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CREATION OF NOVEL GENERATION INHIBITORS WITH POTENTIAL EFFECT AGAINST ALZHEIMER'S DISEASE

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Abstract: *Using fine organic synthesis methods and the latest capabilities of computational chemistry, for the first time, 2-(4-amino-6-phenyl-1,2,5,6-tetrahydro-1,3,5-triazine-2(1H)-ylidene)-malononitrile, which contains a triazine ring and various functional groups in the molecule, was synthesized without the presence of a catalyst through a one-step three-component reaction. Structural analyses were carried out using X-ray and Hirshfeld surface analysis, and it was determined that asymmetric molecules of 2-(4-amino-6-phenyl-1,2,5,6-tetrahydro-1,3,5-triazine-2(1H)-ylidene)-malononitrile and a dimethylformamide solvent molecule in the asymmetric unit crystallize as a racemate in the monoclinic P21/c space group. These molecules exhibit stereochemical activity at the carbon atoms where the triazine rings are attached to the phenyl ring.*

For the first time, theoretical predictions using Density Functional Theory calculations for the synthesis reaction of tetrahydro-s-triazine via a one-step three-component condensation without a catalyst were experimentally tested. Comprehensive theoretical-experimental studies were conducted using quantum chemical calculations to simulate these chemical reactions, leading to significant results. The synthesis under milder conditions and atom-efficient methods obtained through computer simulations further enhances the importance of this work.

This compound has shown high inhibitory effects on acetylcholinesterase in living organisms, and multiple analyses, including "molecular docking" studies, have revealed that in the future, representatives of these inhibitors with different functional groups could potentially be used as drugs against epilepsy, Alzheimer's, and other neurological diseases.

Keywords: *triazine, DFT, enzyme inhibitor, molecular docking, Alzheimer's.*
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1. Introduction

An enzyme inhibitor is a molecule that binds to an enzyme and reduces its activity. As we know, enzymes accelerate chemical reactions that convert substrate molecules into products essential for life. When an enzyme binds to its substrate at the active site, it facilitates the reaction. Enzyme inhibitors, on the other hand, bind to an enzyme at a specific site other than the active site, thereby slowing down the reaction's most challenging step [1-2].

An enzyme inhibitor binds to the enzyme's active site, blocking substrate binding and preventing the enzyme from catalyzing the reaction. It can also bind to a different site on the enzyme, halting the process, which is why it is called an inhibitor [3-4].

An enzyme inhibitor is not just a molecule that binds to enzymes. Enzyme activators bind to enzymes and increase their activity [5-6].

When an inhibitor binds, it prevents the substrate from entering the enzyme's active site and stops the enzyme from catalyzing the

reaction. The inhibitor binding may be reversible or irreversible. Irreversible inhibitors usually change the enzyme chemically by entering the reaction and modifying it. These inhibitors often remove essential amino acids from the enzyme's active site, stopping its function. Conversely, reversible inhibitors bind in a non-covalent manner, allowing the enzyme to return to its active state after dissociation.

Enzyme inhibitors can have various forms depending on whether they bind to the enzyme, the enzyme-substrate complex, or both [7-10].

As mentioned above, drug molecules' selectivity towards enzymes makes enzyme inhibitors valuable for drug discovery and development. Their discovery and development involve intensive research in biochemistry, bioorganic chemistry, and pharmacology. Enzyme inhibitors often have high specificity (no interaction with other proteins) and potential (measured by the dissociation constant showing the concentration needed to inhibit the enzyme) high specificity and potential ensure low toxicity and effective action [11-14].

Acetylcholinesterase (AChE) is an enzyme found in our central and peripheral nervous systems, in nerve and muscle tissues, erythrocytes, and the placenta. AChE quickly breaks down acetylcholine into acetate and choline, rendering it harmless. Butyrylcholinesterase (BChE) is another type of cholinesterase synthesized in the liver and released into the bloodstream. It is found in fatty tissues, the small intestine, lungs, and other organs, as well as in the brain and plasma. BChE hydrolyzes butyrate and other esters of choline [15].

AChE and BChE catalyze the hydrolysis of acetylcholine and similar esters. One AChE molecule can hydrolyze 4×10^5 ACh molecules per minute, and it can maintain this efficiency over 150 cycles. BChE is found in plasma and various tissues, especially the liver.

Differences in enzyme specificity can result in significant toxicological distinctions among organophosphorus compounds. Organophosphorus compounds (OP) inhibit AChE, causing severe neurotoxicity. Research into inhibitors' mechanisms and central nervous system activity has been extensive. OP insecticides significantly inhibit AChE, leading to severe poisoning symptoms [16].

2. Materials and methods

2.1. Synthesis of 2-(4-amino-6-phenyl-1,2,5,6-tetrahydro-1,3,5-triazine-2(1H)-ylidene)malononitrile.

(E)-1-(amino(1H-pyrazol-1-yl)methylene)guanidinium chloride (188 mg, 1 mmol), benzaldehyde (106 mg, 1 mmol), and malononitrile (66 mg, 1 mmol) mixture was stirred in methanol for 5 hours. Then, the solvent was removed under vacuum from the reaction zone and recrystallized from methanol using charcoal to obtain suitable crystals for X-ray analysis by slow evaporation of the DMF solution. The colorless solid (47%) was obtained. Analysis: $C_{27}H_{27}N_{13}O$ calculated for Mr = 549.6: C 59.01, H 4.95, N 33.13; found: C 58.98, H 4.89, N 33.07%. ^{1}H NMR (DMSO-d_6) δ 8.58 (NH), 8.30 (NH), 7.95 (CH), 7.31 - 7.45 (5H, Ar-H), 5.62 (CH), 2.72 and 2.88 (2CH3). ^{13}C NMR (DMSO-d_6) δ 165.17, 162.44, 155.68, 141.91, 128.78, 128.72, 125.73, 119.45, 119.19, 61.867, 37.8. ESI-MS: m/z: 550,5 $[M+H]^+$.

2.2. Details of the Computer Calculations

The Gaussian 16 software package was used for computer calculations. The mechanisms and intermediate stages of all the intermediate steps described in Scheme -1 were calculated using the DFT/B3LYP function with Grimme's empirical dispersion correction (D3). The 6-31G(d,p) basis sets were used for all atoms. The reaction calculation was carried out under the experimental conditions (1 atm and the boiling point of the solvent (methanol) at 337.15 K). All reaction pathways were calculated with the self-consistent reaction field and the dielectric constant of methanol (ε = 32.613). The internal reaction coordinates were used to confirm the relationships between all intermediate stages and transition states. The Cartesian coordinates, total energies, and Gibbs energies of all structures were calculated without geometric constraints [17-20].

2.3. Measurement of AChE Enzyme Activity.

The effect of new compounds on AChE enzyme activity was investigated using Ellman's method. The IC50 and Ki values were determined, and inhibition types were identified. As previously noted, cholinesterases catalyze the breakdown of acetylcholine to choline and acetate. The product of this reaction, 5-thio-2-nitrobenzoic acid, forms a yellow color when reacting with DTNB. The resulting composite color absorbs at 412 nm, and the absorbance is measured at 412 nm within 5 minutes using empty cuvettes as blanks [21-24].

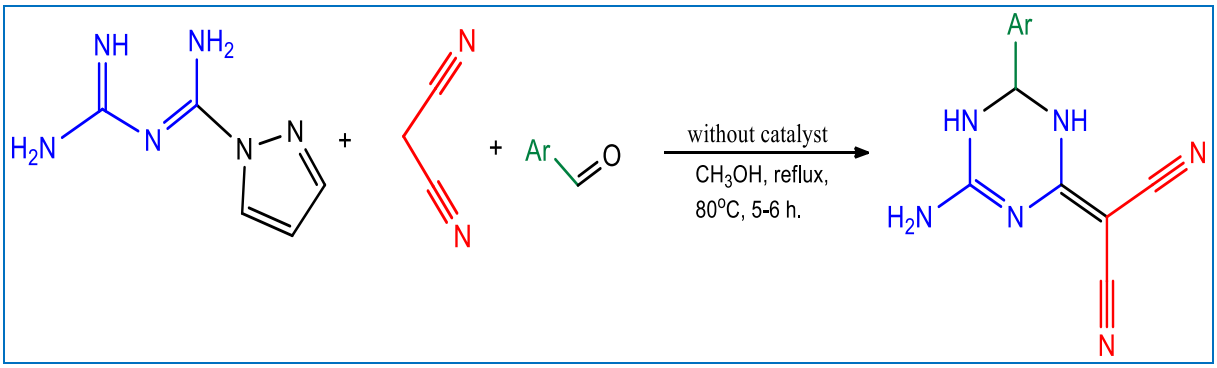
2.4. Molecular Docking Calculations.

In this study, silico docking studies were performed using the AutoDock Vina program. In addition, the DFT/B3LYP theoretical approach and the Gaussian 09W software with the 6-311++G(d,p) basis set were used for the optimization of the structures studied for molecular docking [25-29].

3. Results and Discussion

3.1. Structural Analysis of the Obtained Compound

Triazine derivatives can be synthesized through various methods. The most common methods include nucleophilic aromatic substitution of cyanuric chloride, formation of triazine rings by cycloaddition reactions, and cyclotrimerization of nitriles [30]. Especially, the use of a one-step three-component reaction is effective and easy, allowing for multifunctional compounds to be obtained. Thus, in this study, (E)-1-(amino(1H-pyrazol-1-yl)methylene)guanidinium chloride, benzaldehyde, and malononitrile were synthesized using a one-step three-component reaction to form 2-(4-amino-6-phenyl-5,6-dihydro-1,3,5-triazine-2(1H)-ylidene)malononitrile (Scheme 1).



Scheme 1. Reaction for the synthesis of 2-(4-amino-6-phenyl-5,6-dihydro-1,3,5-triazine-2(1H)-ylidene)malononitrile

The studied compound crystallizes in an asymmetric unit containing two independent molecules (Molecule I and Molecule II) and one dimethylformamide solvent molecule. Fig. 1 shows the overlap of Molecule I and Molecule II in the asymmetric unit with a difference of 0.173 Å.

Both molecules I and II form a dihedral angle of 86.8° (2)° and 86.63° (9)° respectively, for the phenyl ring (I) on C4-C9 and the triazine ring (II) on C16-C21. Each molecule has one stereogenic center. The asymmetric unit consists of a racemic mixture with the C13 atoms linked through N–H···N and N–H···O hydrogen bonds. The molecules are connected in parallel layers via the dimethylformamide solvent molecule.

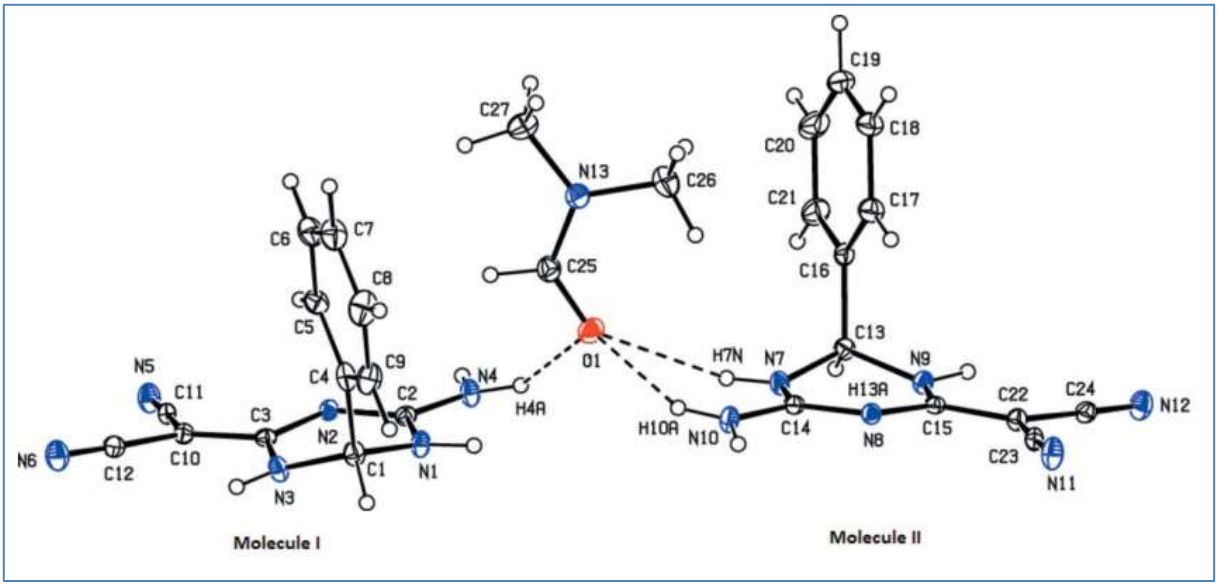
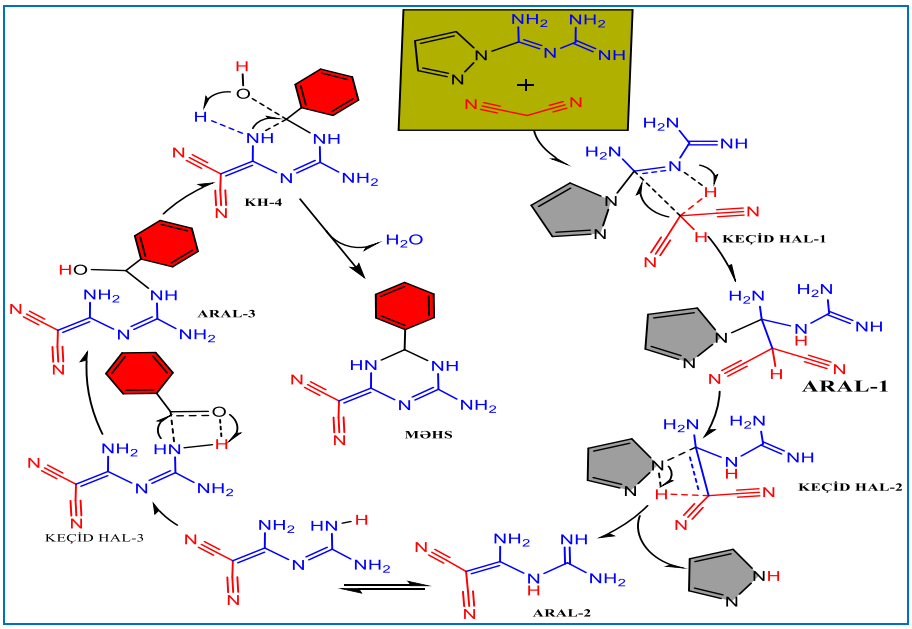


Fig. 1. Molecular structure of the compounds

3.2. DFT Study of the Synthesis Reaction

The reaction mechanism calculated based on Density Functional Theory (DFT) is shown in Scheme 2.



Scheme 2. Mechanism of triazine ring formation and synthesis of tetrahydro-s-triazine (PRO) from pyrazole and malononitrile based on quantum chemical calculations

Based on X-ray analysis, the pyrazole group's nucleophilic addition to the nitrile carbon of malononitrile initiates the formation of the triazine ring. This structure is stabilized by the presence of malononitrile's imine (CH=N) nitrogen atom, which acts as a proton acceptor.

The initial step involves the nucleophilic attack on the nitrile carbon by pyrazole's nitrogen (protonated by hydrogen). This results in the formation of intermediate INT1 and protonation of malononitrile's nitrogen atom. Intermediate INT2 is formed through a series of steps involving proton migration (tautomerization). This is followed by the elimination of a proton from malononitrile's imine nitrogen and the formation of intermediate INT3. The structure of INT3 undergoes a proton transfer to form INT4, followed by the release of an amine proton to

produce the final product, tetrahydro-s-triazine (PRO). The proposed mechanism is confirmed through quantum chemical calculations.

3.3. Study of Enzyme Activity and Inhibitor Effects

We analyzed the enzyme and isoenzyme activities using inhibitors prepared in our laboratory in collaboration with the University of Bartin, Turkey.

As previously noted, acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes play a critical role in the peripheral nervous system. AChE hydrolyzes acetylcholine, terminating neurotransmission. BChE, on the other hand, hydrolyzes butyrylcholine and other esters. This study focused on the inhibitory effects of the newly synthesized compounds on AChE and BChE. The IC50 and Ki values were determined for AChE (Ki = 52.07 ± 8.33 μM, IC50 = 71.5 μM) and BChE (Ki = 165.37 ± 6.94 μM, IC50 = 198.24 μM).

In vitro experiments showed that the newly synthesized compound effectively inhibits AChE and BChE activities. The IC50 values obtained from these experiments confirmed the inhibitor's strong activity.

3.4. Molecular Docking Studies

We performed molecular docking studies to understand the inhibitory mechanisms of the synthesized compounds. The binding affinity of the molecules to the catalytic active sites of AChE was evaluated using AutoDock Vina. High binding scores were obtained, indicating strong interactions with the active sites. The preferred binding modes showed the compound's ability to interact with both hydrophobic and hydrophilic residues in the active site. The calculated binding affinities and docking results are shown in Fig. 2.

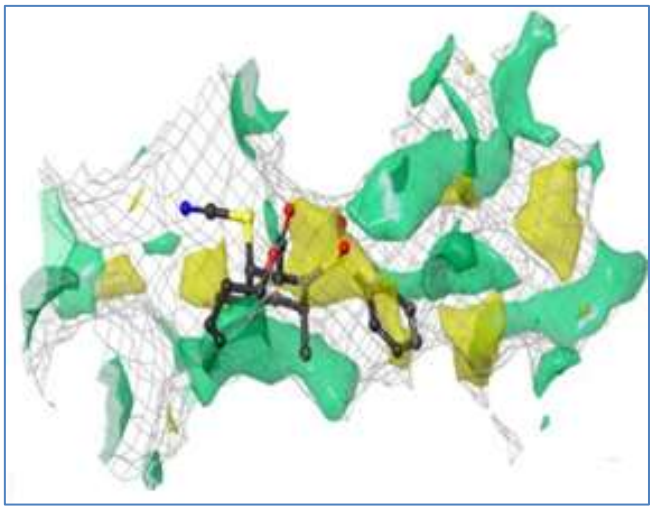


Fig. 2. Evaluation of binding affinity and docking results for the AChE active site. New inhibitor-AChE.

The docking study identified favorable binding modes where the compound fits into the enzyme's active site, forming hydrogen bonds with key residues.

Additionally, the root-mean-square deviation (RMSD) values between the re-docked and co-crystallized ligands were sufficiently good to accept the docking method as accurate. These results also confirmed the reliability of the docking method.

After docking validation, most active compounds were similarly placed in the catalytic active site.

The binding affinities of the docked compounds were analyzed using docking calculations. These scores are presented in Table 1. The new compound showed binding affinity to the AChE enzyme similar to standard inhibitors. Additionally, their binding affinities were consistent with previously well-studied inhibitors.

Table 1. Binding Affinity of the New Inhibitor to the AChE Enzyme

New Inhibitor	Docking Calculations AChE
New Inhibitor	-6.623
TAC [*]	-9.579

[*] *TAC is used as a standard inhibitor for AChE enzyme.*

The interactions between the best-docked compound and enzyme residues were analyzed to understand their possible inhibition mechanism.

The phenyl ring of the new compound fits well with the hydrophobic residues of the AChE enzyme. However, the cyano fragment of the compound is positioned far from the catalytic active site. The carboxyl part of the compound forms a hydrogen bond with the Tyr72 residue and a π-π stacking interaction with the phenyl ring of Tyr341.

In addition to these interactions, the sulfonyl part of Tyr72, Trp286, and Tyr341 residues form aromatic hydrogen bonds. Through a bridge, the Tyr72 residue also forms a hydrogen bond with the Thr75 residue. These interactions likely contribute to the compound's binding affinity. Multiple hydrogen bonds are formed with Arg213, Asn350, Asp352, and Gln353 residues, as shown in Fig. 3.

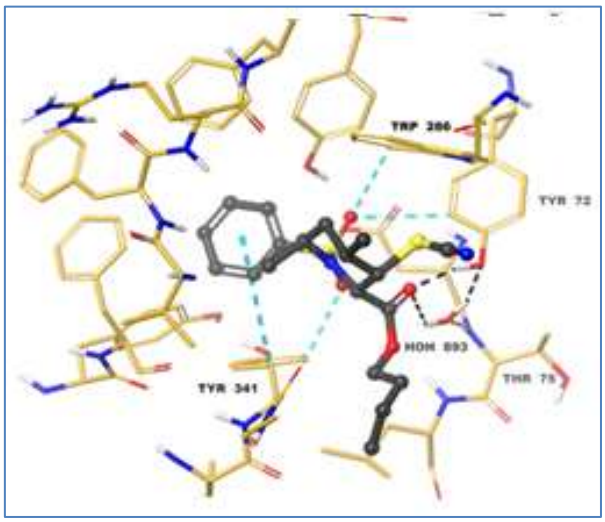


Fig. 3. Best binding site of the new compound in the catalytic active site of the enzyme. The docking compound is represented as black sticks, with residues forming hydrogen bonds shown with black dashed lines, cyan dashed lines for aromatic hydrogen bonds, and blue dashed lines for π-π stacking.

Water molecules, particularly Wat707, Wat751, Wat720, Wat922, Wat708, and Wat701, play a significant role in the enzyme's catalytic active site. They form hydrogen bonds with Glu277, Asp352, Arg213, Glu349, and some hydrophobic residues, facilitating the enzyme's catalytic activity in substrate hydrolysis.

Summarizing the above, the new synthetic compound exhibits AChE inhibitory activity. The IC50 values determined from the experiments are consistent with standard inhibitors across all targets.

Molecular modeling results showed that the new inhibitor binds to the AChE enzyme with a binding affinity of -6.623 kcal/mol. These data confirm the compound's potential effectiveness in treating Alzheimer's disease and preventing retinal damage by inhibiting the enzyme and blocking signal transduction in cells.

Thus, summarizing the above findings, it can be concluded that AChE is a crucial enzyme that controls the transmission of signals in nerve

cells. This enzyme catalyzes the hydrolysis of acetylcholine into choline and acetic acid, allowing active cholinergic neurons to return to normal function. The inhibition of cholinesterase enzymes has a positive effect on treating Alzheimer's disease and other neurodegenerative conditions.

Conclusion

Using fine organic synthesis methods and the latest capabilities of computational chemistry, for the first time, (E)-1-[amino(1H-pyrazol-1-yl)methylene]guanidinium chloride, benzaldehyde, and malononitrile were synthesized without a catalyst, in a one-step, three-component reaction with methanol in a 1:1:1 molar ratio, over 5 hours. The compound 2-(4-amino-6-phenyl-5,6-dihydro-1,3,5-triazine-2(1H)-ylidene)malononitrile was synthesized with a 47% yield. The obtained substance was analyzed by X-ray structure analysis, showing that it crystallizes as a monoclinal racemate in an asymmetric unit with two independent molecules and one dimethylformamide solvent molecule. Each molecule has stereochemical activity at the carbon atoms where the triazine rings are attached to the phenyl ring. Hirshfeld surface analysis provided stability insights, and Van der Waals interactions played a role in monocrystal formation.

Using modern computational program capabilities, DFT calculations for the mechanism of the one-step, three-component reaction were theoretically studied and confirmed by experimental results.

The compound showed high inhibitory effects on the AChE enzyme in our experiments, including molecular docking studies. The results suggest that the compound has potential as a clinical candidate, with different functional group inhibitors showing promise against epilepsy, Alzheimer's disease, and other neurological disorders in future clinical applications.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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ALZEYMER XƏSTƏLİYİNƏ QARŞI POTENSİAL TƏSİRƏ MALİK YENİ NƏSİL İNHİBİTORLARIN YARADILMASI

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Xülasə: Zərif üzvi sintez üsulları və kompüter kimyasının ən son imkanlarından istifadə etməklə birmərhələli üçkomponentli reaksiya vasitəsilə ilk dəfə katalizator iştirakı olmadan molekulda triazin halqası və müxtəlif funksional qrup saxlayan 2-(4-amino-6-fenil-1,2,5,6-tetrahidro-1,3,5-triazin-2(1H)-iliden)-malononitril sintez edilmiş və X-ray, Hirşfeld səthi analizi ilə struktur təhlilləri aparılmışdır. Strukturun tədqiqi rentgen və Hirshfeld səth analizlərindən istifadə edilməklə aparılmışdır və müəyyən edilmişdir ki, 2-(4-amino-6-fenil-1,2,5,6-tetrahidro-1,3,5-triazinin asimmetrik molekulları – 2(1H)-iliden)-malononitril və dimetilformamid həlledici molekulu monoklin rasemat quruluşunda və *P21/c* fəza qrupunda kristallaşır. Bu molekullar triazin halqalarının fenil halqasına bağlandığı karbon atomlarında stereofəallığa malikdir.

İlk dəfə olaraq katalizator olmadan bir mərhələdə üçkomponentli kondensləşmə ilə tetrahidro-s-triazinin sintezi reaksiyası üçün Funksional Sıxlıq Nəzəriyəsi hesablamaları ilə nəzəri proqnozlar təcrübi olaraq test edilmiş, kvant kimyəvi hesablamalarla həmin kimyəvi reaksiyaların simuliyasiyası baxımından əhatəli nəzəri-təcrübi araşdırmalar aparılmış və mühüm nəticələr əldə

olunmuşdur. Kompüter simulyasiyası ilə əldə olunan daha mülayim şəraitdə və atom qənaətcil üsul ilə sintez olunması bu işin önəmini daha da artırmışdır;
Bu birləşmənin canlı orqanizmdə asetilxolinesteraza üzrə yüksək inhibitor təsirlərə malikdir və çoxsaylı analizlər, o cümlədən "molekulyar dokinq" tədqiqatları nəticəsində məlum olmuşdur ki, gələcəkdə bu inhibitorların ayrı-ayrı funksional qrupa malik nümayəndələri epilepsiya, Alzeymer və digər nevroloji xəstəliklərə qarşı qarşı potensial dərman maddələri kimi istifadə oluna bilər.
Açar sözlər: triazin, DFT, enzim inhibitoru, molekulyar dokinq, Alzeymer.

СОЗДАНИЕ ИНГИБИТОРОВ НОВОГО ПОКОЛЕНИЯ С ПОТЕНЦИАЛЬНЫМ ДЕЙСТВИЕМ ПРОТИВ БОЛЕЗНИ АЛЬЦГЕЙМЕРА

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Резюме: Используя методы тонкого органического синтеза и новейшие возможности вычислительной химии, впервые получен 2-(4-амино-6-фенил-1,2,5,6-тетрагидро-1,3,5-триазин-2(1H)-илиден)-малононитрил, содержащий в молекуле триазиновое кольцо и различные функциональные группы, который синтезирован без присутствия катализатора одностадийной трехкомпонентной реакцией. Структурный анализ был проведен с использованием рентгеновского анализа и анализа поверхности Хиршфельда, и было установлено, что что асимметричные молекулы 2-(4-амино-6-фенил-1,2,5,6-тетрагидро-1,3,5-триазина – 2(1H)-илиден)малононитрил и растворителя диметилформамида кристаллизуются в виде рацемата в моноклинной пространственной группе *P21/c*. Эти молекулы проявляют стереохимическую активность у атомов углерода, где триазиновые кольца присоединены к фенильному кольцу.

Впервые экспериментально проверены теоретические предсказания с использованием расчетов теории дифференциального функционала (DFT) для реакции синтеза тетрагидро-s-триазина путем одностадийной трехкомпонентной конденсации без катализатора. Для моделирования этих химических реакций были проведены комплексные теоретико-экспериментальные исследования с использованием квантово-химических расчетов, которые привели к значительным результатам. Синтез в более мягких условиях и атомно-эффективные методы, полученные с помощью компьютерного моделирования, еще больше повышают важность этой работы.

Это соединение продемонстрировало высокие ингибирующие эффекты на ацетилхолинэстеразу в живых организмах, а многочисленные анализы, в том числе исследования «молекулярного стыковки», показали, что в будущем представители этих ингибиторов с разными функциональными группами потенциально могут быть использованы в качестве лекарств против эпилепсии, болезни Альцгеймера, и других неврологических заболеваний.
Ключевые слова: триазин, ТФП, ингибитор ферментов, молекулярный докинг, болезнь Альцгеймера.