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The Thin Line between Promiscuous and Privileged Structures in Medicinal Chemistry

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The concept of privileged structures in medicinal chemistry refers to commonly found substructures in approved drugs and lead small molecules, presenting a broad profile of pharmacological action, i.e., participating in the recognition by several classes of pharmacological targets or by modulating physicochemical properties. Privileged structures are also related to non-toxic effects, which make their use in the design of new drug candidates very attractive. In contrast, another concept also refers to structures or substructures capable of presenting a pleiotropic profile for several pharmacological targets, referred to as promiscuous compounds. Worth mentioning, more recently, a great majority of promiscuous compounds have been classified as Pan Assay Interference Compounds (PAINS). In its great majority, PAINS are electrophilic in nature, capable of covalently reacting indiscriminately with several pharmacological targets, and are associated with specific substructures, which are, in turn, used as an exclusion filter during screening campaigns. This work aims to critically discuss the thin line that separates the two concepts, clarifying their differences from a molecular and pharmacological point of view. Moreover, special considerations regarding PAINS and exclusion filters will be made.

Keywords: privileged structures, privileged scaffolds, frameworks, chemical promiscuity, PAINS

1. Introduction

Privileged structures and promiscuous compounds represent somewhat intriguing and contradictory phenomena in the field of medicinal chemistry, drawing substantial attention due to their significant impact on drug discovery and development. The concept of privileged structures, originally described in the seminal works of Evans *et al.*,[1,2] refers to specific molecular frameworks that are present in the structures of several bioactive small molecules and, consequently, possess a remarkable ability to exhibit diverse biological activities by interacting with multiple pharmacological targets. These privileged structures serve as valuable templates for medicinal chemists, offering a starting point for the design and synthesis of novel bioactive compounds or drug candidates.[3-5]

Concurrently and controversially, the notion of promiscuous compounds has garnered attention for its potential implications in drug development. Compounds that are promiscuous, similar to what is observed for privileged structures, have the unique trait of interacting with various biological targets. This extends their biological effects beyond the initially intended receptors. However, unlike privileged structures, promiscuous compounds are frequently associated with negative side effects and/or toxicity.[6-8]

Despite the intricate relationship between privileged structures and promiscuous compounds it is absolutely necessary to emphasize the nuances of their concepts and understand their roles in drug design and discovery processes.

In addition, it is important to highlight that the concept of promiscuity in medicinal chemistry has been shaped

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throughout the 21st century and its "definition" is also currently related to the concept of Pan Assay Interference Compounds (PAINS).[9]

The exploration of privileged structures and promiscuous compounds represents a dynamic and evolving frontier in medicinal chemistry. Through rigorous scientific inquiry and innovative approaches, researchers from both academia and industry strive to capitalize on the unique attributes of these molecular entities to advance the development of safer and more effective therapeutic innovations.[10-13]

This comprehensive review focuses on discussing and defining important concepts related to privileged structures and promiscuous compounds, bringing to light the fine line that separates the two. We hope that this work will assist in the critical understanding of these concepts in medicinal chemistry, avoiding their mistaken use.

2. Privileged Structures in Medicinal Chemistry

2.1. Classic privileged structures

In this section, classic privileged structures will be highlighted and discussed. These type of privileged structures and scaffolds are understood as those standard motifs deeply exploited and discussed by the medicinal chemistry community.

The classical privileged structures, as elucidated in prior studies, are inherently linked to well-established findings that highlight their notable biological activities. These structures or substructures serve as valuable starting points in the quest for the discovery of novel drugs. Their selection is grounded in the precise understanding of their interaction capabilities with biological targets, thereby enhancing the efficiency of drug discovery and development processes.[3,14]

The 7-azaindole scaffold is considered a privileged structure in medicinal chemistry and has garnered significant attention due to its special physicochemical and pharmacological properties.[15] The ability of nitrogen atoms in the 7-azaindole core to form hydrogen bonds with the hinge region in the adenosine triphosphate (ATP) binding site makes 7-azaindole derivatives crucial sources for kinase inhibitor design.[16]

To date, some 7-azaindole derivatives have been marketed or undergone clinical trials for the treatment of kinase-associated diseases. Vemurafenib (**1**), a serine/threonine-protein kinase B-raf (BRAF) inhibitor was the first U.S. Food and Drug Administration (FDA)-approved drug based on 7-azaindole for the treatment of BRAF-mutated metastatic melanoma (Figure 1).[17] Another example is pexidartinib (**2**), a tyrosine kinase inhibitor selectively targeting colony-stimulating factor 1 receptor (CSF1R), FDA approved in 2019 and available in the market for treating giant cell tumors of the tendon sheath in adult patients (Figure 1).[18] Additionally, decernotinib (**3**), a Janus Kinase 3 (JACK3) inhibitor, has been the subject of clinical trials for the treatment of rheumatoid arthritis (Figure 1).[19]

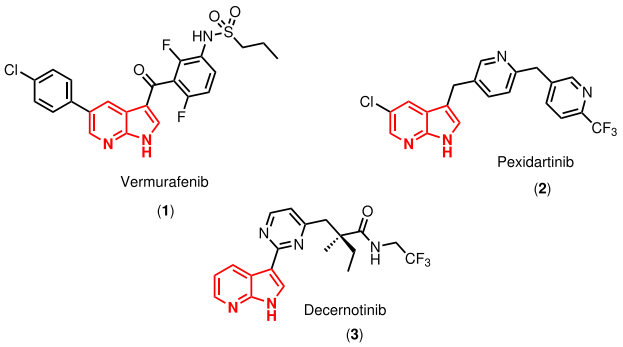


Figure 1. 7-Azaindole-based kinase inhibitors in clinical use or under clinical trial studies.

Most kinase inhibitors are designed to interact with the hinge region, acting as competitive inhibitors with respect to adenosine triphosphate (ATP).[20] Among azaindole-derived kinase inhibitors, three different binding modes with kinases can be observed. The "normal" mode, where the azaindole scaffold binds to the hinge; the "inverted" mode, in which the azaindole binds in the opposite direction at a 180° angle compared to the normal mode; and finally, the "non-hinge" mode, where the azaindole binds to a distinct site away from the hinge region (Figure 2). In the "normal" and "inverted" binding modes, the azaindole subunit can form two hydrogen bonds with amino acid residues in the hinge region. In the "normal" mode, azaindole interacts with GK+1 (adjacent to the gatekeeper amino acid residue) and GK+3 residues through bidentate hydrogen bonds (Figure 2). On the other hand, in the "inverted" binding mode, bidentate hydrogen bonds occur between azaindole and the GK+3 residue (Figure 2).[16,21]

The imidazoles hold a distinctive position in the field of heterocyclic chemistry. Due to their versatile properties in the realms of chemistry and pharmacology, their derivatives have been the focus of interest, as they play a significant role in both biological and pharmaceutical contexts.[22]

In biological systems, imidazole constitutes the main structure of various naturally occurring compounds, such as the amino acid histidine (**4**), the nitrogenous bases guanine (**5**) and adenosine in nucleic acids (**6**), the neurotransmitter histamine (**7**) (Figure 3).[22,23]

The presence of the imidazole nucleus can be observed in a wide variety of chemical compounds of pharmaceutical interest, whether they are of natural or synthetic origin. It presents a classic tautomeric behavior between nitrogen

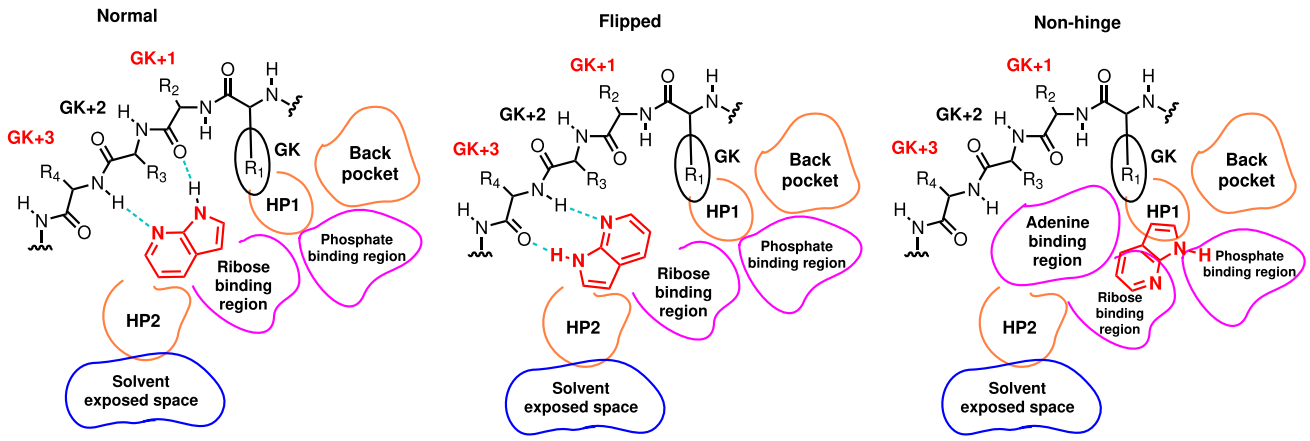


Figure 2. Different interaction modes of privileged azaindole subunit with kinase active binding site.

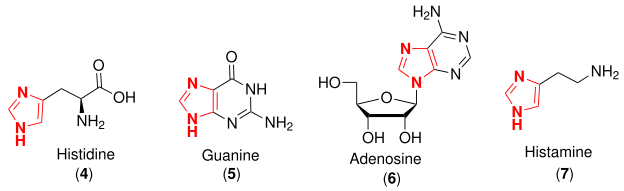


Figure 3. Presence of imidazole in different bioactive natural compounds.

atoms N1 and N3 of the heterocyclic ring that favors its molecular recognition by different receptors. For this reason, imidazole derivatives exhibit a broad spectrum of biological activities, including antibacterial, anticancer, anti-inflammatory, antifungal, antimalarial, antitubercular, and many others.[22-24] Among natural compounds, one example is topsentin (**8**), which exhibits antiviral, antifungal, anticancer, and anti-inflammatory activities (Figure 4).[25] Isonaamine A (**9**) demonstrates anticancer activity by acting as an inhibitor of the epidermal growth factor receptor (EGFR) (Figure 4).[26] Additionally, pilocarpine (**10**) is utilized in the management and treatment of xerostomia and glaucoma (Figure 4).[27]

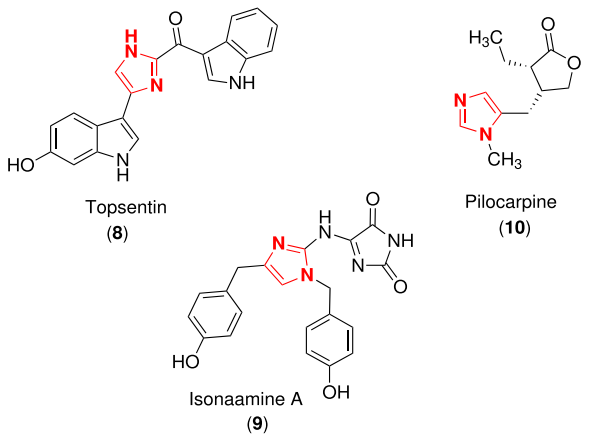


Figure 4. Examples of natural products containing the privileged imidazole ring.

Additionally, there are several drugs containing the imidazole nucleus currently available in the market, such as losartan (**11**) an angiotensin II receptor agonist that is used as an antihypertensive agent.[28] In the structure of losartan (**11**, Figure 5), various pharmacophoric groups play crucial roles in interacting with the angiotensin II (Ang II) receptor. The imidazole heterocycle and the *N*-butyl side chain mimic the His6 and Ile5 side chains of the *C*-terminal region of angiotensin II. Additionally, the tetrazole ring in its structure interacts with the Asp1 and Tyr4 residues of the *N*-terminal region of Ang II, contributing to its pharmacological activity.[29]

Ketoconazole (**12**, Figure 5), an antifungal drug, competitively inhibits sterol 14-α-demethylase (CYP51), a key enzyme in catalyzing the process of oxidative removal of 14-α-methyl during the biosynthesis of ergosterol, the main sterol in fungal membranes.[30] Ketoconazole, like other ergosterol biosynthesis inhibitors in the azole class, has four interaction sites with the CYP51 enzyme. The nitrogen atom in the imidazole ring of ketoconazole at site 1 complexes with the iron of the heme group present in the target enzyme, blocking binding with molecular oxygen. At site 2, oxygen acts as a hydrogen bond acceptor, and the structures at sites 3 and 4 interact with the hydrophobic part of the CYP51 enzyme.[30]

Cimetidine (**13**, Figure 5) is an H_2 receptor antagonist that completely blocks the stimulation of H_2 receptors located in gastric parietal cells by histamine (**7**). Cimetidine's structure is based on the histamine (**7**) prototype, the natural agonist. Due to the imidazole's nature, tautomerism can be observed, influencing molecular recognition by different histamine receptor subtypes (H_1 and H_2). The imidazole ring in cimetidine (**13**) has a methyl group at C-5, contributing to the tautomeric form essential for the desired selectivity for H_2 receptors. The presence of the thioether group on the side chain of its structure provides desirable hydrophobic

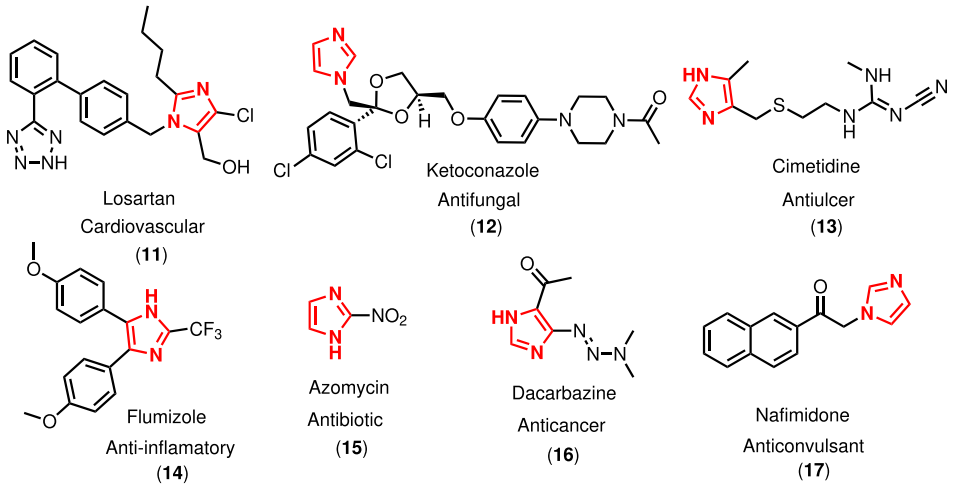


Figure 5. Structure of drugs on market containing privileged imidazole ring.

properties and contributes to inhibiting the tautomeric balance of the heterocyclic ring.[31]

Other interesting examples of drugs containing the privileged imidazole ring include flumizole (**14**, Figure 5)[32] a non-steroidal anti-inflammatory that inhibits the enzyme cyclooxygenase (COX), azomycin (**15**, Figure 5),[33] which has antibiotic activity against Gram-positive bacteria, dacarbazine (**16**, Figure 5),[34] an anticancer agent whose mechanism of action is not very well established, but the main hypothesis is that it inhibits deoxyribonucleic acid (DNA) synthesis as an analog of purines, nafimidone (**17**, Figure 5),[35] an anticonvulsant which, like its metabolite, is capable of inhibiting the main metabolism pathways of important antiepileptic drugs such as phenytoin and carbamazepine and others.

Another heterocycle of extreme importance for medicinal chemists is benzimidazole. This privileged scaffold represents fundamental structures found in diverse libraries of therapeutically relevant agents used in medical research and drug discovery campaigns. Benzimidazole stands out among heterocyclic compounds due to its remarkable biological actions and synthetic applications in medicinal chemistry, serving as an essential building block for the synthesis of a wide range of bioactive compounds.[36,37]

The core benzimidazole nucleus is present in several well-known drugs in current pharmacotherapy for both humans and animals. Among the benzimidazole-containing compounds are omeprazole (**18**), which has anti-inflammatory activity, and interrupts gastric acid secretion by selectively inhibiting the H^+/K^+ ATPase enzyme system; albendazole (**19**), an anthelmintic that acts by inhibiting tubulin polymerization, it also impairs glucose utilization and reduces the parasite's glycogen reserves, which results in decreased ATP production, leading to energy depletion and the subsequent death of the parasite. There is also rabeprazole (**20**), an anti-ulcer drug that also acts by inhibiting the proton pump in gastric parietal cells (H^+/K^+- ATPase), resulting in inhibition of gastric acid production; telmisartan (**21**) an antihypertensive agent; capable of blocking the vasoconstrictive and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to AT1; benomyl (**22**), an antifungal agent that promotes the depolymerization of microtubules; and bendamustine (**23**), a drug with anticancer activity that activates the stress response by damaging DNA, induces apoptosis, inhibits mitotic checkpoints and induces mitotic catastrophe (Figure 6).[38,39]

N-Acylhydrazone (NAH) frameworks are considered privileged structures in medicinal chemistry. This versatile peptidemimetic subunit presents remarkable chemical stability against hydrolysis, the ability to perform putative interactions with different receptors, and synthetic accessibility, facilitating rational modifications during the structural optimization of a lead compound. Such modifications enable the generation of compounds that exhibit affinity and selectivity toward specific pharmacological targets.[3]

Despite significant advances in the last decade in the discovery of small-sized NAH-based drugs, only a few NAHs have received clinical approval. Among these drugs, nitrofurazone (**24**) and nitrofurantoin (**25**), belonging to the chemical class associated with NAHs, namely semicarbazones, were the first compounds approved for clinical use (Figure 7). Both derivatives were approved for the treatment of bacterial infections. Nitrofurazone (**24**) is used topically and its mechanism of action is the inactivation of ribosomal proteins, which inhibits the synthesis of proteins, DNA, ribonucleic acids (RNA), and cell wall synthesis, blocking the aerobic metabolism of bacterial cells.[40] Nitrofurantoin (**25**) is administered orally for treating genitourinary tract infections and is reduced by

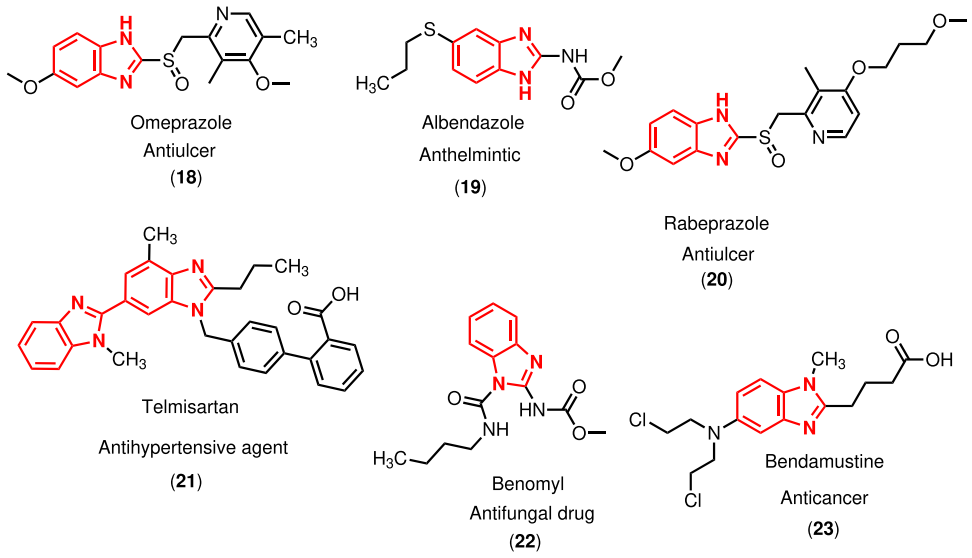


Figure 6. Examples of benzimidazole-containing drugs.

bacterial flavoproteins which generate reactive intermediates that inhibit protein synthesis, aerobic energy metabolism, DNA, RNA, and cell wall synthesis.[41] Another approved drug associated with semicarbazones, carbazochrome (**26**), is used as a hemostatic agent and it is indicated for capillary and parenchymal bleeding. It increases platelet aggregation and forms a platelet buffer by interacting with α-adrenergic receptors on the surface of platelets (Figure 7). The sodium salt of dantrolene (**27**) and its azumolene (**28**) sodium salt analog are also NAH-derived drugs, both approved for treating malignant hyperthermia (MH) and act directly on the contractile mechanism of skeletal muscle, reducing the force of contraction, without showing any effects on neural pathways, the neuromuscular junction or the excitable properties of muscle fiber membranes (Figure 7).[42-44]

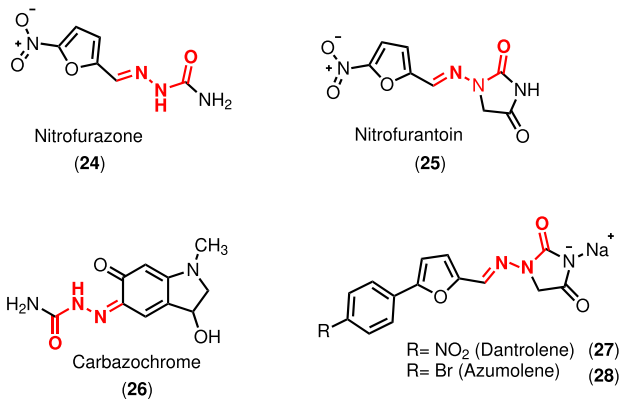


Figure 7. Structure of some approved drugs presenting the NAH privileged framework.

Despite only a few of the drugs and drug candidates containing NAH showed significant advances in the pre-clinical stage in recent years, promising lead compounds derived from NAH are documented in the literature. Among these, it is worth highlighting the compound LASSBio-294 (**29**, Figure 8), which targets the molecular adenosine A2A receptor and has demonstrated selective binding. This NAH derivative was designed for the treatment of heart failure, exhibiting *in vitro* and *in vivo* positive inotropic activity and moderate vasodilation.[45,46]

From this compound (**29**), other NAH analogs have been obtained. Its thiophene regioisomer (**30**) and the *N*-methylated analog (**31**) exhibited a more significant vasodilatory effect. The pharmacological properties of compound **30** appear to be associated with the agonism of muscarinic M3 receptors, while the *N*-methylated analog (**31**) acts as a blocker of Ca^{2+} channel types.[47-49]

Compounds derived from quinolines possess various intriguing properties and find applications in diverse fields, including medicinal chemistry. In this domain, quinolines are deemed privileged structures due to their particular capability to be recognized by distinct biotargets, rendering them pertinent in drug discovery process.[50,51]

The presence of quinoline as a structural constituent can be observed in various compounds, both natural and synthetic, exhibiting a wide range of biological activity. These compounds display diverse pharmacological properties such as analgesic, antibacterial, anti-inflammatory, anticancer, anticonvulsant, and others.[52]

It is known that drugs containing the quinoline ring find broad therapeutic applications in the pharmaceutical domain. Chloroquine (**32**, Figure 9), a commercially available antimalarial, features this subunit. This drug interferes with the parasite's digestion of hemoglobin, so chloroquine accumulates in the digestive vacuole of the parasite, compromising hemoglobin digestion and

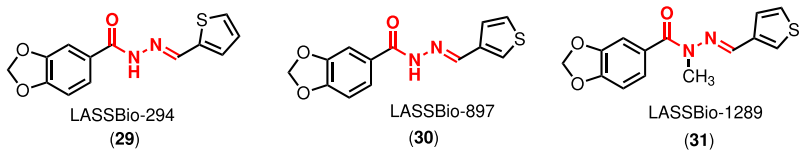


Figure 8. Lead compounds containing NAH framework.

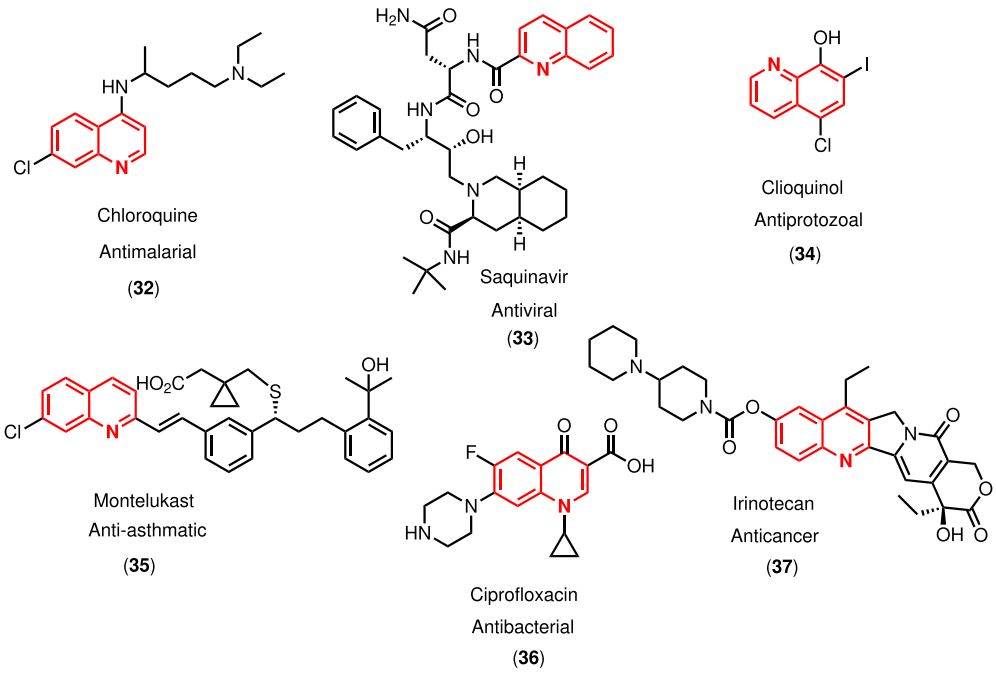


Figure 9. Examples of drugs containing the privileged quinoline ring.

leading to its death. The quinoline ring is important for antimalarial activity and enables chloroquine to inhibit the polymerization of the heme group, a toxic by-product of the parasite's digestion of hemoglobin. By preventing the crystallization of hemozoin from the heme group, chloroquine contributes to the death of the parasite.[53] Besides this drug, there are others such as the antiviral saquinavir (**33**), which acts by blocking a protease enzyme that is necessary for the reproduction of human immunodeficiency virus (HIV). Saquinavir is a competitive peptidomimetic inhibitor that mimics the natural substrate of the viral protease. The quinoline ring present in its structure almost entirely occupies the protease enzyme pocket, helping to inhibit HIV-1 protease activity.[54] The antiprotozoal clioquinol (**34**) can inhibit the activity of enzymes essential for the metabolism of the protozoan resulting in metabolic dysfunction and cell death. The 8-hydroxyquinoline group present in the clioquinol (**34**) structure has both antiprotozoal and antibacterial actions. The presence of the nitrogen atom in the quinoline ring allows this compound to have the chelating properties necessary for inhibiting bacterial biofilms.[55] The antiasthmatic montelukast (**35**) is a selective leukotriene receptor antagonist that inhibits the CysLT1 (cysteine leukotriene) receptor. The quinoline group of montelukast interacts with the hydrophobic region of the CysLT1 receptor binding site and is therefore essential for its activity as it prevents leukotrienes from binding to and activating the receptor, thus blocking the inflammatory and bronchoconstrictive effects mediated by leukotrienes.[56] The antibacterial ciprofloxacin (**36**) which inhibits bacterial topoisomerase type II and topoisomerase IV, which are essential for replication, transcription, repair, and recombination of bacterial DNA. Quinolones, derived from the quinoline nucleus present in ciprofloxacin, bind non-covalently to the enzyme-DNA interface at the active cleavage-binding site, increasing the concentration of enzyme-DNA cleavage complexes.[57] The anticancer drug irinotecan (**37**) also interacts with topoisomerase I, an important enzyme in the cell multiplication process (Figure 9).[52]

The basic structure of benzoxazine can be modified to generate various compounds, each with specific properties. This versatility makes benzoxazine intriguing for chemical synthesis, particularly in the production of compounds with potential biological or pharmacological properties, underscoring its significance in the research and development of new drugs.[58]

In this context, there is a variety of bioactive compounds containing benzoxazine that exhibit diverse pharmacological activities such as anticancer activity, antibacterial effects, antifungal properties, and antituberculosis potential.[58] Among the drugs containing benzoxazine are apararenone (**38**),[59] a non-steroidal mineralocorticoid receptor antagonist under development for the treatment of diabetic nephropathies and non-alcoholic steatohepatitis. In its structure, the sulfonamide group acts as a hydrogen donor/acceptor with Asn770, the fluorophenyl group is directed towards a hydrophobic pocket interacting with Met852 while the heterocyclic benzoxazine ring acts as a linker thus allowing important interactions in the mineralocorticoid receptor (MR) binding pocket.[60] Elbasvir (**39**), an approved drug for the treatment of hepatitis C that inhibits NS5A, a protein essential for the replication of the hepatitis C virus (HCV) (Figure 10),[61] and etifoxine (**40**), a non-benzodiazepine anxiolytic agent indicated for short-term treatment of adjustment disorder. This drug produces its anxiolytic effects by activating the channels containing the β2 and β3 subunits of the GABA-A receptor complex.[62]

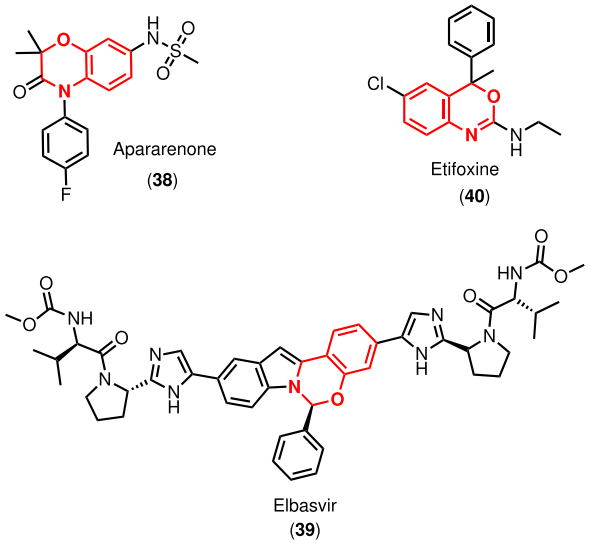


Figure 10. Bioactive compounds featuring the privileged benzoxazine scaffold.

2.2. Emerging privileged structures

It is important to note that several emerging privileged scaffolds have been highlighted in scientific literature and reviewed elsewhere. These include benzoxazine derivatives,[58] chromones,[63] aporphines,[64] indol-3-ylglyoxylamides,[65] thiazolidinediones,[66] 1,3-diazepines,[67] and benzopyrans.[68] Additionally, some works focus on specific therapeutic classes instead of a single privileged structure, such as those targeting bromodomain,[69] antiviral agents,[4] and others. This section will focus on emerging privileged structures that the authors believe deserve more detailed and special attention due to their increasing applicability in drug discovery: covalent warheads and privileged structures for the design of Proteolysis Targeting Chimeras (PROTACs).

2.2.1. Emerging privileged covalent warheads

The discovery and development of covalent warheads is a hot topic in medicinal chemistry, especially regarding kinase inhibition. In this context, certain covalent warheads have recently (from 2010 to 2023) emerged as privileged structures, resulting in the discovery of small molecule kinase inhibitors with improved efficacy.

From a historical perspective, kinases emerged in the 1980s as highly coveted targets for pharmacological interventions. During that time, the feasibility of developing competitive inhibitors targeting the ATP binding site, considering selectivity among different kinases, sparked substantial debates in the scientific community.[70] This approach was considered a challenging barrier, given the remarkable conservation of the ATP binding site among the kinome. The year 1995 witnessed a significant milestone with the approval of fasudil (**41**) in Japan (Figure 11), representing the pioneering small-molecule kinase inhibitor aimed at ROCK1 and ROCK2 to alleviate cerebral vasospasm.[70] Four years later, sirolimus (rapamycin) (**42**), a natural product, secured its position as the first kinase inhibitor to receive FDA approval.[71] Employed in organ transplant rejection prevention, sirolimus (**42**) (Figure 11) targets its mammalian target, mTOR,[72] gaining prominence for its implication in various disease stages.[73] In 2001, imatinib (**43**) (Figure 11) made history as the first synthetic kinase inhibitor to receive FDA approval.[74] These advancements signify remarkable achievements in understanding and manipulating kinases, paving the way for the development of more effective therapies across various medical conditions. These three non-covalent drugs represent historical landmarks that have underpinned and propelled the discovery of new protein kinase inhibitors (PKI), culminating in the current pursuit of covalent inhibitors.

Kinase inhibitors are classified into several categories (type 1, 1.5, 2, 3, 4, 5 and 6).[75,76] Kinases with the Asp-Phe-Gly (DFG)-in motif and the α*C*-in conformation (active state) are inhibited by type 1 inhibitors at the ATP site. At the ATP site, type 2 inhibitors inhibit kinases with the DFG-out conformation and α*C*-in (inactive state). Type 1.5 inhibitors are a subtype of the type-1 inhibitors, binding to an inactive kinase conformation with DFG-in conformation, typical of an active kinase, but with the

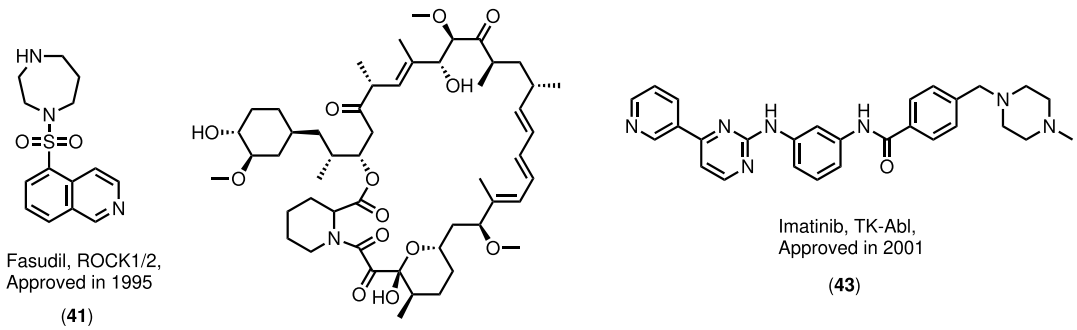


Figure 11. Structures of the first approved kinase inhibitors.

α*C*-helix-out. Protein kinase's small and large lobes are separated by a region where the gatekeeper residue is located. The α*C* helix typically adopts an "out" shape when type 3 inhibitors inhibit kinases at the allosteric site, which is situated near the ATP site. Kinases are inhibited by type 4 inhibitors at a distant allosteric location from the ATP site. Antibodies and their derivatives that target the extracellular domains of receptor tyrosine kinases (RTKs) are also classified as type 4 inhibitors.[75,76] Type 5 bivalent inhibitors target kinases at two distinct binding sites (or domains) at the same time. Type 6 inhibitors form a covalent bond with nucleophilic amino acid residues, with the option of the bond being either irreversible or reversible. In addition, employing the ubiquitin (Ub) breakdown pathway, degraders and molecular glues form another type of kinase inhibitor.[75,76]

Type 6 covalent inhibitors have experienced remarkable prominence in recent years. Afatinib (**44**) stood out as the pioneer of this class, obtaining regulatory approval in 2013. Subsequently, ibrutinib (**45**) and other subsequent drugs followed the same path, as evidenced in Figure 12.[77-79]

Currently, when considering the most targeted molecular entities in terms of covalent inhibition, we can identify a top three ranking based on a literature survey, including scientific articles and patents from 2001 to 2023. It is observed that the protein tyrosine kinase, Bruton's Tyrosine Kinase (BTK) leads the list, occupying the first position with approximately 300 publications, followed by the epidermal growth factor receptor HER2, which has about 210 publications, and finally, the kinase protein Akt, with approximately 150 publications.

Beyond assessing the potency and efficacy of type 6 covalent kinase protein inhibitors (CKPIs), the issue of promiscuity of these agents becomes a point of great relevance in drug discovery. This aspect gains special importance in the face of the considerable number of potential CKPIs currently available, being crucial for optimizing the selectivity and effectiveness of these therapies.[80]

There has been a growing interest in the development of reversible covalent inhibitors,[81-85] as reversibility offers the possibility of minimizing off-target reactions and avoiding permanent modification of target proteins.[85] Conceptually, a reversible covalent inhibitor first establishes non-covalent bonds with its target, and subsequently, the warhead forms a covalent bond, intensifying the interaction and inhibition.[86] To minimize nonspecific reactions, it is desirable for the warhead to have a moderate activation rate and a fast deactivation rate (high K_{off}), allowing for the rapid reversal of off-target conjugations. However, such a combination would result in reduced affinity (K_D, where $K_D = K_{off}/K_{on}$). In other words, a low deactivation rate is sought to maximize the thermodynamic benefit of the warhead (Figure 13).[86] Furthermore, a low dissociation rate is desirable to achieve lasting inhibition, represented by a longer residence time. These paradoxical considerations highlight the need to understand and optimize the kinetics of reversible covalent warheads. Notable examples of efforts in this direction can be found in the literature, demonstrating that slow-dissociating warheads can provide highly potent and long-acting inhibitors in relevant kinases.[81,87,88]

In the context of covalent warheads, both reversible and irreversible, notable examples stand out, considering the interaction of these fragments with specific amino acid residues. Figure 14 illustrates some examples of warheads currently employed in the approach of covalent inhibitors, with irreversible inhibitors highlighted in the red box and the reversible ones in the green box.[89]

As described in the study by Zhao *et al*.,[77] ten privileged warheads were identified and highlighted, as shown in Figure 15. A relevant correlation can be established with the research conducted by Xerxa *et al*.,[90] where an analysis of the frequency of these warheads in covalent kinase inhibitors was undertaken. Notably, the top five prominent

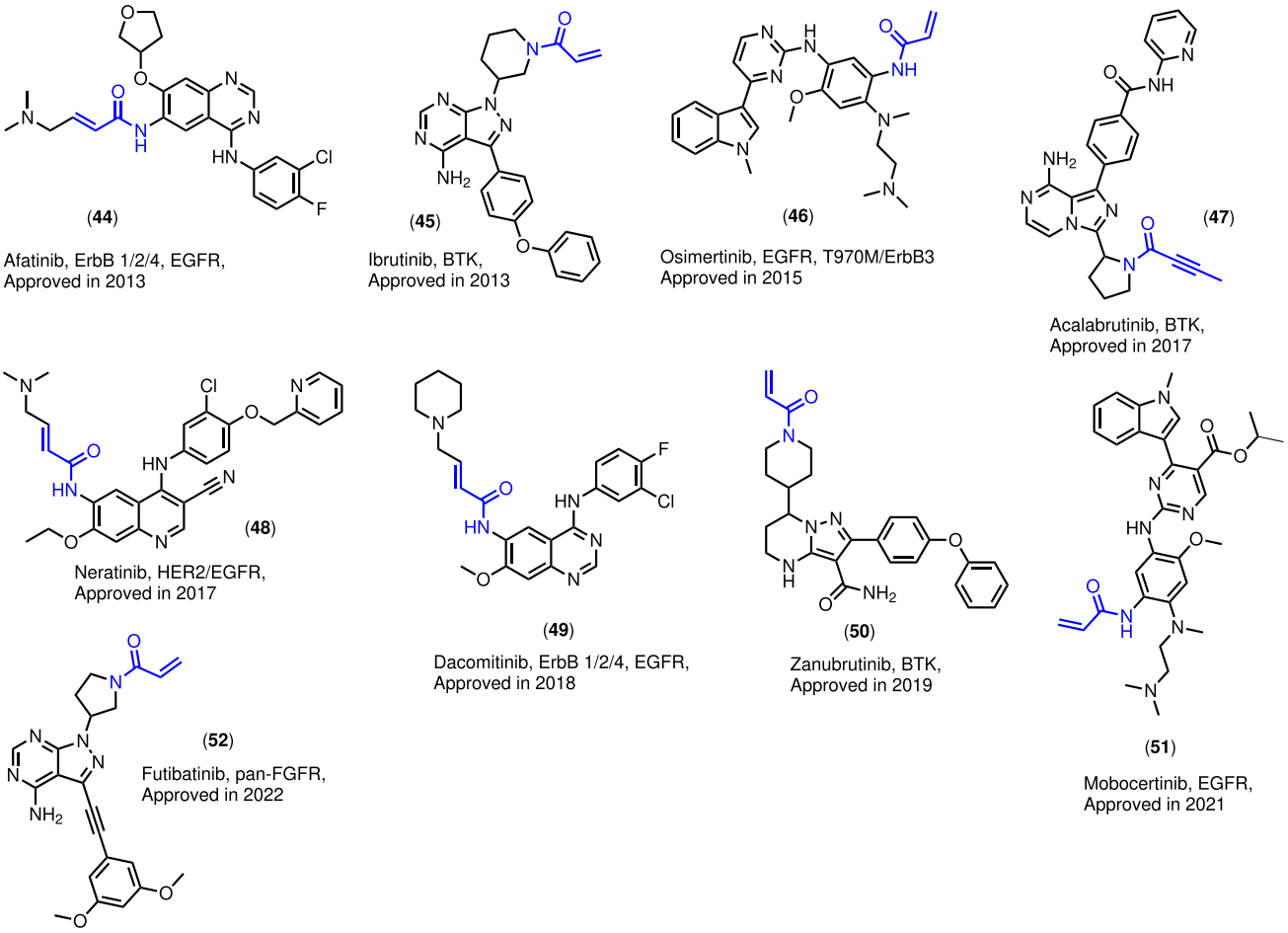


Figure 12. Structures of approved kinase covalent inhibitors (type 6) with their respective targets. Each covalent warhead is highlighted in blue.

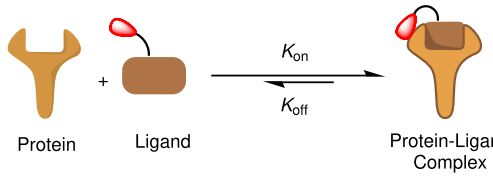


Figure 13. Ideal kinetics for a reversible covalent warhead, where a lower K_{off} compared to K_{on} is observed, providing a longer residence time.

warheads, totaling 13,949 occurrences, were identified as acrylamide (9,861), terminal alkyne (547), acrylate (535), cyanoacrylamide (481), and aldehyde (479).[90]

In the study conducted by Xerxa *et al.*,[90] a meticulous analysis was undertaken regarding various warheads, aiming to quantify the presence of these scaffolds in the scientific literature. Among the most prevalent warheads, which showed occurrences in the range of 450-550 compounds, a subset was selected for a more rigorous evaluation. To these warheads, a promiscuity degree (PD) was assigned. The more targets protein kinases (PKs) that are reported as being inhibited by a given CPKI, the higher the PD value for that CPKI. This is because the PD value is a ratio of the number of PKs that are affected by that particular CPKI. For the compounds in question, a non-promiscuity indicative value (%) was assigned.[90]

As observed, the most selective compounds encompass the cyanoacrylamide (88.8%), aldehydes (86%), acrylate (75.9%), and terminal alkynes (66%) warheads. Remarkably, among the four selected, two of the most selective warheads correspond to the reversible ones, namely aldehyde and cyanoacrylamide, corroborating the indication of reduced off-target impact for reversible warheads. The chemical basis underlying reversibility is elucidated in Scheme 1, exemplified in the case of cyanoacrylamides, where the presence of the withdrawing group (nitrile) allows for a reversible thiol-Michael addition reaction (retro-Michael).[91]

Rilzabrutinib (**92**, Figure 16) (PRN1008) represents a notable example of a reversible covalent inhibitor incorporating the cyanoacrylamide subunit. This compound is currently undergoing phase III clinical evaluation,[92] as registered at the National Library of Medicine[93] under the identifier NCT04562766 and on EudraCT[94] under the number 2020-002063-60. Rilzabrutinib (**92**, Figure 16) is targeted for the treatment of immune thrombocytopenia, exerting its inhibitory activity on the BTK enzyme.[89]

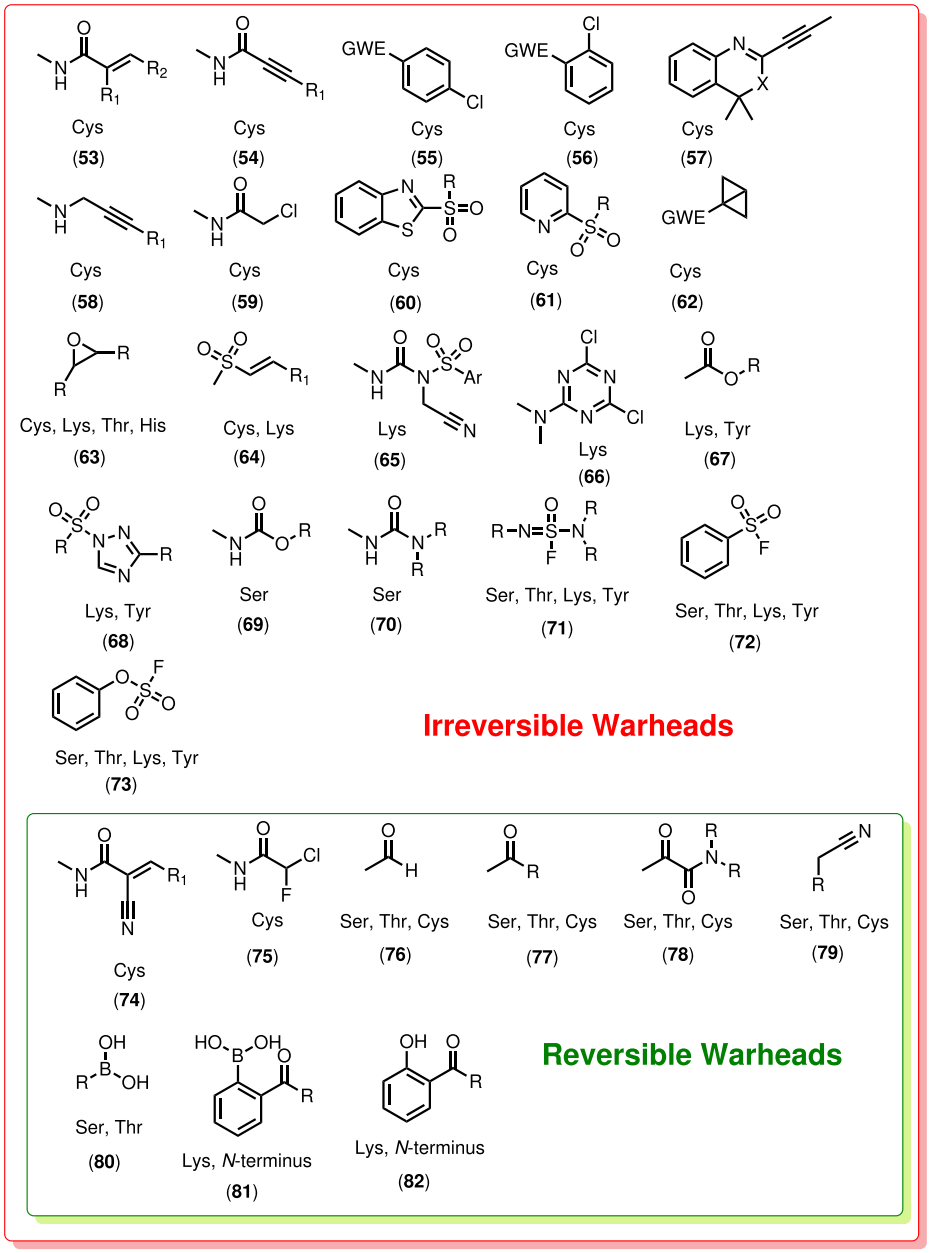


Figure 14. Most used warheads in covalent inhibition approach. In red, warheads classified as irreversible, and in green, warheads classified as reversible.

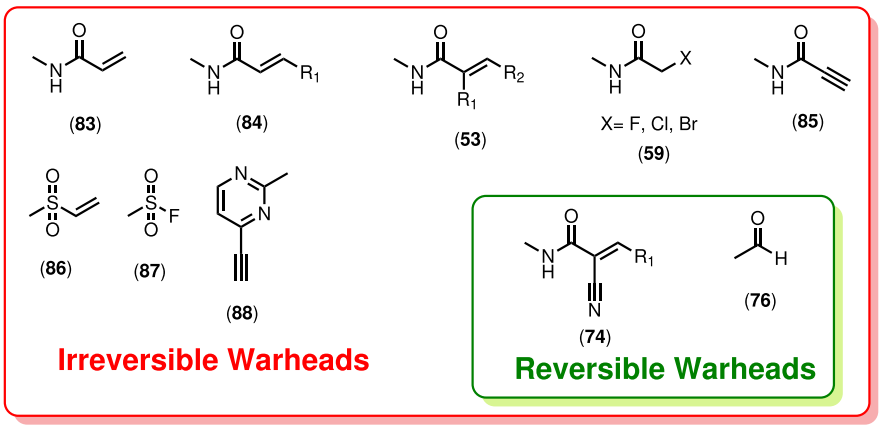
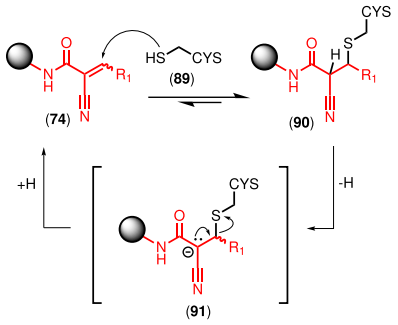


Figure 15. Representation of the ten warheads classified as privileged, highlighted in the study by Xerxa *et al.*[90]



Scheme 1. Mechanism of reversibility of cyanoacrylamides.

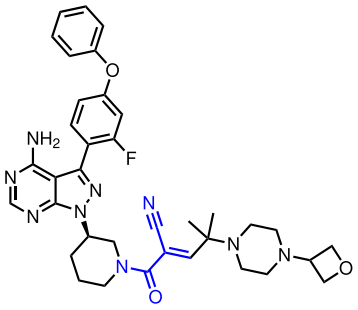
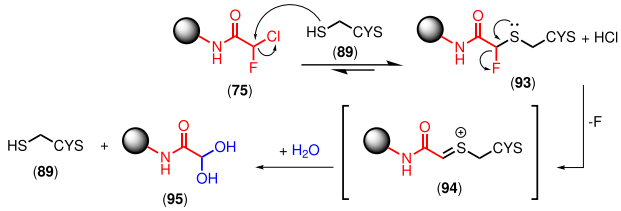


Figure 16. Chemical structure of rilzabrutinib (**92**) (PRN1008) with the cyanoacrylamide subunit highlighted in blue.

Another example highlighting the reversible covalent effect can be observed for α-chlorofluoroacetamides (CFA).[95] It has been demonstrated that the CFA-thiol adduct is gradually hydrolyzed under neutral aqueous conditions, reverting reversibly to an unchanged free thiol (Scheme 2). This reversible hydrolysis contributes to the effective elimination of off-target reactions with solvent-accessible cysteines. This environmentally sensitive hydrolysis may play a crucial role in achieving the high target selectivity of CFA-based covalent inhibitors.[95] It is important to note that the reversible modification of CFA cysteine has a distinct mechanism from that of cyanoacrylamide, which is highly reactive and regenerates the warhead through retro-Michael reaction. In contrast, the initially weakly reactive CFA gains reversible reactivity through the hydrolysis of the cysteine adduct, transforming into the non-reactive glyoxamide hydrated (**95**, Scheme 2).[89]

Evidence indicates that several covalent inhibitors based on CFA have demonstrated superior selectivity towards



Scheme 2. Mechanism of reversibility of α-chlorofluoroacetamides (CFA).

target proteins when compared to analogous inhibitors based on acrylamide.[89]

The highly promising research published by Reja *et al.*,[86] provides another illustration of the reversible covalent inhibition mechanism in action. The study makes a contribution by presenting a novel lysine conjugation chemistry in which a β-hydroxy diazaborine (**101**) is produced by the reversible conjugation of an RMR1 (**100**) warhead with lysine residues (Figure 17). The lysine conjugation caused by RMR1 (**100**) exhibits a substantially longer reverse reaction, with dissociation taking place over the course of hours, in comparison to iminoboronate chemistry (**99**), a known lysine conjugate with quick dissociation kinetics. They demonstrate that RMR1 (**100**) may be grafted onto a peptide structure to form strong reversible covalent inhibitors, whose effectiveness is shown against the recombinant protein as well as in living bacterial cells, using staphylococcal sortase (SrtA) as a model system. Significantly, an inhibitor containing RMR1 (**100**) permits SrtA to remain inhibited for hours after the inhibitor is removed, marking the first instance of the kinetic advantage of lysine-targeted reversible covalent inhibitors.[86] They believe that the RMR1 (**100**) warhead's repertoire for producing reversible covalent inhibitors that target lysine will be significantly increased by tuning it to provide a broad range of kinetic profiles for reversible lysine conjugation.[86] Currently, efforts are being made in this direction.

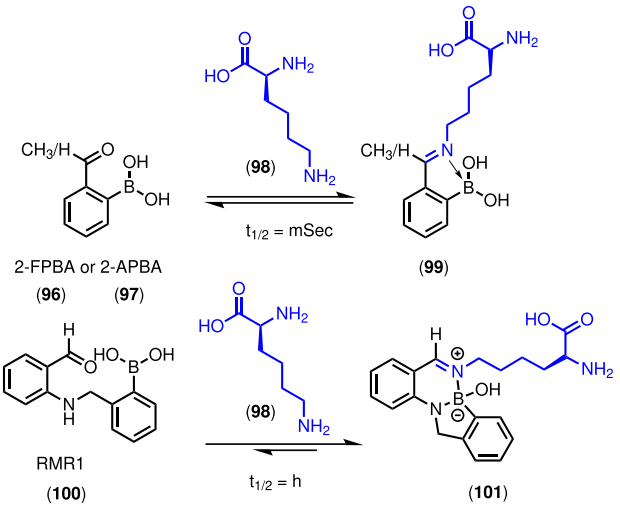


Figure 17. Lysine-targeting covalent warheads.

There are several marketed drugs that are reversible covalent inhibitors (Figure 18). Saxagliptin (**102**) is a reversible covalent drug that functions as an electrophilic warhead with a nitrile group to target the Ser630 residue of dipeptidyl peptidase-4 (DPP-4).[96] The FDA gave its

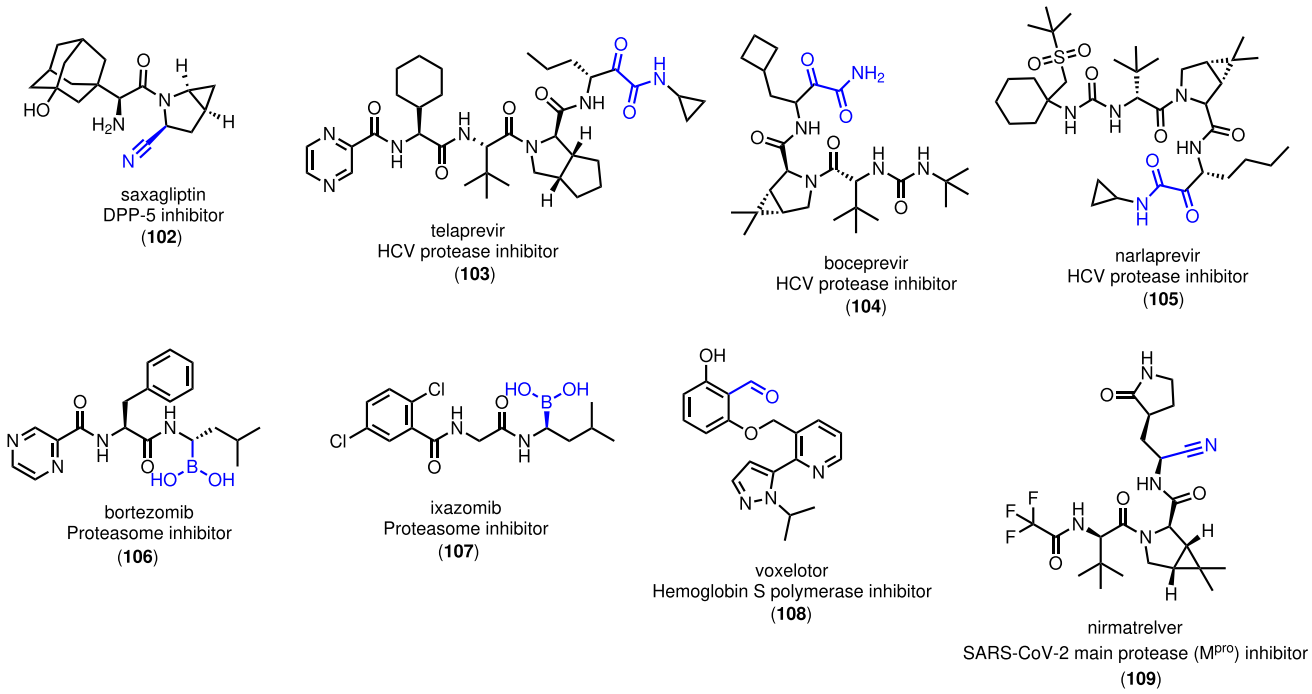


Figure 18. Examples of reversible covalent drugs on the market.

approval in 2009 to treat Type 2 diabetes. The FDA granted licenses for telaprevir (**103**) and boceprevir (**104**), two reversible covalent α-ketoamide-based drugs that interact with the catalytic serine residue of the hepatitis C NS3 serine protease, in 2011.[97] Narlaprevir (**105**) is a potent second-generation inhibitor of the hepatitis C virus (HCV) NS3 protease, with a K_i of 7 nM.[98] In 2016, it was created a reversible covalent drug based on α-ketoamide, which was authorized in Russia for the treatment of hepatitis C. The first inhibitor of the 26*S* proteasome in its class, bortezomib (**106**), targets the *N*-terminal threonine of the 26S proteasome with an electrophilic warhead consisting of boronic acid. The FDA gave its approval in 2003 to treat multiple myeloma.[99] Ixazomib (**107**), an additional 26*S* proteasome inhibitor, is an orally accessible, reversible covalent inhibitor that attaches to the 20*S* proteasome's β5 subunit. It was approved by the FDA in 2015 for use in combination with dexamethasone and lenalidomide to treat individuals with multiple myeloma.[100] In 2019, the FDA authorized voxelotor (**108**) as a treatment for sickle cell disease. By forming an imine, its aldehyde warhead attaches to hemoglobin's *N*-terminal valine in a reversible manner.[101] Another reversible covalent inhibitor that targets a cysteine in the major protease (M^{pro}) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is nitmatrelvir (**109**), which has a nitrile warhead. In 2022, the FDA authorized it for the treatment of coronavirus disease (COVID-19).[102]

PRN473 (**110**) (Figure 19) was studied in a clinical investigation of canine pemphigus foliaceous. In toxicological and canine clinical investigations, PRN473 (**110**) is effectively absorbed in dogs, whereas it is poorly absorbed orally in humans.[103] As a topical drug, PRN473 (**110**) has successfully finished a phase 1 clinical trial. Two selective reversible covalent inhibitors of JAK3, (**111**) and (**112**) (Figure 19), with half maximal inhibitory concentration (IC_{50}) values of 127 and 154 pM, respectively, were discovered by Forster *et al.*[104] Compound **112** showed selectivity over JAK1 (416-fold), JAK2 (1753-fold), and tyrosine kinase 2 (TYK2) (5831-fold), whereas compound (**111**) demonstrated excellent selectivity of 409-, 2724-, and 3614-fold over JAK1, JAK2, and TYK2, respectively. The use of a cyanamide warhead in reversible covalent inhibitor PF-303 (**113**) (Figure 19) as a chemical probe to study the phenotypic of BTK inhibition in mice was also described by Benson *et al.*,[105] PF-303 (**113**) is an oral bioavailable and strong inhibitor of BTK (IC_{50} = 0.64 nM). The 2-formyl tetrahydronaphthyridine urea series underwent further, thorough optimization, which produced roblitinib (**114**) (Figure 19), a therapeutic candidate currently undergoing phase III clinical studies.[106] Roblitinib (**114**) showed promising pharmacokinetic properties and signs of fibroblast growth factor receptor 4 (FGFR4) inhibition in a phase 1-2 research. Hepatocellular carcinoma patients showed clinical effectiveness. NS-062 (**115**) demonstrated stronger target selectivity for EGFR than the corresponding Michael acceptors in a wide range of concentrations (0.1-10 μM) in cells. Oral treatment of

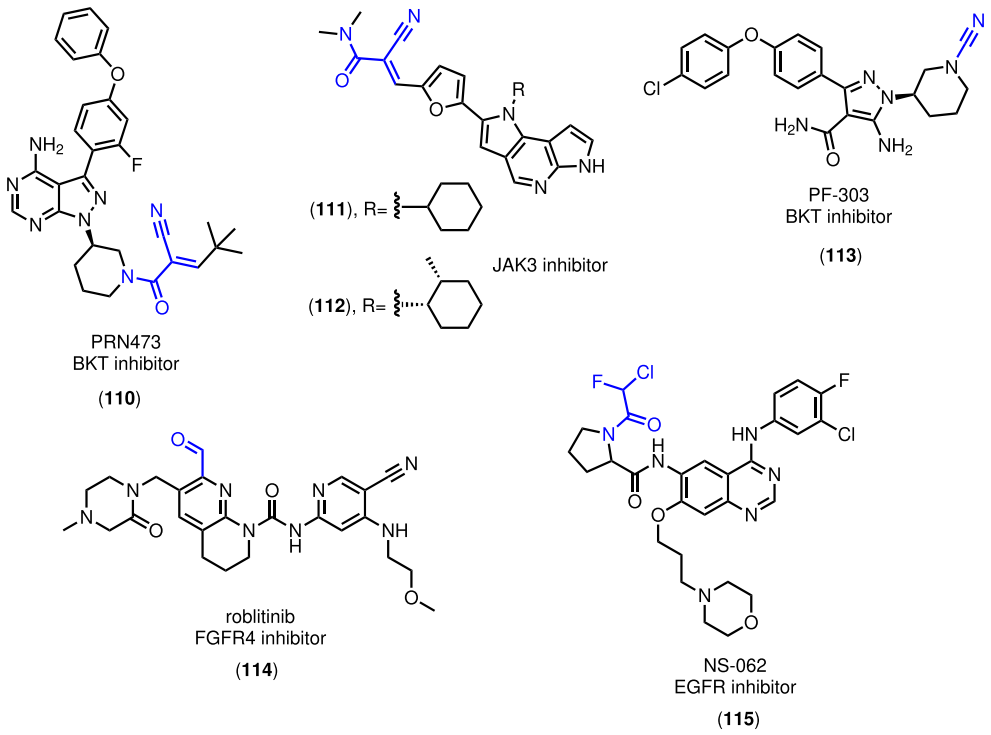


Figure 19. Examples of reversible covalent kinase inhibitors under development.

NS-062 (**115**) greatly inhibited tumor growth in a mouse xenograft model (Figure 19).[95]

2.2.2. Emerging privileged structures for the design of proteolysis targeting chimeras (PROTACs)

The pioneering work published by Sakamoto *et al.*[107] reported the first study on proteolysis targeting chimeras (PROTACs) in 2001. PROTACs are heterobifunctional molecules that have three components: the protein-of-interest (POI) binding moiety, a linker, and E3 ubiquitin ligase binding moiety (Figure 20).[108-110] A POI-PROTAC-E3 ligase ternary complex can be formed when the PROTAC molecule simultaneously bind to both the target protein and E3 ligase.[111,112] Protein degradation by proteases occurs once the target protein is polyubiquitinated due to the hijacking of the ubiquitin-protease system (UPS). In eukaryotic cells, the UPS is the principal mechanism for maintaining protein homeostasis eliminating faulty and damaged proteins.[113,114] Proteins are broken down by the UPS system by substrate-specific ubiquitination and recognition. Three enzymes are involved in the continuous process of ubiquitination: substrate-specific ligases (E3), ubiquitin-activating enzymes (E1), and ubiquitin-conjugating enzymes (E2).[115-118] By creating a ubiquitin-E1 thioester link, E1 binds free ubiquitin (Ub) in an ATP-dependent manner. Later, E1

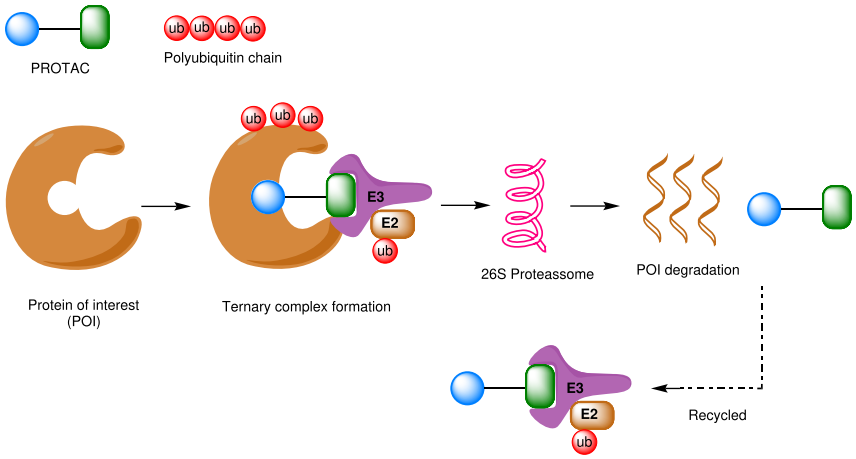


Figure 20. PROTAC-induced degradation of target proteins.

uses *trans*-thioesterification to move the activated Ub to E2.[119] Lastly, E3 ligase recruits the Ub-tagged E2 and target protein to help with ubiquitin labeling on target proteins.[120] These ubiquitination processes can be repeated to produce target proteins with poly-ubiquitin chains attached, which point the designated protein toward the 26S proteasome for breakdown.[121] POI and E3 ligase are recruited by PROTACs concurrently, resulting in their spatial closeness. To eliminate POIs from cells, PROTACs mimic the precise substrate identification of E3 ligase and take use of the intracellular protein degradation pathway.[122]

The most relevant E3 enzymes for the PROTAC approach are outlined, namely Creblon (CRBN), von Hippel-Lindau (VHL), inhibitors of apoptosis proteins (IAP), and mouse double minute 2 (MDM2), with a special focus on the extensively studied CRBN. CRBN is a 442-amino acid protein that forms a Cullin-4-RING E3 ubiquitin ligase (CRL4) complex and interacts with the adaptor protein damaged DNA-binding protein 1 (DDB1).[123,124] Within the CRL4 complex, CRBN acts as a substrate-specificity receptor.[124] Among the known ligands for CRBN, thalidomide (**116**, Figure 21) as an immunomodulatory drug (IMiD) and other IMiD-derived immunomodulatory drugs stand out. Upon binding of IMiDs to CRBN, the E3 ubiquitin ligase activity of CRBN is reconfigured.[124-127] As a result, there is an increase in the recruitment of the transcription factors Ikaros (IKZF1) and Aiolos (IKZF3), leading to their subsequent ubiquitination and proteasomal degradation. This interaction and its consequences are responsible for the observed antiproliferative effects of thalidomide (**116**, Figure 21), pomalidomide (**125**, Figure 21), and lenalidomide (**126**, Figure 21) in multiple myeloma.[124,126,127]

So far, CRBN has demonstrated success as the E3 ligase in PROTACs targeting over 30 distinct proteins, spanning those involved in various cancers[128] and immunological disorders,[129] to the protein associated with the neurodegenerative disease Tau[130] and even the NS3 protein of the hepatitis C virus.[131]

The collection of CRBN ligands with different linker attachment options is presented in Figure 21. The majority of CRBN-targeting PROTACs employ derivatives of pomalidomide (Figure 21, **117**, **118**), 4-hydroxythalidomide (Figure 21, **119**, **120**), alkyl-connected thalidomide derivatives (Figure 21, **121**), or lenalidomide (Figure 21, **122-124**). However, alternatives are possible, including examples with substitution at position 5 of the phthalimide fragment.[132]

Based on data extracted from PROTAC-DB in the work of Weng *et al.*,[133] a statistical analysis was conducted to assess the frequency of various CRBN ligands and linker attachment options used in PROTAC compounds

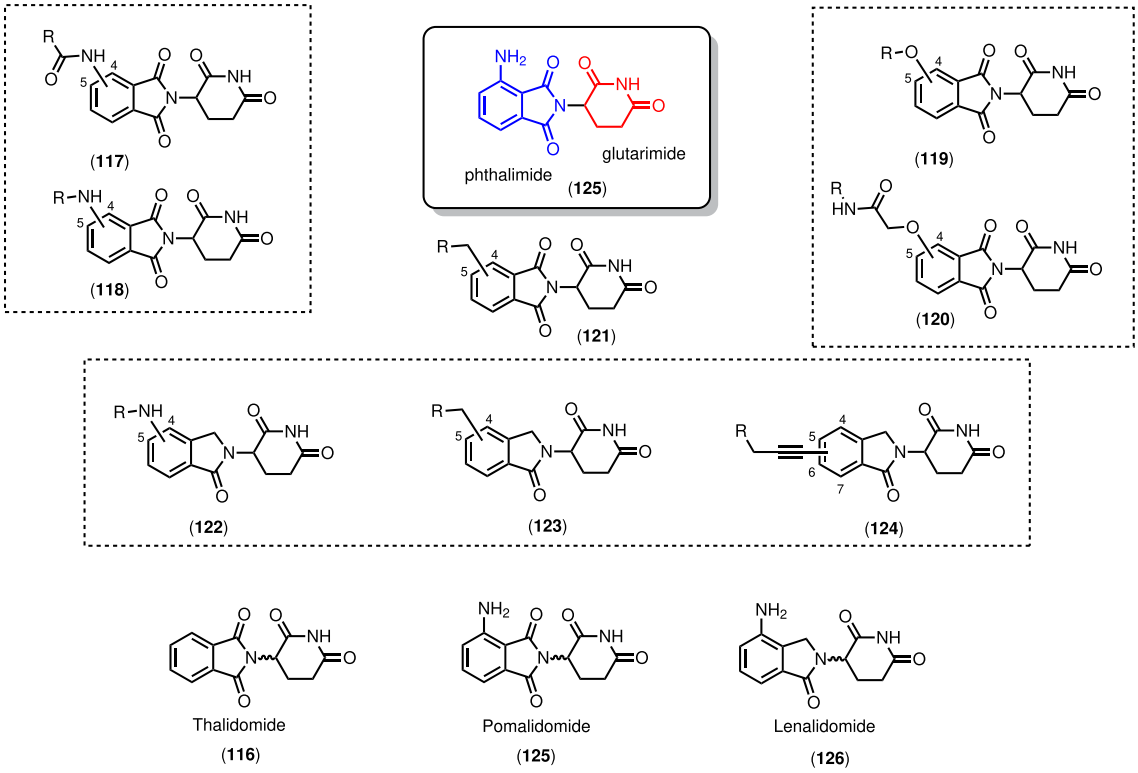


Figure 21. Commonly utilized talidomide-derived CRBN ligands and possible linker attachment styles. (**117-118**) Pomalidomide derivatives; (**119-120**) 4-hydroxythalidomide derivatives; (**121**) alkyl type attachment to thalidomide; (**122-124**) lenalidomide derivatives.

(Figure 22). An overwhelming majority of PROTACs incorporated *N*-alkylated pomalidomide (**133**) as the E3 ligase ligand, while acylated pomalidomide (**129**) was represented with a comparable frequency to 4-hydroxythalidomide derivatives (**127**). Interestingly, the 5-amino derivative (**132**) was employed in approximately 5% of PROTACs. Lenalidomide analogs, especially 4-acylated (**130**) derivatives and alkyl-connected lenalidomide derivatives (**131**), showed similar frequencies at 7 and 6%, respectively.[132]

Protein chemical degraders, exemplified by PROTACs have emerged as a robust strategy to disrupt protein activity in recent years.[134] Notable efforts have been dedicated to the use of covalent inhibitors based on acrylamide as the protein-target binding subunit in PROTACs.[135] Additionally, investigations have been conducted on the application of BTK inhibitors based on cyanacrylamide for PROTAC, as depicted in Figure 23.[82,84]

The work by Guo *et al*.,[84] reports that reversible covalent chemistry based on cyanacrylamide can substantially enhance intracellular accumulation and target engagement in PROTACs. The compound RC-1 (**134**) (Figure 23a) was developed, with an IC_{50} of 33 nM for BTK and 250 nM for CRBN, providing a degradation rate of BTK of 81% at 200 nM. RC-1 (**134**) acts as a reversible covalent inhibitor of BTK in PROTACs, exhibiting high target occupancy and functioning as a kinase inhibitor. This dual functionality, combining inhibitory and degradative properties, constitutes a distinct mechanism of action for PROTACs. The relevance of this reversible covalent strategy is emphasized, as it proves to be generalizable for optimizing other PROTACs,[84] thus opening a pathway to enhance the efficacy of these protein degraders.

In the study conducted by Gabizon *et al.*,[82] the presented data indicate that a significant portion of the degradation induced by irreversible covalent PROTACs is driven by reversible binding before the formation of the covalent bond, while reversible covalent PROTACs predominantly lead to degradation through covalent engagement. These PROTACs demonstrated more pronounced inhibition of B-cell activation compared to ibrutinib (**45**) and exhibited effective degradation of BTK in primary chronic lymphocytic leukemia cells derived from patients. The most potent reversible covalent PROTAC, RC-3 (**135**), showed greater selectivity towards BTK compared to covalent, non-covalent, and irreversible PROTACs. These results suggest the potential for developing covalent PROTACs for a wide range of challenging targets.

3. Promiscuous Structures

3.1. Pan Assay Interference Compounds (PAINS)

Pan Assay Interference Compounds (PAINS) are a major challenge for virtual (VS) and high-throughput screening (HTS) in drug discovery and development.

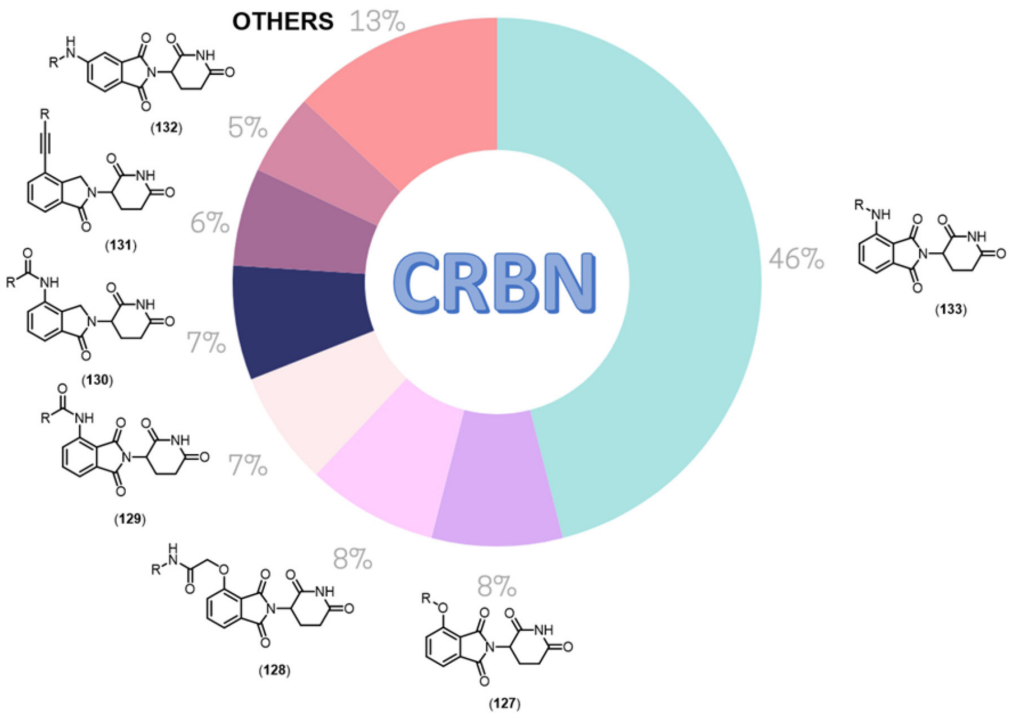


Figure 22. Frequency of CRBN ligands used in PROTAC compounds.

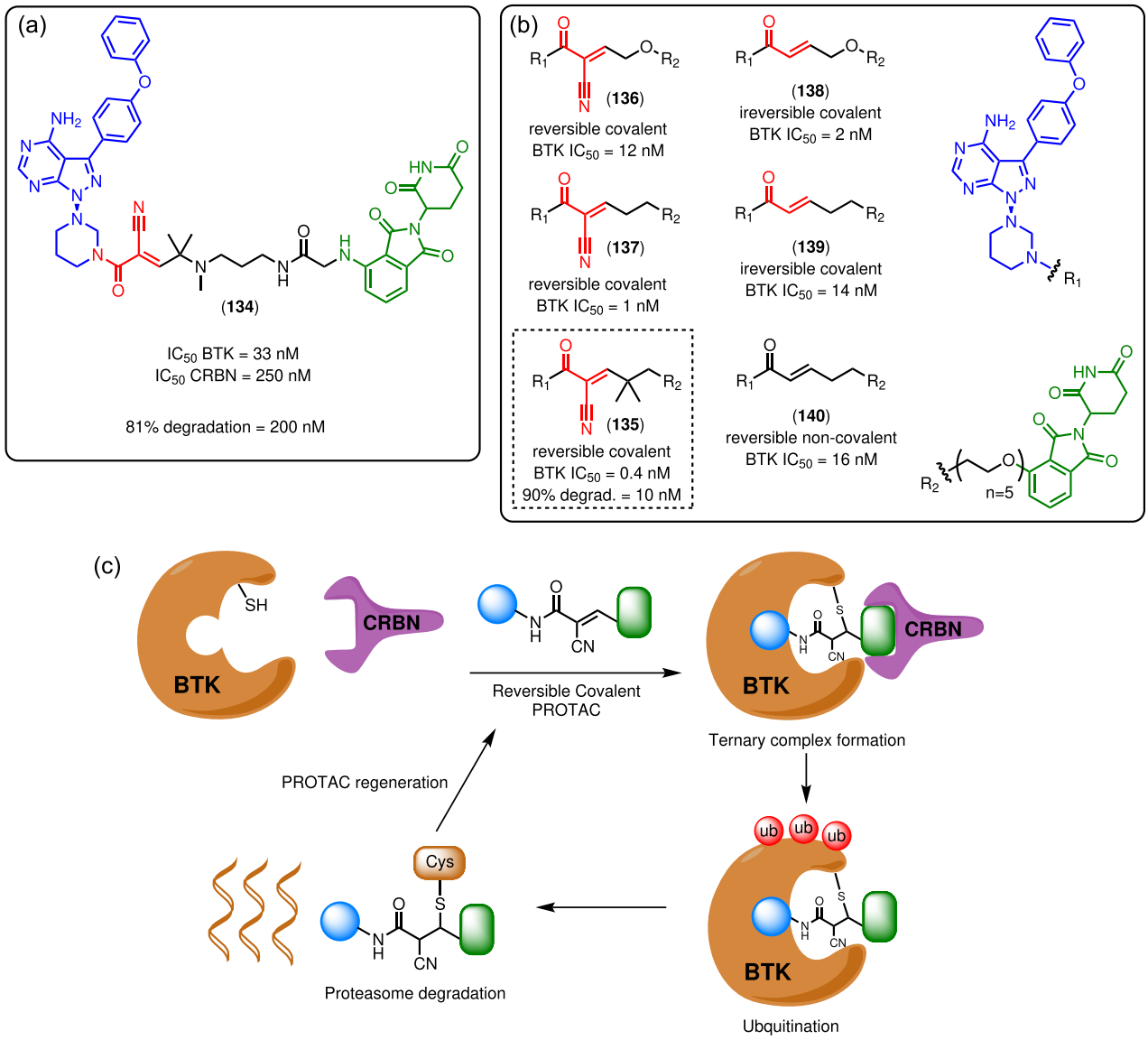


Figure 23. (a) Structure of the compound RC-1 (**134**). (b) Structures from the study by Gabizon *et al.*,[82] with emphasis on the compound RC-3 (**135**). (c) Mechanism of action of a reversible covalent PROTAC.

PAINS are chemical compounds that often give false positive results in screening campaigns, because they interfere with the assay rather than binding specifically to the target of interest, resulting in the identification of frequent hitters, i.e., promiscuous compounds.[9,13] The mechanism behind this promiscuity can be related to aggregate formation[136,137] chemical instability that results in indiscriminately reactivity with proteins[138,139] and those that interfere with assay signaling, for example, by being fluorescent, strongly colored or sequester metal ions that are essential to protein's function.[9,140] Despite three possible mechanisms, most PAINS are covalently reactive compounds.[9] PAINS comprise approximately 400 structural classes. However, a noteworthy observation reveals that over half of the PAINS present in a typical library can be categorized into a mere 16 easily recognizable classes.[9,140] This concentration of PAINS within a limited set of distinct categories underscores the importance of vigilant screening and identification to mitigate potential assay interference in scientific research and drug discovery endeavors.

Some examples of PAINS are toxoflavin, isothiazolones, hydroxyphenyl hydrazones, curcumin, phenol-sulfonamides, rhodanines, enones, quinones, and catechols.[10,140] To identify and remove PAINS from screening library, researchers can use methods, such as: applying substructure filters that flag compounds with known PAINS functional groups[140] and perform a validation of the identified hits.[141]

By identifying and removing PAINS from screening library, researchers can avoid wasting time and resources

on compounds that cannot be developed into drugs and focus on those with genuine biological activity.[140] Despite that, early filtering of screen libraries, without a deeper investigation of the chemical and biochemical effects of certain frameworks in the structure of a drug candidate, has also been questioned.[142,143]

3.2. The thin line between promiscuity and covalent inhibition

Promiscuity and covalent inhibition in medicinal chemistry are two important concepts that relate to the selectivity and efficacy of covalent drugs. Covalent drugs are small molecules that form a covalent bond with their target proteins, resulting in irreversible or pseudo-irreversible inhibition and, consequently, leading to increased residence time.[144-146] Covalent drugs have several advantages over conventional reversible inhibitors, such as increased duration of action, reduced pharmacokinetic sensitivity, and the potential to target shallow binding sites.[147] However, covalent drugs also pose challenges in terms of off-target toxicity and immunogenicity risks, which depend on the compound selectivity and reactivity of the electrophilic warheads that mediate the covalent bond formation. In this scenario, promiscuity refers to the tendency of a covalent drug to indiscriminately react with multiple proteins, which may lead to undesirable side effects. Off-target toxicity may cause idiosyncratic reactions, allergic responses, or organ damage. Therefore, careful design and optimization of covalent drugs are required to balance promiscuity and selectivity, and to minimize off-target toxicity. As previously discussed, some examples of successful covalent inhibitors are afatinib (**44**),[148] ibrutinib (**45**),[149] and osimertinib (**46**)[150] (Figure 12). These covalent inhibitors have shown clinical benefits for patients with cancer by irreversibly inhibiting their target kinases.[151]

In essence, the implementation of optimization steps is crucial for transitioning a given structure from the PAINS condition, primarily associated with compounds exhibiting fragment-like features, to more intricate structures that demand effective recognition by their respective molecular targets. This involves strategically positioning the covalent reactive subunit towards the specific amino acid within the binding site. Moreover, exploring reversible covalent warheads opens up vast opportunities for the development of safe covalent drugs.

3.3. The thin line between promiscuity and multitarget actions

While promiscuity may pose challenges in terms of selectivity and off-target effects, which are linked to toxicity, it also opens new avenues for drug repurposing and the exploration of polypharmacology. Polypharmacology refers to the phenomenon of one drug, with multitarget profile, or the combination of different drugs that results in multiple biological effects by modulating more than one pharmacological target, which may enhance its therapeutic efficacy or reduce its adverse effects.[152] The difference between polypharmacology and promiscuity is that polypharmacology is usually intentional and/or desirable, while promiscuity is usually accidental and undesirable.

Promiscuity can have both positive and negative implications for drug development and therapeutic applications.[11,153] On one hand, promiscuity can enhance drug efficacy by modulating multiple pathways involved in complex diseases, such as cancer, inflammation, or neurodegeneration. For example, aspirin is a drug that has anti-inflammatory, analgesic, antipyretic, and antiplatelet effects by inhibiting cyclooxygenases and has been characterized as a promiscuous drug by modulating other 23 putative targets,[12,154] which opened avenues for drug repositioning for cancer prevention.[155] On the other hand, promiscuity can cause adverse drug reactions by binding off-targets that are unrelated to the desired pharmacological effect.[6] For example, thalidomide (**116**) is a promiscuous drug that binds to various proteins and has teratogenic effects in addition to its immunomodulatory and antiangiogenic activities.[156] On the other hand, delving into the promiscuity of thalidomide (**116**) and its analogs has paved the way for the development and discovery of PROTACs, as previously discussed.

The degree of promiscuity of a compound depends on several factors, such as the chemical structure, the binding mode, the target similarity, and the assay conditions. Promiscuity can be quantified by various metrics, such as the number of targets, the target diversity, or the promiscuity index (PI).[157] The PI is a valuable metric in drug discovery used to quantify the promiscuity of a compound by measuring its interactions with multiple targets relative to the total number of targets tested. A higher PI indicates greater promiscuity, meaning the compound has the potential to interact with a wide range of targets. The PI is calculated using the formula: $PI = n/N$, where: n is the number of targets a compound interacts with and N is the total number of targets tested. For example, if a compound interacts with 5 out of 50 tested targets, its PI would be 0.1 (5/50). The PI provides valuable insights into the selectivity and potential off-target effects of a compound. Compounds with low PI values are more selective and have a narrower range of interactions, making them potentially safer and more suitable for further development. On the other hand, compounds with high PI values may have a

higher risk of off-target effects but could also offer broader therapeutic potential. Studies have utilized the PI to assess and compare the promiscuity of compounds in drug discovery.[158] For example, a study by Lounkine *et al*.,[159] used the PI to analyze the promiscuity of approved drugs and experimental compounds, providing valuable insights into their potential off-target effects. Another study by Hu *et al*.,[157] used the PI to evaluate the promiscuity of kinase inhibitors, highlighting the importance of considering off-target effects in drug design. Overall, the PI is a valuable tool in drug discovery for assessing compound promiscuity and guiding the design of safer and more selective drugs.

Promiscuity can also be visualized by network representations, such as bipartite graphs or heat maps.[160] Promiscuity can be predicted by computational methods, such as ligand-based or target-based approaches, that exploit structural or biological information of compounds and targets.[161]

Promiscuity is an emerging concept in drug discovery that challenges the traditional one drug-one target paradigm and offers new challenges and opportunities for medicinal chemistry and pharmacology. Understanding and exploiting promiscuity can facilitate the design of multitarget drugs, the discovery of novel drug-target interactions, and the optimization of drug safety profiles.

4. Conclusion and Perspectives

The intricate relationship between promiscuity and privileged structures in medicinal chemistry presents both challenges and opportunities. Promiscuity, the ability of a molecule to interact with multiple targets, has been viewed traditionally as a hurdle due to potential off-target effects and lack of selectivity. However, it also offers a gateway to exploring polypharmacology, where a single compound can affect multiple disease pathways, potentially leading to innovative therapeutic interventions. Privileged structures, molecular frameworks with the propensity to interact with diverse biological targets, have been instrumental in drug discovery by serving as scaffolds for synthesizing compounds with desired pharmacological properties. Their inherent promiscuity provides a starting point for designing multi-target drugs and exploring new therapeutic avenues.

Additionally, the ethical considerations surrounding promiscuity and privileged structures necessitate a careful balance between therapeutic innovation and potential risks. Striking a balance between exploiting promiscuity for therapeutic benefits while minimizing adverse effects remains a crucial challenge.

In essence, the intersection of promiscuity and privileged structures in medicinal chemistry represents a dynamic area of research that holds promise for revolutionizing drug discovery and development. Continued exploration and refinement in this field offer immense potential for the creation of safer, more efficient, and targeted therapeutic interventions for various diseases.

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