Research Article
p-ISSN 2527-6298 | e-ISSN 2527-9017

Homepage :
https://journal.ubaya.ac.id/index.php/MPI/index
DOI 10.24123/mpi.v7i2.7437

Virtual Screening, ADMET Evaluation, and Molecular Docking Approach in the Discovery of Novel Potential Sweetening Agent

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Submitted: 09-04-2025, *Revised:* 04-12-2025, *Accepted:* 04-12-2025, *Published regularly: December 2025*

ABSTRACT: *This study presents a comprehensive in silico approach aimed at discovering novel artificial sweetener candidates through an integration of shape-based virtual screening, taste classification, ADMET evaluation, homology modeling, and molecular docking. Using saccharin as a template, compounds were screened from a large high-throughput database employing vROCS software, followed by taste prediction via VirtualTaste and Virtuous Sweet/Bitter. Two promising candidates were identified with Compound 1 exhibiting superior binding affinity against a homology-modeled human T1R2-T1R3 receptor, as evidenced by its docking score of –77.81 kcal/mol. ADMET analysis further revealed favorable pharmacokinetic properties for the compounds, suggesting their potential as safer non-caloric sweeteners. The integrative strategy not only streamlines candidate selection but also underlines the utility of molecular modeling in food science. Nevertheless, experimental validation and sensory evaluation are needed to confirm these findings and establish the compounds' efficacy and safety profiles. These promising results encourage further in vitro and in vivo studies.*

Keywords: *ADMET evaluation; artificial sweeteners; molecular docking; taste receptor modeling; virtual screening*

1. Introduction

Sweetness is one of the important factors in the enjoyment of food and food products. Its presence provides a pleasurable sensation by stimulating the taste buds and activating reward centers in the brain [1]. The high levels of sugar consumption in our society are influenced not only by its taste appeal but also by its pervasive presence in the modern food landscape, making it nearly impossible to avoid [2]. This has contributed to obesity which then leads to various health issues including cardiovascular diseases, type II diabetes mellitus, even cancer [3].

Artificial sweeteners have been introduced as food additives to replace sugar, aiming to reduce caloric intake and manage blood glucose levels. However, many of these compounds exhibit undesirable aftertastes, such as bitterness or a metallic flavor, which can impact their acceptability [4]. Therefore, there is a need to develop new sweetening agents that offer minimal to zero calorie intake while minimizing or eliminating their aftertaste.

Molecular modeling has been used in the field of drug discovery and development as an effective tool for designing and screening new candidates of bioactive compounds prior to their activity evaluation [5]. Beyond pharmaceuticals, molecular modeling has also found in application fields such as food science, where it is employed to investigate interactions between macro- and micronutrients with specific biological targets, as well as to assess food safety and potential hazards [6].

Numerous studies have explored the development of novel sweetening agents through a combination of structure-based approaches and machine-learning classifiers [7-9]. This study aimed to identify new artificial sweeteners by employing virtual screening methods that integrate 3D shape-based similarity, followed by consensus evaluation using a sweetness prediction module. The resulting compounds were then comprehensively evaluated for their ADMET properties and examined for potential binding interactions with human taste receptors using molecular docking and molecular dynamics.

2. Materials and methods

2.1. Hardware and software

The hardware used in this study was a standard personal computer (Intel Core i7-9700F 3.00 GHz, RAM 16 GB) with Windows 10 operating system. A range of software was employed such as vROCS (OpenEye, Cadence Molecular Sciences, Santa Fe, NM, USA) [10], OMEGA (OpenEye, Cadence Molecular Sciences, Santa Fe, NM, USA) [11], Molegro Virtual Docker 7.0 (Molexus, Odder, Denmark) [12], GROMACS 2022.2 [13], gmx_mmpbsa [14], and Uni-GBSA [15]. In addition, several web-based tools were utilized such as VirtualTaste (https://insilico-cyp.charite.de/VirtualTaste/) [16], Virtuous Sweet/Bitter

Figure 1. Virtual screening scheme in this study

(https://virtuous.isi.gr/#/sweetbitter) [17], ADMETLab 3.0 (https://admetlab3.scbdd.com/) [18], AlphaFold (https://alphafold.ebi.ac.uk/) [19], COACH (https://seq2fun.dcmb.med.umich.edu//COACH/) [20], and Verify3D (https://saves.mbi.ucla.edu/) [21].

2.2. Methods

2.2.1. Selection of template molecule and database curation

Among the various artificial sweetening agents available, saccharin was chosen as the template structure for three-dimensional shape-based screening due to its simple and rigid scaffold, making it an ideal starting point for designing small-molecule sweeteners [22]. The three-dimensional structure of saccharin was retrieved from PubChem (CID: 5143) and screened against the Mcule High-Throughput Screening (HTS) database (Mcule, Budapest, Hungary). Prior to the screening process, the database was prepared by generating conformers using the OMEGA software with the rocs module.

2.2.2. Shape-based screening

Initially virtual screening was performed using vROCS software. The molecular shape query of saccharin was then used to screen against the prepared databases to obtain hit compounds with TanimotoCombo score not less than 1.2. Afterwards, the result was removed from duplicate compounds.

2.2.3. In silico taste classification

The molecules obtained from the previous step were evaluated for their predicted taste using two web servers: VirtualTaste and Virtuous Sweet/Bitter. Compounds predicted to have a sweet taste by both algorithms were advanced to the next step.

2.2.4. ADMET evaluation

ADMET evaluation was conducted for the compounds obtained from the previous step. AdmetLab 3.0 was used as the tool to ensure that the potential sweetener compound possesses favorable ADME profile as well as free from toxic moiety.

2.2.5. Homology modeling and binding site prediction of human sweet receptor

Homology modeling was performed to construct the 3D structure of the human T1R2-T1R3 receptor using AlphaFold. The canonical amino acid sequence of the Venus Fly Trap (VFT) domain of the human T1R2-T1R3 receptor was obtained from Q8TE23 and Q7RTX0 reported in the Uniprot database [23]. Next, the obtained amino acid sequences were used to search for templates using hetero-oligomeric protein model building model. The PDB structure (ID 5X2P) of the ligand binding domain of the medaka fish taste receptor T1R2a-T1R3 was used as a template to gene–rate the final model [24]. The binding site prediction was performed using COACH. Ultimately the structure was verified using Verify3D.

2.2.6. Molecular docking

Molecular docking was performed against the constructed receptor using Molegro Virtual Docker 7.0. Binding site area was determined using the previously obtained data. Moldock Score and Moldock SE were used as scoring function and placement function, respectively [12]. The evaluation was undertaken by analyzing both docking scores as well as the amino acid-ligand interactions.

2.2.7. Molecular dynamics and free energy calculation

Protein and ligand complexes were further processed with pdb2gmx module in GROMACS 2022.2. Protein was modeled using the AMBER99SB-ILDN force field [25], while ligand parameters were characterized using GAFF2-based ACPYPE [26], with TIP3P as the water model [27]. The protein-ligand complex was placed in a triclinic simulation box with a minimum distance of 1.0 nm from the box wall. NaCl ions were added to neutralize the system at a speci-

fied concentration. Simulations were run with periodic boundary conditions, using the particle-mesh Ewald method and fast Fourier transform. The energy minimization stage was performed with the steepest descent algorithm up to 50,000 steps. The system was then equilibrated in two phases: first using the NVT ensemble with the Nosé-Hoover thermostat for 125,000 steps, followed by NPT equilibration using the Verlet cut-off scheme [28]. The production simulations were run in the NPT ensemble with Parrinello-Rahman pressure coupling at a temperature of 31^0 K [29]. The entire simulation series was performed with a total production time of 20 ns. Free energy calculations were performed using gmx_MMPBSA combined with Uni-GBSA, applying the Molecular Mechanics Generalized Born Surface Area (MMGBSA) method.

3. Results and discussion

Virtual screening is one of the most powerful tools in the field of molecular modelling, where it has been proven to accelerate the process of discovery of drug. Its applications extend beyond drug development, including the discovery of novel sweeteners. For example, Shoshan-Galeczki et al. utilized virtual screening with a dataset of food-related chemicals (FooDB) and FDA GRAS compounds, employing molecular docking and fingerprint analysis. This approach identified potential sweeteners based on carbohydrate analogs [8]. Similarly, Goel et al. successfully identified potential sweeteners from plant secondary metabolites using a combination of molecular docking and taste classification models [9]. Inspired by the latter approach, this study aims to discover novel artificial sweeteners from commercially available compounds.

Shape-based similarity is a method used to evaluate the resemblance of one molecule to another. This approach relies on the three-dimensional structure of a molecule, represented by its volume or surface. A compound is generally considered similar to a template if there is a significant overlap between their volumes [30]. Due to its efficiency and accuracy, this method is commonly employed as an initial step in virtual screening workflows as shown in Figure 1 [31]. In this study, vROCS software was employed to screen the Mcule HTS database, which consists of over 1.7 million compounds [10]. The structure of saccharin was selected as the template for shape similarity due to its favorable molecular properties, including a compact size and the absence of rotatable bonds. These characteristics were considered advantageous as they minimize the likelihood of diverse interaction modes with the taste receptor and reduce variability in pharmacokinetics and toxicity profiles [32,33].

The ROCS algorithm is used to measure the similarity between two compounds by evaluating not only their three-dimensional shape similarities but also their chemical similarities, as defined by pharmacophore features. This similarity is quantified using Tanimoto Combo scores, which range from 0 to 2; higher scores indicate greater similarity in both shape and features [10,34]. In this study, the default feature of saccharin in the software (Figure 2) was utilized as its already conformed to the AHBX glucophore model of Shallenberger-Acree-Kier [35,36]. Tanimoto Combo score threshold of 1.2 was applied for screening, since it has been widely employed in previous virtual screening studies [37,38]. As a result, 463 compounds with Tanimoto Combo scores ranging from 1.55 to 1.20 were successfully identified. Furthermore, the assessment of structural diversity among the hit compounds, performed using PCA analysis of ECFP4 fingerprints [39], confirmed that the hits occupy a diverse structural landscape (Figure 3). In this visualization, spatial proximity indicates structural similarity, while the color of the points corresponds to the ROCS TanimotoCombo score.

The obtained compounds were subsequently classified in silico for their predicted taste profiles using the VirtualTaste and Virtuous Sweet/Bitter web servers in a parallel way [16,17]. Both

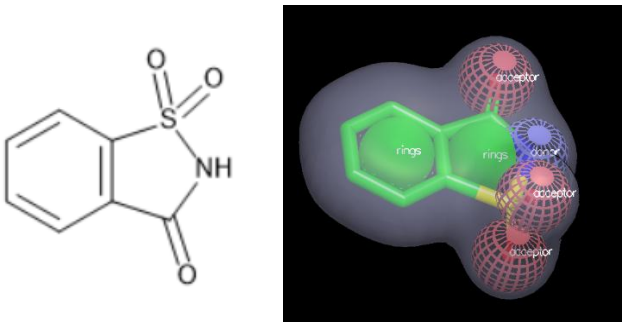

Figure 2. 2D structure of saccharin (left) and its structural features used as search query for the virtual screening step (right)

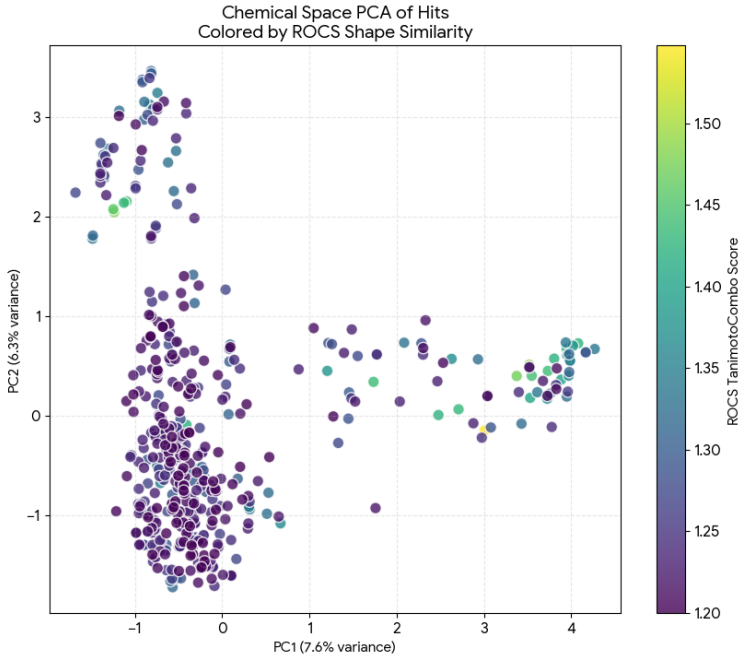

Figure 3. Chemical space visualization of hit compounds using PCA plot

tools predict the taste of compounds based on training datasets of various compounds with known taste profiles, utilizing machine learning algorithms. VirtualTaste employs a Random Forest algorithm, while Virtuous Sweet/Bitter uses a Light Gradient-Boosting machine. This process identified two compounds that satisfied both prediction methods (Figure 4). Structural analysis revealed that both compounds contained moieties commonly associated with sweetness, such as polyhydroxy groups and amino acid-like functional groups [36]. However, Compound 2 was also predicted to have a potential bitter taste by the VirtualTaste web server. This prediction is likely attributable to the presence of a methylthiane moiety, which has been previously linked to bitterness in sucrose analogs [40].

The subsequent step involved evaluating both compounds for ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties using ADMETLab 3.0 and then compared with saccharin (Table 1) [15]. The analysis revealed that Compound 1 exhibited unfavorable absorption characteristics, as indicated by its predicted CaCo-2 permeability, which could potentially be advantageous as a non-caloric sweetener. Additionally, Compound 1 was identified as a predicted substrate of CYP2C9, an enzyme integral to the biotransformation of endogenous molecules such as steroids, melatonin, retinoids, and arachi-

Table 1. ADMET analysis

	Compound 1	Compound 2	Saccharine
Absorption			
CaCo-2 permeability	-5.344 (Negative)	-4.965 (Negative)	-5.978 (Negative)
Pgp inhibitor	Negative	Negative	Negative
Pgp substrate	Negative	Negative	Negative
Distribution			
PPB	34 % (weak binder)	35.5% (weak binder)	94.3% (strong binder)
BBB	Negative	Moderate	Negative
Metabolism			
CYP 1A2	No interaction	No interaction	No interaction
CYP 2C19	No interaction	Substrate	No interaction
CYP 2C9	Substrate	Substrate	No interaction
CYP 2D6	No interaction	Substrate	No interaction
CYP 3A4	No interaction	No interaction	No interaction
Excretion			
T1/2	1.712 hours (short half-life)	1.434 hours (short half-life)	1.722 hours (short half-life)
Toxicity			
hERG blockers	0.024 (low probability)	0.037 (low probability)	0.013 (low probability)
Ames toxicity	0.190 (low probability)	0.114 (low probability)	0.011 (low probability)
Rat oral acute toxicity	0.220 (low probability)	0.030 (low probability)	0.066 (low probability)
Carcinogenicity	0.288 (low probability)	0.210 (low probability)	0.024 (low probability)
Human hepatotoxicity	0.357 (medium probability)	0.459 (medium probability)	0.907 (high probability)

donic acid [41]. Conversely, although Compound 2 possess the same unfavorable absorption characteristics, it was predicted that this compound exhibits moderate BBB penetration, which is unfavorable characteristic for a food additive. Furthermore, this compound also demonstrated interactions with multiple CYP isoforms, including CYP2C19, CYP2C9, and CYP2D6, and displayed a moderate plasma clearance profile. Importantly, both compounds were predicted to possess moderate hepatotoxicity. While this finding warrants cautious interpretation, it is noteworthy that saccharin itself shows a high predicted probability of hepatotoxicity. This prediction is supported by *in vivo* animal studies as well as a reported case in patient, highlighting the need for careful evaluation of potential liver-related adverse effects [42-44]. Although these findings require validation through further studies of our compound, they provide a preliminary framework for further exploration, particularly in the development of a safe novel sweetening agent [45].

Aside from its molecular structure, the interaction between sweetening agents and sweet taste receptors is crucial for understanding the underlying mechanism. However, a significant challenge lies in the absence of a 3D structure for the human T1R2-T1R3 receptor, necessitating the use of homology modeling to predict the protein structure from its primary sequence [46]. In this study, AlphaFold was utilized to construct the receptor structure, employing the ligand-binding

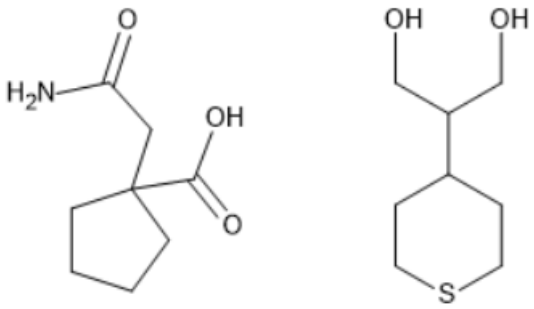

Figure 4. Compounds obtained from virtual screening process; Compound 1 (1-(2-Amino-2-oxoethyl) cyclopentane-1-carboxylic acid (left)) and Compound 2 (2-(Thian-4-yl)propane-1,3-diol (right))

Table 2. Molecular docking result

Compound	Docking score (kcal/mol)	Amino acid residue interaction		
		Hydrogen bond	Electrostatic interaction	Steric interaction
Compound 1	-77.81	C=O amide with Ser146, Glu148 C=O carboxylic acid with Tyr218, O-H carboxylic acid Ser147, Gly168, Ser170	-	C-H cyclopentane ring with Ala302
Compound 2	-71.08	O-H alcohol with Ser147, Gly168, Ser170, O-H alcohol with His145, Gly168	-	-
Saccharin	-74.96	S=O sulfonamide with Ser146, C=O lactam with Ser170	-	C=O lactam with Ser147

domain of medaka fish as a template (Figure 5) [19,24]. The results of protein structure quality analysis show that of the 852 total residues in the protein model, the majority (91.8%) are in the "most favored" region on the Ramachandran map, which reflects stable and ideal phi and psi angle conformations. A total of 6.4% of residues are in the "additionally allowed" region, which is slightly looser but still acceptable, while 1.2% of residues are in the "generously allowed" region which is less common and slightly more susceptible to distortion. Only 0.5% of residues were found in the "disallowed" region, indicating a highly unstable conformation and should be avoided. In addition, this analysis also recorded the number of glycine (69) and proline (49) residues, which are characterized by high flexibility or restriction in the protein structure, respectively. Overall, with more than 90% of the residues in the most favorable regions, the model shows good quality, meeting the standards expected for protein models with a resolution of at least 2.0 Å and an R factor of no more than 20%.

Furthermore, binding site analysis of the protein revealed the following amino acids: Asn 68, Trp 72, His 145, Ser 146, Ser 147, Gly 168, Ala 169, Ser 170, Tyr 218, Glu 301, Ala 302, and Gln 389, with a C-score of 0.41 and a cluster size of 52. The C-score represents the confidence level of the prediction, ranging from 0 to 1, where a higher score indicates greater reliability. Cluster size refers to the total number of templates in a particular cluster. Based on the modeling results using Verify3D, 65.49% of the residues achieved an averaged 3D-1D score ≥ 0.1. This means that fewer than 80% of the amino acids scored ≥ 0.1 in the 3D/1D profile. This area is located in the VFT domain of T1R2 receptor, which is in accordance with the previous study [33,47].

Molecular docking analysis was conducted using the binding site defined by key amino acids identified in the preceding step. The binding site in Molegro was specified as a spherical region, where in this study was centered at coordinates (x = 50, y = 40, z = 5) with a radius of 12. The MolDock SE (Simplex Evolution) algorithm was utilized to generate docking poses through 100 replicates, and the MolDock Score was employed to assess the resulting conformations. Both algorithms were set up to ensure the precision of hydrogen bond interactions by optimizing and enforcing the proper directionality of the hydrogen bonds formed. The findings indicate that although all compounds showed comparable results, Compound 1 exhibits a slightly superior binding score (-77.81 kcal/mol) compared to both Saccharin (-74.96 kcal/mol) and Compound 2 (-71.08 kcal/mol). Additionally, the binding interaction patterns reveal that most compounds interact with the amino acid residues identified through COACH analysis (Table 2). Compound 1 has shown a higher amount of identical hydrogen bond interactions to the predicted amino acid residues compared to other compounds. Compound 1 exhibits hydrogen bond interactions contributed by both its carboxylic acid and amide moiety. In contrast, Compound 2 is predicted to display lower sweetness, attributed to the absence of significant steric and electrostatic interactions. Although it contains a bulky thianylpropane moiety, this group does not engage in any interactions with the surrounding amino acid residues. The detailed plot of ligand-amino acid residues interaction can be seen in Supplementary File.

Ultimately, molecular dynamics simulation of three complexes for 20 ns showed profile of ligand-protein stability. The RMSD plots (Figure 6) show the differences in complex stability over the 20 ns simulation. Saccharin has the lowest and most stable RMSD, generally below 0.4 nm, indicating that the Saccharin-receptor complex maintains a consistent conformation throughout the simulation. This is mainly due to the relatively rigid and planar structure of saccharine. Meanwhile Compound 1 has a slightly higher RMSD, ranging from 0.4-0.7 nm, but remains relatively stable without significant fluctuations, supporting the docking results indicating good affinity for the receptor. In contrast, Compound 2 exhibits the highest RMSD, reaching 1.25-1.7 nm with significant fluctuations since the beginning of the simulation, indicating that the complex is less stable and undergoes significant conformational changes. Overall, these RMSD patterns are consistent with affinity, saccharin is the most stable, followed by compound 1, while compound 2 exhibits the lowest stability during molecular dynamics.

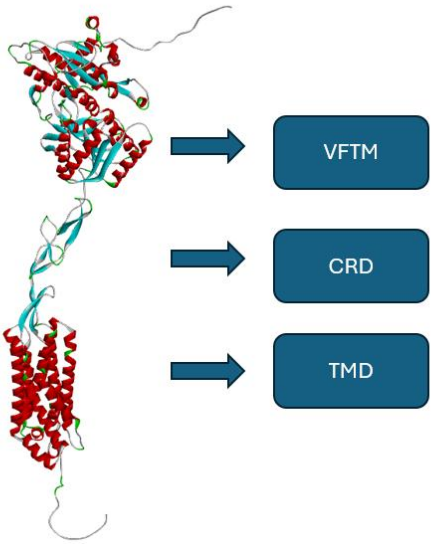

Figure 5. 3D structure of T1R2-T1R3 receptor constructed from homology modelling with its domain

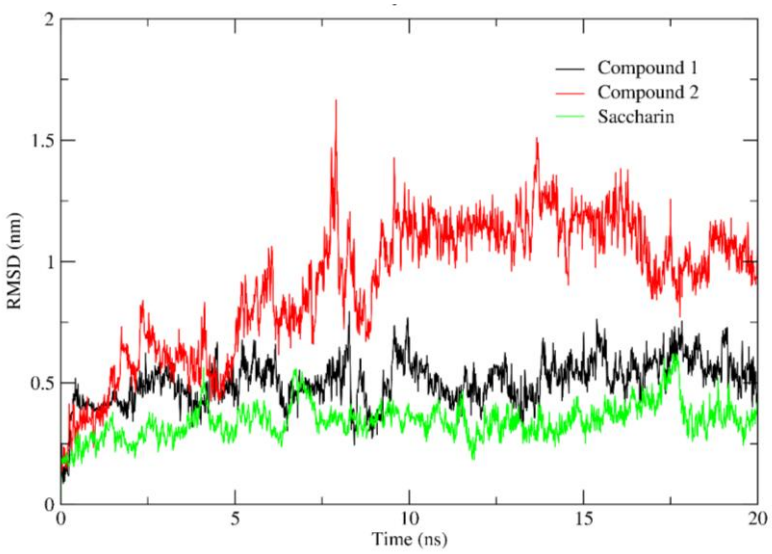

Figure 6. RMSD plot of ligand-protein interaction

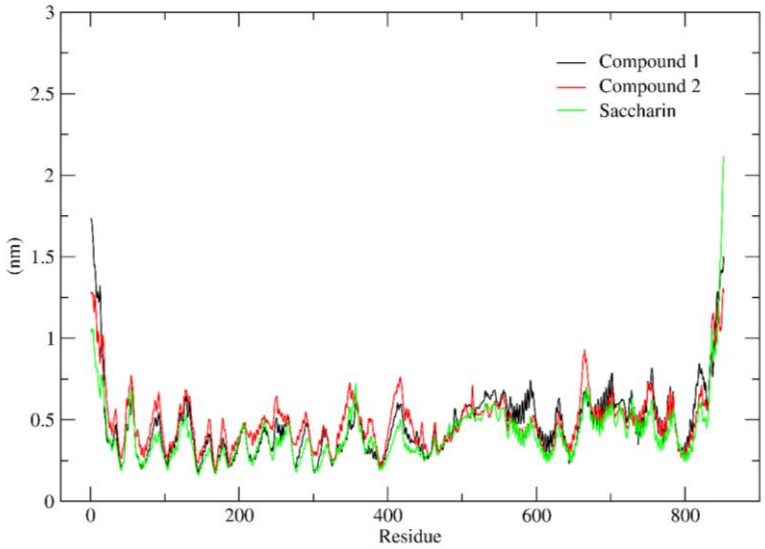

Figure 7. RMSF plot of protein residues in the presence of ligand

The RMSF plot (Figure 7) shows the fluctuation levels of key residues in the binding pocket for the three complexes during MD simulations. Saccharin generally has induced the lowest RMSF values at almost all residues, such as His145 (0.164 nm), Ser146 (0.159 nm), and Ser147 (0.190 nm), indicating that saccharin binding makes this region more stable. Compound 1 shows a fluctuation pattern that is relatively similar to Saccharin, with slightly higher RMSF values but still within the stable range, for example Ser147 (0.209 nm) and Ser170 (0.194 nm), thus supporting the stability of the interaction as reflected in the docking results. In contrast, Compound 2 shows the highest fluctuations at most residues, such as Ser147 (0.284 nm), Glu148 (0.314 nm), Tyr218 (0.339 nm), and Ala302 (0.303 nm), indicating that this complex is less stable and more dynamic in the pocket. Overall, this RMSF pattern shows that Saccharin and Compound 1 are able to maintain a more rigid binding environment than Compound 2, thus in line with better binding affinity.

Free energy calculation using molecular mechanics with generalized born surface area (MMGBSA) results show that Saccharin has the strongest binding energy with a total value of ap-

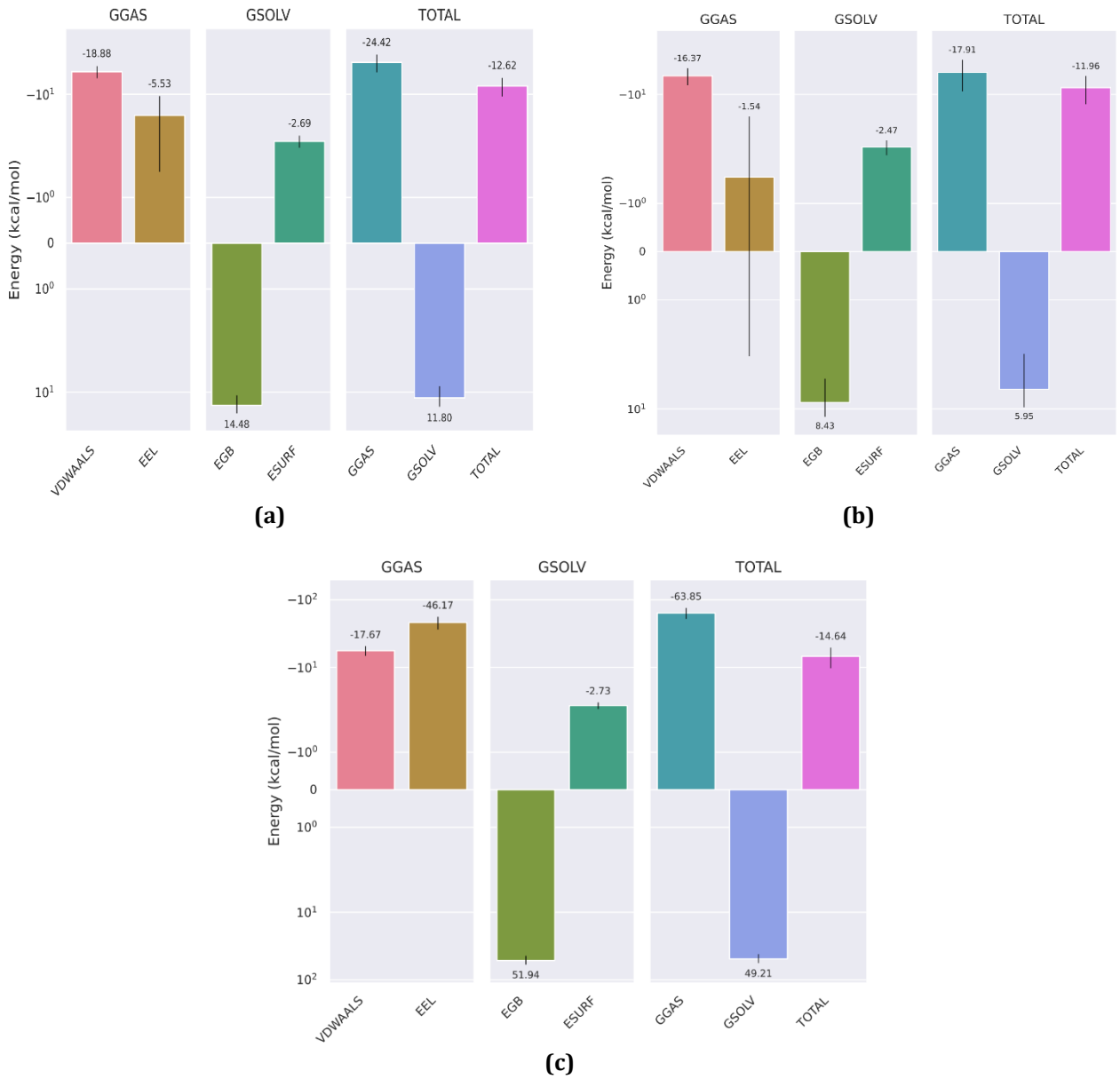

Figure 8. Binding free energy analysis of the three ligands: (a) Compound 1 shows stable interactions; (b) Compound 2 displays weaker energetic contributions; and (c) Saccharin exhibits the strongest and most consistent binding energy

proximately -14.64 kcal/mol, reflecting the stability of its interaction as a reference sweetener (Figure 8). Compound 1 also shows a fairly stable energy of approximately -12.62 kcal/mol, which is in line with the docking results and supports its position as a prime candidate for the virtual screening process. Meanwhile, Compound 2 has a total energy of approximately -11.96 kcal/mol, which is weaker than the other two ligands. Overall, these energy patterns strengthen the finding that Saccharin and Compound 1 are able to maintain a more stable interaction during molecular dynamics, while Compound 2 shows a lower affinity.

Hydrogen bond occupancy analysis (Table 3) shows the stability of interactions between key residues of the sweetener receptor and the three ligands tested during molecular dynamics simulations. Saccharin has the most stable hydrogen bond pattern, characterized by very high occupancy especially in the Ser147-Side (42.66%), Ser147-Main (12.44%), and Ser170-Side (8.39%)

Table 3. Hydrogen bond occupancy of Compound 1, Compound 2, and Saccharin with key residues during molecular dynamics simulation

Donor	Acceptor	Occupancy (%)
Ser147-Main	Compound 1-Side	3.3
Gln389-Side	Compound 1-Side	1.2
Val277-Main	Compound 1-Side	2
Ser147-Side	Compound 1-Side	1
Glu148-Main	Compound 1-Side	0.35
Ser170-Main	Compound 1-Side	0.25
Ser147-Side	Compound 2-Side	0.35
Ser147-Main	Compound 2-Side	0.25
Ser147-Side	Saccharin-Side	42.66
Ser147-Main	Saccharin-Side	12.44
Saccharin-Side	Ser170-Side	8.39
Ser170-Main	Saccharin-Side	2.7
Saccharin-Side	Asp190-Side	0.4
Saccharin-Side	Tyr218-Side	0.75

interactions, confirming its role as a reference ligand with strong affinity. Compound 1 shows several fairly stable hydrogen bonds, such as Ser147-Main (3.3%), VAL277-Main (2.0%), and Gln389-Side (1.2%), indicating that although its binding is not as strong as saccharin, this ligand is still able to maintain a structurally relevant interaction pose in the receptor pocket. In contrast, Compound 2 only produces marginal interactions with occupancy in the range of 0.25-0.35%, indicating a weaker and less stable binding throughout the simulations. Overall, these results support the docking findings that place Compound 1 as a sweetener candidate compared to Compound 2, while also demonstrating the consistency of saccharin's dynamic behavior as a template ligand.

4. Conclusions

This study successfully identified novel artificial sweetener candidates using molecular modeling techniques, combining shape-based virtual screening, taste classification, ADMET evaluation, homology modeling, molecular docking, and molecular dynamics. Two promising compounds were discovered, with Compound 1 demonstrating superior binding affinity and a favorable interaction profile with the human T1R2-T1R3 sweet taste receptor based on its docking score. Despite these advancements, further research is needed to both verify the actual taste (electronic tongue analysis, hedonic taste evaluation) and validate the safety, efficacy, and sensory properties of these compounds through in vitro and in vivo studies.

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