JOURNAL OF PHARMA INSIGHTS AND RESEARCH ISSN NO. 3048-5428

REVIEW ARTICLE

Recent Advances in Synthesis, Mechanism of Action and Therapeutic Applications of Azepines

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Publication history: Received on 15th May 2025; Revised on 11th June 2025; Accepted on 21st June 2025

Article DOI: 10.69613/e2dsks40

Abstract: Seven-membered nitrogen heterocycles, particularly azepines, are important structural scaffolds in medicinal chemistry and drug development. The non-planar, non-aromatic nature of azepines offers unique conformational flexibility, making them valuable building blocks for pharmaceutical compounds. The expansion of five- and six-membered rings through thermal, photochemical, and microwave-assisted methods has led to diverse azepine, azepinone, and azepane derivatives. Molecular docking studies and structure-activity relationship analyses have revealed crucial insights into their binding mechanisms with therapeutic targets. Azepine-based compounds demonstrate broad pharmacological activities, including antipsychotic, antidepressant, anticonvulsant, and anticancer properties. The development of novel synthetic methodologies, particularly environmentally benign approaches, has facilitated the generation of functionalized azepine derivatives. Recent advances in transition metal catalysis and organocatalytic methods have enabled selective transformations while adhering to green chemistry principles. The incorporation of azepine moieties in drug design has resulted in over 60 approved medications, indicating their therapeutic significance. The aim of this review is to discuss about the synthesis, structure-activity relationships, and biological applications of azepine-containing compounds.

Keywords: Azepines; Seven-membered heterocycles; Drug design; Molecular docking; Structure-activity relationships

1. Introduction

Azepines represent a fundamental class of seven-membered heterocyclic compounds containing one nitrogen atom, distinguished by their unique structural and electronic properties that have captivated medicinal chemists for decades. Their structural uniqueness stems from the inherent ring strain characteristic of medium-sized rings and the presence of a Lewis basic nitrogen atom, which contributes to their distinctive chemical reactivity and versatility as pharmacophores [1]. The seven-membered ring system exhibits intermediate characteristics between small rings (which are highly strained) and large rings (which are flexible but entropically disfavored), creating a unique balance of stability and reactivity that makes azepines particularly valuable in drug design.

The non-planar configuration of azepines results in conformational flexibility, a characteristic that has been extensively exploited in medicinal chemistry for developing pharmaceutically active compounds with enhanced selectivity and potency [2]. This conformational adaptability allows azepine-containing molecules to adopt multiple three-dimensional arrangements, enabling them to interact optimally with diverse biological targets. The ring puckering and pseudorotational dynamics of azepines contribute to their ability to access different conformational states, which can be fine-tuned through strategic substitution patterns to achieve desired pharmacological profiles. The azepine scaffold exists in multiple tautomeric forms, with 1H and 3H being the predominant and most pharmaceutically relevant species, each offering distinct electronic properties and reactivity patterns [3]. The 1H-azepine tautomer typically predominates in solution due to thermodynamic stability, while the 3H form can be stabilized through specific substitution patterns or environmental conditions. This tautomeric equilibrium provides additional opportunities for medicinal chemists to modulate biological activity by controlling the predominant tautomeric form through molecular design. The interconversion between these tautomers can also influence metabolic pathways and pharmacokinetic properties of azepine-based drugs.

The molecular architecture of azepines allows for various substitution patterns, leading to diverse chemical entities with broad therapeutic applications spanning multiple therapeutic areas [4]. The seven available positions on the azepine ring provide numerous opportunities for structural modification, enabling the introduction of functional groups that can modulate physicochemical properties, enhance target selectivity, or improve pharmacokinetic parameters. The nitrogen atom serves as a versatile site for substitution, allowing for the introduction of alkyl, aryl, or heterocyclic substituents that can significantly impact the compound's

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biological profile. Additionally, the carbon atoms of the ring can accommodate various functional groups, creating libraries of structurally diverse compounds with tailored properties.

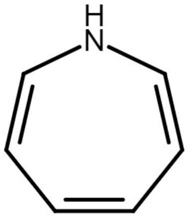
The incorporation of azepine rings into drug molecules has proven particularly beneficial in developing compounds targeting neurological disorders, where the unique pharmacophoric properties of azepines facilitate optimal interactions with neurotransmitter receptors and transporters [5]. The conformational flexibility of azepines enables them to mimic natural neurotransmitters or adopt conformations that complement the binding sites of neurological targets. This has led to the development of highly effective antidepressants, antipsychotics, and anticonvulsants that leverage the unique structural features of the azepine scaffold. The ability of azepines to cross the blood-brain barrier efficiently, combined with their metabolic stability, makes them particularly suitable for central nervous system applications. The pharmaceutical significance of azepines and their derivatives is evidenced by their presence in more than 60 approved medications across various therapeutic categories, representing one of the most successful heterocyclic scaffolds in modern drug development [6]. These approved drugs demonstrate the versatility of the azepine framework, with applications ranging from psychiatric medications like clozapine and imipramine to anticonvulsants such as carbamazepine. The continued success of azepine-based drugs in clinical practice validates the importance of this heterocyclic system and encourages ongoing research into novel azepine derivatives with improved therapeutic profiles.

Traditional synthetic approaches to azepines have relied on ring expansion strategies, typically involving the transformation of smaller ring systems through thermal, photochemical, or metal-mediated processes, while recent developments have focused on more sustainable methodologies that minimize environmental impact [7]. Classical methods such as Schmidt rearrangements, Beckmann rearrangements, and thermal cyclizations have provided reliable access to azepine frameworks but often require harsh reaction conditions or generate significant waste. The evolution toward greener synthetic approaches reflects the pharmaceutical industry's commitment to sustainable chemistry and the development of more efficient, atom-economical processes. The emergence of domino transformations, inspired by natural biosynthetic pathways, has provided efficient one-pot processes that align with green chemistry principles while offering improved synthetic efficiency and reduced waste generation [8].

2. Structural Characteristics and Classification

2.1. Structure

The azepine core consists of a seven-membered heterocyclic ring containing one nitrogen atom. The presence of six carbon atoms and one nitrogen creates unique electronic distributions and conformational preferences. The ring system exhibits significant flexibility due to ring strain and the sp3 hybridization of the nitrogen atom, leading to various possible conformations [13].



Chemical Structure 1. Azepine

2.2. Tautomeric Forms

Azepines exist in four tautomeric forms: 1H, 2H, 3H, and 4H-azepines. Among these, 1H and 3H-azepines demonstrate particular stability and biological relevance. The 1H-azepine tautomer readily undergoes conversion to 3H-azepine under standard conditions, except when the nitrogen bears specific substituents that stabilize the 1H form [14].

2.3. Structural Classifications

2.3.1. Monocyclic Azepines

Monocyclic azepines represent the simplest structural form, containing only the basic seven-membered ring with one nitrogen atom. Their reactivity is primarily governed by the position of the double bonds and the nature of substituents. These compounds serve as important intermediates in the synthesis of more complex azepine derivatives [15].

2.3.2. Fused Azepines

Fused azepine systems incorporate the azepine ring merged with other aromatic or heterocyclic systems. Benzazepines, formed by fusion with one benzene ring, demonstrate significant pharmacological activity. Dibenzazepines, containing two fused benzene rings, constitute an important class of pharmaceutical compounds. Pyrroloazepines, created through fusion with pyrrole ring systems, exhibit unique biological properties. The incorporation of sulfur in thiazepine systems introduces additional functionality and molecular diversity [16].

2.3.3. Azepinones

Azepinone derivatives, characterized by the presence of a carbonyl group within the seven-membered ring, exhibit distinct electronic properties and reactivity patterns. The carbonyl group significantly influences the conformational preferences and chemical behavior of these systems, leading to diverse applications in medicinal chemistry [17].

Table 1. Classification and Physical Properties of Azepine Derivatives

Compound Class	Basic Structure	Melting Point (°C)	Molecular Weight	Log P	Common Substituents
1H-Azepines	7-membered ring	45-80	95-250	1.2-2.8	-H, $-CH_3$, -Ph
3H-Azepines	7-membered ring	60-95	95-280	1.5-3.0	-alkyl, -aryl
Benzazepines	Fused benzene ring	120-180	145-320	2.0-3.5	-OH, $-NH_2$, -Cl
Dibenzazepines	Two fused benzene rings	180-250	195-400	2.8-4.2	-F, $-OCH_3$, $-NO_2$
Azepinones	Carbonyl group	150-220	110-300	1.8-3.2	-COOH, $-SO_2NH_2$

3. Synthesis

3.1. Ring Expansion Method

Ring expansion of five- and six-membered precursors represents a fundamental approach to azepine synthesis. Thermal rearrangements provide controlled transformation pathways under specific temperature conditions. Photochemical processes enable selective ring expansion through excited-state intermediates. Microwave-assisted transformations offer rapid and efficient conversion while maintaining product selectivity. The choice of specific conditions depends on the desired substitution pattern and the nature of the starting materials [18].

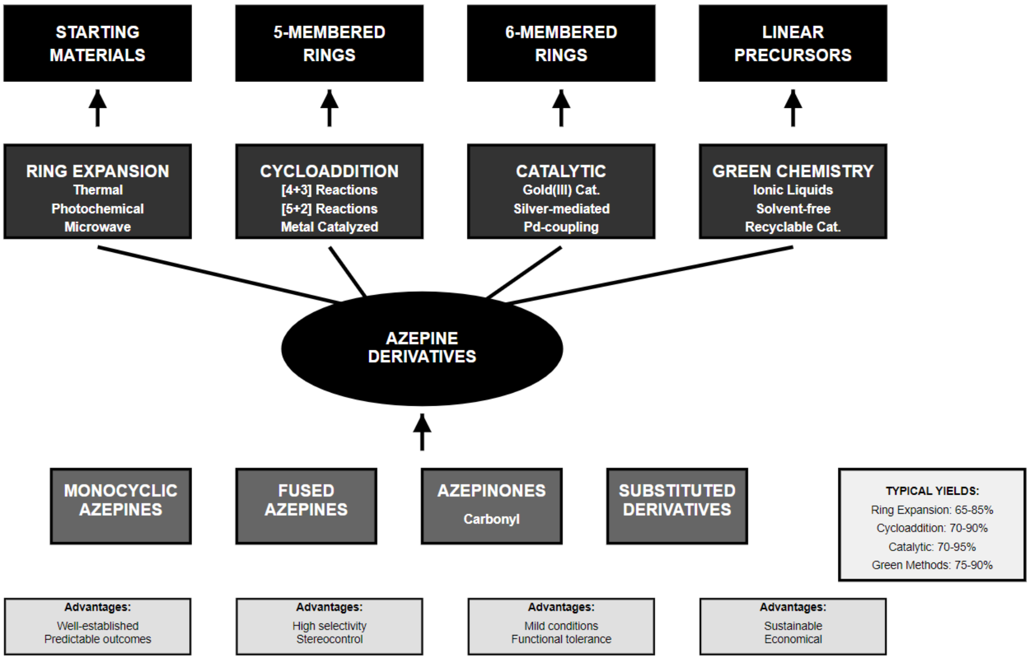


Figure 1. Azepine Synthesis Methods and Reaction Pathways

3.2. Cycloaddition Reactions

Advanced cycloaddition strategies, particularly [4+3] and [5+2] cycloadditions, provide efficient routes to azepine formation. These reactions typically employ transition metal catalysts to control selectivity and enhance reaction rates. The stereochemical outcome can be precisely controlled through careful selection of reaction conditions and catalysts [19].

3.3. Catalytic Methods

Recent developments in catalysis have revolutionized azepine synthesis through various approaches. Gold(III)-catalyzed intermolecular annulations enable selective formation of functionalized azepines. Silver-mediated cycloadditions provide access to complex azepine frameworks. Palladium-catalyzed coupling reactions facilitate the construction of elaborately substituted azepine systems with high efficiency and selectivity [20].

3.4. Green Chemistry

Environmental considerations have spurred the development of sustainable synthetic methods for azepine preparation. Ionic liquid-mediated syntheses provide environmentally benign reaction conditions while maintaining synthetic efficiency. Solvent-free conditions reduce waste generation and improve atom economy. Recyclable catalyst systems enable multiple reaction cycles while minimizing chemical waste [21].

Table 3. Synthetic Methods for Azepine Ring Formation

Method	Starting Materials	Reaction Conditions	Yield (%)	Stereoselectivity	References
Ring Expansion	Cyclohexanone derivatives	Lewis acid, 80°C, 6h	65-85	Moderate	[17, 18]
[4+3] Cycloaddition	Dienes + nitrogen source	Rh catalyst, RT, 12h	70-90	High	[19]
Ring-Closing Metathesis	Diallyl compounds	Grubbs II, DCM, RT	75-95	High	[4]
Beckmann Rearrangement	Oximes	H_2SO_4, heat, 2h	60-80	N/A	[1]
Gold-Catalyzed Cyclization	Alkyne derivatives	Au(III), MeCN, RT	70-85	Moderate	[19]

4. Mechanism of Action

4.1. Molecular Interactions

The pharmacological activities of azepine-based compounds stem from their unique molecular architecture and electronic distribution. The conformational flexibility of the seven-membered ring enables optimal binding interactions with various biological targets. The nitrogen atom serves as a hydrogen bond acceptor, while the ring system can participate in hydrophobic and π-π stacking interactions with receptor binding sites [22].

4.2. Receptor Binding

4.2.1. Neurotransmitter Systems

Azepine derivatives exhibit significant affinity for multiple neurotransmitter receptors. In antidepressant compounds like imipramine, the mechanism involves inhibition of serotonin and norepinephrine reuptake transporters. The tricyclic structure allows for optimal positioning within the transporter binding pocket, leading to effective neurotransmitter modulation [23].

4.2.2. Enzyme Inhibition

Many azepine compounds function as enzyme inhibitors through specific molecular recognition events. The seven-membered ring structure provides appropriate spatial arrangement of functional groups for interaction with enzyme active sites. Molecular docking studies reveal that the azepine scaffold can adopt multiple conformations to maximize binding interactions [24].

4.3. Structure-Activity Relationship

Structure-activity relationship analyses indicate that substituent patterns on the azepine ring significantly influence biological activity. The position and nature of substituents affect receptor binding affinity and selectivity. Electronic effects and stereochemical features play crucial roles in determining the potency and specificity of azepine-based drugs [25].

Table 4. Structure-Activity Relationships of Azepine-Based Drug Candidates

Structural Modification	Effect on Activity	Impact on Properties	Therapeutic Implications
N-alkylation	↑ Lipophilicity	↑ BBB penetration	Enhanced CNS activity
Ring hydroxylation	↑ Hydrophilicity	↓ Half-life	Improved metabolism
Halogenation	↑ Stability	↑ Binding affinity	Enhanced potency
Carbonyl addition	↑ H-bond capacity	↑ Solubility	Better bioavailability
Aromatic fusion	↑ Rigidity	↑ Receptor selectivity	Reduced side effects

5. Therapeutic Applications

5.1. Neurological Disorders

5.1.1. Antidepressant Activity

Azepine-based antidepressants demonstrate significant efficacy in treating major depressive disorders. Tricyclic compounds containing the azepine core modulate monoamine neurotransmitter systems effectively. The molecular framework allows for sustained interaction with neurotransmitter transporters, leading to therapeutic benefits [26].

5.1.2. Antipsychotic Properties

Compounds like clozapine utilize the azepine structure to achieve specific receptor targeting profiles. The unique binding characteristics enable interaction with multiple dopamine and serotonin receptor subtypes, resulting in improved therapeutic outcomes for schizophrenia and related disorders [27].

5.2. Cardiovascular Disorders

Azepine derivatives demonstrate significant activity in cardiovascular medicine. ACE inhibitors containing azepine moieties effectively regulate blood pressure through specific enzyme inhibition. The molecular structure enables optimal binding to the angiotensin-converting enzyme active site [28].

5.3. Anticancer Activity

Recent investigations reveal promising anticancer properties of novel azepine derivatives. These compounds exhibit antiproliferative effects through various mechanisms, including:

- Cell cycle regulation through CDK2 inhibition
- Apoptosis induction in cancer cell lines
- Interference with tubulin polymerization
- Molecular studies indicate specific interactions with key proteins involved in cell proliferation and survival pathways [29].

5.4. Antimicrobial Properties

Azepine-containing compounds demonstrate broad-spectrum antimicrobial activity. The molecular framework allows for effective interaction with bacterial and fungal cellular targets. Recent studies indicate potential applications in addressing antibiotic resistance through novel mechanisms of action [30].

Table 2. Therapeutic Applications and Clinical Significance of Major Azepine-Based Drugs

Drug Name	Chemical Class	Primary Indication	Mechanism of Action	Typical Dosage (mg/day)
Clozapine	Dibenzazepine	Schizophrenia	D2/5-HT2A antagonist	300-900
Imipramine	Dibenzazepine	Depression	SNRI	75-300
Carbamazepine	Dibenzazepine	Epilepsy	Na+ channel blocker	400-1200
Loxapine	Benzazepine	Acute psychosis	D2/5-HT2A antagonist	60-250
Opipramol	Dibenzazepine	Anxiety	Sigma receptor agonist	50-300

6. Challenges in Synthesis

The synthesis of azepine derivatives presents several significant obstacles that continue to challenge synthetic chemists, particularly in controlling stereochemistry and regioselectivity during ring formation and subsequent functionalization reactions. The inherent conformational flexibility of seven-membered rings, while advantageous for biological activity, often complicates selective functionalization and creates substantial difficulties in achieving predictable synthetic outcomes [31]. Unlike their five- and six-membered counterparts, azepines adopt multiple low-energy conformations that can interconvert rapidly at room temperature, making it challenging to predict and control the stereochemical outcome of reactions. This conformational mobility affects the approach of reagents to reactive sites, leading to mixtures of products and reduced selectivity in many synthetic transformations.

The medium ring size of azepines introduces unique thermodynamic and kinetic challenges that distinguish them from both smaller and larger ring systems. Seven-membered rings experience significant transannular strain and angle strain, which can destabilize intermediates and transition states during synthesis. The ring strain energy of azepines falls into an intermediate range that makes ring-closing reactions neither as favorable as those forming five- or six-membered rings nor as straightforward as those forming larger macrocycles. This intermediate stability often results in competitive side reactions, including ring contraction to six-membered systems or ring expansion to eight-membered derivatives, thereby reducing the efficiency of target azepine formation.

Current research focuses on developing more efficient and stereoselective synthetic methodologies that can overcome these inherent challenges while providing access to diverse azepine scaffolds with high levels of structural control [31]. Modern approaches emphasize the development of catalytic systems that can enforce specific conformational preferences during ring formation, thereby improving selectivity. Conformationally constrained precursors and templates have emerged as valuable strategies for directing cyclization reactions toward desired products. Additionally, the use of chiral catalysts and auxiliaries has shown promise in achieving enantioselective azepine synthesis, addressing the growing demand for enantiomerically pure pharmaceutical compounds.

The challenge of regioselectivity becomes particularly acute when functionalizing existing azepine rings, as the multiple available positions can lead to complex product mixtures. Traditional electrophilic aromatic substitution patterns that work well for benzene derivatives often fail to provide predictable outcomes with azepines due to the non-aromatic nature and conformational flexibility of the seven-membered ring. Consequently, researchers have turned to directed metallation strategies, where coordinating groups temporarily bind to metal catalysts and direct functionalization to specific positions. These approaches have shown considerable promise in achieving site-selective C-H activation and subsequent functionalization of azepine frameworks.

Metal-free catalytic systems and environmentally sustainable approaches represent emerging areas of investigation in azepine synthesis, driven by both environmental concerns and the need for more economical synthetic processes [32]. Organocatalytic methods have gained significant attention as they avoid the use of expensive and potentially toxic transition metals while often providing excellent selectivity. Photocatalytic approaches utilizing visible light have emerged as particularly attractive alternatives, enabling mild reaction conditions and reduced waste generation. These photoredox systems can generate reactive intermediates under gentle conditions, minimizing decomposition pathways that often plague traditional high-temperature methods for azepine synthesis.

Biocatalytic approaches have also gained prominence as sustainable alternatives for azepine synthesis, leveraging the exquisite selectivity of enzymatic systems. Engineered enzymes and directed evolution techniques have expanded the scope of biotransformations applicable to azepine formation, offering unprecedented levels of stereochemical control. However, the substrate scope of biocatalytic methods remains limited, and significant research efforts are focused on expanding enzyme tolerance for non-natural azepine precursors. The optimization of azepine-based drugs requires careful balancing of physicochemical properties that directly impact their therapeutic potential and clinical viability. Factors such as lipophilicity, metabolic stability, and blood-brain barrier penetration significantly influence drug efficacy and must be carefully optimized during the drug development process [33]. The seven-membered ring structure of azepines inherently affects these properties in complex ways that differ from more conventional pharmaceutical scaffolds. The conformational flexibility that makes azepines excellent pharmacophores can also lead to increased metabolic lability, as flexible molecules often present multiple sites for enzymatic modification.

Lipophilicity optimization represents a particular challenge for azepine-based drugs, as the seven-membered ring contributes to molecular volume and hydrophobic surface area in ways that can be difficult to predict. The LogP values of azepines often fall outside the optimal range for oral bioavailability, necessitating careful introduction of polar functional groups to achieve appropriate hydrophilic-lipophilic balance. However, such modifications must be made without compromising the essential pharmacophoric features of the azepine scaffold that are responsible for biological activity. Metabolic stability considerations are particularly complex for azepine derivatives due to their susceptibility to various enzymatic transformations. The nitrogen atom in azepines can undergo N-oxidation by flavin-containing monooxygenases, while the ring system itself may be subject to oxidative metabolism by cytochrome P450 enzymes. The conformational flexibility of azepines can expose different regions of the molecule to metabolic enzymes depending on the adopted conformation, making it challenging to predict and modify metabolic soft spots. Strategic introduction of metabolically stable functional groups, such as fluorine substituents, has emerged as an important strategy for improving the metabolic profile of azepine drugs.

Blood-brain barrier penetration represents both an opportunity and a challenge for azepine-based pharmaceuticals, depending on the intended therapeutic target. For central nervous system applications, efficient brain penetration is essential, while for peripheral targets, limiting CNS exposure is often desirable to minimize side effects. The physicochemical properties that govern blood-brain barrier permeation are complex and multifactorial, involving considerations of molecular size, polarity, hydrogen bonding capacity, and efflux pump recognition. Azepines' conformational flexibility can influence their interaction with transport proteins and efflux pumps, making it difficult to predict brain penetration based solely on calculated physicochemical parameters. Recent advances in computational methods aid in predicting drug-like properties and potential metabolic pathways of azepine compounds, providing valuable tools for rational drug design and optimization [33]. Machine learning algorithms trained on large datasets of pharmaceutical compounds have shown considerable promise in predicting ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) properties of azepine derivatives. These computational approaches can rapidly screen large virtual libraries of azepine compounds, identifying those most likely to possess favorable drug-like properties before costly synthesis and testing.

Molecular dynamics simulations have become increasingly sophisticated in their ability to model the conformational behavior of azepines in various environments, including biological membranes and enzyme active sites. These simulations provide insights into the dynamic behavior of azepine drugs that cannot be obtained from static crystal structures, helping to explain structure-activity relationships and guide the design of improved derivatives. However, the computational demands of accurately modeling conformationally flexible systems like azepines remain substantial, and continued advances in computational power and algorithms are needed to fully realize the potential of these approaches.

7. Conclusion

Azepines are versatile class of heterocyclic compounds with vast pharmaceutical importance. Their unique structural features and conformational flexibility are responsible for diverse therapeutic applications. Recent advances in synthetic methodologies have enhanced access to complex azepine derivatives while addressing environmental concerns. The broad spectrum of biological activities, ranging from neurological to anticancer properties, underscores their importance in drug development. Structure-activity relationships and molecular mechanisms continues to guide the design of novel azepine-based therapeutic agents. The use of computational methods, advanced synthetic strategies, and biological evaluation techniques facilitates the rational design of azepine-based drugs.

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