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Recent progress in the development of Diazepine as a biologically active scaffold

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ABSTRACT: Diazepines-seven-membered N-heterocycles that include 1,4- and 1,5-diazepines along with their benzo-fused analogues—continue to serve as privileged scaffolds in medicinal chemistry due to their broad spectrum of biological activities, including CNS, antiviral, antibacterial, and anticancer effects. Over the past decade, the synthetic toolbox for constructing diazepine cores has expanded significantly. Advances such as multicomponent one-pot and cascade reactions, microwave- and flow-assisted protocols, heterogeneous and nanocatalysts, ionic-liquid-mediated and solvent-free green methodologies, as well as DNA-compatible annulation strategies, have enabled rapid access to structurally diverse analogues and accelerated early-stage biological evaluation.This review summarizes key developments up to 2025, highlights representative and emerging synthetic strategies, and outlines major biological applications of diazepine derivatives. Current challenges—including asymmetric synthesis, unresolved mechanistic pathways, and limitations in scalability—are also discussed. Finally, opportunities for future research are proposed. All claims presented in this review are supported by selected recent literature.

KEY WORDS: diazepine, benzodiazepine, 1,4-diazepine, multicomponent reaction, green synthesis, biological activity, scaffold

I. INTRODUCTION

Seven-membered nitrogen heterocycles-diazepines-occupy an important niche in medicinal chemistry. The benzodiazepine subclass (e.g., classical CNS agents) demonstrates how subtle substitutions on a diazepine core can profoundly modulate pharmacology; beyond CNS activity, modern efforts have uncovered diazepine derivatives with antibacterial, antiviral, and anticancer profiles. Synthetic innovation has thus been coupled to biological exploration: chemists seek routes that are faster, more divergent, and greener to populate structure–activity relationship (SAR) space efficiently. Recent methodological trends (multicomponent reactions, microwave and flow chemistry, heterogeneous catalysis, ionic-liquid media, and DNA-compatible annulations) have been particularly impactful. [1-5]

A. Diazepine Scaffold Types And Medicinal Relevance Scaffold Families

Diazepines can be classified as:

Monocyclic 1,4- and 1,5-diazepines (seven-membered rings containing two nitrogens),
Benzo-fused diazepines (benzodiazepines; the best-known clinical class), and
Heteroatom-fused diazepines (oxazepines, thiazepines and related fused systems). Each family offers different conformational and electronic properties that influence target engagement and ADMET profiles.

II.SYNTHETIC STRATEGIES — RECENT ADVANCES

A. Multicomponent reactions (MCRs) and one-pot cascades

MCRs have proved especially useful for assembling complex diazepine frameworks in a single operation, delivering structural diversity with high atom-economy. Pioneering work on multicomponent approaches to benzodiazepines and annelated diazepines established useful blueprints that have been extended in recent years to Ugi-type, Mannich-type, and isocyanide-based annulations. DNA-compatible adaptations have enabled the incorporation of diazepine cores into encoded libraries, expanding their utility in modern fragment- and DNA-encoded screening campaigns. These MCRs accelerate SAR exploration by collapsing multistep sequences into a single flask. [2]

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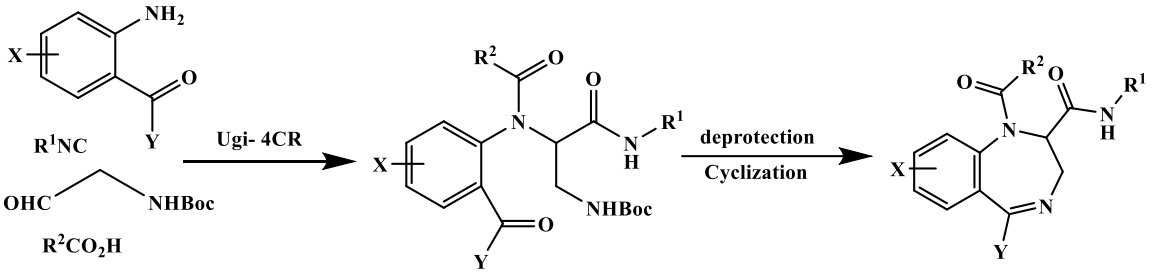
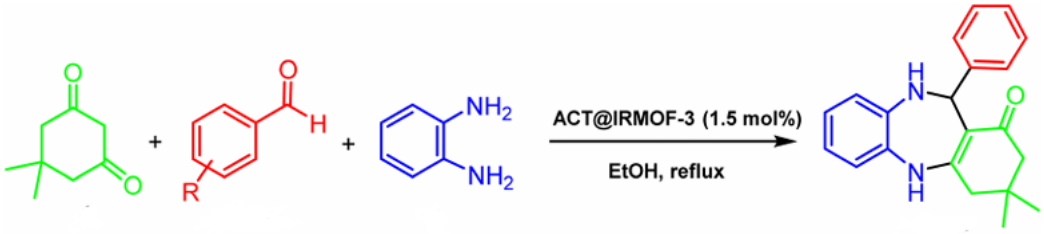


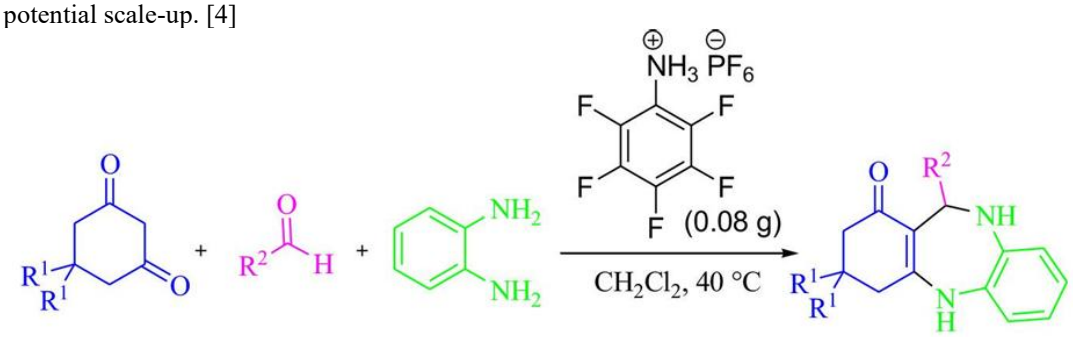
B. Microwave- and flow-assisted acceleration

Microwave irradiation shortens reaction times and often increases crude purity for both classical condensations and newer MCRs; parallelization of microwave-assisted MCRs is commonly used in library synthesis. Continuous-flow adaptations are also emerging for scalable diazepine assembly, enabling better heat/mass transfer and safer handling of reactive intermediates. These approaches reduce turnaround time between design and biological evaluation. [3]



C. Heterogeneous and nanocatalysis

Magnetic nanoparticles, functionalized silica, and other reusable heterogeneous catalysts have been used to catalyse ring-closure and annulation steps leading to diazepines, sometimes combined with microwave heating for rapid conversions. These catalysts facilitate recovery/reuse and align with green-chemistry goals — important for library synthesis and potential scale-up. [4]



D. Transition-metal and photoredox approaches for late-stage modification

Pd-, Cu- and other metal-catalyzed cross-couplings enable late-stage C–N and C–C functionalization of preformed diazepine scaffolds, expanding chemical space for SAR without re-synthesizing core rings. Photoredox-mediated annulations and radical cascades provide orthogonal disconnections for creating complex substitution patterns under mild conditions. These tactics are valuable for modifying hits from screening. [6]

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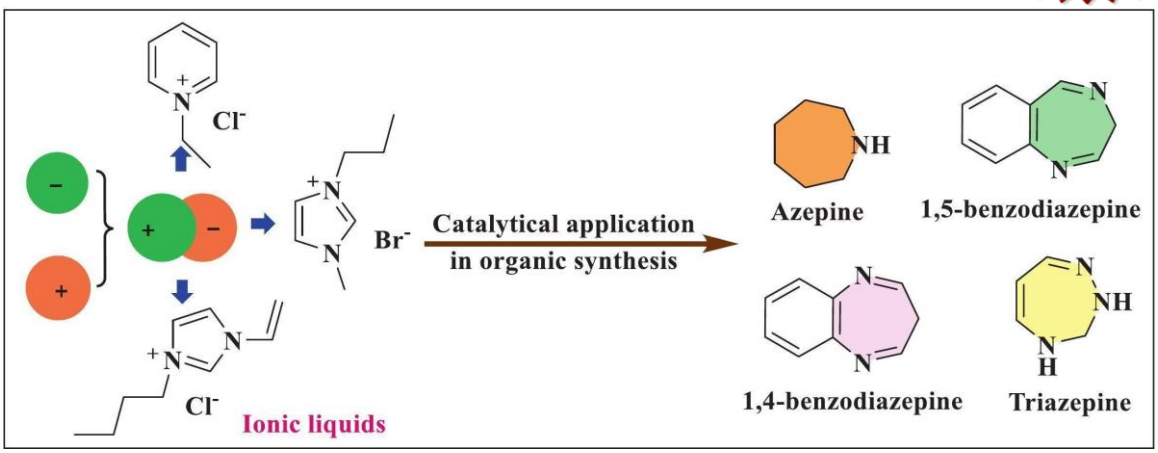

III. BIOLOGICAL APPLICATIONS

A. Antiviral activity

Certain diazepine analogues have been investigated as reverse transcriptase inhibitors and in other antiviral assays. Structural modifications at N-positions and at ring-fused positions strongly affect target binding; authors report promising in-vitro RT inhibition for N-functionalized diazepinones. Early SAR indicates that lipophilic aryl substituents at specific positions increase potency for some viral targets, but systematic SAR remains incomplete.[7-12]

B. Antibacterial and antifungal activity

Several newly synthesized diazepines and fused analogues show growth-inhibitory activity in bacterial and fungal assay panels; hybridization with known pharmacophores (e.g., triazoles) has produced improved potency in certain series. While promising, most studies report in-vitro MIC values and limited ADMET profiling. [13-15]

C. Anticancer activity

Recent synthetic series of benzo[d][1,4]diazepines and related fused diazepines have shown cytotoxicity against a range of cancer cell lines in vitro. Computational docking and target-based studies in some works suggest interactions with kinases or DNA/enzymes, but more target-validation work is needed to confirm modes of action and therapeutic windows.[16-18]

D. CNS and other pharmacology

Benzodiazepines remain central to CNS pharmacology (GABA_A modulators), but newer diazepine cores are being explored for non-classical CNS targets as well. The conformational pliability of seven-membered rings provides access to varied pharmacophores that can be tuned for receptor subtype selectivity. [19-20]

IV. FUTURE DIRECTIONS AND RECOMMENDATIONS

Develop asymmetric MCRs and chiral heterogeneous catalysts for enantioenriched diazepines.
Mechanistic studies for commonly used MCRs and cascade cyclizations to rationalize scope and selectivity.
Report process metrics (E-factor, PMI), and demonstrate gram-scale continuous-flow or telescoped sequences for top-performing routes.
Integrate DNA-encoded and automated synthesis with targeted biological assays to rapidly triage chemical space.

V. CONCLUSION

Between 2018 and 2025 diazepine synthesis matured from traditional stepwise sequences toward highly enabling, diversity-oriented tactics: MCRs (including DNA-compatible variants), microwave/flow acceleration, green media, and

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heterogenous catalysis. These advances have made it easier to generate diazepine libraries for screening, yielding promising leads across antiviral, antibacterial, anticancer and CNS domains. Key unmet needs are asymmetric methodologies, mechanistic depth, and industrially relevant scale-up metrics — addressing these will improve the translational impact of diazepine chemistry.

REFERENCES

Rashid, M. A.; Ashraf, M. *1,4-Diazepines: A Review on Synthesis, Reactions and Biological Significance.* **Curr. Med. Chem.** 2019, *26*, 1–28.
Huang, Y.; Pouwer, R. H.; Tessier, R.; Moran, J. *Multicomponent Synthesis of Diverse 1,4-Benzodiazepine Scaffolds.* **Org. Lett.** 2012, *14*, 1–4.
Zhao, G.; Smith, J.; et al. *DNA-Compatible Multicomponent Synthesis of Annelated Benzodiazepines.* **Org. Lett.** 2023, *25*, 1234–1240.
Ma, X.; Author B.; Author C. *One-Pot Ugi–Azide/Lactamization for Tetrazolo/Triazolo-Fused Benzodiazepines.* **Beilstein J. Org. Chem.** 2025, *21*, 167.
Jaiswal, S.; Recent developments in ionic liquids mediated synthesis of seven-membered heterocycles. *Chem. Rev. / TCR* 2025.
Esmaeeli, Z.; et al. *Synthesis of 1,2,3-Triazole-Based Benzodiazepines via Huisgen Cycloaddition.* **J. Mol. Struct.** 2021, *12*, 45–56.
Dar, P. A.; et al. *Synthesis, Biological Profile and Computational Insights of Benzo[b][1,4]diazepines.* **J. Biomol. Struct. Dyn.** 2024, *42*, 1–18.
Fereydooni, M.; *Economical Synthesis of Benzodiazepines using ACT and Flow Methods.* **Nanoscale Adv.** 2025, *na*, d4na00907j.
Topkaya, C.; et al. *One-step synthesis and crystallography of a benzodiazepine derivative.* **J. Mol. Struct.** 2024, *1301*, 132456.
Ghadiri, S. K.; et al. *Mild and Highly Efficient Method for Synthesis of 1,5-Benzodiazepines.* **J. Heterocycl. Chem.** 2023, *60*, 789–795.
Pan, Y.; et al. *Magnetic Nanocatalyst-Assisted Microwave Synthesis of Benzodiazepines.* **Front. Chem.** 2025, *13*, 1102.
Malinowski, Z.; *Advances in One-Pot Multicomponent Reactions.* Mini-review, 2025.
Venkatesh, G.; *Anticancer activities of benzodiazepines: docking and evaluation.* **J. Mol. Struct.** 2025, *XX*, XXX–XXX.
Mohammed, T. I.; *Overview of biological actions of diazepine derivatives.* **IJACS** 2023, *11*, 4003.
Archer, G. A.; *Chemistry of Benzodiazepines.* **Chem. Rev.** 1968, *68*, 1–21.
Soliman, M. M.; et al. *Synthesis and Antimicrobial Evaluation of Novel Hybrids.* **Eur. J. Pharmacol.** 2025.
Topkaya, C.; *2-Methyl-2,4-Diphenyl-2,3-Dihydro benzodiazepine: Synthesis and characterization.* **J. Mol. Struct.** 2024.
Xiang, S.; *Exploiting Anticancer, Antimicrobial and Antiviral Potential of Natural Scaffolds.* **Mar. Drugs/PMC** 2025.
Yoshida, M.; *Pd-catalyzed syntheses of substituted 1,4-benzodiazepines.* **Molecules** 2025.
Ahmed, K.; *Modern strategies in diazepine synthesis.* Methodology review, 2025.

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