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Synthesis and molecular docking study of ethyl piperidine-1-carboxylate derivative Schiff bases

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Abstract: In the present study, new Schiff bases (**14-16**) were obtained from the condensation reaction of Ethyl 4-aminopiperidine-1-carboxylate and 2/3/4-pyridine carboxyaldehyde compounds. Desired compounds were successfully synthesized with high yields in a short time. Chemical characterization (^{1}H-NMR, ^{13}C-NMR and elemental analysis) and molecular docking studies of the synthesized compounds were performed against the 7XN1 structure (human acetylcholinesterase in complex with tacrine) and reference drug (Donepezil and Tacrine). It was determined that compound **16** (-7.52) had higher binding energy than Tacrine (-7.48), and compounds **14** (-7.34) and **15** (-7.41) showed values close to Tacrine (-7.48). The synthesized compounds can be potent inhibitors for hAChE.

Keywords: Schiff base; microwave; molecular docking; tacrine; donepezil; green chemistry.

1. Introduction

Heterocyclic compounds play a vital role in the drug development process, providing a foundation for the discovery of new mechanisms of action due to their diverse structural features. Among these compounds, nitrogen-containing heterocycles are particularly noteworthy because, thanks to their ability to form hydrogen bonds, they offer the potential for specific binding to target proteins.[1] Heterocyclic compounds have become a rapidly expanding field with significant applications in chemistry, biology, and particularly in medicine.[2,3] These compounds possess important pharmacological effects, such as antimicrobial, antitumor, and antidepressant properties, and have substantial therapeutic potential against various diseases, playing a key role as essential components of synthetic drugs. The synthesis and modification of heterocyclic compounds provide innovative solutions for new drug design and targeted therapeutic approaches.[4,5]

Piperidine and its derivatives stand out among nitrogen-containing heterocyclic compounds and are frequently used in the development and synthesis of many vital pharmaceutical products. Compounds with a piperidine ring have significant potential in various effects, such as depression, anxiety, anticonvulsant, and antinociceptive.[6] Some examples of piperidine ring-containing compounds include Risperidone (**1**), used for symptomatic treatment of schizophrenia,[7] Levobupivacaine (**2**), a long-acting local anesthetic,[8] Clopidogrel (**3**), used as an antiplatelet in coronary diseases,[9] and Donepezil (**4**), used in the treatment of Alzheimer's disease.[10] (Figure 1).

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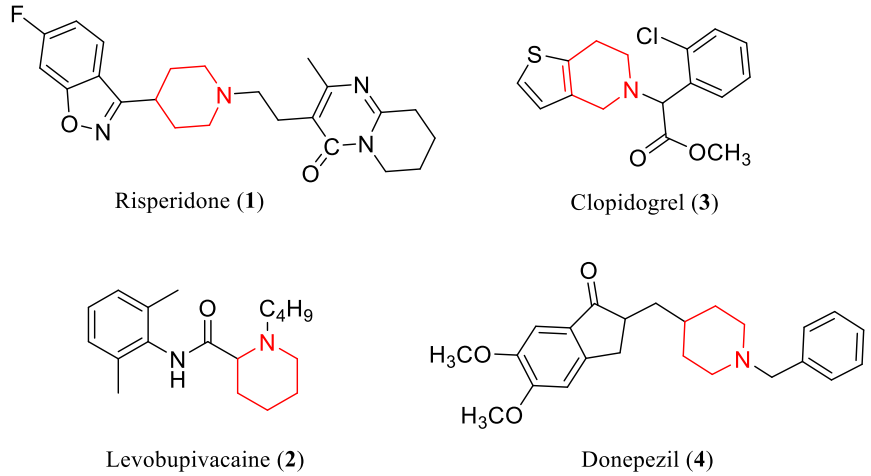

Figure 1. Some drugs containing piperidine ring system

In addition to piperidine, pyridine and its derivatives also hold an important place among nitrogen-containing heterocyclic compounds. Due to their chemical properties, they are used as precursors for various agricultural chemicals and pharmaceuticals.[11] These compounds possess a wide range of medical effects, such as antiviral, anti-HIV, anticancer, antitumor, antibacterial, antimalarial, anti-inflammatory, antidiabetic, and antioxidant properties.[12] For example, compounds like Abiraterone (**5**) for prostate cancer, Enpiroline (**6**) for malaria, Isoniazid (**7**) for tuberculosis, Omeprazole (**8**) for ulcers, and the AChE enzyme inhibitor Tacrine (**9**), used in the prevention of Alzheimer's disease, contain a pyridine skeleton in their structures.[13] (Figure 2).

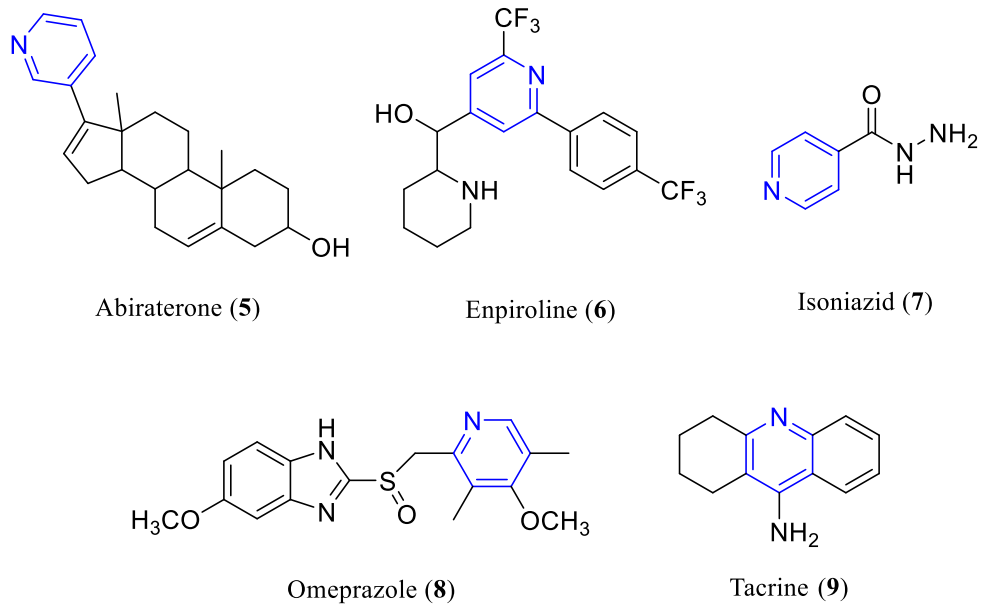

Figure 2. Some drugs containing pyridine ring system

Schiff bases are compounds containing the azomethine (-CH=N-) functional group and were first synthesized in 1864 by Hugo Schiff through the nucleophilic addition reaction of aldehydes or ketones with amines. [14,15] These compounds have become an important topic in medicinal chemistry due to their various biological activities.[16] Schiff bases play crucial roles in the regulation of cellular

metabolism and exhibit a range of beneficial effects such as antibacterial, antiviral, antifungal, antioxidant, anti-inflammatory, anticonvulsant, antidepressant, antihypertensive, antiproliferative and anticancer properties. [17,18,19]

Achieving chemical syntheses in a short time, at low cost, and with high yields is an important goal in research, and chemists have been working on this for many years. [20] In traditional synthesis methods, issues such as the use of toxic solvents, long reaction times, formation of by-products, high temperatures, long durations, and the need for catalysts are present, whereas the microwave method is more advantageous in these respects. [21,22] As one of the green synthesis methods, microwave synthesis allows solvent-free synthesis, reduces the formation of by-products, shortens reaction times, and helps achieve higher yields. These features provide significant advantages of the microwave synthesis method over traditional methods.[22,23]

One of the neurodegenerative diseases, Alzheimer's disease (AD), is an irreversible brain degeneration that progresses with symptoms such as memory loss, disorientation over time, and behavioral changes.[24] Increasing the acetylcholine level in the brain and using acetylcholinesterase (AChE) inhibitors is an important approach in the treatment of this disease. Various AChE inhibitors are being investigated for the treatment of Alzheimer's disease. Current drugs used in the treatment, such as Donepezil (**4**) and Tacrine (**9**), have limited effectiveness and cause severe vomiting, muscle cramps, nausea, hypotension, and respiratory disorders. [25] Therefore, the search for acetylcholinesterase (AChE) inhibitors with fewer side effects is of great importance.[26] Schiff bases, exhibiting different biological properties, have recently been identified as potential therapeutic agents in the treatment of various diseases, increasing research efforts in this area.[27] Key findings have revealed that Schiff bases can function as specific enzyme inhibitors, such as acetylcholinesterase (AChE). [28]

The process of turning pharmaceutical molecules into drugs is a long and costly procedure, involving both in vitro and in vivo testing.[29] Studying the structure-activity relationships of chemical molecules facilitates the design of more effective and selective drugs, while understanding the pharmacological properties of these compounds presents significant potential for medical applications.[30] Molecular docking studies serve as a critical tool in determining the interactions of compounds with target proteins and assessing their potential therapeutic effects. This method helps predict the binding tendencies of ligands to target proteins and is vital in understanding the dynamics of molecular interactions.[31] Therefore, these studies contribute significantly to drug development processes aimed at enhancing the effectiveness of chemical molecules while minimizing side effects. [32]

The literature highlights that nitrogen-containing heterocyclic compounds, Schiff bases, and pyridine and piperidine derivatives have significant pharmacological effects. [6,12,33] The pyridine scaffold is an essential core in many approved drugs, and its derivatives are studied for their biological and pharmacological activities.[34] Based on this, the study aims to synthesize new Schiff bases with a piperidine-carboxylate structure and a pyridine ring, hypothesized to have biological activity potential. Additionally, the microwave method, a green chemistry synthesis technique, was chosen for all syntheses, enabling the rapid and efficient production of the target molecules. Molecular docking analyses of the synthesized compounds will be performed against the acetylcholinesterase (AChE) enzyme. Through this, the potential for these compounds to serve as alternatives to existing treatments, such as Donepezil (**4**) and Tacrine (**9**) will also be evaluated.

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2. Experimental

2.1. Chemical Material and Apparatus

All chemicals used in the study were obtained from Sigma-Aldrich. The reactions were monitored by thin-layer chromatography (TLC) and were conducted using a microwave oven (230 V-50 Hz, 900 W). The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, using a Varian NMR spectrometer with $CDCl_3$ as the solvent. Elemental analysis was performed using a Leco CHNS932 device.

*2.2. General synthesis of Schiff bases **14-16***

The compounds **14-16** synthesized within the scope of the study were illustrated in Figure 3. The syntheses were performed according to the literature.[6,22] Ethyl 4-aminopiperidine-1-carboxylate (**10**) (1 mmol, 1 eq) and pyridine compounds (**11-13**) (1 mmol, 1 eq) were directly exposed to microwave irradiation at 900 W under solvent and catalyst-free conditions in a 5 mL reaction vessel. The reaction progress was monitored by TLC, revealing that the reactions were completed within 5 minutes. The new molecules (**14-16**) were characterized through spectroscopic methods and elemental analysis.

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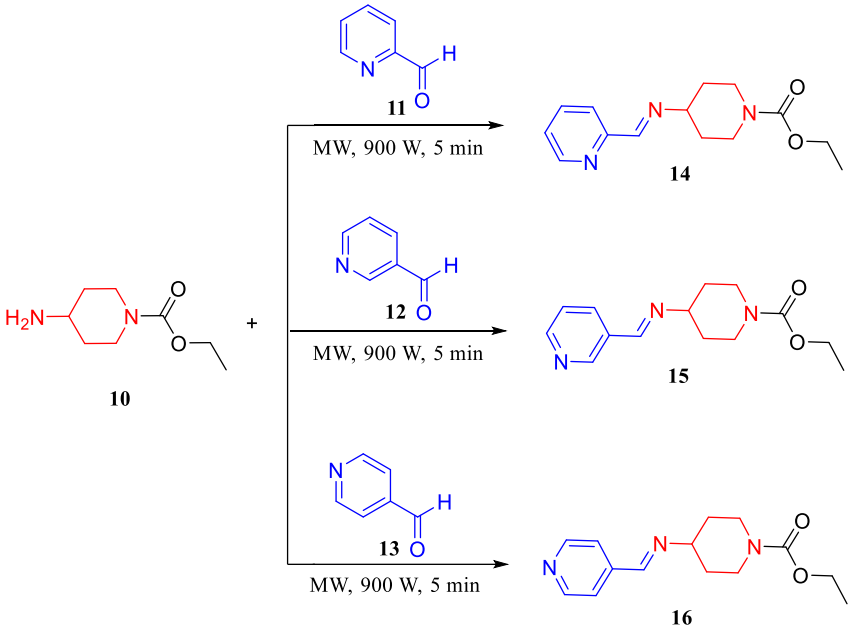

Figure 3. Synthesis of Schiff bases using microwave energy

2.3. Molecular Docking Studies

Molecular docking provides important insights into activity and safety in drug design and development.[31] Acetylcholinesterase (AChE) inhibitors are crucial in the treatment of neurodegenerative diseases such as Alzheimer's disease. The atomic structure of AChE complexes formed with different inhibitors can provide valuable structural information about the interactions between the active site residues and the inhibitors, which can contribute to structure-based drug design. [37]

In this study, in addition to docking studies conducted using the hAChE-tacrine complex structure, docking studies were also performed with Donepezil, Tacrine and newly synthesized compounds (**14-16**). The molecular structures of the target compounds were designed and optimized using ChemDraw 19.0. These structures were then converted into three-dimensional (3D) molecular models and saved in PDB (Protein Data Bank) format using Avogadro, ensuring proper geometry optimization and energy minimization. The crystal structure of human acetylcholinesterase in complex with tacrine (PDB: 7XN1) was retrieved from the protein database. [37,38]

Before molecular docking, ligands and protein structures were prepared using AutoDock Tools 1.5.7. This process included removing water molecules, adding polar hydrogen atoms, and determining appropriate docking parameters. Both ligand and protein molecules were then converted to the PDBQT file format, which is required for docking simulations in AutoDock. Molecular docking was performed to predict the binding affinity and the mode of interaction between the ligands and the active sites of the proteins. The grid parameters were selected with 60 × 60 × 60 Å x, y, z dimensions and a spacing of 0.553 Å. The x, y, z centers for the human acetylcholinesterase in complex with tacrine (PDB: 7XN1) were set as 48.324, -39.995, -30.076. The resulting protein-ligand complexes were analyzed using BioVia Discovery Studio Software, which allows visualization of hydrogen bond interactions, hydrophobic contacts, π-π stacking, and other non-covalent interactions critical for binding stability.

3. Results and Discussions

*3.1. Structural analysis of compounds (**14-16**)*

New chemical syntheses derived from the properties of microwave energy have been carried out in accordance with the goals of green chemistry, which is another aim of this study. Based on previous literature studies, this research used Ethyl 4-aminopiperidine-1-carboxylate (**10**) and various pyridine aldehyde compounds (**11-13**) as starting materials, and new Schiff base compounds (**14-16**) were synthesized without the addition of any catalyst or solvent. According to the analysis results, it was determined that a single compound was formed in each reaction. The spectral data of the compounds are presented below.

*Ethyl (E)-4-((pyridin-2-ylimino)methyl)piperidine-1-carboxylate (**14**)*: 98% yields, yellowish, solid. Mp. 111-114 ^{0}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 – 8.60 (m, 1H), 8.41 (s, 1H), 7.97 (d, *J* = 7.9 Hz, 1H), 7.76- 6.97 (m, *J* = 7.8, 1.7 Hz, 1H), 7.30 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 3H), 3.48 (dt, *J* = 13.8, 6.9 Hz, 1H), 3.13 – 2.95 (m, 2H), 1.83 – 1.67 (m, 4H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.79, 155.84, 154.72, 149.68, 136.80, 125.02, 121.70, 67.09, 61.51, 42.30, 33.18, 14.96. Elemental Analysis: Calcd. C, 64.35; H, 7.33; N, 16.08; Found C, 64.32; H, 7.38; N, 16.11.

*Ethyl (E)-4-((pyridin-3-ylimino)methyl)piperidine-1-carboxylate (**15**)*: 97% yields, yellowish, solid. Mp. 106-109 ^{0}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 – 8.80 (m, 1H), 8.66 – 8.58 (m, 1H), 8.36 (s, 1H), 8.09 (d, *J* = 7.9 Hz, 1H), 7.32 (dd, *J* = 7.9, 4.8 Hz, 1H), 4.12 (dt, *J* = 8.1, 6.6 Hz, 3H), 3.51 – 3.36 (m, 1H), 3.15 – 2.99 (m, 2H), 1.72 (dd, *J* = 10.0, 5.4 Hz, 4H), 1.24 (td, *J* = 7.1, 1.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.92, 155.83, 151.73, 150.48, 134.76, 131.94, 123.88, 67.46, 61.52, 42.22, 33.25, 14.95. Elemental Analysis: Calcd. C, 64.35; H, 7.33; N, 16.08; Found C, 64.34; H, 7.37; N, 16.06.

*Ethyl (E)-4-((pyridin-4-ylimino)methyl)piperidine-1-carboxylate (**16**)*: 97% yields, yellow, viscous. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 – 8.59 (m, 2H), 8.28 (s, 1H), 7.55 (dd, *J* = 4.4, 1.6 Hz, 2H), 4.10 (q, *J* = 7.1 Hz, 3H), 3.50 – 3.36 (m, 1H), 3.04 (dt, *J* = 13.5, 6.8 Hz, 2H), 1.69 (dt, *J* = 13.1, 7.8 Hz, 4H), 1.28 – 1.17 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.90, 155.80, 150.56, 143.13, 122.18, 67.32, 61.52, 42.12, 33.10, 14.93. Elemental Analysis: Calcd. C, 64.35; H, 7.33; N, 16.08; Found C, 64.40; H, 7.28; N, 16.04.

3.2. Molecular Ddocking

Molecular docking studies provide a clearer understanding of the research focus by examining interactions with specific target receptors and offer valuable insights into the efficacy of the compounds.[36] In this study, the 7XN1 structure (human acetylcholinesterase in complex with tacrine) was used for docking analyses with the synthesized compounds (**14-16**) and reference drugs (Tacrine and Donepezil). Tacrine showed conventional hydrogen bond was observed between HIS447 amino acid with the 2.22 A^o bond length. π-π Shaped interaction was between TYR337 (4.39 and 4.95 A^o) and TRP86 (4.05, 4.23,3.55 and 5.59 A^o). Also π- ALKYL interaction with TRP86 (5.01 and 4.31 A^o). Van der Waals interactions were observed between TYR449, GLY448, GLU202, SER203, TYR133, GLY120, GLY121, THR83, TYR341, GLY82, TR1639. All interactions are shown in detail in Figure 4.

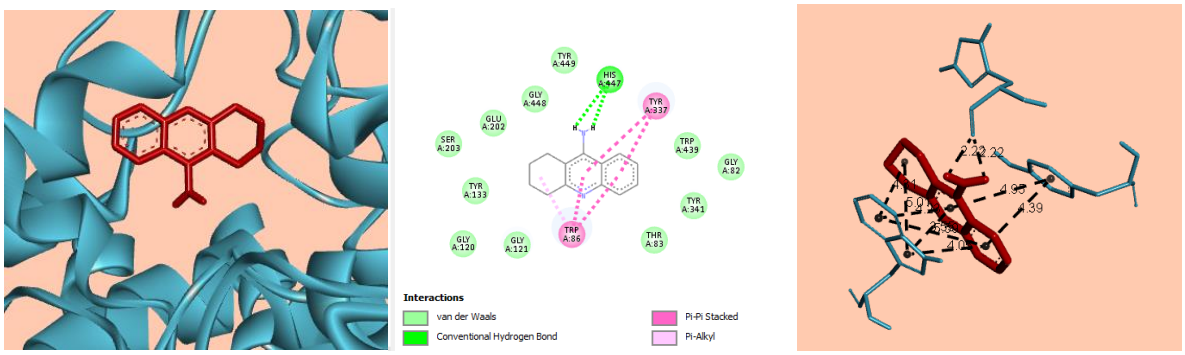

Figure 4. Docking interactions between the protein 7XN1and the Tacrine as the active compound

Donepezil showed conventional hydrogen bonds were observed between PHE295 and ARG266 acids with the 2.51 and 1.65 A° bond lengths, respectively. Carbon Hydrogen Bond was observed between GLN291 (3.25 A°), π-Anion interaction with ASP74 (3.76 A°), π-π shaped interaction was between TYR341 (5.35 A°), alkyl interaction with LEU289(4.08 A°). Also π-Alkyl interaction with TYR341(4.60 A°) and TR1486 (4.56 and 5.08 A°) amino acids. Van der Waals interactions were observed between TYR124, TYR337, PHE338, PHE297, VAL294, SER293, GLU292, TR1639, THR83, TRP86 and GLY82. All interactions are shown in Figure 5.

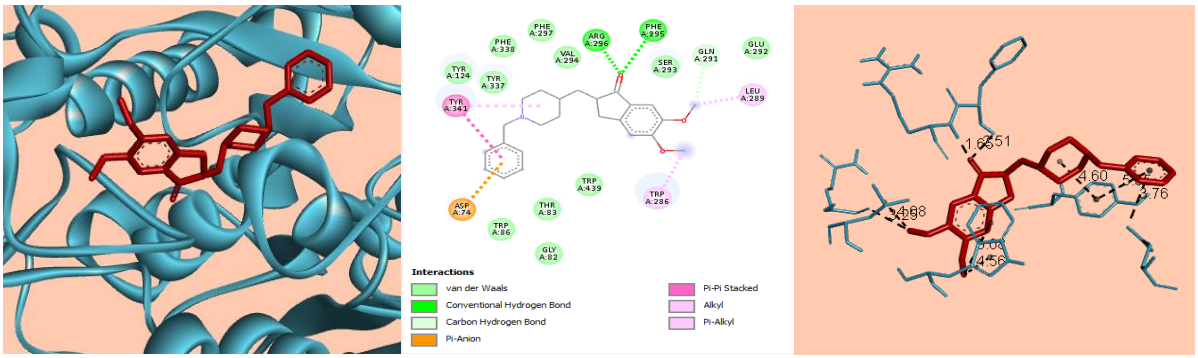

Figure 5. Docking interactions between the protein 7XN1and the Donepezil as the active compound

Compound **14** showed conventional hydrogen bonds were observed between PHE295 amino acid with the 1.87 A° bond length. π-π T-shaped interaction was between TYR341 (5.27 A°), alkyl interaction with VAL294 (4.95 A°). Also π-Alkyl interaction with TR1486 and TRY341 amino acids with the 5.26 and 4.72 A° bond length, respectively. Van der Waals interactions were observed between PHE338, ASP74, TRP86, THR83, TR1639, GLY82, TYR337, TYR124, ARG296, PHE297, SER293. All interactions are shown in Figure 6.

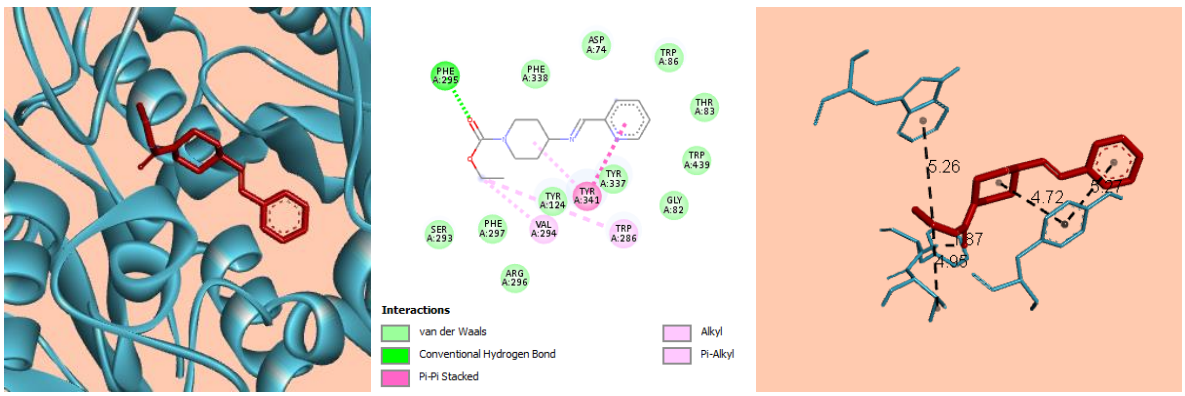

Figure 6. Docking interactions between the protein 7XN1 and compound **14**

Compound **15** showed carbon hydrogen bond observed between HIS447 and TYR337 amino acids with the 2.91 and 3.57 Aº bond length, respectively. π-sigma interaction with TRP86 (3.76 Aº), π-Alkyl interaction with TYR341 (5.20 Aº), TYR337 (4.68 and 4.34 Aº), HIS447 (5.35 Aº), TRP86 (4.15 -4.09Aº). Van der Waals interactions were observed between GLY448, TYR449, GLY82, TR1639, PHE338, VAL294, PHE295, ARG296, TR1486, PHE297, TYR124, ASP74 and THR83. All interactions are shown in Figure 7).

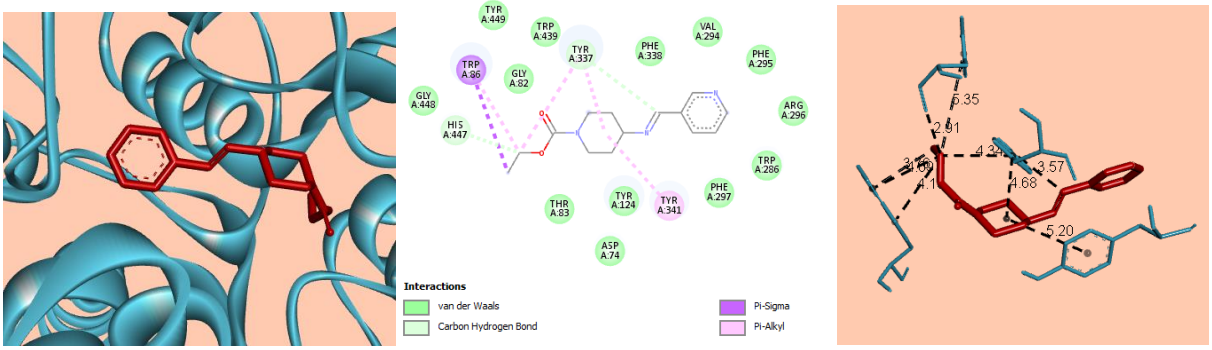

Figure 7. Docking interactions between the protein 7XN1 and compound **15**

Compound **16** showed conventional hydrogen bond observed between PHE295, TYR341, GLY82 and TRP86 amino acids with the 1.95, 2.82, 2.92 and 2.52 Aº bond lengths, respectively. Carbon Hydrogen Bond was observed between GLY82 (2.92 Aº) and TYR337 (3.50 Aº), π-sigma interaction was observed between GLY82 (2.92 Aº) and TRP86 (3.84 Aº). π-alkyl interactions existed between amino acids VAL294 (5.48 Aº), TYR341 (5.082 Aº), TYR337 (5.03 and 3.73 Aº), TR1639 (4.86 and 4.51 Aº), TYR449 (5.09 Aº), GLY82 (2.92 Aº), TRP86 (5.23 Aº), TRP86 (4.18 Aº) amino acids. Van der Waals interactions were observed between THR83, HIS447, ASP74, TYR124, PHE297, TR1486, ARG296 and PHE338. All interactions are shown in Figure 8.

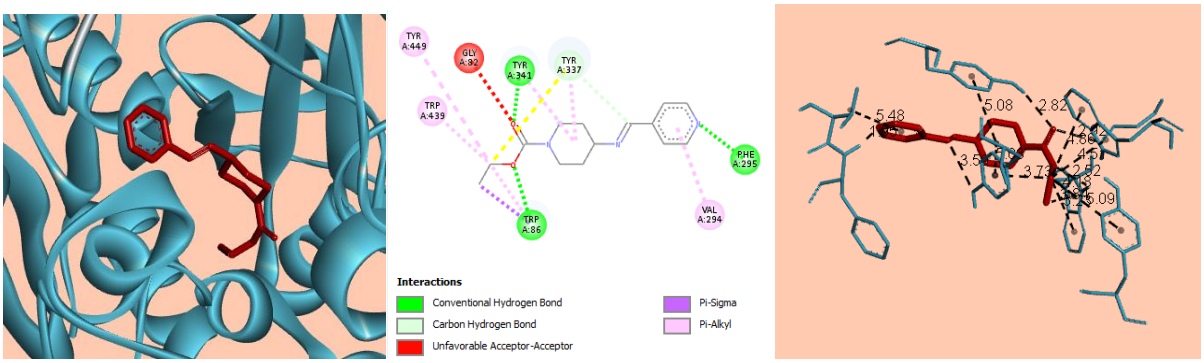

Figure 8. Docking interactions between the protein 7XN1 and the compound **16**.

4. Conclusion

Schiff bases are considered important and versatile compounds in the fields of organic and medicinal chemistry. These compounds exhibit a broad spectrum of biological activities, making them highly promising in the pharmaceutical industry. In this study, the desired Schiff bases (**14-16**) were synthesized via a condensation reaction between Ethyl 4-aminopiperidine-1-carboxylate (**10**) and pyridine aldehyde derivatives (**11-13**) using the microwave method. The obtained Schiff bases have offered significant advantages over the classical synthesis method. They were directly obtained without requiring any purification process, and the target compounds were successfully synthesized with high

yields in a short time. The practical applicability of the microwave method and the elimination of an additional purification step have provided a major advantage to this study. Furthermore, this method offers an environmentally friendly and efficient synthesis approach compared to the classical method, saving both time and resources. To investigate the interactions between AChE protein (7XN1) (human acetylcholinesterase complexed with tacrine) and the synthesized compounds, molecular docking studies were conducted. In this context, molecular docking analyses were performed on the synthesized compounds (**14**-**16**) and reference drugs (Tacrine and Donepezil) using the 7XN1 structure. According to the molecular docking results (PDB ID: 7NN1), the binding energies of the compounds were ranked as follows: Donepezil (-10.53) > Compound **16** (-7.52) > **Tacrine** (-7.48) ≥ Compound **15** (-7.41) > Compound **14** (-7.34). The data obtained indicates that compound **16** has a higher binding energy level than Tacrine, while compounds **14** and **15** show values close to **Tacrine**. All these findings support the potential use of the synthesized Schiff bases as acetylcholinesterase (AChE) enzyme inhibitors.

Conflicts of Interest

No conflict of interest was declared by the author.

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Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/organic-communications

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