HDAC6 INHIBITORS FOR TREATMENT OF METABOLIC DISEASE AND HFPEF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 63/183,914 filed May 4, 2021, U.S. Provisional Patent Application No. 63/210, 690 filed June 15, 2021, and U.S. Provisional Patent Application No. 63/210,676 filed June 15, 2021, the entire disclosures of each of which are incorporated herein by reference in their entireties.

FIELD

[0002] The present disclosure relates to treatment of metabolic disease. The present disclosure also relates to treatment of heart failure with preserved ejection fraction (HFpEF).

BACKGROUND

[0003] Metabolic diseases are a major source of health problems, particularly in countries where high calorie diets are typical. In particular, diet-induced obesity (DIO) affects a growing number of people worldwide. Metabolic diseases associated with obesity include diabetes and pre-diabetes, diabetic cardiomyopathy, metabolic syndrome (a termed for heart-related disorders associated with metabolism), hypertension, and hypertriglyceridemia / dyslipidemia.

[0004] Heart failure with preserved ejection fraction (HFpEF) is a major health problem without effective therapies. This syndrome is rising in prevalence and is associated with high morbidity and mortality. HFpEF, also known as diastolic heart failure, affects at least 2.5 million persons per year in the United States alone. (Gazewood and Turner. Am Fam Physician. 2017 Nov 1;96(9):582-588.) Risk factors include older age, female sex, obesity, hypertension, tobacco use, diabetes mellitus, coronary artery disease (CAD), valvular heart disease, and atrial fibrillation. In 2013, health care expenditures directly attributed to heart failure totaled approximately $30 billion.

[0005] Finding effective pharmaceutical treatments for obesity and associated metabolic diseases remains challenging. There is an unmet need for treatments for metabolic disease.

[0006] Finding effective pharmaceutical treatments for HFpEF also remains challenging. The most common pharmaceutical treatment for HFpEF remains administration of a diuretic. There is an unmet need for treatments for HFpEF.

[0007] The present disclosure addresses these needs.

SUMMARY

[0008] In some embodiments, the present disclosure relates to methods of treating or preventing metabolic disease by administering an HDAC6 inhibitor.

[0009] In some embodiments, the disclosure provides a method of treating a metabolic disease in a subject in need thereof, comprising administering a HDAC6 inhibitor to the subject. In some embodiments, the disclosure provides a method of preventing a metabolic disease in a subject in need thereof, comprising administering a HDAC6 inhibitor to the subject. In some embodiments, the metabolic disease is a metabolic disease associated with obesity, such as diet-induced obesity. In some embodiments, the metabolic disease is not diet-induced. In some embodiments, the metabolic disease is a diabetes, pre-diabetes, diabetic cardiomyopathy, metabolic syndrome, hypertension, hypertriglyceridemia, or dyslipidemia. In some embodiments, the metabolic disease is type 2 diabetes.

[0009a] Disclosed herein is the use of an HDAC6 inhibitor in the manufacture of a medicament for the treatment or prevention of a metabolic disease in a subject in need thereof, wherein a therapeutically effective amount of the HDAC6 inhibitor is to be administered to the subject.

[0010] In some embodiments, the disclosure provides a method of treating or preventing diabetes in a subject in need thereof, comprising administering a HDAC6 inhibitor. In some embodiments, the disclosure provides a method of treating or preventing diabetes mellitus in a subject in need thereof, comprising administering a HDAC6 inhibitor. In some embodiments, the disclosure provides a method of treating or preventing Type 2 diabetes in a subject in need thereof, comprising administering a HDAC6 inhibitor. In some embodiments, the disclosure provides a method of treating or preventing pre-diabetes in a subject in need thereof, comprising administering a HDAC6 inhibitor. In some embodiments, the disclosure provides a method of treating or preventing diabetic cardiomyopathy in a subject in need thereof, comprising administering a HDAC6 inhibitor. In some embodiments, the disclosure provides a method of treating or preventing metabolic syndrome in a subject in need thereof, comprising administering a HDAC6 inhibitor. In some embodiments, the disclosure provides a method of treating or preventing hypertension in a subject in need thereof, comprising administering a HDAC6 inhibitor. In some embodiments, the disclosure provides a method of treating or preventing metabolic hypertriglyceridemia and/or dyslipidemia in a subject in need thereof, comprising administering a HDAC6 inhibitor. In some embodiments, the subject is obese. In other embodiments, the subject is not obese.

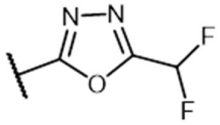
[0011] In some embodiments, the disclosure provides a method of treating or preventing obesity in a subject in need thereof, comprising administering a HDAC6 inhibitor to the subject. The subject may be an obese subject or a subject at risk for obesity.

[0011a] Disclosed herein is the use of an HDAC6 inhibitor in the manufacture of a medicament for the treatment of obesity in a subject in need thereof, wherein a therapeutically effective amount of the HDAC6 inhibitor is to be administered to the subject.

[0012] In some embodiments, the subject has or is at risk for hypertension. In some embodiments, the subject has or is at risk for diabetes (e.g., diabetes mellitus or Type 2 diabetes). In some embodiments, the subject has or is at risk for diabetic cardiomyopathy. In some embodiments, the subject has or is at risk for metabolic syndrome. In some embodiments, the subject has or is at risk for hyperglyceridemia or dyslipidemia.

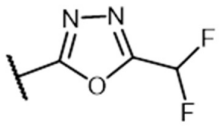
[0013] In some embodiments, the subject is a human. In some embodiments, the subject is at least 65 years old. In some embodiments, the subject is at least 70 years old.

[0014] In some embodiments, the disclosure provides methods of treating metabolic disease (e.g., diabetes, such as diabetes mellitus, or metabolic syndrome) or treating obesity in a subject in need thereof, comprising administering an HDAC6 inhibitor to the subject, wherein the HDAC6 inhibitor is fluoroalkyl-oxadiazole derivative. In some embodiments, the HDAC6 inhibitor is fluoroalkyl-oxadiazole derivative according to the following Formula:



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[0015] In some embodiments, the disclosure provides methods of preventing metabolic disease (e.g., diabetes, such as diabetes mellitus, or metabolic syndrome) in a subject in need thereof, comprising administering an HDAC6 inhibitor to the subject, wherein the HDAC6 inhibitor is fluoroalkyl-oxadiazole derivative. In some embodiments, the HDAC6 inhibitor is fluoroalkyl-oxadiazole derivative according to the following Formula:



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[0016] In some embodiments, the method treats or prevents at least one symptom of metabolic disease. In some embodiments, the method improves glucose tolerance. In some embodiments,

the method improves insulin resistance. In some embodiments, the method reduces glucose level. In some embodiments, the method inhibits inflammatory genes in adipose tissue. In some embodiments, the method reduces body weight of the subject.

[0017] In other embodiments, the disclosure provides an HDAC6 inhibitor for use in a method for treating metabolic disease.

[0018] In other embodiments, the disclosure provides a pharmaceutical composition for use in a method for treating metabolic disease, comprising an HDAC6 inhibitor.

[0019] In other embodiments, the disclosure provides a kit, comprising an HDAC6 inhibitor and instructions for use in a method for treating metabolic disease.

[0020] In other embodiments, the disclosure provides a use of an HDAC6 inhibitor in treating metabolic disease.

[0021] In some embodiments, the present disclosure relates to methods of treating or preventing heart failure with preserved ejection fraction (HFpEF) by administering an HDAC6 inhibitor.

[0021a] Disclosed herein is the use of an HDAC6 inhibitor in the manufacture of a medicament for the treatment or prevention of heart failure with preserved ejection fraction (HFpEF) in a subject in need thereof, wherein a therapeutically effective amount of the HDAC6 inhibitor is to be administered to the subject.

[0022] In some embodiments, the disclosure provides a method of treating heart failure with preserved ejection fraction (HFpEF) in a subject in need thereof, comprising administering a HDAC6 inhibitor to the subject. In some embodiments, the disclosure provides a method of preventing heart failure with preserved ejection fraction (HFpEF) in a subject in need thereof, comprising administering a HDAC6 inhibitor to the subject.

[0023] In some embodiments, the disclosure provides a method of treating or preventing cardiac fibrosis (e.g., associated with HFpEF) in a subject in need thereof, comprising administering a HDAC6 inhibitor to the subject.

[0024] In some embodiments, the disclosure provides a method of treating or preventing diastolic dysfunction (e.g., associated with HFpEF) in a subject in need thereof, comprising administering a HDAC6 inhibitor to the subject.

[0025] In some embodiments, the subject has or is at risk of metabolic disease. In some embodiments, the subject has or is at risk for hypertension. In some embodiments, the subject has or is at risk for diabetes (e.g., diabetes mellitus or Type 2 diabetes). In some embodiments, the subject has or is at risk for coronary artery disease (CAD). In some embodiments, the subject has or is at risk for valvular heart disease. In some embodiments, the subject has or is at risk for atrial fibrillation. In some embodiments, the subject has or is at risk of metabolic syndrome. In some embodiments, the subject is obese.

[0026] In some embodiments, the subject does not have a metabolic disease. In some embodiments, the subject does not have metabolic syndrome. In some embodiments, the subject does not have diabetes (e.g., does not have diabetes mellitus or Type 2 diabetes). In some embodiments, the subject does not have hypertension. In some embodiments, the subject is not obese.

[0027] In some embodiments, the subject is a human. In some embodiments, the subject is at least 65 years old. In some embodiments, the subject is at least 70 years old.

[0028] In some embodiments, the method treats or prevents at least one symptom of HFpEF. In some embodiments, the method reduces left ventricular (LV) mass. In some embodiments, the method reduces LV wall thickness. In some embodiments, the method improves LV relaxation. In some embodiments, the method improves LV filling pressure. In some embodiments, the method prevents heart failure in the subject.

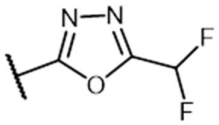
[0029] In some embodiments, the methods described herein reduce cardiac fibrosis (e.g., associated with HFpEF). In some embodiments, administration of an HDAC6 inhibitor is effective to significantly reduce cardiac fibroblast activation in a cell (e.g., in cell culture or in vivo). In some embodiments, administration of an HDAC6 inhibitor is effective to reduce cardiac fibroblast activation in a cell (e.g., in cell culture or in vivo), e.g., by 10%, 20%, 30%, 40%, 50%, 60%, 80%, 90% or more (relative to before administration or in the absence of administration). In some embodiments, administration of an HDAC6 inhibitor is effective to significantly reduce expression of one or more genes associated with fibrosis (e.g., in cells of a subject after administration of an HDAC6 inhibitor to the subject). In some embodiments, administration of an HDAC6 inhibitor is effective to reduce expression of one or more genes associated with fibrosis (e.g., in cells of a subject after administration of an HDAC6 inhibitor to the subject), e.g., by 10%, 20%, 30%, 40%, 50%, 60%, 80%, 90% or more (relative to before administration or in the absence of administration).

[0030] In some embodiments, administration of an HDAC6 inhibitor is effective to significantly reduce TGF-beta receptor signaling (e.g., in cells of a subject after administration of an HDAC6 inhibitor to the subject). In some embodiments, administration of an HDAC6 inhibitor is effective to reduce TGF-beta receptor signaling (e.g., in cells of a subject after administration of an HDAC6 inhibitor to the subject), e.g., by 10%, 20%, 30%, 40%, 50%, 60%, 80%, 90% or more (relative to before administration or in the absence of administration). In some embodiments, administration of an HDAC6 inhibitor is effective to significantly reduce expression of one or more genes associated with TGF-beta receptor signaling (e.g., in cells of a subject after administration of an HDAC6 inhibitor to the subject). In some embodiments, administration of an HDAC6 inhibitor is effective to reduce expression of one or more genes associated with TGF-beta receptor signaling (e.g., in cells of a subject after administration of an HDAC6 inhibitor to the subject), e.g., by 10%, 20%, 30%, 40%, 50%, 60%, 80%, 90% or more (relative to before administration or in the absence of administration).

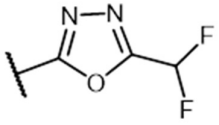
[0031] In some embodiments, the methods described herein reduce cardiac muscle hypertrophy (e.g., associated with HFpEF).

[0032] In some embodiments, the methods described herein reduce mitochondrial dysfunction. In some embodiments, administration of an HDAC6 inhibitor is effective to significantly increase expression of genes associated with oxidative phosphorylation and/or mitochondrial complex I (e.g., in cells of a subject after administration of an HDAC6 inhibitor to the subject). In some embodiments, administration of an HDAC6 inhibitor is effective to increase expression of genes associated with oxidative phosphorylation and/or mitochondrial complex I (e.g., in cells of a subject after administration of an HDAC6 inhibitor to the subject), e.g., by 10%, 20%, 30%, 40%, 50%, 60%, 80%, 90% or more (relative to before administration or in the absence of administration). In some embodiments, administration of an HDAC6 inhibitor is effective to increase (e.g., significantly increase) mitochondrial membrane potential in a cell (e.g., in vitro or in vivo). In some embodiments, administration of an HDAC6 inhibitor is effective to increase (e.g., significantly increase) spare respiratory capacity in a cell (e.g., in cell culture or in vivo).

[0033] In some embodiments, the disclosure provides methods of treating HFpEF in a subject in need thereof, comprising administering an HDAC6 inhibitor, wherein the HDAC6 inhibitor is fluoroalkyl-oxadiazole derivative. In some embodiments, the HDAC6 inhibitor is fluoroalkyl-oxadiazole derivative according to the following Formula:



[0034] In some embodiments, the disclosure provides methods of preventing HFpEF in a subject in need thereof, comprising administering an HDAC6 inhibitor, wherein the HDAC6 inhibitor is fluoroalkyl-oxadiazole derivative. In some embodiments, the HDAC6 inhibitor is fluoroalkyl-oxadiazole derivative according to the following Formula:



[0035] In other embodiments, the disclosure provides an HDAC6 inhibitor for use in a method for treating heart failure with preserved ejection fraction.

[0036] In other embodiments, the disclosure provides a pharmaceutical composition for use in a method for treating heart failure with preserved ejection fraction, comprising an HDAC6 inhibitor.

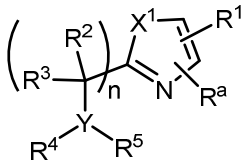
[0037] In other embodiments, the disclosure provides a kit, comprising an HDAC6 inhibitor and instructions for use in a method for treating heart failure with preserved ejection fraction.

[0038] In other embodiments, the disclosure provides a use of an HDAC6 inhibitor in treating heart failure with preserved ejection fraction.

[0039] In some embodiments of any of the methods described herein, the administering to the subject is oral (e.g., oral administering to a human subject). In some embodiments, the treatment reduces or alleviates (i.e., is effective to reduce or alleviate) one or more symptoms or parameters of the disease being treated.

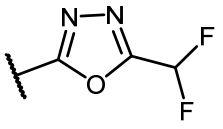
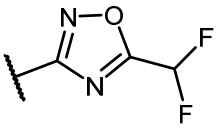
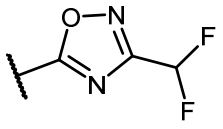
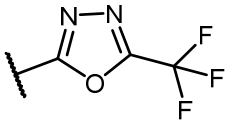
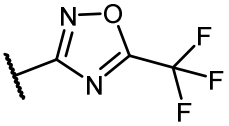
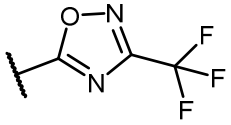
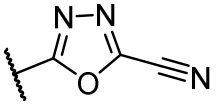
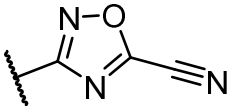
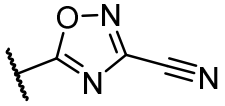
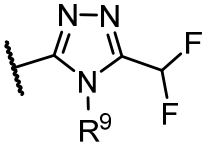
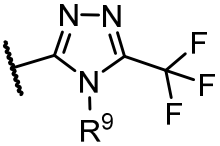
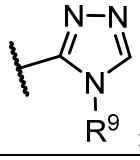
[0040] In some embodiments, the method comprises selecting the HDAC6 inhibitor by performing *in vitro* testing for selective inhibition of HDAC6 on each member of the plurality of candidate compounds, thereby identifying a selected compound for use as the HDAC6 inhibitor.

[0041] In some embodiments, the HDAC6 inhibitor is a compound according to Formula (I):



(I), wherein

R^1 is selected from the group consisting of:

		
		
		
		
and  ;		

R^a is selected from the group consisting of H, halo, C_{1-3} alkyl, cycloalkyl, haloalkyl, and alkoxy;

R^2 and R^3 are independently selected from the group consisting of H, halogen, alkoxy, haloalkyl, aryl, heteroaryl, alkyl, and cycloalkyl each of which is optionally substituted, or R^2 and R^3 together with the atom to which they are attached form a cycloalkyl or heterocyclyl;

R^4 and R^5 are independently selected from the group consisting of H, $–(SO_2)R^2$, $–(SO_2)NR^2R^3$, $–(CO)R^2$, $–(CONR^2R^3)$, aryl, arylheteroaryl, alkylenearyl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, haloalkyl, and alkoxy, each of which is optionally substituted, or R^4 and R^5 together with the atom to which they are attached form a cycloalkyl or heterocyclyl, each of which is optionally substituted;

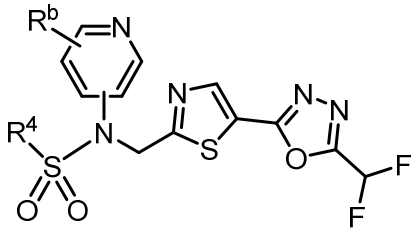
R^9 is selected from the group consisting of H, C_1-C_6 alkyl, haloalkyl, cycloalkyl and heterocyclyl;

X^1 is selected from the group consisting of S, O, NH and NR^6, wherein R^6 is selected from the group consisting of C_1-C_6 alkyl, alkoxy, haloalkyl, cycloalkyl and heterocyclyl;

Y is selected from the group consisting of CR^2, O, N, S, SO, and SO_2, wherein when Y is O, S, SO, or SO_2, R^5 is not present and when R^4 and R^5 together with the atom to which they are attached form a cycloalkyl or heterocyclyl, Y is CR^2 or N; and

n is selected from 0, 1, and 2.

[0042] In some embodiments, the HDAC6 inhibitor is a compound according to Formula (Ik):



(Ik),

or a pharmaceutically acceptable salt thereof,
wherein:

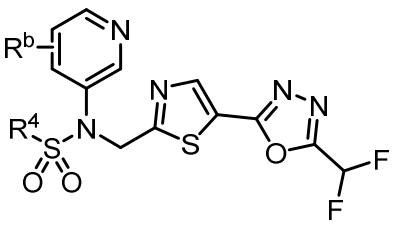
R^b is H, halogen, alkyl, cycloalkyl, -CN, haloalkyl, or haloalkoxy; and

R^4 is alkyl, alkoxy, haloalkyl, or cycloalkyl, each of which is optionally substituted.

[0043] In some embodiments of Formula (Ik), R^b is H, halogen, haloalkyl, or haloalkoxy.

[0044] In some embodiments of Formula (Ik), R^4 is optionally substituted alkyl or cycloalkyl.

[0045] In some embodiments, the HDAC6 inhibitor is a compound according to Formula (Ik-1):



(Ik-1),

or a pharmaceutically acceptable salt thereof,

wherein:

R^b is H, halogen, alkyl, cycloalkyl, -CN, haloalkyl, or haloalkoxy; and

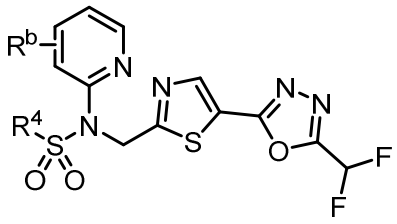
R^4 is alkyl, alkoxy, haloalkyl, or cycloalkyl, each of which is optionally substituted.

[0046] In some embodiments of Formula (Ik-1), R^b is H, halogen, haloalkyl, or haloalkoxy.

[0047] In some embodiments of Formula (Ik-1), R^4 is optionally substituted alkyl or cycloalkyl.

[0048] In some embodiments of Formula (Ik-1), R^4 is alkyl.

[0049] In some embodiments, the HDAC6 inhibitor is a compound according to Formula (Ik-2):



(Ik-2)

or a pharmaceutically acceptable salt thereof,

wherein:

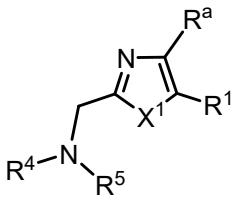
R^b is H, halogen, alkyl, cycloalkyl, -CN, haloalkyl, or haloalkoxy; and

R^4 is alkyl, alkoxy, haloalkyl, or cycloalkyl, each of which is optionally substituted.

[0050] In some embodiments of Formula (Ik-2), R^b is H, halogen, haloalkyl, or haloalkoxy.

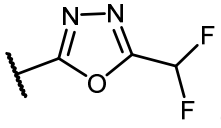
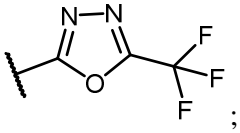
[0051] In some embodiments of Formula (Ik-2), R^4 is optionally substituted alkyl.

[0052] In some embodiments, the HDAC6 inhibitor is a compound is a compound according to Formula I(y):



I(y), or a pharmaceutically acceptable salt thereof,

wherein:

X^1 is S;
R^a is selected from the group consisting of H, halogen, and C_{1-3} alkyl;
R^1 is  or ;

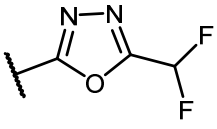
R^2 is selected from the group consisting of alkyl, alkoxy, and cycloalkyl, each of which is optionally substituted;

R^3 is H or alkyl;

R^4 is selected from the group consisting of alkyl, $–(SO_2)R^2$, $–(SO_2)NR^2R^3$, and $–(CO)R^2$; and

R^5 is aryl or heteroaryl; or R^4 and R^5 together with the atom to which they are attached form a heterocyclyl, each of which is optionally substituted.

[0053] In some embodiments of Formula I(y), R^a is H.

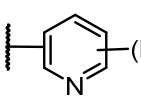
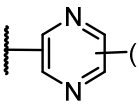
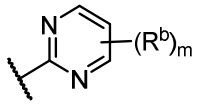
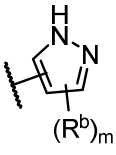
[0054] In some embodiments of Formula I(y), R^1 is .

[0055] In some embodiments of Formula I(y), R^4 is $–(SO_2)R^2$.

[0056] In some embodiments of Formula I(y), $–(SO_2)R^2$ is $–(SO_2)$alkyl, $–(SO_2)$alkyleneheterocyclyl, $–(SO_2)$haloalkyl, $–(SO_2)$haloalkoxy, or $–(SO_2)$cycloalkyl.

[0057] In some embodiments of Formula I(y), R^5 is heteroaryl.

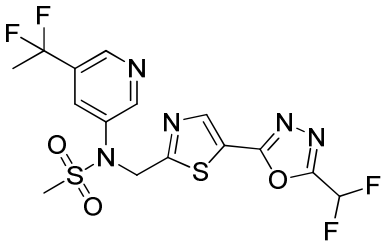
[0058] In some embodiments of Formula I(y), the heteroaryl is a 5- to 6-membered heteroaryl.

[0059] In some embodiments of Formula I(y), the 5- to 6-membered heteroaryl is selected from the group consisting of , , , and , wherein R^b is halogen, alkyl, alkoxy, cycloalkyl, -CN, haloalkyl, or haloalkoxy; and m is 0 or 1.

[0060] In some embodiments of Formula I(y), R^b is F, Cl, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CHF_2$, $-CF_2CH_3$, -CN, $-OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_2H$, and cyclopropyl.

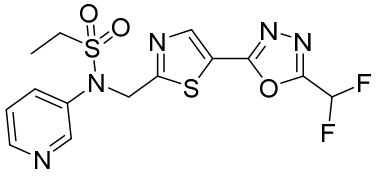
[0061] In some embodiments of Formula I(y), the aryl is selected from the group consisting of phenyl, 3-chlorophenyl, 3-chloro-4-fluorophenyl, 3-trifluoromethylphenyl, 3,4-difluorophenyl, and 2,6-difluorophenyl.

[0062] In some embodiments of Formula I(y), the compound is:



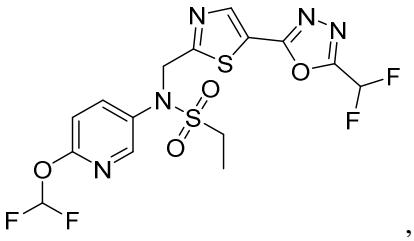
, or a pharmaceutically acceptable salt thereof.

[0063] In some embodiments of Formula I(y), the compound is:



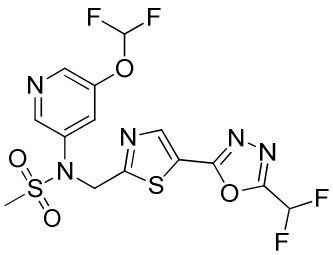
, or a pharmaceutically acceptable salt thereof.

[0064] In some embodiments of Formula I(y), the compound is:



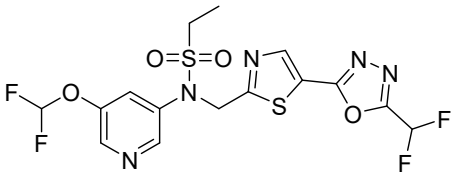
, or a pharmaceutically acceptable salt thereof.

[0065] In some embodiments of Formula I(y), the compound is:

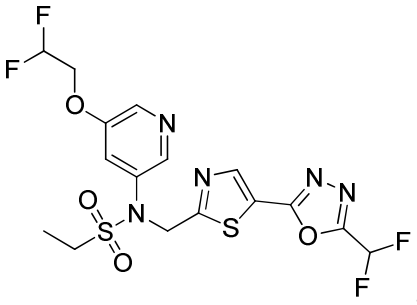


, or a pharmaceutically acceptable salt thereof.

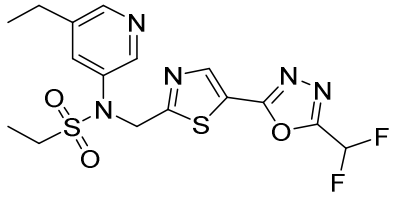
[0066] In some embodiments of Formula I(y), the compound is:


, or a pharmaceutically acceptable salt thereof.

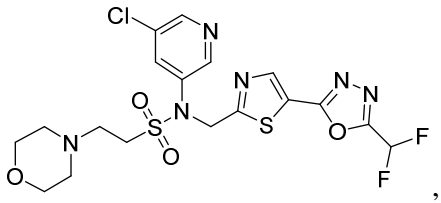
[0067] In some embodiments of Formula I(y), the compound is:


, or a pharmaceutically acceptable salt thereof.

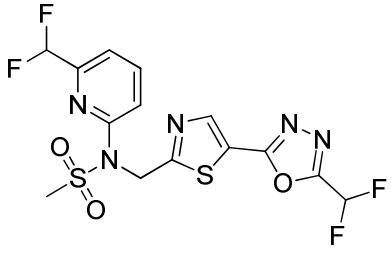
[0068] In some embodiments of Formula I(y), the compound is:


, or a pharmaceutically acceptable salt thereof.

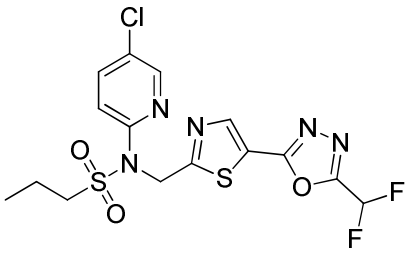
[0069] In some embodiments of Formula I(y), the compound is:


, or a pharmaceutically acceptable salt thereof.

[0070] In some embodiments of Formula I(y), the compound is:

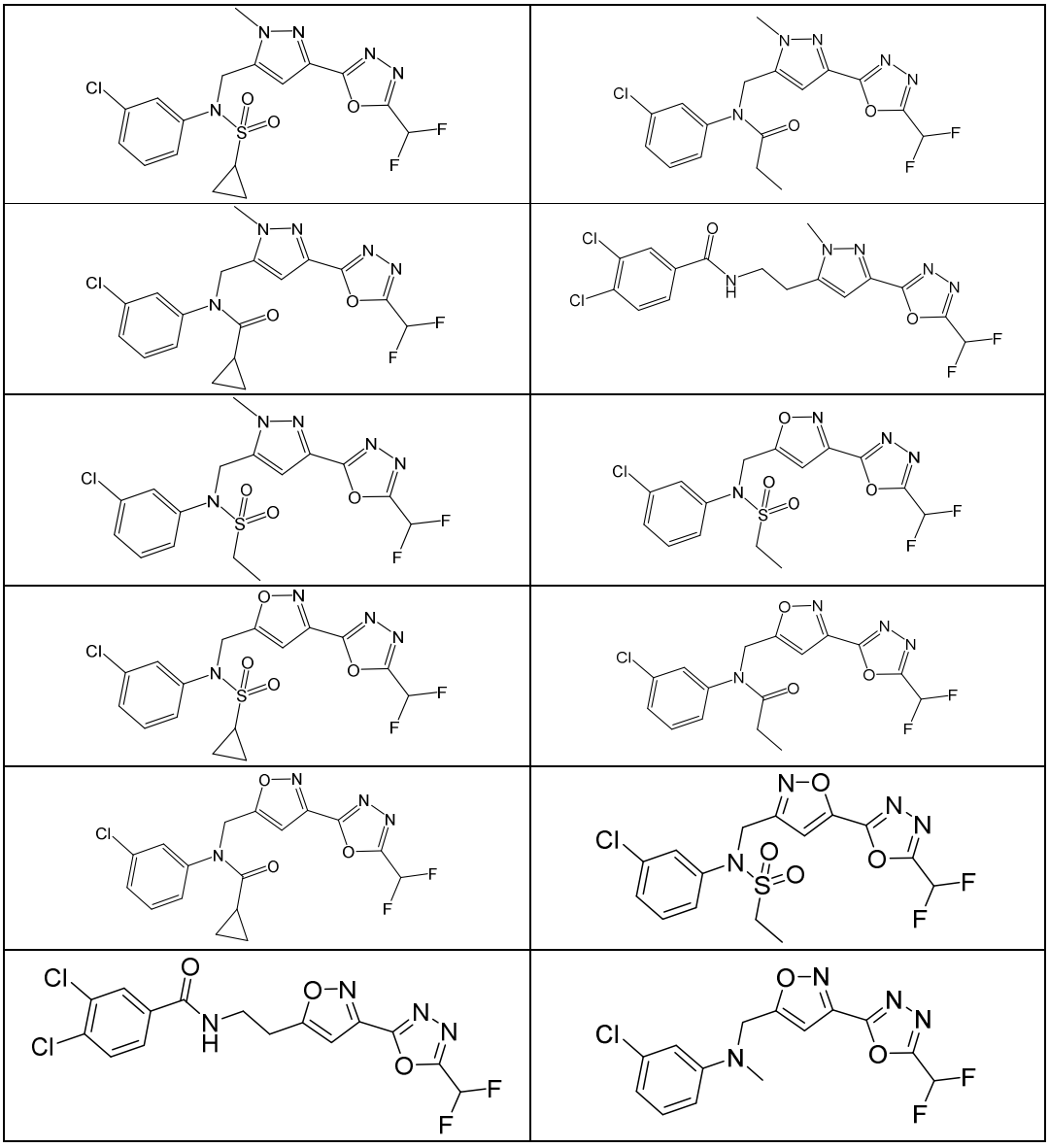

, or a pharmaceutically acceptable salt thereof.

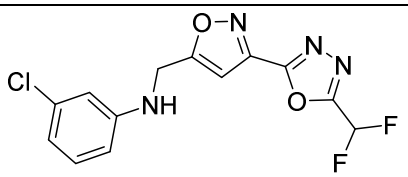
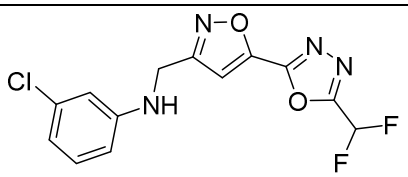
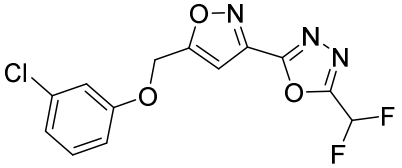
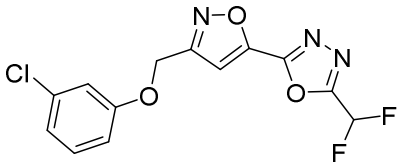
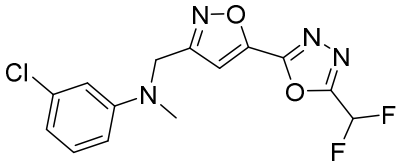
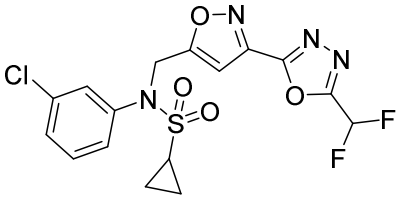
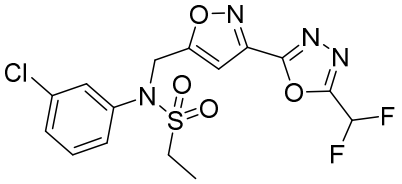
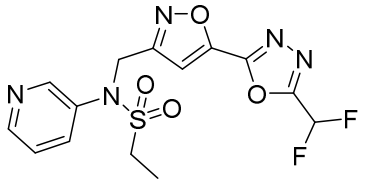
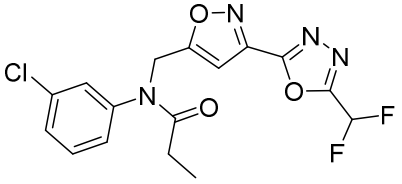
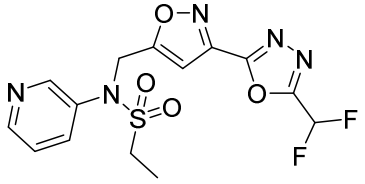
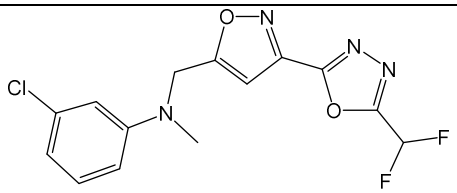
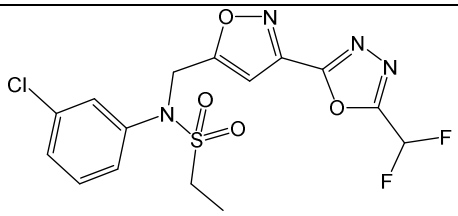
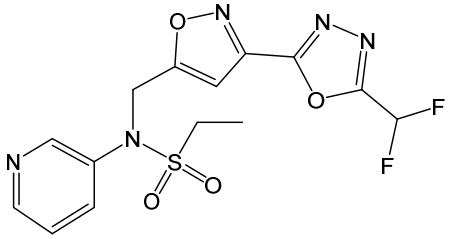
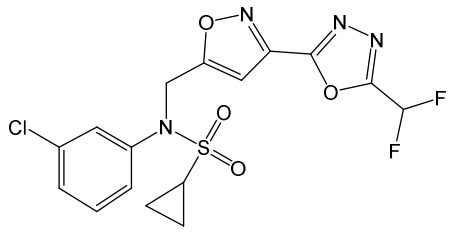
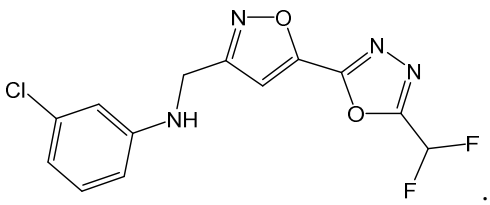
[0071] In some embodiments of Formula I(y), the compound is:



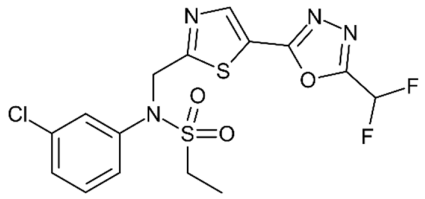
or a pharmaceutically acceptable salt thereof.

[0072] In some embodiments, the HDAC6 inhibitor is selected from the group consisting of:



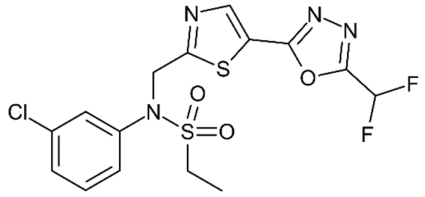
	
	
	
	
	
	
	
and  .	

[0073] In some embodiments, the HDAC6 inhibitor is



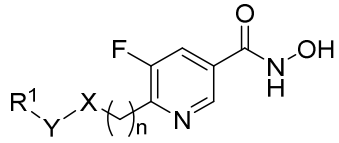
or an analog thereof.

[0074] In some embodiments, the HDAC6 inhibitor is



.

[0075] In some embodiments, the HDAC6 inhibitor is a compound of Formula (II):



(II); wherein

n is 0 or 1;

X is O, NR^4, or $CR^4R^{4'}$;

Y is a bond, CR^2R^3 or $S(O)_2$;

R^1 is selected from the group consisting of H, amido, carbocyclyl, heterocyclyl, aryl, and heteroaryl;

R^2 and R^3 are independently selected from the group consisting of H, halogen, alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, $–(CH_2)–$carbocyclyl, $–(CH_2)–$heterocyclyl, $–(CH_2)–$aryl, and $–(CH_2)–$heteroaryl; or

R^1 and R^2 taken together with the carbon atom to which they are attached form a carbocyclyl or heterocyclyl; or

R^2 and R^3 taken together with the carbon atom to which they are attached form a carbocyclyl or heterocyclyl; and

R^4 and $R^{4'}$ are each independently selected from the group consisting of H, alkyl, $–CO_2–$alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, $–(CH_2)–$carbocyclyl, $–(CH_2)–$heterocyclyl, $–(CH_2)–$aryl, and $–(CH_2)–$heteroaryl; or

R^4 and $R^{4'}$ taken together with the carbon atom to which they are attached form a carbocyclyl or heterocyclyl;

wherein each alkyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently optionally substituted with one or more substituents selected from the group consisting of halogen, haloalkyl, oxo, hydroxy, alkoxy, $–OCH_3$, $–CO_2CH_3$, –C(O)NH(OH),$–CH_3$, morpholine, and –C(O)N-cyclopropyl.

[0076] In some embodiments, the HDAC6 inhibitor is CAY10603, tubacin, rocilinostat (ACY-1215), citarinostat (ACY-241), ACY-738, QTX-125, CKD-506, nexturastat A, tubastatin A, or HPOB. In some embodiments, the HDAC6 inhibitor is tubastatin A. In some embodiments, the HDAC6 inhibitor is ricolinostat. In some embodiments, the HDAC6 inhibitor is CAY10603. In some embodiments, the HDAC6 inhibitor is nexturastat A.

[0077] In some embodiments, the HDAC6 inhibitor is at least 100-fold selective against HDAC6 compared to all other isozymes of HDAC.

[0078] In some embodiments, the HDAC6 inhibitor reduces HDAC6 activity by at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 90%, at least 95%, or at least 98%. In some embodiments, the HDAC6 inhibitor substantially eliminates HDAC6 activity.

BRIEF DESCRIPTION OF DRAWINGS

[0079] FIGs. 1A-1L show that HDAC6 inhibition with TYA-11631 improves glucose tolerance and insulin resistance in diet induced obese mouse model.

[0080] FIG. 1A to **FIG. 1F** show results of intraperitoneal glucose-tolerance tests (GTT) performed by injection of glucose (2 g/kg in saline) after 6 hours fasting. Tail blood glucose levels (mg/dl) were measured with a glucometer before (0 min) and at 15, 30, 45, 60 and 120 min after glucose administration. Diet Induced Obese (DIO) mice at 16 weeks of age developed

severe glucose intolerance compared to controls. **FIG. 1A** shows GTT results in control and DIO mice. Based on glucose AUC level, DIO mice were evenly randomized into four treatment groups to receive Vehicle (n=9) or TYA-11631 at three dosages 3, 10, 30mg/kg (n=10 each). Control mice were also divided to dose orally with vehicle (n=10) or 30 mg/kg TYA-11631 (n=10). To assess the acute response of TYA-11631 on glucose metabolism, GTT was performed at 6h after 1st dose. **FIG. 1B** shows GTT results before dose of TYA-11631. **FIG. 1C** and **FIG. 1D** show GTT results after a single dose of TYA-11631. A single dose of TYA-11631 at all three dosages significantly reduced glucose level. **FIG. 1E** and **FIG. 1F** show GTT results after TYA-11631 treatment for 2 weeks. TYA-11631 treatment for 2 weeks led to a pronounced improvements in glucose tolerance in a dose dependent manner.

[0081] FIG. 1G and **FIG. 1H** show results of intraperitoneal insulin-tolerance tests (ITT) performed by injection of insulin (1U/kg) after 6 hours fasting. Tail blood glucose levels (mg/dl) were measured with a glucometer before (0 min) and at 15, 30, 45, 60 and 120 min after insulin administration. HDAC6 inhibitor (TYA-11631) treatment for 4 weeks improved insulin resistance in DIO mice. 10 and 30mg/kg were significantly reduced glucose AUC (ITT) with comparable activities, 3 mg/kg showed a trend of reduction.

[0082] FIG. 1I shows effects of TYA-11631 on blood glucose in non-fasting mice. Tail blood samples were collected in the morning and measured with a glucometer. TYA-11631 treatment for 6wks led to a dose-dependent reduction of non-fasting glucose, consistent with the data of glucose tolerant test after fasting.

[0083] FIG. 1J and **FIG. 1K** show that treatment with TYA-11631 caused a dose dependent reduction of body wight in DIO mice. **FIG. 1L** shows that no differences in food consumption were observed between groups. Notably, control mice dosed with TYA-11631 30mg/kg for 6wks did not show changes on blood glucose levels and body weights. Bars and error bars show means and SEM. *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001.

[0084] FIG. 2A, FIG. 2B and FIG. 2C show HDAC 6 inhibition with TYA-11631 inhibits inflammatory genes in adipose tissue in diet induce obese mouse model. White adipose tissue (epididymal) was dissected from DIO mice after 6 hours of single dose 30mg/kg TYA-11631. Realtime q-PCR data showed that TYA-11631 remarkably inhibited upregulation of pro-inflammatory genes- *IL-6* (**FIG. 2A**), *IL-10* (**FIG. 2B**) and *TGFb1* (**FIG. 2C**) in white adipose tissue.

[0085] FIGs. 3A-3C show TYA-11018 effects in db/db diabetic mice. **FIG. 3A** shows TYA-11018 led to a dose-dependent reduction of fasting glucose in db/db mice. **FIG. 3B** shows both 1.5 and 15mg/kg significantly decreased blood glucose after 4 hours of dosing/fasting, compared to vehicle treated db/db mice. **FIG. 3C** shows 15mg/kg TYA-11018 significantly reduced fasting glucose after 6 hours of dosing. Bars and error bars show means and SEM.

[0086] FIGs. 4A-4H show mice fed on HFD in combination with moderate TAC develop a cardio-metabolic heart failure phenotype that recapitulates systemic and cardiovascular features of HFpEF in human.

[0087] FIG. 4A shows a schematic overview of HFpEF model induction by concomitant metabolic and moderate pressure overload stress in wildtype mice for 12wks. n=5 mice in control group fed on regular diet without mTAC surgery, n=15 mice in HFpEF model development group induction with HFD/mTAC.

[0088] FIG. 4B and **FIG. 4C** show, respectively, HFD/mTAC induced continuous body weight increase and glucose intolerance compared to the control mice.

[0089] FIG. 4D shows left ventricular ejection fraction (LVEF) was preserved in mice with HFD/mTAC evaluated by echocardiography.

[0090] Significant concentric left ventricular (LV) hypertrophy was present in HFD/mTAC animals, as indicated by increases in LV mass (**FIG. 4E**) and LV diastolic wall thickness (**FIG. 4F**).

[0091] LV diastolic dysfunction with increased left ventricular filling pressure was developed in HFD/mTAC mice as evidenced by decreased e' velocity (**FIG. 4H**) and increased ratio of E/e' (**FIG. 4G**), measured by noninvasive Doppler imaging. Bars and error bars show means and SEM. *P<0.05, **P<0.01, ***p<0.001 Vs. control group.

[0092] FIGs. 5A-5O show oral dosing of TYA-11631 improved glucose tolerance and diastolic dysfunction in HFD/mTAC mice. After the HFpEF phenotypes were established, animals were randomized to dose orally with 30 mg/kg TYA-11631 (n=8) or vehicle (n=7) once per day for six weeks, respectively. n=3 mice in control group dosed with vehicle. Treatment with TYA-11631 led to markedly improved glucose tolerance (**FIG. 5A**), with no difference of body weight change (**FIG. 5B**) compared to vehicle dosed animals. Echocardiographic evaluation (representative echocardiography-derived M-mode tracings, see

FIG. 5D) revealed that TYA-11631 treatment unaltered ejection fraction (**FIG. 5C**), however significantly reduced left ventricular mass (**FIG. 5E**) and LV wall thickness (**FIG. 5F**).

[0093] In addition, noninvasive Doppler imaging (representative pulsed-wave Doppler (**FIG. 5G**) and tissue Doppler (**FIG. 5J**) tracings) and invasive catheterization analysis showed that TYA-11631 treatment sustained improved LV relaxation and LV filling pressures as shown by decreased prolongation of isovolumetric relaxation time (**FIG. 5H**), lower E/A (**FIG. 5I**) and E/e' ratios (**FIG. 5K**), improved e' velocity (**FIG. 5L**), and reduced end diastolic pressure (**FIG. 5M**). Each of these efficacy parameters were normalized to control levels.

[0094] HFD/mTAC mice treated with TYA-11631 showed a trending decrease in heart weight (**FIG. 5N**) and lung weight (**FIG. 5O**), indicating improved LV hypertrophy and pulmonary congestion respectively, consistent with reduced filling pressure. Bars and error bars show means and SEM. *P<0.05, **P<0.01, ****p<0.0001.

[0095] TYA-11631 inhibits upregulation genes commonly associated with HFpEF disease as shown in **FIGs. 6A-6H**. Realtime q-PCR data showed that TYA-11631 significantly inhibited upregulation of genes associated with fibrosis *Postn* (**FIG. 6A**), *Col1a1* (**FIG. 6B**), *Col3a1* (**FIG. 6C**) and *Col5a2* (**FIG. 6D**); cardiac stress, *Nppb* (**FIG. 6E**) and *Myh6* (**FIG. 6F**); and inflammation *Tnfα* (**FIG. 6G**) and *Casp1* (**FIG. 6H**) in heart tissue of HFD/mTAC mice, consistent with the improvements of LV structure and heart function. Bars and error bars show means and SEM.

[0096] FIGs. 7A-7L show that wild-type (WT) mice on high-fat diet coupled with inhibition of constitutive nitric oxide synthases with N[w]-nitro-l-arginine methyl ester (HFD/L-NAME) for eight weeks develop obesity, hypertension and diastolic dysfunction, recapitulating HFpEF phenotypes in humans.

[0097] FIG. 7A shows a schematic overview of HFpEF model induction by concomitant metabolic and hypertensive stress in wildtype mice elicited by a combination of high fat diet and inhibition of constitutive nitric oxide synthase using N^{ω}-nitrol-arginine methyl ester (L-NAME). n=7 mice in control group fed on regular diet, n=26 mice in HFpEF model development group induction with HFD/L-NAME.

[0098] HFD/L-NAME treatment for 8 weeks significantly induced body weight increase (**FIG. 7B**), hypertension (**FIG. 7C**) and glucose intolerance (**FIG. 7D**) compared to the control mice. Echocardiographic evaluation revealed persistent preservation of the left ventricular ejection

fraction (LVEF) (**FIG. 7E**). Significant concentric left ventricular (LV) hypertrophy was present in HFD/L-NAME mice, as indicated by increases in LV mass (**FIG. 7F**) and LV wall thickness at diastole (**FIG. 7G**), without LV chamber dilatation (**FIG. 7H**). In addition, mice concomitantly exposed to HFD/L-NAME exhibited signs of LV diastolic dysfunction with impaired relaxation and increased left ventricular filling pressure, as evidenced by prolonged IVRT (**FIG. 7I**), decreased e' velocity (**FIG. 7J**), and increased ratios of E/e'(**FIG. 7K**), E/A (**FIG. 7L**), measured by noninvasive Doppler imaging. Bars and error bars show means and SEM. *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001 Vs. control group.

[0099] FIGs. 8A-8S show TYA-11631 treatment for 9 weeks improves glucose tolerance and diastolic dysfunction in HFD/L-NAME model.

[0100] FIG. 8A and **FIG. 8B** show results of Glucose tolerance test (GTT) performed after 5 weeks of dosing. Treatment with TYA-11631 markedly improved glucose tolerance in HFD/L-NAME mice, but no changes in control animals.

[0101] FIG. 8C shows plasma insulin level during GTT at the indicated time points (0 and 30 minutes after glucose injection) as measured by a sensitive mouse insulin detection kit (Cat. 80-INSMS-E01, ALPCO). TYA-11631 treatment led to decreased insulin secretion, suggesting that the improved glucose tolerance might be due to improved insulin action/sensitivity.

[0102] FIG. 8D and **FIG. 8E** show, respectively, that treatment with TYA-11631 caused a significant reduction of body wight, but no difference of food consumption in mice fed with HFD/L-NAME.

[0103] FIG. 8F shows that TYA-11631 did not affect systolic blood pressure in HFD/L-NAME mice measured by non-invasive tail cuff method.

[0104] Echocardiography shows that TYA-11631 treatment preserved ejection fraction (**FIG. 8G**), but significantly reduced left ventricular mass (**FIG. 8H**) and LV wall thickness (**FIG. 8I**).

[0105] Noninvasive Doppler imaging and terminal invasive catheterization analysis revealed that treatment with TYA-11631 for 9wks decreased prolongation of isovolumetric relaxation time (**FIG. 8J**), E/A (**FIG. 8K**) and E/e' ratios (**FIG. 8L**), increased e' velocity (**FIG. 8M**), and reduced end diastolic pressure (**FIG. 8N**), indicating the improved LV relaxation and filling pressure. In addition, HFD/L-NAME mice treated with TYA-11631 showed a trending

decrease in lung weight (**FIG. 8O**), suggesting an improved pulmonary congestion, consistent with the reduction of filling pressure.

[0106] Notably, no adverse effects related to TYA-11631 were observed. Control animals dosed with TYA-11631 had no changes on each of LV structural and functional parameters, as well as ECG signals -- QT, QRS, R amplitude and PR intervals (**FIG. 8P**, **FIG. 8Q**, **FIG. 8R** and **FIG. 8S**, respectively), further supporting an overall favorable safety profile of the compound. Bars and error bars show means and SEM. *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001.

[0107] Fig. 9 shows a heatmap of selected genes from significantly altered functional gene sets. Only genes with significant expression differences in each (GO) and WikiPathways (WP) database gene set are shown. Heatmap shows correction of key genes associated with cardiac muscle, fibrosis and mitochondrial function.

[0108] Fig. 10 shows significantly altered gene sets from Gene Ontology (GO) and WikiPathways (WP) databases. Selected categories were based on the normalized enrichment scores (NES) and FDR < 0.25. For each condition, bars on the left indicate data for vehicle-treated HFpEF mice relative to healthy controls, and bars on the right indicate data for HFpEF mice treated with TYA-11631 relative to vehicle. TGFβ: transforming growth factor beta, PDGFR: platelet-derived growth factor receptors, OXPHOS: oxidative phosphorylation.

[0109] FIGs. 11A-11F show correlation of mitochondrial genes and diastolic function. In **FIGs. 11A-11F**, the expression level of genes associated with different subunits of mitochondrial respiratory electron transport chain (NADH:Ubiquinone Oxidoreductase subunits) on the x-axis are plotted against markers of diastolic function (LVPWd and MV E/E') on the y-axis. In particular, Ndufa13 (**Fig. 11A**), Ndufa5 (**Fig. 11B**), Ndufs7 (**Fig. 11C**) on the x-axis are plotted against the marker of diastolic function, LVPWd, on the y-axis. Ndufa13 (**Fig. 11D**), Ndufa5 (**Fig. 11E**), Ndufs7 (**Fig. 11F**)) on the x-axis are plotted against the marker of diastolic function, MV E/E', on the y-axis. For better visualization, the expression levels of genes were plotted on logarithmic scale (log_2 TPM). Values are Pearson correlation coefficients. Black circles indicate data for vehicle treated healthy animals. Dark gray and light gray circles show HFpEF mice treated with vehicle or TYA-11631 respectively. **Fig. 11G** shows increased mitochondrial membrane potential, and **FIG. 11H** shows enhanced reserve respiratory capacity, in human iPSC-derived CMs treated with TYA-11631 (3 μM) (relative to

DMSO control). Oxygen consumption rate values were normalized to nuclear count. Data represent mean values ± SEM.

[0110] FIGs. 12A-12C show expression levels of genes associated with fibrosis Col1a2 (**FIG. 12A**), Col3a1 (**Fig. 12B**), Fbn1 (**Fig. 12C**) on the x-axis plotted against diastolic function parameter, LVPWd, on the y-axis. **FIGs. 12D-12F** show expression levels of genes associated with fibrosis Col1a2 (**Fig. 12D**), Col3a1 (**Fig. 12E**), Fbn1 (**Fig. 12F**) on the x-axis plotted against diastolic function parameter, IVRT, on the y-axis.

[0111] FIGs. 13A-13B show that HDAC6 inhibitors prevent fibroblast activation from TGF-β in human cardiac fibroblasts. **FIG. 13A** shows immunostaining of alpha-SMA (smooth muscle actin) in human cardiac fibroblasts in control (first panel from the top), treated with vehicle in the presence of TGF-beta (second panel from the top) or 1 uM TYA-11631 in the presence of TGF-beta (third panel from the top). 10 ng/ml TGF-beta was used. Scale bars are 50 μM. **FIG. 13B** shows that TYA-11631 (1 uM) effectively reduced TGF-beta induced human cardiac fibroblast activation as measured by alpha-SMA+ cells. Alpha-SMA staining count was determined by blinded analyses. Each point represents 9 images per well. Data represent mean values ± SEM.

[0112] FIGs. 14A shows a single dose of TYA-11018 (a HDAC6 selective inhibitor with similar potency to TYA-11631) significantly improved glucose tolerance to similar levels as Empagliflozin (SGLT2 selective inhibitor, 10 mg/kg) in the established mouse HFpEF model. **Figs. 14B-14D** show that chronic treatment with TYA-11018 for 9 weeks reduced LV hypertrophy (**FIG. 14B**), and improved diastolic function as measured by E/e' (**Fig. 14C**) and end diastolic pressure LVEDP (**Fig. 14D**).

[0113] Real time q-PCR data showed that TYA-11018 treatment for 9 wks led to significant inhibitions of *Nppb* (**FIG. 14E**) and *Col3a1* (**FIG. 14F**) in heart tissue of HFpEF mice compared to vehicle group. Notably, TYA-11018 showed a superior effect on the inhibition of these genes compared to Empagliflozin. Bars and error bars show means.

DETAILED DESCRIPTION

Overview

[0114] The present disclosure relates generally to the demonstration, *in vivo*, of the efficacy of HDAC6 inhibitors in metabolic disease. In particular, as disclosed herein, various physiological indicators of metabolic disease were improved when an animal model of

metabolic disease (including a diet-induced obesity model and a diet-independent diabetes model) was administered an HDAC6 inhibitor. Further, the potency of a large number of various HDAC6 inhibitors against HDAC6 is disclosed herein. Accordingly, the disclosure provides support for use of HDAC6 inhibitors for the treatment of metabolic diseases.

[0115] In some aspects, the disclosure provides a method of treating or preventing metabolic disease (such as any metabolic disease described herein) in a subject in need thereof, comprising administering a therapeutically effective amount of a HDAC6 inhibitor. In some aspects, the disclosure provides a method of treating or preventing metabolic syndrome in a subject in need thereof, comprising administering a therapeutically effective amount of a HDAC6 inhibitor. In some aspects, the disclosure provides a method of treating or preventing diabetes (e.g., diabetes mellitus) in a subject in need thereof, comprising administering a therapeutically effective amount of a HDAC6 inhibitor. In some aspects, the disclosure provides a method of treating obesity in a subject in need thereof, comprising administering a therapeutically effective amount of a HDAC6 inhibitor.

[0116] In some embodiments, provided herein are methods of treating or preventing metabolic disease (e.g., a metabolic disease, e.g., diabetes or metabolic syndrome, or obesity) in a subject in need thereof, comprising orally administering to a human subject a HDAC6 inhibitor.

[0117] In another aspect, the present disclosure relates generally to the demonstration, *in vivo*, of the efficacy of HDAC6 inhibitors in heart failure with preserved ejection fraction (HFpEF). In particular, as disclosed herein, various physiological indicators of HFpEF were improved when an animal model of HFpEF was administered an HDAC6 inhibitor. Further, the potency of a large number of various HDAC6 inhibitors against HDAC6 is disclosed herein. Accordingly, the disclosure provides support for use of HDAC6 inhibitors for the treatment of HFpEF.

[0118] In some aspects, the disclosure provides a method of treating or preventing heart failure with preserved ejection fraction (HFpEF) in a subject in need thereof, comprising administering a therapeutically effective amount of a HDAC6 inhibitor.

[0119] In some embodiments, provided herein are methods of treating or preventing HFpEF in a subject in need thereof, comprising orally administering to a human subject a HDAC6 inhibitor.

[0120] In some aspects, the disclosure provides a method of treating or preventing cardiac fibrosis in a subject in need thereof, comprising administering a therapeutically effective amount of a HDAC6 inhibitor. In some embodiments, provided herein are methods of treating or preventing cardiac fibrosis associated with HFpEF in a subject in need thereof, comprising administering (e.g., orally) to a subject (e.g., a human) a HDAC6 inhibitor.

[0121] In some aspects, the disclosure provides a method of treating or preventing diastolic dysfunction in a subject in need thereof, comprising administering a therapeutically effective amount of a HDAC6 inhibitor. In some embodiments, provided herein are methods of treating or preventing diastolic dysfunction associated with HFpEF in a subject in need thereof, comprising administering (e.g., orally) to a subject (e.g., a human) a HDAC6 inhibitor.

[0122] Advantageously, administration of a selective HDAC6 inhibitor may be less toxic than a pan-HDAC inhibitor. Without being bound by theory, an HDAC6 inhibitor may (1) act as an anti-inflammatory agent by inhibiting pro-inflammatory genes in white adipose tissue, the major source of obesity-related inflammation that leads to insulin resistance and metabolic dysfunction, and/or (2) improve mitochondrial activity/function. Without being bound by theory, an HDAC6 inhibitor may also: 1) directly act at the sarcomere level by protecting microtubules against mechanical damage, 2) improve myocyte compliance, and/or 3) promote autophagic flux and clearance of misfolded and damaged proteins. HDAC6 inhibition may directly stabilize and protect microtubules against damage and protect the Z-disk.

Definitions

[0123] Unless the context indicates otherwise, it is specifically intended that the various features of the invention described herein can be used in any combination. Moreover, the disclosure also contemplates that in some embodiments, any feature or combination of features set forth herein can be excluded or omitted. To illustrate, if the specification states that a complex comprises components A, B and C, it is specifically intended that any of A, B or C, or a combination thereof, can be omitted and disclaimed singularly or in any combination.

[0124] All numerical designations, *e.g.*, pH, temperature, time, concentration, and molecular weight, including ranges, are approximations which are varied (+) or (-) by increments of 1.0 or 0.1, as appropriate, or alternatively by a variation of +/- 15 %, or alternatively 10%, or alternatively 5%, or alternatively 2%. It is to be understood, although not always explicitly stated, that all numerical designations are preceded by the term “about”. It is to be understood that such range format is used for convenience and brevity and should be understood flexibly

to include numerical values explicitly specified as limits of a range, but also to include all individual numerical values or sub-ranges encompassed within that range as if each numerical value and sub-range is explicitly specified. For example, a ratio in the range of about 1 to about 200 should be understood to include the explicitly recited limits of about 1 and about 200, but also to include individual ratios such as about 2, about 3, and about 4, and sub-ranges such as about 10 to about 50, about 20 to about 100, and so forth. It also is to be understood, although not always explicitly stated, that the reagents described herein are merely exemplary and that equivalents of such are known in the art.

[0125] Also as used herein, "and/or" refers to and encompasses any and all possible combinations of one or more of the associated listed items, as well as the lack of combinations when interpreted in the alternative ("or").

[0126] The term "a" or "an" refers to one or more of that entity, i.e. can refer to plural referents. As such, the terms "a," "an," "one or more," and "at least one" are used interchangeably herein. In addition, reference to "an element" by the indefinite article "a" or "an" does not exclude the possibility that more than one of the elements is present, unless the context clearly requires that there is one and only one of the elements.

[0127] Throughout this application, the term "about" is used to indicate that a value includes the inherent variation of error for the device or the method being employed to determine the value, or the variation that exists among the samples being measured. Unless otherwise stated or otherwise evident from the context, the term "about" means within 10% above or below the reported numerical value (except where such number would exceed 100% of a possible value or go below 0%). When used in conjunction with a range or series of values, the term "about" applies to the endpoints of the range or each of the values enumerated in the series, unless otherwise indicated. As used in this application, the terms "about" and "approximately" are used as equivalents.

[0128] As used herein, the term "HDAC6" refers to the enzyme that in humans is encoded by the *HDAC6* gene.

[0129] As used herein, the term "HDAC6 inhibitor" refers to a compound that inhibits at least one enzymatic activity of HDAC6.

[0130] An HDAC6 inhibitor may be a "selective" HDAC6 inhibitor. The term "selective" as used herein refers to selectivity against other HDACs, known in the art as "isozymes." In some

embodiments, the selectivity ratio of HDAC6 over HDAC1 is from about 5 to about 30,0000, e.g., about 5, about 10, about 20, about 30, about 40, about 50, about 60, about 70, about 80, about 90, about 100, about 1000, about 2000, about 3000, about 4000, about 5000, about 6000, about 7000, about 8000, about 9000, about 10,000, about 15,000, about 20,000, about 25,000, or about 30,000, including all values and ranges therebetween.

[0131] For example, a HDAC6 inhibitor may be at least 100-fold selective against HDAC6 compared to all other isozymes of HDAC. In some cases, selectivity may be determined by reference of another HDAC inhibitor, such as a pan-HDAC inhibitor—that is an inhibitor that inhibits HDACs other than HDAC6 in addition to HDAC6. Givinostat is an example of a pan-HDAC6 inhibitor. In some embodiments, a selective HDAC6 inhibitor inhibits HDACs other than HDAC6 at least 100-fold less effectively than givinostat.

[0132] "Alkyl" or "alkyl group" refers to a fully saturated, straight or branched hydrocarbon chain having from one to twelve carbon atoms, and which is attached to the rest of the molecule by a single bond. Alkyls comprising any number of carbon atoms from 1 to 12 are included. An alkyl comprising up to 12 carbon atoms is a C_1-C_{12} alkyl, an alkyl comprising up to 10 carbon atoms is a C_1-C_{10} alkyl, an alkyl comprising up to 6 carbon atoms is a C_1-C_6 alkyl and an alkyl comprising up to 5 carbon atoms is a C_1-C_5 alkyl. A C_1-C_5 alkyl includes C_5 alkyls, C_4 alkyls, C_3 alkyls, C_2 alkyls and C_1 alkyl (*i.e.*, methyl). A C_1-C_6 alkyl includes all moieties described above for C_1-C_5 alkyls but also includes C_6 alkyls. A C_1-C_{10} alkyl includes all moieties described above for C_1-C_5 alkyls and C_1-C_6 alkyls, but also includes C_7, C_8, C_9 and C_{10} alkyls. Similarly, a C_1-C_{12} alkyl includes all the foregoing moieties, but also includes C_{11} and C_{12} alkyls. Non-limiting examples of C_1-C_{12} alkyl include methyl, ethyl, *n*-propyl, *i*-propyl, *sec*-propyl, *n*-butyl, *i*-butyl, *sec*-butyl, *t*-butyl, *n*-pentyl, *t*-amyl, *n*-hexyl, *n*-heptyl, *n*-octyl, *n*-nonyl, *n*-decyl, *n*-undecyl, and *n*-dodecyl. Unless stated otherwise specifically in the specification, an alkyl group can be optionally substituted.

[0133] "Alkylene" or "alkylene chain" refers to a fully saturated, straight or branched divalent hydrocarbon chain radical, and having from one to twelve carbon atoms. Non-limiting examples of C_1-C_{12} alkylene include methylene, ethylene, propylene, *n*-butylene, and the like. The alkylene chain is attached to the rest of the molecule through a single bond and to a radical group (e.g., those described herein) through a single bond. The points of attachment of the alkylene chain to the rest of the molecule and to the radical group can be through one carbon

or any two carbons within the chain. Unless stated otherwise specifically in the specification, an alkylene chain can be optionally substituted.

[0134] "Alkenyl" or "alkenyl group" refers to a straight or branched hydrocarbon chain having from two to twelve carbon atoms, and having one or more carbon-carbon double bonds. Each alkenyl group is attached to the rest of the molecule by a single bond. Alkenyl group comprising any number of carbon atoms from 2 to 12 are included. An alkenyl group comprising up to 12 carbon atoms is a C_2-C_{12} alkenyl, an alkenyl comprising up to 10 carbon atoms is a C_2-C_{10} alkenyl, an alkenyl group comprising up to 6 carbon atoms is a C_2-C_6 alkenyl and an alkenyl comprising up to 5 carbon atoms is a C_2-C_5 alkenyl. A C_2-C_5 alkenyl includes C_5 alkenyls, C_4 alkenyls, C_3 alkenyls, and C_2 alkenyls. A C_2-C_6 alkenyl includes all moieties described above for C_2-C_5 alkenyls but also includes C_6 alkenyls. A C_2-C_{10} alkenyl includes all moieties described above for C_2-C_5 alkenyls and C_2-C_6 alkenyls, but also includes C_7, C_8, C_9 and C_{10} alkenyls. Similarly, a C_2-C_{12} alkenyl includes all the foregoing moieties, but also includes C_{11} and C_{12} alkenyls. Non-limiting examples of C_2-C_{12} alkenyl include ethenyl (vinyl), 1-propenyl, 2-propenyl (allyl), iso-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 1-heptenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl, 1-octenyl, 2-octenyl, 3-octenyl, 4-octenyl, 5-octenyl, 6-octenyl, 7-octenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 4-nonenyl, 5-nonenyl, 6-nonenyl, 7-nonenyl, 8-nonenyl, 1-decenyl, 2-decenyl, 3-decenyl, 4-decenyl, 5-decenyl, 6-decenyl, 7-decenyl, 8-decenyl, 9-decenyl, 1-undecenyl, 2-undecenyl, 3-undecenyl, 4-undecenyl, 5-undecenyl, 6-undecenyl, 7-undecenyl, 8-undecenyl, 9-undecenyl, 10-undecenyl, 1-dodecenyl, 2-dodecenyl, 3-dodecenyl, 4-dodecenyl, 5-dodecenyl, 6-dodecenyl, 7-dodecenyl, 8-dodecenyl, 9-dodecenyl, 10-dodecenyl, and 11-dodecenyl. Unless stated otherwise specifically in the specification, an alkyl group can be optionally substituted.

[0135] "Alkenylene" or "alkenylene chain" refers to an unsaturated, straight or branched divalent hydrocarbon chain radical having one or more olefins and from two to twelve carbon atoms. Non-limiting examples of C_2-C_{12} alkenylene include ethenylene, propenylene, *n*-butenylene, and the like. The alkenylene chain is attached to the rest of the molecule through a single bond and to a radical group (e.g., those described herein) through a single bond. The points of attachment of the alkenylene chain to the rest of the molecule and to the radical group

can be through one carbon or any two carbons within the chain. Unless stated otherwise specifically in the specification, an alkenylene chain can be optionally substituted.

[0136] "Alkynyl" or "alkynyl group" refers to a straight or branched hydrocarbon chain having from two to twelve carbon atoms, and having one or more carbon-carbon triple bonds. Each alkynyl group is attached to the rest of the molecule by a single bond. Alkynyl group comprising any number of carbon atoms from 2 to 12 are included. An alkynyl group comprising up to 12 carbon atoms is a C_2-C_{12} alkynyl, an alkynyl comprising up to 10 carbon atoms is a C_2-C_{10} alkynyl, an alkynyl group comprising up to 6 carbon atoms is a C_2-C_6 alkynyl and an alkynyl comprising up to 5 carbon atoms is a C_2-C_5 alkynyl. A C_2-C_5 alkynyl includes C_5 alkynyls, C_4 alkynyls, C_3 alkynyls, and C_2 alkynyls. A C_2-C_6 alkynyl includes all moieties described above for C_2-C_5 alkynyls but also includes C_6 alkynyls. A C_2-C_{10} alkynyl includes all moieties described above for C_2-C_5 alkynyls and C_2-C_6 alkynyls, but also includes C_7, C_8, C_9 and C_{10} alkynyls. Similarly, a C_2-C_{12} alkynyl includes all the foregoing moieties, but also includes C_{11} and C_{12} alkynyls. Non-limiting examples of C_2-C_{12} alkenyl include ethynyl, propynyl, butynyl, pentynyl and the like. Unless stated otherwise specifically in the specification, an alkyl group can be optionally substituted.

[0137] "Alkynylene" or "alkynylene chain" refers to an unsaturated, straight or branched divalent hydrocarbon chain radical having one or more alkynes and from two to twelve carbon atoms. Non-limiting examples of C_2-C_{12} alkynylene include ethynylene, propynylene, *n*-butynylene, and the like. The alkynylene chain is attached to the rest of the molecule through a single bond and to a radical group (e.g., those described herein) through a single bond. The points of attachment of the alkynylene chain to the rest of the molecule and to the radical group can be through any two carbons within the chain having a suitable valency. Unless stated otherwise specifically in the specification, an alkynylene chain can be optionally substituted.

[0138] "Alkoxy" refers to a group of the formula -OR_a where R_a is an alkyl, alkenyl or alknyl as defined above containing one to twelve carbon atoms. Unless stated otherwise specifically in the specification, an alkoxy group can be optionally substituted.

[0139] "Aryl" refers to a hydrocarbon ring system comprising hydrogen, 6 to 18 carbon atoms and at least one aromatic ring, and which is attached to the rest of the molecule by a single bond. For purposes of this disclosure, the aryl can be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which can include fused or bridged ring systems. Aryls include, but are not limited to, aryls derived from aceanthrylene, acenaphthylene, acephenanthrylene,

anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. Unless stated otherwise specifically in the specification, the "aryl" can be optionally substituted.

[0140] "Carbocyclyl," "carbocyclic ring" or "carbocycle" refers to a rings structure, wherein the atoms which form the ring are each carbon, and which is attached to the rest of the molecule by a single bond. Carbocyclic rings can comprise from 3 to 20 carbon atoms in the ring. Carbocyclic rings include aryls and cycloalkyl, cycloalkenyl, and cycloalkynyl as defined herein. Unless stated otherwise specifically in the specification, a carbocyclyl group can be optionally substituted.

[0141] "Carbocyclylalkyl" refers to a radical of the formula $-R_b-R_d$ where R_b is an alkylene, alkenylene, or alkynylene group as defined above and R_d is a carbocyclyl radical as defined above. Unless stated otherwise specifically in the specification, a carbocyclylalkyl group can be optionally substituted.

[0142] "Cycloalkyl" refers to a stable non-aromatic monocyclic or polycyclic fully saturated hydrocarbon consisting solely of carbon and hydrogen atoms, which can include fused or bridged ring systems, having from three to twenty carbon atoms (e.g., having from three to ten carbon atoms) and which is attached to the rest of the molecule by a single bond. Monocyclic cycloalkyls include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyls include, for example, adamantyl, norbornyl, decalinyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like. Unless otherwise stated specifically in the specification, a cycloalkyl group can be optionally substituted.

[0143] "Cycloalkenyl" refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon consisting solely of carbon and hydrogen atoms, having one or more carbon-carbon double bonds, which can include fused or bridged ring systems, having from three to twenty carbon atoms, preferably having from three to ten carbon atoms, and which is attached to the rest of the molecule by a single bond. Monocyclic cycloalkenyls include, for example, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, and the like. Polycyclic cycloalkenyls include, for example, bicyclo[2.2.1]hept-2-enyl and the like. Unless otherwise stated specifically in the specification, a cycloalkenyl group can be optionally substituted.

[0144] "Cycloalkynyl" refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon consisting solely of carbon and hydrogen atoms, having one or more carbon-carbon triple bonds, which can include fused or bridged ring systems, having from three to twenty carbon atoms, preferably having from three to ten carbon atoms, and which is attached to the rest of the molecule by a single bond. Monocyclic cycloalkynyl include, for example, cycloheptynyl, cyclooctynyl, and the like. Unless otherwise stated specifically in the specification, a cycloalkynyl group can be optionally substituted.

[0145] "Haloalkyl" refers to an alkyl, as defined above, that is substituted by one or more halo radicals, *e.g.*, trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like. Unless stated otherwise specifically in the specification, a haloalkyl group can be optionally substituted.

[0146] "Heterocyclyl," "heterocyclic ring" or "heterocycle" refers to a stable saturated, unsaturated, or aromatic 3- to 20-membered ring which consists of two to nineteen carbon atoms and from one to six heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and which is attached to the rest of the molecule by a single bond. Heterocyclycl or heterocyclic rings include heteroaryls, heterocyclylalkyls, heterocyclylalkenyls, and hetercyclylalkynyls. Unless stated otherwise specifically in the specification, the heterocyclyl can be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which can include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclyl can be optionally oxidized; the nitrogen atom can be optionally quaternized; and the heterocyclyl can be partially or fully saturated. Examples of such heterocyclyl include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. Unless stated otherwise specifically in the specification, a heterocyclyl group can be optionally substituted.

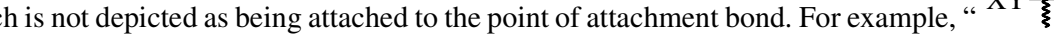
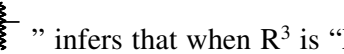
[0147] "Heteroaryl" refers to a 5- to 20-membered ring system comprising hydrogen atoms, one to nineteen carbon atoms, one to six heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, at least one aromatic ring, and which is attached to the rest of the molecule by a single bond. For purposes of this disclosure, the heteroaryl can be a monocyclic,

bicyclic, tricyclic or tetracyclic ring system, which can include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heteroaryl can be optionally oxidized; the nitrogen atom can be optionally quaternized. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[*b*][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (i.e. thienyl). Unless stated otherwise specifically in the specification, a heteroaryl group can be optionally substituted.

[0148] "Heterocyclylalkyl" refers to a radical of the formula $-R_b-R_e$ where R_b is an alkylene, alkenylene, or alkynylene group as defined above and R_e is a heterocyclyl radical as defined above. Unless stated otherwise specifically in the specification, a heterocycloalkylalkyl group can be optionally substituted.

[0149] The term "substituted" used herein means any of the groups described herein (*e.g.,* alkyl, alkenyl, alkynyl, alkoxy, aryl, aralkyl, carbocyclyl, cycloalkyl, cycloalkenyl, cycloalkynyl, haloalkyl, heterocyclyl, and/or heteroaryl) wherein at least one hydrogen atom is replaced by a bond to a non-hydrogen atoms such as, but not limited to: a halogen atom such as F, Cl, Br, and I; an oxygen atom in groups such as hydroxyl groups, alkoxy groups, and ester groups; a sulfur atom in groups such as thiol groups, thioalkyl groups, sulfone groups, sulfonyl groups, and sulfoxide groups; a nitrogen atom in groups such as amines, amides, alkylamines, dialkylamines, arylamines, alkylarylamines, diarylamines, N-oxides, imides, and enamines; a silicon atom in groups such as trialkylsilyl groups, dialkylarylsilyl groups, alkyldiarylsilyl groups, and triarylsilyl groups; and other heteroatoms in various other groups. "Substituted" also means any of the above groups in which one or more hydrogen atoms are replaced by a

higher-order bond (e.g., a double- or triple-bond) to a heteroatom such as oxygen in oxo, carbonyl, carboxyl, and ester groups; and nitrogen in groups such as imines, oximes, hydrazones, and nitriles. For example, "substituted" includes any of the above groups in which one or more hydrogen atoms are replaced with $-NR_gR_h$, $-NR_gC(=O)R_h$, $-NR_gC(=O)NR_gR_h$, $-NR_gC(=O)OR_h$, $-NR_gSO_2R_h$, $-OC(=O)NR_gR_h$, $-OR_g$, $-SR_g$, $-SOR_g$, $-SO_2R_g$, $-OSO_2R_g$, $-SO_2OR_g$, $=NSO_2R_g$, and $-SO_2NR_gR_h$. "Substituted" also means any of the above groups in which one or more hydrogen atoms are replaced with $-C(=O)R_g$, $-C(=O)OR_g$, $-C(=O)NR_gR_h$, $-CH_2SO_2R_g$, $-CH_2SO_2NR_gR_h$. In the foregoing, R_g and R_h are the same or different and independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, haloalkyl, haloalkenyl, haloalkynyl, heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl. "Substituted" further means any of the above groups in which one or more hydrogen atoms are replaced by a bond to an amino, cyano, hydroxyl, imino, nitro, oxo, thioxo, halo, alkyl, alkenyl, alkynyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, haloalkyl, haloalkenyl, haloalkynyl, heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl group. In addition, each of the foregoing substituents can also be optionally substituted with one or more of the above substituents.

[0150] As used herein, the symbol "" (hereinafter can be referred to as "a point of attachment bond") denotes a bond that is a point of attachment between two chemical entities, one of which is depicted as being attached to the point of attachment bond and the other of which is not depicted as being attached to the point of attachment bond. For example, "" indicates that the chemical entity "XY" is bonded to another chemical entity via the point of attachment bond. Furthermore, the specific point of attachment to the non-depicted chemical entity can be specified by inference. For example, the compound CH_3-R^3, wherein R^3 is H or "" infers that when R^3 is "XY", the point of attachment bond is the same bond as the bond by which R^3 is depicted as being bonded to CH_3.

[0151] As used herein, the term "treating" refers to acting upon a disease, disorder, or condition with an agent to reduce or ameliorate harmful or any other undesired effects of the disease, disorder, condition and/or their symptoms.

[0152] As used herein, the term "preventing" refers to reducing the incidence or risk of developing, or delaying the development of, harmful or any other undesired effects of the disease, disorder, condition and/or symptoms

[0153] "Administration," "administering" and the like, refer to administration to a subject by a medical professional or by self-administration by the subject, as well as to indirect administration, which may be the act of prescribing a composition of the invention. Typically, an effective amount is administered, which amount can be determined by one of skill in the art. Any method of administration may be used. Administration to a subject can be achieved by, for example, oral administration, in liquid or solid form, *e.g.* in capsule or tablet form; intravascular injection; intramyocardial delivery; or other suitable forms of administration.

[0154] As used herein, the term "effective amount" and the like refers to an amount that is sufficient to induce a desired physiologic outcome (*e.g.*, increased cardiac function, decreased mortality, or decreased risk/incidence of hospitalization, increased exercise capacity, or reduced expression of one or more biomarkers associated with heart failure—such as BNP). An effective amount can be administered in one or more administrations, applications or dosages. Such delivery is dependent on a number of variables including the time period which the individual dosage unit is to be used, the bioavailability of the composition, the route of administration, etc. It is understood, however, that specific amounts of the compositions for any particular subject depends upon a variety of factors including the activity of the specific agent employed, the age, body weight, general health, sex, and diet of the subject, the time of administration, the rate of excretion, the composition combination, severity of the particular disease being treated and form of administration.

[0155] As used herein, the terms "subject" or "patient" refers to any animal, such as a domesticated animal, a zoo animal, or a human. The "subject" or "patient" can be a mammal like a dog, cat, horse, livestock, a zoo animal, or a human. The subject or patient can also be any domesticated animal such as a bird, a pet, or a farm animal. Specific examples of "subjects" and "patients" include, but are not limited to, individuals with a metabolic disease (e.g., obesity), and individuals with metabolic disease-related characteristics or symptoms. Specific examples of "subjects" and "patients" also include, but are not limited to, individuals with a

cardiac disease or disorder, and individuals with cardiac disorder-related characteristics or symptoms.

[0156] The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0157] The term "pharmaceutically acceptable salts" include those obtained by reacting the active compound functioning as a base, with an inorganic or organic acid to form a salt, for example, salts of hydrochloric acid, sulfuric acid, phosphoric acid, methanesulfonic acid, camphorsulfonic acid, oxalic acid, maleic acid, succinic acid, citric acid, formic acid, hydrobromic acid, benzoic acid, tartaric acid, fumaric acid, salicylic acid, mandelic acid, carbonic acid, etc. Those skilled in the art will further recognize that acid addition salts may be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods.

[0158] As used herein, the term "restores" refers to increasing the level of biochemical or physiological parameter to a level observed in the subject prior to development of disease or condition, or to the level observed in a subject not having the disease or condition.

[0159] As used herein, the term "reduces" refers to decreasing the level of biochemical or physiological parameter.

[0160] As used herein, the term "metabolic disease" refers to a condition causes by either excessive nutrient intake or by the body's failure to properly metabolize nutrients. Metabolic disease includes but is not limited to obesity. It is a cluster of conditions that occur together, associated with heart diseases, type 2 diabetes and stroke. These conditions include hypertension, hyperglycemia, excess body fat and abnormal cholesterol or triglyceride levels.

[0161] The term "obesity" refers to a condition of having too much body fat. Obesity may increase the risk of diabetes, heart disease, stroke, and arthritis. Weight that is higher than what is considered healthy for a given height is described as overweight or obesity. Body Mass Index (BMI) is a screening tool for overweight and obesity. BMI is a person's weight in kilograms divided by the square of height in meters. A calculator for BMI is available at www.cdc.gov at obesity/adult/defining.html. In various embodiments, the subject may have a BMI of 25, 30,

35, 40 or higher, such as a BMI of 25-30, 25-30, or 25-40. In some cases, the subject may have severe obesity (also known as class 3 obesity), defined as a BMI of 40 or greater. Obesity is a chronic disease, also a risk factor for other diseases, such as heart disease, hypertension, stroke, diabetes etc.

[0162] In some embodiments, the methods of the disclosure decrease, prevent, or ameliorate one or more symptoms of metabolic disease. Symptoms of metabolic disease include glucose intolerance, insulin resistance, high glucose level, and inflammation in adipose tissue.

[0163] As used herein, the term "heart failure" refers to a condition in which the heart cannot pump enough blood to meet the body's need.

[0164] "Heart failure (HF) is a complex clinical syndrome that can result from any structural or functional cardiovascular disorder causing systemic perfusion inadequate to meet the body's metabolic demands without excessively increasing left ventricular filling pressures. It is characterized by specific symptoms, such as dyspnea and fatigue, and signs, such as fluid retention. As used herein, "chronic heart failure" or "congestive heart failure" or "CHF" refer, interchangeably, to an ongoing or persistent forms of heart failure. Common risk factors for CHF include old age, diabetes, high blood pressure and being overweight. CHF is broadly classified according to the systolic function of the left ventricle as HF with reduced or preserved ejection fraction (HFrEF and HFpEF). The term "heart failure" does not mean that the heart has stopped or is failing completely, but that it is weaker than is normal in a healthy person. In some cases, the condition can be mild, causing symptoms that may only be noticeable when exercising, in others, the condition may be more severe, causing symptoms that may be life-threatening, even while at rest. The most common symptoms of chronic heart failure include shortness of breath, tiredness, swelling of the legs and ankles, chest pain and a cough. In some embodiments, the methods of the disclosure decrease, prevent, or ameliorate one or more symptoms of CHF (*e.g.*, HFpEF) in a subject suffering from or at risk for CHF (*e.g.*, HFpEF). In some embodiments, the disclosure provides methods of treating CHF and conditions that can lead to CHF.

[0165] As used herein "acute heart failure" or "decompensated heart failure" refer, interchangeably, to a syndrome of the worsening of signs and symptoms reflecting an inability of the heart to pump blood at a rate commensurate to the needs of the body at normal filling pressure. AHF typically develops gradually over the course of days to weeks and then decompensates requiring urgent or emergent therapy due to the severity of these signs or

symptoms. AHF may be the result of a primary disturbance in the systolic or diastolic function of the heart or of abnormal venous or arterial vasoconstriction, but generally represents an interaction of multiple factors, including volume overload. The majority of patients with AHF have decompensation of chronic heart failure (CHF) and consequently much of the discussion of the pathophysiology, presentation, and diagnosis of CHF is directly relevant to an understanding of AHF. In other cases, AHF results from an insult to the heart or an event that impairs heart function, such as an acute myocardial infarction, severe hypertension, damage to a heart valve, abnormal heart rhythms, inflammation or infection of the heart, toxins and medications. In some embodiments, the methods of the disclosure decrease, prevent, or ameliorate one or more symptoms of AHF in a subject suffering from or at risk for AHF. In some embodiments, the disclosure provides methods of treating AHF and conditions that can lead to AHF. AHF may be the result of ischemia associated with myocardial infarction.

[0166] In some embodiments, the methods of the disclosure decrease, prevent, or ameliorate one or more symptoms of heart failure in a subject suffering from or at risk for heart failure associated with HFpEF. The terms “heart failure with preserved ejection fraction” or “diastolic heart failure” are used, interchangeably, refers generally to a form of heart failure is characterized by signs and symptoms of heart failure and a left ventricular ejection fraction (LVEF) greater than 50%. The terms may also encompass heart failure associated with intermediate reductions in LVEF (40% to 49%). In some embodiments, HFpEF comprises HFpEF associated with CHF. In some embodiments, HFpEF comprises HFpEF associated with AHF.

[0167] HFpEF is more common among older patients and women. Typical symptoms include fatigue, weakness, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, edemal. Signs of HFpEF (*e.g.*, HFpEF associated with CHF) may include S3 heart sound, displaced apical pulse, and jugular venous distension. Echocardiographic findings of normal ejection fraction with impaired diastolic function confirm the diagnosis. Measurement of natriuretic peptides (*e.g.*, BNP or NT-proBNP) is useful in the evaluation of patients with suspected heart failure with preserved ejection fraction in the ambulatory setting.

[0168] As used herein, the term “deleterious mutation” refers to a mutation that decreases the function of a gene. Deleterious mutations may include missense mutations, deletions or insertions in coding regions, non-coding mutations that influence gene expression or gene splicing, or others. Deleterious mutations include partial or total deletion of a gene. As used

herein, the term may refer to homozygous or heterozygous mutations in a gene, provided the mutation manifests a phenotypic effect upon the carrier.

[0169] As used herein, the term "left ventricular internal diameter at diastole" or "LVIDd" refers to left ventricular size at diastole.

[0170] As used herein, the term "left ventricular internal diameter at systole" or "LVIDs" refers to left ventricular size at systole.

[0171] As used herein, the term "left ventricular mass" refers to the weight of the left ventricle.

[0172] As used herein, the term "ejection fraction" refers to the amount of blood being bumped out of the left ventricle each time it contracts, expressed as a percentage to the total amount of blood in left ventricle.

[0173] The detailed description of the disclosure is divided into various sections only for the reader's convenience and disclosure found in any section may be combined with that in another section. 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 invention belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention, the preferred methods and materials are now described.

Treating or Preventing Metabolic disease

[0174] Provided herein are methods of treating or preventing metabolic disease with an HDAC6 inhibitor.

Treating or Preventing Heart Failure with Preserved Ejection Fraction (HFpEF)

[0175] Provided herein are methods of treating or preventing Heart Failure with preserved Ejection Fraction (HFpEF) with an HDAC6 inhibitor.

HDAC6 Inhibitors

[0176] Histone deacetylases ("HDAC") are a class of enzymes with deacetylase activity with a broad range of genomic and non-genomic substrates. There are eleven Zinc-dependent HDAC enzymes classified based on sequence identity and catalytic activity (Haberland et al., 2009).

[0177] Histone deacetylase inhibitors have been described as a therapeutic agents in oncology (Yoon and Eom, 2016), neurodegeneration (Butler et al., 2010) autoimmune disease (Choi et

al., 2018), chemotherapy-induced peripheral neuropathy (Krukowski et al., 2017) and cardiac indications (Zhang et al., 2002). Given the role of nuclear HDACs on regulating gene transcription, inhibition of these class of targets is known to have pleiotropic effects in various cell types; most notably resulting in cell toxicities. Therefore, limiting the toxicity of pan-HDAC inhibitors has been a major obstacle in wide-spread utilization for this class of compounds. In addition, significant adverse effects of pan-HDAC inhibitors (e.g. SAHA and Panabinostat) has been observed in the clinic including fatigue, nausea, diarrhea and thrombocytopenia (Subramanian et al., 2010).

[0178] In the cardiac-indication space, most studies have utilized pan-HDAC inhibitors (e.g. SAHA, TSA and Givinostat) for the treatment of pressure-overload rodent models with contractile dysfunction including transverse aortic constriction (TAC) (Cao et al., 2011), hypertension in Dahl salt-sensitive rats (Jeong et al., 2018) and myocardial infarction (Nagata et al., 2019). In addition, HDAC6-selective inhibitors have been used to ameliorate the LV systolic dysfunction of pressure overload rodent mode (Demos-Davies et al., 2014) and provide protection against proteotoxicity in a transgenic cardiomyopathy mouse model (McLendon et al., 2014). However, these experiments in pressure overload rodent models that were all accompanied with reduced ejection fraction and exhibited HFrEF phenotypes, are not predictive of treatment for HFpEF. Pressure overload mediated by conventional transverse aortic constriction induces cardiac hypertrophy followed by heart failure with reduced Ejection Fraction (HFrEF) not HFpEF (Mohammadi et al. 2021). HFpEF is distinct from HFrEF. The two forms of heart failure differ fundamentally in the pathophysiological mechanisms, and extent of myocardial loss/dysfunction, the pattern of remodeling at the chamber and ultrastructural level, and the response to therapeutic interventions. (Schiattarella et al., 2020).

[0179] HDAC6 belongs to the class IIb enzyme and contains two catalytic domains, a ubiquitin binding domain and a cytoplasmic retention domain (Haberland et al., 2009). HDAC6 is predominately a cytoplasmic enzyme and its best-characterized substrates include tubulin, HSP90 and cortactin (Brindisi et al., 2020).

[0180] Pharmacological inhibition of HDAC6 blocks its deacetylase activity, thus resulting in hyperacetylation of its substrates, most notably tubulin (Hubbert et al., 2002).

[0181] HDAC6-selective inhibitors are known to have reduced cytotoxicity due to the cytoplasmic nature of HDAC6 substrates and reduced effects on nuclear targets (including H3K9 and c-MYC) and on global transcription (Nebbioso et al., 2017).

[0182] Hydroxamic acids are zinc chelators and have been used extensively in the development of pan- and HDAC-selective inhibitors. However, most hydroxamic-acid based HDAC inhibitors either lack the desired selectivity or show poor bioavailability with a poor pharmacokinetic profile (Butler et al., 2010; Santo et al., 2012).

[0183] Various selective HDAC6 are known in the art. In addition, using known methods it is routine to screen compounds to identify further selective HDAC6 inhibitors. In particular, given a known HDAC6 inhibitor, a person of skill in the art can identify which analogs of the compound have selective HDAC6 activity.

[0184] In some embodiments, the HDAC6 inhibitor is a gene silencing agent, such as an RNA silencing agent (e.g., siRNA). In some embodiments, the HDAC6 inhibitor is not a gene silencing agent. In some embodiments, the HDAC6 is a small molecule HDAC6 inhibitor.

Known HDAC6 Inhibitors

[0185] In some embodiments, the HDAC6 inhibitor is CAY10603, tubacin, rocilinostat (ACY-1215), citarinostat (ACY-241), ACY-738, QTX-125, CKD-506, nexturastat A, tubastatin A, or HPOB (listed in Table 1), or an analog thereof.

Table 1

Compound	Description	IC_{50}
CAY10603	CAY10603 is a potent and selective HDAC6 inhibitor with IC50 of 2 pM, >200-fold selectivity over other HDACs.	2 pM
Tubacin	Tubacin is a highly potent and selective, reversible, cell-permeable HDAC6 inhibitor with an IC50 of 4 nM, approximately 350-fold selectivity over HDAC1.	4 nM
Rocilinostat (ACY-1215)	Rocilinostat (ACY-1215) is a selective HDAC6 inhibitor with IC50 of 5 nM. It is >10-fold more selective for HDAC6 than HDAC1/2/3 (class I HDACs) with slight activity against HDAC8, minimal activity against HDAC4/5/7/9/11, Sirtuin1, and Sirtuin2. Phase 2.	4.7 nM
Citarinostat (ACY-241)	Citarinostat (ACY-241, HDAC-IN-2) is an orally available selective HDAC6 inhibitor with IC50 of 2.6 nM and 46 nM for HDAC6 and HDAC3, respectively. It has 13 to 18-fold selectivity towards HDAC6 in comparison to HDAC1-3.	2.6 nM

ACY-738	ACY-738 inhibits HDAC6 with low nanomolar potency (IC50=1.7 nM) and a selectivity of 60- to 1500-fold over class I HDACs.	1.7 nM
QTX-125	HDAC6 inhibitor with 11-fold selectivity over HDAC1	0.6 nM
CKD-506	HDAC6 inhibitor with an 80-fold selectivity over HDAC1	2.9 nM
Nexturastat A	Nexturastat A is a potent and selective HDAC6 inhibitor with IC50 of 5 nM, >190-fold selectivity over other HDACs.	5 nM
Tubastatin A	Tubastatin A is a potent and selective HDAC6 inhibitor with IC50 of 15 nM. It is selective against all the other isozymes (1000-fold) except HDAC8 (57-fold).	15 nM
HPOB	HPOB is a potent, selective HDAC6 inhibitor with IC50 of 56 nM, >30-fold selectivity over other HDACs.	56 nM

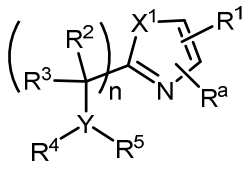
[0186] Further illustrative HDAC6 inhibitors are provided in U.S. Patent Publications Nos. US8227516B2, US20100292169A1, US20070207950A1, US8222423B2, US20100093824A1, US20100216796A1, US8673911B2, US8217076B2, US8440716B2, US20110195432A1, US8624040B2, US9096518B2, US8431538B2, US20120258993A1, US8546588B2, US8513421B2, US20140031368A1, US20120015943A1, US20120015942A1, US20140243335A1, US20130225543A1, US8471026B2, US9238028B2, US8765773B2, USRE47009E1, US20140294856A1, US9512083B2, US9670193B2, US9345905B2, US9409858B2, US9663825B2, US20150119327A1, US20150250786A1, US10041046B2, US9586973B2, US20160069887A1, US20140357512A1, US9751832B2, US20160228434A1, US20150105358A1, US10660890B2, US20160271083A1, US20150176076A1, US20200405716A1, US9890136B2, US10287255B2, US20170173083A1, US10016421B2, US9987258B2, US10568854B2, US10106540B2, US10266489B2, US9993459B2, US10183934B2, US10494354B2, US10494353B2, US10112915B2, US10377726B2, US10829462B2, US10829461B2, US20210009539A1, US20210009538A1, US10239845B2, US10472337B2, US10479772B2, US10464911B2, US10584117B2, US10538498B2, US10011611B2,

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Fluoroalkyl-Oxadiazole Derivatives

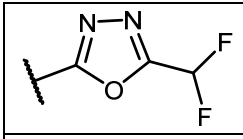
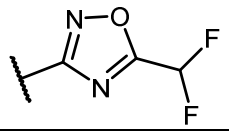
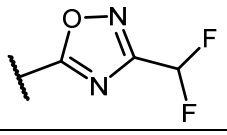
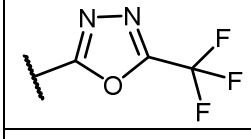
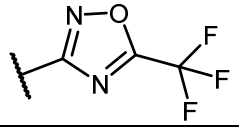
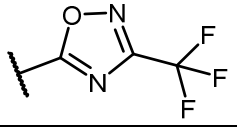
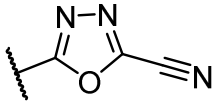
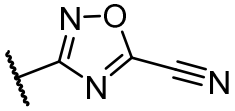
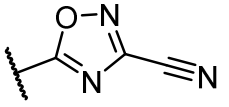
[0187] In some embodiments, the HDAC6 inhibitor is a fluoroalkyl-oxadiazole derivative. Illustrative fluoroalkyl-oxadiazole derivatives that may be used as HDAC6 inhibitors include those described herein and those described in Int'l Pat. Appl. No. PCT/US2020/066439, published as WO2021127643A1 the content of which is incorporated by reference herein in its entirety. PCT/US2020/066439, published as WO2021127643A1, also describes methods of synthesis of such compounds, which are specifically incorporated by reference herein.

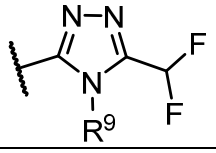
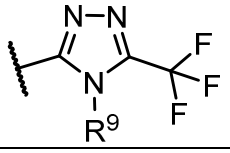
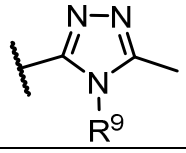
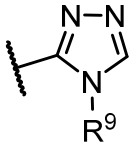
[0188] In some embodiments, the HDAC6 inhibitor is a compound of Formula (I):



(I), wherein

R^1 is selected from the group consisting of:

		
and  ;		

R^a is selected from the group consisting of H, halo, C_{1-3} alkyl, cycloalkyl, haloalkyl, and alkoxy;

R^2 and R^3 are independently selected from the group consisting of H, halogen, alkoxy, haloalkyl, aryl, heteroaryl, alkyl, and cycloalkyl each of which is optionally substituted, or R^2 and R^3 together with the atom to which they are attached form a cycloalkyl or heterocyclyl;

R^4 and R^5 are independently selected from the group consisting of H, $–(SO_2)R^2$, $–(SO_2)NR^2R^3$, $–(CO)R^2$, $–(CONR^2R^3)$, aryl, arylheteroaryl, alkylenearyl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, haloalkyl, and alkoxy, each of which is optionally substituted, or R^4 and R^5 together with the atom to which they are attached form a cycloalkyl or heterocyclyl, each of which is optionally substituted;

R^9 is selected from the group consisting of H, C_1-C_6 alkyl, haloalkyl, cycloalkyl and heterocyclyl;

X^1 is selected from the group consisting of S, O, NH and NR^6, wherein R^6 is selected from the group consisting of C_1-C_6 alkyl, alkoxy, haloalkyl, cycloalkyl and heterocyclyl;

Y is selected from the group consisting of CR^2, O, N, S, SO, and SO_2, wherein when Y is O, S, SO, or SO_2, R^5 is not present and when R^4 and R^5 together with the atom to which they are attached form a cycloalkyl or heterocyclyl, Y is CR^2 or N; and

n is selected from 0, 1, and 2.

[0189] In some embodiments of Formula (I), n is 0. In some embodiments, n is 1. In some embodiments n is 2. In some embodiments, n is 0 or 1. In some embodiments n is 1 or 2. In some embodiments n is 0 or 2.

[0190] In some embodiments of Formula (I), X^1 is O. In some embodiments, X^1 is S. In some embodiments, X^1 is NH. In some embodiments, X^1 is NR^6. In some embodiments, X^1 is selected from the group consisting of S, O, and NR^6. In some embodiments, X^1 is selected from

the group consisting of S, O, and NCH_3. In some embodiments, X^1 is S or O. In some embodiments, X^1 is S or NR^6. In some embodiments, R^6 is C_1-C_6 alkyl.

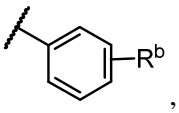
[0191] In some embodiments of Formula (I), R^2 and R^3 are H.

[0192] In some embodiments of Formula (I), Y is N, CR^2, or O. In some embodiments, Y is N or O. In some embodiments, Y is N. In some embodiments, Y is CR^2. In some embodiments, Y is O.

[0193] In some embodiments, R^4 and R^5 are independently selected from the group consisting of H, $–(SO_2)R^2$, $–(SO_2)NR^2R^3$, $–(CO)R^2$, $–(CONR^2R^3)$, aryl, arylheteroaryl, heteroaryl, alkylenearyl, cycloalkyl, alkylenecycloalkyl, heterocyclyl, alkyleneheterocyclyl, alkyl, haloalkyl, and alkoxy, each of which is optionally substituted, or R^4 and R^5 together with the atom to which they are attached form a cycloalkyl or heterocyclyl, each of which is optionally substituted

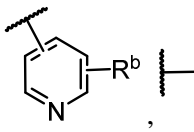
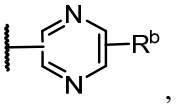
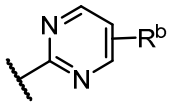
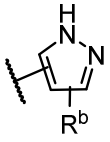
[0194] In some embodiments of Formula (I), R^4 is selected from the group consisting of -C(O)-alkyl, -C(O)-cycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, $-(SO_2)NR^2R^3$, $-SO_2$-alkyl, and $-SO_2$-cycloalkyl, each of which is optionally substituted. In some embodiments, R^4 is selected from the group consisting of -C(O)-alkyl, -C(O)-cycloalkyl, $-SO_2$-alkyl, $-SO_2$-haloalkyl, $-SO_2$-cycloalkyl, and $-(SO_2)NR^2R^3$, each of which is optionally substituted. In some embodiments, aryl is optionally substituted with one or more halogens. In some embodiments of Formula (I), R^4 is selected from the group consisting of $–SO_2$alkyl, $–SO_2$haloalkyl, or $–SO_2$cycloalkyl. In some embodiments of Formula (I), R^4 is selected from the group consisting of $–SO_2Me$, $–SO_2Et$, and $–SO_2$-*c*Pr. In some embodiments, R^2 and R^3 are each independently $–C_{1\text{-}5}$alkyl. In some embodiments, R^2 and R^3 taken together with the nitrogen atom to which they are attached form an optionally substituted heterocyclyl. In some embodiments, the optionally substituted heterocyclyl is morpholine, thiomorpholine, or thiomorpholine 1,1-dioxide.

[0195] In some embodiments of Formula (I), R^5 is aryl, heteroaryl, or cycloalkyl, each of which is optionally substituted.

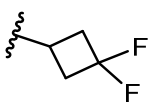
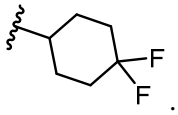
[0196] In some embodiments, R^5 is aryl. In some embodiments, aryl is 

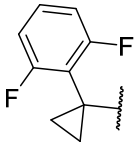
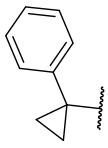
, wherein R^b is one or more selected from the group consisting of halogen, haloalkyl, alkyl, Oalkyl, Ohaloalkyl, alkylene-Ohaloalkyl, cycloalkyl, heterocyclyl aryl, heteroaryl, alkylnitrile, or CN.

In some embodiments, the haloalkyl is selected from CF_3, CF_2CH_3, CHF_2, or CH_2F. In some embodiments, the alkyl is a $–C_{1\text{-}5}$alkyl. In some embodiments, $–C_{1\text{-}5}$alkyl is methyl, ethyl, propyl, *i*-propyl, butyl, or *t*-butyl. In some embodiments, methyl, ethyl, propyl, *i*-propyl, butyl, or *t*-butyl is optionally substituted with OH. In some embodiments, the cycloalkyl is a $C_{3\text{-}6}$cycloalkyl. In some embodiments, the aryl is a phenyl. In some embodiments, the heteroaryl is 5- or 6-membered heteroaryl having 1, 2, or 3 heteroatoms selected from N, O, and S. In some embodiments, the heterocyclyl is a 4- to 7-member heterocyclyl with 1 or 2 heteroatoms selected from N, O, and S. In some embodiments, the Ohaloalkyl is selected from OCF_3, $OCHF_2$, or OCH_2F. In some embodiments, the Oalkyl is O-methyl, O-ethyl, O-propyl, O-*i*-propyl, O-butyl, or O-*t*-butyl.

[0197] In some embodiments, R^5 is heteroaryl. In some embodiments, heteroaryl is an optionally substituted 5- to 14-membered heteroaryl. In some embodiments, heteroaryl is an optionally substituted 5- to 14-membered heteroaryl having 1, 2, or 3 heteroatoms selected from the group consisting of N, O, and S. In some embodiments, the optionally substituted 5- to 14-membered heteroaryl is selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, quinolinyl, isoquinolinyl, quinoxalinyl, cinnolinyl, indolizinyl, azaindolizinyl, indolyl, azaindolyl, benzoxazolyl, benzthiazolyl, benzfuranyl, benzthiophenyl, imidazopyridinyl, imidazopyrazinyl, and benzimidazolyl. In some embodiments, the optionally substituted 5- to 14-membered heteroaryl is selected from the group consisting of pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, benzoxazolyl, imidazopyridinyl, and imidazopyrazinyl. In some embodiments, R^5 is , , , or , wherein R^b is one or more selected from the group consisting of halogen, haloalkyl, alkyl, Oalkyl, Ohaloalkyl, alkylene-Ohaloalkyl, cycloalkyl, heterocyclyl aryl, heteroaryl, alkylnitrile, or CN. In some embodiments, the haloalkyl is selected from CF_3, CF_2CH_3, CHF_2, or CH_2F. In some embodiments, the alkyl is a $–C_{1\text{-}5}$alkyl. In some embodiments, $–C_{1\text{-}5}$alkyl is methyl, ethyl, propyl, *i*-propyl, butyl, or *t*-butyl. In some embodiments, methyl, ethyl, propyl, *i*-propyl, butyl, or *t*-butyl is optionally substituted with OH. In some embodiments, the cycloalkyl is a $C_{3\text{-}6}$cycloalkyl. In some embodiments, the aryl is a phenyl. In some embodiments, the heteroaryl is 5- or 6-membered heteroaryl having 1, 2, or 3 heteroatoms selected from N, O,

and S. In some embodiments, the heterocyclyl is a 4- to 7-member heterocyclyl with 1 or 2 heteroatoms selected from N, O, and S. In some embodiments, the Ohaloalkyl is selected from OCF_3, $OCHF_2$, or OCH_2F. In some embodiments, the Oalkyl is O-methyl, O-ethyl, O-propyl, O-*i*-propyl, O-butyl, or O-*t*-butyl.

[0198] In some embodiments, R^5 is cycloalkyl. In some embodiments, cycloalkyl is a cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, each of which is optionally substituted. In some embodiments, the optionally substituted cycloalkyl is  or .

[0199] In some embodiments, R^5 is selected from the group consisting of phenyl, 3-chlorophenyl, 3-chloro-4-fluorophenyl, 3-trifluoromethylphenyl, 3,4-difluorophenyl, and 2,6-difluorophenyl. In some embodiments, R^5 is cyclopropyl. In some embodiments, R^5 selected from the group consisting of pyridin-3-yl and 1-methylindazole-6-yl. In some embodiments, R^5 is selected from the group consisting of H, phenyl, 3-chlorophenyl, 3-chloro-4-fluorophenyl, 3-trifluoromethylphenyl, 3,4-difluorophenyl, cyclopropyl, pyridin-3-yl, 1-methylindazole-6-yl, 3,3-difluorocyclobutyl, and 4,4-difluorocyclohexyl. In some embodiments, R^5 is 3-chlorophenyl. In some embodiments R^5 is H. In some embodiments, R^5 is , or . In some embodiments, R^5 is $–CH_2CH_2Ph$. In some embodiments, R^5 is selected from the group consisting of H, aryl, heteroaryl, alkylenearyl, cycloalkyl, heterocyclyl, alkyl, and haloalkyl, each of which is optionally substituted, or R^4 and R^5 together with the atom to which they are attached form an optionally substituted heterocyclyl.

[0200] In some embodiments of Formula (I), R^5 is optionally substituted with one or more halogen, haloalkyl, alkyl, Oalkyl, Ohaloalkyl, cycloalkyl, heterocyclyl aryl, or heteroaryl. In some embodiments, the haloalkyl is selected from CF_3, CHF_2, or CH_2F. In some embodiments, the alkyl is a $–C_{1\text{-}5}$alkyl. In some embodiments, $–C_{1\text{-}5}$alkyl is methyl, ethyl, propyl, *i*-propyl, butyl, or *t*-butyl. In some embodiments, the cycloalkyl is a $C_{3\text{-}6}$cycloalkyl. In some embodiments, the aryl is a phenyl. In some embodiments, the heteroaryl is 5- or 6-membered heteroaryl having 1, 2, or 3 heteroatoms selected from N, O, and S. In some embodiments, the heterocyclyl is a 4- to 7-member heterocyclyl with 1 or 2 heteroatoms selected from N, O, and

S. In some embodiments, the Ohaloalkyl is selected from OCF_3, $OCHF_2$, or OCH_2F. In some embodiments, the Oalkyl is O-methyl, O-ethyl, O-propyl, O-*i*-propyl, O-butyl, or O-*t*-butyl.

[0201] In some embodiments of Formula (I), R^4 is H or $-C_{1-5}$alkyl and R^5 is aryl. In some embodiments, R^4 is H or $-C_{1-5}$alkyl and R^5 is heteroaryl. In some embodiments, R^4 is H or $-C_{1-5}$alkyl and R^5 is cycloalkyl. In some embodiments, the $-C_{1-5}$alkyl is methyl, ethyl, or propyl. In some embodiments, the $-C_{1-5}$alkyl is methyl. In some embodiments, the aryl is optionally substituted phenyl. In some embodiments, the heteroaryl is a 5- to 14-membered heteroaryl having 1, 2, or 3 heteroatoms selected from the group consisting of N, O, and S. In some embodiments, the optionally substituted 5- to 14-membered heteroaryl is selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, quinolinyl, isoquinolinyl, quinoxalinyl, cinnolinyl, indolizinyl, azaindolizinyl, indolyl, azaindolyl, benzoxazolyl, benzthiazolyl, benzfuranyl, benzthiophenyl, imidazopyridinyl, imidazopyrazinyl, and benzimidazolyl.In some embodiments, the heteroaryl is a 5- or 6-membered heteroaryl ring. In some embodiments, the 5-membered heteroaryl is optionally substituted pyrazolyl, imidazolyl, or oxazolyl. In some embodiments, the 6-membered heteroaryl is optionally substituted pyridinyl, pyrimidinyl, pyrazinyl, or pyridazinyl. In some embodiments, cycloalkyl is optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments, aryl is optionally substituted with one or more substituents selected from the group consisting of halogen, C_{1-6}haloalkyl, C_{1-6}alkyl, O-C_{1-6}alkyl, O-C_{1-6}haloalkyl, or C_{3-6}cycloalky. In some embodiments, heteroaryl is optionally substituted with one or more substituents selected from the group consisting of halogen, C_{1-6}haloalkyl, C_{1-6}alkyl, O-C_{1-6}alkyl, O-C_{1-6}haloalkyl, or C_{3-6}cycloalky.

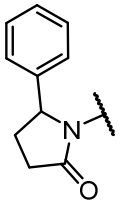
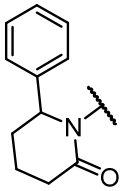
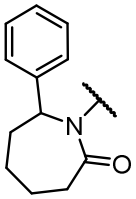
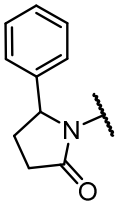
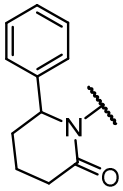
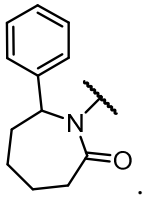
[0202] In some embodiments of Formula (I), R^4 is $-(CO)R^2$ and R^5 is aryl. In some embodiments, R^4 is $-(CO)R^2$ and R^5 is heteroaryl. In some embodiments, R^4 is $-(CO)R^2$ and R^5 is cycloalkyl. In some embodiments, the aryl is optionally substituted phenyl. In some embodiments, the aryl is optionally substituted phenyl. In some embodiments, the heteroaryl is a 5- to 14-membered heteroaryl having 1, 2, or 3 heteroatoms selected from the group consisting of N, O, and S. In some embodiments, the optionally substituted 5- to 14-membered heteroaryl is selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, quinolinyl, isoquinolinyl, quinoxalinyl, cinnolinyl, indolizinyl, azaindolizinyl, indolyl, azaindolyl, benzoxazolyl, benzthiazolyl, benzfuranyl, benzthiophenyl, imidazopyridinyl, imidazopyrazinyl, and

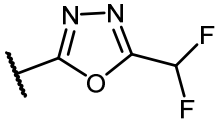
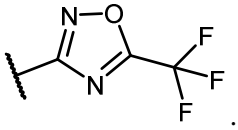
benzimidazolyl. In some embodiments, the heteroaryl is a 5- or 6-membered heteroaryl ring. In some embodiments, the 5-membered heteroaryl is optionally substituted pyrazolyl, imidazolyl, oxazolyl, In some embodiments, the 6-membered heteroaryl is optionally substituted pyridinyl, pyrimidinyl, pyrazinyl, or pyridazinyl. In some embodiments, cycloalkyl is optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments, aryl is optionally substituted with one or more substituents selected from the group consisting of halogen, C_{1-6}haloalkyl, C_{1-6}alkyl, O-C_{1-6}alkyl, O-C_{1-6}haloalkyl, or C_{3-6}cycloalky. In some embodiments, heteroaryl is optionally substituted with one or more substituents selected from the group consisting of halogen, C_{1-6}haloalkyl, C_{1-6}alkyl, O-C_{1-6}alkyl, O-C_{1-6}haloalkyl, or C_{3-6}cycloalky.

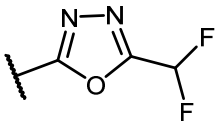
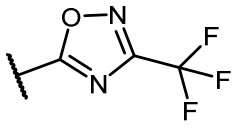
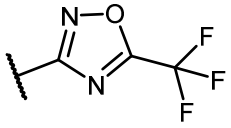
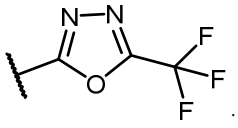
[0203] In some embodiments of Formula (I), R^4 is $-(SO_2)R^2$ and R^5 is aryl. In some embodiments, R^4 is $-(SO_2)R^2$ and R^5 is heteroaryl. In some embodiments, R^4 is $-(SO_2)R^2$ and R^5 is cycloalkyl. In some embodiments, the aryl is optionally substituted phenyl. In some embodiments, the heteroaryl is a 5- to 14-membered heteroaryl having 1, 2, or 3 heteroatoms selected from the group consisting of N, O, and S. In some embodiments, the optionally substituted 5- to 14-membered heteroaryl is selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, quinolinyl, isoquinolinyl, quinoxalinyl, cinnolinyl, indolizinyl, azaindolizinyl, indolyl, azaindolyl, benzoxazolyl, benzthiazolyl, benzfuranyl, benzthiophenyl, imidazopyridinyl, imidazopyrazinyl, and benzimidazolyl. In some embodiments, the heteroaryl is a 5- or 6-membered heteroaryl ring. In some embodiments, the 5-membered heteroaryl is optionally substituted pyrazolyl, imidazolyl, or oxazolyl. In some embodiments, the 6-membered heteroaryl is optionally substituted pyridinyl, pyrimidinyl, pyrazinyl, or pyridazinyl. In some embodiments, cycloalkyl is optionally substituted cyclopropyl, cycloybutyl, cyclopentyl, or cyclohexyl. In some embodiments, aryl is optionally substituted with one or more substituents selected from the group consisting of halogen, C_{1-6}haloalkyl, C_{1-6}alkyl, O-C_{1-6}alkyl, O-C_{1-6}haloalkyl, or C_{3-6}cycloalkyl. In some embodiments, heteroaryl is optionally substituted with one or more substituents selected from the group consisting of halogen, C_{1-6}haloalkyl, C_{1-6}alkyl, O-C_{1-6}alkyl, O-C_{1-6}haloalkyl, or C_{3-6}cycloalkyl. In some embodiments, the C_{1-6}haloalkyl is CF_3, CHF_2, or CH_2F. In some embodiments, the O-C_{1-6}haloalkyl is OCF_3, $OCHF_2$, or OCH_2F. In some embodiments, cycloalkyl is optionally substituted with halogen, C_{1-6}alkyl, or O-C_{1-6}alkyl.

[0204] In some embodiments of Formula (I), R^4 and R^5 together with the atom to which they are attached form a cycloalkyl or heterocyclyl. In some embodiments, R^4 and R^5 together with the atom to which they are attached form a cycloalkyl or heterocyclyl, each of which is optionally substituted. In some embodiments, the cycloalkyl or heterocyclyl is optionally substituted with –$NS(O_2)$(alkyl)(aryl). In some embodiments, the alkyl is $C_{1\text{-}5}$alkyl and the aryl is phenyl optionally substituted with one or more halogen atoms. In some embodiments, the heterocyclyl is a 4- to 10-membered heterocyclyl. In some embodiments the heterocyclyl is a saturated 4- to 7-membered heterocyclyl.

[0205] In some embodiments of Formula (I), n is 0 and R^4 and R^5 together with the atom to which they are attached form an optionally substituted heterocyclyl selected from the group consisting of:

, , and . In some embodiments, the optionally substituted heterocyclyl is . In some embodiments, the optionally substituted heterocyclyl is . In some embodiments, the optionally substituted heterocyclyl is .

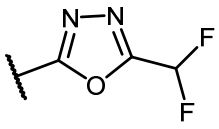
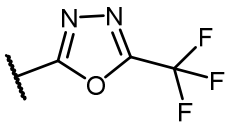
[0206] In some embodiments of Formula (I) R^1 is selected from the group consisting of  and .

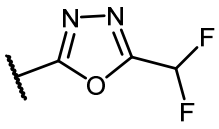
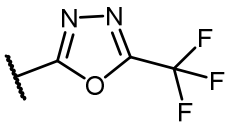
[0207] In some embodiments of Formula (I), R^1 is . In some embodiments, R^1 is . In some embodiments, R^1 is . In some embodiments, R^1 .

[0208] In some embodiments of Formula (I), R^a is H, halo, $C_{1\text{-}3}$alkyl, or haloalkyl. In some embodiments, R^a is H. In some embodiments, R^a is $C_{1\text{-}3}$alkyl. In some embodiments, R^a is haloalkyl. In some embodiments, halo is F. In some embodiments, the $C_{1\text{-}3}$alkyl alkyl is methyl, ethyl or isopropyl. In some embodiments, haloalkyl is CF_3, CHF_2, or CH_2F.

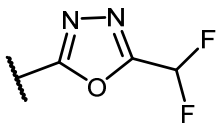
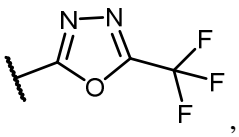
[0209] In some embodiments of Formula (I), Y is CH and R^4 and R^5 are H.

[0210] In some embodiments of Formula (I), Y is N, R^4 is H, and R^5 is ethyl optionally substituted with –N($S(O_2)$alkyl)(aryl) or –N($S(O_2)$cycloalkyl)(aryl). In some embodiments, alkyl is $C_{1\text{-}5}$alkyl, cycloalkyl is $C_{3\text{-}6}$cycloalkyl, and aryl is phenyl optionally substituted with one or more halogen atoms.

[0211] In some embodiments of Formula (I), n is 1, X^1 is O or N, Y is N, R^1 is  or , R^2 and R^3 are H, R^4 is H, -$C_{1\text{-}5}$alkyl, -C(O)alkyl, -C(O)cycloalkyl,-$(SO_2)NR^2R^3$, -SO_2alkyl, -SO_2haloalkyl and -SO_2cycloalkyl, each of which is optionally substituted, and R^5 is aryl, heteroaryl, or cycloalkyl, each of which is optionally substituted.

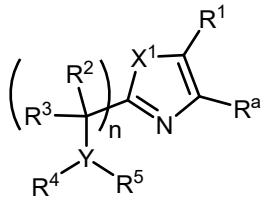
[0212] In some embodiments of Formula (I), n is 1, X^1 is O or N, Y is O, R^1 is  or , R^2 and R^3 are H, and R^5 is aryl, heteroaryl, cycloalkyl, or alkylenecycloalkyl, each of which is optionally substituted.

[0213] In some embodiments of Formula (I), n is 0, X^1 is O or N, Y is N, R^1 is

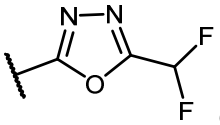
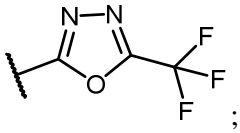
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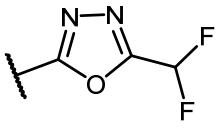
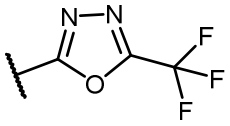
and R^4 and R^5 taken together with the atom to which they are attached form a cycloalkyl or heterocyclyl, each of which is optionally substituted.

[0214] In some embodiments, the present disclosure provides a compound of Formula (Ia) or a pharmaceutically acceptable salt thereof:

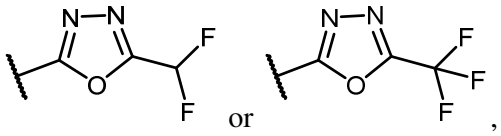
 (Ia), wherein:

[0215] R^1, R^2, R^3, R^4, R^5, R^a, X^1, n, and Y are as defined above for Formula (I).

[0216] In some embodiments of Formula (Ia), R^1 is  or ; n is 1; Y is N; X^1 is S or O; and variables R^2, R^3, R^4, R^5, and R^a are as defined above for Formula (I).

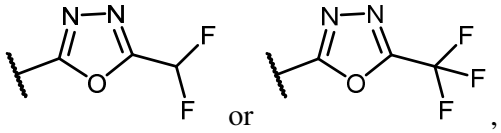
[0217] In some embodiments of Formula (Ia), n is 1, X^1 is S, Y is N, R^1 is  or , R^2 and R^3 are H, R^4 is -SO_2alkyl, -SO_2haloalkyl, or -SO_2cycloalkyl, each of which is optionally substituted, R^5 is heteroaryl, each of which is optionally substituted, and R^a is H or F. In some further embodiments, R^4 is -$SO_2C_{1\text{-}5}$alkyl, -SO_2cyclopropyl, -SO_2CF_3 or -SO_2CHF_2, and the heteroaryl is optionally substituted pyridine or pyrazine. In some further embodiments, the heteroaryl is optionally substituted pyridine.

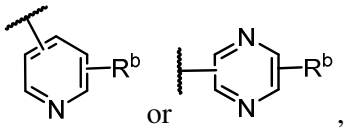
[0218] In some embodiments of Formula (Ia), n is 1, X^1 is S, Y is N, R^1 is

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R^2 and R^3 are H, R^4 is $-SO_2Me$, $-SO_2Et$, or $-SO_2$cyclopropyl, each of which is optionally substituted, R^5 is pyridine or pyrazine, each of which is optionally substituted, and R^a is H. In some embodiments, R^5 is optionally substituted pyridine.

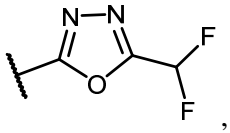
[0219] In some embodiments of Formula (Ia), n is 1, X^1 is S, Y is N, R^1 is

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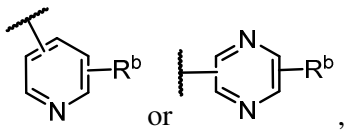
R^2 and R^3 are H, R^4 is $-SO_2$alkyl or $-SO_2$cycloalkyl, each of which is optionally substituted, R^5 is  ,

wherein R^b is selected from the group consisting of halogen, $-C_{1-5}$alkyl, haloalkyl, $-OC_{1-5}$alkyl, -Ohaloalkyl, $-CH_2$Ohaloalkyl, cyclopropyl, and CN, and R^a is H. In some embodiments, the halogen is F or Cl. In some embodiments, the haloalkyl is CF_3, CHF_2, CH_2CF_3, or CF_2CH_3. In some embodiments, the $-C_{1-5}$alkyl is methyl.

[0220] In some embodiments of Formula (Ia), n is 1, X^1 is S, Y is N, R^1 is

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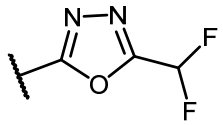
R^2 and R^3 are H, R^4 is $-SO_2Me$, $-SO_2Et$, or $-SO_2$cyclopropyl, each of which is optionally substituted, and R^5 is

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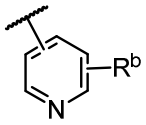
wherein R^b is selected from the group consisting of halogen, $-C_{1-5}$alkyl, haloalkyl, $-OC_{1-5}$alkyl, -Ohaloalkyl, $-CH_2$Ohaloalkyl, cyclopropyl, or CN, and R^a is H. In some embodiments, the

halogen is F or Cl. In some embodiments, the haloalkyl is CF_3, CHF_2, CH_2CF_3, or CF_2CH_3. In some embodiments, the -$C_{1\text{-}5}$alkyl is methyl.

[0221] In some embodiments of Formula (Ia), n is 1, X^1 is S, Y is N, R^1 is

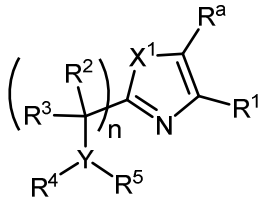


R^2 and R^3 are H, R^4 is -SO_2Me, -SO_2Et, or -SO_2cyclopropyl, each of which is optionally substituted, and R^5 is



wherein R^b is selected from the group consisting of Cl, F, Me, cyclopropyl, CF_3, CHF_2, CF_2CH_3, OCF_3, $OCHF_2$, OCH2CF2H and CN, and R^a is H.

[0222] In some embodiments, the present disclosure provides a compound of Formula (Ib) or a pharmaceutically acceptable salt thereof:



(Ib), wherein:

R^1, R^2, R^3, R^4, R^5, R^a, X^1, n, and Y are as defined above for Formula (I).

[0223] In some embodiments of Formulas (I)-(Ib), each optionally substituted alkyl is independently an optionally substituted $C_{1\text{-}6}$ alkyl. In some embodiments, the $C_{1\text{-}6}$ alkyl is Me or Et.

[0224] In some embodiments of Formulas (I)-(Ib), each optionally substituted haloalkyl is independently an optionally substituted $C_{1\text{-}6}$ haloalkyl. In some embodiments, the $C_{1\text{-}6}$ haloalkyl is CF_3, CHF_2, or CH_2F. In some embodiments, the $C_{1\text{-}6}$ haloalkyl is CF_3 or CHF_2.

[0225] In some embodiments of Formulas (I)-(Ib), each optionally substituted cycloalkyl is independently an optionally substituted $C_{3\text{-}12}$ cycloalkyl. In some embodiments, the cycloalkyl

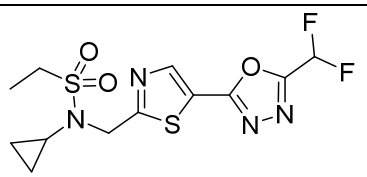
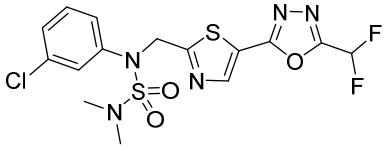
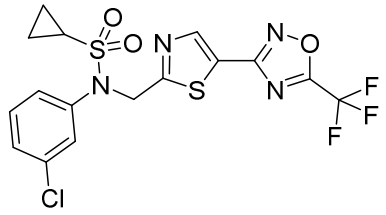
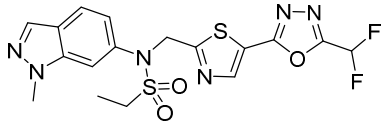
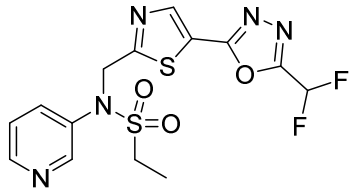
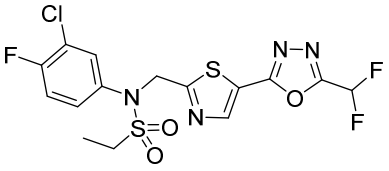
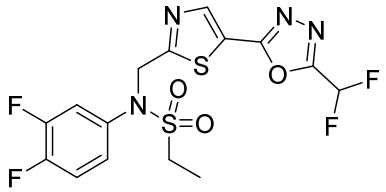
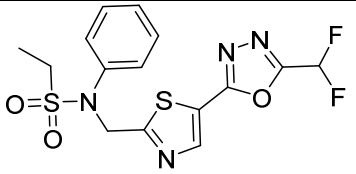
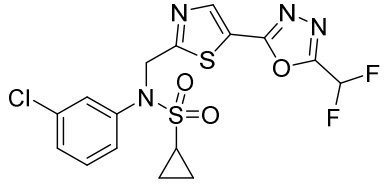
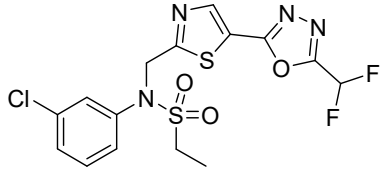
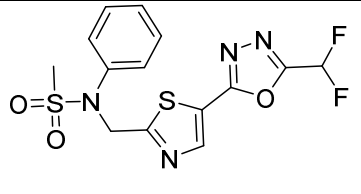
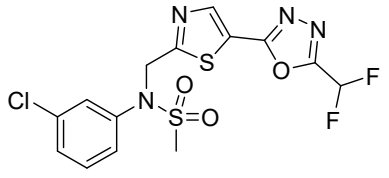
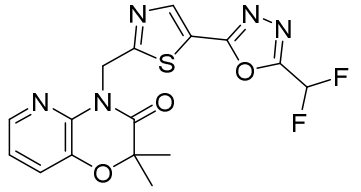
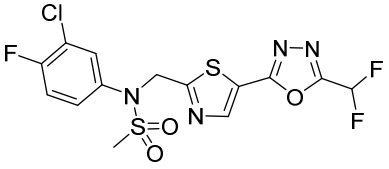
is a C_{3-6} cycloalkyl. In some embodiments, the cycloalkyl is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

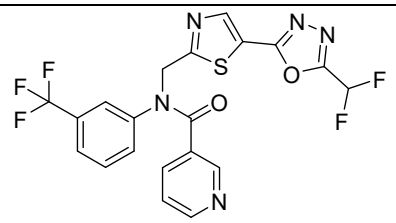
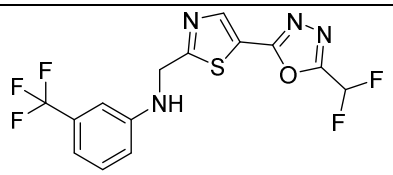
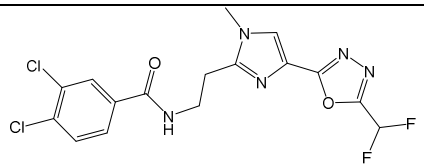
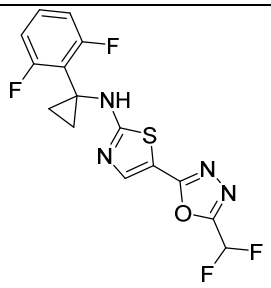
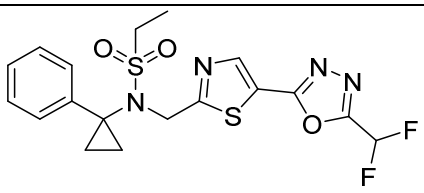
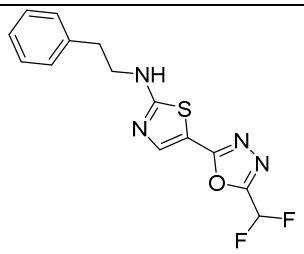
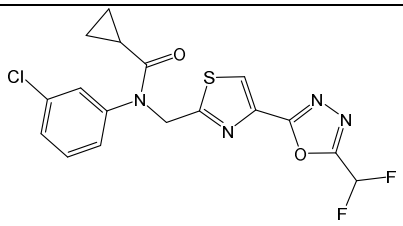
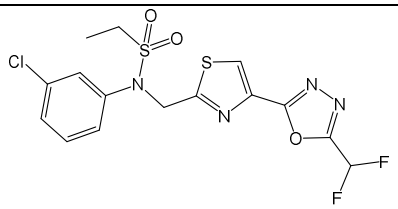
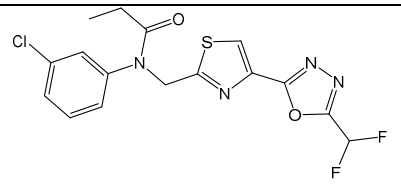
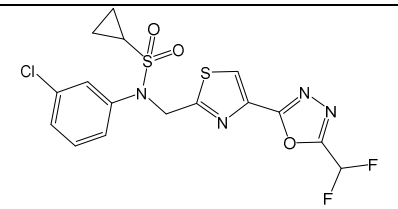
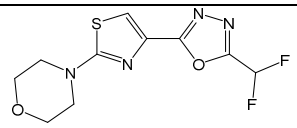
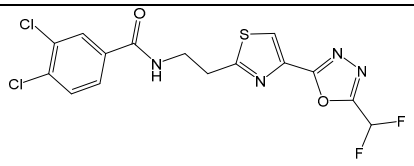
[0226] In some embodiments of Formulas (I)-(Ib), each optionally substituted heterocyclyl is independently an optionally substituted 3-12 membered heterocycloalkyl having 1 or 2 heteroatoms independently selected from N, O, and S. In some embodiments, each optionally substituted heterocyclyl is independently an optionally substituted 3-6 membered heterocycloalkyl having 1 or 2 heteroatoms independently selected from N, O, and S. In further embodiments, the heterocycloalkyl is an optionally substituted 5-membered or 6-membered heterocycle having 1 or 2 heteroatoms independently selected from N, O, and S. In some embodiments, the heterocyclyl is selected from the group consisting of aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, and morpholinyl, and thiomorpholinyl.

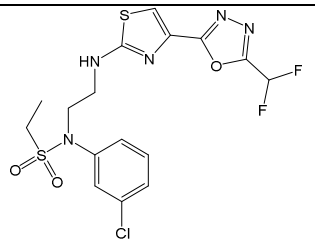
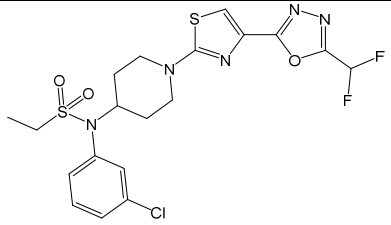
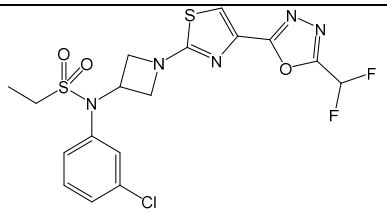
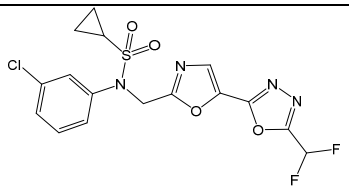
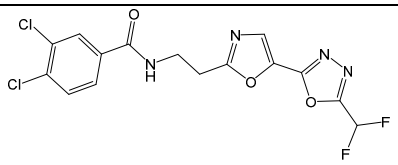
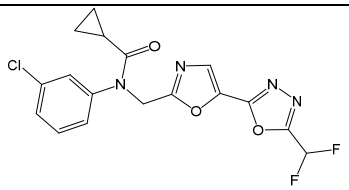
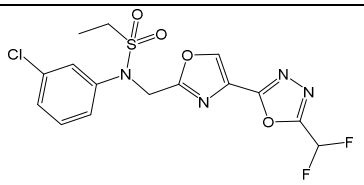
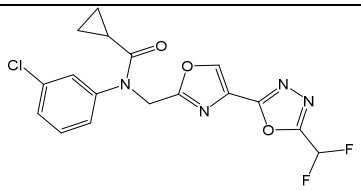
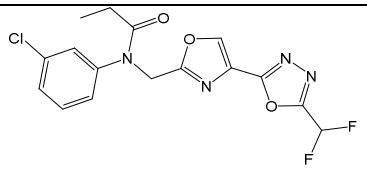
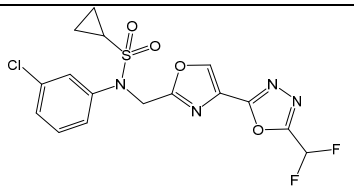
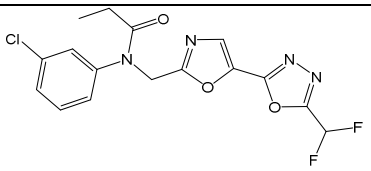
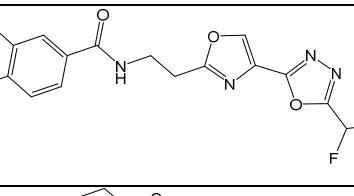
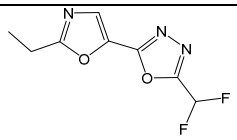
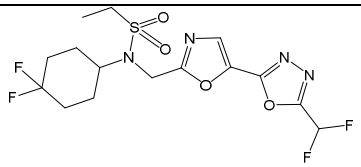
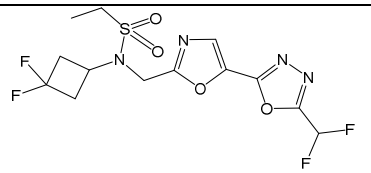
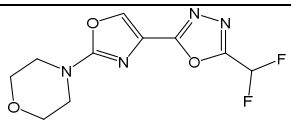
[0227] In some embodiments of Formulas (I)-(Ib), each optionally substituted aryl is independently a C_{6-12} aryl. In further embodiments, the C_{6-12} aryl is an optionally substituted phenyl.

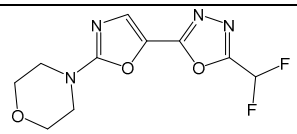
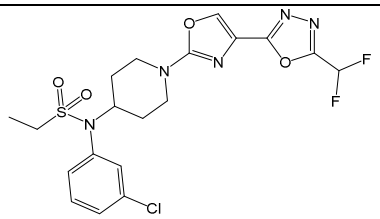
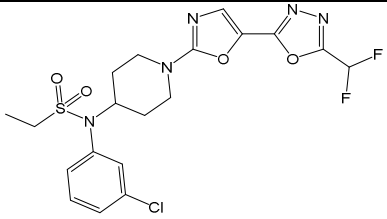
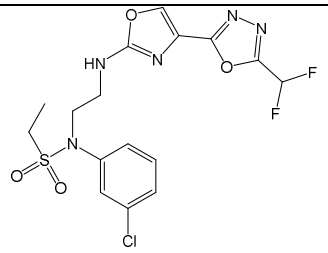
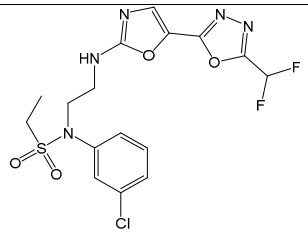
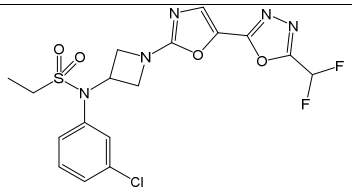
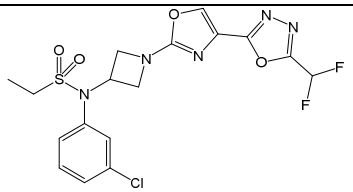
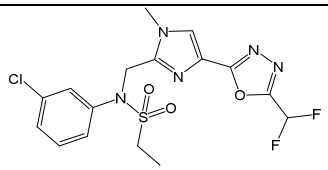
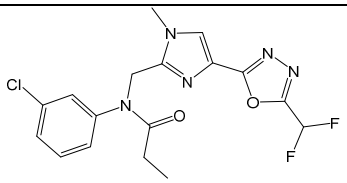
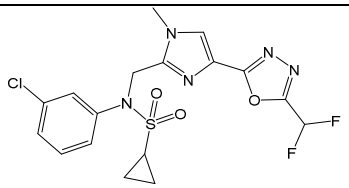
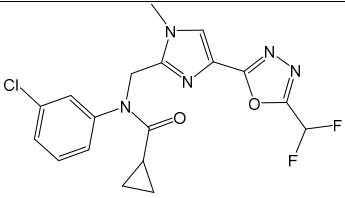
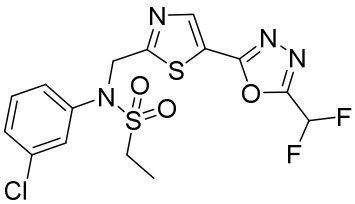
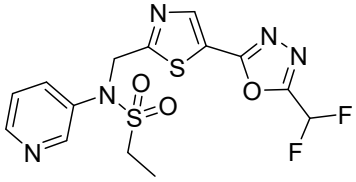
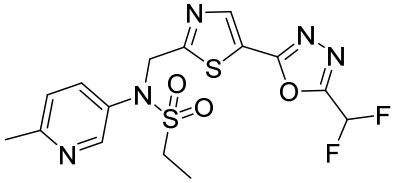
[0228] In some embodiments of Formulas (I)-(Ib), each optionally substituted heteroaryl is independently a 5-12 membered heteroaryl having 1, 2, or 3 heteroatoms independently selected from N, O, and S. In some embodiments, each optionally substituted heteroaryl is independently a 5-12 membered heteroaryl having 3 heteroatoms independently selected from N, O, and S. In some embodiments, each optionally substituted heteroaryl is independently a 5-12 membered heteroaryl having 2 heteroatoms independently selected from N, O, and S. In some embodiments, each optionally substituted heteroaryl is independently a 5-12 membered heteroaryl having 1 heteroatom independently selected from N, O, and S. In further embodiments, each optionally substituted heteroaryl is an optionally substituted 5-membered or 6-membered heteroaryl having 1 heteroatom independently from N, O, and S. In some embodiments, each heteroaryl is independently selected from the group consisting of tetrazole, oxadiazole, thiadiazole, imidazole, pyrazole, thiazole, or oxazole, each of which is optionally substituted.

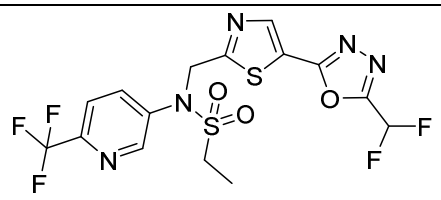
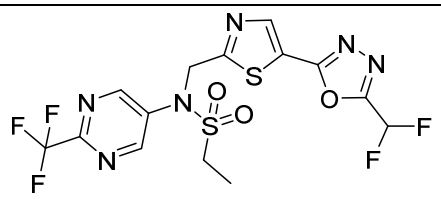
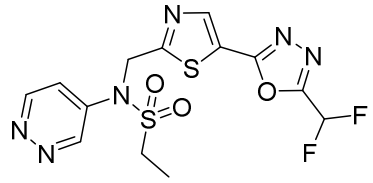
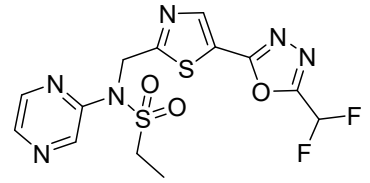
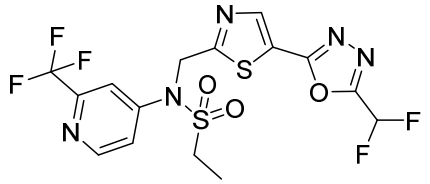
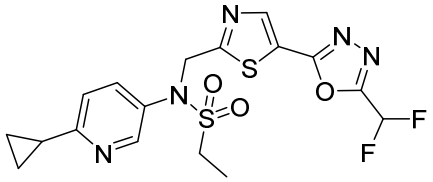
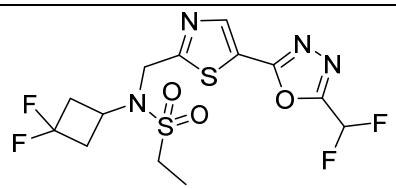
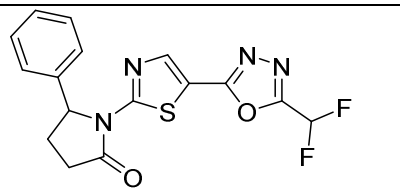
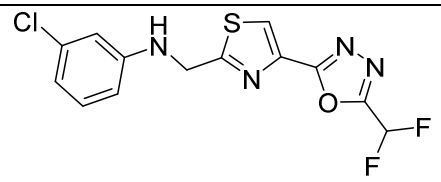
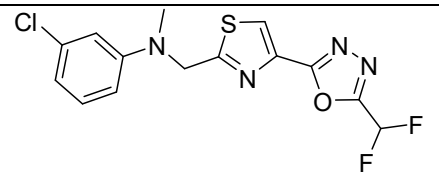
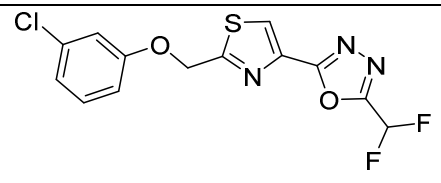
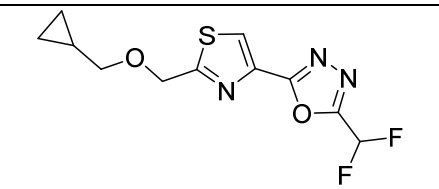
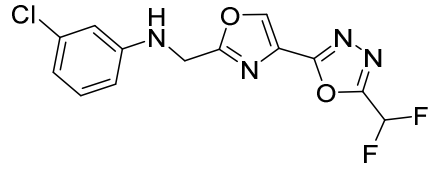
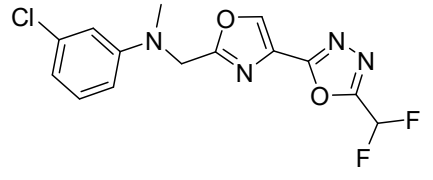
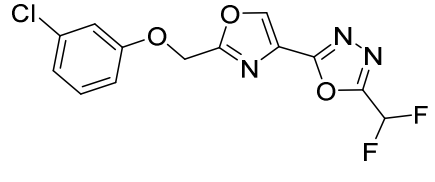
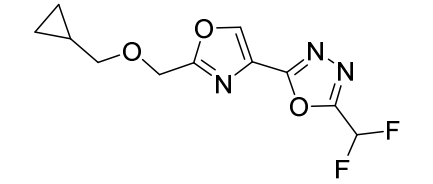
[0229] In some embodiments, the compound of Formula (I) is selected from the group consisting of:

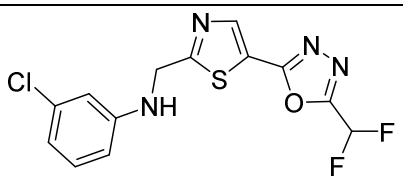
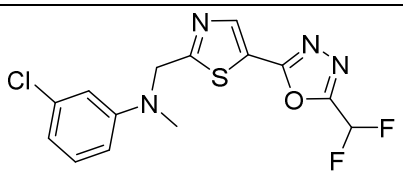
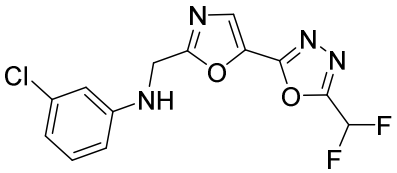
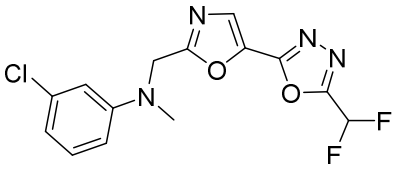
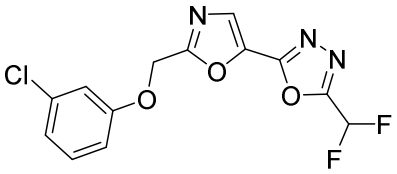
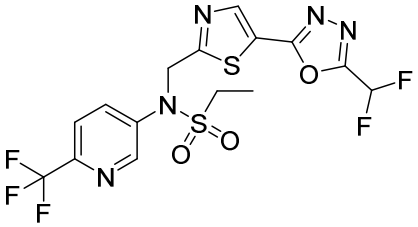
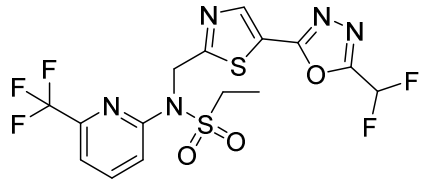
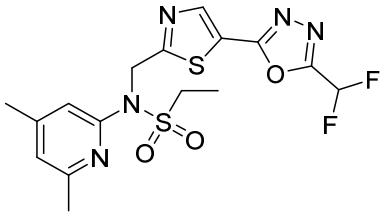
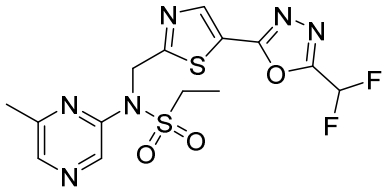
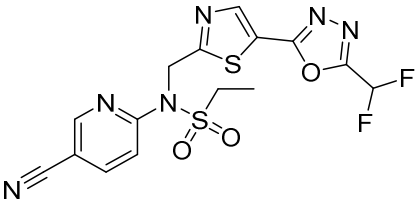
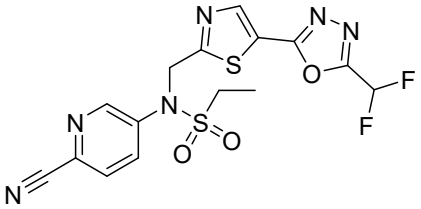
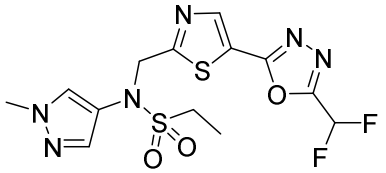
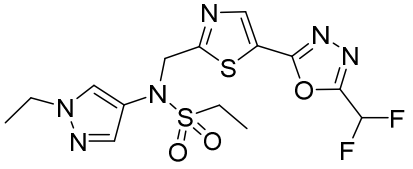
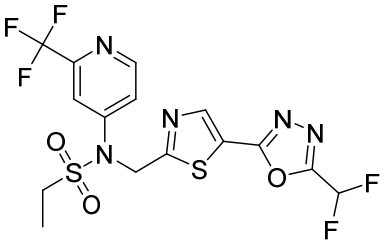
	
	
	
	
	
	
	

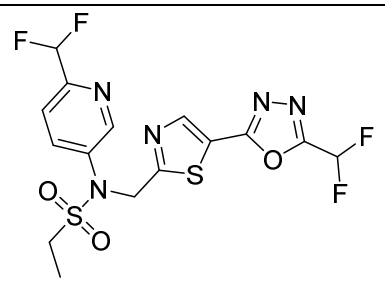
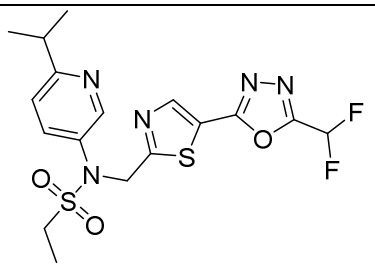
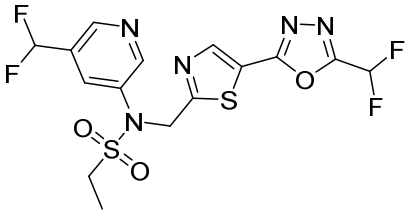
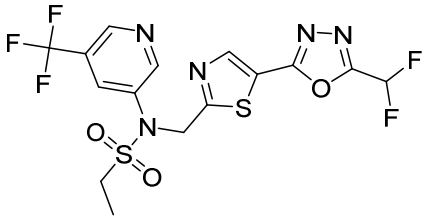
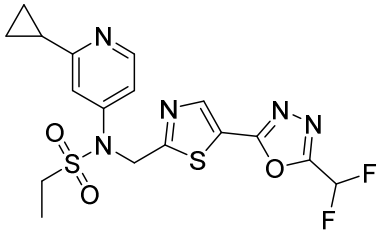
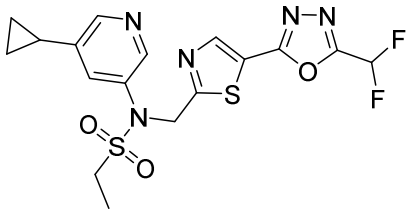
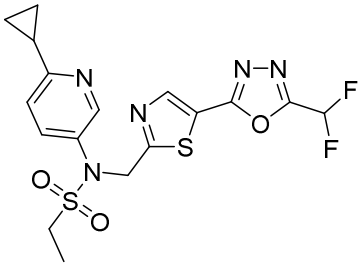
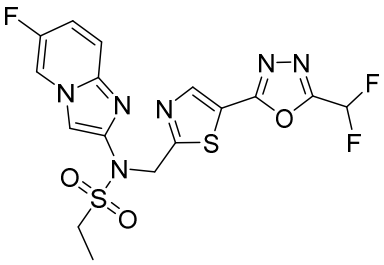
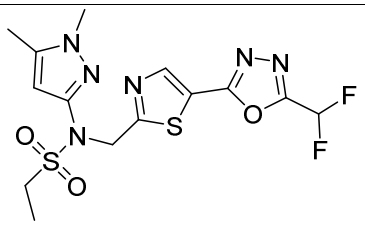
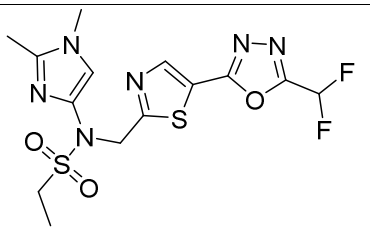
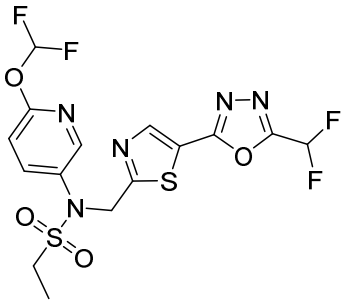
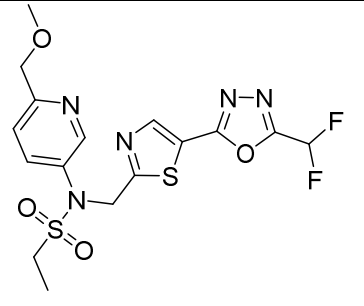
	
	
	
	
	
	

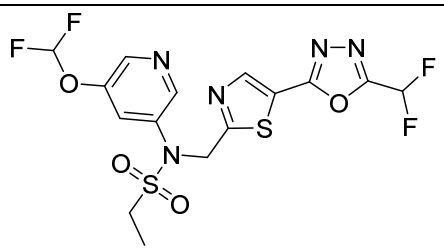
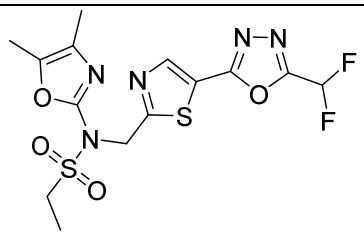
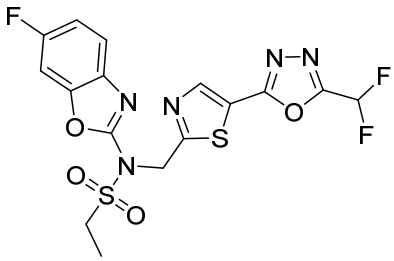
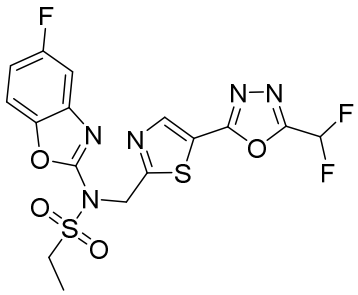
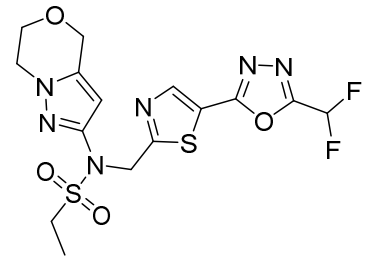
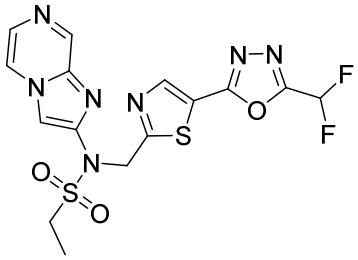
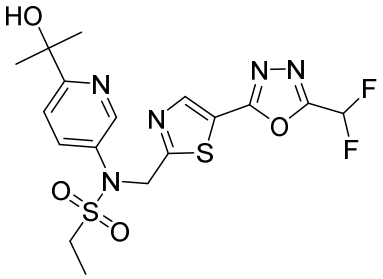
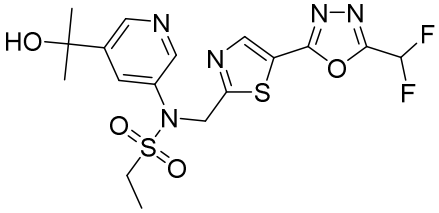
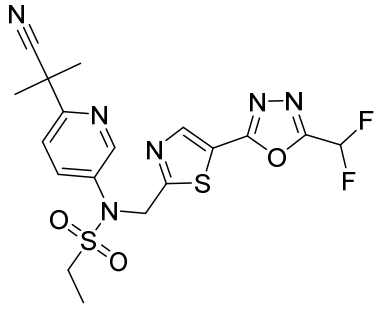
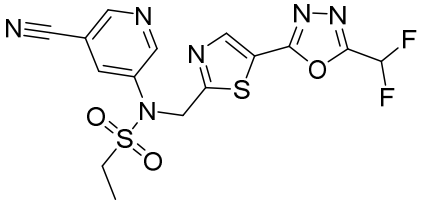
	
	
	
	
	
	
	
	

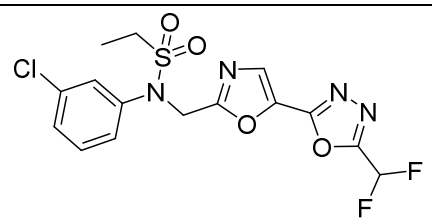
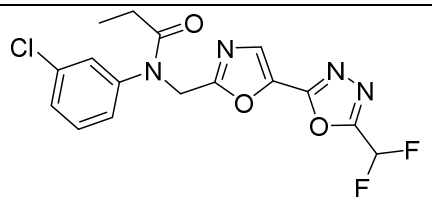
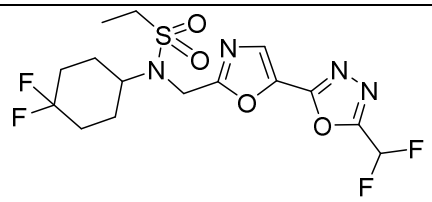
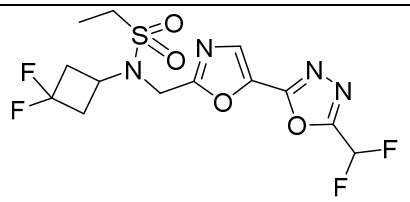
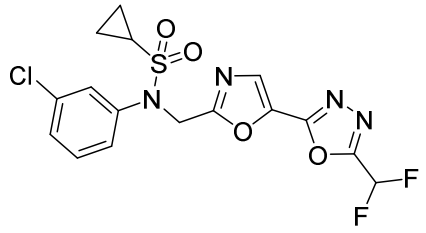
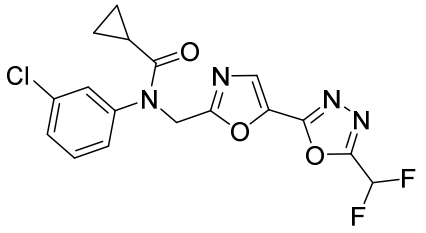
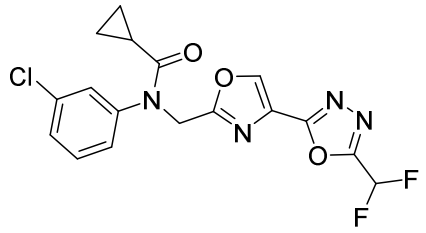
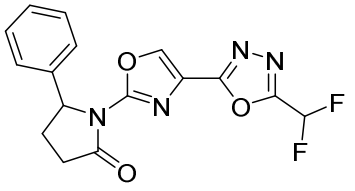
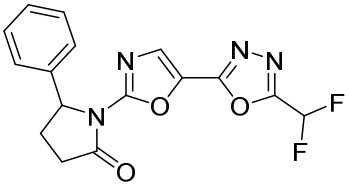
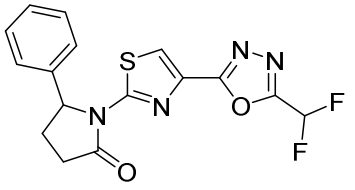
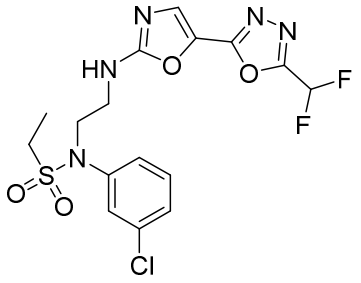
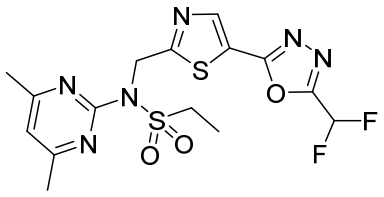
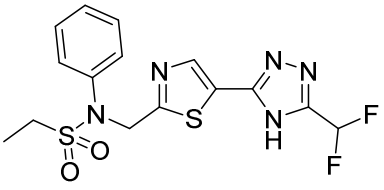
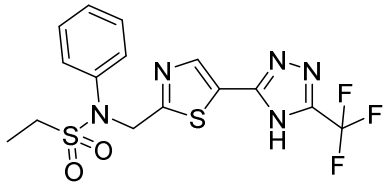
	
	
	
	
	
	
	
	

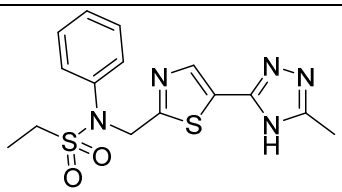
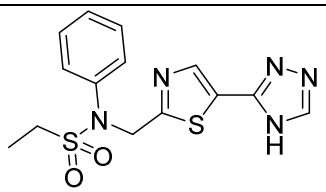
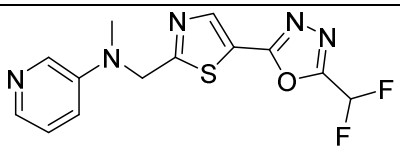
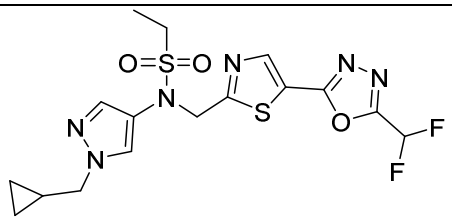
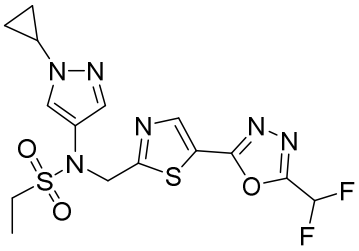
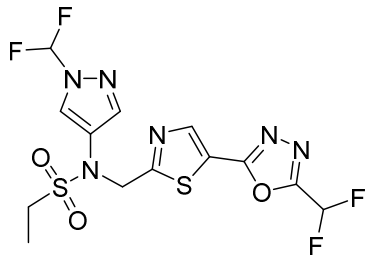
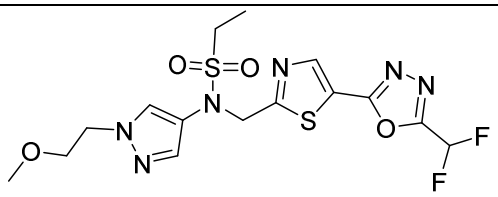
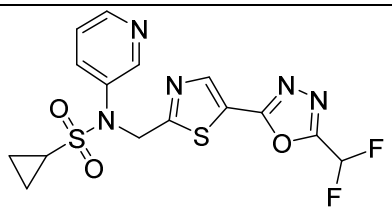
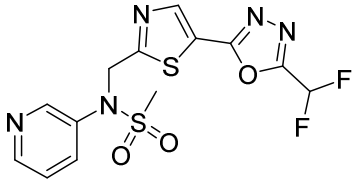
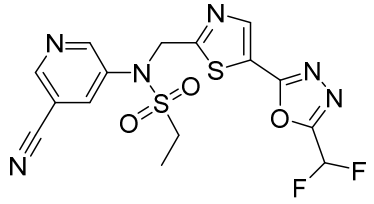
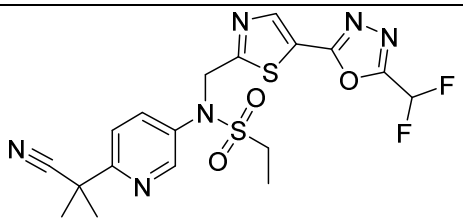
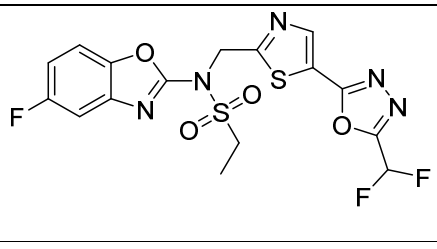
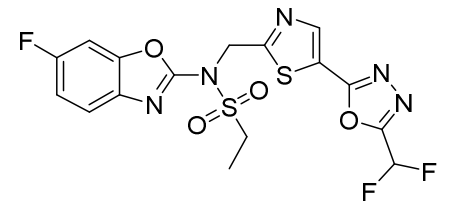
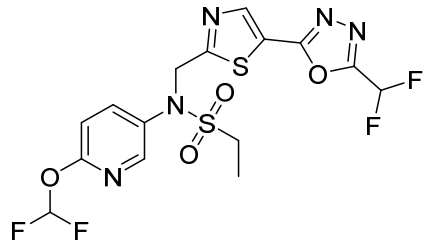
	
	
	
	
	
	
	
	

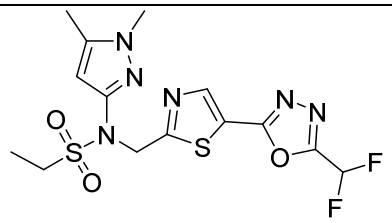
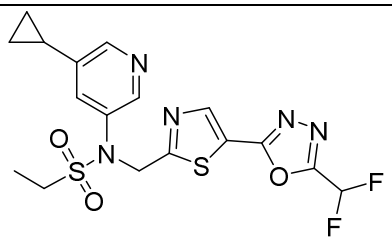
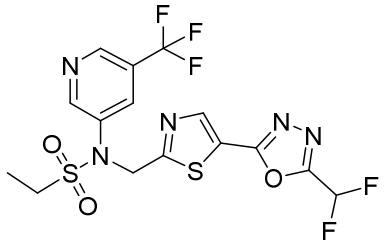
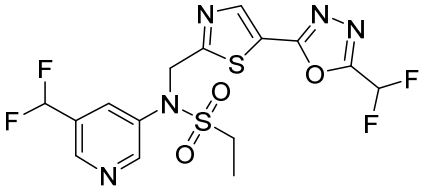
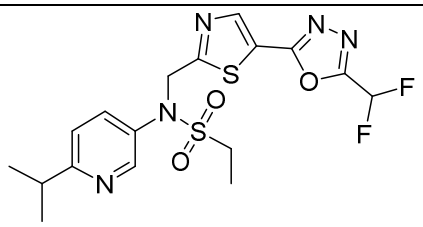
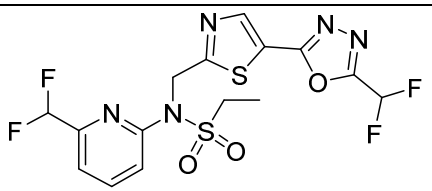
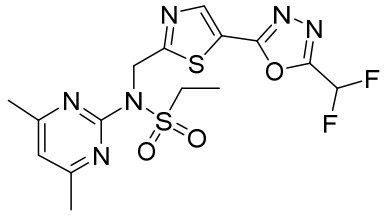
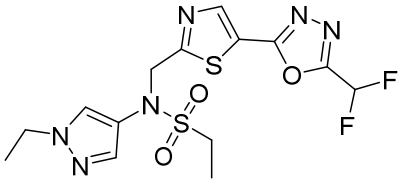
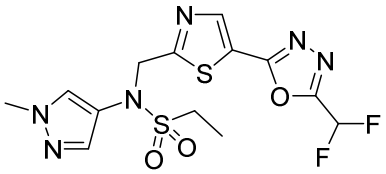
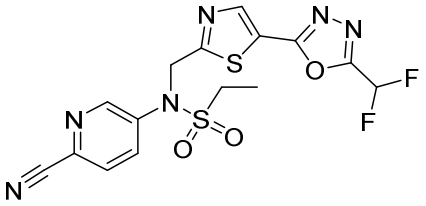
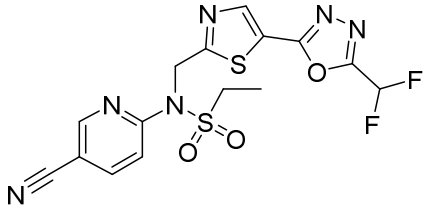
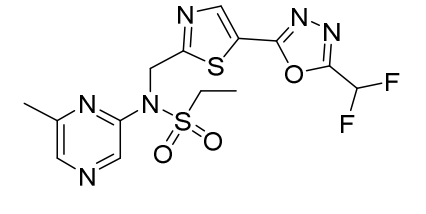
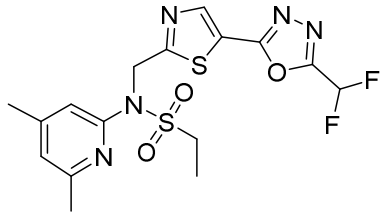
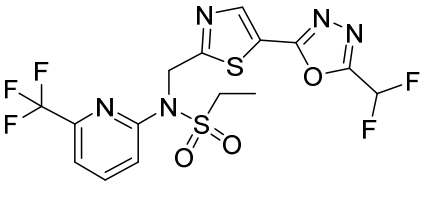
	
	
	
	
	
	
	

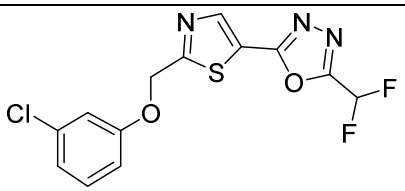
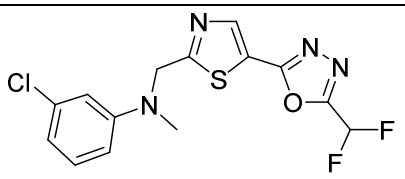
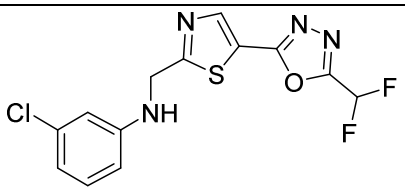
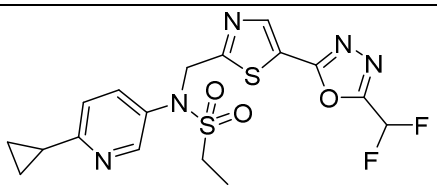
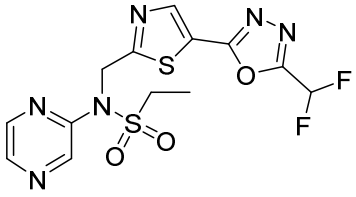
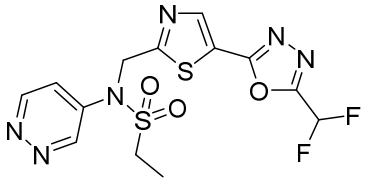
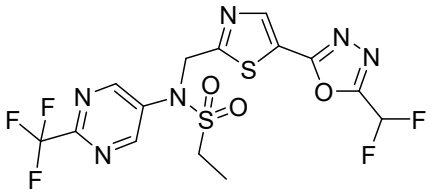
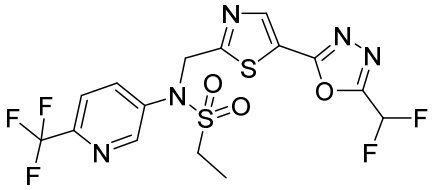
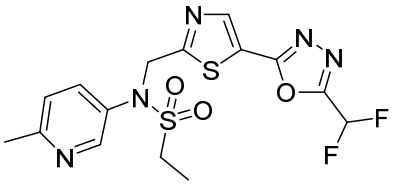
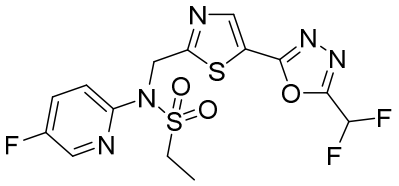
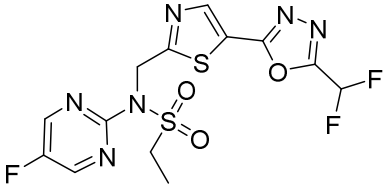
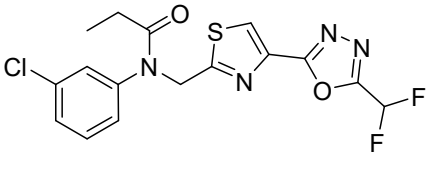
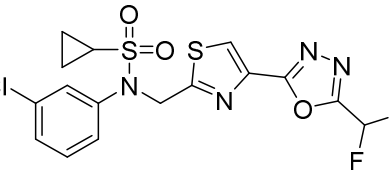
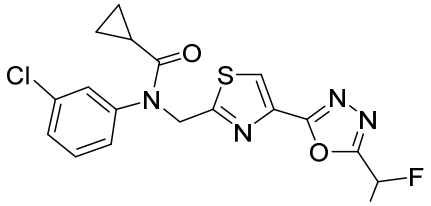
	
	
	
	
	
	

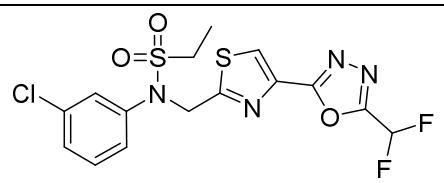
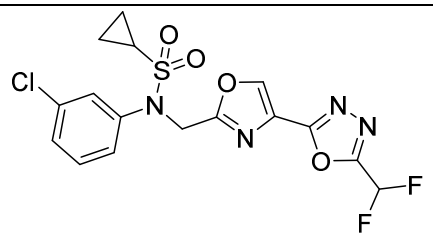
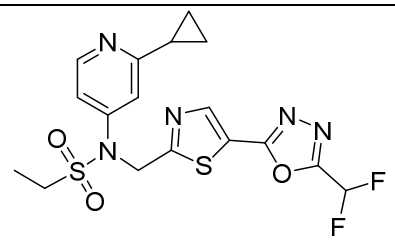
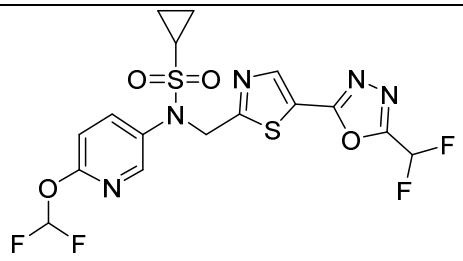
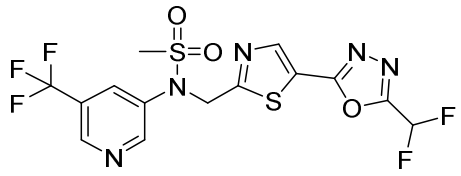
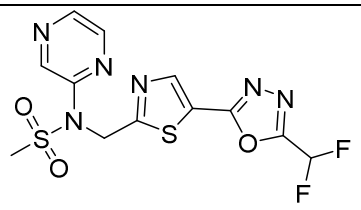
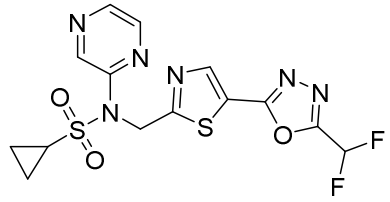
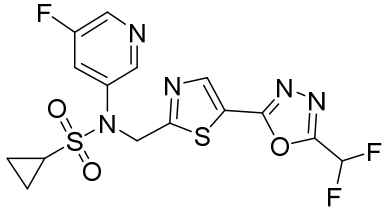
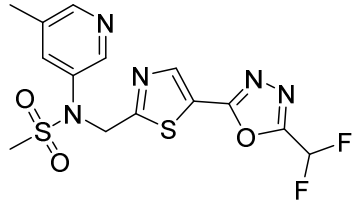
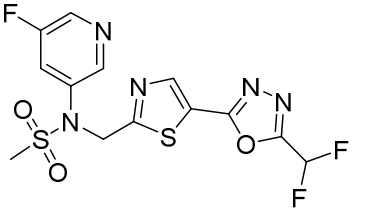
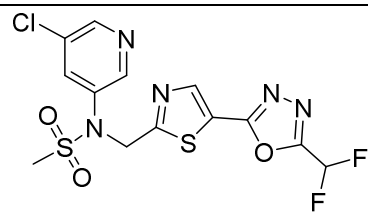
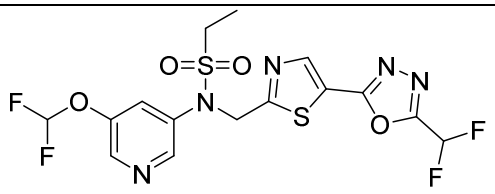
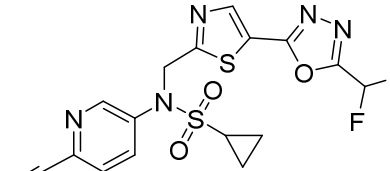
	
	
	
	
	

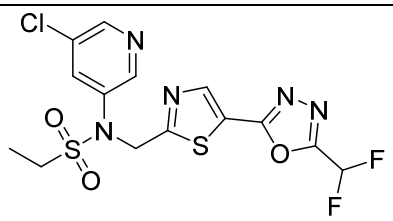
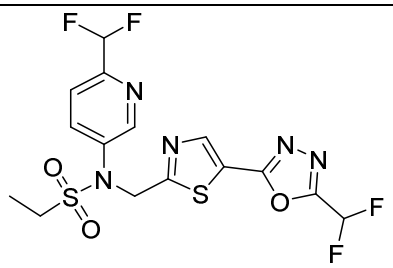
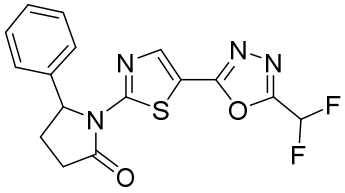
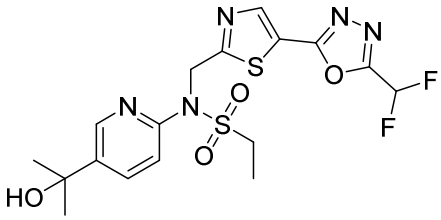
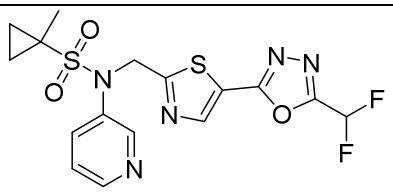
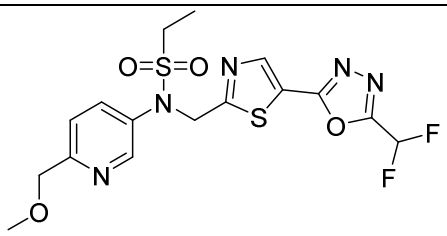
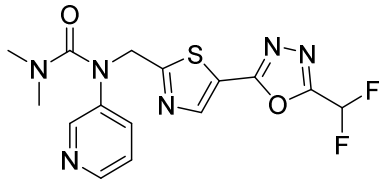
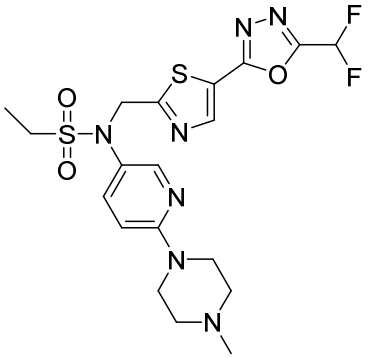
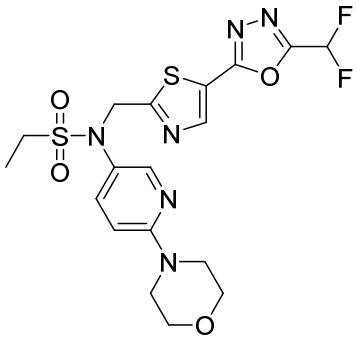
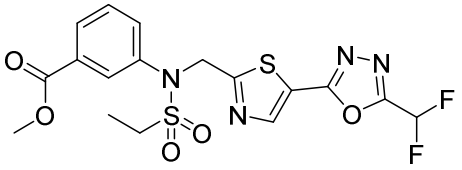
	
	
	
	
	
	
	

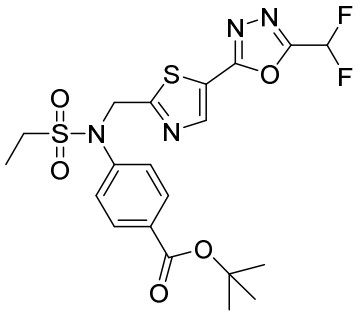
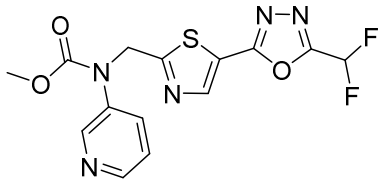
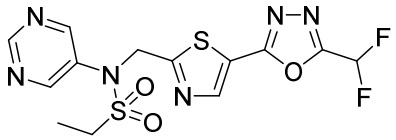
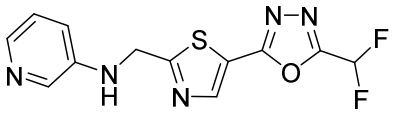
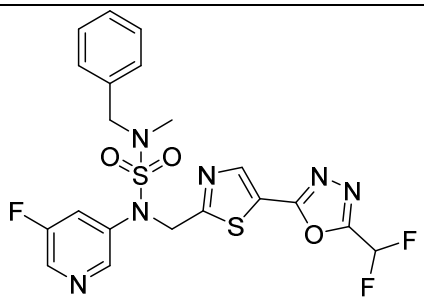
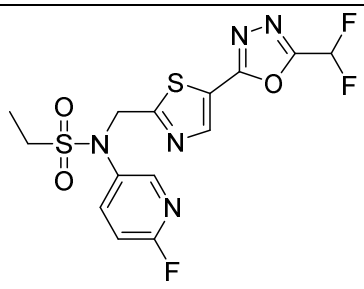
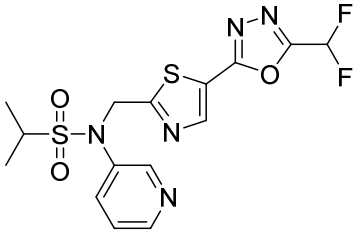
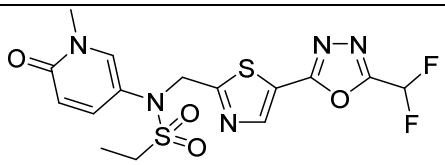
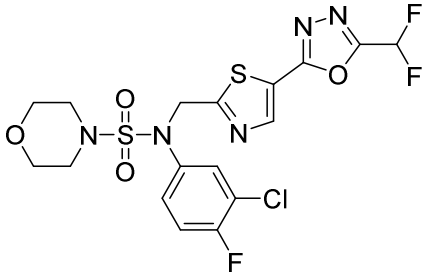
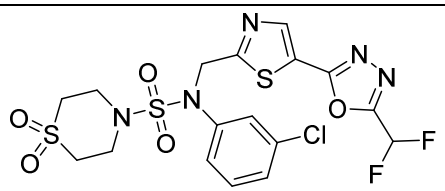
	
	
	
	
	
	
	

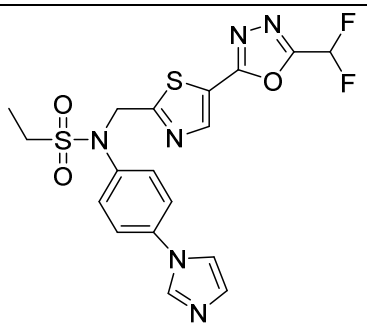
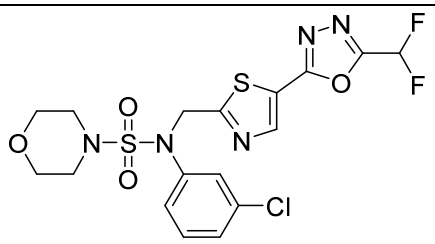
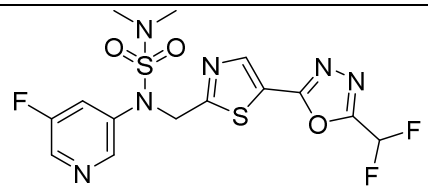
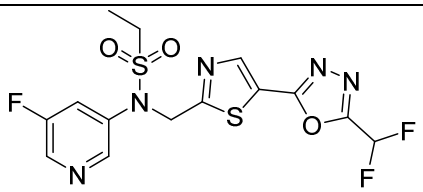
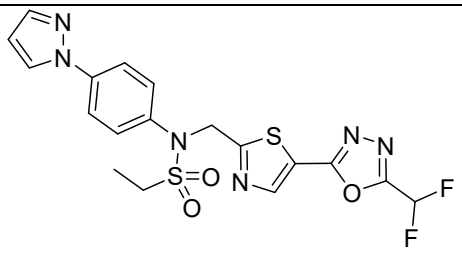
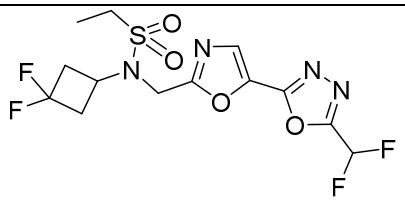
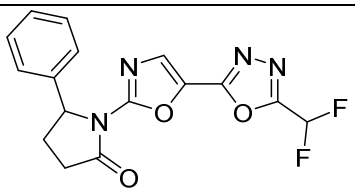
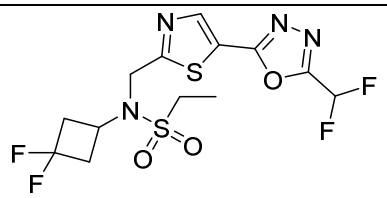
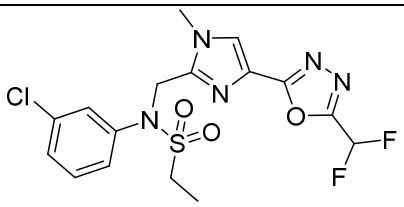
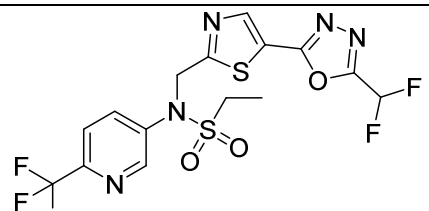
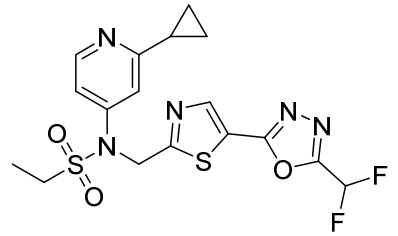
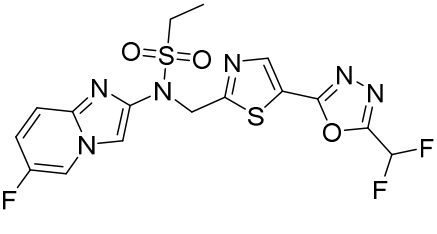
	
	
	
	
	
	
	

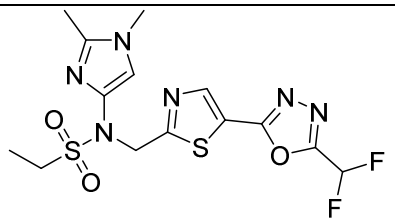
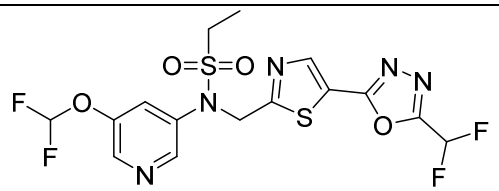
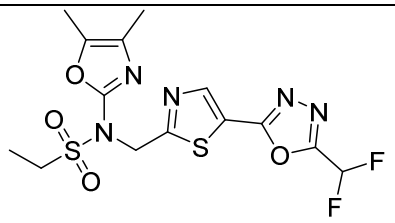
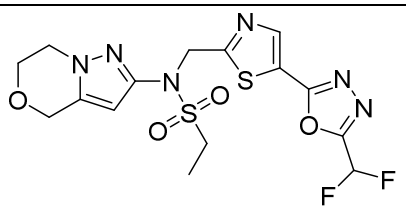
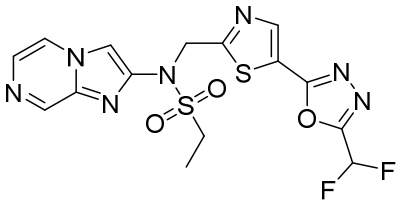
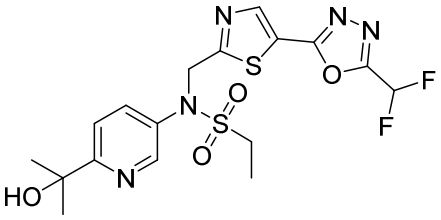
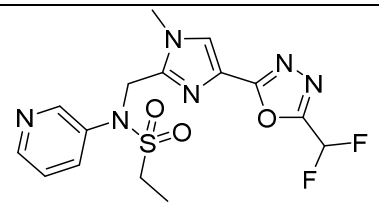
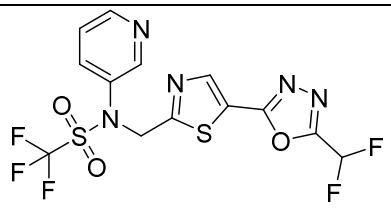
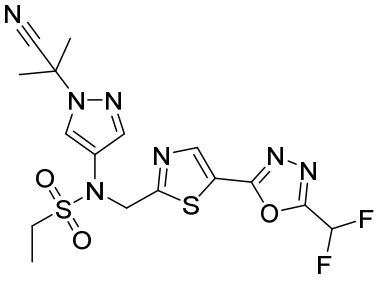
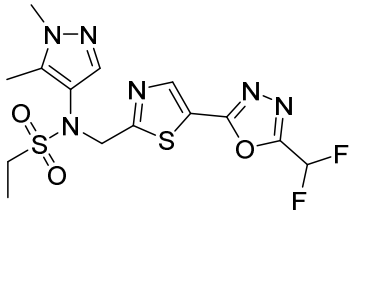
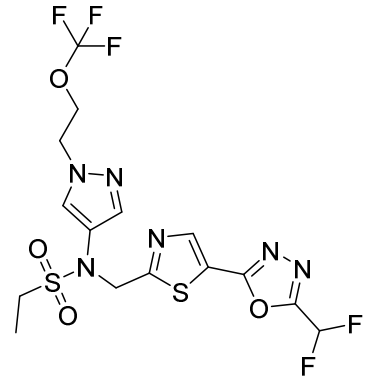
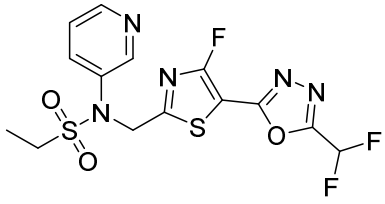
	
	
	
	
	
	
	

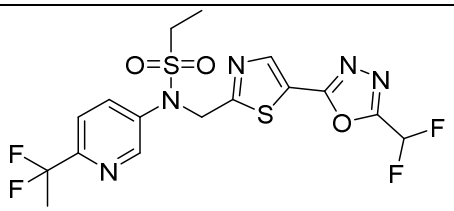
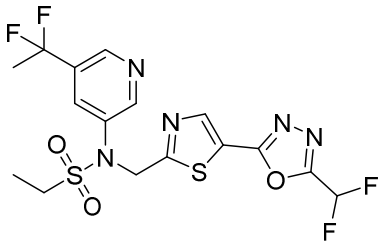
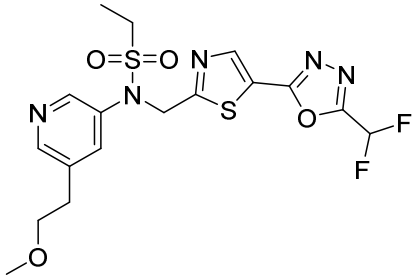
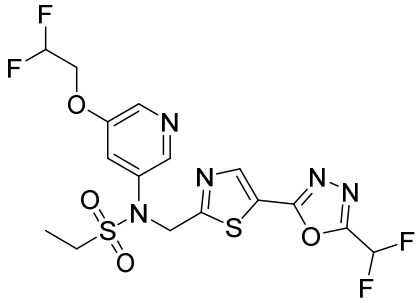
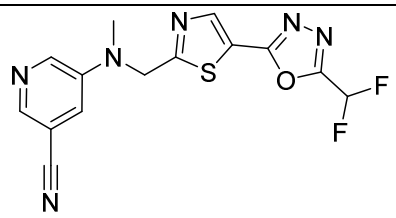
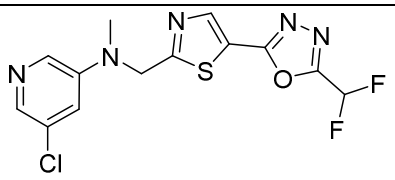
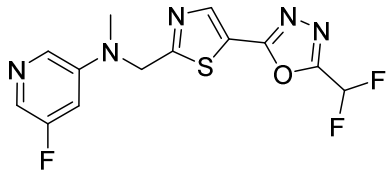
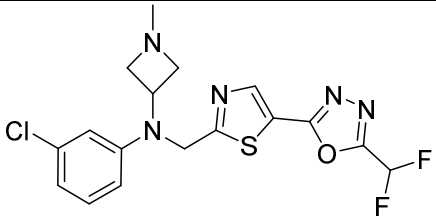
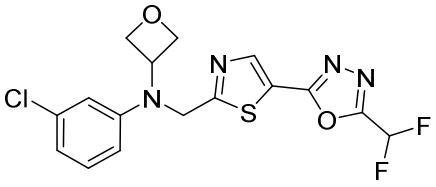
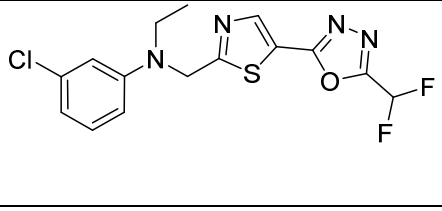
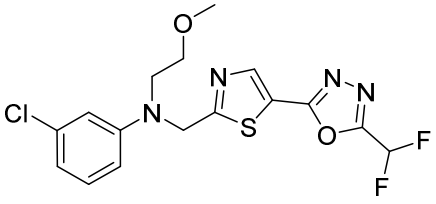
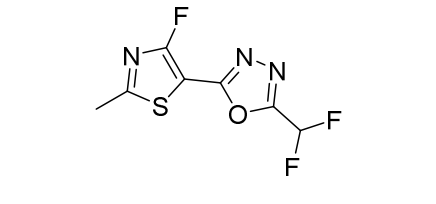
	
	
	
	
	
	
	

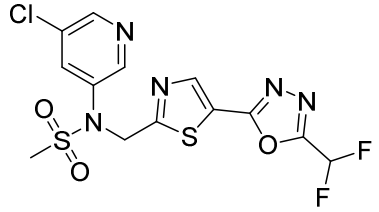
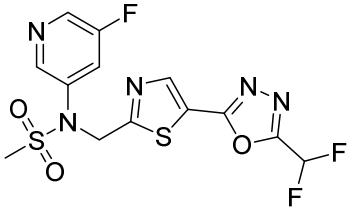
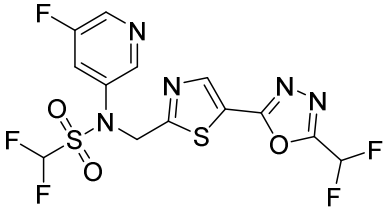
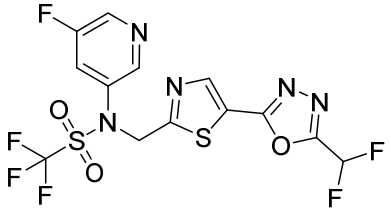
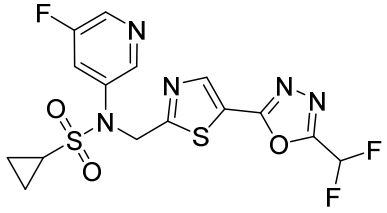
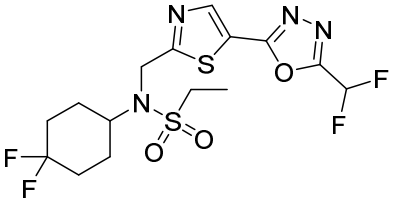
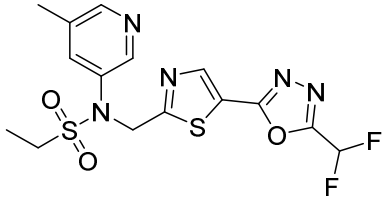
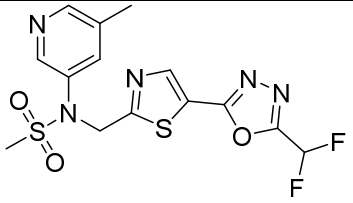
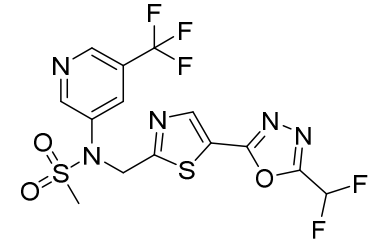
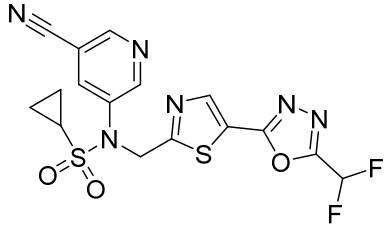
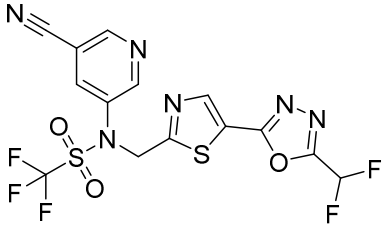
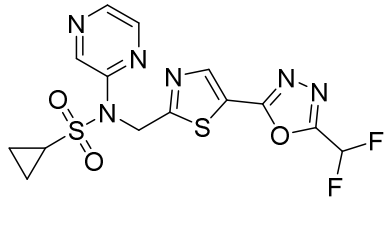
	
	
	
	
	

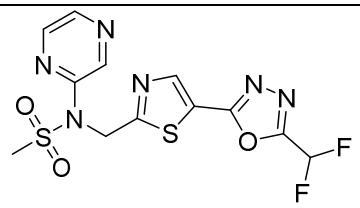
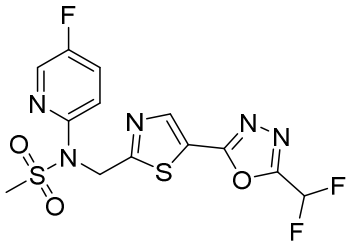
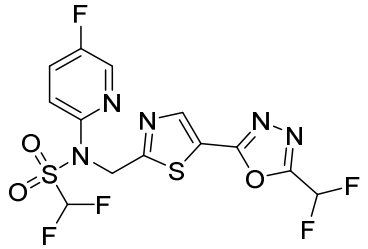
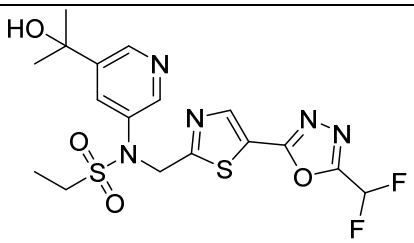
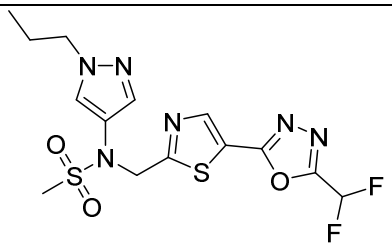
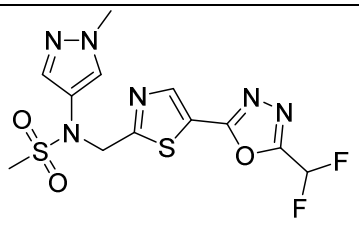
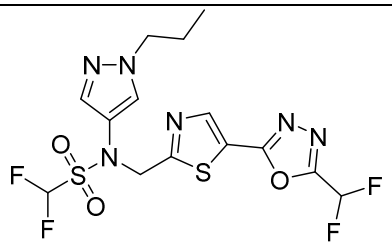
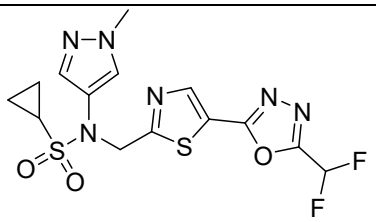
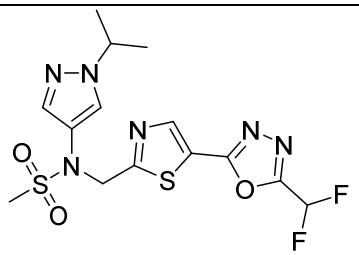
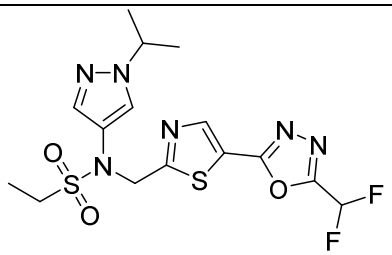
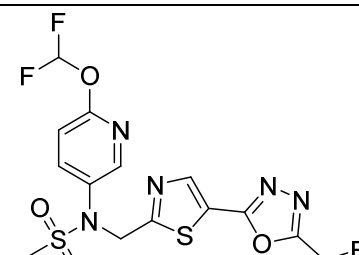
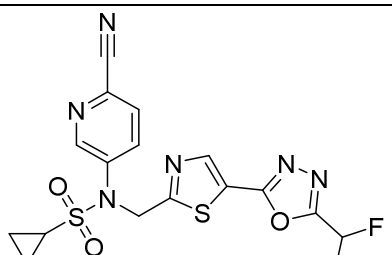
	
	
	
	
	

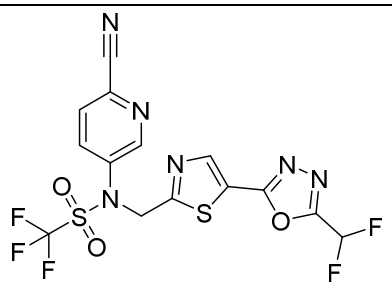
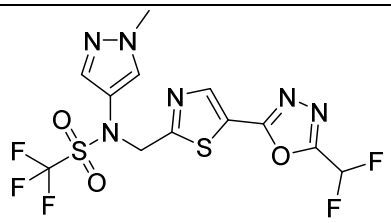
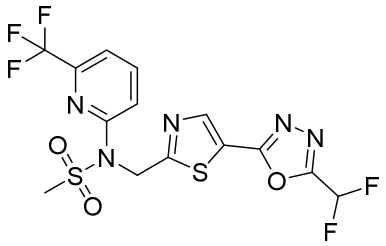
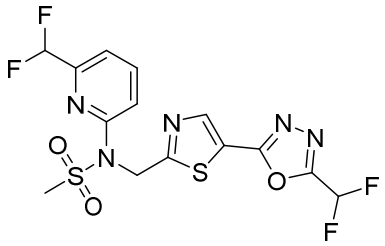
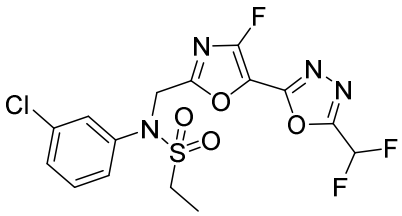
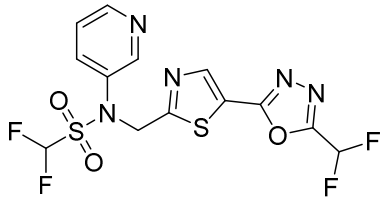
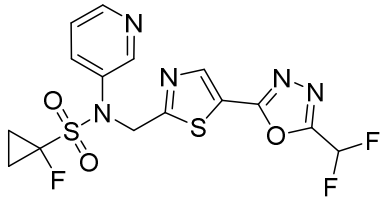
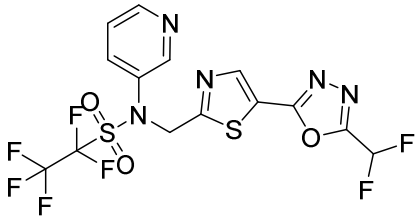
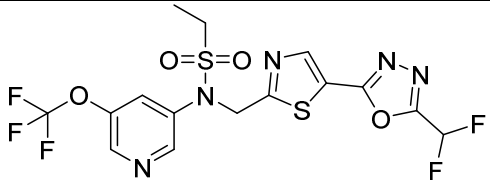
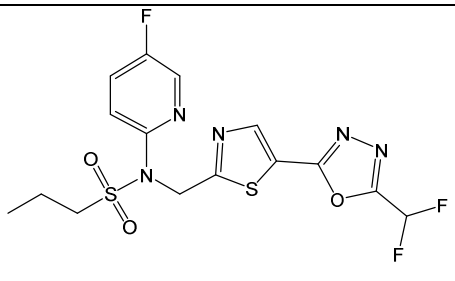
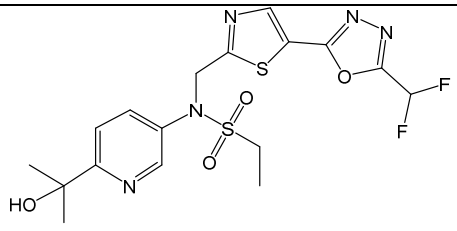
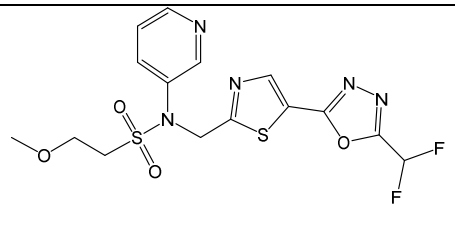
	
	
	
	
	
	

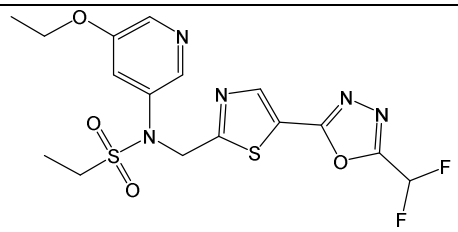
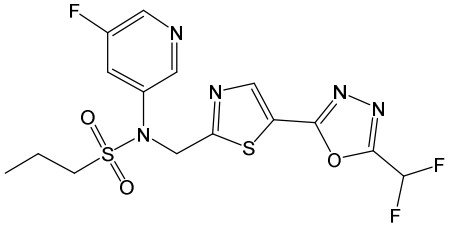
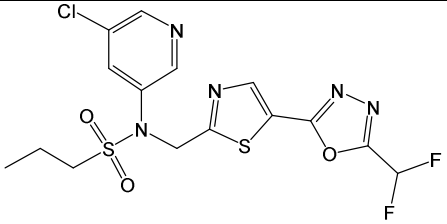
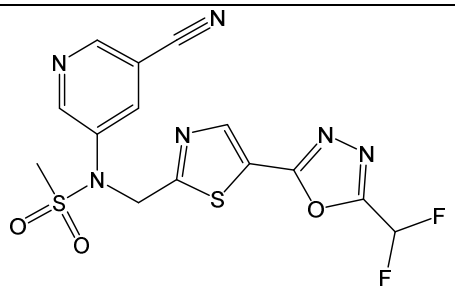
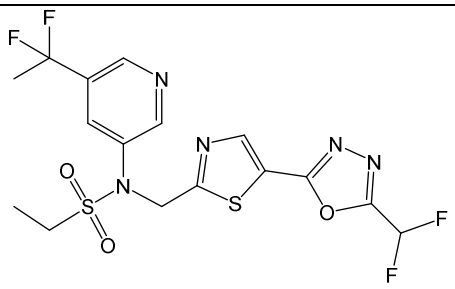
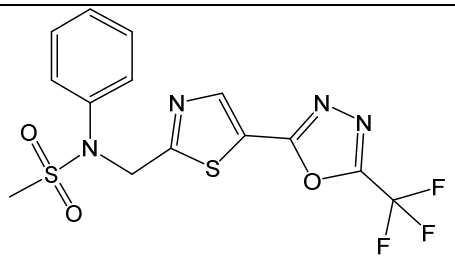
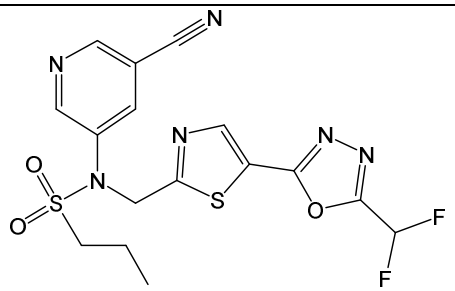
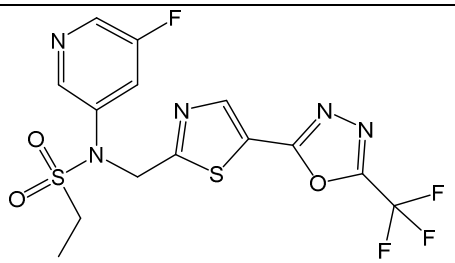
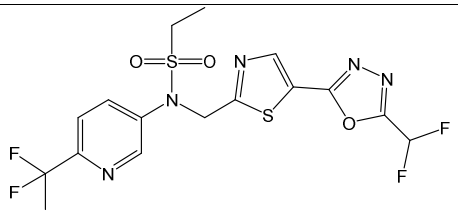
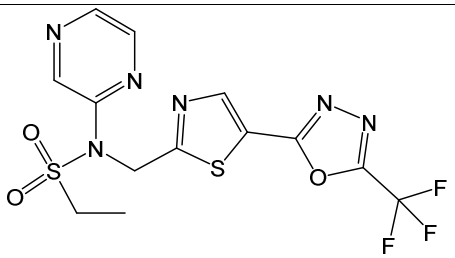
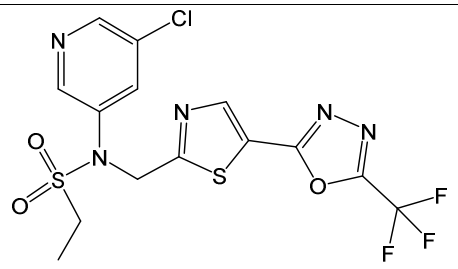
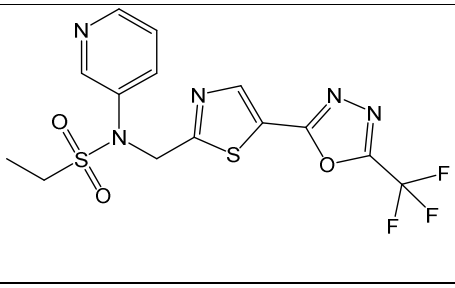
	
	
	
	
	
	

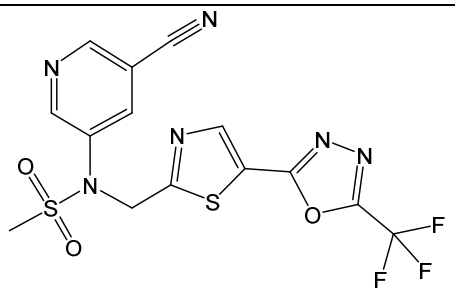
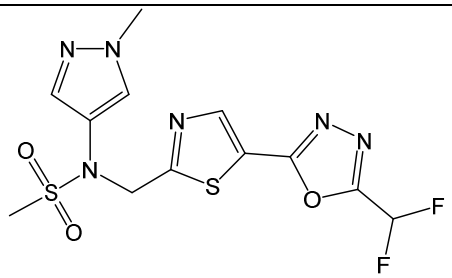
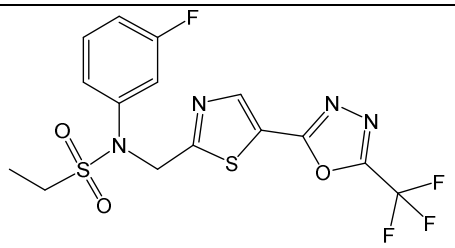
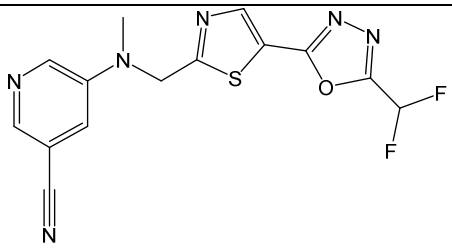
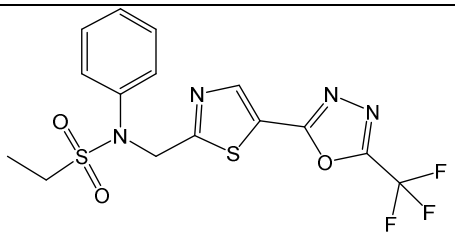
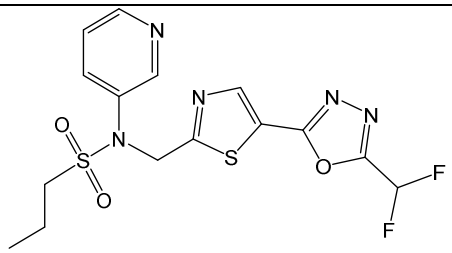
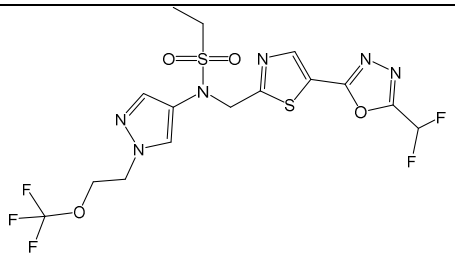
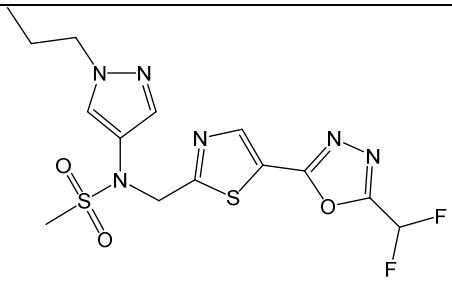
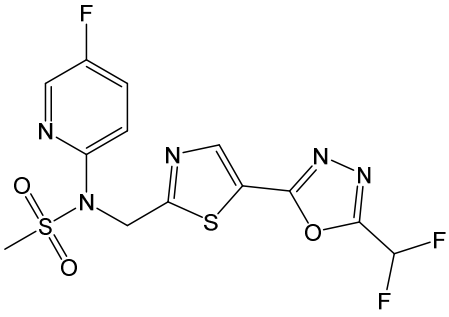
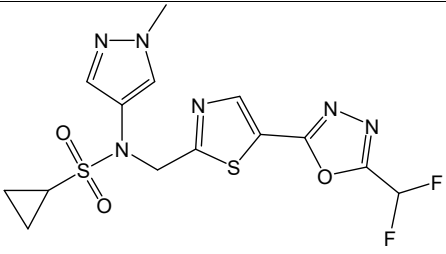
	
	
	
	
	
	

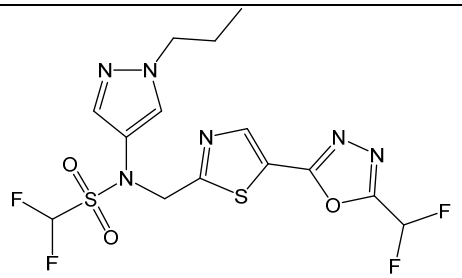
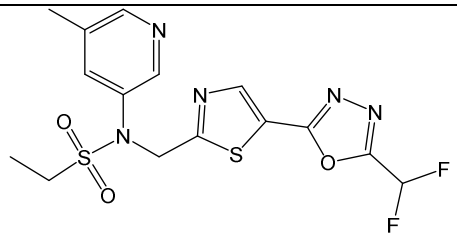
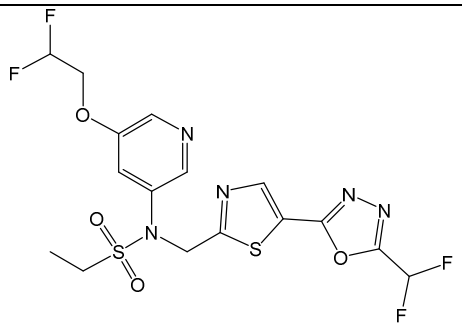
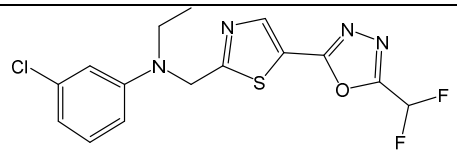
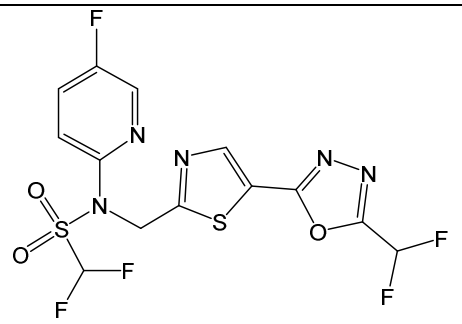
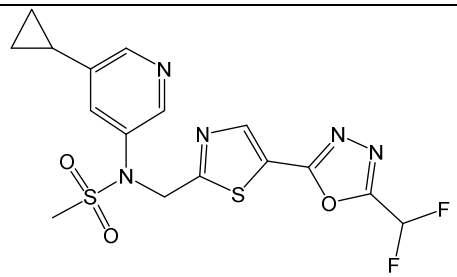
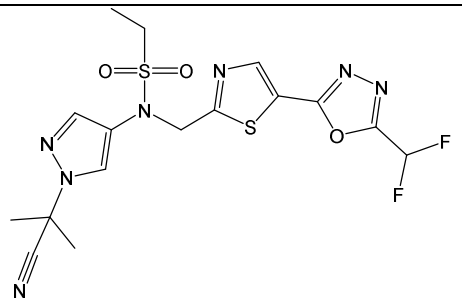
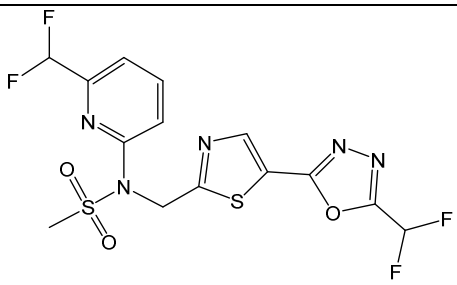
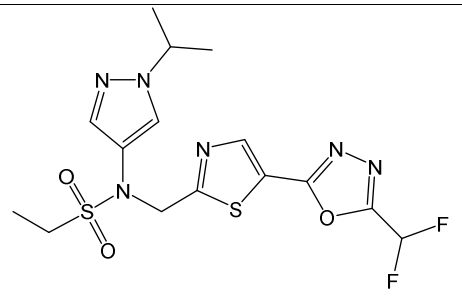
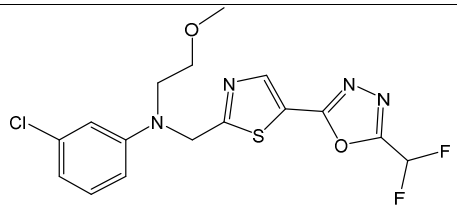
	
	
	
	
	
	

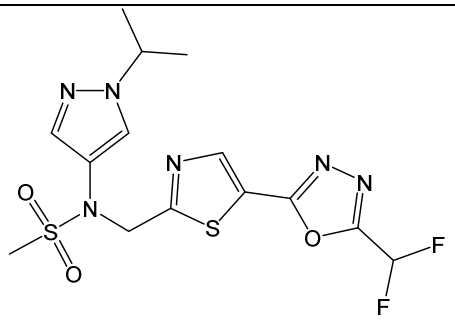
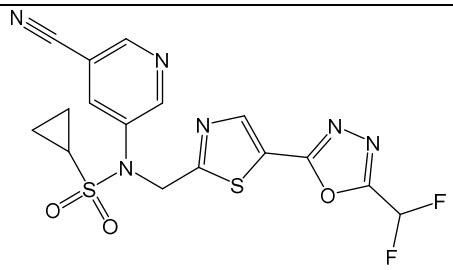
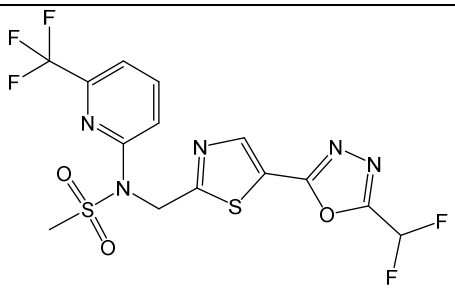
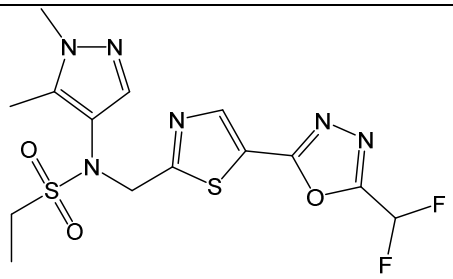
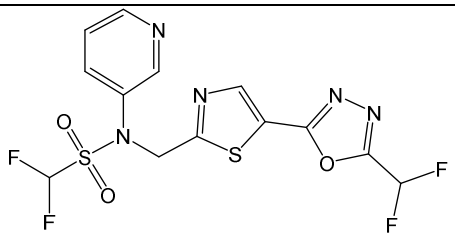
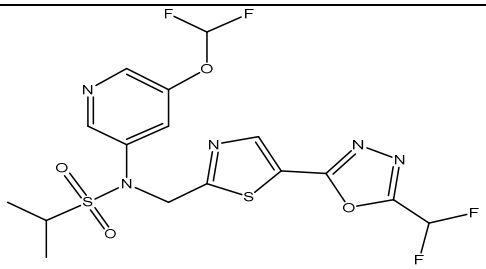
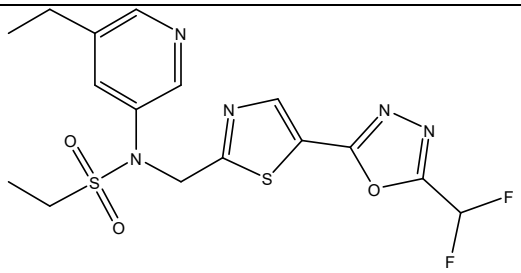
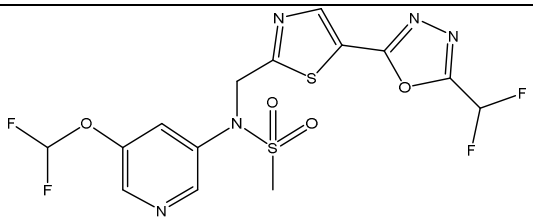
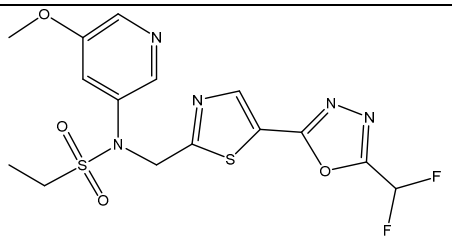
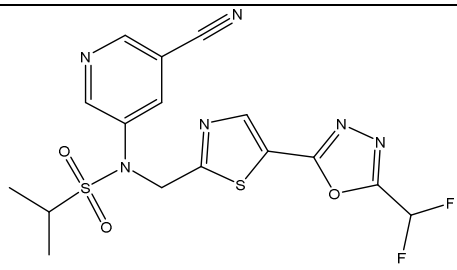
	
	
	
	
	
	

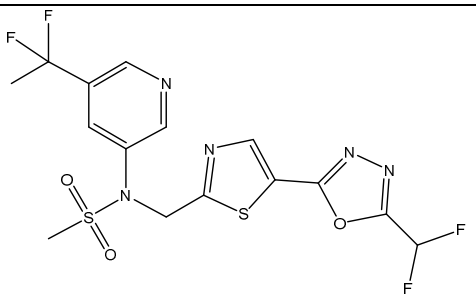
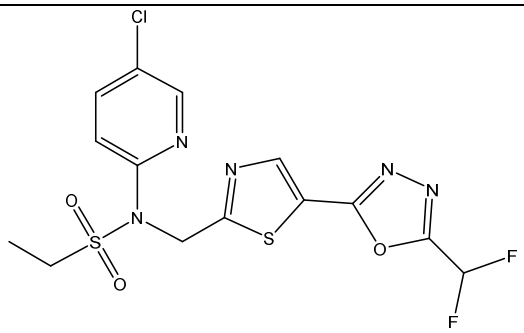
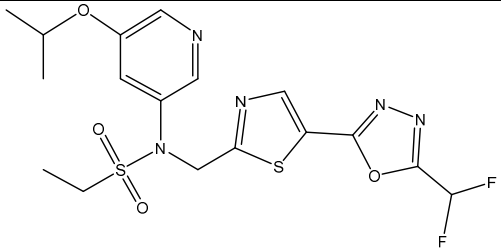
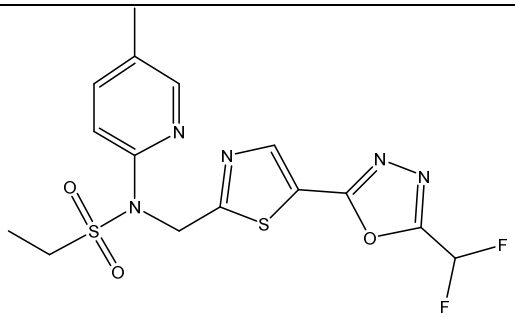
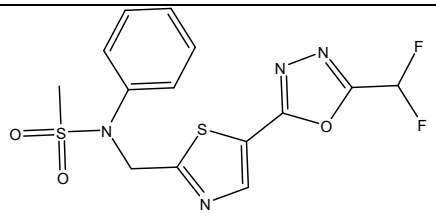
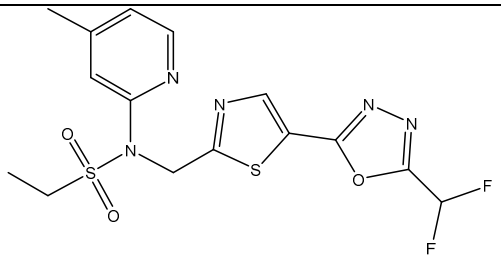
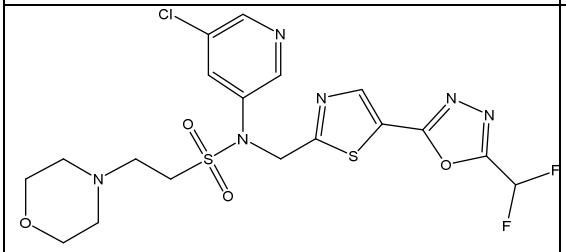
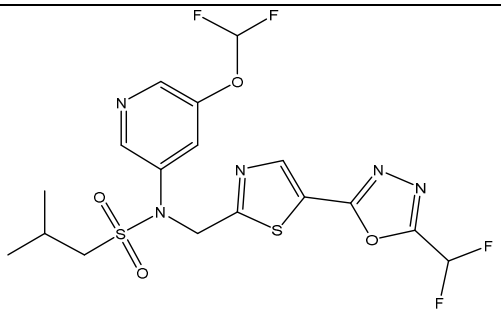
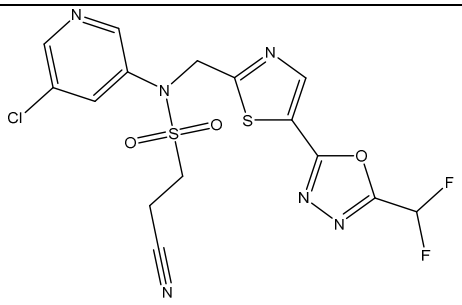
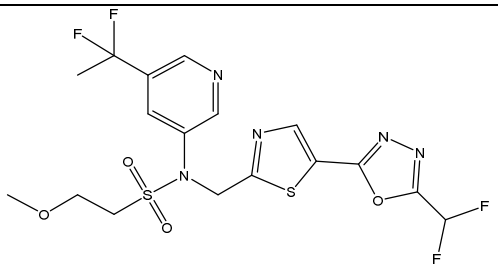
	
	
	
	
	
	

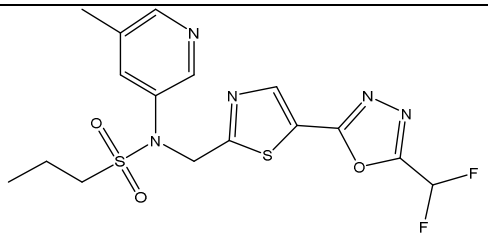
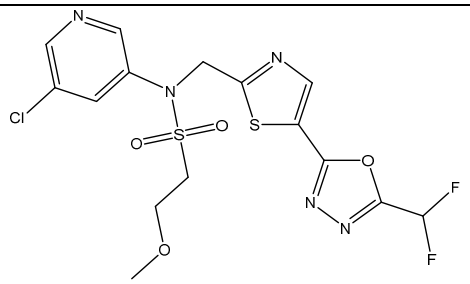
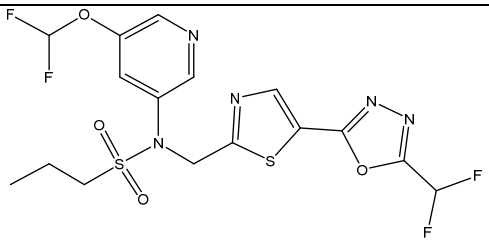
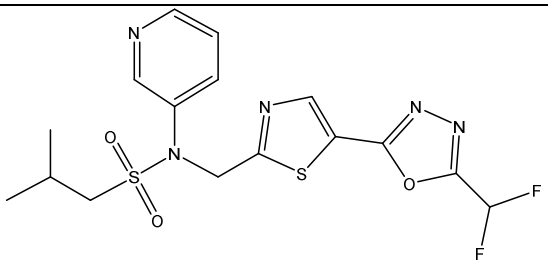
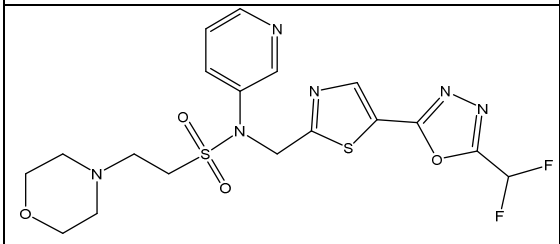
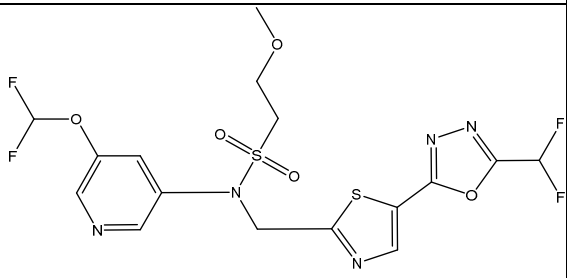
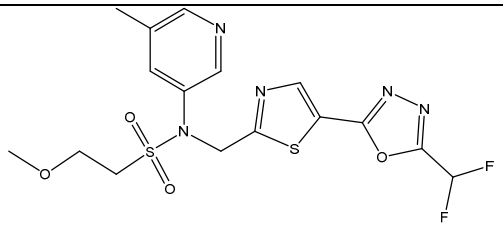
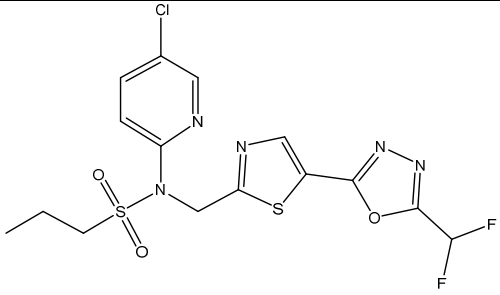
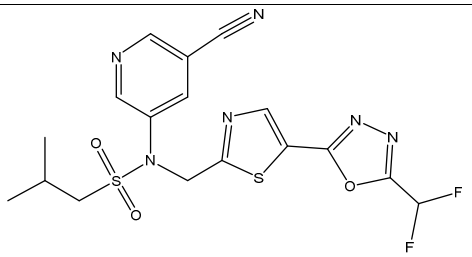
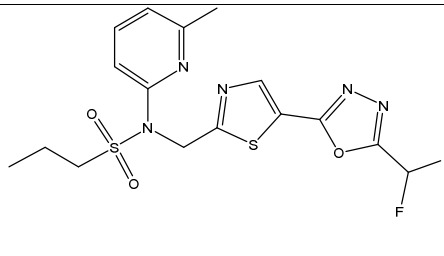
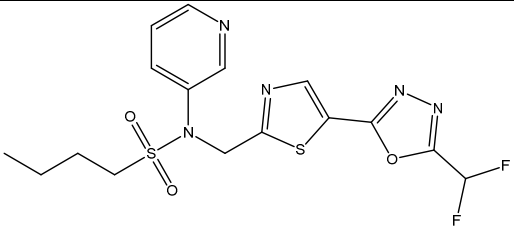
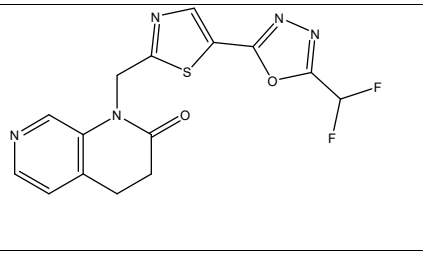
	
	
	
	
	
	

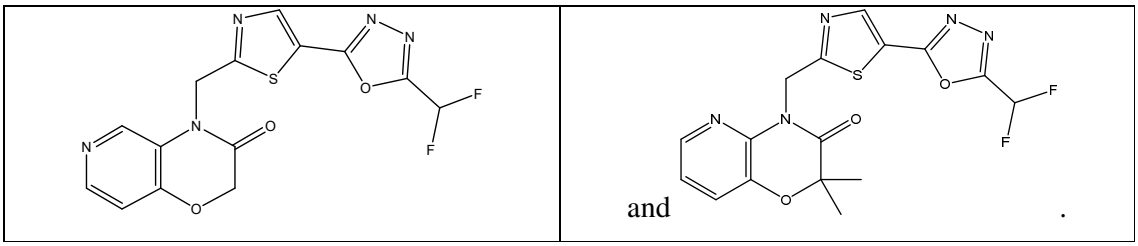
	
	
	
	
	

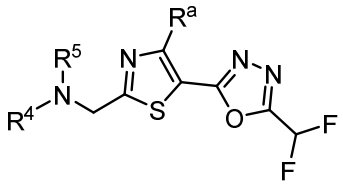
	
	
	
	
	



[0230] In some embodiments, the present disclosure provides a compound of Formula (Ic) or a pharmaceutically acceptable salt thereof:



(Ic),

wherein:

R^a is H, Me, or F; and

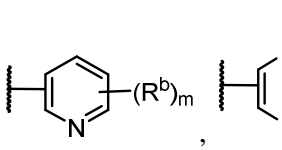
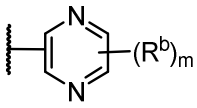
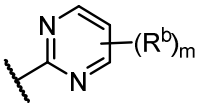
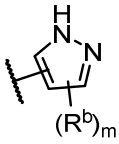
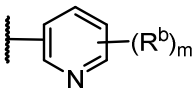
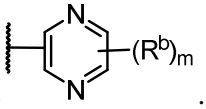
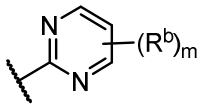
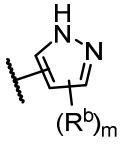
R^4 and R^5 are as defined above in Formula (I).

[0231] In some embodiments of Formula (Ic), R^a is H. In some embodiments, R^a is F. In some embodiments, R^a is Me.

[0232] In some embodiments of Formula (Ic), R^4 is selected from the group consisting of alkylenealkoxy, alkyleneheterocyclyl, -S(O)$_2$alkyl, -S(O)$_2$cycloalkyl, -S(O)$_2$alkylenecycloalkyl, -S(O)$_2$alkyleneheterocyclyl, -S(O)$_2$N(H)alkyleneheterocyclyl, -C(O)alkyl, -C(O)cycloalkyl, -C(O)alkylenecycloalkyl, -C(O)alkyleneheterocyclyl, and -C(O)N(H)alkyleneheterocyclyl. In some embodiments, R^4 is selected from the group consisting of alkyleneheterocyclyl, -S(O)$_2$alkyl, -S(O)$_2$cycloalkyl, -S(O)$_2$alkyleneheterocyclyl, -C(O)alkyleneheterocyclyl, and -C(O)N(H)alkyleneheterocyclyl. In some embodiments, R^4 is selected from the group consisting of -S(O)$_2$alkyl, -S(O)$_2$cycloalkyl, and -S(O)$_2$alkyleneheterocyclyl. In some embodiments, R^4 is -S(O)$_2$alkyl. In some embodiments, R^4 is -S(O)$_2$cycloalkyl. In some embodiments, R^4 is -S(O)$_2$N(H)alkyleneheterocyclyl. In some embodiments, the alkylene is a C_{1-5} alkylene and the heterocyclyl is an optionally substituted 4- to 10-membered heterocyclyl having 1, 2, or 3 heteroatoms selected from the group consisting of N, O, and S. In some embodiments, the alkylene is a C_{1-5} alkylene and the heterocyclyl is an optionally substituted 4- to 7-membered heterocyclyl having 1, 2, or 3 heteroatoms selected from the group consisting of N, O, and S. In some embodiments, the

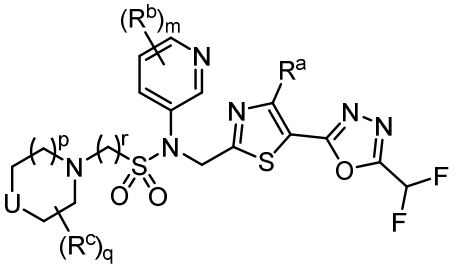
alkylene is a C_{2-4} alkylene and the heterocyclyl is an optionally substituted 6-membered heterocyclyl having 1, 2, or 3 heteroatoms selected from the group consisting of N, O, and S. In some embodiments, the heterocyclyl is selected from the group consisting of piperidine, morpholine, thiomorpholine, thiomorpholine 1-oxide, thiomorpholine 1,1- dioxide, and piperizine, each of which is optionally substituted. In some embodiments, the optional substituent is selected from the group consisting of alkyl, haloalkyl, alkoxy, acyl, sulfonyl, heteroaryl, and heterocyclyl.

[0233] In some embodiments of Formula (Ic), R^5 is selected from the group consisting of:

, , , and . In some embodiments, R^5 is . In some embodiments, R^5 is . In some embodiments, R^5 is . In some embodiments, R^5 is . In some embodiments, R^b is selected from the group consisting of halogen, haloalkyl, alkyl, Oalkyl, Ohaloalkyl, alkylene-Ohaloalkyl, cycloalkyl, heterocyclyl aryl, heteroaryl, alkylnitrile, or CN. In some embodiments, R^b is selected from the group consisting of halo, alkyl, haloalkyl, alkoxy, haloalkoxy, acyl, sulfonyl, cycloalkyl, heteroaryl, and heterocyclyl. In some embodiments, the haloalkyl is selected from CF_3, CF_2CH_3, CHF_2, or CH_2F. In some embodiments, the alkyl is a $–C_{1-5}$alkyl. In some embodiments, $–C_{1-5}$alkyl is methyl, ethyl, propyl, *i*-propyl, butyl, or *t*-butyl. In some embodiments, methyl, ethyl, propyl, *i*-propyl, butyl, or *t*-butyl is optionally substituted with OH. In some embodiments, the cycloalkyl is a C_{3-6}cycloalkyl. In some embodiments, the aryl is a phenyl. In some embodiments, the heteroaryl is 5- or 6-membered heteroaryl having 1, 2, or 3 heteroatoms selected from N, O, and S. In some embodiments, the heterocyclyl is a 4- to 7-member heterocyclyl with 1 or 2 heteroatoms selected from N, O, and S. In some embodiments, the Ohaloalkyl is selected from OCF_3, $OCHF_2$, or OCH_2F. In some embodiments, the Oalkyl is O-methyl, O-ethyl, O-propyl, O-*i*-propyl, O-butyl, or O-*t*-butyl. In some embodiments, R^b is selected from the group consisting of F, Cl, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CHF_2$, $-CF_2CH_3$, $-CN$, $-OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, $-OCHF_2$, $-OCH_2CF_2H$, and

cyclopropyl. In some embodiments, m is 0, 1, or 2. In some embodiments, m is 0 or 1. In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2.

[0234] In some embodiments, the present disclosure provides a compound of Formula (Id) or a pharmaceutically acceptable salt thereof:



(Id),

wherein:

U is NR^d, O, S, S(O), $S(O)_2$, CH_2, CHF, or CF_2;

R^a is H, Me, or F;

R^b is each independently halo, alkyl, haloalkyl, alkoxy, haloalkoxy, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)N(R^e)(R^{e'})$, $-S(O_2)R^e$, cycloalkyl, heteroaryl, or heterocyclyl;

R^c is each independently F, alkyl, haloalkyl, alkoxy, haloalkoxy, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)N(R^e)(R^{e'})$, $-S(O_2)R^e$, heteroaryl, or heterocyclyl, and/or two R^c groups taken together with the carbon atoms to which they are attached form a bridged or fused C_{3-7} cycloalkyl, a bridged or fused 4- to 7-membered heterocyclyl; or a 5- or 6-membered heteroaryl, each of which is optionally substituted;

R^d is H, alkyl, acyl, sulfonyl, cycloalkyl, aryl, or heteroaryl;

R^e and $R^{e'}$ is each independently H, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-CH_2$cycloalkyl, $-CH_2$heterocyclyl, $-CH_2$aryl, or $-CH_2$heteroaryl;

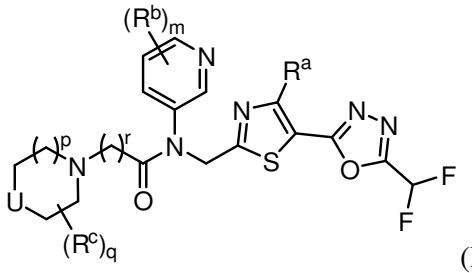
m is 0, 1, 2, or 3;

p is 0, 1, 2, or 3;

q is 0, 1, or 2; and

r is 1, 2, 3, or 4.

[0235] In some embodiments, the present disclosure provides a compound of Formula (Ie) or a pharmaceutically acceptable salt thereof:



(Ie),

wherein:

U is NR^d, O, S, S(O), $S(O)_2$, CH_2, CHF, or CF_2;

R^a is H, Me, or F;

R^b is each independently halo, alkyl, haloalkyl, alkoxy, haloalkoxy, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)N(R^e)(R^{e'})$, sulfonyl, cycloalkyl, heteroaryl, or heterocyclyl;

R^c is each independently F, alkyl, haloalkyl, alkoxy, haloalkoxy, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)N(R^e)(R^{e'})$, $-S(O_2)R^e$, heteroaryl, or heterocyclyl, and/or two R^c groups taken together with the carbon atoms to which they are attached form a bridged or fused C_{3-7} cycloalkyl, a bridged or fused 4- to 6-membered heterocyclyl; or a 5- or 6-membered heteroaryl, each of which is optionally substituted;

R^d is H, alkyl, acyl, sulfonyl, cycloalkyl, aryl, or heteroaryl;

R^e and $R^{e'}$ is each independently H, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-CH_2$cycloalkyl, $-CH_2$heterocyclyl, $-CH_2$aryl, or $-CH_2$heteroaryl;

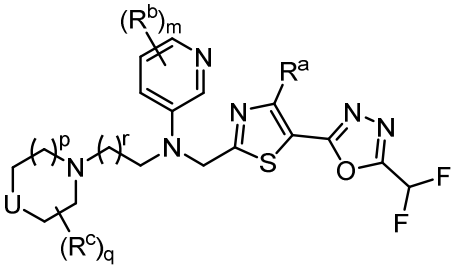
m is 0, 1, 2, or 3;

p is 0, 1, 2, or 3;

q is 0, 1, or 2; and

r is 1, 2, 3, or 4.

[0236] In some embodiments, the present disclosure provides a compound of Formula (If) or a pharmaceutically acceptable salt thereof:



(If),

wherein:

U is NR^d, O, S, S(O), $S(O)_2$, CH_2, CHF, or CF_2;

R^a is H, Me, or F;

R^b is each independently halo, alkyl, haloalkyl, alkoxy, haloalkoxy, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)N(R^e)(R^{e'})$, sulfonyl, cycloalkyl, heteroaryl, or heterocyclyl;

R^c is each independently F, alkyl, haloalkyl, alkoxy, haloalkoxy, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)N(R^e)(R^{e'})$, $-S(O_2)R^e$, heteroaryl, or heterocyclyl, and/or two R^c groups taken together with the carbon atoms to which they are attached form a bridged or fused C_{3-7} cycloalkyl, a bridged or fused 4- to 7-membered heterocyclyl; or a 5- or 6-membered heteroaryl, each of which is optionally substituted;

R^d is H, alkyl, acyl, sulfonyl, cycloalkyl, aryl, or heteroaryl;

R^e and $R^{e'}$ is each independently H, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-CH_2$cycloalkyl, $-CH_2$heterocyclyl, $-CH_2$aryl, or $-CH_2$heteroaryl;

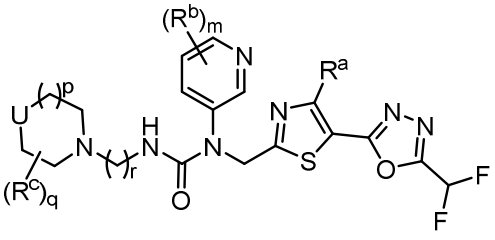
m is 0, 1, 2, or 3;

p is 0, 1, 2, or 3;

q is 0, 1, or 2; and

r is 1, 2, 3, or 4.

[0237] In some embodiments, the present disclosure provides a compound of Formula (Ig) or a pharmaceutically acceptable salt thereof:


(Ig),

wherein:

U is NR^d, O, S, S(O), $S(O)_2$, CH_2, CHF, or CF_2;

R^a is H, Me, or F;

R^b is each independently halo, alkyl, haloalkyl, alkoxy, haloalkoxy, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)N(R^e)(R^{e'})$, sulfonyl, cycloalkyl, heteroaryl, or heterocyclyl;

R^c is each independently F, alkyl, haloalkyl, alkoxy, haloalkoxy, -C(O)R^e, -C(O)OR^e, -C(O)N(R^e)($R^{e'}$), -S(O_2)R^e, heteroaryl, or heterocyclyl, and/or two R^c groups taken together with the carbon atoms to which they are attached form a bridged or fused C_{3-7} cycloalkyl, a bridged or fused 4- to 7-membered heterocyclyl; or a 5- or 6-membered heteroaryl, each of which is optionally substituted;

R^d is H, alkyl, acyl, sulfonyl, cycloalkyl, aryl, or heteroaryl;

R^e and $R^{e'}$ is each independently H, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, -CH_2cycloalkyl, -CH_2heterocyclyl, -CH_2aryl, or -CH_2heteroaryl;

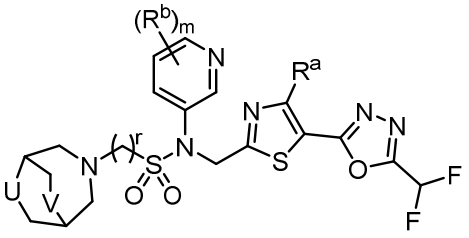
m is 0, 1, 2, or 3;

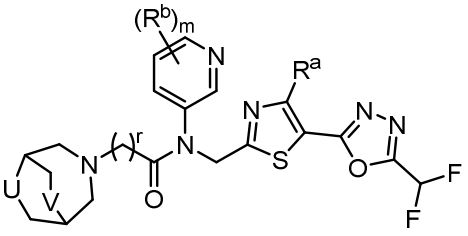
p is 0, 1, 2, or 3;

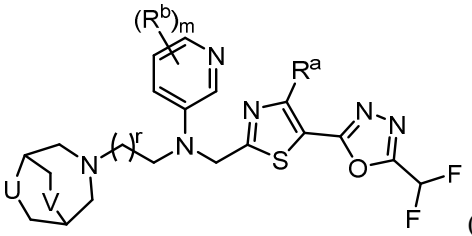
q is 0, 1, or 2; and

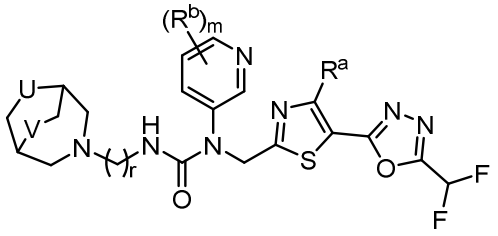
r is 1, 2, 3, or 4.

[0238] In some embodiments, the compound has the formula:


(Id-1),


(Ie-1)


(If-1), or


(Ig-1),wherein:

U, R^a, R^b, m, and r are as defined above in Formulas (Id), (Ie), (If), and (Ig); and

V is O or NR^d.

[0239] In some embodiments of Formulas (Id)-(Ig) and (Id-1)-(Ig-1), U is NR^d, O, or S and V is O. In some embodiments, U is N, O, or S and V is NR^d. In some embodiments, U is NR^d and V is NR^d. In some embodiments, U is O and V is NR^d. In some embodiments, U is S and

V is NR^d. In some embodiments, U is NR^d and V is O. In some embodiments, U is O and V is O. In some embodiments, U is S and V is O.

[0240] In some embodiments of Formulas (Id)-(Ig) and (Id-1)-(Ig-1), U is O, S, $S(O)_2$, CH_2, or NR^d. In some embodiments, U is O, S, CH_2, or NR^d. In some embodiments, U is O, S, or NR^d. In some embodiments, U is O or CH_2. In some embodiments, U is O. In some embodiments, U is S. In some embodiments, U is NR^d. In some embodiments, U is $S(O)_2$.

[0241] In some embodiments of Formulas (Id)-(Ig) and (Id-1)-(Ig-1), R^a is H. In some embodiments, R^a is F. In some embodiments, R^a is Me.

[0242] In some embodiments of Formulas (Id)-(Ig) and (Id-1)-(Ig-1), R^b is halo, alkyl, haloalkyl, alkyl, haloalkoxy, cycloalkyl, heterocyclyl, heteroaryl, or nitrile. In some embodiments, R^b is halo, alkyl, haloalkyl, alkyl, haloalkoxy, cycloalkyl, or nitrile. In some embodiments, the haloalkyl is selected from CF_3, CF_2CH_3, CHF_2, or CH_2F. In some embodiments, the alkyl is a $–C_{1\text{-}5}$alkyl. In some embodiments, $–C_{1\text{-}5}$alkyl is methyl, ethyl, propyl, *i*-propyl, butyl, or *t*-butyl. In some embodiments, the cycloalkyl is a $C_{3\text{-}6}$cycloalkyl. In some embodiments, the heteroaryl is 5- or 6-membered heteroaryl having 1, 2, or 3 heteroatoms selected from N, O, and S. In some embodiments, the heterocyclyl is a 4- to 7-member heterocyclyl with 1 or 2 heteroatoms selected from N, O, and S. In some embodiments, the haloalkoxy is selected from OCF_3, $OCHF_2$, or OCH_2F. In some embodiments, the alkoxy is O-methyl, O-ethyl, O-propyl, O-*i*-propyl, O-butyl, or O-*t*-butyl. In some embodiments, R^b is $-C(O)R^e$, $-C(O)OR^e$, $-C(O)N(R^e)(R^{e'})$.

[0243] In some embodiments of Formulas (Id)-(Ig), R^c is F, $C_{1\text{-}5}$ alkyl, haloalkyl, $C_{1\text{-}5}$ alkoxy, haloalkoxy, acyl, sulfonyl, 5- or 6-membered heteroaryl, or $C_{3\text{-}6}$ heterocyclyl. In some embodiments, R^c is $-C(O)R^e$, $-C(O)OR^e$, $-C(O)N(R^e)(R^{e'})$. In some embodiments, two R^c groups taken together with the carbon atoms to which they are attached form a bridged or fused $C_{3\text{-}7}$ cycloalkyl, a bridged or fused 5- or 6-membered heterocyclyl, or a 5- or 6-membered heteroaryl, each of which is optionally substituted. In some embodiments, two R^c groups taken together with the carbon atoms to which they are attached form an optionally substituted bridged or fused $C_{3\text{-}7}$ cycloalkyl. In some embodiments, two R^c groups taken together with the carbon atoms to which they are attached form an optionally substituted bridged or fused 5- or 6-membered heterocyclyl. In some embodiments, two R^c groups taken together with the carbon atoms to which they are attached form an alkoxy or aminoalkyl bridge. In some embodiments, the optional substituent is one or more R^b, as defined above. In some embodiments, the

optional substituent is selected from the group consisting of F, C_{1-5} alkyl, C_{1-5} alkoxy, CF_3, CF_2H, CFH_2, -OCF_3, -OCF_2H, -$OCFH_2$, -$C(O)R^e$, -$C(O)OR^e$, -$C(O)N(R^e)(R^{e'})$, and -SO_2R^e. In some embodiments, the optional substituent is selected from the group consisting of F, C_{1-5} alkyl, C_{1-5} alkoxy, CF_3, CF_2H, CFH_2, -OCF_3, -OCF_2H, and -$OCFH_2$. In some embodiments, the optional substituent is F or C_{1-5} alkyl. In some embodiments, the optional substituent is F. In some embodiments, the optional substituent is C_{1-5} alkyl. In some embodiments, the C_{1-5} alkyl is methyl. In some embodiments, the C_{1-5} alkyl is ethyl. In some embodiments, the C_{1-5} alkyl is propyl. In some embodiments, the C_{1-5} alkyl is isopropyl.

[0244] In some embodiments of Formulas (Id)-(Ig) and (Id-1)-(Ig-1), R^e and $R^{e'}$ is each independently H, alkyl, cycloalkyl, or -CH_2cycloalkyl. In some embodiments, the alkyl is a –C_{1-5}alkyl. In some embodiments, –C_{1-5}alkyl is methyl, ethyl, propyl, *i*-propyl, butyl, or *t*-butyl. In some embodiments, the cycloalkyl is a C_{3-6}cycloalkyl. In some embodiments, the cycloalkyl is cyclopropyl. In some embodiments, R^e and $R^{e'}$ are H.

[0245] In some embodiments of Formulas (Id)-(Ig) and (Id-1)-(Ig-1), m is 0, 1, or 2. In some embodiments, m is 0 or 1. In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2.

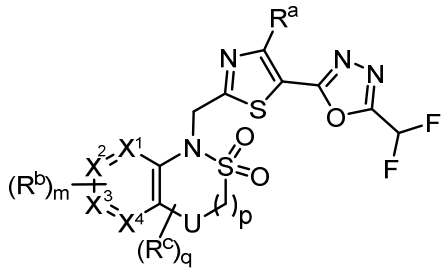
[0246] In some embodiments of Formulas (Id)-(Ig), p is 0, 1, or 2. In some embodiments, p is 0 or 1. In some embodiments, p is 1 or 2. In some embodiments, p is 0. In some embodiments, p is 1. In some embodiments, p is 2.

[0247] In some embodiments of Formulas (Id)-(Ig) and (Id-1)-(Ig-1), r is 1, 2, or 3. In some embodiments, r is 1 or 2. In some embodiments, r is 2 or 3. In some embodiments, r is 1. In some embodiments, r is 2. In some embodiments, r is 3. In some embodiments, r is 4.

[0248] In some embodiments of Formulas (Id)-(Ig), q is 0 or 1. In some embodiments, q is 0. In some embodiments, q is 1. In some embodiments, q is 2.

[0249] In some embodiments of Formulas (Id)-(Ig), r is 1 and p is 1. In some embodiments, r is 2 and p is 1. In some embodiments, r is 3 and p is 1.

[0250] In some embodiments, the present disclosure provides a compound of Formula (Ih) or a pharmaceutically acceptable salt thereof:



(Ih),

wherein:

U is NR^d, O, S, S(O), $S(O)_2$, CH_2, CHF, or CF_2;

X^1, X^2, X^3, and X^4 is each independently CH or N;

R^a is H, Me, or F;

R^b is each independently halo, alkyl, haloalkyl, alkoxy, haloalkoxy, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)N(R^e)(R^{e'})$, $-SO_2R^e$, cycloalkyl, heteroaryl, or heterocyclyl;

R^c is each independently F, alkyl, haloalkyl, alkoxy, or haloalkoxy, and/or two R^c groups taken together with the atoms to which they are attached form an optionally substituted C_{3-7} cycloalkyl;

R^d is H, alkyl, acyl, sulfonyl, cycloalkyl, aryl, or heteroaryl;

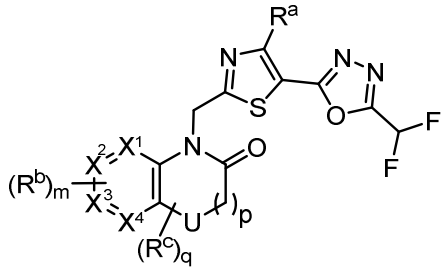
R^e and $R^{e'}$ is each independently H, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-CH_2$cycloalkyl, $-CH_2$heterocyclyl, $-CH_2$aryl, or $-CH_2$heteroaryl;

m is 0, 1, 2, or 3;

p is 0, 1, 2, or 3; and

q is 0, 1, or 2.

[0251] In some embodiments, the present disclosure provides a compound of Formula (Ii) or a pharmaceutically acceptable salt thereof:



(Ii),

wherein:

U is NR^d, O, S, S(O), $S(O)_2$, CH_2, CHF, or CF_2;

X^1, X^2, X^3, and X^4 is each independently CH or N;

R^a is H, Me, or F;

R^b is each independently halo, alkyl, haloalkyl, alkoxy, haloalkoxy, -C(O)R^e, -C(O)OR^e, -C(O)N(R^e)($R^{e'}$), -SO_2R^e, cycloalkyl, heteroaryl, or heterocyclyl;

R^c is each independently F, alkyl, haloalkyl, alkoxy, or haloalkoxy, and/or two R^c groups taken together with the atoms to which they are attached form an optionally substituted C_{3-7} cycloalkyl;

R^d is H, alkyl, -C(O)R^e, sulfonyl, cycloalkyl, aryl, or heteroaryl;

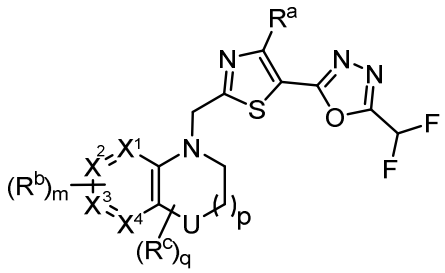
R^e and $R^{e'}$ is each independently H, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, -CH_2cycloalkyl, -CH_2heterocyclyl, -CH_2aryl, or -CH_2heteroaryl;

m is 0, 1, 2, or 3;

p is 0, 1, 2, or 3; and

q is 0, 1, or 2.

[0252] In some embodiments, the present disclosure provides a compound of Formula (Ij) or a pharmaceutically acceptable salt thereof:



(Ij),

wherein:

U is NR^d, O, S, S(O), $S(O)_2$, CH_2, CHF, or CF_2;

X^1, X^2, X^3, and X^4 is each independently CH or N;

R^a is H, Me, or F;

R^b is each independently halo, alkyl, haloalkyl, alkoxy, haloalkoxy, -C(O)R^e, -C(O)OR^e, -C(O)N(R^e)($R^{e'}$), -SO_2R^e, cycloalkyl, heteroaryl, or heterocyclyl;

R^c is each independently F, alkyl, haloalkyl, alkoxy, or haloalkoxy, and/or two R^c groups taken together with the atoms to which they are attached form an optionally substituted C_{3-7} cycloalkyl;

R^d is H, alkyl, -C(O)R^e, sulfonyl, cycloalkyl, aryl, or heteroaryl;

R^e and $R^{e'}$ is each independently H, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, -CH_2cycloalkyl, -CH_2heterocyclyl, -CH_2aryl, or -CH_2heteroaryl;

m is 0, 1, 2, or 3;

p is 0, 1, 2, or 3; and

q is 0, 1, or 2.

[0253] In some embodiments of Formulas (Ih)-(Ij), NR^d, O, S, $S(O)_2$, or CH_2. In some embodiments, U is NR^d, O, S, or CH_2. In some embodiments, U is O or CH_2. In some embodiments, U is O. In some embodiments, U is CH_2. In some embodiments, U is S. In some embodiments, U is $S(O)_2$. In some embodiments, U is NR^d.

[0254] In some embodiments of Formulas (Ih)-(Ij), each of X^1, X^2, X^3, and X^4 is CH. In some embodiments, one of X^1, X^2, X^3, and X^4 is N. In some embodiments, two of X^1, X^2, X^3, and X^4 are N. In some embodiments, X^1 is N and each of X^2, X^3, and X^4 is CH. In some embodiments, X^2 is N and each of X^1, X^3, and X^4 is CH. In some embodiments, X^3 is N and each of X^1, X^2, and X^4 is CH. In some embodiments, X^4 is N and each of X^1, X^2, and X^3 is CH.

[0255] In some embodiments of Formulas (Ih)-(Ij), U is CH_2 and one of X^1, X^2, X^3, and X^4 is N. In some embodiments, U is CH_2, X^1 is N and each of X^2, X^3, and X^4 is CH. In some embodiments, U is CH_2, X^2 is N and each of X^1, X^3, and X^4 is CH. In some embodiments, U is CH_2, X^3 is N and each of X^1, X^2, and X^4 is CH. In some embodiments, U is CH_2, X^4 is N and each of X^1, X^2, and X^3 is CH. In some embodiments, p is 0. In some embodiments, p is 1.

[0256] In some embodiments of Formulas (Ih)-(Ij), U is O and one of X^1, X^2, X^3, and X^4 is N. In some embodiments, U is O, X^1 is N and each of X^2, X^3, and X^4 is CH. In some embodiments, U is O, X^2 is N and each of X^1, X^3, and X^4 is CH. In some embodiments, U is O, X^3 is N and each of X^1, X^2, and X^4 is CH. In some embodiments, U is O, X^4 is N and each of X^1, X^2, and X^3 is CH.

[0257] In some embodiments of Formulas (Ih)-(Ij), R^a is H. In some embodiments, R^a is F. In some embodiments, R^a is Me.

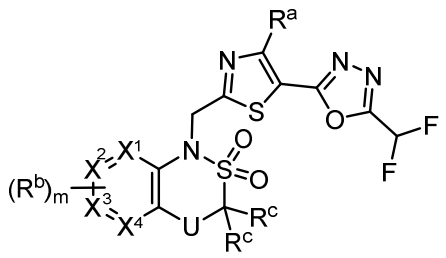
[0258] In some embodiments of Formulas (Ih)-(Ij), R^b is halo, alkyl, haloalkyl, alkyl, haloalkoxy, cycloalkyl, heterocyclyl, heteroaryl, or nitrile. In some embodiments, R^b is halo, alkyl, haloalkyl, alkyl, haloalkoxy, cycloalkyl, or nitrile. In some embodiments, the haloalkyl is selected from CF_3, CF_2CH_3, CHF_2, or CH_2F. In some embodiments, the alkyl is a $–C_{1\text{-}5}$alkyl. In some embodiments, $–C_{1\text{-}5}$alkyl is methyl, ethyl, propyl, *i*-propyl, butyl, or *t*-butyl. In some

embodiments, the cycloalkyl is a C_{3-6}cycloalkyl. In some embodiments, the heteroaryl is 5- or 6-membered heteroaryl having 1, 2, or 3 heteroatoms selected from N, O, and S. In some embodiments, the heterocyclyl is a 4- to 7-member heterocyclyl with 1 or 2 heteroatoms selected from N, O, and S. In some embodiments, the haloalkoxy is selected from OCF_3, $OCHF_2$, or OCH_2F. In some embodiments, the alkoxy is O-methyl, O-ethyl, O-propyl, O-*i*-propyl, O-butyl, or O-*t*-butyl.

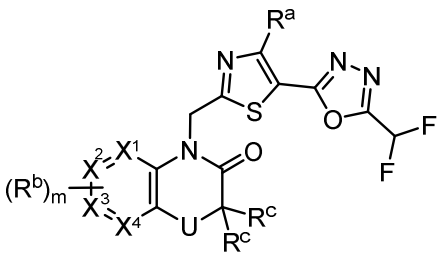
[0259] In some embodiments of Formulas (Ih)-(Ij), R^c is F, C_{1-5} alkyl, haloalkyl, C_{1-5} alkoxy, haloalkoxy, acyl, sulfonyl, 5- or 6-membered heteroaryl, or C_{3-6} heterocyclyl. In some embodiments, R^c is F, C_{1-5} alkyl, haloalkyl, C_{1-5} alkoxy, or haloalkoxy. In some embodiments, R^c is F or C_{1-5} alkyl. In some embodiments, R^c is F or methyl. In some embodiments, R^c is F. In some embodiments, R^c is methyl. In some embodiments, the two R^c groups are attached to the same carbon atom, which can also be referred to as germinal substitution. In some embodiments, two R^c groups taken together with the atoms to which they are attached form an optionally substituted C_{3-6} cycloalkyl. In some embodiments, two R^c groups taken together with the atoms to which they are attached form an optionally substituted cyclopropyl. In some embodiments, the optional substituent is one or more R^b, as defined above. In some embodiments, the optional substituent is selected from the group consisting of F, C_{1-5} alkyl, C_{1-5} alkoxy, CF_3, CF_2H, CFH_2, $-OCF_3$, $-OCF_2H$, $-OCFH_2$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)N(R^e)(R^{e'})$, and $-SO_2R^e$. In some embodiments, the optional substituent is selected from the group consisting of F, C_{1-5} alkyl, C_{1-5} alkoxy, CF_3, CF_2H, CFH_2, $-OCF_3$, $-OCF_2H$, and $-OCFH_2$. In some embodiments, the optional substituent is F or C_{1-5} alkyl. In some embodiments, the optional substituent is F. In some embodiments, the optional substituent is C_{1-5} alkyl. In some embodiments, the C_{1-5} alkyl is methyl. In some embodiments, the C_{1-5} alkyl is ethyl. In some embodiments, the C_{1-5} alkyl is propyl. In some embodiments, the C_{1-5} alkyl is isopropyl. In some embodiments, two optional substituents are attached to the same carbon, which is also referred to as germinal substitution.

[0260] In some embodiments of Formulas (Ih)-(Ij), when U is NR^d, an R^d and R^c taken together with the atoms to which they are attached form a 5- to 7-membered heterocyclyl. In some embodiments, an R^d and R^c taken together with the atoms to which they are attached form a 6-membered heterocyclyl. In some embodiments, the heterocyclyl comprises 1 or 2 heteroatoms selected from N, O, and S.

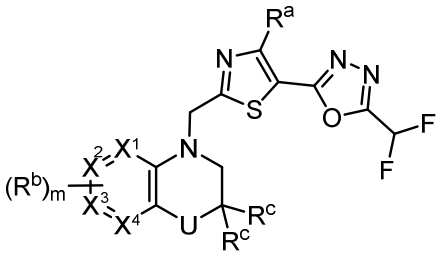
[0261] In some embodiments, the present disclosure provides a compound of Formula (Ih-1), Formula (Ii-1), or Formula (Ij-1):



(Ih-1)



(Ii-1)



(Ij-1)

wherein R^a, R^b, R^c, X^1, X^2, X^3, X^4, U, and m are as defined above in Formula (Ih), Formula (Ii), and Formula (Ij).

[0262] In some embodiments of Formula (Ih-1), Formula (Ii-1), and Formula (Ij-1), each R^c is F. In some embodiments, each R^c is Me. In some embodiments, two R^c groups taken together with the carbon atoms to which they are attached form an optionally substituted C_{3-6} cycloalkyl. In some embodiments, two R^c groups taken together with the carbon atoms to which they are attached form a cyclopropyl or cyclobutyl, each of which is optionally substituted. In some embodiments, two R^c groups taken together with the carbon atoms to which they are attached form an optionally substituted cyclopropyl. In some embodiments, the optional substituent is F or C_{1-5} alkyl. In some embodiments, the optional substituent is F. In some embodiments, the optional substituent is C_{1-5} alkyl. In some embodiments, the C_{1-5} alkyl is methyl. In some embodiments, the C_{1-5} alkyl is ethyl. In some embodiments, the C_{1-5} alkyl is propyl. In some embodiments, the C_{1-5} alkyl is isopropyl. In some embodiments, two optional substituents are attached to the same carbon, which is also referred to as germinal substitution.

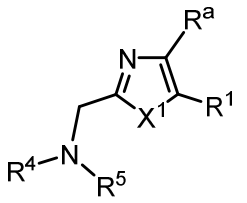
[0263] In some embodiments, R^d is H, alkyl, or cycloalkyl. In some embodiments, R^d is H. In some embodiments, R^d is alkyl. In some embodiments, R^d is cycloalkyl. In some embodiments, alkyl is methyl, ethyl, propyl, isopropyl, or *t*-butyl. In some embodiments, the cycloalkyl is cyclopropyl, cyclopentyl, or cyclohexyl.

[0264] In some embodiments, m is 0, 1, or 2. In some embodiments, m is 0 or 1. In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2.

[0265] In some embodiments, p is 0, 1, or 2. In some embodiments, p is 0 or 1. In some embodiments, p is 1 or 2. In some embodiments, p is 0. In some embodiments, p is 1. In some embodiments, p is 2.

[0266] In some embodiments, q is 0 or 1. In some embodiments, q is 0. In some embodiments, q is 1. In some embodiments, q is 2.

[0267] In some embodiments, the HDAC6 inhibitor has the formula:



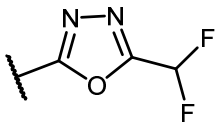
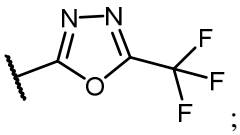
,

or a pharmaceutically acceptable salt thereof,

wherein:

X^1 is S;

R^a is selected from the group consisting of H, halogen, and $C_{1\text{-}3}$ alkyl;

R^1 is  or ;

R^2 is selected from the group consisting of alkyl, alkoxy, and cycloalkyl, each of which is optionally substituted;

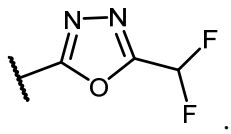
R^3 is H or alkyl;

R^4 is selected from the group consisting of alkyl, $–(SO_2)R^2$, $–(SO_2)NR^2R^3$, and $–(CO)R^2$; and

R^5 is aryl or heteroaryl; or R^4 and R^5 together with the atom to which they are attached form a heterocyclyl, each of which is optionally substituted;

[0268] In some embodiments, R^a is H.

[0269] In some embodiments, R^1 is

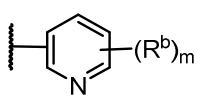
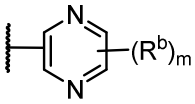
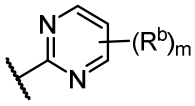
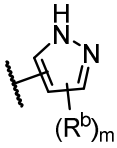


[0270] In some embodiments,R^4 is $–(SO_2)R^2$.

[0271] In some embodiments, $–(SO_2)R^2$ is $–(SO_2)$alkyl, $–(SO_2)$alkyleneheterocyclyl, $–(SO_2)$haloalkyl, $–(SO_2)$haloalkoxy, or $–(SO_2)$cycloalkyl.

[0272] In some embodiments, R^5 is heteroaryl.

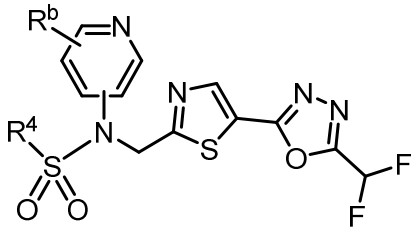
[0273] In some embodiments, the heteroaryl is a 5- to 6-membered heteroaryl

[0274] In some embodiments, the 5- to 6-membered heteroaryl is selected from the group consisting of , , , and , wherein R^b is halogen, alkyl, alkoxy, cycloalkyl, -CN, haloalkyl, or haloalkoxy; and m is 0 or 1.

[0275] In some embodiments, R^b is F, Cl, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CHF_2$, $-CF_2CH_3$, -CN, $-OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_2H$, and cyclopropyl.

[0276] In some embodiments, the aryl is selected from the group consisting of phenyl, 3-chlorophenyl, 3-chloro-4-fluorophenyl, 3-trifluoromethylphenyl, 3,4-difluorophenyl, and 2,6-difluorophenyl.

[0277] In some embodiments, the HDAC6 inhibitor has the Formula (Ik):


(Ik),

or a pharmaceutically acceptable salt thereof,

wherein:

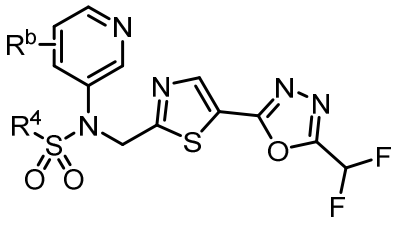
R^b is H, halogen, alkyl, cycloalkyl, -CN, haloalkyl, or haloalkoxy; and

R^4 is alkyl, alkoxy, haloalkyl, or cycloalkyl, each of which is optionally substituted.

[0278] In some embodiments, R^b is H, halogen, haloalkyl, or haloalkoxy.

[0279] In some embodiments, R^4 is optionally substituted alkyl or cycloalkyl.

[0280] In some embodiments, the HDAC6 inhibitor has the structure:



(Ik-1),

or a pharmaceutically acceptable salt thereof,

wherein:

R^b is H, halogen, alkyl, cycloalkyl, -CN, haloalkyl, or haloalkoxy; and

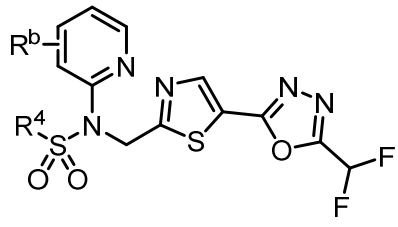
R^4 is alkyl, alkoxy, haloalkyl, or cycloalkyl, each of which is optionally substituted.

[0281] In some embodiments, R^b is H, halogen, haloalkyl, or haloalkoxy.

[0282] In some embodiments, R^4 is optionally substituted alkyl or cycloalkyl.

[0283] In some embodiments, R^4 is alkyl.

[0284] In some embodiments, the HDAC6 inhibitor has the structure:



(Ik-2)

or a pharmaceutically acceptable salt thereof,

wherein:

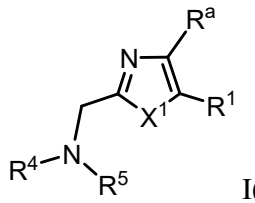
R^b is H, halogen, alkyl, cycloalkyl, -CN, haloalkyl, or haloalkoxy; and

R^4 is alkyl, alkoxy, haloalkyl, or cycloalkyl, each of which is optionally substituted.

[0285] In some embodiments, R^b is H, halogen, haloalkyl, or haloalkoxy.

[0286] In some embodiments, R^4 is optionally substituted alkyl.

[0287] In some embodiments, the HDAC6 inhibitor is a compound having the formula:

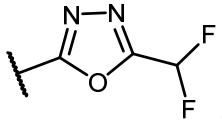
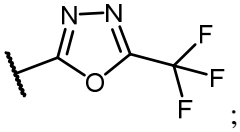

I(y) ,

or a pharmaceutically acceptable salt thereof,

wherein:

X^1 is S;

R^a is selected from the group consisting of H, halogen, and C_{1-3} alkyl;

R^1 is  or  ;

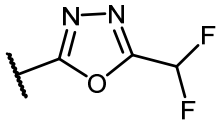
R^2 is selected from the group consisting of alkyl, alkoxy, and cycloalkyl, each of which is optionally substituted;

R^3 is H or alkyl;

R^4 is selected from the group consisting of alkyl, $–(SO_2)R^2$, $–(SO_2)NR^2R^3$, and $–(CO)R^2$; and

R^5 is aryl or heteroaryl; or R^4 and R^5 together with the atom to which they are attached form a heterocyclyl, each of which is optionally substituted.

[0288] In some embodiments of Formula I(y), R^a is H.

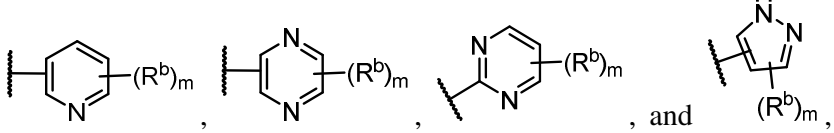
[0289] In some embodiments of Formula I(y), R^1 is  .

[0290] In some embodiments of Formula I(y), R^4 is $–(SO_2)R^2$.

[0291] In some embodiments of Formula I(y), $–(SO_2)R^2$ is $–(SO_2)$alkyl, $–(SO_2)$alkyleneheterocyclyl, $–(SO_2)$haloalkyl, $–(SO_2)$haloalkoxy, or $–(SO_2)$cycloalkyl.

[0292] In some embodiments of Formula I(y), R^5 is heteroaryl.

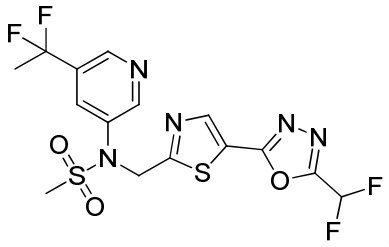
[0293] In some embodiments of Formula I(y), the heteroaryl is a 5- to 6-membered heteroaryl.

[0294] In some embodiments of Formula I(y), the 5- to 6-membered heteroaryl is selected from the group consisting of , wherein R^b is halogen, alkyl, alkoxy, cycloalkyl, -CN, haloalkyl, or haloalkoxy; and m is 0 or 1.

[0295] In some embodiments of Formula I(y), R^b is F, Cl, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CHF_2$, $-CF_2CH_3$, -CN, $-OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_2H$, and cyclopropyl.

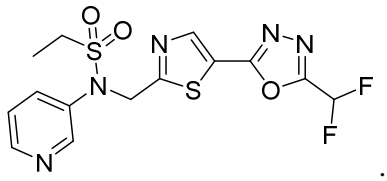
[0296] In some embodiments of Formula I(y), the aryl is selected from the group consisting of phenyl, 3-chlorophenyl, 3-chloro-4-fluorophenyl, 3-trifluoromethylphenyl, 3,4-difluorophenyl, and 2,6-difluorophenyl.

[0297] In some embodiments, the HDAC6 inhibitor has the structure:



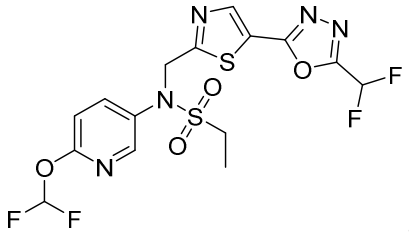
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[0298] In some embodiments, the HDAC6 inhibitor has the structure:



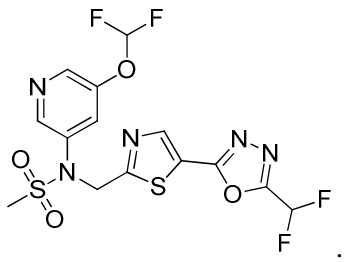
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[0299] In some embodiments, the HDAC6 inhibitor has the structure:

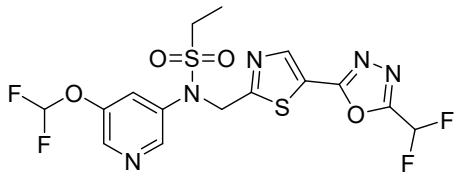


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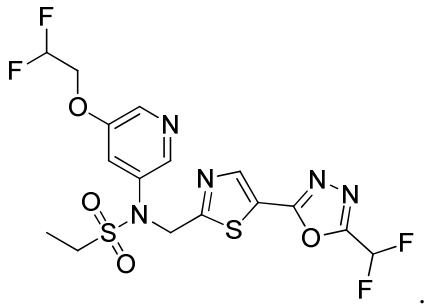
[0300] In some embodiments, the HDAC6 inhibitor has the structure:



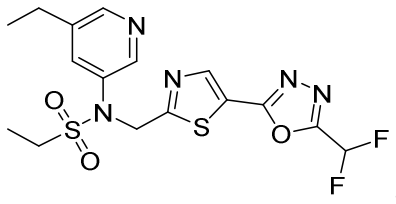
[0301] In some embodiments, the HDAC6 inhibitor has the structure:



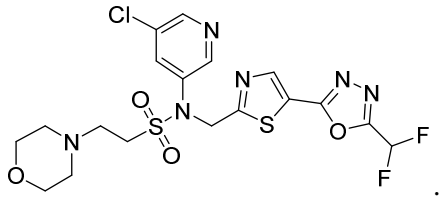
[0302] In some embodiments, the HDAC6 inhibitor has the structure:



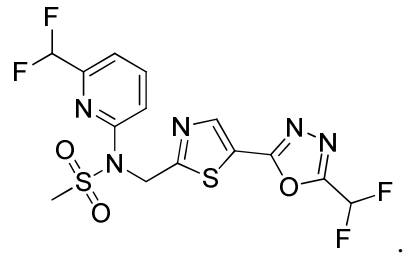
[0303] In some embodiments, the HDAC6 inhibitor has the structure:



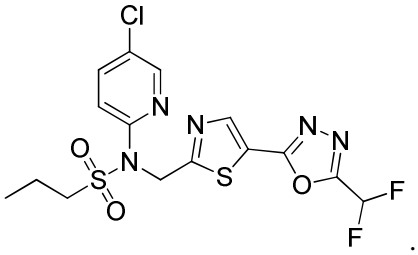
[0304] In some embodiments, the HDAC6 inhibitor has the structure:



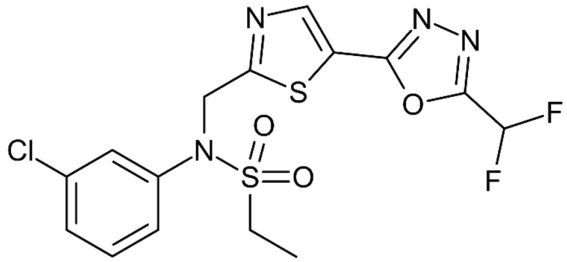
[0305] In some embodiments, the HDAC6 inhibitor has the structure:



[0306] In some embodiments, the HDAC6 inhibitor has the structure:

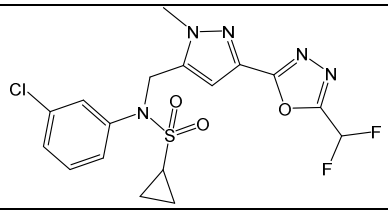
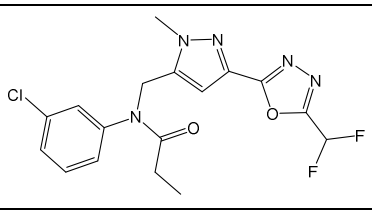


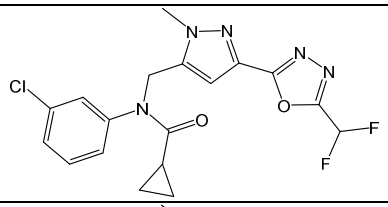
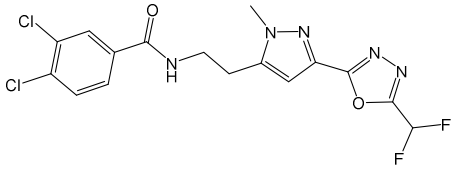
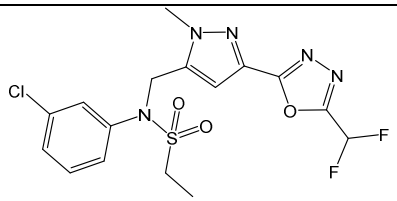
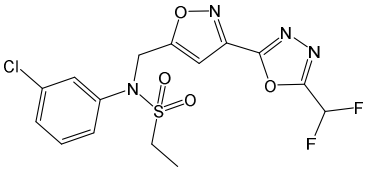
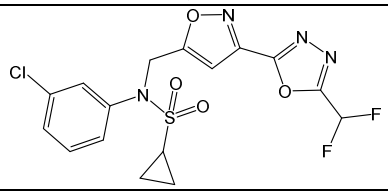
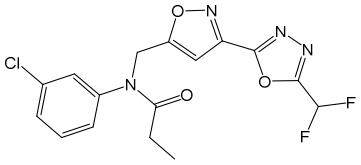
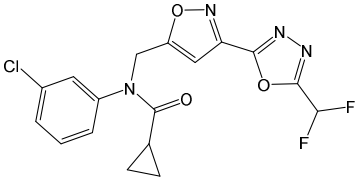
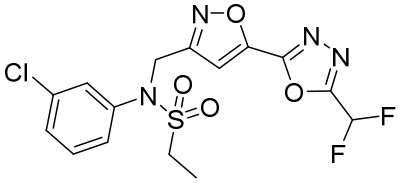
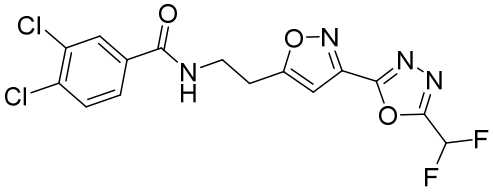
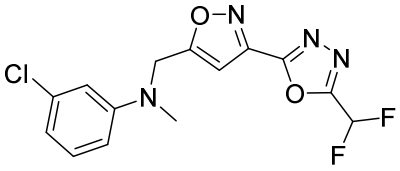
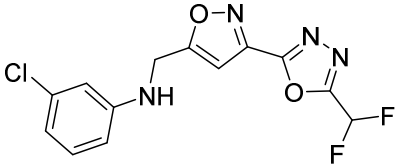
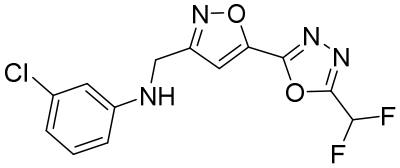
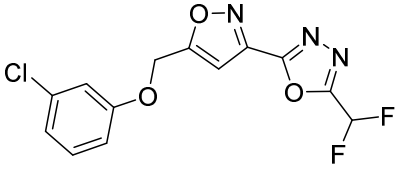
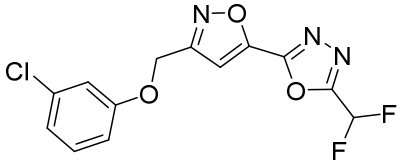
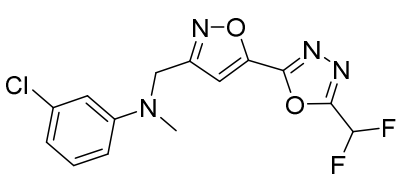
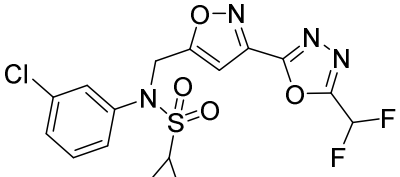
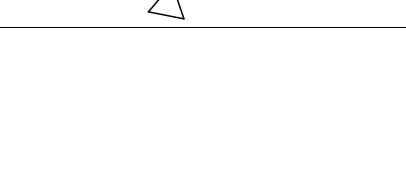
[0307] In some embodiments, the fluoroalkyl-oxadiazole derivative is TYA-018 or an analog thereof. The structure of TYA-018 is

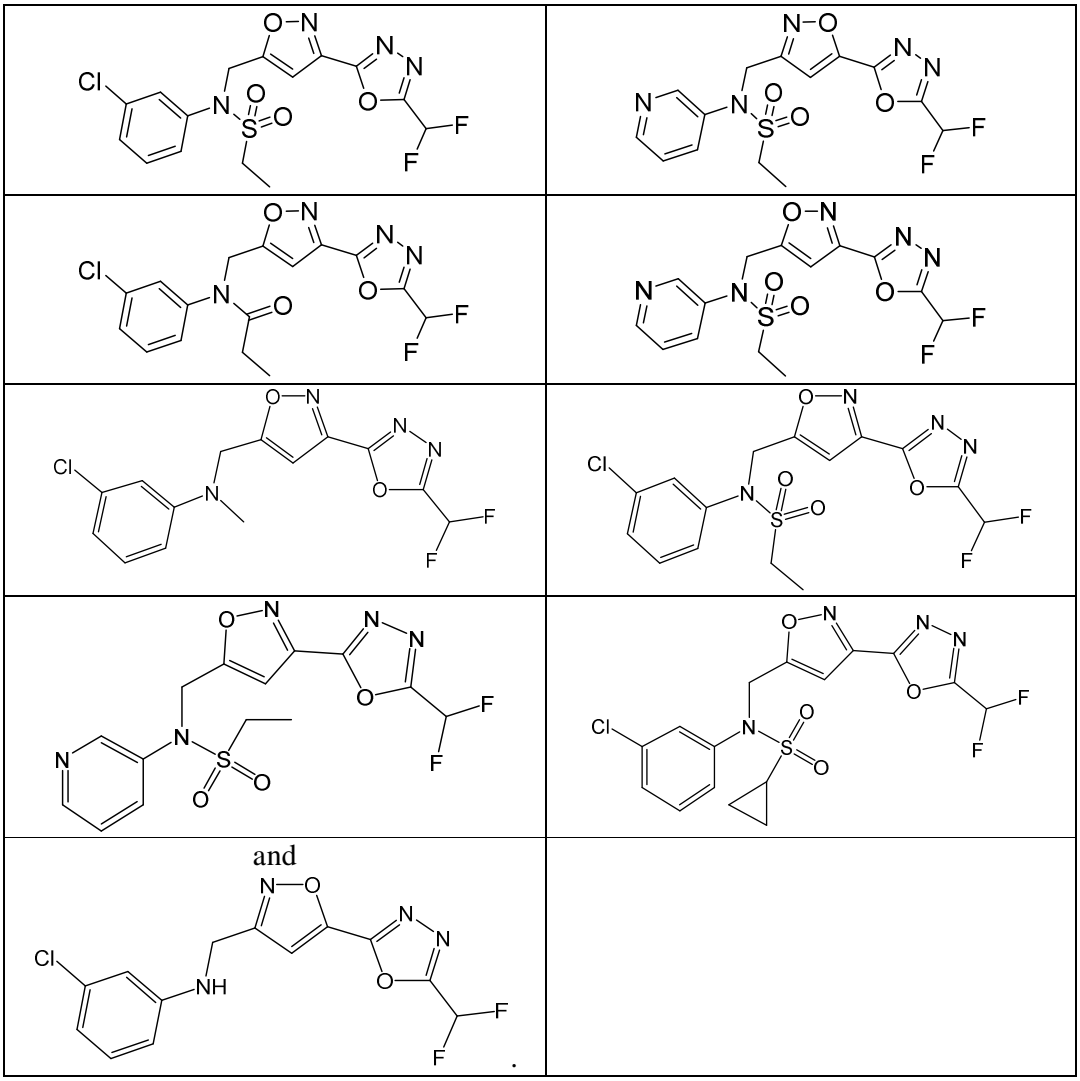


[0308] Analogs of TYA-018 include, without limitation, the compounds listed in Table 2.

Table 2



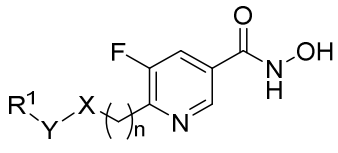
and

.

5-Fluoronicotinamide Derivatives

[0309] In some embodiments, the HDAC6 inhibitor is a 5-fluoronicotinamide derivative. Illustrative 5-fluoronicotinamide derivatives that may be used as HDAC6 inhibitors include those described herein and those described in Int'l Pat. Appl. Pub. No. PCT/US2020/054134, published as WO2021067859A1, the content of which is incorporated by reference herein in its entirety. PCT/US2020/054134, published as WO2021067859A1, also describes methods of synthesis of such compounds, which are specifically incorporated by reference herein.

[0310] In some embodiments, the HDAC6 inhibitor is a compound of Formula (II):



(II); wherein

n is 0 or 1;

X is O, NR^4, or $CR^4R^{4'}$;

Y is a bond, CR^2R^3 or $S(O)_2$; R^1 is selected from the group consisting of H, amido, carbocyclyl, heterocyclyl, aryl, and heteroaryl;

R^2 and R^3 are independently selected from the group consisting of H, halogen, alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, –(CH_2)–carbocyclyl, –(CH_2)–heterocyclyl, –(CH_2)–aryl, and –(CH_2)–heteroaryl; or

R^1 and R^2 taken together with the carbon atom to which they are attached form a carbocyclyl or heterocyclyl; or

R^2 and R^3 taken together with the carbon atom to which they are attached form a carbocyclyl or heterocyclyl; and

R^4 and $R^{4'}$ are each independently selected from the group consisting of H, alkyl, –CO_2–alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, –(CH_2)–carbocyclyl, –(CH_2)–heterocyclyl, –(CH_2)–aryl, and –(CH_2)–heteroaryl; or

R^4 and $R^{4'}$ taken together with the carbon atom to which they are attached form a carbocyclyl or heterocyclyl;

wherein each alkyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently optionally substituted with one or more substituents selected from the group consisting of halogen, haloalkyl, oxo, hydroxy, alkoxy, $–OCH_3$, $–CO_2CH_3$, –C(O)NH(OH),$–CH_3$, morpholine, and –C(O)N-cyclopropyl.

Pharmaceutical Compositions and Kits

[0311] In various embodiments of the present disclosure, pharmaceutical compositions comprising one or more HDAC6 inhibitors disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate, hydrate, tautomer, *N*-oxide, or salt thereof, and a pharmaceutically acceptable excipient or adjuvant is provided. The pharmaceutically acceptable excipients and adjuvants are added to the composition or

formulation for a variety of purposes. In some embodiments, a pharmaceutical composition comprising one or more compounds disclosed herein, or a pharmaceutically acceptable solvate, hydrate, tautomer, *N*-oxide, or salt thereof, further comprises a pharmaceutically acceptable carrier. In some embodiments, a pharmaceutically acceptable carrier includes a pharmaceutically acceptable excipient, binder, and/or diluent. In some embodiments, suitable pharmaceutically acceptable excipients include, but are not limited to, water, salt solutions, alcohol, polyethylene glycols (e.g., polyethylene glycol 300), gelatin, lactose, amylase, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose and polyvinylpyrrolidone.

[0312] In some embodiments, the HDAC6 inhibitor in the pharmaceutical composition described herein is one or more compounds of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), Formula (Id), Formula (Id-1), Formula (Id-2), Formula (Id-3), Formula (Id-4), Formula (Ie), Formula (1e-1), Formula (If), Formula (If-1), Formula (Ig), Formula (Ig-1), Formula (Ih), Formula (Ih-1), Formula (Ii), Formula (Ii-1), Formula (Ij), Formula (Ij-1), Formula (Ik), Formula (Ik-1), Formula (Ik-2), Formula (Ik-3), Formula I(y), or Formula (II). In some embodiments, the HDAC6 inhibitor in the pharmaceutical composition described herein is a compound of Formula (I). In some embodiments, the HDAC6 inhibitor in the pharmaceutical composition described herein is a compound of Formula (Ic). In some embodiments, the HDAC6 inhibitor in the pharmaceutical composition described herein is a compound of Formula (Ik). In some embodiments, the HDAC6 inhibitor in the pharmaceutical composition described herein is a compound of Formula I(y) (which may also be referenced herein as Formula (Iy)).

[0313] In another aspect, the disclosure provides an HDAC6 inhibitor for use in a method for treating metabolic disease.

[0314] In another aspect, the disclosure provides a kit, comprising an HDAC6 inhibitor, or pharmaceutical composition thereof, and instructions for use in a method for treating metabolic disease.

[0315] In another aspect, the disclosure provides use of an HDAC6 inhibitor in treating metabolic disease.

[0316] In another aspect, the disclosure provides an HDAC6 inhibitor for use in a method for treating HFpEF.

[0317] In another aspect, the disclosure provides a kit, comprising an HDAC6 inhibitor, or pharmaceutical composition thereof, and instructions for use in a method for treating HFpEF.

[0318] In another aspect, the disclosure provides use of an HDAC6 inhibitor in treating HFpEF.

Methods of Administration

[0319] The HDAC6 inhibitors described herein (and pharmaceutical compositions comprising such HDAC6 inhibitors) can be administered to a subject by any suitable means disclosed herein or known in the art.

[0320] In some embodiments, the administration of an HDAC6 inhibitor is oral administration. In some embodiments, the method comprises orally administering to a subject an HDAC6 inhibitor of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), Formula (Id), Formula (Id-1), Formula (Id-2), Formula (Id-3), Formula (Id-4), Formula (Ie), Formula (1e-1), Formula (If), Formula (If-1), Formula (Ig), Formula (Ig-1), Formula (Ih), Formula (Ih-1), Formula (Ii), Formula (Ii-1), Formula (Ij), Formula (Ij-1), Formula (Ik), Formula (Ik-1), Formula (Ik-2), Formula (Ik-3), Formula I(y), or Formula (II). In some embodiments, the method comprises orally administering to a subject an HDAC6 inhibitor of Formula (I). In some embodiments, the method comprises orally administering to a subject an HDAC6 inhibitor of Formula (Ic). In some embodiments, the method comprises orally administering to a subject an HDAC6 inhibitor of Formula (Ik). In some embodiments, the method comprises orally administering to a subject an HDAC6 inhibitor of Formula I(y). In some embodiments, the method comprises orally administering to a subject an HDAC6 inhibitor of Formula (II). In some embodiments, oral administration is by means of a tablet or capsule. In some embodiments, a human is orally administered an HDAC6 inhibitor described herein (or a pharmaceutical composition thereof).

[0321] Various dosing schedules of the HDAC6 inhibitors described herein (and pharmaceutical compositions comprising such HDAC6 inhibitors) are contemplated including single administration or multiple administrations over a period of time.

[0322] In some embodiments, an HDAC6 inhibitor described herein (or a pharmaceutical composition comprising the inhibitor) is administered twice a day, once a day, once in two days, once in three days, once a week, once in two weeks, once in three weeks or once a month. In some embodiments, an HDAC6 inhibitor described herein (or a pharmaceutical composition comprising the inhibitor) is administered once a day.

[0323] In some embodiments, an HDAC6 inhibitor described herein (or a pharmaceutical composition comprising the inhibitor) is administered a single time. In some embodiments, an HDAC6 inhibitor described herein (or a pharmaceutical composition comprising the inhibitor) is administered over a period of time, for example, for (or longer than) 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 1 year. In some embodiments, the subject being treated is administered an HDAC6 inhibitor described herein (or a pharmaceutical composition comprising the inhibitor) for at least 1 month, at least 6 weeks, at least 2 months, at least 3 months, or at least 6 months. In some embodiments, the subject being treated is administered an HDAC6 inhibitor described herein (or a pharmaceutical composition comprising the inhibitor) for less than 1 month, 6 weeks, 2 months, 3 months, or 6 months.

[0324] The appropriate dosage of an HDAC6 inhibitor described herein for use in the methods described herein will depend on the type of inhibitor used, the condition of the subject (e.g., age, body weight, health), the responsiveness of the subject, other medications used by the subject, and other factors to be considered at the discretion of the medical practitioner performing the treatment.

[0325] In some embodiments, an HDAC6 inhibitor described herein is administered to the subject in the amount in the range from 1 mg to 500 mg per day. In some embodiments, an HDAC6 inhibitor described herein is administered to a human orally in the amount in the range from 1 mg to 500 mg per day. In some embodiments, an HDAC6 inhibitor described herein is administered to a human orally in a single dose in the amount in the range from 1 mg to 500 mg. In some embodiments, an HDAC6 inhibitor described herein is administered to a human orally in the amount in the range from 1 mg to 500 mg once a day, e.g., over a course of treatment (e.g., for 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 1 year, or longer). In some embodiments, an HDAC6 inhibitor described herein is administered to a human subject in a starting dose between 0.5 and 3 mg/day (e.g., 1 mg/day). In some embodiments, an HDAC6 inhibitor described herein is administered to a human subject in a starting dose of 0.5 mg/day. In some embodiments, an HDAC6 inhibitor described herein is administered to a human subject in a starting dose of 1 mg/day. In some embodiments, an HDAC6 inhibitor described herein is administered to a human

subject in a starting dose of 1.5 mg. In some embodiments, an HDAC6 inhibitor described herein is administered to a human subject in a starting dose of 3 mg. This dose may be escalated or remain the same depending on subject's responsiveness to the treatment. An HDAC6 inhibitor may be administered in an amount that is deemed to be therapeutically effective.

Combination Treatments and Kits

[0326] In some embodiments, the HDAC6 inhibitors described herein (and pharmaceutical compositions comprising such HDAC6 inhibitors) can be administered to a subject in combination with another medication or therapy. In some embodiments, two or three different HDAC6 inhibitors (e.g., out of those described herein) can be administered to a subject.

[0327] In some embodiments, one or more of the HDAC6 inhibitors described herein (and pharmaceutical compositions comprising such HDAC6 inhibitors) can be administered to a subject in combination with one or more therapy different from said one or more HDAC6 inhibitor(s), where the therapy is a cardioprotective therapy, an anti-hypertensive therapy, a hypoglycemic therapy, a therapy for a heart condition (e.g., heart failure), a therapy for HFpEF, or a therapy for metabolic disease. The additional therapy can be any such therapy known in the art. In some embodiments of metabolic disease treatments, an HDAC6 inhibitor described herein (or a pharmaceutical composition comprising such HDAC6 inhibitor) is administered to a subject in combination with another metabolic disease therapy (such as an agent used to treat metabolic disease). In some embodiments of HFpEF treatments, an HDAC6 inhibitor described herein (or a pharmaceutical composition comprising such HDAC6 inhibitor) is administered to a subject in combination with another HFpEF therapy (such as an agent used to treat HFpEF). In some embodiments, an HDAC6 inhibitor described herein (or a pharmaceutical composition comprising such HDAC6 inhibitor) is administered to a subject in combination with a hypoglycemic therapy (such as an agent used to treat hypoglycemia). In some embodiments, an HDAC6 inhibitor described herein (or a pharmaceutical composition comprising such HDAC6 inhibitor) is administered to a subject in combination with an anti-hypertensive therapy (such as an agent used to treat hypertension).

[0328] In some embodiments, an HDAC6 inhibitor described herein (or a pharmaceutical composition comprising such HDAC6 inhibitor) is administered to a subject in combination with an anti-hypertensive agent. For example, and without limitation, any of the following anti-hypertensive agents can be used in combination with HDAC6 inhibitors: thiazide diuretics (*e.g.*, Capozide, Dyazide, Hyzaar, Lopressor HCT, Maxzide, Prinzide, Clorpres, Tenoretic, or

Thalitone), calcium channel blockers (*e.g.*, Amlodipine, Diltiazem, Felodipine, Isradipine, Nicardipine, Nifedipine, Nisoldipine, or Verapamil), ACE inhibitors (*e.g.*, Benazepril, Captopril, Enalapril, Fosinopril, Lisinopril, Moexipril, Perindopril, Quinapril, Ramipril, or Trandolapril), angiotensin II receptor antagonists (ARB) (*e.g.*, Azilsartan, Candesartan, Eprosartan, Irbesartan, Losartan, Olmesartan, Telmisartan, or Valsartan), and beta blockers (*e.g.*, Acebutolol, Atenolol, Bisoprolol, Metoprolol, Nadolol, Nebivolol, or Propranolol).

[0329] In some embodiments, an HDAC6 inhibitor described herein (or a pharmaceutical composition comprising such HDAC6 inhibitor) is administered to a subject in combination with an ACE inhibitor. In some embodiments, an HDAC6 inhibitor described herein (or a pharmaceutical composition comprising such HDAC6 inhibitor) is administered to a subject in combination with a beta blocker. In some embodiments, an HDAC6 inhibitor described herein (or a pharmaceutical composition comprising such HDAC6 inhibitor) is administered to a subject in combination with a thiazide diuretic. In some embodiments, an HDAC6 inhibitor described herein (or a pharmaceutical composition comprising such HDAC6 inhibitor) is administered to a subject in combination with a calcium channel blocker. In some embodiments, an HDAC6 inhibitor described herein (or a pharmaceutical composition comprising such HDAC6 inhibitor) is administered to a subject in combination with an angiotensin II receptor antagonist (ARB).

[0330] In some embodiments, an HDAC6 inhibitor described herein (or a pharmaceutical composition comprising such HDAC6 inhibitor) is administered to a subject in combination with an aldosterone receptor agonist (e.g., spironolactone). In some embodiments, an HDAC6 inhibitor described herein (or a pharmaceutical composition comprising such HDAC6 inhibitor) is administered to a subject in combination with spironolactone.

[0331] In some embodiments, an HDAC6 inhibitor described herein (or a pharmaceutical composition comprising such HDAC6 inhibitor) is administered to a subject in combination with an angiotensin and neprilysin receptor agonist (e.g., sacubitril-valsartan). In some embodiments, an HDAC6 inhibitor described herein (or a pharmaceutical composition comprising such HDAC6 inhibitor) is administered to a subject in combination with angiotensin receptor-neprilysin inhibitor (ARNi). In some embodiments, an HDAC6 inhibitor described herein (or a pharmaceutical composition comprising such HDAC6 inhibitor) is administered to a subject in combination with sacubitril and/or valsartan.

[0332] In some embodiments, an HDAC6 inhibitor described herein (or a pharmaceutical composition comprising such HDAC6 inhibitor) is administered to a subject in combination with a hypoglycemic agent that lowers the level of blood glucose (e.g., an oral hypoglycemic therapy used to treat Type 2 diabetes). For example, and without limitation, any of the following hypoglycemic agents (or classes of agents) can be used in combination with HDAC6 inhibitors: sulfonylureas, meglitinides, biguanides (metformin), thiazolidinediones, alpha-glucosidase inhibitors, DPP4 inhibitors, cycloset, and SGLT2 inhibitors. In some embodiments, an HDAC6 inhibitor described herein (or a pharmaceutical composition comprising such HDAC6 inhibitor) is administered to a subject in combination with an oral hypoglycemic agent (e.g., which is used to treat Type 2 diabetes).

[0333] In some embodiments, an HDAC6 inhibitor described herein (or a pharmaceutical composition comprising such HDAC6 inhibitor) is administered to a subject in combination with a sodium-glucose co-transporter 2 (SLGT2) inhibitor (*e.g.*, empagliflozin).

[0334] In some embodiments, an HDAC6 inhibitor described herein (or a pharmaceutical composition comprising such HDAC6 inhibitor) is administered to a subject before, at the same time, or after the additional therapy. In some embodiments, any HDAC6 inhibitor is administered to a subject in a therapeutically effective amount, and any additional therapy described herein is administered to a subject in a therapeutically effective amount.

[0335] In some embodiments, the subject being treated in accordance with the methods described herein has not received an anti-hypertensive therapy. In some embodiments, the subject being treated in accordance with the methods described herein has not received a hypoglycemic therapy. In some embodiments, the subject being treated in accordance with the methods described herein has not received metabolic disease therapy. In some embodiments, the subject being treated in accordance with the methods described herein has not received HFpEF therapy. In some embodiments, the subject being treated in accordance with the methods described herein has not received a cardioprotective therapy and/or a heart condition (e.g., heart failure) therapy. In some embodiments, the subject being treated in accordance with the methods described herein has not received an SGLT2 inhibitor.

[0336] In some embodiments provided herein are kits comprising an HDAC6 inhibitor described herein (or a pharmaceutical composition comprising the same) and one or more additional agents (e.g., an additional agent for the treatment of metabolic disease, an additional agent for the treatment of HFpEF, an anti-hypertensive agent, and/or a hypoglycemic agent).

In some embodiments, provided herein are kits comprising (i) an HDAC6 inhibitor (e.g., in a therapeutically effective amount), and (ii) one or more additional agents (such as any additional agents described herein, e.g., without limitation, a thiazide diuretic, a calcium channel blocker, an ACE inhibitor, an angiotensin II receptor antagonist (ARB), an SGLT2 inhibitor (*e.g.*, empagliflozin), or a beta blocker (e.g., in a therapeutically effective amount)).

Patient Populations to be Treated

[0337] In some embodiments, the subject is a human. In some embodiments, the human is an adult human. In some embodiments, the human is 60 years of age or older. In some embodiments, the human is over 60 years of age. In some embodiments, the human is 65 years of age or older. In some embodiments, the human is over 65 years of age. In some embodiments, the human is 70 years of age or older. In some embodiments, the human is over 70 years of age. In some embodiments, the subject is a male (e.g., a male at least or older than 60, 65 or 70 years of age). In some embodiments, the subject is a female (e.g., a female at least or older than 60, 65 or 70 years of age).

[0338] In some embodiments, the subject being treated is obese (e.g., has BMI of 30 or higher). In some embodiments, the subject is at risk for obesity (e.g., has BMI of 25 or higher). In some embodiments, the subject being treated has a metabolic disease. In some embodiments, the subject is at risk for metabolic disease. In some embodiments, the subject has (or is at risk for) diabetes. In some embodiments, the subject has (or is at risk for) diabetes mellitus. In some embodiments, the subject has (or is at risk for) pre-diabetes. In some embodiments, the subject has (or is at risk for) diabetic cardiomyopathy. In some embodiments, the subject has (or is at risk for) metabolic syndrome. In some embodiments, the subject has (or is at risk for) hypertension. In some embodiments, the subject has (or is at risk for) hypertriglyceridemia. In some embodiments, the subject has (or is at risk for) dyslipidemia.

[0339] In some embodiments, the subject being treated is not obese (e.g., has BMI of less than 30). In some embodiments, the subject has BMI of less than 25. In some embodiments, the subject being treated does not have a metabolic disease. In some embodiments, the subject being treated does not have diabetes (e.g., does not have diabetes mellitus). In some embodiments, the subject does not have pre-diabetes. In some embodiments, the subject does not have diabetic cardiomyopathy. In some embodiments, the subject does not have metabolic syndrome. In some embodiments, the subject does not have hypertension. In some embodiments, the subject does not have hypertriglyceridemia. In some embodiments, the

subject does not have dyslipidemia. For example, a subject with HFpEF being treated in accordance with the methods described herein may have or not have these conditions.

[0340] In some embodiments, the subject being treated has HFpEF. In some embodiments, the subject being treated is at risk for HFpEF. In some embodiments, the subject has (or is at risk for) cardiac fibrosis. In some embodiments, the subject has (or is at risk for) diastolic dysfunction.

[0341] In some embodiments, the subject has (or is at risk for) coronary artery disease (CAD). In some embodiments, the subject has (or is at risk for) valvular heart disease. In some embodiments, the subject has (or is at risk for) atrial fibrillation.

NUMBERED EMBODIMENTS OF THE INVENTION (I)

1. A method of treating or preventing metabolic disease in a subject in need thereof, comprising administering to the subject a HDAC6 inhibitor.

2. The method of embodiment 1, wherein the subject is obese or at risk for obesity.

3. The method of embodiment 1 or embodiment 2, wherein the metabolic disease is a metabolic disease associated with obesity, optionally diet-induced obesity.

4. The method of any one of embodiments 1-3, wherein the metabolic disease is a diabetes (e.g., diabetes mellitus), pre-diabetes, diabetic cardiomyopathy, metabolic syndrome, hypertension, hypertriglyceridemia, or dyslipidemia.

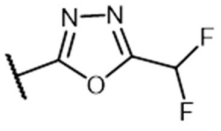
5. The method of embodiment 4, wherein the metabolic disease is diabetes mellitus.

6. The method of embodiment 4, wherein the metabolic disease is metabolic syndrome.

7. A method of treating obesity in a subject in need thereof, comprising administering a to the subject a HDAC6 inhibitor.

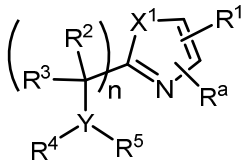
8. The method of embodiments 1-7, wherein the HDAC6 inhibitor is fluoroalkyl-oxadiazole derivative.

9. The method of embodiment 8, wherein the HDAC6 inhibitor is fluoroalkyl-oxadiazole derivative according to the following Formula:



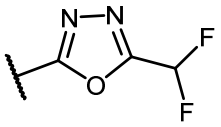
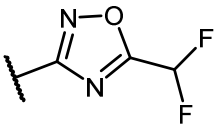
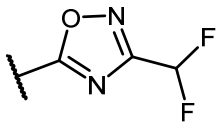
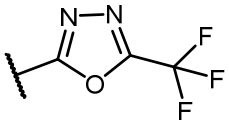
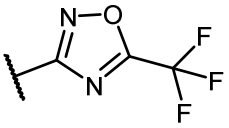
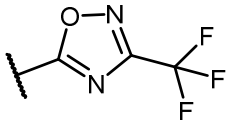
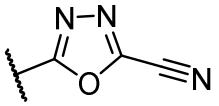
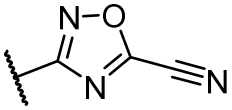
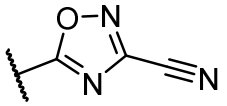
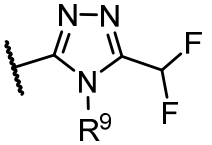
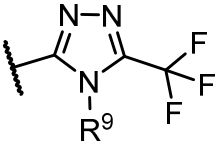
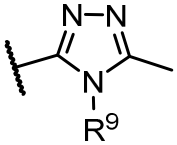
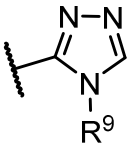
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10. The method of embodiments 1-9, wherein the HDAC6 inhibitor is a compound according to Formula (I):



(I), or pharmaceutically acceptable salt thereof, wherein

R^1 is selected from the group consisting of:

		
		
		
		
and  ;		

R^a is selected from the group consisting of H, halo, C_{1-3} alkyl, cycloalkyl, haloalkyl, and alkoxy;

R^2 and R^3 are independently selected from the group consisting of H, halogen, alkoxy, haloalkyl, aryl, heteroaryl, alkyl, and cycloalkyl each of which is optionally substituted, or R^2 and R^3 together with the atom to which they are attached form a cycloalkyl or heterocyclyl;

R^4 and R^5 are independently selected from the group consisting of H, $–(SO_2)R^2$, $–(SO_2)NR^2R^3$, $–(CO)R^2$, $–(CONR^2R^3)$, aryl, arylheteroaryl, alkylenearyl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, haloalkyl, and alkoxy, each of which is optionally

substituted, or R^4 and R^5 together with the atom to which they are attached form a cycloalkyl or heterocyclyl, each of which is optionally substituted;

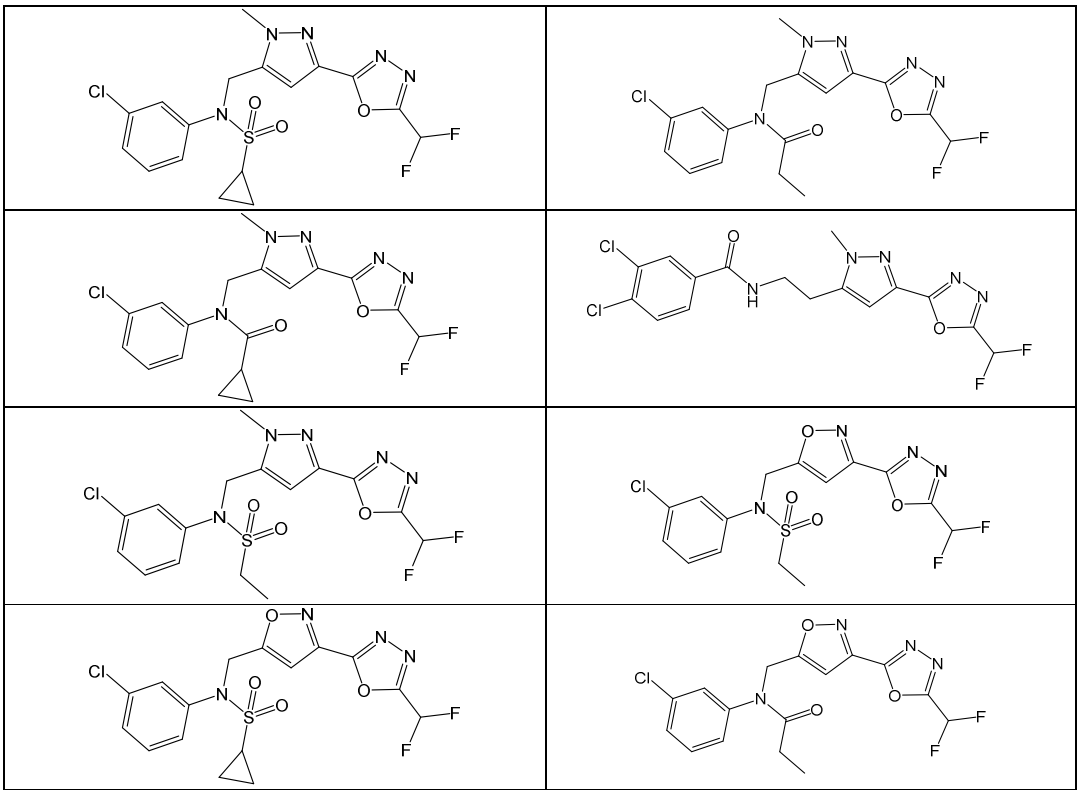
R^9 is selected from the group consisting of H, C_1-C_6 alkyl, haloalkyl, cycloalkyl and heterocyclyl;

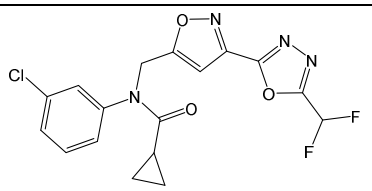
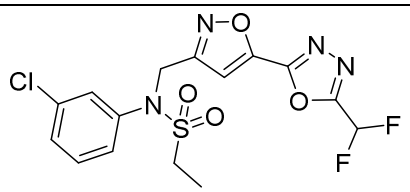
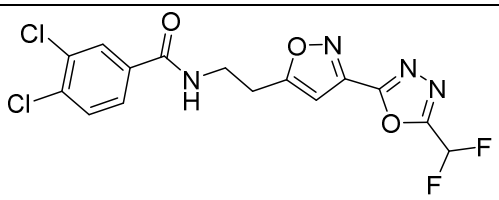
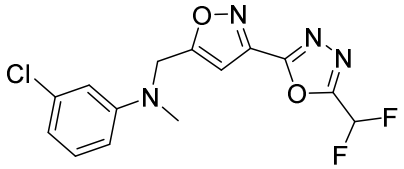
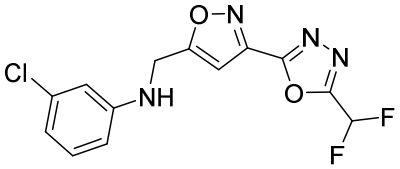
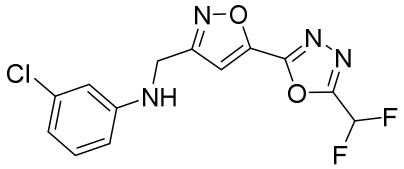
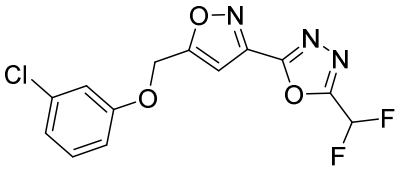
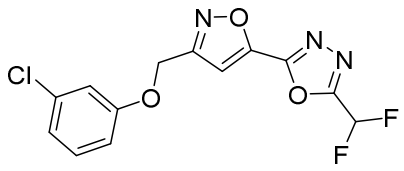
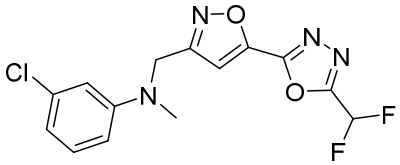
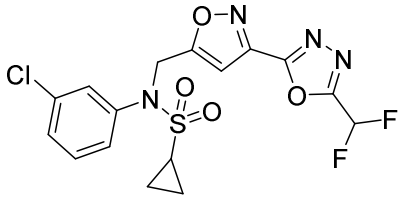
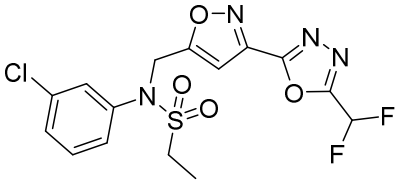
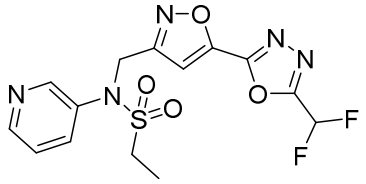
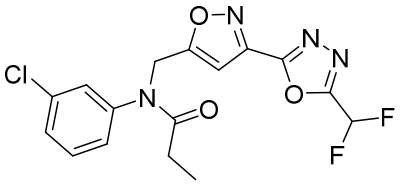
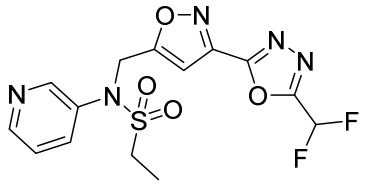
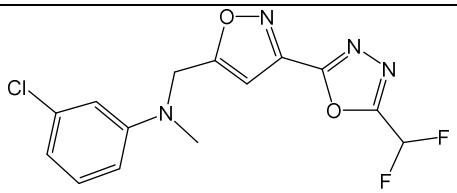
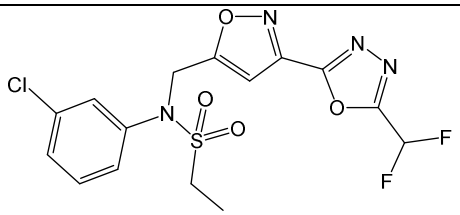
X^1 is selected from the group consisting of S, O, NH and NR^6, wherein R^6 is selected from the group consisting of C_1-C_6 alkyl, alkoxy, haloalkyl, cycloalkyl and heterocyclyl;

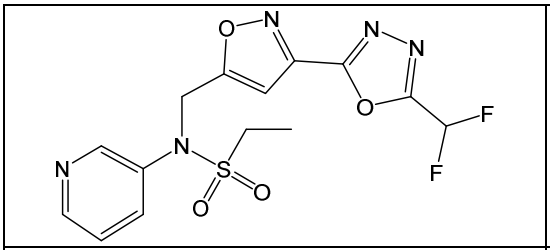
Y is selected from the group consisting of CR^2, O, N, S, SO, and SO_2, wherein when Y is O, S, SO, or SO_2, R^5 is not present and when R^4 and R^5 together with the atom to which they are attached form a cycloalkyl or heterocyclyl, Y is CR^2 or N; and

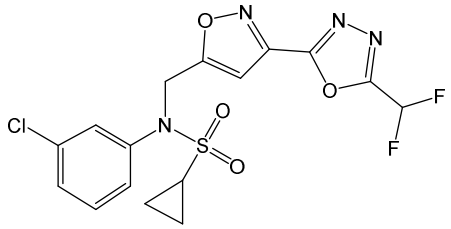
n is selected from 0, 1, and 2.

11. The method of embodiment 10, wherein the HDAC6 inhibitor is selected from the group consisting of:

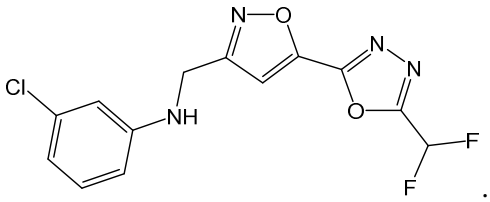


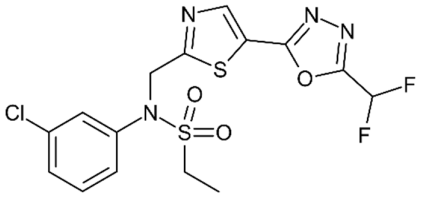




and

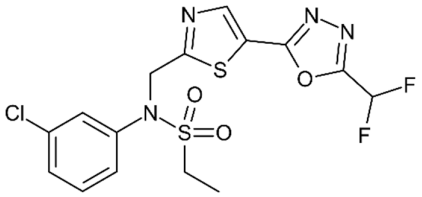


12. The method of embodiment 10, wherein the HDAC6 inhibitor is



or an analog thereof.

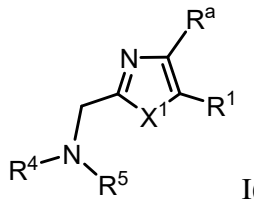
13. The method of embodiment 10, wherein the HDAC6 inhibitor is



14.The method of embodiment 10, wherein the HDAC6 inhibitor is selected from any HDAC6 inhibitor in Table 13 (in Example 7).

15. The method of embodiment 14, wherein the HDAC6 inhibitor is any HDAC6 inhibitor in Table 13 which has an IC_{50} equal to or less than 0.03 μM.

16. The method of embodiment 10, wherein the HDAC6 inhibitor is a compound having the formula:



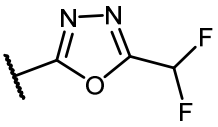
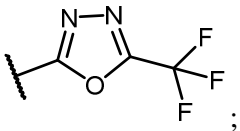
I(y)

or a pharmaceutically acceptable salt thereof,

wherein:

X^1 is S;

R^a is selected from the group consisting of H, halogen, and C_{1-3} alkyl;

R^1 is  or ;

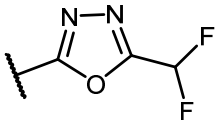
R^2 is selected from the group consisting of alkyl, alkoxy, and cycloalkyl, each of which is optionally substituted;

R^3 is H or alkyl;

R^4 is selected from the group consisting of alkyl, $–(SO_2)R^2$, $–(SO_2)NR^2R^3$, and $–(CO)R^2$; and

R^5 is aryl or heteroaryl; or R^4 and R^5 together with the atom to which they are attached form a heterocyclyl, each of which is optionally substituted.

17. The method of embodiment 16, wherein R^a is H.

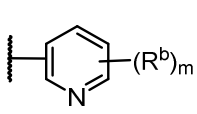
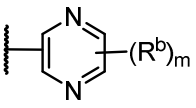
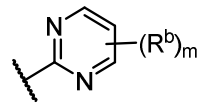
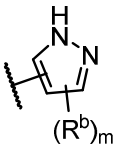
18. The method of embodiment 16 or 17, wherein R^1 is .

19. The method of any one of embodiments 16-18, wherein R^4 is $–(SO_2)R^2$.

20. The method of embodiment 19, wherein $–(SO_2)R^2$ is $–(SO_2)$alkyl, $–(SO_2)$alkyleneheterocyclyl, $–(SO_2)$haloalkyl, $–(SO_2)$haloalkoxy, or $–(SO_2)$cycloalkyl.

21. The method of any one of embodiments 16-20, wherein R^5 is heteroaryl.

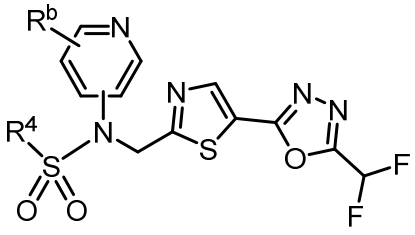
22. The method of embodiment 21, wherein the heteroaryl is a 5- to 6-membered heteroaryl

23. The method of embodiment 22, wherein the 5- to 6-membered heteroaryl is selected from the group consisting of , , , and , wherein R^b is halogen, alkyl, alkoxy, cycloalkyl, -CN, haloalkyl, or haloalkoxy; and m is 0 or 1.

24. The method of embodiment 23, wherein R^b is F, Cl, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CHF_2$, $-CF_2CH_3$, -CN, $-OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_2H$, and cyclopropyl.

25. The method of any one of embodiments 16-24, wherein the aryl is selected from the group consisting of phenyl, 3-chlorophenyl, 3-chloro-4-fluorophenyl, 3-trifluoromethylphenyl, 3,4-difluorophenyl, and 2,6-difluorophenyl.

26. The method of embodiment 10, wherein the HDAC6 inhibitor is a compound having Formula (Ik):

 (Ik),

or a pharmaceutically acceptable salt thereof,

wherein:

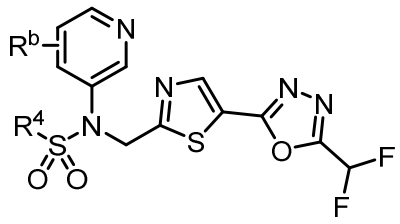
R^b is H, halogen, alkyl, cycloalkyl, -CN, haloalkyl, or haloalkoxy; and

R^4 is alkyl, alkoxy, haloalkyl, or cycloalkyl, each of which is optionally substituted.

27. The method of embodiment 26, wherein R^b is H, halogen, haloalkyl, or haloalkoxy.

28. The method of embodiment 26 or 27, wherein R^4 is optionally substituted alkyl or cycloalkyl.

29. The method of embodiment 26, wherein the HDAC6 inhibitor is a compound having the structure:



(Ik-1), or a pharmaceutically acceptable salt thereof,

wherein:

R^b is H, halogen, alkyl, cycloalkyl, -CN, haloalkyl, or haloalkoxy; and

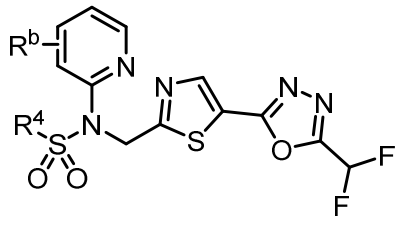
R^4 is alkyl, alkoxy, haloalkyl, or cycloalkyl, each of which is optionally substituted.

30. The method of embodiment 29, wherein R^b is H, halogen, haloalkyl, or haloalkoxy.

31. The method of embodiment 29 or 30, wherein R^4 is optionally substituted alkyl or cycloalkyl.

32. The method of embodiment 29, wherein R^4 is alkyl.

33. The method of embodiment 26, wherein the HDAC6 inhibitor is a compound having the structure:



(Ik-2), or a pharmaceutically acceptable salt thereof,

wherein:

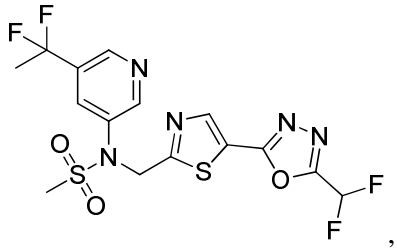
R^b is H, halogen, alkyl, cycloalkyl, -CN, haloalkyl, or haloalkoxy; and

R^4 is alkyl, alkoxy, haloalkyl, or cycloalkyl, each of which is optionally substituted.

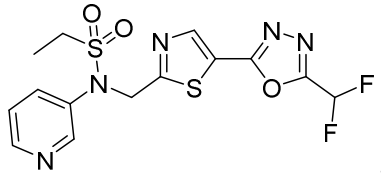
34. The method of embodiment 33, wherein R^b is H, halogen, haloalkyl, or haloalkoxy.

35. The method of embodiment 33 or 34, wherein R^4 is optionally substituted alkyl.

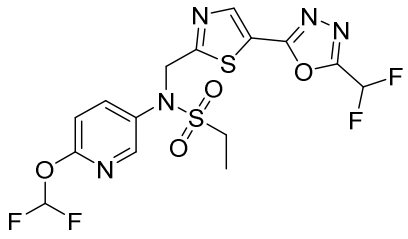
36. The method of embodiment 16, wherein the HDAC6 inhibitor is a compound of Formula:


, or a pharmaceutically acceptable salt thereof.

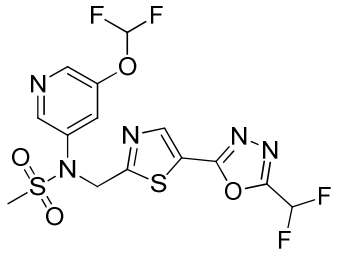
37. The method of embodiment 16, wherein the HDAC6 inhibitor is a compound of Formula:


, or a pharmaceutically acceptable salt thereof.

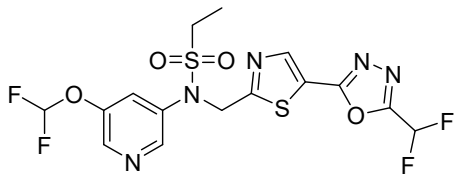
38. The method of embodiment 16, wherein the HDAC6 inhibitor is a compound of Formula:


, or a pharmaceutically acceptable salt thereof.

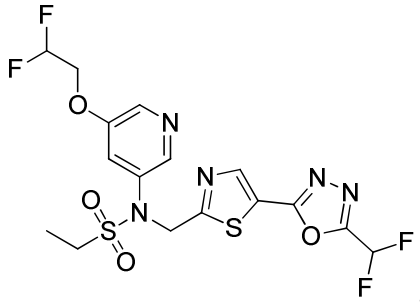
39. The method of embodiment 16, wherein the HDAC6 inhibitor is a compound of Formula:


, or a pharmaceutically acceptable salt thereof.

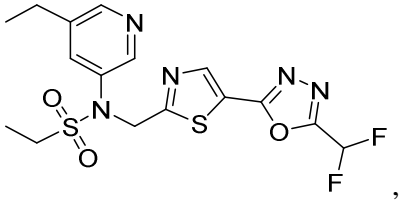
40. The method of embodiment 16, wherein the HDAC6 inhibitor is a compound of Formula:


, or a pharmaceutically acceptable salt thereof.

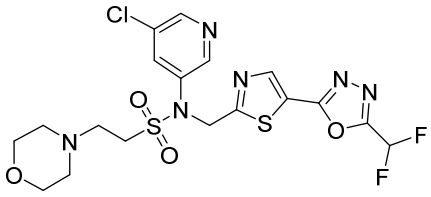
41. The method of embodiment 16, wherein the HDAC6 inhibitor is a compound of Formula:


, or a pharmaceutically acceptable salt thereof.

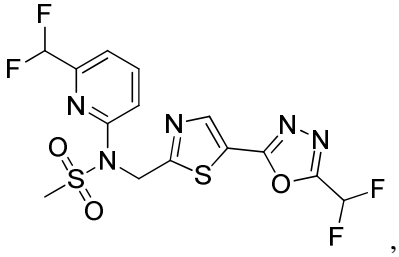
42. The method of embodiment 16, wherein the HDAC6 inhibitor is a compound of Formula:


, or a pharmaceutically acceptable salt thereof.

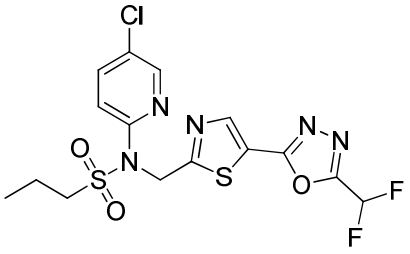
43. The method of embodiment 16, wherein the HDAC6 inhibitor is a compound of Formula:


, or a pharmaceutically acceptable salt thereof.

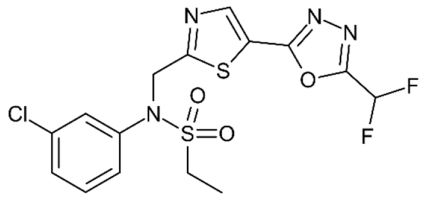
44. The method of embodiment 16, wherein the HDAC6 inhibitor is a compound of Formula:


, or a pharmaceutically acceptable salt thereof.

45. The method of embodiment 16, wherein the HDAC6 inhibitor is a compound of Formula:

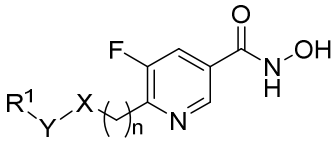

or a pharmaceutically acceptable salt thereof.

46. The method of embodiment 16, wherein the HDAC6 inhibitor is a compound of Formula:



or a pharmaceutically acceptable salt thereof.

47. The method of any one of embodiments 1-7, wherein the HDAC6 inhibitor is a compound of Formula (II):



(II); wherein

n is 0 or 1;

X is O, NR^4, or $CR^4R^{4'}$;

Y is a bond, CR^2R^3 or $S(O)_2$;

R^1 is selected from the group consisting of H, amido, carbocyclyl, heterocyclyl, aryl, and heteroaryl;

R^2 and R^3 are independently selected from the group consisting of H, halogen, alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, –(CH_2)–carbocyclyl, –(CH_2)–heterocyclyl, –(CH_2)–aryl, and –(CH_2)–heteroaryl; or

R^1 and R^2 taken together with the carbon atom to which they are attached form a carbocyclyl or heterocyclyl; or

R^2 and R^3 taken together with the carbon atom to which they are attached form a carbocyclyl or heterocyclyl; and

R^4 and $R^{4'}$ are each independently selected from the group consisting of H, alkyl, –CO_2–alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, –(CH_2)–carbocyclyl, –(CH_2)–heterocyclyl, –(CH_2)–aryl, and –(CH_2)–heteroaryl; or

R^4 and $R^{4'}$ taken together with the carbon atom to which they are attached form a carbocyclyl or heterocyclyl;

wherein each alkyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently optionally substituted with one or more substituents selected from the group consisting of halogen, haloalkyl, oxo, hydroxy, alkoxy, $–OCH_3$, $–CO_2CH_3$, –C(O)NH(OH),$–CH_3$, morpholine, and –C(O)N-cyclopropyl.

48. The method of any one of embodiments 1-7, wherein the HDAC6 inhibitor is CAY10603, tubacin, rocilinostat (ACY-1215), citarinostat (ACY-241), ACY-738, QTX-125, CKD-506, nexturastat A, tubastatin A, or HPOB.

49. The method of any one of the preceding embodiments, wherein the compound is the compound and not the pharmaceutically acceptable salt thereof.

50. The method of any one of embodiments 1-49, wherein the HDAC6 inhibitor is at least 100-fold selective against HDAC6 compared to all other isozymes of HDAC.

51. The method of any one of embodiments 1-50, wherein the administering is oral.

52. The method of any one of embodiments 1-51, wherein the subject is a human.

53. The method of any one of embodiments 1-52, wherein the subject has or is at risk for hypertension.

54. The method of any one of embodiments 1-53, wherein the subject has or is at risk for diabetes mellitus.

55. The method of any one of embodiments 1-54, wherein the subject has or is at risk for diabetic cardiomyopathy.

56. The method of any one of embodiments 1-55, wherein the subject has or is at risk for metabolic syndrome.

57. The method of any one of embodiments 1-56, wherein the subject has or is at risk for hyperglyceridemia or dyslipidemia.

58. The method of any one of embodiments 1-57, wherein the subject is at least 65 years old human.

59. The method of embodiments 58 wherein the subject is at least 70 years old human.

60. The method of any one of embodiments 1-59, wherein the method treats or prevents at least one symptom of metabolic disease.

61. The method of any one of embodiments 1-60, wherein the method improves glucose tolerance.

62. The method of any one of embodiments 1-61, wherein the method improves insulin resistance.

63. The method of any one of embodiments 1-62, wherein the method reduces glucose level.

64. The method of any one of embodiments 1-63, wherein the method inhibits inflammatory genes in adipose tissue.

65. The method of any one of embodiments 1-64, wherein the method prevents heart failure in the subject.

66. An HDAC6 inhibitor for use in a method for treating metabolic disease.

67. The HDAC6 inhibitor of embodiment 66, wherein the HDAC6 inhibitor is any one described in embodiments 8-50.

68. A pharmaceutical composition for use in a method for treating metabolic disease, comprising an HDAC6 inhibitor.

69. The pharmaceutical composition of embodiment 68, wherein the HDAC6 inhibitor is any one described in embodiments 8-50.

70. A kit, comprising an HDAC6 inhibitor and instructions for use in a method for treating metabolic disease.

71. The kit of embodiment 70, wherein the HDAC6 inhibitor is any one described in embodiments 8-50.

72. Use of an HDAC6 inhibitor in treating metabolic disease.

73. The use of embodiment 72, wherein the HDAC6 inhibitor is any one described in embodiments 8-50.

NUMBERED EMBODIMENTS OF THE INVENTION (II)

1. A method of treating or preventing heart failure with preserved ejection fraction (HFpEF) in a subject in need thereof, comprising administering to the subject a HDAC6 inhibitor.

2. A method of treating or preventing diastolic disfunction (e.g., associated with HFpEF) in a subject in need thereof, comprising administering to the subject a HDAC6 inhibitor.

3. A method of treating or preventing cardiac fibrosis (e.g., associated with HFpEF) in a subject in need thereof, comprising administering to the subject a HDAC6 inhibitor.

4. The method of any one of embodiments 1-3, wherein the administering is oral.

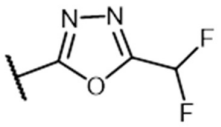
5. The method of any one of embodiments 1-4, wherein the subject is a human.

6. The method of embodiment 5, wherein the subject is at least 65 years old.

7. The method of embodiment 5, wherein the subject is at least 70 years old.

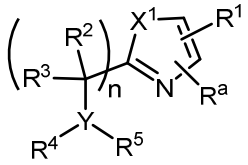
8. The method of embodiments 1-7, wherein the HDAC6 inhibitor is fluoroalkyl-oxadiazole derivative.

9. The method of embodiment 8, wherein the HDAC6 inhibitor is fluoroalkyl-oxadiazole derivative according to the following Formula:



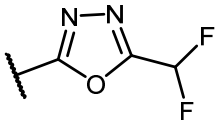
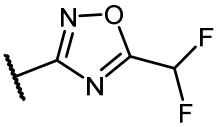
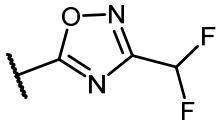
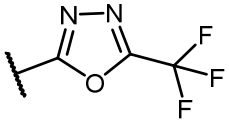
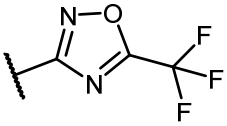
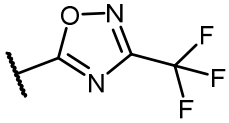
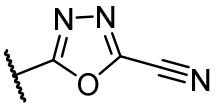
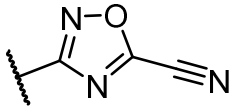
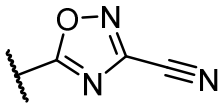
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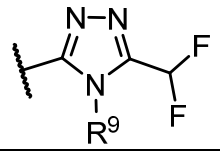
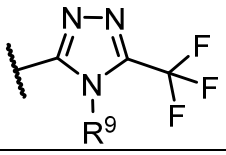
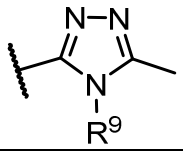
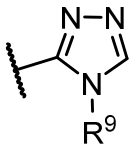
10. The method of embodiments 1-9, wherein the HDAC6 inhibitor is a compound according to Formula (I):



(I), or pharmaceutically acceptable salt thereof, wherein

R^1 is selected from the group consisting of:

		
 and ;		

R^a is selected from the group consisting of H, halo, C_{1-3} alkyl, cycloalkyl, haloalkyl, and alkoxy;

R^2 and R^3 are independently selected from the group consisting of H, halogen, alkoxy, haloalkyl, aryl, heteroaryl, alkyl, and cycloalkyl each of which is optionally substituted, or R^2 and R^3 together with the atom to which they are attached form a cycloalkyl or heterocyclyl;

R^4 and R^5 are independently selected from the group consisting of H, $–(SO_2)R^2$, $–(SO_2)NR^2R^3$, $–(CO)R^2$, $–(CONR^2R^3)$, aryl, arylheteroaryl, alkylenearyl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, haloalkyl, and alkoxy, each of which is optionally substituted, or R^4 and R^5 together with the atom to which they are attached form a cycloalkyl or heterocyclyl, each of which is optionally substituted;

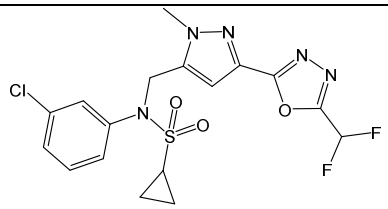
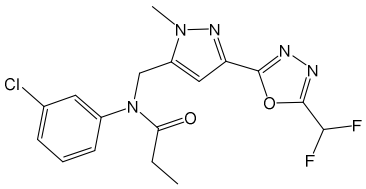
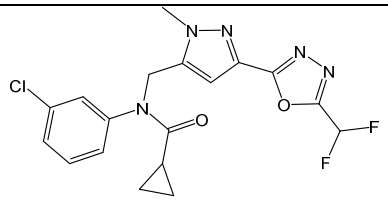
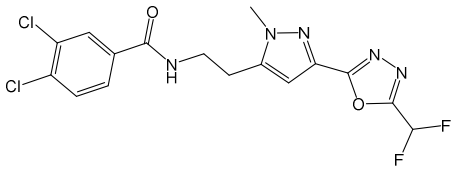
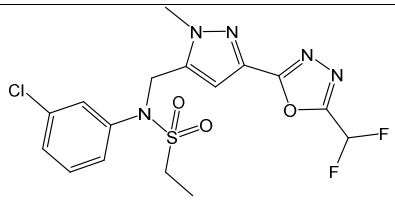
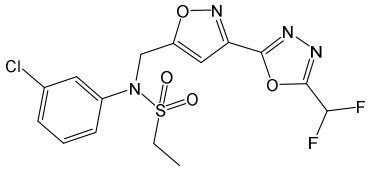
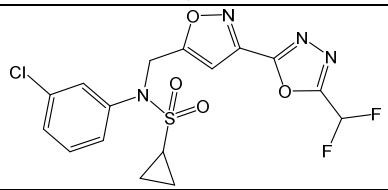
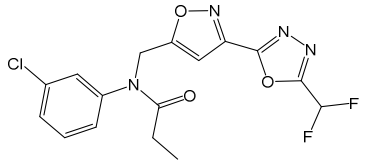
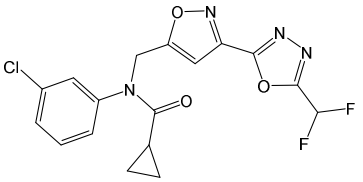
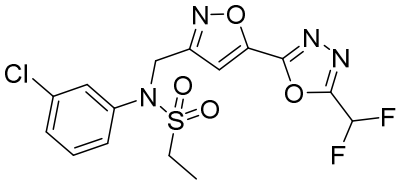
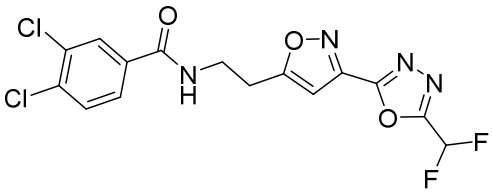
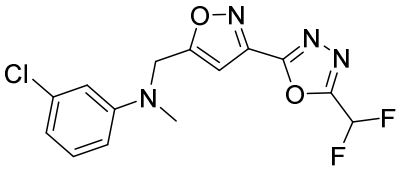
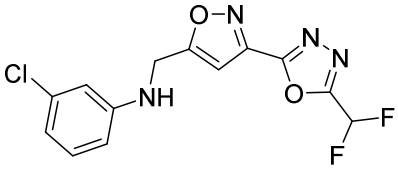
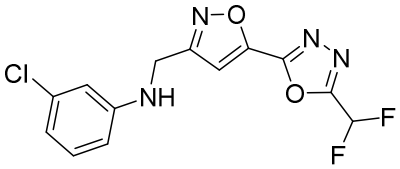
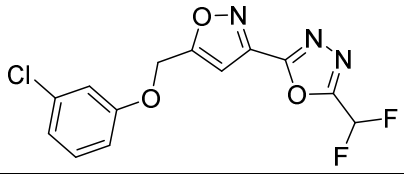
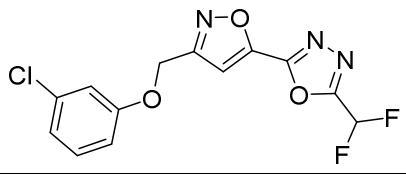
R^9 is selected from the group consisting of H, C_1-C_6 alkyl, haloalkyl, cycloalkyl and heterocyclyl;

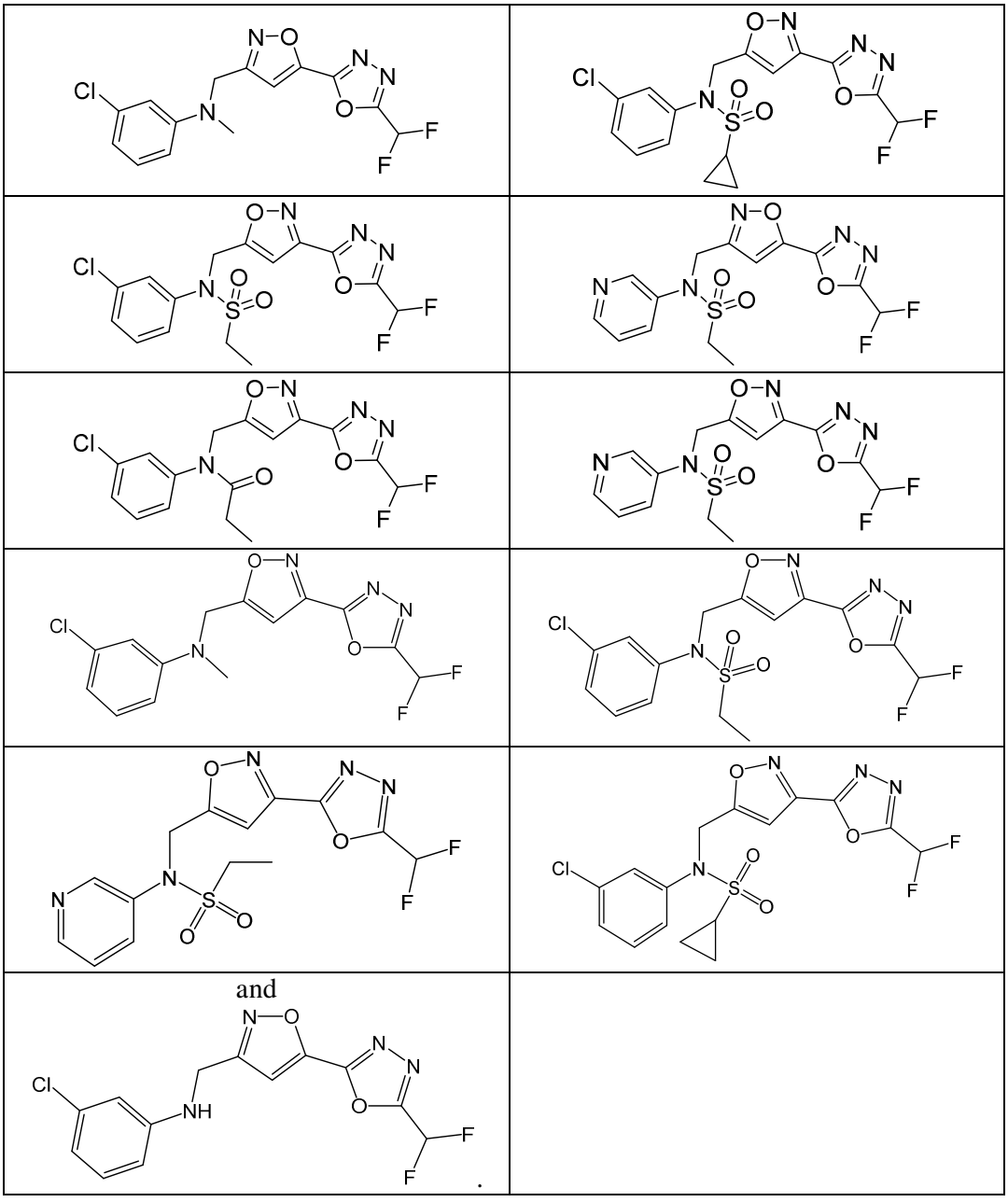
X^1 is selected from the group consisting of S, O, NH and NR^6, wherein R^6 is selected from the group consisting of C_1-C_6 alkyl, alkoxy, haloalkyl, cycloalkyl and heterocyclyl;

Y is selected from the group consisting of CR^2, O, N, S, SO, and SO_2, wherein when Y is O, S, SO, or SO_2, R^5 is not present and when R^4 and R^5 together with the atom to which they are attached form a cycloalkyl or heterocyclyl, Y is CR^2 or N; and

n is selected from 0, 1, and 2.

11. The method of embodiment 10, wherein the HDAC6 inhibitor is selected from the group consisting of:

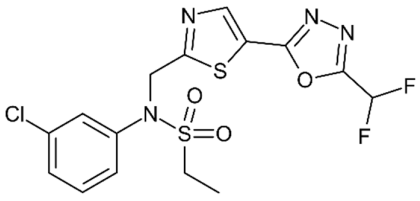
	
	
	
	
	
	
	
	



and

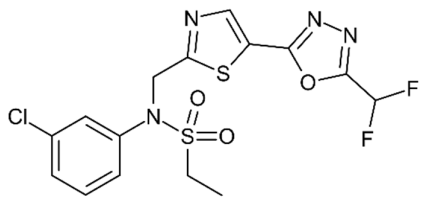
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12. The method of embodiment 10, wherein the HDAC6 inhibitor is



or an analog thereof.

13. The method of embodiment 10, wherein the HDAC6 inhibitor is

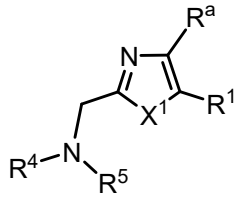


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14.The method of embodiment 10, wherein the HDAC6 inhibitor is selected from any HDAC6 inhibitor in Table 13 (in Example 7).

15. The method of embodiment 14, wherein the HDAC6 inhibitor is any HDAC6 inhibitor in Table 13 which has an IC_{50} equal to or less than 0.03 μM.

16. The method of embodiment 10, wherein the HDAC6 inhibitor is a compound having the formula:



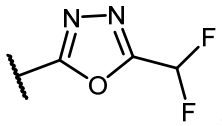
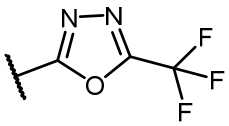
I(y)

or a pharmaceutically acceptable salt thereof,

wherein:

X^1 is S;

R^a is selected from the group consisting of H, halogen, and C_{1-3} alkyl;

R^1 is  or ;

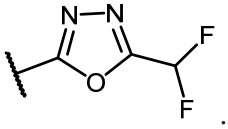
R^2 is selected from the group consisting of alkyl, alkoxy, and cycloalkyl, each of which is optionally substituted;

R^3 is H or alkyl;

R^4 is selected from the group consisting of alkyl, $–(SO_2)R^2$, $–(SO_2)NR^2R^3$, and $–(CO)R^2$; and

R^5 is aryl or heteroaryl; or R^4 and R^5 together with the atom to which they are attached form a heterocyclyl, each of which is optionally substituted.

17. The method of embodiment 16, wherein R^a is H.

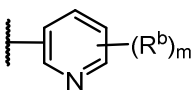
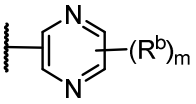
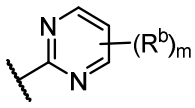
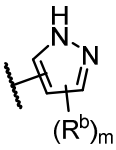
18. The method of embodiment 16 or 17, wherein R^1 is .

19. The method of any one of embodiments 16-18, wherein R^4 is $–(SO_2)R^2$.

20. The method of embodiment 19, wherein $–(SO_2)R^2$ is $–(SO_2)$alkyl, $–(SO_2)$alkyleneheterocyclyl, $–(SO_2)$haloalkyl, $–(SO_2)$haloalkoxy, or $–(SO_2)$cycloalkyl.

21. The method of any one of embodiments 16-20, wherein R^5 is heteroaryl.

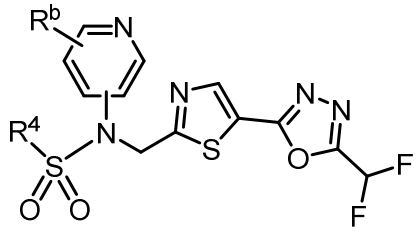
22. The method of embodiment 21, wherein the heteroaryl is a 5- to 6-membered heteroaryl

23. The method of embodiment 22, wherein the 5- to 6-membered heteroaryl is selected from the group consisting of , , , and , wherein R^b is halogen, alkyl, alkoxy, cycloalkyl, -CN, haloalkyl, or haloalkoxy; and m is 0 or 1.

24. The method of embodiment 23, wherein R^b is F, Cl, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CHF_2$, $-CF_2CH_3$, -CN, $-OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_2H$, and cyclopropyl.

25. The method of any one of embodiments 16-24, wherein the aryl is selected from the group consisting of phenyl, 3-chlorophenyl, 3-chloro-4-fluorophenyl, 3-trifluoromethylphenyl, 3,4-difluorophenyl, and 2,6-difluorophenyl.

26. The method of embodiment 10, wherein the HDAC6 inhibitor is a compound having Formula (Ik):


(Ik),

or a pharmaceutically acceptable salt thereof,

wherein:

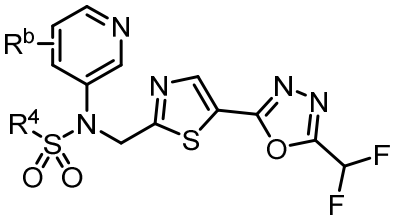
R^b is H, halogen, alkyl, cycloalkyl, -CN, haloalkyl, or haloalkoxy; and

R^4 is alkyl, alkoxy, haloalkyl, or cycloalkyl, each of which is optionally substituted.

27. The method of embodiment 26, wherein R^b is H, halogen, haloalkyl, or haloalkoxy.

28. The method of embodiment 26 or 27, wherein R^4 is optionally substituted alkyl or cycloalkyl.

29. The method of embodiment 26, wherein the HDAC6 inhibitor is a compound having the structure:


(Ik-1), or a pharmaceutically acceptable salt thereof,

wherein:

R^b is H, halogen, alkyl, cycloalkyl, -CN, haloalkyl, or haloalkoxy; and

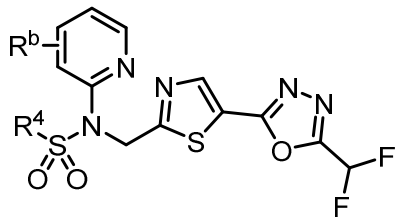
R^4 is alkyl, alkoxy, haloalkyl, or cycloalkyl, each of which is optionally substituted.

30. The method of embodiment 29, wherein R^b is H, halogen, haloalkyl, or haloalkoxy.

31. The method of embodiment 29 or 30, wherein R^4 is optionally substituted alkyl or cycloalkyl.

32. The method of embodiment 29, wherein R^4 is alkyl.

33. The method of embodiment 26, wherein the HDAC6 inhibitor is a compound having the structure:


(Ik-2), or a pharmaceutically acceptable salt thereof,

wherein:

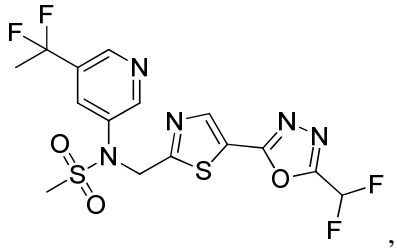
R^b is H, halogen, alkyl, cycloalkyl, -CN, haloalkyl, or haloalkoxy; and

R^4 is alkyl, alkoxy, haloalkyl, or cycloalkyl, each of which is optionally substituted.

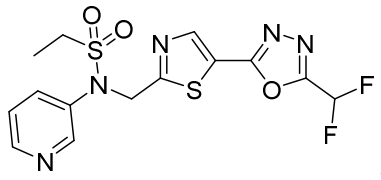
34. The method of embodiment 33, wherein R^b is H, halogen, haloalkyl, or haloalkoxy.

35. The method of embodiment 33 or 34, wherein R^4 is optionally substituted alkyl.

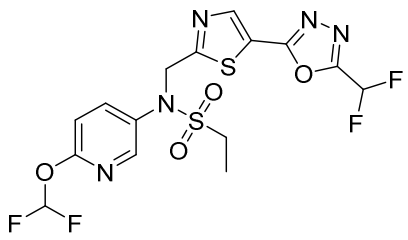
36. The method of embodiment 16, wherein the HDAC6 inhibitor is a compound of Formula:


, or a pharmaceutically acceptable salt thereof.

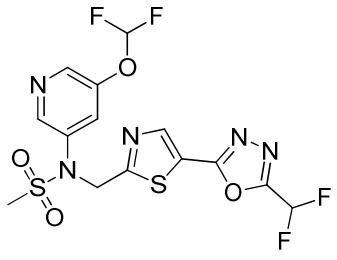
37. The method of embodiment 16, wherein the HDAC6 inhibitor is a compound of Formula:


, or a pharmaceutically acceptable salt thereof.

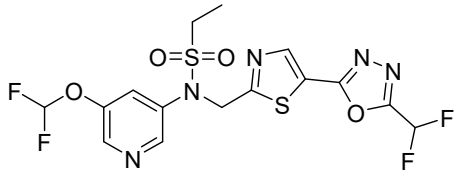
38. The method of embodiment 16, wherein the HDAC6 inhibitor is a compound of Formula:


, or a pharmaceutically acceptable salt thereof.

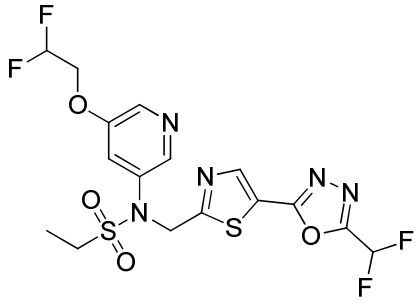
39. The method of embodiment 16, wherein the HDAC6 inhibitor is a compound of Formula:


, or a pharmaceutically acceptable salt thereof.

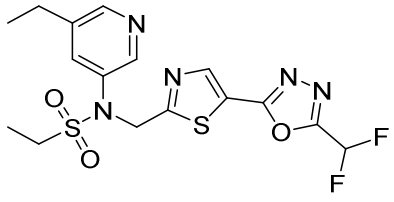
40. The method of embodiment 16, wherein the HDAC6 inhibitor is a compound of Formula:


, or a pharmaceutically acceptable salt thereof.

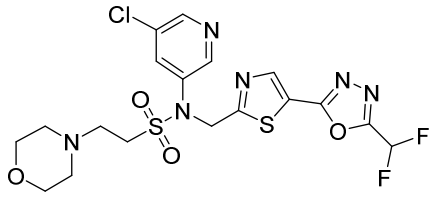
41. The method of embodiment 16, wherein the HDAC6 inhibitor is a compound of Formula:


, or a pharmaceutically acceptable salt thereof.

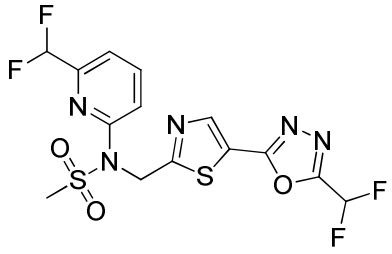
42. The method of embodiment 16, wherein the HDAC6 inhibitor is a compound of Formula:


, or a pharmaceutically acceptable salt thereof.

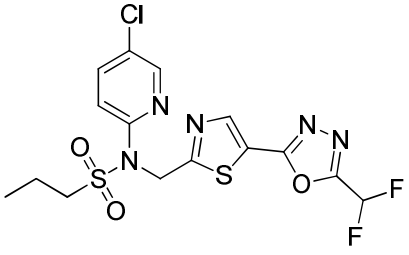
43. The method of embodiment 16, wherein the HDAC6 inhibitor is a compound of Formula:


, or a pharmaceutically acceptable salt thereof.

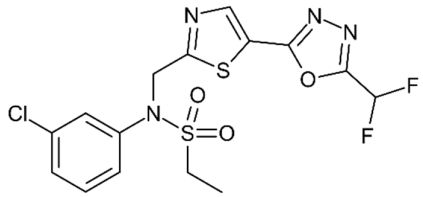
44. The method of embodiment 16, wherein the HDAC6 inhibitor is a compound of Formula:


, or a pharmaceutically acceptable salt thereof.

45. The method of embodiment 16, wherein the HDAC6 inhibitor is a compound of Formula:

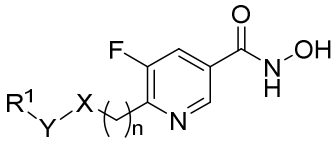

or a pharmaceutically acceptable salt thereof.

46. The method of embodiment 16, wherein the HDAC6 inhibitor is a compound of Formula:



or a pharmaceutically acceptable salt thereof.

47. The method of any one of embodiments 1-7, wherein the HDAC6 inhibitor is a compound of Formula (II):


(II); wherein

n is 0 or 1;

X is O, NR^4, or $CR^4R^{4'}$;

Y is a bond, CR^2R^3 or $S(O)_2$;

R^1 is selected from the group consisting of H, amido, carbocyclyl, heterocyclyl, aryl, and heteroaryl;

R^2 and R^3 are independently selected from the group consisting of H, halogen, alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, –(CH_2)–carbocyclyl, –(CH_2)–heterocyclyl, –(CH_2)–aryl, and –(CH_2)–heteroaryl; or

R^1 and R^2 taken together with the carbon atom to which they are attached form a carbocyclyl or heterocyclyl; or

R^2 and R^3 taken together with the carbon atom to which they are attached form a carbocyclyl or heterocyclyl; and

R^4 and $R^{4'}$ are each independently selected from the group consisting of H, alkyl, –CO_2–alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, –(CH_2)–carbocyclyl, –(CH_2)–heterocyclyl, –(CH_2)–aryl, and –(CH_2)–heteroaryl; or

R^4 and $R^{4'}$ taken together with the carbon atom to which they are attached form a carbocyclyl or heterocyclyl;

wherein each alkyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently optionally substituted with one or more substituents selected from the group consisting of halogen, haloalkyl, oxo, hydroxy, alkoxy, –OCH_3, –CO_2CH_3, –C(O)NH(OH),–CH_3, morpholine, and –C(O)N-cyclopropyl.

48. The method of any one of embodiments 1-7, wherein the HDAC6 inhibitor is CAY10603, tubacin, rocilinostat (ACY-1215), citarinostat (ACY-241), ACY-738, QTX-125, CKD-506, nexturastat A, tubastatin A, or HPOB.

49. The method of any one of the preceding embodiments, wherein the compound is the compound and not the pharmaceutically acceptable salt thereof.

50. The method of any one of embodiments 1-49, wherein the HDAC6 inhibitor is at least 100-fold selective against HDAC6 compared to all other isozymes of HDAC.

51. The method of any one of embodiments 1-50, wherein the subject has or is at risk for hypertension.

52. The method of any one of embodiments 1-51, wherein the subject has or is at risk for diabetes mellitus.

53. The method of any one of embodiments 1-52, wherein the subject has or is at risk for coronary artery disease (CAD).

54. The method of any one of embodiments 1-53, wherein the subject has or is at risk for valvular heart disease.

55. The method of any one of embodiments 1-54, wherein the subject has or is at risk for atrial fibrillation.

56. The method of any one of embodiments 1-55, wherein the method treats or prevents at least one symptom of HFpEF.

57. The method of any one of embodiments 1-56, wherein the method reduces left ventricular (LV) mass.

58. The method of any one of embodiments 1-57, wherein the method reduces LV wall thickness.

59. The method of any one of embodiments 1-58, wherein the method improves LV relaxation.

60. The method of any one of embodiments 1-59, wherein the method improves LV filling pressure.

61. The method of any one of embodiments 1-60, wherein the method prevents heart failure in the subject.

62. An HDAC6 inhibitor for use in a method for treating heart failure with preserved ejection fraction.

63 The HDAC6 inhibitor of embodiment 62, wherein the HDAC6 inhibitor is any one described in embodiments 8-50.

64. A pharmaceutical composition for use in a method for treating heart failure with preserved ejection fraction, comprising an HDAC6 inhibitor.

65. The pharmaceutical composition of embodiment 64, wherein the HDAC6 inhibitor is any one described in embodiments 8-50.

66. A kit, comprising an HDAC6 inhibitor and instructions for use in a method for treating heart failure with preserved ejection fraction.

67. The kit of embodiment 66, wherein the HDAC6 inhibitor is any one described in embodiments 8-50.

68. Use of an HDAC6 inhibitor in treating heart failure with preserved ejection fraction.

69. The use of embodiment 68, wherein the HDAC6 inhibitor is any one described in embodiments 8-50.

EXAMPLES

[0342] The invention is further illustrated by the following examples. The examples below are non-limiting are merely representative of various aspects of the invention.

Example 1: HDAC6 Selective Inhibitors Improve Glucose Tolerance and Insulin Resistance in a Diet-Induced Obesity Mouse Model

[0343] This example demonstrates that histone deacetylase 6 (HDAC6) selective inhibitors improve glucose tolerance and insulin resistance in a diet induced obese mouse model. The diet-induced obesity model closely mimics high-fat/high-density foods that contribute to obesity in humans. (Reviewed in Wang et al. *Methods Mol Biol.* 821:421–433 (2012).)

[0344] FIGs. 1A-1L show that HDAC6 inhibition with TYA-11631 improves glucose tolerance and insulin resistance in a diet induced obese mouse model. TYA-11631 is a compound within Formula (I), as well as within, for example, Formula (Ic), Formula (Ik) and Formula I(y).

[0345] 16-weeks old male Diet-Induced Obese (DIO) C57BL/6J (Cat. 380050) mice and age/gender matched controls (Cat. 000664) were purchased from the Jackson Laboratory®. DIO mice (n=40) were fed a rodent diet with 60 kcal% fat (D12492) and control mice were fed a rodent diet with 10 kcal% fat (D12450B) starting from 6-weeks of age.

[0346] Intraperitoneal glucose-tolerance tests (GTT) were performed by injection of glucose (2 g/kg in saline) after 6 hours fasting. Tail blood glucose levels (mg/dl) were measured with a glucometer before (0 min) and at 15, 30, 45, 60 and 120 min after glucose administration. DIO mice at 16 weeks of age developed severe glucose intolerance compared to controls. (**FIG. 1A**, **FIG. 1B).**

[0347] Based on glucose AUC level, DIO mice were evenly randomized into four treatment groups to receive Vehicle (n=9) or TYA-11631 at three dosages 3, 10, 30mg/kg (n=10 each). Control mice were also divided to dose orally with vehicle (n=10) or 30 mg/kg TYA-11631 (n=10). To assess the acute response of TYA-11631 on glucose metabolism, GTT was performed at 6h after 1st dose. Strikingly, single dose of TYA-11631 at all three test dosages significantly reduced glucose level. (**FIG. 1C**, **FIG. 1D).** TYA-11631 treatment for 2 weeks

led to pronounced improvements in glucose tolerance in dose-dependent manner. (**FIG. 1E**, **FIG. 1F**).

[0348] To evaluate the effects of TYA-11631 on insulin resistance, intraperitoneal insulin-tolerance test (ITT) was performed by injection of insulin (1U/kg) after 6 hours fasting. Tail blood glucose levels (mg/dl) were measured with a glucometer before (0 min) and at 15, 30, 45, 60 and 120 min after insulin administration. HDAC6 inhibitor (TYA-11631) treatment for 4 weeks improved insulin resistance in DIO mice. 10 and 30mg/kg were significantly reduced glucose AUC (ITT) with comparable activities, 3 mg/kg showed a trend of reduction. (**FIG. 1G**, **FIG. 1H**)

[0349] Effects of TYA-11631 on blood glucose were also assessed in non-fasting mice. Tail blood samples were collected in the morning and measured with a glucometer. TYA-11631 treatment for 6wks led to a dose-dependent reduction of non-fasting glucose, consistent with the data of glucose tolerant test after fasting. (**FIG. 1I**)

[0350] Treatment with TYA-11631 caused a dose dependent reduction of body weight in DIO mice. (See **FIG. 1J**, **FIG. 1K**, **FIG. 1L**) No differences of food consumption were observed between groups. Notably, control mice dosed with TYA-11631 30mg/kg for 6wks did not show changes on blood glucose levels and body weights. Bars and error bars show means and SEM. *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001.

[0351] FIGs. 2A-C show HDAC 6 inhibition with TYA-11631 inhibits inflammatory genes in adipose tissue in a diet induced obese mouse model.

[0352] White adipose tissue (epididymal) was dissected from DIO mice after 6 hours of single dose 30mg/kg TYA-11631. Realtime q-PCR data showed that TYA-11631 remarkably inhibited upregulation of pro-inflammatory genes- *IL-6* (**FIG. 2A**), *IL-10* (**FIG. 2B**) and *TGFb1* (**FIG. 2C**) in white adipose tissue. Inhibition or ablation of these genes have been shown to protect mice from diet-induced obesity with improvement of glucose tolerance and insulin sensitivity (*Han et al., PNAS 2020*; *Rajbhandari et al., Cell 2018*).

[0353] Taken together, these data show that histone deacetylase 6 (HDAC6) selective inhibitors improve glucose tolerance and insulin resistance in a diet induced obese mouse model, and suggest a potential molecular mechanism underlying the effect on systemic glucose metabolism.

Example 2: HDAC6 Inhibitors Improve Glucose Metabolism and Symptoms of Metabolic Disease in a Diabetes Mouse Model

[0354] This example demonstrates that histone deacetylase 6 (HDAC6) selective inhibitors improve glucose metabolism and symptoms of metabolic disease in a mouse model of diabetes (independent of high fat diet).

Materials and Methods

[0355] An HDAC6 inhibitor, TYA-11018, was used in this example. TYA-11018 is a compound within Formula (I), as well as within, for example, Formula (Ic) and Formula I(y). Vehicle contained 5% DMSO + 45% PEG-300 in purified water.

Test System:

[0356] 8-week old male *db*/*db* (Cat. 000697, homozygous $Lepr^{db}$) mice and age/gender matched wild type controls (Cat. 000664) were purchased from the Jackson Laboratory (Bar Harbor, ME). Animals were fed with normal chow (LabDiet 5053, 10 kcal% fat diet, St Louis, MO), and housed in an animal research facility in accordance with the National Research Council of the National Academies guidelines for the care and use of laboratory animals. All mice were used for experiments after 1 week of acclimation period.

Baseline Glucose and Animal Randomization:

[0357] Blood samples in the fed state (before administration of TYA-11018 or vehicle alone) were taken from the tail vein for determination of baseline glucose. Based on both body weights and blood glucose levels, *db/db* mice were randomized to three groups to orally receive vehicle or TYA-11018 at two dosages – 1.5 or 15 mg/kg. Wild type mice were dosed orally with vehicle for control.

Single Oral Administration and Blood Glucose Test:

[0358] After single administration of TYA-11018 or vehicle via a stomach tube at a volume of 10 ml/kg, animals were transferred to clean cage and wire top with water bottles for fasting. Blood samples in the fasting state were taken from the tail vein at 0.5, 1, 2, 4 and 6 h after the single dose of TYA-11018 or vehicle for determination of glucose. Blood glucose levels (mg/dL) were measured by AimStrip Plus blood glucose strips used with the AimStrip Plus blood glucose monitoring system (Germaine Laboratories, San Antonio, TX).

Results

Animal Enrollment and Randomization:

[0359] The animals were randomized and enrolled for the single administration study based on body weights and baseline glucose. Body weight and tail blood glucose levels (mg/dL) were measured at fed state, just before TYA-11018 or vehicle administration. *db/db* mice at 9 weeks of age developed severe obesity with hyperglycemia compared to controls. Animals were randomized and evenly distributed into three groups to receive vehicle (n=8) or TYA-11018 of two dosages 1.5 (n=8) and 15 mg/kg (n=9). Controls (age and sex matched wild type mice) were dosed orally with vehicle (n=8) (Table).

Table 3: Animal randomization and group information

Group	Test Article	Dose/QD	Number
Control	Vehicle	n/a	8
db/db diabetic Model	Vehicle	n/a	8
	TYA-11018	1.5mg/kg	8
	TYA-11018	15mg/kg	9

Single Administration of TYA-11018 Dose-dependently Reduced Fasting Glucose in db/db diabetic Mice:

[0360] To assess the acute response of TYA-11018 on glucose metabolism, blood glucose was measured at 0.5, 1, 2, 4 and 6 h after the single dose. As shown in **Fig. 3A-3C**, treatment with TYA-11018 showed a dose-dependent effect on reducing fasting glucose. Four hours after dosing/fasting, both 1.5 and 15mg/kg significantly decreased blood glucose compared to vehicle treated *db/db* diabetic mice. Of note, single administration of 15 mg/kg TYA-11018 normalized fasting glucose in 4 hours. These data support the utility of HDAC6 selective inhibitors in improving glucose metabolism and symptoms of metabolic disease.

Example 3: HDAC6 Selective Inhibitors Improve Cardiac Structure and Heart Function in a HFpEF Mouse Model

[0361] This example demonstrates that histone deacetylase 6 (HDAC6) selective inhibitors improve cardiac structure and heart function in a mouse model of heart failure with preserved ejection fraction (HFpEF).

[0362] First, an animal model of HFpEF was established: Surgically applying moderate trans-aortic constriction (mTAC) in wild type C57BL6 mice fed on high fat diet (HFD) was found

to induce a cardio-metabolic heart failure phenotype that recapitulates systemic and cardiovascular features of HFpEF in human (**FIGs. 4A-4H**).

[0363] HFpEF model animals were dosed orally with 30 mg/kg HDAC6 inhibitor (TYA-11631) or vehicle once per day for six weeks. HDAC6 inhibitor effectively treated HFpEF. The HDAC6 inhibitor treatment regimen significantly reduced left ventricular (LV) mass (**FIG. 5E**) and LV wall thickness (**FIG. 5F**) measured by echocardiograph; and HDAC6 inhibitor treatment improved glucose tolerance (**FIG. 5A**). In addition, TYA-11631 treatment sustained improved LV relaxation and LV filling pressures as shown by decreased prolongation of isovolumetric relaxation time (**FIG. 5H**); lower E/A (**FIG. 5I**) and E/e' ratios (**FIG. 5L**); improved e' velocity (**FIG. 5K**); and reduced end diastolic pressure (**FIG. 5M**). Each of these efficacy parameters were normalized to control levels.

[0364] Furthermore, HFD/mTAC mice treated with TYA-11631 showed a trending decrease in lung weight (**FIG. 5O**), indicating improved pulmonary congestion, consistent with reduced filling pressure. No treatment related adverse events or toxicities were observed in the animals in the study.

[0365] At molecular level, the HDAC6 inhibitor significantly inhibited upregulation of genes commonly associated with fibrosis (*Postn, Col1a1, Col3a1, Col5a2*), cardiac stress (*Nppb*), and inflammation (*Tnfα*) in heart tissue of HFD/mTAC mice (**FIGs. 6A-6H**).

[0366] The results demonstrate that selectively inhibiting HDAC6 reverses a number of adverse pathophysiological processes in HFpEF.

Example 4: HDAC6 Selective Inhibitors Improve Cardiac Structure and Heart Function in a Second HFpEF Mouse Model

[0367] This example demonstrates that histone deacetylase 6 (HDAC6) selective inhibitors improve cardiac structure and heart function in a second mouse model of heart failure with preserved ejection fraction (HFpEF), which recapitulates the vast majority of the clinical features of the syndrome: high-fat diet (HFD) coupled with inhibition of constitutive nitric oxide synthases (NOS) with N[w]-nitro-l-arginine methyl ester (L-NAME). (Schiattarella et al. *Nature* 568(7752): 351–356 (2019)).

[0368] First, the mouse model was validated. HFD/L-NAME treatment significantly induced body weight increase (**FIG. 7B**), hypertension (**FIG. 7C**) and glucose intolerance (**FIG. 7D**) compared to the control mice. Echocardiographic evaluation revealed persistent preservation

of the left ventricular ejection fraction (LVEF) (**FIG. 7E**). Significant concentric left ventricular (LV) hypertrophy was present in HFD/L-NAME mice, as indicated by increases in LV mass (**FIG. 7F**) and LV wall thickness at diastole (**FIG. 7G**), without LV chamber dilatation (**FIG. 7H**). In addition, mice concomitantly exposed to HFD/L-NAME exhibited signs of LV diastolic dysfunction with impaired relaxation and increased left ventricular filling pressure, as evidenced by prolonged IVRT (**FIG. 7I**), decreased e' velocity (**FIG. 7J**), and increased ratios of E/e'(**FIG. 7K**), E/A (**FIG. 7L**), measured by noninvasive Doppler imaging.

[0369] Second, treatment with an HDAC6 inhibitor, TYA-11631, was shown to improve glucose tolerance and diastolic dysfunction in the HFD/L-NAME model.

[0370] Animals were randomized to dose orally with 30 mg/kg TYA-11631 (n=8) or vehicle (n=12) once per day for nine weeks, respectively. In control groups, 6 mice were received vehicle and 8 mice were dosed with 30 mg/kg TYA-11631. As shown in **FIG. 8A** and **FIG. 8B**, Glucose tolerance test (GTT) was performed after 5 weeks of dosing.

[0371] Treatment with TYA-11631 markedly improved glucose tolerance in HFD/L-NAME mice, but no changes in control animals. (**FIG. 8B**) Plasma insulin level during GTT at the indicated time points (0 and 30 minutes after glucose injection) was measured by a sensitive mouse insulin detection kit (Cat. 80-INSMS-E01, ALPCO). TYA-11631 treatment led to decreased insulin secretion, suggesting that the improved glucose tolerance might be due to improved insulin action/sensitivity. (**FIG. 8C**) Treatment with TYA-11631 caused a significant reduction of body wight, but no difference of food consumption in mice fed with HFD/L-NAME. (**FIG. 8D, FIG. 8E**) TYA-11631 did not affect systolic blood pressure in HFD/L-NAME mice measured by non-invasive tail cuff method. (**FIG. 5F**) Echocardiography showed that TYA-11631 treatment preserved ejection fraction (**FIG. 8G**), however significantly reduced left ventricular mass (**FIG. 8H**) and LV wall thickness (**FIG. 8I**).

[0372] Noninvasive Doppler imaging and terminal invasive catheterization analysis revealed that treatment with TYA-11631 for 9wks decreased prolongation of isovolumetric relaxation time (**FIG. 8J**), E/A (**FIG. 8K**) and E/e' ratios (**FIG. 8L**), increased e' velocity (**FIG. 8M**), and reduced end diastolic pressure (**FIG. 8N**), indicating the improved LV relaxation and filling pressure. In addition, HFD/L-NAME mice treated with TYA-11631 showed a trending decrease in lung weight (**FIG. 8O**), suggesting an improved pulmonary congestion, consistent with the reduction of filling pressure.

[0373] Notably, no adverse effects related to TYA-11631 have been observed. Control animals dosed with TYA-11631 has no changes on each of LV structural and functional parameters, as well as ECG signals- QT, QRS, PR intervals and R amplitude (**FIG. 8P**, **FIG. 8Q**, **FIG. 8R** and **FIG. 8S**), further supports an overall favorable safety profile of the compound.

Example 5: HDAC6 Inhibitors Reduce Cardiac Fibrosis and Enhance Mitochondrial Function in a Mouse Model of HFpEF

[0374] This example demonstrates that histone deacetylase 6 (HDAC6) selective inhibitors reduce cardiac fibrosis and enhance mitochondrial function in a mouse model of HFpEF. In particular, this example demonstrates that HDAC6 selective inhibitors (i) correct dysregulated fibrosis and oxidative phosphorylation gene expression in HFpEF model, (ii) increase mitochondrial membrane potential and spare respiratory capacity in human iPSC-CMs, and (iii) prevent fibroblast activation from TGF-beta in primary human cardiac fibroblasts.

[0375] As described below, transcriptional analysis was performed on cardiac tissue from mice with HFpEF using RNA sequencing and qPCR. RNA-Seq data presented here show reduced expression of gene sets associated with hypertrophy, fibrosis, and PDGFR signaling in HFpEF mice treated with TYA-11631. qPCR data further confirmed reduced expression of fibrotic genes which correlated with improved diastolic function. Additionally, RNA-Seq data presented here show that gene sets associated with mitochondrial energy production were enriched in TYA-11631 treated HFpEF mice. The increased expression of mitochondrial genes correlated with improved diastolic function. TYA-11631 was further tested to determine whether it has a direct effect on metabolism in an in-vitro model using human induced pluripotent stem cell–derived cardiomyocytes. The data presented here show enhanced reserve respiratory capacity, indicating improved ATP production in response to stress in TYA-11631 treated human iPSC-derived CMs.

Materials and Methods

[0376] HFpEF was induced surgically by moderate transaortic constriction in high fat diet-fed mice for 12 weeks (mTAC/HFD). After HFpEF phenotypes were established, mice received TYA-11631 (30 mg/kg) or vehicle orally once daily for 6 weeks. TYA-11631 treated mice showed improved cardiac function as measured by reduced left ventricular posterior wall thickness (LVPWd), isovolumic relaxation time (IVRT) and mitral valve E/e' (MV E/e'). TYA-11631 is a compound within Formula (I), as well as within, for example, Formula (Ic), Formula (Ik) and Formula I(y).

Test System

[0377] Twelve-week-old male C57Bl/6NJ mice were purchased from Jackson Laboratories. Mice were maintained under specific pathogen-free conditions and provided with sterile food and water *ad libitum*. Animals were housed in an animal research facility in accordance with the National Research Council of the National Academies guidelines for the care and use of laboratory animals. Animals were allowed to acclimate for 3 days prior to experiment.

[0378] Induced pluripotent stem cell derived cardiomyocytes (iPSC-derived cardiomyocyte): iCell Cardiomyocyte^2 were purchased from Cellular Dynamics (Madison, WI). Cells were cultured in a low-glucose and lipid rich medium to enhance cellular maturation for one week prior to treatment.

RNA Extraction and mRNA Sequencing (RNA-Seq) Method and Analysis

[0379] RNA was extracted from mouse heart tissues (control mice, vehicle-treated n=3, HFpEF mice, vehicle-treated, n=5, and HFpEF mice, TYA-11631-treated, n=6) using the polyA-tail-specific protocol from Illumina (San Diego, CA, Cat. #20020594). RNA library preparation and ribosomal RNA removal was performed on 100 ng RNA using the TruSeq Stranded mRNA kit (Illumina, San Diego, CA, Cat. #20020594) following the manufacturer's instructions. Libraries were sequenced as 100 bp single end reads using Illumina NovaSeq SP with an average of 45.7 million reads per sample. Raw RNA-seq reads in FASTQ format were aligned directly to GENCODE (version M25) for reference transcript assembly (GRCm38.p6 and ensemble 101). Next, a script using *tximport* was used to generate an expression matrix normalized to transcripts per million (TPM). In this analysis, only genes detected in at least 90% of all samples were used. Protein-coding genes were determined using Ensembl release *mus musculus* annotations (GRCm38, Apr 2020) and extracted by *biomaRt* (version 2.46.3). Non-protein-coding and mitochondrial genes were omitted, followed by renormalization to TPM. The generated expression matrix (16,499 genes) was $\log_2$-transformed after adding 1 as the pseudo-count.

[0380] To evaluate functional perturbations, pre-ranked Gene Set Enrichment Analysis was performed using GSEA developed by Broad institute (version 4.1.0). GSEA assesses whether differences in expression of gene sets between two phenotypes are statistically significant (Subramanian, 2005). Prior to analysis, a ranked list was calculated with each gene assigned a score and direction ("+" or "−") based on the *t*-statistics values. Gene sets were only considered statistically significant if the false discovery rate (FDR) was less than 0.25 as determined by

the multiple hypothesis testing correction method (Benjamini, 1995). The normalized enrichment score (NES), which reflects the degree to which a gene set is over-represented in the ranked list and normalized for gene set size, was used to select significantly altered gene sets. The Pearson correlation coefficient was used to calculate correlation between genes of interest and cardiac diastolic function parameters.

RNA Extraction and TaqMan qPCR Analysis Method

[0381] Fifteen to thirty milligrams (15-30 mg) of mouse cardiac tissue (control mice, vehicle-treated n=3, HFpEF mice, vehicle-treated, n=5, and HFpEF mice, TYA-11631-treated, n=6) was placed directly into 500 µL of Tri-Reagent (Zymo research, Irvine, CA, Cat. #R2050-1-200) and snap frozen at -80°C. Samples were thawed and homogenized by Bullet Blender Tissue Homogenizer (Storm Pro BT24M, Next Advance, Troy) for 15 minutes at 4°C. RNA was extracted using the Direct-Zol RNA Miniprep Plus Kit (Zymo research, Irvine, CA, Cat. #R2070) according to manufacturer instruction. Upon collecting RNA, the concentration was determined by NanoDrop (ThermoScientific, Waltham, MA,). cDNA was reverse transcribed from 750 ng of RNA through random hexamers using the SuperScriptIII kit (Invitrogen, Waltham, MA, Cat. #18080051). cDNA samples were diluted 6-fold in nuclease free water. Real-Time qPCR reactions were performed using the Standard TaqMan Universal PCR Master Mix (Applied Biosystems, Waltham, MA, Cat. #43-181-57) with the listed TaqMan probes (Life Technologies, San Diego, CA) in Table 4.

Table 4: TaqMan Probes Used in qPCR Analysis

Gene Probe	Gene ID	Exon Boundary	Amplicon Length (bp)
Col1a1	Mm00801666_g1	49-50	89
Col3a1	Mm01254476_m1	50-51	136
Postn	Mm00450111_m1	3-4	79
Gapdh	Mm99999915_g1	2-3	107

[0382] Real-Time qPCR reactions were performed using the QuantStudio7 Flex Real-Time PCR Systems (Life Technologies, San Diego, CA) with thermal cycling parameters of a 2-minute UNG incubation at 50°C, a 10-minute polymerase activation at 95°C, and 40 PCR cycles consisting of a denaturation for 15 seconds at 95°C and a 1 minute anneal/extension at 60°C. Gene expression was normalized to *Gapdh* as a housekeeping gene. Four technical

replicates were analysed for each sample. Relative gene expression was determined using the $2^{-\Delta\Delta C_T}$ method. Statistical analysis was performed in Prism Version 9 (GraphPad Software, San Diego, CA) using an unpaired *t*-test.

Metabolic Measurements Using Seahorse Oximetry

[0383] The Seahorse Xfe96 Analyzer (Agilent, Santa Clara, CA), which measures oxygen consumption rate (OCR) of live cells in a multi-well plate, was used to assess metabolic activity of human induced pluripotent stem cell-derived cardiomyocytes (iPSC-derived CMs). Seahorse XF96 V3 PS Cell Culture Microplates (Cat. #101085-004) were coated with 100 µL of Matrigel (Corning, Corning, NY, Cat. #356231) in phenol-free DMEM medium at a dilution of 1/100 overnight. The following day, the Matrigel was removed and 25 µL of Plating Medium (Cellular Dynamics, Madison, WI, Cat. #R1151) was added to each well of the Seahorse XF96 V3 PS Cell Culture Microplates. One vial of iCell Cardiomyocytes^2 (~6 million cells, Cellular Dynamics, Madison, WI, Cat. #01434) was thawed in a 37°C water bath for 2 minutes. Cells were seeded directly onto the Seahorse XF96 V3 PS Cell Culture Microplates for a final density of 15,000 cells per well in Plating Medium. The corner wells were excluded for background recordings. Cells were allowed to rest at room temperature for 10 minutes to allow for even distribution of seeding, then placed in a 37°C incubator. Five hours following cell seeding, the medium was changed to Maintenance Medium (Cellular Dynamics, Madison, WI, Cat. #R1151) for 3 days for recovery. Once beating monolayers were observed, the medium was changed to fatty acid enriched Maturation Medium (Feyen, 2020) for one week to increase metabolic maturity of iPSC-derived CMs. Cells were replenished with fresh medium every 3 days. The day of the assay, cells were incubated in starvation medium containing 2 mM glutamine in DMEM (Agilent, Santa Clara, CA, Cat. #103575-100) for one hour. Cells were then treated with DMSO (0.1%) or TYA-11631 (3 µM) in Mercola Medium for 6 hours. Cells were washed and incubated for 1 hour prior to the assay with Seahorse XF DMEM Basal Medium supplemented with 2 mM glutamine, 2 mM pyruvate, and 3 mM glucose. The Seahorse Xfe96 cartridge was prepared according to manufacturer's guidelines. Oxygen consumption rates (OCR) were measured followed by the Mito Stress Test (Agilent, Santa Clara, CA, Cat. #103015-100) with inhibitors injected in the following order: oligomycin (2.5 µM), FCCP (1 µM), rotenone and antimycin A (0.5 µM). OCR was normalized to total nuclear count as measured by Hoechst staining. Basal respiration was calculated as: (last rate measurement before first oligomycin injection) – (minimum rate measurement after

rotenone/antimycin). Reserve respiratory capacity (RRC) was calculated as: (Maximal Respiration after the addition of FFCP) – (Basal Respiration). Statistical analysis was performed in Prism Version 9 (GraphPad Software, San Diego, CA) using an unpaired *t*-test.

Results

Transcriptional Analysis of TYA-11631 Effects on HFpEF Mouse Model by RNA-Seq

[0384] Comprehensive transcriptional profiling of protein coding genes in heart tissue from control mice and HFpEF mice (mTAC/HFD) was performed using RNA sequencing. To evaluate functional perturbations, unbiased gene set enrichment analysis was performed on two comparisons: 1) vehicle-treated HFpEF mouse tissue relative to vehicle-treated control mouse tissue, 2) TYA-11631-treated versus vehicle-treated HFpEF mouse tissue.

[0385] Gene sets associated with muscle hypertrophy and contraction, fibrosis (transforming growth factor β receptor signaling, type I collagen synthesis, extracellular matrix structural constituent), and platelet-derived growth factor receptor (PDGFR) signaling were enriched in vehicle-treated HFpEF animals relative to control and were reversed in HFpEF mice treated with TYA-11631 (**FIG. 9** and **FIG. 10)**. Gene sets associated with mitochondrial function including electron transport chain, oxidative phosphorylation, and complex I were significantly depleted in HFpEF mice treated with vehicle relative to control (**FIG. 9 and FIG. 10**). These mitochondrial gene sets were significantly enriched in HFpEF mice treated with TYA-11631 (**FIG. 9, FIG. 10 and Table 5**).

Table 5:GSEA Categories Altered (FDR<0.25) in HFpEF Mice Treated with Vehicle or TYA-11631

Gene set name	Gene set size	Healthy vs HFpEF (+ vehicle)		HFpEF (+ vehicle vs +TYA-11631)	
		NES	FDR	NES	FDR
Muscle hypertrophy in response to stress	20	-1.25	0.34	1.98	0.09
Regulation of cardiac muscle contraction by calcium ion signaling	23	-1.43	0.21	1.98	0.17
TGFβ receptor signaling in skeletal dysplasias	56	-1.86	0.04	1.68	0.19
Type I collagen synthesis in the context of osteogenesis imperfecta	28	-1.76	0.05	1.64	0.23
Extracellular matrix structural constituent	38	-1.72	0.13	1.77	0.09

conferring tensile strength					
Platelet derived growth factor receptor signaling pathway	52	-1.52	0.15	1.86	0.22
Electron transport chain OXPHOS system in mitochondria	85	2.43	0.00	-1.79	0.13
Mitochondrial complex I assembly model OXPHOS (oxidative phosphorylation) system	46	1.94	0.021	-2.02	0.05

[0386] Pearson correlation coefficient analysis was performed between the expression of genes identified by GSEA analysis and different parameters of LV structure and cardiac diastolic function, including Left ventricular posterior wall thickness at end diastole (LVPWd), and isovolumic relaxation time (IVRT), or mitral valve E/e' (MV E/e'). The expression levels of several genes associated with fibrosis (*Col1a2, Col3a1, Fbn1, Postn, Cilp*) were significantly increased in vehicle-treated HFpEF animals with impaired diastolic function as shown by increased LVPWd and IVRT. TYA-11631 treatment resulted in reduced expression of fibrosis-associated genes in HFpEF mice with improved diastolic function (**FIGS. 12A-12J**, Table 6 and Table 7).

Table 6: Echocardiogram Data and the Expression Level of Fibrotic Genes

Groups		LV structure/Diastolic function parameters		Fibrotic genes				
				Gene symbol				
		LVPW (mm)	IVRT (ms)	*Col1a2*	*Col3a1*	*Fbn1*	*Postn*	*Cilp*
Healthy + vehicle	Replicate 1	0.61	13.64	3.98	5.40	2.71	5.44	1.76
	Replicate 2	0.70	14.72	4.20	6.07	2.37	5.58	1.54
	Replicate 3	0.76	14.04	3.98	4.95	2.49	5.82	1.79
HFpEF + vehicle	Replicate 1	0.87	17.53	4.29	6.60	2.95	5.82	2.29
	Replicate 2	0.92	15.06	4.00	5.51	2.65	5.77	1.58
	Replicate 3	0.89	15.40	4.54	6.04	2.98	6.68	2.61
	Replicate 4	0.79	17.29	4.51	6.39	3.12	6.21	2.39
	Replicate 5	0.78	13.57	4.30	5.80	2.67	6.22	2.48
HFpEF +TYA-11631	Replicate 1	0.70	13.33	4.29	5.54	2.39	6.23	2.09
	Replicate 2	0.66	12.92	4.11	5.17	2.77	4.69	1.46
	Replicate 3	0.63	12.78	3.74	4.50	1.86	5.58	1.43
	Replicate 3	0.66	12.86	4.08	5.23	2.41	6.00	1.57
	Replicate 5	0.63	14.93	3.91	5.20	2.26	5.72	1.26
	Replicate 6	0.63	12.64	4.10	5.36	2.53	4.95	1.26

Vehicle treated healthy animals were used as control.

Table 7: Pearson Correlation Coefficient (r Value) and Statistical Significance (p-Value) Between Echocardiogram Data and Genes Associated with Fibrosis

	LV structure/Diastolic function parameters	*Fibrotic genes*				
		Col1a2	*Col3a1*	*Fbn1*	*Postn*	*Cilp*
r value	LVPWd(mm)	0.55	0.61	0.60	0.56	0.65
	IVRT (ms)	0.53	0.79	0.62	0.43	0.54
p-value	LVPWd (mm)	0.04	0.02	0.02	0.04	0.01
	IVRT (ms)	0.05	0.00	0.02	0.12	0.05

[0387] The expression level of genes associated with different subunits of the mitochondrial respiratory electron transport chain, (NADH:Ubiquinone Oxidoreductase subunits; *Ndufa13, Ndufa13, Ndufa5, Ndufs7, Ndufa1, Ndufa8*) were significantly reduced in vehicle-treated HFpEF animals with impaired diastolic function as shown by increased LVPWd and MV E/e'. In response to TYA-11631 treatment, the expression level of mitochondrial genes increased in HFpEF mice and was positively correlated with improved diastolic function (**FIGS. 11A-11F**, Table 8 and Table 9).

Table 8: Echocardiogram Data and the Expression Level of Mitochondrial Genes

Groups		LV structure/Diastolic function parameters		*Mitochondrial related genes*				
				Gene symbol				
		LVPWd (mm)	MV E/E'	*Ndufa13*	*Ndufa5*	*Ndufs7*	*Ndufa1*	*Ndufa8*
Healthy + vehicle	Rep 1	0.61	24.29	8.44	11.36	10.43	10.30	9.90
	Rep 2	0.70	26.70	8.16	11.16	10.24	10.16	9.84
	Rep 3	0.76	19.74	8.65	11.46	10.49	10.56	10.02
HFpEF + vehicle	Rep 1	0.87	36.25	8.08	10.93	10.21	10.20	9.78
	Rep 2	0.92	36.51	8.21	11.07	10.27	9.95	9.85
	Rep 3	0.89	30.17	8.35	11.35	10.31	10.64	9.93
	Rep 4	0.79	25.34	8.55	11.64	10.56	10.62	10.05
	Rep 5	0.78	35.66	8.41	11.14	10.54	10.38	9.87
HFpEF +TYA-11631	Rep 1	0.70	21.77	8.89	11.66	10.70	10.97	10.01
	Rep 2	0.66	28.59	8.46	11.33	10.67	10.62	9.95
	Rep 3	0.63	26.70	9.01	11.68	10.99	10.80	10.26
	Rep 3	0.66	28.79	8.90	11.53	10.57	10.54	9.97
	Rep 5	0.63	21.91	8.79	11.60	10.81	10.92	10.06
	Rep 6	0.63	22.71	8.56	11.36	10.60	10.58	9.92

Healthy animals treated with vehicle were used as control.

Table 9: Pearson Correlation Coefficient (r) And Statistical Significance (p-Value) Between Echocardiogram Data and Genes Associated with Mitochondria

	LV structure/Diastolic function parameters	*Mitochondrial related genes*				
		Ndufa13	*Ndufa5*	*Ndufs7*	*Ndufa1*	*Ndufa8*
r value	LVPWd (mm)	-0.61	-0.55	-0.67	-0.47	-0.45
	MV E/E'	-0.59	-0.74	-0.48	-0.64	-0.54
p value	LVPWd (mm)	0.02	0.04	0.01	0.09	0.10
	MV E/E'	0.03	0.00	0.08	0.01	0.05

Effects of TYA-11631 on Fibrosis Genes in HFpEF Mouse Model by qPCR

[0388] Fibrotic markers periostin (encoded by the *Postn* gene), collagen 3A1 (encoded by the *Col3a1* gene), and collagen 1A1 (encoded by the *Col1a1* gene), showed a trend in increased expression in HFpEF mouse hearts as measured by qPCR. TYA-11631 treatment significantly reduced the expression of fibrotic genes to near healthy control levels (**Table**).

Table 10: mRNA Expression Levels Measured by qPCR

	RNA Relative Expression Level (Normalized to GAPDH)			
		Gene Symbol		
		Postn	***Col3a1***	***Col1a1***
Healthy +vehicle (control)	Rep 1	0.83	0.68	0.6
	Rep 2	1.15	1.61	1.55
	Rep 3	1.02	0.7	0.85
	Average	1.00	1.00	1.00
	SEM	0.09	0.31	0.28
HFpEF +vehicle	Rep 1	1.57	1.07	1.14
	Rep 2	1.81	1.46	1.58
	Rep 3	3.25	3.94	1.89
	Rep 4	2.47	1.95	1.87
	Rep 5	2.55	2.27	1.15
	Average	2.33	2.14	1.53
	SEM	0.30	0.49	0.16
HFpEF +TYA-11631	Rep 1	1.91	1.23	1.28
	Rep 2	1.02	0.91	1.26
	Rep 3	0.14	0.34	0.62
	Rep 4	1.17	1.16	1.32
	Rep 5	1.17	1.03	0.9
	Average	1.08	0.93	1.08
	SEM	0.28	0.16	0.14

	RNA Expression Level (Raw CT values)				
		Gene Symbol			
		Postn	***Col3a1***	***Col1a1***	***GAPDH***
Healthy +vehicle (control)	Rep 1	33.52	33.66	31.41	24.05
	Rep 2	31.43	30.79	28.42	22.43
	Rep 3	31.77	32.16	29.46	22.6
	Average	32.24	32.20	29.76	23.03
	SEM	0.65	0.83	0.88	0.51
HFpEF +vehicle	Rep 1	31.43	31.83	29.31	22.88
	Rep 2	31.05	31.22	28.67	22.71
	Rep 3	32.48	32.06	30.68	24.99
	Rep 4	30.5	30.69	28.32	22.61
	Rep 5	33.23	33.25	31.8	25.38
	Average	31.74	31.81	29.76	23.71
	SEM	0.49	0.43	0.65	0.61
HFpEF +TYA-11631	Rep 1	30.38	30.86	28.37	22.11
	Rep 2	31.17	31.19	28.29	22.01
	Rep 3	37.09	35.71	32.39	25.09
	Rep 4	31.51	31.38	28.76	22.54
	Rep 5	32.12	32.15	29.91	23.14
	Average	32.45	32.26	29.54	22.98
	SEM	1.19	0.89	0.77	0.56

Rep indicates replicate.

Effects of TYA-11631 on iPSC-CM Metabolic Status

[0389] The metabolic status was compared of human iPSC-derived CMs treated with TYA-11631 (3 μM) to vehicle-treated cells (DMSO). Measurements of basal respiration and reserve respiratory capacity were collected using Seahorse oximetry. While both groups had similar basal respiration rate, TYA-11631-treated human iPSC-derived CMs had higher membrane potential and reserve respiratory capacity, demonstrating greater ATP production, the cells' ability to respond to energetic stress, and a direct effect on cardiomyocytes (**FIGs. 11G** and **11H** and **Table 10**).

Table 11: Metabolic Parameters in Human iPSC-derived CMs.

Group		Basal Respiration	Reserve Respiratory Capacity
DMSO	Replicate 1	89.95	432.70
	Replicate 2	95.31	415.93
	Replicate 3	63.19	233.20
	Replicate 4	87.07	486.64
	Replicate 5	65.76	289.69
	Replicate 6	69.80	306.20
	Replicate 7	123.48	334.96
	Replicate 8	138.68	497.42
	Replicate 9	82.01	423.78
	Replicate 10	106.12	379.22

	Replicate 11	103.52	469.37
	Average	93.17	388.1
	SEM	7.159	26.21
TYA-11631	Replicate 1	118.83	552.00
	Replicate 2	78.80	544.68
	Replicate 3	99.26	519.90
	Replicate 4	79.73	443.36
	Replicate 5	105.14	507.14
	Replicate 6	134.13	628.19
	Average	102.6	532.5
	SEM	8.878	24.79

[0390] Accordingly, TYA-11631 treatment was shown to reduce pathogenic transcriptional signatures activated in a mouse model of HFpEF (gene sets include hypertrophy, fibrosis, and platelet-derived growth factor receptor signaling). Targeted gene expression analysis using qPCR confirmed reduced expression of fibrotic genes which correlated with improved diastolic function. Also, based on RNA-Seq data, TYA-11631 enriched gene sets associated with mitochondrial energy production in HFpEF mice. The increased expression of mitochondrial genes correlated with an improved HFpEF phenotype. In order to functionally assess the metabolic effects of TYA-11631 in vitro, iPSC-derived CMs were used. The data showed increased reserve respiratory capacity in TYA-11631 treated human iPSC-derived CMs, indicating improved ATP production in response to metabolic demand.

[0391] Taken together, these results show that HDAC6 selective inhibitors reverse preexisting diastolic dysfunction through multiple pathways in the heart associated with fibrosis and mitochondrial dysfunction, which both contribute to HFpEF pathogenesis. These results also confirm that HDAC6 selective inhibitors have a direct benefit on the heart in HFpEF models, and that the improvements seen are due to multi-modal mechanisms in the heart and are not only as a result of improvement in systemic metabolism and inflammation.

Example 6: Efficacy of HDAC6 Selective Inhibitor and Empagliflozin in a HFpEF Mouse Model

[0392] The study was designed to side-by-side compare efficacy between TYA-11018 (a selective HDAC6 inhibitor) and Empagliflozin (a selective SGLT2 inhibitor, MedChemExpress LLC), in a mouse model of heart failure with preserved ejection fraction (HFpEF) induced by a combination of high fat diet and inhibition of constitutive nitric oxide synthase using N^{ω}-nitrol-arginine methyl ester (L-NAME). After HFpEF phenotypes were established, mice received 15 mg/kg TYA-11018 or 10 mg/kg Empagliflozin, or vehicle orally

once daily for 9 weeks. Health monitoring was performed weekly with body weights recorded. Glucose tolerance test was performed after 1st dose. Cardiac function was recorded by echocardiography after treatment for 9 weeks. End diastolic pressure (EDP) was measured by PV-Loop at terminal at 9 weeks after dosing.

Test System

[0393] Animals: Cohort of mice with established HFpEF phenotypes and age/sex matched wild type controls were used for dosing study. HFpEF model preparation was accomplished as previously described (Schiattarella, G.G. et al., *Nature* 568, 351–356 (2019)). In brief, 10-week old male C57BL/6J (Cat. 000664) mice were purchased from the Jackson Laboratory (Bar Harbor, ME). After acclimation for 1 week, one group of mice was fed with high fat diet containing 0.07% L-NAME (LabDiet 5G5V, St Louis, MO) for 15 weeks. The control group of mice were fed with normal chow (LabDiet 5053, St Louis, MO). Echocardiography was performed to prove the HFpEF onset before the animals were enrolled in efficacy study. Animals were housed in an animal research facility in accordance with the National Research Council of the National Academies guidelines for the care and use of laboratory animals.

HFpEF model induction

[0394] Ten (10) week old male C57BL/6J (Cat. 000664) mice were purchased from the Jackson Laboratory (Bar Harbor, ME). After acclimation for 1 week, one group of mice was fed a high fat diet containing 0.07% N^{ω}-nitrol-arginine methyl ester (L-NAME) for 15 weeks (modified from the reference by Schiattarella, G.G. et al., *Nature* 568, 351–356 (2019)). A second group of mice was fed with standard chow for controls.

Conventional echocardiography and Doppler imaging

[0395] Transthoracic echocardiography was performed using a VisualSonics Vevo 2100 system equipped with MS400 transducer (Visual Sonics, Toronto, ON). LVEF and other indices of systolic function were obtained from short-axis M-mode scans at the midventricular level, as indicated by the presence of papillary muscles, in conscious, gently restrained mice. Apical four-chamber views were obtained in anaesthetized mice for diastolic function measurements using pulsed-wave and tissue Doppler imaging at the level of the mitral valve. Anesthesia was induced by 5% isoflurane and confirmed by lack of response to firm pressure on one of the hind paws. During echocardiogram acquisition—under body-temperature-controlled conditions—isoflurane was reduced to 1.0–1.5% and adjusted to maintain a heart rate in the range of 450–500 beats per minute. Parameters collected include: left ventricular

ejection fraction (LVEF), left ventricular mass (LV mass), left ventricular end-diastolic posterior wall (LVPWd), peak Doppler blood inflow velocity across the mitral valve during early diastole (E wave), peak Doppler blood inflow velocity across the mitral valve during late diastole (e'), isovolumic relaxation time (IVRT). At the end of the procedures all mice recovered from anesthesia without difficulties.

Intraperitoneal glucose-tolerance test (IP-GTT)

[0396] Intraperitoneal glucose-tolerance tests were performed by injection of glucose (2 g/kg in saline) after 6 hour fasting (from 7 a.m. to 1 p.m.). Tail blood glucose levels (mg/dL) were measured by AimStrip Plus blood glucose strips used with the AimStrip Plus blood glucose monitoring system (Germaine Laboratories, San Antonio, TX) at 0 (baseline, before glucose dose), 15, 30, 45, 60 and 120 minutes after glucose administration.

Animal enrollment and randomization in efficacy test

[0397] After the HFpEF phenotypes were established, with balanced parameters of echocardiography, animals on HFD/L-NAME or control diet were randomized to two groups to receive dosing orally with 30 mg/kg TYA-11631 or vehicle once per day for nine weeks, respectively. TYA-11631 was formulated in the vehicle 5% DMSO + 45% PEG-300 + 50% purified water. Body weights and food consumption were monitored daily during study.

Pressure–volume analysis

[0398] The trachea was exposed by a midline incision from the base of the throat to just above the clavicle. The mice were intubated with a piece of polyethylene-90 tube. After the tube was secured in place by using a 6-0 silk suture, 100% oxygen was gently blown across the opening. The mice receiving ventilation were placed on a warmed (37 °C) pad. The right carotid artery was then isolated. Care was taken to prevent damage to the vagal nerve. The mice were lightly anaesthetized with isoflurane maintaining their heart rates at 450–550 beats per minute. A 1.2F Pressure-Volume Catheter (FTE-1212B-4518, Transonic, Inc, Ithaca, NY) was inserted into the right carotid artery and then advanced into the left ventricle. The transducer was securely tied into place, after it was advanced to the ventricular chamber as evidenced by a change in pressure curves. The hemodynamic parameters were then recorded in close-chest mode.

Animal Randomization

[0399] Mice with established HFpEF phenotypes were randomized to dose orally with 15 mg/kg TYA-11018 or 10 mg/kg Empagliflozin or vehicle (n=12 each group) once per day for nine weeks. In control (non HFpEF) group, 9 mice received vehicle.

Table 12:Animal enrollment and randomization

Group	Diet	Test Article	Dose/QD	Number
Control	Chow	Vehicle	n/a	9
HFpEF	HFD/0.07% L-NAME	Vehicle	n/a	12
		TYA-11018	15 mg/kg	12
		Empagliflozin	10 mg/kg	12

Results

Single dose of TYA-11018 improves fasting glucose and glucose tolerance to similar levels as Empagliflozin

[0400] A glucose tolerance test (IP-GTT) was performed after 6 hours of the 1st dose. Animals were on fasting during the 6 hours. Single oral dose 15mg/kg TYA-11018 markedly reduced fasting glucose and improved glucose tolerance to similar levels as Empagliflozin in the established mouse HFpEF model (**Fig. 14A**).

TYA-11018 treatment for 9 weeks demonstrates comparable efficacy compared to Empagliflozin in HFpEF model

[0401] Echocardiography was used to measure LV structure and function after 9 weeks of treatment. M-Mode echocardiography showed that TYA-11018 treatment preserved ejection fraction and significantly reduced left ventricular mass, similar to that of Empagliflozin. Noninvasive Doppler imaging and terminal invasive catheterization analysis revealed that treatment with both compounds for 9 weeks decreased E/A, E/e' ratios, and reduced end diastolic pressure, indicating the improved LV relaxation and filling pressure. Of note, a superior reduction of E/e' was observed with TYA-11018 compared to Empagliflozin (**Figs. 14B-14F**).

TYA-11018 Inhibits Upregulation of Marker Genes of Cardia Stress and Fibrosis in Heart Tissue

[0402] Heart tissues were collected and processed for gene expression analyses after 9 weeks of treatment. Total RNA was extracted from mouse heart tissues using TRIzol reagent (Invitrogen, Waltham, MA). A total of 500 ng RNA was used for reverse transcription using SuperScript™ III First-Strand Synthesis System (Invitrogen, Waltham, MA). Real-time PCR was performed in duplicate using TaqMan Gene Expression Assay probes with specific primers

for *Nppb* and *Col3a1* gene sequences. The 2−ΔΔCt relative quantification method, using Gapdh for normalization, was used to estimate the amount of target mRNA in samples, and fold ratios were calculated relative to mRNA expressions levels from control samples.

[0403] TYA-11018 remarkably inhibited up-regulation of *Nppb* and *Col3a1*, the two marker genes commonly used to reveal cardiac stress and fibrosis in heart tissue respectively. The gene expression changes in heart tissue were consistent with the improvements of cardiac structure and function. Notably, this selective HDAC6 inhibitor demonstrated superior effects on the inhibition of these genes compared to Empagliflozin. The dramatic effect of the selective HDAC6 inhibitor on pro-fibrotic gene-*Col3a1* also suggest a potential mechanism underlying the effects of HDAC6 inhibition that distinct to SGLT2 inhibition.

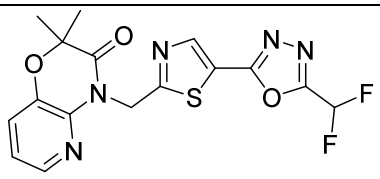
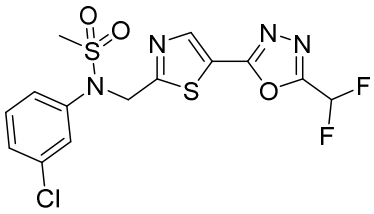
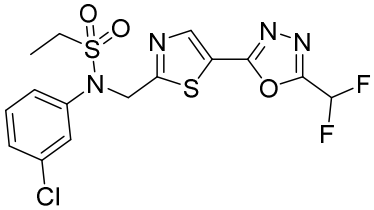
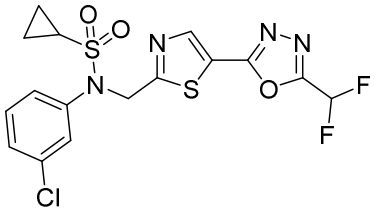
[0404] In summary, the comparable efficacy observed in HFpEF model with HDAC6 inhibition and an SGLT2 inhibitor provides evidence of translatability of these findings to clinical development.

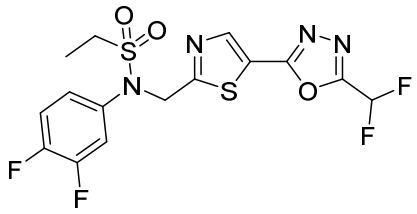
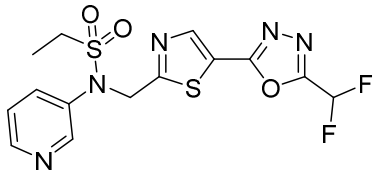
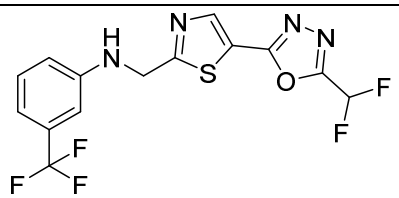
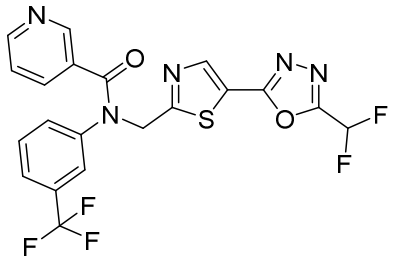
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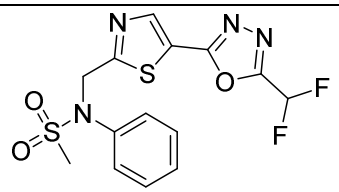
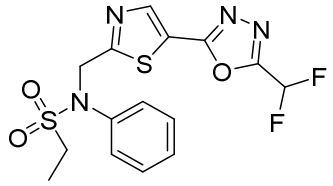
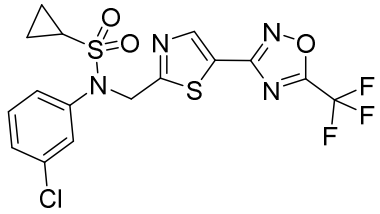
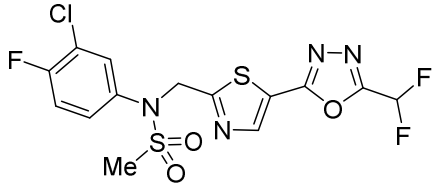
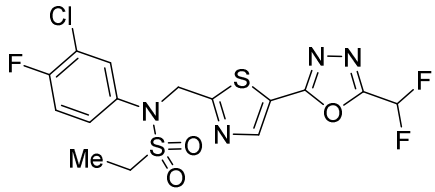
Biochemical Activity and Potency of various HDAC6 Inhibitors of Formula (I)

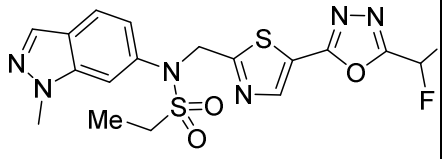
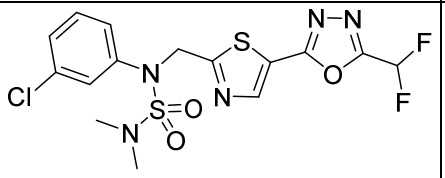
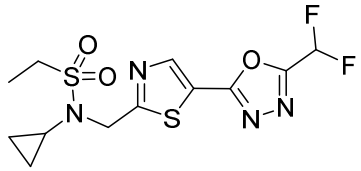
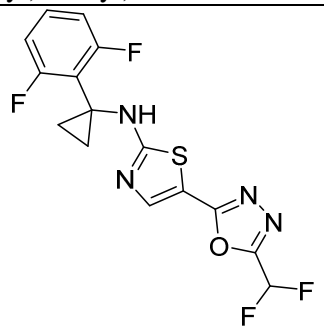
[0405] The compounds disclosed herein, in particular those of Formula (I), were synthesized according to methods disclosed in PCT/US2020/066439, published as WO2021127643A1, which is incorporated herein by reference in its entirety. These compounds were tested for potency against HDAC6 and selectivity against HDAC1 in a biochemical assay. A biochemical assay was adopted using a luminescent HDAC-Glo I/II assay (Promega) and measured the relative activity of HDAC6 and HDAC1 recombinant proteins. Compounds were first incubated in the presence of HDAC6 or HDAC1 separately, followed by addition of the luminescent substrate. The data was acquired using a plate reader and the biochemical IC_{50} were calculated from the data accordingly. Data is tabulated in Table 13. From these studies, it was determined that the compounds of the present disclosure are selective inhibitors of HDAC6 over HDAC1, providing selectivity ratios from about 5 to about 30,0000.

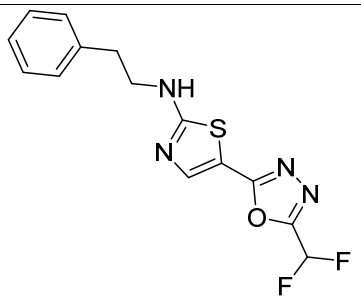
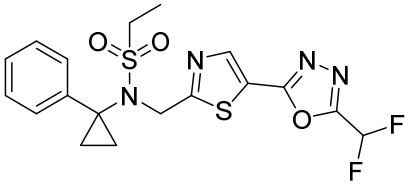
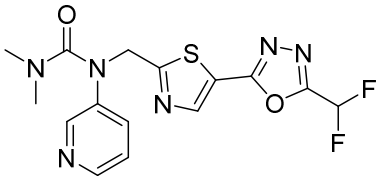
Table 13. Characterization Data and HDAC6 Activity for Compounds of Formula (I).

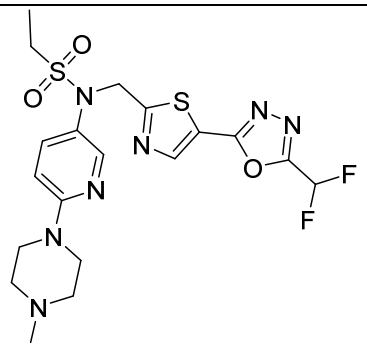
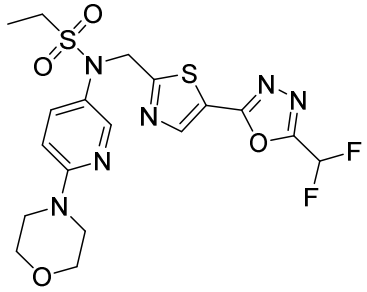
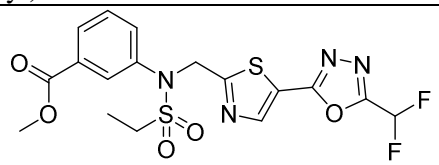
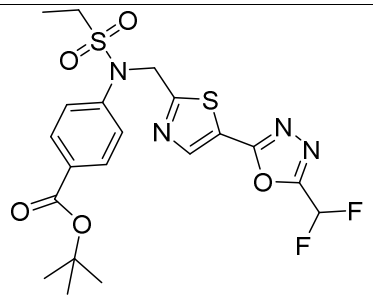
Cmpd	Structure/Name	^{1}H NMR MS (m/z) (RT)	HDAC6 IC_{50} (μM)
I-1	 4-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-2,2-dimethyl-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one	^{1}H NMR (400MHz, $CDCl_3$) δ 8.39 (s, 1 H), 8.01 – 8.05 (m, 1 H), 7.29 (dd, J = 8.1, 1.5 Hz, 1 H), 7.01 (dd, J = 8.1, 1.5 Hz, 1H), 6.89 (t, J = 51.6 Hz, 1 H), 5.70 (s, 2 H) LCMS: RT= 5.00 min, m/z= 394.0	0.107
I-2	 *N*-(3-chlorophenyl)-*N*-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)methanesulfonamide	^{1}H NMR (400MHz, $CDCl_3$) δ 8.39 (s, 1 H), 7.48 (s, 1 H), 7.32 - 7.40 (m, 3 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.25 (s, 2 H), 3.07 (s, 3 H) LCMS: RT= 4.83 min, m/z= 421.0	0.021
I-3	 *N*-(3-chlorophenyl)-*N*-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)ethanesulfonamide	^{1}H NMR (400MHz, $CDCl_3$) δ 8.37 (s, 1 H), 7.48 (s, 1 H), 7.25 - 7.40 (m, 3 H), 6.19 (t, J = 51.6 Hz, 1 H), 5.28 (s, 2 H), 3.18 (q, J = 7.6 Hz, 2 H), 1.44 (t, J = 7.2 Hz, 3 H) LCMS: RT= 4.90 min, m/z= 435.0	0.0044
I-4	 *N*-(3-chlorophenyl)-N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)cyclopropanesulfonamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1 H), 7.40 – 7.70 (m, 5 H), 5.43 (s, 2 H), 2.95 – 3.00 (m, 1 H), 1.00 – 1.05 (m, 2 H), 0.90 – 0.95 (m, 2 H) LCMS: RT= 5.10 min, m/z= 447.0	0.0042

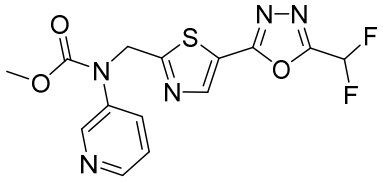
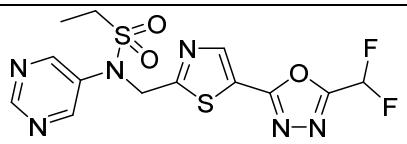
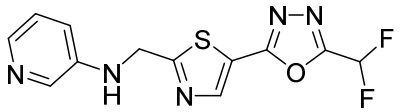
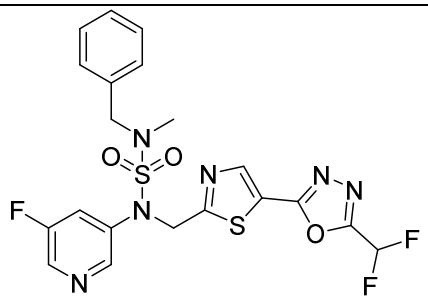
I-5	 *N*-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(3,4-difluorophenyl)ethanesulfonamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 1 H), 7.30 – 7.40 (m, 1 H), 7.15 – 7.25 (m, 2 H), 6.91 (t, J = 51.2 Hz, 1 H), 5.24 (s, 2 H), 3.17 (q, J = 7.6 Hz, 2 H), 1.44 (t, J = 5.7 Hz, 3 H) LCMS: RT= 4.92 min, m/z= 437.0	0.016
I-6	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(pyridin-3-yl)ethanesulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (br s, 1 H), 8.58 (br s, 1 H), 8.38 (s, 1 H), 7.80 – 7.85 (m, 1 H), 7.31 – 7.35 (m 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.30 (s, 2 H), 3.21 (q, J = 7.2 Hz, 2 H), 1.46 (t, J = 7.6 Hz, 1 H) LCMS: RT= 3.39 min, m/z= 402.0	0.029
I-7	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-3-(trifluoromethyl)aniline	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1 H) 7.52 (t, J = 51.2 Hz, 1 H) 7.22 – 7.35 (m, 2 H) 6.89 – 6.87 (m, 3 H) 4.80 (d, J = 6.1 Hz, 2 H) LCMS: RT 5.20 min, m/z= 377.0	0.222
I-8	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(3-(trifluoromethyl)phenyl)nicotinamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 – 8.60 (m, 1 H) 8.41 (s, 1 H) 7.71 (d, J = 7.8 Hz, 1 H), 7.50 (d, J = 7.8 Hz, 1 H), 7.35 – 7.45 (m, 2 H), 7.25 – 7.30 (m, 1 H) 7.20 – 7.25 (m, 1 H) 6.91 (t, J = 51.6 Hz, 1 H) 5.46 (s, 2 H) LCMS: RT= 4.22 min, m/z= 482.0	0.088

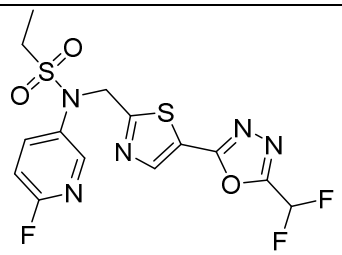
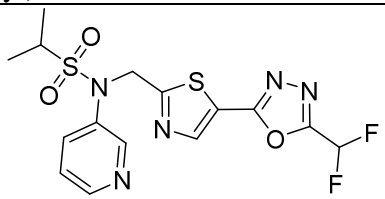
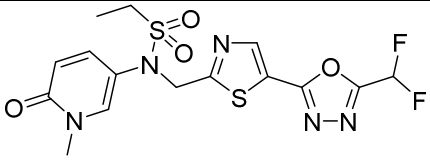
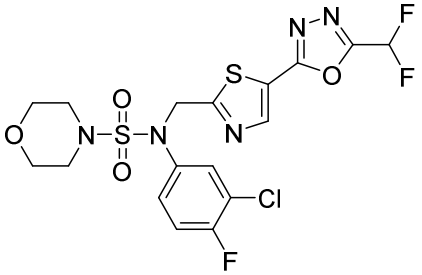
I-9	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-phenylmethanesulfonamide	^{1}H NMR (400MHz, $CDCl_3$) δ= 8.37 (s, 1 H), 7.33 - 7.49 (m, 5 H), 6.90 (t, 1 H, J= 51.6 Hz) 5.27 (s, 2 H), 3.05 (s, 3 H) ppm LCMS: RT= 4.42 min, m/z = 387.0	0.051
I-10	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-phenylethanesulfonamide	^{1}H NMR (400MHz, $CDCl_3$) δ 8.35 (s, 1 H), 7.29 - 7.53 (m, 5 H), 6.90 (t, 1 H, J= 51.5 Hz), 5.30 (s, 2 H), 3.17 (q, J=7.34 Hz, 2 H), 1.45 (t, J=7.46 Hz, 4 H) ppm LCMS: RT= 4.65 min, m/z= 401.0	0.026
I-12	 N-(3-chlorophenyl)-N-((5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)thiazol-2-yl)methyl)cyclopropanesulfonamide	^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 8.39 (s, 1 H) 7.51 (s, 1 H) 7.41 (br s, 1 H) 7.32 (br d, *J*=3.91 Hz, 2 H) 5.27 (s, 2 H) 2.48 - 2.59 (m, 1H) 1.10 - 1.17 (m, 2 H) 0.99 - 1.09 (m, 2 H) LCMS: RT= 5.84 min, m/z= 465	0.869
I-13	 N-(3-chloro-4-fluorophenyl)-N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)methanesulfonamide	^{1}H NMR (400MHz, $CDCl_3$) δ 8.40 (s, 1 H) 7.56 (dd, J=6.36, 2.69 Hz, 1 H) 7.32 - 7.41 (m, 1 H) 7.18 (t, J=8.56 Hz, 1 H) 6.76 - 7.08 (m, 1 H) 5.22 (s, 2 H) 3.07 (s, 3 H) LCMS: RT= 4.93 min, m/z= 438.9	0.021
I-14	 N-(3-chloro-4-fluorophenyl)-N-((5-(5-(difluoromethyl)-1,3,4-	^{1}H NMR (400MHz, $CDCl_3$) δ 8.38 (s, 1 H) 7.54 (dd, J=6.24, 2.32 Hz, 1 H) 7.33 - 7.40 (m, 1 H) 7.16 (t, J=8.68 Hz, 1 H) 6.76 - 7.06 (m, 1 H) 5.23 (s, 2 H) 3.18 (q, J=7.34 Hz, 2 H) 1.45 (t, J=7.34 Hz, 3 H) LCMS: RT= 5.11 min, m/z = 453	0.014

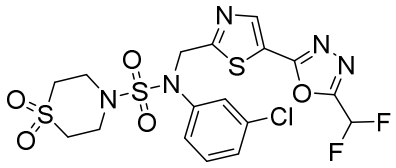
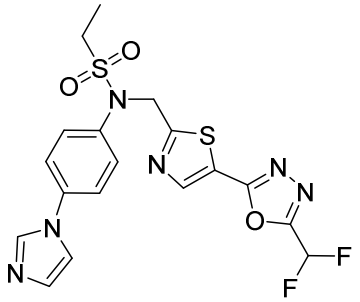
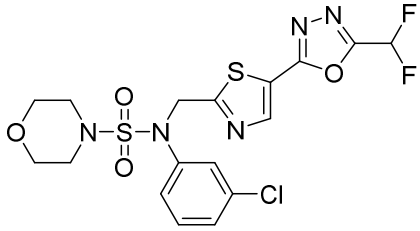
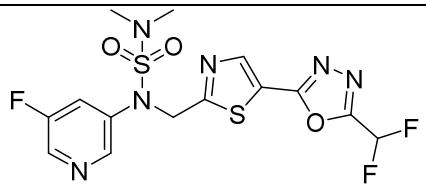
	oxadiazol-2-yl)thiazol-2-yl)methyl)ethanesulfonamide		
I-15	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(1-methyl-1H-indazol-6-yl)ethanesulfonamide	^{1}H NMR (400MHz, $CDCl_3$) δ 8.36 (s, 1 H) 7.98 (d, J=0.98 Hz, 1 H) 7.75 (d, J=8.56 Hz, 1 H) 7.60 (s, 1 H) 7.18 (d, J=8.31 Hz, 1H) 6.75 - 7.05 (m, 1 H) 5.39 (s, 2 H) 4.09 (s, 3 H) 3.19 (q, J=7.17 Hz, 2 H) 1.46 (t, J=7.46 Hz, 3 H) LCMS: RT= 4.43 min, m/z = 455.0.	0.014
I-16	 [(3-chlorophenyl)({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)sulfamoyl]dimethylamine	^{1}H NMR (400MHz, $CDCl_3$) δ 8.36 (s, 1 H) 7.49 (s, 1 H) 7.28-7.42 (m, 3 H) 6.76-6.06 (m, 1 H) 5.17 (s, 2 H) 2.82 (s, 6 H) LCMS: RT= 5.18 min, m/z= 450.0	0.012
I-17	 N-cyclopropyl-N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)ethanesulfonamide	^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 8.42 (s, 1 H) 6.74 - 7.07 (m, 1 H) 4.83 (s, 2 H) 3.21 (q, *J*=7.50 Hz, 2 H) 2.70 (br s, 1 H) 1.41 (t, *J*=7.46 Hz, 3 H) 0.83 - 0.95 (m, 4 H) LCMS: RT= 4.34 min, m/z= 365.0	1.23
I-18	 5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-N-(1-(2,6-	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.62 (br s, 1 H) 7.95 (br s, 1 H) 7.29 - 7.67 (overlapping m, 2 H) 7.02 - 7.18 (m, 2 H) 1.35 (d, *J*=26.80 Hz, 4 H) LCMS: RT= 4.87 min, m/z= 371.1	1.95

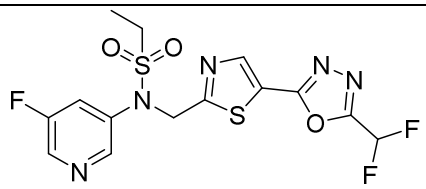
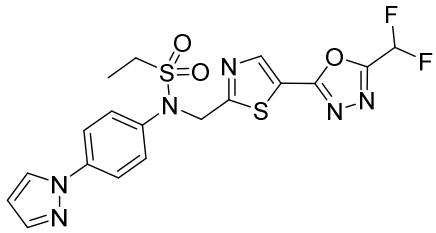
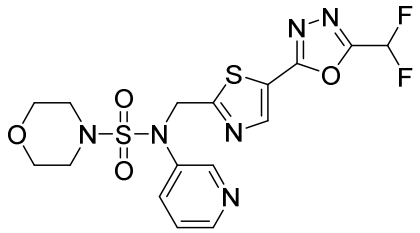
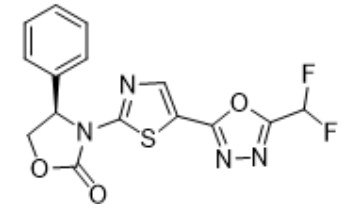
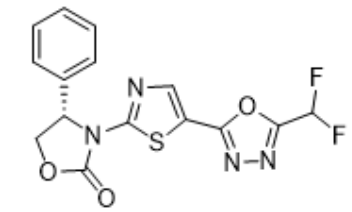
	difluorophenyl)cyclopropyl)thiazol-2-amine		
I-19	 5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-N-phenethylthiazol-2-amine	^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 7.86 (s, 1 H) 7.16 - 7.46 (m, 5 H) 6.68 - 7.03 (m, 1 H) 5.75 (br s, 1 H) 3.64 (br d, *J*=6.11 Hz, 2 H) 3.02 (br t, *J*=6.85 Hz, 2 H) LCMS: RT= 4.73 min, m/z= 323.0.	13.6
I-20	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(1-phenylcyclopropyl)ethanesulfonamide	^{1}H NMR (400MHz, $CDCl_3$-d_3) δ 8.78 (s, 1 H), 8.40 (s, 1 H), 7.50 (d, J=7.34 Hz, 2 H), 7.26-7.38 (m, 4 H), 7.04 (s, 0.25 H), 6.91 (s, 0.5 H), 6.78 (s, 0.25 H), 4.94 (s, 2 H), 2.81 (q, J=7.58 Hz, 2 H), 1.47 (m, 2 H), 1.31-1.22 (m, 5 H). LCMS: RT= 6.12, m/z = 441.1	4.14
I-21	 1-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-3,3-dimethyl-1-(pyridin-3-yl)urea	^{1}H NMR (400 MHz, METHANOL-*d*4) δ ppm 9.55 (s, 1 H) 8.78 (br d, *J*=5.62 Hz, 1 H) 8.52 - 8.59 (m, 2 H) 8.06 (br d, *J*=7.83 Hz, 1 H) 7.26 (t, *J*=51.2 Hz, 1 H) 6.33 (s, 2 H) 3.09 (s, 6 H). LCMS RT= 2.85 min, m/z = 381.1	1.2

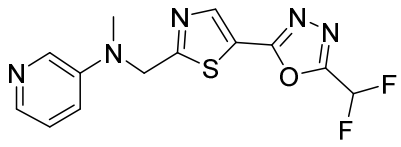
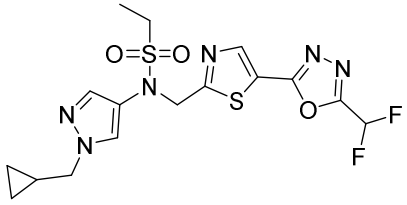
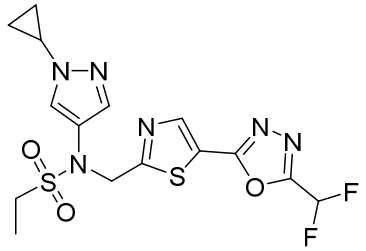
I-22	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)ethanesulfonamide	^{1}H NMR (400 MHz, CD3OD) δ 8.40 (s, 1 H), 8.15 (s, 1 H), 7.63 (m, 1 H), 7.21 (t, J = 51.2 Hz, 1H), 6.79 (m, 1 H), 5.24 (s, 2 H), 3.56 (m, 4 H), 3.25 (q, J = 7.2 Hz, 2 H), 2.51 (m, 4 H), 2.32 (s, 3 H), 1.40 (t, J = 7.2 Hz, 3 H). m/z = 500.1	0.143
I-23	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(6-morpholinopyridin-3-yl)ethanesulfonamide	^{1}H NMR (400 MHz, DMSO-*d*6) δ 8.51 (s, 1 H), 8.18 (s, 1 H), 7.69 (m, 1 H), 7.54 (t, J = 51.2 Hz, 1 H), 6.83 (m, 1 H), 5.28 (s, 1 H), 3.66 (m, 4 H), 3.44 (m, 4 H), 3.30 (q, J = 6.8 Hz, 2 H), 1.29 (t, J = 6.8 Hz, 3 H). m/z = 487.1	0.417
I-24	 methyl 3-(N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)ethylsulfonamido)benzoate	^{1}H NMR (400MHz, DMSO-d_6) δ 8.50 (s, 1 H), 8.08 (s, 1 H), 7.95-7.83 (m, 2 H), 7.67-7.39 (m, 2 H), 5.43 (s, 2 H), 3.86 (s, 3 H), 3.45-3.33 (m, 2), 1.28 (t, J=7.21 Hz, 3 H). LCMS RT = 4.73 min, m/z = 459.1	0.031
I-25	 tert-butyl 4-(N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1 H), 8.01 (m, 2 H), 7.53 (m, 2 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.34 (s, 2 H), 3.21 (q, J = 7.2 Hz, 2 H), 1,57 (s, 9 H), 1.43 (t, J = 7.2 Hz, 3 H). m/z = 501.1	0.101

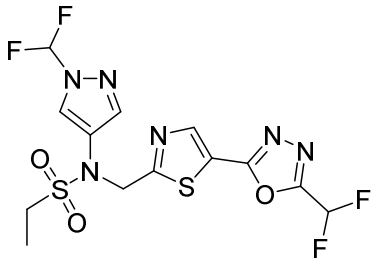
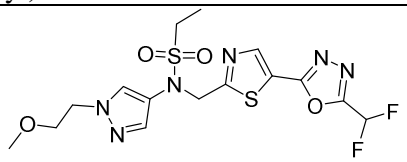
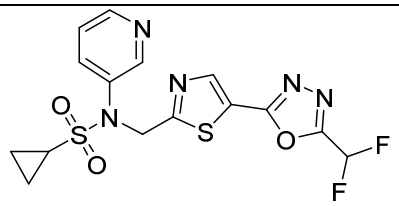
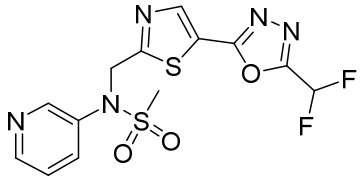
	2-yl)thiazol-2-yl)methyl)ethylsulfonamido)benzoate		
I-26	 methyl ((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)(pyridin-3-yl)carbamate	^{1}H NMR (400 MHz, METHANOL-*d*4) δ ppm 9.55 (s, 1 H) 8.85 (br d, *J*=5.87 Hz, 1 H) 8.57 (s, 1 H) 8.45 (br d, *J*=8.80 Hz, 1 H) 8.06 – 8.13 (m, 1 H) 7.26 (t, *J*=51.2 Hz, 1 H) 3.86 (s, 3 H). LCMS RT = 2.97 min, m/z = 368.0	2.5
I-27	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(pyrimidin-5-yl)ethanesulfonamide	^{1}H NMR (400MHz, DMSO-d_6) δ 9.12 (s, 1 H), 9.00 (s, 2 H), 8.53 (s, 1 H), 7.70-7.30 (m, 1 H), 5.50 (s, 2 H), 3.55-3.40 (m, 2 H), 1.31 (t, -7.34 Hz, 3 H). LCMS RT = 3.84 min, m/z = 403.0	0.050
I-28	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)pyridin-3-amine	^{1}H NMR (400 MHz, METHANOL-*d*4) δ ppm 8.58 (s, 1 H) 8.22 - 8.32 (m, 2 H) 7.69 - 7.78 (m, 2 H) 7.26 (t, *J*=51.2 Hz, 1 H) 6.17 (s, 2 H). LCMS RT = 1.24 min, m/z = 310.1	1.5
I-29		^{1}H NMR (400MHz, $CDCl_3$-d_3) δ 8.55 (s, 1 H), 8.47 (s, 1 H), 8.39 (s, 1 H), 7.67 (d, J=9.05 Hz, 1 H), 7.36-7.28 (m, 2 H), 7.19 (d, J=6.60 Hz, 2 H), 7.04-6.77 (m, 1 H), 5.22 (s, 2 H), 4.25 (s, 2 H), 2.74 (s, 3 H). LCMS RT = 5.23 min, m/z = 511.1	0.041

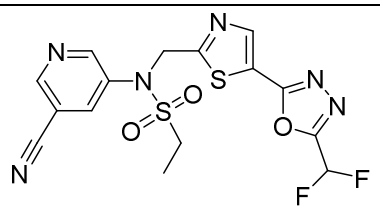
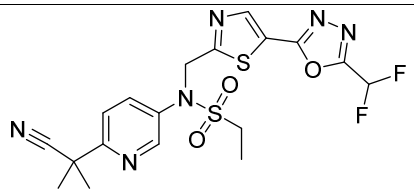
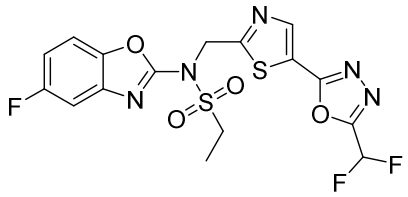
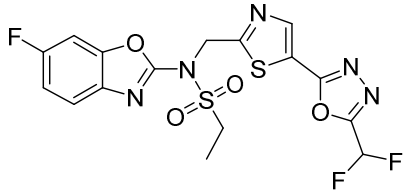
I-30	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(6-fluoropyridin-3-yl)ethanesulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1 H), 8.31 (s, 1 H), 7.94 (m, 1 H), 7.02 (m, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.25 (s, 2 H), 3.21 (q, J = 7.2 Hz, 2 H), 1.21 (t, J = 7.2 Hz, 3 H). m/z = 420.0	0.011
I-31	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(pyridin-3-yl)propane-2-sulfonamide	^{1}H NMR (400 MHz, DMSO-*d*6) δ 8.72 (s, 1 H), 8.50 (m, 2 H), 8.02 (m, 1 H), 7.40-7.66 (m, 2 H), 5.46 (s, 2 H), 3.60 (m, 1 H), 1.34 (d, J = 6.8 Hz, 6 H). m/z = 416.1	0.042
I-32	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)ethanesulfonamide	^{1}H NMR (400MHz, Methanol-d_4) δ 8.47 (s, 1 H), 7.96 (s, 1 H), 7.66 (d, J=9.54, 1 H), 7.35 (s, 0.25 H), 7.22 (s, 0.5 H), 7.09 (s, 0.25 H), 6.53 (d, J=9.54 Hz, 1 H), 5.22 (s, 2 H), 3.56 (s, 3 H), 3.35-3.30 (m, 2 H), 1.43 (t, J=7.34 Hz, 3 H). LCMS RT = 3.53 min, m/z = 432.1	0.411
I-33	 N-(3-chloro-4-fluorophenyl)-N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)morpholine-4-sulfonamide	^{1}H NMR (400 MHz, DMSO-*d*6) δ 8.52 (s, 1 H), 7.86-7.95 (m, 1 H), 7.35-7.69 (m, 3 H), 5.36 (s, 2 H), 3.58 (m, 4 H), 3.20 (m, 4 H). m/z = 510.0	0.047

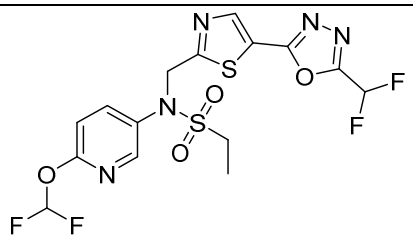
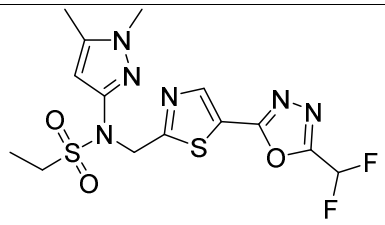
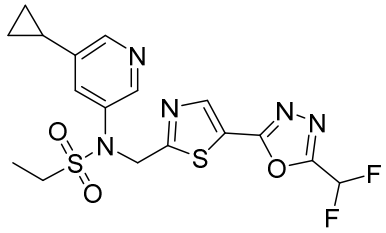
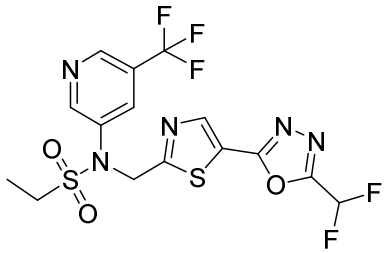
I-34	 N-(3-chlorophenyl)-N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)thiomorpholine-4-sulfonamide 1,1-dioxide	^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.41 (s, 1 H) 7.48 (s, 1 H) 7.30 - 7.40 (m, 3 H) 6.91 (t, *J*=52.4 Hz, 1 H) 5.15 (s, 2 H) 3.73 - 3.82 (m, 4H) 3.05 - 3.13 (m, 4 H). LCMS RT = 4.83 min, m/z = 540.0	0.022
I-35	 N-(4-(1H-imidazol-1-yl)phenyl)-N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)ethanesulfonamide	^{1}H NMR (400 MHz, DMSO-*d*6) δ 8.51 (s, 1 H), 8.27 (s, 1 H), 7.69-7.76 (m, 5 H), 7.3 (t, J = 51.2 Hz, 1 H), 7.10 (s, 1 H), 5.41 (s, 2 H), 3.37 (q, J = 6.8 Hz, 2 H), 1.30 (t, J = 6.8 Hz, 3 H). m/z = 467.0	0.008
I-36	 N-(3-chlorophenyl)-N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)morpholine-4-sulfonamide	^{1}H NMR (400 MHz, DMSO-*d*6) δ 8.52 (s, 1 H), 7.73 (m, 1 H), 7.54-7.58 (m, 2 H), 7.36-7.44 (m, 2 H), 5.38 (s, 2 H), 3.59 (m, 4 H), 3.18 (m, 4 H). m/z = 492.1	0.005
I-37		^{1}H NMR (400MHz, DMSO-d$_6$) δ 8.63 (s, 1 H), 8.54 (d, J=9. Hz, 2 H), 8.10 (d, J=10.0 Hz, 1 H), 7.65-7.39 (m, 1 H), 5.41 (s, 2 H), 2.83 (s, 6 H). LCMS RT = 4.39 min, m/z = 435.1	0.013

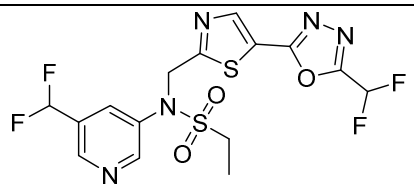
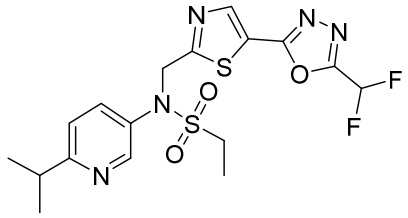
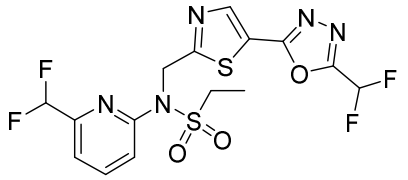
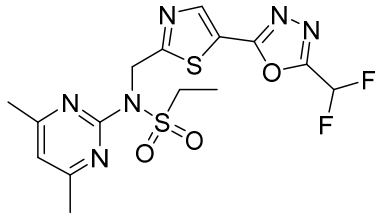
I-38	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(5-fluoropyridin-3-yl)ethanesulfonamide	^{1}H NMR (400MHz, DMSO-d_6) δ 8.62-8.52 (m, H), 8.13-8.09 (m, 1 H), 7.65-7.39 (m, 1 H), 5.46 (s, 2 H), 3.55 -3.45 (m, 2 H), 1.30 (t, J=7.34 Hz, 3 H). LCMS RT = 4.32 min, m/z = 420.0	0.019
I-39	 N-(4-(1H-pyrazol-1-yl)phenyl)-N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)ethanesulfonamide	^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.36 (s, 1 H) 7.90 (s, 1 H) 7.69 - 7.77 (m, 3 H) 7.55 (d, *J*=8.31 Hz, 2 H) 6.90 (t, *J*=52.0 Hz, 1 H) 6.48 (s, 1 H) 5.31 (s, 2 H) 3.19 (d, *J*=7.34 Hz, 2 H) 1.46 (t, *J*=7.46 Hz, 3 H). LCMS RT = 4.67 min, m/z = 467.0	0.010
I-40	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(pyridin-3-yl)morpholine-4-sulfonamide	^{1}H NMR (400 MHz, CD3OD) δ 8.57 (s, 1 H), 8.45 (s, 1 H), 8.27 (m, 1 H), 7.97 (m, 1 H), 7.73 (m, 1 H), 7.22 (t, J = 51.6 Hz, 1 H), 4.88 (s, 2 H), 3.36 (m, 4 H), 3.10 (m, 4 H). m/z = 459.1	4.22
I-43	 (R)-3-(5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)-4-phenyloxazolidin-2-one	^{1}H NMR (400 MHz, METHANOL-d4) δ = 8.07 (s, 1 H) 7.40 (s, 5 H) 7.19 (t, 1 H, J= 51.6 Hz) 5.84 (dd, J=8.80, 3.67 Hz, 1 H) 5.03 (t, J=8.80 Hz, 1 H) 4.48 (dd, J=8.93, 4.03 Hz, 1 H) ppm LCMS: RT= 4.67 min, m/z = 365.1	0.085
I-44		1H NMR (400 MHz, METHANOL-d4) δ= 8.07 (s, 1 H), 7.40 (s, 4 H), 7.33 - 7.38 (m, 1 H), 7.19 (t, 1 H, J= 5.6 Hz), 5.84 (dd, J=8.56, 3.91 Hz, 1 H), 5.03 (t, J=8.93 Hz, 1 H), 4.43 - 4.51 (m, 1 H) ppm LCMS: RT = 4.95 min, m/z = 365.1	8.97

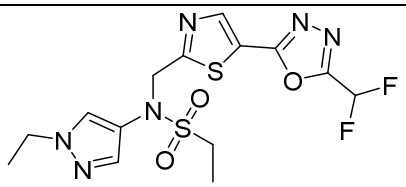
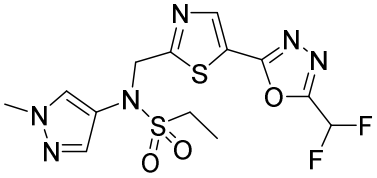
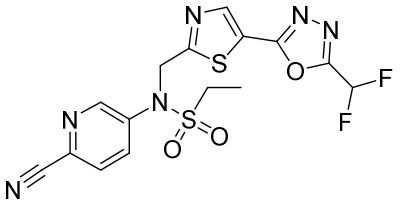
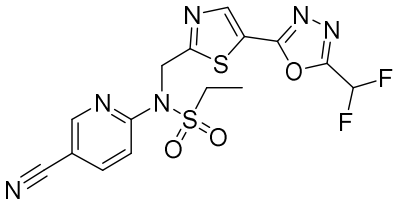
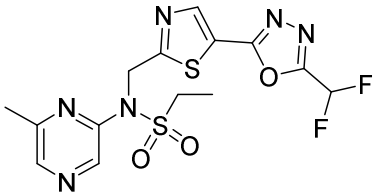
	(S)-3-(5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)-4-phenyloxazolidin-2-one		
I-45	 N-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)ethanesulfonamide	1H NMR (400 MHz, CD3OD) δ ppm 8.55 (s, 1 H), 8.27 – 8.24 (m, 2 H), 7.78 – 7.67 (m, 2 H), 7.23 (t, J = 51.6 Hz, 1 H), 6.15 (s, 2 H), 2.90 (s, 3 H). LCMS RT = 2.431 min, m/z = 324.0	1.3
I-46	 N-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)ethanesulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.40 (s, 1 H), 7.69 (s, 1 H), 7.49 (s, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.17 (s, 2 H), 3.93 (d, J = 7.2 Hz, 2 H), 3.18 (q, J = 7.6 Hz, 2 H), 1.42 (t, J = 7.6 Hz, 3 H), 1.31 – 1.22 (m, 1 H), 0.70 – 0.62 (m, 2 H), 0.38 – 0.32 (m, 2 H). LCMS RT = 2.417 min, m/z = 444.9	0.077
I-47	 N-(1-cyclopropyl-1H-pyrazol-4-yl)-N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)ethanesulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.40 (s, 1 H), 7.65 (s, 1 H), 7.46 (s, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.14 (s, 2 H), 3.58 – 3.52 (m, 1 H), 3.16 (q, J = 8.0 Hz , 2 H), 1.42 (t, J = 8.0 Hz, 3 H), 1.13 – 1.00 (m, 4 H). LCMS RT = 1.223 min, m/z = 430.9	0.070

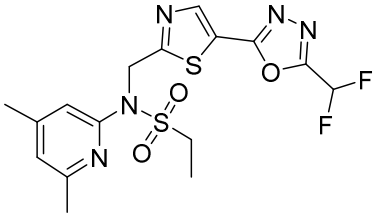
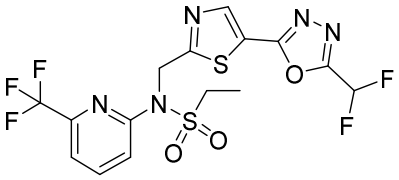
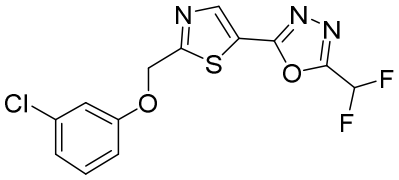
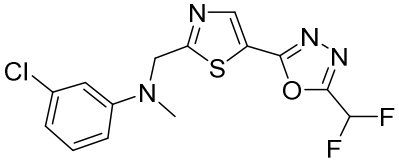
I-48	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(1-(difluoromethyl)-1H-pyrazol-4-yl)ethanesulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.35 (s, 1 H), 7.92 (s, 1 H), 7.66 (s, 1 H), 6.96 (t, J = 60.4 Hz, 1 H), 6.84 (t, J = 45.2 Hz, 1 H), 5.11 (s, 2 H), 3.10 (q, J = 7.2 Hz, 2 H), 1.33 (t, J = 7.6 Hz, 3 H). LCMS RT = 3.543 min, m/z = 441.1	0.262
I-49	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(1-(2-methoxyethyl)-1H-pyrazol-4-yl)ethanesulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.40 (s, 1 H), 7.65 (s, 1 H), 7.51 (s, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.15 (s, 2 H), 4.22 (t, J = 4.8 Hz, 2 H), 3.70 (t, J = 5.2 Hz, 2 H), 3.30 (s, 3 H), 3.17 (q, J = 7.6 Hz, 2 H), 1.41 (t, J = 7.2 Hz, 3 H). LCMS RT = 3.093 min, m/z = 448.9	0.134
I-50	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(pyridin-3-yl)cyclopropanesulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.69 (d, J = 2.0 Hz, 1 H), 8.53 – 8.50 (m, 1 H), 8.30 (s, 1 H), 7.79 – 7.76 (m, 1 H), 7.30 – 7.26 (m, 1 H), 6.83 (t, J = 51.6 Hz, 1 H), 5.23 (s, 2 H), 2.53 – 2.46 (m, 1 H), 1.06 – 0.95 (m, 4 H). LCMS RT = 2.897 min, m/z = 414.1	0.036
I-51	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(pyridin-3-yl)methanesulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.54 (s, 1 H), 8.50 (s, 1 H), 7.93 – 7.90 (m, 1 H), 7.68 (d, J = 8.0 Hz, 1 H), 7.49 – 7.44 (m, 1 H), 6.92 (t, J = 51.6 Hz, 1 H), 5.84 (s, 2 H), 3.00 (s, 3 H). LCMS RT = 1.096 min, m/z = 387.9	0.676

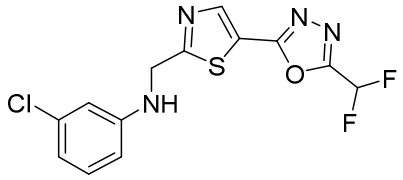
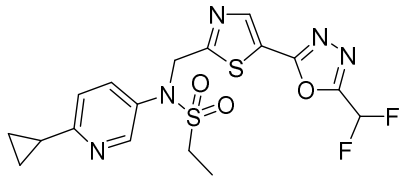
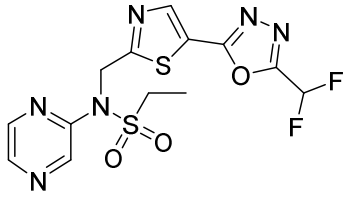
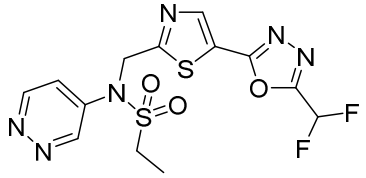
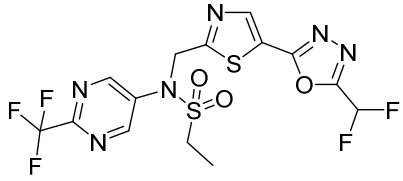
I-52	 N-(5-cyanopyridin-3-yl)-N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)ethanesulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.96 (d, J = 2.8 Hz, 1 H), 8.82 (s, 1 H), 8.42 (s, 1 H), 8.18 – 8.17 (m, 1 H), 6.92 (t, J = 51.6 Hz, 1 H), 5.30 (s, 2 H), 3.21 (q, J = 7.6 Hz, 2 H), 1.44 (t, J = 7.6 Hz, 3 H). LCMS RT = 0.752 min, m/z = 427.1	0.022
I-53	 N-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)ethanesulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.70 (d, J = 2.8 Hz, 1 H), 8.40 (s, 1 H), 7.86 (d, J = 8.4 Hz, 1 H), 7.63 (d, J = 8.4 Hz, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.29 (s, 2 H), 3.22 (q, J = 7.6 Hz, 2 H), 1.75 (s, 6 H), 1.47 (t, J = 7.2 Hz, 3 H). LCMS RT = 0.828 min, m/z = 469.2	0.317
I-54	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(5-fluorobenzo[d]oxazol-2-yl)ethanesulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.45 (s, 1 H), 7.40 – 7.38 (m, 1 H), 7.10 – 6.91 (m, 3 H), 5.40 (s, 2 H), 3.29 (q, J = 7.2 Hz, 2 H), 1.52 (t, J = 7.2 Hz, 3 H). LCMS RT = 3.800 min, m/z = 460.0	0.104
I-55	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(6-fluorobenzo[d]oxazol-2-yl)ethanesulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.44 (s, 1 H), 7.29 – 7.21 (m, 2 H), 7.10 – 7.04 (m, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.42 (s, 2 H), 3.29 (q, J = 7.2 Hz, 2 H), 1.52 (t, J = 7.2 Hz, 3 H). LCMS RT = 0.863 min, m/z = 459.7	0.124

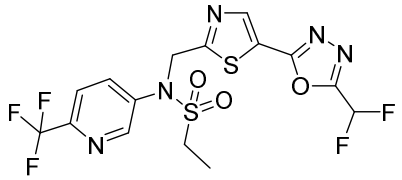
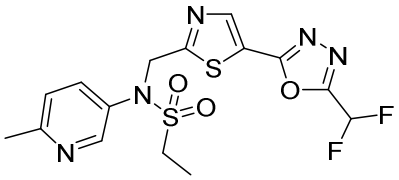
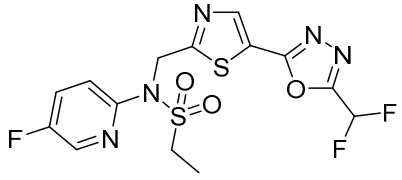
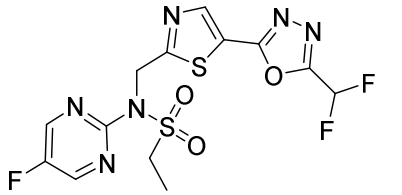
I-56	 N-(6-(difluoromethoxy)pyridin-3-yl)-N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)ethanesulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.39 (s, 1 H), 8.28 (d, J = 2.8 Hz, 1 H), 7.85 (d, J = 8.8 Hz, 1 H), 7.41 (t, J = 51.6 Hz, 1 H), 7.06 – 6.76 (m, 2 H), 5.24 (s, 2 H), 3.20 (q, J = 7.2 Hz, 2 H), 1.47 (t, J = 7.6 Hz, 3 H). LCMS RT = 0.886 min, m/z = 468.1	0.050
I-57	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(1,5-dimethyl-1H-pyrazol-3-yl)ethanesulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.40 (s, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 6.13 (s, 1 H), 5.37 (s, 2 H), 3.70 (s, 3 H), 3.27 (q, J = 7.6 Hz, 2 H), 2.24 (s, 3 H), 1.42 (t, J = 7.2 Hz, 3 H). LCMS RT = 3.486 min, m/z = 418.9	0.117
I-58	 N-(5-cyclopropylpyridin-3-yl)-N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)ethanesulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.45 (s, 1 H), 8.41 (s, 1 H), 8.35 (s, 1 H), 7.46 (s, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.27 (s, 2 H), 3.19 (q, J = 8.0 Hz, 2 H), 1.92 – 1.89 (m, 1 H), 1.45 (t, J = 7.2 Hz, 3 H), 1.11 – 1.05 (m, 2 H), 0.76 – 0.74 (m, 2 H). LCMS RT = 0.992 min, m/z = 442.3	0.025
I-59	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(5-(trifluoromethyl)pyridin-3-yl)ethanesulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.93 (d, J = 2.0 Hz, 1 H), 8.83 (s, 1 H), 8.41 (s, 1 H), 8.10 (s, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.31 (s, 2 H), 3.22 (q, J = 7.6 Hz, 2 H), 1.45 (t, J = 7.6 Hz, 3 H). LCMS RT = 1.190 min, m/z = 469.8	0.030

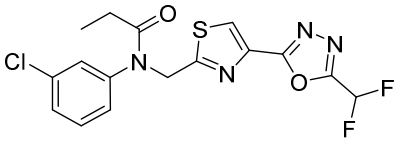
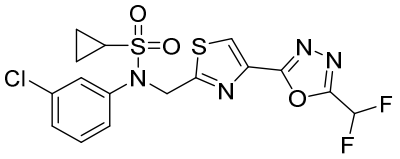
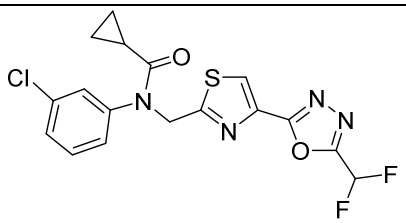
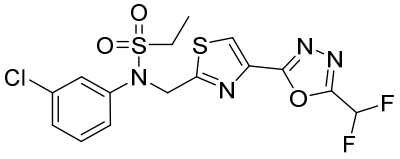
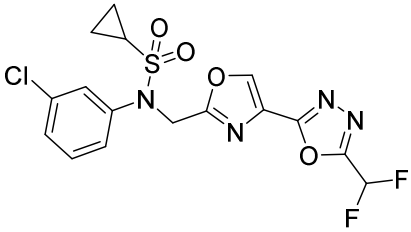
I-60	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(5-(difluoromethyl)pyridin-3-yl)ethanesulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.85 (s, 1 H), 8.73 (s, 1 H), 8.40 (s, 1 H), 7.99 (s, 1 H), 6.91 (t, J = 52.0 Hz, 1 H), 6.74 (t, J = 56.0 Hz, 1 H), 5.31 (s, 2 H), 3.22 (q, J = 4.0 Hz, 2 H), 1.46 (t, J = 8.0 Hz, 3 H). LCMS RT = 2.508 min, m/z = 452.1	0.070
I-61	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(6-isopropylpyridin-3-yl)ethanesulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.59 (d, J = 2.4 Hz, 1 H), 8.38 (s, 1 H), 7.75 – 7.71 (m, 1 H), 7.22 (d, J = 8.0 Hz, 1H), 6.91 (t, J = 51.6 Hz, 1 H), 5.27 (s, 2 H), 3.20 (q, J = 7.2 Hz, 2 H), 3.11 – 3.03 (m, 1 H), 1.47 (t, J = 7.2 Hz, 3 H), 1.29 (d, J = 7.2 Hz, 6 H). LCMS RT = 0.757 min, m/z = 444.2	0.073
I-62	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(6-(difluoromethyl)pyridin-2-yl)ethanesulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.30 (s, 1 H), 7.85 – 7.69 (m, 2 H), 7.39 (d, J = 7.6 Hz, 1 H), 6.81 (t, J = 51.6 Hz, 1 H), 6.47 (t, J = 79.2 Hz, 1 H), 5.54 (s, 2 H), 3.29 (q, J = 7.6 Hz, 2 H), 1.33 (t, J = 7.6 Hz, 3 H). LCMS RT = 2.238 min, m/z = 452.1	0.0206
I-63	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(4,6-dimethylpyrimidin-2-yl)ethanesulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.40 (s, 1 H), 6.89 (t, J = 51.6 Hz, 1 H), 6.77 (s, 1 H), 5.65 (s, 2 H), 3.95 (q, J = 7.6 Hz, 2 H), 2.44 (s, 6 H), 1.39 (t, J = 7.6 Hz, 3 H). LCMS RT = 3.758 min, m/z = 431.2	0.018

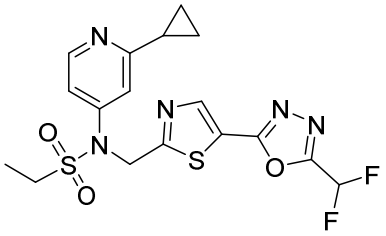
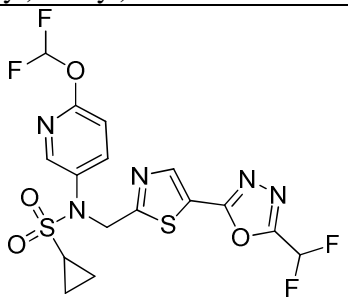
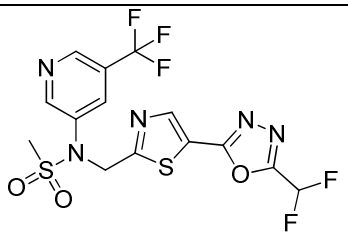
I-64	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(1-ethyl-1H-pyrazol-4-yl)ethanesulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.40 (s, 1 H), 7.60 (s, 1 H), 7.49 (s, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.16 (s, 2 H), 4.12 (q, J = 7.2 Hz, 2 H), 3.17 (q, J = 7.6 Hz, 2 H), 1.50 – 1.40 (m, 6 H). LCMS RT = 1.418 min, m/z = 418.9	0.065
I-65	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(1-methyl-1H-pyrazol-4-yl)ethanesulfonamide	1H NMR (400 MHz, CD3OD) δ ppm 8.33 (s, 1 H), 7.71 (s, 1 H), 7.48 (s, 1 H), 7.11 (t, J = 51.6 Hz, 1 H), 5.10 (s, 2 H), 3.74 (s, 3 H), 3.14 (q, J = 7.2 Hz, 2 H), 1.28 (t, J = 7.2 Hz, 3 H). LCMS RT = 2.950 min, m/z = 404.9	0.022
I-66	 N-(6-cyanopyridin-3-yl)-N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)ethanesulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.87 (s, 1 H), 8.40 (s, 1 H), 8.04 (d, J = 8.4 Hz, 1 H), 7.74 (d, J = 8.4 Hz, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.35 (s, 2 H), 3.23 (q, J = 7.2 Hz, 2 H), 1.43 (t, J = 7.2 Hz, 3 H). LCMS RT = 1.030 min, m/z = 426.8	0.029
I-67	 N-(5-cyanopyridin-2-yl)-N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)ethanesulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.66 (s, 1 H), 8.39 (s, 1 H), 7.96 – 7.78 (m, 2 H), 6.90 (t, J = 51.6 Hz, 1 H), 5.63 (s, 2 H), 3.48 (q, J = 7.6 Hz, 2 H), 1.43 (t, J = 7.6 Hz, 3 H). LCMS RT = 2.180 min, m/z = 427.1	0.037
I-68	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-	1H NMR (400 MHz, CDCl3) δ ppm 8.80 (s, 1 H), 8.39 (s, 1 H), 8.29 (s, 1 H), 6.90 (t, J = 51.6 Hz, 1 H), 5.58 (s, 2 H), 3.38 (q, J = 7.2 Hz, 2 H), 2.55 (s, 3 H), 1.42 (t, J = 7.6 Hz, 3 H). LCMS RT = 1.657 min, m/z = 417.1	0.100

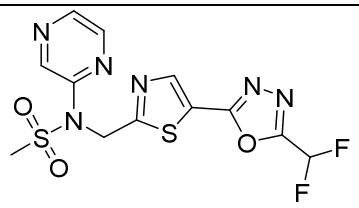
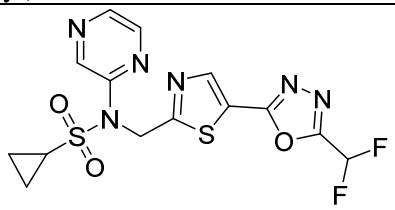
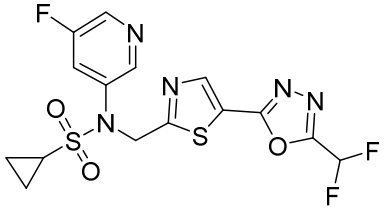
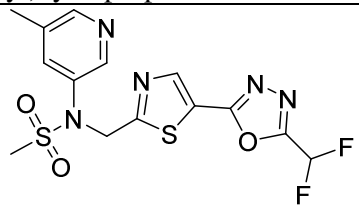
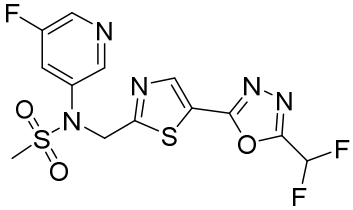
	yl)methyl)-N-(6-methylpyrazin-2-yl)ethanesulfonamide		
I-69	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(4,6-dimethylpyridin-2-yl)ethanesulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.38 (s, 1 H), 7.27 (s, 1 H), 7.02 – 6.72 (m, 2 H), 5.58 (s, 2 H), 3.24 (q, J = 7.6 Hz, 2 H), 2.47 (s, 3 H), 2.33 (s, 3 H), 1.36 (t, J = 7.4 Hz, 3 H). LCMS RT = 3.082 min, m/z = 429.9	0.071
I-70	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(6-(trifluoromethyl)pyridin-2-yl)ethanesulfonamide	1H NMR (400 MHz, CD3OD) δ ppm 8.42 (s, 1 H), 8.07 – 8.02 (m, 1 H), 7.92 – 7.89 (m, 1 H), 7.61 – 7.58 (m, 1 H), 7.19 (t, J = 51.6 Hz, 1 H), 5.62 (s, 2 H), 3.57 (q, J = 7.2 Hz, 2 H), 1.38 (t, J = 7.2 Hz, 3 H). LCMS RT = 2.965 min, m/z = 470.1	0.0281
I-71	 2-(2-((3-chlorophenoxy)methyl)thiazol-5-yl)-5-(difluoromethyl)-1,3,4-oxadiazole	1H NMR (400 MHz, CDCl3) δ ppm 8.49 (s, 1 H), 7.29 – 7.24 (m, 1 H), 7.06 – 7.04 (m, 2 H), 6.94 – 6.78 (m, 2 H), 5.43 (s, 2 H). LCMS RT = 1.840 min, m/z = 344.1	0.251
I-72	 3-chloro-N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-methylaniline	1H NMR (400 MHz, CDCl3) δ ppm 8.55 (s, 1 H), 7.43 – 6.70 (m, 5 H), 4.93 (s, 2 H), 3.26 (s, 3 H). LCMS RT = 3.547 min, m/z = 356.8	0.034

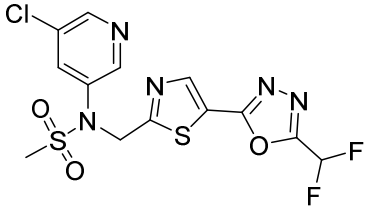
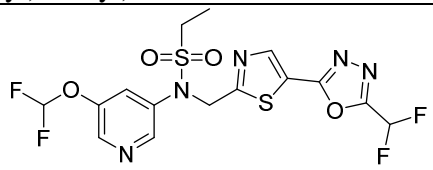
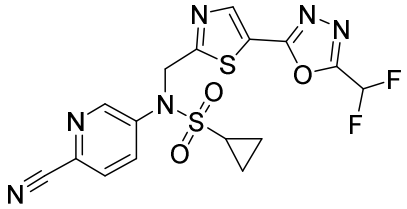
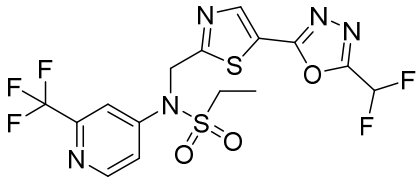
I-73	 3-chloro-N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)aniline	1H NMR (400 MHz, CDCl3) δ ppm 8.37 (s, 1 H), 7.06 – 6.44 (m, 5 H), 4.66 (s, 3 H). LCMS RT = 2.368 min, m/z = 343.1	0.046
I-74	 N-(6-cyclopropylpyridin-3-yl)-N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)ethanesulfonamide	1H NMR (400 MHz, CD3OD) δ ppm 8.46 (d, J = 2.4 Hz, 1 H), 8.41 (s, 1 H), 7.80 (dd, J = 8.4, 2.8 Hz, 1 H), 7.33 – 7.07 (m, 2 H), 5.33 (s, 2 H), 3.31 – 3.27 (m, 2 H), 2.11 – 2.08 (m, 1 H), 1.40 (t, J = 7.2 Hz, 3 H), 1.04 – 0.94 (m, 4 H). LCMS RT = 5.273 min, m/z = 441.9	0.016
I-75	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(pyrazin-2-yl)ethanesulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 9.00 (s, 1 H), 8.43 (d, J = 2.8 Hz, 1 H), 8.39 – 8.35 (m, 2 H), 6.89 (t, J = 51.6 Hz, 1 H), 5.58 (s, 2 H), 3.41 (q, J = 7.6 Hz, 2 H), 1.43 (t, J = 7.2 Hz, 3 H). LCMS RT = 2.823 min, m/z = 403.1	0.023
I-76	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(pyridazin-4-yl)ethanesulfonamide	1H NMR (400 MHz, CD3OD) δ ppm 8.57 (d, J = 7.6 Hz, 1 H), 8.53 (s, 1 H), 8.23 (s, 1 H), 7.42 – 7.40 (m, 1 H), 7.22 (t, J = 51.6 Hz, 1 H), 5.85 (s, 2 H), 3.10 (q, J = 7.6 Hz, 2 H), 1.36 (t, J = 7.2 Hz, 3 H). LCMS RT = 3.671 min, m/z = 402.9	0.097
I-77	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(2-	1H NMR (400 MHz, CDCl3) δ ppm 9.10 (s, 2 H), 8.43 (s, 1 H), 6.92 (t, J = 51.6 Hz, 1 H), 5.32 (d, J = 12 Hz, 2 H), 3.25 (q, J = 7.2 Hz, 2 H), 1.44 (t, J = 7.2 Hz, 3 H). LCMS RT = 2.594 min, m/z = 471.1	0.155

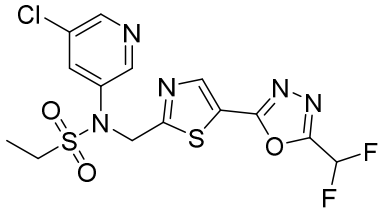
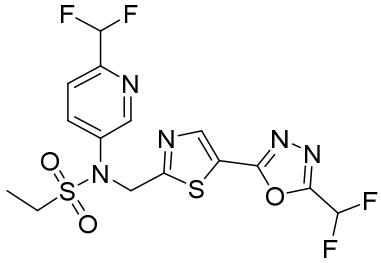
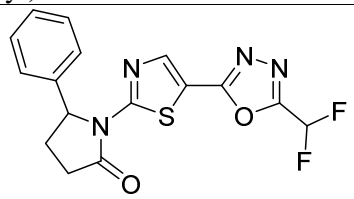
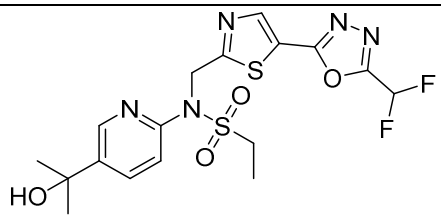
	(trifluoromethyl)pyrimidin-5-yl)ethanesulfonamide		
I-78	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(6-(trifluoromethyl)pyridin-3-yl)ethanesulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.86 (s, 1 H), 8.40 (s, 1 H), 8.10 (d, J = 8.4 Hz, 1 H), 7.74 (d, J = 8.4 Hz, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.34 (s, 2 H), 3.23 (q, J = 7.2 Hz, 2 H), 1.45 (t, J = 7.2 Hz, 3 H). LCMS RT = 0.882 min, m/z = 470.1	0.059
I-79	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(6-methylpyridin-3-yl)ethanesulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.55 (s, 1 H), 8.37 (s, 1 H), 7.73 –7.68 (m, 1 H), 7.20 (d, J = 7.6 Hz, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.27 (s, 2 H), 3.20 (q, J = 7.2 Hz, 2 H), 2.56 (s, 3 H), 1.46 (t, J = 7.2 Hz, 3 H). LCMS RT = 0.616 min, m/z = 416.2	0.073
I-80	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(5-fluoropyridin-2-yl)ethanesulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.37 (s, 1 H), 8.28 (s, 1 H), 7.70 – 7.60 (m, 1 H), 7.50 – 7.40 (m, 1 H), 6.89 (t, J = 51.6 Hz, 1 H), 5.54 (s, 2 H), 3.25 (q, J = 7.2 Hz, 2 H), 1.40 (t, J = 7.6 Hz, 3 H). LCMS RT = 2.661 min, m/z = 419.9	0.0265
I-81	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(5-fluoropyrimidin-2-yl)ethanesulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.49 (s, 2 H), 8.40 (s, 1 H), 6.90 (t, J = 51.6 Hz, 1 H), 5.65 (s, 2 H), 3.91 (q, J = 7.6 Hz, 2 H), 1.45 (t, J = 7.6 Hz, 3 H). LCMS RT = 1.977 min, m/z = 421.1	0.116

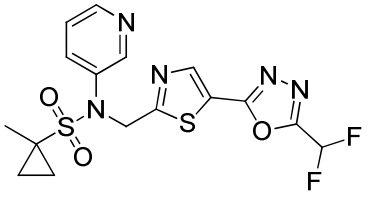
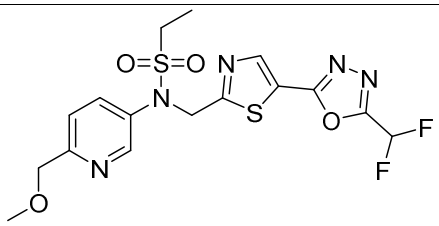
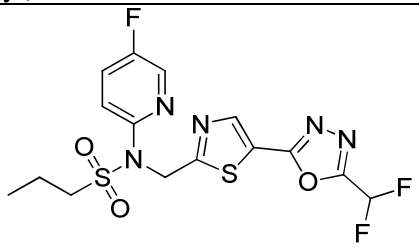
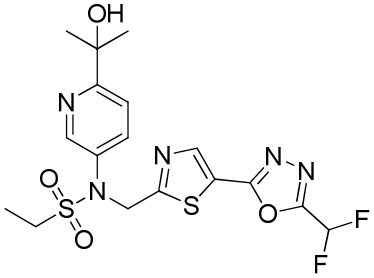
I-82	 N-(3-chlorophenyl)-N-((4-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)propionamide	1H NMR (400 MHz, CDCl3) δ ppm 8.28 (s, 1 H), 7.37 – 7.32 (m, 2 H), 7.25 – 7.23 (m, 1 H), 7.10 – 7.07 (m, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.22 (s, 2 H), 2.19 (q, J = 7.2 Hz, 2 H), 1.21 (t, J = 7.2 Hz, 3 H). LCMS RT = 0.931 min, m/z = 399.1	4.1
I-83	 N-(3-chlorophenyl)-N-((4-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)cyclopropanesulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.26 (s, 1 H), 7.51 (s, 1 H), 7.41 – 7.30 (m, 3 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.32 (s, 2 H), 2.59 – 2.52 (m, 1 H), 1.18 – 1.13 (m, 2 H), 1.08 – 1.04 (m, 2 H). LCMS RT = 0.944 min, m/z = 447.1	0.759
I-84	 N-(3-chlorophenyl)-N-((4-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)cyclopropanecarboxamide	1H NMR (400 MHz, CDCl3) δ ppm 8.27 (s, 1 H), 7.40 – 7.20 (m, 4 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.25 (s, 2 H), 1.50 – 1.40 (m, 1 H), 1.18 – 1.09 (m, 2 H), 0.83 – 0.74 (m, 2 H). LCMS RT = 1.163 min, m/z = 410.8	7.5
I-85	 N-(3-chlorophenyl)-N-((4-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)ethanesulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.26 (s, 1 H), 7.48 (s, 1 H), 7.37 – 7.31 (m, 3 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.32 (s, 2 H), 3.19 (q, J = 7.2 Hz, 2 H), 1.46 (t, J = 7.2 Hz, 3 H). LCMS RT = 0.922 min, m/z = 435.0	0.584
I-86	 N-(3-chlorophenyl)-N-((4-(5-(difluoromethyl)-1,3,4-oxadiazol-	1H NMR (400 MHz, CDCl3) δ ppm 8.36 (s, 1 H), 7.50 (s, 1 H), 7.39 – 7.37 (m, 1 H), 7.33 – 7.30 (m, 2 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.03 (s, 2 H), 2.69 – 2.65 (m, 1 H), 1.09 – 0.90 (m, 4 H). LCMS RT = 3.210 min, m/z = 431.1	8.0

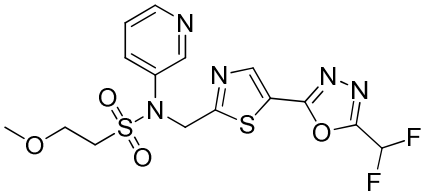
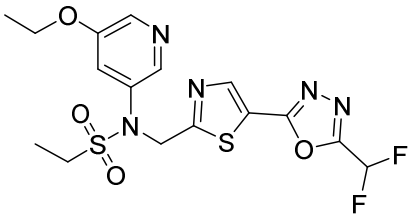
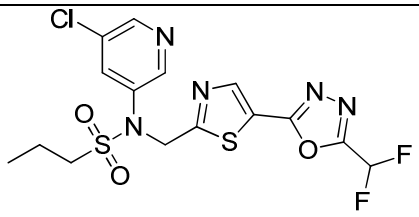
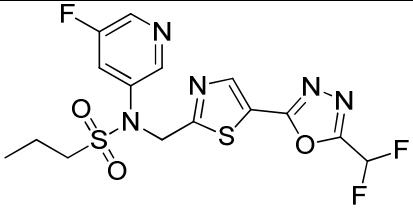
	2-yl)oxazol-2-yl)methyl)cyclopropanesulfonamide		
I-87	 N-(2-cyclopropylpyridin-4-yl)-N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)ethanesulfonamide	1H NMR (400 MHz, CDCl3) δ 8.42 – 8.36 (m, 2 H), 7.31 (s, 1 H), 7.18 – 7.14 (m, 1 H), 6.90 (t, J = 51.6 Hz, 1 H), 5.37 (s, 2 H), 3.26 (q, J = 7.6 Hz, 2 H), 2.04 – 1.95 (m, 1 H), 1.42 (t, J = 7.2 Hz, 3 H), 1.05 – 1.00 (m, 4 H). LCMS RT = 1.094 min, m/z = 441.9	0.039
I-88	 N-(6-(difluoromethoxy)pyridin-3-yl)-N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)cyclopropanesulfonamide	1H NMR (400 MHz, CDCl3) δ 8.39 (s, 1 H), 8.33 (d, J = 2.8 Hz, 1 H), 7.87 (dd, J = 2.8, 8.8 Hz, 1 H), 7.42 (t, J = 72.0 Hz, 1 H), 7.06 – 6.77 (m, 2 H), 5.26 (s, 2 H), 2.64 – 2.48 (m, 1 H), 1.21 – 0.98 (m, 4 H). LCMS RT = 0.957 min, m/z = 479.9	0.048
I-89	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(5-(trifluoromethyl)pyridin-3-yl)methanesulfonamide	1H NMR (400 MHz, CDCl3) δ 8.95 (d, J = 2.4 Hz, 1 H), 8.87 (d, J = 2.4 Hz, 1 H), 8.44 (s, 1 H), 8.13 (s, 1 H), 6.92 (t, J = 51.6 Hz, 1 H), 5.31 (s, 2 H), 3.12 (s, 3 H). LCMS RT = 0.878 min, m/z = 455.9	0.049

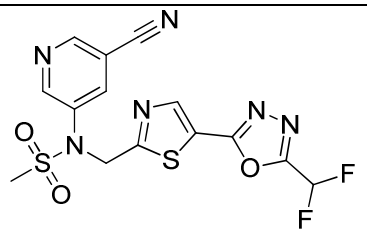
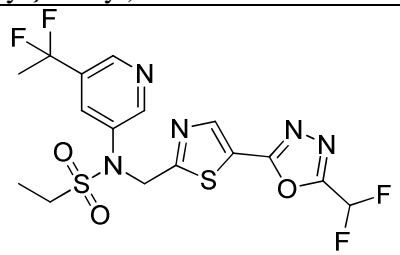
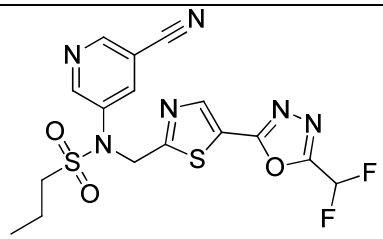
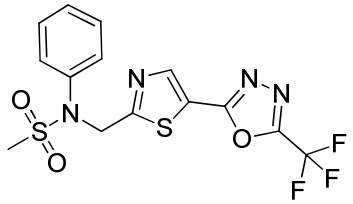
I-90	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(pyrazin-2-yl)methanesulfonamide	1H NMR (400 MHz, CDCl3) δ 9.00 (s, 1 H), 8.47 – 8.36 (m, 3 H), 6.91 (t, J = 51.2 Hz, 1 H), 5.58 (s, 2 H), 3.27 (s, 3 H). LCMS RT = 0.943 min, m/z = 389.1	0.041
I-91	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(pyrazin-2-yl)cyclopropanesulfonamide	1H NMR (400 MHz, CDCl3) δ 9.02 (d, J = 1.2 Hz, 1 H), 8.46 – 8.35 (m, 3 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.58 (s, 2 H), 2.72 – 2.61 (m, 1 H), 1.27 – 1.21 (m, 2 H), 1.11 – 1.01 (m, 2 H). LCMS RT = 1.031 min, m/z = 415.1	0.018
I-92	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(5-fluoropyridin-3-yl)cyclopropanesulfonamide	1H NMR (400 MHz, CDCl3) δ 8.61 (s, 1 H), 8.47 (d, J = 4.0 Hz, 1 H), 8.40 (s, 1 H), 7.68 – 7.62 (m, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.31 (s, 2 H), 2.63 – 2.52 (m, 1 H), 1.17 – 1.02 (m, 4 H). LCMS RT = 2.295 min, m/z = 431.9	0.014
I-93	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(5-methylpyridin-3-yl)methanesulfonamide	1H NMR (400 MHz, CDCl3) δ 8.52 – 8.43 (m, 2 H), 8.40 (s, 1 H), 7.65 (s, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.27 (s, 2 H), 3.10 (s, 3 H), 2.39 (s, 3 H). LCMS RT = 0.828 min, m/z = 401.9	0.055
I-94	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-	1H NMR (400 MHz, CDCl3) δ 8.58 (s, 1 H), 8.49 (s, 1 H), 8.43 (s, 1 H), 7.68 – 7.65 (m, 1 H), 6.92 (t, J = 51.6 Hz, 1 H), 5.29 (s, 2 H), 3.12 (s, 3 H). LCMS RT = 1.877 min, m/z = 406.1	0.025

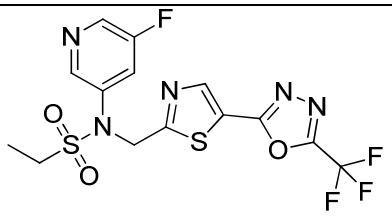
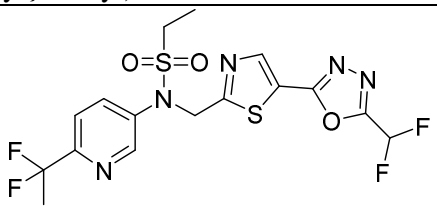
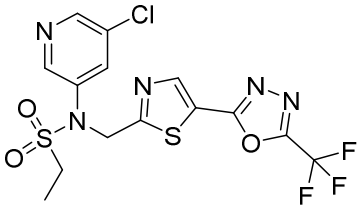
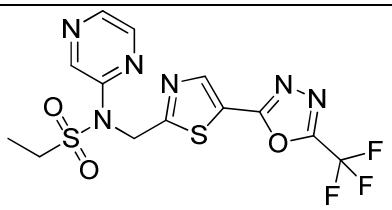
	yl)methyl)-N-(5-fluoropyridin-3-yl)methanesulfonamide		
I-95	 N-(5-chloropyridin-3-yl)-N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)methanesulfonamide	1H NMR (400 MHz, CDCl3) δ 8.62 (d, J = 2.4 Hz, 1 H), 8.57 (d, J = 2.4 Hz, 1 H), 8.43 (s, 1 H), 7.90 (s, 1 H), 6.92 (t, J = 51.6 Hz, 1 H), 5.27 (s, 2 H), 3.11 (s, 3 H). LCMS RT = 2.188 min, m/z = 421.8	0.0235
I-96	 N-(5-(difluoromethoxy)pyridin-3-yl)-N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)ethanesulfonamide	1H NMR (400 MHz, CDCl3) δ 8.63 (s, 1 H), 8.46 (s, 1 H), 8.39 (s, 1 H), 7.68 (s, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 6.58 (t, J = 51.6 Hz, 1 H), 5.29 (s, 2 H), 3.22 (q, J = 7.2 Hz , 2 H), 1.44 (t, J = 7.6 Hz, 3 H). LCMS RT = 0.907 min, m/z = 467.8	0.010
I-97	 N-(6-cyanopyridin-3-yl)-N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)cyclopropanesulfonamide	1H NMR (400 MHz, CDCl3) δ 8.89 (d, J = 2.4 Hz, 1 H), 8.39 (s, 1 H), 8.05 (d, J = 8.4 Hz, 1 H), 7.74 (d, J = 8.8 Hz, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.35 (s, 2 H), 2.59 – 2.53 (m, 1 H), 1.16 – 1.07 (m, 4 H). LCMS RT = 0.859 min, m/z = 439.0	0.010
I-98	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(2-	1H NMR (400 MHz, CDCl3) δ 8.59 (d, J = 5.6 Hz, 1 H), 8.39 (s, 1 H), 7.81 (s, 1 H), 7.61 – 7.53 (m, 1 H), 6.83 (t, J = 51.6 Hz, 1 H), 5.35 (s, 2 H), 3.24 (q, J = 7.2 Hz, 2 H), 1.35 (t, J = 7.2 Hz, 3 H). LCMS RT = 0.956 min, m/z = 469.9	0.069

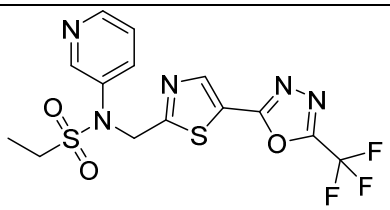
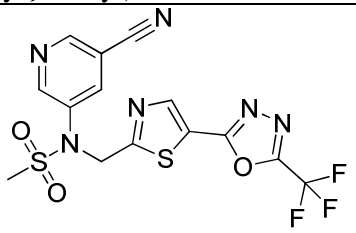
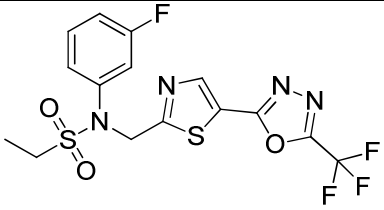
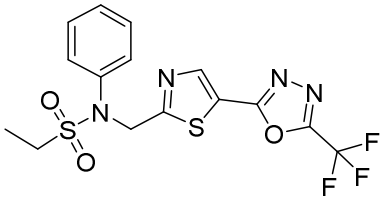
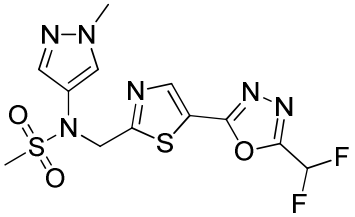
	(trifluoromethyl)pyridin-4-yl)ethanesulfonamide		
I-99	 N-(5-chloropyridin-3-yl)-N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)ethanesulfonamide	1H NMR (400 MHz, CDCl3) δ 8.61 (d, J = 2.0 Hz, 1 H), 8.55 (d, J = 2.0 Hz, 1 H), 8.41 (s, 1 H), 7.89 (t, J = 2.2 Hz, 1 H), 6.92 (t, J = 51.6 Hz, 1 H), 5.28 (s, 2 H), 3.22 (q, J = 7.2 Hz, 2 H), 1.46 (t, J = 7.6 Hz, 3 H). LCMS RT = 2.461 min, m/z = 435.9	0.0189
I-100	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(6-(difluoromethyl)pyridin-3-yl)ethanesulfonamide	1H NMR (400 MHz, CDCl3) δ 8.77 (d, J = 2.4 Hz, 1 H), 8.47 (s, 1 H), 8.01 (dd, J = 2.4, 8.4 Hz, 1 H), 7.69 (d, J = 8.4 Hz, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 6.63 (t, J = 55.2 Hz, 1 H), 5.32 (s, 2 H), 3.21 (q, J = 7.2 Hz, 2 H), 1.45 (t, J = 7.6 Hz, 3 H). LCMS RT = 2.547 min, m/z = 452.1	0.065
I-101	 1-(5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)-5-phenylpyrrolidin-2-one	1H NMR (400 MHz, CDCl3) δ 8.08 (s, 1 H), 7.38 – 7.30 (m, 3 H), 7.18 (d, J = 7.2 Hz, 2 H), 6.88 (t, J = 51.6 Hz, 1 H), 5.80 (d, J = 7.6 Hz, 1 H), 2.93 – 2.74 (m, 3 H), 2.25 – 2.20 (m, 1 H). LCMS RT = 2.937 min, m/z = 362.9	0.171
I-102	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-	1H NMR (400 MHz, CDCl3) δ 8.55 (d, J = 2.0 Hz, 1 H), 8.38 (s, 1 H), 7.86 (d, J = 6.8 Hz, 1 H), 7.60 (d, J = 8.8 Hz, 1 H), 6.89 (t, J = 51.6 Hz, 1 H), 5.58 (s, 2 H), 3.29 (q, J = 7.6 Hz , 2 H), 1.61 (s, 6 H), 1.39 (t, J = 7.6 Hz, 3 H).	0.137

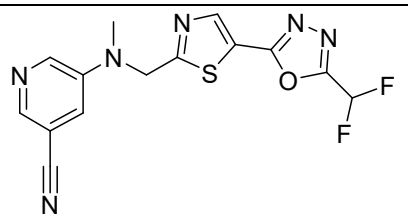
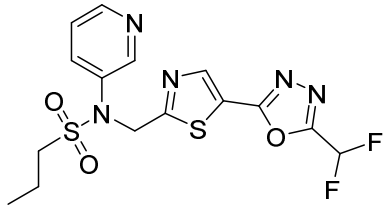
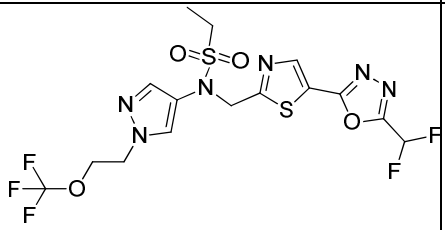
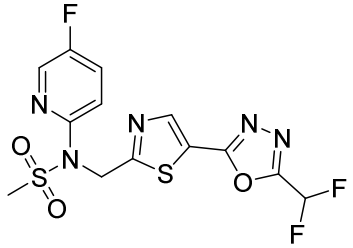
	yl)methyl)-N-(5-(2-hydroxypropan-2-yl)pyridin-2-yl)ethanesulfonamide	LCMS RT = 1.017 min, m/z = 459.9	
I-103	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-1-methyl-N-(pyridin-3-yl)cyclopropane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.74 (d, J = 2.4 Hz, 1 H), 8.58 (d, J = 3.6 Hz, 1 H), 8.35 (s, 1 H), 7.87 – 7.81 (m, 1 H), 7.38 – 7.31 (m, 1 H), 6.90 (t, J = 51.6 Hz, 1 H), 5.35 (s, 2 H), 1.59 (s, 3 H), 1.22 – 1.15 (m, 2 H), 0.79 – 0.72 (m, 2 H). LCMS RT = 0.956 min, m/z = 427.9	0.013
I-104	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(6-(methoxymethyl)pyridin-3-yl)ethanesulfonamide	1H NMR (400 MHz, CDCl3) δ 8.63 (d, J = 2.4 Hz, 1 H), 8.38 (s, 1 H), 7.83 (dd, J = 2.4, 8.0 Hz, 1 H), 7.48 (d, J = 8.4 Hz, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.29 (s, 2 H), 4.57 (s, 2 H), 3.49 (s, 3 H), 3.20 (q, J = 7.6 Hz, 2 H), 1.46 (t, J = 7.6 Hz, 3 H). LCMS RT = 0.789 min, m/z = 446.2	0.051
I-105	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(5-fluoropyridin-2-yl)propane-1-sulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1 H), 8.28 (d, *J* = 3.2 Hz, 1 H), 7.69 – 7.63 (m, 1 H), 7.51 – 7.43 (m, 1 H), 6.89 (t, *J* = 51.6 Hz, 1 H), 5.52 (s, 2 H), 3.20 – 3.14 (m, 2 H), 1.91 – 1.83 (m, 2 H), 1.05 (t, *J* = 7.6 Hz, 3 H). LCMS R_T = 0.684 min, *m/z* = 433.9	0.0268
I-106	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-[6-(2-	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1 H), 8.38 (s, 1 H), 7.85 (d, *J* = 8.8 Hz, 1 H), 7.60 (d, *J* = 8.4 Hz, 1 H), 6.89 (t, *J* = 52.0 Hz, 1 H), 5.58 (s, 2 H), 3.30 (q, *J* = 7.2 Hz, 2 H), 2.63 (s, 1 H), 1.39 (t, *J* = 7.6 Hz, 3 H), 1.30 – 1.23 (m, 6 H). LCMS R_T = 1.467 min, *m/z* = 460.2	0.480

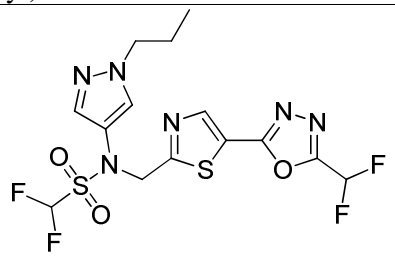
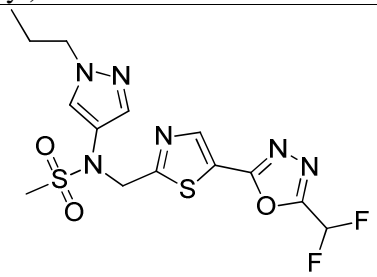
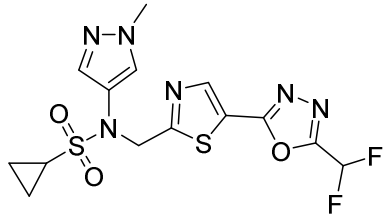
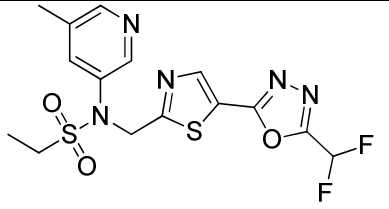
	hydroxypropan-2-yl)pyridin-3-yl]ethane-1-sulfonamide		
I-107	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-2-methoxy-N-(pyridin-3-yl)ethane-1-sulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1 H), 8.57 (d, *J* = 3.6 Hz, 1 H), 8.34 (s, 1 H), 7.91 – 7.88 (m, 1 H), 7.36 – 7.33 (m, 1 H), 6.90 (t, *J* = 51.6 Hz, 1 H), 5.24 (s, 2 H), 3.87 (t, *J* = 5.2 Hz, 2 H), 3.51 (s, 3 H), 3.35 (t, *J* = 5.2 Hz, 2 H). LCMS R_T = 1.284 min, *m/z* = 431.9	0.0212
I-108	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(5-ethoxypyridin-3-yl)ethane-1-sulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1 H), 8.32 – 8.27 (m, 2 H), 7.42 – 7.38 (m, 1 H), 6.92 (t, *J* = 51.6 Hz, 1 H), 5.31 (s, 2 H), 4.10 (q, *J* = 6.8 Hz, 2 H), 3.22 (q, *J* = 7.2 Hz, 2 H), 1.49 – 1.43 (m, 6 H). LCMS R_T = 0.604 min, *m/z* = 446.0	0.0138
I-109	 N-(5-chloropyridin-3-yl)-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)propane-1-sulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 2.0 Hz, 1 H), 8.54 (s, 1 H), 8.40 (s, 1 H), 7.88 (t, *J* = 2.4 Hz, 1 H), 6.91 (t, *J* = 51.6 Hz, 1 H), 5.27 (s, 2 H), 3.22 – 3.00 (m, 2 H), 1.99 – 1.70 (m, 2 H), 1.09 (t, *J* = 7.6 Hz, 3 H). LCMS R_T = 0.668 min, *m/z* = 449.9	0.00392
I-110	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(5-fluoropyridin-3-yl)propane-1-sulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1 H), 8.46 (d, *J* = 2.4 Hz, 1 H), 8.40 (s, 1 H), 7.67 – 7.61 (m, 1 H), 6.91 (t, *J* = 51.6 Hz, 1 H), 5.29 (s, 2 H), 3.19 – 3.09 (m, 2 H), 1.97 – 1.85 (m, 2 H), 1.08 (t, *J* = 7.2 Hz, 3 H). LCMS R_T = 2.144 min, *m/z* = 434.2	0.0104

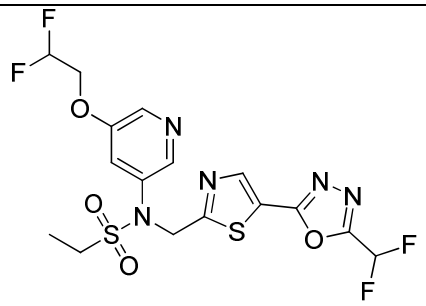
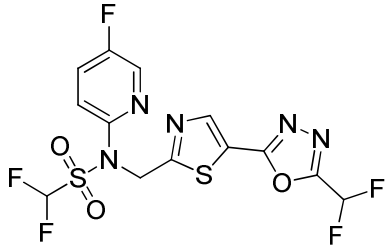
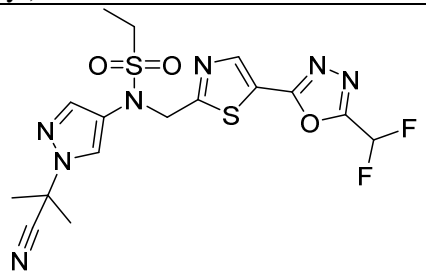
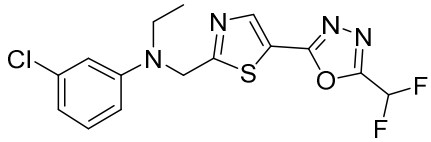
I-111	 N-(5-cyanopyridin-3-yl)-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)methanesulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (d, *J* = 2.4 Hz, 1 H), 8.84 (s, 1 H), 8.45 (s, 1 H), 8.20 (s, 1 H), 6.93 (t, *J* = 51.2 Hz, 1 H), 5.29 (s, 2 H), 3.11 (s, 3 H). LCMS R_T = 1.456 min, *m/z* = 412.8	0.0374
I-112	 N-[5-(1,1-difluoroethyl)pyridin-3-yl]-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)ethane-1-sulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1 H), 8.72 (s, 1 H), 8.40 (s, 1 H), 7.96 (s, 1 H), 6.91 (t, *J* = 52.0 Hz, 1 H), 5.30 (s, 2 H), 3.21 (q, *J* = 7.2 Hz, 2 H), 1.97 (t, *J* = 18.4 Hz, 3 H), 1.46 (t, *J* = 7.6 Hz, 3 H). LCMS R_T = 1.138 min, *m/z* = 466.2	0.0101
I-113	 N-(5-cyanopyridin-3-yl)-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)propane-1-sulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (d, *J* = 2.4 Hz, 1 H), 8.82 (d, *J* = 2.0 Hz, 1 H), 8.42 (s, 1 H), 8.20 – 8.12 (m, 1 H), 6.92 (t, *J* = 51.6 Hz, 1 H), 5.29 (s, 2 H), 3.19 – 3.08 (m, 2 H), 1.98 – 1.85 (m, 2 H), 1.09 (t, *J* = 7.6 Hz, 3 H). LCMS R_T = 1.560 min, *m/z* = 441.2	0.0429
I-114	 N-phenyl-N-({5-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)methanesulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1 H), 7.48 – 7.38 (m, 5 H), 5.28 (s, 2 H), 3.06 (s, 3 H). LCMS R_T = 2.568 min, *m/z* = 404.8	0.354

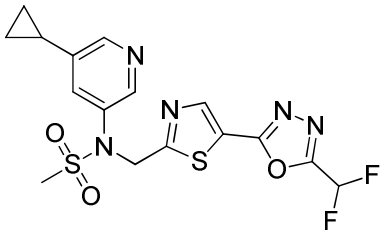
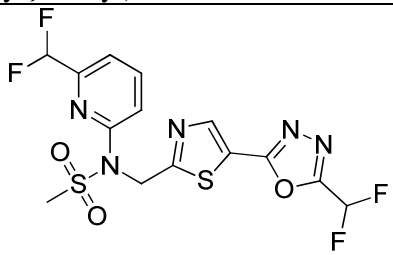
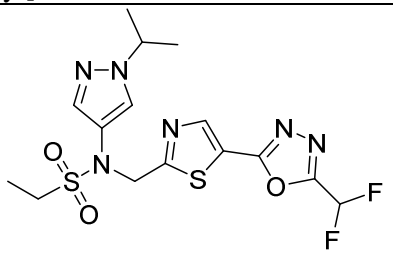
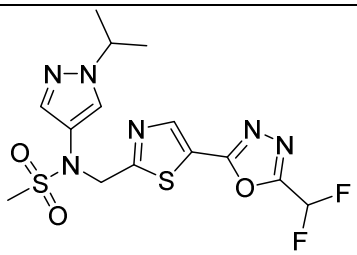
I-115	 N-(5-fluoropyridin-3-yl)-N-({5-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)ethane-1-sulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1 H), 8.47 (d, *J* = 2.4 Hz, 1 H), 8.42 (s, 1 H), 7.68 – 7.63 (m, 1 H), 5.31 (s, 2 H), 3.22 (q, *J* = 7.2 Hz, 2 H), 1.46 (t, *J* = 7.2 Hz, 3 H). LCMS R_T = 0.904 min, *m/z* = 437.9	0.022
I-116	 N-[6-(1,1-difluoroethyl)pyridin-3-yl]-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)ethane-1-sulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, *J* = 2.4 Hz, 1 H), 8.39 (s, 1 H), 7.98 – 7.92 (m, 1 H), 7.70 (d, *J* = 8.4 Hz, 1 H), 6.91 (t, *J* = 51.6 Hz, 1 H), 5.32 (s, 2 H), 3.22 (q, *J* = 7.6 Hz, 2 H), 2.01 (t, *J* = 18.8 Hz, 3 H), 1.46 (t, *J* = 7.6 Hz, 3 H). LCMS R_T = 0.908 min, *m/z* = 465.9	0.0514
I-117	 N-(5-chloropyridin-3-yl)-N-({5-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)ethane-1-sulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 2.4 Hz, 1 H), 8.55 (d, *J* = 2.4 Hz, 1 H), 8.42 (s, 1 H), 7.88 (t, *J* = 2.0 Hz, 1 H), 5.29 (s, 2 H), 3.21 (q, *J* = 4.0 Hz, 2 H), 1.46 (t, *J* = 8.0 Hz, 3 H). LCMS R_T = 2.591 min, *m/z* = 453.8	0.0245
I-118	 N-(pyrazin-2-yl)-N-({5-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)ethane-1-sulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1 H), 8.44 – 8.37 (m, 3 H), 5.58 (s, 2 H), 3.41 (d, *J* = 6.8 Hz, 2 H), 1.43 (t, *J* = 6.8 Hz, 3 H). LCMS R_T = 0.895 min, *m/z* = 420.9	0.0278

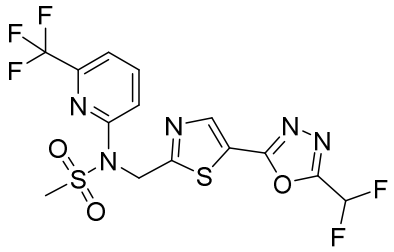
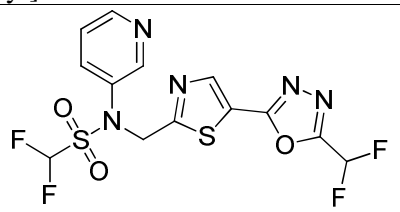
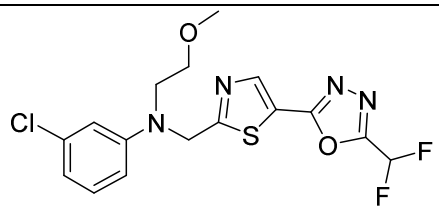
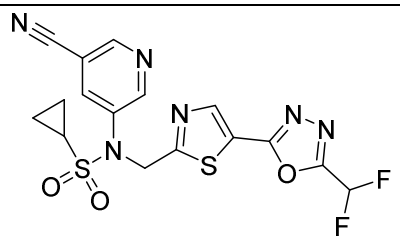
I-119	 N-(pyridin-3-yl)-N-({5-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)ethane-1-sulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1 H), 8.62 – 8.60 (m, 1 H), 8.41 (s, 1 H), 7.86 (d, *J* = 8.0 Hz, 1 H), 7.40 – 7.35 (m, 1 H), 5.32 (s, 2 H), 3.22 (q, *J* = 6.8 Hz, 2 H), 1.48 (t, *J* = 7.2 Hz, 3 H). LCMS R_T = 1.897 min, *m/z* = 420.1	0.042
I-120	 N-(5-cyanopyridin-3-yl)-N-({5-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)methanesulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (d, *J* = 2.8 Hz, 1 H), 8.85 (s, 1 H), 8.46 (s, 1 H), 8.20 (t, *J* = 2.0 Hz, 1 H), 5.30 (s, 2 H), 3.11 (s, 3 H). LCMS R_T = 2.105 min, *m/z* = 431.1	0.111
I-121	 N-(3-fluorophenyl)-N-({5-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)ethane-1-sulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1 H), 7.41 – 7.36 (m, 1 H), 7.28 (s, 1 H), 7.25 – 7.22 (m, 1 H), 7.09 – 7.04 (m, 1 H), 5.30 (s, 2 H), 3.19 (q, *J* = 7.6 Hz, 2 H), 1.45 (t, *J* = 7.2 Hz, 3 H). LCMS R_T = 1.978 min, *m/z* = 437.1	0.0839
I-122	 N-phenyl-N-({5-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)ethane-1-sulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1 H), 7.50 – 7.30 (m, 5 H), 5.31 (s, 2 H), 3.17 (q, *J* = 7.2 Hz, 2 H), 1.45 (t, *J* = 7.2 Hz, 3 H). LCMS R_T = 0.973 min, *m/z* = 419.0	0.0249
I-123		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1 H), 7.57 (s, 1 H), 7.48 (s, 1 H), 6.91 (t, *J* = 51.6 Hz, 1 H), 5.14 (s, 2 H), 3.88 (s, 3 H), 3.03 (s, 3 H).	0.0388

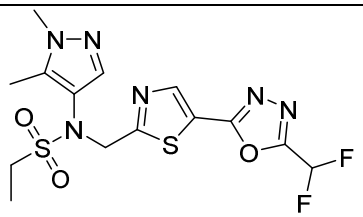
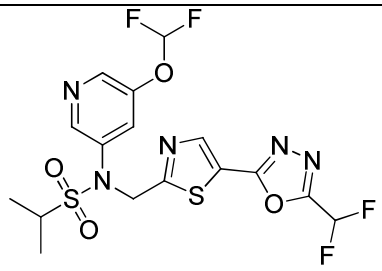
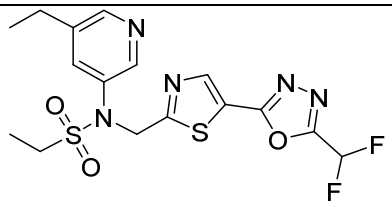
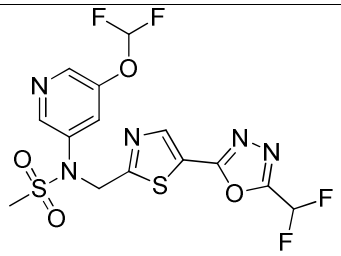
	N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(1-methyl-1H-pyrazol-4-yl)methanesulfonamide	LCMS R_T = 1.057 min, *m/z* = 390.9	
I-124	 5-[({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)(methyl)amino]pyridine-3-carbonitrile	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1 H), 8.41 (s, 1 H), 8.33 (s, 1 H), 7.25 (s, 1 H), 6.90 (t, *J* = 51.6 Hz, 1 H), 4.92 (s, 2 H), 3.27 (s, 3 H). LCMS R_T = 0.971 min, *m/z* = 349.0	0.0636
I-125	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(pyridin-3-yl)propane-1-sulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, *J* = 2.4 Hz, 1 H), 8.60 – 8.56 (m, 1 H), 8.38 (s, 1 H), 7.85 – 7.82 (m, 1 H), 7.39 – 7.32 (m, 1 H), 6.91 (t, *J* = 51.6 Hz, 1 H), 5.29 (s, 2 H), 3.18 – 3.11 (m, 2 H), 1.98 – 1.89 (m, 2 H), 1.09 (t, *J* = 7.2 Hz, 3 H). LCMS R_T = 0.776 min, *m/z* = 416.1	0.0599
I-126	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-{1-[2-(trifluoromethoxy)ethyl]-1H-pyrazol-4-yl}ethane-1-sulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1 H), 7.64 (s, 1 H), 7.57 (s, 1 H), 6.91 (t, *J* = 51.6 Hz, 1 H), 5.16 (s, 2 H), 4.36 – 4.33 (m, 2 H), 4.30 – 4.23 (m, 2 H), 3.15 (q, *J* = 7.6 Hz, 2 H), 1.40 (t, *J* = 7.2 Hz, 3 H). LCMS R_T = 1.043 min, *m/z* = 502.9	0.134
I-127	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1 H), 8.29 (d, *J* = 3.2 Hz, 1 H), 7.67 – 7.61 (m, 1 H), 7.53 – 7.46 (m, 1 H), 6.90 (t, *J* = 51.6 Hz, 1 H), 5.50 (s, 2 H), 3.10 (s, 3 H). LCMS R_T = 0.854 min, *m/z* = 406.1	0.0215

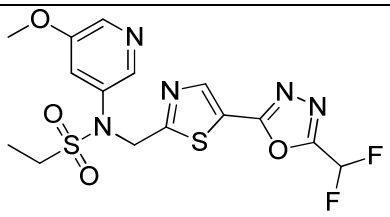
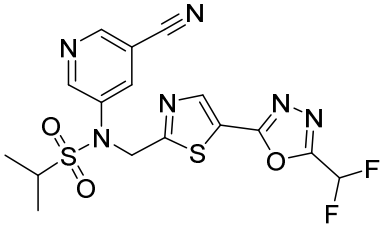
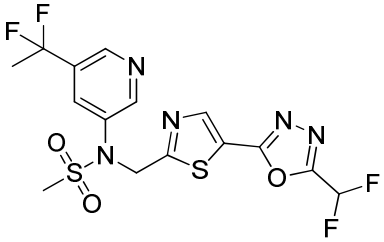
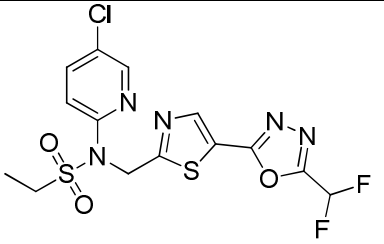
	yl}methyl)-N-(5-fluoropyridin-2-yl)methanesulfonamide		
I-128	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-1,1-difluoro-N-(1-propyl-1H-pyrazol-4-yl)methanesulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1 H), 7.49 (d, *J* = 4.4 Hz, 2 H), 6.92 (t, *J* = 51.6 Hz, 1 H), 6.44 (t, *J* = 53.2 Hz, 1 H), 5.21 (s, 2 H), 4.02 (t, *J* = 7.2 Hz, 2 H), 1.94 – 1.78 (m, 2 H), 0.88 (t, *J* = 7.6 Hz, 3 H). LCMS R_T = 0.901 min, *m/z* = 455.1	0.251
I-129	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(1-propyl-1H-pyrazol-4-yl)methanesulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1 H), 7.58 (s, 1 H), 7.49 (s, 1 H), 6.91 (t, *J* = 51.6 Hz, 1 H), 5.14 (s, 2 H), 4.03 (t, *J* = 7.2 Hz, 2 H), 3.03 (s, 3 H), 1.92 – 1.81 (m, 2 H), 0.90 (t, *J* = 7.2 Hz, 3 H). LCMS R_T = 0.795 min, *m/z* = 418.9	0.118
I-130	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(1-methyl-1H-pyrazol-4-yl)cyclopropanesulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1 H), 7.56 (s, 1 H), 7.52 (s, 1 H), 6.91 (t, *J* = 51.6 Hz, 1 H), 5.15 (s, 2 H), 3.87 (s, 3 H), 2.58 – 2.50 (m, 1 H), 1.20 – 1.15 (m, 2 H), 1.07 – 1.01 (m, 2 H). LCMS R_T = 1.320 min, *m/z* = 416.8	0.0348
I-131	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(5-methylpyridin-3-yl)ethane-1-sulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 2.4 Hz, 1 H), 8.41 (s, 1 H), 8.38 (s, 1 H), 7.65 (s, 1 H), 6.91 (t, *J* = 51.6 Hz, 1 H), 5.29 (s, 2 H), 3.20 (q, *J* = 7.6 Hz, 2 H), 2.37 (s, 3 H), 1.47 (t, *J* = 7.6 Hz, 3 H). LCMS R_T = 0.714 min, *m/z* = 416.2	0.013

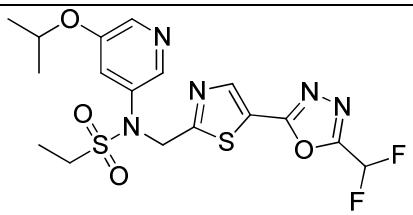
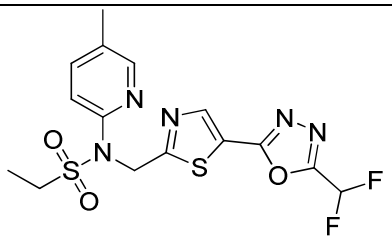
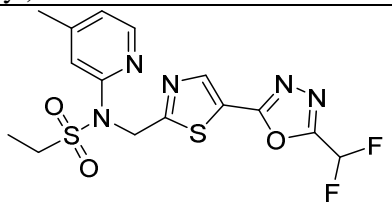
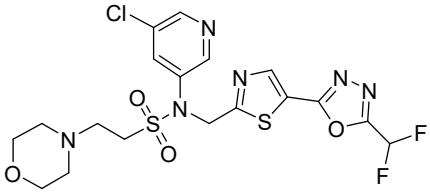
I-132	 N-[5-(2,2-difluoroethoxy)pyridin-3-yl]-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)ethane-1-sulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 2 H), 8.32 (d, *J* = 2.4 Hz, 1 H), 7.45 (t, *J* = 2.4 Hz, 1 H), 6.91 (t, *J* = 51.6 Hz, 1 H), 6.25 – 5.96 (m, 1 H), 5.30 (s, 2 H), 4.30 – 4.20 (m, 2 H), 3.21 (q, *J* = 7.2 Hz, 2 H), 1.46 (t, *J* = 7.6 Hz, 3 H). LCMS R_T = 0.857 min, *m/z* = 482.2	0.00964
I-133	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-1,1-difluoro-N-(5-fluoropyridin-2-yl)methanesulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1 H), 8.30 (d, *J* = 2.8 Hz, 1 H), 7.58 – 7.55 (m, 1 H), 7.54 – 7.48 (m, 1 H), 7.03 (t, *J* = 51.6 Hz, 1 H), 6.33 (t, *J* = 53.6 Hz, 1 H), 5.55 (s, 2 H). LCMS R_T = 0.954 min, *m/z* = 441.9	0.0857
I-134	 N-[1-(1-cyano-1-methylethyl)-1H-pyrazol-4-yl]-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)ethane-1-sulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1 H), 7.83 (s, 1 H), 7.63 (s, 1 H), 6.91 (t, *J* = 51.6 Hz, 1 H), 5.17 (s, 2 H), 3.17 (q, *J* = 7.2 Hz, 2 H), 1.99 (s, 6 H), 1.42 (t, *J* = 7.2 Hz, 3 H). LCMS R_T = 1.012 min, *m/z* = 458.1	0.121
I-135	 3-chloro-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-ethylaniline	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1 H), 7.14 (t, *J* = 8.0 Hz, 1 H), 6.88 (t, *J* = 51.6 Hz, 1 H), 6.76 – 6.74 (m, 2 H), 6.64 – 6.60 (m, 1 H), 4.79 (s, 2 H), 3.58 (q, *J* = 7.2 Hz, 2 H), 1.30 (t, *J* = 7.2 Hz, 3 H).	0.0531

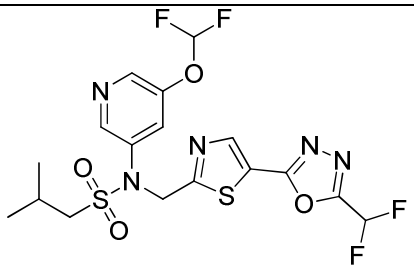
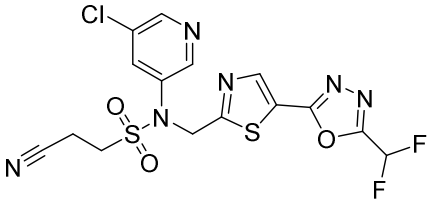
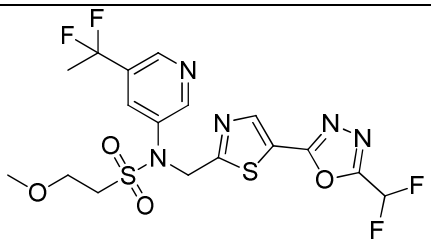
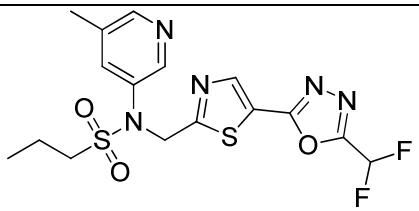
		LCMS R_T = 1.098 min, *m/z* = 370.9	
I-136	 N-(5-cyclopropylpyridin-3-yl)-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)methanesulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1 H), 8.41 (s, 1 H), 8.37 (s, 1 H), 7.46 (s, 1 H), 6.91 (t, *J* = 51.6 Hz, 1 H), 5.25 (s, 2 H), 3.09 (s, 3 H), 1.96 – 1.89 (m, 1 H), 1.14 – 1.06 (m, 2 H), 0.79 – 0.71 (m, 2 H). LCMS R_T = 0.743 min, *m/z* = 427.9	0.013
I-137	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-[6-(difluoromethyl)pyridin-2-yl]methanesulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1 H), 7.90 (t, *J* = 8.0 Hz, 1 H), 7.77 (d, *J* = 8.4 Hz, 1 H), 7.48 (d, *J* = 7.6 Hz, 1 H), 6.89 (t, *J* = 51.6 Hz, 1 H), 6.54 (t, *J* = 55.2 Hz, 1 H), 5.59 (s, 2 H), 3.23 (s, 3 H). LCMS R_T = 0.899 min, *m/z* = 437.9	0.0107
I-138	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-[1-(propan-2-yl)-1H-pyrazol-4-yl]ethane-1-sulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1 H), 7.57 (s, 1 H), 7.46 (s, 1 H), 6.87 (t, *J* = 51.2 Hz, 1 H), 5.12 (s, 2 H), 4.44 – 4.34 (m, 1 H), 3.13 (q, *J* = 7.2 Hz, 2 H), 1.45 (d, *J* = 6.8 Hz, 6 H), 1.39 (t, *J* = 7.2 Hz, 3 H). LCMS R_T = 1.141 min, *m/z* = 433.2	0.043
I-139	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-[1-(propan-2-yl)-	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1 H), 7.58 (s, 1 H), 7.46 (s, 1 H), 6.88 (t, *J* = 51.6 Hz, 1 H), 5.11 (s, 2 H), 4.45 – 4.35 (m, 1 H), 3.00 (s, 3 H), 1.46 (d, *J* = 6.8 Hz, 6 H). LCMS R_T = 0.997 min, *m/z* = 419.2	0.118

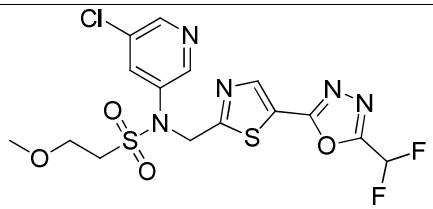
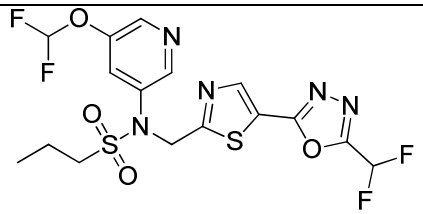
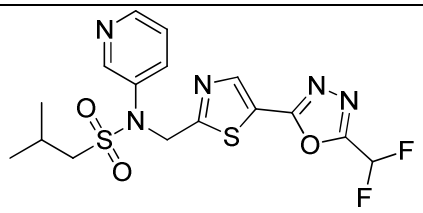
	1H-pyrazol-4-yl]methanesulfonamide		
I-140	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-[6-(trifluoromethyl)pyridin-2-yl]methanesulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1 H), 7.95 – 7.85 (m, 2 H), 7.51 (d, *J* = 7.2 Hz, 1 H), 6.90 (t, *J* = 51.6 Hz, 1 H), 5.61 (s, 2 H), 3.29 (s, 3 H). LCMS R_T = 1.112 min, *m/z* = 455.8	0.0576
I-141	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-1,1-difluoro-N-(pyridin-3-yl)methanesulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 – 8.60 (m, 2 H), 8.39 (s, 1 H), 7.75 (d, *J* = 6.8 Hz, 1 H), 7.39 – 7.36 (m, 1 H), 6.92 (t, *J* = 51.6 Hz, 1 H), 6.49 (t, *J* = 53.2 Hz, 1 H), 5.35 (s, 2 H). LCMS R_T = 0.965 min, *m/z* = 423.8	0.0655
I-142	 3-chloro-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(2-methoxyethyl)aniline	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1 H), 7.13 (t, *J* = 8.0 Hz, 1 H), 6.88 (t, *J* = 89.2 Hz, 1 H), 6.80 – 6.70 (m, 2 H), 6.68 – 6.55 (m, 1H), 4.94 (s, 2 H), 3.74 – 3.71 (m, 2 H), 3.70 – 3.65 (m, 2 H), 3.38 (s, 3 H). LCMS R_T = 1.055 min, *m/z* = 400.9	0.0245
I-143	 N-(5-cyanopyridin-3-yl)-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)cyclopropanesulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (d, *J* = 2.0 Hz, 1 H), 8.83 (s, 1 H), 8.41 (s, 1 H), 8.18 (t, *J* = 2.0 Hz, 1 H), 6.92 (t, *J* = 51.6 Hz, 1H), 5.31 (s, 2 H), 2.59 – 2.50 (m, 1 H), 1.13 – 1.08 (m, 4 H). LCMS R_T = 0.834 min, *m/z* = 439.1	0.0153

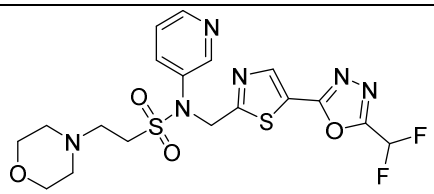
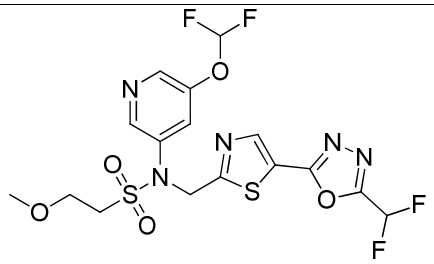
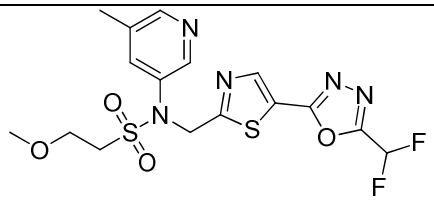
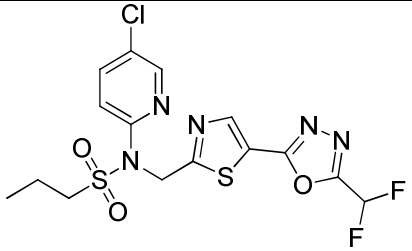
I-144	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(1,5-dimethyl-1H-pyrazol-4-yl)ethane-1-sulfonamide	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1 H), 7.38 (s, 1 H), 6.91 (t, *J* = 51.6 Hz, 1 H), 5.11 (s, 2 H), 3.76 (s, 3 H), 3.20 (q, *J* = 7.2 Hz, 2 H), 2.25 (s, 3 H), 1.47 (t, *J* = 7.4 Hz, 3 H). LCMS R_T = 0.751 min, *m/z* = 419.0	0.102
I-145	 N-[5-(difluoromethoxy)pyridin-3-yl]-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)propane-2-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.61 (d, J = 2.0 Hz, 1 H), 8.45 (d, J = 2.4 Hz, 1 H), 8.38 (s, 1 H), 7.68 (t, J = 2.0 Hz, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 6.58 (t, J = 72.0 Hz, 1 H), 5.31 (s, 2 H), 3.40 – 3.29 (m, 1 H), 1.45 (d, J = 6.8 Hz, 6 H). LCMS RT = 1.625 min, m/z = 482.2	0.0102
I-146	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(5-ethylpyridin-3-yl)ethane-1-sulfonamide	1H NMR (400 MHz, CD3OD) δ 8.59 (s, 1 H), 8.40 (s, 2 H), 8.02 (s, 1 H), 7.19 (t, J = 51.2 Hz, 1 H), 5.40 (s, 2 H), 3.40 – 3.30 (m, 2 H), 2.73 (q, J = 7.6 Hz, 2 H), 1.39 (t, J = 7.6 Hz, 3 H), 1.25 (t, J = 7.6 Hz, 3 H). LCMS RT = 1.215 min, m/z = 430.2	0.0162
I-147	 N-[5-(difluoromethoxy)pyridin-3-yl]-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)methanesulfonamide	1H NMR (400 MHz, CDCl3) δ 8.62 (s, 1 H), 8.49 (s, 1 H), 8.43 (s, 1 H), 7.69 (s, 1 H), 6.92 (t, J = 51.6 Hz, 1 H), 6.59 (t, J = 72.0 Hz, 1 H), 5.28 (s, 2 H), 3.12 (s, 3 H). LCMS RT = 1.512 min, m/z = 453.8	0.019

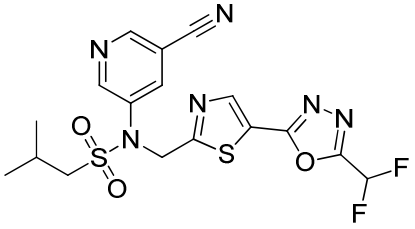
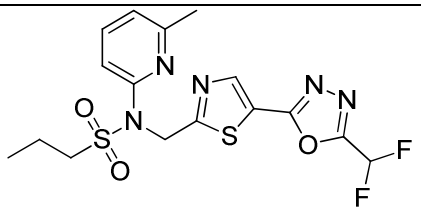
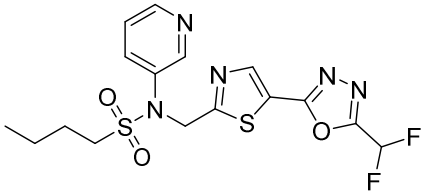
I-148	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(5-methoxypyridin-3-yl)ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.39 (s, 1 H), 8.30 – 8.28 (m, 2 H), 7.38 (s, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.30 (s, 2 H), 3.87 (s, 3 H), 3.21 (q, J = 7.6 Hz, 2 H), 1.46 (t, J = 7.6 Hz, 3 H). LCMS RT = 1.360 min, m/z = 431.9 [M + H]+	0.0192
I-149	 N-(5-cyanopyridin-3-yl)-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)propane-2-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.95 (d, J = 2.8 Hz, 1 H), 8.80 (s, 1 H), 8.39 (s, 1 H), 8.16 (s, 1 H), 6.92 (t, J = 51.6 Hz, 1 H), 5.30 (s, 2 H), 3.39 – 3.25 (m, 1 H), 1.45 (d, J = 6.8 Hz, 6 H). LCMS RT = 1.584 min, m/z = 440.9	0.0231
I-150	 N-[5-(1,1-difluoroethyl)pyridin-3-yl]-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)methanesulfonamide	1H NMR (400 MHz, CDCl3) δ 8.80 (s, 1 H), 8.75 (s, 1 H), 8.43 (s, 1 H), 7.98 (s, 1 H), 6.92 (t, J = 51.6 Hz, 1 H), 5.29 (s, 2 H), 3.12 (s, 3 H), 1.98 (t, J = 18.0 Hz, 3 H). LCMS RT = 1.554 min, m/z = 451.8	0.0255
I-151	 N-(5-chloropyridin-2-yl)-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.37 (d, J = 4.0 Hz, 2 H), 7.74 – 7.67 (m, 2 H), 6.90 (t, J = 51.6 Hz, 1 H), 5.56 (s, 2 H), 3.29 (q, J = 7.2 Hz, 2 H), 1.39 (t, J = 7.2 Hz, 3 H). LCMS RT = 1.826 min, m/z = 436.1	0.0315

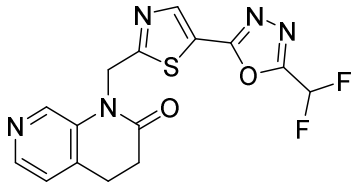
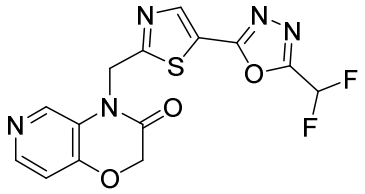
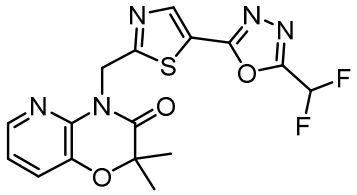
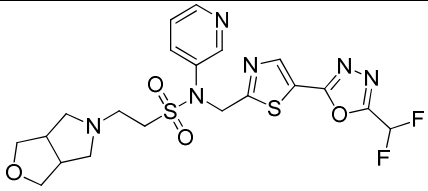
I-152	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-[5-(propan-2-yloxy)pyridin-3-yl]ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.39 (s, 1 H), 8.25 (s, 2 H), 7.35 (s, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.29 (s, 2 H), 4.61 – 4.55 (m, 1 H), 3.25 – 3.18 (m, 2 H), 1.61 (s, 3 H), 1.36 (d, J = 4.4 Hz, 6 H). LCMS RT = 1.666 min, m/z = 459.9	0.0429
I-153	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(5-methylpyridin-2-yl)ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.22 (s, 1 H), 8.10 (s, 1 H), 7.40 (s, 2 H), 6.75 (t, J = 51.6 Hz, 1 H), 5.42 (s, 2 H), 3.09 (q, J = 7.6 Hz, 2 H), 2.18 (s, 3 H), 1.23 (t, J = 7.2 Hz, 3 H). LCMS RT = 1.666 min, m/z = 416.2	0.043
I-155	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(4-methylpyridin-2-yl)ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.39 (s, 1 H), 8.29 (d, *J* = 4.8 Hz, 1 H), 7.47 (s, 1 H), 7.01 (d, *J* = 4.8 Hz, 1 H), 6.90 (t, *J* = 51.6 Hz, 1 H), 5.60 (s, 2 H), 3.28 (q, *J* = 7.6 Hz, 2 H), 2.40 (s, 3 H), 1.39 (t, *J* = 7.2 Hz, 3 H). LCMS RT = 1.635 min, *m/z* = 416.2	0.0528
I-156	 N-(5-chloropyridin-3-yl)-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-2-(morpholin-4-yl)ethane-1-sulfonamide	1H NMR (400 MHz, CD3OD) δ ppm 8.68 (d, J = 2.4 Hz, 1 H), 8.52 (d, J = 2.0 Hz, 1 H), 8.44 (s, 1 H), 8.17 (t, J = 2.0 Hz, 1 H), 7.22 (t, J = 52.0 Hz, 1 H), 5.45 (s, 2 H), 3.73 – 3.70 (m, 4 H), 3.58 (t, J = 7.6 Hz, 2 H), 2.89 (t, J = 6.8 Hz, 2 H), 2.58 – 2.51 (m, 4 H). LCMS RT = 0.992 min, m/z = 521.2	0.00253

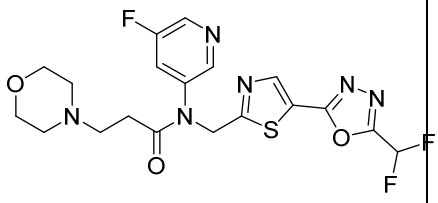
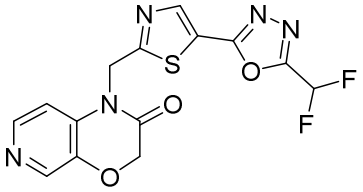
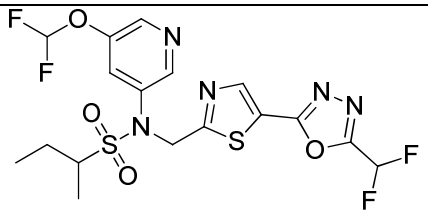
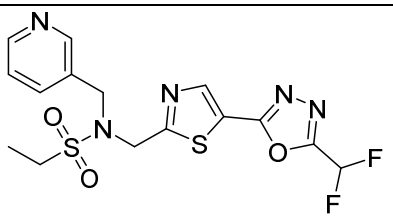
I-157	 N-[5-(difluoromethoxy)pyridin-3-yl]-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-2-methylpropane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.59 (d, J = 2.0 Hz, 1 H), 8.47 (d, J = 2.0 Hz, 1 H), 8.40 (s, 1 H), 7.67 (t, J = 2.4 Hz, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 6.59 (t, J = 72.0 Hz, 1 H), 5.28 (s, 2 H), 3.05 (d, J = 8.0 Hz, 2 H), 2.40 – 2.30 (m, 1 H), 1.12 (d, J = 6.8 Hz, 6 H). LCMS RT = 0.644 min, m/z = 496.1	0.00693
I-158	 N-(5-chloropyridin-3-yl)-2-cyano-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.63 (d, J = 2.4 Hz, 1 H), 8.60 (d, J = 2.0 Hz, 1 H), 8.46 (s, 1 H), 7.91 (t, J = 2.4 Hz, 1 H), 6.93 (t, J = 51.6 Hz, 1 H), 5.30 (s, 2 H), 3.54 (t, J = 7.2 Hz, 2 H), 2.98 (t, J = 7.2 Hz, 2 H). LCMS RT = 0.576 min, m/z = 461.1	0.00722
I-159	 N-[5-(1,1-difluoroethyl)pyridin-3-yl]-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-2-methoxyethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.85 (s, 1 H), 8.56 (s, 1 H), 8.72 (s, 1 H), 8.35 (s, 1 H), 8.01 (s, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.26 (s, 2 H), 3.87 (t, J = 5.2 Hz, 2 H), 3.50 (s, 3 H), 3.36 (t, J = 5.2 Hz, 2 H), 1.97 (t, J = 18.4 Hz, 3 H). LCMS RT = 1.701 min, m/z = 495.9	0.00994
I-160	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(5-methylpyridin-3-yl)propane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.49 (d, J = 2.4 Hz, 1 H), 8.41 (s, 1 H), 8.38 (s, 1 H), 7.65 (s, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.27 (s, 2 H), 3.16 – 3.08 (m, 2 H), 2.37 (s, 3 H), 1.99 – 1.85 (m, 2 H), 1.09 (t, J = 7.2 Hz, 3 H). LCMS RT = 1.815 min, m/z = 430.2	0.0109

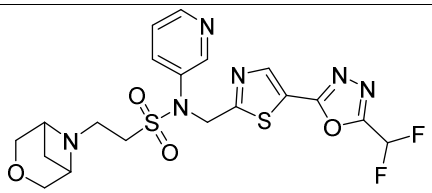
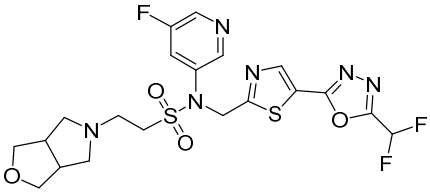
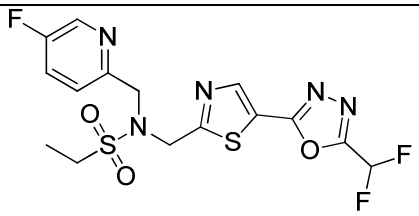
I-161	 N-(5-chloropyridin-3-yl)-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-2-methoxyethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.67 (s, 1 H), 8.53 (s, 1 H), 8.35 (s, 1 H), 7.90 (t, J = 2.0 Hz, 1 H), 6.90 (t, J = 51.6 Hz, 1 H), 5.22 (s, 2 H), 3.86 (t, J = 5.6 Hz, 2 H), 3.49 (s, 3 H), 3.36 (t, J = 5.6 Hz, 2 H). LCMS RT = 1.529 min, m/z = 466.1	0.012
I-162	 N-[5-(difluoromethoxy)pyridin-3-yl]-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)propane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.60 (s, 1 H), 8.47 (s, 1 H), 8.40 (s, 1 H), 7.67 (s, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 6.59 (t, J = 72.0 Hz, 1 H), 5.29 (s, 2 H), 3.19 – 3.11 (m, 2 H), 1.99 – 1.86 (m, 2 H), 1.09 (t, J = 7.2 Hz, 3 H). LCMS RT = 1.794 min, m/z = 481.9	0.0144
I-163	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-2-methyl-N-(pyridin-3-yl)propane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.70 (d, J = 2.4 Hz, 1 H), 8.60 – 8.55 (m, 1 H), 8.41 (s, 1 H), 8.07 – 8.01 (m, 1 H), 7.53 – 7.47 (m, 1 H) , 7.20 (t, J = 51.6 Hz, 1 H), 5.37 (s, 2 H), 3.20 (d, J = 6.4 Hz, 2 H), 2.34 – 2.22 (m, 1 H), 1.10 (d, J = 6.4 Hz, 6 H). LCMS RT = 1.423 min, m/z = 430.2	0.0161

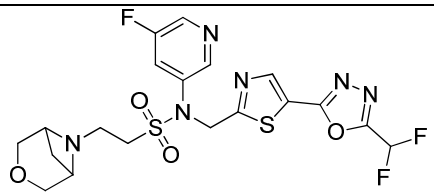
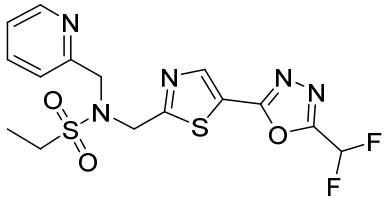
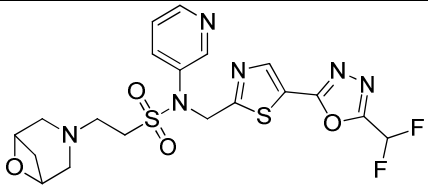
I-164	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-2-(morpholin-4-yl)-N-(pyridin-3-yl)ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.73 (d, J = 2.4 Hz, 1 H), 8.60 – 8.55 (m, 1 H), 8.38 (s, 1 H), 7.87 – 7.81 (m, 1 H), 7.38 – 7.33 (m, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.32 (s, 2 H), 3.76 – 3.72 (m, 4 H), 3.37 (t, J = 7.2 Hz, 2 H), 2.90 (t, J = 6.8 Hz, 2 H), 2.52 – 2.50 (m, 4 H). LCMS RT = 0.430 min, m/z = 487.2	0.0173
I-165	 N-[5-(difluoromethoxy)pyridin-3-yl]-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-2-methoxyethane-1-sulfonamide	1H NMR (400 MHz, CD3OD) δ 8.59 (s, 1 H), 8.40 (s, 2 H), 7.87 (d, J = 2.4 Hz, 1 H), 7.19 (t, J = 51.6 Hz, 1 H), 6.97 (t, J = 72.8 Hz, 1 H), 5.34 (s, 2 H), 3.83 (t, J = 5.2 Hz, 2 H), 3.52 (t, J = 5.6 Hz, 2 H), 3.30 (t, J = 1.6 Hz, 3 H). LCMS RT = 1.533 min, m/z = 498.2	0.0196
I-166	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-2-methoxy-N-(5-methylpyridin-3-yl)ethane-1-sulfonamide	1H NMR (400 MHz, CD3OD) δ 8.49 (s, 1 H), 8.39 (s, 1 H), 8.34 (s, 1 H), 7.87 (s, 1 H), 7.20 (t, J = 51.6 Hz, 1 H), 5.31 (s, 2 H), 3.83 (t, J = 5.2 Hz, 2 H), 3.49 (t, J = 5.6 Hz, 2 H), 3.43 (s, 3 H), 2.38 (s, 3 H). LCMS RT = 2.329 min, m/z = 446.5	0.0266
I-167	 N-(5-chloropyridin-2-yl)-N-({5-[5-(difluoromethyl)-1,3,4-	1H NMR (400 MHz, CDCl3) δ 8.40 – 8.35 (m, 2 H), 7.73 – 7.68 (m, 1 H), 7.66 – 7.60 (m, 1 H), 6.89 (t, J = 51.6 Hz, 1 H), 5.55 (s, 2 H), 3.26 – 3.17 (m, 2 H), 1.93 – 1.81 (m, 2 H), 1.05 (t, J = 7.4 Hz, 3 H).	0.0266

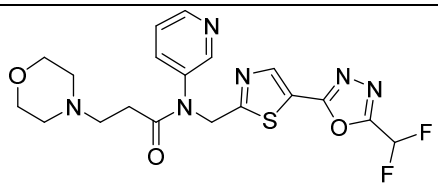
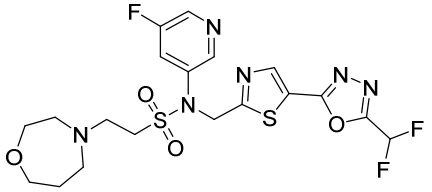
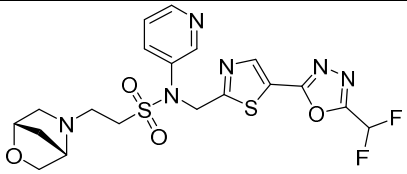
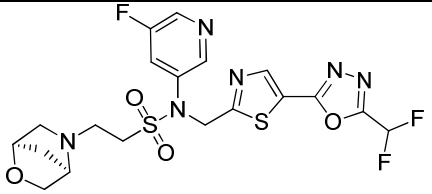
	oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)propane-1-sulfonamide	LCMS RT = 2.072 min, m/z = 449.8	
I-168	 N-(5-cyanopyridin-3-yl)-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-2-methylpropane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.95 (d, J = 2.4 Hz, 1 H), 8.82 (s, 1 H), 8.42 (s, 1 H), 8.16 (s, 1 H), 6.92 (t, J = 52.0 Hz, 1 H), 5.28 (s, 2 H), 3.03 (d, J = 6.4 Hz, 2 H), 2.42 – 2.28 (m, 1 H), 1.12 (d, J = 6.8 Hz, 6 H). LCMS RT = 1.690 min, m/z = 455.2	0.0305
I-169	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(6-methylpyridin-2-yl)propane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.38 (s, 1 H), 7.61 (t, J = 7.6 Hz, 1 H), 7.45 (d, J = 8.4 Hz, 1 H), 7.02 – 6.75 (m, 2 H), 5.59 (s, 2 H), 3.22 – 3.15 (m, 2 H), 2.52 (s, 3 H), 1.93 – 1.80 (m, 2 H), 1.03 (t, J = 7.6 Hz, 3 H). LCMS RT = 1.942 min, m/z = 429.9	0.0309
I-170	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(pyridin-3-yl)butane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.70 (s, 1 H), 8.58 (d, J = 4.8 Hz, 1 H), 8.38 (s, 1 H), 7.90 – 7.80 (m, 1 H), 7.45 – 7.31 (m, 1 H), 6.91 (t, J = 51.2 Hz, 1 H), 5.29 (s, 2 H), 3.21 – 3.06 (m, 2 H), 1.92 – 1.83 (m, 2 H), 1.52 – 1.43 (m, 2 H), 0.96 (t, J = 7.2 Hz, 3 H). LCMS RT = 0.623 min, m/z = 429.9	0.0264

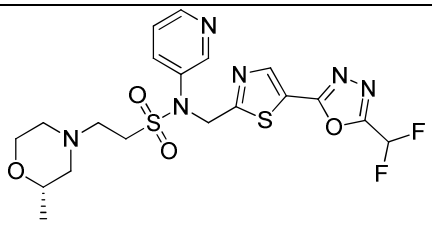
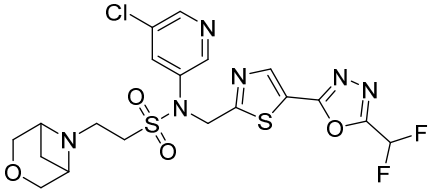
I-171	 1-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-1,2,3,4-tetrahydro-1,7-naphthyridin-2-one	1H NMR (400 MHz, CDCl3) δ 8.55 (s, 1 H), 8.42 (s, 1 H), 8.31 (d, J = 3.6 Hz, 1 H), 7.16 (d, J = 4.4 Hz, 1 H), 6.89 (t, J = 51.6 Hz, 1 H), 5.52 (s, 2 H), 3.04 (t, J = 6.8 Hz, 2 H), 2.81 (t, J = 8.0 Hz, 2 H). LCMS RT = 1.398 min, m/z = 363.9	0.0215
I-172	 4-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-2H,3H,4H-pyrido[4,3-b][1,4]oxazin-3-one	1H NMR (400 MHz, CDCl3) δ 8.52 (s, 1 H), 8.43 (s, 1 H), 8.27 (d, J = 5.6 Hz, 1 H), 6.96 (d, J = 5.2 Hz, 1 H), 6.90 (t, J = 51.6 Hz, 1 H), 5.52 (s, 2 H), 4.85 (s, 2 H). LCMS RT = 0.418 min, m/z = 366.0	0.025
I-173	 4-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-2,2-dimethyl-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one	^{1}H NMR (400MHz, $CDCl_3$) δ 8.39 (s, 1 H), 8.01 – 8.05 (m, 1 H), 7.29 (dd, J = 8.1, 1.5 Hz, 1 H), 7.01 (dd, J = 8.1, 1.5 Hz, 1H), 6.89 (t, J = 51.6 Hz, 1 H), 5.70 (s, 2 H) LCMS: RT= 5.00 min, m/z = 394.0	0.108
I-174	 N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)thiazol-2-yl)methyl)-N-(pyridin-3-yl)-2-(tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-yl)ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.76 (s, 1 H), 8.58 (d, J = 4.4 Hz, 1 H), 8.39 (s, 1 H), 7.89 (d, J = 8.4 Hz, 1 H), 7.40 – 7.35 (m, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.33 (s, 2 H), 3.75 – 3.70 (m, 4 H), 3.49 (t, J = 6.8 Hz, 2 H), 3.07 (t, J = 6.8 Hz, 2 H), 2.99 – 2.96 (m, 4 H), 2.49 (d, J = 6.0 Hz, 2 H). LCMS RT = 1.435 min, m/z = 513.0	0.022

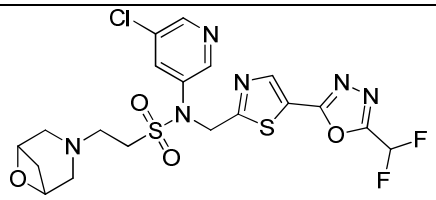
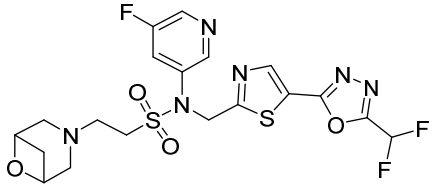
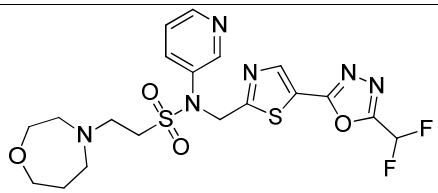
I-175	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(5-fluoropyridin-3-yl)-3-(morpholin-4-yl)propanamide	1H NMR (400 MHz, CDCl3) δ 8.55 (d, J = 2.0 Hz, 1 H), 8.43 – 8.36 (m, 2 H), 7.50 – 7.44 (m, 1 H), 6.92 (t, J = 51.6 Hz, 1 H), 5.20 (s, 2 H), 3.71 – 3.66 (m, 4 H), 2.81 (t, J = 6.8 Hz, 2 H), 2.50 – 2.22 (m, 6 H). LCMS RT = 0.400 min, m/z = 469.2	0.496
I-176	 1-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-1H,2H,3H-pyrido[3,4-b][1,4]oxazin-2-one	1H NMR (400 MHz, CD3OD) δ 8.54 – 8.53 (m, 1 H), 8.13 – 8.10 (m, 1 H), 7.22 (t, J = 51.6 Hz, 1 H), 6.97 – 6.89 (m, 1 H), 5.84 – 5.78 (m, 1 H), 4.72 – 4.45 (m, 4 H). LCMS RT = 1.091 min, m/z = 365.8	2.52
I-177	 N-[5-(difluoromethoxy)pyridin-3-yl]-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)butane-2-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.59 (d, J = 2.0 Hz, 1 H), 8.45 (d, J = 2.4 Hz, 1 H), 8.37 (s, 1 H), 7.67 (t, J = 2.4 Hz, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 6.58 (t, J = 72.0 Hz, 1 H), 5.38 – 5.20 (m, 2 H), 3.15 – 3.07 (m, 1 H), 2.13 – 2.02 (m, 1 H), 1.73 – 1.60 (m, 1 H), 1.43 (d, J = 6.8 Hz, 3 H), 1.05 (t, J = 7.2 Hz, 3 H). LCMS RT = 1.580 min, m/z = 496.2	0.006
I-178	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-[(pyridin-3-yl)methyl]ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.62 – 8.55 (m, 2 H), 8.42 (s, 1 H), 7.88 – 7.82 (m, 1 H), 7.38 – 7.34 (m, 1 H), 6.88 (t, J = 51.6 Hz, 1 H), 4.71 (s, 2 H), 4.60 (s, 2 H), 3.19 (q, J = 7.6 Hz, 2 H), 1.44 (t, J = 7.2 Hz, 3 H). LCMS RT = 1.031 min, m/z = 416.2	4.35

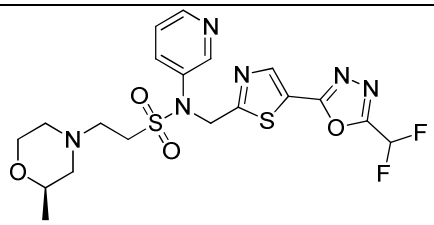
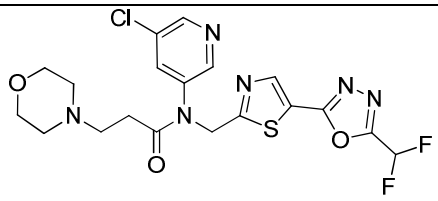
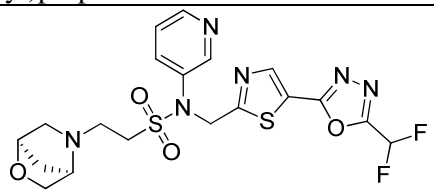
I-179	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-2-{3-oxa-6-azabicyclo[3.1.1]heptan-6-yl}-N-(pyridin-3-yl)ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.76 (d, J = 2.4 Hz, 1 H), 8.58 (d, J = 3.2 Hz, 1 H), 8.38 (s, 1 H), 7.89 – 7.86 (m, 1 H), 7.39 – 7.35 (m, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.34 (s, 2 H), 4.22 (d, J = 11.2 Hz, 2 H), 3.81 (d, J = 11.6 Hz, 2 H), 3.64 (d, J = 6.4 Hz, 2 H), 3.36 – 3.20 (m, 4 H), 2.74 – 2.69 (m, 1 H), 1.91 (d, J = 8.8 Hz, 1 H). LCMS RT = 1.438 min, m/z = 499.0	0.013
I-180	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(5-fluoropyridin-3-yl)-2-{hexahydro-1H-furo[3,4-c]pyrrol-5-yl}ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.62 (s, 1 H), 8.45 (d, J = 2.4 Hz, 1 H), 8.38 (s, 1 H), 7.75 – 7.70 (m, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.35 (s, 2 H), 3.78 – 3.69 (m, 4 H), 3.34 (t, J = 6.8 Hz, 2 H), 2.94 (t, J = 6.4 Hz, 2 H), 2.87 – 2.86 (m, 2 H), 2.72 – 2.68 (m, 2 H), 2.49 – 2.46 (m, 2 H). LCMS RT = 0.417 min, m/z = 531.2	0.010
I-181	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-[(5-fluoropyridin-2-yl)methyl]ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.44 (t, J = 2.0 Hz, 1 H), 8.41 (s, 1 H), 7.44 (d, J = 2.4 Hz, 1 H), 7.42 (s, 1 H), 6.92 (t, J = 51.6 Hz, 1 H), 4.86 (s, 2 H), 4.65 (s, 2 H), 3.23 (q, J = 7.2 Hz, 2 H), 1.42 (t, J = 7.2 Hz, 3 H). LCMS RT = 1.338 min, m/z = 434.2	3.46

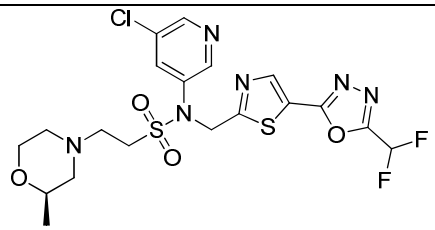
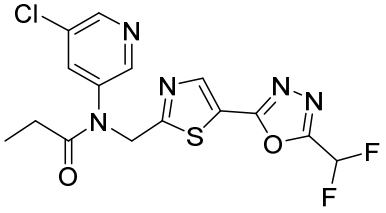
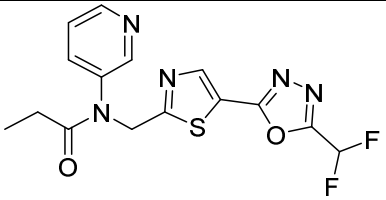
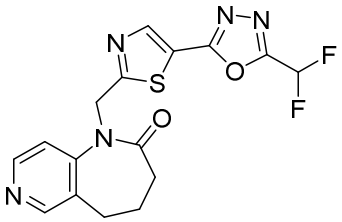
I-182	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(5-fluoropyridin-3-yl)-2-{3-oxa-6-azabicyclo[3.1.1]heptan-6-yl}ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.61 (s, 1 H), 8.46 (d, J = 2.4 Hz, 1 H), 8.39 (s, 1 H), 7.72 – 7.65 (m, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.35 (s, 2 H), 4.19 (d, J = 11.2 Hz, 2 H), 3.78 (d, J = 11.2 Hz, 2 H), 3.56 (d, J = 6.4 Hz, 2 H), 3.29 – 3.25 (m, 2 H), 3.21 – 3.18 (m, 2 H), 2.70 – 2.65 (m, 1 H), 1.89 (d, J = 8.4 Hz, 1 H). LCMS RT = 0.844 min, m/z = 517.3	0.018
I-183	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-[(pyridin-2-yl)methyl]ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.59 (d, J = 4.4 Hz, 1 H), 8.40 (s, 1 H), 7.76 – 7.69 (m, 1 H), 7.39 (d, J = 7.6 Hz, 1 H), 7.25 (s, 1 H), 6.92 (t, J = 51.6 Hz, 1 H), 4.89 (s, 2 H), 4.68 (s, 2 H), 3.25 (q, J = 7.2 Hz, 2 H), 1.42 (t, J = 7.2 Hz, 3 H). LCMS RT = 0.932 min, m/z = 416.2	2.54
I-184	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-2-{6-oxa-3-azabicyclo[3.1.1]heptan-3-yl}-N-(pyridin-3-yl)ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.73 (d, J = 2.4 Hz, 1 H), 8.60 (d, J = 3.2 Hz, 1 H), 8.39 (s, 1 H), 7.89 – 7.82 (m, 1 H), 7.40 – 7.33 (m, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.31 (s, 2 H), 4.53 (d, J = 6.4 Hz, 2 H), 3.46 – 3.42 (m, 2 H), 3.21 – 3.02 (m, 5 H), 2.86 (d, J = 11.2 Hz, 2 H), 2.29 (d, J = 8.4 Hz, 1 H). LCMS RT = 1.352 min, m/z = 498.9	0.014

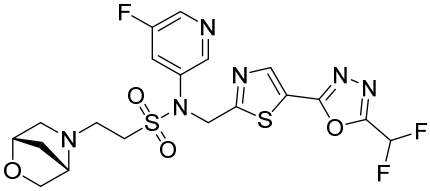
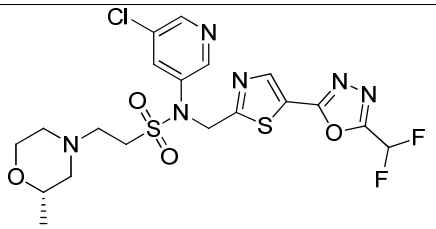
I-185	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-3-(morpholin-4-yl)-N-(pyridin-3-yl)propanamide	1H NMR (400 MHz, CDCl3) δ 8.65 (d, J = 4.4 Hz, 1 H), 8.55 (d, J = 2.4 Hz, 1 H), 8.38 (s, 1 H), 7.63 (d, J = 8.0 Hz, 1 H), 7.43 – 7.39 (m, 1 H), 6.92 (t, J = 51.6 Hz, 1 H), 5.21 (s, 2 H), 3.65 (t, J = 4.4 Hz, 4 H), 2.73 (t, J = 7.2 Hz, 2 H), 2.38 – 2.33 (m, 6 H). LCMS RT = 0.411 min, m/z = 451.2	0.516
I-186	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(5-fluoropyridin-3-yl)-2-(1,4-oxazepan-4-yl)ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.58 (s, 1 H), 8.47 (d, J = 2.4 Hz, 1 H), 8.40 (s, 1 H), 7.70 – 7.67 (m, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.32 (s, 2 H), 3.81 (t, J = 6.4 Hz, 2 H), 3.75 (t, J = 4.8 Hz, 2 H), 3.41 (t, J = 7.2 Hz, 2 H), 3.12 (t, J = 7.6 Hz, 2 H), 2.84 – 2.76 (m, 4 H), 1.97 – 1.92 (m, 2 H). LCMS RT = 0.414 min, m/z = 519.2	0.0276
I-187	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-2-[(1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]-N-(pyridin-3-yl)ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.74 (d, J = 2.4 Hz, 1 H), 8.60 – 8.57 (m, 1 H), 8.38 (s, 1 H), 7.88 – 7.85 (m, 1 H), 7.40 – 7.26 (m, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.37 – 5.25 (m, 2 H), 4.47 (s, 1 H), 4.02 (d, J = 8.4 Hz, 1 H), 3.70 – 3.55 (m, 1 H), 3.58 (s, 1 H), 3.36 (t, J = 6.8 Hz, 2 H), 3.22 – 3.09 (m, 2 H), 3.00 – 2.92 (m, 1 H), 2.60 (d, J = 9.6 Hz, 1 H), 1.86 – 1.80 (m, 2 H). LCMS RT = 0.429 min, m/z = 499.2	0.0247
I-188	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(5-fluoropyridin-3-	1H NMR (400 MHz, CDCl3) δ 8.58 (s, 1 H), 8.47 (d, J = 2.4 Hz, 1 H), 8.39 (s, 1 H), 7.69 – 7.66 (m, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.37 – 5.27 (m, 2 H), 4.47 (s, 1 H), 4.02 (d, J = 8.0 Hz, 1 H), 3.68 (dd, J = 8.4, 1.6 Hz, 1 H), 3.58 (s, 1 H), 3.38 (t, J = 6.8 Hz, 2 H), 3.22 – 3.09 (m, 2 H), 2.98 –	0.0151

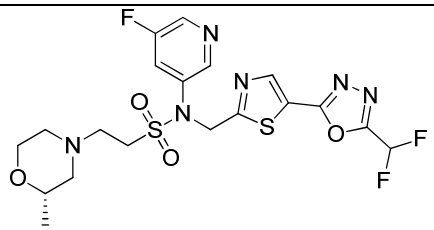
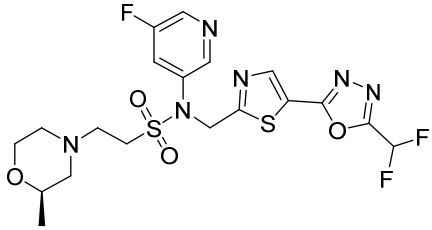
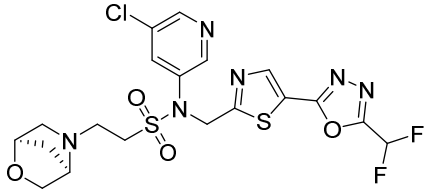
	yl)-2-[(1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]ethane-1-sulfonamide	2.96 (m, 1 H), 2.60 (d, J = 10.0 Hz, 1 H), 1.85 – 1.83 (m, 2 H). LCMS RT = 0.457 min, m/z = 517.2	
I-189	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-2-[(2S)-2-methylmorpholin-4-yl]-N-(pyridin-3-yl)ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.73 (d, J = 2.4 Hz, 1 H), 8.59 (d, J = 3.6 Hz, 1 H), 8.38 (s, 1 H), 7.88 – 7.85 (m, 1 H), 7.39 – 7.35 (m, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.32 (s, 2 H), 3.91 – 3.88 (m, 1 H), 3.71 – 3.62 (m, 2 H), 3.38 (t, J = 6.8 Hz, 2 H), 2.90 (t, J = 7.2 Hz, 2 H), 2.76 – 2.69 (m, 2 H), 2.28 – 2.21 (m, 1 H), 1.93 (t, J = 10.8 Hz, 1 H), 1.17 (d, J = 6.0 Hz, 3 H). LCMS RT = 1.427 min, m/z = 500.9	0.0363
I-190	 N-(5-chloropyridin-3-yl)-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-2-{3-oxa-6-azabicyclo[3.1.1]heptan-6-yl}ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.65 (d, J = 2.4 Hz, 1 H), 8.54 (d, J = 2.4 Hz, 1 H), 8.39 (s, 1 H), 7.95 (t, J = 2.4 Hz, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.34 (s, 2 H), 4.21 (d, J = 11.6 Hz, 2 H), 3.80 (d, J = 11.2 Hz, 2 H), 3.60 (d, J = 6.0 Hz, 2 H), 3.32 – 3.25 (m, 2 H), 3.24 – 3.17 (m, 2 H), 2.77 – 2.63 (m, 1 H), 1.91 (d, J = 8.4 Hz, 1 H). LCMS RT = 0.968 min, m/z = 533.2	0.016

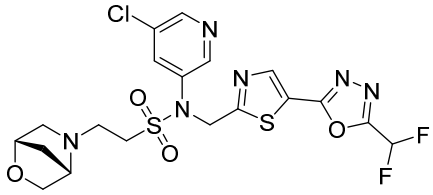
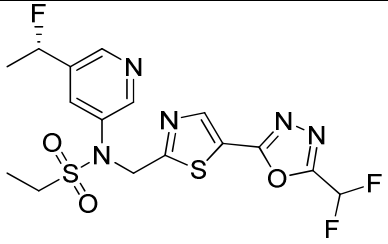
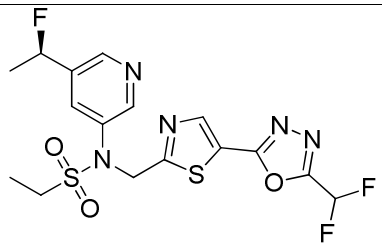
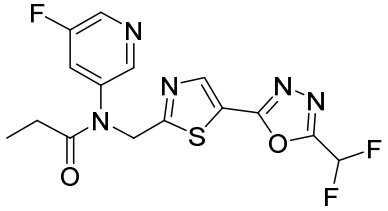
I-191	 N-(5-chloropyridin-3-yl)-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-2-{6-oxa-3-azabicyclo[3.1.1]heptan-3-yl}ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.62 (d, J = 2.0 Hz, 1 H), 8.55 (d, J = 2.0 Hz, 1 H), 8.41 (s, 1 H), 7.90 (t, J = 2.4 Hz, 1 H), 6.91 (t, J = 51.2 Hz, 1 H), 5.29 (s, 2 H), 4.52 (d, J = 6.4 Hz, 2 H), 3.43 (t, J = 6.8 Hz, 2 H), 3.18 (t, J = 7.2 Hz, 2 H), 3.10 (d, J = 10.8 Hz, 2 H), 3.06 – 2.80 (m, 3 H), 2.28 (d, J = 8.0 Hz, 1 H). LCMS RT = 0.482 min, m/z = 533.2	0.0124
I-192	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(5-fluoropyridin-3-yl)-2-{6-oxa-3-azabicyclo[3.1.1]heptan-3-yl}ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.57 (s, 1 H), 8.46 (d, J = 2.4 Hz, 1 H), 8.40 (s, 1 H), 7.73 – 7.61 (m, 1 H), 6.92 (t, J = 51.2 Hz, 1 H), 5.31 (s, 2 H), 4.52 (d, J = 6.0 Hz, 2 H), 3.46 (t, J = 6.8 Hz, 2 H), 3.18 (t, J = 7.6 Hz, 2 H), 3.12 (d, J = 11.0 Hz, 2 H), 3.08 – 3.01 (m, 1 H), 2.86 (d, J = 11.2 Hz, 2 H), 2.27 (d, J = 8.0 Hz, 1 H). LCMS RT = 1.368 min, m/z = 517.2	0.0168
I-193	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-2-(1,4-oxazepan-4-yl)-N-(pyridin-3-yl)ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.73 (d, J = 2.4 Hz, 1 H), 8.58 (d, J = 4.0 Hz, 1 H), 8.38 (s, 1 H), 7.86 (d, J = 8.0 Hz, 1 H), 7.39 – 7.35 (m, 1 H), 6.92 (t, J = 51.6 Hz, 1 H), 5.32 (s, 2 H), 3.80 (t, J = 6.0 Hz, 2 H), 3.75 – 3.73 (m, 2 H), 3.37 (t, J = 7.6 Hz, 2 H), 3.10 (t, J = 6.4 Hz, 2 H), 2.79 – 2.75 (m, 4 H), 1.95 – 1.91 (m, 2 H). LCMS RT = 0.429 min, m/z = 501.2	0.0203

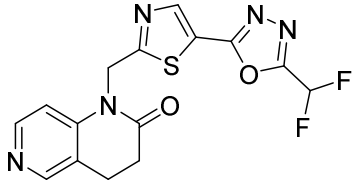
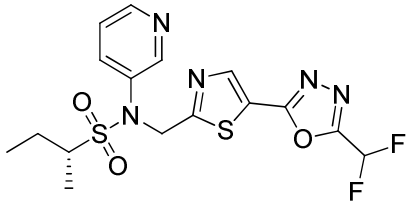
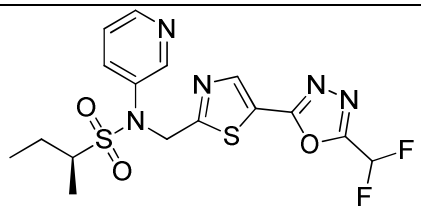
I-194	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-2-[(2R)-2-methylmorpholin-4-yl]-N-(pyridin-3-yl)ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.73 (s, 1 H), 8.59 (d, J = 4.4 Hz, 1 H), 8.38 (s, 1 H), 7.86 – 7.83 (m, 1 H), 7.38 – 7.35 (m, 1 H), 6.91 (t, J = 51.2 Hz, 1 H), 5.31 (s, 2 H), 3.87 – 3.67 (m, 1 H), 3.66 – 3.64 (m, 2 H), 3.64 (t, J = 6.8 Hz, 2 H), 2.89 (t, J = 6.8 Hz, 2 H), 2.74 – 2.67 (m, 2 H), 2.24 – 2.23 (m, 1 H), 1.92 (t, J = 6.8 Hz, 1 H), 1.17 (d, J = 6.8 Hz, 3 H). LCMS RT = 0.748 min, m/z = 501.2	0.0267
I-195	 N-(5-chloropyridin-3-yl)-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-3-(morpholin-4-yl)propanamide	1H NMR (400 MHz, CDCl3) δ ppm 8.62 (s, 1 H), 8.44 (s, 1 H), 8.39 (s, 1 H), 7.72 (s, 1 H), 6.92 (t, J = 51.6 Hz, 1 H), 5.18 (s, 2 H), 3.17 – 3.69 (m, 8 H), 2.86 – 2.83 (m, 2 H), 2.44 – 2.41 (m, 2 H). LCMS RT = 1.381 min, m/z = 485.3	0.312
I-196	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-2-[(1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]-N-(pyridin-3-yl)ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.74 (s, 1 H), 8.59 (d, J = 4.0 Hz, 1 H), 8.39 (s, 1 H), 7.87 (d, J = 8.4 Hz, 1 H), 7.39 – 7.35 (m, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.36 – 5.27 (m, 2 H), 4.48 (s, 1 H), 4.05 (d, J = 8.4 Hz, 1 H), 3.70 – 3.66 (m, 2 H), 3.43 (t, J = 6.8 Hz, 2 H), 3.26 – 3.13 (m, 2 H), 3.03 (d, J = 10.0 Hz, 1 H), 2.66 (d, J = 10.4 Hz, 1 H), 1.95 – 1.85 (m, 2 H). LCMS RT = 1.117 min, m/z = 499.2	0.0497

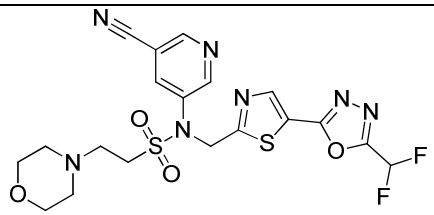
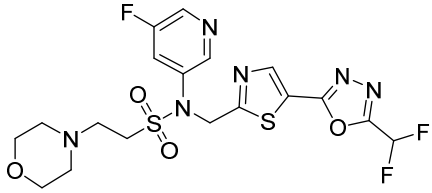
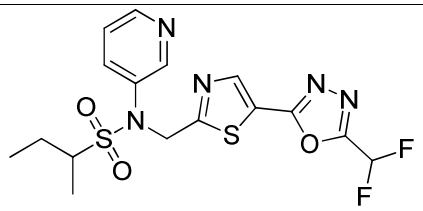
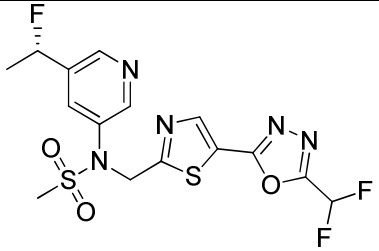
I-197	 N-(5-chloropyridin-3-yl)-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-2-[(2R)-2-methylmorpholin-4-yl]ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.63 (d, J = 2.0 Hz, 1 H), 8.54 (d, J = 2.0 Hz, 1 H), 8.39 (s, 1 H), 7.91 (t, J = 2.0 Hz, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.30 (s, 2 H), 3.93 – 3.85 (m, 1 H), 3.72 – 3.60 (m, 2 H), 3.36 (t, J = 6.8 Hz, 2 H), 2.88 (t, J = 6.8 Hz, 2 H), 2.75 – 2.65 (m, 2 H), 2.28 – 2.17 (m, 1 H), 1.91 (t, J = 10.8 Hz, 1 H), 1.17 (d, J = 6.4 Hz, 3 H). LCMS RT = 1.558 min, m/z = 535.2	0.0472
I-198	 N-(5-chloropyridin-3-yl)-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)propanamide	1H NMR (400 MHz, CDCl3) δ 8.62 (s, 1 H), 8.44 – 8.35 (m, 2 H), 7.67 (t, J = 2.0 Hz, 1 H), 6.92 (t, J = 51.6 Hz, 1 H), 5.18 (s, 2 H), 2.18 (q, J = 7.2 Hz, 2 H), 1.13 (t, J = 7.6 Hz, 3 H). LCMS RT = 1.929 min, m/z = 400.2	0.299
I-199	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(pyridin-3-yl)propanamide	1H NMR (400 MHz, CDCl3) δ 8.64 (d, J = 4.0 Hz, 1 H), 8.53 (s, 1 H), 8.37 (s, 1 H), 7.61 (d, J = 8.0 Hz, 1 H), 7.42 – 7.36 (m, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.20 (s, 2 H), 2.15 (q, J = 7.2 Hz, 2 H), 1.12 (t, J = 7.2 Hz, 3 H). LCMS RT = 1.372 min, m/z = 366.2	0.355
I-200	 1-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-	1H NMR (400 MHz, CDCl3) δ 8.56 (d, J = 5.2 Hz, 1 H), 8.46 (s, 1 H), 8.39 (s, 1 H), 7.36 (d, J = 5.6 Hz, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.33 (s, 2 H), 2.80 (t, J = 7.2 Hz, 2 H), 2.44 (t, J = 7.2 Hz, 2 H), 2.36 – 2.24 (m, 2 H). LCMS RT = 0.993 min, m/z = 378.2	0.125

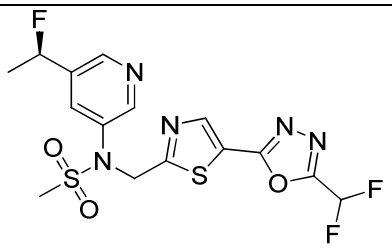
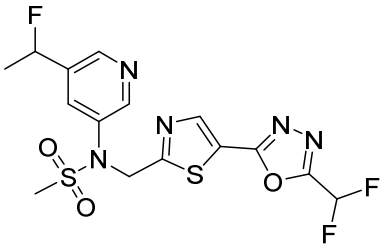
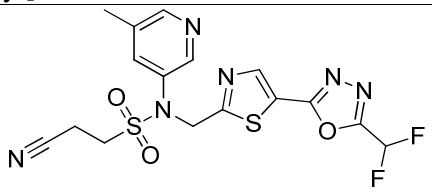
	yl}methyl)-1H,2H,3H,4H,5H-pyrido[4,3-b]azepin-2-one		
I-201	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(5-fluoropyridin-3-yl)-2-[(1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.57 (s, 1 H), 8.46 (d, J = 2.4 Hz, 1 H), 8.39 (s, 1 H), 7.70 – 7.62 (m, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.39 – 5.25 (m, 2 H), 4.46 (s, 1 H), 4.00 (d, J = 8.0 Hz, 1 H), 3.69 – 3.64 (m, 1 H), 3.52 (s, 1 H), 3.34 (t, J = 6.8 Hz, 2 H), 3.19 – 3.07 (m, 2 H), 2.94 (d, J = 10.0 Hz, 1 H), 2.56 (d, J = 10.0 Hz, 1 H), 1.89 – 1.79 (m, 2 H). LCMS RT = 0.459 min, m/z = 517.2	0.0207
I-202	 N-(5-chloropyridin-3-yl)-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-2-[(2S)-2-methylmorpholin-4-yl]ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.63 (s, 1 H), 8.54 (s, 1 H), 8.39 (s, 1 H), 7.91 (s, 1 H), 6.91 (t, J = 51.2 Hz, 1 H), 5.30 (s, 2 H), 3.94 – 3.85 (m, 1 H), 3.74 – 3.62 (m, 2 H), 3.43 (t, J = 6.8 Hz, 2 H), 2.88 (t, J = 6.8 Hz, 2 H), 2.72 (t, J = 12.8 Hz, 2 H), 2.28 – 2.17 (m, 1 H), 1.92 (t, J = 9.6 Hz, 1 H), 1.17 (d, J = 6.0 Hz, 3 H). LCMS RT = 1.561 min, m/z = 535.2	0.0127

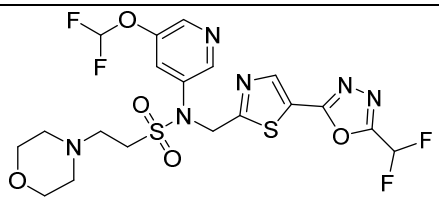
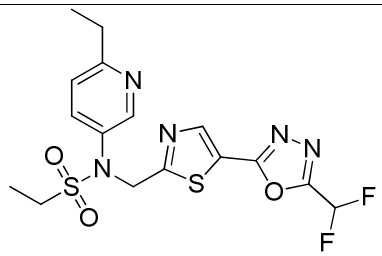
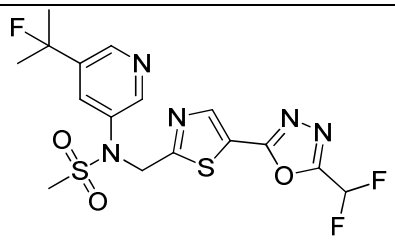
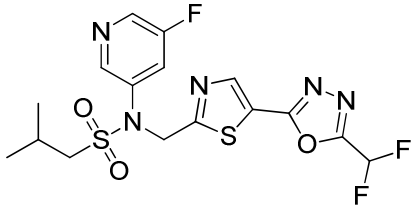
I-203	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(5-fluoropyridin-3-yl)-2-[(2S)-2-methylmorpholin-4-yl]ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.58 (s, 1 H), 8.47 (d, J = 2.4 Hz, 1 H), 8.40 (s, 1 H), 7.68 (d, J = 9.2 Hz, 1 H), 6.92 (t, J = 51.2 Hz, 1 H), 5.32 (s, 2 H), 3.91 – 3.71 (m, 1 H), 3.72 – 3.64 (m, 2 H), 3.41 (t, J = 6.8 Hz, 2 H), 2.91 (t, J = 7.2 Hz, 2 H), 2.73 (t, J = 12.8 Hz, 2 H), 2.29 – 2.22 (m, 1 H), 1.96 – 1.94 (m, 1 H), 1.17 (d, J = 6.4 Hz, 3 H). LCMS RT = 1.660 min, m/z = 519.0	0.0254
I-204	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(5-fluoropyridin-3-yl)-2-[(2R)-2-methylmorpholin-4-yl]ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.58 (s, 1 H), 8.47 (s, 1 H), 8.40 (s, 1 H), 7.70 – 7.66 (m, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.32 (s, 2 H), 3.89 (d, J = 9.6 Hz, 1 H), 3.70 – 3.60 (m, 2 H), 3.37 (t, J = 6.8 Hz, 2 H), 2.88 (t, J = 6.8 Hz, 2 H), 2.72 – 2.65 (m, 2 H), 2.26 – 2.20 (m, 1 H), 1.91 (t, J = 10.4 Hz, 1 H), 1.17 (d, J = 6.0 Hz, 3 H). LCMS RT = 1.664 min, m/z = 518.9	0.0336
I-205	 N-(5-chloropyridin-3-yl)-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-2-[(1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.62 (d, J = 2.0 Hz, 1 H), 8.54 (d, J = 2.0 Hz, 1 H), 8.40 (s, 1 H), 7.91 (t, J = 2.0 Hz, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.40 – 5.21 (m, 2 H), 4.47 (s, 1 H), 4.02 (d, J = 8.0 Hz, 1 H), 3.68 – 3.63 (m, 1 H), 3.56 (s, 1 H), 3.35 (t, J = 6.8 Hz, 2 H), 3.25 – 3.05 (m, 2 H), 3.01 – 2.90 (m, 1 H), 2.59 (d, J = 10.0 Hz, 1 H), 1.93 – 1.80 (m, 2 H). LCMS RT = 0.919 min, m/z = 533.2	0.0159

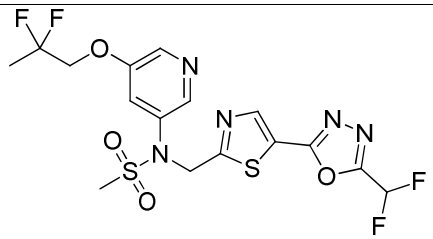
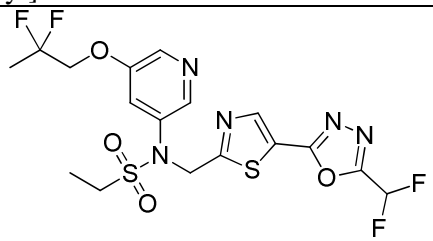
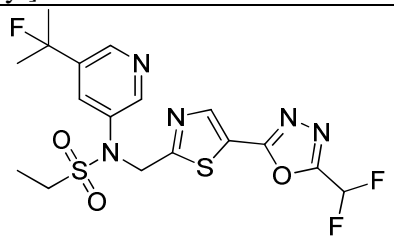
I-206	 N-(5-chloropyridin-3-yl)-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-2-[(1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.62 (d, J = 2.0 Hz, 1 H), 8.54 (d, J = 2.0 Hz, 1 H), 8.39 (s, 1 H), 7.91 (t, J = 2.0 Hz, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.37 – 5.25 (m, 2 H), 4.46 (s, 1 H), 4.01 (d, J = 8.4 Hz, 1 H), 3.69 – 3.62 (m, 1 H), 3.51 (s, 1 H), 3.31 (t, J = 6.8 Hz, 2 H), 3.18 – 3.07 (m, 2 H), 2.93 (d, J = 10.0 Hz, 1 H), 2.56 (d, J = 9.6 Hz, 1 H), 1.89 – 1.84 (q, J = 7.2 Hz, 2 H). LCMS RT = 0.472 min, m/z = 533.2	0.0162
I-207	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-{5-[(1S)-1-fluoroethyl]pyridin-3-yl}ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.67 (d, J = 2.4 Hz, 1 H), 8.56 (s, 1 H), 8.39 (s, 1 H), 7.83 (s, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.79 – 5.60 (m, 1 H), 5.30 (s, 2 H), 3.21 (q, J = 7.2 Hz, 2 H), 1.69 – 1.55 (m, 3 H), 1.46 (t, J = 7.6 Hz, 3 H). LCMS RT = 1.500 min, m/z = 447.8	0.0137
I-208	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-{5-[(1R)-1-fluoroethyl]pyridin-3-yl}ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.67 (d, J = 2.0 Hz, 1 H), 8.56 (s, 1 H), 8.39 (s, 1 H), 7.83 (s, 1 H), 6.91 (t, J = 52.0 Hz, 1 H), 5.78 – 5.62 (m, 1 H), 5.30 (s, 2 H), 3.21 (q, J = 7.2 Hz, 2 H), 1.74 – 1.62 (m, 3 H), 1.46 (t, J = 7.6 Hz, 3 H). LCMS RT = 1.503 min, m/z = 447.8	0.027
I-209	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-	1H NMR (400 MHz, CDCl3) δ 8.54 (d, J = 2.4 Hz, 1 H), 8.39 – 8.35 (m, 2 H), 7.44 – 7.40 (m, 1 H), 6.92 (t, J = 51.6 Hz, 1 H), 5.19 (s, 2 H), 2.19 (q, J = 6.8 Hz, 2 H), 1.13 (t, J = 7.6 Hz, 3 H). LCMS RT = 1.755 min, m/z = 384.2	0.284

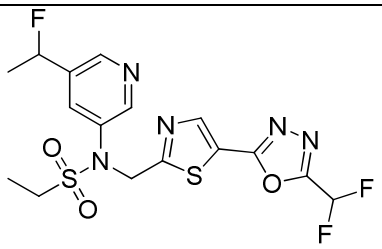
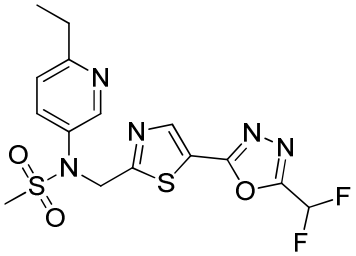
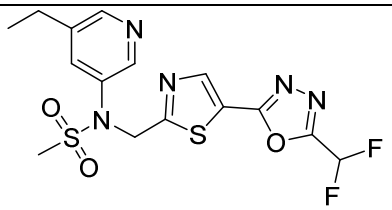
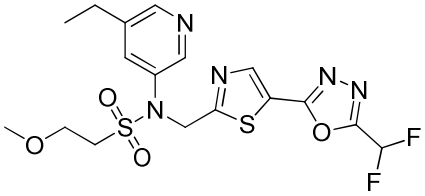
	yl}methyl)-N-(5-fluoropyridin-3-yl)propanamide		
I-210	 1-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-1,2,3,4-tetrahydro-1,6-naphthyridin-2-one	1H NMR (400 MHz, CDCl3) δ 8.49 – 8.37 (m, 3 H), 7.19 (d, J = 5.6 Hz, 1 H), 6.89 (t, J = 51.6 Hz, 1 H), 5.46 (s, 2 H), 3.10 – 3.01 (m, 2 H), 2.91 – 2.80 (m, 2 H). LCMS RT = 0.971 min, m/z = 364.2	0.0487
I-211	 (2R)-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(pyridin-3-yl)butane-2-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.70 (s, 1 H), 8.57 – 8.55 (m, 1 H), 8.35 (s, 1 H), 7.87 – 7.82 (m, 1 H), 7.38 – 7.32 (m, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.38 – 5.20 (m, 2 H), 3.14 – 3.06 (m, 1 H), 2.13 – 2.05 (m, 1 H), 1.72 – 1.65 (m, 1 H), 1.45 (d, J = 6.8 Hz, 3 H), 1.04 (t, J = 7.6 Hz, 3 H). LCMS RT = 0.563 min, m/z = 430.1	0.0137
I-212	 (2S)-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(pyridin-3-yl)butane-2-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.70 (s, 1 H), 8.58 – 8.55 (m, 1 H), 8.35 (s, 1 H), 7.89 – 7.86 (m, 1 H), 7.34 (q, J = 4.8 Hz, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.39 – 5.23 (m, 2 H), 3.14 – 3.06 (m, 1 H), 2.14 – 2.04 (m, 1 H), 1.74 – 1.65 (m, 1 H), 1.45 (d, J = 6.8 Hz, 3 H), 1.04 (t, J = 7.6 Hz, 3 H). LCMS RT = 0.563 min, m/z = 430.1	0.0105

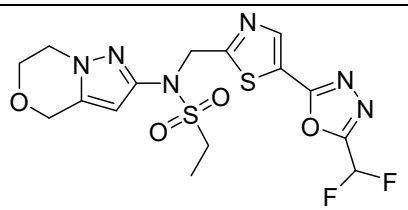
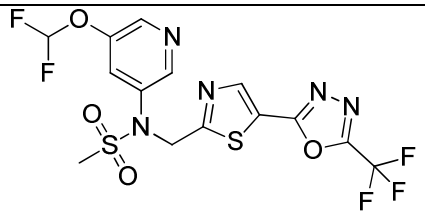
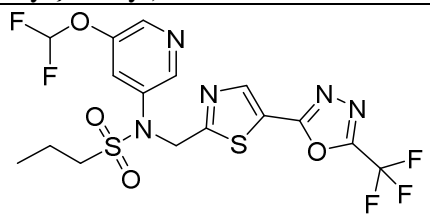
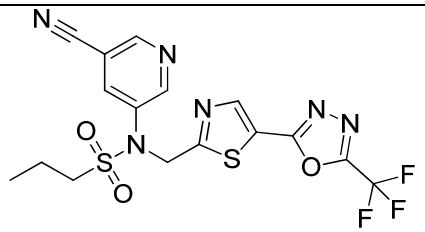
I-213	 N-(5-cyanopyridin-3-yl)-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-2-(morpholin-4-yl)ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.96 (d, J = 2.4 Hz, 1 H), 8.82 (s, 1 H), 8.41 (s, 1 H), 8.19 (s, 1 H), 6.92 (t, J = 51.6 Hz, 1 H), 5.33 (s, 2 H), 3.74 (t, J = 4.8 Hz, 4 H), 3.38 (t, J = 6.8 Hz, 2 H), 2.89 (t, J = 7.2 Hz, 2 H), 2.50 (t, J = 4.8 Hz, 4 H). LCMS RT = 1.295 min, m/z = 512.2	0.0902
I-214	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(5-fluoropyridin-3-yl)-2-(morpholin-4-yl)ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ ppm 8.59 (s, 1 H), 8.47 (d, J = 2.4 Hz, 1 H), 8.40 (s, 1 H), 7.71 – 7.67 (m, 1 H), 6.93 (t, J = 51.6 Hz, 1 H), 5.33 (s, 2 H), 3.78 – 3.72 (m, 4 H), 3.40 (t, J = 6.8 Hz, 2 H), 2.91 (t, J = 6.8 Hz, 2 H), 2.53 – 2.51 (m, 4 H). LCMS RT = 0.908 min, m/z = 505.2	0.0154
I-215	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(pyridin-3-yl)butane-2-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.72 (d, J = 2.8 Hz, 1 H), 8.58 – 8.56 (m, 1 H), 8.35 (s, 1 H), 7.89 – 7.86 (m, 1 H), 7.36 (q, J = 4.8 Hz, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.37 – 5.26 (m, 2 H), 3.14 – 3.05 (m, 1 H), 2.12 – 2.06 (m, 1 H), 1.75 – 1.69 (m, 1 H), 1.45 (d, J = 6.8 Hz, 3 H), 1.04 (t, J = 7.6 Hz, 3 H). LCMS RT = 0.560 min, m/z = 430.1	0.00675
I-216	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-	1H NMR (400 MHz, CDCl3) δ 8.68 (s, 1 H), 8.58 (s, 1 H), 8.42 (s, 1 H), 7.84 (s, 1 H), 6.92 (t, J = 51.6 Hz, 1 H), 5.80 – 5.61 (m, 1 H), 5.29 (s, 2 H), 3.11 (s, 3 H), 1.75 – 1.55 (m, 3 H).	0.0119

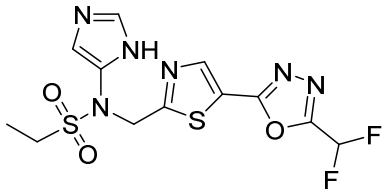
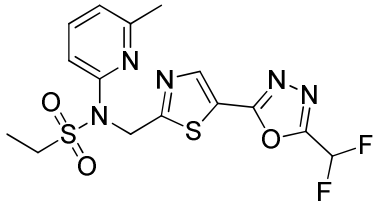
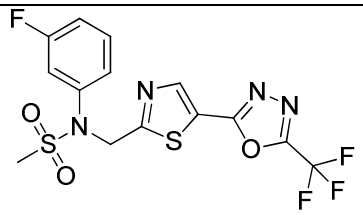
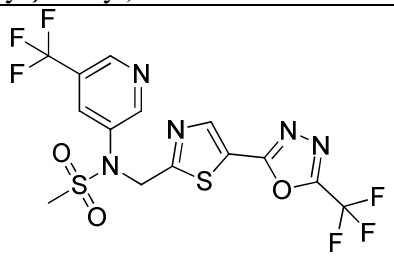
	yl}methyl)-N-{5-[(1S)-1-fluoroethyl]pyridin-3-yl}methanesulfonamide	LCMS RT = 0.550 min, m/z = 434.1	
I-217	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-{5-[(1R)-1-fluoroethyl]pyridin-3-yl}methanesulfonamide	1H NMR (400 MHz, CDCl3) δ 8.70 (s, 1 H), 8.58 (s, 1 H), 8.42 (s, 1 H), 7.86 (s, 1 H), 6.92 (t, J = 51.6 Hz, 1 H), 5.81 – 5.60 (m, 1 H), 5.29 (s, 2 H), 3.11 (s, 3 H), 1.75 – 1.55 (m, 3 H). LCMS RT = 0.551 min, m/z = 434.1	0.0236
I-218	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-[5-(1-fluoroethyl)pyridin-3-yl]methanesulfonamide	1H NMR (400 MHz, CDCl3) δ 8.68 (d, J = 2.4 Hz, 1 H), 8.57 (s, 1 H), 8.41 (s, 1 H), 7.84 (s, 1 H), 6.91 (t, J = 51.2 Hz, 1 H), 5.79 – 5.62 (m, 1 H), 5.28 (s, 2 H), 3.11 (s, 3 H), 1.75 – 1.55 (m, 3 H). LCMS RT = 0.545 min, m/z = 434.1	0.0369
I-219	 2-cyano-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(5-methylpyridin-3-yl)ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.52 (d, J = 2.0 Hz, 1 H), 8.47 (s, 1 H), 8.45 (s, 1 H), 7.65 (s, 1 H), 6.92 (t, J = 51.6 Hz, 1 H), 5.28 (s, 2 H), 3.53 (t, J = 7.6 Hz, 2 H), 2.98 (t, J = 7.2 Hz, 2 H), 2.39 (s, 3 H). LCMS RT = 0.507 min, m/z = 441.1	0.0202

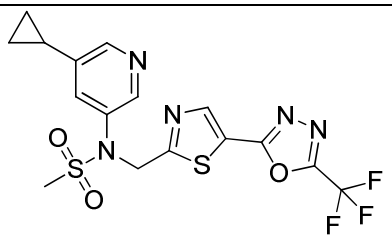
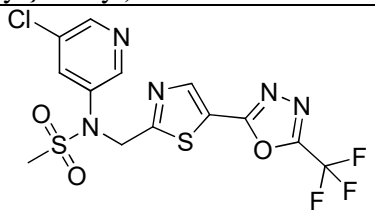
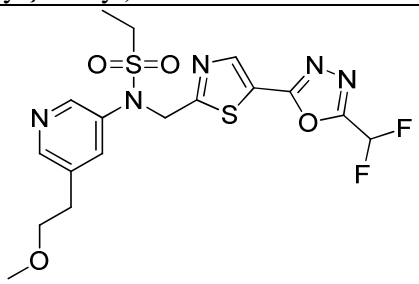
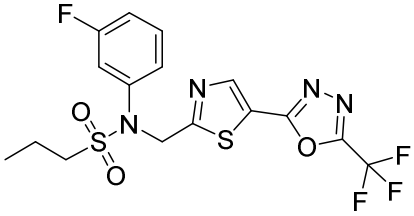
I-220	 N-[5-(difluoromethoxy)pyridin-3-yl]-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-2-(morpholin-4-yl)ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.61 (s, 1 H), 8.46 (s, 1 H), 8.39 (s, 1 H), 7.70 (s, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 6.59 (t, J = 72.0 Hz, 1 H), 5.31 (s, 2 H), 3.77 – 3.69 (m, 4 H), 3.38 (t, J = 6.8 Hz, 2 H), 2.89 (t, J = 7.2 Hz, 2 H), 2.54 – 2.46 (m, 4 H). LCMS RT = 1.504 min, m/z = 553.2	0.0184
I-221	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(6-ethylpyridin-3-yl)ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.58 (d, J = 2.4 Hz, 1 H), 8.37 (s, 1 H), 7.75 – 7.70 (m, 1 H), 7.22 (d, J = 8.4 Hz, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.7 (s, 2 H), 3.20 (q, J = 7.6 Hz , 2 H), 2.83 (q, J = 7.6 Hz , 2 H), 1.46 (t, J = 7.2 Hz, 3 H), 1.30 (t, J = 7.6 Hz, 3 H). LCMS RT = 1.134 min, m/z = 430.2	0.033
I-222	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-[5-(2-fluoropropan-2-yl)pyridin-3-yl]methanesulfonamide	1H NMR (400 MHz, CDCl3) δ 8.64 (d, J = 2.0 Hz, 1 H), 8.60 (s, 1 H), 8.42 (s, 1 H), 7.86 (t, J = 2.0 Hz, 1 H), 6.92 (t, J = 51.6 Hz, 1 H), 5.28 (s, 2 H), 3.11 (s, 3 H), 1.75 (s, 3 H), 1.69 (s, 3 H). LCMS RT = 1.499 min, m/z = 447.9	0.0376
I-223	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(5-fluoropyridin-3-yl)-2-methylpropane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.58 (s, 1 H), 8.47 (d, J = 2.8 Hz, 1 H), 8.40 (s, 1 H), 7.68 – 7.62 (m, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.29 (s, 2 H), 3.05 (d, J = 2.0 Hz, 2 H), 2.40 – 2.30 (m, 1 H), 1.12 (d, J = 6.8 Hz, 6 H). LCMS RT = 1.790 min, m/z = 447.9	0.00563

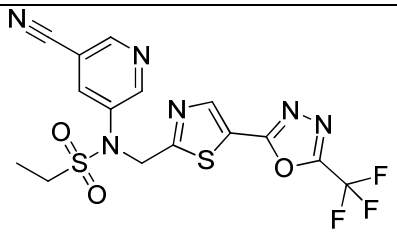
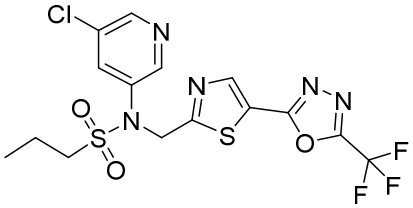
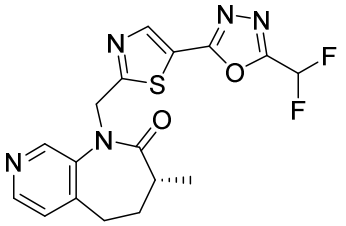
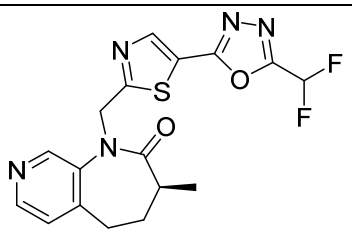
I-224	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-[5-(2,2-difluoropropoxy)pyridin-3-yl]methanesulfonamide	1H NMR (400 MHz, CDCl3) δ 8.42 (s, 1 H), 8.39 – 8.33 (m, 2 H), 7.48 – 7.41 (m, 1 H), 6.92 (t, J = 51.6 Hz, 1 H), 5.28 (s, 2 H), 4.18 (t, J = 11.2 Hz, 2 H), 3.11 (s, 3 H), 1.79 (t, J = 18.8 Hz, 3 H). LCMS RT = 1.492 min, m/z = 482.2	0.0204
I-225	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-[5-(2,2-difluoropropoxy)pyridin-3-yl]ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.42 – 8.36 (m, 2 H), 8.33 (s, 1 H), 7.45 (s, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.30 (s, 2 H), 4.17 (t, J = 11.2 Hz, 2 H), 3.21 (q, J = 7.6 Hz, 2 H), 1.79 (t, J = 18.8 Hz, 3 H), 1.46 (t, J = 7.6 Hz, 3 H). LCMS RT = 1.559 min, m/z = 496.2	0.00601
I-226	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-[5-(2-fluoropropan-2-yl)pyridin-3-yl]ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.66 (d, J = 2.4 Hz, 1 H), 8.59 (d, J = 1.2 Hz, 1 H), 8.40 (s, 1 H), 7.91 – 7.86 (m, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.30 (s, 2 H), 3.21 (q, J = 6.8 Hz, 2 H), 1.75 (s, 3 H), 1.69 (s, 3 H), 1.47 (t, J = 6.4 Hz, 3 H). LCMS RT = 1.510 min, m/z = 462.2	0.0319

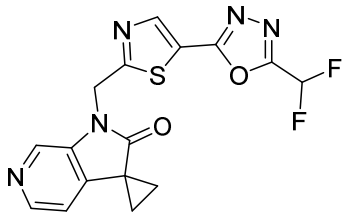
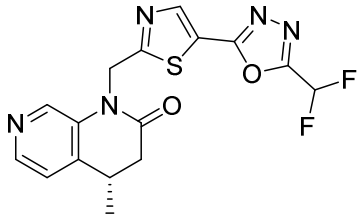
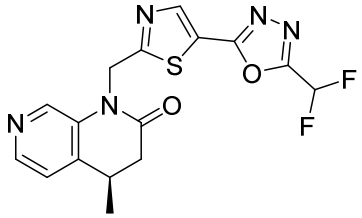
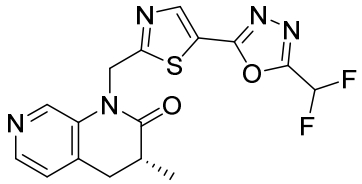
I-227	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-[5-(1-fluoroethyl)pyridin-3-yl]ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.67 (d, J = 2.4 Hz, 1 H), 8.56 (s, 1 H), 8.39 (s, 1 H), 7.83 (s, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.79 – 5.62 (m, 1 H), 5.30 (s, 2 H), 3.21 (q, J = 7.2 Hz, 2 H), 1.74 – 1.56 (m, 3 H), 1.47 (t, J = 7.2 Hz, 3 H). LCMS RT = 1.518 min, m/z = 447.9	0.0123
I-228	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(6-ethylpyridin-3-yl)methanesulfonamide	1H NMR (400 MHz, CD3OD) δ 8.54 (d, J = 2.4 Hz, 1 H), 8.39 (s, 1 H), 7.93 – 7.88 (m, 1 H), 7.35 (d, J = 8.4 Hz, 1 H), 7.17 (t, J = 51.6 Hz, 1 H), 5.31 (s, 2 H), 3.12 (s, 3 H), 2.78 (q, J = 7.6 Hz, 2 H), 1.24 (t, J = 7.6 Hz, 3 H). LCMS RT = 0.981 min, m/z = 416.2	0.0435
I-229	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(5-ethylpyridin-3-yl)methanesulfonamide	1H NMR (400 MHz, CD3OD) δ 8.51 (s, 1 H), 8.42 (s, 1 H), 8.40 (s, 1 H), 7.89 (s, 1 H), 7.18 (t, J = 51.6 Hz, 1 H), 5.35 (s, 2 H), 3.14 (s, 3 H), 2.69 (q, J = 7.2 Hz, 2 H), 1.25 (t, J = 7.6 Hz, 3 H). LCMS RT = 1.099 min, m/z = 416.2	0.0248
I-230	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(5-ethylpyridin-3-yl)-2-methoxyethane-1-sulfonamide	1H NMR (400 MHz, CD3OD) δ 8.50 (d, J = 2.4 Hz, 1 H), 8.38 (s, 1 H), 8.35 (s, 1 H), 7.88 (s, 1 H), 7.18 (t, J = 51.6 Hz, 1 H), 5.31 (s, 2 H), 3.82 (t, J = 5.6 Hz, 2 H), 3.48 (t, J = 5.2 Hz, 2 H), 3.43 (s, 3 H), 2.69 (q, J = 5.2 Hz, 2 H), 1.24 (t, J = 7.6 Hz, 3 H). LCMS RT = 1.752 min, m/z = 460.2	0.033

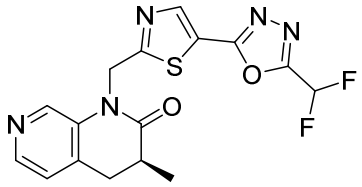
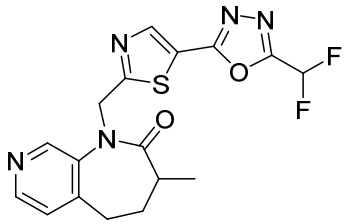
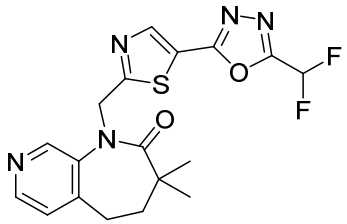
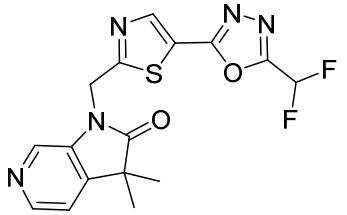
I-231	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-{4H,6H,7H-pyrazolo[3,2-c][1,4]oxazin-2-yl}ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.39 (s, 1 H), 6.90 (t, J = 51.6 Hz, 1 H), 6.12 (s, 1 H), 5.38 (s, 2 H), 4.77 (s, 2 H), 4.12 – 4.06 (m, 4 H), 3.27 (q, J = 7.2 Hz, 2 H), 1.42 (t, J = 7.6 Hz, 3 H). LCMS RT = 0.552 min, m/z = 447.1	0.0924
I-232	 N-[5-(difluoromethoxy)pyridin-3-yl]-N-({5-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)methanesulfonamide	1H NMR (400 MHz, CDCl3) δ 8.63 (d, J = 2.0 Hz, 1 H), 8.51 (d, J = 2.4 Hz, 1 H), 8.46 (s, 1 H), 7.70 (s, 1 H), 6.61 (t, J = 71.6 Hz, 1 H), 5.30 (s, 2 H), 3.13 (s, 3 H). LCMS RT = 1.766 min, m/z = 471.8	0.0342
I-233	 N-[5-(difluoromethoxy)pyridin-3-yl]-N-({5-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)propane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.59 (d, J = 2.0 Hz, 1 H), 8.47 (d, J = 2.4 Hz, 1 H), 8.42 (s, 1 H), 7.67 (t, J = 2.4 Hz, 1 H), 6.59 (t, J = 72.0 Hz, 1 H), 5.29 (s, 2 H), 3.19 – 3.11 (m, 2 H), 1.97 – 1.88 (m, 2 H), 1.08 (t, J = 7.6 Hz, 3 H). LCMS RT = 2.013 min, m/z = 499.9	0.0606
I-234	 N-(5-cyanopyridin-3-yl)-N-({5-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)propane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.95 (d, J = 2.4 Hz, 1 H), 8.82 (s, 1 H), 8.44 (s, 1 H), 8.16 (d, J = 2.4 Hz, 1 H), 5.29 (s, 2 H), 3.18 – 3.11 (m, 2 H), 2.00 – 1.80 (m, 2 H), 1.09 (t, J = 7.2 Hz, 3 H). LCMS RT = 1.811 min, m/z = 459.2	0.184

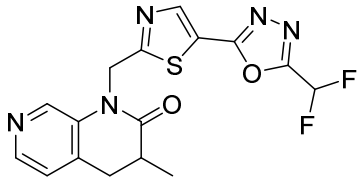
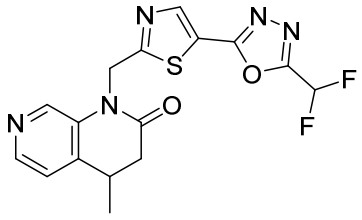
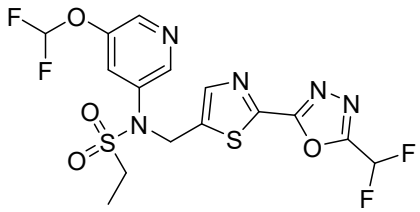
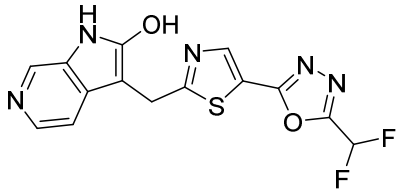
I-235	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(1H-imidazol-5-yl)ethane-1-sulfonamide	1H NMR (400 MHz, CD3OD) δ 8.43 (s, 1 H), 7.99 (s, 1 H), 7.39 – 7.03 (m, 2 H), 5.30 (s, 2 H), 3.39 – 3.28 (m, 2 H), 1.40 (t, J = 7.2 Hz, 3 H). LCMS RT = 1.848 min, m/z = 390.8	0.323
I-236	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(6-methylpyridin-2-yl)ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.39 (s, 1 H), 7.61 (t, J = 8.0 Hz, 1 H), 7.45 (d, J = 8.4 Hz, 1 H), 7.01 (s, 1 H), 6.89 (t, J = 51.6 Hz, 1 H), 5.60 (s, 2 H), 3.27 (q, J = 7.6 Hz, 2 H), 2.52 (s, 3 H), 1.37 (t, J = 7.4 Hz, 3 H). LCMS RT = 1.704 min, m/z = 416.2	0.0592
I-237	 N-(3-fluorophenyl)-N-({5-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)methanesulfonamide	1H NMR (400 MHz, CDCl3) δ 8.41 (s, 1 H), 7.44 – 7.36 (m, 1 H), 7.30 – 7.27 (m, 1 H), 7.24 – 7.20 (m, 1 H), 7.12 – 7.05 (m, 1 H), 5.27 (s, 2 H), 3.07 (s, 3 H). LCMS RT = 1.912 min, m/z = 422.8	0.0992
I-238	 N-({5-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-[5-(trifluoromethyl)pyridin-3-yl]methanesulfonamide	1H NMR (400 MHz, CDCl3) δ 8.95 (d, J = 2.0 Hz, 1 H), 8.87 (s, 1 H), 8.46 (s, 1 H), 8.12 (t, J = 2.0 Hz, 1 H), 5.31 (s, 2 H), 3.12 (s, 3 H). LCMS RT = 1.905 min, m/z = 473.8	0.256

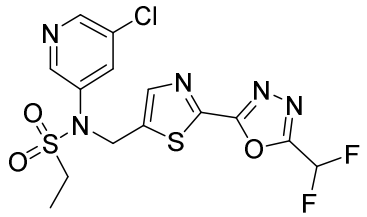
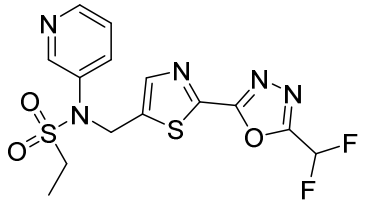
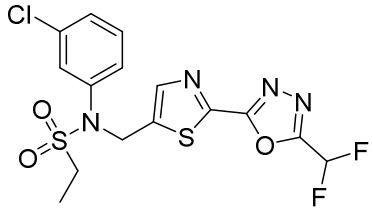
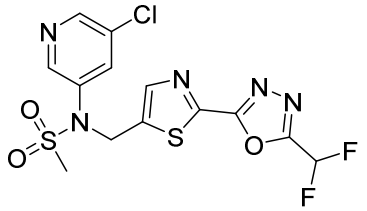
I-239	 N-(5-cyclopropylpyridin-3-yl)-N-({5-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)methanesulfonamide	1H NMR (400 MHz, CDCl3) δ 8.46 (s, 1 H), 8.42 (s, 1 H), 8.37 (s, 1 H), 7.45 (t, J = 2.4 Hz, 1 H), 5.26 (s, 2 H), 3.09 (s, 3 H), 2.00 – 1.90 (m, 1 H), 1.11 – 1.08 (m, 2 H), 0.78 – 0.75 (m, 2 H). LCMS RT = 1.621 min, m/z = 445.9	0.085
I-240	 N-(5-chloropyridin-3-yl)-N-({5-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)methanesulfonamide	1H NMR (400 MHz, CDCl3) δ 8.62 (s, 1 H), 8.57 (s, 1 H), 7.89 (s, 1 H), 5.28 (s, 2 H), 3.11 (s, 3 H). LCMS RT = 2.259 min, m/z = 440.1	0.062
I-241	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-[5-(2-methoxyethyl)pyridin-3-yl]ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.50 (s, 1 H), 8.48 (s, 1 H), 7.80 (s, 1 H), 7.65 (s, 1 H), 6.92 (t, J = 51.6 Hz, 1 H), 5.80 (s, 2 H), 3.60 (t, J = 6.0 Hz, 2 H), 3.33 (s, 3 H), 3.08 (q, J = 7.2 Hz, 2 H), 2.85 (t, J = 6.0 Hz, 2 H), 1.40 (t, J = 7.6 Hz, 3 H). LCMS RT = 0.718 min, m/z = 460.2	0.994
I-242	 N-(3-fluorophenyl)-N-({5-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)propane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.41 (s, 1 H), 7.43 – 7.37 (m, 1 H), 7.27 – 7.26 (m, 1 H), 7.25 – 7.22 (m, 1 H), 7.10 – 7.05 (m, 1 H), 5.30 (s, 2 H), 3.15 – 3.10 (m, 2 H), 1.97 – 1.89 (m, 2 H), 1.09 (t, J = 7.2 Hz, 3 H). LCMS RT = 2.207 min, m/z = 450.8	0.053

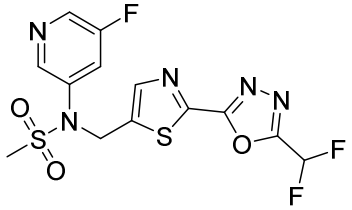
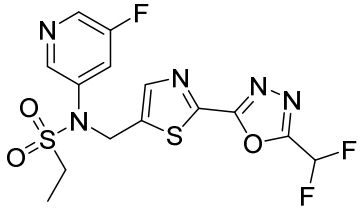
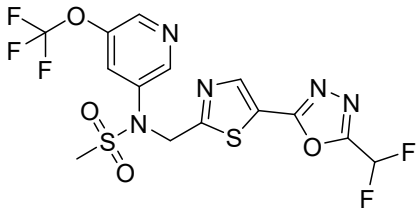
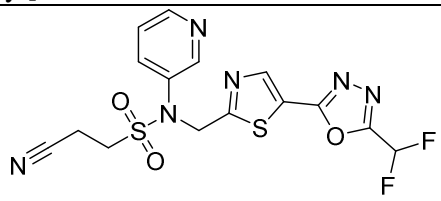
I-243	 N-(5-cyanopyridin-3-yl)-N-({5-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.96 (d, J = 2.4 Hz, 1 H), 8.82 (d, J = 2.0 Hz, 1 H), 8.44 (s, 1 H), 8.17 (t, J = 2.0 Hz, 1 H), 5.30 (s, 2 H), 3.21 (q, J = 7.2 Hz, 2 H), 1.45 (t, J = 7.2 Hz, 3 H). LCMS RT = 1.718 min, m/z = 444.8	0.129
I-244	 N-(5-chloropyridin-3-yl)-N-({5-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)propane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.61 (d, J = 2.4 Hz, 1 H), 8.55 (d, J = 2.4 Hz, 1 H), 8.42 (s, 1 H), 7.88 (t, J = 2.0 Hz, 1 H), 5.28 (s, 2 H), 3.19 – 3.11 (m, 2 H), 1.97 – 1.82 (m, 2 H), 1.09 (t, J = 7.6 Hz, 3 H). LCMS RT = 2.027 min, m/z = 467.8	0.0872
I-245	 (3R)-1-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-3-methyl-1H,2H,3H,4H,5H-pyrido[3,4-b]azepin-2-one	1H NMR (400 MHz, CDCl3) δ 8.96 (s, 1 H), 8.52 (d, J = 5.2 Hz, 1 H), 8.38 (s, 1 H), 7.52 (d, J = 5.2 Hz, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.47 – 5.27 (m, 2 H), 3.09 – 3.04 (m, 1 H), 2.83 – 2.78 (m, 1 H), 2.51 – 2.47 (m, 1 H), 2.26 – 2.21 (m, 1 H), 2.18 – 2.11 (m, 1 H), 1.16 (d, J = 6.4 Hz, 3 H) LCMS RT = 1.250 min, m/z = 392.3.	1.42
I-246	 (3S)-1-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-3-methyl-1H,2H,3H,4H,5H-pyrido[3,4-b]azepin-2-one	1H NMR (400 MHz, CDCl3) δ 8.91 (s, 1 H), 8.50 (d, J = 5.2 Hz, 1 H), 8.37 (s, 1 H), 7.47 (d, J = 5.2 Hz, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.46 – 5.28 (m, 2 H), 3.11 – 2.85 (m, 1 H), 2.84 – 2.71 (m, 1 H), 2.548 – 2.45 (m, 1 H), 2.29 – 2.14 (m, 1 H), 2.18 – 2.07 (m, 1 H), 1.16 (d, J = 6.4 Hz, 3 H) LCMS RT = 1.251 min, m/z = 392.3.	0.039

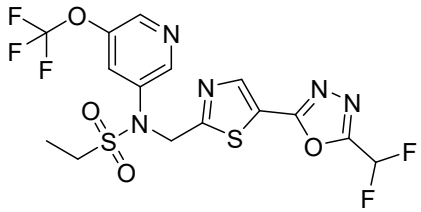
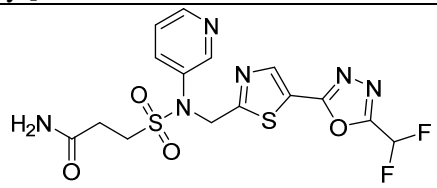
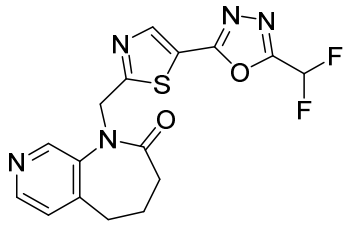
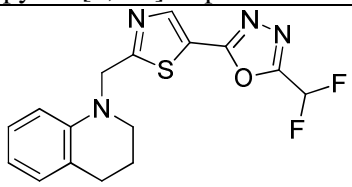
I-247	 1'-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[2,3-c]pyridin]-2'-one	1H NMR (400 MHz, CDCl3) δ 8.47 (s, 1 H), 8.44 – 8.40 (m, 2 H), 7.07 (d, J = 5.2 Hz, 1 H), 6.90 (t, J = 51.6 Hz, 1 H), 5.43 (s, 2 H), 2.17 – 2.10 (m, 2 H), 1.93 – 1.86 (m, 2 H) LCMS RT = 0.970 min, m/z = 376.2.	0.158
I-248	 (4S)-1-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-4-methyl-1,2,3,4-tetrahydro-1,7-naphthyridin-2-one	1H NMR (400 MHz, CDCl3) δ 8.54 (s, 1 H), 8.41 (s, 1 H), 8.35 (d, J = 4.8 Hz, 1 H), 7.19 (d, J = 4.8 Hz, 1 H), 6.89 (t, J = 51.6 Hz, 1 H), 5.62 – 5.46 (m, 2 H), 3.23 – 3.16 (m, 1 H), 2.92 – 2.84 (m, 1 H), 2.66 – 2.55 (m, 1 H), 1.38 (d, J = 6.8 Hz, 3 H) LCMS RT =1.098 min, m/z = 378.3.	0.034
I-249	 (4R)-1-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-4-methyl-1,2,3,4-tetrahydro-1,7-naphthyridin-2-one	1H NMR (400 MHz, CDCl3) δ 8.53 (s, 1 H), 8.40 (s, 1 H), 8.34 (d, J = 4.8 Hz, 1 H), 7.18 (d, J = 4.8 Hz, 1 H), 6.90 (t, J = 51.6 Hz, 1 H), 5.60 – 5.46 (m, 2 H), 3.23 – 3.15 (m, 1 H), 2.90 – 2.81 (m, 1 H), 2.64 – 2.55 (m, 1 H), 1.38 (d, J = 6.8 Hz, 3 H) LCMS RT = 1.028 min, m/z = 378.2.	0.089
I-250	 (3R)-1-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-3-methyl-1,2,3,4-tetrahydro-1,7-naphthyridin-2-one	1H NMR (400 MHz, CDCl3) δ 8.54 (s, 1 H), 8.41 (s, 1 H), 8.31 (d, J = 3.6 Hz, 1 H), 7.18 (d, J = 4.4 Hz, 1 H), 6.89 (t, J = 51.6 Hz, 1 H), 5.62 – 5.36 (m, 2 H), 3.09 – 3.02 (m, 1 H), 2.89 – 2.79 (m, 2 H), 1.35 (d, J = 6.8 Hz, 3 H). LCMS RT = 0.684 min, m/z = 378.2.	0.041

I-251	 (3S)-1-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-3-methyl-1,2,3,4-tetrahydro-1,7-naphthyridin-2-one	1H NMR (400 MHz, CDCl3) δ 8.52 (s, 1 H), 8.41 (s, 1 H), 8.30 (d, J = 4.4 Hz, 1 H), 7.17 (d, J = 4.8 Hz, 1 H), 6.89 (t, J = 51.6 Hz, 1 H), 5.62 – 5.36 (m, 2 H), 3.09 – 3.02 (m, 1 H), 2.89 – 2.79 (m, 2 H), 1.34 (d, J = 6.8 Hz, 3 H). LCMS RT = 0.521 min, m/z = 378.2.	0.034
I-252	 1-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-3-methyl-1H,2H,3H,4H,5H-pyrido[3,4-b]azepin-2-one	1H NMR (400 MHz, CDCl3) δ 8.77 (s, 1 H), 8.46 (d, J = 4.8 Hz, 1 H), 8.37 (s, 1 H), 7.30 (d, J = 4.4 Hz, 1 H), 6.90 (t, J = 51.6 Hz, 1 H), 5.37 (s, 2 H), 2.99 – 2.90 (m, 1 H), 2.70 – 2.66 (m, 1 H), 2.55 – 2.49 (m, 1 H), 2.23 – 2.14 (m, 1 H), 2.18 – 2.04 (m, 1 H), 1.16 (d, J = 6.4 Hz, 3 H). LCMS RT = 1.229 min, m/z = 392.3.	0.073
I-253	 1-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-3,3-dimethyl-1H,2H,3H,4H,5H-pyrido[3,4-b]azepin-2-one	1H NMR (400 MHz, CDCl3) δ 8.84 (s, 1 H), 8.47 (s, 1 H), 8.40 (s, 1 H), 7.42 (s, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.37 (s, 2 H), 2.91 (t, J = 6.0 Hz, 2 H), 2.18 (t, J = 6.4 Hz, 2 H), 1.04 (s, 6 H) LCMS RT = 1.946 min, m/z = 405.9.	0.035
I-254	 1-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-3,3-dimethyl-1H,2H,3H-pyrrolo[2,3-c]pyridin-2-one	1H NMR (400 MHz, CDCl3) δ 8.45 – 8.43 (m, 2 H), 8.29 (s, 1 H), 7.24 (d, J = 4.8 Hz, 1 H), 6.89 (t, J = 51.6 Hz, 1 H), 5.33 (s, 2 H), 1.49 (s, 6 H) LCMS RT = 0.408 min, m/z = 378.1.	0.149

I-255	 1-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-3-methyl-1,2,3,4-tetrahydro-1,7-naphthyridin-2-one	1H NMR (400 MHz, CDCl3) δ 8.59 (s, 1 H), 8.42 (s, 1 H), 8.34 (d, J = 4.8 Hz, 1 H), 7.26 (d, J = 4.8 Hz, 1 H), 6.90 (t, J = 51.6 Hz, 1 H), 5.63 – 5.37 (m, 2 H), 3.13 – 3.06 (m, 1 H), 2.92 – 2.80 (m, 2 H), 1.36 (d, J = 6.4 Hz, 3 H) LCMS RT = 0.583 min, m/z = 378.2.	0.036
I-256	 1-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-4-methyl-1,2,3,4-tetrahydro-1,7-naphthyridin-2-one	1H NMR (400 MHz, CDCl3) δ 8.58 (s, 1 H), 8.45 – 8.34 (m, 2 H), 7.25 (d, J = 4.8 Hz, 1 H), 6.89 (t, J = 51.6 Hz, 1 H), 5.62 – 5.47 (m, 2 H), 3.27 – 3.20 (m, 1 H), 2.94 – 2.82 (m, 1 H), 2.67 – 2.56 (m, 1 H), 1.40 (d, J = 6.8 Hz, 3 H) LCMS RT = 0.580 min, m/z = 378.2.	0.057
I-257	 N-[5-(difluoromethoxy)pyridin-3-yl]-N-({2-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-5-yl}methyl)ethane-1-sulfonamide	1H NMR (400 MHz, CD3OD) δ 8.48 (d, J = 2.4 Hz, 1 H), 8.40 (d, J = 2.4 Hz, 1 H), 7.90 (s, 1 H), 7.77 (t, J = 2.4 Hz, 1 H), 7.23 (t, J = 51.6 Hz, 1 H), 6.97 (t, J = 72.8 Hz, 1 H), 5.35 (s, 2 H), 3.31 (q, J = 7.6 Hz, 2 H), 1.41 (t, J = 7.6 Hz, 3 H) LCMS RT = 1.251 min, m/z = 468.2.	0.231
I-258	 3-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-1H-pyrrolo[2,3-c]pyridin-2-ol	1H NMR (400 MHz, CD3OD) δ 8.40 (s, 1 H), 7.65 (s, 1 H), 7.50 (d, J = 6.8 Hz, 1 H), 7.17 (t, J = 51.6 Hz, 1 H), 6.94 (d, J = 6.8 Hz, 1 H), 4.27 (s, 2 H) LCMS RT = 0.778 min, m/z = 350.2.	0.069

I-259	 N-(5-chloropyridin-3-yl)-N-({2-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-5-yl}methyl)ethane-1-sulfonamide	1H NMR (400 MHz, CD3OD) δ 8.55 – 8.51 (m, 2 H), 8.05 (t, J = 2.4 Hz, 1 H), 7.92 (s, 1 H), 7.25 (t, J = 51.6 Hz, 1 H), 5.36 (s, 2 H), 3.34 (q, J = 7.2 Hz, 2 H), 1.42 (t, J = 7.6 Hz, 3 H) LCMS RT = 1.273 min, m/z = 436.2.	0.121
I-260	 N-({2-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-5-yl}methyl)-N-(pyridin-3-yl)ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.58 (d, J = 2.4 Hz, 1 H), 8.52 – 8.48 (m, 1 H), 7.98 (s, 1 H), 7.87 – 7.66 (m, 1 H), 7.56 (t, J = 51.2 Hz, 1 H), 7.45 – 7.42 (m, 1 H), 5.34 (s, 2 H), 3.37 (q, J = 7.2 Hz, 2 H), 1.30 (t, J = 7.2 Hz, 3 H) LCMS RT = 0.821 min, m/z = 402.2.	0.333
I-261	 N-(3-chlorophenyl)-N-({2-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-5-yl}methyl)ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.00 (s, 1 H), 7.56 (t, J = 51.2 Hz, 1 H), 7.41 – 7.36 (m, 4 H), 5.32 (s, 2 H), 3.36 (q, J = 7.2 Hz, 2 H), 1.29 (t, J = 8.0 Hz, 3 H) LCMS RT = 1.554 min, m/z = 435.1.	0.089
I-262	 N-(5-chloropyridin-3-yl)-N-({2-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-5-yl}methyl)methanesulfonamide	1H NMR (400 MHz, CD3OD) δ 8.61 – 8.47 (m, 2 H), 8.05 (t, J = 2.4 Hz, 1 H), 7.93 (s, 1 H), 7.23 (t, J = 51.6 Hz, 1 H), 5.32 (s, 2 H), 3.16 (s, 3 H) LCMS RT = 1.643 min, m/z = 422.1.	0.110

I-263	 N-({2-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-5-yl}methyl)-N-(5-fluoropyridin-3-yl)methanesulfonamide	1H NMR (400 MHz, CD3OD) δ 8.48 (s, 1 H), 8.46 (d, J = 2.4 Hz, 1 H), 7.93 (s, 1 H), 7.88 – 7.82 (m, 1 H), 7.23 (t, J = 51.6 Hz, 1 H), 5.33 (s, 2 H), 3.16 (s, 3 H) LCMS RT = 1.478 min, m/z = 406.1.	0.108
I-264	 N-({2-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-5-yl}methyl)-N-(5-fluoropyridin-3-yl)ethane-1-sulfonamide	1H NMR (400 MHz, CD3OD) δ 8.48 (s, 1 H), 8.45 (d, J = 2.8 Hz, 1 H), 7.91 (s, 1 H), 7.86 – 7.80 (m, 1 H), 7.24 (t, J = 51.6 Hz, 1 H), 5.35 (s, 2 H), 3.31 (q, J = 7.2 Hz, 2 H), 1.41 (t, J = 7.6 Hz, 3 H). LCMS RT = 1.618 min, m/z = 420.2.	0.087
I-265	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-[5-(trifluoromethoxy)pyridin-3-yl]methanesulfonamide	1H NMR (400 MHz, CDCl3) δ 8.72 (d, J = 2.0 Hz, 1 H), 8.56 (s, 1 H), 8.44 (s, 1 H), 7.80 (s, 1 H), 6.92 (t, J = 51.6 Hz, 1 H), 5.30 (s, 2 H), 3.11 (s, 3 H) LCMS RT = 1.950 min, m/z = 472.1.	0.048
I-266	 2-cyano-N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-(pyridin-3-yl)ethane-1-sulfonamide	1H NMR (400 MHz, CD3OD) δ 8.70 (d, J = 2.8 Hz, 1 H), 8.52 (d, J = 3.6 Hz, 1 H), 8.44 (s, 1 H), 8.07 – 8.01 (m, 1 H), 7.54 – 7.49 (m, 1 H), 7.21 (t, J = 51.6 Hz, 1 H), 5.41 (s, 2 H), 3.72 (t, J = 7.2 Hz, 2 H), 3.05 (t, J = 7.2 Hz, 2 H). LCMS RT = 1.287 min, m/z = 426.8.	0.042

I-267	 N-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-N-[5-(trifluoromethoxy)pyridin-3-yl]ethane-1-sulfonamide	1H NMR (400 MHz, CDCl3) δ 8.71 (s, 1 H), 8.54 (s, 1 H), 8.41 (s, 1 H), 7.79 (s, 1 H), 6.92 (t, J = 51.6 Hz, 1 H), 5.30 (s, 2 H), 3.22 (q, J = 7.6 Hz, 2 H), 1.45 (t, J = 7.6 Hz, 3 H) LCMS RT = 0.328 min, m/z = 486.1	0.044
I-268	 3-[({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)(pyridin-3-yl)sulfamoyl]propanamide	1H NMR (400 MHz, CDCl3) δ 8.75 (d, J = 2.4 Hz, 1 H), 8.62 – 8.55 (m, 1 H), 8.39 (s, 1 H), 7.90 – 7.84 (m, 1 H), 7.40 – 7.33 (m, 1 H), 6.91 (t, J = 52.0 Hz, 1 H), 5.27 (s, 2 H), 3.58 (t, J = 7.2 Hz, 2 H), 2.81 (t, J = 7.2 Hz, 2 H). LCMS RT = 0.783 min, m/z = 444.9.	0.013
I-269	 1-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-1H,2H,3H,4H,5H-pyrido[3,4-b]azepin-2-one	1H NMR (400 MHz, CDCl3) δ 8.77 (s, 1 H), 8.46 (s, 1 H), 8.38 (s, 1 H), 7.28 (s, 1 H), 6.91 (t, J = 51.6 Hz, 1 H), 5.36 (s, 2 H), 2.84 (t, J = 6.8 Hz, 2 H), 2.49 – 2.37 (m, 2 H), 2.37 – 2.23 (m, 2 H). LCMS RT = 1.043 min, m/z = 378.2	0.018
I-270	 1-({5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1,3-thiazol-2-yl}methyl)-1,2,3,4-tetrahydroquinoline	1H NMR (400 MHz, DMSO-d6) δ 8.57 (s, 1 H), 7.51 (t, J = 51.2 Hz, 1 H), 7.00 – 6.90 (m, 2 H), 6.60 – 6.55 (m, 2 H), 4.86 (s, 2 H), 3.47 (t, J = 5.6 Hz, 2 H), 2.75 (t, J = 6.0 Hz, 2 H), 2.02 – 1.92 (m, 2 H) LCMS RT = 1.769 min, m/z = 349.2	0.539

Example 8:

Biochemical Activity and Potency of various HDAC6 Inhibitors of Formula (II)

[0406] The compounds disclosed herein, in particular those of Formula (II), were synthesized according to methods disclosed in WO2021067859, which is incorporated herein by reference in its entirety. These compounds were tested for potency against HDAC6 and selectivity against HDAC1 in a biochemical assay. A biochemical assay was adopted using a luminescent HDAC-Glo I/II assay (Promega) and measured the relative activity of HDAC6 and HDAC1 recombinant proteins. Compounds were first incubated in the presence of HDAC6 or HDAC1 separately, followed by addition of the luminescent substrate. The data was acquired using a plate reader and the biochemical IC_{50} were calculated from the data accordingly. Data is tabulated in Table 14. From these studies, it was determined that the compounds of the present disclosure are selective inhibitors of HDAC6 over HDAC1, providing selectivity ratios from about 5 to about 30,0000.

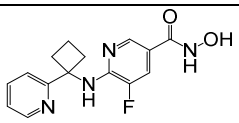
Table 14. Evaluation of HDAC6 Activity and Selectivity for Disclosed Compounds.

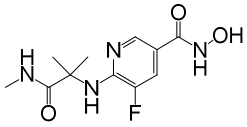
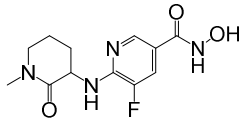
Compound ID	HDAC6 IC50 (nM)
1	136
I-1	12.5
I-6	1.61
I-4	16.7
I-24	146
I-5	6.68
I-7A	1.5
I-7B	4.13
I-2	104
I-10	76.6
I-3	73
IV-1	8.26
IV-4	1.8
I-9A	0.351
IV-2	0.677
IV-3	3.35
I-9B	0.791

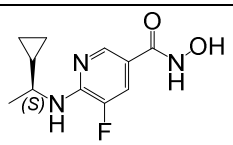
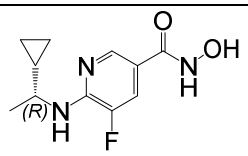
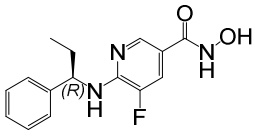
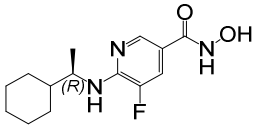
Compound ID	HDAC6 IC50 (nM)
I-11	0.639
I-19	0.425
I-18	1.68
I-16	1.61
I-8B	0.275
I-13	73
I-14	28.3
I-17	1.12
4	1.2
I-25	0.669
IV-9	0.595
I-21	0.601
I-22	3.36
I-23	1.59
III-1	1.79
IV-5	2.04
I-12B	0.809
IV-10	2.3
IV-7	1.1
IV-6	4.06
IV-8	10.3
I-15	2.64
I-20	3.78
I-8A	1.65
5	1.49
I-26A	4.57
I-26B	2.23
6	2.54
I-27	1.13
I-28A	1.81
I-29	13.2

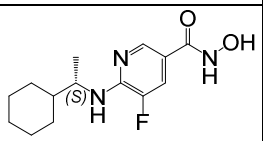
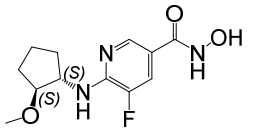
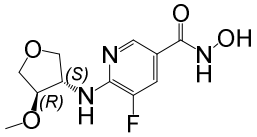
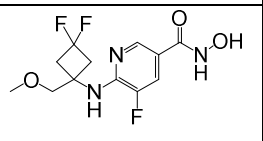
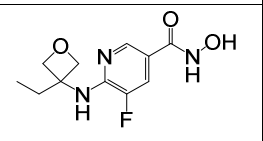
Compound ID	HDAC6 IC50 (nM)
I-30A	1.36
I-30B	7.91
I-31	13.8
I-32	13
I-33	27.9
I-34	2.32
I-35	21.7
I-36	5.22

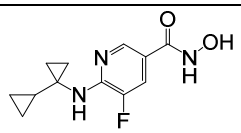
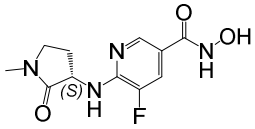
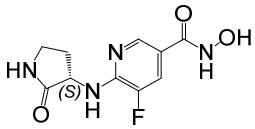
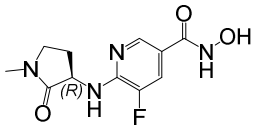
[0407] The structures, chemical names and additional biochemical properties of the compounds described in this example are provided below.

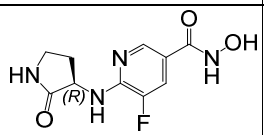
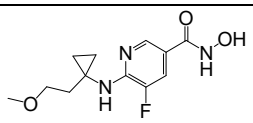
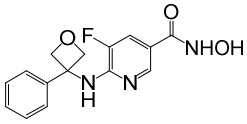
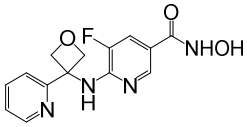
Aldehyde/ Organometallic	Compound	Characterization Data
cyclobutanone/ 2-bromopyridine, and *n*-BuLi	 **I-37**	**^{1}H NMR** (400 MHz, MeOH-*d*4) δ 8.52 (d, J=6.03 Hz, 1 H), 8.03 (s, 1 H), 7.70 (t, J=7.70 Hz, 1 H), 7.58 (d, J=12.2 Hz, 1 H), 7.51 (d, J=8.07 Hz, 1 H), 7.22 (t, J=6.03 Hz, 1 H), 2.89-2.80 (m, 2 H), 2.62-2.52 (m, 2 H), 2.20-2.15 (m, 1 H), 2.12-2.06 (m, 1H). **LC-MS** t_R (min) 1.24 (20-100% ACN with 0.1 %TFA 6 min), m/z $[M+H]^+$ $C_{15}H_{15}FN_4O_2$ requires: 302.3, found: 303.1 **HPLC** t_R (min) 3.68, 95% (20-100% ACN with 0.1 %TFA 10 min.

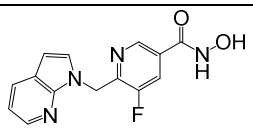
Amine	Compound	Characterization Data
2-amino-N, 2-dimethyl propanamide	 **I-33**	**^{1}H NMR** (400 MHz, MeOH-*d*4) δ 8.24 (s, 1 H), 7.62 (s, 1 H), 7.59 (s, 1 H), 2.69-2.65 (m, 3 H), 1.59 (s, 6 H). **LC-MS**: t_R (min) 1.32 (20-100% ACN with 0.1 %TFA 6 min), m/z $[M+H]^+$ $C_{11}H_{15}FN_4O_2$ requires: 270.3, found: 271.1 **HPLC** t_R (min) 1.57, 95% (20-100% ACN with 0.1 %TFA 10 min.)
3-amino-1-methylpi		**^{1}H NMR** (400 MHz, DMSO-*d*6) δ 11.1-10.9 (br, s, 1 H), 8.98 (s, 1 H), 8.25 (s, 1 H), 7.73-7.53 (m, 1 H), 7.29-7.04 (m, 1 H), 4.80-4.50 (m, 1 H), 3.33-3.28 (m,

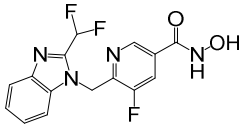
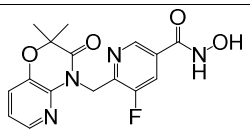
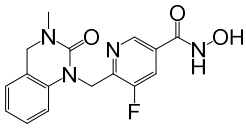
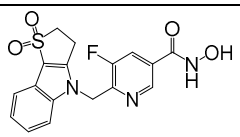
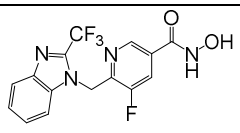
peridin-2-one	**I-35**	2 H), 2.83 (s, 3 H), 2.16-2.00 (m, 1 H), 1.90 (br, s, 3 H). **LC-MS**: tR (min) 1.28 (20-100% ACN with 0.1 %TFA 6 min), m/z $[M+H]^+$ $C_{12}H_{15}FN_4O_2$ requires: 282.3, found: 283.1 **HPLC** tR (min) 3.66, 95% (20-100% ACN with 0.1 %TFA 10 min.)
(S)-1-cyclopropylethan-1-amine	 **I-26A**	**^{1}H NMR** (400 MHz, MeOH-*d*4) δ 7.98 (s, 1 H), 7.32 (d, J=1.71 Hz, 1 H), 7.29 (d, J=1.71 Hz, 1 H), 3.45-3.35 (m, 1 H), 1.07 (d, J=6.60 Hz, 3 H), 0.86-0.74 (m, 1 H), 0.33-0.01 (m, 4 H). **LC-MS**: t_R (min) 2.03 (20-100% ACN with 0.1 %TFA 6 min), m/z $[M+H]^+$ $C_{11}H_{12}FN_3O_2$ requires: 239.3, found: 240.1 **HPLC** t_R (min) 4.37, 95% (20-100% ACN with 0.1 %TFA 10 min.)
(R)-1-cyclopropylethan-1-amine	 **I-26B**	**^{1}H NMR** (400 MHz, MeOH-*d*4) δ 7.98 (s, 1 H), 7.32 (d, J=1.71 Hz, 1 H), 7.29 (d, J=1.47 Hz, 1 H), 3.10-3.07 (m, 1 H), 1.07 (d, J=6.60 Hz, 3 H), 0.90-0.70 (m, 1 H), 0.33-0.00 (m, 4 H). **LC-MS**: t_R (min) 2.03 (20-100% ACN with 0.1 %TFA 6 min), m/z $[M+H]^+$ $C_{11}H_{12}FN_3O_2$ requires: 239.3, found: 240.1 **HPLC** t_R (min) 3.74, 95% (20-100% ACN with 0.1 %TFA 10 min.)
(R)-1-phenylpropan-1-amine	 **I-28A**	**^{1}H NMR** (400 MHz, MeOH-*d*4) δ 8.20 (s, 1 H), 7.56 (d, J=11.7 Hz, 1 H), 7.39 (d, J=7.58 Hz, 2 H), 7.29 (t, J=7.46 Hz, 2 H), 7.24-7.11 (m, 1 H), 5.15-5.02 (m, 1 H), 2.00-1.75 (m, 2 H), 1.02-0.90 (m, 3 H). **LC-MS**: t_R (min) 3.70 (20-100% ACN with 0.1 %TFA 6 min), m/z $[M+H]^+$ $C_{13}H_{15}FN_3O_2$ requires: 289.3, found: 290.1 **HPLC** t_R (min) 5.23, 98% (20-100% ACN with 0.1 %TFA 10 min.)
(R)-1-cyclohexylethylamine	 **I-30A**	**^{1}H NMR** (400 MHz, MeOH-*d*4) δ 8.24 (s, 1H), 7.56 (s, 1 H), 7.53 (s, 1 H), 4.63 (s, 2 H), 4.09 (t, J=6.72 Hz, 1 H), 1.88-1.65 (m, 5 H), 1.55-1.45 (m, 1 H), 1.31-1.22 (m, 3 H), 1.22-1.15 (m, 3 H), 1.10-0.90 (m, 2 H). **LC-MS**: t_R (min) 3.37 (20-100% ACN with 0.1 %TFA 6 min), m/z $[M+H]^+$ $C_{14}H_{20}FN_3O_2$ requires: 281.3, found: 282.2

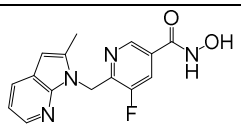
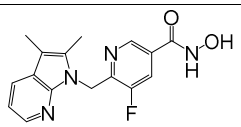
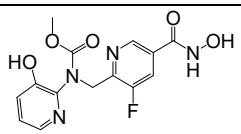
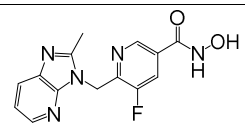
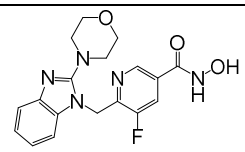
		HPLC t_R (min) 4.84, 97% (20-100% ACN with 0.1 %TFA 10 min.)
(S)-1-cyclohexylethylamine	 **I-30B**	**^{1}H NMR** (400 MHz, MeOH-*d*4) δ 8.24 (s, 1H), 7.56 (s, 1 H), 7.53 (s, 1 H), 4.63 (s, 2 H), 4.09 (t, J=6.97 Hz, 1 H), 1.88-1.65 (m, 5 H), 1.51 (s, 1 H), 1.31-1.20 (m, 3 H), 1.22-1.18 (m, 3 H), 1.10-0.90 (m, 2 H). **LC-MS**: t_R (min) 3.50 (20-100% ACN with 0.1 %TFA 6 min), m/z $[M+H]^+$ $C_{14}H_{20}FN_3O_2$ requires: 281.3, found: 282.1 **HPLC** t_R (min) 5.10, 98% (20-100% ACN with 0.1 %TFA 10 min.)
(1S, 2S)-2-methoxycyclopentylamine	 **I-36**	**^{1}H NMR** (400 MHz, CDCl3-*d*) δ 8.27 (s, 1 H), 7.58-7.39 (m, 1 H), 5.06 (br, s, 1 H), 4.31 (br, s, 1 H), 3.68 (br, s, 1 H), 3.34 (s, 3 H), 2.25- 2.15 (m, 1 H), 1.93-1.88 (m, 1 H), 1.85-1.75 (m, 3 H), 1.50-1.40 (m, 1 H). **LC-MS**: t_R (min) 1.93 (20-100% ACN with 0.1 %TFA 6 min), m/z $[M+H]^+$ $C_{12}H_{16}FN_3O_2$ requires: 269.3, found: 270.1 **HPLC** t_R (min) 3.71, 97% (20-100% ACN with 0.1 %TFA 10 min.)
(3S, 4R)-4-methoxytetrahydrofuran-3-yl)amine	 **I-38**	**^{1}H NMR** (400 MHz, MeOH-*d*4) δ 8.33 (s, 1 H), 7.60 (d, J=11.98 Hz, 1 H), 4.60 (br, s, 1 H), 4.20-4.05 (m, 2 H), 4.00-3.90 (m, 1 H), 3.85-3.75 (m, 2 H), 3.48 (s, 3 H). **LC-MS**: t_R (min) 1.39 (20-100% ACN with 0.1 %TFA 6 min), m/z $[M+H]^+$ $C_{11}H_{14}FN_3O_2$ requires: 271.3, found: 272.1 **HPLC** t_R (min) 2.97, 97% (20-100% ACN with 0.1 %TFA 10 min.)
3,3-difluoro-1-(methoxymethyl)cyclobutan-1-amine	 **I-39**	**^{1}H NMR** (400 MHz, MeOH-*d*4) δ 8.16 (s, 1 H), 7.48 (d, J=12.2 Hz, 1 H), 4.52 (s, 2 H), 3.63 (s, 2 H), 3.26-3.23 (m, 3 H), 2.82-2.72 (m, 4H). **LC-MS**: t_R (min) 3.00 (20-100% ACN with 0.1 %TFA 6 min), m/z $[M+H]^+$ $C_{12}H_{14}F_3N_3O_3$ requires: 305.3, found: 306.1 **HPLC** t_R (min) 5.02, 93% (20-100% ACN with 0.1 %TFA 10 min.)
3-ethyloxetan-3-amine	 **I-40**	**^{1}H NMR** (400 MHz, MeOH-*d*4) δ 8.22 (s, 1 H), 7.59 (d, J=11.98 Hz, 1 H), 4.80 (br, s, 2 H), 4.60 (br, s, 2 H), 2.22 (q, J=6.93 Hz, 2 H), 0.92 (t, J=6.95 Hz, 3 H).

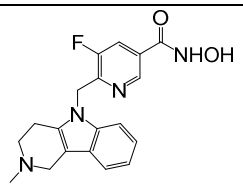
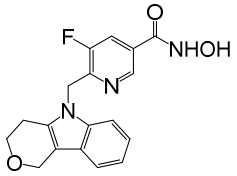
		LC-MS: t_R (min) 1.10 (20-100% ACN with 0.1 %TFA 6 min), m/z $[M+H]^+$ $C_{11}H_{13}FN_3O_3$ requires: 255.2, found: 256.1 **HPLC** t_R (min) 3.80, 99% (20-100% ACN with 0.1 %TFA 10 min.)
1,1'-bi(cyclopropan)-1-amine	 **I-41**	**^{1}H NMR** (400 MHz, MeOH-*d*4) δ 8.07 (s, 1 H), 7.32 (d, J=11.98 Hz, 1 H), 4.40 (br, s, 1 H), 3.08 (s, 1 H), 1.35-1.25 (m, 1 H), 0.48 (d, J=5.38 Hz, 4 H), 0.38-0.42 (m, 2 H), 0.01 (s, 2 H). **LC-MS**: t_R (min) 1.20 (20-100% ACN with 0.1 %TFA 6 min), m/z $[M+H]^+$ $C_{11}H_{13}FN_3O_3$ requires: 251.3, found: 252.1 **HPLC** t_R (min) 3.17, 96% (20-100% ACN with 0.1 %TFA 10 min.)
(S)-1-methyl-2-oxopyrrolidin-3-amine	 **I-42A**	**^{1}H NMR** (400 MHz, DMSO-*d*6) δ 11.05 (br, s, 1 H), 9.00 (br, s, 1 H), 8.50 (br, s, 1 H), 7.65 (d, J=12.0 Hz, 1 H), 7.45 (d, J= 8.80 Hz, 1 H), 4.90-4.80 (m, 1 H), 3.45-3.40 (m, 2 H), 2.76 (s, 3 H), 2.30-2.20 (m, 1 H), 1.90-2.00 (m, 1 H). **LC-MS**: t_R (min) 1.10 (20-100% ACN with 0.1 %TFA 6 min), m/z $[M+H]^+$ $C_{11}H_{13}FN_3O_3$ requires: 268.3, found: 269.1 **HPLC** t_R (min) 1.54, 96% (20-100% ACN with 0.1 %TFA 10 min.)
(S)-2-oxopyrrolidin-3-amine	 **I-43A**	**^{1}H NMR** (400 MHz, DMSO-*d*6) δ 11.05 (br, s, 1 H), 8.95 (br, s, 1 H), 8.25 (s, 1 H), 7.83 (s, 1 H), 7.65 (d, J=12.0 Hz, 1 H), 7.45 (d, J=8.80 Hz, 1 H), 4.70-4.85 (m, 1 H), 3.23 (d, J=6.34 Hz, 2 H), 2.40-2.30 (m, 1 H), 2.15-2.05 (m, 1 H). **LC-MS**: t_R (min) 1.10 (20-100% ACN with 0.1 %TFA 6 min), m/z $[M+H]^+$ $C_{12}H_{16}FN_3O_3$ requires: 254.2, found: 255.1 **HPLC** t_R (min) 1.71, 96% (20-100% ACN with 0.1 %TFA 10 min.)
(R)-1-methyl-2-oxopyrrolidin-3-amine	 **I-42B**	**^{1}H NMR** (400 MHz, DMSO-*d*6) δ 11.05 (br, s, 1 H), 8.99 (br, s, 1 H), 8.25 (s, 1 H), 7.65 (d, J=12.2 Hz, 1 H), 7.42 (d, d, J=8.07 Hz, 1 H), 4.82 (d, J=9.05 Hz, 1 H), 3.34-3.27 (m, 2 H), 2.76 (s, 3 H), 2.40-2.26 (m, 1 H), 2.03-1.92 (m, 1 H). **LC-MS**: t_R (min) 1.20 (20-100% ACN with 0.1 %TFA 6 min), m/z $[M+H]^+$ $C_{12}H_{16}FN_3O3$ requires: 268.3, found: 269.1

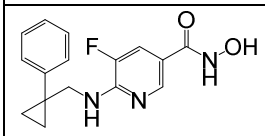
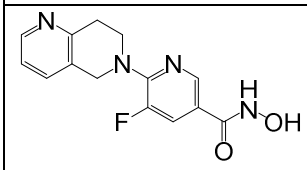
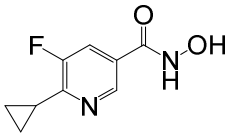
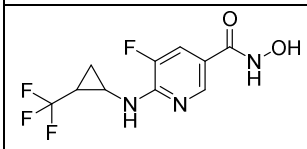
		HPLC t_R (min) 1.75, 99% (20-100% ACN with 0.1 %TFA 10 min.)
(R)-2-oxopyrrolidin-3-amine	 **I-43B**	**^{1}H NMR** (400 MHz, DMSO-*d*6) δ 11.0 (br, s, 1 H), 9.05 (br, s, 1 H), 8.45 (s, 1 H), 7.84 (s, 1 H), 7.65 (d, J=12.0 Hz, 1 H), 7.34 (d, J=8.80 Hz, 1 H), 4.77 (d, J=9.29 Hz, 1 H), 3.18-3.28 (m, 2 H), 2.30-2.40 (m, 1 H), 2.15-2.05 (m, 1 H). **LC-MS**: tR (min) 1.15 (20-100% ACN with 0.1 %TFA 6 min), m/z $[M+H]^+$ $C_{12}H_{16}FN_3O_3$ requires: 254.2, found: 255.1 **HPLC** tR (min) 1.55, 93% (20-100% ACN with 0.1 %TFA 10 min.)
1-(2-methoxyethyl)cyclopropyl)amine	 **I-44**	**^{1}H NMR** (400 MHz, MeOH-*d*4) δ 8.32 (s, 1 H), 7.57 (d, J=11.98 Hz, 1 H), 3.55 (t, J=6.85, 2 H), 3.30 (s, 3 H), 1.96 (t, J=6.85 Hz, 2 H), 0.80 (s, 4 H). **LC-MS**: t_R (min) 1.20 (20-100% ACN with 0.1 %TFA 6 min), m/z $[M+H]^+$ $C_{12}H_{16}FN_3O_3$ requires: 269.3, found: 270.1 **HPLC** t_R (min) 2.07, 99% (20-100% ACN with 0.1 %TFA 10 min.)
3-phenyloxetan-3-amine	 **I-27**	**^{1}H NMR** (400 MHz, DMSO-*d*6) δ 10.95 (br s, 1 H), 8.97 (s, 1 H), 8.38 (m, 1 H), 8.02 (m, 1 H), 7.69 (m, 1 H), 7.53 (m, 2 H), 7.34 (m, 2 H), 7.24 (m, 1 H), 4.99 (m, 2 H), 4.78 (m, 2 H). **LC-MS**: m/z $[M+H]^+$ $C_{15}H_{14}FN_3O_3$ requires: 303.2, found: 304.1 **HPLC** t_R (min) 4.81, 95% (10-100% ACN with 0.1 %TFA 10 min.)
3-(pyridin-2-yl)oxetan-3-amine	 **I-56**	**^{1}H NMR** (400 MHz, DMSO-*d*6) δ 10.97 (br s, 1 H), 8.97 (s, 1 H), 8.63 (m, 1 H), 8.46 (m, 1 H), 7.99 (m, 1 H), 7.71-7.66 (m, 2 H), 7.31-7.15 (m, 2 H), 5.01 (m, 2 H), 4.87 (m, 2 H). **LC-MS**: m/z $[M+H]^+$ $C_{14}H_{13}FN_4O_3$ requires: 304.2, found: 305.1 **HPLC** t_R (min) 1.27, 93% (10-100% ACN with 0.1 %TFA 10 min.)

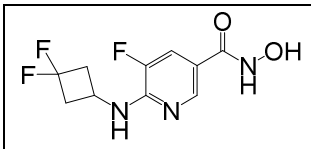
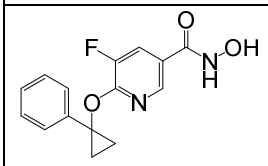
Amine	Compound	Characterization Data
1H-pyrrolo[2,3-	 **5**	**^{1}H NMR** (400 MHz, DMSO-*d*6) δ 11.41 (br s, 1 H), 9.31 (s, 1 H), 8.57 (m, 1 H), 8.18 (m, 1 H), 7.98 (m, 2 H), 7.60 (m, 1 H), 7.08 (m, 1 H), 6.52 (m, 1 H), 5.71 (s, 2 H).

b]pyridine		**LC-MS**: m/z $[M+H]^+$ $C_{14}H_{11}FN_4O_2$ requires: 286.2, found: 287.1 **HPLC** t_R (min) 3.21, 98% (20-100% ACN with 0.1 %TFA 10 min.)
2-(difluoromethyl)-1H-benzo[d]imidazole	 **6**	**^{1}H NMR** (400 MHz, DMSO-*d*6) δ 11.41 (br s, 1 H), 9.32 (s, 1 H), 8.51 (s, 1 H), 8.01 (m, 1 H), 7.63 (m, 1 H), 7.62 (m, 1 H), 7.53-7.27 (m, 3 H), 5.92 (s, 2 H). **LC-MS**: m/z $[M+H]^+$ $C_{15}H_{11}F_3N_4O_2$ requires: 336.2.1, found: 337.1 **HPLC** t_R (min) 4.87, 97% (10-100% ACN with 0.1 %TFA 10 min.)
2,2-dimethyl-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one	 **I-34**	**^{1}H NMR** (400 MHz, DMSO-*d*6) δ 11.37 (br s, 1 H), 9.30 (s, 1 H), 8.52 (s, 1 H), 7.97 (m, 1 H), 7.88 (m, 1 H), 7.44 (m, 1 H), 7.03 (m, 1 H), 5.42 (s, 2 H), 1.51 (s, 6 H). **LC-MS**: m/z $[M+H]^+$ $C_{16}H_{15}FN_4O_4$ requires: 346.3, found: 347.1 **HPLC** t_R (min) 5.04, 100% (10-100% ACN with 0.1 %TFA 10 min.)
3-methyl-3,4-dihydroquinazolin-2(1H)-one	 **I-47**	**^{1}H NMR** (400 MHz, DMSO-*d*6) δ 11.40 (br s, 1 H), 9.30 (s, 1 H), 8.55 (s, 1 H), 7.94 (m, 1 H), 7.15-7.11 (m, 2 H), 6.93 (m, 1 H), 6.74 (m, 1 H), 5.22 (s, 2 H), 4.40 (s, 2 H), 2.90 (s, 3 H). **LC-MS**: m/z $[M+H]^+$ $C_{16}H_{15}FN_4O_3$ requires: 330.3, found: 331.1 **HPLC** t_R (min) 4.93, 100% (10-100% ACN with 0.1 %TFA 10 min.)
3,4-dihydro-2H-thieno[3,2-b]indole 1,1-dioxide	 **I-48**	**^{1}H NMR** (400 MHz, DMSO-*d*6) δ 8.62 (s, 1 H), 8.02 (m, 1 H), 7.56 (m, 2 H), 7.27 (m, 2 H), 5.68 (s, 2 H), 3.94 (m, 2 H), 3.46 (m, 2 H). **LC-MS**: m/z $[M+H]^+$ $C_{17}H_{14}FN_3O_4S$ requires: 375.3, found: 376.1 **HPLC** t_R (min) 4.85, 96% (10-100% ACN with 0.1 %TFA 10 min.)
2-(trifluoromethyl)-1H-benzo[d]imidazole	 **I-49**	**^{1}H NMR** (400 MHz, DMSO-*d*6) δ 11.41 (br s, 1 H), 9.33 (s, 1 H), 8.49 (s, 1 H), 8.04 (m, 1 H), 7.84 (m, 1 H), 7.72 (m, 1 H), 7.44 (m, 2 H), 5.95 (s, 2 H). **LC-MS**: m/z $[M+H]^+$ $C_{15}H_{10}F_4N_4O_2$ requires: 354.2, found: 355.1 **HPLC** t_R (min) 4.94, 98% (10-100% ACN with 0.1 %TFA 10 min.)

2-methyl-1H-pyrrolo[2,3-b]pyridine	 **I-50**	**^{1}H NMR** (400 MHz, DMSO-*d*6) δ 11.39 (br s, 1 H), 9.31 (s, 1 H), 8.51 (s, 1 H), 8.06 (m, 1 H), 7.97 (m, 1 H), 7.84 (m, 1 H), 7.03 (m, 1 H), 6.29 (s, 1 H), 5.69 (s, 2 H), 2.40 (s, 3 H). **LC-MS**: m/z $[M+H]^+$ $C_{15}H_{13}FN_4O_2$ requires: 300.2, found: 301.1 **HPLC** t_R (min) 3.83, 100% (20-100% ACN with 0.1 %TFA 10 min.)
2,3-dimethyl-1H-pyrrolo[2,3-b]pyridine	 **I-51**	**^{1}H NMR** (400 MHz, DMSO-*d*6) δ 11.39 (br s, 1 H), 9.31 (s, 1 H), 8.51 (s, 1 H), 8.05 (m, 1 H), 7.95 (m, 1 H), 7.81 (m, 1 H), 7.01 (m, 1 H), 5.67 (s, 2 H), 2.31 (s, 3 H), 2.21 (s, 3 H). **LC-MS**: m/z $[M+H]^+$ $C_{16}H_{15}FN_4O_2$ requires: 314.3, found: 315.1 **HPLC** t_R (min) 4.17, 100% (20-100% ACN with 0.1 %TFA 10 min.)
oxazolo[4,5-b]pyridin-2(3H)-one	 **I-52**	**^{1}H NMR** (400 MHz, CD_3OD-d_4) δ 8.70 (s, 1 H), 7.98 (m, 2 H), 7.47 (m, 1 H), 7.38 (m, 1 H), 5.06 (s, 2 H), 3.64 (s, 3 H). **LC-MS**: m/z $[M+H]^+$ $C_{14}H_{13}FN_4O_5$ requires: 336.2, found: 337.1 **HPLC** t_R (min) 4.18, 96% (10-100% ACN with 0.1 %TFA 10 min.)
2-methyl-3H-imidazo[4,5-b]pyridine	 **I-53**	**^{1}H NMR** (400 MHz, DMSO-*d*6) δ 11.30 (br s, 1 H), 9.27 (s, 1 H), 8.47 (s, 1 H), 8.12 (m, 1 H), 7.95 (m, 1 H), 7.88 (m, 1 H), 7.15 (m, 1 H), 5.68 (s, 2 H), 2.44 (s, 3 H). **LC-MS**: m/z $[M+H]^+$ $C_{14}H_{12}FN_5O_2$ requires: 301.2, found: 302.1 **HPLC** t_R (min) 3.60, 98% (10-100% ACN with 0.1 %TFA 10 min.)
4-(1H-benzo[d]imidazol-2-yl)morpholine	 **I-54**	**^{1}H NMR** (400 MHz, DMSO-*d*6) δ 11.45 (br s, 1 H), 9.34 (s, 1 H), 8.59 (s, 1 H), 8.03 (m, 1 H), 7.45 (m, 1 H), 7.15-7.03 (m, 3 H), 5.55 (s, 2 H), 3.67 (m, 4 H), 3.14 (m, 4 H). **LC-MS**: m/z $[M+H]^+$ $C_{18}H_{18}FN_5O_3$ requires: 371.3, found: 372.1 **HPLC** t_R (min) 3.66, 95% (10-100% ACN with 0.1 %TFA 10 min.)

2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole	 **IV-10**	**^{1}H NMR** (400 MHz, DMSO-*d*6) δ 11.40 (br s, 1 H), 9.36 (s, 1 H), 8.61 (s, 1 H), 7.95 (m, 1 H), 7.35 (m, 2 H), 7.03-6.94 (m, 2 H), 5.50 (s, 2 H), 3.52 (s, 2 H), 2.83 (m, 2 H), 2.72 (m, 2 H), 2.42 (s, 3 H). **LC-MS**: m/z $[M+H]^+$ $C_{19}H_{19}FN_4O_2$ requires: 354.3, found: 355.2 **HPLC** t_R (min) 4.58, 99% (10-100% ACN with 0.1 %TFA 10 min.)
1,3,4,5-tetrahydropyrano[4,3-b]indole	 **I-29**	**^{1}H NMR** (400 MHz, DMSO-*d*6) δ 11.41 (br s, 1 H), 9.35 (s, 1 H), 8.61 (s, 1 H), 8.01 (m, 1 H), 7.40-7.32 (m, 2 H), 7.06-6.95 (m, 2 H), 5.54 (s, 2 H), 4.78 (s, 2 H), 3.95 (m, 2 H), 2.84 (m, 2 H). **LC-MS**: m/z $[M+H]^+$ $C_{18}H_{16}FN_3O_3$ requires: 341.3, found: 342.1 **HPLC** t_R (min) 4.99, 94% (10-100% ACN with 0.1 %TFA 10 min.)

Compound	Characterization Data
 **I-25**	**^{1}H NMR** (400 MHz, Solvent) δ ppm 8.18 (s, 1 H) 7.50 (br d, J=11.98 Hz, 1 H) 7.31 - 7.38 (m, 2 H) 7.23 (br t, J=7.46 Hz, 2 H) 7.10 - 7.17 (m, 1 H) 3.74 (s, 2 H) 0.93 - 0.99 (m, 2 H) 0.80 - 0.86 (m, 2 H)
 **IV-9**	**^{1}H NMR** (400 MHz, Solvent) δ ppm 8.39 (s, 1 H) 8.35 (d, J=4.65 Hz, 1 H) 7.64 - 7.76 (m, 2 H) 7.27 (dd, J=7.58, 5.14 Hz, 1 H) 4.86 (s, 2 H) 4.03 (t, J=5.87 Hz, 2 H) 3.10 (t, J=5.87 Hz, 2 H)
 **I-23**	**^{1}H NMR** (400 MHz, METHANOL-d4) δ ppm 8.57 (s, 1 H) 7.77 (d, J=10.27 Hz, 1 H) 2.31 - 2.46 (m, 1 H) 1.08 - 1.16 (m, 4 H) LCMS R_T = 2.79 min, *m/z* = 197.1 $[M + H]^+$.
 **I-31**	**^{1}H NMR** (400 MHz, METHANOL-d4) δ ppm 8.34 (s, 1 H) 7.60 (br d, J=11.49 Hz, 1 H) 3.22 - 3.28 (m, 1 H) 1.82 - 1.95 (m, 1 H) 1.21 - 1.31 (m, 1 H) 1.16 (br dd, J=10.03, 4.89 Hz, 1 H)

 **I-32**	**^{1}H NMR** (400 MHz, METHANOL-d4) δ ppm 8.30 (s, 1 H) 7.61 (br d, J=11.74 Hz, 1 H) 4.32 - 4.47 (m, 1 H) 2.94 - 3.12 (m, 2 H) 2.54 - 2.76 (m, 2 H)
 **III-1**	**^{1}H NMR** (400 MHz, METHANOL-d4) δ ppm 8.21 (s, 1 H) 7.82 (br d, J=10.27 Hz, 1 H) 7.25 - 7.32 (m, 4 H) 7.15 - 7.23 (m, 1 H) 1.44 - 1.50 (m, 2 H) 1.36 - 1.43 (m, 2 H)

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INCORPORATION BY REFERENCE

[0430] All references, articles, publications, patents, patent publications, and patent applications cited herein are incorporated by reference in their entireties for all purposes. However, mention of any reference, article, publication, patent, patent publication, and patent application cited herein is not, and should not be taken as an acknowledgment or any form of suggestion that they constitute valid prior art or form part of the common general knowledge in any country in the world.

What is claimed is:

1. Use of an HDAC6 inhibitor in the manufacture of a medicament for the treatment or prevention of a metabolic disease in a subject in need thereof, wherein a therapeutically effective amount of the HDAC6 inhibitor is to be administered to the subject.

2. The use of claim 1, wherein the subject is obese or at risk for obesity.

3. The use of claim 1, wherein the metabolic disease is a metabolic disease associated with obesity, optionally diet-induced obesity.

4. The use of claim 1, wherein the metabolic disease is a diabetes, pre-diabetes, diabetic cardiomyopathy, metabolic syndrome, hypertension, hypertriglyceridemia, or dyslipidemia.

5. The use of claim 4, wherein the metabolic disease is diabetes.

6. Use of an HDAC6 inhibitor in the manufacture of a medicament for the treatment of obesity in a subject in need thereof, wherein a therapeutically effective amount of the HDAC6 inhibitor is to be administered to the subject.

7. The use of any one of claims 1-6, wherein the subject has or is at risk for one of more of: (a) hypertension; (b) metabolic syndrome; (c) diabetes mellitus; (d) diabetic cardiomyopathy; and (e) hyperglyceridemia or dyslipidemia.

8. The use of any one of claims 1-6, wherein the treatment of prevention comprises treating or preventing at least one symptom of metabolic disease.

9. The use of any one of claims 1-6, wherein the treatment or prevention improves glucose tolerance and/or insulin resistance.

10. The use of any one of claims 1-6, wherein the treatment or prevention reduces glucose level.

11. The use of any one of claims 1-6, wherein the treatment or prevention inhibits inflammatory genes in adipose tissue.

12. The use of any one of claims 1-6, wherein the treatment or prevention prevents heart failure in the subject.

13. Use of an HDAC6 inhibitor in the manufacture of a medicament for the treatment or prevention of heart failure with preserved ejection fraction (HFpEF) in a subject in need thereof, wherein a therapeutically effective amount of the HDAC6 inhibitor is to be administered to the subject.

14. The use of claim 13, wherein the subject has or is at risk for one or more of: (a) hypertension; (b) diabetes mellitus; (c) coronary artery disease (CAD); (d) valvular heart disease; and (e) atrial fibrillation.

15. The use of claim 13, wherein the treatment or prevention comprises treating or preventing at least one symptom of HFpEF.

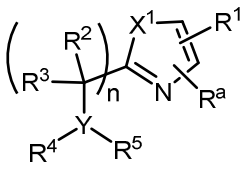
16. The use of claim 13, wherein the treatment or prevention reduces left ventricular (LV) mass and/or LV wall thickness.

17. The use of any one of claims 13-16, wherein the treatment or prevention improves LV relaxation and/or LV filling pressure.

18. The use of any one of claims 13-16, wherein the treatment or prevention prevents heart failure in the subject.

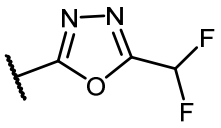
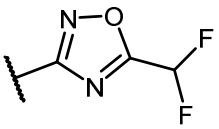
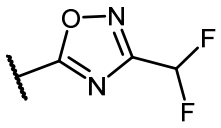
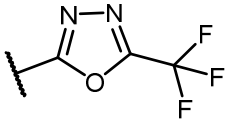
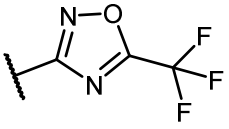
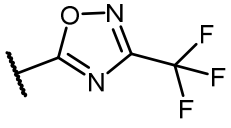
19. The use of any one of claims 1, 6, and 13, wherein the subject is a human.

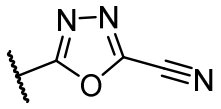
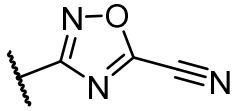
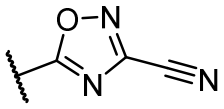
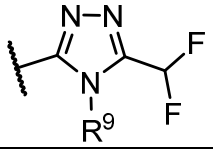
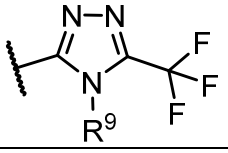
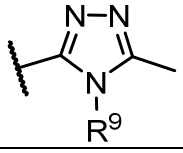
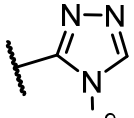
20. The use of any one of claims 1, 6, and 13, wherein the HDAC6 inhibitor is a compound according to Formula (I):



(I), wherein

R^1 is selected from the group consisting of:

		
		
 and ;		

R^a is selected from the group consisting of H, halo, C_{1-3} alkyl, cycloalkyl, haloalkyl, and alkoxy;

R^2 and R^3 are independently selected from the group consisting of H, halogen, alkoxy, haloalkyl, aryl, heteroaryl, alkyl, and cycloalkyl each of which is optionally substituted, or R^2 and R^3 together with the atom to which they are attached form a cycloalkyl or heterocyclyl;

R^4 and R^5 are independently selected from the group consisting of H, $–(SO_2)R^2$, $–(SO_2)NR^2R^3$, $–(CO)R^2$, $–(CONR^2R^3)$, aryl, arylheteroaryl, alkylenearyl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, haloalkyl, and alkoxy, each of which is optionally substituted, or R^4 and R^5 together with the atom to which they are attached form a cycloalkyl or heterocyclyl, each of which is optionally substituted;

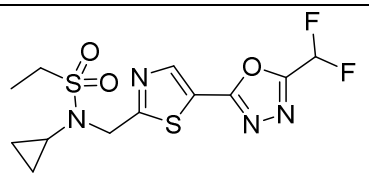
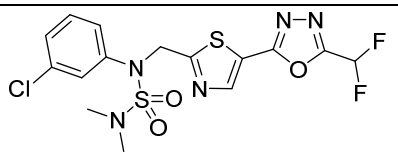
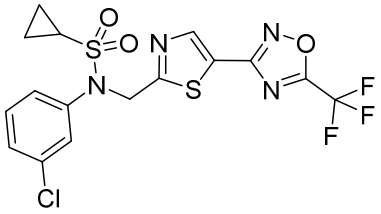
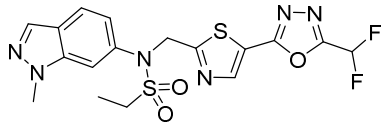
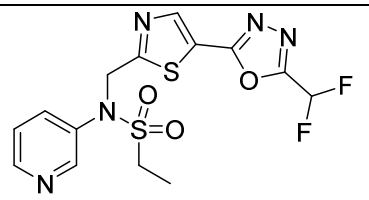
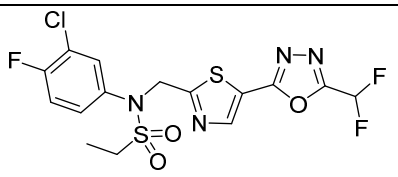
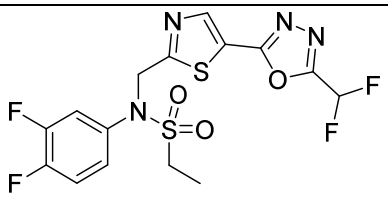
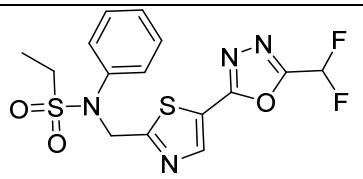
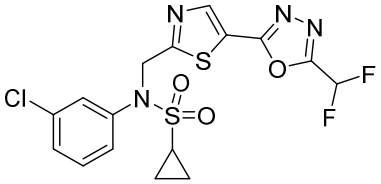
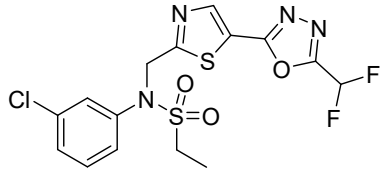
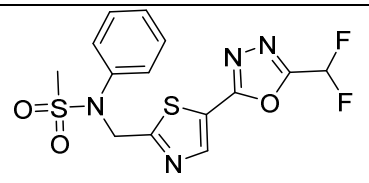
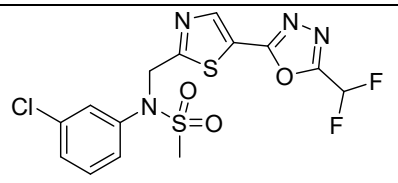
R^9 is selected from the group consisting of H, C_1-C_6 alkyl, haloalkyl, cycloalkyl and heterocyclyl;

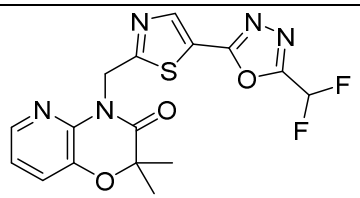
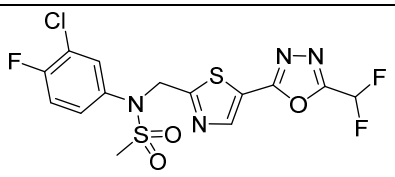
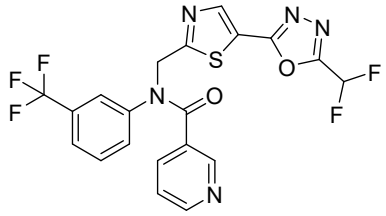
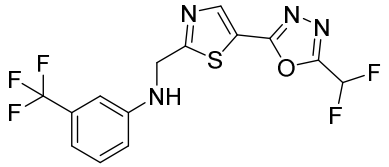
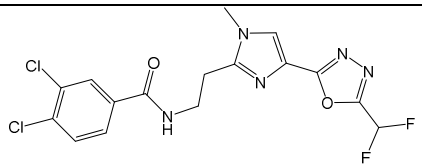
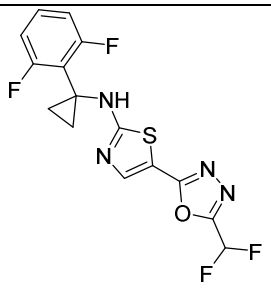
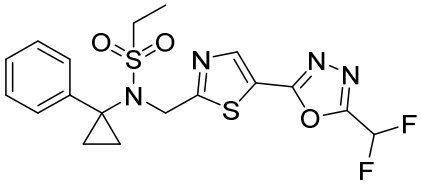
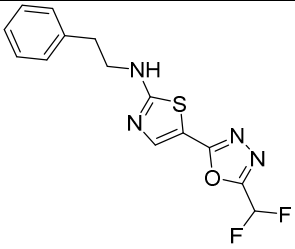
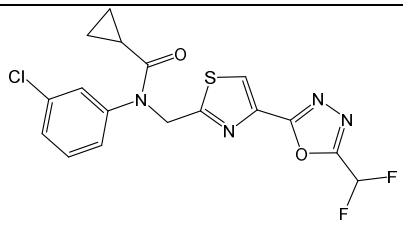
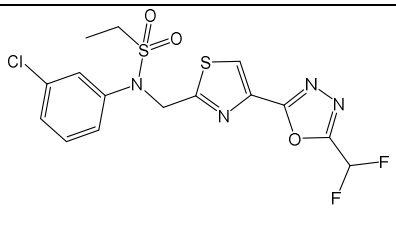
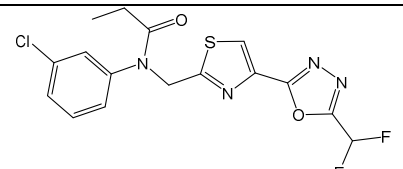
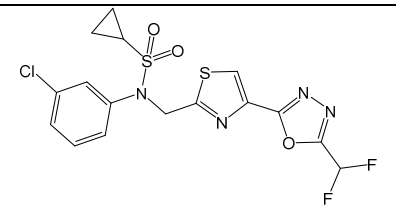
X^1 is selected from the group consisting of S, O, NH and NR^6, wherein R^6 is selected from the group consisting of C_1-C_6 alkyl, alkoxy, haloalkyl, cycloalkyl and heterocyclyl;

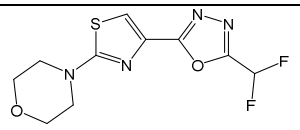
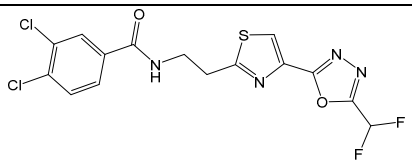
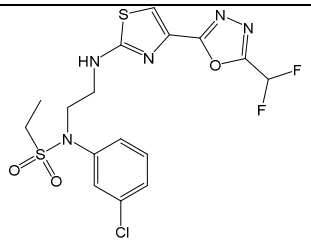
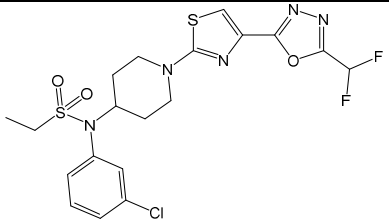
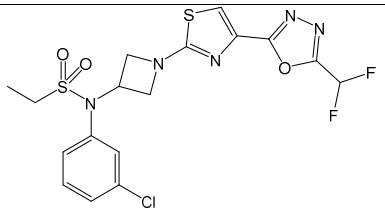
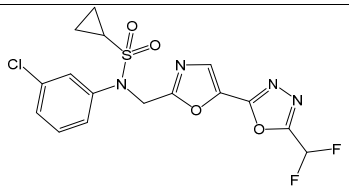
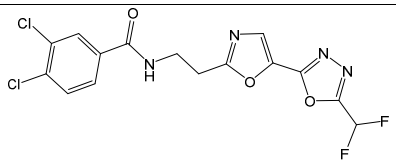
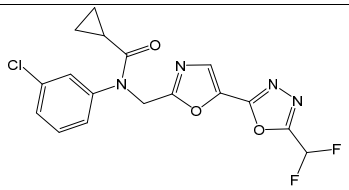
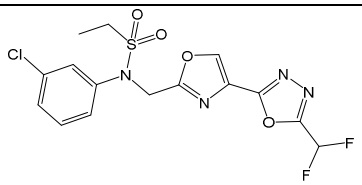
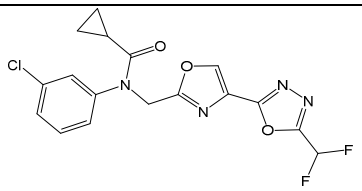
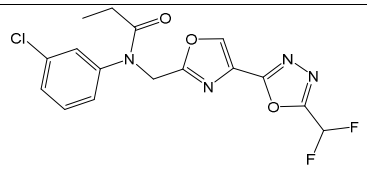
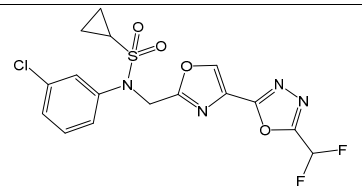
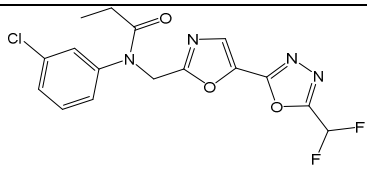
Y is selected from the group consisting of CR^2, O, N, S, SO, and SO_2, wherein when Y is O, S, SO, or SO_2, R^5 is not present and when R^4 and R^5 together with the atom to which they are attached form a cycloalkyl or heterocyclyl, Y is CR^2 or N; and

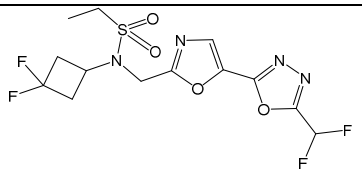
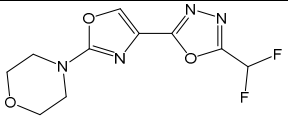
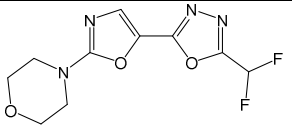
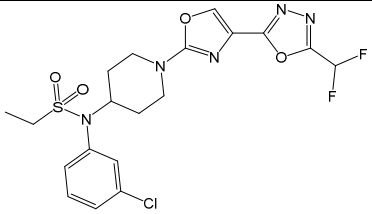
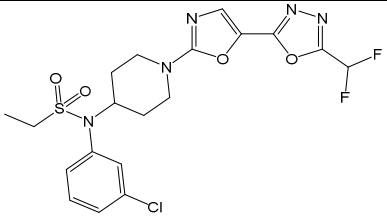
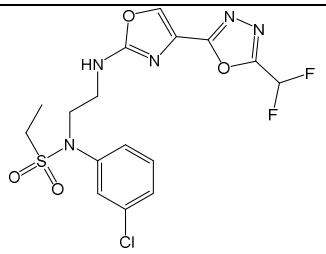
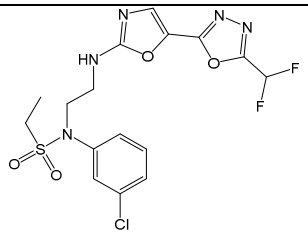
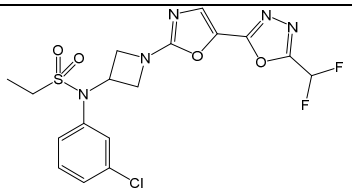
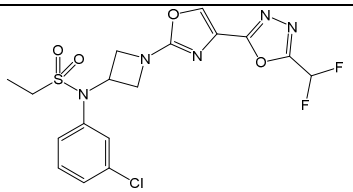
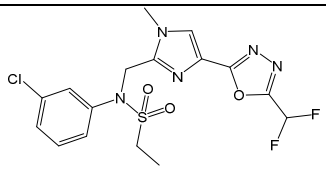
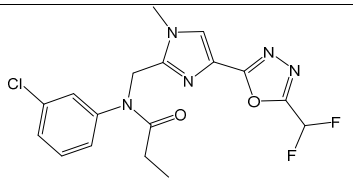
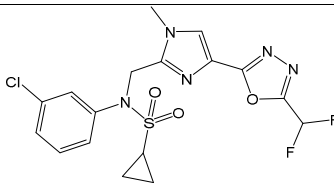
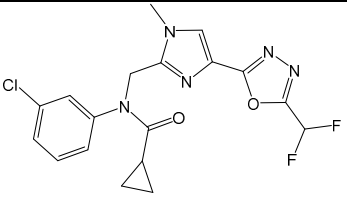
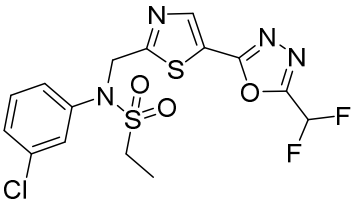
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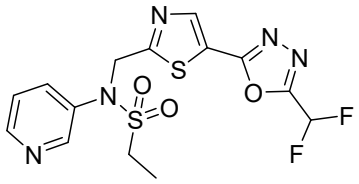
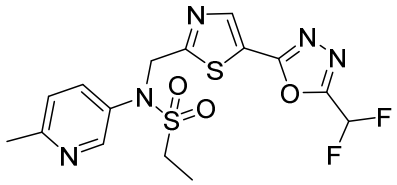
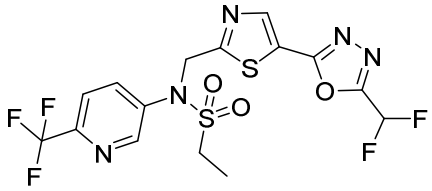
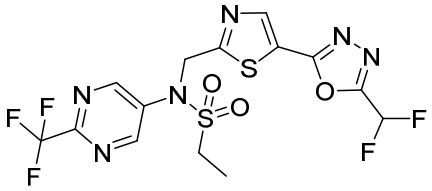
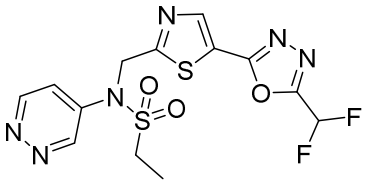
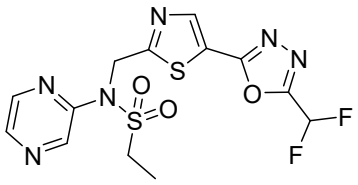
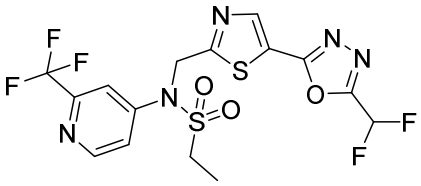
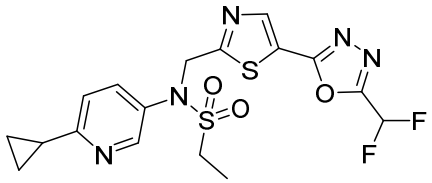
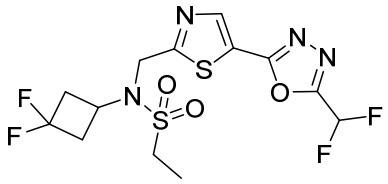
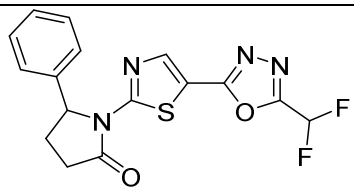
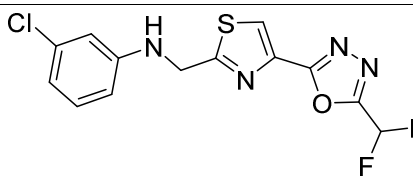
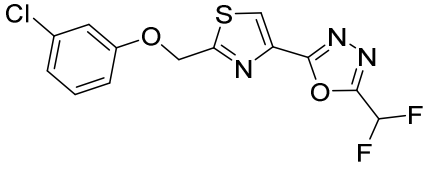
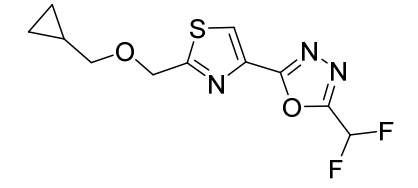
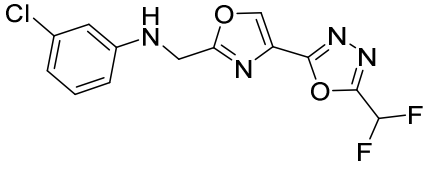
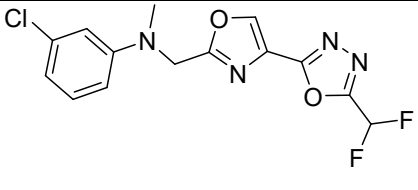
21. The use of claim 20, wherein the HDAC6 inhibitor is selected from the group consisting of:

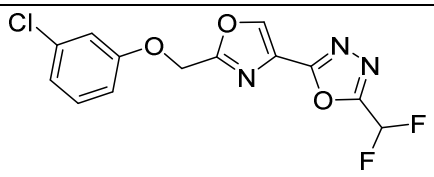
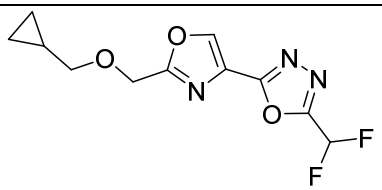
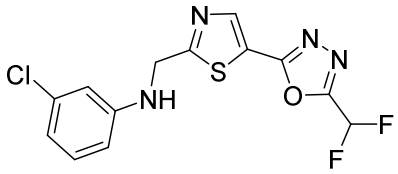
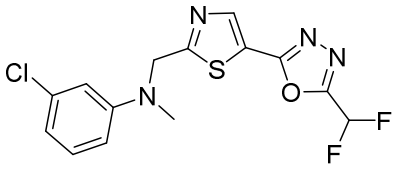
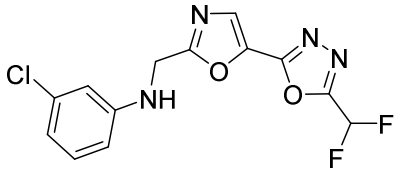
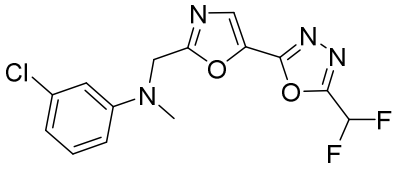
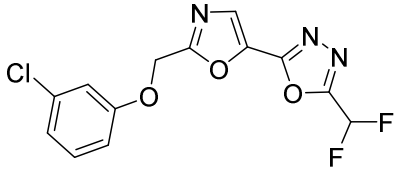
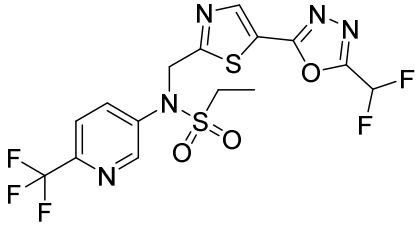
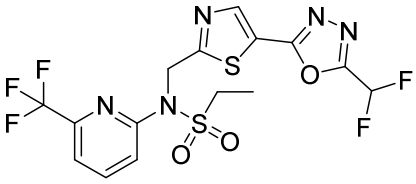
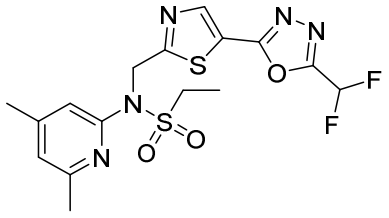
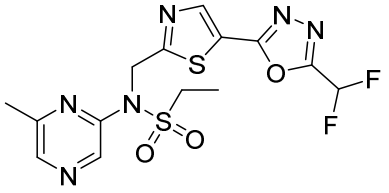
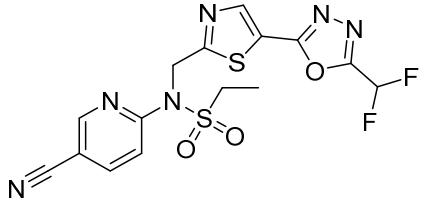
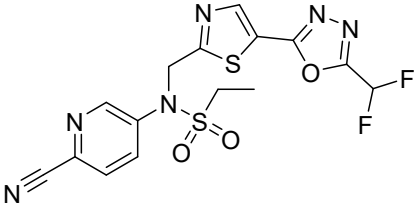
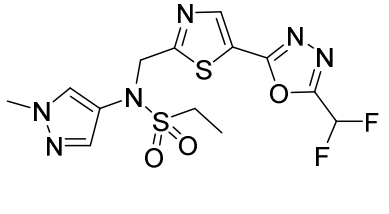
	
	
	
	
	
	

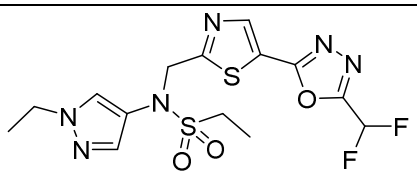
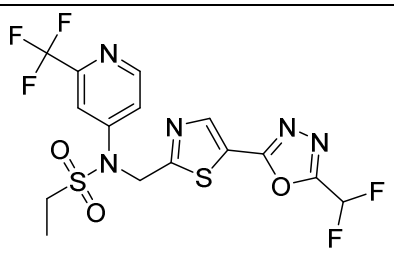
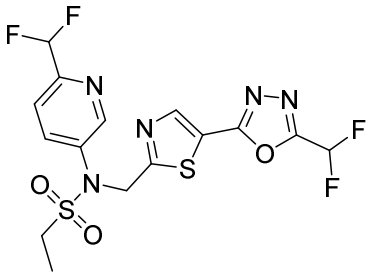
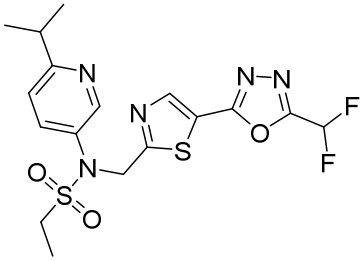
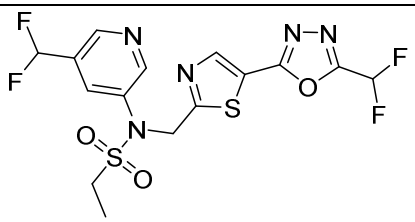
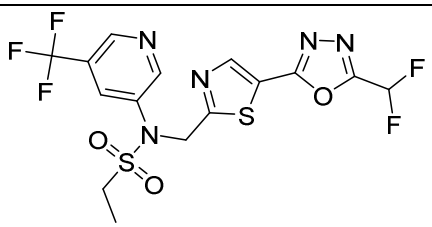
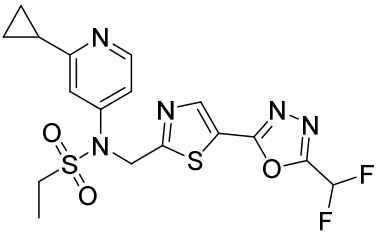
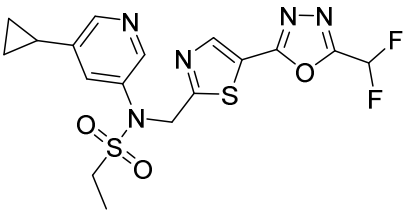
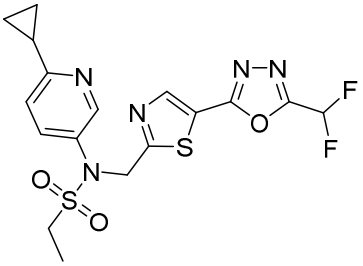
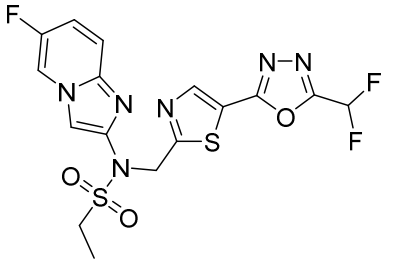
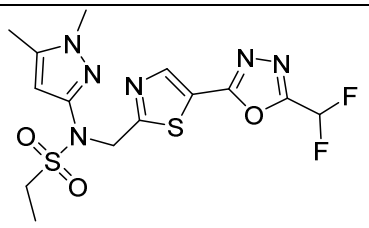
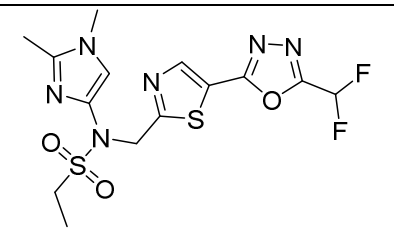
	
	
	
	
	
	

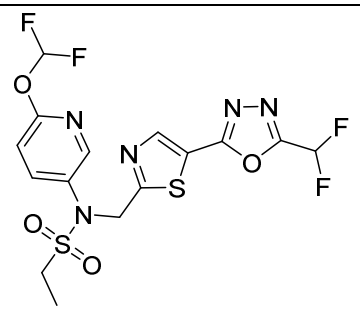
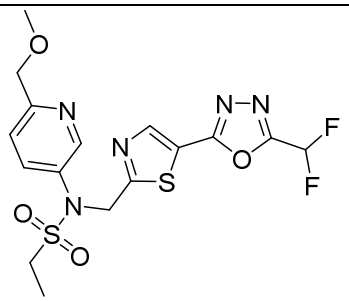
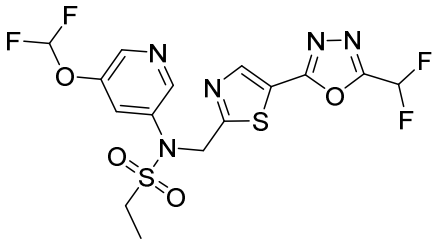
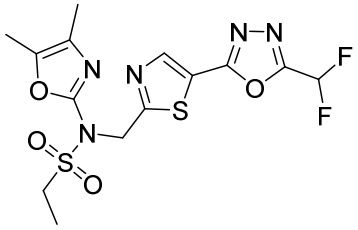
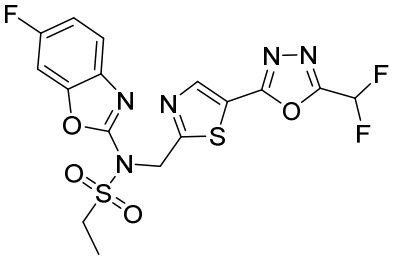
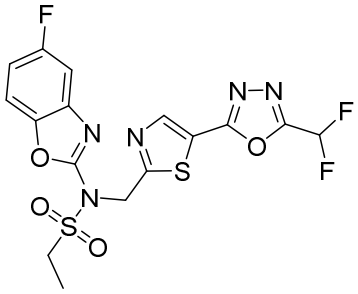
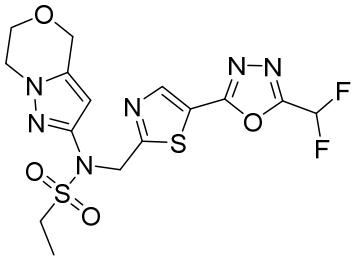
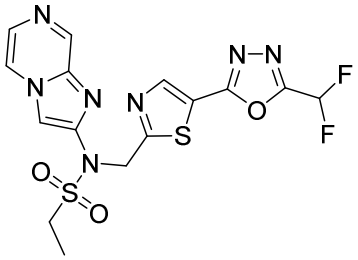
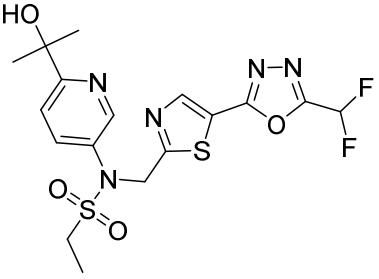
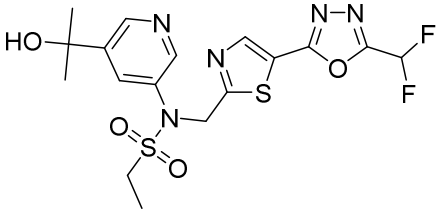
	
	
	
	
	
	
	

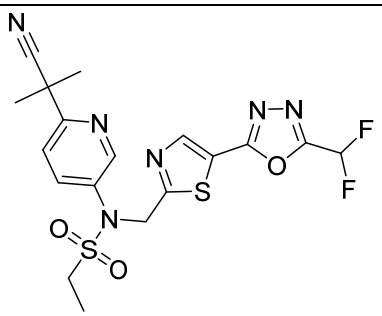
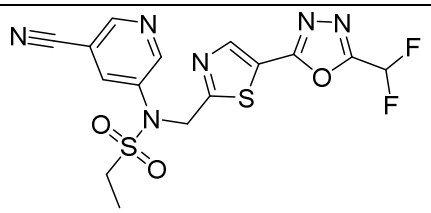
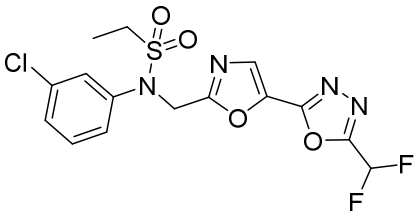
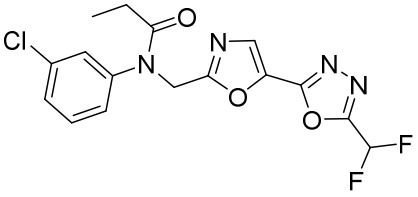
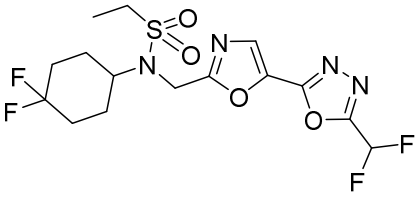
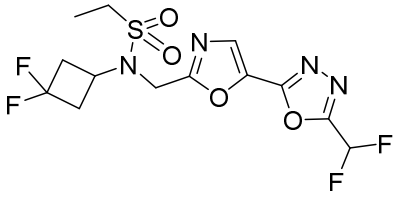
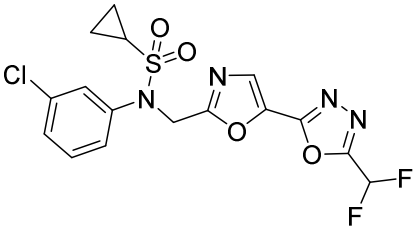
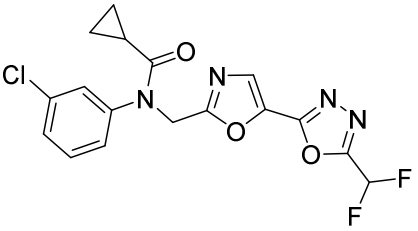
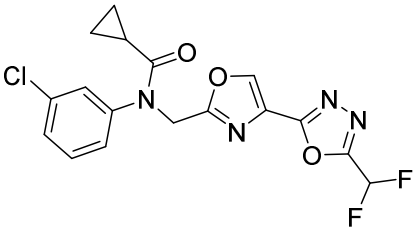
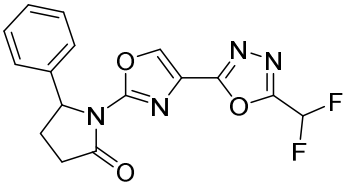
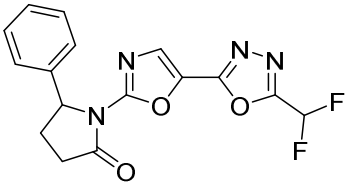
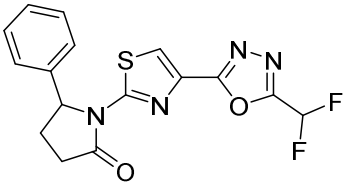
	
	
	
	
	
	
	

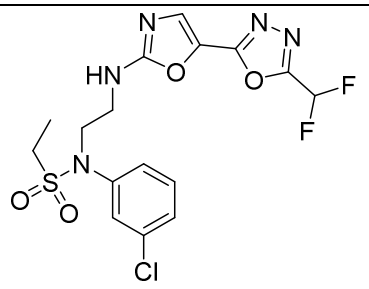
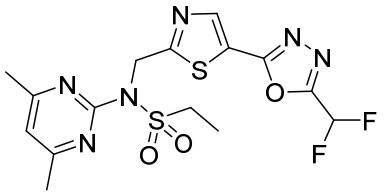
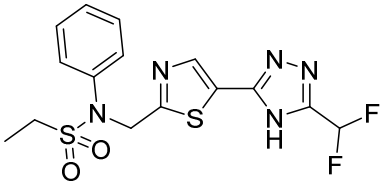
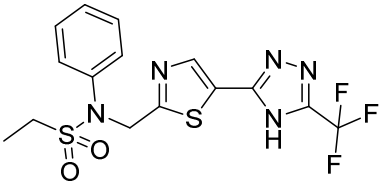
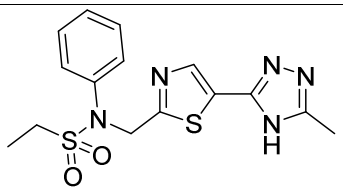
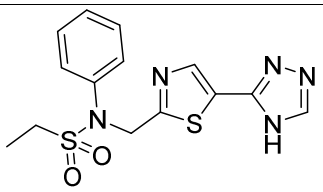
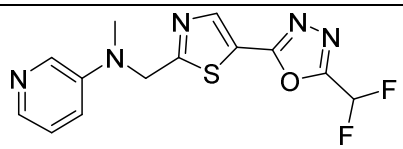
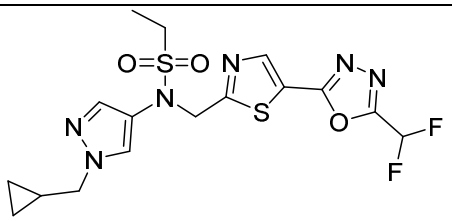
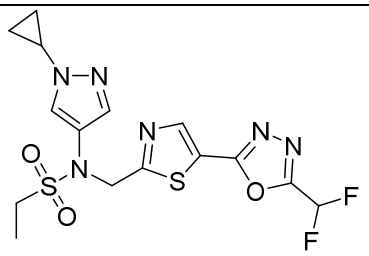
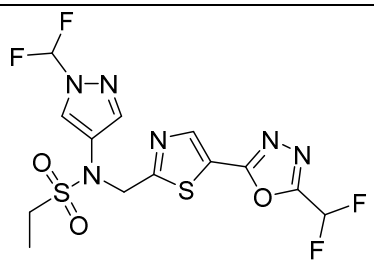
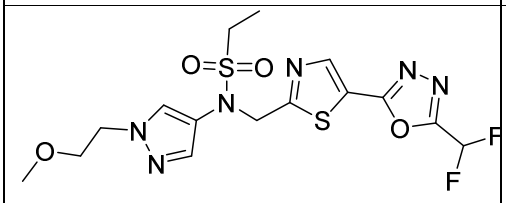
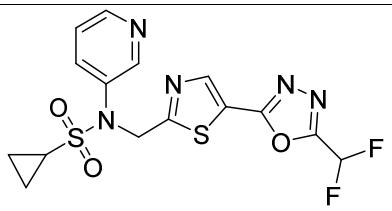
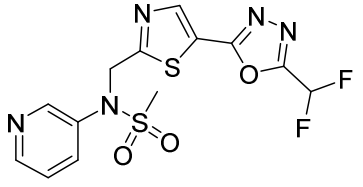
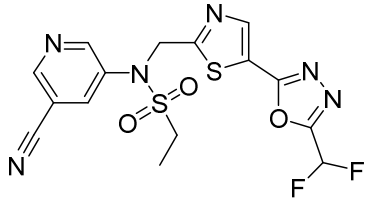
	
	
	
	
	
	
	
	

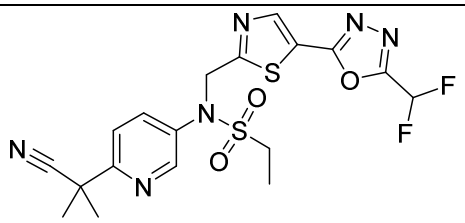
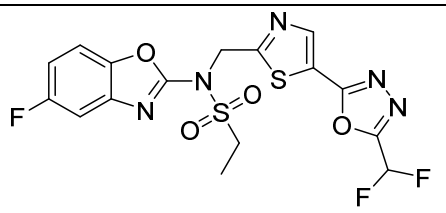
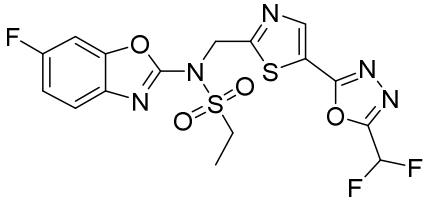
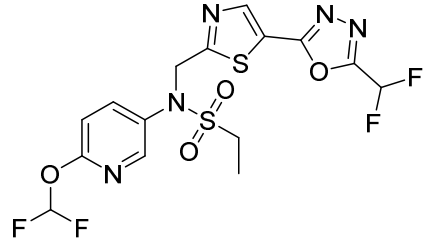
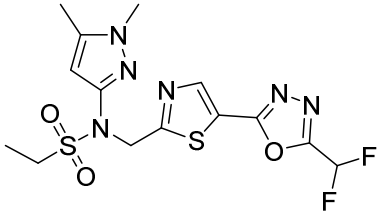
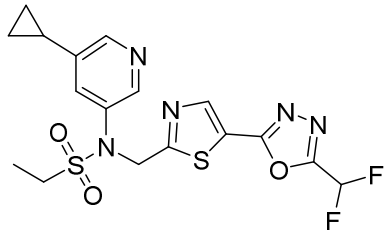
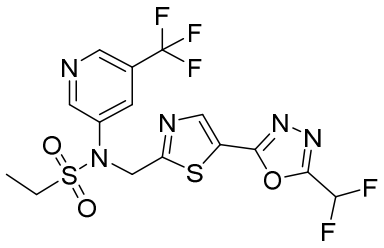
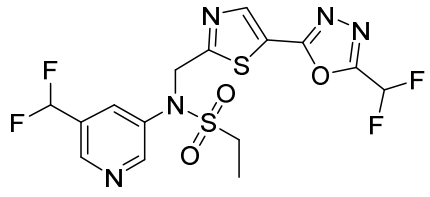
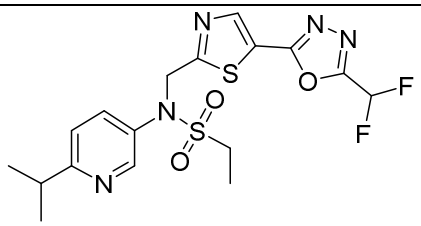
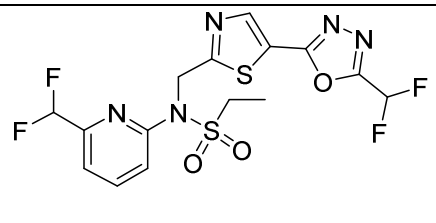
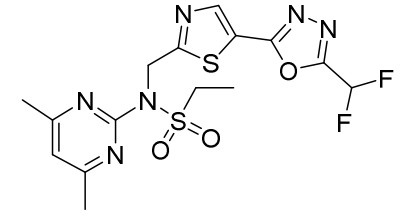
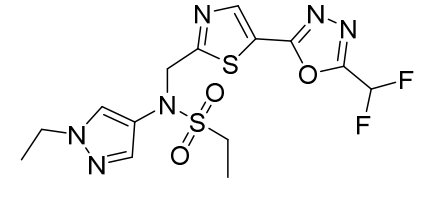
	
	
	
	
	
	
	

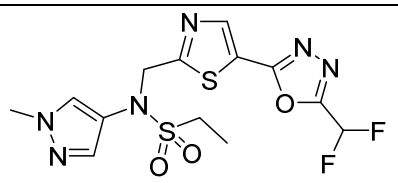
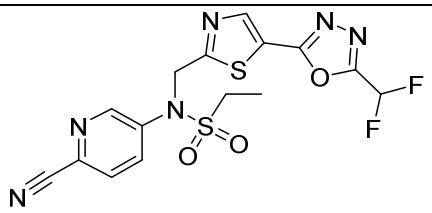
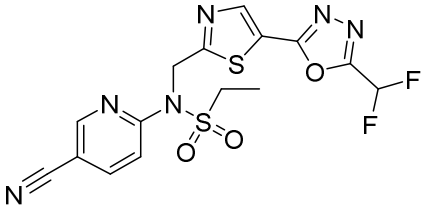
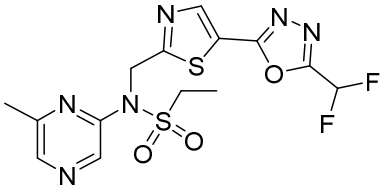
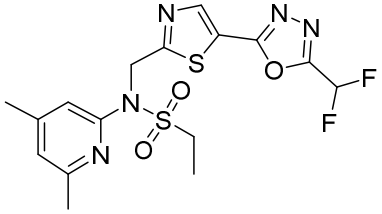
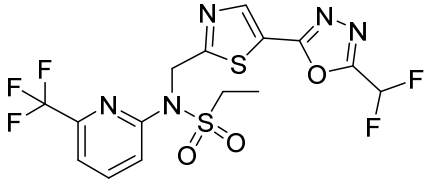
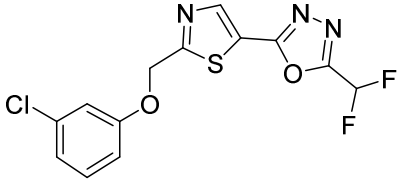
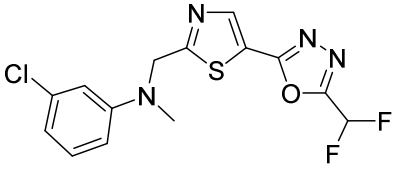
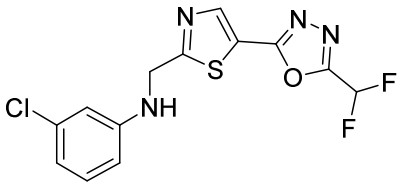
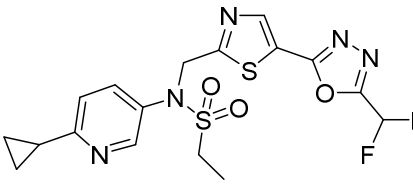
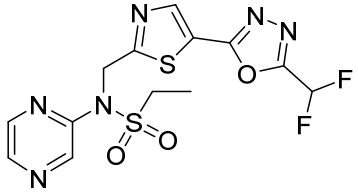
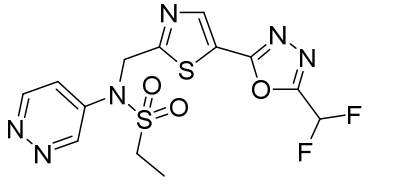
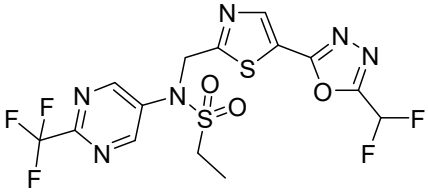
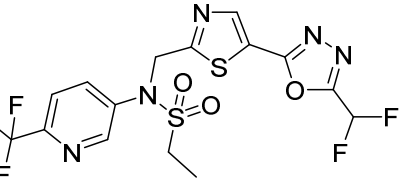
	
	
	
	
	
	

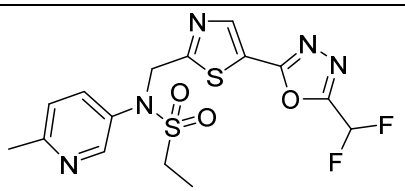
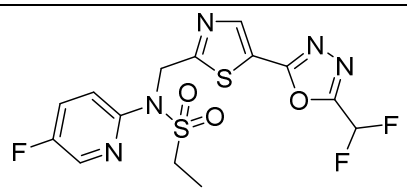
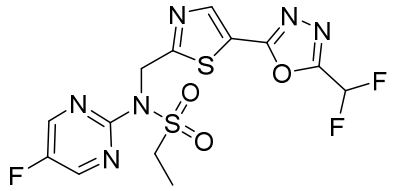
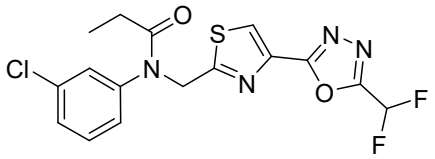
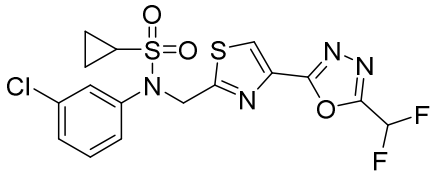
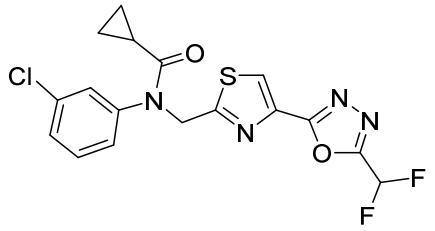
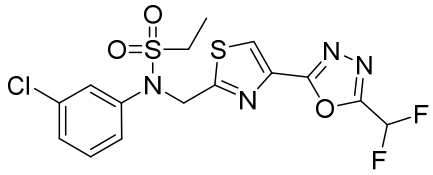
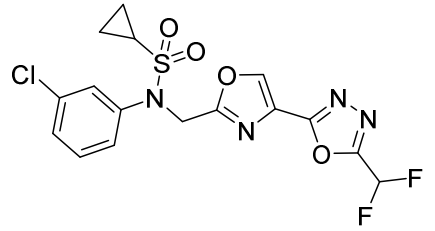
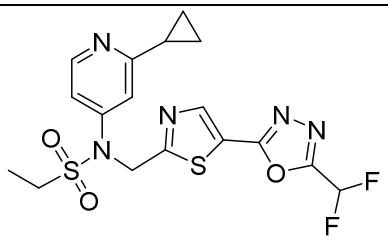
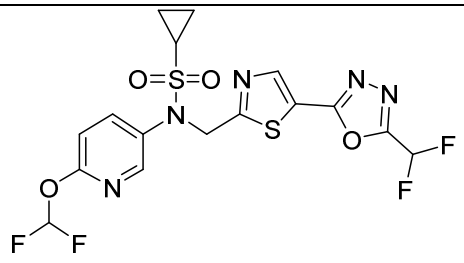
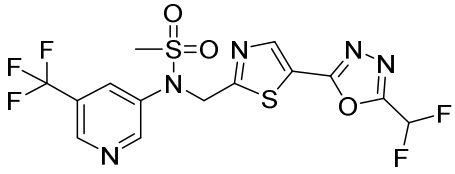
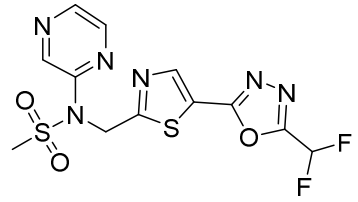
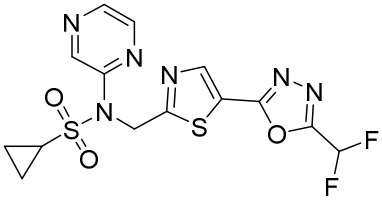
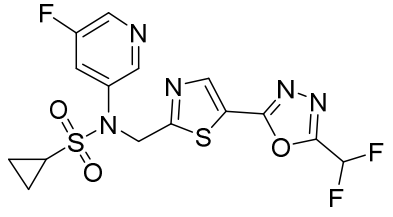
	
	
	
	
	

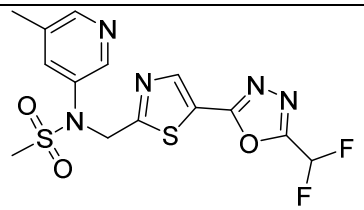
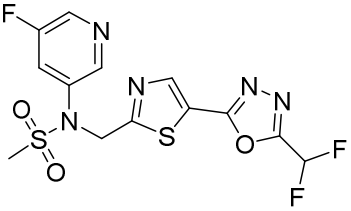
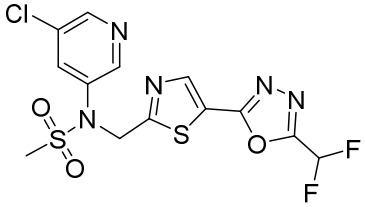
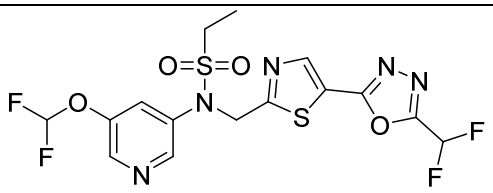
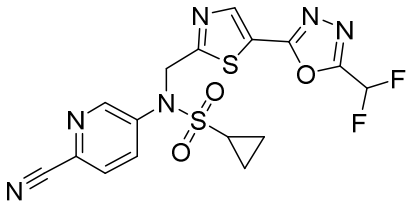
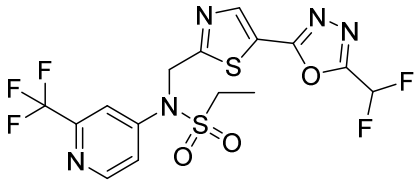
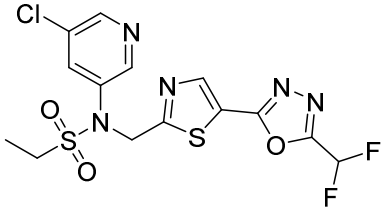
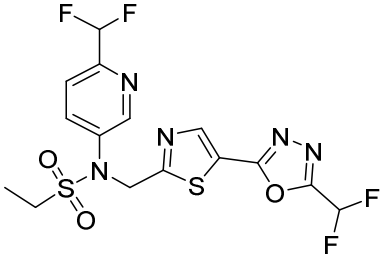
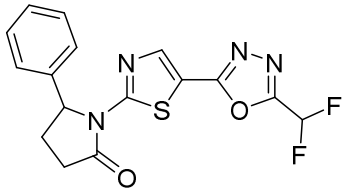
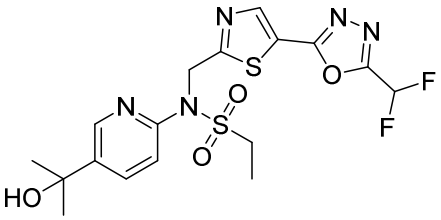
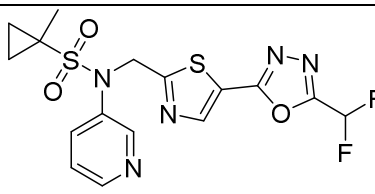
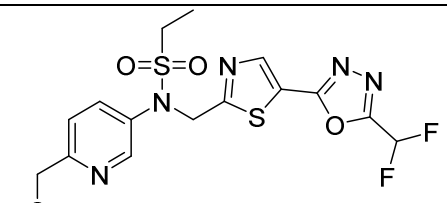
	
	
	
	
	
	

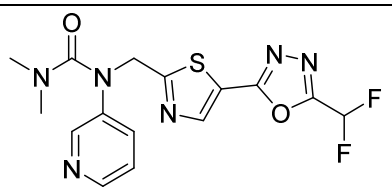
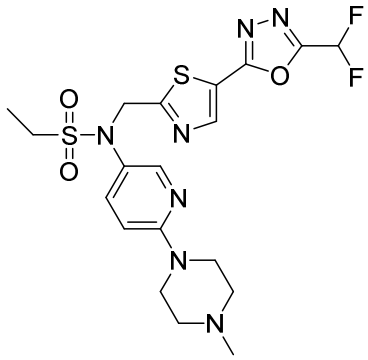
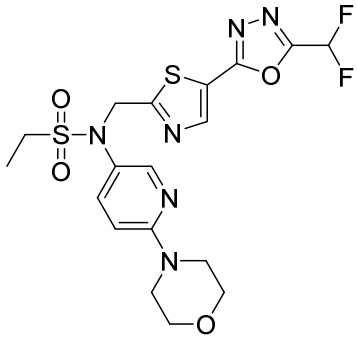
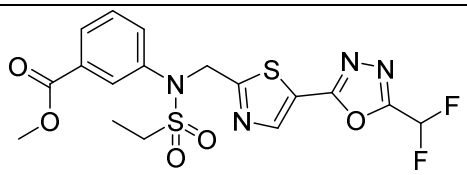
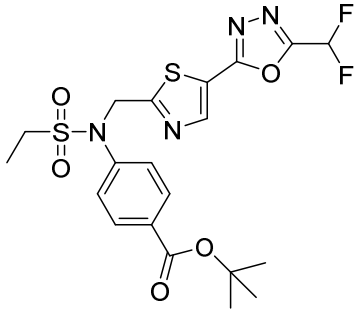
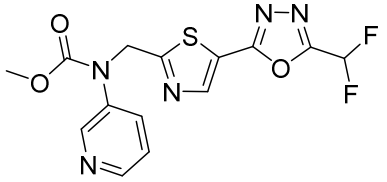
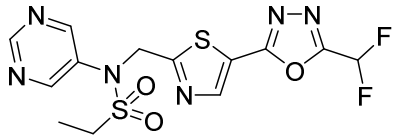
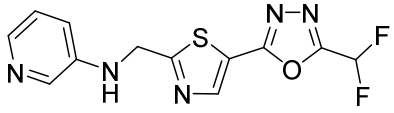
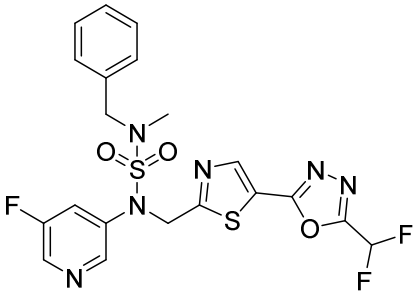
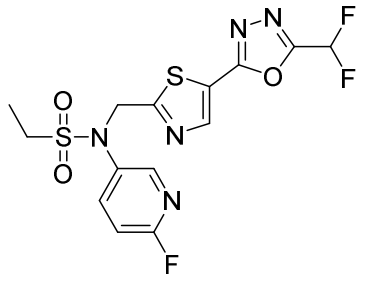
	
	
	
	
	
	
	

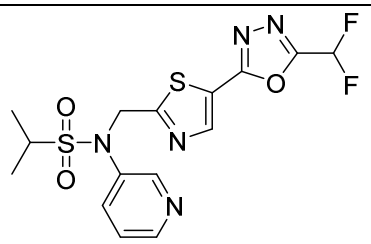
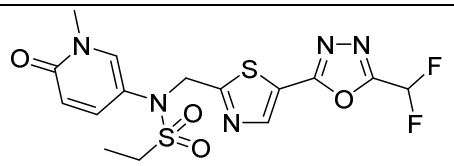
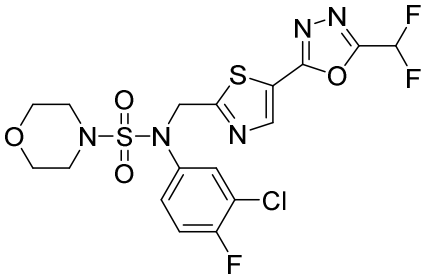
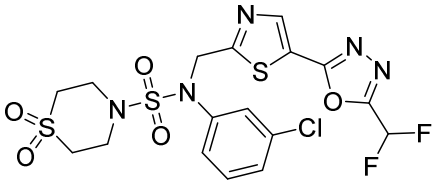
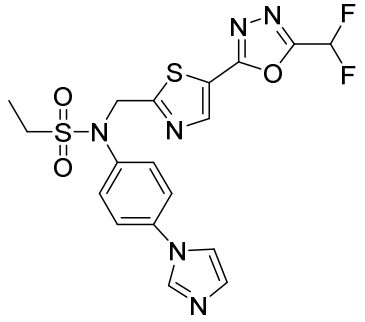
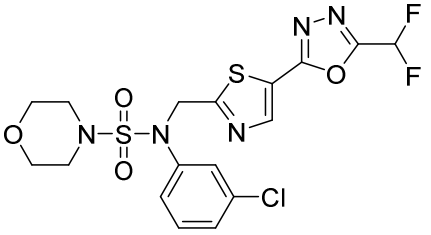
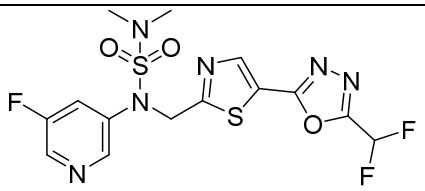
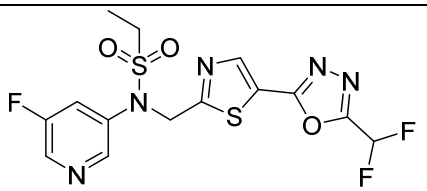
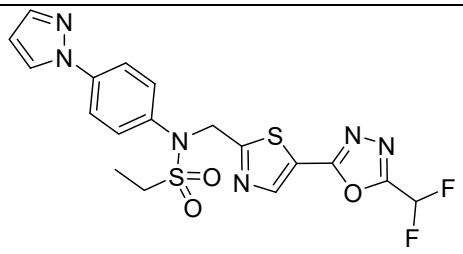
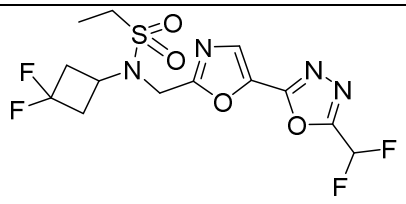
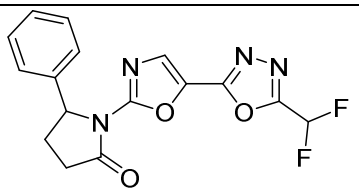
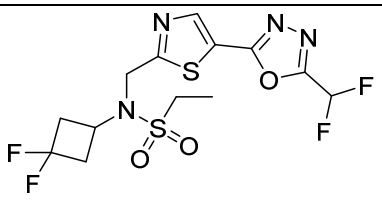
	
	
	
	
	
	

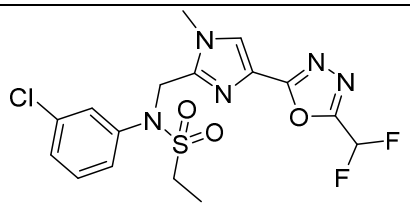
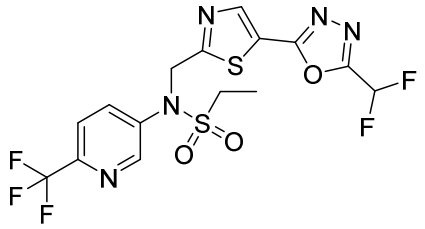
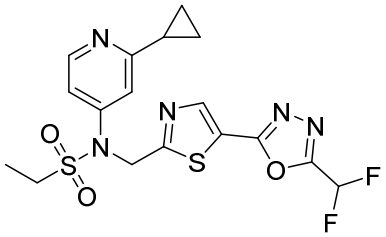
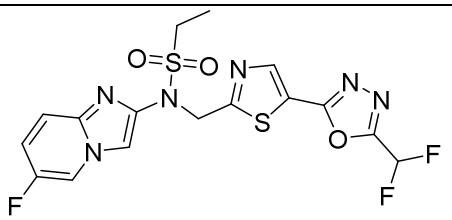
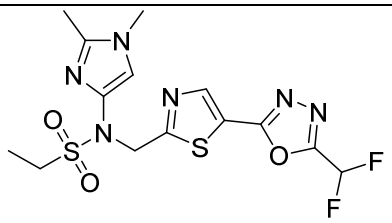
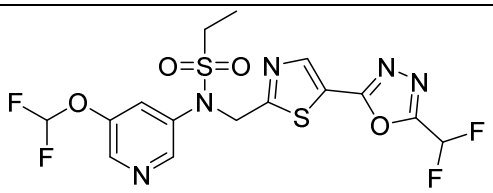
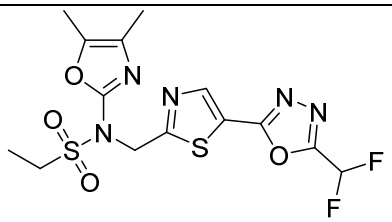
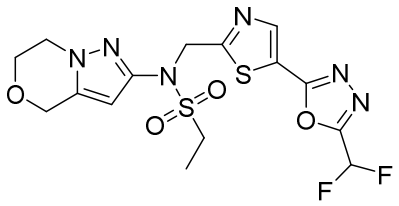
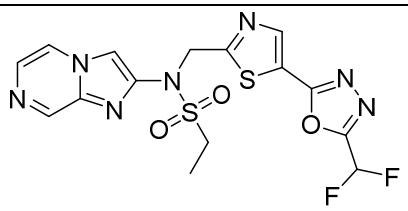
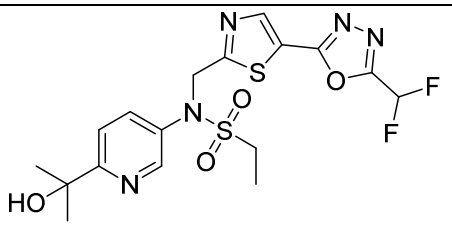
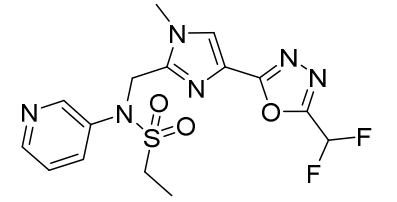
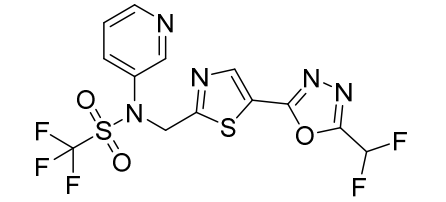
	
	
	
	
	
	
	

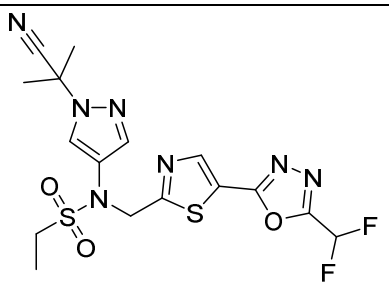
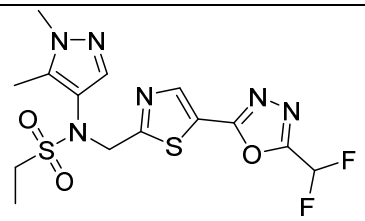
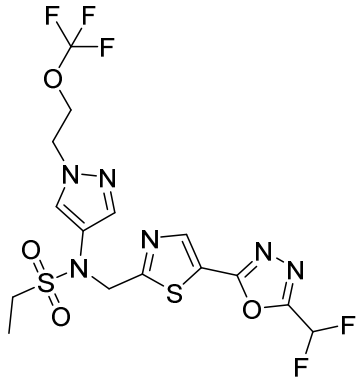
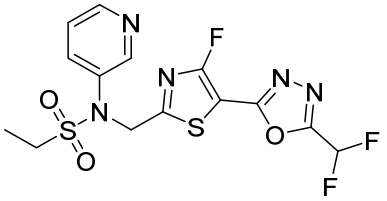
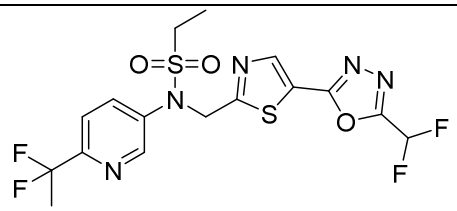
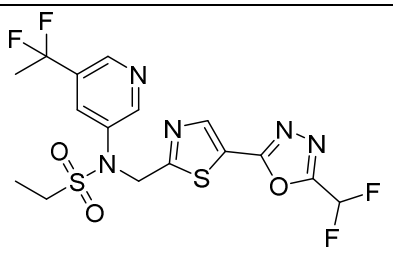
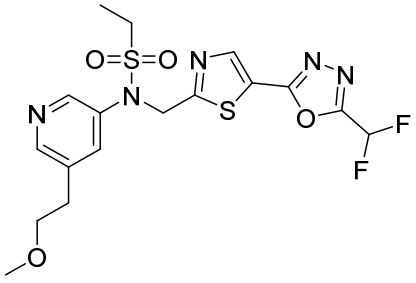
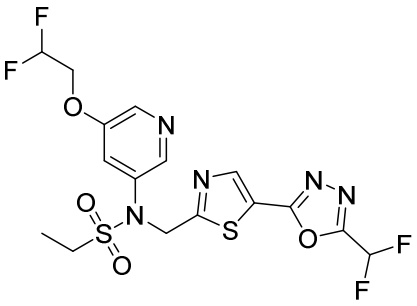
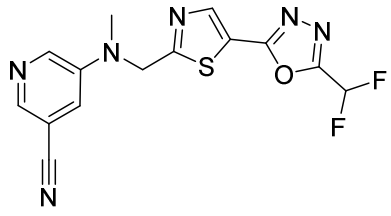
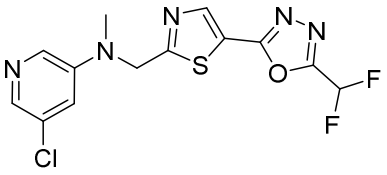
	
	
	
	
	
	
	

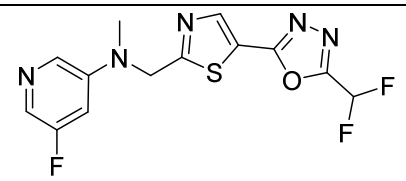
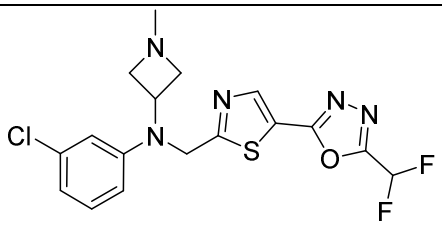
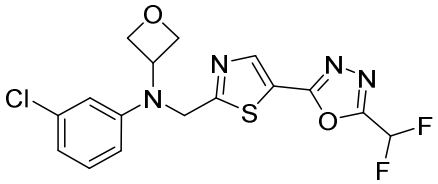
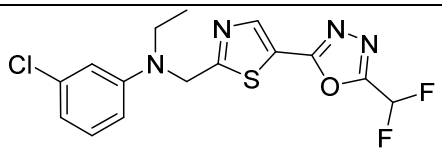
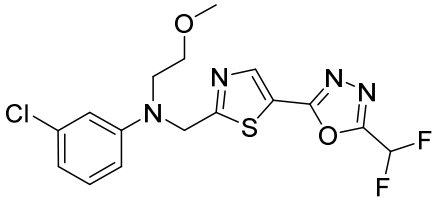
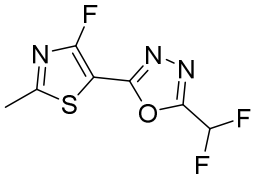
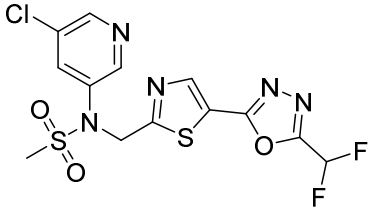
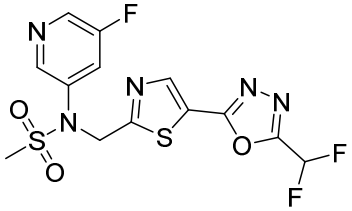
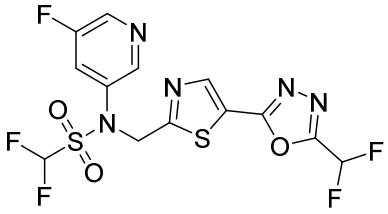
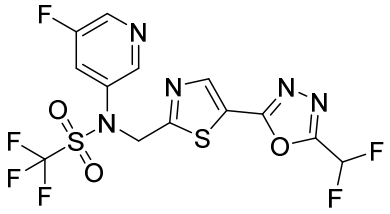
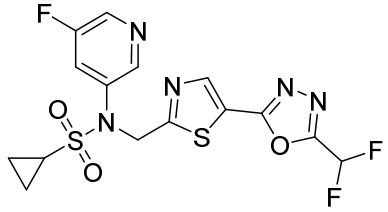
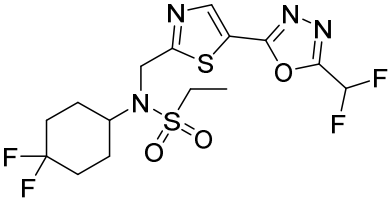
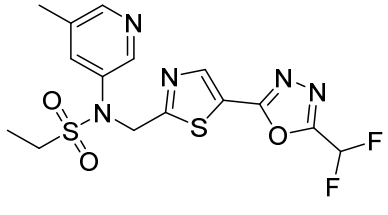
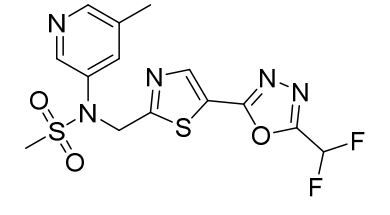
	
	
	
	
	
	

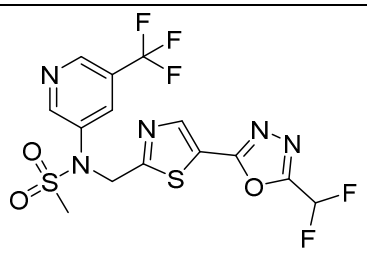
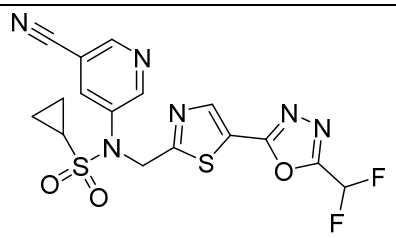
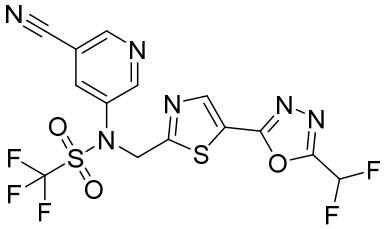
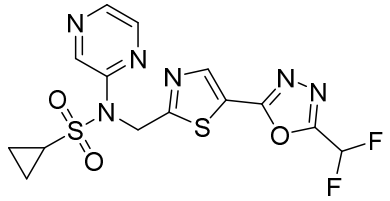
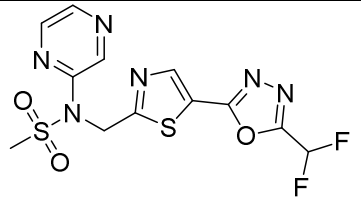
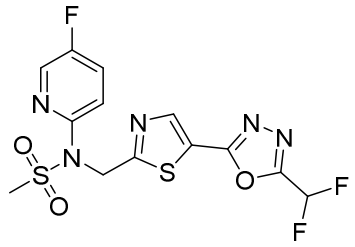
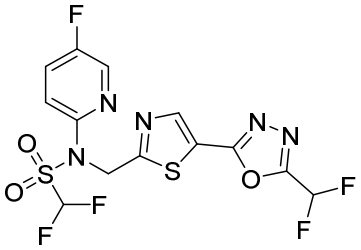
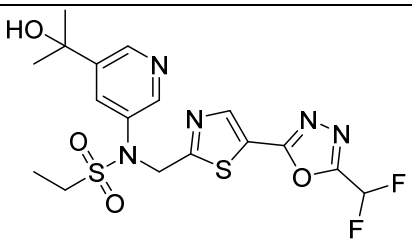
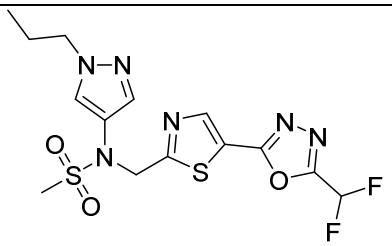
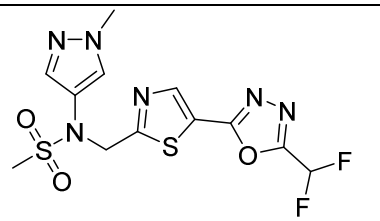
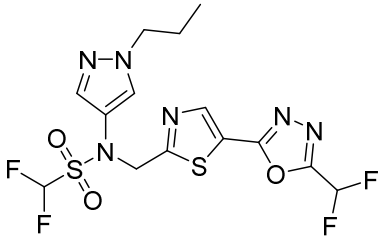
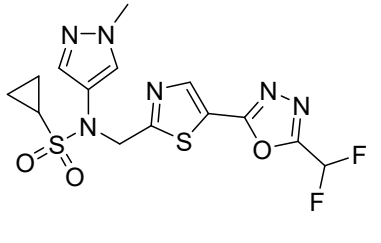
	
	
	
	
	

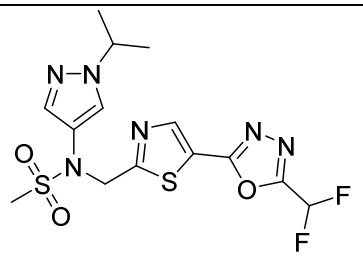
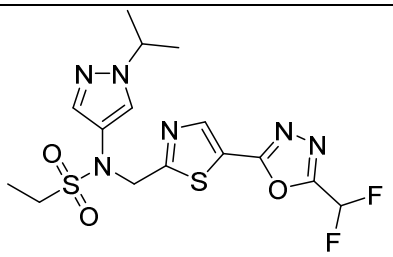
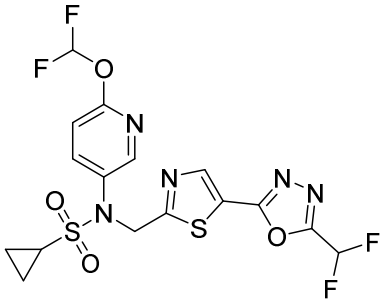
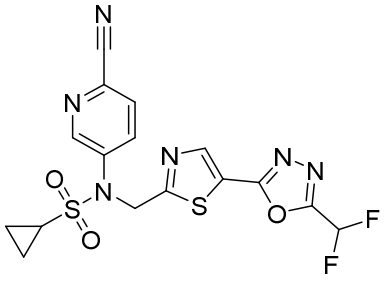
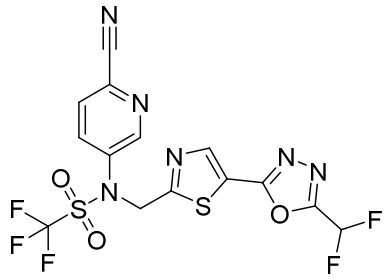
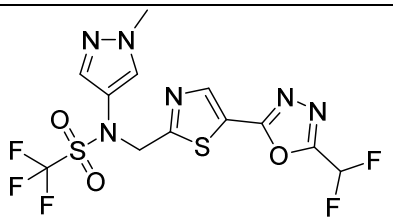
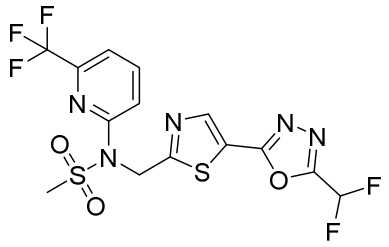
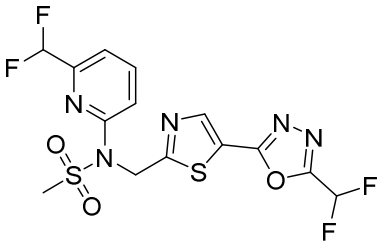
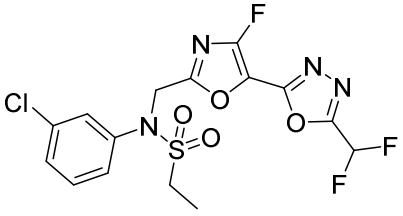
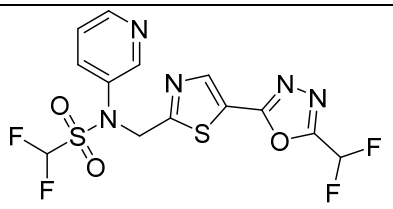
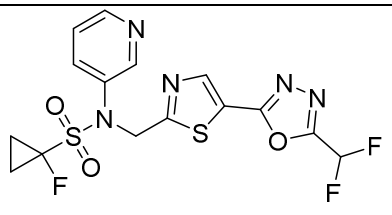
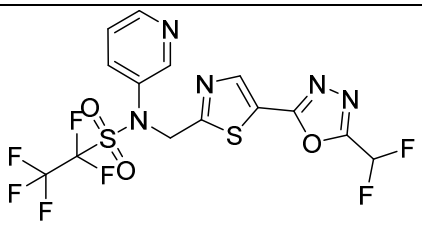
	
	
	
	
	
	

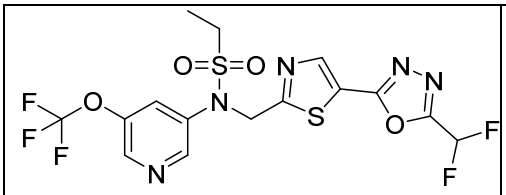
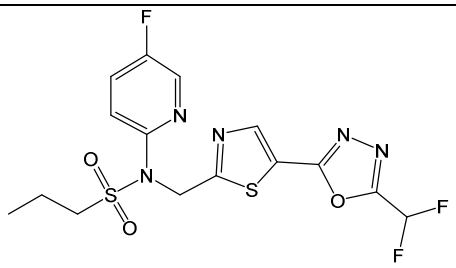
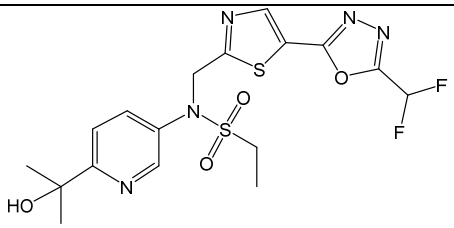
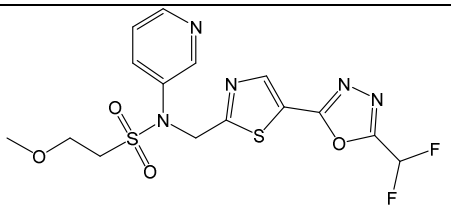
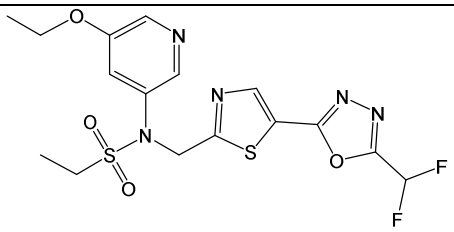
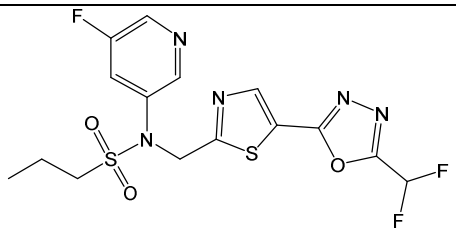
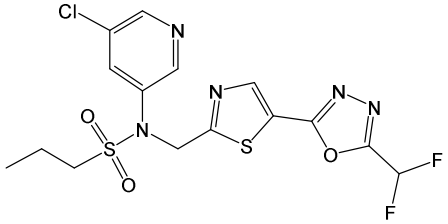
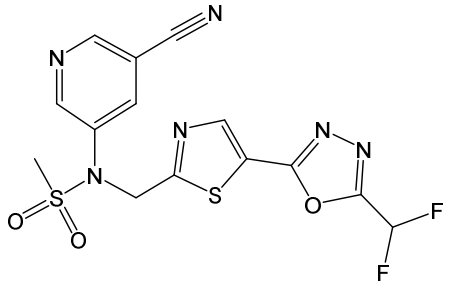
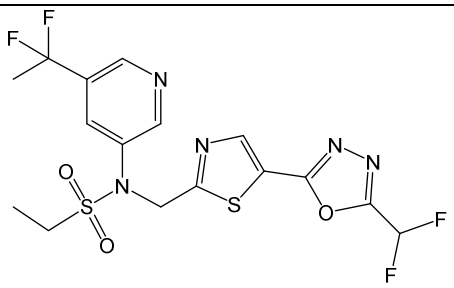
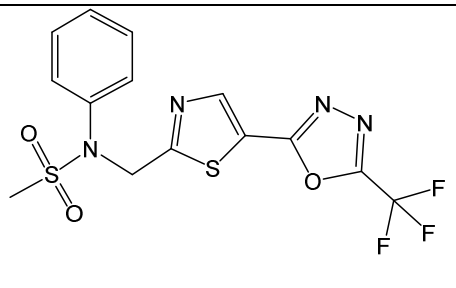
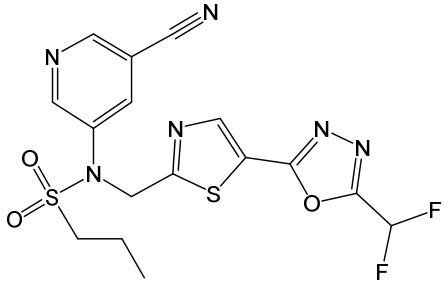
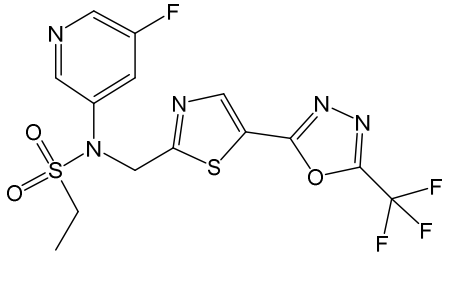
	
	
	
	
	
	

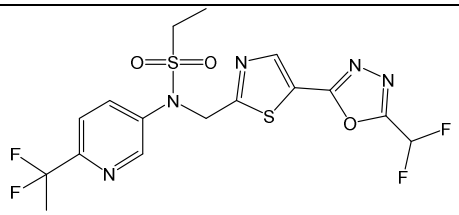
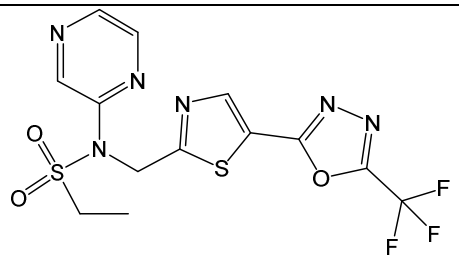
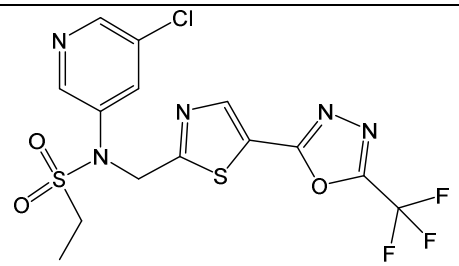
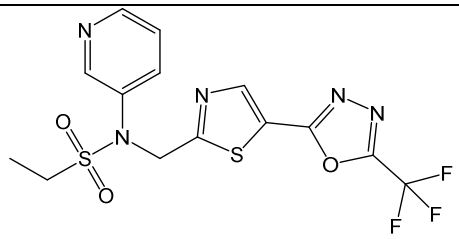
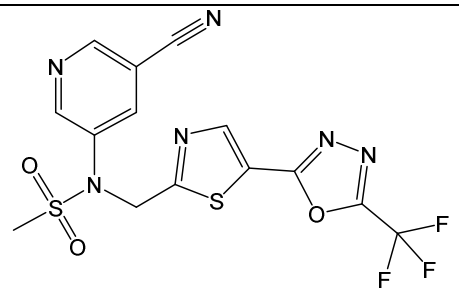
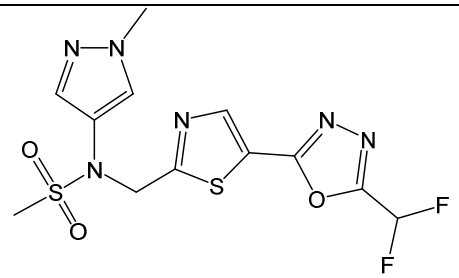
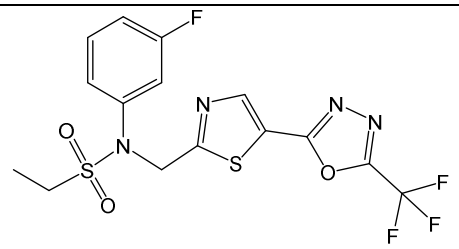
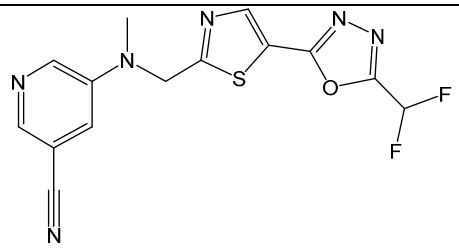
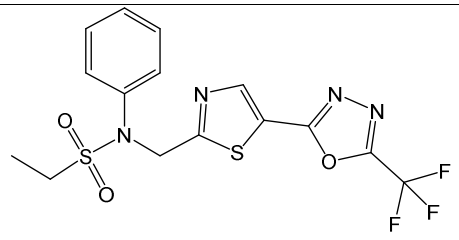
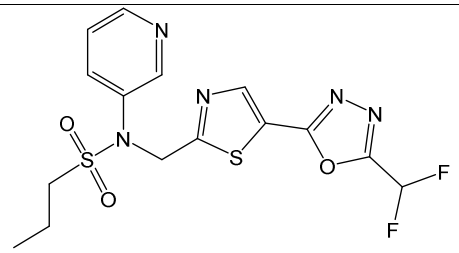
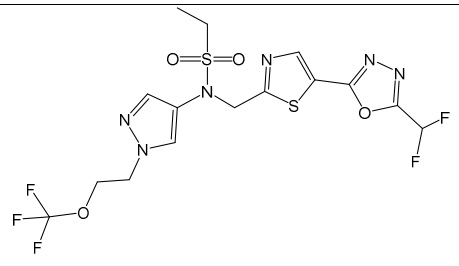
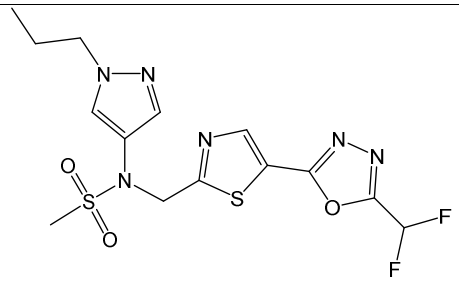
	
	
	
	
	

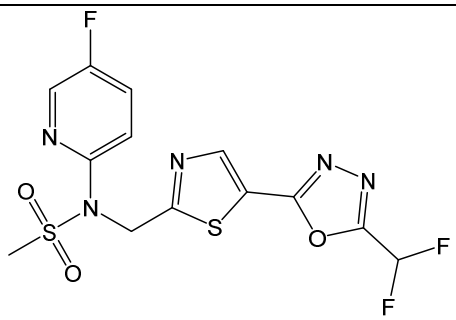
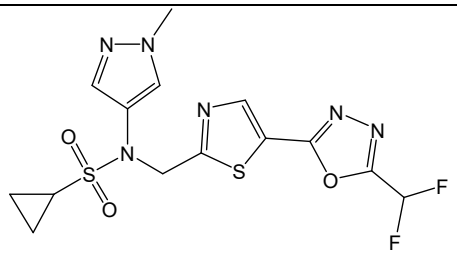
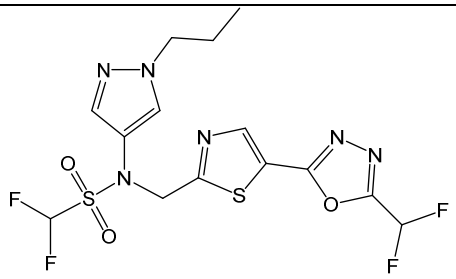
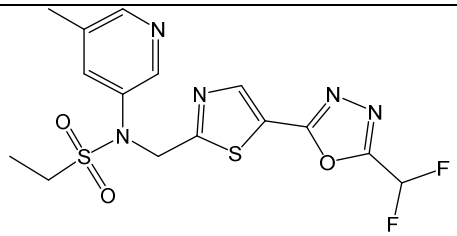
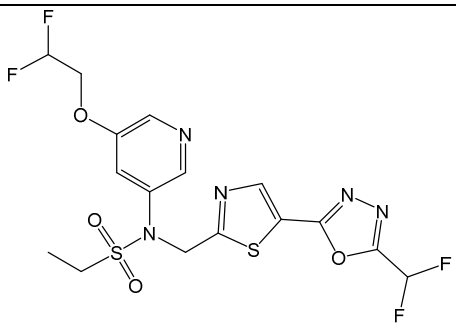
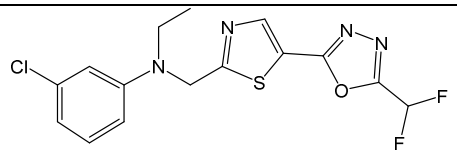
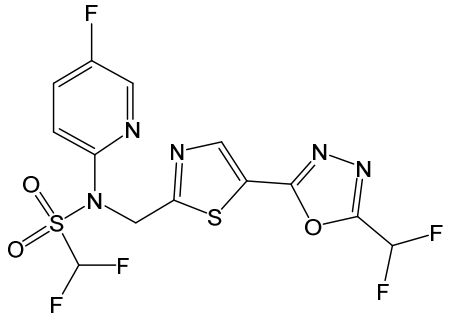
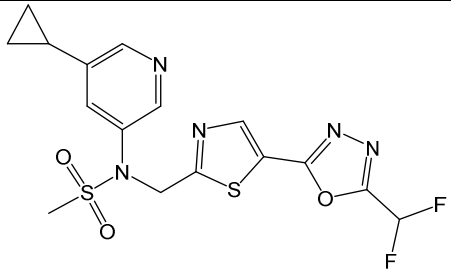
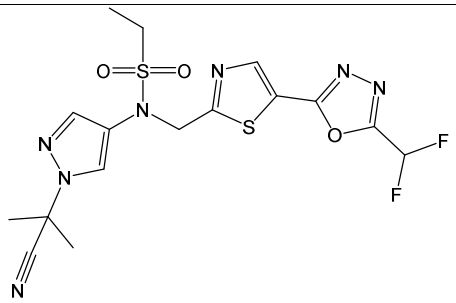
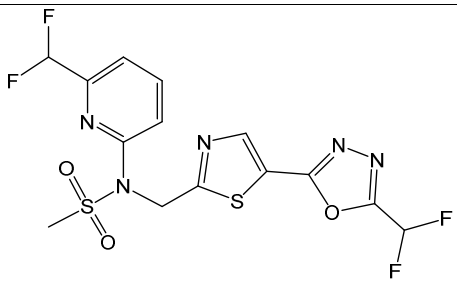
	
	
	
	
	
	
	

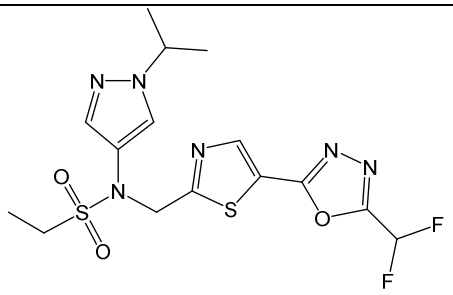
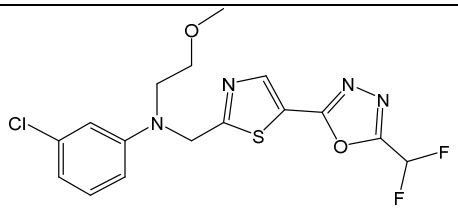
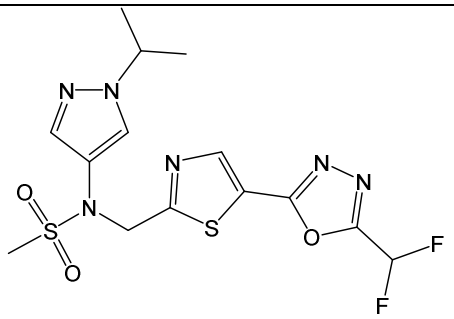
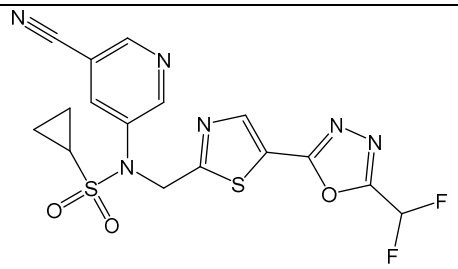
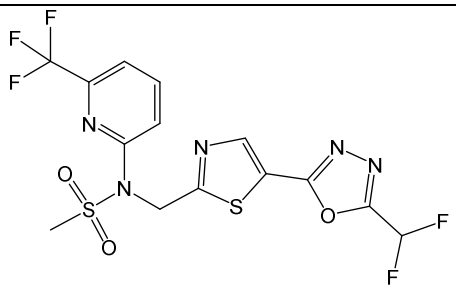
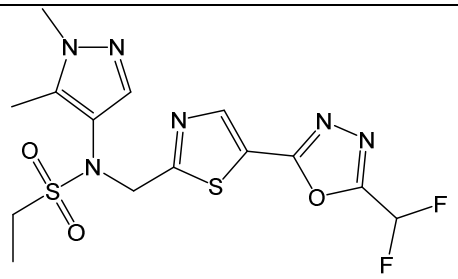
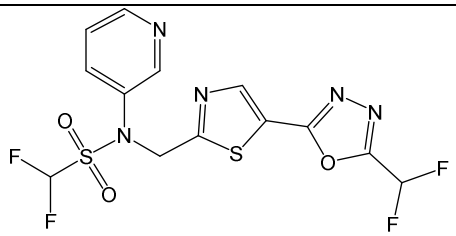
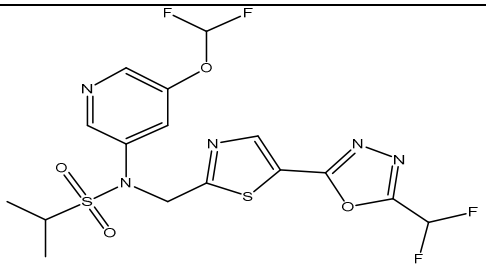
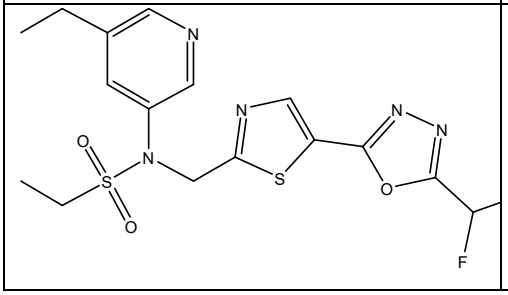
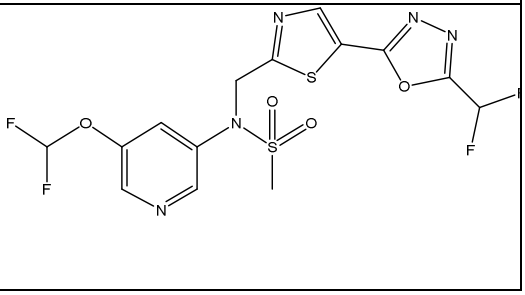
	
	
	
	
	
	

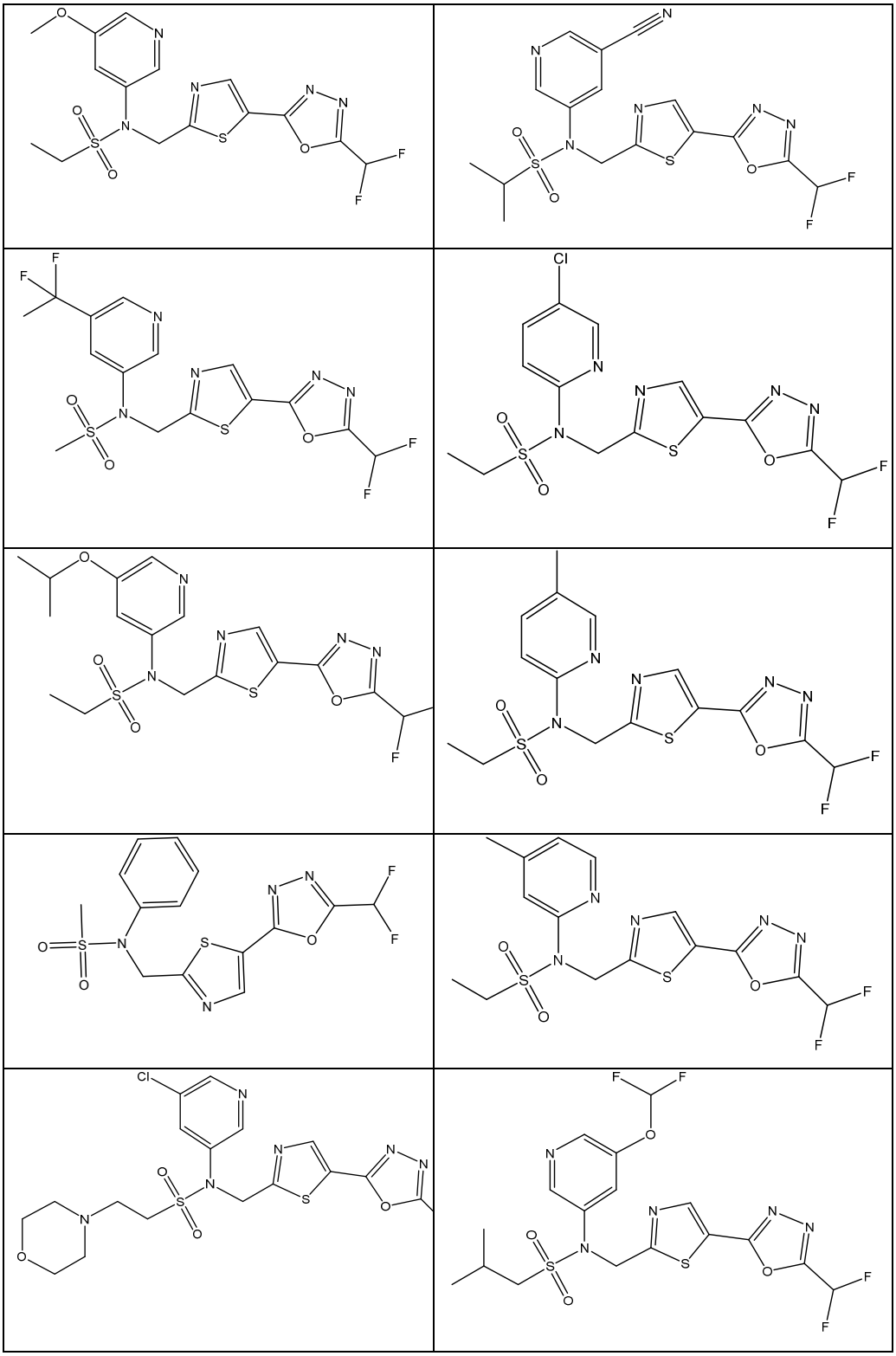
	
	
	
	
	
	

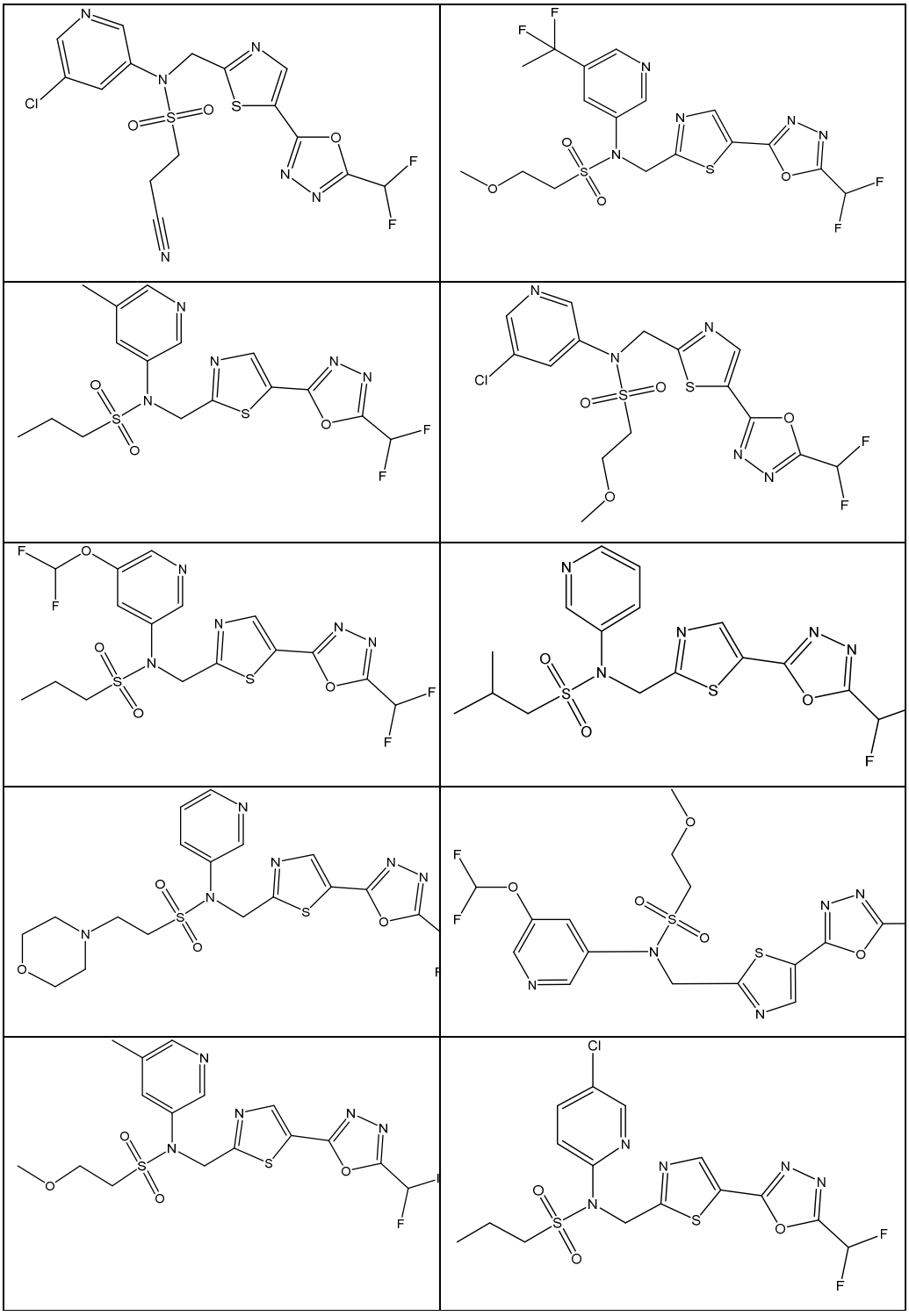
	
	
	
	
	
	

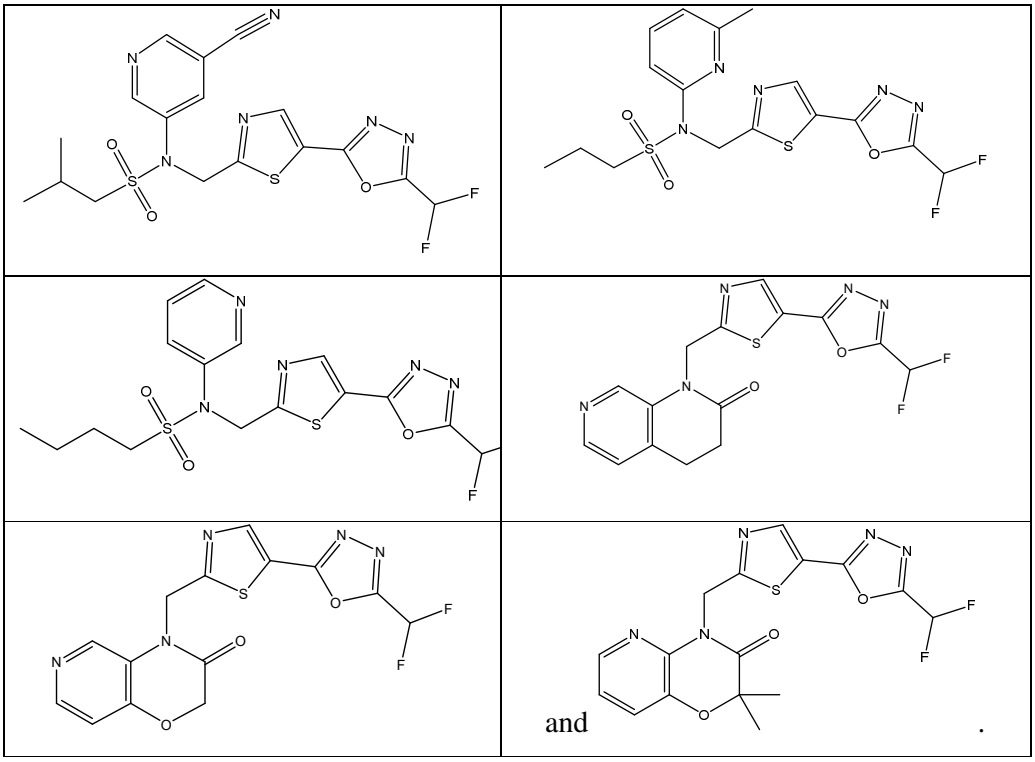
	
	
	
	
	
	



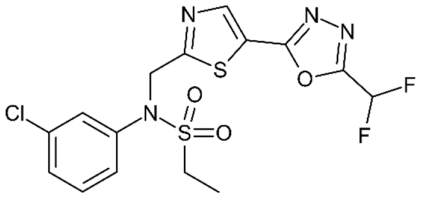




and .

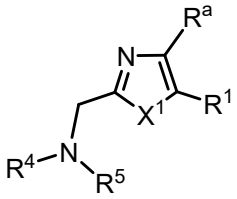
or a pharmaceutically acceptable salt thereof.

22. The use of claim 21, wherein the HDAC6 inhibitor is



or a pharmaceutically acceptable salt thereof.

23. The use of claim 20, wherein the HDAC6 inhibitor is a compound is a compound according to Formula I(y):

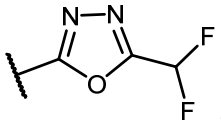
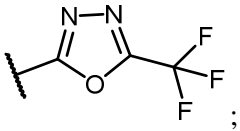


I(y), or a pharmaceutically acceptable salt thereof,

wherein:

X^1 is S;

R^a is selected from the group consisting of H, halogen, and C_{1-3} alkyl;

R^1 is  or ;

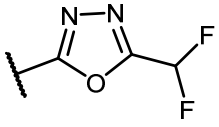
R^2 is selected from the group consisting of alkyl, alkoxy, and cycloalkyl, each of which is optionally substituted;

R^3 is H or alkyl;

R^4 is selected from the group consisting of alkyl, $–(SO_2)R^2$, $–(SO_2)NR^2R^3$, and $–(CO)R^2$; and

R^5 is aryl or heteroaryl; or R^4 and R^5 together with the atom to which they are attached form a heterocyclyl, each of which is optionally substituted.

24. The use of claim 23, wherein R^a is H.

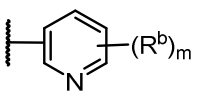
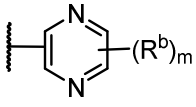
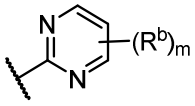
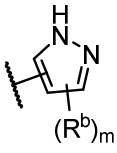
25. The use of claim 23, wherein R^1 is .

26. The use of claim 23, wherein R^4 is $–(SO_2)R^2$.

27. The use of claim 26, wherein $–(SO_2)R^2$ is $–(SO_2)$alkyl, $–(SO_2)$alkyleneheterocyclyl, $–(SO_2)$haloalkyl, $–(SO_2)$haloalkoxy, or $–(SO_2)$cycloalkyl.

28. The use of any one of claims 23-27, wherein R^5 is heteroaryl.

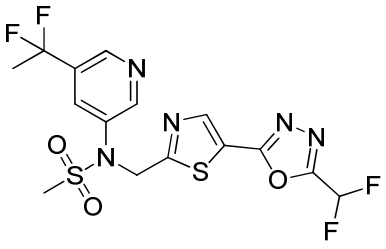
29. The use of claim 28, wherein the heteroaryl is a 5- to 6-membered heteroaryl.

30. The use of claim 29, wherein the 5- to 6-membered heteroaryl is selected from the group consisting of , , , and , wherein R^b is halogen, alkyl, alkoxy, cycloalkyl, -CN, haloalkyl, or haloalkoxy; and m is 0 or 1.

31. The use of claim 30, wherein R^b is F, Cl, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CHF_2$, $-CF_2CH_3$, -CN, $-OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_2H$, and cyclopropyl.

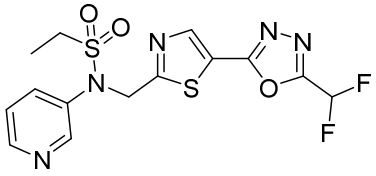
32. The use of any one of claims 23-27, wherein R^5 is aryl and the aryl is selected from the group consisting of phenyl, 3-chlorophenyl, 3-chloro-4-fluorophenyl, 3-trifluoromethylphenyl, 3,4-difluorophenyl, and 2,6-difluorophenyl.

33. The use of claim 23, wherein the compound is:



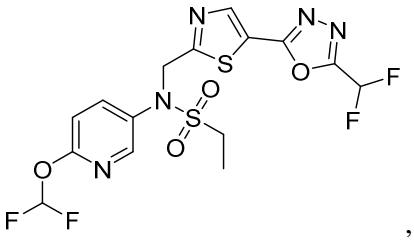
, or a pharmaceutically acceptable salt thereof.

34. The use of claim 23, wherein the compound is:



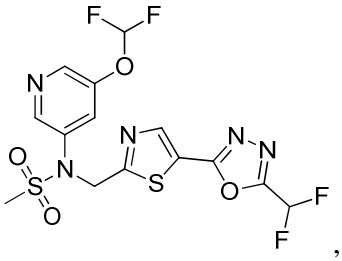
, or a pharmaceutically acceptable salt thereof.

35. The use of claim 23, wherein the compound is:



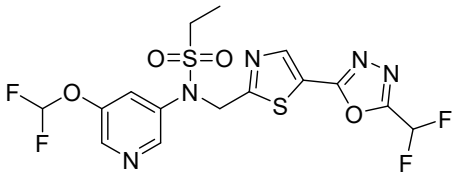
, or a pharmaceutically acceptable salt thereof.

36. The use of claim 23, wherein the compound is:

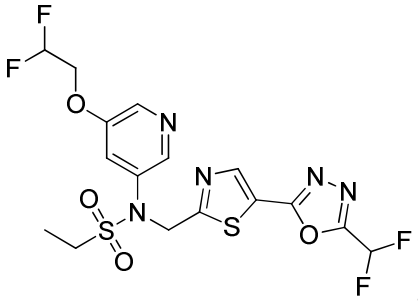


, or a pharmaceutically acceptable salt thereof.

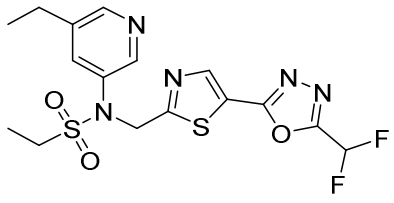
37. The use of claim 23, wherein the compound is:


, or a pharmaceutically acceptable salt thereof.

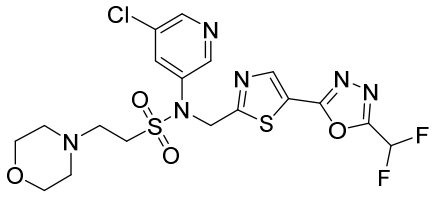
38. The use of claim 23, wherein the compound is:


, or a pharmaceutically acceptable salt thereof.

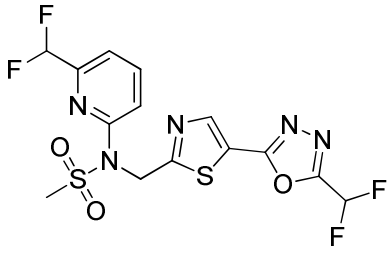
39. The use of claim 23, wherein the compound is:


, or a pharmaceutically acceptable salt thereof.

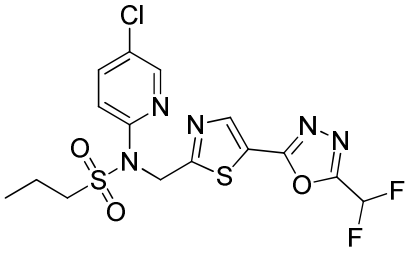
40. The use of claim 23, wherein the compound is:


, or a pharmaceutically acceptable salt thereof.

41. The use of claim 23, wherein the compound is:

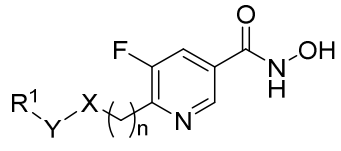

, or a pharmaceutically acceptable salt thereof.

42. The use of claim 23, wherein the compound is:



or a pharmaceutically acceptable salt thereof.

43. The use of any one of claims 1, 6, and 13, wherein the HDAC6 inhibitor is a compound of Formula (II):



(II); wherein

n is 0 or 1;

X is O, NR^4, or $CR^4R^{4'}$;

Y is a bond, CR^2R^3 or $S(O)_2$;

R^1 is selected from the group consisting of H, amido, carbocyclyl, heterocyclyl, aryl, and heteroaryl;

R^2 and R^3 are independently selected from the group consisting of H, halogen, alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, $–(CH_2)–$carbocyclyl, $–(CH_2)–$heterocyclyl, $–(CH_2)–$aryl, and $–(CH_2)–$heteroaryl; or

R^1 and R^2 taken together with the carbon atom to which they are attached form a carbocyclyl or heterocyclyl; or
R^2 and R^3 taken together with the carbon atom to which they are attached form a carbocyclyl or heterocyclyl; and

R^4 and $R^{4'}$ are each independently selected from the group consisting of H, alkyl, $–CO_2–$alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, $–(CH_2)–$carbocyclyl, $–(CH_2)–$heterocyclyl, $–(CH_2)–$aryl, and $–(CH_2)–$heteroaryl; or

R^4 and $R^{4'}$ taken together with the carbon atom to which they are attached form a carbocyclyl or heterocyclyl;

wherein each alkyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently optionally substituted with one or more substituents selected from the group consisting of halogen, haloalkyl, oxo, hydroxy, alkoxy, $–OCH_3$, $–CO_2CH_3$, –C(O)NH(OH),$–CH_3$, morpholine, and –C(O)N-cyclopropyl.

44. The use of any one of claims 1, 6, and 13, wherein the HDAC6 inhibitor is CAY10603, tubacin, ricolinostat (ACY-1215), citarinostat (ACY-241), ACY-738, QTX-125, CKD-506, nexturastat A, tubastatin A, or HPOB.