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Interaction of telmisartan and related sartans with the programmed cell death-ligand 1 (PD-L1) protein dimer: a molecular docking analysis

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Abstract

Background Telmisartan (TLT) is a prototypic angiotensin receptor blocker largely used to treat hypertension worldwide. In addition to its cardioprotective effects, TLT presents pleiotropic activities and notably displays noticeable anti-inflammatory and antitumor effects. The repression of the programmed cell death-1 (PD-1)/programmed death-ligand 1 (PD-L1) immune checkpoint may be implicated antitumor action of TLT, as it is the case with many other compounds equipped with a biphenyl moiety. We have used molecular modeling to compare the interaction of TLT and derivatives with the PD-L1 dimer protein.

Results Two molecules, TLT-dimer and TLT-acylglucuronide, were found to form more stable complexes with PD-L1 than TLT itself. In parallel, the docking analysis performed with a series of 12 sartans led to the identification of Olmesartan as a potential PD-L1 binder. The stacked biphenyl unit of Olmesartan positions the molecule along the groove delimited by the two protein monomers. The flanking tetrazole and imidazole moieties, on each side of the biphenyl unit of Olmesartan, contribute favorably to the protein interaction via specific hydrogen bonding interactions.

Conclusions The computational analysis suggests a possible binding of Olmesartan to PD-L1 dimer and thus offers novel perspectives for the design of small molecules capable of interrupting the PD-1/PD-L1 immune checkpoint. Experimental studies are warranted to validate the hypothesis.

Keywords Telmisartan, Olmesartan, Sartan, Biphenyl, Cancer, Drug-protein binding, Molecular modeling, PD-L1

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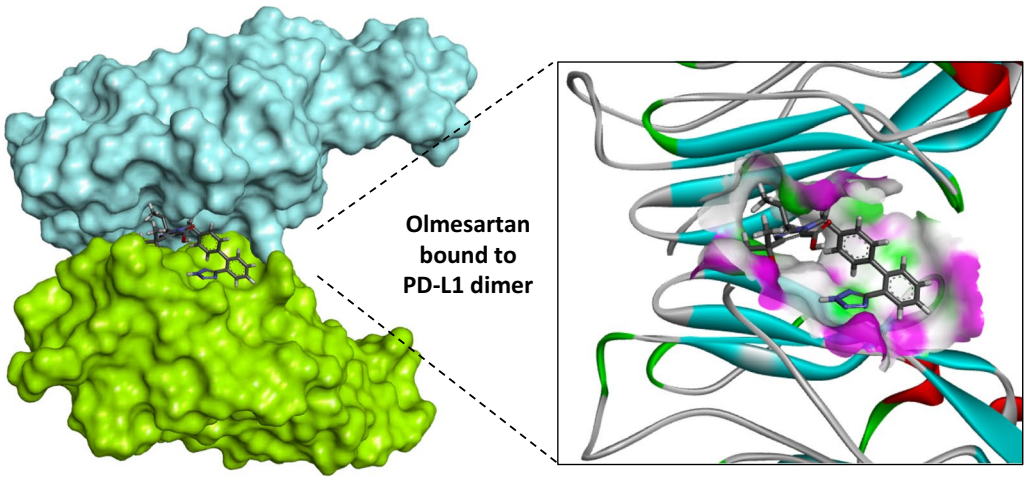
Graphical abstract



Background

Telmisartan (TLT) is one of the most frequently prescribed angiotensin receptor blockers (ARB), selectively inhibiting angiotensin II type 1 receptor (AT1) [1]. It is a classical antihypertensive drug with an excellent safety and pharmacokinetic profile, largely used to reduce arterial blood pressure in patients with hypertension, metabolic syndrome, and those at high cardiovascular risk. TLT is safe and inexpensive, used worldwide, both in Asian and Caucasian populations [2]. The global TLT market size reached US$ 3.6 billion in 2022 and continues to grow; it is expected to reach US$ 4.6 billion by 2030 [3].

This lipophilic drug is often combined with diuretics, notably hydrochlorothiazide, for the management of hypertension, affording a well-tolerated combination to treat patients with mild-to-severe hypertension [4, 5]. The water solubility (9.9 μg/mL) and bioavailability (40–60%) of TLT represent limiting factors but these properties can be improved by reducing the crystal particle size (so as to increase the surface area) and via other options, such as the development of co-amorphous formulations [6, 7].

Through its action on the renin-angiotensin system, TLT has positive effects on lipid and glucose metabolism. It is considered a drug of interest to treat non-alcoholic fatty liver disease (NAFLD) [8]. In addition to blocking angiotensin receptor, TLT has a partial peroxisome proliferator-activated receptor γ (PPARγ)-agonistic effect, which is a useful property to combat diabetes mellitus [9]. In fact, TLT has been shown to exhibit an insulin secretagogue activity, independent of AT1 receptor and PPARγ [10]. Moreover, the compound displays marked anti-inflammatory effects and is also considered a drug of interest to provide protection against Alzheimer's disease [11]. Clearly, TLT displays pleiotropic effects [12, 13].

TLT belongs to a large group of ARBs which includes a dozen of compounds (Fig. 1) with a common pharmacophore structure, but the therapeutic effectiveness of these "sartans" differs one from another [14, 15]. Irbesartan presents a higher bioavailability compared to TLT, but a shorter plasma half-life. Olmesartan displays a lower bioavailability but a higher Tmax (time to maximum plasma concentration). TLT is considered a long-acting sartan whereas Losartan equipped with a tetrazole unit exhibits a medium duration of action. EXP3174 corresponds to the active metabolite of Losartan [16]. Candesartan, Eprosartan, Azilsartan and other analogues (Fig. 1) exhibit specific safety and efficacy profiles [17].

Abundant pharmacological effects have been reported with these sartan products, not limited to cardiovascular effects [15]. In particular, TLT has revealed marked antitumor effects in different models. Recently, the drug was shown to suppress tumor growth in an orthotopic transplant mouse model of glioblastoma, blocking proliferation, migration, and invasion of cancer cells [18, 19]. TLT has demonstrated anticancer activities in different models and cell lines, including prostate, renal, breast and gastric cancers [20–25] and other cancers when the drug is used alone or in combination with targeted therapy or cytotoxic drugs [26–28]. Different mechanisms have been invoked to account for the anticancer effects of TLT, such as a down-regulation of the transcription factor Sox9 [19], the regulation of the epithelial-to-mesenchymal

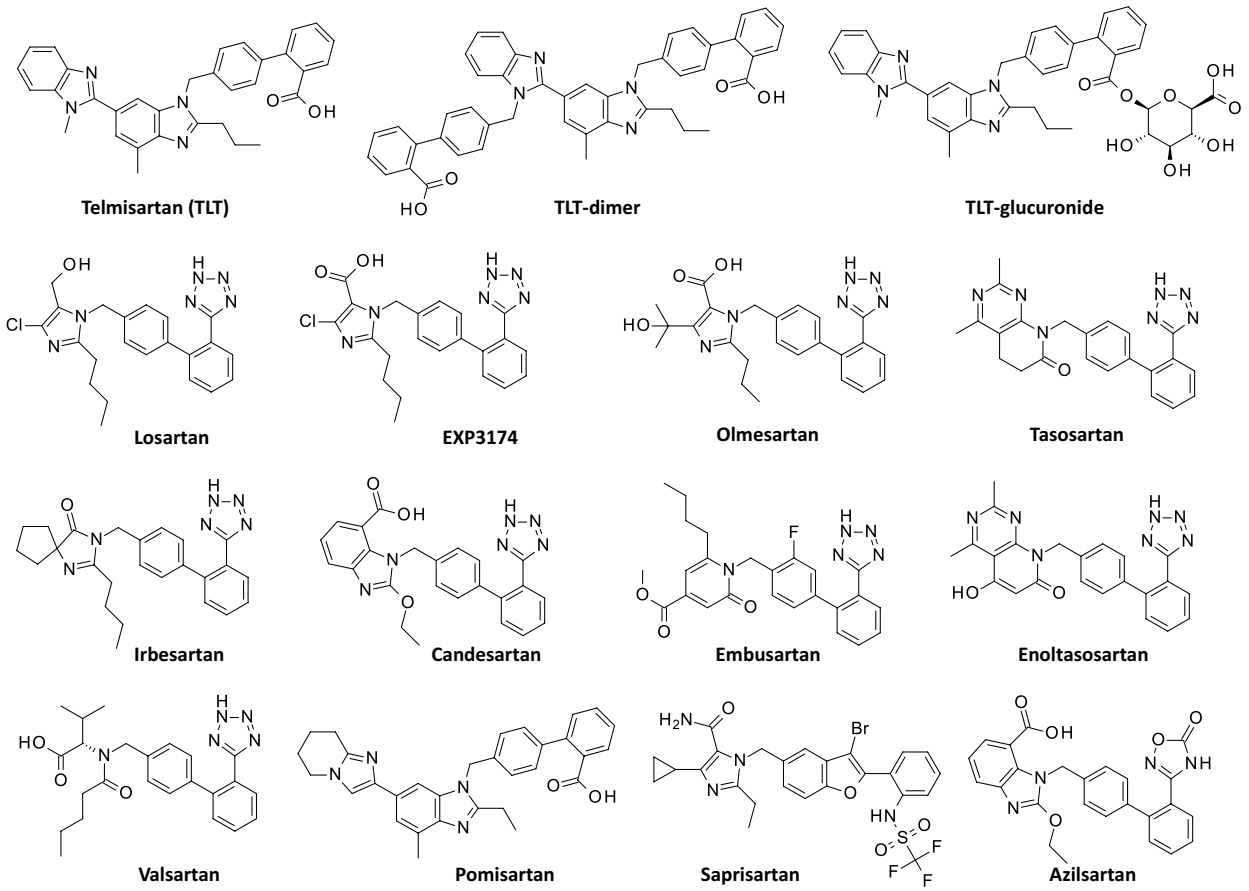


Fig. 1 Structures of the sartan compounds tested here

transition (EMT) via down-regulation of the transcription factor genes *Snail* and *Slug* [27], antagonist targeting of N-cadherin [29] and other mechanisms. Interestingly, it has been observed that TLT can modulate activity of the immune checkpoint PD-1/PD-L1 (Programmed Death (Ligand) 1). It has been demonstrated that the expression of PD-L1 promoted in patients with obesity and metabolic syndrome could be restored by TLT [30]. More recently, it has been demonstrated that TLT combined with the kinase inhibitor osimertinib reduced PD-L1 expression in non-small cell lung cancer tissues [28]. Losartan also revealed an anticancer activity in experimental models of glioblastoma and promoted the activity of an anti-PD1 immunotherapy [31].

Immune checkpoint blockade therapies that target the programmed cell death ligand-1 (PD-L1) or its receptor programmed cell death-1 (PD-1) have revolutionized the treatment of cancers, at least for a number of solid tumors such as melanoma, lung cancer, and renal cancer. Monoclonal antibodies directed against PD-1 or PD-L1 are used to restore the antitumor response of cytotoxic T cells [32]. PD-L1 plays also a role in DNA damage repair [33, 34]. Several antibodies targeting PD-L1 (atezolizumab, avelumab, durvalumab) are already used to treat cancers but new drugs and strategies are needed to reinforce efficacy notably through the development of combination therapies and drug delivery systems [35]. In this context, small molecules targeting PD-L1 are actively searched [36]. Orally available anticancer small molecules that bind to PD-L1 and induce its dimerization have been discovered [37–40]. A few small molecule inhibitors of PD-L1, such as INCB086550, are currently undergoing clinical trials in patients with advanced solid tumors [41]. New drugs targeting PD-L1 are actively searched [42, 43].

The PD-1/PD-L1 checkpoint-associated effects of TLT may be totally indirect, not due to a drug binding to the ligand or its receptor. However, we noticed that most of these sartan compounds possess a biphenyl scaffold as found in many PD-L1-binding small molecules. Biphenyl-based small molecules are intensely studied as antitumor PD-L1 inhibitors [44–46]. The biphenyl unit originates from the first PD-L1 binders discovered by Bristol-Myers

Squibb, such as compound BMS-202 which binds tightly to and induces dimerization of PD-L1 [47–49]. Over the past seven years, numerous biphenyl-containing molecules and hybrid compounds targeting PD-L1 have been designed [50–53]. A biphenyl core is also included in PD-L1 positron emission tomography tracers [54, 55]. It can be found in other drugs which can be combined with monoclonal antibodies targeting PD-1 or PD-L1. For example, the biphenyl-containing drug tazemetostat was shown to combine well with anti-PD-L1 atezolizumab in lymphoma patients [56].

These considerations prompted us to investigate the potential interaction of sartan compounds with the PD-L1 protein using a molecular docking approach, starting from the crystal structure of PD-L1 bound BMS-202 [47]. We have previously used the same approach to identify other PD-L1-binding molecules containing a biphenyl scaffold [57]. Here we examined the potential interaction of TLT, its metabolites and analogous sartan molecules with PD-L1.

Methods

In silico *molecular docking procedure*

The tridimensional structure of the dimeric form of the extracellular domain of PD-L1 was retrieved from the Protein Data Bank (www.rcsb.org) under the PDB code 5J89 [58]. The GOLD 5.3 software (Cambridge Crystallographic Data Centre, Cambridge, UK) was used to perform molecular docking analysis. Prior to the docking operations, the structure of each ligand was optimized using a classical Monte Carlo conformational searching procedure via the BOSS software [59]. Molecular graphics and analysis were performed using Discovery Studio Visualizer, Biovia 2020 (Dassault Systèmes BIOVIA Discovery Studio Visualizer 2020, San Diego, Dassault Systèmes, 2020).

The PD-L1 protein structure (5J89) includes the biphenyl small molecule BMS-202 bound to the interface of two face-to-face monomers. The BMS-202 binding site was considered as the potential binding site for the studied sartan compounds. During the process, the side chains of the following amino acids within the binding site were rendered fully flexible: Tyr56, Met115, Asp122, Tyr123, and Lys124 (monomer A), and Tyr56, Gln66, Met115, Asp122, and Tyr123 (monomer B). A docking grid centered in the volume defined by the central amino acid has been defined based on shape complementarity and geometry considerations. In general, up to 100 poses considered as energetically reasonable are selected during the search for the correct binding mode of the ligand. The decision to select a trial pose is based on ranked poses, using the fitness scoring function (PLP score) [60]. The same procedure was used to establish molecular models for all sartan compounds.

The Boss program and the Molecular Mechanics/Generalized Born Surface Area (MM/GBSA) procedure were used to evaluate free energies of hydration (ΔG, also designated $\Delta\mu_h$ [61] or HFE [62]), in relation with aqueous solubility [63]. The Boss program was also used to evaluate the stability of the receptor-ligand complex through the empirical potential energy of interaction (ΔE) [64, 65]. The empirical potential energy of interaction ΔE calculated for each drug-protein complex was defined using the equation ΔE(interaction) = E(complex)—(E(protein) + E(ligand)), using the Spectroscopic Empirical Potential Energy function SPASIBA [64, 65]. SPASIBA has been specifically developed to provide refined empirical molecular mechanics force field parameters, as described in other studies [64, 66]. Using this specific force field for, Monte Carlo (MC) simulations achieve the same level of convergence as Molecular Dynamics (MD), with less computer time [67].

Results

Docking interactions of TLT and its metabolites with PD-L1

We started our analysis using the structure of the reference compound BMS-202 bound to recombinant PD-L1 (PDB: 5J89) [58]. The drug binds to the interface of two monomers, stabilizing a dimeric form of the protein and defining an extended cavity that can be exploited for drug binding [47]. TLT was docked into the cavity and its capacity to form stable complexes with PD-L1 was evaluated though the calculation of the empirical energy of interaction (ΔE), as reported in Table 1. The analysis indicated that TLT can form complexes with PD-L1 but the calculated ΔE value was superior (less negative) compared to that measured with BMS-202, suggesting a weaker affinity. The two compounds are comparable in

Table 1 Calculated potential energy of interaction (ΔE) and free energy of hydration (ΔG) for the interaction of TLT and derivatives with PD-L1

Compounds	CID[a]	ΔE (kcal/mol)	ΔG (kcal/mol)
Telmisartan	65999	−70.64	−23.50
Telmisartan amide	11978018	−69.45	−17.65
Telmisartan methyl ester	11497808	−70.50	−28.95
Telmisartan glucuronide	16681706	−100.35	−38.90
Telmisartan dimer	59027207	−85.42	−31.95
Telmisartan N-desmethyl	15870912	−82.42	−18.00
Telmisartan terbutyl ester	10076748	−78.00	−15.83
BMS-202	117951478	−82.03	−22.43

[a] Compound Identity number, as defined in PubChem (https://pubchem.ncbi.nlm.nih.gov)

term of hydration free energy (ΔG). TLT is an acid which is a little more favorably hydrated than the reference BMS-202 (Table 1). In general, the free energies of hydration for acidic residues are more favorable than for basic residues [61].

Different derivatives of TLT were then tested, such as the amide and methyl ester forms but no improvement was observed for these two compounds. The two derivatives TLT-terbutyl ester and TLT- N-desmethyl gave slightly better results with a ΔE around −80 kcal/mol, comparable to the value measured with BMS-202. A further improvement of the PD-L1 interaction was observed with two other molecules: a dimeric compound and a glucuronide derivative of TLT (Fig. 1). The TLT dimeric compound corresponds to a minor impurity detected in TLT tablets [68]. This compound has no biological relevance, but the observation suggests that an extension of the drug structure could reinforce drug binding to PD-L1. With this dimer, the drug-protein interaction is stabilized via a variety of van der Walls contacts and π-stacking interactions. But a large portion of the elongated molecule protrudes outside the binding cavity, as shown in Fig. 2. The molecule is too long, not perfectly adapted to the binding surface but nevertheless it offers a linear extended part that inserts well into the protein interface.

The case of TLT-acylglucuronide derivative (Fig. 1) is more interesting because it corresponds to a major phase II liver metabolite of TLT [69]. It is an inactive elimination product, formed in the liver and excreted through the hepatobiliary system but an intestinal deconjugation of the TLT glucuronide metabolite restoring the parent compound via the enterohepatic recirculation can occur [70]. We found that the compound TLT-glucuronide has a capacity to form very stable complexes with PD-L1, with an empirical potential energy of interaction ΔE of −100 kcal/mol calculated for this glycosyl conjugate bound to the interface of the PD-L1 dimer. In this case, the acyl-β-D-glucuronide moiety projects toward the concave (inward) face of the dimeric protein structure and contributes significantly to the protein interaction via two hydrogen bonds with residues Tyr123 and

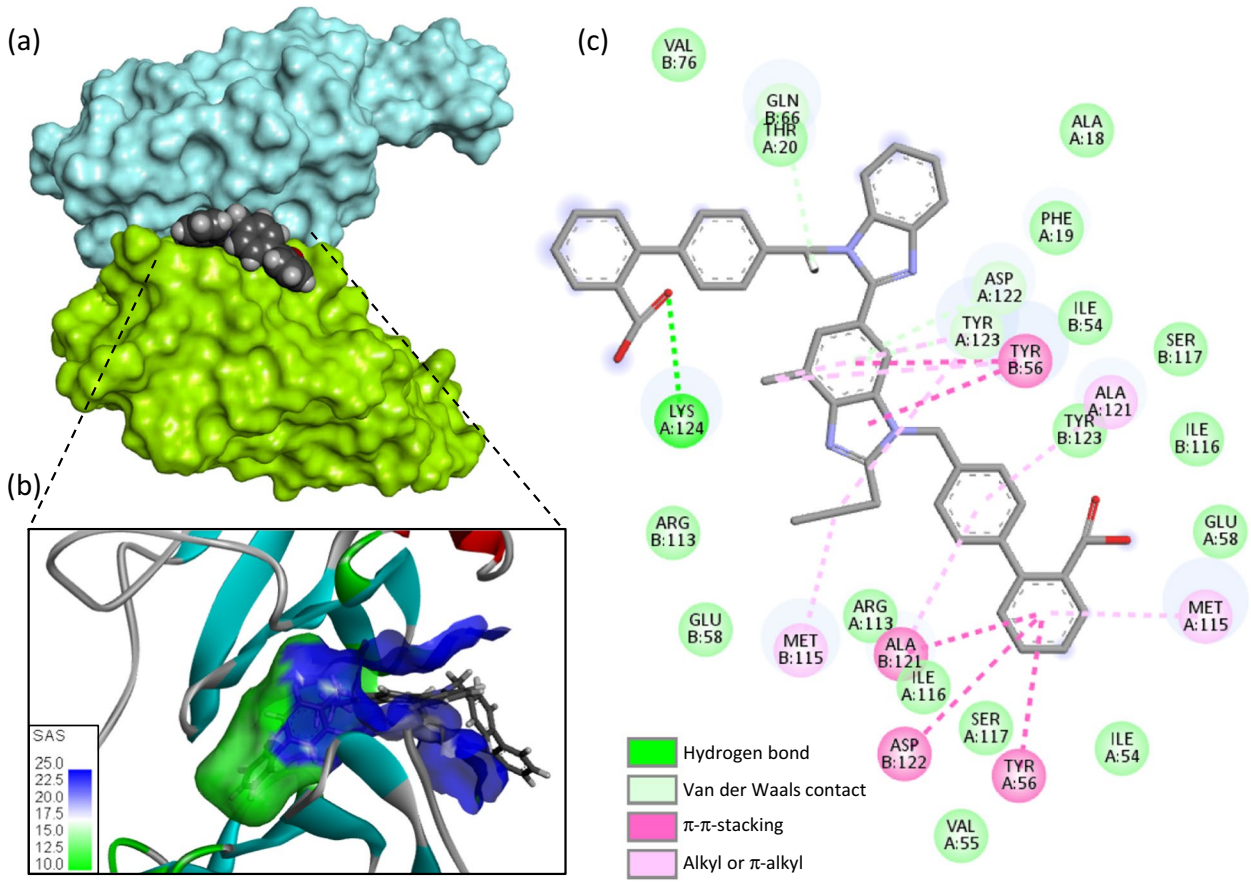


Fig. 2 Molecular model of the TLT dimer bound to the dimeric form of PD-L1. **a** The TLT-dimer compound bound at the interface of the two PD-L1 units (in cyan and green). **b** A close-up view of the PD-L1-bound ligand with the solvent-accessible surface (SAS) surrounding the drug binding zone (color code indicated). **c** Binding map contacts for TLT-dimer bound to PD-L1 (color code indicated)

Lys124, whereas the two benzimidazole units are inserted into the narrow protein groove in the hydrophobic part of the channel (Fig. 3). This 1-*O*-acylglucuronide of TLT is a stable circulating product, with a low binding to human serum albumin, but it is rapidly cleared (clearance of 180 ml/min/kg compared with 15.6 ml/min/kg for TLT), resulting in a low systemic exposure [71]. Therefore, this TLT-glucuronide may not contribute to blocking PD-L1 but here again, the information is important in terms of drug design. The substitution of the acid function of TLT on the biphenyl portion apparently represents a suitable option to obtain novel PD-L1 binders.

Docking interactions of other sartans with PD-L1

The modeling analysis was extended to a series of 12 sartans, including close analogues of TLT such as the benzimidazole Pomisartan and different analogues bearing a tetrazole unit attached to the biphenyl core, such as Candesartan and Valsartan. For each compound, molecular models were constructed and their potential interaction with PD-L1 was evaluated through the calculations of the empirical energy of interaction (ΔE) and energy of hydration (ΔG or hydration free energy HFE). The values are collated in Table 2. Binding maps are shown in Additional file 1: Fig. S1. No profound improvement was observed compared to TLT. The weaker binder was the imidazolinone derivative Irbesartan and the best compound was the imidazole derivative Olmesartan, but all compounds gave ΔE values higher (less negative) than that calculated with the reference BMS-202. Losartan active metabolite EXP3174 emerged as a poor binder, as it is the case with Enoltasosartan.

The investigation was extended to search for other compounds susceptible to bind to PD-L1, but no compound better than Olmesartan was identified. For examples, we tested derivatives of the AT1 antagonist Eprosartan (lacking a biphenyl unit) which has been shown recently to exhibit antioxidative and anti-inflammatory properties [72] but we found no improved binding when testing Eprosartan (CID: 5281037; ΔE = −66.85 kcal/mol), methyl-Eprosartan (CID: 45358786; ΔE = −75.40 kcal/mol), and ethyl-Eprosartan (CID: 10049536; ΔE = −79.80 kcal/mol).

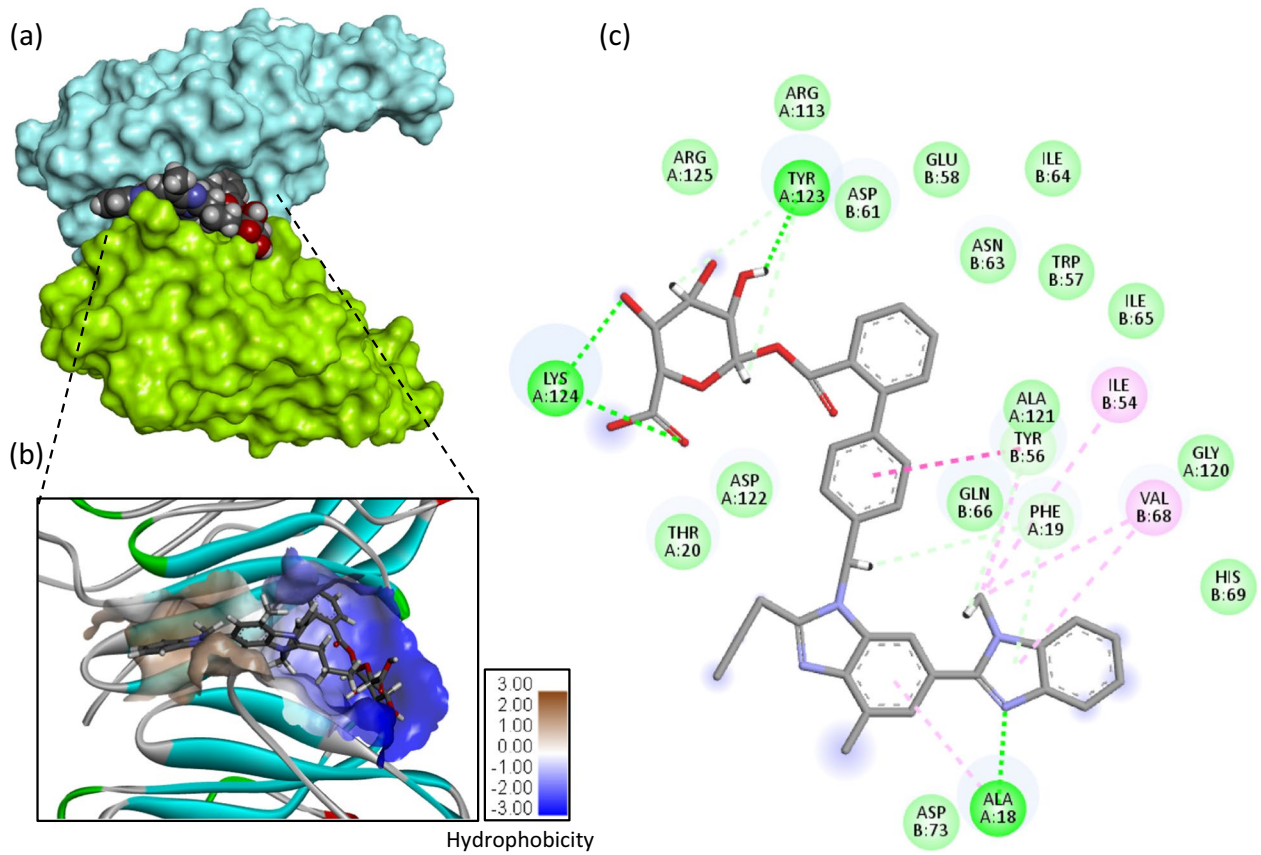


Fig. 3 Molecular model of TLT-glucuronide bound to the dimeric form of PD-L1. **a** The TLT-acylglucuronide compound bound at the interface of the two PD-L1 units (in cyan and green). **b** A close-up view of the PD-L1-bound ligand with the hydrophobicity surrounding the drug binding zone (color code indicated). **c** Binding map contacts for TLT-glucuronide bound to PD-L1 (color code as in Fig. 2)

Table 2 Calculated potential energy of interaction (ΔE) and free energy of hydration (ΔG) for the interaction of selected sartans with PD-L1

Compounds	CID[a]	ΔE (kcal/mol)	ΔG (kcal/mol)
Azilsartan	135415867	−76.30	−20.70
Candesartan	2541	−62.45	−10.10
Embusartan	133000	−72.20	−17.4
Enoltasosartan	546936559	−65.60	−14.90
EXP3174	108185	−66.90	−19.42
Irbesartan	3749	−64.55	−17.05
Losartan	3961	−78.53	−14.52
Olmesartan	158781	−80.60	−16.65
Pomisartan	3050407	−78.60	−19.40
Saprisartan	60921	−77.50	−21.80
Tasosartan	60919	−78.60	−19.20
Telmisartan	65999	−70.64	−23.50
Valsartan	60846	−69.35	−15.05

[a] Compound Identity number, as defined in PubChem (https://pubchem.ncbi.nlm.nih.gov)

Among these sartan compounds, the best molecule for interacting with PD-L1 is Olmesartan with its biphenyl unit stacking over residue Tyr56 and its tetrazole unit H-bonding to Asp122. It is interesting to note that the other side of the molecule is also well engaged in the protein interaction, with the 2-OH group on the propyl-imidazole moiety implicated in two vicinal H-bonds with Ala18 and Phe19. Olmesartan emerges as a potential PD-L1 binder. The best binding pose selected with Olmesartan is not ideal because there is only a van der Walls contact (a weak attraction) between the biphenyl unit and residue Tyr123, in addition to the essential stacking interaction with residue Tyr56. There exists an alternative pose, less favorable in terms of computed energies (ΔE = −70.00 kcal/mol and ΔG = −18.60 kcal/mol), but characterized by a stacking interaction between the tetrazole unit of Olmesartan and Tyr123 (Additional file 1: Fig. S2).

Discussion

The established anticancer activity of TLT and the presence of a biphenyl unit in the drug structure prompted us to investigate the potential binding of TLT and derivatives to the immune checkpoint ligand PD-L1. The modeling analysis suggests that drugs like TLT and Olmesartan could interact with PD-L1, thus possibly playing a role in their antitumor action. The hypothesis remains weak at present but there are interesting elements to consider. A moderate reduced cancer-specific mortality has been noted among users of angiotensin receptor blockers (ARB) [73]. ARB seem to exhibit a significant overall protective against lung, bladder and colorectal cancers [74]. The anticancer activity of TLT has been well characterized in different experimental tumor models and its analogue Olmesartan has been shown to exert an antitumor action, notably in pancreatic cancer, and cervical cancer through an upregulation of microRNA miR-205 and inhibition of VEGF-A expression [75–78]. It displays also a significant anti-inflammatory action [79]. This biphenyl drug was shown to potentiate the anti-angiogenic effect of sorafenib [80]. Irbesartan has been shown also to repress the proliferation of cancer cells [81] and to overcome chemoresistance [82]. Therefore, there are good reasons to investigate further the antitumor potential and immune effects of these sartan drugs. Very interestingly, Irbesartan has been found to activate an immune response and in particular the infiltration of $CD8^+$ T cells in relapsed tumors [83]. ARB can facilitate tumor infiltration by effector T cells [84]. It is therefore conceivable that ARB can modulate the PD-1/PD-L1 checkpoint (Fig. 4).

Here we observed that Olmesartan is better adapted than TLT for binding to PD-L1. Olmesartan is perhaps not the best sartan to study because it can induce digestive tract injuries (parenthetically a side effects commonly observed also with immune checkpoint inhibitors). However, the observations further attest of the benefit of considering diverse biphenyl compounds has potential PD-L1 binders. Recent studies have underlined the possibility to affect the functionality of the PD-1/PD-L1 checkpoint with diverse biphenyl or biaryl compounds and the great benefits of computational approaches to identify novel PD-L1 binders [85–89]. Our study brings another brick in the wall, suggesting to consider further some of the sartan compounds as potential modular of the PD-L1 checkpoint. The mode of binding of these sartans at the interface of the PD-L1 dimer is similar to that observed with the reference ligand BMS-202 (Fig. 5).

In conclusion, our molecular docking analysis has identified the drug Olmesartan as a potential binder to the immune checkpoint protein PD-L1. The drug has the capacity to interact with the PD-L1 dimer, via its biphenyl core. The study provides guidance for the design of novel PD-L1 binders, based on the structure of diverse sartan compounds.

Abbreviations

ARB	Angiotensin receptor blockers
AT1	Angiotensin II type 1 receptor
PPARγ	Peroxisome proliferator-activated receptor γ
PD-1	Programmed cell death-1
PD-L1	Programmed death-ligand 1
TLT	Telmisartan

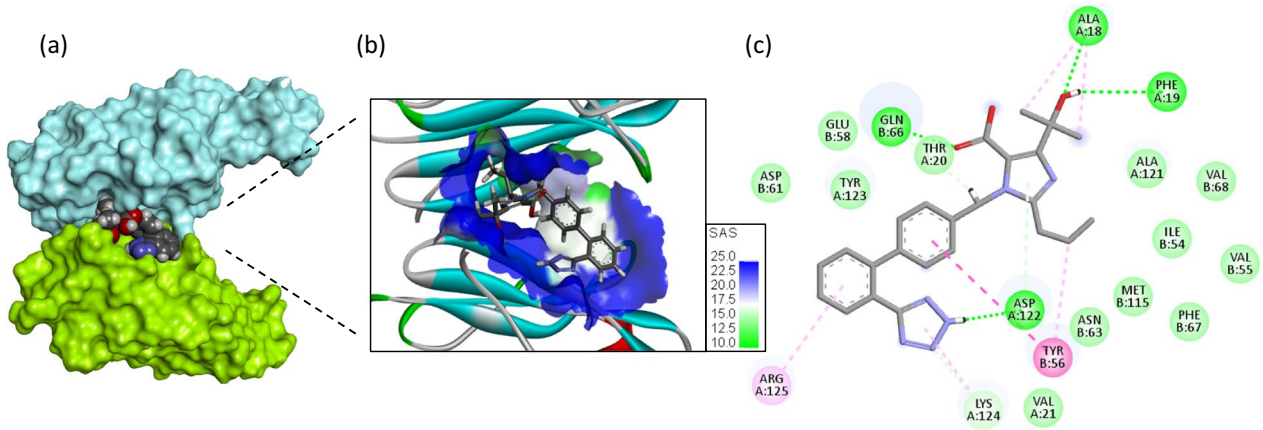


Fig. 4 Molecular model of the Olmesartan bound to the dimeric form of PD-L1. **a** Olmesartan bound at the interface of the two PD-L1 units (in cyan and green). **b** A close-up view of the PD-L1-bound ligand with the solvent-accessible surface (SAS) surrounding the drug binding zone (color code indicated). **c** Binding map contacts for Olmesartan bound to PD-L1 dimer (color code as in Fig. 2)

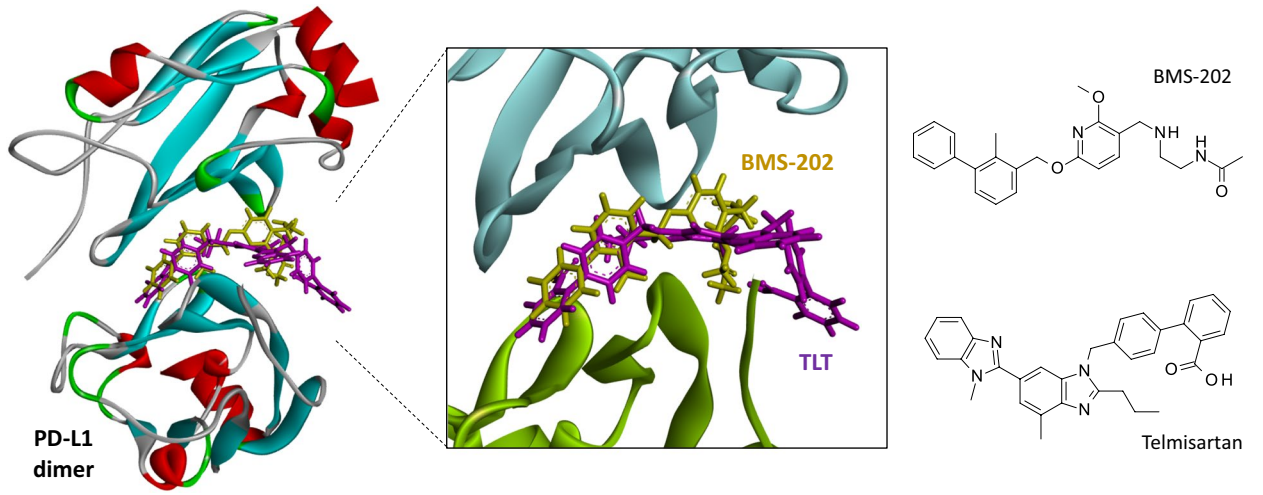


Fig. 5 Molecular model of the PD-L1 dimer stabilized with TLT (magenta) or the reference ligand BMS-202 (yellow), with the two molecules superimposed at the junction between the two PD-L1 monomers. The chemical structures of the two molecules are shown

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43094-023-00574-1.

Additional file 1: Fig. S1. Binding map contacts for the different drugs and compounds bound to PD-L1 dimer. **Fig. S2**. Binding map contacts for the two best binding poses determined with Olmesartan. (left) The best binding pose, as shown in Fig. 4 and (right) the second-best binding pose.

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Author contributions
GV: Investigation; Visualization; Software. CB: Conceptualization; Visualization; Writing—original draft; Writing—review and editing.

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Availability of data and materials
Not applicable (no data).

Declarations

Ethics approval and consent to participate
Not concerned.

Consent for publication
The two authors have approved the manuscript.

Competing interests
The authors declare no conflict of interest associated with this publication.

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