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Research Article

Computational Insights into Cholesteryl Carbamate Derivatives: A Density Functional Theory and Molecular Docking Approach

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ABSTRACT

In the study, a series of novel cholesterol carbamate derivatives were computationally investigated using density functional theory (DFT) and molecular docking methods to evaluate their global reactivity and potential biological interactions. Ten derivatives, incorporating aliphatic and aromatic amide functionalities, were modeled and optimized using the B3LYP/6-31G level of theory. Key global descriptions such as HOMO-LUMO energy gap (ΔE), chemical hardness (η), softness (S), electronegativity (χ), and global electrophilicity index (ω) were calculated to assess the stability and reactivity of each compound. Among them, the 4-nitroaniline derivative (C8) displayed the lowest energy gap (ΔE = 2.68 eV), highest electrophilicity index (ω = 5.5140), and highest dipole moment (8.73 D), suggesting strong reactivity and potential for favorable interactions with biological targets. Furthermore, molecular docking studies against calf thymus DNA (ct-DNA) revealed that C8 exhibited the most favorable binding, with a binding energy of −7.90 kcaL/mole and an inhibition constant of 1.61 μM. Compounds C4 and C7 also showed promising interactions, supported by their moderate energy gaps and high electron-donating capacities. The combined computational approach offers valuable insights into the electronic features and the binding potential of cholesteryl carbamate derivatives, paving the way for future biological and experimental validations.

Key words: Binding energy, Bioactive compounds, Cholesteryl carbamate derivatives, Density functional theory, Molecular docking.

1. INTRODUCTION

Cholesterol derivatives have gained significant attention due to their potential biological activities, including antimicrobial, anticancer, and anti-inflammatory properties [1-13]. Among them, carbamate derivatives, in particular, are known for their chemical stability and broad pharmacological potential. Incorporating aromatic and aliphatic amides into the cholesterol framework may enhance the biological activity and molecular interactions of these compounds.

Computational approaches, such as density functional theory (DFT) [13-15] and molecular docking, provide valuable insights into the structural stability, electronic reactivity, and binding potential of newly designed molecules [16]. These *in silico* techniques are widely used in drug discovery to predict the behavior of candidate molecules before experimental validation.

This study aims to evaluate the global reactivity descriptors and docking behavior of 10 novel cholesteryl carbamate derivatives, with the goal of identifying promising bioactive compounds for further biological investigation.

2. COMPUTATIONAL METHODS

2.1. DFT Calculations

All molecular structures were optimized using Gaussian software with the B3LYP functional and 6-31G basis set [Figure 1]. The calculations were performed in a gas phase with a singlet spin state. Global reactivity descriptors [17-19] such as HOMO and LUMO energies, energy gap (ΔE), chemical potential (μ), chemical hardness (η), softness (S), electronegativity (χ), electrophilicity index (ω), and dipole moment were computed. Gaussview was used for molecule structure building and visualization.

2.2. Molecular Docking

Molecular docking studies [19,20] were performed using AutoDock 4.2 to assess the binding affinities of the 10 cholesteryl carbamate compounds against calf thymus DNA (ct-DNA), selected as the model biomolecular target due to its relevance in DNA-interacting drug target. Ligands were prepared by energy minimization and saved in PDBQT format, whereas the ct-DNA structure was processed

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by adding polar hydrogens and charges. Grid box parameters were defined to enclose the entire binding region of the DNA. Docking simulations were carried out using the Lamarckian genetic algorithm. For each ligand, 10 docking poses were generated and ranked based on their binding energy (ΔG). Additional parameters, including the estimated inhibition constants (Ki), free energy (A), internal energy, and entropy (S) were calculated at a standard physiological temperature (298.15 K).

3. RESULTS AND DISCUSSION

3.1. Global Reactivity Descriptors

The calculated global reactivity parameters, including HOMO-LUMO energies, energy gap (ΔE), chemical potential (μ), chemical hardness (η), softness (S), electronegativity (χ), electrophilicity index (ω), and dipole moment, are presented in Table 1. The HOMO-LUMO energy gap serves as an important indicator of molecular reactivity and stability. A lower energy gap indicates higher chemical reactivity and ease of electron transfer. Among the studied compounds, C8 (4-nitroaniline derivative) exhibited the lowest energy gap (ΔE = 2.68 eV), highest electrophilicity index (ω = 5.514), and highest dipole moment (8.73 D), suggesting strong reactivity and a high tendency to accept electrons. This is attributed to the electron-withdrawing nitro group, which significantly enhances the compound's polarity and electrophilic behavior.

Compounds C2 and C5 also demonstrated relatively low energy gaps, whereas C1 had the highest ΔE value (6.33 eV), indicating it is the least reactive among the series. These findings suggest that the nature of the substituent on the amide group greatly influences the reactivity profile of cholesterol carbamate derivatives.

3.2. Molecular Electrostatic Potential (ESP), HOMO, and LUMO Visualizations

The ESP maps [Figure 2] depict the charge distribution across the molecules. Regions of negative potential (Red) indicate electron-rich zones, likely to engage in electrophilic interactions, whereas blue zones correspond to electron-deficient regions, favorable for nucleophilic attacks. The HOMO and LUMO plots further highlight the frontier molecular orbitals and electron delocalization. In most derivatives, the HOMO was delocalized over the aromatic/amino moieties, whereas the LUMO extended toward the carbamate or sterol region. The spatial separation facilitates efficient intramolecular charge transfer and supports the reactivity trend observed in the DFT calculations.

3.3. Molecular Docking Results

Docking simulations were performed to evaluate the interaction potential of the synthesized compounds with ct-DNA, a biologically relevant target for many anticancer and antimicrobial drugs. The docking parameters-binding energy (ΔG), inhibition constant (Ki), free energy, internal energy, and entropy are listed in Table 2.

Docking studies [Figure 3] were successfully conducted for all the 10 designed cholesteryl carbamate derivatives. Among them, compounds C8, C4, C5, C7, and C10 exhibited the most favorable interactions with ct-DNA, supported by their low binding energy and inhibition constants.

The best binding interaction was observed for compound C8 (4-nitroaniline derivatives), which showed the highest binding affinity, with a binding energy of −7.90 kcaL/moL and an inhibition constant (Ki) of 1.61 μM, confirming its strong infinity for the

Table 1: Global reactivity parameters of sulfonamides- energy (E), ionization energy (I), electron affinity (A), energy gap (ΔE), Chemical potential (μ), Electronegativity (μ), hardness (η), and softness (S), global electrophilicity index (ω), electron accepting power (ω^+), electron-donating power (ω^-), (energy is in a.u, global parameters are in eV).

S. No.	Energy	HOMO (eV)	LUMO (eV)	ΔE=LUMO -HOMO	Ionisation potential	Electron affinity	Chemical potential μ=−(I.P+E.A)/2	Electronegativity =χ	Chemical hardness η=(I.P-E.A)/2	Global index ω=μ**2/2η	e- accepting power $\omega^+ = \frac{(IP+3EA)^2}{16(IP-EA)}$	e- donating power $\omega^- = \frac{(3I+A)^2}{16(I-A)}$	Dipole moment (D)
1	−1468.82	−6.2997	0.02857	6.33	6.29	−0.02	−3.13	3.13	3.164	1.553	0.381	3.708	6.0090
2	−1452.78	−6.3408	−0.6508	5.68	6.34	0.65	−3.49	3.49	2.844	2.147	0.755	4.542	5.5251
3	−1570.48	−6.2510	−0.13985	6.11	6.25	0.13	−3.195	3.19	3.055	1.670	0.455	4.20	2.1077
4	−1645.66	−5.4479	−0.19861	5.24	5.44	0.19	−2.82	2.82	2.624	1.518	0.434	4.006	3.4757
5	−1534.80	−6.1508	−0.81009	5.34	6.15	0.81	−3.48	3.48	2.670	2.268	0.861	5.286	2.1575
6	−1531.17	−6.1933	−0.16517	6.02	6.19	0.16	−3.17	3.17	3.014	1.676	0.463	4.777	1.9987
7	−1990.76	−6.1587	−0.47211	5.68	6.158	0.47	−3.31	3.31	2.843	1.932	0.630	5.305	4.9092
8	−0.23861	−6.4929	−2.67896	3.81	6.49	2.67	−4.58	4.58	1.906	5.514	3.459	9.977	8.7324
9	−0.22788	−6.2009	−0.12381	6.07	6.20	0.12	−3.16	3.16	3.038	1.645	0.444	5.316	8.7324
10	−0.2198	−5.9810	−1.27267	4.70	5.98	1.27	−3.62	3.62	2.354	2.793	1.274	7.127	2.1462

Table 2: Molecular docking results off cholesteryl carbamate derivatives with ct-DNA: Binding energy (ΔG), inhibition constant (Ki) uM, free energy A, internal energy, and entropy (*S=4.58 kcaL/moL/k, unless otherwise specified) at 298.15 K.

S. no.	Binding energy (ΔG, kcaL/mol)	Inhibition constant (Ki, uM)	Free energy (A kcaL/mole)	Internal energy (kcaL/moL)
1	−6.55	15.76	−1370.16	−5.92
2	−6.49	17.46	−1370.25	−6.01
3	−7.07	6.55	−1370.44	−6.20
4	−7.71	2.25	−1371.00	−6.76
5	−7.29	4.56	−1370.30	−6.06
6	−6.82	9.95	−1370.46	−6.22
7	−7.54	2.97	−1370.93	−6.69
8	−7.90	1.61	−1371.36	−7.13
9	−7.00	7.43	−1370.61	−6.37
10	−7.17	5.56	−1371.04	−6.81

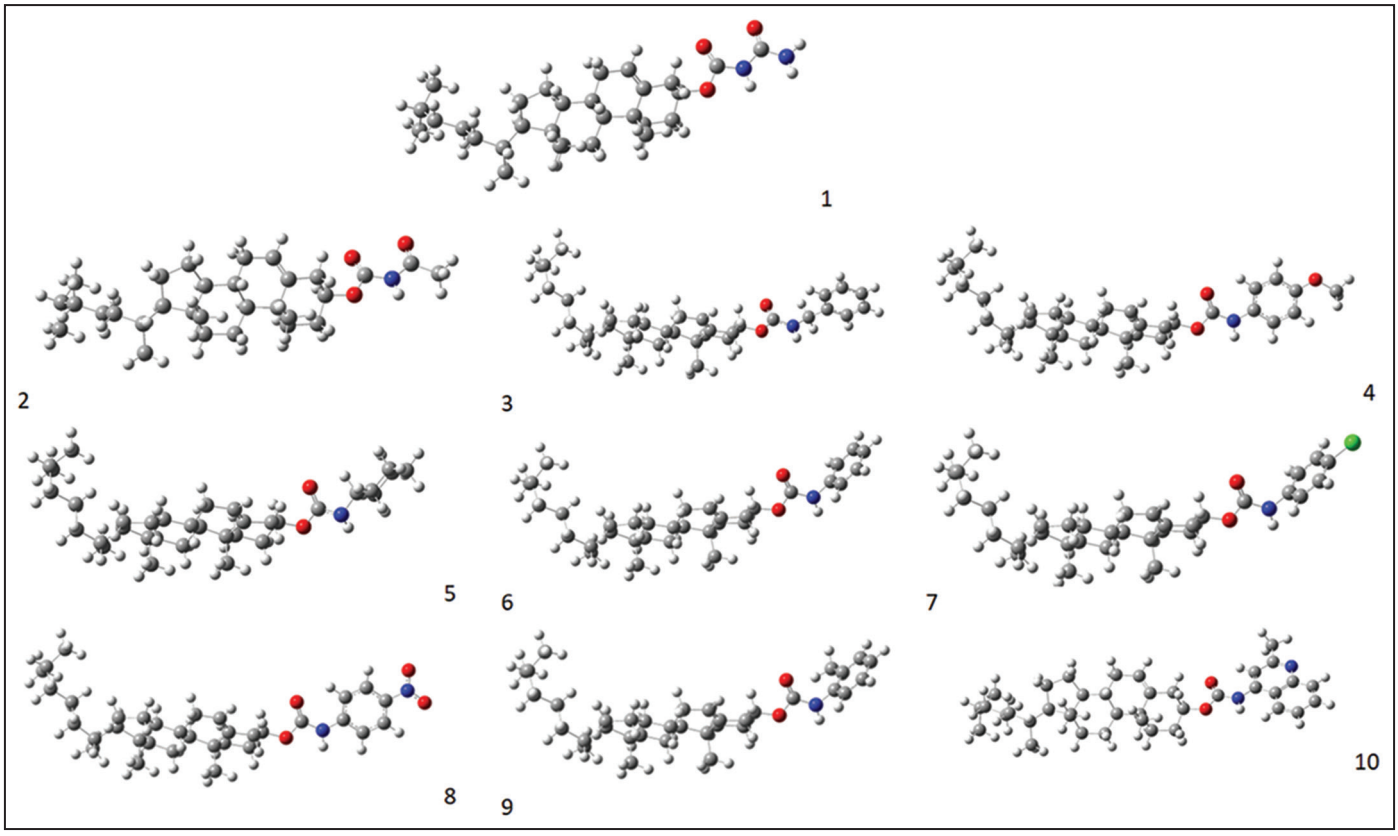

Figure 1: Modeled structures of 10 cholesteryl carbamate derivatives.

DNA groove. This correlates well with its high electrophilicity and dipole moment, which likely enhance its ability to form hydrogen bonds and π–π stacking with the DNA base pairs. Compound C4 (methoxybenzylamine derivative) and C7 (4-chloroaniline derivative) also exhibited strong binding affinities, with ΔG values of −7.71 and −7.54 kcaL/moL, respectively. These interactions are attributed to electron-donating and halogen groups promoting favorable van der Waals and electrostatic interactions with the DNA helix. In addition, C5 and C10 also displayed good binding profiles, whereas other derivatives displayed moderate activity. These findings are consistent with the DFT results and support the structure-activity relationship observed in this study.

Figures show the docked poses of selected compounds C8, C4, and C7 clearly illustrate group binding and stabilization through hydrogen bonding and π–π stacking, providing visual confirmation of molecular interaction modes. The docking results correlate well with the DFT findings, confirming that derivatives with electron-withdrawing groups have better binding potential due to their enhanced reactivity and favorable electronic distribution.

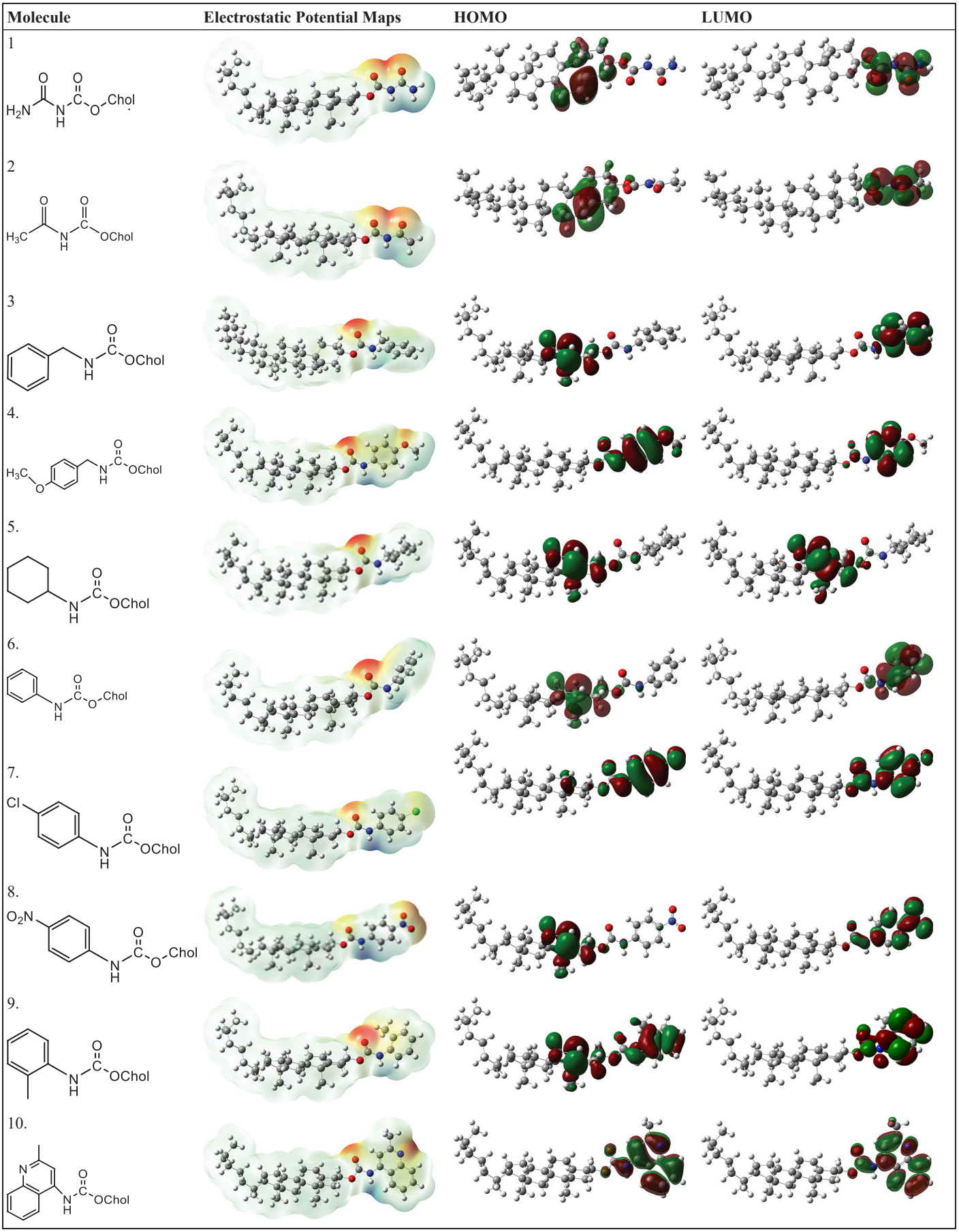

Figure 2: ChemDraw structures, molecular orbital energy diagrams HOMO and LUMO, and electrostatic potential Maps (ESP) of Compounds.

1 Figure 1: Molecular docking interaction of compound C8 (4-nitroaniline derivative) with ct-DNA
Left: 3D binding pose shows groove binding and hydrogen bond stabilization. Right: 2D interaction map highlighting hydrogen bonding, π–π stacking, and van der Waals interactions with base pairs DT:A7, DC:A9, and DG:A10.

2 Figure 2: Docking interaction of compound C4 (methoxybenzylamine derivative) with ct-DNA
Left: 3D pose (left) shows π-alkyl interactions and groove binding;
Right: 2D map (right) highlights van der Waals and hydrogen bonding with base pairs DT:A8, DC:A9, and DG:A10.

3 Figure 3: Docking interaction of compound C5 (cyclohexylamine derivative) with ct-DNA.
Left: 3D pose shows hydrogen bonding and hydrophobic embedding into the DNA groove; Right: 2D map confirms key carbon-hydrogen bond contacts with DA:A6 and DT:A7.

4 Figure 4: Docking interaction of compound C7 (4-chloroaniline derivative) with ct-DNA. π–π T-shaped and π-alkyl interactions dominate the binding, stabilizing the ligand within the minor groove.
Left: 3D binding pose shows relevant binding mode.
Right: 2D interaction map shows hydrogen bonding, π–π stacking, or van der Waals contacts.

5 Figure 5: Docking of compound C10 (quinoline derivative) with ct-DNA
Left: 3D binding pose shows relevant binding mode.
Right: 2D interaction map shows van der Waals, conventional hydrogen bonding, π–π stacking, or van der Waals contacts

Figure 3: Molecular docking interactions of selected compounds with ct-DNA. (a) Compound C8 (4-nitroaniline derivative): groove binding and hydrogen bonding stabilization. (b) Compound C4 (methoxy benzylamine derivative): π-alkyl interactions and groove binding. (c) Compound C5 (cyclohexylamine derivative): hydrogen bonding and hydrophobic embedding into the DNA groove. (d) Compound C7 (4-chloroaniline derivative): π–π T-shaped and π–alkyl interactions within the minor groove. (e) Compound C10 (quinoline derivative): relevant binding mode showing van der Waals and π–π interactions.

4. CONCLUSION

The combined DFT and molecular docking analysis of cholesterol carbamate derivatives highlights the influence of different termites on their electronic properties and binding affinities. Among them, compound C8 emerged as the most promising candidate for further biological evaluation and development of cholesterol-based bioactive molecules.

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