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REVIEW ARTICLE

Progress on biphenyl derivatives as PD-1/PD-L1 inhibitors

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Abstract

Cancer immunotherapy has achieved a leap from the laboratory to the clinic, especially for therapeutic applications based on programmed cell death-1 (PD-1) and its ligand (PD-L1) that target tumour immune escape and growth. At present, 13 PD-1/PD-L1 monoclonal antibodies (mAbs) have been approved as PD-1/PD-L1 inhibitors by the United States Food and Drug Administration (FDA). However, inherent limitations of mAbs, including poor bioavailability and immunogenicity, have led researchers to pursue alternatives and develop small-molecule inhibitors with low molecular weight. Biphenyl derivatives are small-molecule inhibitors of PD-1/PD-L1 with advantages of oral bioavailability, high tumour penetration and better pharmacokinetic properties. In this work, we review progress and structure-activity relationship analysis of biphenyl derivatives as PD-1/PD-L1 inhibitors. The conclusions could contribute to the design of PD-1/PD-L1 inhibitor candidates for cancer immunotherapy.

Keywords PD-1/PD-L1 inhibitors · Biphenyl derivatives · Structure-activity relationship · Cancer immunotherapy

Introduction

Cancer immunotherapy is a highly promising new therapeutic modality to defeat cancer [1, 2]. Unlike traditional cancer treatments such as chemotherapy and radiotherapy, cancer immunotherapy kills tumour cells by activating or mobilising the body's immune system, rather than targeting the tumour itself [3]. Cancer immunotherapies, including cancer vaccines [4], tumour-infiltrating lymphocyte adoptive cell therapy [5], chimeric antigen receptor T cell (CAR-T) therapy [6] and immune checkpoint suppression [7] have achieved great clinical success and brought new hope to cancer patients.

Immune checkpoints act as regulators of the immune system, ensuring appropriate responses by stimulating or inhibiting checkpoint molecules to maintain balance. Several immune checkpoints have been identified including cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), programmed cell death-1 (PD-1) and its ligand programmed cell death-ligand 1 (PD-L1), T cell membrane protein 3 (TIM-3), lymphocyte activation gene 3 (LAG3), V-domain immunoglobulin suppressor of T cell activation (VISTA) and galectin-9 (Gal-9) [8–10]. Among these, CTLA-4 has made rapid progress in clinical studies, and its monoclonal antibody (mAb) ipilimumab was authorised for treating metastatic melanoma by the US Food and Drug Administration (FDA) in 2011 [11]. Encouraged by this, development of immune checkpoint inhibitors accelerated, especially PD-1/PD-L1 immune checkpoint inhibition [12, 13].

PD-1, also known as CD279, belongs to the CD28 family and is expressed in T cells, regulatory T cells (Tregs), depletion T cells, B cells, natural killer cells, natural killer T cells (NKT), dendritic cells (DCs) and tumour-associated macrophages (TAMs) [14, 15]. Human PD-1 (hPD-1) consists of 288 amino acids and is a type I monomeric surface transmembrane glycoprotein composed of a single Ig variable-type (IgV) extracellular domain, a transmembrane domain and a cytoplasmic domain. The cytoplasmic domain contains two structural motifs: an immune tyrosine-based inhibitory motif (ITIM) and an immune receptor inhibitory tyrosine-based switch motif (ITSM) [16]. Two ligands of the PD-1 molecule, PD-L1

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Table 1 PD-1/PD-L1-blocking biphenyl-based agents under clinical development

Code name	Target	Organisation	Stage of development	Registration number/time
IMMH-010	PD-L1	Tianjin Chasesun Pharmaceutical Co., Ltd	Phase I (malignant neoplasms)	NCT04343859/ 2020-03-23
INCB-086550	PD-L1	Incyte Corporation	Phase 2 (immune checkpoint inhibitor-naïve selected solid tumours)	EUCTR2020-000157-27-HU/ 2020-07-02
MAX-10181	PD-L1	Maxinovel Pty., Ltd	Phase I (solid tumour)	NCT04122339/ 2019-09-29
AN-4005	PD-L1	Adlai Nortye Biopharma Co., Ltd	Phase I (advanced solid tumour, advanced lymphoma)	NCT0499384/2021-07-07
BPI-371153	PD-L1	Betta Pharmaceuticals Co., Ltd	Phase I (advanced solid tumours; lymphoma; NSCLC; HCC)	NCT05341557/ 2022-04-18
ASC-61	PD-L1	Gannex pharm Co., Ltd	Phase I (advanced solid tumours)	NCT05287399/ 2022-02-23

The above data are from the drug R&D database of YAOZH network (https://www.yaozhi.com/), as of 26 July 2023

(CD274) and PD-L2 (CD273), belong to the B7 family and share 37% sequence homology. PD-L1 is widely expressed and has been detected in antigen-presenting cells, non-lymphoid organs and non-hematopoietic cells [17, 18], while PD-L2 expression is limited mainly to DCs and a few tumour lines [19]. PD-L1 is a type I transmembrane protein possessing extracellular IgV and IgC domains, transmembrane domains and intracellular domains. When PD-1 engages with PD-L1, the intracellular ITIM and ITSM motifs of PD-1 are phosphorylated. Phosphorylated ITIM and ITSM recruit Src homology region 2 domain-containing phosphatase-1 (SHP-1) and SHP-2 into the intracellular domain of PD-1 [20]. SHP-1 and SHP-2 can inhibit downstream T cell receptor signalling pathways (TCRs) including phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) and RAS/mitogen activated protein kinase (MAPK)/extracellular-signal regulated kinase (ERK) pathway [21–23]. These actions decrease T cell activation, proliferation and survival, and reduce the production of cytokines such as interferon-γ (IFN-γ) and interleukin 2 (IL-2). The PD-1/PD-L1 interaction releases co-inhibitory signals to activated T cells, inducing apoptosis and inactivating T cells [24, 25].

However, all marketed drugs targeting PD-1/PD-L1 are mAbs. Targeting immune checkpoints using mAbs is a novel approach to cancer therapy, for which James P. Allison and Tasuku Honjo won the 2018 Nobel Prize in Medicine [26, 27]. Despite the clinical efficacy of mAbs, inherent shortcomings, including low oral bioavailability, poor tumour penetration and severe immune-related adverse events limit their clinical application [28, 29]. Low molecular weight PD-1/PD-L1 inhibitors are receiving much attention due to their high oral bioavailability, high tumour penetration and better pharmacokinetic properties [30]. Initial studies on low molecular weight (LMW) PD-1/PD-L1 inhibitors were based on polypeptides and macrocyclic peptides. These inhibitors mimic key antibody residues and are capable of antagonising PD-1/PD-L1 pathway signalling and restoring the functions of T-cells. However, they have mostly been reported in patents and no more information has been disclosed, except for CA-170. This first-in-class oral inhibitor inhibited VISTA and PD-L1 with half maximal inhibitory concentration (IC_{50}) values of 17 nM and 37 nM, respectively, but there was no direct binding between CA-170 and PD-L1 according to nuclear magnetic resonance (NMR) binding, homogenous time-resolved fluorescence (HTRF) and cell-based activation assays [31].

Other LMW PD-1/PD-L1 inhibitors include oxadiazole and thiadiazine [32, 33], sulfamonomethoxine and sulfamethizole [34], and 2-methyl-biphenyl derivatives [35, 36]. There have been no further advances except for biphenyl derivatives, for which several compounds have entered clinical trials in recent years (Table 1). Although many biphenyl derivatives have been studied as PD-1/PD-L1 inhibitors, progress and structure-activity relationship (SAR) analysis has not been reviewed. Herein, we focus on progress and SAR analysis of biphenyl derivatives as PD-1/PD-L1 inhibitors. The findings could contribute to the design of PD-1/PD-L1 inhibitors as candidates for cancer immunotherapy.

Biphenyl derivatives

In 2015, Bristol-Myers Squibb (BMS) reported PD-1/PD-L1 small-molecule inhibitors with a biphenyl scaffold [35]. X-ray crystallography was subsequently used to determine

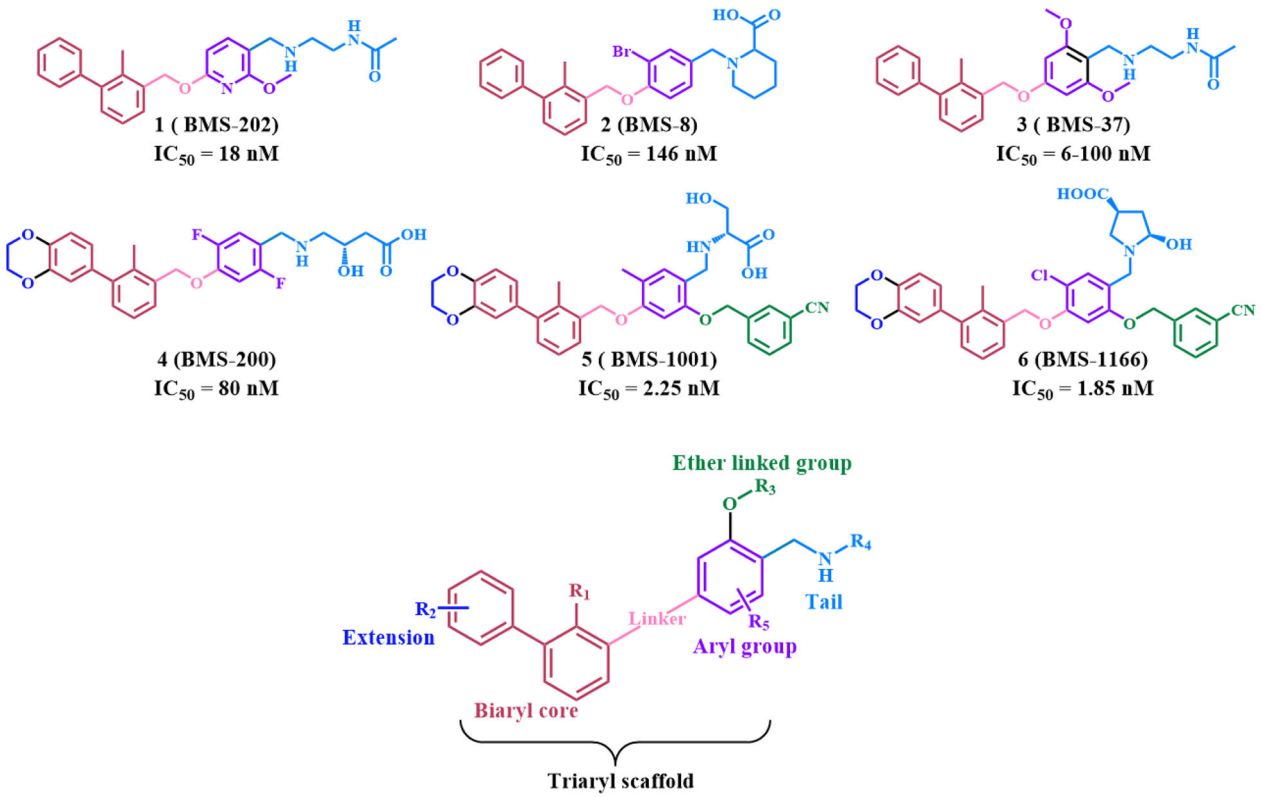


Fig. 1 Core structures of PD-L1 biphenyl small-molecule inhibitors

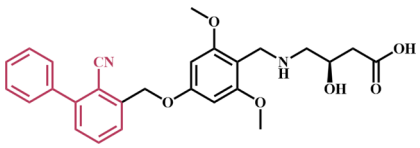
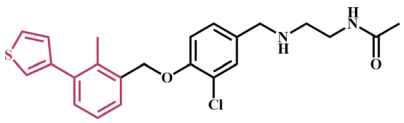
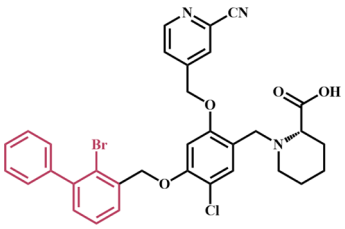
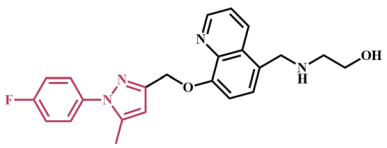
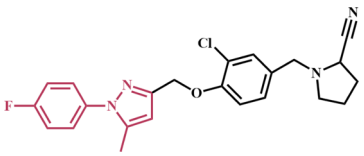
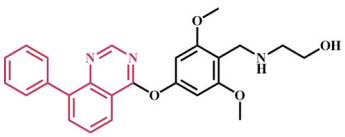
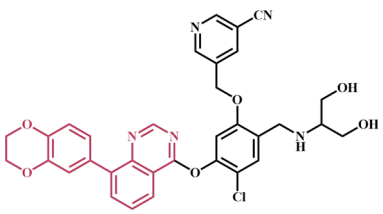
complexes of PD-L1 protein and BMS inhibitors, including BMS-202, BMS-8, BMS-37, BMS-200, BMS-1001 and BMS-1166 (Fig. 1). Based on the results, the general formula of biphenyl derivatives was deduced (Fig. 1), which includes biaryl core, linker, aryl group, tail, extension and ether group junction regions. SAR analysis showed that the biaryl core, aryl group and linker were responsible for core activity and hydrophobicity. The tail is exposed to solvent, engages in hydrogen bonding interactions with PD-L1, and is required for high potency. Extensions and ether bond junctions are not key structural elements but can improve pharmacokinetic characteristics. Design strategies and SAR analysis of biphenyl derivatives are discussed below.

The biaryl core of biphenyl derivatives

Since scientists from BMS first reported (2-methyl-3-biphenylyl) methanol scaffold inhibitors targeting PD-L1 in 2015, biphenyl derivatives have proved to be promising lead compounds for further modification. In 2016, the Holak group determined cocrystal structures of BMS-202 and BMS-8 as PD-L1 antagonists, and found that these inhibitors prevented the PD-1/PD-L1 interaction by causing PD-L1 to dimerise [37]. After revealing the binding mode of BMS compounds, the Holak group also identified the biphenyl core as the minimal fragment responsible for PD-L1 binding using the ^{1}H-^{15}N heteronuclear multiple-quantum coherence (HMQC) NMR method [38]. Therefore, the biphenyl core is the most important pharmacophore for inhibiting PD-1/PD-L1 interaction. Besides the 2-methyl-3-bipheny moiety, studies from BMS incorporated the 2-cyano-3-biphenyl and 2-methyl-3-(thiophen-3-yl) benzyl moiety in the biphenyl core [35]. Compounds 7 and 8 displayed IC_{50} values of 0.006–0.10 μM and 0.11–1.0 μM, respectively, in HTRF binding assays. The HTRF assay is a highly sensitive, robust approach for measuring activity and probing molecular interactions in vitro using europium cryptate-labelled anti-Ig molecules [39]. SAR analysis showed that the proximal phenyl ring of the biphenyl group favoured substitution of the cyano group, while the distal phenyl ring can be substituted by thiophene. Moreover, activity data showed that replacement of 1,4-benzodioxane in the distal phenyl ring increased activity. A series of biphenyl-based small molecules as PD-L1 inhibitors were prepared with bromine substituted at the proximal phenyl ring, and compound 9 impeded PD-1/PD-L1 interactions in the femtomolar range ($IC_{50} = 0.08$ pM) in HTRF binding assays [40] (Table 2).

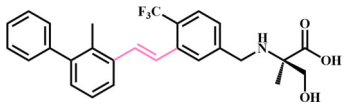
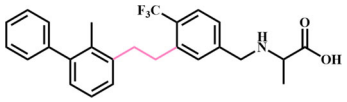
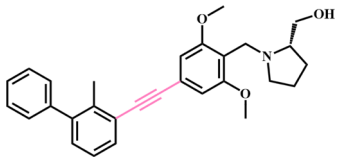
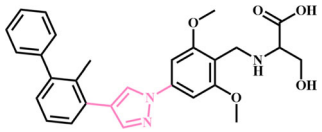
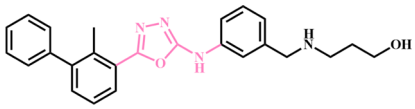
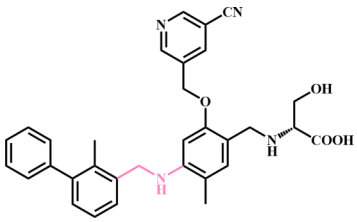
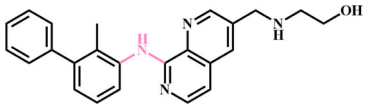
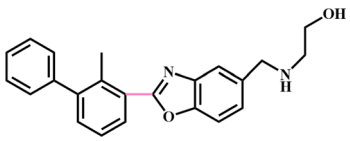
In 2020, two classes of novel immunomodulatory inhibitors of PD-1/PD-L1 interaction were reported in which 5-methypyrrole was introduced to replace the proximal phenyl ring of the biphenyl [41]. Additionally, small

Table 2 Examples of biphenyl-based small-molecule inhibitors with a biaryl core (red)

S.No.	Structure	Measurement method	Activity	Source/Ref
7		HTRF	0.006−0.10 μM	BMS [35]
8		HTRF	0.11−1.00 μM	
9			0.08 pM	Institute of Materia Medical [40]
10		HTRF	2.9 μM	Yan Jianfa [41]
11			2.9 μM	
12		HTRF	>1000 nM	Ma et al. [42]
13			5 nM	

substituents such as halogens and methyl groups were tolerated in the distal phenyl ring. Compounds 10 and 11 exhibited IC_{50} values of ~2.9 μm in HTRF binding assays. As a new starting point, this scaffold can be further optimised. Another group developed a series of benzoheterocyclic compounds in 2021 [42]. Via ring expansion, the

Table 3 Examples of biphenyl-based small-molecule inhibitors with modified linkers (pink)

S.No.	Structure	Measurement method	Activity	Source/Ref
14		HTRF	18 nM	Maxinovel [44, 103]
15			44 nM	
16			1.34 mM	
17			>10 mM	
18		HTRF	56 nM	Syntron [46]
19		HTRF	12 nM	Li et al. [43]
20		HTRF	≤10 nM	Incyte [47–49]
21			≤10 nM	

proximal phenyl ring was converted into a quinazoline moiety to give lead compound 12, for which the IC_{50} value was at the micromolar level in HTRF binding assays. Further SAR studies showed that replacement of 1,4-benzodioxane in the distal phenyl ring and linking the benzonitrile or cyanopyridine to the central phenyl through an ether bond could significantly increase activity. The optimised compound 13 inhibited the PD-1/PD-L1 interaction with an IC_{50} value of 5 nM in HTRF binding assays, compared with 83 nM for the BMS-37 control. In conclusion, the biphenyl scaffold is the core structural element inhibiting PD-1/PD-L1 interaction, and it can only be partially replaced by

Table 3 (continued)

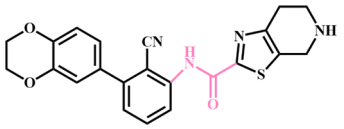
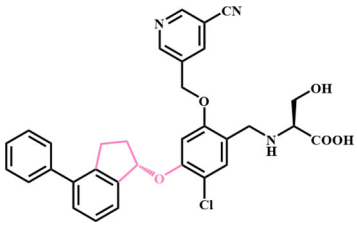
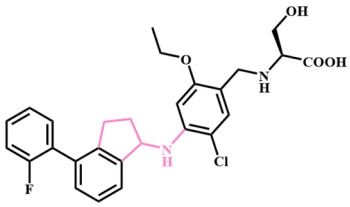
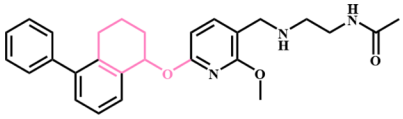
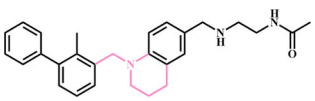
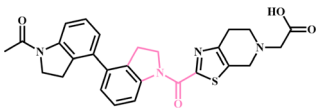
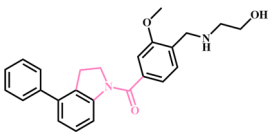
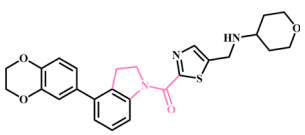
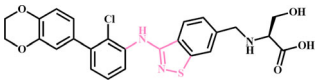
S.No.	Structure	Measurement method	Activity	Source/Ref
22			≤100 nM	
23		ELISA	≤100 nM	Chemocentryx [50, 51]
24			500−5 nM	
25		HTRF	1.4 nM	Guangzhou Wellhealth [52]
26			0.75 nM	
27		HTRF	≤25 nM	Betta [53]
28		HTRF	132.8 nM	Qin et al. [54, 55]
29			11.2 nM	

Table 3 (continued)

S.No.	Structure	Measurement method	Activity	Source/Ref
30		HTRF	8.5 nM	Chen et al. [56]

aromatic rings. SAR analysis showed that the proximal aromatic ring of the biaryl group tolerates substitution of small group (e.g., methyl, Br, Cl, CN) while the distal phenyl ring favours the replacement of 1,4-benzodioxane.

The linker region of biphenyl derivatives

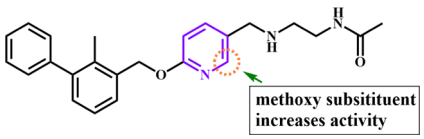
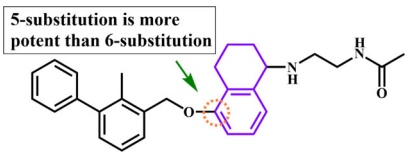
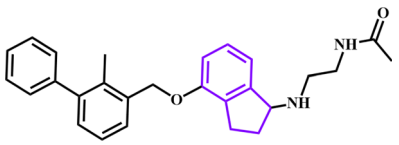
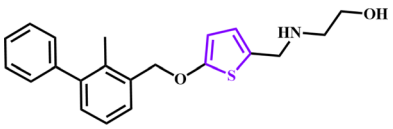
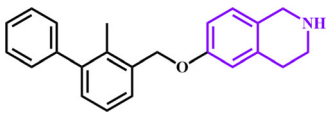
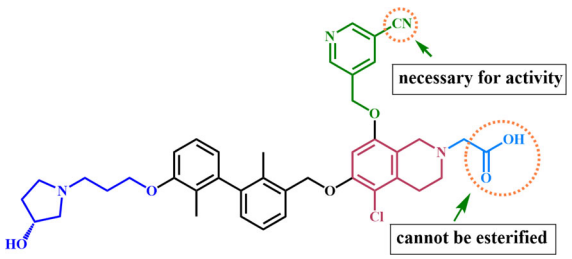
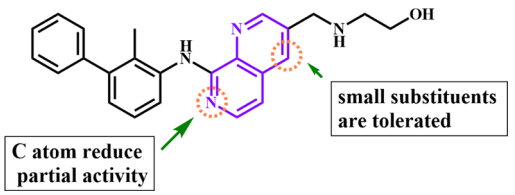
In patents from BMS, the linker is composed of a methylene ether, which is used to connect the biphenyl and aromatic ring, increasing the flexibility of the structure. SAR analysis showed that the methylene ether is not a key pharmacophore [43]. Patents were published by Guangzhou Maxinovel Pharmaceuticals in which the aromatic benzyl ether linker of biphenyl derivatives was converted to aromatic acetylene, aromatic ethylene, aromatic ethyl or aromatic heterocyclic. Compounds 14, 15, 16 and 17 displayed IC_{50} values of 18 nM, 44 nM, 1.34 mM and >10 mM, respectively, as measured by HRTF assay [44, 45]. In addition, Syntron Corporation reported a class of heterocyclic amino compounds with a five-membered linker [46]. The highly active compound 18 had an IC_{50} value of 56 nM measured by HTRF binding assay. The above indicated that reducing the flexibility of the linker decreases the activity of the compound. Li et al. developed a series of aliphatic amine-linked triaryl derivatives by changing the linker, and compound 19 was the most active ($IC_{50} = 12$ nM) according to HRTF binding assay [43]. SAR analysis revealed an interaction between aliphatic amines and the Ala121 residue, which improved structural stability and activity. In 2018 and 2019, Incyte Company published several novel scaffolds with modification of the linker [47–49], including removing the linker and secondary amine and amide group connection, with compounds 20, 21 and 22 having IC_{50} values < 10 nM, <10 nM and <100 nM, respectively, measured by HRTF binding assay. These results showed that modifying flexibility of the linker can increase activity (Table 3).

A significant number of new structures has been developed by incorporating bioisosterism principles. In 2019, Chemocentryx combined the methylene in the methylene ether linkage chain with the biphenyl to form a ninhydrin [50], and compound 23 exhibited an IC_{50} value < 100 nM in enzyme-linked immunosorbent assay (ELISA). The oxygen in the linked chain was then replaced with nitrogen via bioisosterism to generate inden-amine compounds [51], and compound 24 showed an IC_{50} value of 5–500 nM in ELISA. Guangzhou Wellhealth Bio-pharmaceutical Co. LTD reported new structures in which the linker is combined with the proximal phenyl ring or the aromatic ring to form a five-membered or six-membered ring [52], and compounds 25 and 26 displayed IC_{50} values of 1.4 nM and 0.75 nM, respectively, in HRTF binding assays. Compared with BMS-202, these compounds showed better metabolic stability in vitro and higher oral utilisation by liver microsomes. Betta Company produced dihydroindole compounds by combining amide link chains with the biphenyl [53], and compound 27 showed an IC_{50} value < 25 nM in HRTF binding assays. Qin et al. (year) combined the amide link chain with benzene on both sides to form dihydroindoles via the collage strategy [54], and the activity was higher than for the aromatic ring; compound 28 (A13) strongly inhibited the PD-1/PD-L1 interaction and increase IFN-γ secretion in in vitro immune experiments, and compound 13 showed low toxicity. Molecular docking experiments showed that the indole portion of compound 28 not only had hydrophobic effects through Met115 and Ala121, like the 2-methylphenyl group in BMS-37, but also interacted with Try123 to stabilise the inhibitor conformation [54]. Qin et al. (year) then optimised the 4-phenyldihydroindole to generate compound 29 (A30) with ultra-high activity [55]; the IC_{50} value was 11.2 nM in HTRF binding assays. Chen et al. (year) also designed a class of benzoisothiazole scaffold compounds via collation and bioelectron isoarrangement strategies, and compound 30 (CH20) had an IC_{50} value of 8.5 nM in HRTF binding assays [56]. Moreover, by removing the linking chains to improve structural rigidity, good activity and drugability was achieved [57–59], mainly because the central triphenyl was stabilised by extensive hydrophobic contacts with $_{B}$Tyr56, $_{A}$Met115, $_{B}$Met115, $_{A}$Ala121 and $_{B}$Ala121 [57].

The aryl group of biphenyl derivatives

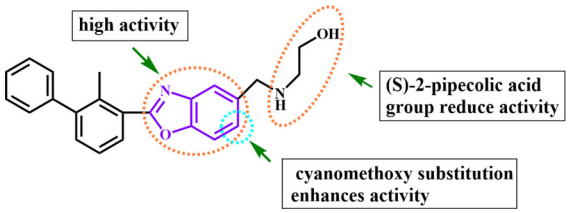
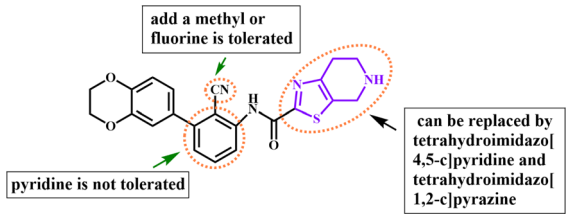
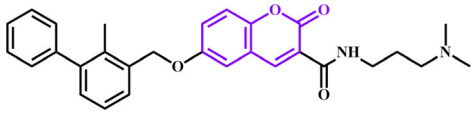
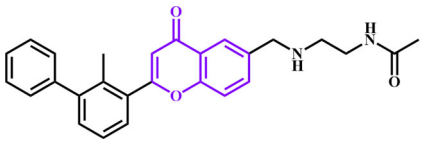
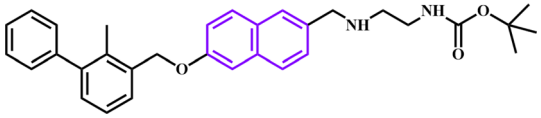
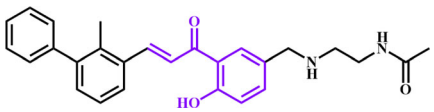
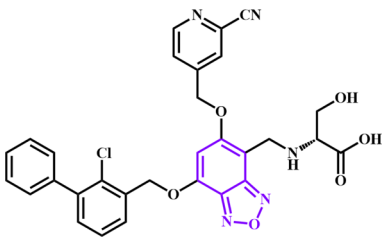
Since BMS reported the terphenyl scaffold PD-1/PD-L1 inhibitor in 2015, the aryl group was known to be an important pharmacophore due to hydrophobic and π-π

Table 4 Examples of biphenyl-based small-molecule inhibitors with a modified aryl group (purple)

S.No.	Structure	Measurement method	Activity	Source/Ref
31		HTRF	0.11–1.00 μM	BMS Company [35, 60]
32			0.11–1.00 μM	
33			0.11–1.00 μM	
34			0.11–1.00 μM	
35			1.076 μM	
36			2.0 nM	
37		HTRF	≤10 nM	Incyte [47–49]

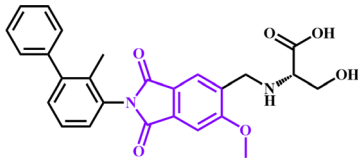
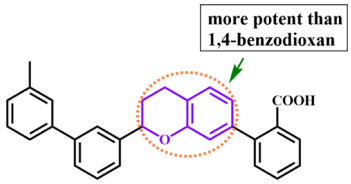
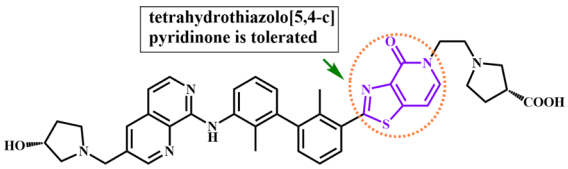
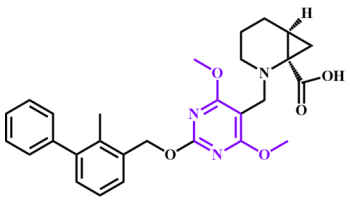
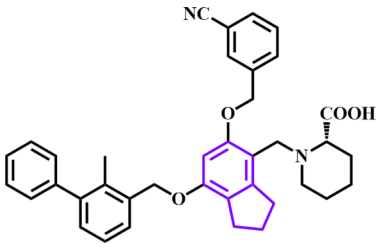
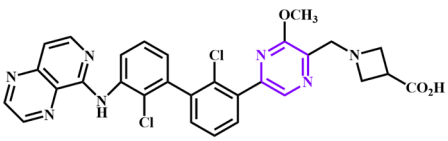
interactions with Try56. Patents reported by BMS showed that, besides the phenyl moiety, the aromatic ring can include pyridine, 1,2,3,4-tetrahydronaphthalene, hydrindene, thiophene and 1,2,3,4-tetrahydroisoquinoline [35], and compounds 31, 32, 33, 34 and 35 displayed IC_{50} values of 0.11–1.00 μM in HRTF binding assays. The

Table 4 (continued)

S.No.	Structure	Measurement method	Activity	Source/Ref
38			≤10 nM	
39			≤100 nM	
40		HTRF	PD-1/PD-L1 inhibition ratio = 70% ~ 100% (5 μM)	Ma et al. [61]
41		HTRF	1.428 μM	Southern Medical University [62–64]
42			1−10 μM	
43			5.387 μM	
44		HTRF	1.787 nM	Sun et al. [65]

2-position of the central pyridine of compound 31 can tolerate methoxy substituents, and BMS-202 displayed an IC_{50} value of 18 nM in HTRF binding assays. Moreover, activity data showed that the 1,2,3,4-tetrahydronaphthalene substituent at the 5-position was more potent than at the 6-position. In 2019, BMS optimised isoquinoline

Table 4 (continued)

S.No.	Structure	Measurement method	Activity	Source/Ref
45		HTRF	6.1 nM	Peng et al. [66]
46		HTRF	Inhibition ratio = 29.5% at 8 nM	Shanghai Longwood [67, 68]
47			≤100 nM	
48		HTRF	<100 nM	Jubilant Prodel LLC [71, 72]
49			<100 nM	
50		ELISA	≤10 nM	Chemocentryx [73]

derivatives by adding an extension, tail and ether group junction, significantly improving the activity of compounds [60]; compound 36 exhibited an IC_{50} value of 2.0 nM in HRTF binding assays. In 2018 and 2019, Incyte Corporation reported several novel series of biphenyl-based small-molecule inhibitors of PD-1/PD-L1 interaction. Besides the modified linker, Incyte Corporation also reported fused heterocyclic rings in aryl groups [47–49], and compounds 37, 38 and 39 respectively showed IC_{50} values < 10 nM, <10 nM and <100 nM in HRTF binding assays (Table 4).

Coumarins possess antitumor activity, and Ma et al. from Huaqiao University designed biphenyl-based coumarin

derivatives in 2019 [61], among which compound 40 achieved 70–100% inhibition of the PD-1/PD-L1 interaction in vitro at a concentration of 5 μM in HTRF binding assays. Moreover, using Sorafenib as a positive control, the compounds were tested for antitumor activity in MCF-7 human breast cancer cells and A549 human non-small cell carcinoma cells. The IC_{50} values of compound 40 for MCF-7 and A549 cells were 6.27 μM and 10.937 μM, respectively, compared with 10.87 μM and 11.24 μM for sorafenib. In the same year, Southern Medical University successively published three new lead structure patents [62–64] based on structures of natural compounds including flavonoids, naphthalene and chalcone. The IC_{50} values of representative structures 41, 42 and 43 were 1.428 μM, 1–10 μM and 5.387 μM, respectively, in HTRF binding assays. Two months later, Sun et al. from China Pharmaceutical University reported benzodiazole compounds [65] for which the IC_{50} value of compound 44 was 1.787 nM in HTRF binding assays. Experiments showed that the compounds could significantly block inhibition of PD-L1 in human PBMC cells and tumour cells, and secretion of IFN-γ by human T cells. Moreover, they could promote the proliferation of T cells and enhance the immune function of T cells. In 2021, Peng et al. from China Pharmaceutical University proposed a class of o-benzoylimide compounds [66], among which compound 45 displayed an excellent IC_{50} value of 6.1 nM in HTRF binding assays.

Shanghai Longwood Biopharmaceuticals Co., Ltd. also explored the aromatic ring. In 2019, the company published a series of fused-ring compounds, including five-membered heterocyclic fused six-membered heterocyclic, six-membered heterocyclic fused six-membered heterocyclic, and dihydrogen five-membered or tetrahydrogen six-membered heterocyclic fused six-membered heterocyclic aromatic compounds [67]. The representative compound 46 achieved 29.5% inhibition of the PD-1/PD-L1 interaction in vitro at a concentration of 8 nM in HTRF binding assays. SAR analysis reveals that replacement of chromane in the aromatic position with 1,4-benzodioxane could decrease activity. In the following year, a class of five-membered diheterocyclic pyridinone derivatives was reported [68], among which compound 47 exhibited an IC_{50} value < 100 nM in HTRF binding assays. SAR analysis revealed tolerance of thiazole, oxazole, imidazole, furan and thiophene in place of the five-membered heterocyclic part of the aromatic group. Meanwhile, activity data showed that the pyridione part in the aromatic group could be displaced by dihydro-2*H*-pyridine-2-one. Furthermore, changing the extension part, Shanghai Longwood Biopharmaceuticals developed a significant number of compounds in which the aromatic group was a pentadiheterocyclic pyridinone structure [69, 70].

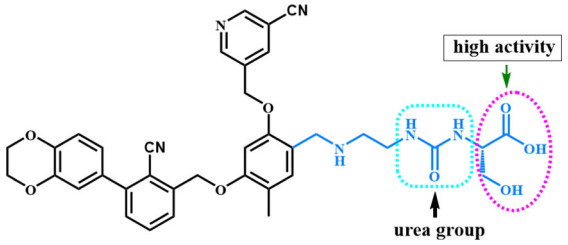
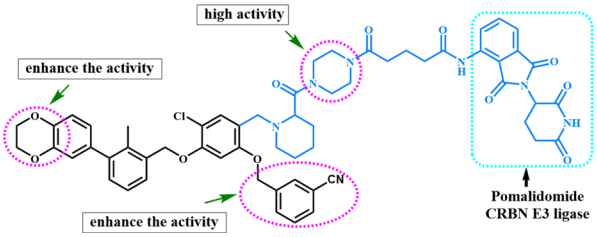
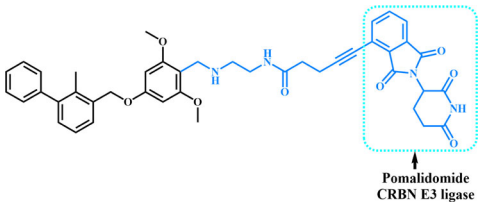
In 2020, Jubilant Prodel LLC reported a new class of biphenyl inhibitors with pyrimidine as the aromatic part [71], and compound 48 showed an IC_{50} value < 100 nM in HTRF binding assays. In December of the same year, the company reported a novel class of compounds whose aromatic part was indene or tetrahydronaphthalene [72], differing from BMS compounds because the benzene ring counterpoint is substituted with indene or tetrahydronaphthalene. Compound 49 displayed an IC_{50} value < 100 nM in HTRF binding assays. In 2021, Chemocentryx reported a class of biphenyl inhibitors with pyrazine as the aromatic part [73, 74], and compound 50 showed an IC_{50} value ≤ 10 nM in ELISA.

The tail of biphenyl derivatives

The tail of biphenyl derivatives directly interacts with solvent and plays an important electrostatic role. This part is composed of the main chains and side chains of residues $_{L}$Asp122 to $_{L}$Arg125, and the side chain of $_{L}$Asp26 flanks a shallow groove in which there are multiple hydrogen bond donors and receptors. Therefore, the tail is composed of residues with hydrogen bond donors and receptors. BMS have extensively investigated the tail structure. However, the tail of biphenyl compounds is protected as a general feature in most patents. Only a class of urea compounds reported by Shenzhen Chipscreen Biosciences Co. Ltd. directly protected the structure of the tail [75]. Representative compound 51 showed an IC_{50} value of 15.78 nM in HTRF binding assays, indicating these compounds possessed good PD-1/PD-L1 binding activity in vitro. Further SAR studies showed that compounds with a 1-carboxy-2-hydroxythan-1-yl tail displayed higher activity. The 3-(4,5-dimethylthiazol-2-yl)-5(3-carboxymethonyphenol)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) cell viability assay was used as a routine cytotoxicity detection approach to evaluate the growth activity of the Jurkat T-cell leukaemia cell line, and the results showed that all 14 compounds could maintain more than 90% cell activity. When measuring the bioactivity of PD-1 signalling inhibition at the cellular level, blocking or inhibiting the PD-1/PD-L1 interaction can enhance T cell activity and IL-2 secretion. ELISA showed that the representative compound had obvious activity for promoting IL-2 secretion by human T cells (>50%) (Table 5).

PROTACs is a novel strategy for removing unwanted proteins by hijacking the ubiquitin-proteasome system [76]. Recent studies showed that the PD-L1 protein is subject to ubiquitin-proteasome-mediated protein degradation [77]. The Chen group from Southern Medical University discovered a class of m-resorcinol diphenyl ether analogues using the PROTAC strategy that can be used as both inhibitors and depressants of PD-L1 [78]. By analysing the cocrystal structure of the dimeric PD-L1 protein and the

Table 5 Examples of biphenyl-based small-molecule inhibitors with a modified tail (sky blue)

S.No.	Structure	Measurement method	Activity	Source/Ref
51		HTRF	15.78 nM	Shenzhen Chipscreen [75]
52		HTRF	39.2 nM	Chen group [78]
53		HTRF	21 μM	Yang group [81]

BMS-8 complex, it was found that the piperidine 2-carboxylate tail group of BMS-8 was exposed to solvent, making it a suitable site for E3 ligase to bind to linkers and ligands. Furthermore, pomalidomide was selected as the ligand of CRBN (cereblon) E3 ligase due to its appropriate molecular weight [79] and immunomodulatory activity [80]. Combining pomalidomide and PD-1/PD-L1 inhibitors could achieve a synergistic effect, and this hypothesis was tested using a series of novel chlorophenol diphenyl ether PROTAC molecules targeting the PD-1/PD-L1 pathway. Compound 52 (P22) was one of the best-performing compounds, with an IC_{50} value of 39.2 nM in HTRF binding assays. Further SAR studies showed that introducing piperazine into the tail linking chain increased the activity of P22 5-fold. In addition, P22 significantly restored immunosuppression in co-culture models of Hep3B/OS-8/hPD-L1 and CD3 T cells. Flow cytometry and western blotting results also proved that P22 could moderately reduce the PD-L1 protein abundance in a lysosome-dependent manner. These results indicated that PD-1/PD-L1 small-molecule inhibitors were likely to serve as PD-L1-targeted PROTAC molecules. Compound P22 can be used as the starting point for PROTAC-like degradation of PD-L1. In addition, the Yang group from Nankai University reported new PROTAC molecules, among which compound 53 (21a) showed the best performance, with an IC_{50} value of 21 μM in HTRF binding assays [81]. Moreover, compound 21a could significantly reduce PD-L1 protein abundance, promote the invasion of CD8 + T cells, and inhibit the growth of MC-38 cells in vivo.

The ether group junction of biphenyl derivatives

In 2017, BMS also reported compounds with a scaffold based on the biphenyl core as inhibitors of PD-1/PD-L1 and CD80/PD-L1 with an aliphatic linker or aromatic groups at the ether group junction [82]. Addition of cyanopyridine or benzonitrile at the ether group junction had a positive impact on SAR. Furthermore, replacement of the distal phenyl ring with 1,4-benzodioxane significantly improved binding affinity. The IC_{50} values of the most potent compounds were in the range of 0.6–10 nM according to HTRF assays. The SAR-modified compound 54 displayed an IC_{50} value of 0.95 nM as determined by HTRF assay. Holak's research showed that the benzonitrile portion of BMS-1001 occupies pockets composed of $_{B}$Arg113, $_{B}$Tyr123, $_{B}$Arg125

Table 6 Examples of biphenyl-based small-molecule inhibitors with a modified ether group junction (green)

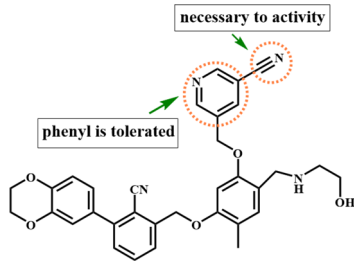
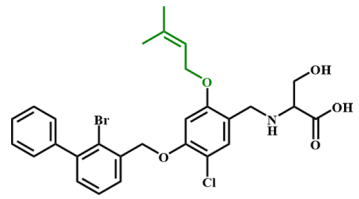
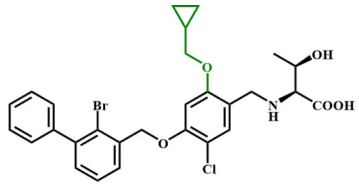
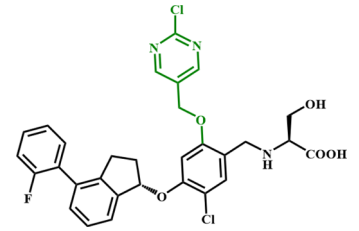
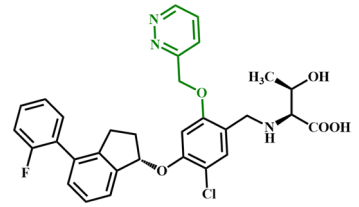
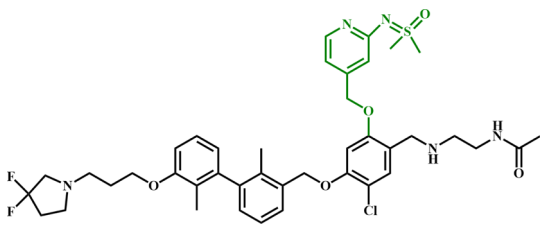
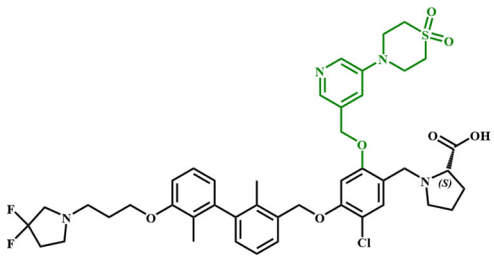
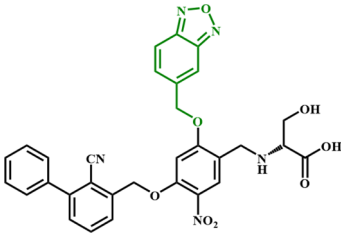
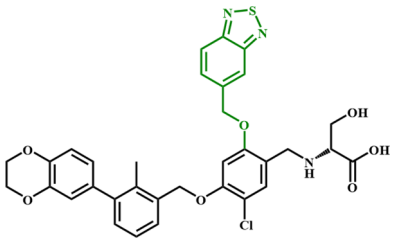
S.No.	Structure	Measurement method	Activity	Source/Ref
54		HTRF	0.92 nM	BMS [82]
55		HTRF	10.2 nM	Institute of Material Medica [83]
56			18.2 nM	
57		ELISA	<100 nM	Chemocentryx [50]
58			100−500 nM	
59		HTRF	6.6 nM	Guangzhou Wellhealth [84]

Table 6 (continued)

S.No.	Structure	Measurement method	Activity	Source/Ref
60			16 nM	
61		HTRF	1.97 nM	Sun et al. [85]
62			6.46 nM	

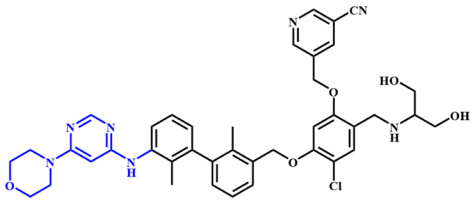
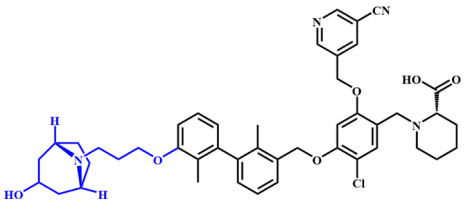
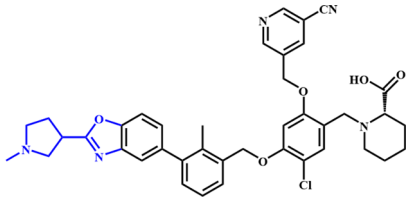
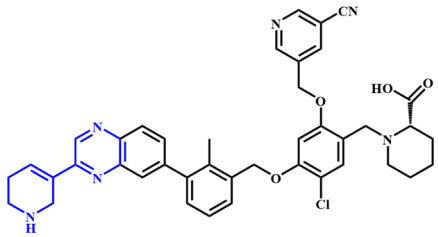
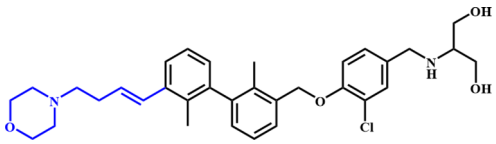
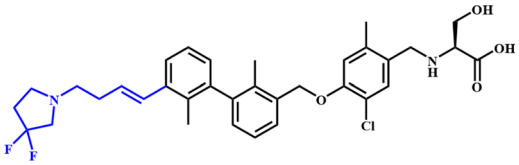
and $_{A}$Asp61, providing additional hydrophobic π-π and hydrogen bonding interactions [38]. Hydrophobic interactions occurred between the phenyl group of benzonitrile and $_{A}$Tyr123, and hydrogen bonding occurred between the cyanogen group of benzonitrile and Asp61, which increased the activity of these compounds by more than an order of magnitude in vitro (Table 6).

Based on docking experiments and SAR analysis, the cyano group on the pyridine ring in the ether junction of biphenyl derivatives results in high activity. However, pharmaceutical company scientists are still exploring the ether group junction for novel compounds. The Institute of Materia Medica, Chinese Academy of Medical Science reported a series of 2-site brominated biphenyl compounds for which the ether junction was optimised, and compounds 55 and 56 were the most active with IC_{50} values of 10.2 nM and 18.2 nM, respectively, according to HTRF binding assays [83]. In 2019, Chemocentryx reported a series of compounds with optimised ether junctions [50]. The ether junction part consisted of a pyridine-acetonitrile scaffold with good activity ($IC_{50} < 100$ nM). Other scaffolds included pyrimidine and diazine, for which compounds 57 and 58 had IC_{50} values < 100 nM and 100–500 nM, respectively, based on ELISA.

In 2020, Guangzhou Wellhealth Bio-pharmaceutical Co. LTD. reported biphenyl small-molecule inhibitors with a dimethyl oxyphosphorus group, dimethyl sulphonimide or morpholino-1,1-oxide group [84] at the ether junction, among which compounds 59 and 60 had IC_{50} values of 6.6 nM and 16 nM, respectively, by HTRF binding assay, compared with 42 nM for the BMS-202 control. Biological activity evaluation experiments revealed very good tumour immunotherapy in vitro, promotion of the secretion of IFN-γ by T cells in a co-culture system, and significantly stimulated production of IFN-γ by T cells. In a pharmacokinetic study, compound 60 exhibited good pharmacokinetic characteristics as well as good stability and drug properties in terms of particle stability and plasma protein binding rate.

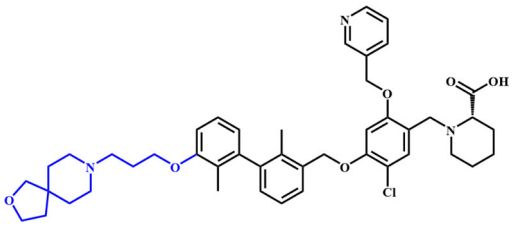
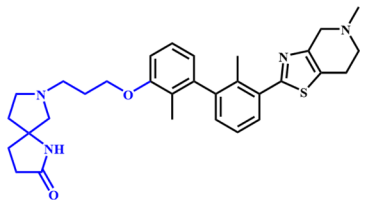
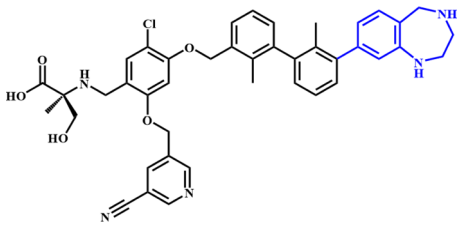
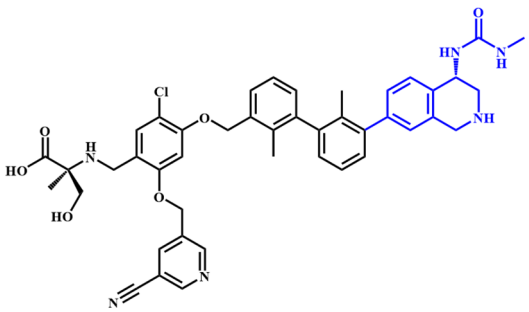
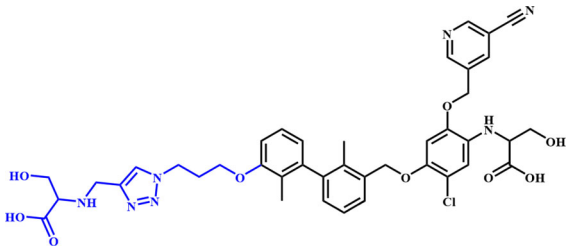
In the same year, Sun et al. from China Pharmaceutical University reported compounds in which the ether junction was replaced with 2,1,3-benzodiazole or thiadiazole [85], and compounds 61 and 62 inhibited PD-1 and PD-L1 protein abundance by 99% at a concentration of 10 nM, with IC_{50} values of 1.97 nM and 4.64 nM, respectively, in

Table 7 Examples of biphenyl-based small-molecule inhibitors with a modified extension (royal blue)

S.No.	Structure	Measurement method	Activity	Source/Ref
63		HTRF	0.21−10 nM	BMS [36, 87]
64			0.21−10 nM	
65			0.67 nM	
66			1.7 nM	
67		HTRF	1.0 nM	Shenzhen Chipscreen [88]
68			2.0 nM	

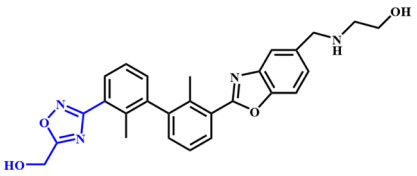
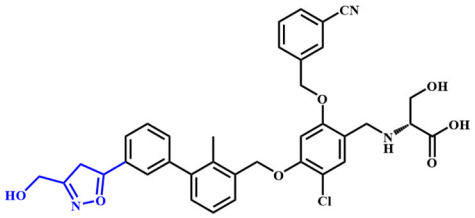
HTRF binding assays, compared with, 64% inhibition and an IC_{50} value of 34.31 nM for the BMS-1016 control. Moreover, the compounds performed well at blocking the hPD-L1 protein, inhibiting IFN-γ secretion from human peripheral blood mononuclear cells (PBMCs), inhibiting cell proliferation, inhibiting IFN-γ secretion from human T cells, and inhibiting IL-2 secretion from Jurkat cells. A Biacore molecular interaction instrument was used to determine that the combination and hPD-L1 protein bound strongly with a K_D value of 0.5 nM. Nuclear factor of

Table 7 (continued)

S.No.	Structure	Measurement method	Activity	Source/Ref
69		HTRF	1.1 nM	HEC Pharm. [89, 90]
70			0.76 nM	
71		Alpha LISA	0.064 nM	Gilead Sciences [91]
72			0.064 nM	
73		HTRF	0.1−10 nM	Xu et al. [92]

activated T-cells (NFAT) reporter gene PD-1/PD-L1 blocking experiments showed that the compounds could significantly interrupt PD-1/PD-L1 interaction in cells, with EC_{50} values between 0.21 and 3.64 μM. NFAT is a high-activity test method involving Bio-Glo Luciferase reagent and the chemiluminescence technique to probe the influence of antibodies or small-molecule compounds on the PD-1/PD-L1 interaction.

Table 7 (continued)

S.No.	Structure	Measurement method	Activity	Source/Ref
74		HTRF	0.1−20 nM	Zhang et al. [93]
75			0.1−20 nM	

Extension of biphenyl derivatives

Scientists from BMS expanded on the first biphenyl patent [35]. Katarzyna Guzik et al. found that, in contrast to BMS-202, BMS-200 is perpendicular to the C, F and G chains of PD-L1, creating an interface similar to the PD-1-interacting surface [86]. The linear arrangement of the compound leads to the formation of a 16 Å long cylindrical hydrophobic channel between the two hPD-L1 monomers. The 2,3-dihydro-1,4-phenyldioxybenzyl group of the inhibitor BMS-200 causes $_{A}$Tyr56 C(β)−C(γ) to move 77° around the C(α)−C(β) axis, making this part of the compound accessible to solvent, thus turning the deep hydrophobic crack into a deep hydrophobic tunnel. This suggests that the ligand-binding sites of PD-L1 are more flexible than previously believed, and redefines the pharmacophore model previously described, creating new possibilities for further design of PD-L1 inhibitors (Table 7).

In 2018, BMS disclosed a patent related to extending biphenyl derivatives [36]. Representative compounds 63 and 64 had IC_{50} values in the range of 0.21 to10 nM based on HTRF binding assays. In July the following year, BMS reported another class of compounds with a fused heterocyclic structure at the distal phenyl ring in the biphenyl moiety, and elaborated on the extension [87]. Compounds 65 and 66 displayed IC_{50} values of 0.67 nM and 1.7 nM, respectively, in HTRF binding assays. Other compounds had IC_{50} values between 0.18 and 10.0 nM in HTRF binding assays. In 2020, Shenzhen Chipscreen Biosciences designed a series of biphenyl derivatives with an olefin moiety at the extension [88]. Representative compounds 67 and 68 had the ability to inhibit the PD-1/PD-L1 interaction at the nanomolar level in HTRF binding assays. In October of the same year, HEC Pharm reported biphenyl derivatives with a spiral ring structure added at the extension [89, 90], and compounds 69 and 70 exhibited the IC_{50} values of 1.1 and 0.76 nM, respectively, in HTRF binding assays.

The extension structures designed by Gilead Sciences were mainly C2-symmetric or pseudo-symmetric, hence the molecular weight is large, ranging from 500 to 1100 Da, as described below. In addition, Gilead Sciences designed a series of 9-, 10- or 11-fused-ring heterocyclic or heteraryl compounds at the extension in 2021 [91]. Compounds 71 and 72 showed IC_{50} values of 0.064 nM based on binding of protein pairs using the microbead amplification luminescence adjacent homogeneity assay (ALPHA) platform. In the same year, Xu et al. from China Pharmaceutical University reported a new biphenyl derivative with a triazole ring in the extension [92]. Representative compound 73 had an IC_{50} value of 0.1–10 nM in HTRF binding assays, and the affinity between the compound and hPD-L1 was 0.1–10 nM. The compounds in the patent were found to enhance the expression of INF-γ in a dose-dependent manner, significantly more effectively than BMS-202 but slightly lower than Keytruda (5 μM/mL), thereby enhancing the anti-tumour efficacy of T cells. In August of the same year, Zhang et al. from China Pharmaceutical University reported heterocyclic biphenyl compounds [93], and compounds 74 and 75 showed IC_{50} values between 0.1 and 20 nM in time-resolved fluorescence resonance energy transfer (TR-FRET) experiments, compared with an IC_{50} value of 18.7 nM for the BMS-202 positive control.

C2-symmetric and pseudo-symmetric structures of biphenyl derivatives

In 2019, BMS published a series of C2-symmetric and pseudo-symmetric compounds [82], among which compounds 76 and 77 showed IC_{50} values of 0.04 nM and 0.04–20 nM, respectively, in HTRF binding assays. Meanwhile, Basu et al. revealed the binding pattern of C2-symmetric compounds and proteins, among which LH1306 and LH1307 showed strong inhibition of the PD-1/PD-L1 interaction [94]. The cocrystal structure of LH1307 and the PD-L1 protein revealed a molecular arrangement similar to that of the PD-L1/BMS-200 complex previously reported by Guzik et al. (Fig. 2). The symmetrical structure of compound LH1307 facilitates the expansion of the channel, which is generated by the overall movement of a PD-L1 molecule in the dimer. All β chains (ABCDEFG), but not C' chains, participate in this transfer, resulting in an overall rotation of 15° with respect to the BMS-202/PD-L1 structure. Furthermore, the C2-symmetric structure enables the dimer to exhibit greater symmetry than previously described (Table 8).

Incyte Corporation again reported a class of pseudo-symmetric tetrahydroimidazolium[4,5-C]pyridine derivatives in 2019 [95], During T cell activation using artificial antigen-presenting cells (Aapcs), compounds 79 and 80 displayed EC_{50} values for IFNg secretion <10 nM and between 10 and to 100 nM, respectively. In 2020, Gilead Sciences reported a C2-symmetrical structure containing ninhydrin [96], and compound 81 had an IC_{50} value of 0.051 nM in AlphaLISA. Shanghai Longwood Biopharmaceuticals published a class of nitrogen-containing heterocyclic symmetric and pseudo-symmetric compounds [68], among which compounds 82 and 83 had IC_{50} values < 100 nM in HTRF binding assays.

In addition, Betta reported C2-symmetric biphenyl derivatives [97], among which compounds 84 and 85 had IC_{50} values of 0.21 nM and 0.37 nM, respectively, in HTRF binding assays. The IC_{50} values of most compounds in the patent were <25 nM. In September the following year, Betta reported another biphenyl symmetrical structure [98], representative compounds 86 and 87 showed IC_{50} values of 0.13 nM and 33 nM, respectively, in HTRF binding assays, and pseudosymmetric compound 86 showed better activity. In addition, the EC_{50} value of compound 86 was 24 nM in NFAT experiments. Chemocentryx also reported C2-symmetric or pseudo-symmetric compounds with ninhydrin [99], and compounds 88 and 89 had IC_{50} values < 100 nM in the ELISA. A class of C2-symmetric biphenyl compounds incorporating five-membered heterocycles was reported by Syntron [100], and representative compound 90 showed an IC_{50} value of 30.9 nM in HTRF assays.

The cyclic structure of biphenyl derivatives

In 2019, Guangzhou Dankang Medical Biological Co. Ltd. published a class of biphenyl cyclic PD-1/PD-L1 inhibitors [101], among which compounds 91 and 92 displayed IC_{50} values of 1.1 and 1.2 nM, respectively, in HTRF binding assays, compared with 39 nM for the BMS-202 control. In vitro metabolic stability experiments compared compounds 1164, 1250 and 1305 in patent CN106536515A, and some

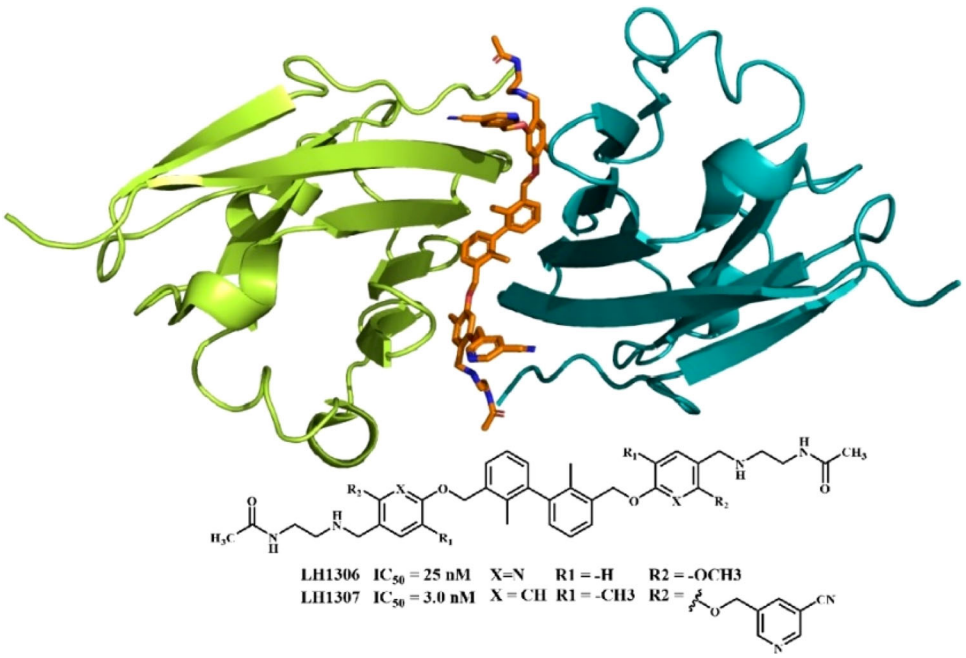
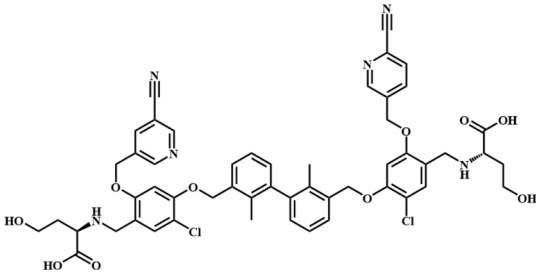
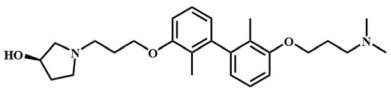
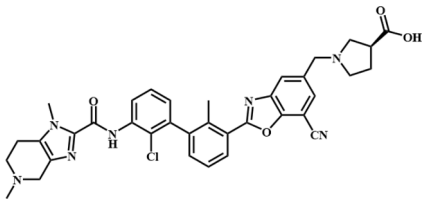
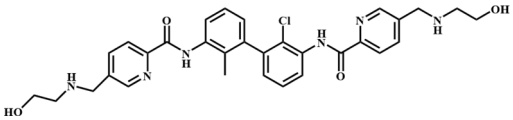
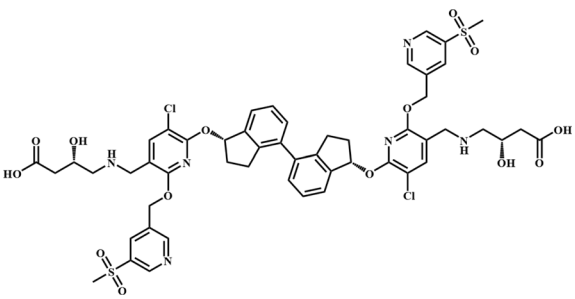
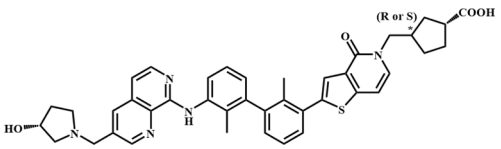


Fig. 2 Cocrystal structure of the C2-symmetric compound LH1307 (orange) and the PD-L1 dimer (PDB code: 6RPG). The structure of LH1306 and LH1307 is shown at the bottom

Table 8 Examples of biphenyl-based C2-symmetric or pseudo-symmetric small-molecule inhibitors

S.No.	Structure	Measurement method	Activity	Source/Ref
76		HRTF	0.04 nM	BMS [82]
77			0.04−20 nM	
79		Alphascreen	≤10 nM	Incyte [95]
80		HRTF	≤10 nM	
81		Alpha LISA	0.051 nM	Gilead Sciences [96]
82		HRTF	<100 nM	Shanghai Longwood [68]

compounds showed better metabolic stability. In pharmacokinetic studies on compound 91 and reference compound 1250, compound 91 showed better pharmacokinetic characteristics and higher oral bioavailability; the average bioavailability of compounds 91 and 1250 was 66.38% and 22.90%, respectively. In 2020, Chemocentryx released a series of macrocyclic immunomodulators consisting of combined aromatic macrocyclic compounds [102]. The IC_{50} value measured by ELISA was <2uM, compared with <100 nM for compounds 93 and 94 (Table 9).

Table 8 (continued)

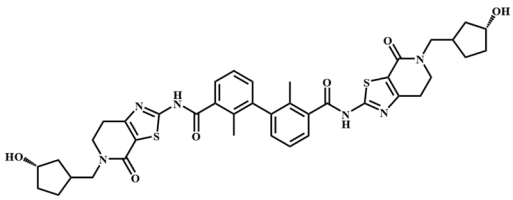
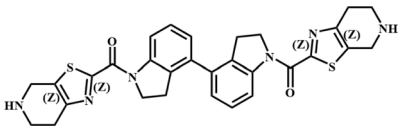
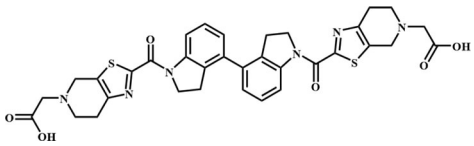
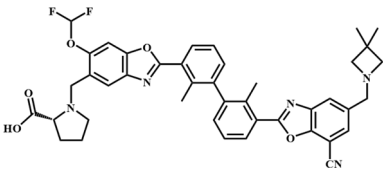
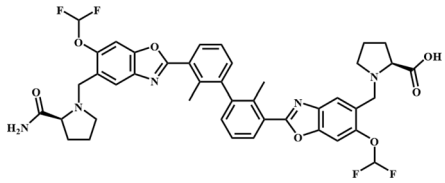
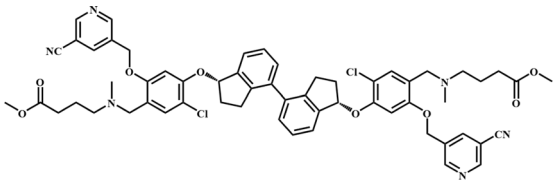
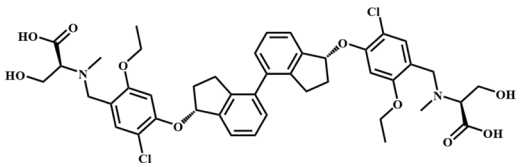
S.No.	Structure	Measurement method	Activity	Source/Ref
83			<100 nM	
84		HRTF	0.21 nM	Betta [97, 98]
85			0.37 nM	
86			0.13 nM	
87			0.33 nM	
88		ELISA	<100 nM	Chemocentryx [99]
89			<100 nM	

Table 8 (continued)

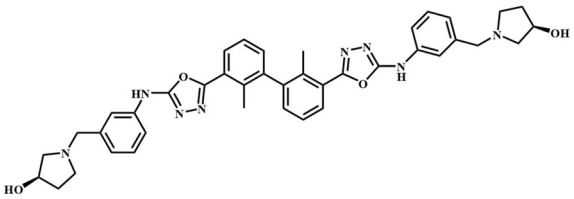
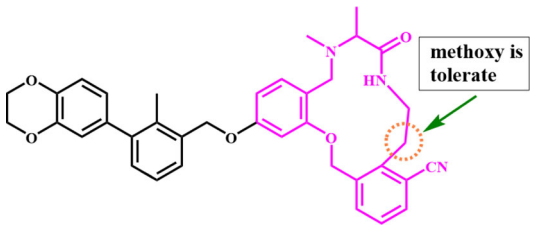
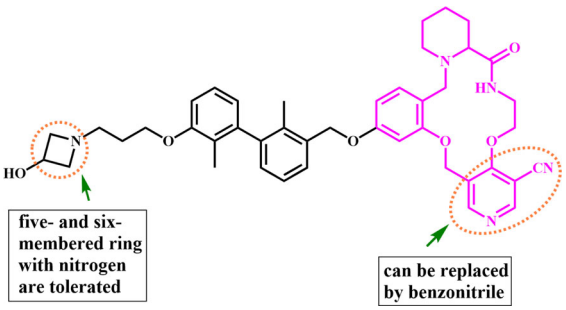
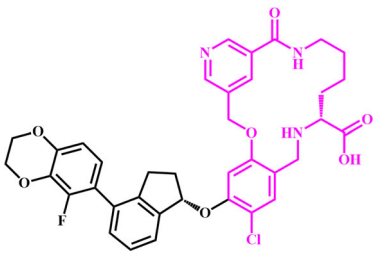
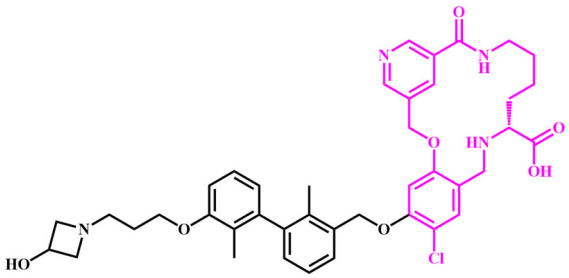
S.No.	Structure	Measurement method	Activity	Source/Ref
90		HRTF	30.9 nM	Syntron [100]

Table 9 Examples of biphenyl-based small-molecule inhibitors with cyclic compounds (fuchsia)

S.No.	Structure	Measurement method	Activity	Sources/Ref
91		HRTF	1.2 nM	Guangzhou Wellhealth [101]
92			1.1 nM	
93		ELISA	<100 nM	Chemocentryx [102]
94			<100 nM	

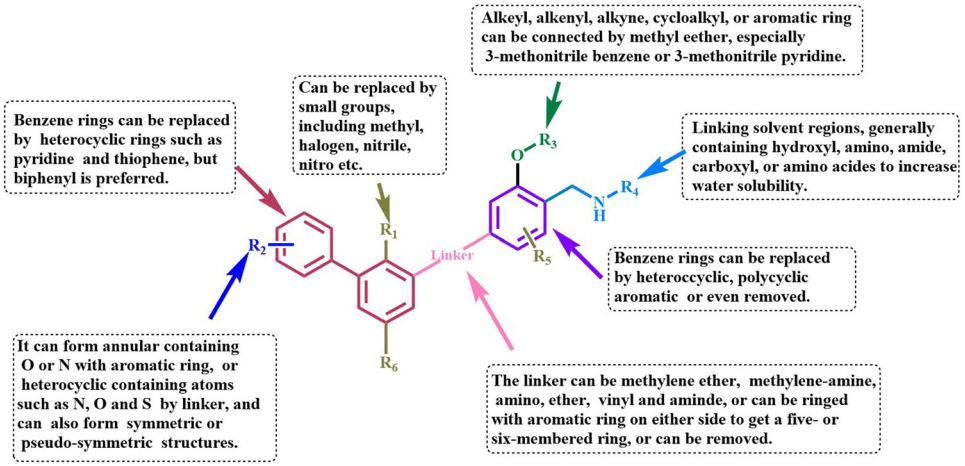


Fig. 3 Summary of SAR analysis of small-molecule inhibitors based on biphenyl derivatives

Conclusion

PD-1/PD-L1 protein-protein interaction (PPI) is a target with a large interacting surface, which makes it difficult to design small-molecule inhibitors. Small-molecule inhibitors based on biphenyls can induce dimerisation of PD-L1, effectively prevent binding between PD-1 and PD-L1, and regulate the activity of immune cells. In this work, we summarised small-molecule inhibitors based on biphenyls and performed SAR analysis (Fig. 3). For both biphenyls and biaryls, the activity of compounds could be significantly improved by rational design of the extension, the ether group junction and the tail. The linker is not an essential pharmacophore, but is useful for designing novel structures. In conclusion, the structure of existing compounds can serve as starting points for designing new molecular frameworks. However, due to the limited number of existing PD-1/PD-L1 small-molecule inhibitors, there is ample opportunity to explore novel inhibitors with optimised therapeutic efficacy. Structure-based drug design strategies driven by crystal structure and pharmacophore models may lead to improved small-molecule drugs. In addition, we believe that with the rapid development of small-molecule inhibitors of the PD-1/PD-L1 pathway, more compounds with significant immunomodulatory activities and good drug-like properties will appear in the future.

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Author contributions YLW and SRW designed the research; SRW performed the collection and analysis of data; SRW and HY drafted the article.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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