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1 Review

Substituted 2-Phenyl Imidazolidines: Synthetic Strategies, Biological Activities, Mechanistic Insights, and Nanocarrier-Based Advancements

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Abstract Substituted 2-phenyl imidazolidines present a structurally diversified family of heterocycles with several medicinal potentials. Their significance is due mostly to the presence of the phenyl group at the C-2 position, which enhances lipophilicity, rigidity, electronic distribution, and molecular recognition.

This review summarises the current advances in the synthesis, biological activity, mechanistic understanding, and nanocarrier-based administration of 2-phenyl imidazolidine derivatives. Amongst the most successful synthetic methodologies described are the classical cyclisation processes, condensation pathways, urea/thiourea-based procedures, green chemistry approaches, and nanocatalyst-assisted techniques. These protocols ensure that highly functionalized derivatives are easily accessible.

The biological activities of phenyl imidazolidines encompass anticancer, antibacterial, anti-inflammatory, CNS-modulating, antioxidant, and enzyme-inhibitory properties. Accordingly, a mechanistic study shows these phytochemicals interact with major molecular targets like DNA, tubulin, and other enzymes, leading to cell cycle arrest, induction of apoptosis, regulation of reactive oxygen species, and enzyme inhibition. The computational techniques enhance the optimisation based on SAR through the explanation of electrical behaviour and binding interactions.

Recent advances in nanotechnology have enabled the encapsulation of these derivatives within polymeric nanoparticles, lipid-based carriers, metal-doped nano-systems, and hybrid nano-structures. These platforms improve therapeutic effectiveness owing to an increase in solubility, stability, and targeted delivery.

This review combines synthetic, biological, mechanistic, and formulation factors to serve as a backbone for logical drug design. It highlights the potential of 2-phenyl imidazolidines as attractive scaffolding in the development of new medicinal compounds.

Keywords 2-Phenyl Imidazolidines, Synthetic Strategies, Biological Activities, Mechanistic Insights, Structure–Activity Relationship (SAR), Nanocarrier-Based Drug Delivery

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1. Introduction

The saturated five-membered heterocycles belong to a flexible class of imidazolidines that are of great interest in the fields of chemical biology, materials science, and modern medicinal chemistry. Because of their structural variability, ease of modification, and ability to form various non-covalent interactions, they can be regarded as ideal scaffolds in drug development efforts. Of particular note with regard to the family mentioned above, 2-phenyl imidazolidines have recently appeared as a significant subgroup because the presence of a phenyl ring at the C-2 position of the parent heterocycle noticeably influences its physicochemical, electronic, and biological properties. This provides broader possibilities for molecular recognition, increases the π-electron distribution, and enhances the conformational rigidity-all factors necessary for the interaction with a wide range of biomolecular targets[1].

Within the last decade, 2-phenyl imidazolidine frameworks have drawn much attention due to their wide scope of biological activities, including anticancer, antibacterial, antiviral, anti-inflammatory, CNS-modulating, and enzyme-inhibitory effects. These compounds can form hydrogen bonds, participate in π-π stacking, and have structural features that influence important enzyme functions. For such biomolecules, this relationship is key to their biological role. Many studies identify how structural changes may directly impact pharmacokinetic behaviour, cytotoxicity, and receptor affinity. Examples of these modifications include substitution at N, the nature of fused rings, and electron-donating/-withdrawing groups on the phenyl ring. 2-Phenyl imidazolidines are promising lead compounds in drug design for the treatment of cancer. Induction of cell-cycle arrest, activation of apoptosis, inhibition of topoisomerase, and modulation of pathways of oxidative stress are observed[2].

The interest in this area has been revived due to recent developments in drug delivery systems through nanotechnology. Complexation of imidazolidine-based drugs with nanocarriers, such as polymeric nanoparticles, metal-based nanosystems, liposomes, and dendrimers, results in improved solubility, stability, targeted distribution, and controlled release, which increases the expansion of their therapeutic applications. Research on this topic seems fragmented instead of being a holistic presentation. Most of the works refer only to studies on synthetic techniques, biological evaluations, or refer only to the specific combination of nanocarriers[3].

Accordingly, this work aims to provide an in-depth, integrated, comprehensive review of substituted 2-phenyl imidazolidines. The discussion will cover the following topics: (i) state-of-the-art synthetic methodologies and approaches for structural transformation; (ii) an overview of the pharmacological activities, with a main emphasis on anticancer ones; (iii) understanding related to the mechanism from molecular biology and computational studies; and (iv) recent formulation methodologies involving nanocarriers. Putting all these together, it is envisioned that the present study will represent a useful source that would help in developing novel therapeutic agents using the 2-phenyl imidazolidine backbone, facilitate future drug design activities, and enhance the process of SAR studies[4].

2. Imidazolidine Ring System

2.1 Structure and Fundamental Features

The imidazolidines are saturated heterocycles with a five-membered ring containing two nitrogen atoms at positions 1 and 3, such as 1,3-diazacyclopentane. Unlike their unsaturated congeners, imidazoles and benzimidazoles, imidazolidines are not aromatic. As a consequence, their structure is more flexible and amenable to a number of functionalization methodologies. With several stereogenic centres around the C-2 and C-4 positions, there are many possible diastereomers and enantiomers. This stereochemistry is relevant, since small changes in ring twist, nitrogen hybridisation, and substituent orientation can have significant effects on both receptor binding affinity and selectivity[2].

The imidazolidine polarity distribution and hydrogen bonding ability vary between its different conformations, such as envelope and twist forms. Both of the endocyclic nitrogen atoms contribute to its basicity and can form strong coordination

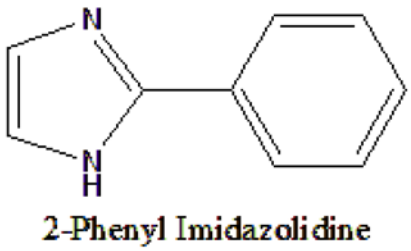

Figure 1: Basic Structure of 2-Phenyl Imidazolidine Ring

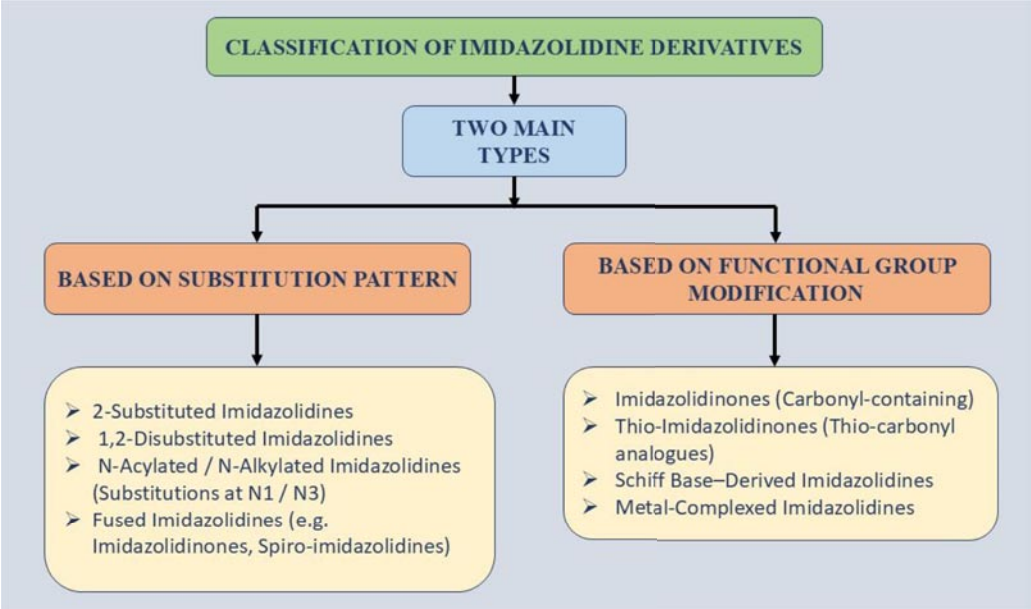

Figure 2: Classification Chart of Imidazolidine Derivatives

complexes with metal ions in medicinal chemistry and nanomaterial development[5].

2.2 Classification of Imidazolidine Derivatives

Imidazolidines are grouped based on:

a. Substitution Pattern

1. 2-substituted imidazolidines
2. 1,2-disubstituted derivatives
3. N-acylated or N-alkylated analogues
4. Fused imidazolidines (e.g., imidazolidinones, imidazolidine-based spirocycles)

b. Functional Group Modification

1. Carbonyl-containing imidazolidinones
2. Thio-imidazolidinones
3. Schiff base–derived imidazolidines
4. Metal-complexed imidazolidines

The ring's versatility shows how it can be used to improve the structure of drug development[2].

Comparison with Related Heterocyclic Systems

Imidazole vs. Imidazolidine

Imidazole is a flat aromatic heterocyclic, while imidazolidine is flexible and is not aromatic.

1. Imidazole possesses stronger π-electron delocalisation, a more stable structure, and a better balance of acidity and basicity.

2. Due to greater structural flexibility and less aromatic stabilisation, imidazolidines exhibit superior binding to flexible pockets in enzymes[6].

Benzimidazole vs. Imidazolidine

Benzimidazole has a fused benzene ring, which helps:

1. Higher rigidity
2. Improved electron-rich aromatic interactions
3. Greater metabolic stability

In contrast, imidazolidines allow rapid structural modification and greater solubility, providing different therapeutic advantages[7].

Oxazolidines vs. Imidazolidines

In oxazolidines, an oxygen atom replaces a nitrogen atom.

1. Oxazolidines exhibit reduced basicity and distinct hydrogen bonding patterns.

2. Imidazolidines maintain dual hydrogen-bond donor/acceptor capability, which is crucial for drug–target interactions.

Even though similar heterocycles have important roles in medicine, imidazolidines strike a good balance between structural flexibility, adjustable electronic properties, and compatibility with biological systems[8].

2.3 Importance of Phenyl Substitution at the C-2 Position

The presence of a phenyl ring attached to C-2 significantly changes the chemical and biological properties of imidazolidines.

a. Electronic Effects

The phenyl ring enhances π-electron density and stabilises certain conformations, often improving ligand–receptor complementarity[9].

b. Enhanced Lipophilicity

This improves:

1. Membrane permeability

2. Bioavailability
3. Pharmacokinetic behaviour

The presence of 2-phenyl derivatives makes them appealing choices for creating drugs that focus on the central nervous system and for treating cancer[10].

c. π-π and Hydrophobic Interactions

1. The binding effectiveness improves due to the aromatic component with:
2. DNA base pairs
3. Aromatic amino acid residues (Phe, Tyr, Trp)
4. Hydrophobic enzyme pockets[11].

2.4 Increased Structural Rigour

The substitution with the phenyl group improves selectivity of binding and reduces off-target interactions, minimising extra conformational flexibility. In conclusion, it is the phenyl group that converts the imidazolidine ring into a framework compatible with drug-like properties and receptors. Based on this, 2-phenyl imidazolidines became a unique structure in medicinal chemistry[12].

2.5 Rationale of the Review

Lack of Focused Reviews on 2-Phenyl Imidazolidines

Although interest in the chemistry of imidazolidines is increasing, most reports either focus on closely related heterocycles such as imidazolidinones, oxazolidines, or benzimidazoles or deal with the structure in very general terms. Only a few detailed studies have specifically focused on 2-phenyl imidazolidines. The current trend in the literature to compartmentalise biological activity, synthetic methodologies, and mechanistic studies can blur what might otherwise be a coherent understanding of the relationships among structure, function, and mechanism. Researchers attempting to prepare 2-phenyl imidazolidine derivatives typically need to consult a wide variety of sources, which can minimise efficiency and further impede the systematic design of new therapeutic agents[13].

Need for Consolidated Mechanistic and Nanocarrier-Based Insights

Nanocarrier delivery approaches have emerged as important tools for enhancing pharmacokinetics, solubility, bioavailability, and target specificity, in parallel with the chemical and biological investigation of these materials. Although metal-doped nanostructures, polymeric nanoparticles, lipid-based carriers, and hybrid systems have been utilised to enhance therapeutic efficacy, such advances are seldom considered within a molecular design or mechanistic analysis framework[14].

Examples of such mechanistic studies, most often provided separately, include molecular docking, QSAR studies, DFT, and in vitro and in vivo evaluations. It is very critical to integrate such data if one wants to understand fully how the structural features, electronic properties, and substituent patterns influence target binding, pharmacodynamics, and toxicity profiles. Thus, a more integrated approach, involving synthetic chemistry with associated biological activity, mechanistic understanding, and nanocarrier formulation, is mandatory for guiding rational design and translational research[15].

2.6 Benefits for Future Drug Design

This review seeks to fill the existing knowledge gap by providing a unified perspective on 2-phenyl imidazolidines. The benefits of such an integrative approach include:

1. Medicinal Chemistry Guidance: Understand SAR and substitution effects to optimise potency, selectivity, and metabolic stability.
2. Improved Mechanistic Understanding: Relate the molecular properties to pharmacological outcomes, cellular effects, and interaction with a target.
3. Encouraging Nanocarrier Development: Resolving transport and solubility problems to improve in vivo performance.
4. This approach encourages rational drug design by providing a common roadmap for future studies developing therapeutic candidates based on the 2-phenyl imidazolidine scaffolds.

The study connects synthetic techniques, biological evaluation, mechanistic insights, and nanocarrier formation into one comprehensive resource to support the rational design and application of 2-phenyl imidazolidines in drug development[16].

3. Chemistry and Synthetic Routes of Substituted 2-Phenyl Imidazolidines

The 2-phenyl imidazolidine scaffold has drawn much interest from synthetic chemists due to its structural versatility and medicinal importance. In fact, a variety of synthesis routes have been reported to date: from classical cyclisation methods to modern green chemistry approaches and nanocatalyst-assisted reactions. Such protocols enable the regioselective installation of substituents on both the imidazolidine ring and the 2-phenyl position, providing a myriad of derivatives for biological evaluation[17].

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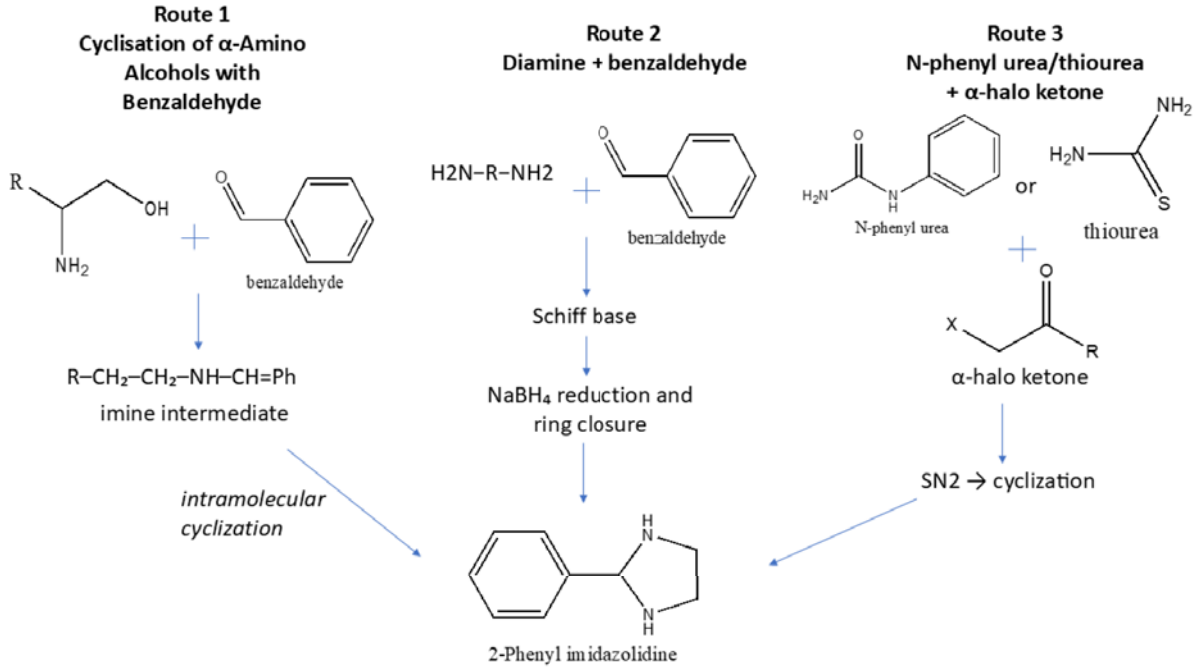

Figure 3: Classical Synthetic Routes for 2-Phenyl Imidazolidine Derivatives

Illustrates the three major classical synthetic approaches for 2-phenyl imidazolidine derivatives: (Route 1) cyclisation of α-amino alcohols with benzaldehydes to form an imine intermediate followed by intramolecular cyclization; (Route 2) condensation of diamines with benzaldehydes forming Schiff bases, followed by $NaBH_4$ reduction and ring closure; and (Route 3) N-phenyl urea/thiourea reaction with α-halo ketones through an SN2 process leading to cyclization. All routes converge to the formation of the 2-phenyl imidazolidine scaffold.

3.1 Classical Synthetic Methods

Cyclisation of α-Amino Alcohols with Phenyl-Substituted Carbonyls

One of the earlier approaches involves the acid- or base-catalysed condensation of α-amino alcohols with benzaldehyde or phenyl ketones. Typically, the amine undergoes nucleophilic attack on the carbonyl group to produce an imine intermediate, which subsequently is intramolecularly cyclized to generate the imidazolidine ring. Advantages include moderate yields and the use of simple, accessible reagents. Disadvantages: Sometimes it requires high temperatures or long reaction times. A typical example is the condensation of 2-amino-1-phenylethanol with derivatives of benzaldehyde, which produces 2-phenyl imidazolidines[18].

Condensation of 1,2-Diamines with Benzaldehyde Derivatives

A general method involves the reaction of substituted benzaldehydes with 1,2-diamines like ethylenediamine, forming Schiff bases that can be subsequently reduced to the saturated imidazolidine structure. Reduction is usually effected by sodium borohydride, $NaBH_4$, or by catalytic hydrogenation[19].

1. Advantages: allows the addition of more N-substituents.
2. Disadvantages: needs to be well managed in order not to cause side effects or severe degradation.

Cyclisation via Ureas or Thioureas

Intramolecular cyclisation of phenyl-substituted ureas or thioureas by means of acid-mediated cyclisation or heating produces the imidazolidine framework. For example, N-phenyl thiourea reacts with α-halo ketones to afford derivatives of 2-phenyl imidazolidines. This method is especially useful for the preparation of N-acyl or N-thio derivatives since it allows functionalization at both nitrogen positions[20].

3.2 Green and Sustainable Synthetic Approaches

The development of green chemistry highlighted the following different ways of synthesising 2-phenyl imidazolidine in an environmentally friendly manner[21].

Detailed caption: highlights modern sustainable and catalytic approaches for synthesising 2-phenyl imidazolidines. Green chemistry methodologies include microwave-assisted synthesis, solvent-

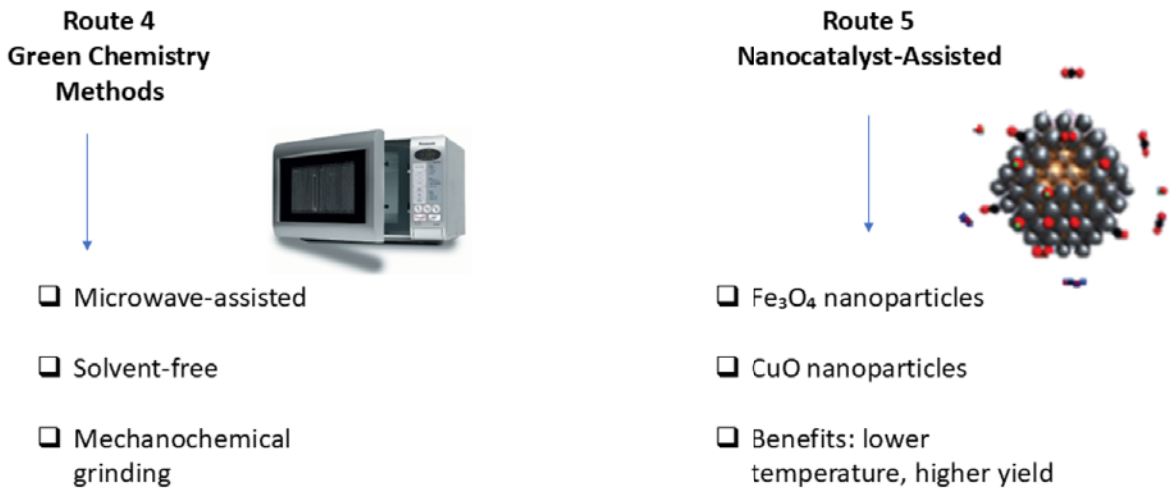

Figure 4: Green Chemistry and Nanocatalyst-Assisted Approaches for the Synthesis of 2-Phenyl Imidazolidines

free reactions, and mechanochemical grinding. Nanocatalyst-assisted methods employ Fe_3O_4 and CuO nanoparticles, offering advantages such as lower reaction temperature, improved yields, and enhanced reaction efficiency.

Cyclisation Without Solvents

The mechanical or microwave-assisted grinding methods avoid waste and shorten the reaction time, enabling the cyclisation of diamines with aldehydes in the absence of solvents.

• It has the advantages of energy efficiency, fast reactions, and high yields[22].

Biocatalyst and Enzyme-mediated Synthesis

Enzyme-mediated transformations, particularly those involving cyclisation by lipase or transaminase, enable the enantioselective synthesis of chiral imidazolidines under mild conditions.

Advantages include a high stereoselectivity and very low environmental impact[23].

3.3 Modern Synthetic Strategies

Multicomponent Reactions (MCRs)

Highly substituted 2-phenyl imidazolidines can be synthesised in a single reaction vessel by multicomponent methods, such as Ugi or Mannich strategies, using readily available amines, aldehydes, and isocyanides.

• It features significant functional diversity, atom-economic synthesis, and rapid generation of compound libraries[24].

Transition-Metal-Catalysed Methods

1. Pd-catalysed C–N cyclisation reactions can selectively result in the formation of N-substituted imidazolidines.

2. Cu-catalysed coupling techniques can incorporate different aryl or heteroaryl groups into the imidazolidine structure.

3. These allow the preparation of derivatives that are difficult or impossible to prepare by other methods[25].

Ionic-Liquid Mediated and Mechanochemical Approaches

Ionic liquids play the role of solvent and catalyst to favour reaction conditions that are sustainable and reusable. Besides, mechanochemical techniques, such as ball-milling, enable the synthesis of 2-phenyl imidazolidines under solvent-free conditions, with high yields and negligible waste production[26].

3.4 Structure–Activity Relationship Considerations in Synthesis

The stereochemistry and substitution pattern are directly related to the synthesis method chosen, and this consequence can affect biological activity. Important highlights include:

1. Electron-donating or -withdrawing groups can be added to the 2-phenyl ring to change cytotoxicity or antibacterial activity.

2. Inclusion of N-substituents aimed at enhancing lipophilicity, metabolic stability, or binding selectivity.

3. Chiral or asymmetric synthesis produces enantiomerically pure compounds, which often are required in applications with enzymes or the central nervous system.

Through the judicious choice of synthetic methods that take 2-phenyl imidazolidine derivatives to specific biological and pharmacokinetic properties, the gap between chemical design and therapeutic potential can be successfully closed[27].

4. Biological Activities of 2-Phenyl Imidazolidines

Substituted 2-phenyl imidazolidines can exhibit a wide range of biological activities because of their flexible skeletons, capacity for hydrogen bonding, and aromatic interactions. The results of combining an easily adaptable imidazolidine ring with a phenyl group include anticancer, antibacterial, antioxidant, CNS-modulating, and enzyme-inhibitory activities, which enable excellent interaction with different molecular targets. The following sections present a summary of the principal pharmacological activities so far identified[20].

4.1 Anticancer Activity

In vitro, cytotoxicity properties against A549-lung, HT-29-colon, MCF-7-breast, and HeLa-cervix cell lines have been displayed by phenyl imidazolidine derivatives. Investigative studies indicate several mechanisms of action:

1. Cell-cycle inhibition: Some derivatives induce an arrest at either the G0/G1 or the G2/M phase, therefore impeding division.

2. Induction of apoptosis: Studies have shown that both the intrinsic and extrinsic pathways of apoptosis are turned on; this usually follows mitochondrial disruption and caspase activation.

3. Inhibition of topoisomerase: Some compounds impede the activity of topoisomerase I and II, hence inhibiting DNA replication.

4. Generation of reactive oxygen species (ROS): Some derivatives selectively generate ROS in cancer cells, thus inducing cytotoxicity by oxidative stress[22].

SAR insights:

1. Para-substituted halogens on the 2-phenyl ring generally enhance anticancer activity.

2. Electron-donating groups can improve selectivity toward specific cancer types.

3. N-substitution influences cellular uptake and metabolic stability[18].

4.2 Antimicrobial and Antifungal Activity

2 Activity against Gram-positive and Gram-negative bacteria, as well as fungi, was exhibited by phenyl imidazolidines, indicating their possible use as broad-spectrum antibacterial agents. The mechanisms proposed for these compounds include: 1. Disruption of microbial cell membranes. 2. Inhibition of bacterial DNA gyrase and topoisomerase IV. 3. Interference with the formation of fungal cell walls and ergosterol metabolism. Results of SAR: 1. Antibacterial activity is enhanced mostly by electron-withdrawing groups present on the 2-phenyl ring. 2. N-acylation increases membrane permeability and may reduce vulnerability to the bacterial efflux pumps[22].

4.3 Antioxidant and Anti-Inflammatory Activity

Several derivatives of 2-phenyl imidazolidine have been tested for anti-inflammatory and radical-scavenging activities. The presence of the phenolic or methoxy group on the phenyl ring augmented the scavenging ability of DPPH and ABTS radicals. These in vitro studies demonstrate that modulation of the COX-2 and NF-κB pathways can mitigate inflammatory responses. These results suggest therapeutic possibilities for chronic inflammatory diseases and oxidative stress[16].

4.4 Central Nervous System (CNS) Activity

The capability of 2-phenyl imidazolidines to penetrate through the blood-brain barrier has advanced the study of their action on the central nervous system:

1. GABAergic modulation: Some derivatives act as positive modulators and could potentially have applications in anticonvulsant or anxiolytic treatments.

2. Neuroprotection: These compounds have shown potential in models of neurodegenerative disease by reducing oxidative stress and preventing the death of neuronal cells.

3. Inhibition of CNS enzymes: Some compounds show effectiveness in treating Parkinson's and Alzheimer's diseases through their inhibition of acetylcholinesterase and monoamine oxidase enzymes[28].

SAR elements:

1. Lipophilic N-substituents enhance CNS absorption.

2. Electron-rich 2-phenyl groups enhance the selectivity of receptor binding[29].

4.5 Enzyme Inhibitory Activity

Several important enzymes associated with human diseases are inhibited by the phenyl imidazolidines:

1. Cholinesterases represent a benefit in the treatment of neurodegenerative conditions.

2. Tyrosinase: Anti-melanogenic treatments could well be possible.

3. Kinases: They are responsible for several signalling pathways considered important in the development of cancers.

4. Topoisomerases: These facilitate anticancer effects by inhibiting DNA replication[30].

SAR studies indicate that the arrangement and electronic nature of the substituents on the 2-phenyl ring are important elements, along with N-substitution patterns, which influence an enzyme's efficacy and specificity[31].

5. Mechanistic Insights of 2-Phenyl Imidazolidines

Understanding the molecular mechanisms underlying the action of 2-phenyl imidazolidines is an important principle in the rational design of drugs. Mechanistic studies provide important information on intracellular pathways, target interactions, and structure-activity relationships that enable the optimisation of therapeutic efficacy and specificity[32].

5.1 Molecular Target Interactions

In general, phenyl imidazolidines are capable of binding various molecular targets to exhibit their biological action:

1. Microtubules and tubulin: Many anticancer drugs bind to the vinblastine or colchicine site and inhibit polymerisation, arrest the cell cycle, and induce apoptosis.

2. DNA/nucleic acids: The aromatic 2-phenyl substituents can π–π stack with DNA base pairs, possibly giving rise to intercalation, strand stabilisation, or inhibition of topoisomerase activity.

3. Enzymes: The hydrophobic phenyl ring and two nitrogen atoms facilitate easier binding to the active sites of tyrosinase, kinases, acetylcholinesterase, and monoamine oxidase. Hydrogen bonding and π-π interactions further enhance potency and specificity[29].

5.2 Cell Signalling and Biological Pathways

Mechanistic studies have identified critical pathways affected by 2-phenyl imidazolidines:

1. Apoptotic pathways: Evidence has shown that tumour cells induce caspase-3 and caspase-9 through intrinsic mitochondrial mechanisms.

2. The management of oxidative stress: Antioxidant substances protect healthy cells against oxidative damage; at the same time, the production of certain ROS in tumour cells may induce apoptosis.

3. Inflammation pathways: Inhibition of COX-2 and NF-κB signalling is one of the ways to reduce inflammation.

4. Neuroprotective effects: GABAergic receptor modulation and cholinesterase inhibition may enhance central nervous system activity by offering neuroprotection and anticonvulsant effects[13].

5.3 Structure–Activity Relationship (SAR) and

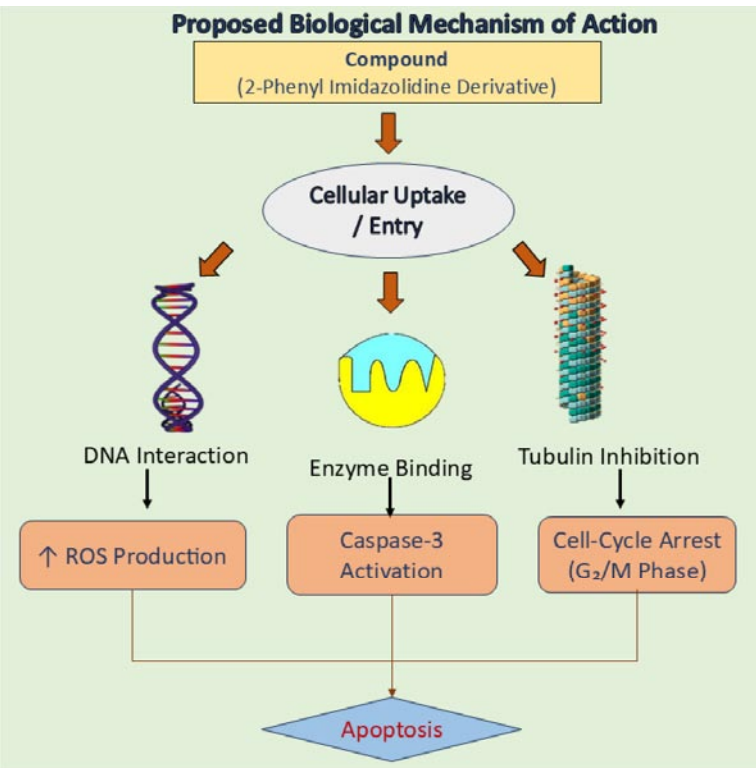

Figure 5: Proposed biological mechanism of action of 2-phenyl imidazolidine derivatives.

Mechanistic Correlation

The documented biological effects have been explained through mechanistic investigations and analyses of the structure-activity relationship.

1. Electron-withdrawing groups on the 2-phenyl ring significantly enhance enzyme inhibition and cytotoxicity.

2. Electron-donating groups often potentiate antioxidant activity and CNS modulation.

3. N-substituents have a direct effect on target engagement, pharmacokinetic behaviour, lipophilicity, and receptor affinity.

4. Stereochemistry: Chiral centres at C-2 and C-4 determine the binding orientation at active sites, thereby determining selectivity and potency.

Medicinal chemists use mechanistic insights from SAR data to predict the activity of novel derivatives and develop molecules with an optimal therapeutic profile[33].

5.4 Computational and Molecular Modelling Studies

Computational methodologies provide further insight into the molecular behaviour of 2-phenyl imidazolidines:

1. Molecular docking: It predicts hydrophobic and hydrogen-bond interactions in addition to favourable binding modes with enzymes, DNA, or receptors.

2. Density Functional Theory: This theory predicts stability and reactivity based on the analysis of reactive sites and electronic distribution.

3. QSAR links molecular properties such as logP, steric variables, and HOMO–LUMO energy levels to observable biological activity.

4. Molecular dynamics simulations provide dynamic insights into ligand-target interactions, conformational flexibility, and solvation effects.

Integration of computational data with experimentally obtained data helps in better understanding the molecular mechanism of action and further helps to develop practical modification strategies[10].

6. Nanocarrier Strategies for 2-Phenyl Imidazolidines

The 2-phenyl imidazolidine derivatives may have biological activity; however, they mostly cause problems due to their poor solubility, limited bioavailability, fast metabolism, and nonspecific distribution. Nanocarrier delivery methods, on the other hand, represent one practical solution to these problems since they increase the efficacy of treatment and lessen side effects. Some techniques of delivering 2-phenyl imidazolidines using flexible nanocarriers have been reported in a number of recent studies[34].

6.1 Polymeric Nanoparticles

Examples of biodegradable polymer-based nanoparticles used to deliver hydrophobic derivatives of 2-phenyl imidazolidine are PLGA, chitosan, and PEGylated polymers. These include two key benefits: protection against enzymatic degradation and controlled and extended release. The mechanism of endocytosis allows for better cellular absorption. Mechanism: The drug is either encapsulated or bonded to the polymer in response to changes in pH or enzymatic activity and is released over time. These nanoparticles have been utilised for two purposes: improved bioavailability in living organisms and increased cytotoxic effects on cancer cell lines[14].

6.2 Lipid-Based Nanocarriers

Lipid-based systems such as liposomes, solid lipid nanoparticles, and nanostructured lipid carriers offer improved biocompatibility and solubilization for lipophilic 2-phenyl imidazolidines.

• Benefits

i. High encapsulation efficiency.

ii. Surface modifications for targeted delivery: e.g., folate, transferrin.

iii. Ability to cross biological barriers, including the blood–brain barrier.

• Applications: In preclinical studies, liposomal delivery has been shown to increase anticancer efficacy, reduce systemic toxicity, and improve the therapeutic index[35].

6.3 Metal-Doped and Hybrid Nanocarriers

2-Phenyl imidazolidines are used to modify metal-doped nanoparticles, particularly silver, gold, and copper, for utilising synergic benefits:

• Benefits

i. Dual therapeutic action from drugs and metal ions.

ii. Enhanced production of ROS in cancer cells; iii. Antimicrobial activity that involves the disruption of membranes.

Hybrid systems combine metallic cores with either polymeric or lipid-based carriers, providing improved stability, drug loading, and targeted delivery[36].

6.4 Targeted Delivery Approaches

Nanocarriers can be designed for either passive or

active targeting:

1. Passive targeting relies on the Enhanced Permeability and Retention effect present in tumours to selectively accumulate drugs.

2. Active targeting relies on the attachment of ligands, such as antibodies, peptides, or small molecules, to the surface that enables receptor-mediated uptake by target cells.

Both strategies minimise systemic exposure and off-target effects by increasing the localised concentration of 2-phenyl imidazolidines at the site of disease[10].

6.5 Benefits and Challenges

Advantages

1. Improved solubility and bioavailability.

2. Characteristics of prolonged and controlled drug release.

3. Improved therapeutic effectiveness with reduced side effects.

4. Delivery specifically to damaged tissues or tumours[37].

Obstacles

1. Challenges of scaling up and maintaining consistent quality in the manufacturing process for nanoparticles.

2. Potential for toxicity or other immune reactions to the carrier.

3. Stability during storage and in biological environments. Application of nanocarrier techniques can, despite obstacles, facilitate the transformation of 2-phenyl imidazolidine derivatives into therapeutically effective drugs[38].

7. Conclusion

In general, 2-phenyl imidazolidines are very flexible and biologically rich molecules with a unique structure, including an imidazolidine ring and a phenyl ring at position 2, which can be precisely controlled and varied. There are various methods for synthesising these compounds, ranging from traditional and eco-friendly procedures to nanocatalyst-mediated and multi-component reactions. Their large number and broad spectrum of biological activities make it easy to diversify. Mechanistic knowledge about interactions with DNA, enzymes, biological pathways, and redox processes helps diversify these molecules. Advances made with regard to nanocarriers for drug delivery improve stability, solubility, bioavailability, and selectivity.

Author contribution

Each author contributed significantly to the article's conceptualisation, design, data collection, and interpretation. They also participated in the article's drafting or critical revision.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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