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A study of N-Heterocycles in Anticancer Drug Discovery from 2020-2024

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KEYWORDS

Nitrogen heterocycles; anticancer agents; indole; quinoline; triazole; medicinal chemistry.

ABSTRACT:

Nitrogen-containing heterocycles remain among the most productive scaffolds in anticancer drug discovery because they tune physicochemical properties, allow key hydrogen-bonding interactions, and support diverse modes of target engagement. Between 2020 and 2024 there was sustained medicinal-chemistry activity across classical scaffolds (indoles, quinolines/quinazolines, benzimidazoles, pyridines/pyrimidines, triazoles) and substantial clinical progress for KRAS-G12C inhibitors — small molecules built on heterocyclic cores — alongside many kinase and tubulin-targeting heterocycles advancing in trials. This study distils the 2020–2024 literature to illustrate scaffold-target pairings, SAR trends, recent approvals, and future directions.

1. Introduction

Nitrogen-containing heterocycles (N-heterocycles) occupy a central place in medicinal chemistry and oncology drug discovery. Their privileged status arises from unique physicochemical properties — tunable basicity, capacity for hydrogen bonding, and structural diversity — that allow fine control of target engagement, pharmacokinetics and bioavailability (Kumar, A. *et al*., 2023). Over the last decade N-heterocyclic scaffolds (pyridines, pyrimidines, indoles, imidazoles, triazoles, benzimidazoles, quinolines and related fused systems) have repeatedly furnished lead series and approved small-molecule anticancer agents, accounting for a large fraction of clinically useful kinase inhibitors, topoisomerase modulators and other targeted therapies (Kerru, N. *et al*.,2020) The period 2020–2024 has seen accelerated progress on several fronts that make a dedicated review timely. First, an appreciable number of new small-molecule oncology approvals and late-stage clinical candidates continue to feature N-aromatic heterocycles as core motifs, underscoring their clinical relevance and synthetic tractability. Structural analyses of recent FDA approvals show that nitrogen-aromatic heterocycles remain among the most common moieties in newly authorized small molecules, reflecting both design preference and success in translating heterocyclic chemistry into patient-facing therapies (Kumar, A. *et al*., 2023, Jha KT, *et al*., 2023)

Second, medicinal chemistry during 2020–2024 has diversified how N-heterocycles are used: beyond serving as simple pharmacophores, they are now engineered as hinge-binding motifs in kinase inhibitors, scaffolds for protein–protein interaction modulators, covalent warheads (in suitably substituted heterocycles), and linkers in targeted hybrid molecules (Luo W., *et al*., 2024). Structure–activity relationship (SAR) studies have refined substituent patterns and ring fusion strategies that optimize selectivity across kinase subfamilies, tubulin binding sites, epigenetic enzymes (HDACs, BET bromodomains) and DNA-interacting targets. Recent scaffold-focused reviews (for example quinolines and other fused N-heterocycles) highlight these target-directed design trends.

Third, advances in synthetic methodology and enabling chemistry — notably the wider adoption of reliable click-type couplings (CuAAC), C–H functionalization, flow chemistry and greener protocols — have dramatically expanded accessible chemical space around N-heterocyclic cores. These methodological gains accelerate SAR campaigns, fragment growing, and library generation, enabling faster iteration from concept

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to potent leads and facilitating scaffold hopping in programs targeting resistant or difficult oncogenic drivers.

Finally, the 2020–2024 window has produced abundant high-quality preclinical and mechanistic data for N-heterocycle-based series, including improved in vivo target engagement studies, crystal structures of heterocycle–protein complexes, and emerging clinical biomarker stratification strategies that increase the likelihood of translational success (Mo, X., *et al*., 2024). These developments collectively warrant a focused synthesis of progress, emphasizing scaffold classes, representative clinical candidates/approvals, SAR principles, synthetic advances, and outstanding challenges such as selectivity for mutant oncokinases, overcoming multidrug resistance and optimizing ADMET profiles.

This review study will therefore (i) summarize the major N-heterocyclic scaffolds exploited in anticancer agents since 2020, (ii) discuss notable FDA approvals and late-stage candidates that use these scaffolds, (iii) examine structure–activity and structure–function relationships across key target classes (kinases, tubulin, topoisomerases, epigenetic regulators), (iv) highlight enabling synthetic and fragment-based strategies that expanded scaffold space, and (v) identify gaps and future opportunities for N-heterocycle-driven oncology discovery.

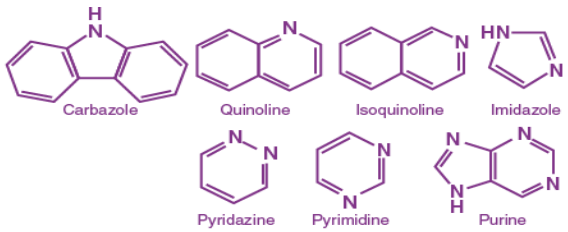

Figure 1: N-Heterocycles in Anticancer Drug

2. Overview of major N-heterocyclic scaffolds in oncology

2.1 Indole and fused indole systems

Indole is a privileged scaffold: widespread in kinase inhibitors, tubulin binders, and topoisomerase modulators. Recent reviews (2020–2024) describe extensive SAR and optimization campaigns for antiproliferative activity and improved selectivity. Representative recent syntheses, hybridization strategies and lead compounds are discussed (Mo, X *et al*., 2024).

2.2 Quinoline, quinazoline, and related aza-arenes

Quinoline/quinazoline scaffolds remain prominent kinase inhibitor cores (EGFR, CDKs, etc.). There has been focused work on kinase-directed quinoline derivatives and green synthetic methods to access functionalized quinolines. Recent reviews (2023–2024) highlight new quinoline kinase inhibitors and optimization strategies (U.S. Food and Drug Administration 2024).

2.3 Triazoles (1,2,3- and 1,2,4-)

Triazoles frequently act as bioisosteres and linkers in hybrid molecules; click chemistry enabled rapid assembly of triazole-linked conjugates with antiproliferative effects. Several reviews summarize 1,2,3- and 1,2,4-triazole anticancer hybrids and their mechanisms. (Alam, M. M. 2022).

2.4 Imidazoles, benzimidazoles and pyrazoles

These scaffolds often interact with nucleic acids or enzymes and are present in both small molecules and prodrugs; recent SAR studies show promise as inhibitors of multiple cancer-relevant enzymes (e.g., HDACs, kinases).

2.5 Pyridines, pyrimidines and fused aza-heterocycles

Pyrimidine cores are classic ATP-mimetic kinase inhibitor motifs (e.g., many targeted kinase drugs derive from pyrimidine cores); new fused heterocycles target diverse pathways including PARP, PI3K and more (Dhillon S. 2023).

3. Synthetic methodologies and strategies (2020–2024)

Emphasize click chemistry (triazole formation), multicomponent reactions, transition metal catalysis, and greener/flow/photoredox methods for assembling N-heterocycles. These methods accelerate analogue libraries and SAR exploration. All other methodologies mention in table number 1.

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Table no. 1: Methodologies

Year	Method (short)	Scaffold	Main advantages	Rreference
2024	Microwave-assisted & green one-pot routes	Indole	Fast, energy-efficient, improved yields; solvent reduction (green)	Almalki *et al*., review on green indole synthesis (2024).
2023	Modular two-step from o-haloanilines (Pd/Ni cross-coupling + cyclization)	Indole	High modularity (diverse substituents), scalable, good functional-group tolerance	J. Org. Chem. (Indole from o-haloanilines, 2023).
2024	Oxidative annulation / C–H activation (transition-metal catalyzed)	Quinolines	Direct C–H functionalization avoids prefunctionalization; atom-economical; amenable to late-stage functionalization	Liao *et al*., review on quinoline oxidative annulation (2025/2024 summary).
2024	Nanocatalyst-assisted Friedländer / oxidative protocols	Quinolines	Recyclable catalysts, milder conditions, improved selectivity; greener profile	Keri *et al*., nanocatalyzed quinoline protocols (2024).
2022–2024	Cu-catalyzed azide–alkyne cycloaddition (CuAAC, "click") & variant oxidative routes	1,2,3- and 1,2,4-Triazoles	Regioselective, high yields, tolerant to many functionalities; robust for library synthesis & drug-like libraries	Khandelwal (2024)
2023	Metal-free oxidative cyclization / acid-catalyzed condensations	Benzimidazole	Avoids transition-metals, simple workup, scalable, often one-pot from o-phenylenediamine + aldehyde	Chung *et al*., (2023).
2023	Heterogeneous & homogeneous catalysis (S-block, p-block, TM) for benzimidazoles	Benzimidazole	Broad catalyst choice for optimization; certain catalysts enable milder, greener processes	Choudhary review (2023).
2022–2024	Modified Hantzsch / multicomponent reactions (MCRs) & Biginelli adaptations	Pyrimidine derivatives	Convergent assembly (MCR) → high efficiency, structural diversity; good for rapid SAR exploration	Nammalwar *et al*., (2024).
2022	Biocatalysis / enzyme-enabled approaches for N-heterocycles	Various N-heterocycles	High chemo-/stereo-selectivity, mild conditions, greener, potential for late-stage functionalization	Feng *et al*., (2022).

4. Structure–Activity Relationships (SAR) and representative lead series

- Present short SAR summaries for each scaffold:

➔ Indoles: substitution at C-3 and N-1 often modulates tubulin or kinase activity; fused indoles improve planarity for DNA intercalation.

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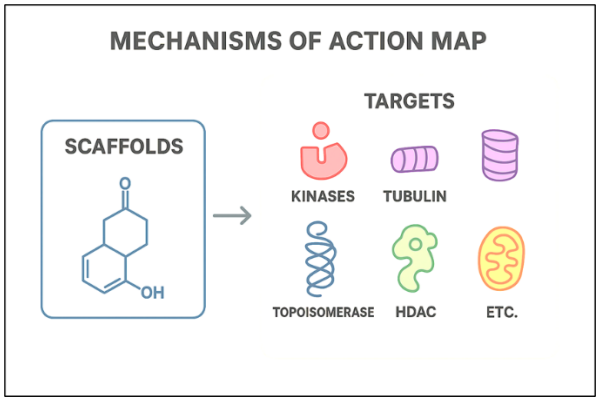
- ➔ Quinoline/quinazoline: hinge-binding substituents in kinase pockets; lipophilic tails and solubilizing groups tune pharmacokinetics.
- ➔ Triazoles: act as rigid linkers; substitution on adjacent rings controls target engagement.

5. Mechanisms of action and molecular targets

N-heterocycles act through multiple mechanisms: ATP-competitive kinase inhibition, microtubule destabilization, topoisomerase inhibition, DNA intercalation/alkylation, epigenetic enzyme inhibition (HDAC), and targeted degradation (PROTACs built with N-heterocyclic ligands). mentioned below figure 1.

Figure 2: Mechanisms of action map and molecular targets



6.Clinical progress and approvals (2020–2024)

Briefly summarize notable approvals and late-stage candidates that contain N-heterocycles (small molecules approved in 2023–2024 included several N-heterocyclic drugs). Emphasize translational challenges (toxicities, resistance) (U.S. Food and Drug Administration 2024).

7. Hybrid molecules, conjugates and emerging modalities

Triazole-based hybrids, heterocycle-linked PROTACs, antibody–drug conjugates (ADCs) with heterocyclic payloads—examples where heterocyclic motifs provide potency/selectivity and synthetic handles for conjugation. (Alam, M. M. 2022).

8. Challenges: selectivity, ADMET, resistance, and formulation

Off-target kinase activity, solubility limits for planar heterocycles, efflux transporter issues, and the emergence of resistance mutations. Discuss medicinal chemistry strategies (polar surface area tuning, prodrugs, covalent inhibitors, combination therapy) to overcome these.

9. Conclusion

Nitrogen-containing heterocycles continue to be central to anticancer drug discovery. Recent synthetic innovations, the rise of triazole-mediated conjugates, and renewed focus on kinase-directed quinolines and indole scaffolds have yielded promising preclinical candidates and clinical leads. Continued interdisciplinary work (synthetic chemistry, structural biology, pharmacology, AI) is needed to translate scaffold innovation into safer, more effective cancer therapies.

10. Authors' Contributions

JKT, SV, and VCD designed & planned manuscripts and carried out the work. Both authors were involved in scientific discussion and analysis of the data. Both authors read and approved the final manuscript.

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