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

REVIEW ARTICLE

A Review on the Role of Heterocyclic Scaffolds in Drug Discovery

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Publication history: Received on 2nd August 2025; Revised on 14th September 2025; Accepted on 18th September 2025

Article DOI: 10.69613/yj37ha36

Abstract: Heterocyclic compounds form the structural core of a vast majority of therapeutic agents. Certain heterocyclic motifs, designated as "privileged structures," show a significant capacity to bind with high affinity to diverse biological targets. This versatility is often attributed to their rigid, defined 3D architectures, which present the main pharmacophoric elements (e.g., hydrogen bond donors/acceptors, aromatic/hydrophobic regions) in pre-organized spatial arrangements. These arrangements are frequently complementary to binding sites within large protein families, such as G protein-coupled receptors (GPCRs), kinases, and ion channels. The identification of these compounds has profoundly influenced medicinal chemistry, serving as validated starting points for the design of compound libraries and facilitating the exploration of chemical space around biologically relevant scaffolds. The current perspective extends beyond simple promiscuity; the focus is now on utilizing these core structures as templates for lead optimization, where subtle modifications at specific vectors can steer binding affinity and selectivity toward a single, desired target while minimizing off-target interactions. This review studies the evolution of the privileged structure concept, highlighting examples and their impact, and details the strategic application of these scaffolds in fragment-based and structure-based design, showing their enduring utility in developing novel therapeutics.

Keywords: Heterocyclic Chemistry; Privileged Structures; Drug Discovery; Medicinal Chemistry; Pharmacophore

1. Introduction

The structural versatility of modern pharmaceuticals is overwhelmingly dominated by heterocyclic chemistry. Heterocycles, cyclic compounds containing at least one heteroatom (most commonly nitrogen, oxygen, or sulfur) within their ring system, are fundamental building blocks in medicinal chemistry. It is estimated that well over 80% of all small-molecule drugs approved by regulatory agencies incorporate at least one heterocyclic ring [1]. This prevalence is not coincidental; it arises from the unique and highly advantageous properties that these motifs impart to a molecule.

The functional importance of heterocycles is twofold, spanning both pharmacodynamic and pharmacokinetic properties. From a pharmacodynamic standpoint, heteroatoms and the ring systems they inhabit provide a rich array of functionalities. They can act as hydrogen bond donors or acceptors, serve as bioisosteric replacements for other groups, engage in pi-stacking or cation-pi interactions, and fix the conformation of flexible side chains [2]. These interactions are the basis of molecular recognition and are critical for high-affinity binding to biological targets like enzymes, receptors, and nucleic acids. Nature itself provides the blueprint, with heterocycles forming the core of essential biomolecules, including the nucleobases of DNA and RNA, the majority of vitamins (e.g., riboflavin, thiamine), and numerous alkaloids with potent biological activities [3].

From a pharmacokinetic perspective, the inclusion of heterocyclic rings is a primary strategy for modulating the absorption, distribution, metabolism, and excretion (ADME) profile of a drug candidate. Heteroatoms can introduce polarity, altering a compound's solubility and lipophilicity (LogP), which in turn governs its ability to permeate biological membranes [4]. Furthermore, specific heterocycles can be introduced to block sites of metabolic attack (e.g., by cytochrome P450 enzymes) or, conversely, to serve as a metabolically labile handle for controlled clearance, thereby fine-tuning the drug's half-life [5]. Within the vast universe of heterocycles, a specific subset has been identified and classified as "privileged structures." This term was first introduced by Evans and co-workers in 1988 to describe molecular scaffolds that are capable of providing high-affinity ligands for more than one type of biological target [6]. The seminal work centered on the 1,4-benzodiazepine scaffold, a motif famously associated with GABA-A

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receptor modulators like diazepam [7]. Evans demonstrated that this same scaffold could be repurposed, through divergent chemical modification, to produce a potent and selective cholecystokinin (CCK) receptor antagonist.

This discovery suggested that the benzodiazepine framework was not just a successful scaffold for one target but a "privileged" one that could be adapted to interact with distinct protein classes. The rationale posits that these scaffolds possess a defined three-dimensional geometry that mimics a common recognition motif, such as a peptide turn or a specific constellation of pharmacophoric points [8]. This pre-organization allows them to fit, with high affinity, into the binding sites of multiple proteins. This insight proved transformative for drug discovery, particularly during the rise of high-throughput screening and combinatorial chemistry. Instead of designing libraries based on random chemical structures, medicinal chemists could create "focused" libraries centered around these biologically-validated privileged cores, significantly increasing the hit rate for new biological targets [9].

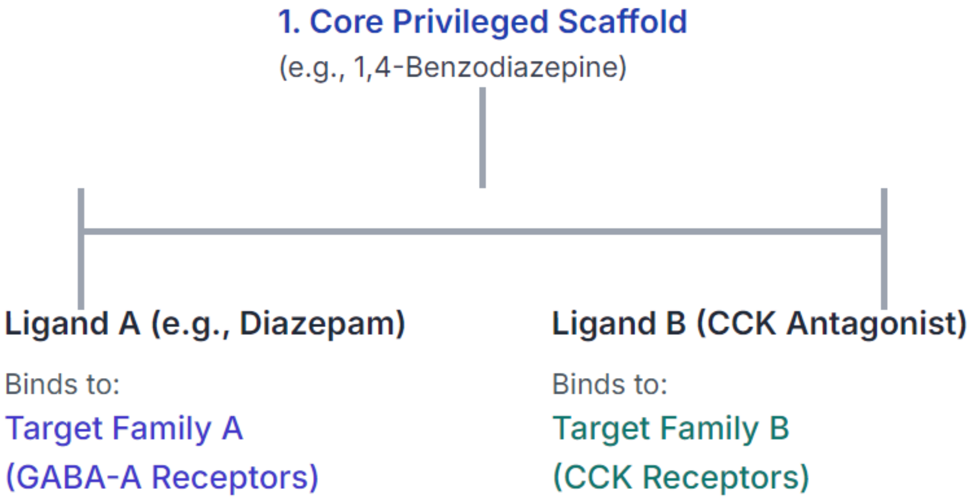


Figure 1. The Privileged Structure Concept

The subsequent sections provide a detailed survey of prominent heterocyclic classes that have achieved "privileged" status. The structural features that confer this versatility are analyzed, alongside case studies of their evolution from promiscuous binders to highly selective therapeutic agents. Moreover, the modern application of these motifs in contemporary drug design strategies, such as fragment-based lead discovery (FBLD) and structure-based design, is discussed, showing their persistent value in the generation of novel therapeutics.

2. Prominent Privileged Scaffolds in Medicinal Chemistry

The privileged structure concept has been validated by the recurrent appearance of specific heterocyclic cores across a multitude of drugs targeting diverse protein families. The following sections detail some of the most prominent examples.

2.1. The Benzodiazepine Scaffold

As mentioned, the 1,4-benzodiazepine seven-membered ring system is the canonical example of a privileged structure [6]. Its discovery as a potent cholecystokinin (CCK) antagonist, diverging from its classical role as a central nervous system (CNS) depressant (GABA-A modulator), was a paradigm shift. The structural basis for this versatility lies in its non-planar, conformationally constrained, yet flexible framework. This scaffold can display substituents in precise three-dimensional vectors that effectively mimic the spatial arrangement of amino acid side chains in peptide ligands, particularly β-turns [10]. This peptido-mimetic quality allows it to serve as a high-affinity ligand for various peptide receptors. For instance, modified benzodiazepine cores have yielded potent antagonists for vasopressin [11], farnesyltransferase [12], and tachykinin NK-2 receptors, validating its "privileged" status.

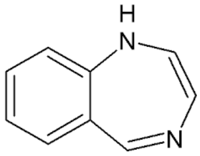
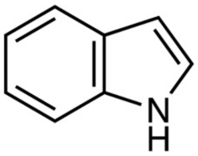
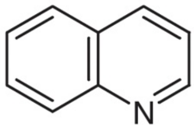
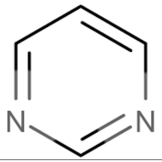
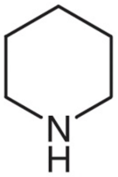
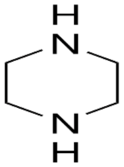
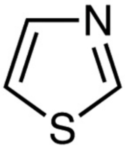
2.2. Nitrogen-Containing Aromatic Heterocycles

Nitrogen-based heterocycles are arguably the most significant class, given their role in hydrogen bonding, salt formation (modulating solubility), and pi-stacking interactions.

2.2.1. The Indole Nucleus

The indole scaffold is a quintessential privileged structure, present in the essential amino acid tryptophan and its derivatives, such as the neurotransmitter serotonin and the hormone melatonin [13]. This natural prevalence ensures that many biological targets have evolved to recognize and bind this motif. Consequently, indole-based compounds are abundant in medicine. Examples include the 5-HT receptor agonist sumatriptan for migraines, the non-steroidal anti-inflammatory drug (NSAID) indomethacin, and potent alkaloids like vincristine [14]. In modern oncology, the indole core is central to numerous protein kinase inhibitors. The 2-indolinone core of sunitinib, for example, forms hydrogen bonds within the ATP-binding hinge region of multiple receptor tyrosine kinases [15]. The indole's utility stems from the N-H group (a critical H-bond donor) and the aromatic surface (for pi-stacking and hydrophobic interactions), combined with multiple, synthetically accessible positions (e.g., C3, C5) for functionalization.

Table 1. Examples of Privileged Heterocyclic Scaffolds and Associated Therapeutic Classes

Scaffold	**Structure**	**Structural Features**	**Associated Therapeutic Classes**
1,4-Benzodiazepine		7-membered diazepine ring fused to benzene. Non-planar, β-turn mimetic.	Anxiolytics, Anticonvulsants, Receptor Antagonists (e.g., CCK)
Indole		5-membered pyrrole ring fused to benzene. Aromatic, H-bond donor (N-H).	Serotonin (5-HT) Agonists, Kinase Inhibitors, Anti-inflammatories
Quinoline		6-membered pyridine ring fused to benzene. Rigid, planar, basic nitrogen.	Antimalarials, Kinase Inhibitors (e.g., EGFR), Antibacterials
Pyrimidine		6-membered aromatic ring with two nitrogen atoms (1,3-diaza). H-bond acceptors, nucleobase mimic.	Kinase Inhibitors, Antivirals, Anticancer (Antimetabolites)
Piperidine		6-membered saturated ring with one nitrogen. Basic nitrogen (pKa ~8-11), defined 3D chair conformation.	CNS-active agents (Opioids, Antipsychotics), Antihistamines
Piperazine		6-membered saturated ring with two nitrogen atoms (1,4-diaza). Two vectors for substitution, modulates solubility/pKa.	Antihistamines, Antipsychotics, Kinase Inhibitors
Thiazole		5-membered aromatic ring with nitrogen and sulfur. Stable amide bioisostere, H-bond acceptor, metal chelation.	Antibiotics (Penicillins), Kinase Inhibitors, H2 Antagonists

2.2.2. The Quinoline and Isoquinoline Scaffolds

Quinoline, a fused bicyclic aromatic system, is another scaffold with a long history in medicine, originating with the antimalarial alkaloid quinine. This led to the development of synthetic analogs like chloroquine and mefloquine [16]. The scaffold's rigid, planar, and lipophilic nature, combined with the basicity of the ring nitrogen, makes it an effective pharmacophore. Its modern resurgence is seen in oncology, where the 4-anilinoquinoline scaffold is the basis for several kinase inhibitors, including gefitinib and lapatinib, which target the epidermal growth factor receptor (EGFR) [17]. The related isoquinoline core is similarly prevalent, found in the opioid morphine and the vasodilator papaverine.

2.2.3. The Pyrimidine and Purine Scaffolds

As the core components of nucleobases, the pyrimidine and purine scaffolds are inherently "privileged" for targets involved in nucleic acid metabolism and signaling. This has made them a cornerstone of antiviral (e.g., zidovudine) and anticancer chemotherapy (e.g., 5-fluorouracil, mercaptopurine) [18]. Beyond anti-metabolites, these scaffolds are recognized by protein kinases, which bind the purine core of ATP. This recognition has been exploited to an extraordinary degree. By decorating the purine or related pyrimidine rings with appropriate substituents, highly potent and selective kinase inhibitors have been developed. Imatinib, which targets the Bcr-Abl kinase, features a 4-(pyridin-3-yl)pyrimidin-2-amine core [19]. Similarly, the CDK4/6 inhibitor palbociclib is a pyrido[2,3-d]pyrimidine, demonstrating the power of these "kinase-privileged" frameworks [20].

2.3. Saturated Nitrogen Heterocycles

While aromatic systems are critical, saturated heterocycles play an equally important role, primarily by providing defined 3D geometry and a basic nitrogen center.

2.3.1. The Piperidine Moiety

The simple piperidine ring is one of the most frequently encountered heterocycles in CNS-active drugs. The basic nitrogen is typically protonated at physiological pH, allowing for a strong ionic interaction with acidic residues (e.g., aspartate) in receptor binding sites [21]. This motif is the core of the opioid analgesic fentanyl, the ADHD medication methylphenidate, and the antipsychotic haloperidol. The ring's chair conformation also serves to position substituents in defined axial and equatorial orientations, which is often critical for selective receptor engagement [22].

2.3.2. The Piperazine "Blockbuster" Motif

Piperazine, a six-membered ring with two nitrogen atoms, has been called a "blockbuster" scaffold due to its presence in an unusually high number of top-selling drugs [23]. Examples span multiple therapeutic classes, including the antidepressant vortioxetine, the antihistamine cetirizine, and the kinase inhibitor imatinib. The scaffold's advantages are numerous: (1) the two nitrogen atoms modulate pKa and solubility; (2) the N1 and N4 positions provide two distinct substitution vectors, allowing it to bridge two different pharmacophoric regions; and (3) it often imparts favorable ADME properties, including improved metabolic stability and reduced plasma protein binding [24].

2.4. Oxygen- and Sulfur-Containing Heterocycles

2.4.1. Benzofuran and Benzothiophene

The benzofuran and benzothiophene scaffolds are often employed as bioisosteres of indole. Replacing the indole N-H group with an oxygen (benzofuran) or sulfur (benzothiophene) atom removes a hydrogen bond donor capability while retaining the overall shape and aromaticity [25]. This substitution can be used to fine-tune electronic properties, lipophilicity, and metabolic stability. Benzofuran is found in the antiarrhythmic drug amiodarone and the antidepressant vilazodone [26]. Benzothiophene is the core of the selective estrogen receptor modulator (SERM) raloxifene and the antiasthmatic drug zileuton [27].

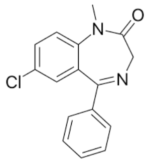
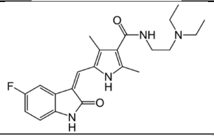
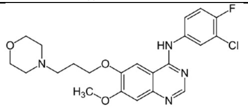
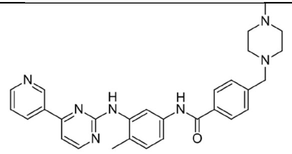
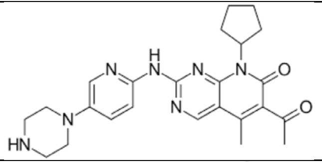
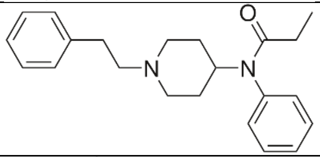
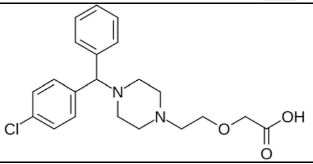
2.4.2. Azoles: Thiazole, Oxazole, and Imidazole

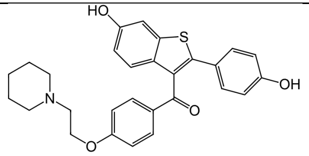
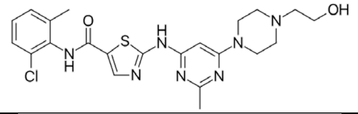
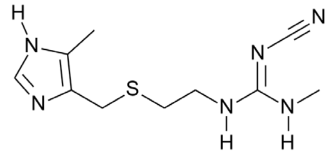
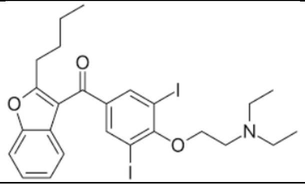
Five-membered azole rings are ubiquitous in medicinal chemistry, often acting as stable bioisosteric replacements for amide or ester groups, which are prone to hydrolysis [28]. The 1,3-thiazole ring, for instance, is the main component of vitamin B1 and the penicillin antibiotic backbone. It is now frequently used in kinase inhibitors like dasatinib [29]. Imidazole, present in the amino acid histidine, is a highly versatile scaffold. It can act as an H-bond donor, acceptor, or a base, and it is the mainligand for metal ions in metalloenzymes (e.g., in cytochrome P450). This functionality is exploited in drugs like the antifungal agent clotrimazole and the H2 receptor antagonist cimetidine [30].

Table 2. Common Heterocyclic Bioisosteres for Functional Groups.

Original Group	**Heterocyclic Bioisostere**	**Rationale and Common Effects**
Indole	Benzofuran, Benzothiophene	Removes H-bond donor (N-H). Modifies electronics, lipophilicity, and metabolic N-oxidation.
Amide (-CONH-)	1,3,4-Oxadiazole, 1,3-Thiazole	Improves metabolic stability (resists hydrolysis). Retains H-bond acceptor sites. Can alter conformation.
Ester (-COO-)	1,3,4-Oxadiazole, Furan	Improves metabolic stability (resists hydrolysis). Removes H-bond donor potential of hydrolyzed acid.
Carboxylic Acid (-COOH)	1H-Tetrazole	Maintains acidic pKa (~4-5). Increases metabolic stability. Increases lipophilicity vs. carboxylate anion.
Benzene Ring	Pyridine, Thiophene	Introduces H-bond acceptor (Py-N) or polarity (S). Modulates solubility, pKa, and blocks metabolism (e.g., *para*-hydroxylation).

Table 3. Selected Drug Examples from the Text, Their Heterocyclic Cores, and Targets.

Drug Name	**Structure**	**Heterocycle(s)**	**Primary Target / Mechanism**	**Therapeutic Area**
Diazepam		1,4-Benzodiazepine	GABA-A Receptor Modulator	Anxiolytic
Sunitinib		Indolinone, Pyrrole	Multi-Receptor Tyrosine Kinase (VEGFR, PDGFR) Inhibitor	Oncology
Gefitinib		Quinoline, Aniline	EGFR Tyrosine Kinase Inhibitor	Oncology
Imatinib		Pyrimidine, Piperazine	Bcr-Abl Kinase Inhibitor	Oncology (CML)
Palbociclib		Pyrido[2,3-d]pyrimidine	CDK4/6 Inhibitor	Oncology (Breast Cancer)
Fentanyl		Piperidine, Aniline	μ-Opioid Receptor Agonist	Analgesic
Cetirizine		Piperazine	Histamine H1 Receptor Antagonist	Antihistamine (Allergy)

Drug Name	Structure	Heterocycle(s)	Primary Target / Mechanism	Therapeutic Area
Raloxifene		Benzothiophene	Selective Estrogen Receptor Modulator (SERM)	Osteoporosis
Dasatinib		Thiazole, Pyrimidine	Multi-Kinase (BCR-ABL, Src) Inhibitor	Oncology
Cimetidine		Imidazole, Guanidine	Histamine H_2 Receptor Antagonist	Anti-ulcer
Amiodarone		Benzofuran	Potassium/Sodium Channel Blocker	Antiarrhythmic

3. Strategic Application of Privileged Scaffolds in Modern Drug Design

The identification of privileged structures has evolved from a retrospective classification to a proactive strategy in contemporary drug design. These validated motifs serve as high-quality starting points for lead generation campaigns, significantly enhancing the efficiency of discovery programs.

Table 4. Strategic Roles of Privileged Scaffolds in Modern Drug Design

Design Strategy	Principle	Role of the Privileged Scaffold
Focused Library Design	Synthesize a library of compounds around a "biologically-validated" core.	Serves as the central template, increasing the hit-rate of the library against specific target families (e.g., GPCRs, kinases).
Fragment-Based Lead Discovery (FBLD)	Identify low-molecular-weight fragments with high "ligand efficiency" and grow/link them.	Acts as an ideal "anchor fragment," providing the initial high-efficiency binding (e.g., hinge-binding) to build upon.
Structure-Based Drug Design (SBDD)	Use 3D protein structure to design high-affinity ligands.	Provides a known, rigid, and "bind-able" core that can be docked *in silico* as a starting point for designing novel substituents.
Scaffold Hopping	Replace a known ligand's core with a structurally novel, bioisosteric core.	Serves as the *new* replacement core. Used to generate novel IP, escape patent space, or improve ADME properties.

3.1. Exploiting Privileged Scaffolds in Fragment-Based Lead Discovery (FBLD)

Fragment-based lead discovery (FBLD) has emerged as a powerful engine for hit identification, focusing on screening low-molecular-weight compounds (typically < 300 Da) that bind with low affinity but high "ligand efficiency" [31]. Privileged heterocyclic scaffolds are often ideal fragments. By their very nature, they represent the minimal structural unit required for recognition by a protein family.

A heterocyclic fragment, such as an aminopyrimidine or an indazole, can form one or two key hydrogen-bonding interactions with a target, for example, in the hinge region of a protein kinase [32]. These fragments serve as "anchor points." Because they are already "biologically validated" and possess favorable physicochemical properties, they are superior starting points for optimization. The FBLD process then involves "growing" the fragment by adding substituents at its available vectors, or "linking" it to other fragments, to build up affinity and selectivity [33]. The use of a privileged core as the anchor fragment leverages the accumulated knowledge associated with that scaffold, accelerating the hit-to-lead process.

3.2. Structure-Based Drug Design (SBDD) and Scaffold Hopping

The vast repository of protein-ligand co-crystal structures, particularly for large families like kinases and GPCRs, has made structure-based drug design (SBDD) a central practice. Privileged structures are instrumental in this context. A known privileged core can be docked *in silico* into a new target's active site as a starting hypothesis for ligand design [34].

More powerfully, these scaffolds are central to the concept of "scaffold hopping." This strategy involves replacing the core of a known ligand (e.g., a patented competitor compound) with a bioisosteric, but structurally novel, heterocyclic system while retaining the original pharmacophoric display of the main substituents [35]. For example, a 1,4-benzodiazepine core might be replaced by a novel tricyclic furanopyrimidine that projects its substituents in the same 3D vectors. This search for novel, bioisosteric heterocycles is computationally intensive and relies on a deep knowledge of the geometric and electronic properties of different ring systems. This approach is highly valuable for generating novel intellectual property and improving the ADME properties of an existing lead series [36].

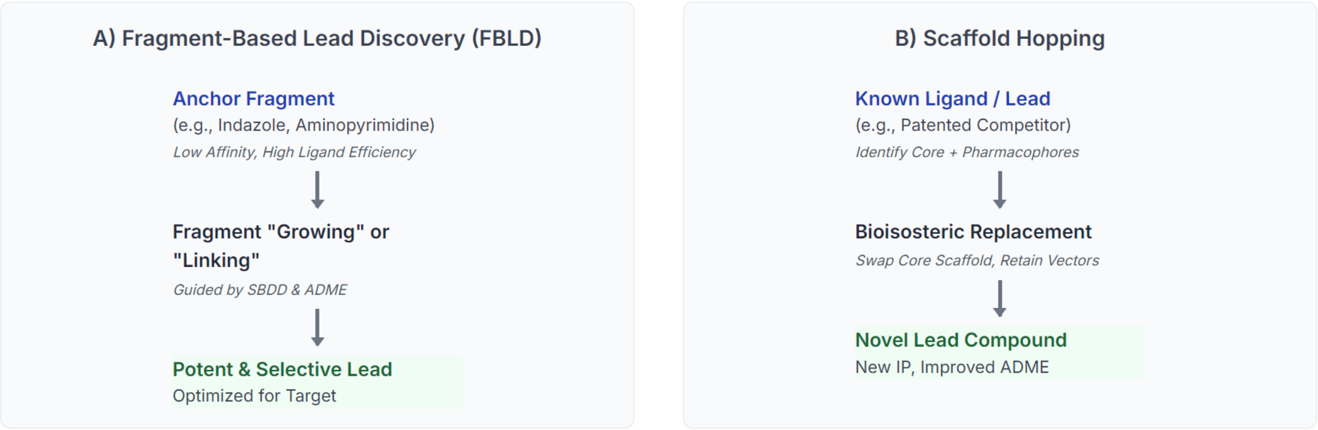


Figure 2. Modern Strategies for Scaffold Application in Drug Design

3.3. The Evolution to Selective Ligands

The original definition of a privileged structure centered on its "promiscuity"—the ability to bind multiple targets. While this is useful for library design, the ultimate goal of drug development is selectivity to avoid off-target toxicity. The modern perspective on privileged structures is therefore more nuanced. The scaffold is seen as a template for exploring "biologically relevant" chemical space, but selectivity is achieved by decorating the core at its specific exit vectors [37].

A single privileged core, such as a 2-aminopyrimidine, can be found in inhibitors of hundreds of different kinases. The scaffold itself provides the one or two anchor H-bonds to the hinge. Selectivity is dictated entirely by the substituents that occupy the adjacent hydrophobic pockets and solvent-exposed regions, which differ significantly between kinase family members [38]. Thus, the medicinal chemist does not seek a promiscuous drug, but rather uses a promiscuous *scaffold* as a starting point. Through iterative SBDD and chemical elaboration, the ligand is "steered" toward high-affinity and selective binding to a single, desired target. The "privilege" of the scaffold, in this context, is its inherent "bind-ability" and synthetic tractability, which provides a robust platform for optimization [39].

4. Conclusion

Heterocyclic scaffolds are, and will remain, the backbone of small-molecule therapeutics. The concept of "privileged structures," which began as an observation of recurrent motifs, has matured into a sophisticated design principle. These core molecules show evolutionarily conserved solutions for molecular recognition, offering pre-organized, 3D arrangements of pharmacophoric features that are highly complementary to the binding sites of major protein families. Their utility is no longer measured by their promiscuity, but by their value as "biologically-validated" starting points. In modern medicinal chemistry, privileged scaffolds serve as ideal fragments for FBLD, provide templates for structure-based design, and act as robust platforms for optimization. The challenge has shifted from simply *finding* ligands based on these cores to *engineering* them with exquisite selectivity. Medicinal chemists can more efficiently navigate complex chemical space and accelerate the development of safer, more effective medicines by leveraging these powerful templates. The continued discovery of novel heterocyclic ring systems, combined with advanced computational methods to predict their bioisosteric potential, ensures that this structural class will continue to be central to the future of drug discovery

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