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REVIEW

Small molecules targeting protein–protein interactions for cancer therapy

Defa Wu[a,†], Yang Li[a,†], Lang Zheng[a], Huan Xiao[a], Liang Ouyang[a], Guan Wang[a,*], Qiu Sun[a,b,*]

[a]*Department of Biotherapy, Cancer Center and State Key Laboratory of Biotherapy, Innovation Center of Nursing Research, West China Hospital, Sichuan University /West China School of Nursing, Sichuan University, Chengdu 610041, China*
[b]*West China Medical Publishers, West China Hospital, Sichuan University, Chengdu 610041, China*

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Abstract Protein–protein interactions (PPIs) are fundamental to many biological processes that play an important role in the occurrence and development of a variety of diseases. Targeting the interaction between tumour-related proteins with emerging small molecule drugs has become an attractive approach for treatment of human diseases, especially tumours. Encouragingly, selective PPI-based therapeutic agents have been rapidly advancing over the past decade, providing promising perspectives for novel therapies for patients with cancer. In this review we comprehensively clarify the discovery and development of small molecule modulators of PPIs from multiple aspects, focusing on PPIs in disease, drug design and discovery strategies, structure-activity relationships, inherent dilemmas, and future directions.

*Corresponding authors.
E-mail addresses: guan8079@163.com (Guan Wang), sunqiu@scu.edu.cn (Qiu Sun).
†These authors made equal contributions to this work.

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1. Introduction

Protein−protein interactions (PPIs) play pivotal roles in numerous physiological and pathological processes[1,2]. Upstream signalling molecules can induce signalling cascade of PPIs that ultimately aim to regulate a wide variety of cellular processes such as proliferation, invasion, and apoptosis[3]. However, anomalous interactions between proteins within human cells cause a variety of diseases, especially tumour formation. Exemplarily, both the tumour suppressor p53 and its negative mediator mouse double minute 2 (MDM2) are crucial for tumour development. MDM2 counteracts the effects of the tumour suppressor p53 by physically binding to p53 and suppressing its transcriptional activity[4]. Tumour progression is highly correlated with complex interactions between tumour cells, surrounding normal cells and the extracellular matrix. The close interplay between tumour-related proteins is important for this process. Thus, targeting PPIs offers opportunities to directly target pathways that drive tumour progression. Therapeutic agents based on selective PPIs have been rapidly advancing, offering new hope for curing cancers.

There are different types of PPI modulators, which can be classified into antibodies, peptides, and small molecules. Table 1 summarizes the advantages and disadvantages of these modulators. Previous studies have shown that PPIs can be inhibited or stabilized through directly bind to a few key residues at the PPI interface by orthosteric modulators or indirectly bind to active regions outside the PPI interface that can induce conformational changes by allosteric modulators (Fig. 1)[5−7]. Allosteric modulation, whereby allosteric modulator targets a site far from the orthosteric active site, exerts superior selectivity on the target system. The PPI inhibition tends to be simpler than the stabilization because allosteric inhibition needs only disturb few key residues, since allosteric inhibition requires only a few critical residues to be perturbed, whereas stabilization requires the binding of multiple residues at the PPI interface. For allosteric inhibitors, it is frequently necessary to identify active sites that change the spatial structure of proteins, while for stabilizers it is necessary to analyse more complex protein interactions; consequently, the design of stabilizers is more challenging, which contributes to the uneven distribution of PPI regulator types.

The design of drugs based on PPIs has become a hot topic. However, the bulk of reported PPI modulators have been fortuitously identified, and systematic design, screening, and technology platforms for the identification of PPI modulators are still scarce. Moreover, the design of PPI-targeted small molecule drugs has seemed intractable due to the lack of drug-binding pockets on PPI interspaces compared to traditional pharmacophore-based targets. Thankfully, with the development of structural biology and computational chemistry, several tumour-related PPIs have become more tractable for medicinal chemistry, including C-Myc−MAX, Menin−MLL, Keap1−Nrf2, and others[8−10]. Moreover, several small molecule PPI modulators have been reported that have advanced to preclinical studies and different stages of clinical investigation. In this review, current knowledge on therapeutic PPI modulators for cancer therapy is summarized. Furthermore, this review will serve to speculate on the potential and future directions of PPI targeting, with a discussion focused on the development of advanced technologies for drug discovery.

Table 1 The advantages and disadvantages of the three types of PPI modulators.

Modulator	Advantage	Disadvantage
Antibodies	High efficiency Target specificity	Side effects Off-target
Peptides	High affinity Target specificity	Short half-life Poor oral administration
Small molecules	Oral administration Penetrate cell membrane	Low selectivity Low-druggability

2. Research progress on PPI modulators

Inhibition and stabilization of PPIs are two different strategies resulting in two types of PPI regulators, inhibitors and stabilizers, both of which play an important role in disease, especially for some solid tumours with low cure rates. Research focused on finding PPI modulators that regulate PPIs has made considerable progress in recent decades[11]. However, there are significant impediments to the development of PPI modulators. Here, we focus on examples that have been successful, especially the design, discovery, and conformational relationships of modulators, to provide guidance for the design of PPI modulators.

2.1. PPI inhibitors

Inhibition of PPIs is rapidly becoming an attractive approach for new therapeutics, and the search for such inhibitors is aided by the establishment of systematic approaches for high-throughput screening, structure-based design, fragment-based design and so on. The following examples of PPI inhibitors that represent classic cancer therapy drugs are discussed in this section.

2.1.1. Inhibitors of the Bcl-2 gene family

Cell apoptosis is an important process of cellular life. Naturally, apoptosis can be induced *via* both intrinsic and extrinsic pathways[12]. In particular, members of the B-cell lymphoma 2 (*Bcl-2*) gene family exert a key role in regulating apoptosis by controlling proapoptotic (Bid, Bax, and Bak) and antiapoptotic intracellular signals (Bcl-2, Bcl-XL, and Mcl-1) (Fig. 2A)[13]. However, dysregulation of the specific *Bcl-2* gene family contributes to tumour progression and survival of tumour cells. Consequently, targeting the antiapoptotic Bcl-2 family is considered a therapeutic strategy for tumour treatment. Structurally, the hydrophobic cavities of antiapoptotic proteins bind to the hydrophobic surface of the alpha-helical BH3 domain, which is essential for PPIs that can promote the dimerization of proapoptotic sensitizer proteins with antiapoptotic proteins. Antiapoptotic and proapoptotic proteins interact through the BH3 domain, which inhibits apoptosis function, disrupts the PPI, and restores apoptosis ability[14]. Therefore, it is a good choice to develop rational BH3 domain mimics for hydrophobic surface pocket of anti-apoptotic protein[15]. Identification and characterization of small molecule inhibitors of the Bcl-2 family of proteins has been reported. These inhibitors can be divided into three types according to their targets: Bcl-2 inhibitors, Bcl-XL inhibitors, and MCL-1 inhibitors.

2.1.1.1. Bcl-2 inhibitors. The Bcl-2 protein is the most studied antiapoptotic protein of the Bcl-2 family and interacts with proapoptotic proteins to affect mitochondrial outer membrane permeability (MOMP). ABT-737, a promising paninhibitor of Bcl

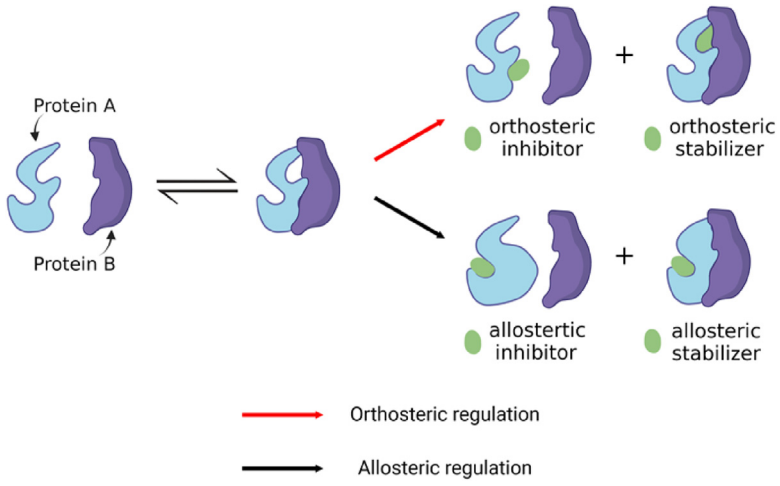


Figure 1 Mechanisms for PPI modulators: allosteric and orthosteric.

designed by AbbVie (Fig. 2B), exerts remarkable inhibitory potency against Bcl-2, Bcl-xl and Bcl-w[16]. Preliminary SAR studies have shown that (i) introduction of an acylsulfonamide maintained the correct positioning of the acidic proton; (ii) the 3-nitro-4-(2-phenylthioethyl) aminophenyl group efficiently occupied a binding site; and (iii) the lipophilic group 4-chlorobiphenyl was added to piperazine to access a deep pocket. Recent studies have reported that ABT-737 showed significant antiproliferative inhibitory efficacy against kidney cancer cells and enhanced the sensitivity of ovarian carcinoma cells to naftopidil[17]. However, ABT-737 is limited by its poor oral bioavailability and low absorption. Thus, ABT-263, as an alternative to ABT-737, was prepared by AbbVie (Fig. 2B)[18]. In subsequent experiments, researchers reversed the related structures of ABT-263 through the removal and replacement of key binding elements and found that the thiophenyl group was unnecessary and that the introduction of an indole group formed an important hydrogen bond with Asp103 of Bcl-2, which finally resulted in the inhibitor ABT-199 (Fig. 2C). The cocrystal structure shows that the tetrahydropyran ring and the 7-azaindole ring occupy two protein binding pockets (Fig. 2D). Specifically, it has a high target affinity ($K_i < 0.01$ nmol/L) and showed good selection for Bcl-2, with a low affinity for Bcl-XL, Mcl-1, and Bcl-w *in vitro* studies. In addition, ABT-199 has a good safety profile *in vivo* and is currently used for the treatment of chronic lymphocytic leukaemia[19,20].

2.1.1.2. Bcl-XL inhibitors. The Bcl-XL protein is associated with many physiological processes, especially tumour formation, and can bind to proapoptotic proteins. In 2013, Guillaume Lessene et al.[21] discovered a highly selective inhibitor WEHI-539 based on high-throughput screening (Fig. 3A). WEHI-539 showed a significant inhibitory effect on Bcl-XL with an IC_{50} value of 1.1 nmol/L. Further efforts in structure-based chemistry led to a selective inhibitor A-1155463, discovered by Tao et al.[22] (Fig. 3A). A-1155463 has a strong K_i value in the picomolar range, and *in vivo* studies have demonstrated that A-1155463 inhibits H146 small cell lung cancer xenograft tumour growth with multiple doses. Specifically, through NMR fragment screening and structure-based design, they replaced the benzylamine group with propargylamine and introduced a fluorine atom into the benzene ring, which significantly improved the ability of the inhibitor to target Bcl-XL and its physicochemical properties. In 2021, they connected core skeleton **6** and active skeleton **7** to form an amide bond and then discovered a new small molecule inhibitor, A-1293102 (Fig. 3B). The cocrystal structure shows that the nitrogen and amide protons on the benzothiazole ring form hydrogen bonds with Leu108 and Ser106, and the nitrogen atom and the oxygen atom on the thiazole part form hydrogen bonds with Arg139 and Asn136, respectively. One of the sulfonyl oxygen atoms formed bidentate hydrogen bonds with Asn136 and Gly138, and the benzenesulfonamide part occupied the hydrophobic pocket (Fig. 3C and D). These cause A-1293102 to exhibit a binding affinity in the picomolar range to Bcl-XL and effectively inhibits Bcl-XL-related tumour cells, which provides another chemical probe for the discovery of Bcl-XL inhibitors[23].

2.1.1.3. Mcl-1 inhibitors. Mcl-1 is a very promising cancer target in the Bcl protein family[24]. However, drug resistance limits its application[25,26]. Several recent studies have found that down-regulating the stability of Mcl-1 in tumour cells can improve tumour sensitivity to drugs[27,28]. For example, Mcl-1 inhibition increases the sensitivity of breast cancer cells to dasatinib[29]. In 2016, Johannes et al.[30] obtained compound **9** by screening a DNA-encoded library and then discovered compound **10** (Fig. 4A). It has good inhibitory activity against Mcl-1 with an IC_{50} value of 3 nmol/L. However, this macrocyclic peptide is not stable *in vivo*, so researchers have focused on natural products. In 2018, Samra et al.[31] discovered compound **14**, a dual Mcl-1/Bcl-2 inhibitor with good binding affinities that can induce apoptosis in Mcl-1/Bcl-2-dependent B-cell lymphoma cells (Fig. 4B). Specifically, based on Meiogynin A (a pan-Bcl-2 inhibitor), compounds **12** and **13**, they synthesized a series of side-chain derivatives optimizing the side chain group. In particular, the introduction of a triazole group to the side chain enhances selectivity and finally led to the dual inhibitor **14** of Bcl-2 and Mcl-1. Although it is a very promising compound, moving towards clinical trials remains a challenge.

Overall, inhibitors targeting different Bcl proteins are more diversified, including selective inhibitors, dual-target inhibitors, and Mcl-1 inhibitors, which have been popular in recent years. Some successful examples, such as the application of ABT-199, have inspired the development of small molecule inhibitors targeting the Bcl protein family. However, the drug properties of small molecule inhibitors remain a concern. In particular, a large molecular weight has advantages in targeting PPIs, but violates the

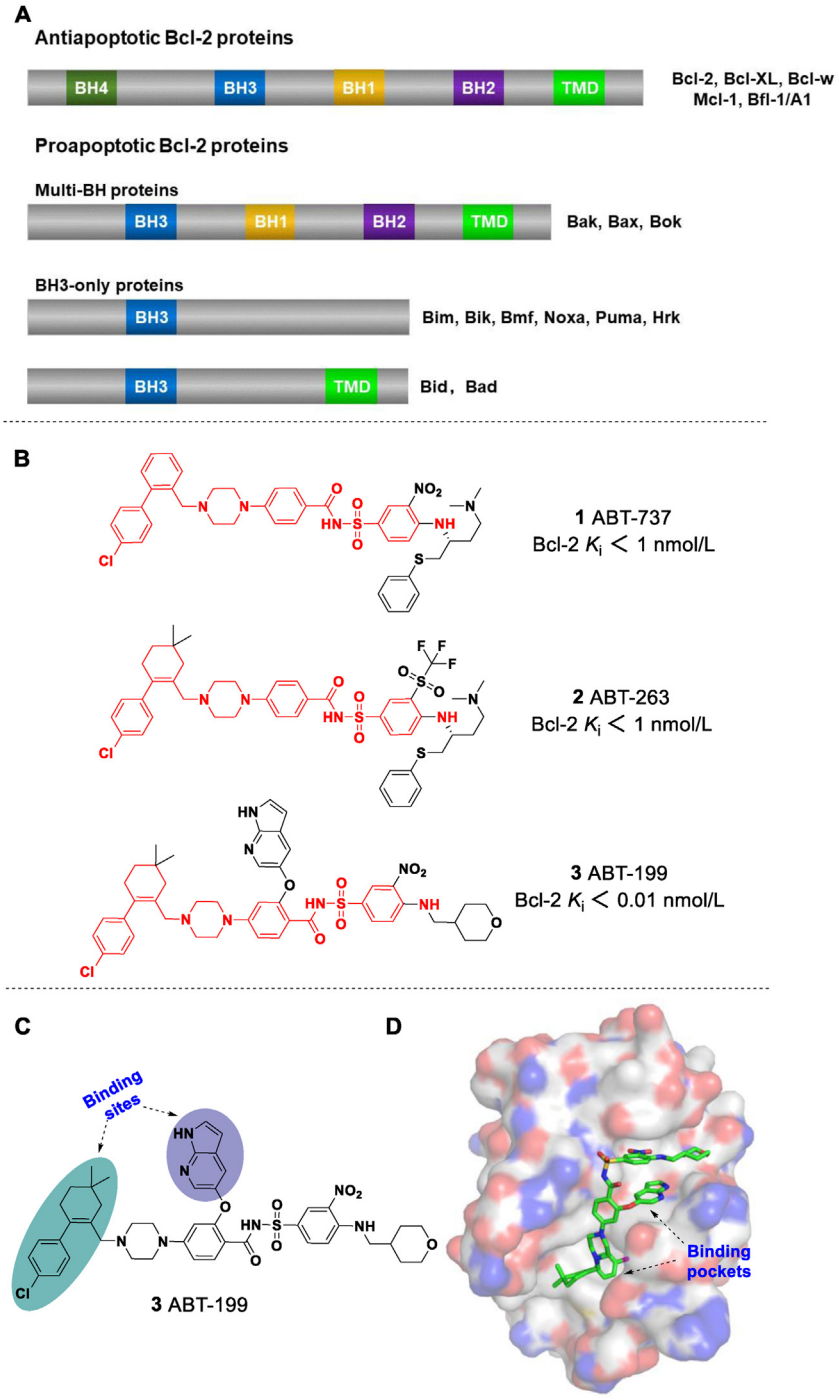


Figure 2 Inhibitors of the Bcl protein family. (A) Two categories of the Bcl protein family: anti-apoptotic Bcl-2 proteins and pro-apoptotic Bcl-2 proteins. The proapoptotic Bcl-2 proteins have two categories: multi-BH proteins and BH3-only proteins. (B) Chemical structures of the Bcl-2 inhibitors. (C) Chemical structure of ABT-199 and its indicated binding mode. (D) The cocrystal structure of Bcl with ABT-199 (PDB: 6O0K). The protein is illustrated with surface atoms, and compound atoms are in different colours: C, green; N, blue; O, red; S, brown; Cl, pink.

rules of druggability. The design of classical inhibitors depends on the BH3 domain, but the new generation of inhibitors should not only be limited to the inherent development strategy but also need to aim at homologous protein domain differences, explore the structure−activity relationship of new small molecule inhibitors, and enhance selectivity and the possibility of druggability.

2.1.2. *XIAP inhibitors*

Antiapoptotic factors play an essential role in regulating cell signalling, cell proliferation, and differentiation; in particular, they have a strong inhibitory effect on the apoptosis family, and inhibitors of apoptosis (IAPs) are representative of these factors[32−34]. These are known to include eight members, including NAIP, c-

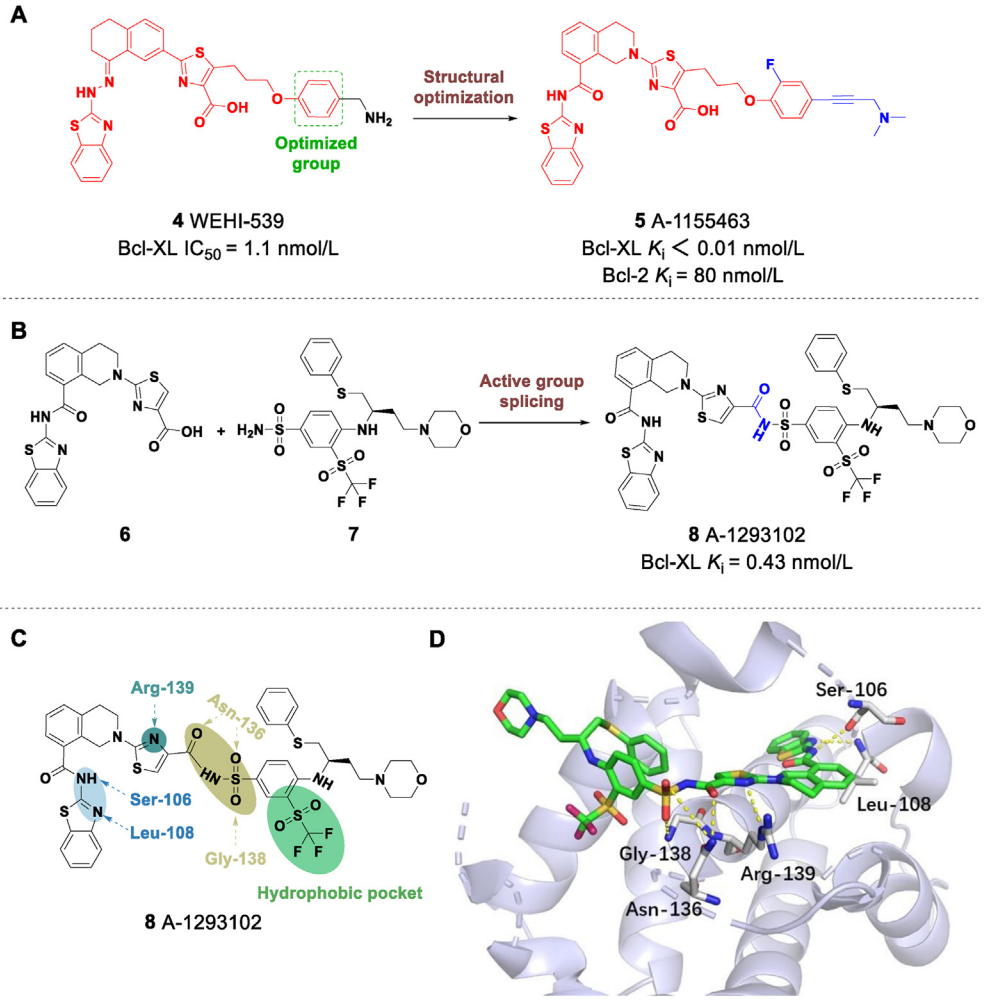


Figure 3 Inhibitors of Bcl-XL. (A) Chemical structures of WEHI-539 and A-1155463. (B) Design of the inhibitor A-1293102: chemical structures of **6**–**8**. (C) Chemical structure of A-1293102 and its indicated binding mode. (D) The cocrystal structure of Bcl with A-1293102 (PDB:7LH7). The protein is illustrated with white–blue ribbons, and the hydrogen bonds are depicted in yellow dashed lines. Compound atoms are in different colours: C, green; N, blue; O, red; S, brown; F, warm pink.

IAP1, c-IAP2, XIAP, survivin, Bruce, ILP-2 and Livin. Among these, X-linked inhibitor of apoptosis (XIAP) is the most potent IAP and contains two BIR domains (types 1 and 2), a ubiquitin-associated (UBA) domain and a RING domain (Fig. 5A). Specifically, the BIR2 domain of XIAP binds to the proapoptotic proteins caspase-3 and caspase-7, and the BIR3 domain binds to the pro-apoptotic protein caspase-9, thus inhibiting apoptosis[35,36]. Structurally, the design of inhibitors is predominantly aimed at mimicking the structure of Smac, a second mitochondrial-derived caspase activator designed from the BIR domain and whose N-terminal amino (Ala1-Val2-Pro3-Ile4, shorthand for AVPI) binds to the BIR domain, preventing XIAP from interacting with pro-apoptotic proteins and promoting apoptosis[37].

Smac-based drug design is divided into four categories: AVPI-based Smac polypeptide mimics, conformation-constrained monovalent IAP antagonists, bivalent IAP inhibitors, and non-alanine IAP antagonists. (i) AVPI-based Smac polypeptide mimics. GDC-0512, the first Smac mimic to start, was developed in 2012 by Flygare et al.[38] (Fig. 5B). It is a pan-IAP inhibitor of c-IAP1, c-IAP2, ML-IAP, and XIAP with K_i values of 17, 43, 14, and 28 nmol/L that efficiently inhibits breast cancer cell proliferation. Later, several comparable compounds were reported. By replacing one of the N atoms with a C atom and adding an oxazole ring to GDC-0512, the optimized inhibitor CUDC-427 exhibits a K_i of less than 60 nmol/L for XIAP and antitumour activity in a dose-dependent manner in breast cancer xenografts (Fig. 5B)[39–41]. LCL-161, an IAP inhibitor for the treatment of advanced solid tumours, is another classic drug (Fig. 5B). Similar to GDC-0512 and CUDC-427, the parent nucleus of LCL-161 has anticancer action in many cancer cell lines. It inhibits XIAP in HEK293 cells and cIAP1 in MDA-MB-231 cells with IC_{50} values of 35 and 0.4 nmol/L, respectively[40,42]. Although these inhibitors have a high binding affinity, their low cell permeability prevents their clinical development. Using nonnatural amino acids as the starting point for structural optimization might be an effective solution[43]. (ii) Conformation-constrained monovalent IAP antagonists. The most significant characteristic of this class of inhibitors is their bicyclic lactam structure. In 2004, Sun et al.[44] utilized structure-based design to discover a highly potent conformationally restricted Smac mimic, SM-122, with a K_i value of 25 nmol/L for binding to the BIR3 domain of the XIAP protein (Fig. 5C). By modifying the structure of SM-122 they developed SM-337, a powerful orally accessible diazabicyclic small molecule mimic of the second mitochondria-derived activator of caspases, which

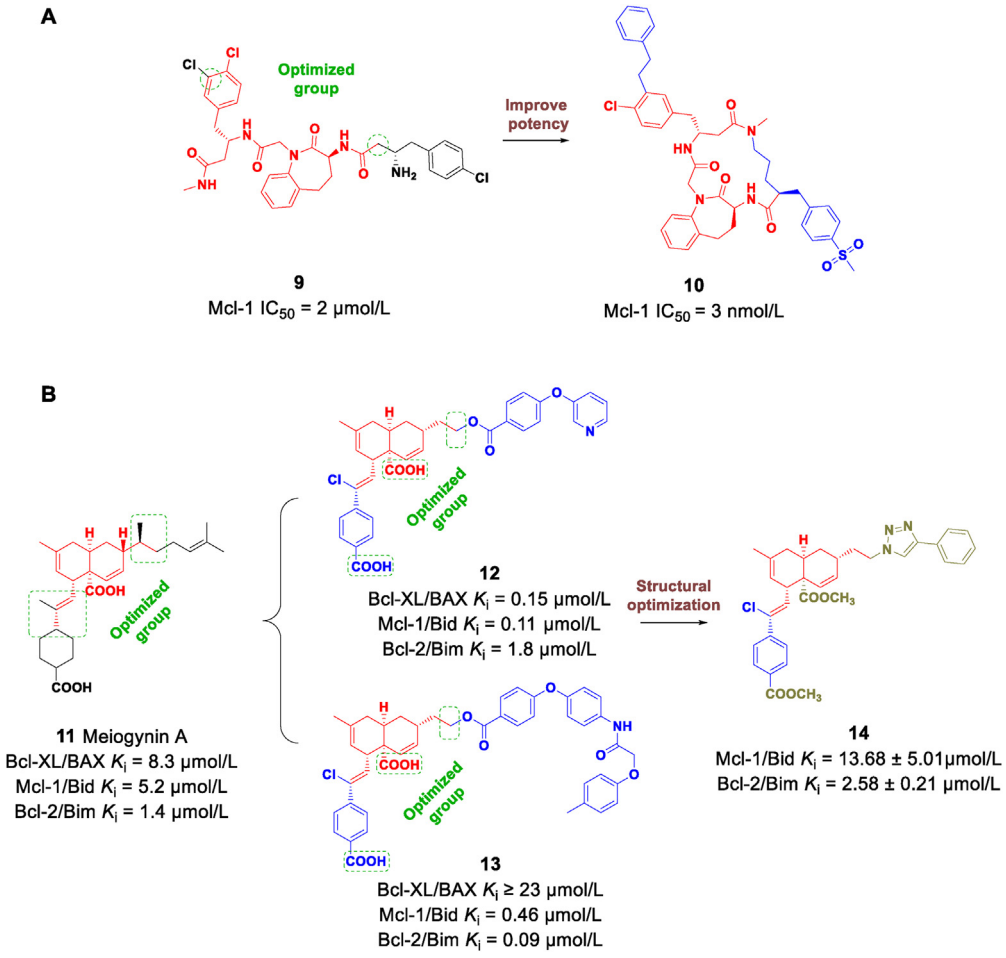


Figure 4 Chemical structures of MCL-1 inhibitors. (A) Chemical structures of **9** and **10**. (B) Chemical structures of **11**–**14**.

binds to XIAP, c-IAP1, and c-IAP2 with K_i values of 8.4, 1.5, and 4.2 nmol/L, respectively (Fig. 5C)[45]. Obviously, they also built an inhibitor, SM-1295, that targets c-IAP1/2 specifically (Fig. 5C). The K_i value of the BIR3 domain of c-IAP is over 1000 times greater than that of XIAP[46]. These mimetics provide additional strategies and tools for designing drugs that target IAP. (iii) Bivalent IAP inhibitors. Designing bivalent inhibitors that mimic the structures of Smac peptides to target BIR3 and BIR2 of XIAP is a superior technique compared to the majority of monovalent IAP inhibitors that absence of selection. For instance, TetraLogic Pharmaceuticals discovered the inhibitor birinapant (Fig. 6A), which includes two AVPI mimics with a linker that can target XIAP and interacts with the BIR3 domains of XIAP, c-IAP1, c-IAP2 and the single BIR domain of ML-IAP with K_d values of 50, 1, 36, and 1 nmol/L, respectively. It also induces degradation of the c-IAP1 and c-IAP2 proteins and blocks TNF-mediated NF-κB activation more effectively than monovalent inhibitors[41,47,48]. (iv) Nonalanine IAP antagonists identified by fragment-based drug discovery (FBDD). Instead of employing conventional AVIP as the design starting point, researchers used structure-based design to find numerous active nonalanine segments and optimized the segments for future study. In 2017, Tamanini et al.[41] discovered the inhibitor AT-IAP, a strong dual antagonist of XIAP and c-IAP1, by structure-based drug design (Fig. 6B). AT-IAP targets the BIR3 domain of the XIAP protein and the BIR3 domain of the c-IAP1 protein with IC_{50} values of 5.1 and 0.32 nmol/L, respectively. To increase metabolic stability and cardiac safety, a hydroxymethyl group was added to the pyridine ring, resulting in ASTX660 (Fig. 6B). The cocrystal structure shows that morpholine occupy the valine-binding pocket, and the fluorinated phenyl group is located on the hydrophobic side of the binding pocket. Additionally, a water molecule regulates the hydrogen bond interaction between the piperazine cyclic tertiary amine and Trp323 (Fig. 6C and D). ASTX660 is a potent inhibitor of c-IAP1 and XIAP with IC_{50} values of 0.22 and 2.8 nmol/L, respectively, that can induce TNF-dependent apoptosis and inhibit tumour growth in cancer cells with improved metabolic stability and cardiac safety and is currently being evaluated in a phase I/II clinical trial (NCT02503423)[49–51].

The majority of XIAP inhibitors contain AVPI active groups, and selective targeting of XIAP has received increasing attention. It is possible to increase selectivity with the development of bivalent inhibitors, which can increase effectiveness while minimizing the negative effects induced by pan-inhibition. Other novel strategies, such as proteolysis-targeting chimaera technology, combining different active groups with target degradation proteins, particularly some potent SMAC mimics and monovalent inhibitors, and assembling them into macromolecular compounds for degradation, are also possible for the development of XIAP inhibitors.

2.1.3. Inhibitors of the MDM2–p53 interaction

The *p53* gene is a human tumour suppressor gene, with an encoded product p53 protein, a transcription factor that regulates

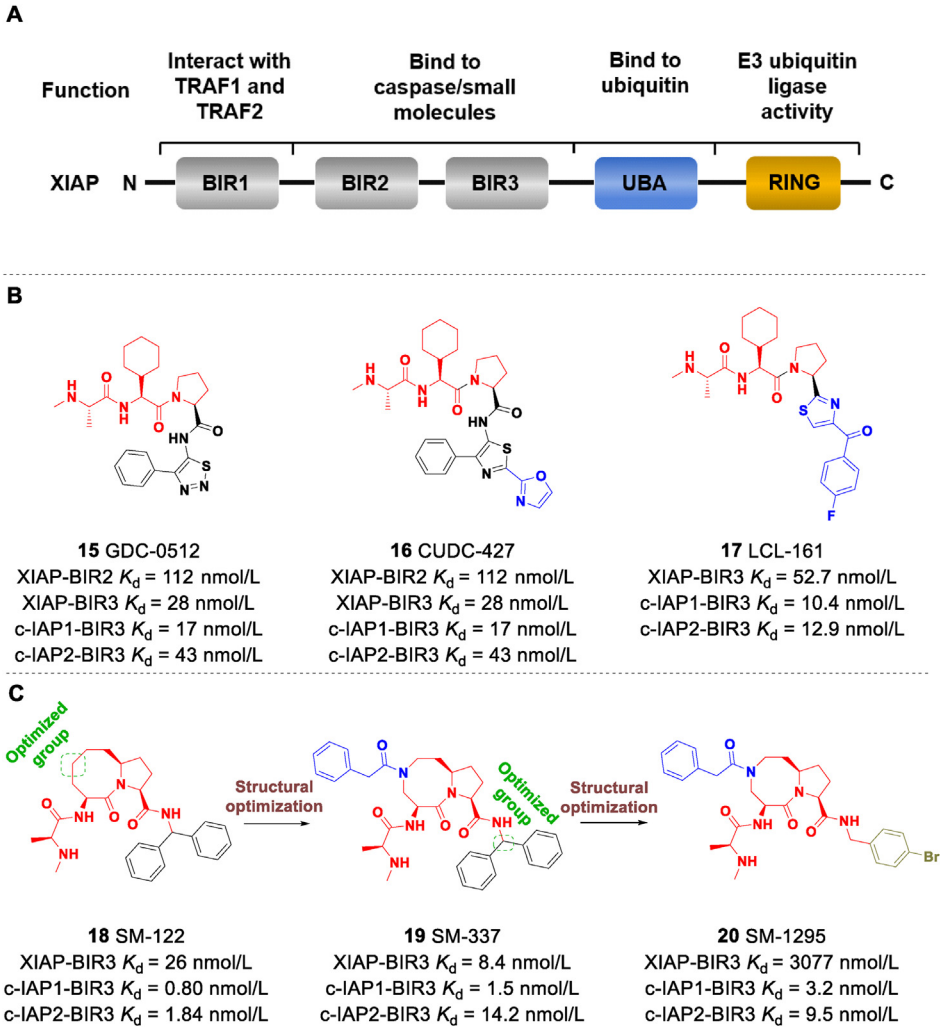


Figure 5 Inhibitors of XIAP. (A) Functional domains of XIAP, including three BIR domains, a UBA domain and a RING domain. (B) Chemical structures of inhibitors **15**−**20**: AVPI-based Smac polypeptide mimics **15**−**17**. (C) Conformation-constrained monovalent IAP antagonists**18**−**20**.

the cell cycle, promotes cell apoptosis and maintains genome stability[52,53]. Several studies have shown that the wild-type *p53* gene is a tumour suppressor and that the mutant *p53* gene is a tumour promoter. Notably, mutations in the *p53* gene are closely related to the occurrence and development of various cancers. In addition, mutations in the *p53* gene and interactions between the p53 protein and other proteins can cause inactivation of its normal function[54,55]. Many therapeutic strategies for targeting p53, including restoring p53 function through gene therapy, inhibiting the p53−MDM2 interaction, and restoring mutant p53 to wild-type p53, have been explored, with the most commonly used drug design strategy is to disrupt the p53−MDM2 PPI[56−58]. MDM2 is a critical negative regulator of p53, which can interact with the p53 protein to exert its function, and it is also an E3 ubiquitin ligase that can directly tag the p53 protein, resulting in ubiquitinated protein[59,60]. This PPI is associated with a variety of cancers, such as liver cancer, breast cancer, nasopharyngeal carcinoma and neuroblastoma[61−63].

X-ray protein crystallography reveals the main three key hydrophobic residues in the α-helix formed by the p53 protein (Phe19, Trp23, Leu26) (Fig. 7A)[64,65]. The primary strategy of PPI inhibitors is to imitate the p53 pocket (Phe19, Trp23, Leu26 pocket) in MDM2 to competitively bind to MDM2, thereby releasing wild-type p53 to exert an antitumour effect[58,66]. Most MDM2−p53 inhibitors are competitive inhibitors designed considering the p53 pocket in MDM2. In 2004, Vassilev et al.[67] discovered a class of imidazoline-containing compounds named Nutlins by using surface plasmon resonance technology and screening the imidazole compound library, which is the first class of potent small molecule inhibitors targeting MDM2−P53 (Fig. 7B). These molecules bind to the hydrophobic pockets of MDM2 (particularly Phe19, Trp23, and Leu26) to disrupt PPI and exert moderate inhibitory potency with IC_{50} values in the nanomole range[68]. Later, in 2013, Vu et al.[69]discovered the inhibitor RG7112 (Fig. 7B). RG7112 showed good inhibitory activity against PPI with an IC_{50} value of 18 nmol/L. Specifically, they modified the structure of Nutlin-3, mainly the ring bound to Phe19. They replaced the 4-methoxyl group with a *tert*-butyl group to improve its stability and used new piperazine ring derivatives to replace the previous piperazine ring. The cocrystal structure of MDM2−RG7112 shows that this compound binds to three pockets (Phe19, Trp23 and Leu26) (Fig. 7C and D). After a

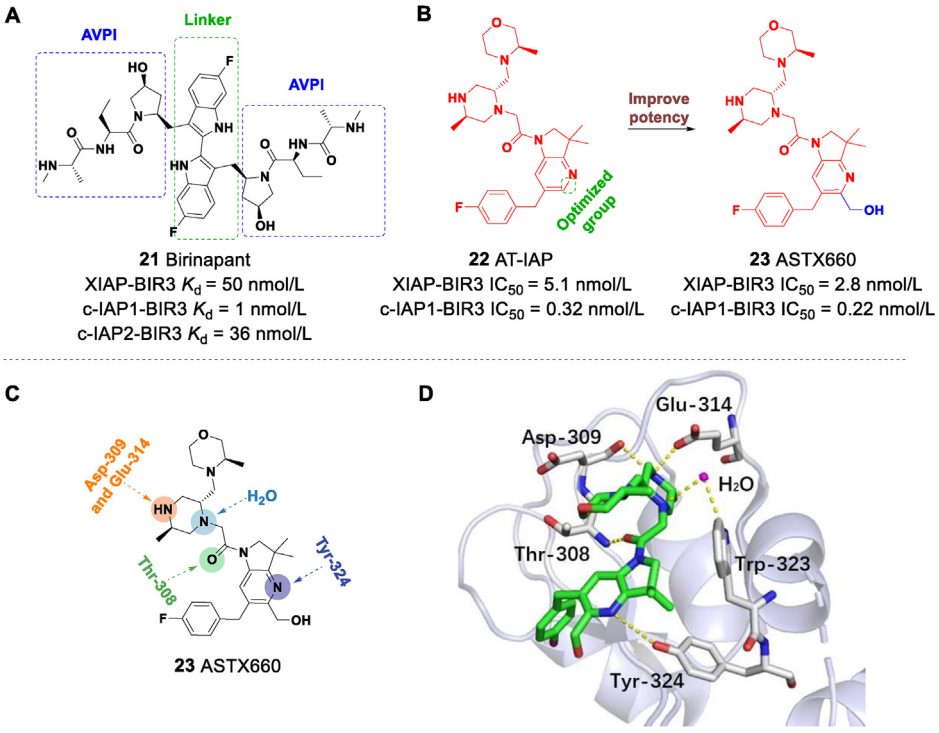


Figure 6 Chemical structures of inhibitors **21**−**23**: (A) Bivalent IAP inhibitor birinapant. (B) Nonalanine IAP antagonists **22** and **23**. (C) Chemical structure of ASTX660 and its indicated binding mode. (D) The cocrystal structure of XIAP with ASTX660 (PDB: 5OQW). The protein is illustrated with white-blue ribbons, and the hydrogen bonds are depicted in yellow dashed lines. Compound atoms are in different colours: C, green; N, blue; O, red; F, warm pink.

single oral administration of a 50 mg/kg dose, the pharmacokinetic parameters shows that the half-life of RG7112 is 8.8 h, and the AUG is 251.2 μg·h/mL. In particular, as the first experimental MDM2 inhibitor to enter clinical studies for the treatment of advanced solid tumours, it can effectively activate wild-type p53 and inhibit tumour growth in models of amplification of the *MDM2* gene and MDM2 protein overexpression[68,70]. To further improve its inhibitory activity, Ding et al.[71] further modified the structure of compound **28**, resulting in an optimized inhibitor RG7388 (Fig. 8A). Specifically, the cocrystal structure of MDM2−compound **28** shows that the binding mode is similar to the binding mode of MDM2−RG7112 (Fig. 8B and C). Then, the researchers chose a benzene ring derivative with more steric hindrance to replace the lipid chains and retained the substituent group of the oxygen atom in the benzene ring. This makes RG7388 exert strong inhibitory effects with an IC_{50} value of 6 nmol/L, and pharmacokinetic studies have shown that it has good bioavailability, moderate half-life, and metabolic stability, which can be used as a useful tool to study this PPI[70].

Several small molecule inhibitors that show good selectivity and pharmacokinetic specificity and have promising potential for cancer therapy have appeared in clinical trials. There are still obstacles to the development of these PPI inhibitors, notably acquired resistance and toxicity. Historically, acquired drug resistance has been a common issue in tumour therapy. The development of new MDM2−p53 PPI inhibitors, the construction of dual inhibitors targeting MDM2 and MDMX, the combination of drugs, the use of molecular glue technology, and the development of MDM2−PROTAC degraders are possible solutions to this issue[72,73]. In addition to activating p53 in tumour cells, these medications can also activate p53 in normal cells, resulting in unpleasant side effects. RG7112, for instance, can produce thrombocytopenia in a dose-dependent manner[74]. Therefore, the focus of research is on determining an optimal dosage that controls toxicity while maintaining potent anticancer action.

2.1.4. *Inhibitors of the CD40−CD40L interaction*

CD40 is a member of the tumour necrosis factor receptor superfamily (TNFRSF) and is a type I membrane glycoprotein that is frequently expressed on antigen-presenting cells (APCs) and B cells. Membrane CD40 (mCD40) and soluble CD40 (sCD40) can form a noncovalent homodimer, and sCD40 can act as a natural CD40 antagonist[75,76]. In addition to CD40L, Hsp70 and OspA also act as ligands for CD40[77,78]. CD40L (or CD154) is a type II membrane glycoprotein that is frequently expressed on the surface of T lymphocytes and appears in two different forms: membrane CD40L (mCD40L) and soluble CD40L (sCD40L). It can form trimers and bind to receptors. In addition to CD40, integrins αIIbβ3, α5β1, αMβ2, and αvβ3 can also bind to CD40L[79,80]. The CD40−CD40L interaction is the second signal source for lymphocyte activation, and it can influence the activation of T cells and B cells by engaging in costimulatory signalling (Fig. 9A)[76,81]. Costimulatory molecules can be divided into two categories: the immunoglobulin superfamily (IGSF) and the tumour necrosis factor receptor family (TNFRF), of which the CD40−CD40L interaction was the first TNFRSF costimulatory molecule identified and which is one of the most extensively studied TNFRSFs[82,83]. This PPI has been shown to be a stimulating immune checkpoint involved in the regulation of

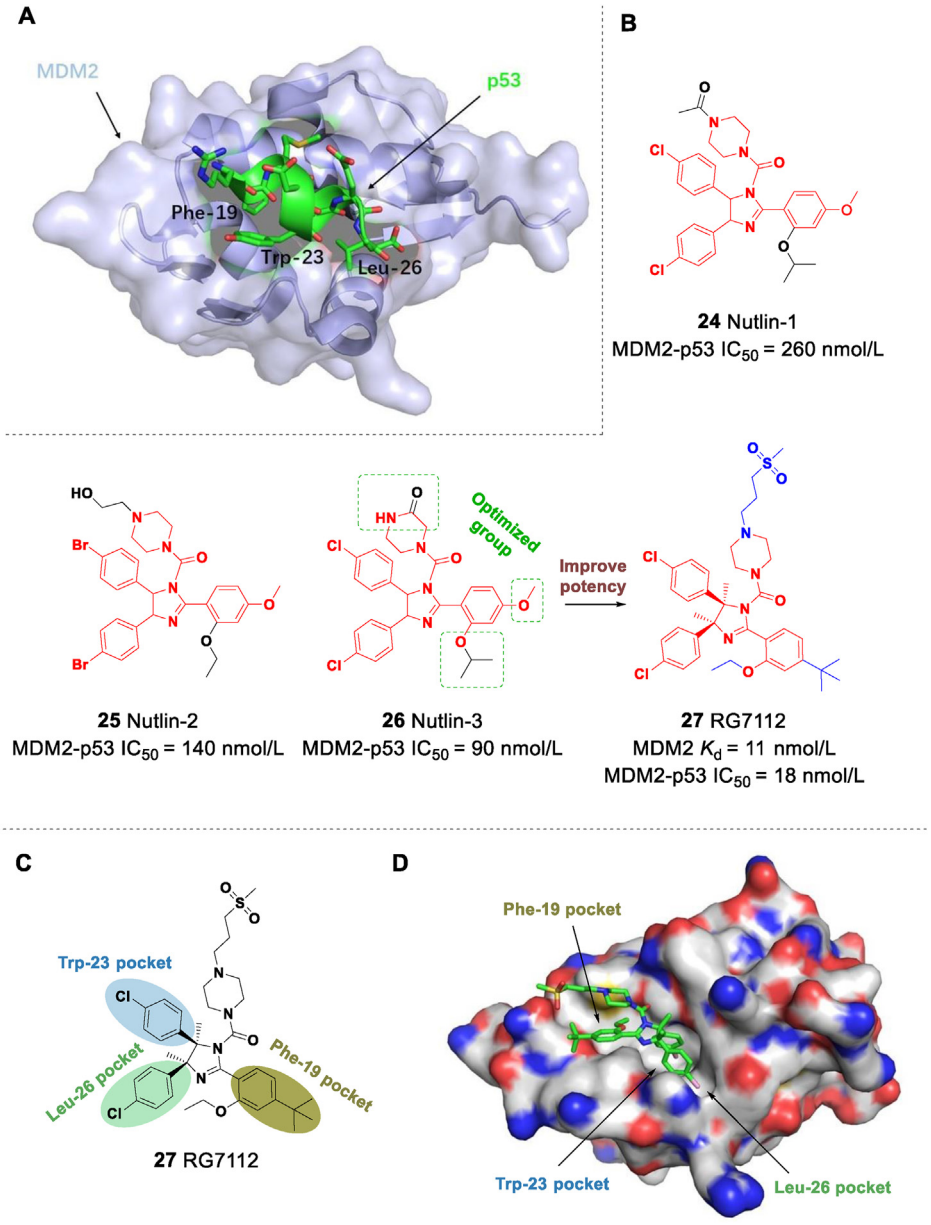


Figure 7 Inhibitors of MDM2−p53. (A) The complex of MDM2−p53 (PDB: 1T4F). (B) MDM2−p53 inhibitors **24**−**27**: design of the inhibitor RG7112. (C) Chemical structure of RG7112 and its indicated binding mode. (D) The cocrystal structure of MDM2 with RG7112 (PDB:4IPF). The protein is illustrated with surface atoms. Compound atoms are in different colours: C, green; N, blue; O, red; S, brown; Cl, pink.

physiological and pathological processes such as thrombosis, tissue inflammation, and haematopoiesis and its abnormal expression affects humoral and cellular immunity[84−86]. Therefore, the rational design of inhibitors that disrupt PPIs to combat immune dysregulation-related diseases and inhibit tumour escape are current research hotspots.

The drug design of small molecules targeting this PPI focuses on two aspects: direct targeting of CD40 (mainly antibody drugs) and CD40L (especially natural ligand analogues). Rarely have small molecule inhibitors been documented for therapeutic use, although antibodies dominate clinical applications. In 2009, Margolles-Clark et al.[87] reported that several small organic azo dyes can inhibit the CD40−CD40L interaction. In particular, based on suramin, a competitive protein tyrosine phosphatase (PTPases) inhibitor that has been reported to inhibit PPI, they discovered a class of naphthalene sulfonic acid derivatives **30**−**33** through an iterative structural similarity search and activity screening method, which can be used as a starting point for drug design targeting this PPI (Fig. 9B). Specifically, they replaced the chromophore azo linker with an amide linker while preserving the aromatic ring, and the bicyclic linker also showed stronger activity than the monocyclic linker. Subsequently, a series of synthetic small molecule inhibitors showed promising *in vitro* activity[88], among which the DRI-C21045 inhibitor has good selectivity and inhibitory activity, with an IC_{50} value of 0.17 μmol/L. DRI-C21045 can block CD40L-induced NF-κB activation, the expression of markers in THP, and B-cell proliferation and activation, according to *in vitro* mechanistic studies. Compounds **30**−**33** bind to CD40L instead of CD40. Considering the similarity of the structures, it is reasonable to speculate that this series

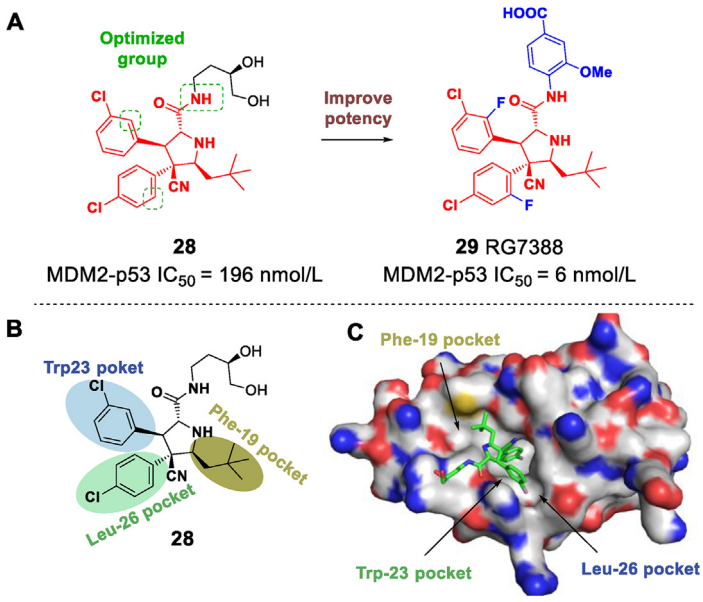


Figure 8 Design of the inhibitor RG7388. (A) Chemical structure of **28** and **29**. (B) Chemical structure of **28** and its indicated binding mode. (C) The cocrystal structure of MDM2 with **28** (PDB:4JRG). The protein is illustrated with surface atoms. Compound atoms are in different colours: C, green; N, blue; O, red; CN, orange; Cl, pink.

of small molecule inhibitors have the same binding mode and may disrupt this PPI in an allosteric manner, which provides a feasible idea for developing small molecule inhibitors to target the CD40−CD40L interaction.

Rarely have small molecule inhibitors been documented that target CD40−CD40L; nonetheless, various small molecule inhibitors with comparable active groups, such as the biphenyl group and the naphthalene sulfonic acid group, have been

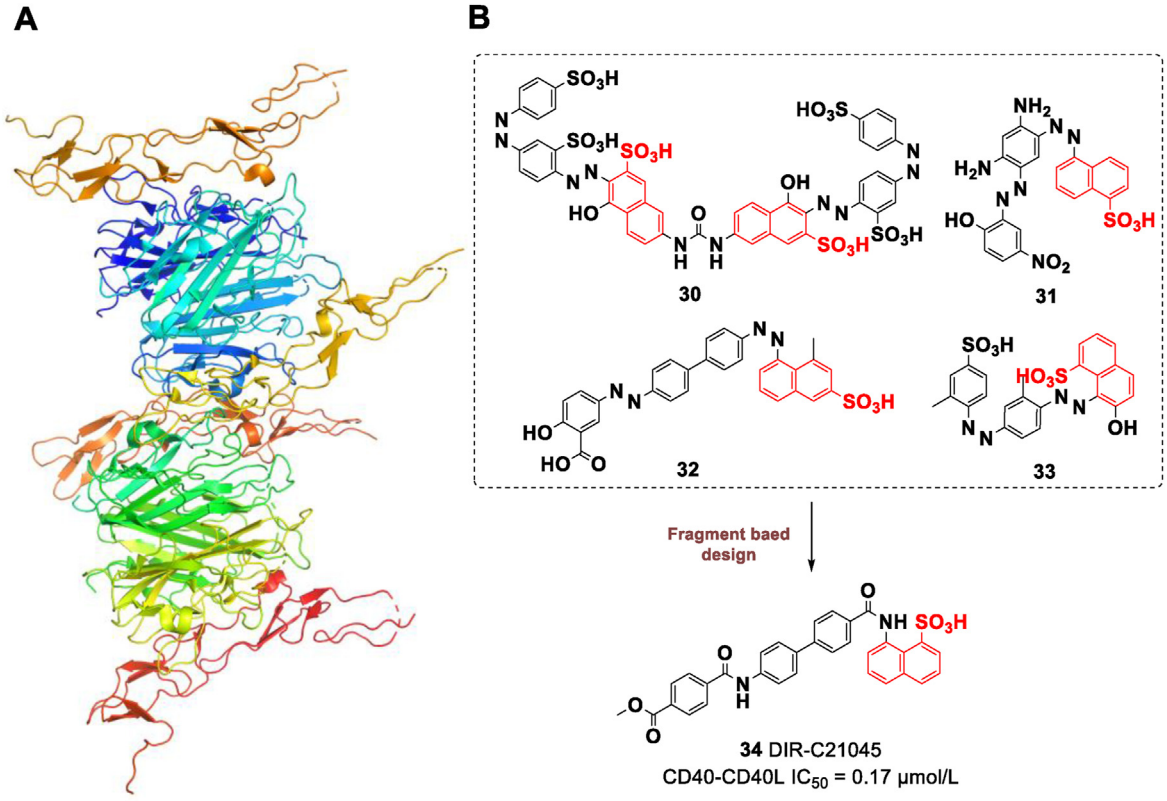


Figure 9 CD40−CD40L inhibitors. (A) The crystal structure of CD40−CD40L. (PDB:3QD6). (B) Design of inhibitor DIR-C21045.

described. Finding hotspots at the CD40−CD40L interface and examining the interactions between these active groups and hotspots provides more data for the design of small molecule inhibitors, which is an inspiration for structure-oriented drug design.

2.1.5. *Inhibitors of the PD1−PDL1 interaction*

PD1 is a key immunosuppressive molecule that belongs to the immune checkpoint and can promote apoptosis in antigen-specific T cells and inhibit apoptosis in regulatory T cells[89,90]. Its ligands are predominantly PDL1 and PDL2[90,91]. The key PDL1 receptors are PD1 and CD80. The PD1−PDL1 interaction causes programmed cell death, which is necessary to control autoimmunity, but the CD80−PDL1 interaction restricts T-cell activity, and the PDL2−PD1 interaction reduces immune cell function[89,92]. PDL2 can bind to another receptor, RGMB, to boost T-cell activation; hence, PDL2 can limit T-cell proliferation and induce T-cell death[93,94]. Therefore, it is challenging to utilize PDL2 as a direct tumour target. However, it is associated with anti-PD1 therapy and is expected to be used as an alternate therapy[95,96]. This PPI is expressed in several types of tumour cells. Its elimination has been found to be an effective anticancer approach because it stimulates the ability of T cells to attack tumours[90−92,97]. Various antibodies, peptides, and nonpolypeptide small molecule inhibitors have been employed clinically with variable degrees of success up to this point.

Small molecule inhibitors targeting PD1−PDL1 are mainly divided into three categories: (i) Biphenyl derivatives. Representatives of this class of inhibitors are a series of compounds produced by BMS Corporation, with IC_{50} values reaching the nanomolar level, which provides excellent probes and lead compounds for the design of small molecule inhibitors targeting PD1−PDL1 (Fig. 10A). In 2022, Wang et al.[98] discovered lead compound **41** with an IC_{50} value of 64.11 μmol/L. The structure of compound **40** was then altered by substituting the nitro group in nitrobenzene with a benzene ring. Subsequently, they explored the effect of substituent position on inhibitory activity, resulting in compounds **42** and **43** with IC_{50} values of 2.64 and 100 μmol/L, respectively. Compound **44**, a bifunctional inhibitor with an IC_{50} value of 27.8 nmol/L, was produced by altering the substituents of the aminobenzene portion (Fig. 10B). Compound **44** exhibits excellent *in vivo* anticancer activities. It inhibited PPI and accelerated the internalization and degradation of PD-L1. (ii) Natural product derivatives. Such inhibitors include caffeoylquinic acid compounds, of which 1-caffeoylquinic acid is the most well-known (Fig. 10C); it targets NF-κB and can resist oxidative stress with an IC_{50} value of 87.28 μmol/L. In 2018, Han et al.[99] examined the affinity and inhibition of caffeoylquinic acid compounds on the interaction of PD-1−PDL1 and discovered that 1-caffeoylquinic acid had an excellent inhibitory impact. (iii) Amino acid interface mimics. The PPI-targeting action of these compounds is achieved by the incorporation of amino acid residues that can interact with proteins and the use of complex heterocycles as the skeleton. CA-170, a small molecule inhibitor inspired by amino acids at the interface of PDL1, is the prototypical chemical (Fig. 10D). CA-170 had strong inhibitory activity against this PPI, with an EC_{50} of 17 nmol/L. It generates a new heterocyclic oxadiazole as the molecular skeleton, urea as the linker, and L-Ser, D-Asn, and L-Thr linked by the linker. This is the first small molecule inhibitor of PD1−PDL1 to achieve clinical testing (NCT02812875). *In vivo* preclinical data shows that CA-170 can significantly eliminate the inhibition of PDL1-induced T cells, stimulate IFN-γ production, and promote T-cell differentiation and proliferation[100,101]. This successful example not only inspires the design of PD1-related inhibitors but also benefits the design of other PPI inhibitors towards interface mimics.

Research on small molecule inhibitors of PD1−PDL1 is considerably behind that of antibodies, and there are no small molecule drugs on the market. Although a large number of small molecule PD1−PDL1 inhibitors have been discovered, the majority show modest inhibitory efficacy. Primarily, the difficulty of developing small molecule inhibitors is attributable to the intrinsic challenges of targeting PPI modulators, which are in opposition to the conventional Lipinski rule. Both oral bioavailability and specific targeting affinity sometimes necessitate greater molecular weights, which are not optimal for the design of small molecules. The turning point occurred when hot spots were discovered. In 2015, researchers determined the complex structure of the PPI and identified three major hot spot areas on PDL1 (Fig. 11). Tyr56, Glu58, Met115, and Tyr123 constitute the initial hotspot area. Met115, Ala121, and Tyr123 make up the second hotspot area. The third hotspot area is comprised of the main chain and the side chains spanning residues Asp122 to Arg125 and is flanked by the side chain of Asp26. This work provides a structural foundation for the design of small molecule pharmaceuticals[102].

2.1.6. *Inhibitors of the Hsp90−Cdc37−client interaction*

Hsp90 is a member of the family of heat shock proteins. As a molecular chaperone with five subtypes, including Hsp90A, Hsp92B, Hsp90C, TRAP, and HTPG, it is involved in the maturation of various client proteins and is related to several human disorders[103,104]. The N-terminal domain controls the binding of ATP, the middle domain interacts with client proteins and is the focus of ATP hydrolysis, and the C-terminal domain is responsible for dimerization[105,106]. ATPase activity is crucial to the process of Hsp molecular chaperone circulation. Breaking the ATP−Hsp bond is therefore one of the most researched Hsp-targeting techniques. However, its potential toxicity and reactivity to heat shock make this a contentious approach; thus, it is essential to identify alternative inhibitors. To perform its molecular chaperone function, Hsp90 requires cochaperones to form a complex. Cdc37 is an important cochaperone that can control the ATPase cycle in the Hsp90 protein, guide certain client proteins to Hsp90, and form a ternary complex with client proteins and Hsp90[107,108]. The Hsp90−Cdc37 complex interacts with hundreds of client proteins, and its wide involvement makes it a potential therapeutic target[109,110]. Based on the properties of its PPI, the design of its inhibitors focuses primarily on how to disrupt the PPI to inactivate Hsp90 and impede the maturation of client proteins to combat Hsp90-related diseases[110,111].

Currently, there are two primary kinds of PPI inhibitors: those targeting the Cdc37−client protein interaction and those targeting the Hsp90−Cdc37 interaction. (i) Inhibitors that target the Hsp90−Cdc37 interaction interface are predominantly natural compounds, such as the macromolecular lactone elaiophylin, which disrupts PPIs without affecting the ATP pocket of Hsp90 (Fig. 12)[112]. However, few small molecule compounds have been reported. In 2019, Wang et al.[113] screened the key residue sites of the Hsp90−Cdc37 interface, identified potential binding sites on Cdc37 (Arg167, Gln208, Arg246) and Hsp90 (Arg46, Glu47, Tyr61, Gln133), and then selected lead compound **47** from among 33 compounds (Fig. 12). After structural optimization, the PPI inhibitor DDO-5936 was discovered (Fig. 12). Experiments with tumour xenografts also indicate that it significantly inhibits mouse

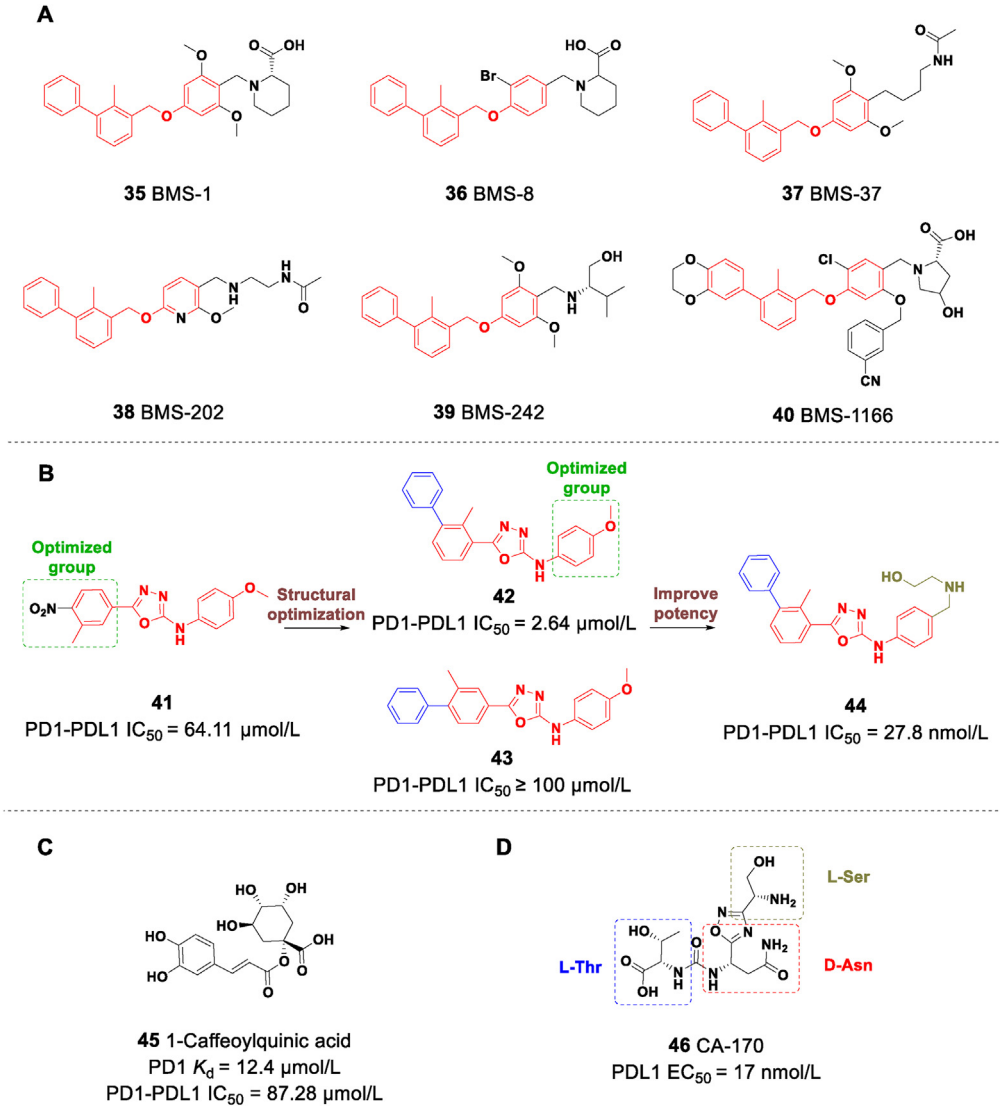


Figure 10 PD-1−PDL1 inhibitors **35**−**46**. (A) Chemical structure of **38**−**40** produced by BMS Corporation. (B) Chemical structure of **41**−**44**. (C) Chemical structure of 1-caffeoylquinic acid. (D) Chemical structure of CA-170.

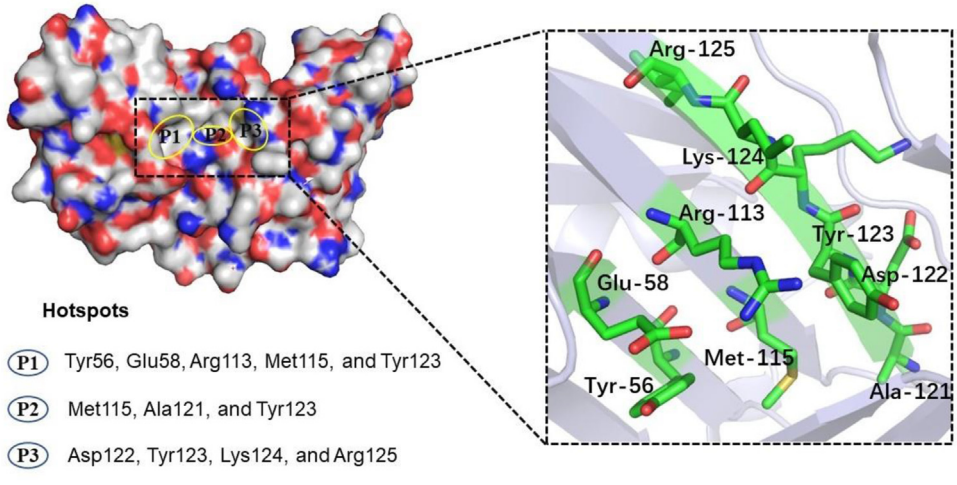


Figure 11 Structure of the complex of human programmed death-1 (PD-1) and its PD-L1 ligand (PDB: 4ZQK). There are three main hotspots: 1) Tyr56, Glu58, Arg113, Met115, and Tyr123; 2) Met115, Ala121, and Tyr123; and 3) the main and side chains form extension grooves, from Asp122 to Arg125, and the two sides are Asp26.

colon cancer. In 2020, the research team further optimized DDO-5936 by substituting the tetrahydrofuran ring with a piperazine ring and generated compound **49** with the highest *in vitro* binding affinity (Fig. 12). It increases antiproliferative activity, preferred stability in plasma and microsomes, and oral efficacy *in vivo* compared to DDO-5936, providing a viable option for Hsp90-targeted cancer treatment[113]. Another example is derived from natural substances. Based on the pharmacophore model and molecular docking study of conglobatin A, Siddiqui et al.[114] obtained a series of derivatives with micromolar affinity. This class of molecules is capable of interrupting the Hsp90−Cdc37 interface without attaching to the ATP pocket. Two inhibitors, X1540 and X1742, have been proven in *in vitro* and *in vivo* experiments to inhibit cancer cell proliferation and microtumour growth, providing a novel alternative technique for targeting this PPI (Fig. 12). (ii) As an alternate therapeutic, it is also viable to target Cdc37−client protein[115]. Cdc37 client protein inhibitors have two critical regulatory points: 1) Phosphorylation-specific targeting of the conserved Ser13 site: Dephosphorylation control of Ser13 influences the activity of Hsp90-dependent protein kinases, which is essential for the binding of Cdc37 to protein kinases, according to previous studies[116,117]. Furthermore, Ser13 phosphorylation of Cdc37 is regulated by CK2; hence, inhibition of CK2 can decrease Cdc37 phosphorylation and protein kinase levels[118,119]. 2) The dephosphorylation of Cdc37, which is mediated by PP5 (a serine/threonine-protein phosphatase) and is essential for the release of client proteins. However, this type of inhibitor is still under investigation[119,120].

Indeed, Cdc37 is a viable target, as evidenced by its intimate relationship with Hsp90 and the client protein. PPI inhibitors based on this protein have been discovered to have strong inhibitory capacity but are not yet clinically relevant. Meanwhile, their on-target activity and potential for off-target activity should be evaluated. Using them as probes to analyse PPI inhibitors of Hsp90 and to obtain novel active compounds based on structure optimization will be the primary technique for finding such inhibitors in the future, particularly when employing natural products with demonstrated significant activity.

2.1.7. *Inhibitors of the C-Myc−MAX interaction*

C-Myc, N-Myc, and L-Myc belong to the Myc class of nuclear protein oncogenes. The *Myc* gene encodes an important transcription factor, the C-Myc protein, which is overexpressed or physically altered in approximately 70% of human malignant tumours[121,122]. It consists primarily of an N-terminal transactivation domain (TAD), the highly conserved transcription element Myc box (MB), a central region involved in stability, and a C-terminal basic helix-loop-helix leucine zipper (bHLHLZ) domain (Fig. 13A). It interacts with recombinant human Myc-associated factor X (MAX) to form a heterodimer that recognizes and binds to the E-box sequence (CACGTG) of DNA (Fig. 13B)[122,123]. This PPI is considered a viable target because it controls gene expression and stimulates the transcription of regulated genes[124−126]. Myc was once difficult to therapeutically target due to its lack of a well-defined ligand binding site and its wide PPI interface; nevertheless, it now has the potential to be medicinal[125,127].

The most prominent inhibitor is Omomyc, a mimic of the bHLHLZ domain of C-Myc that overcomes the challenge of lacking typical small molecule binding pockets[128]. It has two primary antitumour mechanisms: (i) Omomyc forms a dimer to limit the binding of the C-Myc−MAX heterodimer to DNA, thus inhibiting Myc-mediated transcription; (ii) Omomyc directly binds MAX to inhibit Myc-mediated transcription[128,129]. As a peptide, it is susceptible to degradation *in vivo*. Consequently, it is difficult to make the required structural alterations to Omomyc to

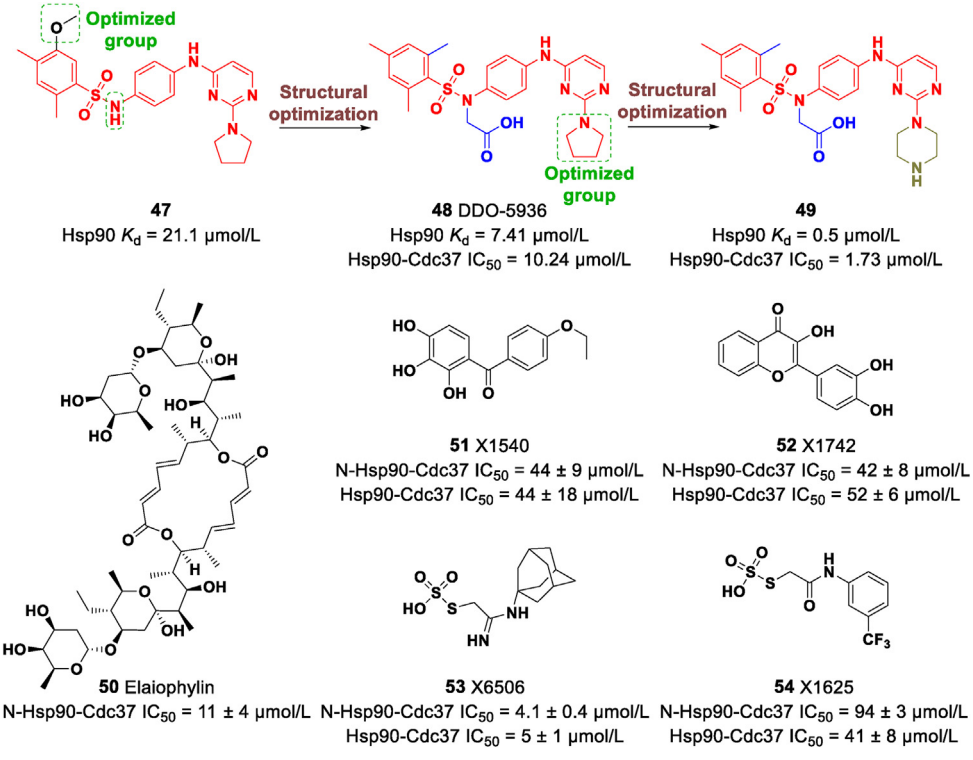


Figure 12 Chemical structure of inhibitors **47**−**54**.

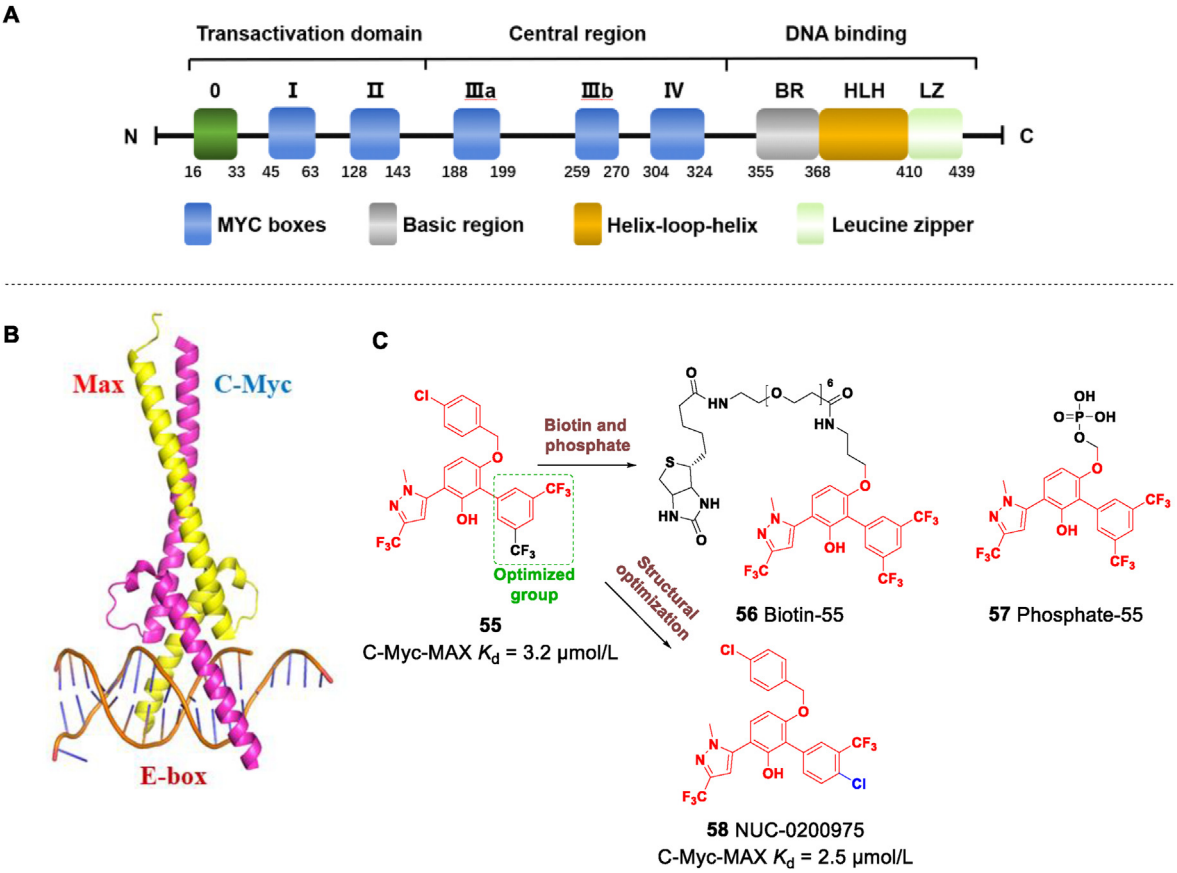


Figure 13 Inhibitors of C-Myc−MAX. (A) Functional domain structure of the C-Myc protein. (B) Cocrystal structure of DNA-bound basic helix loop helix leucine zipper (bHLHZip) domains of C-Myc−Max (PDB:1NKP). (C) Chemical structure of **55**−**58**.

prevent its deterioration[129]. Using macropinocytosis to transfer Omomyc directly into cancer cells, for instance, may be a potential technique[130]. In 2019, Han et al.[131] developed active compound **55** with a K_d value of 3.2 μmol/L by combining computer-aided drug design and quick screening in mice (Fig. 13C). To further examine its interaction with the Myc protein, they synthesized biotin-**55** and soluble phosphate-**55**, which are derivatives of compound **55** (Fig. 13C). They found that compound **55** decreases Myc protein stability by modulating Myc-Threonine **58** phosphorylation, and the binding site of compound **55** to the Myc protein was determined by comparing it with previously reported inhibitor binding sites (amino acid 366−378)[132]. Subsequently, they analysed the structure−activity connection of compound **55**, changed the substituents at various places, and replaced *m*-trifluoromethyl benzene with *ortho*-chloro-substituted trifluoromethyl benzene. With a K_d value of 2.5 μmol/L, the inhibitor MUC-0200975 is produced with increased tolerability at significantly higher doses (Fig. 13C). It inhibits Myc-dependent cancer cell viability and suppresses Myc transcriptional activity, providing a basis for the design of chemical probes and potential anticancer treatment drugs.

As a widely distributed oncoprotein, C-Myc is a target for pharmacological treatment; nevertheless, small molecule inhibitors have not yet reached clinical trials, possibly due to low affinity and targeting selectivity: (i) it is difficult for small molecule inhibitors to target endogenous C-Myc protein; (ii) it is challenging for small molecule inhibitors to selectively bind to bHLHZip motifs of C-Myc. In conclusion, resolving these challenges is the future path of small molecule inhibitor research.

2.1.8. *Inhibitors of the Menin−MLL interaction*

The *MLL* gene, also known as the mixed lineage leukaemia gene, encodes a protease that mediates the methylation of histone H3 lysine 4 (H3K4) and has a crucial function in the regulation of gene expression and cell proliferation[133−135]. Chromosomal translocation or rearrangement of MLL, which produces the MLL fusion gene and encodes the oncogenic MLL fusion protein, is highly correlated with the development of acute myeloid leukemia[135,136]. The Menin protein is a crucial oncogenic cofactor of the MLL fusion protein in acute leukaemia; it interacts directly with the amino terminus of the MLL fusion protein, leading to overexpression of the *MEIS1* and *HOXA* genes which stimulate the appearance of MLL[136,137]. Therefore, interrupting the Menin−MLL interaction has been developed as a treatment method for MLL[135,136,138,139].

Few studies on small molecule Menin−MLL inhibitors have been conducted in recent years. Only the inhibitors KO-539 (NCT04067336) and SNDX-5613 (NCT04065399) have entered clinical trials (Fig. 14A)[138]. SNDX-5613 has a K_i of 0.149 nmol/L and an IC_{50} of 10−20 nmol/L for blocking this PPI, but study of KO-539 has not yielded relevant information. In 2018, based on a previously reported moderately potent reversible inhibitor MIV-6, Xu et al.[140] replaced the free primary amine with a metabolically stable cyano group, introduced azacyclic butane to the nitrogen

atom of tetrahydropyridine as a linker, and connected the cyclobutyl sulfonyl group to covalently combine Cys329. Simultaneously, the addition of a dimethylamino methyl group to the acrylamide group boosted its solubility, while the insertion of reverse carbamate into cyclopentane and fluorine atoms into the benzene ring enhanced its binding affinity. After a series of tweaks, they obtained M-525, a first-of-its-kind, irreversible and powerful Menin−MLL interaction inhibitor with an IC_{50} of 3.3 nmol/L (Fig. 14B). Then, they replaced the cyano group with azetidine and the dimethylaminomethyl group with tetrahydropyridine, obtaining the covalent inhibitor M-808, which has strong cellular activity but low oral bioavailability in mice with an IC_{50} of 2.6 nmol/L (Fig. 14B)[141]. To enhance its oral bioavailability, they replaced the Michael acceptor group with a diazabiheterocycle, inserted a methoxy group, and eventually obtained the inhibitor M-1121 (Fig. 14B). The cocrystal structure of M-1121 in complex with Menin shows that the 2,5-diazabicyclo [2.2.1] group establishes hydrophobic interactions with Menin and places the acrylamide group in a position that can form a covalent bond with the sulphur atom in Cys329 of Menin (Fig. 14C and D). This is a covalent and orally active inhibitor that could eventually and continuously cause tumour regression with an IC_{50} value of 10.3 nmol/L, which prompted the investigation and development of this inhibitor[142].

Mixed lineage leukaemia has long been considered an incurable disease, but the studies of small Menin−MLL interaction inhibitors have yielded information towards MLL therapy. Although there are several varieties of small molecule inhibitors such as the thienopyrimidine series, the pyrimidine series, and the "propeller-type" series, only two inhibitors have entered clinical trials that possess

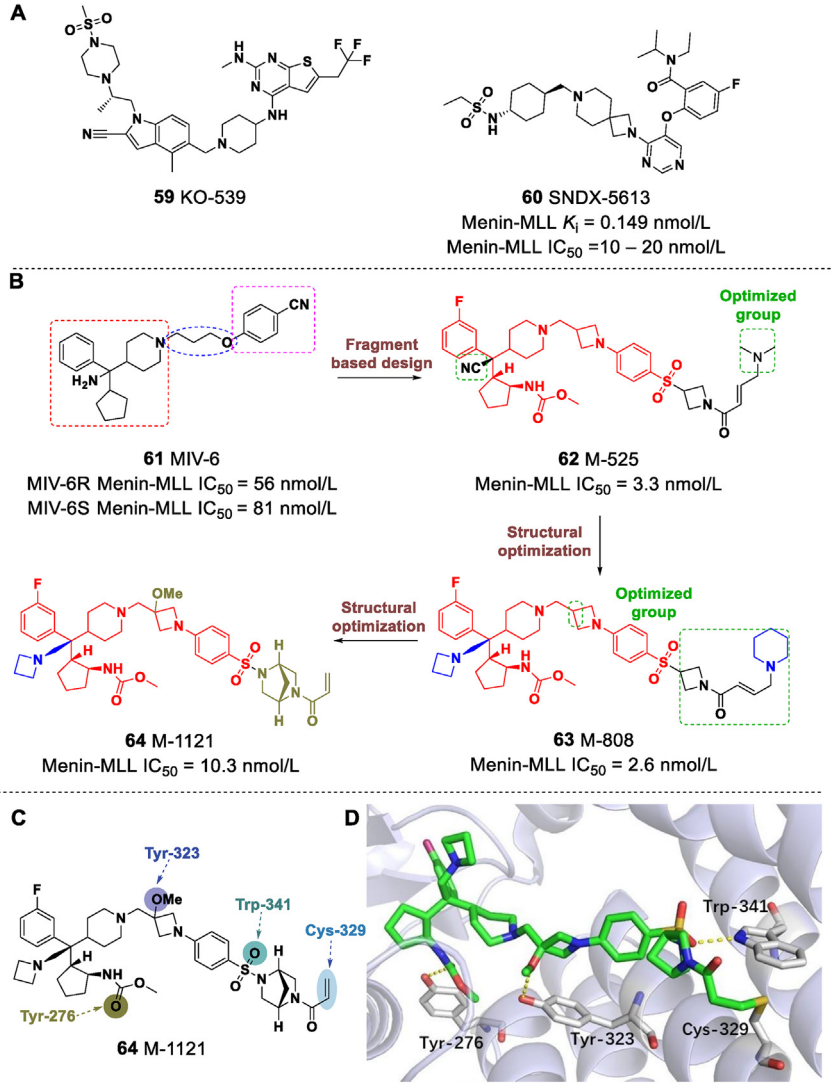


Figure 14 Inhibitors of Menin−MLL. (A) Chemical structures of KO-639 and SNDX-5613. (B) Design of the M-1121 inhibitor: chemical structure of **61**−**64**. (C) Chemical structure of M-1121 and its indicated binding mode. (D) The cocrystal structure of Menin with M-1121 (PDB:7M4T). The protein is illustrated with white−blue ribbons, and the hydrogen bonds are depicted in yellow dashed lines. Compound atoms are in different colours: C, green; N, blue; O, red; S, orange; F, warm pink.

good drug-like properties. Therefore, future research will focus on enhancing pharmacokinetic properties and identifying new structural scaffolds, especially highly active probes.

2.1.9. *Inhibitors of the Keap1−Nrf2 interaction*

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor belonging to the Cap'n'collar (CNC) family, with seven Neh domains. Nrf2 activation is essential for antioxidation and endogenous and external cell damage. It is a key transcription factor that modulates antioxidative stress and stimulates the expression of several genes and is implicated in numerous physiological processes including autophagy, apoptosis, and inflammasome signalling[10,143,144]. Kelch-like ECH-associated protein 1 (Keap1) is a Cullin3 (Cul3)-dependent E3 ubiquitin ligase complex substrate adapter protein with three functional domains: BTB, IVR, and Kelch/DGR[144]. As a negative regulator of Nrf2, it forms an active E3 ubiquitin ligase complex (Keap1−Cul3−E3) with Cul3 and Rbx1[144−146]. The Keap1−Nrf2−ARE signalling pathway is an antioxidant stress route that plays a crucial role in generating the body's antioxidant response and is broadly implicated in modulating physiological processes including redox homeostasis, amino acid metabolism, and DNA repair. This PPI stimulates Nrf2 ubiquitination and degradation and breaks the Keap1−Nrf2 contact with the Keap1−Nrf2 interaction, hence activating Nrf2, which in turn activates downstream signalling to control cellular physiology[144,147,148]. It has become a key therapeutic target for cancer, degenerative diseases, and autoimmune disorders[149,150]. Aberrant Keap1−Nrf2 interaction is most prominent in non-small cell lung cancer, commonly known as a Nrf2-dependent malignancy. Targeting this PPI is a novel therapeutic option for incurable diseases such as lung cancer[151−153].

The Keap1−Nrf2 interaction has been the subject of many studies on the discovery of inhibitors, mostly small compounds and peptides. Numerous strategies have been applied to the development of peptide inhibitors, with a primary emphasis on improving the affinity, selectivity, and stability of peptides[154−156]. In contrast, the majority of current research on small molecule inhibitors focuses on improving affinity and cellular activity. In 2019, Heightman et al.[157,158] reported three of the most important active pieces, namely, acid (**65**), planar acceptor (**66**), and sulfonamide (**68**) (Fig. 15A). The structure of these compounds was subsequently improved by incorporating the planar fragment into the planar acceptor−4-chlorophenopropionic acid, which occupies the acid site and yields active hit **67** with the substituted scaffold of phenyl methylbenzotriazole propionic acid (Fig. 15A). Then a benzenesulfonamide was substituted into the *ortho* position of the chloro substituent, yielding compound **69** with an IC_{50} of 69 nmol/L (Fig. 15A). The structure of compound **69** was further optimized with the use of cocrystal structure, NMR solution conformational and molecular modelling studies, and a potent inhibitor **70** with an IC_{50} of 20 nmol/L in FP detection was achieved (Fig. 15A). A study of the stereoisomer of compound **70** revealed that (*R*, *S*) was the preferred configuration, resulting in the most potent compound **71** (K_d = 1.3 nmol/L; EC_{50} = 12 nmol/L) (Fig. 15A). The cocrystal structure of Keap1 domain-compound **71** shows that compound **71** has good hydrogen bond interactions with Keap1, including Gln530, Ser555 and Arg483. In particular, the benzotriazole core produces a π-stacking interaction with Tyr525, and the benzene ring has a π-stacking interaction with Tyr334 (Fig. 15B and C). This is a high-affinity probe that interferes with the Keap1−Nrf2 interaction, providing a novel strategy to target Keap1−Nrf2 and enhancing the high affinity and cellular activity of small molecule inhibitors.

Several potent inhibitors have been reported and some have shown favorable pharmacokinetic properties over the past few years. Specifically, inhibitors with a 1,4-diaminethaphene core or a 3-phenylpropanoic acid core have been the main focus of Keap1−Nrf2 inhibitor research. Both focus on the conformation-based technique for structural optimization and the necessity of a preformed structure to boost binding affinity and are primarily designed to replicate the ETGE motif of Nrf2. Although some substances have demonstrated favourable pharmacokinetic qualities, possible off-target effects should not be disregarded, especially the carcinogenic effect due to excessive activation of Nrf2. To address these issues, the use of other Nrf2 motifs as imitation targets may be a potential future research topic. In addition, it is important to explore other pharmacological mechanisms of Keap1−Nrf2, such as its potential in the treatment of Alzheimer's disease.

2.1.10. *Inhibitors of the Kras−SOS1 interaction*

Kras protein is a small GTPase encoded by the *Kras* gene. Kras is a member of the Ras protein family, and Kras mutations are associated with aberrant tumour development and proliferation[159,160]. They exist in two states: an active form bound to GTP and an inactive form bound to GDP. SOS1 is a critical regulator of the Kras protein, as it is a guanine nucleotide exchange factor (GEF) that can bind to GDP-bound Kras, enhance GDP exchange to GTP, and convert inactive Kras protein to active Kras protein[161,162]. There are now a variety of Kras protein inhibitors with various mechanisms including directly targeting Kras mutants, indirectly controlling the protease that attaches to the plasma membrane, and reducing RAS signalling by blocking Ras effectors[163]. Indirect targeting of the GEF protein that controls Kras activity has become a potential option after the development of its inhibitors targeting directly proved unsatisfactory due to druggability[164−166].

In 2021, Ramharter et al.[167] discovered an inhibitor BI-68BS with an IC_{50} in the picomole range (Fig. 16A). In particular, they introduced an amino group into the benzene ring to form a hydrogen bond, introduced the strong electron withdrawing trifluoromethyl group to increase the acidity of the amino group, and changed the methoxy group to a phenol-hydroxy-linked tetrahydrofuran, resulting in the inhibitor BI-3406 with an IC_{50} of 4 nmol/L (Fig. 16A). Additionally, BI-3406 (**73**) was effective in conjunction with the upstream EGFR inhibitor erlotinib against Kras-mutant colorectal carcinoma cells *in vivo* (Fig. 16B). The reported compounds are based on high-throughput screening and contain a quinazoline skeleton, while few compounds with additional skeletons have been reported (Fig. 16). The conversion of the *N*1-quinazoline nitrogen (**76**) to the phthalazine core (**77**) is readily tolerated (Fig. 17A)[168]. Ketcham et al.[169] used a simplified class of 6,7-dimethoxy-substituted phthalazines as a starting point and found that C4-methyl substitution can inhibit the metabolism mediated by aldehyde oxidase in component S9 of the human liver. Substitution of C7 with piperazine can greatly enhance activity, but substitution of C6 has little effect on binding. The C6 carbon atom is swapped with nitrogen to decrease lipophilicity, and neutral morpholine replaces basic piperazinyl to increase bioavailability in mice. Subsequently, *O*-tolyl cyanide was introduced to C1-benzyl amine, and the cocrystal structure revealed that the electron-withdrawing group cyano may increase the edge-to-face contact with Phe890. The *O*-dimethazine core produces a π-stacking interaction with His905, N−H from the C1-benzylamine substituent produces a critical hydrogen bond with Asn879, and the nitrogen at

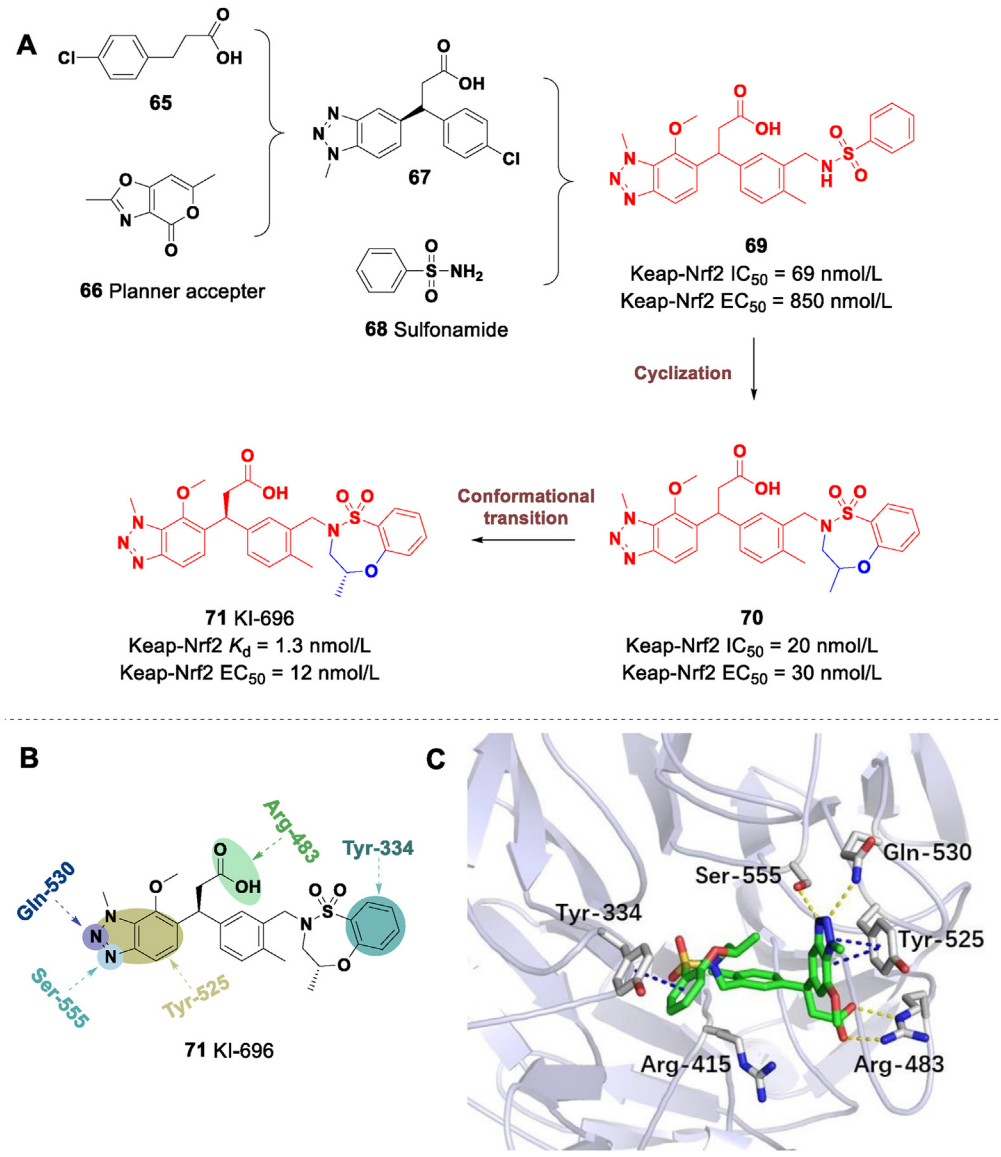


Figure 15 Design of the inhibitor KI-696. (A) Chemical structure of **66**−**71**. (B) Chemical structure of KI-696 and its indicated binding mode. (C) The cocrystal structure of Keap1 with KI-696 (PDB:5fnu). The protein is illustrated with white−blue ribbons, and hydrogen bonds and π-stacking interactions are represented by yellow and red dashed lines, respectively. Compound atoms are in different colours: C, green; N, blue; O, red; S, orange.

the 3-position of the phthalazine core is protonated, which can form a salt bridge with the carboxylate of Glu902 (Fig. 17B and C). The above modifications eventually resulted in the inhibitor MRTX0902, a selective, brain-penetrant, and orally bioavailable inhibitor of SOS1−Kras with an IC_{50} of 29 nmol/L (Fig. 17A). Notably, this inhibitor has a novel skeleton, that is distinct from others previously discovered, offering useful insights for the design of inhibitors targeting the Kras−SOS1 interaction.

Due to the lack of small molecule binding sites and pockets on the surface of proteins, Kras has long been regarded as a non-accessible target; thus, indirect targeting of SOS1 to impede the formation of the SOS1−Kras complex to modulate downstream signalling is an extremely intriguing therapeutic strategy. However, as a novel target, the study of SOS1 is incomplete, and most active molecules contain a single core structure. Consequently, the investigation of new active skeletons and pharmacophore groups may become a future priority.

2.2. *PPI stabilizers*

Stabilization of PPIs represents a promising mode of modulation because binding to the PPI complex is energetically favourable compared with inhibition of PPI complex formation. However, the study of PPI stabilizers has been limited to certain specific proteins, and to even fewer tumour-related proteins, the more classical ones being 14-3-3 proteins and microtubules. This review mainly considers these two protein-related PPI targets as the basis for the study of PPI stabilizers.

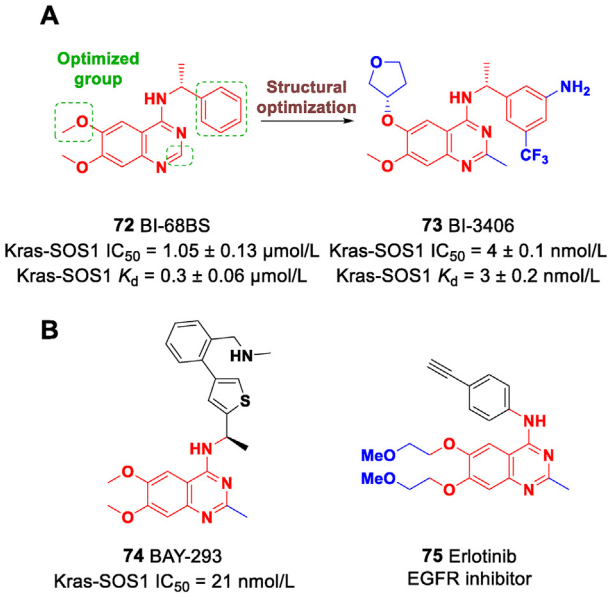


Figure 16 Kras−SOS1 inhibitors **72**−**75**. (A) Chemical structures of BI-68BS and BI-3406. (B) Chemical structure of BAY-293 and the EGFR inhibitor erlotinib.

2.2.1. Stabilizers of 14-3-3 protein−protein interaction

The 14-3-3 proteins are a family of signal transduction adapter proteins found in eukaryotes, having seven isoforms (σ, β, γ, ε, ζ, η, and τ) that bind to ligand proteins. They regulate essential life processes such as cell signal transmission, cell cycle control, and apoptosis[170−172]. The 14-3-3 proteins interact with hundreds of proteins, including 14-3-3−HSPB6[173] and 14-3-3−Hd3a[174]. Numerous human diseases such as cancer, neurodegeneration, and reproductive problems have been linked to the interaction between the 14-3-3 proteins and their ligand proteins, making them an interesting pharmacological target[175,176]. Two regulatory strategies can influence the interaction between 14-3-3 proteins. One approach involves the use of protein−protein interaction inhibitors, and recent studies indicate that molecular tweezers can disrupt 14-3-3 interactions with partner proteins. The other method involves the use of stabilizers, such as molecular glue, which can bind to protein−protein interfaces and enhance protein−protein interactions. This approach may

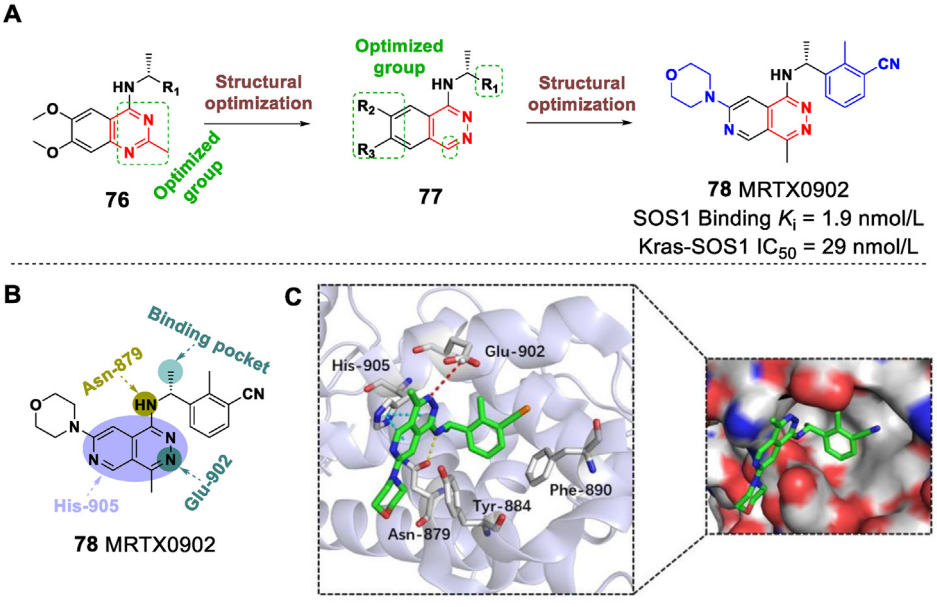


Figure 17 Design of the inhibitor MRTX0902. (A) Chemical structure of **76**−**78**. (B) Chemical structure of MRTX0902 and its indicated binding mode. (C) The cocrystal structure of SOS1 with MRTX0902 (PDB:7UKR). The protein is illustrated with white−blue ribbons and the hydrogen bonds, the salt bridge and the π-stacking interaction are depicted in yellow, red and blue dashed lines, respectively. Compound atoms are in different colours: C, green; N, blue; O, red; CN, orange.

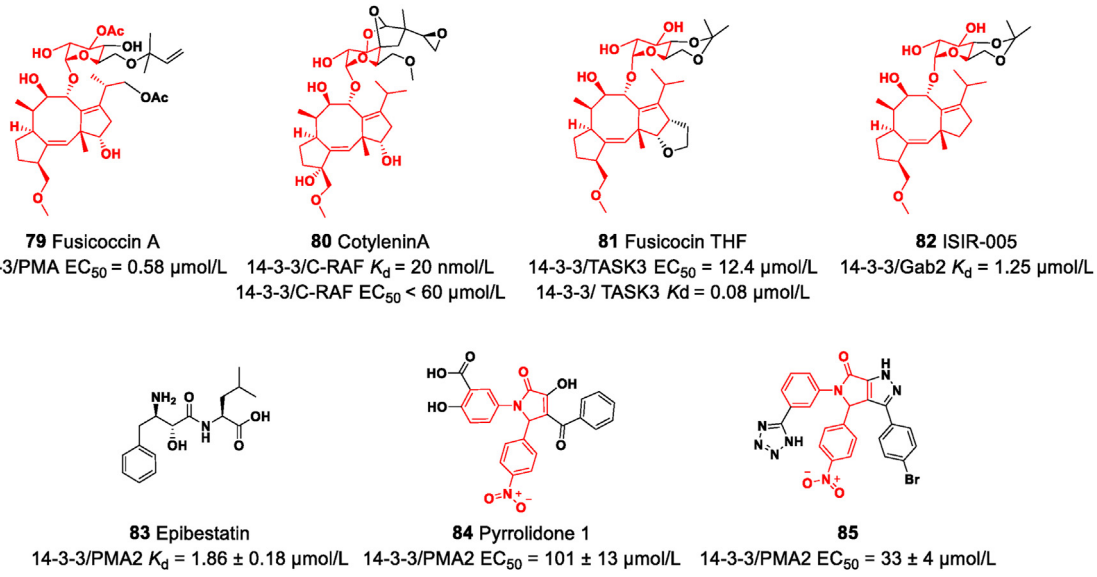


Figure 18 Chemical structure of inhibitors **79**–**85**.

help stabilize the interaction between 14-3-3 proteins and their partners[177,178]. Current stabilizers consist mainly of peptides and terpenoids whose primary goal is to stabilize the macromolecular complex so that it can perform its original function[179].

Two classic examples of 14-3-3 PPI stabilizers are fusicoccin A (**79**) and cotylenin A (**80**) (Fig. 18). (i) Fusicoccin A has an EC_{50} of 0.58 μmol/L for stabilizing the interaction between the 14-3-3 protein and H^+-ATPase (PMA)[180]. It is a diterpenoid glycoside derived from plant pathogens with 5-8-5 rings that can bind to 14-3-3 protein receptors to bridge the PPI interface gap and stabilize the 14-3-3−PMA complex[181]. Based on structural design and semisynthetic approaches, researchers discovered that fusicoccin analogues **81** and ISIR-005 can maintain the binary structure of the 14-3-3 protein (Fig. 18). Compound **81** enhances the 14-3-3−TASK3 protein's PPI stability by a factor of 20[182]. ISIR-005 stabilizes binding to the Gab2pT391 site but not to the Gab2pS210 site; it can increase the stability of the interaction between 14-3-3 protein and Gab2 by 5.3-fold[183]. (ii) Cotylenin A is a fungal natural product that binds to the inhibitory 14-3-3 interaction sites pSer233 and pSer259 on C-RAF but not to the activating interaction site pSer621, stabilizing the 14-3-3−Raf relationship with a K_d of 20 nmol/L[184,185]. Furthermore, researchers identified two stabilizers, eplbestatin and pyrrolldone1, from a library of 37,000 chemicals through high-throughput screening, which can stabilize the 14-3-3−PMA2 protein interaction (Fig. 18). After optimizing the structure of pyrrolidone1 (EC_{50} = 101 ± 13 μmol/L), they discovered that the stability of compound **85** (EC_{50} = 33 ± 4 μmol/L) is much greater than that of pyrrolidone1 *in vivo* (Fig. 18). This offers a foundation for the investigation of improved stabilizers for the 14-3-3−PAM2 interaction[186,187].

The majority of 14-3-3 protein interactions have identical binding patterns, mainly binding to phosphopeptides[170]. Most stabilizers are discovered serendipitously and lacked strategies for identification and development. Increasing the contacts between small molecule modulators and PPI ligands and then identifying particular hot spots is a possible strategy that can improve the specificity and show a very low general toxicity profile[188,189]. The design of PPI stabilizers is therefore dependent on structure-based drug design, fragment-based drug design, and high-throughput screening approaches.

2.2.2. *Stabilizers of microtubules*

Microtubules are essential components of the eukaryotic cytoskeleton and play an important role in regulating cell shape, cell division, signal transduction, and other processes[190,191]. Tubulin refers to the proteins that compose microtubules, with two major types: α tubulin and β tubulin (Fig. 19A). The two proteins frequently interact as heterodimers, leading to the dynamic polymerization and depolymerization features of microtubules. Furthermore, cell structure, organelle location, and function depend on the integrity of the microtubule structure[191]. During mitosis, microtubules create spindles that pull chromosomes towards the cell poles and further promote cell growth[192]. Interfering with the structure and dynamics of microtubules impedes spindle formation, resulting in cell cycle arrest and eventual death. Using PPIs to trigger apoptosis in tumour cells is a viable cancer therapeutic method[192−194]. Currently, its primary drug design is based on two concepts: one is to increase the polymerization of tubulin and block its depolymerization to stabilize microtubules, termed stabilizer (MSA); and the other is to promote microtubule depolymerization and inhibit its polymerization, termed destabilizer (MDA). The conventional belief is that only MDA can bind to tubulin; however, researchers acquired the crystal structures of tubulin and MSA using X-diffraction technology and discovered that MSA can attach to tubulin, providing fresh ideas for structure-oriented drug design[193,195,196].

The anticancer drug paclitaxel is a microtubule stabilizer of the first generation (Fig. 19B)[197]. In the 1960s, researchers extracted paclitaxel from pacific cedar and used X-rays to define its molecular structure as a tricyclic diterpene[198]. Additional research through direct photolabeling of tubulin revealed three binding sites for paclitaxel on microtubules[199,200]. They belong to three different analogues: (i) β-tubulin amino acid residues 217−231—the binding site of 3′-*p*-azido Taxol[201]; (ii) N-terminal 31 amino acids of β-tubulin—the binding site of 2-*m*-azido Taxol[202]; and (iii) Arg282 in

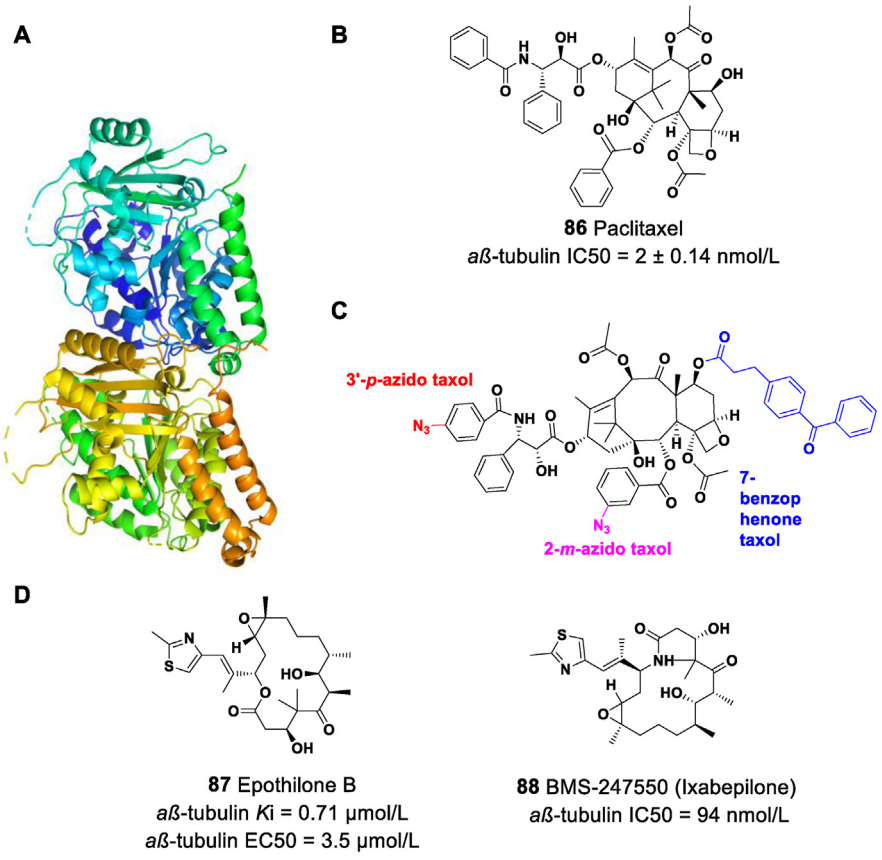


Figure 19 Microtubule stabilizers. (A) The crystal structure of $\alpha\beta$-microtubule (PDB:4FFB). (B) Chemical structures of paclitaxel. (C) Photolabelling sites on β-tubulin obtained with three analogues of paclitaxel. (D) Chemical structures of **87** and **88**.

β-tubulin—the binding site of 7-benzophenone Taxol (Fig. 19C)[203]. Based on the three binding sites of paclitaxel on microtubules, many taxanes employed as microtubule stabilizers have been developed. However, the emergence of paclitaxel-resistant tumours in patients has encouraged scientists to explore new stabilizers to fight against paclitaxel-insensitive or paclitaxel-resistant cancers[204]. In the 1990s, epothilone was regarded as a unique natural substance for the treatment of cancer, but the instability of its metabolism *in vivo* is the greatest obstacle to its development (Fig. 19D)[205]. Following a series of studies on the metabolic stability of epothilone, Bristol-Myers Squibb (BMS) discovered that the lactam compound BMS-247550 (ixabepilone, **88**) is a semisynthetic analogue of the natural product epothilone B (**87**) with an IC_{50} of 94 nmol/L (Fig. 19D). Subsequent studies have also demonstrated excellent pharmacokinetic properties, providing additional impetus for the development of small molecule microtubule stabilizers[206,207].

The microtubule has three conventional binding sites: paclitaxel, vincristine, and colchicine. Undoubtedly, a comprehensive examination of the binding site mechanism favours the design of stabilizers, especially in addressing the poor water solubility of paclitaxel natural products. Consideration should be given to structure-based designs, such as the side chain molecules of paclitaxel and some active small molecules, as well as to structure-activity relationships, to synthesize some potential antitumour drugs *via* semi-synthesis or chemical coupling, which is of great importance for the design of current microtubule stabilizers.

3. Current clinical development status and observations

Small molecule drugs that target protein−protein interactions (PPIs) have shown promise as potential therapeutics for a variety of diseases. However, development of small molecule drugs for PPIs presents several challenges including achieving effective druggability *in vivo* and developing drugs that specifically target a particular PPI.

Despite these challenges, there are several small molecule drugs for PPIs that have entered clinical trials and the market. For example, venetoclax, a small molecule drug that targets the B-cell lymphoma 2 (BCL-2) protein, has been approved for the treatment of chronic lymphocytic leukaemia and small lymphocytic lymphoma. In clinical trials, several other small molecule drugs targeting PPIs are currently being evaluated for the treatment of various diseases, including cancer, viral infections, and neurological disorders. We summarized some representative small molecule drugs related to PPIs that are approved by the FDA or in clinical studies in Table 2.

To improve the druggability of small molecule drugs for PPIs, researchers are exploring new strategies such as using small molecules that bind to allosteric sites on the protein surface or using larger molecules that can disrupt the PPI by steric hindrance. Additionally, advances in structural biology and computational methods are enabling researchers to design more effective small molecule drugs for PPIs.

Overall, small molecule drugs for PPIs have the potential to become important therapeutics for a variety of diseases, but continued

Table 2 Small molecule drugs for protein−protein interactions that are approved by the FDA or in clinical studies.

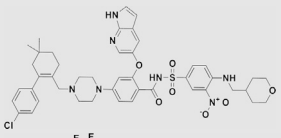
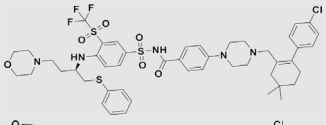
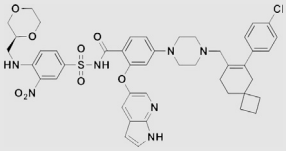
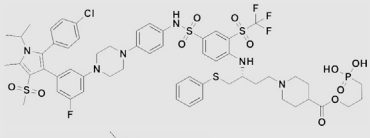
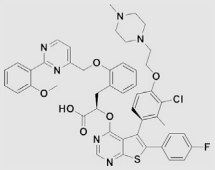
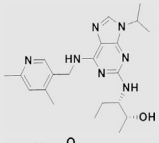
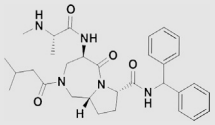
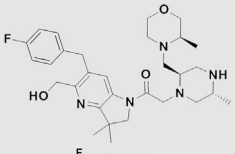
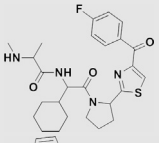
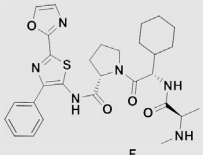
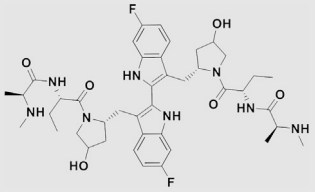
Target	Drug	Chemical structure	Disease	Phase	NCT number	Status	Ref.
Bcl-2	Venetoclax		Chronic lymphocytic leukaemia	–	–	Approved in 2016	20
	Navitoclax		Chronic lymphocytic leukaemia	II	NCT01087151	Completed	18
	APG-2575		Chronic lymphocytic leukaemia	II	NCT05147467	Recruiting	208
	Pelcitoclax		Neuroendocrine tumours	I	NCT04893759	Recruiting	209
	S-64315		Acute myeloid leukaemia	II	NCT04629443	Active, not recruiting	210
Bcl-2	Fadraciclib		Leukaemia	II	NCT05168904	Recruiting	211
XIAP	Xevinapant		Head and neck cancer	III	NCT05386550	Recruiting	212
	ASTX660		Solid tumours	II	NCT02503423	Active, not recruiting	213
	LCL-161		Breast cancer	II	NCT01617668	Completed	214
	GDC-0917		Solid cancers	I	NCT01226277	Completed	215
XIAP	Birinapant		Solid tumours	II	NCT01188499	Completed	216

Table 2 (*continued*)

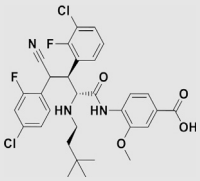
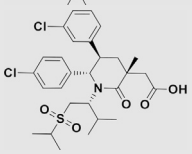
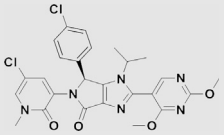
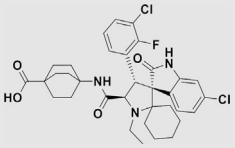
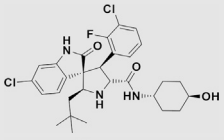
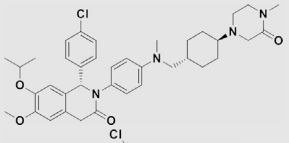
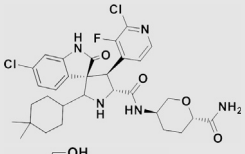
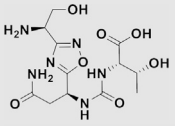
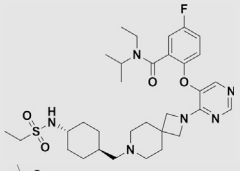
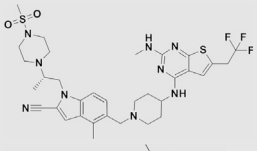
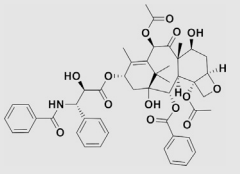
Target	Drug	Chemical structure	Disease	Phase	NCT number	Status	Ref.
MDM2–p53	Idasanutlin		Leukaemia, myeloid, acute	III	NCT02545283	Terminated	71
	navtemadlin		Small-cell lung cancer	II	NCT05027867	Recruiting	217
	Siremadlin		Acute myeloid leukaemia	II	NCT05447663	Recruiting	218
MDM2–p53	APG-115		Patients with advanced solid tumour	I	NCT02935907	Completed	219
	SAR405838		Neoplasm malignant	I	NCT01636479	Completed	220
	CGM097		Solid tumour with p53 wild type status	I	NCT01760525	Completed	221
	Milademetan		Solid tumours	II	NCT05012397	Recruiting	222
PD1–PDL1	CA-170		Lymphomas	I	NCT02812875	Completed	223
Menin–MLL	Revumenib		Acute lymphoblastic leukaemia	II	NCT04065399	Recruiting	224
	Ziftomenib		Mixed lineage leukaemia	II	NCT04067336	Recruiting	225
Microtubule	Paclitaxel		Ovarian cancer	–	–	Approved in 1992	226

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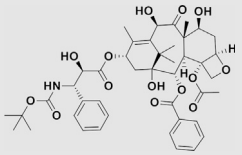
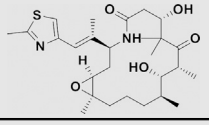
Table 2 (*continued*)

Target	Drug	Chemical structure	Disease	Phase	NCT number	Status	Ref.
	Docetaxel		Breast cancer	—	—	Approved in 2007	227
	Ixabepilone		Breast cancer	—	—	Approved in 1998	207

research and development is necessary to address the challenges in developing these drugs and to improve their clinical efficacy.

4. Conclusions and future prospects

4.1. Conclusions

In recent decades, significant progress has been made in identifying, developing, and optimizing small molecules that target protein−protein interactions (PPIs). High-resolution protein structure analysis tools, such as X-ray crystal diffraction, nuclear magnetic resonance, and cryo-electron microscopy, have enabled the characterization of PPI complexes at an atomic level, facilitating the discovery of potential targets and rational drug design. Most PPI-targeting drugs require hotspots, which are now being identified using advanced computational tools like Q-SiteFinder that calculate the interaction energy between a methyl probe and its binding pocket. ProteoChip, a technology that uses protein microarrays, has also played an important role in PPI discovery. The construction of synthetic methodology-based libraries and physical/virtual compound libraries for high-throughput screening is another approach that has significantly facilitated the discovery of unconventional PPI targets.

Molecular glue, which mimics surface residues and acts as an adhesive to stabilize or degrade PPI complexes, offers a new approach to developing potent selective binders. Protein targeting chimeras (PROTAC) are also considered a promising technology for the development of PPI modulators. The technology has a wide range of applications, high activity, and the ability to target non-druggable proteins more effectively than traditional modulators. PROTAC shows promise for improving selectivity and overcoming drug resistance, offering new insights into the development of novel PPI modulators. Overall, these advances in PPI-targeting drugs and technologies hold great potential for developing more effective drugs targeting specific PPIs.

4.2. Prospects

Currently, targeted molecular therapies based on the inhibition of PPIs are considered to be an effective clinical strategy for the treatment of tumours. However, despite substantial progress in this area, there are still formidable obstacles yet to be overcome. Specifically, more than 10,000 PPIs have been identified, but only a few hundred have been examined and even fewer have been used as therapeutic targets. Therefore, finding ways to design PPI modulators logically and efficiently remains a challenge. The PPI interaction function is still unknown and PPI complex structure is difficult to characterize. However, with the advent of structural biology and computer-aided drug design, we have been able to obtain crystal-clear structures of PPI complexes and accurately analyse PPI hotspots and binding pockets, which has spurred the development of PPI modulators. Characterizing protein−protein interaction (PPI) structures has been a focus of research for decades, as it is essential for the logical design of PPI-targeted modulators. While significant progress has been made in this area, the determination of PPI interaction mechanisms remains a work in progress. The range of PPI modulators has expanded considerably from the initial discovery of natural products to include various classes of molecules, such as antibodies, peptidomimetics, cyclic peptides and other classes of molecules. Traditional PPI modulator designs focus on the PPI interface and mostly rely on the presence of hotspots and pockets, however, directly targeting the PPI interface is often challenging. In contrast, the development of allosteric modulators is not impeded by interface pockets or hotspots; such modulators can be particularly useful for regulating PPIs that are challenging to use orthostatic modulators. While the design of allosteric modulators presents a challenging task due to the limited number of rational design methods available. Random lead discovery and optimization remain the primary approaches to designing therapeutic candidates. However, with the increasing demand for highly effective and selective drugs, there is a growing need for more rational drug design strategies to develop allosteric modulators. Consequently, advancements in allosteric drug design have enabled the development of PPI modulators through logical prediction of allosteric active sites, resulting in many feasible approaches. Despite the rapid development of PPI modulators, the current imbalance between the number of PPI inhibitors and PPI stabilizers has become apparent. Therefore, there is an urgent need to develop PPI stabilizers to address this trend and facilitate the discovery of new PPI targets.

Future efforts to target PPIs will be considerably expedited by recent advances in the field, especially in cancer therapy. At the same time, new concepts such as AUTAC, RIPTAC, ENDTAC are being proposed to enrich the drug discovery of targeted PPIs. It is easy to see from previous studies that antitumour PPI modulators seem to be the current industry trend, notably those targeting PD1−PDL1 and MDM2−P53. Intriguingly, all anti-PD-1 drugs on the market are antibodies, unrivalled by other types. Since their discovery, targets such as p53 have drawn interest, although it seems that the development of this pharmacological target has been sluggish compared to its investment, with poor results. Research and development towards these objectives are daunting. A decade ago, it would have been difficult to assert a future moment to shine for PD1. It is now difficult to predict the dynamics and trends of the whole sector over the next decade. What we can predict is that

in the postgenomic age, PPIs will garner a growing amount of interest, and the development of PPI modulators for the treatment of malignancies will advance.

Acknowledgments

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Author contributions

Qiu Sun and Guan Wang conceived the project and supervised the project. Defa Wu and Yang Li summed up the literature, drafted the manuscript and drew the figures. Lang Zheng and Huan Xiao collected and organized the inhibitors. Defa Wu and Yang Li proofread the structures and figures. Qiu Sun and Guan Wang revised the manuscript. All authors approved the final manuscript.

Conflicts of interest

The authors declare no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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