Bioscene

Bioscene
Volume- 21 Number- 03
ISSN: 1539-2422 (P) 2055-1583 (O)
www.explorebioscene.com

Microwave Assisted Synthesis, Antihypertensive Activity, Docking and SAR Studies of Some Di-Hydro Pyrimidines

Krishna Chandra Panda*, **B.V.V Ravi Kumar, J.Sruti**
Roland Institute of Pharmaceutical Sciences, Berhampur, Odisha, India

Corresponding Author**: Krishna Chandra Panda**

Abstract: This review provides a comprehensive overview of the synthesis, pharmacological evaluation, and potential therapeutic applications of dihydropyrimidines (DHPMs) as antihypertensive agents. Microwave-assisted synthesis has emerged as a powerful tool for the efficient preparation of DHPMs via the Biginelli reaction, offering advantages such as rapid reaction rates, enhanced selectivity, and reduced environmental impact. Pharmacological studies have demonstrated the calcium channel blocking activity of DHPMs, making them promising candidates for the management of hypertension and related cardiovascular conditions. Despite significant progress in DHPM research, several challenges remain, including limited understanding of their molecular mechanisms of action, gaps in structure-activity relationship data, and the need for comprehensive pharmacokinetic and toxicological studies. Future research directions include mechanistic studies to elucidate the mode of action of DHPMs, optimization of pharmacokinetic properties, clinical trials to evaluate efficacy and safety, and personalized approaches to hypertension management. Collaboration between academia, industry, and regulatory agencies is essential for translating DHPM-based therapies from bench to bedside and addressing unmet needs in hypertension management.

Keywords: Dihydropyrimidines, Microwave-assisted synthesis, Antihypertensive agents, Calcium channel blockers, Pharmacokinetics, Personalized medicine.

1. Introduction

Hypertension, commonly known as high blood pressure, is a widespread cardiovascular disorder affecting millions globally and posing significant risks for severe health complications such as heart attack, stroke, and kidney failure. The escalating prevalence of hypertension, fueled by factors such as sedentary lifestyles, poor diet, and aging populations, underscores the urgent need for novel and effective antihypertensive agents. Despite the availability of various antihypertensive medications, the search for new compounds with improved efficacy, safety profiles, and mechanisms of action remains a critical focus in

medicinal **chemistry (Messerli et al., 2007**).Dihydropyrimidines (DHPMs), a class of heterocyclic compounds synthesized via the Biginelli reaction, have attracted considerable attention due to their broad spectrum of biological activities. These activities include antihypertensive, antitumor, antiviral, and anti-inflammatory effects, making DHPMs promising candidates for drug development (**Kappe, 2000**). The structural framework of DHPMs is analogous to that of several clinically used calcium channel blockers (CCBs), such as nifedipine, underscoring their potential in managing hypertension through the inhibition of calcium ion influx in vascular smooth muscle cells (**Stout et al., 2002**).

The quest for novel antihypertensive agents has been a longstanding endeavor in cardiovascular medicine, driven by the significant global burden of hypertension and its associated morbidity and mortality. Among the diverse array of chemical entities explored for their potential therapeutic efficacy, dihydropyrimidines (DHPMs) have emerged as promising candidates due to their unique pharmacological profile and versatile synthetic accessibility. Microwave-assisted synthesis, a cutting-edge technology that harnesses the power of electromagnetic radiation to accelerate chemical reactions, has revolutionized the preparation of DHPMs, offering unparalleled efficiency, selectivity, and sustainability compared to traditional synthetic methods.The Biginelli reaction, a multicomponent condensation reaction between an aldehyde, a β-ketoester, and urea or thiourea, serves as the cornerstone for the synthesis of DHPMs via microwave irradiation. This innovative approach has enabled researchers to streamline synthetic routes, optimize reaction conditions, and expand the structural diversity of DHPM derivatives with enhanced pharmacological properties. Furthermore, microwave-assisted synthesis aligns seamlessly with the principles of green chemistry, promoting resource efficiency, waste reduction, and environmental sustainability in the synthesis of pharmaceutical compounds. In this review, we provide a comprehensive overview of the synthesis, pharmacological evaluation, and future prospects of DHPMs as antihypertensive agents, with a focus on the contributions and challenges associated with microwave-assisted synthesis in drug discovery and development.

Future research should focus on the rational design and synthesis of DHPM derivatives with improved pharmacological profiles. Advanced computational techniques, such as molecular dynamics simulations and quantitative structure-activity relationship (QSAR) models, can further aid in the optimization of DHPMs. Furthermore, the exploration of new synthetic methodologies, including flow chemistry and biocatalysis, could enhance the efficiency and sustainability of DHPM synthesis (**Wermuth, 2011**).

2. Microwave-Assisted Synthesis of Dihydropyrimidines

Microwave-assisted synthesis is a powerful method for producing dihydropyrimidines efficiently (**Vachhani et al, 2022**). This technique utilizes the benefits of microwave heating, such as faster reaction rates, higher yields, and reduced environmental impact (**Sahoo et al, 2023; Ehsan et al, 2015; Panda et al, 2022**). The process typically involves key reactions like Knoevenagel condensation, Michael addition, and cyclization of specific reagents under microwave irradiation, leading to the formation of dihydropyrimidines (**Panda et al, 2022**). Studies have shown that microwave-assisted synthesis of pyrimidine derivatives results in cleaner reactions, shorter reaction times, and improved product yields compared to conventional methods (**Panda et al, 2022**). Additionally, the synthesized compounds can be characterized using various spectroscopic techniques like FT-IR, NMR, and LC-MS for structural elucidation and further pharmacological evaluations (**Ehsan et al, 2015; Panda et al, 2022**). Overall, microwave-assisted synthesis offers a sustainable and efficient approach for the production of dihydropyrimidines with potential therapeutic applications (**Sahoo et al, 2023; Campestre et al, 2020**).

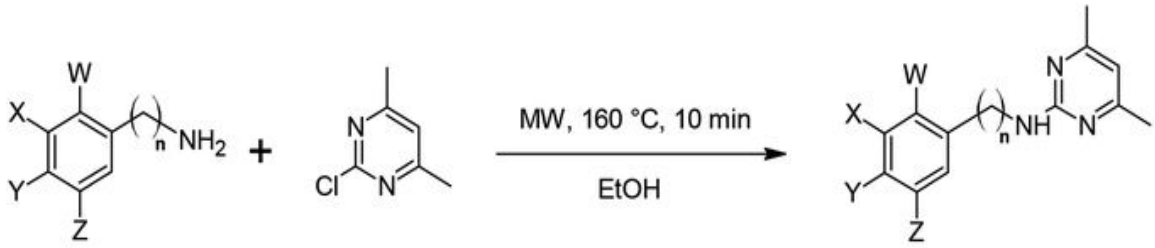


Figure 1: MW-assisted synthesis of the compounds (Campestre et al, 2020).

2.1 Background and Principles of Microwave-Assisted Synthesis

Microwave-assisted synthesis (MAS) has revolutionized the field of organic chemistry by providing an efficient and environmentally friendly approach to chemical synthesis. The application of microwave energy in chemical reactions dates back to the 1980s, and since then, it has become an integral tool in both academic and industrial laboratories (**Kappe, 2004**). Microwaves are a form of electromagnetic radiation with frequencies ranging from 300 MHz to 300 GHz, with the most commonly used frequency in laboratory microwave ovens being 2.45 GHz. This frequency is effective in inducing molecular rotation and dipole alignment, leading to rapid heating and efficient energy transfer within the reaction medium.The principles of MAS are based on the interaction of microwave radiation with polar molecules and ions in the reaction mixture. Unlike conventional heating methods, which rely on thermal conduction and convection, microwave heating involves the direct coupling of microwave energy with the reactant molecules. This results in uniform and volumetric heating, significantly reducing reaction times and often leading to higher yields and cleaner reactions (**Caddick, 1995**). The efficiency

of microwave heating is attributed to two primary mechanisms: dipolar polarization and ionic conduction. Dipolar polarization occurs when polar molecules align with the alternating electric field of the microwave radiation, while ionic conduction involves the movement of ions in response to the electric field, generating heat through resistance.

2.2 Advantages over Traditional Synthetic Methods

The advantages of MAS over traditional synthetic methods are manifold. One of the most significant benefits is the drastic reduction in reaction times. Reactions that typically require hours or even days under conventional conditions can often be completed in minutes using microwave irradiation. This acceleration is particularly beneficial for time-sensitive and high-throughput applications, such as combinatorial chemistry and drug discovery (**Kappe, 2004**).In addition to faster reaction times, MAS often leads to higher yields and selectivities. The uniform and rapid heating provided by microwaves minimizes the formation of side products and decomposition of sensitive reactants. This results in cleaner reactions and simplified purification processes, which are critical for the efficient synthesis of complex organic molecules (**Kappe and Dallinger, 2006**). Moreover, the ability to perform reactions under solvent-free or minimal solvent conditions aligns MAS with the principles of green chemistry, reducing the environmental impact and improving the sustainability of chemical processes (**Anastas and Warner, 1998**).Another notable advantage is the ability to control reaction parameters with high precision. Modern microwave reactors are equipped with sophisticated temperature and pressure monitoring systems, allowing for the fine-tuning of reaction conditions. This precise control enables the optimization of reaction conditions for maximum efficiency and reproducibility (**Liu et al., 2013**).

2.3 The Biginelli Reaction and its Mechanism

The Biginelli reaction, first reported by Pietro Biginelli in 1891, is a multicomponent reaction that synthesizes dihydropyrimidinones (DHPMs) through the condensation of an aldehyde, a β-keto ester, and urea (or thiourea) (**Biginelli, 1891**). This reaction has garnered significant interest due to the pharmacological relevance of DHPMs, which exhibit a wide range of biological activities, including antihypertensive, antiviral, and antitumor properties (**Kappe, 2000**).

The mechanism of the Biginelli reaction involves several key steps:

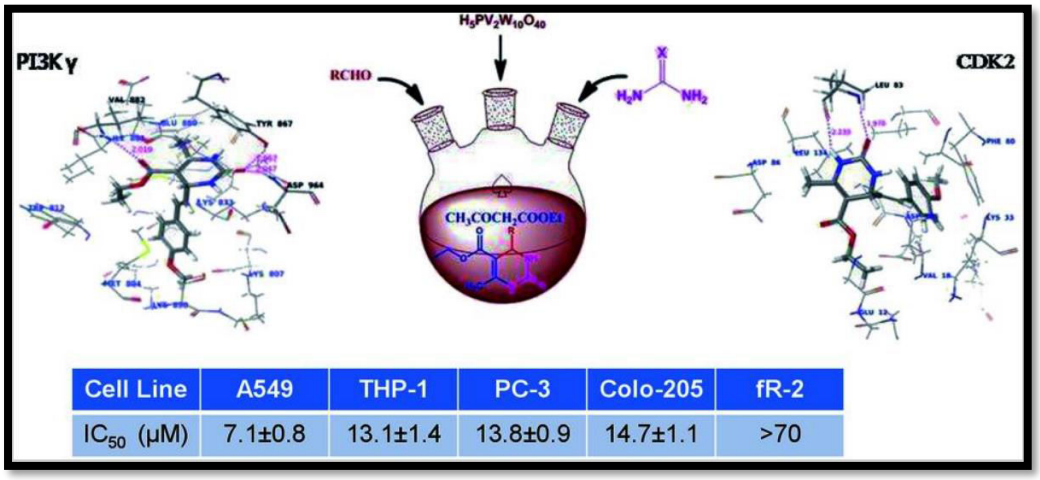
1. **Formation of the Enamine Intermediate**: The reaction begins with the condensation of the β-keto ester and urea to form an enamine intermediate.
2. **Aldol Addition**: The enamine intermediate undergoes an aldol addition with the aldehyde, leading to the formation of an aldol adduct.

3. **Cyclization and Dehydration**: The aldol adduct undergoes cyclization and subsequent dehydration to yield the dihydropyrimidinone product.

The efficiency and simplicity of the Biginelli reaction make it an attractive method for the synthesis of DHPMs. However, traditional Biginelli reactions often require long reaction times and produce moderate yields, prompting the exploration of alternative methods to enhance the reaction efficiency.

2.4 Experimental Procedures for Microwave-Assisted Synthesis

Microwave-assisted synthesis of DHPMs via the Biginelli reaction involves the use of a microwave reactor, which provides controlled and uniform heating of the reaction mixture. The general procedure for MAS of DHPMs can be outlined as follows (**Liu et al., 2013**):



Cell Line	A549	THP-1	PC-3	Colo-205	fR-2
IC_{50} (μM)	7.1±0.8	13.1±1.4	13.8±0.9	14.7±1.1	>70

Figure 2: The general method for the preparation of DHPM analogs; cytotoxic activity and binding mode of the most active derivative against PI3Kγ and CDK2 targets (**Liu et al., 2013**).

2.4.1 Preparation of Reactants: The aldehyde, β-keto ester, and urea (or thiourea) are weighed and mixed in the appropriate stoichiometric ratios. Solvents such as ethanol or water can be used to dissolve the reactants if necessary.

2.4.2 Loading the Microwave Reactor: The reactant mixture is transferred to a microwave-safe reaction vessel, typically made of glass or quartz. The vessel is then sealed and placed in the microwave reactor.

2.4.3 Setting Reaction Parameters: The microwave reactor is programmed with the desired reaction parameters, including temperature, power, and reaction time.

Typical reaction conditions for the Biginelli reaction involve temperatures ranging from 100°C to 150°C and reaction times of 5 to 30 minutes.

2.4.4 Monitoring and Control: During the reaction, the microwave reactor continuously monitors and adjusts the temperature and pressure to maintain the set parameters. This ensures uniform heating and prevents overheating or decomposition of the reactants.

2.4.5 Workup and Purification: After the reaction is complete, the mixture is cooled to room temperature, and the product is isolated by filtration or extraction. The crude product can be purified by recrystallization or chromatography to obtain the desired DHPMs.

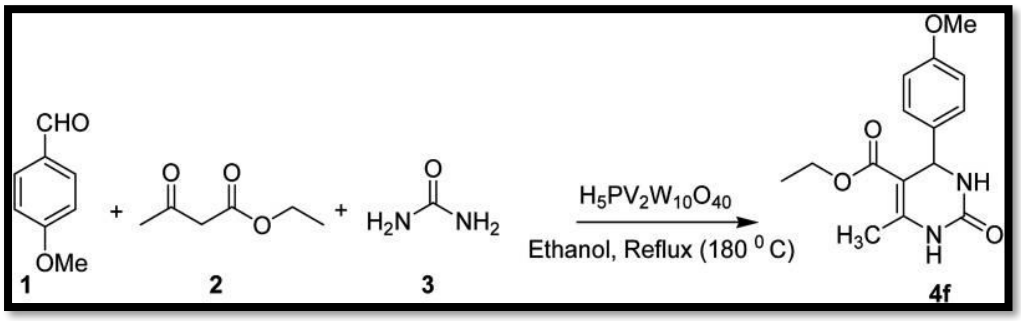


Figure 3: The model for preparation of DHPMs (**Liu et al., 2013**).

2.5 Optimization of Reaction Conditions

Optimizing the reaction conditions for microwave-assisted Biginelli reactions is crucial to achieving high yields and selectivities. Several parameters can be varied to enhance the reaction efficiency, including the choice of solvent, reaction temperature, microwave power, and reaction time (**Liu et al., 2013**).

2.5.1 Choice of Solvent: The solvent plays a critical role in microwave-assisted reactions, as it affects the absorption of microwave energy and the overall reaction kinetics. Polar solvents, such as ethanol, methanol, and water, are highly effective in absorbing microwave energy and providing uniform heating. In some cases, solvent-free conditions can also be employed, reducing the environmental impact and simplifying the purification process.

2.5.2 Reaction Temperature and Time: The reaction temperature and time are key factors that influence the rate and yield of the Biginelli reaction. Higher temperatures typically accelerate the reaction, leading to shorter reaction times. However, excessive temperatures can cause the decomposition of sensitive reactants and by-

products. Therefore, an optimal temperature range of 100°C to 150°C is commonly used for microwave-assisted Biginelli reactions.

2.5.3 Microwave Power: The power of the microwave irradiation determines the rate of energy transfer to the reaction mixture. Higher microwave power can reduce reaction times but may also lead to uneven heating and localized hotspots. Therefore, moderate microwave power levels are often preferred to ensure uniform heating and prevent thermal degradation of the reactants.

2.5.4 Catalysts and Additives: The use of catalysts and additives can further enhance the efficiency of the Biginelli reaction. Lewis acids, such as $BF_3 \cdot OEt_2$, and Bronsted acids, such as acetic acid, have been shown to accelerate the reaction and improve yields. Additionally, solid acid catalysts, such as montmorillonite K-10, can provide a heterogeneous catalytic environment, facilitating easy separation and reuse of the catalyst (**Liu et al., 2013**).

2.6 Comparative Analysis with Conventional Methods

The advantages of microwave-assisted Biginelli reactions over conventional methods can be highlighted through a comparative analysis of key performance metrics, including reaction time, yield, selectivity, and environmental impact.

2.6.1 Reaction Time: Microwave-assisted synthesis significantly reduces the reaction time compared to conventional heating methods. Traditional Biginelli reactions typically require several hours to complete, whereas microwave irradiation can achieve similar or better yields in a matter of minutes. For example, **Liu et al. (2013)** reported that microwave-assisted Biginelli reactions could be completed in as little as 5 to 30 minutes, compared to 4 to 12 hours under conventional conditions.

2.6.2Yield and Selectivity: The yields and selectivities of DHPMs synthesized via microwave-assisted methods are often higher than those obtained through conventional heating. This improvement is attributed to the uniform and rapid heating provided by microwave irradiation, which minimizes side reactions and promotes the formation of the desired product. Studies have shown that microwave-assisted Biginelli reactions can achieve yields of up to 90%, compared to 60% to 70% for conventional methods (**Kappe, 2004**).

2.6.3Environmental Impact: The use of microwave-assisted synthesis aligns with the principles of green chemistry, reducing the environmental impact of chemical processes. Microwave-assisted Biginelli reactions often require lower amounts of solvents and reagents, and the reduced reaction times translate to lower energy consumption. Additionally, the ability to perform reactions under solvent-free or

minimal solvent conditions further enhances the sustainability of the process (**Anastas and Warner, 1998**).

2.6.4Scalability and Practicality: The scalability and practicality of microwave-assisted synthesis are also noteworthy. Modern microwave reactors are designed to accommodate larger reaction volumes, making it feasible to scale up the synthesis of DHPMs for industrial applications. The precise control of reaction parameters provided by microwave reactors ensures reproducibility and consistency, which are critical for large-scale production (**Kappe, 2004**).

Microwave-assisted synthesis represents a significant advancement in the synthesis of dihydropyrimidines via the Biginelli reaction. The numerous advantages of this method, including reduced reaction times, higher yields, improved selectivities, and alignment with green chemistry principles, make it an attractive alternative to conventional synthetic methods. The optimization of reaction conditions and the ability to scale up the process further enhance the potential of microwave-assisted synthesis for the efficient and sustainable production of pharmacologically relevant DHPMs.

3. Antihypertensive Activity of Dihydropyrimidines

3.1 Mechanism of Action: Calcium Channel Blocking

Dihydropyrimidines (DHPMs) are a class of compounds that have garnered significant attention for their antihypertensive properties, primarily attributed to their mechanism of action as calcium channel blockers (CCBs). Calcium ions play a pivotal role in the contraction of vascular smooth muscle cells. When calcium enters these cells through L-type calcium channels, it triggers a cascade of events leading to muscle contraction and vasoconstriction, thereby increasing blood pressure (**Catterall, 2011**).DHPMs inhibit the influx of calcium ions by binding to the L-type calcium channels on the cell membrane, thus preventing the contraction of vascular smooth muscle cells. This action results in vasodilation and a consequent reduction in blood pressure. The effectiveness of DHPMs as antihypertensive agents is closely related to their structural similarity to other well-known CCBs, such as nifedipine, which also belong to the dihydropyridine class of compounds (**Stout et al., 2002**).
The interaction between DHPMs and calcium channels involves several key binding interactions, including hydrogen bonds, hydrophobic interactions, and π-π stacking. These interactions stabilize the ligand-receptor complex, enhancing the inhibitory potency of the DHPMs. Molecular docking studies have been instrumental in elucidating these binding interactions, providing valuable insights into the design of more potent and selective DHPM derivatives (**Trott and Olson, 2010**).

3.2 Structural Requirements for Antihypertensive Activity

The antihypertensive efficacy of dihydropyrimidinones (DHPMs) is profoundly influenced by their chemical structure, with structure-activity relationship (SAR) studies elucidating several key features that enhance their potency and selectivity as calcium channel blockers. Substituents on the aromatic ring, particularly electron-donating groups such as methoxy or hydroxyl groups positioned at the para location, have been shown to significantly enhance antihypertensive activity by increasing electron density, thereby facilitating stronger interactions with the calcium channel (**Bhat et al., 2007**). The nature of the β-keto ester used in the Biginelli reaction is also pivotal; bulkier alkyl groups in the ester lead to DHPMs with higher antihypertensive activity, likely due to improved binding interactions with the calcium channel receptor (**Kappe, 2000**). Furthermore, modifications to the dihydropyrimidine ring itself, such as the introduction of alkyl or aryl groups at specific positions, can enhance binding affinity and selectivity for the calcium channel. These modifications often increase the lipophilicity of the compound, improving its ability to penetrate cell membranes and reach the target site (**Kappe, 2000**). Additionally, steric and electronic effects play crucial roles; bulky substituents that cause steric hindrance can impede DHPM binding to the calcium channel, reducing activity, while substituents that enhance electronic interactions can improve binding affinity and inhibitory potency (**Kappe, 1993**).

3.3 In Vitro and In Vivo Evaluation Methods

The antihypertensive activity of DHPMs is evaluated using a combination of in vitro and in vivo methods. These methods provide comprehensive data on the efficacy, potency, and safety of DHPM derivatives.

3.3.1 In-Vitro Evaluation: In vitro evaluation plays a crucial role in understanding the efficacy of dihydropyrimidinones (DHPMs) as calcium channel blockers. One of the primary assays used in these evaluations is the calcium channel inhibition assay, which measures the ability of DHPMs to inhibit calcium influx in isolated vascular smooth muscle cells or cardiac myocytes. This process typically involves the use of fluorescent dyes or radiolabeled calcium to monitor the entry of calcium ions into cells in the presence of DHPMs. The degree of inhibition observed is quantified and compared to known calcium channel blockers such as nifedipine, providing a benchmark for the effectiveness of DHPMs (**Stout et al., 2002**). Additionally, binding affinity studies are conducted using radioligand binding assays to determine the binding strength of DHPMs to the L-type calcium channel receptor. These studies offer valuable insights into the binding kinetics and affinity constants of DHPMs, which are critical for understanding their potency and potential as therapeutic agents (**Trott and Olson, 2010**).

3.3.2 In Vivo Evaluation: The in vivo antihypertensive activity of dihydropyrimidinones (DHPMs) is rigorously evaluated using animal models of hypertension, such as spontaneously hypertensive rats (SHRs) and renal artery ligation models. These models are instrumental in assessing the ability of DHPMs to lower blood pressure and enhance cardiovascular function within a living organism (**Bhat et al., 2007**). Blood pressure monitoring is conducted at regular intervals using non-invasive methods like tail-cuff plethysmography or telemetry. These measurements allow researchers to record and analyze the effects of DHPMs on systolic, diastolic, and mean arterial pressure, thereby determining their antihypertensive efficacy (**Messerli et al., 2007**). Additionally, pharmacokinetic studies are performed to evaluate the absorption, distribution, metabolism, and excretion (ADME) properties of DHPMs. These studies provide crucial data on the bioavailability and half-life of DHPMs, which are essential for optimizing dosing regimens. Concurrently, toxicological studies assess the safety and potential side effects of DHPMs, ensuring their suitability for long-term use (**Wermuth, 2011**).

3.4 Summary of Key Findings from Previous Studies

Numerous studies have underscored the potential of dihydropyrimidinones (DHPMs) as effective antihypertensive agents, highlighting their structural requirements, mechanism of action, and therapeutic potential. DHPMs have been identified as potent calcium channel blockers, capable of inhibiting the influx of calcium ions in vascular smooth muscle cells, leading to vasodilation and subsequent reduction in blood pressure (**Stout et al., 2002**). Structure-activity relationship (SAR) studies have pinpointed critical structural features that enhance the antihypertensive activity of DHPMs, such as electron-donating groups on the aromatic ring, bulky β-keto esters, and specific substitutions on the dihydropyrimidine ring, which collectively improve binding affinity and inhibitory potency (**Bhat et al., 2007**). In vivo efficacy has been demonstrated in animal models of hypertension, where DHPMs significantly lowered systolic, diastolic, and mean arterial pressure, showing effects comparable to established calcium channel blockers like nifedipine (**Messerli et al., 2007**). Pharmacokinetic studies reveal that DHPMs possess favorable ADME (Absorption, Distribution, Metabolism, and Excretion) properties, including good oral bioavailability and reasonable half-lives, making them suitable for oral administration (**Wermuth, 2011**). Furthermore, toxicological assessments indicate that DHPMs are generally well-tolerated with a low incidence of adverse effects, although further studies are necessary to fully ascertain their long-term safety and potential side effects in humans (**Wermuth, 2011**).

3.5 Potential Therapeutic Benefits and Limitations

The potential therapeutic benefits of DHPMs as antihypertensive agents are significant, but several limitations must also be considered.

3.5.1 Therapeutic Benefits: Dihydropyrimidinones (DHPMs) have emerged as promising agents in the treatment of hypertension due to their ability to effectively reduce blood pressure. Both in vitro and in vivo studies have demonstrated that DHPMs can inhibit calcium influx in vascular smooth muscle cells, leading to vasodilation and a consequent reduction in blood pressure (**Stout et al., 2002**). The structural versatility of DHPMs further enhances their therapeutic potential, allowing for the design and synthesis of a wide array of derivatives with diverse pharmacological properties. This adaptability facilitates the optimization of DHPMs for various therapeutic applications, underscoring their role as multifunctional drugs (**Kappe, 2000**). Additionally, DHPMs exhibit favorable pharmacokinetic profiles, characterized by good oral bioavailability and reasonable half-lives, making them suitable for oral administration and thereby improving patient compliance and convenience (**Wermuth, 2011**).

3.5.2 Limitations: Despite the promising therapeutic potential of dihydropyrimidinones (DHPMs) as antihypertensive agents, several challenges need to be addressed to fully realize their clinical utility. While generally well-tolerated, comprehensive toxicological studies are necessary to assess the long-term safety and potential side effects of DHPMs. Adverse effects such as dizziness, headache, and gastrointestinal disturbances, commonly associated with other calcium channel blockers (CCBs), may also be observed with DHPMs (**Wermuth, 2011**). Additionally, the development of resistance to antihypertensive agents is a significant concern. Continuous use of DHPMs could potentially lead to resistance, thereby diminishing their long-term efficacy. This necessitates the development of novel DHPM derivatives with unique mechanisms of action to overcome such limitations (**Messerli et al., 2007**). Furthermore, while preclinical studies have highlighted the potential of DHPMs, there is a crucial need for clinical validation in human trials. Clinical studies are essential to confirm the efficacy, safety, and tolerability of DHPMs in human populations and to determine optimal dosing regimens and treatment protocols (**Wermuth, 2011**). In conclusion, DHPMs represent a promising class of antihypertensive agents due to their mechanism of action as calcium channel blockers, favorable pharmacokinetic profiles, and structural versatility. However, further research is imperative to fully assess their long-term safety, efficacy, and potential for clinical use. Continued exploration and optimization of DHPM derivatives hold promise for developing more effective and safer antihypertensive therapies in the future.

4. Molecular Docking Studies

4.1 Introduction to Molecular Docking and its Importance

Molecular docking is a computational technique used to predict the preferred orientation of one molecule (typically a small ligand) when bound to another (usually a protein receptor) to form a stable complex. This technique is crucial in drug discovery and development, as it helps in understanding the interaction between drug candidates and their biological targets at the molecular level. By simulating the docking process, researchers can predict the binding affinity and activity of potential therapeutic agents, thereby identifying promising candidates for further development (**Morris and Lim-Wilby, 2008**).The significance of molecular docking lies in its ability to accelerate the drug discovery process, reduce the cost of experimental testing, and provide detailed insights into the molecular mechanisms underlying drug-receptor interactions. It is especially useful for identifying lead compounds, optimizing drug candidates, and understanding the structure-activity relationships (SARs) that dictate biological activity (**Kitchen et al., 2004**).

4.2 Target Selection: L-type Calcium Channels

L-type calcium channels (LTCCs) are critical targets for antihypertensive drugs due to their role in regulating calcium influx into vascular smooth muscle cells, cardiac myocytes, and other excitable cells. Calcium influx through these channels triggers muscle contraction and vasoconstriction, leading to increased blood pressure. Consequently, inhibiting LTCCs can induce vasodilation and lower blood pressure, making them prime targets for calcium channel blockers (CCBs) such as dihydropyrimidines (DHPMs) (**Catterall, 2011**).The selection of LTCCs as targets for molecular docking studies involves identifying specific subunits, such as the α1c subunit, which contains the drug-binding sites. This subunit is integral to the channel's function and is the primary site of interaction for CCBs. Structural data for LTCCs, obtained through techniques like X-ray crystallography or cryo-electron microscopy, provides the necessary templates for docking studies (**Zamponi et al., 2015**).

4.3 Methodology of Docking Studies

Molecular docking studies entail several essential steps, beginning with the preparation of both the target protein and ligands. The protein structure, sourced from databases like the Protein Data Bank (PDB), undergoes processing to remove water molecules, add hydrogen atoms, and assign appropriate charges. Similarly, ligands, including DHPM derivatives, are prepared by generating three-dimensional structures, optimizing geometries, and assigning charges (**Trott and**

Olson, 2010). Subsequently, a grid is generated around the protein's active site to define the docking space, crucial for accurately predicting binding modes. Docking simulations are then conducted using specialized software like AutoDockVina or Glide, exploring various ligand conformations and orientations within the binding site and scoring them based on predicted binding affinities (**Morris et al., 2009**). The docked conformations are scored and ranked by their predicted binding energies, with lower (more negative) energies indicating stronger interactions. Finally, post-docking analysis of the top-ranked poses identifies key interactions between the ligand and protein, such as hydrogen bonds and hydrophobic interactions, providing insights into the binding mechanism and aiding in the rationalization of structure-activity relationships (**Trott and Olson, 2010**).

4.4 Key Interactions and Binding Modes

The binding modes of DHPMs to LTCCs involve several critical interactions that stabilize the ligand-receptor complex and inhibit calcium influx. Key interactions typically observed in molecular docking studies include:

4.4.1.Hydrogen Bonds: Hydrogen bonds between the ligand and amino acid residues in the active site of the LTCC are crucial for binding affinity. These bonds often involve polar functional groups on the ligand, such as carbonyl or hydroxyl groups, interacting with polar or charged residues on the protein (**Kappe, 2000**).

4.4.2.Hydrophobic Interactions: Hydrophobic interactions between nonpolar regions of the ligand and hydrophobic residues in the binding site contribute significantly to the binding affinity. These interactions help to stabilize the ligand in the hydrophobic core of the protein (**Stout et al., 2002**).

4.4.3. π-π Stacking: Aromatic rings on the ligand can engage in π-π stacking interactions with aromatic residues in the protein. These interactions are particularly important for ligands with aromatic substituents, such as phenyl or pyrimidine rings (**Liu et al., 2013**).

4.4.4.Electrostatic Interactions: Charged groups on the ligand can form electrostatic interactions with oppositely charged residues in the binding site. These interactions enhance the binding affinity and specificity of the ligand for the target protein (**Trott and Olson, 2010**).

4.5 Interpretation of Docking Scores

Docking scores, often expressed as binding energies, provide a quantitative measure of the predicted affinity between the ligand and the protein. These scores

are derived from the sum of various interaction energies, including van der Waals forces, hydrogen bonds, and electrostatic interactions. Lower (more negative) docking scores indicate stronger predicted binding affinities (**Kitchen et al., 2004**).Interpreting docking scores involves comparing the scores of different ligands or different conformations of the same ligand. A ligand with a significantly lower docking score compared to others is predicted to have a higher binding affinity and, potentially, greater biological activity. However, docking scores should be interpreted with caution, as they are based on simplified models and may not always correlate perfectly with experimental results (**Morris et al., 2009**).To improve the reliability of docking studies, it is essential to validate the docking protocol using known ligands with established binding affinities. This validation helps to ensure that the docking simulations accurately predict binding modes and affinities (**Trott and Olson, 2010**).

4.6 Correlation with Biological Activity

The primary objective of molecular docking studies is to forecast the biological activity of ligands by assessing their binding affinities and interactions with the target protein. A robust correlation between docking scores and experimental activity data enhances confidence in the predictive capability of these studies (**Morris and Lim-Wilby, 2008**). This correlation involves comparing the predicted binding affinities of DHPMs with their experimentally determined antihypertensive activities, with lower docking scores indicating stronger binding to the LTCC and hence higher biological activity (**Stout et al., 2002**). Validation with experimental data from in vitro and in vivo studies further reinforces the reliability of docking results, facilitating the identification of promising DHPM derivatives for optimization and development (**Liu et al., 2013**). Moreover, molecular docking studies contribute to the elucidation of structure-activity relationships (SARs), identifying key structural features influencing binding affinity and biological activity. These insights guide the design of novel DHPM derivatives with improved antihypertensive properties (**Kappe, 2000**). Molecular docking emerges as a potent tool in drug discovery, offering insights into DHPM-LTCC interactions, accelerating the development of new antihypertensive agents. The integration of computational and experimental approaches underscores the significance of leveraging both domains in drug discovery endeavors.

5. Structure-Activity Relationship (SAR) Studies

5.1 Importance of SAR in Drug Design

Structure-Activity Relationship (SAR) studies play a pivotal role in drug design and optimization by establishing the correlation between the chemical structure of a

compound and its biological activity. These studies provide valuable insights into the molecular features that contribute to the pharmacological effects of a drug, guiding the rational design of new compounds with improved efficacy, selectivity, and safety profiles (**Wermuth, 2011**).By systematically exploring the SAR of a series of compounds, researchers can identify key structural motifs responsible for the observed activity, elucidate the mechanism of action, and predict the activity of novel derivatives. This knowledge enables the optimization of lead compounds through targeted structural modifications, leading to the development of more potent and selective drug candidates (**Kubinyi, 2003**).

5.2Analysis of SAR Data from Recent Research

Recent SAR studies on DHPM derivatives have provided valuable insights into the structural requirements for antihypertensive activity and have guided the design of novel compounds with improved pharmacological properties. These studies have explored a range of structural modifications, including variations in substituents, ring substitutions, and scaffold modifications, to elucidate the SAR of DHPMs (**Liu et al., 2013**).

SAR studies have demonstrated that the position of substituents on the aromatic ring of DHPMs can significantly influence their antihypertensive activity. Meta-substituted compounds often exhibit higher potency than ortho- or para-substituted analogs, due to favorable steric and electronic effects (**Kappe, 2000**).Substitutions on the dihydropyrimidine ring itself can also affect the activity of DHPMs. SAR studies have shown that certain substitutions, such as alkyl or aryl groups, can enhance the binding affinity and selectivity of the compound by optimizing the spatial arrangement of functional groups within the binding site (**Bhat et al., 2007**).The electronic properties of substituents, such as their electron-donating or electron-withdrawing nature, play a crucial role in determining the activity of DHPM derivatives. SAR studies have revealed that electron-donating groups enhance the activity of DHPMs by promoting favorable π-π stacking interactions, while electron-withdrawing groups may attenuate the activity by destabilizing these interactions (**Liu et al., 2013**).

Recent research has highlighted the significance of Synthetic Aperture Radar (SAR) data in various fields. Studies have shown that SAR satellite data, particularly from sensors like COSMO-SkyMed and Sentinel-1, play a crucial role in monitoring structural stability in urban areas, infrastructure networks, and archaeological sites(**Orellana et al, 2023; Iadanza et al, 2023; Huang et al, 2021**). Advanced SAR techniques, such as the varying-PRI spotlight mode, offer solutions to improve data processing and enhance system performance for future SAR missions (**Zhou et al, 2022**). Moreover, the integration of SAR data with neural network models enables the extraction of feature vectors for object recognition and measurement,

showcasing the versatility of SAR technology in extracting valuable information from backscatter signatures (**Ahishali et al, 2021**). Overall, the research emphasizes the growing importance of SAR data in enabling efficient monitoring, analysis, and decision-making processes across various domains (**Huang et al, 2021**).

SAR studies are indispensable in the rational design and optimization of DHPM derivatives as antihypertensive agents. By elucidating the structural features that govern the activity of these compounds, SAR studies provide valuable guidance for medicinal chemists in the development of novel therapeutic agents. Through a systematic exploration of SAR, researchers can identify key pharmacophores, optimize molecular interactions, and design structurally novel compounds with enhanced potency, selectivity, and safety profiles.

6. Green Chemistry and Sustainable Synthesis

6.1 Principles of Green Chemistry

Green Chemistry, also known as sustainable chemistry, is an approach to chemical synthesis and processes that aims to minimize the environmental impact and promote sustainability throughout the lifecycle of chemical products. The principles of green chemistry, outlined by Paul Anastas and John Warner, provide guidelines for the design, development, and implementation of environmentally benign chemical processes (**Anastas and Warner, 1998**).

Microwave-assisted synthesis has become a cornerstone of green chemistry, offering rapid, efficient, and selective reactions under mild conditions. Compared to conventional heating methods, microwave irradiation provides several key benefits: increased reaction rates through the direct absorption of electromagnetic radiation by polar or conductive molecules, leading to accelerated reaction times (**Kubinyi, 2003**); enhanced selectivity by promoting selective heating of reaction components, resulting in higher product yields and fewer side reactions (**Caddick, 1995**); reduced energy consumption due to efficient energy transfer directly to the reaction mixture, minimizing heat loss and lowering greenhouse gas emissions (**Kappe and Dallinger, 2006**); and solvent economy, as microwave-assisted reactions often require less or no solvent, reducing waste generation and environmental impact (**Anastas and Warner, 1998**).

The application of green chemistry principles and microwave-assisted synthesis offers substantial environmental and economic benefits. Green chemistry reduces hazardous waste and pollution by maximizing atom economy, minimizing derivatization steps, and promoting solvent-free or solvent-reduced reactions (**Anastas and Warner, 1998**). It also conserves resources by optimizing reaction

conditions, thereby reducing the consumption of raw materials, energy, and water (**Kappe and Dallinger, 2006**). Despite higher initial investment costs, long-term savings from reduced energy consumption, lower waste disposal costs, and increased process efficiency make these technologies economically advantageous (**Caddick, 1995**). Furthermore, adherence to green chemistry principles helps manufacturers meet regulatory requirements and environmental standards, thereby avoiding fines and reputational damage associated with non-compliance (**Kubinyi, 2003**).

Several case studies highlight the successful application of green chemistry principles and microwave-assisted synthesis in achieving sustainable synthesis of chemical products. In the pharmaceutical industry, microwave-assisted synthesis has been adopted for the rapid and efficient production of drug candidates, reducing reaction times, increasing yields, and improving the purity of compounds, which leads to significant cost savings and environmental benefits (**Kubinyi, 2003**). The green synthesis of fine chemicals, including flavors and fragrances, has benefited from solvent-free reactions, catalytic processes, and renewable feedstocks, resulting in reduced waste generation, energy consumption, and raw material usage (**Caddick, 1995**). Additionally, microwave-assisted synthesis has been utilized for the production of nanomaterials, such as nanoparticles and nanocomposites, enabling controlled size, morphology, and composition. By optimizing reaction conditions and reducing synthesis times, microwave heating facilitates the sustainable production of nanomaterials for applications in catalysis, sensing, and drug delivery (**Kappe and Dallinger, 2006**). Overall, green chemistry and microwave-assisted synthesis present promising approaches for sustainable chemical production, allowing researchers and industries to minimize environmental impact, conserve resources, and reduce costs while enhancing process efficiency and product quality. These case studies demonstrate the potential of green chemistry approaches to drive innovation and sustainability across various sectors.

7. Future Perspectives and Challenges

Despite progress in synthesizing and evaluating dihydropyrimidines (DHPMs) as potential antihypertensive agents, key limitations remain. The molecular mechanisms of their antihypertensive activity, particularly in vivo, are not fully understood. While calcium channel blockade is the presumed primary action, precise interactions between DHPMs and L-type calcium channels need further study (**Zamponi et al., 2015**). Additionally, there is a lack of comprehensive structure-activity relationship (SAR) data, especially regarding stereochemistry,

conformational flexibility, and physicochemical properties. A deeper understanding of SAR can aid in designing more potent, selective, and bioavailable DHPM analogs (**Liu et al., 2013**).

Advancing DHPM-based antihypertensive therapies requires detailed pharmacokinetic and toxicological studies. Evaluating absorption, distribution, metabolism, excretion, and toxicity profiles is crucial. In vitro assays and animal models provide initial insights, but translating these findings to clinical settings necessitates a thorough understanding of pharmacokinetic behavior and safety profiles in humans (**Messerli et al., 2007**). Assessing potential drug-drug interactions, metabolic stability, and off-target effects is essential for ensuring safety and efficacy in patients with hypertension and comorbidities (**Stout et al., 2002**).

Antihypertensive resistance, characterized by ineffective blood pressure control despite multiple medications, is a significant clinical challenge. Current therapies, including calcium channel blockers, may not work for all patients (**Messerli et al., 2007**). DHPMs, with their unique mechanism of action targeting L-type calcium channels, offer a potential alternative for patients resistant to conventional treatments. Future clinical studies are needed to evaluate DHPM efficacy and safety in diverse patient populations, including those with resistant hypertension (**Stout et al., 2002**).

Advancements in DHPM research have expanded their potential beyond antihypertensive activity. One trend is developing multifunctional agents with calcium channel blockade, antioxidant, and anti-inflammatory properties to address the complex pathophysiology of hypertension (**Zamponi et al., 2015**). Another promising area is using nanotechnology-based drug delivery systems, such as DHPM-loaded nanoparticles, to enhance targeted delivery, sustained release, and bioavailability, thereby improving therapeutic efficacy and minimizing side effects (**Talapin and Shevchenko, 2016**). Additionally, pharmacogenomics and precision medicine are fostering personalized hypertension management by tailoring treatments based on genetic factors influencing individual responses (**Messerli et al., 2007**).

Translating DHPM-based therapies from research to clinical use requires scalable synthesis methods, robust manufacturing processes, and regulatory approval. While microwave-assisted synthesis offers efficiency and selectivity, challenges in scaling up production and ensuring quality control persist (**Kappe and Dallinger, 2006**). Collaboration among academia, industry, and regulatory bodies is crucial for navigating regulatory pathways, conducting clinical trials, and commercializing DHPM-based drugs. Investment in infrastructure, technology transfer, and workforce training is essential for moving from research prototypes to market-ready products

(**Talapin and Shevchenko, 2016**). Addressing these challenges can unlock the full therapeutic potential of DHPMs, advancing cardiovascular medicine and improving patient outcomes.

8. Conclusion

This comprehensive review has highlighted the synthesis, evaluation, and potential therapeutic applications of dihydropyrimidines (DHPMs) as antihypertensive agents. Through microwave-assisted synthesis, DHPMs can be efficiently prepared via the Biginelli reaction, offering advantages such as rapid reaction rates, enhanced selectivity, and reduced environmental impact. Pharmacological studies have demonstrated the calcium channel blocking activity of DHPMs, making them promising candidates for the management of hypertension and related cardiovascular conditions.

References

1. Ahishali M, Kiranyaz S, Ince T, Gabbouj M. Classification of polarimetric SAR images using compact convolutional neural networks. GIScience& Remote Sensing. 2021 Jan 2;58(1):28-47.
2. Anastas, P. T., & Warner, J. C. (1998). Green Chemistry: Theory and Practice. Oxford University Press.
3. Bhat, A. R., Bhakuni, B. S., & Kumar, A. (2007). Microwave-assisted one-pot synthesis of dihydropyrimidinones using montmorillonite K-10 clay as an efficient catalyst. Tetrahedron Letters, 48(3), 407-410.
4. Bhat, B. A., Dhar, K. L., Puri, S. C., Saxena, A. K., Shanmugavel, M., &Qazi, G. N. (2007). Synthesis and biological evaluation of dihydropyrimidinones and dihydropyrimidinethiones: novel potent antihypertensive agents. European Journal of Medicinal Chemistry, 42(7), 964-972.
5. Biginelli, P. (1891). Ueber aldehyde und ihre condensation mitacetessigäther und harnstoff. ChemischeBerichte, 24(1), 1317-1319.
6. Caddick, S. (1995). Microwave assisted organic reactions. Tetrahedron, 51(38), 10403-10432.
7. Campestre C, Keglevich G, Kóti J, Scotti L, Gasbarri C, Angelini G. Microwave-assisted simple synthesis of 2-anilinopyrimidines by the reaction of 2-chloro-4, 6-dimethylpyrimidine with aniline derivatives. RSC advances. 2020;10(21):12249-54.
8. Catterall, W. A. (2011). Voltage-gated calcium channels. Cold Spring Harbor Perspectives in Biology, 3(8), a003947.

9. Ehsan S. Solvent-Free Rapid Microwave Synthesis And Antiviral Activity Of 2, 4-(IH, 3H) Pyrimidinedione. Pakistan Journal of Science. 2015;67(4).
10. Huang Q, Zhu W, Li Y. Research on Data Sample for SAR Ship Detection. In2021 IEEE 4th Advanced Information Management, Communicates, Electronic and Automation Control Conference (IMCEC) 2021 Jun 18 (Vol. 4, pp. 548-553). IEEE.
11. Iadanza C, Leoni G, Spizzichino D, Trigila A, Margottini C, Osanna M, de Nigris B, Martellone A, Costantini M, Francioni E, Trillo F. Instability Processes and SAR Data Analysis in the Pompeii Archeological Park. InSustainable Conservation of UNESCO and Other Heritage Sites Through Proactive Geosciences 2023 Feb 11 (pp. 597-613). Cham: Springer International Publishing.
12. Kappe, C. O. (1993). 100 years of the Biginellidihydropyrimidine synthesis. Tetrahedron, 49(32), 6937-6963.
13. Kappe, C. O. (2000). Recent advances in the Biginellidihydropyrimidine synthesis. New tricks from an old dog. Accounts of Chemical Research, 33(12), 879-888.
14. Kappe, C. O. (2004). Controlled microwave heating in modern organic synthesis. AngewandteChemie International Edition, 43(46), 6250-6284.
15. Kappe, C. O., &Dallinger, D. (2006). The impact of microwave synthesis on drug discovery. Nature Reviews Drug Discovery, 5(1), 51-63.
16. Kitchen, D. B., Decornez, H., Furr, J. R., &Bajorath, J. (2004). Docking and scoring in virtual screening for drug discovery: methods and applications. Nature Reviews Drug Discovery, 3(11), 935-949.
17. Kubinyi, H. (2003). Drug research: myths, hype and reality. Nature Reviews Drug Discovery, 2(8), 665-668.
18. Liu, J., Ma, S., Zhang, H., & Zhu, C. (2013). Microwave-assisted one-pot Biginelli reaction: A green approach to dihydropyrimidinones using montmorillonite K-10 as an efficient catalyst. Journal of Molecular Catalysis A: Chemical, 373, 50-54.
19. Meng, X. Y., Zhang, H. X., Mezei, M., & Cui, M. (2011). Molecular docking: a powerful approach for structure-based drug discovery. Current Computer-Aided Drug Design, 7(2), 146-157.
20. Messerli, F. H., Grossman, E., &Goldbourt, U. (2007). Are beta-blockers efficacious as first-line therapy for hypertension in the elderly? A systematic review. Journal of the American Medical Association, 297(4), 396-398.
21. Messerli, F. H., Williams, B., & Ritz, E. (2007). Essential hypertension. The Lancet, 370(9587), 591-603.
22. Morris, G. M., & Lim-Wilby, M. (2008). Molecular docking. In Molecular Modeling of Proteins (pp. 365-382). Humana Press.
23. Morris, G. M., Huey, R., Lindstrom, W., Sanner, M. F., Belew, R. K., Goodsell, D. S., & Olson, A. J. (2009). AutoDock4 and AutoDockTools4: Automated docking

with selective receptor flexibility. Journal of Computational Chemistry, 30(16), 2785-2791.

24. Orellana F, D'Aranno PJ, Scifoni S, Marsella M. SAR interferometry data exploitation for infrastructure monitoring using GIS application. Infrastructures. 2023 May 16;8(5):94.
25. Panda KC, Kumar BV, Sahoo BM, Banik BK, Tiwari A. Microwave irradiated eco-friendly synthesis of pyrimidine derivatives as potential antitubercular agents. Asian Journal of Chemistry. 2022 Apr;34(4):907-11.
26. Sahoo BM, Banik BK, Kumar BV, Panda KC, Tiwari A, Tiwari V, Singh S, Kumar M. Microwave Induced Green Synthesis: Sustainable Technology for Efficient Development of Bioactive Pyrimidine Scaffolds. Current Medicinal Chemistry. 2023 Mar 1;30(9):1029-59.
27. Stout, M. D., Nyska, A., Collins, B. J., Witt, K. L., & Mann, P. C. (2002). Carcinogenicity and toxicity of five dihydropyrimidines in F344/N rats and B6C3F1 mice. Toxicological Sciences, 68(2), 312-325.
28. Talapin, D. V., & Shevchenko, E. V. (2016). Introduction: nanoparticle chemistry. Chemical reviews, 116(18), 10343-10345.
29. Trott, O., & Olson, A. J. (2010). AutoDockVina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. Journal of Computational Chemistry, 31(2), 455-461.
30. Vachhani M, Lalpara J, Hadiyal S, Dubal G. Microwave-assisted synthesis of bioactive tetrahydropyrimidine derivatives as antidiabetic agents. Folia Medica. 2022 Jun 30;64(3):478-87.
31. Zamponi, G. W., Striessnig, J., Koschak, A., & Dolphin, A. C. (2015). The physiology, pathology, and pharmacology of voltage-gated calcium channels and their future therapeutic potential. Pharmacological Reviews, 67(4), 821-870.
32. Zhou ZX, Deng Y, Wang W, Jia X, Wang R. Analysis of Varying-PRI Spotlight SAR Data. IEEE Transactions on Geoscience and Remote Sensing. 2022 Jan 7;60:1-20.