interactions in the compound **5** complex primarily involved residues ARG147 and THR150, suggesting that a consistent interaction motif is essential for binding affinity.

In the case of compound **8**, the analysis highlighted hydrogen bond interactions with ALA154 and ASN187. A notable pi-sigma bond with THR150 was observed, and ALA239 and LYS1190 facilitated pi-alkyl interactions. Additionally, HIS158 formed in a pi-pi Ti-shaped bond interaction, a specific form of noncovalent interaction that contributes to the overall stability of the complex. For compound **9**, conventional hydrogen bonds with LYS73, ASN74, and GLY238 were instrumental in maintaining the stability of the complex. Furthermore, a pi-sigma bond with LEU155 combined with pi-cation interactions involving ARG147 and ARG1191, and a pi-pi Ti-shaped bond interaction involving HIS158 highlighted the compound's robust binding profile. These detailed observations suggest that the structural modifications implemented in compounds **4**, **5**, **8**, and **9** notably enhanced their binding properties. These enhancements as predicted theoretically are expected to elevate the efficacy of these agents as potential therapeutic agents, particularly in the context of HSDD.

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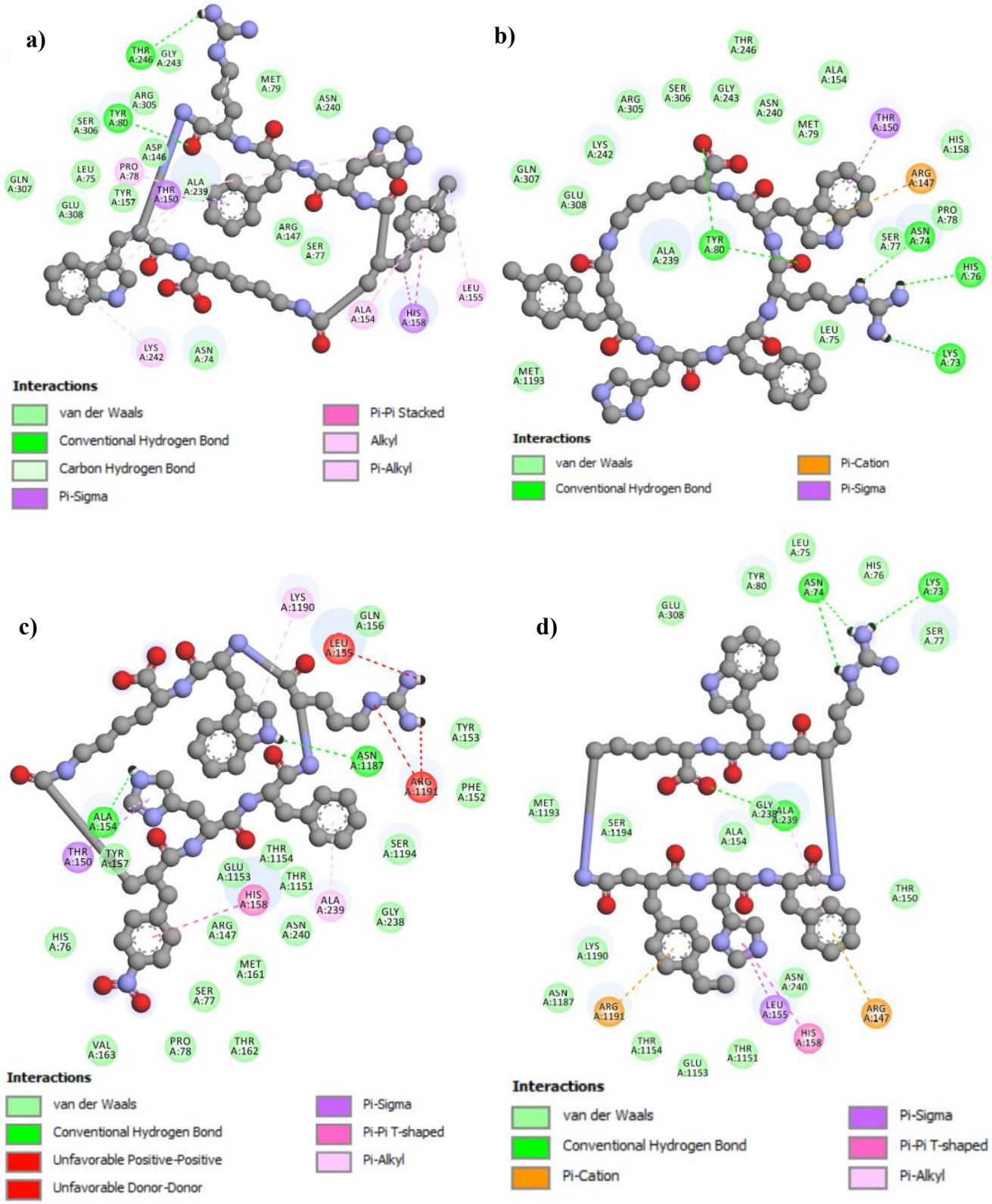

Figure 3. 2D protein–ligand interactions of the hit compounds. **(a)** compound **4**; **(b)** compound **5**; **(c)** compound **8**; **(d)** compound **9**.
Source: Elaborated by the authors.

3.2. MD simulation analysis

In this study, we utilized the RMSD and calculated free energies to further validate the potential efficacy of the selected compounds. The RMSD was used to assess the stability of the receptor–ligand complexes throughout the 100-nanosecond (ns) MD simulation (Chen *et al.*, 2016). This metric evaluates the deviation of the backbone atoms of the receptor from their original conformation when bound to the ligands (Sharma *et al.*, 2021). Specifically, we examined the interactions of compound **8** and the reference compound with MC4R.

As illustrated in **Fig. 4a** and **4b**, the RMSD of the protein and ligand's RMSD of the reference drug deviate more than that of the hit drug. Thus, the predicted RMSD values indicated that

the receptor–ligand complex involving compound **8** demonstrated greater stability than the complex with the reference compound over the 100 ns simulation. This finding suggested that compound **8** maintains a more stable interaction with the receptor, potentially reflecting a more favorable binding mode.

The RMSF is a metric used to quantify the average deviation of individual atomic positions from their mean coordinates over time in molecular dynamics simulations (Vander *et al.*, 2024). This approach provides insights into the flexibility or stability of different molecule regions, such as a protein, with higher RMSF values indicating greater atomic mobility (Muhammad *et al.*, 2023). Examining the RMSF of the complexes, both showed similar general fluctuation patterns across the residues, with peaks and troughs at comparable positions (**Fig. 4c**). This finding suggested that the protein's overall structure is preserved in both states, with some regions being inherently more flexible than others. At several points along with the residue sequence, Comp8-6w25 had higher RMSF values than did the reference compound. This indicates that the residues in these regions are more flexible when the compound is present. Some regions showed relatively low RMSF values, indicating that stable parts of the protein did not fluctuate much during the simulation. Compared with the reference state, Comp8-6w25 appears to increase the flexibility of certain residues in the protein. These differences might indicate regions where the compound binds or induces conformational changes, affecting the protein's dynamics.

The radius of gyration (Rg) is a crucial parameter in molecular dynamics (MD) simulations, used to quantify a molecular structure's overall compactness or spatial distribution, such as a protein (Forouzesh and Onufriev, 2020; Muhammad Rehman *et al.*, 2023). The Rg values fluctuate between approximately 28.5 Å and 31.5 Å for both complexes, indicating that the protein maintains a relatively compact structure throughout the simulation (**Fig. 4d**). Both complexes show fluctuations in Rg over the simulation time, which is normal as proteins undergo conformational changes during dynamic simulations. However, the reference seems to have periods where it dips lower, indicating more transient compaction, while Comp8-6w25 shows less dramatic decreases, suggesting a steadier, slightly more expanded state. **Table 2** presents the computed binding free energies of compound **8** and a reference compound in complex with MC4R.

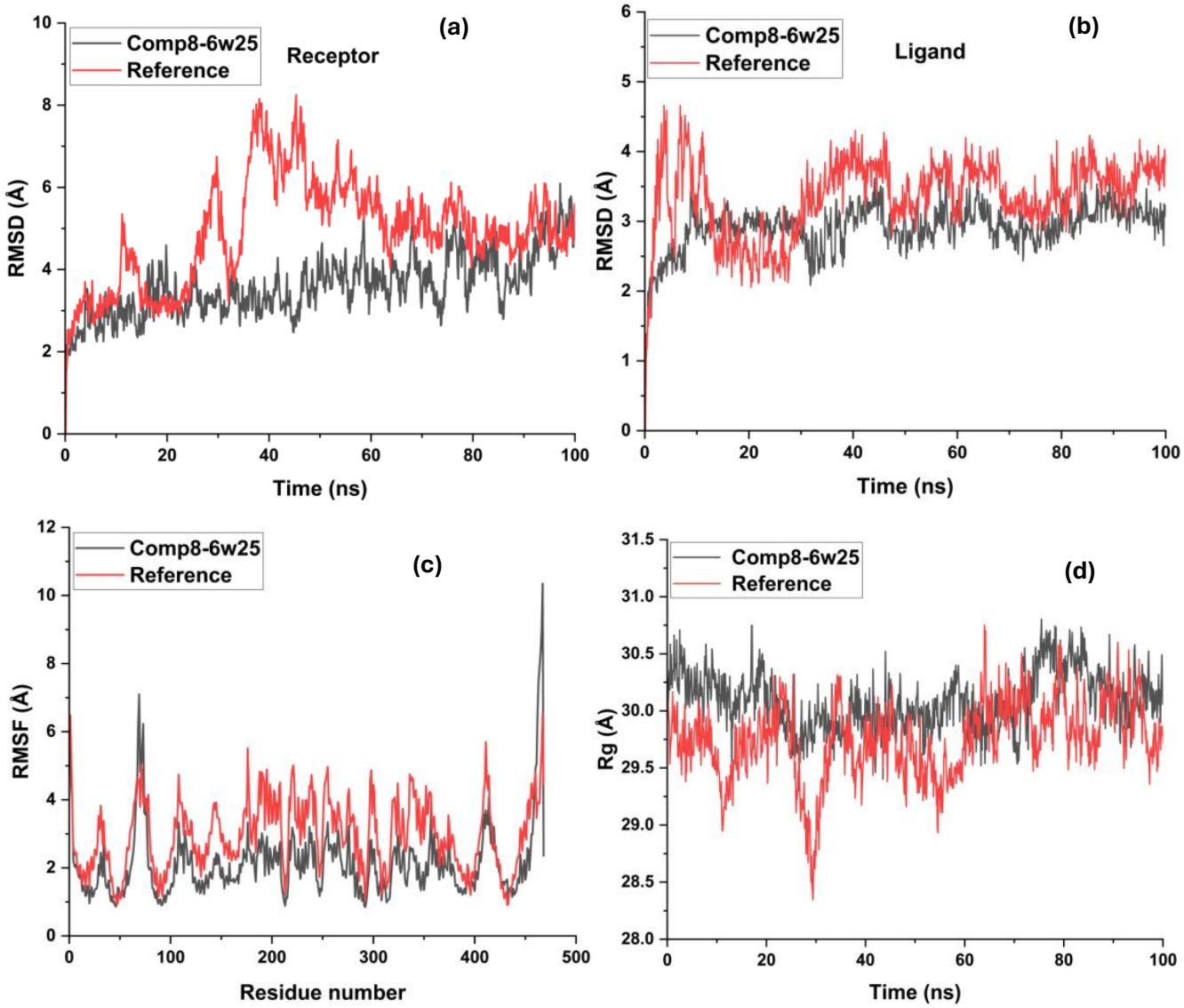

Figure 4. MD simulation of the complexes over a 100 ns production run **(a)** receptor RMSD, **(b)** ligand RMSD, **(c)** RMSF, **(d)** Rg.
Source: Elaborated by the authors.

Table 2. Calculated binding energies for compounds **4**, **5**, **8**, **9** and the reference compound against the target compound.

Compound	ΔG_{gas} (kJ/mol)	ΔG_{solv} (kJ/mol)	ΔG_{GBSA} (kJ/mol)
Comp4-6w25	−95.01	122.45	−207.46
Comp5-6w25	−48.94	225.39	−146.82
Comp8-6w25	−2272.12	2061.99	−210.12
Comp9-6w25	−77.12	57.01	−194.89
Ref-6w25	−1311.08	1177.20	−133.87

Source: Elaborated by the authors.

The calculations were performed using the generalized Born surface area (MMGBSA) method, a widely applied computational technique for estimating the binding free energy between ligands and proteins (Forouzesh and Onufriev 2020). MMGBSA provides insights into the stability and strength of ligand–protein interactions, which are crucial for understanding potential efficacy in drug design. The free energy of binding was found to be more favorable for compound **8**, with a binding energy of –210.12 kJ/mol, greater than that of the reference drug, with a binding energy of –133.87 kJ/mol. Also, as shown in **Table 2**, it was observed that ΔG_{gas} was more favorable to the binding of compound **8** to the studied receptor, while ΔG_{solv} was not favorable for the molecular binding of compound **8** to MC4R. It also showed that the change in Gibbs free energy in the gas phase and solvation for Comp8-6w25 reaction is expected to be more spontaneous than other studied interactions.

According to the findings reported by Oyebamiji *at al*. (2023), a lower binding energy indicates a stronger interaction and greater potency of the ligand in inhibiting the target. Therefore, compound **8** has a more negative binding energy than the reference compound, suggesting it is a more potent inhibitor of MC4R. This finding aligns with the predictions from the induced fit docking method, which identified compound **8** as the most promising candidate among those tested. These results underscore the potential of compound **8** as a highly effective inhibitor, as it not only maintains a stable binding conformation but also has a significantly lower binding energy, indicating that it strongly and favorably interacts with MC4R.

Moreover, the calculated binding energies for compounds **4**, **5**, and **9** revealed their potency to be better than that of the reference drug but lower than that of compound **8**. This still confirmed the potential efficiency of compound **8** as a probable melanocortin-4 receptor inhibitor for treating hypoactive sexual desire disorder.

3.3. Calculated descriptors for selected compounds

This study analyzed three key descriptors to evaluate the reactivity of the selected compounds compared to the other studied compounds. Specifically, we focused on the energies of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), as well as the energy gap between these orbitals, to assess the reactivity and interaction potential of the compounds (Miar *et al.*, 2021).

The calculated HOMO energies for compound **8** and the reference compound were –5.84 eV and –5.45 eV, respectively. According to Semire *et al*. (2023), a higher HOMO indicates a greater capacity of the compound to donate electrons to its surroundings, which can be a measure of its nucleophilicity and potential reactivity. As shown in **Table 3**, the reference compound has a HOMO value that suggests that it can significantly release electron to the neighboring compounds than the selected studied compound (Compound **8**).

Table 3. Calculated descriptors for the studied compounds.

	HOMO (eV)	LUMO (eV)	Energy Gap (eV)
Compound 8	−5.84	−2.86	2.98
Reference	−5.45	−1.07	4.38

Source: Elaborated by the authors.

As depicted in **Table 3** and revealed in **Fig. 5**, compound **8** demonstrated a lower energy gap than the reference compound. This smaller energy gap implies that compound **8** has a greater capacity to accept electrons and thus exhibits higher reactivity than the reference compound. This enhanced electron acceptance capability makes compound **8** more reactive, aligning with its predicted ability to inhibit MC4R more effectively. Overall, the analysis of the HOMO and LUMO energies, along with the energy gap, reveals that compound **8** is more reactive than the reference compound and has greater potential for interaction. This insight into the electronic properties of the compounds contributes to understanding their chemical behavior and potential efficacy in various applications.

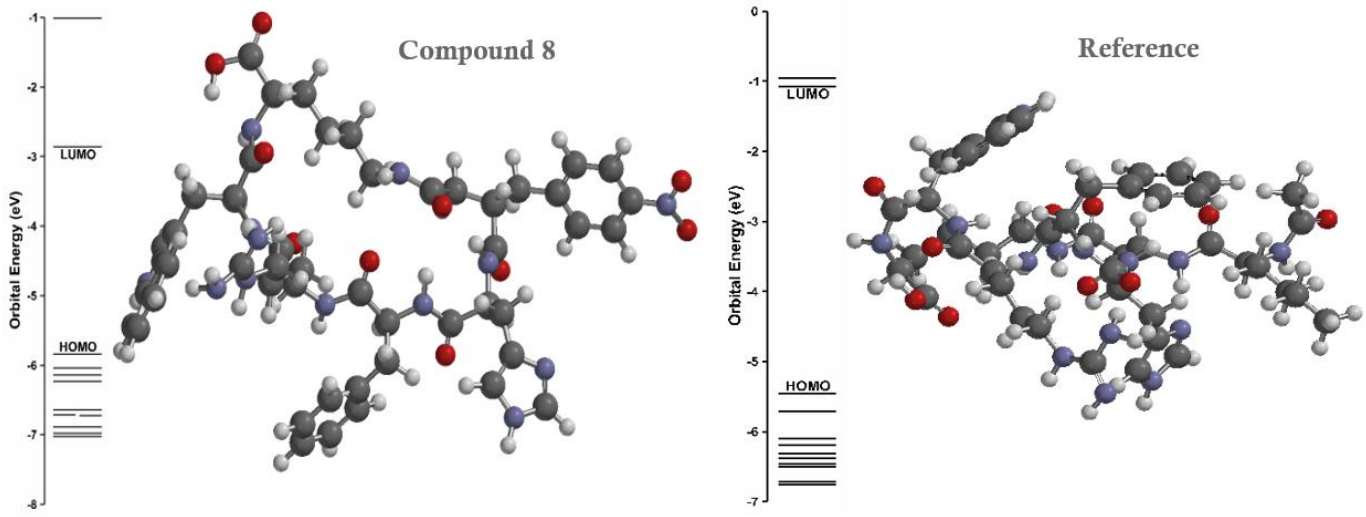

Figure 5. Orbital energy profiles of compound **8** and the reference drug.
Source: Elaborated by the authors.

3.4. ADMET analysis of compound 8 and the reference compound

ADMET analysis refers to examining a drug's pharmacokinetics and plays a crucial role in drug discovery and development (Guan *et al.*, 2019). This analysis provides insights into the distribution and metabolism of a drug within an organism and its physiological effects on the body (Li *et al.*, 2019). In this study, compound 8 and bremelanotide were selected for comprehensive ADMET evaluation, as detailed in Table 4. Factors such as blood–brain barrier (BBB) penetration, human intestinal absorption, Caco-2 permeability, P-glycoprotein substrate and inhibitor, and renal organic cation transporter were considered for assessment. The distribution of the proteins was evaluated based on subcellular localization. In the metabolism category, we investigated interactions with CYP450 enzymes, including CYP450 2C9, 2D6, and 3A4 as substrates and CYP450 1A2, 2C9, 2D6, 2C19, and 3A4 as inhibitors, along with CYP inhibitory promiscuity. Toxicity was assessed through various parameters, including human ether-a-go-go-related gene (hERG) inhibition, AMES toxicity, carcinogenicity, and specific toxicity to fish, Tetrahymena pyriformis, and Honeybee, as well as biodegradation and acute oral toxicity. More so, it was observed that compound 8 may be mutagenic when compared to the report for Ames toxicity of the referenced compound.

The results indicated that both compound 8 and bremelanotide exhibited similar profiles across these factors. This similarity suggests that compound 8 has comparable potential as a medication, demonstrating a fair level of oral absorption and an acceptable safety profile. Consequently, compound 8 shows promise as a therapeutic agent with potential efficacy on par with the established reference compound.

Table 4. ADMET prediction profile for the reference drug and compound 8.

Absorption & Distribution	Bremelanotide	Compound 8
Blood–Brain Barrier (BBB)	BBB-	BBB-
Human Intestinal Absorption	0.9039	0.7879
Caco-2 Permeability	0.8349	0.6882
P-glycoprotein Substrate	Yes	Yes
P-glycoprotein Inhibitor	No	No
Renal Organic Cation Transporter	No	No
Metabolism		
CYP450 2C9 substrate	No	No
CYP450 2D6 substrate	No	No
CYP450 3A4 substrate	Yes	No
CYP450 1A2 Inhibitor	No	No
CYP450 2C9 Inhibitor	No	No
CYP450 2C19 Inhibitor	No	No
CYP450 3A4 Inhibitor	No	No
CYP Inhibitory Promiscuity	Low	Low
Excretion		
Biodegradation	No	No
Toxicity		
Ames Toxicity	No	Yes
Acute Oral Toxicity	III	III
hERG2 Inhibition	No	No
Carcinogenicity	No	No
Tetrahymena Pyriformis Toxicity	High	High
Fish Toxicity	High	High

Source: Elaborated by the authors.

4. Conclusions

This study investigated fourteen peptide-based derivatives as potential drugs for HSDD. Four compounds showed potential ability to inhibit MC4R more strongly than the reference drug (–8.68 kJ/mol). Compound 8 showed the greatest inhibitory potential among the compounds tested, as evidenced by its superior predicted binding affinity of –40.50 kJ/mol. MD simulations confirmed these findings, demonstrating stable and favorable molecular interactions. Through MMGBSA calculations, the potency of Compound 8 was optimized, and the results further revealed key structural characteristics that contributed to its function and reactivity. These insights highlighted how its molecular composition supports its role as an effective inhibitor. Additionally, compound 8 exhibited pharmacokinetic properties like those of the reference compound, particularly according to the ADMET profiles. This finding suggested that Compound 8 not only binds well to the receptor but also shares favorable drug-like properties with the reference substance. Overall, the study positions Compound 8 as a promising candidate for further development, given its strong receptor inhibition ability, structural stability, and pharmacokinetic similarity to known compounds.

Authors' contribution

Conceptualization: Abel Kolawole Oyebamiji; Sunday Adewale Akintelu; **Data curation:** Oluwakemi Ebenezer; **Formal Analysis:** Sunday Adewale Akintelu; **Funding acquisition:** Abel Kolawole Oyebamiji; Sunday Adewale Akintelu; **Investigation:** Abel Kolawole Oyebamiji; **Methodology:** Abel Kolawole Oyebamiji; Sunday Adewale Akintelu; Samson Olusegun Afolabi; **Project administration:** Samson Olusegun Afolabi; **Resources:** Samson Olusegun Afolabi; **Software:** Abel Kolawole Oyebamiji; Samson Olusegun Afolabi; **Supervision:** Emmanuel Temitope Akintayo; **Validation:** Cecilia Olufunke Akintayo; **Visualization:** Cecilia Olufunke Akintayo; **Writing – original draft:** Abel Kolawole Oyebamiji; Samson Olusegun Afolabi; **Writing – review & editing:** Abel Kolawole Oyebamiji; Sunday Adewale Akintelu; Oluwakemi Ebenezer; Emmanuel Temitope Akintayo; Cecilia Olufunke Akintayo; Samson Olusegun Afolabi.

Conflict of interest

The authors declare that there is no conflict of interest.

Data availability statement

All data sets were generated or analyzed in the current study.

Artificial Intelligence usage statement

The authors declare that they did not use Artificial Intelligence tools at any stage of the preparation, correction, or evaluation of this work.

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