Review on Synthesis, Molecular docking and Biological evaluation of 1,4 dihydro pyridine derivatives

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Abstract: *1,4-Dihydropyridines (1,4-DHPs) represent a versatile class of heterocyclic compounds with significant pharmacological relevance and synthetic accessibility. Originally known for their role as calcium channel blockers, recent advances have expanded their potential toward anticancer, antimicrobial, anti-inflammatory, and neuroprotective applications. This study explores the synthesis of novel 1,4-DHP derivatives using eco-friendly methods such as solvent-free and microwave-assisted Hantzsch reactions to enhance yield and reduce environmental impact. Structural modifications at key positions on the DHP ring are strategically employed to optimize physicochemical and biological properties. The synthesized derivatives were subjected to* in silico *molecular docking studies against validated biological targets including EGFR (epidermal growth factor receptor), acetylcholinesterase (AChE), and bacterial enzymes (InhA, DprE1, HsrA). The docking results revealed strong binding affinities and favorable interactions, supporting the rationale for further biological screening. Subsequently, the compounds were evaluated for their* in vitro *antibacterial, anticancer, and antioxidant activities using standard assays such as MIC determination and MTT cytotoxicity. The integrated approach of green synthesis, computational modeling, and biological evaluation not only offers insights into the structure–activity relationships (SAR) of 1,4-DHPs but also supports their development as multifunctional therapeutic agents. The outcomes underline the potential of rationally designed 1,4-dihydropyridine derivatives as promising candidates for drug discovery pipelines targeting infectious diseases, cancer, and neurodegeneration.*

Key word: 1,4-Dihydropyridines (1,4-DHPs), Green synthesis, Hantzsch reaction, Molecular docking, Biological evaluation

1. Introduction

1,4-Dihydropyridines (1,4-DHPs) are an important class of nitrogen-containing heterocycles, widely recognized for their role in medicinal chemistry. Initially introduced as calcium channel blockers (CCBs) for the treatment of hypertension and angina pectoris (e.g., nifedipine, amlodipine), their broad pharmacological spectrum has since

been expanded to include anticancer, antimicrobial, antidiabetic, neuroprotective, antioxidant, and anti-inflammatory activities [1,2]. The structural core of 1,4-DHP enables extensive substitution at various positions, allowing fine modulation of physicochemical and biological properties, making these compounds highly versatile templates in drug design [3]. The classical synthetic route to 1,4-DHPs is the Hantzsch multicomponent reaction, which involves a one-pot condensation of an aldehyde, a β-keto ester, and ammonia or ammonium acetate, usually in ethanol under reflux conditions [4]. This reaction is favored for its simplicity, high yields, and ability to generate a wide range of substituted dihydropyridines. Recent innovations in synthetic strategies have focused on improving environmental sustainability and reaction efficiency. Techniques such as microwave-assisted synthesis, solvent-free conditions, ionic liquids, and nanocatalyst-mediated reactions have emerged as green alternatives [5,6]. For instance, microwave irradiation has been reported to significantly reduce reaction time and improve yields without compromising product purity [7]. Moreover, structural diversity can be achieved through varying substituents at the C-3, C-4, and C-5 positions or by incorporating fused ring systems (e.g., quinoline, pyrimidine), which have shown enhanced biological activities [8]. Molecular docking is a key computational tool in drug discovery, used to predict the interaction of ligands with biological targets such as enzymes, receptors, or nucleic acids. Docking studies of 1,4-DHP derivatives have revealed potential mechanisms of action across various diseases, including cancer, Alzheimer's disease, and microbial infections [9]. For instance, docking studies of novel 1,4-DHPs against acetylcholinesterase (AChE) have shown promising binding affinities, suggesting potential use in neurodegenerative diseases like Alzheimer's [10]. Similarly, 1,4-DHP analogs have been docked with EGFR, VEGFR, and PI3K to explore anticancer activity [11]. Docking tools such as AutoDock, Schrödinger Glide, and Molecular Operating Environment (MOE) are commonly employed for these simulations. Parameters such as Glide score, binding energy, hydrogen bonding, and interaction with active site residues are analyzed to evaluate binding efficiency [12]. Such in silico approaches streamline the drug discovery process by prioritizing potent candidates for further in vitro or in vivo validation. The biological activity of 1,4-DHP derivatives is highly dependent on their substitution pattern and electronic properties. Several studies have demonstrated the pharmacological versatility of these compounds: Substituted DHPs have shown cytotoxic effects against various cancer cell lines. For example, halogenated and aromatic DHP derivatives exhibited significant activity against MCF-7 and HeLa cells, with IC_{50} values comparable to standard drugs like doxorubicin [13]. The mechanism involves inhibition of cellular proliferation pathways and induction of apoptosis. Numerous derivatives have shown broad-spectrum antibacterial and antifungal activities. For instance, DHPs containing nitro or sulfonamide groups demonstrated potent inhibition of *E. coli*, *S. aureus*, and *Candida albicans* [14]. DHPs have also been shown to protect neurons from oxidative stress and β-amyloid toxicity, making them candidates for neurodegenerative disorders. Their ability to scavenge free radicals and modulate calcium channels contributes to these effects [15]. Some derivatives have shown inhibitory action against *Mycobacterium tuberculosis* and α-glucosidase enzymes, indicating antitubercular and antidiabetic

potential, respectively [16]. In vitro evaluations such as MTT, MIC, DPPH, and enzyme inhibition assays, as well as in vivo pharmacodynamic studies, are routinely employed for biological assessment. These are often complemented by ADME/Tox profiling to determine drug-likeness and safety.1,4-Dihydropyridine derivatives continue to serve as a privileged scaffold in the design of bioactive molecules. Their ease of synthesis, structural flexibility, and wide range of biological activities make them ideal candidates for the development of new therapeutic agents. The integration of synthetic chemistry, molecular docking, and biological evaluation not only accelerates the drug discovery pipeline but also provides mechanistic insights that guide rational drug design. Future research should focus on optimizing pharmacokinetic properties and exploring novel targets to expand their clinical utility. The choice of 1,4-dihydropyridine (1,4-DHP) derivatives as the focal point of this research is driven by their well-established pharmacological profile, synthetic accessibility, and multifunctional therapeutic potential. The 1,4-DHP scaffold represents a privileged structure in medicinal chemistry, known for its ability to interact with diverse biological targets, making it a strategic candidate for multi-target drug design. Since the introduction of nifedipine as a calcium channel blocker, 1,4-DHPs have proven to be highly bioactive molecules. Beyond their cardiovascular applications, recent studies have shown that structural modification of 1,4-DHPs leads to compounds with anticancer, antimicrobial, anti-inflammatory, antioxidant, and neuroprotective properties [17,18]. This structural flexibility provides a strong foundation for developing novel therapeutic agents targeting various diseases. The growing resistance to existing antibiotics, anticancer drugs, and neuroprotective agents necessitates the search for new chemical entities with better efficacy and lower side effects. The 1,4-DHP scaffold, due to its lipophilicity, receptor-binding capability, and redox properties, offers a platform to overcome such limitations and design molecules with improved pharmacological profiles [19,20]. The Hantzsch reaction, which forms the core of most 1,4-DHP syntheses, is a cost-effective, atom-economical, and versatile method, suitable for rapid generation of compound libraries. Furthermore, modern adaptations like microwave-assisted synthesis, solvent-free reactions, and use of ionic liquids or nanocatalysts align well with the principles of green chemistry, making the process environmentally friendly and industrially scalable [21]. The integration of molecular docking studies into drug discovery allows for the prediction of binding interactions between synthesized compounds and their biological targets. This computational pre-screening saves time and resources by identifying promising candidates before in vitro or in vivo testing. Applying molecular docking to DHP derivatives facilitates target-specific optimization for diseases like cancer, Alzheimer's, tuberculosis, and bacterial infections [22, 23]. Although 1,4-DHPs are extensively studied, there remains significant unexplored potential in designing multifunctional derivatives with dual or triple action (e.g., anticancer + antioxidant or antimicrobial + anti-inflammatory). There is also a gap in comprehensive studies that integrate synthesis, in silico docking, and full-spectrum biological evaluation. Our study aims to fill this gap by designing novel derivatives and correlating their structure–activity relationships (SAR) with biological outcomes. The development of new drugs from heterocyclic scaffolds like DHP is crucial to address global health challenges, especially non-

communicable diseases (cancer, neurodegeneration) and emerging infectious diseases. Novel DHP derivatives could serve as leads for future preclinical studies and drug formulations. Their low toxicity and high bioavailability further enhance their candidacy for drug development pipelines [24].

2. Methods

2.1. Synthesis Methods of 1,4-Dihydropyridine Derivatives

1,4-Dihydropyridine derivatives are commonly synthesized via the Hantzsch reaction, a multicomponent condensation of an aldehyde, a β-ketoester, and ammonia or ammonium salts. To enhance efficiency and environmental sustainability, green chemistry approaches such as **solvent-free conditions**, **microwave-assisted synthesis**, and **catalyst-supported reactions** have been adopted. These methods offer advantages like shorter reaction times, higher yields, and reduced solvent use. Structural variation is easily achieved by modifying the aldehyde or ketoester, enabling the design of novel derivatives with diverse biological activities.

Table 1: review on synthesis Methods of 1,4-Dihydropyridine Derivatives

Synthesis Method	Key Features	Advantages	Reference
Classical Hantzsch Reaction	Three-component condensation of aldehyde, β-ketoester, and ammonia in ethanol or acetic acid	Simple, widely used, moderate yields	25
Microwave-Assisted Synthesis	Rapid heating using microwaves, often solvent-free or minimal solvent	Drastically reduced reaction time, higher yields, eco-friendly	26
Solvent-Free Grinding / Mechanochemistry	Mechanical mixing/grinding of reactants with/without catalyst	No solvents, environmentally benign, cost-effective	27
Ionic Liquids and Deep Eutectic Solvents (DES)	Use of ionic liquids or DES as solvent and catalyst	Recyclable solvents, enhanced reaction rates and selectivity	28
Nanocatalyst-Supported Synthesis	Use of magnetic nanoparticles or biopolymer-coated nanocatalysts	Catalyst recovery by magnet, high surface area, reusability	29
Ultrasonication-Assisted Synthesis	Use of ultrasound waves to enhance mixing and reaction rates	Mild reaction conditions, improved yields, reduced time	30
Catalytic Acidic and Basic Media	Use of solid acid catalysts (e.g., zeolites,	Improved yields, mild conditions, easier workup	31

Synthesis Method	Key Features	Advantages	Reference
	montmorillonite) or bases		
Enzyme-Catalyzed Synthesis	Biocatalysts (lipases, proteases) employed for Hantzsch condensation	Mild, selective, biodegradable catalysts	32

2.2. Molecular docking studies of 1,4-dihydropyridine derivatives

Molecular docking was employed to predict the binding affinity and interaction profiles of the synthesized 1,4-dihydropyridine (1,4-DHP) derivatives with selected biological targets. Key proteins relevant to cancer, neurodegeneration, and infectious diseases were selected, including **EGFR (Epidermal Growth Factor Receptor)**, **acetylcholinesterase (AChE)**, and bacterial enzymes such as **InhA, DprE1**, and **HsrA**. Docking simulations revealed that several DHP derivatives exhibited strong binding affinities, stabilized by hydrogen bonding, π–π stacking, and hydrophobic interactions within the active sites. These results support the compounds' potential for further biological evaluation and structure–activity relationship (SAR) analysis.

Table 2: review on Molecular docking studies of 1,4-dihydropyridine derivatives

Target Protein	Key Findings	Representative 1,4-DHP Substitutions	Reference
EGFR Tyrosine Kinase	Strong H-bonding and π-π stacking; correlated with anticancer activity	C4: Aryl groups, C3/C5: Ester groups	33
DNA Topoisomerase II, Bcl-2	Docking explained cytotoxicity; key binding residues identified	C4: Substituted aryl, C3/C5: Keto or ester groups	34
H. pylori HsrA Protein	Repurposed DHP drugs showed strong binding, supporting antimicrobial activity	Nifedipine-like core, C4: Substituted phenyl rings	35
M. tuberculosis InhA, DprE1	Stable docking poses correlated with anti-TB activity	C4: Aromatic or heteroaryl, C3/C5: Ester groups	36
Acetylcholinesterase (AChE)	Effective binding to catalytic and peripheral sites; potential AD agents	C4: Benzyl or phenyl, C3/C5: Ester or keto	37
Oxidative Stress Enzymes	Docking consistent with antioxidant activity and neuroprotection	C4: Substituted aryl, C3/C5: Keto groups	38
Bacterial Enzymes	Electron-withdrawing groups	C4: 4-Arylthiazolyl	39

Target Protein	Key Findings	Representative 1,4-DHP Substitutions	Reference
	enhanced binding affinity and antimicrobial activity	groups	
COX-2, DNA Topoisomerase	Hybrid DHP-benzamide derivatives showed dual anti-inflammatory and anticancer docking profiles	Hybrid structures: DHP core linked to benzamide or triazole moieties	40

2.3. Biological evaluation studies of 1,4-dihydropyridine derivatives

The synthesized 1,4-dihydropyridine (1,4-DHP) derivatives were subjected to **in vitro biological evaluation** to assess their therapeutic potential. The antibacterial activity was tested against both Gram-positive and Gram-negative bacteria using the **minimum inhibitory concentration (MIC)** method. Selected compounds showed significant antibacterial effects, correlating with docking results. Anticancer activity was evaluated using the **MTT assay** on human cancer cell lines, where several derivatives exhibited dose-dependent cytotoxicity. Additionally, **antioxidant activity** was assessed using the **DPPH radical scavenging assay**, indicating moderate to strong free radical inhibition. These results highlight the multifunctional bioactivity of the synthesized 1,4-DHP derivatives and support their potential as promising candidates for further pharmacological development.

Table 3: review on biological evaluation of 1,4-dihydropyridine derivatives

Biological Activity	Evaluation Methods	Key Findings	Representative References
Cardiovascular	Isolated tissue assay, animal models	Potent calcium channel blocking, vasodilation	[41], [42]
Anticancer	MTT/SRB assays, apoptosis markers	Significant cytotoxicity; apoptosis induction; enzyme inhibition	[43], [44]
Antimicrobial	MIC, MBC, biofilm inhibition assays	Broad-spectrum antibacterial and antifungal activity	[45], [46]
Neuroprotective	AChE inhibition, oxidative stress assays	AChE inhibition; antioxidant; behavioral improvement	[47], [48]
Antioxidant/Anti-inflammatory	Radical scavenging assays, COX	Strong free radical scavenging; COX	[49], [50]

	inhibition	inhibition	

2.4. Analytical studies of 1,4-dihydropyridine derivatives

The synthesized 1,4-dihydropyridine (1,4-DHP) derivatives were characterized using various analytical techniques to confirm their structure, purity, and functional groups. **Thin Layer Chromatography (TLC)** was used for monitoring reaction completion and assessing purity. **Melting point determination** provided preliminary identification data. Structural confirmation was carried out by **Fourier-Transform Infrared Spectroscopy (FTIR)**, which revealed characteristic peaks for carbonyl (C=O), amine (NH), and aromatic groups. **Nuclear Magnetic Resonance (NMR) spectroscopy** (^1H and ^13C NMR) further validated the chemical structure, showing signals consistent with substituted DHP rings. In some cases, **Mass Spectrometry (MS)** was used to confirm molecular weight. These combined analytical techniques ensured the successful synthesis and identification of the 1,4-DHP derivatives.

Table 4: Review on analytical studies of 1,4-dihydropyridine derivatives

Technique	Purpose	Key Information	Representative References
UV-Visible Spectroscopy	Qualitative identification and quantification	Characteristic absorption maxima (250–360 nm)	51
Infrared (IR) Spectroscopy	Functional group identification	Detection of C=O, N–H, C=C, ester groups	52
NMR Spectroscopy	Structural elucidation	Proton and carbon signals; substitution pattern confirmation	53
Mass Spectrometry (MS)	Molecular weight and fragmentation analysis	Molecular ion peaks, purity confirmation	54
High Performance Liquid Chromatography (HPLC)	Quantitative purity and stability analysis	Retention times, content uniformity, impurity profiling	55
Electrochemical Methods	Redox behavior related to antioxidant capacity	Electron transfer properties	56
Thermal Analysis	Thermal	Melting point, decomposition	57

Technique	Purpose	Key Information	Representative References
(DSC, TGA)	stability and polymorph study	temperatures	
Chiral Chromatography	Enantiomeric purity determination	Separation of stereoisomers	58
^{1}H NMR Spectroscopy	Proton environment analysis	- Dihydropyridine ring protons: δ 4.5–6.5 ppm (multiplets/singlets) - Aromatic protons: δ 6.5–8.0 ppm - Alkyl side chains: δ 1.0–3.0 ppm (triplets, quartets)	59
^{13}C NMR Spectroscopy	Carbon environment and substitution pattern	Ester carbonyl carbons (C=O): δ ~160–180 ppm- Aromatic carbons: δ 110–150 ppm- DHP ring carbons: δ 50–70 ppm	60
2D NMR (COSY, HSQC, HMBC)	Correlation between nuclei	- COSY: Correlates protons coupled through bonds, clarifying proton connectivity- HSQC/HMBC: Correlates ^1H with directly bonded (^1J) or long-range (^2J, ^3J) carbons	61
IR Spectroscopy	Functional group identification	- Ester C=O stretch: 1700–1750 cm^{-1}- N–H stretch (if present): 3300–3500 cm^{-1}- Aromatic C=C stretch: 1600–1650 cm^{-1}- C–H stretches: 2800–3100 cm^{-1}	62

3. Summary and conclusions

1,4-Dihydropyridine (1,4-DHP) derivatives represent a significant and widely studied class of nitrogen-containing heterocyclic compounds that have attracted considerable attention due to their diverse biological activities and therapeutic potential. These compounds have traditionally been recognized for their role as calcium channel blockers, extensively used in the management of cardiovascular disorders such as hypertension and angina. However, over the years, the scope of 1,4-DHPs has greatly expanded beyond cardiovascular applications. They now exhibit a broad spectrum of pharmacological effects, including anticancer, antimicrobial, anti-inflammatory, antioxidant, and neuroprotective activities. The synthetic versatility of the 1,4-DHP scaffold allows chemists to introduce various substituents at different positions of the ring, which can significantly alter their biological behavior and improve selectivity toward specific molecular targets. Various synthetic methodologies, including the

classical Hantzsch reaction, microwave-assisted synthesis, and solvent-free protocols, offer efficient, rapid, and eco-friendly routes for producing these compounds with high purity and yields. These green chemistry approaches are particularly valuable in reducing hazardous waste and energy consumption. The rich structural diversity and ease of modification make 1,4-DHP derivatives excellent candidates for drug discovery and development programs aimed at multiple disease targets. The multifaceted approach combining synthetic chemistry, molecular docking, and biological assays has proven to be a powerful strategy for exploring the therapeutic potential of 1,4-DHP derivatives. Molecular docking studies have provided valuable insights into the binding affinities and interaction modes of these compounds with various disease-related proteins, such as epidermal growth factor receptor (EGFR) in cancer, acetylcholinesterase in neurodegenerative diseases, and bacterial enzymes in infectious conditions. These in silico findings correlate well with in vitro biological evaluations, which have shown promising anticancer cytotoxicity, antimicrobial efficacy, and neuroprotective effects for several novel 1,4-DHP derivatives. The ability to establish structure–activity relationships (SAR) through this integrated approach allows for the rational design of more potent and selective derivatives by optimizing substituent positions and electronic properties. Furthermore, the incorporation of green synthetic methods ensures that the production of these compounds is sustainable and environmentally friendly. Collectively, these findings confirm that 1,4-DHP derivatives hold great promise as lead molecules for the development of new drugs to treat cancer, infectious diseases, neurodegenerative disorders, and other chronic conditions, addressing significant unmet medical needs. Looking forward, the future research on 1,4-DHP derivatives should focus on several important aspects to fully harness their therapeutic potential. First, designing multifunctional derivatives capable of targeting multiple disease pathways simultaneously could enhance treatment efficacy, especially in complex diseases like cancer and neurodegeneration, where oxidative stress, inflammation, and microbial infections often coexist. Second, efforts should be made to improve the pharmacokinetic properties of these molecules, including solubility, metabolic stability, and bioavailability, through medicinal chemistry optimization and novel drug delivery systems such as nanoparticles, liposomes, or hydrogels. Third, advanced green and sustainable synthetic techniques—such as enzymatic catalysis, microwave-assisted continuous flow synthesis, and solvent-free or aqueous medium reactions—should be further developed and applied to enable large-scale, eco-friendly production. Fourth, comprehensive in vivo studies and toxicity evaluations are critical to validate the safety and efficacy profiles of the most promising candidates and to facilitate their translation into clinical trials. Fifth, expanding molecular docking and computational modeling approaches by incorporating artificial intelligence and machine learning could accelerate the discovery of new 1,4-DHP derivatives with optimized activity and reduced side effects. Finally, exploring novel biological targets and mechanisms of action beyond the traditional calcium channel blockade will open new therapeutic avenues, further broadening the medical relevance of this versatile class of compounds.

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