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Simple Synthesis of New Bioactive Nitrogenous Compounds with In Silico Study †

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Abstract: A new derivative of nitrogenous compounds has been successfully synthesized through a simple reaction, resulting in an excellent yield. These molecules underwent theoretical simulation studies to verify their anti-Alzheimer and anti-cancer effects, such as Acetylcholinesterase, and cancer, such as Tubulin**.**

Keywords: nitrogenous compounds; ADMET study; anti-Alzheimer; anti-cancer; docking studies; theoretical simulation study

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1. Introduction

Nitrogenous compounds have significant biological activity and play a crucial role in the treatment of numerous diseases such as diabetes [1], Alzheimer's [2,3], and cancer [4]. Their ability to interact with various biological targets makes them valuable in drug development and therapeutic applications. develop medicament treats more than one disease it's verry important, and interesting to reduce number of medicinal medicaments in the future.

This study focuses on anti-Alzheimer's and anti-cancer chromophores to inhibit both diseases with the same remedy.

Inhibition of acetylcholinesterase aims to alleviate the symptoms of the disease, as this enzyme is responsible for the degradation of acetylcholine in the brain [5]. And Inhibition of tubulin can stop cell division in cancerous cells and may help overcome resistance to medication in the treatment of various cancers [6]. However, a limitation of some drugs is their non-selective binding to tubulin.

For this study, we use 3-hydrazinyl-1,2,4-triazine with quinoline to synthesize new nitrogenous compound derivatives, which will then be evaluated as potential anti-Alzheimer's and anti-cancer agents through advanced docking studies. This approach will involve assessing the compounds' interactions with specific biological targets implicated in Alzheimer's, such as acetylcholinesterase, and in cancer, such as tubulin.

Furthermore, a comprehensive ADMET analysis will be conducted to evaluate the pharmacokinetic profiles of these compounds, to study their effectiveness in both AChE and tubulin.

2. Materials and Methods

2.1. Material Used

The ligand was prepared using the Avogadro program, while target preparation was carried out in Chimera version 1.16. Energy minimization was performed using Swiss-PdbViewer (SPDBV) version 4.1, and the visualization and analysis were conducted using BIOVIA Discovery Studio 2021.3.

2.2. Methods

2.2.1. Ligand Preparation

Preparation of derivative compounds for docking studies involved to designing small molecules, optimize their geometry, and minimize their energy. The resulting structures were then saved in the .pdb format.

2.2.2. Targets Preparation

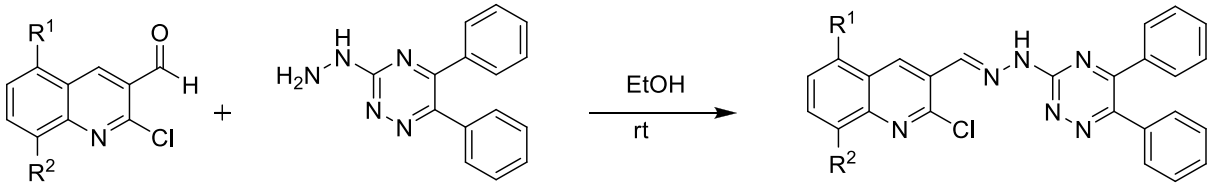
The acetylcholinesterase (AChE) protein (PDB ID: 4m0e) [7], and tubulin protein (PDB ID: 1sa0) [8], were obtained in .pdb format from the Protein Data Bank. The targets were prepared by removing water molecules, trimming unnecessary chains, and adding polar hydrogens. Energy minimization was then performed, and the results were visualized and analyzed.

2.2.3. Synthesis of Compounds

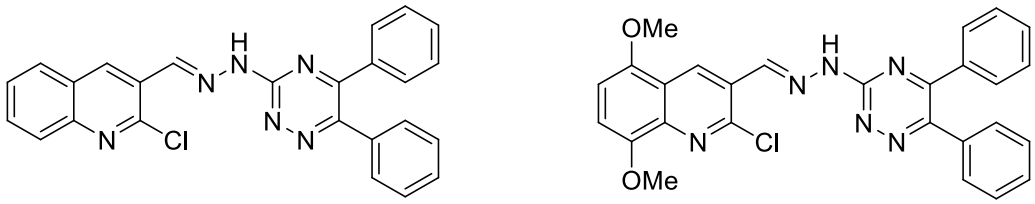
An equimolar mixture of quinoline derivatives and 3-hydrazinyl-5,6-diphenyl-1,2,4-triazine was stirred at room temperature in ethanol (EtOH) without a catalyst. The precipitate was then filtered, washed with EtOH, and recrystallized from EtOH.

3. Results and Discussion

The general procedure for synthesizing these compounds (Scheme1) was successfully completed, resulting in the formation of (E)-2-chloro-3-((2-(5,6-diphenyl-1,2,4-triazin-3-yl)hydrazono)methyl)quinoline and (E)-2-chloro-3-((2-(5,6-diphenyl-1,2,4- triazin-3-yl)hydrazono)methyl)-5,8-dimethoxyquinoline (Figure 1), with excellent yields. The synthesis involved a simple condensation reaction between quinoline derivatives and 3-hydrazinyl-1,2,4-triazine at room temperature without the use of a catalyst. The structures of the compounds were confirmed by NMR spectroscopy (Scheme 1).



Scheme 1. General procedure for synthesis.



A1 91%

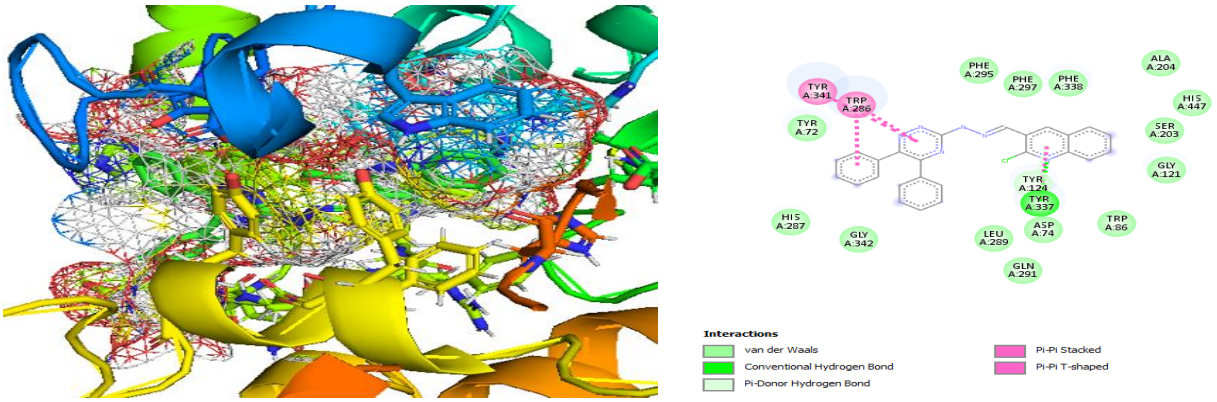
A2 94%

Figure 1. Structures and yields of the prepared derivatives.

3.1. Docking Study

the simulations of these compounds were evaluated for their inhibitory ability using Chimera, where the active site of the target atoms is fixed and the chromophore is flexible. As is well known, this program use a genetic algorithm (GA) to dock flexible ligands into protein binding site.

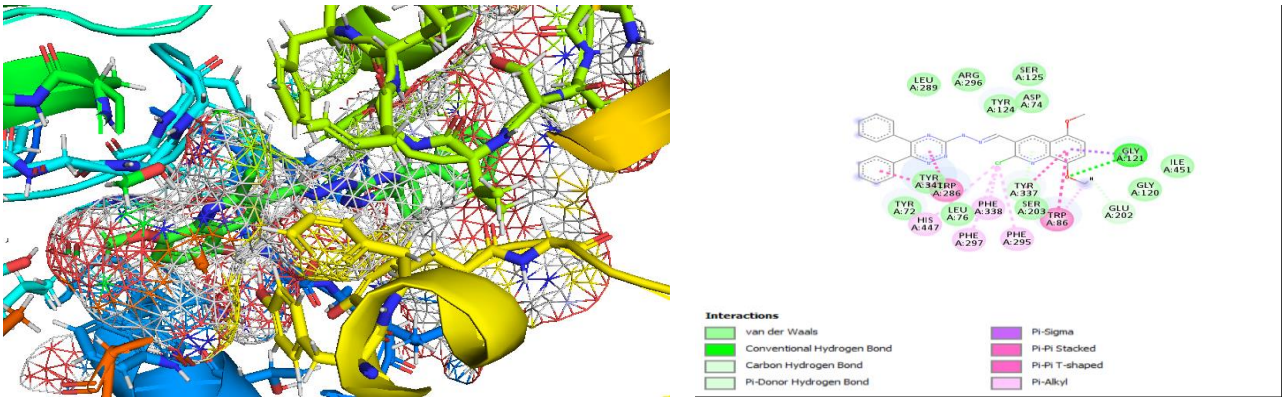
molecular docking study indicated a strong affinity and high scores within the active sites of acetylcholinesterase and tubulin, highlighting their potential for anti-Alzheimer's and anticancer activities (Figures 2–5).



A1 with AChE

Figure 2. Simulation of A1 in the active site of AChE.

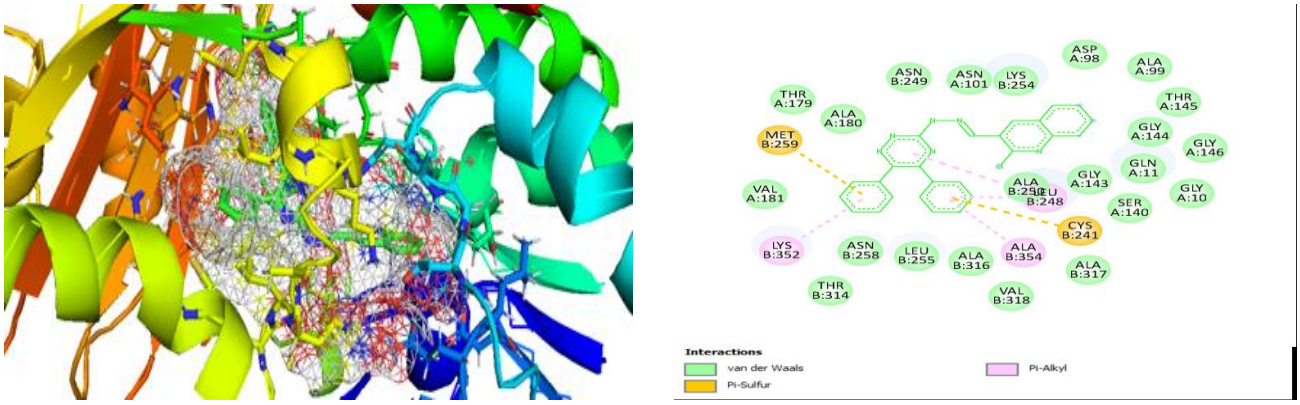
As we can see in (Figure 2), A1 is inside AChE with good affinity due to Van der Waals interactions with PHE A: 295, PHE A: 297, PHE A: 338, ALA A: 204, HIS A: 447, SER A: 203, GLY A: 121, TRP A: 86, ASP A: 74, LEU A: 289, GLN A: 291, GLY A: 342, HIS A: 287, TYR A: 72, a conventional hydrogen bond with TYR A: 337, a Pi-Donor hydrogen bond with TYR A: 124, and Pi-Pi stacked and T-shaped bonds with TYR A: 341 and TRP A: 286. These interactions demonstrate high affinity and a docking score of −10.5 kcal/mol, indicating good binding.



A2 with AChE

Figure 3. Simulation of A2 in the active site of AChE.

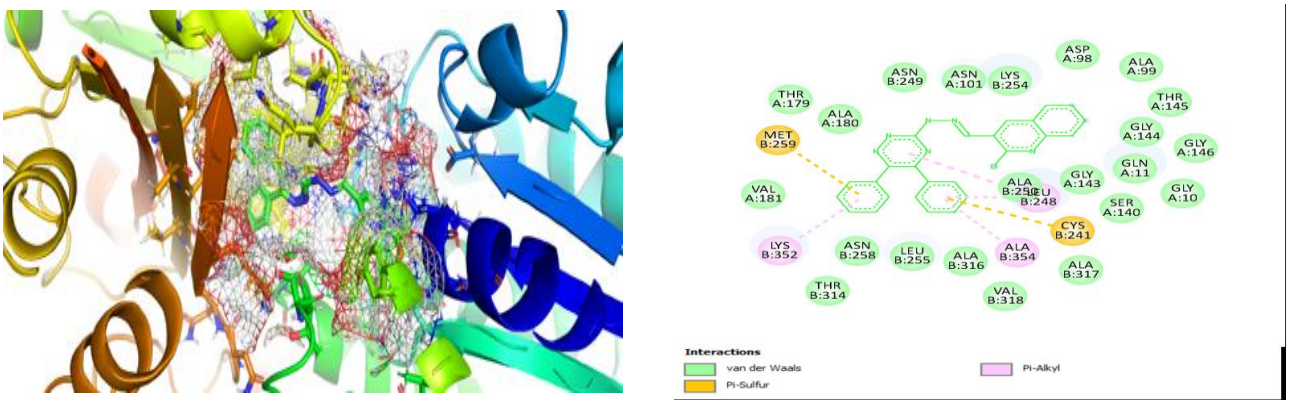
Similarly, A2 is inside AChE (Figure 3) with high affinity due to Van Der Waals interaction with LEU A: 289, ARG A: 296, SER A: 125, TYP A: 124, ASP A: 74, TYR A: 341, TYR A: 72, LEU A: 76, SER A: 203, GLY A: 120, ILE A: 451, hydrogen bond interactions with GLY A: 121, GLU A: 202, and TYR A: 337, a Pi-Sigma bond with GLY A: 121, and Pi-Pi (stacked, T-shaped, alkyl) bonds with TRP A: 286, TRP A: 86, PHE A: 338, HIS A: 447, PHE A: 297, and PHE A: 295. These interactions demonstrate high affinity and a docking score of −9.5 kcal/mol, indicating good binding.



A1 with TUBULIN

Figure 4. Simulation of A1 in the active site of Tubulin.

For tubulin, a1 in active site of Tubulin (Figure 4), there are Van der Waals interactions with THR A: 179, ALA A: 180, ASN B: 249, ASN A: 101, LYS B: 254, ASP A: 98, ALA A: 99, THR A: 145, GLY A: 144, GLY A: 146, GLN A: 11, GLY A: 10, GLY A: 143, SER A: 140, ALA B: 250, ALA B: 317, VAL B: 318, ALA B: 316, LEU B: 255, ASN B: 258, THR B: 314, VAL A: 181, Pi-Sulfur interactions with CYS B: 241 and MET B: 259, and Pi-Alkyl interactions with LYS B: 352, ALA B: 354, and LEU B: 248. These interactions indicate a strong affinity, with a docking score of −11.0 kcal/mol, suggesting a favorable binding.



A1 with TUBULIN

Figure 5. Simulation of A2 in the active site of Tubulin.

For compound a2 can be considered a very good inhibitor of Tubulin due to its numerous interactions (Figure 5), including van der Waals with ALA A: 180, THR A: 179, ASN B: 249, ASN A: 101, ALA A: 100, THR A: 145, GLY A: 144, GLY A: 146, SER A: 140, GLY A: 10, GLN A: 11, GLN A: 143, VAL B: 318, ASN B: 258, THR B: 314, VAL A: 181, hydrogen bonds with LYS B: 254, ALA A: 12, ASP A: 98, Pi-Sulfur interactions with MET B: 259, and Pi-Alkyl and Alkyl interactions with ALA A: 99, ALA B: 316, LYS B: 352, CYS B: 241, ALA B: 250, ALA B: 354, LEU B: 255, LEU B: 248, TYR A: 224,. These interactions demonstrate high affinity, with a docking score of −10.4 kcal/mol, suggesting that this compound could be considered a potential inhibitor.

3.2. Pharmacokinetic Study

According to the ADMET study by SwissADME (http: //www.swissadme.ch/index.php), both A1 and A2 adhere to Lipinski's rules and Veber's rules. By ADMETSAR, both compounds are able to cross the blood-brain barrier, which suggests they may reach the brain and potentially be effective as anti-Alzheimer's agents. Additionally, we used admetSAR(http: //lmmd.ecust.edu.cn/admetsar1) to confirm that they are non-AMES

toxic and non-carcinogenic. For P-glycoprotein, A2 acts as an inhibitor, which may provide a solution for anti-cancer treatment without falling into the trap of drug resistance (Table 1).

Table 1. Table of ADMET study results.

Entries	Lipinski's Rules	Veber's Rules	BBB	AMES Toxic	Carcinogenic	P-Glycoprotein Inhibitor
A 1	+	+	+	−	−	−
A 2	+	+	+	−	−	+

Significance: Yes (+); No (−).

4. Conclusions

Nitrogenous compounds were successfully synthesized with excellent yields using a simple condensation reaction between quinoline derivatives and 3-hydrazinyl-1,2,4-triazine, without the need for a catalyst. These compounds have demonstrated effective inhibition of AChE and tubulin in docking studies, exhibiting high affinity and good scoring, particularly compound A2, which shows strong interactions within the active site. Additionally, the ADMET study indicates that these compounds can cross the blood-brain barrier (BBB), suggesting their potential as anti-Alzheimer's agents. Moreover, A2 is an inhibitor of P-glycoprotein, which could offer a solution for anti-cancer treatment while avoiding drug resistance issues associated with the P-glycoprotein enzyme.

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Conflicts of Interest: The author declare no conflict of interest.

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