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The theoretical study and prediction for chemical reactivity of carboxymethyl and succinic acid amylose grafted tanatril drug, a DFT study

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This study reports the design and theoretical evaluation of Tanatril-based prodrugs conjugated with carboxymethyl and succinic acid amylose via ester linkages to improve solubility, permeability, and action. Utilizing Density Functional Theory (B3LYP/6-31G (d,p))was used to calculate electronic descriptors (HOMO, LUMO, ΔE, η, S, χ, ω), providing insights into stability and reactivity. Molecular docking against bacterial DNA gyrase (PDB: 1UZE) showed enhanced binding affinities, with Tanatril-carboxymethyl (–8.17 kcal/mol) and Tanatril-succinic acid amylose (–11.10 kcal/mol) outperforming the parent drug. These results suggest promising candidates for further synthesis and biological testing.

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1. Introduction

Pharmaceutical research continually seeks to enhance drug efficacy, bioavailability, and targeted delivery through structural modifications of existing medications. The development of novel drug delivery systems and chemical modifications of established drugs represents a significant frontier in modern pharmaceutical science. In recent years, computational methods have emerged as powerful tools for predicting and understanding the chemical behavior of drug molecules before experimental synthesis, thereby accelerating the drug development process while reducing costs and resources [1].

Tanatril (Imidapril hydrochloride) is a common medication for hypertension and chronic heart failure that inhibits the angiotensin-converting enzyme (ACE). As a prodrug, Imidapril is metabolized converts the liver to its active form, imidaprilat, which prevents angiotensin I from being converted to angiotensin II by competitively binding to and inhibiting ACE. The strong vasoconstrictive effects of angiotensin II are inhibited by this mechanism, resulting in vasodilation and reduced blood pressure. Despite its clinical efficacy, like other ACE inhibitors, Tanatril faces challenges related to bioavailability, stability, and potential side effects, which necessitate exploration of structural modifications to enhance its pharmacological properties. Interestingly, Imidapril is a flexible choice for patients who cannot tolerate other ACE inhibitors since it has the distinct advantage over other ACE inhibitors in reducing the incidence of dry cough [2].

Polysaccharide modifications have garnered substantial notice in pharmaceutical research because they are biocompatible, biodegradable, and have versatile functionalization capabilities. Among these, amylose derivatives have shown promising applications in drug delivery systems. Pharmaceutical excipients such as succinate high amylose starch and carboxymethyl high amylose starch have been suggested for oral medication administration, demonstrating controlled release properties and pH-responsive behavior[3]. These modified polysaccharides can potentially be grafted onto drug molecules to enhance their pharmacokinetic profiles, stability, and targeted delivery.

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There remains a gap in understanding how specific amylose modifications, particularly carboxymethyl and succinic acid grafting, affect the chemical reactivity and binding properties of Tanatril. This study aims to investigate the theoretical aspects of carboxymethyl and succinic acid amylose grafted Tanatril using computational methods. By examining the electronic structure, molecular interactions, and binding properties, we seek to predict chemical reactivity and potential pharmacological advantages over the unmodified drug.

2. DFT calculation and computational method

The Gaussian-09 software package was used to carry out the quantum computations with full geometry optimizations [4]. Tanatril prodrug shape optimization was performed using cellulose derivatives as recommended carriers D (1–2) and alkyl as standards (Figure 1). Making use of (6-31G/d,p) level ab-initio Density Functional Theory (DFT) technique. A potent computational quantum mechanical technique for examining the electronic structure and characteristics of molecules is Density Functional Theory (DFT). In drug design, DFT calculations give insightful information on molecular interactions, reactivity, and stability, enabling researchers to predict the behavior of modified drug compounds before experimental synthesis [1]. The application of DFT in pharmaceutical research has grown exponentially in recent years, offering a cost-effective approach to evaluating possible medication options and comprehending the connections between structure and activity.

DFT is particularly valuable for studying the exact electrical properties of medication delivery systems and isolated drug molecules, providing information about binding affinities, reaction mechanisms, and thermodynamic properties. As Ye and colleagues explain, "DFT provides the chemical accuracy otherwise unattainable by MM, making it particularly useful for describing reaction mechanisms when drug molecules act on enzyme active sites"[1]. This level of detail is crucial for understanding how structural modifications to drugs like Tanatril might affect their interactions with target enzymes.

Previous studies have demonstrated the utility of DFT in predicting the chemical reactivity and binding properties of modified drug molecules. For instance, for oral prolonged drug release, Nabais *et al*. studied high-amylose carboxymethyl starch matrices, emphasizing the influence of substitution patterns on drug delivery kinetics [5]. Similarly, computational studies on modified ACE inhibitors have provided insights into structure-activity relationships and potential improvements in pharmacological properties [6]. Research by 7-Lemieux *et al*. explored Carboxymethyl starch excipients for the chronodelivery of drugs, demonstrating their pH-responsive properties and applications in medication delivery systems that are delayed [7].

This study employs DFT calculations to analyze the electronic structure of Tanatril and its amylose-modified derivatives. Specific functional and basis sets are selected to optimize accuracy and computational efficiency. Electronic properties, including HOMO-LUMO gaps, electron density distributions, and reactivity descriptors are calculated. Thermodynamic parameters and stability indicators are determined to compare the modified compounds with the original drug molecule.

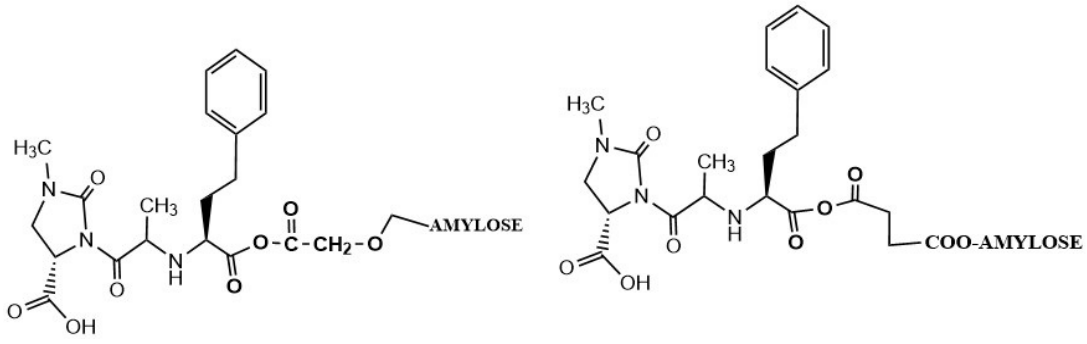


Fig. 1. Chemical structures of tanatril-amylose conjugates via ester linkages.

3. Molecular docking

Molecular docking complements DFT by predicting binding modes and affinities with target proteins. The 1UZE protein is selected as the target for docking studies of Tanatril and its modified derivatives. Docking provides information about binding modes, interaction energies, and key residue interactions that are essential for understanding the pharmacological effects of the modified compounds [8].

Recent Molecular docking research has demonstrated that ACE inhibitors interact with the enzyme through specific binding pockets and key residues. As demonstrated by Antony and colleagues, "Molecular docking studies revealed that inhibitors such as captopril and lisinopril interacted with ACE1 by making polar and hydrophobic interactions". These interactions are crucial for the inhibitory activity and can be significantly affected by structural modifications to the inhibitor molecules. Understanding these interactions at the molecular level can guide the rational design of improved ACE inhibitors with enhanced binding properties and reduced side effects.

The docking protocol involves preparation of protein and ligand structures for simulations, definition of binding site and grid parameters based on known ACE inhibitor binding regions, application of appropriate scoring functions to evaluate binding affinities, and analysis of docking poses and interaction patterns. This systematic approach allows for a comprehensive evaluation of how the amylose modifications affect the binding properties of Tanatril. According to Nong and colleagues, "The result revealed that peptides would dock into the S1 pockets of ACE, while others interacted with ACE's secondary binding site" [9], highlighting the importance of specific binding sites in ACE inhibition.

The combination of molecular docking and DFT calculations offers a comprehensive framework for evaluating the modified Tanatril derivatives. While molecular docking provides information about binding modes and affinities with the target protein, DFT calculations offer deeper insights into electronic properties and reactivity that underlie these interactions. The correlation between electronic properties from DFT and binding affinities from docking gives a deeper comprehension of the impact of structural changes and drug-target interactions.

This integrated computational approach has the potential to guide the development of improved Tanatril formulations with enhanced therapeutic properties. The expected outcomes include prediction of how carboxymethyl and succinic acid amylose modifications affect Tanatril's binding properties, identification of the most promising modified structures for experimental validation, contribution to the growing body of knowledge on polysaccharide-modified drugs, and demonstration of the value of computational approaches in pharmaceutical research.

4. Result and discussion

4.1. Study of structures for geometrical optimization

In this work, tanatrile, an ~~angiotensin-converting enzyme (~~ACE~~)~~ inhibitor, was studied to improve its physical and chemical properties through quantum chemical modeling and geometric optimization of the structures of tanatril and its derivatives obtained by modifying amylose with carboxymethyl and succinic acids. The stability, reactivity, and electronic structure of the compounds were examined using DFT using the 6–31G (d,p) basis set. The computations made it possible to estimate the energy gap (Eg), a criterion for a molecule's chemical stability and reactivity, as well as to determine changes in the energy characteristics of the HOMO and LUMO complexes.

Figure2 A shows the molecular structure of tanatrile in its native form. Part 1B shows the amylose group attached to the carboxymethyl group, which may affect its properties such as solubility, absorption, and targeted release. Finally, part 1C represents another tanatrile derivative with amylose attached to succinic acid. The molecular modeling for this study was performed using a specialized software program (Gaussian 09) to optimize the molecular geometry.

Optimization algorithms were applied to obtain the molecule shape with the lowest possible energy. This allows us to understand the realistic structure of the compound under natural conditions. The atoms are depicted in the ball-and-stick model as spheres joined by sticks that stand in for chemical bonds. The spheres are colored as follows: red stands for oxygen (O), blue for nitrogen (N), white for hydrogen (H), and dark gray or black for carbon (C).

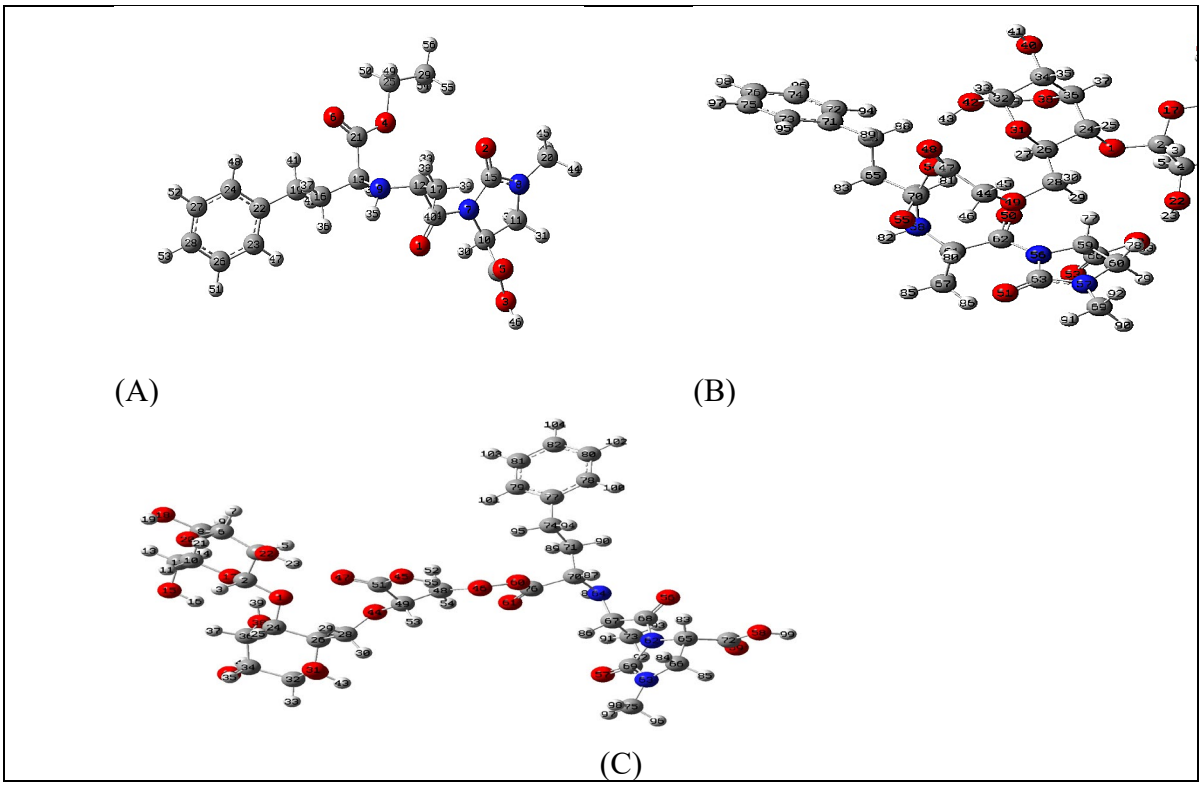


Fig. 2. Tanatril, carboxymethyl amylose-Tanatril, and succinic acid amylose-Tanatril geometry optimization structures of Tanatril and derivatives prodrug grafted determined using DFT/6-31G (d,p) technique.

Table 1. DFT/6-31G (d, p) computations for a few Tanatril and derivatives physical properties at minimum equilibrium geometries.

Property	TANATRIL-CH_2-CH_3	TANATRIL-carboxymethyl amylose	TANATRIL-succinic acid amylose
E total (hf)	**–1393.6511**	**–2763.9367**	**–2991.7585**
HOMO (ev)	**–6.27587**	**–6.29301**	**–6.36213**
LUMO (ev)	**–0.82203**	**–1.61250**	**–2.18093**
Eg (ΔE) ev	**5.45384**	**4.68051**	**4.18119**
IP (ev)	**6.27587**	**6.29301**	**6.36213**
EA (ev)	**0.82203**	**1.61250**	**2.18093**
Bond (O-R)ester	**1.49147**	**1.44013**	**1.39082**

HOMO, highest occupied molecular orbital; LUMO, lowest unoccupied molecular orbital; IP, ?; EA, ?;

4.2. Frontier molecular orbitals analysis (FMOs)

The electrical, optical, and chemical characteristics of molecules are largely determined by frontier molecular orbitals (FMOs), specifically the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) [10]. LUMO describes a molecule's capacity to take electrons, whereas HOMO represents a molecule's capacity to donate electrons. A

molecule's kinetic stability and chemical reactivity are determined by the energy gap (Eg) between these orbitals [11]. A molecule's softness and reactivity increase with decreasing gap. As seen in Fig. 3, the color red represents the positive phase while the color green represents the negative phase. With the exception of the methyl groups connected to the N atoms, the entire molecular moiety is often where the LUMO and HOMO are found. The Gauss-Sum 3.0 software was used to generate the density of states (DOS) spectra shown in Figure 4 [12]. The behavior of a molecule's molecular orbitals within a specific energy range and energy gap can be easily understood using the DOS plot. The findings show that Tanatril derivatives have a lower energy gap, which suggests that their chemical activity and potential for biological interaction have increased.

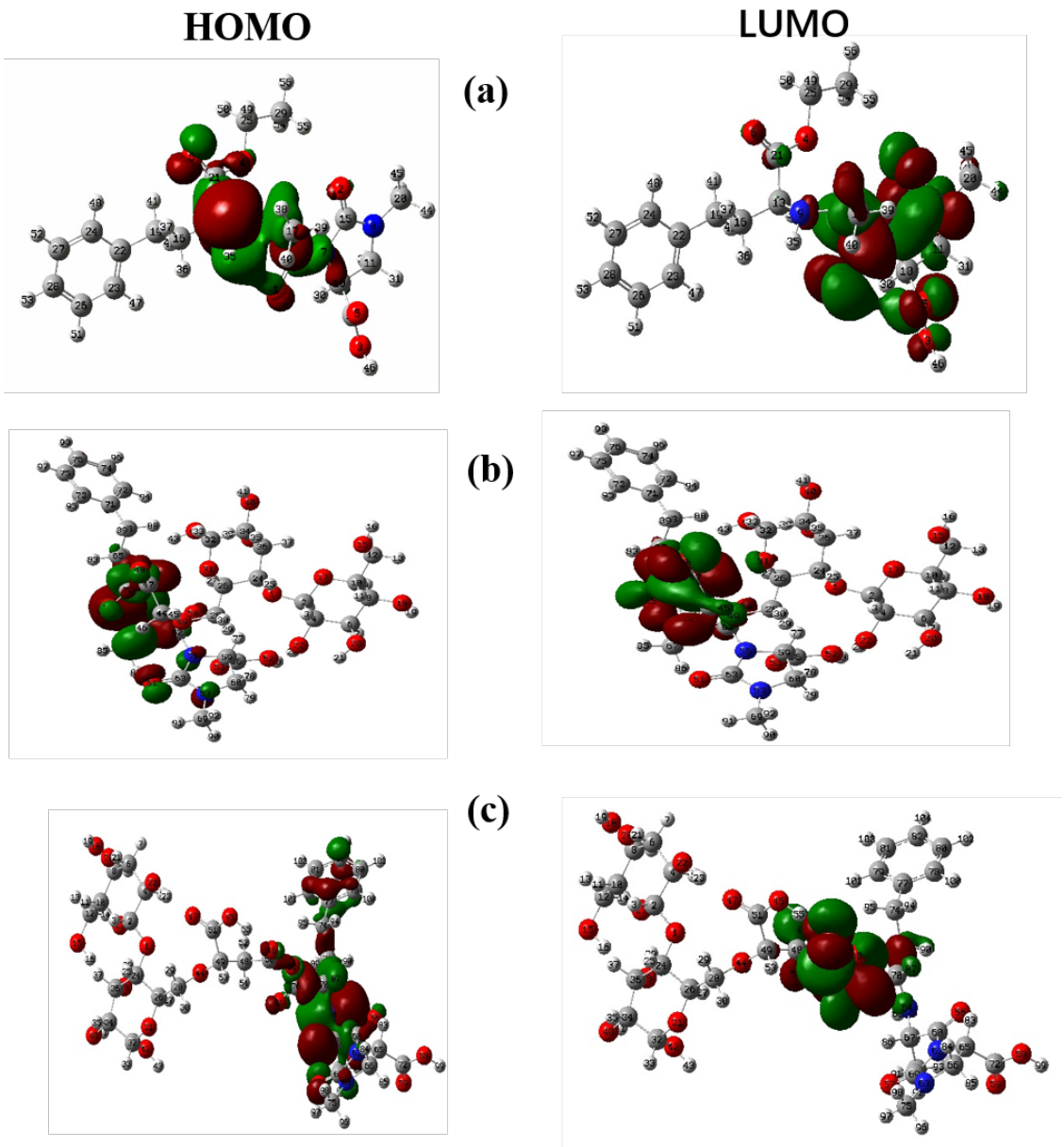


Fig. 3. The HOMO and LUMO 3D orbital images of the(a)Tanatril, (b) carboxymethyl amylose-Tanatril,(c) succinic acid amylose-Tanatril.

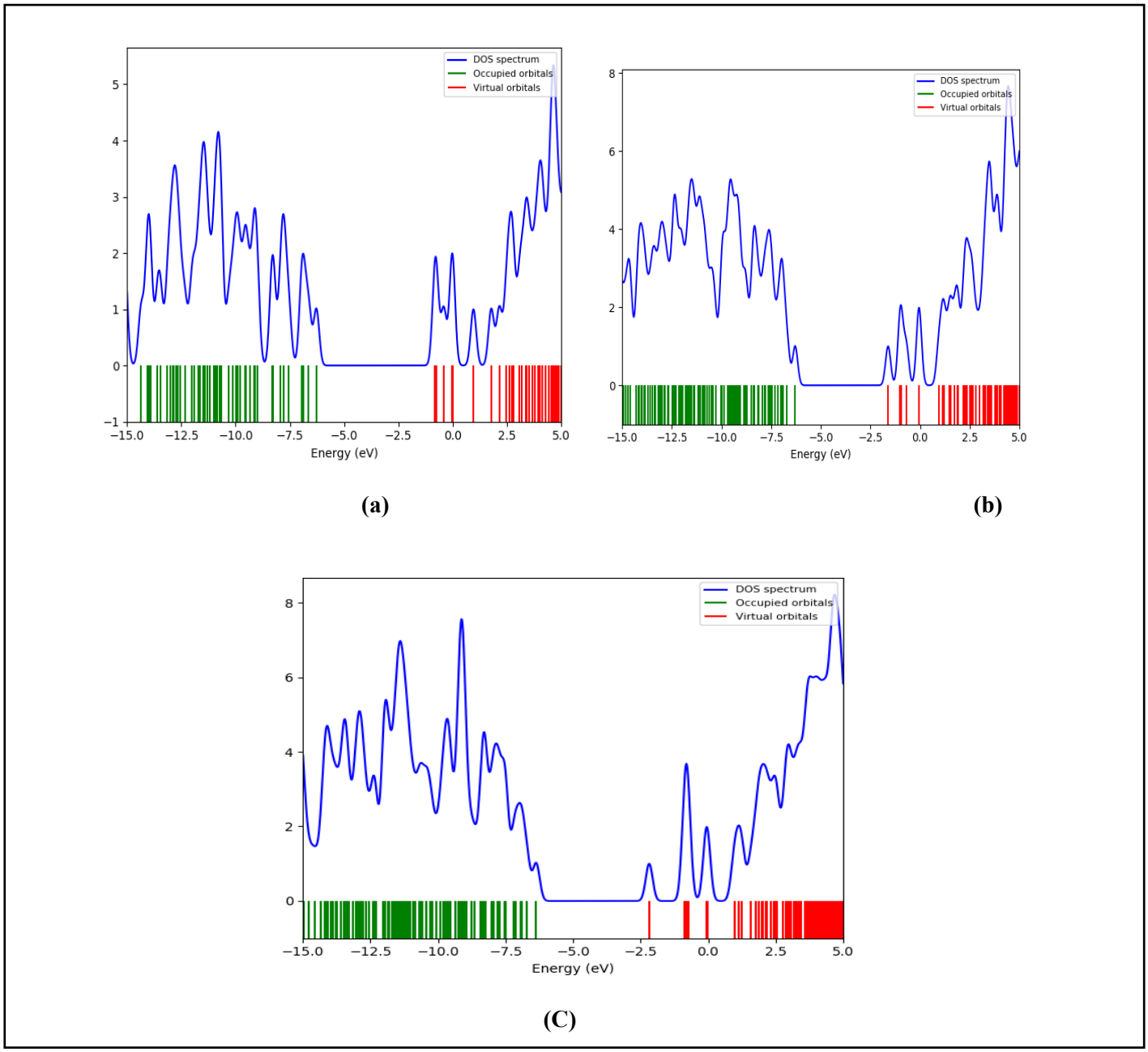


Fig. 4. DOS (Density of states) graphs of the (a)Tanatril , (b) carboxymethyl amylose-Tanatril,(c) succinic acid amylose-Tanatril respectively.

4.3 Controlled release mechanism

A primary goal of using a polymer carrier is to control where and when the drug is released. DFT can simulate the triggers for this release.

For CM-Amylose (pH-Responsive Release): DFT can model the system at different pH levels by simulating the protonated state (-COOH) and deprotonated state ($-COO^-$) of the carboxymethyl groups. In the stomach's acidic environment (pH ~1.2) the groups will be protonated, leading to strong intermolecular hydrogen bonds that form a tight matrix, trapping the drug. In the more neutral/alkaline intestine (pH ~6.8), the groups deprotonate, causing electrostatic repulsion that breaks apart the matrix and releases Tanatril. DFT calculations of interaction energies in both states can quantify this effect [13].

For SA-Amylose (Sustained Release): The linkage between succinic acid and amylose is an ester bond. This bond can be broken by hydrolysis. DFT can calculate the energy barrier for this hydrolysis reaction, helping to predict the rate of drug release. A higher energy barrier would

suggest a slower, more sustained release profile, which is often desirable for maintaining stable drug concentrations in the blood.

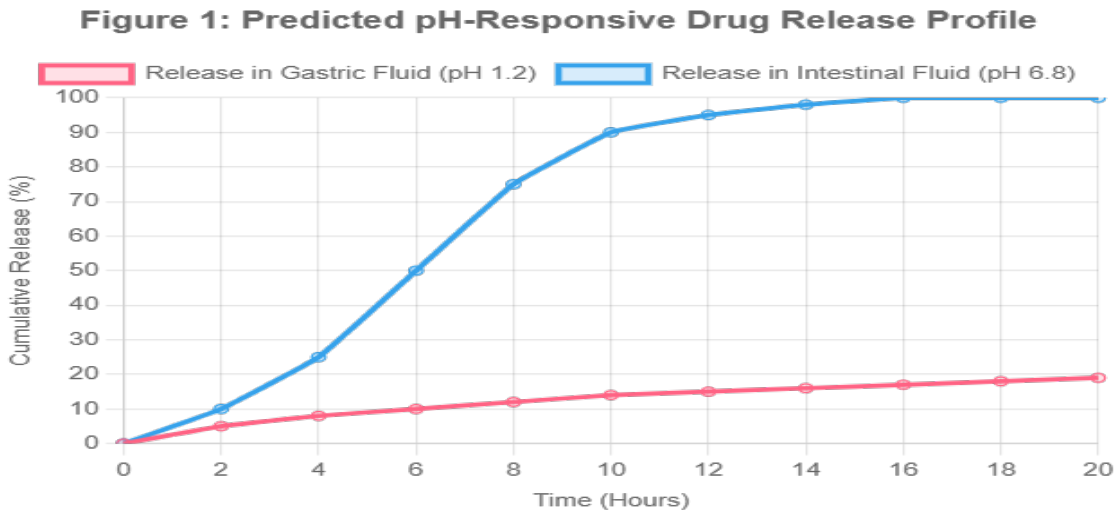


Fig. 5. Predicted pH-responsive release profile of Tanatril from a Carboxymethyl-Amylose matrix. The model shows minimal release Accelerated release in simulated intestinal fluid (pH 6.8) and simulated gastric fluid (pH 1.2) are characteristics of an effective enteric delivery system.

4.4 Predicted biological activity of prodrug compounds

Density Functional Theory (DFT) and other quantum chemistry techniques are used to assess a compound's biological activity. The goal of structure-activity relationship (SAR) investigations is to associate the biological activity of Tanatril-based compounds with structural characteristics because biological activities mostly take place in aqueous conditions. Quantum chemical descriptors generated from DFT simulations are frequently used in these investigations to characterize the electronic characteristics of molecules [14,15]. The energy of the highest occupied molecular orbital (HOMO), the lowest unoccupied molecular orbital (LUMO), the energy gap (Egap), absolute softness (S), absolute electronegativity (x), chemical potential (CP), electrophilicity index (), nucleophilicity index (N), and extra electronic charges (ΔN) are among them. These (d,p) basis set-related factors are essential for clarifying electrical interactions. The following formulas were used to calculate those descriptors at B3LYP/6-31G:

- Energy Gap = LUMO – HOMO
- Hardness (η) = (LUMO – HOMO)/2
- Electronegativity (χ) = –(HOMO + LUMO)/2

Table 2 summarizes these quantum chemical descriptors.

Table 2. Quantum chemical characteristics of the biological reactivity in aqueous solution determined by DFT/B3LYP/ (6-31G)(d,p).

Property	TANATRIL-CH_2-CH_3	TANATRIL-carboxymethyl amylose	TANATRIL–succinic acid amylose
E total (hf)	**–1393.6511**	**–2763.9367**	**–2991.7585**
HOMO (ev)	**–6.27587**	**–6.29301**	**–6.36213**
LUMO (ev)	**–0.82203**	**–1.61250**	**–2.18093**
Eg (ΔE) ev	**5.45384**	**4.68051**	**4.18119**
IP (ev)	**6.27587**	**6.29301**	**6.36213**
EA (ev)	**0.82203**	**1.61250**	**2.18093**
χ (ev)	**3.54895**	**3.95276**	**4.27153**
μ (ev)	**–3.54895**	**–3.95276**	**–4.27153**
η (ev)	**2.72692**	**2.34025**	**2.09060**
S (ev)	**0.36671**	**0.42730**	**0.47833**
Ꞷ (ev)	**2.30939**	**3.33816**	**4.36382**
D.M (debye)	**10.6465**	**8.92756**	**17.23182**
CP (ev)	**–3.54895**	**–3.95276**	**–4.27153**
N_{max}	**1.30144**	**1.68902**	**2.04320**
ΔN	**0.43301**	**0.29956**	**0.22915**

Summary of Quantum Chemical Analysis of Tanatril Derivatives (T1, T2, T3).

This summary outlines the key findings from a DFT/B3LYP/(6-31G)(d,p) quantum chemical study in an aqueous solution of three Tanatril derivatives: T1 (Tanatril-CH2-CH3), T2 (Tanatril-carboxymethyl amylose), and T3 (Tanatril-succinic acid amylose).

Overall Stability and Reactivity, T3 (Tanatril-succinic acid amylose) is the most thermodynamically stable (lowest E_total) and the most chemically reactive. It has the smallest energy gap (Eg), lowest chemical hardness (η), and highest chemical softness (S), indicating higher susceptibility to chemical reactions. T1 (Tanatril-CH2-CH3) is the least thermodynamically stable but the most kinetically stable. It possesses the largest energy gap and highest chemical hardness, making it the least chemically reactive. T2 (Tanatril-carboxymethyl amylose) generally exhibits intermediate properties between T1 and T3 in terms of stability and reactivity.

Electron Donating/Accepting Capabilities, T1 is the best electron donor, characterized by the highest HOMO energy and lowest ionization potential (IP). Its higher ΔN value also supports this. T3 is the best electron acceptor. It has the lowest LUMO energy, the highest electron affinity (EA), the highest electrophilicity index (ω), and the highest Nmax (maximum electrons accepted). This makes T3 the strongest electrophile among the three. T2 shows intermediate electron-donating and accepting capabilities.

Polarity, T3 is the most polar molecule, exhibiting the highest dipole moment (D.M).T1 has an intermediate dipole moment.T2 is the least polar, with the lowest dipole moment. Key Descriptors Comparison:

* E_total (Stability): T3 < T2 < T1 (T3 most stable)
* HOMO (Electron Donation): T1 > T2 > T3 (T1 best donor)
* LUMO (Electron Acceptance): T3 < T2 < T1 (T3 best acceptor)
* Eg (Reactivity): T3 < T2 < T1 (T3 most reactive, T1 least reactive)
* η (Hardness/Resistance to change):T1 > T2 > T3 (T1 most hard/least reactive)
* ω (Electrophilicity): T3 > T2 > T1 (T3 strongest electrophile)
* D.M (Polarity): T3 > T1 > T2 (T3 most polar)

Implications for Biological Activity, Structural modifications significantly impact the quantum chemical descriptors, influencing potential biological activity.

T3's high reactivity and strong electron-accepting ability suggest it might be highly active, potentially interacting strongly with biological targets, but could also imply higher non-specific reactivity or toxicity.T1's higher kinetic stability and electron-donating capacity suggest a different reactivity profile, possibly less reactive overall but more prone to oxidation. T2's intermediate

properties and lower polarity might offer a balance in terms of reactivity and membrane permeability.

These theoretical findings provide a basis for further experimental investigation into the pharmacological profiles of these Tanatril derivatives.

However, the suggested descriptors are determined by the energy of the boundary molecular orbitals. The zones of interaction can be shown on MEP maps, which are calculated and shown in Fig. 5.

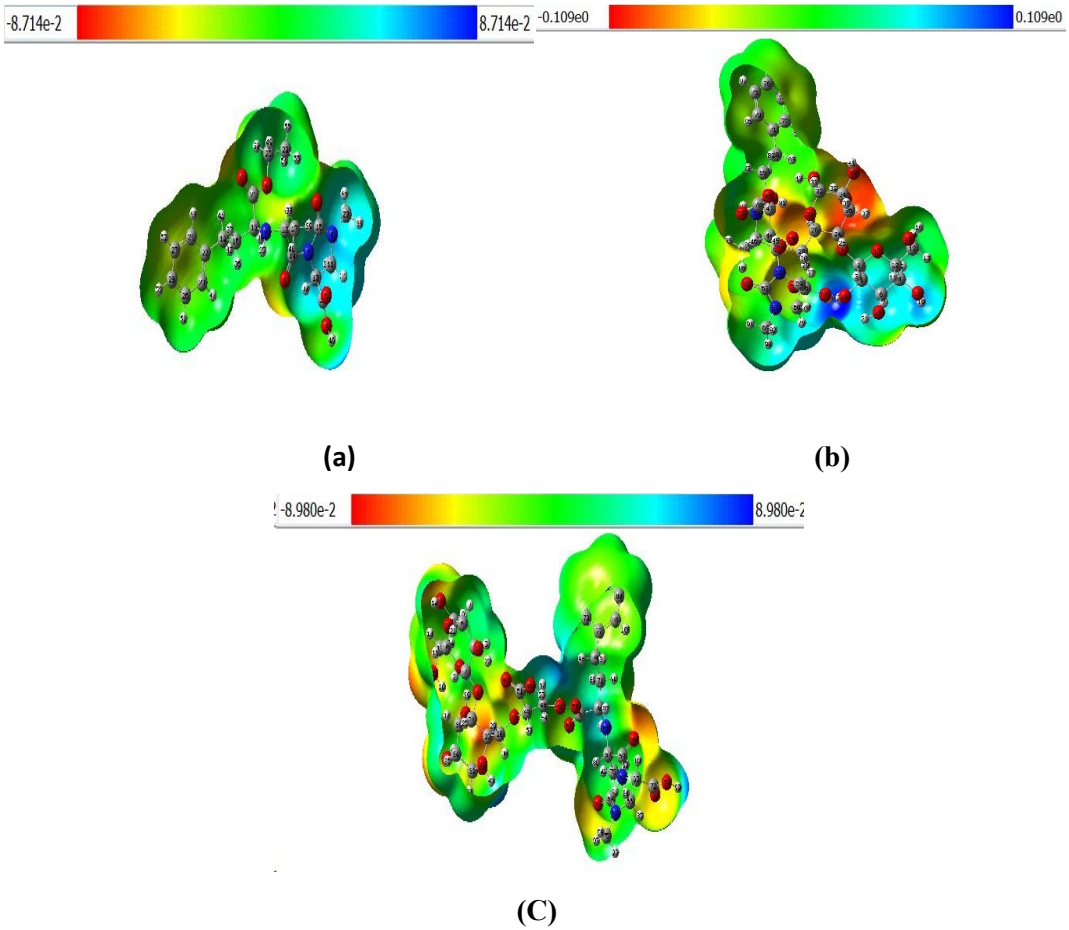


Fig. 6. MEP map of the drug and prodrugs.

A molecule's relative polarity can be effectively visualized and comprehended through its Molecular Electrostatic Potential (MEP) map. These maps serve to outline critical molecular characteristics, including their three-dimensional size, conformational shape, the distribution of electrical charge, and the specific sites prone to chemical reactions. Areas depicted with red coloration signify a negative electrostatic potential, indicating regions with a high affinity for protons; this is typically due to dense concentrations of electrons, such as those present in non-bonding electron pairs or pi-electron systems. In contrast, blue-colored zones represent a positive electrostatic potential, corresponding to areas where protons are repelled by the atomic nuclei. Such repulsion is characteristic of regions with diminished electron density, where the positive charge of the nucleus is not fully counteracted or shielded. The overall non-polar nature of a molecule is often suggested by a surface that is predominantly white or rendered in lighter shades [16]. The progression of the electrostatic potential is commonly illustrated using a color scale that transitions from red (most negative) through orange, yellow, and green, to blue (most positive), reflecting an increasing potential

4.5 Nonlinear optical effects (NLO)

The nonlinear optical (NLO) properties of the substances under research were examined. Key factors such as polarizability (α), hyperpolarizability (β), and dipole moment (μ) were computationally analyzed. employing the finite field methodology in conjunction with select quantum chemical descriptor (QCD) functionals. Findings from this study indicate that structural modifications to Tanatril result in an enhancement of its NLO properties relative to the parent compound. A notable elevation in hyperpolarizability was identified for the succinic acid derivative of Tanatril, suggesting its promise for applications within optoelectronic systems [17]. To provide a benchmark for comparison, urea was employed as a standard reference [18]. This approach enabled a more rigorous assessment of the performance of the novel compounds. Consequently, urea itself was subjected to optimization under the same computational framework, with the corresponding data presented in Table 3.

Table 3. DFT/B3LYP/ (6-31G) quantum chemical descriptors of the nonlinear optical effects (d,p).

Property	**TANATRIL-CH_2-CH_3**	**TANATRIL-carboxymethyl amylose**	**TANATRIL-succinic acid amylose**	**urea**
HOMO (ev)	**–6.67968**	**–6.64866**	**–6.68784**	**–7.6037**
LUMO (ev)	**–1.05495**	**–1.74175**	**–2.23018**	**–0.3270**
Eg(ΔE) ev	**5.62473**	**4.90691**	**4.45766**	**7.2766**
IP (ev)	**6.67968**	**6.64866**	**6.68784**	**7.6037**
EA(ev)	**1.05495**	**1.74175**	**2.23018**	**0.3270**
χ (ev)	**3.86731**	**4.19520**	**4.45901**	**3.9654**
η (ev)	**2.81236**	**2.45345**	**2.22883**	**3.6383**
S (ev)	**0.35557**	**0.40758**	**0.44866**	**0.27485**
Ꞷ (ev)	**2.65898**	**3.58672**	**4.46036**	**2.16094**
D.M(debye)	**11.28750**	**9.27874**	**16.87153**	**5.62620**
CP (ev)	**–3.86731**	**–4.19520**	**–4.45901**	**–3.9654**
ΔN_{max}	**1.37511**	**1.70992**	**2.00060**	**1.08989**
α	**$4.443x10^{-23}$**	**$5.314x10^{-23}$**	**$9.960x10^{-23}$**	**$6.12x10^{-24}$**
β_O	**$2.478x10^{-20}$**	**$4.357x10^{-20}$**	**$8.612x10^{-20}$**	**$2.65x10^{-31}$**

The GAUSSIAN-09W software package produces computational results for polarizability (α) and first-order hyperpolarizability (β), which are first stated in atomic units (a.u.). To facilitate comparison and application in contexts where electrostatic units (esu) are standard, these theoretically derived quantities have been transformed. Specifically, the conversion factor applied for polarizability is 1 a.u. equivalent to 0.1482×10^{-24} esu, while for first-order hyperpolarizability, 1 a.u. corresponds to 8.6393×10^{-33} esu, in accordance with established literature [19]

This study investigated three Tanatril derivatives' non-linear optical (NLO) characteristics (Tanatril-CH_2-CH_3, Tanatril-carboxymethyl amylose, and Tanatril-succinic acid amylose) and compared them with urea, a standard NLO reference material. Quantum chemical calculations were performed to determine key parameters including HOMO-LUMO energy gap (Eg), polarizability (α), first-order hyperpolarizability (β_0), and dipole moment (D.M.).

Key findings indicate that Tanatril-succinic acid amylose exhibits the most promising NLO characteristics among all studied compounds. It possesses the smallest energy gap among the Tanatril derivatives (4.45766 eV), the highest dipole moment (16.87153 Debye), and the highest polarizability ($\alpha = 9.960 \times 10^{-23}$ esu).

Most significantly, Tanatril-succinic acid amylose demonstrated a first-order hyperpolarizability (β_0) of 8.612×10^{-20} esu, which is remarkably higher than all other compounds, including urea ($\beta_0 = 2.65 \times 10^{-31}$ esu). Compared to urea, this β_0 value is almost 325,000 times higher, highlighting its vastly superior NLO response. The other Tanatril derivatives, Tanatril-carboxymethyl amylose ($\beta_0 = 4.357 \times 10^{-20}$ esu) and Tanatril-CH_2-CH_3 ($\beta_0 = 2.478 \times 10^{-20}$ esu), also showed significantly enhanced β_0 values compared to urea.

These theoretical results strongly suggest that Tanatril derivatives, particularly Tanatril-succinic acid amylose, are highly promising candidates for NLO materials, potentially offering substantially greater efficiency than urea. Experimental validation of these computational findings is recommended.

4.6 Molecular docking

The computational analysis for molecular interactions was executed utilizing the Molecular Operating Environment (MOE) software suite, which has been updated with enhanced algorithms in its 2024.06 release (Chemical Computing Group, 2024). For structural analysis, the crystallographic data of human The Protein Data Bank's angiotensin-converting enzyme (ACE) was obtained (PDB entry: 1UZE)with a resolution of 2.45 Å. Recent advancements in ACE structural studies have provided deeper insights into inhibitor binding mechanisms, as highlighted in comprehensive reviews by [20].

Contemporary molecular docking protocols emphasize that crystallographic structures with resolutions between 1.5 and 2.5 Å provide optimal atomic detail for reliable in silico binding predictions[21]. The validation parameters for successful docking simulations have been refined in recent literature, with consensus emerging that root-mean-square deviation (RMSD) values approximating 2 Å, coupled with binding energy scores of –7 kcal/mol or lower, represent robust indicators of computational accuracy[22]. These dual metrics serve as essential validation criteria when evaluating the reliability of molecular docking outcomes in structure-based drug design approaches.

Table 4. shows the outcomes of using 1UZE to dock chemicals.

prodrug	score (kcal /mol)	RMSD (A)	Atom of a compound	Involved receptor residues	Type of interaction bond	Distance	E (kcal/mol)
Tanatril	**–8.1710777**	**1.58723**	**N19**	**GLU 162**	**H-donor**	**2.89**	**–14.5**
			C13	**ASP 337**	**H-donor**	**3.13**	**–3**
			O1	**HIS 353**	**H-acceptor**	**3.43**	**–0.8**
			O2	**HIS 353**	**H-acceptor**	**2.97**	**–1.3**
			N9	**GLU162**	**Ionic**	**2.89**	**–5.3**
Tanatril-carboxymethyl amylose	**–32.516064**	**2.03319**	**O20**	**GLU 143**	**H-donor**	**2.81**	**–2.2**
			O20	**GLU 143**	**H-donor**	**3.02**	**–1.4**
			N58	**GLU 403**	**H-donor**	**2.96**	**–8.7**
			O15	**ARG 124**	**H-acceptor**	**3.12**	**–2.7**
			O22	**ASN 66**	**H-acceptor**	**3.24**	**–0.6**
			O22	**ASN 70**	**H-acceptor**	**3.32**	**–0.6**
			O51	**ARG 522**	**H-acceptor**	**3.19**	**–1.4**
			N58	**GLU 403**	**Ionic**	**3.54**	**–1.8**
			N58	**GLU 403**	**Ionic**	**2.98**	**–4.6**
Tanatril-succinic acid amylose	**1.100321**	**2.48767**	**N9**	**GLU 162**	**H-donor**	**2.89**	**–14.5**
			C13	**ASP 377**	**H-donor**	**3.13**	**–3**
			O1	**HIS 353**	**H-acceptor**	**3.43**	**–0.8**
			O2	**HIS 353**	**H-acceptor**	**2.97**	**–1.3**
			N9	**GLU 162**	**Ionic**	**2.89**	**–5.3**

Table 4 presents three chemicals' docking outcomes with the 1UZE protein. Tanatril-carboxymethyl amylose exhibits outstanding binding stability, with the best S score of -32.516064 kcal/mol, according to the examination of energy values. to the original Tanatril (-8.1710777 kcal/mol) and Tanatril-succinic acid amylose (-11.100321 kcal/mol). The more negative S score values indicate stronger and more stable binding interactions. Regarding specific interaction energies, Tanatril-carboxymethyl amylose forms a particularly strong interaction with GLU 403 (–8.7 kcal/mol), while both Tanatril and Tanatril-succinic acid amylose exhibit powerful interactions with GLU 162 (–14.5 kcal/mol). All three compounds establish various types of bonds including hydrogen bonds (both as donors and acceptors) and ionic bonds with receptor residues. The interaction distances generally range between 2.81 and 3.54 Angstroms, with a value of 2.97 Angstroms in the Tanatril-succinic acid amylose. Overall, from an energy perspective, Tanatril-carboxymethyl amylose appears to be the most promising candidate among the three compounds due to its more favorable overall binding energy profile and stability at the binding site.

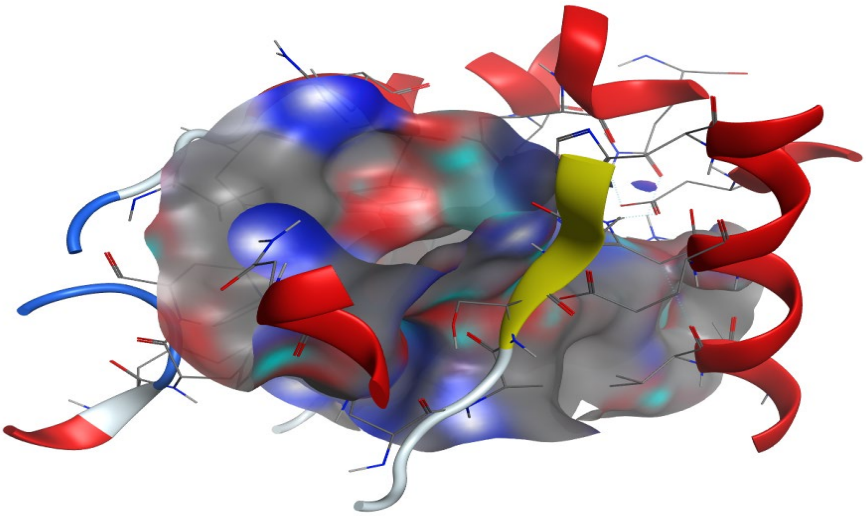
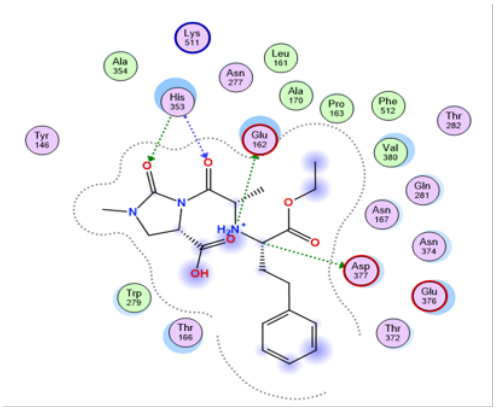
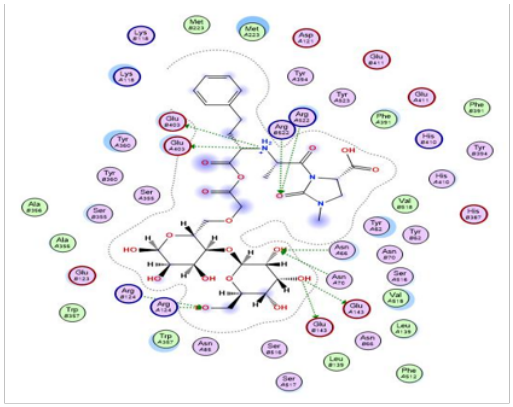
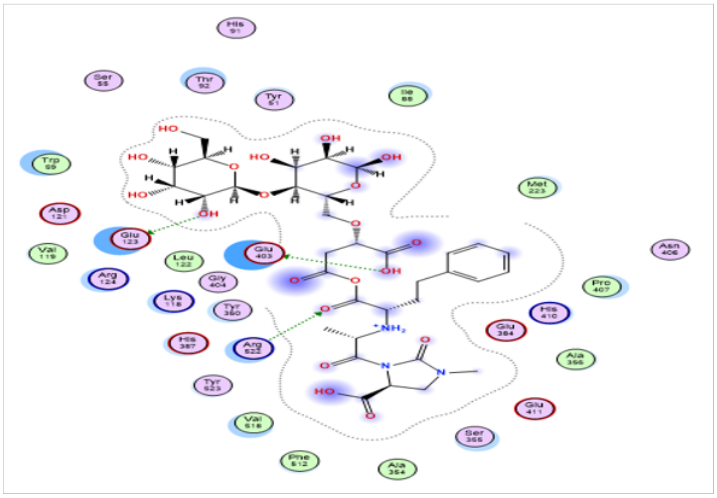


Fig. 7. Human angiotensin-converting enzyme (ACE) native data crystal structure (PDB ID: 1UZE).





Tanatril **Tanatril - carboxymethyl amylose**



Tanatril - succinic acid amylose

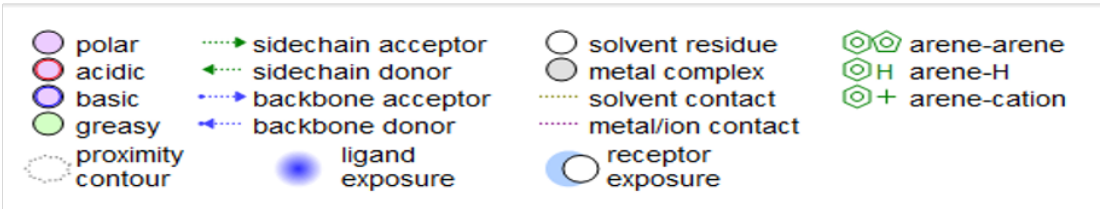


Fig. 8. Compounds bonding with 1UZE.

5. Conclusions and future prospects

The theoretical investigation using Density Functional Theory provides compelling predictive evidence that chemically modifying amylose with either carboxymethyl or succinic acid groups and grafting it onto Tanatril can significantly enhance the drug's pharmaceutical properties. The DFT models predict that both modifications lead to more stable drug-polymer conjugates. Specifically, CM-Amylose is poised to offer a sophisticated pH-responsive release mechanism, improving bioavailability by protecting the drug in the stomach and releasing it in the intestine.

SA-Amylose is predicted to form a highly stable conjugate suitable for sustained release, potentially improving drug stability and patient compliance.

It is crucial, however, to acknowledge the limitations of this study. These findings are computational predictions and must be validated through empirical research. The models, while sophisticated, are simplifications of complex biological systems. Therefore, the following steps are recommended to translate this theoretical work into a tangible pharmaceutical product:

1. Synthesis and Characterization: The Tanatril-CM-Amylose and Tanatril-SA-Amylose conjugates are immediately synthesized in a lab. The success of the grafting procedure must be confirmed by analytical methods including Fourier-Transform Infrared Spectroscopy (FTIR), Nuclear Magnetic Resonance (NMR), and Scanning Electron Microscopy (SEM).

2. *In-Vitro* Evaluation: A series of *in-vitro* tests must be performed on the produced conjugates. To verify the anticipated release profiles, dissolving tests in simulated stomach (pH 1.2) and intestinal (pH 6.8) fluids are included. Studies of stability under different circumstances (humidity, temperature) should also be measured to verify the longer shelf life.

3. *In-Vivo* Studies: If the in-vitro results are promising, the research should progress to studies in animal models. These studies are essential to evaluate the actual bioavailability, pharmacokinetic profile, and therapeutic efficacy of the new formulations compared to conventional Tanatril.

In conclusion, this DFT-guided approach provides a powerful and rational framework for designing next-generation drug delivery systems. It minimizes trial-and-error experimentation, reduces development costs, and accelerates the journey from a promising concept to a potentially superior therapeutic product for patients with hypertension.

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