

METHODS OF USING RAD51 INHIBITORS FOR TREATMENT OF PANCREATIC CANCER

RELATED APPLICATIONS

This application claims priority to, and the benefit of, U.S. Provisional Application Nos. 62/864,861, filed on June 21, 2019, and 62/895,138, filed on September 3, 2019, the contents of each of which are incorporated herein in their entirety.

BACKGROUND

RAD51 is a eukaryote gene. The protein encoded by this gene is a member of the RAD51 protein family which assists in repair of DNA double strand breaks. RAD51 family members are homologous to the bacterial RecA, Archaeal RadA and yeast RAD51. The protein is highly conserved in most eukaryotes, from yeast to humans. In humans, RAD51 is a 339-amino acid protein that plays a major role in homologous recombination of DNA during double strand break (DSB) repair. RAD51 catalyzes strand transfer between a broken sequence and its undamaged homologue to allow re-synthesis of the damaged region (see homologous recombination models).

Studies have demonstrated a sensitization to certain DNA damaging therapies associated with cellular defects in proteins that promote HR DNA repair. This sensitization is particularly dramatic for DNA cross-linking chemotherapeutic drugs (30-100 times) and ionizing radiation (3-5 times) (Godthelp et al., "Mammalian Rad51C contributes to DNA cross-link resistance, sister chromatid cohesion and genomic stability," *Nucleic Acids Res.*, 30:2172-2182, 2002; Tebbs et al., "Correction of chromosomal instability and sensitivity to diverse mutagens by a cloned cDNA of the XRCC3 DNA repair gene," *Proc. Natl. Acad. Sci. USA*, 92:6354-6358, 1995; Takata et al., "Chromosome instability and defective recombinational repair in knockout mutants of the five Rad51 paralogs," *Mol. Cell Biol.*, 21:2858-2866, 2001; Liu et al., "XRCC2 and XRCC3, new human Rad51-family members, promote chromosome stability and protect against DNA cross-links and other damages," *Mol. Cell*, 1:783-793, 1998).

Several groups have recently demonstrated that HR can be partially inhibited in order to sensitize cells to DNA damaging therapies. Inhibition of XRCC3 (a RAD51 paralog protein), has been demonstrated using a synthetic peptide corresponding to another paralog protein. This peptide sensitized Chinese Hamster Ovary (CHO) cells to cisplatin and inhibited the formation of sub-nuclear RAD51 foci in response to DNA damage (Connell et

al., Cancer Res., 64:3002-3005, 2004). Other researchers have inhibited the expression of the RAD51 protein itself (Russell et al., Cancer Res., 63:7377-7383, 2003; Hansen et al., Int. J. Cancer, 105:472-479, 2003; Ohnishi et al., Biochem. Biophys. Res. Commun., 245:319-324, 1998; Ito et al., J. Gene Med., 7(8):1044-1052, 2005; Collins et al., Nucleic Acids Res., 29:1534-1538, 2001) or blocked its function by over-expressing a dominant negative BRC peptide fragment derived from BRCA2 (Chen et al., J. Biol. Chem., 274:32931-32935, 1999). In view of the connection between increased sensitivity to certain DNA damaging therapies and cellular defects in HR DNA repair-related proteins, there is a need for additional compounds that inhibit RAD51.

While AID expression is normally transient and restricted to activated B-cells, several cancers show constitutive, ectopic AID expression including pancreatic cancer. AID is a promiscuous DNA damaging enzyme that targets widespread locations throughout the genome, leading to high levels of DNA replication stress. AID expressing cells become critically dependent on the homologous recombination factor RAD51 to survive this DNA replication stress.

SUMMARY

In one aspect, the present disclosure provides a method of treating pancreatic cancer, the method comprising administering a therapeutically effective dose of a composition of the present disclosure, *e.g.*, a composition comprising a RAD51 inhibitor of the present disclosure, to a subject in need thereof.

In one aspect, the present disclosure provides a method of treating pancreatic cancer, the method comprising administering a therapeutically effective dose of a RAD51 inhibitor of the present disclosure, to a subject in need thereof.

In one aspect, the present disclosure provides a method of treating pancreatic cancer, the method comprising administering a therapeutically effective dose of Compound 67A or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

In one aspect, the present disclosure provides a composition (*e.g.*, a composition comprising a RAD51 inhibitor of the present disclosure) for use in treating pancreatic cancer in a subject in need thereof.

In one aspect, the present disclosure provides a RAD51 inhibitor of the present disclosure for use in treating pancreatic cancer in a subject in need thereof.

In one aspect, the present disclosure provides Compound 67A or a pharmaceutically acceptable salt thereof for use in treating pancreatic cancer in a subject in need thereof.

In one aspect, described herein is a use of a composition (*e.g.*, a composition comprising a RAD51 inhibitor of the present disclosure) in the manufacture of a medicament for the treatment of pancreatic cancer in a subject in need thereof.

In one aspect, described herein is a use of a RAD51 inhibitor of the present disclosure in the manufacture of a medicament for the treatment of pancreatic cancer in a subject in need thereof.

In one aspect, described herein is a use of Compound 67A or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of pancreatic cancer in a subject in need thereof.

Although Applicant does not wish to be bound by any mechanism, it is believed that the compounds of the present disclosure inhibit RAD51 by binding to MDC1 and causing reduced ability to form active complexes of RAD51.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG 1 shows the method for three pancreatic PDX models treated with vehicle or Compound 67A at 80 mg/kg QD or 1 and 40 mg/kg QD.

FIGs 2A-2B show Model 1, Model 2, and Model 3 re-randomized treatments with vehicle and Compound 67A at 1 mg/kg split into three groups (*i.e.* vehicle, 1 mg/kg, and 80 mg/kg; FIG. 2A); and re-randomized treatments with Compound 67A at 40 mg/kg and 80 mg/kg treatment arms split into three groups (*i.e.* 80 mg/kg, 14 day dosing holiday followed by 80 mg/kg, 21 day dosing holiday followed by 80 mg/kg; FIG. 2B).

FIGs 3A-3B show Compound 67A anti-tumor activity measured by tumor volumes (FIG. 3A) and percent tumor growth inhibition (FIG. 3B) in Model 1.

FIGs 4A-4B show Compound 67A anti-tumor activity measured by tumor volumes (FIG. 4A) and percent tumor growth inhibition (FIG. 4B) in Model 2.

FIGs 5A-5B show Compound 67A anti-tumor activity measured by tumor volumes (FIG. 5A) and percent tumor growth inhibition (FIG. 5B) in Model 3.

FIGs 6A-6C show Compound 67A anti-tumor activity measured by tumor volumes (FIG. 6A), change in tumor volume at day 49 as compared to day 0 (FIG. 6B), and progression free survival (FIG. 6C) in Model 2.

FIGs 7A-7C show Compound 67A anti-tumor activity measured by tumor volumes with

Compound 67A at 80 mg/kg continuously (FIG. 7A), after a 14 day dosing holiday (FIG. 7B), and after a 21 day dosing holiday (FIG. 7C) in Model 2.

FIG 8A shows Compound 67A anti-tumor activity measured by tumor volumes in PDX mouse Model A after administration of Compound 67A at 80 mg/kg once daily or once every other day.

FIG 8B shows Compound 67A anti-tumor activity measured by tumor volumes in PDX mouse Model A after administration of Compound 67A at 80 mg/kg based on tumor volume at the start of administration.

FIG 9A shows Compound 67A anti-tumor activity measured by tumor volumes in PDX mouse Model B after administration of Compound 67A at 80 mg/kg once daily or once every other day.

FIG 9B shows Compound 67A anti-tumor activity measured by tumor volumes in PDX mouse Model B after administration of Compound 67A at 80 mg/kg based on tumor volume at the start of administration.

FIGs 9C-9D show Compound 67A anti-tumor activity measured by tumor volumes in PDX mouse Model B after administration of Compound 67A at 80 mg/kg based on dosing holiday (FIG. 9C) and tumor growth during and post dosing holiday (FIG. 9D).

FIG 10A shows Compound 67A anti-tumor activity measured by tumor volumes in PDX mouse Model C after administration of Compound 67A at 80 mg/kg once daily or once every other day.

FIG 10B shows Compound 67A anti-tumor activity measured by tumor volumes in PDX mouse Model C after administration of Compound 67A at 80 mg/kg based on tumor volume at the start of administration.

FIGs 10C-10D show Compound 67A anti-tumor activity measured by tumor volumes in PDX mouse Model C after administration of Compound 67A at 80 mg/kg based on dosing holiday (FIG. 9C) and tumor growth during and post dosing holiday (FIG. 9D).

DETAILED DESCRIPTION

Applicant has developed compounds which are effective inhibitors of RAD51 (see Examples 1–75) for use in treating pancreatic cancer. The RAD51 inhibitors of the present disclosure inhibit homologous recombination by altering the nucleocytoplasmic distribution of RAD51 following DNA damage induction. The RAD51 inhibitors of the present disclosure reduce the repair of AID-induced DNA double strand breaks, leading to AID-

dependent cytotoxicity in both normal and malignant cells. Some of these RAD51 inhibitors have superior cell permeability as measured in Caco-2 cells (see Example 76). Among the RAD51 inhibitors with good cell permeability, several have superior metabolic stability (as measured by a liver microsome assay, see Example 77) and exposure, including oral exposure (see Example 79).

In some embodiments, the present disclosure provides a method of treating a subject with a disease which can be ameliorated by inhibition of RAD51, by administering to the subject an effective amount of one or more disclosed compounds, or a pharmaceutically acceptable salt thereof, or the corresponding pharmaceutical composition. Diseases which can be ameliorated by inhibition of RAD51 include treating cancer, autoimmune disease, immune deficiency, or neurodegenerative disease.

In some embodiments, described herein is a method of treating pancreatic cancer, the method comprising administering a therapeutically effective dose of a composition of the present disclosure, *e.g.*, a composition comprising a RAD51 inhibitor of the present disclosure, to a subject in need thereof.

In some embodiments, described herein is a method of treating pancreatic cancer, the method comprising administering a therapeutically effective dose of a RAD51 inhibitor of the present disclosure, to a subject in need thereof.

In some embodiments, described herein is a method of treating pancreatic cancer, the method comprising administering a therapeutically effective dose of Compound 67A or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

In some embodiments, described herein is a composition (*e.g.*, a composition comprising a RAD51 inhibitor of the present disclosure) for use in treating pancreatic cancer in a subject in need thereof.

In some embodiments, described herein is a RAD51 inhibitor of the present disclosure for use in treating pancreatic cancer in a subject in need thereof.

In some embodiments, described herein is Compound 67A or a pharmaceutically acceptable salt thereof for use in treating pancreatic cancer in a subject in need thereof.

In some embodiments, described herein is a use of a composition (*e.g.*, a composition comprising a RAD51 inhibitor of the present disclosure) for the treatment of pancreatic cancer in a subject in need thereof.

In some embodiments, described herein is a use of a RAD51 inhibitor of the present disclosure for the treatment of pancreatic cancer in a subject in need thereof.

In some embodiments, described herein is a use of Compound 67A or a pharmaceutically acceptable salt thereof for the treatment of pancreatic cancer in a subject in need thereof.

In some embodiments, described herein is a use of a composition (*e.g.*, a composition comprising a RAD51 inhibitor of the present disclosure) in the manufacture of a medicament for the treatment of pancreatic cancer in a subject in need thereof.

In some embodiments, described herein is a use of a RAD51 inhibitor of the present disclosure in the manufacture of a medicament for the treatment of pancreatic cancer in a subject in need thereof.

In some embodiments, described herein is a use of Compound 67A or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of pancreatic cancer in a subject in need thereof.

In some embodiments, the subject is a mammal.

In some embodiments, the subject is a human.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 1 mg/m² to about 500 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 2 mg/m² to about 500 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 3 mg/m² to about 500 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 1 mg/m² to about 400 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 2 mg/m² to about 400 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 3 mg/m² to about 400 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 1 mg/m² to about 300 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 2 mg/m² to about 300 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 3 mg/m² to about 300 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 1 mg/m² to about 280 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 1 mg/m² to about 260 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 1 mg/m² to about 240 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 1 mg/m² to about 220 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 1 mg/m² to about 200 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 1 mg/m² to about 180 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 1 mg/m² to about 160 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 1 mg/m² to about 140 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 1 mg/m² to about 120 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 1 mg/m² to about 100 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 2 mg/m² to about 280 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 2 mg/m² to about 260 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 2 mg/m² to about 240 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 2 mg/m² to about 220 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 2 mg/m² to about 200 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 2 mg/m² to about 180 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 2 mg/m² to about 160 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 2 mg/m² to about 140 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 2 mg/m² to about 120 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 2 mg/m² to about 100 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 3 mg/m² to about 280 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 3 mg/m² to about 260 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 3 mg/m² to about 240 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 3 mg/m² to about 220 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 3 mg/m² to about 200 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 3 mg/m² to about 180 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 3 mg/m² to about 160 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 3 mg/m² to about 140 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 3 mg/m² to about 120 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 3 mg/m² to about 100 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/m² to about 500 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/m² to about 500 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/m² to about 500 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/m² to about 500 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/m² to about 500 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/m² to about 500 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 120 mg/m² to about 500 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 140 mg/m² to about 500 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 160 mg/m² to about 500 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 180 mg/m² to about 500 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 200 mg/m² to about 500 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 220 mg/m² to about 500 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 240 mg/m² to about 500 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 260 mg/m² to about 500 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 280 mg/m² to about 500 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/m² to about 400 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/m² to about 400 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/m² to about 400 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/m² to about 400 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/m² to about 400 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/m² to about 400 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 120 mg/m² to about 400 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 140 mg/m² to about 400 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 160 mg/m² to about 400 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 180 mg/m² to about 400 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 200 mg/m² to about 400 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 220 mg/m² to about 400 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 240 mg/m² to about 400 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 260 mg/m² to about 400 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 280 mg/m² to about 400 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/m² to about 300 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/m² to about 300 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/m² to about 300 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/m² to about 300 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/m² to about 300 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/m² to about 300 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 120 mg/m² to about 300 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 140 mg/m² to about 300 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 160 mg/m² to about 300 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 180 mg/m² to about 300 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 200 mg/m² to about 300 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 220 mg/m² to about 300 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 240 mg/m² to about 300 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 260 mg/m² to about 300 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 280 mg/m² to about 300 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/m² to about 280 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/m² to about 260 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/m² to about 240 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/m² to about 220 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/m² to about 200 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/m² to about 180 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/m² to about 160 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/m² to about 140 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/m² to about 280 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/m² to about 260 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/m² to about 240 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/m² to about 220 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/m² to about 200 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/m² to about 180 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/m² to about 160 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/m² to about 140 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/m² to about 280 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/m² to about 260 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/m² to about 240 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/m² to about 220 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/m² to about 200 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/m² to about 180 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/m² to about 160 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/m² to about 140 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/m² to about 280 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/m² to about 260 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/m² to about 240 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/m² to about 220 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/m² to about 200 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/m² to about 180 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/m² to about 160 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/m² to about 140 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/m² to about 280 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/m² to about 260 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/m² to about 240 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/m² to about 220 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/m² to about 200 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/m² to about 180 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/m² to about 160 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/m² to about 140 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/m² to about 280 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/m² to about 260 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/m² to about 240 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/m² to about 220 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/m² to about 200 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/m² to about 180 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/m² to about 160 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/m² to about 140 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/m² to about 240 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/m² to about 240 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/m² to about 240 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/m² to about 240 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/m² to about 240 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/m² to about 240 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 120 mg/m² to about 240 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) of about 1 mg/m², about 2 mg/m², about 3 mg/m², about 4 mg/m², about 5 mg/m², about 10 mg/m², about 20 mg/m², about 30 mg/m², about 40 mg/m², about 50 mg/m², about 60 mg/m², about 70 mg/m², about 80 mg/m², about 90 mg/m², about 100 mg/m², about 120 mg/m², about 140 mg/m², about 160 mg/m², about 180 mg/m², about 200 mg/m², about 220 mg/m², about 240 mg/m², about 260 mg/m², about 280 mg/m², about 300 mg/m², about 320 mg/m², about 340 mg/m², about 360 mg/m², about 380 mg/m², about 400 mg/m², about 420 mg/m², about 440 mg/m², about 460 mg/m², about 480 mg/m², or about 500 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) of about 1 mg/m², about 2 mg/m², about 3 mg/m², about 4 mg/m², about 5 mg/m², about 10 mg/m², about 20 mg/m², about 30 mg/m², about 40 mg/m², about 50 mg/m², about 60 mg/m², about 70 mg/m², about 80 mg/m², about 90 mg/m², about 100 mg/m², about 120 mg/m², about 140 mg/m², about 160 mg/m², about 180 mg/m², about 200 mg/m², about 220 mg/m², about 240 mg/m², about 260 mg/m², about 280 mg/m², or about 300 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) of about 3±2 mg/m², 3±1.8 mg/m², 3±1.6 mg/m², 3±1.5 mg/m², 3±1.4 mg/m², 3±1.3 mg/m², 3±1.2 mg/m², 3±1.1 mg/m², 3±1 mg/m², 3±0.9 mg/m², 3±0.8 mg/m², 3±0.7 mg/m², 3±0.6 mg/m², 3±0.5 mg/m², 3±0.4 mg/m², 3±0.3 mg/m², 3±0.2 mg/m², or 3±0.1 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) of about 3 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) of about 50±45 mg/m², 50±40 mg/m², 50±35 mg/m², 50±30 mg/m², 50±25 mg/m², 50±20 mg/m², 50±15 mg/m², 50±10 mg/m², 50±9 mg/m², 50±8 mg/m², 50±7 mg/m², 50±6 mg/m², 50±5 mg/m², 50±4 mg/m², 50±3 mg/m², 50±2 mg/m², or 50±1 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) of about 50 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) of about 120±100 mg/m², 120±90 mg/m², 120±80 mg/m², 120±70 mg/m², 120±60 mg/m², 120±50 mg/m², 120±45 mg/m², 120±40 mg/m², 120±35 mg/m², 120±30 mg/m²,

120±25 mg/m², 120±20 mg/m², 120±15 mg/m², 120±10 mg/m², 120±9 mg/m², 120±8 mg/m², 120±7 mg/m², 120±6 mg/m², 120±5 mg/m², 120±4 mg/m², 120±3 mg/m², 120±2 mg/m², or 120±1 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) of about 120 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) of about 240±100 mg/m², 240±90 mg/m², 240±80 mg/m², 240±70 mg/m², 240±60 mg/m², 240±50 mg/m², 240±45 mg/m², 240±40 mg/m², 240±35 mg/m², 240±30 mg/m², 240±25 mg/m², 240±20 mg/m², 240±15 mg/m², 240±10 mg/m², 240±9 mg/m², 240±8 mg/m², 240±7 mg/m², 240±6 mg/m², 240±5 mg/m², 240±4 mg/m², 240±3 mg/m², 240±2 mg/m², or 240±1 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) of about 240 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) of about 300±100 mg/m², 300±90 mg/m², 300±80 mg/m², 300±70 mg/m², 300±60 mg/m², 300±50 mg/m², 300±45 mg/m², 300±40 mg/m², 300±35 mg/m², 300±30 mg/m², 300±25 mg/m², 300±20 mg/m², 300±15 mg/m², 300±10 mg/m², 300±9 mg/m², 300±8 mg/m², 300±7 mg/m², 300±6 mg/m², 300±5 mg/m², 300±4 mg/m², 300±3 mg/m², 300±2 mg/m², or 300±1 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) of about 300 mg/m².

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/day to about 500 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/day to about 500 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/day to about 500 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/day to about 500 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/day to about 500 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/day to about 500 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 150 mg/day to about 500 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 200 mg/day to about 500 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 250 mg/day to about 500 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 300 mg/day to about 500 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 350 mg/day to about 500 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 400 mg/day to about 500 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 450 mg/day to about 500 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/day to about 450 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/day to about 450 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/day to about 450 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/day to about 450 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/day to about 450 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/day to about 450 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 150 mg/day to about 450 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 200 mg/day to about 450 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 250 mg/day to about 450 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 300 mg/day to about 450 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 350 mg/day to about 450 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 400 mg/day to about 450 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/day to about 400 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/day to about 400 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/day to about 400 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/day to about 400 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/day to about 400 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/day to about 400 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 150 mg/day to about 400 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 200 mg/day to about 400 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 250 mg/day to about 400 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 300 mg/day to about 400 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 350 mg/day to about 400 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/day to about 350 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/day to about 350 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/day to about 350 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/day to about 350 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/day to about 350 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/day to about 350 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 150 mg/day to about 350 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 200 mg/day to about 350 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 250 mg/day to about 350 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 300 mg/day to about 350 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/day to about 300 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/day to about 300 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/day to about 300 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/day to about 300 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/day to about 300 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/day to about 300 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 150 mg/day to about 300 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 200 mg/day to about 300 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 250 mg/day to about 300 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/day to about 250 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/day to about 250 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/day to about 250 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/day to about 250 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/day to about 250 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/day to about 250 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 150 mg/day to about 250 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 200 mg/day to about 250 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/day to about 200 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/day to about 200 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/day to about 200 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/day to about 200 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/day to about 200 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/day to about 200 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 150 mg/day to about 200 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/day to about 150 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/day to about 150 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/day to about 150 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/day to about 150 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/day to about 150 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/day to about 150 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/day to about 100 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/day to about 100 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/day to about 100 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/day to about 100 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/day to about 100 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/day to about 90 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/day to about 90 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/day to about 90 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/day to about 90 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/day to about 80 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/day to about 80 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/day to about 80 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/day to about 70 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/day to about 70 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/day to about 60 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 50 mg/day, about 60 mg/day, about 70 mg/day, about 80 mg/day, about 90 mg/day, about 100 mg/day, about 110 mg/day, about 120 mg/day, about 130 mg/day, about 140 mg/day, about 150 mg/day, about 160 mg/day, about 170 mg/day, about 180 mg/day, about 190 mg/day, about 200 mg/day, about 210 mg/day, about 220 mg/day, about 230 mg/day, about 240 mg/day, about 250 mg/day, about 260 mg/day, about 270 mg/day, about 280 mg/day, about 290 mg/day, about 300 mg/day, about 310 mg/day, about 320 mg/day, about 330 mg/day, about 340 mg/day, about 350 mg/day, about 360 mg/day, about 370 mg/day, about 380 mg/day, about 390 mg/day, about 400 mg/day, about 410 mg/day, about 420 mg/day, about 430 mg/day, about 440 mg/day, about 450 mg/day, about 460 mg/day, about 470 mg/day, about 480 mg/day, about 490 mg/day, or about 500 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 50 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 60 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 70 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 80 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 90 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 100 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 110 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 120 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 130 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 140 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 150 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 160 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 170 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 180 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 190 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 200 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 210 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 220 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 230 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 240 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 250 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 260 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 270 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 280 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 290 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 300 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 310 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 320 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 330 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 340 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 350 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 360 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 370 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 380 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 390 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 400 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 410 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 420 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 430 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 440 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 450 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 460 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 470 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 480 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 490 mg/day.

In some embodiments, the RAD51 inhibitor is administered at a dosage (*e.g.*, human dosage) at about 500 mg/day.

In some embodiments, the RAD51 inhibitor is administered once daily, for example, at any of the dosage described herein.

In some embodiments, the RAD51 inhibitor is administered once daily, for example, at any of the dosage described herein, for one day per week.

In some embodiments, the RAD51 inhibitor is administered once daily, for example, at any of the dosage described herein, for two days per week.

In some embodiments, the RAD51 inhibitor is administered once daily, for example, at any of the dosage described herein, for three days per week.

In some embodiments, the RAD51 inhibitor is administered once daily, for example, at any of the dosage described herein, for four days per week.

In some embodiments, the RAD51 inhibitor is administered once daily, for example, at any of the dosage described herein, for five days per week.

In some embodiments, the RAD51 inhibitor is administered once daily, for example, at any of the dosage described herein, for six days per week.

In some embodiments, the RAD51 inhibitor is administered once daily, for example, at any of the dosage described herein, for seven days per week.

In some embodiments, the RAD51 inhibitor is administered once daily, for example, at any of the dosage described herein, for two weeks.

In some embodiments, the RAD51 inhibitor is administered once daily, for example, at any of the dosage described herein, for three weeks.

In some embodiments, the RAD51 inhibitor is administered once daily, for example, at any of the dosage described herein, for four weeks.

In some embodiments, the RAD51 inhibitor is administered, for example, at any of the dosage described herein, once every other day.

In some embodiments, the RAD51 inhibitor is administered, for example, at any of the dosage described herein, once every other day for four days.

In some embodiments, the RAD51 inhibitor is administered, for example, at any of the dosage described herein, once every other day for 6 days.

In some embodiments, the RAD51 inhibitor is administered, for example, at any of the dosage described herein, once every other day for two weeks.

In some embodiments, the RAD51 inhibitor is administered, for example, at any of the dosage described herein, once every other day for three weeks.

In some embodiments, the RAD51 inhibitor is administered, for example, at any of the dosage described herein, once every other day for four weeks.

In some embodiment, the RAD51 inhibitor is administered, for example, at any of the dosage described herein, without a dosing holiday.

In some embodiment, the RAD51 inhibitor is administered, for example, at any of the dosage described herein, followed by a dosing holiday.

In some embodiment, the RAD51 inhibitor is administered, for example, at any of the dosage described herein, for two weeks followed by a dosing holiday.

In some embodiment, the RAD51 inhibitor is administered, for example, at any of the dosage described herein, for three weeks followed by a dosing holiday.

In some embodiment, the RAD51 inhibitor is administered, for example, at any of the dosage described herein, for four weeks followed by a dosing holiday.

In some embodiment, the RAD51 inhibitor is administered, for example, at any of the dosage described herein, followed by a 7-day dosing holiday.

In some embodiments, the RAD51 inhibitor is administered, for example, at any of the dosage described herein, followed by a 14-day dosing holiday.

In some embodiments, the RAD51 inhibitor is administered, for example, at any of the dosage described herein, followed by a 21-day dosing holiday.

In some embodiments, the RAD51 inhibitor is administered, for example, at any of the dosage described herein, followed by a 28-day dosing holiday.

In some embodiments, the RAD51 inhibitor is administered, for example, at any of the dosage described herein, followed by a 35-day dosing holiday.

In some embodiments, the RAD51 inhibitor is administered, for example, at any of the dosage described herein, followed by a 42-day dosing holiday.

In some embodiments, the RAD51 inhibitor is administered, for example, at any of the dosage described herein, followed by a 49-day dosing holiday.

In some embodiments, the RAD51 inhibitor is administered at about 300 mg/m² followed by a 7-day dosing holiday.

In some embodiments, the RAD51 inhibitor is administered at about 300 mg/m² followed by a 14-day dosing holiday.

In some embodiments, the RAD51 inhibitor is administered at about 300 mg/m² followed by a 21-day dosing holiday.

In some embodiments, the RAD51 inhibitor is administered at about 300 mg/m² followed by a 28-day dosing holiday.

In some embodiments, the RAD51 inhibitor is administered at about 240 mg/m² followed by a 7-day dosing holiday.

In some embodiments, the RAD51 inhibitor is administered at about 240 mg/m² followed by a 14-day dosing holiday.

In some embodiments, the RAD51 inhibitor is administered at about 240 mg/m² followed by a 21-day dosing holiday.

In some embodiments, the RAD51 inhibitor is administered at about 240 mg/m² followed by a 28-day dosing holiday.

In some embodiments, the RAD51 inhibitor is administered at about 120 mg/m² followed by a 7-day dosing holiday.

In some embodiments, the RAD51 inhibitor is administered at about 120 mg/m² followed by a 14-day dosing holiday.

In some embodiments, the RAD51 inhibitor is administered at about 120 mg/m² followed by a 21-day dosing holiday.

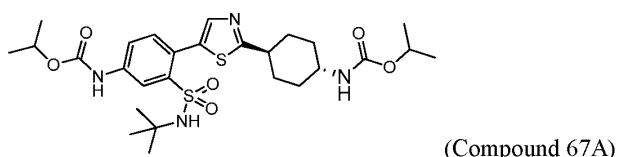
In some embodiments, the RAD51 inhibitor is administered at about 120 mg/m² followed by a 28-day dosing holiday.

In some embodiments, the RAD51 inhibitor is administered at about 50 mg/m² followed by a 7-day dosing holiday.

In some embodiments, the RAD51 inhibitor is administered at about 50 mg/m² followed by a 14-day dosing holiday.

In some embodiments, the RAD51 inhibitor is administered at about 50 mg/m² followed by a 21-day dosing holiday.

In some embodiments, the RAD51 inhibitor is administered at about 50 mg/m² followed by a 28-day dosing holiday. In some embodiments, the RAD51 inhibitor is Compound 67A:



or a pharmaceutically acceptable salt thereof.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 1 mg/m² to about 500 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 2 mg/m² to about 500 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 3 mg/m² to about 500 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 1 mg/m² to about 400 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 2 mg/m² to about 400 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 3 mg/m² to about 400 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 1 mg/m² to about 300 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 2 mg/m² to about 300 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 3 mg/m² to about 300 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 1 mg/m² to about 280 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 1 mg/m² to about 260 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 1 mg/m² to about 240 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 1 mg/m² to about 220 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 1 mg/m² to about 200 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 1 mg/m² to about 180 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 1 mg/m² to about 160 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 1 mg/m² to about 140 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 1 mg/m² to about 120 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 1 mg/m² to about 100 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 2 mg/m² to about 280 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 2 mg/m² to about 260 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 2 mg/m² to about 240 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 2 mg/m² to about 220 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 2 mg/m² to about 200 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 2 mg/m² to about 180 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 2 mg/m² to about 160 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 2 mg/m² to about 140 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 2 mg/m² to about 120 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 2 mg/m² to about 100 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 3 mg/m² to about 280 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 3 mg/m² to about 260 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 3 mg/m² to about 240 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 3 mg/m² to about 220 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 3 mg/m² to about 200 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 3 mg/m² to about 180 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 3 mg/m² to about 160 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 3 mg/m² to about 140 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 3 mg/m² to about 120 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 3 mg/m² to about 100 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/m² to about 500 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/m² to about 500 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/m² to about 500 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/m² to about 500 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/m² to about 500 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/m² to about 500 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 120 mg/m² to about 500 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 140 mg/m² to about 500 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 160 mg/m² to about 500 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 180 mg/m² to about 500 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 200 mg/m² to about 500 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 220 mg/m² to about 500 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 240 mg/m² to about 500 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 260 mg/m² to about 500 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 280 mg/m² to about 500 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/m² to about 400 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/m² to about 400 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/m² to about 400 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/m² to about 400 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/m² to about 400 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/m² to about 400 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 120 mg/m² to about 400 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 140 mg/m² to about 400 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 160 mg/m² to about 400 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 180 mg/m² to about 400 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 200 mg/m² to about 400 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 220 mg/m² to about 400 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 240 mg/m² to about 400 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 260 mg/m² to about 400 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 280 mg/m² to about 400 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/m² to about 300 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/m² to about 300 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/m² to about 300 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/m² to about 300 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/m² to about 300 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/m² to about 300 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 120 mg/m² to about 300 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 140 mg/m² to about 300 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 160 mg/m² to about 300 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 180 mg/m² to about 300 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 200 mg/m² to about 300 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 220 mg/m² to about 300 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 240 mg/m² to about 300 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 260 mg/m² to about 300 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 280 mg/m² to about 300 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/m² to about 280 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/m² to about 260 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/m² to about 240 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/m² to about 220 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/m² to about 200 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/m² to about 180 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/m² to about 160 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/m² to about 140 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/m² to about 280 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/m² to about 260 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/m² to about 240 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/m² to about 220 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/m² to about 200 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/m² to about 180 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/m² to about 160 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/m² to about 140 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/m² to about 280 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/m² to about 260 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/m² to about 240 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/m² to about 220 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/m² to about 200 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/m² to about 180 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/m² to about 160 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/m² to about 140 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/m² to about 280 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/m² to about 260 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/m² to about 240 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/m² to about 220 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/m² to about 200 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/m² to about 180 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/m² to about 160 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/m² to about 140 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/m² to about 280 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/m² to about 260 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/m² to about 240 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/m² to about 220 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/m² to about 200 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/m² to about 180 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/m² to about 160 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/m² to about 140 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/m² to about 280 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/m² to about 260 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/m² to about 240 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/m² to about 220 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/m² to about 200 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/m² to about 180 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/m² to about 160 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/m² to about 140 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 120 mg/m² to about 240 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) of about 1 mg/m², about 2 mg/m², about 3 mg/m², about 4 mg/m², about 5 mg/m², about 10 mg/m², about 20 mg/m², about 30 mg/m², about 40 mg/m², about 50 mg/m², about 60 mg/m², about 70 mg/m², about 80 mg/m², about 90 mg/m², about 100 mg/m², about 120 mg/m², about 140 mg/m², about 160 mg/m², about 180 mg/m², about 200 mg/m², about 220 mg/m², about 240 mg/m², about 260 mg/m², about 280 mg/m², about 300 mg/m², about 320 mg/m², about 340 mg/m², about 360 mg/m², about 380 mg/m², about 400 mg/m², about 420 mg/m², about 440 mg/m², about 460 mg/m², about 480 mg/m², or about 500 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) of about 1 mg/m², about 2 mg/m², about 3 mg/m², about 4 mg/m², about 5 mg/m², about 10 mg/m², about 20 mg/m², about 30 mg/m², about 40 mg/m², about 50 mg/m², about 60 mg/m², about 70 mg/m², about 80 mg/m², about 90 mg/m², about 100 mg/m², about 120 mg/m², about 140 mg/m², about 160 mg/m²,

about 180 mg/m², about 200 mg/m², about 220 mg/m², about 240 mg/m², about 260 mg/m², about 280 mg/m², or about 300 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) of about 3±2 mg/m², 3±1.8 mg/m², 3±1.6 mg/m², 3±1.5 mg/m², 3±1.4 mg/m², 3±1.3 mg/m², 3±1.2 mg/m², 3±1.1 mg/m², 3±1 mg/m², 3±0.9 mg/m², 3±0.8 mg/m², 3±0.7 mg/m², 3±0.6 mg/m², 3±0.5 mg/m², 3±0.4 mg/m², 3±0.3 mg/m², 3±0.2 mg/m², or 3±0.1 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) of about 3 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) of about 50±2 mg/m², 50±1.8 mg/m², 50±1.6 mg/m², 50±1.5 mg/m², 50±1.4 mg/m², 50±1.3 mg/m², 50±1.2 mg/m², 50±1.1 mg/m², 50±1 mg/m², 50±0.9 mg/m², 50±0.8 mg/m², 50±0.7 mg/m², 50±0.6 mg/m², 50±0.5 mg/m², 50±0.4 mg/m², 50±0.3 mg/m², 50±0.2 mg/m², or 50±0.1 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) of about 50 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) of about 120±100 mg/m², 120±90 mg/m², 120±80 mg/m², 120±70 mg/m², 120±60 mg/m², 120±50 mg/m², 120±45 mg/m², 120±40 mg/m², 120±35 mg/m², 120±30 mg/m², 120±25 mg/m², 120±20 mg/m², 120±15 mg/m², 120±10 mg/m², 120±9 mg/m², 120±8 mg/m², 120±7 mg/m², 120±6 mg/m², 120±5 mg/m², 120±4 mg/m², 120±3 mg/m², 120±2 mg/m², or 120±1 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) of about 120 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) of about 240±100 mg/m², 240±90 mg/m², 240±80 mg/m², 240±70 mg/m², 240±60 mg/m², 240±50 mg/m², 240±45 mg/m², 240±40 mg/m², 240±35 mg/m², 240±30 mg/m², 240±25 mg/m², 240±20 mg/m², 240±15 mg/m², 240±10 mg/m², 240±9 mg/m², 240±8 mg/m², 240±7 mg/m², 240±6 mg/m², 240±5 mg/m², 240±4 mg/m², 240±3 mg/m², 240±2 mg/m², or 240±1 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) of about 240 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) of about 300 ± 100 mg/m², 300 ± 90 mg/m², 300 ± 80 mg/m², 300 ± 70 mg/m², 300 ± 60 mg/m², 300 ± 50 mg/m², 300 ± 45 mg/m², 300 ± 40 mg/m², 300 ± 35 mg/m², 300 ± 30 mg/m², 300 ± 25 mg/m², 300 ± 20 mg/m², 300 ± 15 mg/m², 300 ± 10 mg/m², 300 ± 9 mg/m², 300 ± 8 mg/m², 300 ± 7 mg/m², 300 ± 6 mg/m², 300 ± 5 mg/m², 300 ± 4 mg/m², 300 ± 3 mg/m², 300 ± 2 mg/m², or 300 ± 1 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) of about 300 mg/m².

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/day to about 500 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/day to about 500 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/day to about 500 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/day to about 500 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/day to about 500 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/day to about 500 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 150 mg/day to about 500 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 200 mg/day to about 500 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 250 mg/day to about 500 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 300 mg/day to about 500 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 350 mg/day to about 500 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 400 mg/day to about 500 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 450 mg/day to about 500 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/day to about 450 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/day to about 450 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/day to about 450 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/day to about 450 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/day to about 450 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/day to about 450 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 150 mg/day to about 450 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 200 mg/day to about 450 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 250 mg/day to about 450 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 300 mg/day to about 450 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 350 mg/day to about 450 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 400 mg/day to about 450 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/day to about 400 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/day to about 400 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/day to about 400 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/day to about 400 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/day to about 400 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/day to about 400 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 150 mg/day to about 400 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 200 mg/day to about 400 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 250 mg/day to about 400 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 300 mg/day to about 400 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 350 mg/day to about 400 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/day to about 350 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/day to about 350 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/day to about 350 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/day to about 350 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/day to about 350 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/day to about 350 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 150 mg/day to about 350 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 200 mg/day to about 350 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 250 mg/day to about 350 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 300 mg/day to about 350 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/day to about 300 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/day to about 300 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/day to about 300 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/day to about 300 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/day to about 300 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/day to about 300 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 150 mg/day to about 300 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 200 mg/day to about 300 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 250 mg/day to about 300 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/day to about 250 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/day to about 250 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/day to about 250 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/day to about 250 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/day to about 250 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/day to about 250 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 150 mg/day to about 250 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 200 mg/day to about 250 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/day to about 200 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/day to about 200 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/day to about 200 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/day to about 200 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/day to about 200 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/day to about 200 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 150 mg/day to about 200 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/day to about 150 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/day to about 150 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/day to about 150 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/day to about 150 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/day to about 150 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 100 mg/day to about 150 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/day to about 100 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/day to about 100 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/day to about 100 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/day to about 100 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 90 mg/day to about 100 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/day to about 90 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/day to about 90 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/day to about 90 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 80 mg/day to about 90 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/day to about 80 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/day to about 80 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 70 mg/day to about 80 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/day to about 70 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 60 mg/day to about 70 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) ranging from about 50 mg/day to about 60 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) at about 50 mg/day, about 60 mg/day, about 70 mg/day, about 80 mg/day, about 90 mg/day, about 100 mg/day, about 110 mg/day, about 120 mg/day, about 130 mg/day, about 140 mg/day, about 150 mg/day, about 160 mg/day, about 170 mg/day, about 180 mg/day, about 190 mg/day, about 200 mg/day, about 210 mg/day, about 220 mg/day, about 230 mg/day, about 240 mg/day, about 250 mg/day, about 260 mg/day, about 270 mg/day, about 280 mg/day, about 290 mg/day, about 300 mg/day, about 310 mg/day, about 320 mg/day, about 330 mg/day, about 340 mg/day, about 350 mg/day, about 360 mg/day, about 370 mg/day, about 380 mg/day, about 390 mg/day, about 400 mg/day, about 410 mg/day, about 420 mg/day, about 430 mg/day, about 440 mg/day, about 450 mg/day, about 460 mg/day, about 470 mg/day, about 480 mg/day, about 490 mg/day, or about 500 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt thereof, is administered at a dosage (*e.g.*, human dosage) at about 50 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt thereof, is administered at a dosage (e.g., human dosage) at about 60 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt thereof, is administered at a dosage (e.g., human dosage) at about 70 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt thereof, is administered at a dosage (e.g., human dosage) at about 80 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt thereof, is administered at a dosage (e.g., human dosage) at about 90 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt thereof, is administered at a dosage (e.g., human dosage) at about 100 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt thereof, is administered at a dosage (e.g., human dosage) at about 110 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt thereof, is administered at a dosage (e.g., human dosage) at about 120 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt thereof, is administered at a dosage (e.g., human dosage) at about 130 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt thereof, is administered at a dosage (e.g., human dosage) at about 140 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt thereof, is administered at a dosage (e.g., human dosage) at about 150 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt thereof, is administered at a dosage (e.g., human dosage) at about 160 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt thereof, is administered at a dosage (e.g., human dosage) at about 170 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt thereof, is administered at a dosage (e.g., human dosage) at about 180 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt thereof, is administered at a dosage (e.g., human dosage) at about 190 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt thereof, is administered at a dosage (e.g., human dosage) at about 200 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt thereof, is administered at a dosage (e.g., human dosage) at about 210 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt there, is administered at a dosage (e.g., human dosage) at about 220 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt there, is administered at a dosage (e.g., human dosage) at about 230 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt there, is administered at a dosage (e.g., human dosage) at about 240 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt there, is administered at a dosage (e.g., human dosage) at about 250 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt there, is administered at a dosage (e.g., human dosage) at about 260 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt there, is administered at a dosage (e.g., human dosage) at about 270 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt there, is administered at a dosage (e.g., human dosage) at about 280 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt there, is administered at a dosage (e.g., human dosage) at about 290 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt there, is administered at a dosage (e.g., human dosage) at about 300 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt there, is administered at a dosage (e.g., human dosage) at about 310 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt there, is administered at a dosage (e.g., human dosage) at about 320 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt there, is administered at a dosage (e.g., human dosage) at about 330 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt there, is administered at a dosage (e.g., human dosage) at about 340 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt there, is administered at a dosage (e.g., human dosage) at about 350 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt there, is administered at a dosage (e.g., human dosage) at about 360 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt there, is administered at a dosage (e.g., human dosage) at about 370 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt thereof, is administered at a dosage (e.g., human dosage) at about 380 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt thereof, is administered at a dosage (e.g., human dosage) at about 390 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt thereof, is administered at a dosage (e.g., human dosage) at about 400 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt thereof, is administered at a dosage (e.g., human dosage) at about 410 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt thereof, is administered at a dosage (e.g., human dosage) at about 420 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt thereof, is administered at a dosage (e.g., human dosage) at about 430 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt thereof, is administered at a dosage (e.g., human dosage) at about 440 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt thereof, is administered at a dosage (e.g., human dosage) at about 450 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt thereof, is administered at a dosage (e.g., human dosage) at about 460 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt thereof, is administered at a dosage (e.g., human dosage) at about 470 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt thereof, is administered at a dosage (e.g., human dosage) at about 480 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt thereof, is administered at a dosage (e.g., human dosage) at about 490 mg/day.

In some embodiments, Compound 67A, or a pharmaceutically acceptable salt thereof, is administered at a dosage (e.g., human dosage) at about 500 mg/day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered once daily, for example, at any of the dosage described herein.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered once daily, for example, at any of the dosage described herein, for one day per week.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered once daily, for example, at any of the dosage described herein, for two days per week.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered once daily, for example, at any of the dosage described herein, for three days per week.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered once daily, for example, at any of the dosage described herein, for four days per week.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered once daily, for example, at any of the dosage described herein, for five days per week.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered once daily, for example, at any of the dosage described herein, for six days per week.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered once daily, for example, at any of the dosage described herein, for seven days per week.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered once daily, for example, at any of the dosage described herein, for two weeks.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered once daily, for example, at any of the dosage described herein, for three weeks.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered once daily, for example, at any of the dosage described herein, for four weeks.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered once, for example, at any of the dosage described herein, every other day.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered once, for example, at any of the dosage described herein, every other day for four days.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered once, for example, at any of the dosage described herein, every other day for six days.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered once, for example, at any of the dosage described herein, every other day for two weeks.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered once, for example, at any of the dosage described herein, every other day for three weeks.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered once, for example, at any of the dosage described herein, every other day for four weeks.

In some embodiment, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered, for example, at any of the dosage described herein, without a dosing holiday.

In some embodiment, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered, for example, at any of the dosage described herein, followed by a dosing holiday.

In some embodiment, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered, for example, at any of the dosage described herein, for one week followed by a dosing holiday.

In some embodiment, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered, for example, at any of the dosage described herein, for two weeks followed by a dosing holiday.

In some embodiment, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered, for example, at any of the dosage described herein, for three weeks followed by a dosing holiday.

In some embodiment, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered, for example, at any of the dosage described herein, for four weeks followed by a dosing holiday.

In some embodiment, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered, for example, at any of the dosage described herein, followed by a 7-day dosing holiday.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered, for example, at any of the dosage described herein, followed by a 14-day dosing holiday.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered, for example, at any of the dosage described herein, followed by a 21-day dosing holiday.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered, for example, at any of the dosage described herein, followed by a 28-day dosing holiday.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered, for example, at any of the dosage described herein, followed by a 35-day dosing holiday.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered, for example, at any of the dosage described herein, followed by a 42-day dosing holiday.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered, for example, at any of the dosage described herein, followed by a 49-day dosing holiday.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at about 300 mg/m² followed by a 7-day dosing holiday.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at about 300 mg/m² followed by a 14-day dosing holiday.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at about 300 mg/m² followed by a 21-day dosing holiday.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at about 300 mg/m² followed by a 28-day dosing holiday.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at about 240 mg/m² followed by a 7-day dosing holiday.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at about 240 mg/m² followed by a 14-day dosing holiday.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at about 240 mg/m² followed by a 21-day dosing holiday.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at about 240 mg/m² followed by a 28-day dosing holiday.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at about 120 mg/m² followed by a 7-day dosing holiday.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at about 120 mg/m² followed by a 14-day dosing holiday.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at about 120 mg/m² followed by a 21-day dosing holiday.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at about 120 mg/m² followed by a 28-day dosing holiday.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at about 50 mg/m² followed by a 7-day dosing holiday.

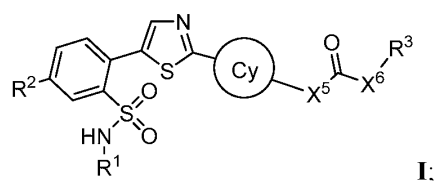
In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at about 50 mg/m² followed by a 14-day dosing holiday.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at about 50 mg/m² followed by a 21-day dosing holiday.

In some embodiments, Compound 67A, or the pharmaceutically acceptable salt thereof, is administered at about 50 mg/m² followed by a 28-day dosing holiday.

RAD51 Inhibitors

In a first embodiment, the RAD51 inhibitor is a compound represented by Structural Formula I:



or a pharmaceutically acceptable salt thereof, wherein:

the thiazole ring is optionally substituted with -F or -Cl;

Cy is -(C₃-C₇)cycloalkyl, bridged (C₆-C₁₂) cycloalkyl, or a 4-12 membered heterocyclic ring, each of which is optionally substituted with one or more groups selected from the group consisting of halogen, -OH, (C₁-C₄)alkyl, and (C₁-C₄)alkoxy;

when X⁵ is connected with a nitrogen ring atom of Cy, X⁵ is absent;

when X⁵ is connected with a carbon ring atom of Cy, X⁵ is NR^a or O;

X^6 is NR^a or O;

R^1 is (C_1-C_5) alkyl;

R^3 is (C_1-C_5) alkyl, $-CH_2$ -phenyl, $-(C_3-C_7)$ cycloalkyl, $-CH_2-(C_3-C_7)$ cycloalkyl, $-CH_2$ -monocyclic 3-7 membered heterocyclic ring, or monocyclic 3-7 membered heterocyclic ring, wherein the (C_1-C_5) alkyl, $-(C_3-C_7)$ cycloalkyl, phenyl or monocyclic 3-7 membered heterocyclic ring represented by R^3 or in the group represented by R^3 is optionally substituted with one or more groups selected from the group consisting of halogen, $-OH$, (C_1-C_4) alkyl, halomethyl, halomethoxy, $-CN$, and (C_1-C_4) alkoxy;

R^2 is $-NR^aC(O)O(C_1-C_4)$ alkyl; $-NR^aC(O)NR^a(C_1-C_4)$ alkyl; $-NR^aC(O)O(C_2-C_4)$ alkenyl; $-NR^aC(O)NR^a(C_2-C_4)$ alkenyl; $-NR^aC(O)O-(C_3-C_6)$ cycloalkyl; $-NR^aC(O)NR^a-(C_3-C_7)$ cycloalkyl; $-NR^aC(O)O$ -phenyl; $-NR^aC(O)NR^a$ -phenyl; $-NR^aC(O)O$ -monocyclic 3-7 membered heterocyclic ring; $-NR^aC(O)NR^a$ -monocyclic 3-7 membered heterocyclic ring; $-NR^aC(O)O$ -monocyclic 5-6 membered heteroaromatic ring; $-NR^aC(O)NR^a$ -monocyclic 5-6 membered heteroaromatic ring;

wherein the (C_1-C_4) alkyl and the (C_2-C_4) alkenyl in the group represented by R^2 are each optionally and independently substituted with one or more groups selected from the group consisting of halogen, N_3 , $-OR^a$, $-NR^aR^a$, $-(C_3-C_6)$ cycloalkyl, phenyl, a monocyclic 3-7 membered heterocyclic ring, and a monocyclic 5-6 membered heteroaromatic ring;

wherein the (C_3-C_7) cycloalkyl in the group represented by R^2 is optionally substituted with one or more groups selected from the group consisting of halogen, $-CH_3$, $=O$, $-OR^a$ and $-NR^aR^a$;

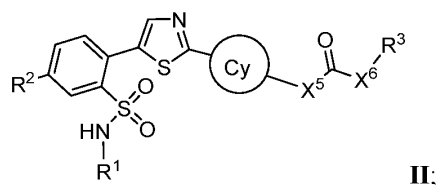
wherein the phenyl in the group represented by R^2 is optionally substituted with one or more groups selected from the group consisting of halogen, $-CH_3$, halomethyl, halomethoxy, $-CN$, $-OR^a$, and $-N_3$;

wherein the heterocyclic ring in the group represented by R^2 is optionally substituted with one or more groups selected from the group consisting of $=O$, halogen, $-OR^a$, $-CH_3$, halomethyl, and halomethoxy;

wherein the heteroaromatic ring in the group represented by R^2 is optionally substituted with one or more groups selected from the group consisting of halogen, $-CN$, $-CH_3$, halomethyl, halomethoxy, $-OR^a$ and $-NR^aR^a$; and

each R^a is independently $-H$ or $-CH_3$.

In a second embodiment, the RAD51 inhibitor is a compound represented by Structural Formula II:



or a pharmaceutically acceptable salt thereof, wherein

the thiazole ring is optionally substituted with -F or -Cl;

Cy is cyclohexyl or a 6-membered monocyclic heterocyclic ring;

X⁵ and X⁶ are each independently NRᵃ or O;

R¹ is (C₁-C₅)alkyl;

R³ is (C₁-C₅)alkyl or monocyclic 3-7-membered heterocyclic ring;

R² is -NRᵃC(O)O(C₁-C₄)alkyl; -NRᵃC(O)NRᵃ(C₁-C₄)alkyl; -NRᵃC(O)O(C₂-C₄)alkenyl;

-NRᵃC(O)NRᵃ(C₂-C₄)alkenyl; -NRᵃC(O)-O(C₃-C₆)cycloalkyl; -NRᵃC(O)NRᵃ-(C₃-C₆)cycloalkyl; -NRᵃC(O)O-phenyl; -NRᵃC(O)NRᵃ-phenyl; -NRᵃC(O)O-monocyclic 3-7 membered heterocyclic ring; -NRᵃC(O)NRᵃ-monocyclic 3-7 membered heterocyclic ring; -NRᵃC(O)O-monocyclic 5-6 membered heteroaromatic ring; -NRᵃC(O)NRᵃ-monocyclic 5-6 membered heteroaromatic ring;

wherein the (C₁-C₄)alkyl and the (C₂-C₄)alkenyl in the group represented by R² are each optionally and independently substituted with one or more halogen, N₃, -ORᵃ, -NRᵃRᵃ, -(C₃-C₆)cycloalkyl, phenyl, monocyclic 3-7-membered heterocyclic ring, or monocyclic 5-6-membered heteroaromatic ring;

wherein the -(C₃-C₆)cycloalkyl in the group represented by R² is optionally substituted with one or more halogen, -CH₃, -ORᵃ or -NRᵃRᵃ;

wherein the phenyl in the group represented by R² is optionally substituted with one or more halogen, -CH₃, halomethyl, halomethoxy, -ORᵃ, or -N₃;

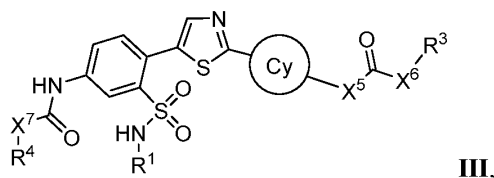
wherein the heterocyclic ring in the group represented by R² is optionally substituted with one or more =O, halogen, -CH₃, halomethyl, or halomethoxy;

wherein the heteroaromatic ring in the group represented by R² is optionally substituted with one or more halogen, -CH₃, halomethyl, halomethoxy, -ORᵃ or -NRᵃRᵃ; and each Rᵃ is independently -H or -CH₃.

In a third embodiment, the RAD51 inhibitor is a compound according to Structural Formula **I**, or a pharmaceutically acceptable salt thereof, wherein Cy is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl; azetidiny, azepanyl, diazaspiro[4.4]nonyl, diazaspiro[3.5]nonyl, diazepanyl, dihydroimidazole, dihydrofuranyl, dihydropyranyl, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyranyl, hexahydropyridazinyl, hexahydropyrimidinyl, hydantoinyl, indolyl, isoindolyl, morpholyl, oxiranyl, oxetanyl, piperidinyl, piperazinyl, pyrrolidinonyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydroimidazole, tetrahydroindolyl, tetrahydropyranyl, tetrahydrothienyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, thiomorpholyl, tropanyl, valerolactamyl; bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[4.3.1]decyl, bicyclo[3.3.1]nonyl, bornyl, bornenyl, norbornyl, norbornenyl, 6,6-dimethylbicyclo[3.1.1]heptyl, tricyclobutyl, adamantyl; azanorbornyl, quinuclidinyl, isoquinuclidinyl, tropanyl, azabicyclo[2.2.1]heptanyl, 2-azabicyclo[3.2.1]octanyl, azabicyclo[3.2.1]octanyl, azabicyclo[3.2.2]nonanyl, azabicyclo[3.3.0]nonanyl, azabicyclo[3.3.1]nonanyl, diazabicyclo[2.2.1]heptanyl, diazabicyclo[3.2.1]octanyl, octahydropyrrolo[3,4-b]pyrrolyl, octahydropyrrolo[3,4-c]pyrrolyl; and the remaining variables are as defined in the first embodiment.

In a fourth embodiment, the RAD51 inhibitor is a compound according to Structural Formula **I** or **II**, or a pharmaceutically acceptable salt thereof, wherein Cy is cyclohexyl, morpholyl, thiomorpholyl, piperidinyl, piperazinyl, hexahydropyridazinyl, hexahydropyrimidinyl, valerolactamyl, dihydropyranyl, dihydropyridinyl, dihydropyrimidinyl, dihydrothiopyranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydropyrimidinyl, or tetrahydrothiopyranyl; and the remaining variables are as defined in the first, second, and/or third embodiments.

In a fifth embodiment, the RAD51 inhibitor is a compound represented by Structural Formula **III**,



or a pharmaceutically acceptable salt thereof, wherein:

X⁷ is NH or O;

R^4 is (C₁–C₄)alkyl, (C₃–C₆)cycloalkyl, or a monocyclic 3-7 membered heterocyclic ring;

wherein the (C₁–C₄)alkyl represented by R^4 is optionally substituted with one or more groups selected from the group consisting of halogen, N₃, –OR^a, –NR^aR^a, –(C₃–C₆)cycloalkyl, phenyl, a monocyclic 3-7 membered heterocyclic ring, and a monocyclic 5-6 membered heteroaromatic ring,

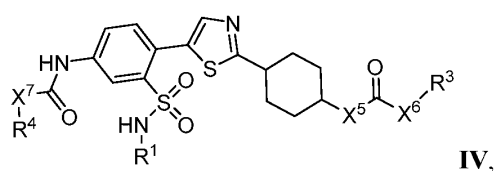
wherein the (C₃–C₆)cycloalkyl or the monocyclic 3-7 membered heterocyclic ring represented by R^4 , the (C₃–C₆)cycloalkyl or the monocyclic 3-7 membered heterocyclic ring in the group represented by R^4 is optionally substituted with one or more groups selected from the group consisting of halogen, –OR^a, =O, and –CH₃,

wherein the phenyl in the group represented by R^4 is optionally substituted with one or more groups selected from the group consisting of halogen, –CH₃, halomethyl, halomethoxy, –OR^a, and –N₃;

wherein the heteroaromatic ring in the group represented by R^4 is optionally substituted with one or more groups selected from the group consisting of halogen and –CH₃; and the remaining variables are as defined in the first, second, third, and/or fourth embodiments.

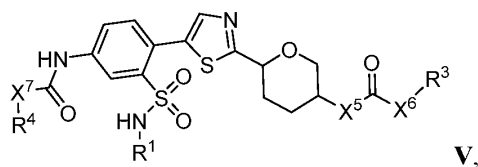
In a sixth embodiment, the RAD51 inhibitor is a compound according to Structural Formula **III**, or a pharmaceutically acceptable salt thereof, wherein X⁷ is NH or O; R³ is (C₁–C₅)alkyl; and R^4 is (C₁–C₄)alkyl wherein the (C₁–C₄)alkyl represented by R^4 is optionally substituted with one or more halogen, –OR^a, –NR^aR^a, –(C₃–C₆)cycloalkyl, phenyl (optionally substituted by one or more halogen, –CH₃, halomethyl, halomethoxy, OR^a or N₃), monocyclic 3–7-membered heterocyclic ring (optionally substituted by =O, halogen or –CH₃), or monocyclic 5–6-membered heteroaromatic ring (optionally substituted by halogen or –CH₃); and the remaining variables are as defined in the first, second, third, fourth and/or fifth embodiments.

In a seventh embodiment, the RAD51 inhibitor is a compound represented by Structural Formula **IV**,



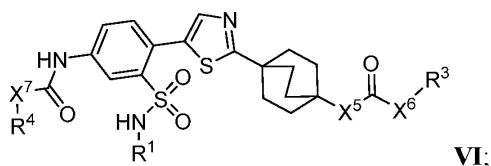
or a pharmaceutically acceptable salt thereof; and the variables are as defined in the first, second, third, fourth, fifth and/or sixth embodiments.

In an eighth embodiment, the RAD51 inhibitor is a compound represented by Structural Formula **V**,



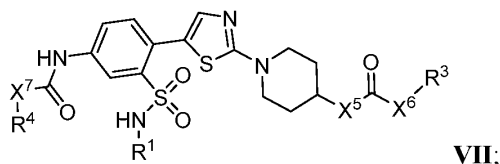
or a pharmaceutically acceptable salt thereof; and the variables are as defined in the first, second, third, fourth, fifth and/or sixth embodiments.

In a ninth embodiment, the RAD51 inhibitor is a compound represented by Structural Formula **VI**:



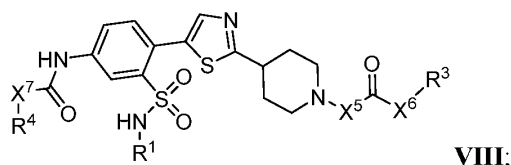
or a pharmaceutically acceptable salt thereof; and the variables are as defined in the first, second, third, fourth, fifth and/or sixth embodiments.

In a tenth embodiment, the RAD51 inhibitor is a compound represented by Structural Formula **VII**:



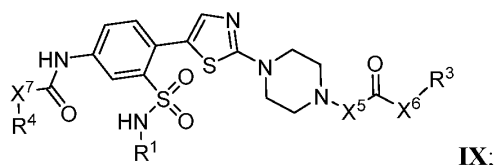
or a pharmaceutically acceptable salt thereof; and the variables are as defined in the first, second, third, fourth, fifth and/or sixth embodiments.

In an eleventh embodiment, the RAD51 inhibitor is a compound represented by Structural Formula **VIII**:



or a pharmaceutically acceptable salt thereof; and the variables are as defined in the first, second, third, fourth, fifth and/or sixth embodiments.

In a twelfth embodiment, the RAD51 inhibitor is a compound represented by Structural Formula **IX**:



or a pharmaceutically acceptable salt thereof; and the variables are as defined in the first, second, third, fourth, fifth and/or sixth embodiments.

In a thirteenth embodiment, the RAD51 inhibitor is a compound according to Structural Formula **I**, **II**, or **III**, or a pharmaceutically acceptable salt thereof, wherein Cy is azetidiny1 or pyrrolidinyl, and the nitrogen ring atom is connected with the thiazole ring; and the remaining variables are as defined in the first, second, third, fourth, fifth and/or sixth embodiments.

In a fourteenth embodiment, the RAD51 inhibitor is a compound according to Structural Formula **I**, **II**, or **III**, or a pharmaceutically acceptable salt thereof, wherein Cy is 1,7-diazaspiro[4.4]nonyl, 2,7-diazaspiro[4.4]nonyl, 2,7-diazaspiro[3.5]nonyl, 1,4-diazepanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 3,8-diazabicyclo[3.2.1]octanyl, octahydropyrrolo[3,4-b]pyrrolyl, or octahydropyrrolo[3,4-c]pyrrolyl, and the two nitrogen ring atoms are connected with the thiazole ring and the $-X^5C(O)X^6R^3$ moiety, respectively; and the remaining variables are as defined in the first, second, third, fourth, fifth and/or sixth embodiments.

In a fifteenth embodiment, the RAD51 inhibitor is a compound according to Structural Formula **III**, **IV**, **V**, **VI**, **VII**, **VIII**, or **IX**, or a pharmaceutically acceptable salt thereof, wherein R^4 is $-(C_1-C_3)alkyl$, $(C_3-C_6)cycloalkyl$, or a monocyclic 3-7 membered heterocyclic ring, wherein the $-(C_1-C_3)alkyl$ is optionally substituted with (i) phenyl optionally substituted by one or more halogen or $-CH_3$; (ii) a monocyclic 5-6 membered heteroaromatic ring optionally substituted by one or more halogen or $-CH_3$; or (iii) a monocyclic 3-7 membered heterocyclic ring optionally substituted by one or more groups selected from the group consisting of halogen and $-CH_3$; and the remaining variables are as defined in the first, second, third, fourth, fifth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, and/or fourteenth embodiments.

In a sixteenth embodiment, the RAD51 inhibitor is a compound according to Structural Formula **III**, **IV**, **V**, **VI**, **VII**, **VIII**, or **IX**, or a pharmaceutically acceptable salt thereof, wherein R^4 is $-(C_1-C_3)alkyl$, $-CHR^a-phenyl$, $-CHR^a-5-6$ membered heteraromatic

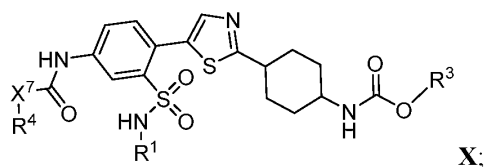
ring, or -CHR^a-3-7 membered monocyclic heterocyclic ring, wherein the phenyl, 5-6 membered heteraromatic ring or 3-7 membered monocyclic heterocyclic ring in the group represented by R⁴ is optionally substituted one or more groups selected from the group consisting of halogen and -CH₃; and the remaining variables are as defined in the first, second, third, fourth, fifth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, and/or fourteenth embodiments.

In a seventeenth embodiment, the RAD51 inhibitor is a compound according to Structural Formula **III**, **IV**, **V**, **VI**, **VII**, **VIII**, or **IX**, or a pharmaceutically acceptable salt thereof, wherein R⁴ is -(C₁-C₃)alkyl, optionally substituted with (i) phenyl optionally substituted by one or more halogen, -CH₃, halomethyl, halomethoxy, OR^a, or N₃; (ii) a monocyclic 5-6-membered heteroaromatic ring optionally substituted by one or more halogen or -CH₃; or (iii) a monocyclic 3-7-membered heterocyclic ring optionally substituted by one or more =O or -CH₃; and the remaining variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, and/or fourteenth embodiments.

In an eighteenth embodiment, the RAD51 inhibitor is a compound according to Structural Formula **III**, **IV**, **V**, **VI**, **VII**, **VIII**, or **IX**, or a pharmaceutically acceptable salt thereof, wherein R⁴ is -(C₁-C₃)alkyl, optionally substituted with (i) phenyl optionally substituted by one or more halogen, -CH₃, halomethyl, halomethoxy, OR^a, or N₃; (ii) a monocyclic 5-6-membered heteroaromatic ring optionally substituted by one or more halogen or -CH₃; or (iii) a monocyclic 3-7-membered heterocyclic ring optionally substituted by one or more =O or -CH₃; and the remaining variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, and/or seventeenth embodiments.

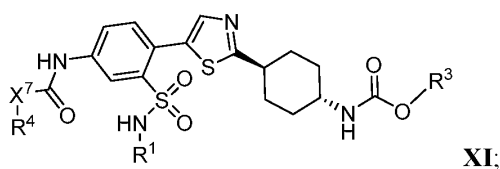
In a nineteenth embodiment, the RAD51 inhibitor is a compound according to Structural Formula **I**, **III**, **IV**, **V**, **VI**, **VII**, **VIII**, or **IX**, or a pharmaceutically acceptable salt thereof, wherein R³ is (C₁-C₄)alkyl, -(C₄-C₆)cycloalkyl, -CH₂-phenyl, -CH₂-monocyclic 4-6 membered heterocyclic ring, or monocyclic 4-6 membered heterocyclic ring, wherein the phenyl or monocyclic 4-6 membered heterocyclic ring represented by R³ or in the group represented by R³ is optionally substituted with one or more groups selected from the group consisting of halogen, -OR^a, and -CH₃; and the remaining variables are as defined in the first, third, fourth, fifth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, sixteenth, seventeenth, and/or eighteenth embodiments.

In a twentieth embodiment, the RAD51 inhibitor is a compound represented by Structural Formula **X**:



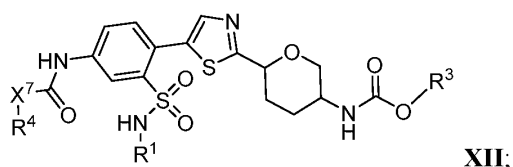
or a pharmaceutically acceptable salt thereof; and the variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, fifteenth, sixteenth, seventeenth, eighteenth, and/or nineteenth embodiments.

In a twenty first embodiment, the RAD51 inhibitor is a compound represented by Structural Formula **XI**:



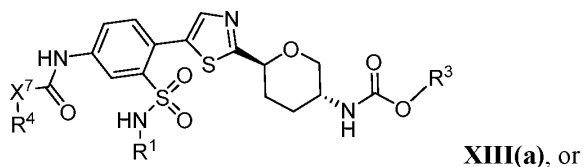
or a pharmaceutically acceptable salt thereof; and the variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, fifteenth, sixteenth, seventeenth, eighteenth, and/or nineteenth embodiments.

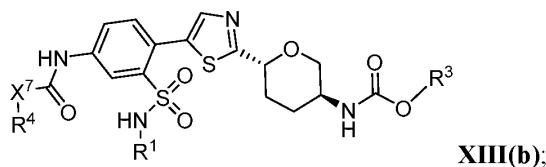
In a twenty second embodiment, the RAD51 inhibitor is a compound represented by Structural Formula **XII**:



or a pharmaceutically acceptable salt thereof; and the variables are as defined in the first, second, third, fourth, fifth, sixth, eighth, fifteenth, sixteenth, seventeenth, eighteenth, and/or nineteenth embodiments.

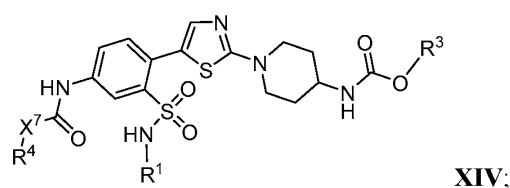
In a twenty third embodiment, the RAD51 inhibitor is a compound represented by Structural Formula **XIII(a)** or **XIII(b)**:





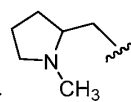
or a pharmaceutically acceptable salt thereof; and the variables are as defined in the first, second, third, fourth, fifth, sixth, eighth, fifteenth, sixteenth, seventeenth, eighteenth, and/or nineteenth embodiments.

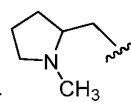
In a twenty fourth embodiment, the RAD51 inhibitor is a compound represented by Structural Formula **XIV**:



or a pharmaceutically acceptable salt thereof; and the variables are as defined in the first, second, third, fourth, fifth, sixth, tenth, fifteenth, sixteenth, seventeenth, eighteenth, and/or nineteenth embodiments.

In a twenty fifth embodiment, the RAD51 inhibitor is a compound according to Structural Formula **I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII(a), XIII(b), XIV**, or a pharmaceutically acceptable salt thereof, wherein R³ is isopropyl, *tert*-butyl, cyclobutyl,

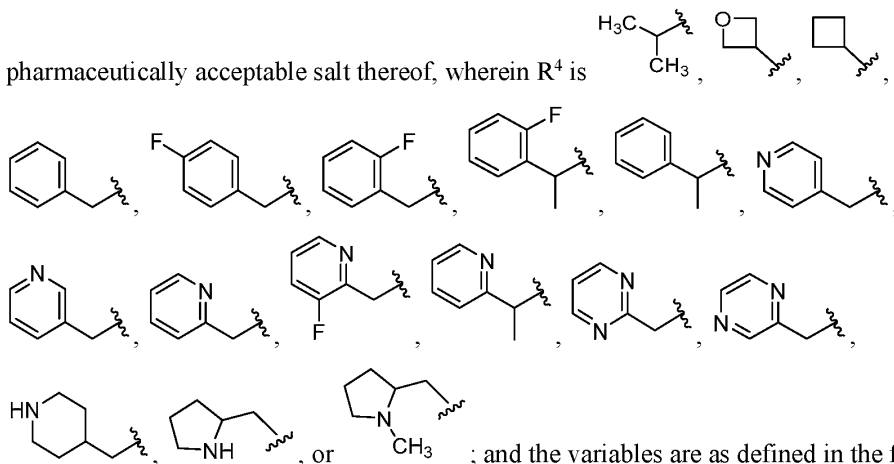


cyclopentyl, benzyl, oxetanyl, tetrahydro-2H-pyranyl, or ; and the variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, sixteenth, seventeenth, eighteenth, nineteenth, twentieth, twenty first, twenty second, twenty third and/or twenty fourth embodiments. In an alternative embodiment, R³ is isopropyl or oxetanyl. In another alternative embodiment, R³ is isopropyl.

In a twenty sixth embodiment, the RAD51 inhibitor is a compound according to Structural Formula **I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII(a), XIII(b), XIV**, or a pharmaceutically acceptable salt thereof, wherein R¹ is *tert*-butyl; and the variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, sixteenth, seventeenth, eighteenth, nineteenth, twentieth, twenty first, twenty second, twenty third, twenty fourth, and/or twenty fifth embodiments.

In a twenty seventh embodiment, the RAD51 inhibitor is a compound according to Structural Formula III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII(a), XIII(b), XIV, or a

pharmaceutically acceptable salt thereof, wherein R^4 is



; and the variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, sixteenth, seventeenth, eighteenth, nineteenth, twentieth, twenty first, twenty second, twenty third, twenty fourth, twenty fifth, and/or twenty sixth embodiments.

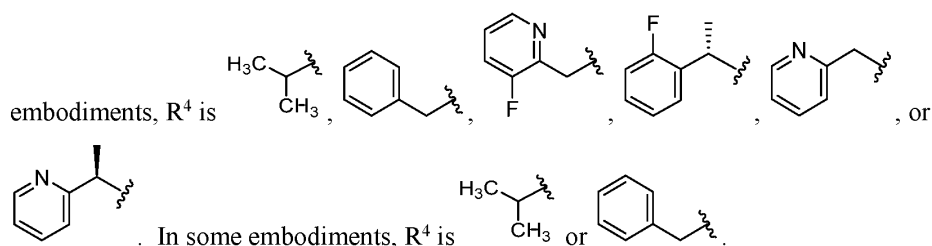
In some embodiments, R^4 is

. In another alternative embodiment,

R^4 is

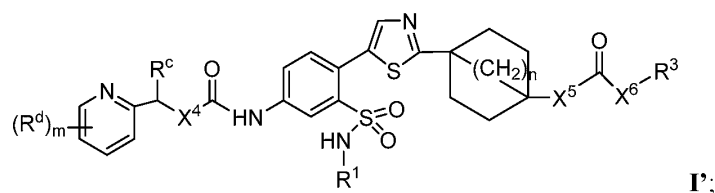
. In some embodiments, R^4 is

. In some



The present disclosure provides a compound for use in treating pancreatic cancer represented by Structural Formula **I'**.

In a first embodiment, the RAD51 inhibitor is a compound represented by Structural Formula **I'**:



or a pharmaceutically acceptable salt thereof, wherein:

the thiazole ring is optionally substituted with -F or -Cl;

X^4 is NR^a or O;

X^5 and X^6 are each independently NR^b or O;

R^1 is (C_1-C_5) alkyl;

R^3 is (C_1-C_5) alkyl, $-(C_3-C_7)$ cycloalkyl, or $-(CH_2)_q$ heterocyclyl (wherein the heterocyclyl is a monocyclic 3-7-membered heterocyclic ring optionally substituted with one or more occurrences of methyl), or benzyl (wherein the benzyl ring is optionally substituted with one or more occurrences of halogen, methoxy, halomethoxy, methyl, halomethyl, or cyano);

each of R^a , R^b , and R^c is independently hydrogen or methyl;

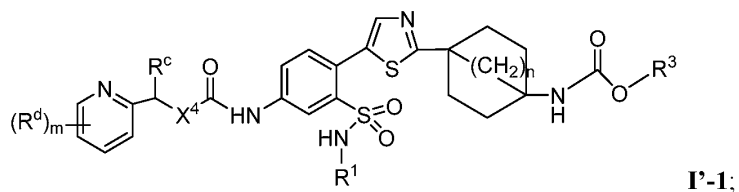
R^d is independently halogen, methoxy, halomethoxy, methyl, halomethyl, or cyano;

m is 0, 1, 2, or 3;

n is 0, 1, or 2; and

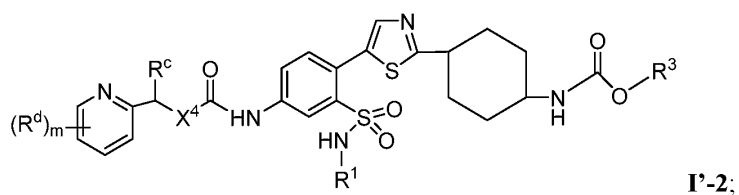
q is 0 or 1.

In a second embodiment, the RAD51 inhibitor is a compound represented by Structural Formula **I'-1**:



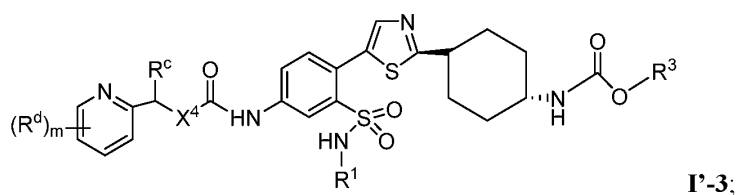
or a pharmaceutically acceptable salt thereof, and the variables are as defined in the first embodiment.

In a third embodiment, the RAD51 inhibitor is a compound represented by Structural Formula **I'-2**:



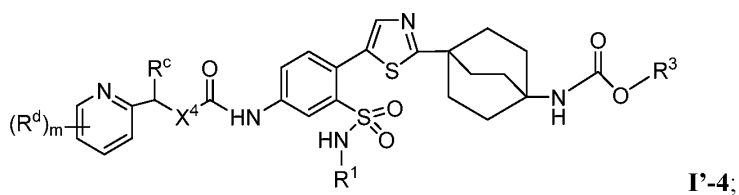
or a pharmaceutically acceptable salt thereof, and the variables are as defined in the first embodiment.

In a fourth embodiment, the RAD51 inhibitor is a compound represented by Structural Formula **I'-3**:



or a pharmaceutically acceptable salt thereof, and the variables are as defined in the first embodiment.

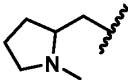
In a fifth embodiment, the RAD51 inhibitor is a compound represented by Structural Formula **I'-4**:



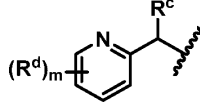
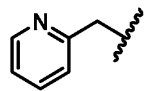
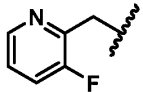
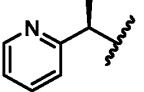
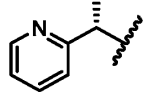
or a pharmaceutically acceptable salt thereof, and the variables are as defined in the first embodiment.

In a sixth embodiment, the RAD51 inhibitor is a compound according to Structural Formula **I'**, **I'-1**, **I'-2**, **I'-3**, or **I'-4**, or a pharmaceutically acceptable salt thereof, wherein X^4 is NH, and the remaining variables are as defined in the first embodiment.

In a seventh embodiment, the RAD51 inhibitor is a compound according to Structural Formula **I'**, **I'-1**, **I'-2**, **I'-3**, or **I'-4**, or a pharmaceutically acceptable salt thereof, wherein R^3 is (C₁–C₄)alkyl, -(C₄–C₆)cycloalkyl, -(CH₂)_qheterocyclyl (wherein the heterocyclyl is a monocyclic 4-6-membered heterocyclic ring optionally substituted with one methyl), or benzyl, and the remaining variables are as defined in the first and/or sixth embodiments. In some embodiments, R^3 is isopropyl, *tert*-butyl, cyclobutyl, cyclopentyl, oxetanyl, benzyl,

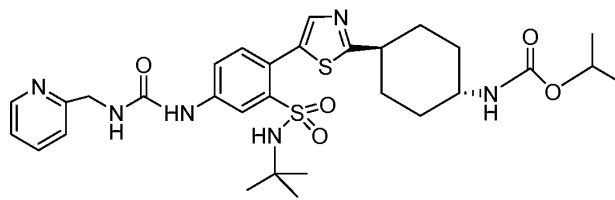
tetrahydro-2H-pyran-2-yl, or . In some embodiments, R^3 is isopropyl or oxetanyl.

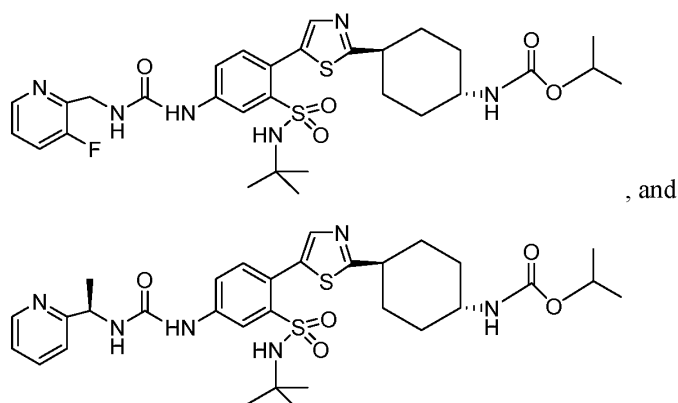
In an eighth embodiment, the RAD51 inhibitor is a compound according to Structural Formula **I'**, **I'-1**, **I'-2**, **I'-3**, or **I'-4**, or a pharmaceutically acceptable salt thereof, wherein R^d is halogen, and m is 0 or 1, and the remaining variables are as defined in the first, sixth,

and/or seventh embodiments. In some embodiments,  is , , , or .

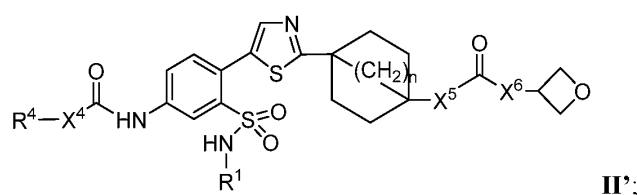
In a ninth embodiment, the RAD51 inhibitor is a compound according to Structural Formula **I'**, **I'-1**, **I'-2**, **I'-3**, or **I'-4**, or a pharmaceutically acceptable salt thereof, wherein R^1 is *tert*-butyl, and the remaining variables are as defined in the first, sixth, seventh, and/or eighth embodiments.

In a tenth embodiment, the RAD51 inhibitor is a compound, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:





In an eleventh embodiment, the RAD51 inhibitor is a compound represented by Structural Formula II':



or a pharmaceutically acceptable salt thereof, wherein:

the thiazole ring is optionally substituted with -F or -Cl;

X⁴ is NR^a or O;

X⁵ and X⁶ are each independently NR^b or O;

R¹ is (C₁-C₅)alkyl;

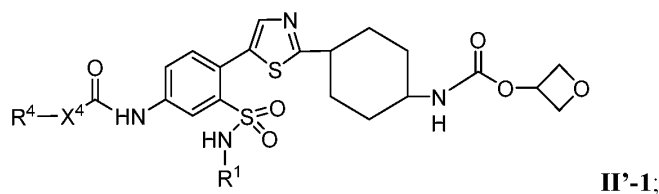
R⁴ is (C₁-C₄)alkyl, -(C₃-C₇)cycloalkyl, -(CH(R^c))_q-heterocycl (wherein the heterocycl is a monocyclic 3-7-membered heterocyclic ring optionally substituted with one or more occurrences of methyl), -(CH(R^c))_q-phenyl (wherein the phenyl ring is optionally substituted with one or more occurrences of halogen, methoxy, halomethoxy, methyl, halomethyl, or cyano), or -(CH(R^c))_q-2-pyridinyl (wherein the 2-pyridinyl ring is optionally substituted with one or more occurrences of halogen, methoxy, halomethoxy, methyl, halomethyl, or cyano);

each of R^a, R^b, and R^c is independently hydrogen or methyl;

n is 0, 1, or 2; and

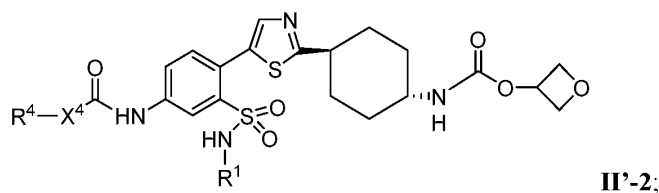
q is 0 or 1.

In a twelveth embodiment, the RAD51 inhibitor is a compound represented by Structural Formula **II'-1**:



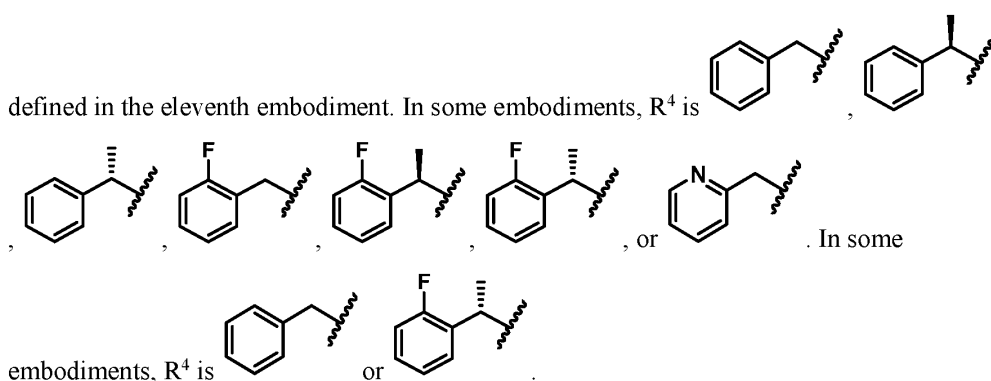
or a pharmaceutically acceptable salt thereof, and the variables are as defined in the eleventh embodiment.

In a thirteenth embodiment, the RAD51 inhibitor is a compound represented by Structural Formula **II'-2**:



or a pharmaceutically acceptable salt thereof, and the variables are as defined in the eleventh embodiment.

In a fourteenth embodiment, the RAD51 inhibitor is a compound according to Structural Formula **II'**, **II'-1** or **II'-2**, or a pharmaceutically acceptable salt thereof, wherein R^4 is isopropyl, oxetanyl, cyclobutyl, $-\text{CH}_2$ -2-pyrrolidinyl, $-\text{CH}_2$ -*N*-methyl-2-pyrrolidinyl, $-\text{CH}_2$ -3-piperidinyl, $-\text{CH}_2$ -2-pyrazinyl, $-\text{CH}_2$ -2-pyrimidinyl, $-\text{CH}(\text{R}^c)$ -phenyl, or $-\text{CH}(\text{R}^c)$ -2-pyridinyl, and that the phenyl and 2-pyridinyl rings are each independently and optionally substituted with one or more occurrences of halogen, and the remaining variables are as

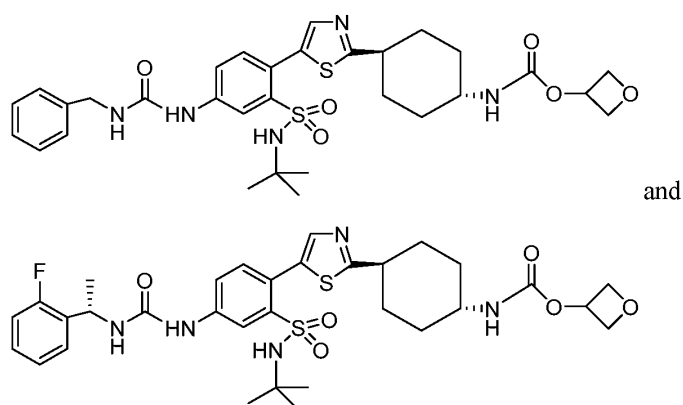


In a fifteenth embodiment, the RAD51 inhibitor is a compound according to Structural Formula **II'**, **II'-1** or **II'-2**, or a pharmaceutically acceptable salt thereof, wherein

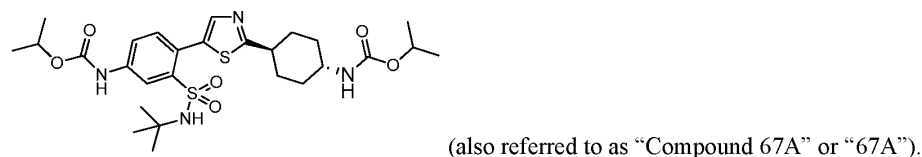
X⁴ is NH, and the remaining variables are as defined in the eleventh and/or fourteenth embodiments.

In a sixteenth embodiment, the RAD51 inhibitor is a compound according to Structural Formula II', II'-1 or II'-2, or a pharmaceutically acceptable salt thereof, wherein R¹ is *tert*-butyl, and the remaining variables are as defined in the eleventh, fourteenth, and fifteenth embodiments.

In a seventeenth embodiment, the RAD51 inhibitor is a compound selected from the group consisting of:



In an eighteenth embodiment, the RAD51 inhibitor is a compound of:



Also included are the compounds disclosed in the Exemplification, both in the pharmaceutically acceptable salt form and in the neutral form.

The term "pharmaceutically acceptable salt" refers to a pharmaceutical salt that is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, and allergic response, and is commensurate with a reasonable benefit/risk ratio. Pharmaceutically-acceptable salts are well known in the art. For example, S. M. Berge *et al.* describes pharmacologically acceptable salts in *J. Pharm. Sci.*, 1977, 66, 1-19.

Included in the present teachings are pharmaceutically acceptable salts of the compounds disclosed herein. Compounds having basic groups can form pharmaceutically acceptable salts with pharmaceutically acceptable acid(s). Suitable pharmaceutically

acceptable acid addition salts of the compounds described herein include salts of inorganic acids (such as hydrochloric acid, hydrobromic, phosphoric, metaphosphoric, nitric, and sulfuric acids) and of organic acids (such as acetic acid, benzenesulfonic, benzoic, ethanesulfonic, methanesulfonic, succinic, and trifluoroacetic acid acids). Compounds of the present teachings with acidic groups such as carboxylic acids can form pharmaceutically acceptable salts with pharmaceutically acceptable base(s). Suitable pharmaceutically acceptable basic salts include ammonium salts, alkali metal salts (such as sodium and potassium salts) and alkaline earth metal salts (such as magnesium and calcium salts).

Definitions

The term “halo” as used herein means halogen and includes fluoro, chloro, bromo and iodo.

The term “alkyl” used alone or as part of a larger moiety, such as “alkoxy” or “haloalkyl” and the like, means saturated aliphatic straight-chain or branched monovalent hydrocarbon radical. Unless otherwise specified, an alkyl group typically has 1-5 carbon atoms, *i.e.* (C₁-C₅)alkyl. As used herein, a “(C₁-C₅)alkyl” group means a radical having from 1 to 5 carbon atoms in a linear or branched arrangement. Examples include methyl, ethyl, *n*-propyl, *iso*-propyl, and the like.

The term “alkoxy” means an alkyl radical attached through an oxygen linking atom, represented by -O-alkyl. For example, “(C₁-C₄)alkoxy” includes methoxy, ethoxy, propoxy, and butoxy.

The terms “haloalkyl” and “haloalkoxy” means alkyl or alkoxy, as the case may be, substituted with one or more halogen atoms.

An “alkylene group” is a saturated aliphatic branched or straight-chain divalent hydrocarbon radical. Unless otherwise specified, an alkylene group typically has 2-6 carbon atoms, *e.g.* (C₂-C₆)alkylene.

The term “alkenyl” means branched or straight-chain monovalent hydrocarbon radical containing at least one double bond. Alkenyl may be mono or polyunsaturated, and may exist in the E or Z configuration. Unless otherwise specified, an alkenyl group typically has 2-6 carbon atoms, *i.e.*, (C₂-C₆)alkenyl. For example, “(C₂-C₄) alkenyl” means a radical having from 2-4 carbon atoms in a linear or branched arrangement.

The term “cycloalkyl” means a monocyclic saturated hydrocarbon ring system. For example, a C₃-C₆ cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Unless otherwise described, a “cycloalkyl” has from three to seven ring carbon atoms.

A bridged cycloalkyl means a bicyclic non-aromatic hydrocarbon ring system in which the two rings share at least three adjacent ring carbon atoms. A bridged cycloalkyl typically has 6-12 ring carbon atoms. Examples include, but are not limited to, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[4.3.1]decyl, bicyclo[3.3.1]nonyl, bornyl, bornenyl, norbornyl, norbornenyl, 6,6-dimethylbicyclo[3.1.1]heptyl, tricyclobutyl, and adamantyl.

The terms “heterocyclyl”, “heterocyclic ring”, and “heterocyclic group”, are used interchangeably herein, and means a saturated or unsaturated non-aromatic 4-10 membered ring radical containing from 1 to 4 ring heteroatoms, which may be the same or different, selected from N, O, or S. It can be monocyclic, bicyclic or tricyclic (*e.g.*, a fused or bridged bicyclic or tricyclic ring). Examples of include, but are not limited to, azetidiny, morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, dihydroimidazole, dihydrofuranyl, dihydropyranyl, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyranyl, tetrahydroimidazole, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, and tetrahydrothiopyranyl. A heterocyclic ring optionally contains one or more double bonds and/or is optionally fused with one or more aromatic rings (for example, tetrahydronaphthyridine, indolinone, dihydropyrrolotriazole, imidazopyrimidine, quinolinone, dioxaspirodecane).

Examples of 3–7 membered monocyclic heterocyclic ring include, but are not limited to, azetidiny, morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, dihydroimidazole, dihydrofuranyl, dihydropyranyl, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyranyl, tetrahydroimidazole, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, and tetrahydrothiopyranyl.

A bridged heterocyclyl means a bicyclic non-aromatic ring system containing from 1 to 4 ring heteroatoms in which the two rings share at least three adjacent ring atoms. A bridged heterocyclyl typically has 6-12 ring atoms. Examples include, but are not limited to,

azanorbornyl, quinuclidinyl, isoquinuclidinyl, tropanyl, azabicyclo[3.2.1]octanyl, azabicyclo[2.2.1]heptanyl, 2-azabicyclo[3.2.1]octanyl, azabicyclo[3.2.1]octanyl, azabicyclo[3.2.2]nonanyl, azabicyclo[3.3.0]nonanyl, and azabicyclo[3.3.1]nonanyl.

The terms “heteroaryl”, “heteroaromatic”, “heteroaryl ring”, “heteroaryl group”, “heteroaromatic ring”, and “heteroaromatic group”, are used interchangeably herein. “Heteroaryl” when used alone or as part of a larger moiety as in “heteroaralkyl” or “heteroarylalkoxy”, refers to aromatic ring groups having five to ten ring atoms selected from carbon and at least one (typically 1 to 4, more typically 1 or 2) heteroatoms (*e.g.*, oxygen, nitrogen or sulfur). “Heteroaryl” includes monocyclic rings and polycyclic rings in which a monocyclic heteroaromatic ring is fused to one or more other aromatic or heteroaromatic rings. “Heteroaryl” includes monocyclic and bicyclic ring systems.

“Monocyclic 5–6 membered heteroaromatic ring (or heteroaryl)” means a monocyclic heteroaromatic ring having five or six ring atoms selected from carbon and at least one (typically 1 to 3, more typically 1 or 2) heteroatoms (*e.g.*, oxygen, nitrogen or sulfur). Examples of monocyclic 5-6 membered heteroaromatic ring groups include furanyl (*e.g.*, 2-furanyl, 3-furanyl), imidazolyl (*e.g.*, N-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), isoxazolyl (*e.g.*, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), oxadiazolyl (*e.g.*, 2-oxadiazolyl, 5-oxadiazolyl), oxazolyl (*e.g.*, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), pyrazolyl (*e.g.*, 3-pyrazolyl, 4-pyrazolyl), pyrrolyl (*e.g.*, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), pyridyl (*e.g.*, 2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (*e.g.*, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl), pyridazinyl (*e.g.*, 3-pyridazinyl), thiazolyl (*e.g.*, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), isothiazolyl, triazolyl (*e.g.*, 2-triazolyl, 5-triazolyl), tetrazolyl (*e.g.*, tetrazolyl), and thienyl (*e.g.*, 2-thienyl, 3-thienyl).

If a group is described as being “substituted,” a non-hydrogen substituent replaces a hydrogen on a carbon or nitrogen of the substituent. Thus, for example, a substituted alkyl is an alkyl wherein at least one non-hydrogen substituent is in the place of a hydrogen substituent on the alkyl substituent. To illustrate, monofluoroalkyl is alkyl substituted with a fluoro substituent, and difluoroalkyl is alkyl substituted with two fluoro substituents. It should be recognized that if there is more than one substitution on a substituent, each non-hydrogen substituent can be identical or different (unless otherwise stated). As used herein, many moieties (*e.g.*, alkyl, cycloalkyl, or a heterocyclic ring) are referred to as being either “substituted” or “optionally substituted”. When a moiety is modified by one of these terms, unless otherwise noted, it denotes that any portion of the moiety that is known to one skilled

in the art as being available for substitution can be substituted, which includes one or more substituents. If more than one substituent is present, then each substituent is independently selected. Such means for substitution are well-known in the art and/or taught by the instant disclosure. The optional substituents can be any substituents that are suitable to attach to the moiety. A person of ordinary skill in the art will recognize that the compounds and definitions provided do not include impermissible substituent patterns (*e.g.*, methyl substituted with 5 different groups, and the like). Such impermissible substitution patterns are clearly recognized by a person of ordinary skill in the art. When a group is described as being optionally substituted by “one or more” substituents, it denotes that the group is optionally substituted by one, two, three, four, five or six substituents. In one embodiment, a group is optionally substituted by 1-3 substituents. In one embodiment, a group is optionally substituted by 1-2 substituents. In one embodiment, a group is optionally substituted by one substituent.

Suitable substituents are those which do not have a significant adverse effect on the ability of the compound to inhibit RAD51. Where suitable substituents are not specifically enumerated, exemplary substituents include, but are not limited to, halo, -CN, alkyl, alkoxy, halomethyl, halomethoxy, (C₁-C₅)alkyl, halo(C₁-C₅)alkyl, (C₁-C₅)alkoxy, -NO₂, -OR^c, -NR^aR^b, -S(O)_iR^a, -NR^aS(O)_iR^b, -S(O)_iNR^aR^b, -C(=O)OR^a, -OC(=O)OR^a, -C(=S)OR^a, -O(C=S)R^a, -C(=O)NR^aR^b, -NR^aC(=O)R^b, -C(=S)NR^aR^b, -NR^aC(=S)R^b, -NR^a(C=O)OR^b, -O(C=O)NR^aR^b, -NR^a(C=S)OR^b, -O(C=S)NR^aR^b, -NR^a(C=O)NR^aR^b, -NR^a(C=S)NR^aR^b, -C(=S)R^a, -C(=O)R^a, (C₃-C₆)cycloalkyl, monocyclic heteroaryl and phenyl, wherein the (C₃-C₆)cycloalkyl, monocyclic heteroaryl and phenyl substituents are optionally and independently substituted with -CH₃, halomethyl, halo, methoxy or halomethoxy. Each R^a and each R^b are independently selected from -H and (C₁-C₅)alkyl, wherein the (C₁-C₅)alkyl group represented by R^a or R^b is optionally substituted with hydroxyl or (C₁-C₃)alkoxy; R^c is -H, halo(C₁-C₅)alkyl or (C₁-C₅)alkyl, wherein the (C₁-C₅)alkyl group represented by R^c is optionally substituted with hydroxyl or (C₁-C₃)alkoxy; and i is 0, 1, or 2. =O is also a suitable substituent for alkyl, cycloalkyl, and a heterocyclic ring.

Compounds having one or more chiral centers can exist in various stereoisomeric forms. Stereoisomers are compounds that differ only in their spatial arrangement. Stereoisomers include all diastereomeric, enantiomeric, and epimeric forms as well as racemates and mixtures thereof.

The term “geometric isomer” refers to cyclic compounds having at least two substituents, wherein the two substituents are both on the same side of the ring (*cis*) or wherein the substituents are each on opposite sides of the ring (*trans*). When a disclosed compound is named or depicted by structure without indicating stereochemistry, it is understood that the name or the structure encompasses one or more of the possible stereoisomers, or geometric isomers, or a mixture of the encompassed stereoisomers or geometric isomers.

When a geometric isomer is depicted by name or structure, it is to be understood that the named or depicted isomer exists to a greater degree than another isomer, that is that the geometric isomeric purity of the named or depicted geometric isomer is greater than 50%, such as at least 60%, 70%, 80%, 90%, 99%, or 99.9% pure by weight. Geometric isomeric purity is determined by dividing the weight of the named or depicted geometric isomer in the mixture by the total weight of all of the geometric isomers in the mixture.

Racemic mixture means 50% of one enantiomer and 50% of its corresponding enantiomer. When a compound with one chiral center is named or depicted without indicating the stereochemistry of the chiral center, it is understood that the name or structure encompasses both possible enantiomeric forms (*e.g.*, both enantiomerically-pure, enantiomerically-enriched or racemic) of the compound. When a compound with two or more chiral centers is named or depicted without indicating the stereochemistry of the chiral centers, it is understood that the name or structure encompasses all possible diastereomeric forms (*e.g.*, diastereomerically pure, diastereomerically enriched and equimolar mixtures of one or more diastereomers (*e.g.*, racemic mixtures) of the compound.

Enantiomeric and diastereomeric mixtures can be resolved into their component enantiomers or stereoisomers by well-known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Enantiomers and diastereomers also can be obtained from diastereomerically- or enantiomerically-pure intermediates, reagents, and catalysts by well-known asymmetric synthetic methods.

When a compound is designated by a name or structure that indicates a single enantiomer, unless indicated otherwise, the compound is at least 60%, 70%, 80%, 90%, 99% or 99.9% optically pure (also referred to as “enantiomerically pure”). Optical purity is the

weight in the mixture of the named or depicted enantiomer divided by the total weight in the mixture of both enantiomers.

When the stereochemistry of a disclosed compound is named or depicted by structure, and the named or depicted structure encompasses more than one stereoisomer (*e.g.*, as in a diastereomeric pair), it is to be understood that one of the encompassed stereoisomers or any mixture of the encompassed stereoisomers is included. It is to be further understood that the stereoisomeric purity of the named or depicted stereoisomers is at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight. The stereoisomeric purity in this case is determined by dividing the total weight in the mixture of the stereoisomers encompassed by the name or structure by the total weight in the mixture of all of the stereoisomers.

Pharmaceutical Compositions

The compounds disclosed therein are RAD51 inhibitors. The pharmaceutical composition of the present disclosure comprises one or more RAD51 inhibitors, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

“Pharmaceutically acceptable carrier” and “pharmaceutically acceptable diluent” refer to a substance that aids the formulation and/or administration of an active agent to and/or absorption by a subject and can be included in the compositions of the present disclosure without causing a significant adverse toxicological effect on the subject. Non-limiting examples of pharmaceutically acceptable carriers and/or diluents include water, NaCl, normal saline solutions, lactated Ringer’s, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer’s solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrrolidone, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with or interfere with the activity of the compounds provided herein. One of ordinary skill in the art will recognize that other pharmaceutical excipients are suitable for use with disclosed compounds.

The pharmaceutical compositions of the present teachings optionally include one or more pharmaceutically acceptable carriers and/or diluents therefor, such as lactose, starch, cellulose and dextrose. Other excipients, such as flavoring agents; sweeteners; and preservatives, such as methyl, ethyl, propyl and butyl parabens, can also be included. More

complete listings of suitable excipients can be found in the Handbook of Pharmaceutical Excipients (5th Ed., Pharmaceutical Press (2005)). A person skilled in the art would know how to prepare formulations suitable for various types of administration routes. Conventional procedures and ingredients for the selection and preparation of suitable formulations are described, for example, in Remington's Pharmaceutical Sciences (2003 - 20th edition) and in The United States Pharmacopeia: The National Formulary (USP 24 NF19) published in 1999. The carriers, diluents and/or excipients are "acceptable" in the sense of being compatible with the other ingredients of the pharmaceutical composition and not deleterious to the recipient thereof.

The term "dosage holiday", also referred to as "drug holiday," refers to a period of time wherein the subject is not administered or administered at a lower dosage the therapeutic (*i.e.*, RAD51 inhibitor). The timing of a dosage holiday depends on the timing of the regular dosing regimen and the purpose for taking the dosage holiday (*e.g.*, to regain drug sensitivity and/or to reduce unwanted side effects of continuous, long- term administration). In some embodiments, the dosage holiday may be a reduction in the dosage of the drug (*e.g.*, to below the therapeutically effective amount for a certain interval of time). In other embodiments, administration of the dosage is stopped for a certain interval of time before administration is started again at the same or different dosing regimen (*e.g.*, at a lower or higher dose and/or frequency of administration). A dosage holiday of the disclosure may thus be selected from a wide range of time-periods and dosage regimens.

Additional Aspects of Methods of Treatment

In some embodiments, the subject can be a subject determined to have an increased level of DNA damage occurring in one or more cell types relative to a reference level. As used herein, "DNA damage" refers to breaks, nicks, and mutations of the DNA present in a cell. In some embodiments, the DNA damage can comprise one or more of single-strand breaks (*e.g.*, "nicks"), double strand breaks (DSBs), and mutations. In some embodiments, the DNA damage can be one or more DSBs. As used herein, "mutation" refers to a change or difference in the genetic material of a cell as compared to a reference wildtype cell, *e.g.* a deletion, an insertion, a SNP, a gene rearrangement, and/or the introduction of an exogenous gene or sequence.

In some embodiments, the subject can be determined to have an increased level of DNA damage if the subject is determined to have an increased level and/or activity of a DNA

damage process or DNA editing enzyme. As used herein, "DNA damage process" refers to any activity or process in a cell which causes one or more types of DNA damage to occur.

In some embodiments, an increased level of DNA damage can be an increased level of mutations, *e.g.*, by determining the overall mutation status in all or a portion of the genome of a cell. An overall mutation status at least 2% greater, *e.g.* 2% greater or more, 3% greater or more, 5% greater or more, 10% greater or more, or 20% greater or more than the overall mutation status in a reference cell can be indicative of an increased, elevated, and/or significant level of a DNA editing enzyme activity. In some embodiments, the level of hyper mutations can be determined. In some embodiments, the overall mutation status in the whole genome or a portion thereof can be determined using FISH, whole genome sequencing, high throughput sequencing, exome sequencing, hybridization, and/or PCR. In some embodiments the activity of a DNA editing enzyme can be measured by determining the level of hypermutations in the specific target genes including, but not limited to IGH, BCL6, MYC, BCL1 1A, CD93, PIM1 and/or PAX5. In some embodiments the DNA editing enzyme is AID. In some embodiments, a level of mutation in specific target genes including IGH, BCL6, MYC, BCL1 1A, CD93, PIM1 and/or PAX5 which is at least 2% greater, *e.g.* 2% greater or more, 3% greater or more, 5% greater or more, 10% greater or more, or 20% greater or more than the level of mutation in IGH, BCL6, MYC, BCL1 1A, CD93, PIM1 and/or PAX5 in a reference cell can be indicative of an increased, elevated, and/or significant level of AID activity.

In some embodiments, an increased level of DNA damage can be an increased level of double strand breaks (DSBs). The level of DSBs can be determined, by way of non-limiting example, by karyotyping, by γ -H2AX foci formation, and/or by using FISH analysis to detect DNA double strand breaks, *e.g.* DNA breakage detection fish (DBD-FISH) (Volpi and Bridger, BioTechniques, Vol. 45, No. 4, October 2008, pp. 385-409).

In some embodiments, an increased level of DNA damage can be an increased level of single strand breaks. The level of single-strand breaks in DNA can be determined, by way of non-limiting example, by COMET assays, FISH, or the use of single-strand break-specific probes. Detection of DNA breaks, both single and double -stranded is known in the art and described further, at, *e.g.*, Kumari et al. EXCLI Journal 2009 7:44-62 and Motalleb et al. Research Journal of Applied Sciences, Engineering and Technology. 2012 4: 1888-1894; each of which is incorporated by reference herein in its entirety.

In some embodiments, an increased level of activity of a DNA damage process can comprise an increased level and/or activity of a DNA editing enzyme. In some embodiments, the technology described herein is directed to treating cells having an active DNA editing enzyme with a compound of the present disclosure. In some embodiments, the technology described herein is directed to treating cells having an increased level and/or activity of a DNA editing enzyme with a compound of the present disclosure. As used herein, "DNA editing enzyme" refers to an enzyme which normally catalyzes the mutation, exchange or excision of DNA segments, particularly enzymes which can generate or promote the generation of point mutations, DNA single strand breaks, DNA double-strand breaks or protein-DNA adducts. A DNA editing enzyme, as referred to herein, is not necessarily site-specific in its action. Similarly, it is not necessarily cell specific. In some embodiments, the cell is a B cell expressing a detectable amount of such an enzyme.

Non-limiting examples of DNA editing enzymes include, but are not limited to Recombination Activating Gene 1 (RAG1; NCBI Gene ID: 5896), Recombination Activating Gene 2 (RAG2; NCBI Gene ID: 5897), Sporulation-specific protein 11 (SPO1 1; NCBI Gene ID: 23626), APOBEC family members a Type 1 Topoisomerase; a Type 2 Topoisomerase; and/or AID. In some embodiments, the DNA editing enzyme can be AID.

In some embodiments, the DNA editing enzyme can be a member of the APOBEC (apolipoprotein B mRNA editing enzyme, catalytic polypeptide -like) family. As used herein "APOBEC family" refers to a family of cytidine deaminase enzymes having an N-terminal zinc-dependent cytidine deaminase catalytic domain comprising and a C-terminal pseudocatalytic domain. Non-limiting examples of APOBEC family members include AID, APOBEC 1 (*e.g.*, NCBI Gene ID: 339), APOBEC2 (*e.g.*, NCBI Gene ID: 10930), APOBEC3A (*e.g.*, NCBI Gene ID: 200315), APOBEC3B (*e.g.*, NCBI Gene ID: 9582), APOBEC3C (*e.g.*, NCBI Gene ID: 27350), APOBEC3D (*e.g.*, NCBI Gene ID: 140564), APOBEC3E (*e.g.*, NCBI Gene ID: 140564), APOBEC3F (*e.g.*, NCBI Gene ID: 200316), APOBEC3G (*e.g.*, NCBI Gene ID: 60489), APOBEC3H (*e.g.*, NCBI Gene ID: 164668), and APOBEC4 (*e.g.*, NCBI Gene ID: 403314).

In some embodiments, the DNA editing enzyme can be a Type 1 topoisomerase. In some embodiments, the DNA editing enzyme can be a Type 2 topoisomerase. Topoisomerases generate breaks in DNA to help uncoil or relax the strand. Type II topoisomerases hydrolyze ATP to generate DSB cuts, while Type I topoisomerases generate single-stranded breaks. Non-limiting examples of Type II topoisomerases can include

topoisomerase II (*e.g.*, NCBI Gene ID: 7153 and 7155). Non-limiting examples of Type I topoisomerases can include topoisomerase I (*e.g.*, NCBI Gene ID: 7150).

Embodiments of the technology described herein are based on the discovery that the compounds described herein can inhibit DNA repair mechanisms, *e.g.*, homologous repair. Activation-induced cytidine deaminase (AID, or AICDA, also known as ARP2, CDA2 or HIGM2), a DNA-editing enzyme that is a member of the apolipoprotein B mRNA editing enzymes, catalytic polypeptide-like (APOBEC), will cause widespread genomic breaks and cell death in cells with diminished homologous recombination ability (*e.g.* cells with diminished DNA double strand break repair abilities). Accordingly, provided herein is a method of causing cell death comprising detecting increased expression of a DNA-editing enzyme (*e.g.* AID) in a cell and thereafter contacting the cell with a compound of the present disclosure; thereby resulting in cell death. Accordingly, provided herein is a method of causing cell death comprising increasing expression of a DNA-editing enzyme (*e.g.* AID) in a cell and thereafter contacting the cell with a compound of the present disclosure; thereby resulting in cell death. Accordingly, provided herein is a method of causing cell death comprising administering to a cell a therapeutically effective amount of a DNA editing enzyme (*e.g.* AID) and thereafter contacting the cell with a compound of the present disclosure; thereby resulting in cell death.

AID, encoded by the AICDA gene (NCBI Gene ID: 57379), is required for proper B-cell function and is most prominently expressed in centroblast B-cells. The protein is involved in somatic hypermutation, gene conversion, and class-switch recombination of immunoglobulin genes. AID is normally expressed almost exclusively in antigen-activated germinal center B-cells, where it initiates immunoglobulin isotype class switching (Manis et al. 2002, Trends Immunol, 23, 31-39; Chaudhuri and Alt, Nat Rev Immunol, 2004, 4, 541-552; Longerich et al., Curr Opin Immunol, 2006, 18, 164-174; Chaudhuri et al., Adv Immunol 2007, 94, 157-214). AID is required for somatic hypermutation and immunoglobulin class switching in activated B cells. AID expression is regulated by CD40 ligand, B-cell receptor, IL4R, or Toll-like receptor stimulation (Crouch et al., J Exp Med 2007 204: 1145-1156; Muramatsu et al., J Biol Chem 1999 274: 18470-6). After activation, AID is transiently upregulated, induces point mutations or DNA double strand breaks in a sequence nonspecific manner within immunoglobulin genes, and is then downregulated (Longerich et al., Curr Opin Immunol, 2006, 18, 164-176; Chaudhuri et al., Adv Immunol 2007, 94, 157-214). Overall, AID is active in only a tiny population of normal cells (antigen-

activated B-cells) at any given time. The genomic rearrangements and mutations controlled by AID lead to the development of antigen-recognition diversity, receptor editing and lymphoid effector function required for functional adaptive immunity (Mills, et al. *Immunol Rev* 2003 194:77-95). Recently it has been reported that AID has off-target point mutation activities (Liu, M. et al., *Nature* 2008, 451, 841-845; Liu and Schatz, *Trends Immunol.* 2009, 30, 173-181; Perez-Duran et al., *Carcinogenesis*. 2007, 28(12):2427-33). Robbiani et al. has reported off-target activities of AID in B- cells, especially c-myc/IgH translocations (Robbiani et al., *Mol Cell* 2009, 36(4):631-41). AID expression accelerates the rate of tumor development in Bcl6 transgenic mice (Pasqualucci et al., 2008, *Nat. Genet.* 40, 108-112). However, deregulated AID does not necessarily cause malignancy or translocation-associated cancer on its own in B cells (Muto et al., 2006, *Proc. Natl. Acad. Sci. USA* 103, 2752-2757; Okazaki et al., 2003, *J. Exp. Med.* 197, 1173-1181; Shen et al., 2008, *Mol. Immunol.* 45, 1883-1892). In addition, despite its obligate role in c-myc/IgH translocation, AID is not required for the development of plasmacytosis or plasmacytoma in IL-6 transgenic or pristane-treated mice, respectively (Kovalchuk et al., 2007, *J. Exp. Med.* 204, 2989-3001; Ramiro et al., 2004, *J. Exp. Med.* 200, 1103-1110). However, most human B cell lymphoma-associated translocations do not involve c-myc, and many do not involve Ig genes (Kuppers, 2005, *Oncogene* 20, 5580-5594).

Overexpression of AID has been reported in chronic lymphocytic leukemia (CLL) (Hancer et al. *Leuk Lymphoma*. 2011 Jan;52(1):79-84; Heintel et al., *Leukemia*. 2004 Apr; 18(4):756-62). Further, AID expression has been shown to be correlated with blast crisis B lineage leukemia and therapy resistance in myeloid leukemia and to be associated with generally poor prognosis in chronic B lymphocytic leukemia (Mao et al., *Br J Dermatol* 2001, 145: 117-122; Chaudhuri et al., *Nature* 2004, 430:992-8). Further expression of AID in tumor cells from a variety of cancers has been reported including but not limited to lung, breast, gastric, colon, intestinal, liver cancer and choriangiocarcinoma (Greeve et al., *Blood* 2003, 101, 3574-3580; Feldhahn et al., *J Exp Med* 2007, 204, 1157-1166; Kotani et al., *PNAS USA* 2007, 104, 1616-1620; Engels et al., 2008, *Appl Immunohistochem Mol Morphol* 16, 521-529; Klemm et al., 2009, *Cancer Cell* 6, 232-245; Palacios et al., 2010, *Blood* 115(22), 4488-4496; Leuenberger et al., 2009, *Mod Pathol* 32, 177-186; Gruber et al., 2010, *Cancer Res* 70, 7411-7420; inflammatory cancer (Marusawa 2008, *Int J Biochem Cell Biol.* 40, 399-402); follicular lymphoma (Hardianti et al., 2004, *Leukemia* 18, 826-831; Shikata et al., 2012, *Cancer Sci.* 103(3):415-21); thyroid cancer (Qiu et al. 2012, *Mod Pathol* 25(1),36-45);

breast cancer (Borchert et al. 2011, BMC Cancer 11:347); Marusawa, et al., 2011, Adv Immunol 111 : 109-41; Zhang et al. 2012, Hum Pathol 43(3):423-34; Komori et al., 2008, Hepatology 47(3):888-896; Hockley 2010, Leukemia 24(5): 1084-6; adult T-cell leukemia (Nakamura et al., 2011, Br J Dermatol. 165(2):437-9). All of the references in the foregoing paragraph are incorporated by reference herein in their entireties.

Elevated levels of AID have been reported in arthritis (Xu et al. Scand. J. Immunol. 2009, 296, 2033-6) and in the MRL/Fas(lpr/lpr) mouse lupus model (White et al. 2011, Autoimmunity 44(8), 585-98). All of the references in the foregoing paragraph are incorporated by reference herein in their entireties.

When DSB repair is inhibited, the extent of the DSBs generated by AID is much higher than previously suspected and the extent of genomic damage is so severe as to result in cell death. Accordingly, in one embodiment of the technology described herein, there is provided a method of treatment comprising: (a) selecting a subject having cells that express elevated levels of activation-induced cytidine deaminase (AID); and (b) administering a therapeutically effective amount of an inhibitor of double strand break repair (*e.g.* a compound of the present disclosure) to the subject; wherein an elevated level of AID is a level of AID that is higher than the level of AID in cells of the same type from a healthy individual. In some embodiments, the cells expressing elevated levels of AID are B cells. In some embodiments, the B cell expressing elevated levels of AID is a cancerous B cells or a B cell associated with autoimmune disease. In some embodiments, the subject can be a human subject.

Methods provided herein treat cancers and/or autoimmune disorders by inhibiting DNA double strand break repair. Methods provided herein treat pancreatic cancer by inhibiting DNA double strand break repair. This inhibition proves lethal to cells expressing AID, as AID generates widespread genomic breaks, and the treatment with a double strand break repair inhibitor prevents the repair of these lesions which are being generated by the cell itself. This results in cell death in the subject which is specific to the cells expressing AID, *e.g.* cancerous B cells and/or autoimmune cells. Accordingly, as described herein, in one embodiment there is provided a treatment paradigm that selectively induces self-destruction of certain diseased cells, while reducing the unintended side effects in healthy tissues.

In some embodiments, an increased level and/or activity of a DNA editing enzyme can be an increased level of DNA editing enzyme mRNA. mRNA levels can be assessed

using, *e.g.*, biochemical and molecular biology techniques such as Northern blotting or other hybridization assays, nuclease protection assay, reverse transcription (quantitative RT-PCR) techniques, RNA-Seq, high throughput sequencing and the like. Such assays are well known to those in the art. In one embodiment, nuclear "run-on" (or "run-off") transcription assays are used (see *e.g.* Methods in Molecular Biology, Volume: 49, Sep-27-1995, Page Range: 229-238). Arrays can also be used; arrays, and methods of analyzing mRNA using such arrays have been described previously, *e.g.* in EP0834575, EP0834576, W096/31622, U.S. Pat. No. 5,837,832 or WO98/30883. WO97/10365 provides methods for monitoring of expression levels of a multiplicity of genes using high density oligonucleotide arrays.

In some embodiments, a subject can be determined to have an increased level of DNA damage occurring in one or more cell types relative to a reference level if the subject has been exposed to an agent that is known to cause such DNA damage. Non-limiting examples of such agents can include a viral infection with a DNA integrating virus (*e.g.* adeno-associated virus, retrovirus, human T-lymphotropic virus, HIV-1, oncovirus, hepatitis virus, hepatitis B virus); DNA damaging chemicals (*e.g.* acetaldehyde, polycyclic aromatic hydrocarbons, benzenes, nitrosamines, tobacco smoke, aflatoxin, and the like); DNA damaging chemotherapeutic agents (*e.g.* bleomycin, mitomycin, nitrogen mustards (*e.g.* mechlorethamine, cyclophosphamide, melphalan, chlorambucil, ifosfamide and busulfan), nitrosoureas (*e.g.*, N-Nitroso-N-methylurea (MNU), carmustine (BCNU), lomustine (CCNU) and semustine (MeCCNU), fotemustine and streptozotocin), tetrazines (*e.g.*, dacarbazine, mitozolomide and temozolomide), aziridines (*e.g.*, thiotepa, mitomycin and diaziquone (AZQ)), cisplatins (*e.g.*, cisplatin, carboplatin and oxaliplatin) procarbazine and hexamethylmelamine); and ionizing or ultraviolet radiation. Exposure to such agents can be the result of an accident, infection and/or environmental exposure or the result of a therapeutic administration of such agents.

In some embodiments, the increased level of DNA damage can be occurring in a cell type affected by the cancer, autoimmune disease, and/or neurodegenerative disease. In some embodiments, the subject is determined to have an increased level of DNA damage occurring in a cell selected from the group consisting of: a cancer cell (*e.g.*, pancreatic cancer cell); an immune system cell; or a nervous system cell.

In some embodiments, the DNA editing enzyme can be AID. In some embodiments, the level of AID can be the level of AID in a blood cell. In some embodiments, the level of AID can be the level of AID in a B cell.

In some embodiments, an increased level of AID can be a detectable level of AID, *e.g.*, as described below herein.

In some embodiments, the subject can be a human subject.

Methods provided herein treat cancers and/or autoimmune disorders by inhibiting DNA double strand break repair. Methods provided herein treat a pancreatic cancer by inhibiting DNA double strand break repair. This inhibition proves lethal to cells expressing AID, as AID generates widespread genomic breaks, and the treatment with a double strand break repair inhibitor prevents the repair of these lesions which are being generated by the cell itself. This results in cell death in the subject which is specific to the cells expressing AID, *e.g.* cancerous B cells and/or autoimmune cells. Accordingly, as described herein, in one embodiment there is provided a treatment paradigm that selectively induces self-destruction of certain diseased cells, while reducing the unintended side effects in healthy tissues.

Methods of detecting cancers in patients with increased levels of DNA damage or increased levels of DNA editing enzymes are disclosed in WO2016/094897, incorporated herein by reference.

In some embodiments, the cancer to be treated is a type with high expression of a DNA editing enzyme. In some embodiments, the cancer to be treated is a B-cell neoplasm.

Another embodiment is a method of treating a cancer by administering to the subject an effective amount of one or more disclosed compounds, or a pharmaceutically acceptable salt thereof, or the corresponding pharmaceutical composition. In one aspect, the cancer is selected from the group consisting of lymphoma, leukemia, and a plasma cell neoplasm. In another aspect, the cancer selected from the group consisting of carcinoma and sarcoma.

In some embodiments, the cancer to be treated is pancreatic cancer.

In some embodiments, the pancreatic cancer is exocrine pancreatic cancer. In some embodiments, the exocrine pancreatic cancer is adenocarcinoma. In some embodiments, the exocrine pancreatic cancer is squamous cell carcinoma. In some embodiments, the exocrine pancreatic cancer is adenosquamous carcinoma. In some embodiments, the exocrine pancreatic cancer is colloid carcinoma.

In some embodiments, the pancreatic cancer is neuroendocrine pancreatic cancer. In some embodiments, the neuroendocrine pancreatic cancer is a nonfunctioning neuroendocrine tumor. In some embodiments, the neuroendocrine pancreatic cancer is gastrinoma. In some

embodiments, the neuroendocrine pancreatic cancer is insulinoma. In some embodiments, the neuroendocrine pancreatic cancer is glucagonoma.

In some embodiments, the neuroendocrine pancreatic cancer is a VIPoma (i.e., an islet cell tumor which affects the vasoactive intestinal peptides). In some embodiments, the neuroendocrine pancreatic cancer is a somatostatinoma (i.e., an islet cell tumor which affects the somatostatin).

In some embodiments, the pancreatic cancer is benign precancerous lesions.

In some embodiments, the cancer to be treated is a lymphoma. Lymphomas which can be treated by the disclosed methods include Non-Hodgkin's lymphoma; Burkitt's lymphoma; small lymphocytic lymphoma; lymphoplasmacytic lymphoma; MALT lymphoma; follicular lymphoma; diffuse large B-cell lymphoma; and T-cell lymphoma.

Lymphoma is a malignancy in the lymphatic cells of the immune system (*e.g.* B cells, T cells, or natural killer (NK) cells). Lymphomas often originate in the lymph nodes and present as solid tumors. They can metastasize to other organs such as the brain, bone, or skin. Extranodal sites are often located in the abdomen. Lymphomas are closely related to the lymphoid leukemia and in some cases a particular form of cancer is categorized as both a lymphoma and a leukemia.

Leukemias which can be treated by the disclosed methods include acute lymphoblastic leukemia (ALL); Burkitt's leukemia; B-cell leukemia; B-cell acute lymphoblastic leukemia; chronic lymphocytic leukemia (CLL); acute myelogenous leukemia (AML); chronic myelogenous leukemia (CML); and T-cell acute lymphoblastic leukemia (T-ALL).

In some embodiments the cancer to be treated is B-cell neoplasms, B-cell leukemia, B-cell acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, Burkitt's leukemia, acute myelogenous leukemia and/or T-ALL. The maturation of B cells most typically ceases or substantially decreases when the foreign antigen has been neutralized. Occasionally, however, proliferation of a particular B cell will continue unabated; such proliferation can result in a cancer referred to as "B-cell lymphoma" or a "B-cell leukemia." In some embodiments the cancer to be treated is chronic lymphocytic leukemia (CLL) or chronic myelogenous leukemia (CML).

In some embodiments the cancer to be treated is a plasma cell neoplasm. Examples for plasma cell neoplasms include multiple myeloma; plasma cell myeloma; plasma cell leukemia and plasmacytoma.

Carcinomas which can be treated by the disclosed methods include colon cancer; liver cancer; gastric cancer; intestinal cancer; esophageal cancer; breast cancer; ovarian cancer; head and neck cancer; lung cancer; and thyroid cancer.

Sarcomas which can be treated by the disclosed methods include soft tissue sarcoma and bone sarcoma.

Any cancer characterized by high levels of DNA damage and/or DNA editing enzyme expression can be treated with a compound as described herein, *e.g.* a compound of the present disclosure. For example, sarcomas, epithelial cell cancer (carcinomas), colon cancer, gastric cancer, intestinal cancer, liver cancer, hepatocellular cancer, breast cancer, thyroid cancer, esophageal cancer, lung cancer, brain cancer, head and neck cancer, melanoma, renal cancer, prostate cancer, hemangioma, rhabdomyosarcoma, chondrosarcoma, osteosarcoma, fibrosarcoma and cholangiocarcinoma may be characterized by high levels of a DNA editing enzyme expression, *e.g.* AID. In some embodiments the cancer to be treated is colon cancer, liver cancer, gastric cancer, intestinal cancer, breast cancer, lung cancer, thyroid cancer and/or cholangiocarcinoma.

Some cancers that can be treated by the disclosed methods include cancer of the bladder, blood, bone, bone marrow, brain, breast, colon, esophagus, gastrointestinal, gum, head, kidney, liver, lung, nasopharynx, neck, ovary, prostate, skin, stomach, testis, tongue, or uterus. In addition, the cancer may be of the following histological type, though it is not limited to these: neoplasm, malignant; carcinoma; carcinoma, undifferentiated; giant and spindle cell carcinoma; sarcomas; small cell carcinoma; papillary carcinoma; squamous cell carcinoma; lymphoepithelial carcinoma; basal cell carcinoma; pilomatrix carcinoma; transitional cell carcinoma; papillary transitional cell carcinoma; adenocarcinoma; gastrinoma, malignant; cholangiocarcinoma; hepatocellular carcinoma; combined hepatocellular carcinoma and cholangiocarcinoma; trabecular adenocarcinoma; adenoid cystic carcinoma; adenocarcinoma in adenomatous polyp; adenocarcinoma, familial polyposis coli; solid carcinoma; carcinoid tumor, malignant; bronchiole-alveolar adenocarcinoma; papillary adenocarcinoma; chromophobe carcinoma; acidophil carcinoma; oxyphilic adenocarcinoma; basophil carcinoma; clear cell adenocarcinoma; granular cell carcinoma; follicular adenocarcinoma; papillary and follicular adenocarcinoma; nonencapsulating sclerosing carcinoma; adrenal cortical carcinoma; endometrioid carcinoma; skin appendage carcinoma; apocrine adenocarcinoma; sebaceous adenocarcinoma; ceruminous adenocarcinoma; mucoepidermoid carcinoma; cystadenocarcinoma; papillary

cystadenocarcinoma; papillary serous cystadenocarcinoma; mucinous cystadenocarcinoma; mucinous adenocarcinoma; signet ring cell carcinoma; infiltrating duct carcinoma; medullary carcinoma; lobular carcinoma; inflammatory carcinoma; Paget's disease, mammary; acinar cell carcinoma; adenosquamous carcinoma; adenocarcinoma w/squamous metaplasia; thymoma, malignant; ovarian stromal tumor, malignant; thecoma, malignant; granulosa cell tumor, malignant; androblastoma, malignant; sertoli cell carcinoma; Leydig cell tumor, malignant; lipid cell tumor, malignant; paraganglioma, malignant; extra-mammary paraganglioma, malignant; pheochromocytoma; glomangiosarcoma; malignant melanoma; amelanotic melanoma; superficial spreading melanoma; malignant melanoma in giant pigmented nevus; epithelioid cell melanoma; blue nevus, malignant; sarcoma; fibrosarcoma; fibrous histiocytoma, malignant; myxosarcoma; liposarcoma; leiomyosarcoma; rhabdomyosarcoma; embryonal rhabdomyosarcoma; alveolar rhabdomyosarcoma; stromal sarcoma; mixed tumor, malignant; mullerian mixed tumor; nephroblastoma; hepatoblastoma; carcinosarcoma; mesenchymoma, malignant; brenner tumor, malignant; phyllodes tumor, malignant; synovial sarcoma; mesothelioma, malignant; dysgerminoma; embryonal carcinoma; teratoma, malignant; struma ovarii, malignant; choriocarcinoma; mesonephroma, malignant; hemangiosarcoma; hemangioendothelioma, malignant; Kaposi's sarcoma; hemangiopericytoma, malignant; lymphangiosarcoma; osteosarcoma; juxtacortical osteosarcoma; chondrosarcoma; chondroblastoma, malignant; mesenchymal chondrosarcoma; giant cell tumor of bone; Ewing's sarcoma; odontogenic tumor, malignant; ameloblastic odontosarcoma; ameloblastoma, malignant; ameloblastic fibrosarcoma; pinealoma, malignant; chordoma; glioma, malignant; ependymoma; astrocytoma; protoplasmic astrocytoma; fibrillary astrocytoma; astroblastoma; glioblastoma; oligodendroglioma; oligodendroblastoma; primitive neuroectodermal; cerebellar sarcoma; ganglioneuroblastoma; neuroblastoma; retinoblastoma; olfactory neurogenic tumor; meningioma, malignant; neurofibrosarcoma; neurilemmoma, malignant; granular cell tumor, malignant; malignant lymphoma; Hodgkin's disease; Hodgkin's; paraganuloma; malignant lymphoma, small lymphocytic; malignant lymphoma, large cell, diffuse; malignant lymphoma, follicular; mycosis fungoides; other specified non-Hodgkin's lymphomas; malignant histiocytosis; multiple myeloma; mast cell sarcoma; immunoproliferative small intestinal disease; leukemia; lymphoid leukemia; plasma cell leukemia; erythroleukemia; lymphosarcoma cell leukemia; myeloid leukemia; basophilic leukemia; eosinophilic

leukemia; monocytic leukemia; mast cell leukemia; megakaryoblastic leukemia; myeloid sarcoma; and hairy cell leukemia.

In another embodiment for the disclosed method, the cancer is characterized by mutations in the *mutS* homologues (e.g., MSH2, MSH3, and MSH6), *mutL* homologues (e.g. MLH1), or mismatch repair endonuclease PMS2. Mutations are changes in the genetic code. They include point mutations and frameshift mutations. In a point mutation, one nucleotide is swapped out for another. Therefore, the mutation occurs at a single point or location within the DNA strand. Frameshift mutations are due to either insertions or deletions of nucleotides. This causes the entire DNA strand to elongate or to shrink in size. Thus, frameshift mutations may alter all of the codons that occur after the deletion or insertion. The mutations referred to herein include, but are not limited to, insertions, deletions, duplications, inversions, or other recognized point mutations. It has now been found that RAD51 inhibitors are particularly effective in treating cancers with mutations in MSH (e.g. *MSH6*), MLH, or PMS2.

MutS Homolog 2 (*MSH2*) is a protein that in humans is encoded by the *MSH2* gene, which is located on chromosome 2. *MSH2* is a tumor suppressor gene and, for example, a caretaker gene that codes for a DNA mismatch repair (MMR) protein, *MSH2*, which forms a heterodimer with *MSH6* to make the human MutS α mismatch repair complex. It also dimerizes with *MSH3* to form the MutS β DNA repair complex. *MSH2* is involved in many different forms of DNA repair, including transcription-coupled repair, homologous recombination, and base excision repair. Examples of the mutations in *MSH2* include, but are not limited to, g.47630253_47630254del, g.47702411_47702421del, g.47709913_47709915inv, g.47635629_47635634del, g.47637227_47637236dup, g.47639550_47639561del, g.(?_47630206)_(47710367_?)del, g.(?_47630206)_(47643569_47656880)del, g.47630263_47643568del, g.(?_47630206)_(47657081_47672686)del, g.47630263_47657080del, g.(?_47630206)_(47672797_47690169)del, g.47630263_47672796del, g.(?_47630206)_(47672797_47690169)del, g.(?_47630206)_(47693948_47698103)del, g.47630263_47693947del, g.(?_47630206)_(47698202_47702163)del, g.(?_47630206)_(47630542_47635539)del, g.(?_47630206)_(47708011_47709917)del, g.(?_47630206)_(47635695_47637232)del, g.(?_47630206)_(47635695_47637232)del, g.(?_47630206)_(47637512_47639552)del, g.(?_47630206)_(47639700_47641407)del, g.(?_47630206)_(47641558_47643434)del, g.47618487_47650860delins(155), g.47628578_47638433del, g.47595033_47662777del, g.47583175_47667707del,

g.47625602_47636880del, g.47554933_47699909del, g.47629508_47649552del,
g.47629375_47651274del, g.(?_47630206)_(47630542_47635539)del,
g.(?_47630206)_(47635695_47637232)del, g.47643509_47643510del,
g.47643529_47643530dup, g.47656746_47657199dup, g.47656661_47663325del,
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g.(47643569_47656880)_(47657081_47672686)dup,
g.(47643569_47656880)_(47672797_47690169)del,
g.(47643569_47656880)_(47693948_47698103)del, g.47656881_47693947del,
g.(47643569_47656880)_(47702410_47703505)del, g.47656881_47656882ins(173),
g.47656901_47656902insA, g.47656903del, g.47656912del, g.47630440del, g.47656923del,
g.47656931_47656932dup, g.47656943del, g.47656943_47656949delinsCCCAGA,
g.47656948dup, g.47656996dup, g.47657000_47657001dup, g.47630449del,
g.47657007dup, g.47657008del, g.47657020_47657023dup, g.47657025_47657026del,
g.47657026dup, g.47657030_47657031del, g.47657047_47657050del, g.47657053del,
g.47657053_47657057del, g.47657064del, g.47657073dup, g.47657312_47676594del,
g.47668611_47674615del, g.47672116_47675123del, g.47666463_47677632del,
g.47666403_47677572del, g.(47657081_47672686)_(47710367_?)del,
g.(47657081_47672686)_(47710367_?)inv,
g.47671507_47675022delinsCATCTCTTTGAAAA, g.47657278_47676557del,
g.47672687_47672796del, g.(47657081_47672686)_(47672797_47690169)del,
g.(47657081_47672686)_(47672797_47690169)del,
g.(47657081_47672686)_(47693948_47698103)del,
g.(47657081_47672686)_(47698202_47702163)del,
g.(47657081_47672686)_(47708011_47709917)del, g.47672691dup, g.47672697dup,
g.47672721_47672744delins47672748_47672771inv, g.47672728_47672729del,
g.47672731dup, g.47672750_47672751insGG, g.47672755_47672758del,
g.47672762_47672763del, g.47630466_47630494del, g.47686194_47697740del,
g.(47672797_47690169)_(47710367_?)del,
g.(47672797_47690169)_(47690294_47693796)del,

g.(47672797_47690169)_(47693948_47698103)del, g.47690170_47693947del,
g.(47672797_47690169)_(47693948_47698103)del,
g.(47672797_47690169)_(47693948_47698103)dup,
g.(47672797_47690169)_(47705659_47707834)del, g.47690173del, g.47690191del,
g.47690216_47690217dup, g.47690227del, g.47690227dup, g.47690228_47690232del,
g.47690230_47690231del, g.47690240del, g.47690240_47690243del, g.47630475del,
g.47630475_47630476del, g.47690259_47690260delinsCT, g.47690277dup, g.47690280del,
g.47690283dup, g.(47690294_47693796)_(47702410_47703505)del,
g.47630484_47630485insG, g.47693838_47693839del, g.47693862del, g.47693864del,
g.47693873del, g.47693880dup, g.47693913del, g.47693924_47693925dup, g.47630493del,
g.47697730_47706125del, g.(47693948_47698103)_(47710367_?)del,
g.(47693948_47698103)_(47698202_47702163)del,
g.(47693948_47698103)_(47705659_47707834)del, g.47698107del, g.47698109del,
g.47698109_47698110insA, g.47630496del, g.47698118del, g.47698125del, g.47698129dup,
g.47698138_47698139del, g.47698142_47698146del, g.47698144dup,
g.47698147_47698148del, g.47698147_47698148dup, g.47698147_47698148insT,
g.47698159del, g.47698162del, g.47698506_47703472del, g.47701803_47708848del,
g.(47698202_47702163)_(47710367_?)del,
g.(47698202_47702163)_(47702410_47703505)del,
g.(47698202_47702163)_(47703711_47705410)del,
g.(47698202_47702163)_(47705659_47707834)del, g.47702164del,
g.47702175_47702176insA, g.47702183_47702186del, g.47702185_47702186insCT,
g.47702190_47702192del, g.47702191dup, g.47702192_47702193del, g.47702213del,
g.47702231del, g.47702242dup, g.47702257del, g.47702262_47702263dup,
g.47630516_47630517dup, g.47630517del, g.47630517dup, g.47702289_47702290inv,
g.47702293_47702296del, g.47702301dup, g.47702315del, g.47702315del,
g.47702328_47702329del, g.47630522dup, g.47702339del, g.47702371_47702374dup,
g.47702384_47702385del, g.47702386_47702389del, g.47702388del,
g.47702388_47702389del, g.47702390del, g.47702390_47702391del,
g.47702400_47702401del, g.47703506_47703710del, g.47703506_47708010del,
g.47703510del, g.47703515del, g.47703521_47703522del, g.47703535_47703536del,
g.47703546_47703547del, g.47703548_47703611dup, g.47630534del, g.47703571dup,
g.47703574_47703581del, g.47703585dup, g.47630350del, g.47632107_47668733del,

g.47703613del, g.(47630542_47635539)_(47643569_47656880)del,
g.(47630542_47635539)_(47643569_47656880)inv,
g.(47630542_47635539)_(47657081_47672686)del, g.47635540_47657080del,
g.(47630542_47635539)_(47672797_47690169)del,
g.(47630542_47635539)_(47690294_47693796)del,
g.(47630542_47635539)_(47705659_47707834)del, g.47635540_47635694del,
g.(47630542_47635539)_(47635695_47637232)del,
g.(47630542_47635539)_(47635695_47637232)del,
g.(47630542_47635539)_(47637512_47639552)del, g.47703635dup, g.47703641dup,
g.47635542_47635549del, g.47703660_47703663del, g.47703667dup, g.47630351dup,
g.47703704del, g.47703826_47707938del,
g.(47703711_47705410)_(47705659_47707834)del, g.47705428_47705431del,
g.47705437_47705438insA, g.47635551_47635552del, g.47705440_47705441del,
g.47705461del, g.47705490del, g.47705494del, g.47705495del, g.47635557_47635558del,
g.47705505del, g.47705535dup, g.47705547del, g.47705560_47705561dup, g.47705561dup,
g.47705562dup, g.47705588del, g.47705608_47705609del, g.47705618dup, g.47705627dup,
g.47635571_47635601delins(217), g.(47705659_47707834)_(47710367_?)del,
g.(47705659_47707834)_(47708011_47709917)del, g.47707842_47707843del,
g.47707861del, g.47707861_47707874dup, g.47707878_47707884del,
g.47707878_47707884del, g.47707883del, g.47707895_47707905del, g.47707897del,
g.47707901_47707902del, g.47707905_47707906del, g.47707921del, g.47635583dup,
g.47635583_47635584del, g.47707969_47707973del, g.47707996_47707997ins(115),
g.47708009_47708010del, g.(47708011_47709917)_(47710367_?)del,
g.47635591_47635592del, g.47635597_47635618dup, g.47635606_47635607del,
g.47630359dup, g.47635672del, g.47635675_47635678del, g.47630364dup, g.47635680dup,
g.47636862_47639040del, g.47636781_47638831del, g.47636753_47638155del,
g.47636552_47638597del, g.(47635695_47637232)_(47643569_47656880)del,
g.(47635695_47637232)_(47643569_47656880)del,
g.(47635695_47637232)_(47657081_47672686)del,
g.(47635695_47637232)_(47672797_47690169)del,
g.(47635695_47637232)_(47698202_47702163)del,
g.(47635695_47637232)_(47637512_47639552)del,
g.(47635695_47637232)_(47641558_47643434)del, g.47637234del,

g.47637246_47637247del, g.47637253_47637254del, g.47637254_47637255del,
g.47637254_47637255del, g.47637265del, g.47637274del, g.47637282del, g.47637320del,
g.47637372_47637375del, g.47637377_47637449dup, g.47637379del, g.47637384del,
g.47637394_47637395del, g.47637396_47637397del, g.47637417del,
g.47637427_47637435del, g.47637437_47637439del, g.47637453del, g.47637458dup,
g.47637479_47637482dup, g.47637482dup, g.47637504_47637505del,
g.47637508_47637511del, g.47638050_47653430del, g.47638302_47648462del,
g.47638478_47648643del, g.(47637512_47639552)_(47710367_?)del,
g.(47637512_47639552)_(47643569_47656880)del, g.47639553_47643568del,
g.(47637512_47639552)_(47657081_47672686)del,
g.(47637512_47639552)_(47657081_47672686)del,
g.(47637512_47639552)_(47672797_47690169)del,
g.(47637512_47639552)_(47639700_47641407)del,
g.(47637512_47639552)_(47641558_47643434)del, g.47639557_47639561del,
g.47639582_47639586delinsTAAT, g.47639583_47639584del, g.47639594del,
g.47639594dup, g.47639598del, g.47639603_47639604del, g.47639611_47639612del,
g.47639612del, g.47639618_47639621del, g.47639624_47639628delinsTTA,
g.47630401dup, g.47639632dup, g.47639638_47639641dup, g.47639638_47639641dup,
g.47639639del, g.47639639del, g.47639642dup, g.47630403_47630404insC, g.47639653del,
g.47639666del, g.47639666_47639669del, g.47639668del, g.47639670_47639673delinsTT,
g.47639674_47639675dup, g.47639695_47639696del, g.47639707_47642985del,
g.47641402_47642007del, g.(47639700_47641407)_(47643569_47656880)del,
g.47641408_47643568del, g.(47639700_47641407)_(47657081_47672686)del,
g.(47639700_47641407)_(47672797_47690169)del,
g.(47639700_47641407)_(47641558_47643434)del,
g.(47639700_47641407)_(47641558_47643434)del, g.47641410del,
g.47641425_47641426del, g.47641426_47641429del, g.47630412del, g.47641451del,
g.47641454dup, g.47641455dup, g.47641469del, g.47641478del, g.47641488_47641491del,
g.47641496_47641497del, g.47641503del, g.47641513_47641514dup,
g.47641530_47641537dup, g.47642509_47655432del,
g.(47641558_47643434)_(47643569_47656880)del,
g.(47641558_47643434)_(47693948_47698103)del, g.47630424_47630433del,

g.47643450dup, g.47643462_47643463del, g.47643462_47643463ins(4),
g.47643464_47643465insNC_000022.10:35788169_35788352, g.47643465dup.

MutS Homolog 3 (*MSH3*) is a human homologue of the bacterial mismatch repair protein MutS that participates in the mismatch repair (MMR) system. MSH3 typically forms the heterodimer MutS β with MSH2 in order to correct long insertion/deletion loops and base-base mispairs in microsatellites during DNA synthesis. Deficient capacity for MMR is found in approximately 15% of colorectal cancers, and somatic mutations in the *MSH3* gene can be found in nearly 50% of MMR-deficient colorectal cancers. Examples of the mutations in *MSH3* include, but are not limited to, g.79970809del.

MSH6 encodes MutS homologue 6 (*MSH6*), a member of the Mutator S (MutS) family of proteins that are involved in DNA mismatch repair (MMR). The *MSH6* protein forms a heterodimer with MutS homologue 2 (*MSH2*) in both human and yeast. Human *MSH2/6* recognizes single base-base mismatches and short insertion/deletion loops. Upon recognition of a mismatch, *MSH2/6* complex binds and exchanges ADP for ATP, resulting in a conformational change to the complex that precedes base pair dissolution, base excision, and repair.

MSH6 mutations include frameshift and/or nonsense mutations and can result in non-functional *MSH6* and loss of protein expression. Examples include a frameshift mutation at *MSH6* amino acid residue 290 and a compounding missense T1189I.

Inactivating *MSH6* mutations can be detected in cancers by routine diagnostics methods. These methods include, but are not limited to, obtaining cancer cells and other diagnostic indicators such as peripheral blood mononuclear cells (PBMCs), PBMC subpopulations, circulating blasts (CD34⁺ cells), circulating tumor cells and circulating exosomes cancer cells by biopsy and blood tests and by obtaining lymphatic or other bodily fluids. It is then determined from the cancer cells or other diagnostic indicators whether the cancer exhibits an inactivating *MSH6* mutation is by methodology known in the art, for example, direct DNA sequencing and multiplex ligation dependent probe amplification, RNA sequencing (RNA-Seq), microarray, quantitative PCR, or NanoStringTM gene expression panels, or *MSH6* protein by immunohistochemistry, flow cytometry, immunocytochemistry or Western blot. Methods for identifying inactivating *MSH6* mutations are disclosed in Houlleberghs H, Goverde A, Lusseveld J, Dekker M, Bruno MJ, et al. (2017) Suspected Lynch syndrome associated *MSH6* variants: A functional assay to determine their

pathogenicity. PLOS Genetics 13(5):

e1006765. <https://doi.org/10.1371/journal.pgen.1006765>.

Examples of the mutations in *MSH6* include, but are not limited to,

g.48032846_48032849del, g.48032846_48032849del, g.48032846_48032849del,
g.48033337_48033342del, g.48033420_48033422del, g.(?_48010221)_(48034092)del,
g.(?_48010221)_(48018263_48023032)del, g.47998510_48020183del,
g.48007276_48020272del, g.48026207del, g.48026223del, g.48026223del,
g.48026257_48026261del, g.48026261_48026265del, g.48026312_48026313del,
g.48026398del, g.48026543_48026544dup, g.48026693dup, g.48026702del, g.48026712del,
g.48026718dup, g.48026736_48026737delinsAG, g.48026736_48026737delinsG,
g.48026750_48026751del, g.48026754_48026757del, g.48026756_48026759del,
g.48026759_48026760del, g.48026906del, g.48026928_48026931del, g.48026941dup,
g.48026991del, g.48027023_48027024del, g.48027079del, g.48027079_48027082dup,
g.48027167_48027168del, g.48027172_48027173dup, g.48027178_48027185del,
g.48027184_48027185del, g.48027272_48027275del, g.48027470_48027471del,
g.48027501_48027502del, g.48027501_48027502delTG, g.48027657dup,
g.48027691_48027694del, g.48027733_48027736dup, g.48027794_48027796delinsC,
g.48027841_48027842del, g.48027887del, g.48027890dup, g.48027973_48027980del,
g.48028067del, g.48028098del, g.48028106del, g.48028175_48028176del,
g.48028241_48028242del, g.48028241_48028242delTT, g.48028272_48028284dup,
g.48028277_48028278del, g.48030558_48030559del, g.48030126_48032394del,
g.48030568del, g.48030581_48030584del, g.48030584_48030585dup, g.48030607del,
g.48030645_48030646insT, g.48030647del, g.48030647dup, g.48030649dup,
g.48030654_48030660del, g.48030659dup, g.48030697_48030698del, g.48030698del,
g.48030706del, g.48030710dup, g.48030727_48030728insC, g.48030765_48030829del,
c.3438+797_3438+798insTATins1839_3439-428,
c.3438+797_3438+798insTATins1839_3439-428, g.48032121_48032122del,
g.48032123_48032124del, g.48032124dup, g.48032126_48032129del,
g.48032129_48032130insA, g.48032129_48032132dup,
g.(48032167_48032756)_(48034092_?)del, g.48032809_48032812del, g.48032835dup,
g.48032846_48032849del, g.48033374_48033402dup, g.48033395_48033398del,
g.48033421_48033433del, g.48033425_48033428dup, g.48033453_48033454insA,
g.48033494_48033523del, g.48033495_48033496del, g.48033593dup,

g.48033610_48033613dup, g.48033629_48033635del, g.48033636_48033639dup,
 g.48033676_48033682del, g.48033707dup, g.48033709_48033716dup,
 g.48033721_48033724dup, g.48033727_48033730dup, g.48033728_48033746dup,
 g.(48033742_48033743)_(48033742_48033743)ins(32), g.48033746dup,
 g.48033748_48033751del, g.48033758_48033768del, g.48033773_48033774insATCA,
 g.48033773_48033776dup, g.48033785_48033789dup, g.48033887_48033910inv,
 g.(48018263_48023032)_(48032167_48032756)del,
 g.(48018263_48023032)_(48023203_48025749)del, g.48023097_48023098del,
 g.48025773dup, g.48025832del, g.48025860_48025861insT, g.48025884_48025885del,
 g.48025967dup.

MutL homolog 1, colon cancer, nonpolyposis type 2 (*E. coli*) is a protein that in humans is encoded by the *MLH1* gene located on Chromosome 3. It is a gene commonly associated with hereditary nonpolyposis colorectal cancer.

Examples of the mutations in *MSH6* include, but are not limited to,

g.37089113_37089115del, g.37089175del, g.37090379_37090393del,
 g.37038201_37038202del, g.37042531_37042542del, g.37053339_37053355del,
 g.37053354del, g.37053590_37053591insT, g.37034841_37092337del,
 g.(?_37034841)_(37092337_?)del, g.(?_37034841)_(37061955_37067127)del,
 g.(?_37034841)_(37035155_37038109)del, g.(?_37034841)_(37035155_37038109)del,
 g.(?_37034841)_(37070424_37081676)del, g.(?_37034841)_(37083823_37089009)del,
 g.37034841_37083822del, g.(?_37034841)_(37038201_37042445)del,
 g.(?_37034841)_(37042545_37045891)del, g.37034841_37042544del,
 g.(?_37034841)_(37042545_37045891)del, g.(?_37034841)_(37042545_37045891)del,
 g.(?_37034841)_(37045966_37048481)del, g.(?_37034841)_(37050397_37053310)del,
 g.(?_37034841)_(37059091_37061800)del, g.37034658_37038806del,
 g.36961079_37138741del, g.37061923del, g.37061927del, g.37061933del, g.37061939del,
 g.37061942dup, g.37035140_37035141del, g.37070417del, g.37070417_37070418insT,
 g.37070419dup, g.37070422_37070423insT, g.37080355_37083368del,
 g.(37070424_37081676)_(37092337_?)del,
 g.(37070424_37081676)_(37081786_37083758)del,
 g.(37070424_37081676)_(37083823_37089009)del, g.37038148_37038151del,
 g.37038149del, g.37038149dup, g.37081690_37081691del, g.37081691_37081692del,
 g.37081706_37081708del, g.37081710_37081711del, g.37035053_37035066del,

g.37038154del, g.37038154_37038157del, g.37081738_37081739del, g.37081740del,
g.37081753dup, g.37081757_37081761dup, g.37081782_37081783insAAGT,
g.37081787_37081793delinsATTT, g.(37081786_37083758)_(37083823_37089009)del,
g.(37081786_37083758)_(37089175_37090007)del, g.37083759del, g.37083780dup,
g.37083781_37083784del, g.37083781_37083784delCTCA, g.37083808_37083809del,
g.37083816del, g.37086069_37089606del, g.37084092_37089247del,
g.37084590_37089786del, g.(37083823_37089009)_(37092337_?)del,
g.(37083823_37089009)_(37089175_37090007)del, g.37089010_37089174del,
g.(37083823_37089009)_(37090509_37091976)del, g.37089023del,
g.37089026_37089027del, g.37089027del, g.37089036del, g.37089036dup, g.37038168dup,
g.37089042del, g.37089047del, g.37089050_37089053del, g.37089056_37089057del,
g.37089061_37089062del, g.37089078_37089096del, g.37089090dup, g.37089099dup,
g.37089107_37089110dup, g.37089109_37089110del, g.37089130_37089132del,
g.37089130_37089132delAAG, g.37089131delinsTTCTT, g.37089133del, g.37089133delG,
g.37089144del, g.37089155del, g.37089155_37089161del, g.37089158_37089161del,
g.37089162_37089166del, g.37089171del,
g.(37089175_37090007)_(37090101_37090394)del, g.37035056_37035072del,
g.37090013del, g.37090015dup, g.37038183_37038184del, g.37090024_37090037dup,
g.37090025_37090053dup, g.37090027dup, g.37038184dup, g.37090031_37090032insT,
g.37090041del, g.37090057del, g.37090064_37090067del, g.37038188del, g.37090082del,
g.37090086_37090087del, g.37090087_37090088del, g.37090097_37090101delinsC,
g.37090099del, g.37038191dup, g.(37090101_37090394)_(37092337_?)del,
g.37035057_37035073del, g.37090405dup, g.37090411_37090415del, g.37090414del,
g.37038194del, g.37038198del, g.37090472_37090478del, g.37039445_37059613dup,
g.37039760_37052440del, g.37090481_37090482del, g.37090483_37090484del,
g.37090483_37092045del, g.37040732_37043185delinsACATAGTA,
g.37042445_37042446del, g.(37038201_37042445)_(37042545_37045891)del,
g.(37038201_37042445)_(37048555_37050304)del,
g.(37038201_37042445)_(37050397_37053310)del,
g.(37038201_37042445)_(37053591_37055922)del, g.37090497_37090498del,
g.37090497_37090498delTC, g.37090504_37090507del,
g.(37090509_37091976)_(37092337_?)del, g.(37090509_37091976)_(37092337_?)dup,
g.37091977_37091978del, g.37091978_37091987del, g.37042448_37042451del,

g.37091984_37091990del, g.37042451_37042453del, g.37092020_37092021del,
g.37092022_37092068dup, g.37092027_37092028del, g.37092027_37092028dup,
g.37092030dup, g.37092052_37092055del, g.37092054_37092055del,
g.37092068_37092071dup, g.37092091dup, g.37092094_37092097delins(30),
g.37092096_37092106del, g.37092097del, g.37092125_37092126delAA,
g.37092125_37092126del, g.37092139_37092142dup, g.37092142dup, g.37035060dup,
g.37042469_37042470del, g.37042470del, g.37042482dup, g.37042485del, g.37042499del,
g.37042546dup, g.37044472_37046589del, g.37045648_37049941del,
g.37045095_37054651del, g.37045072_37046861del,
g.(37042545_37045891)_(37045966_37048481)del,
g.(37042545_37045891)_(37092337_?)del,
g.(37042545_37045891)_(37048555_37050304)del,
g.(37042545_37045891)_(37050397_37053310)del, g.37045892_37050396del,
g.37035069del, g.37045926del, g.37045931del, g.37045939_37045940dup,
g.37045957_37045958del, g.37045963del, g.37035075del, g.37048067_37049287del,
g.(37045966_37048481)_(37048555_37050304)del,
g.(37045966_37048481)_(37050397_37053310)del, g.37048483del,
g.37048483_37048503delinsT, g.37048486_37048487delinsGTT, g.37048489del,
g.37048490del, g.37035076_37035077insCCCA, g.37035077_37035078dup,
g.37048505_37048508del, g.37048521del, g.37048529dup, g.37035082dup,
g.37049873_37052281del, g.37049839_37052249del, g.37049800_37052209del,
g.37049640_37050445del, g.37050305_37050396del,
g.(37048555_37050304)_(37050397_37053310)del, g.37050305_37050396del,
g.37050319_37050320del, g.37050339del, g.37050348del, g.37050353_37050354del,
g.37050354dup, g.37050364del, g.37050375_37050376insGA, g.37035090del,
g.37050382_37050383delinsAT, g.37050382_37050383delinsCT, g.37050390_37050396del,
g.37052950_37060990del, g.(37050397_37053310)_(37067499_37070274)dup,
g.(37050397_37053310)_(37053591_37055922)del,
g.(37050397_37053310)_(37056036_37058996)del, g.37053353del,
g.37053510_37053511del, g.37035099del, g.37053545_37053546insT, g.37053562del,
g.37053578del, g.37053578dup, g.37053585del, g.37053586_37053589del, g.37053591del,
g.37053590_37053591delinsAT, g.37055920_37055921del, g.37055914_37055938del,
g.(37053591_37055922)_(37070424_37081676)del,

g.(37053591_37055922)_(37083823_37089009)del,
g.(37053591_37055922)_(37059091_37061800)del, g.37035105del, g.37055928dup,
g.37035106_37035116del, g.37055938del, g.37035108del, g.37055972_37055975del,
g.37055976_37055979del, g.37035111del, g.37055990dup, g.37035114del, g.37035116del,
g.37056036del, g.37056037dup, g.37058993_37059001del,
g.(37056036_37058996)_(37070424_37081676)del,
g.(37056036_37058996)_(37059091_37061800)del, g.37058997_37059000del,
g.37059014_37059017del, g.37059017_37059021del, g.37059027_37059030dup,
g.37035122del, g.37059062_37059063insT, g.37059065_37059066del, g.37059066del,
g.37059066dup, g.37059072_37059073del, g.37059072_37059073dup,
g.37059090_37059093del, g.37061595_37061913del, g.37061308_37066756del,
g.37061207_37063077del, g.(37059091_37061800)_(37092337_?)del,
g.(37059091_37061800)_(37061955_37067127)del, g.37061801_37061954del,
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g.37061817del, g.37061837_37061838dup, g.37061844del, g.37061851dup, g.37061855dup,
g.37061870del, g.37061904_37061906del, g.37061910del, g.37035047del,
g.[37049179_37051317delinsTG;37051667_37054327delinsCA].

Human *PMS2* related genes are located at bands 7p12, 7p13, 7q11, and 7q22. Exons 1 through 5 of these homologues share high degree of identity to human *PMS2*. The product of this gene is involved in DNA mismatch repair. The protein forms a heterodimer with *MLH1* and this complex interacts with *MSH2* bound to mismatched bases. Defects in this gene are associated with hereditary nonpolyposis colorectal cancer, with Turcot syndrome, and are a cause of supratentorial primitive neuroectodermal tumors.

Examples of the mutations in *PMS2* include, but are not limited to,

g.(?_6012870)_(6048737_?)del, g.6012870_6048737del,
g.(6027252_6029430)_(6048737_?)del, g.(6045663_6048627)_(6048737_?)del,
g.6029554del, g.6029499dup, g.6029495_6029496del, g.6029462_6029463delinsTAAA,
g.5992485_6028601del, g.(6018328_6022454)_(6027252_6029430)del,
g.(6013174_6017218)_(6027252_6029430)del, g.6027226_6027227ins(20), g.6027175del,
g.6027090dup, g.6036705_6044207delinsCG, g.6026666dup, g.6026628del, g.6043671del,
g.6026565dup, g.6026565dupT, g.6018315_6018316del, g.6018306_6018310del,
g.6018306_6018310delAGTTA, g.6043633_6043634dup, g.6018256_6018259del,
g.6015623_6017501del, g.6016429_6017479del, g.6017300_6017303del,

g.6045579_6045674delinsATTT, g.(6043690_6045522)_(6045663_6048627)del,
 g.(?_6012870)_(6042268_6043320)del, g.(6035265_6036956)_(6042268_6043320)del,
 g.6038283_6039384del, g.6038901del, g.6038851dup,
 g.(6035265_6036956)_(6037055_6038738)del,
 g.6037019_6037024delinsCTTCACACACA, g.6036980del, g.6036958dup,
 g.6035323_6035324insJN866832.1, g.(6022623_6026389)_(6035265_6036956)del,
 g.(6031689_6035164)_(6035265_6036956)del, g.6035204_6035207del,
 g.6035205_6035206del, g.(?_6012870)_(6031689_6035164)del,
 g.(6027252_6029430)_(6031689_6035164)del,
 g.(6029587_6031603)_(6031689_6035164)del, g.6028725_6029882del,
 g.(?_6012870)_(6029587_6031603)del.

The present disclosure provides a method of treating patients with Lynch syndrome to reduce the likelihood of from developing or treating cancers derived from Lynch syndrome, by administering to the subject an effective amount of one or more disclosed compounds, or a pharmaceutically acceptable salt thereof, or the corresponding pharmaceutical composition.

Lynch syndrome is a hereditary disorder caused by a mutation in a mismatch repair gene in which affected individuals have a higher than normal chance of developing colorectal cancer, endometrial cancer, and various other types of aggressive cancers, often at a young age – also called hereditary nonpolyposis colon cancer (HNPCC).

The mutations of specific mismatch repair (MMR) genes including but not limited to MLH1, MSH2, MSH6, PMS2, and EPCAM-TACSTD1 deletions are responsible for Lynch syndrome. These genes work in repairing mistakes made when DNA is copied in preparation for cell division. The defects in the genes disallow repair of DNA mistakes and as cells divide, errors stack and uncontrollable cell growth may result in cancer.

Those with Lynch syndrome carry up to an 85% risk of contracting colon cancer as well as a higher than average risk for endometrial cancer, stomach cancer, pancreatic cancer, kidney/ureter tract cancer, hepatobiliary tract cancer, gastric tract cancer, prostate cancer, ovarian cancer, gallbladder duct cancer, brain cancer, small intestine cancer, breast cancer, and skin cancer.

In some embodiments for the disclosed method, the method is a method of treating cancer derived from Lynch syndrome, selected from the group consisting of colon cancer, endometrial cancer, stomach cancer, pancreatic cancer, kidney/ureter tract cancer,

hepatobiliary tract cancer, gastric tract cancer, prostate cancer, ovarian cancer, gallbladder duct cancer, brain cancer, small intestine cancer, breast cancer, and skin cancer.

In some embodiments, the method is a method of treating autoimmune disease. Exemplary autoimmune diseases include lupus erythematosus; Wiskott-Aldrich syndrome; autoimmune lymphoproliferative syndrome; myasthenia gravis; rheumatoid arthritis (RA); lupus nephritis; multiple sclerosis; systemic lupus erythematosus; discoid lupus; subacute cutaneous lupus erythematosus; cutaneous lupus erythematosus including chilblain lupus erythematosus; chronic arthritis; Sjogren's syndrome; inflammatory chronic rhinosinusitis; colitis; celiac disease; inflammatory bowel disease; Barrett's esophagus; inflammatory gastritis; autoimmune nephritis; autoimmune vasculitis; autoimmune hepatitis; autoimmune carditis; autoimmune encephalitis; autoimmune diabetes; autoimmune diabetes nephritis; psoriasis; Graft-versus-host disease (GvHD); and autoimmune mediated hematological disease.

In some embodiments, the method is a method of treating immune deficiency selected from the group consisting of Autoimmune Lymphoproliferative Syndrome (ALPS), Autoimmune polyglandular syndrome type 1 (APS-1), BENTA Disease, Caspase Eight Deficiency State (CEDS), Chronic Granulomatous Disease (CGD), Common Variable Immunodeficiency (CVID), Congenital Neutropenia Syndromes, CTLA4 Deficiency, DOCK8 Deficiency, GATA2 Deficiency, Glycosylation Disorders With Immunodeficiency, hyper-immunoglobulin E syndrome (HIES), Hyper-Immunoglobulin M (Hyper-IgM) Syndromes, Leukocyte adhesion deficiency (LAD), LRBA deficiency, PI3 Kinase disease, PLCG2-associated antibody deficiency and immune dysregulation (PLAID), severe combined immunodeficiency (SCID), STAT3 gain-of-function disease, Warts, Hypogammaglobulinemia, Infections, and Myelokathexis Syndrome (WHIMS), X-Linked Agammaglobulinemia (XLA), X-Linked Lymphoproliferative Disease (XLP), and XMEN Disease.

As used herein, the term "immune deficiency" refers to a condition in which a portion or some portions of cell components constituting an immune system are defective or dysfunction, so that a normal immune mechanism is damaged. In other words, "immune deficiency" means a condition under which: congenital immunity and/or acquired immunity are suppressed and/or decreased. In some embodiments, the immune -deficiency subject is an immunocompromised subject. Non-limiting examples of immune deficiencies can include

AIDS, hypogammaglobulinemia, agammaglobulinemia, granulocyte deficiency, chronic granulomatous disease, asplenia, SCID, complement deficiency, and/or sickle cell anemia.

In some embodiments, the method is a method of treating a neurodegenerative disorder selected from the group consisting of multiple sclerosis, Parkinson's disease (PD), Alzheimer's disease (AD), Dentatorubropallidoluysian atrophy (DRPLA), Huntington's Disease (HD), Spinocerebellar ataxia Type 1 (SCA1), Spinocerebellar ataxia Type 2 (SCA2), Spinocerebellar ataxia Type 3 (SCA3), Spinocerebellar ataxia 6 (SCA6), Spinocerebellar ataxia Type 7 (SCA7), Spinocerebellar ataxia Type 8 (SCA8), Spinocerebellar ataxia Type 12 (SCA12), Spinocerebellar ataxia Type 17 (SCA17), Spinobulbar Muscular Ataxia/Kennedy Disease (SBMA), Fargile X syndrome (FRAXA), Fragile XE mental retardation (FRAXE), and Myotonic dystrophy (DM).

A "subject" is a mammal, preferably a human, but can also be an animal in need of veterinary treatment, *e.g.*, companion animals (*e.g.*, dogs, cats, and the like), farm animals (*e.g.*, cows, sheep, pigs, horses, and the like) and laboratory animals (*e.g.*, rats, mice, guinea pigs, and the like).

In some embodiments, the methods disclosed herein further comprise co-administering an effective amount of a DNA repair inhibitor, a DNA damage response (DDR) inhibitor, a DNA damaging agent or an immunomodulatory agent to the subject being treated for cancer, in addition to an effective amount of a disclosed RAD51 inhibitor.

The term "DNA repair inhibitor" refers to any agent that targets components/processes which a cell uses to repair mutations or changes in DNA and restore the DNA to its original state and prevents the repair of DNA. Examples of DNA repair inhibitors include: RPA inhibitors, APE1 inhibitors, DNA ligase inhibitors, DNA polymerase inhibitors, Parp inhibitors etc.

The term "DNA damage response inhibitor" refers to any agent that targets components/processes involved in detecting DNA lesions, signaling the presence of DNA damage, and/or promote the repair of DNA damage. Examples of DNA damage response inhibitors include checkpoint inhibitors, ATM and ATR inhibitors, DNA-PK inhibitors, etc.

The term "DNA damaging agent" refers to any agent that directly or indirectly damages DNA for which homologous recombination could repair the damage. The DNA damaging agents is selected from the group consisting of: exposure to a DNA damaging chemical; exposure to a chemotherapeutic agent; exposure to a radiochemotherapy, and exposure to ionizing or ultraviolet radiation. Some examples of DNA-damaging

chemotherapeutic agents include alkylating agents, nitrosoureas, anti-metabolites, plant alkaloids, plant extracts and radioisotopes. Some examples of the chemotherapeutic agents also include DNA-damaging drugs, for example, 5-fluorouracil (5-FU), capecitabine, S-1 (Tegafur, 5-chloro-2,4-dihydroxypyridine and oxonic acid), 5-ethynyluracil, arabinosyl cytosine (ara-C), 5-azacytidine (5-AC), 2',2'-difluoro-2'-deoxycytidine (dFdC), purine antimetabolites (mercaptopurine, azathiopurine, thioguanine), gemcitabine hydrochlorine (Gemzar), pentostatin, allopurinol, 2-fluoro-arabinosyl-adenine (2F-ara-A), hydroxyurea, sulfur mustard (bischloroethylsulfide), mechlorethamine, melphalan, chlorambucil, cyclophosphamide, ifosfamide, thiotepa, AZQ, mitomycin C, dianhydrogalactitol, dibromoducitol, alkyl sulfonate (busulfan), nitrosoureas (BCNU, CCNU, 4-methyl CCNU or ACNU), procarbazine, decarbazine, rebeccamycin, anthracyclins such as doxorubicin (adriamycin; ADR), daunorubicin (Cerubicine), idarubicin (Idamycin) and epirubicin (Ellence), anthracyclin analogs such as mitoxantrone, actinomycin D, non-intercalating topoisomerase inhibitors such as epipodophyllotoxins (etoposide or VP16, teniposide or VM-26), podophylotoxin, bleomycin (Bleo), pepleomycin, compounds that form adducts with nucleic acid including platinum derivatives, *e.g.*, cisplatin (CDDP), trans analog of cisplatin, carboplatin, iproplatin, tetraplatin and oxaliplatin, as well as camptothecin, topotecan, irinotecan (CPT-11), and SN-38. Some examples of nucleic acid damaging treatments include radiation *e.g.*, ultraviolet (UV), infrared (IR), or .alpha.-, .beta.-, or .gamma.- radiation, as well as environmental shock, *e.g.*, hyperthermia.

“Immunomodulatory agent” means an agent that modulates an immune response to an antigen but is not the antigen or derived from the antigen. “Modulate”, as used herein, refers to inducing, enhancing, suppressing, directing, or redirecting an immune response. Such agents include immunostimulatory agents, such as adjuvants, that stimulate (or boost) an immune response to an antigen but is not an antigen or derived from an antigen. There are several distinct types of immunomodulatory agents, which include, but are not limited to, Toll-like Receptor (TLR) agonists and Toll-like Receptor (TLR) antagonists. Such agents also include immunosuppressants. The immunomodulatory agent is selected from the group consisting of immune checkpoint modulators, Toll-like receptor (TLR) agonists, cell-based therapies, cytokines and cancer vaccines.

In some embodiments, the subject is determined to have an increased level and/or activity of a DNA damage process or DNA editing enzyme. In one aspect of this embodiment, the DNA editing enzyme is selected from the group consisting of activation

induced cytidine deaminase (AID or AICDA), APOBEC2, APOBEC3A, APOBEC3C, APOBEC3D, APOBEC3F, APOBEC3G, APOBEC3H, APOBEC4, a Type 1 Topoisomerase, a Type 2 Topoisomerase, Recombination Activating Gene 1 (RAG 1), and Recombination Activating Gene 2 (RAG2).

In some embodiments, blood cells obtained from the subject have been determined to have a detectable level of activation-induced cytidine deaminase (AID).

In some embodiments, B cells obtained from the subject have been determined to have a detectable level of activation-induced cytidine deaminase (AID).

In some embodiments, the detectable level of activation-induced cytidine deaminase (AID) is statistically significantly higher than the level of AID expressed in unactivated B-cells or normal non-immune cells from a healthy subject.

Methods of Administration and Dosage Forms

The precise amount of compound administered to provide an “effective amount” to the subject will depend on the mode of administration, the type, and severity of the disease, and on the characteristics of the subject, such as general health, age, sex, body weight, and tolerance to drugs. The skilled artisan will be able to determine appropriate dosages depending on these and other factors. When administered in combination with other therapeutic agents, *e.g.*, when administered in combination with an anti-cancer agent, an “effective amount” of any additional therapeutic agent(s) will depend on the type of drug used. Suitable dosages are known for approved therapeutic agents and can be adjusted by the skilled artisan according to the condition of the subject, the type of condition(s) being treated and the amount of a compound of the disclosure being used by following, for example, dosages reported in the literature and recommended in the *Physician's Desk Reference* (57th ed., 2003).

The term “effective amount” means an amount when administered to the subject which results in beneficial or desired results, including clinical results, *e.g.*, inhibits, suppresses or reduces the symptoms of the condition being treated in the subject as compared to a control. For example, a therapeutically effective amount can be given in unit dosage form (*e.g.*, 0.1 mg to about 50 g per day, alternatively from 1 mg to about 5 grams per day).

The terms “administer”, “administering”, “administration”, and the like, as used herein, refer to methods that may be used to enable delivery of compositions to the desired site of biological action. These methods include, but are not limited to, intraarticular (in the joints), intravenous, intramuscular, intratumoral, intradermal, intraperitoneal, subcutaneous,

orally, topically, intrathecally, inhalationally, transdermally, rectally, and the like.

Administration techniques that can be employed with the agents and methods described herein are found in *e.g.*, Goodman and Gilman, *The Pharmacological Basis of Therapeutics*, current ed.; Pergamon; and Remington's, *Pharmaceutical Sciences* (current edition), Mack Publishing Co., Easton, Pa.

In addition, the disclosed RAD51 inhibitors can be co-administered with other therapeutic agents. As used herein, the terms "co-administration", "administered in combination with", and their grammatical equivalents, are meant to encompass administration of two or more therapeutic agents to a single subject, and are intended to include treatment regimens in which the agents are administered by the same or different route of administration or at the same or different times. In some embodiments the one or more compounds described herein will be co-administered with other agents. These terms encompass administration of two or more agents to the subject so that both agents and/or their metabolites are present in the subject at the same time. They include simultaneous administration in separate compositions, administration at different times in separate compositions, and/or administration in a composition in which both agents are present. Thus, in some embodiments, the compounds described herein and the other agent(s) are administered in a single composition. In some embodiments, the compounds described herein and the other agent(s) are admixed in the composition.

The particular mode of administration and the dosage regimen will be selected by the attending clinician, taking into account the particulars of the case (*e.g.*, the subject, the disease, the disease state involved, the particular treatment). Treatment can involve daily or multi-daily or less than daily (such as weekly or monthly etc.) doses over a period of a few days to months, or even years. However, a person of ordinary skill in the art would immediately recognize appropriate and/or equivalent doses looking at dosages of approved compositions for treating a RAD51 mediated disease using the disclosed RAD51 inhibitors for guidance.

The compounds or the corresponding pharmaceutical compositions taught herein can be administered to a patient in a variety of forms depending on the selected route of administration, as will be understood by those skilled in the art. The compounds of the present teachings may be administered, for example, by oral, parenteral, buccal, sublingual, nasal, rectal, patch, pump or transdermal administration and the pharmaceutical compositions formulated accordingly. Parenteral administration includes intravenous, intraperitoneal,

subcutaneous, intramuscular, transepithelial, nasal, intrapulmonary, intrathecal, rectal and topical modes of administration. Parenteral administration can be by continuous infusion over a selected period of time.

The pharmaceutical composition of the disclosure is formulated to be compatible with its intended route of administration. In an embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous, subcutaneous, intramuscular, oral, intranasal, or topical administration to human beings. In preferred embodiments, the pharmaceutical composition is formulated for intravenous administration.

Typically, for oral therapeutic administration, a compound of the present teachings may be incorporated with excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like.

Typically for parenteral administration, solutions of a compound of the present teachings can generally be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, DMSO and mixtures thereof with or without alcohol, and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

Typically, for injectable use, sterile aqueous solutions or dispersion of, and sterile powders of, a compound described herein for the extemporaneous preparation of sterile injectable solutions or dispersions are appropriate.

EXAMPLES

Abbreviations:

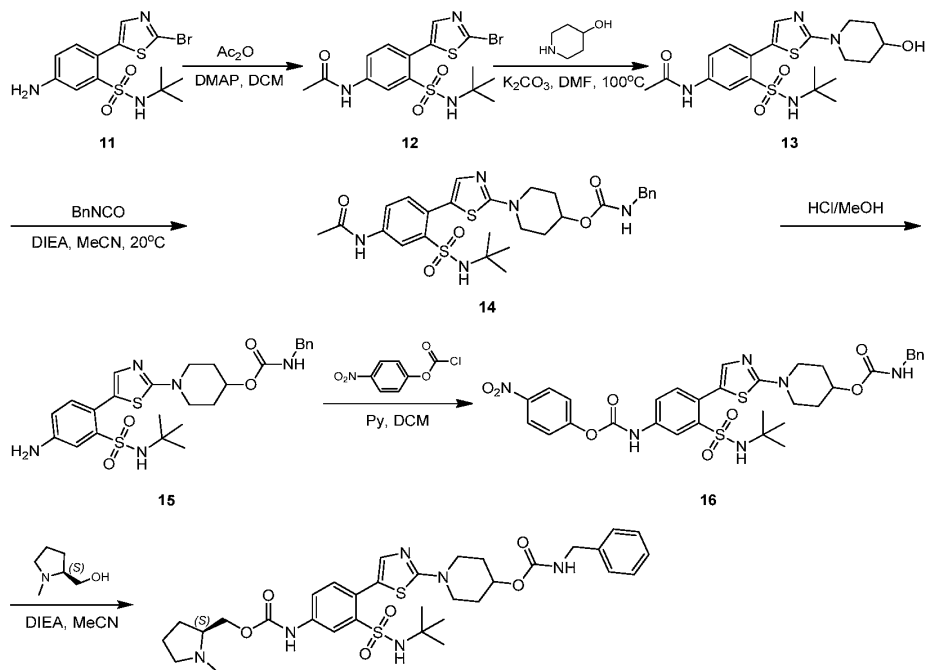
Ac	acetyl
ACN	acetonitrile
aq	aqueous
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
br.	broad
d	doublet (only when used within ¹ H NMR spectra)
DCM	dichloromethane
DIEA(DIPEA)	diisopropylethylamine
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
dppf	1,1'-bis(diphenylphosphino) ferrocene

eq	equivalent
EtOAc	ethyl acetate
hr	hour
HBTU	<i>N,N,N',N'</i> -tetramethyl-O-(1 <i>H</i> -benzotriazol-1-yl)uronium hexafluorophosphate
HPLC	high performance liquid chromatography
LC-MS	liquid chromatography coupled to mass spectrometry
m	multiplet
MS ESI	mass spectra, electrospray ionization
NBS	<i>N</i> -bromosuccinimide
NMR	nuclear magnetic resonance
prep	preparative
Py	pyridine
s	singlet
sat	saturated
SFC	supercritical fluid chromatography
t	triplet
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
Tol	toluene

General Method	Reaction Name
A	<i>Substitution Reaction</i>
B	<i>Suzuki Reaction A</i>
C	<i>Deprotection of Boc group A (TFA)</i>
D	<i>Acylation Reaction</i>
E	<i>Urea Formation</i>
F	<i>Deprotection of Boc group B (HCl)</i>
G	<i>Reduction with Fe</i>
H	<i>Carbamate Formation</i>
I	<i>Hydrogenation</i>
J	<i>Bromination</i>
K	<i>Suzuki Reaction B</i>
L	<i>Thionation</i>
M	<i>Cyclization</i>
N	<i>Coupling Reaction</i>
O	<i>Hydrolysis Reaction</i>

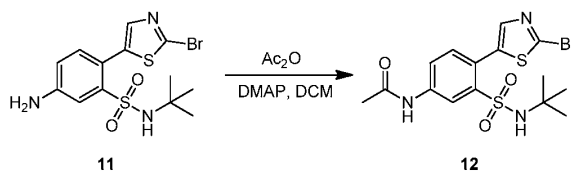
Example 1. Synthesis of (S)-(1-methylpyrrolidin-2-yl)methyl 4-(2-(4-((benzylcarbamoyl oxy)piperidin-1-yl)thiazol-5-yl)-3-(N-(tert-butyl)sulfamoyl)phenyl)carbamate

Scheme 1:



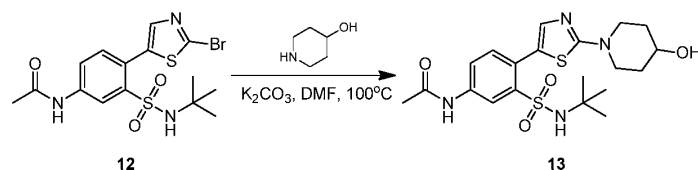
Ex. 1

General method D for preparation of sulfonamide compound 12.



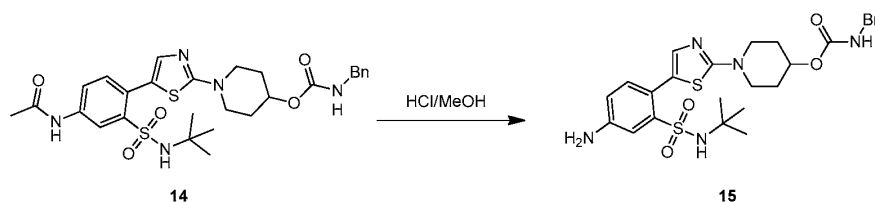
To a solution of **5-amino-2-(2-bromothiazol-5-yl)-N-tert-butyl-benzenesulfonamide** (5 g, 12.8 mmol, 1 *eq.*) in DCM (30 mL) were added DMAP (156 mg, 1.3 mmol, 0.1 *eq.*) and Ac₂O (1.96 g, 19.2 mmol, 1.5 *eq.*). The mixture was stirred at 20°C for 1 hr, and then washed with 1M HCl (50 mL) and sat.aq.Na₂CO₃ (50 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether: Ethyl acetate = 5:1 to 2:1) to give **N-[4-(2-bromothiazol-5-yl)-3-(tert-butylsulfamoyl)phenyl]acetamide** (1.5 g, 3.5 mmol, 27% yield) as a yellow solid. ESI [M+H] = 433.9/431.9

General method A for preparation of sulfonamide compound 13.



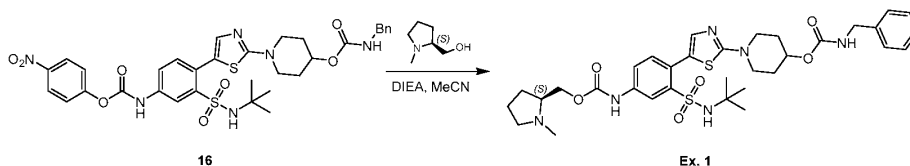
To a solution of *N*-[4-(2-bromothiazol-5-yl)-3-(tert-butylsulfamoyl)phenyl]acetamide (700 mg, 1.6 mmol, 1 *eq.*) in DMF (20 mL) were added K₂CO₃ (448 mg, 3.3 mmol, 2 *eq.*) and piperidin-4-ol (246 mg, 2.4 mmol, 1.5 *eq.*). The mixture was stirred at 100°C for 12 hrs and then poured into H₂O (100 mL). The aqueous phase was extracted with EtOAc (50 mL x 3), the combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether: Ethyl acetate = 1:2) to give *N*-[3-(tert-butylsulfamoyl)-4-[2-(4-hydroxy-1-piperidyl)thiazol-5-yl]phenyl]acetamide (550 mg, 1.2 mmol, 13.2% yield) as a yellow solid. ¹H NMR (400MHz, CHLOROFORM-*d*) δ = 8.26 (dd, *J*=2.2, 8.6 Hz, 2H), 7.93 (d, *J*=2.4 Hz, 1H), 7.37 (d, *J*=8.4 Hz, 1H), 7.31 (s, 1H), 4.02 - 3.94 (m, 1H), 3.88 - 3.80 (m, 2H), 3.30 (ddd, *J*=3.5, 9.2, 13.1 Hz, 2H), 2.21 (s, 3H), 2.03 - 1.95 (m, 2H), 1.67 (dtd, *J*=4.0, 8.7, 13.0 Hz, 2H), 1.09 (s, 9H). ESI [M+H] = 453.1

General method F for preparation of sulfonamide compound 15.



[1-[5-[4-acetamido-2-(tert-butylsulfamoyl)phenyl]thiazol-2-yl]-4-piperidyl] N-benzylcarbamate (380 mg, 649 μmol, 1 *eq.*) was dissolved into HCl/MeOH (4 M, 20 mL) and the mixture was stirred at 20°C for 1 hr. The mixture was concentrated, diluted with sat.aq.Na₂CO₃ (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether: Ethyl acetate = 10:1 to 1:1) to give *[1-[5-[4-amino-2-(tert-butylsulfamoyl)phenyl]thiazol-2-yl]-4-piperidyl] N-benzylcarbamate* (300 mg, 552 μmol, 85% yield) as a yellow solid. ESI [M+H] = 544.2

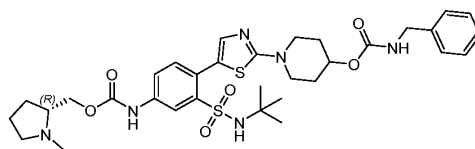
General method H for preparation of Example 1.



To a solution of [(2S)-1-methylpyrrolidin-2-yl]methanol (42 mg, 367 μ mol, 2 *eq.*) and DIEA (71.11 mg, 550 μ mol, 3 *eq.*) in MeCN (5 mL) was added a solution of [1-[5-[2-(*tert*-butylsulfamoyl)-4-[(4-nitrophenoxy)carbonylamino]phenyl]thiazol-2-yl]-4-piperidyl] *N*-benzylcarbamate (130 mg, 184 μ mol, 1 *eq.*) in DCM (2 mL) and the mixture was refluxed for 1 hr. The mixture was concentrated and the residue was purified by prep-HPLC to give (*S*)-(1-methylpyrrolidin-2-yl)methyl (4-(2-(4-((benzylcarbamoyl)oxy)piperidin-1-yl)thiazol-5-yl)-3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)carbamate (19.87 mg, 28.8 μ mol, 15.7% yield, 99.3% purity) as a pale yellow solid. ^1H NMR (400MHz, DMSO- d_6) δ = 10.06 (s, 1H), 8.26 (d, J =2.0 Hz, 1H), 7.71 (t, J =6.2 Hz, 1H), 7.60 (dd, J =2.3, 8.5 Hz, 1H), 7.37 - 7.14 (m, 7H), 6.94 (s, 1H), 4.81 - 4.71 (m, 1H), 4.16 (br d, J =6.2 Hz, 2H), 4.10 - 4.03 (m, 1H), 4.02 - 3.96 (m, 1H), 3.73 - 3.63 (m, 2H), 3.28 (br s, 2H), 2.94 - 2.87 (m, 1H), 2.44 - 2.37 (m, 1H), 2.30 (s, 3H), 2.18 - 2.05 (m, 1H), 1.99 - 1.82 (m, 3H), 1.68 - 1.52 (m, 5H), 1.12 - 1.03 (m, 9H). ESI $[M+H]^+$ = 685.2

Example 2. Synthesis of [1-[5-[2-(*tert*-butylsulfamoyl)-4-[(2*R*)-1-methylpyrrolidin-2-yl]methoxycarbonylamino]phenyl]thiazol-2-yl]-4-piperidyl] *N*-benzylcarbamate.

The following compound was synthesized via same method by the key intermediate 16.

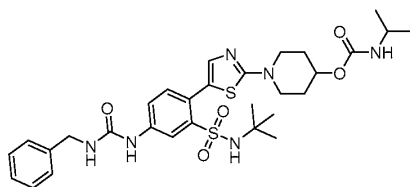
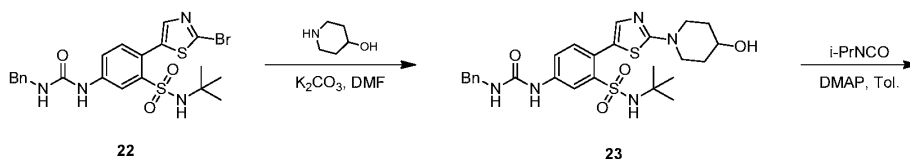


Ex. 2

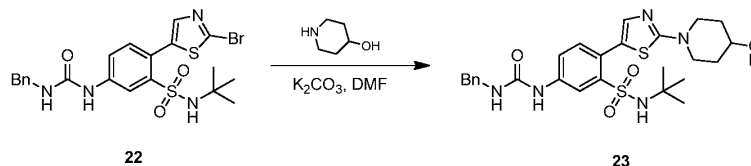
[1-[5-[2-(*tert*-butylsulfamoyl)-4-[(2*R*)-1-methylpyrrolidin-2-yl]methoxycarbonylamino]phenyl]thiazol-2-yl]-4-piperidyl] *N*-benzylcarbamate. ^1H NMR (400MHz, DMSO- d_6) δ = 10.07 (s, 1H), 8.29 (d, J =2.2 Hz, 1H), 7.73 (t, J =6.2 Hz, 1H), 7.63 (dd, J =2.3, 8.5 Hz, 1H), 7.39 - 7.19 (m, 7H), 6.94 (s, 1H), 4.80 (td, J =4.1, 8.0 Hz, 1H), 4.20 (br d, J =6.1 Hz, 2H), 4.14 - 4.07 (m, 1H), 4.06 - 3.99 (m, 1H), 3.72 (br d, J =13.6 Hz, 2H), 3.29 - 3.22 (m, 2H), 2.98 - 2.92 (m, 1H), 2.45 - 2.41 (m, 1H), 2.33 (s, 3H), 2.22 - 2.13 (m, 1H), 2.02 - 1.79 (m, 3H), 1.72 - 1.56 (m, 5H), 1.20 - 1.03 (m, 9H). ESI $[M+H]^+$ = 685.2

Example 3. Synthesis of [1-[5-[4-(benzylcarbamoylamino)-2-(*tert*-butylsulfamoyl)phenyl]thiazol-2-yl]-4-piperidyl] *N*-isopropylcarbamate.

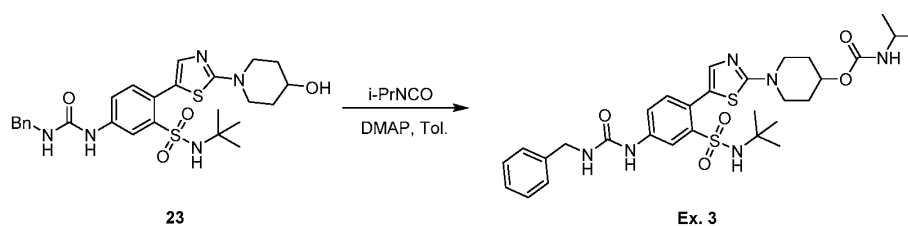
Scheme 2:



Ex. 3

Preparation of compound 23.

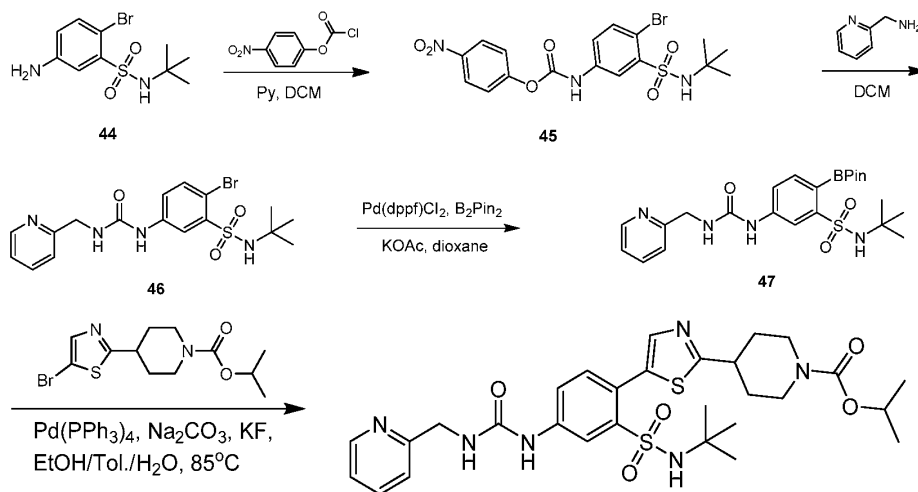
General method A, *1-benzyl-3-[3-(tert-butylsulfamoyl)-4-[2-(4-hydroxy-1-piperidyl)thiazol-5-yl]phenyl]urea*. ESI [M+H] = 544.1

Preparation of Ex. 3.

To a solution of *1-benzyl-3-[3-(tert-butylsulfamoyl)-4-[2-(4-hydroxy-1-piperidyl)thiazol-5-yl]phenyl]urea* (50 mg, 91.96 μmol , 1 *eq.*) in Tol. (2 mL), were added DMAP (22.47 mg, 183.92 μmol , 2 *eq.*) and [isopropyl(methyl)-azanylidene] methanone (78.26 mg, 919.62 μmol , 10 *eq.*). The mixture was stirred at 100°C for 4 hrs and then concentrated. The residue was purified by prep-TLC (Petroleum ether/EtOAc=1:3) and then acidic prep-HPLC to give *[1-[5-[4-(benzylcarbamoylamino)-2-(tert-butylsulfamoyl)phenyl]thiazol-2-yl]-4-piperidyl] N-isopropylcarbamate* (28.31 mg, 99.2% purity) as a yellow solid. ^1H NMR (400MHz, METHANOL- d_4) δ = 8.29 (d, J=2.0 Hz, 1H), 7.71 (dd, J=2.0, 8.3 Hz, 1H), 7.43 (d, J=8.8 Hz, 1H), 7.35 (d, J=3.9 Hz, 5H), 7.27 (dt, J=2.7, 5.7 Hz, 1H), 4.98 - 4.93 (m, 1H), 4.43 (s, 2H), 3.90 - 3.59 (m, 5H), 2.19 - 2.07 (m, 2H), 1.99 - 1.86 (m, 2H), 1.22 (s, 9H), 1.16 (d, J=6.8 Hz, 6H). ESI [M+H] = 629.1

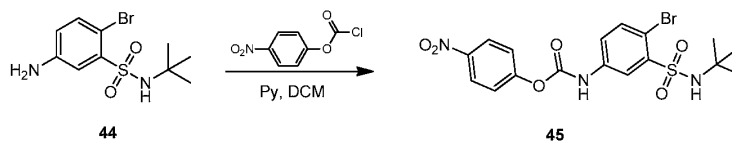
Example 4. Synthesis of isopropyl 4-[5-[2-(tert-butylsulfamoyl)-4-(2-pyridylmethyl carbamoylamino)phenyl]thiazol-2-yl]piperidine-1-carboxylate.

Scheme 3:



Ex. 4

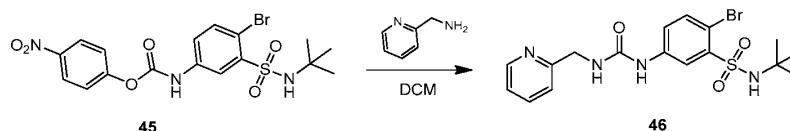
Preparation of compound 45



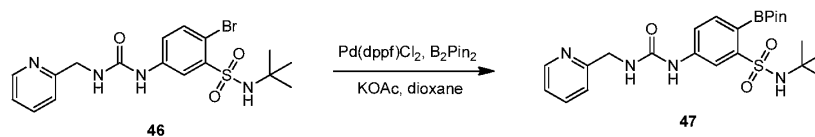
General method D, *4-nitrophenyl (4-bromo-3-(N-(tert-butyl)sulfamoyl)phenyl) carbamate*.

ESI [M+H] = 474.1

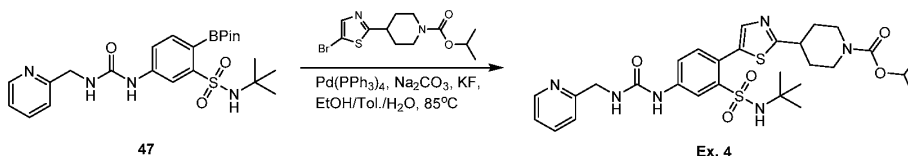
General method E for preparation of sulfonamide compound 46.



To a solution of 2-pyridylmethanamine (352 mg, 3.3 mmol, 5 *eq.*) and DIEA (84 mg, 650 μ mol, 1 *eq.*) in DCM (3 mL) was added the solution of *(4-nitrophenyl) N-[4-bromo-3-(tert-butylsulfamoyl)phenyl]carbamate* (307 mg, 650 μ mol, 1 *eq.*) in DCM (3 mL). The mixture was stirred at 25°C for 1 hr, then diluted with DCM (30 mL) and washed with H₂O (20 mL x 2). The organic layer was concentrated and the residue was purified by prep-TLC (SiO₂, Petroleum ether: Ethyl acetate = 0:1) to give *1-[4-bromo-3-(tert-butylsulfamoyl)phenyl]-3-(2-pyridylmethyl)urea* (180 mg, crude) as a yellow solid. ESI [M+H] = 441.2/443.2

Preparation of compound 47

A mixture of **1-[4-bromo-3-(tert-butylsulfamoyl)phenyl]-3-(2-pyridylmethyl)urea** (140 mg, 317.21 μmol , 1 *eq.*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (322.21 mg, 1.27 mmol, 4 *eq.*), Pd(dppf)Cl₂ (116.05 mg, 158.61 μmol , 0.5 *eq.*) and KOAc (93.39 mg, 951.64 μmol , 3 *eq.*) in dioxane (4 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 80°C for 12 hrs under N₂ atmosphere. The mixture was concentrated and the residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/0 to 1:1) to give **1-[3-(tert-butylsulfamoyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-3-(2-pyridylmethyl)urea** (50 mg, 89.37 μmol , 28.17% yield, 87.3% purity). ESI [M+H]⁺=489.4

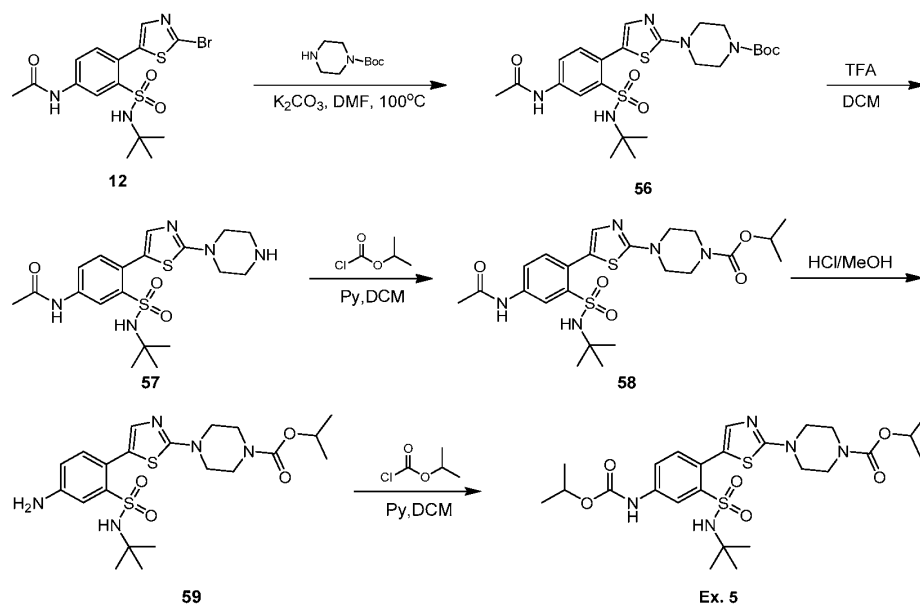
General method K for preparation of compound Ex. 4

A mixture of **1-[3-(tert-butylsulfamoyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-3-(2-pyridylmethyl)urea** (26.38 mg, 54.01 μmol , 1.2 *eq.*), **isopropyl 4-(5-bromothiazol-2-yl)piperidine-1-carboxylate** (15 mg, 45.01 μmol , 1 *eq.*), Na₂CO₃ (9.54 mg, 90.02 μmol , 2 *eq.*), KF (7.85 mg, 135.04 μmol , 3 *eq.*) and Pd(PPh₃)₄ (5.20 mg, 4.50 μmol , 0.1 *eq.*) in H₂O (0.1 mL)/EtOH (0.3 mL)/Tol. (0.3 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 85°C for 12 hrs under N₂ atmosphere. The reaction mixture was filtered and concentrated. The residue was purified by prep-TLC (SiO₂, Petroleum ether/Ethyl acetate=1/2) and then prep-HPLC (TFA condition) to give **isopropyl 4-[5-[2-(tert-butylsulfamoyl)-4-(2-pyridylmethylcarbamoylamino)phenyl]thiazol-2-yl]piperidine-1-carboxylate** (6.36 mg, 8.21 μmol , 18.24% yield, 94.07% purity, TFA) as a pale yellow solid. ¹H NMR (400MHz, METHANOL-d₄) δ = 8.75 (br d, J=5.6 Hz, 1H), 8.53 (br t, J=7.9 Hz, 1H), 8.34 (d, J=2.0 Hz, 1H), 8.04 (br d, J=8.1 Hz, 1H), 7.92 (br t, J=6.5 Hz, 1H), 7.75 (s, 1H), 7.69 (dd, J=2.3, 8.4 Hz, 1H), 7.39 (d, J=8.3 Hz, 1H), 4.94 - 4.92 (m, 1H), 4.77 (s, 2H), 4.24 (br d, J=13.4 Hz, 2H), 3.31 - 3.25 (m, 1H), 3.02 (br s, 2H), 2.15 (br d,

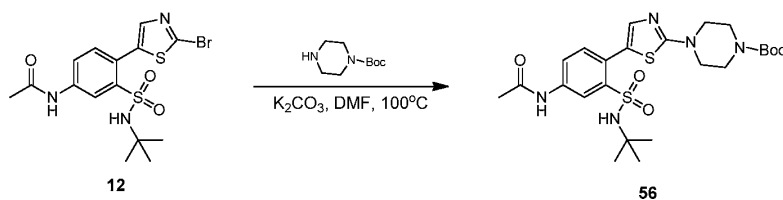
J=11.5 Hz, 2H), 1.76 (dq, J=4.2, 12.3 Hz, 2H), 1.28 (d, J=6.2 Hz, 6H), 1.11 (s, 9H). ESI [M+H] = 615.2

Example 5. Synthesis of isopropyl 4-[5-[2-(tert-butylsulfamoyl)-4-(isopropoxycarbonyl amino)phenyl]thiazol-2-yl]piperazine-1-carboxylate.

Scheme 4:

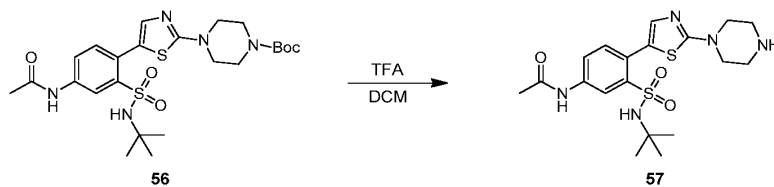


Preparation of compound 56



General method A, *tert-butyl 4-[5-[4-acetamido-2-(tert-butylsulfamoyl)phenyl]thiazol-2-yl]piperazine-1-carboxylate*. ESI [M+H] = 538.2

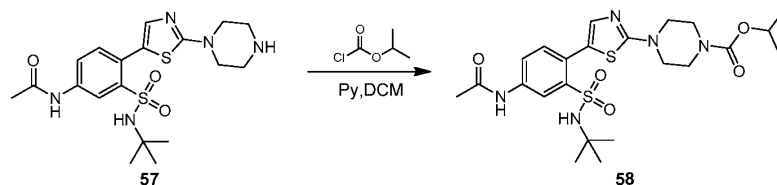
General method C for preparation of sulfonamide compound 57.



To a solution of *tert-butyl 4-[5-[4-acetamido-2-(tert-butylsulfamoyl)phenyl]thiazol-2-yl]piperazine-1-carboxylate* (110 mg, 205 μmol , 1 eq.) in DCM (2 mL) was added TFA (1

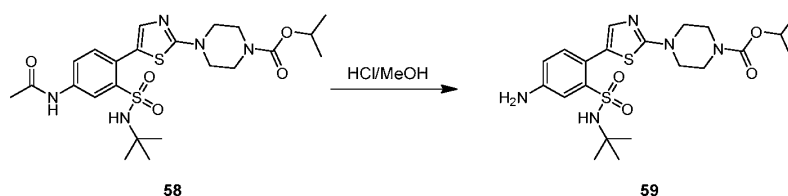
mL) and the mixture was stirred at 25°C for 30 mins. The mixture was concentrated to give *N*-[3-(*tert*-butylsulfamoyl)-4-(2-piperazin-1-ylthiazol-5-yl)phenyl]acetamide (80 mg, 183 μ mol, 89.4% yield) as a yellow solid. ESI [M+H] = 438.2

Preparation of compound 58



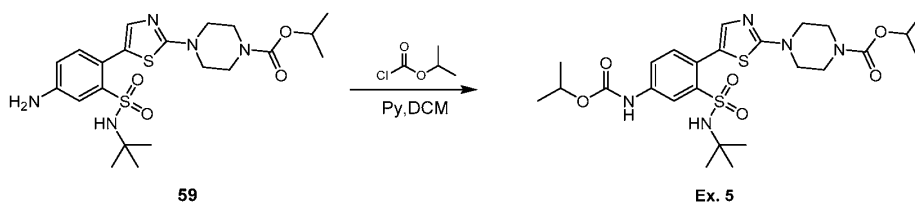
General method D, *isopropyl 4-[5-[4-(tert-butylsulfamoyl)-2-aminophenyl]thiazol-2-yl]piperazine-1-carboxylate*. ESI [M+H] = 524.1

Preparation of compound 59



General method F, *isopropyl 4-[5-[4-amino-2-(tert-butylsulfamoyl)phenyl]thiazol-2-yl]piperazine-1-carboxylate*. ESI [M+H] = 482.1

Preparation of compound Ex. 5

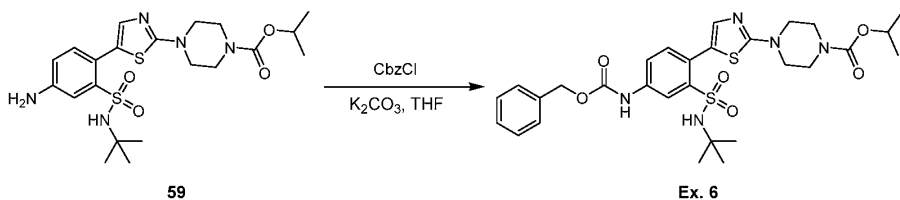


General method D, *isopropyl 4-[5-[2-(tert-butylsulfamoyl)-4-(isopropoxycarbonylamino)phenyl]thiazol-2-yl]piperazine-1-carboxylate*. ^1H NMR (400MHz, METHANOL- d_4) δ = 8.22 (d, J =2.1 Hz, 1H), 7.56 (dd, J =2.2, 8.3 Hz, 1H), 7.30 (d, J =8.3 Hz, 1H), 7.20 (s, 1H), 4.94 - 4.81 (m, 2H), 3.61 - 3.43 (m, 8H), 1.20 (dd, J =6.2, 14.5 Hz, 12H), 1.07 (s, 9H). ESI [M+H] = 568.3

Example 6. Synthesis of *isopropyl 4-[5-[4-(benzyloxycarbonylamino)-2-(tert-butylsulfamoyl)phenyl]thiazol-2-yl]piperazine-1-carboxylate*

Scheme 5:

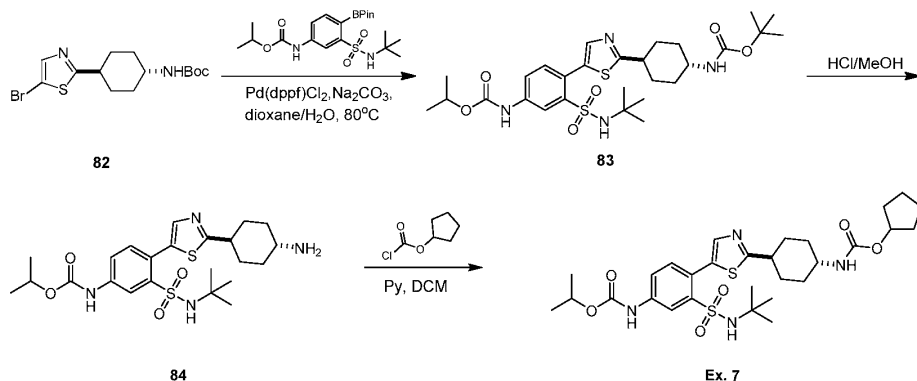
Preparation of compound Ex. 6



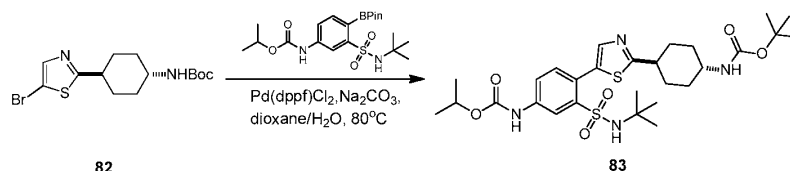
General method D, *isopropyl 4-[5-[4-(benzyloxycarbonylamino)-2-(tert-butylsulfamoyl)phenyl]thiazol-2-yl]piperazine-1-carboxylate*. ^1H NMR (400MHz, METHANOL- d_4) δ = 8.33 (d, J =2.0 Hz, 1H), 7.68 (dd, J =2.2, 8.4 Hz, 1H), 7.45 - 7.27 (m, 7H), 5.21 (s, 2H), 4.94 - 4.88 (m, 1H), 3.68 - 3.51 (m, 8H), 1.27 (d, J =6.4 Hz, 6H), 1.19 - 1.11 (m, 9H). ESI $[M+H]^+$ = 616.3

Example 7. Synthesis of *trans-isopropyl N-[3-(tert-butylsulfamoyl)-4-[2-[4-(cyclopentoxycarbonylamino)cyclohexyl]thiazol-5-yl]phenyl]carbamate*.

Scheme 6:



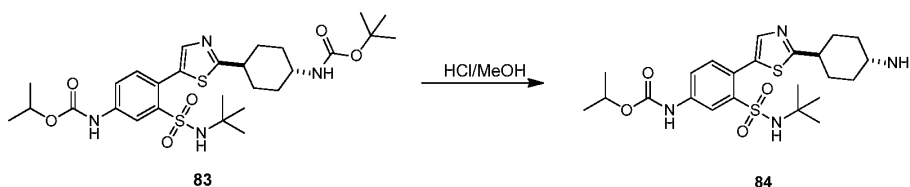
General method B for preparation of sulfonamide compound 83.



To a mixture of *tert-butyl (trans-4-(5-bromothiazol-2-yl)cyclohexyl)carbamate* (1.3 g, 3.6 mmol, 2 eq.) and *isopropyl N-[3-(tert-butylsulfamoyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate* (800 mg, 1.8 mmol, 1 eq.) in dioxane (12 mL) and H_2O (2 mL) were added Na_2CO_3 (579 mg, 5.5 mmol, 3 eq.) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (133 mg, 182 μmol , 0.1 eq.). The mixture was stirred at 80°C for 12 hrs under N_2 atmosphere and then concentrated. The residue was diluted with H_2O (5 mL) and extracted with ethyl acetate (5 mL x 3), dried over Na_2SO_4 , filtered and concentrated. The residue was purified by column

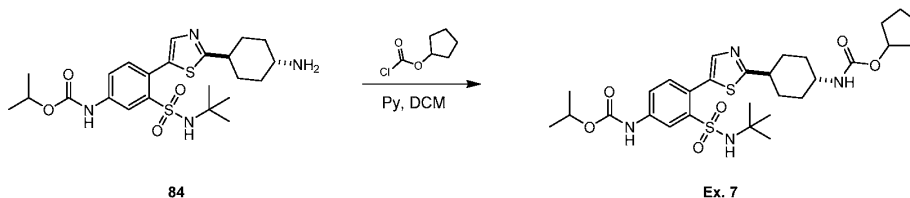
chromatography (SiO₂, Petroleum ether: Ethyl acetate = 1:0 to 3:1) to give *trans-isopropyl-N-[4-[2-[4-(tert-butoxycarbonylamino)cyclohexyl]thiazol-5-yl]-3-(tert-butylsulfamoyl)phenyl]carbamate* (660 mg, crude), in which 60 mg was purified by prep-HPLC (column: Agela Durashell C18 150X25 5u; mobile phase: [water(0.04%NH₃H₂O)-ACN]; B%: 60%-90%, 10min) to give pure **compound 83** (40.92 mg, 99.64% purity) as a white solid for delivery. ¹H NMR (400MHz, DMSO-d₆) δ = 10.06 (s, 1H), 8.32 (d, J=2.1 Hz, 1H), 7.70 - 7.60 (m, 2H), 7.38 (d, J=8.4 Hz, 1H), 6.96 (s, 1H), 6.81 (br d, J=7.9 Hz, 1H), 4.99 - 4.87 (m, 1H), 3.27 (br s, 1H), 2.94 - 2.84 (m, 1H), 2.13 (br d, J=11.7 Hz, 2H), 1.90 (br d, J=11.1 Hz, 2H), 1.63 - 1.49 (m, 2H), 1.39 (s, 9H), 1.33 (br d, J=14.4 Hz, 2H), 1.28 (d, J=6.4 Hz, 6H), 1.07 (s, 9H). ESI [M+H] = 595.3

Preparation of compound 84



General method F, *trans-isopropyl N-[4-[2-(4-aminocyclohexyl)thiazol-5-yl]-3-(tert-butylsulfamoyl)phenyl]carbamate*. ESI [M+H] = 495.2

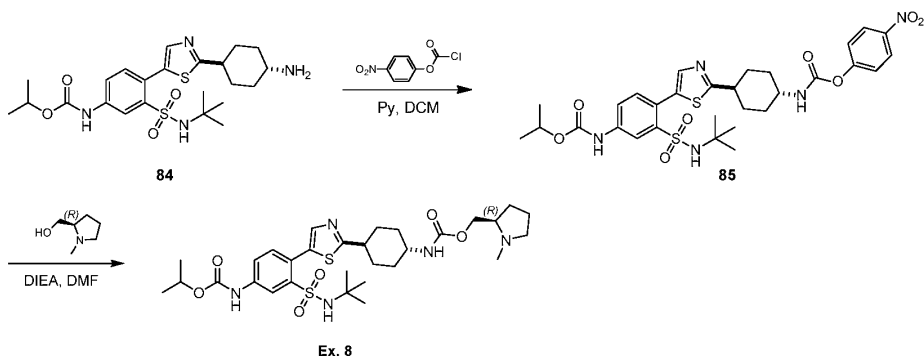
Preparation of Ex. 7



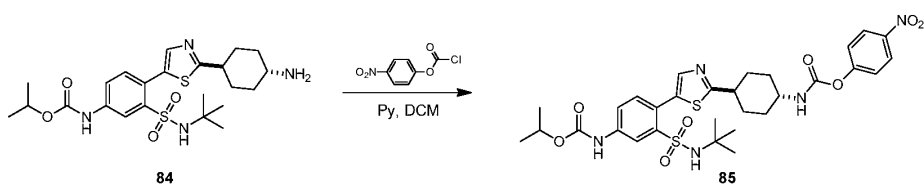
General method D, *trans-isopropyl N-[3-(tert-butylsulfamoyl)-4-[2-[4-(cyclopentoxycarbonylamino)cyclohexyl]thiazol-5-yl]phenyl]carbamate*. ¹H NMR (400MHz, DMSO-d₆) δ = 10.04 (s, 1H), 8.29 (d, J=2.2 Hz, 1H), 7.61 - 7.59 (m, 2H), 7.35 (d, J=8.8 Hz, 1H), 7.00 (br d, J=7.9 Hz, 1H), 6.96 - 6.93 (m, 1H), 4.96 - 4.87 (m, 2H), 3.29 - 3.22 (m, 1H), 2.87 (br t, J=11.8 Hz, 1H), 2.10 (br d, J=12.7 Hz, 2H), 1.88 (br d, J=12.7 Hz, 2H), 1.75 (br s, 2H), 1.61 - 1.48 (m, 8H), 1.36 - 1.27 (m, 2H), 1.25 (d, J=6.1 Hz, 6H), 1.04 (s, 9H). ESI [M+Na] = 629.3

Example 8. Synthesis of *[(2R)-1-methylpyrrolidin-2-yl]methyl N-[4-[5-[2-(tert-butylsulfamoyl)-4-(isopropoxycarbonylamino)phenyl]thiazol-2-yl]cyclohexyl]carbamate*.

Scheme 7:

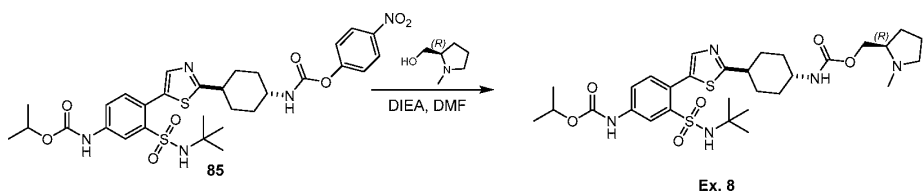


Preparation of compound 85



General method D, *trans*-(4-nitrophenyl) *N*-[4-[5-[2-(*tert*-butylsulfamoyl)-4-(isopropoxycarbonylamino)phenyl]thiazol-2-yl]cyclohexyl]carbamate. ESI [M+H] = 660.2

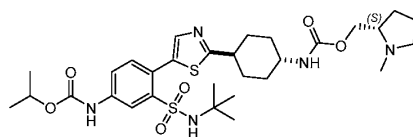
Preparation of compound Ex. 8



General method H, [(2*R*)-1-methylpyrrolidin-2-yl]methyl *N*-[4-[5-[2-(*tert*-butylsulfamoyl)-4-(isopropoxycarbonylamino)phenyl]thiazol-2-yl]cyclohexyl]carbamate. ¹H NMR (400MHz, METHANOL-*d*₄) δ = 8.38 (s, 1H), 7.80 - 7.73 (m, 1H), 7.69 (dd, *J*=2.2, 8.4 Hz, 1H), 7.40 (d, *J*=8.3 Hz, 1H), 5.05 - 5.00 (m, 1H), 4.48 (br dd, *J*=3.0, 12.8 Hz, 1H), 4.21 (br dd, *J*=7.2, 12.6 Hz, 1H), 3.78 - 3.66 (m, 2H), 3.57 - 3.46 (m, 1H), 3.22 (td, *J*=8.3, 11.2 Hz, 1H), 3.07 - 3.01 (m, 3H), 2.43 - 1.99 (m, 8H), 1.98 - 1.88 (m, 1H), 1.80 - 1.66 (m, 2H), 1.47 (q, *J*=12.5 Hz, 2H), 1.34 (d, *J*=6.2 Hz, 6H), 1.20 - 1.12 (m, 9H). ESI [M+H] = 636.2

Example 9. Synthesis of isopropyl (3-(*N*-(*tert*-butyl)sulfamoyl)-4-(2-((1*S*,4*r*)-4-(((*S*)-1-methylpyrrolidin-2-yl)methoxy)carbonyl)amino)cyclohexyl)thiazol-5-yl)phenyl)carbamate.

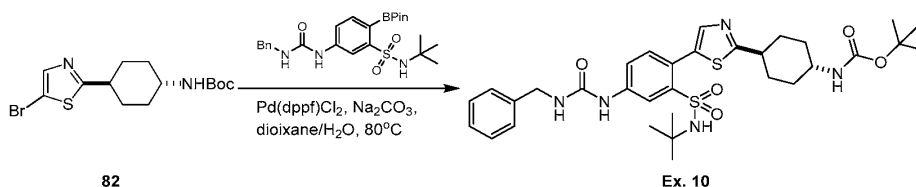
The following compound was synthesized via same method by the key intermediate 85.



Ex. 9

^1H NMR (METHANOL- d_4 , 400MHz): δ = 8.34 (d, J =2.2 Hz, 1H), 7.71 (s, 1H), 7.66 (dd, J =8.5, 2.1 Hz, 1H), 7.36 (d, J =8.4 Hz, 1H), 4.93-5.04 (m, 1H), 4.46 (dd, J =13.0, 2.9 Hz, 1H), 4.18 (dd, J =13.0, 7.1 Hz, 1H), 3.64-3.75 (m, 2H), 3.42-3.58 (m, 1H), 3.12-3.25 (m, 1H), 3.00-3.06 (m, 3H), 1.97-2.39 (m, 8H), 1.84-1.96 (m, 1H), 1.64-1.77 (m, 2H), 1.44 (q, J =12.6 Hz, 2H), 1.31 (d, J =6.2 Hz, 6H), 1.13 (s, 9H). ESI $[M+H]^+$ = 636.3

Example 10. Synthesis of *trans-tert-butyl N-[4-[5-[4-(benzylcarbamoylamino)-2-(tert-butylsulfonyl)phenyl]thiazol-2-yl]cyclohexyl]carbamate*.



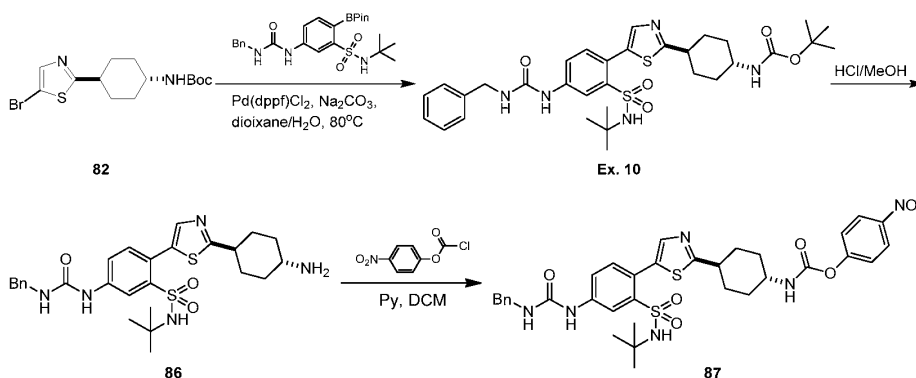
82

Ex. 10

General method B, *trans-tert-butyl N-[4-[5-[4-(benzylcarbamoylamino)-2-(tert-butylsulfonyl)phenyl]thiazol-2-yl]cyclohexyl]carbamate*. ^1H NMR (400MHz, METHANOL- d_4) δ = 8.24 (d, J =2.4 Hz, 1H), 7.72 - 7.66 (m, 2H), 7.37 - 7.29 (m, 5H), 7.28 - 7.21 (m, 1H), 4.40 (s, 2H), 3.39 (br t, J =11.6 Hz, 1H), 2.98 (tt, J =3.4, 12.1 Hz, 1H), 2.25 - 2.17 (m, 2H), 2.04 (br d, J =11.5 Hz, 2H), 1.67 (dq, J =2.9, 12.9 Hz, 2H), 1.44 (s, 9H), 1.41 - 1.32 (m, 2H), 1.10 (s, 9H). ESI $[M+H]^+$ = 642.3

Example 11. Synthesis of *[(2R)-1-methylpyrrolidin-2-yl]methyl N-[4-[5-[4-(benzylcarbamoylamino)-2-(tert-butylsulfonyl)phenyl]thiazol-2-yl]cyclohexyl]carbamate*.

Scheme 8:

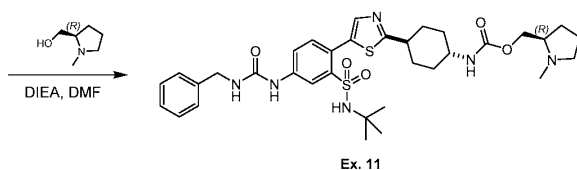


82

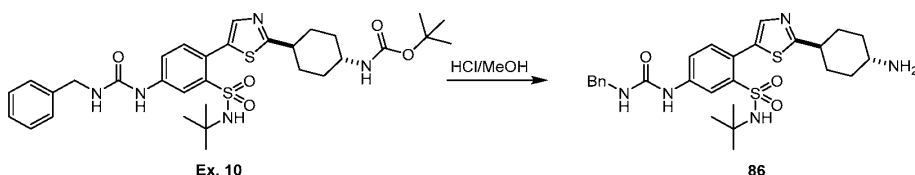
Ex. 10

86

87

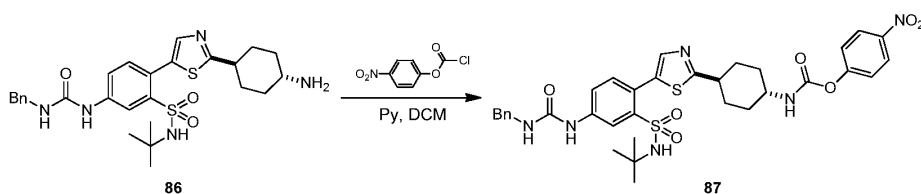


Preparation of compound 86



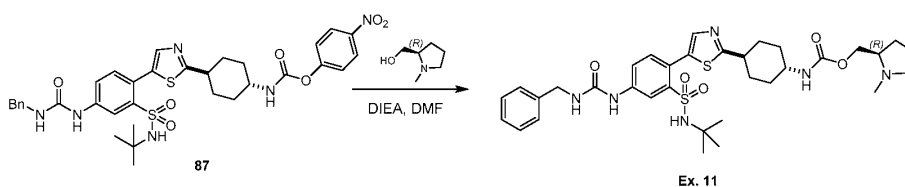
General method F, *trans*-1-[4-[2-(4-aminocyclohexyl)thiazol-5-yl]-3-(tert-butylsulfamoyl)phenyl]-3-benzyl-urea. ESI [M+H] = 542.3

Preparation of compound 87



General method D, *trans*-(4-nitrophenyl) N-[4-[5-[4-(benzylcarbamoylamino)-2-(tert-butylsulfamoyl)phenyl]thiazol-2-yl]cyclohexyl]carbamate.

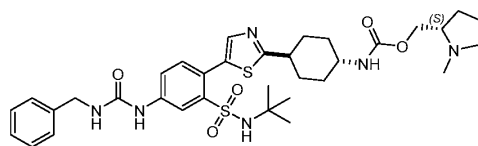
Preparation of Ex. 11



General method H, [(2R)-1-methylpyrrolidin-2-yl]methyl N-[4-[5-[4-(benzylcarbamoylamino)-2-(tert-butylsulfamoyl)phenyl]thiazol-2-yl]cyclohexyl]carbamate.

¹H NMR (400MHz, METHANOL-d₄) δ = 8.30 (d, J=2.2 Hz, 1H), 7.79 (s, 1H), 7.70 (dd, J=2.3, 8.4 Hz, 1H), 7.42 - 7.31 (m, 5H), 7.27 (dt, J=2.6, 5.7 Hz, 1H), 4.54 - 4.41 (m, 3H), 4.21 (dd, J=7.1, 12.7 Hz, 1H), 3.79 - 3.66 (m, 2H), 3.52 (br t, J=11.6 Hz, 1H), 3.26 - 3.17 (m, 1H), 3.04 (s, 3H), 2.42 - 1.98 (m, 8H), 1.97 - 1.87 (m, 1H), 1.80 - 1.65 (m, 2H), 1.54 - 1.40 (m, 2H), 1.15 (s, 9H). ESI [M+H] = 683.3

Example 12. Synthesis of ((S)-1-methylpyrrolidin-2-yl)methyl ((1R,4S)-4-(5-(4-(3-benzylureido)-2-(N-(tert-butyl)sulfamoyl)phenyl)thiazol-2-yl)cyclohexyl)carbamate
The following compound was synthesized via same method by the key intermediate 87.

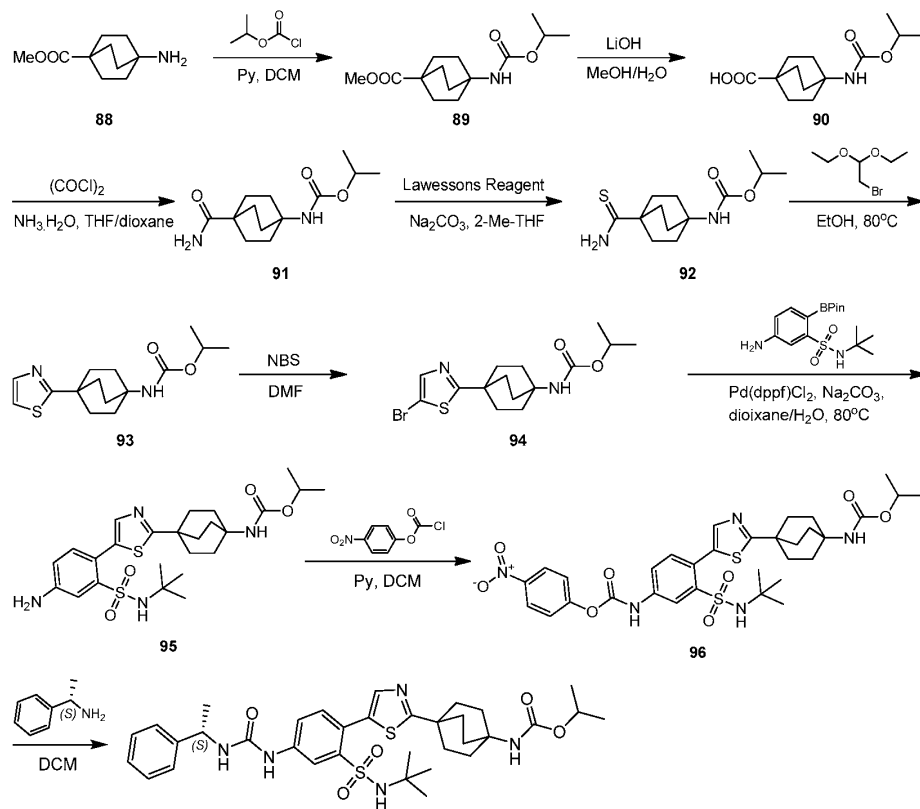


Ex. 12

¹H NMR (400MHz, METHANOL-d₄) δ = 8.29 (d, J=2.3 Hz, 1H), 7.83 - 7.74 (m, 1H), 7.73 - 7.65 (m, 1H), 7.43 - 7.31 (m, 5H), 7.30 - 7.22 (m, 1H), 4.55 - 4.35 (m, 3H), 4.21 (br dd, J=7.1, 12.7 Hz, 1H), 3.79 - 3.61 (m, 2H), 3.58 - 3.42 (m, 1H), 3.23 (br s, 1H), 3.08 - 3.02 (m, 3H), 2.43 - 1.98 (m, 8H), 1.97 - 1.86 (m, 1H), 1.80 - 1.65 (m, 2H), 1.54 - 1.39 (m, 2H), 1.19 - 1.07 (m, 9H). ESI [M+H] = 683.3

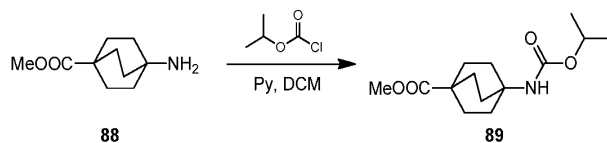
Example 13. Synthesis of isopropyl (S)-(4-(5-(2-(N-(tert-butyl)sulfamoyl)-4-(3-(1-phenylethyl)ureido)phenyl)thiazol-2-yl)bicyclo[2.2.2]octan-1-yl)carbamate.

Scheme 9:



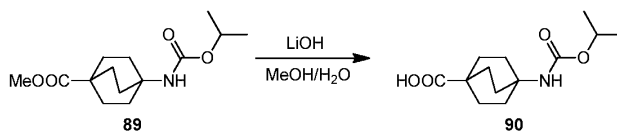
Ex. 13

Preparation of compound 89



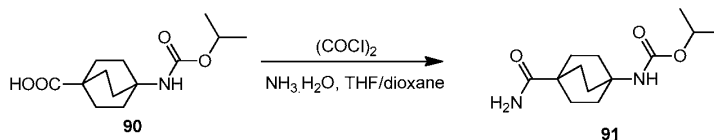
General method D, **4-(isopropoxycarbonylamino)bicyclo[2.2.2]octane-1-carboxylate**.

General method O for preparation of compound 90



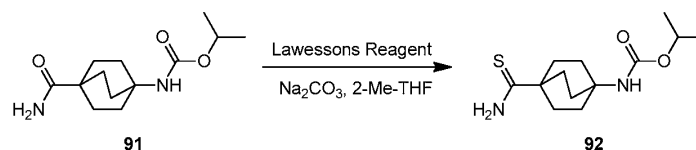
To a solution of **methyl 4-(isopropoxycarbonylamino)bicyclo[2.2.2]octane-1-carboxylate** (400 mg, 1.49 mmol, 1 *eq.*) in MeOH (5 mL), was added LiOH (106.70 mg, 4.46 mmol, 3 *eq.*) in H₂O (5 mL) and the mixture was stirred at 50°C for 1 hr. The mixture was concentrated to remove MeOH and then extracted with MTBE (10 mL*2). The pH of aqueous phase was adjusted to 1-2 by adding 4 N HCl solution and then extracted with EtOAc (10 mL*3). The combined organic phase was dried over Na₂SO₄, filtered and concentrated to give **4-(isopropoxycarbonylamino)bicyclo[2.2.2]octane-1-carboxylic acid** (270 mg, crude) as a yellow solid. ¹H NMR (400MHz, CHLOROFORM-d) δ = 4.86 (br d, J=6.4 Hz, 1H), 4.46 (br s, 1H), 2.00 - 1.80 (m, 12H), 1.23 (br d, J=5.9 Hz, 6H).

General method N for preparation of compound 91



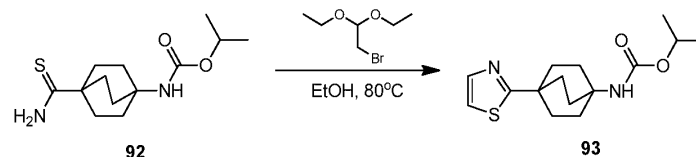
To a solution of **4-(isopropoxycarbonylamino)bicyclo[2.2.2]octane-1-carboxylic acid** (270 mg, 1.06 mmol, 1 *eq.*) in DCM (5 mL), were added DMF (7.73 mg, 105.75 μ mol, 0.1 *eq.*) and (COCl)₂ (201.34 mg, 1.59 mmol, 1.5 *eq.*). The mixture was stirred at 26°C for 0.2 hr and then concentrated. The residue was dissolved into THF (5 mL) and was added into NH₃.H₂O (741.24 mg, 5.29 mmol, 5 *eq.*) in dioxane (5 mL) dropwise. Then the mixture was stirred at 26°C for 0.3 hr. The mixture was concentrated and diluted with EtOAc (20 mL) and washed with H₂O (10 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated to give **isopropyl N-(1-carbamoyl-4-bicyclo[2.2.2]octanyl)carbamate** as a yellow solid. ¹H NMR (400MHz, CHLOROFORM-d) δ = 5.43 (br s, 1H), 5.17 (br s, 1H), 4.85 - 4.71 (m, 1H), 4.35 (br s, 1H), 1.82 (s, 12H), 1.13 (d, J=6.2 Hz, 6H). ESI[M+H]=255.2

General method L for preparation of compound 92



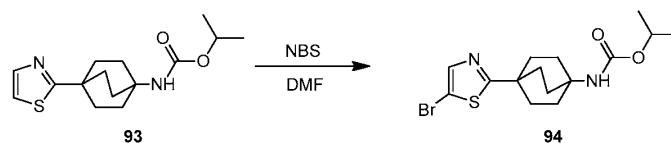
To a solution of *isopropyl N-(1-carbamoyl-4-bicyclo[2.2.2]octanyl)carbamate* (60 mg, 235.92 μmol , 1 *eq.*) in 2-Me-THF (2 mL), was added 2,4-bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4dithiadiphosphetane (95.42 mg, 235.92 μmol , 1 *eq.*) and the mixture was stirred at 80°C for 0.5 hr. The mixture was poured into sat. aq. Na_2CO_3 (10 mL) and extracted with EtOAc (10 mL*3). The combined organic phase was dried over Na_2SO_4 , filtered and concentrated. The residue was purified by prep-TLC (Petroleum ether/Ethyl acetate = 2:3) to give *isopropyl N-(1-carbamothioyl-4-bicyclo[2.2.2]octanyl)carbamate* (30 mg, crude) as a yellow solid. ESI $[\text{M}+\text{H}] = 271.1$

General method M for preparation of compound 93



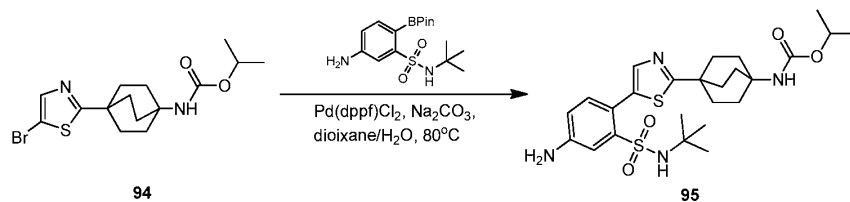
To a solution of *isopropyl N-(1-carbamothioyl-4-bicyclo[2.2.2]octanyl)carbamate* (85 mg, 314.36 μmol , 1 *eq.*) in EtOH (2 mL), were added $\text{TsOH} \cdot \text{H}_2\text{O}$ (119.59 mg, 628.72 μmol , 2 *eq.*) and 2-bromo-1,1-diethoxyethane (123.90 mg, 628.72 μmol , 2 *eq.*). The mixture was stirred at 80°C for 1 hr and then concentrated and diluted with EtOAc (30 mL). The mixture was washed with sat. aq. Na_2CO_3 (10 mL*2) and the combined organic phase was dried over Na_2SO_4 , filtered and concentrated. The residue was purified by prep-TLC (Petroleum ether/Ethyl acetate = 3:1) to give *isopropyl N-(1-thiazol-2-yl-4-bicyclo[2.2.2]octanyl)carbamate* (80 mg, crude) as a yellow solid. ESI $[\text{M}+\text{H}] = 295.3$

Preparation of compound 94



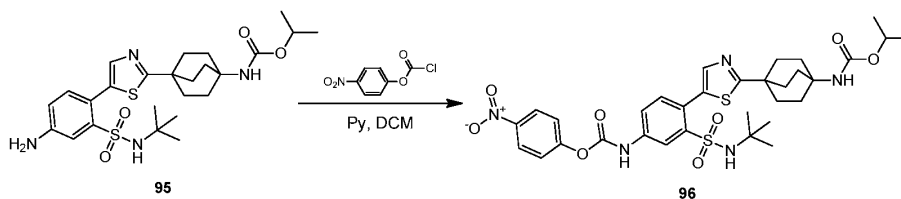
General method J, *isopropyl N-[1-(5-bromothiazol-2-yl)-4-bicyclo[2.2.2]octanyl]carbamate*. ESI $[\text{M}+\text{H}] = 375.2/373.2$

Preparation of compound 95



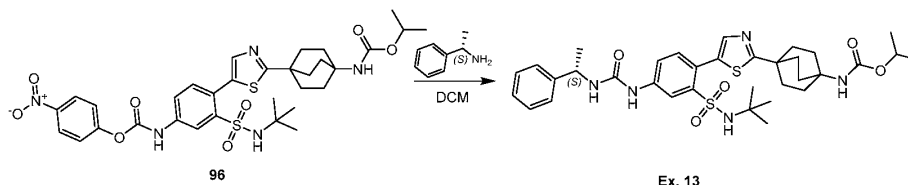
General method B, *isopropyl N-[1-[5-[4-amino-2-(tert-butylsulfamoyl)phenyl]thiazol-2-yl]-4-bicyclo[2.2.2]octanyl]carbamate*. ESI [M+H] = 521.2

Preparation of compound 96



General method D, *(4-nitrophenyl) N-[3-(tert-butylsulfamoyl)-4-[2-[4-(isopropoxycarbonylamino)-1-bicyclo[2.2.2]octanyl]thiazol-5-yl]phenyl]carbamate*. ESI [M+H] = 686.4

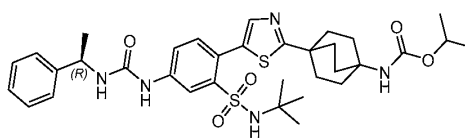
Preparation of Ex. 13



General method E, *isopropyl N-[1-[5-[2-(tert-butylsulfamoyl)-4-[(1S)-1-phenylethyl]carbamoylamino]phenyl]thiazol-2-yl]-4-bicyclo[2.2.2]octanyl]carbamate*. ¹H NMR (400MHz, METHANOL-d₄) δ = 8.21 (d, J=2.3 Hz, 1H), 7.75 (s, 1H), 7.67 (dd, J=2.3, 8.3 Hz, 1H), 7.41 - 7.32 (m, 5H), 7.29 - 7.23 (m, 1H), 4.99 - 4.93 (m, 1H), 4.83 - 4.76 (m, 1H), 2.17 - 2.08 (m, 6H), 2.07 - 1.99 (m, 6H), 1.51 (d, J=7.0 Hz, 3H), 1.22 (br d, J=6.0 Hz, 6H), 1.12 (s, 9H). ESI [M+H] = 668.3

Example 14. Synthesis of isopropyl (R)-(4-(5-(2-(N-(tert-butyl)sulfamoyl)-4-(3-(1-phenylethyl)ureido)phenyl)thiazol-2-yl)bicyclo[2.2.2]octan-1-yl)carbamate.

The following compound was synthesized via same method by the key intermediate 96.

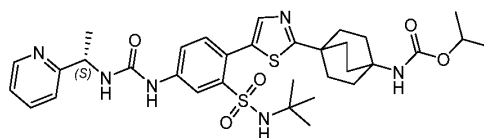


Ex. 14

¹H NMR (400MHz, METHANOL-d₄) δ = 8.18 (d, J=2.6 Hz, 1H), 7.74 - 7.69 (m, 1H), 7.64 (dd, J=2.2, 8.3 Hz, 1H), 7.38 - 7.29 (m, 5H), 7.26 - 7.19 (m, 1H), 4.92 (q, J=7.0 Hz, 1H), 4.82 - 4.71 (m, 1H), 2.15 - 2.05 (m, 6H), 2.04 - 1.95 (m, 6H), 1.48 (d, J=7.0 Hz, 3H), 1.20 (br d, J=6.1 Hz, 6H), 1.09 (s, 9H). ESI [M+H] = 668.3

Example 15. Synthesis of isopropyl (S)-(4-(5-(2-(N-(tert-butyl)sulfamoyl)-4-(3-(1-(pyridin-2-yl)ethyl)ureido)phenyl)thiazol-2-yl)bicyclo[2.2.2]octan-1-yl)carbamate.

The following compound was synthesized via same method by the key intermediate 96.

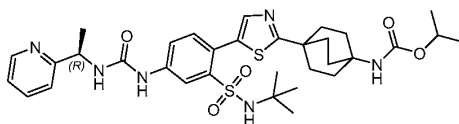


Ex. 15

¹H NMR (400MHz, METHANOL-d₄) δ = 8.72 (d, J=5.6 Hz, 1H), 8.46 (t, J=7.9 Hz, 1H), 8.28 (d, J=2.3 Hz, 1H), 8.02 (d, J=7.9 Hz, 1H), 7.85 (t, J=6.6 Hz, 1H), 7.72 (s, 1H), 7.63 (dd, J=2.3, 8.4 Hz, 1H), 7.35 (d, J=8.4 Hz, 1H), 5.13 (q, J=7.1 Hz, 1H), 4.84 - 4.74 (m, 1H), 2.15 - 2.07 (m, 6H), 2.07 - 1.98 (m, 6H), 1.65 (d, J=7.1 Hz, 3H), 1.22 (br d, J=6.1 Hz, 6H), 1.09 (s, 9H). ESI [M+H] = 669.2

Example 16. Synthesis of isopropyl (R)-(4-(5-(2-(N-(tert-butyl)sulfamoyl)-4-(3-(1-(pyridin-2-yl)ethyl)ureido)phenyl)thiazol-2-yl)bicyclo[2.2.2]octan-1-yl)carbamate.

The following compound was synthesized via same method by the key intermediate 96.



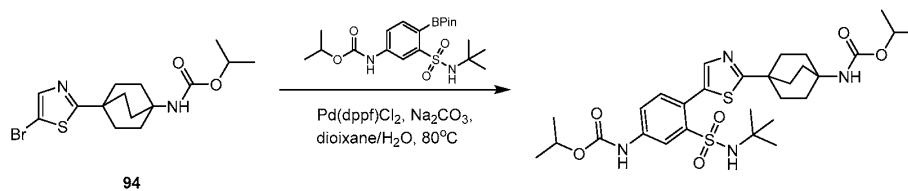
Ex. 16

¹H NMR (400MHz, METHANOL-d₄) δ = 8.75 (d, J=5.1 Hz, 1H), 8.57 (dt, J=1.5, 7.9 Hz, 1H), 8.29 (d, J=2.2 Hz, 1H), 8.11 (d, J=8.1 Hz, 1H), 7.98 - 7.90 (m, 1H), 7.75 (s, 1H), 7.62 (dd, J=2.3, 8.3 Hz, 1H), 7.36 (d, J=8.4 Hz, 1H), 5.15 (q, J=7.1 Hz, 1H), 4.84 - 4.75 (m, 1H), 2.16 - 2.07 (m, 6H), 2.06 - 1.97 (m, 6H), 1.67 (d, J=7.2 Hz, 3H), 1.22 (br d, J=6.1 Hz, 6H), 1.09 (s, 9H). ESI [M+H] = 669.2

Example 17. Synthesis of isopropyl N-[3-(tert-butylsulfamoyl)-4-[2-[4-(isopropoxycarbonyl amino)-1-bicyclo[2.2.2]octanyl]thiazol-5-yl]phenyl]carbamate.

Scheme 10:

Preparation of compound Ex. 17

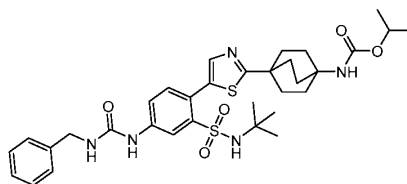


Ex. 17

General method B, *isopropyl N-[3-(tert-butylsulfamoyl)-4-[2-[4-(isopropoxycarbonyl amino)-1-bicyclo[2.2.2]octanyl]thiazol-5-yl]phenyl]carbamate*. ^1H NMR (400MHz, METHANOL- d_4) δ = 8.33 (d, J =2.0 Hz, 1H), 7.74 (s, 1H), 7.66 (dd, J =2.2, 8.4 Hz, 1H), 7.36 (d, J =8.4 Hz, 1H), 5.03 - 4.91 (m, 1H), 4.78 (br d, J =6.4 Hz, 1H), 2.16 - 2.05 (m, 6H), 2.04 - 1.95 (m, 6H), 1.31 (d, J =6.4 Hz, 6H), 1.20 (br d, J =6.0 Hz, 6H), 1.11 (s, 9H). ESI $[M+H]^+$ = 607.3

Example 18. Synthesis of isopropyl (4-(5-(4-(3-benzylureido)-2-(N-(tert-butyl)sulfamoyl)phenyl)thiazol-2-yl)bicyclo[2.2.2]octan-1-yl)carbamate.

The following compound was synthesized via same method by the key intermediate 94.

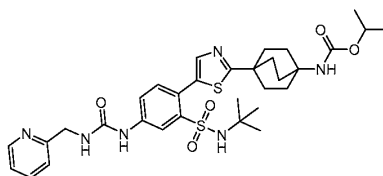


Ex. 18

^1H NMR (400MHz, METHANOL- d_4) δ = 8.26 (d, J =2.2 Hz, 1H), 7.77 (s, 1H), 7.72 (dd, J =2.4, 8.4 Hz, 1H), 7.38 - 7.33 (m, 5H), 7.27 (td, J =2.6, 8.6 Hz, 1H), 4.80 (br d, J =5.7 Hz, 1H), 4.43 (s, 2H), 2.17 - 2.10 (m, 6H), 2.06 - 2.00 (m, 6H), 1.25 - 1.20 (m, 6H), 1.13 (s, 9H). ESI $[M+H]^+$ = 654.1

Example 19. Synthesis of isopropyl (4-(5-(2-(N-(tert-butyl)sulfamoyl)-4-(3-(pyridin-2-ylmethyl)ureido)phenyl)thiazol-2-yl)bicyclo[2.2.2]octan-1-yl)carbamate.

The following compound was synthesized via same method by the key intermediate 94.



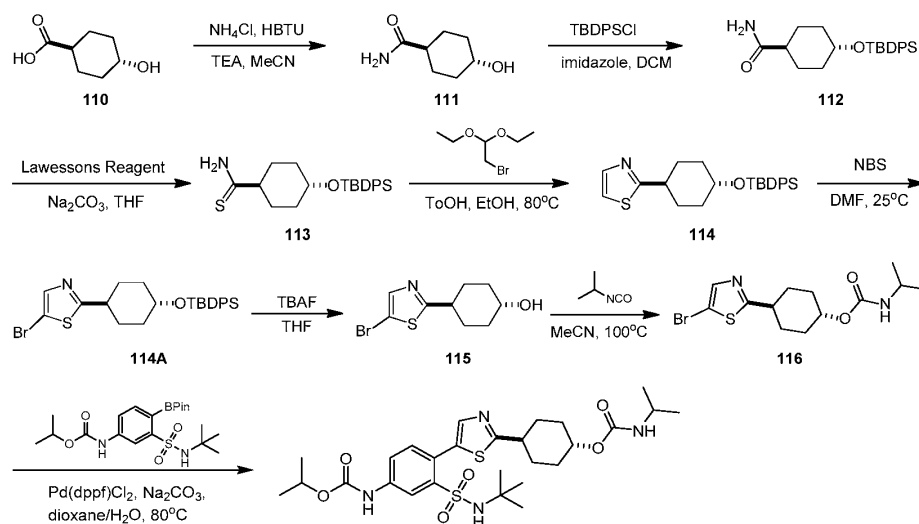
Ex. 19

^1H NMR (400MHz, METHANOL- d_4) δ = 8.73 (d, J =5.7 Hz, 1H), 8.51 (dt, J =1.3, 7.9 Hz, 1H), 8.31 (d, J =2.2 Hz, 1H), 8.02 (d, J =8.3 Hz, 1H), 7.90 (t, J =6.8 Hz, 1H), 7.72 (s, 1H), 7.66

(dd, J=2.2, 8.3 Hz, 1H), 7.35 (d, J=8.3 Hz, 1H), 4.75 (s, 3H), 2.15 - 1.93 (m, 12H), 1.20 (br d, J=6.1 Hz, 6H), 1.07 (s, 9H). ESI [M+H] = 655.3

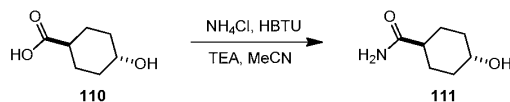
Example 20. Synthesis of *trans*-isopropyl *N*-[3-(*tert*-butylsulfamoyl)-4-[2-[4-(isopropylcarbamoyloxy)cyclohexyl]thiazol-5-yl]phenyl]carbamate.

Scheme 11:



Ex. 20

Preparation of compound 111.



To a solution of *trans*-4-hydroxycyclohexanecarboxylic acid (1 g, 6.94 mmol, 1 *eq.*) in MeCN (10 mL), were added HBTU (2.89 g, 7.63 mmol, 1.1 *eq.*) and TEA (2.11 g, 20.81 mmol, 2.90 mL, 3 *eq.*) followed by addition of NH₄Cl (742.07 mg, 13.87 mmol, 2 *eq.*) and the mixture was stirred at 26°C for 1 hr. The mixture was then filtered and dried to give *trans*-4-hydroxycyclohexanecarboxamide (1 g, crude) as a white solid which can be used without any purification.

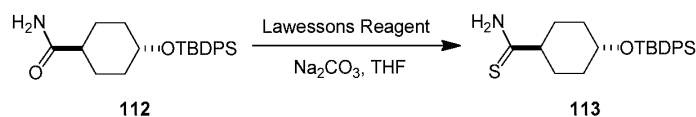
Preparation of compound 112.



To a solution of *trans*-4-hydroxycyclohexanecarboxamide (12 g, 83.81 mmol, 1 *eq.*) in DCM (150 mL), were added IMIDAZOLE (11.41 g, 167.62 mmol, 2 *eq.*) and tert-butyl-

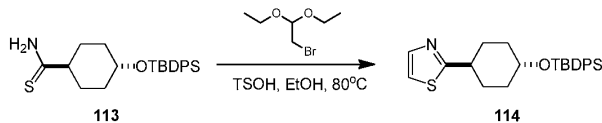
chloro-diphenyl-silane (27.64 g, 100.57 mmol, 25.83 mL, 1.2 eq.). The mixture was stirred at 26°C for 12 hrs and then poured into 1N HCl (200 mL) and the organic phase was washed with sat. aq. Na₂CO₃ (100 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated. The residue was washed with a solution (petroleum ether : EtOAc=10:1, 100 mL) and then filtered. The filter cake was dried to give **trans-4-[tert-butyl(diphenyl)silyl]oxycyclohexanecarboxamide** (31.5 g, crude). ¹H NMR (400MHz, METHANOL-d₄) δ = 7.72 - 7.64 (m, 4H), 7.49 - 7.36 (m, 6H), 3.69 - 3.55 (m, 1H), 2.21 - 2.08 (m, 1H), 1.96 - 1.83 (m, 2H), 1.82 - 1.69 (m, 2H), 1.50 - 1.23 (m, 4H), 1.12 - 0.98 (m, 9H).

Preparation of compound 113.



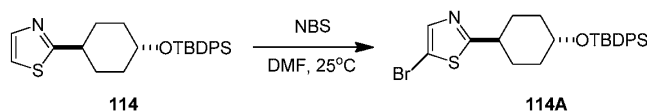
General method L, **trans-4-[tert-butyl(diphenyl)silyl]oxycyclohexanecarbothioamide**. ¹H NMR (400MHz, METHANOL-d₄) δ = 7.73 - 7.64 (m, 4H), 7.52 - 7.36 (m, 6H), 3.73 - 3.59 (m, 1H), 2.59 - 2.44 (m, 1H), 1.91 (br d, J=8.3 Hz, 2H), 1.80 - 1.66 (m, 2H), 1.57 - 1.35 (m, 4H), 1.08 - 1.04 (m, 9H). ESI [M+H] = 398.1

Preparation of compound 114.



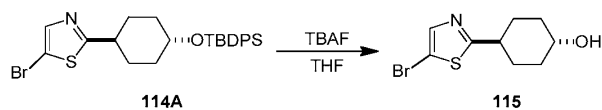
General method M, **trans-tert-butyl-diphenyl-(4-thiazol-2-ylcyclohexoxy)silane**. ¹H NMR (400MHz, METHANOL-d₄) δ = 7.63 - 7.55 (m, 5H), 7.42 - 7.25 (m, 7H), 4.05 - 3.96 (m, 1H), 2.97 (tt, J=3.7, 11.7 Hz, 1H), 2.05 (dq, J=3.2, 12.5 Hz, 2H), 1.84 - 1.62 (m, 4H), 1.44 (tt, J=2.9, 13.5 Hz, 2H), 1.01 - 0.98 (m, 9H). ESI [M+H] = 422.2

Preparation of compound 114A.



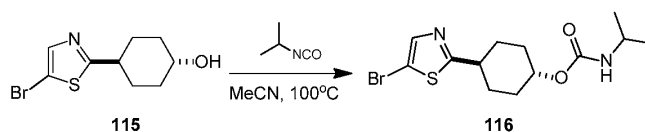
General method J, **trans-[4-(5-bromothiazol-2-yl)cyclohexoxy]-tert-butyl-diphenyl-silane** (1.8 g, crude). ESI [M+H] = 502.0

Preparation of compound 115.



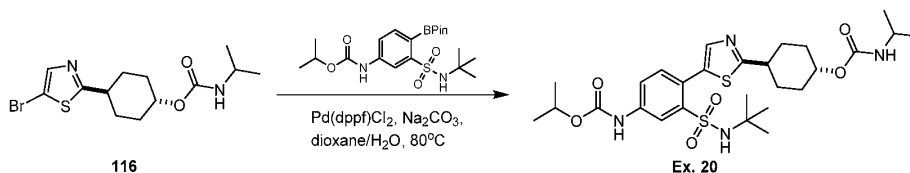
To a solution of *trans*-[4-(5-bromothiazol-2-yl)cyclohexoxy]-*tert*-butyl-diphenyl-silane (1.5 g, 3.00 mmol, 1 *eq.*) in THF (10 mL), was added TBAF (1 M, 4.49 mL, 1.5 *eq.*) and the mixture was stirred at 26°C for 12 hrs and then concentrated. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate=20:1-1:1) to afford *trans*-4-(5-bromothiazol-2-yl)cyclohexanol (500 mg, 1.91 mmol, 63.64% yield) as a yellow solid.

Preparation of compound 116.



To a solution of *trans*-4-(5-bromothiazol-2-yl)cyclohexanol (500 mg, 1.91 mmol, 1 *eq.*) in DMF (5 mL), were added 2-isocyanatopropane (486.93 mg, 5.72 mmol, 3 *eq.*) and DIEA (739.47 mg, 5.72 mmol, 3 *eq.*). The mixture was stirred at 100°C for 40 hrs and then poured into H₂O (50 mL) and extracted with EtOAc (10 mL*3). The combined organic phase was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate=10:1-1:1) to afford *trans*-[4-(5-bromothiazol-2-yl)cyclohexyl] N-isopropylcarbamate (180 mg, 518.33 μ mol, 27.18% yield) as a yellow solid. ¹H NMR (400MHz, METHANOL-d₄) δ = 7.61 (s, 1H), 3.85 - 3.64 (m, 2H), 3.15 - 2.99 (m, 1H), 1.98 - 1.83 (m, 6H), 1.73 (br d, J=13.5 Hz, 2H), 1.14 - 1.12 (m, 6H). ESI [M+H] = 347.1/349.1

Preparation of Ex. 20.

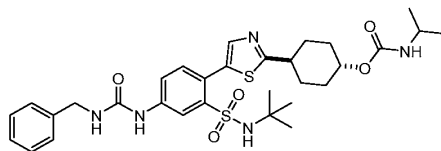


General method B, *trans*-isopropyl N-[3-(*tert*-butylsulfamoyl)-4-[2-[4-(isopropylcarbamoyloxy)cyclohexyl]thiazol-5-yl]phenyl]carbamate. ¹H NMR (400MHz, METHANOL-d₄) δ = 8.34 (d, J=2.0 Hz, 1H), 7.75 (s, 1H), 7.67 (dd, J=2.0, 8.4 Hz, 1H), 7.37 (d, J=8.4 Hz, 1H), 5.05 - 4.93 (m, 1H), 4.89 (br s, 1H), 3.83 - 3.64 (m, 1H), 3.15 (br s, 1H), 2.12 - 1.88 (m, 6H), 1.84 - 1.64 (m, 2H), 1.31 (d, J=6.2 Hz, 6H), 1.19 - 1.04 (m, 15H). ESI [M+H] = 581.4

Example 21. Synthesis of (1*r*,4*r*)-4-(5-(4-(3-benzylureido)-2-(N-(*tert*-butyl)sulfamoyl)

phenyl)thiazol-2-yl)cyclohexyl isopropylcarbamate

The following compound was synthesized via same method by the key intermediate 116.

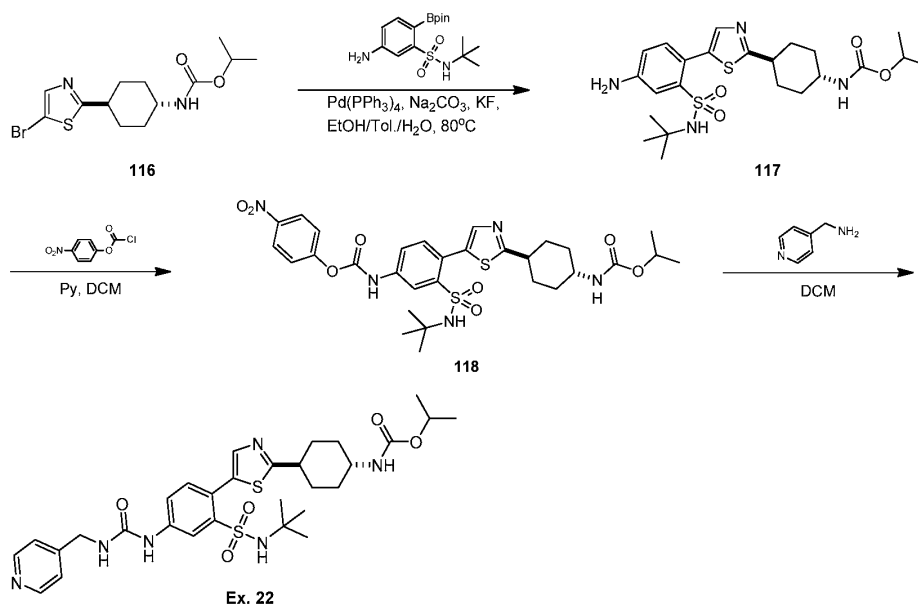


Ex. 21

^1H NMR (400MHz, METHANOL- d_4) δ = 8.24 (d, J =2.2 Hz, 1H), 7.74 (s, 1H), 7.69 (dd, J =2.4, 8.4 Hz, 1H), 7.40 - 7.28 (m, 5H), 7.28 - 7.17 (m, 1H), 4.89 (br s, 1H), 4.41 (s, 2H), 3.79 - 3.64 (m, 1H), 3.14 (br s, 1H), 2.04 - 1.94 (m, 6H), 1.84 - 1.65 (m, 2H), 1.16 - 1.08 (m, 15H). ESI $[\text{M}+\text{H}] = 628.4$

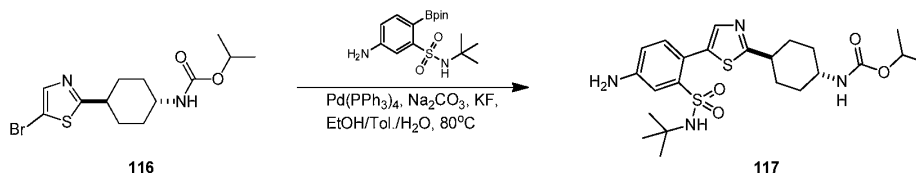
Example 22. Synthesis of *trans*-isopropyl *N*-[4-[5-[2-(*tert*-butylsulfamoyl)-4-(4-pyridylmethylcarbamoylamino)phenyl]thiazol-2-yl]cyclohexyl]carbamate.

Scheme 12:



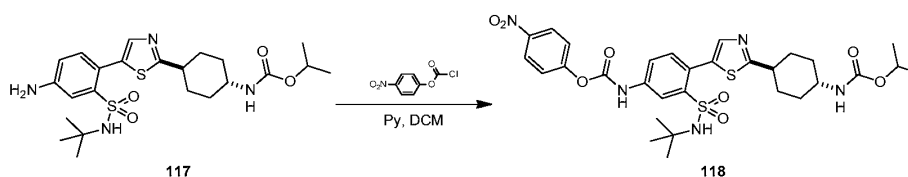
Ex. 22

Preparation of compound 117.



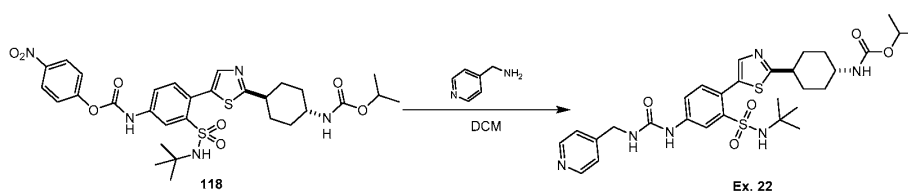
General method K, *trans-isopropyl N-[4-[5-[4-amino-2-(tert-butylsulfamoyl)phenyl]thiazol-2-yl]cyclohexyl]carbamate*. ^1H NMR (400MHz, METHANOL- d_4) δ = 7.68 - 7.57 (s, 1H), 7.43 (d, J =2.4 Hz, 1H), 7.13 (d, J =8.2 Hz, 1H), 6.82 (dd, J =2.4, 8.2 Hz, 1H), 4.84 - 4.77 (m, 1H), 3.44 (tt, J =3.9, 11.5 Hz, 1H), 2.97 (tt, J =3.6, 12.1 Hz, 1H), 2.26 - 2.13 (m, 2H), 2.11 - 2.02 (m, 2H), 1.67 (dq, J =3.0, 12.9 Hz, 2H), 1.49 - 1.32 (m, 2H), 1.22 (dd, J =2.5, 6.7 Hz, 6H), 1.09 (s, 9H). ESI $[\text{M}+\text{H}]$ =495.2

Preparation of compound 118.



General method D, *trans-(4-nitrophenyl) N-[3-(tert-butylsulfamoyl)-4-[2-[4-(isopropoxycarbonylamino)cyclohexyl]thiazol-5-yl]phenyl]carbamate*. ESI $[\text{M}+\text{H}]$ =660.1

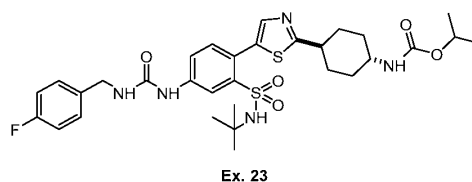
Preparation of Ex. 22.



General method E, *trans-isopropyl N-[4-[5-[2-(tert-butylsulfamoyl)-4-(4-pyridylmethylcarbamoylamino)phenyl]thiazol-2-yl]cyclohexyl]carbamate*. ^1H NMR (400MHz, METHANOL- d_4) δ = 8.79 (d, J =6.7 Hz, 2H), 8.34 (d, J =2.3 Hz, 1H), 8.07 (d, J =6.6 Hz, 2H), 7.76 (s, 1H), 7.69 (dd, J =2.3, 8.4 Hz, 1H), 7.39 (d, J =8.3 Hz, 1H), 4.85 - 4.83 (m, 1H), 4.73 (s, 2H), 3.47 (tt, J =3.6, 11.5 Hz, 1H), 3.04 (tt, J =3.4, 12.0 Hz, 1H), 2.30 - 2.19 (m, 2H), 2.09 (br d, J =10.1 Hz, 2H), 1.71 (dq, J =3.0, 12.9 Hz, 2H), 1.43 (dq, J =3.3, 12.6 Hz, 2H), 1.24 (br d, J =6.1 Hz, 6H), 1.12 (s, 9H). ESI $[\text{M}+\text{H}]$ =629.2

Example 23. Synthesis of isopropyl ((1*r*,4*r*)-4-(5-(2-(N-(tert-butyl)sulfamoyl)-4-(3-(4-fluorobenzyl)ureido)phenyl)thiazol-2-yl)cyclohexyl)carbamate

The following compound was synthesized via same method by the key intermediate 118.

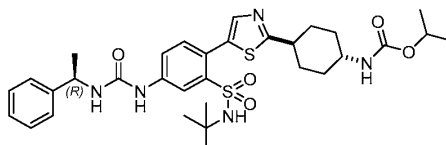


Ex. 23

¹H NMR (400MHz, METHANOL-d₄) δ = 8.27 (d, J=2.3 Hz, 1H), 7.77 (s, 1H), 7.71 (dd, J=2.4, 8.4 Hz, 1H), 7.38 (td, J=2.7, 8.6 Hz, 3H), 7.12 - 7.04 (m, 2H), 5.00 - 4.92 (m, 1H), 4.41 (s, 2H), 3.54 - 3.41 (m, 1H), 3.05 (tt, J=3.5, 12.0 Hz, 1H), 2.13 - 2.05 (m, 2H), 2.05 - 2.04 (m, 2H), 1.72 (dq, J=3.0, 12.8 Hz, 2H), 1.43 (dq, J=3.2, 12.5 Hz, 2H), 1.24 (br d, J=6.1 Hz, 6H), 1.14 (s, 9H). ESI [M+H] = 646.2

Example 24. Synthesis of isopropyl ((1R,4r)-4-(5-(2-(N-isopropylsulfamoyl)-4-(3-((R)-1-phenylethyl)ureido)phenyl)thiazol-2-yl)cyclohexyl)carbamate

The following compound was synthesized via same method by the key intermediate 118.

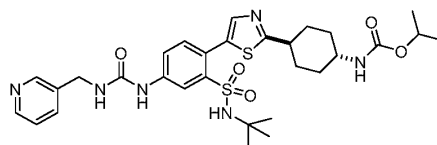


Ex. 24

¹H NMR (400MHz, METHANOL-d₄) δ = 8.20 (d, J=2.2 Hz, 1H), 7.73 (s, 1H), 7.64 (dd, J=2.4, 8.4 Hz, 1H), 7.38 - 7.29 (m, 5H), 7.26 - 7.19 (m, 1H), 4.94 - 4.89 (m, 1H), 4.81 (br d, J=6.2 Hz, 1H), 3.44 (tt, J=3.9, 11.6 Hz, 1H), 3.01 (tt, J=3.5, 12.0 Hz, 1H), 2.26 - 2.17 (m, 2H), 2.10 - 2.01 (m, 2H), 1.68 (dq, J=2.9, 12.8 Hz, 2H), 1.48 (d, J=7.1 Hz, 3H), 1.43 - 1.33 (m, 2H), 1.21 (br d, J=6.2 Hz, 6H), 1.10 (s, 9H). ESI [M+H] = 642.3

Example 25. Synthesis of isopropyl ((1r,4r)-4-(5-(2-(N-(tert-butyl)sulfamoyl)-4-(3-(pyridin-3-ylmethyl)ureido)phenyl)thiazol-2-yl)cyclohexyl)carbamate.

The following compound was synthesized via same method by the key intermediate 118.

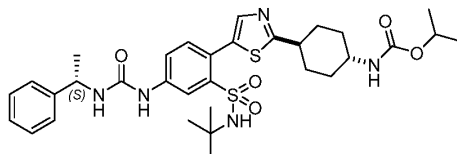


Ex. 25

¹H NMR (400MHz, METHANOL-d₄) δ = 8.84 (s, 1H), 8.74 (d, J=5.7 Hz, 1H), 8.60 (d, J=8.2 Hz, 1H), 8.30 (d, J=2.2 Hz, 1H), 8.04 (dd, J=5.8, 7.8 Hz, 1H), 7.72 (s, 1H), 7.65 (dd, J=2.4, 8.4 Hz, 1H), 7.36 (d, J=8.4 Hz, 1H), 4.85 - 4.77 (m, 1H), 4.60 (s, 2H), 3.44 (tt, J=3.9, 11.5 Hz, 1H), 3.10 - 2.93 (m, 1H), 2.28 - 2.17 (m, 2H), 2.13 - 2.01 (m, 2H), 1.69 (dq, J=3.0, 12.8 Hz, 2H), 1.50 - 1.33 (m, 2H), 1.22 (br d, J=6.2 Hz, 6H), 1.09 (s, 9H). ESI [M+H] = 629.3

Example 26. Synthesis of isopropyl ((1S,4r)-4-(5-(2-(N-(tert-butyl)sulfamoyl)-4-(3-((S)-1-phenylethyl)ureido)phenyl)thiazol-2-yl)cyclohexyl)carbamate.

The following compound was synthesized via same method by the key intermediate 118.

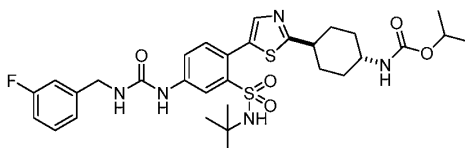


Ex. 26

^1H NMR (400MHz, METHANOL- d_4) δ = 8.19 (d, J =2.4 Hz, 1H), 7.70 (s, 1H), 7.65 (dd, J =2.4, 8.4 Hz, 1H), 7.39 - 7.30 (m, 5H), 7.26 - 7.21 (m, 1H), 4.93 (q, J =6.5 Hz, 1H), 4.83 - 4.81 (m, 1H), 3.49 - 3.40 (m, 1H), 3.05 - 2.96 (m, 1H), 2.22 (br d, J =11.7 Hz, 2H), 2.06 (br d, J =11.5 Hz, 2H), 1.73 - 1.62 (m, 2H), 1.49 (d, J =6.8 Hz, 3H), 1.43 - 1.36 (m, 2H), 1.22 (br d, J =6.0 Hz, 6H), 1.10 (s, 9H). ESI[M+H]⁺ = 642.3

Example 27. Synthesis of isopropyl ((1r,4r)-4-(5-(2-(N-(tert-butyl)sulfamoyl)-4-(3-(3-fluorobenzyl)ureido)phenyl)thiazol-2-yl)cyclohexyl)carbamate.

The following compound was synthesized via same method by the key intermediate 118.

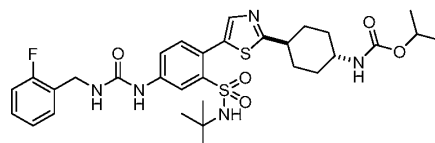


Ex. 27

^1H NMR (400MHz, METHANOL- d_4) δ = 8.27 (d, J =2.2 Hz, 1H), 7.74 (s, 1H), 7.71 (dd, J =2.3, 8.3 Hz, 1H), 7.40 - 7.32 (m, 2H), 7.18 (d, J =7.7 Hz, 1H), 7.10 (br d, J =9.9 Hz, 1H), 6.99 (dt, J =2.2, 8.5 Hz, 1H), 4.87 (br s, 1H), 4.44 (s, 2H), 3.47 (tt, J =3.8, 11.6 Hz, 1H), 3.02 (tt, J =3.5, 12.0 Hz, 1H), 2.24 (br d, J =12.2 Hz, 2H), 2.14 - 2.04 (m, 2H), 1.71 (dq, J =3.0, 12.9 Hz, 2H), 1.50 - 1.36 (m, 2H), 1.24 (br d, J =6.1 Hz, 6H), 1.14 (s, 9H). ESI [M+H]⁺ = 646.2

Example 28. Synthesis of isopropyl ((1r,4r)-4-(5-(2-(N-(tert-butyl)sulfamoyl)-4-(3-(2-fluorobenzyl)ureido)phenyl)thiazol-2-yl)cyclohexyl)carbamate.

The following compound was synthesized via same method by the key intermediate 118.



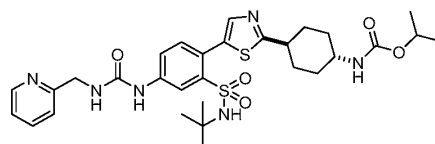
Ex. 28

^1H NMR (400MHz, METHANOL- d_4) δ = 8.23 (d, J =2.2 Hz, 1H), 7.71 (s, 1H), 7.68 (dd, J =2.4, 8.4 Hz, 1H), 7.41 (dt, J =1.5, 7.6 Hz, 1H), 7.35 (d, J =8.4 Hz, 1H), 7.29 (ddt, J =1.8, 5.5, 7.7 Hz, 1H), 7.15 (dt, J =1.0, 7.6 Hz, 1H), 7.11 - 7.05 (m, 1H), 4.81 (br s, 1H), 4.46 (s, 2H), 3.45 (tt, J =3.7, 11.6 Hz, 1H), 3.00 (tt, J =3.5, 12.0 Hz, 1H), 2.27 - 2.18 (m, 2H), 2.06 (br d,

J=10.1 Hz, 2H), 1.69 (dq, J=3.1, 12.9 Hz, 2H), 1.46 - 1.34 (m, 2H), 1.22 (br d, J=6.2 Hz, 6H), 1.11 (s, 9H). ESI [M+H]⁺ = 646.2

Example 29. Synthesis of isopropyl ((1*r*,4*r*)-4-(5-(2-(N-(tert-butyl)sulfamoyl)-4-(3-(pyridin-2-ylmethyl)ureido)phenyl)thiazol-2-yl)cyclohexyl)carbamate.

The following compound was synthesized via same method by the key intermediate 118.

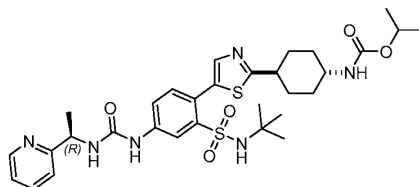


Ex. 29

¹H NMR (400MHz, METHANOL-d₄) δ = 8.79 - 8.73 (m, 1H), 8.56 (dt, J=1.5, 7.9 Hz, 1H), 8.35 (d, J=2.2 Hz, 1H), 8.06 (d, J=8.1 Hz, 1H), 7.94 (t, J=6.4 Hz, 1H), 7.77 (s, 1H), 7.69 (dd, J=2.3, 8.4 Hz, 1H), 7.39 (d, J=8.3 Hz, 1H), 4.86 - 4.83 (m, 1H), 4.79 (s, 2H), 3.47 (tt, J=3.9, 11.6 Hz, 1H), 3.05 (tt, J=3.5, 12.0 Hz, 1H), 2.29 - 2.21 (m, 2H), 2.09 (br d, J=10.1 Hz, 2H), 1.71 (dq, J=2.9, 12.8 Hz, 2H), 1.43 (dq, J=3.3, 12.6 Hz, 2H), 1.24 (br d, J=6.2 Hz, 6H), 1.11 (s, 9H). ESI [M+H]⁺ = 629.3

Example 30. Synthesis of isopropyl ((1*R*,4*r*)-4-(5-(2-(N-(tert-butyl)sulfamoyl)-4-(3-((*R*)-1-(pyridin-2-yl)ethyl)ureido)phenyl)thiazol-2-yl)cyclohexyl)carbamate.

The following compound was synthesized via same method by the key intermediate 118.

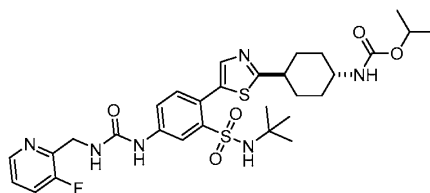


Ex. 30

¹H NMR (400MHz, METHANOL-d₄) δ = 8.73 (d, J=5.7 Hz, 1H), 8.53 (dt, J=1.8, 7.9 Hz, 1H), 8.28 (d, J=2.2 Hz, 1H), 8.08 (d, J=8.3 Hz, 1H), 7.94 - 7.85 (m, 1H), 7.80 - 7.68 (m, 1H), 7.61 (dd, J=2.2, 8.3 Hz, 1H), 7.35 (d, J=8.3 Hz, 1H), 5.13 (q, J=7.0 Hz, 1H), 4.85 - 4.78 (m, 1H), 3.49 - 3.39 (m, 1H), 3.08 - 2.96 (m, 1H), 2.22 (br d, J=12.3 Hz, 2H), 2.06 (br d, J=10.1 Hz, 2H), 1.76 - 1.61 (m, 5H), 1.49 - 1.34 (m, 2H), 1.22 (br d, J=6.1 Hz, 6H), 1.14 - 1.02 (m, 9H). ESI [M+H]⁺ = 643.3

Example 31. Synthesis of isopropyl ((1*r*,4*r*)-4-(5-(2-(N-(tert-butyl)sulfamoyl)-4-(3-((3-fluoropyridin-2-yl)methyl)ureido)phenyl)thiazol-2-yl)cyclohexyl)carbamate.

The following compound was synthesized via same method by the key intermediate 118.

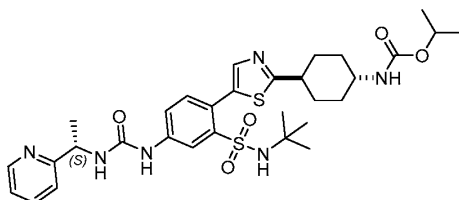


Ex. 31

^1H NMR (400MHz, METHANOL- d_4) δ = 8.42 (d, J =4.8 Hz, 1H), 8.28 (d, J =2.2 Hz, 1H), 7.78 - 7.62 (m, 3H), 7.44 (td, J =4.4, 8.5 Hz, 1H), 7.38 (d, J =8.4 Hz, 1H), 4.86 - 4.81 (m, 1H), 4.65 (s, 2H), 3.47 (ddd, J =4.0, 7.7, 11.4 Hz, 1H), 3.10 - 3.00 (m, 1H), 2.25 (br d, J =12.1 Hz, 2H), 2.09 (br d, J =10.5 Hz, 2H), 1.72 (dq, J =3.0, 12.9 Hz, 2H), 1.43 (dq, J =3.2, 12.6 Hz, 2H), 1.24 (br d, J =6.1 Hz, 6H), 1.14 (s, 9H). ESI $[M+H]^+ = 647.2$

Example 32. Synthesis of isopropyl ((1S,4r)-4-(5-(2-(N-(tert-butyl)sulfamoyl)-4-(3-((S)-1-(pyridin-2-yl)ethyl)ureido)phenyl)thiazol-2-yl)cyclohexyl)carbamate.

The following compound was synthesized via same method by the key intermediate 118.

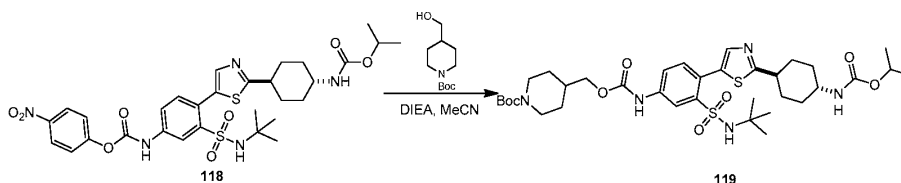


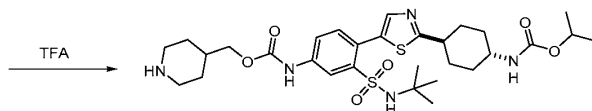
Ex. 32

^1H NMR (400MHz, METHANOL- d_4) δ = 8.72 (d, J =5.3 Hz, 1H), 8.50 (dt, J =1.8, 7.9 Hz, 1H), 8.27 (d, J =2.2 Hz, 1H), 8.05 (d, J =8.3 Hz, 1H), 7.88 (t, J =6.6 Hz, 1H), 7.72 (s, 1H), 7.61 (dd, J =2.6, 8.3 Hz, 1H), 7.34 (d, J =8.8 Hz, 1H), 5.12 (q, J =7.0 Hz, 1H), 4.87 - 4.68 (m, 1H), 3.51 - 3.38 (m, 1H), 3.01 (tt, J =3.3, 12.0 Hz, 1H), 2.21 (br d, J =11.8 Hz, 2H), 2.10 - 1.97 (m, 2H), 1.76 - 1.57 (m, 5H), 1.48 - 1.33 (m, 2H), 1.22 (d, J =6.1 Hz, 6H), 1.13 - 1.00 (m, 9H). ESI $[M+H]^+ = 643.3$

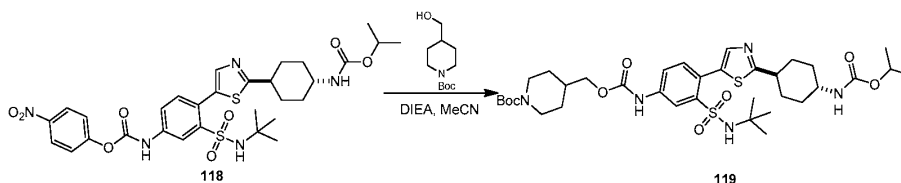
Example 33. Synthesis of *trans*-4-piperidylmethyl *N*-[3-(*tert*-butylsulfamoyl)-4-[2-[4-(isopropoxycarbonylamino)cyclohexyl]thiazol-5-yl]phenyl]carbamate.

Scheme 13:

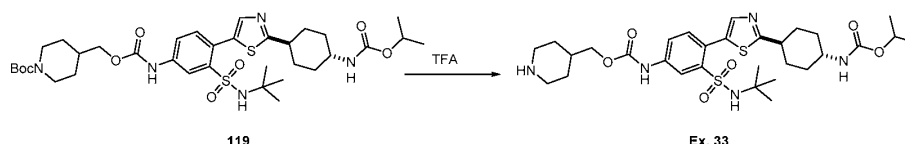




Ex. 33

Preparation of compound 119.

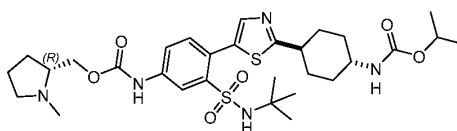
General method H, *trans-tert-butyl 4-[[3-(tert-butylsulfamoyl)-4-[2-[4-(isopropoxycarbonylamino)cyclohexyl]thiazol-5-yl]phenyl]carbamoyloxymethyl]piperidine-1-carboxylate*. ESI [M+H] = 736.5

Preparation of Ex. 33.

General method C, *trans-4-piperidylmethyl N-[3-(tert-butylsulfamoyl)-4-[2-[4-(isopropoxycarbonylamino)cyclohexyl]thiazol-5-yl]phenyl]carbamate*. ¹H NMR (400MHz, METHANOL-d₄) δ = 8.37 (d, J=2.2 Hz, 1H), 7.78 (s, 1H), 7.68 (br d, J=7.9 Hz, 1H), 7.40 (d, J=8.4 Hz, 1H), 4.86 - 4.78 (m, 1H), 4.11 (d, J=6.2 Hz, 2H), 3.50 - 3.39 (m, 3H), 3.11 - 2.96 (m, 3H), 2.23 (br d, J=12.3 Hz, 2H), 2.13 - 1.98 (m, 5H), 1.70 (dq, J=2.8, 12.8 Hz, 2H), 1.60 - 1.34 (m, 4H), 1.22 (br d, J=6.2 Hz, 6H), 1.11 (s, 9H). ESI [M/2+H] = 318.6

Example 34. Synthesis of isopropyl ((1R,4r)-4-(5-(2-(N-(tert-butyl)sulfamoyl)-4-(((R)-1-methylpyrrolidin-2-yl)methoxy)carbonyl)amino)phenyl)thiazol-2-yl)cyclohexyl)carbamate.

The following compound was synthesized via same method by the key intermediate 118.



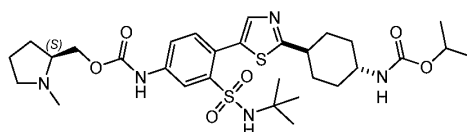
Ex. 34

¹H NMR (400MHz, METHANOL-d₄) δ = 8.41 (d, J=2.2 Hz, 1H), 7.80 - 7.73 (m, 2H), 7.45 (d, J=8.4 Hz, 1H), 4.86 - 4.81 (m, 1H), 4.67 (dd, J=3.2, 12.8 Hz, 1H), 4.35 (dd, J=7.1, 12.8 Hz, 1H), 3.85 - 3.71 (m, 2H), 3.47 (tt, J=3.9, 11.6 Hz, 1H), 3.26 (td, J=8.1, 11.5 Hz, 1H), 3.10

(s, 3H), 3.08 - 2.98 (m, 1H), 2.46 - 2.35 (m, 1H), 2.30 - 2.18 (m, 3H), 2.15 - 1.95 (m, 4H), 1.72 (dq, J=3.1, 12.9 Hz, 2H), 1.43 (dq, J=3.3, 12.6 Hz, 2H), 1.25 (br d, J=6.2 Hz, 6H), 1.13 (s, 9H). ESI [M+H] = 636.3

Example 35. Synthesis of isopropyl ((1S,4r)-4-(5-(2-(N-(tert-butyl)sulfamoyl)-4-((((S)-1-methylpyrrolidin-2-yl)methoxy)carbonyl)amino)phenyl)thiazol-2-yl)cyclohexyl)carbamate.

The following compound was synthesized via same method by the key intermediate 118.

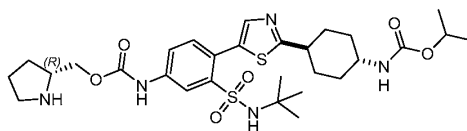


Ex. 35

¹H NMR (400MHz, METHANOL-d₄) δ = 8.41 (d, J=2.0 Hz, 1H), 7.80 - 7.71 (m, 2H), 7.44 (d, J=8.3 Hz, 1H), 4.86 - 4.79 (m, 1H), 4.67 (dd, J=3.2, 13.0 Hz, 1H), 4.40 - 4.31 (m, 1H), 3.87 - 3.66 (m, 2H), 3.47 (tt, J=3.8, 11.6 Hz, 1H), 3.26 (td, J=8.3, 11.4 Hz, 1H), 3.10 (s, 3H), 3.04 (tt, J=3.4, 12.0 Hz, 1H), 2.48 - 2.33 (m, 1H), 2.30 - 2.16 (m, 3H), 2.15 - 1.92 (m, 4H), 1.72 (dq, J=2.7, 12.8 Hz, 2H), 1.51 - 1.36 (m, 2H), 1.25 (br d, J=6.4 Hz, 6H), 1.13 (s, 9H). ESI [M/2+H] = 318.6

Example 36. Synthesis of isopropyl ((1R,4r)-4-(5-(2-(N-(tert-butyl)sulfamoyl)-4-((((R)-pyrrolidin-2-yl)methoxy)carbonyl)amino)phenyl)thiazol-2-yl)cyclohexyl)carbamate.

The following compound was synthesized via same method by the key intermediate 118.

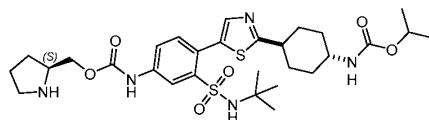


Ex. 36

¹H NMR (400MHz, METHANOL-d₄) δ = 8.38 (br d, J=2.2 Hz, 1H), 7.75 - 7.66 (m, 2H), 7.41 (d, J=8.4 Hz, 1H), 4.81 (br s, 1H), 4.48 (br dd, J=3.4, 12.5 Hz, 1H), 4.33 (dd, J=7.8, 12.5 Hz, 1H), 3.93 (dq, J=3.6, 8.0 Hz, 1H), 3.49 - 3.33 (m, 3H), 3.00 (ddd, J=3.5, 8.5, 12.0 Hz, 1H), 2.30 - 2.18 (m, 3H), 2.10 - 2.00 (m, 3H), 1.85 (qd, J=8.5, 12.9 Hz, 2H), 1.74 - 1.61 (m, 2H), 1.46 - 1.34 (m, 2H), 1.22 (br d, J=6.2 Hz, 6H), 1.09 (s, 9H). ESI [M/2+H] = 311.6

Example 37. Synthesis of isopropyl ((1S,4r)-4-(5-(2-(N-(tert-butyl)sulfamoyl)-4-(((S)-pyrrolidin-2-yl)methoxy)carbonyl)amino)phenyl)thiazol-2-yl)cyclohexyl)carbamate.

The following compound was synthesized via same method by the key intermediate 118.

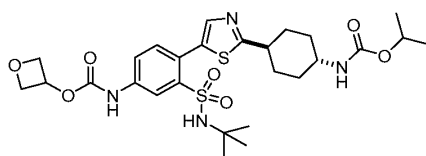


Ex. 37

^1H NMR (400MHz, METHANOL- d_4) δ = 8.38 (d, J =1.8 Hz, 1H), 7.79 - 7.68 (m, 2H), 7.41 (d, J =8.2 Hz, 1H), 4.85 - 4.78 (m, 1H), 4.49 (dd, J =3.4, 12.5 Hz, 1H), 4.33 (dd, J =7.9, 12.3 Hz, 1H), 3.94 (dq, J =3.4, 8.0 Hz, 1H), 3.49 - 3.40 (m, 1H), 3.40 - 3.33 (m, 2H), 3.08 - 2.97 (m, 1H), 2.31 - 2.19 (m, 3H), 2.17 - 2.00 (m, 4H), 1.85 (qd, J =8.5, 13.0 Hz, 1H), 1.75 - 1.62 (m, 2H), 1.46 - 1.35 (m, 2H), 1.22 (br d, J =6.2 Hz, 6H), 1.10 (s, 9H). ESI $[M/2+H] = 311.6$

Example 38. Synthesis of isopropyl ((1r,4r)-4-(5-(2-(N-(tert-butyl)sulfamoyl)-4-(((oxetan-3-yloxy)carbonyl)amino)phenyl)thiazol-2-yl)cyclohexyl)carbamate.

The following compound was synthesized via same method by the key intermediate 118.

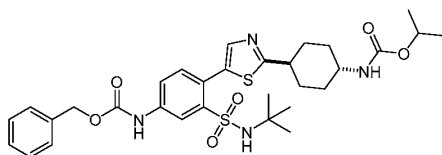


Ex. 38

^1H NMR (METHANOL- d_4 , 400MHz): δ = 8.33 (s, 1H), 7.63-7.72 (m, 2H), 7.38 (d, J =8.4 Hz, 1H), 5.50 (br t, J =5.5 Hz, 1H), 4.92 (t, J =6.9 Hz, 2H), 4.81-4.83 (m, 1H), 4.64-4.73 (m, 2H), 3.44 (br t, J =11.7 Hz, 1H), 2.99 (br t, J =11.8 Hz, 1H), 2.21 (br d, J =12.3 Hz, 2H), 2.06 (br d, J =11.7 Hz, 2H), 1.59-1.75 (m, 2H), 1.30-1.47 (m, 2H), 1.21 (br d, J =6.0 Hz, 6H), 1.10 ppm (s, 9H). ESI $[M+H] = 595.1$

Example 39. Synthesis of benzyl (3-(N-(tert-butyl)sulfamoyl)-4-(2-((1r,4r)-4-(isopropoxycarbonyl)amino)cyclohexyl)thiazol-5-yl)phenyl)carbamate.

The following compound was synthesized via same method by the key intermediate 118.



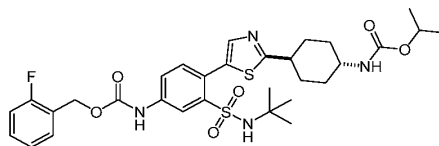
Ex. 39

^1H NMR (400MHz, METHANOL- d_4) δ = 8.36 (s, 1H), 7.75 - 7.67 (m, 2H), 7.46 - 7.28 (m, 6H), 5.28 - 5.14 (m, 2H), 4.85 - 4.76 (m, 1H), 3.47 (br d, J =11.8 Hz, 1H), 3.01 (br s, 1H),

2.23 (br d, J=12.7 Hz, 2H), 2.07 (br d, J=14.5 Hz, 2H), 1.70 (br d, J=11.0 Hz, 2H), 1.40 (br d, J=12.7 Hz, 2H), 1.22 (br d, J=6.1 Hz, 6H), 1.12 (s, 9H). ESI [M+H] = 629.2

Example 40. Synthesis of 2-fluorobenzyl (3-(N-(tert-butyl)sulfamoyl)-4-(2-((1r,4r)-4-(isopropoxycarbonyl)amino)cyclohexyl)thiazol-5-yl)phenyl)carbamate.

The following compound was synthesized via same method by the key intermediate 118.

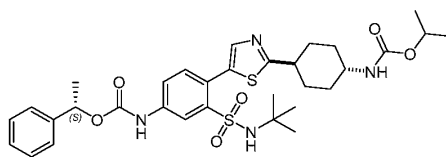


Ex. 40

¹H NMR (400MHz, METHANOL-d₄) δ = 8.36 (s, 1H), 7.77 - 7.63 (m, 2H), 7.52 (t, J=7.0 Hz, 1H), 7.44 - 7.31 (m, 2H), 7.23 - 7.08 (m, 2H), 5.29 (s, 2H), 4.83 (br s, 1H), 3.46 (br d, J=11.8 Hz, 1H), 3.00 (br t, J=11.8 Hz, 1H), 2.22 (br d, J=12.7 Hz, 2H), 2.07 (br d, J=11.4 Hz, 2H), 1.76 - 1.62 (m, 2H), 1.47 - 1.35 (m, 2H), 1.22 (br d, J=6.1 Hz, 6H), 1.12 (s, 9H). ESI [M+H] = 647.2

Example 41. Synthesis of (S)-1-phenylethyl (3-(N-(tert-butyl)sulfamoyl)-4-(2-((1r,4S)-4-(isopropoxycarbonyl)amino)cyclohexyl)thiazol-5-yl)phenyl)carbamate.

The following compound was synthesized via same method by the key intermediate 118.

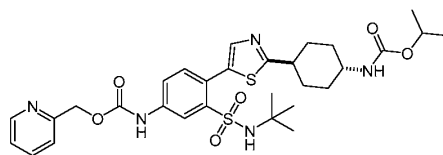


Ex. 41

¹H NMR (400MHz, METHANOL-d₄) δ = 8.35 (br s, 1H), 7.81 - 7.65 (m, 2H), 7.48 - 7.36 (m, 5H), 7.31 (br d, J=6.8 Hz, 1H), 5.89 (br d, J=6.2 Hz, 1H), 4.85 (br d, J=5.5 Hz, 1H), 3.47 (br s, 1H), 3.03 (br s, 1H), 2.24 (br d, J=11.2 Hz, 2H), 2.08 (br d, J=11.0 Hz, 2H), 1.71 (q, J=11.9 Hz, 2H), 1.61 (br d, J=6.4 Hz, 3H), 1.49 - 1.37 (m, 2H), 1.24 (br d, J=5.4 Hz, 6H), 1.13 (s, 9H). ESI [M+H] = 643.2

Example 42. Synthesis of pyridin-2-ylmethyl (3-(N-(tert-butyl)sulfamoyl)-4-(2-((1r,4r)-4-((isopropoxycarbonyl)amino)cyclohexyl)thiazol-5-yl)phenyl)carbamate.

The following compound was synthesized via same method by the key intermediate 118.

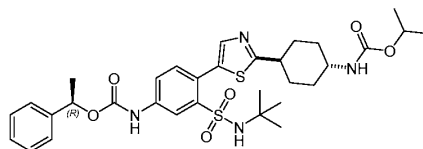


Ex. 42

^1H NMR (400MHz, METHANOL- d_4) δ = 8.56 (br d, J =4.5 Hz, 1H), 8.38 (d, J =1.8 Hz, 1H), 7.94 - 7.87 (m, 1H), 7.78 - 7.72 (m, 2H), 7.59 (br d, J =7.8 Hz, 1H), 7.44 - 7.38 (m, 2H), 5.32 (s, 2H), 4.85 (td, J =5.9, 12.0 Hz, 1H), 3.47 (br t, J =11.8 Hz, 1H), 3.07 - 2.96 (m, 1H), 2.24 (br d, J =12.3 Hz, 2H), 2.13 - 2.04 (m, 2H), 1.77 - 1.65 (m, 2H), 1.48 - 1.37 (m, 2H), 1.24 (br d, J =6.1 Hz, 6H), 1.14 (s, 9H). ESI $[M+H]^+$ = 630.2

Example 43. Synthesis of (R)-1-phenylethyl (3-(N-(tert-butyl)sulfamoyl)-4-(2-((1R,4R)-4-(isopropoxycarbonyl)amino)cyclohexyl)thiazol-5-yl)phenyl)carbamate.

The following compound was synthesized via same method by the key intermediate 118.

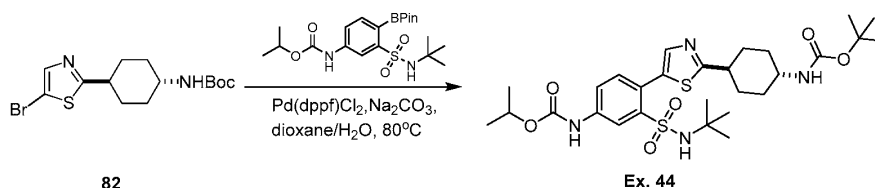


Ex. 43

^1H NMR (400MHz, DMSO- d_6) δ = 8.28 (d, J =2.2 Hz, 1H), 7.70 - 7.57 (m, 2H), 7.47 - 7.24 (m, 7H), 7.05 - 6.84 (m, 2H), 5.82 (q, J =6.6 Hz, 1H), 4.79 - 4.65 (m, 1H), 3.35 - 3.24 (m, 1H), 2.88 (tt, J =3.4, 11.9 Hz, 1H), 2.11 (br d, J =11.7 Hz, 2H), 1.89 (br d, J =9.9 Hz, 2H), 1.54 (d, J =6.6 Hz, 5H), 1.30 (br s, 2H), 1.14 (d, J =6.2 Hz, 6H), 1.08 - 0.99 (m, 9H). ESI $[M+H]^+$ = 643.3

Example 44. Synthesis of *trans*-isopropyl N-[4-[2-[4-(tert-butoxycarbonylamino)cyclohexyl]thiazol-5-yl]-3-(tert-butylsulfamoyl)phenyl]carbamate.

Scheme 14:



82

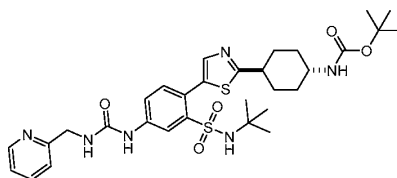
Ex. 44

General method B, *trans*-isopropyl N-[4-[2-[4-(tert-butoxycarbonylamino)cyclohexyl]thiazol-5-yl]-3-(tert-butylsulfamoyl)phenyl]carbamate. ^1H NMR (400MHz, DMSO- d_6) δ = 10.06 (s, 1H), 8.32 (d, J =2.1 Hz, 1H), 7.70 - 7.60 (m, 2H), 7.38 (d, J =8.4 Hz, 1H), 6.96 (s, 1H), 6.81 (br d, J =7.9 Hz, 1H), 4.99 - 4.87 (m, 1H), 3.27 (br s, 1H), 2.94 - 2.84 (m, 1H), 2.13

(br d, J=11.7 Hz, 2H), 1.90 (br d, J=11.1 Hz, 2H), 1.63 - 1.49 (m, 2H), 1.39 (s, 9H), 1.33 (br d, J=14.4 Hz, 2H), 1.28 (d, J=6.4 Hz, 6H), 1.07 (s, 9H). ESI [M+H]⁺=595.1

Example 45. Synthesis of tert-butyl ((1r,4r)-4-(5-(2-(N-(tert-butyl)sulfamoyl)-4-(3-(pyridin-2-ylmethyl)ureido)phenyl)thiazol-2-yl)cyclohexyl)carbamate.

The following compound was synthesized via same method by the key intermediate 82.

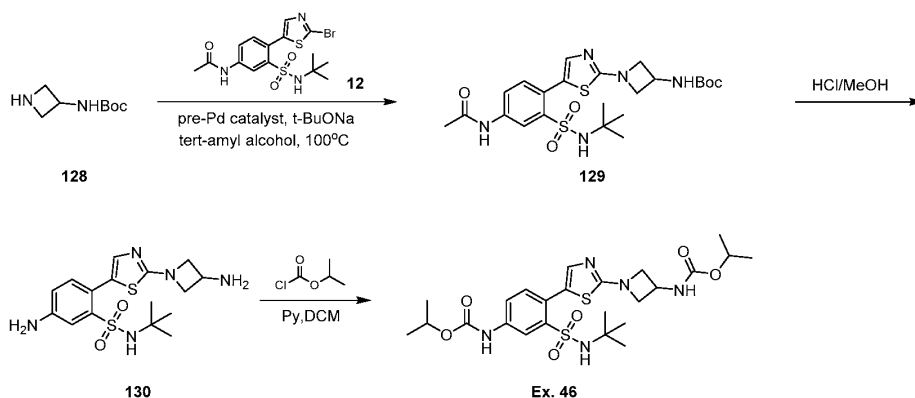


Ex. 45

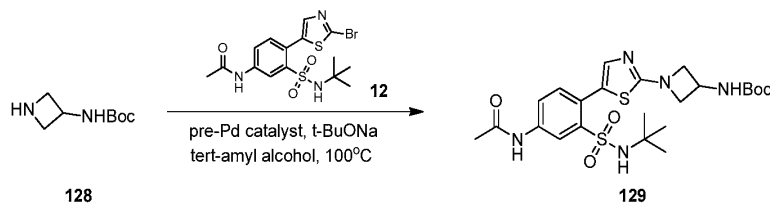
¹H NMR (400MHz, METHANOL-d₄) δ = 8.17 (d, J=2.2 Hz, 1H), 7.75 - 7.59 (m, 2H), 7.43 - 7.22 (m, 3H), 7.21 - 7.03 (m, 2H), 4.53 (m, 2H), 3.43 (br t, J=1.8 Hz, 1H), 2.99 (br t, J=12.1 Hz, 1H), 2.22 (br d, J=12.7 Hz, 2H), 2.06 (br d, J=10.5 Hz, 2H), 1.77 - 1.60 (m, 2H), 1.58 - 1.34 (m, 11H), 1.09 (s, 9H). ESI [M+H]⁺=643.3

Example 46. Synthesis of isopropyl N-[3-(tert-butylsulfamoyl)-4-[2-[3-(isopropoxycarbonyl amino)azetidin-1-yl]thiazol-5-yl]phenyl]carbamate.

Scheme 15:



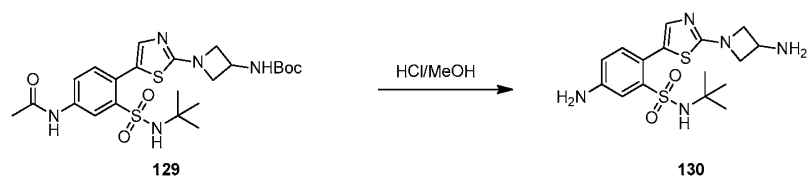
Preparation of compound 129.



A mixture of tert-butyl N-(azetidin-3-yl)carbamate hydrochloride (72.40 mg, 346.94 μmol , 1.50 *eq.*), *N*-[4-(2-bromothiazol-5-yl)-3-(tert-butylsulfamoyl)phenyl] acetamide (100 mg,

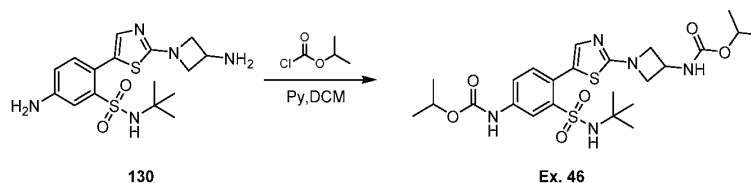
231.29 μmol , 1 *eq.*), *t*-BuONa (66.68 mg, 693.87 μmol , 3 *eq.*), [2-(2-aminoethyl)phenyl]-chloro-palladium;diter-butyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane (15.88 mg, 23.13 μmol , 0.1 *eq.*) in *tert*-amyl alcohol (2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100°C for 12 hrs under N_2 atmosphere and then concentrated. The residue was diluted with Ethyl acetate (20 mL) and washed with H_2O (20 mL). The organic layer was dried and concentrated and the residue was purified by prep-TLC (EtOAc) to give *tert*-butyl *N*-[1-[5-[4-acetamido-2-(*tert*-butylsulfamoyl)phenyl]thiazol-2-yl]azetidin-3-yl]carbamate (46 mg, crude) as a yellow solid. ESI $[\text{M}+\text{H}] = 524.3$

Preparation of compound 130.



General method F, *5-amino-2-[2-(3-aminoazetidin-1-yl)thiazol-5-yl]-*N*-tert-butyl-benzenesulfonamide*. ESI $[\text{M}+\text{H}] = 382.0$

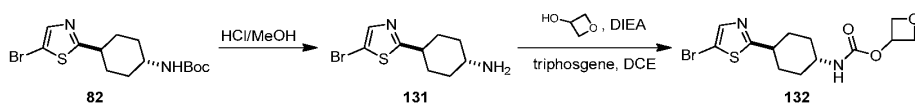
Preparation of Example 46

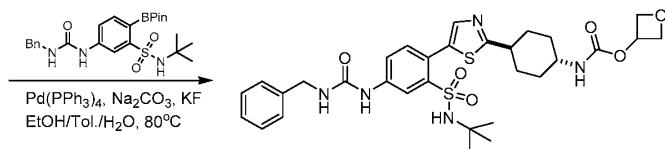


General method D, *isopropyl N-[3-(tert-butylsulfamoyl)-4-[2-[3-(isopropoxycarbonyl amino)azetidin-1-yl]thiazol-5-yl]phenyl]carbamate*. ^1H NMR (400MHz, METHANOL- d_4) δ = 8.35 (d, $J=2.0$ Hz, 1H), 7.67 (dd, $J=2.2, 8.4$ Hz, 1H), 7.45 - 7.32 (m, 2H), 5.04 - 4.94 (m, 1H), 4.92 - 4.88 (m, 1H), 4.73 - 4.63 (m, 1H), 4.56 (br t, $J=8.5$ Hz, 2H), 4.27 (br s, 2H), 1.31 (d, $J=6.2$ Hz, 6H), 1.27 - 1.19 (m, 15H). ESI $[\text{M}+\text{H}] = 554.2$

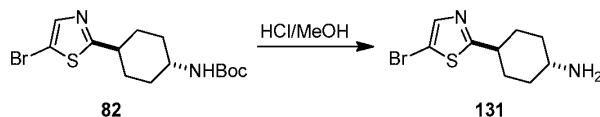
Example 47. Synthesis of *trans*-oxetan-3-yl *N*-[4-[5-[4-(benzylcarbamoylamino)-2-(*tert*-butylsulfamoyl)phenyl]thiazol-2-yl]cyclohexyl]carbamate

Scheme 16:

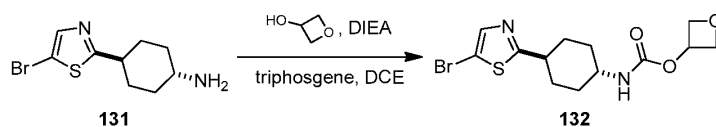




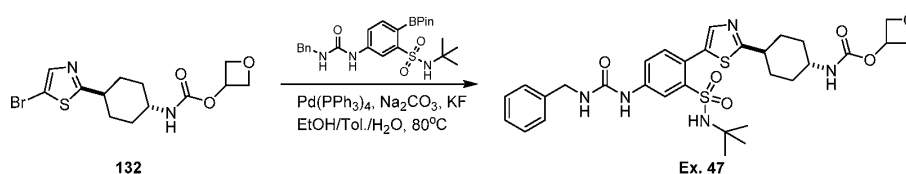
Ex. 47

Preparation of compound 131.

General method F, *trans-4-(5-bromothiazol-2-yl)cyclohexanamine*. ESI [M+H]
=260.9/262.9

Preparation of compound 132.

To a solution of oxetan-3-ol (1.15 g, 15.51 mmol, 3 eq.) in DCE (10 mL) were added DIEA (3.34 g, 25.84 mmol, 4.50 mL, 5 eq.) and TRIPHOSGENE (1.53 g, 5.17 mmol, 1 eq.). The mixture was stirred at 25-50°C for 1 hr and then added a solution of *trans-4-(5-bromothiazol-2-yl)cyclohexanamine* (1.35 g, 5.17 mmol, 1 eq.), DIEA (3.34 g, 25.84 mmol, 4.50 mL, 5 eq.) in DCE (10 mL). The mixture was stirred at 25°C for 0.5 hr. The mixture was concentrated and the residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=30/1 to 5:1) to give *trans-oxetan-3-yl N-[4-(5-bromothiazol-2-yl)cyclohexyl]carbamate* (1.5 g, crude) as a white solid. ESI [M+H] =363.1/361.1

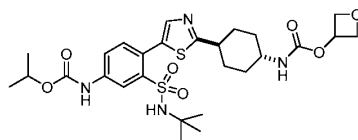
Preparation of Ex. 47

Ex. 47

General method K, *trans-oxetan-3-yl N-[4-[5-[4-(benzylcarbamoylamino)-2-(tert-butylsulfamoyl)phenyl]thiazol-2-yl]cyclohexyl]carbamate*. ¹H NMR (400MHz, METHANOL-d₄) δ = 8.23 (d, J=2.2 Hz, 1H), 7.71 - 7.66 (m, 2H), 7.37 - 7.29 (m, 5H), 7.24 (br s, 1H), 5.40 - 5.27 (m, 2H), 4.66 - 4.55 (m, 3H), 4.40 (s, 2H), 3.45 (br d, J=11.0 Hz, 1H), 3.00 (br t, J=11.8 Hz, 1H), 2.22 (br d, J=13.0 Hz, 2H), 2.07 (br d, J=11.2 Hz, 2H), 1.74 - 1.63 (m, 2H), 1.47 - 1.37 (m, 2H), 1.10 (s, 9H). ESI [M+H] =642.3

Example 48. Synthesis of oxetan-3-yl ((1*r*,4*r*)-4-(5-(2-(*N*-(*tert*-butyl)sulfamoyl)-4-((isopropoxycarbonyl)amino)phenyl)thiazol-2-yl)cyclohexyl)carbamate.

The following compound was synthesized via same method by the key intermediate 132.

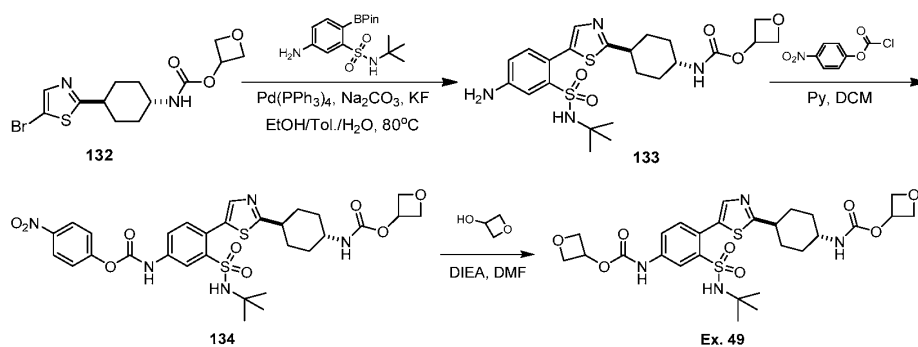


Ex. 48

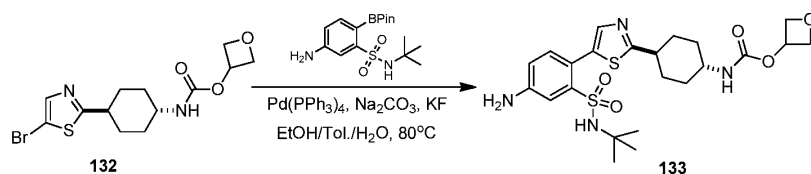
¹H NMR (400MHz, METHANOL-d₄) δ = 8.33 (d, J=2.0 Hz, 1H), 7.71 - 7.64 (m, 2H), 7.36 (d, J=8.4 Hz, 1H), 5.41 - 5.27 (m, 2H), 4.98 (td, J=6.4, 12.6 Hz, 1H), 4.87 (br s, 1H), 4.63 - 4.56 (m, 2H), 3.45 (br d, J=12.3 Hz, 1H), 3.00 (br t, J=12.0 Hz, 1H), 2.22 (br d, J=13.0 Hz, 2H), 2.11 - 2.02 (m, 2H), 1.74 - 1.63 (m, 2H), 1.42 (q, J=12.7 Hz, 2H), 1.31 (d, J=6.2 Hz, 6H), 1.11 (s, 9H). ESI [M+H] = 595.3

Example 49. Synthesis of *trans*-oxetan-3-yl *N*-[3-(*tert*-butylsulfamoyl)-4-[2-[4-(oxetan-3-yl)oxycarbonylamino]cyclohexyl]thiazol-5-yl]phenyl]carbamate

Scheme 17:

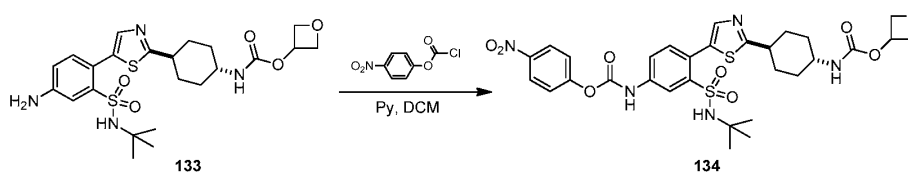


Preparation of compound 133.



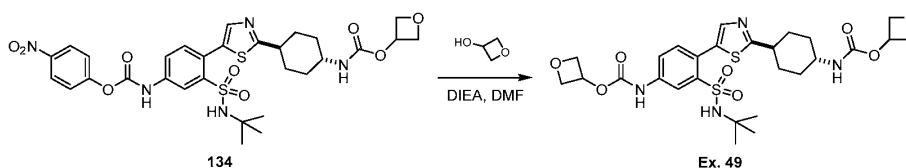
General method K, *trans*-oxetan-3-yl *N*-[4-[5-[4-amino-2-(*tert*-butylsulfamoyl)phenyl]thiazol-2-yl]cyclohexyl]carbamate. ESI [M+H] = 509.0

Preparation of compound 134.



General method D, *trans*-oxetan-3-yl N-[4-[5-[2-(tert-butylsulfamoyl)-4-[(4-nitrophenoxy)carbonylamino]phenyl]thiazol-2-yl]cyclohexyl]carbamate. ESI [M+H]
=674.2

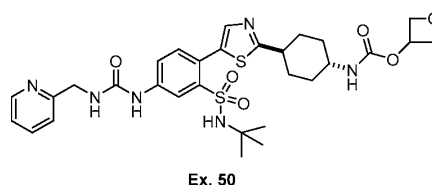
Preparation of Example 49.



General method H, *trans*-oxetan-3-yl N-[3-(tert-butylsulfamoyl)-4-[2-[4-(oxetan-3-yl)oxycarbonylamino]cyclohexyl]thiazol-5-yl]phenyl]carbamate. ¹H NMR (400MHz, DMSO-d₆) δ = 10.39 (s, 1H), 8.28 (d, J=2.2 Hz, 1H), 7.71 - 7.58 (m, 2H), 7.48 - 7.34 (m, 2H), 6.97 (s, 1H), 5.50 - 5.39 (m, 1H), 5.32 - 5.20 (m, 1H), 4.87 - 4.68 (m, 4H), 4.61 - 4.36 (m, 4H), 3.30 - 3.23 (m, 1H), 3.01 - 2.82 (m, 1H), 2.12 (br d, J=11.7 Hz, 2H), 1.90 (br d, J=10.4 Hz, 2H), 1.66 - 1.47 (m, 2H), 1.43 - 1.26 (m, 2H), 1.04 (s, 9H). ESI [M+H] =609.2

Example 50. Synthesis of oxetan-3-yl ((1*r*,4*r*)-4-(5-(2-(N-(tert-butyl)sulfamoyl)-4-(3-(pyridin-2-ylmethyl)ureido)phenyl)thiazol-2-yl)cyclohexyl]carbamate.

The following compound was synthesized via same method by the key intermediate 134.

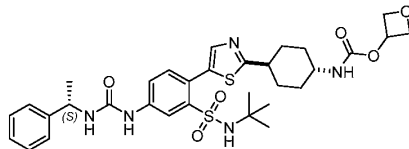


¹H NMR (400MHz, METHANOL-d₄) δ = 8.49 (d, J=4.8 Hz, 1H), 8.25 (d, J=2.2 Hz, 1H), 7.82 (dt, J=1.8, 7.7 Hz, 1H), 7.73 - 7.63 (m, 2H), 7.45 (d, J=7.9 Hz, 1H), 7.38 - 7.26 (m, 2H), 5.39 - 5.28 (m, 1H), 4.84 (br s, 1H), 4.70 - 4.56 (m, 3H), 4.53 (s, 2H), 3.44 (br t, J=12.1 Hz, 1H), 3.06 - 2.92 (m, 1H), 2.22 (br d, J=13.2 Hz, 2H), 2.07 (br d, J=11.0 Hz, 2H), 1.79 - 1.60 (m, 2H), 1.50 - 1.35 (m, 2H), 1.10 (s, 9H). ESI [M+H] =643.2

Example 51. Synthesis of oxetan-3-yl ((1*S*,4*r*)-4-(5-(2-(N-(tert-butyl)sulfamoyl)-4-(3-((S)-

1-phenylethyl)ureido)phenyl)thiazol-2-yl)cyclohexyl)carbamate.

The following compound was synthesized via same method by the key intermediate 134.

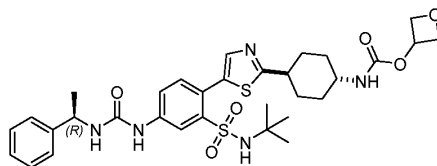


Ex. 51

^1H NMR (400MHz, METHANOL- d_4) δ = 8.19 (d, J =2.2 Hz, 1H), 7.70 - 7.63 (m, 2H), 7.39 - 7.30 (m, 5H), 7.27 - 7.20 (m, 1H), 5.35 (t, J =5.7 Hz, 1H), 4.92 (q, J =6.8 Hz, 2H), 4.84 (br s, 1H), 4.60 (t, J =6.4 Hz, 2H), 3.49 - 3.38 (m, 1H), 3.05 - 2.95 (m, 1H), 2.22 (br d, J =12.3 Hz, 2H), 2.10 - 2.02 (m, 2H), 1.74 - 1.61 (m, 2H), 1.49 (d, J =7.1 Hz, 3H), 1.45 - 1.34 (m, 2H), 1.09 (s, 9H). ESI $[M+H]^+$ = 656.3

Example 52. Synthesis of oxetan-3-yl ((1R,4r)-4-(5-(2-(N-(tert-butyl)sulfamoyl)-4-(3-((R)-1-phenylethyl)ureido)phenyl)thiazol-2-yl)cyclohexyl)carbamate.

The following compound was synthesized via same method by the key intermediate 134.

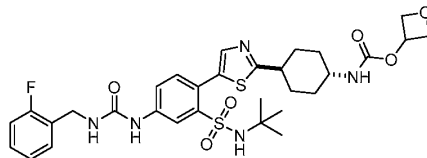


Ex. 52

^1H NMR (400MHz, METHANOL- d_4) δ = 8.19 (d, J =2.2 Hz, 1H), 7.75 - 7.61 (m, 2H), 7.42 - 7.18 (m, 6H), 5.35 (quin, J =5.7 Hz, 1H), 5.01 - 4.87 (m, 3H), 4.70 - 4.52 (m, 2H), 3.51 - 3.38 (m, 1H), 3.06 - 2.92 (m, 1H), 2.22 (br d, J =11.9 Hz, 2H), 2.07 (br d, J =11.7 Hz, 2H), 1.77 - 1.62 (m, 2H), 1.54 - 1.35 (m, 5H), 1.10 (s, 9H). ESI $[M+H]^+$ = 656.2

Example 53. Synthesis of oxetan-3-yl ((1r,4r)-4-(5-(2-(N-(tert-butyl)sulfamoyl)-4-(3-(2-fluorobenzyl)ureido)phenyl)thiazol-2-yl)cyclohexyl)carbamate.

The following compound was synthesized via same method by the key intermediate 134.



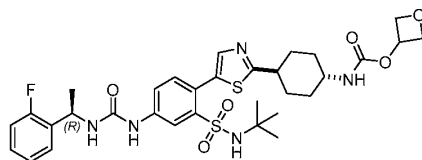
Ex. 53

^1H NMR (400MHz, METHANOL- d_4) δ = 8.23 (d, J =2.4 Hz, 1H), 7.75 - 7.63 (m, 2H), 7.46 - 7.24 (m, 3H), 7.20 - 7.03 (m, 2H), 5.43 - 5.28 (m, 1H), 4.85 (br s, 2H), 4.67 - 4.56 (m, 2H),

4.47 (s, 2H), 3.53 - 3.37 (m, 1H), 3.08 - 2.93 (m, 1H), 2.29 - 1.99 (m, 4H), 1.78 - 1.61 (m, 2H), 1.53 - 1.35 (m, 2H), 1.11 (s, 9H). ESI [M+H] = 660.2

Example 54. Synthesis of oxetan-3-yl ((1*R*,4*r*)-4-(5-(2-(*N*-(*tert*-butyl)sulfamoyl)-4-(3-((*R*)-1-(2-fluorophenyl)ethyl)ureido)phenyl)thiazol-2-yl)cyclohexyl)carbamate.

The following compound was synthesized via same method by the key intermediate 134.

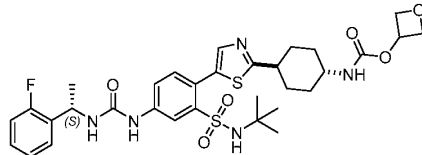


Ex. 54

¹H NMR (400MHz, METHANOL-d₄) δ = 8.20 (d, J=2.3 Hz, 1H), 7.73 - 7.65 (m, 2H), 7.45 - 7.39 (m, 1H), 7.38 - 7.26 (m, 2H), 7.21 - 7.04 (m, 2H), 5.37 (quin, J=5.7 Hz, 1H), 5.20 (q, J=7.0 Hz, 1H), 4.89 - 4.86 (m, 2H), 4.65 - 4.59 (m, 2H), 3.52 - 3.41 (m, 1H), 3.08 - 2.96 (m, 1H), 2.24 (br d, J=12.2 Hz, 2H), 2.13 - 2.05 (m, 2H), 1.76 - 1.64 (m, 2H), 1.52 (d, J=7.0 Hz, 3H), 1.47 - 1.39 (m, 2H), 1.12 (s, 9H). ESI [M+H] = 674.2

Example 55. Synthesis of oxetan-3-yl ((1*S*,4*r*)-4-(5-(2-(*N*-(*tert*-butyl)sulfamoyl)-4-(3-((*S*)-1-(2-fluorophenyl)ethyl)ureido)phenyl)thiazol-2-yl)cyclohexyl)carbamate.

The following compound was synthesized via same method by the key intermediate 134.

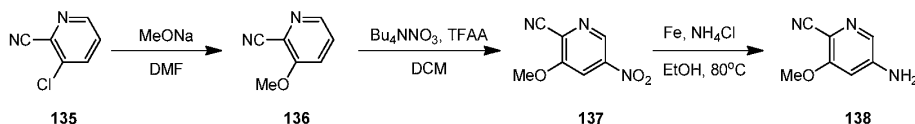


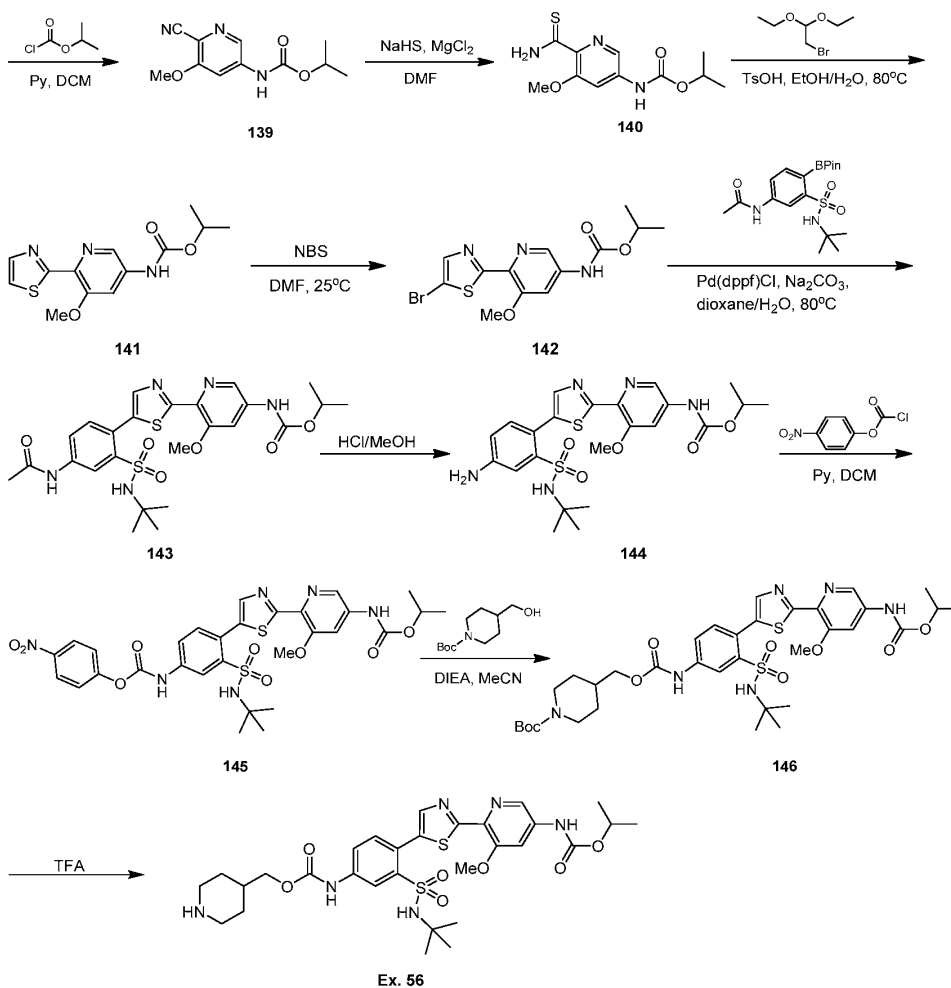
Ex. 55

¹H NMR (400MHz, METHANOL-d₄) δ = 8.17 (d, J=2.2 Hz, 1H), 7.75 - 7.59 (m, 2H), 7.43 - 7.22 (m, 3H), 7.21 - 7.03 (m, 2H), 5.39 - 5.28 (m, 1H), 5.17 (q, J=7.0 Hz, 1H), 4.90 - 4.87 (m, 1H), 4.84 (s, 1H), 4.66 - 4.54 (m, 2H), 3.43 (br t, J=11.8 Hz, 1H), 2.99 (br t, J=12.1 Hz, 1H), 2.22 (br d, J=12.7 Hz, 2H), 2.06 (br d, J=10.5 Hz, 2H), 1.77 - 1.60 (m, 2H), 1.58 - 1.34 (m, 5H), 1.09 (s, 9H). ESI [M+H] = 674.2

Example 56. Synthesis of 4-piperidylmethyl *N*-[3-(*tert*-butylsulfamoyl)-4-[2-[5-(isopropoxycarbonylamino)-3-methoxy-2-pyridyl]thiazol-5-yl]phenyl]carbamate

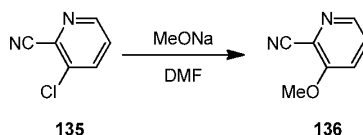
Scheme 18:





Ex. 56

Preparation of compound 136.



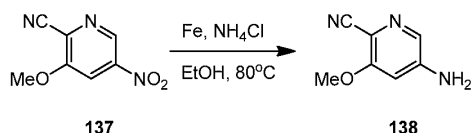
Na (8.75 g, 380.60 mmol, 9.02 mL, 1.51 *eq.*) was added into MeOH (300 mL) portionwise and after Na was dissolved, the mixture was concentrated to dryness. The resulting gray solid (NaOMe) was added into DMF (300 mL) and **3-chloropyridine-2-carbonitrile** (35 g, 252.61 mmol, 1 *eq.*) was added at 0°C . The reaction mixture was stirred at 20°C for 12 hrs and then diluted with H_2O (800 mL) and filtered. The cake dried to give **3-methoxypyridine-2-carbonitrile** (25 g, crude) as a white solid. ESI $[\text{M}+\text{H}] = 135.1$

Preparation of compound 137



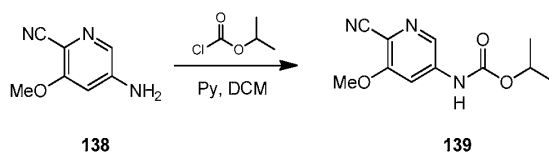
To a solution of **3-methoxypyridine-2-carbonitrile** (24.5 g, 182.65 mmol, 1 *eq.*) in DCM (450 mL) was added a mixture of Bu₄NNO₃ (83.30 g, 273.59 mmol, 1.5 *eq.*) and TFAA (57.54 g, 273.98 mmol, 38.11 mL, 1.5 *eq.*) in DCM (150 mL) dropwise at 0°C. The mixture was stirred at 20°C for 12 hrs and then poured into sat. aq. NaHCO₃ (300 mL) at 0°C and the organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=20/1 to 10:1) to give **3-methoxy-5-nitro-pyridine-2-carbonitrile** (27 g, crude) as a white solid. ¹H NMR (400MHz, CHLOROFORM-d) δ = 9.06 (d, J=2.2 Hz, 1H), 8.13 (d, J=2.2 Hz, 1H), 4.16 - 4.08 (m, 3H). ESI [M+H] =180.1

General method G for preparation of compound 138.



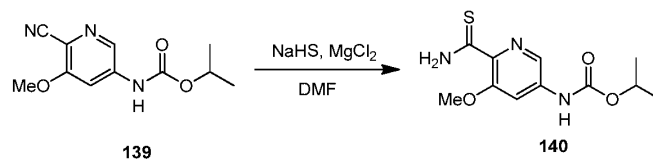
To a solution of **3-methoxy-5-nitro-pyridine-2-carbonitrile** (27 g, 151 mmol, 1 *eq.*) in THF (100 mL)/EtOH (500 mL) were added Fe (4 g, 754 mmol, 5 *eq.*) and a solution of NH₄Cl (24.2 g, 452 mmol, 3 *eq.*) in H₂O (50 mL). The mixture was stirred at 80°C for 30 mins, then diluted with THF (500 mL) and filtered. The filtrate was concentrated, diluted with H₂O (500 mL) and then extracted with DCM (400 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to give **5-amino-3-methoxy-pyridine-2-carbonitrile** (14.5 g, crude) as a pale yellow solid. ESI [M+H] =150.1

Preparation of compound 139.



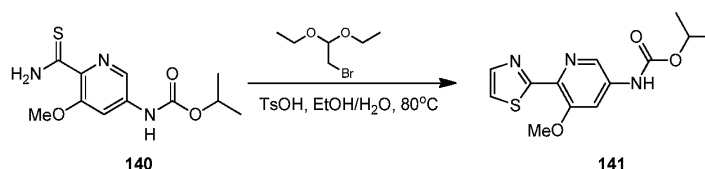
General method D, **isopropyl N-(6-cyano-5-methoxy-3-pyridyl)carbamate**. ¹H NMR (400MHz, METHANOL-d₄) δ = 8.13 (d, J=2.2 Hz, 1H), 7.95 (d, J=1.8 Hz, 1H), 5.04 - 4.95 (m, 1H), 3.96 (s, 3H), 1.31 (d, J=6.2 Hz, 6H). ESI [M+H] =236.1

Preparation of compound 140.



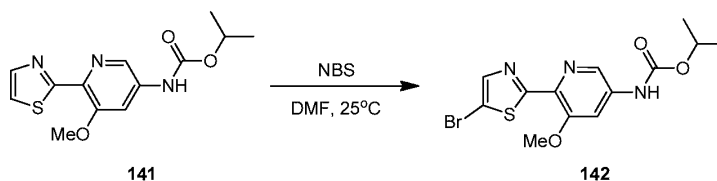
To a solution of *isopropyl N-(6-cyano-5-methoxy-3-pyridyl)carbamate* (16 g, 68.02 mmol, 1 *eq.*) in DMF (200 mL) were added NaHS (19.06 g, 340.08 mmol, 5 *eq.*) and then MgCl₂ (19.43 g, 204.05 mmol, 8.37 mL, 3 *eq.*). The mixture was stirred at 25°C for 12 hrs and then poured into H₂O (500ml) and extracted with DCM (40 mL * 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was washed with a solution (Petroleum ether : EtOAc= 8:1), filtered and the filter cake was dried to give *isopropyl N-(6-carbamothioyl-5-methoxy-3-pyridyl)carbamate* (21 g, crude) as a yellow solid. ¹H NMR (400MHz, DMSO-d₆) δ = 9.92 - 9.84 (m, 2H), 9.38 (br s, 1H), 8.08 (d, J=1.8 Hz, 1H), 7.66 (s, 1H), 4.89 (spt, J=6.3 Hz, 1H), 3.74 (s, 3H), 1.24 (d, J=6.1 Hz, 6H). ESI [M+H]⁺ =270.0

Preparation of compound 141.



General method M, *isopropyl N-(5-methoxy-6-thiazol-2-yl-3-pyridyl)carbamate* ¹H NMR (400MHz, DMSO-d₆) δ = 10.07 (s, 1H), 8.26 (d, J=2.0 Hz, 1H), 7.88 (d, J=3.1 Hz, 1H), 7.85 (d, J=1.3 Hz, 1H), 7.71 (d, J=3.3 Hz, 1H), 4.91 (spt, J=6.2 Hz, 1H), 3.88 (s, 3H), 1.26 (d, J=6.4 Hz, 6H). ESI [M+H]⁺ =294.1

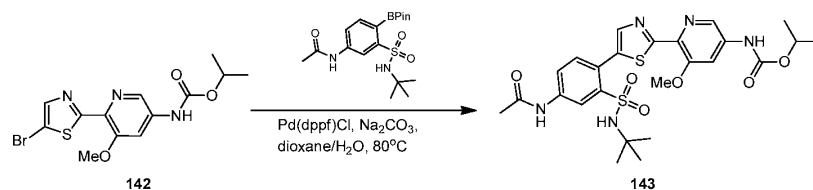
Preparation of compound 142.



General method J, *isopropyl N-[6-(5-bromothiazol-2-yl)-5-methoxy-3-pyridyl] carbamate*.

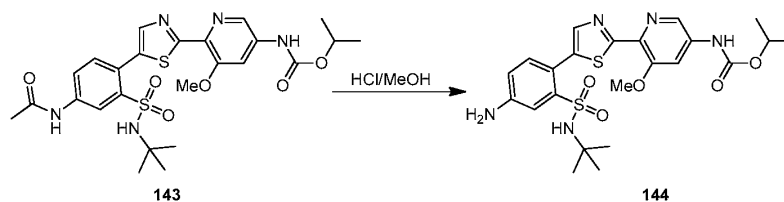
¹H NMR (400MHz, DMSO-d₆) δ = 10.17 (s, 1H), 8.28 (d, J=1.8 Hz, 1H), 8.08 - 7.86 (m, 2H), 4.99 (br s, 1H), 3.93 (s, 3H), 1.29 (d, J=6.4 Hz, 6H). ESI [M+H]⁺ =371.8/373.8

Preparation of compound 143.



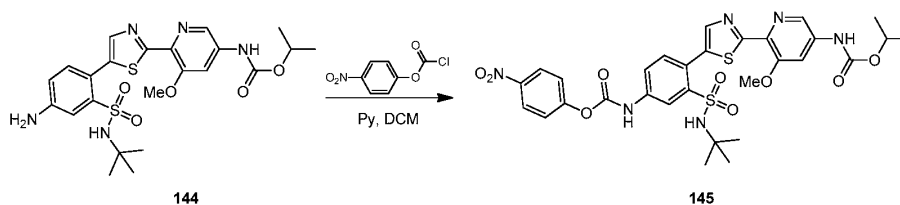
General method B, *isopropyl N-[6-[5-[4-acetamido-2-(tert-butylsulfamoyl)phenyl]thiazol-2-yl]-5-methoxy-3-pyridyl]carbamate*. ESI [M+H] = 562.0

Preparation of compound 144.



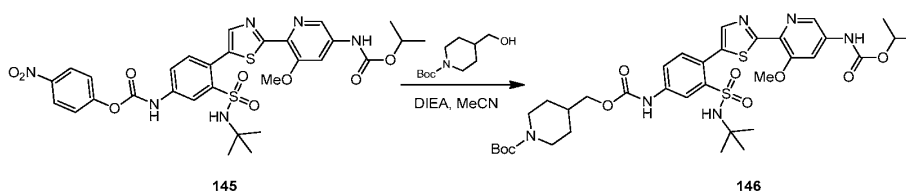
General method F, *isopropyl N-[6-[5-[4-amino-2-(tert-butylsulfamoyl)phenyl]thiazol-2-yl]-5-methoxy-3-pyridyl]carbamate*. ESI [M+H] = 520.2

Preparation of compound 145.



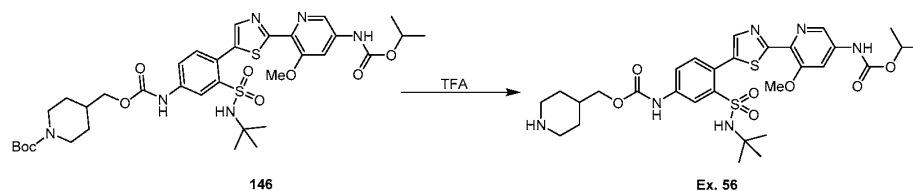
General method D, *(4-nitrophenyl) N-[3-(tert-butylsulfamoyl)-4-[2-[5-(isopropoxycarbonylamino)-3-methoxy-2-pyridyl]thiazol-5-yl]phenyl]carbamate*. ESI [M+H] = 685.1

Preparation of compound 146.



General method H, *tert-butyl 4-[[3-(tert-butylsulfamoyl)-4-[2-[5-(isopropoxycarbonylamino)-3-methoxy-2-pyridyl]thiazol-5-yl]phenyl]carbamoyloxymethyl]piperidine-1-carboxylate*. ESI [M+H] = 761.4

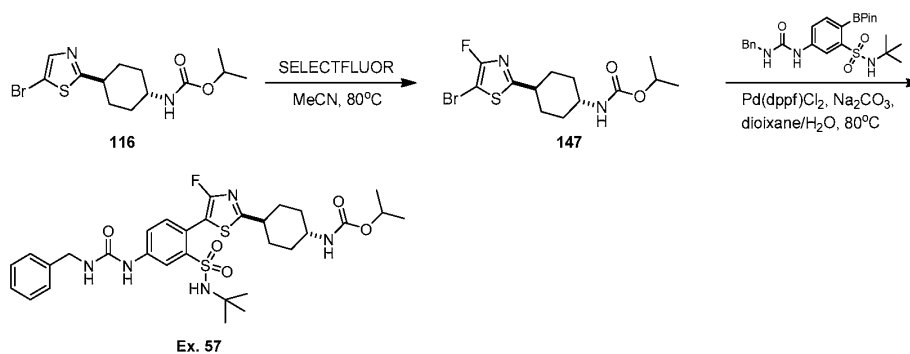
Preparation of Ex. 56



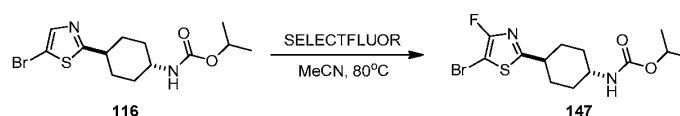
General method C, **4-piperidylmethyl N-[3-(tert-butylsulfamoyl)-4-[2-[5-(isopropoxycarbonylamino)-3-methoxy-2-pyridyl]thiazol-5-yl]phenyl]carbamate**. ^1H NMR (400MHz, DMSO- d_6) δ = 10.19 - 10.10 (m, 2H), 8.35 (d, J =2.1 Hz, 1H), 8.30 (d, J =1.8 Hz, 1H), 7.89 (s, 2H), 7.68 (dd, J =2.0, 8.4 Hz, 1H), 7.46 (d, J =8.4 Hz, 1H), 7.12 (br s, 1H), 4.95 (td, J =6.2, 12.5 Hz, 1H), 3.98 (d, J =6.5 Hz, 2H), 3.93 (s, 3H), 3.00 (br d, J =12.1 Hz, 2H), 2.70 - 2.56 (m, 2H), 1.77 (br d, J =4.0 Hz, 1H), 1.67 (br d, J =12.1 Hz, 2H), 1.30 (d, J =6.2 Hz, 6H), 1.16 (br dd, J =3.4, 12.0 Hz, 2H), 1.09 (s, 9H). ESI $[\text{M}+\text{H}]^+ = 661.3$

Example 57. Synthesis of *trans-isopropyl N-[4-[5-[4-(benzylcarbamoylamino)-2-(tert-butylsulfamoyl)phenyl]-4-fluoro-thiazol-2-yl]cyclohexyl]carbamate*.

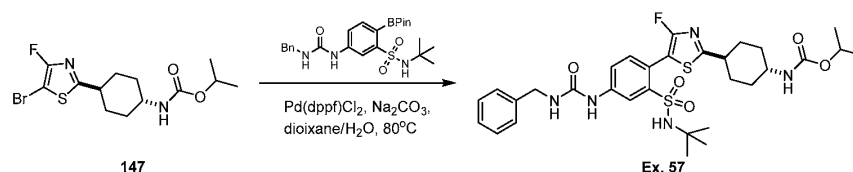
Scheme 19:



Preparation of compound 147



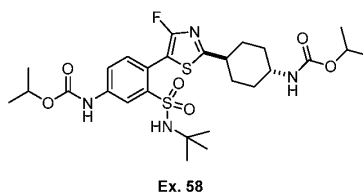
To a solution of *trans-isopropyl N-[4-(5-bromothiazol-2-yl)cyclohexyl]carbamate* (1.50 g, 4.32 mmol, 1 *eq.*) in ACN (20 mL) was added 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane ditetrafluoroborate (3.06 g, 8.64 mmol, 2 *eq.*) and the mixture was stirred at 80°C for 12 hrs. The mixture was then concentrated and the residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=3/1 to 3:1) to give *trans-isopropyl N-[4-(5-bromo-4-fluoro-thiazol-2-yl) cyclohexyl]carbamate* (0.2 g, 547.55 μmol , 12.68% yield) as yellow gum. ESI $[\text{M}+\text{H}]^+ = 365.1/367.1$

Preparation of Ex. 57

General method B, *trans-isopropyl N-[4-[5-[4-(benzylcarbamoylamino)-2-(tert-butylsulfamoyl)phenyl]-4-fluorothiazol-2-yl]cyclohexyl]carbamate*. ^1H NMR (400MHz, METHANOL- d_4) δ = 8.24 (d, J =2.0 Hz, 1H), 7.67 (dd, J =2.0, 8.4 Hz, 1H), 7.37 - 7.29 (m, 5H), 7.24 (br d, J =2.6 Hz, 1H), 4.82 - 4.77 (m, 1H), 4.40 (s, 2H), 3.42 (br t, J =11.6 Hz, 1H), 2.87 (br t, J =12.0 Hz, 1H), 2.20 (br d, J =12.3 Hz, 2H), 2.05 (br d, J =11.0 Hz, 2H), 1.69 - 1.57 (m, 2H), 1.43 - 1.30 (m, 2H), 1.21 (br d, J =5.7 Hz, 6H), 1.15 (s, 9H). ESI $[\text{M}+\text{H}]^+ = 646.2$

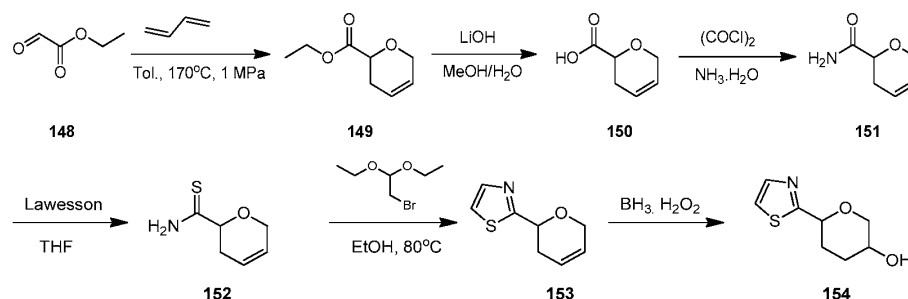
Example 58. Synthesis of isopropyl ((1*r*,4*r*)-4-(5-(2-(*N*-(tert-butyl)sulfamoyl)-4-((isopropoxycarbonyl)amino)phenyl)-4-fluorothiazol-2-yl)cyclohexyl)carbamate

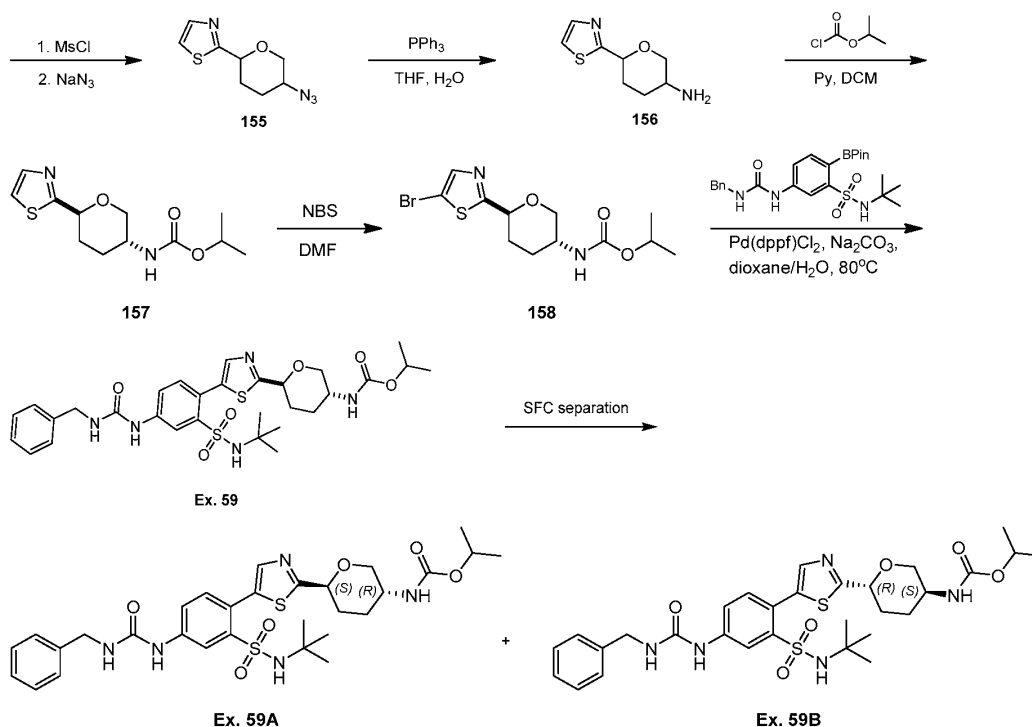
The following compound was synthesized via same method by the key intermediate 147.



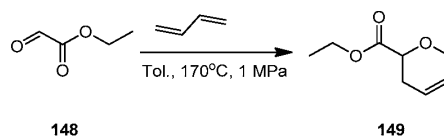
^1H NMR (400MHz, METHANOL- d_4) δ = 8.35 (s, 1H), 7.69 (br d, J =8.1 Hz, 1H), 7.37 (d, J =8.3 Hz, 1H), 5.01 (td, J =6.1, 12.4 Hz, 1H), 4.83 (br s, 1H), 3.53 - 3.39 (m, 1H), 2.96 - 2.85 (m, 1H), 2.23 (br d, J =12.3 Hz, 2H), 2.08 (br d, J =10.5 Hz, 2H), 1.75 - 1.60 (m, 2H), 1.47 - 1.38 (m, 2H), 1.34 (d, J =6.2 Hz, 6H), 1.24 (br d, J =6.0 Hz, 6H), 1.18 (s, 9H). ESI $[\text{M}+\text{H}]^+ = 599.2$

Example 59. Synthesis of *trans-isopropyl N-[6-[5-[4-(benzylcarbamoylamino)-2-(tert-butylsulfamoyl)phenyl]thiazol-2-yl]tetrahydropyran-3-yl]carbamate*

Scheme 20:

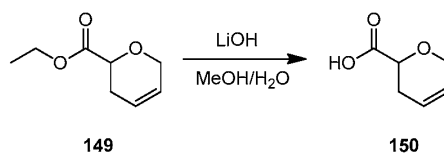


Preparation of compound 149



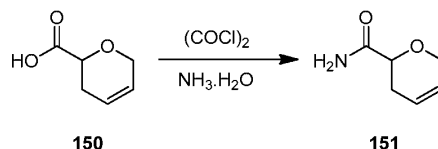
To a solution of **ethyl 2-oxoacetate** (250 g, 1.22 mol, 1 *eq.*) in Tol. (1.5 L), were added **buta-1,3-diene** (92.72 g, 1.71 mol, 149.55 mL, 1.4 *eq.*) and 2,6-ditert-butyl-4-methyl-phenol (5.40 g, 24.49 mmol, 0.02 *eq.*). The mixture was stirred at 170°C for 8 hrs in high pressure tube under 1 MPa and then concentrated. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate=100:1-10:1) to afford **ethyl 3,6-dihydro-2H-pyran-2-carboxylate** (26 g, 166.48 mmol, 13.60% yield) as yellow oil. ¹H NMR (400MHz, CHLOROFORM-d) δ = 5.82 - 5.74 (m, 1H), 5.71 - 5.64 (m, 1H), 4.36 - 4.27 (m, 1H), 4.23 - 4.12 (m, 4H), 2.39 - 2.23 (m, 2H), 1.24 (t, J=7.1 Hz, 3H).

Preparation of compound 150



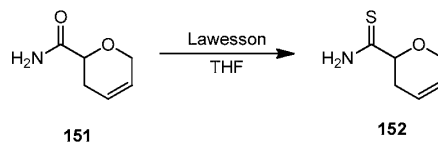
General method O, *3,6-dihydro-2H-pyran-2-carboxylic acid*. ^1H NMR (400MHz, CHLOROFORM- d) δ = 5.88 (qdd, J =2.3, 5.1, 10.2 Hz, 1H), 5.80 - 5.71 (m, 1H), 4.43 - 4.19 (m, 3H), 2.53 - 2.31 (m, 2H)

Preparation of compound 151



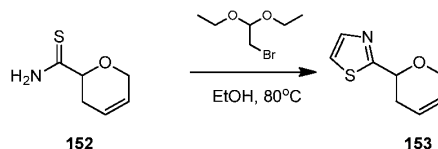
General method N, *3,6-dihydro-2H-pyran-2-carboxamide*. ^1H NMR (400MHz, CHLOROFORM- d) δ = 6.50 (br s, 1H), 5.89 - 5.76 (m, 1H), 5.67 (br d, J =9.8 Hz, 1H), 5.50 (br s, 1H), 4.22 (br s, 2H), 3.97 (dd, J =3.9, 10.8 Hz, 1H), 2.49 - 2.35 (m, 1H), 2.28 - 2.09 (m, 1H)

Preparation of compound 152



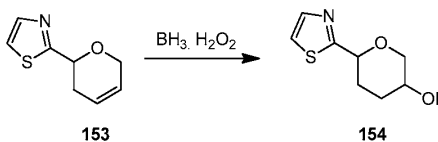
General method L, *3,6-dihydro-2H-pyran-2-carbothioamide*. ESI $[\text{M}+\text{H}]=144.1$

Preparation of compound 153



General method M, *2-(3,6-dihydro-2H-pyran-2-yl)thiazole*. ^1H NMR (400MHz, CHLOROFORM- d) δ = 7.69 (d, J =2.9 Hz, 1H), 7.26 (d, J =2.9 Hz, 1H), 5.93 - 5.83 (m, 1H), 5.70 - 5.63 (m, 1H), 4.86 (dd, J =3.9, 9.8 Hz, 1H), 4.33 (br s, 2H), 2.61 - 2.37 (m, 2H). ESI $[\text{M}+\text{H}]=168.1$

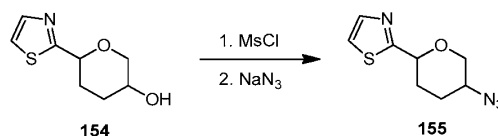
Preparation of compound 154



To a solution of *2-(3,6-dihydro-2H-pyran-2-yl)thiazole* (13 g, 77.74 mmol, 1 eq.) in THF (150 mL), was added $\text{BH}_3\text{-Me}_2\text{S}$ (10 M, 15.55 mL, 2 eq.) at 0 °C dropwise and the mixture was stirred at 26°C for 2 hrs. Then the mixture was quenched by NaOH (62.19 g, 1.55 mol, 20 eq.) in H_2O (150 mL) slowly at 0 °C followed by addition of H_2O_2 (264.42 g, 2.33 mol,

224.09 mL, 30% purity, 30 eq.). The mixture was stirred at 26°C for another 12 hrs. The mixture was quenched by sat.aq.Na₂SO₃ solution (1 L) and extracted with EtOAc (1 L*2). The combined organic phased was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column (Petroleum ether : EtOAc= 5:1-1:1) to afford **6-thiazol-2-yltetrahydropyran-3-ol** (7 g, crude) as a yellow solid. ESI [M+H]=186.2

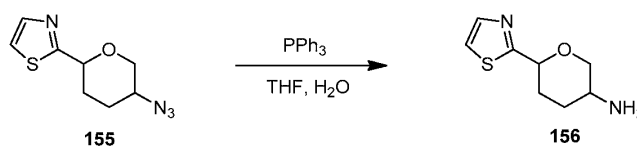
Preparation of compound 155



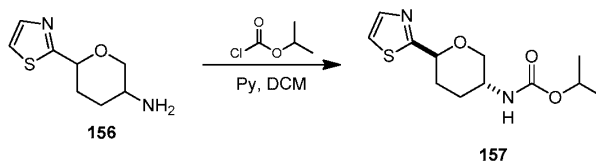
To a solution of **6-thiazol-2-yltetrahydropyran-3-ol** (7 g, 37.79 mmol, 1 eq.) in DCM (100 mL), were added TEA (7.65 g, 75.58 mmol, 10.52 mL, 2 eq.) and methanesulfonyl chloride (6.49 g, 56.68 mmol, 4.39 mL, 1.5 eq.) dropwise at 0 °C and the mixture was stirred at 26°C for 2 hrs. The mixture was diluted with DCM (100 mL) and washed with water (200 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated to give crude **(6-thiazol-2-yltetrahydropyran-3-yl) methanesulfonate** (7 g, crude) as yellow oil which can be used directly.

To a solution of **(6-thiazol-2-yltetrahydropyran-3-yl) methanesulfonate** (7 g, 26.58 mmol, 1 eq.) in DMF (60 mL), was added azidosodium (8.64 g, 132.91 mmol, 5 eq.) and the mixture was stirred at 80°C for 12 hrs and then poured into sat.aq.Na₂CO₃ (500 mL) and extracted with EtOAc (200 mL*3). The combined organic phase was washed with brine (200 mL) and dried over Na₂SO₄, filtered and concentrated to give crude **2-(5-azidotetrahydropyran-2-yl)thiazole** (5 g, crude) as yellow oil which can be used without any purification.

Preparation of compound 156

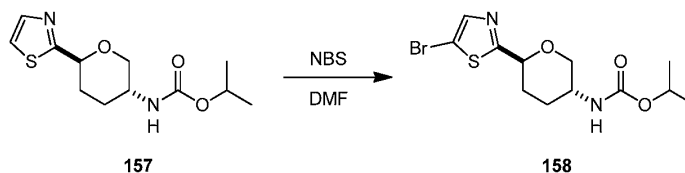


To a solution of **2-(5-azidotetrahydropyran-2-yl)thiazole** (5 g, 23.78 mmol, 1 eq.) in THF (80 mL) and H₂O (40 mL), was added PPh₃ (9.36 g, 35.67 mmol, 1.5 eq.). The mixture was stirred at 50°C for 12 hrs and then poured into 4N HCl solution (100 mL) and extracted with EtOAc (50 mL*2). Then the aqueous phase was basified by sat.aq.Na₂CO₃ until pH>12 and extracted with a solution (DCM/MeOH = 5:1) (100 mL*3). The combined organic phase was dried over Na₂SO₄, filtered and concentrated to give crude **6-thiazol-2-yltetrahydropyran-3-amine** (3 g, crude) as yellow oil. ESI [M+H] =185.2

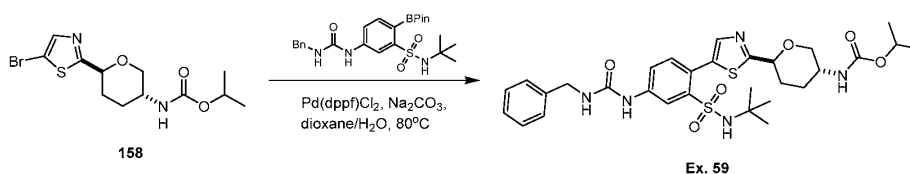
Preparation of compound 157

General method D, *trans-isopropyl N-(6-thiazol-2-yltetrahydropyran-3-yl)carbamate*. ^1H NMR (400MHz, METHANOL- d_4) δ = 7.74 (d, J =3.3 Hz, 1H), 7.55 (d, J =3.3 Hz, 1H), 4.86 - 4.77 (m, 2H), 4.64 (dd, J =2.4, 10.8 Hz, 1H), 4.12 (ddd, J =2.0, 4.6, 10.8 Hz, 1H), 3.75 - 3.55 (m, 1H), 2.32 - 2.20 (m, 1H), 2.16 - 2.03 (m, 1H), 1.81 - 1.54 (m, 2H), 1.22 (br d, J =6.2 Hz, 6H). ESI $[\text{M}+\text{H}] = 271.2$

Note: Cpd.157 was purified by prep-TLC and then prep-HPLC to separate out other isomers.

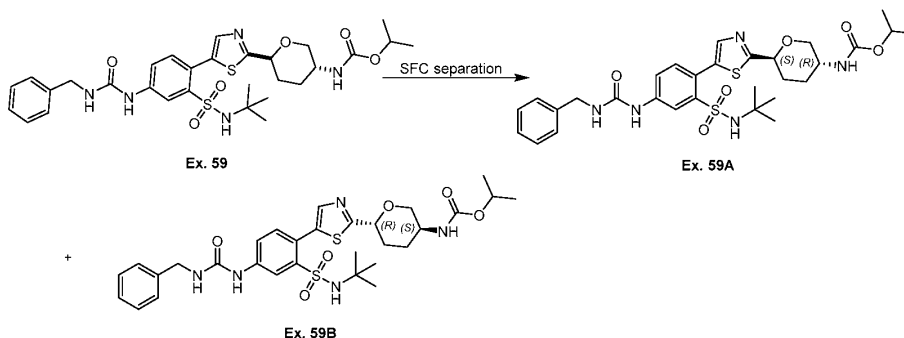
Preparation of compound 158

General method J, *trans-isopropyl N-[6-(5-bromothiazol-2-yl)tetrahydropyran-3-yl]carbamate*. ESI $[\text{M}+\text{H}]=351.1/349.1$

Preparation of compound Ex. 59

General method B, *trans-isopropyl N-[6-[5-[4-(benzylcarbamoylamino)-2-(tert-butylsulfamoyl)phenyl]thiazol-2-yl]tetrahydropyran-3-yl]carbamate*. ^1H NMR (400MHz, METHANOL- d_4) δ = 8.24 (d, J =2.2 Hz, 1H), 7.74 (s, 1H), 7.68 (dd, J =2.2, 8.4 Hz, 1H), 7.37 - 7.29 (m, 5H), 7.27 - 7.19 (m, 1H), 4.84 - 4.78 (m, 2H), 4.64 (dd, J =2.0, 11.0 Hz, 1H), 4.40 (s, 2H), 4.12 (br dd, J =3.2, 10.7 Hz, 1H), 3.69 - 3.58 (m, 1H), 2.33 - 2.26 (m, 1H), 2.13 (br d, J =10.4 Hz, 1H), 1.82 - 1.71 (m, 1H), 1.69 - 1.57 (m, 1H), 1.26 - 1.19 (m, 6H), 1.10 (s, 9H). ESI $[\text{M}+\text{H}] = 630.3$

Preparation of compound Ex. 59A and Ex. 59B

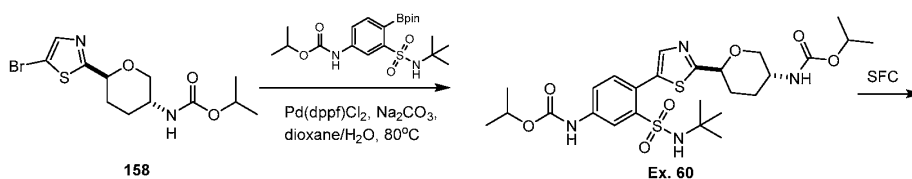


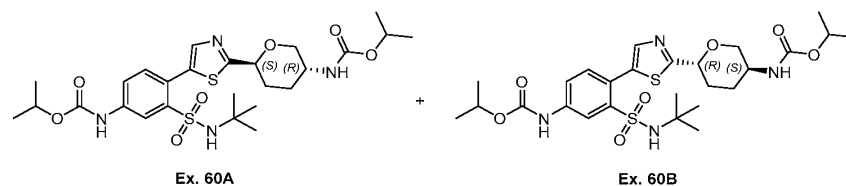
Ex. 59 was further separated by SFC (condition: Instrument: Thar SFC80 preparative SFC; Column: Chiralpak IC-H 250*30mm i.d. 5u; Mobile phase: A for CO₂ and B for MeOH(0.1%NH₃.H₂O); Gradient: B%=42%; Flow rate70g/min; Wavelength:220 nm; Column temperature: 40°C; System back pressure: 100 bar to give **Ex. 59A**. ¹H NMR (400MHz, METHANOL-d₄) δ = 8.27 (d, J=2.2 Hz, 1H), 7.77 (s, 1H), 7.72 (dd, J=2.3, 8.3 Hz, 1H), 7.40 - 7.33 (m, 5H), 7.30 - 7.23 (m, 1H), 4.89 - 4.79 (m, 2H), 4.67 (dd, J=2.3, 11.0 Hz, 1H), 4.43 (s, 2H), 4.16 (br dd, J=3.0, 10.9 Hz, 1H), 3.67 (br t, J=10.9 Hz, 1H), 2.33 (br dd, J=2.6, 13.1 Hz, 1H), 2.16 (br d, J=10.6 Hz, 1H), 1.88 - 1.58 (m, 2H), 1.31 - 1.22 (m, 6H), 1.13 (s, 9H). ESI [M+H]⁺=630.2

Ex. 59B: ¹H NMR (400MHz, METHANOL-d₄) δ = 8.25 (d, J=2.2 Hz, 1H), 7.76 (s, 1H), 7.70 (dd, J=2.2, 8.3 Hz, 1H), 7.37 (s, 1H), 7.36 - 7.31 (m, 4H), 7.28 - 7.18 (m, 1H), 4.87 - 4.74 (m, 1H), 4.65 (br d, J=9.2 Hz, 1H), 4.41 (s, 2H), 4.19 - 4.04 (m, 1H), 3.63 (br d, J=10.5 Hz, 1H), 3.34 (br s, 1H), 2.31 (br d, J=13.2 Hz, 1H), 2.13 (br d, J=10.1 Hz, 1H), 1.84 - 1.72 (m, 1H), 1.71 - 1.58 (m, 1H), 1.22 (d, J=6.1 Hz, 6H), 1.11 (s, 9H). ESI [M+H]⁺=630.3

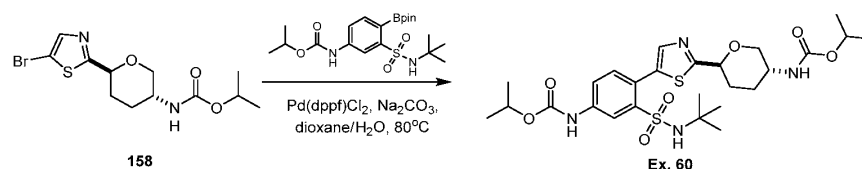
Example 60. Synthesis of *trans*-isopropyl *N*-[6-[5-[2-(*tert*-butylsulfamoyl)-4-(isopropoxycarbonylamino)phenyl]thiazol-2-yl]tetrahydropyran-3-yl]carbamate

Scheme 21:





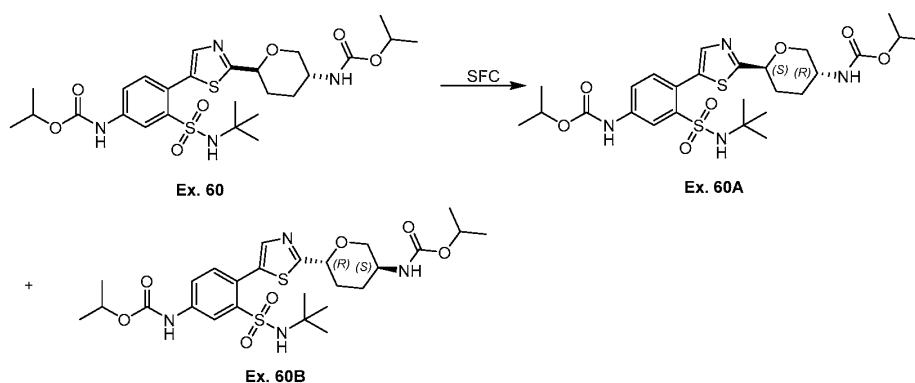
Preparation of Ex. 60



General method B, *trans-isopropyl N-[6-[5-[2-(tert-butylsulfamoyl)-4-*

(isopropoxycarbonylamino)phenyl]thiazol-2-yl]tetrahydropyran-3-yl]carbamate. ¹H NMR (400MHz, METHANOL-d₄) δ = 8.37 (d, J=2.0 Hz, 1H), 7.79 (s, 1H), 7.70 (dd, J=2.4, 8.3 Hz, 1H), 7.40 (d, J=8.3 Hz, 1H), 5.01 (spt, J=6.3 Hz, 1H), 4.87 - 4.79 (m, 1H), 4.68 (dd, J=2.4, 11.2 Hz, 1H), 4.16 (dd, J=2.9, 10.8 Hz, 1H), 3.72 - 3.60 (m, 1H), 3.38 - 3.34 (m, 1H), 2.39 - 2.29 (m, 1H), 2.16 (br d, J=12.2 Hz, 1H), 1.89 - 1.74 (m, 1H), 1.72 - 1.59 (m, 1H), 1.39 - 1.21 (m, 12H), 1.14 (s, 9H). ESI [M+H]⁺ = 583.3

Preparation of compound Ex. 60A and Ex. 60B



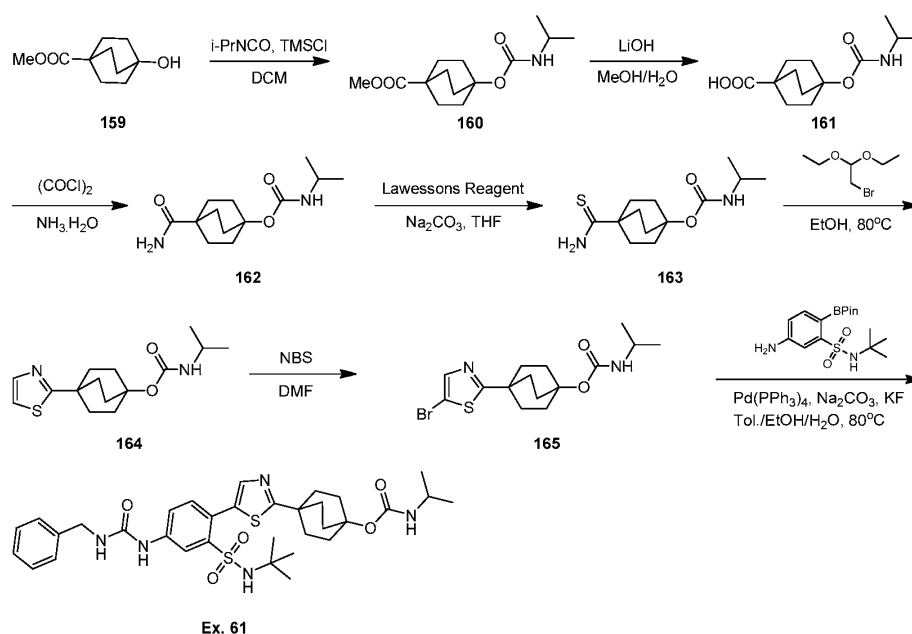
Ex. 60 was further separated by SFC (**condition:** Instrument: Thar SFC80 preparative SFC; Column: Chiralpak IC-H 250*30mm i.d. 5u; Mobile phase: A for CO₂ and B for MeOH(0.1%NH₃.H₂O); Gradient: B%=38%; Flow rate:65g/min; Wavelength:220 nm; Column temperature: 40 °C; System back pressure: 100 bar) to give **Ex. 60A**: ¹H NMR (400MHz, METHANOL-d₄) δ = 8.37 (d, J=2.2 Hz, 1H), 7.78 (s, 1H), 7.70 (dd, J=2.0, 8.4 Hz, 1H), 7.40 (d, J=8.3 Hz, 1H), 5.05 - 4.95 (m, 1H), 4.90 - 4.81 (m, 1H), 4.67 (dd, J=2.4, 11.1 Hz, 1H), 4.70 - 4.64 (m, 1H), 4.16 (br dd, J=2.9, 10.9 Hz, 1H), 3.73 - 3.62 (m, 1H), 2.33

(br dd, J=2.8, 13.2 Hz, 1H), 2.16 (br d, J=11.9 Hz, 1H), 1.86 - 1.74 (m, 1H), 1.70 - 1.61 (m, 1H), 1.34 (d, J=6.2 Hz, 6H), 1.25 (br d, J=6.1 Hz, 6H), 1.14 (s, 9H). ESI [M+H]⁺=583.3

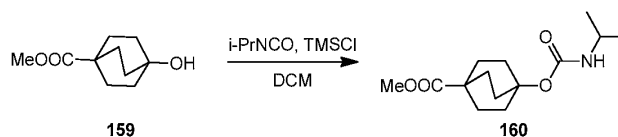
Ex. 60B: ¹H NMR (400MHz, METHANOL-d₄) δ = 8.34 (d, J=2.2 Hz, 1H), 7.80 - 7.72 (m, 1H), 7.67 (dd, J=2.0, 8.6 Hz, 1H), 7.36 (d, J=8.3 Hz, 1H), 4.98 (spt, J=6.2 Hz, 1H), 4.85 - 4.75 (m, 1H), 4.65 (dd, J=2.4, 11.2 Hz, 1H), 4.13 (br dd, J=3.1, 11.0 Hz, 1H), 3.72 - 3.56 (m, 1H), 3.33 (s, 1H), 2.30 (br dd, J=2.6, 13.2 Hz, 1H), 2.13 (br d, J=11.4 Hz, 1H), 1.85 - 1.71 (m, 1H), 1.69 - 1.57 (m, 1H), 1.31 (d, J=6.1 Hz, 6H), 1.27 - 1.17 (m, 6H), 1.11 (s, 9H). ESI [M+H]⁺=583.2

Example 61. Synthesis of [1-[5-[4-(benzylcarbamoylamino)-2-(tert-butylsulfamoyl)phenyl]thiazol-2-yl]-4-bicyclo[2.2.2]octanyl] N-isopropylcarbamate.

Scheme 22:



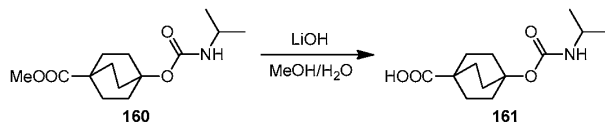
Preparation of compound 160.



To a solution of *methyl 4-hydroxybicyclo[2.2.2]octane-1-carboxylate* (0.4 g, 2.17 mmol, 1 eq.) in DCM (10 mL) were added TMSCl (23.59 mg, 217.12 μmol, 0.1 eq.) and 2-isocyanatopropane (554.33 mg, 6.51 mmol, 3 eq.). The mixture was stirred at 25°C for 12 hrs and then washed with 1 N HCl (20 mL) and sat. aq. Na₂CO₃ (20 mL). The organic layer was

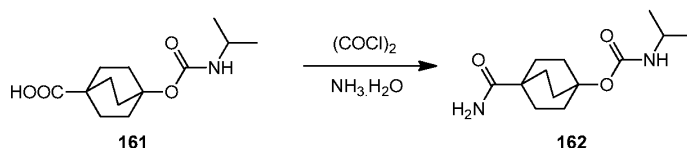
dried over Na₂SO₄, filtered and concentrated to give **methyl 4-(isopropylcarbamoyloxy)bicyclo[2.2.2]octane-1-carboxylate** (0.45 g, crude) as a yellow gum. ¹H NMR (400MHz, CHLOROFORM-d) δ = 4.34 (br s, 1H), 3.72 - 3.61 (m, 1H), 3.56 (s, 3H), 1.94 (br d, J=7.7 Hz, 6H), 1.90 - 1.81 (m, 6H), 1.08 - 1.00 (m, 6H). ESI [M+H] = 269.9

Preparation of compound 161.



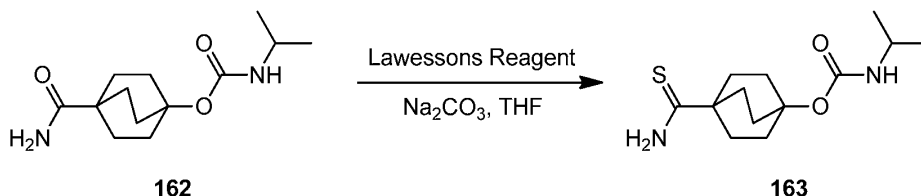
General method O, **4-(isopropylcarbamoyloxy)bicyclo[2.2.2]octane-1-carboxylic acid**. ¹H NMR (400MHz, CHLOROFORM-d) δ = 4.32 (br s, 1H), 3.71 - 3.60 (m, 1H), 1.93 (br s, 6H), 1.88 (br d, J=9.3 Hz, 6H), 1.05 (d, J=6.5 Hz, 6H). ESI [M+H] = 256.0

Preparation of compound 162.



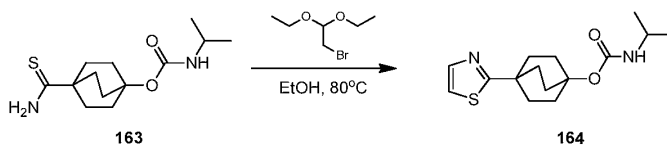
General method N, **(1-carbamoyl-4-bicyclo[2.2.2]octanyl) N-isopropylcarbamate**. ¹H NMR (400MHz, CHLOROFORM-d) δ = 5.56 - 5.31 (m, 2H), 4.34 (br s, 1H), 3.72 - 3.57 (m, 1H), 1.96 (br s, 6H), 1.97 - 1.93 (m, 1H), 1.92 - 1.80 (m, 6H), 1.05 (d, J=6.6 Hz, 6H). ESI [M+H] = 255.3

Preparation of compound 163.



General method L, **(1-carbamothioyl-4-bicyclo[2.2.2]octanyl) N-isopropylcarbamate**. ESI [M+H] = 271.3

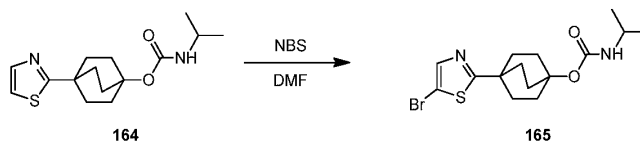
Preparation of compound 164.



General method M, *(1-thiazol-2-yl-4-bicyclo[2.2.2]octanyl) N-isopropylcarbamate*. ESI

[M+H] = 295.0

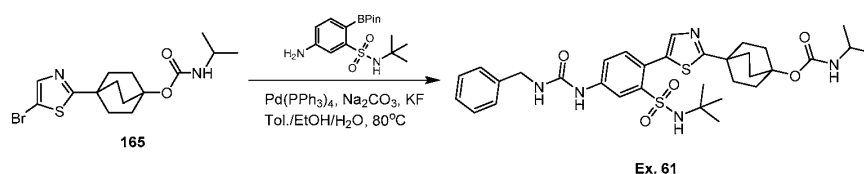
Preparation of compound 165



General method J, *[1-(5-bromothiazol-2-yl)-4-bicyclo[2.2.2]octanyl] N-isopropylcarbamate*.

ESI [M+H] = 372.8/374.8

Preparation of Ex. 61.

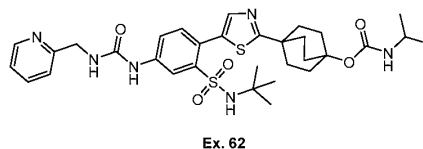


General method K, *[1-[5-[4-(benzylcarbamoylamino)-2-(tert-butylsulfamoyl)phenyl]thiazol-2-yl]-4-bicyclo[2.2.2]octanyl] N-isopropylcarbamate*. ¹H NMR (400MHz,

METHANOL-d₄) δ = 8.26 (d, J=2.2 Hz, 1H), 7.74 - 7.68 (m, 2H), 7.38 - 7.32 (m, 4H), 7.30 - 7.23 (m, 1H), 4.43 (s, 2H), 3.71 - 3.61 (m, 1H), 2.18 (s, 12H), 1.16 - 1.09 (m, 15H). ESI [M+H] = 654.3

Example 62. Synthesis of 4-(5-(2-(N-(tert-butyl)sulfamoyl)-4-(3-(pyridin-2-ylmethyl)ureido)phenyl)thiazol-2-yl)bicyclo[2.2.2]octan-1-yl isopropylcarbamate.

The following compound was synthesized via same method by the key intermediate 165.

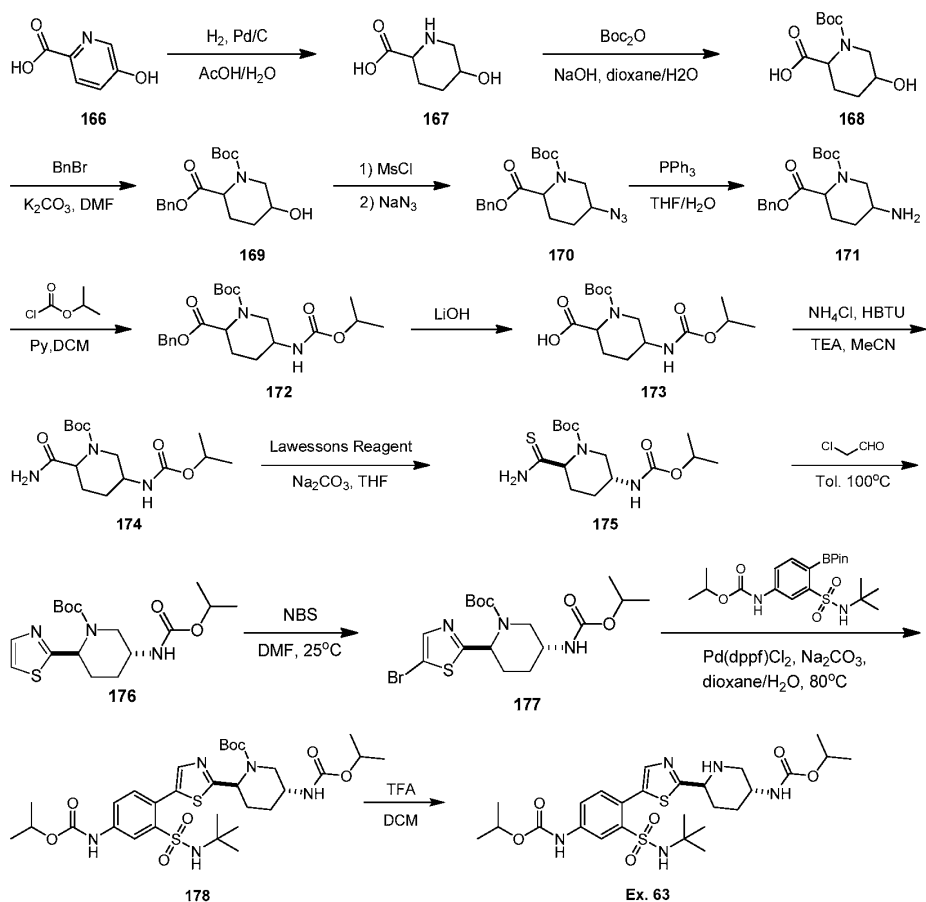


Ex. 62

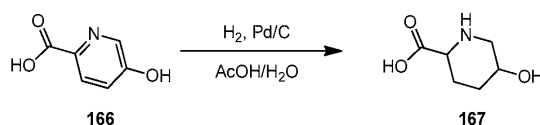
¹H NMR (400MHz, METHANOL-d₄) δ = 8.77 (br s, 1H), 8.62 - 8.52 (m, 1H), 8.34 (br s, 1H), 8.12 - 8.03 (m, 1H), 7.96 (br d, J=5.5 Hz, 1H), 7.79 - 7.66 (m, 2H), 7.43 - 7.35 (m, 1H), 4.78 (br s, 2H), 3.67 (br dd, J=6.2, 13.0 Hz, 1H), 2.19 (br s, 12H), 1.17 - 1.09 (m, 15H). ESI [M/2+H] = 328.2

Example 63. Synthesis of *trans*-isopropyl N-[6-[5-[2-(tert-butylsulfamoyl)-4-(isopropoxycarbonylamino)phenyl]thiazol-2-yl]-3-piperidyl]carbamate

Scheme 23:

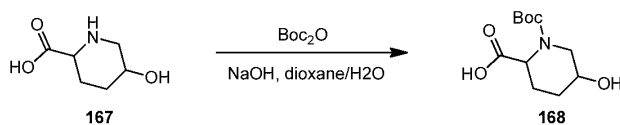


General method I for preparation of compound 167.



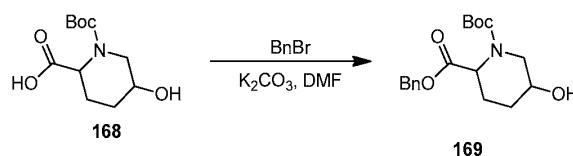
To a solution of **5-hydroxypyridine-2-carboxylic acid** (60 g, 431 mmol, 1 eq.) in AcOH (200 mL)/H₂O (600 mL) was added wet Pd/C (2 g, 10% content) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (50 psi) at 50°C for 12 hrs, then filtered and concentrated to give **5-hydroxypiperidine-2-carboxylic acid** (62.61 g, crude) as a yellow oil. ESI [M+H] = 146.5

Preparation of compound 168



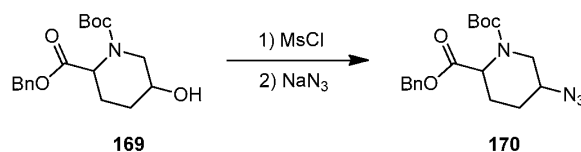
To a mixture of **5-hydroxypiperidine-2-carboxylic acid** (62 g, 427.13 mmol, 1 *eq.*) and Boc_2O (102.54 g, 469.84 mmol, 107.94 mL, 1.1 *eq.*) in dioxane (500 mL) was added NaOH (34.17 g, 854.25 mmol, 2 *eq.*) and the mixture was stirred at 25 °C for 18 hrs. The mixture was then concentrated to remove dioxane and the pH was adjusted to 2-3 by addition of 1N HCl solution. The aqueous phase was extracted with 2-Me-THF (500 mL * 3). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated to give **1-tert-butoxycarbonyl-5-hydroxy-piperidine-2-carboxylic acid** (40 g, crude) as yellow oil. ESI $[\text{M}+\text{Na}] = 267.9$

Preparation of compound 169



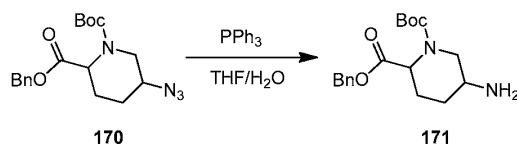
General method A, ***O*₂-benzyl *O*₁-tert-butyl 5-hydroxypiperidine-1,2-dicarboxylate**. ESI $[\text{M}+\text{Na}] = 358.0$

Preparation of compound 170

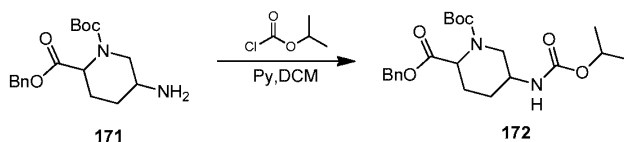


A mixture of ***O*₂-benzyl *O*₁-tert-butyl 5-hydroxypiperidine-1,2-dicarboxylate** (10 g, 29.82 mmol, 1 *eq.*), TEA (3.62 g, 35.78 mmol, 4.98 mL, 1.2 *eq.*) in DCM (100 mL) was added methanesulfonyl chloride (4.10 g, 35.78 mmol, 2.77 mL, 1.2 *eq.*) at 0 °C and the mixture was stirred at 25°C 1 hr. The mixture was then washed with H_2O (50 mL) and the organic layer was dried and concentrated. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=40/1 to 5:1) to afford ***O*₂-benzyl *O*₁-tert-butyl 5-methylsulfonyloxypiperidine-1,2-dicarboxylate** (9.5 g, 18.98 mmol, 63.65% yield, 82.6% purity) as yellow oil.

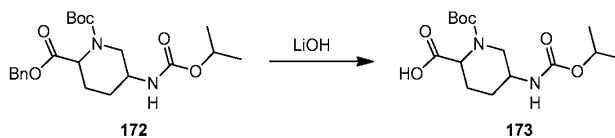
A mixture of ***O*₂-benzyl *O*₁-tert-butyl 5-methylsulfonyloxypiperidine-1,2-dicarboxylate** (9.5 g, 22.98 mmol, 1 *eq.*), NaN_3 (8.96 g, 137.85 mmol, 6 *eq.*) in DMF (20 mL) was stirred at 100°C for 4 hrs. Then the mixture was quenched with sat. aq. Na_2SO_3 (30 mL) and extracted with EtOAc (100 mL * 3). The combined organic layers were washed with brine (40 mL * 3), dried over Na_2SO_4 , filtered and concentrated to give ***O*₂-benzyl *O*₁-tert-butyl 5-azidopiperidine-1,2-dicarboxylate** (8.82 g, crude) as yellow oil.

Preparation of compound 171

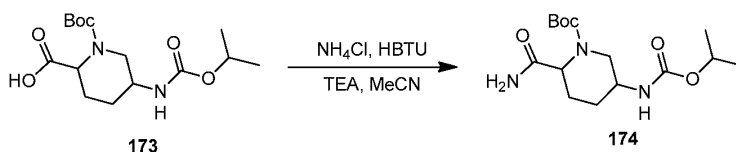
A mixture of *O2-benzyl O1-tert-butyl 5-azidopiperidine-1,2-dicarboxylate* (8 g, 22.20 mmol, 1 *eq.*), triphenylphosphane (8.73 g, 33.30 mmol, 1.5 *eq.*), in H₂O (50 mL) and THF (50 mL) was stirred at 45°C for 4 hrs. The mixture was concentrated to remove the THF and pH was adjusted to 2-3 by addition of 1N HCl solution. The aqueous phase was extracted with MTBE (30 mL) and then aqueous phase was basified to adjust pH to 9 and extracted with EtOAc (50 mL * 3). The combined organic layers were dried over Na₂SO₄ filtered and concentrated to give *O2-benzyl O1-tert-butyl 5-aminopiperidine-1,2-dicarboxylate* (6 g, crude) as yellow oil. ESI [M+H]=335.2

Preparation of compound 172

General method D, *O2-benzyl O1-tert-butyl 5-(isopropoxycarbonylamino)piperidine-1,2-dicarboxylate*. ESI [M+H] =421.2

Preparation of compound 173

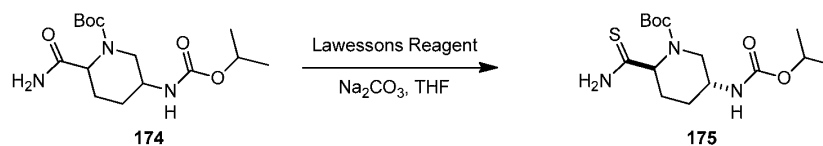
General method O, *1-tert-butoxycarbonyl-5-(isopropoxycarbonyloxy)piperidine-2-carboxylic acid*. ESI [M+H] =331.2

Preparation of compound 174

A mixture of *1-tert-butoxycarbonyl-5-(isopropoxycarbonylamino)piperidine-2-carboxylic acid* (1.3 g, 3.93 mmol, 1 *eq.*), NH₄Cl (315.73 mg, 5.90 mmol, 1.5 *eq.*), TEA (1.19 g, 11.80 mmol, 1.64 mL, 3 *eq.*) and HBTU (1.64 g, 4.33 mmol, 1.1 *eq.*) in ACN (10 mL) as stirred at 25°C for 2 hrs and then concentrated. The mixture was then poured into H₂O (20 mL) and

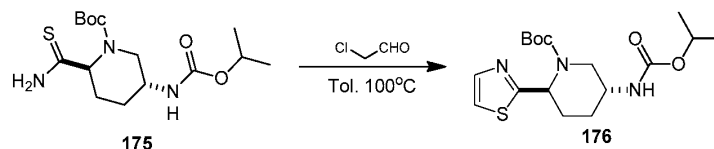
extracted with EtOAc (20ml*3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The mixture was purified by prep-HPLC(column: Phenomenex Gemini C18 250*50 10u;mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN];B%: 10%-40%,20min) to give **tert-butyl 2-carbamoyl-5-(isopropoxycarbonylamino)piperidine-1-carboxylate** (1 g, 3.01 mmol, 76.38% yield, 99% purity) as a white solid. ESI [M+H] =330.2

Preparation of compound 175



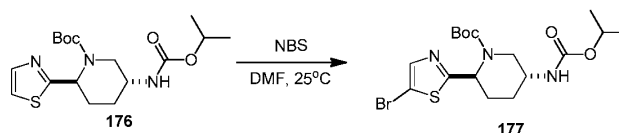
General method L, **trans-tert-butyl 2-carbamothioyl-5-(isopropoxycarbonylamino)piperidine-1-carboxylate**. ESI [M+H] =346.1

Preparation of compound 176



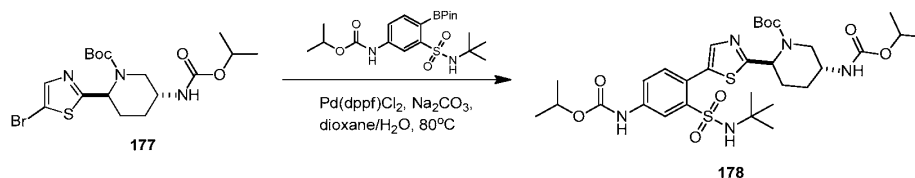
To a solution of **trans-tert-butyl 2-carbamothioyl-5-(isopropoxycarbonylamino)piperidine-1-carboxylate** (650 mg, 1.88 mmol, 1.0 eq.) in tol. (20 mL) were added BUFFER (784.76 mg, 2.82 mmol, 1.5 eq.) and 2-chloroacetaldehyde (3.69 g, 18.82 mmol, 3.03 mL, 10 eq.). The mixture was stirred at 100°C for 1.5 hrs and then poured into water (20 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was dried over Na₂SO₄, filtered and concentrated. The residue was purified by basic prep-HPLC to give **trans-tert-butyl 5-(isopropoxycarbonylamino)-2-thiazol-2-ylpiperidine-1-carboxylate** (80 mg, 216.52 umol, 11.51% yield) as a yellow solid. ¹H NMR (400MHz, METHANOL-d₄) δ = 7.75 (d, J=3.4 Hz, 1H), 7.58 (d, J=2.9 Hz, 1H), 5.60 (br s, 1H), 4.95 - 4.90 (m, 1H), 4.23 (br d, J=14.7 Hz, 1H), 3.68 (br s, 1H), 3.11 - 2.94 (m, 1H), 2.42 - 2.31 (m, 1H), 2.30 - 2.17 (m, 1H), 1.93 - 1.79 (m, 1H), 1.75 - 1.64 (m, 1H), 1.50 (s, 9H), 1.30 - 1.23 (m, 6H)

Preparation of compound 177



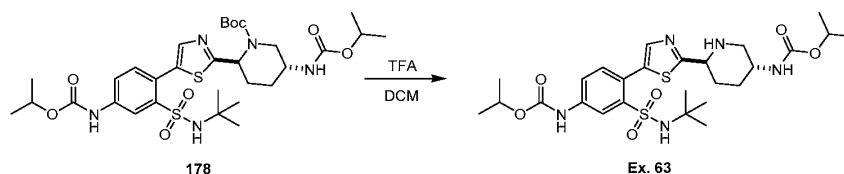
General method J, *trans-tert-butyl 2-(5-bromothiazol-2-yl)-5-(isopropoxycarbonylamino)piperidine-1-carboxylate*. ESI [M+H]⁺ = 450.2/448.2

Preparation of compound 178



General method B, *trans-tert-butyl 2-[5-[2-(tert-butylsulfamoyl)-4-(isopropoxycarbonylamino)phenyl]thiazol-2-yl]-5-(isopropoxycarbonylamino)piperidine-1-carboxylate*. ESI [M+H]⁺ = 682.3

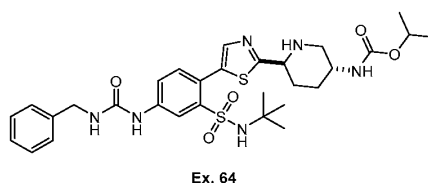
Preparation of Ex. 63



General method C, *trans-isopropyl N-[6-[5-[2-(tert-butylsulfamoyl)-4-(isopropoxycarbonylamino)phenyl]thiazol-2-yl]-3-piperidyl]carbamate*. ¹H NMR (400MHz, METHANOL-d₄) δ = 8.40 (d, J=2.0 Hz, 1H), 7.86 (s, 1H), 7.65 (dd, J=2.2, 8.4 Hz, 1H), 7.38 (d, J=8.4 Hz, 1H), 5.05 - 4.94 (m, 1H), 4.85 - 4.81 (m, 1H), 4.67 (dd, J=2.9, 11.9 Hz, 1H), 3.92 - 3.82 (m, 1H), 3.60 (br dd, J=3.6, 11.8 Hz, 1H), 2.92 (t, J=11.9 Hz, 1H), 2.48 (br dd, J=3.2, 14.2 Hz, 1H), 2.22 - 2.03 (m, 2H), 1.82 - 1.70 (m, 1H), 1.32 (d, J=6.4 Hz, 6H), 1.24 (br d, J=6.2 Hz, 6H), 1.19 (s, 9H). ESI [M+H]⁺ = 582.2

Example 64. Synthesis of isopropyl ((3R,6S)-6-(5-(4-(3-benzylureido)-2-(N-(tert-butyl)sulfamoyl)phenyl)thiazol-2-yl)piperidin-3-yl)carbamate.

The following compound was synthesized via same method by the key intermediate 178.

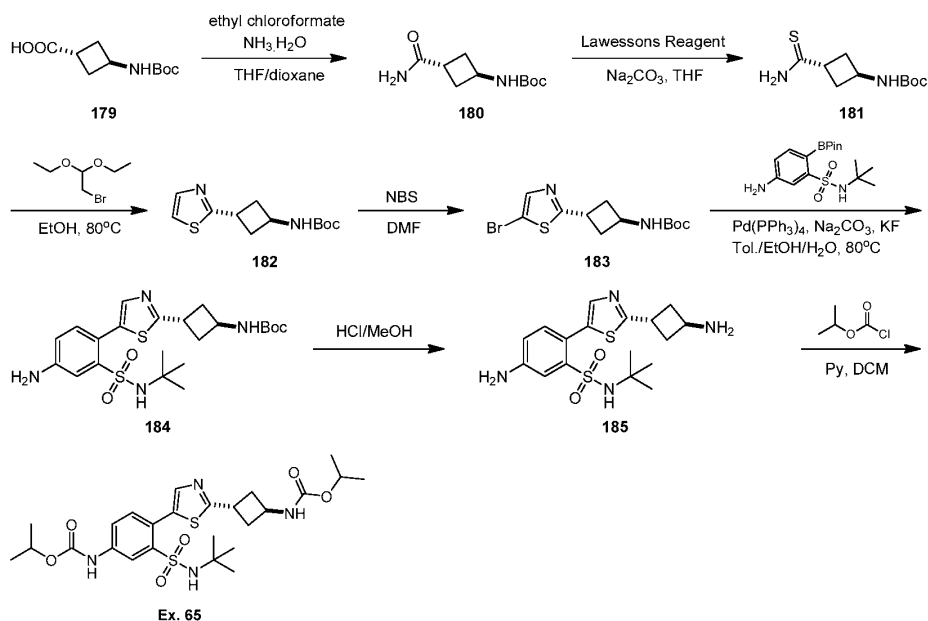


¹H NMR (400MHz, METHANOL-d₄) δ = 8.30 (d, J=2.2 Hz, 1H), 7.86 (s, 1H), 7.66 (dd, J=2.2, 8.4 Hz, 1H), 7.38 - 7.20 (m, 6H), 4.85 - 4.82 (m, 1H), 4.70 (dd, J=3.2, 12.0 Hz, 1H), 4.42 (s, 2H), 3.93 - 3.82 (m, 1H), 3.62 (br dd, J=3.5, 11.7 Hz, 1H), 3.00 - 2.90 (m, 1H), 2.52 -

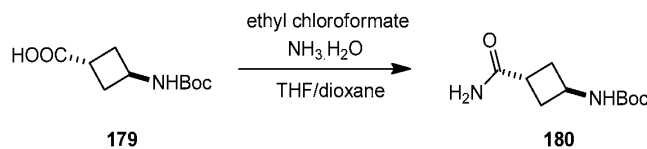
2.44 (m, 1H), 2.23 - 2.04 (m, 2H), 1.84 - 1.70 (m, 1H), 1.26 - 1.21 (m, 6H), 1.18 (s, 9H). ESI [M+H]⁺ = 629.2

Example 65. Synthesis of isopropyl N-[3-(tert-butylsulfamoyl)-4-[2-[3-(isopropoxycarbonyl amino)cyclobutyl]thiazol-5-yl]phenyl]carbamate

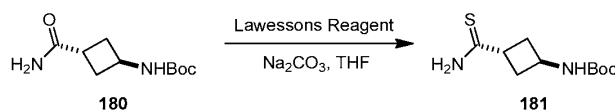
Scheme 24:



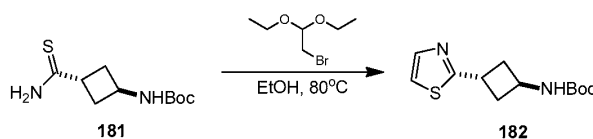
Preparation of compound 180



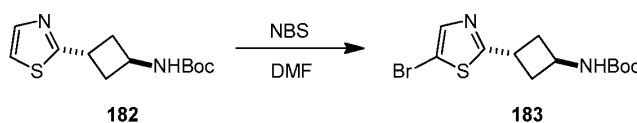
To a solution of *trans*-3-(tert-butoxycarbonylamino)cyclobutanecarboxylic acid (500 mg, 2.32 mmol, 1 *eq.*), DIEA (750.54 mg, 5.81 mmol, 1.01 mL, 2.5 *eq.*) in THF (10 mL) was added ETHYL CHLOROFORMATE (277.29 mg, 2.56 mmol, 1.1 *eq.*) and the mixture was stirred 0°C for 1 hr. Then it was added into NH₃·H₂O (1.30 g, 9.29 mmol, 1.43 mL, 25% purity, 4 *eq.*) in THF (10 mL) and dioxane (10 mL) and the mixture was stirred at 25°C for 1 hr. The mixture was washed with 1N HCl (20 mL), sat.aq.Na₂CO₃ (20 mL) and the organic phase was dried over Na₂SO₄, filtered and concentrated to give *trans*-tert-butyl N-(3-carbamoylcyclobutyl) carbamate (0.39 g, crude) as a white solid. ¹H NMR (400MHz, DMSO-d₆) δ = 7.20 - 7.07 (m, 2H), 6.71 (br s, 1H), 4.09 - 4.00 (m, 1H), 2.72 (br t, J=9.3 Hz, 1H), 2.23 (br t, J=8.7 Hz, 2H), 2.01 (q, J=9.8 Hz, 2H), 1.34 (s, 9H). ESI [M+Na]⁺ = 237.1

Preparation of compound 181

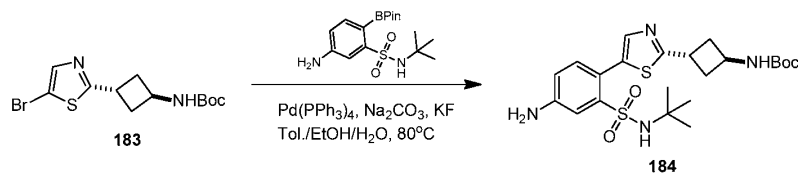
General method L, *trans-tert-butyl N-(3-carbamothioylcyclobutyl)carbamate*. ^1H NMR (400MHz, DMSO- d_6) δ = 9.33 (br s, 1H), 9.02 (br s, 1H), 7.18 (br d, J =5.5 Hz, 1H), 4.16 - 4.03 (m, 1H), 3.33 (br s, 1H), 2.45 (br d, J =12.2 Hz, 2H), 2.15 (br d, J =6.5 Hz, 2H), 1.37 (br s, 9H)

Preparation of compound 182

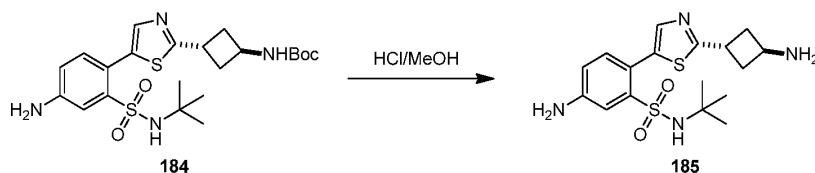
General method M, *trans-tert-butyl N-(3-thiazol-2-ylcyclobutyl)carbamate*. ^1H NMR (400MHz, CHLOROFORM- d) δ = 7.62 (d, J =3.2 Hz, 1H), 7.14 (dd, J =3.3, 8.3 Hz, 1H), 4.79 (br s, 1H), 4.34 (br s, 1H), 3.47 - 3.36 (m, 1H), 2.81 (br d, J =8.8 Hz, 1H), 2.66 (ddd, J =4.5, 7.9, 12.8 Hz, 1H), 2.46 - 2.34 (m, 1H), 2.17 - 2.09 (m, 1H), 1.38 (s, 9H). ESI[M+H]=255.3

Preparation of compound 183

General method J, *trans-tert-butyl N-[3-(5-bromothiazol-2-yl)cyclobutyl]carbamate*. ESI[M+H]=335.1/333.1

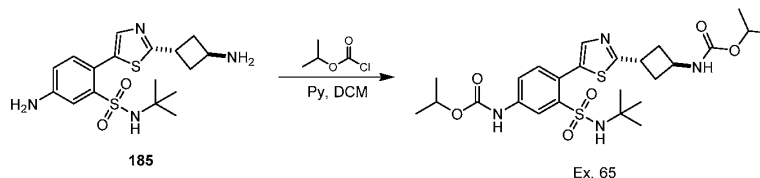
Preparation of compound 184

General method K, *trans-tert-butyl N-[3-[5-[4-amino-2-(tert-butylsulfamoyl)phenyl]thiazol-2-yl]cyclobutyl]carbamate*. ESI [M+H]=481.0

Preparation of compound 185

General method F, *trans*-5-amino-2-[2-(3-aminocyclobutyl)thiazol-5-yl]-N-tert-butylbenzenesulfonamide. ESI [M+H] = 381.2

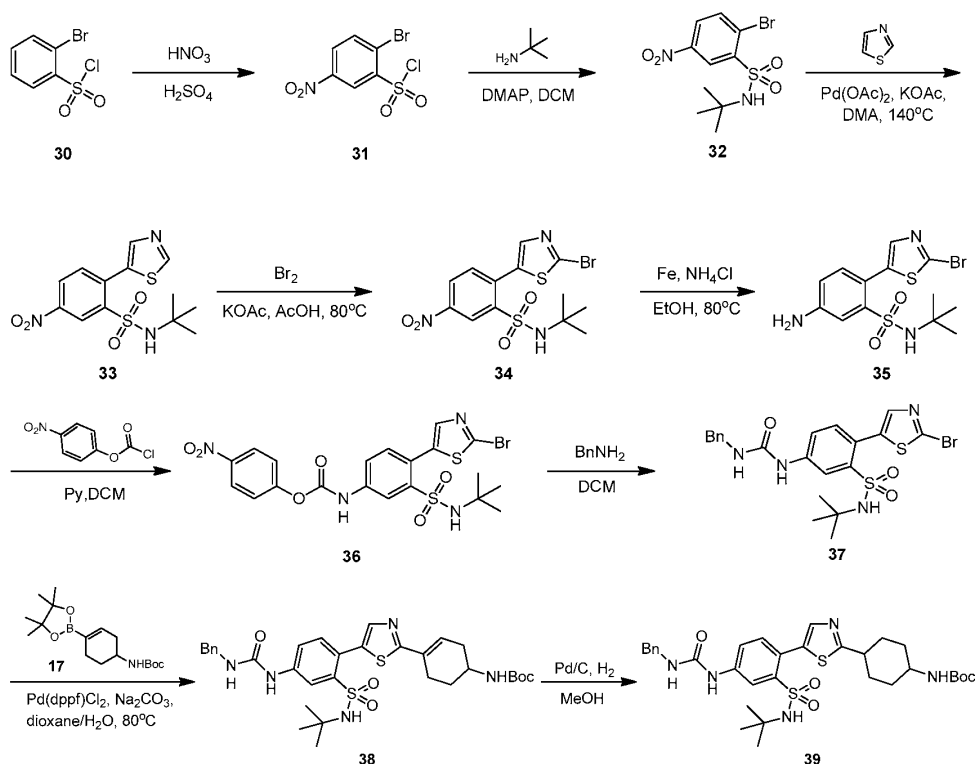
Preparation of Ex. 65

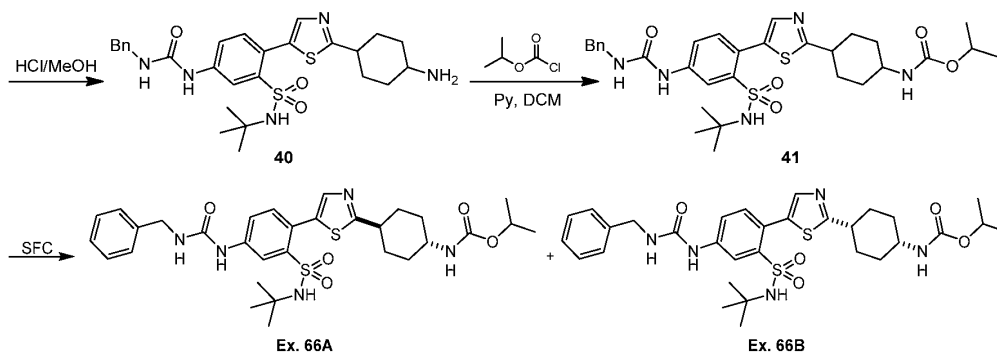


General method D, *isopropyl N-[3-(tert-butylsulfamoyl)-4-[2-[3-(isopropoxycarbonylamino)cyclobutyl]thiazol-5-yl]phenyl]carbamate*. ¹H NMR (400MHz, METHANOL-d₄) δ = 8.34 (d, J=1.5 Hz, 1H), 7.76 - 7.65 (m, 2H), 7.38 (t, J=8.5 Hz, 1H), 5.04 - 4.94 (m, 1H), 4.82 (br d, J=6.4 Hz, 1H), 4.42 - 4.32 (m, 0.5H), 4.13 (br t, J=8.0 Hz, 0.5H), 3.87 - 3.78 (m, 0.5H), 3.58 - 3.48 (m, 0.5H), 2.82 (dq, J=2.6, 7.9 Hz, 1H), 2.72 - 2.64 (m, 1H), 2.60 - 2.50 (m, 1H), 2.34 - 2.23 (m, 1H), 1.31 (d, J=6.2 Hz, 6H), 1.22 (br d, J=6.0 Hz, 6H), 1.13 (s, 9H). ESI [M+H] = 553.4

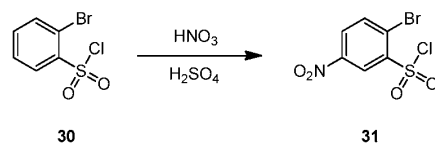
Examples 66A and 66B

Scheme 25:



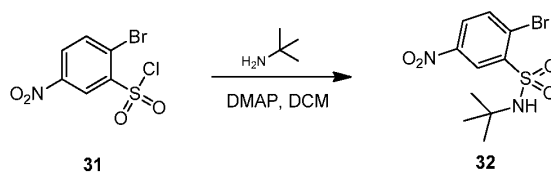


Preparation of compound 31.



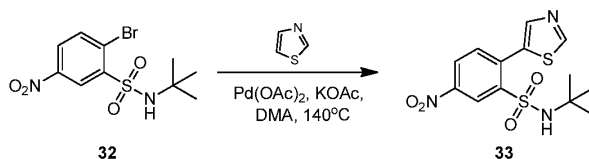
To a solution of **2-bromobenzenesulfonyl chloride** (100.00 g, 391.36 mmol, 1.00 *eq.*) in H_2SO_4 (1.0 L) was added a solution of HNO_3 (79.95 g, 1.21 mol, 57.11 mL, 95% purity, 3.08 *eq.*) in H_2SO_4 (0.50 L) drop-wise at 0°C . The mixture was stirred at 26°C for 2 hrs. TLC (Petroleum ether: EtOAc = 10:1, R_f = 0.40) showed the reaction was complete. The mixture was added slowly to ice water (5 L) with vigorous stirring and then filtered. The filter cake was washed with H_2O (1 L X 3) and dried to give **2-bromo-5-nitro-benzenesulfonyl chloride** (105.00 g, crude) as a yellow solid. ^1H NMR (400MHz, CHLOROFORM-d) δ = 8.98 (d, J = 2.4 Hz, 1H), 8.37 (dd, J = 2.5, 8.7 Hz, 1H), 8.09 (d, J = 8.6 Hz, 1H).

Preparation of compound 32.



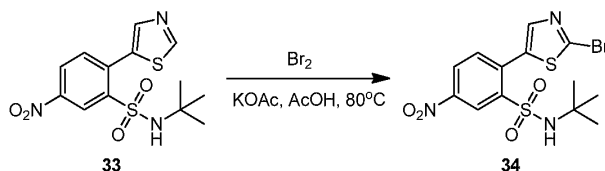
To a mixture of **2-methylpropan-2-amine** (200 g, 2.73 mol, 287.36 mL, 3.29 *eq.*) and DMAP (10 g, 81.85 mmol, 0.1 *eq.*) in DCM (2 L) was added **2-bromo-5-nitro-benzenesulfonyl chloride** (250 g, 831.91 mmol, 1 *eq.*) portionwise at 0°C . The mixture was warmed to 15°C and stirred for 1 hr. LCMS showed the reaction was complete. The mixture was washed with HCl (1 N, 2 L), sat. aq. NaHCO_3 (500 mL) and brine (500 mL), dried over Na_2SO_4 , filtered and concentrated to give **2-bromo-N-tert-butyl-5-nitro-benzenesulfonamide** (240 g, crude) as a gray solid. ESI $[M+H]^+$ = 336.9/338.9.

Preparation of compound 33.



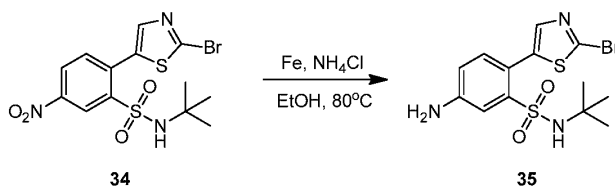
To a solution of **2-bromo-N-tert-butyl-5-nitrobenzenesulfonamide** (35 g, 103.80 mmol, 1 *eq.*) in DMA (300 mL), were added thiazole (26.51 g, 311.40 mmol, 3 *eq.*), Pd(OAc)₂ (2.33 g, 10.38 mmol, 0.1 *eq.*) and KOAc (30.56 g, 311.40 mmol, 3 *eq.*). The mixture was stirred at 140°C for 16 hrs under N₂. LCMS showed the reaction was complete, the mixture was poured into water (3 L) and filtered. The filter cake was washed with water (200 mL x 3) and then dried to give **N-tert-butyl-5-nitro-2-thiazol-5-ylbenzenesulfonamide** (25.1 g, crude) as a black brown solid. ¹H NMR (400MHz, DMSO-d₆) δ = 9.30 (s, 1H), 8.81 (d, J=2.4 Hz, 1H), 8.46 (dd, J=2.4, 8.3 Hz, 1H), 8.12 (s, 1H), 7.83 (d, J=8.3 Hz, 1H), 7.60 (s, 1H), 1.07 (s, 9H). ESI [M+H] = 342.0.

Preparation of compound 34.



To a solution of **N-tert-butyl-5-nitro-2-thiazol-5-ylbenzenesulfonamide** (15 g, 43.94 mmol, 1 *eq.*) in AcOH (200 mL), were added KOAc (21.56 g, 219.68 mmol, 5 *eq.*) and Br₂ (35.11 g, 219.68 mmol, 5 *eq.*). The mixture was stirred at 80°C for 3 hrs. LCMS showed the reaction was complete, the mixture was quenched by sat.aq.Na₂CO₃ (1 L) and extracted with EtOAc (300 mL x 3). The combined organic phase was dried over Na₂SO₄, filtered and concentrated to give **2-(2-bromothiazol-5-yl)-N-tert-butyl-5-nitrobenzenesulfonamide** (18 g, crude) as a green solid which was used without any purification.

Preparation of compound 35.

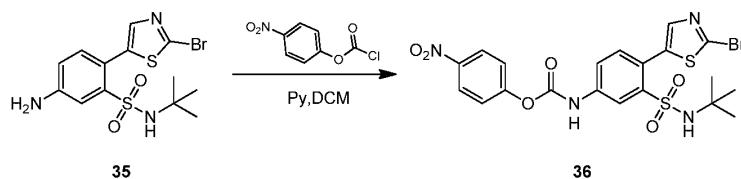


To a solution of **2-(2-bromothiazol-5-yl)-N-tert-butyl-5-nitrobenzenesulfonamide** (8.5 g, 20.22 mmol, 1 *eq.*) in EtOH (70 mL), THF (40 mL) and H₂O (20 mL), were added Fe (3.39 g, 60.67 mmol, 3 *eq.*) and NH₄Cl (3.25 g, 60.67 mmol, 2.12 mL, 3 *eq.*). The mixture was

stirred at 90°C for 1 hr. LCMS showed the reaction was complete. The mixture was filtered, the filtrate was concentrated to remove organic solvent and extracted with DCM (200 mL x 2). The organic phase was dried over Na₂SO₄, filtered and concentrated to afford **5-amino-2-(2-bromothiazol-5-yl)-N-tert-butyl benzenesulfonamide** (6 g, crude) as a yellow solid.

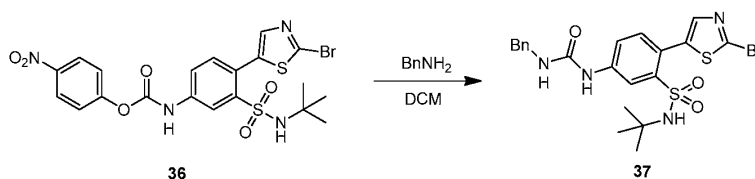
¹H NMR showed the structure was correct. ¹H NMR (400MHz, DMSO-d₆) δ = 7.58 - 7.52 (m, 1H), 7.30 (d, J=2.4 Hz, 1H), 7.11 (d, J=8.3 Hz, 1H), 6.99 (s, 1H), 6.73 (dd, J=2.4, 8.3 Hz, 1H), 5.94 (s, 2H), 1.07 (s, 9H). ESI [M+H] = 390.0/392.0.

Preparation of compound 36.



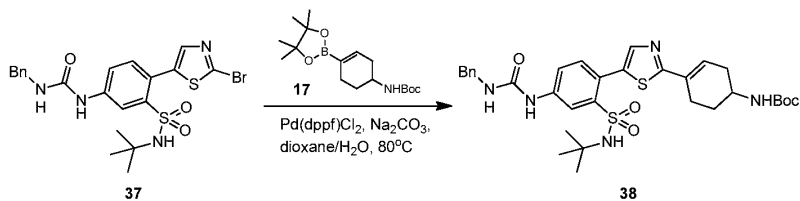
General method D, **(4-nitrophenyl) N-[4-(2-bromothiazol-5-yl)-3-(tert-butylsulfamoyl)phenyl]carbamate** as DCM solution ESI [M+H] = 555.0/557.0

Preparation of compound 37.



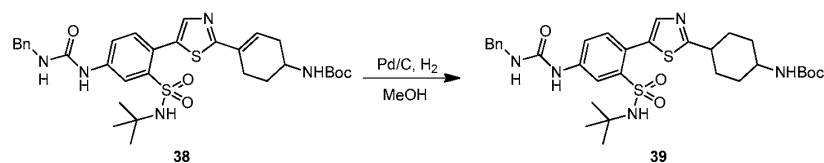
General method H, **1-benzyl-3-[4-(2-bromothiazol-5-yl)-3-(tert-butylsulfamoyl)phenyl]urea**. ESI [M+H] = 523.0/525.0.

Preparation of compound 38.



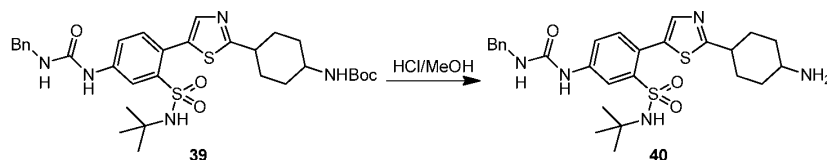
General method B (*Suzuki reaction*), **tert-butyl-N-[4-[5-[4-(benzylcarbamoylamino)-2-(tert-butylsulfamoyl)phenyl]thiazol-2-yl]cyclohex-3-en-1-yl]carbamate (Compound 38)**.

To a solution of **Compound 17** (1 eq.) in dioxane and H₂O, were added Pd(dppf)Cl₂ (0.1 eq.), **Compound 37** (0.9 eq.) and Na₂CO₃ (3 eq.). The mixture was stirred at 80°C for 12 hrs under N₂. LCMS showed the reaction was complete. The mixture was concentrated and the residue was purified by prep-TLC (PE/EtOAc=1:1) to yield product **38**. ESI [M+H] = 640.5

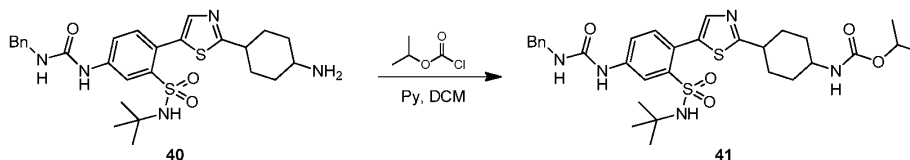
Preparation of compound 39.

tert-butyl N-[4-[5-[4-(benzylcarbamoylamino)-2-(tert-butylsulfamoyl)phenyl]thiazol-2-yl]cyclohexyl]carbamate.

To a solution of **Compound 38** (1 eq.) and AcOH (0.1 eq.) in EtOAc was added Pd/C (10% purity, 1.00 eq.). The mixture was stirred under H₂ (15 psi) at 40°C for 1 hr. LCMS showed the reaction was complete and then the mixture was filtered and concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 10/1 to 1:1) to give **Compound 39**. ESI [M+H] = 642.5

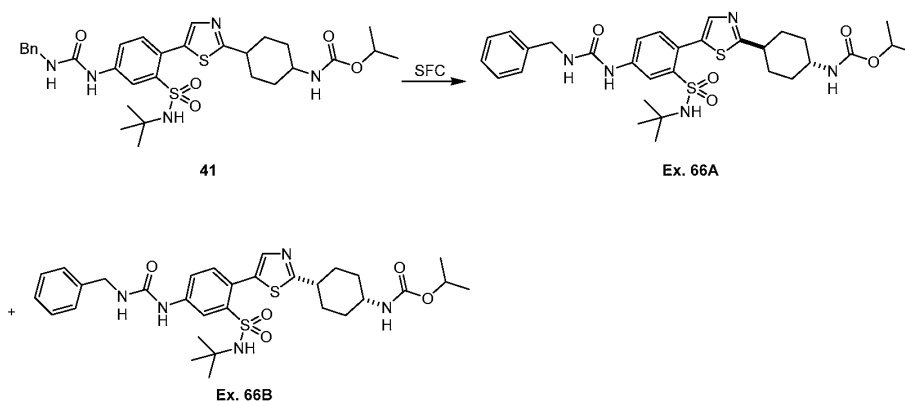
Preparation of compound 40.

General method F, **1-[4-[2-(4-aminocyclohexyl)thiazol-5-yl]-3-(tert-butylsulfamoyl)phenyl]-3-benzyl-urea**. ESI [M+H] = 542.5.

Preparation of compound 41

General method D, **isopropyl N-[4-[5-[4-(benzylcarbamoylamino)-2-(tert-butylsulfamoyl)phenyl]thiazol-2-yl]cyclohexyl]carbamate**, ESI [M+H] = 628.3.

Preparation of Compound Ex. 66A and Ex. 66B.



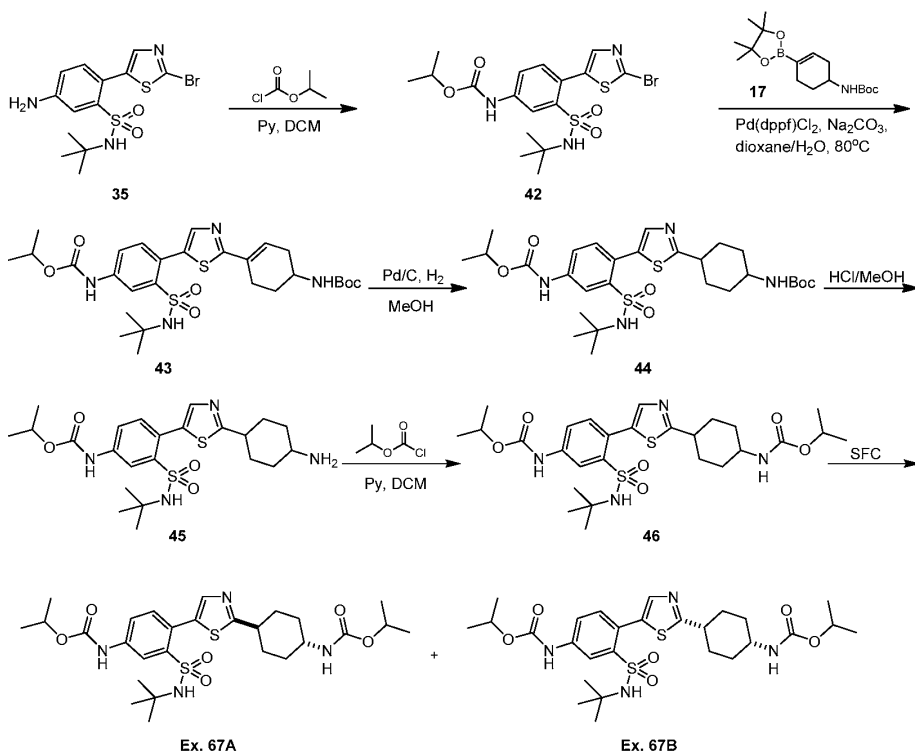
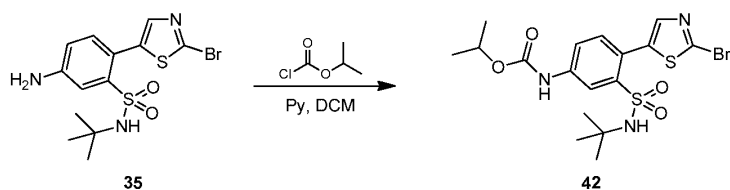
Compound 41 was separated by SFC (Instrument: Thar SFC80 preparative SFC; Column: Chiralpak AD-H 250*30mm i.d. 5 μ ; Mobile phase: A for CO₂ and B for IPA(0.1%NH₃H₂O); Gradient: B%=42%; Flow rate:70 g/min; Wavelength:220 nm; Column temperature: 40°C; System back pressure: 100 bar; Cycle time:20 min; Injection amount: 4 mg per injection), and then purified by prep-HPLC (Column: Luna C18 100*30 5 μ ; mobile phase: [water(0.1%TFA)-ACN];B%: 35%-75%,5min). ***trans-isopropyl N-[4-[5-[4-(benzylcarbamoylamino)-2-(tert-butylsulfamoyl)phenyl]thiazol-2-yl]cyclohexyl]carbamate*** Ex. 66A (11.54 mg, 18.38 μ mol, 5.53% yield, 100% purity) and ***cis-isopropyl N-[4-[5-[4-(benzylcarbamoylamino)-2-(tert-butylsulfamoyl)phenyl]thiazol-2-yl]cyclohexyl]carbamate*** Ex. 66B (9.38 mg, 14.94 μ mol, 4.50% yield, 100% purity) were obtained.

Trans-isopropyl N-[4-[5-[4-(benzylcarbamoylamino)-2-(tert-butylsulfamoyl)phenyl]thiazol-2-yl]cyclohexyl]carbamate, ¹H NMR (400MHz, METHANOL-d₄) δ = 8.24 (d, J=2.2 Hz, 1H), 7.72 (s, 1H), 7.69 (dd, J=2.6, 8.3 Hz, 1H), 7.37 - 7.30 (m, 5H), 7.27 - 7.22 (m, 1H), 4.85 - 4.78 (m, 1H), 4.41 (s, 2H), 3.50 - 3.39 (m, 1H), 3.06 - 2.96 (m, 1H), 2.22 (br d, J=11.8 Hz, 2H), 2.07 (br d, J=10.1 Hz, 2H), 1.76 - 1.62 (m, 2H), 1.41 (dq, J=3.1, 12.7 Hz, 2H), 1.22 (br d, J=6.1 Hz, 6H), 1.11 (s, 9H). ESI [M+H] = 628.2.

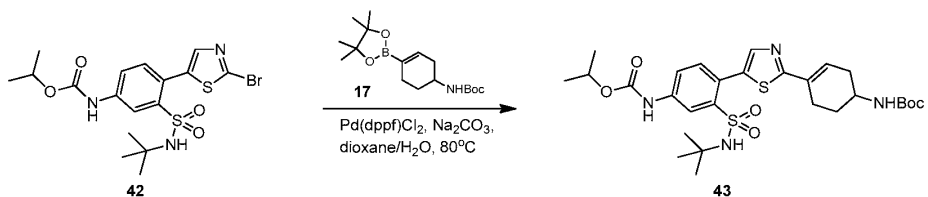
Cis-isopropyl N-[4-[5-[4-(benzylcarbamoylamino)-2-(tert-butylsulfamoyl)phenyl]thiazol-2-yl]cyclohexyl]carbamate. ¹H NMR (400MHz, METHANOL-d₄) δ = 8.25 (d, J=2.2 Hz, 1H), 7.74 (s, 1H), 7.70 (dd, J=2.2, 8.3 Hz, 1H), 7.38 - 7.30 (m, 5H), 7.28 - 7.22 (m, 1H), 4.82 (br d, J=6.1 Hz, 1H), 4.41 (s, 2H), 3.74 (br s, 1H), 3.20 - 3.13 (m, 1H), 2.03 - 1.95 (m, 4H), 1.86 - 1.72 (m, 4H), 1.23 (d, J=6.1 Hz, 6H), 1.12 (s, 9H). ESI [M+H] = 628.2.

Examples 67A and 67B

Scheme 26:

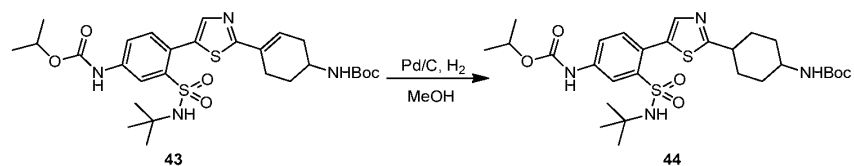
**Preparation of compound 42.**

General method D, *isopropyl N-[4-(2-bromothiazol-5-yl)-3-(tert-butylsulfamoyl)phenyl]carbamate*. ESI [M+H] = 476.0/478.0.

Preparation of compound 43

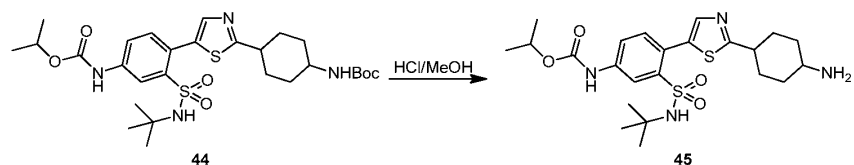
General method B, *isopropyl N-[4-[2-[4-(tert-butoxycarbonylamino)cyclohexen-1-yl]thiazol-5-yl]-3-(tert-butylsulfamoyl)phenyl]carbamate*. ESI [M+H] = 593.3.

Preparation of compound 44.



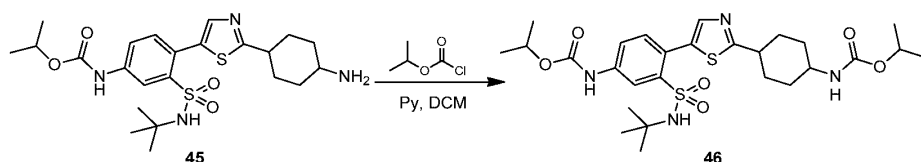
General method I, *isopropyl N-[4-[2-[4-(tert-butoxycarbonylamino)cyclohexyl]thiazol-5-yl]-3-(tert-butylsulfamoyl)phenyl]carbamate*. ESI [M+H] = 595.3.

Preparation of compound 45.



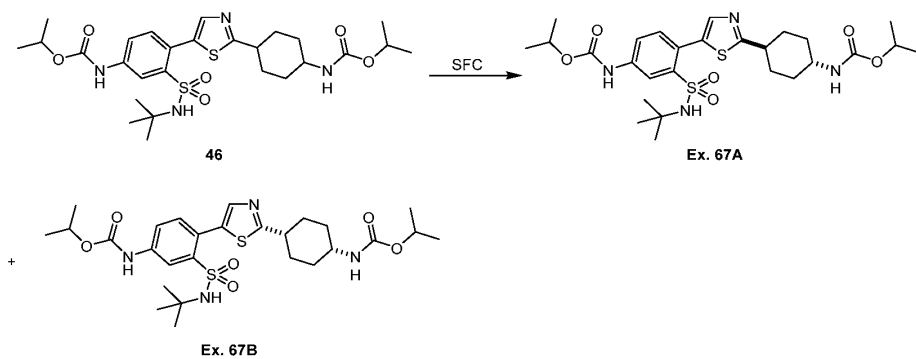
General method F, *isopropyl N-[4-[2-(4-aminocyclohexyl)thiazol-5-yl]-3-(tert-butylsulfamoyl)phenyl]carbamate*. ESI [M+H] = 495.2.

Preparation of compound 46.



General method D, *isopropyl N-[3-(tert-butylsulfamoyl)-4-[2-[4-(isopropoxycarbonylamino)cyclohexyl]thiazol-5-yl]phenyl]carbamate*. ESI [M+H] = 581.2.

Preparation of Ex. 67A and Ex. 67B.



Compound 46 was separated by SFC (Instrument: Thar SFC80 preparative SFC; Column: ChiralpakAD-H 250*30mm i.d. 5u; Mobile phase: A for CO₂ and B for IPA(0.1%NH₃H₂O); Gradient: B%=30%; Flow rate:70 g/min; Wavelength:220 nm; Column temperature: 40°C; System back pressure: 100 bar; Cycle time:8 min; Injection amount: 3 mg per injection); and then purified by prep-HPLC (Column: Agela Durashell C18 150*25 5u; mobile phase:

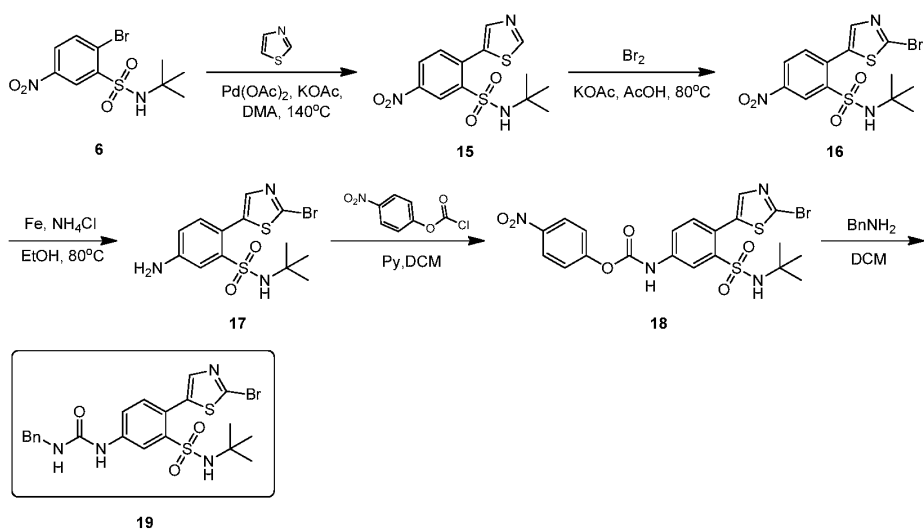
[water(0.1%TFA)-ACN];B%: 55%-85%,12min), *trans-isopropylN-[3-(tert-butylsulfamoyl)-4-[2-[4-(isopropoxycarbonylamino)cyclohexyl]thiazol-5-yl]phenyl]carbamate* Ex. 67A (5.76 mg, 100% purity) and *cis-isopropylN-[3-(tert-butylsulfamoyl)-4-[2-[4-(isopropoxycarbonylamino)cyclohexyl]thiazol-5-yl]phenyl]carbamate* Ex. 67B (3.95 mg, 100% purity) were obtained as a pale yellow solid.

Trans-isopropylN-[3-(tert-butylsulfamoyl)-4-[2-[4-(isopropoxycarbonylamino)cyclohexyl]thiazol-5-yl]phenyl]carbamate (Compound S12). ¹H NMR (400MHz, METHANOL-d₄) δ = 8.37 (d, J=2.3 Hz, 1H), 7.75 (s, 1H), 7.69 (dd, J=2.2, 8.4 Hz, 1H), 7.40 (d, J=8.3 Hz, 1H), 5.01 (td, J=6.3, 12.5 Hz, 1H), 4.86 - 4.82 (m, 1H), 3.52 - 3.42 (m, 1H), 3.04 (tt, J=3.5, 12.0 Hz, 1H), 2.35 - 2.19 (m, 2H), 2.15 - 1.99 (m, 2H), 1.72 (dq, J=3.0, 12.9 Hz, 2H), 1.43 (dq, J=3.3, 12.6 Hz, 2H), 1.34 (d, J=6.2 Hz, 6H), 1.25 (br d, J=6.1 Hz, 6H), 1.14 (s, 9H). ESI [M+H] = 581.2.

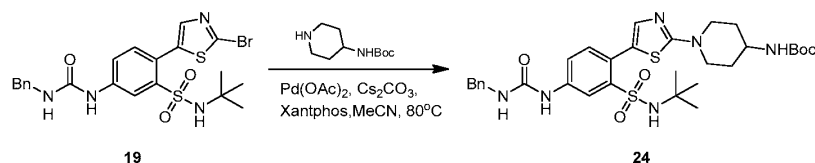
Cis-isopropylN-[3-(tert-butylsulfamoyl)-4-[2-[4-(isopropoxycarbonylamino)cyclohexyl]thiazol-5-yl]phenyl]carbamate (Compound S13). ¹H NMR (400MHz, METHANOL-d₄) δ = 8.37 (d, J=2.2 Hz, 1H), 7.76 (s, 1H), 7.70 (dd, J=2.2, 8.3 Hz, 1H), 7.40 (d, J=8.3 Hz, 1H), 5.01 (td, J=6.3, 12.5 Hz, 1H), 4.84 (br s, 1H), 3.77 (br s, 1H), 3.23 - 3.15 (m, 1H), 2.05 - 1.98 (m, 4H), 1.89 - 1.72 (m, 4H), 1.34 (d, J=6.2 Hz, 6H), 1.25 (d, J=6.1 Hz, 6H), 1.16 (s, 9H). ESI [M+H] = 581.2

Example 68. Synthesis of isopropyl N-[1-[5-[4-(benzylcarbamoylamino)-2-(tert-butylsulfamoyl)phenyl]thiazol-2-yl]-4-piperidyl]carbamate.

Scheme 27:

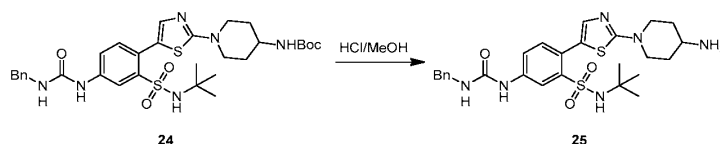


Preparation of compound 24.



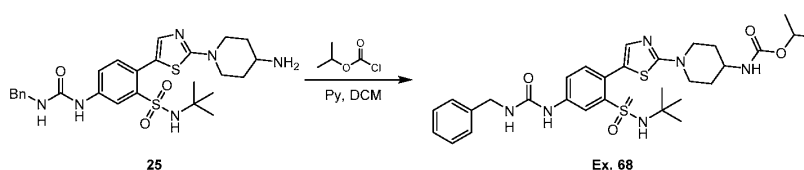
A mixture of **1-benzyl-3-[4-(2-bromothiazol-5-yl)-3-(tert-butylsulfamoyl)phenyl]urea** (0.06 g, 114.62 μmol , 1.0 eq.), **tert-butyl N-(4-piperidyl)carbamate** (40 mg, 199.72 μmol , 1.74 eq.), **Xantphos** (6.63 mg, 11.46 μmol , 0.1 eq.), **Pd(OAc)₂** (2.57 mg, 11.46 μmol , 0.1 eq.) and **Cs₂CO₃** (112.04 mg, 343.86 μmol , 3.0 eq.) in **ACN** (3 mL) was heated to 80°C for 12 hrs under N₂. LCMS showed the reaction was complete and the mixture was concentrated. The residue was purified by prep-TLC (Petroleum ether: Ethyl acetate = 1:1) to give **tert-butyl N-[1-[5-[4-(benzylcarbamoylamino)-2-(tert-butylsulfamoyl)phenyl]thiazol-2-yl]-4-piperidyl]carbamate** (0.03 g, crude) as a yellow solid. ESI [M+H] = 643.1.

Preparation of compound 25.



Tert-butyl N-[1-[5-[4-(benzylcarbamoylamino)-2-(tert-butylsulfamoyl)phenyl]thiazol-2-yl]-4-piperidyl]carbamate (30 mg, 46.67 μmol , 1.0 eq.) was dissolved into **HCl/MeOH** (4M, 1 mL) and the mixture was stirred at 20°C for 0.5 hr. LCMS showed the reaction was complete and the mixture was concentrated to give **1-[4-[2-(4-amino-1-piperidyl)thiazol-5-yl]-3-(tert-butylsulfamoyl)phenyl]-3-benzyl-urea** (27 mg, crude, HCl salt) as a yellow solid. ESI [M+H] = 543.2.

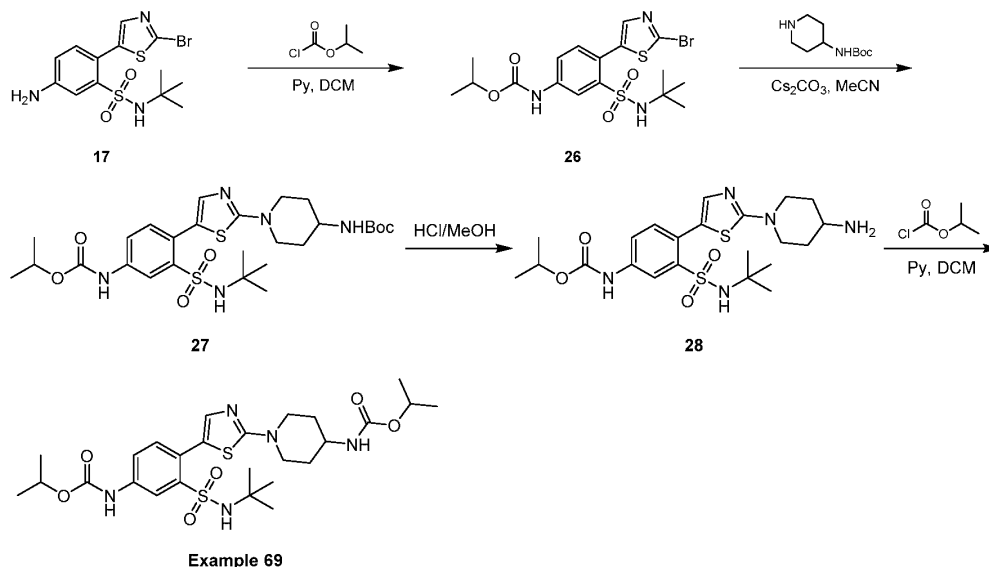
Preparation of Ex. 68.



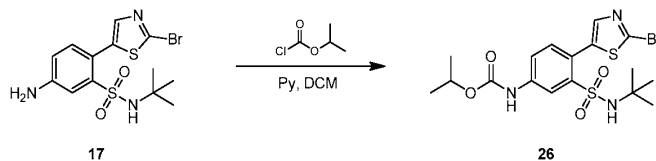
General method D, **isopropyl N-[1-[5-[4-(benzylcarbamoylamino)-2-(tert-butylsulfamoyl)phenyl]thiazol-2-yl]-4-piperidyl]carbamate**. ¹H NMR (400MHz, METHANOL-d₄) δ = 8.24 (d, J=2.2 Hz, 1H), 7.69 (dd, J=2.4, 8.4 Hz, 1H), 7.39 (d, J=8.4 Hz, 1H), 7.36 - 7.19 (m, 6H), 4.82 - 4.73 (m, 1H), 4.40 (s, 2H), 3.92 (br d, J=13.7 Hz, 2H), 3.75 - 3.68 (m, 1H), 3.43 (br t, J=11.0 Hz, 2H), 2.10 - 2.02 (m, 2H), 1.71 - 1.60 (m, 2H), 1.22 (br d, J=6.2 Hz, 6H), 1.18 (s, 9H). ESI [M+H] = 629.2.

Example 69. Synthesis of isopropyl N-[1-[5-[2-(tert-butylsulfamoyl)-4-(isopropoxy carbonylamino)phenyl]thiazol-2-yl]-4-piperidyl]carbamate.

Scheme 28:

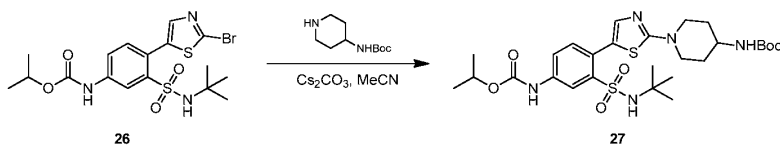


Preparation of compound 26.



General method D, *isopropyl N-[4-(2-bromothiazol-5-yl)-3-(tert-butylsulfamoyl)phenyl]carbamate*. ESI [M+H] = 478.0/476.0.

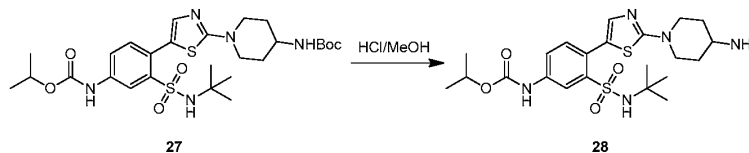
Preparation of compound 27.



To a solution of *isopropyl N-[4-(2-bromothiazol-5-yl)-3-(tert-butylsulfamoyl)phenyl]carbamate* (0.05 g, 104.95 μmol , 1.0 eq.) in MeCN (2 mL) were added Cs_2CO_3 (102.59 mg, 314.86 μmol , 3.0 eq.), KI (17.42 mg, 104.95 μmol , 1.0 eq.) and tert-butyl N-(4-piperidyl)carbamate (105.10 mg, 524.76 μmol , 5.0 eq.). The mixture was stirred at 95°C for 12 hrs and then concentrated. The residue was purified by prep-TLC (SiO_2 , Petroleum ether: Ethyl acetate = 4:3) to give *N-[4-[2-[4-(tert-butoxycarbonylamino)-1-piperidyl]thiazol-5-yl]-*

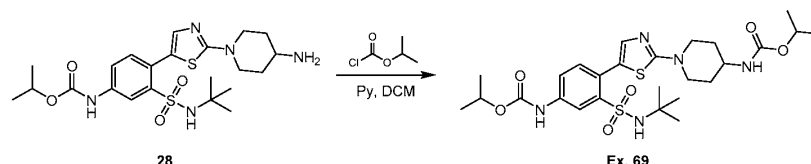
3-(*tert*-butylsulfamoyl) phenyl]carbamate (0.025 g, crude) as a white solid. ESI [M+H] = 596.2.

Preparation of compound 28.



*Isopropyl N-[4-[2-[4-(*tert*-butoxycarbonylamino)-1-piperidyl]thiazol-5-yl]-3-(*tert*-butylsulfamoyl)phenyl]carbamate* (0.025 g, 41.96 μ mol, 1.0 eq.) was dissolved into HCl/MeOH (4M, 1.5 mL) and the mixture was stirred at 20°C for 0.5 hr. LCMS showed the reaction was complete and the mixture was concentrated to give the *N*-[4-[2-(4-amino-1-piperidyl)thiazol-5-yl]-3-(*tert*-butylsulfamoyl)phenyl] carbamate (0.02 g, crude, HCl salt) as a white solid. ESI [M+H] = 496.2.

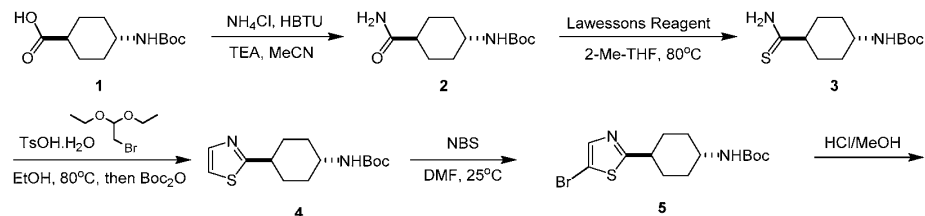
Preparation of Ex. 69.

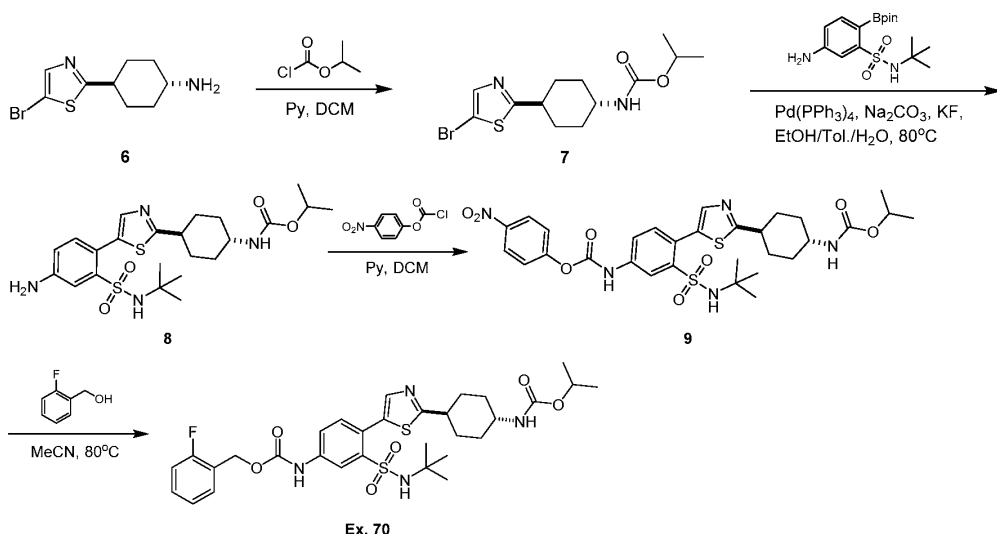


General method D, *isopropyl N-[1-[5-[2-(*tert*-butylsulfamoyl)-4-(isopropoxy carbonylamino)phenyl]thiazol-2-yl]-4-piperidyl]carbamate*. ^1H NMR (400MHz, METHANOL- d_4) δ = 8.35 (s, 1H), 7.66 (br d, J =8.4 Hz, 1H), 7.42 (d, J =8.4 Hz, 1H), 7.31 (s, 1H), 4.98 (td, J =6.2, 12.5 Hz, 1H), 4.84 - 4.77 (m, 1H), 3.93 (br d, J =13.5 Hz, 2H), 3.77 - 3.67 (m, 1H), 3.44 (br t, J =12.3 Hz, 2H), 2.06 (br dd, J =3.1, 13.2 Hz, 2H), 1.71 - 1.61 (m, 2H), 1.31 (d, J =6.4 Hz, 6H), 1.23 (br d, J =6.2 Hz, 6H), 1.19 (s, 9H). ESI [M+H] = 582.2.

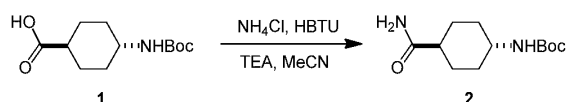
Example 70. Synthesis of trans-isopropyl N-[4-[5-[2-(*tert*-butylsulfamoyl)-4-(2-fluorophenyl)methoxy carbonylamino]phenyl]thiazol-2-yl]cyclohexyl]carbamate.

Scheme 29:



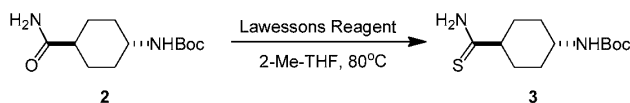


Preparation of compound 2.



To a mixture of *trans*-4-(*tert*-butoxycarbonylamino)cyclohexanecarboxylic acid (65.0 g, 267.2 mmol, 1.0 *eq.*), NH₄Cl (21.4 g, 400.7 mmol, 1.5 *eq.*) and TEA (801.5 mmol, 111.6 mL, 3 *eq.*) in MeCN (1.3 L) was added HBTU (111.5 g, 293.9 mmol, 1.1 *eq.*) and the mixture was stirred at 25°C for 3 hrs. The mixture was filtered and then the filter cake was washed with petroleum ether (200 mL) and dried to give *trans*-*tert*-butyl *N*-(4-carbamoylcyclohexyl)carbamate (140 g, crude, 2 batches) as a white solid. ¹H NMR (METHANOL-d₄, 400MHz) δ = 3.25-3.34 (m, 1H), 2.14 (tt, J=12.3, 3.5 Hz, 1H), 1.83-1.99 (m, 4H), 1.52 (qd, J=13.1, 2.9 Hz, 2H), 1.42 (s, 9H), 1.21 (qd, J=12.7, 3.5 Hz, 2H)

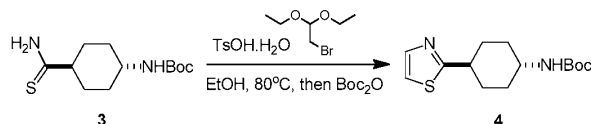
Preparation of compound 3.



A mixture of *trans*-*tert*-butyl *N*-(4-carbamoylcyclohexyl)carbamate (90.0 g, 371.4 mmol, 1.0 *eq.*), Na₂CO₃ (39.4 g, 371.4 mmol, 1.0 *eq.*) and Lawesson's reagent (82.6 g, 204.3 mmol, 0.55 *eq.*) in 2-Me-THF (600 mL) was stirred at 80°C for 2 hrs and then the reaction mixture was poured into H₂O (200 mL). The aqueous phase was extracted with EtOAc (500 mL x 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to give *trans*-*tert*-butyl *N*-(4-carbamothioylcyclohexyl)carbamate (180 g, crude, 2 batches) as a

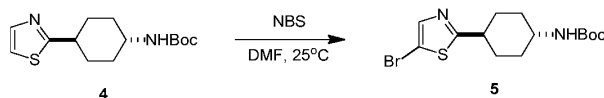
white solid. ^1H NMR (METHANOL- d_4 , 400MHz) δ = 3.35-3.46 (m, 1H), 2.87-3.00 (m, 1H), 2.09-2.20 (m, 2H), 1.99-2.09 (m, 2H), 1.54-1.68 (m, 2H), 1.26-1.45 (m, 2H), 1.14-1.25 (m, 9H)

Preparation of compound 4.



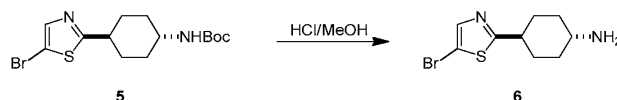
A mixture of *trans-tert-butyl N-(4-carbamothiolcyclohexyl)carbamate* (180.0 g, 696.7 mmol, 1.0 *eq.*), 2-bromo-1,1-diethoxy-ethane (137.3 g, 696.7 mmol, 1.0 *eq.*) and TsOH.H₂O (265 g, 1.4 mol, 2 *eq.*) in EtOH (2.0 L) was stirred at 80°C for 6 hrs. Then the mixture was cooled to RT and adjusted to PH=9 with aq.sat.Na₂CO₃ and Boc₂O (152 g, 696.7 mmol, 1 *eq.*) was added. The mixture was stirred at 30°C for 3 hrs, then concentrated and diluted with H₂O (2 L). The mixture was extracted with EtOAc (800 mL x 3) and the combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was triturated with petroleum ether (1.5 L) to give *trans-tert-butyl N-(4-thiazol-2-ylcyclohexyl) carbamate* (70 g, 247.87 mmol, 35.58% yield) as a white solid. ^1H NMR (METHANOL- d_4 , 400MHz) δ = 7.67 (d, J=3.1 Hz, 1H), 7.44 (d, J=3.5 Hz, 1H), 3.33-3.44 (m, 1H), 2.93-3.06 (m, 1H), 2.12-2.21 (m, 2H), 2.00-2.09 (m, 2H), 1.57-1.71 (m, 2H), 1.41-1.48 (m, 9H), 1.29-1.38 (m, 1H), 1.13-1.28 (m, 1H).

Preparation of compound 5.



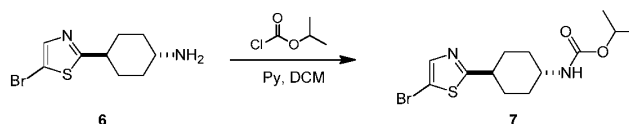
A mixture of *trans-tert-butyl N-(4-thiazol-2-ylcyclohexyl)carbamate* (68 g, 240.8 mmol, 1 *eq.*) and NBS (47.1 g, 264.9 mmol, 1.1 *eq.*) in DMF (500 mL) was stirred at 25°C for 10 hrs and then poured into H₂O (2 L) and extracted with EtOAc (500 mL x 3). The combined organic layers were washed with brine (300 mL x 5), dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether: Ethyl acetate = 20:1 to 10:1) to give *trans-tert-butyl N-[4-(5-bromothiazol-2-yl)cyclohexyl]carbamate* (78 g, crude) as a yellow solid. ESI [M+H] = 363.0/361.0

Preparation of compound 6.



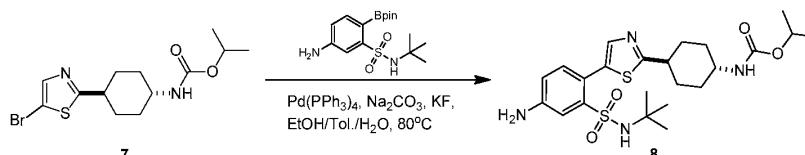
A mixture of *trans-tert-butyl N-[4-(5-bromothiazol-2-yl)cyclohexyl]carbamate* (50 g, 138.4 mmol, 1 *eq.*) in HCl/MeOH (4 M, 700 mL) was stirred at 25°C for 0.5 hr and then concentrated to give *trans-4-(5-bromothiazol-2-yl) cyclohexanamine* (45 g, crude, HCl salt) as a yellow solid. ESI [M+H] = 263.0/261.0

Preparation of compound 7.



To a solution of *trans-4-(5-bromothiazol-2-yl)cyclohexanamine* (45 g, HCl salt, 172.3 mmol, 1 *eq.*), Pyridine (61.5 mmol, 69.5 mL, 5 *eq.*) and DMAP (4.2 g, 34.5 mmol, 0.2 *eq.*) in DCM (300 mL) was added isopropyl carbonochloridate (258.5 mmol, 35.9 mL, 1.5 *eq.*) dropwise at 0°C. The mixture was stirred at 25°C for 0.5 hr and then washed with HCl (1N, 1 L) and sat.aq.Na₂CO₃ (1 L). The organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether: Ethyl acetate=15:1 to 10:1) to give *trans-isopropyl N-[4-(5-bromothiazol-2-yl)cyclohexyl]carbamate* (37 g, 106.55 mmol, 61.84% yield) as a yellow solid. ¹H NMR (METHANOL-d₄, 400MHz) δ = 7.60 (s, 1H), 4.81 (dt, J=12.2, 6.2 Hz, 1H), 3.41 (tt, J=11.6, 4.0 Hz, 1H), 2.88-3.00 (m, 1H), 2.10-2.20 (m, 2H), 1.98-2.07 (m, 2H), 1.55-1.68 (m, 2H), 1.30-1.43 (m, 2H), 1.21 (br d, J=6.2 Hz, 6H).

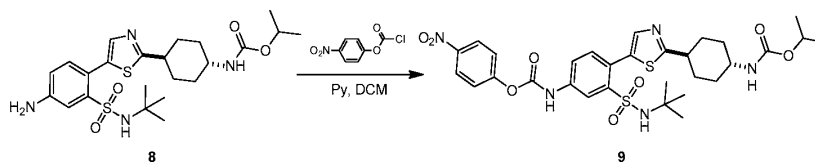
Preparation of compound 8.



A mixture of *trans-isopropyl N-[4-(5-bromothiazol-2-yl)cyclohexyl]carbamate* (16.2 g, 46.7 mmol, 1 *eq.*), *5-amino-N-tert-butyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide* (19.9 g, 56.1 mmol, 1.2 *eq.*), KF (4.1 g, 70.1 mmol, 1.5 *eq.*), Na₂CO₃ (14.9 g, 140.2 mmol, 3 *eq.*) and Pd(PPh₃)₄ (1.6 g, 1.4 mmol, 0.03 *eq.*) in toluene (150 mL), EtOH (150 mL) and H₂O (50 mL) stirred at 80°C for 6 hrs under N₂ atmosphere. The reaction mixture was concentrated and the residue was diluted with H₂O (100 mL) and extracted with EtOAc (100 mL x 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether: Ethyl acetate= 20:1 to 1:1) to give *trans-isopropyl N-[4-[5-[4-amino-2-(tert-butylsulfamoyl)phenyl]thiazol-2-yl]cyclohexyl]carbamate* (13 g, 26.3 mmol, 56.2% yield) as a white solid.

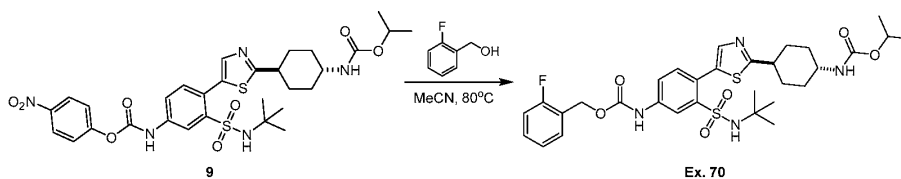
^1H NMR (400MHz, METHANOL- d_4) δ = 7.65 - 7.60 (m, 1H), 7.43 (d, J =2.2 Hz, 1H), 7.13 (d, J =8.3 Hz, 1H), 6.83 (dd, J =2.6, 8.3 Hz, 1H), 4.81 (br s, 1H), 3.76 - 3.71 (m, 1H), 3.05 - 2.86 (m, 1H), 2.20 (br d, J =12.3 Hz, 2H), 2.06 (br d, J =10.5 Hz, 2H), 1.75 - 1.60 (m, 2H), 1.47 - 1.34 (m, 2H), 1.22 (br d, J =6.1 Hz, 6H), 1.09 (s, 9H).

Preparation of compound 9.



To a solution of *trans-isopropyl N-[4-[5-[4-amino-2-(tert-butylsulfamoyl)phenyl]thiazol-2-yl]cyclohexyl]carbamate* (250 mg, 505.4 μmol , 1 *eq.*) in DCM (4 mL) were added DMAP (6.2 mg, 50.5 μmol , 0.1 *eq.*), Pyridine (120 mg, 1.5 mmol, 3 *eq.*) and (4-nitrophenyl) carbonochloridate (153 mg, 758 μmol , 1.5 *eq.*). The mixture was stirred at 25°C for 0.5 hr and used directly for the next step. ESI $[\text{M}+\text{H}] = 660.2$

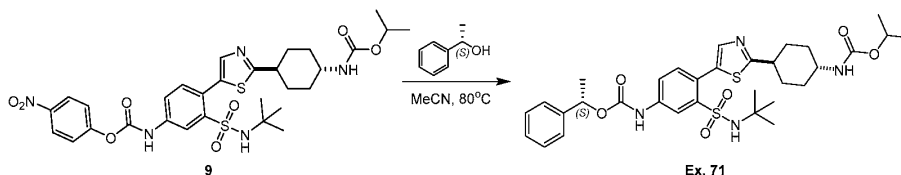
Preparation of compound Ex. 70.



To a solution of (2-fluorophenyl)methanol (45.9 mg, 363.8 μmol , 3 *eq.*) and DIEA (47 mg, 363.8 μmol , 3 *eq.*) in MeCN (1 mL) was added the above solution (1 mL). The mixture was stirred at 80°C for 1 hr, then concentrated and the residue was purified by prep-HPLC (Column: Waters Xbridge 150*25 5u; Mobile phase: [water (10 mM NH_4HCO_3)-ACN]; B%: 42%-72%, 12 min) to give *trans-isopropyl N-[4-[5-[2-(tert-butylsulfamoyl)-4-[(2-fluorophenyl)methoxy carbonylamino]phenyl]thiazol-2-yl]cyclohexyl]carbamate* (16.34 mg, 25.26 μmol , 20.83% yield, 100% purity) as a yellow solid. ^1H NMR (400MHz, METHANOL- d_4) δ = 8.36 (s, 1H), 7.77 - 7.63 (m, 2H), 7.52 (t, J =7.0 Hz, 1H), 7.44 - 7.31 (m, 2H), 7.23 - 7.08 (m, 2H), 5.29 (s, 2H), 4.83 (br s, 1H), 3.46 (br d, J =11.8 Hz, 1H), 3.00 (br t, J =11.8 Hz, 1H), 2.22 (br d, J =12.7 Hz, 2H), 2.07 (br d, J =11.4 Hz, 2H), 1.76 - 1.62 (m, 2H), 1.47 - 1.35 (m, 2H), 1.22 (br d, J =6.1 Hz, 6H), 1.12 (s, 9H). ESI $[\text{M}+\text{H}] = 647.2$

Example 71. Synthesis of *trans*-(1S)-1-phenylethyl N-[3-(tert-butylsulfamoyl)-4-[2-[4-(isopropoxycarbonylamino)cyclohexyl]thiazol-5-yl]phenyl]carbamate.

Scheme 30:

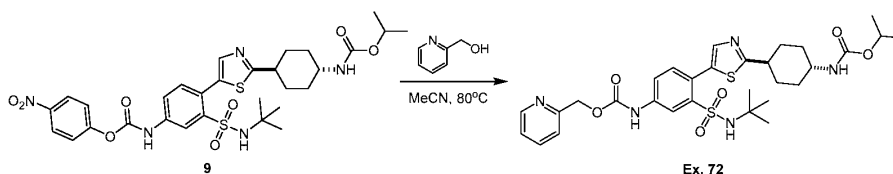


Preparation of Ex. 71.

To a solution of (1S)-1-phenylethanol (29.6 mg, 242.5 μmol , 2 *eq.*) and DIEA (47 mg, 363.8 μmol , 3 *eq.*) in MeCN (2 mL) was added a solution of *trans*-(4-nitrophenyl) N-[3-(tert-butylsulfamoyl)-4-[2-[4-(isopropoxycarbonylamino)cyclohexyl]thiazol-5-yl]phenyl]carbamate (80 mg, 121.25 μmol , 1 *eq.*) in DCM (1 mL). The mixture was stirred at 80°C for 1 hr, then concentrated and the residue was purified by prep-HPLC (Column: Nano-Micro UniSil 5-100 C18 ULTRA 100*250mm 5 μm ; mobile phase: [water(0.1%TFA)-ACN]; B%: 55%-80%, 11min) to give *trans*-[(1S)-1-phenylethyl] N-[3-(tert-butylsulfamoyl)-4-[2-[4-(isopropoxycarbonylamino)cyclohexyl]thiazol-5-yl]phenyl]carbamate (12.19 mg, 18.77 μmol , 15.48% yield, 99% purity) as a white solid. ^1H NMR (400MHz, METHANOL- d_4) δ = 8.35 (br s, 1H), 7.81 - 7.65 (m, 2H), 7.48 - 7.36 (m, 5H), 7.31 (br d, J=6.8 Hz, 1H), 5.89 (br d, J=6.2 Hz, 1H), 4.85 (br d, J=5.5 Hz, 1H), 3.47 (br s, 1H), 3.03 (br s, 1H), 2.24 (br d, J=11.2 Hz, 2H), 2.08 (br d, J=11.0 Hz, 2H), 1.71 (q, J=11.9 Hz, 2H), 1.61 (br d, J=6.4 Hz, 3H), 1.49 - 1.37 (m, 2H), 1.24 (br d, J=5.4 Hz, 6H), 1.13 (s, 9H). ESI [M+H] = 643.2

Example 72. Synthesis of N-[3-(tert-butylsulfamoyl)-4-[2-[4-(isopropoxycarbonylamino) cyclohexyl]thiazol-5-yl]phenyl]carbamate.

Scheme 31:



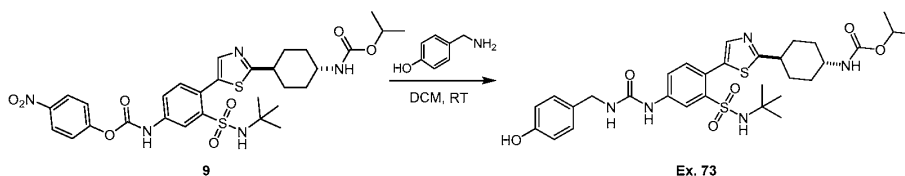
Preparation of Ex. 72.

To a solution of 2-pyridylmethanol (26.5 mg, 242.5 μmol , 2 *eq.*) and DIEA (47 mg, 363.8 μmol , 3 *eq.*) in MeCN (2 mL) was added a solution of *trans*-(4-nitrophenyl) N-[3-(tert-butylsulfamoyl)-4-[2-[4-(isopropoxycarbonylamino)cyclohexyl]thiazol-5-yl]phenyl]carbamate (80 mg, 121.3 μmol , 1 *eq.*) in DCM (1 mL). The mixture was stirred at 80°C for 1 hr, then concentrated and the residue was purified by prep-HPLC (Column: Waters Xbridge 150*25 5 μm ; Mobile phase: [water (0.04% $\text{NH}_3\text{H}_2\text{O}$ + 10 mM NH_4HCO_3)-ACN]; B%: 35%-65%, 10 min) to give *trans*-2-pyridylmethyl N-[3-(tert-butylsulfamoyl)-4-[2-[4-(isopropoxycarbonylamino)cyclohexyl]thiazol-5-yl]phenyl]carbamate (12.19 mg, 18.77 μmol , 15.48% yield, 99% purity) as a white solid.

[2-[4-(isopropoxycarbonylamino)cyclohexyl]thiazol-5-yl]phenyl]carbamate (18.59 mg, 28.82 μ mol, 23.77% yield, 97.65% purity) as a pale yellow solid. ^1H NMR (400MHz, METHANOL- d_4) δ = 8.56 (br d, J =4.5 Hz, 1H), 8.38 (d, J =1.8 Hz, 1H), 7.94 - 7.87 (m, 1H), 7.78 - 7.72 (m, 2H), 7.59 (br d, J =7.8 Hz, 1H), 7.44 - 7.38 (m, 2H), 5.32 (s, 2H), 4.85 (td, J =5.9, 12.0 Hz, 1H), 3.47 (br t, J =11.8 Hz, 1H), 3.07 - 2.96 (m, 1H), 2.24 (br d, J =12.3 Hz, 2H), 2.13 - 2.04 (m, 2H), 1.77 - 1.65 (m, 2H), 1.48 - 1.37 (m, 2H), 1.24 (br d, J =6.1 Hz, 6H), 1.14 (s, 9H). ESI $[\text{M}+\text{H}] = 630.2$

Example 73. Synthesis of trans-isopropyl N-[4-[5-[2-(tert-butylsulfamoyl)-4-[(4-hydroxyphenyl)methylcarbamoylamino]phenyl]thiazol-2-yl]cyclohexyl]carbamate.

Scheme 32:

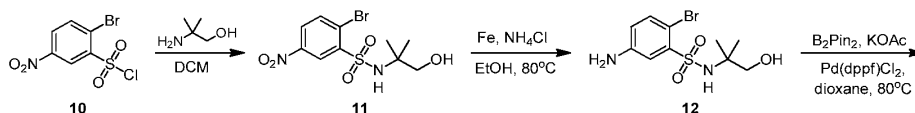


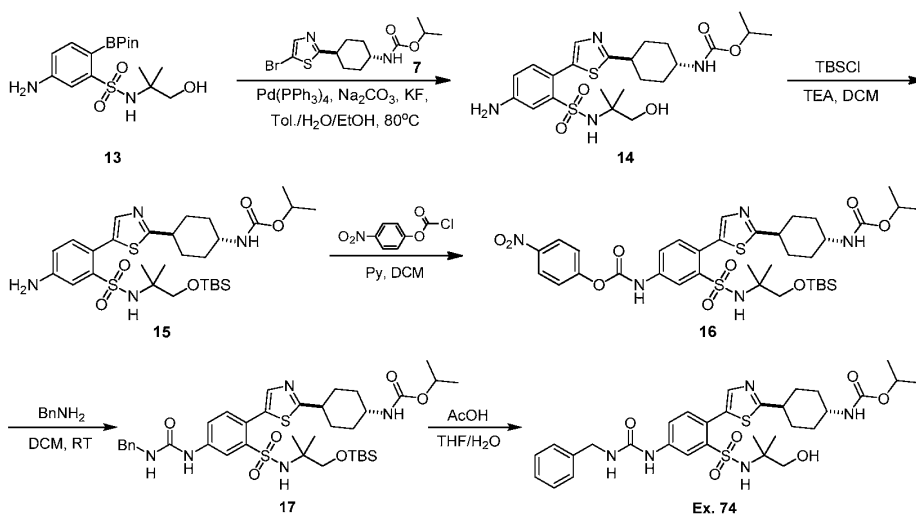
Preparation of Ex. 73.

To a solution 4-(aminomethyl) phenol (74.7 mg, 606.5 μ mol, 3 *eq.*) and DIEA (78.4 mg, 606.5 μ mol, 3 *eq.*) in DCM (2 mL) was added *trans*-(4-nitrophenyl) N-[3-(tert-butylsulfamoyl)-4-[2-[4-(isopropoxycarbonylamino)cyclohexyl]thiazol-5-yl]phenyl]carbamate (133.4 mg, 202.2 μ mol, 1 *eq.*) in DCM (2 mL). The mixture was stirred at 25°C for 1 hr, then concentrated and the residue was purified by prep-HPLC (TFA condition) to give *trans*-isopropyl N-[4-[5-[2-(tert-butylsulfamoyl)-4-[(4-hydroxyphenyl)methylcarbamoylamino]phenyl]thiazol-2-yl]cyclohexyl]carbamate (23.56 mg, 35.99 μ mol, 17.80% yield, 98.35% purity) as a white solid. ^1H NMR (400MHz, METHANOL- d_4) δ = 8.24 (d, J =2.2 Hz, 1H), 7.77 (s, 1H), 7.69 (dd, J =2.2, 8.3 Hz, 1H), 7.36 (d, J =8.3 Hz, 1H), 7.16 (d, J =8.8 Hz, 2H), 6.75 (d, J =8.3 Hz, 2H), 4.85 - 4.74 (m, 1H), 4.30 (s, 2H), 3.45 (s, 1H), 3.15 - 2.97 (m, 1H), 2.23 (br d, J =12.3 Hz, 2H), 2.08 (br d, J =13.2 Hz, 2H), 1.79 - 1.63 (m, 2H), 1.48 - 1.34 (m, 2H), 1.22 (br d, J =6.1 Hz, 6H), 1.12 (s, 9H). ESI $[\text{M}+\text{H}] = 644.2$

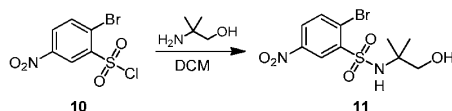
Example 74. Synthesis of trans-isopropyl N-[4-[5-[4-(benzylcarbamoylamino)-2-[(2-hydroxy-1,1-dimethyl-ethyl)sulfamoyl]phenyl]thiazol-2-yl]cyclohexyl]carbamate.

Scheme 33:



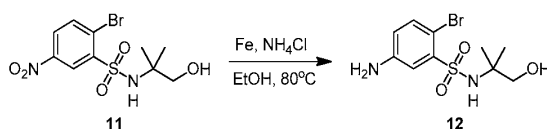


Preparation of compound 11.



To a mixture of **2-amino-2-methyl-propan-1-ol** (3 g, 33.7 mmol, 5.1 *eq.*) and DMAP (80 mg, 654.8 μmol , 0.98 *eq.*) in DCM (50 mL) was added **2-bromo-5-nitro-benzenesulfonyl chloride** (2 g, 6.66 mmol, 1 *eq.*). The mixture was stirred at 20°C for 30 mins, then washed with 1N HCl (20 mL) and sat.aq. NaHCO_3 (20 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated to give **2-bromo-N-(2-hydroxy-1,1-dimethyl-ethyl)-5-nitro-benzenesulfonamide** (1.7 g, 4.8 mmol, 72.3% yield) as a yellow gum. ESI $[\text{M}+\text{H}] = 355.0/353.0$

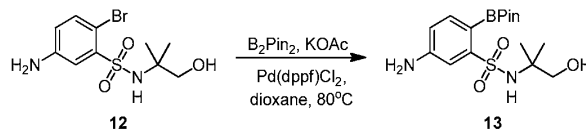
Preparation of compound 12.



A mixture of **2-bromo-N-(2-hydroxy-1,1-dimethyl-ethyl)-5-nitro-benzenesulfonamide** (1.7 g, 4.8 mmol, 1 *eq.*), Fe (1.5 g, 26.9 mmol, 5.6 *eq.*) and NH_4Cl (800 mg, 14.9 mmol, 3.1 *eq.*) in EtOH (15 mL)/ H_2O (7.5 mL)/THF (7.5 mL) was stirred at 80°C for 2 hrs. The reaction mixture was concentrated to remove EtOH, diluted with H_2O (100 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography (SiO_2 , Petroleum ether: Ethyl acetate = 100:1 to 1:1) to give **5-amino-2-bromo-N-(2-hydroxy-1,1-dimethyl-**

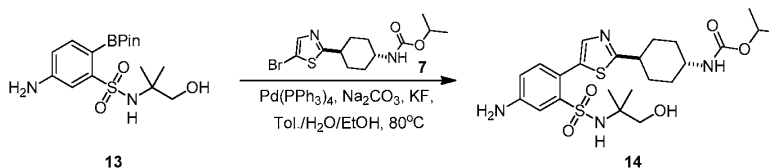
ethyl)benzenesulfonamide (1.1 g, 3.4 mmol, 70.7% yield) as a pale yellow solid. ESI [M+H]⁺ = 325.0/323.0

Preparation of compound 13.



A mixture of **5-amino-2-bromo-N-(2-hydroxy-1,1-dimethyl-ethyl) benzenesulfonamide** (400 mg, 1.24 mmol, 1 *eq.*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (942.8 mg, 3.7 mmol, 3 *eq.*), Pd(dppf)Cl₂ (90.6 mg, 123.8 μmol, 0.1 *eq.*) and KOAc (364.4 mg, 3.7 mmol, 3 *eq.*) in dioxane (4 mL) was stirred at 80°C for 12 hrs under N₂ atmosphere and then concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether: Ethyl acetate = 50:1 to 3:1) to give **5-amino-N-(2-hydroxy-1,1-dimethyl-ethyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide** (201 mg, crude) as a white solid. ¹H NMR (400MHz, METHANOL-d₄) δ = 7.53 (d, J=8.0 Hz, 1H), 7.28 (d, J=2.4 Hz, 1H), 6.75 (dd, J=6.4 Hz, 1H), 3.35 (s, 2H), 1.36 (s, 12H), 1.10 (s, 6H).

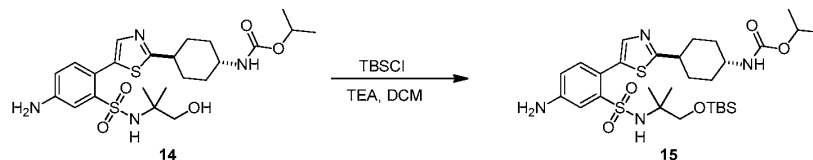
Preparation of compound 14.



A mixture of **5-amino-N-(2-hydroxy-1,1-dimethyl-ethyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide** (140.7 mg, 380.1 μmol, 1.2 *eq.*), **trans-isopropyl N-[4-(5-bromothiazol-2-yl)cyclohexyl]carbamate** (110 mg, 316.7 μmol, 1 *eq.*), Na₂CO₃ (100.7 mg, 950.3 μmol, 3 *eq.*), KF (27.6 mg, 475.1 μmol, 1.5 *eq.*) and Pd(PPh₃)₄ (36.6 mg, 31.7 μmol, 0.1 *eq.*) in toluene (1 mL)/EtOH (1 mL)/H₂O (0.3 mL) was stirred at 80°C for 12 hrs under N₂ atmosphere. The reaction mixture was concentrated, diluted with H₂O (10 mL) and extracted with EtOAc (10 mL x 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was purified by prep-TLC (SiO₂, Ethyl acetate) to give **trans-isopropyl N-[4-[5-[4-amino-2-[(2-hydroxy-1,1-dimethyl-ethyl)sulfamoyl]phenyl]thiazol-2-yl]cyclohexyl]carbamate** (117 mg, crude) as a yellow solid. ¹H NMR (400MHz, METHANOL-d₄) δ = 7.63 (d, J=7.0 Hz, 1H), 7.44 (d, J=2.2 Hz, 1H), 7.15 (d, J=8.3 Hz, 1H), 6.83 (dd, J=2.4, 8.1 Hz, 1H), 4.85 - 4.78 (m, 1H), 3.50 - 3.39 (m,

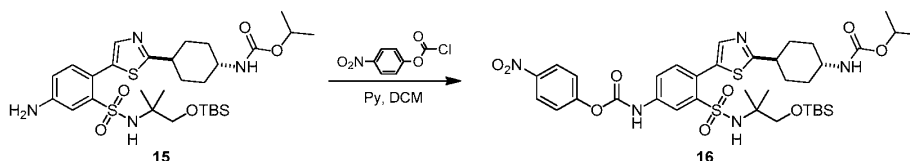
1H), 3.25 (s, 2H), 3.03 - 2.91 (m, 1H), 2.21 (br t, J=6.1 Hz, 2H), 2.12 - 2.00 (m, 2H), 1.75 - 1.60 (m, 2H), 1.45 - 1.33 (m, 2H), 1.28 - 1.19 (s, 6H), 1.03 (s, 6H)

Preparation of compound 15.



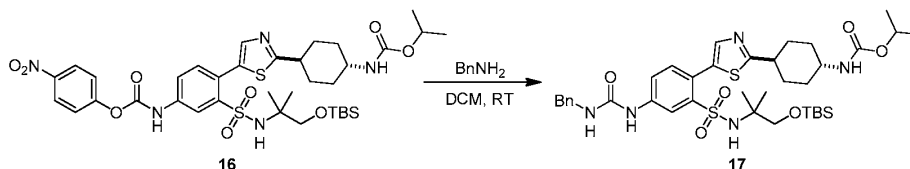
To a solution of *trans-isopropyl N-[4-[5-[4-amino-2-[(2-hydroxy-1,1-dimethyl-ethyl)sulfamoyl]phenyl]thiazol-2-yl]cyclohexyl]carbamate* (90 mg, 176.3 μmol , 1 *eq.*) in DCM (1 mL) were added TEA (53.5 mg, 528.7 μmol , 3 *eq.*), DMAP (2.2 mg, 17.6 μmol , 0.1 *eq.*) and TBSCl (66.4 mg, 440.6 μmol , 2.5 *eq.*). The mixture was stirred at 30°C for 12 hrs and then concentrated. The residue was purified by prep-TLC (SiO₂, Petroleum ether: Ethyl acetate = 2:1) to give *trans-isopropyl N-[4-[5-[4-amino-2-[[2-[tert-butyl(dimethyl)silyl]oxy-1,1-dimethyl-ethyl]sulfamoyl]phenyl]thiazol-2-yl]cyclohexyl]carbamate* (120 mg, crude) as a pale yellow solid. ESI [M+H] = 625.2

Preparation of compound 16.



To a solution of *trans-isopropyl N-[4-[5-[4-amino-2-[[2-[tert-butyl(dimethyl)silyl]oxy-1,1-dimethyl-ethyl]sulfamoyl]phenyl]thiazol-2-yl]cyclohexyl]carbamate* (90 mg, 144 μmol , 1 *eq.*) in DCM (1 mL) were added DMAP (1.8 mg, 14.4 μmol , 0.1 *eq.*), pyridine (34.2 mg, 432 μmol , 3 *eq.*) and (4-nitrophenyl) carbonochloridate (43.5 mg, 216 μmol , 1.5 *eq.*). The mixture was stirred at 25°C for 0.5 hr and used into the next step directly without further purification. ESI [M+H] = 790.3

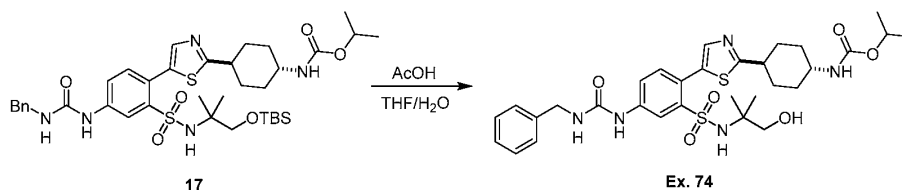
Preparation of compound 17.



To a solution of phenylmethanamine (36 mg, 336 μmol , 3 *eq.*) in DCM (1 mL) was added a solution of *trans-(4-nitrophenyl) N-[3-[[2-[tert-butyl(dimethyl)silyl]oxy-1,1-dimethyl-ethyl]sulfamoyl]-4-[2-[4-(isopropoxycarbonylamino)cyclohexyl]thiazol-5-*

yl][phenyl]carbamate (88.5 mg, 112 μ mol, 1 *eq.*) in DCM (1 mL) and the mixture was stirred at 25°C for 0.5 hr. The reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (10 mL x 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was purified by prep-TLC (SiO₂, Petroleum ether: Ethyl acetate = 1:1) to give *trans-isopropyl N-[4-[5-[4-(benzylcarbamoylamino)-2-[[2-[tert-butyl(dimethyl)silyl]oxy-1,1-dimethyl-ethyl]sulfamoyl]phenyl]thiazol-2-yl]cyclohexyl]carbamate* (93 mg, crude) as a yellow gum. ESI [M+H] = 758.4

Preparation of Ex. 74.



A mixture of *trans-isopropyl N-[4-[5-[4-(benzylcarbamoylamino)-2-[[2-[tert-butyl(dimethyl)silyl]oxy-1,1-dimethyl-ethyl]sulfamoyl]phenyl]thiazol-2-yl]cyclohexyl]carbamate* (84.9 mg, 112 μ mol, 1 *eq.*) in AcOH (0.5 mL)/THF (0.5 mL)/H₂O (0.5 mL) was stirred at 80°C for 0.5 hr. Then the mixture was concentrated and the residue was purified by prep-HPLC (TFA condition) to give *trans-isopropyl N-[4-[5-[4-(benzylcarbamoylamino)-2-[(2-hydroxy-1,1-dimethyl-ethyl)sulfamoyl]phenyl]thiazol-2-yl]cyclohexyl]carbamate* (5.86 mg, 9.10 μ mol, 8.13% yield, 100% purity) as a yellow solid. ¹H NMR (400MHz, METHANOL-d₄) δ = 8.25 (d, J=2.6 Hz, 1H), 7.81 - 7.66 (m, 2H), 7.40 - 7.30 (m, 5H), 7.28 - 7.22 (m, 1H), 4.82 (td, J=6.0, 12.5 Hz, 1H), 4.41 (s, 2H), 3.45 (br t, J=11.6 Hz, 1H), 3.28 (s, 2H), 3.00 (br t, J=11.8 Hz, 1H), 2.23 (br d, J=13.2 Hz, 2H), 2.11 - 2.00 (m, 2H), 1.77 - 1.60 (m, 2H), 1.48 - 1.32 (m, 2H), 1.22 (br d, J=6.1 Hz, 6H), 1.05 (s, 6H). ESI [M+H] = 644.3

Example 75. Compound Primary Screening

1. BACKGROUND

Primary screening was a phenotypic screen that utilized the synthetic lethal interaction between AID and RAD51 to identify compounds that were both potent and on target. AID expressing cells are dependent upon RAD51 for survival; inhibiting RAD51 in AID positive cells results in a cytotoxic effect. Based on such an effect, compounds that were potent in AID positive cells and were significantly less potent in AID negative cells were identified.

2. MATERIALS AND SUPPLIES

Plastic ware and consumables needed for this experiment include: Cell Culture media; Evaporation Buffer media; 100% DMSO; 96 well U-bottom sterile culture plates; 250mL bottle; 1.5mL Opaque amber epi tubes; Epi Tube rack; 300mL reservoirs; 25mL reservoir; 25mL serological pipette tips; 5mL serological pipette tips P1000 Pipette Tips; and P200 Pipette Tips.

Equipment needed for this experiment include: Viaflo 384 liquid handler; Eppendorf serological pipette; Eppendorf P1000 Pipette; and Eppendorf P200 Pipette

Daudi Cell Culture and WI-38 Cell Cultures were also needed for this experiment.

Lastly, compounds (*e.g.*, the compounds of this disclosure) to be tested are needed.

3. PROCEDURE

All steps were performed in a sterile environment inside the Biosafety cabinet.

The first step was to set up a cell killing assay in the Daudi cell line (AID positive). A 96 well u-bottom plate was prepared by writing the experiment number, plate number, date and initials in the top right corner of the plate lid. With a sterile 300ml reservoir, and 25ml serological pipette, evaporation buffer media was pipetted into reservoir in 25ml increments. Using the liquid handler, 150ul of evaporation buffer media was pipetted from reservoir into rows A and H, and Columns 1 and 12 of the 96 well u-bottom plate. Cell cultures were counted to obtain the density of cells per ml, and the culture viability. The cell density information was used to obtain 1,000,000 cells from culture using a 5mL serological pipette into an epi tube. The cell density information from the culture was used to calculate the number of cells and volume of media needed for the assay to seed 1250 cells in 130ul of media per available culture well in the 96 well u-bottom plate. Rows B through F were used for cells (50 wells in total), with row G left for an empty media control. The calculation was overestimated by 10mL to account for the dead volume in the 300ml reservoir. Once the media volume was calculated, the appropriate volume of media was pipetted in 25mL increments into the 250mL bottle using a 25mL serological pipette. The 250ml bottle was capped tightly, and placed into a 37°C water bath for 2 minutes. While the culture media was warming, 10mL of fresh media was pipetted from the 500mL culture media bottle into a sterile 25mL reservoir. Using the Eppendorf multichannel pipette, 130ul of media was pipetted from the 25mL reservoir into row G of the 96 well u-bottom plate. Once the 250mL bottle of media was warmed, the volume of culture needed was pipetted into the bottle, and mixed gently with a 25mL serological pipette as to not create bubbles, and then the contents of the bottle were pipetted into a new 300mL reservoir. Using the liquid handler, 130ul of

culture was pipetted from the 300mL reservoir into rows B through F of the 96 well u-bottom plate. Once the culture was added, the plate was placed into a 37°C incubator until the compound master plate was prepared for use.

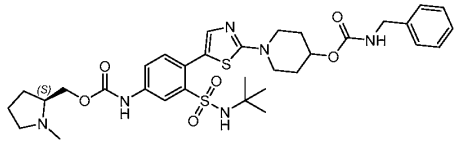
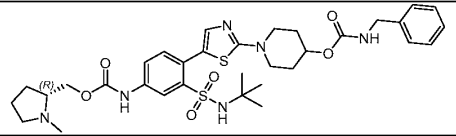
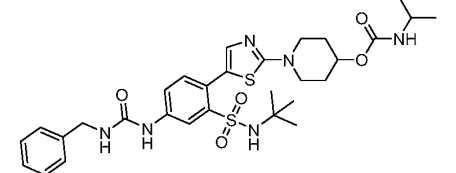
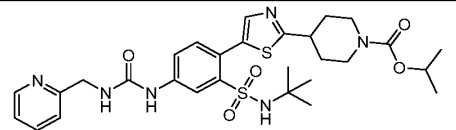
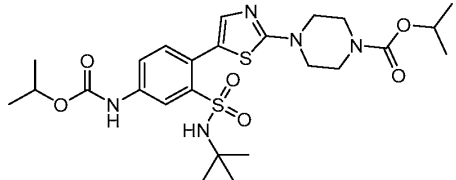
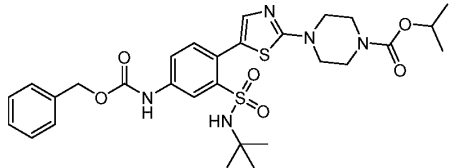
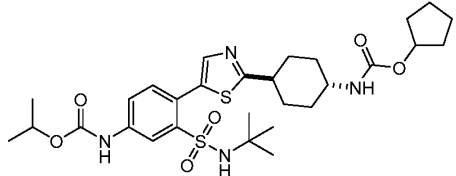
Two 96 well u-bottom plates were prepared by writing the master plate name in the upper right corner of the plate lid. Labeling one DMSO master and the other Media Master. The compounds of interest were obtained from the laboratory freezer, and placed into a 25 well storage box with a lid, and set the box aside. The compounds were vortexed after thawing but before use. Using an automatic multichannel pipette, 20ul of 100% DMSO was pipetted into wells B3-B11 through G3-G11 of the DMSO master plate. For each compound on the master plate, 50ul of the compound were pipetted in the appropriate well of row 2 (reference plate map to determine appropriate well). A serial dilution was prepared beginning by aspirating 20ul from row 2 and mixing with row 3, repeating until row 11 was reached. Using the liquid handler, 194ul of Daudi media was dispensed into wells B2-B11 through G2-G11 of the Media master plate. Using the liquid handler, 6ul from the DMSO master plate was aspirated and dispensed into the media master plate, mixing 100ul twice.

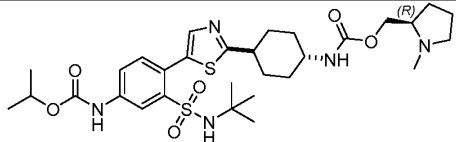
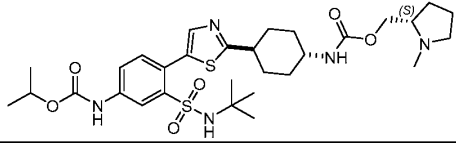
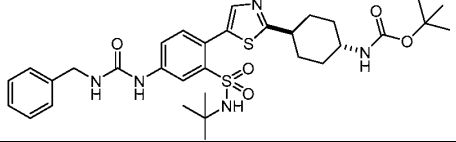
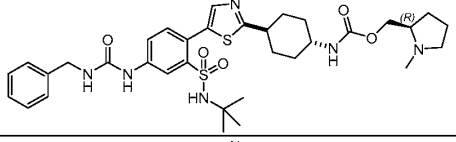
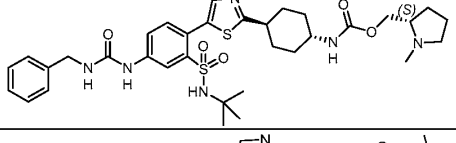
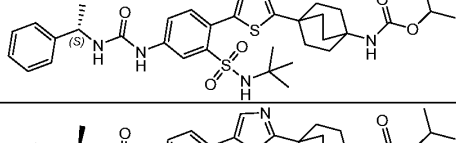
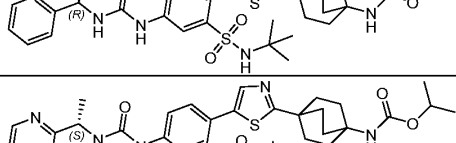
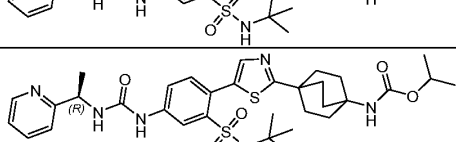
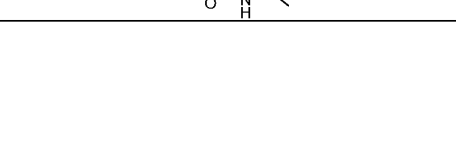
Compounds from master plate were then added to the culture plate. The culture plates were removed from the incubator, and set inside the biosafety cabinet. Using a liquid handler, 20ul from wells B2 to B11 through G2 to G11 of master plate were aspirated, and dispensed into wells B2 to B11 through G2 to G11 of culture plate. This set was continued with each culture plate. Once the culture plates acquired their 20ul of compound dilutions, they were placed back into the incubator, until their reads on Day 7 of experiment. Cell death was measured on Day 7 of the experiment using Cell-Titer Glo and a Promega Plate reader.

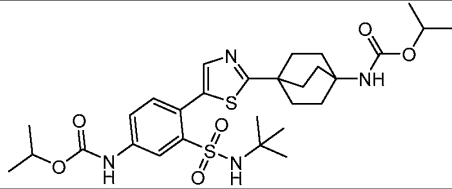
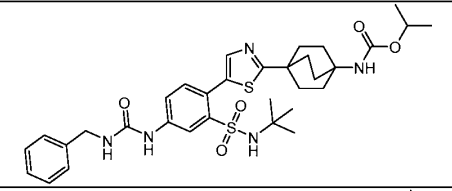
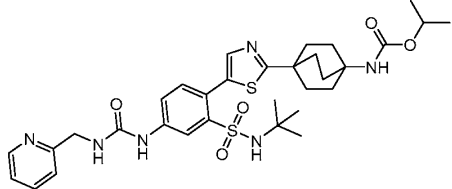
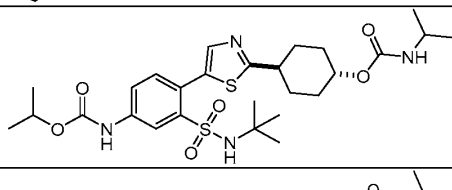
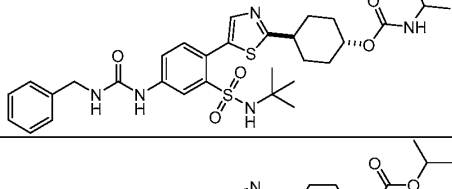
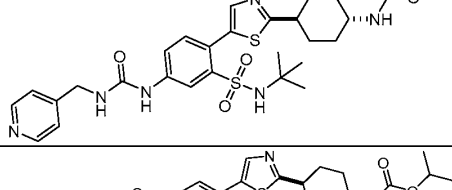
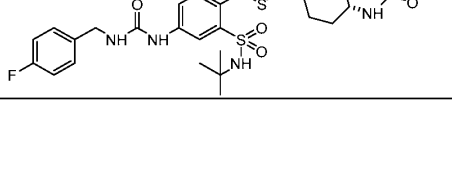
Percent cell death and EC_{50} values were calculated by comparing the cell viability of the compound treated wells to the non-treated wells. Normalized RLU values were obtained by subtracting the media well values from each of the wells in the same column, and then dividing that value by the DMSO treated cells values. The percent kill was then calculated by subtracting the normalized RLU value from 1 and multiplying by 100. The average normalized percent kill value and standard error of the mean was then calculated. The kill values were then inputted into Prism with the corresponding standard errors. In Prism a non-linear regression line was plotted with the data points using a semi-log scale, and the EC_{50} value was calculated. For compounds that showed good potency in the Daudi cell line, the assay was repeated using WI-38 cells (AID negative).

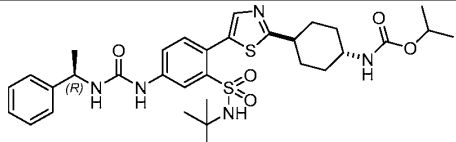
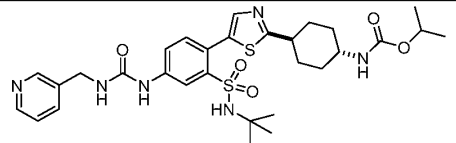
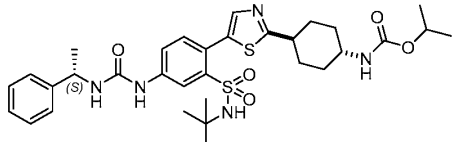
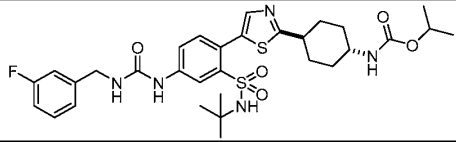
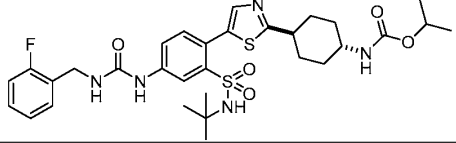
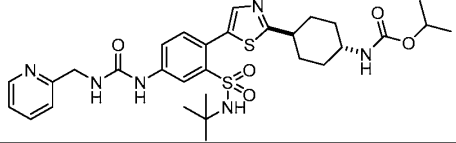
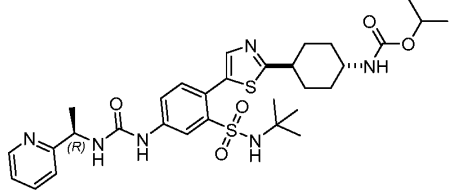
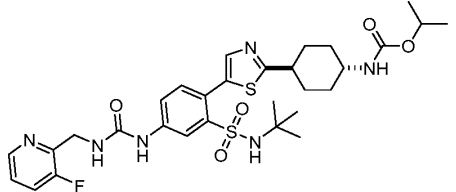
Screening Data

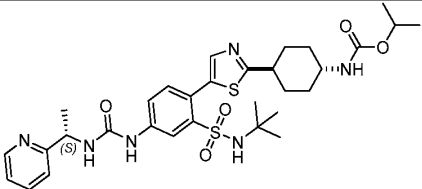
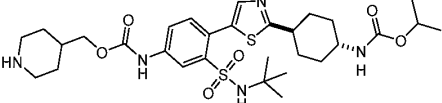
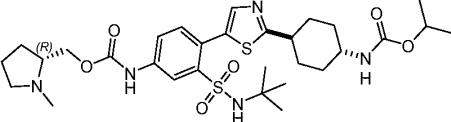
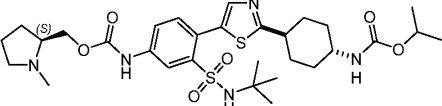
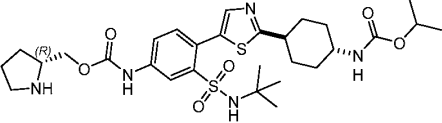
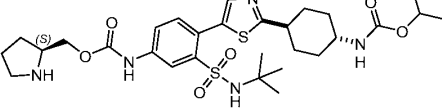
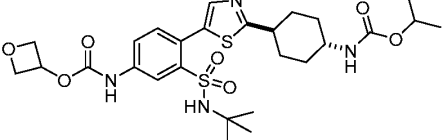
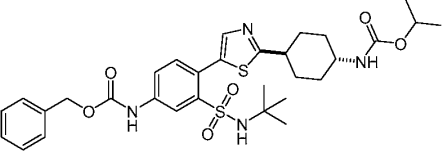
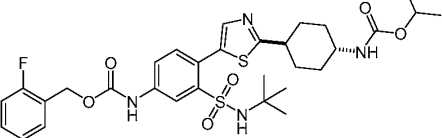
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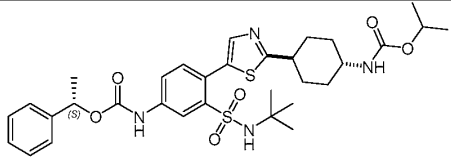
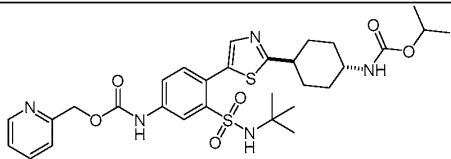
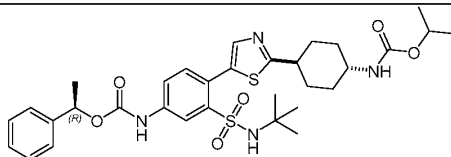
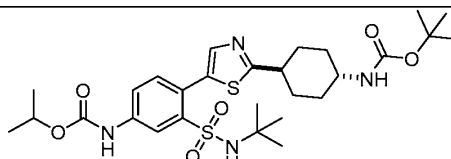
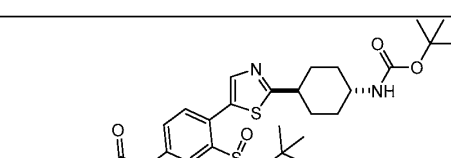
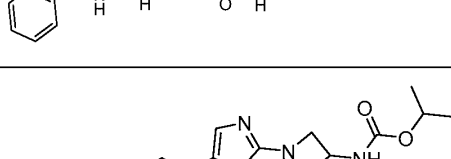
Compound No.	Structure	AID+ EC ₅₀ (μM) A = ≤ 0.1 μM B = ≤ 1 μM C = > 1 μM ND = Not Determined	AID- EC ₅₀ (μM) A = ≤ 0.1 μM B = ≤ 1 μM C = > 1 μM ND = Not Determined
Ex. 1		C	ND
Ex. 2		C	ND
Ex. 3		A	C
Ex. 4		C	C
Ex. 5		C	ND
Ex. 6		C	ND
Ex. 7		B	ND

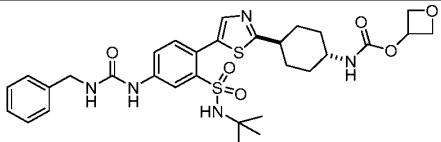
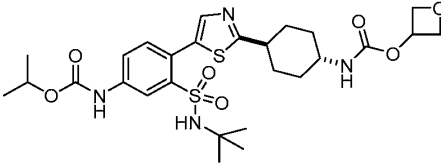
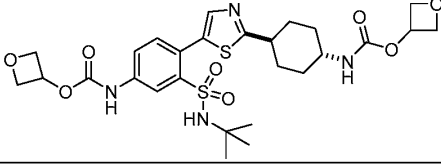
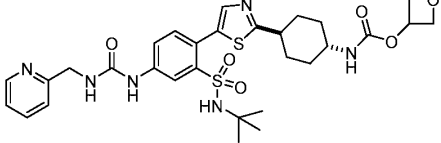
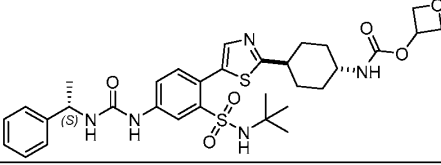
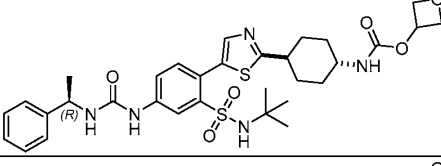
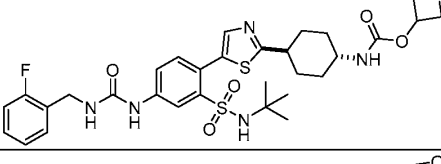
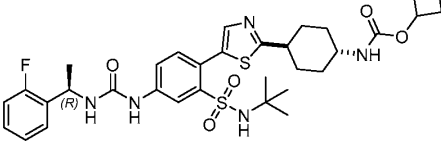
Compound No.	Structure	AID+ EC ₅₀ (μM) A = ≤ 0.1 μM B = ≤ 1 μM C = > 1 μM ND = Not Determined	AID- EC ₅₀ (μM) A = ≤ 0.1 μM B = ≤ 1 μM C = > 1 μM ND = Not Determined
Ex. 8		C	ND
Ex. 9		B	ND
Ex. 10		A	C
Ex. 11		B	ND
Ex. 12		B	ND
Ex. 13		A	C
Ex. 14		A	C
Ex. 15		A	C
Ex. 16		A	C

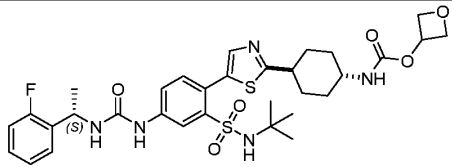
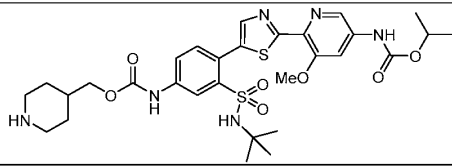
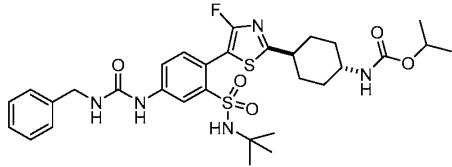
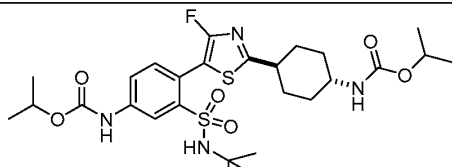
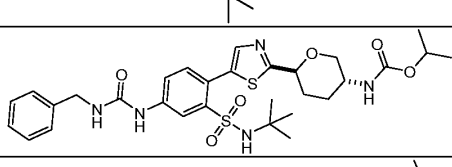
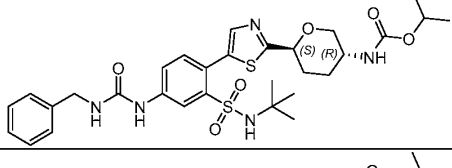
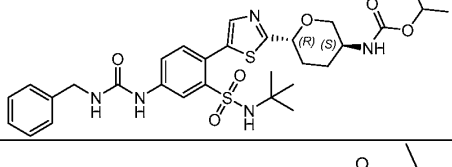
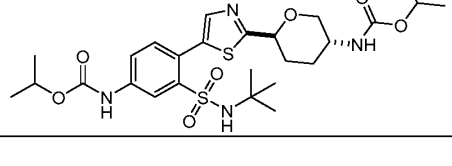
Compound No.	Structure	AID+ EC ₅₀ (μM) A = ≤ 0.1 μM B = ≤ 1 μM C = > 1 μM ND = Not Determined	AID- EC ₅₀ (μM) A = ≤ 0.1 μM B = ≤ 1 μM C = > 1 μM ND = Not Determined
Ex. 17		B	C
Ex. 18		A	C
Ex. 19		A	C
Ex. 20		C	ND
Ex. 21		A	ND
Ex. 22		B	ND
Ex. 23		A	ND

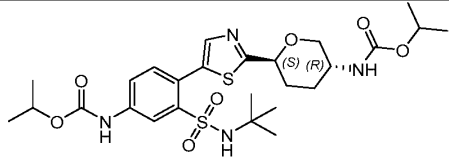
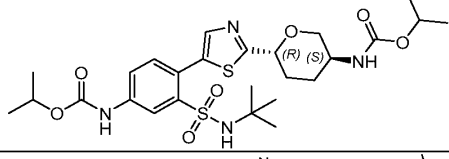
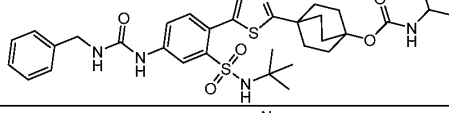
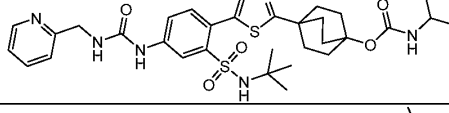
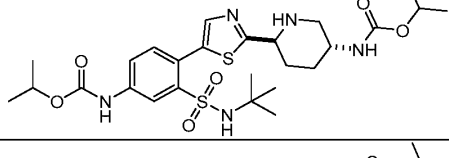
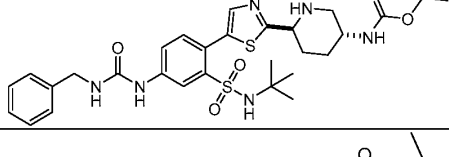
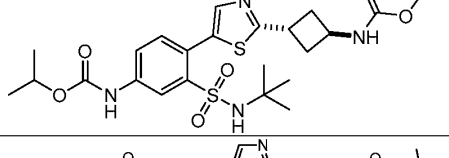
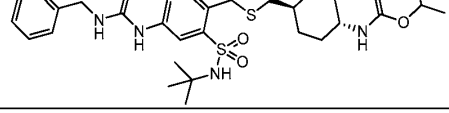
Compound No.	Structure	AID+ EC ₅₀ (μM) A = ≤ 0.1 μM B = ≤ 1 μM C = > 1 μM ND = Not Determined	AID- EC ₅₀ (μM) A = ≤ 0.1 μM B = ≤ 1 μM C = > 1 μM ND = Not Determined
Ex. 24		A	C
Ex. 25		A	ND
Ex. 26		A	C
Ex. 27		A	C
Ex. 28		A	ND
Ex. 29		A	C
Ex. 30		A	C
Ex. 31		A	C

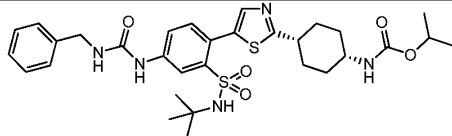
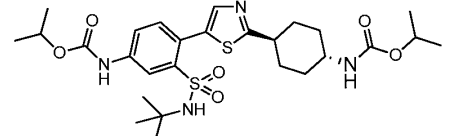
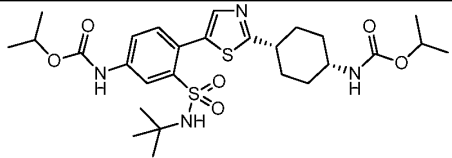
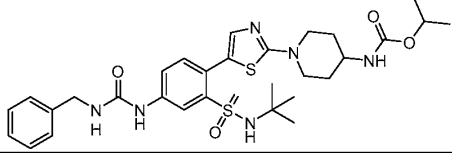
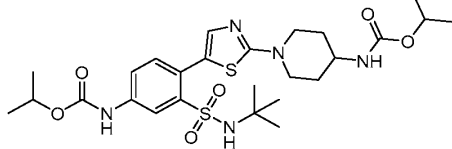
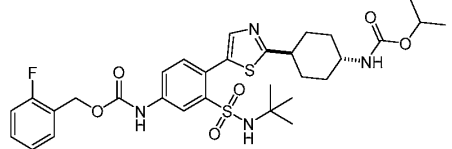
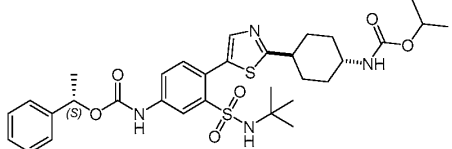
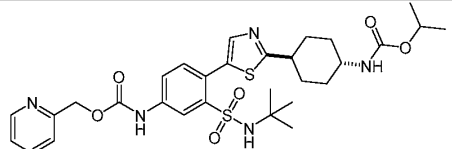
Compound No.	Structure	AID+ EC₅₀ (μM) A = ≤ 0.1 μM B = ≤ 1 μM C = > 1 μM ND = Not Determined	AID- EC₅₀ (μM) A = ≤ 0.1 μM B = ≤ 1 μM C = > 1 μM ND = Not Determined
Ex. 32		A	C
Ex. 33		C	ND
Ex. 34		B	ND
Ex. 35		B	ND
Ex. 36		B	ND
Ex. 37		B	ND
Ex. 38		A	C
Ex. 39		A	C
Ex. 40		A	C

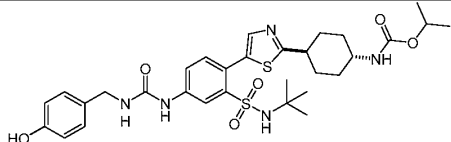
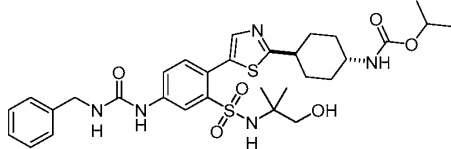
Compound No.	Structure	AID+ EC ₅₀ (μM) A = ≤ 0.1 μM B = ≤ 1 μM C = > 1 μM ND = Not Determined	AID- EC ₅₀ (μM) A = ≤ 0.1 μM B = ≤ 1 μM C = > 1 μM ND = Not Determined
Ex. 41		A	C
Ex. 42		A	C
Ex. 43		B	C
Ex. 44		C	ND
Ex. 45		A	ND
Ex. 46		C	C
Ex. 47		A	C

Compound No.	Structure	AID+ EC ₅₀ (μM) A = ≤ 0.1 μM B = ≤ 1 μM C = > 1 μM ND = Not Determined	AID- EC ₅₀ (μM) A = ≤ 0.1 μM B = ≤ 1 μM C = > 1 μM ND = Not Determined
			
Ex. 48		B	C
Ex. 49		B	C
Ex. 50		A	C
Ex. 51		A	C
Ex. 52		A	C
Ex. 53		A	C
Ex. 54		A	C

Compound No.	Structure	AID+ EC ₅₀ (μM) A = ≤ 0.1 μM B = ≤ 1 μM C = > 1 μM ND = Not Determined	AID- EC ₅₀ (μM) A = ≤ 0.1 μM B = ≤ 1 μM C = > 1 μM ND = Not Determined
Ex. 55		A	C
Ex. 56		B	ND
Ex. 57		A	C
Ex. 58		B	C
Ex. 59		A	C
Ex. 59A		B	C
Ex. 59B		A	C
Ex. 60		B	C

Compound No.	Structure	AID+ EC ₅₀ (μM) A = ≤ 0.1 μM B = ≤ 1 μM C = > 1 μM ND = Not Determined	AID- EC ₅₀ (μM) A = ≤ 0.1 μM B = ≤ 1 μM C = > 1 μM ND = Not Determined
Ex. 60A		C	C
Ex. 60B		B	C
Ex. 61		C	C
Ex. 62		C	C
Ex. 63		B	ND
Ex. 64		A	C
Ex. 65		B	C
Ex. 66A		A	C

Compound No.	Structure	AID+ EC ₅₀ (μM) A = ≤ 0.1 μM B = ≤ 1 μM C = > 1 μM ND = Not Determined	AID- EC ₅₀ (μM) A = ≤ 0.1 μM B = ≤ 1 μM C = > 1 μM ND = Not Determined
Ex. 66B		B	ND
Ex. 67A		B	C
Ex. 67B		C	ND
Ex. 68		B	ND
Ex. 69		C	ND
Ex. 70		A	C
Ex. 71		A	C
Ex. 72		A	C

Compound No.	Structure	AID+ EC ₅₀ (μM) A = ≤ 0.1 μM B = ≤ 1 μM C = > 1 μM ND = Not Determined	AID- EC ₅₀ (μM) A = ≤ 0.1 μM B = ≤ 1 μM C = > 1 μM ND = Not Determined
Ex. 73		A	C
Ex. 74		A	C

Example 76. Bi-directional Caco-2 permeability

Bi-directional Caco-2 permeability was assayed. Caco-2 cells were seeded onto permeable polycarbonate supports and allowed to differentiate for about 3 weeks prior to being used in the assays. The cells were then exposed to the compounds from either the apical or basolateral sides and incubated at 37C for up to 90 minutes under light agitation. Compound transport was then measured using LC/MS/MS analysis at 30, 60, and 90 minutes.

Table 2

Example No.	Caco-2 Results				
	AB Papp (cm/sec x 10 ⁶)	BA Papp (cm/sec x 10 ⁶)	BA/AB Ratio	AB Recovery %	BA Recovery %
Ex. 5	5.9	2.2	0.4	34.7	80.8
Ex. 7	1.7	2.1	1.2	55.9	92
Ex. 10	1.2	1.5	1.3	59.9	87.2
Ex. 17	2.8	2.1	0.8	47.2	81.9
Ex. 20	9.4	10.4	1.1	44.8	96.6
Ex. 21	3.6	10.7	3	58.6	78.3
Ex. 22	1.1	21	18.7	83.1	89
Ex. 27	0.7	0.5	0.7	92	107.1
Ex. 28	1.9	3.3	1.7	66.9	81

Example No.	Caco-2 Results				
	AB Papp (cm/sec x 10 ⁶)	BA Papp (cm/sec x 10 ⁶)	BA/AB Ratio	AB Recovery %	BA Recovery %
Ex. 29	10.9	24.1	2.2	93.9	90.9
Ex. 30	11.5	15.7	1.4	79.8	115.6
Ex. 31	12.8	13.6	1.1	70.5	92.3
Ex. 34	0.4	45.2	103.9	98.2	96.8
Ex. 35	0.4	41	99.1	98.8	107.5
Ex. 38	17.9	22.9	1.3	73.3	82.3
Ex. 44	3.2	4.2	1.3	36.2	69.4
Ex. 45	7.6	10.8	1.4	73.6	84.4
Ex. 47	8.7	12.4	1.4	65.3	80.7
Ex. 48	23.1	16	0.7	80.1	90.3
Ex. 50	2	29.1	14.6	87.7	98.1
Ex. 51	9.9	10.5	1.1	65	85.7
Ex. 52	7.4	10.9	1.5	64.1	91.7
Ex. 53	9.3	9.7	1	63.1	90.9
Ex. 55	6.5	7	1.1	65.2	83.8
Ex. 57	1.3	3.5	2.7	61.9	86.8
Ex. 58	5.1	3.4	0.7	52.3	83.5
Ex. 59	3.1	15	4.8	61.5	91.5
Ex. 59A	3.1	9.6	3.1	55.6	85.5
Ex. 59B	4.6	9.7	2.1	56.2	82
Ex. 60	15.6	13.3	0.9	59.8	90.8
Ex. 60A	12	11.2	0.9	55.3	86
Ex. 60B	11.6	13.5	1.2	51.2	84.3
Ex. 63	10.5	26.7	2.5	83.6	90

Example No.	Caco-2 Results				
	AB Papp (cm/sec x 10 ⁶)	BA Papp (cm/sec x 10 ⁶)	BA/AB Ratio	AB Recovery %	BA Recovery %
Ex. 64	2.2	27.4	12.5	79.7	95.9
Ex. 66A	2.9	3.9	1.4	64.9	81.2
Ex. 67A	10.5	6.9	0.7	50.7	78.6

Example 77. Human Liver Microsome Stability

The stability of the claimed compounds was determined in the presences of human liver microsomes. The compounds were incubated with the microsomes at 37 °C for 45 minutes. Samples were analyzed using LC-MS/MS. Data analysis included half-life, clearance rate, and the percentage of hepatic blood flow (%QH) for each of the compounds in the different species. Below are liver microsome assay data of representative compounds, which show that the claimed compounds have superior metabolic stability.

Table 3

	Human Liver Microsome Stability		
	Half Life (min)	Clearance (μg/min/mg)	% QH
Ex. 29	20.5	68.0	78.8
Ex. 31	22.4	61.9	77.3
Ex. 66A	77.6	18.2	49.6
Ex. 67A	>300	<4.6	<20.3

Example 78. Cell Line Screen

The activity of the claimed compounds was measured in a variety of cell lines with different expression levels of activation induced cytidine deaminase (AICDA). The potency assay was repeated in all of the listed cell lines and the EC₅₀ values recorded.

Table 4

Cell Line (Cancer Type)	AICDA Expression	EC ₅₀ (nM) Ex. 29	EC ₅₀ (nM) Ex. 31	EC ₅₀ (nM) Ex. 66A	EC ₅₀ (nM) Ex. 67A
Daudi (Lymphoma)	High	43	20	18	311
WSU-FSCCL (Lymphoma)	Negative	67	<40	25	344
U-698-M (Lymphoma)	High	113	31	88	791
CCRF-SB (Leukemia)	High	1283	2164	183	932
KYSE-70 (Head and Neck)	Low	4660	4701	2639	2629
SNU-1	Negative	n.d.	n.d.	609	2927

Cell Line (Cancer Type)	AICDA Expression	EC ₅₀ (nM) Ex. 29	EC ₅₀ (nM) Ex. 31	EC ₅₀ (nM) Ex. 66A	EC ₅₀ (nM) Ex. 67A
(Gastric)					
KG-1 (Leukemia)	Negative	>10000	8785	3067	2995
KYSE-510 (Head and Neck)	Negative	>10000	>10000	4516	3403
SNU-5 (Gastric)	Low	n.d.	n.d.	2941	3845
TOV-1120D (Ovary)	Negative	9172	n.d.	2377	4924
OV56 (Ovary)	Low	9086	n.d.	5944	7228
ARPE19/HPV16 (HPV Immortalized RPE)	Negative	>10000	>10000	>10000	>10000
WI-38 (Normal Human Lung Fibroblast)	Negative	>10000	>10000	>10000	>10000

n.d. not determined

Example 79. Pharmacokinetic (PK)

PK studies in mice were used to determine the fate of the compounds in a whole organism. Rats were treated with the compounds either orally or via IV at the indicated doses and followed for up to 24 hours. Plasma samples were taken at different time points and analyzed by LC-MS.

Table 5

po @ 80 mg/kg (Formulation: 30% PEG400, 10% Vitamin E TPGS in water)		Ex. 29	Ex. 31	Ex. 66A	Ex. 67A
Rat Female	T _{1/2} (hr)	4.66	4.75	2.59	11.5
	F (%) @ 5 mg/kg	8.39	2.77	3.31	86.5
Rat Male	T _{1/2} (hr)	3.97	3.79	1.86	6.46
	F (%) @ 5 mg/kg	3.69	1.49	2.55	46.9

Example 80. Compound 67A Activity in Pancreatic Cancer Cell Lines

Cells were harvested during the logarithmic growth period and cells were counted using Count-star. The cell concentrations were adjusted to 4.44×10^4 cells/mL with respective culture medium. 90 μ L cell suspensions was added to two 96-well plates (plates A and B) with the final cell density of 4×10^3 cells/well (cell concentration were adjusted according to the data base or density optimization assay). One plate was used for the day 0 reading, the second plate was treated with compound and incubated for seven days with medium replacement at 72 hours.

For the day 0 reading, 10 μ L of culture medium was added to each well of plate A. The vehicle control was 0.25 % v/v DMSO. The plate was equilibrated and its content was at room temperature for approximately 30 minutes. 50 μ L CellTiter-Glo reagent was added to each well. The contents were mixed for 5 minutes on an orbital shaker to induce cell lysis. The plate was allowed to incubate at room temperature for 20 minutes to stabilize luminescent signal. Luminescence (for day 0) was recorded using EnVision Multi Label Reader.

For the day 7 reading, a 10 $\times$ solution of test article was prepared (100 μ M of test article in media with 3.16-fold serial dilutions was used to achieve 9 dose levels). 10 μ L (10 $\times$) of Compound 67A was dispensed into each well (triplicate for each drug concentration) of plate B. The DMSO final concentration in culture medium was 0.25% [v/v]).

The test plate B was incubated for 72 hours in the humidified incubator at 37°C with 5% CO₂. 80 μ L of media containing Compound 67A was aspirated with liquid handling Biomek FXP. 80 μ L fresh culture media containing 1 $\times$ Compound 67A solutions was added to each well. The mixture was incubated for an additional 96 hours in a humidified incubator at 37°C with 5% CO₂ (168 hours total), and then measured by CTG assay. The plate was equilibrated and its content brought to room temperature for approximately 30 minutes. 50 μ L of CellTiter-Glo reagent was added to each well. The contents were mixed for 5 minutes on an orbital shaker to induce cell lysis. The plates were allowed to incubate at room temperature for 20 minutes to stabilize the luminescent signal. Luminescence was then recorded.

The data was then displayed graphically using GraphPad Prism 5.0. Absolute IC₅₀ (EC₅₀), was calculated by fitting a dose-response curve using a nonlinear regression model with a sigmoidal dose response. The formula for calculating surviving rate is shown below and the absolute IC₅₀ (EC₅₀) was then calculated according to the dose-response curve generated by GraphPad Prism 5.0.

$$\text{The surviving rate (\%)} = \frac{(\text{LumTest article} - \text{LumMedium control})}{(\text{LumNontreated} - \text{LumMedium control})} \times 100\%$$

For IC₅₀ values shown in Table 6, “A” means IC₅₀ < 10 μ M; “B” means IC₅₀ ranging between 10 μ M and 25 μ M; “C” means IC₅₀ ranging between 25 μ M and 35 μ M; “D” means IC₅₀ ranging between 35 μ M and 50 μ M; “E” means IC₅₀ > 50 μ M; “Nd” means Not determined.

Table 6

Cell Line	IC50 (μM)
AsPC-1	C
BxPC-3	B
Capan-1	E
Capan-2	A
CFPAC-1	C
HPAF-II	B
HuP-T4	B
KP4	C
MIA PaCa-2	B
Panc 05.04	C
Panc 10.05	D
PANC-1	D
PL45	C
SU.86.86	Nd
SW1990	E

Example 81. PDX model 1

Activity of Compound 67A ("67A") was assessed in 3 different mouse PDX models with various levels of AID expression (low, medium, and high) (Figure 1). All models showed greater than 50% tumor growth inhibition with 67A treatment at 80 mg/kg QD (Low: 63%, Medium: 104%, high: 79%). For the medium expressing PDX model, the activity of 67A at two additional doses (1 mg/kg and 40 mg/kg) was examined. A response of 36% TGI at 1 mg/kg QD and a response of 96% TGI at 40 mg/kg QD was observed.

Next, a cross over experiment (Table 7) was performed to determine the activity of 67A in large, established tumors. On day 46 of treatment, vehicle treated and 1 mg/kg QD treated mice from the medium expressing PDX model were re-randomized into three treatment groups: vehicle, 1 mg/kg QD, and 80 mg/kg QD (Figure 2A). Tumor regression in the now 80 mg/kg treated cohort with a %TGI of 137 was observed.

The 40 and 80 mg/kg treatment groups were also re-randomized into three new groups: 80 mg/kg QD, 14 day dosing holiday followed by 80 mg/kg QD, and 21 day dosing holiday followed by 80 mg/kg QD (Figure 2B). During drug holiday, the tumors steadily began to grow at the same doubling rate as the vehicle control, and tumor growth was observed in the animals with tumors. Once treatment resumed with Compound 67A, the growth of the tumors was suppressed. The 80 mg/kg QD treatment group continued to show repressed tumor growth with a final %TGI of 96.

Table 7

Model	Tumor Characterization	Passage Number	AICDA Fold Gene Expression*
Model 1	Primary; Adenocarcinoma; Poorly Differentiated; Stage II	6	0.86
Model 2	Primary; Adenocarcinoma; Moderately Differentiated; Stage II	6	5.85
Model 3	Primary; Adenocarcinoma; Moderately Differentiated; Stage IV	5	9.85

*Fold change in expression determined by comparing the individual model RPKM score to the mean RPKM score of the entire PDX collection.

Compound 67A anti-tumor activity in Model 1

Engrafted mice were treated with either vehicle or Compound 67A at 80 mg/kg QD for 52 days. Tumor volumes were measured twice weekly and followed over the course of the experiment. The results demonstrated that Compound 67A treatment was successful (see Figures 3A and 3B). Percent tumor growth inhibition was calculated for each Compound 67A treated animal on day 52.

Compound 67A anti-tumor activity in Model 2, Part 1

Engrafted mice were treated with either vehicle or Compound 67A at 1, 40, or 80 mg/kg QD for 45 days. Tumor volumes were measured twice weekly and followed over the course of the experiment. The results demonstrated that Compound 67A treatment was successful (see Figures 4A and 4B). Percent tumor growth inhibition was calculated for each Compound 67A treated animal on day 45.

Compound 67A anti-tumor activity in Model 2, Part 2

Animals treated with vehicle and 1 mg/kg QD from Model 2, Part 1 were re-randomized and treated with either vehicle or Compound 67A at 1 mg/kg QD or 80 mg/kg QD (Figure 2A). Tumor volumes were measured twice weekly and followed for 49 days (Figure 6A). Change in tumor volume on day 49 as compared to day 0 was calculated for vehicle and Compound 67A at 80 mg/kg treated animals (Figure 6B). Progression free

survival was measured as stasis of tumor volume and graphed for vehicle and Compound 67A at 80 mg/kg treated animals (Figure 6C).

Compound 67A anti-tumor activity after dosing holidays in Model 2, Part 3

Animals treated with Compound 67A at 40 and 80 mg/kg QD from Model 2, Part 1 were re-randomized and treated with either vehicle or Compound 67A at 80 mg/kg QD continuously, Compound 67A at 80 mg/kg after a 14 day dosing holiday, or Compound 67A at 80 mg/kg after a 21 day dosing holiday (Figure 2B). Tumor volumes were measured twice weekly and followed for 49 days. The results demonstrated that Compound 67A treatment was successful (see Figures 7A-7C).

Compound 67A anti-tumor activity in Model 3

Engrafted mice were treated with either vehicle or Compound 67A at 80 mg/kg QD for 33 days. Tumor volumes were measured twice weekly and followed over the course of the experiment. The results demonstrated that Compound 67A treatment was successful (see Figures 3A and 3B). Percent tumor growth inhibition was calculated for each Compound 67A treated animal on day 33.

Compound 67A showed anti-cancer activity in all Models (i.e. Model 1, Model 2, and Model 3) of pancreatic cancer tested with a mean % TGI ranging from 62% to 104%. Compound 67A is also active in large established tumors, and dosing holidays did not lead to the development of resistance. In Model 2 one partial responder and one tumor-free responder was observed. The data demonstrate that 67A has anti-cancer activity in multiple preclinical models of pancreatic cancer.

Example 82. PDX model 2

Activity of Compound 67A ("67A") was assessed in 3 different mouse PDX models of pancreatic cancer engrafted onto the flanks of immunocompromised mice. The three models tested were Model A (CTG-0955), Model B (CTG-1462), and Model C (CTG-1295). Tumors were allowed to reach a mean tumor volume of 500 mm³ prior to dosing. The dosing groups were as follows:

- Vehicle;
- Compound 67A at 80 mg/kg orally, once daily;
- Compound 67A at 80 mg/kg orally, once daily for four weeks, followed by a dosing holiday until tumors reach 1000 mm³, at which point administration of Compound 67A at 80 mg/kg orally, once daily is reinitiated;
- Compound 67A at 80 mg/kg orally, daily every other week; and

- Compound 67A at 80 mg/kg orally, every other day.

All models were measured twice per week and showed anti-tumor activity in larger tumors, similar to the observations of Example 80. Dosing of Compound 67A daily resulted in greater anti-tumor activity in comparison to every other day dosing. Reinitiating treatment with Compound 67A after a dosing holiday resulted in slowed tumor growth or tumor shrinkage, depending on the initial sensitivity of the model.

Compound 67A anti-tumor activity in Model A

The dosing groups were analyzed to determine %TGI relative to continuous dosing in comparison to every other day dosages (FIG. 8A), as well as comparison of tumor volume (FIG. 8B). Tumor regression in the cohort treated with a continuous dosage of Compound 67A at 80 mg/kg with a %TGI of 52 was observed. Tumor regression in the cohort treated with an every other day dosage of Compound 67A at 80 mg/kg with a %TGI of 20 was observed. Tumor regression in the cohort with a 200mm³ tumor treated daily with Compound 67A with a %TGI of 64 was observed. Tumor regression in the cohort with a 500mm³ tumor treated with Compound 67A with a %TGI of 52 was observed.

Compound 67A anti-tumor activity in Model B

The dosing groups were analyzed to determine %TGI relative to continuous dosing in comparison to every other day dosages (FIG. 9A), comparison of tumor volume (FIG. 9B), and analysis of post holiday dosing (FIG. 9C). Tumor regression in the cohort treated with a continuous dosage of Compound 67A at 80 mg/kg with a %TGI of 68 was observed. Tumor regression in the cohort treated with an every other day dosage of Compound 67A at 80 mg/kg with a %TGI of 54 was observed. Tumor regression in the cohort with a 200mm³ tumor treated daily with Compound 67A with a %TGI of 79 was observed. Tumor regression in the cohort with a 500mm³ tumor treated with Compound 67A with a %TGI of 68 was observed.

Treatment with oral Compound 67A administered daily for four weeks at 80 mg/kg showed a decrease in tumor growth. After four weeks, a dosing holiday was implemented until the tumor growth reached 1000 mm³ (i.e., about 6 days for Model B). At this point, administration of Compound 67A daily at 80 mg/kg was resumed. Post dosing holiday treatment exhibited a decrease in tumor progression (FIG. 9D).

Compound 67A anti-tumor activity in Model C

The dosing groups were analyzed to determine %TGI relative to continuous dosing in comparison to every other day dosages (FIG. 10A), comparison of tumor volume (FIG. 10B),

and analysis of post holiday dosing (FIG. 10C). Tumor regression in the cohort treated with a continuous dosage of Compound 67A at 80 mg/kg with a %TGI of 93 was observed. Tumor regression in the cohort treated with an every other day dosage of Compound 67A at 80 mg/kg with a %TGI of 65 was observed. Tumor regression in the cohort with a 200mm³ tumor treated daily with Compound 67A with a %TGI of 104 was observed. Tumor regression in the cohort with a 500mm³ tumor treated with Compound 67A with a %TGI of 93 was observed.

Treatment with oral Compound 67A administered daily for four weeks at 80 mg/kg showed a decrease in tumor growth. After four weeks, a dosing holiday was implemented until the tumor growth reached 1000 mm³ (i.e., about 48 days for Model C). At this point, administration of Compound 67A daily at 80 mg/kg was resumed. Post dosing holiday treatment exhibited a decrease in tumor progression (FIG. 10D).

EQUIVALENTS

The details of one or more embodiments of the disclosure are set forth in the accompanying description above. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, the preferred methods and materials are now described. Other features, objects, and advantages of the disclosure will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms include plural referents unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. All patents and publications cited in this specification are incorporated by reference.

The foregoing description has been presented only for the purposes of illustration and is not intended to limit the disclosure to the precise form disclosed, but by the claims appended hereto.