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REVIEW

An updated patent review of MALT1 inhibitors (2021–present)

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ABSTRACT

Introduction: MALT1 paracaspase acts as a molecular scaffold and a proteolytic enzyme in immune cells. MALT1 has emerged as a promising drug target for cancer therapy, and especially for targeting MALT1 in aggressive lymphomas. Drug discovery programs have yielded potent and selective MALT1 protease inhibitors. First-in-class MALT1 inhibitors have been moved to early clinical trials to evaluate safety and efficacy.

Areas covered: This review will provide an update regarding the mode of action, the chemical space and therapeutic use of MALT1 inhibitors based on recent patents and the scientific literature (05/2021–12/2024).

Expert opinion: Allosteric inhibition is the preferred mode of action to inhibit the MALT1 protease. Chemical advances largely focus on improving binding and inhibition in the allosteric site of MALT1. New composition of matter has been generated, but a clinical proof for the safety and efficacy of allosteric MALT1 inhibitors is still pending. We still lack potent and selective competitive or covalent MALT1 inhibitors, indicating the challenges with targeting the active site. Further, MALT1 protein degraders and MALT1 scaffolding inhibitors have been developed, which may have distinct inhibitory profiles compared to allosteric MALT1 protease inhibitors, but more potent and selective compounds are needed to judge the feasibility and usefulness of these approaches.

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1. Introduction

The human*Mucosa Associated Lymphoid Tissue Lymphoma Translocation Gene 1* (*MALT1*) codes for the MALT1 paracaspase (also termed PCASP1), a protein involved in controlling innate and adaptive immune responses. Most knowledge on the function of MALT1 stems from work in T and B lymphocytes, where MALT1 is a subunit of the CARD11/CARMA1-BCL10-MALT1 (CBM) complex that is assembled after T or B cell antigen receptor (TCR/BCR) ligation [1,2]. The CBM complex is critical for initiating the canonical NF-κB signaling pathway in activated lymphocytes. In addition, MALT1 protease function is activated at the CBM complex, which modulates immune activation by the cleavage of distinct substrates. Alternative CBM complexes utilizing varying CARD/CARMA proteins (e.g. CARD9, CARD10/CARMA3 and CARD14/CARMA2) exist primarily in cells outside the lymphocyte lineage, where they control responses to innate pattern recognition receptors, G-protein-coupled receptors or growth factor receptors [3]. Recent reviews, including our preceding evaluation of MALT1 patents (2013–2021), provide a comprehensive overview on the physiological and pathological roles of MALT1 [4–7]. For this patent update, we will only briefly summarize the background of MALT1 as both a molecular scaffold for cell signaling and a proteolytic enzyme that modulates cellular responses by cleaving a distinct set of substrates.

MALT1 is a multi-domain protein, which directly interacts with the CBM subunit BCL10 via the MALT1 N-terminal death domain (DD) (Figure 1(a)). In addition, MALT1 contains three immunoglobulin-like domains (Ig1–3), two TRAF6 binding motifs (T6BMs) and a catalytically active paracaspase (PCASP) domain with high homology to caspases. Despite the existence of the PCASP domain, MALT1 was initially described to execute non-catalytic scaffolding functions by binding to TRAF6, thereby bridging TCR/BCR-induced CBM complex formation to the downstream effector pathways NF-κB, JNK and p38 [8–10]. In 2008, about 10 years after the original discovery of MALT1, the laboratories of Margot Thome and Rudi Beyaert were able to assign a proteolytic function to MALT1 [11,12]. Currently, approximately 20–30 MALT1 substrates have been identified, whose cleavage impacts diverse cellular processes such as CBM auto-regulation (MALT1 auto-cleavage, BCL10), cell signaling and ubiquitination (A20, CYLD, and HOIL-1), cell adhesion (Tensin-3), and transcriptional (RelB) and post-transcriptional (Regnase-1, Roquin-1/2) gene regulation [13,14].

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Article highlights

- MALT1 has attracted major interest for the treatment of lymphoid malignancies and other cancer.
- This review summarizes MALT1 inhibitors patented the period (2021–2024).
- Recent focus has been on the development of MALT1 allosteric inhibitors, scaffolding inhibitors, and protein degraders.
- Combination therapy with inhibitors of BTK or BCL-2 as a promising option for treatment of aggressive BCR-addicted lymphomas.
- Several compounds are currently undergoing early clinical validation.

From what we know today, activation of MALT1 scaffolding and protease functions are intimately connected, taking place at the CBM complex in the context of BCL10 filaments [15,16]. However, genetic studies have provided evidence that MALT1 scaffolding function is retained when MALT1 protease is defective and, vice versa, MALT1 proteolytic activity occurs even in a constitutive manner in the absence of TRAF6 interaction [17–20]. Thus, MALT1 serves as a bifurcation point after antigen receptor (AgR) engagement to coordinate transcriptional responses by MALT1 scaffolding, with processes controlling post-transcriptional gene expression, modulation of cell signaling, and cell adhesion by MALT1 protease (Figure 1(b)) [14]. Nevertheless, we still do not fully understand how the intricate balance between MALT1 scaffolding and protease activities controls immune activation while at the same time maintaining immune homeostasis. Both MALT1 protease-defective (paracaspase mutant) and MALT1 scaffolding-defective (TRAF6 binding mutant) mice develop severe autoimmune and inflammatory diseases, emphasizing the relevance of fully understanding the dual functions of MALT1 for therapeutic targeting [17–20].

For several reasons, MALT1 has attracted attention as a potential drug target. MALT1 protease activity drives survival and proliferation of non-Hodgkin's-lymphoma (NHL), including subsets of diffuse large B cell lymphomas (DLBCL) and mantle cell lymphoma (MCL), whose growth relies on chronic BCR signaling [4,7,21]. MALT1 protease inhibition has been shown to impair canonical NF-κB signaling, thereby inducing growth inhibition and apoptosis in MALT1-dependent activated B cell-like (ABC) DLBCL, while MALT1-independent germinal center B cell-like (GCB) DLBCL were not affected [22–25]. Further, structural studies uncovered that MALT1 paracaspase confers a unique enzymatic activity that can be selectively inhibited [26–29]. MALT1 PCASP and closely related caspase domains share the same overall fold, but their active centers are distinct. The active site in the PCASP domain is formed by loops 1, 3 and 4 (Figure 2(a,b)). The catalytic dyad formed by Cys464 and His415 shows a clear preference for arginine, which is favored by an interaction with negatively charged Asp365 and Glu500 at the bottom of the S1-binding pocket (Figure 2(c)). Thus, in contrast to caspases that contain basic residues at this position and cleave

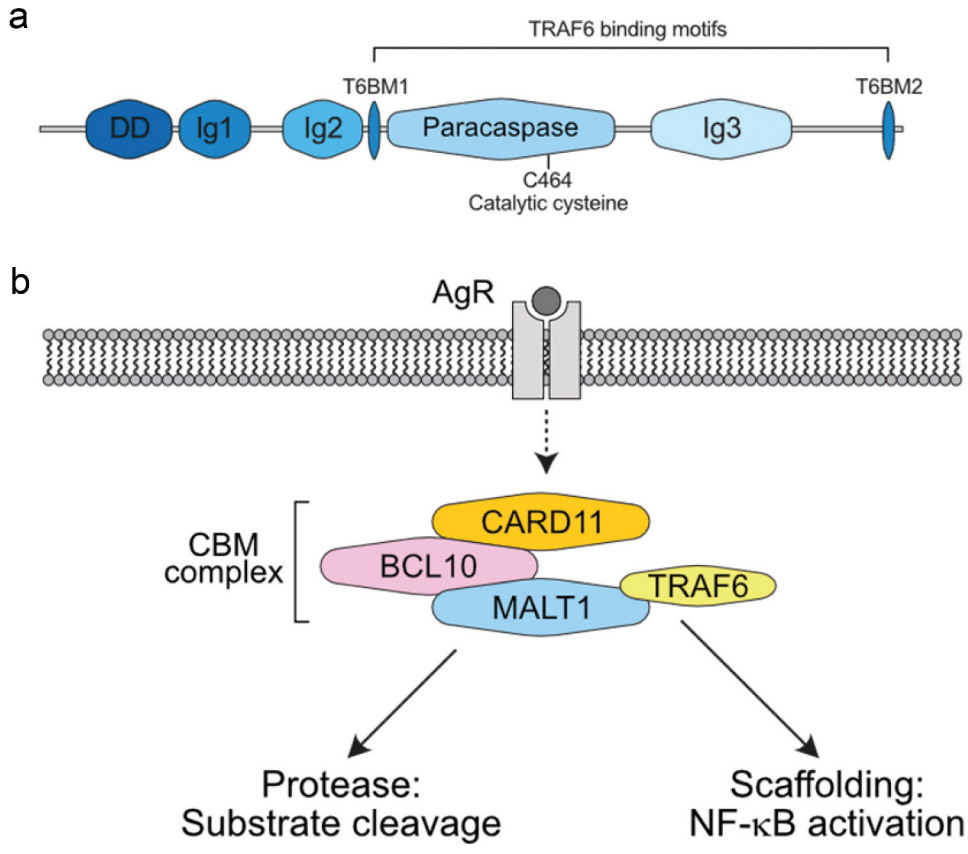

Figure 1. MALT1 background. (a) MALT1 paracaspase domain structure. N-terminal death domain (DD), immunoglobulin-like 1–3 (Ig1–3) domains, paracaspase domain (PCASP) with catalytic cysteine 464, TRAF6 binding domain 1 and 2 (T6BM1, 2). (b) MALT1 scaffolding and protease function. Downstream of antigen receptor (AgR), the CARD11, BCL10-MALT1 (CBM) complex is assembled. MALT1 binding to TRAF6 via T6BMs activates NF-κB signaling in a non-enzymatic manner. In parallel, MALT1 protease is activated and cleaves substrates.

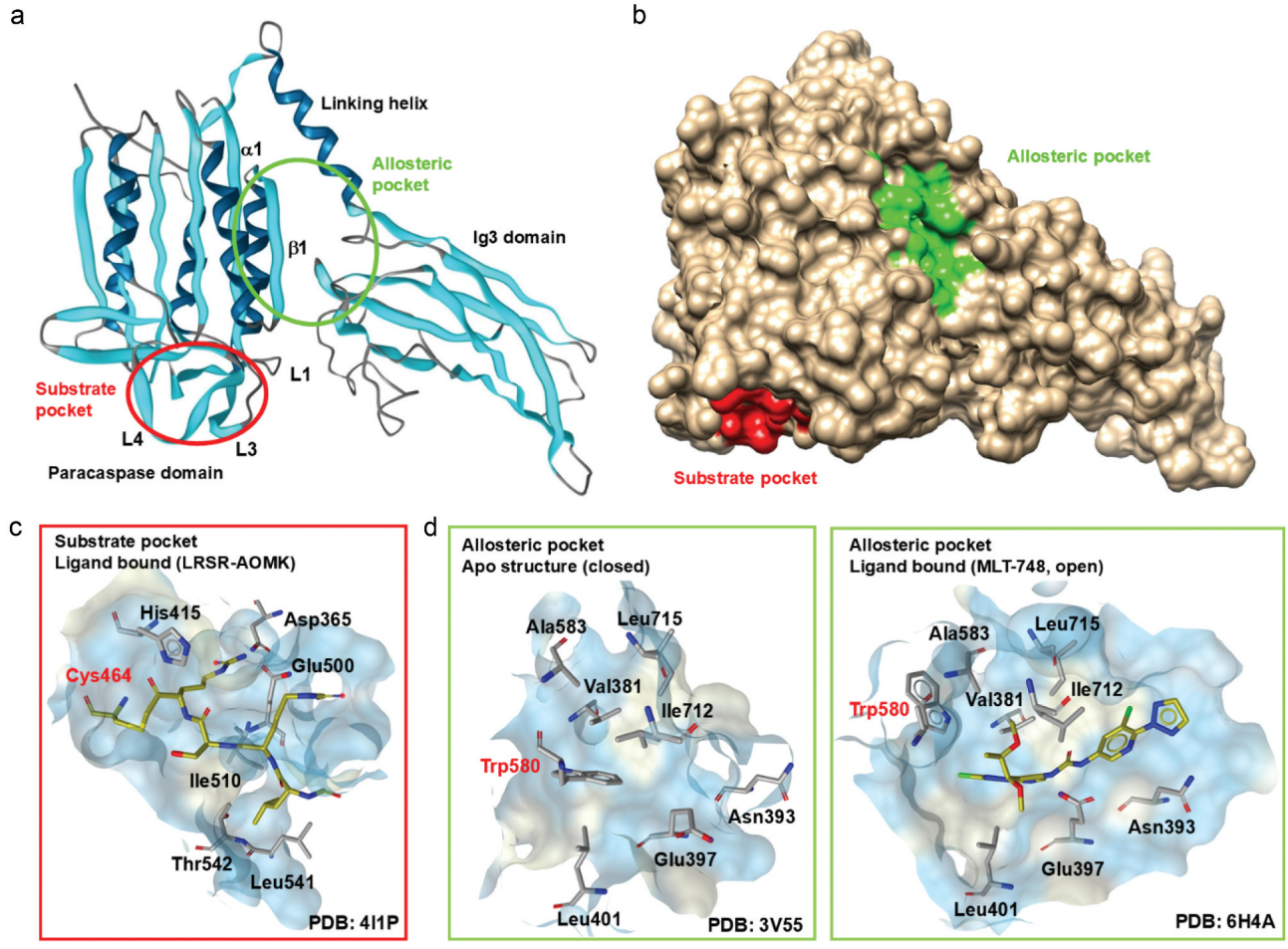

Figure 2. MALT1 structure and activation. (a) Crystal structure of MALT1 PCASP-Ig3 domains. (b) Surface of the protein with substrate binding pocket (red) and allosteric binding pocket (green). (c) Cys464 and His415 from the catalytic dyad and residues in the substrate binding pocket important for the interaction with the substrate peptide (PDB: 4I1P, tetrapeptidic inhibitor LRSR-AOMK bound covalently to Cys464, gold, [30]). (d) Left: allosteric binding pocket in the apo-structure (PDB: 3V55, [28]) and Trp580 inside the pocket. Right: allosteric pocket with bound MALT1 inhibitor MLT-748 (1, gold) and residues important for the interactions between the ligand and the protein (PDB: 6H4A, [26]). Trp580 is flipped out of the binding pocket.

C-terminal aspartates, MALT1 cleaves after arginine and efficient cleavage relies on the presence of the Ig3 domain C-terminal to the PCASP domain [31]. Importantly, an allosteric binding pocket in MALT1 is positioned at the interface between the PCASP and Ig3 domains (Figure 2(b)), which is a unique feature distinguishing MALT1 from other proteases including caspases. The allosteric pocket is formed by the α1 helix and β2 sheet of the PCASP domain and linking helix and comprises several hydrophobic residues including Val381, Leu401, Ala583, Ile712, Leu715 (Figure 2(d)). Consequently, this pocket shows a strong preference for ligands with high proportions of lipophilic moieties. In its ligand-free form, the hydrophobic part of this binding pocket is occupied by Trp580, which stabilizes MALT1 in the inactive state and is moved out of the pocket upon protease activation [26,28]. Drug discovery campaigns have demonstrated that binding of compounds to this allosteric site reveals an intriguing mode of MALT1 inhibition without causing non-specific effects on caspases [22,27]. Upon binding of inhibitory ligands, like thioridazine or MLT-748, in the allosteric pocket, Trp580 is flipping out of the pocket (Figure 2(d)) [26,27], and binding of compounds at this site stabilizes the inactive conformation of MALT1 by preventing the structural rearrangements in the PCASP and Ig3 domains, which are required to open the active site and allow substrate recognition. Thus, potent and selective compounds have been developed that exploit this unconventional mode of MALT1 binding and inhibition, some of which are currently in clinical evaluation.

Primarily based on the patent literature, we will summarize recent advances in the development of allosteric MALT1 inhibitors, but we will also describe some other approaches to develop active site protease inhibitors, or compounds designed to inhibit MALT1 protease and scaffolding functions such as proteolysis targeting chimeras (PROTACs) and inhibitors preventing MALT1 binding within the CBM complex.

2. Patent evaluation 2021-present

For an overview, relevant MALT1 patent applications since May 2021 are summarized in Table 1.

2.1. Evolution of allosteric MALT1 inhibitor compounds

In Hamp et al. (2021), we described that potent and selective MALT1 inhibitors have been developed by optimizing

Table 1. Overview of MALT1 patents 2021 – 2024.

Entry	WO Number	Priority date	Company	Class	Title	Ref.
1	WO2021/134004	27.12.2019	Schrödinger	Cyclic urea	Cyclic compounds and methods of using same	[32]
2	WO2021/138298	30.12.2019	Rheos Medicine	Carboxamides	Malt1 modulators and uses thereof	[33]
3	WO2021/207343	8.4.2020	Rheos Medicine Medivir	Ureas	Malt1 inhibitors and uses thereof	[34]
4	WO2022/081967	16.10.2020	Rheos Medicines	Amines	Malt1 modulators and uses thereof	[35]
5	WO2022/081995	16.10.2020	Rheos Medicine Medivir	Amines	Malt1 modulators and uses thereof	[36]
6	WO2022/106857	23.11.2020	Exscientia Limited	(trisubstituted) amines	Malt-1 modulators	[37]
7	WO2022/164789	26.1.2021	Schrödinger	Carboxamides	Tricyclic compounds useful in the treatment of cancer, autoimmune and inflammatory disorders.	[38]
8	WO 2022/184716	3.3.2021	Janssen Pharmacutica		Combination therapy using a MALT1 inhibitor and a BTK inhibitor	[39]
9	WO2022/204386	25.3.2021	University of Pittsburgh		Small molecules and there use as Malt1 inhibitors	[40]
10	WO2022/235698	3.5.2021	Nurix	Protacs	Compounds for inhibiting or degrading target proteins, compositions, comprising the same, methods of their making, and methods of their use.	[41]
11	WO2022/262855	18.6.2021	Tuojie Biotech	Carboxamides	MALT1 inhibitor, and preparation method therefor and use thereof	[42]
12	WO2023/279986 (US2024/0336594)	5.7.2021	Betta Pharmaceuticals	Carboxamides	Six-membered aryl or heteroaryl amide, and composition and use thereof	[43]
13	WO2023/107721	10.12.2021	Rheos Medicines		Methods for treating diseases using MALT1 inhibitors.	[44]
14	WO2023/143249	28.1.2022	Shanghai Qilu Pharmaceutical Research and Development Centre	Protacs	Protein degradation compound targeting MALT1	[45]
15	WO2023/149450	2.2.2022	Ono Pharmaceuticals	Ureas	Cancer treatment agent including Malt1 inhibiting drug as active ingredient	[46]
16	WO2023/148501	3.2.2022	C4X Discovery Limited	Various struct. classes	Heterocyclic derivatives as MALT1 inhibitors.	[47]
17	WO2023/164175	25.2.2022	Tegid Therapeutics Inc.	PROTACs	Protacs of MALT1	[48]
18	WO2023/192506	31.3.2022	Rarified Biosciences	Amines	MALT1 modulators and use thereof	[49]
19	WO2023/192913	31.3.2022	AbbVie	Amines	Thiazolo[5,4-b]pyridine MALT-1 inhibitors	[50]
20	WO2023/218203	13.5.2022	C4X Discovery Limited	Amines	Dihydroindenederivative4sa s MALT1 Inhibitors	[51]
21	WO2024/020534	22.7.2022	Schrödinger	Carboxamides	Cyclic compounds and methods of using same	[52]
22	WO2024/044344	26.8.2022	HotSpot Therapeutics	Sulfonamides	Pyridinylsulfonamide compounds and their use in therapy	[53]
23	WO2024/044730	26.8.2022	HotSpot Therapeutics	Sulfonamides	Pyrazolylsulfonamide compounds and their use in therapy	[54]
24	WO2024/059524	12.9.2022	HotSpot Therapeutics	Carboxamides	Pyrazolylcarboxamide compounds and their use in therapy	[55]
25	WO2024/059559	12.9.2022	HotSpot Therapeutics	Carboxamides	Isothiazolylcarboxamide compounds and their use in therapy	[56]
26	WO2024/125628	16.12.2022	Jiangsu Hengrui Pharmaceuticals	Carboxamides, prodrugs	Phosphate ester prodrug of MALT1 inhibitor	[57]
27	WO2024/133859	23.12.2022	Janssen Pharmaceutica, JNJ Investment	Trisubstituted amines	Malt1 inhibitors	[58]
28	WO2024/182599	1.3.2023	Rarified Biosciences	Amines	Compositions and methods for treating MALT1 associated diseases	[59]

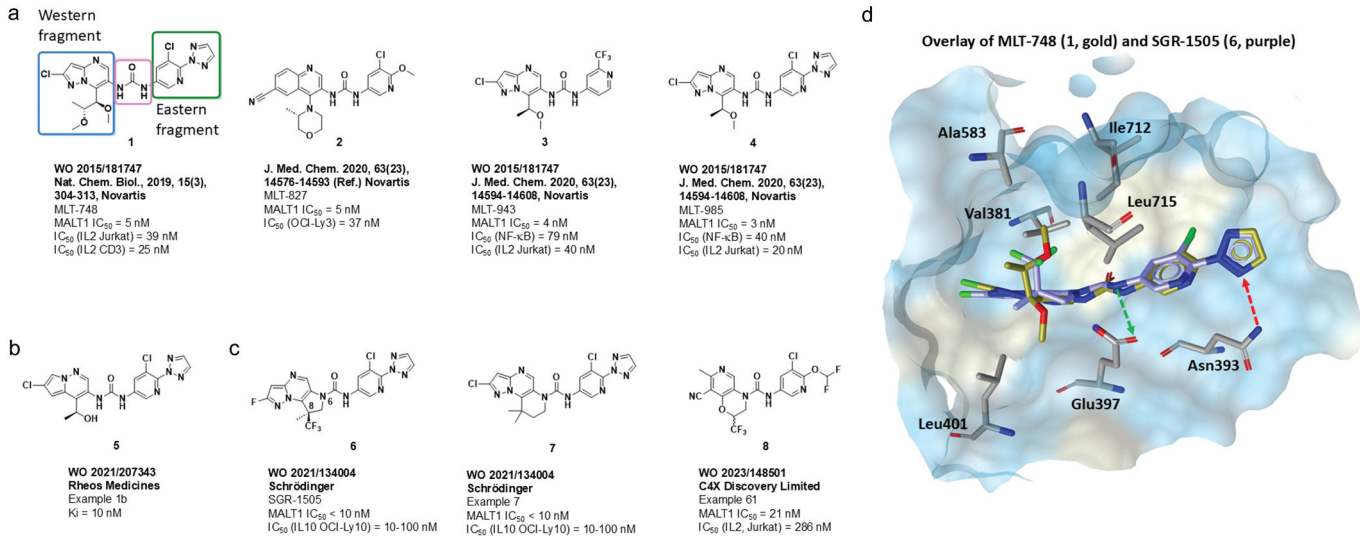

Figure 3. Urea-based inhibitors. (a and b) urea-based of MALT1 inhibitors developed by (1–5), (c) Partially cyclized urea inhibitors (6–8). (d) Proposed binding mode of SGR-1505 (purple) (overlay with MLT-748 - gold) in the allosteric binding pocket of the MALT1 protease (PDB: 6H4A). Docking studies were performed with SeeSAR 13.1 software and results were evaluated using LigandScout 4.4.9 software.

binding to an allosteric pocket of MALT1 formed in the hinge between the paracaspase (PCASP) and Ig3 domains [6,26,27] (Figure 2(c)). Compounds binding to this site prevent the conformational rearrangements necessary for opening the active site and thus substrate recognition and cleavage. The MLT-series of inhibitors from Novartis, containing a central urea linking moiety, yielded highly potent and selective MALT1 inhibitors such as MLT-748 (**1**) and MLT-827 (**2**) with low IC_{50} values in biochemical and cellular MALT1 inhibition assays [26,60] (Figures 2(c) and 3(a)). MLT-748 (compound **1**) is comprised of a central urea moiety, an eastern fragment represented by 3-chloropyridine with an additional triazole substituent at position two and a western fragment (pyrazolo[1,5-*a*]pyrimidine) with a branched side chain for optimal hydrophobic interactions. Co-crystallization revealed the exact binding of MLT-748 in the allosteric pocket of MALT1 (Figure 2(c)) [6,26,27]. However, these potent allosteric MALT1 inhibitors often suffer from poor water solubility at physiological pH, which hinders *in vivo* availability [60,61]. By scaffold morphing, pyrazolopyrimidine urea compounds were developed with improved solubility and subsequent optimization of metabolic stability led to favorable pharmacokinetic properties and adequate target occupancy *in vivo* [61,62]. The program featured MLT-943 (**3**) and MLT-985 (**4**) as excellent orally bioavailable tool compounds for effective MALT1 inhibition in multiple preclinical models (Figure 3(a)) [20,62,63]. However, prolonged treatment of rats and dogs with MLT-943 provoked an Immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX)-like pathology caused by loss of peripheral immune tolerance. The pathology is highly reminiscent of the autoimmune syndrome caused by the genetic inactivation of MALT1 protease in mice, suggesting an on-target adverse event [17–19,63]. Since Novartis aimed at long-term clinical use of MALT1 inhibitors to treat autoimmune diseases, safety assessment led to termination of the program. However, based on the MLT-series, several companies went on to develop structurally similar but nevertheless distinct compounds. While the eastern part of MLT-985 (**4**) and derivatives containing triazolo-pyridine was mainly well preserved, the central urea linker and the western pyrazolo-pyrimidine offered a certain degree of freedom to move, add, or remove nitrogen atom(s) in both heterocycles and to generate previously undescribed structures that offered novel chemical space for providing intellectual property. Some of these compounds have entered clinical trials evaluating safety and efficacy for treating NHL, an indication that may tolerate or even profit from lowering peripheral immune tolerance.

2.1.1. *Urea-containing allosteric MALT1 inhibitors*

Following the development of pyrazolopyrimidine urea-derivatives (Figure 3(a), **2-4**) (**WO2015/181747**) [64], only one new patent has been disclosed in the reporting period that retained the central urea moiety of the Novartis series of MALT1 inhibitors (Figure 3(b)). However, some use patents have been published to describe utilization of previously described compounds in other disease contexts (see below). It can be speculated that recurring solubility problems arising from the planar structure of the bisaryl urea core encouraged its replacement. Additionally, several of the compounds described possess a short half-life which requires repeated high doses to achieve the desired biological effect [62] (Figure 3(b)). Retaining the urea moiety may add affinity, because, while mainly van-der-Waals bonding is observed in the allosteric pocket, the eastern nitrogen atom in the central urea can form a polar interaction with the Glu397 residue outside the pocket [26,62]. SAR results reflected the critical role of hydrogen bonding to Glu397 which also has been shown for MALT1-inhibiting phenothiazine-derivatives (**WO2014/207067**) [27,65], but a detailed analysis of how strongly this interaction contributes to binding of urea-containing compounds is still missing. Rheos Medicines and Medivir, who previously worked on urea-based MALT1

inhibitors, published a patent in 2021 (**WO2021/207343**) [34] where the standard western MLT-series heterocycle previously described by Novartis (see **1-4**) is changed to pyrrolo[1,2-b] pyridazine (Figure 3(b), **5**), a structural moiety not covered by previous patents. Optimal eastern substituents are identical to the best Novartis compound MLT-985 (**4**). The subsequent patent **WO2023/107721** [44] featured REO-703, a compound already reported in **WO2021/207343** (example 34) [34], and mainly focuses on methods for treating diseases (see below).

2.1.2. Partially cyclized urea moiety

One of the first attempts to move away from the free urea moiety was a series of inhibitors discovered by researchers at Schrödinger Inc. Using their proprietary free energy perturbation technology (FEP+), Schrödinger performed a large-scale virtual screening campaign and obtained molecules that demonstrate strong MALT1 affinity and inhibition as well as anti-proliferative activity in MALT1-dependent lymphoma cells [66]. As a result of this work, Schrödinger disclosed a patent in 2021 describing a new class of tricyclic MALT1 inhibitors called 7,8-dihydro-6 h-pyrazolo[1,5-*a*]pyrrolo[2,3-e]pyrimidines (Figure 3(c), **6**) displaying an evident structural similarity to the previously described MLT inhibitor series developed by Novartis (**WO2021/134004**) [32]. The major difference of the clinical candidate SGR-1505 (**6**) to the previously disclosed Novartis compounds is the incorporation of the western nitrogen atom from the urea moiety into a heterocyclic ring. The majority of compounds described in this patent have a nitrogen ring incorporated into a five-membered ring, but there are also examples where a six-membered ring is present (Figure 3(c), **7**). Docking studies of **6** (SeeSAR 13.1 software package, examined and evaluated using LigandScout 4.4.9 software) based on the structure of MLT-748 (**1**) with MALT1 (PDB 6H4A) suggest that this nitrogen does not form a critical H-bond, while the second NH group of the urea forms a hydrogen bond with Glu397 (Figure 3(d)). This structural change rigidizes the side chain, thus enabling a predefined position of the small lipophilic substituents and optimized hydrophobic contacts within the binding pocket, specifically with Val381, Leu401, Ala583, Ile712 and Leu715. The NH group further interacts with the carboxylic group of the Glu397 residues and Asn393 forms a hydrogen bond with the triazole nitrogen. Fascinatingly, the eastern fragment is completely retained, indicating the high degree of optimization for the interactions it forms. Calculated cLogP values (using ChemOffice 22.2) suggest that these structural changes result in an increase by one (3.00 for SGR-1505 (**6**) versus 1.95 for MLT-985 (**4**)), however, the absence of the hydrogen bond donor may improve physicochemical compound properties. Besides SGR-1505, several other compounds showed low nanomolar cellular activity and potent anti-tumor growth effects, but their structures remain undisclosed.

C4X Discovery Limited took a similar approach with a partially cyclized urea moiety and conserved eastern fragment known from the MLT-748 inhibitor (**1**) (Figure 3(c), **8**) **(WO2023/148501)** [47]. In contrast to Schrödinger's series, they incorporated the western nitrogen of the urea exclusively into a 6-membered aliphatic ring, preferably piperidine, piperazine or morpholine. This ring is further connected to an aromatic ring bearing additional lipophilic substituents, such as chlorine, bromine or a methyl group, thus enhancing the hydrophobic interaction with the binding pocket. Furthermore, it is substituted with a trifluoromethyl group at the position equivalent to the position 8 in the series of inhibitors described by Schrödinger. Even though the exact stereochemistry of the trifluoromethyl group is not disclosed, it is noteworthy that the active isomer has an IC_{50} value of 17 nM while the activity of its enantiomer is approximately 100 times lower.

2.1.3. Urea to carboxamide switch

In a continuation of this series by Schrödinger, these inhibitors were further optimized and an additional patent (**WO2022/164789**) [38] describes close analogs, to be precise 7,8-dihydro-6 h-cyclopenta[e]pyrazolo[1,5-a]pyrimidines, where a pyrrolidine ring is replaced by a cyclopentane ring and a central carboxamide group replaces the urea moiety (Figure 4(a), **9-12**). The major consequence of this structural change is the introduction of an additional stereogenic center at position 6. Racemic mixtures were synthesized and later separated, enabling the testing of individual enantiomers. The direct analog of SGR-1505 with a 6(*S*), 8(*R*) stereochemistry (**10**) is described with an inhibitory activity in the same range as SGR-1505 (<10 nM); differences cannot be traced due to binning of the results. However, clearly, the stereochemistry of both positions plays a crucial role for the inhibitory activity. The stereochemistry at the 6-position is further highlighted with the 8,8-dimethyl analogue, where the 6-*S*-enantiomer (Figure 4(a), **13**) retains a low nanomolar activity (<10 nM) but the 6-(*R*)-enantiomer (**14**) shows a more than 10–100-fold loss of efficacy. Furthermore, an additional stereogenic center also changes the conformation of the molecule and reduces its planarity, a structural change often resulting in improved solubility. Described exchange of the western nitrogen atom from the urea moiety by a carbon atom results in a calculated reduction of the cLogP value by half a log unit (for compounds **7** and **10**, calculated with ChemOffice 22.2).

The substituent in the 8-position was further investigated and described in a third patent from Schrödinger (**WO2024/020534**) [52]. In the previous two patents, methyl and trifluoromethyl groups were typically investigated as substituents in the 8-position, and in the following patent the scope was further expanded to 5-membered heterocycles, primarily pyrazole and thiazole moieties (**15**). Docking suggests that this substituent plays an important role for optimal hydrophobic interactions with the binding pocket (not shown). Additionally, the introduced structural change further reduces the cLogP value (2.49 for **9** and 2.21 for **15**) as calculated with ChemOffice 22.2 software. This structural change retains the stereocenter at position 6 and emphasizes once more the importance of the stereochemistry for activity, with a clear preference for the *S*-isomer. For position 8, the preferred stereochemistry is *R*. Other stereoisomers show significantly reduced potency in both enzyme and cell assays. This is in accordance with our docking studies, where only compound **15** delivered valuable poses and interactions within the binding pocket in accordance with previous literature.

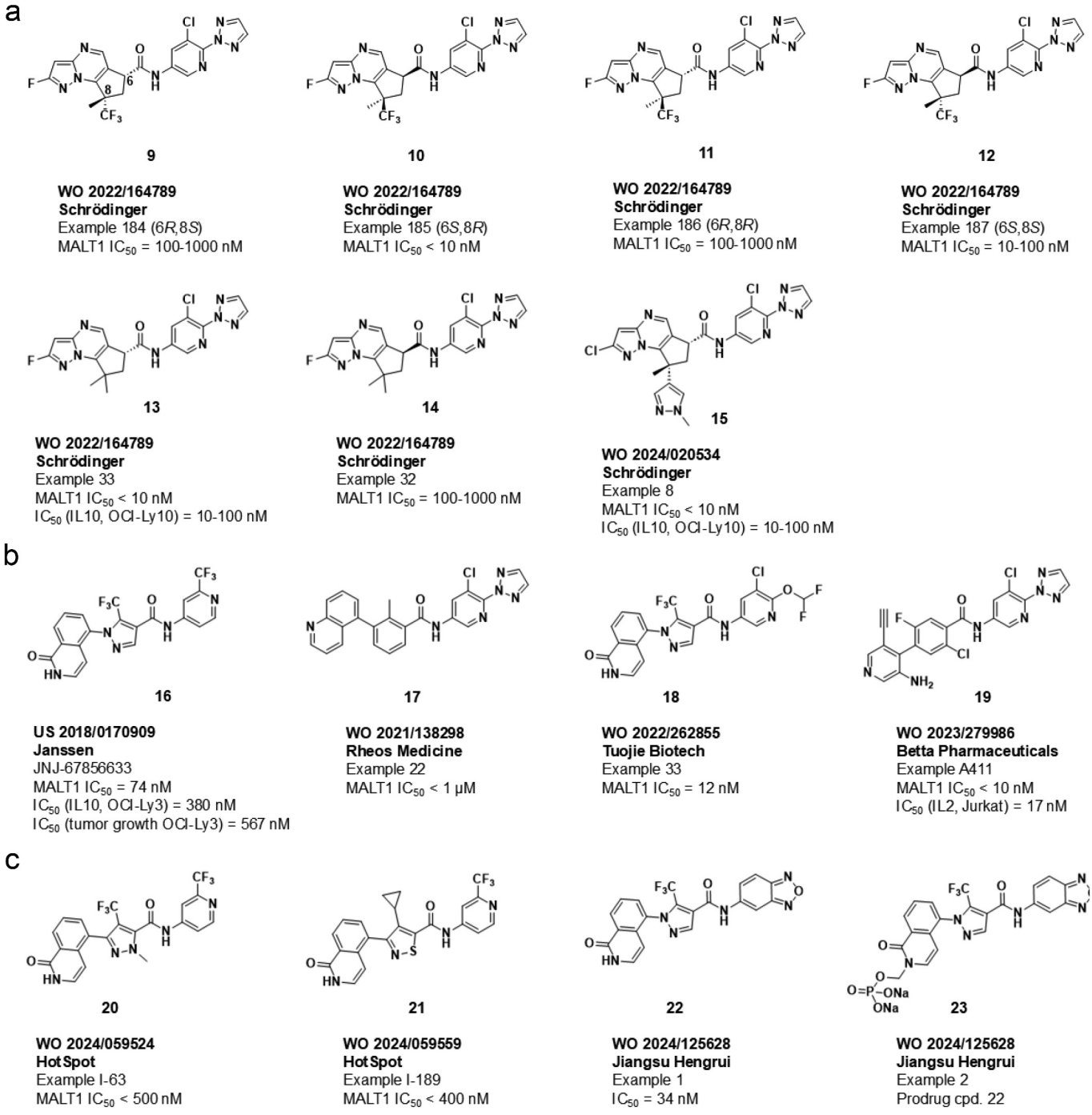

Figure 4. Carboxamide MALT1 inhibitors. (a) Two pairs of enantiomers (**9-12**) pointing out the importance of the stereochemistry at positions 6 and 8, that is further highlighted by two additional examples (**13** and **14**) and inhibitor **15** with a larger substituent at position 8. (b) Carboxamide inhibitor from Janssen (**16**) that progressed into the clinical trials and close analogues (**17-19**). (c) Further close analogues of Janssen clinical candidate (**20-22**) and a prodrug example (**23**).

The most advanced MALT1 inhibitor from the carboxamide structural class so far is JNJ-67856633 (Figure 4(b), compound **16**) (**US 2018/0170909**) [67], which seems to have inspired research at different start-up companies. Rheos Medicines further explored the role of the central ring and expanded the chemical space by synthesizing several compounds from the group of methyl-substituted aryl and heteroaryl carboxamides (**17**). They focused solely on the western part, leaving the eastern part (frequently composed of 2-trifluoromethyl-pyridine and 2-triazolo pyridines) almost untouched, but very few compounds display inhibitory activities <1 μM, indicating that a high degree of optimization will be necessary (**WO2021/138298**) [33]. Tuojie Biotech developed structurally closely related inhibitors (**18**) (**WO2022/262855**) [42] in which the western fragment is identical with compound 16, but the eastern fragment represents a 3-chloro substituted pyridine with a difluoromethoxy substituent as a potential bioisostere replacement for a methoxy group. A further patent originating from Betta Pharmaceuticals describes a series of biaryl carboxamides

(**19**) (**WO 2023/279986**) [43] with a highly conserved eastern fragment from MLT-748. The claimed aryl groups on the western side are five or six-membered rings with or without heteroatoms. Numerous additional substituents were described to increase the potency, optimize lipophilic contacts, change the torsion angle between the two rings and impact pharmacokinetic properties. Compound **19** as well as several other compounds showed low nanomolar inhibitory activity as well as strong inhibition of IL-2 secretion in the range of Novartis MLT-985 (**4**). HotSpot Therapeutics published two patents in 2024 describing compounds varying from Janssen compound **16**, with an altered 5-membered central ring. The original 5-trifluoromethyl pyrazole was exchanged by 1-methyl-4-trifluoromethyl pyrazole (Figure 4(c), compound **20**), now describing a C-C- linkage (**WO2024/059524**) [55] or an isothiazole core (**21**) (**WO2024/059559**) [56], respectively. However, MALT1 inhibitor activity of these compounds dropped considerably (5–7-fold compared to compound **16**). Additional structurally related compounds and their polymorphs were developed by Jiangsu Hengrui Pharmaceuticals (Figure 4(c), compounds **22** and **23**). A modified inhibitor with a benzoxadiazole moiety (**22**) displayed an IC_{50} of 34 nM (**WO2024/125628**) [57]. In addition, they developed a phosphonic acid prodrug (**23**), thus addressing the poor solubility of this class of compounds. The disodium salt of the phosphonic acid prodrug displays a comparable half-life to the non-prodrug compound **22**, but possesses increased solubility and thus likely improved bioavailability. The efficacy of the prodrug approach remains to be determined.

2.1.4. Sulfonamides

In parallel to carboxamides, sulfonamide derivatives have been explored as MALT1 inhibitors. Initially, sulfonamide-containing MALT1 inhibitors were published by Novartis (Figure 5(a), **24** and **25**) and structural analyses uncovered that compound **24** binds to the allosteric binding pocket as observed for urea-containing inhibitors (PDB:6YN9) [68]. The Novartis inhibitor MLT-208 (**25**) shows a potent MALT1 inhibitory activity with an IC_{50} value of 15 nM and good cellular activity with an IC_{50} of 53 nM in an IL-2 reporter gene assay in Jurkat cells [68]. Recently, HotSpot Therapeutics published two patents (**WO2024/044344**, **WO2024/044730**) [53,54] covering a wide range of sulfonamides as exemplified by compounds **26-28** (Figure 5(b)), which display a very high similarity to Novartis molecules. Most of the compounds described in **WO2024/044344** [53] are close derivatives of 3-pyridinesulfonamide, where the western and central part of MLT-208 (**25**), 1-methylindazole, is commonly preserved. The eastern part consists of a pyridine ring (like in MLT-208) or a similar nitrogen containing heterocycle, with the main differentiating features being its substituents. Biochemical MALT1 inhibition and cellular activation of NF-κB in reporter assays from the HotSpot compounds is difficult to assess, as only category A–D molecules are depicted with potencies ranging from IC_{50} <400 nM (A) to IC_{50} >2500 nM (D). Importantly, HotSpot claims that many of the described sulfonamides in both patents differentially inhibit MALT1 protease activity and NF-κB signaling (Figure 5(b)). For instance, compound **26** inhibits MALT1 and NF-κB with similar potencies, while compounds **27** or **28** inhibit protease activity without affecting NF-κB signaling, or vice versa. This lack of correlation between MALT1 and NF-κB inhibition in some compounds is difficult to understand. Docking studies using docking SeeSAR 13.1 and LigandScout 4.4.9 software suggests that compounds **26** and **27** bind to the allosteric pocket, similar to sulfonamide **24** (PDB:6YN9) (Figure 5(c)), which is closely correlated to MALT1 protease inhibition [26,27]. Docking suggests similar binding poses of **26** and **27**, the only changes being the ethyl to methoxy exchange at the indazole and changes in the pyrazole moiety,

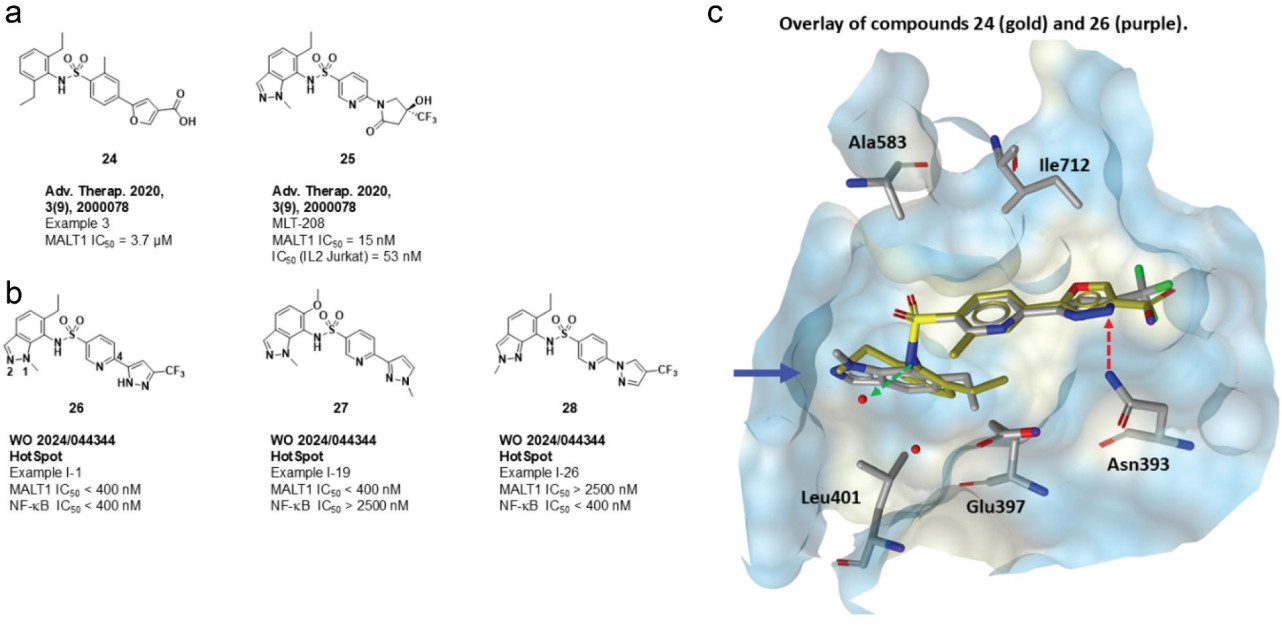

Figure 5. Sulfonamide inhibitors. (a) Representative inhibitors from sulfonamide class (**24**, **25**) developed by Novartis. (b) Representative sulfonamides with differential effects on MALT1 and nf-kB inhibition (**26-28**) (c) Proposed binding mode of the sulfonamide inhibitor **26** (docking) overlayed with crystallized compound **24** (PDB:6YN9); the blue arrows indicates a potential clash of the 2-methyl group of compound **28** with the protein surface.

resulting in altered positioning of one pyrazole nitrogen in the pocket; however, more subtle differences in potency cannot be retrieved as the activity is only given as <400 nM. In principle, also poor cellular uptake may explain the lack of NF-κB inhibition in case of compound **27**, but there are no obvious structural features causing a strong difference to **26**. While loss of MALT1 inhibition for the 2-methyl indazole derivative **28** can be rationalized, as the 2-methyl group may cause a clash with the protein pocket (as indicated with an arrow in Figure 5(c)), loss of binding in the allosteric site is hard to reconcile with retaining high potency of cellular NF-κB inhibition. Potentially, compound **28** could dynamically change the pocket and thereby impede the interaction of MALT1 to downstream effectors such as TRAF6 without inhibiting protease activity, but this has neither been shown nor reported for any other allosteric MALT1 inhibitor. It remains possible that compounds like **28** also act on other sites in MALT1 (e.g. MALT1-TRAF6 interface) or even other cellular targets besides MALT1. Thus, it will be important to present data assessing the effect of sulfonamides like compound **28** on CBM complex formation and MALT1-TRAF6 binding, as well as effects on MALT1-independent NF-κB pathways such as responses to pro-inflammatory cytokines.

Of note, HotSpot Therapeutics presented data on their frontrunner MALT1 inhibitor HST-1021 on the annual meeting of the American Society of Hematology (ASH) 2023 [69]. The structure of HST-1021 has not been disclosed, and it is unclear if the compound belongs to the class of sulfonamides. However, they report on the development of a first-in-class allosteric MALT1 scaffolding inhibitor, which would in principle be in line with an inhibitory mechanism shown for compound **28** (Figure 5(b)). In contrast to JNJ-67856633 (**16**), HST-1021 potently inhibits IκBα phosphorylation and thus NF-κB signaling, but leaves MALT1-catalyzed cleavage of BCL10 intact in DLBCL cells with oncogenic CARD11 [69]. HST-1021 shows high potency in killing NF-κB-dependent lymphomas, even if they are resistant to JNJ-67856633. Importantly, HST-1021 does not induce depletion of regulatory T (Treg) cell as reported for Novartis urea-containing derivatives MLT-943 [63], suggesting that HST-1021 may have a better safety profile that will allow long-term dosing. However, putative inhibition of MALT1-TRAF6 interaction may come with other detrimental side effects such as autoimmune inflammation, as observed in mice and humans carrying mutations in T6BMs of MALT1 [20,70]. A filing of investigational new drug (IND) for HST-1021 has been anticipated for 2024, but a clinical program has not yet been initiated. Overall, the structure and the mode of action of HST-1021 need to be disclosed to better judge the approach.

2.1.5. Switch to aromatic amines

As a next step in the evolution of the central moiety, the carboxamide/sulfonamide group was replaced by an aromatic amine, connecting two fragments consisting of different aryl, heteroaryl or aliphatic groups. Astra Zeneca identified MALT1 inhibitors of this class by screening a library of 1.8 million compounds, leading to the identification of a symmetrical hit with an IC_{50} of 2.2 µM which bound to the allosteric site of MALT1 as confirmed by X-ray crystallography [71]. Inspired by its low micromolar activity and good synthetic accessibility, they performed further optimization, resulting in lead compound 8 (Figure 6(a), **29**) with a biochemical IC_{50} of 0.3 µM and cellular IC_{50} of 3.2 µM in direct MALT1 protease assays. In

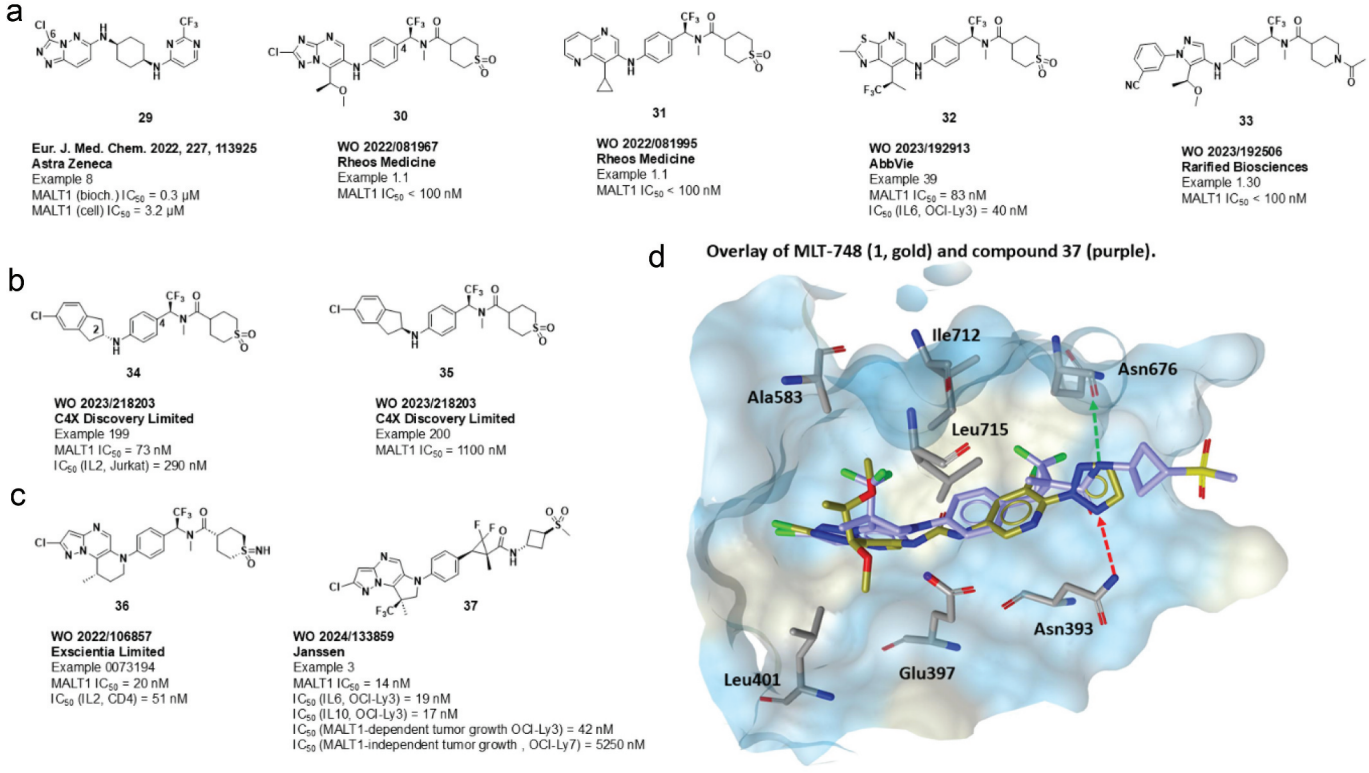

Figure 6. Aromatic amines. (a) Aryl amines with the first example from Astra Zeneca (**29**). Inhibitor **30** indicates the new trend in the development of eastern fragment used in series described later (**31**, **32**, **34**, **35**). (b) The importance of the stereochemistry in the class of indenes (**34** and **35**). (c) Tertiary amines **36** and **37**. (d) Predicted binding pose of inhibitor 37 (purple) and overlay with MLT-748 (gold) in the allosteric binding pocket.

addition, this compound displays low clearance and a good selectivity profile. Furthermore, the improved lead compound has a 6-fold increased potency compared to the initial hit and is less lipophilic, resulting in a 100-fold increase in its lipophilic ligand efficiency (LLE) value, an important guidance in drug optimization processes (3.4 compared to 1.4). Optimization of the western part again underlined the importance of hydrophobic interactions, as removal of the trifluoromethyl group led to a significant loss of activity. Among the heterocycles tested, the well-precedented western [1,2,4]triazolo[4,3-d]pyridine moiety showed the best activity. Alterations of the substituent at the 6-position, which occupies a hydrophobic pocket formed by MALT1 residues Val344 and Ala345, demonstrated a clear preference for small lipophilic groups, such as chlorine, bromine, methylthio or trifluoromethyl substituents.

Rheos Medicines described two series of MALT1 inhibitors comprising arylamines (Figure 6(a), **30** and **31**). The central part is represented by an aniline bearing an additional 4-substitutent. The western fragment is comprised of different combinations of two fused aromatic rings, one five-membered and one six-membered ring or two six-membered rings, respectively (**WO2022/081967**, **WO2022/081995**) [55,56]. Several compounds are described to possess an inhibitory activity below 100 nM, but no further details are provided. The western fragment remained mainly unchanged from previously described inhibitors with urea moieties. According to our docking studies, the amine group compounds can still retain the interaction with the MALT1 Glu397 residue. On the other side, the classical 3-chloro-2-(2-triazolo)pyridine as an eastern fragment was further replaced with a 4-benzylamine that was additionally derivatized with various carboxylic acids. The carbonyl oxygen of the introduced amide group serves as a hydrogen bond acceptor and interacts with the Asn393 residue. As a small hydrophobic substituent, a trifluoromethyl group was introduced to the benzylic position with the preferred S-configuration, occupying a small hydrophobic pocket formed by Leu383, Leu386, Ala394 and Ile712 residues. Among other substituents, benzylamine was often substituted with tetrahydro-2 h-thiopyran 1,1-dioxide-4-carboxylic acid (see **30**) and our docking studies of compound **30** (not shown) suggest that this part of the inhibitor is pointing out of the binding pocket and does not seem to form any crucial interaction. However, we assume that its main purpose is to reduce the cLogP value. Calculations imply that the cLogP value (0.59) is almost two units lower compared to its simple acetyl substituted analogue (2.34).

Example 39 (Figure 5(a), **32**) from the AbbVie patent (**WO2023/192913**) [50] contains a western fragment similar to the one of their clinical candidate ABBV-525 (**45**) (see Figure 7), but the core was replaced by a simplified aniline bearing a structurally novel eastern fragment (as seen with compound **30**). It has an IC_{50} of 83 nM in the biochemical assay and an IC_{50} of 40 nM for MALT1-dependent IL-6 release in the DLBCL cell line OCI-LY3. It is also worth noting that the described compounds, even though they do not exhibit very low nanomolar activities *in vitro*, perform well in the cellular assays. Rarified Biosciences described a series of compounds from the class of aryl amines that could be classified as hybrid compounds between carboxamides and aryl amines (**33**). They comprise a substituted pyrazole on the western side, a motif, commonly present in the series of carboxamide inhibitors, and the aniline on the eastern side that is further substituted on the position 4 and represents a commonly used moiety in the class of arylamine inhibitors. (**WO2023/192506**) [49]. In a second patent by Rarified Biosciences (**WO2024/182599**) [59], compounds represent different hybrids of a western part of previously described Novartis or Janssen inhibitors and an eastern part derived from a Rheos inhibitor. However, no inhibitory activities are reported.

C4X Discovery Limited developed a series of MALT1 inhibitors based on the dihydroindene scaffold substituted at position 2 with an aniline or 3-aminopyridine (**WO2023/218203**) [51]. This middle part is further substituted at position 4 with already described moieties. The trifluoromethyl group has a retained (S) stereochemistry and occupies a hydrophobic pocket, and the carbonyl group is suggested to interact with the Asn393 residue (Figure 6(b), **34** and **35**, docking not shown). Most of the compounds were separated by chiral column chromatography and single enantiomers were tested. There was a clear preference for one isomer, but stereochemistry is in most cases not disclosed. A comparison of compound **34** and **35** from this patent reveals that the preferred enantiomer has an *S*-configuration at position 2 of the dihydroindene ring. This is also supported by our docking studies, where only compound **34** delivers relevant poses.

A similar strategy was used by Exscentia Limited, who merged with Recursion in 2024. Similar to Schrödinger, Exscentia used a computational approach to design new allosteric MALT1 inhibitors based on prior knowledge of the binding mode. Compounds described in patent **WO2022/106857** [37] could be interpreted as a hybrid of Schrödinger's tricyclic core and the novel eastern heterocycle first described in the patent from Rheos Medicines (**WO2022/081967**) [35]. In comparison to previously published anilines, the aniline nitrogen was in this case incorporated in a third ring, transforming it into a tri-substituted amine (Figure 6(c), **36**). This change disables the possibility of a hydrogen bond interaction with the frequently found Glu397 residue of MALT1. Surprisingly, these compounds still showed a low nanomolar activity in biochemical and cell based assays. Exscientia described data on their clinical candidate compound EXS73565 (now REC-3565) at ENA (EORTC-NCI-AACR symposium) 2024 in Spain, showing high potency alone or in combination with Bruton's Tyrosine kinase (BTK) inhibition [72].

Janssen described a similar series of compounds, relying on the tricyclic core discovered by Schrödinger (**WO2024/133859**) [58] and substituted the nitrogen with a 4-substituted phenyl moiety (**37**). Instead of a trifluoromethyl group described in the previous patents covering a wide range of anilines, they introduced a difluoro-substituted cyclopropane carboxylic acid moiety with defined stereochemistry. The carboxylic group is further derivatized with different polar amines bearing sulfonyl groups, a strategy aiming to increase hydrophilicity. The stereochemistry on the western part is *R* as disclosed in the

case of compounds developed by Schrödinger. Docking studies of compound **37** suggest that the western part is well aligned with the structure of MLT-748 (**1**) (Figure 6(d)). There is no observed interaction with the Glu397 side chain carboxylic group due to the absence of the hydrogen bond donor in the central part of the inhibitor. The difluorocyclopropane ring forms hydrophobic interactions with Leu383, Leu386 and Ala394 (as does the chlorine atom of MLT-748 (**1**)), and the carbonyl group forms a hydrogen bond with the Gln393 residue, an interaction commonly observed in previous co-crystal structures of MALT1 inhibitors. Interestingly, our docking suggests a further possible interaction between the amide nitrogen and the backbone carbonyl group of Gln676. Most inhibitors with similar eastern part contain a reversed amide and a methylated nitrogen, preventing formation of this potential interaction. Further substituents on the eastern fragment, such as the methylsulfonyl group, do not directly interact with the binding pocket but do according to our cLogP calculations probably contribute to the reduced lipophilicity of this class of inhibitors. This is in line with previous sulfone-containing derivatives like **31** or **33**. Overall, compound **37** of **WO2024/133859** [58] is potent not only in biochemical assays (IC_{50} 14 nM) but also in cellular assays (IC_{50} < 20 nM for IL-6 and IL-10), where high selectivity in killing MALT1-dependent versus MALT1-independent DLBCL cells (IC_{50} 42 nM versus 5.2 µM) is retained (Figure 6(c)).

2.1.6. Substrate-binding pocket inhibitors

In comparison to the allosteric-binding pocket, the MALT1 substrate-binding pocket has attracted less attention for the development of inhibitors. However, the group of Hong Liu has performed a screen of 40,000 small molecules, identifying 1000 hits that were further evaluated in a concentration-response assay [73]. Based on biochemical activity, 19 compounds with low micromolar activity were selected for further examination and 15 of these molecules shared a common 5-oxo-1-thioxo-4,5-dihydro-1 h-thiazolo[3,4-a]quinazoline scaffold (Figure 7(a)). To further validate this structural class, 300 additional compounds bearing this structural moiety were tested, resulting in 17 additional hits that exhibited an IC_{50} <10 µM in biochemical MALT1 inhibition and suppression of growth of the MALT1-dependent DLBCL cell lines HBL1 and TMD8. Further, rational drug design aimed to develop two groups of activities: MALT1 inhibitors (1) targeting the allosteric-binding pocket like previous compounds and (2) covalently and irreversibly binding to the paracaspase active site. Optimization of allosteric MALT1 inhibitors yielded compounds with single digit micromolar activities, indicating that the 5-oxo-1-thioxo-4,5-dihydro-1 h-thiazolo[3,4-a]quinazoline scaffold requires further optimization to reach potency seen in other classes. However, by incorporating different warhead moieties which can interact with the Cys464 residue in the substrate-binding pocket, such as 2-chloroacetyl for **38** and bromomethyl for **39**, the authors suggest that based on the same scaffold, they could develop several covalent inhibitors with low micromolar IC_{50} in biochemical MALT1 inhibition assays. For example, 20c (**38)** inhibited MALT1 with an IC_{50} of 5.3 µM and showed approximately 15-fold higher potency in killing MALT1-dependent versus -independent lymphoma cells (Figure 7(a)). In a second publication, further structural optimization delivered an additional class of compounds in which pyrimidinone to the 2-thioxo-2,3-dihydrothiazole ring was introduced, yielding a 2-thioxo-2,3-dihydrothiazolo[4,5-d]pyrimidin-7(6 h)-ones scaffold [74]. For example, 10 m (Figure 7(a), **39**) showed increased potency (IC_{50} 1.7 µM). Although killing of MALT1-dependent lymphoma cells *in vitro* was comparable between compounds **38** and **39**, **39** showed improved antitumor activity in *vivo* in ABC DLBCL xenotransplantation models. However, the mode of action of the compounds has not

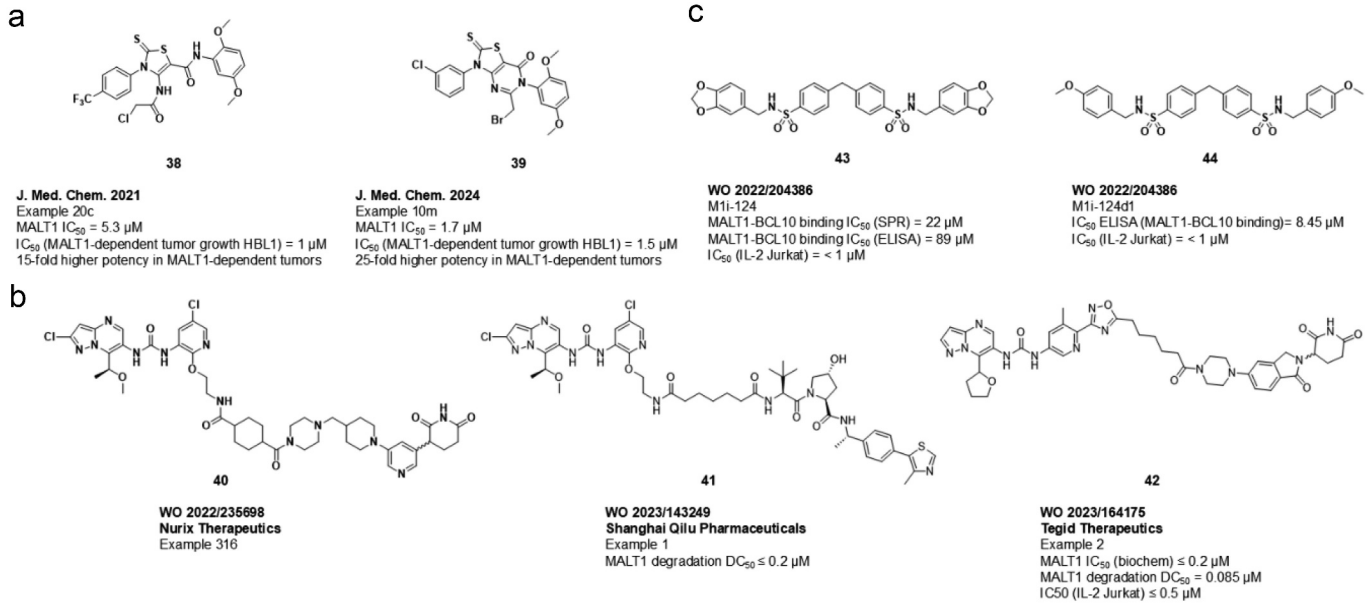

Figure 7. MALT1 inhibitors with alternative modes of action. (a) Covalent MALT1 inhibitors binding to the substrate pocket (**38, 39**). (b) MALT1 degrading PROTACs (**40–42**). (c) MALT1-BCL10 binding (scaffolding inhibitors) (**43-44**).

been completely resolved. Wash out experiments and mass spectrometry suggest that compound **39** is covalently bound to MALT1, but it has not been shown that Cys464 in the active center is attacked. Further, optimization was performed based on molecular docking, but no crystal structure showing the binding of the compounds to the active center has been published. Further, it needs to be addressed how similar molecules can at the same time bind to the hydrophobic allosteric and the hydrophilic active sites in MALT1 [73]. To aid in future optimization of potency and selectivity in these scaffolds, it will be important to answer these questions.

2.2. Other inhibitor classes

Whereas allosteric inhibitors selectively target the protease function of MALT1, other attempts aim to increase the efficacy of MALT1 inhibition by targeting both scaffolding and proteolytic functions. This can either be achieved by targeted degradation using for instance PROTACs, or by inhibitors which prevent the recruitment of MALT1 to the CBM complex, which would also abolish all downstream functions.

2.2.1. PROTACs and degraders

A small number of patents have been filed describing newly developed PROTACs for the degradation of MALT1 protein (Figure 7(b)). These efforts follow an initial patent by Cornell University on PROTACS, which was covered in the first reporting period (**WO2018/085247**) [6,75]. In this patent, urea-based Novartis-like MLT-moieties were used, with linkage of the cereblon recruiter from either the western heterocycle or the eastern pyridine substituent. In the latter, the linkage was achieved via a pyrazolo instead of a triazolo substituent at the pyridine. The vast majority of newly described PROTACs utilize urea-based inhibitors, including those from Nurix Therapeutics, which claims the synthesis of many PROTACs against oncogenic proteins including MALT1, for which they again link the cereblon-binding moiety to a urea-containing allosteric MALT1 inhibitor (**40**). Instead of the commonly used thalidomide-like cereblon linkers, here shorter pyridyl-glutarimide, a rigidized alkyl linker, was used as pioneered by Arvinas. However, no data on activity are provided (**WO2022/235698**) [41]. In a Chinese patent by Shanghai Qilu Therapeutics, a series of urea-analogs fused to the von Hippel Lindau (VHL) E3 ligase binder were used to generate MALT1 PROTACs (**41**), but further verification besides a MALT1 DC_{50} (half-maximal degradation concentration) ≤0.2 µM is needed (**WO2023/143249**) [45]. Tegid therapeutic synthesized cereblon binding-based PROTACs, in which the linker exits from the oxadiazole of the eastern fragment (**42**) (**WO2023/164175**) [48]. Even though triazole seemed to be the preferred eastern fragment substructure for MALT1 inhibitors and pyrazole has been described before (see above), the 1,2,4-oxadiazole ring may have been chosen to generate new composition of matter and to avoid PROTACs already claimed in **WO2018/085247** [75]. With a MALT1 inhibition IC_{50} ≤0.2 µM *in vitro* and DC_{50} of 0.085 µM for inducing MALT1 degradation in cells, compound **42** shows high potency as a MALT1 inhibitor and degrader, which also translates into a decent IC_{50} for inhibition of IL-2 release in Jurkat T cells. Since the previous patent **WO2018/085247** only states percent degradation for their PROTACs, it is difficult to directly compare potencies, but it seems that compound **42** shows favorable cellular activity in degrading MALT1. Overall, compounds **40** and **41** display a downregulation of MALT1 protein expression in target cells with an EC_{50} below 200 nM. However, data on the efficacy and selectivity of these compounds, for instance in killing MALT1-dependent and -independent lymphoma cells *in vitro* and *in vivo*, have not yet been published, making it difficult to judge the potency and specificity of the approach. Further analyses are warranted.

A recent abstract presented at ASH meeting 2024 disclosed data from the University of Cincinnati in cooperation with Eilean Therapeutics on a new MALT1-directed degrader ZE66–0205, whose chemical structure has not yet been disclosed [76]. At low concentrations of 50 nM, ZE66–0205 was described to completely degrade MALT1 within 48 h. Accordingly, ZE66–0205 shows high potency in inhibiting MALT1 protease activity (IC_{50} = 38 nM, TMD8 cells) and IL-2 release (IC_{50} = 9 nM, Jurkat T cells). ZE66–0205 kills MALT1-dependent ABC DLBCL cells independent of BTK or CARD11 mutational status. Pharmacodynamic analyses in mice proved high efficacy of ZE66–0205 in degrading MALT1 *in vivo* and ZE66–0205 was toxic to MALT1-dependent OCI-LY3 cells in xenograft mouse models. Overall, the researchers present encouraging data on the feasibility of the approach, but many questions regarding the chemical structure, the exact mode of action, and the safety profile in comparison to MALT1 protease inhibitors need to be addressed in the future. No corresponding patent of University of Cincinnati or Eilean Therapeutics has been published to date.

2.2.2. Inhibitors of MALT1-BCL10 interaction

In the past, most MALT1 inhibitors have targeted the protease activity of MALT1 while leaving scaffolding function with regard to the binding of MALT1 to BCL10 and the formation of the CBM complex intact. Researchers from the University of Pittsburgh filed a patent for therapeutic administration of a class of small molecule MALT1 inhibitors claiming a novel mode of action (Figure 7(c), **43** and **44**) (**WO2022/204386**) [40]. Using *in silico* screening, M1i-124 (**43**) has been identified as a compound that binds to the MALT1 Ig1–2 region that is necessary for interaction with BCL10. *In vitro*, M1i-124 disrupts the binding of MALT1 to BCL10 with an IC_{50} of 22 µM in surface plasmon resonance (SPR) and 89 µM in an ELISA-based protein–protein interaction assay. M1i-124 (**43**) and M1i-124d1 (**44**) are symmetric compounds where two phenylsulfonamide moieties are connected by a central methylene group. The nitrogen of the sulfonamide group is further substituted with electron-rich benzyl moieties. Removal of one oxygen in M1i-124d1 (**44**) at the N-substituent increases potency by a factor of approximately 10 in the ELISA-based interaction assay. Recruitment of MALT1 to BCL10 is critical for all CBM complex downstream functions including MALT1 substrate cleavage and NF-κB activation [16]. In line with the proposed mode of action, M1i-124 and M1i-12d1 inhibit both TCR-induced MALT1 scaffolding (NF-κB signaling) and

protease (RelB and N4BP1 cleavage) as well as IL-2 release in Jurkat T cells in a dose-dependent manner. Further, cytokine secretion (IL-10 and IL-6) and growth and survival of MALT1-dependent ABC DLBCL cell line OCI-LY3 and TMD8 are impaired by both compounds, while MALT1-independent GCB DLBCL cells are largely unaffected. M1i-124 shows good oral bioavailability and stability, and in mouse xenografts growth of TMD8 ABC DLBCL tumors is suppressed following daily dosage of M1i-124. Of note, these symmetric compounds may be prone to show a certain promiscuity for binding to proteins and they lack many functional groups for specific interaction to the target. Along this line, while micromolar concentrations are required to inhibit MALT1-BCL10 binding *in vitro*, strong cellular effects, for instance inhibited cytokine release (IL-2, IL-6 and IL-10) are detected at sub-micromolar concentrations, suggesting that the inhibitors may not act through MALT1 inhibition. Even though it is attractive to inhibit all MALT1 functions by preventing its binding to the BCL10 and the CBM complex, structural analyses, and further chemical optimization may be required to prove the validity and specificity of this approach. Thus far, no manuscript has been published by the authors of the Pittsburgh patent to further clarify these findings.

3. Patents claiming medical use for MALT1 inhibitors

Several companies have put focus on potential clinical use of MALT1 inhibitors from different structural classes rather than solely on their synthesis. Janssen claimed use of MALT1 inhibitors, specifically JNJ-67856633 (16), in combination with BTK inhibitors like ibrutinibor, Roche's BTKi RN486 or JNJ-64264681 (**WO 2022/184716**) [39]. Rheos published a patent in 2023 (**WO2023/107721**) [44] that focuses on methods for treating different diseases, such as autoimmune disorders, inflammatory and allergic disorders using different MALT1 inhibitors. Their selection of MALT1 inhibitors covers various compounds from the classes of ureas, aryl amines and carboxamides, respectively. Furthermore, different administrations and doses are described within the patent. It is additionally claimed that the inhibitors and methods for their administration allow for the treatment of mentioned diseases without the reduction of Treg cells. Later that year, Ono Pharmaceuticals published a patent (**WO2023/149450**) [46] where they mostly discuss inhibitors from the class of ureas previously described by Takeda Pharmaceutical (**WO2020/111087**) [77]. They focused solely on their use in cancer treatment and claim that combination of MALT1 inhibitor and clinically used anticancer drugs (such as ibrutinib) can have a beneficial effect on the treatment outcome.

4. MALT1 inhibitors in clinical trials

Janssen Research & Development were the first to initiate a phase I study evaluating safety and efficacy of the MALT1 inhibitor **JNJ-67856633** (**16**) (JNJ-6633; NCT03900598) (Figure 8), which was started in April 2019. The main goal is to determine the maximum tolerated dose of inhibitor in participants with relapsed/refractory B-cell non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL). Further, based on preclinical data showing superior efficacy by combining MALT1 and BTK inhibitors [78,79], Janssen launched a second trial in 2021 to study the combinatorial treatment of MALT1 inhibitor JNJ-6633 with the proprietary Bruton's kinase inhibitor JNJ-64264681 (NCT04876092). Primary aims of both studies were to define in dose escalation trials the dose-limiting toxicities and potential adverse events to come to a recommended phase 2 dose (RP2D), but secondary aims also included overall and complete response rates (ORR and CRR) in lymphoma patients. Both studies are no longer recruiting, but final results have not been posted. Some data have been published for JNJ-6633 monotherapy (NCT03900598) [80]. 109 patients received oral 50–600 mg JNJ-6633 once daily (QD). Treatment-related adverse events (AEs) were seen in most patients (97.2%) with hyperbilirubinemia observed in 44%. Even though maximum tolerated dose was not reached, this adverse event was considered for setting RP2D to 300 mg daily. The authors conclude from the preliminary data that JNJ-6633 elicits a manageable hematological and non-hematological safety profile and shows some clinical activity in indolent and aggressive lymphomas that deserves further evaluation in an expansion cohort.

Since 2021, several other phase 1 clinical trials have been initiated to evaluate safety and efficacy different MALT1 inhibitors in the treatment of B cell malignancies. **SGR-1505** (Figure 8) from Schrödinger is evaluated in a first-in-human, single center, dose escalation study to evaluate the safety, tolerability, PK and PD of SGR-1505 tablets in healthy participants (ACTRN12623000358640p). Preliminary data in humans showed target engagement consistent with MALT1 protease inhibition [66]. SGR-1505 (NCT05544019) entered phase 1 clinical trials in 2023 in subjects with relapsed/refractory B-cell lymphomas. An amendment is planned to test the combination of SGR-1505 with BTK and BCL-2 inhibitors. In 2023, Ono Pharmaceuticals also started to investigate safety, tolerability, PK, PD, and efficacy of **ONO-7018** in relapsed/refractory NHL

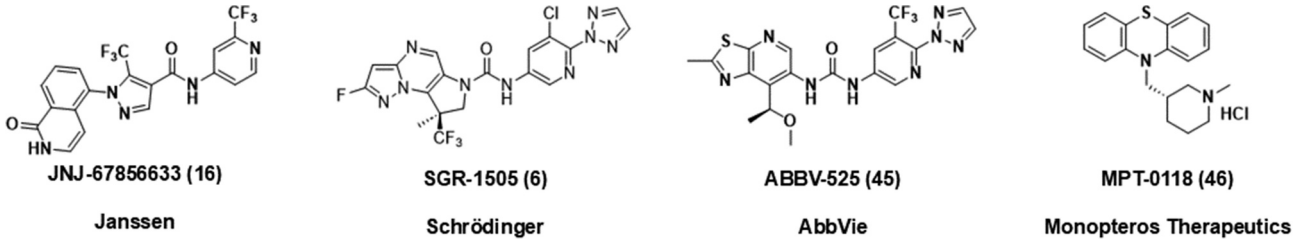

Figure 8. MALT1 inhibitors in clinical trials.

or CLL patient (NCT05515406). A second trial with the same compound focusing on relapsed/refractory NHL was launched recently in November 2024 (NCT06622226). The structure of ONO-7018 (previously known as CTX-177 developed by Chordia Therapeutics) has not been disclosed, but preclinical data suggested high efficacy as a single agent, or in combination with BTK inhibition, or to overcome BTK resistance in various lymphoma models [81,82]. In addition, AbbVie MALT1 inhibitor **ABBV-525** alone or in combination with BCL2 inhibitor venetoclax effectively killed ABC DLBCL tumor cells (Figure 7) [83] and entered into phase 1 clinical development in approximately 100 participants with B cell malignancies (NCT05618028). It will be important to obtain human data on the safety and efficacy of these novel clinical candidates, but results of are not expected before 2026. Finally, other developers announced that they are planning clinical trials. With its clinical candidate **EXS73565/REC-3565**, Exscientia/Recursion is aiming for clinical trial application (CTA) still in 2024. The chemical structure of EXS73565has not been released, but besides the high potency, Exscientia reported on a potentially improved safety profile, because in contrast to JNJ-6633, EXS73565is not inhibiting UGT1A1 (UDP Glucuronosyltransferase Family 1 Member A1), which may drive hyperbilirubinaemia observed in the phase 1 clinical trial [72,80]. Further, alternative approaches are aiming to inhibit MALT1 protease and scaffolding functions, like the MALT1 degrader **ZE66–0205** (University of Cincinnati and Eilean Therapeutics) and the potential MALT1 scaffolding inhibitor **HST-1021** (HotSpot Therapeutics), both structures have not yet been disclosed.

One clinical trial by Monopteros Therapeutics administering **MPT-0118** (Figure 8) does not aim to develop the MALT1 inhibitor for the treatment of lymphomas, but is evaluating its ability to reprogram suppressive Treg cells in the tumor microenvironment (TME) into pro-inflammatory and IFNγ-producing Treg cells that can boost anti-tumor immunity [21]. In several preclinical murine tumor models, as well as patient-derived organotypic tumor spheroids (PDOTS), MPT-0118 (*S*-mepazine) sensitized the tumor cells for treatment with an anti-PD1 checkpoint blocker [84]. A clinical trial evaluating the safety and efficacy of MPT-0118 in subjects with advanced or metastatic refractory solid tumors was started in 2021. An abstract at ESMO 2023 indicated that 17 patients were dosed and that MPT-0118 demonstrated good tolerability with no immune-related toxicities and some single-agent activity in immunologically cold tumors. An RP2D was set to 200 mg/day, warranting further analyses, but the status of the trial is unknown.

5. Conclusion

The identification of novel MALT1 inhibitors is still an active field of research, and in the period covered in this patent report (May 2021–December 2024), 28 new patent applications were filed and in total seven clinical trials have been launched. All clinical candidates are in early clinical development, and we still lack data on safety and efficacy of the compounds in human subjects. Obtaining robust clinical data will be of utmost importance and in case of favorable results may even spark further development of MALT1 inhibitors, especially with the goal to not only inhibit MALT1 protease activity but also to abolish its scaffolding function by protein degraders or protein–protein interaction inhibitors to prevent MALT1 recruitment to the CBM complex.

6. Expert opinion

With respect to the chemical space, most of the pursued optimization efforts focus on developing inhibitors for the allosteric pocket. Here, most inhibitors contain structurally conserved motifs, like isoquinoline, isoquinolone, or alternative bicyclic heterocycles as western fragments and triazolo or trifluoromethyl pyridines as preferred eastern fragments. The urea linker system could successfully be cyclized or replaced by carboxamides or anilines, which likely improves the overall physicochemical properties of the resulting compounds. In the class of aniline inhibitors, new eastern fragments have been developed and thoroughly optimized. In addition, substituents for increasing water solubility could be introduced at the eastern part of the scaffold. It is interesting to observe that lead candidates of companies devoted to state-of-the-art molecular modeling or generative AI still contain eastern and western fragments of very high similarity to previously described compounds optimized within more traditional medicinal chemistry campaigns (compare SGR-1505 compound **6** to Novartis MLT-748 compound **1**). This may suggest that the allosteric pocket of MALT1 calls for well-defined binders to achieve optimal activity.

Of note, no competitive or covalent MALT1 active site inhibitors have been developed with a potency and selectivity that warrants further clinical development. Structural analyses demonstrated that MALT1 PCASP and caspase domains share the same overall fold and the need to dimerize for catalytic activation [28,29]. However, while acidic residues (Asp365 and Glu500) in the active site of MALT1 favor cleavage after arginine, caspases contain basic amino acids (e.g. Arg179 and Arg341 in CASP9) in the vicinity of the active site supporting aspartate at the P1 position for cleavage [29]. So far, MI-2 is the only covalent and irreversible active site inhibitor, but structural information on the mode of action is still missing, and the lack of specificity has prevented further clinical development [23,60,85]. Thus, despite the differences in the active site of MALT1 and caspases, the development of highly potent and selective MALT1 inhibitors apparently remains challenging. In line, since several years no further pre-clinical advances have been reported on the development of MALT1 peptide-derived MALT1 active site inhibitors (see [6]). In general, MALT1 active site inhibitors are expected to have a similar safety profile regarding loss of peripheral immune tolerance. However, competitive inhibitors may have certain advantages over allosteric MALT1 inhibitors because they only bind to an active enzyme, whereas allosteric inhibitors need to constantly bind even to the inactive protease with the potential need for higher drug concentrations for continuous effective inhibition. Thus, lower concentrations of competitive or covalent inhibitors may cause less severe adverse events, but so far, the development of such potent and selective active site MALT1 inhibitors has not been successful.

Alternative approaches have been attempted for targeting not only MALT1 protease activity but also MALT1 scaffolding functions and thus downstream NF-κB signaling. These efforts include the complete removal of MALT1 using PROTACs or degraders or the synthesis of direct scaffolding inhibitors that act as protein–protein interaction (PPI) inhibitors to prevent CBM complex formation. Especially MALT1 PROTACs and degraders show promising activities both *in vitro* and in cellular assays. All MALT1 PROTACs disclosed to date are built on variations of the urea-type MALT1 inhibitors initially introduced by Novartis. The linker is attached at the side chain in the western fragment or either directly at the pyridine ring in the eastern fragment or alternatively on the 5-membered ring (triazole, pyrazole, or oxadiazole). In comparison to previously reported MALT1 PROTACs, degraders described within this review mostly contain a more rigid linker. Reducing the flexibility of the linker leads to more defined three-dimensional positions of both ligand and E3 ligase recruiter and improved cellular uptake. This has been shown to be key for companies like Arvinas. It is not unexpected that the first series of degraders are based on urea-type compounds as these were the first reported potent MALT1 inhibitors [62]. However, it will be interesting to see how representatives of the second generation of allosteric MALT1 inhibitors will perform as MALT1-ligands in PROTACs. Overall, data on MALT1 PROTACs have not yet been published in peer-reviewed journals and *in vivo* studies in animal models are urgently needed to judge the efficacy and safety of these approaches.

Besides the removal of MALT1, an attempt has been made to develop PPI inhibitors that directly target the binding of MALT1 and BCL10 (**WO 2022/204386**). Certainly, more work is needed to fully understand the behavior of these compounds. While binding occurs at micromolar concentrations, cellular effects are reported to be in the sub-micromolar range. It should be noted that these kinds of symmetric lipophilic molecules can show some promiscuous and aggregation behavior, and the electron-rich benzylic structures may be subject to metabolism. Nevertheless, it may be worthwhile to intensify the development of PROTACs and scaffolding compounds because these novel types of MALT1 inhibitors are expected to display activity and selectivity profiles that are distinct from pure MALT1 protease inhibitors. Selective genetic or pharmacologic inactivation of MALT1 protease induces autoimmunity caused by the reduction of immunosuppressive Treg cells [19,63]. In addition, combined inactivation of MALT1 scaffolding and protease functions leads to Treg depletion, but the simultaneous loss of effector functions of conventional T cells prevents autoimmune reactions observed by the selective loss of protease function [20]. Thus, MALT1 PROTACs and scaffolding inhibitors may have better safety profiles with regard to autoimmunity, but this may come at the expense of severe immunodeficiency and higher risks for viral, bacterial, or fungal infections as observed in patients with MALT1 deficiencies [86].

The results published by Novartis that sustained MALT1 inhibition leads to loss of peripheral immune tolerance and intestinal inflammation has discouraged further developments of MALT1 inhibitors to treat autoimmune and inflammatory diseases [63]. Of note, these severe on target adverse effects are fully reversible after stopping treatment, also indicating that side effects may be manageable. Further, it needs to be seen if all compounds have similar detrimental effects as described for the MALT1 inhibitors from Novartis that were optimized for very high target occupancy in the circulation. Thus, clinical exploration of potential beneficial effects of MALT1 inhibition is still ongoing and is focused on clinical trials in cancer, especially lymphoid malignancies. In BCR-addicted NHL and CLL, MALT1 acts downstream of most oncogenic driver mutations in the BCR signaling pathway and accordingly, MALT1 inhibitors kill lymphoma cells that are resistant to BTK inhibitors [78,87,88]. Thus, MALT1 inhibitors may be used as an alternative therapy to overcome primary or secondary resistances to BTK inhibitors and simultaneous BTK and MALT1 inhibition may also reduce the chances for developing such drug resistances. Moreover, MALT1 inhibition conferred a stronger dependency on anti-apoptotic BCL2 expression in ABC DLBCL cell models, and combination of MALT1 inhibitor ABBV-525 (AbbVie) with the BCL2 inhibitor venetoclax significantly synergized in killing ABC DLBCL cells in preclinical models [83]. These are encouraging results opening avenues for combining MALT1 inhibition with approved medications for lymphoma therapy. In the future, MALT1 inhibitors may even be added to combinatorial trials like ViPOR (venetoclax, ibrutinib, prednisone, Obinutuzumab (anti-CD20 antibody), and lenalidomide), which aims at curative treatment of relapsed or refractory DLBCL by simultaneous targeting of multiple survival pathways [89]. Overall, the significantly enriched clinical pipeline of MALT1 inhibitors will enable evaluation of druggability of this pathway in cancer and potentially in other diseases in the near future.

Declaration of interest

Authors are employees of Helmholtz Zentrum München. D.K. is an inventor of MALT1 inhibitor patents. 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. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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