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2-Aminobenzothiazoles in anticancer drug design and discovery

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Abstract

Cancer is one of the major causes of mortality and morbidity worldwide. Substantial research efforts have been made to develop new chemical entities with improved anticancer efficacy. 2-Aminobenzothiazole is an important class of heterocycles containing one sulfur and two nitrogen atoms, which is associated with a broad spectrum of medical and pharmacological activities, including antitumor, antibacterial, antimalarial, anti-inflammatory, and antiviral activities. In recent years, an extraordinary collection of potent and low-toxicity 2-aminobenzothiazole compounds have been discovered as new anticancer agents. Herein, we provide a comprehensive review of this class of compounds based on their activities against tumor-related proteins, including tyrosine kinases (CSF1R, EGFR, VEGFR-2, FAK, and MET), serine/threonine kinases (Aurora, CDK, CK, RAF, and DYRK2), PI3K kinase, BCL-X_L, HSP90, mutant p53 protein, DNA topoisomerase, HDAC, NSD1, LSD1, FTO, mPGES-1, SCD, hCA IX/XII, and CXCR. In addition, the anticancer potentials of 2-aminobenzothiazole-derived chelators and metal complexes are also described here. Moreover, the design strategies, mechanism of actions, structure-activity relationships (SAR) and more advanced stages of pre-clinical development of 2-aminobenzothiazoles as new anticancer agents are extensively reviewed in this article. Finally, the examples that 2-aminobenzothiazoles showcase an advantage over other heterocyclic systems are also highlighted.

Keywords

2-Aminobenzothiazole; Anticancer; Inhibitors; Kinase; Epigenetic enzymes; Drug design; Chelator; Metal complexes

1. Introduction

Cancer, characterized by the uncontrolled and aggressive proliferation of abnormal cells, is one of the deadliest diseases in the world. In 2020, 19.3 million people around the world suffered from cancer, and approximately 10.0 million died from this disease.[1] Unfortunately, the morbidity and mortality of cancer will continuously increase, and there will be an estimated 29-37 million new cancer cases by 2040.[2] Among various cancer treatments, chemotherapy continues to represent the most effective treatment of most

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cancers, and to date almost 332 anticancer drugs have been approved by U.S. Food and Drug Administration (FDA). Unfortunately, resistance often develops to the majority of these drugs.[3-5] Besides, most chemotherapy drugs are nonspecific and very toxic, and demonstrate a narrow therapeutic index.[3] Thus, the discovery and development of new, potent, and selective anticancer agents with low toxicity still represent an urgent medical need.

Nitrogen/sulfur-containing heterocycles are biologically important scaffolds, and they are widely present in a number of natural products and commercially available drugs.[6-8] As a crucial family of such heterocycles, 2-aminobenzothiazole has attracted vast attention due to its broad application as a privileged structure in medicinal chemistry and drug discovery research. Structurally, the 2-aminobenzothiazole moiety is comprised of a benzothiazole ring and an amino group. Benzothiazole is a heterocycle containing a benzene ring fused to the 4,5-positions of thiazole ring, which exerts a wide range of biological activities.[9-11] The amino group of 2-aminobenzothiazole is an active and useful functionality, which could be tethered to many structural fragments or form various fused heterocycles.[12] In addition, the 2-aminobenzothiazole core (exocyclic nitrogen, cyclic sulfur, and cyclic nitrogen) could provide suitable coordination site(s) for metals. Furthermore, 2-aminobenzothiazole acts as a bioisostere for aniline, 2-aminothiazole, 2-aminobenzimidazole, and other nitrogen- or oxygen-containing heterocycles. At the structural level, the 2-aminobenzothiazole fragment can be involved in formation of hydrogen bonds (as a hydrogen bond acceptor and/or donor), chalcogen bonds, as well as **π-π** stacking/van der Waals contacts with the specific amino acid residues on target proteins, which contribute to inhibitory activity.

The 2-aminobenthiazole scaffold has been extensively explored to construct the structurally diverse analogues with excellent biological activity against various biological targets. Significantly, several therapeutic agents containing this fragment have been approved for clinical application. For instance, riluzole (Fig. 1) is an important 2-aminobenzothiazole-based drug used for the treatment of amyotrophic lateral sclerosis, a lethal neurodegenerative disease.[13, 14] Multiple studies have shown that it also manifests promising antitumor effects on a panel of human solid cancer cell lines.[15-17] Frentizole (Fig. 1) is a nontoxic antiviral and immune suppressive agent used clinically in rheumatoid arthritis and systemic lupus erythematosus.[18] Tioxidazole (Fig. 1) is an anthelmintic drug utilized for curing parasitic infections.[19] The rational study on 2-aminobenzothiazoles as anticancer agents involves the investigation of the SAR and mechanisms of action of these compounds. Such study can provide insights into how their chemical structures can be modified to improve the potency and selectivity. To date, no comprehensive overview of 2-aminobenzothiazole compounds as new potential anticancer agents has been reported. To fill this gap, this review focuses on summarizing the recent developments (2015-2022) of 2-aminobenzothiazole derivatives as new antineoplastic agents based on their protein targets, including tyrosine kinases (CSF1R, EGFR, VEGFR-2, FAK, and MET), serine/threonine kinases (Aurora, CDK, CK, RAF, and DYRK2), PI3K kinase, BCL-X_L, HSP90, mutant p53 protein, HDAC, NSD1, LSD1, FTO, DNA topoisomerases, mPGES-1, SCD, hCA IX/XII, and CXCR receptor. In addition, the anticancer potentials of 2-aminobenzothiazole-derived chelators and 2-aminobenzothiazole-metal complexes are also presented here. Moreover, the design strategies, mechanism of actions and SAR studies of these anticancer agents

along with their preclinical development are described. Furthermore, the advantages of 2-aminobenzothiazoles over other heterocyclic systems are also highlighted. We hope this work will shed light on rational drug design and lead optimization to afford more potent 2-aminobenzothiazole-containing anticancer agents.

2. 2-Aminobenzothiazole derivatives as anticancer agents

2.1. Inhibition of tyrosine kinases

Protein tyrosine kinases (PTKs) catalyze transfer of the γ-phosphate of ATP to hydroxyl groups of tyrosine residues on target proteins.[20] They are mainly divided into receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases. RTKs play an important role in fundamental cellular processes including cell proliferation, migration, metabolism, and cell cycle.[20-22] All RTKs share a similar protein structure which includes a ligand-binding extracellular domain, a single transmembrane helix, and a catalytic intracellular kinase domain.[21, 23] Dysregulation, aberrant activation, and mutations in the RTKs are linked to human cancers as well as resistance to anticancer therapies.

2.1.1. Inhibition of CSF1R kinase—The colony-stimulating factor 1 receptor (CSF1R or c-FMS) belongs to the type of class III RTK family that also contains stem-cell factor receptor (c-KIT), FMS-like tyrosine kinase-3 (FLT3), and platelet-derived growth factor receptor (PDGFR) α/β.[24, 25] Activation of CSF1R occurs upon binding one of its ligands, macrophage colony stimulating factor (CSF1) or IL-34, followed by transphosphorylation of its intracellular domain, subsequently stimulating autophosphorylation for signal transduction. Tumor-associated macrophages (TAMs), as the critical regulatory immune cells, could promote tumor progression, resulting in poor prognosis of a variety of cancers. There are two phenotypes of TAMs, M1 and M2, which have antitumor and protumor functions, respectively. Inhibiting the polarization or survival of M2 macrophages through blocking CSF-1R signal transduction has emerged as a promising strategy for cancer immunotherapy.[24, 26]

Compound **1** (BLZ945, Fig. 2) developed by Novartis was a potent small-molecule CSF1R inhibitor (IC_{50} = 1 nM) with a >3200-fold selectivity for CSF1R over other related RTK kinases (e.g., cKIT IC_{50} = 3.2 μM and FLT3 IC_{50}= 9.1 μM).[27] Compound **1** was able to reduce M2 macrophage polarization and effectively block tumor progression and improve survival. Currently, **1** is undergoing first-in-human phase I/II clinical trials as a single agent or in combination with a monoclonal antibody PDR001 for treatment of advanced solid tumors (NCT02829723). Compound **2** (Fig. 2), an active isomer of **1**, was generated by CYP2C8 and CYP3A4 mediated-oxidation followed by aldo–keto cytosolic reductases catalyzed-reduction.[28] It also displayed potent inhibitory activity against CSF1R (IC_{50} = 5.5 nM) and excellent selectivity profile over the PDGFRβ kinase (IC_{50} = 13 μM).

2-Aminobenzothiazole **3** (Fig. 2) was found to exhibit highly potent suppressive activity against CSF1R kinase (IC_{50} = 1.4 nM) and had an acceptable selectivity profile when tested against a panel of 468 kinases.[29] It also demonstrated suitable *in vivo* PK profiles across species and had good oral bioavailability. Treatment of PANC02 tumors with **3** decreased tumor macrophages and CSF1R protein levels to a similar extent as those treated with

BLZ945. In an MC38 xenograft model, **3** reduced tumor growth by 62% at a subcutaneous dose of 200 mg/kg.[29]

The 4-methoxylated analogue **4** (Fig. 3) maintained single-digit nanomolar inhibitory activity toward CSF1R (IC_{50} = 4.0 nM) and manifested a remarkable enhancement in selectivity for related type III kinases (K_d = 30 μM), but it demonstrated unfavorable metabolic turnover profiles (e.g., rat Cl_{int} = 98 mL/min/kg).[29] The presence of F or Cl atom at the C7 position of 2-aminobenzothiazole scaffold in compound **4** was tolerated for potency but impaired the selectivity for CSF1R, and replacing the methoxyl group with a trifluoromethoxy motif resulted in a drop in CSF1R inhibition activity. Decreasing the cLogP by substitution of 2-amino-3-chloropyridine with 2-aminopyrimidine in the hinge region resulted in enhanced microsomal stability, as seen with compound **5** (IC_{50} = 21 nM, K_d = 6.7 nM, and rat Cl_{int} = 24 mL/min/kg). Reversing the stereochemistry of the amino and hydroxyl groups on the cyclohexyl ring delivered compound **6** with increased potency while maintaining excellent selectivity (IC_{50} = 7.0 nM and K_d = 4.1 nM), as illustrated in Fig. 3. Introducing a Cl atom at the C7 position of benzothiazole core led to further improvement in potency, with compound **7** having IC_{50} values of 2 nM and 60 nM against CSF1R kinase and MSNF60 cells, respectively. Encouragingly, both compounds **6** and **7** possessed suitable *in vivo* PK properties with reasonable half-life and excellent oral bioavailability in rats and mice, but only moderate oral bioavailability in dogs.[29] To further boost the potency of this class of inhibitors, the 2-aminopyrimidine fragment was then functionalized through *N*-arylation, instead of *N*-acylation (amide was hydrolytically unstable).[29] Among them, the *N*-methylpyrazole-containing compound **8** (IACS-9439) stood out as the most promising CSF1R inhibitor (IC_{50} = 1.7 nM and K_d = 1.0 nM) and elicited outstanding antiproliferative activity against MSNF60 cells with an IC_{50} value of 7 nM (Fig. 3). It not only showed improved potency in the pCSF1R cellular target engagement assay relative to BLZ945 but also displayed superior selectivity across RTK kinases (cKIT K_d = 17000 nM; FLT3 K_d = 9500 nM; PDGFRα K_d = 1900 nM; PDGFRβ K_d = 450 nM).[29] Notably, chlorination of **8** gave rise to analogue **9**, which maintained the low nanomolar CSF1R suppressive activity (IC_{50} = 1.2 nM) but showed higher clearance in rat and human microsomes. Given its excellent potency and selectivity profile, **8** was further evaluated. It was found that **8** possessed desirable *in vivo* PK profiles and superior oral bioavailability across several species, especially rat and mouse (*F* = 81 and 100%, respectively). Moreover, **8** could significantly restrain the migration of macrophages and reprogram M2-like macrophages to the M1 phenotype. Concomitantly, subcutaneous administration of **8** remarkably attenuated the MC38 murine colon tumor growth and reversed the immunosuppressive tumor microenvironment with the increased M1/M2 ratio, highlighting **8** as a promising candidate for cancer immunotherapy. [29]

2.1.2. Suppression of EGFR kinase—EGFR (HER1/ErbB1), a transmembrane glycoprotein, belongs to the tyrosine kinase family that also consists of ErbB2 (HER2/neu), ErbB3 (HER3), and ErbB4 (HER4).[30] It acts a key mediator in activating multiple cellular signaling pathways involved in cell survival and proliferation, migration, angiogenesis, and cell death.[30] Upregulation or mutation of EGFR can aberrantly trigger EGFR-dependent pathways, resulting in various types of solid malignancies, such as non-small-cell lung

cancer (NSCLC), prostate, breast, stomach, ovarian, and cervical cancer.[30, 31] Thus, targeting EGFR has been extensively pursued, with the development of a number of promising inhibitors utilized in clinical oncology.

Mokhtar and coworkers developed a new set of EGFR inhibitors using a structure-based design strategy.[32] Among them, 2-aminobenzothiazoles **10** and **11** exerted robust inhibitory activity against EGFR kinase with IC_{50} values of 94.7 and 54.0 nM, respectively (Fig. 4). However, these two compounds only displayed moderate suppressive activity towards HeLa, HCT-116, MCF-7, HepG2, and PC-3 cell lines. It was found that replacement of 2,5-dimethoxylphenyl group in compound **11** with 2-thienyl, 5-bromo-2-thienyl and 9-anthracenyl moieties dramatically compromised the antiproliferative potency. In a similar study, Allam *et al.* reported 2-aminobenzothiazole congener **12** as a potent EGFR inhibitor (IC_{50} = 96 nM) (Fig. 4).[33] Introducing a nitro or ethoxyl group at the C6 position of 2-aminobenzothiazole scaffold in compound **12** decreased the EGFR inhibition activity. In contrast to compounds **10** and **11**, analogue **12** showed significantly improved antiproliferative activity against MCF-7 cells (IC_{50} = 2.49 ± 0.12 μM). Especially, compound **12** was active against PC9 and HCC827 cell lines harboring mutant EGFR (IC_{50} values of 1.05 ± 0.02 μM and 3.43 ± 0.066 μM, respectively), but exerted minimal cytotoxic activity towards the normal WI38 fibroblast cells (IC_{50} = 82.8 ± 4.14 μM). Flow cytometry analysis suggested **12** could induce apoptosis and G2/M phase arrest. Computational analysis of **12** revealed that the nitrogen atom within the pyridyl ring forms a hydrogen bond with residue Met793 and the benzothiazole ring is deeply inserted into the hydrophobic pocket of EGFR kinase. The amino group at C2 position of benzothiazole core was involved in hydrogen bonding interactions with the residue Asp855.[33]

In 2020, Sever *et al.* synthesized a new series of 2-aminobenzothiazole derivatives and investigated their antitumor potential.[34] In this series, compound **13** (Fig. 4) emerged as the most potent antiproliferative agent, exhibiting IC_{50} values of 6.43 ± 0.72, 9.62 ± 1.14 and 8.07 ± 1.36 μM against HCT116, A549, and A375 cell lines, respectively. It also exerted the least cytotoxicity against normal cell line PBMCs (IC_{50} > 300 μM), indicative of superior cellular selectivity. Meanwhile, compound **13** effectively blocked enzymatic activity of EGFR (IC_{50} = 2.80 μM). In this study, they found that replacement of the 2-aminobenzothiazole moiety with a 2-aminothiazole motif severely impaired the antiproliferative activity, supporting the crucial role of 2-aminobenzothiazole scaffold in improving the antiproliferative potency. In addition, the rank order of cytotoxicity for the substitution on the benzothiazole scaffold was found to be OEt > H > Me > NO_2.

In the same year, Abdellatif *et al.* developed a new class of 2-aminobenzothiazole compounds as potential antitumor agents.[35] Compounds **14**-**18** (Fig. 4) manifested the most pronounced cell growth inhibition in PC3, MCF-7, A549, HCT-116, and MDA-MB-231 cell lines, having IC_{50} values ranging from 0.315 to 2.66 μM. These analogues also potently blocked EGFR activity with IC_{50} values in the range of 0.173-1.08 μM, which could shed light on its good cellular potency.

2.1.3. Blockade of VEGFR-2 kinase—Angiogenesis is the process of new blood vessel growth, which plays a crucial role in physiological conditions, such as embryonic

development, pregnancy, and menstruation.[36] Nevertheless, deregulated angiogenesis is closely related with several pathologies including cancer, since it is pivotal to the rapid proliferation and migration of tumor cells.[37] VEGFR-2 (also known as FLK1), a type III transmembrane tyrosine kinase receptor, is the major signal transducer for angiogenesis.[36, 38] Hence, inhibition of angiogenesis via blockade of VEGFR-2 kinase activity has emerged as an effective approach for anticancer therapy.

Based upon a structure-based drug design strategy, Bhanushali *et al.* identified 2-aminobenzothiazole derivative **19** as a potent VEGFR-2 inhibitor with an IC_{50} value of 0.5 μM (Fig. 5).[39] Compound **19** also exhibited good inhibitory effect on chick chorioallantoic membrane and vasculogenic vessel formation. The SAR studies suggested that substituting the benzothiazole moiety with other aryl motifs (e.g., phenyl, pyridyl, thiazoyl or oxazoyl group) significantly compromises the anti-angiogenic activity and introducing a methyl group on the benzothiazole scaffold results in the reduced activity. The molecular docking study revealed that the benzothiazole ring of **19** penetrates the hydrophobic cavity formed by the DFG loop of the VEGFR-2 kinase, and the amide NH and benzothiazole nitrogen are engaged in the hydrogen bonding interactions with the side chain carbonyl of Glu883 and the backbone NH of Asp1044, respectively.[39]

Molecular hybridization as an important drug design strategy involves the rational design of new chemical entities by covalent fusion of two or more existing pharmacophores.[40-42] Thiazolidinedione (TZD) and cyanothiouracil (CT) fragments have been widely utilized in the design of novel anticancer drugs. Hence, El-Helby *et al.* incorporated the TZD or CT moiety with classic 2-aminobenzothiazole scaffold for the design of new VEGFR-2 inhibitors.[43] All synthesized hybrid molecules were investigated for their antiproliferative activities using HepG2, HCT-116 and MCF-7 cell lines. For the 2-aminobenzothiazole-TZD series, compound **20** (Fig. 5) demonstrated the strongest inhibitory activity against these three tumor cell lines with IC_{50} values of 9.99, 7.44 and 8.27 μM, respectively. The SAR results revealed that introduction of a substituent on the phenyl ring significantly enhances the cytotoxic activity, while shifting the substituent from C4 position to C2 position leads to a remarkable decline in activity. With regard to the 2-aminobenzothiazole-CT series, it was found that the methyl group on the phenyl ring was optimal for the antiproliferative potency and the corresponding compound **21** (Fig. 5) suppressed the proliferation of tumor cells with IC_{50} values ranging from 10.34 to 12.14 μM. It should be noted that compounds **20** and **21** potently inhibited VEGFR-2 kinase with IC_{50} values of 0.15 and 0.19 μM respectively, which were comparable to the clinical drug sorafenib.[43]

To further investigate the SAR of 2-aminobenzothiazole-TZD hybrids targeting angiogenesis, an essential hallmark of cancer, Upadhyay *et al.* installed diverse substituents on the benzothiazole scaffold and replaced the phenyl group with a pyridyl motif at the TZD terminal portion.[44] All hybrid compounds were screened to determine their effects on proliferation of human umbilical vein endothelial cells (HUVEC), and the results suggested that compounds with substituted phenyl group generally display more potent HUVEC inhibitory activity than those with the 2-pyridyl moiety. Further studies revealed that compound **22** (Fig. 5) with chlorophenyl and 6-methylbenzothiazole motifs shows the most potent inhibition of VEGFR-2 (IC_{50} = 0.6 μM), which could effectively reduce the

cellular migration and capillary-like tube formation of HUVECs and block the formation of new capillaries on the growing chick chorioallantoic membranes.[44]

In an attempt to explore new VEGFR inhibitors as potential anticancer agents, twenty 2-aminobenzothiazole derivatives were designed and synthesized by Reddy *et al.*[45] Amongst them, compound **23** stood out as the most potent VEGFR-2 inhibitor (IC_{50} = 97 nM, Fig. 5). In agreement with its good enzymatic inhibition, **23** displayed excellent antiproliferative activity towards all tested cancer cell lines (HT-29, PC-3, A549, and U87MG) but marginal cytotoxicity against normal cells (HEK-293T). In a transgenic zebrafish model, **23** could dose-dependently inhibit the formation of intersegmental vessels.[45] Interestingly, the presence of electron-withdrawing groups (R^1 and R^2) at the C6 position of benzothiazole skeleton and phenyl ring was found to be beneficial for the antiproliferative potency.

2.1.4. Inhibition of FAK kinase—Focal adhesion kinase (FAK), also known as PTK2, is a non-receptor tyrosine kinase that primarily transduces signaling from cell adhesion to multiple biological cellular functions, including cell survival, proliferation, migration, and embryonic development.[46] FAK is a 125kD protein that is comprised of three domains (*N*-terminal FERM domain, central catalytic kinase domain, and C-terminal domain).[46, 47] FAK overexpression has been found in many solid tumors, in which FAK kinase is also implicated in promoting metastasis. Therefore, it is considered as a promising target for the development of novel anticancer drugs.

The Altintop group designed and synthesized a set of 2-aminobenzothiazoles containing 1,3,4-oxadiazole moiety and investigated their anticancer activity against C6 rat glioma and A549 human lung adenocarcinoma cell lines.[48] The most active compound **24** (Fig. 6) exhibited appreciable antiproliferative effects on these two cell lines, with IC_{50} values of 4.63 ± 0.85 and 39.33 ± 4.04 μM, respectively. The cytotoxicity data revealed that changing the 6-methoxyl group on the 2-aminobenzothiazole nucleus in compound **24** with a Cl atom substantially reduces the inhibitory potency. Compound **24** could also promote apoptosis, trigger mitochondrial membrane depolarization, and induce caspase-3 activation in both cell lines. Moreover, **24** effectively blocked the enzymatic activity of FAK with an IC_{50} value of 19.5 ± 2.12 μM. *In silico* molecular docking study indicated that **24** could form **π**-**π** stacking with Phe568 residue and present a salt bridge and **π**-cation with Lys457 residue in the active site of FAK.[48] Overall, these studies suggested that **24** represents a new class of ATP-competitive FAK inhibitors.

2.1.5. Inhibition of MET kinase—MET, also termed as hepatocyte growth factor receptor (HGFR), encoded by MET proto-oncogene is a member of the receptor tyrosine kinase family.[49] Hepatocyte growth factor (HGF), also known as scatter factor (SF), is the high affinity and naturally occurring ligand of MET.[49] Activation of the MET/HGF signaling pathway results in multiple cellular responses including proliferation and survival, scattering, angiogenesis, motility, and invasion.[49, 50] The physiological function of the MET/HGF signaling pathway is restricted to embryonic development, wound healing, and tissue regeneration processes.[49, 50] Overexpression of MET and/or aberrant activation of this signaling pathway occurs in various solid tumors. In addition, this abnormal signaling is

often associated with tumor aggressiveness, metastasis, and poor prognosis, and is involved in the development of therapeutic resistance, remarkably decreasing survival rates.[49, 51]

The Gong group designed and synthesized a new subset of 2-aminobenzothiazole derivatives bearing a 4-phenoxyquinoline moiety, with the goal of developing potent c-MET inhibitors. The cytotoxicity of these compounds against HT-29, MKN-450 and H460 cell lines was assessed.[52] All tested compounds demonstrated higher cytotoxic activity against MKN-450 and H460 cell lines as compared to HT-29 cell line. Among them, compound **25** was found to be the most potent molecule with IC_{50} values of 0.06 ± 0.01, 0.01 ± 0.003, and 0.18 ± 0.02 μM against MKN-45, H460 and HT-29 cells, respectively (Fig. 7). Also, **25** exhibited the strongest inhibitory activity against c-MET kinase (IC_{50} = 17.6 ± 1.17 nM) and manifested superior kinase selectivity. Notably, this compound displayed very weak potency against EGFR (IC_{50} > 20 μM) and moderate VEGFR-2 inhibition activity (IC_{50} = 3.36 μM), indicating superior kinase selectivity. In this study, the authors also found that the presence of 4,7-diCH_3 (R^1) group on the 2-aminobenzothiazole core was favorable for antiproliferative activity, and the potency trend for R^1 substituent was 4,7-diCH_3 > H > 5-Br > 4-OCF_3 > 6-Cl > 4-F,6-Br. Additionally, it appeared that the R^2 substituent had no significant influence on the antiproliferative potency.[52]

Using the promising anticancer agent **26** (SC745689)[53] as a template, Moosavi and coworkers developed a novel series of 2-aminobenzothiazoles containing 3,4-dihydropyrimidin-2(1H)-one motif as potential MET inhibitors using a scaffold hopping strategy (Fig. 7).[54] The SAR studies showed that substitution of benzothiazole scaffold with other aromatic rings (e.g., pyridine and benzene) significantly decreases the activity, indicating the importance of benzothiazole for antiproliferative activity. In addition, the introduction of 5,6-diMe or 6-EtO group (R^1) on the 2-aminobenzothiazole nucleus was conducive to improving the cytotoxic activity. As for R^2 group, the isopropyl was deleterious to the cytotoxicity. In this series, compounds **27-31** (Fig. 7) could block the proliferation of lung EBC-1 and gastric MKN-45 cancer cell lines harboring MET gene amplification, with IC_{50} values in the range of 14.6–18.8 μM and 15.0–18.7 μM, respectively. The homogenous time resolved fluorescence assay revealed that compounds **27**, **29** and **30** suppress MET kinase at a concentration of 100 μM by 55.8%, 52.4% and 54.9%, respectively. Molecular docking studies confirmed the interactions of compound **27** with the active site of the MET kinase enzyme, such as two hydrogen bonding interactions with Asp1164 and Ile1084, and a **π-π** interaction with Tyr1230.[54] However, further improvement in MET inhibition activity for compound **27** is warranted.

In another study by Sanofi,[55] benzimidazole analogue **32** was claimed as a potent MET inhibitor with an IC_{50} value of 10 nM (Fig. 8). Nonetheless, this compound exhibited affinity toward tubulin (IC_{50} = 2 μM). Optimization of **32** through bioisosteric replacement afforded a highly selective and potent compound **33**, which did not bind to tubulin (IC_{50} > 25 μM). In comparison to **32**, benzothiazole analogue **33** was more lipophilic and demonstrated decreased aqueous solubility. To tune the physicochemical properties, **33** was further modified by substituting the carbamate unit with a urea moiety and introducing a variety of hydrophilic nitrogen-containing functionalities at the C2 position of the benzothiazole core. This decoration culminated in the discovery of compound

34 (SAR125844, Fig. 8), a development candidate with an IC_{50} value of 4 nM against MET tyrosine kinase. It also demonstrated very potent inhibitory activity against MET mutants (MET^{L1195V} IC_{50} = 64 nM; MET^{M1250T} IC_{50} = 6 nM; MET^{Y1230H} IC_{50} = 204 nM) and robust antiproliferative activity against MKN45 cells (IC_{50} = 7 nM). Co-complex structural analysis indicated that **34** tightly interacts with MET Y1230H mutant residues Met1160, Lys1161 and Asp1222 through several hydrogen bonding interactions. Significantly, **34** exerted favorable druggability properties for intravenous administration and promoted sustained target engagement in a MET-amplified tumor model.[55] The evidence of anticancer efficacy fostered the evaluation of **34** in a phase II clinical study for NSCLC patients with MET amplification (NCT02435121).

2.2. Inhibition of serine/threonine kinases

Human serine/threonine kinases (STKs) are enzymes that modulate protein activity by phosphorylation of serine and threonine amino acid residues. STKs are involved in multiple signal transduction pathways controlling cell metabolism, cell division, and angiogenesis. Deregulated activation of these protein kinases has fueled tumor initiation and progression.[56] As such, the development of effective inhibitors against certain STKs has been regarded as an alternative approach for oncology therapeutics.

2.2.1. Inhibition of Aurora kinase—Aurora kinases (Aurora A, B and C), members of serine/threonine kinase family of enzymes, are critical regulators of cell cycle and mitosis.[57] They are highly overexpressed in various human cancer cell lines.[57] Deregulation of Aurora kinase activity causes mitotic abnormalities, genomic instability and ultimately tumorigenesis. Consequently, considerable efforts have been devoted to developing inhibitors of Aurora kinases.

Through bioisosteric replacement of 2-aminobenzoxazoles previously identified Aurora B kinase inhibitors, the Jeon group developed a new class of Aurora B inhibitors with a 2-aminobenzothiazole scaffold (Fig. 9).[58] These 2-aminobenzothiazoles exhibited significantly improved inhibitory activity and selectivity for Aurora B kinase as compared to the corresponding 2-aminobenzoxazole analogues. The SAR results are summarized as follows: 1. The *para*-substitution on the phenyl ring was beneficial for the Aurora B inhibition activity; 2. Replacing the urea group with amide or sulfonamide moiety compromised the inhibitory activity, while the thiourea motif was tolerated; 3. Substituting the morpholinyl fragment with dimethylamino or piperidinyl group decreased the potency. The representative compounds **35** and **36** can effectively inhibit the enzymatic activity of Aurora B with IC_{50} values of 0.09 and 0.12 μM, respectively. Molecular modeling study showed that the 2-aminobenzothiazole nucleus of **36** occupies the adenine-binding region of Aurora B kinase and interacts with Ala157 and Glu155 in the hinge backbone via two hydrogen bonds. Additional critical hydrogen bonding interaction was observed between the urea carbonyl oxygen and the catalytic Lys106. Moreover, the oxygen C6 alkoxyl portion that pointed toward solvent-exposed region formed a water-mediated hydrogen bond with Glu161.[58] A mechanistic study revealed that both compounds **35** and **36** could reduce the histone H3S10 phosphorylation levels and induce G2/M cell cycle arrest in HeLa

cells.[58] Hence, **35** and **36** could be considered as promising lead compounds for further investigations.

2.2.2. Inhibition of CDK kinase—The cyclin-dependent protein kinases (CDKs) are serine/threonine protein kinases that belong to the CMGC family (CDKs, mitogen-activated protein kinases, glycogen synthase kinases, and CDK-like kinases).[59, 60] CDKs are involved not only in the cell cycle but also in the other critical cellular processes, such as gene transcription, insulin secretion, glycogen synthesis and neuronal functions.[61, 62] In view of the function of CDKs, a large number of CDK inhibitors with diverse structural features have been developed in the past few years, including 2-aminobenzothiazole class compounds.

In 2019, the Zhao group incorporated the aminopyridine motif into the 2-aminobenzothiazole scaffold for development of a new class of CDK2 kinase inhibitors as potential anticancer agents (Fig. 10).[63] Analogues **37** and **38** potently inhibited the CDK2 kinase, with IC_{50} values of 37.8 and 21.7 nM, respectively. Both compounds manifested submicromolar or single-digit micromolar activity against HeLa and HCT116 cell lines, but were not active or less effective in PC-3 and MDA-MB-231 cells. To further improve the anticancer potency, the authors introduced various substituents on the benzothiazole core and pyrimidine ring on the basis of the structure of compounds **37** and **38**. The optimized compound **39** (Fig. 10) displayed significant enhancement in cellular potency relative to compounds **37** and **38**, having IC_{50} values of 0.45, 0.70, 0.92, and 1.80 μM against these four tumor cell lines, respectively. Coherently, **39** elicited robust CDK2 inhibitory activity (IC_{50} = 15.4 nM), which was approximately 3-fold more potent than the positive control AZD-5438 (Fig.10). In HeLa cells, **39** could block the cell cycle progression at G2/M phase and induce apoptosis in a concentration-dependent manner. The SAR analysis suggested that the electron-withdrawing groups (e.g., methylsulfonyl and sulfamoyl groups) are preferred for the antiproliferative activity, whereas the electron-donating substituents are detrimental to the inhibitory potency. Besides, replacing the methyl group on the pyrimidine ring with a F atom dramatically compromised the cytotoxicity.[63]

In a similar study, Abdelazeem *et al.* devised another series of 2-aminobenzothiazole-derived CDK2 inhibitors, in which the 1,2,4-triazole moiety was fused with a benzothiazole core.[64] Compound **40** (Fig. 10) demonstrated low micromolar inhibitory activity against CDK2 (IC_{50} = 4.29 μM). **40** also exhibited potent cell-killing activity against A549, MCF-7 and Hep3B tumor cell lines with IC_{50} values of 3.55, 3.17 and 4.32 μM, respectively. In addition, **40** could efficiently trigger apoptosis through the activation of caspase-3/7 in A549 cells. It is essential to emphasize that replacement of 2-aminobenzothiazole fragment in **40** with other nitrogen-containing heterocycles led to a great loss of cytotoxic activity. [64]

Compound **41** (Fig. 10), a 2-aminobenzothiazole derivative, remarkably suppressed tumor cell proliferation and decreased tumor burden *in vivo*.[65] The mechanism studies revealed that **41** induces G2/M cell cycle arrest in leukemic cell lines (Nalm6, K562, REH, and Molt4) and breast cancer cell lines (MCF-7 and EAC), which is associated with the elevated levels of ROS and DNA double strand breaks. Moreover, **41** could cause the pronounced reduction in phosphorylation level of CDK1 and upregulate the expression of CyclinB1

protein (a G2/M phase specific marker) in Nalm6 cells. To probe the possibility of **41** targeting cyclin dependent kinases involved in cell cycle regulation, docking studies of **41** with CDK1 and CDK2 kinases were performed. The results indicated that **41** can bind to the catalytic site of CDK1 and CDK2 with binding energies of −10.36 and −9.02 kcal/mol, respectively.[65] Briefly, when binding to CDK1, the thiourea of **41** made two hydrogen bonds with residue Ile10, and 2-aminotetrahydrobenzothiazole of **41** formed another two hydrogen bonds with residue Leu83 and Glu81. When binding to CDK2, **41** formed three hydrogen bonds with residue Asp145 and Leu83. Notably, both binding patterns revealed the involvement of amino acid residue Leu83 in hydrogen bonding interactions which were crucial to the potency of CDK1 and CDK2 inhibitors. Thus, inactivation of CDK1 and CDK2 kinases could be the potential mechanism of compound **41** behind the observed G2/M cell cycle arrest, in addition to ROS generation and DNA breaks.[65]

2.2.3. Inhibition of CK kinase—Casein kinase 1 (CK1) is a highly conserved and ubiquitously expressed serine/threonine kinase in mammals, participating in the phosphorylation of a broad range of proteins. Six isoforms (α, γ1, γ2, γ3, δ, and ε) exist in humans and their various alternative splice variants have been characterized in the CK1 family that plays crucial regulatory roles in numerous biological processes including cell proliferation, cell apoptosis, DNA repair, inflammation, circadian rhythm as well as signaling pathways (e.g., Wnt/β-catenin signaling and hedgehog pathways).[66, 67] Since deregulation of CK1 expression and activity is linked to tumor progression, there is intensive interest to develop CK1-specific inhibitors as oncology tools.

Compound **42** (IWP-2, Fig. 11) exhibited potent inhibitory activity against ^{wt}CK1δ, ^{wt}CK1δKD (C-terminal truncated form of ^{wt}CK1δ) and ^{wt}CK1ε with IC_{50} values of 0.93, 0.32, and 4.03 μM, respectively.[68] Of note, compared to wild-type CK1δ, **42** demonstrated even stronger inhibitory effect on the gatekeeper mutant ^{M82F}CK1δ (IC_{50} = 0.04 μM). Analysis of the crystal structure of compound **42**/CK1δ complex revealed that 2-aminobenzothiazole fragment fits snugly into the hydrophobic pocket I, with residue Leu85 forming the key hydrogen bonding interactions, and the thieno-pyrimidone moiety occupies the solvent-exposed hydrophobic region II (Fig. 11). Consistent with potent ^{M82F}CK1δ suppression, compound **42** strongly inhibited the proliferation of eight tumor cell lines within the single-digit micromolar range.[68]

Compound **43** bearing a trifluoromethyl group (Fig. 11) exerted increased potency against ^{wt}CK1δ and ^{wt}CK1ε kinases (IC_{50} values of 0.09 and 0.56 μM, respectively) and showed high kinase selectivity.[68] Compound **44** (Fig. 11), an analogue of **43**, strongly inhibited enzymatic activity of ^{wt}CK1δ (IC_{50} = 0.09 μM).[69] It also exhibited a significant repressive effect on cell viability of HCT-116, HT-29, SW480 and SW620 colon cell lines, having the greatest potency against SW620 cells derived from primary tumor and metastasis of the same patient (IC_{50} = 3.0 μM).

Casein kinase 2 (CK2) is highly expressed in cancer and has also been considered a potential therapeutic target.[70, 71] More recently, Wang *et al.* reported the design and synthesis of a series of 2-aminobenzothiazoles containing a chromone moiety as novel CK2 inhibitors.[72] Among these synthesized derivatives, compound **45** (Fig. 11) represented the most active

CK2 inhibitor (IC_{50} = 0.08 μM), showing the strongest cell growth inhibition in HL-60 cancer cells (IC_{50} = 0.25 μM). Treatment of HL-60 cells with compound **45** resulted in the stabilization of CK2, implying that **45** is able to bind to CK2 in cells. Also, **45** was found to inhibit the proliferation of HL-60 cells by inducing apoptosis and G0/G1 cell cycle arrest in a dose- and time-dependent fashion. Moreover, **45** remarkably suppressed the expressions of *p*-α-catenin, *p*-AKT (S129), *p*-p21, Survivin and *p*-STAT3, and enhanced the cleavage of PARP level.[72] This work paved the way for further development of 2-aminobenzothiazole compounds as potent CK2 inhibitors.

2.2.4. Inhibition of RAF kinase—The RAF family of protein kinases (ARAF, BRAF, and CRAF) are critical effectors of the RAS/RAF/MEK/ERK pathway that regulates cell growth, proliferation, and survival.[73, 74] This pathway is activated by oncogenic mutations in many types of cancer. BRAF is one of the proteins frequently mutated to an active form during tumor development. Among various BRAF mutations, V600E ($BRAF^{V600E}$) emerges as the most active mutant.[73, 75, 76] Its *in vitro* kinase activity is almost 10.7-fold greater than that of wild-type BRAF.[75] Similar to BRAF, CRAF (RAF-1) kinase is implicated in the abnormal proliferation of melanoma.[77] CRAF is also overexpressed in various solid cancers. Hence, discovery of $BRAF^{V600E}$/CRAF inhibitors has received a great deal of attention. Intriguingly, a distinct feature for recently reported inhibitors is the common occurrence of a 2-aminobenzothiazole motif.

Compound **46** (TAK-632, Fig. 12) showed robust $BRAF^{V600E}$ inhibition activity (IC_{50} = 2.4 nM), good BRAF selectivity, and desirable PK profiles.[78] The cocrystal structure of **46** with BRAF kinase revealed favorable H-bonding and sulfur-carbonyl interactions. It should be noted that, in contrast to urea group, the methylene of acetamide could provide more flexibility to fit into the back pocket of BRAF. Significantly, **46** exhibited dose-dependent antitumor efficacy in human melanoma A375 ($BRAF^{V600E}$) xenograft model with no signs of body weight loss.[78] Moreover, **46** could efficiently delay the HMVII ($NRAS^{Q61K}$/$BRAF^{G469V}$) tumor growth and restore body weight loss associated with HMVII tumor-induced cachexia. Collectively, these results implied that **46** is a selective pan-RAF kinase inhibitor with excellent anticancer efficacy and could serve as a clinic candidate for the treatment of human cancer harboring either $BRAF^{V600E}$ or NRAS mutation.[78]

Based upon the structure of the approved RAF inhibitor sorafenib, El-Damasy *et al.* developed a new series of 2-aminobenzothiazole congeners as dual $BRAF^{V600E}$ and CRAF inhibitors through isosteric replacement of the central phenyl ring with a benzothiazole scaffold.[79] Among them, compound **47** was found to be the most potent inhibitor with IC_{50} values of 0.095 μM and 0.015 μM against $BRAF^{V600}$ and CRAF, respectively (Fig. 12). The cellular-based assay indicated that another interesting compound **48** ($BRAF^{V600E}$ IC_{50} = 0.131 μM and CRAF IC_{50} = 0.111 μM) manifests the best antiproliferative activity, surpassing sorafenib over 57 human cancer cell lines. The SAR studies indicated that the presence of Cl atom at the *para*-position of phenyl ring is favorable for RAF inhibition activity and compounds with di-substitutions are more cytotoxic than those with mono-substitution (Fig. 12). Further studies suggested that compounds **47** and **48** demonstrate minimized hERG and CYP450 inhibition, indicative of their desirable safety profiles.[79]

Accordingly, these two compounds could be considered as promising leads for further studies.

2.2.5. Inhibition of DYRK2 kinase—Dual-specificity tyrosine-phosphorylation-regulated kinases (DYRKs) belong to the CMGC family of protein kinases and are pleiotropic regulators of cellular functions such as cell survival, cell differentiation and gene transcription.[80, 81] In humans, the DYRKs are comprised of five members: DYRK1A, DYRK1B, DYRK2, DYRK3, and DYRK4.[80, 81] Among them, DYRK2 is the most extensively studied as a potential target for cancer treatment. However, most small-molecule DYRK2 inhibitors lack selectivity over DYRK family members and exhibit poor drug-like properties.

To develop more potent and selective DYRK2 inhibitors, the Yang group performed a high-throughput screening (HTS) and identified the anti-DYRK2 hit **49** (IC_{50} = 263 nM and K_d = 4.21 μM),[81] as shown in Fig.13. Chemical optimization of **49** led to discovery of 2-aminobenzothiazole derivative **50** (YK-2-69) that manifested approximately 29-fold and 46-fold improvement in DYRK2 inhibitory potency and binding affinity (IC_{50} = 9 nM and K_d = 92 nM, respectively). Of particular note, changing the 2-aminobenzothiazole scaffold in compound **50** with pyrazolo[1,5-a]pyrimidine moiety abrogated the DYRK2 inhibition activity. Compound **50** also displayed exquisite selectivity over the DYRK subfamily and a panel of 370 kinases. Impressively, **50** demonstrated favorable safety properties with the maximum tolerated dose (MTD) of > 10,000 mg/kg and desirable pharmacokinetic profiles (e.g., F = 56%). In addition, **50** exerted more potent suppressive effect on tumor growth than first-line drugs enzalutamide and palbociclib in DU145 and PC-3 xenograft mouse models.[81] The mechanism studies suggested that **50** exhibits superior anti-prostate cancer efficacy via synergistic regulation on multiple pathways (e.g., DYRK2-4E-BP1 and DYRK2-RRS1-p21/27-CDK4/6) to promote apoptosis and block proliferation.[81] Collectively, the highly potent and selective DYRK2 inhibitor **50** with favorable druggability might be used as a valuable chemical probe for further biological studies and also considered as a potential candidate for treatment of prostate cancer.

2.3. Inhibition of PI3K kinases

Phosphoinositide 3-kinases (PI3Ks) are a family of lipid kinases that can catalyze the phosphorylation of the inositol ring of phosphoinositide and are secondary messengers which help to transduce signals.[82] PI3Ks are key regulators of the PI3K/AKT/mTOR (mammalian target of rapamycin) signaling pathway that is essential to control cell survival, growth, motility, and metabolism.[83] Deregulated activation of PI3Ks has been implicated in tumor angiogenesis, tumorigenesis, and conferring resistance to antineoplastic drugs.[84] PI3Ks can be divided into three classes (class I, II, and III) according to their structural differences and substrate specificity. Of these, the most extensively investigated members in cancer development are the class I PI3Ks (class IA: PI3Kα, PI3Kβ, and PI3Kδ; class IB: PI3Kγ) that are directly activated by cell surface receptors.[84, 85] In the past several years, a number of PI3K inhibitors with different structure types have been developed, including the privileged scaffold 2-aminobenzothiazole.

PIK-93 (Fig. 14) has been reported to exhibit potent inhibitory activity against PI4Ks and PI3Ks, especially for class Ib member PI3Kγ (IC_{50} = 16 nM and K_i = 7 nM).[86] Taking PIK-93 as a starting point, Collier *et al.* presented a structure-guided development of potent and isoform-selective 2-aminobenzothiazole-based PI3Kγ inhibitors.[87] The initial lead optimization efforts were focused on C6 position of benzothiazole scaffold derived from ring fusion of the phenylthiazole core. The representative compound **51** with 4,5-dimethoxypyridine showed the highest binding affinity toward PI3Kγ (K_i = 1 nM). This remarkable enhancement in potency was rationalized by several favorable hydrogen bonding interactions with the ATP binding site of PI3Kγ (Fig. 14). Subsequent substitution of the acetamide moiety with a chain-extended urea fragment resulted in compound **52** (Fig. 14) which demonstrated considerably improved selectivity for PI3Kγ over PI3Kα/δ while maintaining good PI3Kγ potency (K_i = 2 nM). Intriguingly, the PI3Kγ selectivity order for *N*-alkyl substituent was propyl > ethyl > methyl > H and extending the urea chain length gave rise to the improved PI3Kγ selectivity. Also, **52** suppressed MCP-1 induced chemotaxis of THP-1 cells and the proliferation of MCF-7 cells with IC_{50} values of 0.083 and 7.4 μM, respectively.[88] Notably, in the structure of **52**-PI3Kγ complex, hydrogen bond between 5-methoxy substituent and residue Lys833 was not observed. In addition, the propyl group was found to occupy a newly formed binding cleft adjacent to the ATP binding site.[87]

In a similar work, Gao *et al.* designed and synthesized a novel series of 2-aminobenzothiazole analogues as potential PI3Kβ inhibitors.[89] The typical compounds **53** exerted potent activity against PI3Kβ (IC_{50} = 0.02 μM), with excellent selectivity over other class I PI3K subunits and mTOR (Fig. 14). In agreement with its PI3Kβ inhibitory potency, **53** strongly repressed the growth of prostate PC-3 and DU145 cancer cells, with IC_{50} values of 0.35 and 0.62 μM, respectively. Additionally, it showed low cytotoxicity against the normal fibroblast MRC-5 cells (IC_{50} = 33.11 μM), indicating good cellular selectivity.

Very recently, the Yar group reported a set of new 2-aminobenzothiazole derivatives as new anticancer agents targeting PI3Kα kinase.[90] Compound **54** was characterized as the most potent PI3Kα inhibitor (IC_{50} = 1.03 nM, Fig. 14). **54** also exerted significant growth-inhibitory activity against MCF-7 cells. Moreover, it effectively suppressed the migration of MCF-7 cells and induced cell cycle arrest. Furthermore, **54** dose-dependently triggered apoptosis by decreasing the levels of antiapoptotic proteins BCL-X_L and MCL-1.

2.4. Inhibition of topoisomerase

DNA topoisomerases are nuclear enzymes which make transient DNA strand breaks, allowing the cell to manipulate the topology of its DNA. They are essential for DNA replication, transcription, chromosomal segregation, and DNA recombination.[91] Topoisomerases are classified as type I and II in terms of their reaction mechanism, amino acid sequence, and structure. The type I enzymes cleave only one strand of duplex DNA, whereas the type II enzymes cut both strands.[92] The essential role of these enzymes in cell processes and their elevated level in solid tumors make topoisomerase inhibition as an important mechanism for cancer therapy.[93, 94] Current topoisomerase-targeted agents are limited by some side effects (e.g., dose-limiting toxicity, drug resistance, and cardiotoxicity),

despite their efficiency in the clinic. To improve the potency and decrease adverse effects, new topoisomerase inhibitors have been developed in the past few years, including 2-aminobenzothiazole-based inhibitors of topoisomerases.

By incorporating the β-naphthol fragment and 2-aminobenzothiazole moiety, Nagaraju and colleagues designed and synthesized a library of 2-aminobenzothiazole derivatives as potential topoisomerase I inhibitors (Fig. 15).[95] Among them, compounds **55**, **56** and **57** could efficiently bind to DNA and showed comparable topoisomerase I inhibition activity to camptothecin. Also, these compounds displayed strong cell growth inhibition towards HeLa cells with IC_{50} values of 5.20, 5.54 and 4.63 μM, respectively. The cytotoxicity data suggested that replacement of the methoxyl group at C6 position of 2-aminobenzothiazole scaffold with a Cl atom abolishes the activity, however, the methyl group is tolerated. In addition, installation of the electron-withdrawing group (R) on the phenyl ring significantly enhanced the antiproliferative activity.[95]

Sović *et al.* developed a set of new 2-aminobenzothiazole derivatives as potential topoisomerase inhibitors (Fig. 15).[96] Among them, compounds **58** and **59** demonstrated the highest cellular potency (IC_{50} values ranging from 0.15 to 1.0 μM), and compounds **60** and **61** exhibited the best DNA intercalation activity. Further topoisomerase assay suggested that compound **60**, which exerts the highest topoisomerase I inhibitory activity, is more potent than campthotecin. Especially, both compounds **58** and **60** manifested notable topoisomerase II inhibitory properties, which were comparable to etoposide.

To explore new topoisomerase IIα inhibitors as promising anticancer agents, a total of thirty 2-aminobenzothiazoles bearing β-carboline moiety were rationally designed and synthesized by Tokala *et al.*[97] All derivatives showed cytotoxic potential against a panel of human tumor cell lines, wherein compounds **62** and **63** (Fig. 15) manifested the strongest inhibitory potency towards A549 cells (IC_{50} = 1.81 and 1.46 μM, respectively) and limited cytotoxic activity against human normal lung epithelial cells BEAS-2B (IC_{50} > 58 μM). In addition, these two compounds demonstrated potent intercalative topoisomerase-II inhibitory effect by blocking the conversion of catenated kDNA into decatenated DNA. The SAR studies revealed that introducing the methyl group (R^1) on the benzothiazole ring decreases the cytotoxicity, and the substituent (R^2) in the order of improved cytotoxicity is NO_2 > Cl > H > Me. Additionally, changing the phenyl group with 2-thiophenyl moiety reduced the cytotoxic potency.

2.5. Inhibition of BCL-X_L

Apoptosis, or programmed cell death, is a highly conserved process that is critical for cellular homeostasis and development. The proteins of B cell lymphoma protein 2 (BCL-2) family are the fundamental and key regulators of the intrinsic apoptosis pathway, which consists of anti-apoptotic (pro-survival) proteins (e.g., BCL-2, BCL-X_L, MCL-1, BFL-1 and BCL-$_w$), pro-apoptotic BH3-only proteins (e.g., BID, BIM, PUMA, NOXA, BAD, and HRK), and pro-apoptotic effectors (e.g., BAK and BAX).[98, 99] BCL-X_L is frequently overexpressed in solid tumors and hematological malignancies, and its overexpression or activation is linked to poor prognosis and drug resistance.[98-100]

Tao *et al* at AbbVie took advantage of NMR fragment screening and structure-based design strategies, delivering compound **64** (A-1155463, Fig. 16) which demonstrated picomolar binding affinity to BCL-X_L (K_i < 0.01 nM) and > 1000-fold selectivity over other BCL-2 family members (e.g., BCL-2 K_i = 80 nM).[101] The cocrystal structure revealed that the 2-aminobenzothiazole moiety of **64** interacts with Leu108 and Ser106 in the hydrophobic P2 pocket via essential hydrogen bonds. In addition, 2-fluoro atom in **64** was proximal to the side chains of Val141 and Phe97 within the hydrophobic P4 pocket and made favorable van der Waals contacts. Administration of **64** to tumor bearing SCID-Beige mice resulted in modest tumor growth inhibition, possibly due to its poor solubility and oral absorption. It should be noted that **64** represented a first reported selective BCL-X_L inhibitor showing *in vivo* efficacy.[101, 102]

To develop 2-aminobenzothiazole-based selective BCL-X_L inhibitors with suitable oral exposure profiles, researchers at AbbVie selected pyridine-containing compound **65** (K_i = 164 nM) as a starting template for further SAR exploration.[103] Considering that nitrogen-containing heterocycles with fine-tuning physicochemical properties and decreasing the number of rotatable bonds could impart better drug-like properties such as oral absorption, they next introduced rigid 5-methylpyrazole linker to the pyridine ring of **65** instead of a conformationally flexible propyloxy unit. The resulting compound **66** showed substantial improvement in target affinity (K_i = 0.027 nM), low micromolar activity in MOLT-4 cells in the presence of 10% human serum (EC_{50} = 1610 nM), and a suitable level of oral absorption (F = 17%).[103] Further optimization of **66** through increasing the pharmacophore sp^3-fraction and occupying lipophilic volume of the P4 pocket culminated in the identification of compound **67** (A-1331852, K_i < 0.01 nM, Fig. 16) which exhibited over 250-fold increase in antiproliferative activity against MOLT-4 cells (EC_{50} = 6.3 nM) and maintained high selectivity for BCL-2-dependent RS4;11 cells (EC_{50} > 5000 nM).[103] Compound **67** demonstrated modest bioavailability (F = 11-13%). Further *in vivo* studies demonstrated that **67** has the potential to augment the efficacy of docetaxel and irinotecan in xenograft solid tumor models and reduce neutropenia caused by inhibition of BCL-X_L.[102, 103]

Very recently, the AbbVie group reported a novel series of BCL-X_L inhibitors based upon structure-based design and molecular hybridization strategies **(**Fig. 17).[104] The promising compound **68** was featured by integrating the pharmacophores of selective BCL-X_L inhibitor **64** and ABT-737, while another benchmark molecule **69** (A-1293102) contained the same structural elements of **64** and ABT-263 (navitoclax, Fig. 17). Both compounds displayed picomolar K_i value against BCL-X_L (K_i values of 0.14 and 0.43 nM, respectively) and high selectivity over BCL-2 and MCL-1. Interestingly, **69** exhibited strong cellular potency against BCL-X_L dependent MOLT-4 cells (EC_{50} = 80 nM), whereas **68** did not show any cell-killing activity in the same line (EC_{50} > 5000 nM). This can be explained by faster on- and off-rate binding kinetics and shorter residence time of **68** as compared to **69** (K_{on} 2.18×10^7 $M^{-1}S^{-1}$ vs 5.88×10^5 $M^{-1}S^{-1}$; K_{off} 1.09×10^{-2} S^{-1} vs 2.34×10^{-3} S^{-1}; $t_{1/2}$ 1 min vs 49 min). Further investigation into the binding mode revealed that the benzothiazole moiety of **69** binds to the hydrophobic P2 pocket through two key hydrogen bonds as described previously, likely explaining the observed selectivity. The carbonyl oxygen and nitrogen atom of the central thiazole moiety interacted with respective residue Asn136

and Arg139 through hydrogen bonds.[104] Another two hydrogen bond interactions were observed between one of the sulfonyl oxygen atoms with residues Asn136 and Gly138. Taken together, the highly potent and selective BCL-X_L inhibitor **69** could represent an invaluable tool compound for further biological studies.

Proteolysis Targeting Chimeras (PROTACs) are an emerging modality with the potential to modulate protein targets which are challenging to target using traditional small molecules. PROTACs are bifunctional molecules wherein one ligand for a protein of interest (POI) is linked to another ligand for an E3 ligase such as von Hippel–Lindau (VHL) or cereblon (CRBN), leading to target poly-ubiquitination and proteasomal degradation of POI.[105-108] PROTACs have many advantages over small molecule inhibitors, such as the potential of overcoming drug resistance and low-dose toxicity as a result of catalytic properties.

To develop BCL-X_L degrader, researchers at GlaxoSmithKline chose a well-established BCL-X_L inhibitor **64** (A1155463, Fig. 16) which well occupied the bind site as a BCL-X_L-targeting ligand.[109] The co-crystal structure of BCL-X_L with **64** revealed a solvent-exposed vector through the propargylic amine, providing a potential tethering site for the design of degrader (Fig. 18). For this reason, degrader **70** was developed by conjugation of **64** to the VHL E3 ligase binder. **70** selectively degraded BCL-X_L in THP-1 cells (DC_{50} = 4.8 nM, D_{max} = 76%), which was equipotent to clinical candidate DT2216.[109]

2.6. Inhibition of HSP90

Heat shock protein 90 (HSP90) is a molecular chaperone that plays an important role in cellular proteostasis and is responsible for the folding and maturation of client proteins including protein kinases (AKT, CDK4/6, RAF1, HER2, and SRC), transcription factors (p53, and Hif1) and telomerase, all of which are closely associated with ten hallmarks of cancer.[110, 111] This supports HSP90 as an attractive target for the discovery of novel anticancer agents. The HSP90 polypeptide is a homodimer, and each monomer contains an ATP-hydrolyzing *N*-terminal domain, middle domain, and C-terminal domain.[112] So far at least 18 HSP90 *N*-terminal inhibitors have entered clinical trials, yet none of them have been successful, due to the strong activation of the heat shock response (HSR) that upregulates the HSP90 protein level and ultimately results in cytoprotective effects. Therefore, recent focus of HSP90 research centered on the design of inhibitors has shifted towards C-terminal domain and protein–protein interactions (e.g., HSP90-CDC37).

The Blagg group reported a series of HSP90 C-terminal inhibitors derived from a 2-aminobenzothiazole-based scaffold.[113] Several compounds were found to exert potent antiproliferative activity against both MCF-7 and SKBr3 breast cancer cell lines. Among them, the most active compound **71** (Fig. 19) displayed an EC_{50} value of 0.86 and 7.03 μM against SKBr3 and MCF-7 cells, respectively. Besides, **71** could remarkably downregulate the expression of Hsp90 client proteins (e.g., AKT, CDK4, HER2 and RAF-1), a hallmark of HSP90 C-terminal inhibition, and did not cause HSR effect. The SAR trends of this class compounds can be summarized as follows: 1. Replacement of the ethyl oxalyl group with 2-oxo-2-phenylacetamide or acetamide moiety totally abrogated the cytotoxic activity; 2. Changing the indole ring with pyrimidine or phenyl ring reduced the inhibitory potency; 3. The substituent at the C5 position of indole ring in the order of improved antiproliferative

potency was OMe > Me > Et; 4. Shifting the methoxyl group from C5 position to C6 position led to the reduced activity.

Using a ligand-based design approach and structure-based pharmacophore model, the Tomašič group devised and synthesized a new library of 2-aminobenzothiazole derivatives as HSP90 C-terminal inhibitors.[114] Initial SAR elaboration of phenyl group revealed that the activity order for C4 substituent is I > Br > Cl > F > H > OMe and replacement of phenyl group with benzyl moiety significantly diminishes the antiproliferative activity. Subsequent SAR exploration of benzothiazole core indicated that 4-aminopiperidine fragment is optimal for activity. The representative compounds **72** and **73** (Fig. 19) exhibited the highest cellular potency with EC_{50} values of 2.8 ± 0.1 and 3.9 ± 0.1 μM, respectively. Mechanistically, compound **73** demonstrated dose-dependent downregulation of HSP90 client proteins (AKT, c-RAF, and Erα) without induction of HSR, which was consistent with the Blagg's study[113].

Jin *et al.* rationally designed and synthesized a set of 2-aminobenzothiazole-18β-glycyrrhetinic acid hybrids targeting the HSP90-CDC37 interaction.[115] Most compounds showed low micromolar disruption activity against HSP90-CDC37, with compound **74** having the highest potency (IC_{50} = 0.14 ± 0.03 μM, Fig. 19). Structure and activity survey suggested that the F atom at C6 position of benzothiazole ring is optimal for the potency and altering the F atom from C6 position to C4 position substantially decreases the activity. Consistent with the strong HSP90-CDC37 inhibition, hybrid molecule **74** potently evaded the growth of A549 tumor cells (IC_{50} = 4.04 ± 0.66 μM). Also, **74** was capable of reversing multidrug-resistance in NCI-H460/DOX lung cells (resistant factor = 1.36). Moreover, **74** induced dose-dependent degradation of HSP90 client proteins, implying that the anticancer activity of **74** is, at least in part, ascribed to HSP90 inhibition. However, it should be noted that both HSP70 and HSP20 were upregulated upon treatment of tumor cells with **74**. Hence, how to minimize the HSR toxicity during the optimization might be a concern for this class of compounds.

2.7. Reactivation of mutant p53

p53 is a tumor suppressor protein that acts crucial roles in cell cycle arrest, DNA damage response, apoptosis, and senescence.[116, 117] In human cancers, p53 is the most commonly mutated protein with more than half of cancers carrying a mutation in p53 (e.g., $p53^{Y220C}$ and $p53^{R175H}$). Mutant p53 abolishes the tumor-suppressive function and manifests a dominant-negative effect on remaining wild-type p53, thereby blocking its anticancer property.[118, 119] Additionally, mutant p53 may interact with diverse transcriptional factors or co-factors to induce tumor-promoting responses such as inflammation and metabolic reprogramming. Thus, reactivation of mutant p53 to restore its wild-type function represents a promising strategy for the development of novel anticancer therapeutics.

In 2018, the Fersht group discovered a novel class of small-molecule Y220C stabilizers employing a structure-guided design strategy (Fig. 20).[120] A biophysical screen of a halogen-enriched fragment library identified a 2-iodophenol-containing compound **75** that bound to the Y220C pocket (K_d = 820 μM). The computational modeling studies revealed that the iodine atom at C3 position of phenyl ring forms a halogen bond with Leu145,

and the hydroxyl group at C2 position of phenyl ring creates two hydrogen bonds with a water molecule bridging residues Val147 and Asp228. The carboxylate at C1 pointed toward solvent exposed region (subsite 1). Hydrophobic contacts were also observed between the iodine atom at C5 position and the hydrophobic channel towards subsite 2. Optimization of hit **75** targeting the subsite 3 (central pocket) and subsite 2 resulted in compound **76** with approximately 58-fold improved activity (K_d = 14 μM). The SAR studies suggested that substituting the carboxylic group with amide, hydroxamic acid, dihydroindazolone or dimethylamino motif dramatically reduces the potency. In addition, the flexible thiother linker was optimal. Furthermore, introduction of pyrrole functionality on the phenyl ring resulted in a significant increase in activity.

To boost the hydrophobic contacts and reduce unfavorable entropy through impeding the C-S bond rotation, they devised and synthesized compound **77** (K_d = 4 μM). This new chemical probe stabilized p53-Y220C *in vitro* and exhibited 3.5-fold increase in affinity relative to **76**. However, its potent binding affinity did not translate into cellular activity as compound **77** showed relatively low cytotoxicity against all cell lines tested, possibly because of its low cell permeability.[120] Further amidation of **77** resulted in compound **78** (MB725, Fig. 20), which induced selective viability reduction in several tumor cell lines with a p53-Y220C mutation while being well tolerated in control cell lines, and upregulated transcription of specific p53 target genes responsible for apoptosis and cell cycle arrest in a p53-Y220C dependent fashion.[120] These data implied that 2-aminobenzothiazole derivative **78** could restore the p53-Y220C transcriptional activity, paving the way for development of potent and non-toxic Y220C-mutant p53 reactivators in antineoplastic therapy.

Given the limitations of thiosemicarbazones (toxicity and poor solubility), the Carpizo group sought to exploit an alternative ZMC scaffold as potential clinical lead candidates.[121] Taking ZMC1 as a lead, they replaced the thiosemicarbazone moiety with benzothiazolyl hydrazone, resulting in compound **79** (K_{Zn} = 119 nM), as shown in Fig. 21. It effectively killed ovarian carcinoma cells TOV-112D (R175H mutant) with an EC_{50} value of 0.055 μM but was ineffective for p53 wild type and p53 null cell lines, suggesting excellent allele cellular selectivity. Unfortunately, **79** also suffered from low aqueous solubility. Optimization of **79** through adding a solubilizing polyether or alkylamine fragment led to the respective compound **80** and **81**, which displayed the improved zinc binding affinity over **79** (K_{Zn} = 22 nM for compound **80** and K_{Zn} = 55 nM for compound **81**). Nevertheless, alkylamine **81** strongly inhibited the potassium channel hERG that was correlated with serious cardiovascular risks. Further elaboration of **81** by removal of the lipophilic base (dimethylamine) resulted in compounds **82** and **83** devoid of hERG liabilities (Fig. 21), maintaining potent zinc-binding affinity (K_{Zn} = 22 and 79 nM, respectively). Unexpectedly, these two compounds were unable to initiate mutant p53 refolding.[121] Further *in vivo* study revealed that **79** is well tolerated up to 30 mg/kg without significant weight loss, whereas the MTD of ZMC1 is only 5 mg/kg. **79** also significantly suppressed tumor growth by 72% at 5.73 mg/kg. Hence, this work validated the general design principle that replacing the thiocarbamoyl group with a benzothiazole moiety could attenuate toxicity and retain anticancer efficacy, and meanwhile provide a framework for the development of more potent zinc-binding and p53 refolding agents.[121]

2.8. Inhibition of HDAC

Histone deacetylases (HDACs), a class of epigenetic enzymes, regulate the expression and activity of numerous proteins involved in cancer initiation and progression. By removal of acetyl groups from histones, HDACs create a non-permissive chromatin conformation which prevents the transcription of genes that encode proteins involved in tumorigenesis.[122, 123] There are 18 human HDACs divided into four classes: class I (HDAC1, 2, 3 and 8), class II (IIa: HDAC4, 5, 7, 9; IIb: HDAC6, 10) and class IV (HDAC11) that are Zn^{2+}-dependent, while class III (Sirtuin1-7) is NAD^{+}-dependent.[124, 125] The overexpression and aberrant recruitment of HDACs (especially class I and II) are positively correlated with tumorigenesis and tumor development. Inhibition of HDACs has been demonstrated to trigger apoptosis, cell differentiation, and cell cycle arrest.

Vorinostat (SAHA) is first approved HDAC inhibitor for the treatment of several types of lymphoma. Riluzole is a drug used to treat amyotrophic lateral sclerosis, the antitumor potency of which has been well documented.[16, 17] Taking advantage of the molecular hybridization strategy, Xu *et al.* devised and discovered 2-aminobenzothiazole-SAHA conjugate **84** as a potential anticancer agent targeting HDAC (Fig. 22).[126] In comparison with SAHA, this hybrid molecule displayed 2-fold and 7-fold more potent total HDAC and HDAC6 isoform inhibitory activity with IC_{50} values of 0.12 ± 0.01 μM and 0.012 ± 0.002 μM, respectively. In addition, **84** demonstrated 27.5-fold and 275-fold selectivity for HDAC6 over HDAC2 and HDAC8, respectively. Significantly, in an MDA-MB-231 xenograft model, **84** demonstrated better *in vivo* efficacy than SAHA (tumor growth inhibition (TGI): 59% vs 33%) at a dose of 30 mg/kg once daily without noticeable toxicity.

In another study, a series of 2-aminotetrahydrobenzothiazole-SAHA hybrids were designed and synthesized.[127] Of these, compound **85** (Fig. 22) was proved to be the most potent inhibitor with IC_{50} values of 1.4, 12.1, 5.6, and 4.6 nM against class I HDAC1, HDAC2, HDAC3 and class IIb HDAC6, respectively. Meanwhile, **85** was capable of increasing the expression of acetylated histone H3 and acetylated α-tubulin in a dose-dependent fashion. Docking simulations on **85** revealed that the hydroxamate moiety forms favorable bidentate interactions with the Zn^{2+} ion of HDAC6 and it interacts with Asp460 and His574 via two hydrogen bonds. In line with its strong anti-HDACs activity, **85** demonstrated potent antiproliferative activity against all 6 tested cancer cell lines with IC_{50} values in the single digit micromolar range, which was more active or comparable relative to SAHA. Notably, minimal cytotoxicity was observed in normal cell lines treated with **85**. In addition, **85** demonstrated good *in vivo* efficacy in an A549 zebrafish xenograft model.[127]

In search of non-hydroxamate HDAC inhibitors, the Ramaa group used the same fragment assembly strategy and identified benzothiazole-thiazolidinedione hybrid **86** (Fig. 22) as a selective HDAC8 inhibitor (HDAC8 IC_{50} = 9.3 μM; HDAC1/3/4/5/7 IC_{50} > 50 μM; HDAC2 IC_{50} = 41 μM).[128] In a follow-up study, compound **87** was characterized as the most potent HDAC4 inhibitor with good isoform selectivity (HDAC4 IC_{50} = 0.75 μM; HDAC1 IC_{50} = 7.4 μM; HDAC3 IC_{50} = 3.1 μM; HDAC6 IC_{50} = 15 μM; HDAC7 IC_{50} = 13 μM; HDAC8 IC_{50} = 12 μM).[129] However, in contrast to compound **87**, the ethoxylated analogue **88** (Fig. 22) displayed much better antiproliferative activity and broader coverage in panel of

tumor cell lines, albeit with less potent HDACs inhibition (e.g., HDAC4 IC_{50} = 4.9 μM and HDAC7/8 IC_{50} > 50 μM). Interestingly, **88** could induce the accumulation of acetylated H3 but not acetylated α-tubulin, supporting its HDAC4 selectivity.[129]

2.9. Inhibition of NSD1

The nuclear receptor-binding SET domain (NSD) family, a class of histone methyltransferases (HMTs), is categorized into three types, NSD1, NSD2 (MMSET/WHSC1) and NSD3 (WHSC1L1).[130] These structurally similar enzymes mono- and di-methylate histone H3 lysine 36 (H3K36), which contribute to regulate the chromatin integrity and gene expression.[131] Aberrant expression or mutation of NSDs is associated with the occurrence of some human malignancies.[130] The role of NSD1 in cancer is complicated and increased expression of NSD1 drives a particular hematological cancer, whereas loss-of function mutation in NSD1 characterizes a wide variety of solid human cancers.[132, 133] The well-recognized oncogenic role of NSD1 is linked to its translocation with the NUP98 gene, which predominantly occurs in pediatric patients with acute leukemia.[132, 133] All NSD HMTs have highly conserved catalytic SET domain, which features a unique autoinhibitory loop that blocks the access of histone lysine substrates to the active site.[134]

Recently, we developed and characterized first-in-class irreversible small-molecule inhibitors of NSD1 targeting the catalytic SET domain (Fig. 23).[135] By conducting fragment-based screening of almost 1600 fragment-like molecules, we identified 2-aminobenzothiazole **89** (BT1) that bound to the SET domain of NSD1. An analogue of **89**, 2-amino-4-hydroxy-6-bromobenzothiazole **90** (BT2) suppressed NSD1 activity with an IC_{50} value of 66 μM. Mapping the binding of **90** to the NSD1 SET domain by ^{1}H-^{15}N HSQC spectrum showed strong chemical shift perturbations for residues in the autoinhibitory loop including Cys2062. Thus, we developed an irreversible ligand **91** (BT3). Analysis of the crystal structure of NSD1 bound to **91** confirmed the covalent binding interaction of **91** to Cys2062. **91** fitted well into the binding pocket of the SET domain and formed well-defined interactions including four key hydrogen bonds and two favorable chalcogen bonds (Fig. 23).

To explore the irreversible inhibitors, the small electrophile aziridine was next introduced at the C6 position of 2-aminobenzothiazole core.[135] The resulting compound **92** (BT4) covalently bound to NSD1 as validated by MS and NMR. Further optimization of **92** gave rise to compound **93** (BT5) with significantly improved NSD1 inhibitory activity (IC_{50} = 5.8 μM). Of note, compounds containing acrylamide moiety weakly interacted with NSD1 and replacement of 2-methylaziridine by 2-ethylaziridine decreased the binding affinity. In addition, replacement of hydroxyl group with methoxyl group abrogated the activity. Encouragingly, **93** was highly selective against epigenetic enzymes and protein kinases.[135] Moreover, **93** effectively blocked the proliferation of NUP98-NSD1 cells (GI_{50} = 0.87 μM). Further mechanism of action studies revealed that **93** could downregulate the expression levels of leukemia-relevant target genes (*HOXA9* and *MEIS1*), decrease global H3K36me2 levels and impair the colony formation of acute myeloid leukemia (AML) cells with *NUP98-NSD1* translocation but not with MLL-ENL translocation or in normal $CD34^{+}$ progenitor

cells. Altogether, our efforts led to the discovery of **93**, a valuable chemical probe, that can irreversibly bind to all three NSD SET domains but showed distinct preference toward NSD1. Further optimization of **93** to develop next generation of potent and selective NSD inhibitors with drug-like properties is underway.

2.10. Inhibition of LSD1

Lysine-specific demethylase 1 (LSD1), also known as KDM1A, AOF2, BHC110 or KIAA0601, is a flavin adenine dinucleotide (FAD)-dependent amino oxidase that catalyzes the demethylation of H3K4 and H3K9 via amine oxidation.[136, 137] LSD1 is aberrantly expressed in diverse cancers, where it promotes proliferation, impedes differentiation, and enhances cell motility.[137, 138] In addition, the high level of LSD1 is correlated with poor prognosis.[137, 138] Its pivotal role in cancer therapy compelled researchers to develop a new class of LSD1 inhibitors.

Alnabulsi *et al*. reported the discovery of novel reversible LSD1 inhibitors by employing a computational fragment-based drug design approach.[139] Two sets of chemically diverse fragments from the Maybridge Ro3 2000 diversity fragment library were docked into two active LSD1 sites: a hydrophobic F pocket adjacent to the FAD binding pocket, and a hydrophilic negatively charged S pocket. On the basis of docking scores and total binding energy values, a set of 2-aminobenzothiazole derivatives were synthesized and their enzymatic inhibitory activities were evaluated. Compound **94** exerted an IC_{50} value of 43.8 μM against LSD1 enzyme (Fig. 24). Optimization of **94** by replacing the methylene unit with a rigid phenyl group led to compound **95**, achieving almost 2.4-fold gain in potency (IC_{50} = 18.4 μM). The authors have suggested that further development of potent LSD1 inhibitors with potential anticancer activity is currently undergoing, using **95** as a lead compound.

2.11. Inhibition of FTO

N^6-methyladenosine (m^6A) is the most abundant epitranscriptomic modification of mRNA. This dynamic modification is regulated by three classes of proteins, known as “writers” (e.g., METTL3, METTL14 and METTL16), “readers” (YTHDF1–3 and YTHDC1–2), and “erasers” (FTO and ALKBH5).[140] FTO, the fat mass obesity-associated protein, is an Fe(II)- and 2-oxoglutarate-dependent dioxygenase that predominantly catalyzes m^6A demethylation.[141] Dysregulation of FTO is linked to tumorigenesis and poor prognosis. In multiple cancer types, FTO is upregulated and plays a crucial tumor-promoting role.[142, 143] Thus, intense interest has been focused on the development of small-molecule inhibitors targeting FTO for cancer therapy.

In 2021, the Rana group reported the design and biochemical characterization of a new class of FTO inhibitors with improved physicochemical properties over existing inhibitor meclofenamic acid (MA).[144] Compound **96** (FTO-04, Fig. 25) was found to selectively block the enzymatic activity of FTO (IC_{50} = 3.39 μM), which was almost 3.7-fold more potent than MA. It should be noted that replacement of 2-aminobenzothiazole scaffold in compound **96** with other aromatic rings such as 2-methoxynaphthalene, 2-methylquinoline or (2-methoxyphenyl)methanol dramatically reduced the FTO inhibition

activity. Significantly, **96** inhibited neurosphere formation in multiple patient-derived glioblastoma stem cell (GSC) lines but had no effect on the growth of healthy neural stem cell-derived neurospheres. Consistent with its potent FTO inhibition, **107** could markedly augment m6A and m6Am levels in GSCs. Overall, these data supported 2-aminobenzothiazole **96** as a potential anti-FTO lead for further medicinal chemistry investigation.

2.12. Inhibition of mPGES-1

Microsomal prostaglandin E synthase-1 (mPGES-1) is the terminal enzyme responsible for the production of the pro-tumorigenic prostaglandin E2 (PGE2).[145, 146] mPGES-1 is overexpressed in various human cancers, and it is considered a validated and promising target in cancer treatment.

In 2020, the Bifulco group developed a new class of mPGES-1 inhibitors featuring a 2-aminobenzothiazole scaffold based upon a combinatorial virtual screening campaign approach.[145] Compounds **97-99** exerted the most potent inhibitory activity against mPGES-1 in a cell-free system with IC_{50} values of 1.7 ± 0.2, 1.4 ± 0.2, and 0.7 ± 0.1 μM, respectively (Fig. 26). These compounds could concentration-dependently reduce the cytokine-induced PGE2 production in A549 cells where mPGES-1 was overexpressed. They also showed good cell growth inhibition and induced G0/G1 cell cycle arrest in a time- and concentration-dependent fashion in A549 cells. Thus, these compounds could be reckoned as anti-mPGES-1 leads for a further medicinal chemistry campaign.

2.13. Inhibition of SCD

An increase in the expression of stearoyl-CoA desaturase (SCD), an enzyme that converts saturated fatty acids to monounsaturated fatty acids, has been reported in a wide range of cancer cells, and this increase is positively correlated with tumor growth rates.[147, 148] Inhibition of SCD represents a potential approach for cancer treatment.[149] However, clinical development of SCD inhibitors has been impeded by the on-target toxicity. Particularly, SCD inactivation in the skin results in the atrophy of sebocytes.[150] Thus, identification of new chemotypes as SCD inhibitors with minimized skin toxicity has gained considerable attention.

Scientists from UT Southwestern Medical Center identified the hit **100** (Fig. 27), an irreversible SCD inhibitor, through an unbiased HTS campaign using 12 distinct NSCLC cell lines.[150, 151] Compound **100** displayed IC_{50} values < 1 μM against a subset of NSCLC cell lines (e.g., H2122 cells IC_{50} = 0.058 μM) but > 5 μM against other NSCLC lines (e.g., H2009 cells IC_{50} = 22 μM). Single-digit nanomolar activity against H2122 cells was achieved when the 4-amino group was substituted with a phenone group (compound **101**, IC_{50} = 8 nM). Despite excellent *in vitro* potency, **101** suffered from poor PK profiles (e.g., C_{max} = 0.3 μM and AUC = 0.6 μM·h). Further modification resulted in compound **102** (SW206638, Fig. 27) with low logP and significant improvement in plasma pharmacokinetic properties (e.g., C_{max} = 1.5 μM and AUC = 3.0 μM·h). One noteworthy finding was that the antiproliferative activity of compound **102** was substantially reduced when the benzothiazole core was replaced with benzimidazole, benzoxazole, thiazole, or

phenyl-thiazole. Compound **102** potently blocked the enzymatic activity of SCD with an IC_{50} value of 54 nM. Consistently, a significant reduction in H2122-derived tumor growth was observed following a 25 mg/kg intraperitoneal dose of **102** twice a day (BID). In addition, **102** displayed higher antitumor efficacy and lower skin toxicity than the canonical SCD inhibitor Xenon-45. The enantiomer **(*R*)-102** exerted robust antiproliferative activity against H2122 cells (IC_{50} = 21 nM, Fig. 27).[151] Mechanistically, **(*R*)-102** functioned as a prodrug that could be transformed into active analogue **(*R*)-103** (H2122 cells IC_{50} = 8 nM) mediated by CYP4F11 which was expressed in sensitive NSCLC cell lines but not expressed in insensitive NSCLC cell lines. The SCD inhibitor **(*R*)-104** showed a similar selectivity pattern, and the same metabolite **(*R*)-103** was also monitored in H2122 cells. In the modified tumor xenograft model, **(*R*)-103** significantly arrested tumor growth at the dose of 10 mg/kg via subcutaneous BID administration, and no obvious toxicity was observed. Collectively, this tumor-activated prodrug strategy offered the promise to exploit potent SCD inhibitors and avoid toxicity correlating with systemic SCD suppression.[151]

2.14. Inhibition of hCA IX/XII

Human carbonic anhydrases (hCAs) are ubiquitous zinc-metalloenzymes which catalyze the reversible interconversion between carbon dioxide and bicarbonate.[152, 153] hCAs are categorized into 15 isoforms on the basis of their tissue distribution and kinetic properties, such as cytosolic (hCA I, II, III, VII, and XIII), mitochondrial (hCA VA and VB), membrane-bound (hCA IV, IX, XII, XIV, and XV), secreted (hCA VI) isoenzymes.[153] Amongst them, hCA IX and hCA XII are overexpressed in many tumors but sparsely present in normal tissues. In addition, hCA IX and hCA XII are related with hypoxic solid tumors inducing tumor growth and metastasis. Pharmacological inhibition of hCA IX/XII has become a promising approach for cancer treatment.[154] As a consequence, many small-molecule hCA IX/XII inhibitors belonging to diverse classes have been investigated for their antineoplastic potentials, including 2-aminobenzothiazole derivatives.

Compound **105** (Fig. 28) exerted good hCA IX/XII suppressive activity (hCA IX K_i = 0.079 μM and hCA XII K_i = 0.76 μM) as well as excellent selectivity over the cytosolic hCA I and II (K_i > 50 μM).[155] Compound **106** (Fig. 28) bearing a sulfonamide moiety effectively blocked the enzymatic activity of hCA IX and XII, with K_i values of 10 nM and 46.5 nM, respectively.[156] 2-Aminobenzothiazole derivative **107** (Fig. 28) was reported as a highly potent hCA IX/XII inhibitor (K_i = 4.1 and 6.7 nM, respectively).[157] However, both compounds **106** and **107** also showed pronounced inhibitory potency towards physiologically dominant hCA I and II subtypes. Compound **108** that featured a 4-methoxyphenyl substituted piperazine-dithiocarbamate tail displayed strong and selective inhibition activity against hCA IX isoform (Fig. 28), with a K_i value of 30.9 nM.[158] This compound was found to be active against MCF-7 cells. Very recently, the Supuran group developed a set of new 2-aminobenzothiazole-based inhibitors of hCA IX/XII.[159] The representative compound **109** manifested excellent potency and selectivity towards cancer-related isozymes (hCA IX K_i = 48.9 nM and hCA XII K_i = 57.5 nM), as shown in Fig.28. Consistent with the hCA IX/XII suppression, **109** elicited good antiproliferative activity against breast cancer T-47D and MCF-7 cells, having IC_{50} values of 6.73 and

9.16 μM, respectively.[159] These data revealed the potential of hCA IX/XII inhibition for designing 2-aminobenzothiazole-derived anticancer agents.

2.15. Inhibition of CXCR

CXCR1 and CXCR2, known as interleukin-8 receptor A (IL-8RA) and interleukin-8 receptor B (IL-8RB) respectively, are members of the cell surface G protein-coupled receptors (GPCR) family.[160] Both of them mediate the initiation and development of various cancers. Accumulating evidence shows that CXCR1/2 inhibition profoundly suppresses the progression of cancers and augments the therapeutic effect.[160-162]

Compound **110** (Fig. 29) that possessed electron-withdrawing substituents on both benzothiazole and phenyl rings manifested pronounced CXCR2 inhibition activity (IC_{50} = 0.3 μM).[163] In addition, **110** exerted potent antiproliferative activity against ovarian OVCAR-8 and CXCR2-U2OS cell lines with IC_{50} values of 4.9 and 2.9 μM, respectively. Compound **111** (Fig. 29), an analogue of **110**, presented strong inhibitory activity against the solid and hematological tumor cell lines with IC_{50} values ranging from 2 to 5 μM, especially renal cell carcinoma (RCC) and head and neck squamous cell carcinoma (HNSCC) where CXCR1/2 were highly expressed.[164] This compound showed low cytotoxicity against normal primary kidney cells 15S and Mel202 (IC_{50} > 10 μM). Notably, it was found to be equally efficient on parental and resistant RCC and HNSCC cells. Moreover, **111** demonstrated reasonable PK properties (e.g., $t_{1/2}$ = 191 min and T_{max} = 30 min). Further *in vivo* studies indicated that **111** remarkably reduced the growth of experimental RCC or HNSCC tumors with no weight loss observed. [164] Altogether, these results suggested that **111** may represent a therapeutic tool for further RCC and HNSCC investigation.

2.16. Chelators

Transition metals such as iron, copper, and zinc are essential for critical biological processes, including gene expression, oxygen transport, and respiration.[165] Tumor cells require these nutrients for their rapid proliferation, particularly iron. As such, trapping the iron in tumors provides new perspectives for antineoplastic treatments.[166, 167] In the past few years, a library of chelators as promising anticancer agents including 2-aminobenzothiazole analogues have been disclosed.

Triapine, a tridentate *N*-pyridyl thiosemicarbazone (Fig. 30), is a potent ribonucleotide reductase inhibitor currently undergoing phase I and II clinical trials. In accordance with the binding mode of triapine (N–N–S terdentate coordination), the Zhu group utilized a cyclization strategy and identified compound **112** with robust cellular potency.[168] Of note, substitution of the 2-aminobenzothiazole moiety in compound **112** with a 2-aminobenzimidazole motif significantly compromised the antiproliferative activity. **112** showed good mouse liver microsomal stability and acceptable pharmacokinetic properties (e.g., C_{max} = 673 μg/L and F = 25%).

In an MV4;11 xenograft model, treatment of mice with **112** at an oral dose of 30 mg/kg (BID) significantly inhibited tumor growth, with no impact on body weight. Further studies revealed that, unlike triapine, **112** preferentially suppresses the proliferation of

hematopoietic tumor cells by inducing copper-dependent mitochondria ROS production and mitochondrial dysfunction. It was also able to enhance thioredoxin-interacting protein expression, attenuate the thioredoxin activity, and activate the JNK and p38 MAPK pathway, which potentiated its antitumor activity.[168]

2-aminobenzothiazole derivative **113** (Fig. 31), an NNS donor chelator, was substantially more effective for MDR tumor cell lines as compared to the corresponding parental cells lines, having IC_{50} values ranging from 0.014 to 0.28 μM.[169] The ONS donor chelator **114** demonstrated 2-fold more potent cytotoxicity against MES-SA_mCh/doxorubicin cells than the corresponding sensitive cell line (MES-SA_mCh).[169] Another interesting chelator **115** (Fig. 31), in which three substituents were installed on the benzothiazole scaffold, exerted strong suppressive activity against MDR Colo320 colonic adenocarcinoma cells (IC_{50} = 0.188 μM).[170] Similarly, **115** was more effective for MDR Colo320 cells than that for doxorubicin-sensitive Colo205 colon tumor cells. These results suggested that development of 2-aminobenzothiazole-derived chelators could be a potential strategy to conquer MDR.

2.17. Ligands of metal-based anticancer agents

Platinum-based drugs, such as cisplatin, carboplatin, and oxaliplatin are used in the treatment of approximately 50% of cancers.[171, 172] Following the success of platinum-based drugs and considering their adverse effects and drug resistance, new metal-based anticancer agents have been developed through integration of the heterocyclic motif and metal.[173] Of these heterocycles, functionalized 2-aminobenzothiazole as a ligand has captured intensive attention.

Compounds **116**-**118** (Fig. 32) manifested potent antiproliferative activity against a panel of tumor cancer cell lines with IC_{50} values ranging from 3.77 to 7.43 μM, which were equipotent to the standard anticancer drug cisplatin.[174] The mechanistic study suggested that the inhibition of cell viability is attributed to the cleavage or fragmentation of DNA of these cancer cells resulting from active species (hydroxyl radicals). Rao and coworkers reported several metal complexes as potential anticancer agents.[175] Among them, compound **119** (Cu complexes) was found to intercalate stronger and promote DNA cleavage more efficiently than other metal complexes (Fig. 32). Consistently, **119** exerted the strongest *in vitro* cytotoxic activity against HeLa and MCF-7 cell lines. Interestingly, all metal complexes showed higher cytotoxicity than the parent ligand in both cell lines.

The Mostafa group developed several new 2-aminobenzothiazole-based metal complexes.[176] Among them, compounds **120** and **121** (Fig. 32) were demonstrated to be more active than cisplatin, with IC_{50} values of 1.26 and 1.78 μM against MDA-MB231 and OVCAR-8 cell lines, respectively. These two compounds were capable of binding to CT-DNA through intercalation and inhibition of DNA synthesis. In a follow-up study, a subset of new complexes of V(IV), Ru(III), Pd(II), Pt(II) and Ag(I) derived from 2-hydrazinobenzothiazole were designed and synthesized.[177] Compound **122** (Fig. 32) emerged as the strongest metal complex, achieving IC_{50} values of 5.15, 9.9, 13.1 and 17.7 μg/mL against EAC, HepG2, MCF-7 and HCT-116 cell lines, respectively. More recently, Nádia *et al.* reported that compound **123** (Fig. 32) exerted higher antiproliferative activity than 5-FU against HCT-116 cells, with an IC_{50} value of 16.6 μM.[178] It induced the cell cycle arrest at S phase

and effectively suppressed cell migration. Overall, these results indicated that development of aminobenzothiazole-metal complexes is an important strategy to explore new chemical entities as anticancer agents.

2.18. Miscellaneous

The Liu group at Peking University carried out a substructure virtual searching and identified a new class of 2-aminobenzothiazole compounds as promising antineoplastic agents.[179] In this study, 2-aminobenzothiazole **124** (Fig. 33), deemed as the most potent compound, showed potent and specifically suppressive activity against HPV18-positive cervical cancer cell lines (HeLa and C4-1) with IC_{50} values of 0.38 and 0.44 μM, respectively. Notably, the amino group on the benzothiazole scaffold was indispensable for antiproliferative potency. The following mechanism study suggested that **124** could repress transcription, especially those related to the oncoprotein E7 cellular pathway (e.g., E7/Rb/E2F-1/DNMT1), which are crucial to tumorigenesis. Further proteomics investigation indicated that E7 might be degraded through E3 ubiquitin ligases by activating the NEDD8. Importantly, in the HeLa xenograft model, **124** manifested robust inhibition of tumor growth without noticeable adverse effects.[179]

To seek novel chemical entities with anticancer activity, Mistry et al. attached a 2-aminobenzothiazole moiety to alkaloid berberine using the molecular hybridization strategy.[180] Compound **125** (Fig. 33) presented the highest antiproliferative potency against HeLa, CaSki, and SK-OV-3 cell lines, with IC_{50} values of 5.474, 5.311, and 32.61 μg/mL, respectively. Dadmal *et al.* developed a number of triazole and isoxazole-tagged benzothiazole hybrids.[181] Among them, **126** and **127** (Fig. 33) stood out as the most promising molecules, inhibiting the growth of tumor cells with IC_{50} values in the range of 1.57-2.415 μM. These two compounds could promote apoptosis through caspase-dependent apoptotic process via the mitochondrial pathway. An interesting family of cytotoxic compounds was obtained by tethering a 2-aminobenzothiazole core and another bioactive heterocycle via copper catalyzed azide-alkyne cycloadditions (CuAAC). Compound **128** showed the strongest inhibitory activity against SW1882 colorectal cell line. Further studies indicated that **128** is able to intercalate with Ct-DNA through the minor groove (Fig. 33).[182]

The Hranjec group disclosed that compound **129** (Fig. 33) exhibited strong inhibitory activity against HeLa cells with an IC_{50} value of 1.16 μM, which was approximately 7.6-fold more potent than standard drug 5-FU.[183] In a follow-up study, they found that its analogue **130** (Fig. 33) potently inhibited the proliferation of MCF-7 cells (IC_{50} = 40 nM).[184] However, further modification of **130** led to derivatives **131** and **132** with a great loss of activity, indicating that the presence of amino protonated moiety on the benzo[b]thiophene skeleton is unfavorable for antiproliferative potency.[184]

Videnovic and colleagues developed new 2-aminobenzothiazole chemotypes and assessed their antiproliferative activities.[185] Compounds **133** and **134** (Fig. 33) exerted outstanding inhibitory potency against various tumor cells, especially NT2/D1 cells (IC_{50} of 0.2 μM and 0.1 μM, respectively). The amide analogue **135** had weaker antiproliferative activity

than compounds **133** and **134** against NT2/D1 cells. Interestingly, compound **134** was noncytotoxic to MCF-7 cells (IC_{50} > 100 μM), but compound **135** showed moderate suppressive effect on MCF-7 cells. The possible mechanism of action of these compounds was then investigated. In MCF-7 cells, 2-aminobenzothiazole analogues **133** and **135** were found to exhibit antiproliferative activity by arresting cell cycle in G2/M phase and triggering apoptosis. In NT2/D1 cells, induction of apoptosis and migration together with invasiveness could contribute to the cytotoxic potential of compounds **133** and **134**.[185] However, the exact target(s) of 2-aminobenzothiazoles **133** and **134** on NT2/D1 cells remains uncertain.

A new series of 2-aminobenzothiazole derivatives bearing a 2-anilinopyridyl functionality were designed and evaluated for their antineoplastic potentials.[186] Among them, **136** and **137** (Fig. 33) were found to be the most active compounds with IC_{50} values of 1.03 and 1.69 μM against MCF-7 cells, respectively. In a similar work, Saipriya *et al.* reported that compound **138** (Fig. 33) displayed excellent activity with an IC_{50} value of 2.517 μg/mL against HeLa cells, which was 6.8-fold more active than cisplatin (IC_{50} = 17.2 μg/mL).[187] Very recently, JawalePatil *et al.* integrated a 2-aminobenzothiazole pharmacophore and naphthalimide moiety, delivering compound **139** that possessed low micromolar inhibitory potency against B16F10 cells.[188] Compound **140** was found to repress the viability of a panel of cancer cell lines with IC_{50} values in the range of 2.23-3.75 μM (Fig. 33).[189] Especially, **140** displayed comparable activity to doxorubicin against MDA-MB-231 cells. The mechanistic study suggested that **140** induces apoptosis in MDA-MB-231 cells by downregulation of Bcl-2 and upregulation of Bax protein levels. [189]

Based on the structure of the Twist1 inhibitor harmine, the Zhai group devised and developed a novel class of 2-aminobenzothiazole-containing compounds employing the scaffold hopping strategy.[190] Among them, compound **141** (Fig. 33) possessed the most pronounced antiproliferative effect on A549 and H2228 cells with corresponding IC_{50} value of 2.03 μM and 9.80 μM, which was superior to the lead harmine. In a consistent manner, **141** demonstrated effective reduction of Twist1 level in a dose-dependent pattern. In this study, substituting the piperidine group in **141** with piperazine, pyrrole, azetidine, or alkylamines resulted in a significant decrease in antiproliferative activity. The reduction in activity was also observed when the linker length of **141** was shortened.

3. Conclusion and perspective

2-Aminobenzothiazoles have been used as privileged scaffolds in drug design and discovery. It is evident that 2-aminobenzothiazole derivatives demonstrate immense potential as anticancer agents. Intriguingly, a large number of 2-aminobenzothiazole analogues were identified through screening, bioisosteric replacement, scaffold hopping, structure/fragment-based drug design and molecular hybridization strategies. In this study, we systematically summarize the recent developments of 2-aminobenzothiazoles as the privileged structures in the design and discovery of anticancer agents targeting tumor-related proteins (Table 1). In particular, the anticancer potentials of 2-aminobenzothiazole-derived chelators and 2-aminobenzothiazole-metal complexes are also detailed. In addition, the examples in which the 2-aminobenzothiazoles exert better performance in enzymatic inhibition and/or cellular

activity than other heterocycles are highlighted. In this review, we also summarize some key SARs of these 2-aminobenzothiazole derivatives. For instance, the important feature of NSD1 inhibitors possesses the 2-aminobenzothiazole scaffold. Compounds bearing acrylamide moiety weakly interacted with NSD1, and substitution of 2-methylaziridine with 2-ethylaziridine compromised the binding affinity. In addition, changing the hydroxyl group with a methoxyl group substantially abolished the binding to NSD1. Importantly, the 2-aminobenzothiazole motif formed two hydrogen bonds with residue Thr1994 and SAM, respectively, and the sulfur atom within benzothiazole ring made contacts with residues Asp2065 and Gly2066 through two key chalcogen bonds. These favorable interactions underscore the vital role of the 2-aminobenzothiazole scaffold in drug design.

However, the antiproliferative activity observed for some 2-aminobenzothiazole derivatives does not entirely correspond to their inhibition against a particular target, warranting more detailed studies to progress with their development. On the other hand, many 2-aminobenzothiazole derivatives have been reported to demonstrate excellent inhibitory activity against the specific target(s) (e.g., hCA IX/XII and EGFR). Nevertheless, there is no PK or *in vivo* data available for these inhibitors on the anticancer efficacy as of yet. Hybridization of 2-aminobenzothiazole motif with other pharmacophores could be an important approach to deliver new anticancer agents with higher potency. Besides, conversion of 2-aminobenzothiazole-based inhibitors into degraders and further development of 2-aminobenzothiazole-derived chelators would be new directions in the future to combat cancer drug resistance and achieve anticancer efficacy. We anticipate that, with the help of effective design strategies and in-depth SAR studies, safe and efficacious 2-aminobenzothiazole-based antitumor molecules with selective target engagement can be developed. This chemotype offers tremendous opportunities to explore new chemical space in future anticancer drug discovery programs.

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Abbreviations

BCL-2	B cell lymphoma protein 2
BID	twice a day
CDKs	cyclin-dependent protein kinases
CK1	casein kinase 1
CK2	casein kinase 2
CSF1R	colony-stimulating factor 1 receptor
CT	cyanothiouracil
DYRKs	dual-specificity tyrosine-phosphorylation-regulated kinases

FAK	focal adhesion kinase
FLT3	FMS-like tyrosine kinase-3
FTO	fat mass obesity-associated protein
5-FU	5-fluorouracil
HGF	hepatocyte growth factor
HDACs	histone deacetylases
hCAs	human carbonic anhydrases
HSR	heat shock response
HSP90	heat shock protein 90
HTS	high-throughput screening
HNSCC	head and neck squamous cell carcinoma
LSD1	lysine-specific demethylase 1
MDR	multidrug resistance
mPGES-1	microsomal prostaglandin E synthase-1
MTD	maximum tolerated dose
NSCLC	non-small-cell lung cancer
NSD	nuclear receptor-binding SET domain
PDGFR	platelet-derived growth factor receptor
ROS	reactive oxygen species
PI3Ks	phosphoinositide 3-kinases
PTKs	protein tyrosine kinases
RCC	renal cell carcinoma
SAR	structure-activity relationships
SCD	stearoyl-CoA desaturase
STKs	serine/threonine kinases
TAMs	tumor-associated macrophages
TZD	thiazolidinedione
ZMCs	zinc metallochaperones

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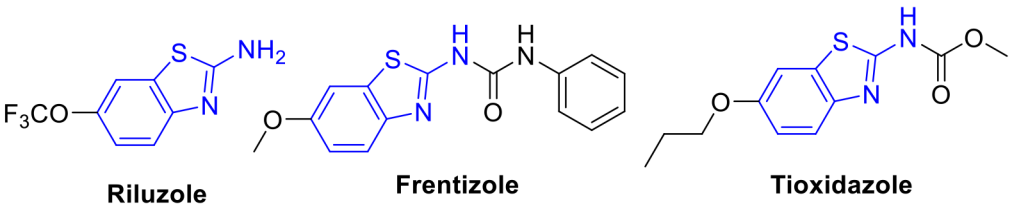


Fig. 1.
Representative examples of 2-aminobenzothiazole scaffold in commercial drugs.

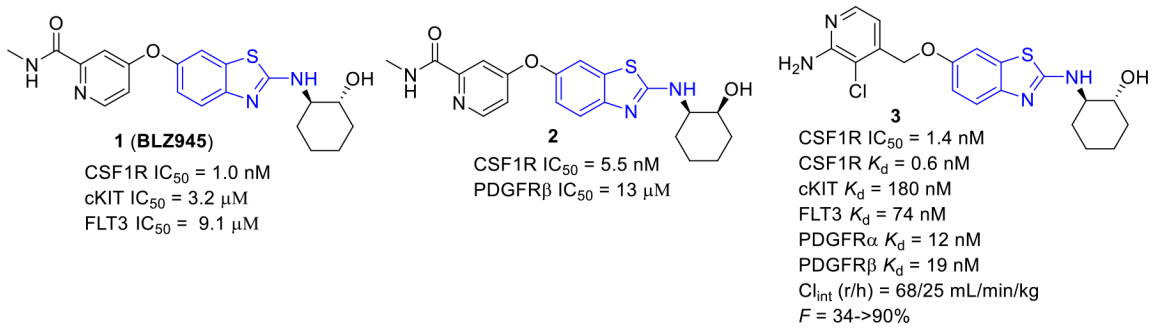


Fig. 2.

Chemical structures of 2-aminobenzothiazole-based CSF1R inhibitors **1**–**3**.

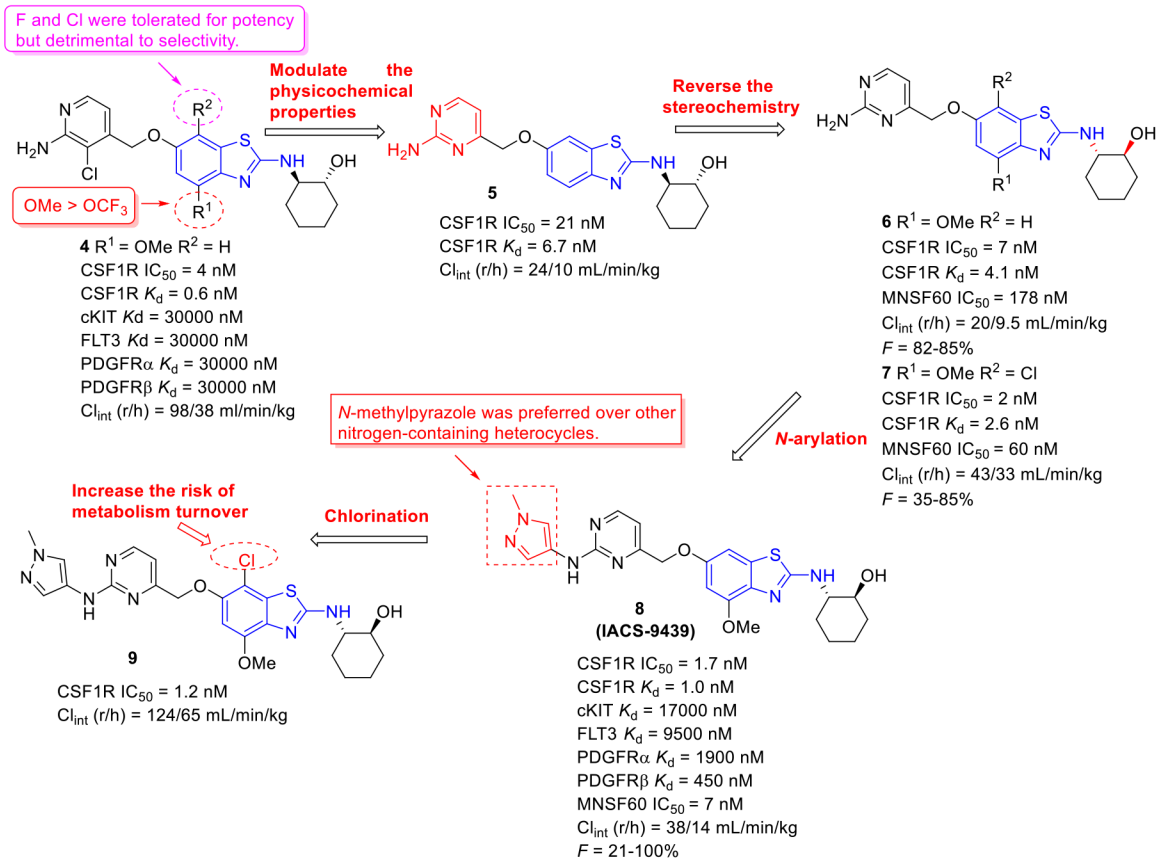


Fig. 3.

Medicinal chemistry strategy for the discovery of CSF1R inhibitor **8** (IACS-9439).

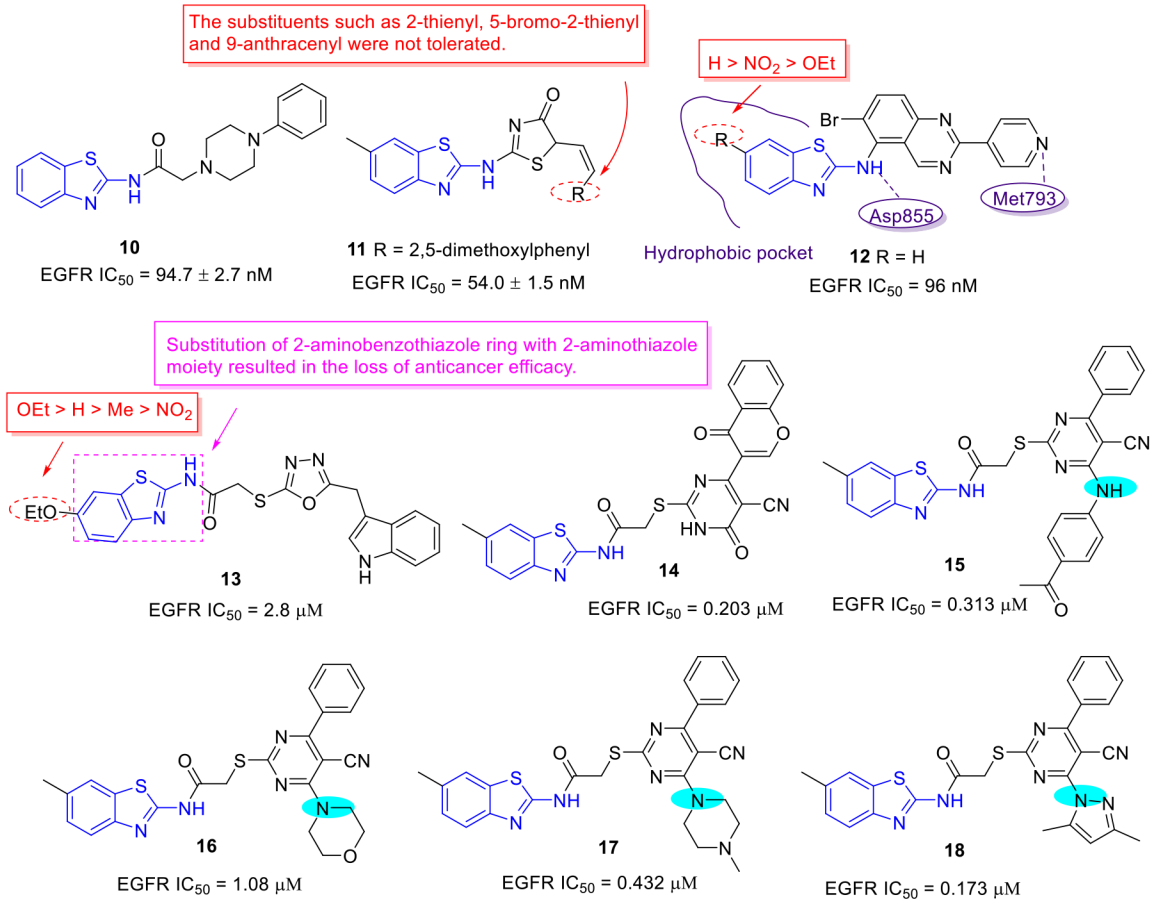


Fig. 4.

Chemical structures of 2-aminobenzothiazole derivatives **10**–**18** as EGFR inhibitors.

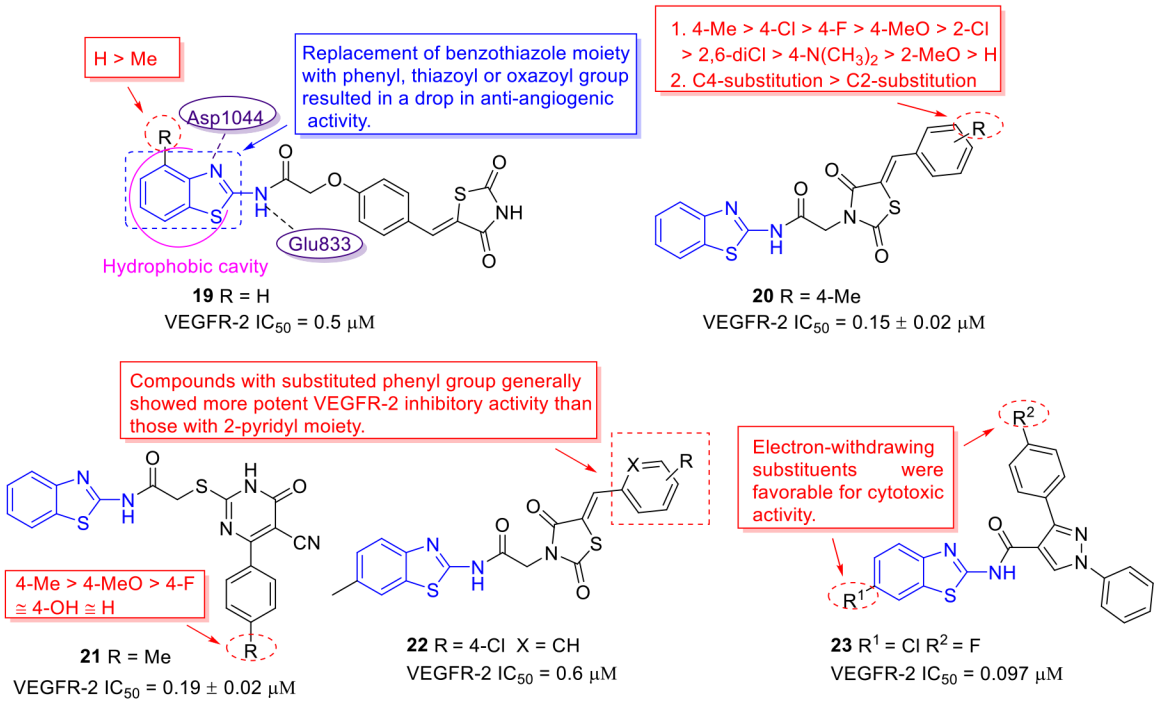


Fig. 5.

Chemical structures of 2-aminobenzothiazole derivatives **19**–**23** as VEGFR-2 inhibitors.

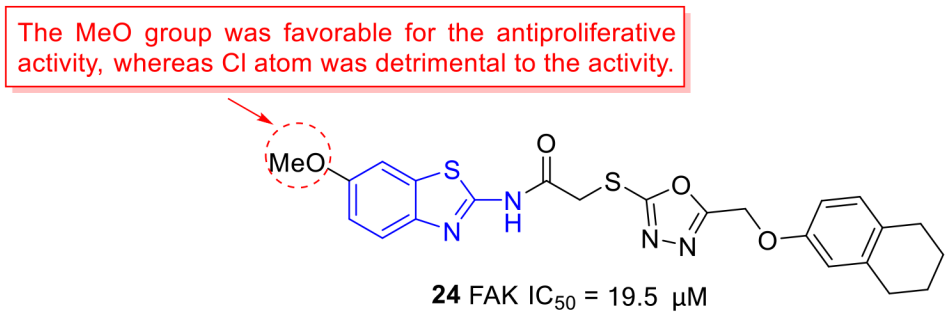


Fig. 6.

Chemical structure of 2-aminobenzothiazole derivative **24** as an FAK inhibitor.

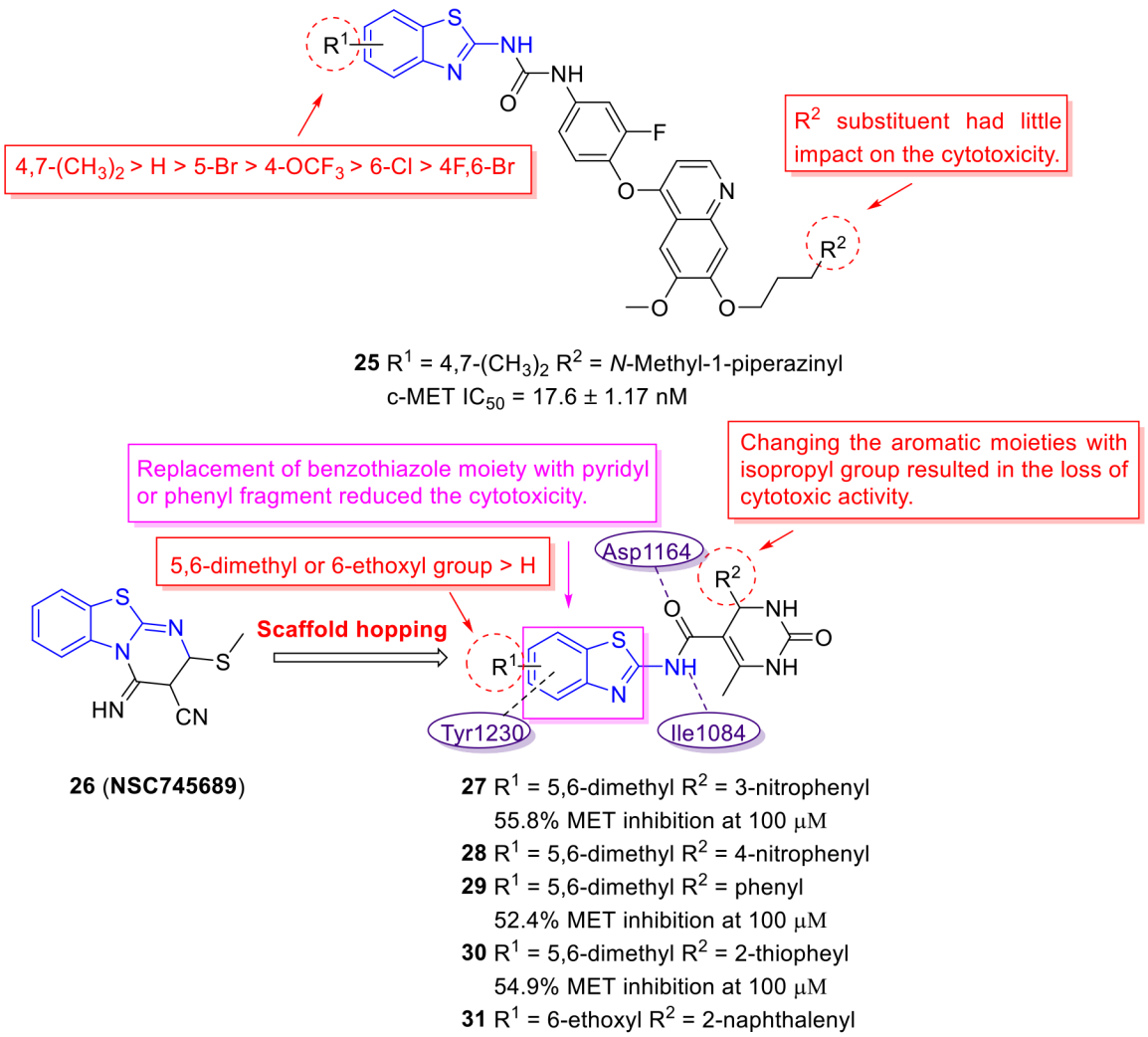


Fig. 7.

Chemical structures of 2-aminobenzothiazole derivatives **25**–**31** as MET inhibitors.

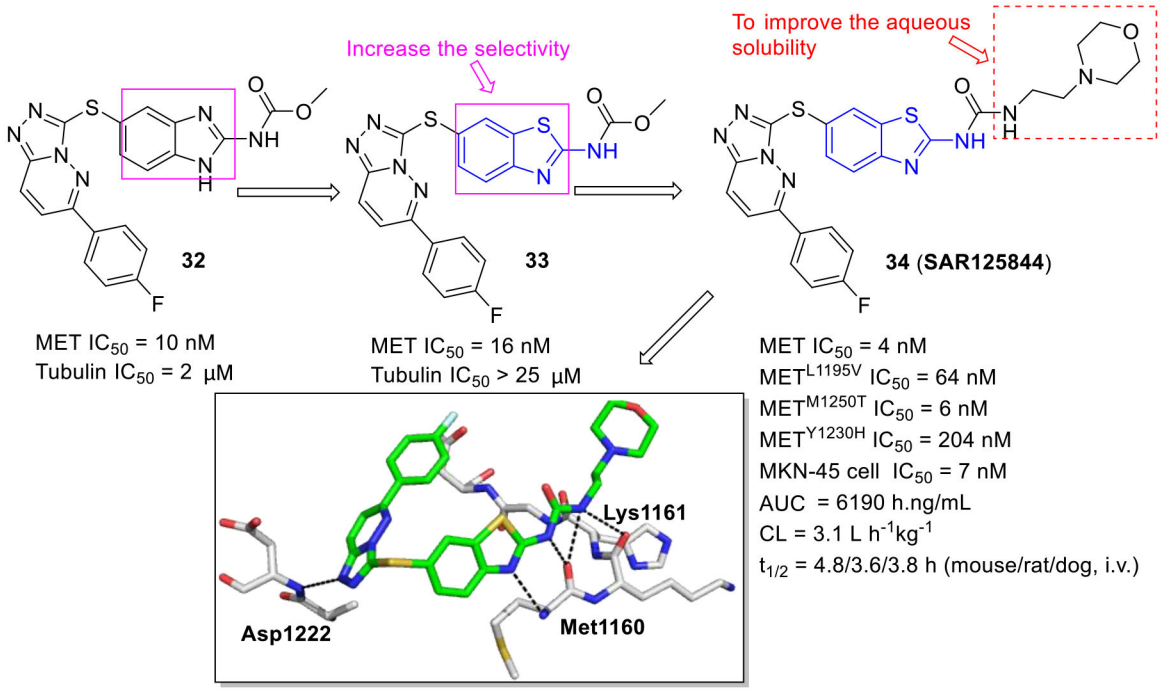


Fig. 8.

Identification of 2-aminobenzothiazole derivative **34** (SAR125844) as a MET inhibitor. Crystal structure of **34** with the MET^{Y1230H} (PDB code 5HO6).

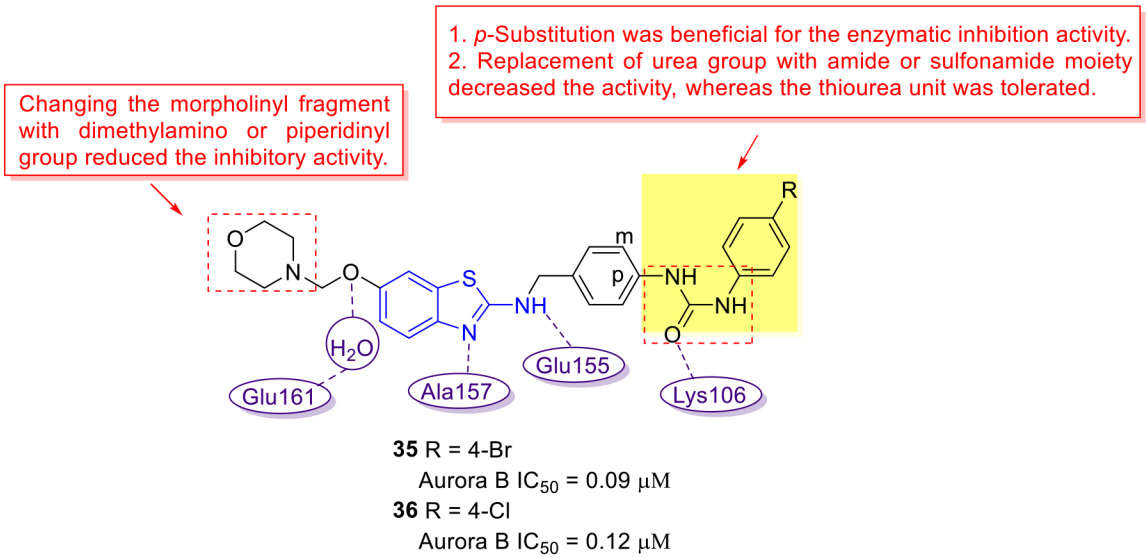


Fig. 9.

Chemical structures of 2-aminobenzothiazole derivatives **35** and **36** as Aurora kinase B inhibitors.

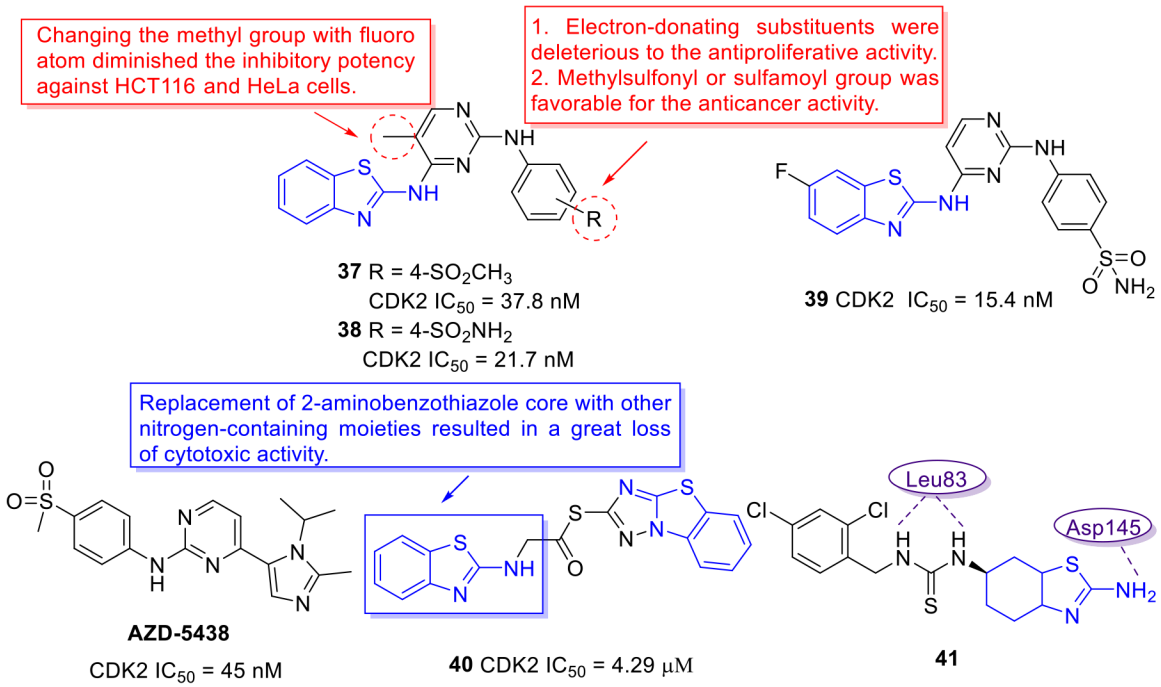


Fig. 10.

Chemical structures of AZD-5438 and 2-aminobenzothiazole derivatives **37**–**41** as CDK2 kinase inhibitors.

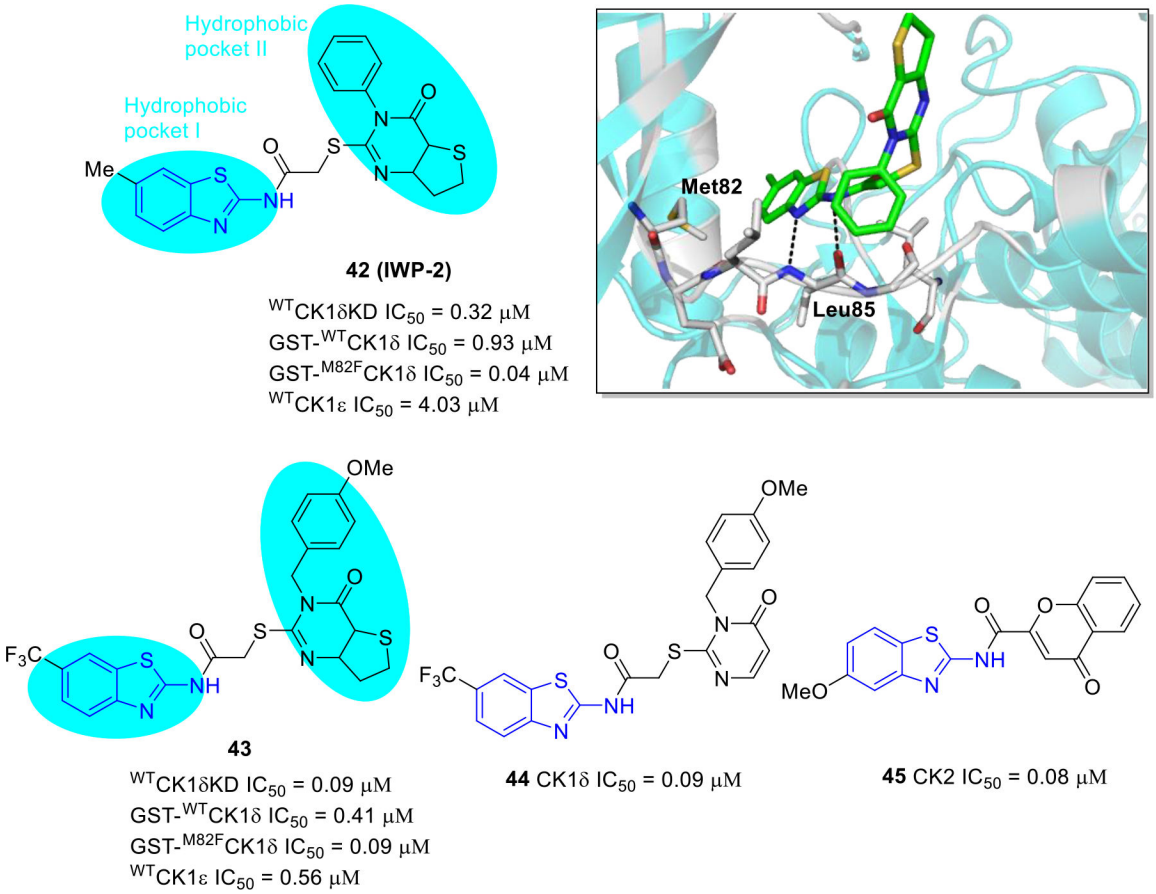


Fig. 11.

Chemical structures of 2-aminobenzothiazole derivatives **42-45** as CK kinase inhibitors. Crystal structure of **42** with the CK1δ (PDB code 5OKT).

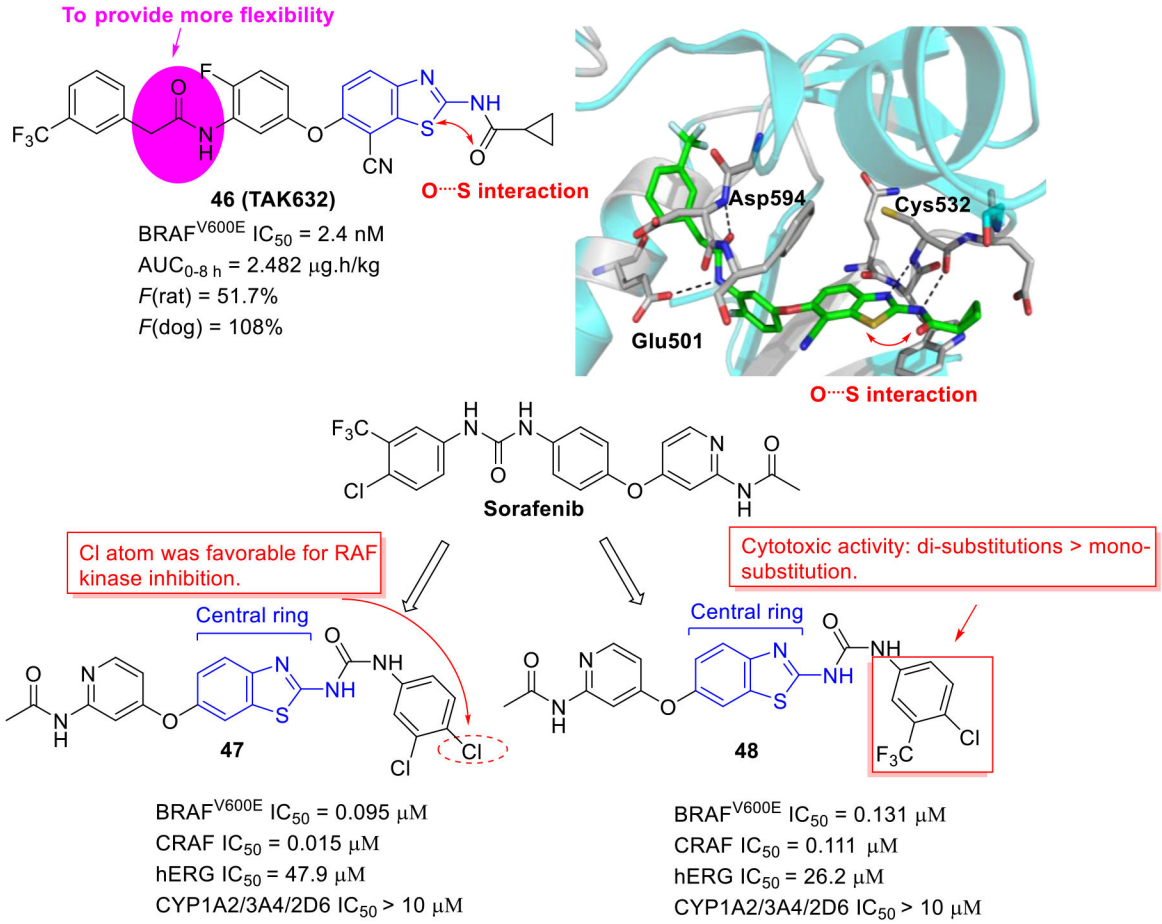


Fig. 12.

Chemical structures of 2-aminobenzothiazole derivatives **46-48** as RAF inhibitors. The crystal structure of **46** (TAK632) with BRAF (PDB code 4KSP).

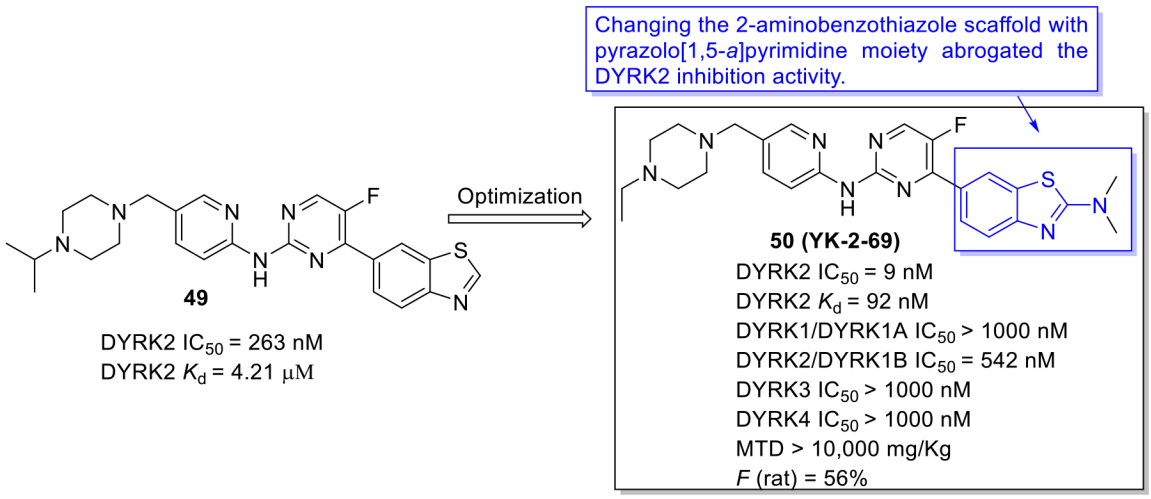


Fig. 13.

Discovery of 2-aminobenzothiazole derivative **50** (YK-2-69) as an exquisitely potent and selective DYRK2 inhibitor.

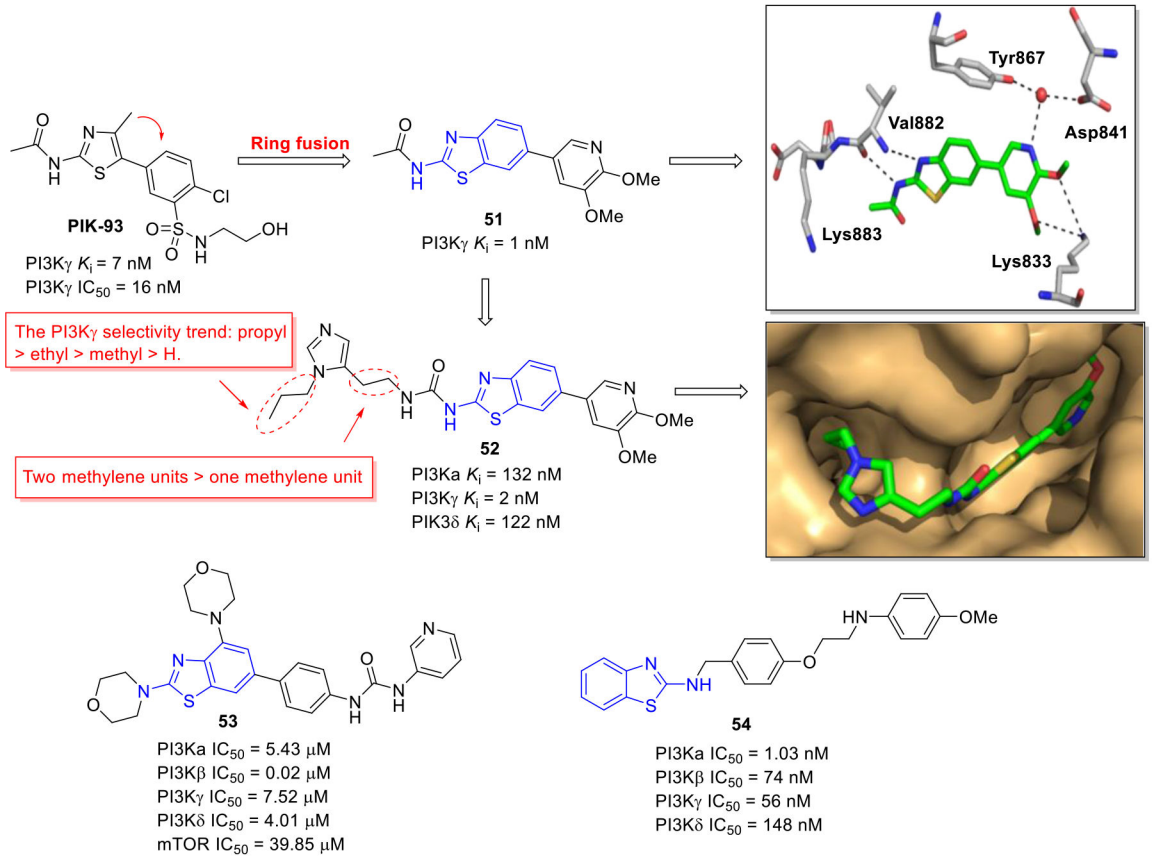


Fig. 14.

Chemical structures of 2-aminobenzothiazole derivatives **51**–**54** as PI3K inhibitors. X-ray crystal structure of **51** and **52** bound to PI3Kγ (PDB code 4PS8 and 4PS3, respectively).

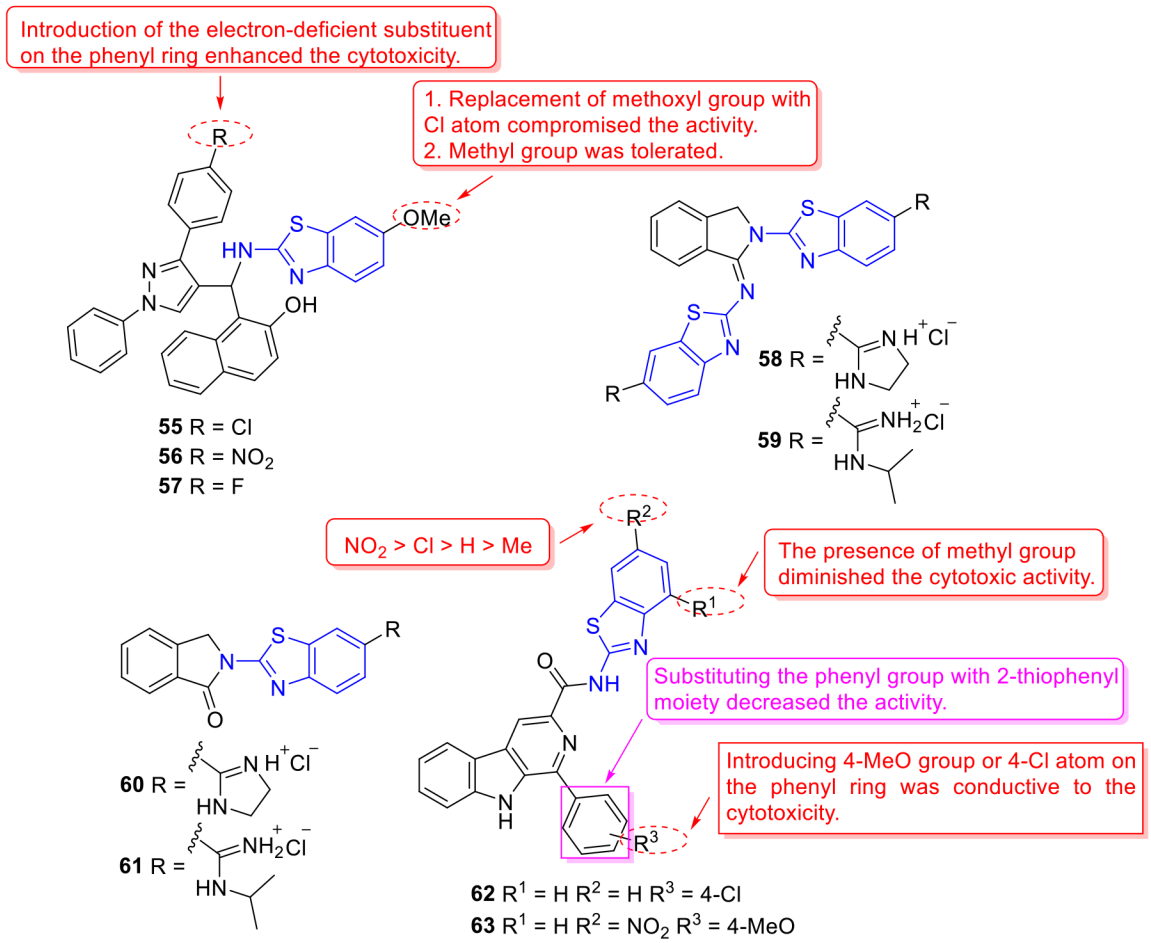


Fig. 15.

Chemical structures of 2-aminobenzothiazole derivatives **55–63** as topoisomerase inhibitors.

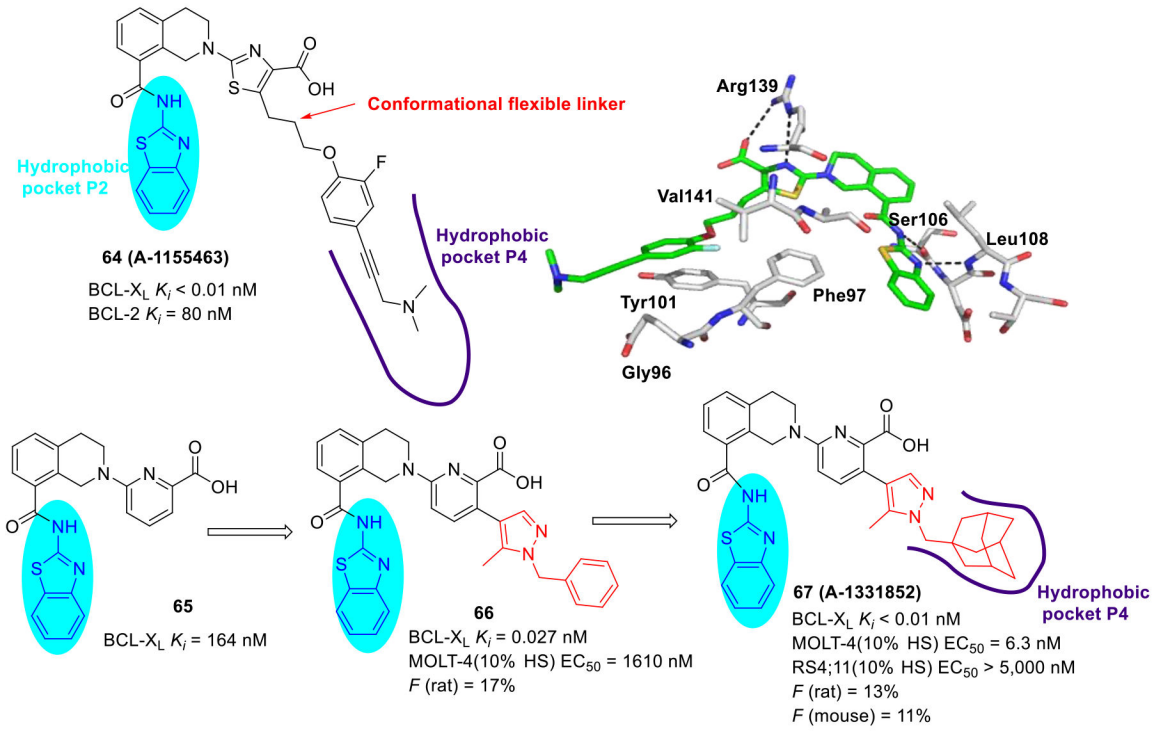


Fig. 16.

Structure-guided development of potent BCL-X$_L$ inhibitor **67** (A-1331852). X-ray crystal structure of **64** bound to BCL-X$_L$ (PDB code 4QVX).

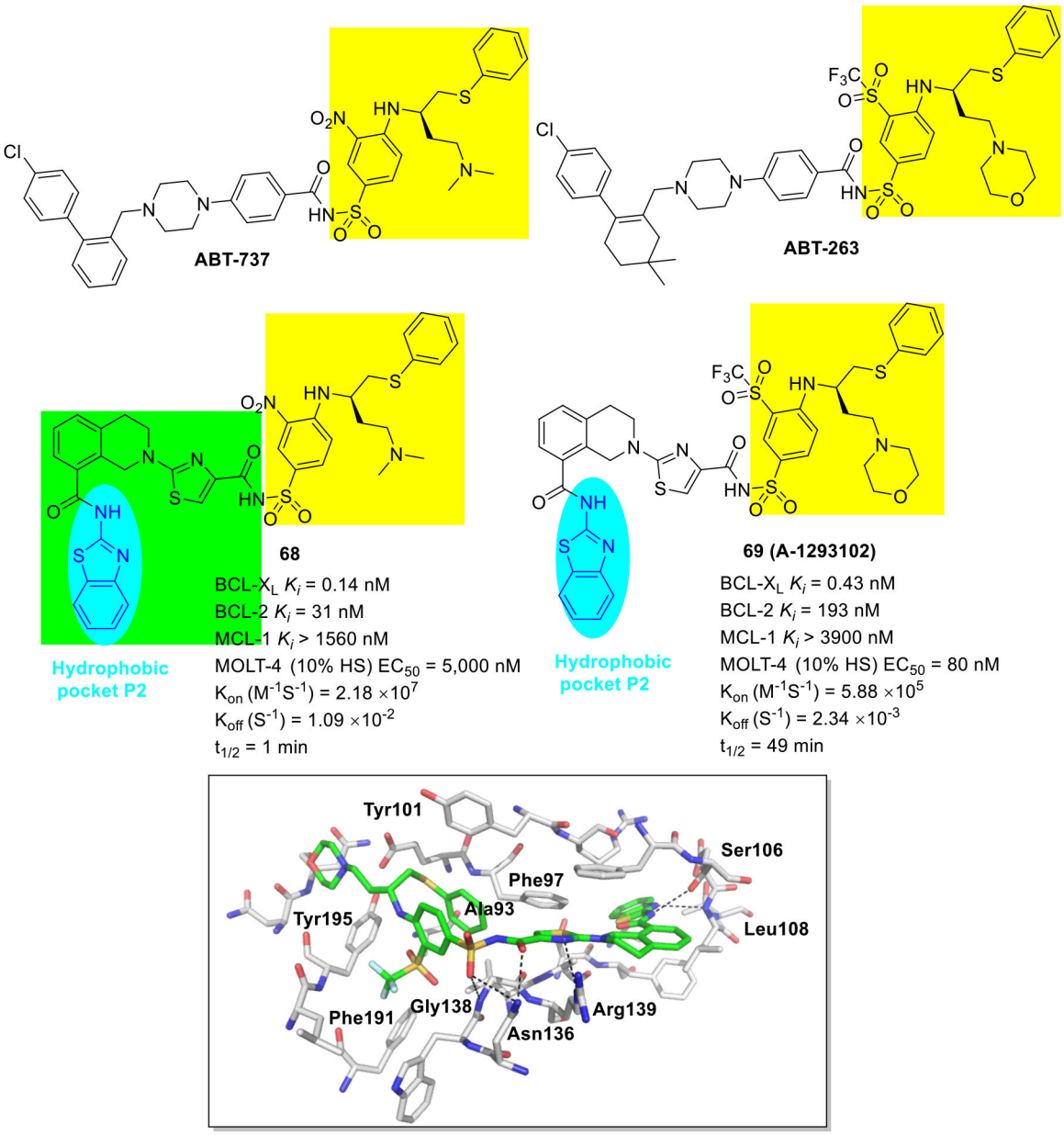


Fig. 17.

Chemical structures of 2-aminobenzothiazole derivatives **68** and **69** as BCL-X_L inhibitors. X-ray crystal structure of **69** bound to BCL-XL (PDB code 7LH7).

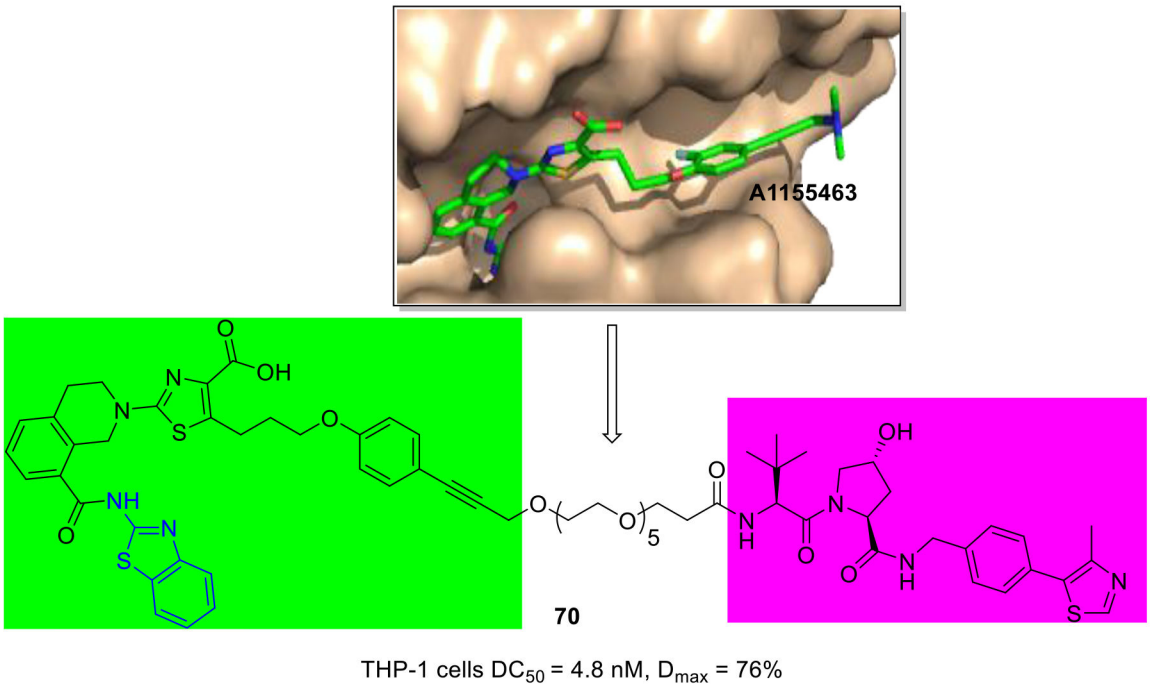


Fig. 18.

Chemical structure of BCL-X_L degrader **70**. X-ray crystal structure of **64** (A1155463) bound to BCL-XL (PDB code 4QVX).

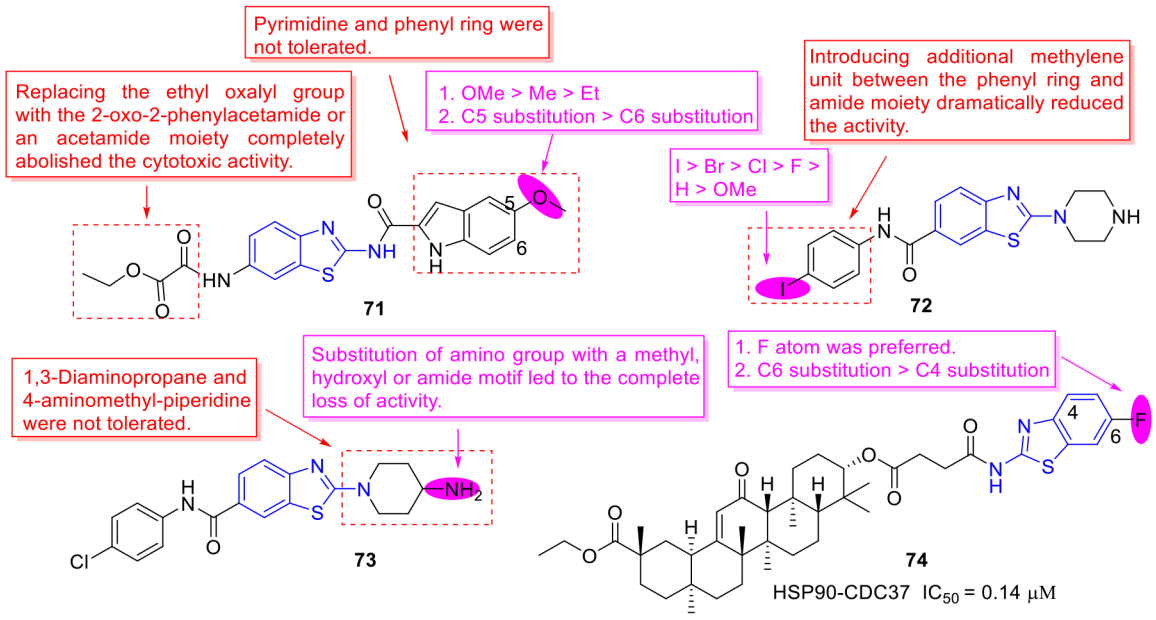


Fig. 19.

Chemicals structures of 2-aminobenzothiazole derivatives **71**–**73** as HSP90 C-terminal inhibitors and analogue **74** as a HSP90-CDC37 inhibitor.

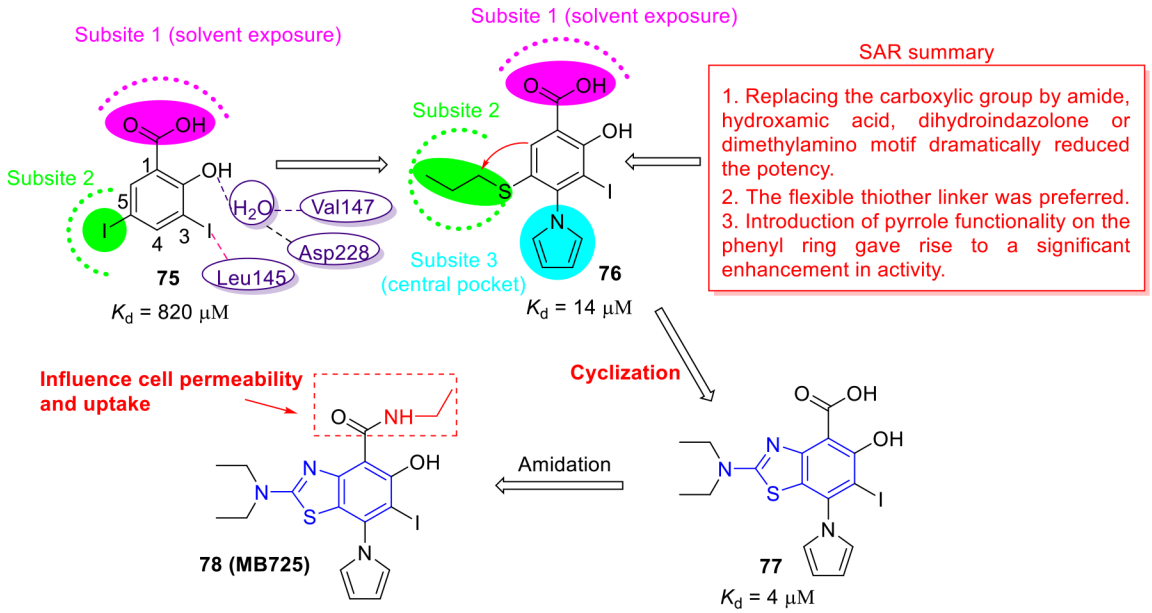


Fig. 20.

Discovery of 2-aminobenzothiazole **78** (MB725) as a mutant p53 reactivator.

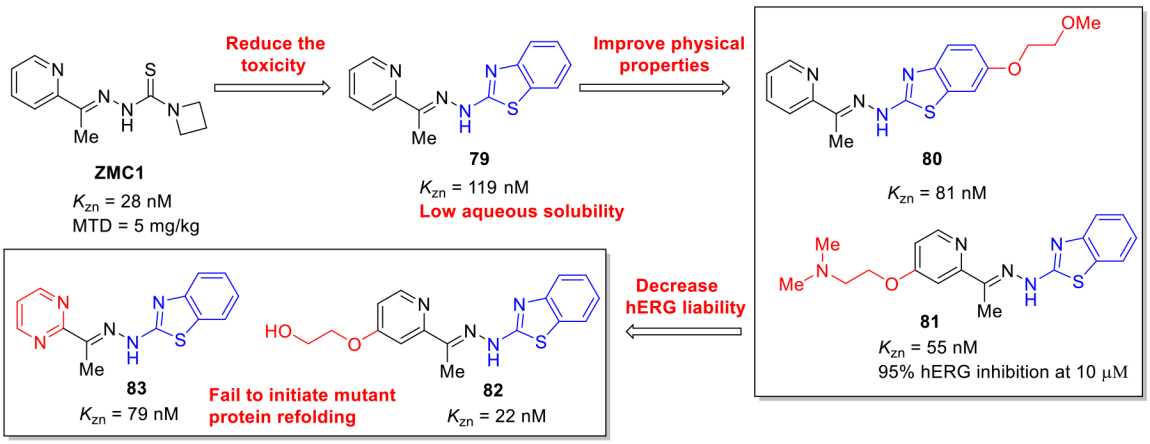


Fig. 21.

Development of 2-aminobenzothiazole derivatives as mutant p53 reactivators.

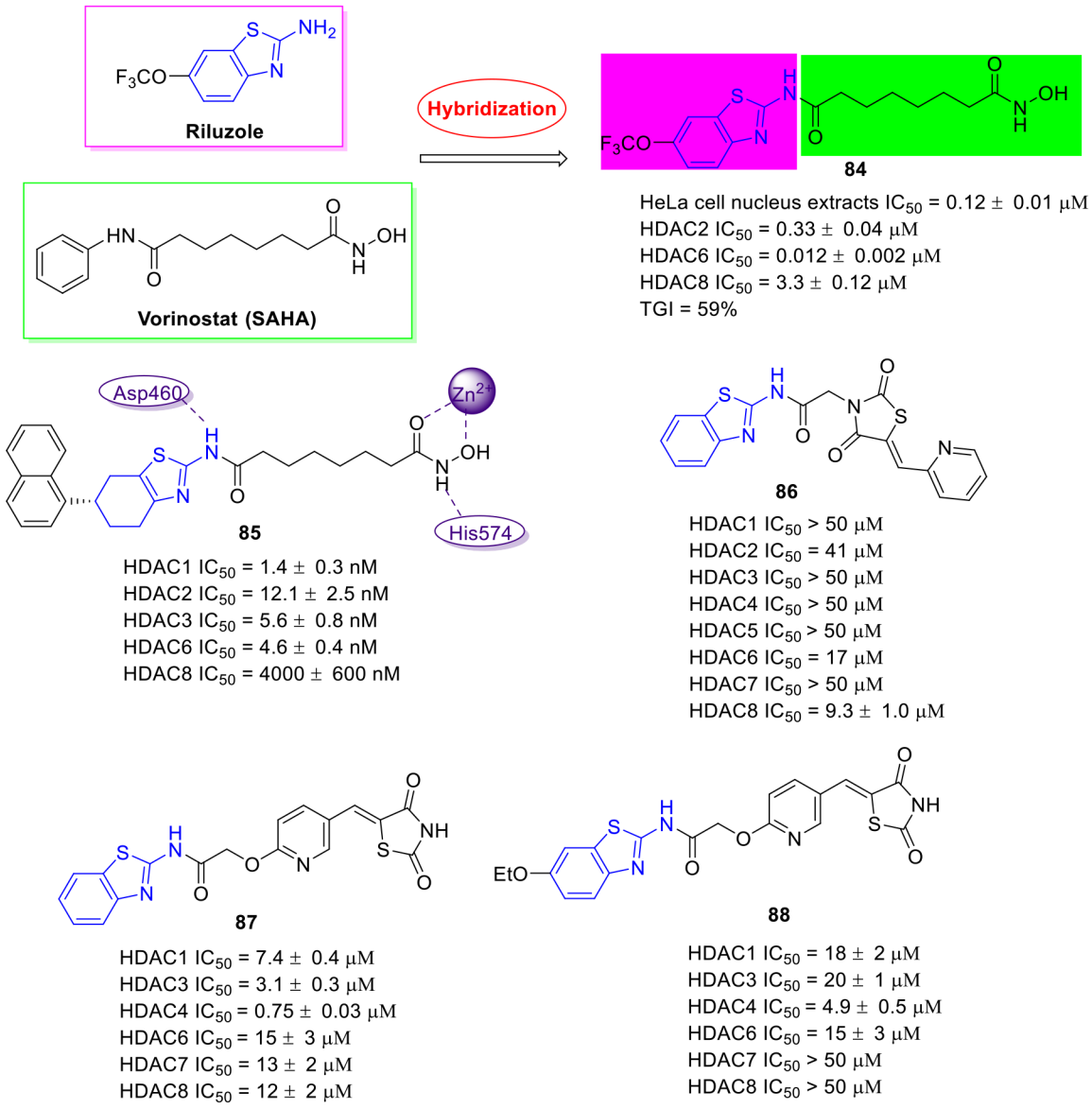


Fig. 22.

Chemical structures of 2-aminobenzothiazole derivatives **84**–**88** as HDAC inhibitors.

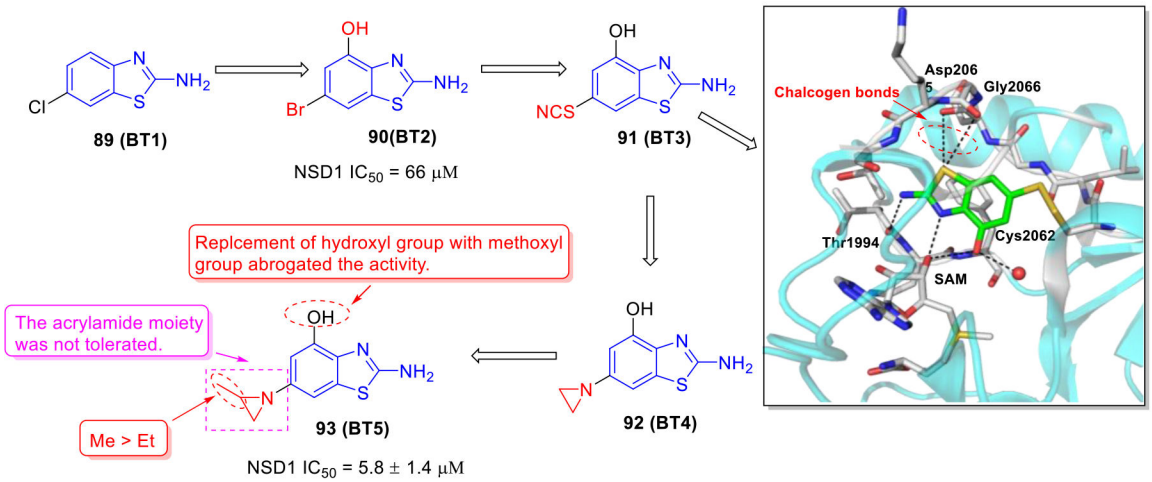


Fig. 23.

Discovery of 2-aminobenzothiazole **93** (BT5) as a first-in-class NSD1 inhibitor. X-ray crystal structure of **91** (BT3) bound to NSD1 SET domain (PDB code 6KQQ).

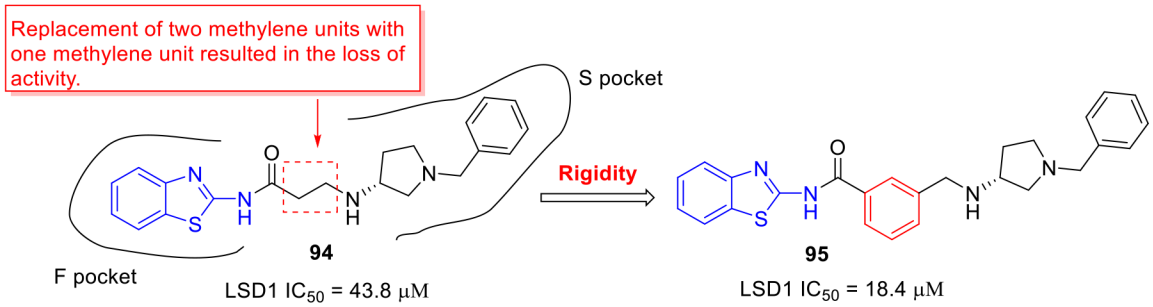


Fig. 24.

Identification of 2-aminobenzothiazole derivative **95** as an LSD1 inhibitor.

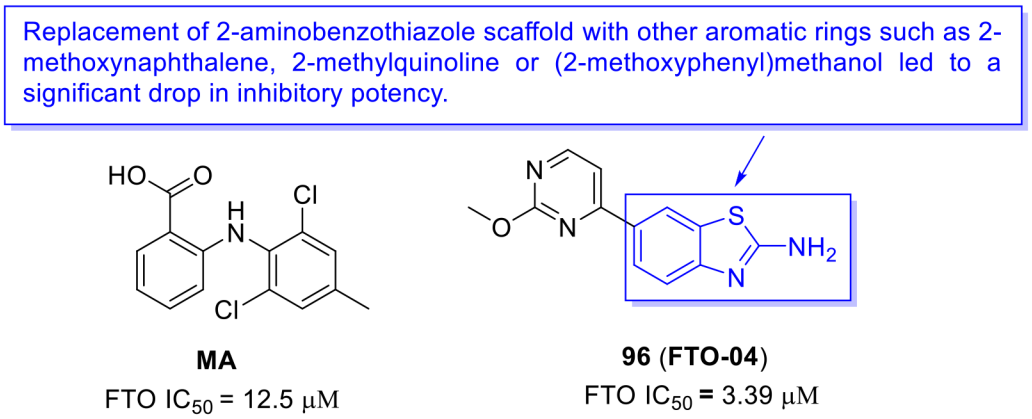


Fig. 25.

Chemical structures of MA and 2-aminobenzothiazole-based FTO inhibitor **96** (FTO-04).

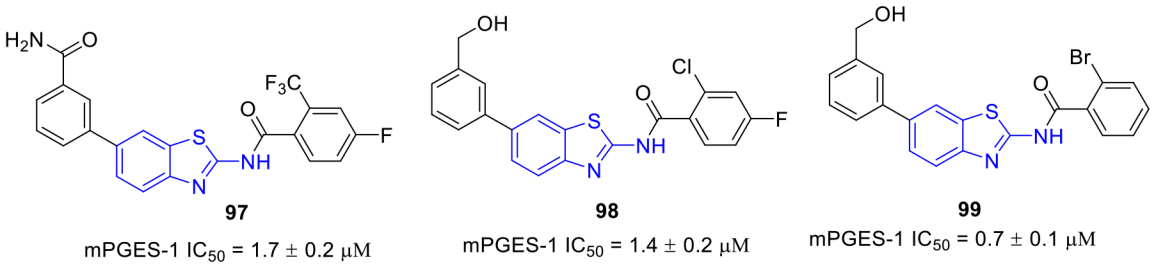


Fig. 26.

Chemical structures of 2-aminobenzothiazole derivatives **97**–**99** as mPGES-1 inhibitors.

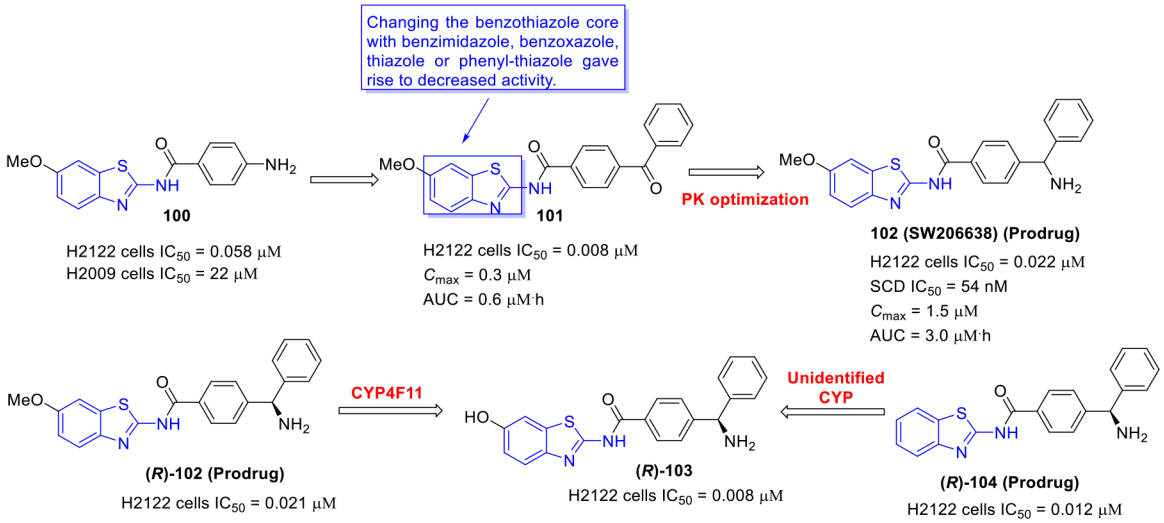


Fig. 27.

Chemical structures of 2-aminobenzothiazole derivatives **100**–**104** as SCD inhibitors.

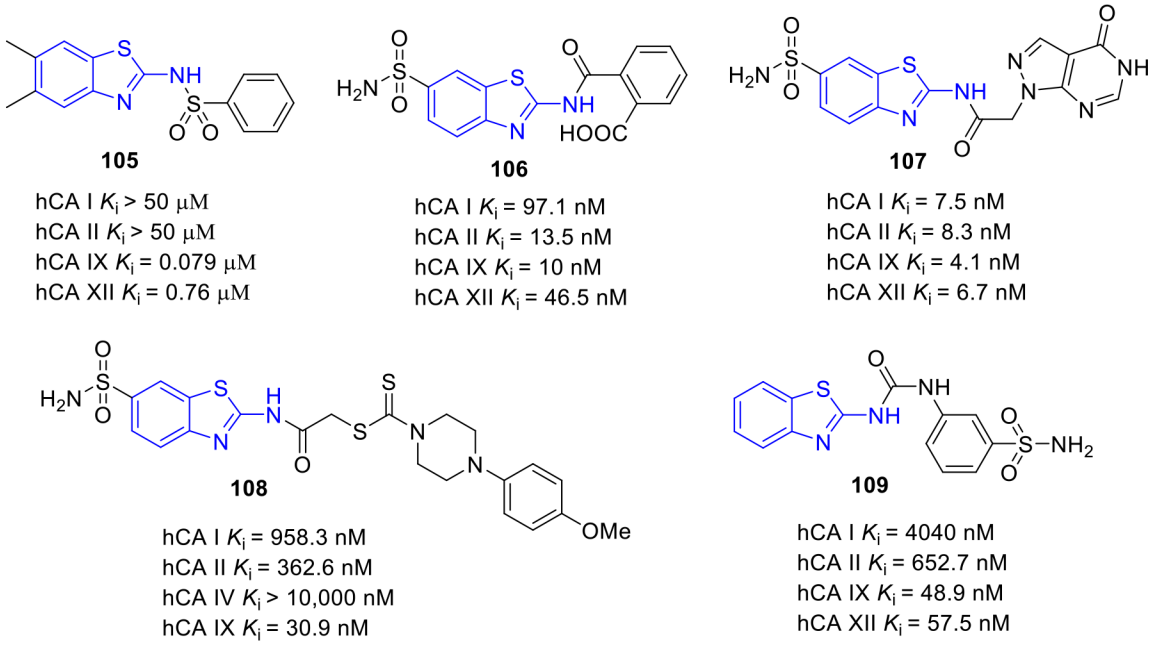


Fig. 28.

Chemical structures of 2-aminobenzothiazole derivatives **105-109** as hCA IX/XII inhibitors.

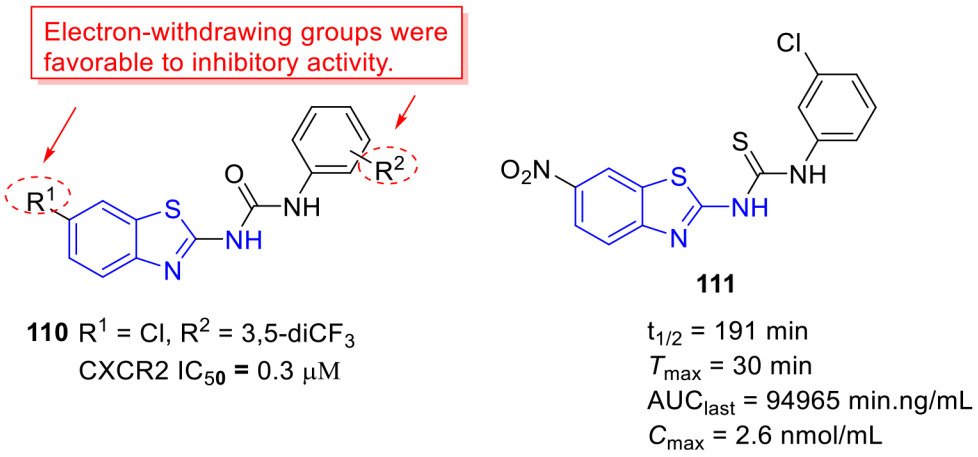


Fig. 29.

Chemical structures of 2-aminobenzothiazole derivatives **110** and **111** as CXCR inhibitors.

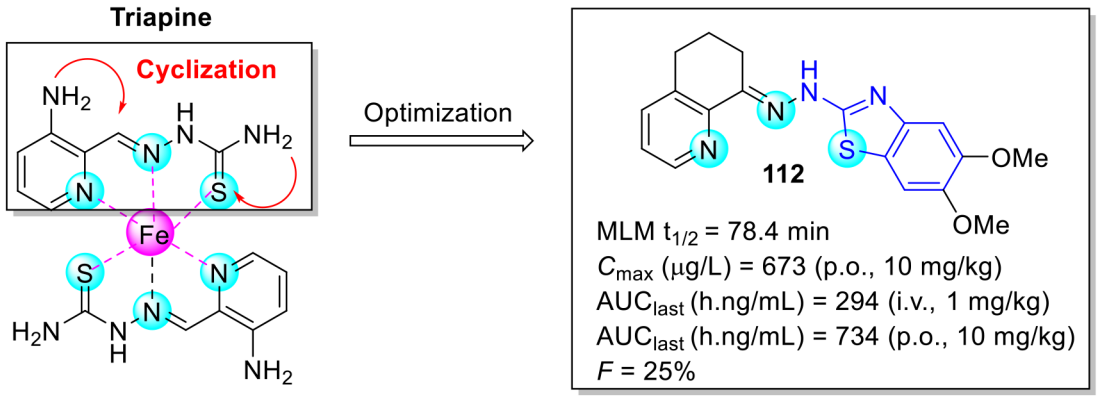


Fig. 30.

Lead optimization development of chelator **112** based on triapine.

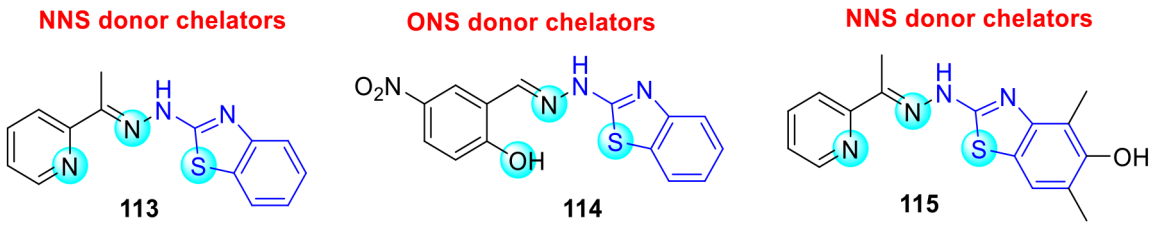


Fig. 31.
Exploration of 2-aminobenzothiazole-derived chelators for overcoming multidrug resistance.

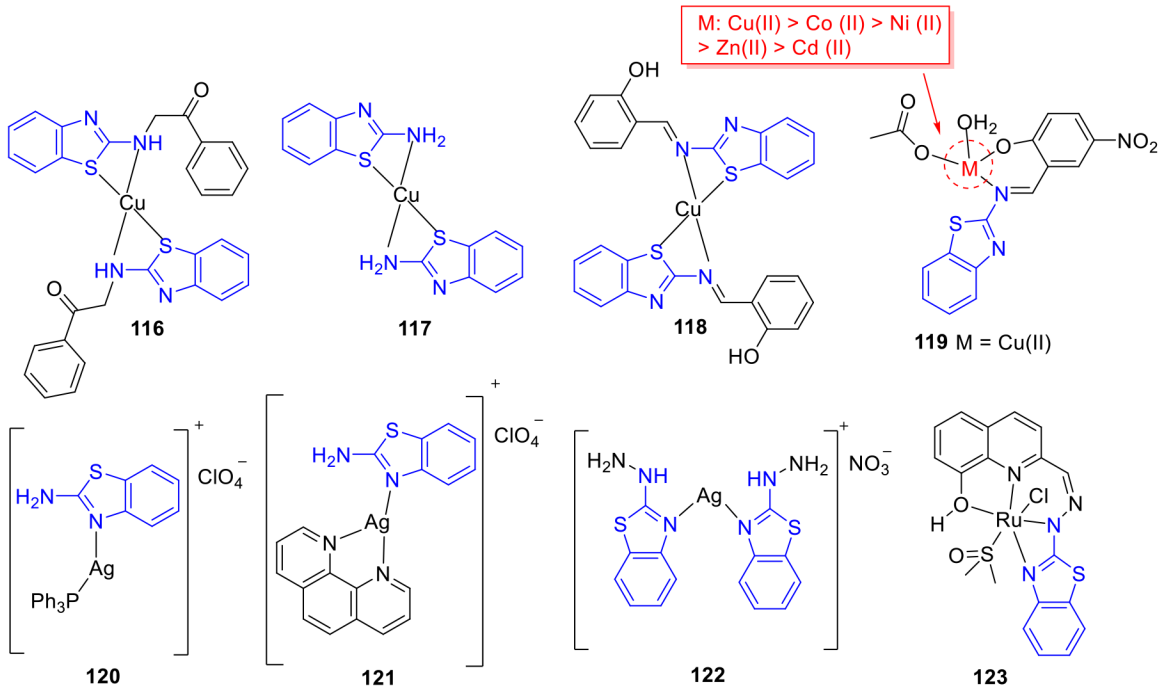


Fig. 32.
Chemical structures of metal-based complexes **116**–**123**.

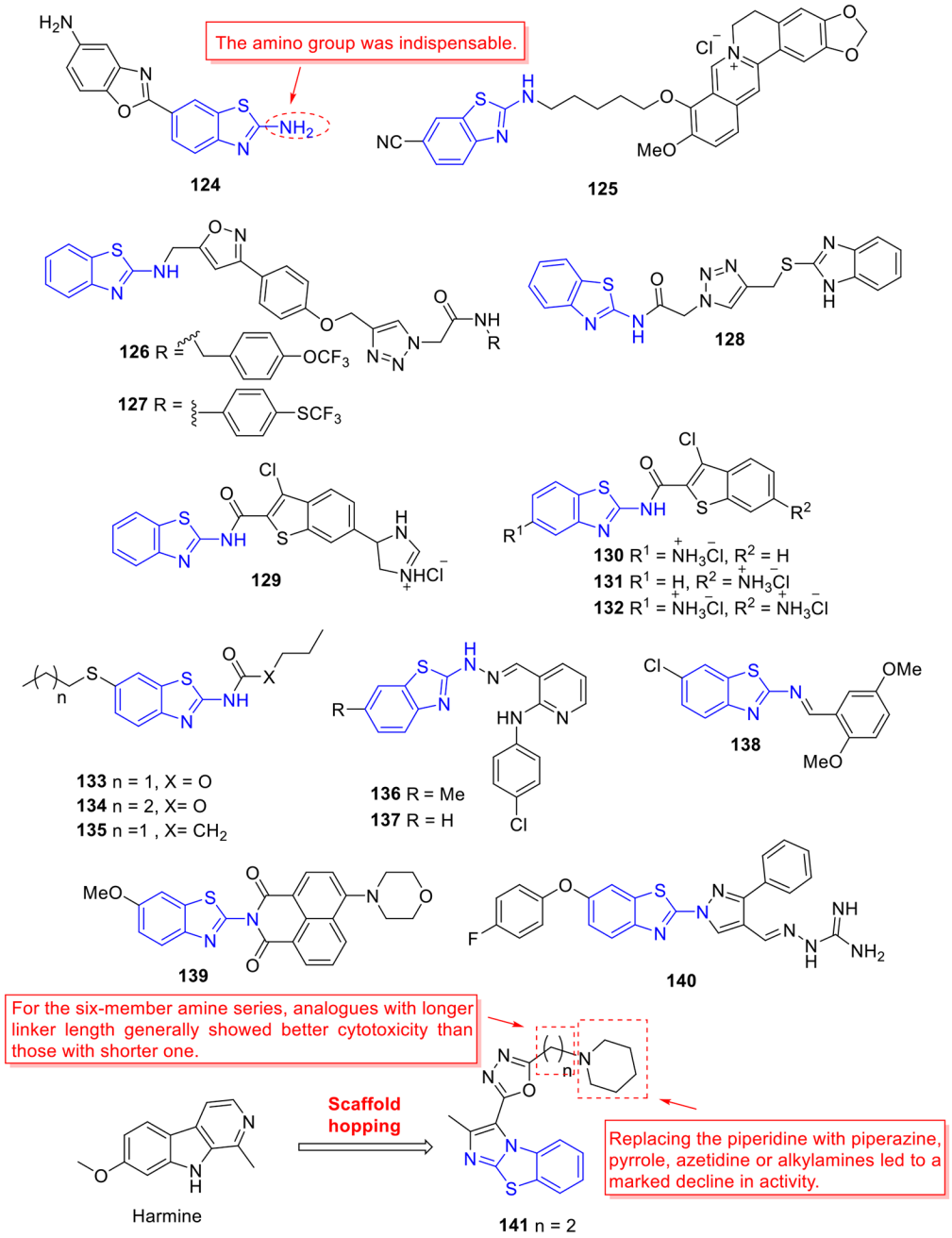
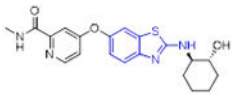
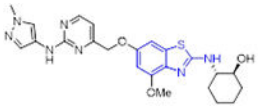
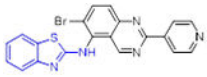
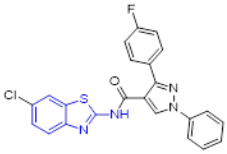
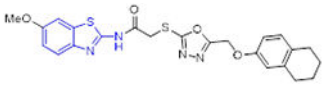
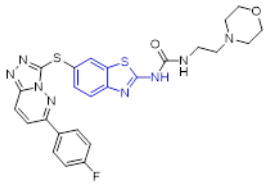
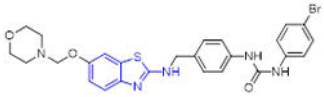
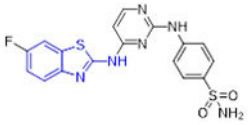
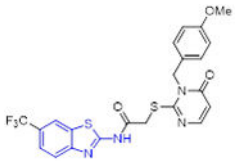


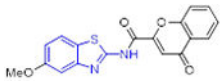
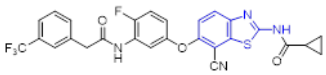
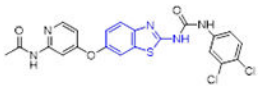
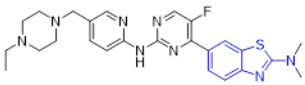
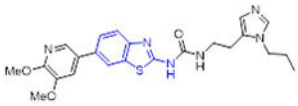
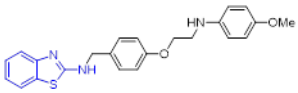
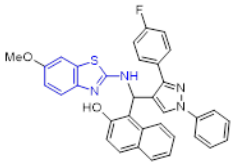
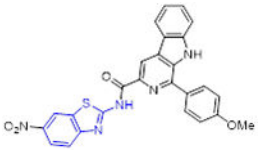
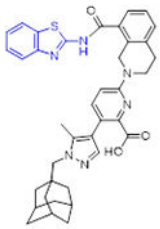
Fig. 33.

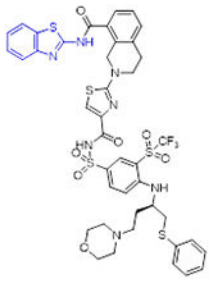
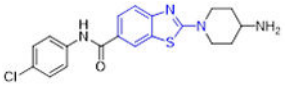
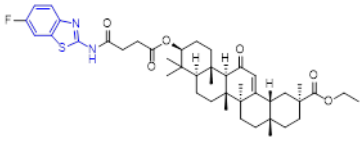
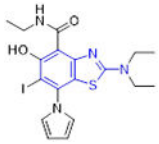
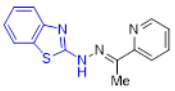
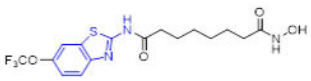
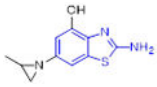
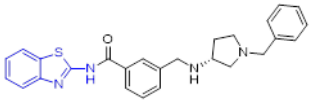
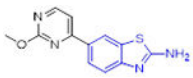
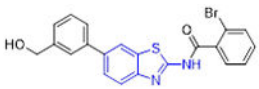
Chemical structures of 2-aminobenzothiazole derivatives **124**–**141**.

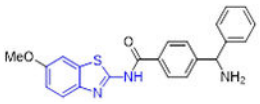
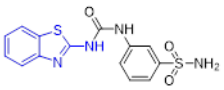
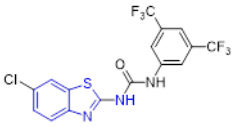
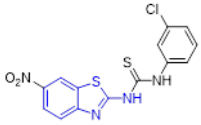
Table 1.

Representative 2-aminobenzothiazole derivatives and their molecular targets.

Compd.	Chemical structure	Target	Bioactivity	Reference
1 (BLZ945)		CSF1R	IC_{50} = 1.0 nM	[27]
8 (IACS-9439)		CSF1R	IC_{50} = 1.7 nM K_d = 1.0 nM	[29]
12		EGFR	IC_{50} = 96 nM	[33]
23		VEGFR-2	IC_{50} = 97 nM	[45]
24		FAK	IC_{50} = 19.5 μM	[48]
34 (SAR125844)		MET	IC_{50} = 4 nM	[55]
35		Aurora B	IC_{50} = 0.09 μM	[58]
39		CDK2	IC_{50} = 15.4 nM	[63]
44		CK1δ	IC_{50} = 0.09 μM	[69]

Compd.	Chemical structure	Target	Bioactivity	Reference
45		CK2	IC_{50} = 0.08 μM	[72]
46 (TAK632)		$BRAF^{V600E}$	IC_{50} = 2.4 nM	[78]
47		$BRAF^{V600E}$	IC_{50} = 0.095 μM	[79]
50 (YK-2-69)		DYRK2	IC_{50} = 9 nM K_d = 92 nM	[81]
52		PI3Kγ	IC_{50} = 2 nM	[87]
54		PI3Kα	IC_{50} = 1.03 nM	[90]
57		Topoisomerase I	-	[95]
63		Topoisomerase IIα	-	[97]
67 (A-1331852)		$BCL\text{-}X_L$	K_i < 0.01 nM	[103]

Compd.	Chemical structure	Target	Bioactivity	Reference
69 (A-1293102)		BCL-X_L	K_i = 0.43 nM	[104]
73		HSP90	-	[114]
74		HSP90-CDC37	IC_{50} = 0.14 μM	[115]
78 (MB725)		Mutant p53	-	[120]
79		Mutant p53	K_{Zn} = 119 nM	[121]
84		HDAC6	IC_{50} = 12 nM	[126]
93 (BT5)		NSD1	IC_{50} = 5.8 μM	[135]
95		LSD1	IC_{50} = 18.4 μM	[139]
96 (FTO-04)		FTO	IC_{50} = 3.39 μM	[144]
99		mPGES-1	IC_{50} = 0.7 μM	[145]

Compd.	Chemical structure	Target	Bioactivity	Reference
102		SCD	IC_{50} = 54 nM	[150]
109		hCA IX/XII	K_i = 48.9/57.5 nM	[159]
110		CXCR2	IC_{50} = 0.3 μM	[163]
111		CXCR1/2	-	[164]