



Review article

Applications of oxetanes in drug discovery and medicinal chemistry

Guang Huang^{*}, Devon Hucek, Tomasz Cierpicki, Jolanta Grembecka

Department of Pathology, University of Michigan, Ann Arbor, MI, 48109, USA

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ABSTRACT

The compact and versatile oxetane motifs have gained significant attention in drug discovery and medicinal chemistry campaigns. This review presents an overview of the diverse applications of oxetanes in clinical and preclinical drug candidates targeting various human diseases, including cancer, viral infections, autoimmune disorders, neurodegenerative conditions, metabolic disorders, and others. Special attention is given to biologically active oxetane-containing compounds and their disease-related targets, such as kinases, epigenetic and non-epigenetic enzymes, and receptors. The review also details the effect of the oxetane motif on important properties, including aqueous solubility, lipophilicity, pKa, P-glycoprotein (P-gp) efflux, metabolic stability, conformational preferences, toxicity profiles (e.g., cytochrome P450 (CYP) suppression and human ether-a-go-go related gene (hERG) inhibition), pharmacokinetic (PK) properties, potency, and target selectivity. We anticipate that this work will provide valuable insights that can drive future discoveries of novel bioactive oxetane-containing small molecules, enabling their effective application in combating a wide range of human diseases.

1. Introduction

Oxetane is an oxygen-containing four-membered heterocycle, which exhibits significant strain energy (c.a. 106 kJ mol⁻¹) [1] and adopts a nearly planar structure. The oxetane moiety is characterized by its small size and polarity, occupying a similar volume to a gem-dimethyl group [2] and possessing comparable dipole, similar lone pair spatial orientation and hydrogen bonding properties to a carbonyl group [3–5]. The presence of an oxygen atom in the oxetane ring reduces gauche interactions, resulting in a relatively planar structure relative to cyclobutane rings [5]. These unique features make oxetanes highly appealing in drug discovery and medicinal chemistry applications. In particular, oxetanes have found extensive use as surrogates for gem-dimethyl, carbonyl, and morpholinyl groups, offering improved physicochemical properties [2,6–10]. The compact, polar, electron-withdrawing, and sp³-rich characteristics of the oxetane moiety also make it suitable for incorporation as a pendant motif, contributing to improved drug-like properties [5–7,11]. By leveraging these advantages, oxetanes have emerged as valuable scaffolds in the pursuit of novel therapeutic agents.

Currently, the U.S. Food and Drug Administration (FDA) has approved four oxetane-containing drugs (Fig. 1). Paclitaxel (1, Taxol) and its semisynthetic derivatives docetaxel (2, Taxotere) and cabazitaxel (3, Jevtana) play vital roles as chemotherapeutics in the clinical treatment of breast cancer, lung cancer, ovarian cancer, prostate cancer, and

non-small cell lung cancer [12–14]. These compounds feature an oxetane motif fused to the cyclohexyl C-ring. It is worth noting that the presence of an oxetane D-ring in paclitaxel allows it to act as a hydrogen bond acceptor or alternatively as a conformational lock for the structure [15,16]. Another FDA-approved drug, orlistat (4, also known as tetrahydrolipstatin and Xenical, Fig. 1), contains an oxetane moiety and is widely recognized for its potent and irreversible inhibition of pancreatic and gastric lipases, leading to reduced absorption of dietary fats [17,18]. Orlistat also inhibits the thioesterase domain of fatty acid synthase, an enzyme closely associated with tumor progression, thereby interfering with cellular fatty acid synthesis [19,20]. Multiple studies have revealed its promising *in vitro* and/or *in vivo* anticancer activity [19,21].

Although many excellent reviews have been published on various aspects of oxetanes, such as their synthetic strategies [5,22–24], applications in polymer chemistry [25], and biological activity of natural products [26], an in-depth examination specifically focusing on the application of oxetanes in drug discovery and medicinal chemistry is currently lacking. In this study, we aim to provide a comprehensive overview primarily concentrating on oxetane-containing clinical and preclinical drug candidates for the treatment of various human diseases, including cancer, viruses, autoimmune disorders, neurodegenerative conditions, metabolic disorders, abdominal aortic aneurysm, acute kidney injury, and others. We also emphasize the biological targets of these candidates (i.e., kinases, non-epigenetic and epigenetic enzymes,

^{*} Corresponding author.

E-mail address: huanggu@umich.edu (G. Huang).

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and receptors), as reported in primary literature from 2014 to early 2023. It is important to note that this review does not cover oxetane-containing bioactive molecules reported in patent literature. Moreover, we highlight the impact of the oxetane moiety on the key physicochemical properties, P-gp efflux, metabolic stability, conformational preferences, and toxicity profiles, including CYP suppression and hERG inhibition, PK properties, potency, as well as target selectivity of the host molecule. These thorough analyses will provide valuable insights into understanding the role of the oxetane moiety in drug design and medicinal chemistry. It is our hope that this work might provide a reference for future discovery of new oxetane-containing biologically active small molecules for treating diverse human diseases.

2. Oxetanes in anticancer drug discovery

2.1. ALDH1A inhibitors

Aldehyde dehydrogenases (ALDH) are a group of enzymes that use NAD(P)^+ as a cofactor to convert aldehydes into their corresponding carboxylic acids [27,28]. Highly expressed ALDHs in various types of cancer are associated with subpopulations of cells that are resistant to chemotherapy and radiotherapy. ALDH activity is frequently used to identify cancer stem-like cells, and the ALDH1A subfamily (ALDH1A1, ALDH1A2, and ALDH1A3) has been individually linked to chemoresistant cells [27]. Therefore, the development of ALDH1A inhibitors could be a direct approach to target these resistant cell populations.

The discovery of oxetane-containing compounds has been crucial in the exploration of potent inhibitors of ALDH1A subfamily enzymes. Pyrazolopyrimidinone compound **5** (CM39, Fig. 2) was identified from a high-throughput screening and displayed good inhibitory activity against ALDH1A1 ($\text{IC}_{50} = 0.9 \mu\text{M}$) [29]. However, it suffered from poor metabolic stability and aqueous solubility as shown in Fig. 2. Guided by the cocrystal structure of **5**-ALDH1A1 complexes, the Larsen group developed oxetane-containing compound **6** as a robust inhibitor of the ALDH1A subfamily with IC_{50} values ranging from 0.08 to 0.25 μM [29]. Oxetane **6** displayed excellent selectivity over the homologous ALDH2 isoform and significantly improved metabolic stability over **5**. Importantly, **6** was able to abolish the CD133⁺ putative tumor stem cell pool, synergize with cisplatin, and achieve efficacious concentrations *in vivo* [29]. Further optimization of **6**, aided by metabolism identification, led to the discovery of compounds **7** and **8** with increased biochemical potencies, improved cellular ALDH1A inhibition in high-grade serous cell lines, and significant enhancement in microsomal stability and aqueous solubility (Fig. 2) [30]. Altering the N atom in compound **8** from *ortho* position to *meta* position afforded compound **9**, which resulted in 3.15-fold gain in aqueous solubility but dramatically impaired microsomal stability ($t_{1/2} = 2.7 \text{ min}$) and ALDH1A3 inhibition activity ($\text{IC}_{50} = 0.25 \mu\text{M}$). Oxetanyl analogue **10** maintained potent ALDH1A suppression but demonstrated remarkably enhanced microsomal stability ($t_{1/2} > 60 \text{ min}$) relative to compound **7**. As shown in

Fig. 2, compounds **7** and **10** achieved higher exposure than compound **8**, although **8** was more soluble [30]. Especially, these three compounds exceeded the concentration at which they suppressed ALDH1A by more than 50% *in vitro*. Compounds **7** and **8** could reverse chemoresistance in the SKOV3-TR line and synergize with Taxol in patient-derived tumor spheroids [30]. Thus, the presence of an oxetane moiety at the pyrazolopyrimidinone ring was found to contribute not only to increasing potency but also to improving the aqueous solubility.

2.2. AXL inhibitors

Receptor tyrosine kinase AXL, a member of the TAM (TYRO3, AXL, MER) family, regulates multiple vital cellular processes such as cell survival, proliferation, differentiation, motility, and adhesion. The overexpression or overactivation of the AXL protein is linked to tumor angiogenesis, poor prognosis, and drug resistance. Therefore, AXL is an attractive target for anticancer therapies [31,32].

Indazole hit **11** (Fig. 3) was identified by screening the in-house expanded fragment library [33]. It possessed micromolar AXL inhibitory activity ($\text{IC}_{50} = 28.4 \mu\text{M}$) and good ligand binding efficiencies ($\text{LE} = 0.39$). Subsequent fragment optimization of **11**, guided by docking studies, produced the oxetane-containing compound **12** with a dramatic gain of potency ($\text{IC}_{50} = 320 \text{ nM}$). Changing the methyl group in oxetanyl compound **12** with *p*-methoxyphenyl group resulted in compound **13**, which exhibited a further increase in biochemical potency and intracellular affinity with IC_{50} values of 41.5 and 11.4 nM, respectively. Moreover, compound **13** demonstrated higher exposure level and maximum concentration in mice than compound **12** (Fig. 3). Consistent with robust AXL inhibitory potency, compound **13** effectively suppressed the proliferation of ovarian KOV3 cells ($\text{GI}_{50} = 1.02 \mu\text{M}$). Oxetanyl derivative **13** also showed a dose-dependent reduction of pAXL and downstream pERK1/2 levels, supporting its on-target activity [33].

2.3. BCL-2 inhibitors

The intrinsic apoptosis pathway is regulated by the B cell lymphoma protein 2 (BCL-2) family of proteins. This family includes anti-apoptotic (pro-survival) proteins such as BCL-2, BCL-X_L, and MCL-1, pro-apoptotic BH3-only proteins such as BIM and BAD, and pro-apoptotic effectors such as BAK and BAX [34]. BCL-2 is frequently overexpressed in tumor cells, making it a promising target for the development of small molecule anticancer drugs [35,36].

Compound **14** (ABT-263, navitoclax, Fig. 4), is an orally bioavailable BCL-2 and BCL-X_L dual inhibitor that has entered phase I/II clinical trial for the treatment of various cancers, including chronic lymphocytic leukemia (CLL) and small cell lung cancer (SCLC) [36]. However, **14** suffers from on-target and dose-limiting thrombocytopenia caused by BCL-X_L inhibition. Analysis of the co-crystal structure of **14** in complex with BCL-2 implied that **14** well occupies the BH3 binding groove, with two high affinity interaction P2 and P4 hot spots. Guided by the

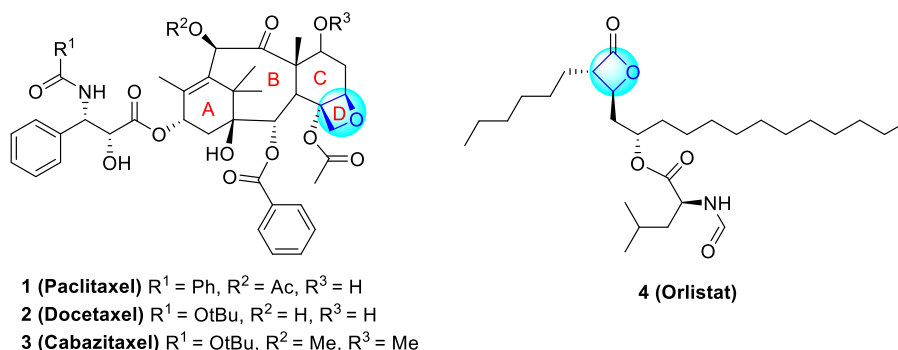


Fig. 1. FDA approved oxetane-containing drugs 1–4.

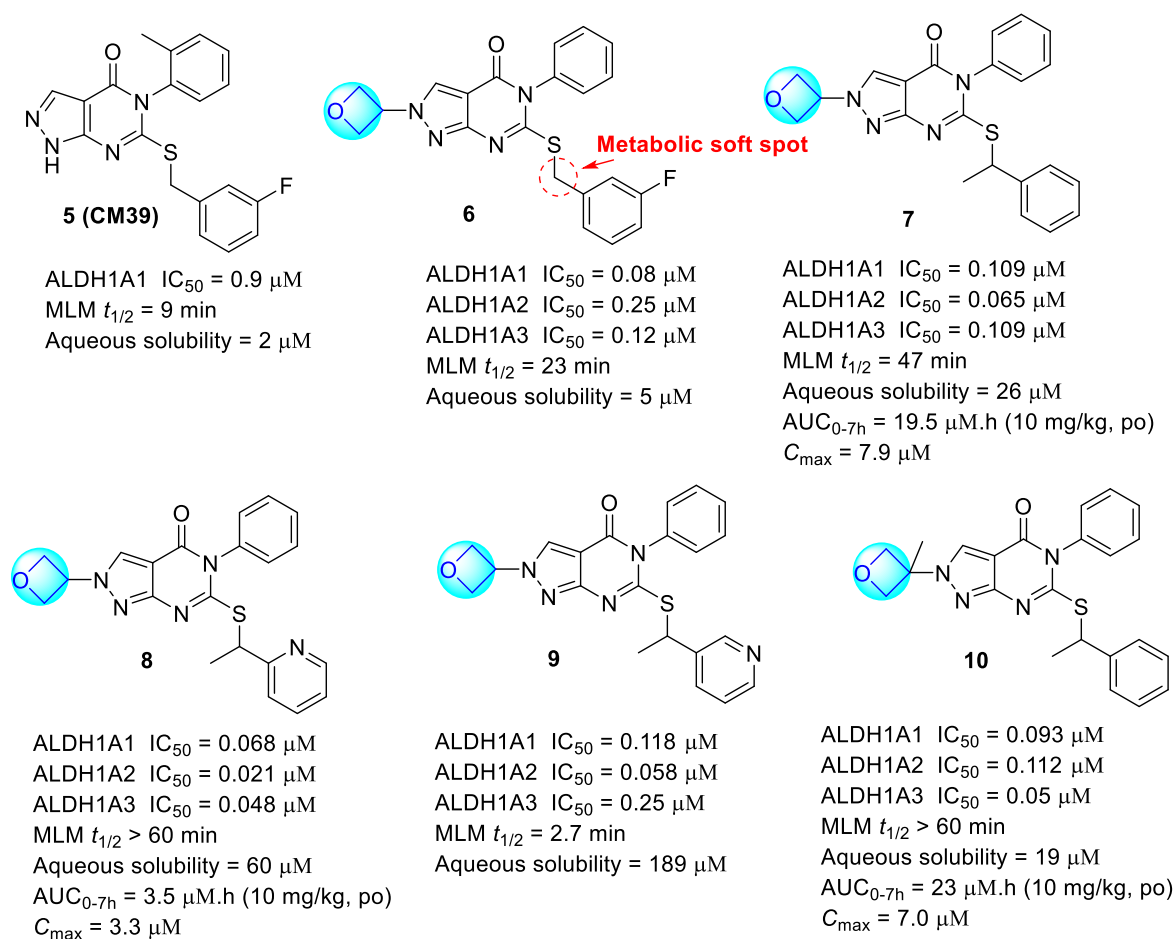


Fig. 2. Chemical structures, *in vitro* potency, physicochemical and PK properties of ALDH1A inhibitors 5–10.

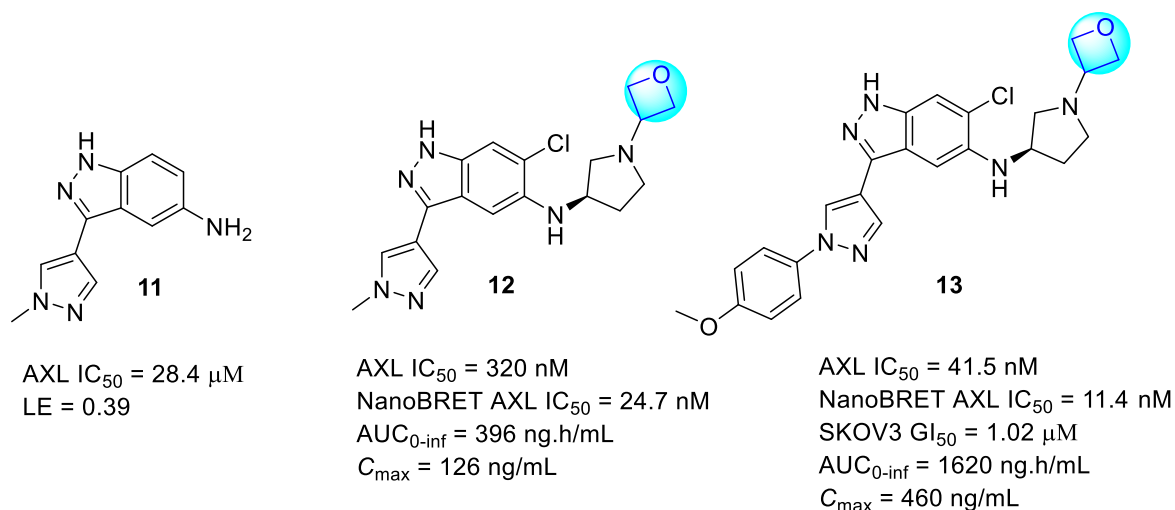


Fig. 3. Chemical structures, *in vitro* potency, and PK properties of AXL inhibitors 11–13.

co-crystal structure analysis, Liu and co-workers exploited the P4 pocket by replacing the phenyl thioether moiety with heterocycle-substituted alkylamino groups [37]. Among them, the oxetane-containing compound **15** exhibited outstanding BCL-2 inhibitory activity (IC_{50} = 17.3 nM) and significant selectivity for BCL-2 (Fig. 4). Notably, the BCL-X_L/BCL-2 selectivity factor (SF) of **15** was much higher than that of **14** [37].

2.4. BTK inhibitors

Bruton's tyrosine kinase (BTK), a nonreceptor tyrosine kinase from the Tec family, is expressed primarily in B and myeloid cells and is involved in B cell antigen receptor (BCR) signaling. Its critical role in B cell development and its presence in various B cell malignancies, such as CLL, have made it an attractive therapeutic target [38]. Triazine

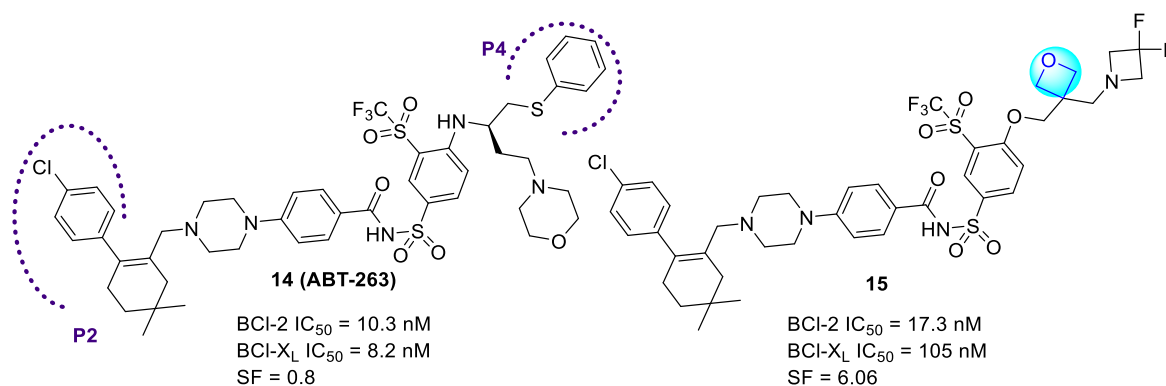


Fig. 4. Chemical structures and *in vitro* potency of BCL-2 inhibitors **14** and **15**.

compound **16** was a highly selective BTK inhibitor (IC₅₀ = 17.4 nM, Fig. 5), but it exhibited weak antiproliferative activity against tumor cells [39]. Molecular modeling analysis indicated that the NH at the 2-position, the NH₂ at the 4-position, and the nitrogen atom in the triazine ring of **16** form favorable hydrogen bonds with the BTK kinase hinge region, and morpholine moiety points toward solvent-exposed region. Based upon these results, Kawahata and co-workers took advantage of cyclization strategy (cyclization between the 1-position and the NH at the 2-position of the triazine ring) and investigated the effect of C6-substituent at the new pyrrolopyrimidine ring on the biological activity [39]. The resulting compound **17**, a tetrahydropyridine analogue bearing an acetyl group, manifested 24.5-fold increased enzymatic inhibition activity and more potent cellular potency relative to the hit **16** (IC₅₀ = 0.71 nM for BTK and 5 nM for OCI-Ly10 cells). Nonetheless, this compound displayed very low Caco-2 permeability (below the detection limit). Subsequent optimization of **17** through incorporating an oxetane moiety into the tetrahydropyridine scaffold resulted in compound **18** (AS-1763), which demonstrated superior potency against wild-type and mutant BTK (IC₅₀ = 0.85 and 0.99 nM, respectively), the highest cellular activity (IC₅₀ = 2 nM for OCI-Ly10 cells), and substantially improved permeability (P_{app} = 1.42×10^{-6}

cm/s) [39]. Moreover, **18** inhibited BTK with >260-fold selectivity over 98% of the kinome tested. Furthermore, compound **18** demonstrated desirable PK profiles with good oral bioavailability of 60.8% in mice and 68.1% in dogs (Fig. 5). *In vivo*, **18** efficiently induced tumor regression in both BTK^{WT} OCI-Ly10 and BTK^{C481S} OCI-Ly10 xenograft models without abnormal clinical observation or weight loss, whereas ibrutinib was not effective in BTK^{C481S} OCI-Ly10 xenograft model (Table 1). Given outstanding *in vitro* potencies, PK profiles, and *in vivo* efficacies, **18** has

Table 1

In vivo studies of BTK inhibitor **18** (AS-1763).

Compd.	Tumor xenograft model	Administration	Dose (mg/kg)	TGI (%)
18	BTK ^{WT} OCI-Ly10	BID	6	74.5
18	BTK ^{WT} OCI-Ly10	BID	20	81.6
18	BTK ^{WT} OCI-Ly10	BID	60	111.8
Ibrutinib	BTK ^{WT} OCI-Ly10	BID	25	E
18	BTK ^{C481S} OCI-Ly10	BID	60	73
Ibrutinib	BTK ^{C481S} OCI-Ly10	QD	25	NE

E: the antitumor activity of ibrutinib was comparable to that of **18** at a dose of 6 mg/kg; BID: twice daily; QD: once daily; NE: Not effective.

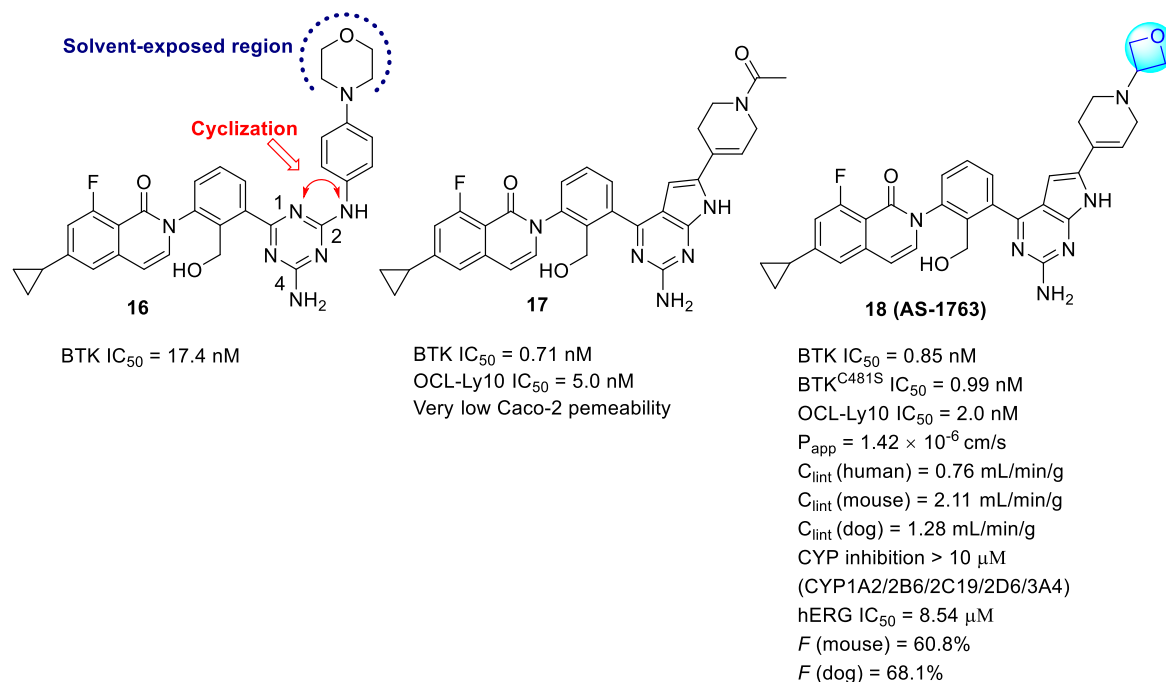


Fig. 5. Chemical structures, *in vitro* potency, physicochemical and PK properties of BTK inhibitors **16**–**18**.

advanced to phase 1 clinical trial. It was important to note that the oxetane substitution at the tetrahydropyridine in **18** contributed to enhancing the potency and improving notable physicochemical and PK properties [39].

2.5. ChK1 inhibitor

Checkpoint kinase 1 (ChK1) is a serine/threonine kinase that plays a crucial role in mediating G2/M cell cycle, and in preventing cells with damaged DNA from entering mitosis [40,41]. ChK1 also coordinates various aspects of DNA repair. As such, inhibition of ChK1 has become a promising therapeutic approach in oncology. Gazzard et al. described the discovery of the 1,7-diazacarbazole series of ChK1 inhibitors and the identification of oxetane **20** (GNE-145, Fig. 6) as a particularly attractive preclinical candidate [41]. The advanced lead compound **19** displayed single-digit nanomolar ChK1 activity ($IC_{50} = 4.4$ nM) and high potency in a phosphorylation of histone H3 (pHH3) assay ($EC_{50} = 172$ nM). However, this compound also showed potent inhibition of acetylcholine esterase (AChE), which posed a potential safety concern. The authors proposed that the exposed basic amine in the molecule might be responsible for this AChE activity by mimicking the cationic moiety of AChE via ionization. To reduce the pKa of the distal piperidine nitrogen, the geminal dimethyl group in compound **19** was then replaced with an oxetane unit. The resulting compound **20** demonstrated exceptionally potent biochemical and cellular potency ($IC_{50} = 2.5$ nM and $EC_{50} = 72.8$ nM) and greatly improved selectivity over AChE enzyme ($IC_{50} = 2.42$ μ M). Notably, oxetane **20**, in combination with gemcitabine, manifested good *in vivo* pharmacodynamic effect and was efficacious in a mouse p53 mutant xenograft model [41].

2.6. EZH2 inhibitors

Histone methyltransferase EZH2 (enhancer of zeste homolog 2), which is the catalytic subunit of the PRC2 (polycomb repressive complex 2), can alter downstream target gene expression through trimethylation of histone 3 on lysine 27 [42,43]. EZH2 is commonly mutated in hematologic malignancies and frequently overexpressed in solid tumors, with its expression level associated with poor prognosis. Consequently, targeting EZH2 has become a prominent focus in cancer therapy research [43].

Compound **21** (Fig. 7) manifested outstanding EZH2 suppressive activity in enzymatic and cell-based assays along with impressive tumor regression effects *in vivo* [44]. Nonetheless, compound **21** demonstrated unfavorable metabolic stability and poor thermodynamic solubility. These undesirable attributes prohibited its further development. To address these issues, Kung et al. took advantage of ligand-based and physicochemical-property based strategies and introduced an sp^3 hybridized carbon atom at the C7 position of the lactam moiety present in

21 as a surrogate for a dimethylisoxazole group [44]. These optimization efforts led to the identification of an oxetane-containing compound **22** (PF-06821497) that showed the best overlap of EZH2 inhibitory potency, *in vitro* ADME properties, pharmacodynamic effects, low toxicity as well as robust *in vivo* antitumor efficacy observed in pre-clinical models [44]. Currently, compound **22** is in clinical phase I (NCT03460977) for the treatment of follicular lymphoma, castration-resistant prostate cancer, and SCLC [45].

2.7. FTO inhibitors

m^6 -methyladenosine (m^6A) is the most prevalent internal modification found in mRNA. This dynamic modification is regulated by three categories of proteins referred to as “writers” (i.e., METTL3, METTL14, and METTL16), “readers” (YTHDF1–3 and YTHDC1–2), and “erasers” (FTO and ALKBH5) [46]. FTO, known as the fat mass obesity-associated protein, is an Fe(II)- and 2-oxoglutarate-dependent dioxygenase that predominantly catalyzes m^6A demethylation [47]. Dysregulation of FTO is linked to tumorigenesis and poor prognosis in multiple cancers [48]. Accordingly, there has been significant interest in the development of various types of small-molecule inhibitors, including those incorporating an oxetane moiety, targeting FTO in cancer therapy.

Oxetanyl compound **23** exerted potent enzymatic inhibition activity of FTO and significant selectivity over the homolog demethylase ALKBH5, with IC_{50} values of 0.35 μ M and >40 μ M, respectively (Fig. 8) [49]. Docking studies suggested that hydrogen bonds and π - π stacking interactions are responsible for its tight binding, and the oxetane moiety establishes the favorable hydrogen bond interaction with Ser 229. However, **23** displayed low antiproliferative potency. By contrast, FTO inhibitor **24**, an analogue of **23**, elicited strong antiproliferative effects in multiple cancer models (e.g., glioblastoma, acute myeloid leukemia, and gastric cancer), which was comparable to clinical drug 5-fluorouracil. In gastric tumor cells, **24** was able to increase m^6A levels and downregulate Wnt/PI3K-Akt signaling in a manner similar to FTO knockdown [49].

2.8. FLT3/PDGFR inhibitors

Compound **25** (crenolanib, also known as CP-868,596, Fig. 9) is an oxetanyl derivative initially developed as an inhibitor of platelet-derived growth factor receptor (PDGFR) [50]. Compound **25** was also found to be a selective and potent type I pan-FLT3 (FMS-like tyrosine kinase 3) inhibitor with activity against FLT3/ITD, FLT3/D835, and FLT3/F691 mutations [51]. In addition, compound **25** displayed superior potency against various FLT3 mutations in Ba/F3 transfected cells with IC_{50} values ranging from 1.3 to 67.8 nM [52]. It is currently being investigated in 12 clinical trials for the treatment of acute myeloid leukemia and is also being studied as a potential treatment for diffuse

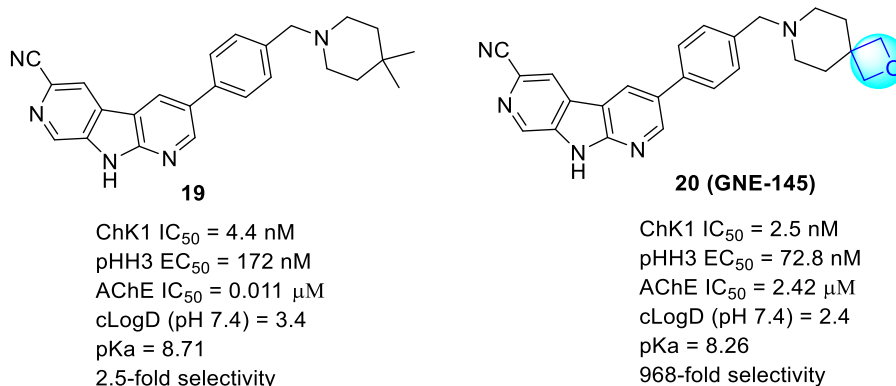


Fig. 6. Chemical structures and *in vitro* potency of ChK1 inhibitors **19** and **20** (GNE-145).

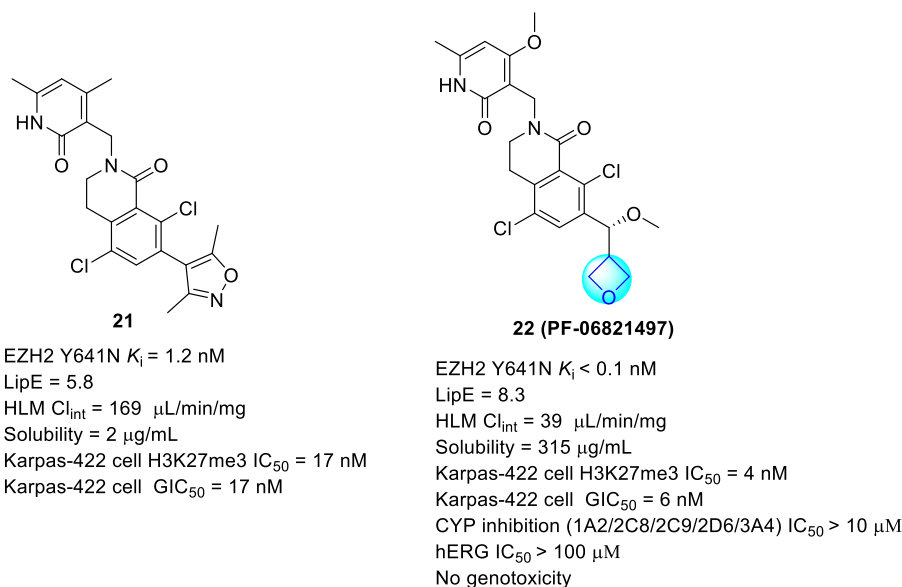


Fig. 7. Chemical structures, *in vitro* potency, and physicochemical properties of EZH2 inhibitors **21** and **22** (PF-06821497).

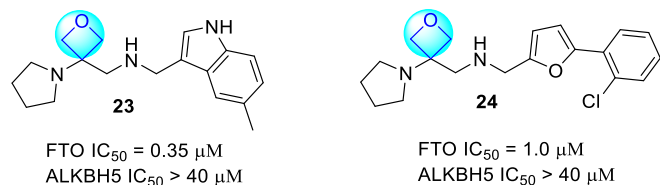
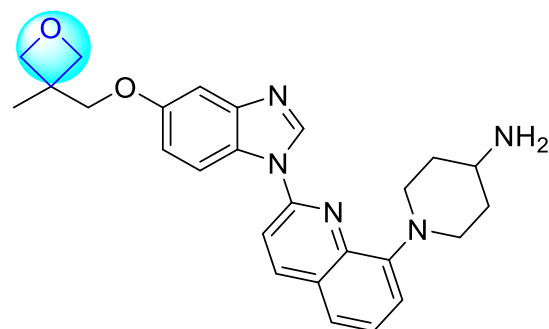


Fig. 8. Chemical structures and *in vitro* potency of FTO inhibitors **23** and **24**.



25 (crenolanib)

PDGFR α K_d = 2.1 nM
 PDGFR β K_d = 3.2 nM
 FLT3 K_d = 0.74 nM
 Ba/F3 ITD pFLT3 IC_{50} = 1.3 nM
 Ba/F3 ITD/D835Y pFLT3 IC_{50} = 8.7 nM
 Ba/F3 ITD/F691L pFLT3 IC_{50} = 67.8 nM

Fig. 9. Chemical structure and *in vitro* potency of FLT3/PDGFR inhibitor **25** (crenolanib).

intrinsic pontine glioma and progressive or refractory high-grade glioma.

2.9. IDO1 inhibitors

Indoleamine 2,3-dioxygenase 1 (IDO1) is a heme-containing enzyme that catalyzes the oxidation of L-tryptophan as the first and rate-limiting step of the kynurenine pathway [53,54]. The overexpression of IDO1 is associated with poor prognosis in various type of cancers. Given its involvement in promoting cancer immune evasion, IDO1 has gained significant attention as a crucial therapeutic target in cancer immunotherapy [53,54]. In 2020, White and colleagues performed an affinity-based screening and identified diamide **26** as a promising anti-IDO1 hit which showed potent inhibition of *N*-formylkynurenine production in HeLa cells (IC_{50} = 9.0 nM), coupled with excellent unbound potency (IC_{50} = 22 nM) in the whole blood (WB) assay [55]. Nonetheless, compound **26** suffered from high clearance and poor aqueous solubility (Fig. 10). Given that the high lipophilicity is likely responsible for undesirable solubility and metabolic stability, their initial efforts focused on the exploration of an alternative substituent (polar functionality) for the *n*-propyl group and cyclobutene moiety [55]. As shown in Fig. 10, the resulting compound **29** containing oxetane and fluorophenyl group proved to be a quite potent IDO1 inhibitor, showing significantly improved potency and metabolic profile over the hit **26**. The replacement of oxetane in compound **29** with hydroxycyclobutane remarkably compromised the inhibitory activity, as seen with compound **27**. Subsequent optimization of **29** led to 2-pyridyl oxetane **30** with further enhanced solubility and metabolic stability as well as PK properties while preserving robust anti-IDO1 activity. Notably, although analogue **28** manifested comparable potency relative to compound **30**, it possessed higher metabolic turnover and lower aqueous solubility. In addition, oxetane **30** demonstrated improved off-target profile over the corresponding cyclobutane **28** [55]. Overall, these results suggested that introducing the oxetane fragment is favorable to improve the potency, off-target profile, PK properties, conjugated with metabolic stability and solubility.

To mitigate the amide hydrolysis and improve the IDO1 inhibition of hit **26**, researchers from Merck attempted to replace the amide with heteroaromatic pyridyl rings [56]. The representative compound **31** with 4-hydroxymethylpyridine displayed over 18-fold enhancement in unbound WB potency, but this compound had high clearance, poor

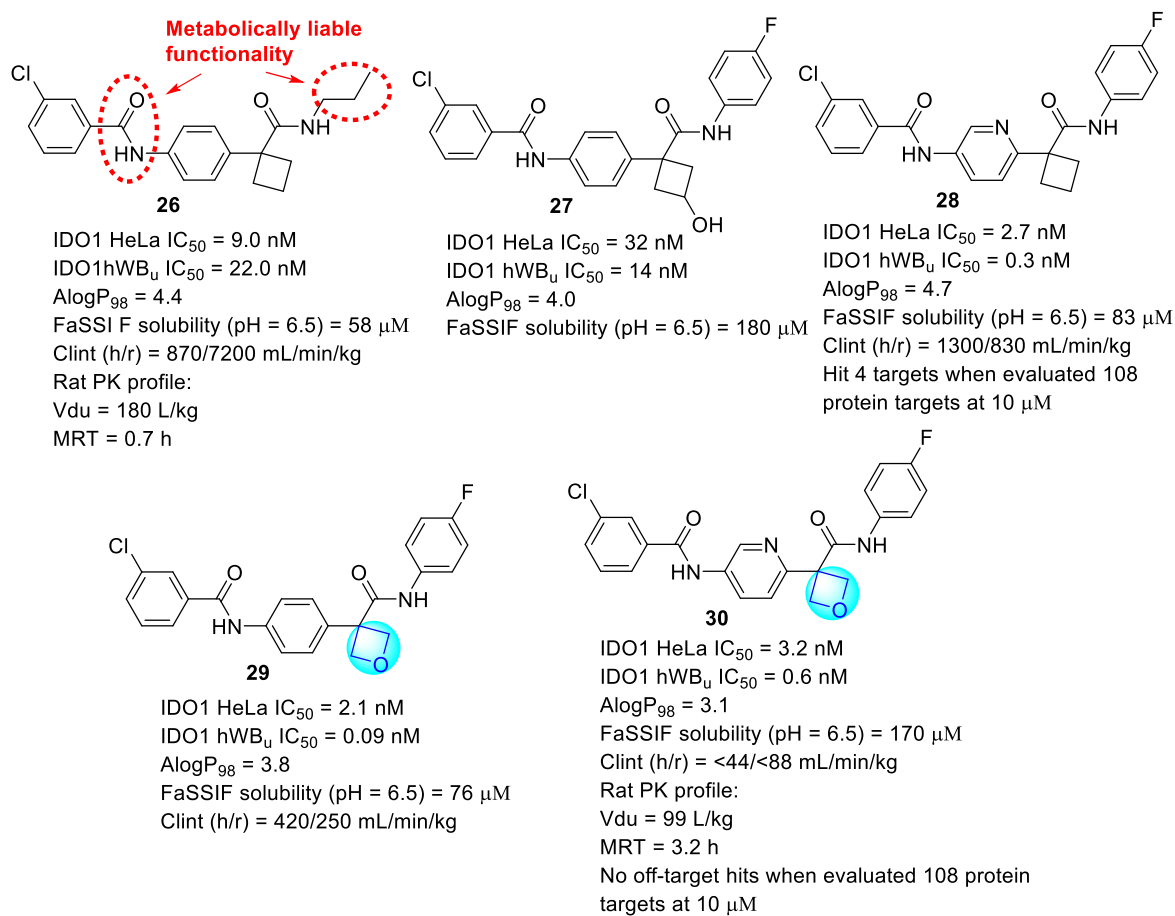


Fig. 10. Chemical structures, *in vitro* potency, and PK properties of IDO1 inhibitors 26–30.

solubility and strong CYP2C9 suppression (Fig. 11). Despite excellent metabolic stability, difluorocyclobutyl compound **32** still potently inhibited CYP2C9 and showed moderate hERG inhibition and low solubility. Interestingly, oxetane-containing compound **33** demonstrated significantly improved physicochemical properties and off-target profiles over both compounds **31** and **32** while maintaining single-digit nanomolar IDO1 potency. Oxetane **33** occupied active site pockets of IDO1 and formed several favorable hydrogen bonds, which was consistent with its high binding affinity (K_i = 0.15 nM). To block the metabolism of primary alcohol, they then developed a gem-dimethyl analogue **34** which manifested favorable potency, off-target profile, *in vitro* ADME and preclinical PK properties (Fig. 11). Oxetane derivative **34** also showed high chemical stability and no genotoxicity based on results from a 5-strain Ames, and delayed tumor growth *in vivo* [56]. In summary, examples **31**–**34** highlight the crucial role of the oxetane motif in improving the potency, physicochemical properties, off-target, PK, and toxicity profiles.

2.10. MMP-13 inhibitors

Another notable application of the oxetane moiety is observed in the development of small molecule inhibitors that target matrix metalloproteinase 13 (MMP-13) in breast cancer [57]. By incorporating the oxetane moiety, these inhibitors aim to enhance the physicochemical properties and microsomal turnover. Compound **35** (RF036, Fig. 12) demonstrated highly potent and selective MMP-13 inhibition (K_i = 2.7 nM) but suffered from poor metabolic stability and low solubility. Replacement of the methyl group with oxetane unit and substitution of the sulfur atom present in **35** with carbon or nitrogen resulted in corresponding compound **36** and **37**, which maintained the low nanomolar

inhibitory potency and exquisite selectivity for MMP-13. Importantly, these two oxetanyl derivatives exhibited significantly improved metabolic stability and aqueous solubility over compound **35**, as illustrated in Fig. 12. It was also found that both compounds could effectively block MMP-13-mediated osteoclastogenesis but spare collagenolysis [57].

2.11. MNK inhibitors

Mitogen-activated protein kinase (MAPK) interacting kinases 1 and 2 (MNK1 and MNK2) play a fundamental role in the activation and regulation of translation initiation factor 4E (eIF4E). Accumulating evidence has revealed dysregulation of eIF4E and MNK1/2 in various cancers, making this axis an active and promising area of interest for the development of new cancer therapeutics [58–60]. In 2020, Kwiatkowski et al. identified benzamide-pyridine **38** (Fig. 13) as potent dual MNK1 and MNK2 inhibitors (IC_{50} = 0.88 and 0.34 μ M, respectively) [61]. Consistently, it displayed potent inhibition of phosphorylation of eIF4E in Hela cells (IC_{50} = 0.86 μ M). This compound also demonstrated good *in vitro* ADME properties and decent PK profiles (i.e., F = 61%). Installation of *N*-methylpyrazole moiety on the pyridine ring led to a slight increase in biochemical and cellular potency, as seen with compound **39**. Through the replacement of a methyl group in compound **39** with an oxetane unit, compound **40** demonstrated an additional enhancement in MNK inhibitory potency (MNK1 IC_{50} = 0.2 μ M and MNK2 IC_{50} = 0.089 μ M) and suppression of eIF4E (IC_{50} = 0.2 μ M). Oxetane **40** did not show CYP and hERG inhibition and was stable in an *in vitro* human and mouse liver microsomal assay (Fig. 13). The favorable *in vitro* ADME properties translated into favorable *in vivo* PK in mice. Significantly, oxetane **40** demonstrated significant improvement in exposure, clearance, and bioavailability relative to compound **38** [61].

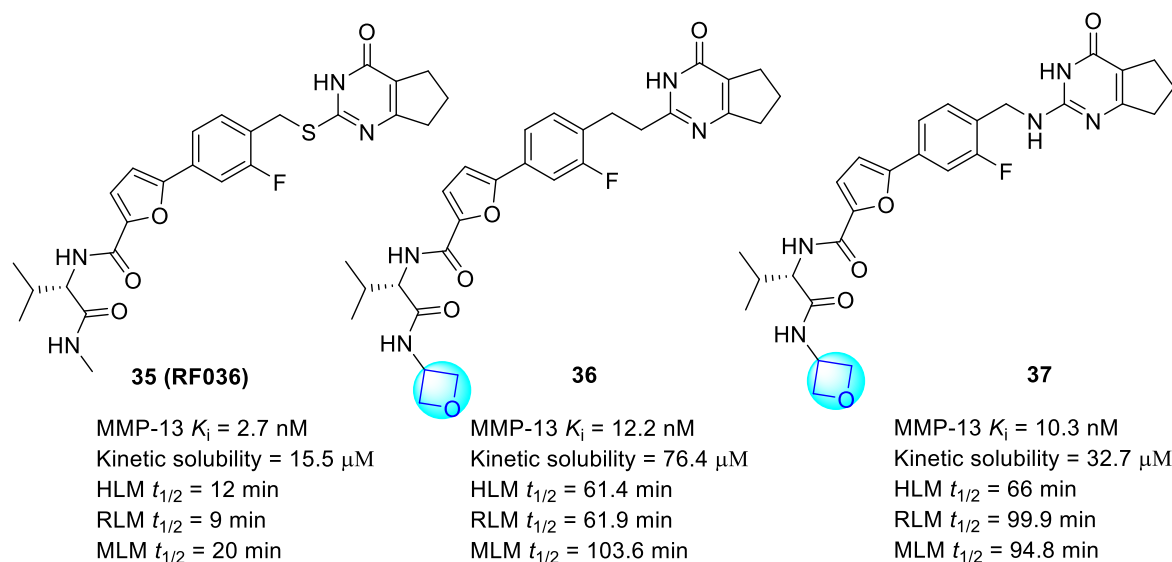


Fig. 12. Chemical structures, *in vitro* potency, and physicochemical properties of MMP-13 inhibitors 35–37.

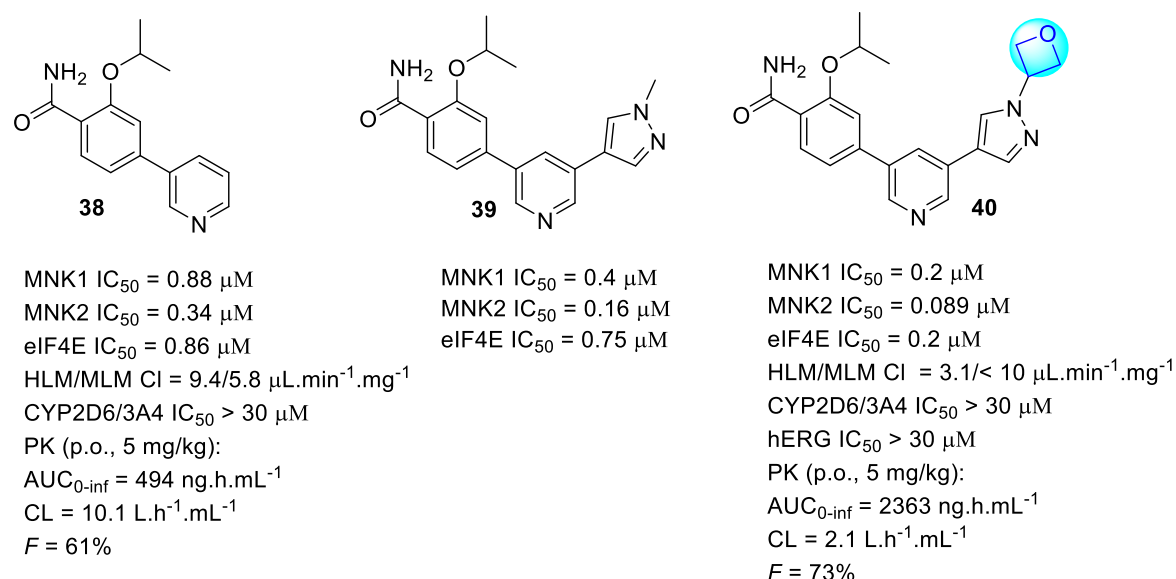


Fig. 13. Chemical structures, *in vitro* potency, physicochemical properties, and PK properties of MNK inhibitors 38–40.

compound **44** suffered from CYP3A4 TDI liability (IC_{50} = 2.5 μ M). To attenuate the CYP3A4 TDI, increase the cellular potency and improve the aqueous solubility, these researchers devised the pyrimidoamino-tropane scaffold through installation of the ethylene bridge at the carbon atoms adjacent to the piperidine nitrogen. The corresponding compound **45** showed substantially improved overall profiles over compound **44** (Fig. 14). Subsequent optimization of compound **45** led to compound **46** (GNE-555) with further gain in mTOR potency (K_i = 1.5 nM), anti-proliferative activity (EC_{50} values of 29 and 75 nM against PC3 and MCF-7 cells, respectively), and kinase selectivity. Oxetane **46** was an orally available, highly selective, and metabolically stable mTOR inhibitor, which exhibited comparable efficacy at less than half the dose of clinical drug **43** in *in vivo* studies [67].

2.13. PHGDH inhibitors

Phosphoglycerate dehydrogenase (PHGDH), an enzyme that catalyzes the first and rate-determining step of serine biosynthesis, is

abnormally overexpressed in numerous malignant tumor cells [68,69]. PHGDH is a promising target for cancer treatment. Compound **47** (Fig. 15), identified from fragment-based screening, demonstrated potent inhibitory activity against PHGDH (IC_{50} = 0.24 μ M) but lacked cellular activity [70]. In an effort to enhance its pharmacological activity by reducing the polar surface area (PSA), Mullarky and colleagues conducted structural modifications on compound **47** [70]. One of the modifications involved replacing the chiral hydroxymethyl group with an oxetane moiety, resulting in comparable or improved activity relative to compound **47**. Among them, compound **48** stood out as the most potent PHGDH inhibitor (IC_{50} = 0.015 μ M), showing almost 90% inhibition of serine synthesis pathway at 10 μ M. Given the low membrane permeability liability of the carboxylate, these investigators next turned to a prodrug strategy for further improving potency in cell-based assays. The resulting compound **49** (IC_{50} = 1.46 μ M) exerted significant inhibition of $^{13}C_3$ -serine synthesis and effectively blocked the proliferation of Carney cells [70]. This study underscores the crucial role of the oxetane group in enhancing cell membrane permeability.

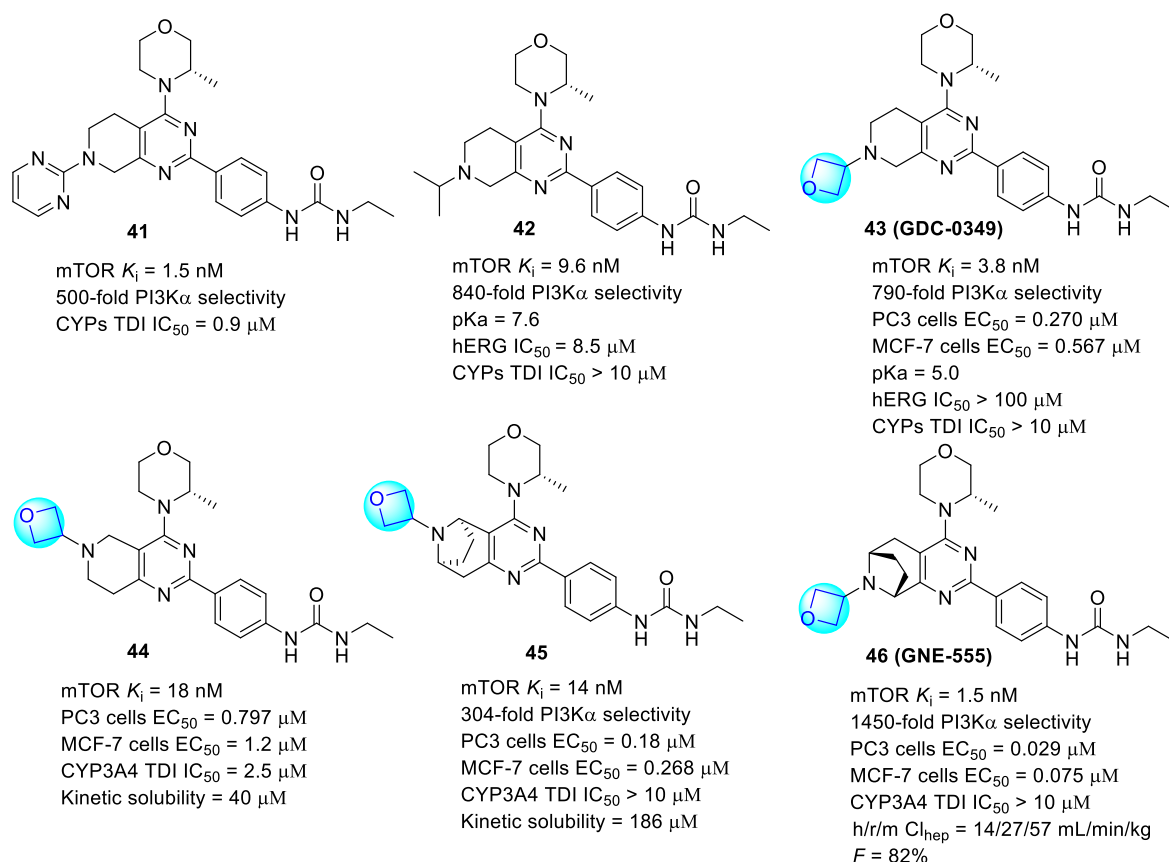


Fig. 14. Chemical structures, *in vitro* potency, physicochemical properties, and PK properties of mTOR inhibitors 41–46.

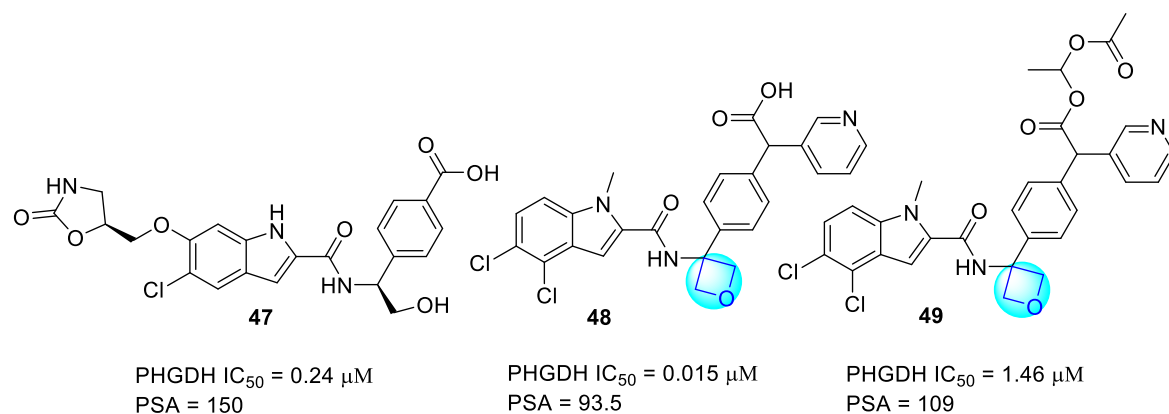


Fig. 15. Chemical structures and *in vitro* potency of PHGDH inhibitors 47–49.

2.14. PRMT5 inhibitors

The protein arginine methyltransferase 5 (PRMT5) is a major enzyme involved in mono- and symmetric dimethylation of arginine residues [71–73]. Upregulation of PRMT5 expression is frequently observed in various human malignancies and is often associated with poor patient survival. Pharmacological inhibition of PRMT5 represents a promising strategy for therapeutic intervention in multiple types of human cancers. As a result, several research groups have undertaken drug discovery efforts to develop potent and selective inhibitors of PRMT5, including those incorporating an oxetane moiety.

Oxetanyl compound **50** (EPZ015666, Fig. 16) was an orally available PRMT5 inhibitor (IC_{50} = 22 nM) that displayed broad selectivity against

a panel of other histone methyltransferases [74,75]. Treatment of mantle cell lymphoma (MCL) cell lines with compound **50** led to inhibition of SmD3 (PRMT5 substrate) methylation and cell growth arrest, with IC_{50} values in the submicromolar range (e.g., Z-138 cells GI_{50} = 351 nM). Compound **50** also demonstrated low plasma clearance and low to moderate *in vitro* clearance in human and mouse, in part due to the incorporation of an oxetane ring [75,76]. However, higher clearance was observed in dog liver microsomes and hepatocytes, which translated to a relatively higher *in vivo* turnover rate in dogs. Metabolite profiling in hepatocytes revealed that the metabolites **50-M1** and **50-M2** are generated by oxidation of oxetane ring predominantly catalyzed by CYP2D isoforms, whereas **50-M3** was produced via an *N*-dealkylation reaction (Fig. 17) [76]. Notably, oral dosing of compound **50** showed

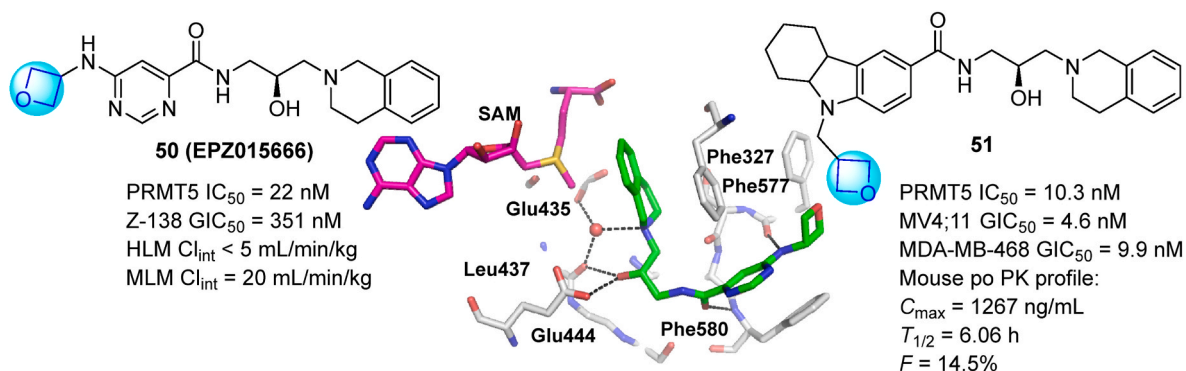


Fig. 16. Chemical structures, *in vitro* potency, and PK properties of PRMT5 inhibitors **50** (EPZ015666) and **51**. Crystal structure of compound **50** with PRMT5 (PDB code 4X61).

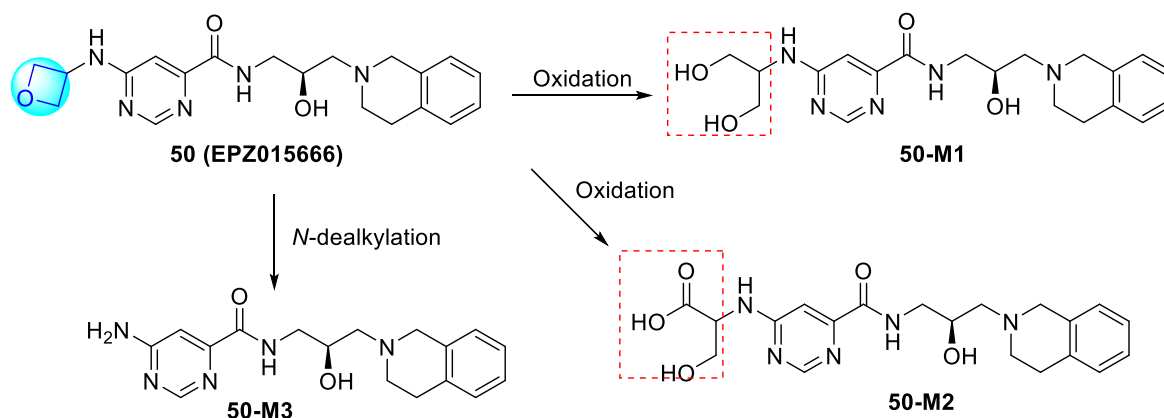


Fig. 17. Metabolism of oxetane-containing compound **50** (EPZ015666).

dose-dependent anticancer activity in several MCL xenograft models. X-ray crystallography analysis revealed the key cation- π interaction between compound **50** and cofactor SAM, multiple favorable hydrogen bond interactions, and a π - π stacking interaction between tetrahydroisoquinoline ring and residue Phe327 (Fig. 16).

Recently, Tang and co-workers designed and synthesized a series of new tetrahydroisoquinoline derivatives [77]. Among them, compound **51** bearing an oxetane moiety potently inhibited the enzymatic activity of PRMT5 (IC_{50} = 4.2 nM) and effectively blocked tumor cell proliferation (Fig. 16). Importantly, oxetanyl analogue **51** demonstrated acceptable pharmacokinetic profiles and impressive antitumor efficacy in an MV4-11 xenograft model. In addition, computational modeling suggested that the oxetane motif present in compound **51** is extended to

the hydrophobic pocket and makes the hydrogen bonding interaction with residue Phe327 [77].

2.15. TNKI inhibitors

The unique utility of oxetane is to improve aqueous solubility and bioavailability, as exemplified by compound **53** (OBD9) targeting traf2 and Nck-interacting kinase (TNIK) [78]. TNIK is a downstream signal protein of the Wnt/ β -catenin pathway and implicated in several forms of cancer [79–81]. Compound **52** (mebendazole, Fig. 18) is an anthelmintic drug originally used for curing parasitic infections, the anti-neoplastic potential of which has been recently disclosed. However, this compound was subjected to extremely poor aqueous solubility and low

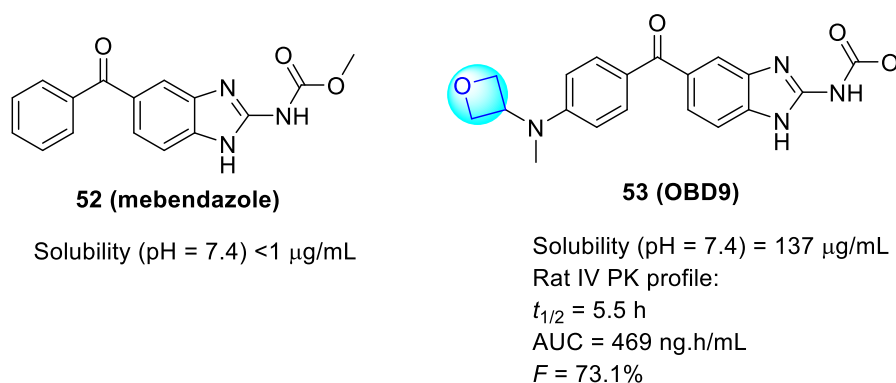


Fig. 18. Chemical structures, aqueous solubility, and PK properties of **52** (mebendazole) and TNIK inhibitor **53**.

bioavailability that impeded its clinical development in oncology. To surmount these problems, the Zetter group incorporated the oxetane motif at the phenyl ring [82]. The optimized compound **53** (Fig. 18) achieved over 137-fold enhancement in water solubility and manifested potent antiproliferative activity against several tumor cell lines [82]. It remarkably evaded the tumor growth without noticeable toxicity in a prostate cancer xenograft model. In a follow-up study, oxetane derivative **53** was found to induce the autophagic degradation of TNIK and downregulate the protein levels of several Wnt downstream targets [78]. Importantly, **53** showed good oral bioavailability and strongly suppressed the growth of colon cancer *in vivo* [78].

3. Oxetanes in antiviral drug discovery

3.1. RSV inhibitors

Respiratory syncytial virus (RSV) is the leading cause of pediatric respiratory disease [83,84]. There is a major unmet medical need for treating RSV infections and prophylaxis. In recent years, attempts to combat RSV infection have mostly focused on the inhibition of membrane or fusion viral polymerase activity. Benzimidazole derivative **54** was a modest RSV fusion (F) inhibitor but displayed desirable microsomal clearance and permeability (Fig. 19). Taking compound **54** as a starting point, Feng and co-workers developed compound **55** with over 98-fold enhancement in anti-RSV potency ($EC_{50} = 25$ nM) [85]. A further structure-activity relationship (SAR) study on the hydroxyethyl group at N1 position of benzimidazole scaffold culminated in identification of oxetanyl compound **56** that showed single-digit nanomolar inhibitory potency, favorable physicochemical properties, good *in vivo* pharmacokinetics in mice, and excellent safety profile (Fig. 19). In a BALB/c mouse model of RSV infection, compound **56** exerted dose-dependent antiviral efficacy [85]. As such, the presence of oxetane substitution improved the activity and pharmacokinetic profile of **56**. In another study, researchers from AstraZeneca Pharmaceuticals investigated the anti-RSV effect of various secondary amines substituted at the pyridine ring [86]. Among them, compound **57** (AZ-27) bearing an

oxetane spiro-fused piperidine moiety stood out as the most potent inhibitor of RSV L protein ($EC_{50} = 10$ nM). It could block the initiation of *de novo* RNA synthesis at the promoter [87]. Notably, replacement of oxetane moiety with 1-methylazetidine, 1-actylazetidine or tetrahydropyran substantially compromised the anti-RSV activity.

Applications of oxetane to regulate basicity of the terminal amine is the focal point of anti-RSV drug discovery efforts, which is critical to reduce the volume of distribution (Vss) while maintaining effective RSV inhibition activity (Fig. 20). Aminoquinolines represented by compound **58** were reported as a new class of inhibitors of RSV F fusion [88]. Nevertheless, compound **58** showed negligible oral exposure which could be ascribed to its low cellular permeability (Fig. 20). To enhance the permeability and oral bioavailability, diverse modifications were carried out at the aminoethyl fragment. The resulting compound **59** achieved favorable permeability but elicited decreased anti-RSV activity and high Vss correlated with unexpected accumulation of the compound in undesired tissues. Replacing the gem-di-methyl group of **59** with an oxetane ring yielded compound **60** with remarkably improved anti-RSV effect and excellent *in vivo* oral activity [88]. The decreased Vss of **60** can be attributed to the declined basicity of the terminal amine group by the adjacent electron-withdrawing oxetanyl group. A molecular docking study suggested that the oxetane moiety primarily contributed toward restricting the conformation of the ethylamine head group, although it does not establish any interaction with RSV F protein. Ultimately, the transformation of quinoline in compound **60** to a quinazoline led to the discovery of clinical candidate **61** (RO-0529, Ziresovir) as shown in Fig. 20. Compound **61** manifested a larger safety window with the preferred pharmacokinetics relative to compound **60**. Importantly, compound **61** demonstrated promising *in vivo* anti-RSV efficacy [89]. Currently, compound **61** is undergoing clinical trials for the treatment of RSV infections (NCT03699202 and NCT04231968).

3.2. HCV inhibitors

Conformationally restricted nucleosides have been explored extensively as antivirals for treatment of hepatitis C virus (HCV) (Fig. 21). The

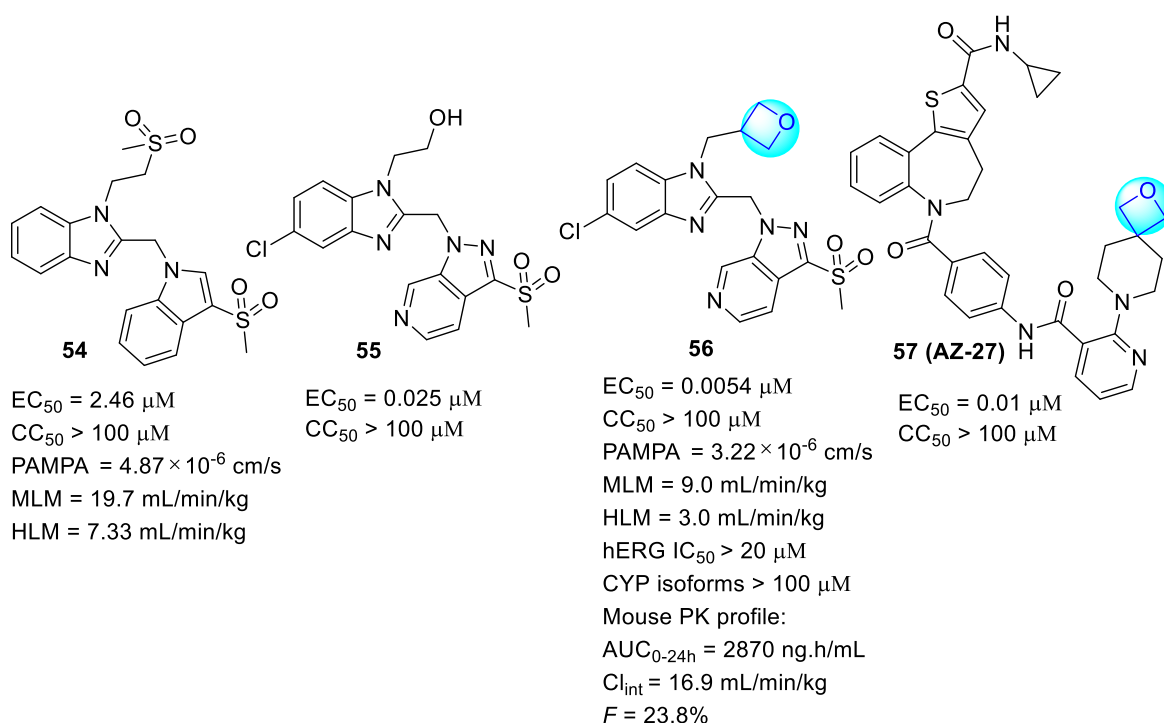


Fig. 19. Chemical structures, *in vitro* potency, physicochemical and PK properties of RSV inhibitors **54–57**.

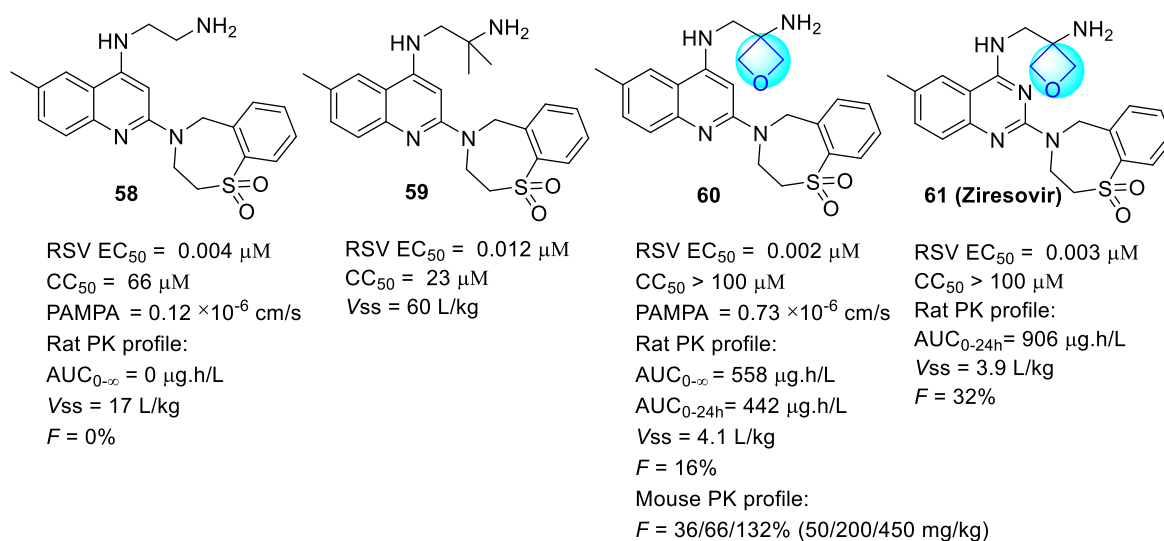


Fig. 20. Chemical structures, *in vitro* potency, physicochemical and PK properties of RSV inhibitors 58–61.

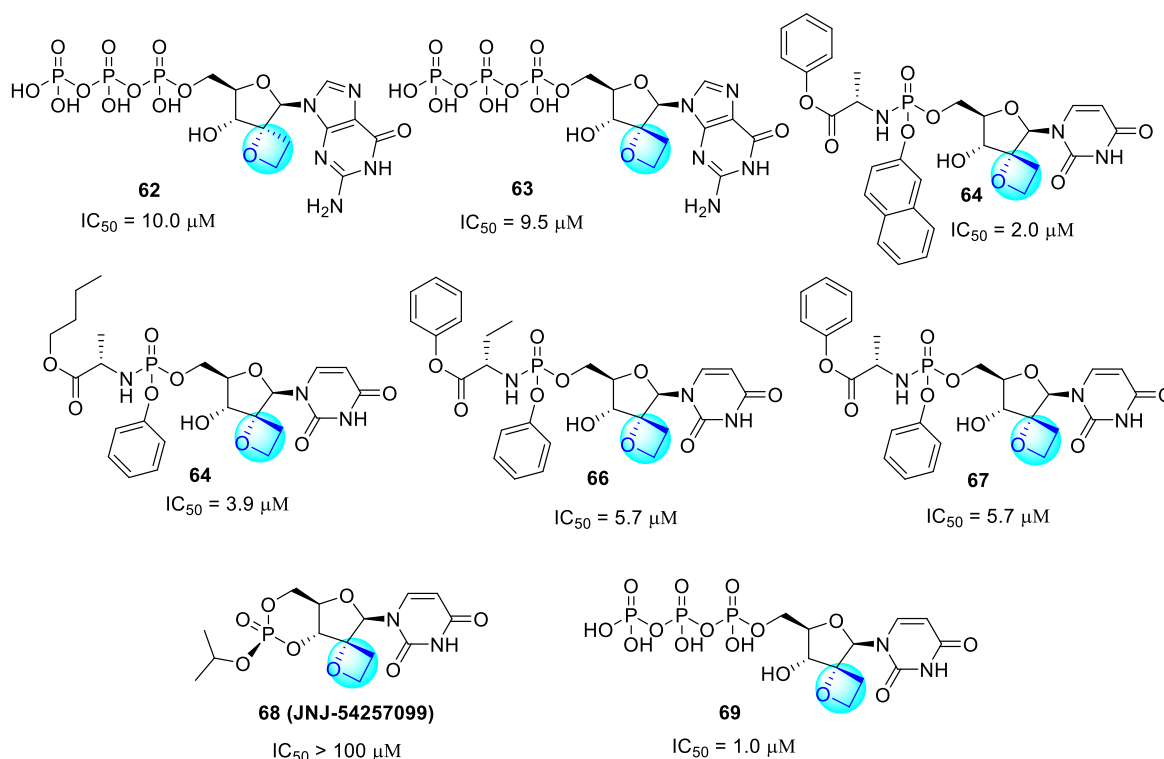


Fig. 21. Chemical structures and *in vitro* potency of HCV inhibitors 62–69.

oxetane guanosine triphosphate **62** displayed modest inhibition of HCV NS5B polymerase (IC₅₀ = 10 μM) [90]. Its stereoisomer **63** retained similar potent activity against both wild-type and S282T HCV NS5B polymerase (IC₅₀ = 9.5 and 10.4 μM, respectively) [91]. The phosphoramidate prodrugs **64–67** carrying a 2'-spirooxetane moiety represented a new class of HCV NS5B RNA-dependent RNA polymerase (RdRp) inhibitors, exhibiting EC₅₀ values ranging from 2.0 to 5.7 μM, with no apparent cytotoxicity (CC₅₀ > 98.4 μM) [92]. Cyclic phosphate ester **68** (JNJ-54257099, also known as AL-704) was a 2'-deoxy-2'-spirooxetane uridine nucleotide prodrug that was endowed with HCV RdRp inhibitory activity [93]. Upon metabolism, these phosphoramidate prodrugs could be converted into the same and active

triphosphate metabolite **69** (IC₅₀ = 1.0 μM). Of particular note, compound **68** demonstrated attractive off-target safety, favorable PK profiles, and pronounced *in vivo* antiviral efficacy [93]. However, further development of compound **68** was discontinued following completion of phase I clinical studies due to insufficient inhibition activity against HCV genotype 1.

4. Oxetanes in anti-autoimmune diseases drug discovery

4.1. BTK inhibitors

Apart from hematologic malignancies, BTK inhibition has emerged

as a promising therapeutic strategy for treating various inflammatory and autoimmune diseases due to its critical role in immunity [94,95]. Significant progress has been made in developing BTK inhibitors as potential clinical interventions for these conditions. Based upon the structure of compound **70** (RN486, Fig. 22), the Xiang group designed and synthesized a series of 5-phenylpyridin-2(1H)-one derivatives [96]. Among them, compound **71** stood out as the most promising BTK inhibitor ($IC_{50} = 16$ nM), which displayed nearly equivalent enzymatic potency but approximately 3.4-fold stronger suppressive activity in a Ca^{2+} flux assay as compared to compound **70** (Fig. 22). Further PK studies revealed that compound **71** exhibits higher exposure and maximum plasma concentration and lower systemic clearance as well as better bioavailability than **70**. This significant improvement in the PK profile of compound **71** could be ascribed to the incorporation of 3-oxetane that modulated the basicity of the piperazine moiety. Importantly, **71** effectively delayed the rheumatoid arthritis (RA) progression in a collagen-induced arthritis model [96].

The Young group at Genentech disclosed compound **72** (G-278) as a single-digit nanomolar BTK inhibitor ($IC_{50} = 4.0$ nM) [97,98]. It also exhibited potent inhibition of BCR-stimulated CD69 expression on B cells in WB assay ($IC_{50} = 35$ nM) and desirable physicochemical properties, as depicted in Fig. 23. Nevertheless, oxetane **72** suffered from dose-limiting toxicities with unacceptably low safety margins in animal models, including hepatotoxicity. These liabilities made this compound unsuitable for the treatment of RA. In a follow-up study, the Young group focused their efforts on reducing the hepatocyte cytotoxicity by lowering log D and pKa, while maintaining or improving WB potency and PK properties [98]. Initial optimization of the tricyclic H3 motif and central benzene ring in compound **72** led to pyridine analogue **73** ($K_i = 1.8$ nM) with roughly 2-fold increase in WB potency and metabolic stability. PK studies suggested that **73** demonstrates good bioavailability but high clearance and short half-life time ($F = 65.1\%$, $CL_{hep} = 165$ mL/min/kg, and $t_{1/2} = 0.4$ h, respectively). Subsequent replacement of the piperazine moiety with an azetidine motif gave compound **74** with almost 4.2-fold improvement in biochemical potency but compromised the metabolic stability and WB potency. Ultimately, they optimized the piperazine ring to increase van der Waals contacts with the edge of the protein and impact the conformation of the ring itself using the small substituents. This optimization led to discovery of oxetanyl derivative **75** (GDC-0853, fenebrutinib) with outstanding BTK potency ($K_i = 0.91$ nM) and desirable physicochemical properties and PK profiles (Fig. 23) [98]. Compound **75**, an orally available, potent, highly selective, reversible BTK inhibitor, is currently being evaluated in clinical trials for

the treatment of various autoimmune diseases, such as RA, lupus, and progressive multiple sclerosis. It has been shown to be well-tolerated in clinical studies and has a favorable safety profile [99].

Recently, Owens and co-workers disclosed compound **76** (Fig. 23) which showed potent inhibition of BTK activity and CD69 expression on anti-IgM-stimulated B cells in human WB assay, with IC_{50} values of 0.8 and 128 nM, respectively [100]. In addition, this compound had excellent solubility and relatively low *in vitro* clearance as illustrated in Fig. 23. Unfortunately, it strongly inhibited the hERG channel, which hampered its further development. Afterward, Owens and colleagues shifted their focus on reducing the basicity of compound **76** to mitigate hERG toxicity. Their efforts culminated in discovery of compound **77** (PRN1008, rilzabrutinib) as a potent, selective, reversible covalent and orally available inhibitor of BTK (Fig. 23). Despite lower solubility, oxetane derivative **77** showed marginal effect on inhibition of hERG channel when compared to the dimethylpiperazine counterpart **76**. This significant improvement in hERG profile could be attributed to the electron-withdrawing nature of the oxetanyl group that diminished the basicity of piperazine [100]. Currently, compound **77** is undergoing clinical trials for the treatment of several autoimmune diseases, including immune thrombocytopenia, pemphigus vulgaris, and IgG4-related disease [101–103].

Compound **80** (BIIB091, Fig. 24) is a potent, highly selective, and reversible BTK inhibitor for the treatment of multiple sclerosis [104]. Researchers from Biogen began their BTK inhibitor discovery chemistry with 2-aminopyrimidine scaffold. Initial SAR investigations led to identification of benzoannulene analogue **78** with excellent biochemical and WB potency (BTK $IC_{50} < 0.5$ nM and CD69 $IC_{50} = 0.104$ μ M). Yet, compound **78** demonstrated high microsomal clearance in both rat and human liver microsome and low solubility at pH 6.8. Subsequent medicinal chemistry efforts focused on lowering the lipophilicity to improve drug-like properties. Benzoazepine **79** improved the microsomal stability and aqueous solubility but exhibited a slight decrease in biochemical and WB potency. To mitigate the potential risk of off-target effects associated with strongly basic functional groups, the researchers then sought to reduce the pKa of the benzoazepine moiety by replacing the methyl group with an oxetane motif. This modification resulted in compound **80**, which exhibited enhanced BTK inhibition activity ($IC_{50} < 0.5$ nM) and WB potency ($IC_{50} = 0.07$ μ M) as well as exquisite kinase selectivity, while maintaining desirable solubility. Compound **80** demonstrated favorable *in vitro* and *in vivo* safety profiles and good PK properties in animal models (e.g., $F = 31$ –89%). Consistently, **80** induced a significant reduction of the anti-NP IgM antibody titers *in vivo*

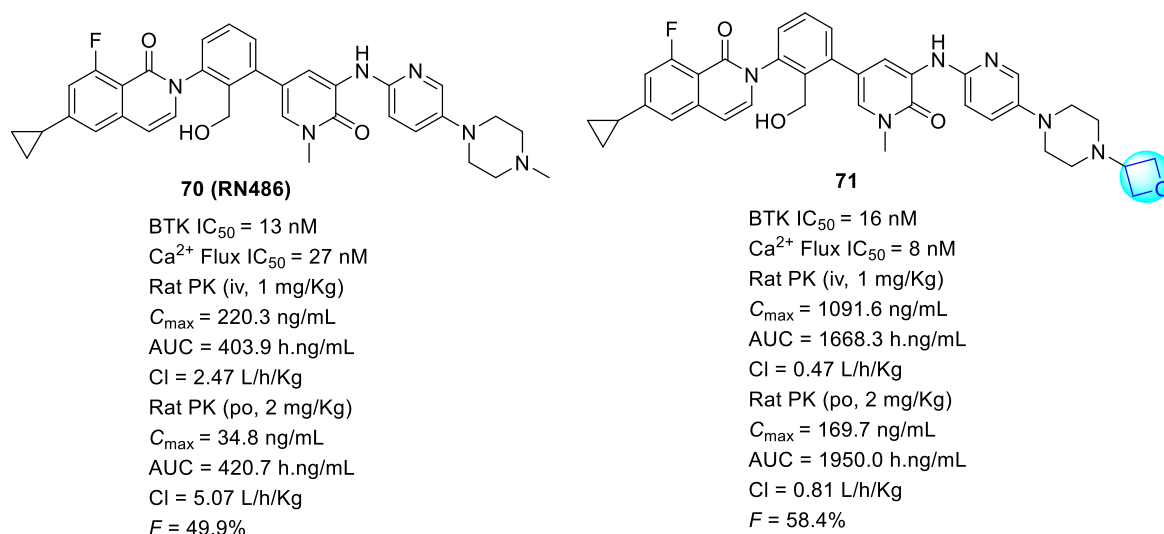


Fig. 22. Chemical structures, *in vitro* potency, and PK properties of BTK inhibitors **70** and **71**.

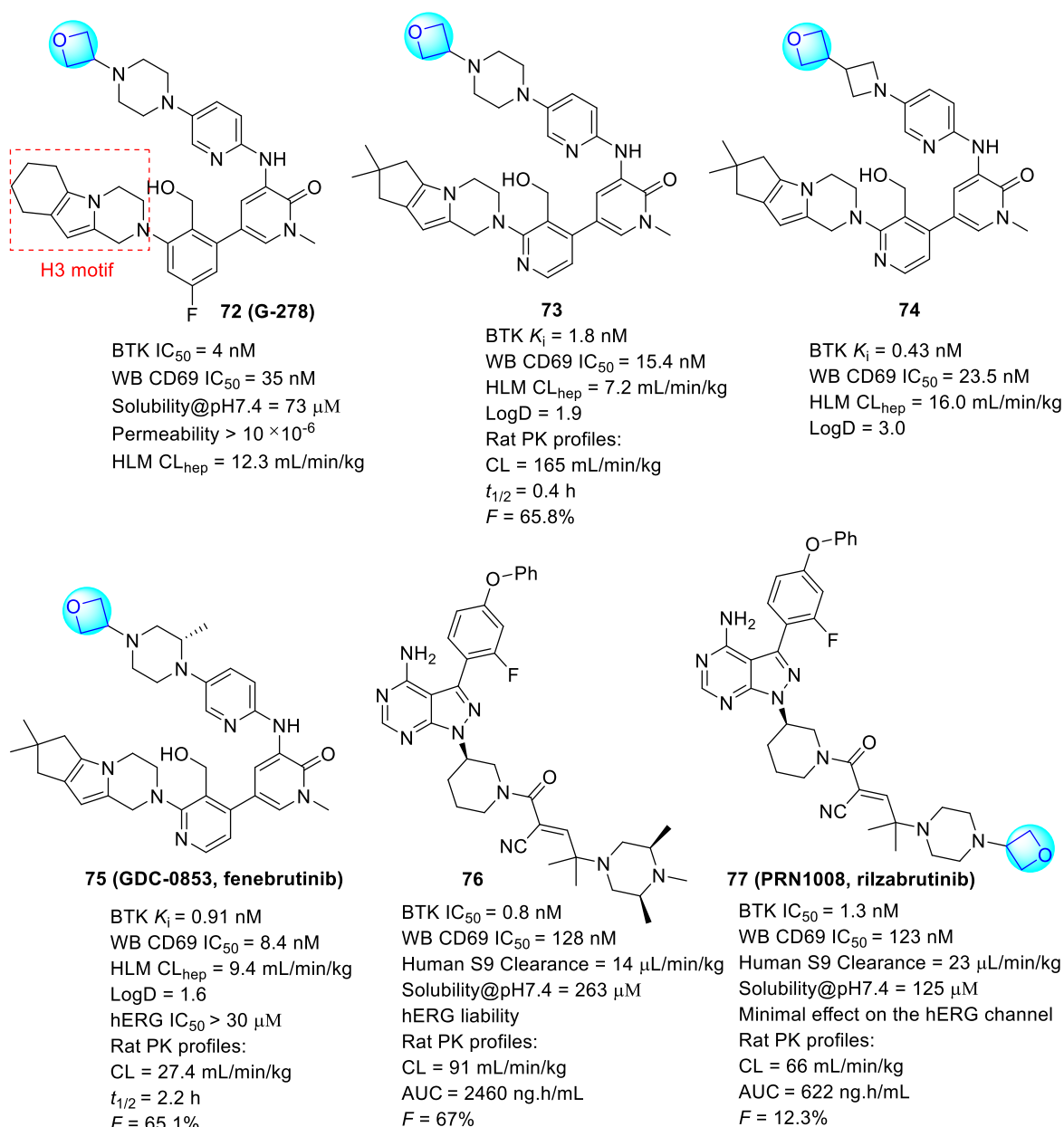


Fig. 23. Chemical structures, *in vitro* potency, and PK properties of BTK inhibitors 72–77.

[104].

Bradshaw and co-workers detailed their efforts to develop a novel series of potent and selective reversible covalent BTK inhibitors using an inverted-cyanoacrylamide approach [105]. The early lead compound **81** displayed potent inhibition of BTK enzymatic activity (IC_{50} = 16 nM) but no BTK occupancy after washout, as illustrated in Fig. 25. Optimization of the capping group in compound **81** by incorporating a 3-oxetanyl group led to compound **82** with substantially improved biochemical potency (IC_{50} = 1.9 nM) and BTK occupancy (Fig. 25), which also had superior residence time (167 ± 21 h). In addition, compound **82** exhibited high potency in a CD69 expression assay (IC_{50} = 240 nM). Moreover, the orally bioavailable inhibitor **82** demonstrated sustained BTK occupancy *in vivo* [105].

4.2. Protein kinase C θ inhibitors

Protein kinase C θ (PKC θ), a member of a large family of serine/threonine kinases, plays an important role in T cell biology and

represents an attractive therapeutic target for the treatment of autoimmune diseases [106,107]. Collier and co-workers performed biochemical screening and identified lead compound **83** that showed high affinity for inhibition of PKC θ (K_i = 3 nM, Fig. 26) [108]. It demonstrated micromolar cell potency for the inhibition of IL-2 release from peripheral blood mononuclear cells (PBMCs) following stimulation with anti-CD3/CD28 (IC_{50} = 2.6 μ M). However, it exhibited poor selectivity against PKC δ isoform (K_i = 12 nM) and other kinases (e.g., ROCK K_i = 6 nM and JAK2 K_i = 13 nM). Chemical optimization of compound **83** led to cyclobutane analogue **84** that potently suppressed the enzymatic activity of PKC θ (K_i = 3 nM) and secretion of IL-2 from stimulated PBMCs and was isoform selective against PKC α and δ . Nonetheless, compound **84** had hERG liability (IC_{50} = 0.7 μ M) and exhibited strong cytotoxicity against human fibroblast cell line-1 (HFL-1) with an IC_{50} value of 0.65 μ M. Cyclobutane **84** also demonstrated micromolar inhibitory activity against CYP2C9/2D6. Further optimization of **84** resulted in oxetane derivatives **85** and **86** with significant improvement in isoform selectivity and safety profiles (i.e., hERG IC_{50} > 10 μ M and

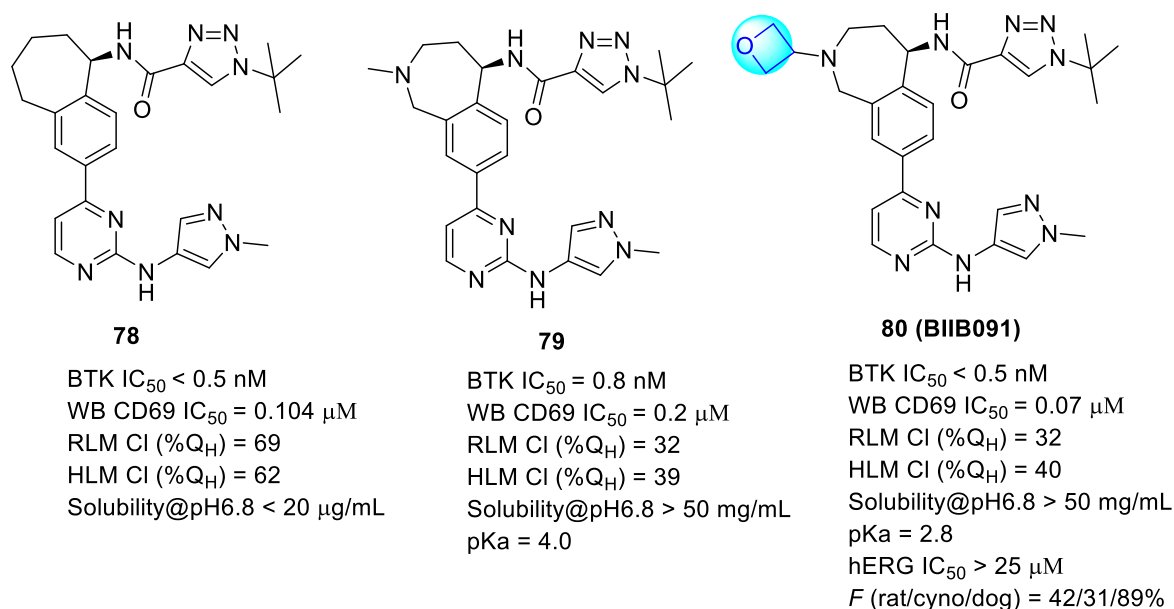


Fig. 24. Chemical structures, *in vitro* potency, and physicochemical properties of BTK inhibitors 78–80.

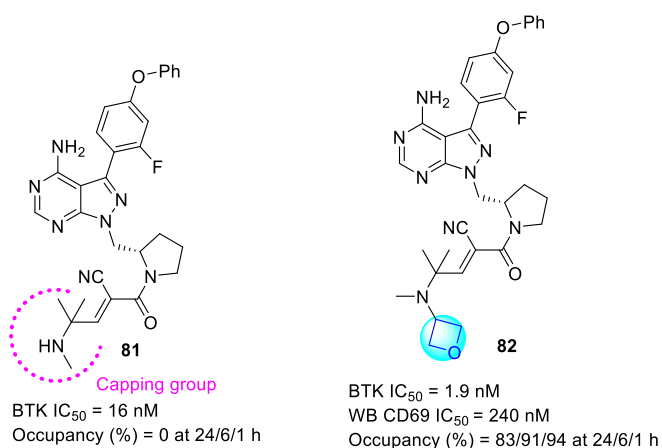


Fig. 25. Chemical structure and *in vitro* potency of reversible covalent BTK inhibitors 81 and 82.

CYP2C9/2D6 $IC_{50} > 30$ μ M), maintaining single-digit nanomolar PKC θ inhibition activity ($K_i = 8$ and 6 nM, respectively). Oxetanes **85** and **86** displayed enhanced metabolic stability and lower cytotoxicity against HFL-1 cells relative to cyclobutane **84** (Fig. 26). Significantly, oxetane **86** showed good selectivity when profiled against a panel of kinases, receptors, and ion-channels. Moreover, **86** demonstrated good aqueous solubility and bioavailability, which effectively ameliorated symptoms of experimental autoimmune encephalomyelitis [108]. These results revealed that the introduction of an oxetane motif adjacent to a primary amine optimizes *in vitro* ADMET properties and kinase selectivity.

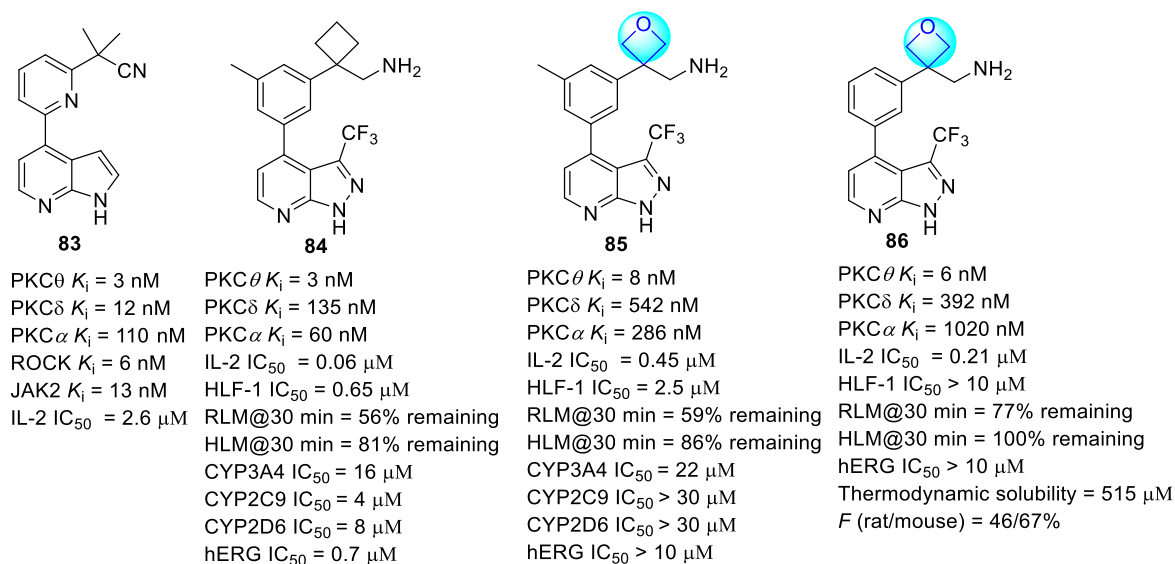
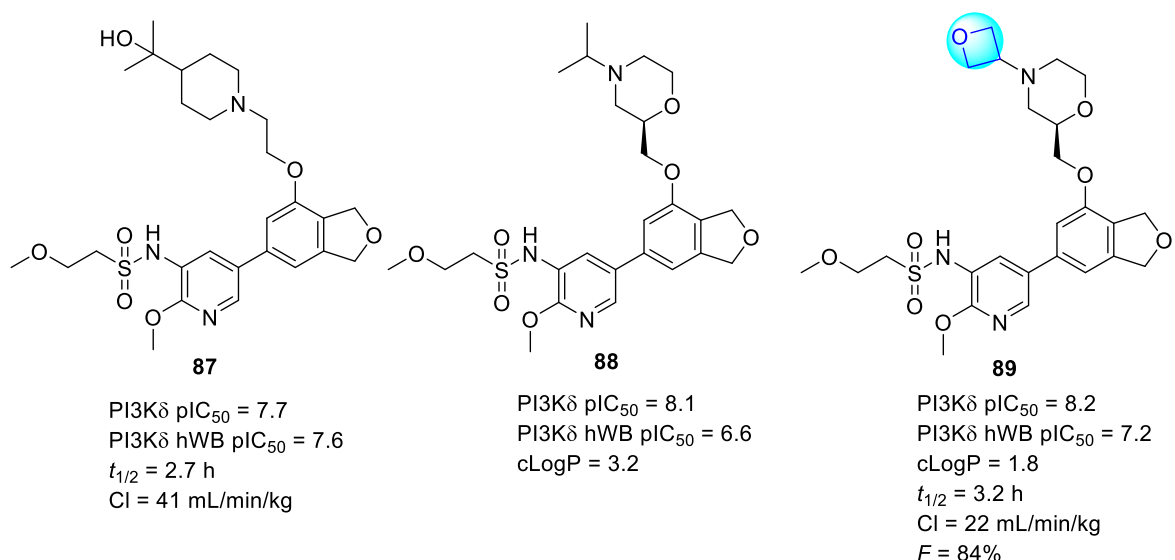
4.3. PI3K δ inhibitors

Henley et al. at GlaxoSmithKline reported the structure-based optimization of dihydroisobenzofuran-based PI3K δ inhibitors and identification of potent and orally bioavailable compound **89** (Fig. 27) [109]. The advanced lead compound **87** exhibited good biochemical and cellular potency (PI3K $pIC_{50} = 7.7$ and PI3K hWB $pIC_{50} = 7.6$) but with moderate clearance (Cl = 41 mL/min/kg). Subsequent optimization of compound **87** by introducing bulky morpholine fragment afforded

compound **88** with improved PI3K δ inhibition activity but showing a significant drop in WB potency. To decrease the lipophilicity, the authors replaced the isopropyl group with an oxetane motif and obtained compound **89** that strongly blocked the enzymatic activity of PI3K ($pIC_{50} = 8.2$ and hWB $pIC_{50} = 7.2$) and demonstrated desirable pharmacokinetic profiles (e.g., F = 84% and Cl = 22 mL/min/kg). Notably, compound **89** had promising PI3K δ selectivity over Vps34 (PIK3C3, class III PI3K), which might confer superior toxicological safety cover for its predicted clinical exposure [109].

4.4. SYK inhibitors

Spleen tyrosine kinase (SYK), also known as a tyrosine protein kinase, is a vital mediator of signaling in a range of immune cell types, including B-cells, monocytes, and macrophages [110–112]. Compound **90** (GDC-9973, entospletinib), a selective SYK inhibitor, is under clinical evaluation for hematological malignancies (Fig. 28) [113]. A BID dosing regimen and drug-drug interaction with proton pump inhibitors (PPI) correlating with low pH-dependent solubility precluded development of compound **90** in inflammatory diseases [114]. Metabolite identification studies with **90** revealed extensive oxidative metabolism of the morpholine ring. To disrupt this metabolism, Blomgren and co-workers sought to modify the morpholine portion [114]. The resulting compound **91** bearing *N*-oxetane piperazine moiety showed improved SYK inhibition, metabolic stability, and solubility at pH 2 over compound **90**, as illustrated in Fig. 28. However, compound **91** suffered from almost 27-fold and 2.2-fold loss in cellular potency (pBLNK $EC_{50} = 53$ nM) and WB potency (CD63 $EC_{50} = 385$ nM), respectively. Subsequent replacement of indazole ring with 2-aminopyrazine motif culminated in discovery of a potent and selective SYK inhibitor **92** (GS-9876, lanraplenib) with further gain in inhibition activity ($IC_{50} = 6.2$ nM), metabolic stability (Cl < 0.11 L/h/kg), and solubility (99 μ M at pH7.4) [114]. Compound **92** achieved a 2.2-fold improvement in cellular potency that translated to a significant enhancement in WB potency relative to oxetane **91**. In addition, this compound possessed favorable pharmacokinetic profiles suitable for QD administration and did not have any interactions with PPI. Oxetane **92** is currently undergoing clinical evaluation for the treatment of various autoimmune conditions [114].

Fig. 26. Chemical structures, *in vitro* potency, and PK properties of PKC θ inhibitors **83–86**.Fig. 27. Chemical structures, *in vitro* potency, and PK properties of PI3K δ inhibitors **87–89**.

5. Oxetane in neurodegenerative diseases drug discovery

5.1. BACE1 inhibitors

β -site amyloid precursor protein cleaving enzyme 1 (BACE1) is the β -secretase enzyme required for the formation and accumulation of the neurotoxic β -amyloid ($A\beta$) peptides that play an important role in the pathogenesis of Alzheimer's disease (AD) [115–117]. As a result, BACE1 has garnered considerable interest as a potential therapeutic target for the development of AD treatments. Dineen and co-workers identified a highly potent BACE1 inhibitor **95** (AMG-8718, Fig. 29) [118]. An advanced lead compound **93** displayed single-digit nanomolar biochemical and cellular potency with IC₅₀ values of 4.6 and 2.8 nM, respectively. This compound also showed good permeability, low hERG binding activity, and low P-gp efflux ratio. Nevertheless, the oxidative demethylation of the methoxy group rendered the compound poorly metabolically stable. Alkynol **94**, the metabolite of compound **93**, exhibited high potency (BACE1 IC₅₀ = 1.2 nM and BACE1 cellular IC₅₀

= 5.6 nM), low clearance and hERG activity. However, the high P-gp efflux ratio was observed for compound **93**. Dineen and colleagues devised a 3-methyloxetane moiety to balance P-gp efflux and microsomal turnover, and this effort culminated in the identification of inhibitor **95** (AMG-8718) with improved enzymatic and functional potency (IC₅₀ = 0.7 and 4.4 nM, respectively). Although this compound was a moderate P-gp substrate, it induced robust and sustained reductions of CSF and brain $A\beta$ in a rat pharmacodynamic model. The cocrystal structure revealed that compound **95** forms several favorable interactions with BACE1 (Fig. 29). In particular, the oxetane oxygen interacted with residue Arg128 via a hydrogen bond [118].

5.2. DLK inhibitors

Dual leucine zipper kinase (DLK, MAP3K12), a member of mitogen-activated protein kinase family, exerts a critical influence on neuronal development by regulating axon regeneration and degeneration through its downstream c-Jun N-terminal kinase (JNK) pathway [119–121]. The

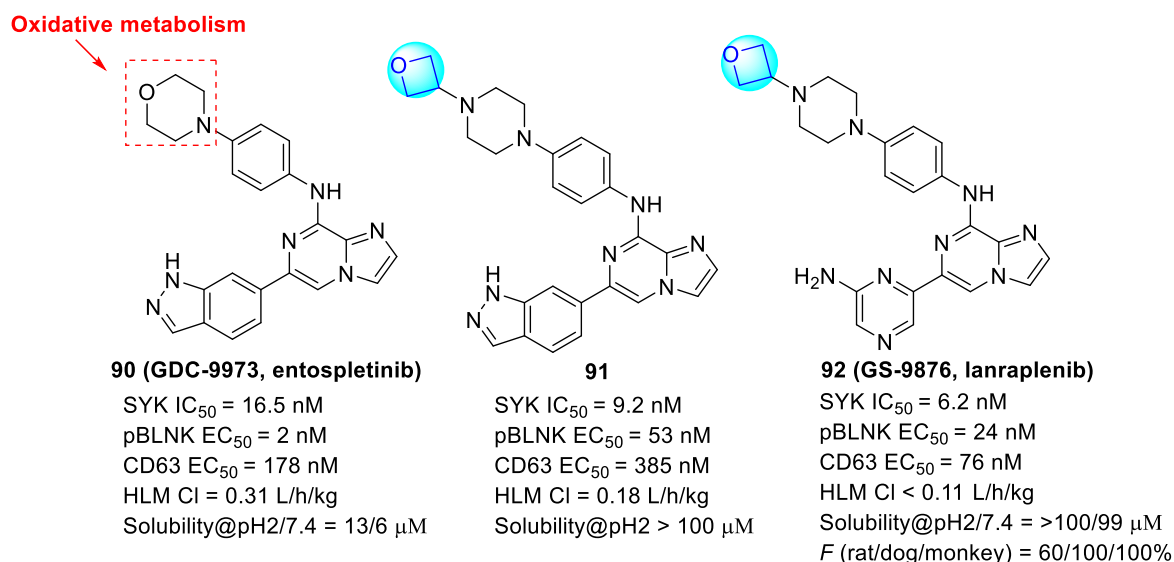


Fig. 28. Chemical structures, *in vitro* potency, and PK properties of SYK inhibitors 90–92.

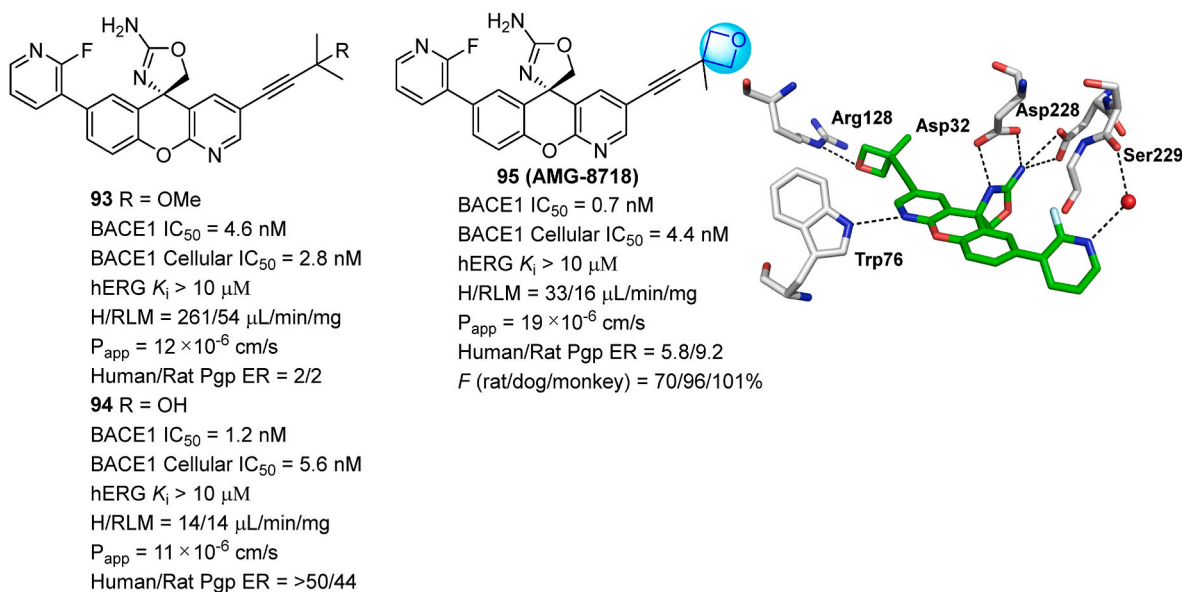


Fig. 29. Chemical structures, *in vitro* potency, physicochemical and PK properties of BACE1 inhibitors 93–95. The crystal structure of 95 (AMG-8718) with BACE1 (PDB code 4RCD).

involvement of DLK in the pathogenesis of numerous neurodegenerative diseases underscores its significance in these conditions. Targeting DLK through pharmacological inhibition holds therapeutic potential for various indications, including acute neuronal injury and chronic neurodegenerative disorders [122,123].

Patel et al. at Genentech developed the lead compound **96** with good DLK potency (K_i = 25 nM) and acceptable efflux ratio (BA/AB = 2.2) and lipophilic ligand efficiency (LipE = 3.5) [124], as shown in Fig. 30. Compound **96** also elicited protection of primary rat dorsal root ganglion (DRG) neurons with an IC₅₀ of 0.18 μM. This lead compound was optimized to produce **97** (GNE-3511, Fig. 30) with a pendent oxetane moiety, which proved to be the most potent inhibitor (DLK K_i < 0.5 nM and pJNK IC₅₀ = 30 nM). The *N*-oxetanylazetidine **97** possessed a lower tPSA but higher LipE value, which reduced the efflux ratio compared to compound **96**. In addition, **97** demonstrated potent protection of DRG in an *in vitro* axon degeneration assay (IC₅₀ = 0.107 μM), excellent kinase selectivity, and good brain penetration in rat following oral dosing

(B_u/P_u = 0.7). Furthermore, the orally available DLK inhibitor **97** displayed dose-dependent activity in two different animal models of neurodegenerative disease [124].

Using the scaffold hopping strategy, Patel et al. identified pyrazole analogue **98** (Fig. 30), a potent, selective, and brain-penetrant inhibitor of DLK (K_i = 42 nM, pJNK IC₅₀ = 536 nM and B_u/P_u = 0.35) [125]. Compound **98** exhibited reasonable pharmacokinetic properties (e.g., t_{1/2} = 1.7 h and F = 58%) and good activity in an optic nerve injury model. In a follow-up study, Patel and co-workers took compound **98** as a template and optimized the pyrazole scaffold using structure- and property-based design (HBD ≤ 1 and tPSA < 80) [126]. These efforts led to the identification of compounds **99** and **100** with significantly improved DLK potency and kinase selectivity (Fig. 30). These two oxetanyl derivatives showed higher lipophilic ligand efficiency and lower turnover in liver microsomes than compound **98**. In addition, oxetanes **99** and **100** demonstrated promising PK profiles and excellent central nervous system (CNS) penetration. Specially, compound **100**

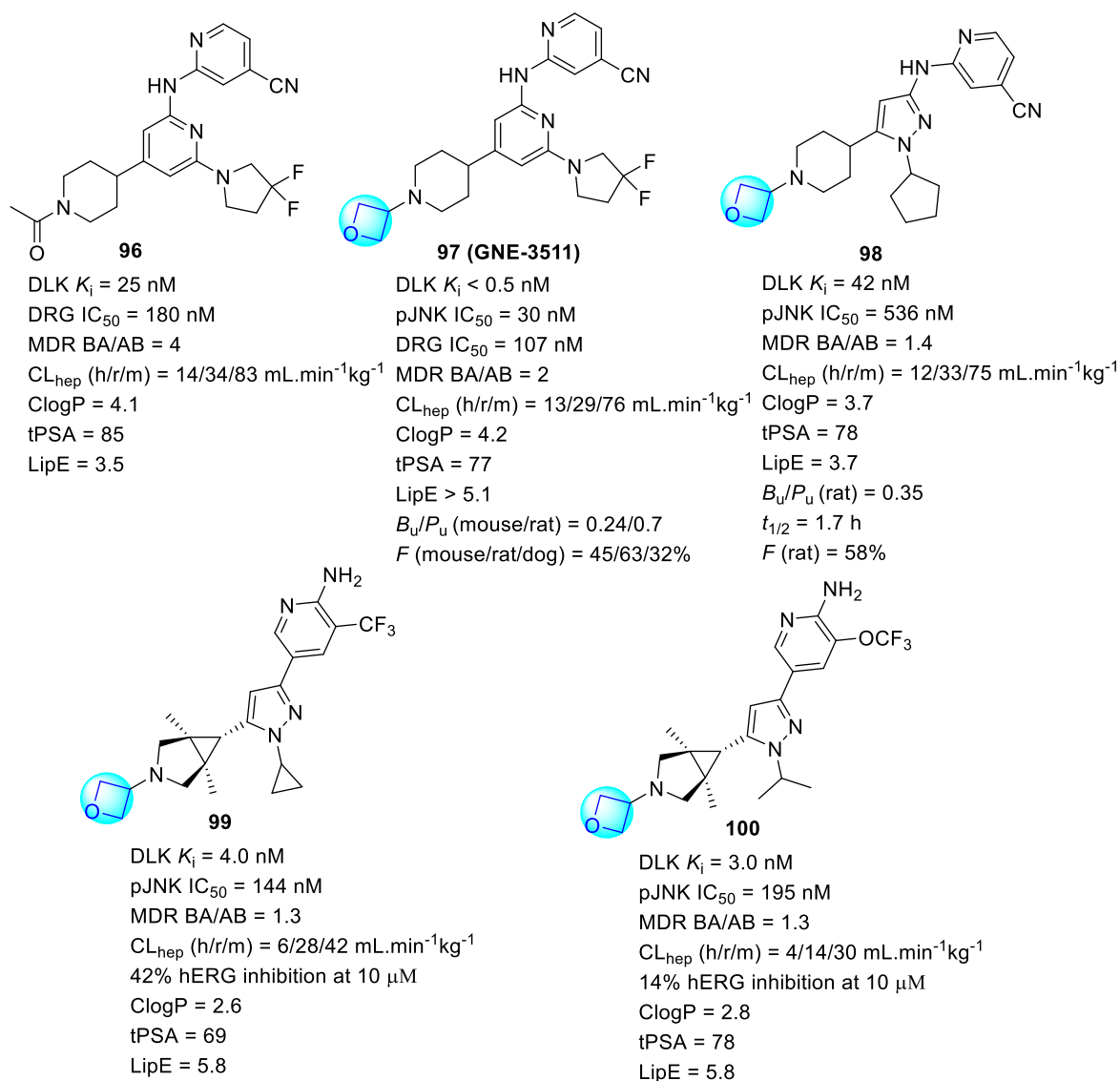


Fig. 30. Chemical structures, *in vitro* potency, and physicochemical properties of DLK inhibitors 96–100.

demonstrated superior rat exposure and better stability in higher species liver microsomes. As a result, further studies were conducted with compound **100**, which showed good tolerance at various concentrations and favorable *in vitro* safety properties [126].

5.3. JNK3 inhibitors

JNK3, alternatively known as MAPK10, is primarily expressed in the brain, while its two isoforms JNK1 and JNK2 are ubiquitously expressed

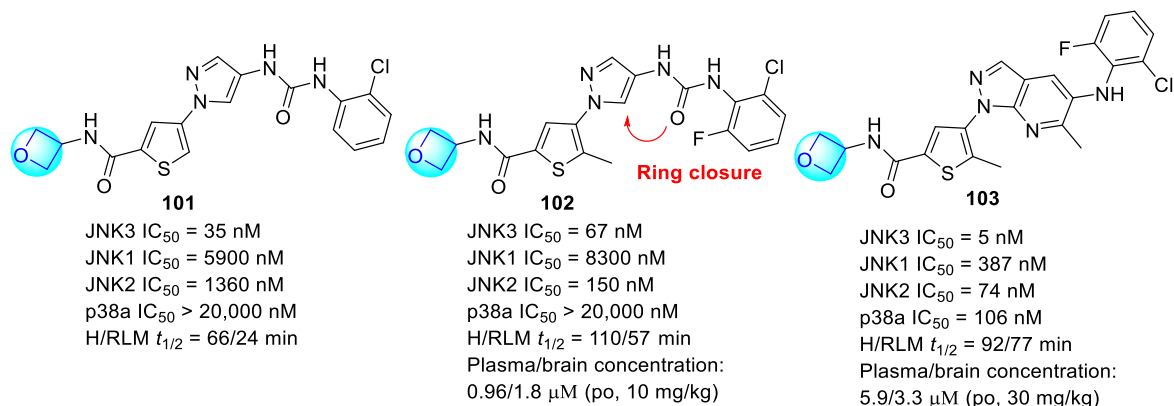


Fig. 31. Chemical structures and *in vitro* potency of JNK3 inhibitors 101–103.

[127,128]. JNK3 is implicated in the pathogenesis of various neurodegenerative diseases, including AD, Parkinson's disease (PD), Huntington disease (HD), stroke, and others. Consequently, JNK3 has emerged as a highly promising therapeutic target for these CNS diseases [129,130]. Numerous JNK3 inhibitors have been discovered and developed, with a particular focus on those that feature an oxetane moiety.

Feng et al. developed a series of JNK3 inhibitors based on a thiophene-pyrazolourea chemotype [131]. Among them, oxetane amide **101** strongly blocked the enzymatic activity of JNK3 ($IC_{50} = 35$ nM), showed good isoform and kinases selectivity, and exerted high stability in human liver microsome ($t_{1/2} = 66$ min) as shown in Fig. 31. Despite a slight decrease in JNK3 potency ($IC_{50} = 67$ nM), the 6-F substituted analogue **102** manifested a significant improvement in microsomal stability (HLM $t_{1/2} = 110$ min and RLM $t_{1/2} = 57$ min). Compound **102** also showed high selectivity against p38 α ($IC_{50} > 20$ μ M) and maintained a high isoform selectivity against JNK1 (>120 -fold). Furthermore, oxetanyl analogue **102** possessed high brain penetration (Fig. 31). In an extension of work, Feng and co-workers adopted a ring closure strategy based upon the advanced lead compound, oxetane amide **102** [132]. This effort led to the discovery of azaindazole compound **103**, an orally available and potent JNK3 inhibitor (brain concentration 3.3 μ M and JNK3 $IC_{50} = 5$ nM) which also exhibited excellent microsomal stability ($t_{1/2} > 75$ min). However, compound **103** displayed decreased p38 α selectivity relative to oxetanyl derivative **102** [132].

5.4. LRRK2 inhibitors

Leucine-rich repeat kinase 2 (LRRK2) is a multifunctional protein, and kinase activating missense mutations in LRRK2 are pathogenically linked to neurodegenerative PD [133]. Accordingly, inhibition of LRRK2 is regarded as a promising therapeutic strategy for PD [134–136]. Estrada et al. reported a set of aminopyrazole inhibitors of LRRK2 [137]. The early lead compound **104** (Fig. 32), in which the electron-withdrawing 3-oxetyl group was incorporated to modulate the basicity of the piperidine nitrogen, exhibited pronounced biochemical (LRRK2 $K_i = 2$ nM) and cellular potency (pLRRK2 $K_i = 20$ nM). This compound also demonstrated excellent stability when incubated in human and rat liver microsomes or hepatocytes. Unfortunately, it had suboptimal brain penetration ($B_u/P_u = 0.06$) and high efflux ratio (ER = 5.1). To overcome these issues, Estrada and colleagues conducted further optimization, including the exchange of the piperidiny group in **104** with fluoro-piperidiny system and the replacement of the methylpyrazole with a chloropyrazole, resulting in compound **105** (GNE-9605, LRRK2 $K_i = 2$ nM and pLRRK2 $K_i = 20$ nM) [137]. Compound **105**

exhibited a significant improvement in *in vivo* unbound brain penetration ($B_u/P_u = 0.51$) and drug efflux (ER = 0.81) and retained metabolic stability when assayed in human liver microsomes and hepatocytes [137].

6. Oxetanes in drug discovery for other diseases

6.1. BMP potentiators

Bone morphogenetic proteins (BMPs) belong to the transforming growth factor- β (TGF β) superfamily and act pivotal roles in embryonic development and tissue homeostasis [138]. Aberrant BMP signaling has been implicated in various pathological conditions [138,139]. Therefore, there is a pressing need for chemical agents that can effectively mimic or enhance BMP signaling, making them valuable tools in biomedical research and potential therapeutic interventions.

Macrolide lactone **106** (FK506, also known as tacrolimus) is a widely used immunosuppressive drug to support organ transplants that inhibited both 12-kDa FK506-binding protein (FKBP12) and calcineurin [140,141]. Recently, Larraufie and co-workers performed a high-throughput screening and identified compound **106** as a potent BMP potentiator by sequestering FKBP12 from BMP type I receptors (Fig. 33) [142]. Considering that calcineurin inhibition was not required for BMP potentiation and associated with adverse effects such as nephrotoxicity, these researchers decided to employ late-stage functionalization on compound **106** and developed drug candidates that did not possess the undesirable calcineurin activity while preserving potent FKBP12 inhibitory activity. To prevent interactions between calcineurin and the molecule, a diverse set of steric hindrance groups were introduced at the calcineurin-binding portion. The optimized compound **107** (oxTFK) bearing an oxetane moiety exhibited pronounced potency, high selectivity, and good ADME properties (Fig. 33). Significantly, oxetanyl compound **107** showed improved *in vivo* safety profile over compound **106**. Additionally, compound **107** demonstrated high efficacy in maintaining renal function in an acute kidney injury (AKI) mouse model, making it as a promising candidate for future development as a first-in-class therapeutic for AKI [142].

6.2. CTSS inhibitors

Cathepsin S (CTSS), a lysosomal protease, is a member of the cysteine cathepsin protease family which promotes degradation of damaged proteins in the endolysosomal pathway [143,144]. Aberrant CTSS expression and regulation are associated with the pathogenesis of several diseases, including abdominal aortic aneurysm (AAA) [143, 145]. Jadhav et al. at Lilly disclosed the identification of a new series of non-covalent inhibitors of CTSS using a medium-throughput focused cassette screening, followed by optimization of the resulting hit **108** (Fig. 34) [146]. Compound **108** exhibited inhibitory activity against human CTSS (hCTSS) and mouse CTSS (mCTSS) with IC_{50} values of 4000 and 3900 nM, respectively. To decrease the pKa of the distal piperazine nitrogen and diminish the lipophilicity, Jadhav and co-workers replaced the *N*-methyl group of the piperazine in **108** with a 3-oxetanyl group, resulting in compound **109** with over 300-fold improvement in Cat S inhibitory potency. Further optimization by exchanging the benzylic carbon in **109** with oxygen furnished compound **110** (LY3000328) with superior potency (hCTSS $IC_{50} = 7.7$ nM and mCTSS $IC_{50} = 1.67$ nM). Oxetanes **109** and **110** were highly selective and did not show CYP inhibition and hERG blockade liability. In addition, these two compounds possessed desirable physicochemical properties and PK profiles, as depicted in Fig. 34. Following evaluation of their *in vivo* drug disposition and efficacy in a CaCl₂-induced AAA mouse model, oxetane **110** was identified as the most promising candidate for clinical development [146].

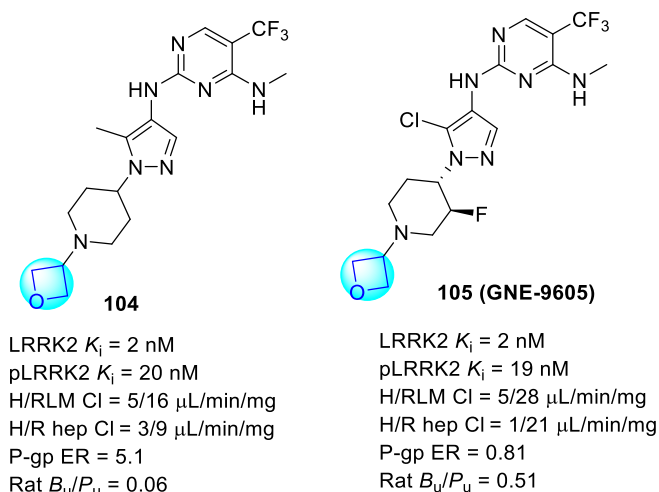


Fig. 32. Chemical structures, *in vitro* potency, and physicochemical properties of LRRK2 inhibitors **104** and **105**.

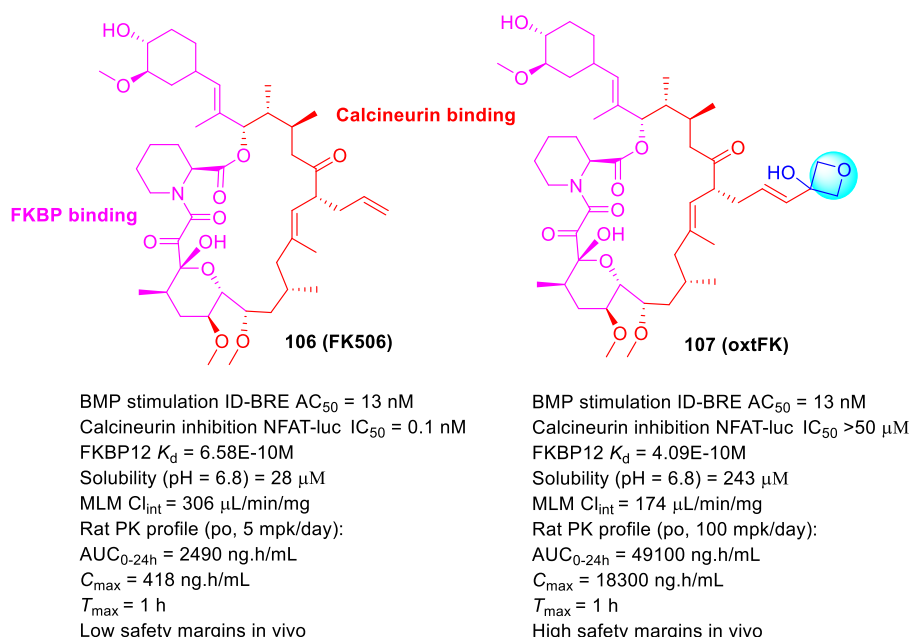


Fig. 33. Chemical structures, *in vitro* potency, and PK properties of BMP potentiators **106** (FK506) and **107** (oxFK506).

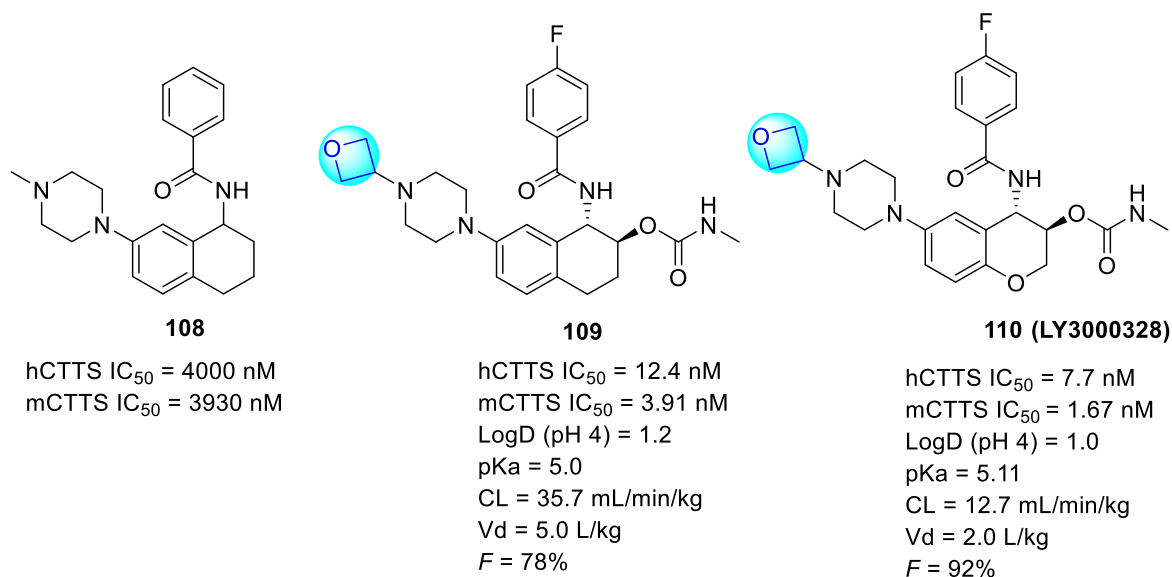


Fig. 34. Chemical structures, *in vitro* potency, and PK properties of CTTS inhibitors **108**–**110**.

6.3. GLP-1R agonists

The glucagon-like peptide-1 receptor (GLP-1R), a member of the Class B GPCR superfamily, participates in numerous biologically significant signaling pathways [147,148]. Due to its pivotal role in insulin secretion, the GLP-1R represents a promising target for the treatment of Type 2 diabetes mellitus (T2DM). In 2020, Ma and co-workers reported that oxetane-containing compound **111** (RGT1383, Fig. 35) acted as a full agonist for cAMP signaling, exhibiting an EC_{50} value of 0.2 nM [149]. They also found that it functioned as a partial agonist for β -arrestin-mediated signaling, with maximal arrestin recruitment observed at approximately 30%. In 2022, Griffith et al. at Pfizer unveiled the discovery of compound **113** (danuglipron, PF-06882961, Fig. 35), an orally bioavailable and potent small molecule GLP-1R agonist (EC_{50} = 1.1 nM) that selectively activates the GLP-1R in primates and humans

[150]. One of the early lead structures was the 6-aza-benzimidazole **112** that was active in the cAMP assay (EC_{50} = 2600 nM). Nevertheless, compound **112** was quite lipophilic (log D7.4 = 5.7), showing high metabolic intrinsic clearance in human liver microsomes (CL_{int} = 140 mL/min/kg) and human hepatocytes (CL_{int} = 55 mL/min/kg). Optimization of the benzimidazole scaffold in compound **112** through incorporation of methylene-linked oxetane and carboxylic acid motif gave rise to compound **113** with significantly lower lipophilicity and rate of clearance (Fig. 35) [150]. Phase 1 clinical data revealed that compound **113** has favorable safety, tolerability, and pharmacokinetic profiles [151,152]. Compound **113** is currently in phase 2 clinical development for the treatment of T2DM (NCT03985293).

Although compound **113** (danuglipron) showed promising efficacy in stimulating cAMP production, it also exhibited inhibition of the hERG ion channel (IC_{50} = 4.3 μ M) and required BID administration due to its

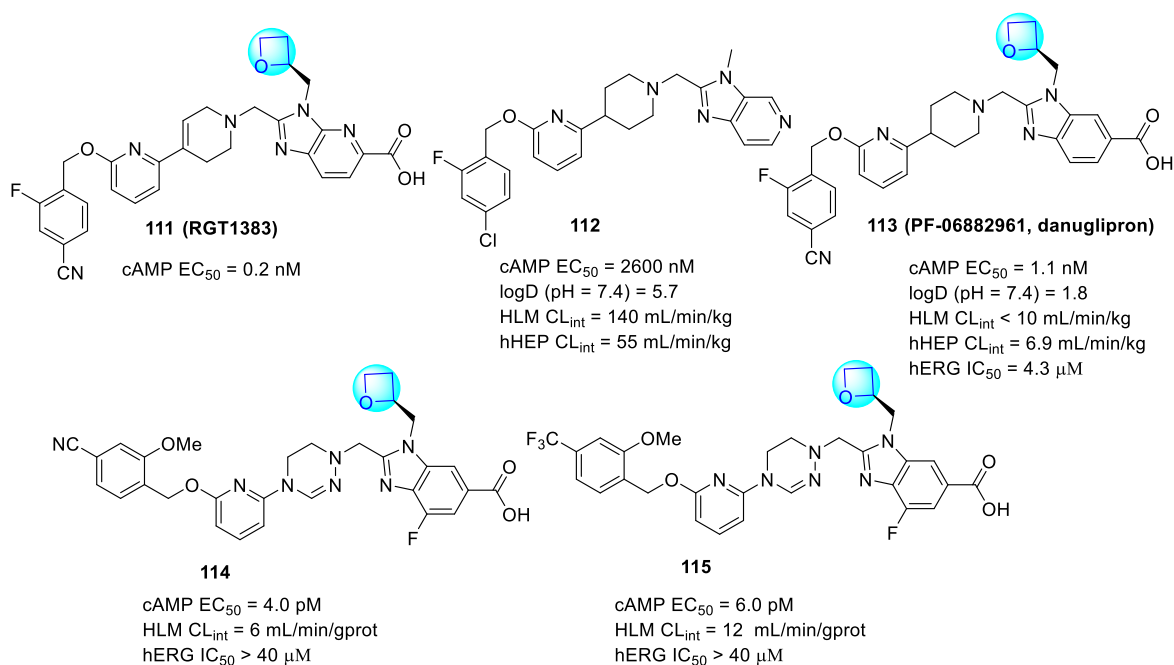


Fig. 35. Chemical structures, *in vitro* potency, and physicochemical properties of GLP-1R agonists 111–115.

short duration of action. Recently, Chen and colleagues have developed a new class of 5,6-dihydro-1,2,4-triazine compounds derived from the piperidine ring of compound 113, which do not have hERG liability (IC_{50} > 40 μ M) [153]. Among these derivatives, compounds 114 and 115 demonstrated highly potent cAMP activity, with EC_{50} values of 4 and 6 pM, respectively (Fig. 35), surpassing the potency of compound 113. Furthermore, both compounds exhibited excellent microsomal stability, with compound 114 displaying a HLM CL_{int} of 6 mL/min/gprot and compound 115 showing a HLM CL_{int} of 12 mL/min/gprot. However, compound 115 exhibited higher cellular permeability than compound 114. Further *in vivo* profiling revealed that compound 115 effectively decreases glucose excursion and inhibits food intake via hGLP-1R, indicating its potential for the treatment of T2DM and obesity [153].

6.4. MCHr1 antagonists

Compound 118 (AZD1979, Fig. 36), a melanin concentrating hormone receptor 1 (MCHr1) antagonist, was designed in a drug discovery program for the treatment of obesity [154,155]. This compound contained a strained heterocycle in the form of a spiro-oxetanylazetidiny-fused ring system. The advanced lead 116

elicited high MCHr1 potency (IC_{50} = 34 nM) and showed excellent permeability with no efflux (ER = 0.37) [154]. Nonetheless, it had an IC_{50} of 5 μ M against hERG channel and moderate microsomal turnover. Incorporation of oxetane motif on the pyrrolidine ring led to lower pKa and hERG potency, as seen with compound 117. Yet, it displayed higher metabolic turnover (74 μ L/min/mg) and weaker MCHr1 potency (IC_{50} = 45 nM). To further optimize the physicochemical properties and enhance metabolic stability while maintaining a wider MCHr1 potency margin over the hERG channel, the spirooxetane-pyrrolidine moiety was replaced by spirooxetane-azetidine functionality. The resulting compound 118 demonstrated improved MCHr1 potency (IC_{50} = 23 nM), microsomal stability (13 μ L/min/mg), and hERG blockade (IC_{50} = 22 μ M) over compound 117. Significantly, this candidate compound had promising PK properties and exerted robust effect on weight loss when dosed orally in a dietary induced obesity mouse model [154]. However, further study on this candidate drug was terminated after assessing the safety and tolerability of compound 118 (NCT02072993).

In a study on the metabolic pathways of compound 118, Li et al. found that the microsomal epoxide hydrolase (mEH) mediated the hydrolysis of the spiro-oxetane ring of 118, furnishing the diol metabolite 119 (Fig. 37A) [156]. In an extension of this work, Li and co-workers discovered an unusual glutathione (GSH) conjugation of an azetidine

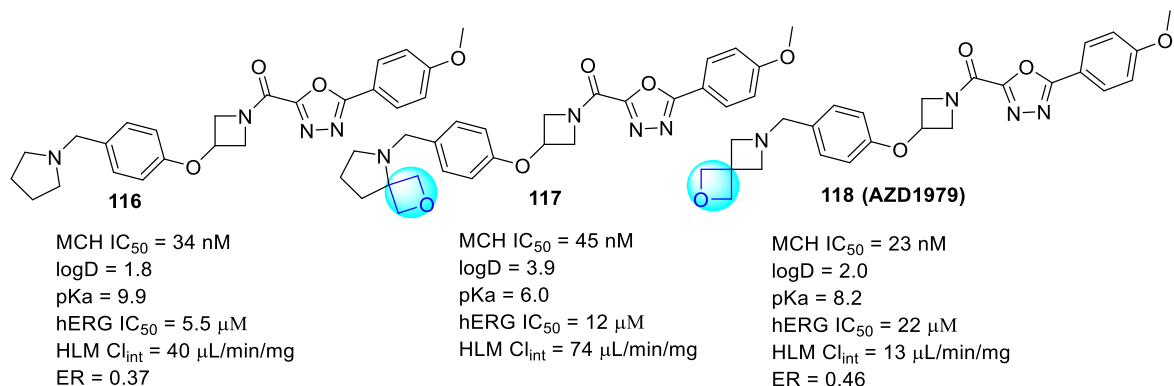


Fig. 36. Chemical structures, physicochemical properties, and *in vitro* potency MCHr1 antagonist 116–118.

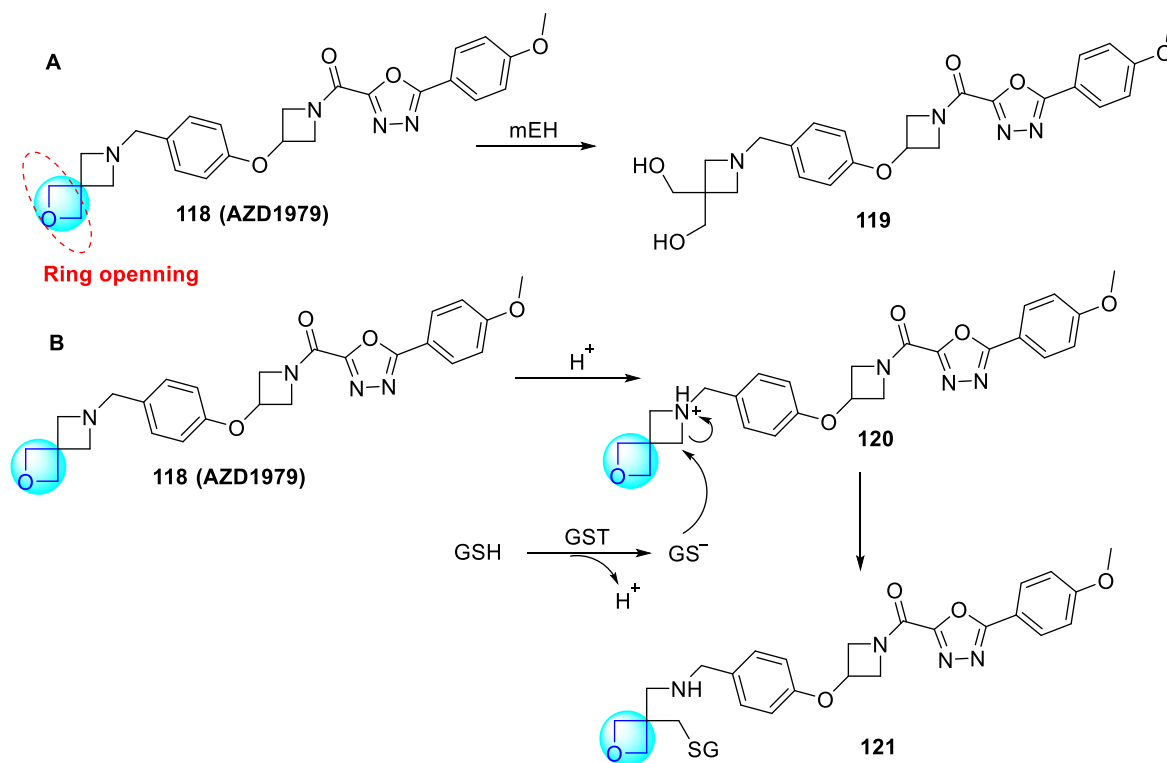


Fig. 37. Metabolism of oxetane-containing spirocycle 118.

ring in compound 118, which was catalyzed by glutathione S-transferase (GST) instead of P450s [157]. Compound 121 is another metabolite derived from GST-catalyzed nucleophilic attack by GSH thiolate anion (GS^-) on the α carbon atom of the strained spiro-azetidine moiety (Fig. 37B) [157].

6.5. MMP-13 inhibitors

Osteoarthritis is a prevalent degenerative disease characterized by the progressive deterioration of articular cartilage and chronic inflammation in the surrounding tissues. Among the matrix metalloproteinases, MMP-13 plays a key role in the degradation of cartilage, particularly in its ability to cleave type II collagen [158,159]. Alongside cancer, MMP-13 is also an attractive target for osteoarthritis therapy. In 2022, Fuerst and colleagues began SAR optimization of benzenesulfonamide scaffold as potent and selective MMP-13 inhibitors [160]. These SAR studies led to identification of oxetanyl derivative 122 ($\text{IC}_{50} = 235$ nM), which was further modified to provide compound 123 ($\text{IC}_{50} = 42$ nM), as illustrated in Fig. 38. In addition, the SAR results revealed that

replacement of oxetane moiety in compound 123 with piperazine, thiomorpholine dioxide, cyclopropane and azetidine results in a great loss of activity. Compound 123 showed excellent selectivity profiles among the MMP family and effectively suppressed collagenolysis *in vitro* studies. Molecular docking studies indicated that the oxetane ring of 123 is pointed towards the Zn^{2+} ion for chelating the metal ion, which might contribute to its selectivity [160].

Additional examples of applications of oxetanes in antifibrotic and analgesic drug discovery are given in Supplementary data.

7. Conclusion and perspectives

In conclusion, this review provides a comprehensive overview of applications of oxetanes in drug discovery and medicinal chemistry campaigns, shedding light on the pivotal role of oxetane rings in clinical and preclinical drug candidates aimed at treating a wide variety of human diseases (Table 2). The incorporation of oxetane motifs to replace methyl, gem-dimethyl, cyclobutyl, morpholinyl, and carbonyl groups showcases compelling advantages in terms of improving the

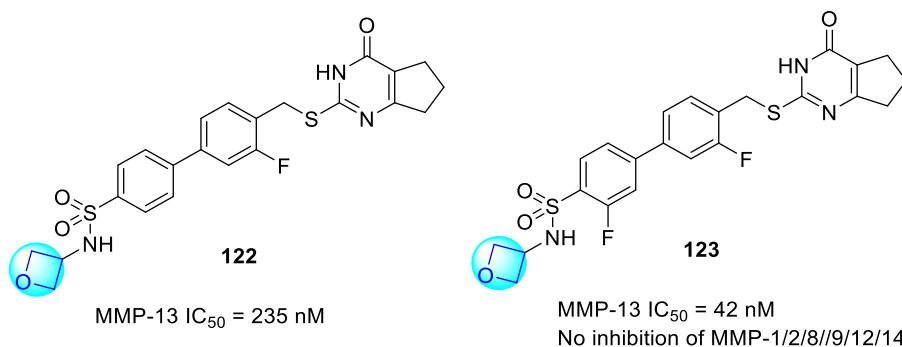
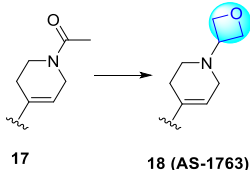
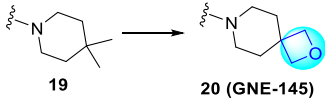
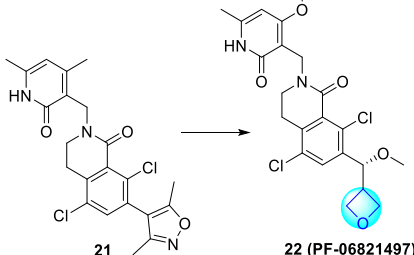
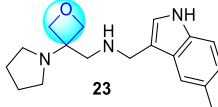
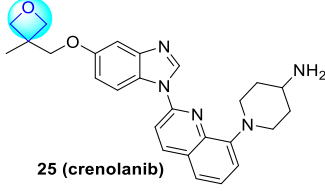
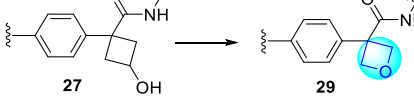
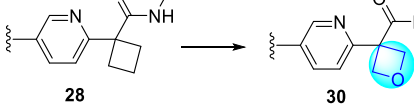
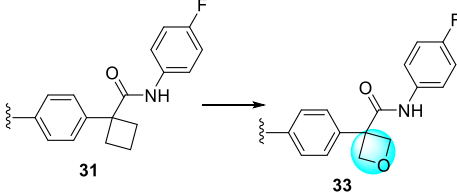
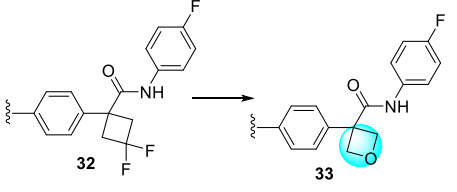


Fig. 38. Chemical structures and *in vitro* potency of MMP-13 inhibitors 122 and 123.

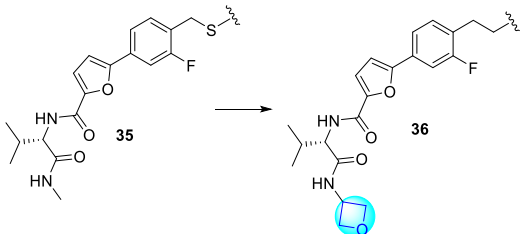
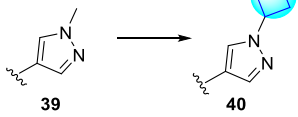
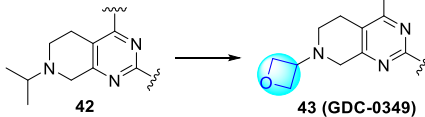
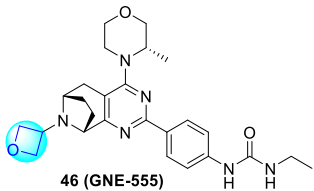
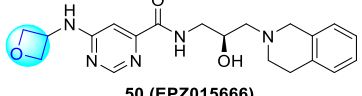
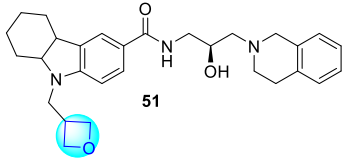
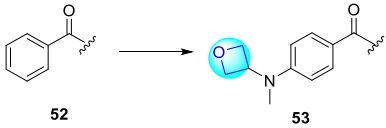
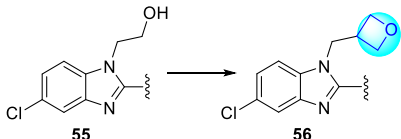
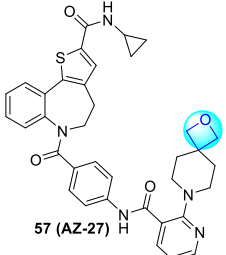
Table 2

Summary of the contribution of an oxetane ring towards potency, target selectivity, drug-like properties in this article.

Properties	Contribution	Compound/candidate example	Mechanism of action	Pharmacological area
Permeability and PK	Increase	 17 18 (AS-1763)	BTK inhibitor	Cancer
Potency and target selectivity	Increase	 19 20 (GNE-145)	ChK1 inhibitor	Cancer
Potency, microsomal stability, and aqueous solubility	Increase	 21 22 (PF-06821497)	EZH2 inhibitor	Cancer
Interaction with the target	Hydrogen bond acceptor	 23	FTO inhibitor	Cancer
–	–	 25 (crenolanib)	FLT3/PDGFR inhibitor	Cancer
Potency	Increase	 27 29	IDO1 inhibitor	Cancer
Aqueous solubility and microsomal stability	Increase		IDO1 inhibitor	Cancer
Lipophilicity and off-target effects	Decrease	 28 30	IDO1 inhibitor	Cancer
Potency, aqueous solubility, and microsomal stability	Increase		IDO1 inhibitor	Cancer
Lipophilicity, hERG inhibition, and CYP inhibition	Decrease	 31 33	IDO1 inhibitor	Cancer
Potency, and aqueous solubility	Increase		IDO1 inhibitor	Cancer
Lipophilicity, hERG inhibition, and CYP inhibition	Decrease	 32 33	IDO1 inhibitor	Cancer

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Table 2 (continued)

Properties	Contribution	Compound/candidate example	Mechanism of action	Pharmacological area
Aqueous solubility and microsomal stability	Increase	 <p>35 → 36</p>	MMP-13 inhibitor	Cancer
Potency	Increase	 <p>39 → 40</p>	MNK inhibitor	Cancer
Potency pKa, hERG inhibition, and CYP inhibition	Increase Decrease	 <p>42 → 43 (GDC-0349)</p>	mTOR inhibitor	Cancer
pKa	Decrease	 <p>46 (GNE-555)</p>	mTOR inhibitor	Cancer
Microsomal stability Lipophilicity	Increase Decrease	 <p>50 (EPZ015666)</p>	PRMT5 inhibitor	Cancer
Interaction with the target	Hydrogen bond acceptor	 <p>51</p>	PRMT5 inhibitor	Cancer
Aqueous solubility and PK	Increase	 <p>52 → 53</p>	TNIK inhibitor	Cancer
Potency	Increase	 <p>55 → 56</p>	RSV fusion (F) inhibitor	RSV
Potency	Increase	 <p>57 (AZ-27)</p>	RSV fusion (L) inhibitor	RSV

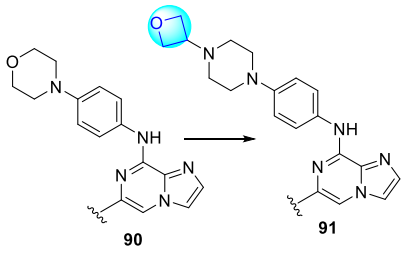
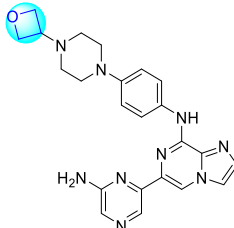
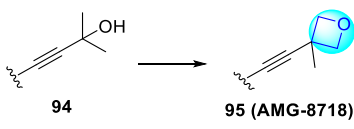
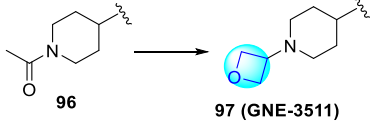
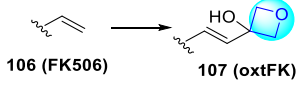
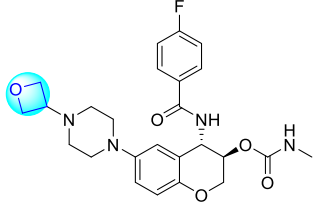
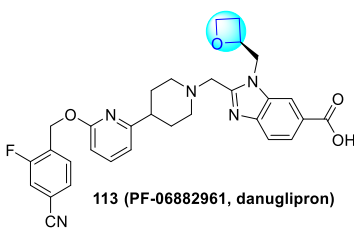
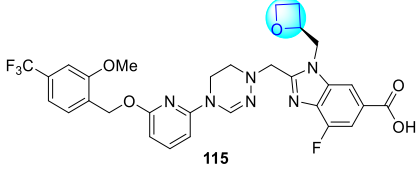
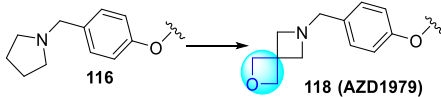
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Table 2 (continued)

Properties	Contribution	Compound/candidate example	Mechanism of action	Pharmacological area
Potency, permeability, and PK Basicity of the terminal amine Interaction with the target	Increase Reduce Conformational restriction	 58 → 60	RSV fusion (F) inhibitor	RSV
Basicity of the terminal amine	Reduce	 61 (Ziresovir)	RSV fusion (F) inhibitor	RSV
Interaction with the target	Conformational restriction	 68 (JNJ-54257099)	NS5B polymerase inhibitor	HCV
Potency and PK Basicity of the piperazine moiety	Increase Decrease	 70 (RN486) → 71	BTK inhibitor	Autoimmune disease
Basicity of the piperazine moiety	Decrease	 75 (GDC-0853, fenebrutinib)	BTK inhibitor	Autoimmune disease
hERG inhibition	Decrease	 76 → 77 (PRN1008, rilzabrutinib)	BTK inhibitor	Autoimmune disease
Potency pKa of the benzazepine moiety	Increase Reduce	 79 → 80 (BIIB091)	BTK inhibitor	Autoimmune disease
Potency	Increase	 81 → 82	BTK inhibitor	Autoimmune disease
Target selectivity hERG, inhibition, and CYP inhibition	Increase Decrease	 84 → 85	PKC9 inhibitor	Autoimmune disease
Target selectivity and potency Lipophilicity	Increase Decrease	 88 → 89	PI3Kδ inhibitor	Autoimmune disease

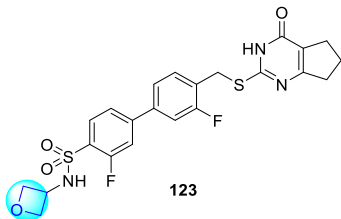
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Table 2 (continued)

Properties	Contribution	Compound/candidate example	Mechanism of action	Pharmacological area
Metabolic stability and aqueous solubility	Increase	 <p>90 → 91</p>	SYK inhibitor	Autoimmune disease
Metabolic stability and aqueous solubility	Increase	 <p>92 (GS-9876, lanraplenib)</p>	SYK inhibitor	Autoimmune disease
P-gp efflux Binding	Decrease Hydrogen bond acceptor	 <p>94 → 95 (AMG-8718)</p>	BACE1 inhibitor	AD
Potency, microsomal stability, and brain penetration P-gp efflux	Increase Decrease	 <p>96 → 97 (GNE-3511)</p>	DLK inhibitor	Neurodegenerative disease
Potency, microsomal stability, aqueous solubility, PK properties and safety margins <i>in vivo</i>	Increase	 <p>106 (FK506) → 107 (oxtFK)</p>	BMP potentiator	AKI
Potency Lipophilicity and pKa of the distal piperazine nitrogen	Increase Reduce	 <p>110 (LY3000328)</p>	CTSS inhibitor	AAA
Microsomal stability Lipophilicity	Increase Decrease	 <p>111 (PF-06882961, danuglipron)</p>	GLP-1R agonist	T2DM
Microsomal stability	Increase	 <p>115</p>	GLP-1R agonist	T2DM and obesity
Potency and microsomal stability pKa and hERG inhibition	Increase Decrease	 <p>116 → 118 (AZD1979)</p>	MCHR1 antagonist	Obesity

(continued on next page)

Table 2 (continued)

Properties	Contribution	Compound/candidate example	Mechanism of action	Pharmacological area
Potency Interaction with the target	Increase Chelating with Zn ²⁺ ion	 123	MMP-13 inhibitor	Osteoarthritis

potency, target specificity, P-gp efflux, physicochemical and PK properties, and safety profiles of host molecules.

However, the design of oxetane-containing bioactive compounds faces a significant challenge posed by their potential metabolic instability and unexpected metabolic pathways. Despite the general decrease in lipophilicity and increase in metabolic stability observed upon introducing an oxetane moiety, studies have shown that oxetane motifs can undergo ring-opening via CYP-mediated oxidation (e.g., EPZ015666) or nonoxidative metabolic routes like hydrolysis by human mEH (e.g., AZD1979). Thus, careful consideration of these metabolic pathways becomes crucial during the design phase to ensure that the metabolic fate of oxetane-containing compounds aligns with the desired therapeutic outcomes.

Driven by the ever-increasing interest in exploring novel chemical entities, it is anticipated that there will be a proactive pursuit of new scaffolds incorporating oxetane motifs within the small-molecule therapeutics. This pursuit will be specifically directed towards addressing disease-associated targets that remain unliganded or undrugged, thereby broadening the horizons of therapeutic possibilities.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Abbreviations

ALDH	aldehyde dehydrogenase
AChE	acetylcholine esterase
AD	Alzheimer's disease
BCL-2	B cell lymphoma protein 2
BTK	Bruton's tyrosine kinase
BCR	B cell antigen receptor
BID	twice daily
BACE1	β -site amyloid precursor protein cleaving enzyme 1
BMPs	bone morphogenetic proteins
CCL	chronic lymphocytic leukemia
ChK1	checkpoint kinase 1
CNS	central nervous system

CTSS	Cathepsin S
DLK	dual leucine zipper kinase
DRG	dorsal root ganglion
EZH2	enhancer of zeste homolog 2
eIF4E	translation initiation factor 4E
FDA	Food and Drug Administration
FLT3	FMS-like tyrosine kinase 3
FKBP12	12-kDa FK506-binding protein
GLP-1R	glucagon-like peptide-1 receptor
GSH	glutathione
GST	glutathione S-transferase
hERG	human ether-a-go-go related gene
HCV	hepatitis C virus
HFL-1	human fibroblast cell line-1
HD	Huntington disease
IDO1	Indoleamine 2,3-dioxygenase 1
LRRK2	Leucine-rich repeat kinase 2
MMP-13	matrix metalloproteinase 13
mTOR	mammalian target of rapamycin
MCL	mantle cell lymphoma
MCHr1	melanin concentrating hormone receptor 1
mEH	microsomal epoxide hydrolase
P-gp	P-glycoprotein
PK	pharmacokinetic
pHH3	phosphorylation of histone H3
PRC2	polycomb repressive complex 2
PDGFR	platelet-derived growth factor receptor
PI3K	phosphatidylinositol-3-kinase
PHGDH	phosphoglycerate dehydrogenase
PRMT	protein arginine methyltransferase
PKC θ	Protein kinase C θ
PBMCs	peripheral blood mononuclear cells
PD	Parkinson's disease
QD	once daily
RSV	respiratory syncytial virus
RA	rheumatoid arthritis
SCLC	small cell lung cancer
SYK	spleen tyrosine kinase
SAR	structure-activity relationship
TDI	time-dependent inhibition
TNIK	traf2 and Nck-interacting kinase
T2DM	type 2 diabetes mellitus
Vss	volume of distribution
WB	whole blood

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejmech.2023.115802>.

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