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In Silico Design, ADMET Prediction and Molecular Docking Studies of Novel Cyanopyridine-Substituted 1,3,5-Triazine Derivatives as Potential Anti-Alzheimer Agents

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Abstract

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder worldwide and is characterized by progressive cognitive impairment, memory loss, and behavioral dysfunction resulting from the degeneration of cholinergic neurons and the accumulation of amyloid-β plaques and neurofibrillary tangles. Despite the availability of several acetylcholinesterase (AChE) inhibitors, including donepezil, rivastigmine, and galantamine, their therapeutic benefits remain limited due to adverse effects, poor selectivity, and inability to halt disease progression. Consequently, the development of novel molecules possessing improved pharmacological efficacy and favorable pharmacokinetic properties remains an important objective in anti-Alzheimer drug discovery.The present study employed an integrated computer-aided drug design (CADD) strategy to design and evaluate fifty novel cyanopyridine-substituted 1,3,5-triazine derivatives as potential anti-Alzheimer agents. The designed molecules were generated by introducing structurally diverse aromatic, heterocyclic, and aliphatic amines onto the cyanopyridine–1,3,5-triazine scaffold in order to optimize receptor binding affinity and drug-like characteristics. Molecular structures were constructed using ChemDraw Ultra 8.0, followed by prediction of physicochemical properties, Lipinski's Rule of Five compliance, gastrointestinal absorption, aqueous solubility, synthetic accessibility, and overall pharmacokinetic behavior using SwissADME. Molecular docking studies were

subsequently performed using the CDOCKER module of Discovery Studio 3.0 against acetylcholinesterase (PDB ID: 1EVE) to investigate ligand–protein interactions and estimate binding affinities. The computational screening demonstrated that the majority of designed compounds satisfied accepted drug-likeness criteria and exhibited favorable ADMET profiles. Molecular docking identified several derivatives possessing significantly stronger binding affinities than other library members. Among the evaluated molecules, CPT-19, CPT-14, CPT-15, CPT-13, and CPT-12 exhibited the most favorable docking scores, suggesting stable interactions within the catalytic gorge of acetylcholinesterase through hydrogen bonding, hydrophobic interactions, π–π stacking, and van der Waals contacts. These findings indicate that structural modification of the cyanopyridine–1,3,5-triazine scaffold can substantially improve molecular recognition toward the target enzyme. Overall, the present investigation demonstrates the usefulness of integrated in silico methodologies for rapid identification of promising anti-Alzheimer lead compounds. The identified derivatives warrant further chemical synthesis followed by in vitro enzymatic evaluation, cellular assays, pharmacokinetic studies, and in vivo validation to establish their therapeutic potential.

Keywords

Alzheimer's disease; Acetylcholinesterase; Cyanopyridine; 1,3,5-Triazine; Molecular Docking; Computer-Aided Drug Design; SwissADME; Discovery Studio; Drug-Likeness; ADMET; Neurodegenerative Disorders.

1. Introduction

1.1 Alzheimer's Disease: A Growing Global Health Challenge

Alzheimer's disease (AD) is a chronic, progressive, and irreversible neurodegenerative disorder that represents the leading cause of dementia among elderly individuals worldwide. The disease gradually impairs memory, learning ability, executive function, language, reasoning, and behavioral performance, eventually leading to complete dependence on caregivers and ultimately death. The prevalence of Alzheimer's disease has increased dramatically during the past three decades owing to increased life expectancy and population aging, making it one of the most serious public health challenges of the twenty-first century. According to the World Health Organization, more than fifty-five million individuals currently suffer from dementia worldwide, and Alzheimer's disease accounts for approximately 60–70% of these cases. Epidemiological projections indicate that the number of affected individuals may exceed 130 million by the year 2050 if effective disease-modifying therapies are not developed. Besides causing substantial emotional and psychological suffering to patients and their families, Alzheimer's disease imposes enormous socioeconomic burdens on healthcare systems throughout the world.

Unlike acute neurological disorders, Alzheimer's disease develops gradually over several decades before the appearance of clinical symptoms. During this preclinical period, progressive neuronal degeneration occurs within the hippocampus and cerebral cortex, resulting in irreversible synaptic dysfunction and cognitive decline. Consequently, considerable research efforts have been devoted toward understanding the molecular mechanisms responsible for disease progression and identifying novel therapeutic targets capable of delaying or preventing neurodegeneration.

1.2 Pathophysiology of Alzheimer's Disease

The pathogenesis of Alzheimer's disease is highly complex and multifactorial. Several interconnected molecular events contribute to neuronal dysfunction, including amyloid-β plaque formation, intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein, oxidative stress, mitochondrial dysfunction, chronic neuroinflammation, excitotoxicity, cholinergic neuronal degeneration, and impaired neurotransmission.Among these pathological mechanisms, cholinergic dysfunction remains one of the earliest and most consistently observed biochemical abnormalities in Alzheimer's disease. Degeneration of cholinergic neurons within the basal forebrain significantly decreases acetylcholine concentrations in the cerebral cortex and hippocampus, resulting in progressive impairment of memory formation and cognitive processing.Acetylcholine is a major neurotransmitter responsible for learning, attention, and memory. Its concentration within synaptic clefts is regulated by acetylcholinesterase (AChE), an enzyme that rapidly hydrolyzes acetylcholine following neurotransmission. Excessive enzymatic degradation further aggravates cholinergic deficiency in Alzheimer's disease, making AChE inhibition one of the most successful symptomatic therapeutic strategies currently available.

1.3 Current Therapeutic Strategies

Currently approved pharmacological treatments for Alzheimer's disease include acetylcholinesterase inhibitors such as donepezil, rivastigmine, and galantamine, together with the NMDA receptor antagonist memantine. These drugs temporarily improve cognitive function by enhancing cholinergic neurotransmission or reducing glutamate-mediated excitotoxicity. However, none of these medications effectively halt neuronal degeneration or reverse disease progression.Recently approved monoclonal antibodies targeting amyloid-β have shown encouraging clinical outcomes in selected patient populations; nevertheless, their high cost, limited accessibility, modest clinical benefit, requirement for intravenous administration, and risk of amyloid-related imaging abnormalities have restricted widespread application.Consequently, there remains an urgent need to develop novel, orally active, safe, selective, and cost-effective therapeutic agents possessing improved efficacy and pharmacokinetic characteristics.

1.4 Acetylcholinesterase as a Therapeutic Target

Acetylcholinesterase (EC 3.1.1.7) is among the most extensively investigated molecular targets in Alzheimer's drug discovery. The enzyme contains a deep catalytic gorge composed of aromatic amino acid residues capable of accommodating structurally diverse ligands.Inhibition of AChE prolongs the residence time of acetylcholine within synaptic clefts, thereby enhancing cholinergic neurotransmission and improving cognitive performance. Because of its well-characterized crystal structure and established therapeutic relevance, acetylcholinesterase serves as an ideal target for computational drug discovery approaches.Advances in structural biology have enabled the determination of several high-resolution crystal structures of human and electric eel acetylcholinesterase. Among these, the crystal structure represented by Protein Data Bank ID **1EVE** has been widely employed for molecular docking investigations owing to its well-defined active site geometry and validated ligand-binding characteristics.

1.5 Importance of Cyanopyridine and 1,3,5-Triazine Scaffolds

Nitrogen-containing heterocyclic compounds constitute one of the most important classes of biologically active molecules in medicinal chemistry. Among these, the 1,3,5-triazine nucleus has attracted significant attention because of its remarkable versatility in drug development.The triazine scaffold exhibits a broad spectrum of pharmacological activities including anticancer, antimicrobial, antiviral, anti-inflammatory, antimalarial, anticonvulsant, antioxidant, and neuroprotective effects. The presence of three nitrogen atoms within the aromatic ring provides excellent opportunities for structural diversification through nucleophilic substitution reactions, enabling medicinal chemists to optimize biological activity and pharmacokinetic properties.Similarly, cyanopyridine derivatives have emerged as promising pharmacophores in neurological drug discovery. Their rigid aromatic framework, electron-withdrawing cyano functionality, and ability to participate in hydrogen bonding and π-interactions facilitate strong molecular recognition within enzyme active sites.Combining cyanopyridine with the 1,3,5-triazine scaffold therefore represents a rational medicinal chemistry strategy to generate multifunctional molecules capable of enhanced acetylcholinesterase inhibition.

1.6 Role of Computer-Aided Drug Design

Drug discovery is traditionally a lengthy, expensive, and labor-intensive process requiring synthesis and biological evaluation of thousands of compounds before identifying a single successful drug candidate. Modern computer-aided drug design (CADD) techniques have revolutionized this process by enabling rapid virtual screening of compound libraries prior to experimental synthesis.

Computational approaches such as molecular docking, pharmacophore modeling, ADMET prediction, and molecular property analysis substantially reduce development costs while improving the probability of identifying biologically active lead compounds.SwissADME has become one of the most widely utilized platforms for evaluating physicochemical properties, gastrointestinal absorption, blood–brain barrier permeability, water solubility, drug-likeness, medicinal chemistry friendliness, and synthetic accessibility. Likewise, Discovery Studio provides robust molecular docking algorithms capable of predicting ligand–protein binding orientations and interaction energies with high reliability.Integration of these computational tools enables systematic prioritization of promising lead compounds before undertaking expensive laboratory investigations.

1.7 Rationale of the Present Study

Considering the therapeutic significance of acetylcholinesterase inhibition and the favorable pharmacological characteristics of cyanopyridine and 1,3,5-triazine pharmacophores, the present investigation was undertaken to design a focused library of fifty novel cyanopyridine-substituted 1,3,5-triazine derivatives. Structural modifications involving aromatic, heterocyclic, and aliphatic amines were introduced to improve binding affinity, physicochemical properties, and predicted pharmacokinetic behavior.The designed molecules were evaluated using an integrated computational workflow involving molecular design, physicochemical property prediction, ADMET assessment, and molecular docking against acetylcholinesterase (PDB ID: 1EVE). Compounds exhibiting favorable docking scores and acceptable drug-like characteristics were identified as promising lead candidates for subsequent synthesis and biological evaluation.This study highlights the potential of rational molecular design combined with computer-aided drug discovery techniques to accelerate the identification of novel anti-Alzheimer agents while reducing the cost and time associated with conventional drug development.

Literature Review

2.1 Alzheimer's Disease: Current Research Perspective

Alzheimer's disease (AD) is the most common form of dementia and represents one of the greatest medical challenges associated with aging. It is characterized by progressive deterioration of memory, cognition, language, reasoning, and executive functions. Since its first description by Alois Alzheimer in 1906, extensive research has been conducted to understand its molecular basis and identify effective therapeutic interventions. Despite decades of investigation, currently available drugs only provide symptomatic relief and fail to stop or reverse disease progression. Consequently, considerable attention has shifted toward the discovery of novel chemical entities capable of targeting multiple pathological pathways simultaneously. Recent advances in molecular biology, structural biology,

medicinal chemistry, and computer-aided drug design (CADD) have significantly accelerated anti-Alzheimer drug discovery. Numerous heterocyclic scaffolds, particularly nitrogen-containing compounds, have demonstrated promising acetylcholinesterase inhibitory activity and neuroprotective potential.

2.2 Pathophysiology of Alzheimer's Disease

Alzheimer's disease is recognized as a multifactorial disorder involving numerous interconnected pathological mechanisms rather than a single molecular defect. The classical pathological hallmarks include extracellular deposition of amyloid-β (Aβ) plaques and intracellular accumulation of hyperphosphorylated tau protein forming neurofibrillary tangles.Beyond these characteristic lesions, increasing evidence suggests that oxidative stress, mitochondrial dysfunction, impaired calcium homeostasis, chronic neuroinflammation, cerebrovascular abnormalities, cholinergic dysfunction, insulin resistance, and genetic susceptibility collectively contribute to neuronal degeneration. Breijyeh and Karaman (2020) comprehensively reviewed Alzheimer's disease and emphasized that the complexity of disease pathology necessitates the development of multitarget therapeutic agents capable of simultaneously modulating multiple biochemical pathways. They highlighted that future drug discovery should integrate computational methods with rational medicinal chemistry to identify compounds possessing improved efficacy and reduced toxicity. Similarly, Giri et al. (2016) reported that oxidative stress and neuroinflammation amplify neuronal injury initiated by amyloid-β accumulation. Their work demonstrated that interactions among amyloid deposition, tau pathology, mitochondrial damage, and inflammatory mediators accelerate neuronal apoptosis and synaptic dysfunction. Silva et al. (2025) further emphasized that Alzheimer's disease progresses silently over several years before clinical symptoms appear. Their review suggested that early diagnosis combined with targeted therapies offers the greatest opportunity to delay disease progression and improve patient quality of life.

2.3 Cholinergic Hypothesis

Among the numerous hypotheses proposed to explain Alzheimer's disease pathology, the cholinergic hypothesis remains one of the most extensively validated.The hypothesis suggests that degeneration of cholinergic neurons located within the basal forebrain results in decreased acetylcholine concentrations throughout the cerebral cortex and hippocampus. This neurotransmitter deficiency directly contributes to learning impairment, memory loss, and cognitive decline.

Acetylcholinesterase (AChE) rapidly hydrolyzes acetylcholine after neurotransmission. Consequently, inhibition of this enzyme increases acetylcholine concentration at neuronal

synapses, thereby improving cognitive performance.Donepezil, Rivastigmine, and Galantamine remain the principal FDA-approved acetylcholinesterase inhibitors used clinically. However, these drugs exhibit limitations including gastrointestinal adverse effects, hepatotoxicity, poor selectivity, short biological half-life, and inability to modify disease progression. Therefore, medicinal chemists continue searching for safer and more potent acetylcholinesterase inhibitors.

2.4 Computer-Aided Drug Design in Alzheimer's Drug Discovery

Computer-Aided Drug Design (CADD) has become an indispensable component of modern pharmaceutical research. Virtual screening substantially reduces the time and financial investment associated with conventional drug discovery. Brogi et al. (2020) highlighted that computational methodologies have revolutionized medicinal chemistry by enabling rapid identification of promising lead compounds before synthesis. Their review described the growing importance of molecular docking, pharmacophore modeling, molecular dynamics simulations, quantitative structure–activity relationship (QSAR) studies, and artificial intelligence-assisted drug design. The authors further emphasized that integrated computational workflows considerably reduce dependence on laboratory animal experimentation while increasing the success rate of lead optimization.

Modern computational techniques permit:

- Virtual library generation
- Drug-likeness prediction
- ADMET screening
- Molecular docking
- Binding energy estimation
- Lead optimization

Consequently, CADD has become an essential strategy for neurodegenerative drug discovery.

2.5 Importance of ADMET Prediction

One of the primary causes of clinical drug failure is poor pharmacokinetic behavior rather than insufficient biological activity.Daina, Michielin, and Zoete (2017) developed SwissADME, one of the most widely used free computational platforms for predicting physicochemical properties and pharmacokinetic characteristics.

SwissADME evaluates:

- Molecular weight
- Lipophilicity (LogP)
- Hydrogen bond donors
- Hydrogen bond acceptors
- Topological Polar Surface Area (TPSA)
- Water solubility
- Gastrointestinal absorption
- Blood–brain barrier permeability
- Bioavailability
- Medicinal chemistry friendliness
- Synthetic accessibility

The platform allows medicinal chemists to eliminate compounds possessing poor pharmacokinetic properties before expensive synthesis and biological evaluation. For central nervous system drugs, BBB permeability and gastrointestinal absorption represent particularly important parameters because therapeutic molecules must effectively reach neuronal tissue following oral administration.

2.6 Molecular Docking as a Lead Optimization Tool

Molecular docking predicts the orientation of small molecules within receptor binding pockets while estimating interaction energies. Monteiro et al. (2018) reported that docking studies provide valuable information regarding:

- Hydrogen bonding
- Hydrophobic interactions
- Electrostatic interactions
- π–π stacking
- Van der Waals contacts

These interactions collectively determine ligand affinity toward the receptor.

Discovery Studio's CDOCKER algorithm utilizes CHARMm molecular mechanics force fields combined with molecular dynamics simulation to generate highly reliable docking poses.

Compared with traditional docking methods, CDOCKER provides:

- Improved conformational sampling

- Enhanced docking accuracy
- Reliable interaction energy calculation
- Better prediction of ligand orientation

Consequently, Discovery Studio has become one of the most widely used molecular docking platforms in pharmaceutical research.

2.7 Therapeutic Importance of 1,3,5-Triazine Derivatives

2

Nitrogen-containing heterocyclic compounds have occupied a central position in medicinal chemistry for several decades.

Among them, the 1,3,5-triazine scaffold exhibits exceptional pharmacological versatility owing to:

- Three nitrogen atoms
- High synthetic flexibility
- Ease of nucleophilic substitution
- Excellent receptor binding characteristics

Numerous triazine derivatives have demonstrated:

- Anticancer activity
- Antiviral activity
- Antimicrobial activity
- Anti-inflammatory activity
- Antimalarial activity
- Antioxidant activity
- Acetylcholinesterase inhibition

Structural modification of the triazine nucleus allows medicinal chemists to fine-tune molecular properties while improving biological activity.

2.8 Cyanopyridine Pharmacophore

The cyanopyridine scaffold has emerged as another promising pharmacophore in neurological drug discovery.

The cyano functional group contributes:

- Increased electronic polarization

- Enhanced hydrogen bond acceptor capability
- Greater receptor specificity
- Improved molecular rigidity

Several cyanopyridine derivatives have demonstrated:

- Anti-inflammatory activity
- Antioxidant activity
- Kinase inhibition
- Neuroprotective activity
- Enzyme inhibition

Combining cyanopyridine with the triazine nucleus therefore represents a rational medicinal chemistry strategy for designing potent acetylcholinesterase inhibitors.

2.9 Recent Advances in Anti-Alzheimer Drug Development (2015–2025)

Giri et al. (2016)

The authors emphasized oxidative stress and chronic neuroinflammation as central contributors to Alzheimer's disease progression. Their findings suggested that multitarget therapeutic agents may provide greater clinical benefit than single-target drugs.

Daina et al. (2017)

Developed SwissADME, enabling rapid prediction of pharmacokinetic behavior and drug-likeness, thereby transforming early-stage drug discovery.

Monteiro et al. (2018)

Demonstrated the usefulness of molecular docking for predicting acetylcholinesterase inhibition and identifying lead compounds prior to synthesis.

Armstrong (2019)

Reviewed major Alzheimer's disease risk factors including aging, genetics, hypertension, diabetes, obesity, and cardiovascular disorders. The author concluded that disease prevention should combine lifestyle modification with pharmacological intervention.

Breijyeh and Karaman (2020)

Published one of the most comprehensive reviews on Alzheimer's disease, discussing amyloid cascade, tau pathology, oxidative stress, inflammation, and emerging therapeutic strategies.

Brogi et al. (2020)

Highlighted recent developments in computational drug design, emphasizing virtual screening and molecular docking for neurodegenerative diseases.

Dolatshahi et al. (2021)

Reported that diabetes, hypertension, obesity, smoking, and cardiovascular disease significantly increase Alzheimer's disease risk.

FDA Therapeutic Advances (2023–2025)

Recent FDA approvals of monoclonal antibodies targeting amyloid-β have introduced disease-modifying therapy into clinical practice. Although promising, these treatments remain associated with high cost, infusion requirements, and limited patient eligibility.

Isaković et al. (2025)

Reviewed stem-cell therapy as a future strategy for neuronal regeneration. Their work suggested that stem-cell transplantation may restore damaged neuronal circuits and improve cognitive function.

Silva et al. (2025)

Highlighted the importance of early diagnosis, precision medicine, biomarker-guided therapy, and personalized treatment strategies for slowing Alzheimer's disease progression.

2.10 Research Gap

Despite considerable advances in Alzheimer's disease research, several challenges remain unresolved:

- Existing acetylcholinesterase inhibitors produce only symptomatic improvement.
- Most approved drugs possess undesirable adverse effects.
- Drug resistance and poor selectivity remain significant concerns.

- Few compounds successfully combine strong enzyme inhibition with favorable pharmacokinetic properties.
- Development of orally active, BBB-permeable, multitarget inhibitors remains limited.
- Many promising compounds fail during clinical development because of poor ADMET characteristics.

Furthermore, only a limited number of studies have investigated **cyanopyridine-substituted 1,3,5-triazine derivatives** specifically as acetylcholinesterase inhibitors using an integrated computational workflow combining molecular design, ADMET prediction, and molecular docking.

2.11 Rationale of the Present Investigation

Based on the literature reviewed, combining the **cyanopyridine pharmacophore** with the **1,3,5-triazine scaffold** offers a promising strategy for developing novel anti-Alzheimer agents. The present study therefore focuses on the design of a structurally diverse library of cyanopyridine-substituted 1,3,5-triazine derivatives, followed by comprehensive computational evaluation using SwissADME and Discovery Studio.

This integrated in silico approach aims to identify lead molecules with enhanced acetylcholinesterase binding affinity, favorable physicochemical properties, acceptable pharmacokinetic behavior, and improved drug-likeness. The findings are expected to facilitate the selection of promising candidates for future synthesis, in vitro biological evaluation, and in vivo pharmacological studies.

3. Plan of Work and Materials & Methods

3.1 Plan of Work

The present investigation was designed to identify novel cyanopyridine-substituted 1,3,5-triazine derivatives as potential acetylcholinesterase (AChE) inhibitors using an integrated computer-aided drug discovery (CADD) approach. The overall workflow consisted of rational molecular design, physicochemical property prediction, ADMET evaluation, molecular docking, and selection of promising lead compounds. The methodology minimized experimental costs while allowing rapid screening of structurally diverse molecules prior to chemical synthesis.

The research workflow comprised the following sequential steps:

1. Comprehensive literature survey on Alzheimer's disease, acetylcholinesterase inhibitors, cyanopyridine derivatives, and 1,3,5-triazine analogues.
2. Design of a focused molecular library consisting of fifty novel cyanopyridine-substituted 1,3,5-triazine derivatives.
3. Drawing and optimization of chemical structures using ChemDraw Ultra 8.0.
4. Evaluation of physicochemical properties and drug-likeness using SwissADME.
5. Assessment of ADMET characteristics, including gastrointestinal absorption, Lipinski's Rule of Five compliance, lipophilicity, aqueous solubility, and synthetic accessibility.
6. Preparation of the target protein (acetylcholinesterase, PDB ID: 1EVE).
7. Ligand preparation and energy minimization.
8. Molecular docking using the CDOCKER protocol implemented in BIOVIA Discovery Studio 3.0.
9. Analysis of protein–ligand interactions and docking scores.
10. Ranking of lead compounds according to binding affinity and interaction profiles.
11. Identification of promising molecules for future synthesis and biological evaluation.

3.2 Materials

The present study was entirely computational and therefore required no experimental chemicals or biological samples. All molecular structures, protein files, and computational analyses were generated using established cheminformatics and molecular modeling software.

Software and Databases

Software/Database	Version	Purpose
ChemDraw Ultra	8.0	Structure drawing
SwissADME	Web Server	ADMET prediction
Discovery Studio	3.0	Molecular docking
Protein Data Bank (PDB)	Online	Protein retrieval
PubChem	Online	Structure verification

3.3 Research Design

The investigation followed a computational drug discovery strategy employing structure-based drug design (SBDD). Acetylcholinesterase was selected as the biological target because inhibition of this enzyme remains the most successful therapeutic strategy for symptomatic treatment of Alzheimer's disease.

Novel derivatives were designed by retaining the cyanopyridine–1,3,5-triazine pharmacophore while introducing structurally diverse aromatic, heterocyclic, and aliphatic amines. This strategy aimed to optimize enzyme binding, improve pharmacokinetic properties, and enhance drug-likeness.

3.4 Design of Molecular Library

The cyanopyridine-substituted 1,3,5-triazine scaffold served as the parent pharmacophore for molecular design.

Different substituents possessing electron-donating and electron-withdrawing properties were incorporated into the scaffold to investigate their influence on acetylcholinesterase inhibition.

A total of fifty derivatives were generated using medicinal chemistry principles emphasizing:

- Electronic effects
- Steric effects
- Hydrophobicity
- Hydrogen bonding capability
- Molecular flexibility
- Drug-likeness

Representative substituents included:

- Fluoroaniline
- Bromoaniline
- Morpholine
- Piperazine
- Pyrimidine
- Sulfonamide
- Benzimidazole
- Pyrrole

- Piperidine
- Methylamine
- Cyclohexylamine
- Aniline
- Thiourea derivatives

The resulting molecular diversity enabled systematic evaluation of structure–activity relationships (SAR).

3.5 Structure Drawing

All designed compounds were constructed using ChemDraw Ultra Version 8.0.

The software facilitated:

- Two-dimensional molecular construction
- Structural validation
- Molecular formula generation
- Molecular weight calculation
- Export of structures in compatible formats

Each designed ligand was carefully checked for structural correctness before further computational analysis.

3.6 Physicochemical Property Prediction

Physicochemical descriptors significantly influence oral bioavailability and pharmacological activity.

SwissADME was employed to calculate:

- Molecular weight (MW)
- Topological Polar Surface Area (TPSA)
- Hydrogen bond donors
- Hydrogen bond acceptors
- Number of rotatable bonds
- Lipophilicity (LogP)
- Water solubility (LogS)
- Gastrointestinal absorption
- Bioavailability score

These descriptors were used to evaluate whether the designed compounds possessed characteristics suitable for orally active central nervous system drugs.

3.7 Drug-Likeness Evaluation

Drug-likeness was evaluated primarily using Lipinski's Rule of Five.

According to Lipinski, orally active compounds generally satisfy the following criteria:

- Molecular weight ≤500 Da
- LogP ≤5
- Hydrogen bond donors ≤5
- Hydrogen bond acceptors ≤10

Compounds violating multiple criteria generally exhibit poor oral absorption and limited bioavailability.

SwissADME additionally calculated medicinal chemistry alerts and synthetic accessibility scores to determine the feasibility of future laboratory synthesis.

3.8 ADMET Prediction

Early prediction of pharmacokinetic behavior is essential for successful drug development.

SwissADME was used to estimate:

Absorption

- Gastrointestinal absorption
- Water solubility

Distribution

- Blood–brain barrier permeability
- Lipophilicity

Metabolism

Predicted metabolic behavior based on physicochemical descriptors.

Excretion

Overall pharmacokinetic profile.

Toxicological Indicators

Although SwissADME is not a toxicity prediction platform, medicinal chemistry filters were examined to identify compounds with undesirable structural alerts.

The combined ADMET assessment enabled early elimination of molecules possessing unfavorable pharmacokinetic characteristics.

3.9 Protein Preparation

The three-dimensional crystal structure of acetylcholinesterase (AChE) was obtained from the Protein Data Bank.

Target Protein

- Enzyme: Acetylcholinesterase
- PDB ID: **1EVE**

Protein preparation was performed using Discovery Studio 3.0.

The preparation procedure included:

- Removal of crystallographic water molecules
- Removal of co-crystallized ligands
- Correction of bond orders
- Addition of missing hydrogen atoms
- Assignment of protonation states
- Energy minimization using the CHARMm force field

The active binding pocket was defined based on the coordinates of the native ligand present in the crystal structure.

3.10 Ligand Preparation

All fifty designed molecules underwent ligand preparation before docking.

The preparation process involved:

- Conversion of 2D structures into 3D conformations
- Addition of hydrogen atoms
- Assignment of ionization states
- Geometry optimization
- Energy minimization using the CHARMm force field

Energy-minimized structures served as docking inputs.

3.11 Molecular Docking

Protein–ligand interaction studies were carried out using BIOVIA Discovery Studio Version 3.0.

The CDOCKER protocol, a CHARMm-based molecular dynamics docking algorithm, was employed.

Docking consisted of:

- Random ligand placement
- High-temperature molecular dynamics
- Simulated annealing
- Final energy minimization
- Selection of the best docking pose

Each ligand generated multiple conformations, and the pose exhibiting the highest interaction energy and most favorable orientation within the active site was selected.

3.12 Protein–Ligand Interaction Analysis

Following docking, ligand–protein interactions were analyzed using Discovery Studio Visualizer.

The following interactions were examined:

- Conventional hydrogen bonds
- Carbon–hydrogen bonds
- π–π stacking
- π–alkyl interactions
- Alkyl interactions
- Electrostatic interactions
- Van der Waals contacts

- Hydrophobic interactions

These interactions collectively determine ligand stability within the catalytic gorge of acetylcholinesterase.

3.13 Binding Energy Analysis

Binding affinity was evaluated using the docking score generated by CDOCKER.

Compounds exhibiting:

- More negative binding energies
- Greater interaction energies
- Multiple hydrogen bonds
- Favorable hydrophobic interactions

were considered superior inhibitors.

The docked compounds were ranked according to their binding energies to identify the most promising lead molecules.

3.14 Selection of Lead Compounds

Lead compounds were selected based on multiple computational criteria:

- Compliance with Lipinski's Rule of Five
- Favorable ADMET profile
- High gastrointestinal absorption
- Acceptable lipophilicity
- Synthetic accessibility
- Strong docking score
- Stable ligand–protein interactions
- Favorable binding orientation

Compounds satisfying all these criteria were prioritized for future synthesis and biological evaluation.

3.15 Statistical and Computational Analysis

All computational data were analyzed descriptively.

Docking scores were compared among the fifty designed compounds to establish a ranking based on predicted binding affinity.

Physicochemical descriptors and ADMET parameters were evaluated collectively to identify compounds possessing the most balanced pharmacokinetic profiles.

No inferential statistical analysis was performed because the investigation consisted exclusively of computational predictions.

3.16 Overall Computational Workflow

The computational workflow adopted in the present investigation can be summarized as follows:

Literature Survey
↓
Design of Cyanopyridine–1,3,5-Triazine Derivatives
↓
Chemical Structure Drawing (ChemDraw Ultra 8.0)
↓
Drug-Likeness and ADMET Prediction (SwissADME)
↓
Protein Preparation (PDB ID: 1EVE)
↓
Ligand Preparation
↓
Molecular Docking (Discovery Studio 3.0 – CDOCKER)
↓
Protein–Ligand Interaction Analysis
↓
Lead Compound Selection
↓
Recommendation for Future In Vitro and In Vivo Studies

4. Result and Discussion

4.1 Overview of the Computational Study

The present investigation employed an integrated computer-aided drug discovery (CADD) strategy to evaluate a library of fifty newly designed cyanopyridine-substituted 1,3,5-triazine derivatives for their potential anti-Alzheimer activity. The workflow comprised molecular design, physicochemical property prediction, ADMET analysis, molecular docking, and protein–ligand interaction studies targeting acetylcholinesterase (AChE; PDB ID: 1EVE). The primary objective was to identify compounds with favorable drug-like properties and strong binding affinity toward the catalytic site of AChE, a validated therapeutic target in Alzheimer's disease. The computational strategy enabled rapid prioritization of promising lead molecules before experimental synthesis and biological testing.

4.2 Physicochemical Property Analysis

The physicochemical properties of all fifty designed compounds were calculated using SwissADME. The evaluated descriptors included molecular weight (MW), topological polar surface area (TPSA), lipophilicity (iLOGP), aqueous solubility (LogS), gastrointestinal (GI) absorption, Lipinski's Rule of Five compliance, and synthetic accessibility.

The molecular weights of the designed derivatives ranged from approximately **311 to 605 Da**, indicating that most compounds fell within or close to the preferred range for orally active small molecules. Several higher-molecular-weight derivatives remained acceptable because CNS-active compounds may tolerate modest deviations when compensated by favorable permeability and binding affinity.

TPSA values generally ranged between **120 and 180 Å²**, reflecting the presence of multiple nitrogen-containing heterocyclic rings and hydrogen-bonding functionalities. While higher TPSA values may reduce passive membrane permeability, several compounds retained predicted high gastrointestinal absorption, suggesting a balanced physicochemical profile.

The calculated iLOGP values (approximately **0.7–3.8**) indicated moderate lipophilicity. Such values are generally considered advantageous because excessive lipophilicity can reduce aqueous solubility and increase metabolic liabilities, whereas insufficient lipophilicity may impair blood–brain barrier penetration.

Overall, the calculated physicochemical descriptors suggested that the designed cyanopyridine–1,3,5-triazine derivatives possess favorable characteristics for further development as orally administered CNS-active molecules.

4.3 Drug-Likeness Assessment

Drug-likeness prediction represents a critical early-stage filter in drug discovery. Most designed compounds complied with **Lipinski's Rule of Five**, indicating satisfactory oral drug-like behavior.

The majority of derivatives exhibited:

- acceptable molecular weight,
- moderate lipophilicity,
- suitable hydrogen-bonding capacity,
- reasonable molecular flexibility,
- favorable synthetic accessibility.

These findings suggest that the molecular modifications introduced into the cyanopyridine–triazine scaffold did not compromise fundamental pharmaceutical characteristics.

4.4 ADMET Analysis

SwissADME analysis demonstrated encouraging pharmacokinetic behavior across the designed compound library. Most compounds showed either **high or acceptable predicted gastrointestinal absorption**, supporting the possibility of oral administration.

Water solubility predictions varied according to substituent type. Aromatic derivatives generally exhibited moderate solubility, whereas compounds containing polar heterocyclic substituents displayed improved aqueous solubility. Such variation is expected because hydrogen-bonding functionality and polarity directly influence dissolution behavior.

Synthetic accessibility scores ranged from approximately **2.7 to 5.3**, indicating that the majority of derivatives should be synthetically feasible using conventional medicinal chemistry techniques.

Overall, the ADMET evaluation identified several compounds possessing balanced physicochemical and pharmacokinetic characteristics suitable for progression into further studies.

4.5 Molecular Docking Analysis

Molecular docking was performed using the **CDOCKER** module of Discovery Studio 3.0 against acetylcholinesterase (PDB ID: 1EVE). The docking algorithm generated multiple conformations for each ligand, and the best binding pose was selected based on interaction energy and orientation within the catalytic gorge.

The docking results demonstrated considerable variation in binding affinity among the fifty designed derivatives, indicating that structural modifications significantly influenced receptor recognition.

Compounds exhibiting more negative binding energies generally formed:

- multiple hydrogen bonds,
- π–π stacking interactions,
- hydrophobic contacts,
- van der Waals interactions,
- electrostatic interactions.

These interactions collectively stabilize ligand binding within the enzyme active site and may enhance inhibitory potency.

4.6 Top-Ranked Compounds

Based on binding energy, the ten highest-ranked compounds were identified as the most promising lead candidates.

Rank	Compound	Binding Energy (kcal/mol)	Interpretation
1	CPT-19	-675.0330	Highest predicted binding affinity
2	CPT-14	-657.3116	Excellent enzyme interaction
3	CPT-15	-651.7876	Strong ligand stability
4	CPT-13	-602.3877	Very favorable docking
5	CPT-12	-580.4392	Strong catalytic site binding
6	CPT-20	-536.4961	Good binding affinity

Rank	Compound	Binding Energy (kcal/mol)	Interpretation
7	CPT-27	-507.4174	Stable interaction profile
8	CPT-50	-505.3374	Favorable docking orientation
9	CPT-9	-406.5074	Moderate binding
10	CPT-23	-436.4794	Moderate to good interaction

Among all compounds, **CPT-19** exhibited the strongest predicted interaction with acetylcholinesterase, suggesting that its substituent pattern provides an optimal balance of hydrogen bonding and hydrophobic interactions within the catalytic gorge.

4.7 Protein–Ligand Interaction Analysis

Detailed visualization of docked complexes demonstrated that the highest-ranking compounds interacted extensively with amino acid residues lining the catalytic gorge of acetylcholinesterase.

The principal interactions observed included:

- Conventional hydrogen bonding
- π–π stacking
- π–alkyl interactions
- Hydrophobic interactions
- Van der Waals contacts
- Carbon–hydrogen bonding

Hydrogen bonds contributed significantly to binding specificity, whereas aromatic π–π interactions enhanced ligand stabilization inside the narrow active-site gorge.

Hydrophobic interactions further strengthened ligand binding by improving complementarity with the aromatic residues surrounding the catalytic pocket.

Collectively, these interactions indicate that the designed compounds possess favorable molecular recognition characteristics necessary for potent acetylcholinesterase inhibition.

4.8 Structure–Activity Relationship (SAR)

The present investigation provides valuable insight into the structure–activity relationships of cyanopyridine-substituted 1,3,5-triazine derivatives.

Influence of Electron-Donating Groups

Compounds containing electron-donating aromatic substituents generally demonstrated superior docking performance. These substituents enhanced electron density, promoting stronger π–π interactions with aromatic amino acid residues within the enzyme active site.

Influence of Electron-Withdrawing Groups

Fluoro- and bromo-substituted derivatives also exhibited favorable docking scores. Halogen atoms increase lipophilicity and may participate in halogen bonding, improving receptor recognition.

Role of Heterocyclic Amines

Morpholine-, piperazine-, pyrimidine-, and benzimidazole-containing derivatives displayed improved hydrogen-bonding potential due to the presence of multiple nitrogen atoms. These interactions contributed to stable ligand–protein complexes.

Effect of Steric Bulk

Bulky substituents occasionally reduced docking scores because steric hindrance interfered with optimal accommodation inside the catalytic gorge.

Contribution of the Cyanopyridine–Triazine Scaffold

The cyanopyridine nucleus provides molecular rigidity and electron-withdrawing characteristics, whereas the triazine ring offers multiple nitrogen atoms capable of hydrogen bonding. Together, these pharmacophores create a highly versatile scaffold suitable for acetylcholinesterase inhibition.

4.9 Comparative Evaluation of Lead Compounds

Among the designed molecules, **CPT-19**, **CPT-14**, and **CPT-15** consistently exhibited:

- strongest docking scores,
- multiple hydrogen bonds,

- stable hydrophobic interactions,
- excellent drug-likeness,
- acceptable ADMET properties.

These compounds therefore represent the most promising candidates for future synthesis and biological evaluation.

Although docking scores alone cannot confirm biological activity, they provide strong preliminary evidence supporting further experimental investigation.

4.10 Significance of the Computational Strategy

The integrated computational workflow employed in this study significantly accelerated lead identification.

Compared with conventional drug discovery, the present strategy offers several advantages:

- reduced experimental cost,
- decreased laboratory workload,
- rapid virtual screening,
- improved lead prioritization,
- early elimination of poor candidates,
- enhanced understanding of ligand–protein interactions.

The combined use of ChemDraw, SwissADME, and Discovery Studio enabled systematic evaluation of molecular properties before synthesis, thereby increasing the likelihood of identifying biologically active compounds.

4.11 Limitations of the Present Study

Despite encouraging findings, several limitations should be acknowledged.

1. The study was entirely computational and therefore cannot confirm biological activity.
2. Docking scores estimate binding affinity but do not directly measure enzyme inhibition.
3. Blood–brain barrier permeability requires experimental validation.
4. Pharmacokinetic predictions remain theoretical until confirmed in vivo.
5. Toxicological safety has not yet been experimentally evaluated.

Future studies should therefore include:

- chemical synthesis of the lead compounds,
- in vitro acetylcholinesterase inhibition assays,
- cytotoxicity studies,
- molecular dynamics simulations,
- enzyme kinetics,
- blood–brain barrier permeability studies,
- pharmacokinetic evaluation,
- animal studies in Alzheimer's disease models.

4.12 Overall Discussion

The present computational investigation successfully demonstrated that rational modification of the cyanopyridine–1,3,5-triazine scaffold can substantially influence acetylcholinesterase binding affinity and predicted pharmacokinetic behavior. The integration of physicochemical screening, ADMET prediction, and molecular docking enabled efficient prioritization of lead candidates from a library of fifty designed molecules. Among them, **CPT-19**, **CPT-14**, **CPT-15**, **CPT-13**, and **CPT-12** emerged as the most promising compounds due to their favorable docking scores, stable protein–ligand interactions, and acceptable drug-like properties. These findings support the continued exploration of cyanopyridine-substituted 1,3,5-triazine derivatives as a promising platform for the development of novel acetylcholinesterase inhibitors and potential therapeutics for Alzheimer's disease.

Conclusion

The present investigation successfully demonstrated the application of an integrated computer-aided drug design (CADD) approach for the identification of novel cyanopyridine-substituted 1,3,5-triazine derivatives as potential acetylcholinesterase (AChE) inhibitors for the management of Alzheimer's disease. By combining rational molecular design, physicochemical property evaluation, ADMET prediction, and molecular docking studies, a focused library of fifty compounds was systematically screened to identify promising lead candidates.

The physicochemical analysis indicated that the majority of the designed molecules possessed favorable molecular properties, including acceptable molecular weight, balanced lipophilicity, appropriate hydrogen-bonding capacity, and satisfactory compliance with Lipinski's Rule of Five. Furthermore, SwissADME prediction demonstrated encouraging pharmacokinetic characteristics such as high gastrointestinal absorption, acceptable drug-

likeness, and reasonable synthetic accessibility, suggesting that the designed derivatives possess desirable pharmaceutical attributes for oral drug development.

Molecular docking studies performed using the CDOCKER protocol against acetylcholinesterase (PDB ID: 1EVE) revealed significant differences in binding affinity among the designed compounds. The docking analysis showed that several derivatives established stable interactions with the catalytic gorge through hydrogen bonding, hydrophobic interactions, π–π stacking, π–alkyl interactions, and van der Waals forces. Among all evaluated molecules, **CPT-19**, **CPT-14**, **CPT-15**, **CPT-13**, and **CPT-12** demonstrated the most favorable docking scores and interaction profiles, indicating strong affinity toward the active site of acetylcholinesterase. These observations suggest that appropriate substitution on the cyanopyridine–1,3,5-triazine scaffold plays a crucial role in enhancing receptor binding and may contribute to improved inhibitory activity.

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The structure–activity relationship (SAR) analysis further demonstrated that both the nature and position of substituents significantly influence molecular recognition within the enzyme active site. Electron-donating groups, heterocyclic amines, and appropriately positioned aromatic substituents generally improved ligand stability and receptor interactions, whereas excessive steric bulk tended to reduce docking efficiency. These findings provide valuable guidance for future structural optimization of this pharmacophore.

An important strength of the present work is the integration of multiple computational techniques into a unified drug discovery pipeline. The combined application of molecular design, drug-likeness prediction, ADMET evaluation, and molecular docking enabled rapid prioritization of lead compounds while minimizing experimental cost and reducing the number of molecules requiring synthesis. Such computational strategies are increasingly recognized as efficient tools for accelerating early-stage pharmaceutical research.

Nevertheless, the present study has certain limitations. The computational predictions require experimental validation through chemical synthesis, in vitro acetylcholinesterase inhibition assays, cytotoxicity studies, blood–brain barrier permeability evaluation, pharmacokinetic investigations, molecular dynamics simulations, and in vivo efficacy studies using appropriate Alzheimer's disease animal models. These experimental studies will be essential to confirm the therapeutic potential of the identified lead compounds.

In conclusion, the findings of this investigation indicate that cyanopyridine-substituted 1,3,5-triazine derivatives represent a promising class of acetylcholinesterase inhibitors with potential application in the treatment of Alzheimer's disease. The lead compounds identified in this study, particularly **CPT-19**, **CPT-14**, and **CPT-15**, merit further

experimental investigation and may serve as valuable starting points for the development of next-generation anti-Alzheimer agents. Overall, the present work contributes to the growing body of evidence supporting the use of integrated computer-aided drug design approaches in modern medicinal chemistry and provides a rational foundation for future anti-Alzheimer drug discovery programs.

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