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A Comprehensive Review on Bioactive Nitrogen-Containing Heterocyclic Compounds: Synthesis and Biological Applications

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Abstract
Nitrogen-containing heterocycles are the most prevalent structural class in small-molecule therapeutics. Structural surveys of United States Food and Drug Administration (FDA)-approved drugs show that 59% of unique small-molecule drugs approved up to 2012 contained a nitrogen heterocycle, a share that rose to 82% among drugs approved between 2013 and 2023. This review consolidates current knowledge on the synthesis and biological applications of the most important nitrogen heterocycles in medicinal chemistry: pyrimidines, imidazoles and benzimidazoles, pyrazoles, 1,2,3- and 1,2,4-triazoles, indoles, and quinolines and quinazolines. The physicochemical basis of their privileged status, including hydrogen-bonding capacity, tunable basicity, aromatic stacking and bioisosteric utility, is discussed first. Synthetic approaches are then surveyed, from classical condensation and cyclization chemistry to multicomponent reactions, copper-catalysed azide–alkyne cycloaddition, palladium-catalysed carbon–nitrogen cross-coupling, and microwave-assisted and green-chemistry methods. Biological applications are examined scaffold by scaffold and by therapeutic area, with emphasis on anticancer, antimicrobial, antiparasitic, anti-inflammatory and central nervous system activities, representative approved drugs, and recurring structure–activity relationship trends. Molecular hybridization, in which two pharmacophores are joined in a single molecule, is evaluated as a design strategy. Persistent challenges, including drug resistance, off-target toxicity, the gap between in vitro potency and in vivo efficacy, and the environmental cost of synthesis, are outlined together with future directions. The review is intended as a consolidated reference for synthetic and medicinal chemists working on nitrogen-heterocyclic drug discovery.

***Keywords**: Nitrogen heterocycles; Medicinal chemistry; Multicomponent reactions; Anticancer agents; Antimicrobial agents; Structure–activity relationship; Molecular hybridization*

1. Introduction

Heterocyclic compounds, cyclic molecules in which at least one ring atom is an element other than carbon, form the structural backbone of modern pharmacotherapy. Among them, nitrogen-containing heterocycles hold a dominant position. More than 85% of biologically active compounds are reported to be heterocycles or to contain a heterocyclic ring, with nitrogen heterocycles the most frequent framework.[1,2] A systematic analysis of FDA-approved pharmaceuticals found that 59% of unique small-molecule drugs approved up to 2012 contained at least one nitrogen heterocycle.[3] A follow-up analysis of 321 small-molecule drugs approved between January 2013 and December 2023 showed that this proportion had risen to 82%, accompanied by an increase in the number of nitrogen heterocycles per drug and a marked rise in fused nitrogen ring systems, driven largely by newly approved anticancer agents.[4]

The same analyses show that the pharmacopoeia is built from a relatively small set of recurring rings. Pyridine has overtaken piperidine as the most frequently occurring nitrogen heterocycle in recent approvals, while pyrimidine, pyrazole and morpholine have risen sharply in frequency.[4] An earlier survey of ring systems across marketed drugs similarly found that a limited number of rings recur widely and that genuinely new ring systems enter approved drugs only slowly.[5] This concentration on a few privileged scaffolds reflects both their favourable interactions with biological targets and the maturity of the synthetic chemistry available to build and decorate them.

Several reviews have covered individual scaffolds or narrow time windows.[2,6] The present review takes an integrated view. Section 2 sets out the physicochemical features that make nitrogen heterocycles privileged in drug design. Section 3 surveys synthetic strategies, from classical cyclocondensations to click chemistry, cross-coupling and green methods. Section 4 examines the major scaffolds individually, and Section 5 regroups their applications by therapeutic area. Section 6 assesses molecular hybridization as a design strategy, and Section 7 discusses current challenges and future directions.

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2. Physicochemical Basis of the Privileged Status of Nitrogen Heterocycles

The pharmacological value of nitrogen heterocycles stems from a combination of electronic and structural properties that few other ring classes offer together.

- **Hydrogen bonding.** Pyridine-type (sp^2 imine) nitrogens act as hydrogen-bond acceptors, while pyrrole-type N–H groups act as donors. Rings such as imidazole, pyrazole, benzimidazole and indole can therefore engage complementary residues in enzyme active sites and receptor pockets.
- **Tunable basicity.** Ring nitrogen basicity varies widely across scaffolds and can be modulated by substitution, allowing chemists to adjust ionization at physiological pH and, with it, solubility, permeability and target binding.
- **Aromatic stacking and planarity.** Planar heteroaromatic and fused systems such as quinoline, quinazoline and indole support π–π stacking with aromatic amino-acid side chains and intercalation-type interactions with nucleic acids.
- **Metal coordination.** Azole nitrogens coordinate metal ions; this is the basis of how imidazole and triazole antifungals bind the haem iron of fungal lanosterol 14α-demethylase.
- **Bioisosterism.** Heterocycles are widely used as bioisosteric replacements for labile or poorly behaved functional groups, for example tetrazoles for carboxylic acids and oxadiazoles or triazoles for amide bonds, to improve metabolic stability and pharmacokinetics while retaining target engagement.[7]

These properties also help drug candidates meet empirical guidelines for oral bioavailability. Lipinski's rule of five, which flags poor absorption or permeation when a molecule has more than five hydrogen-bond donors, more than ten hydrogen-bond acceptors, a molecular weight above 500 or a calculated log P above 5,[8] is easier to satisfy when compact heteroaromatic rings replace larger lipophilic carbocycles. Replacing a phenyl ring with pyridine or pyrimidine, for example, typically lowers lipophilicity and increases aqueous solubility, which is consistent with the rising frequency of these rings in recent approvals.[4]

3. Synthetic Strategies for Bioactive Nitrogen Heterocycles

Synthetic access determines which scaffolds can be explored at scale. Table 1 summarises the main strategic families discussed in this section.

Principal Synthetic Strategies for Bioactive Nitrogen Heterocycles

Strategy	Representative scaffolds	Key features	Refs.
Classical cyclocondensation (Fischer, hydrazine–dicarbonyl, Skraup/Friedländer, o-phenylenediamine condensation)	Indoles, pyrazoles, quinolines, benzimidazoles	Inexpensive starting materials; often harsh conditions; regioselectivity issues with unsymmetrical substrates	9
Multicomponent reactions (Biginelli, Hantzsch, Ugi, Groebke–Blackburn–Bienaymé)	Dihydropyrimidinones, dihydropyridines, fused imidazoles	One-pot; high atom economy; rapid library generation	10,11
Copper-catalysed azide–alkyne cycloaddition (CuAAC)	1,4-Disubstituted 1,2,3-triazoles; hybrids	Regiospecific; mild; high yields; modular linker chemistry	12–14
Pd-catalysed C–N cross-coupling (Buchwald–Hartwig)	Aminated pyrimidines, quinazolines, quinolines	Late-stage diversification; process-scale applicability	15
Microwave-assisted and green methods	Most azoles and azines	Shorter reaction times; reduced solvent and energy use	16,17

Table 1 *Principal Synthetic Strategies for Bioactive Nitrogen Heterocycles*

3.1 Classical Condensation and Cyclization Reactions

Much of heterocyclic chemistry still rests on named cyclocondensation reactions developed in the late nineteenth and early twentieth centuries. Indoles are classically prepared by the Fischer indole synthesis, the acid-catalysed rearrangement of arylhydrazones, alongside a large family of later methods that have been reviewed from the standpoint of practical, scalable synthesis.[9] Pyrazoles are commonly built by condensing hydrazines with 1,3-dicarbonyl compounds or

their equivalents. Benzimidazoles are typically obtained by condensing *o*-phenylenediamines with carboxylic acids, aldehydes or their derivatives. Quinolines are accessible through the Skraup, Doebner–Miller, Combes and Friedländer reactions, which construct the pyridine ring onto an aniline or 2-aminoaryl carbonyl precursor. These methods remain valuable because they use inexpensive starting materials, but they often require strong acids, high temperatures or long reaction times, and they can give regioisomeric mixtures with unsymmetrical substrates.

3.2 Multicomponent Reactions

Multicomponent reactions (MCRs) combine three or more starting materials in a single operation to give a product that incorporates most of their atoms. They are attractive for medicinal chemistry because they generate structural diversity rapidly, reduce purification steps and display high atom economy.[10] The Biginelli reaction, a three-component condensation of an aldehyde, a β-keto ester and urea, gives 3,4-dihydropyrimidin-2(1*H*)-ones, a scaffold that attracted renewed interest once its pharmacological potential, including calcium channel modulation, was recognised.[11] The Hantzsch dihydropyridine synthesis, isocyanide-based Ugi and Passerini reactions, and the Groebke–Blackburn–Bienaymé reaction for fused imidazoles are further MCRs widely used to build nitrogen-heterocyclic libraries.[10]

3.3 Click Chemistry: Azide–Alkyne Cycloaddition

Kolb, Finn and Sharpless[12] introduced "click chemistry" as a philosophy favouring modular, wide-scope, high-yielding reactions that run under simple conditions and generate only inoffensive by-products. The thermal Huisgen 1,3-dipolar cycloaddition of azides and alkynes is slow and gives mixtures of 1,4- and 1,5-disubstituted 1,2,3-triazoles. In 2002, two groups independently showed that copper(I) catalysis accelerates the reaction and makes it regiospecific for the 1,4-isomer.[13,14] The copper-catalysed azide–alkyne cycloaddition (CuAAC) has since become one of the most widely used reactions in medicinal chemistry and chemical biology; it delivers 1,2,3-triazoles in good to excellent yields, including on multigram scale.[18] Ruthenium catalysis provides complementary access to 1,5-disubstituted triazoles.[19] Because the triazole ring is both stable and able to participate in hydrogen bonding and dipole interactions, CuAAC is used not only to install a pharmacophore but also to link two pharmacophores into a hybrid molecule (Section 6).

3.4 Transition-Metal-Catalysed C–N Bond Formation

Palladium-catalysed carbon–nitrogen cross-coupling (Buchwald–Hartwig amination) allows aryl and heteroaryl halides to be coupled with amines and nitrogen heterocycles under comparatively mild conditions. Its applications span the synthesis of heterocycles, the late-stage functionalization of drug candidates and process-scale pharmaceutical manufacture.[15] In medicinal chemistry, the method is particularly important for attaching amine-bearing side chains to heteroaromatic cores such as pyrimidines, quinazolines and quinolines, a structural motif common to many kinase inhibitors.

3.5 Enabling Technologies and Green Synthesis

Controlled microwave heating can shorten reaction times from hours to minutes and frequently improves yields and product purity, which has made it a standard tool for heterocycle synthesis and library generation.[16] More broadly, the twelve principles of green chemistry, which call for waste prevention, atom economy, safer solvents and auxiliaries, energy efficiency and catalysis in place of stoichiometric reagents, provide a framework for evaluating heterocyclic syntheses.[17] Multicomponent and click reactions align well with these principles. Solvent-free conditions, aqueous media, recyclable heterogeneous and nanocatalysts, and ultrasound activation are increasingly reported for benzimidazole, pyrazole, triazole and quinoline synthesis, although claims of greenness should be supported by quantitative metrics such as atom economy or E-factor rather than asserted.

4. Major Bioactive Nitrogen-Heterocyclic Scaffolds

Figure 1 shows the core ring systems discussed below with their conventional atom numbering, which is used throughout for substitution positions. Table 2 lists representative approved drugs for each scaffold. The scaffolds are treated in order of increasing structural complexity, from monocyclic rings to fused bicyclic systems.

Figure 1

Core Nitrogen-Heterocyclic Scaffolds Discussed in This Review, With Conventional Ring Numbering

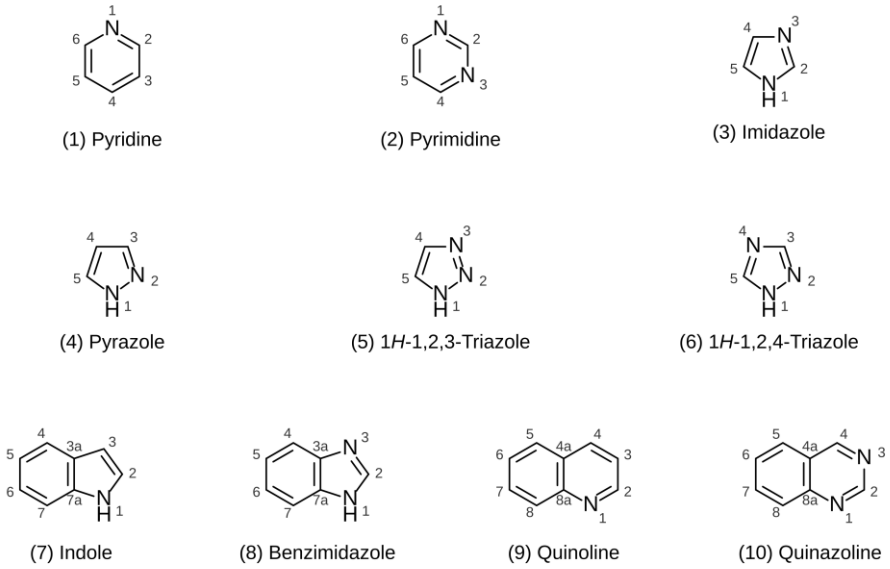


Table 2

Representative Approved Drugs Containing Major Nitrogen-Heterocyclic Scaffolds

Scaffold	Representative drugs	Principal therapeutic use
Pyrimidine	5-Fluorouracil; zidovudine; trimethoprim; imatinib	Anticancer; antiretroviral; antibacterial; kinase inhibitor (CML)
Imidazole	Ketoconazole; clotrimazole; metronidazole	Antifungal; antiprotozoal and anti-anaerobic
Benzimidazole	Albendazole; omeprazole; bendamustine	Anthelmintic; proton-pump inhibitor; anticancer
Pyrazole	Celecoxib; crizotinib	COX-2-selective anti-inflammatory; kinase inhibitor (lung cancer)
1,2,4-Triazole	Fluconazole; voriconazole; letrozole; anastrozole	Antifungal; aromatase inhibitor (breast cancer)
1,2,3-Triazole	Tazobactam; rufinamide	β-Lactamase inhibitor; antiepileptic
Indole	Indomethacin; sumatriptan; vincristine	Anti-inflammatory; antimigraine; anticancer
Quinoline / 4-quinolone	Chloroquine; mefloquine; ciprofloxacin	Antimalarial; antibacterial
Quinazoline	Gefitinib; erlotinib; prazosin	EGFR kinase inhibitor (lung cancer); antihypertensive

4.1 Pyrimidines

Pyrimidine, a six-membered ring with nitrogen atoms at positions 1 and 3, is the core of the nucleobases cytosine, thymine and uracil. This biological ubiquity underlies the success of pyrimidine antimetabolites such as 5-fluorouracil and nucleoside analogues such as zidovudine, which interfere with nucleic acid synthesis in cancer cells and viruses, respectively. Synthetic pyrimidine derivatives have been reported with anticancer, antimicrobial and anti-inflammatory activities, among others.[20] The 2-anilinopyrimidine motif is especially important in oncology. Imatinib, developed by rational optimization of a phenylaminopyrimidine lead to inhibit the BCR-ABL tyrosine kinase in chronic myeloid leukaemia, demonstrated the clinical potential of targeted kinase inhibition.[21] Pyrimidine was among the largest climbers in frequency among drugs approved from 2013 to 2023.[4]

4.2 Imidazoles and Benzimidazoles

Imidazole is a five-membered aromatic ring with two nitrogen atoms in a 1,3-relationship; it is present in histidine and histamine and is electron-rich, allowing imidazole derivatives to bind a wide range of enzymes and receptors through diverse non-covalent interactions.[22] Imidazole-based compounds have been explored as anticancer, antifungal, antibacterial, antitubercular, anti-inflammatory and antiviral agents. Clinically, azole antifungals such as ketoconazole and clotrimazole inhibit fungal ergosterol biosynthesis, and the nitroimidazole metronidazole is used against anaerobic bacteria and protozoa.

Benzimidazole, the benzo-fused analogue, forms part of the structure of vitamin B12 and structurally resembles naturally occurring biomolecules such as the purine bases.[23,24] Benzimidazole derivatives possess broad-spectrum pharmacological properties together with generally favourable bioavailability, safety and stability profiles,[23] and their antimicrobial potential has been reviewed in detail.[25] Approved examples include the anthelmintic albendazole, the proton-pump inhibitor omeprazole and the alkylating anticancer agent bendamustine. Structure–activity relationship (SAR) analyses organised by substitution pattern around the benzimidazole nucleus show that the nature and position of substituents largely determine potency and the type of activity observed.[24] Drug resistance and the cost of some synthetic routes remain obstacles to further development.[23]

4.3 Pyrazoles

Pyrazole is a five-membered ring with two adjacent nitrogen atoms. Pyrazole derivatives have been reported with a broad range of activities, including antimicrobial, anticancer and anti-inflammatory effects.[26,27] The 1,5-diarylpyrazole celecoxib, a selective cyclooxygenase-2 inhibitor, is the best-known pyrazole drug, and pyrazole is also present in kinase inhibitors such as crizotinib. Pyrazole was one of the fastest-rising heterocycles among drugs approved in 2013–2023.[4] Synthetic access is straightforward through hydrazine–dicarbonyl condensation and 1,3-dipolar cycloadditions, although control of regiochemistry with unsymmetrical substrates requires care.

4.4 Triazoles

Two triazole isomers are important in medicine. 1,2,4-Triazoles feature in the antifungals fluconazole and voriconazole, which coordinate the haem iron of fungal cytochrome P450-dependent lanosterol 14α-demethylase, and in the aromatase inhibitors letrozole and anastrozole used in hormone-receptor-positive breast cancer. 1,2,3-Triazoles, made readily accessible by CuAAC, are present in the β-lactamase inhibitor tazobactam and the antiepileptic rufinamide. The 1,2,3-triazole ring is metabolically robust, has a strong dipole moment, and can serve as a bioisostere of the amide bond[7]; its value as a pharmacophore in its own right is reviewed by Dheer et al.[18] Triazole-containing compounds and hybrids have been evaluated as anticancer, antimicrobial, antitubercular, antiviral, antidiabetic, antimalarial, antileishmanial and neuroprotective agents.[19]

4.5 Indoles

Indole, a benzene ring fused to pyrrole, is one of the most widespread heterocycles in natural products and biological systems. It is the core of the amino acid tryptophan and of the neurotransmitter serotonin, and it occurs in a very large number of alkaloids. Indole is regarded as a privileged scaffold because its derivatives bind with high affinity to many receptors and enzymes.[28] Synthetic and natural indoles have been reported with anticancer, anticonvulsant, antimicrobial, antitubercular, antimalarial, antiviral and antidiabetic activities.[28] Recent work has emphasised activity against drug-resistant cancer cells and pathogens and applications in metabolic and neurodegenerative disease.[29] Approved indole-containing drugs include the anti-inflammatory indomethacin, the antimigraine agent sumatriptan, and the bis-indole vinca alkaloid vincristine.

Quinazoline, the benzo-fused pyrimidine, is particularly prominent among kinase inhibitors. The 4-anilinoquinazolines gefitinib and erlotinib inhibit the epidermal growth factor receptor (EGFR) tyrosine kinase in non-small-cell lung cancer, and the quinazoline prazosin is an α1-adrenoceptor antagonist used in hypertension. Quinoline and quinazoline alkaloids together display antitumour, antimalarial, antibacterial, antifungal, antiparasitic, antiviral, antiplatelet and anti-inflammatory activities.[30]

5. Biological Applications by Therapeutic Area

5.1 Anticancer Agents

Oncology is the therapeutic area in which nitrogen heterocycles have had the greatest recent impact. The rise in fused nitrogen heterocycles among drugs approved from 2013 to 2023 has been attributed largely to newly approved anticancer agents.[4] The scaffolds represented among nitrogen-heterocyclic anticancer agents include pyrimidine, quinolone, carbazole, pyridine, imidazole, benzimidazole, triazole, β-lactam, indole, pyrazole, quinazoline and quinoxaline,[2] and their cellular targets span protein kinases, topoisomerases, tubulin and DNA. Protein kinase inhibitors exemplify this trend; the large majority of FDA-approved small-molecule kinase inhibitors are indicated for neoplastic disease, and their structures typically feature a heteroaromatic core, often a pyrimidine, quinazoline, pyrazole or fused pyrrolopyrimidine, that binds the ATP site of the kinase.

5.2 Antibacterial and Antifungal Agents

Antimicrobial resistance has made the discovery of new anti-infectives urgent. A systematic analysis estimated that bacterial antimicrobial resistance was associated with 4.95 million deaths in 2019 and was directly attributable for 1.27 million of them.[34] Nitrogen heterocycles are central to existing antibacterial and antifungal therapy: fluoroquinolones target bacterial DNA gyrase and topoisomerase IV, the diaminopyrimidine trimethoprim inhibits bacterial dihydrofolate reductase, and imidazole and triazole antifungals inhibit ergosterol biosynthesis. New benzimidazole,[25] indole,[29] pyrazole[27] and triazole[19] derivatives continue to be reported with antibacterial and antifungal activity. However, much of this literature reports only in vitro minimum inhibitory concentrations, and relatively few compounds progress to cytotoxicity, pharmacokinetic and in vivo efficacy evaluation.

5.3 Antiparasitic Agents

Quinolines have been the mainstay of antimalarial chemotherapy since quinine, but resistance in *Plasmodium falciparum* has eroded the efficacy of chloroquine and related agents, prompting the design of new quinolines and quinoline hybrids.[31] Benzimidazole carbamates such as albendazole remain first-line anthelmintics, and nitroimidazoles treat protozoal infections. Triazole and indole derivatives have also been evaluated against leishmanial and plasmodial parasites.[19,28]

5.4 Anti-inflammatory, Analgesic and Central Nervous System Agents

The pyrazole celecoxib and the indole indomethacin are established anti-inflammatory drugs, and pyrazole derivatives remain a rich source of anti-inflammatory and analgesic leads.[26,27] In the central nervous system, indole-based tryptamine analogues such as sumatriptan act on serotonin receptors, the 1,2,3-triazole rufinamide is used in epilepsy, and indole derivatives with anticonvulsant activity have been reported.[28]

5.5 Antiviral Agents

Pyrimidine and purine nucleoside analogues, exemplified by zidovudine, are the foundation of antiviral nucleoside therapy, and pyrimidine derivatives continue to be investigated as antiviral agents.[20] Indole and triazole derivatives have also shown antiviral activity in preclinical studies.[19,28]

6. Challenges and Future Perspectives

- **Resistance.** Resistance has eroded several heterocyclic drug classes, including quinoline antimalarials and azole antifungals. Designing compounds with new mechanisms, or hybrids that address resistance mechanisms directly, remains a priority.
- **Selectivity and toxicity.** Basic nitrogen heterocycles can carry off-target liabilities, and azoles can inhibit human cytochrome P450 enzymes, causing drug–drug interactions. Early, systematic profiling of selectivity and metabolic stability is essential.
- **From in vitro potency to in vivo efficacy.** Many reports describe in vitro activity alone. Progress requires standardised assays, appropriate reference drugs, cytotoxicity counter-screens and in vivo validation, together with transparent reporting of inactive compounds and negative results.
- **Sustainable synthesis.** Green methods should be benchmarked with quantitative metrics, and scalability should be demonstrated rather than assumed.[17]

- **Exploration of chemical space.** Because new ring systems enter approved drugs slowly,[5] underexplored heterocycles and new substitution patterns represent an opportunity. Computational tools, including structure-based design and machine-learning models trained on curated datasets, can help prioritise synthesis.

7. Conclusions

Nitrogen heterocycles have moved from being common to being nearly ubiquitous in new small-molecule drugs, with more than four in five drugs approved between 2013 and 2023 containing at least one.[4] Their success rests on a rare combination of hydrogen-bonding capacity, tunable basicity, aromatic stacking, metal coordination and bioisosteric versatility, supported by a mature and still expanding synthetic toolbox that now includes multicomponent reactions, click chemistry, palladium-catalysed C–N coupling and microwave-assisted and greener methods. Pyrimidines, imidazoles and benzimidazoles, pyrazoles, triazoles, indoles, and quinolines and quinazolines each contribute approved drugs across oncology, infectious disease, inflammation and neurology. Future progress will depend less on reporting further in vitro activities and more on rigorous pharmacological validation, early attention to selectivity and safety, sustainable and scalable synthesis, and the deliberate exploration of new heterocyclic chemical space.

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