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Computational Screening of Functional Monomers for Esculetin Recognition Using a Semiempirical Tight-Binding Approach

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ABSTRACT

Esculetin is a bioactive coumarin derivative with reported antioxidant, anti-inflammatory, and anticancer activities. Despite its pharmacological relevance, achieving selective molecular recognition of esculetin in complex systems remains challenging. Computational screening of functional monomers offers a rational strategy to identify candidates capable of forming stable noncovalent interactions with the target molecule. In this study, 21 monomers were evaluated using a semiempirical extended tight-binding (xTB) approach. Initial screening was performed through automated interaction site screening (aISS) to estimate interaction energies. The aISS results identified 4-vinylbenzeneboronic acid as having the most favorable interaction energy (-312.87 kcal/mol), followed by 2-Acrylamido-2-methyl-1-propanesulfonic acid (-25.34 kcal/mol), p-vinylbenzoic acid (-24.71 kcal/mol), trans-3-(3-pyridyl)acrylic acid (-23.04 kcal/mol), and 9-vinylcarbazole (-22.17 kcal/mol). To evaluate dynamic stability, selected complexes were subjected to molecular dynamics simulations. The results showed that 2-Acrylamido-2-methyl-1-propanesulfonic acid exhibited the lowest average energy (-76.301 kcal/mol), followed by p-vinylbenzoic acid (-70.03 kcal/mol) and 4-vinylbenzeneboronic acid (-69.70 kcal/mol). Metadynamics simulations further confirmed this trend, with total energy (Etot) values of -76.23 kcal/mol, -69.96 kcal/mol, and -69.64 kcal/mol for the same monomers, respectively. The consistency between molecular dynamics and metadynamics analyses indicates that 2-Acrylamido-2-methyl-1-propanesulfonic acid forms the most energetically stable complex with esculetin under simulated conditions. This study provides a computational basis for selecting functional monomers for esculetin recognition systems and supports further experimental validation.

Keywords: Esculetin, Monomer, Automated Interaction Site Screening, Molecular Dynamics, Extended tight-binding

Introduction

Esculetin is a bioactive coumarin derivative with well-documented antioxidant, anti-inflammatory, and anticancer activities [1]. It occurs naturally in plants such as Sonchus grandifolius, Aesculus turbinata, and Pluchea indica, and its pharmacological effects are largely attributed to its catechol moiety, which enables efficient scavenging of reactive oxygen and nitrogen species [2]. Mechanistically, esculetin modulates key inflammatory and oxidative pathways, including NF-κB, MAPK, TGF-β signaling, and PI3K/FoxO1 cascades, supporting its therapeutic relevance [2] [3]. Despite these promising properties, selective molecular recognition of esculetin in complex systems remains a challenge, particularly for analytical and separation applications.

Molecular recognition strategies such as molecularly imprinted polymers (MIPs) have been widely investigated for selective extraction and sensing applications due to their robustness and chemical stability [4]. Although MIPs are typically synthesized through copolymerization of functional monomers and crosslinkers around a template molecule, rational monomer selection remains a critical determinant of binding specificity

and affinity [5]. Previous studies have reported that 4-vinylpyridine-based polymers exhibit superior recognition toward esculetin compared with methacrylic acid and acrylamide systems [6]. Previous studies on esculetin-imprinted polymers have mainly focused on a limited number of conventional monomers, such as methacrylic acid and 4-vinylpyridine, with evaluation often based only on static interaction analysis or experimental performance [7] [8]. Comprehensive computational screening integrating aISS, molecular dynamics, and metadynamics for systematic comparison of multiple monomer candidates toward esculetin recognition remains limited.

Computational chemistry offers an efficient strategy to screen monomer-template interactions prior to experimental validation. In particular, semiempirical extended tight-binding (xTB) methods provide a balanced compromise between computational cost and quantum mechanical accuracy. The GFN-xTB family, enables reliable geometry optimization, conformational sampling, and noncovalent interaction analysis across large molecular systems [9]. GFN2-xTB, in particular, incorporates multipole electrostatics and density-dependent dispersion corrections, improving the description of hydrogen bonding and π-π interactions that are central to monomer-esculetin complex formation [10]. Compared with conventional aISS alone, xTB-based molecular dynamics and metadynamics simulations allow a more realistic evaluation of energetic stability and configurational behavior over time.

Based on these considerations, this study performs a computational screening of functional monomers for esculetin recognition using automated interaction site screening (aISS), molecular dynamics, and metadynamics within the extended tight-binding framework. Interaction energies and stability profiles are evaluated to identify monomers capable of forming energetically favorable and dynamically stable complexes with esculetin. By integrating aISS-based affinity estimation with enhanced sampling simulations, this work provides a quantum chemically informed foundation for rational monomer selection in esculetin recognition systems.

METHODS

Automated Interaction Site Screening (aISS)

A total of 21 functional monomers were selected for computational screening based on the availability of their chemical structures in public databases [5]. The electronic properties of the esculetin molecule and monomers were calculated using the geometries, frequencies, and non-covalent interactions extended tight binding (GFNn-xTB) method [11]. These calculations were performed on.xyz coordinate files for each molecule. An initial interaction energy screening was conducted using a grid-based approach to identify potential interaction sites. Three search methods were employed: pocket search, stack search, and angular search, each assessing different possible molecular interaction configurations. DMSO was employed as an implicit solvent model during the screening calculations. Once interaction sites were identified, a genetic algorithm was applied to optimize the configuration of the fragments. Automated Interaction Site Screening (aISS) was employed to identify favorable monomer-esculetin interaction geometries. The generated complexes were subsequently optimized and evaluated using the GFN2 [11]. This entire process was executed via Linux command lines using xTB software. The binding energies and types of chemical bonds, were analyzed using Biovia Discovery Studio.

Molecular Dynamics

The optimized structures obtained from aISS were subjected to molecular dynamics simulations using xTB. The simulations were conducted at 298.15 K for a total duration of 10 nanoseconds (ns), with a time step of 4 femtoseconds (fs). The NVT ensemble (constant Number of particles, Volume, and Temperature) was applied to maintain consistent system conditions throughout the simulation. To enhance simulation stability, the effective mass of hydrogen atoms was increased by a factor of 4. The SHAKE algorithm was employed to constrain bonds involving hydrogen atoms. Self-consistent charge (SCC) convergence was set with an accuracy tolerance of 2.0. Initial velocities were generated randomly following the Maxwell-Boltzmann distribution [9]. Molecular dynamics simulations were performed using module

under gas-phase conditions without an explicit or implicit solvent model. Root mean square deviation (RMSD) was used to analyze molecular motion, and the results were visualized using visual molecular dynamics (VMD) [12].

Metadynamics

The final structures from molecular dynamics simulations were further analyzed using metadynamics to account for RMSD-based biases. Several parameters were set for metadynamics simulations. The save parameter specified the maximum number of structures meeting RMSD criteria, while kpush defined the scaling factor for these criteria. The alp parameter determined the width of Gaussian potentials used in RMSD calculations. The coord parameter referred to an external file initializing RMSD criteria, and atoms specified the list of atoms considered in RMSD calculations (defaulting to all atoms if unspecified). The simulation results included potential energy (Epot), accurate SCC potential energy (Epot SCC), kinetic energy (Ekin), total energy (Etot), and system temperature in Kelvin (T), which reflected the average kinetic energy of the particles. All simulations were conducted using xTB [9].

RESULT AND DISCUSSION

A total of 21 candidate monomers were analyzed using automated interaction site screening (aISS) with esculetin as the template. The aISS method is designed to automatically predict the non-covalent interaction geometry, binding energy of complex molecular systems, and identify as well as analyze the potential interactions between monomers and esculetin.

The results of the aISS analysis (Table 1) revealed three monomers with the most negative interaction energies with esculetin. These monomers are 4-vinylbenzeneboronic acid (-312.87 kcal/mol), 2-Acrylamido-2-methyl-1-propanesulfonic acid (-25.34 kcal/mol), p-vinylbenzoic acid (-24.71 kcal/mol). The negative interaction energy values reflect the strength of attraction between the monomers and the target fragment, which is critical for forming stable complexes through non-covalent interactions. The binding affinity, hydrogen bonding, non-classical hydrogen bonds, and π-π interactions are key factors influencing the stability and strength of these interactions [13]. Binding affinity, measured in kcal/mol, quantifies the interaction strength between esculetin and the monomers [14]. Comparing the binding energy of each template-monomer complex helps to determine the level of interaction and the type of binding involved. A more negative binding energy indicates stronger binding interactions [14].

Other factors, such as the choice of solvent, also play a crucial role in determining the stability of the complex. Selecting an appropriate solvent can minimize intermolecular disruptions and maximize interactions between the monomer and the target molecule. Using solvents with compatible polarity enhances the stability of the complex, leading to molecularly imprinted polymers with higher selectivity and adsorption capacity [15]. In this study, dimethyl sulfoxide (DMSO) was used as the solvent in the aISS simulations due to its

Table 1. Automated interaction site screening

No	Monomer	Interaction energy (kcal/mol)
1	2-Acrylamido-2-methyl-1-propanesulfonic acid	-25.34
2	2-Hydroxyethyl methacrylate	-14.25
3	2-Naphthyl methacrylate	-19.07
4	2-Vinylpyridin	-14.52
5	4-Cyanostyrene	-13.13
6	4-Vinylbenzeneboronic acid	-312.87
7	4-Vinylpyridine	-15.27
8	9-Vinylcarbazole	-22.17
9	Acrylamide	-14.89
10	Acrylic acid	-13.36
11	Acrylonitrile	-11.49
12	Allylamine	-14.70
13	Itaconic acid	-14.54
14	Methacrylamide	-15.32
15	Methacrylic acid	-17.76
16	N-(2-Hydroxyethyl)acrylamide	-16.68
17	N-(3-aminopropyl) methacrylamide	-15.67
18	N-vinylpyrrolidone	-10.10
19	p-vinylbenzoic acid	-24.71
20	Styrene	-11.42
21	trans-3-(3-pyrydyl)acrylic acid	-23.04

excellent hydrogen bond-accepting (HBA) ability. DMSO forms strong intermolecular hydrogen bonds with esculetin, contributing to stabilization of the complex. Furthermore, DMSO significantly influences the absorption and emission spectra shifts of esculetin, indicating its pronounced stabilizing effect [16]. Among the three monomers identified, 4-vinylbenzeneboronic acid stands out due to its exceptionally strong interaction energy, suggesting its high potential for effective molecular imprinting with esculetin.

Based on the Automated Interaction Site Screening results presented in Table 1, 4-vinylbenzeneboronic acid exhibits the lowest interaction energy (-312.87 kcal/mol) among all candidate monomers. This markedly negative value suggests a very strong interaction with the target fragment, esculetin. Structurally, 4-vinylbenzeneboronic acid consists of three key functional groups: boronic acid ($-B(OH)_2$), phenyl, and vinyl groups.

The boronic acid moiety is known to form reversible covalent interactions with cis-diol-containing compounds, including phenolic structures such as esculetin. Previous studies have demonstrated that boronic acid-containing monomers can enhance affinity in the formation of molecularly imprinted polymers (MIPs) for molecular recognition applications [15]. The phenyl ring contributes to complex stabilization through π-π stacking interactions with the aromatic system of esculetin [17]. Meanwhile, the vinyl group supports free-radical polymerization, preserving the integrity of the imprinted cavity and ensuring structural stability of the polymer matrix [18] [19].

Despite the highly negative interaction energy observed for 4-vinylbenzeneboronic acid (-312.87 kcal/mol), the result should be interpreted cautiously because non-covalent interaction energies reported in aISS studies are typically much smaller. This unusually strong interaction may be associated with the interaction between the boronic acid moiety and the hydroxyl groups of esculetin. In comparison, 2-acrylamido-2-methyl-1-propanesulfonic acid (-25.34 kcal/mol), p-vinylbenzoic acid (-24.71 kcal/mol), trans-3-(3-pyridyl)acrylic acid (-23.04 kcal/mol), and 9-vinylcarbazole (-22.17 kcal/mol) exhibited interaction energies within a more chemically reasonable range.

2-Acrylamido-2-methyl-1-propanesulfonic acid contains both amide and sulfonic acid functional groups, which enable hydrogen bonding and electrostatic interactions with hydroxyl and carbonyl groups of esculetin. Hydrogen bonding plays a primary role in stabilizing ligand-receptor complexes by influencing molecular orientation and specificity. Similarly, p-vinylbenzoic acid and trans-3-(3-pyridyl)acrylic acid contain aromatic rings capable of π-π stacking interactions, as well as polar functional groups that may participate in hydrogen bonding [17].

9-vinylcarbazole, characterized by its extended aromatic structure, likely stabilizes the complex predominantly through π-π stacking and van der Waals interactions. Although van der Waals forces are weaker than hydrogen bonding, they contribute cumulatively to overall binding stability [14]. Other monomers in Table 1, such as methacrylic acid (-17.76 kcal/mol), N-(2-hydroxyethyl)acrylamide (-16.68 kcal/mol), methacrylamide (-15.32 kcal/mol), and 4-vinylpyridine (-15.27 kcal/mol), exhibit moderate interaction energies. These values are consistent with commonly reported functional monomers in MIP synthesis, where hydrogen bonding and ionic interactions contribute significantly to recognition properties [20].

Various non-covalent interactions collectively determine the strength and specificity of ligand-receptor binding. Hydrogen bonding occurs between a hydrogen atom bound to an electronegative atom and a lone electron pair on another atom [14]. π-π stacking interactions arise from electronic interactions between aromatic rings [17]. Van der Waals forces provide additional stabilization through dispersion interactions [14], while ionic interactions between oppositely charged groups further enhance affinity [13]. The synergistic contribution of these interactions is fundamental in designing molecularly imprinted polymers with high selectivity and binding performance.

Given the unusually large interaction energy observed in Table 1, monomers with interaction energies in the range of -20 to -25 kcal/mol may represent more chemically plausible and experimentally feasible candidates for esculetin-imprinted polymer

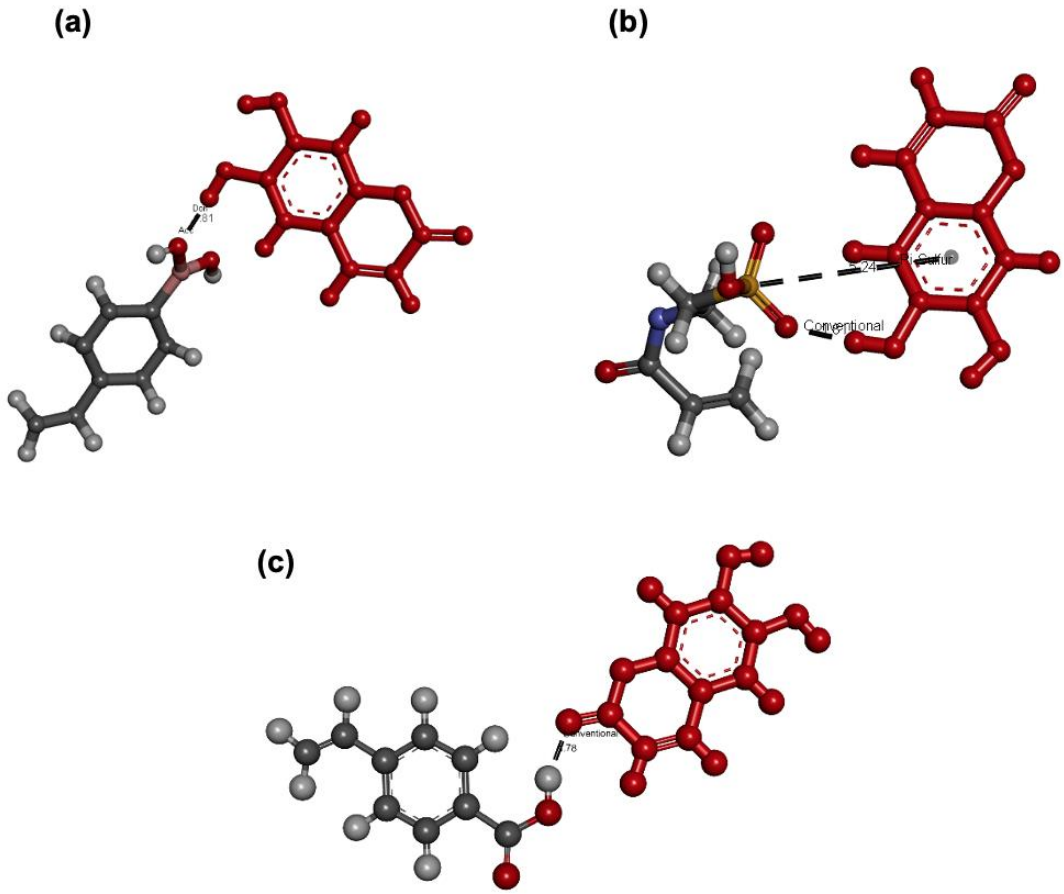

Figure 1. The three monomers showing the most negative interaction energies: (a) 4-vinylbenzeneboronic acid, (b) 2-acrylamido-2-methyl-1-propanesulfonic acid, and (c) p-vinylbenzoic acid.

development. Despite its unusually low interaction energy, 4-vinylbenzeneboronic acid was selected for further molecular dynamics and metadynamics simulations because it ranked first in the initial aISS screening. These additional simulations were performed to verify whether the strong interaction predicted by the static model remained stable under dynamic conditions. Therefore, its inclusion was intended as a validation step rather than solely as a consequence of its energy value.

Figure 1 indicates that 4-vinylbenzeneboronic acid, 2-acrylamido-2-methyl-1-propanesulfonic acid (AMPS), and p-vinylbenzoic acid form the most stable pre-polymerization complexes, as reflected by their more negative interaction energies. This stability is supported by the geometric parameters of the noncovalent interactions. AMPS forms a hydrogen bond with a distance of 1.81 Å and additionally shows a π-sulfur interaction at 5.24 Å, suggesting a cooperative contribution to complex stabilization. Similarly, 4-vinylbenzeneboronic acid exhibits a hydrogen bond distance of 1.81 Å, consistent with a strong and directional interaction, likely enhanced by the dual donor-acceptor character of the boronic acid group. Notably, p-vinylbenzoic acid presents a slightly shorter hydrogen bond distance of 1.78 Å, which typically indicates a strong and well-oriented interaction. Hydrogen bond lengths within the 1.7-2.0 Å range are generally associated with strong binding in organic systems, reinforcing the interpretation that these monomers have favorable spatial and chemical compatibility with the template. Together, the energetic and geometric data suggest that hydrogen bonding plays a dominant role, while additional interactions such as π–sulfur contacts may provide synergistic stabilization in the pre-polymerization stage.

Table 2. Energy profile of monomer-template complexes during molecular dynamics simulation

No	Monomer	Lowest Energy (Kcal/mol)	Highest Energy (Kcal/mol)	Average Energy (Kcal/mol)
1	2-Acrylamido-2-methyl-1-propanesulfonic acid	-76.34	-76.28	-76.30
2	4-vinylbenzeneboronic acid	-69.74	-69.69	-69.70
3	p-vinylbenzoic acid	-70.07	-70.02	-70.03

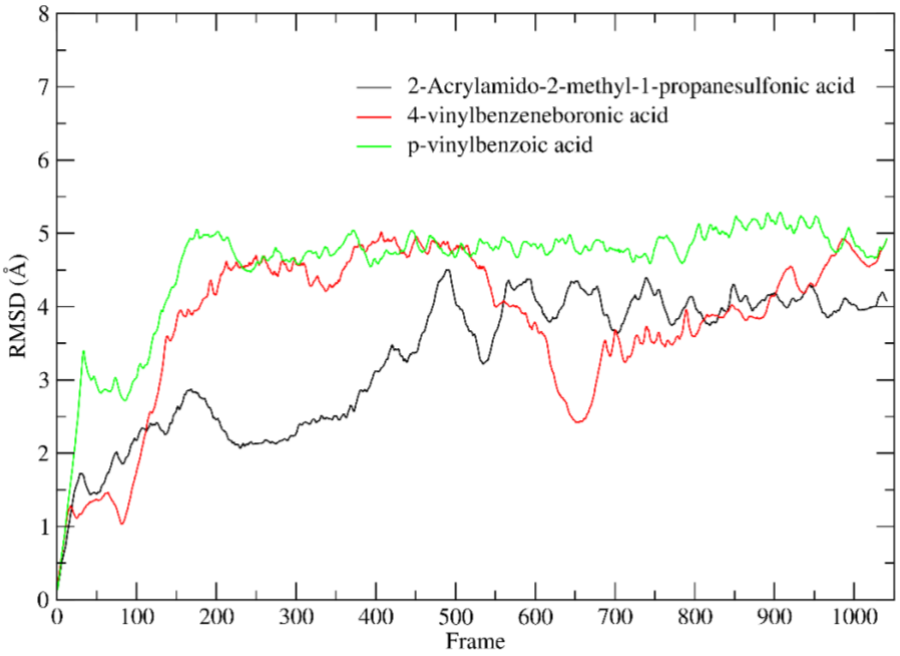

Figure 2. Root mean square deviation (RMSD) plots of the complexes formed between esculetin and the three selected monomers: 2-acrylamido-2-methyl-1-propanesulfonic acid, 4-vinylbenzeneboronic acid, and p-vinylbenzoic acid during a 10-nanosecond molecular dynamics simulation.

RMSD calculations were performed based on the molecular dynamics trajectories of the monomer-esculetin complexes. Prior to aISS, the monomers and esculetin existed as separate molecules with different atomic compositions and coordinate systems, making direct RMSD calculations inappropriate. Following complex formation during the molecular dynamics simulations, RMSD analysis could be validly applied to evaluate the conformational stability and structural behavior of the resulting complexes over time. Based on the RMSD plot in figure 2, all three monomer-template complexes exhibit an initial increase during the early frames, reflecting structural adjustment from the starting conformation toward a more energetically favorable state, followed by a relatively stable plateau phase. Quantitatively, 2-acrylamido-2-methyl-1-propanesulfonic acid exhibits the lowest average RMSD value (3.29 Å), indicating the smallest structural deviation and suggesting relatively stable conformational behavior throughout the simulation. 4-vinylbenzeneboronic acid shows a slightly higher average RMSD (3.81 Å), reflecting moderate fluctuations while still maintaining structural stability after equilibration. In contrast, p-vinylbenzoic acid presents the highest average RMSD value (4.56 Å), indicating greater structural deviation and lower dynamic stability during the simulation period with more pronounced oscillations around the 3-4 Å range, implying greater conformational flexibility within the complex. None of the systems show continuous drift or abrupt spikes after

stabilization, which indicates that all complexes remain structurally stable during the simulation window. The dynamic behavior indicates that the AMPS complex possesses the highest conformational stability among the evaluated systems, while p-vinylbenzoic acid demonstrates comparatively higher flexibility, although the complex remains globally stable during the simulation period.

As presented in Table 2, the simulations report the lowest, highest, and average potential energies for each selected monomer. The average energy value is particularly relevant, as more negative values generally indicate greater energetic stability of the complex during the simulation trajectory. Among the evaluated monomers, 2-Acrylamido-2-methyl-1-propanesulfonic acid exhibited the lowest average energy (-76.30 kcal/mol), followed by p-vinylbenzoic acid (-70.03 kcal/mol) and 4-vinylbenzeneboronic acid (-69.70 kcal/mol). The relatively narrow energy range between the lowest and highest values for each monomer suggests stable interaction profiles with minimal fluctuation throughout the simulation. Although 4-vinylbenzeneboronic acid exhibited an exceptionally low interaction energy in the aISS calculations, the average energy obtained during molecular dynamics simulations was considerably less negative. This difference indicates that the highly favorable interaction predicted by the static screening was partially reduced under dynamic conditions due to conformational fluctuations and molecular flexibility during the simulation.

Although 4-vinylbenzeneboronic acid showed the most favorable interaction energy in the aISS docking results, molecular dynamics analysis indicates that 2-Acrylamido-2-methyl-1-propanesulfonic acid forms the most energetically stable complex under dynamic conditions. This difference likely arises because aISS evaluates optimized static conformations, whereas molecular dynamics considers conformational fluctuations over time. Docking aISS primarily estimates binding affinity based on optimized static conformations, whereas molecular dynamics evaluates the temporal stability of the system and the energetic landscape. These results suggest that AMPS forms more stable hydrogen-bonding interactions during molecular dynamics and metadynamics simulations

To understand and explore the configurational space of a molecular system more comprehensively, particularly when conformational transitions involve crossing energy barriers that are difficult to sample using conventional molecular dynamics, metadynamics is employed. This method is especially useful for investigating monomer-ligand interactions in molecular systems, as it enables enhanced sampling of relevant conformational states and facilitates the estimation of energetically favorable binding structures [21]. By biasing selected collective variables, metadynamics accelerates the exploration of the free-energy landscape and provides deeper insight into interaction stability.

Metadynamics simulations performed using the xTB method generated values for potential energy (Epot), kinetic energy (Ekin), total energy (Etot), and temperature (T) for the selected monomer-esculetin complexes (Table 3). The potential energy reflects configurational stability, whereas kinetic energy and temperature describe the dynamic behavior of the system during the simulation. The total energy (Etot), which integrates both potential and kinetic contributions, serves as an indicator of system stability under enhanced sampling conditions.

Table 3. Thermodynamic parameters of monomer-template complexes derived from metadynamics simulation

No	Monomer	*Metadynamics*			
		Epot (Kcal/mol)	Ekin (Kcal/mol)	Etot (Kcal/mol)	T (Kelvin)
1	2-Acrylamido-2-methyl-1-propanesulfonic acid	-76.28	4.25	-76.23	344.00
2	4-vinylbenzeneboronic acid	-69.69	4.36	-69.64	344.21
3	p-vinylbenzoic acid	-70.01	4.43	-69.96	373.20

Among the evaluated monomers, 2-acrylamido-2-methyl-1-propanesulfonic acid exhibited the lowest total energy (-76.23 kcal/mol), with an Epot value of -76.28 kcal/mol and Ekin of 4.25 kcal/mol at 344.00 K. This indicates a more energetically favorable and stable complex formation with esculetin. In comparison, p-vinylbenzoic acid showed a total energy of -69.96 kcal/mol (Epot -70.01 kcal/mol, Ekin 4.43 kcal/mol) at 373.20 K, while 4-vinylbenzeneboronic acid presented a total energy of -69.64 kcal/mol (Epot -69.69 kcal/mol, Ekin 4.36 kcal/mol) at 344.21 K.

The consistently lower potential and total energy values observed for 2-acrylamido-2-methyl-1-propanesulfonic acid suggest greater configurational stability during enhanced sampling. Although the three monomers display relatively close kinetic energy values, the difference in potential energy contributions appears to determine the stability ranking. These findings are in agreement with the molecular dynamics results, where 2-acrylamido-2-methyl-1-propanesulfonic acid also demonstrated the most favorable average energy profile.

Automated Interaction Site Screening (aISS) is used as an initial screening based on static configurations to identify candidate monomers with high interaction affinity, while molecular dynamics evaluates the stability of the complex under dynamic conditions by considering thermal fluctuations and conformational changes throughout the simulation time [22]. Metadynamics extends the exploration of conformational space by allowing the system to bypass local energy minima, thus providing additional information regarding the stability of the complex in various conformational states [23]. Therefore, the energy values from the three methods cannot be directly compared because they are obtained from different approaches. In this study, aISS results are used for the initial selection of candidate monomers, while molecular dynamics and metadynamics results are considered more representative for evaluating complex stability because they consider molecular flexibility and system dynamics more realistically. Monomers that exhibit favorable and stable energies across these approaches are considered to have greater potential for forming selective and stable recognition sites in future MIP design. The metadynamics analysis strengthens the conclusion that sulfonic acid-containing monomers exhibit a more stable energetic interaction with esculetin under dynamic and enhanced sampling conditions. Nevertheless, these computational findings should be interpreted within the theoretical framework applied, and experimental validation remains necessary to confirm practical applicability.

CONCLUSIONS

This study shows that a semiempirical extended tight-binding approach can be effectively used to screen and prioritize functional monomers for esculetin recognition. From the initial screening of 21 monomers using automated interaction site screening (aISS), 4-vinylbenzeneboronic acid exhibited the most negative interaction energy in the static aISS analysis, indicating strong initial binding affinity. However, molecular dynamics and metadynamics simulations provided a more realistic view of how these complexes behave over time. The molecular dynamics results indicated that 2-acrylamido-2-methyl-1-propanesulfonic acid had the lowest average energy (-76.30 kcal/mol), suggesting high energetic stability, while p-vinylbenzoic acid and 4-vinylbenzeneboronic acid also maintained stable energy profiles within a comparable range. This trend was supported by metadynamics, where all three monomers showed favorable total energy (Etot) values, with 2-acrylamido-2-methyl-1-propanesulfonic acid being slightly more stable under enhanced sampling conditions. The dynamic simulations further highlight the stability of 2-acrylamido-2-methyl-1-propanesulfonic acid. Overall, the computational results suggest that 4-vinylbenzeneboronic acid, 2-acrylamido-2-methyl-1-propanesulfonic acid, and p-vinylbenzoic acid are promising monomer candidates for esculetin recognition systems.

CONFLICT OF INTEREST

The authors declare there are no competing interests.

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REFERENCES

[1]. Garg SS, Gupta J, Sahu D, Liu C-J. Pharmacological and Therapeutic Applications of Esculetin. Int J Mol Sci. 2022;23(20):12643. https://doi.org/10.3390/ijms232012643
[2]. Liang C, Ju W, Pei S, Tang Y, Xiao Y. Pharmacological Activities and Synthesis of Esculetin and Its Derivatives: A Mini-Review. Molecules. 2017;22(3):387. https://doi.org/10.3390/molecules22030387
[3]. Cai T, Cai B. Pharmacological activities of esculin and esculetin: A review. Medicine (Baltimore). 2023;102(40):e35306. https://doi.org/10.1097/MD.0000000000035306
[4]. Asnawi A, Febrina E, Aligita W, Aman LO, Razi F. Molecular docking and molecular dynamics study of 3-hydroxybutyrate with polymers for diabetic ketoacidosis-targeted molecularly imprinted polymers. J Pharm Pharmacogn Res. 2024;12(5):822–36. https://doi.org/10.56499/jppres23.1926_12.5.822
[5]. Gunawan U, Ibrahim S, Ivansyah AL, Damayanti S. Unraveling multi-template molecularly imprinted polymer for selective extraction of triazole antifungals: Theoretical and experimental investigation. React Funct Polym. 2024;200:105915. https://doi.org/10.1016/j.reactfunctpolym.2024.105915
[6]. Razwan Sardar M, Jin Y, Kong G, Li H, Lin J-M. Molecularly imprinted polymer for pre-concentration of esculetin from tobacco followed by the UPLC analysis. Sci China Chem. 2014;57(12):1751–9. https://doi.org/10.1007/s11426-014-5180-1
[7]. Suryana S, Mutakin, Rosandi Y, Hasanah AN. An Update on Molecularly Imprinted Polymer Design through a Computational Approach to Produce Molecular Recognition Material with Enhanced Analytical Performance. Molecules. 2021;26(7):1891. https://doi.org/10.3390/molecules26071891
[8]. Rajpal S, Mishra P, Mizaikoff B. Rational In Silico Design of Molecularly Imprinted Polymers: Current Challenges and Future Potential. Int J Mol Sci. 2023;24(7):6785. https://doi.org/10.3390/ijms24076785
[9]. Grimme S, Bannwarth C, Shushkov P. A Robust and Accurate Tight-Binding Quantum Chemical Method for Structures, Vibrational Frequencies, and Noncovalent Interactions of Large Molecular Systems Parametrized for All spd-Block Elements (Z = 1–86). J Chem Theory Comput. 2017;13(5):1989–2009. https://doi.org/10.1021/acs.jctc.7b00118
[10]. Bannwarth C, Ehlert S, Grimme S. GFN2-xTB - An Accurate and Broadly Parametrized Self-Consistent Tight-Binding Quantum Chemical Method with Multipole Electrostatics and Density-Dependent Dispersion Contributions. J Chem Theory Comput. 2019;15(3):1652–71. https://doi.org/10.1021/acs.jctc.8b01176
[11]. Plett C, Grimme S. Automated and Efficient Generation of General Molecular Aggregate Structures. Angew Chemie Int Ed. 2023;62(4). https://doi.org/10.1002/anie.202214477
[12]. Humphrey W, Dalke A, Schulten K. VMD: Visual molecular dynamics. J Mol Graph. 1996;14(1):33–8. https://doi.org/10.1016/0263-7855(96)00018-5
[13]. Pantsar T, Poso A. Binding Affinity via Docking: Fact and Fiction. Molecules. 2018;23(8):1899. https://doi.org/10.3390/molecules23081899
[14]. Ahmed U, Sundholm D, Johansson MP. The effect of hydrogen bonding on the π depletion and the π–π stacking interaction. Phys Chem Chem Phys. 2024;26(43):27431–8. https://doi.org/10.1039/D4CP02889A
[15]. Xu Z, Uddin KMA, Kamra T, Schnadt J, Ye L. Fluorescent Boronic Acid Polymer Grafted on Silica Particles for Affinity Separation of Saccharides. ACS Appl Mater Interfaces. 2014;6(3):1406–14. https://doi.org/10.1021/am405531n
[16]. Liu Y, Yang D, Shi D, Sun J. A TD-DFT study on the hydrogen bonding of three esculetin complexes in electronically excited states: Strengthening and weakening. J Comput Chem. 2011;32(16):3475–84. https://doi.org/10.1002/jcc.21932
[17]. Li X, Long Y, Zhang C, Sun C, Hu B, Lu P, et al. Hydrogen Bond and π-π Stacking Interaction: Stabilization Mechanism of Two Metal Cyclo-N5 --Containing Energetic Materials. ACS omega. 2022;7(8):6627–39. https://doi.org/10.1021/acsomega.1c05961
[18]. WULFF G. ChemInform Abstract: Molecular Imprinting in Cross-Linked Materials with the Aid of Molecular Templates - A Way towards Artificial Antibodies. ChemInform. 1995;26(51):1812–32. https://doi.org/10.1002/chin.199551298
[19]. Shi H, Zhuang Q, Zheng A, Guan Y, Wei D, Xu X. Study of the radical polymerization mechanism and its application in the preparation of high-performance PMMA by reactive extrusion. RSC Adv. 2023;13(11):7225–36. https://doi.org/10.1039/D2RA06441C
[20]. Mohanty M, Mohanty PS. Molecular docking in organic, inorganic, and hybrid systems: a tutorial review. Monatshefte für Chemie - Chem Mon. 2023;154(7):683–707. https://doi.org/10.1007/s00706-023-03076-1
[21]. Zuo K, Kranjc A, Capelli R, Rossetti G, Nechushtai R, Carloni P. Metadynamics simulations of ligands binding to protein surfaces: a novel tool for rational drug design. Phys Chem Chem Phys. 2023;25(20):13819–24. https://doi.org/10.1039/D3CP01388J
[22]. Olsson GD, Wiklander JG, Nicholls IA. Using Molecular Dynamics in the Study of Molecularly Imprinted Polymers. In: Molecularly Imprinted Polymers. 2021. p. 241–68. https://doi.org/10.1007/978-1-0716-1629-1_21
[23]. Bussi G, Laio A. Using metadynamics to explore complex free-energy landscapes. Nat Rev Phys. 2020;2(4):200–12. https://doi.org/10.1038/s42254-020-0153-0