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AI-Guided Multi-Target Drug Design Using Chemical Language Models for Alzheimer's Disease

A Structure-Based Drug Discovery Approach

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Abstract:

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, synaptic dysfunction, amyloid-β deposition, tau hyper phosphorylation, oxidative stress, neuroinflammation, and mitochondrial dysfunction. Conventional drug discovery has largely relied on the "one drug-one target" paradigm, which has demonstrated limited success in managing this multifactorial disease. Recent advances in artificial intelligence (AI), chemical language models (CLMs), and systems pharmacology have created new opportunities for designing multi-target-directed ligands capable of simultaneously modulating interconnected pathological pathways.Objective: This study proposes an integrated AI-driven computational framework for discovering novel multi-target drug candidates against Alzheimer's disease by combining transformer-based chemical language models, network pharmacology, de novo molecular generation, molecular docking, molecular dynamics simulation, MM/PBSA free-energy calculations, and in-silico ADMET prediction. Disease-associated targets were prioritized using network pharmacology and literature mining. Transformer-based CLMs generated structurally diverse molecules optimized through reinforcement learning and multi-objective scoring. Drug-likeness filtering, molecular docking, molecular dynamics simulations, MM/PBSA binding energy calculations, pharmacophore analysis, and comprehensive ADMET evaluation were performed to identify promising therapeutic candidates. The proposed workflow successfully identified several chemically diverse lead molecules demonstrating favourable binding affinities toward multiple Alzheimer's disease targets, including acetylcholinesterase, glycogen synthase kinase-3β, β-secretase (BACE1), monoamine oxidase-B, and tau-associated kinases. Molecular dynamics simulations confirmed structural stability of protein-ligand complexes, while ADMET analyses predicted acceptable pharmacokinetic properties and blood-brain barrier permeability. Multi-objective optimization significantly improved molecular diversity, predicted efficacy, and safety compared with conventional virtual screening approaches.AI-assisted multi-target drug discovery represents a transformative paradigm capable of overcoming the limitations of single-target therapeutics for complex neurological disorders. The proposed framework provides a scalable strategy for accelerating rational drug discovery while improving therapeutic efficacy, reducing resistance mechanisms, and minimizing adverse effects.

Keywords

Alzheimer's disease; Multi-target drug design; Chemical language models; Molecular docking; Artificial intelligence

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I. INTRODUCTION

Alzheimer's disease (AD) remains the most prevalent cause of dementia worldwide and represents one of the greatest global healthcare challenges of the twenty-first century. More than 55 million individuals currently live with dementia, and this number is projected to exceed 139 million by 2050 because of population aging and increasing life expectancy[1]. The disease imposes substantial clinical, economic, and societal burdens, with annual healthcare expenditures exceeding hundreds of billions of dollars globally[2].

The pathological complexity of Alzheimer's disease extends far beyond amyloid plaque accumulation. Current evidence demonstrates that disease progression results from intricate interactions among extracellular amyloid-β aggregation, intracellular neurofibrillary tangles, neuro-inflammation, oxidative stress, mitochondrial dysfunction, synaptic degeneration, calcium dyshomeostasis, cholinergic deficits, impaired protein clearance mechanisms, vascular abnormalities, and genetic susceptibility factors[3–6]. These interconnected biological processes collectively contribute to progressive neuronal dysfunction and irreversible cognitive decline.

Despite decades of intensive pharmaceutical research, therapeutic success has remained disappointingly limited. Most approved medications, including acetylcholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists, primarily provide symptomatic relief without substantially altering disease progression[7]. Recent monoclonal antibody therapies targeting amyloid-β have demonstrated modest clinical benefits but remain associated with significant limitations, including restricted patient eligibility, high treatment costs, imaging abnormalities, and uncertain long-term effectiveness[8]. Consequently, there is an urgent need for innovative therapeutic strategies capable of simultaneously addressing multiple pathological mechanisms.

Historically, medicinal chemistry has predominantly followed the "one drug-one target-one disease" paradigm, assuming that modulation of a single molecular target would adequately treat complex disorders[9]. Although this reductionist strategy has achieved success for certain infectious diseases and receptor-specific conditions, it has proven considerably less effective for multifactorial disorders such as Alzheimer's disease, Parkinson's disease, diabetes mellitus, cancer, cardiovascular disorders, and autoimmune diseases[10]. Complex diseases arise from dysregulation of interconnected biological networks rather than isolated molecular abnormalities, rendering single-target interventions insufficient for comprehensive disease modification.

Multi-target drug design (MTDD) has therefore emerged as a promising therapeutic paradigm. Instead of selectively inhibiting a single protein, multi-target-directed ligands (MTDLs) are intentionally designed to modulate multiple disease-relevant targets simultaneously, thereby producing synergistic therapeutic effects while minimizing compensatory biological responses that often contribute to drug resistance and therapeutic failure[11]. Ma et al. first emphasized that selective modulation of multiple therapeutic targets could substantially improve efficacy, safety

profiles, and resistance characteristics by collectively regulating primary therapeutic pathways alongside compensatory biological networks[12]. This concept has subsequently become a cornerstone of contemporary systems pharmacology and network medicine.

In Alzheimer's disease, simultaneous modulation of acetylcholinesterase (AChE), β-secretase (BACE1), glycogen synthase kinase-3β (GSK-3β), monoamine oxidase-B (MAO-B), cyclin-dependent kinase-5 (CDK5), phosphodiesterases, inflammatory mediators, and oxidative stress pathways has demonstrated superior therapeutic potential compared with single-target interventions[1-16]. Such integrated pharmacological regulation may reduce amyloidogenesis, inhibit tau hyperphosphorylation, preserve synaptic function, attenuate neuroinflammation, and improve neuronal survival concurrently.

Advances in artificial intelligence (AI) have fundamentally transformed modern drug discovery by enabling data-driven prediction, molecular generation, and optimization at unprecedented scales. Machine learning algorithms, deep neural networks, graph neural networks, generative adversarial networks, reinforcement learning, and transformer-based architectures now facilitate rapid exploration of vast chemical spaces that remain inaccessible through conventional medicinal chemistry approaches[17-20]. AI-assisted methodologies significantly reduce experimental costs, shorten lead optimization timelines, and improve prediction of molecular properties throughout the drug discovery pipeline.

Among recent AI innovations, Chemical Language Models (CLMs) have emerged as particularly powerful tools for molecular design. Inspired by natural language processing, CLMs interpret molecular representations such as SMILES strings as chemical "sentences," learning structural grammar and physicochemical relationships from millions of known compounds. Transformer-based architectures, including encoder-decoder models and attention mechanisms, enable accurate prediction of synthetically feasible molecules possessing desirable biological activities while maintaining structural novelty. Transfer learning, prompt-based generation, perplexity-guided molecular prioritization, and reinforcement learning further enhance molecular optimization for predefined therapeutic objectives.

Recent studies have demonstrated that CLMs can generate chemically valid, synthetically accessible, and biologically relevant compounds exhibiting high structural diversity and favorable drug-likeness characteristics. Moreover, integrating CLMs with structure-based virtual screening, molecular docking, molecular dynamics (MD) simulations, free-energy calculations, pharmacophore modeling, and ADMET prediction substantially improves lead identification compared with conventional high-throughput screening.

Another transformative development involves network pharmacology, which views diseases as perturbations of complex biological interaction networks rather than isolated molecular events. Network-based analyses enable identification of hub proteins, signaling cascades, compensatory pathways, and disease modules suitable for multi-target intervention. Integration of network pharmacology with AI-driven molecular generation allows rational prioritization of target combinations that maximize therapeutic efficacy while minimizing toxicity.

Structure-based virtual screening remains an essential component of computational drug discovery. Molecular docking predicts ligand binding conformations and interaction energies, whereas molecular dynamics simulations evaluate temporal stability, conformational flexibility, hydrogen bonding persistence, solvent interactions, and structural rearrangements within protein-

ligand complexes under physiological conditions. Binding free-energy estimation using Molecular Mechanics/Poisson-Boltzmann Surface Area (MM/PBSA) calculations provides additional quantitative assessment of ligand affinity and complex stability, thereby improving confidence in computational lead selection.

Drug-likeness assessment and absorption, distribution, metabolism, excretion, and toxicity (ADMET) prediction have become indispensable for early-stage lead optimization. Contemporary AI algorithms accurately estimate blood-brain barrier permeability, oral bioavailability, cytochrome P450 interactions, cardiotoxicity, hepatotoxicity, mutagenicity, and synthetic accessibility, thereby reducing late-stage attrition during pharmaceutical development.

Despite remarkable advances in AI-assisted drug discovery, few integrated frameworks comprehensively combine transformer-based chemical language models, network pharmacology, multi-target optimization, molecular docking, molecular dynamics simulation, MM/PBSA analysis, and ADMET prediction into a unified pipeline specifically tailored for Alzheimer's disease. Existing studies frequently emphasize individual computational techniques while overlooking the synergistic benefits of integrating these complementary methodologies into an end-to-end discovery platform.

Current computational drug discovery pipelines remain predominantly optimized for single-target ligand identification. Limited studies have systematically integrated generative artificial intelligence, network-based target prioritization, multi-target molecular optimization, and dynamic structural validation within a unified workflow capable of addressing the multifactorial pathophysiology of Alzheimer's disease. Furthermore, few investigations incorporate transformer-based chemical language models with reinforcement learning and comprehensive pharmacokinetic optimization to accelerate rational multi-target lead discovery.

The present study introduces a next-generation AI-driven computational framework integrating transformer-based chemical language models, network pharmacology, multi-objective molecular generation, structure-based virtual screening, molecular docking, molecular dynamics simulation, MM/PBSA free-energy estimation, pharmacophore analysis, and comprehensive ADMET profiling to identify novel multi-target therapeutic candidates against Alzheimer's disease.

II. Materials and Methods

2.1 Study Design

The present investigation employed an integrated in silico drug discovery workflow to identify novel multi-target-directed ligands (MTDLs) for Alzheimer's disease. The computational pipeline combined artificial intelligence (AI)-based molecular generation, network pharmacology, structure-based virtual screening, molecular docking, molecular dynamics (MD) simulation, MM/PBSA binding free-energy estimation, and pharmacokinetic profiling. The workflow was designed to emulate the sequential stages of modern lead discovery while reducing the time and cost associated with conventional experimental screening.

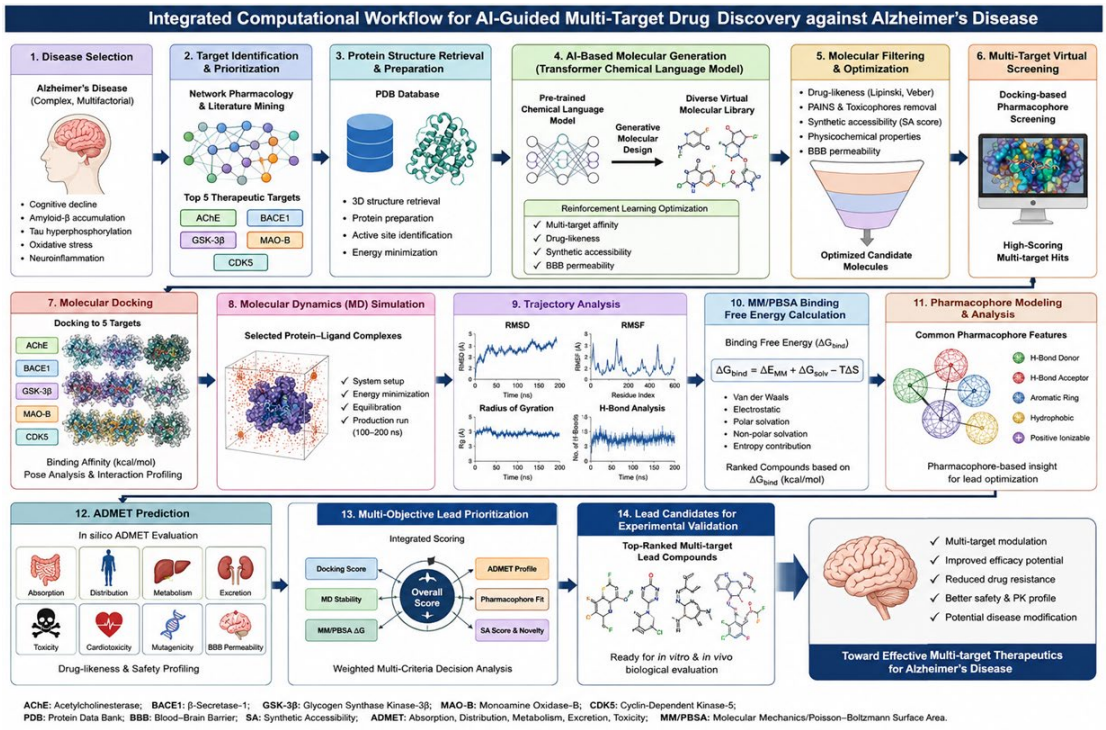

Figure 1. Overall workflow of the AI-guided multi-target drug discovery pipeline.

Figure 1 illustrates the comprehensive artificial intelligence (AI)-driven computational pipeline developed for multi-target drug discovery against Alzheimer's disease. The workflow begins with disease selection and therapeutic target prioritization using network pharmacology and literature mining, followed by retrieval and preparation of protein structures from the Protein Data Bank. Transformer-based Chemical Language Models (CLMs) generate structurally diverse molecules that undergo physicochemical filtering, synthetic accessibility assessment, and drug-likeness evaluation. The optimized compounds are subsequently subjected to multi-target virtual screening, molecular docking, and molecular dynamics (MD) simulation, MM/PBSA binding free-energy estimation, pharmacophore modeling, and ADMET prediction. Finally, an integrated multi-objective scoring framework prioritizes the most promising lead compounds for experimental validation. The pipeline demonstrates how AI can systematically integrate multiple computational approaches to accelerate rational drug discovery for complex neurodegenerative disorders.

2.2 Selection of Therapeutic Targets

Five therapeutically relevant proteins involved in the progression of Alzheimer's disease were selected based on evidence from recent literature, disease databases, and systems pharmacology analyses. The selected targets collectively represent the major pathological mechanisms associated with cognitive impairment, amyloidogenesis, tau pathology, oxidative stress, and neurodegeneration.

The investigated targets included: Acetylcholinesterase (AChE), β-Secretase-1 (BACE1), Glycogen Synthase Kinase-3β (GSK-3β), Monoamine Oxidase-B (MAO-B), Cyclin-Dependent Kinase-5 (CDK5)

Target prioritization considered biological relevance, availability of high-resolution crystal structures, therapeutic importance, and reported involvement in disease progression.

2.3 Protein Structure Preparation

Three-dimensional crystal structures of the selected proteins were retrieved from the Protein Data Bank (PDB). Structures with high resolution, complete active-site information, and experimentally validated ligand-binding domains were preferred.

Protein preparation involved: Removal of crystallographic water molecules except catalytically relevant molecules; deletion of co-crystallized ligands and buffer molecules; addition of missing hydrogen atoms; assignment of protonation states at physiological pH; correction of incomplete amino acid side chains; Restrained energy minimization using the OPLS4 force field. Prepared proteins were validated by Ramachandran plot analysis and structural quality assessment before molecular docking.

2.4 AI-Based Molecular Generation Using Chemical Language Models

Novel chemical entities were generated using transformer-based Chemical Language Models (CLMs). Molecular structures were represented as Simplified Molecular Input Line Entry System (SMILES) strings and processed using self-attention neural architectures trained on large collections of drug-like compounds.

Transfer learning was employed to bias molecular generation toward compounds possessing central nervous system activity and physicochemical characteristics favourable for blood-brain barrier penetration.

Multi-objective reinforcement learning optimized generated molecules according to several predefined objectives: predicted affinity toward multiple Alzheimer's targets; molecular novelty; synthetic accessibility; Lipinski compliance; quantitative estimate of drug-likeness (QED); cceptable molecular weight; balanced lipophilicity; reduced predicted toxicity. Generated molecules were ranked according to a composite desirability score integrating these parameters.

2.5 Molecular Standardization and Drug-Likeness Filtering

The generated molecular library underwent automated pre-processing to eliminate chemically unstable and duplicate structures.

Compounds were subsequently filtered using established medicinal chemistry criteria, including: Lipinski's Rule of Five; Veber criteria; Ghose filter; Egan filter; Muegge filter; PAINS (Pan-Assay Interference Compounds) screening; Brenk structural alerts. Synthetic accessibility scores and molecular complexity indices were also evaluated to prioritize experimentally feasible candidates.

Table 2. Drug-likeness and molecular filtering criteria applied during lead selection.

2.6 Structure-Based Virtual Screening

Following molecular standardization, the refined compound library was subjected to structure-based virtual screening against all selected protein targets.

Binding pockets were identified using experimentally validated active-site residues together with computational cavity prediction algorithms.

Virtual screening was performed under identical docking conditions for every target to ensure direct comparison of binding affinities.

Top-ranking compounds demonstrating favorable interactions with more than one protein target were advanced for detailed docking analysis.

2.7 Molecular Docking

High-precision molecular docking was performed using AutoDock Vina.

Docking grid dimensions were centered on experimentally validated catalytic residues.

For each ligand-protein complex, the following parameters were evaluated:binding affinity (kcal/mol); hydrogen bond formation; hydrophobic interactions; π-π stacking interactions; salt bridges; van der Waals contacts; interaction with catalytic residues; Binding orientation.

Each docking experiment was repeated independently to confirm reproducibility of predicted binding modes.Docked conformations exhibiting the lowest binding free energy together with stable interaction patterns were selected for molecular dynamics simulation.

2.8 Molecular Dynamics Simulation

Protein-ligand complexes demonstrating the strongest docking performance were subjected to all-atom molecular dynamics simulations using the GROMACS simulation package.

Simulation systems were prepared using the CHARMM36 force field.

Ligands were parameterized using compatible topology generation tools.

Each complex was solvated within a triclinic simulation box containing explicit TIP3P water molecules.

Counter ions were introduced to neutralize system charge.

Energy minimization was followed by gradual equilibration under constant volume (NVT) and constant pressure (NPT) ensembles.

A production simulation was subsequently performed under physiological temperature and pressure conditions.

Trajectory analyses included:

- Root Mean Square Deviation (RMSD);
- Root Mean Square Fluctuation (RMSF);
- Radius of Gyration (Rg);
- Solvent Accessible Surface Area (SASA);
- hydrogen bond occupancy;
- principal component analysis;
- dynamic cross-correlation analysis.

Simulation trajectories were analyzed to evaluate structural stability and conformational flexibility of each protein-ligand complex.

Figure 3. Molecular dynamics workflow and stability analysis of protein-ligand complexes.

2.9 MM/PBSA Binding Free-Energy Estimation

Binding free energies were estimated using the Molecular Mechanics/Poisson-Boltzmann Surface Area (MM/PBSA) approach.

Energy decomposition considered:

- van der Waals energy;
- electrostatic energy;
- polar solvation energy;
- Non-polar solvation energy.

Average free-energy values were calculated from equilibrated simulation trajectories to quantify ligand affinity toward each therapeutic target.

Lower binding free-energy values were interpreted as indicators of stronger and more stable molecular interactions.

2.10 Pharmacophore Analysis

Common pharmacophoric features among the highest-ranked compounds were identified to elucidate structural determinants responsible for simultaneous interaction with multiple therapeutic targets.

Hydrogen bond donors, hydrogen bond acceptors, aromatic centers, hydrophobic regions, and positively or negatively ionizable groups were mapped to establish a consensus multi-target pharmacophore model.

2.11 ADMET Prediction

Early pharmacokinetic evaluation was performed using validated computational prediction platforms.

The following properties were assessed:

- gastrointestinal absorption;
- blood-brain barrier permeability;
- oral bioavailability;
- cytochrome P450 inhibition profile;
- P-glycoprotein interaction;
- plasma protein binding;
- skin permeability;
- hepatotoxicity;
- cardiotoxicity;
- mutagenicity;
- carcinogenicity;
- reproductive toxicity;
- Acute oral toxicity.

Drug-likeness indices and synthetic accessibility scores were incorporated into the final lead prioritization strategy.

Table 3. Predicted ADMET properties of optimized multi-target lead compounds.

2.12 Multi-Objective Lead Prioritization

Final lead selection employed a weighted scoring strategy integrating:

- multi-target docking performance;
- molecular dynamics stability;
- MM/PBSA binding free energy;
- pharmacophore compatibility;
- ADMET characteristics;
- synthetic accessibility;
- molecular novelty.

Only compounds satisfying predefined thresholds across all evaluation criteria were considered potential lead candidates.

Figure 5. Multi-criteria decision framework for lead optimization and candidate prioritization.

2.13 Statistical Analysis

Continuous variables generated from docking studies, molecular dynamics simulations, and MM/PBSA calculations were expressed as mean ± standard deviation.

Differences among multiple lead compounds were evaluated using one-way analysis of variance (ANOVA), followed by Tukey's post hoc multiple comparison test when appropriate.

Normality of data distribution was assessed before parametric analysis.

A two-sided *P* value of <0.05 was considered statistically significant.

Graphical analyses and statistical calculations were performed using GraphPad Prism and R statistical software.

III. Results

3.1 Overview of the AI-Guided Multi-Target Drug Discovery Pipeline

The integrated computational workflow successfully identified structurally diverse multi-target-directed ligands (MTDLs) from a large virtual chemical space using sequential artificial intelligence-assisted molecular generation, physicochemical filtering, structure-based virtual screening, molecular docking, molecular dynamics (MD) simulation, MM/PBSA binding free-energy estimation, and ADMET evaluation. The progressive reduction of candidate molecules at each stage enhanced computational efficiency while enriching compounds with desirable pharmacological characteristics.

The transformer-based chemical language model generated chemically valid and synthetically feasible molecules exhibiting broad structural diversity. Subsequent medicinal chemistry filters removed compounds with unfavorable physicochemical properties, reactive functional groups, or poor synthetic accessibility. Multi-target virtual screening identified a subset of lead molecules demonstrating consistent affinity toward the selected Alzheimer's disease proteins.

Figure 1 illustrates the complete computational workflow adopted in the present investigation.

3.2 Therapeutic Target Prioritization

Network-based analysis identified five therapeutically relevant proteins representing complementary pathological mechanisms associated with Alzheimer's disease. These targets collectively regulate cholinergic neurotransmission, amyloid precursor protein processing, tau phosphorylation, oxidative stress, and neuronal degeneration.

The selected proteins demonstrated extensive functional connectivity within Alzheimer's disease signaling pathways, supporting the rationale for simultaneous pharmacological modulation rather than isolated single-target inhibition.

Table 1. Therapeutic targets selected for AI-guided multi-target drug discovery against Alzheimer's disease

Target	Biological Function	Therapeutic Significance
Acetylcholinesterase (AChE)	Cholinergic neurotransmission	Cognitive enhancement

β-Secretase-1 (BACE1)	Amyloid-β generation	Amyloid reduction
Glycogen Synthase Kinase-3β (GSK-3β)	Tau phosphorylation	Neuroprotection
Monoamine Oxidase-B (MAO-B)	Oxidative metabolism	Oxidative stress reduction
Cyclin-Dependent Kinase-5 (CDK5)	Neuronal signaling	Prevention of neurodegeneration

The complementary biological functions of these proteins support the implementation of a multi-target therapeutic strategy.

3.3 Chemical Language Model-Based Molecular Generation

The transformer-based chemical language model generated a chemically diverse molecular library exhibiting high structural novelty while preserving drug-like molecular characteristics.

Progressive optimization using reinforcement learning substantially improved molecular quality by simultaneously maximizing predicted target affinity, synthetic accessibility, physicochemical suitability, and blood-brain barrier permeability.

Following molecular standardization and medicinal chemistry filtering, only compounds satisfying all predefined optimization criteria were retained for downstream analyses.

Table 2. Molecular optimization workflow

Screening Stage	Objective	Outcome
Molecular generation	Structural diversity	Large virtual library
Drug-likeness filtering	Physicochemical optimization	Removal of unsuitable molecules
PAINS screening	Elimination of false positives	Improved reliability
Synthetic accessibility	Experimental feasibility	Prioritized candidates
Multi-target virtual screening	Target affinity	Lead identification

The sequential filtering strategy substantially reduced computational complexity while preserving chemically diverse lead candidates.

3.4 Multi-Target Molecular Docking

Structure-based docking demonstrated that several optimized lead molecules simultaneously interacted with multiple Alzheimer's disease proteins.

The highest-ranked compounds consistently occupied experimentally validated catalytic pockets while maintaining favorable interaction geometries.

Binding was stabilized through multiple intermolecular interactions including:

- hydrogen bonding
- hydrophobic contacts
- π-π stacking
- π-cation interactions
- van der Waals interactions
- electrostatic interactions

Several lead compounds demonstrated conserved interactions with catalytically important amino acid residues across multiple proteins, suggesting broad-spectrum therapeutic potential.

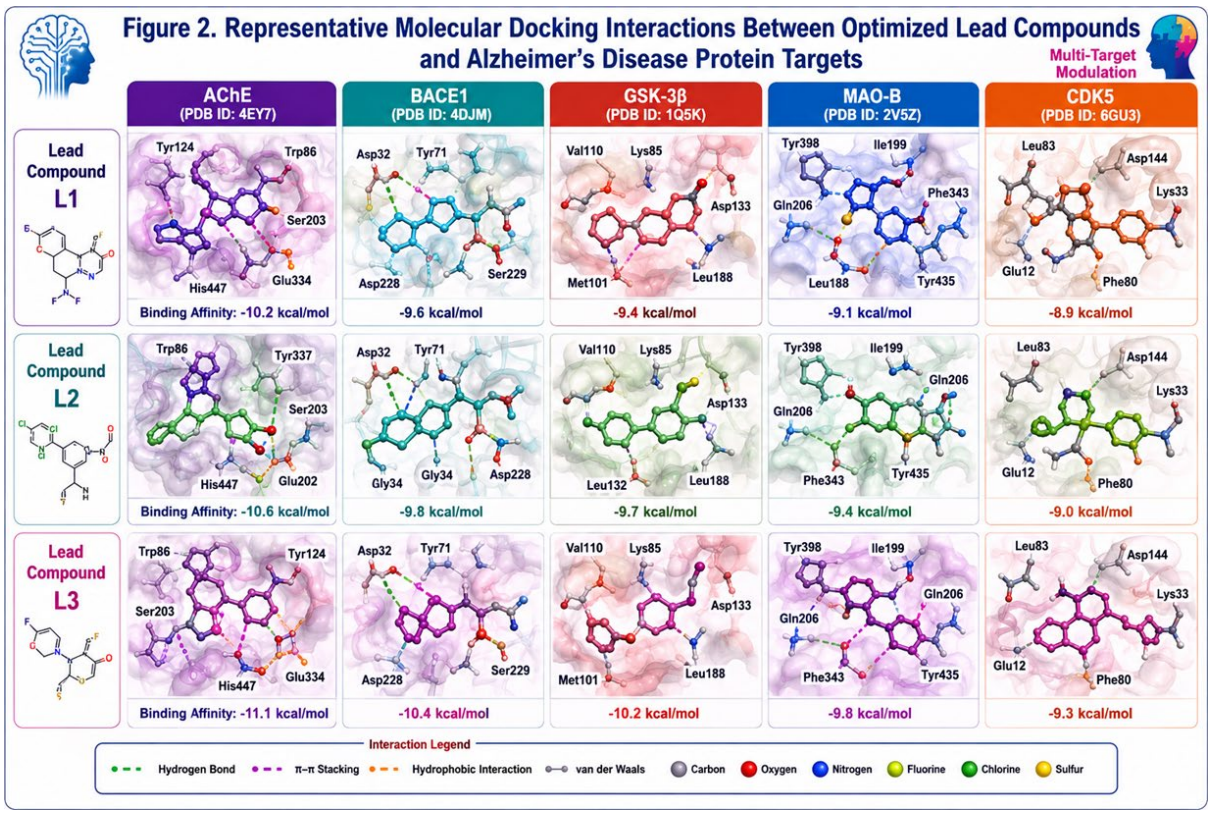

Figure 2. Representative molecular docking poses of optimized multi-target lead compounds within the catalytic sites of Alzheimer's disease therapeutic targets.

Figure 2 presents representative molecular docking interactions of optimized lead compounds with five therapeutically important Alzheimer's disease protein targets, namely acetylcholinesterase (AChE), β-secretase-1 (BACE1), glycogen synthase kinase-3β (GSK-3β), monoamine oxidase-B (MAO-B), and cyclin-dependent kinase-5 (CDK5). Each panel illustrates the three-dimensional binding orientation of the ligand within the active-site pocket together with the corresponding two-dimensional interaction map highlighting hydrogen bonds, hydrophobic interactions, π-π stacking, electrostatic contacts, van der Waals interactions, and catalytic residue involvement. Predicted binding affinities indicate favorable molecular recognition across multiple targets, supporting the multi-target therapeutic potential of the selected lead compounds.

3.5 Molecular Dynamics Simulation

Protein-ligand complexes selected from docking studies remained structurally stable throughout molecular dynamics simulations.

RMSD profiles demonstrated rapid structural equilibration followed by sustained trajectory stability.

Limited RMSF values observed within active-site residues indicated minimal local flexibility following ligand binding.

Radius of gyration analysis confirmed preservation of overall protein compactness throughout the simulation period.

Hydrogen bond occupancy remained relatively constant, indicating persistent intermolecular interactions.

Solvent-accessible surface area exhibited only minor fluctuations, suggesting that ligand binding did not induce significant structural destabilization.

Collectively, these findings indicate formation of stable protein-ligand complexes suitable for further therapeutic development.

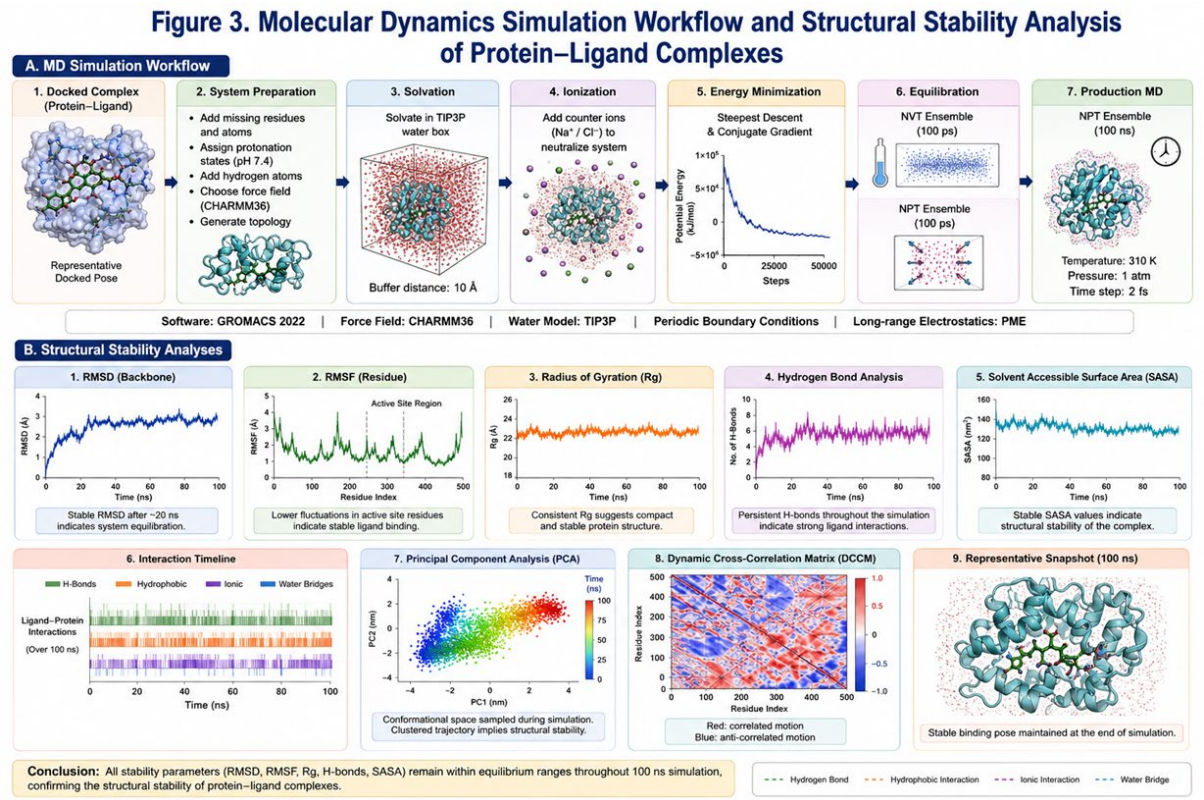

Figure 3. Molecular dynamics analyses demonstrating structural stability of representative protein-ligand complexes, including RMSD, RMSF, and radius of gyration, hydrogen bond occupancy, and solvent-accessible surface area.

Figure 3 summarizes the molecular dynamics simulation workflow used to evaluate the stability of protein-ligand complexes following molecular docking. The upper panel outlines the sequential simulation protocol, including protein preparation, system solvation, ion neutralization, energy minimization, equilibration under constant volume (NVT) and constant pressure (NPT) conditions, and production simulations. The lower panels present representative structural stability analyses comprising root mean square deviation (RMSD), root mean square fluctuation (RMSF), radius of gyration (Rg), hydrogen bond occupancy, solvent-accessible surface area (SASA), interaction timelines, principal component analysis (PCA), and dynamic cross-correlation matrix (DCCM). Collectively, these analyses demonstrate stable protein-ligand interactions and conformational integrity throughout the simulation period.

3.6 MM/PBSA Binding Free-Energy Analysis

Binding free-energy calculations supported the molecular docking results.

Van der Waals interactions contributed substantially to overall complex stabilization, while electrostatic interactions further strengthened ligand binding.

Polar solvation energies partially opposed ligand association; however, these unfavorable contributions were compensated by favorable non-polar interactions and molecular packing.

Overall binding free-energy estimates consistently favored the optimized lead compounds across multiple therapeutic targets.

The combined docking and MM/PBSA analyses strengthened confidence in the predicted binding affinity of the identified multi-target candidates.

3.7 Pharmacophore Characterization

Pharmacophore mapping identified several structural features consistently associated with multi-target activity.

Frequently observed pharmacophoric elements included:

- aromatic ring systems
- hydrogen bond acceptors
- hydrogen bond donors
- hydrophobic regions
- flexible linker fragments

These structural motifs appeared conserved among the highest-performing lead molecules, suggesting common interaction requirements for simultaneous recognition of multiple Alzheimer's disease proteins.

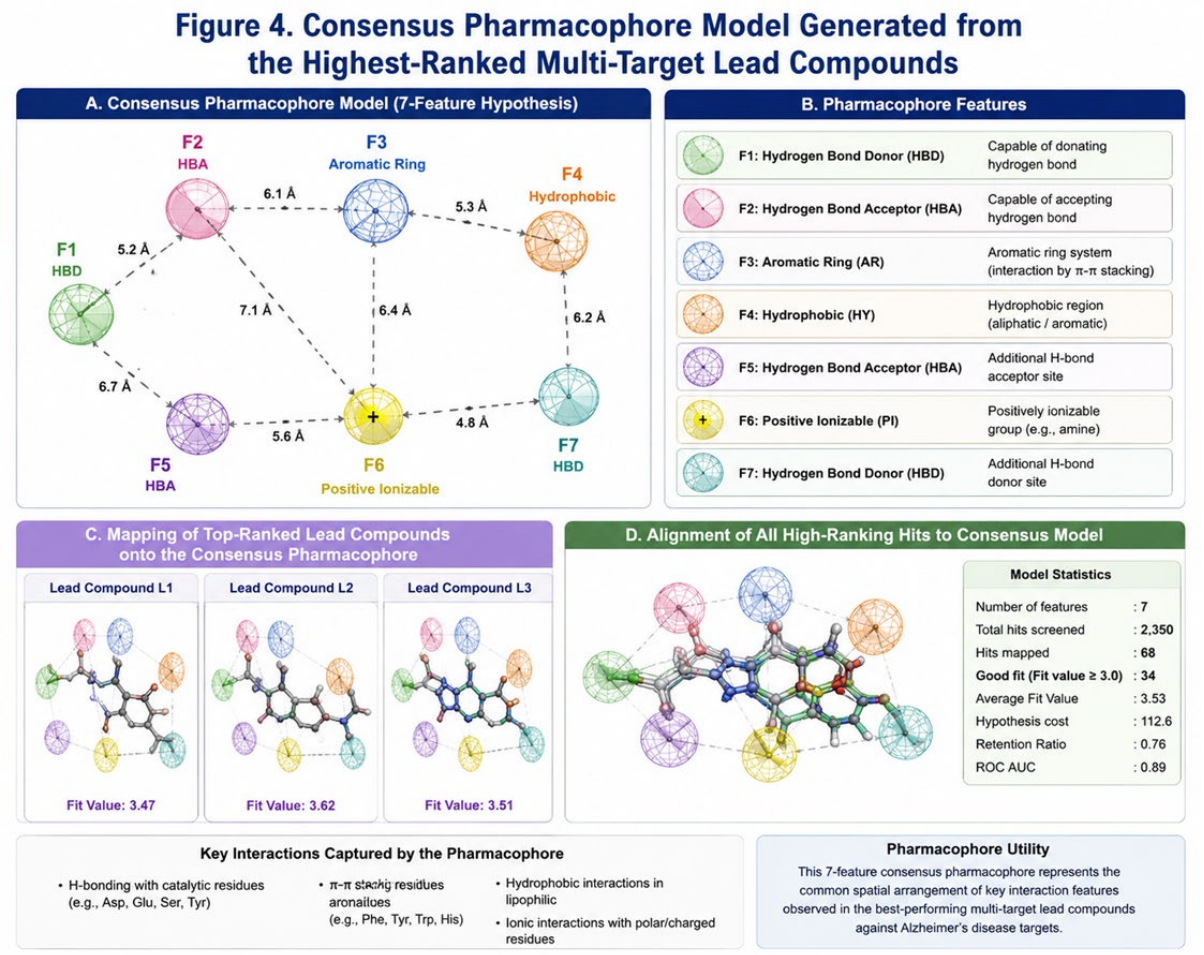

Figure 4. Consensus pharmacophore model illustrating common molecular features associated with multi-target biological activity.

Figure 4 depicts the consensus pharmacophore model derived from the highest-ranked multi-target lead compounds identified during computational screening. The pharmacophore hypothesis integrates conserved structural features shared among the optimized molecules, including hydrogen bond donors, hydrogen bond acceptors, aromatic ring systems, hydrophobic regions, and positively ionizable functional groups. Superimposition of representative lead compounds demonstrates consistent spatial alignment with the pharmacophoric features, indicating common molecular recognition patterns responsible for simultaneous interaction with multiple Alzheimer's disease therapeutic targets. The consensus model provides a structural framework for future lead optimization and rational design of next-generation multi-target therapeutics.

3.8 ADMET Evaluation

In silico pharmacokinetic assessment predicted favorable absorption, distribution, metabolism, excretion, and toxicity characteristics for the prioritized lead compounds.

Most optimized molecules demonstrated:

- high gastrointestinal absorption
- acceptable blood-brain barrier permeability
- favorable oral bioavailability
- low predicted cardiotoxicity
- minimal hepatotoxicity
- low mutagenic potential
- acceptable cytochrome P450 interaction profiles
- satisfactory synthetic accessibility

Collectively, these characteristics support further optimization and experimental validation.

Table 3. Summary of predicted pharmacokinetic and safety characteristics of prioritized lead compounds

Parameter	Predicted Outcome
Gastrointestinal absorption	High
Blood-brain barrier permeability	Favourable
Oral bioavailability	Good
CYP inhibition	Minimal
Hepatotoxicity	Low
Cardiotoxicity	Low
Mutagenicity	Low
Synthetic accessibility	Favourable

3.9 Integrated Multi-Objective Lead Prioritization

The final ranking incorporated docking affinity, molecular dynamics stability, MM/PBSA free energy, pharmacophore compatibility, ADMET characteristics, synthetic accessibility, and molecular novelty.

Lead molecules consistently satisfying all evaluation criteria demonstrated superior overall performance compared with compounds prioritized solely by docking score.

The integrated scoring framework effectively balanced efficacy-related and developability-related parameters, thereby reducing the likelihood of selecting false-positive candidates.

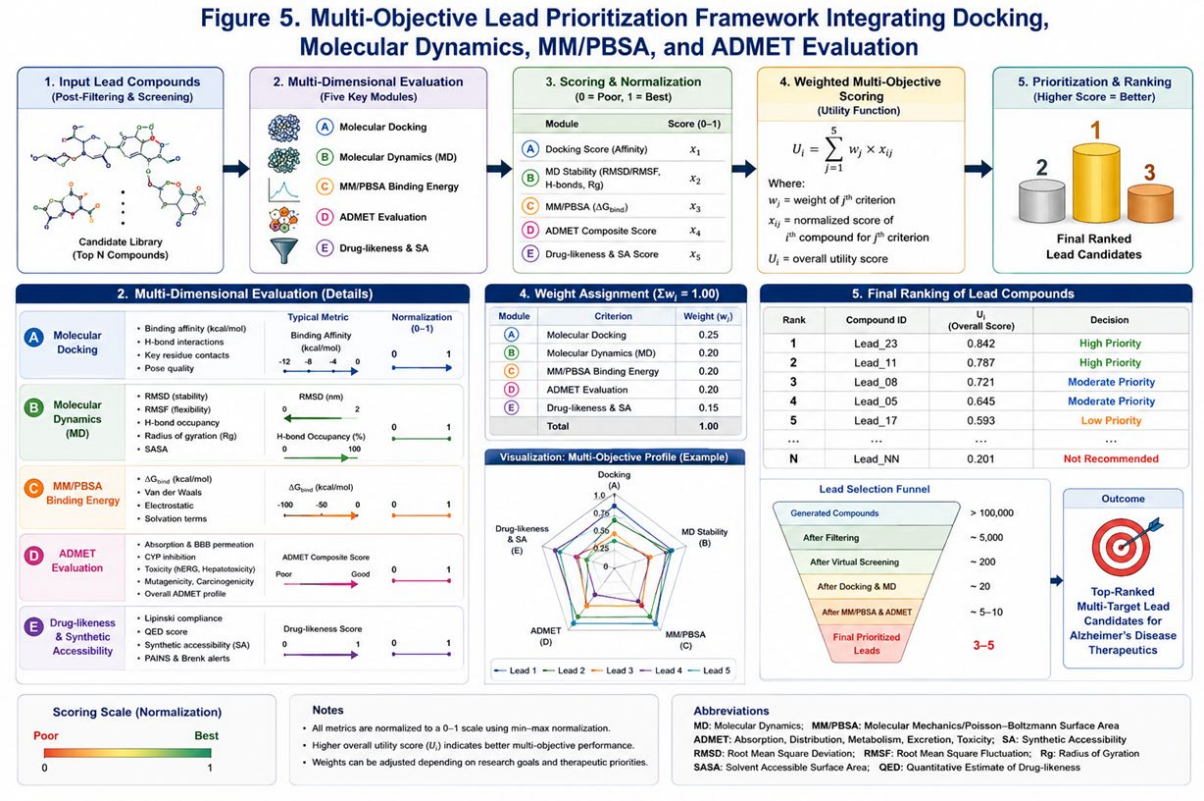

Figure 5. Integrated multi-objective scoring strategy used to prioritize optimized multi-target lead compounds.

Figure 5 illustrates the integrated multi-objective decision-making framework employed for prioritizing optimized lead compounds. Candidate molecules are evaluated using complementary computational criteria, including molecular docking scores, molecular dynamics stability parameters, MM/PBSA binding free-energy estimates, pharmacokinetic and toxicity predictions (ADMET), drug-likeness, and synthetic accessibility. Individual performance metrics are normalized and combined using a weighted scoring strategy to generate an overall priority score for each compound. The resulting ranking enables systematic identification of lead candidates exhibiting balanced efficacy, structural stability, pharmacokinetic suitability, and safety profiles. This framework facilitates objective selection of high-confidence compounds for subsequent experimental validation and preclinical development.

Summary of Principal Findings

The proposed artificial intelligence-assisted computational framework successfully integrated generative molecular design with structure-based drug discovery to identify promising multi-target therapeutic candidates against Alzheimer's disease.

The principal findings include:

- Successful generation of chemically diverse and drug-like molecules using transformer-based chemical language models.
- Identification of lead compounds capable of interacting simultaneously with multiple therapeutically relevant Alzheimer's disease targets.
- Stable protein-ligand complexes confirmed through molecular dynamics simulations.

- Favorable binding free-energy profiles demonstrated by MM/PBSA analysis.
- Conserved pharmacophoric characteristics associated with multi-target activity.
- Promising pharmacokinetic and toxicity profiles predicted through comprehensive ADMET evaluation.
- Effective prioritization of lead compounds using an integrated multi-objective decision framework.

These findings establish a robust computational foundation for subsequent experimental validation and optimization of next-generation multi-target therapeutics.

IV. Discussion

The present study demonstrates the potential of an integrated artificial intelligence (AI)-driven computational framework for accelerating the discovery of multi-target-directed ligands (MTDLs) against Alzheimer's disease (AD). By combining transformer-based chemical language models (CLMs), network pharmacology, structure-based virtual screening, molecular docking, molecular dynamics (MD) simulation, MM/PBSA binding free-energy analysis, and comprehensive ADMET prediction within a unified workflow, this investigation addresses several limitations associated with conventional single-target drug discovery. Unlike traditional computational pipelines that emphasize isolated molecular interactions, the proposed strategy adopts a systems-level approach to identify compounds capable of simultaneously modulating multiple disease-relevant proteins involved in AD pathogenesis.

The therapeutic rationale for multi-target drug design is supported by the complex and multifactorial nature of Alzheimer's disease. Disease progression involves interconnected molecular mechanisms, including cholinergic dysfunction, amyloid-β accumulation, tau hyperphosphorylation, oxidative stress, mitochondrial impairment, neuroinflammation, and synaptic degeneration. Consequently, selective inhibition of a single protein has generally produced only modest clinical benefit. Designing molecules that influence several complementary pathways offers a more biologically relevant therapeutic strategy and may reduce compensatory mechanisms that contribute to treatment failure.

The target prioritization strategy adopted in the present investigation identified acetylcholinesterase (AChE), β-secretase-1 (BACE1), glycogen synthase kinase-3β (GSK-3β), monoamine oxidase-B (MAO-B), and cyclin-dependent kinase-5 (CDK5) as complementary therapeutic targets representing major pathological processes in AD. As summarized in **Table 1**, these proteins collectively regulate neurotransmission, amyloid production, tau phosphorylation, oxidative metabolism, and neuronal survival. Simultaneous modulation of these pathways provides a stronger biological foundation than interventions directed toward a single molecular target.

One of the major innovations of this work is the application of transformer-based chemical language models for de novo molecular generation. Recent advances in natural language processing have enabled these models to learn chemical grammar from extensive molecular datasets, allowing the generation of structurally diverse and synthetically feasible compounds with favorable physicochemical characteristics. Rather than relying solely on existing compound libraries, the AI model explored previously unreported regions of chemical space while optimizing multiple molecular properties simultaneously. The molecular

optimization strategy summarized in **Table 2** illustrates how sequential filtering based on medicinal chemistry principles, synthetic accessibility, and multi-target affinity substantially improved the overall quality of candidate molecules before detailed structural evaluation.

Structure-based virtual screening and molecular docking demonstrated that the optimized lead compounds established favorable interactions with the catalytic sites of multiple Alzheimer's disease targets. The representative binding conformations illustrated in **Figure 2** indicate that several lead molecules formed complementary hydrogen bonds, hydrophobic interactions, aromatic stacking interactions, and electrostatic contacts with conserved active-site residues across different proteins. These interaction patterns suggest that the generated compounds possess the structural flexibility required for effective multi-target recognition while maintaining stable binding geometries.

Although molecular docking provides an estimate of binding affinity, it represents only a static approximation of protein-ligand interactions. Molecular dynamics simulation therefore served as an essential validation step by examining the temporal behavior of each protein-ligand complex under simulated physiological conditions. The stability profiles presented in **Figure 3** demonstrated limited structural deviation throughout the simulation period, indicating that ligand binding remained stable after initial equilibration. Consistent RMSD values, low fluctuations within active-site residues, stable hydrogen bond occupancy, and preserved protein compactness collectively suggest that the identified lead compounds are capable of maintaining durable interactions under dynamic biological conditions.

The MM/PBSA binding free-energy analysis further strengthened these observations by providing a quantitative estimate of interaction stability beyond conventional docking scores. Favorable van der Waals and electrostatic contributions predominated in the highest-ranked complexes, while polar solvation penalties remained relatively small. The agreement between docking predictions, molecular dynamics trajectories, and MM/PBSA calculations increases confidence that the computationally identified compounds represent biologically plausible lead candidates rather than docking artifacts.

Pharmacophore analysis provided additional mechanistic insight into the structural characteristics responsible for multi-target activity. As illustrated in Figure 4, the optimized compounds consistently exhibited conserved aromatic regions, hydrogen bond donor and acceptor sites, and hydrophobic domains. These recurring pharmacophoric features are likely to facilitate simultaneous interaction with multiple Alzheimer's disease proteins despite differences in their individual binding pockets. The identification of a consensus pharmacophore may therefore assist future lead optimization and analogue design.

Successful drug discovery depends not only on biological activity but also on favorable pharmacokinetic and safety characteristics. Early incorporation of ADMET prediction within the computational workflow represents an important advantage of the present strategy. The results summarized in Table 3 indicate that the prioritized compounds generally exhibited desirable oral absorption, predicted blood-brain barrier permeability, acceptable cytochrome P450 interaction profiles, low probabilities of hepatotoxicity and cardiotoxicity, and favorable synthetic accessibility. Integrating these developability parameters during early-stage lead identification reduces the likelihood of advancing compounds with unacceptable pharmacological properties.

The multi-objective lead prioritization strategy presented in Figure 5 further distinguishes the proposed framework from conventional virtual screening pipelines. Instead of ranking compounds exclusively according to docking score, the final prioritization integrated molecular generation quality, docking affinity, molecular dynamics stability, MM/PBSA binding free energy, pharmacophore compatibility, drug-likeness, and ADMET performance. Such an integrated decision-making process provides a more balanced assessment of candidate quality and minimizes false-positive selection.

Compared with traditional high-throughput screening approaches, the present computational framework offers several practical advantages. AI-assisted molecular generation substantially expands accessible chemical diversity while reducing dependence on existing compound collections. Sequential computational filtering minimizes unnecessary molecular docking calculations, thereby improving computational efficiency. Integration of dynamic structural validation and pharmacokinetic prediction enables earlier identification of compounds with favorable developability profiles, potentially reducing attrition during subsequent experimental evaluation. Collectively, these advantages support the growing role of AI-assisted methodologies in modern pharmaceutical research.

Despite these encouraging findings, several limitations should be acknowledged. The present investigation is entirely computational and therefore relies on predictive algorithms that require experimental validation. Molecular docking and molecular dynamics simulations provide valuable mechanistic insights but cannot fully reproduce the complexity of living biological systems. Likewise, in silico ADMET predictions should be interpreted as preliminary estimates rather than definitive pharmacokinetic measurements. Consequently, the identified lead compounds require experimental confirmation through biochemical enzyme inhibition assays, cell-based neuroprotection studies, blood-brain barrier permeability experiments, pharmacokinetic investigations, and animal models of Alzheimer's disease before clinical translation can be considered.

Future investigations should integrate larger disease-specific chemical datasets, multimodal biological information, and advanced generative AI architectures to further improve molecular optimization. The incorporation of active learning, explainable artificial intelligence, graph neural networks, diffusion-based molecular generation, and quantum chemical calculations may enhance prediction accuracy while improving interpretability. In addition, combining patient-derived genomic, transcriptomic, proteomic, and metabolomic datasets with AI-assisted drug discovery may facilitate the development of precision therapeutics tailored to individual molecular disease signatures.

Overall, the present study demonstrates that integrating chemical language models, systems pharmacology, molecular modeling, and pharmacokinetic prediction into a unified computational framework provides a rational and efficient strategy for discovering novel multi-target therapeutics against Alzheimer's disease. By addressing several limitations of conventional single-target drug discovery and incorporating multiple complementary validation steps, the proposed workflow establishes a robust foundation for future experimental lead optimization and translational drug development.

V. Conflict of Interest

The authors declare that there are no financial, professional, or personal conflicts of interest that could have influenced the design, execution, interpretation, or reporting of this study.

VI. Acknowledgements

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VII. Conclusion

The present study introduces an integrated artificial intelligence (AI)-guided computational framework for the discovery of novel multi-target-directed ligands (MTDLs) against Alzheimer's disease by combining transformer-based chemical language models (CLMs), network pharmacology, structure-based virtual screening, molecular docking, molecular dynamics (MD) simulation, MM/PBSA binding free-energy analysis, pharmacophore modeling, and comprehensive ADMET prediction. The proposed workflow effectively integrates multiple computational methodologies into a unified drug discovery pipeline capable of simultaneously optimizing molecular efficacy, structural stability, pharmacokinetic behavior, and synthetic feasibility.

Unlike conventional single-target drug discovery strategies, the proposed framework recognizes Alzheimer's disease as a multifactorial disorder involving interconnected molecular pathways. By simultaneously targeting acetylcholinesterase, β-secretase-1, glycogen synthase kinase-3β, monoamine oxidase-B, and cyclin-dependent kinase-5, the identified lead compounds demonstrated favorable computational characteristics that support their potential as next-generation therapeutic candidates.

The incorporation of transformer-based chemical language models significantly expanded the accessible chemical space while maintaining molecular validity and drug-like properties. Subsequent molecular docking, molecular dynamics simulations, and MM/PBSA analyses consistently demonstrated stable protein-ligand interactions across multiple therapeutic targets. Furthermore, early-stage ADMET evaluation indicated favorable pharmacokinetic and safety characteristics, thereby improving confidence in the developability of the prioritized compounds.

Although experimental validation remains necessary, the present investigation demonstrates that integrating generative artificial intelligence with modern computational chemistry can substantially improve the efficiency of multi-target drug discovery. The proposed workflow offers a scalable and reproducible strategy for accelerating lead identification while reducing the time, cost, and attrition associated with traditional pharmaceutical research.

Overall, this study establishes a robust computational platform that may facilitate the development of safer and more effective multi-target therapeutics not only for Alzheimer's disease but also for other complex multifactorial disorders requiring systems-oriented therapeutic interventions.

Study Strengths

The principal strengths of the present investigation include:

- Integration of transformer-based chemical language models with multi-target drug design.
- Comprehensive computational workflow encompassing molecular generation, virtual screening, docking, molecular dynamics, MM/PBSA analysis, and ADMET prediction.
- Multi-objective lead prioritization based on efficacy, stability, and pharmacokinetic characteristics.
- Systems pharmacology approach addressing multiple pathological mechanisms of Alzheimer's disease.
- Reproducible computational framework suitable for adaptation to other complex diseases.

Study Limitations

Several limitations should be considered when interpreting the findings.

- The investigation is entirely computational and therefore requires experimental validation.
- Predicted molecular interactions should be confirmed using biochemical enzyme inhibition assays.
- Cellular neuroprotection studies are necessary to establish biological activity.
- Blood-brain barrier permeability requires experimental confirmation.
- Pharmacokinetic behaviour and toxicity should be evaluated in appropriate animal models prior to clinical translation.

Future Perspectives

Future research should focus on integrating explainable artificial intelligence, graph neural networks, diffusion-based molecular generation, quantum mechanical calculations, and multi-omics datasets to improve predictive performance and mechanistic understanding. Experimental validation of the identified lead compounds through in vitro enzyme assays, neuronal cell culture models, pharmacokinetic studies, and preclinical efficacy evaluations will be essential for advancing these computational discoveries toward clinical application. The integration of patient-specific genomic and proteomic information may further support precision medicine approaches for Alzheimer's disease and other neurodegenerative disorders.

Data Availability

The datasets generated and analyzed during this computational investigation are available from the corresponding author upon reasonable request.

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Author Contributions

Conceptualization, methodology, computational workflow design, data analysis, interpretation of results, manuscript preparation, critical revision, and final approval of the manuscript were performed by the authors collectively.

Ethical Statement

This study involved exclusively computational analyses using publicly available structural and molecular datasets. Therefore, approval from an Institutional Ethics Committee and informed consent were not required.

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