

Research Article

Density Functional Theory Investigation of Some Uridine Derivatives with Anti-Alzheimer Potential

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ABSTRACT

Uridine is an important nucleoside involved in RNA biosynthesis and phospholipid metabolism in the brain. In the present study, uridine and several of its derivatives were theoretically investigated as potential inhibitors of Alzheimer's disease. The electron charge density at eight sensitive sites, including hydrogen acceptor atoms (N1, O4, O5, and O6) and hydrogen donor atoms (O1, O2, O3, and N2), was examined through the calculation and comparison of electric field gradients (EFGs) and nuclear quadrupole coupling constants (NQCCs). The results indicate that the presence of a phosphate group in compound 3 increases the electron density at the O1 atom compared with the other studied compounds. This finding is further supported by Natural Bond Orbital (NBO) analysis. The obtained results suggest that O1 may act as the most active site in these compounds, and its electron density appears to be directly related to their biological activity. Therefore, any structural modification or substitution that increases the electron density at this atom may contribute to the development of more effective therapeutic agents for Alzheimer's disease. All calculations were performed using Density Functional Theory (DFT) at the B3LYP/6-31G* level of theory. The HOMO–LUMO and molecular docking analyses consistently highlighted compound 3 as the most promising derivative among the investigated compounds, exhibiting favorable electronic characteristics and the strongest predicted binding affinity toward AChE.

KEYWORDS

Uridine, Uridine monophosphate, Alzheimer, NQCCs, NBO.

1. Introduction

Alzheimer's disease (AD), characterized by a gradual decline in cognitive abilities due to neurodegeneration, stands as the primary determinant of cognitive deficits in older individuals [1]. Contemporary research indicates a correlation between diminished blood uridine concentrations in AD dementia patients and the disease's clinical trajectory, implying a potential link between uridine levels and AD progression [2, 3]. This observed reduction in uridine may stem from inadequate nutritional intake among AD patients or an elevated requirement for uridine in the repair of synaptic membranes [4, 5]. Uridine serves as a foundational component for CDP-choline synthesis, a critical intermediary in the generation of cell membrane phospholipids, notably playing a vital role in the production of phosphatidylcholine (lecithin). As a principal constituent of the cell membrane, phosphatidylcholine is fundamental to preserving the structural integrity and operational efficiency of these membranes, and it is indispensable for the development of neuronal cell membranes. Prior investigations have documented beneficial outcomes of uridine supplementation on the formation of synaptic membranes and synaptic function [4,6,7], suggesting a therapeutic potential for mitigating synaptic dysfunction in AD.

The observation that diminished uridine concentrations correlate with clinical advancement in Alzheimer's disease (AD) patients builds upon prior cross-sectional research [8,9], which consistently reported reduced uridine levels in cerebrospinal fluid and plasma among individuals with mild cognitive impairment (MCI) and AD when contrasted with control groups. Uridine, a key precursor in phospholipid synthesis, is indispensable for the structural integrity of neuronal cell membranes. Elevated uridine concentrations may exert a beneficial influence on

synaptic function and the formation of synaptic membranes, potentially mitigating the synaptic dysfunction characteristic of AD [10,11]. The observed correlation between lower uridine levels and AD could potentially stem from reduced dietary intake of uridine or an augmented requirement for this compound to facilitate the regeneration of synaptic membranes in the context of AD pathogenesis [12].

Uridine (1) is a naturally occurring nucleoside and one of the four major constituents of ribonucleic acid (RNA), which plays a fundamental role in numerous biological processes, including brain function. Uridine and some of its related molecules can also help the central nervous system work by sending signals [13]. Uridine and several of its derivatives may exhibit antimetabolite activity when their extracellular concentrations exceed the physiological range [14, 15]. In addition to studies on the biological role of uridine, several computational and experimental investigations have reported that uridine derivatives can exhibit significant biological activities and favorable pharmacokinetic properties. For example, molecular docking and related studies on benzoyl uridine esters have demonstrated potential interactions with important viral targets, indicating the potential of uridine-based scaffolds in drug design [16].

Examining the electronic structure of these compounds and understanding how the charge is distributed, as well as the charge density on atoms that can act as pharmacophores, can be very useful and help in proposing more effective and practical structures. One of the very precise and well-tested methods is the calculation of the quadrupolar coupling constants of atoms. This quantity, based on the principles of nuclear quadrupole resonance (NQR) spectroscopy, is a measure of the quadrupolar charge density.

The electric charge distribution of quadrupolar nuclei can be calculated via the NQR method. The quantum mechanical approach can be used to define the charge distribution of molecules and complexes, while the electric field gradient (EFG) is estimated at any point around the quadrupolar nucleus that has a nuclear electric quadrupole moment (Q). The result of the interaction of EFG and Q is the splitting of the nucleus energy levels, and finally, the values of the nuclear quadrupole coupling constants (NQCCs) are measures of these interactions. The components of the NQCC tensor can be acquired via quantum chemical calculations. The charge density at the nucleus is determined by the NQCC of the nucleus [17-18]. To examine uridine and some of its derivatives (Figure 1), we studied charge density of some effective atoms. The eight pharmacophore points identified in the studied molecules were classified as Hydrogen acceptor sites (N1, O4, O5, O6) and hydrogen donor sites (O1, O2, O3, N2).

This study looks at how molecular topology can be a reliable tool for finding new lead compounds to treat Alzheimer's and may be useful for better drug design.

2. Computational Details

Uridine contains one primary hydroxyl group, two secondary hydroxyl groups, and one NH group, which are expected to influence its electronic properties. Therefore, knowing the charge density of the mentioned atoms and how the charge is distributed on them as active sites can be an effective aid in suggesting more useful derivatives. For this purpose, electric field gradient (EFG) and nuclear quadrupole coupling constants (NQCCs) were calculated.

All compounds optimized without any constraints using Gaussian 09 [19] at the B3LYP/6-31G* level. EFG calculations were performed on the selected compounds to compare the oxygen, hydrogen and nitrogen

charge densities in the considered compounds and the nuclear quadrupole coupling constants (NQCCs) for mentioned atoms were computed. The methodology for determining NQCC parameters has been detailed in several publications [20,21]. The EFG is characterized as a traceless symmetric second-rank tensor. Its principal components are designated as q_{zz} , q_{yy} , and q_{xx} , arranged in the order of decreasing absolute value. The NQCC is defined by the expression:

$$\text{NQCC} = e^2 Q q_{zz} / h$$

which is measured in hertz, with h : Planck constant and Q : the nuclear electric quadrupole moment. The nuclear electric quadrupole moments are regarded as fixed constants rather than variable parameters [22]. Based on the various reported quadrupole moment values for atoms, we selected $Q(^{17}\text{O})=25.58$ mb, $Q(^2\text{H})=2.86$ mb and $Q(^{14}\text{N})=20.44$ mb as noted by Pyykko[23]. Calculated NQCCs of some effective atoms reported in tables 1-3.

Following that, calculations for natural bond orbital (NBO) were conducted at the B3LYP/6-31G* theoretical level, with the findings presented in table 4.

3. Results And Discussion

3.1. Calculated NQCCs and charge density

Examining the above results shows that in the studied compounds, the charge density of the relevant quadrupolar atoms is almost equal; only the ether oxygen atoms (O₂, O₃) in compound 2 have a higher NQCC values compared to the O₂ and O₃ oxygen atoms in the other two compounds about 1 MHz. These points indicate a reduction in the electron density of the mentioned oxygen atom. The results of the calculations in tables 1-3 also show that the presence of the phosphate group in compound 3 leads to a decrease in O₁-NQCC of compound 3.

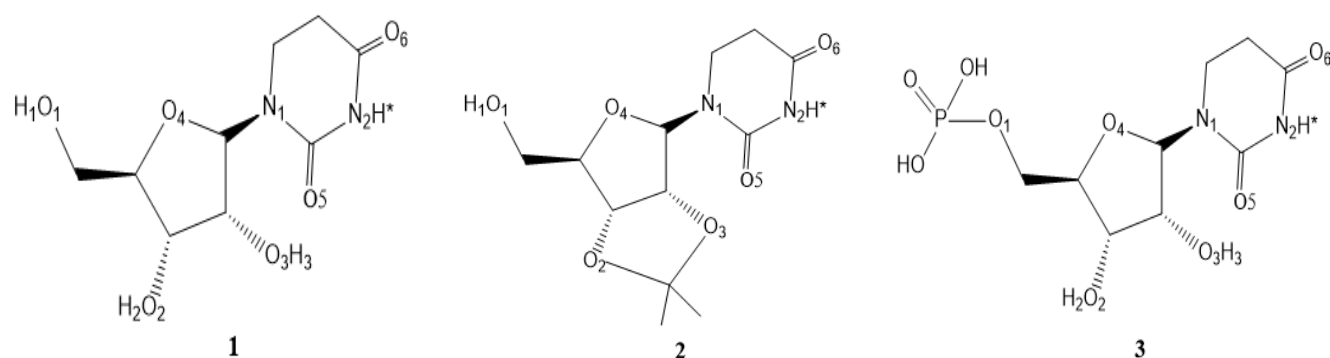


Figure 1. Structures of 1-3

Table 1. Calculated NQCCs of 1

atom	EFG	NQCC	atom	EFG	NQCC
O ₁	1.904	11.45	H ₁	0.443	297.88
O ₂	1.714	10.31	H ₂	0.435	292.50
O ₃	1.760	10.58	H ₃	0.396	266.28
O ₄	1.846	11.10	H*	0.373	250.81
O ₅	1.363	8.20	N ₁	0.824	3.96
O ₆	1.558	9.37	N ₂	0.754	3.62

¹⁷O- NQCCs and ¹⁴N-NQCCs in MHz, ²H-NQCCs in KHz

Table 2. Calculated NQCCs of 2

atom	EFG	NQCC	atom	EFG	NQCC
O ₁	1.883	11.32	H ₁	0.441	296.53
O ₂	1.837	11.05	H ₂	---	---
O ₃	1.865	11.22	H ₃	---	---
O ₄	1.805	10.86	H*	0.373	250.81
O ₅	1.361	8.18	N ₁	0.831	3.99
O ₆	1.560	9.38	N ₂	0.760	3.65

¹⁷O- NQCCs and ¹⁴N-NQCCs in MHz, ²H-NQCCs in KHz

Table 3. Calculated NQCCs of 3

atom	EFG	NQCC	atom	EFG	NQCC
O ₁	1.584	9.53	H ₁	---	---
O ₂	1.716	10.32	H ₂	0.435	292.50
O ₃	1.766	10.62	H ₃	0.400	268.96
O ₄	1.817	10.93	H*	0.372	250.14
O ₅	1.361	8.18	N ₁	0.831	3.99
O ₆	1.562	9.39	N ₂	0.758	3.64

¹⁷O- NQCCs and ¹⁴N-NQCCs in MHz, ²H-NQCCs in KHz

This result indicates an increase in the charge density of O₁ atom in compound 3. In justification of the above points, it can be noted that in quadrupolar atoms with non-bonding electron pairs, such as oxygen and nitrogen, the increase in charge density leads to an increase in the symmetry of the electric field gradient and

consequently a decrease in the nuclear quadrupole coupling constant of these atoms.

3.2. NBO Analysis

Analyzing natural bond orbitals (NBO) was also conducted to further investigate the charge density of oxygen atoms in various uridine

derivatives. NBO analysis can help predict conjugative interactions and examine molecular reactivity [24]. To explore electron delocalization in the oxygen of these derivatives, E(2) stabilization energies were analyzed to characterize donor–acceptor interactions using the B3LYP/6-31G* theoretical method. This analysis involved the interaction between the occupied donor NBO(i) and the unoccupied acceptor NBO(j). The formula for stabilization energy E(2) is described as:

$$E(2) = \Delta E_{ij} = q_i \frac{F_{ij}^2}{\varepsilon_i - \varepsilon_j}$$

where q_i represents the natural population of the donor NBO(i), F_{ij} indicates the off-diagonal element of the Fock matrix in the NBO basis, and ε_i and ε_j denote the energies of the donor and acceptor NBOs, respectively. The most important donor–acceptor interactions obtained for the investigated uridine derivatives are summarized in table 4. Compounds 1 and 2 exhibit very similar interaction patterns, indicating only minor differences in their electronic structures. In contrast, compound 3 shows several additional interactions involving the O1 atom and the phosphate group. Particularly significant are the interactions ($\text{LpO1} \rightarrow \sigma^*_{\text{P-O}}$) and ($\sigma_{\text{O1-P}} \rightarrow \sigma^*_{\text{P-O}}$), which are absent in compounds 1 and 2. These interactions provide additional pathways for electron delocalization involving the O1 atom. Furthermore, the stabilization energies associated with these interactions are relatively large, indicating efficient electron-density transfer within the phosphate moiety.

It is also observed that the interactions in which O1 acts as an electron acceptor are generally stronger than those in which it acts as a donor. Consequently, the net effect of these interactions is an increase in the electron density around the O1 atom in compound 3. This conclusion is fully

consistent with the NQCC results, which showed a significant reduction in the O1-NQCC value for compound 3. Therefore, both NBO and NQCC analyses identify O1 as the most electronically affected site upon phosphorylation of uridine.

Table 4. Donor and Acceptor NBOs of the studied uridine derivatives

Interaction (donor→acceptor)	E(2) (Kcal mol ⁻¹)
1	
$\sigma_{\text{C-C}} \rightarrow \sigma^*_{\text{C-O6}}$	24.21
$\text{LpO5} \rightarrow \sigma^*_{\text{C-N1}}$	27.95
$\text{LpO5} \rightarrow \sigma^*_{\text{C-N2}}$	25.26
$\text{LpO6} \rightarrow \sigma^*_{\text{C-C}}$	18.23
$\text{LpO6} \rightarrow \sigma^*_{\text{C-N2}}$	30.66
$\text{LpN1} \rightarrow \sigma^*_{\text{C-O5}}$	57.10
$\text{LpN1} \rightarrow \sigma^*_{\text{C-C}}$	38.69
$\text{LpN2} \rightarrow \sigma^*_{\text{C-O5}}$	63.91
$\text{LpN2} \rightarrow \sigma^*_{\text{C-O6}}$	48.60
2	
$\sigma_{\text{C-C}} \rightarrow \sigma^*_{\text{C-O6}}$	23.58
$\text{LpO5} \rightarrow \sigma^*_{\text{C-N1}}$	28.08
$\text{LpO5} \rightarrow \sigma^*_{\text{C-N2}}$	25.39
$\text{LpO6} \rightarrow \sigma^*_{\text{C-C}}$	18.40
$\text{LpO6} \rightarrow \sigma^*_{\text{C-N2}}$	30.58
$\text{LpN1} \rightarrow \sigma^*_{\text{C-O5}}$	56.82
$\text{LpN1} \rightarrow \sigma^*_{\text{C-C}}$	38.73
$\text{LpN2} \rightarrow \sigma^*_{\text{C-O5}}$	63.59
$\text{LpN2} \rightarrow \sigma^*_{\text{C-O6}}$	48.83
3	
$\sigma_{\text{C-C}} \rightarrow \sigma^*_{\text{C-O6}}$	23.90
$\text{LpO5} \rightarrow \sigma^*_{\text{C-N1}}$	28.04
$\text{LpO5} \rightarrow \sigma^*_{\text{C-N2}}$	25.24
$\text{LpO6} \rightarrow \sigma^*_{\text{C-C}}$	18.40
$\text{LpO6} \rightarrow \sigma^*_{\text{C-N2}}$	30.72
$\text{LpN1} \rightarrow \sigma^*_{\text{C-O5}}$	56.46
$\text{LpN1} \rightarrow \sigma^*_{\text{C-C}}$	38.43
$\text{LpN2} \rightarrow \sigma^*_{\text{C-O5}}$	63.93
$\text{LpN2} \rightarrow \sigma^*_{\text{C-O6}}$	48.46
$\sigma_{\text{O1-P}} \rightarrow \sigma^*_{\text{P-O}}$	24.91
$\text{LpO1} \rightarrow \sigma^*_{\text{P-O}}$	15.52
$\sigma_{\text{O-P}} \rightarrow \sigma^*_{\text{P-O1}}$	16.37
$\sigma_{\text{O-P}} \rightarrow \sigma^*_{\text{P-O1}}$	13.99
$\sigma_{\text{O-P}} \rightarrow \sigma^*_{\text{P-O1}}$	24.30

Previous studies [16] have demonstrated the biological activity and inhibitory potential of

uridine derivatives against Alzheimer's disease, with uridine monophosphate showing superior activity among the compounds investigated. In the present study, the electronic structures of selected uridine derivatives were comparatively analyzed using DFT calculations to gain insight into the possible electronic factors underlying their different biological performances. The results suggest that the charge density on the O1 oxygen atom may play a key role in determining the biological activity of these compounds. Substituents capable of increasing the electron density at this oxygen atom may enhance the inhibitory potential of uridine derivatives. Although this observation is based on theoretical calculations, it provides a plausible electronic explanation for the reported differences in biological activity and may serve as a useful guideline for the rational design of more potent uridine-based anti-Alzheimer agents.

3.3. Frontier Molecular Orbital (HOMO–LUMO) Analysis

To further investigate the electronic properties and reactivity of the studied uridine derivatives, frontier molecular orbital (FMO) analysis was performed based on the HOMO and LUMO energies calculated at the B3LYP/6-31G* level. The HOMO–LUMO energy gap (ΔE) was determined as the difference between the LUMO and HOMO energies. In addition, several global reactivity descriptors, including ionization potential (I), electron affinity (A), electronegativity (χ), chemical potential (μ), chemical hardness (η), chemical softness (S), and electrophilicity index (ω), were calculated from the HOMO and LUMO energies. The following relationships were employed:

$$I = -E_{HOMO}$$

$$A = -E_{LUMO}$$

$$\chi = \frac{I + A}{2}$$

$$\mu = -\frac{I + A}{2}$$

$$\eta = \frac{I - A}{2}$$

$$S = \frac{1}{2\eta}$$

$$\omega = \frac{\mu^2}{2\eta}$$

Electronegativity (χ) represents the tendency of a molecular system to attract electron density. Chemical hardness (η) describes the resistance of a molecular system to changes in its electronic distribution or charge transfer. Chemical softness (S) is the reciprocal of chemical hardness and is generally associated with the tendency of a molecular system to undergo electronic reorganization. In general, a harder molecule is more resistant to charge transfer, whereas a softer molecule is more readily polarizable and reactive. The electron affinity (A) and ionization potential (I) were estimated from the LUMO and HOMO energies, respectively, according to the equations given above. The HOMO is generally associated with electron-donating ability, whereas the LUMO is associated with electron-accepting ability.

The calculated HOMO–LUMO energies and global reactivity descriptors are presented in Table 5. The HOMO energies become progressively more negative from compound 1 to compound 3, changing from -6.2915 to -6.4475 eV. Similarly, the LUMO energies decrease from -0.6631 eV for compound 1 to -0.8079 eV for compound 3. The calculated HOMO–LUMO gaps are very similar for the three derivatives, ranging from 5.6284 to 5.6396 eV. Therefore, the HOMO–LUMO energy gap alone does not indicate a substantial difference in the overall electronic stability or reactivity of

the investigated compounds. The calculated chemical hardness values are also very similar, with values of 2.8142, 2.8145, and 2.8198 eV for

compounds 1, 2, and 3, respectively. Consequently, only minor differences are observed in the corresponding softness values.

Table 5. HOMO–LUMO energies and global reactivity descriptors of uridine derivatives 1–3 at the B3LYP/6-31G* level.

Parameter	Compound 1	Compound 2	Compound 3
HOMO(eV)	-6.2915	-6.3607	-6.4475
LUMO(eV)	-0.6631	-0.7317	-0.8079
ΔE (eV)	5.6284	5.6290	5.6396
χ (eV)	3.4773	3.5462	3.6277
μ (eV)	-3.4773	-3.5462	-3.6277
η (eV)	2.8142	2.8145	2.8198
S (eV ⁻¹)	0.17767	0.17765	0.17732
ω (eV)	2.1484	2.2341	2.3335

Table 6. Molecular docking results of uridine derivatives 1–3 and the reference ligand donepezil.

Modes (kcal/mol)	Ligand			
	Donepezil	1	2	3
1	-12.2	-7.3	-8.1	-8.3
2	-11.7	-7.1	-7.7	-8.0
3	-11.7	-7.1	-7.5	-7.9
4	-11.1	-7.0	-7.4	-7.8
5	-10.2	-7.0	-7.4	-7.8
6	-10.0	-7.0	-7.4	-7.6
7	-9.8	-6.9	-7.4	-7.6
8	-9.8	-6.9	-7.4	-7.5
9	-9.7	-6.8	-7.4	-7.4

These results suggest that the three derivatives possess comparable resistance to changes in their electronic distributions. In contrast, the electronegativity increases from 3.4773 eV for compound 1 to 3.6277 eV for compound 3. The chemical potential becomes progressively more negative in the same order, indicating an increasing tendency to attract or accept electron density.

A gradual increase in the electrophilicity index is also observed, from 2.1484 eV for compound 1 to 2.2341 eV for compound 2 and 2.3335 eV for compound 3. Thus, compound 3 exhibits the highest electrophilicity among the investigated derivatives. Although the differences in hardness and softness are relatively small, the systematic increase in electronegativity, the magnitude of the chemical potential, and the electrophilicity index provide

additional information regarding the electronic characteristics of the studied compounds. These findings complement the NQCC and NBO results and, together with the molecular docking results, support compound 3 as the derivative with the most favorable overall computational profile. Nevertheless, these global electronic descriptors should be regarded as complementary electronic indicators and should not, by themselves, be considered direct evidence of biological activity.

3.4. Molecular Docking Results

AutoDock Vina was used to perform molecular docking calculations to examine how uridine derivatives 1–3 might bind to the chosen site on the 4EY7 receptor. Human acetylcholinesterase (AChE) was chosen as the molecular docking target due to its well-documented role in the

cholinergic system and its significance as a therapeutic target for Alzheimer's disease. The 3D crystal structure of recombinant human AChE bound to donepezil was retrieved from the Protein Data Bank (PDB ID: 4EY7). This structure was solved by X-ray crystallography at 2.35 Å resolution and includes donepezil (E20) as a co-crystallized ligand. Having a high-resolution experimental structure of a clinically relevant AChE inhibitor provides a good structural basis for assessing how well the studied uridine derivatives bind. Furthermore, the ligand–AChE complex determined experimentally allows the binding site to be defined using a biologically relevant conformation of the enzyme bound to an inhibitor. Therefore, PDB ID 4EY7 was chosen to examine if compounds 1–3 could bind favorably to the active site of human AChE and to compare their predicted binding affinities with those of the reference inhibitor, donepezil. To ensure a consistent comparison, the identical receptor structure, docking box, and search parameters were used for all three compounds. The docking box was centered at $x = -13.9875$, $y = -43.9055$, and $z = 27.1085$ Å, with dimensions of $24 \times 18 \times 22$ Å. An exhaustiveness value of 16 was used, resulting in the generation of nine binding modes for each ligand.

As illustrated in Table 6, compound 3 demonstrated the most advantageous predicted binding affinity among the examined uridine derivatives, achieving a best docking score of -8.3 kcal/mol. Compound 2 attained the second-best score at -8.1 kcal/mol, whereas compound 1 displayed a relatively weaker predicted affinity of -7.3 kcal/mol. Consequently, the predicted binding affinity ranking for the three uridine derivatives is as follows: $3 > 2 > 1$. The disparity between compounds 3 and 2 is merely 0.2

kcal/mol, suggesting that their predicted binding affinities are quite similar. Thus, this minor difference should not be construed as conclusive evidence of a significant variation in biological activity. Nonetheless, the more favorable score for compound 3 may be attributed to the presence of its phosphate-containing group, which adds extra oxygen atoms that can engage in polar and hydrogen-bonding interactions within the binding site. In comparison, the reference ligand donepezil yielded a considerably more favorable docking score of -12.2 kcal/mol in the same binding site. Therefore, under the computational parameters utilized in this study, all three uridine derivatives exhibited less favorable predicted binding affinities than donepezil. These results highlight the differences in the predicted receptor-binding characteristics of the uridine derivatives, with compound 3 achieving the most favorable docking score in this series.

4. Conclusion

In this study, the electronic properties of uridine and two related derivatives were investigated using density functional theory (DFT) calculations at the B3LYP/6-31G* level. Electric field gradients (EFGs), nuclear quadrupole coupling constants (NQCCs), and Natural Bond Orbital (NBO) analyses were employed to examine the charge-density distribution at selected oxygen, nitrogen, and hydrogen atoms.

The calculated NQCC values revealed that most quadrupolar atoms exhibit only minor variations in charge density among the studied compounds. However, significant changes were observed for the O1 atom upon phosphorylation. The presence of the phosphate group in compound 3 resulted in a noticeable decrease in both EFG

and NQCC values of O1, indicating an increase in electron density around this atom.

The NBO analysis further confirmed this observation by revealing several additional donor–acceptor interactions involving O1 and the phosphate group that were absent in the other compounds. These interactions enhance electron delocalization and contribute to the increased electron density at the O1 site. The excellent agreement between NQCC and NBO results identifies O1 as the most electronically sensitive site in the investigated molecules.

Overall, the results demonstrate that phosphorylation significantly modifies the local electronic environment of uridine derivatives. The combined NQCC and NBO analyses provide valuable information about charge-density distribution and electronically active sites, which may be useful for the rational design and further investigation of biologically active uridine-based compounds.

The observed sensitivity of the O1 site to structural modification suggests that this position may play an important role in determining the electronic and biological properties of uridine derivatives. These findings, together with previous reports on the biological activities of uridine-based compounds, may support future experimental and computational studies on their biological potential. The HOMO–LUMO and molecular docking analyses consistently highlighted compound 3 as the most promising derivative among the investigated compounds, exhibiting favorable electronic characteristics and the strongest predicted binding affinity toward AChE.

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مطالعه برخی مشتقات اوریدین با پتانسیل ضد آلزایمر با استفاده از نظریه تابعی چگالی

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چکیده

اوریدین یکی از نوکلئوتیدهای مهم زیستی است که در بیوسنتز RNA و متابولیسم فسفولیپیدها نقش دارد و به دلیل ارتباط بالقوه آن با عملکرد سیستم عصبی و بیماری آلزایمر مورد توجه قرار گرفته است. در این پژوهش، اوریدین و دو مشتق آن به منظور بررسی ویژگی‌های الکترونی و توزیع چگالی بار با استفاده از نظریه تابعی چگالی (DFT) در سطح B3LYP/6-31G* مورد مطالعه نظری قرار گرفتند. چگالی الکترونی در هشت جایگاه حساس مولکولی، شامل اتم‌های گیرنده پیوند هیدروژنی (N1، O4، O5 و O6) و اتم‌های دهنده پیوند هیدروژنی (O1، O2، O3 و N2)، از طریق محاسبه و مقایسه گرادیان میدان الکتریکی (EFG) و ثابت‌های جفت‌شدگی چهارقطبی هسته‌ای (NQCC) ارزیابی شد. نتایج نشان داد که تغییرات چگالی الکترونی در بیشتر اتم‌های مورد بررسی نسبتاً ناچیز است. با این حال، حضور گروه فسفات در ترکیب ۳ موجب کاهش مقدار NQCC اتم O1 و در نتیجه افزایش چگالی الکترونی در این جایگاه شد. تحلیل اوربیتال طبیعی پیوندی (NBO) نیز این یافته را تأیید کرد و وجود برهم‌کنش‌های اضافی دهنده-گیرنده مرتبط با O1 و گروه فسفات را نشان داد که موجب افزایش دلوکالیزاسیون الکترونی و انتقال چگالی بار به این ناحیه می‌شوند. تطابق مناسب نتایج NQCC و NBO نشان داد که O1 حساس‌ترین و فعال‌ترین جایگاه الکترونی در مشتقات مورد مطالعه است. همچنین، تحلیل‌های HOMO-LUMO و داکینگ مولکولی، به طور همسو، ترکیب ۳ را به عنوان امیدبخش‌ترین مشتق در میان ترکیبات مورد بررسی شناسایی کردند که دارای ویژگی‌های الکترونی مطلوب و قوی‌ترین میل اتصال پیش‌بینی شده به آنزیم استیل‌کولین‌استراز (AChE) بود. این یافته‌ها نشان می‌دهد که افزایش چگالی الکترونی در اتم O1 می‌تواند در طراحی مشتقات جدید اوریدین با ویژگی‌های زیستی مطلوب‌تر مورد توجه قرار گیرد و اطلاعات نظری ارزشمندی برای توسعه ترکیبات دارای فعالیت بالقوه ضد آلزایمر فراهم کند.

واژه‌های کلیدی

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