Chapter 1
Overview of Protein-Protein Interactions and Small-Molecule Inhibitors Under Clinical Development

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1.1 Introduction

Protein-protein interactions (PPIs) regulate a number of biological processes both in normal and disease states [1]. It is estimated that human interactome, the complex network of PPIs, contains about 130,000–650,000 types of PPI [2, 3]. The pivotal importance of PPIs makes them a rich source of targets for the development of novel therapeutic drugs. There are several ways to modulate PPI complexes including inhibition, stabilization, direct binding, and allosteric binding. A direct PPI modulator binds to the interaction surface of one protein, thereby sterically preventing or stabilizing the binding to its protein partner. In contrast, an allosteric modulator binds at a distant region outside of the protein interaction interface and remotely acts on the protein binding by triggering conformational change. For the type of binding effect, PPI inhibitors compete with one of the protein partners and prevent its binding, which represent a major approach in current PPI-based drug discovery. Another way to interfere with the PPI-associated biological functions is the stabilization of PPI complexes. PPI stabilizers bind to the regions at or near the PPI interface and promote the binding without competing with any of the protein partners [4]. Also, the therapeutic effects of PPI stabilizers are attracting increasing research interests [4–6]. Currently, most PPI modulators in clinical development are small-molecule inhibitors [7] and this chapter will mainly focus on design strategies and case studies of small-molecule PPI inhibitors.

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1.2 Challenges in the Discovery of Small-Molecule PPI Inhibitors

Although PPIs represent promising targets for the development of new generation of clinical therapeutics, the design of selective and potent small-molecule inhibitors is rather changeling as compared to that for traditional targets (e.g., proteinase, kinases, G protein-coupled receptors) [8–10]. The nature of the PPI interfaces is significantly different from that of traditional drug targets, which have well-defined pockets for binding small molecules [11]. The PPI interface is generally large (about 1,500–3,000 $Å^2$), flat (often exposed to solvent) [12], and dominated with hydrophobic and charged characteristics [13, 14]. Such features bring difficulties to discover small molecules that can effectively interrupt PPIs. First, a potent PPI inhibitor is required to have large molecular weight (MW) and high hydrophobicity so that it can cover a large and hydrophobic surface area. However, such a binder may have poor solubility and face pharmacokinetic problems. Second, the natural binder of a specific PPI interface is the protein counterpart itself, whose amino acids involved in PPIs are not contiguous. Thus, the protein or peptide involved in PPI cannot be used as a good starting point for the design and identification of small-molecule inhibitors. Third, existing compound libraries are mainly collected or constructed for traditional drug targets, which cannot effectively cover the chemical space of PPI inhibitors. Therefore, it is highly challenging to find a high-quality hit or lead through high-throughput screening (HTS) of PPI inhibitors. Moreover, validation of a PPI inhibitor from artifactual binding requires more biological assays than that for traditional targets.

1.3 Structures and Classifications of PPIs

Despite these challenges, remarkable progress has been achieved in the discovery and development of small-molecule PPI inhibitors [15–17]. The knowledge of the topological features of PPI interfaces is critically important for the identification of small-molecule inhibitors. Generally, PPI interface consists of a core region and a rim region [18]. According to the PPI buried surface area and binding affinity, PPI interfaces can be generally classified into four categories: “tight and wide,” “tight and narrow,” “loose and narrow,” and “loose and wide” [19]. The properties and examples of the four classes of PPIs are depicted in Table 1.1 and Fig. 1.1. Among them, the “narrow and tight” PPIs are more druggable to design small-molecule inhibitors, whereas the “loose and wide” is the most difficult to be targeted by small molecules.

In Arkin’s review, PPIs can be classified into primary peptide epitopes, secondary structure epitopes, and tertiary structural epitopes according to the complexity of epitopes (Table 1.2) [20]. The difficulties in identifying small-molecule inhibitors increase as the interface becomes more complex (from primary to tertiary

Table 1.1 Features of four classes of PPI interfaces according to the contact area and binding affinity

PPI type	Contact area (Å^2)	Affinity (K_d, nM)	Examples	Description
Tight and wide	>2500	<200	β-Catenin/Tcf4 Hsp70/NEF RGS4/Gα cMyc/Max	Large buried and convoluted (or discontinuous) contact areas with tight affinities. Difficult to be targeted by small-molecule inhibitors
Tight and narrow	<2500	<200	IL-2/IL-2Rα MDM2/p53 Bcl-2/BH3 XIAP/caspase 9	High affinity binding in a relatively small surface area. Deep pockets engaged by less than five hot spot residues. Excellent druggability
Loose and narrow	<2500	>200	Hsp70/Hsp40 Hsp90/TPR ZipA/FtsZ	Weak binding but relatively small contact areas. Transient interactions, relatively shallow binding pockets and difficult to obtain structural data. Challenging targets for small-molecules binding
Loose and wide	>2500	>200	Ras/SOS	Large surface areas and weak affinities. Particularly challenging for discovering small-molecule inhibitors

Abbreviations Tcf4, transcription factor 4; Hsp70, heat shock protein 70; NEF, nucleotide exchange factor; RGS4, G protein signaling 4; MAX, MYC–associated factor X; IL-2, interleukin-2; IL-2R, interleukin-2 receptor; MDM2, mouse double minute 2; Bcl, B-cell lymphoma; BH3, BCL–2 homology domain 3; XIAP, X-linked inhibitor of apoptosis protein; TPR, tetratricopeptide repeat; ZipA, cell division protein ZipA; FtsZ, filamenting temperature-sensitive mutant Z; Ras, a small GTP-binding protein; SOS, a guanine nucleotide exchange factor

epitopes). The primary peptide epitope consists of a primary linear protein as one side of the interface sequence. This type of PPI interface is particularly amenable to be targeted by drug-like small molecules. The secondary structure epitopes mainly include α-helix, β-sheet, and extended peptides. Key residues on the peptide are not continuous in the primary sequence, which are centered on two to three subpockets. The secondary structural epitopes have also been proven tractable to small-molecule inhibition. Tertiary structural epitopes require multiple sequences with discontinuous binding sites, which are the most challenging targets with limited successful examples.

More recently, Skidmore et al. divided PPIs into a series of structural classes including globular protein–globular protein interactions, globular protein–peptide interactions, and peptide–peptide interactions [21]. These structural classes can be further differentiated depending on whether the peptides have continuous epitope or

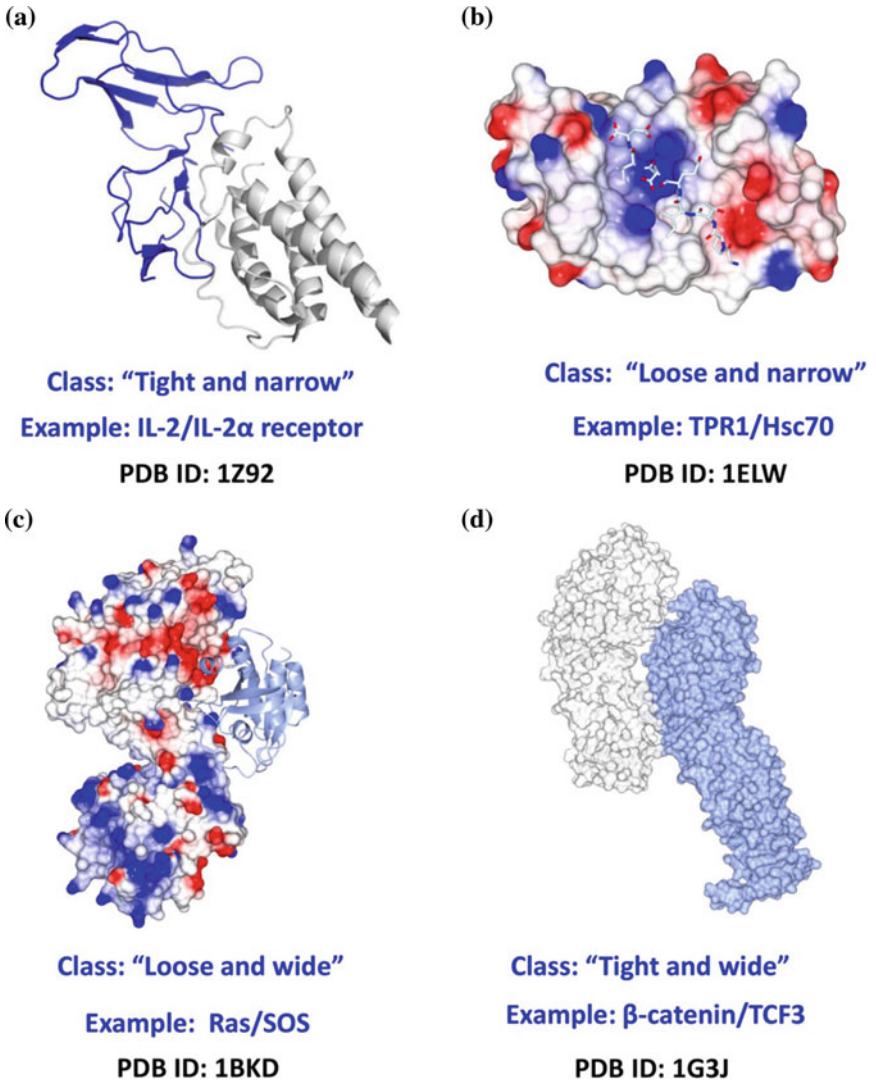


Fig. 1.1 Topological features of four classes of PPIs according to the PPI contact area and binding affinity

undergo substantial conformational changes upon binding (Fig. 1.2). PPIs between globular proteins are highly challenging for small-molecule drug discovery [22]. In contrast, globular protein–peptide interactions have been proven to be more druggable. The difficulty in targeting peptide–peptide interactions depends on whether there is a defined binding site.

1.4 "Hot Spots" as Structural Basis for the Design of Small-Molecule PPI Inhibitors

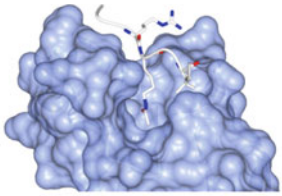
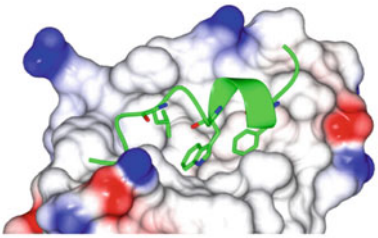
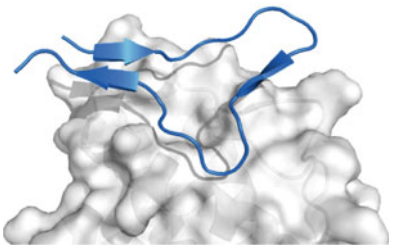
The concept of "hot spots" in PPI interfaces was introduced by Clackson and Wells in 1995 [23], which means a few key residues are responsible for the majority of the binding free energy in PPI [18, 23]. Notably, the surface area of "hot spots" is significantly smaller than the entire PPI interface [24]. Recent studies indicated that the existence of "hot spots" was prevalent in PPI interfaces [18]. They account for an average of 9.5% of the interfacial residues and are generally located in the core regions [25]. Another important feature of "hot spots" is the conformational change upon binding small molecules [26, 27]. When a small molecule binds to the PPI interface, the opening of so-called transient pockets that facilitate the ligand binding can be observed [28, 29]. "Hot spot" residues are highly adaptive with low energy barriers for conformational changes. The flexibility of "hot spots" for small-molecules binding has been observed in a number of PPI targets such as IL-2 receptor α (IL-2Rα) [28], Bcl-X_L [30], HDM2 [31], and HPV-18-E2 [32]. "Hot spot" residues are often enriched in tryptophan (21%), arginine (13.3%), and tyrosine (12.3%), which allow adaptive conformational change and form various interactions to accommodate small molecules [25]. The existence and dynamic features of "hot spots" offer an opportunity to underscore the challenge to identify small-molecule PPI inhibitors.

The "hot spots" of PPI interfaces can be determined by alanine scanning mutagenesis [23, 25, 33] in combination with structural biology studies. The former can measure the contribution of each residue to the binding affinity with the partner protein by serially mutating each residue to alanine. Moreover, X-ray crystallography enables to provide key structural information about the distribution and orientation of these hot spot residues in PPI interfaces. Also, solving crystal structures of the target protein in free state and in complex with different ligands is helpful to understand the dynamic properties of the "hot spots," which is highly valuable for inhibitor design. Computational methods, such as molecular dynamics (MD) simulations, are complementary tools to investigate the dynamic features of the "hot spots" [34–39].

1.5 Overview of Strategies for the Design of Small-Molecule PPI Inhibitors

Recently, important progress has been made in the discovery and development of small-molecule PPI inhibitors [20, 39–51]. Herein, state-of-the-art strategies of PPI-based drug discovery will be briefly introduced. More details about the advantages and limitations of the methodologies and successful examples can refer to our recent review [52]. The first step for the discovery of small-molecule PPI inhibitors is to determine the structure of the PPI interface (Fig. 1.3) [53]. Due to

Table 1.2 Properties and examples of primary, secondary, and tertiary epitopes

PPI Type	Description	Examples
Primary peptide epitopes	 **Example:** Bromodomain/histone (PDB ID: 2WP1) **Description:** Short, continuous and linear peptides.	LFA1/ICAM1 cIAP/SMAC Bromodomain/histone Integrase/LEDGF VHL/HIF1α
Secondary structural epitopes	 **Example:** MDM2/p53 (PDB ID: 1YCR) **Description:** α-Helix, β-sheet, and extended peptides	Bcl family/BH3 MDM2/p53 PDK1/PIF-tide Menin/MLL p300 CH1 domain/HIF1a
Tertiary structural epitopes	 **Example:** IL-2/IL-2R (PDB: 1Z92) **Description:** discontinuous binding sites, and larger and shallower interfaces.	IL-2/IL-2Rα HPV11 E1/E2

the flexibility of PPI interface, the availability of structures from different statuses (unbound protein, protein-protein complex, protein–inhibitors complex) can significantly improve the efficiency of inhibitor design. Then, druggability assessment

Abbreviations LFA1, leukocyte function-associated molecule 1; ICAM1, intercellular adhesion molecule 1; IAP, inhibitor of apoptosis proteins; SMAC, second mitochondrial activator of caspases; LEDGF, lens endothelial growth factor; VHL, Von Hippel–Lindau disease tumor suppressor; HIF1α, hypoxia-inducible factor 1α; PDK1, 3-phosphoinositide-dependent protein kinase-1; PIF-tide, PDK1-interacting fragment; menin, a tumor suppressor associated with multiple endocrine neoplasia type 1; MLL, mixed lineage leukemia; CH1, cysteine–histidine-rich 1; HPV11, human papilloma virus-11; E1, a kind of replication initiation factor; E2, a kind of transcription factor

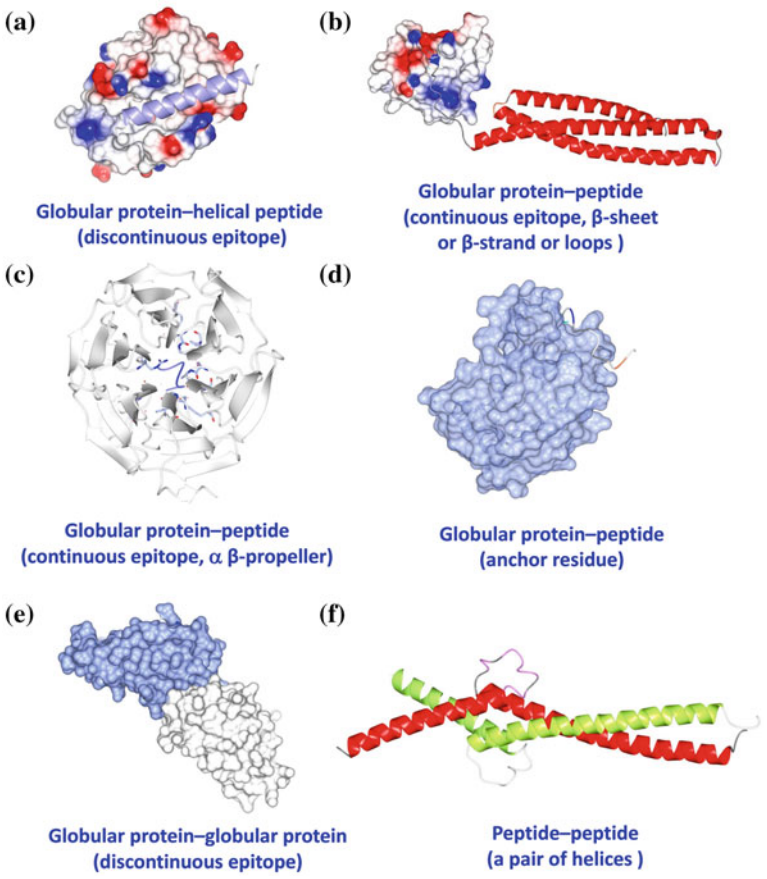


Fig. 1.2 Classification of PPIs and examples. **a** Bcl-X_L–BAD (PDB ID: 2XA0); **b** XIAP–SMAC (PDB ID: 1G73); **c** KEAP1 (Kelch-like ECH-associated protein 1)-NRF2 (nuclear factor erythroid 2-related factor 2) (PDB ID: 2DYH); **d** bromodomains (PDB ID: 3UVW); **e** IL-2–IL-2R (PDB ID: 1Z92); **f** MYC–MAX (PDB ID: 1NKP)

is necessary to evaluate whether the protein has well-defined binding sites or pockets to accommodate small molecules because the success in designing PPI inhibitors largely depends on the target type [54]. The next important step is the

identification of the "hot spots" on the PPI interface [55, 56]. After establishing assays for biological evaluation, the strategy to discover initial hits depends on the properties of PPI hot spots. Currently, screening strategies, designing strategies, and synthetic strategies represent three major methods for small-molecule PPI inhibitor discovery. Screening strategies mainly include HTS, fragment screening, and virtual screening [39], which aim to discover PPI inhibitors from known compound libraries. Among them, fragment screening in combination with fragment-based drug design (FBDD) has the advantages of higher hit rate and better ligand efficiency (LE). Designing strategies focus on building novel small molecules to mimic the key interactions of the hot spot residues, which are used as the starting points for substructure search, bioisostere design, and de novo design. Besides hot spot residues, key secondary structure motif (i.e., α-helix, β-turn, and β-strand) involved in PPI interface can also be for inhibitor design. A new scaffold decorated with the side chains of hot spot residues is designed to mimic spatial orientation and interactions of the original secondary structure. Synthetic strategies aim to explore new chemical space for PPI inhibitor screening by developing efficient synthetic methods to construct new libraries with chemical diversity and complexity. When initial hits are available, validation studies are necessary to exclude false positives. Secondary assays to determine the kinetic and thermodynamic parameters (e.g., association and dissociation rates) as well as solving the structures of protein–hit complexes are important for selecting suitable hits for further optimization. Structural optimization of the hits and leads aims to improve the binding affinity, therapeutic effects, and drug-likeness, and the strategies are similar to those for traditional targets. Finally, drug candidates can be obtained for preclinical and clinical trials until they are marked for therapeutic application.

1.6 Small-Molecule PPI Inhibitors Under Clinical Development

The discovery and development of PPIs inhibitors have been greatly accelerated with better understanding of the structure and functions of PPIs and numerous medicinal chemistry efforts in this field [57]. Up to now, a great number of highly potent small-molecule PPI inhibitors have been identified and several of them are marketed or under different stages of clinical evaluations. According to a recent review by Abell and Skidmore [21], small-molecule PPI inhibitors in clinical development are summarized in Table 1.3. On April 11, 2016, venetoclax (ABT-199) was approved by FDA for the treatment of chronic lymphocytic leukemia (CLL) with 17p deletion, which represents the first marketed small-molecule PPI inhibitor [58]. Subsequently, lifitegrast (SAR 1118) [59], a small-molecule inhibitor of LFA-1/ICAM-1, was approved for the treatment of dry eye syndrome on July 11, 2016. Here, the drug discovery and medicinal chemistry optimization process of venetoclax and lifitegrast were briefly introduced.

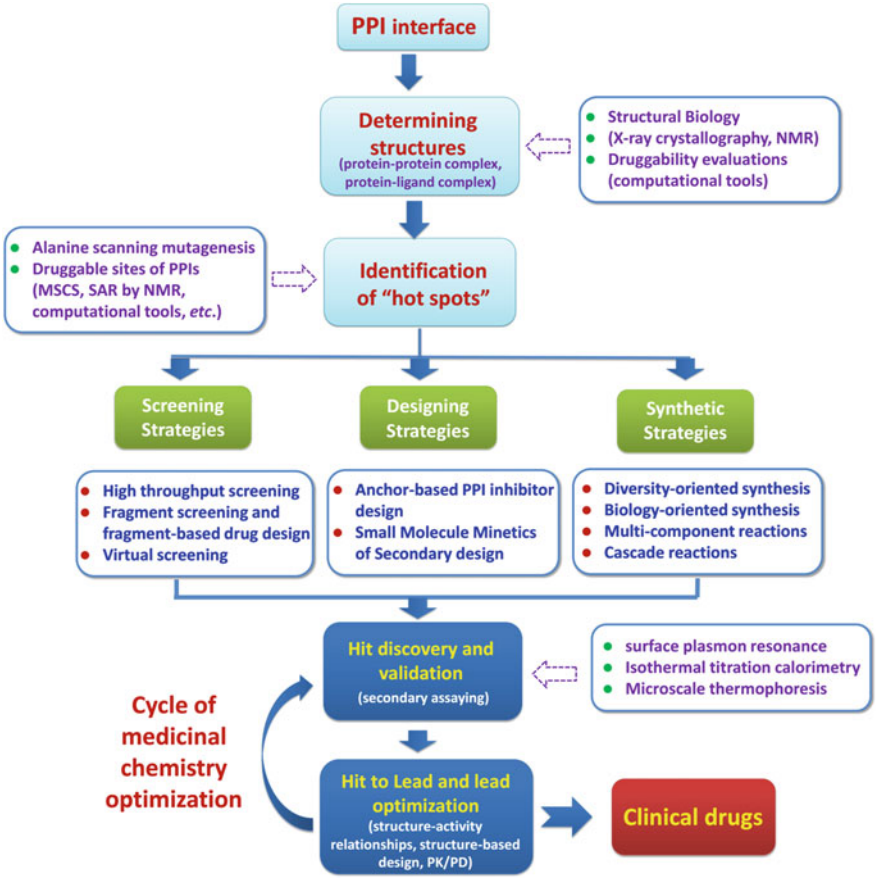


Fig. 1.3 Current strategies for the design and development of small-molecule PPI inhibitors

1.6.1 Fragment-Based Discovery of Bcl-2 Inhibitor Venetoclax

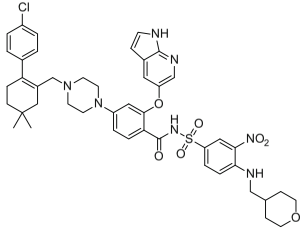
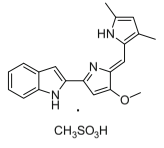
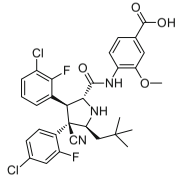
The discovery and development of Bcl-2 inhibitor venetoclax represent one of the most successful examples of PPI-based drug discovery [91]. Bcl (B-cell lymphoma) family of proteins (e.g., Bcl-X_L, Bcl-2, Bcl-w, and Mcl-1) is anti-apoptotic proteins, whose interactions with pro-apoptotic proteins such as Bak, Bax, and Bad play key roles in both normal and abnormal apoptotic processes [92]. Initial drug discovery efforts were focused on the non-selective Bcl-2/Bcl-X_L/Bcl-w inhibitor navitoclax (ABT-263) [93]. NMR structural studies revealed that the Bcl-X_L/BAK interface was a long and hydrophobic groove [94]. The "hot spots" include several hydrophobic and charged residues (e.g., Ile85, Leu78, and Asp83). ABT-263 was discovered by a combination of NMR-based fragment screening, parallel synthesis

and structure-based design and ADME optimization. Initially, the research group from Abbot screened a library containing 10,000 fragments using ^{15}N HSQC NMR spectroscopy [95]. Weak fragment hits **31** (K_i = 300 μM) and **32** (K_i = 4,300 μM) were found to occupy two different subsites of Bcl-X_L (Fig. 1.4) [96]. Guided by the structural information of Bcl-X_L/fragment complexes, the two fragment hits were linked by the acylsulfonamide group to maintain the key interactions and followed by optimization of the substitution of acylsulfonamide to yield inhibitor **33** (K_i = 36 μM) with improved affinity with Bcl-X_L. Further structure-based optimization of lead compound **33** led to the discovery of ABT-737 (**34**) as a highly potent Bcl-X_L inhibitor ($K_i \leq$ 1 nM), which successfully mimicked the α-helical BH3 domain of BAK [30, 97, 98]. However, ABT-737 is not orally bioavailable and subsequent medicinal chemistry optimizations generated clinical candidate ABT-263 (**35**) [99]. ABT-263 showed subnanomolar affinities for Bcl-2, Bcl-XL, and Bcl-W with improved bioavailability [100]. Surprisingly, ABT-263 performed poorly in clinical trials probably due to its non-selective profile. Thus, further clinical evaluations were performed on the selective Bcl-2 inhibitor venetoclax [101, 102]. Venetoclax selectively blocks Bcl-2 protein, leading to programmed cell death of CLL cells.

1.6.2 Discovery of LFA-1/ICAM-1 Inhibitor Lifitegrast for the Treatment of Dry Eye Syndrome

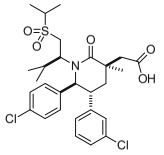
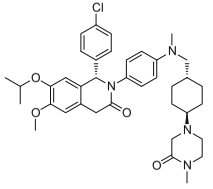
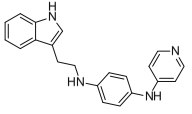
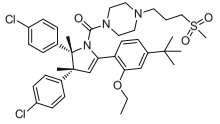
The PPI between LFA-1 and ICAM-1 is essential in lymphocyte and immune system function. Small-molecule LFA-1/ICAM-1 inhibitors can be used to develop novel drugs for the treatment of dry eye. The ICAM-1 epitope containing discontinuous residues Glu34, Lys39, Met64, Tyr66, Asn68, and Gln73 was identified as "hot spots." Gadek et al. designed compounds **36** (IC_{50} = 47 nM) and **37** (IC_{50} = 1.4 nM) as potent LFA-1 inhibitors. Their structures were embedded with the carboxylic acid, sulfide, phenol, and carboxamide groups to mimic the ICAM-1 hot spots (Fig. 1.5) [103]. Structure–activity relationship (SAR) analysis revealed that the inhibitors shared a "left-wing"–"central scaffold"–"right-wing" structural mode. Based on this assumption, Zhong et al. designed bicyclic tetrahydroisoquinoline (THIQ) as the central scaffold and discovered a highly active LFA-1 inhibitor **38** (IC_{50} = 9 nM) with good in vivo efficacy [104]. Further optimization studies were focused on improving pharmacokinetic profiles and successfully discovered lifitegrast (**9**) as a new drug for the treatment of dry eye [59, 105].

Table 1.3 Overview of representative small-molecule PPI inhibitors in clinical application or clinical development

Compound name and chemical structures	MW	Target (activity)	Therapeutic area	Status	Discovery strategy	References
 Venetoclax (ABT-199, 1)	868.44	Bcl protein family Bcl-2 ($K_i \leq$ 0.01 nM) Bcl-xL (K_i = 48 nM) Bcl-w (K_i= 245 nM) Mcl-1(K_i > 444 nM)	Cancer	Approved	FBDD	[60]
 Obatoclax mesylate (GX15-070, 2)	413.49	Bcl-2 (K_i = 0.22 μM)	Cancer	Phase 3	SBDD	[61]
 Idasanutlin (RG7388, 3)	616.48	MDM2-p53 MDM2 (K_i = 30 nM)	Cancer	Phase 3	HTS	[62]

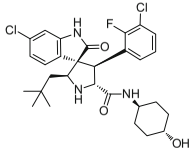
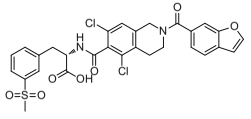
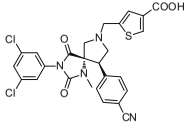
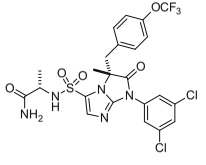
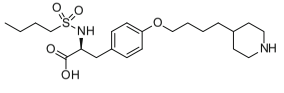
(continued)

Table 1.3 (continued)

Compound name and chemical structures	MW	Target (activity)	Therapeutic area	Status	Discovery strategy	References
 AMG-232 (4)	568.55	MDM2-p53 MDM2 (K_i = 0.045 nM)	Cancer	Phase 2	SBDD	[63]
 CGM097 (5)	659.26	MDM2-p53 MDM2 (K_i= 1.6 nM)	Cancer	Phase 1	Virtual screening	[64]
 Serdemetan (JNJ-26854165, 6)	328.41	MDM2-p53 (no activity reported)	Cancer	Phase 1	Virtual screening	[65, 66]
 RG7112 (7)	726.80	MDM2 (K_i= 10.7 nM)	Cancer	Phase 1 (discontinued)	HTS	[67, 68]

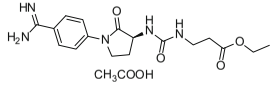
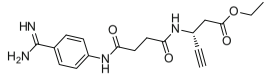
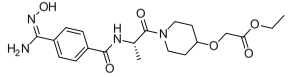
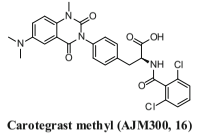
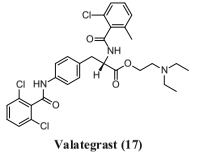
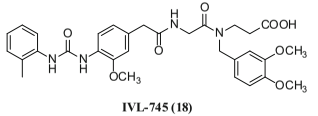
(continued)

Table 1.3 (continued)

Compound name and chemical structures	MW	Target (activity)	Therapeutic area	Status	Discovery strategy	References
 SAR-405838 (8)	562.50	MDM2 (K_i = 0.88 nM)	Cancer	Phase 1 (discontinued)	SBDD	[69]
 Lifitegrast (SAR 1118, 9)	615.48	LFA1-ICAM1 LFA-1 (IC_{50} = 9 nM)	Dry eye	Approved	SBDD	[65]
 BMS-587101 (10)	555.43	LFA-1 (IC_{50} = 20 nM)	Psoriasis	Phase 2 (discontinued)	SBDD	[70, 71]
 BIRT2584 (11)	606.40	LFA-1 (K_i < 10 μM)	Psoriasis	Phase 2 (discontinued)	SBDD	[72]
 Tirofiban (12)	440.60	αIIbβ3 (IC_{50} = 32 nM)	Cardiovascular	Approved	Virtual screening	[73]

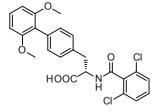
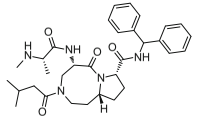
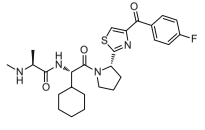
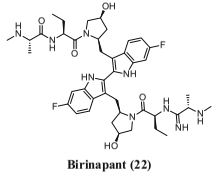
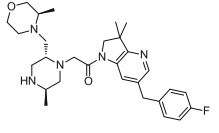
(continued)

Table 1.3 (continued)

Compound name and chemical structures	MW	Target (activity)	Therapeutic area	Status	Discovery strategy	References
 Orbofiban (13)	421.45	αIIbβ3 (IC_{50} = 80 nM)	Cardiovascular	Phase 3 (discontinued)	Peptidomimetics and SBDD	[74]
 Xemilofiban (14)	358.39	αIIbβ3 (IC_{50} = 67 nM)	Cardiovascular	Phase 3 (discontinued)	Peptidomimetics and SBDD	[75]
 Sibrafiban (15)	420.46	αIIbβ3 (IC_{50} = 38 nM)	Cardiovascular	Phase 3 (discontinued)	Peptidomimetics and SBDD	[76]
 Carotegrast methyl (AJM300, 16)	555.41	α4β1/α4β7 (IC_{50} range: 0.94 nM ~ 26 nM)	Ulcerative colitis	Phase 3	Peptidomimetics	[77]
 Valategrast (17)	604.95	α2β1 (IC_{50} = 0.214 μM)	Asthma	Phase 2 (discontinued)	Virtual screening	[78]
 IVL-745 (18)	592.64	α4β1 (IC_{50} < 100 nM)	Asthma	Phase 2 (discontinued)	Virtual screening	[79, 80]

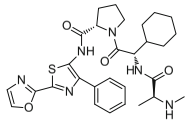
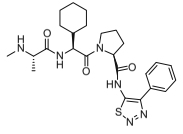
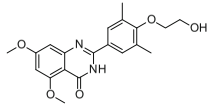
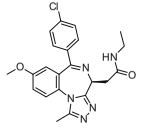
(continued)

Table 1.3 (continued)

Compound name and chemical structures	MW	Target (activity)	Therapeutic area	Status	Discovery strategy	References
 Firategrast (SB-683699, 19)	474.33	α4β7-CS1 (IC_{50} = 0.077 μM) α4β1-CS1 (IC_{50} = 0.85 μM)	Multiple sclerosis	Phase 2 (discontinued)	Peptidomimetics	[81]
 AT-406 (20)	561.71	IAPs c-IAP1 (K_i= 1.9 nM) c-IAP2 (K_i = 5.1 nM) XIAP (K_i = 66.4 nM)	Cancer	Phase 2	Peptidomimetics and SBDD	[82]
 LCL-161(21)	500.63	IAPs (no activity reported)	Cancer	Phase 2	Peptidomimetics and SBDD	[83]
 Birinapant (22)	805.96	IAPs c-IAP1 (K_i < 1 nM) c-IAP2 (K_i = 36 nM) XIAP (K_i= 45 nM)	Cancer	Phase 2	SBDD	[84]
 ASTX-660 (23)	509.66	IAPs c-IAP1 (EC_{50} = 0.32 nM), XIAP (EC_{50} = 5.1 nM)	Cancer	Phase 2	SBDD and virtual screening	

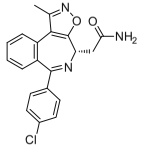
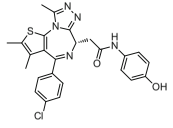
(continued)

Table 1.3 (continued)

Compound name and chemical structures	MW	Target (activity)	Therapeutic area	Status	Discovery strategy	References
 CUDC-427 (24)	564.7	IAPs c-IAP1, c-IPA2 and XIAP (K_i < 60 nM)	Cancer	Phase 1	SBDD	[85]
 GDC-0152 (25)	498.64	IAPs c-IAP1 (K_i = 17 nM) c-IAP2 (K_i = 43 nM) XIAP (K_i = 28 nM) ML-IAP (K_i = 14 nM)	Cancer	Phase 1 (discontinued)	SBDD	[86]
 Apabetalone (RVX-208, 26)	370.4	BET BRD—bromodomain BRD2-4 (IC_{50} range: 1.9–7.7 nM)	Cardiovascular	Phase 3	Screening	[87]
 GSK525762 (27)	423.9	BET BRD—bromodomain BRD2-4 (IC_{50} range: 32.5–42.5 nM)	Cancer	Phase 2	Screening	[88]

(continued)

Table 1.3 (continued)

Compound name and chemical structures	MW	Target (activity)	Therapeutic area	Status	Discovery strategy	References
 CPI-0610 (29)	365.81	BET BRD—bromodomain BRD4 (IC_{50} = 39 nM)	Cancer	Phase 1	FBDD	[89]
 OTX015 (MK-8628, 30)	491.99	BET BRD—bromodomain BRD2-4 (IC_{50} range: 10–19 nM)	Cancer	Phase 1	SBDD	[90]

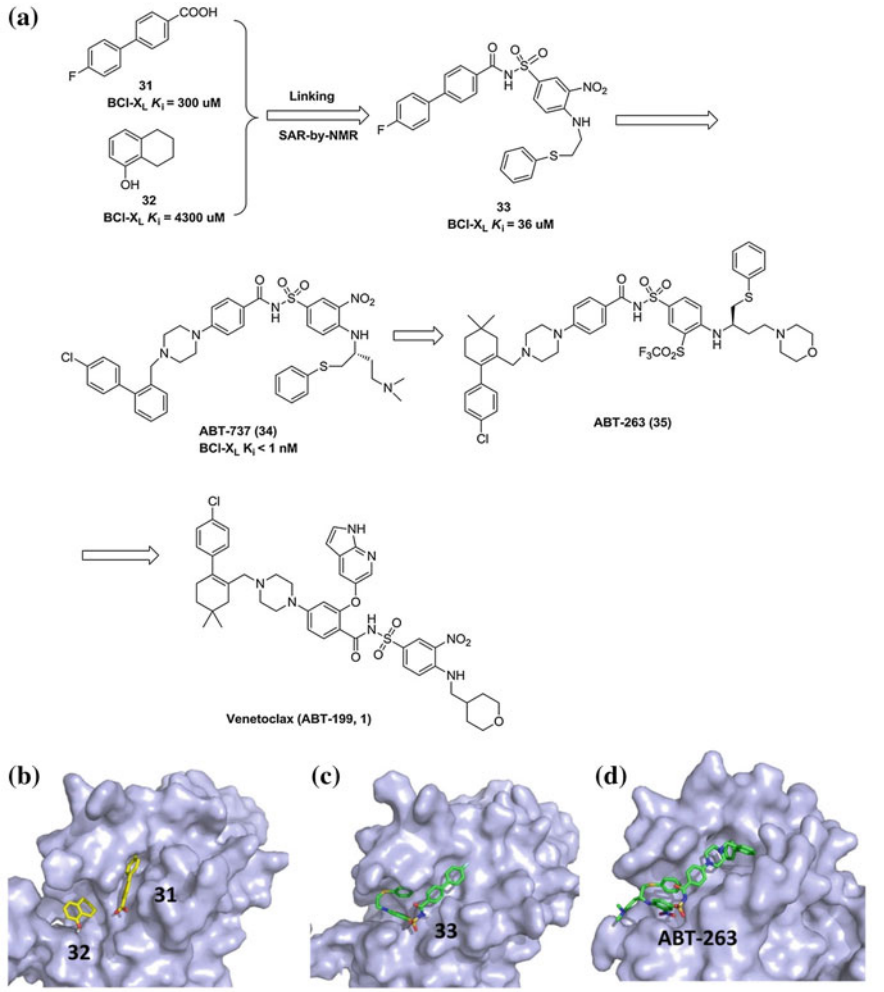


Fig. 1.4 Fragment-based design of Bcl-2 inhibitor venetoclax (**a**). The binding modes of the Bcl-X_L inhibitors (**b**–**d**) were generated from the crystal structures in PDB database (PDB codes: 1YSG, 1YSI, and 2YXJ)

1.7 Conclusions

With the progress of structural biology studies of PPIs, the identification of "hot spots" for inhibitor design as well as numerous medicinal chemistry efforts, the development of small-molecule PPI inhibitors has come into reality with two marketed drugs and a number of clinical candidates. The encouraging success has attracted increasing interests and activities from both pharmaceutical industry and academia. Deeper understanding of the structures, functions, and dynamics of PPIs

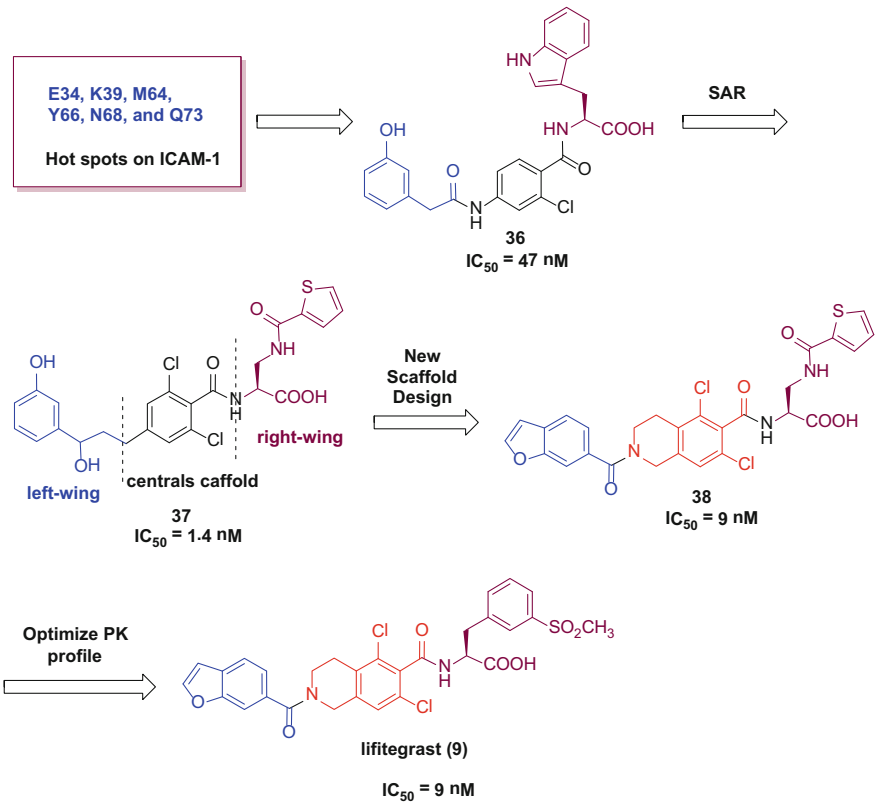


Fig. 1.5 Drug design process of LFA-1/ICAM-1 inhibitor lifitegrast

is highly desirable to improve the efficiency of PPI-based drug discovery. Also, the drug design principles and drug-like criteria for PPI inhibitors need to be further investigated. Taken together, with increasing knowledge and experience gained for small-molecule PPI inhibitors, more challenging PPI targets will become accessible to drug discovery. It is expected that more PPI inhibitors will come into clinical application in the near future.

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