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A patent review on PD-1/PD-L1 antagonists: small molecules, peptides, and macrocycles (2015-2018)

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REVIEW



A patent review on PD-1/PD-L1 antagonists: small molecules, peptides, and macrocycles (2015-2018)

Shabnam Shaabani^a, Harmen P.S. Huizinga^a, Roberto Butera^a, Ariana Kouchi^a, Katarzyna Guzik^b, Katarzyna Magiera-Mularz^b, Tad A. Holak^b and Alexander Dömling^a

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ABSTRACT

Introduction: The protein–protein interaction PD1/PD-L1 is an important immune checkpoint and several recently approved monoclonal antibodies show promising anti cancer activities in the clinical practice. However, only a small percentage of cancer patients benefit from PD1/PD-L1 directed mAbs. Moreover, some patients experience immune related side effects upon treatment with these mAbs. Recently, several atomic-resolution structures of human PD1/PD-L1, and small molecules, peptides and mAbs with PD-L1 and PD1 open the field for structure based drug design. Small molecules and peptides targeting PD1/PD-L1 promise to enhance tumor activity while showing less immune related side effects.

Areas covered: We reviewed the small molecules classes and peptides targeting PD1/PD-L1.

Expert opinion: Currently approved PD1/PD-L1 directed therapeutics show room for improvement. Three classes of non mAb small molecule classes have been discovered so far: (cyclic) peptides as direct competitive PD1/PD-L1 antagonists; small molecules disrupting PD1/PD-L1 and inducing a PD-L1 dimerization; and a small molecule class of unknown mode-of-action. An example of the later group CA-170 is currently investigated in a Phase 1 trial in patients with advanced solid tumors and lymphomas. Potential advantages of small molecules over mAbs include high distribution and better tumor penetration, improved PK/PD, less side effects and oral bioavailability.

ARTICLE HISTORY

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KEYWORDS

Programmed death-1; PD-1; PD-L1; immune checkpoint; T-cell exhaustion; immunology

1. Introduction

Targeting the immune checkpoint inhibitor pathway is a highly promising new therapeutic modality to fight cancer. Programmed death 1 (PD-1) is expressed on activated T-cells while programmed death ligand-1 (PD-L1) is commonly expressed on the surface of dendritic cells or macrophages. PD-1 and PD-L1 belong to the so-called inhibitory checkpoints which naturally regulate the immune response to minimize, for example, the possibility of chronic auto-immune inflammation. When cancer cells overexpress PD-L1 and undergo an interaction with T-cell PD-1, this interaction can halt or limit the development of the T-cell response. The PD-1/PD-L1 pathway represents an adaptive immune resistance mechanism which is used by tumors to escape immune surveillance. PD-L1 expressed on the cancer cells binds to PD-1 the membrane receptor on the activated T-cell, which leads to the inhibition of the cytotoxic T-cell. These deactivated T-cells remain inhibited in the tumor microenvironment and are called T-cell exhaustion. Expression of PD-L1 on cancer cells correlates with reduced survival in many different types of cancers, highlighting this pathway as a target for immunotherapy. Thus, antagonizing PD-1/PD-L1 protein–protein interaction (PPI) was hypothesized to activate the immune system against cancer. Amongst immune checkpoints, PD-1/PD-L1 is the most prominent and currently successfully used in clinical practice. Five monoclonal antibodies (mAbs) are already approved for the treatment of multiple oncological malignancies either targeting PD-1 (nivolumab, pembrolizumab) or PD-L1

(avelumab, atezolizumab, durvalumab). Many clinical trials on anti-PD-1 and PD-L1 antibodies are currently in progress. PD-1/PD-L1 directed antitumor therapy has shown impressive results with durable clinical responses. However, only a fraction of patients respond to immune checkpoint therapy, depending on the cancer type. Although, monoclonal antibody therapy is less toxic than most chemotherapy drugs, some immune-related adverse effects (irAEs), with deadly outcome were reported. This has been attributed – mostly to the long half-life time of mAbs. Other side effects such as pneumonitis, myositis, autoimmune hypophysitis, immune thrombocytopenia, bullous pemphigoid-like skin lesions and overt eosinophilia, psoriasis are reported. Small molecules targeting PD-1/PD-L1 potentially can have other side effect profile, a better tissue penetration with potentially higher efficacy and a tuneable half-life time. Moreover, polypharmacology can be designed to synergistically bind to several targets such as PD-1, V-domain Ig suppressor of T-cell activation (VISTA), TIM-3 and LAG3. Therefore, design and discovery of small molecules and peptides antagonizing PD-1/PD-L1 is ongoing (Figure 1) and the intellectual property landscape from 2015 to 2018 is summarized here [1].

2. Body

2.1. Small molecules

Researchers at Bristol-Myers Squibb (BMS) company discovered multiple small molecules for the inhibition of the PD-1/

Article highlights

- Targeting the immune checkpoint inhibitor pathway is a highly promising new therapeutic modality to fight cancer.
- PD-1/PD-L1 directed checkpoint inhibitor therapy of malignant tumors is a breakthrough in oncology.
- Structure-based design of PD-1/PD-L1 antagonists is achievable now.
- Three general non-mAb PD-1/PD-L1 antagonists are currently known, peptidic direct PD-1 antagonists, small molecule PD-L1 dimerizer, and small molecules of unknown mode-of-action.
- Small molecules and peptides can potentially reduce irAEs, lead to higher efficacy and to a larger number of responders.

PD-L1 axis. These compounds are useful in cancers that suppress the immune system and in metastases that express the PD-L1 ligand. The described molecules can also be potentially used in combination with regular anti-cancer therapies such as radiotherapy, standard immunotherapy and chemotherapy. They can also be useful in HIV, infectious diseases, and in hepatitis.

The general structure **1** for one series of these compounds is shown in Scheme 1 [2]. For the determination of the ability of these compounds to bind to PD-L1, PD-1/PD-L1 homogeneous time-resolved fluorescence (HTRF) binding assay was used and the measured IC_{50} values were in the range of 0.006 μ M–10 μ M for 297 described compounds (Scheme 1).

BMS chemists also disclosed 1,3-dihydroxy phenyl derivatives with general structure **2** that inhibit PD-1/PD-L1 PPI with IC_{50} values in the range of 0.60 nM–20 μ M. However, no *in vivo* characterization of these small molecules have been performed in this trial (Scheme 1) [3].

The first co-crystal structures of hPD-L1 complexed with small molecular weight inhibitors (examples **1** and **2**, Scheme 1) disclosed in the BMS patent were reported previously [4]. More recently, structural studies revealed that examples **3** and **4** induce conformational changes in the PD-L1 binding site, upon the complex formation (Scheme 1). Thus,

it presents several opportunities for the design of more potent inhibitors of PD-1/PD-L1 interaction [5,6].

Another class of 1,3-dihydroxy phenyl derivatives with general structure **3** was disclosed by BMS as immunomodulators which are useful for the treatment of various disorders, including cancer and infectious diseases. The binding properties (IC_{50}) of these compounds to PD-1/PD-L1 were determined using HTRF binding assay. [7]

BMS researchers reported more potent PD-1/PD-L1 inhibitors (IC_{50} 0.21 nM–10 μ M) with general structure **4** that include the extended sidechains of the phenyl group [8]. Some representative examples with IC_{50} values of less than 1 nM are shown in Scheme 1.

BMS researchers in their recently published patent reported biaryl compounds with general structure **5** as inhibitors of PD-1/PD-L1 and CD80/PD-L1 PPIs [9]. The compounds with a (pseudo)symmetric structure (examples **9**, **10**) are characterized with the lowest IC_{50} values.

Arising International LLC researchers recently disclosed (pseudo)symmetric compounds with general structure **6** as inhibitors of PD-1/PD-L1 and CD80/PD-L1 PPIs (Scheme 2). Based on docking experiments, example **11** was selected as ligand binding to the PD-L1 dimer (pdb code of PD-L1 dimer: 5J8O). As shown in the patent, the hydrophobic channel accommodates the core scaffold in the center and two (pseudo)symmetrical side chains attached to the core are extended to either side of the dimer interface. It is believed that these inhibitors can effectively induce/stabilize PD-L1 dimer formation, therefore potently disrupting PD-1/PD-L1 and CD80/PD-L1 PPIs. To assess the antagonist activity of the compounds, HTRF binding assay using extracellular domains of PD-1 and PD-L1 proteins was performed. In this class of compounds, the structures containing biaryl group have the lowest IC_{50} values (example **11**, Scheme 2). A nonbiphenyl compound characterized with IC_{50} in the range of 0.1–25 μ M (example **12**) is also mentioned in the patent [10].

Chemists from the company Polaris Pharmaceuticals Inc. have also described biaryl derivatives binding to the PD-1/PD-L1 and

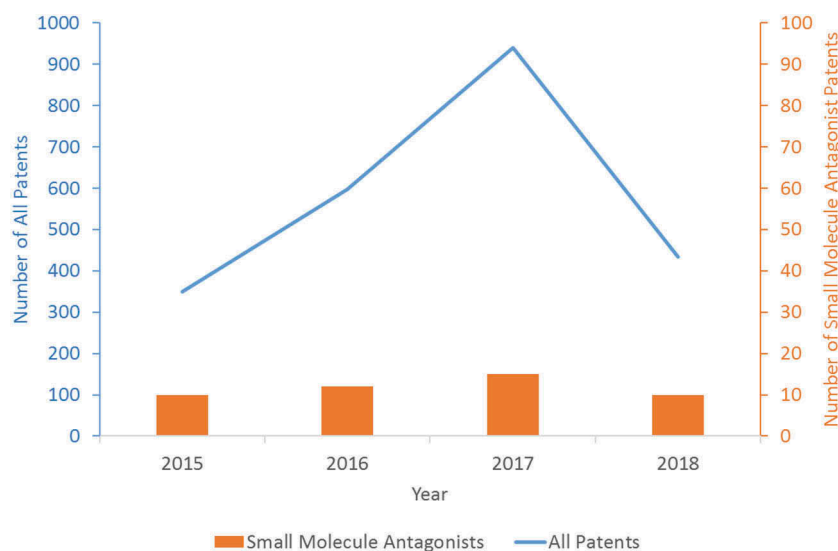
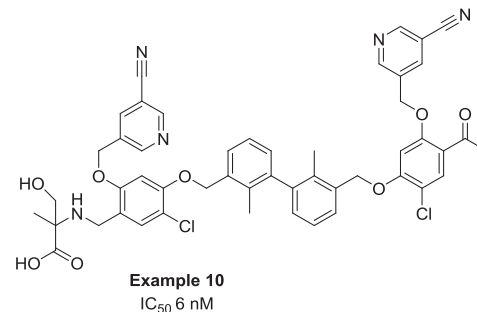
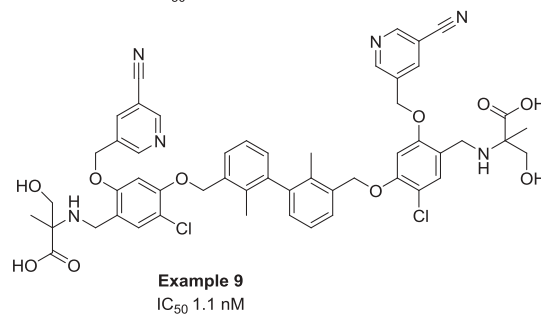
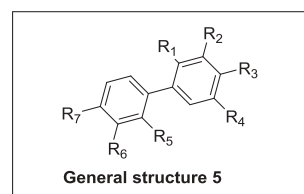
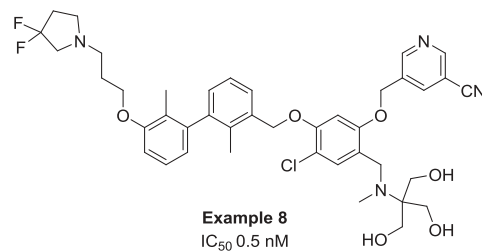
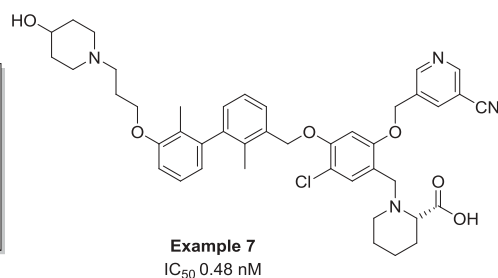
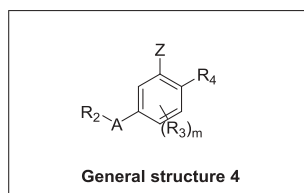
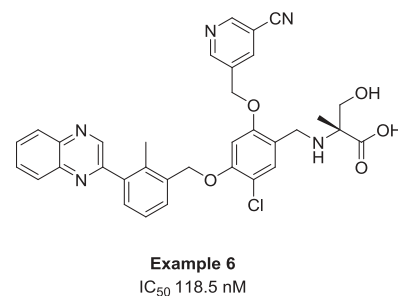
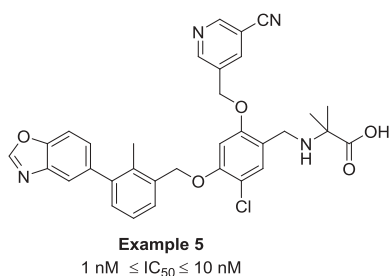
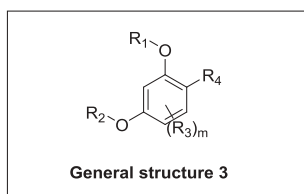
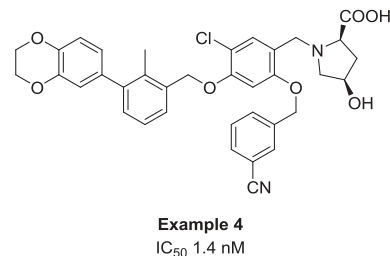
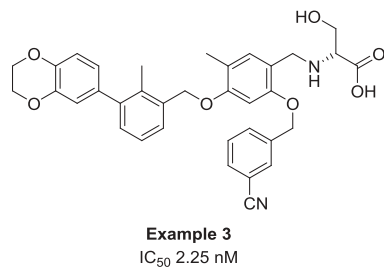
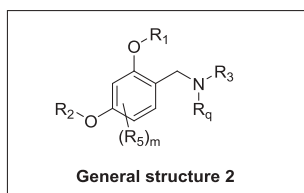
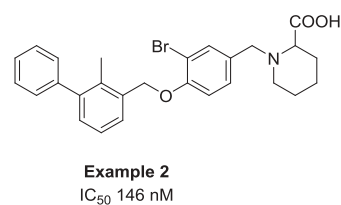
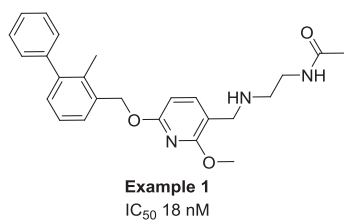
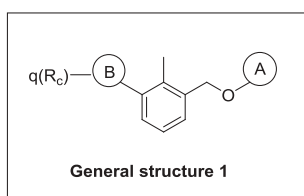
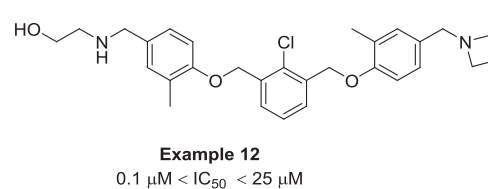
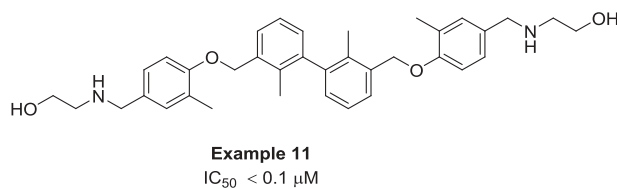
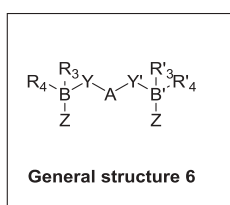


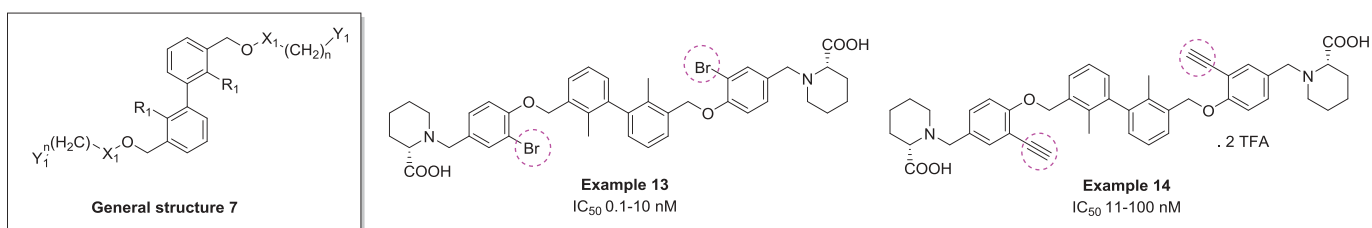
Figure 1. Comparison of increase of patents associated to PD-1/PD-L1 PPI and small molecules targeting PD-1/PD-L1 PPI.



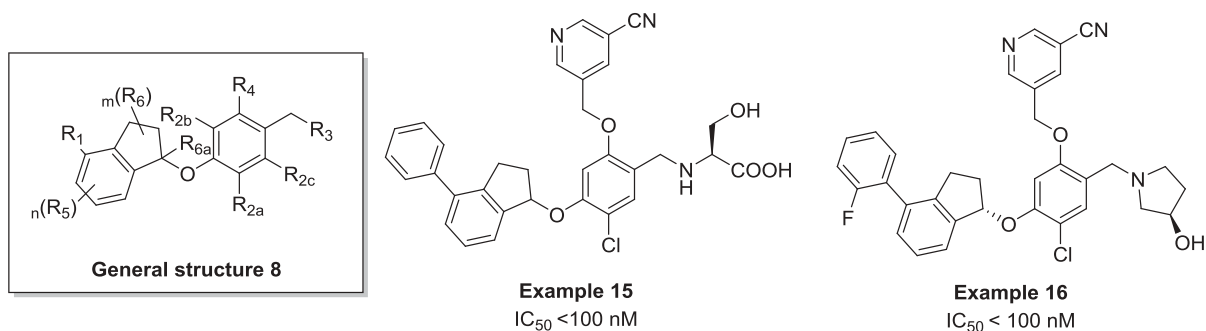
Scheme 1. The general structures and examples of the compounds patented by BMS.



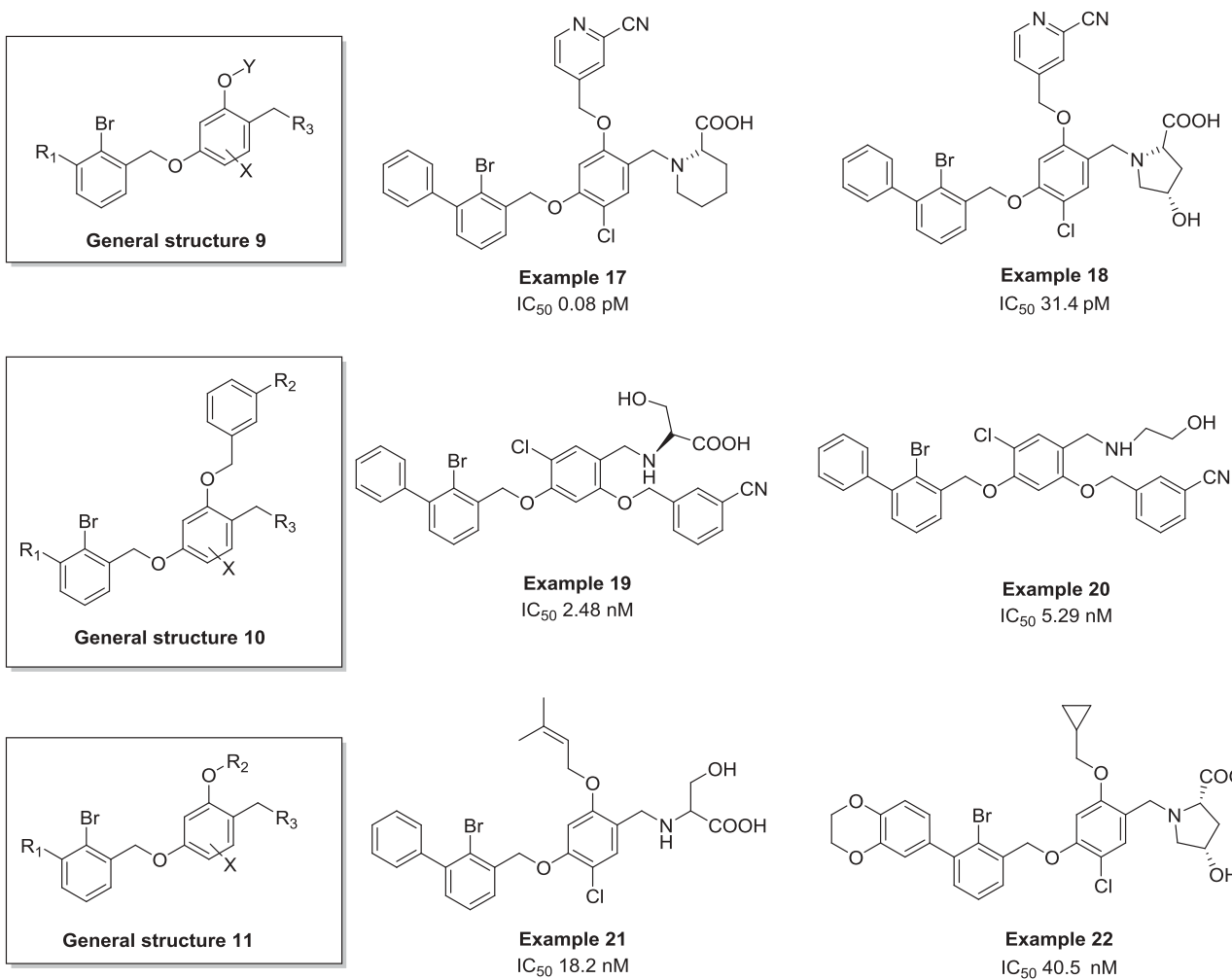
Scheme 2. The general structure and examples of the compounds patented by Arising International LLC.



Scheme 3. The general structure and examples of the compounds patented by Polaris Pharmaceuticals Inc.



Scheme 4. The general structure and examples of the compounds patented by Chemocentryx Inc.



Scheme 5. The general structures and examples of the compounds patented by Institute of Materia Medica (Chinese Academy of Medical Sciences).

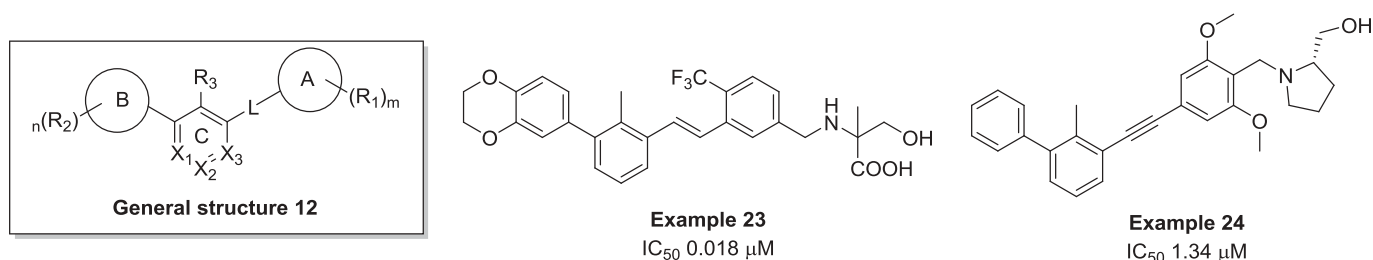
CD80/PD-L1 axes (Scheme 3). The disclosed general structure **7** consists of a tetra-aromatic ring system, similar to the BMS compounds superimposed within distal phenyl ring of biphenyl moiety. All of these compounds are symmetrical biphenyls and their ability to block PD-1/PD-L1 interaction was established based on enzyme-linked immunosorbent assay (ELISA). Replacing the Br groups by acetylene moieties on the phenyl group in this class of compounds caused a significant reduction in the IC₅₀ value (examples **13**, **14**, Scheme 3) [11].

Chemocentrix Inc. researchers published immunomodulatory compounds with general structure **8** as shown in Scheme 4. These compounds were evaluated as inhibitors of the PD-1 pathway by biochemical interaction assay based on ELISA platform by human PD-L1. IC₅₀ values of the most potent compounds are less than 100 nM (examples **15**, **16**) [12].

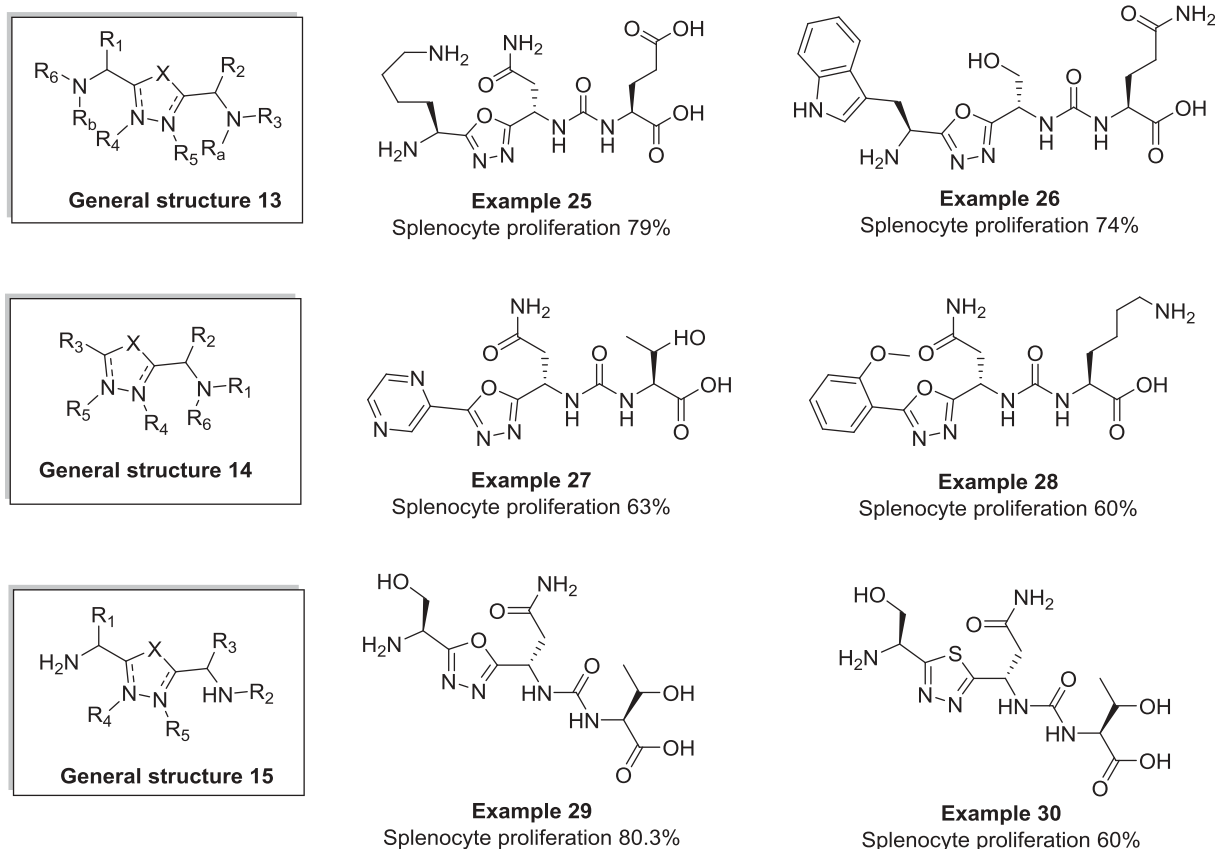
The Institute of Materia Medica (Chinese Academy of Medical Sciences) has filed patents for bromobenzyl ether

derivatives of general structures **9** [13], **10** [14] and **11** [15] (Scheme 5). Core structure includes a tetra substituted 1,3-dioxophenyl with an appendant bromobenzyl ether. The disclosed compounds are potential therapeutics for treating diseases related to PD-1/PD-L1 signal channels such as cancers, infectious diseases and autoimmune disorders. The biological activity as inhibitors of PD-1/PD-L1 axis was determined by HTRF PD-1/PD-L1 Binding Assay (Cisbio). The strong binding affinity of the compounds to PD-L1 was evaluated using Biacore.

Guangzhou Maxinovel Pharmaceuticals Co., Ltd. disclosed aromatic acetylene or aromatic ethylene derivatives as PD-1/PD-L1 inhibitors [16]. The bioactivity of the compounds was assessed by HTRF using Cisbio PD-1/PD-L1 binding assay kit. Out of 69 compounds reported in the patent, 3 are acetylene derivatives. Changing the acetylene moiety in example **24** to an ethylene moiety, example **23**, the IC₅₀ value has

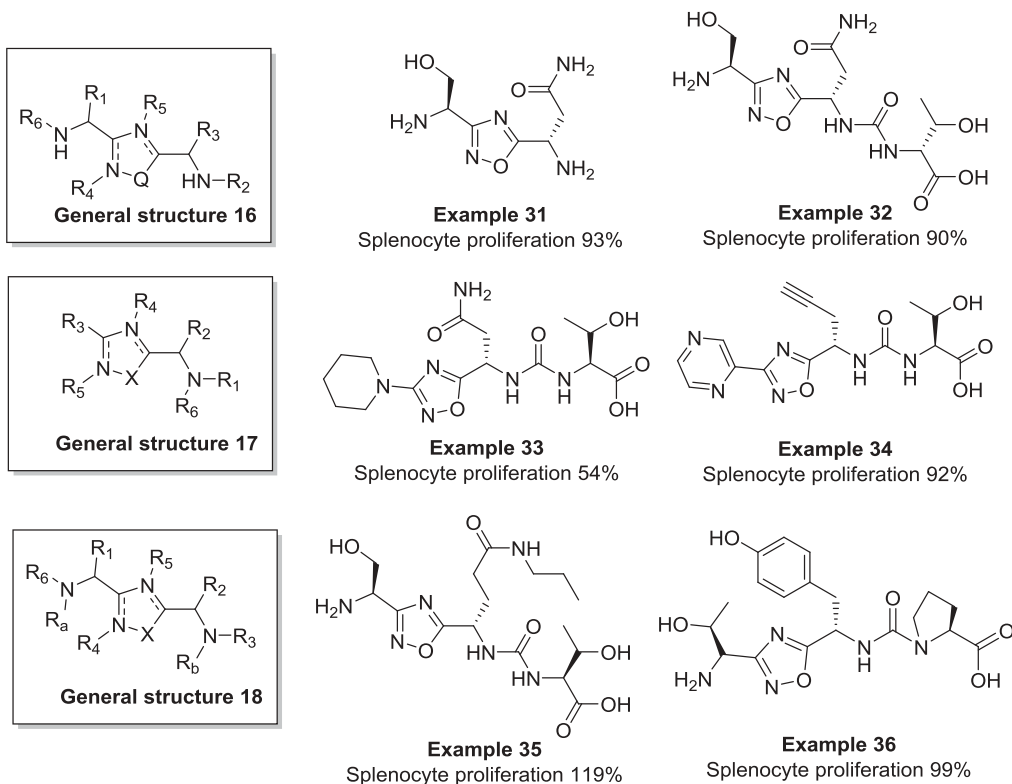


Scheme 6. The general structure and examples of the compounds patented by Guangzhou Maxinovel Pharmaceuticals Co., Ltd.

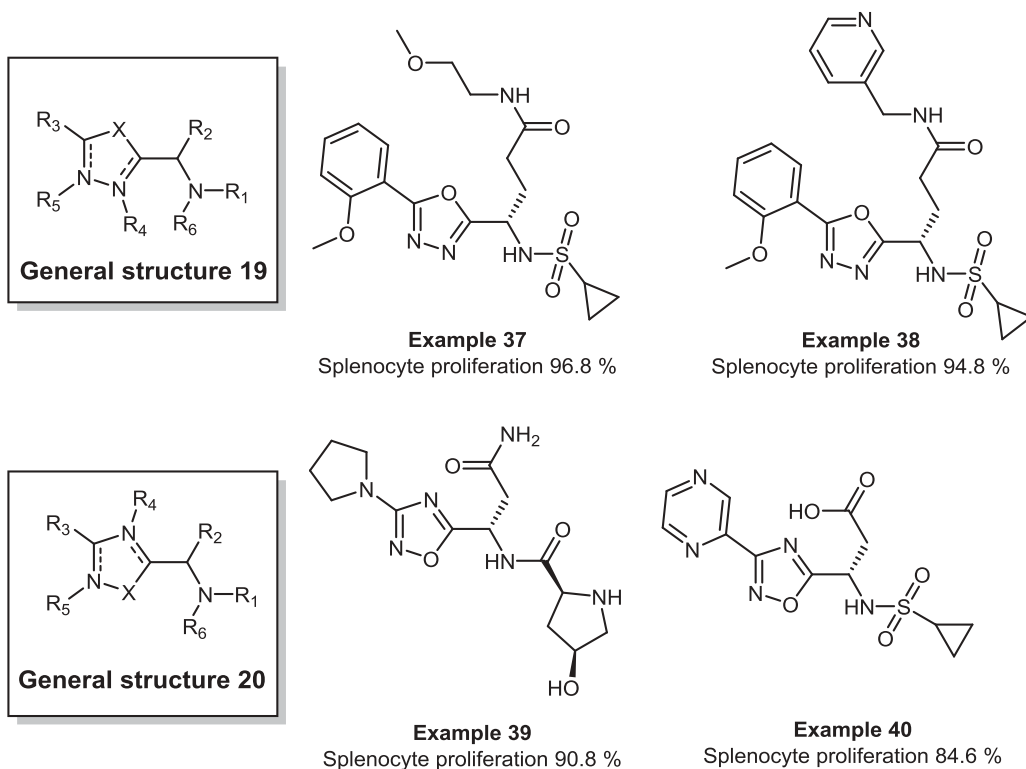


Scheme 7. The general structures and examples of 1,3,4-oxadiazoles and 1,3,4-thiadiazole patented by Aurigene Discovery Technologies Ltd.

decreased from 1.34 nM to 18 nM (Scheme 6). Recently, L1 antagonists efficacy of single agent or combination in Maxinovel Pharmaceuticals described orally active PD-1/PD- mouse models [17].



Scheme 8. The general structures of the claimed 3-substituted-1,2,4-oxadiazoles and thiadiazoles scaffolds and examples of the 3-substituted-1,2,4-oxadiazoles patented by Aurigene Discovery Technologies Ltd.



Scheme 9. The general structures of the claimed 3-substituted-1,2,4-oxadiazoles and thiadiazoles scaffolds and examples of the 3-substituted-1,2,4-oxadiazoles patented by Aurigene Discovery Technologies Ltd.

Researchers from Aurigene Discovery Technologies Limited in Bangalore, India, discovered oxadiazole and thiadiazole structures which are inhibitors of the PD-1/PD-L1 interaction.

General structures (**13** [18], **14** [19] and **15** [20]) of 1,3,4-oxadiazoles and 1,3,4-thiadiazoles are shown in Scheme 7. The inhibition activity of these compounds was measured by percent rescue of mouse splenocyte proliferation in the presence of recombinant mouse PD-L1 (general structure **13** and **14**) and recombinant mouse PD-L1/PD-L2 (general structure **15**) at 100 nM compound concentration. Example **30** shows 92% splenocyte proliferation at 100 nM compound concentration which is the highest among 1,3,4-oxadiazoles and 1,3,4-thiadiazoles reported by this group [20]. Oxadiazoles compared to thiadiazoles show better activity and the most active compounds in this class contain primary amine and urea moieties [18,19].

Scientists from Aurigene Ltd. have also claimed 1,2,4-oxadiazoles and 1,2,4-thiadiazoles with general structures **16** [21], **17** [22] and **18** [23] as inhibitors of PD-1/PD-L1 pathway (Scheme 8). The inhibition activities of the compounds were assessed by rescue of mouse splenocyte proliferation in the presence of recombinant mouse PD-L1/PD-L2 (general structure **16**) and recombinant mouse PD-L1 (general structures **17**, **18**). Representative examples with the highest percent rescue of splenocyte proliferation at 100 nM compound concentration are shown in Scheme 8[21–23].

Recently, researchers from Aurigene Ltd. disclosed cyclic substituted-1,3,4-oxadiazole and thiadiazole compounds of general structure **19** [24] and substituted-1,2,4-oxadiazole compounds of general structure **20** [25]. Similarly to previous disclosures, any example with thiadiazole core is not directly presented in the patent. The compounds are claimed to enhance the immune response, therefore can be used for the treatment of disorders, comprising aberrations of the PD-1 pathway. Among the reported compounds in these patents, example **37** have highest percent rescue of mouse splenocyte proliferation in the presence of recombinant PD-L1/PD-L2 at 100 nM concentration of the compound. However, it should be noted that mouse and human PD-L1 differ in amino acid sequence.

Incyte Corporation filed patents for 5 series of compounds with general structures **21** [26], **22** [27], **27** [28], **28** [29], **29** [30], **24** [31], **25** [32], **26** [33] and **23** [34] as shown in Scheme 10. These compounds modulate PD-1/PD-L1 PPI and are useful in treating, preventing or ameliorating diseases and disorders such as cancer or infections. PD-1/PD-L1 HTRF binding assay with recombinant human PD-L1 protein was used to validate the activity of these compounds.

Dömling from the University of Groningen in the Netherlands filed a patent with 60 examples of the general structure **30** as inhibitors of the PD-1/PD-L1 PPI (Scheme 11). The binding affinity of these compounds was analyzed by differential scanning fluorimetry (DSF) and NMR using recombinant human PD-1 and PD-L1 proteins and all of them showed activity (IC_{50}) in the range of 0.001–1000 μ M [35].

2.2. Peptides

Several peptides and peptidomimetic compounds that inhibit the PD-1/PD-L1 pathway were discovered. In 2014, researchers

from Aurigene Ltd. have reported compounds with the general structure **31** (Scheme 12). The activity of these compounds was determined by carboxyfluorescein diacetate succinimidyl ester (CFSE) proliferation assay. CFSE is a dye that passively diffuses into cells and binds to intracellular proteins.

One of the most promising compounds of this group is example **61** which was found to have a 4-fold induction of the splenocyte proliferation at 100 nM concentration as compared to the background (the proliferation of splenocytes while exposed to PD-L or a tumor). Interestingly, this compound was also subjected to *in vivo* activity test-on metastasis of B16F10 melanoma in female mice. The 64% reduction of the metastasis was observed at 5 mg/kg dose of the compound [36].

Researchers from Aurigene Ltd. have also described potent peptides with general structure **32** (Scheme 12). Most active compounds in this class contain 1,2-disubstituted hydrazine and urea moieties. The best example **63** induces a recovery of the splenocyte proliferation of 87% at a compound concentration of 100 nM [37].

2.3. Macrocycles

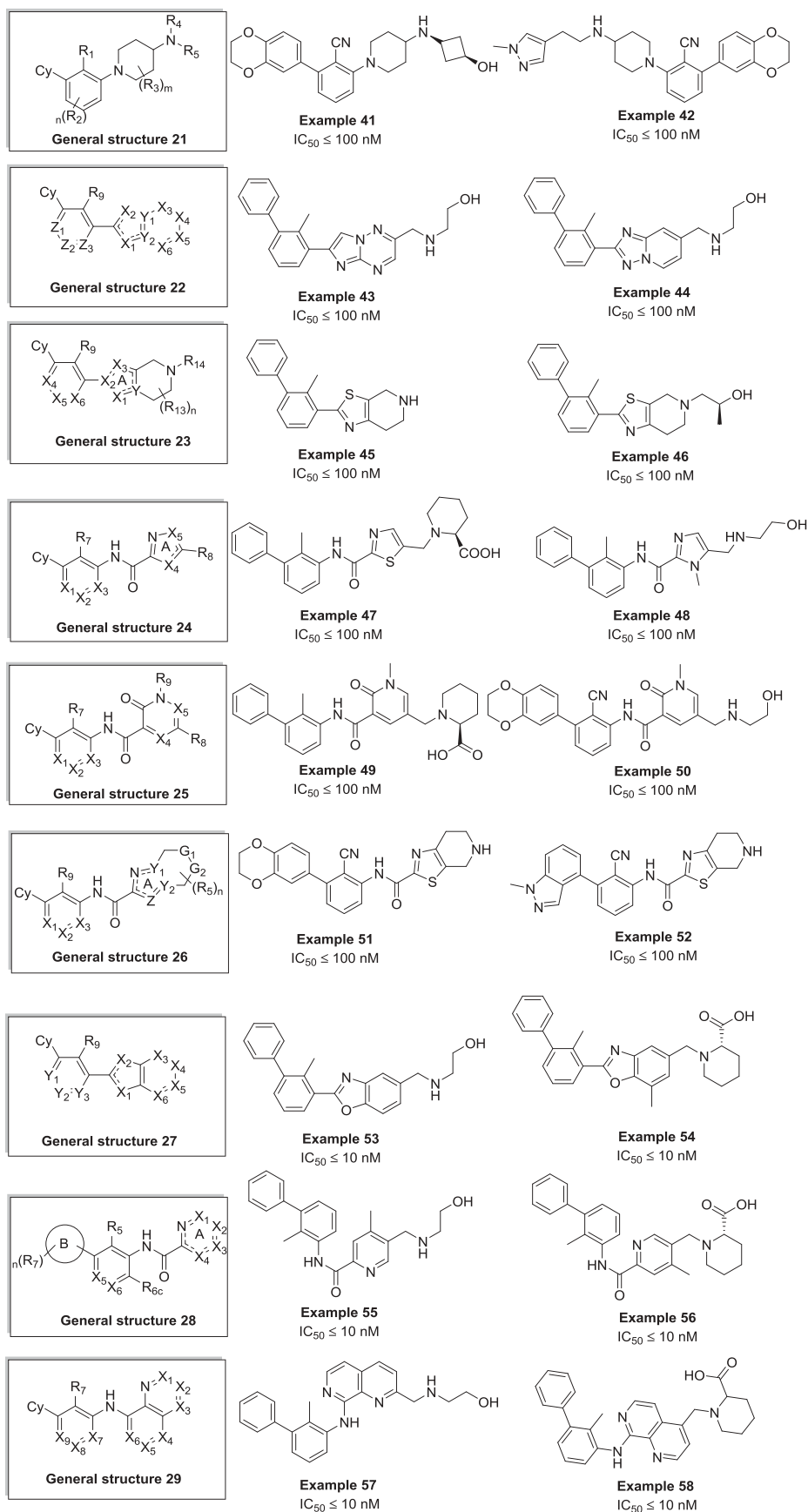
Several PD-1/PD-L1 inhibitors based on macrocyclic peptide structures were reported. These molecules have been proven to be effective antagonists for this PPI by biochemical and cell-based experiments.

The blockage of the PD-1/PD-L1 PPI by these macrocycles results in enhanced T-cell response and thus improving the immune system. The modulation of this PPI is relevant for the improvement of cancer therapy, HIV therapy, chronic viral infections, and numerous other immunological diseases.

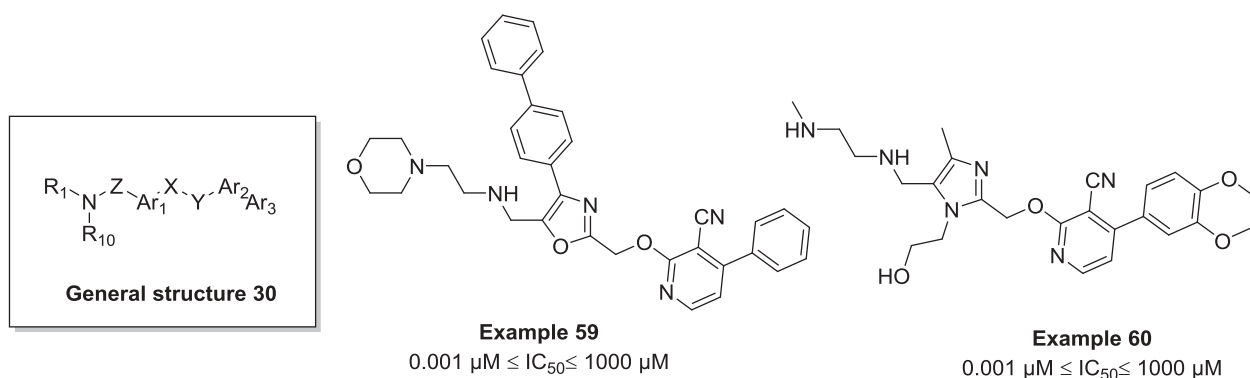
Over the last couple of years, researchers from BMS company have reported a vast number of macrocyclic compounds that show activity in inhibiting the PD-1/PD-L1 pathway.

Macrocycles with general structure **33** [38,39] disclosed by BMS company are claimed to inhibit PD-1/PD-L1 and PD-L1/CD80 PPIs (Scheme 13). The macrocycle core contains in all cases a thioether bond. The ability of these macrocycles to bind to PD-L1 was investigated using a PD-1/PD-L1 HTRF binding assay and the IC_{50} values of examples **65**, **66** and **67** were established (Scheme 13) [38]. The ability of these macrocycles to promote IFN γ secretion was assessed by the cytomegalovirus (CMV) – specific T-cell function assay. The response of for example **66** is EC_{50} of 300 nM. These results show that PD-L1 binding with these macrocycles inhibitors can enhance IFN γ release in a memory T-cell population generated from previous exposure to a persistent antigen. The ability of these macrocycles to bind to PD-L1 was tested in cell binding assays using Jurkat mouse B and a human lung adenocarcinoma cell lines. Cell binding hPD-L1/PD-1 IC_{50} for examples **66** and **67** are 10 nM and 1400 nM, respectively.

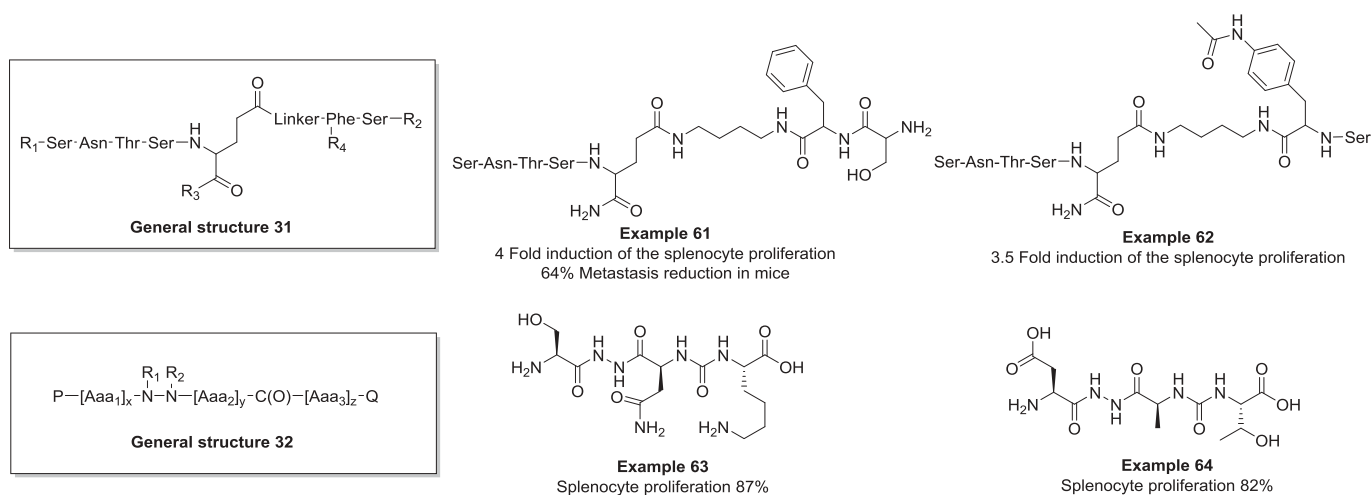
Recently, in-depth characterization of three macrocyclic peptide inhibitors disclosed by BMS researchers were published (examples **65**, **66**, and **67**). It was shown that these macrocyclic compounds directly bind to PD-L1, antagonize this protein signaling and similar to antibodies can restore



Scheme 10. The general structures and examples of the compounds patented by Incyte Corporation.



Scheme 11. The general structure and examples of the compounds patented by University of Groningen.



Scheme 12. The general structures and examples of the compounds patented by Aurigene Ltd.

the function of T-cells. Moreover, the cocrystal structures of examples **65** and **66** in the complex with PD-L1 protein were proven recently [40].

Bristol-Myers Squibb described also macrocyclic peptides with general structures **34** [41–45] and **35** [46] which were characterized by nanomolar and submicromolar activities in the HTRF binding assay. The most potent examples of these inhibitors of PD-1/PD-L1 and PD-L1/CD80 interactions with IC₅₀ values in the range of 2.5 nM–8 nM are shown in Scheme 14. All of these compounds consist of sulfide bonds and indole ring in their structure. Among all of the macrocyclic compounds reported by BMS company, example **68** has the lowest IC₅₀ value of 2.5 nM in HTRF human PD-L1/PD-1 binding assay. An interesting class of macrocyclic compounds with general structure **34** claimed as inhibitors of PD-1/PD-L1 and PD-L1/CD80 PPIs are bicyclic macrocycles. Example **72** as a representative of the bicyclic macrocycles with the lowest HTRF IC₅₀ value reported for this class of macrocycles is shown in Scheme 14 [45].

The macrocyclic peptides **36** [47], **37** [48] claimed as therapeutic agents capable of antagonizing the PD-1/PD-L1 pathway were also described by Aurigene Ltd (Scheme 15). Example **74** exhibited 82% rescue of splenocyte proliferation at 100 nM compound concentration [47]. Compounds **75** and **76** showed a 4.6

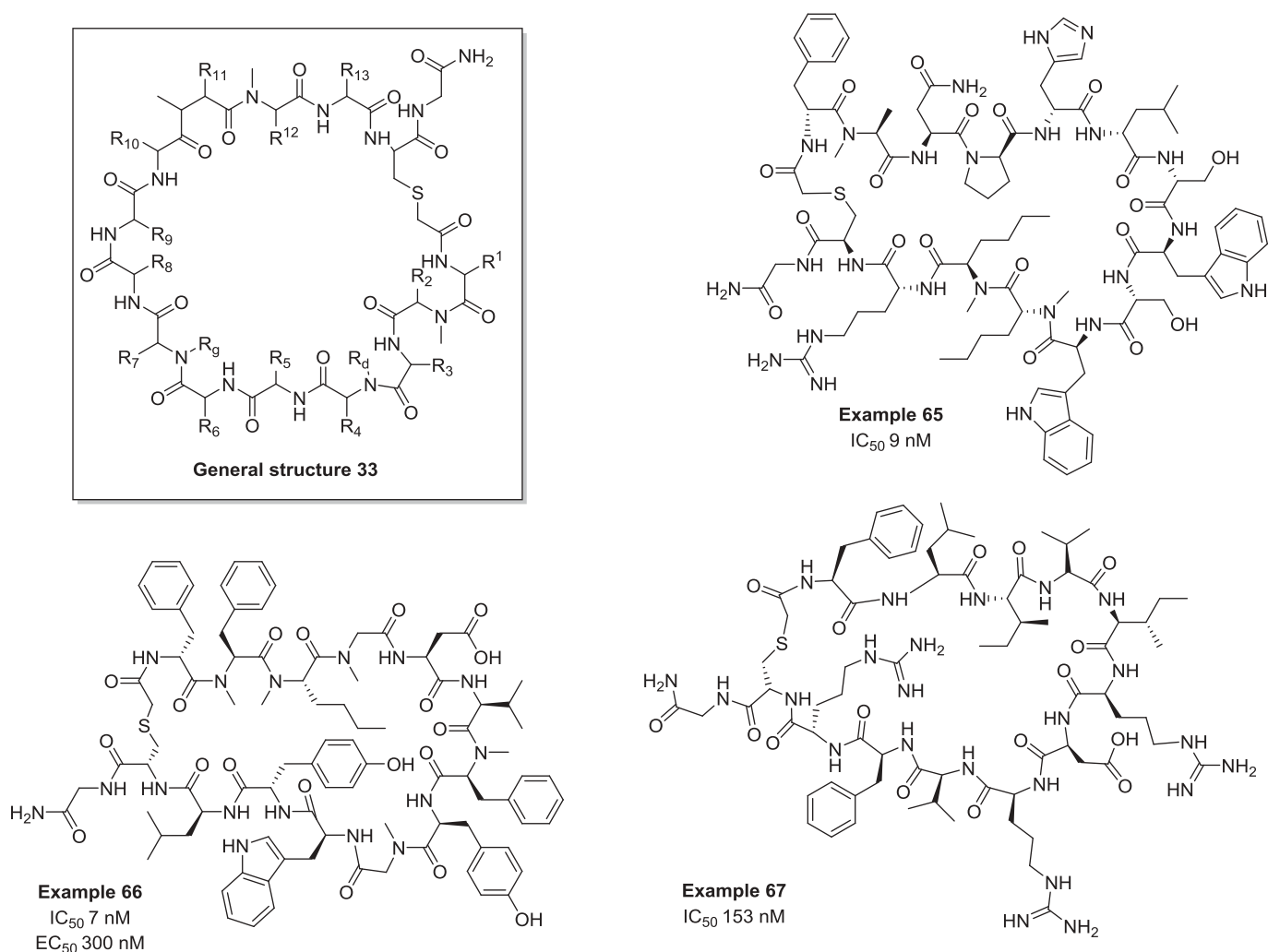
and 4.3 fold induction of splenocyte proliferation, in the CFSE assay, respectively. Peptide **76** was also tested *in vivo* on B16F10 melanoma and reduced metastasis of the melanoma in female mice by 54% when it was dosed at 5 mg/kg [48].

In 2015, the company Aurigene Ltd. patented also macrocyclic compounds inhibiting the PD-1/PD-L1 pathway. The general structure **38** and some examples with splenocyte recoveries ranging between 91% and 95%, determined by CFSE proliferation assay, are shown in Scheme 16 [49].

Researchers from the same company invented macrocyclic PD-1 inhibitors with a slightly different general structure **39** (Scheme 16). The CFSE assay for this class of compounds showed restoration of splenocyte proliferation ranging from 66% to 91% at 100 nM compound concentration [50].

3. Expert opinion

PD-1/PD-L1 directed checkpoint inhibitor therapy of malignant tumors is a breakthrough in oncology. Currently, several monoclonal antibodies are approved for therapy. Despite very promising clinical results in different tumor types, the response rate is rather low and durable responses are observed in a restricted number of patients. Although, the side effects are generally lower than in conventional cancer therapy and the mAbs are



Scheme 13. The general structure and examples of the macrocycles patented by BMS company.

well tolerated there are reports of irAEs. Some of them have led to deadly outcome. Small molecules and peptides can potentially reduce irAEs, lead to higher efficacy and to a larger number of responders. The field of patents of small molecules and peptides targeted against the PD-1/PD-L1 axis was exploding in the last couple of years. The mode-of-action of several bioactive small molecules and cyclic peptides antagonizing PD-1/PD-L1 has been elucidated and published [4–6,40]. Thus structure-based design of PD-1/PD-L1 antagonists is achievable now and has been recently comprehensively reviewed [51]. Currently, two classes of small molecules can be distinguished. The first class of molecules is based on amphipathic substituted (hetero)biphenyls with a bulky hydrophobic substituent in ortho position. The second class includes peptidomimetic compounds with often heterocyclic amide isosteres or macrocyclic variations thereof. In addition, a number of patents describe peptidic macrocyclic peptides which seem to mimic the mAbs directed against PD-L1. Currently there is one small molecule antagonist, designated as CA-170, in a Phase 1 trial in patients with advanced solid tumors and lymphomas (Clinical trial identification: NCT02812875). CA-170 is an orally available small molecule that directly targets the PD-L1, PD-L2 and VISTA immune checkpoints. This small molecule antagonist was licensed by Curis in collaboration with

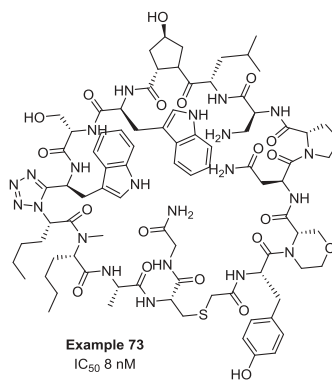
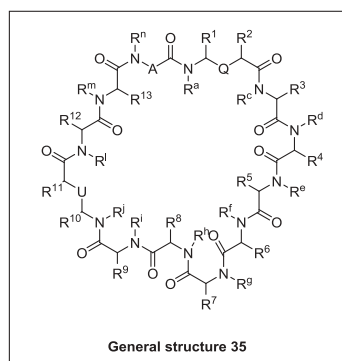
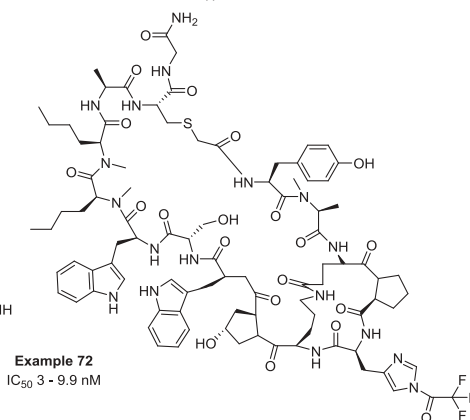
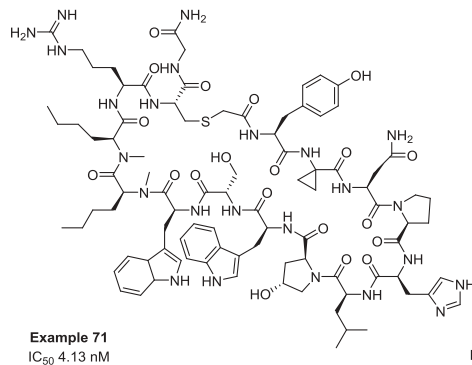
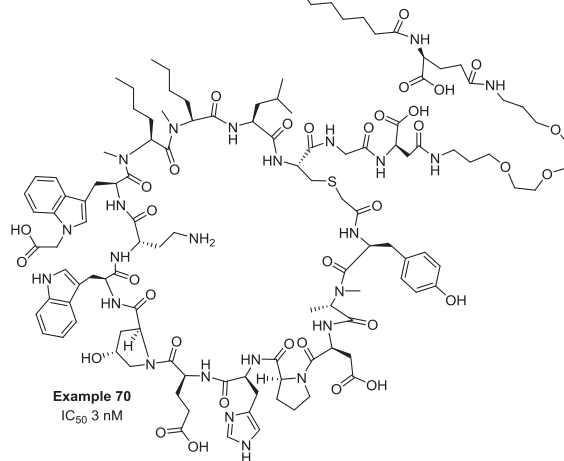
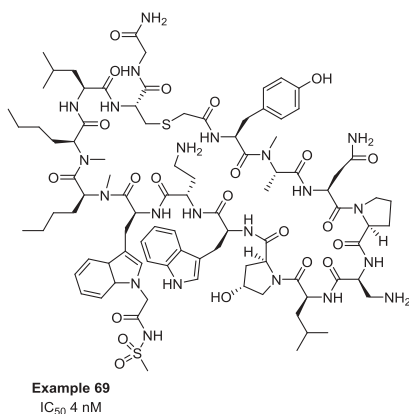
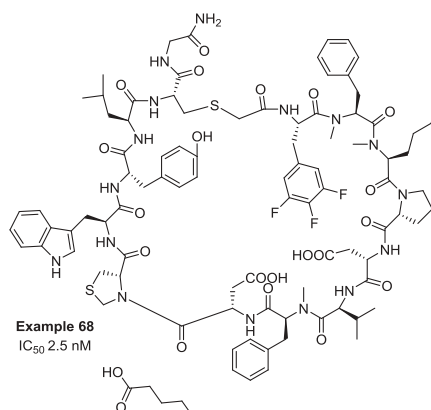
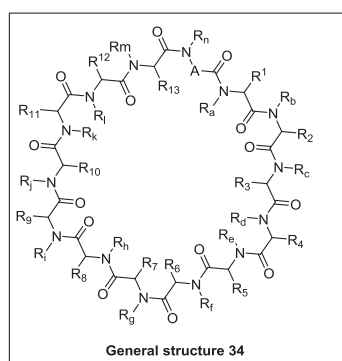
Aurigene. A new orally bioavailable small molecule PD-1/PD-L1 antagonist was recently disclosed by Maxinovel. It would be highly interesting to see future results of the first small molecular weight PD-1/PD-L1 directed therapeutics entering clinical trials.

Acknowledgement

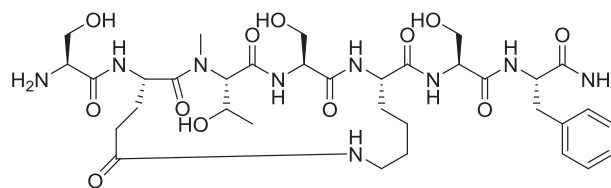
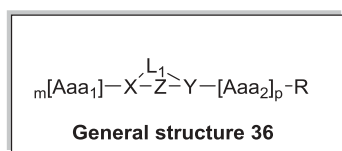
K.M.M.supported by the Foundation for Polish Science (FNP)

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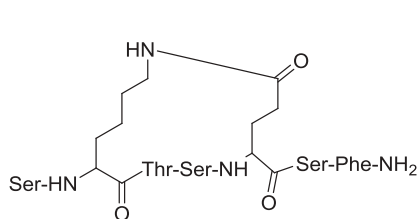
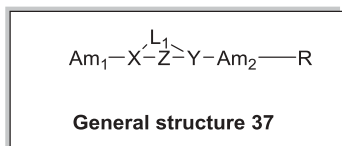
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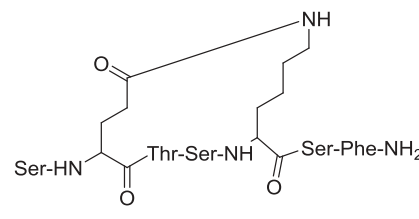
Scheme 14. The general structures and examples of the macrocycles patented by BMS company.



Example 74
Splenocyte proliferation 82%



Example 75
Splenocyte proliferation 60%
4.6 Fold induction of splenocyte proliferation



Example 76
Splenocyte proliferation 57%
4.3 Fold induction of splenocyte proliferation
54% Metastasis reduction in mice

Scheme 15. Cyclic peptides and examples patented by Aurigene Ltd.

Declaration of interest

AD is a cofounder of SMIO BV. TH is a shareholder of SMIO BV. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

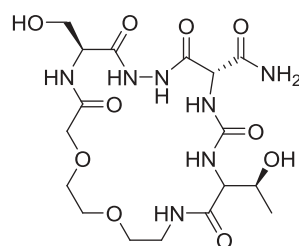
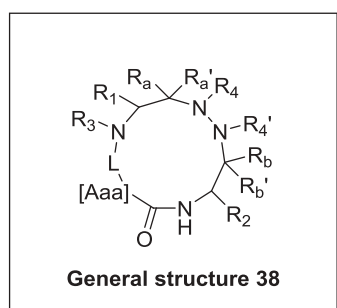
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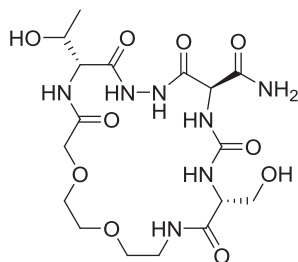
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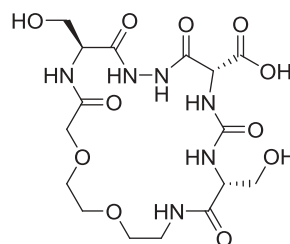
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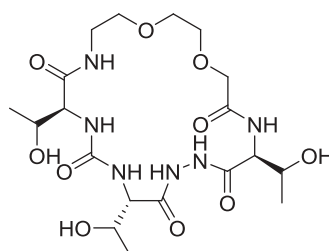
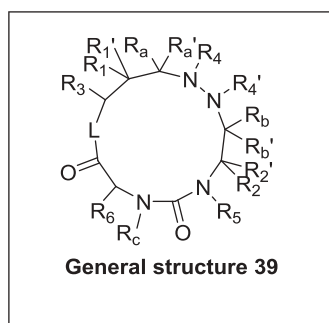
Splenocyte proliferation recovery 95%



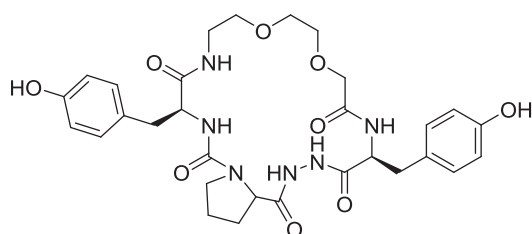
Splenocyte proliferation recovery 94%



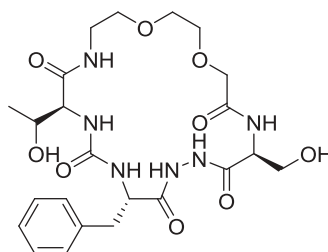
Splenocyte proliferation recovery 91%



Splenocyte proliferation recovery 91%



Splenocyte proliferation recovery 76%



Splenocyte proliferation recovery 66%

Scheme 16. Macrocycles and examples patented by Aurigene Ltd.

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