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Hikaru Ishikura & James A. Bull

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REVIEW

Synthetic oxetanes in drug discovery: where are we in 2025?

Hikaru Ishikura and James A. Bull

Department of Chemistry, Imperial College London, London, UK

ABSTRACT

Introduction: Oxetanes are increasingly prevalent motifs in medicinal chemistry. While oxetanes feature famously in the taxol family, it was not until the recent approval of rilzabrutinib that they have been validated in a fully synthetic drug. These four-membered oxygen-containing rings are valued for their ability to modulate key physicochemical properties such as polarity, lipophilicity, and metabolic stability. Their incorporation can improve aqueous solubility, reduce metabolic liability, reduce basicity of adjacent amines, and redirect metabolic clearance away from cytochrome P450 enzymes.

Areas covered: This review examines the role of the oxetane in nine clinical candidates, one very recently approved, two recently discontinued clinical candidates, two tool compounds, and three lead compounds disclosed in 2024. Recent advances indexed in SciFinder-n (2017–2024) in the process-scale and laboratory-scale synthetic routes are discussed, highlighting ongoing innovation required to access these motifs efficiently and sustainably.

Expert opinion: The regulatory approval of rilzabrutinib and likely approval of ziresovir provide confidence in using oxetanes as important elements in drug design. While oxetanes have so far been incorporated primarily as pendant groups to optimize physicochemical properties, their use as scaffolding and binding elements presents an exciting opportunity. Enhanced synthetic accessibility to oxetane derivatives will expedite their inclusion in drug discovery campaigns.

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Clinical candidates; medicinal chemistry; neurology; oncology; oxetanes; physicochemical properties; process chemistry; respiratory diseases

1. Introduction

Oxetanes are four-membered oxygen-containing heterocycles that have gained increasing attention in drug discovery. Their features of low molecular weight, high polarity, and three-dimensionality, as well as their effect on molecular properties, have been identified as commonly beneficial in drug design. Their incorporation can lead to improvements in aqueous solubility, target affinity, and overall pharmacokinetic profiles [1,2]. However, the validation in approved drugs, until very recently, has been lacking, which has changed with the approval of Sanofi's rilzabrutinib in September 2025. The beneficial attributes of the oxetane ring have also prompted their exploration as potential isosteric replacements for a variety of functional groups. Early work by Stepan and coworkers at Pfizer investigated 2- and 3-substituted oxetanes as metabolically stable alternatives to tetrahydrofuran scaffolds [3,4].

3,3-Disubstituted oxetanes are particularly well-studied as isosteric replacements and do not introduce a chiral center. Seminal reports from Carreira in collaboration with Rogers-Evans (Roche), demonstrated the utility of oxetanes as replacement groups for *gem*-dimethyl groups, effectively blocking metabolically labile methylene positions without an adverse increase in lipophilicity [5]. Subsequent reports proposed oxetanes as carbonyl replacements, specifically in the case of ketones and cyclic amides, where they maintained similar dipole moment, geometry, hydrogen-bonding capacity, and lipophilicity, while enhancing metabolic stability [6,7]. Aminooxetanes have been examined as peptide bond mimics, offering improved metabolic stability and promoting macrocyclisation [8–14]. In addition, oxetanes have also been evaluated as carbonyl isosteres in diarylketones [15], benzamides [16], thioesters [17–20], carboxylic acids [21], and *N*-acylsulfonamides [22] imparting benefits including improved chemical and metabolic stability, increase in permeability, and decrease in local acidity. Oxetanes have also been proposed as replacements for *tert*-butyl groups, resulting in reduced lipophilicity (Log*D*) and improved metabolic stability compared to the parent compound [23,24].

Duncton demonstrated the metabolic stability of oxetane motifs with more than half of a library of 3-aryloxetanes unreactive with glutathione on incubation with human liver microsomes (HLM) and nicotinamide adenine dinucleotide phosphate (NADPH) cofactor [25]. Further investigations into the metabolic clearance pathway of oxetanes revealed the crucial role of human microsomal epoxide hydrolase (mEH). Ring-opening of the oxetane ring by mEH was identified as a major metabolic pathway for oxetane-containing drug candidate AZD1979 [26,27]. Subsequent studies revealed oxetane metabolism by mEH is not unique to AZD1979, and that oxetanes can be strategically employed to redirect metabolism away from cytochrome P450 enzymes [28,29].

Despite their favorable physicochemical properties, synthetic oxetanes remain underrepresented in approved therapeutics. Importantly, however, oxetanes feature in eight

CONTACT James A. Bull j.bull@imperial.ac.uk Department of Chemistry, Imperial College London, Molecular Sciences Research Hub, White City Campus, Wood Lane, London W12 0BZ, UK

Article highlights

- Oxetanes are becoming increasingly prevalent motifs in medicinal chemistry.
- Oxetanes confer beneficial physicochemical properties due to their low molecular weight, high polarity, and three dimensionality.
- Oxetane has been included as a pendant motif in several oxetane clinical candidates, where the role of the oxetane is known, as well as the recently FDA-approved drug rilzabrutinib to modulate physicochemical properties such as lipophilicity and the basicity of adjacent amines.
- New oxetane-containing lead compounds disclosed in 2024 highlight the potential to use oxetanes to engage residues in hydrophobic pockets.
- While laboratory-scale synthetic access to oxetanes has advanced, further innovation is needed to enable scalable and sustainable routes for commercial manufacturing.

further small-molecule clinical candidates, indicative of the improved confidence in use of this ring system. In this review, we examine the role of the oxetane in United States Food and Drug Administration (FDA) approved rilzabrutinib and clinical candidates (fenebrutinib, BIIB091, docirbrutinib, ziresovir, mevrometostat, crenolanib, ALG-000184, and GDC-0349) as well as the recently discontinued lanraplenib and danuglipron (Figure 1). We also highlight selected oxetane-containing tool compounds and newly disclosed lead structures reported in 2024. In addition, we explore modern synthetic strategies that have enabled access to this increasingly valuable motif. Prior applications in drug discovery up to 2016 and earlier synthetic methods have been comprehensively reviewed elsewhere [1,2,6,7,30–33]. Taxane derivatives, including paclitaxel and docetaxel, are not discussed here, but have been reviewed recently [34]. Readers are further directed to complementary reviews which may be of interest [35–37].

2. Oxetanes in drug discovery

Oxetane-containing clinical candidates were identified using Inxight Drugs [38], with a substructure query filtered for investigational drugs. The results were manually triaged to exclude taxane derivatives and heteroatomic substitution at the 2-position (e.g. β-lactones) and to ensure active development of the clinical candidate. The resulting compounds span a range of therapeutic areas including oncology, neurology, and respiratory diseases. In this section, we classify these candidates based on their protein targets and examine the impact of the introduction of the oxetane moiety on pharmacokinetic properties. Additionally, we highlight key considerations related to process development and successful scale-up associated with these compounds focusing on the requirements of the 4-membered rings.

2.1. Bruton's tyrosine kinase (BTK) inhibitors

The approved drug rilzabrutinib and three of the other oxetane-containing clinical candidates are Bruton's tyrosine kinase (BTK) inhibitors; rilzabrutinib, fenebrutinib, BIIB091, and docirbrutinib.

Rilzabrutinib is a covalent, reversible BTK inhibitor developed by Sanofi, and is a landmark FDA drug approval as the first compound containing the cyanoacrylamide warhead, as well as the first synthetic-oxetane-containing compound [39]. It was approved by the FDA following successful completion of Phase III clinical trials for persistent or chronic immune thrombocytopenia (ClinicalTrials.gov ID: NCT04562766) [40–43]. Rilzabrutinib has also been granted orphan drug designation in the United States for two rare diseases after demonstrating efficacy in Phase II clinical trials for warm autoimmune hemolytic anemia (ClinicalTrials.gov ID: NCT05002777) and IgG4-related disease (ClinicalTrials.gov ID: NCT04520451) [44–46]. In addition, it advanced to Phase III clinical trials for chronic spontaneous urticaria following successful Phase II clinical trials (ClinicalTrials.gov ID: NCT05107115) [47] and met primary and secondary endpoints for Phase II clinical trials in moderate-to-severe asthma (ClinicalTrials.gov ID: NCT05104892). Although rilzabrutinib did not meet primary efficacy endpoints in Phase III trials for pemphigus (NCT05018806) and Phase II trials for atopic dermatitis (NCT05018806), it was well tolerated and demonstrated an acceptable safety profile.

The oxetane moiety was introduced during lead optimization to modulate basicity of a piperazine substituent, while maintaining high solubility and permeability and minimizing efflux [48]. Co-crystallization of rilzabrutinib with BTK revealed distinct roles for the oxetanylpiperazine ring in different binding modes (PDB: 7L5P). In the non-covalent complex, the oxetanylpiperazine ring is solvent exposed, whereas in the covalent complex, it engages in key van der Waals interactions with the glycine-rich loop following binding with Cys481 [48]. These findings highlight the critical contribution of both the piperazine and oxetane moieties to the binding conformation and stability of the covalent complex, as modifications to this region were shown to significantly disrupt binding interactions and resulted in off-target activity.

Fenebrutinib is an orally bioavailable, non-covalent inhibitor of BTK, developed by Genentech. It is currently in Phase III clinical trials for relapsing-remitting (ClinicalTrials.gov ID: NCT04586023, NCT04586010) and primary progressive (ClinicalTrials.gov ID: NCT04544449) multiple sclerosis (MS). In addition, fenebrutinib successfully met the primary endpoint in a Phase II clinical trial for chronic spontaneous urticaria (ClinicalTrials.gov ID: NCT03137069) [49]. It was evaluated in a Phase II clinical trial for systemic lupus erythematosus, however, did not meet the primary end point despite an acceptable safety profile (ClinicalTrials.gov ID: NCT02908100) [50]. The structure of fenebrutinib was first disclosed in 2018, following optimization of a series of BTK inhibitors bearing a tricyclic core [51–53]. A previous generation BTK inhibitor, GDC-0834, suffered from rapid amide bond hydrolysis *in vivo* [54–56], which was mitigated by introduction of the tricyclic core, however, this resulted in low kinetic solubility [51]. During subsequent structure activity relationship (SAR) studies, an oxetane moiety was introduced on a piperazine substituent, located in a partially solvent exposed region of the protein, to reduce the calculated pK_{aH} from 7.8 to 6.3 [51]. Despite achieving high potency, good selectivity, and an acceptable pharmacokinetic profile, the resulting compound, G-278, exhibited dose-limiting hepatotoxicity in rat and dog tolerability studies [52].

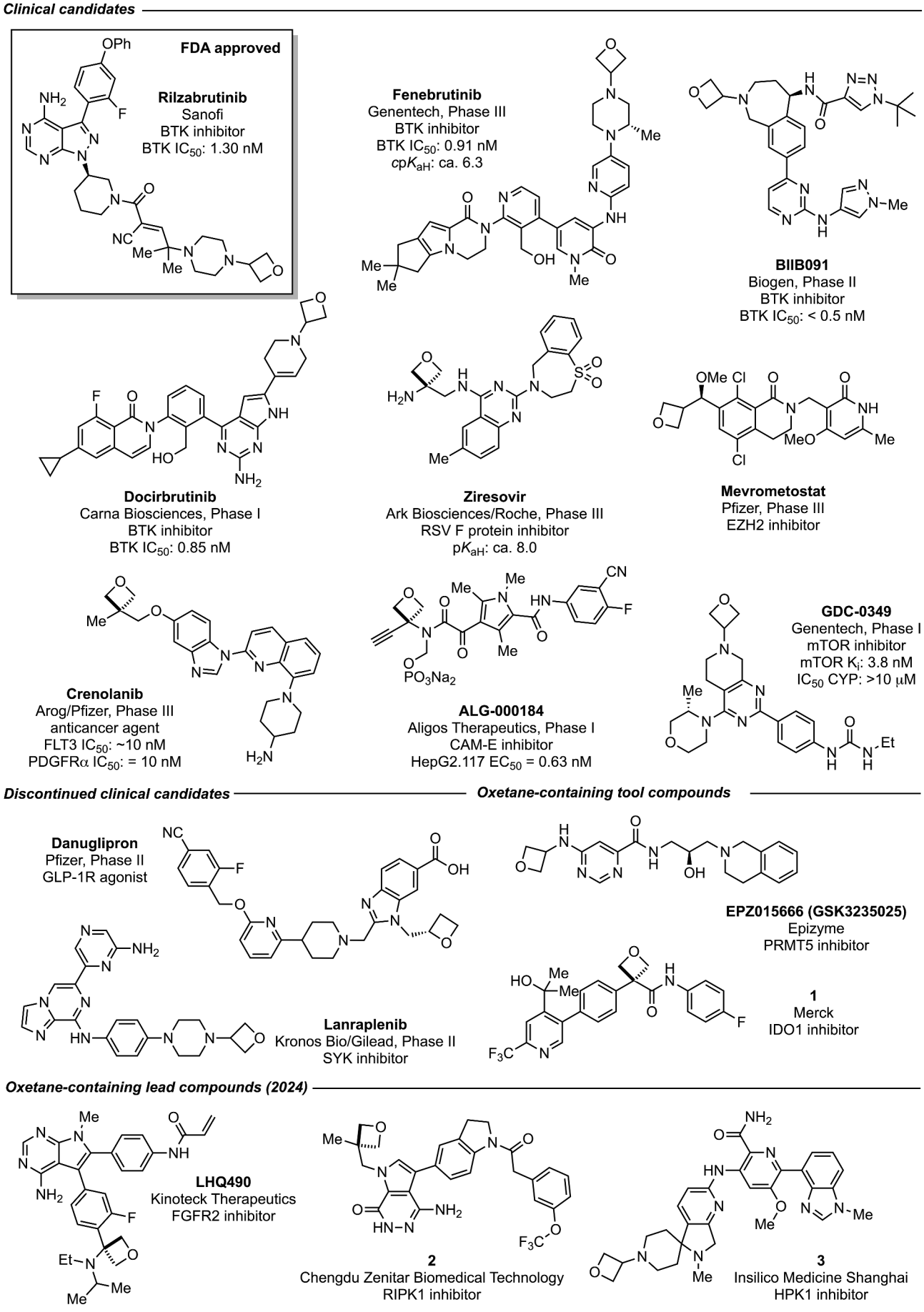

Figure 1. Oxetane-containing FDA approved rilzabrutinib, clinical candidates, danuglipron, and oxetane-containing leads disclosed in 2024.

Following computational modeling, incorporation of an (*S*)-methyl group adjacent to the piperazine nitrogen enhanced van der Waals interactions with the protein surface and imparted conformational rigidity, conferring improved cellular potency and overall pharmacokinetic profile [52,53].

BIIB091 is a non-covalent, reversible BTK inhibitor developed by Biogen. It is currently undergoing Phase II clinical trials for relapsing MS (ClinicalTrials.gov identifier: NCT05798520) [57]. As in rilzabrutinib and fenebrutinib, the oxetane moiety was strategically introduced to modulate amine basicity to prevent off-target effects such as hERG inhibition. The introduction of the oxetane on the benzoazepine core in place of a methyl group led to a decrease in pK_a from 4.0 to 2.8 (c.f. ethylmethoxy, pK_a 3.1; trifluoroethylamine, pK_a 2.7). The oxetane uniquely reduced basicity and conferred improved cell potency, while retaining favorable physicochemical properties including solubility, lipophilicity, and metabolic stability [58]. Co-crystal structures with BTK revealed the oxetane substituent was oriented toward the solvent front, while the benzoazepine core was aligned with the P-loop (PDB: 7LTZ). The 2-aminopyrimidine moiety formed two key hydrogen bonds with Tyr-476 and Met-477 residues in the hinge region, while the amide linker formed a hydrogen bond with Lys-430, enabling the *tert*-butyl-triazole group to sequester Tyr-551 into an inactive conformation, resulting in the observed kinome selectivity for BTK [58].

Docirbrutinib is an orally bioavailable, non-covalent BTK inhibitor developed by Carna Biosciences. It is currently undergoing Phase I clinical trials for chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), or non-Hodgkin's lymphoma (ClinicalTrials.gov identifier: NCT05602363). In this case, introduction of the oxetane moiety on a tetrahydropyridine substituent led improved Caco-2 permeability and an over two-fold increase in potency over the next most active compound of the campaign. Computational modeling studies suggested that the oxetanyltetrahydropyridine ring sits in solvent-exposed region and does not directly participate in binding [59].

2.2. Respiratory syncytial virus fusion protein (RSV F) inhibitor

Ziresovir is an orally bioavailable respiratory syncytial virus (RSV) fusion (F) protein inhibitor originally disclosed by Roche and further developed by Shanghai Ark Biopharmaceuticals. It is currently under priority review by the National Medical Products Administration (NMPA) of China with Breakthrough Therapy designation following successful completion of Phase III clinical trials (ClinicalTrials.gov identifier: NCT04231968) [60]. Ziresovir is notable as the first oral anti-RSV therapy to complete Phase III clinical trials with positive results and the first non-oncology investigational drug to receive Breakthrough Therapy designation by the NMPA.

In 2018, Roche disclosed a series of benzoazepinequnoline derivatives as novel RSV F inhibitors [61]. However, the high lipophilicity and basicity of the amine head group in these compounds led to elevated volumes of distribution (V_{ss}), contributing to undesired bioaccumulation [61]. Introduction of the oxetane ring was described as the 'highlight of the discovery,' reducing the basicity of the adjacent terminal amine from pK_{aH} 10.4 to 8.0 [61,62]. This modification effectively lowered V_{ss} while maintaining high potency [61,62]. Computational docking studies revealed that while the oxetane itself does not directly participate in target binding, the primary amine and secondary amine within the oxetane-containing head group form H-bond interactions with Asp486. The oxetane was found to play a key role in conformational and basicity control. Notably, the oxetane linker was uniquely effective, with alternative alkyl linkers demonstrating lower potency and therapeutic indexes [62].

2.3. Enhancer of zeste homolog 2 (EZH2) inhibitor

Mevrometostat is an orally bioavailable enhancer of zeste homolog 2 (EZH2) inhibitor, developed by Pfizer. It is currently undergoing Phase III clinical trials in combination with enzalutamide for metastatic castrate-resistant prostate cancer that has become resistant to hormone therapy (ClinicalTrials.gov identifier: NCT06551324) and in androgen receptor pathway inhibitor-naïve patients (ClinicalTrials.gov identifier: NCT06629779). In addition, mevrometostat is undergoing Phase I clinical trials for relapsed/refractory small cell lung cancer, castration-resistant prostate cancer, and follicular lymphoma (ClinicalTrials.gov identifier: NCT03460977).

In 2016, Pfizer disclosed a series of pyridone-containing 3,4-dihydroisoquinoline-1(2*H*)-ones as novel enhancers of EZH2 inhibitors [63]. Although the lead compounds from this series displayed exceptionally high potency (IC_{50}: 1.15 nM), they were limited by low metabolic stability in HLM clearance assays and poor thermodynamic solubility. A methoxymethyl-oxetane pendant motif was introduced during SAR optimization as a less lipophilic analog of tetrahydrofuran rings to maximize lipophilic ligand efficiency (LipE) and enhance metabolic stability by reducing Log*D* and increasing three-dimensional character [64]. This modification afforded a compound with an optimal Log*D* of 1.9, as well as improved metabolic stability and solubility. Control of the α-stereocenter was crucial, as the (+)-(*R*) enantiomer exhibited a 16-fold increase in potency compared to the (–)-(*S*) enantiomer. Co-crystal structures with EZH2 revealed potential donor–π interactions between the oxetane ring hydrogens and the Tyr111 side chain, contributing to the increased potency of the oxetane-containing series over other analogues (PDB: 4W2R) [64].

The initial discovery route to protected-mevrometostat (**4**) involved Grignard addition, formed from aryl bromide **5**, to oxetane-3-carboxaldehyde (**6**) followed by resolution by chiral chromatography (Figure 2) [63,64]. In later campaigns, an alternative approach involving oxidation of the alcohol to ketone **7**, followed by enzymatic reduction and methylation was employed. However, the use of oxetane aldehyde **6** posed several challenges for scalability, including high cost, water solubility, and difficulties in distillation due to the high energy and low thermal onset of the fragment. To address these issues, key intermediate **8** was identified to circumvent the use of oxetane aldehyde **6**, while leveraging the selectivity of the ketoreductase to induce enantioselectivity. Ashcroft *et al*. at Pfizer recently reported a robust strategy to access key

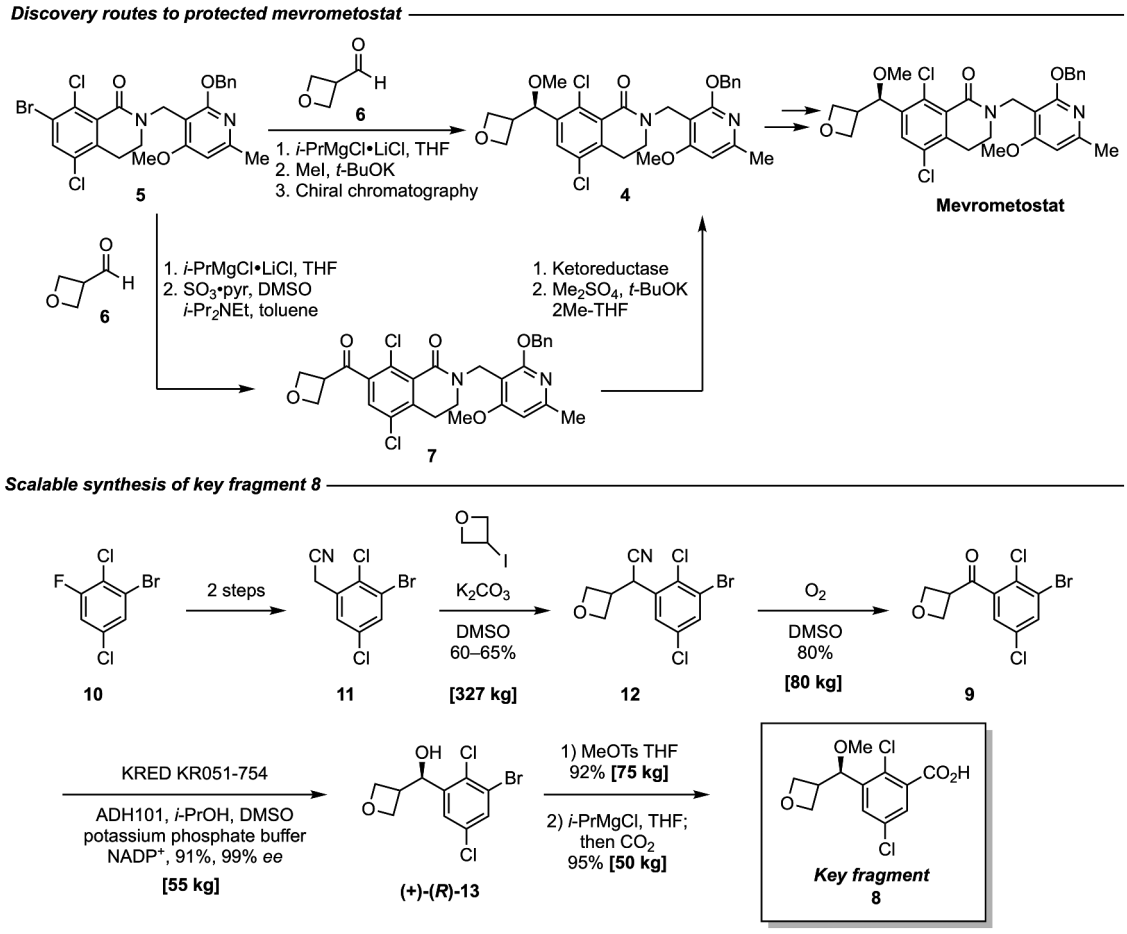

Figure 2. Discovery and process routes to access protected mevrometostat and key intermediate **8**.

intermediate **8** on a 50 kg scale, achieving an overall yield of 28% over seven steps from widely available raw materials [65].

Ultimately, oxidative decyanation was identified as a cost-effective, site-selective, and scalable approach to access oxetane-ketone **9** as a precursor for **8**. Alkylation of arylacetonitrile **11** with 3-iodooxetane afforded oxetane-containing intermediate **12**. It is notable that though significantly less expensive than aldehyde **6**, 3-iodooxetane remained the most expensive reagent in the process. Oxidative decyanation using oxygen gas gave ketone **9**, which was selectively reduced to the (+)-(*R*) enantiomer in 91% yield and 99% purity by an in-house engineered variant of *S. salmonicolor* aldehyde reductase, KRED KR051-754. Methylation, followed by halogen-magnesium exchange and addition into CO_2 gave **8** in 95% yield and 98.5% purity on a 50 kg scale. Notably, during workup, pH was carefully maintained above 2.0 to prevent ring-opening of the oxetane moiety into the corresponding 1,3-diol or 1,3-chloropropanol [65].

2.4. Platelet-derived growth factor receptor (PDGFR) and FMS-like tyrosine kinase 3 (FLT3) inhibitor

Crenolanib is a platelet-derived growth factor receptor (PDGFR) and a type I pan-FMS-like tyrosine kinase 3 (pan-FLT3) inhibitor, discovered by Pfizer and developed by Arog Pharmaceuticals. It is currently undergoing Phase III clinical trials for advanced or metastatic gastrointestinal stromal tumors (GIST) with a D842V mutation in the PDGFR-A gene (ClinicalTrials.gov identifier: NCT02847429) and acute relapsed or refractory acute myeloid leukemia with FLT3 mutations (ClinicalTrials.gov identifier: NCT03250338, NCT03258931) [66–70]. Crenolanib was granted Fast Track designation by the FDA for treatment of GIST and Orphan Drug designation by the European Medicines Agency (EMA) for the treatment of acute myeloid leukemia and soft tissue sarcoma. No further information is currently available on the specific role of the oxetane moiety in crenolanib.

2.5. Capsid assembly modulator

ALG-000184 is an orally bioavailable prodrug of ALG-001075, a potent hepatitis B virus capsid assembly modulator-empty (CAM-E), developed by Aligos Therapeutics. It successfully completed Phase I clinical trials for the treatment of chronic hepatitis B (ClinicalTrials.gov identifier: NCT04536337), with Phase II clinical trials currently planned (ClinicalTrials.gov identifier: NCT06963710). In addition, ALG-000184 is undergoing Phase I clinical trials to probe drug–drug interactions with itraconazole and carbamazepine (ClinicalTrials.gov identifier: NCT06672900).

The oxetane group was introduced during lead optimization studies to prevent glutathione (GSH) adduct formation,

a key metabolic liability observed in previous generations of CAM-Es [71]. Among various strained saturated (hetero)cycles, only the oxetane effectively blocked GSH addition to the neighboring acetylene group, providing the optimal balance of steric and electronic properties. To further improve aqueous solubility, a methylene phosphate ester was appended to the amino-oxetane during the final stages of lead optimization. Computational docking studies suggest the terminal oxetane and propargyl groups are solvent exposed and do not participate in target binding [71]. The favorable pre-clinical profile and success in phase I clinical trials of ALG-000184 has since prompted the development of a related oxetane-containing CAM-E, AIC263282 [72].

2.6. Mammalian target of rapamycin (mTOR) inhibitor

GDC-0349 is an orally bioavailable, selective mammalian target of rapamycin (mTOR) inhibitor, developed by Genentech. It completed phase I clinical trials for locally advanced or metastatic solid tumors or non-Hodgkin's lymphoma; however, no results have been posted (ClinicalTrials.gov identifier: NCT01356173). Subsequent preclinical studies have shown that GDC-0349 also inhibits the proliferation of non-small cell lung cancer cells [73]. The oxetane moiety was introduced during SAR optimization studies to modulate the basicity of a neighboring amine, lowering the pK_{aH} from 7.6 to 5.0, as well as lowering hERG inhibition from IC_{50} of 8.5 nM to > 100 nM [74].

2.7. Recently discontinued clinical candidates

Lanraplenib and danuglipron have recently been discontinued from clinical development, however, offer useful insights into the role of the oxetane motif, and scalable synthesis of oxetane-containing molecules. Lanraplenib was an orally bioavailable spleen tyrosine kinase (SYK) inhibitor, discovered by Gilead Sciences and further developed by Kronos Bio. It was evaluated in Phase I clinical trials for impaired renal function (ClinicalTrials.gov identifier: NCT02959138), and Phase II clinical trials for moderately-to-severely active cutaneous Lupus erythematosus (ClinicalTrials.gov identifier: NCT03134222) and active Sjogren's syndrome (ClinicalTrials.gov identifier: NCT03100942); however, it failed to meet the primary endpoints in these studies [75,76]. Following low enrollment in Phase II clinical trials for lupus membranous nephropathy (ClinicalTrials.gov identifier: NCT03285711) and disappointing results in Phase Ib clinical trials for acute relapsed or refractory acute myeloid leukemia with FLT3 mutations (ClinicalTrials.gov identifier: NCT05028751) lanraplenib was discontinued [77,78].

The oxetane group was introduced as a pendant motif to modulate the basicity of an adjacent piperazine moiety, successfully reducing the calculated pK_{aH} from 8.0 to 6.4 [79]. This modification also enhanced solubility at pH 2.0 and increased Caco-2 permeability, while maintaining the improved metabolic stability and oral bioavailability over the first generation SYK inhibitor Entospletinib.

Danuglipron was an orally bioavailable glucagon-like peptide-1 receptor (GLP-1 R) agonist, developed by Pfizer. It was evaluated in Phase II clinical trials for type 2 diabetes (ClinicalTrials.gov identifier: NCT03985293, NCT04617275, NCT04707313) as a twice daily formulation and in Phase I clinical trials as a once daily formulation (ClinicalTrials.gov identifier: NCT06568731, NCT06567327) [80,81]. Despite meeting key pharmacokinetic objectives, and displaying a safety profile inline with FDA-approved GLP-1 R agents, Pfizer decided to discontinue danuglipron following a single potential drug-induced liver injury and resulting review of clinical data and input from regulators [82]. This follows the discontinuation of Pfizer's first generation oxetane-containing GLP-1 R inhibitor, lotiglipron, due to elevated levels of liver transaminases (ClinicalTrials.gov identifier: NCT05671653, NCT05788328, NCT05579977) [83].

A methylene-linked oxetane group was introduced during the final stages of SAR optimization as a small, polar head group to increase potency, conferring a ~ 100-fold increase in potency compared to a simple methyl group [84]. To overcome limitations such as potential hERG inhibition and suboptimal activity relative to native GLP-1, several derivatives of danuglipron have since been disclosed (Figure 3(a)). In 2024, Huadong Medicine reported that replacement of a benzonitrile group with a 3-phenyloxetane group resulted in improved potency (EC_{50}: 0.12 to 0.03 nM) and reduced hERG inhibition (hERG IC_{50}: 5.8 to 15.9 μM) relative to danuglipron, ultimately yielding lead compound DD202-114 [85]. Similarly, researchers at Zhejiang University found that substitution with a 3-phenyldifluorocyclobutane in the same position enhanced potency (EC_{50}: 0.12 to 0.05 nM), oral bioavailability, and reduced hERG inhibition [86]. Computational docking studies indicated that **14** maintained key polar interactions with LYS197 and ARG380, while the fluorobenzene group reduced steric clash with the protein compared to danuglipron. The oxetane group was also proposed to form hydrophobic interactions with adjacent residues [86]. Alternative optimization efforts have focused on eliminating the terminal carboxylic acid group to mitigate hepatotoxicity, resulting in compound **15** with an EC_{50} of 0.07 nM [87]. Most recently, Chengdu DIAO Pharmaceutical disclosed DA-302168S, featuring combined modification of the terminal benzonitrile group and bridging pyridine group, and replacement of the piperidine group with a fluorobenzene. This candidate demonstrated improved potency (cAMP EC_{50}: 0.12 to 0.03 nM) and significantly reduced hERG inhibition (hERG IC_{50}: > 30 μM) [88]. DA-302168S has successfully completed Phase I clinical trials (ClinicalTrials.gov identifier: NCT06534320, NCT06534346, NCT06541730), with Phase II clinical trials planned (ClinicalTrials.gov identifier: NCT06953063).

The development of danuglipron and structurally related GLP-1 R agonists has prompted significant investment by Pfizer into optimizing the synthesis of PF-06878031, a key oxetane-containing structural fragment of this compound class. (*S*)-Oxetan-2-ylmethyl tosylate **(*S*)-16**, which could be accessed by tosylation of oxetane alcohol **(*S*)-17**, was initially identified as a key fragment for installation of the oxetane functionality [89,90]. Following a systematic retrosynthetic evaluation guided by SELECT criteria (Safety, Environmental, Legal, Economics, Control, and Throughput), five potential synthetic routes were identified: three involved intramolecular cyclization, one involved ring contraction of a bromo-furanone, and one a ring expansion of a chiral epoxide. Only one of the cyclization routes was successful, reacting **(*S*)-18** with KHMDS afforded the benzyl-protected oxetane **(*S*)-**

19 in 36% yield, which was subsequently deprotected under standard hydrogenation conditions to afford oxetane alcohol **(*S*)-17** (Figure 3(b)). While feasible, the overall modest yield rendered it suboptimal for further development [90].

Another viable route was achieved from oxetane ester **rac-21**, formed by ring contraction, and then selective enzymatic hydrolysis to provide the required enantiomer (Figure 3(b)) [90]. From a screen of 230 hydrolases, CES-P1 was identified for further development, with the use of 2-MeTHF as a cosolvent enhancing selectivity and reducing overhydrolysis. Reduction of ester **(*S*)-21** to the corresponding alcohol using $NaBH_4$ in the presence of metal salt additives enabled clean conversion and minimal ring-opening of the oxetane functionality. Purification by distillation afforded the oxetane alcohol **(*S*)-17** in 18% overall yield over three steps.

The final route, progressed on multi kg scales, employed the Corey–Chaykovsky sulfur ylide for ring-expansion of readily available chiral epoxide (*S*)-benzyl glycidyl ether **(*S*)-22** [90]. Post-reaction purification by column chromatography was necessary to remove catalyst poisoning sulfur residues before hydrogenation to afford oxetane alcohol **(*S*)-17** in two steps from commercial epoxide **(*S*)-22** in 49% overall yield.

With the oxetane tosylate **(*S*)-16** in hand, the Pfizer R&D team developed an improved route to key fragment PF-06878031 to improve yield, safety, step count, and sustainability. Key improvements were in reducing process mass intensity (reducing amounts of solvent and excess reagents), eliminating the use of DMF and nitro-functionalized intermediates, and minimizing the number of hydrogenation steps [89]. An initial alkylation of the

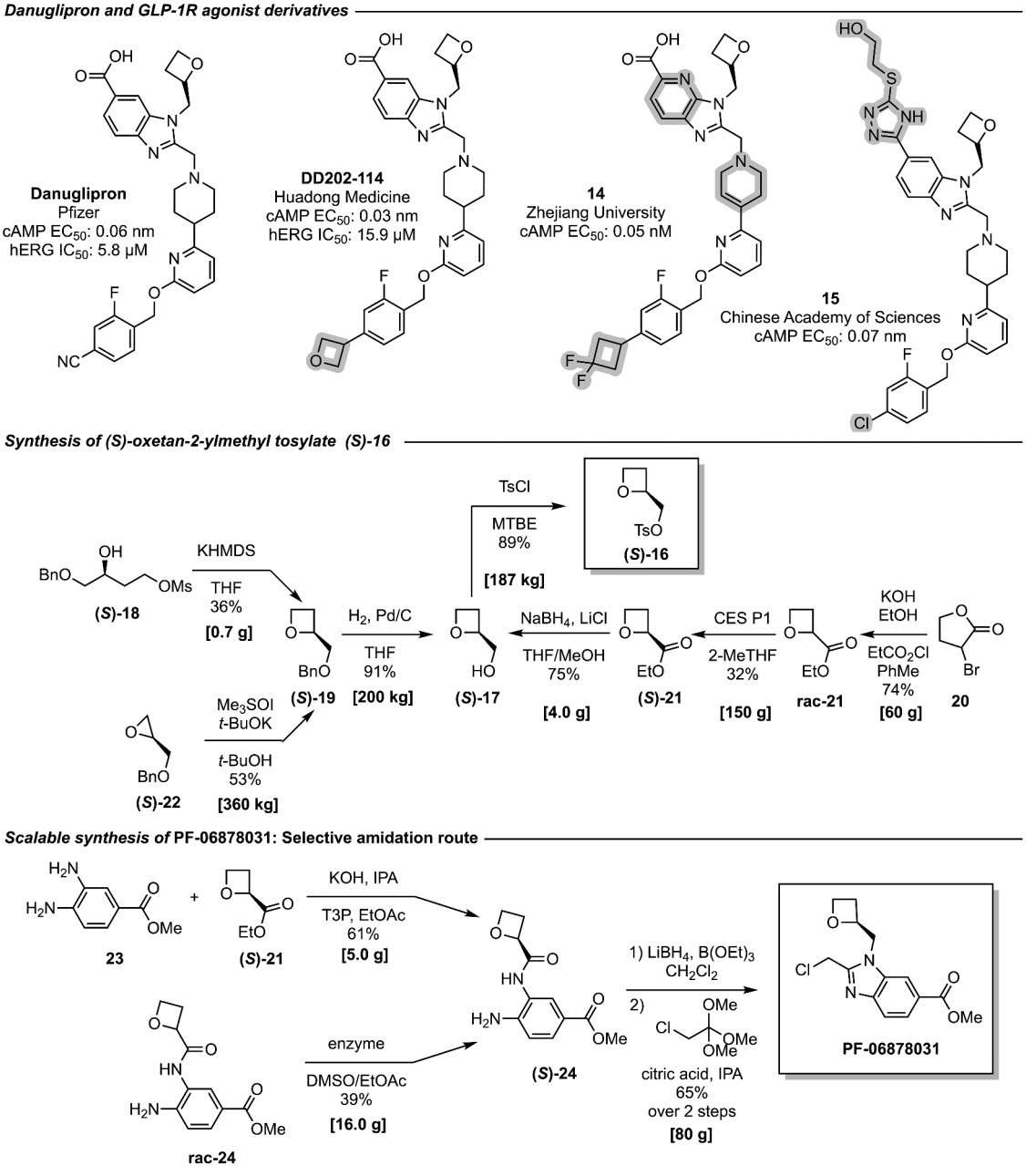

Figure 3. (a) Danuglipron derivatives to improve potency (EC_{50} of cyclic adenosine monophosphate accumulation assay with cells expressing human GLP-1R) and reduce hERG inhibition. (b) Proposed and realized routes to (*S*)-oxetan-2-ylmethyl tosylate **16**. (c) Process scale synthetic routes to PF-06878031.

benzimidazole core, which gave modest regioselectivity, was eventually adapted to an alternative route involving selective amidation [91]. Regioselective mono-amidation of di-aniline **23** was achieved by careful control of the reaction temperature (10°C) using T3P in EtOAc to afford the (*S*)-amide **(*S*)-24** in 61% yield (Figure 3(c)). Conditions for the resolution of oxetane ester **(*S*)-21** were also improved from 34% yield with 93% *ee* using CES-P1 to 41% yield with 99% *ee* using an in-house Pnb esterase enzyme MC050-947. Alternatively, resolution of racemic amide **rac-24**, synthesized under the same conditions from **rac-21**, using esterase ECS-ES10 gave the (*S*)-amide **(*S*)-24** in 98% *ee* and 39% yield. Chemoselective reduction of the amide in the presence of both the ester and oxetane functionalities proved difficult, with a combined borohydride/borate system effective in minimizing reduction of the oxetane. Final cyclization with 2-chloro-1,1,1-trimethoxyethane and citric acid as a catalyst afforded PF-06878031 in 40% overall yield over three steps in 99.9% purity. This selective amidation route offered a significant reduction in cost, as well as removing a hydrogenation step and chromatographic purification, to provide an attractive route for the manufacture of clinical supplies and has been used to generate >1.5 MT of >99% purity of PF-06878031 [91].

2.8. Oxetane-containing tool compounds

Oxetane-containing tool compounds have been suitable for *in vivo* testing of protein arginine methyltransferase 5 (PRMT5) and indole-amine 2,3-dioxygenase (IDO1) inhibition mechanisms. EPZ015866 (GSK3203591) is an orally bioavailable PRMT5 inhibitor, developed by Epizyme. It exhibits high selectivity for PRMT5 over an array of other histone methyltransferases and demonstrated potent antiproliferative effects in both *in vitro* and *in vivo* models mantle cell lymphoma (MCL) [92]. Further metabolic profiling and identification studies revealed low intrinsic clearance in human, mouse, and rat liver microsomes, but higher clearance in dog liver microsomes [93]. The major metabolic pathway was determined to be CYP2D15-mediated oxetane ring scission. The inclusion of the oxetane functionality maintained antiproliferative activity while sufficiently reducing cLog*D* to mitigate clearance by liver microsomes [94]. Taken together, EPZ015866 (GSK3203591) presents a validated chemical probe with favorable human metabolic stability, enabling further investigation into the mechanism of PRMT5 inhibition in cancer and other diseases.

Compound **1** (Figure 3) is a potent indole-amine 2,3-dioxygenase (IDO1) inhibitor suitable for once every 3 weeks oral or parenteral dosing, developed by Merck [95]. Replacement of a cyclobutyl ring in the lead compound, identified in an automated ligand identification screen, with an oxetane significantly improved unbound whole blood potency to 0.09 nM. The oxetane analog also exhibited the lower Alog*P* 98 and higher selectivity compared to other substituents, such as a *gem*-difluorocyclobutane. To enable scale-up, scientists at Merck developed kilogram-scale syntheses of key intermediate 3-(4-bromophenyl)oxetane-3-carboxylic acid, which involved either a tosylation and cyclization approach or a direct Mitsunobu reaction to form the oxetane ring. These optimized synthetic routes enabled access to the 3-aryl oxetane-3-carboxylic acid on a multi-kilogram scale in 19% overall yield over six steps for the tosylate displacement route or 18% overall yield over three steps for the Mitsunobu route, representing a significant improvement over the previously reported 3% overall yield [95].

2.9. Oxetane-containing lead compounds from 2024

Oxetanes are now routinely screened in drug discovery campaigns during SAR optimization. To examine the recent applications, the medicinal chemistry literature was surveyed for relevant reports in 2024 featuring oxetanes as a substructure using SciFinder-n, excluding taxane derivatives and heteroatomic substitution at the 2-position (e.g. β-lactones). For the purposes of this study, the literature was limited to journal articles published in the following journals: *ACS Medicinal Chemistry Letters*, *Bioorganic and Medicinal Chemistry*, *Bioorganic and Medicinal Chemistry Letters*, *ChemMedChem*, *European Journal of Medicinal Chemistry*, *Journal of Medicinal Chemistry*, *Medicinal Chemistry Research*, *MedChemComm*, and *RSC Medicinal Chemistry*. The search was further filtered to include only cases where the substance role was biological study, therapeutic use, pharmacological activity, biological study (unclassified), pharmacokinetics, and biological use (unclassified). The resulting publications were then manually triaged to ensure only synthetic oxetane compounds meeting the above criteria were included. Among the 46 medicinal chemistry publications in 2024 that included oxetanes in screening, three ultimately selected an oxetane-containing compound as their final lead. Notably, in two of these cases, the oxetane moiety was employed to directly engage residues in a hydrophobic pocket; representing a novel application distinct from that observed in the clinical candidates discussed earlier, where oxetanes were primarily used as a pendant motif to modulate physicochemical properties.

LHQ490 is a fibroblast growth factor receptor 2 (FGFR2) inhibitor developed by Kinoteck Therapeutics. A co-crystal of an earlier lead compound with FGFR2 revealed that a 4-methylpyrimidine moiety extended into a hydrophobic back pocket defined by Met538 and Phe645 residues (PDB: 8STG) [96]. To optimize interactions with this pocket, the 4-methylpyrimidine was replaced with an oxetane functionality. This modification significant improved potency against IL-3 independent BaF3 cells expressing FGFR2 (BaF3-FGFR2), while enhancing selectivity over both parental BaF3 and BaF3-FGFR1 cell lines. Computational modeling further confirmed that LHQ490 retains a key hydrogen bond with FGFR2 hinge residue Glu565 and that the oxetane moiety engages the hydrophobic back pocket as intended [96].

Compound **2** (Figure 1) is a type-II receptor-interacting serine/threonine-protein kinase 1 (RIPK1) inhibitor developed by Chengdu Zenitar Biomedical Technology. An oxetane substituent was introduced on the N1 position to engage a polar Asn99 residue near the hydrophobic pocket, which maintained the RIPK1 potency and increased the partial antinecroptotic cellular efficacy [97].

Compound **3** (Figure 1) is a hematopoietic progenitor kinase 1 (HPK1) inhibitor developed by Insilico Medicine Shanghai. During SAR optimization of a spirocyclic ring located in the solvent-exposed region, replacement with

a pendant oxetane moiety yielded a compound with comparable enzymatic inhibition, cellular potency, and germinal center kinase-like kinase selectivity [98]. Importantly, this modification also led to improved metabolic stability and enhanced oral bioavailability relative to other spirocyclic analogues tested.

3. Modern synthetic strategies to access oxetanes

The attractive nature of oxetanes for medicinal chemistry has driven the development of synthetic methodologies toward a wider range of oxetane scaffolds. Approaches that can strategically introduce oxetanes at different synthetic stages, as well as an understanding of the stability of the ring to the synthetic conditions is important to accelerate discovery.

Expanding the scope of the literature search carried out in Section 2.9 to encompass the period of 2017–2024 identified 273 relevant reports featuring oxetanes as a substructure. Mono-3-substituted oxetanes and spiro-oxetanes were the most frequently encountered, followed by 3,3-disubstituted and mono-2-substituted variants. In most cases, the oxetane motifs were derived directly from simple, commercially available reagents. Among the 155 publications that described synthetic procedures, the most commonly used building block was 3-amino-oxetane (41 instances), introduced via amide coupling, Buchwald–Hartwig cross-coupling, reductive amination, S_NAr, and related transformations (Figure 4). This was followed by oxetanone (25 instances), employed primarily in reductive aminations and organometallic additions to yield 3,3-disubstituted oxetanols. Oxetanes bearing a leaving group at the 3-position (23 instances) were typically introduced via transition-metal-catalyzed cross-coupling reactions. Oxetan-3-ol (11 instances) was also utilized as a nucleophile. For spirocyclic systems, 2-oxa-6-azaspiro[3.3]heptane (22 instances) was frequently employed to install spiro-oxetane units, using similar chemistry to that of 3-amino-oxetane, starting from either the free amine or its (hemi)oxalate salt.

The stability of oxetane rings toward ring-opening is often a subject of scrutiny. While 3,3-disubstituted oxetanes are generally considered more robust, their stability remains difficult to predict and can be context-dependent. The successful incorporation of oxetanes into multiple clinical candidates suggests that ring instability is not an intrinsic liability; however, reactivity has only been studied on a case-by-case basis. Reports of ring-opening events are typically influenced by the nature of adjacent substituents, the presence or absence of peripheral basic sites, and, notably, the proximity of internal nucleophiles [99]. For instance, β-oxetane carboxylic acids have been shown to undergo isomerization into lactones via intramolecular ring-opening and subsequent cyclization [100]. Likewise, under strongly acidic conditions, internal nucleophiles such as hydroxyl or amine groups can trigger ring-opening and further intramolecular cyclization, leading to structural rearrangements or degradation [101–104].

Recently, scientists at Enamine released a comprehensive analysis of the chemical stability of the oxetane core to common transformation in medicinal chemistry on a kilogram-scale (Figure 4) [105]. Transformations were categorized into eight distinct classes: C–C/C = C/C ≡ C bond formation, reactions with electrophiles, reactions with nucleophiles, reactions with acidic catalyst, reactions in alkaline media, reduction, oxidation, and hydrogenation. They found C–C/C = C/C ≡ C bond formation, reactions with electrophiles, reactions in alkaline media, and oxidation reactions proceeded smoothly with no extra precautions necessary to accommodate the oxetane core. Reactions with nucleophiles, reactions with acidic catalyst, and hydrogenation required some optimization to suppress ring-opening of the oxetane and ensure high yields. Notably, significant difficulties were encountered in the use of aluminum and boron hydride reagents to reduce neighboring functionalities due to concurrent reduction of the oxetane ring. For examples, temperatures between −10 and −30°C were found to be necessary with $LiAlH_4$ for the reduction of an ester to an alcohol, although $NaBH_4$ could be employed at 0°C as a milder alternative. Nonetheless, the oxetane ring was found to be broadly stable across a range of reaction conditions, enabling the successful synthesis of over 100 novel oxetane-containing fragments.

To capture the synthetic efforts of the wider community, the scope of the literature search was further broadened to include journal articles published in English in all MEDLINE-indexed journals. This section highlights selected recent innovations in oxetane synthesis from the above search, while referring readers to comprehensive reviews for in-depth coverage of earlier methods [30–33].

3.1. Synthesis of mono-substituted oxetanes

Mono-substituted oxetanes are most commonly synthesized by displacement of a leaving group in the 3-position. Alternative functionality can be installed through transition-metal catalyzed cross-coupling reactions or radical coupling reactions, such as the Minisci or Giese-type reactions, from 3-halo-oxetanes [25,106]. 3-Amino-oxetanes can be accessed either from the 3-amino-oxetane through amide-coupling, Buchwald-Hartwig, or S_NAr reactions or alternatively from reductive amination of oxetan-3-one. Recently, Grygorenko disclosed an S_NAr-based approach beginning from 3-cyano-oxetane [107]. In this method, deprotonation at the 3-position followed by nucleophilic attack into electron-deficient heteroarenes and subsequent hydrolysis and decarboxylation enabled the multi-gram synthesis of 3-heteroaryl-substituted oxetanes.

3.2. Synthesis of disubstituted oxetanes

Disubstituted oxetanes have traditionally been synthesized via cyclization strategies, including Williamson etherification and Paternò–Büchi cyclization [30,108]. Recent advances have improved access to the required 1,3-diol precursors for the former method [109,110], while significant progress in visible-light-mediated Paternò–Büchi reactions has been made by Ouyang [111], Dell'Amico [112], Schindler [113], and Yoon [114].

In their seminal reports, Carreira and coworkers at Roche described the synthesis of various 3,3-disubstituted oxetanes through nucleophilic attack on oxetane Michael acceptors,

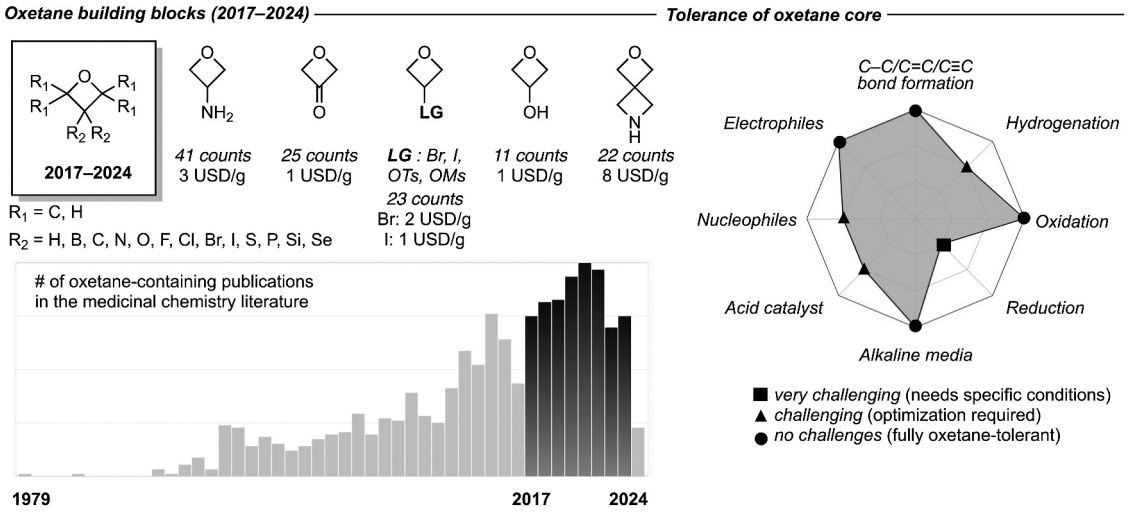

Figure 4. (a) Building blocks utilized to access oxetane scaffolds in medicinal chemistry. (b) Tolerance of the oxetane core towards common synthetic transformation in medicinal chemistry.

which are conveniently prepared in a single step from oxetan-3-one [5–7]. This strategy was employed in peptidomimetics for the synthesis of oxetane-containing amino acid building blocks [8–11], which can offer benefits such as enhanced macrocyclization efficiency and increased stability to enzymatic degradation [12,13]. This approach is also routinely found in small molecule drug discovery campaigns to access amino-oxetanes, including in the preparation of amino-oxetane containing N^6-methyladenosine demethylase fat mass- and obesity-associated protein inhibitor [115]. More recent developments have focused on the catalytic enantioselective addition to oxetane Michael acceptors using chiral organocatalysts such as thioureas [116], *N*-sulfinylureas [117], squaramides [118], and peptides [119]. The resulting products can undergo cyclization to yield enantioenriched oxetane spirocycles, an emerging and synthetically valuable motif.

The growing interest in amino-oxetane motifs, both as potential amide isosteres and as valuable motifs in their own right, has driven significant synthetic innovation (Figure 5(a)). Brubaker and Ellman independently developed methods for the arylation of oxetane imines to access primary amino-oxetanes, through the use of organometallic reagents or Rh catalysis [120,121]. Huestis and Terret developed a complementary approach using a dual photoredox/nickel-catalyzed system for the decarboxylative arylation of 3-amino-oxetane 3-carboxylic acids [122]. Further functionalization of these primary amino-oxetanes was demonstrated by Fessard and Salomé [123]. More recently, Bull reported a defluorosulfonylation reaction of oxetane sulfonyl fluorides to reveal an oxetane carbocation, which was efficiently trapped by a range of nucleophiles including amines, heterocycles, sulfoximines, and phosphonates [124,125]. This methodology was exploited by Leeper in the synthesis of pyruvate dehydrogenase inhibitors, wherein the oxetane coordinates the Mg^{2+} ion, affording improved inhibition and enhanced esterase stability relative to traditional amide linkers [126]. Zhang published a complementary methodology, exploiting oxetanyl trichloroacetimidates to access oxetane carbocations in a transformation reminiscent of the Schmidt glycosylation, suitable for reaction with aniline, alcohol, and phenol nucleophiles [127]. Alternatively, Soós employed Katritzky's benzotriazole chemistry for the strain-release functionalization of spring-loaded oxetane Mannich adducts with secondary amines [128]. Similarly, Koh and Gaunt have independently shown single-electron reduction of oxetane iminium ions and subsequent trapping can yield amino-oxetanes in a single step from oxetan-3-one [129,130].

3,3-Diaryloxetanes have been studied as attractive isosteres for diaryl ketones, offering mitigation of electrophilic and photochemical liabilities, and have also shown promise as alternatives to diaryl methylene, *gem*-dimethyl, and cyclobutanes [15]. Bull developed a lithium-catalyzed Friedel–Crafts alkylation of oxetanols, generating the oxetane carbocation via selective C–OH bond cleavage to enable access to electron-rich diaryloxetanes (Figure 5(b)) [131]. In a complementary strategy, Baran recently reported the bidirectional functionalization of oxetane α-bromo acids, allowing for the synthesis of electron-deficient and diheteroaryl oxetanes [132].

Recent efforts have focused on merging the advantageous features of the oxetane ring with fluorine, a key element in drug design. Grygorenko developed 2-substituted 3,3-difluoroxetanes as a promising fluorinated motifs and non-classical isostere of numerous functional groups, including the *tert*-butyl group [133]. Intramolecular nucleophilic substitution of 2,2-difluoro-3-haloalcohols afforded 2-substituted 3,3-difluoroxetane building blocks on multi-gram scales. Chan, Liu, and Koh have reported the synthesis of an alternative regioisomer of this interesting building block, a 3-substituted 2,2-difluoroxetane, via difluorocarbene insertion into epoxides [134].

The renaissance of single-electron transformations in synthetic chemistry has significantly expanded the retrosynthetic disconnections available for incorporating oxetanes into complex scaffolds. The commercial availability of 3-methyloxetane-3-carboxylic acid has led to its use as a substrate in broader reaction scopes [135–138]. Notably, scientists at Janssen have showcased the utility of MacMillan's metallaphotoredox

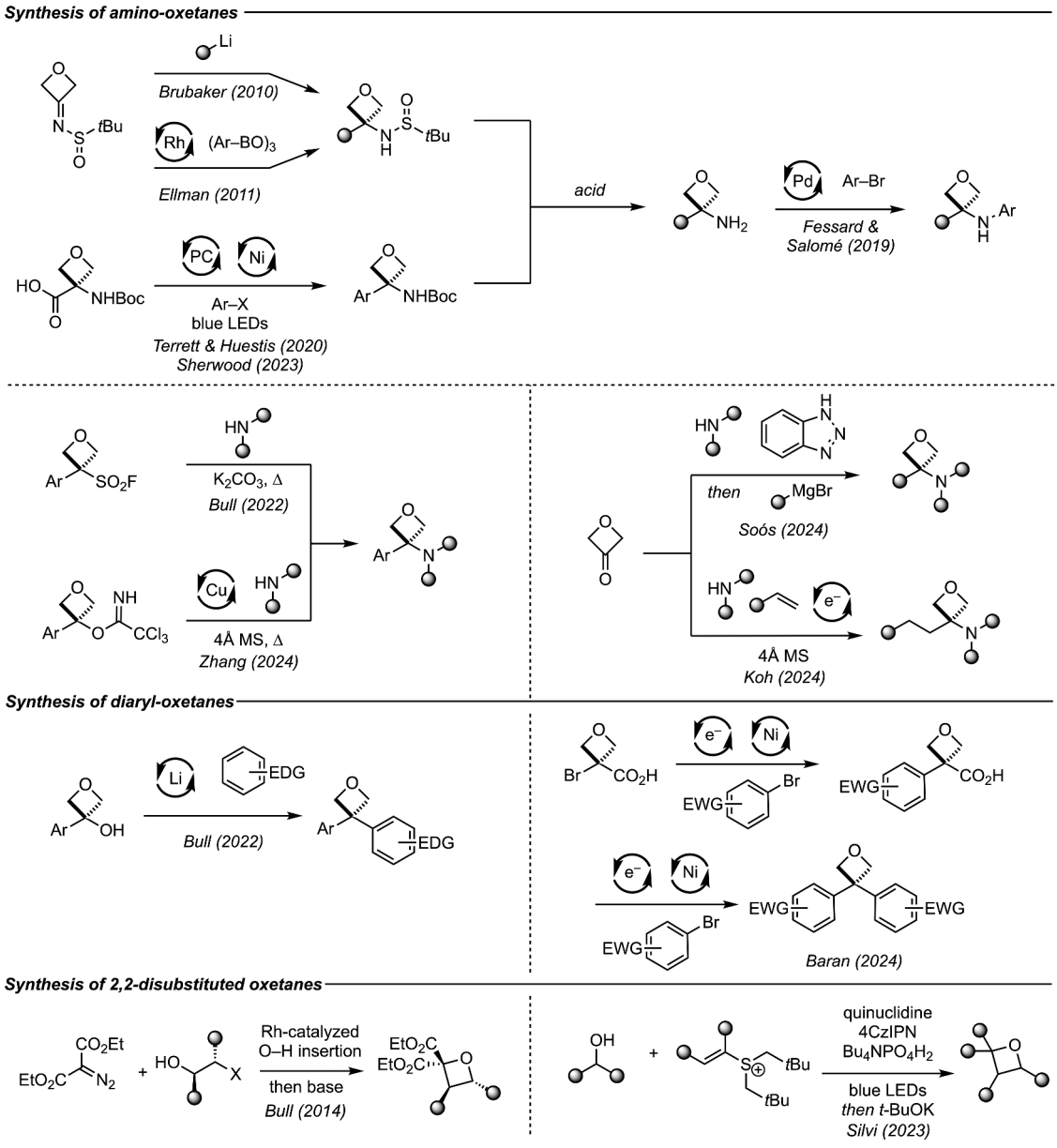

Figure 5. Selected recent advances in the synthesis of disubstituted oxetane derivatives. (a) Amino-oxetanes. (b) Diaryloxetanes. c) 2,2-Disubstituted oxetanes.

deoxygenative coupling chemistry in an automated high-throughput workflow, underscoring its potential for rapid oxetane-based library synthesis [139,140].

Shenvi developed a strategy involving hydrogen atom transfer from an iron species to an oxetane alkylidene species to generate the tertiary radical, which is then trapped by a nickel species for arylation [141]. Another approach by Ackermann and Johansson demonstrated Ru-catalyzed late-stage *meta*-C–H functionalization of complex drug molecules with oxetanes [142]. Furthermore, Bull conducted in-depth studies on the reactivity of tertiary benzylic oxetane radicals, concluding that these benzylic radicals occupy a unique zone of stability that promotes reactivity while minimizing decomposition [143]. Additionally, analogous decarboxylative functionalization has been demonstrated at the 2-position of the oxetane ring [144].

Although these 2,2-disubstitued systems are less studied, several robust methodologies have been developed for their synthesis. Bull demonstrated cyclization strategies to access a diverse array of 2,2-disubstituted oxetanes Rh-catalyzed carbene O–H insertion followed by C–C bond formation [145–147]. Alternatively, Silvi reported the radical addition of an α-hydroxyl radical to an activated alkene, followed by *in situ* cyclization to furnish the 2,2-disubstituted oxetane [148].

Spirocyclic oxetanes can be accessed through similar strategies to other disubstituted oxetanes, such as the Paternó-Büchi reaction or Michael addition followed by cyclization [116–119,149]. Alternative approaches involve [2 + 2] or [3 + 2] cycloadditions from suitable oxetane alkylidene precursors [150–156]. In medicinal chemistry, however, spirocyclic oxetanes are most frequently introduced using the commercially available 2-oxa-6-azaspiro[3.3]heptane amine-building block

[1,6,157–159]. Recent improvements in its synthesis, such as isolating the compound as the sulfonate salt instead of the oxalate salt [160], as well as reports of scalable, cost-efficient procedures have further enhanced the utility of this spirocyclic oxetane motif [161–163].

4. Conclusion

Oxetanes have emerged as versatile and increasingly valuable motifs in drug discovery and development due to their potential to modulate physicochemical properties. Initial studies highlighted oxetanes as isosteric replacements for *gem*-dimethyl and carbonyl groups, owing to their polarity and favorable metabolic stability. More recently, oxetanes have been widely employed in drug discovery as pendant groups to fine-tune physicochemical properties; improving solubility (as exemplified by mevrometostat) or reducing amine basicity (as seen in BTK inhibitors like rilzabrutinib, ziresovir, and GDC-0349) without compromising lipophilicity or metabolic clearance. The recent FDA approval of oxetane containing rilzabrutinib and the presence of oxetanes in eight other small molecule clinical candidates is a testament to their utility in modern drug discovery. The successful process-scale synthesis of several oxetane-containing clinical candidates reinforces their practical viability, with interest and application of this motif expected to grow. Furthermore, the synthetic accessibility of oxetane scaffolds has significantly improved, enabling broader exploration in SAR studies.

5. Expert opinion

FDA approval of the first fully synthetic oxetane-containing drug, Rilzabrutinib, was granted while we were writing this review, and further approvals appear imminent. Rilzabrutinib remains under regulatory review in the EU [43]. Ziresovir is also under regulatory review in China, with Shanghai Ark Biopharmaceuticals partnering with WuXi STA for commercial supply [164]. In parallel, data from the Phase III clinical trials for fenebrutinib and mevrometostat are expected by the end of 2025 [165–167]. These crucial developments will further bolster confidence in the broader adoption of oxetanes as a viable motif in drug development.

Among the clinical candidates outlined in this review, the oxetane was introduced to modulate neighboring amine basicity in five compounds, influence neighboring acetylene reactivity in one compound, and to adjust lipophilicity and permeability in the other two compounds. The inductive electron-withdrawing nature of the oxetane significantly lowers the pK_{aH} of nearby basic groups (by approximately 2.7 units when positioned α, 1.9 units when β, 0.7 units when γ, and 0.3 units when δ) allowing for modulation or elimination of basicity-related liabilities. Structurally, the three sp^3 -hybridized tetrahedral carbon atoms contribute to enhanced molecular three-dimensionality, which can improve aqueous solubility, while their small size and high polarity, can shield metabolically vulnerable positions without substantially increasing molecular weight or lipophilicity. Moreover, the moderate ring strain of oxetanes may be harnessed to steer metabolic clearance toward mEH rather than cytochrome P450 enzymes, reducing the risk of drug–drug interactions and associated hepatotoxicity.

This use as a pendant motif contrasts with the earlier literature [5–7], where oxetanes were primarily investigated as isosteric replacements. Nonetheless, their hydrogen-bonding resemblance to carbonyl groups positions oxetanes still as promising carbonyl bioisosteres, offering potential benefits such as improved solubility, avoidance of carbonyl-specific metabolic degradation, and novel IP opportunities. However, the geometrical differences, notably in carboxylic acid derivatives, based on different preferred dihedral angles suggest applications as different design elements may be more productive. Two lead compounds disclosed in 2024 have demonstrated the potential for oxetanes to engage polar residues in hydrophobic pockets [96,97]. Taken together, these findings underscore the untapped versatility of the oxetane scaffold to fulfill multiple roles in drug design.

While significant advances have been made in developing synthetic methodology for accessing oxetane derivatives on a laboratory-scale, scaling up remains a significant challenge, as demonstrated by work from Pfizer and Merck on PF-06821497 [65], PF-06878031 [89–91], and the IDO1 inhibitors [95]. The current availability of oxetane building blocks suitable for process-scale transformations is limited, with many being cost-prohibitive or requiring bespoke in-house synthesis. More cost-effective and scalable routes to access complex oxetane intermediates are still required.

Furthermore, despite significant methodological progress, achieving specific substitution patterns on oxetanes remains synthetically challenging. While late stage oxetane ring construction can be effective, it typically results in linear synthetic routes that limit the rapid generation of analogues. Thus, the continued innovation in synthetic methodology is essential to enable broader exploration of diverse oxetane scaffolds during hit-to-lead and lead optimization efforts. This includes new reagents for the introduction of different oxetane classes, with varied and different substitution patterns, and to facilitate facile late stage diversification.

Finally, oxetane rings can be susceptible to ring-opening, particularly under acidic or high-temperature conditions. While 3,3-disubstituted oxetanes are generally more robust, even these can undergo ring-opening in the presence of properly located internal nucleophiles (e.g. alcohols or amines to form 5 or 6 membered rings) under acidic conditions. Instability under harsh conditions may also complicate multistep, large-scale synthesis. Consequently, oxetanes are often installed in the later stages of synthesis to avoid subjecting the oxetane functionality to various reaction and work-up conditions. In this context, systematic evaluations of oxetane core stability under common synthetic conditions, such as those recently undertaken by Enamine, along with more data on different oxetane classes are valuable for expanding their reliable use in synthetic workflows [105]. More comprehensive and systematic data on the pharmacological and ADME profiles of oxetane-containing compounds are also needed to inform structure–property relationships and improve predictive accuracy in medicinal chemistry.

Moreover, despite the growing popularity in small molecular drug discovery, with 273 publications reporting oxetanes as a substructure since 2017, their applications in drug discovery platforms such monoclonal antibodies (mAbs) and RNA-targeted drugs remain underexplored. Encouragingly, proof-of-concept studies have demonstrated the site-selective incorporation of oxetanes into proteins and antibodies, with early data suggesting enhanced immunogenic activity and increased resistance to proteolytic degradation [19,20]. Similarly, oxetane-modified antisense oligodeoxyribonucleotides have shown potential as gene-silencing agents [168]. These findings indicate that there is untapped utility of oxetanes in biologics and nucleic acid therapeutics representing a promising frontier for future research and development.

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ORCID

Hikaru Ishikura http://orcid.org/0000-0003-2057-6341
James A. Bull http://orcid.org/0000-0003-3993-5818

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Carreira EM, Fessard TC. Four-membered ring-containing spirocycles: synthetic strategies and opportunities. Chem Rev. 2014;114(16):8257–8322. doi: 10.1021/cr500127b
2. Bauer M R, Fruscia PD, Lucas Sc C, et al. Put a ring on it: application of small aliphatic rings in medicinal chemistry. RSC Med Chem. 2021;12(4):448–471. doi: 10.1039/D0MD00370K
3. Stepan AF, Karki K, McDonald WS, et al. Metabolism-directed design of oxetane-containing arylsulfonamide derivatives as γ-secretase inhibitors. J Med Chem. 2011;54(22):7772–7783. doi: 10.1021/jm200893p
4. Stepan AF, Kauffman GW, Keefer CE, et al. Evaluating the differences in cycloalkyl ether metabolism using the design parameter "lipophilic metabolism efficiency" (LipMete) and a matched molecular pairs analysis. J Med Chem. 2013;56(17):6985–6990. doi: 10.1021/jm4008642
5. Wuitschik G, Rogers-Evans M, Müller K, et al. Oxetanes as promising modules in drug discovery. Angew Chem Int Ed. 2006;45(46):7736–7739. doi: 10.1002/anie.200602343

•• **Seminal work by Carreira and F. Hoffmann–La Roche proposing oxetanes as valuable motifs for drug discovery.**

6. Wuitschik G, Carreira EM, Wagner B, et al. Oxetanes in drug discovery: structural and synthetic insights. J Med Chem. 2010;53(8):3227–3246. doi: 10.1021/jm9018788

• **Early work by Carreira and F. Hoffmann–La Roche detailing the synthesis of various oxetane-containing building blocks and the effect of oxetanes on physicochemical properties.**

7. Burkhard JA, Wuitschik G, Rogers-Evans M, et al. Oxetanes as versatile elements in drug discovery and synthesis. Angew Chem Int Ed. 2010;49(48):9052–9067. doi: 10.1002/anie.200907155

• **Early minireview by Carreira and F. Hoffmann–La Roche offering a perspective on oxetanes as valuable motifs for drug discovery.**

8. McLaughlin M, Yazaki R, Fessard TC, et al. Oxetanyl peptides: novel peptidomimetic modules for medicinal chemistry. Org Lett. 2014;16(16):4070–4073. doi: 10.1021/ol501590n
9. Möller GP, Müller S, Wolfstädter BT, et al. Oxetanyl amino acids for peptidomimetics. Org Lett. 2017;19(10):2510–2513. doi: 10.1021/acs.orglett.7b00745
10. Powell NH, Clarkson GJ, Notman R, et al. Synthesis and structure of oxetane containing tripeptide motifs. Chem Commun. 2014;50(63):8797–8800. doi: 10.1039/C4CC03507K
11. Beadle JD, Knuhtsen A, Hoose A, et al. Solid-phase synthesis of oxetane modified peptides. Org Lett. 2017;19(12):3303–3306. doi: 10.1021/acs.orglett.7b01466
12. McDougall L, Draper ER, Beadle JD, et al. Enzymatically-stable oxetane-based dipeptide hydrogels. Chem Commun. 2018;54(14):1793–1796. doi: 10.1039/C7CC09701H
13. Roesner S, Saunders GJ, Wilkening I, et al. Macrocyclisation of small peptides enabled by oxetane incorporation. Chem Sci. 2019;10(8):2465–2472. doi: 10.1039/C8SC05474F
14. Roesner S, Beadle JD, Tam LKB, et al. Development of oxetane modified building blocks for peptide synthesis. Org Biomol Chem. 2020;18(28):5400–5405. doi: 10.1039/D0OB01208D
15. Dubois MAJ, Croft RA, Ding Y, et al. Investigating 3,3-diaryloxetanes as potential bioisosteres through matched molecular pair analysis. RSC Med Chem. 2021;12(12):2045–2052. doi: 10.1039/D1MD00248A
16. Ishikura H, Begg CS, Rojas JJ, et al. Do amino-oxetanes resemble amides? A matched molecular pairs property and structural comparison [internet]. ChemRxiv; 2025 [cited 2025 Sep 16]. Available from: https://chemrxiv.org/engage/chemrxiv/article-details/68b042f2a94eede1541acb03
17. Croft RA, Mousseau JJ, Choi C, et al. Lithium-catalyzed thiol alkylation with tertiary and secondary alcohols: synthesis of 3-sulfanyl-oxetanes as bioisosteres. Chem: Eur J. 2018;24(4):818–821. doi: 10.1002/chem.201705576
18. Ellis BD, Milligan JC, White AR, et al. An oxetane-based polyketide surrogate to probe substrate binding in a polyketide synthase. J Am Chem Soc. 2018;140(15):4961–4964. doi: 10.1021/jacs.7b11793
19. Boutureira O, Martínez-Sáez N, Brindle KM, et al. Site-selective modification of proteins with oxetanes. Chem: Eur J. 2017;23(27):6483–6489. doi: 10.1002/chem.201700745
20. Martínez-Sáez N, Sun S, Oldrini D, et al. Oxetane grafts installed site-selectively on native disulfides to enhance protein stability and activity in vivo. Angew Chem Int Ed. 2017;56(47):14963–14967. doi: 10.1002/anie.201708847

• **Proof-of-concept studies on the grafting of oxetanes to proteins to resulting in enhanced protein stability and immunogenic activity.**

21. Lassalas P, Oukoloff K, Makani V, et al. Evaluation of oxetan-3-ol, thietan-3-ol, and derivatives thereof as bioisosteres of the carboxylic acid functional group. ACS Med Chem Lett. 2017;8(8):864–868. doi: 10.1021/acsmedchemlett.7b00212
22. Francisco KR, Varricchio C, Paniak TJ, et al. Structure property relationships of N-acylsulfonamides and related bioisosteres. Eur J Med Chem. 2021;218:113399. doi: 10.1016/j.ejmech.2021.113399
23. Barnes-Seeman D, Jain M, Bell L, et al. Metabolically stable tert-butyl replacement. ACS Med Chem Lett. 2013;4(6):514–516. doi: 10.1021/ml400045j
24. Mukherjee P, Pettersson M, Dutra JK, et al. Trifluoromethyl oxetanes: synthesis and evaluation as a tert-butyl isostere. ChemMedChem. 2017;12(19):1574–1577. doi: 10.1002/cmdc.201700333

25. Duncton MAJ, Estiarte MA, Tan D, et al. Preparation of aryloxetanes and arylazetidines by use of an alkyl–aryl Suzuki coupling. Org Lett. 2008;10(15):3259–3262. doi: 10.1021/ol8011327
26. Li X-Q, Hayes MA, Grönberg G, et al. Discovery of a novel microsomal epoxide hydrolase–catalyzed hydration of a spiro oxetane. Drug Metab Dispos. 2016;44(8):1341–1348. doi: 10.1124/dmd.116.071142
27. Li X-Q, Grönberg G, Bangur E-H, et al. Metabolism of strained rings: glutathione S-transferase–catalyzed formation of a glutathione-conjugated spiro-azetidine without prior bioactivation. Drug Metab Dispos. 2019;47(11):1247–1256. doi: 10.1124/dmd.119.088658
28. Toselli F, Fredenwall M, Svensson P, et al. Oxetane substrates of human microsomal epoxide hydrolase. Drug Metab Dispos. 2017;45(8):966–973. doi: 10.1124/dmd.117.076489
29. Toselli F, Fredenwall M, Svensson P, et al. Hip to be square: oxetanes as design elements to alter metabolic pathways. J Med Chem. 2019;62(16):7383–7399. doi: 10.1021/acs.jmedchem.9b00030
•• **A study from AstraZeneca highlighting alternative mEH-catalyzed hydrolysis of oxetanes as a major metabolic pathway.**
30. Bull JA, Croft RA, Davis OA, et al. Oxetanes: recent advances in synthesis, reactivity, and medicinal chemistry. Chem Rev. 2016;116(19):12150–12233. doi: 10.1021/acs.chemrev.6b00274
•• **Review paper detailing synthetic methodology to access oxetanes.**
31. Rojas JJ, Bull JA. 2.04 - Oxetanes and oxetenes: monocyclic. In: Black D, Cossy J Stevens C, editors. Compr heterocycl chem IV. Oxford: Elsevier; 2022. p. 212–256.
32. Kaur N. Oxetane synthesis. Oxford: Elsevier; 2023.
33. Ishikura H, Bull JA. Chapter four - recent advances in the synthesis of 3,3-disubstituted oxetanes. In: Scriven E Ramsden C, editors. Adv heterocycl chem. Cambridge (MA): Academic Press; 2024. p. 159–209.
34. Wang C, Aguilar A, Ojima I. Strategies for the drug discovery and development of taxane anticancer therapeutics. Expert Opin Drug Discov. 2022;17(11):1193–1207. doi: 10.1080/17460441.2022.2131766
35. Rojas JJ, Bull JA. Oxetanes in drug discovery campaigns. J Med Chem. 2023;66(18):12697–12709. doi: 10.1021/acs.jmedchem.3c01101
• **Perspective on oxetanes in drug discovery campaigns in 2023, highlighting the rapidly evolving field.**
36. Huang G, Hucek D, Cierpicki T, et al. Applications of oxetanes in drug discovery and medicinal chemistry. Eur J Med Chem. 2023;261:115802. doi: 10.1016/j.ejmech.2023.115802
37. Symes OL, Ishikura H, Bull JA. Oxetanes and thietanes. In: Leftheris K, Meanwell N, Myers M Abraham D, editors. Burgers med chem drug discov. Hoboken (NJ): John Wiley & Sons, Ltd; 2025. p. 1–43.
38. Siramshetty VB, Grishagin I, Nguyễn Đ-T, et al. Ncats inxight drugs: a comprehensive and curated portal for translational research. Nucleic Acids Res. 2022;50(D1):D1307–D1316. doi: 10.1093/nar/gkab918
39. Research C for DE. Fda approves drug to treat adults with persistent or chronic immune thrombocytopenia. FDA; [cited 2025 Sep 16]. Available from: https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-drug-treat-adults-persistent-or-chronic-immune-thrombocytopenia
40. Kuter DJ, Bussel JB, Cooper N, et al. Luna3 phase III multicenter, double-blind, randomized, placebo-controlled trial of the oral BTK inhibitor rilzabrutinib in adults and adolescents with persistent or chronic immune thrombocytopenia. Blood. 2021;138(Supplement 1):1010. doi: 10.1182/blood-2021-144504
41. Kuter DJ, Bussel JB, Ghanima W, et al. Rilzabrutinib versus placebo in adults and adolescents with persistent or chronic immune thrombocytopenia: luna 3 phase III study. Ther Adv Hematol. 2023;14:20406207231205431. doi: 10.1177/20406207231205431
42. Kuter DJ, Ghanima W, Cooper N, et al. Safety and efficacy of rilzabrutinib vs placebo in adults with immune thrombocytopenia: the phase 3 LUNA3 study. Blood. 2025;145(24):2914–2926. doi: 10.1182/blood.2024027336
43. Press release: ash: rilzabrutinib demonstrated significant patient benefit in the first positive phase 3 study of a BTK inhibitor in ITP. [cited 2025 May 29]. Available from: https://www.sanofi.com/en/media-room/press-releases/2024/2024-12-07-16-30-00-2993342
44. Cooper N, Kuter DJ, Frederiksen H, et al. Part a efficacy and safety of oral Bruton tyrosine kinase inhibitor (BTKi) rilzabrutinib in patients with warm autoimmune hemolytic anemia (wAIHA): multicenter, open-label, phase 2b study. Blood. 2024;144(Supplement 1):3836. doi: 10.1182/blood-2024-200325
45. Long L, Baker M, Carruthers M, et al. Ab0756 immune-mediated basis for a phase 2a clinical study comparing rilzabrutinib vs glucocorticoids in rituximab-refractory patients with IgG4-related disease. Ann Rheum Dis. 2021;80(Suppl 1):1406–1406. doi: 10.1136/annrheumdis-2021-eular.407
46. Press release: rilzabrutinib granted orphan drug designation in the US for two rare diseases with no approved medicines. [cited 2025 May 29]. Available from: https://www.sanofi.com/en/media-room/press-releases/2025/2025-04-03-05-00-00-3054815
47. Giménez-Arnau A, Ferrucci S, Ben-Shoshan M, et al. Rilzabrutinib in antihistamine-refractory chronic spontaneous urticaria. JAMA Dermatol. 2025;161(7):e250733. doi: 10.1001/jamadermatol.2025.0733
48. Owens TD, Brameld KA, Verner EJ, et al. Discovery of reversible covalent Bruton's tyrosine kinase inhibitors PRN473 and PRN1008 (rilzabrutinib). J Med Chem. 2022;65(7):5300–5316. doi: 10.1021/acs.jmedchem.1c01170
49. Metz M, Sussman G, Gagnon R, et al. Fenebrutinib in H1 antihistamine-refractory chronic spontaneous urticaria: a randomized phase 2 trial. Nat Med. 2021;27(11):1961–1969. doi: 10.1038/s41591-021-01537-w
50. Isenberg D, Furie R, Jones NS, et al. Efficacy, safety, and pharmacodynamic effects of the Bruton's tyrosine kinase inhibitor fenebrutinib (GDC-0853) in systemic lupus erythematosus: results of a phase II, randomized, double-blind, placebo-controlled trial. Arthritis Rheumatol. 2021;73(10):1835–1846. doi: 10.1002/art.41811
51. Wang X, Barbosa J, Blomgren P, et al. Discovery of potent and selective tricyclic inhibitors of Bruton's tyrosine kinase with improved druglike properties. ACS Med Chem Lett. 2017;8(6):608–613. doi: 10.1021/acsmedchemlett.7b00103
52. Crawford JJ, Johnson AR, Misner DL, et al. Discovery of GDC-0853: a potent, selective, and noncovalent Bruton's tyrosine kinase inhibitor in early clinical development. J Med Chem. 2018;61(6):2227–2245. doi: 10.1021/acs.jmedchem.7b01712
53. Crawford JJ, Zhang H. Discovery and development of non-covalent, reversible Bruton's tyrosine kinase inhibitor fenebrutinib (GDC-0853). Complete acc integr drug discov dev recent ex pharm ind vol 2 [internet]. Am Chem Soc. 2019:239–266. doi: 10.1021/bk-2019-1332.ch009
54. Young WB, Barbosa J, Blomgren P, et al. Potent and selective Bruton's tyrosine kinase inhibitors: discovery of GDC-0834. Bioorg Med Chem Lett. 2015;25(6):1333–1337. doi: 10.1016/j.bmcl.2015.01.032
55. Young WB, Barbosa J, Blomgren P, et al. Discovery of highly potent and selective Bruton's tyrosine kinase inhibitors: pyridazinone analogs with improved metabolic stability. Bioorg Med Chem Lett. 2016;26(2):575–579. doi: 10.1016/j.bmcl.2015.11.076
56. Liu L, Halladay JS, Shin Y, et al. Significant species difference in amide hydrolysis of GDC-0834, a novel potent and selective Bruton's tyrosine kinase inhibitor. Drug Metab Dispos. 2011;39(10):1840–1849. doi: 10.1124/dmd.111.040840
57. Bame E, Tang H, Burns JC, et al. Next-generation Bruton's tyrosine kinase inhibitor BIIB091 selectively and potently inhibits B cell and Fc receptor signaling and downstream functions in B cells and myeloid cells. Clin Transl Immunol. 2021;10(6):e1295.
58. Hopkins BT, Bame E, Bajrami B, et al. Discovery and preclinical characterization of BIIB091, a reversible, selective BTK inhibitor for the treatment of multiple sclerosis. J Med Chem. 2022;65(2):1206–1224. doi: 10.1021/acs.jmedchem.1c00926
59. Kawahata W, Asami T, Kiyoi T, et al. Discovery of AS-1763: a potent, selective, noncovalent, and orally available inhibitor of Bruton's

tyrosine kinase. J Med Chem. 2021;64(19):14129–14141. doi: 10.1021/acs.jmedchem.1c01279
60. Zhao S, Shang Y, Yin Y, et al. Ziresovir in hospitalized infants with respiratory syncytial virus infection. N Engl J Med. 2024;391(12):1096–1107. doi: 10.1056/NEJMoa2313551
61. Zheng X, Liang C, Wang L, et al. Discovery of benzoazepinequinoline (BAQ) derivatives as novel, potent, orally bioavailable respiratory syncytial virus fusion inhibitors. J Med Chem. 2018;61(22):10228–10241. doi: 10.1021/acs.jmedchem.8b01394
62. Zheng X, Gao L, Wang L, et al. Discovery of ziresovir as a potent, selective, and orally bioavailable respiratory syncytial virus fusion protein inhibitor. J Med Chem. 2019;62(13):6003–6014. doi: 10.1021/acs.jmedchem.9b00654
63. Kung P-P, Rui E, Bergqvist S, et al. Design and synthesis of pyridone-containing 3,4-dihydroisoquinoline-1(2H)-ones as a novel class of enhancer of zeste homolog 2 (EZH2) inhibitors. J Med Chem. 2016;59(18):8306–8325. doi: 10.1021/acs.jmedchem.6b00515
64. Kung P-P, Bingham P, Brooun A, et al. Optimization of orally bioavailable enhancer of zeste homolog 2 (EZH2) inhibitors using ligand and property-based design strategies: identification of development candidate (R)-5,8-dichloro-7-(methoxy(oxetan-3-yl)methyl)-2-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3,4-dihydroisoquinolin-1(2H)-one (PF-06821497). J Med Chem. 2018;61(3):650–665. doi: 10.1021/acs.jmedchem.7b01375
65. Ashcroft CP, Berne AM, Blasberg F, et al. Development of a cost-efficient process toward a key synthetic intermediate of the EZH2 inhibitor PF-06821497. Org Process Res Dev. 2024;28(6):2260–2268. doi: 10.1021/acs.oprd.3c00477
- **A study on the process scale synthesis of 3-substituted oxetane-containing synthetic intermediate.**
66. Heinrich MC, Griffith D, McKinley A, et al. Crenolanib inhibits the drug-resistant PDGFRA D842V mutation associated with imatinib-resistant gastrointestinal stromal tumors. Clin Cancer Res. 2012;18(16):4375–4384. doi: 10.1158/1078-0432.CCR-12-0625
67. Smith CC, Lasater EA, Lin KC, et al. Crenolanib is a selective type I pan-FLT3 inhibitor. Proc Natl Acad Sci. 2014;111(14):5319–5324. doi: 10.1073/pnas.1320661111
68. Galanis A, Ma H, Rajkhowa T, et al. Crenolanib is a potent inhibitor of FLT3 with activity against resistance-conferring point mutants. Blood. 2014;123(1):94–100. doi: 10.1182/blood-2013-10-529313
69. Randhawa JK, Kantarjian HM, Borthakur G, et al. Results of a phase II study of Crenolanib in relapsed/refractory acute myeloid leukemia patients (pts) with activating FLT3 mutations. Blood. 2014;124(21):389. doi: 10.1182/blood.V124.21.389.389
70. Wang ES, Goldberg AD, Tallman M, et al. Crenolanib and intensive chemotherapy in adults with newly diagnosed FLT3-mutated AML. J Clin Oncol. 2024;42(15):1776–1787. doi: 10.1200/JCO.23.01061
71. Vendeville S, Amblard F, Bassit L, et al. The discovery and preclinical profile of ALG-000184, a prodrug of the potent hepatitis B virus capsid assembly modulator ALG-001075. J Med Chem. 2024;67(23):21126–21142. doi: 10.1021/acs.jmedchem.4c01814
72. Lesch B, Birkmann A, Bonsmann S, et al. Discovery of AIC263282, a hepatitis B virus capsid assembly modulator ready for candidate profiling. J Med Chem. 2025;68(6):6361–6371. doi: 10.1021/acs.jmedchem.4c02838
73. Yang H, Zhao J, Zhao M, et al. GDC-0349 inhibits non-small cell lung cancer cell growth. Cell Death Dis. 2020;11(11):1–13. doi: 10.1038/s41419-020-03146-w
74. Pei Z, Blackwood E, Liu L, et al. Discovery and biological profiling of potent and selective mTOR inhibitor GDC-0349. ACS Med Chem Lett. 2013;4(1):103–107. doi: 10.1021/ml3003132
75. Werth VP, Fleischmann R, Robern M, et al. Filgotinib or lanraplenib in moderate to severe cutaneous lupus erythematosus: a phase 2, randomized, double-blind, placebo-controlled study. Rheumatology. 2022;61(6):2413–2423. doi: 10.1093/rheumatology/keab685
76. Price E, Bombardieri M, Kivitz A, et al. Safety and efficacy of filgotinib, lanraplenib and tirabrutinib in Sjögren's syndrome: a randomized, phase 2, double-blind, placebo-controlled study. Rheumatology. 2022;61(12):4797–4808. doi: 10.1093/rheumatology/keac167
77. Baker M, Chaichian Y, Genovese M, et al. Phase II, randomised, double-blind, multicentre study evaluating the safety and efficacy of filgotinib and lanraplenib in patients with lupus membranous nephropathy. RMD Open. 2020;6(3):e001490. doi: 10.1136/rmdopen-2020-001490
78. Kronos Bio announces pipeline update and p300 KAT inhibitor development candidate - Kronos Bio. [cited 2025 Jun 4]. Available from: https://ir.kronosbio.com/news-releases/news-release-details/kronos-bio-announces-pipeline-update-and-p300-kat-inhibitor/
79. Blomgren P, Chandrasekhar J, Di Paolo JA, et al. Discovery of lanraplenib (GS-9876): a once-daily spleen tyrosine kinase inhibitor for autoimmune diseases. ACS Med Chem Lett. 2020;11(4):506–513. doi: 10.1021/acsmedchemlett.9b00621
80. Saxena AR, Frias JP, Brown LS, et al. Efficacy and safety of oral small molecule glucagon-like peptide 1 receptor agonist danuglipron for glycemic control among patients with type 2 diabetes: a randomized clinical trial. JAMA Netw Open. 2023;6(5):e2314493. doi: 10.1001/jamanetworkopen.2023.14493
81. Saxena AR, Frias JP, Gorman DN, et al. Tolerability, safety and pharmacodynamics of oral, small-molecule glucagon-like peptide-1 receptor agonist danuglipron for type 2 diabetes: a 12-week, randomized, placebo-controlled, phase 2 study comparing different dose-escalation schemes. Diabetes Obes Metab. 2023;25(10):2805–2814. doi: 10.1111/dom.15168
82. Pfizer provides update on oral GLP-1 receptor agonist danuglipron | Pfizer. [cited 2025 Jun 4]. Available from: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-provides-update-oral-glp-1-receptor-agonist
83. Amin NB, Frederich R, Tsamandouras N, et al. Evaluation of an oral small-molecule glucagon-like peptide-1 receptor agonist, lotiglipron, for type 2 diabetes and obesity: a dose-ranging, phase 2, randomized, placebo-controlled study. Diabetes Obes Metab. 2025;27(1):215–227. doi: 10.1111/dom.16005
84. Griffith DA, Edmonds DJ, Fortin J-P, et al. A small-molecule oral agonist of the human glucagon-like peptide-1 receptor. J Med Chem. 2022;65(12):8208–8226. doi: 10.1021/acs.jmedchem.1c01856
85. Zhang Z, Pan H, Guo L, et al. Design and evaluation of 3-phenyloxetane derivative agonists of the glucagon-like peptide-1 receptor. J Med Chem. 2024;67(17):14820–14839. doi: 10.1021/acs.jmedchem.4c01177
86. Miao L, Lou J, Xu S, et al. Discovery of new difluorocyclobutyl derivatives as effective glucagon-like peptide-1 receptor agonists with reduced hERG inhibitory activities. J Med Chem. 2025;68(7):7662–7692. doi: 10.1021/acs.jmedchem.5c00231
87. Wang X, Yun Y, Chen L, et al. A novel approach to exploit small-molecule glucagon-like peptide-1 receptor agonists with high potency. Bioorg Med Chem. 2024;107:117761. doi: 10.1016/j.bmc.2024.117761
88. Dong G, Ye Q, Li W, et al. Discovery and evaluation of DA-302168S as an efficacious oral small-molecule glucagon-like peptide-1 receptor agonist. J Med Chem. 2025;68(9):9555–9583. doi: 10.1021/acs.jmedchem.5c00242
89. Brea O, Buck J, Carson N, et al. Development of the synthetic route to PF-06878031 part 1: selective alkylation route. Org Process Res Dev. 2024;28(7):2433–2445. doi: 10.1021/acs.oprd.4c00053
- **A study on the process scale synthesis of chiral 2-substituted oxetane-containing synthetic intermediates.**
90. Badland M, Brown MS, Carson N. Methodologies for the formation of 2-substituted oxetanes: synthesis of (S)-oxetan-2-ylmethyl tosylate. Org Process Res Dev. 2025;29(2):574–583. doi: 10.1021/acs.oprd.4c00514
- **A study on the process scale synthesis of chiral 2-substituted oxetane-containing synthetic intermediates.**
91. Brown MS, Buck J, Critcher DJ, et al. Development of the synthetic route to PF-06878031 part 2: amide reduction route. Org Process Res Dev. 2024;28(7):2446–2461. doi: 10.1021/acs.oprd.4c00054
- **A study on the process scale synthesis of chiral 2-substituted oxetane-containing synthetic intermediates.**

92. Chan-Penebre E, Kuplast KG, Majer CR, et al. A selective inhibitor of PRMT5 with in vivo and in vitro potency in MCL models. Nat Chem Biol. 2015;11(6):432–437. doi: 10.1038/nchembio.1810
93. Rioux N, Duncan Kenneth W, Lantz Ronald J, et al. Species differences in metabolism of EPZ015666, an oxetane-containing protein arginine methyltransferase-5 (PRMT5) inhibitor. Xenobiotica. 2016;46(3):268–277. doi: 10.3109/00498254.2015.1072253
94. Duncan KW, Rioux N, Boriack-Sjodin PA, et al. Structure and property guided design in the identification of PRMT5 tool compound EPZ015666. ACS Med Chem Lett. 2016;7(2):162–166. doi: 10.1021/acsmedchemlett.5b00380
95. Li D, Sloman DL, Achab A, et al. Oxetane promise delivered: discovery of long-acting IDO1 inhibitors suitable for Q3W oral or parenteral dosing. J Med Chem. 2022;65(8):6001–6016. doi: 10.1021/acs.jmedchem.1c01670
• **A study on the process scale synthesis of oxetane carboxylic acid intermediates.**
96. Li H, Ke R, Zhou Y, et al. Discovery of LHQ490 as a highly selective fibroblast growth factor receptor 2 (FGFR2) inhibitor. Eur J Med Chem. 2024;272:116473. doi: 10.1016/j.ejmech.2024.116473
97. Zhang C, Chen Y, Li Y, et al. Discovery of 4-amino-1,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyridazin-7-one derivatives as potential receptor-interacting serine/threonine-protein kinase 1 (RIPK1) inhibitors. Eur J Med Chem. 2024;265:116076. doi: 10.1016/j.ejmech.2023.116076
98. Peng J, Ding X, Chen CX, et al. Discovery of pyridine-2-carboxamides derivatives as potent and selective HPK1 inhibitors for the treatment of cancer. J Med Chem. 2024;67(23):21520–21544. doi: 10.1021/acs.jmedchem.4c02421
99. Ahmad S, Yousaf M, Mansha A, et al. Ring-opening reactions of oxetanes: a review of methodology development and synthetic applications. Synth Commun. 2016;46(17):1397–1416. doi: 10.1080/00397911.2016.1208245
100. Chalyk B, Grynyova A, Filimonova K, et al. Unexpected isomerization of oxetane-carboxylic acids. Org Lett. 2022;24(26):4722–4728. doi: 10.1021/acs.orglett.2c01402
101. Zhang R, Guo W, Duan M, et al. Asymmetric desymmetrization of oxetanes for the synthesis of chiral tetrahydrothiophenes and tetrahydroselenophenes. Angew Chem Int Ed. 2019;58(50):18055–18060. doi: 10.1002/anie.201910917
102. Liu S, Zang Y, Huang H, et al. In(OTf)3-catalyzed synthesis of 2,3-dihydro-1H-benzo[e]indoles and 2,3-dihydrobenzofurans via [3 + 2] annulation. Org Lett. 2020;22(21):8219–8223. doi: 10.1021/acs.orglett.0c02729
103. Rojas JJ, Torrisi E, Dubois MAJ, et al. Oxetan-3-ols as 1,2-bis-electrophiles in a Brønsted-acid-catalyzed synthesis of 1,4-dioxanes. Org Lett. 2022;24(12):2365–2370. doi: 10.1021/acs.orglett.2c00568
104. Albitz K, Tóth S, Csókás D, et al. Unlocking oxetane potential: modular synthetic platform for the concise synthesis of acyclic oligo-isoprenoids and terpenoids. Angew Chem Int Ed. 2025;64(4):e202416441. doi: 10.1002/anie.202416441
105. Litskan EV, Semenchenko OV, Lynnyk SV, et al. Oxetane as a part of modern medicinal chemistry toolbox: the advanced synthesis of 3,3-disubstituted building blocks. Org Chem Front. 2025;12(13):3775–3785. doi: 10.1039/D5QO00572H
•• **A study from Enamine detailing the tolerance of the oxetane core to a range of common medicinal chemistry transformations.**
106. Duncton MAJ, Estiarte MA, Johnson RJ, et al. Preparation of heteroaryloxetanes and heteroarylazetidines by use of a Minisci reaction. J Org Chem. 2009;74(16):6354–6357. doi: 10.1021/jo9010624
107. Sierov DI, Dzhulai IV, Siryk KI, et al. Multigram synthesis of α- and γ-((hetera)cyclo)alkylpyridines through α-arylation of (hetero)aliphatic nitriles. Eur J Org Chem. 2023;26(34):e202300538. doi: 10.1002/ejoc.202300538
108. D'Auria M. The Paternò–Büchi reaction – a comprehensive review. Photochem Photobiol Sci. 2019;18(10):2297–2362. doi: 10.1039/c9pp00148d
109. Guo Y-A, Lee W, Krische MJ. Enantioselective synthesis of oxetanes bearing all-carbon quaternary stereocenters via iridium-catalyzed C–C bond-forming transfer hydrogenation. Chem – Eur J. 2017;23(11):2557–2559. doi: 10.1002/chem.201606046
110. Sedano C, Velasco R, Suárez-Pantiga S, et al. Merging α-lithiation and aldol-Tishchenko reaction to construct polyols from benzyl ethers. Org Lett. 2020;22(20):8070–8075. doi: 10.1021/acs.orglett.0c03014
111. Li H-F, Cao W, Ma X, et al. Visible-light-driven [2 + 2] photocycloadditions between benzophenone and C=C bonds in unsaturated lipids. J Am Chem Soc. 2020;142(7):3499–3505. doi: 10.1021/jacs.9b12120
112. Mateos J, Vega-Peñaloza A, Franceschi P, et al. A visible-light Paternò–Büchi dearomatisation process towards the construction of oxeto-indolinic polycycles. Chem Sci. 2020;11(25):6532–6538. doi: 10.1039/D0SC01569E
113. Rykaczewski KA, Schindler CS. Visible-light-enabled Paternò–büchi reaction via triplet energy transfer for the synthesis of oxetanes. Org Lett. 2020;22(16):6516–6519. doi: 10.1021/acs.orglett.0c02316
114. Zheng J, Dong X, Yoon TP. Divergent photocatalytic reactions of α-ketoesters under triplet sensitization and photoredox conditions. Org Lett. 2020;22(16):6520–6525. doi: 10.1021/acs.orglett.0c02314
115. Huff S, Kummetha IR, Zhang L, et al. Rational design and optimization of m6A-RNA demethylase FTO inhibitors as anticancer agents. J Med Chem. 2022;65(16):10920–10937. doi: 10.1021/acs.jmedchem.1c02075
116. Phelan JP, Patel EJ, Ellman JA. Catalytic enantioselective addition of thioacids to trisubstituted nitroalkenes. Angew Chem. 2014;126(42):11511–11514. doi: 10.1002/ange.201406971
117. Phelan JP, Ellman JA. Catalytic enantioselective addition of pyrazol-5-ones to trisubstituted nitroalkenes with an N-sulfinylurea organocatalyst. Adv Synth Catal. 2016;358(11):1713–1718. doi: 10.1002/adsc.201600110
118. Ding R, Wolf C. Organocatalytic asymmetric synthesis of α-oxetanyl and α-azetidinyl tertiary alkyl fluorides and chlorides. Org Lett. 2018;20(3):892–895. doi: 10.1021/acs.orglett.8b00039
119. Budinská A, Lefebvre Q, Wennemers H. Enantioselective conjugate addition of aldehydes to oxetane- and azetidine-containing nitroolefins: an entry to spirocyclic pyrrolidines. Org Lett. 2025;27(16):4190–4195. doi: 10.1021/acs.orglett.5c00844
120. Hamzik PJ, Brubaker JD. Reactions of oxetan-3-tert-butylsulfinimine for the preparation of substituted 3-aminooxetanes. Org Lett. 2010;12(5):1116–1119. doi: 10.1021/ol100119e
121. Jung HH, Buesking AW, Ellman JA. Highly functional group compatible Rh-catalyzed addition of arylboroxines to activated N-tert-butanesulfinyl ketimines. Org Lett. 2011;13(15):3912–3915. doi: 10.1021/ol201438k
122. Kolahdouzan K, Khalaf R, Grandner JM, et al. Dual photoredox/nickel-catalyzed conversion of aryl halides to aryl aminooxetanes: computational evidence for a substrate-dependent switch in mechanism. ACS Catal. 2020;10(1):405–411. doi: 10.1021/acscatal.9b03596
123. Bollenbach M, Lecroq W, Wagner P, et al. On water N-arylation of oxetanylamines for the preparation of N-aryl-oxetanylamines; potentially useful aryl-amide isosteres. Chem Commun. 2019;55(11):1623–1626. doi: 10.1039/C8CC09110B
124. Rojas JJ, Croft RA, Sterling AJ, et al. Amino-oxetanes as amide isosteres by an alternative defluorosulfonylative coupling of sulfonyl fluorides. Nat Chem. 2022;14(2):160–169. doi: 10.1038/s41557-021-00856-2
• **A study describing the modular synthesis of amino-oxetanes as benzamide bioisosteres for medicinal chemistry applications.**
125. Symes OL, Ishikura H, Begg CS, et al. Harnessing oxetane and azetidine sulfonyl fluorides for opportunities in drug discovery. J Am Chem Soc. 2024;146(51):35377–35389. doi: 10.1021/jacs.4c14164
126. Chan AHY, Ho TCS, Leeper FJ. Thiamine analogues featuring amino-oxetanes as potent and selective inhibitors of pyruvate dehydrogenase. Bioorg Med Chem Lett. 2024;98:129571. doi: 10.1016/j.bmcl.2023.129571

127. Tian D, Chen G, Wang X, et al. Modular access to functionalized oxetanes as benzoyl bioisosteres. J Am Chem Soc. 2024;146(26):18011–18018. doi: 10.1021/jacs.4c04504
128. Spránitz P, Sőregi P, Hegedüs K, et al. Strain-release-driven modular synthesis of oxetane-based amide bioisosteres: concise, robust and scalable approach. Angew Chem Int Ed. 2024;63(42):e202410554.
129. Liu W-Q, Lee BC, Song N, et al. Electrochemical synthesis of c(sp3)-rich amines by aminative carbofunctionalization of carbonyl compounds. Angew Chem Int Ed. 2024;63(26):e202402140. doi: 10.1002/anie.202402140
130. Phelps JM, Kumar R, Robinson JD, et al. Multicomponent synthesis of α-branched amines via a zinc-mediated carbonyl alkylative amination reaction. J Am Chem Soc. 2024;146(13):9045–9062. doi: 10.1021/jacs.3c14037
131. Croft RA, Mousseau JJ, Choi C, et al. Structurally divergent lithium catalyzed Friedel–Crafts reactions on oxetan-3-ols: synthesis of 3,3-diaryloxetanes and 2,3-dihydrobenzofurans. Chem – Eur J. 2016;22(45):16271–16276. doi: 10.1002/chem.201604031
132. Massaro L, Neigenfind P, Feng A, et al. Triply convergent Ni-electrocatalytic assembly of 1,1-diaryl cyclobutanes, azetidines, and oxetanes [internet]. ChemRxiv; 2024 [cited 2024 Nov 28]. Available from: https://chemrxiv.org/engage/chemrxiv/article-details/67256a8b5a82cea2fac3771c
133. Liashuk OS, Fedinchyk A, Melnykov KP, et al. 3,3-difluorooxetane–a versatile functional group for bioisosteric replacements in drug discovery. Chem: Eur J. 2024;30(72):e202403277. doi: 10.1002/chem.202403277
134. Tan T-D, Zhou F, Quirion KP, et al. Catalytic difluorocarbene insertion enables access to fluorinated oxetane isosteres. Nat Chem. 2025;17(5):719–726. doi: 10.1038/s41557-024-01730-7
135. Shore DGM, Wasik KA, Lyssikatos JP, et al. Minisci alkylations of electron-deficient pyrimidines with alkyl carboxylic acids. Tetrahedron Lett. 2015;56(27):4063–4066. doi: 10.1016/j.tetlet.2015.04.123
136. Genovino J, Lian Y, Zhang Y, et al. Metal-free-visible light C–H alkylation of heteroaromatics via hypervalent iodine-promoted decarboxylation. Org Lett. 2018;20(11):3229–3232. doi: 10.1021/acs.orglett.8b01085
137. Salgueiro DC, Chi BK, Guzei IA, et al. Control of redox-active ester reactivity enables a general cross-electrophile approach to access arylated strained rings. Angew Chem Int Ed. 2022;61(33):e202205673. doi: 10.1002/anie.202205673
138. Guo J, Norris D, Ramirez A, et al. Unlocking tertiary acids for metallaphotoredox C(sp2)–C(sp3) decarboxylative cross-couplings. ACS Catal. 2023;13(18):11910–11918. doi: 10.1021/acscatal.3c03353
139. Dong Z, MacMillan DWC. Metallaphotoredox-enabled deoxygenative arylation of alcohols. Nature. 2021;598(7881):451–456. doi: 10.1038/s41586-021-03920-6
140. Liu W, Mulhearn J, Hao B, et al. Enabling deoxygenative C(sp2)-C(sp3) cross-coupling for parallel medicinal chemistry. ACS Med Chem Lett. 2023;14(6):853–859. doi: 10.1021/acsmedchemlett.3c00118
141. Green SA, Vásquez-Céspedes S, Shenvi RA. Iron–nickel dual-catalysis: a new engine for olefin functionalization and the formation of quaternary centers. J Am Chem Soc. 2018;140(36):11317–11324. doi: 10.1021/jacs.8b05868
142. Guillemard L, Ackermann L, Johansson MJ. Late-stage meta-C–H alkylation of pharmaceuticals to modulate biological properties and expedite molecular optimisation in a single step. Nat Commun. 2024;15(1):3349. doi: 10.1038/s41467-024-46697-8
143. Dubois MAJ, Rojas JJ, Sterling AJ, et al. Visible light photoredox-catalyzed decarboxylative alkylation of 3-aryl-oxetanes and azetidines via benzylic tertiary radicals and implications of benzylic radical stability. J Org Chem. 2023;88(10):6476–6488. doi: 10.1021/acs.joc.3c00083
144. McFee EC, Rykaczewski KA, Schindler CS. Photoredox-catalyzed decarboxylation of oxetane-2-carboxylic acids and unique mechanistic insights. Angew Chem Int Ed. 2025;64(5):e202405125. doi: 10.1002/anie.202405125
145. Morgan KF, Hollingsworth IA, Bull JA. 2-(aryl-sulfonyl)oxetanes as designer 3-dimensional fragments for fragment screening: synthesis and strategies for functionalisation. Chem Commun. 2014;50(40):5203–5205. doi: 10.1039/C3CC46450D
146. Davis OA, Bull JA. Synthesis of di-, tri-, and tetrasubstituted oxetanes by rhodium-catalyzed o–h insertion and c–c bond-forming cyclization. Angew Chem Int Ed. 2014;53(51):14230–14234. doi: 10.1002/anie.201408928
147. Davis A, Croft R, Bull J. Synthesis of diversely functionalised 2,2-disubstituted oxetanes: fragment motifs in new chemical space. Chem Commun. 2015;51(84):15446–15449. doi: 10.1039/C5CC05740J
148. Paul S, Filippini D, Ficarra F, et al. Oxetane synthesis via alcohol C–H functionalization. J Am Chem Soc. 2023;145(29):15688–15694. doi: 10.1021/jacs.3c04891
149. Michalska WZ, Halcovitch NR, Coote SC. Synthesis of functionalized spirocyclic oxetanes through Paternò–Büchi reactions of cyclic ketones and maleic acid derivatives. Chem Commun. 2023;59(6):784–787. doi: 10.1039/D2CC06459F
150. Murray PRD, Bussink WMM, Davies GHM, et al. Intermolecular crossed [2 + 2] cycloaddition promoted by visible-light triplet photosensitization: expedient access to polysubstituted 2-oxaspiro[3.3]heptanes. J Am Chem Soc. 2021;143(10):4055–4063. doi: 10.1021/jacs.1c01173
151. Jones B, Proud M, Sridharan V. Synthesis of oxetane/azetidine containing spirocycles via the 1,3-dipolar cycloaddition reaction. Tetrahedron Lett. 2016;57(25):2811–2813. doi: 10.1016/j.tetlet.2016.05.053
152. Fjelbye K, Marigo M, Clausen R, et al. Preparation of spirocyclic β-proline esters: geometrically restricted building blocks for medicinal chemistry. Synlett. 2016;28(2):231–234. doi: 10.1055/s-0036-1588902
153. Chalyk BA, Isakov AA, Butko MV, et al. Synthesis of 6-azaspiro[4.3]alkanes: innovative scaffolds for drug discovery. Eur J Org Chem. 2017;2017(31):4530–4542. doi: 10.1002/ejoc.201700536
154. Chalyk BA, Butko MV, Yanshyna OO, et al. Synthesis of spirocyclic pyrrolidines: advanced building blocks for drug discovery. Chem: Eur J. 2017;23(66):16782–16786. doi: 10.1002/chem.201702362
155. Deng H, Jia R, Yang W-L, et al. Ligand-controlled switch in diastereoselectivities: catalytic asymmetric construction of spirocyclic pyrrolidine-azetidine/oxe(thie)tane derivatives. Chem Commun. 2019;55(51):7346–7349. doi: 10.1039/C9CC03589C
156. Chalyk BA, Izhyk VV, Danyleiko K, et al. Synthesis of spirocyclic and fused isoxazoline building blocks. Eur J Org Chem. 2023;26(22):e202300282. doi: 10.1002/ejoc.202300282
157. Wuitschik G, Rogers-Evans M, Buckl A, et al. Spirocyclic oxetanes: synthesis and properties. Angew Chem Int Ed. 2008;47(24):4512–4515. doi: 10.1002/anie.200800450
158. Burkhard JA, Wagner B, Fischer H, et al. Synthesis of azaspirocycles and their evaluation in drug discovery. Angew Chem Int Ed. 2010;49(20):3524–3527. doi: 10.1002/anie.200907108
159. Natho P, Colella M, Luisi R. Strained spiro heterocycles as potential bioisosteres: an update on the synthesis of heteroatom-containing spiro[2.3]hexanes and spiro[3.3]heptanes. Chem Commun. 2025;61(36):6579–6594. doi: 10.1039/D5CC00656B
160. van der Haas RNS, Dekker JA, Hassfeld J, et al. Synthesis and properties of 2-oxa-6-azaspiro[3.3]heptane sulfonate salts. Synthesis. 2017;49(11):2394–2401. doi: 10.1055/s-0036-1588733
161. Johansson A, Löfberg C, Antonsson M, et al. Discovery of (3-(4-(2-oxa-6-azaspiro[3.3]heptan-6-ylmethyl)phenoxy)azetidin-1-yl)(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)methanone (AZD1979), a melanin concentrating hormone receptor 1 (MCHr1) antagonist with favorable physicochemical properties. J Med Chem. 2016;59(6):2497–2511. doi: 10.1021/acs.jmedchem.5b01654
162. Golden M, Legg D, Milne D, et al. The development of a manufacturing route to an MCHr1 antagonist. Org Process Res Dev. 2016;20(3):675–682. doi: 10.1021/acs.oprd.6b00006
163. Cardoso FSP, Kadam AL, Nelson RC, et al. Practical and scalable two-step process for 6-(2-fluoro-4-nitrophenyl)-2-oxa-6-azaspiro[3.3]heptane: a key intermediate of the potent antibiotic drug candidate TBI-223. Org Process Res Dev. 2023;27(7):1390–1399. doi: 10.1021/acs.oprd.3c00148
164. WuXi STA forms strategic partnership with Ark Biopharmaceutical for the commercial supply of ziresovir | WuXi STA. [cited 2025 Jun

15]. Available from: https://sta.wuxiapptec.com/wuxi-sta-forms-strategic-partnership-with-ark-biopharmaceutical-for-the-commercial-supply-of-ziresovir/
165. Mevpro-1 prostate cancer clinical trial NCT # 06551324|Pfizer. [cited 2025 Jun 15]. Available from: https://www.pfizerclinicaltrials.com/nct06551324-prostate-cancer-trial
166. Mevpro-2 prostate cancer clinical trial C2321003 | Pfizer [Internet]. [cited 2025 Jun 15]. Available from: https://www.pfizerclinicaltrials.com/nct06629779-metastatic-prostate-cancer-trial
167. Roche's fenebrutinib demonstrated near-complete suppression of disease activity and disability progression for up to 48 weeks in patients with relapsing multiple sclerosis. [cited 2025 Jun 15]. Available from: https://www.roche.com/media/releases/med-cor-2024-09-04
168. Opalinska JB, Kalota A, Gifford LK, et al. Oxetane modified, conformationally constrained, antisense oligodeoxyribonucleotides function efficiently as gene silencing molecules. Nucleic Acids Res. 2004;32(19):5791–5799.