

BENZOTHIA(DIA)ZEPINE COMPOUNDS FOR TREATMENT OF HBV AND HDV**CROSS-REFERENCE TO RELATED APPLICATION**

This application claims benefit of U.S. Provisional Application No. 63/446,976, filed
5 February 20, 2023 and U.S. Provisional Application No. 63/534,249, filed August 23, 2023,
the contents of which are hereby incorporated by reference.

BACKGROUND

Hepatitis B virus (HBV) causes viral hepatitis that can further lead to chronic liver
10 disease and increase the risk of liver cirrhosis and liver cancer (hepatocellular carcinoma).
Worldwide, about 2 billion people have been infected with HBV, around 296 million people
were chronically infected in 2019 according to the World Health Organization website, and
every year HBV infection causes more than one half million deaths. HBV can be spread by
body fluids: from mother to child, by sex, and via blood products. Children born to HBV-
15 positive mothers may also be infected, unless vaccinated at birth.

The HBV particle is composed of a lipid envelope studded with the hepatitis B
surface antigen (HBsAg) that surrounds the viral core. The core is composed of a protein
shell, or capsid, built of 120 core protein (Cp) dimers, which in turn contains the relaxed
circular DNA (rcDNA) viral genome as well as viral and host proteins. In an infected cell, the
20 genome is found as a covalently closed circular DNA (cccDNA) in the host cell nucleus. The
cccDNA is the template for viral RNAs and thus viral proteins. In the cytoplasm, Cp
assembles around a complex of full-length viral RNA (the so-called pregenomic RNA or
pgRNA and viral polymerase (P). After capsid assembly, P reverse transcribes the pgRNA to
rcDNA within the confines of the capsid to generate the DNA-filled viral core.

25 At present, chronic HBV is primarily treated with nucleos(t)ide analogs (e.g.,
entecavir) that suppress the virus while the patient remains on treatment, but do not eliminate
the infection, even after many years of treatment. Once a patient starts taking nucleos(t)ide
analogs, most must continue taking them or risk the possibility of a life-threatening immune
response due to viral rebound. Further, nucleotide therapy may lead to the emergence of
30 antiviral drug resistance.

The only FDA approved alternative to nucleos(t)ide analogs is treatment with interferon α or pegylated interferon α . Unfortunately, the adverse event incidence and profile of interferon α can result in poor tolerability, and many patients are unable to complete therapy. Moreover, only a small percentage of patients are considered appropriate for
5 interferon therapy, as only a small subset of patients is likely to have a sustained clinical response to a course of interferon therapy. As a result, interferon-based therapies are used in only a small percentage of all diagnosed patients who elect treatment.

Thus, current HBV treatments can range from palliative to watchful waiting. Nucleotide analogs suppress virus production, treating the symptom, but leave the infection
10 intact. Interferon α has severe side effects and less tolerability among patients and is successful as a finite treatment strategy in only a small minority of patients. There is a clear on-going need for more effective treatments for HBV infections.

Another form of viral hepatitis is hepatitis D virus (HDV), a defective RNA virus that causes chronic viral hepatitis and eventual cirrhosis. However, the HDV life cycle is
15 dependent on the presence of HBsAg for viral particle assembly. Thus, in a small set of patients infected with HBV, HDV presents as coinfection/superinfection with HBV. See for example, Sagnelli *et al.*, Life (Basel). 2021 Feb; 11(2): 169, Published online 2021 Feb 22. doi: 10.3390/life11020169, herein incorporated by reference with regard to such background teaching. For patients already infected with HBV, coinfection/superinfection with HDV can
20 further exacerbate the symptoms of HBV, increasing the likelihood of complications, rapid disease progression and/or death. Chronic HBV/HDV infection is also associated with the development of hepatocellular carcinoma (HCC). Like HBV, treatment options for HDV infection or HBV/HDV coinfection, are limited and include those used to treat HBV. Thus, there is a need for effective therapeutic options for the treatment of HDV infection or
25 HBV/HDV coinfection/superinfection.

WO2022253997 relates to relates to 1,5-benzothiazepine and 1,2,5-benzothiadiazepine derivatives of formula (I). These compounds are bile acid modulators having apical sodium-dependent bile acid transporter (ASBT) and/or liver bile acid transport (LBAT) inhibitory activity. The invention also relates to pharmaceutical compositions
30 comprising these compounds and to the use of these compounds in the treatment of

cardiovascular diseases, fatty acid metabolism and glucose utilization disorders, gastrointestinal diseases and liver diseases.

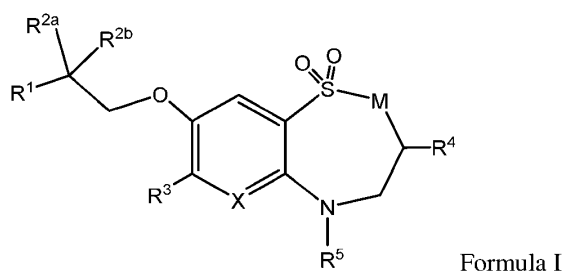
WO2023237728 to Albireo relates to methods for treating hepatitis B and/or D with an Na⁺/taurocholate co-transporting polypeptide (NTCP) inhibitor such as a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a compound of formula (II), or a pharmaceutically acceptable salt thereof. Such methods can include decreasing the concentration of hepatitis B DNA, decreasing the concentration of hepatitis D DNA, decreasing hepatitis B surface antigen, and decreasing hepatitis B core antigen (HBcAg).

NTCP functions as a cellular receptor for viral entry of HBV and HDV, which in turn is the major cause of liver disease and HCC. There is a need for additional bile acid modulating compounds that have an improved profile with respect to potency, safety, selectivity and/or bioavailability.

SUMMARY

The present disclosure provides, in part, benzothia(dia)zepine compounds and pharmaceutical compositions thereof, useful for inhibition of HBV or HDV replication, inhibition of HBV or HDV viral entry, and methods of treating HBV infections, HDV infection or HBV/HDV coinfection.

In one aspect, the disclosure provides a compound of Formula I:



or a pharmaceutically acceptable salt thereof, where the variables are described in the detailed description.

In another aspect, the disclosure provides pharmaceutical compositions comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In another aspect, the disclosure provides a method of treating an HBV infection in a subject in need thereof, comprising: administering to the subject a therapeutically effective amount of compound of Formula I, or a pharmaceutically acceptable salt thereof.

5 In another aspect, the disclosure provides a method of treating an HBV infection in a subject in need thereof, comprising: administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In another aspect, the disclosure provides a method of treating an HDV infection in a subject in need thereof, comprising: administering to the subject a therapeutically effective
10 amount of compound of Formula I, or a pharmaceutically acceptable salt thereof.

In another aspect, the disclosure provides a method of treating an HDV infection in a subject in need thereof, comprising: administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

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BRIEF DESCRIPTION OF DRAWINGS

Figure 1 shows the ORTEP plot for Example 10b.

Figure 2 shows the ORTEP plot for Example 11a.

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DETAILED DESCRIPTION

Hepatitis delta, also known as hepatitis D, is a liver infection caused by the hepatitis delta virus (HDV), resulting in the most severe form of viral hepatitis known in humans. HDV is a single-stranded, circular RNA virus. It relies on the hepatitis B virus (HBV) to infect and replicate in liver cells. HDV is a defective virus that lacks the ability to produce its
25 own envelope proteins and is thus dependent on the presence of HBV that provides the envelope proteins. New HDV progeny particles can only be produced in a liver cell that is already infected with HBV.

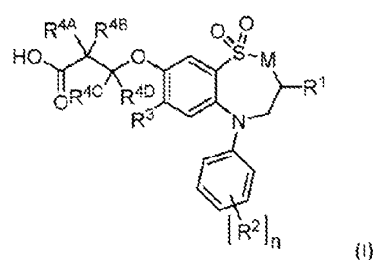
Worldwide, approximately 300 million people are chronically infected with HBV. An estimated 15-20 million are also chronically infected with hepatitis delta. Coinfections lead to
30 more serious liver disease than HBV infection alone. They are associated with faster

progression to liver fibrosis, increased risk of liver cancer, and early decompensated cirrhosis and liver failure that may lead to a fatal outcome within days if not transplanted. Hepatitis delta can be acquired either through coinfection: infection with hepatitis B and delta at the same time. It can also be acquired by superinfection: infection with hepatitis D after a person
 5 has already acquired hepatitis B.

There is currently no vaccine for hepatitis delta. However, it can be prevented by getting the hepatitis B vaccine to help eliminate the risk of infection with HBV. The entry inhibitor Hepcludex (myrcludex B, Bulevirtide, BLV) was approved for HDV in July of 2020 in the European Union, and as of June 2023, is available in France, Germany, Austria, Italy,
 10 and the UK. The drug binds to the essential HDV receptor on liver cells and by doing so prevents infection of the cell. Binding of BLV to NTCP simultaneously inhibits its natural biological function of transporting bile acid into the cell. Previously, the only treatment for hepatitis delta found to be somewhat effective was pegylated interferon alpha, which acts by stimulating the body's innate immune system to fight the virus.

While Hepcludex is a 47-amino acid peptide, inhibiting Na⁺-taurocholate cotransporting polypeptide (NTCP), the viral entry receptor, requiring subcutaneous (SubQ) dosing, the small-molecule oral bioavailable NTCP inhibitors of the present invention provide more flexible dosing, increased convenience, and greater combinational options with
 15 other HBV/HDV therapies.

WO2022/253997 to Albireo relates to 1,5-benzothiazepine and 1,2,5-benzothiadiazepine derivatives of formula (I):

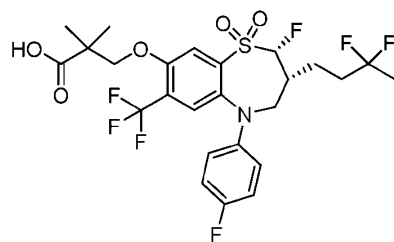


These compounds are bile acid modulators having apical sodium-dependent bile acid transporter (ASBT) and/or liver bile acid transport (LBAT) inhibitory activity. The invention
 25 also relates to pharmaceutical compositions comprising these compounds and the use of these

compounds in the treatment of cardiovascular diseases, fatty acid metabolism and glucose utilization disorders, gastrointestinal diseases, and liver diseases.

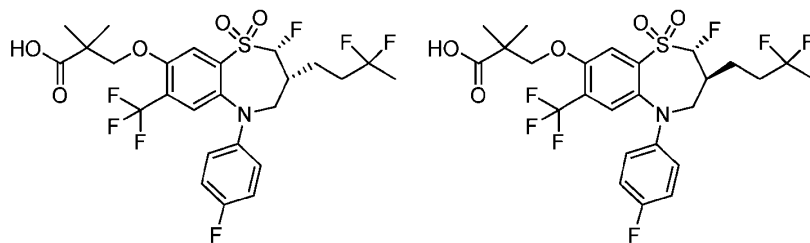
Applicants note that the Compounds of formula (I) in WO2022/253997 are chiral due to the presence of a chiral center at the carbon atom bearing R^1 . In addition, M is limited to -CH₂- and -NR⁵-, wherein R⁵ is hydrogen or C₁₋₄alkyl; R¹ is limited to C₁₋₄alkyl, and R³ is limited to hydrogen, halo, cyano, C₁₋₄alkyl, C₃₋₆cycloalkyl, C₁₋₄alkoxy, C₃₋₆cycloalkoxy, C₁₋₄alkylthio, C₃₋₆cycloalkylthio, amino, N-(C₁₋₄alkyl)amino, and N,N-di(C₁₋₄alkyl)amino. Thus, there is no teaching or suggestion of a haloalkyl substituent at R¹ or R³, or of M being a substituted carbon atom. Notably, when M is a mono-substituted carbon atom, a new chiral center is introduced resulting in four diastereomers.

In contrast, Example 10b is an exemplary compound of the present invention, with a structure and absolute stereochemistry as shown below:



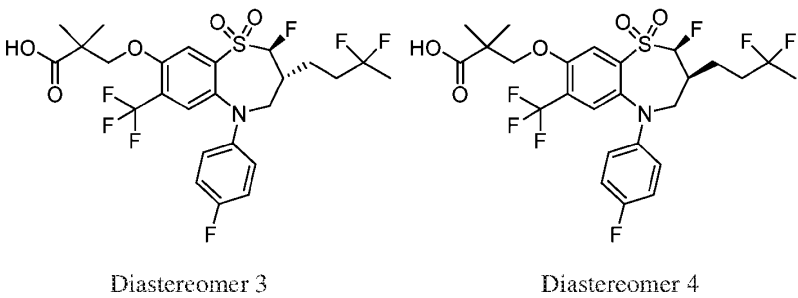
Example 10b

wherein haloalkyl groups are introduced at R¹ (i.e., -CH₂CH₂CF₂CH₃) and R³ (i.e., CF₃) and M is a mono-substituted carbon atom (i.e., -CHF-), resulting in a second chiral center outside the scope of WO2022/253997. Applicants have discovered one or more of these structural modifications results in unexpectedly improved biological activity against HBV and HDV, selectivity profiles, and PK profiles. The compound of Example 10b can exist as four diastereomers:



Diastereomer 1

Diastereomer 2



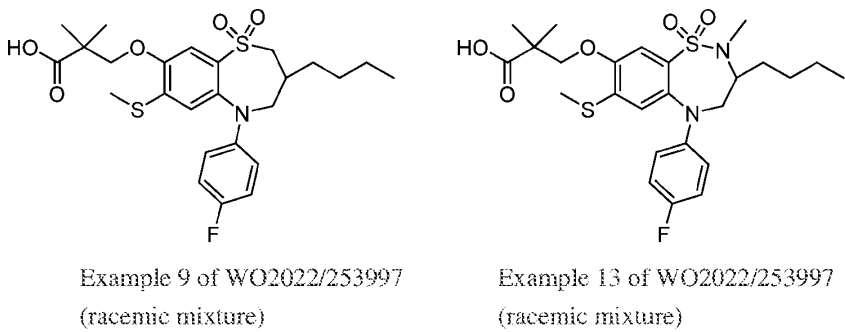
Potency and transporter selectivity comparison data for each of these four diastereomers are provided in TABLE 1.

5 TABLE 1: Potency and transporter selectivity comparison data for each of the four diastereomers of the compound of Example 10b of the present invention

	Diastereomer 1	Diastereomer 2	Diastereomer 3	Diastereomer 4
HBeAg EC ₅₀ (nM)	4.2	68.3	22.2	1174
NTCP IC ₅₀ (nM)	7.3	28	17	524
Ratio of ASBT IC ₅₀ / NTCP IC ₅₀ (Fold)	323	NA	226	58

As used herein, Diastereomer 1 of Example 10b of the present invention is also referred to as Compound 1.

10 For comparison purposes, Applicants have made and tested the compounds of Example 9 and Example 13 of WO2022/253997 according to procedures known in the art. Both are described in WO2022/253997 as racemic mixtures of the corresponding enantiomers.



Example 14, *enantiomer 1* and Example 14, *enantiomer 2* are the isolated *R* and *S* enantiomers (absolute stereochemistry unassigned) of Example 13. Table 8 of WO2022/253997 shows that Example 9 and Example 13 have similar NTCP (hLBAT) inhibitory activity but Example 14, *enantiomer 2* is significantly more active at inhibiting NTCP (hLBAT) than Example 14, *enantiomer 1*. However, no assay data is provided directly demonstrating biologic activity against HDV or HBV.

TABLE 2 provides potency and transporter selectivity comparison data for Compound 1 vs the compounds of Examples 9 and 14 of WO2022/253997.

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TABLE 2: Potency and transporter selectivity comparison data

	Compound 1	Example 9 (racemate)	Example 9 (best enantiomer)	Example 14 (enantiomer 2)
HBeAg EC ₅₀ (nM)	4.2	108	45	24
NTCP IC ₅₀ (nM)	7.3	34.5	75.6	21
ASBT IC ₅₀ (nM)	2,400	NA	NA	190
Ratio of ASBT IC ₅₀ / NTCP IC ₅₀ (Fold)	323	NA	NA	9

As shown in the table, Compound 1 had half-maximal inhibitory concentration (IC₅₀) values of 7.3 and 2,400 nM vs human NTCP and ASBT, respectively, with an NTCP-selectivity ratio (ASBT IC₅₀/NTCP IC₅₀) of >320-fold. Compound 1 also prevented HBV infection of human hepatoma cells with an IC₅₀ of 4.2 nM without affecting cell viability.

In contrast, Example 14 (enantiomer 2) had IC₅₀ values of 21 and 190 nM vs human NTCP and ASBT, respectively, with an NTCP-selectivity ratio (ASBT IC₅₀/NTCP IC₅₀) of 9-fold. This compound prevented HBV infection of human hepatoma cells with an IC₅₀ of 24 nM without affecting cell viability. Likewise, Example 9 (best enantiomer) had an IC₅₀ of 75.6 nM vs human NTCP and prevented HBV infection of human hepatoma cells with an IC₅₀ of 45 nM without affecting cell viability.

Thus, in hepatoma cells infected with HBV, Compound 1 exhibited a higher anti-HBV potency than Example 14 (enantiomer 2), with an IC₅₀ value approximately 6-times

lower. In comparison to Example 9 (best enantiomer), the IC₅₀ value was approximately 11-times lower. Compound 1 also inhibited NTCP more effectively, with an IC₅₀ value approximately 3-times lower than that of Example 14 (enantiomer 2) and approximately 10-times lower than that of Example 9 (best enantiomer. Finally, Compound 1 demonstrated a
5 NTCP-selectivity (ASBT IC₅₀/NTCP IC₅₀) that was approximately 36-times higher than that of Example 14 (enantiomer 2), indicating its superior selectivity.

TABLE 3 provides monkey PK profile comparison data for Compound 1 vs Albireo compound A7387. Data for Compound 1 was acquired using methods and procedures described herein, while data for A7387 is digitized from an Albireo 2023 AASLD poster,
10 1481-C | PRECLINICAL CHARACTERIZATION OF THE NOVEL, ORALLY BIOAVAILABLE NTCP INHIBITOR A7387. Although the structure of A7387 was not disclosed in the poster, WO2023237728 refers to Example 14 of WO2022/253997 as Compound 2, and provides primate *in vivo* results on p. 77, cross-referencing Compound 2 as A7387.

15 TABLE 3: Monkey PK Profile Comparison for Compound 1 vs A7387

Dose (mg/kg)	Compound	AUC ₀₋₂₄ (hr*ng/mL)	C _{max} (ng/mL)	T _{1/2} (hr)
3	Compound 1	58178	5147	14
3	A7387	13784	2299	3
3	Ratio	4.2	2.2	4.2
10	Compound 1	290412	23100	17
10	A7387	18733	1694	6
10	Ratio	15.5	13.6	2.6
30	Compound 1	1082543	64900	13
30	A7387	321545	26405	4
30	Ratio	3.4	2.5	3.6

In monkeys, after an oral dose of 3 mg/kg, Compound 1 exhibited higher exposure, with an AUC₀₋₂₄ of 58178 hr*ng/mL and a C_{max} of 5147 ng/mL, which were 320% and 120% higher, respectively, than those observed for A7387.

In monkeys, after an oral dose of 10 mg/kg, Compound 1 exhibited higher exposure,
5 with an AUC₀₋₂₄ of 290412 hr*ng/mL and a C_{max} of 23100 ng/mL, which were 1450% and 1260% higher, respectively, than those observed for A7387.

In monkeys, after an oral dose of 30 mg/kg, Compound 1 exhibited higher exposure, with an AUC₀₋₂₄ of 1082543 hr*ng/mL and a C_{max} of 64900 ng/mL, which were 240% and 150% higher, respectively, than those observed for A7387.

10 The apparent oral PK terminal half-life of Compound 1 ranged from 13-17 hours, which were 160% - 320% longer than those observed for A7387.

The features and other details of the present disclosure will now be more particularly described. Before further description of the present disclosure, certain terms employed in the
15 specification, examples and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and as understood by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

20 I. Definitions

The term “alkenyl” as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon double bond. Exemplary alkenyl groups include, but are not limited to, a straight or branched group of 2-6 carbon atoms, referred to herein as C₂₋₆alkenyl. Exemplary alkenyl groups include, but are not limited to, vinyl, allyl,
25 butenyl, and pentenyl, etc.

The term “alkoxy” as used herein refers to a straight or branched alkyl group attached to oxygen (i.e., alkyl-O-). Exemplary alkoxy groups include, but are not limited to, alkoxy groups of 1-6 or 1-4 carbon atoms, referred to herein as C₁₋₆alkoxy and C₁₋₄alkoxy, respectively. Exemplary alkoxy groups include, but are not limited to methoxy, ethoxy, and
30 isopropoxy, etc.

The term “alkoxyalkyl” as used herein refers to an alkyl group substituted with an alkoxy group. Examples include, but are not limited to, $\text{CH}_3\text{CH}_2\text{OCH}_2-$, $\text{CH}_3\text{OCH}_2\text{CH}_2-$ and CH_3OCH_2- , etc.

The term “alkyl” as used herein refers to a saturated straight or branched hydrocarbon. Exemplary alkyl groups include, but are not limited to, straight or branched hydrocarbons of 1-6 or 1-4 carbon atoms, referred to herein as C_{1-6} alkyl and C_{1-4} alkyl, respectively. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, 2-methyl-1-butyl, 3-methyl-2-butyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, neopentyl, and n-hexyl, etc. The term “alkylene” as used herein refers to a biradical alkyl group.

The term “alkynyl” as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon triple bond. Exemplary alkynyl groups include, but are not limited to, straight or branched groups of 2-6 carbon atoms, referred to herein as C_{2-6} alkynyl. Exemplary alkynyl groups include, but are not limited to, ethynyl, propynyl, butynyl, pentynyl, hexynyl, and methylpropynyl, etc.

The term “carbonyl” as used herein refers to the biradical $-\text{C}(\text{O})-$.

The term “coinfection” as used herein refers to simultaneous infection of a host by more than one viral pathogen.

The term “cyano” as used herein refers to the radical $-\text{CN}$.

The term “cycloalkyl” as used herein refers to a saturated monocyclic hydrocarbon group of, for example, 3-7 carbons, referred to herein as C_{3-7} monocycloalkyl, or bicyclic hydrocarbon ring structure of, for example, 5-12 carbons, referred to herein as C_{5-12} bicycloalkyl. For bicyclic cycloalkyl groups, the two rings may be attached through the same or different carbons. Exemplary monocycloalkyl groups include, but are not limited to, cycloheptyl, cyclohexyl, cyclopentyl, cyclopentenyl, cyclobutyl and cyclopropyl. Exemplary bicycloalkyl groups include, but are not limited to, spiro[2.5]octanyl, spiro[3.5]nonanyl, spiro[4.5]decanyl, spiro[5.5]undecanyl, spiro[2.4]heptanyl, spiro[3.4]octanyl, spiro[4.4]nonanyl, spiro[2.3]hexanyl, spiro[3.3]heptanyl, decahydronaphthalene, octahydro-1*H*-indene, bicyclo[4.2.0]octanyl, bicyclo[4.1.0]heptanyl, octahydropentalenyl,

bicyclo[3.2.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[2.2.2]octanyl, bicyclo[2.2.1]heptanyl, bicyclo[3.1.1]heptanyl, and bicyclo[1.1.1]pentanyl.

The terms “halo” or “halogen” as used herein refer to F, Cl, Br or I.

The term “haloalkyl” as used herein refers to an alkyl group substituted with one or more halogen atoms. For example, haloC₁₋₆alkyl refers to a straight or branched alkyl group of 1-6 carbon atoms substituted with one or more halogen atoms. Examples include, but are not limited to, -CH₂F, -CHCl₂, -CHF₂, -CF₃, CF₃CH₂-, CH₃CF₂-, CF₃CCl₂-, and CF₃CF₂-.

The term “haloalkoxy” as used herein refers to an alkoxy group substituted with one or more halogen atoms. Examples include, but are not limited to, CCl₃O-, CF₃O-, CHF₂O-, CF₃CH₂O-, and CF₃CF₂O-.

The terms “heteroaryl” as used herein refers to a 5-6 membered monocyclic aromatic group, referred to herein as monocyclo₅₋₆heteroaryl, or 8-12 membered bicyclic aromatic ring system, referred to herein as bicyclo₈₋₁₂heteroaryl, containing one to four independently selected heteroatoms, such as nitrogen, oxygen and sulfur. Where possible, the heteroaryl ring may be linked to the adjacent radical through carbon or nitrogen. Examples of monocyclo₅₋₆heteroaryl groups include, but are not limited to, furanyl, thiophenyl (also referred to as thienyl), pyrrolyl, thiazolyl, oxazolyl, isothiazolyl, isoxazolyl, imidazolyl, pyrazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, 1,2,4-triazolyl, pyridinyl (also referred to as pyridyl), pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl and tetrazolyl. Examples of bicyclo₈₋₁₂heteroaryl groups include, but are not limited to, benzofuranyl, isobenzofuranyl, benzo[*b*]thiophenyl, benzo[*c*]thiophenyl, indolyl, isoindolyl, benzo[*d*]isoxazolyl, benzo[*c*]isoxazolyl, benzo[*d*]oxazolyl, benzo[*d*]isothiazolyl, benzo[*c*]isothiazolyl, benzo[*d*]thiazolyl, indazolyl, benzo[*d*]imidazolyl, benzo[*d*]imidazolyl, and benzo[*d*][1,2,3]triazolyl.

The term “heterocycloalkyl” refers to a monocycloalkyl group, for example a C₃₋₇monocycloalkyl, or a bicycloalkyl group, for example C₅₋₁₂bicycloalkyl, wherein 1-3 of the carbon atoms are replaced with independently selected heteroatoms, such as nitrogen, oxygen, and sulfur (including its oxidation states: S(O) and SO₂), herein referred to as mono₃₋₇heterocycloalkyl and bi₅₋₁₂heterocycloalkyl, respectively. Examples of mono₃₋₇

heterocycloalkyl groups include, but are not limited to, aziridinyl, oxiranyl, thiiranyl 1,1-dioxide, oxetanyl, azetidiny, thietanyl 1,1-dioxide, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, tetrahydro-2H-pyranyl, morpholinyl, thiomorpholinyl, and piperazinyl. Examples of bi₅₋₁₂heterocycloalkyl groups include, but are not limited to, 1,4-dioxaspiro[4.5]decanyl
 5 and 1,5-dioxaspiro[5.5]undecanyl.

The terms “hydroxy” and “hydroxyl” as used herein refers to the radical -OH.

The term “hydroxyalkyl” as used herein refers to an alkyl group substituted with one or more hydroxy groups. Examples include, but are not limited to, HOCH₂-, HOCH₂CH₂-, CH₃CH(OH)CH₂- and HOCH₂CH(OH)CH₂-.

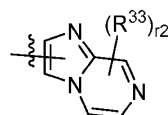
10 The term “hydroxyalkoxy” as used herein refers to an alkoxy group substituted with one or more hydroxy groups. Examples include but are not limited to HOCH₂O-, HOCH₂CH₂O-, CH₃CH(OH)CH₂O- and HOCH₂CH(OH)CH₂O-.

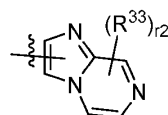
The term “R^aR^bNC₁₋₆ alkyl-,” as used herein refers to an alkyl group substituted with a R^aR^bN- group, as defined herein. Examples include but are not limited to NH₂CH₂-,
 15 NH(CH₃)CH₂-, N(CH₃)₂CH₂CH₂- and CH₃CH(NH₂)CH₂-.

The term “R^aR^bNC₁₋₆alkoxy,” as used herein refers to an alkoxy group substituted with a R^aR^bN- groups, as defined herein. Examples include but are not limited to NH₂CH₂-, NH(CH₃)CH₂O-, N(CH₃)₂CH₂CH₂O-, and CH₃CH(NH₂)CH₂O-.

The term “oxo” as used herein refers to the radical =O.

20 As used herein, when a bicyclic ring is shown with a floating point of attachment



and/or floating substituents, for example as in , it signifies that the bicyclic ring can be attached via a carbon atom on either ring, and that the substituents (e.g., the R³³ group(s)) can be independently attached to either or both rings.

The terms “individual,” “patient,” or “subject” are used interchangeably and include
 25 any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans. The compounds or pharmaceutical compositions of the disclosure can be administered to a mammal, such as a human, but can also be administered to other mammals such as an animal in need of

veterinary treatment, *e.g.*, domestic animals (*e.g.*, dogs, cats, and the like), farm animals (*e.g.*, cows, sheep, pigs, horses, and the like) and laboratory animals (*e.g.*, rats, mice, guinea pigs, dogs, primates, and the like). The mammal treated in the methods of the disclosure is desirably a mammal in which treatment of HBV infection is desired.

5 The term “modulation” includes antagonism (*e.g.*, inhibition), agonism, partial antagonism and/or partial agonism.

 The term “pharmaceutically acceptable” include molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate. For human administration, preparations should meet
10 sterility, pyrogenicity, and general safety and purity standards as required by FDA Office of Biologics standards.

 The term “pharmaceutically acceptable carrier” or “pharmaceutically acceptable excipient” as used herein refers to any and all solvents, dispersion media, coatings, isotonic and absorption delaying agents, fillers, and the like, that are compatible with pharmaceutical
15 administration. The use of such media and agents for pharmaceutically active substances is well known in the art. The compositions may also contain other active compounds providing supplemental, additional, or enhanced therapeutic functions.

 The term “pharmaceutical composition” as used herein refers to a composition comprising at least one compound as disclosed herein formulated together with one or more
20 pharmaceutically acceptable excipients.

 The term “pharmaceutically acceptable salt(s)” as used herein refers to salts of acidic or basic groups that may be present in compounds used in the compositions. Compounds included in the present compositions that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to
25 prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, *i.e.*, salts containing pharmacologically acceptable anions, including, but not limited to, malate, oxalate, chloride, bromide, iodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate,
30 fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate,

methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate and pamoate (i.e., 1,1'-methylene-*bis*-(2-hydroxy-3-naphthoate)) salts. Compounds included in the present compositions that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include alkali metal or alkaline earth metal salts, particularly calcium, magnesium, sodium, lithium, zinc, potassium, and iron salts. Compounds included in the present compositions that include a basic or acidic moiety may also form pharmaceutically acceptable salts with various amino acids. The compounds of the disclosure may contain both acidic and basic groups; for example, one amino and one carboxylic acid group. In such a case, the compound can exist as an acid addition salt, a zwitterion, or a base salt.

The term “therapeutically effective amount” or “effective amount” as used herein refers to the amount of the subject compound that will elicit the biological or medical response of a tissue, system or animal, (e.g., mammal or human) that is being sought by the researcher, veterinarian, medical doctor or other clinician. The compounds or pharmaceutical compositions of the disclosure are administered in therapeutically effective amounts to treat a disease. Alternatively, a therapeutically effective amount of a compound is the quantity required to achieve a desired therapeutic and/or prophylactic effect.

The term “treating” includes any effect, e.g., lessening, reducing, modulating, or eliminating, a viral infection, that results in the improvement of the disease.

The compounds of the disclosure may contain one or more chiral centers and, therefore, exist as stereoisomers. The term “stereoisomers” when used herein consist of all enantiomers or diastereomers. These compounds may be designated by the symbols “(+)”, “(-)”, “R” or “S,” depending on the configuration of substituents around the stereogenic carbon atom, but the skilled artisan will recognize that a structure may denote a chiral center implicitly. The present disclosure encompasses various stereoisomers of these compounds and mixtures thereof. Mixtures of enantiomers or diastereomers may be designated “(±)” in nomenclature, but the skilled artisan will recognize that a structure may denote a chiral center implicitly.

The compounds of the disclosure may contain one or more double bonds and, therefore, exist as geometric isomers resulting from the arrangement of substituents around a

carbon-carbon double bond. The symbol $\equiv$ denotes a bond that may be a single, double or triple bond as described herein. Substituents around a carbon-carbon double bond are designated as being in the “*Z*” or “*E*” configuration wherein the terms “*Z*” and “*E*” are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting double
5 bonds encompass both the “*E*” and “*Z*” isomers. Substituents around a carbon-carbon double bond alternatively can be referred to as “cis” or “trans,” where “cis” represents substituents on the same side of the double bond and “trans” represents substituents on opposite sides of the double bond.

Compounds of the disclosure may contain a carbocyclic or heterocyclic ring and
10 therefore, exist as geometric isomers resulting from the arrangement of substituents around the ring. The arrangement of substituents around a carbocyclic or heterocyclic ring are designated as being in the “*Z*” or “*E*” configuration wherein the terms “*Z*” and “*E*” are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting carbocyclic or heterocyclic rings encompass both “*Z*” and “*E*” isomers. Substituents around
15 a carbocyclic or heterocyclic ring may also be referred to as “cis” or “trans”, where the term “cis” represents substituents on the same side of the plane of the ring and the term “trans” represents substituents on opposite sides of the plane of the ring. Mixtures of compounds wherein the substituents are disposed on both the same and opposite sides of plane of the ring are designated “cis/trans.”

20 Individual enantiomers and diastereomers of compounds of the present disclosure can be prepared synthetically from commercially available starting materials that contain asymmetric or stereogenic centers, or by preparation of racemic mixtures followed by resolution methods well known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary,
25 separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary, (2) salt formation employing an optically active resolving agent, (3) direct separation of the mixture of optical enantiomers on chiral liquid chromatographic columns or (4) kinetic resolution using stereoselective chemical or enzymatic reagents. Racemic mixtures can also be resolved into their component
30 enantiomers by well-known methods, such as chiral-phase liquid chromatography or

crystallizing the compound in a chiral solvent. Stereoselective syntheses, a chemical or enzymatic reaction in which a single reactant forms an unequal mixture of stereoisomers during the creation of a new stereocenter or during the transformation of a pre-existing one, are well known in the art. Stereoselective syntheses encompass both enantiomeric and
5 diastereoselective transformations and may involve the use of chiral auxiliaries. For examples, see Carreira and Kvaerno, *Classics in Stereoselective Synthesis*, Wiley-VCH: Weinheim, 2009.

The compounds disclosed herein can exist in solvated as well as unsolvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is
10 intended that the disclosure embrace both solvated and unsolvated forms. In one embodiment, the compound is amorphous. In one embodiment, the compound is a single polymorph. In another embodiment, the compound is a mixture of polymorphs. In another embodiment, the compound is in a crystalline form.

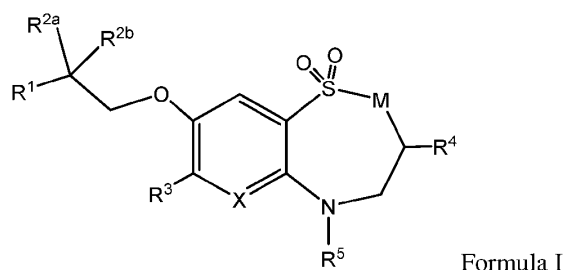
The disclosure also embraces isotopically labeled compounds of the disclosure which
15 are identical to those recited herein, except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl ,
20 respectively. For example, a compound of the disclosure may have one or more H atom replaced with deuterium.

Certain isotopically-labeled disclosed compounds (*e.g.*, those labeled with ^3H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (*i.e.*, ^3H) and carbon-14 (*i.e.*, ^{14}C) isotopes are particularly preferred for their ease of preparation and
25 detectability. Further, substitution with heavier isotopes such as deuterium (*i.e.*, ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability (*e.g.*, increased *in vivo* half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labeled compounds of the disclosure can generally be prepared by following procedures analogous to those disclosed in the examples herein by
30 substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

The term “prodrug” refers to compounds that are transformed *in vivo* to yield a disclosed compound or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (such as by esterase, amidase, phosphatase, oxidative and or reductive metabolism) in various locations (such as in the intestinal lumen or upon transit of the intestine, blood or liver). Prodrugs are well known in the art (for example, see Rautio, Kumpulainen, *et al.*, Nature Reviews Drug Discovery 2008, 7, 255).

II. Benzothia(dia)zepine Compounds

In one aspect, the present disclosure provides a compound of Formula I



, or a pharmaceutically acceptable salt thereof, wherein:

M is NR^x or CR^yR^z ;

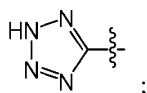
X is N or CH;

R^a , R^b and R^c are independently selected for each occurrence from the group consisting of hydrogen, C_{1-6} alkyl, halo C_{1-6} alkyl and C_{3-6} monocycloalkyl;

R^x is hydrogen or C_{1-4} alkyl;

R^y and R^z are independently selected from the group consisting of hydrogen, halo, CN, C_{1-4} alkyl, and halo C_{1-4} alkyl;

R^1 is OH, CH_3 , $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{OC}_{1-6}$ alkyl, $-\text{P}(\text{O})(\text{OH})_2$, $-\text{S}(\text{O})_2\text{OH}$ or



R^{2a} and R^{2b} are independently selected from the group consisting of hydrogen, halo, OH methyl, ethyl and CH_2OH ; or R^{2a} and R^{2b} together with the carbon atom to which they are attached form a $\text{C}=\text{CH}_2$, C_{3-6} monocycloalkyl, oxetanyl, tetrahydrofuranyl,

tetrahydropyranyl or 1,3-dioxanyl group, wherein the C₃₋₆monocycloalkyl, oxetanyl, tetrahydrofuranlyl, tetrahydropyranyl or 1,3-dioxanyl group is optionally substituted with 1 to 3 independently selected halo or methyl groups;

R³ is selected from the group consisting of hydrogen, halogen, cyano, R^aR^bN-, C₁₋₄alkyl, haloC₁₋₄alkyl, C₁₋₄alkoxy, haloC₁₋₄alkoxy, C₁₋₄alkylthio, haloC₁₋₄alkylthio, C₃₋₇monocycloalkyl, C₃₋₇monocycloalkyloxy, C₃₋₇monocycloalkylthio, C₃₋₇monocycloalkyl-CH₂-thio, and C₅₋₁₂bicycloalkylthio, wherein the C₃₋₇monocycloalkyl, C₃₋₇monocycloalkyloxy, C₃₋₇monocycloalkylthio, C₃₋₇monocycloalkyl-CH₂-thio, and C₅₋₁₂bicycloalkylthio group is optionally substituted with 1 to 3 halo groups;

R⁴ is hydrogen, C₁₋₄alkyl, haloC₁₋₄alkyl, hydroxyC₁₋₄alkyl, CH₃SO₂CH₂CH₂-, CH₃SO₂CH₂CH₂CH₂-, R^{4a}CH₂- or R^{4a}CH₂CH₂-;

R^{4a} is phenyl, imidazolyl, N-methylimidazolyl, or C₃₋₆monocycloalkyl optionally substituted with 1 to 3 halo groups;

R⁵ is phenyl, C₃₋₇monocycloalkyl or C₅₋₁₂bicycloalkyl, wherein the phenyl, C₃₋₇monocycloalkyl or C₅₋₁₂bicycloalkyl is optionally substituted with one to six substituents independently selected from the group consisting of halo, OH, CN, HOC(O)-, R^aR^bN-, R^aR^bNS(O)_q-, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, haloC₁₋₄alkyl, hydroxyC₁₋₄alkyl-, R^aR^bNC₁₋₄alkyl-, C₁₋₄alkoxy, haloC₁₋₄alkoxy, hydroxyC₁₋₄alkoxy-, R^aR^bNC₁₋₄alkoxy-, C₁₋₃alkoxyC₁₋₄alkyl-, haloC₁₋₃alkoxyC₁₋₄alkyl-, R^aR^bNC(O)-, C₁₋₄alkylC(O)-, C₁₋₄alkoxyC(O)-, C₁₋₄alkylC(O)O-, C₁₋₄alkylS(O)_q-, C₁₋₄alkylS(O)_qNR^c-, C₁₋₆alkylS(O)_qC₁₋₄alkyl-, C₁₋₄alkylC(O)C₁₋₆alkyl-, and C₁₋₆alkylC(O)OC₁₋₄alkyl-; and

q is independently selected for each occurrence from the group consisting of 0, 1 and 2;

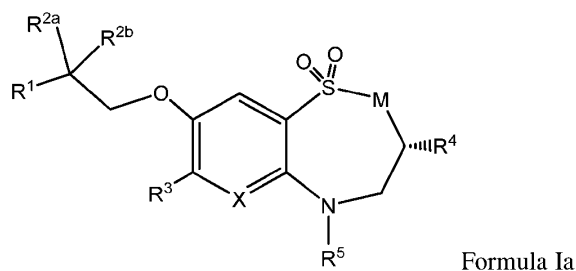
with the proviso that: R³ is haloC₁₋₄alkyl; M is CR^yR^z and at least one of R^y and R^z is halo, CN, C₁₋₄alkyl, or haloC₁₋₄alkyl; or R⁴ is haloC₁₋₄alkyl, hydroxyC₁₋₄alkyl, CH₃SO₂CH₂CH₂-, CH₃SO₂CH₂CH₂CH₂-, R^{4a}CH₂- or R^{4a}CH₂CH₂-; or a combination thereof.

The following embodiments further describe a compound of Formula I, or a pharmaceutically acceptable salt thereof. It will be appreciated that all chemically allowable

combinations of the embodiments described herein are envisioned as further embodiments of the invention.

In certain embodiments, the Compound of Formula I is of Formula Ia

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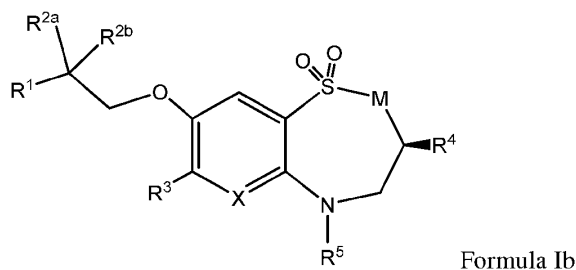


Formula Ia

or a pharmaceutically acceptable salt thereof.

10

In certain embodiments, the Compound of Formula I is of Formula Ib



Formula Ib

or a pharmaceutically acceptable salt thereof.

15

In certain embodiments, X is N.

In certain embodiments, X is CH.

In certain embodiments, M is NR^x.

20

In certain embodiments, M is NH or NCH₃.

In certain embodiments, M is CR^yR^z.

5 In certain embodiments, M is -CH₂-.

In certain embodiments, M is CR^yR^z and at least one of R^y and R^z is halo, CN, C₁₋₄alkyl, or haloC₁₋₄alkyl.

10 In certain embodiments, M is -CH(CH₃)-, -CF(CH₃)-, is -CHF-, -C(CH₃)₂- or -CF₂-.

In certain embodiments, M is -CF(CH₃)-.

In certain embodiments, M is -C(CH₃)₂-.

15

In certain embodiments, M is -CHF-.

In certain embodiments, M is -CF₂-.

20 In certain embodiments, R¹ is C(O)OH.

In certain embodiments, R¹ is S(O)₂OH.

In certain embodiments, R¹ is P(O)(OH)₂.

25

In certain embodiments, R^{2a} and R^{2b} are independently selected from the group consisting of hydrogen, halo, OH and methyl.

In certain embodiments, R^{2a} and R^{2b} are methyl.

30

In certain embodiments, R^{2a} is hydrogen and R^{2b} are methyl.

In certain embodiments, R^{2a} and R^{2b} together with the carbon atom to which they are attached form a $C=CH_2$, cyclopropyl, cyclobutyl, or oxetanyl group, wherein the cyclopropyl
5 or cyclobutyl group is optionally substituted with 1-3 halo groups.

In certain embodiments, R^{2a} and R^{2b} together with the carbon atom to which they are attached form a $C=CH_2$, cyclopropyl, cyclobutyl, or oxetanyl group.

10 In certain embodiments, R^{2a} and R^{2b} together with the carbon atom to which they are attached form a cyclopropyl group.

In certain embodiments, R^3 is C_{5-12} bicycloalkylthio-.

15 In certain embodiments, R^3 is halo C_{3-7} monocycloalkylthio-.

In certain embodiments, R^3 is halo C_{1-2} alkyl-.

In certain embodiments, R^3 is CF_3 .

20

In certain embodiments, R^4 is halo C_{1-4} alkyl-, hydroxy C_{1-4} alkyl-, $CH_3SO_2CH_2CH_2$ -, $CH_3SO_2CH_2CH_2CH_2$ -, $R^{4a}CH_2$ - or $R^{4a}CH_2CH_2$ -.

In certain embodiments, R^4 is halo C_{1-4} alkyl-.

25

In certain embodiments, R^4 is halo C_{3-4} alkyl-.

In certain embodiments, R^4 is n-butyl substituted with 1 to 6 halo atoms.

30 In certain embodiments, R^4 is n-butyl substituted with 1 to 6 F atoms.

In certain embodiments, R^4 is $-\text{CH}_2\text{CH}_2\text{CF}_2\text{CH}_3$.

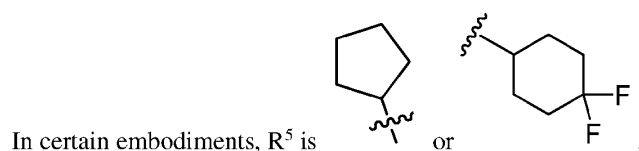
In certain embodiments, R^4 is n-propyl substituted with 1 to 6 halo atoms.

5

In certain embodiments, R^4 is n-propyl substituted with 1 to 6 F atoms.

In certain embodiments, R^4 is $-\text{CH}_2\text{CH}_2\text{CF}_3$.

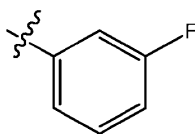
- 10 In certain embodiments, R^5 is C_{3-7} monocycloalkyl optionally substituted with one to six substituents independently selected from the group consisting of halo, OH, CN, HOC(O)- , $\text{R}^a\text{R}^b\text{N-}$, $\text{R}^a\text{R}^b\text{NS(O)}_q\text{-}$, $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{2-4}\text{alkenyl}$, $\text{C}_{2-4}\text{alkynyl}$, $\text{haloC}_{1-4}\text{alkyl}$, $\text{hydroxyC}_{1-4}\text{alkyl-}$, $\text{R}^a\text{R}^b\text{NC}_{1-4}\text{alkyl-}$, $\text{C}_{1-4}\text{alkoxy}$, $\text{haloC}_{1-4}\text{alkoxy}$, $\text{hydroxyC}_{1-4}\text{alkoxy-}$, $\text{R}^a\text{R}^b\text{NC}_{1-4}\text{alkoxy-}$, $\text{C}_{1-3}\text{alkoxyC}_{1-4}\text{alkyl-}$, $\text{haloC}_{1-3}\text{alkoxyC}_{1-4}\text{alkyl-}$, $\text{R}^a\text{R}^b\text{NC(O)-}$, $\text{C}_{1-4}\text{alkylC(O)-}$, $\text{C}_{1-4}\text{alkoxyC(O)-}$, $\text{C}_{1-4}\text{alkylC(O)O-}$, $\text{C}_{1-4}\text{alkylS(O)}_q\text{-}$, $\text{C}_{1-4}\text{alkylS(O)}_q\text{NR}^c\text{-}$, $\text{C}_{1-6}\text{alkylS(O)}_q\text{C}_{1-4}\text{alkyl-}$, $\text{C}_{1-4}\text{alkylC(O)C}_{1-6}\text{alkyl-}$, and $\text{C}_{1-6}\text{alkylC(O)OC}_{1-4}\text{alkyl-}$.
- 15



- 20 In certain embodiments, R^5 is C_{5-12} bicycloalkyl optionally substituted with one to six substituents independently selected from the group consisting of halo, OH, CN, HOC(O)- , $\text{R}^a\text{R}^b\text{N-}$, $\text{R}^a\text{R}^b\text{NS(O)}_q\text{-}$, $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{2-4}\text{alkenyl}$, $\text{C}_{2-4}\text{alkynyl}$, $\text{haloC}_{1-4}\text{alkyl}$, $\text{hydroxyC}_{1-4}\text{alkyl-}$, $\text{R}^a\text{R}^b\text{NC}_{1-4}\text{alkyl-}$, $\text{C}_{1-4}\text{alkoxy}$, $\text{haloC}_{1-4}\text{alkoxy}$, $\text{hydroxyC}_{1-4}\text{alkoxy-}$, $\text{R}^a\text{R}^b\text{NC}_{1-4}\text{alkoxy-}$, $\text{C}_{1-3}\text{alkoxyC}_{1-4}\text{alkyl-}$, $\text{haloC}_{1-3}\text{alkoxyC}_{1-4}\text{alkyl-}$, $\text{R}^a\text{R}^b\text{NC(O)-}$, $\text{C}_{1-4}\text{alkylC(O)-}$, $\text{C}_{1-4}\text{alkoxyC(O)-}$, $\text{C}_{1-4}\text{alkylC(O)O-}$, $\text{C}_{1-4}\text{alkylS(O)}_q\text{-}$, $\text{C}_{1-4}\text{alkylS(O)}_q\text{NR}^c\text{-}$, $\text{C}_{1-6}\text{alkylS(O)}_q\text{C}_{1-4}\text{alkyl-}$, $\text{C}_{1-4}\text{alkylC(O)C}_{1-6}\text{alkyl-}$, and $\text{C}_{1-6}\text{alkylC(O)OC}_{1-4}\text{alkyl-}$.
- 25

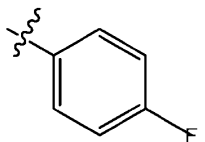
In certain embodiments, R^5 is phenyl optionally substituted with one to six substituents independently selected from the group consisting of halo, OH, CN, HOC(O)- , $R^aR^b\text{N-}$, $R^aR^b\text{NS(O)}_q\text{-}$, $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{2-4}\text{alkenyl}$, $\text{C}_{2-4}\text{alkynyl}$, $\text{haloC}_{1-4}\text{alkyl}$, $\text{hydroxyC}_{1-4}\text{alkyl-}$, $R^aR^b\text{NC}_{1-4}\text{alkyl-}$, $\text{C}_{1-4}\text{alkoxy}$, $\text{haloC}_{1-4}\text{alkoxy}$, $\text{hydroxyC}_{1-4}\text{alkoxy-}$, $R^aR^b\text{NC}_{1-4}\text{alkoxy-}$, $\text{C}_{1-3}\text{alkoxyC}_{1-4}\text{alkyl-}$, $\text{haloC}_{1-3}\text{alkoxyC}_{1-4}\text{alkyl-}$, $R^aR^b\text{NC(O)-}$, $\text{C}_{1-4}\text{alkylC(O)-}$, $\text{C}_{1-4}\text{alkoxyC(O)-}$, $\text{C}_{1-4}\text{alkylC(O)O-}$, $\text{C}_{1-4}\text{alkylS(O)}_q\text{-}$, $\text{C}_{1-4}\text{alkylS(O)}_q\text{NR}^c\text{-}$, $\text{C}_{1-6}\text{alkylS(O)}_q\text{C}_{1-4}\text{alkyl-}$, $\text{C}_{1-4}\text{alkylC(O)C}_{1-6}\text{alkyl-}$, and $\text{C}_{1-6}\text{alkylC(O)OC}_{1-4}\text{alkyl-}$.

In certain embodiments, R^5 is



10

In certain embodiments, R^5 is



In certain embodiments, X is CH, R^3 is $\text{haloC}_{1-4}\text{alkyl-}$ and R^4 is $\text{haloC}_{1-4}\text{alkyl-}$.

15

In certain embodiments, X is CH, R^3 is CF_3 and R^4 is $-\text{CH}_2\text{CH}_2\text{CF}_2\text{CH}_3$.

In certain embodiments, X is CH, R^3 is CF_3 and R^4 is $-\text{CH}_2\text{CH}_2\text{CF}_3$.

20

In certain embodiments, X is CH, M is $-\text{CHF-}$, R^3 is $\text{haloC}_{1-4}\text{alkyl-}$, and R^4 is $\text{haloC}_{1-4}\text{alkyl-}$.

In certain embodiments, X is CH, M is $-\text{CHF-}$, R^3 is CF_3 , and R^4 is $-\text{CH}_2\text{CH}_2\text{CF}_2\text{CH}_3$.

In certain embodiments, X is CH, M is $-\text{CHF-}$, R^3 is CF_3 , and R^4 is $-\text{CH}_2\text{CH}_2\text{CF}_3$.

25

In certain embodiments, X is CH, M is -CHF-, R¹ is C(O)OH, R³ is haloC₁₋₄alkyl-, and R⁴ is haloC₁₋₄alkyl-.

In certain embodiments, X is CH, M is -CHF-, R¹ is C(O)OH, R³ is CF₃ and R⁴ is -
 5 CH₂CH₂CF₂CH₃.

In certain embodiments, X is CH, M is -CHF-, R¹ is C(O)OH, R³ is CF₃ and R⁴ is -
 CH₂CH₂CF₃.

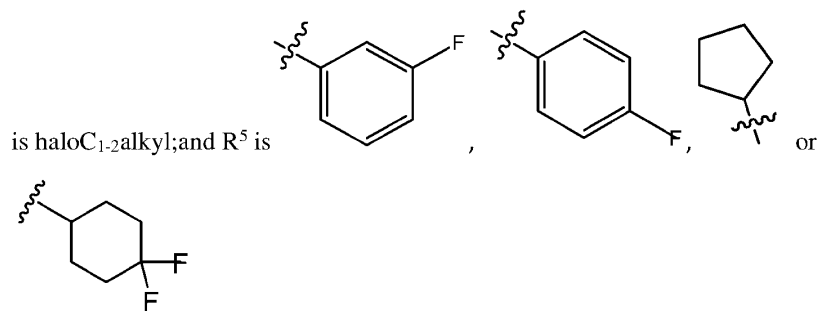
10 In certain embodiments, X is CH, M is -CHF-, R¹ is C(O)OH, R³ is haloC₁₋₄alkyl-, R⁴
 is haloC₁₋₄alkyl-, and R⁵ is phenyl optionally substituted with one to six substituents
 independently selected from the group consisting of halo, OH, CN, HOC(O)-, R^aR^bN-,
 R^aR^bNS(O)_q-, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, haloC₁₋₄alkyl, hydroxyC₁₋₄alkyl-, R^aR^bNC₁₋₄
 4alkyl-, C₁₋₄alkoxy, haloC₁₋₄alkoxy, hydroxyC₁₋₄alkoxy-, R^aR^bNC₁₋₄alkoxy-, C₁₋₃alkoxyC₁₋₄
 15 4alkyl-, haloC₁₋₃alkoxyC₁₋₄alkyl-, R^aR^bNC(O)-, C₁₋₄alkylC(O)-, C₁₋₄alkoxyC(O)-, C₁₋₄
 4alkylC(O)O-, C₁₋₄alkylS(O)_q-, C₁₋₄alkylS(O)_qNR^c-, C₁₋₆alkylS(O)_qC₁₋₄alkyl-, C₁₋₆
 4alkylC(O)C₁₋₆alkyl-, and C₁₋₆alkylC(O)OC₁₋₄alkyl-.

In certain embodiments, X is CH, M is -CHF-, R¹ is C(O)OH, R³ is CF₃, R⁴ is -
 20 CH₂CH₂CF₂CH₃, and R⁵ is phenyl optionally substituted with one to six substituents
 independently selected from the group consisting of halo, OH, CN, HOC(O)-, R^aR^bN-,
 R^aR^bNS(O)_q-, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, haloC₁₋₄alkyl, hydroxyC₁₋₄alkyl-, R^aR^bNC₁₋₄
 4alkyl-, C₁₋₄alkoxy, haloC₁₋₄alkoxy, hydroxyC₁₋₄alkoxy-, R^aR^bNC₁₋₄alkoxy-, C₁₋₃alkoxyC₁₋₄
 4alkyl-, haloC₁₋₃alkoxyC₁₋₄alkyl-, R^aR^bNC(O)-, C₁₋₄alkylC(O)-, C₁₋₄alkoxyC(O)-, C₁₋₄
 25 4alkylC(O)O-, C₁₋₄alkylS(O)_q-, C₁₋₄alkylS(O)_qNR^c-, C₁₋₆alkylS(O)_qC₁₋₄alkyl-, C₁₋₆
 4alkylC(O)C₁₋₆alkyl-, and C₁₋₆alkylC(O)OC₁₋₄alkyl-.

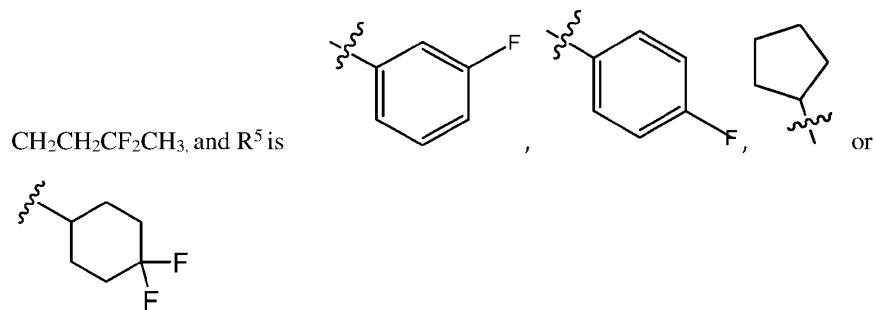
In certain embodiments, X is CH, M is -CHF-, R¹ is C(O)OH, R³ is CF₃, R⁴ is -
 CH₂CH₂CF₃, and R⁵ is phenyl optionally substituted with one to six substituents
 30 independently selected from the group consisting of halo, OH, CN, HOC(O)-, R^aR^bN-,

$R^a R^b NS(O)_{q^-}$, $C_{1-4}alkyl$, $C_{2-4}alkenyl$, $C_{2-4}alkynyl$, $haloC_{1-4}alkyl$, $hydroxyC_{1-4}alkyl$ -, $R^a R^b NC_{1-4}alkyl$ -, $C_{1-4}alkoxy$, $haloC_{1-4}alkoxy$, $hydroxyC_{1-4}alkoxy$ -, $R^a R^b NC_{1-4}alkoxy$ -, $C_{1-3}alkoxyC_{1-4}alkyl$ -, $haloC_{1-3}alkoxyC_{1-4}alkyl$ -, $R^a R^b NC(O)$ -, $C_{1-4}alkylC(O)$ -, $C_{1-4}alkoxyC(O)$ -, $C_{1-4}alkylC(O)O$ -, $C_{1-4}alkylS(O)_{q^-}$, $C_{1-4}alkylS(O)_{q^-}NR^c$ -, $C_{1-6}alkylS(O)_qC_{1-4}alkyl$ -, $C_{1-4}alkylC(O)C_{1-6}alkyl$ -, and $C_{1-6}alkylC(O)OC_{1-4}alkyl$ -.
 5

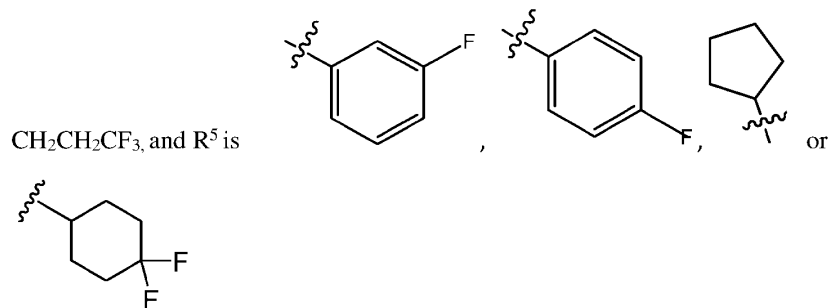
In certain embodiments, X is CH, M is -CHF-, R^1 is C(O)OH, R^3 is $haloC_{1-2}alkyl$, R^4



In certain embodiments, X is CH, M is -CHF-, R^1 is C(O)OH, R^3 is CF_3 , R^4 is -



In certain embodiments, X is CH, M is -CHF-, R¹ is C(O)OH, R³ is CF₃, R⁴ is -



5 In certain embodiments, the compound of Formula I is of Formula Ia, X is CH, R³ is haloC₁₋₄alkyl- and R⁴ is haloC₁₋₄alkyl-.

In certain embodiments, the compound of Formula I is of Formula Ia, X is CH, R³ is CF₃ and R⁴ is -CH₂CH₂CF₂CH₃.

10

In certain embodiments, the compound of Formula I is of Formula Ia, X is CH, R³ is CF₃ and R⁴ is -CH₂CH₂CF₃.

15 In certain embodiments, the compound of Formula I is of Formula Ia, X is CH, M is -CHF-, R³ is haloC₁₋₄alkyl-, and R⁴ is haloC₁₋₄alkyl-.

In certain embodiments, the compound of Formula I is of Formula Ia, X is CH, M is -CHF-, R³ is CF₃, and R⁴ is -CH₂CH₂CF₂CH₃.

20 In certain embodiments, the compound of Formula I is of Formula Ia, X is CH, M is -CHF-, R³ is CF₃, and R⁴ is -CH₂CH₂CF₃.

In certain embodiments, the compound of Formula I is of Formula Ia, X is CH, M is -CHF-, R¹ is C(O)OH, R³ is haloC₁₋₄alkyl-, and R⁴ is haloC₁₋₄alkyl-.

25

In certain embodiments, the compound of Formula I is of Formula Ia, X is CH, M is -CHF-, R¹ is C(O)OH, R³ is CF₃ and R⁴ is -CH₂CH₂CF₂CH₃.

In certain embodiments, the compound of Formula I is of Formula Ia, X is CH, M is -CHF-, R¹ is C(O)OH, R³ is CF₃ and R⁴ is -CH₂CH₂CF₃.

In certain embodiments, the compound of Formula I is of Formula Ia, X is CH, M is -CHF-, R¹ is C(O)OH, R³ is haloC₁₋₄alkyl-, R⁴ is haloC₁₋₄alkyl-, and R⁵ is phenyl optionally substituted with one to six substituents independently selected from the group consisting of halo, OH, CN, HOC(O)-, R^aR^bN-, R^aR^bNS(O)_q-, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, haloC₁₋₄alkyl, hydroxyC₁₋₄alkyl-, R^aR^bNC₁₋₄alkyl-, C₁₋₄alkoxy, haloC₁₋₄alkoxy, hydroxyC₁₋₄alkoxy-, R^aR^bNC₁₋₄alkoxy-, C₁₋₃alkoxyC₁₋₄alkyl-, haloC₁₋₃alkoxyC₁₋₄alkyl-, R^aR^bNC(O)-, C₁₋₄alkylC(O)-, C₁₋₄alkoxyC(O)-, C₁₋₄alkylC(O)O-, C₁₋₄alkylS(O)_q-, C₁₋₄alkylS(O)_qNR^c-, C₁₋₆alkylS(O)_qC₁₋₄alkyl-, C₁₋₄alkylC(O)C₁₋₆alkyl-, and C₁₋₆alkylC(O)OC₁₋₄alkyl-.

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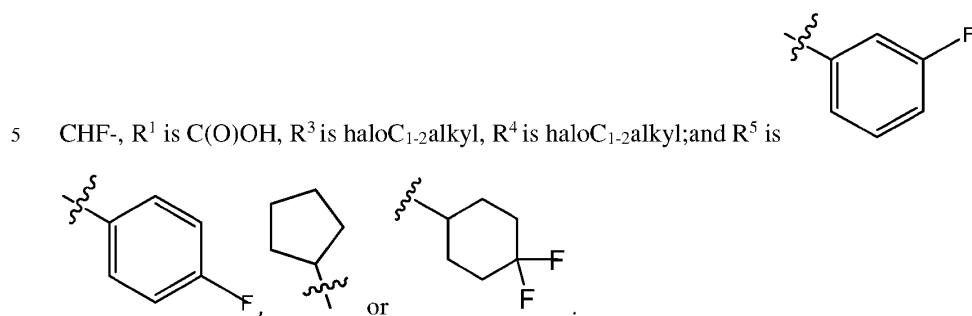
In certain embodiments, the compound of Formula I is of Formula Ia, X is CH, M is -CHF-, R¹ is C(O)OH, R³ is CF₃, R⁴ is -CH₂CH₂CF₂CH₃, and R⁵ is phenyl optionally substituted with one to six substituents independently selected from the group consisting of halo, OH, CN, HOC(O)-, R^aR^bN-, R^aR^bNS(O)_q-, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, haloC₁₋₄alkyl, hydroxyC₁₋₄alkyl-, R^aR^bNC₁₋₄alkyl-, C₁₋₄alkoxy, haloC₁₋₄alkoxy, hydroxyC₁₋₄alkoxy-, R^aR^bNC₁₋₄alkoxy-, C₁₋₃alkoxyC₁₋₄alkyl-, haloC₁₋₃alkoxyC₁₋₄alkyl-, R^aR^bNC(O)-, C₁₋₄alkylC(O)-, C₁₋₄alkoxyC(O)-, C₁₋₄alkylC(O)O-, C₁₋₄alkylS(O)_q-, C₁₋₄alkylS(O)_qNR^c-, C₁₋₆alkylS(O)_qC₁₋₄alkyl-, C₁₋₄alkylC(O)C₁₋₆alkyl-, and C₁₋₆alkylC(O)OC₁₋₄alkyl-.

In certain embodiments, the compound of Formula I is of Formula Ia, X is CH, M is -CHF-, R¹ is C(O)OH, R³ is CF₃, R⁴ is -CH₂CH₂CF₃, and R⁵ is phenyl optionally substituted with one to six substituents independently selected from the group consisting of halo, OH, CN, HOC(O)-, R^aR^bN-, R^aR^bNS(O)_q-, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, haloC₁₋₄alkyl, hydroxyC₁₋₄alkyl-, R^aR^bNC₁₋₄alkyl-, C₁₋₄alkoxy, haloC₁₋₄alkoxy, hydroxyC₁₋₄alkoxy-, R^aR^bNC₁₋₄alkoxy-, C₁₋₃alkoxyC₁₋₄alkyl-, haloC₁₋₃alkoxyC₁₋₄alkyl-, R^aR^bNC(O)-, C₁₋

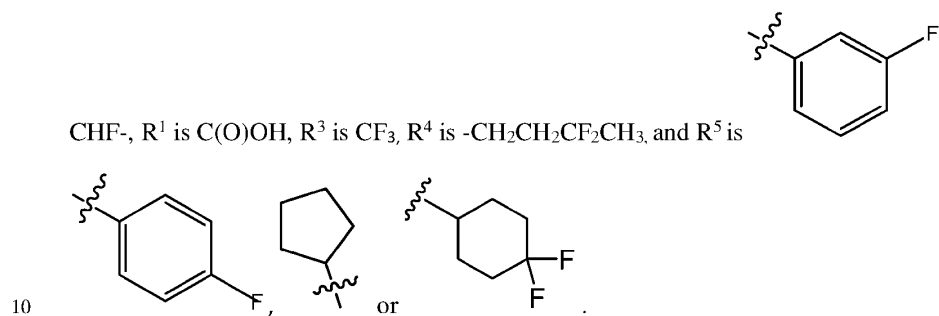
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4alkylC(O)-, C₁₋₄alkoxyC(O)-, C₁₋₄alkylC(O)O-, C₁₋₄alkylS(O)_q-, C₁₋₄alkylS(O)_qNR^c-, C₁₋₆alkylS(O)_qC₁₋₄alkyl-, C₁₋₄alkylC(O)C₁₋₆alkyl-, and C₁₋₆alkylC(O)OC₁₋₄alkyl-.

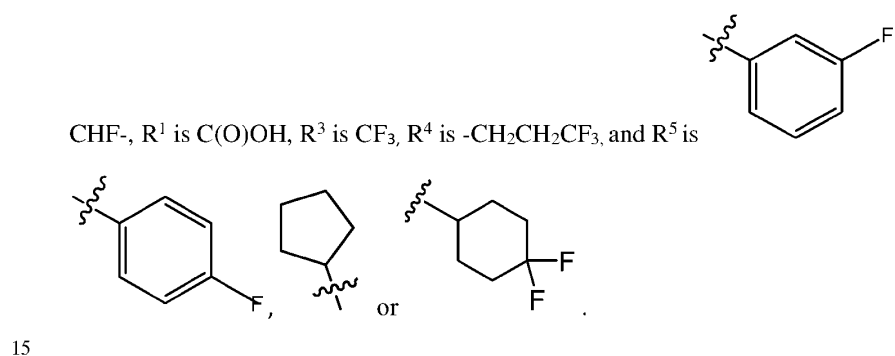
In certain embodiments, the compound of Formula I is of Formula Ia, X is CH, M is -



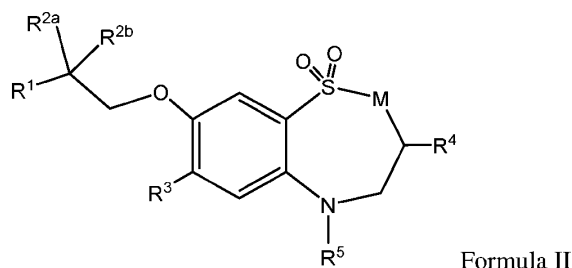
In certain embodiments, the compound of Formula I is of Formula Ia, X is CH, M is -



In certain embodiments, the compound of Formula I is of Formula Ia, X is CH, M is -



In some embodiments of the present invention, the compound of Formula I is of
Formula II

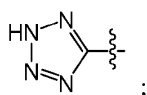


, or a pharmaceutically acceptable salt thereof, wherein:

5 M is -CHF-, -CH(CH₃)-, -CF(CH₃)-, -CF₂- or -C(CH₃)₂-;

R^a, R^b and R^c are independently selected for each occurrence from the group
consisting of hydrogen, C₁₋₆alkyl, haloC₁₋₆alkyl and C₃₋₆monocycloalkyl;

R¹ is OH, CH₃, -C(O)NH₂, -C(O)OH, -C(O)OC₁₋₆alkyl, -P(O)(OH)₂, -S(O)₂OH or



10 R^{2a} and R^{2b} are independently selected from the group consisting of hydrogen, halo,
OH methyl, ethyl and CH₂OH; or R^{2a} and R^{2b} together with the carbon atom to which they
are attached form a C=CH₂, C₃₋₆monocycloalkyl, oxetanyl, tetrahydrofuranyl,
tetrahydropyranyl or 1,3-dioxanyl group, wherein the C₃₋₆monocycloalkyl, oxetanyl,
tetrahydrofuranyl, tetrahydropyranyl or 1,3-dioxanyl group is optionally substituted with 1 to
15 3 independently selected halo or methyl groups;

R³ is selected from the group consisting of hydrogen, halogen, cyano, R^aR^bN-, C₁₋₄
alkyl, haloC₁₋₄alkyl, C₁₋₄alkoxy, haloC₁₋₄alkoxy, C₁₋₄alkylthio, haloC₁₋₄alkylthio, C₃₋₇
monocycloalkyl, C₃₋₇monocycloalkyloxy, C₃₋₇monocycloalkylthio, C₃₋₇monocycloalkyl-
CH₂-thio, and C₅₋₁₂bicycloalkylthio, wherein the C₃₋₇monocycloalkyl, C₃₋₇
monocycloalkyloxy, C₃₋₇monocycloalkylthio, C₃₋₇monocycloalkyl-CH₂-thio, and C₅₋₁₂
bicycloalkylthio group is optionally substituted with 1 to 3 halo groups;

R⁴ is haloC₃₋₄alkyl;

R⁵ is phenyl, C₃₋₇monocycloalkyl or C₅₋₁₂bicycloalkyl, wherein the phenyl, C₃₋₇
monocycloalkyl or C₅₋₁₂bicycloalkyl is optionally substituted with one to six substituents

independently selected from the group consisting of halo, OH, CN, HOC(O)-, R^aR^bN -,
 $R^aR^bNS(O)_{q-}$, $C_{1-4}alkyl$, $C_{2-4}alkenyl$, $C_{2-4}alkynyl$, $haloC_{1-4}alkyl$, $hydroxyC_{1-4}alkyl$ -, $R^aR^bNC_{1-4}alkyl$ -,
 $C_{1-4}alkoxy$, $haloC_{1-4}alkoxy$, $hydroxyC_{1-4}alkoxy$ -, $R^aR^bNC_{1-4}alkoxy$ -, $C_{1-3}alkoxyC_{1-4}alkyl$ -,
 $haloC_{1-3}alkoxyC_{1-4}alkyl$ -, $R^aR^bNC(O)$ -, $C_{1-4}alkylC(O)$ -, $C_{1-4}alkoxyC(O)$ -, $C_{1-4}alkylC(O)O$ -,
 $C_{1-4}alkylS(O)_{q-}$, $C_{1-4}alkylS(O)_{q-}NR^c$ -, $C_{1-6}alkylS(O)_qC_{1-4}alkyl$ -, $C_{1-4}alkylC(O)C_{1-6}alkyl$ -, and $C_{1-6}alkylC(O)OC_{1-4}alkyl$ -, and

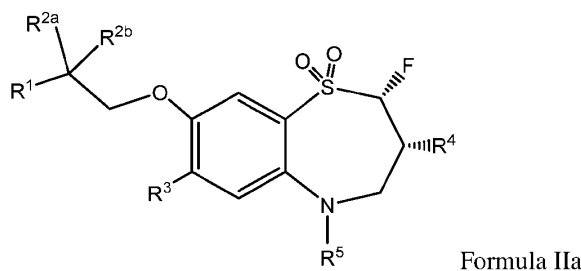
q is independently selected for each occurrence from the group consisting of 0, 1 and 2.

10

The following embodiments further describe a compound of Formula II, or a pharmaceutically acceptable salt thereof. It will be appreciated that all chemically allowable combinations of the embodiments described herein are envisioned as further embodiments of the invention.

15

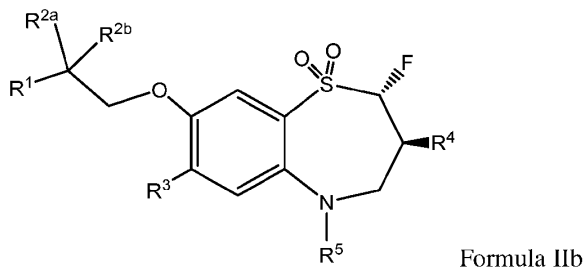
In certain embodiments, the compound of Formula II is of Formula IIa



, or a pharmaceutically acceptable salt thereof.

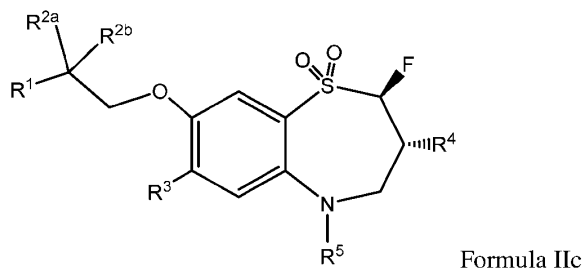
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In certain embodiments, the compound of Formula II is of Formula IIb



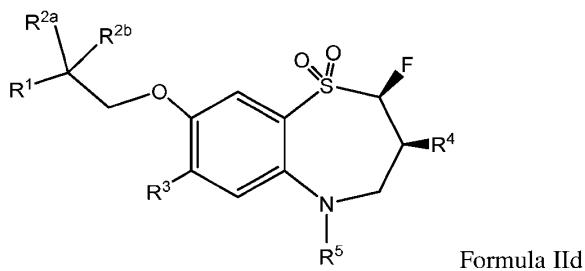
, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the compound of Formula II is of Formula IIc



5 , or a pharmaceutically acceptable salt thereof.

In certain embodiments, the compound of Formula II is of Formula IId



, or a pharmaceutically acceptable salt thereof.

10

In certain embodiments, M is -CHF-, -CH(CH₃)- or -CF(CH₃)-.

In certain embodiments, M is -CHF-.

15

In certain embodiments, M is -CH(CH₃)-.

In certain embodiments, M is -CF(CH₃)-.

In certain embodiments, M is -CF₂- or -C(CH₃)₂-.

20

In certain embodiments, M is -CF₂-.

In certain embodiments, M is $-\text{C}(\text{CH}_3)_2-$.

In certain embodiments, R^1 is $\text{C}(\text{O})\text{OH}$.

5

In certain embodiments, R^1 is $\text{S}(\text{O})_2\text{OH}$.

In certain embodiments, R^1 is $\text{P}(\text{O})(\text{OH})_2$.

10 In certain embodiments, R^{2a} and R^{2b} are independently selected from the group consisting of hydrogen, halo, OH and methyl.

In certain embodiments, R^{2a} and R^{2b} are methyl.

15 In certain embodiments, R^{2a} is hydrogen and R^{2b} are methyl.

In certain embodiments, R^{2a} and R^{2b} together with the carbon atom to which they are attached form a $\text{C}=\text{CH}_2$, cyclopropyl, cyclobutyl, or oxetanyl group, wherein the cyclopropyl or cyclobutyl group is optionally substituted with 1-3 halo groups.

20

In certain embodiments, R^{2a} and R^{2b} together with the carbon atom to which they are attached form a $\text{C}=\text{CH}_2$, cyclopropyl, cyclobutyl, or oxetanyl group.

25 In certain embodiments, R^{2a} and R^{2b} together with the carbon atom to which they are attached form a cyclopropyl group.

In certain embodiments, R^3 is $\text{C}_{5-12}\text{bicycloalkylthio-}$.

In certain embodiments, R^3 is $\text{haloC}_{3-7}\text{monocycloalkylthio-}$.

30

In certain embodiments, R^3 is haloC₁₋₂alkyl-.

In certain embodiments, R^3 is CF₃.

5 In certain embodiments, R^4 is n-butyl substituted with 1 to 6 halo atoms.

In certain embodiments, R^4 is n-butyl substituted with 1 to 6 F atoms.

In certain embodiments, R^4 is -CH₂CH₂CF₂CH₃.

10

In certain embodiments, R^4 is n-propyl substituted with 1 to 6 halo atoms.

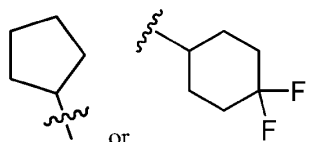
In certain embodiments, R^4 is n-propyl substituted with 1 to 6 F atoms.

15 In certain embodiments, R^4 is -CH₂CH₂CF₃.

In certain embodiments, R^5 is C₃₋₇monocycloalkyl optionally substituted with one to six substituents independently selected from the group consisting of halo, OH, CN, HOC(O)-, R^aR^bN -, $R^aR^bNS(O)_q$ -, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, haloC₁₋₄alkyl, hydroxyC₁₋₄alkyl-,
 20 $R^aR^bNC_{1-4}$ alkyl-, C₁₋₄alkoxy, haloC₁₋₄alkoxy, hydroxyC₁₋₄alkoxy-, $R^aR^bNC_{1-4}alkoxy-, C₁₋₃alkoxyC₁₋₄alkyl-, haloC₁₋₃alkoxyC₁₋₄alkyl-, $R^aR^bNC(O)$ -, C₁₋₄alkylC(O)-, C₁₋₄alkoxyC(O)-, C₁₋₄alkylC(O)O-, C₁₋₄alkylS(O)_q-, C₁₋₄alkylS(O)_qNR^c-, C₁₋₆alkylS(O)_qC₁₋₄alkyl-, C₁₋₄alkylC(O)C₁₋₆alkyl-, and C₁₋₆alkylC(O)OC₁₋₄alkyl-.$

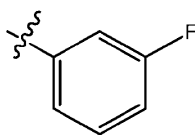
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In certain embodiments, R^5 is

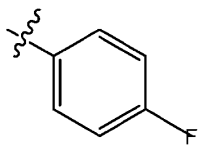


In certain embodiments, R^5 is phenyl optionally substituted with one to six substituents independently selected from the group consisting of halo, OH, CN, HOC(O)-,

R^aR^bN- , $R^aR^bNS(O)_q-$, $C_{1-4}alkyl$, $C_{2-4}alkenyl$, $C_{2-4}alkynyl$, $haloC_{1-4}alkyl$, $hydroxyC_{1-4}alkyl-$,
 $R^aR^bNC_{1-4}alkyl-$, $C_{1-4}alkoxy$, $haloC_{1-4}alkoxy$, $hydroxyC_{1-4}alkoxy-$, $R^aR^bNC_{1-4}alkoxy-$, C_{1-}
 $3alkoxyC_{1-4}alkyl-$, $haloC_{1-3}alkoxyC_{1-4}alkyl-$, $R^aR^bNC(O)-$, $C_{1-4}alkylC(O)-$, $C_{1-4}alkoxyC(O)-$,
 $C_{1-4}alkylC(O)O-$, $C_{1-4}alkylS(O)_q-$, $C_{1-4}alkylS(O)_qNR^c-$, $C_{1-6}alkylS(O)_qC_{1-4}alkyl-$, C_{1-}
 5 $4alkylC(O)C_{1-6}alkyl-$, and $C_{1-6}alkylC(O)OC_{1-4}alkyl-$.



In certain embodiments, R^5 is



In certain embodiments, R^5 is

10

In certain embodiments, R^3 is $haloC_{1-4}alkyl-$ and R^4 is $-CH_2CH_2CF_2CH_3$.

In certain embodiments, R^3 is $haloC_{1-4}alkyl-$ and R^4 is $-CH_2CH_2CF_3$.

15

In certain embodiments, R^3 is CF_3 and R^4 is $-CH_2CH_2CF_2CH_3$.

In certain embodiments, R^3 is CF_3 and R^4 is $-CH_2CH_2CF_3$.

In certain embodiments, M is $-CHF-$ and R^3 is $haloC_{1-4}alkyl-$.

20

In certain embodiments, M is $-CHF-$ and R^3 is CF_3 .

In certain embodiments, M is $-CHF-$, R^3 is $haloC_{1-4}alkyl-$, and R^4 is $-$
 $CH_2CH_2CF_2CH_3$.

25

In certain embodiments, M is -CHF-, R³ is haloC₁₋₄alkyl-, and R⁴ is -CH₂CH₂CF₃.

In certain embodiments, M is -CHF-, R³ is CF₃, and R⁴ is -CH₂CH₂CF₂CH₃.

5 In certain embodiments, M is -CHF-, R³ is CF₃, and R⁴ is -CH₂CH₂CF₃.

In certain embodiments, M is -CHF-, R¹ is C(O)OH, and R³ is haloC₁₋₄alkyl.

In certain embodiments, M is -CHF-, R¹ is C(O)OH, R³ is haloC₁₋₄alkyl and R⁴ is -
10 CH₂CH₂CF₂CH₃.

In certain embodiments, M is -CHF-, R¹ is C(O)OH, R³ is haloC₁₋₄alkyl and R⁴ is -
CH₂CH₂CF₃.

15 In certain embodiments, M is -CHF-, R¹ is C(O)OH, R³ is CF₃, and R⁴ is -
CH₂CH₂CF₂CH₃.

In certain embodiments, M is -CHF-, R¹ is C(O)OH, R³ is CF₃, and R⁴ is -
CH₂CH₂CF₃.

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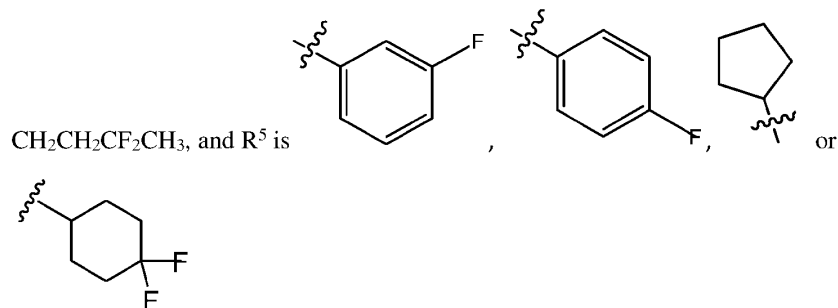
In certain embodiments, M is -CHF-, R¹ is C(O)OH, R³ is haloC₁₋₄alkyl-, R⁴ is -
CH₂CH₂CF₂CH₃, and R⁵ is phenyl optionally substituted with one to six substituents
independently selected from the group consisting of halo, OH, CN, HOC(O)-, R^aR^bN-,
R^aR^bNS(O)_q-, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, haloC₁₋₄alkyl, hydroxyC₁₋₄alkyl-, R^aR^bNC₁₋₄
25 4alkyl-, C₁₋₄alkoxy, haloC₁₋₄alkoxy, hydroxyC₁₋₄alkoxy-, R^aR^bNC₁₋₄alkoxy-, C₁₋₃alkoxyC₁₋₄
4alkyl-, haloC₁₋₃alkoxyC₁₋₄alkyl-, R^aR^bNC(O)-, C₁₋₄alkylC(O)-, C₁₋₄alkoxyC(O)-, C₁₋₄
4alkylC(O)O-, C₁₋₄alkylS(O)_q-, C₁₋₄alkylS(O)_qNR^c-, C₁₋₆alkylS(O)_qC₁₋₄alkyl-, C₁₋₄
4alkylC(O)C₁₋₆alkyl-, and C₁₋₆alkylC(O)OC₁₋₄alkyl-.

In certain embodiments, M is -CHF-, R¹ is C(O)OH, R³ is haloC₁₋₄alkyl-, R⁴ is -CH₂CH₂CF₃, and R⁵ is phenyl optionally substituted with one to six substituents independently selected from the group consisting of halo, OH, CN, HOC(O)-, R^aR^bN-, R^aR^bNS(O)_q-, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, haloC₁₋₄alkyl, hydroxyC₁₋₄alkyl-, R^aR^bNC₁₋₄alkyl-, C₁₋₄alkoxy, haloC₁₋₄alkoxy, hydroxyC₁₋₄alkoxy-, R^aR^bNC₁₋₄alkoxy-, C₁₋₃alkoxyC₁₋₄alkyl-, haloC₁₋₃alkoxyC₁₋₄alkyl-, R^aR^bNC(O)-, C₁₋₄alkylC(O)-, C₁₋₄alkoxyC(O)-, C₁₋₄alkylC(O)O-, C₁₋₄alkylS(O)_q-, C₁₋₄alkylS(O)_qNR^c-, C₁₋₆alkylS(O)_qC₁₋₄alkyl-, C₁₋₄alkylC(O)C₁₋₆alkyl-, and C₁₋₆alkylC(O)OC₁₋₄alkyl-.

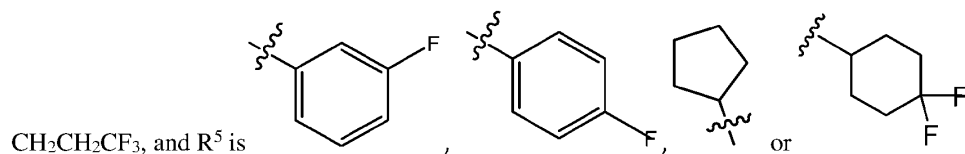
In certain embodiments, M is -CHF-, R¹ is C(O)OH, R³ is CF₃, R⁴ is -CH₂CH₂CF₂CH₃, and R⁵ is phenyl optionally substituted with one to six substituents independently selected from the group consisting of halo, OH, CN, HOC(O)-, R^aR^bN-, R^aR^bNS(O)_q-, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, haloC₁₋₄alkyl, hydroxyC₁₋₄alkyl-, R^aR^bNC₁₋₄alkyl-, C₁₋₄alkoxy, haloC₁₋₄alkoxy, hydroxyC₁₋₄alkoxy-, R^aR^bNC₁₋₄alkoxy-, C₁₋₃alkoxyC₁₋₄alkyl-, haloC₁₋₃alkoxyC₁₋₄alkyl-, R^aR^bNC(O)-, C₁₋₄alkylC(O)-, C₁₋₄alkoxyC(O)-, C₁₋₄alkylC(O)O-, C₁₋₄alkylS(O)_q-, C₁₋₄alkylS(O)_qNR^c-, C₁₋₆alkylS(O)_qC₁₋₄alkyl-, C₁₋₄alkylC(O)C₁₋₆alkyl-, and C₁₋₆alkylC(O)OC₁₋₄alkyl-.

In certain embodiments, M is -CHF-, R¹ is C(O)OH, R³ is CF₃, R⁴ is -CH₂CH₂CF₃, and R⁵ is phenyl optionally substituted with one to six substituents independently selected from the group consisting of halo, OH, CN, HOC(O)-, R^aR^bN-, R^aR^bNS(O)_q-, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, haloC₁₋₄alkyl, hydroxyC₁₋₄alkyl-, R^aR^bNC₁₋₄alkyl-, C₁₋₄alkoxy, haloC₁₋₄alkoxy, hydroxyC₁₋₄alkoxy-, R^aR^bNC₁₋₄alkoxy-, C₁₋₃alkoxyC₁₋₄alkyl-, haloC₁₋₃alkoxyC₁₋₄alkyl-, R^aR^bNC(O)-, C₁₋₄alkylC(O)-, C₁₋₄alkoxyC(O)-, C₁₋₄alkylC(O)O-, C₁₋₄alkylS(O)_q-, C₁₋₄alkylS(O)_qNR^c-, C₁₋₆alkylS(O)_qC₁₋₄alkyl-, C₁₋₄alkylC(O)C₁₋₆alkyl-, and C₁₋₆alkylC(O)OC₁₋₄alkyl-.

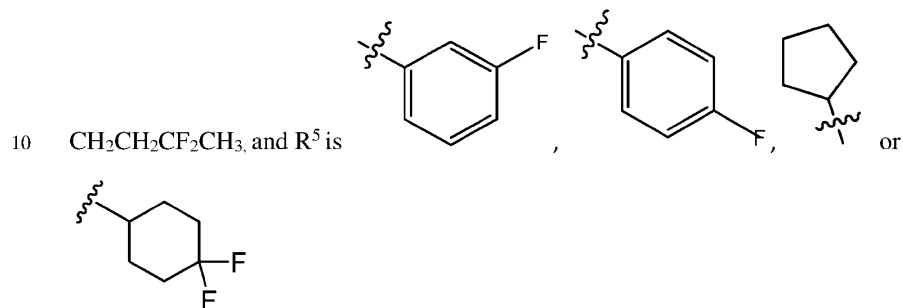
In certain embodiments, M is -CHF-, R¹ is C(O)OH, R³ is haloC₁₋₂alkyl, R⁴ is -



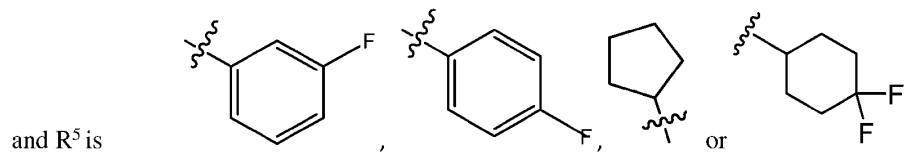
5 In certain embodiments, M is -CHF-, R¹ is C(O)OH, R³ is haloC₁₋₂alkyl, R⁴ is -



In certain embodiments, M is -CHF-, R¹ is C(O)OH, R³ is CF₃, R⁴ is -



In certain embodiments, M is -CHF-, R¹ is C(O)OH, R³ is CF₃, R⁴ is -CH₂CH₂CF₃,



15

In certain embodiments, the compound of Formula II is of Formula IIa, R³ is haloC₁₋₄alkyl- and R⁴ is -CH₂CH₂CF₂CH₃.

In certain embodiments, the compound of Formula II is of Formula IIa, R³ is haloC₁₋₄alkyl- and R⁴ is -CH₂CH₂CF₃.

In certain embodiments, the compound of Formula II is of Formula IIa, R³ is CF₃ and R⁴ is -CH₂CH₂CF₂CH₃.

In certain embodiments, the compound of Formula II is of Formula IIa, R³ is CF₃ and R⁴ is -CH₂CH₂CF₃.

In certain embodiments, the compound of Formula II is of Formula IIa, M is -CHF-, R³ is haloC₁₋₄alkyl-, and R⁴ is -CH₂CH₂CF₂CH₃.

In certain embodiments, the compound of Formula II is of Formula IIa, M is -CHF-, R³ is haloC₁₋₄alkyl-, and R⁴ is -CH₂CH₂CF₃.

In certain embodiments, the compound of Formula II is of Formula IIa, M is -CHF-, R³ is CF₃, and R⁴ is -CH₂CH₂CF₂CH₃.

In certain embodiments, the compound of Formula II is of Formula IIa, M is -CHF-, R³ is CF₃, and R⁴ is -CH₂CH₂CF₃.

In certain embodiments, the compound of Formula II is of Formula IIa, M is -CHF-, R¹ is C(O)OH, R³ is haloC₁₋₄alkyl-, and R⁴ is -CH₂CH₂CF₂CH₃.

In certain embodiments, the compound of Formula II is of Formula IIa, M is -CHF-, R¹ is C(O)OH, R³ is haloC₁₋₄alkyl-, and R⁴ is -CH₂CH₂CF₃.

In certain embodiments, the compound of Formula II is of Formula IIa, M is -CHF-, R¹ is C(O)OH, R³ is CF₃ and R⁴ is -CH₂CH₂CF₂CH₃.

5 In certain embodiments, the compound of Formula II is of Formula IIa, M is -CHF-, R¹ is C(O)OH, R³ is CF₃ and R⁴ is -CH₂CH₂CF₃.

In certain embodiments, the compound of Formula II is of Formula IIa, M is -CHF-, R¹ is C(O)OH, R³ is haloC₁₋₄alkyl-, R⁴ is -CH₂CH₂CF₂CH₃, and R⁵ is phenyl optionally substituted with one to six substituents independently selected from the group consisting of
 10 halo, OH, CN, HOC(O)-, R^aR^bN-, R^aR^bNS(O)_q-, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, haloC₁₋₄alkyl, hydroxyC₁₋₄alkyl-, R^aR^bNC₁₋₄alkyl-, C₁₋₄alkoxy, haloC₁₋₄alkoxy, hydroxyC₁₋₄alkoxy-, R^aR^bNC₁₋₄alkoxy-, C₁₋₃alkoxyC₁₋₄alkyl-, haloC₁₋₃alkoxyC₁₋₄alkyl-, R^aR^bNC(O)-, C₁₋₄alkylC(O)-, C₁₋₄alkoxyC(O)-, C₁₋₄alkylC(O)O-, C₁₋₄alkylS(O)_q-, C₁₋₄alkylS(O)_qNR^c-, C₁₋₆alkylS(O)_qC₁₋₄alkyl-, C₁₋₄alkylC(O)C₁₋₆alkyl-, and C₁₋₆alkylC(O)OC₁₋₄alkyl-.

In certain embodiments, the compound of Formula II is of Formula IIa, M is -CHF-, R¹ is C(O)OH, R³ is haloC₁₋₄alkyl-, R⁴ is -CH₂CH₂CF₃, and R⁵ is phenyl optionally substituted with one to six substituents independently selected from the group consisting of halo, OH,
 20 CN, HOC(O)-, R^aR^bN-, R^aR^bNS(O)_q-, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, haloC₁₋₄alkyl, hydroxyC₁₋₄alkyl-, R^aR^bNC₁₋₄alkyl-, C₁₋₄alkoxy, haloC₁₋₄alkoxy, hydroxyC₁₋₄alkoxy-, R^aR^bNC₁₋₄alkoxy-, C₁₋₃alkoxyC₁₋₄alkyl-, haloC₁₋₃alkoxyC₁₋₄alkyl-, R^aR^bNC(O)-, C₁₋₄alkylC(O)-, C₁₋₄alkoxyC(O)-, C₁₋₄alkylC(O)O-, C₁₋₄alkylS(O)_q-, C₁₋₄alkylS(O)_qNR^c-, C₁₋₆alkylS(O)_qC₁₋₄alkyl-, C₁₋₄alkylC(O)C₁₋₆alkyl-, and C₁₋₆alkylC(O)OC₁₋₄alkyl-.

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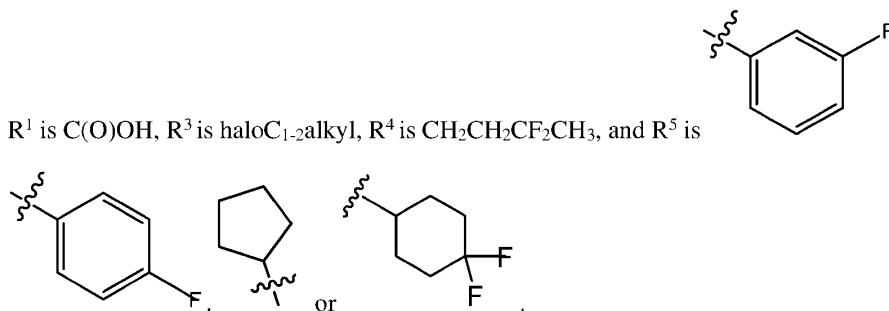
In certain embodiments, the compound of Formula II is of Formula IIa, M is -CHF-, R¹ is C(O)OH, R³ is CF₃, R⁴ is -CH₂CH₂CF₂CH₃, and R⁵ is phenyl optionally substituted with one to six substituents independently selected from the group consisting of halo, OH, CN, HOC(O)-, R^aR^bN-, R^aR^bNS(O)_q-, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, haloC₁₋₄alkyl,
 30 hydroxyC₁₋₄alkyl-, R^aR^bNC₁₋₄alkyl-, C₁₋₄alkoxy, haloC₁₋₄alkoxy, hydroxyC₁₋₄alkoxy-,

$R^a R^b NC_{1-4}alkoxy-$, $C_{1-3}alkoxyC_{1-4}alkyl-$, $haloC_{1-3}alkoxyC_{1-4}alkyl-$, $R^a R^b NC(O)-$, $C_{1-4}alkylC(O)-$, $C_{1-4}alkoxyC(O)-$, $C_{1-4}alkylC(O)O-$, $C_{1-4}alkylS(O)_q-$, $C_{1-4}alkylS(O)_qNR^c-$, $C_{1-6}alkylS(O)_qC_{1-4}alkyl-$, $C_{1-4}alkylC(O)C_{1-6}alkyl-$, and $C_{1-6}alkylC(O)OC_{1-4}alkyl-$.

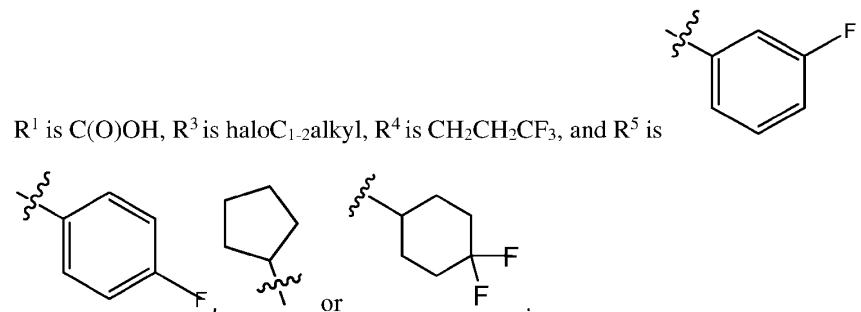
- 5 In certain embodiments, the compound of Formula II is of Formula IIa, M is $-CHF-$, R^1 is $C(O)OH$, R^3 is CF_3 , R^4 is $-CH_2CH_2CF_3$, and R^5 is phenyl optionally substituted with one to six substituents independently selected from the group consisting of halo, OH, CN, $HOC(O)-$, $R^a R^b N-$, $R^a R^b NS(O)_q-$, $C_{1-4}alkyl$, $C_{2-4}alkenyl$, $C_{2-4}alkynyl$, $haloC_{1-4}alkyl$, $hydroxyC_{1-4}alkyl-$, $R^a R^b NC_{1-4}alkyl-$, $C_{1-4}alkoxy$, $haloC_{1-4}alkoxy$, $hydroxyC_{1-4}alkoxy-$,
- 10 $R^a R^b NC_{1-4}alkoxy-$, $C_{1-3}alkoxyC_{1-4}alkyl-$, $haloC_{1-3}alkoxyC_{1-4}alkyl-$, $R^a R^b NC(O)-$, $C_{1-4}alkylC(O)-$, $C_{1-4}alkoxyC(O)-$, $C_{1-4}alkylC(O)O-$, $C_{1-4}alkylS(O)_q-$, $C_{1-4}alkylS(O)_qNR^c-$, $C_{1-6}alkylS(O)_qC_{1-4}alkyl-$, $C_{1-4}alkylC(O)C_{1-6}alkyl-$, and $C_{1-6}alkylC(O)OC_{1-4}alkyl-$.

In certain embodiments, the compound of Formula II is of Formula IIa, M is $-CHF-$,

- 15 R^1 is $C(O)OH$, R^3 is $haloC_{1-2}alkyl$, R^4 is $CH_2CH_2CF_2CH_3$, and R^5 is

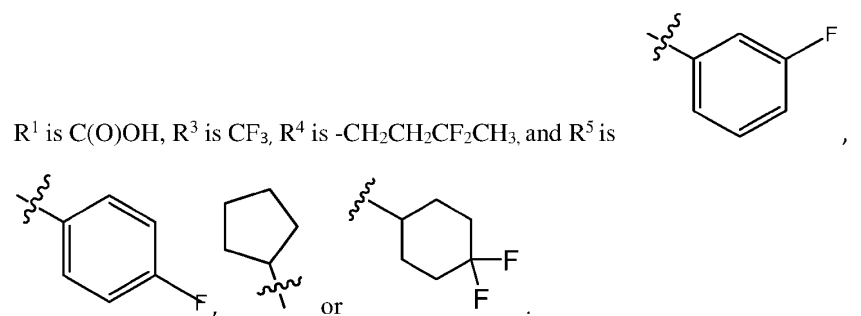


In certain embodiments, the compound of Formula II is of Formula IIa, M is -CHF-,



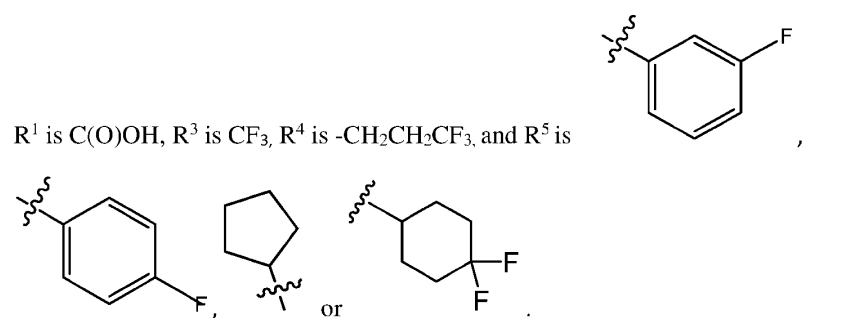
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In certain embodiments, the compound of Formula II is of Formula IIa, M is -CHF-,



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In certain embodiments, the compound of Formula II is of Formula IIa, M is -CHF-,



15 III. Pharmaceutical Compositions and Kits

In another aspect, the disclosure provides pharmaceutical compositions comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In particular, the present disclosure provides pharmaceutical compositions comprising compounds as disclosed herein formulated together with one or more pharmaceutically acceptable carriers. These formulations include those suitable for oral, rectal, topical, buccal, parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous), rectal, vaginal, or aerosol administration, although the most suitable form of administration in any given case will depend on the degree and severity of the condition being treated and on the nature of the particular compound being used. For example, disclosed compositions may be formulated as a unit dose, and/or may be formulated for oral or subcutaneous administration.

In another aspect, the disclosure provides a pharmaceutical composition comprises a compound according to any combination of the Examples described herein, or a pharmaceutically acceptable salt and/or stereoisomer thereof.

Exemplary pharmaceutical compositions of this disclosure may be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains one or more compounds of the disclosure, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external, enteral or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The active object compound is included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of the disease.

For preparing solid compositions such as tablets, the principal active ingredient may be mixed with a pharmaceutical carrier, e.g., conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g., water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the disclosure, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly

throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the subject composition is mixed with one or more
5 pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca
10 starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, acetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof;
15 and (10) coloring agents. In the case of capsules, tablets and pills, the compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more
20 accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the subject composition moistened with an inert liquid diluent.
25 Tablets, and other solid dosage forms, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders.
30 Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions,

microemulsions, solutions, suspensions, syrups and elixirs. In addition to the subject composition, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, cyclodextrins and mixtures thereof.

Suspensions, in addition to the subject composition, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Formulations for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing a subject composition with one or more suitable non-irritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the body cavity and release the active agent.

Dosage forms for transdermal administration of a subject composition include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active component may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

The ointments, pastes, creams and gels may contain, in addition to a subject composition, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays may contain, in addition to a subject composition, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays may additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Compositions and compounds of the present disclosure may alternatively be administered by aerosol. This is accomplished by preparing an aqueous aerosol, liposomal preparation or solid particles containing the compound. A non-aqueous (e.g., fluorocarbon propellant) suspension could be used. Sonic nebulizers may be used because they minimize exposing the agent to shear, which may result in degradation of the compounds contained in the subject compositions. Ordinarily, an aqueous aerosol is made by formulating an aqueous solution or suspension of a subject composition together with conventional pharmaceutically acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular subject composition, but typically include non-ionic surfactants (Tweens, Pluronic, or polyethylene glycol), innocuous proteins like serum albumin, sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars or sugar alcohols. Aerosols generally are prepared from isotonic solutions.

Pharmaceutical compositions of this disclosure suitable for parenteral administration comprise a subject composition in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and non-aqueous carriers which may be employed in the pharmaceutical compositions of the disclosure include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate and cyclodextrins. Proper fluidity may be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

In another aspect, the disclosure provides enteral pharmaceutical formulations including a disclosed compound and an enteric material; and a pharmaceutically acceptable carrier or excipient thereof. Enteric materials refer to polymers that are substantially insoluble in the acidic environment of the stomach, and that are predominantly soluble in intestinal

fluids at specific pHs. The small intestine is the part of the gastrointestinal tract (gut) between the stomach and the large intestine, and includes the duodenum, jejunum, and ileum. The pH of the duodenum is about 5.5, the pH of the jejunum is about 6.5 and the pH of the distal ileum is about 7.5. Accordingly, enteric materials are not soluble, for example, until a pH of about 5.0, of about 5.2, of about 5.4, of about 5.6, of about 5.8, of about 6.0, of about 6.2, of about 6.4, of about 6.6, of about 6.8, of about 7.0, of about 7.2, of about 7.4, of about 7.6, of about 7.8, of about 8.0, of about 8.2, of about 8.4, of about 8.6, of about 8.8, of about 9.0, of about 9.2, of about 9.4, of about 9.6, of about 9.8, or of about 10.0. Exemplary enteric materials include cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), hydroxypropyl methylcellulose acetate succinate (HPMCAS), cellulose acetate trimellitate, hydroxypropyl methylcellulose succinate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, cellulose propionate phthalate, cellulose acetate maleate, cellulose acetate butyrate, cellulose acetate propionate, copolymer of methylmethacrylic acid and methyl methacrylate, copolymer of methyl acrylate, methylmethacrylate and methacrylic acid, copolymer of methylvinyl ether and maleic anhydride (Gantrez ES series), ethyl methacrylate-methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer, natural resins such as zein, shellac and copal colophonium, and several commercially available enteric dispersion systems (e. g., Eudragit L30D55, Eudragit FS30D, Eudragit L100, Eudragit S100, Kollicoat EMM30D, Estacryl 30D, Coateric, and Aquateric). The solubility of each of the above materials is either known or is readily determinable *in vitro*. The foregoing is a list of possible materials, but one of skill in the art with the benefit of the disclosure would recognize that it is not comprehensive and that there are other enteric materials that would meet the objectives of the present disclosure.

Advantageously, the disclosure also provides kits for use by e.g., a consumer in need of HBV infection treatment. Such kits include a suitable dosage form such as those described above and instructions describing the method of using such dosage form to mediate, reduce or prevent HBV infection. The instructions would direct the consumer or medical personnel to administer the dosage form according to administration modes known to those skilled in the art. Such kits could advantageously be packaged and sold in single or multiple kit units. An

example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process recesses are formed in the plastic foil. The recesses have the size and shape of the tablets or capsules to be packed. Next, the tablets or capsules are placed in the recesses and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic foil and the sheet.

Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

It may be desirable to provide a memory aid on the kit, *e.g.*, in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the tablets or capsules so specified should be ingested. Another example of such a memory aid is a calendar printed on the card, *e.g.*, as follows “First Week, Monday, Tuesday, . . . etc. . . . Second Week, Monday, Tuesday, . . .” etc. Other variations of memory aids will be readily apparent. A “daily dose” can be a single tablet or capsule or several pills or capsules to be taken on a given day. Also, a daily dose of a first compound can consist of one tablet or capsule while a daily dose of the second compound can consist of several tablets or capsules and vice versa. The memory aid should reflect this.

IV. Methods

In a further aspect, a method for treating a hepatitis B infection in a patient in need thereof is provided, comprising administering to a subject or patient an effective amount of a disclosed compound, and/or administering a first disclosed compound and optionally, an additional, different disclosed compound(s). In another embodiment, a method for treating a hepatitis B infection in a patient in need thereof is provided, comprising administering to a subject or patient a therapeutically effective amount of a disclosed pharmaceutical

composition or a pharmaceutical composition comprising a disclosed compound, or two or more disclosed compounds, and a pharmaceutically acceptable excipient.

With regard to HBV/HDV coinfection, HDV encodes HDAg, the HDV protein responsible for HDV RNA replication. HDV infection is facilitated by the interaction of
5 HDAg with HBV viral envelope protein HBsAg, for both entry into the hepatocytes and assembly and release of the HDV virions. See for example, Negro, Cold Spring Harb Perspect Med. 2014 Nov 3;4(11):a021550. doi: 10.1101/cshperspect.a021550, herein incorporated by reference with regard to such background teaching. Thus, because HDV infection is dependent on the presence of an existing HBV infection, strategies for treating
10 HBV/HDV coinfection may focus on targeting HBV alone, HDV alone or both viruses together.

Thus, the present disclosure also contemplates a method of treating an HBV or HDV infection, or HBV/HDV coinfection, in a patient in need thereof, comprising administering to a subject or patient an effective amount of a disclosed compound, and/or administering a first
15 disclosed compound and optionally, an additional, different disclosed compound(s). In another embodiment, a method for treating an HBV or HDV infection or HBV/HDV coinfection in a patient in need thereof is provided, comprising administering to a subject or patient a therapeutically effective amount of a disclosed pharmaceutical composition or a pharmaceutical composition comprising a disclosed compound, or two or more disclosed
20 compounds, and a pharmaceutically acceptable excipient.

Without being bound by any theory, methods of treatment may be facilitated by various mechanisms of action. One possibility for treatment involves targeting machinery involved in viral particle assembly. In the case of HBV, inhibiting assembly of the HBV envelope or core by targeting HBsAg would disrupt assembly of the HBV particles. A second
25 strategy would be to inhibit viral replication of HBV and/or HDV. Existing antiviral therapies may apply this approach in the form of replication inhibitors that target, for example, a specific viral RNA polymerase.

Thus, another aspect of the disclosure is a method for inhibiting HBV or HDV viral replication in a patient in need thereof, comprising administering to a subject or patient an
30 effective amount of a disclosed compound, and/or administering a first disclosed compound

and optionally, an additional, different disclosed compound(s). In another embodiment, a method for inhibiting HBV or HDV viral replication in a patient in need thereof is provided, comprising administering to a subject or patient a therapeutically effective amount of a disclosed pharmaceutical composition or a pharmaceutical composition comprising a disclosed compound, or two or more disclosed compounds, and a pharmaceutically acceptable excipient.

Methods of treatment may further include targeting the network of bile acid transport proteins that are believed to be the “gateway” of entry for HBV or HDV infection into the hepatocyte. See for example, Slijepcevic *et al.*, Digestive Diseases, 2017;35:251-258, herein incorporated by reference with regard to such background teaching. The bile acid transport system comprising the sodium taurocholate co-transporting polypeptide (NTCP) and apical sodium dependent bile acid transporter (ASBT) are a set of receptors that ensure effective bile acid transport between the ileum and hepatocyte. HBV/HDV coinfection of hepatocytes is believed to be mediated via the NTCP receptor, making it a possible target for treatment. Without being bound by any theory, an “entry inhibitor” may target any of the possible bile acid transport receptors, including, but not limited to the sodium taurocholate co-transporting polypeptide (NTCP) and apical sodium dependent bile acid transporter (ASBT) to prevent entry of either HBV or HDV virus into the cells. Such entry inhibitors may target all or a portion of the transport receptors to inhibit viral entry.

Thus, another aspect of the disclosure is a method of inhibiting viral entry in hepatocytes in a patient in need thereof, comprising administering to a subject or patient an effective amount of a disclosed compound, and/or administering a first disclosed compound and optionally, an additional, different disclosed compound(s). In another embodiment, a method inhibiting viral entry in hepatocytes in a patient in need thereof is provided, comprising administering to a subject or patient a therapeutically effective amount of a disclosed pharmaceutical composition or a pharmaceutical composition comprising a disclosed compound, or two or more disclosed compounds, and a pharmaceutically acceptable excipient.

Regardless of the mechanism targeted, treatment for patients dealing with HBV or HDV infection or HBV/HDV coinfection may be measured by seroconversion of any of the

viral antigens, including but not limited to HBsAg or HBeAg, or maintenance of undetectable levels of these antigens.

For use in accordance with the aspects described herein, the appropriate dosage of the compounds described herein is expected to vary depending on, for example, the particular
5 compound employed, the mode of administration, and the nature and severity of the infection to be treated as well as the specific infection to be treated and is within the purview of the treating physician. Usually, an indicated administration dose may be in the range between about 0.1 to about 1000 µg/kg body weight. In some cases, the administration dose of the compound may be less than 400 µg/kg body weight. In other cases, the administration dose
10 may be less than 200 µg/kg body weight. In yet other cases, the administration dose may be in the range between about 0.1 to about 100 µg/kg body weight. The dose may be conveniently administered once daily, or in divided doses up to, for example, four times a day or in sustained release form.

A compound of the present disclosure may be administered by any conventional
15 route, in particular: enterally, topically, orally, nasally, e.g., in the form of tablets or capsules, via suppositories, or parenterally, e.g., in the form of injectable solutions or suspensions, for intravenous, intra-muscular, sub-cutaneous, or intra-peritoneal injection. Suitable formulations and pharmaceutical compositions will include those formulated in a conventional manner using one or more physiologically acceptable carriers or excipients, and
20 any of those known and commercially available and currently employed in the clinical setting. Thus, the compounds may be formulated for oral, buccal, topical, parenteral, rectal or transdermal administration or in a form suitable for administration by inhalation or insufflation (either orally or nasally).

For oral administration, pharmaceutical compositions may take the form of, for
25 example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycollate); or wetting agents (e.g.,
30 sodium lauryl sulphate). Tablets may be coated by methods well known in the art. Liquid

preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, 5 cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g., methyl or propyl-p-hydroxybenzoates or sorbic acid). Preparations may also contain buffer salts, flavoring, coloring, and sweetening agents as appropriate.

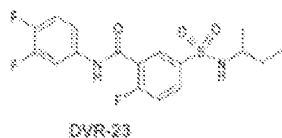
10 Preparations for oral administration may also be suitably formulated to give controlled-release or sustained release of the active compound(s) over an extended period. For buccal administration the compositions may take the form of tablets or lozenges formulated in a conventional manner known to the skilled artisan.

A disclosed compound may also be formulated for parenteral administration by 15 injection e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain additives such as suspending, stabilizing and/or dispersing agents. Alternatively, the compound may be in powder form for constitution with 20 a suitable vehicle, e.g., sterile pyrogen-free water, before use. Compounds may also be formulated for rectal administration as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

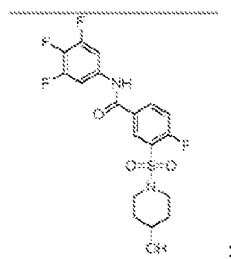
Also contemplated herein are methods and compositions that include a second active agent or administering a second active agent. For example, in addition to being infected with 25 HBV, a subject or patient can further have HBV infection-related co-morbidities, i.e., diseases and other adverse health conditions associated with, exacerbated by, or precipitated by being infected with HBV. Contemplated herein are disclosed compounds in combination with at least one other agent that has previously been shown to treat these HBV-infection-related conditions.

In some cases, a disclosed compound may be administered as part of a combination therapy in conjunction with one or more antivirals. Example antivirals include nucleoside analogs, interferon α , and other assembly effectors, for instance heteroaryldihydropyrimidines (HAPs) such as methyl 4-(2-chloro-4-fluorophenyl)-6-methyl-2-(pyridin-2-yl)-1,4-dihydropyrimidine-5-carboxylate (HAP-1). For example, provided herein is a method of treating a patient suffering from hepatitis B infection comprising administering to the patient a first amount of a disclosed compound and a second amount of an antiviral, or other anti HBV agent, for example a second amount of a second compound selected from the group consisting of: an HBV capsid assembly promoter (for example,

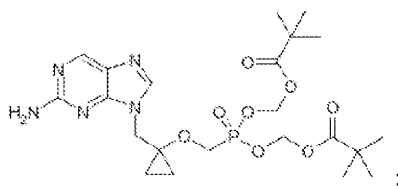
GLS4, BAY 41-4109, AT-130, DVR-23 (e.g., as depicted below),



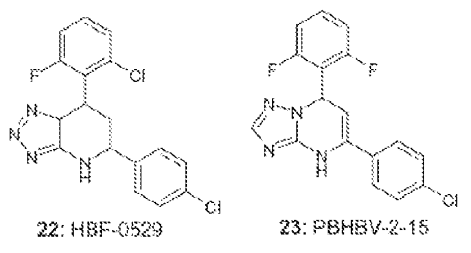
NVR 3-778, NVR1221 (by code); and N890 (as depicted below):



other capsid inhibitors such as those disclosed in the following patent applications hereby incorporated by reference: WO2014037480, WO2014184328, WO2013006394, WO2014089296, WO2014106019, WO2013102655, WO2014184350, WO2014184365, WO2014161888, WO2014131847, WO2014033176, WO2014033167, and WO2014033170; Nucleos(t)ide analogs interfering with viral polymerase, such as entecavir (Baraclude), Lamivudine, (Epivir-HBV), Telbivudine (Tyzeka, Sebivo), Adefovir dipivoxil (Hepsera), Tenofovir (Viread), Tenofovir alafenamide fumarate (TAF), prodrugs of tenofovir (e.g. AGX-1009), L-FMAU (Clevudine), LB80380 (Besifovir) and:

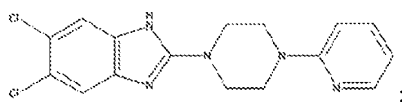


viral entry inhibitors such as Myrcludex B and related lipopeptide derivatives; HBsAg secretion inhibitors such as REP 9AC' and related nucleic acid-based amphipathic polymers, HBF-0529 (PBHBV-001), PBHBV-2-15 as depicted below:

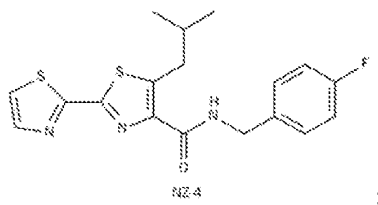


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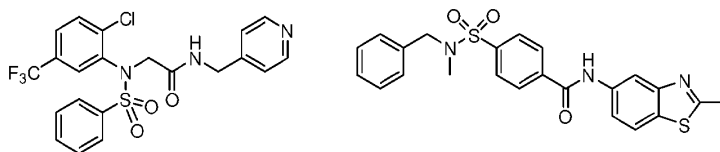
and BM601 as depicted below:



disruptors of nucleocapsid formation or integrity such as NZ-4/W28F:



10 cccDNA formation inhibitors such as BSBI-25, CCC-0346, CCC-0975 (as depicted below):



HBe directed transbodies such as those described in Wang Y, et al, Transbody against hepatitis B virus core protein inhibits hepatitis B virus replication in vitro, Int.

Immunopharmacol (2014), located at [//dx.doi.org/10.1016/j.intimp.2015.01.028](https://doi.org/10.1016/j.intimp.2015.01.028); antiviral

15 core protein mutant (such as Cp183-V124W and related mutations as described in

WO/2013/010069, WO2014/074906, each incorporated by reference); inhibitors of HBx-interactions such as RNAi, antisense and nucleic acid based polymers targeting HBV RNA;,, e.g., RNAi (for example ALN-HBV, ARC-520, TKM-HBV, ddRNAi), antisense (ISIS-HBV), or nucleic acid based polymer: (REP 2139-Ca); immunostimulants such as Interferon
5 alpha 2a (Roferon), Intron A (interferon alpha 2b), Pegasys (peginterferon alpha 2a), Pegylated IFN 2b, IFN lambda 1a and PEG IFN lambda 1a, Wellferon, Roferon, Infergen, lymphotoxin beta agonists such as CBE11 and BS1); Non-Interferon Immune enhancers such as Thymosin alpha-1 (Zadaxin) and Interleukin-7 (CYT107); TLR-7/9 agonists such as GS-9620, CYT003, Resiquimod; Cyclophilin inhibitors such as NVP018; OCB-030; SCY-635;
10 Alisporivir; NIM811 and related cyclosporine analogs; vaccines such as GS-4774, TG1050, Core antigen vaccine; SMAC mimetics such as birinapant and other IAP-antagonists; Epigenetic modulators such as KMT inhibitors (EZH1/2, G9a, SETD7, Suv39 inhibitors), PRMT inhibitors, HDAC inhibitors, SIRT agonists, HAT inhibitors, WD antagonists (e.g. OICR-9429), PARP inhibitors, APE inhibitors, DNMT inhibitors, LSD1 inhibitors, JMJD
15 HDM inhibitors, and Bromodomain antagonists; kinase inhibitors such as TKB1 antagonists, PLK1 inhibitors, SRPK inhibitors, CDK2 inhibitors, ATM & ATR kinase inhibitors; STING Agonists; Ribavirin; N-acetyl cysteine ; NOV-205 (BAM205); Nitazoxanide (Alinia), Tizoxanide; SB 9200 Small Molecule Nucleic Acid Hybrid (SMNH); DV-601; Arbidol; FXR agonists (such as GW 4064 and Fexaramin); antibodies, therapeutic proteins, gene therapy,
20 and biologics directed against viral components or interacting host proteins.

In some embodiments, the disclosure provides a method of treating a hepatitis B infection in a patient in need thereof, comprising administering a first compound selected from any one of the disclosed compounds, and one or more other HBV agents each selected from the group consisting of HBV capsid assembly promoters, HBF viral polymerase
25 interfering nucleosides, viral entry inhibitors, HBsAg secretion inhibitors, disruptors of nucleocapsid formation, cccDNA formation inhibitors, antiviral core protein mutant, HBc directed transbodies, RNAi targeting HBV RNA, immunostimulants, TLR-7/9 agonists, cyclophilin inhibitors, HBV vaccines, SMAC mimetics, epigenetic modulators, kinase inhibitors, and STING agonists. In some embodiments, the disclosure provides a method of

treating a hepatitis B infection in a patient in need thereof, comprising administering an amount of a disclosed compound, and administering another HBV therapeutic.

In some embodiments, the disclosure further provides a method of treating HBV or HDV infection or HBV/HDV coinfection in a patient in need thereof, comprising

5 administering a first compound selected from any one of the disclosed compounds, and one or more other additional antivirals, the one or more additional antivirals include HDV therapies and one or more of HBV agents each selected from the group consisting of HBV capsid assembly promoters, HBF viral polymerase interfering nucleosides, viral entry inhibitors, HBsAg secretion inhibitors, disruptors of nucleocapsid formation, cccDNA

10 formation inhibitors, antiviral core protein mutant, HBc directed transbodies, RNAi targeting HBV RNA, immunostimulants, TLR-7/9 agonists, cyclophilin inhibitors, HBV vaccines, SMAC mimetics, epigenetic modulators, kinase inhibitors, and STING agonists. In some embodiments, the disclosure provides a method of treating a HBV or HBV infection or HBV/HDV coinfection in a patient in need thereof, comprising administering an amount of a

15 disclosed compound, and administering another HBV therapeutic or an HDV therapeutic.

In some embodiments, the first and second amounts together comprise a pharmaceutically effective amount. The first amount, the second amount, or both may be the same, more, or less than effective amounts of each compound administered as monotherapies. Therapeutically effective amounts of a disclosed compound and antiviral may be co-

20 administered to the subject, i.e., administered to the subject simultaneously or separately, in any given order and by the same or different routes of administration. In some instances, it may be advantageous to initiate administration of a disclosed compound first, for example one or more days or weeks prior to initiation of administration of the antiviral. Moreover, additional drugs may be given in conjunction with the above combination therapy.

25 In another embodiment, a disclosed compound may be conjugated (e.g., covalently bound directly or through molecular linker to a free carbon, nitrogen (e.g., an amino group), or oxygen (e.g., an active ester) of a disclosed compound), with a detection moiety, for e.g., a fluorophore moiety (such a moiety may for example re-emit a certain light frequency upon binding to a virus and/or upon photon excitation). Contemplated fluorophores include

30 AlexaFluor® 488 (Invitrogen) and BODIPY FL (Invitrogen), as well as fluorescein,

rhodamine, cyanine, indocarbocyanine, anthraquinones, fluorescent proteins, aminocoumarin, methoxycoumarin, hydroxycoumarin, Cy2, Cy3, and the like. Such disclosed compounds conjugated to a detection moiety may be used in e.g., a method for detecting HBV or biological pathways of HBV infection, e.g., *in vitro* or *in vivo*; and/or methods of assessing
5 new compounds for biological activity.

V. Examples

The compounds described herein can be prepared in a number of ways based on the teachings contained herein and synthetic procedures known in the art. In the description of
10 the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, can be chosen to be the conditions standard for that reaction, unless otherwise indicated. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule should be
15 compatible with the reagents and reactions proposed. Substituents not compatible with the reaction conditions will be apparent to one skilled in the art, and alternate methods are therefore indicated. The starting materials for the examples are either commercially available or are readily prepared by standard methods from known materials.

At least some of the compounds identified as “intermediates” herein are contemplated
20 as compounds of the disclosure.

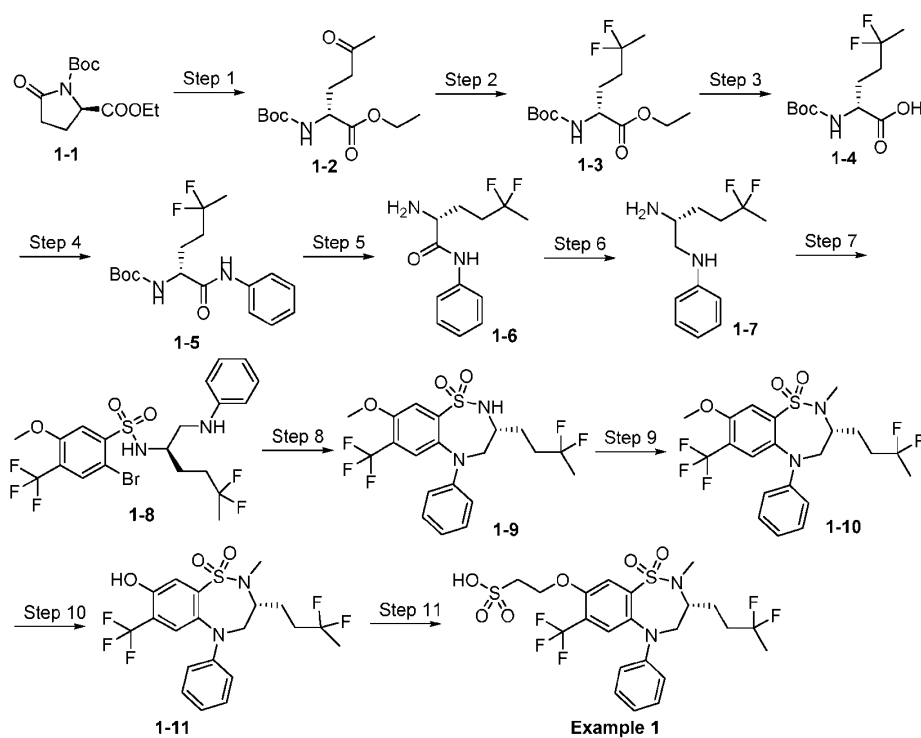
Abbreviations:

	AcOH	Acetic acid
	ACN	Acetonitrile
25	aq.	Aqueous
	BAST	Bis(2-methoxyethyl)aminosulfur trifluorid
	Boc ₂ O	Di-tert-butyl dicarbonate
	nBuLi	n-Butyllithium
	compd.	Compound
30	concd.	Concentrated

	COSY	Homonuclear correlation spectroscopy
	DCM	Dichloromethane
	DIAD	Diisopropyl azodicarboxylate
	DIEA	Diisopropyl ethylamine
5	DMF	N,N-Dimethylformamide
	DMS	Dimethylsulfide
	DMSO	Dimethyl sulfoxide
	EA, EtOAc	Ethyl acetate
	Et ₃ N	Triethylamine
10	ESI	Electrospray ionization
	HATU	Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium
	h, hr	Hour(s)
	HMBC	Heteronuclear multiple bond correlation
	HPLC	High performance liquid chromatography
15	HSQC	Heteronuclear single quantum coherence
	IPA, iPrOH	Isopropanol
	LiHMDS	Lithium bis(trimethylsilyl)amide
	LCMS	Liquid chromatography–mass spectrometry
	MeOH	Methanol
20	MS	Mass spectrometry
	NOESY	Nuclear Overhauser effect spectroscopy
	NFSI	N-Fluorobenzenesulfonimide
	NMP	N-Methyl-2-pyrrolidone
	NMR	Nuclear magnetic resonance
25	PE	Petroleum ether
	rac.	Racemic
	rel.	Relative
	R _f	Retention factor
30	rt, r.t.	Room temperature

	RT, t_R	Retention time
	sat.	Saturated
	SFC	Supercritical Fluid Chromatography
	TEA	Triethylamine
5	TFA	Trifluoroacetic acid
	THF	Tetrahydrofuran
	TLC	Thin-layer chromatography

Example 1. (R)-2-((3-(3,3-difluorobutyl)-2-methyl-1,1-dioxido-5-phenyl-7-(trifluoromethyl)-
 10 2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)ethane-1-sulfonic acid



Scheme 1

Example 1

Step 1. Synthesis of (R)-ethyl 2-((tert-butoxycarbonyl)amino)-5-oxohexanoate (1-2). To a solution of 1-(tert-butyl) 2-ethyl (R)-5-oxopyrrolidine-1,2-dicarboxylate (**1-1**) (38.0 g, 147.9
 15 mmol) in THF (380 mL) was added MeMgBr (51.8 mL, 155.3 mmol, 3.0M) drop wise in an

ice bath under nitrogen. The mixture was stirred at rt for 6 hr. The resulting mixture was then quenched with sat. aq. NH_4Cl solution (200 mL). The mixture was extracted with EA (200 mL x 2) and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 , and concentrated. The residue was purified by silica gel column chromatography (20% EA/PE (v/v)) to give **1-2** (32.0 g, 79%) as a yellow solid. TLC: 25% EA/ PE (v/v) (R_f : 0.4). MS (ESI): calcd. for $\text{C}_{13}\text{H}_{23}\text{NO}_5$: 273.2; Found: 174.1 [$\text{M} - \text{Boc} + 1$] $^+$.

Step 2. Synthesis of (R)-ethyl 2-((tert-butoxycarbonyl)amino)-5,5-difluorohexanoate (1-3). To a solution of **1-2** (32 g, 117.2 mmol) in THF (320 mL) was added BAST (77.7 g, 351.6 mmol) drop wise in an ice bath under nitrogen, and the reaction mixture was stirred at rt for 4 days. The reaction mixture was poured into sat aq. NaHCO_3 solution (150 mL) slowly at 0°C and extracted with EA (150 mL x 2). The combined organic layer was washed with brine, dried over Na_2SO_4 , and concentrated. The residue was purified by silica gel column chromatography (8% EA/PE (v/v)) to give **1-3** (13.8 g, 40%) as a yellow oil. TLC: 10% EA/ PE (v/v) (R_f : 0.4). MS (ESI): calcd. for $\text{C}_{13}\text{H}_{23}\text{F}_2\text{NO}_4$: 295.2 MS Found: 196.2 [$\text{M} - \text{Boc} + 1$] $^+$.

Step 3. Synthesis of (R)-2-((tert-butoxycarbonyl)amino)-5,5-difluorohexanoic acid (1-4). To a solution of **1-3** (13.8 g, 46.8 mmol) in THF/ H_2O = 5/1 (v/v) (100 mL) was added LiOH (3.4 g, 140.3 mmol). After stirring at rt for 4 hr, the reaction mixture was diluted with water (100 mL), acidified with 1N aq. HCl solution to pH ~ 3, and concentrated to remove organic solvent. The residue was extracted with EA (100 mL x 2). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 , and concentrated. The residue was dried in vacuo to give **1-4** (11.3 g, 90%) as a yellow oil, which was used in the next step without further purification. TLC: 35% EA/ PE (v/v) (R_f : 0.4). MS (ESI): calcd. for $\text{C}_{11}\text{H}_{19}\text{F}_2\text{NO}_4$: 267.1; Found: 168.2 [$\text{M} - \text{Boc} + 1$] $^+$.

Step 4. Synthesis of (R)-tert-butyl (5,5-difluoro-1-oxo-1-(phenylamino)hexan-2-yl)carbamate (1-5). To a stirred solution of **1-4** (11.3 g, 42.3 mmol) and DIEA (16.4 g, 127.0

mmol) in THF (100 mL) was added HATU (24.1 g, 63.5mmol) in small portions in an ice bath under nitrogen. After stirring for 40 min, PhNH₂ (5.9 g, 63.5mmol) was added drop wise. The resulting mixture was stirred at rt for 16 hr and then concentrated. The residue was diluted with H₂O (150 mL) and extracted with EA (150 mL x 2). The combined organic
5 extracts were washed with brine (150 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography (25% EA/PE (v/v)) to give **1-5** (7.6 g, 53%) as a yellow oil. TLC: 30% EA/ PE (v/v) (R_f: 0.4). MS (ESI): calcd. for C₁₇H₂₄F₂N₂O₃: 342.2; Found: 287.2 [M - tBu + 1]⁺.

10 **Step 5. Synthesis of (R)-2-amino-5,5-difluoro-N-phenylhexanamide (1-6).** A solution of **1-5** (7.6 g, 22.2 mmol) and TFA (20 mL) in DCM (40 mL) was stirred at room temperature for 4 hr and concentrated. The residue was diluted with DCM (100 mL) and basified to pH ~ 8 with sat. aq. NaHCO₃ solution. The resulting mixture was extracted with DCM (100 mL x 4). The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and
15 concentrated. The residue was dried in vacuo to give crude **1-6** (4.8 g, 89%) as a yellow oil, which was used for the next step without further purification. TLC: 8% MeOH/ DCM (v/v) (R_f: 0.5). MS (ESI): calcd. for C₁₂H₁₆F₂N₂O: 242.2; Found: 243.2 [M + 1]⁺.

Step 6. Synthesis of (R)-5,5-difluoro-N1-phenylhexane-1,2-diamine (1-7). To a stirred
20 solution of **1-6** (4.8 g, 19.8 mmol) in THF (100 mL) was added LAH (23.8 mL, 59.5 mmol, 2.5 M in THF) drop wise at 0°C. The resulting mixture was stirred at 70°C for 4 hr. The reaction was quenched with H₂O (2.3 mL) and 15% aq. NaOH solution (2.3 mL) at 0°C. The resulting mixture was dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography (10% MeOH/DCM (v/v)) to give **1-7** (3.8 g, 84%) as a colorless oil.
25 TLC: 10% CH₃OH/DCM (v/v) (R_f: 0.3). MS (ESI): calcd. for C₁₂H₁₈F₂N₂: 228.1; Found: 229.3 [M + 1]⁺.

Step 7. Synthesis of (R)-2-bromo-N-(5,5-difluoro-1-(phenylamino)hexan-2-yl)-5-methoxy-4-(trifluoromethyl)benzenesulfonamide (1-8). To a stirred solution of **1-7** (1.0 g,

4.39 mmol) and TEA (886 mg, 8.77 mmol) in THF (10 mL) was added 2-bromo-5-methoxy-4-(trifluoromethyl)benzenesulfonyl chloride (2.3 g, 6.59 mmol) in portions at rt. After stirring at rt for 16 hr, the mixture was diluted with H₂O (30 mL) and extracted with EA (25 mL x 2). The combined organic extracts were dried over Na₂SO₄ and concentrated. The residue was purified by silica gel column chromatography (30% EA/PE (v/v)) to give **1-8** (1.6 g, 67%) as a yellow solid. TLC: 30% EA/PE (v/v) (R_f: 0.4). MS (ESI): calcd. for C₂₀H₂₂BrF₅N₂O₃S: 544.0; Found: 545.1 [M + 1]⁺.

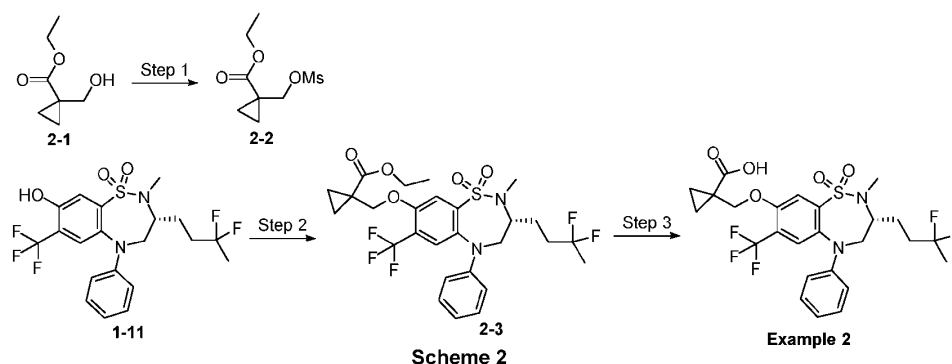
Step 8. Synthesis of (R)-3-(3,3-difluorobutyl)-8-methoxy-5-phenyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (1-9). A suspension of **1-8** (1.6 g, 2.94 mmol), picolinic acid (72 mg, 0.59 mmol), K₂CO₃ (1.2 g, 8.82 mmol), and CuI (38 mg, 0.59 mmol) in DMF (20 mL) was stirred at 90°C for 3 hours under N₂ atmosphere. The reaction mixture was then cooled at rt, diluted with water (30 mL), and extracted with EA (25 mL x 3). The combined organic extracts were washed with sat. aq. LiCl solution (30 mL) and brine (30 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give crude **1-9** (1.2 g, 88.2%) as a brown oil, which was used for the next step without further purification. TLC: 25% EA/PE (v/v) (R_f: 0.4). MS (ESI): calcd. for C₂₀H₂₁F₅N₂O₃S: 464.1; Found: 465.1 [M + 1]⁺.

Step 9. Synthesis of (R)-3-(3,3-difluorobutyl)-8-methoxy-2-methyl-5-phenyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (1-10). To a suspension of **1-9** (1.2 g, 2.59 mmol) and Cs₂CO₃ (1.1 g, 3.36 mmol) in NMP (10 mL) was added MeI (1.1 g, 7.77 mmol) in an ice bath. The reaction mixture was stirred at rt for 3 hr and diluted with H₂O (30 mL). The resulting mixture was extracted with EA (30 mL x 2). The combined organic layer was washed with brine (30 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give crude **1-10** (1.1 g, 88.9%) as a brown oil, which was used for the next step without further purification. TLC: 25% EA/PE (v/v) (R_f: 0.6). MS (ESI): calcd. for C₂₁H₂₃F₅N₂O₃S: 478.1; Found: 479.1 [M + 1]⁺.

Step 10. Synthesis of (R)-3-(3,3-difluorobutyl)-8-hydroxy-2-methyl-5-phenyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (1-11). To a solution of **1-10** (1.1 g, 2.30 mmol) in DMF (6.0 mL) was added NaSMe (1.6 g, 23.0 mmol), and the reaction mixture was stirred at 100°C for 16 hr. The reaction mixture was diluted with water (30 mL), acidified with 4 N aq. HCl solution to pH 5~6, and extracted with EA (50 mL x 3). The combined organic layer was washed with sat. aq. LiCl solution (25 mL) and brine (25 mL), dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by silica gel column chromatography (35% EA/PE (v/v)) to give **1-11** (1.0 g, 93.5%) as a colorless oil. TLC: 40% EA/PE (v/v) (R_f: 0.4). MS (ESI): calcd. for C₂₀H₂₁F₅N₂O₃S: 464.1; Found: 465.3 [M + 1]⁺.

Step 11. Synthesis of (R)-2-((3-(3,3-difluorobutyl)-2-methyl-1,1-dioxido-5-phenyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)ethanesulfonic acid (Example 1). To a suspension of **1-11** (450 mg, 0.97 mmol) and Cs₂CO₃ (1264 mg, 3.88 mmol) in DMF (10 mL) was added sodium 2-bromoethane-1-sulfonate (611 mg, 2.91 mmol), and the reaction mixture was stirred at 130°C for 16 hours. The reaction mixture was diluted with water (20 mL) and acidified with 4N aq. HCl solution to pH ~5. The resulting mixture was extracted with EA (25 mL x 3). The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by prep-HPLC to give **Example 1** (112 mg, 20.2%) as a white solid. TLC: 5% MeOH/EA (v/v) (R_f: 0.5). MS (ESI): calcd. for C₂₂H₂₅F₅N₂O₆S₂: 572.1; Found: 573.0 [M + 1]⁺. ¹H NMR (400 MHz, CD₃OD): δ 7.69 (s, 1H), 7.47 (s, 1H), 7.25 – 7.17 (m, 2H), 6.83 (t, J = 7.2 Hz, 1H), 6.78 – 6.66 (m, 2H), 4.56 (t, J = 8.0 Hz, 2H), 4.20 – 4.05 (m, 1H), 4.00 – 3.82 (m, 1H), 3.52 – 3.38 (m, 1H), 3.37 – 3.32 (m, 2H), 2.64 (s, 3H), 2.11 – 1.92 (m, 2H), 1.86 – 1.75 (m, 2H), 1.62 (t, J = 18.8 Hz, 3H) ppm.

Example 2. (R)-1-(((3-(3,3-difluorobutyl)-2-methyl-1,1-dioxido-5-phenyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid



Step 1. Synthesis of ethyl 1-(((methylsulfonyl)oxy)methyl)cyclopropane-1-carboxylate (2-2).

To a stirred solution of ethyl 1-(hydroxymethyl)cyclopropane-1-carboxylate (**2-1**) (100 mg, 0.69 mmol) and TEA (209 mg, 2.07 mmol) in DCM (5 mL) was added MsCl (119 mg, 1.04 mmol). After stirring at rt for 1 hr, the reaction mixture was added ice-cold water (10 mL) and extracted with DCM (20 mL x 3). The combined organic layer was washed with water (20 mL) and brine (20 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give **2-2** (140 mg, 91%) as a yellow oil. TLC: 10% EA/PE (v/v) (R_f: 0.6) (Phosphomolybdic Acid). MS (ESI): calcd. for C₈H₁₄O₅S: 222.1; Found: 240.1 [M + 18]⁺.

Step 2. Synthesis of ethyl (R)-1-(((3,3-difluorobutyl)-2-methyl-1,1-dioxido-5-phenyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylate (2-3).

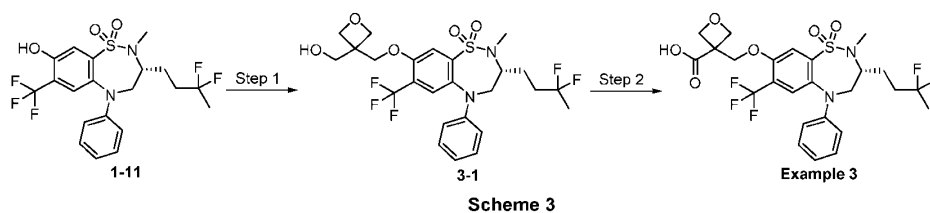
To a stirred solution of **1-11** (75 mg, 0.16 mmol) and Cs₂CO₃ (156 mg, 0.48 mmol) in DMF (2 mL) was added **10-2** (71 mg, 0.32 mmol) and the reaction mixture was heated at 70 °C for 3 hr. After completion of the reaction (monitored by LCMS), the reaction mixture was added into water (10 mL). The precipitate was collected by filtration, washed with water (5 mL x 3), and dried in vacuo to give crude **2-3** (120 mg) as a white solid, which was used for the next step without further purification. TLC: 40% EA/PE (v/v) (R_f: 0.5). MS (ESI): calcd. for C₂₇H₃₁F₅N₂O₅S: 590.2; Found: 591.3 [M + 1]⁺.

Step 3. Synthesis of (R)-1-(((3-(3,3-difluorobutyl)-2-methyl-1,1-dioxido-5-phenyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid (Example 2). To a stirred solution of **2-3** (80 mg, crude product, 0.11 mmol) in MeOH/H₂O = 2/1 (v/v) (3 mL) was added NaOH (22 mg, 0.55 mmol) and the reaction mixture was stirred at rt for 2 hr. After completion of the reaction (monitored by LCMS), the reaction mixture was neutralized with 1 N aq. HCl solution and concentrated to remove organic solvent. The residue was diluted with water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by prep-HPLC to give

Example 2 (28 mg, 45%) as a white solid. TLC: 10% MeOH/DCM (v/v) (R_f 0.5). MS (ESI): calcd. for C₂₅H₂₇F₅N₂O₅S: 562.2; Found: 563.2 [M + 1]⁺. ¹H NMR (400 MHz, CD₃OD,): δ 7.65 (s, 1H), 7.46 (s, 1H), 7.23 – 7.19 (m, 2H), 6.83 (t, J = 7.2 Hz, 1H), 6.73 (d, J = 7.2 Hz, 2H), 4.41 – 4.32 (m, 2H), 4.18 – 3.87 (m, 2H), 3.37 – 3.33 (m, 1H), 2.64 (s, 3H), 2.12 – 1.92 (m, 2H), 1.85 – 1.78 (m, 2H), 1.62 (t, J = 18.4 Hz, 3H), 1.35 – 1.31 (m, 2H), 1.13 – 1.09 (m, 2H) ppm.

Example 3. (R)-3-(((3-(3,3-difluorobutyl)-2-methyl-1,1-dioxido-5-phenyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)methyl)oxetane-3-carboxylic acid

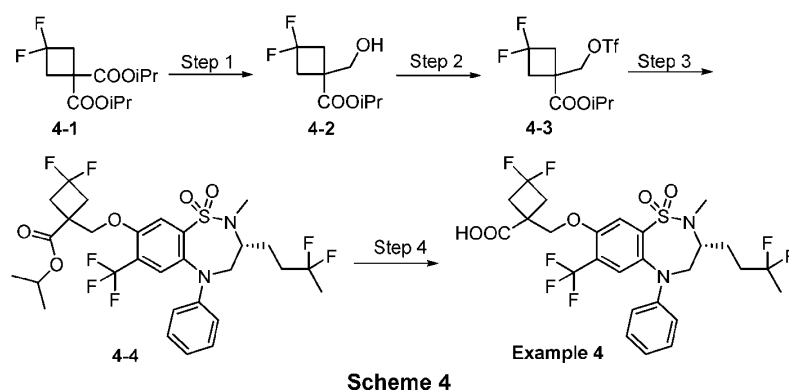
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Step 1. Synthesis of (R)-3-(3,3-difluorobutyl)-8-((3-(hydroxymethyl)oxetan-3-yl)methoxy)-2-methyl-5-phenyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (3-1). To a solution of **1-11** (200 mg, 0.43 mmol) in DMF (8 mL) were added (3-(bromomethyl)oxetan-3-yl)methanol (156 mg,

0.86 mmol) and Cs_2CO_3 (420 mg, 1.29 mmol). The mixture was stirred at 70 °C overnight. The reaction mixture was treated with LiCl solution (8 mL) and extracted with ethyl acetate (10 mL x 2). The combined organic extracts were dried with anhydrous Na_2SO_4 and concentrated. The residue was dried in vacuo to give crude **3-1** (243 mg) as a brown solid, which was used for the next step without further purification. MS (ESI): calcd. for $\text{C}_{25}\text{H}_{29}\text{F}_5\text{N}_2\text{O}_5\text{S}$: 564.2; Found: 565.2 $[\text{M} + 1]^+$.

- Step 2. Synthesis of (R)-3-(((3-(3,3-difluorobutyl)-2-methyl-1,1-dioxido-5-phenyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)methyl)oxetane-3-carboxylic acid (Example 3).** To a solution of **3-1** (crude 243 mg, 0.43 mmol) in DCM (10 mL) was added Dess-Martin reagent (729 mg, 1.72 mmol). After stirring at rt for 5 hr, the reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by prep-HPLC to give **Example 3** (60 mg, 24%) as a white solid. MS (ESI): calcd. for $\text{C}_{25}\text{H}_{27}\text{F}_5\text{N}_2\text{O}_6\text{S}$: 578.2; Found: 579.3 $[\text{M} + 1]^+$. ^1H NMR (400 MHz, CD_3OD): δ 7.73 (s, 1H), 7.49 (s, 1H), 7.22 (dd, $J = 8.6, 7.4$ Hz, 2H), 6.84 (t, $J = 7.4$ Hz, 1H), 6.75 (d, $J = 7.6$ Hz, 2H), 4.97 (dd, $J = 5.8, 2.2$ Hz, 2H), 4.75 (dd, $J = 5.8, 1.4$ Hz, 2H), 4.52 (s, 2H), 4.24 – 4.06 (m, 1H), 4.00 – 3.85 (m, 1H), 3.60 – 3.35 (m, 1H), 2.65 (s, 3H), 2.15 – 1.90 (m, 2H), 1.87 – 1.75 (m, 2H), 1.62 (t, $J = 18.4$ Hz, 3H) ppm.
- Example 4. (R)-1-(((3-(3,3-difluorobutyl)-2-methyl-1,1-dioxido-5-phenyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)methyl)-3,3-difluorocyclobutane-1-carboxylic acid



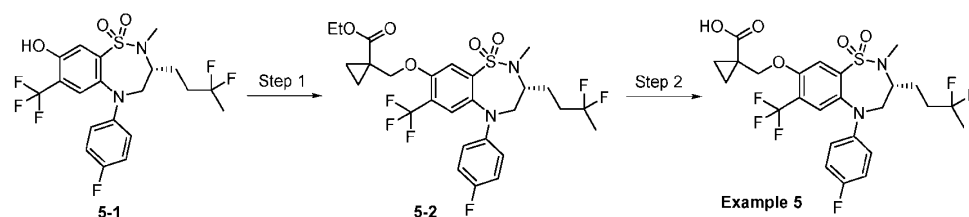
Step 1. Synthesis of isopropyl 3,3-difluoro-1-(hydroxymethyl)cyclobutanecarboxylate (4-2). To a solution of diisopropyl 3,3-difluorocyclobutane-1,1-dicarboxylate (**4-1**) (2.0 g, 7.60 mmol) in anhydrous THF (60 mL) was added 1N lithium tri-tert-butoxyaluminum hydride in THF (18.9 mL, 18.9 mmol) at 0 °C. After stirring at 70 °C for 16 hr, the reaction was quenched with saturated aq. NH₄Cl solution at 0 °C until no bubbling was observed. The mixture was diluted with water (80 mL), concentrated to remove organic solvent, and extracted with EA (30 mL x 3). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography (PE/EA = 1/1 (v/v)) to give **4-2** (0.85 g, 54%) as a pale-yellow oil. MS (ESI): calcd. for C₉H₁₄F₂O₃: 208.2; Found: 209.2 [M + 1]⁺.

Step 2. Synthesis of isopropyl 3,3-difluoro-1-(((trifluoromethyl)sulfonyl)oxy)methyl)cyclobutanecarboxylate (4-3). To a solution of **4-2** (400 mg, 1.92 mmol), 2,6-dimethylpyridine (308 mg, 2.88 mmol) in DCM (5 mL) was added Tf₂O (400 mg, 1.92 mmol) at -78 °C. After stirring at -78 °C for 1 hr, the mixture was diluted with water (30 mL) and extracted with DCM (30 mL x 3). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give crude **4-3** (200 mg, 31%) as a yellow solid, which was used for the next step without further purification.

Step 3. Synthesis of (R)-isopropyl 1-(((3-(3,3-difluorobutyl)-2-methyl-1,1-dioxido-5-phenyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)methyl)-3,3-difluorocyclobutanecarboxylate (4-4). To a solution of **1-11** (100 mg, 0.21 mmol), Cs₂CO₃ (205 mg, 0.63 mmol) in DMF (3 mL) was added **4-3** (200 mg, 0.59 mmol), and the reaction mixture was stirred at rt for 16 hr. Next, the reaction mixture was diluted with water (20 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with LiCl solution (50 mL) and brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give crude **4-4** (160 mg, 84%) as a yellow solid, which was used for the next step without further purification. MS (ESI): calcd. for C₂₉H₃₃F₇N₂O₅S: 654.2; Found: 655.4 [M+1]⁺.

Step 4. Synthesis of (R)-1-(((3-(3,3-difluorobutyl)-2-methyl-1,1-dioxido-5-phenyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)methyl)-3,3-difluorocyclobutanecarboxylic acid (Example 4). To a solution of **4-4** (150 mg, 0.23 mmol) in THF (4 mL) was added 1N aq. LiOH solution (1 mL) and the reaction mixture was stirred at rt for 16 hr. The reaction mixture was adjusted to pH = 6 with 1 N aq. HCl solution and then purified by prep-HPLC to give **Example 4** (30 mg, 24%) as an off-white solid. MS (ESI): calcd. for C₂₆H₂₇F₇N₂O₅S: 612.2; Found: 613.0 [M + 1]⁺. ¹H NMR (400 MHz, CD₃OD): δ 7.68 (s, 1H), 7.47 (s, 1H), 7.26 – 7.18 (m, 2H), 6.85 (t, *J* = 7.2 Hz, 1H), 6.76 (d, *J* = 4.0 Hz, 2H), 4.47 (s, 2H), 4.25 – 4.05 (m, 1H), 3.99 – 3.84 (m, 1H), 3.62 – 3.40 (m, 1H), 3.15 – 3.00 (m, 2H), 2.89 – 2.74 (m, 2H), 2.66 (s, 3H), 2.14 – 1.90 (m, 2H), 1.88 – 1.74 (m, 2H), 1.62 (t, *J* = 18.4 Hz, 3H) ppm.

Example 5. (R)-1-(((3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid

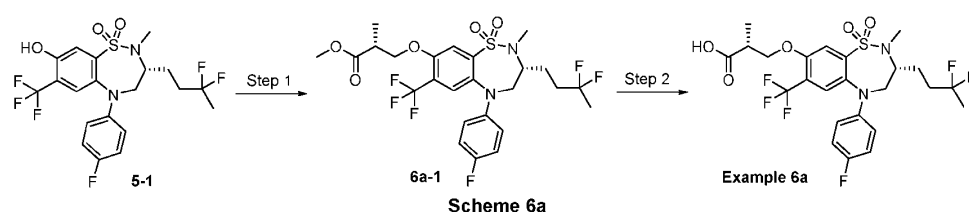


Scheme 5

- Step 1. Synthesis of (R)-ethyl 1-(((3,3-difluorobutyl)-5-(4-fluorophenyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)methyl)cyclopropanecarboxylate (5-2).** To a stirred solution of **5-1** (140 mg, 0.29 mmol), which was readily prepared by following the same procedure for preparing **1-11** by replacing aniline with 4-F-aniline, and Cs_2CO_3 (284 mg, 0.87 mmol) in DMF (4 mL) was added ethyl 1-(((methylsulfonyl)oxy)methyl)cyclopropane-1-carboxylate (116 mg, 0.53 mmol). After stirring at 65 °C for 3 hr, the reaction mixture was added into water (10 mL).
- The precipitate was filtered, washed with water (10 mL x 3), and dried in vacuo to give crude **5-2** (120 mg) as a white solid, which was used in the next step without further purification. TLC: EA/PE = 3/7 (v/v) (R_f : 0.5). MS (ESI): calcd. for $\text{C}_{27}\text{H}_{30}\text{F}_6\text{N}_2\text{O}_5\text{S}$: 608.2; Found: 609.2 $[\text{M} + 1]^+$.
- Step 2. Synthesis of (R)-1-(((3,3-difluorobutyl)-5-(4-fluorophenyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)methyl)cyclopropanecarboxylic acid (Example 5).** To a stirred solution of **5-2** (120 mg, crude product, 0.20 mmol) in MeOH/ H_2O = 2/1 (v/v) (6 mL) was added NaOH (79 mg, 1.97 mmol) and the reaction mixture was stirred at rt for 16 hr. After completion of the reaction (monitored by LCMS), the reaction mixture was neutralized with 1 N aq. HCl solution and concentrated to remove organic solvent. The residue was diluted with water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by prep-HPLC to give **Example 5** (49 mg, 43%) as a white solid. TLC: EA/PE = 1/1 (v/v) (R_f : 0.5). MS (ESI): calcd. for $\text{C}_{25}\text{H}_{26}\text{F}_6\text{N}_2\text{O}_5\text{S}$: 580.1; Found: 581.3 $[\text{M} + 1]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ

7.64 (s, 1H), 7.41 (s, 1H), 6.97 (t, $J = 8.4$ Hz, 2H), 6.77-6.74 (m, 2H), 4.39-4.32 (m, 2H), 4.12-3.86 (m, 2H), 3.40-3.33 (m, 1H), 2.64 (s, 3H), 2.10-1.92 (m, 2H), 1.82-1.76 (m, 2H), 1.61 (t, $J = 18.4$ Hz, 3H), 1.35-1.34 (m, 2H), 1.13-1.11 (m, 2H) ppm.

- 5 Example 6a. (R)-3-(((R)-3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)-2-methylpropanoic acid



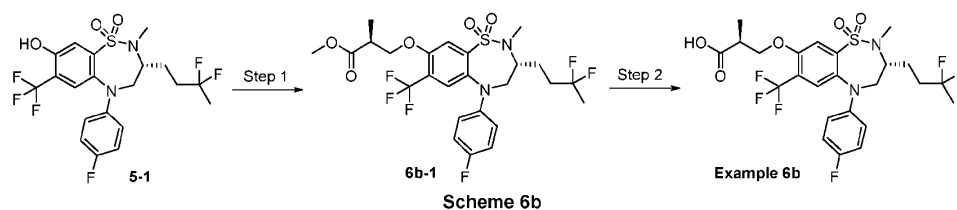
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- Step 1. Synthesis of methyl (R)-3-(((R)-3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)-2-methylpropanoate (5-2).** To a solution of **5-1** (1.5 g, 3.1 mmol) in toluene (15 mL) was added methyl (R)-3-hydroxy-2-methylpropanoate (1.8 g, 15.2 mmol) and PPh₃ (2.4 g, 9.3 mmol). Then DIAD (6.3 g, 31.1 mmol) was added at 110 °C under a nitrogen atmosphere. After stirring at 110 °C for 4 hr, the reaction mixture was poured into water and extracted with EtOAc (200 mL x 3). The combined organic extracts were dried with anhydrous Na₂SO₄ and concentrated. The residue was purified by silica gel column to give **6a-1** (1.6 g, 89%) as a yellow solid. MS (ESI): calcd. for C₂₆H₃₀F₆N₂O₅S: 582.1; Found:
- 20 583.2 [M + 1]⁺.

- Step 2. Synthesis of (R)-3-(((R)-3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)-2-methylpropanoic acid (Example 6a).** To a solution of **6a-1** (1.6 g, 2.7 mmol) in THF (40 mL)/H₂O (10 mL) was added LiOH (660 mg, 27.5 mmol). After stirring at rt for 4 hr, the reaction was poured into water. The mixture was adjusted to pH = 3 with 3 N aq. HCl
- 25

solution and the resulting mixture was extracted with EA (100 mL x 3). The combined organic extracts were dried with anhydrous Na₂SO₄ and concentrated. The residue was purified by prep-HPLC to give **Example 6a** (600 mg, 40%) as a white solid. MS (ESI): calcd. for C₂₄H₂₆F₆N₂O₅S: 568.1; Found: 569.2 [M + 1]⁺. ¹H NMR (400 MHz, CD₃OD): δ 7.63 (s, 1H), 7.41(s, 1H), 6.98 – 6.94 (m, 2H), 6.77 – 6.76 (m, 2H), 4.36 – 4.32 (m, 1H), 4.26 – 4.23 (m, 1H), 4.08 – 4.04 (m, 1H), 4.02 – 3.89 (m, 1H), 3.48 – 3.46 (m, 1H), 2.98 – 2.85 (m, 1H), 2.64 (s, 3H), 2.07-1.93 (m, 2H), 1.81 – 1.76 (m, 2H), 1.61 (t, J = 18.4 Hz, 3H), 1.32 (d, J = 7.2 Hz, 3H) ppm.

- 10 **Example 6b.** (S)-3-(((R)-3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)-2-methylpropanoic acid



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Following the same procedure for preparing **Example 6a** by replacing methyl (R)-3-hydroxy-2-methylpropanoate with its enantiomer methyl (S)-3-hydroxy-2-methylpropanoate,

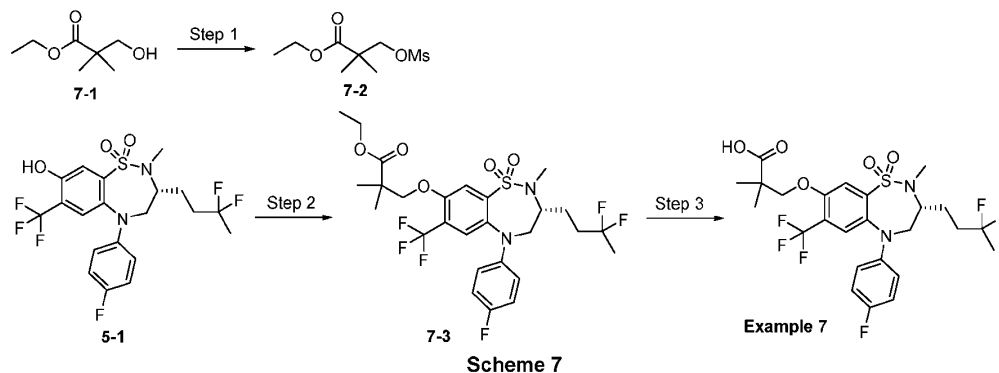
Example 6b was obtained as a white solid. MS (ESI): calcd. for C₂₄H₂₆F₆N₂O₅S: 568.1;

Found: 569.2 [M + 1]⁺. ¹H NMR (400 MHz, CD₃OD): δ 7.67 (s, 1H), 7.56(s, 1H), 7.19 - 7.13

- 20 (m, 1H), 6.51 - 6.47 (m, 1H), 6.42 - 6.34 (m, 2H), 4.40 - 4.36 (m, 1H), 4.30 - 4.26 (m, 1H), 4.10 - 4.02 (m, 2H), 3.47 - 3.33 (m, 1H), 2.98 - 2.93 (m, 1H), 2.59 (s, 3H), 2.10 - 1.96 (m, 2H), 1.88 - 1.78 (m, 2H), 1.62 (t, J = 18.4 Hz, 3H), 1.32 (d, J = 7.2 Hz, 3H) ppm.

Example 7. (R)-3-((3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-2-methyl-1,1-dioxido-7-

- 25 (trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid

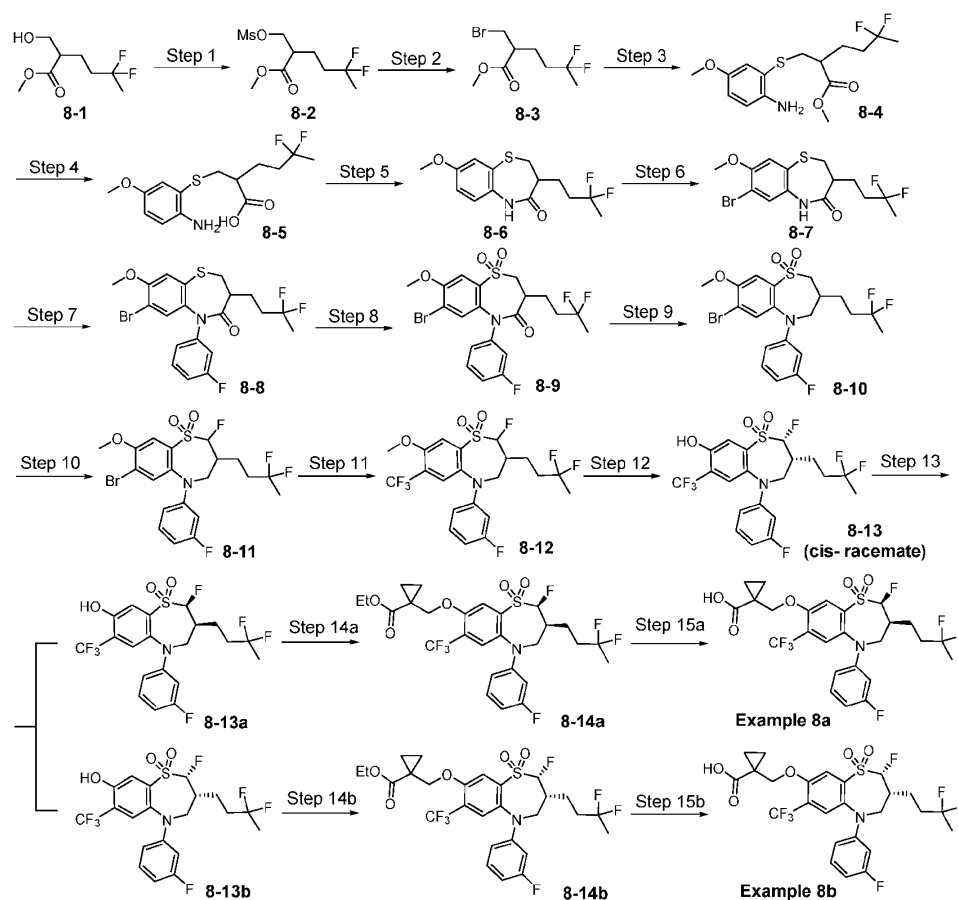


Step 1. Synthesis of ethyl 2,2-dimethyl-3-((methanesulfonyl)oxy)propanoate (7-2). To a solution of ethyl 3-hydroxy-2,2-dimethylpropanoate (**7-1**) (1.5 g, 10.26 mmol) in DCM (30 mL) was added TEA (2.08 g, 20.56 mmol), followed by methanesulfonic anhydride (2.68 g, 15.39 mmol) was added at 0 °C. After stirring at rt for 2 hr, the reaction mixture was diluted with H₂O (80 mL) and extracted with DCM (30 mL x 2). The combined organic extracts were dried with anhydrous Na₂SO₄ and concentrated. The residue was dried in vacuo to give crude **7-2** (2.8 g, 100%, crude) as a pale-yellow oil, which was used in the next step without purification, MS (ESI): calcd. for C₈H₁₆O₅S: 224.1; Found: 242.2 [M + 18]⁺.

Step 2. Synthesis of (R)-ethyl 3-((3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)-2,2-dimethylpropanoate (7-3). To a solution of **5-1** (1.5 g, 3.1 mmol) in DMF (10 mL) were sequentially added K₂CO₃ (1.29 g, 9.33 mmol) and **7-2** (1.4 g, 6.2 mmol, crude). After stirring at 110 °C for 48 hr, the reaction was diluted with H₂O (80 mL) and extracted with EA (50 mL x 3). The combined organic extracts were washed with sat. aq. LiCl solution (100 mL) and brine, dried with anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/PE = 0% to 40% (v/v)) to give **7-3** (1.8 g, 95 %) as a yellow solid. MS (ESI): calcd. for C₂₇H₃₂F₆N₂O₅S: 610.2; Found: 611.0 [M + 1]⁺.

Step 3. Synthesis of (R)-3-((3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid (Example 7). A solution of **7-3** (1.8 g, 2.95 mmol) in CH₃OH/THF/H₂O (8 mL/8 mL/8 mL) was added LiOH·H₂O (1.24 g, 29.55 mmol). After
5 stirring at 35 °C for 3 hr, the reaction mixture was diluted with H₂O (100 mL), adjusted to pH = 2 with 2 N aq. HCl solution, and extracted with EtOAc (60 mL x 3). The combined organic extracts were dried with anhydrous Na₂SO₄ and concentrated. The residue was purified by reversed column (CH₃CN/H₂O = 40% (v/v)) to give **Example 7** (740 mg, 43%) as a white solid. MS (ESI): calcd. for C₂₅H₂₈F₆N₂O₅S: 582.2; Found: 582.8 [M + 1]⁺. ¹H NMR (400
10 MHz, CD₃OD): δ 7.61 (s, 1H), 7.42 (s, 1H), 6.96 (t, J = 8.8 Hz, 2H), 6.77 – 6.76 (m, 2H), 4.18 (s, 2H), 4.09 – 3.88 (m, 2H), 3.47 – 3.46 (m, 1H), 2.64 (s, 3H), 2.07 – 1.90 (m, 2H), 1.80 – 1.78 (m, 2H), 1.61 (t, J = 18.4 Hz, 3H), 1.33 (s, 6H) ppm.

Examples 8a and 8b. 1-(((2R,3S)-3-(3,3-difluorobutyl)-2-fluoro-5-(3-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid (8a) and 1-(((2S,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(3-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid (8b)



Scheme 8

Step 1. Synthesis of methyl 5,5-difluoro-2-((methylsulfonyl)oxy)methyl)hexanoate (8-2).

To a stirred solution of methyl 5,5-difluoro-2-((hydroxymethyl)hexanoate (**8-1**) (100 g, 509.70 mmol) and TEA (154.73 g, 1529.10 mmol) in DCM (1000 mL) was added MsCl (70.06 g, 611.64 mmol) dropwise at 0°C. After stirring at rt for 2 hr, the reaction mixture was added H₂O (500 mL) at 0°C. The resulting mixture was extracted with DCM (1000 mL x 2). The combined organic extracts were washed with brine (1000 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give **8-2** (110 g, 79%) as a brown liquid, which was used for the next step without further purification.

Step 2. Synthesis of methyl 2-((bromomethyl)-5,5-difluorohexanoate (8-3). To a stirred solution of **8-2** (110 g, 401.05 mmol) in acetone (500 mL) was added lithium bromide (104.48 g, 1203.15 mmol) in portions at rt. After stirring at 60 °C for 3 hr, the mixture was allowed to cool down to rt and added H₂O (200 mL) at rt. The resulting mixture was
5 extracted with EA (300 mL x 2). The combined organic extracts were washed with brine (300 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give **8-3** (100 g, 96%) as a brown liquid, which was used in the next step without further purification. ¹H NMR (300 MHz, CDCl₃): δ 3.77 (s, 3H), 3.56 (qd, J = 10.2, 6.4 Hz, 2H), 2.94 – 2.81 (m, 1H), 2.02 – 1.80 (m, 4H), 1.62 (t, J = 18.4 Hz, 3H) ppm.

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Step 3. Synthesis of methyl 2-(((2-amino-5-methoxyphenyl)thio)methyl)-5,5-difluorohexanoate (8-4). To a stirred solution of 2-amino-5-methoxybenzenethiol (60 g, 386.55 mmol) and Cs₂CO₃ (151.60 g, 463.85 mmol) in ACN (500 mL) was added **8-3** (100.15 g, 386.56 mmol) dropwise at rt. After stirring at rt for 4 hr, the reaction mixture was
15 added water (50 mL) at rt. The resulting mixture was extracted with EA (500 mL x 2). The combined organic extracts were washed with brine (500 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography eluted with PE/EA = 4/1 (v/v) to give **8-4** (80 g, 62%) as a brown liquid. MS (ESI): calcd. for C₁₅H₂₁F₂NO₃S: 333.1; Found: 334.1 [M + 1]⁺.

20

Step 4. Synthesis of 2-(((2-amino-5-methoxyphenyl)thio)methyl)-5,5-difluorohexanoic acid (8-5). To a stirred solution of **8-4** (94 g, 281.95 mmol) in dioxane (800 mL) and H₂O (200 mL) was added LiOH (20.26 g, 845.87 mmol) at rt. The resulting mixture was stirred at rt for 2 hr. The mixture was acidified with 2 N aq. HCl solution to pH ~ 6. The resulting
25 mixture was extracted with EA (100 mL x 2). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na₂SO₄, and concentrated. This residue was dried in vacuo to give **8-5** (80 g, 89%) as a brown solid, which was used in the next step without further purification. MS (ESI): calcd. for C₁₄H₁₉F₂NO₃S: 319.1; Found: 320.1 [M + 1]⁺.

Step 5. Synthesis of 3-(3,3-difluorobutyl)-8-methoxy-2,3-dihydrobenzo[b][1,4]thiazepin-

4(5H)-one (8-6). To a stirred solution of **8-5** (80 g, 250.49 mmol) and HATU (104.77 g, 275.54 mmol) in DCM (1000 mL) was added DIEA (38.85 g, 300.59 mmol) dropwise at rt. The reaction mixture was stirred at rt for 2 hr and then added H₂O (50 mL). The resulting mixture was extracted with DCM (50 mL x 2). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography eluted with PE/EA = 7/3 (v/v) to give **8-6** (67 g, 89%) as a yellow solid. MS (ESI): calcd. for C₁₄H₁₇F₂NO₂S: 301.1; Found: 302.1 [M + 1]⁺.

Step 6. Synthesis of 7-bromo-3-(3,3-difluorobutyl)-8-methoxy-2,3-

dihydrobenzo[b][1,4]thiazepin-4(5H)-one (8-7). To a stirred solution of **8-6** (32 g, 106.18 mmol) in DCM (200 mL) and ACN (200 mL) was added NBS (20.79 g, 116.80 mmol) in portions at rt. The resulting mixture was stirred at rt for 4 hr and then added H₂O (100 mL) at rt. The resulting mixture was extracted with DCM (200 mL x 2). The combined organic extracts were washed with brine (200 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by trituration with PE/EA = 1/1 (v/v) (300 mL). The precipitated solid was collected by filtration, washed with PE/EA = 1/1 (v/v) (100 mL), and dried in vacuo to give **8-7** (22 g, 54%) as a white solid. MS (ESI): calcd. for C₁₄H₁₆BrF₂NO₂S: 379.0; Found: 380.0 [M + 1]⁺. ¹H NMR (300 MHz, CDCl₃): δ 7.39 (s, 1H), 7.34 (s, 1H), 7.14 (s, 1H), 3.94 (s, 3H), 3.53 (dd, *J* = 11.3, 6.0 Hz, 1H), 3.02 (t, *J* = 11.9 Hz, 1H), 2.68 (ddd, *J* = 16.4, 9.3, 5.2 Hz, 1H), 2.17 – 2.00 (m, 1H), 2.04 – 1.70 (m, 1H), 1.68 – 1.47 (m, 5H) ppm.

Step 7. Synthesis of 7-bromo-3-(3,3-difluorobutyl)-5-(3-fluorophenyl)-8-methoxy-2,3-

dihydrobenzo[b][1,4]thiazepin-4(5H)-one (8-8). To a solution of **8-7** (3 g, 7.89 mmol) in DMF (30 mL) were added 1-fluoro-3-iodobenzene (1.75 g, 7.89 mmol), CuI (1.50 g, 7.89 mmol) and K₂CO₃ (3.27 g, 23.67 mmol) at rt under nitrogen atmosphere. The resulting mixture was stirred at 130 °C for 16 hr and then cooled to rt and added water (100 mL). The resulting mixture was extracted with EtOAc (30 mL x 3). The combined organic extracts were washed with brine (30 mL x 3), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography eluted

with PE/EA = 3/1 (v/v) to give **8-8** (3 g, 80%) as a yellow solid. MS (ESI): calcd. for $C_{20}H_{19}BrF_3NO_2S$: 473.0; Found: 474.0 $[M + 1]^+$.

Step 8. Synthesis of 7-bromo-3-(3,3-difluorobutyl)-5-(3-fluorophenyl)-8-methoxy-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one 1,1-dioxide (8-9). A solution of **8-8** (3 g, 6.33 mmol) in THF (40 mL) and H₂O (20 mL) was added Oxone® (63.81 g, 379.500 mmol) at rt. After stirring at rt for 16 hr, the mixture was filtered, and the filtered cake was washed with ethyl acetate (25 mL x 3). The filtrate was concentrated, and the residue was diluted with sat. aq. NaHCO₃ solution (25 mL) and EtOAc (150 mL). The separated organic layer was washed with sat. aq. NaHCO₃ solution and brine, dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give **8-9** (2.5 g, 78%) as a yellow solid, which was used in the next step without further purification. MS (ESI): calcd. for $C_{20}H_{19}BrF_3NO_4S$: 505.0; Found: 506.0 $[M + 1]^+$.

Step 9. Synthesis of 7-bromo-3-(3,3-difluorobutyl)-5-(3-fluorophenyl)-8-methoxy-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (8-10). To a solution of **8-9** (2.5 g, 4.94 mmol) in THF (30 mL) was added 1 M BH₃-Me₂S in THF (2.81 mL, 29.622 mmol) at rt. After stirring at 75 °C for 16 hr, the mixture was cooled to 0 °C, added ice water (30 mL), and concentrated to remove organic solvent. The resulting mixture was extracted with EtOAc (30 mL x 3). The combined organic extracts were washed with brine (10 mL x 3), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography eluted with PE/EA = 5/1 (v/v) to give **8-10** (1.6 g, 67%) as a yellow solid. MS (ESI): calcd. for $C_{20}H_{21}BrF_3NO_3S$: 491.0; Found: 492.0 $[M + 1]^+$.

Step 10. Synthesis of 7-bromo-3-(3,3-difluorobutyl)-2-fluoro-5-(3-fluorophenyl)-8-methoxy-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (8-11). To a solution of **8-10** (1.6 g, 3.25 mmol) in THF (20 mL) was added LiHMDS (6.5 mL, 1 mol/L in THF) dropwise at -78 °C. After stirring at -78 °C for 30 min, NFSI (1.23 g, 3.90 mmol) dropwise at -78 °C. The resulting mixture was stirred at -78 °C for an additional 2 hr. The reaction mixture was added sat. aq. NH₄Cl solution at rt and then concentrated to remove

organic solvent. The resulting mixture was diluted with water (25 mL) and extracted with EtOAc (25 mL x 3). The combined organic extracts were washed with brine (10 mL x 3), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography eluted with PE/EA = 5/1 (v/v) to give **8-11** (1 g, 60%) as
5 a yellow solid. MS (ESI): calcd. for C₂₀H₂₀BrF₄NO₃S: 509.0; Found: 510.0 [M + 1]⁺.

Step 11. Synthesis of 3-(3,3-difluorobutyl)-2-fluoro-5-(3-fluorophenyl)-8-methoxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (8-12). To a solution of **8-11** (400 mg, 0.78 mmol) in DMF (5 mL) were added methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (602.30 mg, 3.14 mmol) and CuBr (224.87 mg, 1.57 mmol) at rt under
10 nitrogen atmosphere. The resulting mixture was stirred at 120 °C for 16 hr and then added water (15 mL) at rt. The resulting mixture was extracted with EtOAc (10 mL x 3). The combined organic extracts were washed with brine (10 mL x 3), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by prep-TLC (PE/EA = 3/1
15 (v/v)) to give **8-12** (200 mg, 51%) as a yellow solid. MS (ESI): calcd. for C₂₁H₂₀F₇NO₃S: 499.1; Found: 500.1 [M + 1]⁺.

Step 12. Synthesis of rac-(2R,3S)-3-(3,3-difluorobutyl)-2-fluoro-5-(3-fluorophenyl)-8-hydroxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (8-13). To a solution of **8-12** (200 mg, 0.40 mmol) in DMSO (5 mL) was added lithium chloride (509.25 mg, 12.00 mmol) at rt. The resulting mixture was stirred at 140 °C for 8 hr and then
20 added water (15 mL) at rt. The mixture was acidified with sat. aq. citric acid solution to pH ~ 5. The resulting mixture was extracted with EtOAc (15 mL x 3). The combined organic extracts were washed with brine (10 mL x 3), dried over anhydrous Na₂SO₄, and
25 concentrated. The residue was purified by prep-TLC (PE/EA = 3/1 (v/v)) to give the cis-racemic **8-13** (50 mg, 26%) as a yellow solid. MS (ESI): calcd. for C₂₀H₁₈F₇NO₃S: 485.1; Found: 486.2 [M + 1]⁺.

Step 13. Synthesis of (2R,3S)-3-(3,3-difluorobutyl)-2-fluoro-5-(3-fluorophenyl)-8-hydroxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (8-
30

13a) and (2S,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(3-fluorophenyl)-8-hydroxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (8-13b). The racemic **8-13** (40 mg) was separated by prep-SFC with the following condition: Column: (R, R)-WHELK-O1-Kromasil, 3*25 cm, 5 μ m; Mobile Phase A: CO₂; Gradient: isocratic 20 %
5 B; RT1(min) = 2.6 (**8-13a** as a single diastereomer, the stereochemistry was arbitrarily assigned); RT2(min) = 3.6 (**8-13b** as a single diastereomer, the stereochemistry was arbitrarily assigned); Sample Solvent: MeOH-HPLC; Injection Volume: 4 mL) to give **8-13a** (15 mg) as light yellow solid and **8-13b** (15 mg) as light yellow solid. MS (ESI): calcd. for C₂₀H₁₈F₇NO₃S: 485.1; Found: 486.2 [M + 1]⁺.

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Step 14a. Synthesis of ethyl 1-(((2R,3S)-3-(3,3-difluorobutyl)-2-fluoro-5-(3-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylate (8-14a). To a solution of **8-13a** (15 mg, 0.03 mmol) in DMF (2 mL) were added ethyl 1-(bromomethyl)cyclopropane-1-carboxylate (9.20
15 mg, 0.045 mmol) and CsCO₃ (20.40 mg, 0.06 mmol) at rt. After stirring at 80 °C for 2 hr, the reaction mixture was cooled to rt, added water (15 mL), and extracted with EtOAc (10 mL x 3). The combined organic extracts were washed with brine (10 mL x 3), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by prep-TLC (PE/EA = 3/1 (v/v)) to give **8-14a** (16 mg, 79%) as a yellow solid (single diastereomer, the stereochemistry
20 was arbitrarily assigned). MS (ESI): calcd. for C₂₇H₂₈F₇NO₅S: 611.2; Found: 612.1 [M + 1]⁺.

Step 15a. Synthesis of 1-(((2R,3S)-3-(3,3-difluorobutyl)-2-fluoro-5-(3-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid (Example 8a). To a solution of **8-14a** (16
25 mg, 0.025mmol) in 1,4-dioxane (4 mL) were added LiOH (35.25 mg, 1.47 mmol) and H₂O (1 mL) at rt. After stirring at rt for 16 hr, the reaction mixture was diluted with water (10 mL) and concentrated to remove organic solvent. The residue was acidified with sat. aq. citric acid solution to pH ~ 5 and extracted with EtOAc (10 mL x 3). The combined organic extracts
30 were washed with brine (10 mL x 2), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by prep-HPLC with the following condition: Column: SunFire Prep C18

OBD Column, 19*150 mm, 5 μ m; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN;
Flow rate: 30 mL/min; Gradient: 50% B to 78% B in 8 min; Wavelength: 220 nm, 254 nm;
RT1 (min) = 6.38 to give **Example 8a** (10 mg, 69%) as a white solid (single diastereomer,
the stereochemistry was arbitrarily assigned). MS (ESI): calcd. for C₂₅H₂₄F₇NO₅S: 583.1;
5 Found: 584.2 [M + 1]⁺. ¹H NMR (300 MHz, CD₃OD): δ 7.82 (s, 1H), 7.64 (s, 1H), 7.22 –
7.15 (m, 1H), 6.52 – 6.50 (m, 1H), 6.47 – 6.39 (m, 1H), 6.32 (d, *J* = 12.0 Hz, 1H), 5.69 (d, *J*
= 45.6 Hz, 1H), 4.43 (s, 2H), 4.19 (d, *J* = 14.4 Hz, 1H), 3.24 (s, 1H), 2.86 – 2.65 (m, 1H),
2.22 – 2.08 (m, 2H), 1.78 – 1.71 (m, 2H), 1.65 (t, *J* = 18.6 Hz, 3H), 1.33 (s, 2H), 1.13 (s, 2H)
ppm.

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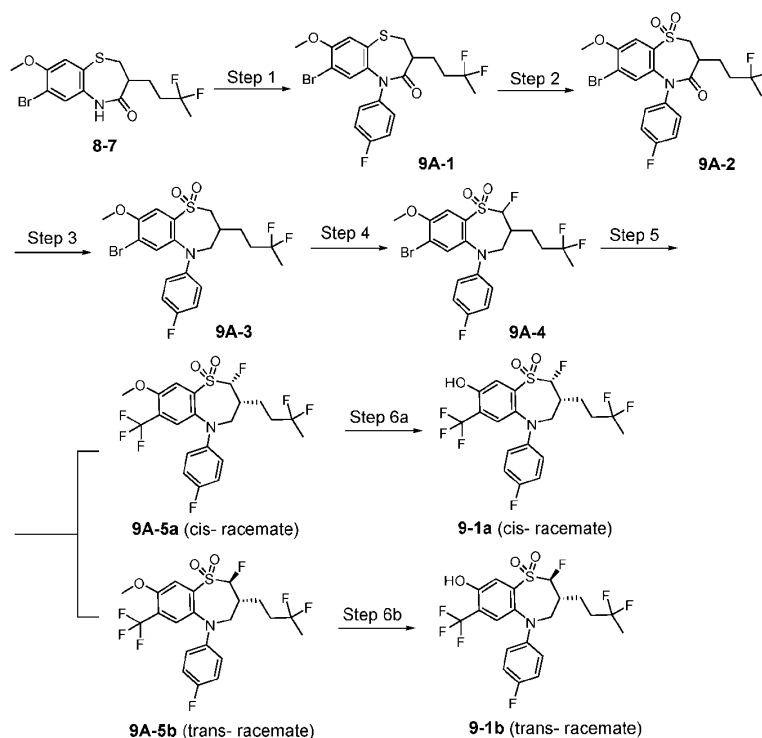
Step 14b. Synthesis of ethyl 1-(((2S,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(3-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylate (8-14b). Following the same procedure as
described for preparing **8-14a** by replacing **8-13a** with **8-13b** (15 mg, 0.03 mmol), **8-14b** (15
15 mg, 79 %) was obtained as a yellow solid (single diastereomer, the stereochemistry was
arbitrarily assigned). MS (ESI): calcd. for C₂₇H₂₈F₇NO₅S: 611.2; Found: 612.1 [M + 1]⁺.

Step 15b. Synthesis of 1-(((2S,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(3-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-

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yl)oxy)methyl)cyclopropane-1-carboxylic acid (Example 8b). Following the same
procedure as described for preparing **Example 8a** by replacing **8-14a** with **8-14b** (16 mg,
0.025 mmol), **Example 8b** (10 mg, 69%) as a white solid (single diastereomer, the
stereochemistry was arbitrarily assigned). Prep-HPLC condition: Column: SunFire Prep C18
OBD Column, 19*150 mm, 5 μ m; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN;
25 Flow rate: 30 mL/min; Gradient: 55% B to 75% B in 8 min; Wavelength: 220 nm, 254 nm;
RT1 (min) = 5.92. MS (ESI): calcd. for: C₂₅H₂₄F₇NO₅S: 583.1; Found: 584.2 [M + 1]⁺. ¹H
NMR (300 MHz, CD₃OD): δ 7.82 (s, 1H), 7.64 (s, 1H), 7.20 – 7.15 (m, 1H), 6.53 – 6.50 (m,
1H), 6.47 (d, *J* = 2.1 Hz, 1H), 6.42 – 6.31 (m, 1H), 5.69 (d, *J* = 45.0 Hz, 1H), 4.43 (s, 2H),
4.18 (d, *J* = 15.6 Hz, 1H), 3.26 (s, 1H), 2.86 – 2.65 (m, 1H), 2.19 – 2.11 (m, 2H), 1.78 – 1.71
30 (m, 2H), 1.66 (t, *J* = 6.9 Hz, 3H), 1.35 (s, 2H), 1.12 (s, 2H) ppm.

Synthesis of rac-(2S,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-8-hydroxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (9-1) and rac-(2R,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-8-hydroxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (9-1b)



Step 1. Synthesis of 7-bromo-3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-8-methoxy-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (9A-1). A solution of 7-bromo-3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-8-methoxy-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (**8-7**) (20 g, 52.60 mmol), (4-fluorophenyl)boronic acid (14.72 g, 105.19 mmol), and Et₃N (15.97 g, 0.16 mol) in DMF (300 mL) was treated with Cu(OAc)₂ (14.33 g, 78.90 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h under oxygen atmosphere. The mixture was allowed to cool down to room temperature and diluted with EtOAc (300 mL) and sat. aq. NH₄Cl solution (900 mL). The resulting solution was extracted with EtOAc (300 mL x 3).

The combined organic layers were washed with water (300 mL x 3) and brine (300 mL), dried over anhydrous Na₂SO₄, and concentrated. This residue was dried in vacuo to give crude **9A-1** (25 g) as a black solid, which was used in the next step without purification. MS (ESI): calcd. for C₂₀H₁₉BrF₃NO₂S: 473.0; Found: 473.9 [M + 1]⁺. ¹H NMR (300 MHz, CDCl₃): δ 7.22 (s, 1H), 7.19 (s, 1H), 7.18 – 7.13 (m, 2H), 7.11 – 7.04 (m, 2H), 3.96 (s, 3H), 3.51 (dd, *J* = 11.1, 6.0 Hz, 1H), 3.10 – 2.95 (m, 1H), 2.88 – 2.77 (m, 1H), 2.15 (m, 1H), 2.05 – 1.86 (m, 1H), 1.86 – 1.74 (m, 1H), 1.61 (t, *J* = 18.6 Hz, 4H) ppm.

Step 2. Synthesis of 7-bromo-3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-8-methoxy-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one 1,1-dioxide (9A-2). To a stirred solution of 7-bromo-3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-8-methoxy-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (**9A-1**) (25 g, 52.71 mmol) in THF (500 mL) and H₂O (500 mL) was added Oxone® (107 g, 0.31 mol) in portions at rt. The resulting mixture was stirred at rt for 16 h. The resulting mixture was filtered. The filtrate was concentrated to remove organic solvent, and the residue was extracted with EtOAc (100 mL x 2). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give crude **9A-2** (24 g) as a brown solid, which was used in the next step without further purification. MS (ESI): calcd. for C₂₀H₁₉BrF₃NO₄S: 505.0; Found: 506.0 [M + 1]⁺. ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.47 (s, 1H), 7.42 (s, 1H), 7.38 – 7.24 (m, 4H), 4.00 (s, 3H), 4.09 – 3.88 (m, 1H), 3.75 (dd, *J* = 13.6, 12.0 Hz, 1H), 2.99 (dd, *J* = 12.0, 5.7 Hz, 1H), 2.01 – 1.80 (m, 4H), 1.58 (t, *J* = 18.9 Hz, 3H) ppm.

Step 3. Synthesis of 7-bromo-3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-8-methoxy-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (9A-3). To a stirred solution of 7-bromo-3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-8-methoxy-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one 1,1-dioxide (**9A-2**) (24 g, 47.40 mmol) in THF (120 mL) was added 10 M BH₃•Me₂S in THF (48 mL) dropwise at rt. The resulting mixture was stirred at 60 °C for 16 hr. The reaction was quenched by the addition of H₂O (100 mL) at rt. The resulting mixture was extracted with EtOAc (200 mL x 2). The combined organic

layers were washed with brine (200 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography using PE/EA = 2/1 (v/v) as eluent to give **9A-3** (20 g, 85.7%) as a brown solid. MS (ESI): calcd. for C₂₀H₂₁BrF₃NO₃S: 491.0; Found: 492.0 [M + 1]⁺. ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.61 (s, 1H), 7.52 (s, 1H),
5 7.02 (t, *J* = 8.8 Hz, 2H), 6.64 (dd, *J* = 8.6, 4.4 Hz, 2H), 4.21 (d, *J* = 15.1 Hz, 1H), 3.98 (s, 3H), 3.60 (dd, *J* = 14.9, 3.4 Hz, 1H), 3.42 – 3.28 (m, 1H), 3.16 (s, 1H), 2.27 (s, 1H), 2.15 – 1.93 (m, 2H), 1.70 – 1.39 (m, 5H) ppm.

Step 4. Synthesis of 7-bromo-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-8-methoxy-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (9A-4). To a solution of 7-bromo-3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-8-methoxy-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (**9A-3**) (2.5 g, 5.07 mmol) in tetrahydrofuran (50 mL) was added dropwise LiHMDS (1 mol/L in THF) (2.8 mL, 10.15 mmol) at -78 °C under N₂ atmosphere. The reaction mixture was stirred at -78 °C for 30 mins. Then a solution
15 of NFSI (1.60 g, 5.07 mmol) in tetrahydrofuran (5 mL) was added dropwise and the mixture was stirred at -78 °C for 30 mins. The reaction was quenched with sat. aq. NH₄Cl solution (50 mL), and then the mixture was extracted with EtOAc (50 mL x 2). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography using PE/EA = 3/1 (v/v) as
20 eluent to give **9A-4** (1.5 g, 57.9%) as a brown solid. MS (ESI): calcd. for C₂₀H₂₀BrF₄NO₃S: 509.0; Found: 510.0 [M + 1]⁺. ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.66 (s, 1H), 7.54 (s, 1H), 7.11 – 6.96 (m, 2H), 6.66 (m, 2H), 6.12 – 5.77 (m, 1H), 4.22 – 4.11 (m, 1H), 4.05 – 3.95 (m, 3H), 3.27 – 3.12 (m, 1H), 2.68 – 2.36 (m, 1H), 2.33 – 1.90 (m, 3H), 1.73 – 1.38 (m, 4H) ppm.

Step 5. Synthesis of rac-(2R,3S)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-8-methoxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (9A-5a) and rac-(2R,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-8-methoxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (9A-5b). To a stirred solution of rac-7-bromo-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-8-methoxy-
2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (**9A-4**) (170 g, 0.33 mol) and methyl
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2,2-difluoro-2-(fluorosulfonyl)acetate (384 g, 2 mol) in DMF (3.4 L) was added CuBr (95.57 g, 0.67 mol) in portions at rt under N₂ atmosphere. The resulting mixture was stirred at 130°C for 16 h under N₂ atmosphere. The mixture was allowed to cool down to rt. The reaction was quenched by the addition of H₂O (10 L) at rt. The resulting mixture was extracted with EA (3 L x 2). The combined organic layers were washed with brine (3 L), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography using PE/EA = 3/1 (v/v) as eluent to give **9A-5a** (60 g, 36.1%, cis- racemate) as a yellow solid and **9A-5b** (45 g, 27.1%, trans- racemate) as a yellow solid, respectively.

9A-5a: MS (ESI): calcd. for C₂₁H₂₀F₇NO₃S: 499.1; Found: 500.1 [M + 1]⁺. ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.73 (s, 1H), 7.67 (s, 1H), 7.10 – 7.02 (m, 23H), 6.71 – 6.60 (m, 2H), 6.10 (d, *J* = 44.4 Hz, 1H), 4.19 (d, *J* = 15.6 Hz, 1H), 4.06 (s, 3H), 3.22 (dd, *J* = 15.9, 11.4 Hz, 1H), 2.76 – 2.44 (m, 1H), 2.30 – 1.96 (m, 3H), 1.74 – 1.56 (m, 4H) ppm.

9A-5b: MS (ESI): calcd. for C₂₁H₂₀F₇NO₃S: 499.1; Found: 500.1 [M + 1]⁺. ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.71 (s, 1H), 7.45 (s, 1H), 7.10 (t, *J* = 8.7 Hz, 2H), 6.89 (s, 2H), 5.95 (dd, *J* = 44.1, 6.9 Hz, 1H), 4.03 (s, 3H), 4.01 – 3.59 (m, 2H), 2.45 – 2.39 (m, 1H), 2.14 – 1.89 (m, 2H), 1.86 – 1.71 (m, 1H), 1.70 – 1.55 (m, 1H), 1.49 (t, *J* = 18.9 Hz, 3H) ppm.

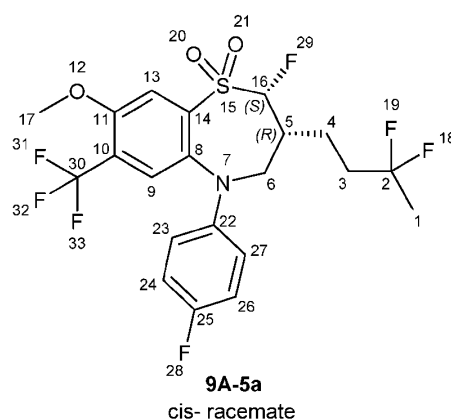
Step 6a. Synthesis of rac-(2R,3S)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-8-hydroxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (9-1a). A mixture of rac-(2R,3S)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-8-methoxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (60 g, 0.12 mol) (**9A-5a**) in DMSO (600 mL) was added LiCl (50.5 g, 1.21 mol) at room temperature. After stirring at 140°C for 16 h under nitrogen atmosphere, the mixture was cooled to room temperature and diluted with water (2000 mL). The resulting mixture was extracted with EtOAc (1000 mL x 2). The combined organic layers were washed with brine (1000 mL x 4), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography using PE/EA = 8/1 (v/v) as eluent to give **9-1a** (43 g, 73.7%, cis- racemate) as a yellow oil. MS (ESI): calcd. for C₂₀H₁₈F₇NO₃S: 485.1; Found: 486.3 [M + 1]⁺. ¹H NMR (300 MHz, DMSO-*d*₆): δ 11.68 (s, 1H), 7.70 (s, 1H), 7.56 (s, 1H), 7.03 (t, *J* = 9.0 Hz, 2H), 6.62 (dd, *J* = 9.3, 4.5 Hz, 2H), 6.03 (d, *J* = 44.4 Hz, 1H), 4.15 (d, *J* = 15.9 Hz, 1H),

3.20 (dd, $J = 15.9, 11.4$ Hz, 1H), 2.69 – 2.60 (m, 1H), 2.22 – 2.06 (m, 2H), 1.61 (t, $J = 18.9$ Hz, 5H) ppm.

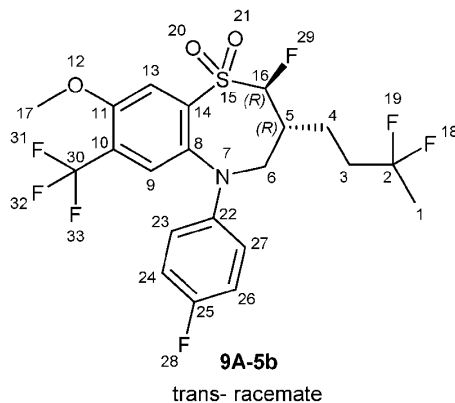
rac-(2R,3S)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-8-hydroxy-7-(trifluoromethyl)-
5 2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (**9-1a**) was separated by SFC (Column:
(R,R)-WHELK-O1, 50*4.6 mm, 3.5 μ m; Co-eluent: MeOH; Gradient (B%): 10% to 50% in
2.0 min, hold 50% for 1.0 min; Back pressure (bar): 150; Flow (mL/min): 3.0; Column
temperature ($^{\circ}$ C): 35; UV detection wavelength: 220 nm) to give (2S,3R)-3-(3,3-
difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-8-hydroxy-7-(trifluoromethyl)-2,3,4,5-
10 tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (**154-4**) ($t_R = 0.43$ min; single diastereomer) as
a white solid; and (2R,3S)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-8-hydroxy-7-
(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide ($t_R = 0.69$ min; single
diastereomer) as a white solid, respectively.

15 **Step 6b. Synthesis of rac-(2R,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-8-
hydroxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (9-
1b).** A mixture of rac-(2R,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-8-methoxy-
7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (**9A-5b**) (45 g,
90.10 mmol) DMSO (450 mL) was added LiCl (38.19 g, 0.90 mol) at room
20 temperature. After stirring at 140 $^{\circ}$ C for 16 h under nitrogen atmosphere, the mixture was
cooled to room temperature and diluted with water (2000 mL). The resulting mixture was
extracted with EtOAc (1000 mL x 2). The combined organic layers were washed
with brine (1000 mL x 4), dried over anhydrous Na₂SO₄, and concentrated. The residue was
purified by silica gel column chromatography using PE/EA = 8/1 (v/v) as eluent to give **9-1b**
25 (30 g, 68.6%) as a yellow oil. MS (ESI): calcd. for C₂₀H₁₈F₇NO₃S: 485.1; Found: 486.2 [M +
1]⁺. ¹H NMR (300 MHz, DMSO-*d*₆): δ 11.53 (s, 1H), 7.68 (s, 1H), 7.38 (s, 1H), 7.06 (t, $J =$
8.7 Hz, 2H), 6.86 – 6.76 (m, 2H), 5.88 (dd, $J = 44.4, 7.8$ Hz, 1H), 3.82 (s, 2H), 2.42 (s, 1H),
2.15 – 1.84 (m, 2H), 1.84 – 1.70 (m, 1H), 1.69 – 1.60 (m, 1H), 1.52 (t, $J = 18.9$ Hz, 3H) ppm.

- Relative stereochemistry determination of rac-(2R,3S)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-8-methoxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (9A-5a) and rac-(2R,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-8-methoxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (9A-5b). ¹H, ¹³C, ¹⁹F, H-H COSY, C-H HSQC, C-H HMBC, H-H NOESY, and F-H NOESY NMR techniques were employed to elucidate the relative stereochemistry of the cis- racemate 9A-5a and the corresponding trans- racemate 9A-5b.



- ¹H NMR (400 MHz, CDCl₃): δ 7.75 (s, 1H, H13), 7.53 (s, 1H, H9), 7.04 – 6.93 (m, 2H, H24&H26), 6.70 – 6.60 (m, 2H, H23&H27), 5.32 (d, J = 60.0, 1H, H16), 4.12 – 4.00 (m, 1H, H6'), 4.05 (s, 3H, H17), 3.34 (dd, J = 15.8, 11.2 Hz, 1H, H6''), 2.87 – 2.67 (m, 1H, H5), 2.13 – 1.97 (m, 2H, H3), 1.84 – 1.57 (m, 2H, H4), 1.68 (t, J = 18.4 Hz, 3H, H1) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 157.15 (d, J = 240.0 Hz, C25), 155.68 (C11), 141.84 (d, J = 2.0 Hz, C22), 139.50 (14), 138.03 (C8), 129.28 (q, J = 5.0 Hz, C9), 125.64 (q, J = 32.1 Hz, C10), 123.29 (t, J = 238.7 Hz, C2), 122.11 (q, J = 273.7 Hz, C30), 116.57 (d, J = 7.6 Hz, C23&C27), 116.21 (d, J = 22.6 Hz, C24&C26), 114.07 (C13), 101.61 (d, J = 222.9 Hz, C16), 56.87 (C17), 48.50 (d, J = 2.0 Hz, C6), 37.71 (d, J = 18.6 Hz, C5), 35.00 (t, J = 26.0 Hz, C3), 23.64 (t, J = 27.7 Hz, C1), 21.78 (C4) ppm. ¹⁹F NMR (376 MHz, CDCl₃): δ -63.33 (F31, F32&F33), -91.54 (d, J = 240.0 Hz, F18), -92.55 (d, J = 240.1 Hz, F19), -124.24 (F28), -197.24 (F29) ppm. F-H NOESY NMR data suggested F29 has correlation with H4 but not with H5.

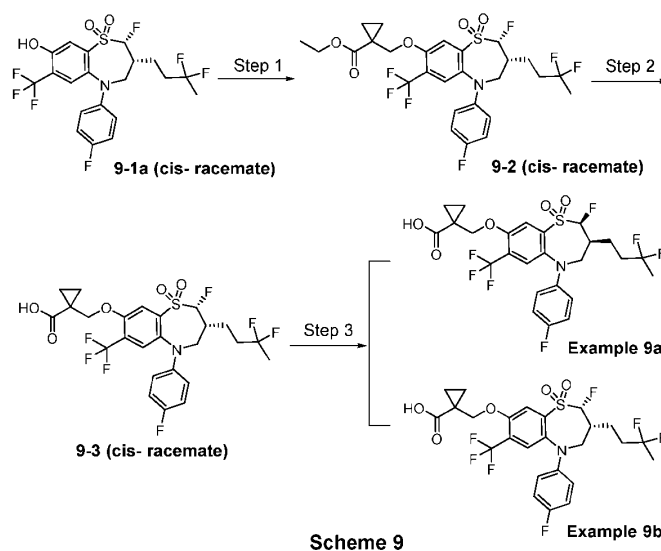


¹H NMR (400 MHz, CDCl₃): δ 7.70 (s, 1H, H13), 7.28 (s, 1H, H9), 7.08 – 6.96 (m, 4H, H23, H24, H26&H27), 5.26 (dd, J = 44.8, 5.2 Hz, 1H, H16), 4.12 (d, J = 9.6 Hz, 1H, H6'), 4.02 (s, 3H, H17), 3.63 (d, J = 15.2 Hz, 1H, 6''), 2.47 – 2.37 (m, 1H, H5), 2.03 – 1.81 (m, 4H, H3&H4), 1.47 (t, J = 18.4 Hz, 3H, H1) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 158.58 (d, J = 243.2 Hz, C25), 154.21 (C11), 143.71 (C 22), 140.51 (C8), 136.87 (C14), 126.72 (9), 125.51 (q, J = 32.1 Hz, C10), 123.63 (t, J = 238.5 Hz, C2), 122.12 (q, J = 273.8 Hz, C30), 122.00 (C23&C27), 116.52 (d, J = 22.6 Hz, C24&C26), 112.83 (C13), 101.97 (d, J = 216.1 Hz, C16), 56.78 (C17), 49.38 (C6), 41.51 (d, J = 18.7 Hz, C5), 35.31 (t, J = 25.9 Hz, C3), 23.07 (t, J = 27.6 Hz, C1), 21.12 (C4) ppm. ¹⁹F NMR (376 MHz, CDCl₃): δ -63.36 (F31, F32&F33), -90.41 (d, J = 247.8 Hz, F18), -91.48 (d, J = 238.7 Hz, F19), -119.97 (F28), -176.92 (F29) ppm. F-H NOESY NMR data suggested F29 has correlation with H5 but not with H4.

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Examples 9a and 9b. 1-((((2R,3S)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid (9a) and 1-((((2S,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid (9b)

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Scheme 9

Step 1. Synthesis of rac-ethyl 1-(((2S,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylate (9-2). To a stirred solution of **9-1a** (30 mg, 0.06 mmol), which was prepared by following the same procedure as described for preparing the racemic **8-13** and replacing 3-fluoro-iodobenzene with 4-fluoro-iodobenzene, and cesium carbonate (40.40 mg, 0.12 mmol) in DMF (2 mL) was added ethyl 1-(bromomethyl)cyclopropane-1-carboxylate (19.20 mg, 0.09 mmol) dropwise at rt. After stirring at 80 °C for 3 hr, the reaction mixture was cooled to rt, added water (10 mL), and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by prep-TLC (PE/EA = 4/1 (v/v)) to give **9-2** (30 mg, 79%) as a brown solid. MS (ESI): calcd. for C₂₇H₂₈F₇NO₅S: 611.2; Found: 500.2 [M + 1]⁺.

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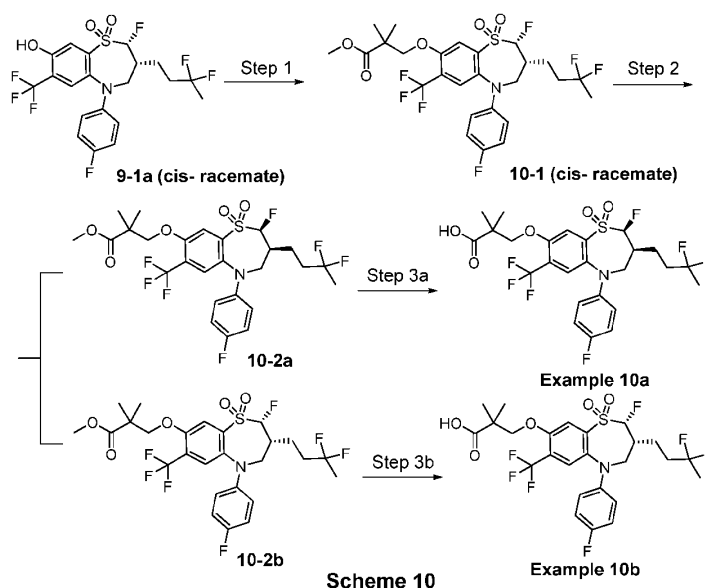
Step 2. Synthesis of rac-1-(((2S,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid (9-3). A solution of **9-2** (30 mg, 0.05 mmol) and LiOH (5.87 mg, 0.24 mmol) in 1,4-dioxane (4 mL) and H₂O (1 mL) was stirred at rt for

16 h. The mixture was acidified with 2 N aq. HCl solution to pH ~ 4. The resulting mixture was concentrated to remove organic solvent, diluted with water (10 mL), and extracted with EA (10 mL x 2). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by prep-HPLC with the following condition: Column: XBridge Shield RP18 OBD Column, 19*250 mm, 10µm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 55% B to 78% B in 8 min, 78% B; Wavelength: 220 nm, 254 nm; RT1 (min) = 5.26 to give **9-3** (15 mg) as a white solid.

Step 3. Synthesis of 1-(((2R,3S)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid (Example 9a) and 1-(((2S,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid (Example 9b). The racemic **9-3** (15 mg) was purified by prep-SFC with the following condition: (Column: CHIRAL ART Cellulose-SC, 3*25 cm, 5 µm; Mobile Phase A: CO₂, Mobile Phase B: MeOH; Flow rate: 80 mL/min; Gradient: isocratic 25% B; Wavelength: 220 nm; RT1 (min) = 3.0; RT2 (min) = 3.5; Sample Solvent: MeOH: CAN = 2: 1 (v/v); Injection Volume: 2 mL to give **Example 9a** (single diastereomer, the stereochemistry was arbitrarily assigned) (4.1 mg) as a white solid. MS (ESI): calcd. for C₂₅H₂₄F₇NO₅S: 583.1; Found: 584.2 [M + 1]⁺. ¹H NMR (300 MHz, CD₃OD): δ 7.80 (s, 1H), 7.54 (s, 1H), 6.96 (t, J = 9.0 Hz, 2H), 6.71 – 6.66 (m, 2H), 5.67 (d, J = 45.3 Hz, 1H), 4.42 (s, 2H), 4.18 (d, J = 15.0 Hz, 1H), 3.27 – 3.21 (m, 1H), 2.77 – 2.63 (m, 1H), 2.21 – 2.03 (m, 2H), 1.79 – 1.57 (m, 5H), 1.31 (s, 2H), 1.07 (s, 2H) ppm; and **Example 9b** (single diastereomer, the stereochemistry was arbitrarily assigned) (2.2 mg) as a white solid. MS (ESI): calcd. for C₂₅H₂₄F₇NO₅S: 583.1; Found: 584.2 [M + 1]⁺. ¹H NMR (300 MHz, CD₃OD): δ 7.83 (s, 1H), 7.55 (s, 1H), 6.98 (t, J = 8.7 Hz, 2H), 6.73 – 6.69 (m, 2H), 5.68 (d, J = 45.3 Hz, 1H), 4.45 (s, 2H), 4.20 (d, J = 15.6 Hz, 1H), 3.32 – 3.26 (m, 1H), 2.82 – 2.65 (m, 1H), 2.24 – 2.07 (m, 2H), 1.79 – 1.59 (m, 5H), 1.31 (s, 2H), 1.06 (s, 2H) ppm.

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Examples 10a and 10b. 3-(((2R,3S)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid (10a) and 3-(((2S,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid (10b)



Scheme 10

Step 1. Synthesis of rac- methyl 3-(((2S,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoate (10-1). To a stirred solution of rac-(2S,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-8-hydroxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (9-1a) (1.20 g, 2.47 mmol) and Cs₂CO₃ (2.42 g, 7.41 mmol) in DMF(50 mL) were added KI (1.23 g, 7.41 mmol) and methyl 2,2-dimethyl-3-((methylsulfonyl)oxy)propanoate (1.04 g, 4.94 mmol) dropwise at rt. The resulting mixture was stirred at 100°C for 16 h. The mixture was allowed to cool down to rt. The reaction was quenched by the addition of H₂O (150 mL) at rt. The resulting mixture was extracted with EA (50 mL x 2). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column

chromatography, eluted with PE/EtOAc = 2/1 (v/v) to give **10-1** (800 mg, 54.0%) as a brown solid. MS (ESI): calcd. for C₂₆H₂₈F₇NO₅S: 599.2; Found: 600.2 [M + 1]⁺.

Step 2. Synthesis of methyl 3-(((2R,3S)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoate (10-2a) and methyl 3-(((2S,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoate (10-2b). The product rac-methyl 3-(((2S,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoate (800 mg) was purified by Prep-SFC with the following conditions: Column: (R, R)-WHELK-O, 3*25 cm, 5 μm; Mobile Phase A: CO₂, Mobile Phase B: MeOH; Flow rate: 80 mL/min; Gradient: isocratic 20% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 3.8; RT2(min): 6.5; Sample Solvent: MeOH; Injection Volume: 9 mL. The collected fractions were concentrated, and the residue was dried in vacuo to give **10-2a** (260 mg) (single diastereomer, the stereochemistry was arbitrarily assigned) and **10-2b** (240 mg) (single diastereomer, the stereochemistry was arbitrarily assigned) as a white solid, respectively. MS (ESI): calcd. for C₂₆H₂₈F₇NO₅S: 599.2; Found: 600.2 [M + 1]⁺.

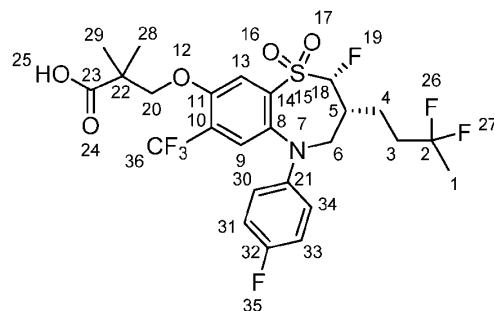
Step 3a. Synthesis of 3-(((2R,3S)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid (Example 10a). A solution of **10-2a** (260 mg, 0.43 mmol) and LiOH (31.25 mg, 1.30 mmol) in 1,4-dioxane (12 mL) and H₂O (3 mL) was stirred at rt for 16 hr. The mixture was acidified to pH = 4 with 2 N aq. HCl solution and extracted with EA (10 mL x 2). Subsequently, the combined organic extracts were washed with brine (10 mL), dried over anhydrous Na₂SO₄, and concentrated. The crude product was purified by prep-HPLC with the following conditions: Column: SunFire Prep C18 OBD 5μm 30*150mm Column; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 40% to 80 % B in 8 min; Wavelength: 254 nm/220 nm; RT1(min): 2.69. The collected solution was concentrated under vacuum to remove ACN and the resulting solution was

lyophilized to give **Example 10a** (168 mg) (single diastereomer, the stereochemistry was arbitrarily assigned) as a white solid. MS (ESI): calcd. for $C_{25}H_{26}F_7NO_5S$: 585.1; Found: 586.2 $[M + 1]^+$. 1H NMR (300 MHz, CD_3OD): δ 7.79 (s, 1H), 7.57 (s, 1H), 7.02 – 6.96 (m, 2H), 6.75 – 6.70 (m, 2H), 5.70 (d, $J = 45.3$ Hz, 1H), 4.29 – 4.18 (m, 3H), 3.38 – 3.34 (m, 1H), 2.80 – 2.69 (m, 1H), 2.20 – 2.07 (m, 2H), 1.79 – 1.57 (m, 5H), 1.37 (s, 6H) ppm.

Step 3b. Synthesis of 3-(((2S,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid (Example 10b). A solution of **10-2b** (240 mg, 0.40 mmol) and LiOH (28.85 mg, 1.20 mmol) in 1,4-dioxane (12 mL) and H_2O (3 mL) was stirred at rt for 16 h. The mixture was acidified to pH = 4 with 2 N aq. HCl solution and extracted with EA (10 mL x 2). Subsequently, the combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , and concentrated. The crude product was purified by prep-HPLC with the following conditions: Column: SunFire Prep C18 OBD $5\mu m$ 30*150 mm Column; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 40% to 80 % B in 8 min; Wavelength: 254 nm/220 nm; RT1(min): 1.87. The collected solution was concentrated under vacuum to remove ACN and the resulting solution was lyophilized to give **Example 10b** (163 mg) (single diastereomer, the stereochemistry was arbitrarily assigned) as a white solid. MS (ESI): calcd. for $C_{25}H_{26}F_7NO_5S$: 585.1; Found: 586.2 $[M + 1]^+$. 1H NMR (300 MHz, CD_3OD): δ 7.79 (s, 1H), 7.57 (s, 1H), 7.02 – 6.96 (m, 2H), 6.75 – 6.70 (m, 2H), 5.70 (d, $J = 45.3$ Hz, 1H), 4.29 – 4.18 (m, 3H), 3.38 – 3.34 (m, 1H), 2.80 – 2.66 (m, 1H), 2.20 – 2.06 (m, 2H), 1.79 – 1.57 (m, 5H), 1.37 (s, 6H) ppm.

Relative stereochemistry determination of 3-(((2S,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid (Example 10b).

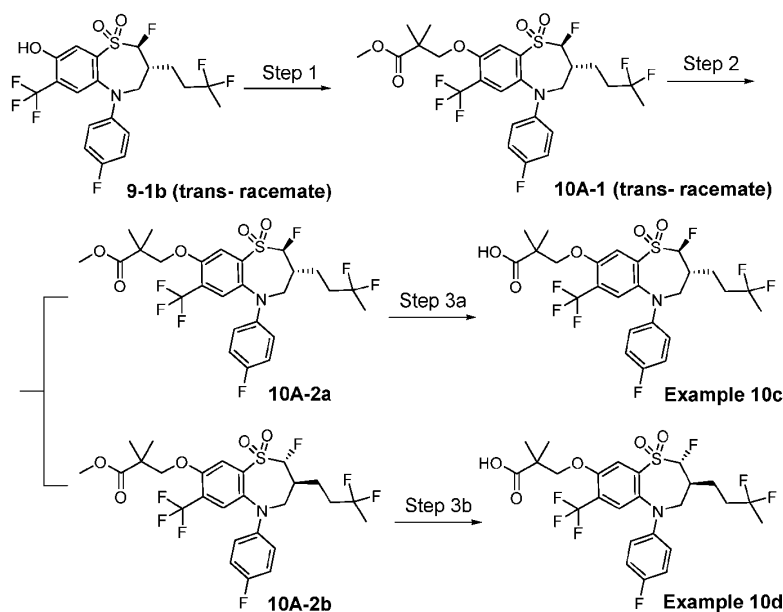
^1H , ^{13}C , ^{19}F , H-H COSY, C-H HSQC, C-H HMBC, H-H NOESY, and F-H NOESY NMR techniques were employed to elucidate the relative stereochemistry of **Example 10b**.



Example 10b
(single diastereomer)

^1H NMR (300 MHz, CD_3OD): δ 7.79 (s, 1H, H13), 7.57 (s, 1H, H9), 7.06 – 6.91 (m, 2H, H33&H31), 6.78 – 6.65 (m, 2H, H34&H30), 5.69 (d, $J = 45.2$ Hz, 1H, H18), 4.27 (d, $J = 8.6$ Hz, 1H, H20'), 4.23 (d, $J = 8.6$ Hz, 1H, H20''), 4.26 – 4.15 (m, 1H, H6'), 3.31 (dd, $J = 16.0$, 11.2 Hz, 1H, H6''), 2.82–2.62 (m, 1H, H5), 2.28 – 1.99 (m, 2H, H3), 1.81 – 1.65 (m, 2H, H4), 1.65 (t, $J = 18.5$ Hz, 3H, H1), 1.37 (s, 6H, H28&H29) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ 177.77 (C23), 156.90 (d, $J = 237.4$ Hz, C32), 154.84 (C11), 142.37 (C21), 140.35 (C14), 138.30 (C8), 129.17 (q, $J = 4.6$ Hz, C9), 124.97 (q, $J = 31.9$ Hz, C10), 123.79 (t, $J = 237.6$ Hz, C2), 127.33 – 116.85 (m, C36), 116.16 (d, $J = 7.7$ Hz, C34&C30), 115.31 (d, $J = 22.7$ Hz, C31&C33), 114.27 (C13), 101.98 (d, $J = 219.9$ Hz, C18), 75.47 (C20), 47.68 (C6), 42.65 (C22), 37.61 (d, $J = 18.5$ Hz, C5), 34.36 (t, $J = 25.9$ Hz, C3), 22.12 (t, $J = 27.7$ Hz, C1), 21.59 – 21.30 (m, C4), 21.19 (C28&C29). ^{19}F NMR (282 MHz, CD_3OD): δ -64.47 (F37, F38&F39), -92.72 (d, $J = 10.9$ Hz, F26&F27), -127.48 (F35), -199.65 (F19) ppm. F-H NOESY NMR data suggested F19 has correlation with H4 but not with H5.

Examples 10c and 10d. 3-(((2R,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid (10c) and 3-(((2S,3S)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid (10d)



Scheme 10A

- Step 1. Synthesis of rac-methyl 3-(((2R,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoate (**9-1b**).** To a stirred solution of rac-(2R,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-8-hydroxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (**9-1b**, trans-racemate) (200 mg, 0.41 mmol) and Cs_2CO_3 (402.73 mg, 1.24 mmol) in DMF (5 mL) were added KI (205.19 mg, 1.24 mmol) and methyl 2,2-dimethyl-3-((methylsulfonyl)oxy)propanoate (137.36 mg, 0.62 mmol) dropwise at room temperature. The resulting mixture was stirred for 16 h at 100 °C. The mixture was allowed to cool down to room temperature, followed by adding water to quench the reaction. The resulting mixture was extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , and concentrated. The residue was purified by Prep-TLC (PE / EA = 5 / 1 (v/v)) to give **10A-1**

(130 mg, 52.63%, trans- racemate) as a white solid. MS (ESI): calcd. for $C_{26}H_{28}F_7NO_5S$: 599.2; Found: 600.1 $[M + 1]^+$.

Step 2. Synthesis of methyl 3-(((2R,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-

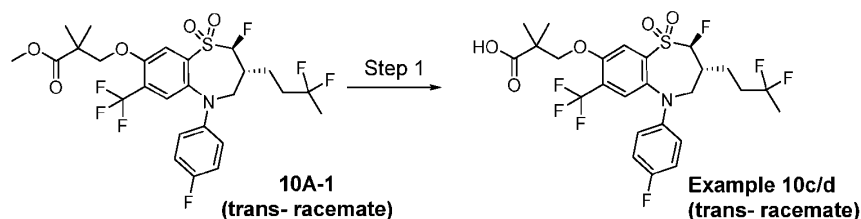
5 **fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoate (10A-2a) and methyl 3-(((2S,3S)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-**
tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoate (10A-2b). rac-Methyl 3-(((2R,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoate
10 **(10A-1)** (90 mg) was purified by Prep- Chiral-HPLC (Column: CHIRALPAK IC, 2*25 cm, 5 μ m; Mobile Phase A: Hex--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 25 mL/min; Gradient: isocratic 10; Wavelength: 240 nm; RT1 (min): 5.6; RT2 (min): 7.2; Sample Solvent: EtOH--HPLC; Injection volume: 1 mL; Number of runs: 5). The collected fractions
15 were concentrated, and the residue was dried in vacuo to give **10A-2a** (25 mg, 56%, single diastereomer, MS (ESI): calcd. for $C_{26}H_{28}F_7NO_5S$: 599.2; Found: 600.1 $[M + 1]^+$) and **10A-2b** (24 mg, 53%, single diastereomer, MS (ESI): calcd. for $C_{26}H_{28}F_7NO_5S$: 599.2; Found: 600.1 $[M + 1]^+$) as a white solid, respectively.

20 **Step 3a. Synthesis of 3-(((2R,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid (Example 10c).** A solution of methyl 3-(((2R,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoate (10A-2a) (25 mg, 0.05
25 mmol) and LiOH (7.85 mg, 0.35 mmol) in 1,4-dioxane (4 mL) and H₂O (1 mL) was stirred at 50 °C for 12 h. Next, the mixture was acidified to pH = 4 with 2 N aq. HCl solution. The resulting mixture was extracted with EA (10 mL x 2). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by prep-HPLC (Column: Sunfire Prep C18 OBD Column, 19*150mm, 5 μ m; Mobile
30 Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 30 mL/min; Gradient: 50% to

80 % B in 8 min; Wavelength: 254 nm/220 nm; RT1(min): 5.94). The collected fractions were concentrated, and the residue was lyophilized to give **Example 10c** (15.2 mg, 62%, single diastereomer) as a white solid. MS (ESI): calcd. for C₂₅H₂₆F₇NO₅S: 585.1; Found: 586.1 [M + 1]⁺. ¹H NMR (300 MHz, CD₃OD): δ 7.75 (s, 1H), 7.33 (s, 1H), 7.09 - 7.04 (m, 4H), 5.59 (dd, J = 44.1, 6.0 Hz, 1H), 4.26 - 4.10 (m, 3H), 3.73 - 3.59 (m, 1H), 2.45 - 2.44 (m, 1H), 2.05 - 1.75 (m, 4H), 1.45 (t, J = 18.3 Hz, 3H), 1.36 (s, 6H) ppm.

Step 3b. Synthesis of 3-(((2S,3S)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid (Example 10d). A solution of methyl 3-(((2S,3S)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoate (**10A-2b**) (24 mg, 0.04 mmol) and LiOH (7.05 mg, 0.14 mmol) in 1,4-dioxane (4 mL) and H₂O (1 mL) was stirred at rt for 12 h. The mixture was acidified to pH = 4 with 2 N aq. HCl solution. The resulting mixture was extracted with EA (10 mL x 2). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by Prep-HPLC (Column: Sunfire Prep C18 OBD Column, 19*150mm, 5μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 30 mL/min; Gradient: 50% to 80 % B in 8 min; Wavelength: 254 nm/220 nm; RT1(min): 5.94). The collected fractions were concentrated, and the residue was lyophilized to give **Example 10d** (14.3 mg, 61%, single diastereomer) as a white solid. MS (ESI): calcd. for C₂₅H₂₆F₇NO₅S: 585.1; Found: 586.1 [M + 1]⁺. ¹H NMR (300 MHz, CD₃OD): δ 7.75 (s, 1H), 7.33 (s, 1H), 7.09 - 7.04 (m, 4H), 5.59 (dd, J = 44.1, 6.0 Hz, 1H), 4.26 - 4.23 (m, 2H), 4.20 - 4.11 (m, 1H), 3.74 - 3.70 (m, 1H), 2.46 - 2.44 (m, 1H), 2.05 - 1.80 (m, 4H), 1.45 (t, J = 18.3 Hz, 3H), 1.36 (s, 6H) ppm.

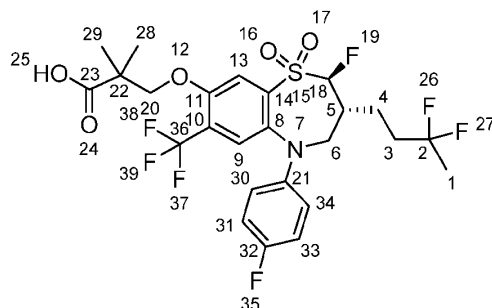
Examples 10c/d. rac-3-(((2R,3S)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid.



Step 1. Synthesis of rac-3-(((2R,3S)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid (Example 10c/d). A solution of rac-ethyl 1-(((2R,3S)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylate (10A-1, trans-racemate) (40 mg, 0.24 mmol) in dioxane (4 mL) was treated with water (1 mL) for 3 min at room temperature under nitrogen atmosphere, followed by the addition of LiOH (47.62 mg, 2.26 mmol) dropwise at room temperature. The resulting mixture was stirred at 50°C for 12 h. Next, the mixture was acidified to pH = 3 with concd. aq. HCl solution. The resulting mixture was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Column: Sunfire Prep C18 OBD Column, 19*150mm, 5µm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 30 mL/min mL/min; Gradient: 50% to 75 % B in 8 min; Wavelength: 254 nm/220 nm; RT1(min): 5.94). The collected fractions were concentrated under vacuum to remove ACN and resulting solution was dried by lyophilization to give **Example 10c/d** (10.4 mg, 48.6%, trans- racemate) as a white solid. MS (ESI): calcd. for C₂₅H₂₈F₇NO₅S: 585.1; Found: 586.1 [M + 1]⁺. ¹H NMR (300 MHz, CD₃OD): δ 7.75 (s, 1H), 7.33 (s, 1H), 7.09 - 7.04 (m, 4H), 5.59 (dd, J = 44.1, 5.8 Hz, 1H), 4.26 - 4.13 (m, 3H), 3.74 - 3.69 (m, 1H), 2.45 - 2.41 (m, 1H), 2.05 - 1.78 (m, 4H), 1.45 (t, J = 18.3 Hz, 3H), 1.36 (s, 6H) ppm.

Relative stereochemistry determination of rac-(2R,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-8-methoxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (Example 10c/d). ¹H, ¹³C, ¹⁹F, H-H COSY,

C-H HSQC, C-H HMBC, H-H NOESY, and F-H NOESY NMR techniques were employed to elucidate the relative stereochemistry of the trans- racemate **Example 10c/d**.



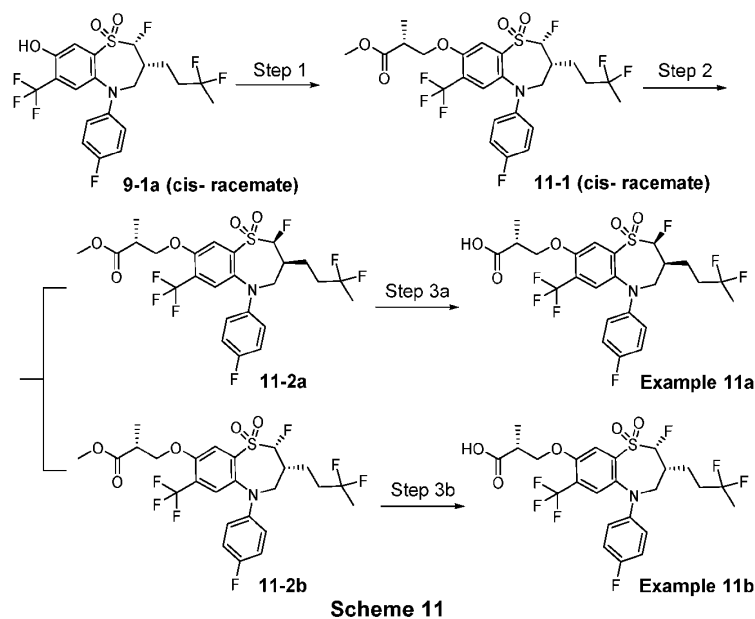
Example 10c/d
(trans- racemate)

^1H NMR (300 MHz, CD_3OD): δ 7.75 (s, 1H, H13), 7.33 (s, 1H, H9), 7.12 – 6.99 (m, 4H, H34, H33 H31&H30), 5.59 (dd, J = 44.2, 5.7 Hz, 1H, H18), 4.22 (s, 2H, H20), 4.22 – 4.12 (m, 1H, H6'), 3.73 – 3.69 (m, 1H, H6''), 2.45 (s, 1H, H5), 2.05 – 1.80 (m, 4H, H4&H3), 1.45 (t, J = 18.6 Hz, 3H, H1), 1.36 (s, 6H, H28&H29) ppm. ^{13}C NMR (76 MHz, CD_3OD): δ 178.06 (C23), 155.06 (d, J = 228.8 Hz, C32), 153.50 (C11), 143.96 (C21), 140.66 (C14), 138.08 (C8), 126.86 (C9), 124.86 (q, J = 31.8 Hz, C10), 126.86 – 120.46 (m, C2), 120.57 (C36), 115.81 (C31&C33), 115.51 (C30&C34), 113.16 (C13), 102.53 (d, J = 245.5 Hz, C18), 75.52 (C20), 48.77 (C6), 42.59 (C22), 41.12 (d, J = 15.2 Hz, C5), 34.86 (t, J = 25.6 Hz, C3), 22.26 – 21.27 (m, C1), 21.28 (C28&C29), 20.93 – 20.55 (C4) ppm. ^{19}F NMR (282 MHz, CD_3OD): δ -64.51 (F37, F38&F39), -92.49 (F26&F27), -123.43 (F35), -178.25 (F19). F-H NOESY NMR data suggested F19 has correlation with H5 but not with H4.

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Examples 11a and 11b. (R)-3-(((2R,3S)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2-methylpropanoic acid (11a) and (R)-3-(((2S,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2-methylpropanoic acid (11b)

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Scheme 11

- Step 1. Synthesis of rac-methyl (R)-3-(((2S,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2-methylpropanoate (11-1).** To a stirred solution of rac-(2S,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-8-hydroxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (**9-1a**) (1.2 g, 2.47 mmol) and DIAD (1.29 g, 9.89 mmol) in DMF (50 mL) were added triphenylphosphine (2.59 g, 9.89 mmol) and methyl (R)-3-hydroxy-2-methylpropanoate (0.58 g, 4.944 mmol) at rt under N₂ atmosphere. The resulting mixture was stirred at 110°C for 6 hr. The mixture was allowed to cool down to rt. The reaction was quenched with H₂O at rt. The resulting mixture was extracted with EA (50 mL x 2). Next, the combined organic extracts were washed with brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography (PE/EA = 3/1 (v/v)) to give **11-1** (700 mg, 48.36%) as a brown solid. MS (ESI): calcd. for C₂₅H₂₆F₇NO₅S: 585.1; Found: 586.2 [M + 1]⁺.

Step 2. Synthesis of methyl (R)-3-(((2R,3S)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-

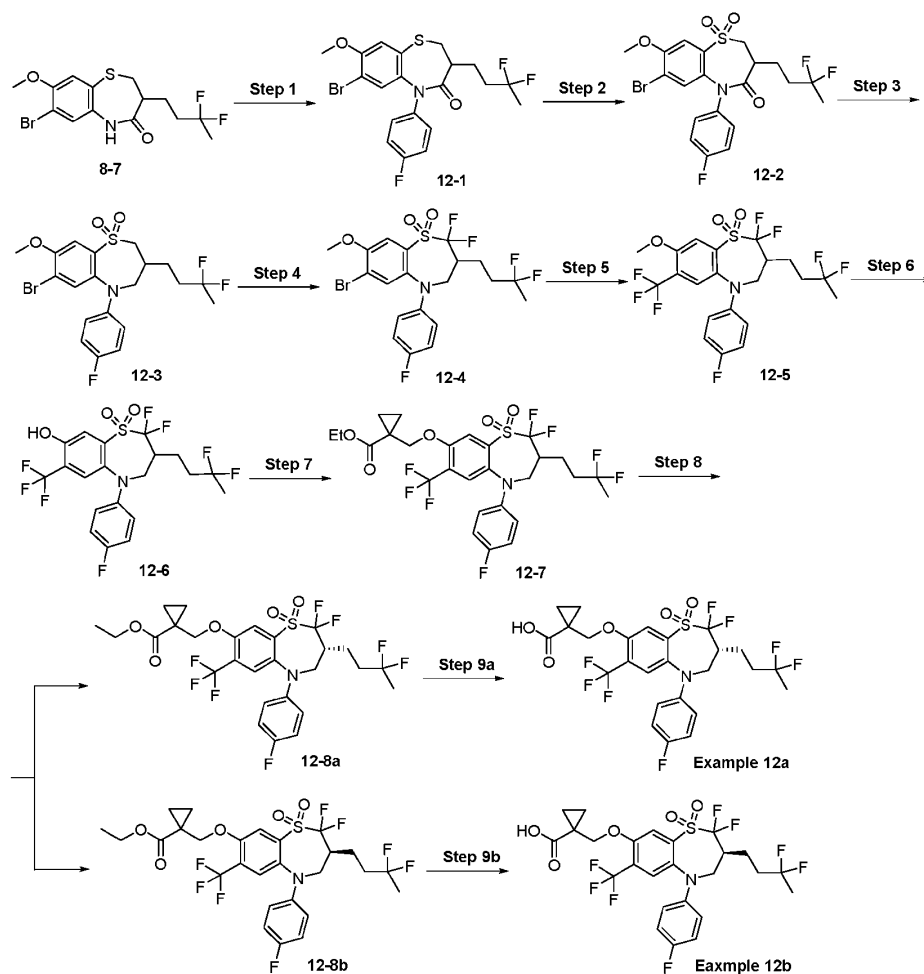
8-yl)oxy)-2-methylpropanoate (**11-2a**) and methyl (R)-3-(((2S,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2-methylpropanoate (**11-2b**). The product rac-methyl (R)-3-(((2S,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2-methylpropanoate (**11-1**) (700 mg) was purified by Prep-SFC with the following conditions: Column: (R, R)-WHELK-O, 3*25 cm, 5 µm; Mobile Phase A: CO₂, Mobile Phase B: MeOH; Flow rate: 80 mL/min; Gradient: isocratic 30% B; Column temperature (°C): 35; Back pressure(bar): 100; Wavelength: 220 nm; RT1(min): 3.3; RT2(min): 4.8; Sample solvent: MeOH; Injection volume: 5 mL. The collected solution was concentrated in vacuo to give **11-2a** (270 mg) (single diastereomer, the stereochemistry was arbitrarily assigned) and **11-2b** (260 mg) (single diastereomer, the stereochemistry was arbitrarily assigned) as a white solid, respectively. MS (ESI): calcd. for C₂₅H₂₆F₇NO₅S: 585.1; Found: 586.2 [M + 1]⁺.

Step 3a. Synthesis of (R)-3-(((2R,3S)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2-methylpropanoic acid (Example 11a). A solution of **11-2a** (270 mg, 0.46 mmol) and LiOH (33.23 mg, 1.38 mmol) in 1,4-dioxane (12 mL) and H₂O (3 mL) was stirred at rt for 16 hr. The mixture was acidified to pH = 4 with 2 N aq. HCl solution. The resulting mixture was extracted with EA (10 mL x 2). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na₂SO₄, and concentrated. The crude product (300 mg) was purified by prep-HPLC with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5µm; Mobile Phase A: Water (10 mmol/L NH₄HCO₃ + 0.05%NH₃*H₂O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 55% B in 10 min; Wavelength: 254 nm/220 nm; RT1(min): 1.29. The collected solution was concentrated under vacuum to remove ACN and resulting solution was lyophilized to give **Example 11a** (108 mg) (single diastereomer, the stereochemistry was arbitrarily assigned) as a white solid. MS (ESI): calcd. for C₂₄H₂₄F₇NO₅S: 571.1; Found: 572.2 [M + 1]⁺. ¹H NMR (300 MHz, CD₃OD): δ 7.79 (s, 1H), 7.54 (s, 1H), 6.97 (t, J = 8.7 Hz, 2H), 6.70 (dd, J = 9.1, 4.2 Hz, 2H), 5.68 (d, J = 45.3 Hz, 1H), 4.41 – 4.28 (m, 2H), 4.18 (d, J = 15.9 Hz, 1H), 3.28 –

3.20 (m, 1H), 3.01 – 2.93 (m, 1H), 2.77 – 2.63 (m, 1H), 2.21 – 2.04 (m, 2H), 1.81 – 1.55 (m, 5H), 1.33 (d, $J = 7.2$ Hz, 3H) ppm.

Step 3b. Synthesis of (R)-3-(((2S,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2-methylpropanoic acid (Example 11b). A solution of **11-2b** (260 mg, 0.44 mmol) and LiOH (32.02 mg, 1.33 mmol) in 1,4-dioxane (12 mL) and H₂O (3 mL) was stirred at rt for 16 hr. The mixture was acidified to pH = 4 with 2 N aq. HCl solution and extracted with EA (10 mL x 2). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na₂SO₄, and concentrated. The crude product (300 mg) was purified by prep-HPLC with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μ m; Mobile Phase A: Water (10mmol/L NH₄HCO₃+0.05%NH₃•H₂O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 55% B in 10 min; Wavelength: 254 nm/220 nm; RT1(min): 0.92. The collected solution was concentrated under vacuum to remove ACN and resulting solution was lyophilized to give **Example 11b** (single diastereomer, the stereochemistry was arbitrarily assigned) (106 mg) as a white solid. MS (ESI): calcd. for: C₂₄H₂₄F₇NO₅S: 571.1; Found: 572.2 [M + 1]⁺. ¹H NMR (300 MHz, CD₃OD): δ 7.79 (s, 1H), 7.54 (s, 1H), 6.97 (t, $J = 8.7$ Hz, 2H), 6.70 (dd, $J = 9.1, 4.2$ Hz, 2H), 5.68 (d, $J = 45.3$ Hz, 1H), 4.44 – 4.30 (m, 1H), 4.28 – 4.20 (m, 1H), 4.18 (d, $J = 15.9$ Hz, 1H), 3.28 – 3.20 (m, 1H), 2.98 – 2.92 (m, 1H), 2.78 – 2.63 (m, 1H), 2.20 – 2.03 (m, 2H), 1.77 – 1.57 (m, 5H), 1.33 (d, $J = 7.2$ Hz, 3H) ppm.

Examples 12a and 12b. (R)-1-(((3-(3,3-difluorobutyl)-2,2-difluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid (12a) and (S)-1-(((3-(3,3-difluorobutyl)-2,2-difluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid (12b)



Scheme 12

Step 1. Synthesis of 7-bromo-3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-8-methoxy-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (12-1). A solution of **8-7** (11 g, 28.93 mmol), 1-fluoro-4-iodo- (9.63 g, 43.39 mmol), CuI (5.51 g, 28.93 mmol), and K₂CO₃ (11.99 g, 86.78 mmol) in DMF (110 mL) was stirred at 130 °C for 6 h under nitrogen atmosphere. The mixture was allowed to cool down to rt and diluted with water (150 mL). The aqueous layer was extracted with EtOAc (150 mL x 2). The combined organic extracts were washed with water (200 mL x 5) and brine (200 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography (PE/EA = 3/1 (v/v)) to give **12-1**

(10.5 g, 76.5%) as a dark yellow solid. MS (ESI): calcd. for $C_{20}H_{19}BrF_3NO_2S$: 473.0; Found: 474.0 $[M + 1]^+$.

Step 2. Synthesis of 7-bromo-3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-8-methoxy-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one 1,1-dioxide (12-2). A solution of **12-1** (10.5 g, 22.14 mmol) and Oxone[®] (27.92 g, 166.02 mmol) in THF (200 mL) and H₂O (100 mL) was stirred at rt for 16 h. The resulting mixture was filtered, and the filter cake was washed with EtOAc (120 mL x 3). The mixture was acidified to pH 8 with sat. aq. NaHCO₃. The resulting mixture was extracted with EtOAc (150 mL x 2). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give crude **12-2** (12.6 g, 89.9%) as a brown solid, which was used in the next step without further purification. MS (ESI): calcd. for $C_{20}H_{19}BrF_3NO_4S$: 505.0; Found: 506.0 $[M + 1]^+$.

Step 3. Synthesis of 7-bromo-3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-8-methoxy-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (12-3). A solution of **12-2** (12.6 g, 24.89 mmol) and BH₃·DMS (16.52 mL, 174.20 mmol) in THF (100 mL) was stirred at 60 °C for 16 h. Subsequently, the reaction mixture was allowed to cool down to 0 °C with ice-water, added MeOH (50 mL) (dropwise) at 0 °C, and concentrated under vacuum. The residue was dissolved in water (150 mL) and the resulting mixture was extracted with EtOAc (100 mL x 3). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography (PE/EA = 4/1 (v/v)) to give **12-3** (8.2 g, 66.9%) as a light brown oil. MS (ESI): calcd. for $C_{20}H_{21}BrF_3NO_3S$: 491.0; Found: 492.0 $[M + 1]^+$.

Step 4. Synthesis of 7-bromo-3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-8-methoxy-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (12-4). A solution of **12-3** (2 g, 4.06 mmol) in THF (30 mL) was added with LiHMDS (2.04 g, 12.19 mmol) at -78 °C for 30 min under nitrogen atmosphere. After stirring at -78 °C for 30 min, a solution of NFSI (3.20 g, 10.16 mmol) in THF (20 mL) was added at -78 °C dropwise. The resulting mixture was

stirred at -78 °C for 3 h under nitrogen atmosphere, followed by adding water (100 mL) at 0 °C. Subsequently, the mixture was concentrated to remove organic solvent, and the residue was extracted with EtOAc (80 mL x 3). The combined organic extracts were washed with brine (80 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography (PE/EA = 3/1 (v/v)) to give **12-4** (1.6 g, 67.1%) as a yellow solid. MS (ESI): calcd. for C₂₀H₁₉BrF₅NO₃S: 527.0; Found: 528.0 [M + 1]⁺. ¹H NMR (400 MHz, CDCl₃): δ 7.73 (s, 1H), 7.63 (s, 1H), 7.02 (t, *J* = 8.4 Hz, 2H), 6.72 – 6.68 (m, 2H), 4.22 – 4.15 (m, 1H), 4.03 (s, 3H), 3.47 – 3.43 (m, 1H), 2.95 – 2.91 (m, 1H), 2.07 – 2.01 (m, 2H), 1.72 – 1.68 (m, 5H) ppm.

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Step 5. Synthesis of 3-(3,3-difluorobutyl)-2,2-difluoro-5-(4-fluorophenyl)-8-methoxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (12-5). A solution of **12-4** (1.1 g, 2.08 mmol) in DMF (15 mL) was treated with methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (1.60 g, 8.33 mmol) and CuBr (1.79 g, 12.49 mmol) at rt under nitrogen atmosphere. After stirring at 130 °C for 16 h under nitrogen atmosphere, the mixture was cooled down to rt, diluted with water (50 mL), and extracted with EtOAc (50 mL x 3). The combined organic extracts were washed with water (50 mL x 5) and brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography (PE/EA = 3/1 (v/v)) to give **12-5** (900 mg, 75.19%) as a light-yellow oil. MS (ESI): calcd. for C₂₁H₁₉F₈NO₃S: 517.1; Found: 518.0 [M + 1]⁺.

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Step 6. Synthesis of 3-(3,3-difluorobutyl)-2,2-difluoro-5-(4-fluorophenyl)-8-hydroxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (12-6). A solution of **12-5** (900 mg, 1.74 mmol) in DMSO (15 mL) was treated with LiCl (1.47 g, 34.78 mmol) at rt. After stirring at 140 °C for 8 h, the reaction mixture was cooled down to rt, diluted with water (50 mL), and acidified to pH 5 with citric acid (10% w/w). The resulting mixture was extracted with EtOAc (50 mL x 3). The combined organic extracts were washed with water (50 mL x 5) and brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography (PE/EA = 3/1 (v/v)) to give

12-6 (700 mg, 76.0%) as a light-yellow oil. MS (ESI): calcd. for $C_{20}H_{17}F_8NO_3S$: 503.1; Found: 504.0 $[M + 1]^+$.

Step 7. Synthesis of ethyl 1-(((3-(3,3-difluorobutyl)-2,2-difluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylate (12-7). A solution of **12-6** (160 mg, 0.32 mmol) in DMF (6 mL) was treated with ethyl 1-(((methylsulfonyl)oxy)methyl)cyclopropane-1-carboxylate (105.96 mg, 0.477 mmol), KI (211.04 mg, 1.27 mmol), and CS_2CO_3 (414.22 mg, 1.27 mmol) at rt. After stirring at 100 °C for 16 h, the mixture was cooled down to rt, diluted with water (15 mL), and extracted with EtOAc (20 mL x 3). The combined organic extracts were washed with water (20 mL x 5) and brine (20 mL), dried over anhydrous Na_2SO_4 , and concentrated. The residue was purified by silica gel column chromatography (PE/EA = 3/1 (v/v)) to give **12-7** (80 mg, 36.0%) as a light-yellow oil. MS (ESI): calcd. for $C_{27}H_{27}F_8NO_5S$: 629.1; Found: 630.1 $[M + 1]^+$.

Step 8. Synthesis of ethyl (R)-1-(((3-(3,3-difluorobutyl)-2,2-difluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylate (12-8a) and ethyl (S)-1-(((3-(3,3-difluorobutyl)-2,2-difluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylate (12-8b). Compound **12-7** (80 mg) was purified by prep-HPLC (Column: (R, R)-WHELK-O, 3*25 cm, 5 μ m; Mobile Phase A: CO_2 , Mobile Phase B: MeOH; Flow rate: 80 mL/min; Gradient: isocratic 30% B; Wavelength: 220 nm) to give **12-8a** (35 mg), MS (ESI): calcd. for $C_{27}H_{27}F_8NO_5S$: 629.1; Found: 630.1 $[M + 1]^+$ and **12-8b** (33 mg), MS (ESI): calcd. for $C_{27}H_{29}F_6NO_5S$: 593.2; Found: 630.1 $[M + 1]^+$ as a white solid, respectively.

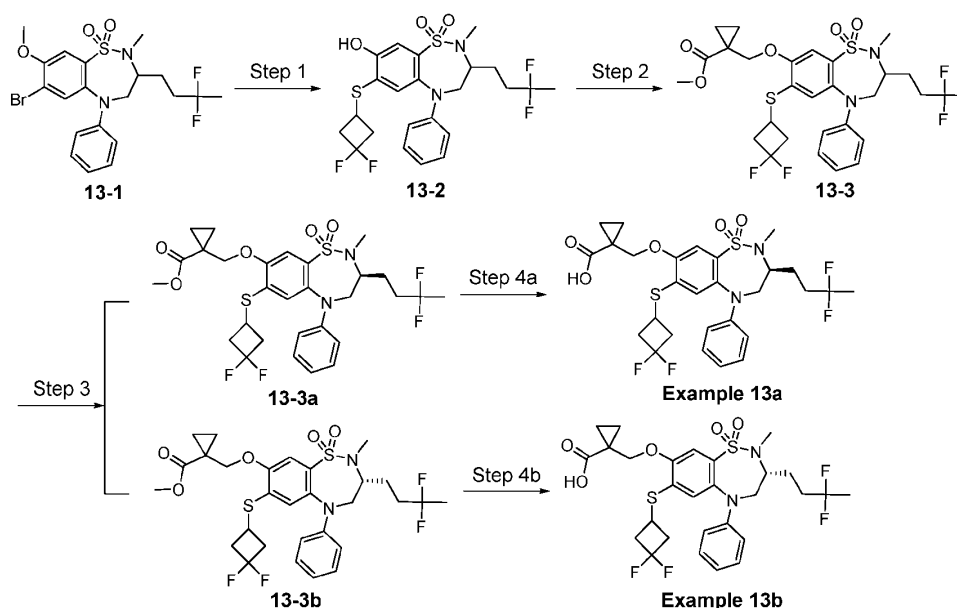
Step 9a. Synthesis of (R)-1-(((3-(3,3-difluorobutyl)-2,2-difluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid (Example 12a). A solution of **12-8a** (35 mg, 0.06 mmol) in dioxane (5 mL) and H_2O (1 mL) was treated with LiOH (5.33 mg, 0.23

mmol) at rt. After stirring at 40 °C for 16 h, the mixture was cooled down to rt, acidified to pH 3 with 2 N aq. HCl solution, and extracted with EtOAc (15 mL x 3). The combined organic extracts were washed with brine (15 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by prep-HPLC (Column: XBridge Shield RP18 OBD
5 Column, 19*150 mm, 5µm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 45% B to 60% B in 8 min, 60% B; Wavelength: 254/220 nm) to give **Example 12a** (18.2 mg, 53.5%) as a white solid. MS (ESI): calcd. for C₂₅H₂₃F₈NO₅S: 601.1; Found: 602.1 [M + 1]⁺. ¹H NMR (400 MHz, CD₃OD): δ 7.82 (s, 1H), 7.52 (s, 1H), 7.00 (t, J = 8.4 Hz, 2H), 6.77 (s, 2H), 4.43 (s, 2H), 4.33 - 4.21 (m, 1H), 3.59 - 3.41 (m, 1H),
10 3.01 - 2.81 (m, 1H), 2.17 - 1.94 (m, 3H), 1.65 - 1.56 (m, 4H), 1.37 - 1.30 (m, 2H), 1.19-1.06 (m, 2H) ppm.

Step 9b. (S)-1-(((3-(3,3-difluorobutyl)-2,2-difluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid (Example 12b). A solution of **12-8b** (33
15 mg, 0.05 mmol) in dioxane (5 mL) and H₂O (1 mL) was treated with LiOH (5.28 mg, 0.22 mmol) at rt. After stirring at 40 °C for 16 hr, the mixture was cooled down to rt, acidified to pH 3 with 2 N aq. HCl solution, and extracted with EtOAc (15 mL x 3). The combined organic extracts were washed with brine (15 mL), dried over anhydrous Na₂SO₄, and
20 concentrated. The residue was purified by prep-HPLC (Column: XBridge Shield RP18 OBD Column, 19*150 mm, 5µm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 45% B to 60% B in 8 min, 60% B; Wavelength: 254/220 nm) to give **Example 12b** (21.2 mg, 66.9%) as a white solid. MS (ESI): calcd. for C₂₅H₂₃F₈NO₅S: 601.1; Found: 602.1 [M + 1]⁺. ¹H NMR (400 MHz, CD₃OD): δ 7.83 (s, 1H), 7.52 (s, 1H),
25 7.00 (t, J = 8.4 Hz, 2H), 6.78 (s, 2H), 4.40 (s, 2H), 4.24 - 4.18 (m, 1H), 3.59 - 3.41 (m, 1H), 3.05 - 2.80 (m, 1H), 2.17 - 1.93 (m, 3H), 1.65 - 1.51 (m, 4H), 1.38 - 1.30 (m, 2H), 1.18 - 1.12 (m, 2H) ppm.

Examples 13a and 13b. (S)-1-(((3-(3,3-difluorobutyl)-7-((3,3-difluorocyclobutyl)thio)-2-methyl-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-

yl)oxy)methyl)cyclopropane-1-carboxylic acid (13a) and (R)-1-(((3-(3,3-difluorobutyl)-7-((3,3-difluorocyclobutyl)thio)-2-methyl-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid (13b)



Scheme 13

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Step 1. 3-(3,3-difluorobutyl)-7-((3,3-difluorocyclobutyl)thio)-8-hydroxy-2-methyl-5-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (13-2) To a stirred mixture of 7-bromo-3-(3,3-difluorobutyl)-8-methoxy-2-methyl-5-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (**13-1**) (1 g, 2.04 mmol), which was prepared by following the same procedure used for preparing **1-10**, replacing 2-bromo-4-trifluoromethyl-5-methoxyphenylsulfonyl chloride with 2,4-dibromo-5-methoxyphenylsulfonyl chloride, and using the racemic version of **1-7**, and 3,3-difluorocyclobutanethiol (0.89 g, 7.15 mmol) in DMF (15 mL) was added NaH (55% suspension in mineral oil) (0.446 g, 18.59 mmol) portion wise at 0 °C. After stirring at 0 °C for 30 min and rt for 2 hr, the mixture was stirred at 70 °C for 12 hr. subsequently, the mixture was diluted with ice water (5 mL), acidified with sat. aq. NaHSO₄ solution and extracted with EtOAc (50 mL x 3). The combined organic extracts were washed with water,

and brine, dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by prep-HPLC to give **13-2** (700 mg, 66%) as a white solid.

Step 2. Synthesis of methyl 1-(((3-(3,3-difluorobutyl)-7-((3,3-difluorocyclobutyl)thio)-2-methyl-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)methyl)cyclopropanecarboxylate (13-3). A mixture of **13-2** (0.2 g, 0.39 mmol), cesium carbonate (0.314 g, 0.96 mmol) and methyl 1-(bromomethyl)cyclopropanecarboxylate (0.112 g, 0.58 mmol) in DMF (2 mL) was stirred at 60 °C for 16 hr. The mixture was cooled to rt and filtered. The filtrate was purified by prep-HPLC to give **13-3** (0.172 g, 71%) as a white solid.

Step 3. Synthesis of methyl (S)-1-(((3-(3,3-difluorobutyl)-7-((3,3-difluorocyclobutyl)thio)-2-methyl-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylate (13-3a) and methyl (R)-1-(((3-(3,3-difluorobutyl)-7-((3,3-difluorocyclobutyl)thio)-2-methyl-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylate (13-3b). The racemic **13-3** (140 mg) was separated by chiral HPLC (Column: CHIRALPAK IF (250 × 21 mm, 5 μm)-II, Mobile phase: Hexane:IPA:MeOH, 80:10:10 (v/v/v); Flow Rate: 12 mL/min; Column Temperature: 24°C; Wavelength: 205 nm. t_R 1 = 20.60 min (single enantiomer, the stereochemistry was arbitrarily assigned); and t_R 2 = 27.17 min (single enantiomer, the stereochemistry was arbitrarily assigned)) to give **13-3a** (45.3 mg) and **13-3b** (45.2 mg) as a white solid, respectively.

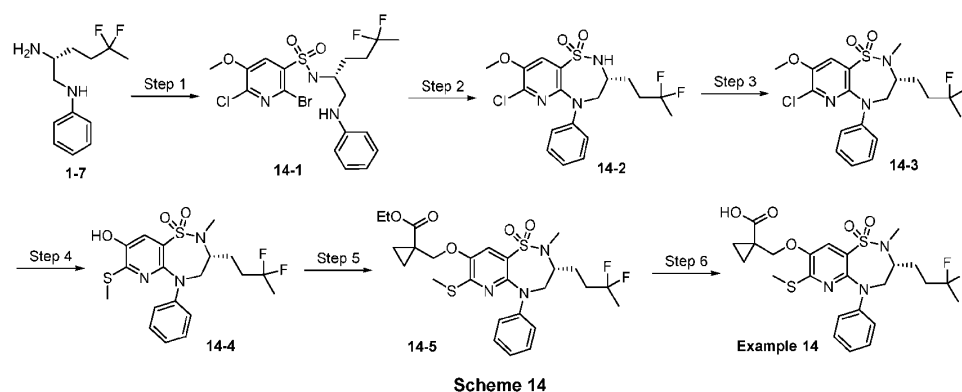
Step 4a. Synthesis of (S)-1-(((3-(3,3-difluorobutyl)-7-((3,3-difluorocyclobutyl)thio)-2-methyl-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)methyl)cyclopropanecarboxylic acid (Example 13a). To a stirred solution of **13-3a** (45.3 mg, 71.82 μmol) in THF/H₂O = 4/1 (v/v) (2 mL) was added lithium hydroxide hydrate (9.0 mg, 214.0 μmol). After stirring at rt for 12 hr, the reaction mixture was adjusted to pH

~2 using 2 N aq. HCl solution. The resulting mixture was purified by prep-HPLC to give

Example 13a (24.8 mg, 56%) as a white solid (single enantiomer, the stereochemistry was arbitrarily assigned). MS (ESI): calcd. for $C_{28}H_{32}F_4N_2O_5S_2$: 616.2; Found: 614.9 $[M - 1]^-$. 1H NMR (500 MHz, DMSO- d_6): δ 12.45 (s, 1H), 7.27 (s, 1H), 7.14 (t, $J = 7.8$ Hz, 2H), 6.95 (s, 1H), 6.70 (t, $J = 7.3$ Hz, 1H), 6.63 (d, $J = 8.1$ Hz, 2H), 4.21 (q, $J = 9.8$ Hz, 2H), 4.06 (d, $J = 16.0$ Hz, 1H), 3.82 (s, 2H), 3.13 (s, 1H), 2.99 (d, $J = 12.4$ Hz, 1H), 2.64 – 2.50 (m, 2H), 2.47 (s, 3H), 1.98 (tt, $J = 16.3, 8.2$ Hz, 2H), 1.83 (t, $J = 7.0$ Hz, 1H), 1.63 (t, $J = 18.9$ Hz, 4H), 1.20 (t, $J = 3.5$ Hz, 2H), 1.06 (q, $J = 3.3$ Hz, 2H) ppm.

Step 4b. Synthesis of (R)-1-(((3-(3,3-difluorobutyl)-7-((3,3-difluorocyclobutyl)thio)-2-methyl-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)methyl)cyclopropanecarboxylic acid (Example 13b). Following the same procedure as described in Step 4a and replacing **13-3a** with **13-3b** (45.2 mg, 71.66 μ mol), **Example 13b** (27.5 mg, 63%) was obtained as a white solid (single enantiomer, the stereochemistry was arbitrarily assigned). MS (ESI): calcd. for $C_{28}H_{32}F_4N_2O_5S_2$: 616.2; Found: 614.9 $[M - 1]^-$. 1H NMR (500 MHz, DMSO- d_6): δ 12.45 (s, 1H), 7.27 (s, 1H), 7.14 (t, $J = 7.8$ Hz, 2H), 6.95 (s, 1H), 6.70 (t, $J = 7.3$ Hz, 1H), 6.63 (d, $J = 8.1$ Hz, 2H), 4.21 (q, $J = 9.8$ Hz, 2H), 4.06 (d, $J = 15.9$ Hz, 1H), 3.82 (s, 2H), 3.26 (s, 1H), 3.13 (s, 1H), 2.98 (s, 1H), 2.64 – 2.50 (m, 2H), 2.47 (s, 3H), 1.98 (tt, $J = 16.2, 8.0$ Hz, 2H), 1.83 (d, $J = 8.4$ Hz, 1H), 1.63 (t, $J = 18.9$ Hz, 4H), 1.21 (d, $J = 3.0$ Hz, 2H), 1.06 (s, 2H) ppm.

Example 14. (R)-1-(((3-(3,3-difluorobutyl)-2-methyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydropyrido[2,3-f][1,2,5]thiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid



Step 1. Synthesis of (R)-2-bromo-6-chloro-N-(5,5-difluoro-1-(phenylamino)hexan-2-yl)-5-methoxypyridine-3-sulfonamide (14-1).

To a stirred solution of (R)-5,5-difluoro-N1-phenylhexane-1,2-diamine (**1-7**) (1.0 g, 4.1 mmol) and TEA (1.2 g, 12.3 mmol) in DCM (20 mL) was added a solution of 2,6-dibromo-5-methoxypyridine-3-sulfonyl chloride (1.9 g, 5.3 mmol) in DCM (5 mL) at 0°C. The resulting reaction mixture was stirred at rt for 5 hr. After completion of the reaction (monitored by LCMS), the reaction mixture was quenched with ice-cold water (40 mL) and the aqueous layer was extracted with EA (40 mL x 3). The combined organic extracts were washed with water (40 mL) and brine (40 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography (EA/PE = 1/5 (v/v)) to give **14-1** (1.2 g, 57%) as a yellow solid. TLC: EA/PE = 1/5 (v/v) (R_f: 0.4). MS (ESI): calcd. for C₁₈H₂₁BrClF₂N₃O₃S: 511.0; Found: 512.1 [M + 1]⁺.

Step 2. Synthesis of (R)-7-chloro-3-(3,3-difluorobutyl)-8-methoxy-5-phenyl-2,3,4,5-tetrahydropyrido[2,3-f][1,2,5]thiadiazepine 1,1-dioxide (14-2).

To a stirred solution of **14-1** (1.2 g, 2.4 mmol) and K₂CO₃ (972 mg, 7.1 mmol) in DMF (30 mL) was added Cu (150 mg, 2.35 mmol) and the resulting mixture was heated at 115 °C for 5 hr. After completion of the reaction (monitored by LCMS), the reaction mixture was quenched with saturated aq. NH₄Cl solution (100 mL), and the aqueous layer was extracted with EA (50 mL x 3). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give crude **14-2** (1.2 g) as a

brown solid, which was used for the next step without further purification. TLC: EA/PE = 1/5 (v/v) (R_f : 0.5). MS (ESI): calcd. for $C_{18}H_{20}ClF_2N_3O_3S$: 431.1; Found: 432.2 $[M + 1]^+$.

Step 3. Synthesis of (R)-7-chloro-3-(3,3-difluorobutyl)-8-methoxy-2-methyl-5-phenyl-

5 **2,3,4,5-tetrahydropyrido[2,3-f][1,2,5]thiadiazepine 1,1-dioxide (14-3).** To a stirred solution of **14-2** (1.2 g, crude product, 2.78 mmol) and Cs_2CO_3 (2.7 g, 8.4 mmol) in NMP (20 mL) was added MeI (1.2 g, 8.4 mmol) and the reaction mixture was stirred at rt for 3 hr. After completion of the reaction (monitored by LCMS), the reaction mixture was quenched with ice-cold water (50 mL) and the aqueous layer was extracted with EA (50 mL x 3). The
10 combined organic extracts were washed with water (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4 , and concentrated. The residue was purified by silica gel column chromatography (EA/PE = 1/4 (v/v)) to give **14-3** (1.1 g, 89%) as a yellow solid. TLC: EA/PE = 3/7 (v/v) (R_f : 0.4). MS (ESI): calcd. for $C_{19}H_{22}ClF_2N_3O_3S$: 445.1; Found: 446.2 $[M + 1]^+$.

15

Step 4. Synthesis of (R)-3-(3,3-difluorobutyl)-8-hydroxy-2-methyl-7-(methylthio)-5-

phenyl-2,3,4,5-tetrahydropyrido[2,3-f][1,2,5]thiadiazepine 1,1-dioxide (14-4). To a stirred solution of **14-3** (1.1 g, 2.5 mmol) in DMF (10 mL) was added CH_3SNa (519 mg, 7.4 mmol) and the reaction mixture was heated at 95 °C for 16 hr. After completion of the reaction
20 (monitored by LCMS), the reaction mixture was quenched with ice water (20 mL) and the aqueous layer was extracted with EA (25 mL x 3). The combined organic extracts were washed with water (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4 , and concentrated. The residue was purified by silica gel column chromatography (EA/PE = 1/4 (v/v)) to give **14-4** (450 mg, 41%) as a yellow solid. TLC: EA/PE = 3/7 (v/v) (R_f : 0.6). MS
25 (ESI): calcd. for $C_{19}H_{23}F_2N_3O_3S_2$: 443.1; Found: 444.1 $[M + 1]^+$.

Step 5. Synthesis of (R)-ethyl 1-(((3-(3,3-difluorobutyl)-2-methyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydropyrido[2,3-f][1,2,5]thiadiazepin-8-

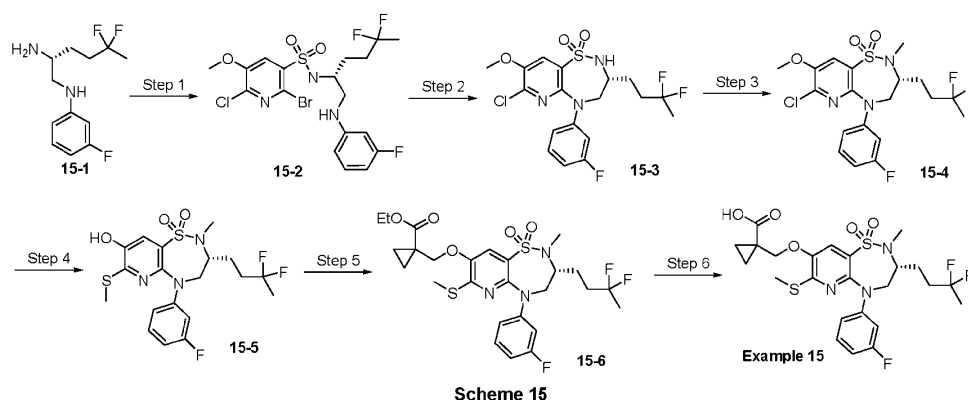
yl)oxy)methyl)cyclopropanecarboxylate (14-5). To a stirred solution of **14-4** (50 mg, 0.11 mmol) and Cs_2CO_3 (110 mg, 0.34 mmol) in DMF (3 mL) was added ethyl 1-

(((methylsulfonyl)oxy)methyl)cyclopropane-1-carboxylate (50 mg, 0.23 mmol) and the reaction mixture was heated at 65 °C for 3 hr. After completion of the reaction (monitored by LCMS), the reaction mixture was added into water (10 mL). The precipitate was filtered, washed with water (10 mL x 3), and dried in vacuo to give crude **14-5** (58 mg) as a yellow solid, which was used for the next step without further purification. TLC: EA/PE = 3/7 (v/v) (R_f: 0.5). MS (ESI): calcd. for C₂₆H₃₃F₂N₃O₅S₂: 569.2; Found: 570.2 [M + 1]⁺.

Step 6. Synthesis of (R)-1-(((3-(3,3-difluorobutyl)-2-methyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydropyrido[2,3-f][1,2,5]thiadiazepin-8-

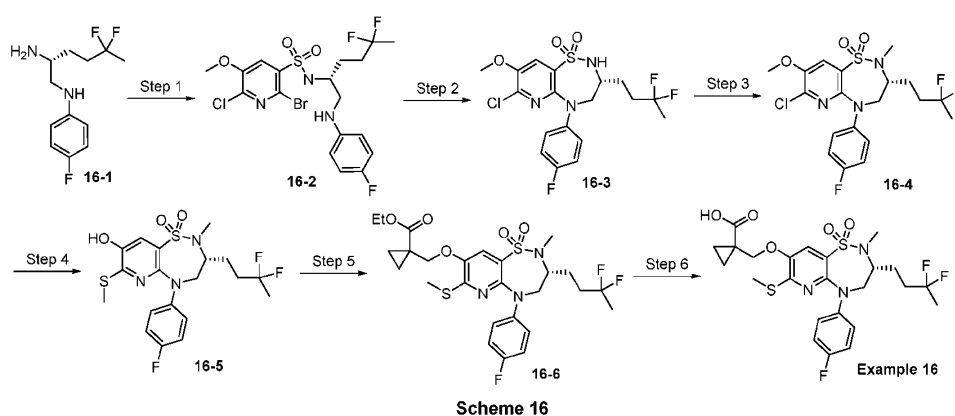
yl)oxy)methyl)cyclopropanecarboxylic acid (Example 14). To a stirred solution of **14-5** (58 mg, crude product, 0.10 mmol) in MeOH/H₂O = 2/1 (v/v) 3 mL) was added NaOH (43 mg, 1.02 mmol) and the reaction mixture was stirred at rt for 16 hr. After completion of the reaction (monitored by LCMS), the reaction mixture was neutralized with 1 N aq. HCl solution. The aqueous layer was extracted with EA (10 mL x 3) and the combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by prep-HPLC to give **Example 14** (31 mg, 56%) as a white solid. TLC: EA/PE = 3/2 (v/v) (R_f: 0.5). MS (ESI): calcd. for C₂₄H₂₉F₂N₃O₅S₂: 541.2; Found: 542.2 [M + 1]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.45 (s, 1H), 7.33 – 7.29 (m, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 7.04 (t, *J* = 7.2 Hz, 1H), 4.24 – 4.04 (m, 4H), 3.79 – 3.69 (m, 1H), 2.87 (s, 3H), 2.13 – 1.89 (m, 6H), 1.73 – 1.69 (m, 1H), 1.59 (t, *J* = 18.4 Hz, 3H), 1.34 – 1.31 (m, 2H), 1.12 – 1.09 (m, 2H) ppm.

Example 15. (R)-1-(((3-(3,3-difluorobutyl)-5-(3-fluorophenyl)-2-methyl-7-(methylthio)-1,1-dioxido-2,3,4,5-tetrahydropyrido[2,3-f][1,2,5]thiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid



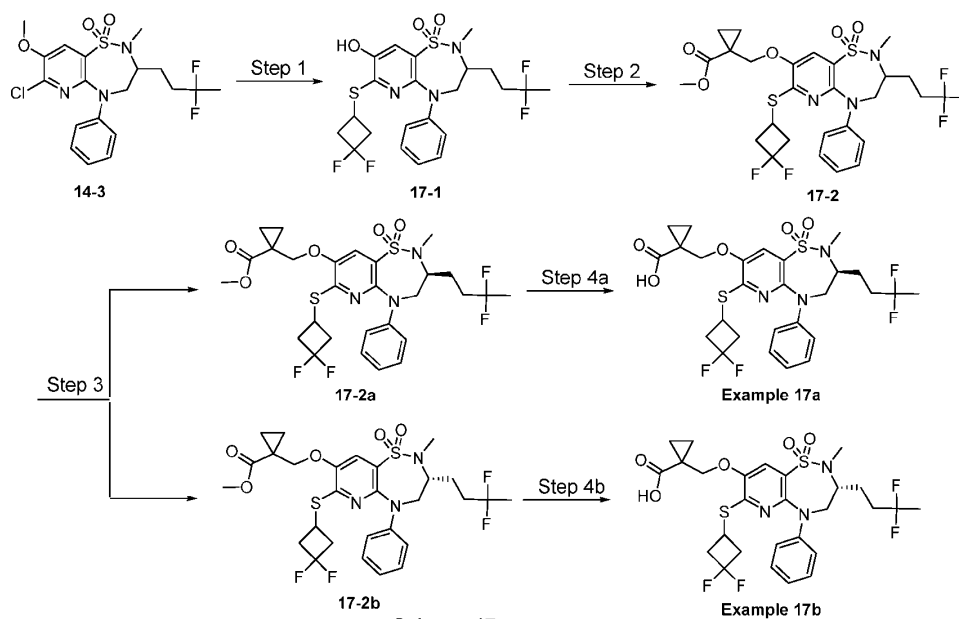
Following the same procedure as that for preparing **Example 14** by replacing aniline with 3-F-aniline, **Example 15** was obtained (16 mg) as a white solid. TLC: EA/PE = 1/1 (v/v) (R_f : 0.3). MS (ESI): calcd. for $C_{24}H_{28}F_3N_3O_5S_2$: 559.1; Found: 560.2 $[M + 1]^+$. 1H NMR (400 MHz, DMSO- d_6): δ 7.50 (s, 1H), 7.25 (q, J = 8.0 Hz, 1H), 6.77 – 6.73 (m, 1H), 6.70 – 6.65 (m, 2H), 4.27 (q, J = 10.0 Hz, 2H), 4.14 – 4.07 (m, 1H), 3.91 – 3.85 (m, 2H), 2.76 (s, 3H), 2.17 (s, 3H), 2.12 – 1.96 (m, 2H), 1.91 – 1.77 (m, 2H), 1.61 (t, J = 18.4 Hz, 3H), 1.33 – 1.31 (m, 2H), 1.11 – 1.10 (m, 2H) ppm

Example 16. (R)-1-(((3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-2-methyl-7-(methylthio)-1,1-dioxido-2,3,4,5-tetrahydropyrido[2,3-f][1,2,5]thiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid



Following the same procedure as that for preparing **Example 14** by replacing aniline with 4-F-aniline, **Example 16** was obtained (12 mg) as a white solid. TLC: EA/PE = 1/1 (v/v) (R_f : 0.3). MS (ESI): calcd. for $C_{24}H_{28}F_3N_3O_5S_2$: 559.1; Found: 560.2 $[M + 1]^+$. 1H NMR (400
 5 MHz, DMSO- d_6): δ 7.44 (s, 1H), 7.17 – 7.13 (m, 2H), 7.10 – 7.04 (m, 2H), 4.27 – 4.18 (m, 3H), 4.00 – 3.96 (m, 1H), 3.77 – 3.70 (m, 1H), 2.90 (s, 3H), 2.14 – 1.92 (m, 6H), 1.71 – 1.67 (m, 1H), 1.59 (t, J = 18.4 Hz, 3H), 1.31 – 1.29 (m, 2H), 1.08 – 1.05 (m, 2H) ppm.

Examples 17a and 17b. (S)-1-(((3-(3,3-difluorobutyl)-7-((3,3-difluorocyclobutyl)thio)-2-
 10 methyl-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydropyrido[2,3-f][1,2,5]thiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid (17a) and (R)-1-(((3-(3,3-difluorobutyl)-7-((3,3-difluorocyclobutyl)thio)-2-methyl-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydropyrido[2,3-f][1,2,5]thiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid (17b)



15

Step 1. Synthesis of 3-(3,3-difluorobutyl)-7-((3,3-difluorocyclobutyl)thio)-8-hydroxy-2-methyl-5-phenyl-2,3,4,5-tetrahydropyrido[2,3-f][1,2,5]thiadiazepine 1,1-dioxide (17-1).

To a stirred mixture of **14-3** (1 g, 8.05 mmol) at -10 °C in DMF (15 mL) was added NaH (55% suspension in mineral oil) (0.502 g, 20.92 mmol) portion wise. The reaction mixture was allowed to react at this temperature for 0.5 h and then stirred at rt for 2 hr. Subsequently, the temperature was raised to 70 °C and the reaction mixture was kept under stirring for 12 hr. Next, the reaction mixture was diluted with iced water (15 mL), acidified by sat. aq. NaHSO₄ solution and extracted by EtOAc (25 mL x 3). The combined organic extracts were washed with water and brine, dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by prep-HPLC to give **17-1** (768 mg, 64%) as an off-white solid.

Step 2. Synthesis of Methyl 1-(((3-(3,3-difluorobutyl)-7-((3,3-difluorocyclobutyl)thio)-2-methyl-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydropyrido[2,3-f][1,2,5]thiadiazepin-8-yl)oxy)methyl)cyclopropanecarboxylate (17-2). A mixture of **17-1** (0.245 g, 0.47 mmol), cesium carbonate (0.384 g, 1.18 mmol), and methyl 1-(bromomethyl)cyclopropanecarboxylate (0.137 g, 0.71 mmol) in DMF (2.5 mL) was stirred at 60 °C for 16 hr. Subsequently, the mixture was diluted with iced water (15 mL) and extracted with EtOAc (15 mL x 3). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by prep-HPLC to give **17-2** (0.222 g, 75%) as an off-white solid.

Step 3. Chiral separation of methyl 1-(((3-(3,3-difluorobutyl)-7-((3,3-difluorocyclobutyl)thio)-2-methyl-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydropyrido[2,3-f][1,2,5]thiadiazepin-8-yl)oxy)methyl)cyclopropanecarboxylate (17-2). Compd. **17-2** (170 mg) was separated by chiral HPLC to give **17-2a** (77 mg) and **17-2b** (79 mg) as a white solid, respectively. The stereochemistry of the single enantiomer was arbitrarily assigned.

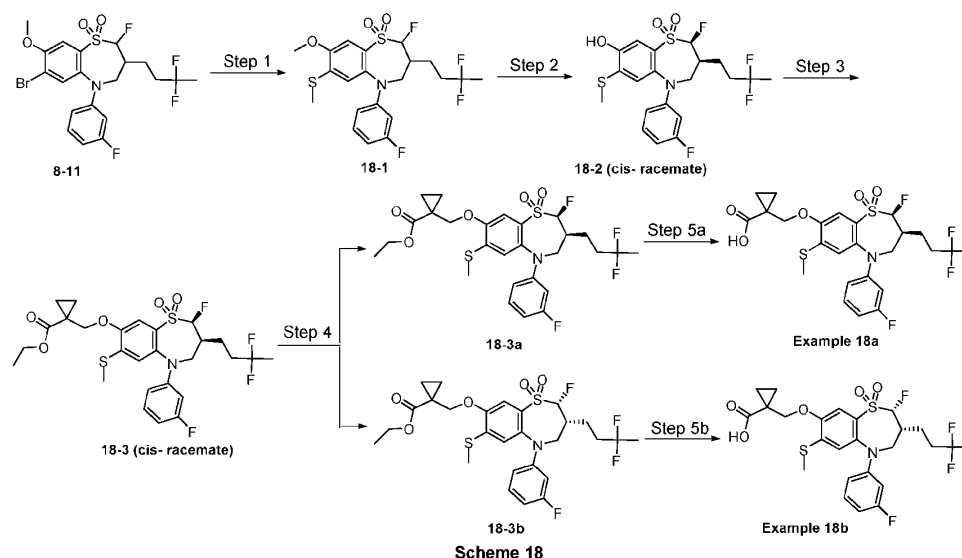
Prep-HPLC conditions: Column: CHIRALPAK IB (250 × 20 mm, 5 μm); Mobile phase: Hexane/IPA/MeOH = 70/15/15 (v/v/v); Flow Rate: 20 mL/min; Column Temperature: 24 °C; and Wavelength: 205 nm. t_R = 13.03 min (single enantiomer **17-2a**); and t_R = 18.59 min (single enantiomer **17-2b**).

Step 4a. Synthesis of (S)-1-(((3-(3,3-difluorobutyl)-7-((3,3-difluorocyclobutyl)thio)-2-methyl-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydropyrido[2,3-f][1,2,5]thiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid (Example 17a). To a stirred solution of **17-2a** (77.3 mg, 0.12 mmol) in THF/H₂O = 4/1 (v/v) (2 mL) was added lithium hydroxide hydrate (15.3 mg, 0.36 mmol), and the reaction mixture was stirred at rt for 12 hr. Subsequently, the mixture was acidified with 2 N aq. HCl solution to pH ~2. The resulting mixture was purified by prep-HPLC to give **Example 17a** (55.1 mg, 73%) as a white solid. MS (ESI): calcd. for C₂₇H₃₁F₄N₃O₅S₂: 617.2; Found: 616.2 [M – 1][–]. ¹H NMR (500 MHz, DMSO-*d*₆): δ 12.41 (s, 1H), 7.43 (s, 1H), 7.31 (t, *J* = 7.7 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 7.04 (t, *J* = 7.4 Hz, 1H), 4.21 – 4.14 (m, 2H), 4.10 (d, *J* = 16.1 Hz, 1H), 3.96 (s, 1H), 3.68 (s, 1H), 3.38 (d, *J* = 16.4 Hz, 3H), 2.77 (s, 3H), 2.55 (s, 1H), 2.41 (s, 1H), 2.04 – 1.89 (m, 2H), 1.75 (s, 1H), 1.68 (d, *J* = 8.9 Hz, 1H), 1.59 (t, *J* = 18.9 Hz, 3H), 1.18 (q, *J* = 3.9 Hz, 2H), 1.01 (q, *J* = 3.9 Hz, 2H) ppm.

Step 4b. Synthesis of (R)-1-(((3-(3,3-difluorobutyl)-7-((3,3-difluorocyclobutyl)thio)-2-methyl-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydropyrido[2,3-f][1,2,5]thiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid (Example 17b). To a stirred solution of **17-2b** (78.9 mg, 0.12 mmol) in THF/H₂O = 4/1 (v/v) (2 mL) was added lithium hydroxide hydrate (15.6 mg, 0.37 mmol) and the reaction mixture was stirred at rt for 12 hr. Subsequently, the mixture was acidified with 2 N aq. HCl solution to pH ~2. The resulting mixture was purified by HPLC to give **Example 17b** (53.9 mg, 71%). MS (ESI): calcd. for C₂₇H₃₁F₄N₃O₅S₂: 617.2; Found: 616.2 [M – 1][–]. ¹H NMR (500 MHz, DMSO-*d*₆): δ 12.42 (s, 1H), 7.43 (s, 1H), 7.31 (t, *J* = 7.8 Hz, 2H), 7.09 (d, *J* = 7.9 Hz, 2H), 7.04 (t, *J* = 7.4 Hz, 1H), 4.21 – 4.14 (m, 2H), 4.10 (d, *J* = 15.8 Hz, 1H), 3.96 (s, 1H), 3.68 (s, 1H), 3.37 (s, 3H), 2.77 (s, 3H), 2.55 (s, 1H), 2.41 (s, 1H), 2.04 – 1.93 (m, 2H), 1.75 (s, 1H), 1.68 (d, *J* = 5.9 Hz, 1H), 1.59 (t, *J* = 18.9 Hz, 3H), 1.18 (q, *J* = 3.8 Hz, 2H), 1.01 (q, *J* = 3.8 Hz, 2H) ppm.

Examples 18a and 18b. 1-(((2R,3S)-3-(3,3-difluorobutyl)-2-fluoro-5-(3-fluorophenyl)-7-(methylthio)-1,1-dioxido-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid (18a) and 1-(((2S,3R)-3-(3,3-difluorobutyl)-

2-fluoro-5-(3-fluorophenyl)-7-(methylthio)-1,1-dioxido-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)methyl)cyclopropane-1-carboxylic acid (**18b**)



5

Step 1. Synthesis of 3-(3,3-difluorobutyl)-2-fluoro-5-(3-fluorophenyl)-8-methoxy-7-(methylthio)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (18-1**).** A solution of **8-11** (900 mg, 1.76 mmol) and MeSNa (1.23 g, 17.64 mmol) in DMF (10 mL) was stirred at 60 °C for 2 hr. The mixture was cooled to rt and then quenched with water. The resulting mixture was extracted with EtOAc (10 mL x 3), and the combined organic extracts were washed with brine (10 mL x 1), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA (10/1 (v/v)), to give **18-1** (500 mg, 59.4%) as a white solid. MS (ESI): calcd. for C₂₁H₂₃F₄NO₃S₂: 477.1; Found: 478.0 [M + 1]⁺.

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Step 2. Synthesis of rac-(2R,3S)-3-(3,3-difluorobutyl)-2-fluoro-5-(3-fluorophenyl)-8-hydroxy-7-(methylthio)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (18-2**).** A solution of **18-1** (500 mg, 1.05 mmol) and LiCl (443.85 mg, 10.47 mmol) in DMSO (5 mL) was stirred at 140 °C for 16 h. The mixture was cooled to rt and then quenched with water.

The resulting mixture was extracted with EtOAc (5 mL x 3). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA (5/1 (v/v)), to give **18-2** (240 mg, 49.5%) as a white solid. MS (ESI): calcd. for C₂₀H₂₁F₄NO₃S₂: 463.1; Found: 464.0 [M + 1]⁺.

Step 3. Synthesis of rac-ethyl 1-(((2R,3S)-3-(3,3-difluorobutyl)-2-fluoro-5-(3-fluorophenyl)-7-(methylthio)-1,1-dioxido-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylate (18-3). To a stirred solution of **18-2** (80 mg, 0.17 mmol) and Cs₂CO₃ (224.94 mg, 0.69 mmol) in DMF (10 mL) were added KI (114.61 mg, 0.69 mmol) and ethyl 1-(((methylsulfonyl)oxy)methyl)cyclopropane-1-carboxylate (57.54 mg, 0.26 mmol) dropwise at rt. The resulting mixture was stirred at 100 °C for 16 h. The mixture was cooled to rt and then quenched with water. The resulting mixture was extracted with EtOAc (10 mL x 3), and the combined organic extracts were washed with brine (10 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by prep-TLC (PE/EA = 5/1 (v/v)) to give **18-3** (60 mg, 59.0%) as a white solid. MS (ESI): calcd. for C₂₇H₃₁F₄NO₅S₂: 589.2; Found: 590.1 [M + 1]⁺.

Step 4. Synthesis of ethyl 1-(((2R,3S)-3-(3,3-difluorobutyl)-2-fluoro-5-(3-fluorophenyl)-7-(methylthio)-1,1-dioxido-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylate (18-3a) and ethyl 1-(((2S,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(3-fluorophenyl)-7-(methylthio)-1,1-dioxido-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylate (18-3b). Compd. **18-3** (60 mg) was purified by prep-Chiral-HPLC with the following conditions: Column: CHIRALPAK ID, 3*25 cm, 5 μm; Mobile Phase A: Hex-HPLC, Mobile Phase B: EtOH-HPLC; Flow rate: 35 mL/min; Gradient: isocratic 20; Wavelength: 254 nm; RT1 (min): 15.8; RT2 (min): 20.3; Sample Solvent: EtOH-HPLC; Injection Volume: 2 mL; Number of Runs: 5. The collected fractions were concentrated to dryness to give **18-3a** (19 mg) (RT2 = 20.3 min, single diastereomer, the stereochemistry was arbitrarily assigned) and **18-3b** (25 mg) (RT1 = 15.8 min, single diastereomer, the stereochemistry was arbitrarily

assigned) as a white solid, respectively. MS (ESI): calcd. for $C_{27}H_{31}F_4NO_5S_2$: 589.2; Found: 590.2 $[M + 1]^+$.

Step 5a. Synthesis of 1-(((2R,3S)-3-(3,3-difluorobutyl)-2-fluoro-5-(3-fluorophenyl)-7-

5 **(methylthio)-1,1-dioxido-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid (Example 18a).** A solution of **18-3a** (19 mg, 0.03 mmol) and LiOH (7.72 mg, 0.32 mmol) in 1,4-dioxane (4 mL) and H₂O (1 mL) was stirred for 24 h at 40°C. The mixture was acidified to pH = 4 with 2 N aq. HCl solution. The resulting mixture was extracted with EA (10 mL x 2). The combined organic extracts were
10 washed with brine (10 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by prep-HPLC with the following conditions: Column: SunFire Prep C18 OBD 5 μ m 30*150 mm Column; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 40% to 80 % B in 8 min; Wavelength: 254 nm/220 nm; RT1 (min): 4.48. The collected solution was concentrated under vacuum to remove ACN and resulting
15 solution was lyophilized to give **Example 18a** (17 mg) (single diastereomer, the stereochemistry was arbitrarily assigned) as a white solid. MS (ESI): calcd. for $C_{25}H_{27}F_4NO_5S_2$: 561.1; Found: 562.2 $[M + 1]^+$. ¹H NMR (300 MHz, CD₃OD): δ 7.52 (s, 1H), 7.22 – 7.14 (m, 2H), 6.50 – 6.42 (m, 2H), 6.34 – 6.30 (m, 1H), 5.58 (d, J = 45.3 Hz, 1H), 4.39 – 4.32 (m, 2H), 4.16 (d, J = 15.9 Hz, 1H), 3.37 (s, 1H), 2.86 – 2.72 (m, 1H), 2.41 (s, 3H),
20 2.23 – 2.05 (m, 2H), 1.79 – 1.61 (m, 5H), 1.40 – 1.36 (m, 2H), 1.20 – 1.17 (m, 2H) ppm.

Step 5b. Synthesis of 1-(((2S,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(3-fluorophenyl)-7-

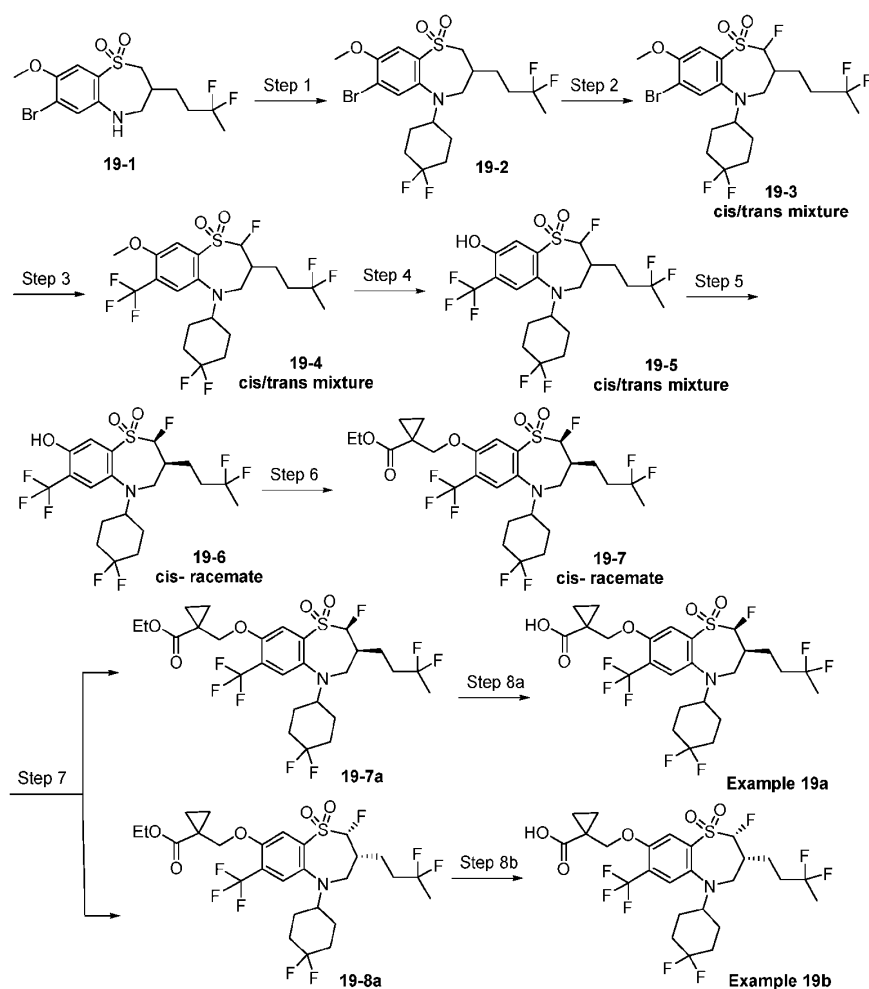
(methylthio)-1,1-dioxido-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid (Example 18b). A solution of methyl **18-3b**
25 (25 mg, 0.04 mmol) and LiOH (10.15 mg, 0.42 mmol) in 1,4-dioxane (4 mL) and H₂O (1 mL) was stirred for 24 h at 40°C. The mixture was acidified to pH = 4 with 2 N aq. HCl solution. The resulting mixture was extracted with EA (10 mL x 2). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by prep-HPLC with the following conditions: Column: SunFire
30 Prep C18 OBD 5 μ m 30*150 mm Column; Mobile Phase A: Water (0.1% FA), Mobile Phase

B: ACN; Flow rate: 60 mL/min; Gradient: 40% to 80 % B in 8 min; Wavelength: 254 nm/220 nm; RT1 (min): 2.84. The collected solution was concentrated under vacuum to remove ACN and resulting solution was lyophilized to give **Example 18b** (22 mg) (single diastereomer, the stereochemistry was arbitrarily assigned) as a white solid. MS (ESI): calcd. for

- 5 $C_{25}H_{27}F_4NO_5S_2$: 561.1; Found: 562.2 $[M + 1]^+$. 1H NMR (300 MHz, CD_3OD): δ 7.52 (s, 1H), 7.22 - 7.14 (m, 2H), 6.50 - 6.42 (m, 2H), 6.35 - 6.29 (m, 1H), 5.58 (d, $J = 45.3$ Hz, 1H), 4.36 (s, 2H), 4.16 (d, $J = 15.9$ Hz, 1H), 3.38 (s, 1H), 2.83 - 2.72 (m, 1H), 2.41 (s, 3H), 2.23 - 2.05 (m, 2H), 1.78 - 1.61 (m, 5H), 1.40 - 1.36 (m, 2H), 1.20 - 1.17 (m, 2H) ppm.

Examples 19a and 19b. 1-(((2R,3S)-3-(3,3-difluorobutyl)-5-(4,4-difluorocyclohexyl)-2-fluoro-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid (19a) and 1-(((2S,3R)-3-(3,3-difluorobutyl)-5-(4,4-difluorocyclohexyl)-2-fluoro-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-

5 tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid (19b)



Scheme 19

Step 1. Synthesis of 7-bromo-3-(3,3-difluorobutyl)-5-(4,4-difluorocyclohexyl)-8-methoxy-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (19-2). To a stirred

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solution of 7-bromo-3-(3,3-difluorobutyl)-8-methoxy-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (**19-1**) (3 g, 7.53 mmol), which was readily prepared by BH_3 reduction of 7-bromo-3-(3,3-difluorobutyl)-8-methoxy-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one 1,1-dioxide (**8-7**), and 4,4-difluorocyclohexan-1-one (3.03 g, 22.60 mmol) in THF (50 mL) was added PhSiH_3 (2.45 g, 22.60 mmol) and Bu_2SnCl_2 (4.58 g, 15.06 mmol) at rt. The resulting mixture was refluxed for 24 h. The mixture was cooled to rt and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA = 4/1 (v/v), to give **19-2** (2.6 g, 66.8%) as a brown liquid. MS (ESI): calcd. for $\text{C}_{20}\text{H}_{26}\text{BrF}_4\text{NO}_3\text{S}$: 515.1; Found: 516.0 $[\text{M} + 1]^+$.

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Step 2. Synthesis of 7-bromo-3-(3,3-difluorobutyl)-5-(4,4-difluorocyclohexyl)-2-fluoro-8-methoxy-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (19-3). In a 250 mL round bottom flask, to a solution of **19-2** (2.6 g, 5.04 mmol) in THF (20 mL) was added dropwise 1M LiHMDS in THF (10.07 mL, 10.07 mmol) at -78°C under N_2 atmosphere. The reaction mixture was stirred at -78°C for 30 min. Then a solution of NFSI (1.59 g, 5.04 mmol) in 2 mL THF was added dropwise and the mixture was stirred for another 4 h. The reaction was quenched with sat. aq. NH_4Cl solution (20 mL), and then the mixture was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4 , and concentrated. The residue was purified by flash chromatography (PE/EA = 2/1 (v/v)) to give **19-3** (1 g, 37.2%) as a brown solid. MS (ESI): calcd. for $\text{C}_{20}\text{H}_{25}\text{BrF}_5\text{NO}_3\text{S}$: 533.1; Found: 534.0 $[\text{M} + 1]^+$.

Step 3. Synthesis of 3-(3,3-difluorobutyl)-5-(4,4-difluorocyclohexyl)-2-fluoro-8-methoxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (19-4). To a stirred solution of **19-3** (650 mg, 1.22 mmol) and methyl 2,2-difluoro-2-sulfoacetate (1402.05 mg, 7.30 mmol) in DMF (10 mL) was added CuBr (872.44 mg, 6.08 mmol) in portions at rt under N_2 atmosphere. The resulting mixture was stirred at 130°C for 16 hr under N_2 atmosphere. The mixture was cooled to rt and then quenched by H_2O (5 mL). The resulting mixture was extracted with EA (10 mL x 2). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , and concentrated. The residue was

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purified by silica gel column chromatography, eluted with PE/EA = 2/1 (v/v), to give **19-4** (400 mg, 62.8%) as a brown solid. MS (ESI): calcd. for C₂₁H₂₅F₈NO₃S: 523.1; Found: 524.0 [M + 1]⁺.

5 **Step 4. Synthesis of rac-(2R,3R)-3-(3,3-difluorobutyl)-5-(4,4-difluorocyclohexyl)-2-fluoro-8-hydroxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (19-5).** To a stirred solution of **19-4** (350 mg, 0.67 mmol) and 1-dodecanethiol (676.63 mg, 3.35 mmol) in DMF (5 mL) was added NaOMe (180.60 mg, 3.35 mmol) at rt. The resulting mixture was stirred at 100°C for 2 h under N₂ atmosphere. The mixture was
10 cooled to rt and then quenched with H₂O (5 mL). The resulting mixture was extracted with EA (10 mL x 2). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA = 2/1 (v/v), to give **19-5** (180 mg, 52.8%) as a brown solid. MS (ESI): calcd. for C₂₀H₂₃F₈NO₃S: 509.1; Found: 510.0 [M + 1]⁺.

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Step 5. Synthesis of rac-(2S,3R)-3-(3,3-difluorobutyl)-5-(4,4-difluorocyclohexyl)-2-fluoro-8-hydroxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (19-6). To a stirred solution of **19-5** (180 mg, 0.35 mmol) in THF (10 mL) was added LiHMDS (3.50 mL, 3.5 mmol) dropwise at -40°C under N₂ atmosphere. The resulting
20 mixture was stirred for 2 h at -40°C. The reaction was quenched by the addition of sat. aq. NH₄Cl (100 mL) at -40°C. The resulting mixture was extracted with EA (10 mL x 2). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA = 2/1 (v/v), to give **19-6** (120 mg, 77.0%) as a yellow solid. MS (ESI): calcd. for
25 C₂₀H₂₃F₈NO₃S: 509.1; Found: 510.0 [M + 1]⁺.

Step 6. Synthesis of rac-ethyl 1-(((2S,3R)-3-(3,3-difluorobutyl)-5-(4,4-difluorocyclohexyl)-2-fluoro-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylate (19-7).
30 To a stirred solution of **19-6** (65 mg, 0.19 mmol) and Cs₂CO₃ (125.10 mg, 0.38 mmol) in

DMF (2 mL) were added KI (42.36 mg, 0.27 mmol) and ethyl 1-(((methylsulfonyl)oxy)methyl)cyclopropane-1-carboxylate (179.17 mg, 0.49 mmol) dropwise at rt. The resulting mixture was stirred at 100°C for 16 hr. The mixture was allowed to cool down to rt and quenched with H₂O (5 mL). The resulting mixture was extracted with EA (5 mL x 2). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by prep-TLC (PE/EA = 4/1 (v/v)) to give **19-7** (60 mg, 75.7%) as a brown solid. MS (ESI): calcd. for C₂₇H₃₃F₈NO₅S: 635.2; Found: 636.1 [M + 1]⁺.

Step 7. Synthesis of ethyl 1-(((2R,3S)-3-(3,3-difluorobutyl)-5-(4,4-difluorocyclohexyl)-2-fluoro-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylate (19-7a) and ethyl 1-(((2S,3R)-3-(3,3-difluorobutyl)-5-(4,4-difluorocyclohexyl)-2-fluoro-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylate (19-7b). Compd. **19-7** (60 mg) was purified by prep-SFC with the following condition: Column: (R, R)-WHELK-O, 3*25 cm, 5 µm; Mobile Phase A: CO₂, Mobile Phase B: MeOH; Flow rate: 80 mL/min; Gradient: isocratic 30% B; Column Temperature (°C): 35; Back Pressure (bar): 100; Wavelength: 220 nm; RT1 (min): 3.3; RT2 (min): 4.8; Sample Solvent: MeOH; Injection Volume: 5 mL. The collected fractions were concentrated under vacuum to give **19-7a** (27 mg) (RT2 = 4.8 min, single diastereomer, stereochemistry was arbitrarily assigned) and **19-7b** (26 mg) (RT1 = 3.3 min, single diastereomer, stereochemistry was arbitrarily assigned) as a white solid, respectively. MS (ESI): calcd. for C₂₇H₃₃F₈NO₅S: 635.2; Found: 636.1 [M + 1]⁺.

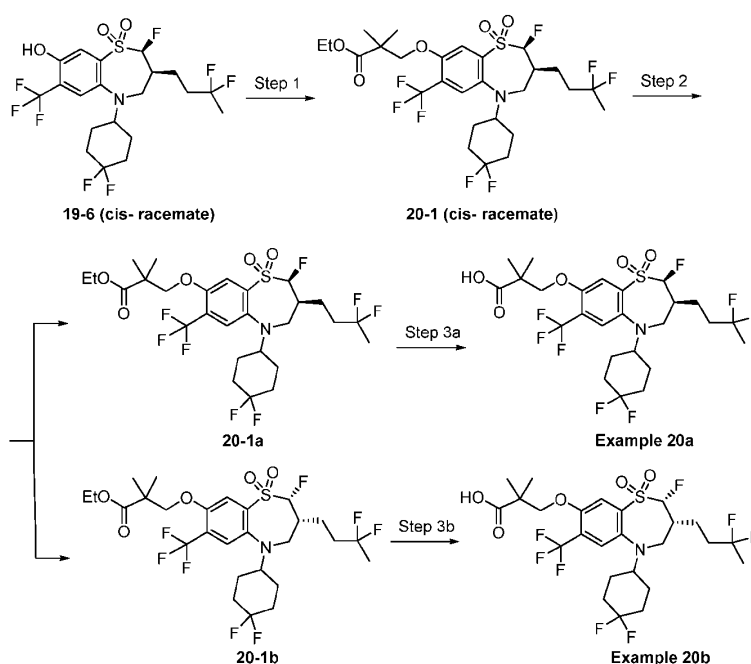
Step 8a. Synthesis of 1-(((2R,3S)-3-(3,3-difluorobutyl)-5-(4,4-difluorocyclohexyl)-2-fluoro-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid (Example 19a). A solution of **19-7a** (27 mg, 0.04 mmol) and LiOH (3.20 mg, 0.13 mmol) in 1,4-dioxane (4 mL) and H₂O (1 mL) was stirred at rt for 16 h. The mixture was acidified to pH = 4 with 2 N aq. HCl solution. The resulting mixture was extracted with EA (5 mL x 2). The combined organic extracts were

washed with brine (5 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue (30 mg) was purified by prep-HPLC with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5µm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 60mL/min mL/min; Gradient: 55% B to 78% B in 8 min; Wavelength: 254 nm/220 nm; RT1(min): 1.88. The collected solution was concentrated under vacuum to remove ACN and resulting solution was dried by lyophilization to give **Example 19a** (10 mg) (single diastereomer, the stereochemistry was arbitrarily assigned) as a white solid. MS (ESI): calcd. for C₂₅H₂₉F₈NO₅S: 607.2; Found: 608.2 [M + 1]⁺. ¹H NMR (300 MHz, CD₃OD): δ 7.67 (s, 1H), 7.54 (s, 1H), 5.60 (d, *J* = 46.2 Hz, 1H), 4.34 – 4.27 (m, 2H), 3.54 – 3.45 (m, 1H), 3.32 – 3.31 (m, 1H), 2.85 – 2.76 (m, 1H), 2.57 – 2.34 (m, 1H), 2.15 – 1.83 (m, 9H), 1.77 – 1.56 (m, 6H), 1.34 – 1.29 (m, 2H), 1.12 – 1.08 (m, 2H) ppm.

Step 8b. Synthesis of 1-(((2S,3R)-3-(3,3-difluorobutyl)-5-(4,4-difluorocyclohexyl)-2-fluoro-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid (Example 19b). A solution of **19-7b** (26 mg, 0.04 mmol) and LiOH (3.20 mg, 0.13 mmol) in 1,4-dioxane (4 mL) and H₂O (1 mL) was stirred for 16 h at rt. The mixture was acidified to pH = 4 with 2N aq. HCl solution. The resulting mixture was extracted with EA (5 mL x 2). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue (30 mg) was purified by prep-HPLC with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5µm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 60mL/min mL/min; Gradient: 55% B to 78% B in 8 min; Wavelength: 254 nm/220 nm; RT1(min): 1.37. The collected solution was concentrated under vacuum to remove ACN and resulting solution was dried by lyophilization to give **Example 19b** (10 mg) (single diastereomer, the stereochemistry was arbitrarily assigned) as a white solid. MS (ESI): calcd. for C₂₅H₂₉F₈NO₅S: 607.2; Found: 608.2 [M + 1]⁺. ¹H NMR (300 MHz, CD₃OD): δ 7.67 (s, 1H), 7.54 (s, 1H), 5.60 (d, *J* = 46.2 Hz, 1H), 4.34 – 4.27 (m, 2H), 3.58 – 3.45 (m, 1H), 3.32 – 3.31 (m, 1H), 2.85 – 2.76 (m, 1H), 2.57 – 2.34 (m, 1H), 2.18 – 1.83 (m,

9H), 1.77 – 1.52 (m, 6H), 1.35 – 1.26 (m, 2H), 1.17 – 1.09 (m, 2H) ppm.

Examples 20a and 20b. 3-(((2R,3S)-3-(3,3-difluorobutyl)-5-(4,4-difluorocyclohexyl)-2-fluoro-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid (20a) and 3-(((2S,3R)-3-(3,3-difluorobutyl)-5-(4,4-difluorocyclohexyl)-2-fluoro-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid (20b)



Scheme 20

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Step 1. Synthesis of rac-ethyl 3-(((2R,3S)-3-(3,3-difluorobutyl)-5-(4,4-difluorocyclohexyl)-2-fluoro-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoate (20-1). To a stirred solution of the cis- racemate **19-6** (115 mg, 0.23 mmol) and Cs₂CO₃ (221.32 mg, 0.68 mmol) in DMF (5 mL) were added KI (112.42 mg, 0.68 mmol) and methyl 2,2-dimethyl-3-((methylsulfonyl)oxy)propanoate (142.37 mg, 0.68 mmol) dropwise at rt. The resulting mixture was stirred for at 100°C 16 h. The mixture was cooled to rt and quenched with H₂O

(5 mL). The resulting mixture was extracted with EA (5 mL x 2). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by prep-TLC (PE/EA = 4/1 (v/v)) to give **20-1** (65 mg, 46.2%) as a brown solid. MS (ESI): calcd. for C₂₆H₃₃F₈NO₅S: 623.2; Found: 624.1 [M + 1]⁺.

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Step 2. Synthesis of ethyl 3-(((2R,3S)-3-(3,3-difluorobutyl)-5-(4,4-difluorocyclohexyl)-2-fluoro-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoate (20-1a) and ethyl 3-(((2S,3R)-3-(3,3-difluorobutyl)-5-(4,4-difluorocyclohexyl)-2-fluoro-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-

10 **tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoate (20-1b).** Compd. **20-1** (65 mg) was purified by prep-HPLC with the following conditions: Column: CHIRALPAK IC 3*25 cm, 5 μm; Mobile Phase A: Hex-HPLC, Mobile Phase B: EtOH-HPLC; Flow rate: 25 mL/min; Gradient: isocratic 20; Wavelength: 254 nm; RT1 (min): 4.3; RT2 (min): 5.9; Sample Solvent: EtOH-HPLC; Injection Volume: 0.5 mL; Number of Runs: 5. The collected
15 fractions were concentrated under vacuum to give **20-1a** (26 mg) (RT1 = 4.3 min, single diastereomer, the stereochemistry was arbitrarily assigned) and **20-1b** (27 mg) (RT1 = 5.9 min, single diastereomer, the stereochemistry was arbitrarily assigned) as a white solid, respectively. MS (ESI): calcd. for C₂₆H₃₃F₈NO₅S: 623.2; Found: 624.1 [M + 1]⁺.

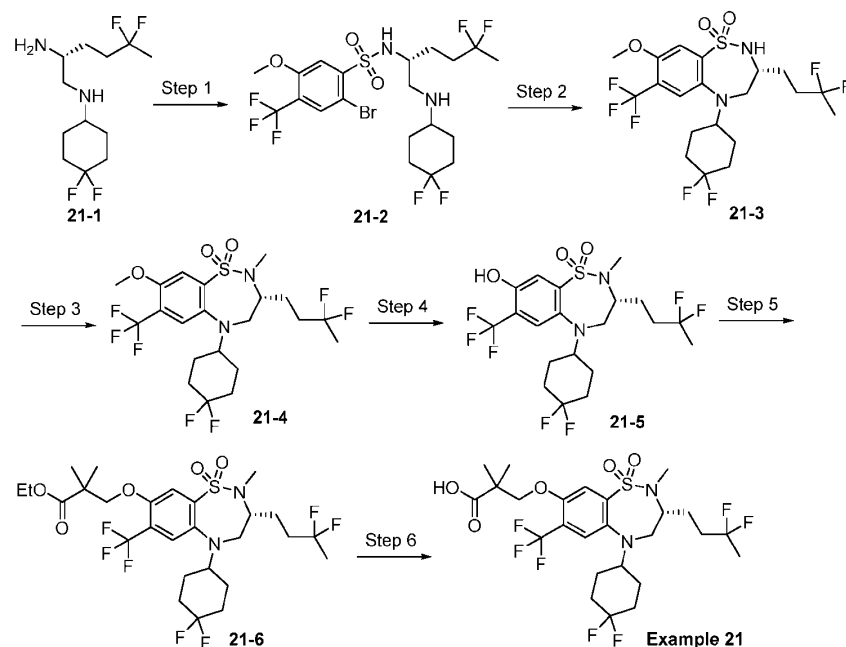
20 **Step 3a. Synthesis of 3-(((2R,3S)-3-(3,3-difluorobutyl)-5-(4,4-difluorocyclohexyl)-2-fluoro-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid (Example 20a).** A solution of **20-1a** (26 mg, 0.04 mmol) and LiOH (3.20 mg, 0.13 mmol) in 1,4-dioxane (4 mL) and H₂O (1 mL) was stirred for 16 h at rt. The mixture was acidified to pH = 4 with 2 N aq. HCl solution. The resulting
25 mixture was extracted with EA (5 mL x 2). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue (30 mg) was purified by prep-HPLC with the following conditions: Column: Xbridge Prep Shield RP18 5 μm OBD 30*150mm Column; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 40% to 60 % B in 8 min; Wavelength: 254 nm/220 nm; RT1
30 (min): 1.95. The collected fractions were concentrated under vacuum to remove ACN and the

resulting solution was dried by lyophilization to give **Example 20a** (14 mg) (single diastereomer, the stereochemistry was arbitrarily assigned) as a white solid. MS (ESI): calcd. for $C_{25}H_{31}F_8NO_5S$: 609.2; Found: 610.2 $[M + 1]^+$. 1H NMR (300 MHz, CD_3OD): δ 7.67 (s, 1H), 7.58 (s, 1H), 5.64 (d, $J = 46.5$ Hz, 1 H), 4.17 (s, 2H), 3.56 – 3.50 (m, 1H), 3.32 – 3.18 (m, 1H), 2.88 – 2.79 (m, 1H), 2.60 – 2.35 (m, 1H), 2.47 – 1.80 (m, 9H), 1.80 – 1.55 (m, 6H), 1.35 (s, 6H) ppm.

Step 3b. Synthesis of 3-(((2S,3R)-3-(3,3-difluorobutyl)-5-(4,4-difluorocyclohexyl)-2-fluoro-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid (Example 20b). A solution of **20-1b** (27 mg, 0.04 mmol) and LiOH (3.20 mg, 0.13 mmol) in 1,4-dioxane (4 mL) and H_2O (1 mL) was stirred for 16 h at rt. The mixture was acidified to pH = 4 with 2 N aq. HCl solution. The resulting mixture was extracted with EA (5 mL x 2). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4 , and concentrated. The residue (30 mg) was purified by prep-HPLC with the following conditions: Column: Xbridge Prep Shield RP18 5 μ m OBD 30*150mm Column; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 40 % to 60 % B in 8 min; Wavelength: 254 nm/220 nm; RT1 (min): 1.72. The collected fractions were concentrated under vacuum to remove ACN and resulting solution was dried by lyophilization to give **Example 20b** (13 mg) (single diastereomer, the stereochemistry was arbitrarily assigned) as a white solid. MS (ESI): calcd. for $C_{25}H_{31}F_8NO_5S$: 609.2; Found: 610.2 $[M + 1]^+$. 1H NMR (300 MHz, CD_3OD): δ 7.67 (s, 1H), 7.58 (s, 1H), 5.64 (d, $J = 46.2$ Hz, 1 H), 4.17 (s, 2H), 3.56 – 3.50 (m, 1H), 3.34 – 3.30 (m, 1H), 2.88 – 2.79 (m, 1H), 2.60 – 2.35 (m, 1H), 2.47 – 1.80 (m, 9H), 1.80 – 1.55 (m, 6H), 1.35 (s, 6H) ppm.

Example 21. (R)-3-((3-(3,3-difluorobutyl)-5-(4,4-difluorocyclohexyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)-2,2-

dimethylpropanoic acid



Scheme 21

- 5 **Step 1. Synthesis of (R)-2-bromo-N-(1-((4,4-difluorocyclohexyl)amino)-5,5-difluorohexan-2-yl)-5-methoxy-4-(trifluoromethyl)benzenesulfonamide (21-2).** To a stirred solution of (R)-N1-(4,4-difluorocyclohexyl)-5,5-difluorohexane-1,2-diamine (**21-1**) (500 mg, 1.85 mmol), which was prepared by following the same procedure of **1-7** and replacing aniline with 4,4-difluorocyclohexylamine, and TEA (374 mg, 3.7 mmol) in THF (6
- 10 mL) was added a solution of 2-bromo-5-methoxy-4-(trifluoromethyl)benzenesulfonyl chloride (781 mg, 2.22 mmol) in THF (2 mL) at 0°C. The resulting reaction mixture was stirred at rt for 3 hr. After completion of the reaction (monitored by LCMS), the reaction mixture was quenched with ice-cold water (30 mL) and the aqueous layer was extracted with EA (15 mL x 3). The combined organic layer was washed with water (20 mL) and brine (20
- 15 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography (30% EA/PE) to give **21-2** (60 mg, 55.3%) as a yellow solid. TLC: 30% EA/PE (v/v) (R_f: 0.4). MS (ESI): calcd. for C₂₀H₂₆BrF₇N₂O₃S: 586.1; Found: 587.2 [M

+ 1]⁺.

Step 2. Synthesis of (R)-3-(3,3-difluorobutyl)-5-(4,4-difluorocyclohexyl)-8-methoxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (21-3). To a stirred solution of **21-2** (600 mg, 1.0 mmol) and K₂CO₃ (276 mg, 2.0 mmol) in DMF (5 mL) was added CuI (190 mg, 1.0 mmol) and the mixture was heated at 100 °C for 3 hr. After completion of the reaction (monitored by LCMS), the reaction mixture was quenched with saturated aq. NH₄Cl solution (15 mL) and the aqueous layer was extracted with EA (20 mL x 3). The combined organic layer was washed with water (30 mL) and brine (30 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give crude **21-3** (450 mg) as a yellow oil, which was used in the next step without further purification. TLC: 15% EA/PE (v/v) (R_f: 0.5). MS (ESI): calcd. for C₂₀H₂₅F₇N₂O₃S: 506.1; Found: 507.2 [M + 1]⁺.

Step 3. Synthesis of (R)-3-(3,3-difluorobutyl)-5-(4,4-difluorocyclohexyl)-8-methoxy-2-methyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (21-4). To a stirred solution of **21-3** (450 mg, crude product, 0.89 mmol) and Cs₂CO₃ (580 mg, 1.78 mmol) in NMP (5 mL) was added MeI (379 mg, 2.67 mmol) and the reaction was stirred at rt for 5 hr. After completion of the reaction (monitored by LCMS), the reaction mixture was quenched with ice-cold water (20 mL) and the aqueous layer was extracted with EA (15 mL x 3). The combined organic layer was washed with water (20 mL) and brine (20 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography (20% EA/PE (v/v)) to give **21-4** (300 mg, 56%) as a yellow solid. TLC: 30% EA/PE (v/v) (R_f: 0.4). MS (ESI): calcd. for C₂₁H₂₇F₇N₂O₃S: 520.2; Found: 521.2 [M + 1]⁺.

Step 4. Synthesis of (R)-3-(3,3-difluorobutyl)-5-(4,4-difluorocyclohexyl)-8-hydroxy-2-methyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (21-5). To a stirred solution of **21-4** (300 mg, 0.58 mmol) in DMF (3 mL) was added CH₃SNa (203 mg, 2.9 mmol) and the reaction was heated at 95 °C for 16 hr. After

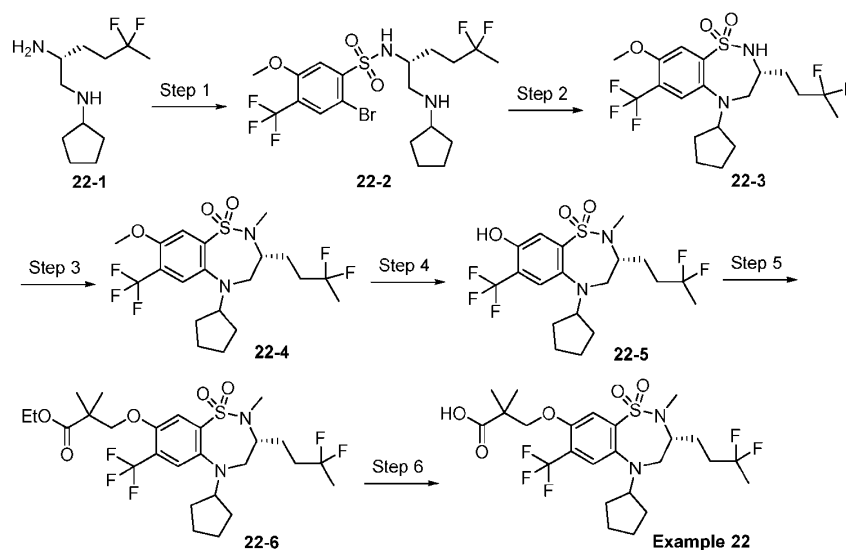
completion of the reaction (monitored by LCMS), the reaction was quenched with ice water (12 mL) and the aqueous layer was extracted with EA (15 mL x 3). The combined organic layer was washed with water (20 mL) and brine (20 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography (20% EA/PE (v/v)) to give **21-5** (150 mg, 51%) as a yellow solid. TLC: 30% EA/PE (v/v) (R_f: 0.6). MS (ESI): calcd. for C₂₀H₂₅F₇N₂O₃S: 506.1; Found: 507.2 [M + 1]⁺.

Step 5. Synthesis of ethyl (R)-3-((3-(3,3-difluorobutyl)-5-(4,4-difluorocyclohexyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)-2,2-dimethylpropanoate (21-6). To a stirred solution of **21-5** (150 mg, 0.30 mmol) and Cs₂CO₃ (293 mg, 0.9 mmol) in DMF (2 mL) was added ethyl 2,2-dimethyl-3-((methylsulfonyl)oxy)propanoate (134 mg, 0.6 mmol). The reaction was heated at 100 °C for 3 hr. After completion of the reaction (monitored by LCMS), the reaction was poured into water (10 mL) and extracted with EA (15 mL x 3). The combined organic layer was washed with water (10 mL x 3), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography to give **21-6** (70 mg, 37%) as a white solid. TLC: 40% EA/PE (v/v) (R_f: 0.5). MS (ESI): calcd. for C₂₇H₃₇F₇N₂O₅S: 634.2; Found: 635.2 [M + 1]⁺.

Step 6. Synthesis of (R)-3-((3-(3,3-difluorobutyl)-5-(4,4-difluorocyclohexyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid (Example 21). To a stirred solution of **21-6** (40 mg, 0.064) in MeOH/THF/H₂O (1 mL/1 mL/0.5 mL) was added LiOH·H₂O (14.3 mg, 0.34 mmol) and the reaction mixture was stirred at rt for 3 hr. After completion of the reaction (monitored by LCMS), the reaction was neutralized with 1 N aq. HCl solution. The aqueous layer was extracted with EA (10 mL x 3). The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by prep-HPLC to give **Example 21** (20 mg, 53%) as a white solid. MS (ESI): calcd. for C₂₅H₃₃F₇N₂O₅S: 606.2; Found: 607.3 [M + 1]⁺. ¹H NMR (400 MHz, CDCl₃): δ 7.47 (s, 1H), 7.26 (s, 1H), 4.09 – 4.03 (m, 2H), 3.41 (s, 2H), 3.16 (s, 2H), 2.61 (s, 2H), 2.17 (m, J = 40.2 Hz, 4H), 2.06 – 1.77 (m, 6H), 1.65 (t, J =

30.1 Hz, 5H), 1.32 (d, J = 2.1 Hz, 6H) ppm.

Example 22. (R)-3-((5-cyclopentyl-3-(3,3-difluorobutyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid



Scheme 22

Step 1. Synthesis of (R)-2-bromo-N-(1-(cyclopentylamino)-5,5-difluorohexan-2-yl)-5-methoxy-4-(trifluoromethyl)benzenesulfonamide (22-2). To a stirred solution of (R)-N1-cyclopentyl-5,5-difluorohexane-1,2-diamine (**22-1**) (1.0 g, 4.5 mmol), which was prepared by following the same procedure of **1-7** and replacing aniline with cyclopentamine, and TEA (1.4 g, 13.5 mmol) in THF (10 mL) was added a solution of 2-bromo-5-methoxy-4-(trifluoromethyl)benzenesulfonyl chloride (1.9 g, 5.4 mmol) in THF (10 mL) at 0°C. The resulting reaction mixture was stirred at rt for 3 hr. After completion of the reaction (monitored by LCMS), the reaction mixture was quenched with ice-cold water (40 mL) and the aqueous layer was extracted with EA (40 mL x 3). The combined organic extracts were washed with water (40 mL) and brine (40 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography (30% EA/PE

(v/v)) to give **22-2** (1.05 g, 49%) as a yellow solid. TLC: 30% EA/PE (v/v) (R_f : 0.4). MS (ESI): calcd. for $C_{19}H_{26}BrF_5N_2O_3S$: 536.1; Found: 537.2 $[M + 1]^+$.

Step 2. Synthesis of (R)-5-cyclopentyl-3-(3,3-difluorobutyl)-8-methoxy-7-

5 **(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (22-3)**. To a stirred solution of **22-2** (1.05 g, 2.0 mmol) and K_2CO_3 (828 mg, 6.0 mmol) in DMF (15 mL) was added Cu (640 mg, 10.0 mmol) and heated at 115 °C for 16 hr. After completion of the reaction (monitored by LCMS), the reaction mixture was quenched with saturated aq. NH_4Cl (30 mL) solution, and the aqueous layer was extracted with EA (50 mL x 3). The combined
10 organic extracts were washed with water (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4 , and concentrated. The residue was dried in vacuo to give crude **22-3** (1.0 g) as a yellow oil, which was used in the next step without further purification. TLC: 15% EA/PE (v/v) (R_f : 0.5). MS (ESI): calcd. for $C_{19}H_{25}F_5N_2O_3S$: 456.2; Found: 457.3 $[M + 1]^+$.

15 **Step 3. Synthesis of (R)-5-cyclopentyl-3-(3,3-difluorobutyl)-8-methoxy-2-methyl-7-**

(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (22-4). To a stirred solution of **22-3** (1.0 g, crude product, 2.0 mmol) and Cs_2CO_3 (2.0 g, 6.0 mmol) in NMP (20 mL) was added MeI (852 mg, 6.0 mmol) and the reaction mixture was stirred at rt for 5 hr. After completion of the reaction (monitored by LCMS), the reaction mixture was
20 quenched with ice-cold water (50 mL), and the aqueous layer was extracted with EA (50 mL x 3). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4 , and concentrated. The residue was purified by silica gel column chromatography (20% EA/PE (v/v)) to give **22-4** (500 mg, 53%) as a yellow solid. TLC: 30% EA/PE (v/v) (R_f : 0.4). MS (ESI): calcd. for $C_{20}H_{27}F_5N_2O_3S$: 470.2; Found: 471.3
25 $[M + 1]^+$.

Step 4. Synthesis of (R)-5-cyclopentyl-3-(3,3-difluorobutyl)-8-hydroxy-2-methyl-7-

(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (22-5). To a stirred solution of **22-4** (500 mg, 1.06 mmol) in DMF (10 mL) was added CH_3SNa (382 mg,
30 5.30 mmol) and the reaction mixture was heated at 95 °C for 16 hr. After completion of the

reaction (monitored by LCMS), the reaction mixture was quenched with ice water (20 mL) and the aqueous layer was extracted with EA (30 mL x 3). The combined organic extracts were washed with water (30 mL) and brine (30 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography (20% EA/PE (v/v)) to give **22-5** (620 mg, 64%) as a yellow solid. TLC: 30% EA/PE (v/v) (R_f: 0.6). MS (ESI): calcd. for C₁₉H₂₅F₅N₂O₃S: 456.2; Found: 457.3 [M + 1]⁺.

Step 5. Synthesis of ethyl (R)-3-((5-cyclopentyl-3-(3,3-difluorobutyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)-2,2-dimethylpropanoate (22-6). To a stirred solution of **22-5** (150 mg, 0.33 mmol) and Cs₂CO₃ (323 mg, 0.99 mmol) in DMF (2 mL) was added ethyl 2,2-dimethyl-3-((methylsulfonyl)oxy)propanoate (148 mg, 0.66 mmol). The reaction was heated at 100 °C for 3 hr. After completion of the reaction (monitored by LCMS), the reaction was poured into water (10 mL) and extracted with EA (15 mL x 3). The combined organic extracts were washed with water (10 mL x 3), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography (20% EA/PE (v/v)) to give **22-6** (60 mg, 31%) as a white solid. TLC: 40% EA/PE (v/v) (R_f: 0.5). MS (ESI): calcd. for

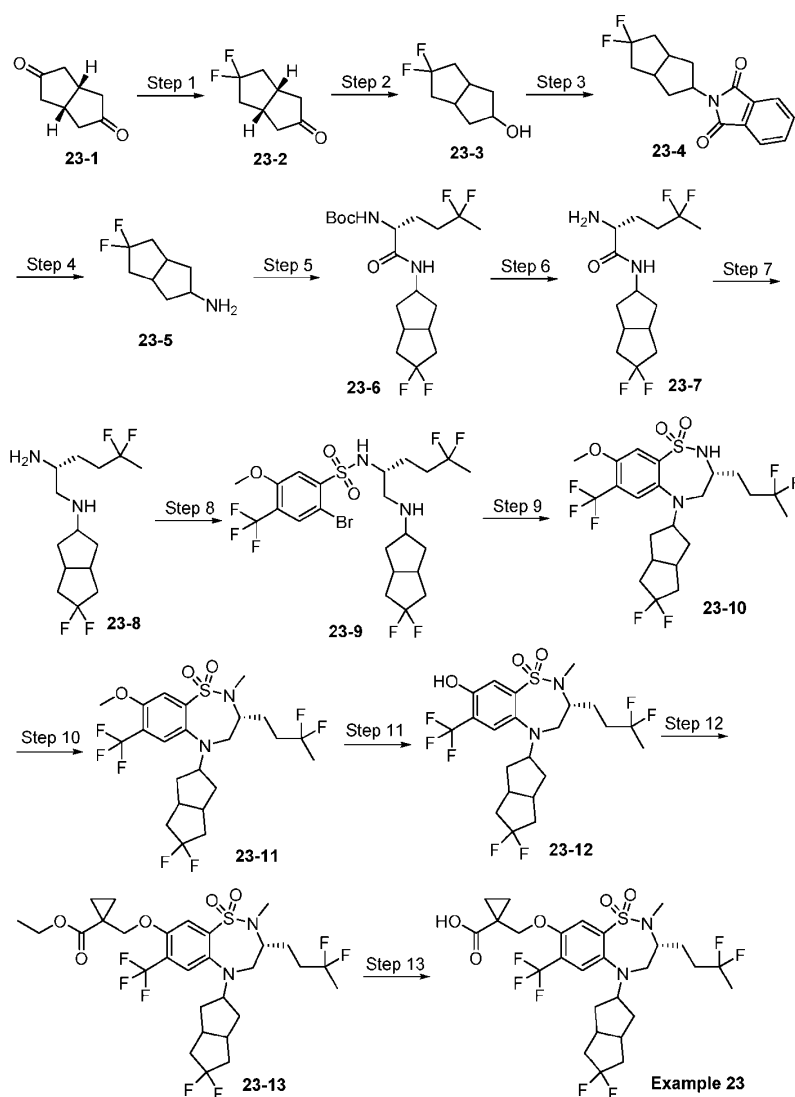
C₂₆H₃₇F₅N₂O₅S: 584.2; Found: 585.2 [M + 1]⁺.

Step 6. Synthesis of (R)-3-((5-cyclopentyl-3-(3,3-difluorobutyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)-2,2-

- 5 **dimethylpropanoic acid (Example 22).** To a stirred solution of **22-6** (40 mg, 0.068) in MeOH/THF/H₂O (1 mL/1 mL/0.5 mL) was added LiOH·H₂O (14.3 mg, 0.34 mmol) and the reaction was stirred at rt for 3 hr. After completion of the reaction (monitored by LCMS), the reaction was neutralized with 1 N aq. HCl solution. The aqueous layer was extracted with EA (10 mL x 3), and the combined organic extracts were dried over anhydrous Na₂SO₄ and
- 10 concentrated. The residue was purified by prep-HPLC to give **Example 22** (26 mg, 68%) as a white solid. MS (ESI): calcd. for C₂₄H₃₃F₅N₂O₅S: 556.2; Found: 557.3 [M + 1]⁺. ¹H NMR (400 MHz, CDCl₃): δ 7.45 (s, 1H), 7.27 (s, 1H), 4.06 (dd, J = 16.5, 8.1 Hz, 2H), 3.86 (dd, J = 22.4, 15.2 Hz, 1H), 3.16 (s, 1H), 2.64 (s, 4H), 1.96 (ddd, J = 29.2, 26.0, 22.5 Hz, 5H), 1.84 – 1.42 (m, 10H), 1.32 (t, J = 23.8 Hz, 6H) ppm.

15

Example 23. 1-(((3R)-3-(3,3-difluorobutyl)-5-(5,5-difluorooctahydropentalen-2-yl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid



Scheme 23

Step 1. Synthesis of (3aR,6aS)-5,5-difluorohexahydropentalen-2(1H)-one (23-2). To a stirred solution of (3aS,6aS)-tetrahydropentalene-2,5(1H,3H)-dione (**23-1**) (13.8 g, 0.1 mol) in DCM (200 mL) was added DAST (48.3 g, 0.3 mol) in small portions at 0°C. After stirring at rt for 16 h, the reaction mixture was diluted with saturated aq. NaHCO₃ (200 mL). The reaction was extracted with EA (150 mL x 2). The combined organic extracts were washed with brine (100 mL x 2), dried over anhydrous Na₂SO₄, concentrated. The residue was

purified by silica gel column chromatography, eluted with PE/EA = 3/1 (v/v), to give **23-2** (8.0 g, 50%) as a colorless oil. TLC: 20% EA/ PE (R_f: 0.4). MS (ESI): calcd. for C₈H₁₀F₂O: 160.1; Found: 160.2 [M+H]⁺.

5 **Step 2. Synthesis of 5,5-difluorooctahydropentalen-2-ol (23-3).** To a solution of **23-2** (3.16 g, 19.8 mmol) in MeOH (30 ml) was added NaBH₄ (1.55 g, 40 mmol) in an ice bath. The reaction was stirred for 2 h at room temperature. The reaction was monitored by TLC. The starting material disappeared and a new spot was detected. The reaction mixture was poured into water (50 mL) and extracted with EA (70 mL x 3). The combined organic extracts were
10 washed with brine (100 mL x 2), dried over anhydrous Na₂SO₄, concentrated. The residue was dried in vacuo to give crude **23-3** (2.95 g, 92%) as a colorless oil, which was used for the next step without further purification. TLC: 25% EA/PE (v/v) (R_f: 0.5). MS (ESI): calcd. for C₈H₁₂F₂O: 162.1; Found: 162.2 [M+H]⁺.

15 **Step 3. Synthesis of 2-(5,5-difluorooctahydropentalen-2-yl)isoindoline-1,3-dione (23-4).** To a solution of **23-3** (2.95 g, 18.2 mmol), isoindoline-1,3-dione (3.21 g, 21.9 mmol), and PPh₃ (6.17 g, 27.3 mmol) in THF (100 ml) was added DIAD (6.62 g, 32.8 mmol) in an ice bath. The reaction was stirred at rt for 6 h. The reaction was concentrated, and the residue was purified by silica gel column chromatography (20% EA/PE (v/v)) to give **23-4** (3.8 g,
20 72%) as a white solid. TLC: 15% EA/ PE (v/v) (R_f: 0.5). MS (ESI): calcd. for C₁₆H₁₅F₂NO₂: 291.1; Found: 292.3 [M+H]⁺.

Step 4. Synthesis of 5,5-difluorooctahydropentalen-2-amine (23-5). To a solution of **23-4** (3.8 g, 13.1 mmol) in MeOH (30 ml) was added NH₂NH₂ (4.1 g, 65.3 mmol). The reaction
25 was stirred at 60°C for 5 h. The mixture was filtered and solid was washed with MeOH (20 mL). The filtrate was concentrated. The residue was diluted with Et₂O (100 ml) and filtered. The filtrate was acidified with 4N HCl in dioxane (20 mL). After stirring for 30 min, the solution was concentrated in vacuo to give a crude product, which was mixed with ACN (40 mL). The solid was collected and dried in vacuo to give **23-5** (1.5 g, 58%) as a pale-yellow
30 solid, which was used in the next step without further purification. TLC: 15% MeOH/ DCM

(v/v) (R_f : 0.3). MS (ESI): calcd. for $C_8H_{13}F_2N$: 161.1; Found: 162.2 $[M+H]^+$.

Step 5. Synthesis of tert-butyl ((2R)-1-((5,5-difluorooctahydropentalen-2-yl)amino)-5,5-difluoro -1-oxohexan-2-yl)carbamate (23-6). To a solution of (R)-2-((tert-butoxycarbonyl)amino)-5,5-difluorohexanoic acid (1.2 g, 4.49 mmol) in DMF (15.0 ml) was added DIEA (2.0 g, 15.7 mmol) and HATU (2.56 g, 6.74 mmol) in an ice bath. After stirring for 30 min, **23-5** (885 mg, 4.49 mmol) was added. The reaction was stirred at rt for 16 h. The reaction mixture was quenched with H_2O (30 ml) and extracted with EA (40 mL x 2). The combined organic extracts were washed with brine, dried over Na_2SO_4 , and concentrated. The residue was purified by silica gel column chromatography (35% EA/PE (v/v)) to give **23-6** (1.2 g, 65%) as a colorless oil. TLC: 35% EA/PE (v/v) (R_f : 0.3). MS (ESI): calcd. for $C_{19}H_{30}F_4N_2O_3$: 410.2; Found: 355.2 $[M + H - 56]^+$.

Step 6. Synthesis of (2R)-2-amino-N-(5,5-difluorooctahydropentalen-2-yl)-5,5-difluorohexanamide (23-7). To a solution of **23-6** (370 mg, 0.90 mmol) in DCM (9.0 ml) was added TFA (3.0 ml) in an ice bath. The reaction mixture was stirred at rt for 2 hr and concentrated. The residue was diluted with saturated aq. $NaHCO_3$ solution and extracted with DCM (30 mL x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was dried in vacuo to give crude **23-7** (260 mg, 93%) as a yellow oil, which was used in the next step without further purification. MS (ESI): calcd. for $C_{14}H_{22}F_4N_2O$: 310.2; Found: 311.2 $[M+H]^+$.

Step 7. Synthesis of (2R)-N1-(5,5-difluorooctahydropentalen-2-yl)-5,5-difluorohexane-1,2-diamine (23-8). To a solution of **23-7** (260 mg, 0.84 mmol) in THF (6 ml) was added LAH (2.5 M in THF, 1.7 ml) in an ice bath. The reaction mixture was stirred at 60 °C for 16 hr and cooled to 0 °C. The reaction mixture was quenched with H_2O (160 mg), followed by 10% aq. NaOH solution (w/w) (160 mg) and Et_2O (50 mL). The resulting mixture was dried over anhydrous Na_2SO_4 and concentrated. The residue was dried in vacuo to give crude **23-8** (200 mg, 81%) as a yellow oil, which was used in the next step without further purification. TLC: 12% MeOH/DCM (v/v) (R_f : 0.3). MS (ESI): calcd. for $C_{14}H_{24}F_4N_2$: 296.2; Found:

297.1 [M+H]⁺.

Step 8. Synthesis of 2-bromo-N-((2R)-1-((5,5-difluorooctahydropentalen-2-yl)amino)-5,5-difluorohexan-2-yl)-5-methoxy-4-(trifluoromethyl)benzenesulfonamide (23-9). To a solution of **23-8** (250 mg, 1.06 mmol) in DCM (3.0 ml) and TEA (375 mg, 3.71 mmol) was added sulfonyl chloride (373 mg, 1.06 mmol) in an ice bath. The reaction was stirred at rt for 16 hr. The reaction mixture was quenched with H₂O (10 mL) and extracted with EA (10 mL x 2). The combined organic extracts were washed with brine, dried over Na₂SO₄, and concentrated. The residue which was purified by silica gel column chromatography (50% EA/PE (v/v)) to give **23-9** (400 mg, 62%) as a yellow oil. TLC: 50% EA/PE (v/v) (R_f: 0.3). MS (ESI): calcd. for C₂₂H₂₈BrF₇N₂O₃S: 612.1; Found: 613.2 [M+H]⁺.

Step 9. Synthesis of (3R)-3-(3,3-difluorobutyl)-5-(5,5-difluorooctahydropentalen-2-yl)-8-methoxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (23-10). To a solution of **23-9** (100 mg, 0.16 mmol) and K₂CO₃ (67 mg, 0.48 mmol) in DMF (2.0 mL) was added Cu (21 mg, 0.32 mmol) under nitrogen atmosphere. The reaction was stirred at 120 °C for 16 hr. The reaction mixture was quenched with H₂O (10 mL) and extracted with EA (20 mL x 2). The combined organic extracts were washed with brine, dried over Na₂SO₄, and concentrated. The residue was dried in vacuo to give crude **23-10** (100 mg) as a yellow oil, which was used in the next step without further purification. TLC: 35% EA/PE (v/v) (R_f: 0.3). MS (ESI): calcd. for C₂₂H₂₇F₇N₂O₃S: 532.2; Found: 533.3 [M+H]⁺.

Step 10. Synthesis of (3R)-3-(3,3-difluorobutyl)-5-(5,5-difluorooctahydropentalen-2-yl)-8-methoxy-2-methyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (23-11). To a stirred solution of **23-10** (1.3 g, 2.44 mmol) and K₂CO₃ (507 mg, 3.66 mmol) in NMP (13 mL) was added MeI (0.46 mL, 7.32 mmol) in portions at 0°C. After stirring at rt for 2 hr, the reaction mixture was diluted with H₂O (20 mL). The resulting mixture was extracted with EA (30 mL x 2), and the combined organic extracts were washed with brine (10 mL x 2), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA = 3/1 (v/v), to give **23-11**

(692 mg, 52%) as a colorless oil. TLC: 33% EA/PE (v/v) (R_f : 0.5). MS (ESI): calcd. for $C_{23}H_{29}F_7N_2O_3S$: 546.2; Found: 546.7 $[M+H]^+$.

Step 11. Synthesis of (3R)-3-(3,3-difluorobutyl)-5-(5,5-difluorooctahydropentalen-2-yl)-8-hydroxy-2-methyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (23-12). To a solution of **23-11** (40 mg, 0.073 mmol) in DMF (0.5 mL) was added MeSNa (21 mg, 0.292 mmol), and the reaction was stirred at 100°C for 16 hr. The reaction mixture was diluted with sat. aq. NH_4Cl solution (10 mL), acidified to pH = 5~6 with 4 N aq. HCl solution, and extracted with EA (10 mL x 2). The combined organic extracts were washed with sat. aq. LiCl solution (10 mL) and brine (10 mL), dried over Na_2SO_4 , and concentrated. The residue was purified by silica gel column chromatography (60% EA/PE (v/v)) to give **23-12** (33 mg, 87%) as a colorless oil. TLC: 40% EA/PE (v/v) (R_f : 0.3). MS (ESI): calcd. for $C_{22}H_{27}F_7N_2O_3S$: 532.2; Found: 532.8 $[M+H]^+$

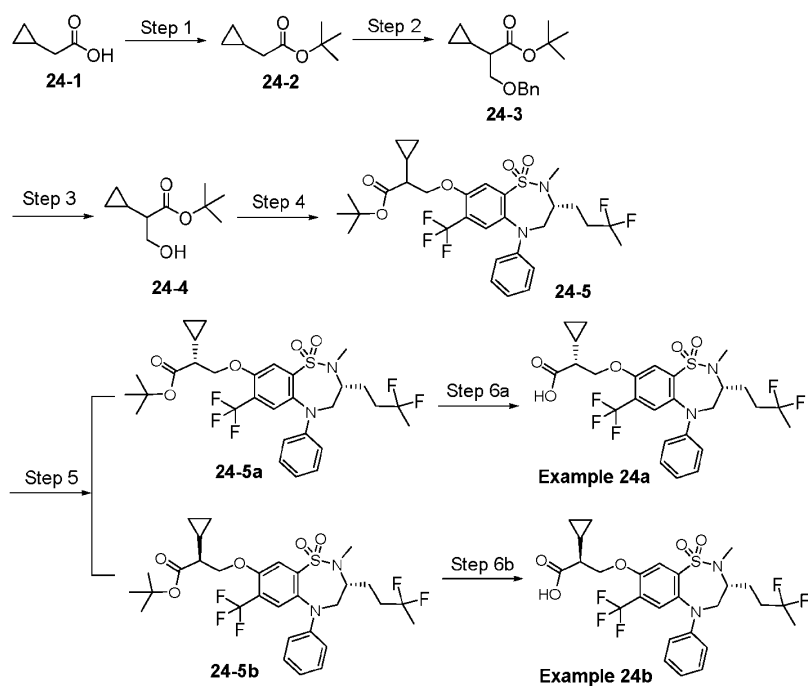
Step 12. Synthesis of ethyl 1-(((3R)-3-(3,3-difluorobutyl)-5-(5,5-difluorooctahydropentalen-2-yl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylate (23-13). To a solution of **23-12** (113 mg, 0.205 mmol) and Cs_2CO_3 (200 mg, 0.615 mmol) in DMF (1 mL) was added ethyl 1-(((methylsulfonyl)oxy)methyl)cyclopropane-1-carboxylate (82 mg, 0.369 mmol) at rt, and the reaction mixture was stirred at 70°C for 5 hr. Subsequently, the mixture was diluted with water (5 mL) and extracted with EA (10 mL x 2). The combined organic extracts were washed with sat. aq. LiCl solution (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4 , and concentrated. The residue was purified by silica gel column chromatography (30% EA/PE (v/v)) to give **23-13** (96 mg, 71%) as a white solid. TLC: 40% EA/PE (v/v) (R_f : 0.5). MS (ESI): calcd. for $C_{29}H_{37}F_7N_2O_5S$: 658.2; Found: 659.0 $[M+H]^+$. 1H NMR (400 MHz, CD_3OD): δ 7.51 (s, 1H), 7.40 (s, 1H), 4.25 (s, 2H), 4.13 (q, J = 7.1 Hz, 3H), 3.98 – 3.56 (m, 1H), 3.44 – 3.34 (m, 1H), 2.90 – 2.49 (m, 5H), 2.39-2.16 (m, 2H), 2.17 – 1.69 (m, 10H), 1.62 (t, J = 18.5 Hz, 4H), 1.30 (dd, J = 7.1, 4.2 Hz, 2H), 1.24 –

1.13 (m, 3H), 1.09 (dd, J = 7.1, 4.1 Hz, 2H) ppm.

Step 13. Synthesis of 1-(((3R)-3-(3,3-difluorobutyl)-5-(5,5-difluorooctahydropentalen-2-yl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-

5 **tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid (Example 23).** To a solution of **23-13** (20 mg, 0.030 mmol) in MeOH/THF/H₂O (0.75 mL, v/v/v = 1/2/2) was added NaOH (12 mg, 0.303 mmol), and the reaction was stirred at rt for 3 hr. After completion of the reaction, the reaction mixture solution was diluted with water (5 mL), acidified to pH = 6~7 with 3N aq. HCl solution, and extracted with EA (10 mL x 2). The
10 combined organic extracts were dried over Na₂SO₄ and concentrated. The residue was purified by prep-HPLC to give **Example 23** (10.6 mg, 56%) as a white solid. TLC: 10% MeOH/DCM (v/v) (R_f: 0.5). MS (ESI): calcd. for C₂₇H₃₃F₇N₂O₅S: 630.2, Found: 631.2 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 7.51 (s, 1H), 7.40 (s, 1H), 4.25 (dd, J = 20.4, 9.6 Hz, 2H), 4.13 (s, 1H), 4.05 – 3.64 (m, 1H), 3.44 – 3.34 (m, 1H), 2.88 – 2.43 (m, 5H), 2.38 –
15 2.19 (m, 2H), 2.17 – 1.69 (m, 10H), 1.62 (t, J = 18.5 Hz, 4H), 1.30 (dd, J = 6.6, 3.9 Hz, 2H), 1.08 (d, J = 2.6 Hz, 2H) ppm.

Examples 24a and 24b. (R)-2-cyclopropyl-3-(((R)-3-(3,3-difluorobutyl)-2-methyl-1,1-dioxido-5-phenyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)propanoic acid (24a) and (S)-2-cyclopropyl-3-(((R)-3-(3,3-difluorobutyl)-2-methyl-
20 1,1-dioxido-5-phenyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)propanoic acid (24b)



Scheme 24

- Step 1. Synthesis of tert-butyl 2-cyclopropylacetate (24-2).** To a solution of 5 g (50 mmol) of cyclopropylacetic acid (24-1) in 25 ml of dichloromethane at 0 °C was added a drop of
- 5 DMF, followed by 6.99 g (55 mmol) of oxalyl chloride dropwise. The reaction mixture was stirred between 0°C and 10°C for 2 h and then concentrated under reduced pressure. The residue was briefly (about 5 min) dried under high vacuum and then taken up in dry THF (10 mL), and the resulting mixture was cooled to 0°C. Subsequently, 1 M potassium tert-butoxide in THF (45 mL, 45 mmol) was added dropwise, and the mixture was stirred at rt for 2 hr and
- 10 then concentrated. The residue was added diethyl ether and 0.5 N aq. NaOH solution. The organic layer was dried over anhydrous MgSO₄ and concentrated. The residue was briefly dried in vacuo to give crude 24-2 (2.1 g, 27%) as a pale-yellow oil, which was used in the next step without further purification.
- 15 **Step 2. Synthesis of tert-butyl 3-(benzyloxy)-2-cyclopropylpropanoate (24-3).** Compd. 24-2 (4 g, 25.6 mmol) in 30 mL of THF was added HMPA (1.38 g, 76.8 mmol) and LDA

(38.4 mL, 76.8 mmol, 2.0 mol/L in THF/n-heptane) at -78 °C. After the solution was stirred at -78 °C for 20 min, a solution of ((chloromethoxy)methyl)benzene (6 g, 38.4 mmol) in THF (10 mL) was added dropwise. The reaction mixture was stirred at -78 °C for 2 h and then warmed to rt. After stirring at rt for 5 hr, the reaction mixture was quenched with sat. aq.

5 NH₄Cl solution (10 mL) and concentrated. The residue was diluted with DCM and washed with water. The organic layer was dried with anhydrous Na₂SO₄ and concentrated. The residue was purified by silica gel column chromatography to give **24-3** (1.8 g, 26%).

Step 3. Synthesis of tert-butyl 2-cyclopropyl-3-hydroxypropanoate (24-4). A mixture of
10 **24-3** (1 g, 3.6 mmol) and 10% Pd/C (200 mg) in MeOH (20 mL) was stirred at rt under an atmosphere of H₂ overnight. The mixture was filtered, and the residue was dried in vacuo to give crude **24-4** (450 mg, 67%), which was used in the next step without further purification.

Step 4. Synthesis of tert-butyl 2-cyclopropyl-3-(((R)-3-(3,3-difluorobutyl)-2-methyl-1,1-dioxido-5-phenyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)propanoate (24-5). To a solution of (R)-3-(3,3-difluorobutyl)-8-hydroxy-2-methyl-5-phenyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (**1-11**) (374 mg, 0.81 mmol) in toluene (4 mL) was added triphenylphosphine (637 mg, 2.43 mmol) and **24-4** (450 mg, 2.42 mmol). The solution was warmed to 110 °C and then DIAD (4.9 g,
20 24.2) was added. After stirring at 110 °C for 4 hr, the reaction mixture was cooled to rt and diluted with EA (20 mL). The organic layer was washed with brine, dried with anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography to give **24-5** (130 mg, 15%) as a pale-yellow solid. MS (ESI): calcd. for C₃₀H₃₇F₅N₂O₅S: 632.2; Found: 633.2 [M + 1]⁺.

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Step 5. Synthesis of tert-butyl (R)-2-cyclopropyl-3-(((R)-3-(3,3-difluorobutyl)-2-methyl-1,1-dioxido-5-phenyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)propanoate (24-5a) and tert-butyl (S)-2-cyclopropyl-3-(((R)-3-(3,3-difluorobutyl)-2-methyl-1,1-dioxido-5-phenyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)propanoate (24-5b). Compd. **24-5** was
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separated by chiral SFC to give **24-5a** and **24-5b** as a white solid, respectively. The stereochemistry of the 2-cyclopropyl-3-hydroxypropanoic acid moiety was arbitrarily assigned. MS (ESI): calcd. for C₃₀H₃₇F₅N₂O₅S: 632.2; Found: 633.2 [M + 1]⁺.

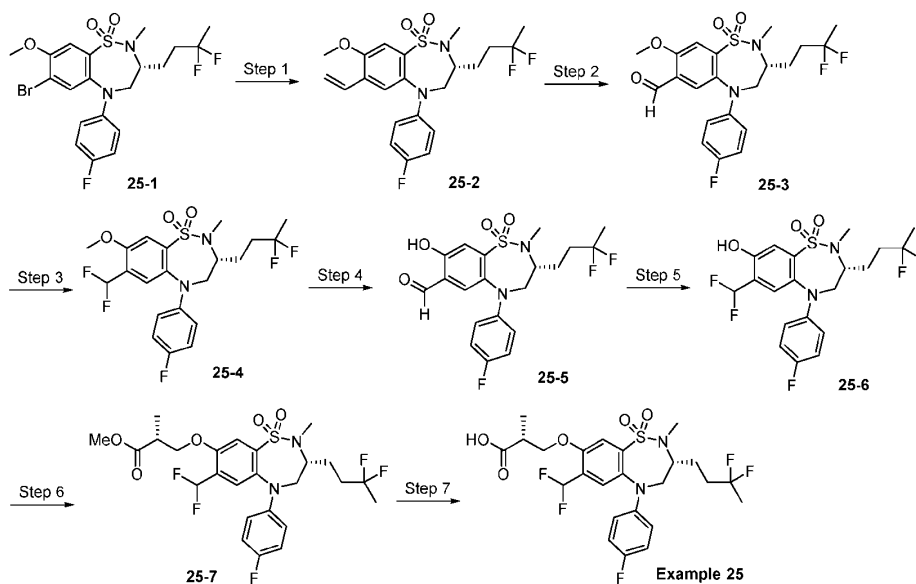
- 5 **Step 6a. Synthesis of (S)-2-cyclopropyl-3-(((R)-3-(3,3-difluorobutyl)-2-methyl-1,1-dioxido-5-phenyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)propanoic acid (Example 24a).** A mixture of **24-5a** (80 mg, 0.13 mmol) in DCM (5 mL) was added TFA (1 ml) dropwise at rt. After stirring at rt for 5 hr, the mixture was concentrated and the residue was purified by prep-HPLC to give **Example 24a** (35 mg, 48%).
- 10 MS (ESI): calcd. for C₂₆H₂₉F₅N₂O₅S: 576.2; Found: 577.2 [M + 1]⁺. ¹H NMR (400 MHz, DMSO-d₆): δ 7.62 (s, 1H), 7.56 (s, 1H), 7.19 (t, J = 8.0 Hz, 2H), 6.77 (t, J = 7.2 Hz, 1H), 6.75 – 6.66 (m, 2H), 4.41 (d, J = 6.4 Hz, 2H), 4.17 – 4.13 (m, 1H), 3.85 – 3.81 (m, 1H), 3.57 – 3.52 (m, 1H), 2.62 (s, 3H), 2.13 – 1.99 (m, 3H), 1.95 – 1.84 (m, 1H), 1.70 – 1.60 (m, 4H), 1.00 – 0.70 (m, 1H), 0.65 – 0.48 (m, 2H), 0.46 – 0.43 (m, 2H) ppm.

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- Step 6b. Synthesis of (S)-2-cyclopropyl-3-(((R)-3-(3,3-difluorobutyl)-2-methyl-1,1-dioxido-5-phenyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)propanoic acid (Example 24a).** Following the same procedure for preparing **Example 24a** by replacing **24-5a** with **24-5b** (78 mg, 0.13 mmol), **Example 24b** (33 mg,
- 20 48%) was obtained as a white solid. MS (ESI): calcd. for C₂₆H₂₉F₅N₂O₅S: 576.2; Found: 577.2 [M + 1]⁺. ¹H NMR (400 MHz, DMSO-d₆): δ 7.62 (s, 1H), 7.56 (s, 1H), 7.19 (t, J = 8.0 Hz, 2H), 6.77 (t, J = 7.2 Hz, 1H), 6.75 – 6.66 (m, 2H), 4.41 (d, J = 6.4 Hz, 2H), 4.17 – 4.13 (m, 1H), 3.85 – 3.81 (m, 1H), 3.57 – 3.52 (m, 1H), 2.62 (s, 3H), 2.13 – 1.99 (m, 3H), 1.95 – 1.84 (m, 1H), 1.70 – 1.60 (m, 4H), 1.00 – 0.70 (m, 1H), 0.65 – 0.48 (m, 2H), 0.46 – 0.43 (m,
- 25 2H) ppm.

Example 25. (R)-3-(((R)-3-(3,3-difluorobutyl)-7-(difluoromethyl)-5-(4-fluorophenyl)-2-methyl-1,1-dioxido-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)-2-

methylpropanoic acid



Scheme 25

- 5 **Step 1. Synthesis of (R)-3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-8-methoxy-2-methyl-7-vinyl-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (25-2).** (R)-7-bromo-3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (**25-1**) (400 mg, 0.79 mmol), which was readily prepared by following the procedure for preparing **1-10** by replacing aniline with 4-fluoroaniline and 2-bromo-4-trifluoromethyl-5-methoxybenzene sulfonyl chloride with 2,4-dibromo-5-methoxybenzene sulfonyl chloride, in dioxane (4 mL) was added Pd(dppf)Cl₂ (57 mg, 0.079 mmol), Na₂CO₃ (251 mg, 2.37 mmol), and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (365 mg, 2.37 mmol) at rt under N₂. The mixture was stirred at 100 °C overnight, diluted with water (15 mL) at rt, and extracted with EA (15 mL x 3). The organic
- 10 extracts were washed with brine, dried with anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography using EA/PE as eluent to give **25-2** (300 mg, 84%) as a pale-yellow solid. MS (ESI): calcd. for C₂₂H₂₅F₃N₂O₃S: 454.2; Found: 455.2 [M + 1]⁺.

Step 2. Synthesis of (R)-3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine-7-carbaldehyde 1,1-dioxide (25-3). To a mixture of **25-2** (300 mg, 0.66 mmol) in dioxane/H₂O (4/1 (v/v), 6 mL) were added osmium tetroxide (2.5% wt in t-BuOH, 336 mg, 0.033 mmol) and sodium periodate (570 mg, 2.64 mmol) at rt. After stirring at rt for 3 hr, the mixture was diluted with water (20 mL) and extracted with EtOAc (15 mL x 3). The combined extracts were dried with anhydrous Na₂SO₄ and concentrated. The residue was purified by silica gel column chromatography using EA/PE as eluent to give **25-3** (240 mg, 80%) as a pale-yellow solid. MS (ESI): calcd. for C₂₁H₂₃F₃N₂O₄S: 456.1; Found: 457.2 [M + 1]⁺.

Step 3. Synthesis of (R)-3-(3,3-difluorobutyl)-7-(difluoromethyl)-5-(4-fluorophenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (25-4). To a solution of **25-3** (220 mg, 0.48 mmol) in DCM (3 mL) was added DAST (387 mg, 2.4 mmol) at rt. After stirring at rt for 2 days, the reaction mixture was poured into sat. aq. NaHCO₃ solution (20 mL). The resulting mixture was extracted with DCM (15 mL x 3), and the combined organic extracts were washed with brine, dried with anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give crude **25-4** (180 mg, 78%) as a brown oil, which was used in the next step without further purification. MS (ESI): calcd. for C₂₁H₂₃F₅N₂O₃S: 478.1; Found: 479.1 [M + 1]⁺.

Step 4. Synthesis of (R)-3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-8-hydroxy-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine-7-carbaldehyde 1,1-dioxide (25-5). Compd. **25-4** (180 mg, 0.31 mmol) was added to a solution of NaSMe in DMF (100 mg/mL, 1.08 mL) at rt. After stirring at 100 °C for 3 hr, the reaction mixture was diluted with water (10 mL) at rt and then extracted with EA (15 mL x 2). The combined organic extracts were washed with brine, dried with anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography using EA/PE as eluent to give **25-5** (150 mg, 85%) as a pale-yellow solid. MS (ESI): calcd. for C₂₀H₂₁F₃N₂O₄S: 442.1; Found: 443.1 [M + 1]⁺.

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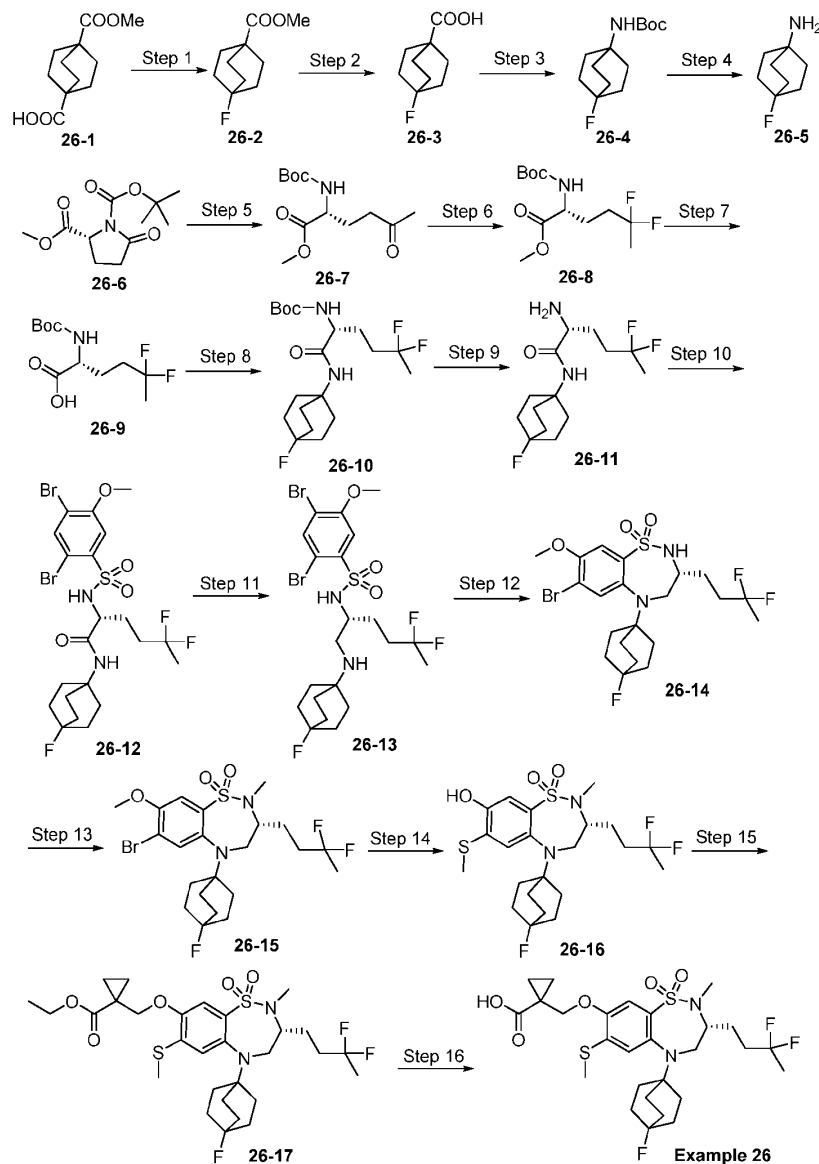
Step 5. Synthesis of (R)-3-(3,3-difluorobutyl)-7-(difluoromethyl)-5-(4-fluorophenyl)-8-hydroxy-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (25-6). To a mixture of **25-5** (130 mg, 0.29 mmol) in DCM (3 mL) was added DAST (387 mg, 2.4 mmol) at rt. After stirring at rt for 2 days, the reaction mixture was poured into sat. aq. NaHCO₃ solution (20 mL), and the resulting mixture was extracted with DCM (15 mL x 3). The combined organic extracts were washed with brine, dried with anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give crude **25-6** (130 mg) as a brown solid, which was used in the next step without further purification. MS (ESI): calcd. for C₂₀H₂₁F₅N₂O₃S 464.1; Found: 465.1 [M + 1]⁺.

Step 6. Synthesis of methyl (R)-3-(((R)-3-(3,3-difluorobutyl)-7-(difluoromethyl)-5-(4-fluorophenyl)-2-methyl-1,1-dioxido-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)-2-methylpropanoate (25-7). A solution of **25-6** (130 mg, 0.28 mmol) in toluene (1.5 mL) was added methyl (R)-3-hydroxy-2-methylpropanoate (165 mg, 1.4 mmol) and triphenylphosphine (221 mg, 0.84 mmol) at rt. After the solution was warmed to 110 °C, DIAD (565 mg, 2.8 mmol) was added, and the resulting reaction mixture was stirred at 110 °C for 5 hr. Subsequently, the mixture was concentrated, and the residue was purified by silica gel column chromatography using EA/PE as eluent to give **25-7** (130 mg, 82%) as a pale-yellow solid. MS (ESI): calcd. for C₂₅H₂₉F₅N₂O₅S :564.2; Found: 565.1 [M + 1]⁺.

Step 7. Synthesis of (R)-3-(((R)-3-(3,3-difluorobutyl)-7-(difluoromethyl)-5-(4-fluorophenyl)-2-methyl-1,1-dioxido-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)-2-methylpropanoic acid (Example 25). To a solution of **25-7** (130 mg, 0.23 mmol) in THF/H₂O (4:1 (v/v), 5 ml) was added LiOH·H₂O (97 mg, 2.3 mmol) at rt. After stirring at rt overnight, the reaction mixture was adjusted to pH = 2~3 with 10% aqueous HCl solution. The resulting mixture was extracted with EA (10 mL x 2), and the combined organic extracts were washed with brine, dried with anhydrous Na₂SO₄, and concentrated. The residue was purified by pre-HPLC to give **Example 25** (8 mg, 6.3%) as a white solid. MS (ESI): calcd. for C₂₄H₂₇F₅N₂O₅S: 550.2; Found: 551.2 [M + 1]⁺. ¹H NMR (400 MHz, CDCl₃): δ 7.51 (d, J = 6.8 Hz, 1H), 7.37 (s, 1H), 6.94 (t, J = 8.6 Hz, 2H), 6.81 (s, 1H), 6.69 (d, J = 11.7 Hz, 2H),

4.36 – 4.25 (m, 1H), 4.21 (dd, J = 8.8, 5.3 Hz, 1H), 3.95 (d, J = 15.6 Hz, 2H), 3.41 (s, 1H), 3.06 (dd, J = 12.4, 6.9 Hz, 1H), 2.64 (s, 3H), 2.14 – 1.71 (m, 11H), 1.61 (t, J = 18.4 Hz, 5H), 1.37 (d, J = 7.2 Hz, 4H) ppm.

- 5 Example 26. (R)-1-(((3-(3,3-difluorobutyl)-5-(4-fluorobicyclo[2.2.2]octan-1-yl)-2-methyl-7-(methylthio)-1,1-dioxido-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid



Step 1. Synthesis of methyl 4-fluorobicyclo[2.2.2]octane-1-carboxylate (26-2). Into a 250 mL 3-necked round-bottom flask were added 4-(methoxycarbonyl)bicyclo[2.2.2]octane-1-carboxylic acid (**26-1**) (10 g, 47.12 mmol), water (100 mL), and Selectfluor (33.38 g, 94.23 mmol) at rt. The resulting mixture was stirred at 70°C for 24 hr under nitrogen atmosphere.

The mixture was cooled to rt and acidified to pH = 5 with sat. aq. citric acid solution. The resulting mixture was extracted with EtOAc (100 mL x 2). The combined organic extracts were washed with brine (100 mL x 2), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give **26-2** (8 g, 91.2%) as a white solid, which was used in the next step without further purification. MS (ESI): calcd. for C₁₀H₁₅FO₂: 186.1; Found: 187.1 [M + 1]⁺.

Step 2. Synthesis of 4-fluorobicyclo[2.2.2]octane-1-carboxylic acid (26-3). Into a 250 mL round-bottom flask were added **26-2** (8 g, 42.96 mmol), THF (80 mL), water (10 mL), and LiOH (3.09 g, 128.87 mmol) at rt. The resulting mixture was stirred at rt for 24 hr under nitrogen atmosphere. The mixture was acidified to pH = 5 with 2 N aq. HCl solution and extracted with EtOAc (100 mL x 2). The combined organic extracts were washed with brine (100 mL x 2), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give **26-3** (7 g, 94.6%) as a colorless oil, which was used in the next step without further purification. MS (ESI): calcd. for C₉H₁₃FO₂: 172.1; Found: 173.1 [M + 1]⁺.

Step 3. Synthesis of tert-butyl N-{4-fluorobicyclo[2.2.2]octan-1-yl}carbamate (26-4). Into a 250 mL round-bottom flask were added **26-3** (7 g, 40.65 mmol), 2-methyl-2-propanol (70 mL), DPPA (16.78 g, 60.98 mmol), and TEA (12.34 g, 121.95 mmol) at rt. The resulting mixture was stirred at 85 °C for 24 hr under nitrogen atmosphere. The mixture was cooled to rt, diluted with water (100 mL), and extracted with EtOAc (100 mL x 2). The combined organic extracts were washed with brine (100 mL x 2), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give **26-4** (9 g, 91.0%) as a light brown oil, which was used in the next step without further purification. MS (ESI): calcd. for C₁₃H₂₂FNO₂: 243.2; Found: 244.3 [M + 1]⁺.

Step 4. Synthesis of 4-fluorobicyclo[2.2.2]octan-1-amine (26-5). Into a 250 mL round-bottom flask were added **26-4** (9 g, 36.99 mmol) and HCl (gas) in dioxane (4 M, 90 mL) at rt. The resulting mixture was stirred at rt for 24 hr under nitrogen atmosphere. The resulting mixture was diluted with water (90 mL), basified to pH = 8 with sat. aq. NaHCO₃, and

extracted with EtOAc (50 mL x 2). The combined organic extracts were washed with brine (50 mL x 2), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give **26-5** (5 g, 94.40%) as a white solid, which was used in the next step without further purification. MS (ESI): calcd. for C₈H₁₄FN: 143.1; Found: 144.2 [M + 1]⁺.

5

Step 5. Synthesis of methyl (R)-2-((tert-butoxycarbonyl)amino)-5-oxohexanoate (26-7).

Into a 500 mL 3-necked round-bottom flask were added 1-(tert-butyl) 2-methyl (R)-5-oxopyrrolidine-1,2-dicarboxylate (30 g, 123.33 mmol), THF (300 mL), and 3 M MeMgBr solution in diethyl ether (17.65 g, 147.99 mmol) at -55°C. The resulting mixture was stirred at -20°C for 18 hr under nitrogen atmosphere. The reaction was quenched with sat. aq. NH₄Cl at 0 °C and concentrated to remove organic solvent. The resulting mixture was extracted with EtOAc (150 mL x 3). The combined organic extracts were washed with brine (150 mL x 2), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA (5/1 (v/v)), to give **26-7** (20 g, 62.5%) as a colorless oil. MS (ESI): calcd. for: C₁₂H₂₁NO₅: 259.1; Found: 331.1 [M + Na + ACN]⁺.

15

Step 6. Synthesis of methyl (R)-2-((tert-butoxycarbonyl)amino)-5,5-difluorohexanoate (26-8).

Into a 500 mL 3-necked round-bottom flask were added **26-7** (20 g, 77.13 mmol), DCM (200 mL), and DAST (37.30 g, 231.39 mmol) at 0°C. The resulting mixture was stirred at rt for 12 h under nitrogen atmosphere. The reaction was quenched with sat. aq. NaHCO₃ at 0°C and concentrated to remove organic solvent. The resulting mixture was extracted with EtOAc (200 mL x 2). The combined organic extracts were washed with brine (200 mL x 2), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA (8/1 (v/v)), to give **26-8** (2.8 g, 12.9%) as a colorless oil. MS (ESI): calcd. for: C₁₂H₂₁F₂NO₄: 281.1; Found: 282.1 [M + 1]⁺.

25

Step 7. Synthesis of (R)-2-((tert-butoxycarbonyl)amino)-5,5-difluorohexanoic acid (26-9).

Into a 100 mL 3-necked round-bottom flask were added **26-8** (2.8 g, 9.95 mmol), THF (30 mL), water (7.5 mL), and LiOH (0.72 g, 29.86 mmol) at rt. The resulting mixture was stirred at rt for 24 hr under nitrogen atmosphere. The mixture was acidified to pH = 5 with 1 N aq.

30

HCl solution and concentrated to remove organic solvent. The resulting mixture was extracted with EtOAc (30 mL x 2). The combined organic extracts were washed with brine (30 mL x 2), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give crude **26-9** (2.5 g) as a light brown oil, which was used in the next step without further purification. MS (ESI): calcd. for C₁₁H₁₉F₂NO₄: 267.1; Found: 253.1 [M – Boc + 1]⁺.

Step 8. Synthesis of tert-butyl (R)-(5,5-difluoro-1-((4-fluorobicyclo[2.2.2]octan-1-yl)amino)-1-oxohexan-2-yl)carbamate (26-10). Into a 50 mL 3-necked round-bottom flask were added **26-9** (2.5 g, 9.35 mmol), DMF (25 mL), HATU (4.27 g, 11.22 mmol), DIEA (1.81 g, 14.03 mmol), and **26-5** (1.61 g, 11.22 mmol) at rt. The resulting mixture was stirred at rt for 4 hr under nitrogen atmosphere. The reaction was quenched with water at 0 °C. The resulting mixture was extracted with EtOAc (30 mL x 2). The combined organic extracts were washed with brine (30 mL x 2), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give crude **26-10** (2.3 g, 62.6%) as a brown oil, which was used in the next step without further purification. MS (ESI): calcd. for C₁₉H₃₁F₃N₂O₃: 392.2; Found: 393.2 [M + 1]⁺.

Step 9. Synthesis of (R)-2-amino-5,5-difluoro-N-(4-fluorobicyclo[2.2.2]octan-1-yl)hexanamide (26-11). Into a 100 mL round-bottom flask were added **26-10** (2.3 g, 5.86 mmol) and HCl in EtOAc (2 M, 25 mL) at rt. The resulting mixture was stirred at rt for 16 hr under nitrogen atmosphere. The mixture was basified to pH = 8 with saturated aq. NaHCO₃ solution. The resulting mixture was extracted with EtOAc (25 mL x 2). The combined organic extracts were washed with brine (25 mL x 2), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give crude **26-11** (1.6 g, 93.4%) as a light brown oil, which was used in the next step without further purification. MS (ESI): calcd. for C₁₄H₂₃F₃N₂O: 292.2; Found: 293.2 [M + 1]⁺.

Step 10. Synthesis of (R)-2-((2,4-dibromo-5-methoxyphenyl)sulfonamido)-5,5-difluoro-N-(4-fluorobicyclo[2.2.2]octan-1-yl)hexanamide (26-12). Into a 50 mL round-bottom flask were added **26-11** (1.8 g, 6.16 mmol), 2,4-dibromo-5-methoxybenzenesulfonyl chloride (2.69

g, 7.39 mmol), THF (18 mL), and TEA (1.87 g, 18.47 mmol) at rt. The resulting mixture was stirred at rt for 16 h under nitrogen atmosphere. The resulting mixture was diluted with water (50 mL) and concentrated to remove organic solvent. The resulting mixture was extracted with EtOAc (50 mL x 2). The combined organic extracts were washed with brine (50 mL x 2), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA (3/1 (v/v)) to give **26-12** (1.5 g, 39.3%) as a yellow solid. MS (ESI): calcd. for C₂₁H₂₇BrF₃N₂O₄S: 618.0; Found: 618.9 [M + 1]⁺.

Step 11. Synthesis of (R)-2,4-dibromo-N-(5,5-difluoro-1-((4-fluorobicyclo[2.2.2]octan-1-yl)amino)hexan-2-yl)-5-methoxybenzenesulfonamide (26-13). Into a 50 mL round-bottom flask were added **26-12** (1.5 g, 2.42 mmol), THF (30 mL), and BH₃•Me₂S (0.75 mL, 7.91 mmol) at rt. The resulting mixture was stirred at 75°C for 16 h under nitrogen atmosphere. The reaction was quenched with MeOH at 0°C. The resulting mixture was stirred at 75°C for 2 h. The mixture was cooled to rt and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA (5/1 (v/v)), to give **26-13** (1.0 g, 68.2%) as a brown solid. MS (ESI): calcd. for C₂₁H₂₉Br₂F₃N₂O₃S: 604.0; Found: 605.0 [M + 1]⁺.

Step 12. Synthesis of (R)-7-bromo-3-(3,3-difluorobutyl)-5-(4-fluorobicyclo[2.2.2]octan-1-yl)-8-methoxy-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (26-14). Into a 40 mL vial were added **26-13** (1.0 g, 1.65 mmol), DMSO (10 mL), K₂CO₃ (0.69 g, 4.947 mmol), and CuI (0.16 g, 0.83 mmol) at rt. The resulting mixture was stirred at 130°C for 16 h under nitrogen atmosphere. The mixture was cooled to rt and diluted with water (20 mL). The resulting mixture was extracted with EtOAc (30 mL x 2). The combined organic extracts were washed with brine (30 mL x 2), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA (1/1 (v/v)) to give **26-14** (200 mg, 23.1%) as a brown solid. MS (ESI): calcd. for C₂₁H₂₈BrF₃N₂O₃S: 524.1; Found: 525.1 [M + 1]⁺.

Step 13. Synthesis of (R)-7-bromo-3-(3,3-difluorobutyl)-5-(4-fluorobicyclo[2.2.2]octan-1-yl)-8-methoxy-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (26-

15) Into an 8 mL vial were added **26-14** (200 mg, 0.38 mmol), DMF (2 mL), Cs₂CO₃ (373.21 mg, 1.14 mmol), and MeI (64.83 mg, 0.46 mmol) at rt. The resulting mixture was stirred at rt for 16 h under nitrogen atmosphere. The resulting mixture was diluted with water (10 mL) and extracted with EtOAc (20 mL x 2). The combined organic extracts were washed
5 with brine (20 mL x 2), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA (1/1 (v/v)) to give **26-15** (145 mg, 70.6%) as a brown oil. MS (ESI): calcd. for C₂₂H₃₀BrF₃N₂O₃S: 538.1; Found: 539.1 [M + 1]⁺.

10 **Step 14. Synthesis of (R)-3-(3,3-difluorobutyl)-5-(4-fluorobicyclo[2.2.2]octan-1-yl)-8-hydroxy-2-methyl-7-(methylthio)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (26-16).** Into an 8 mL vial were added **26-15** (90 mg, 0.17 mmol), DMF (3 mL), and MeSNa (64.31 mg, 0.92 mmol) at rt. The resulting mixture was stirred at 60°C for 2 h under nitrogen atmosphere. The mixture was cooled to rt, diluted with water (10 mL), and
15 extracted with EtOAc (20 mL x 4). The combined organic extracts were washed with brine (10 mL x 3), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA (4/1 (v/v)), to give **26-16** (50 mg, 60.8%) as a brown solid. MS (ESI): calcd. for C₂₂H₃₁F₃N₂O₃S₂: 492.2; Found: 493.2 [M + 1]⁺.

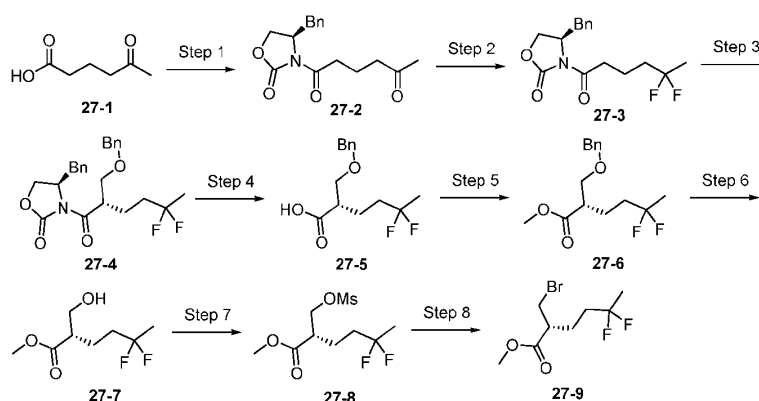
20 **Step 15. Synthesis of ethyl (R)-1-(((3-(3,3-difluorobutyl)-5-(4-fluorobicyclo[2.2.2]octan-1-yl)-2-methyl-7-(methylthio)-1,1-dioxido-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylate (26-17).** Into an 8 mL vial were added **26-16** (50 mg, 0.10 mmol), DMF (1 mL), ethyl 1-(bromomethyl)cyclopropane-1-carboxylate (25.22
25 mg, 0.12 mmol), and Cs₂CO₃ (99.52 mg, 0.30 mmol) at rt. The resulting mixture was stirred at 80°C for 16 h under nitrogen atmosphere. The mixture was cooled to rt, diluted with water (20 mL), and extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with brine (20 mL x 2), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA (3/1 (v/v)), to give **26-17** (8

mg, 12.7%) as a brown solid. MS (ESI): calcd. for $C_{29}H_{41}F_3N_2O_5S_2$: 618.2; Found: 619.2 $[M + 1]^+$.

Step 16. Synthesis of (R)-1-(((3-(3,3-difluorobutyl)-5-(4-fluorobicyclo[2.2.2]octan-1-yl)-
5 **2-methyl-7-(methylthio)-1,1-dioxido-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-**
yl)oxy)methyl)cyclopropane-1-carboxylic acid (Example 26). Into an 8 mL vial were
added **26-17** (8 mg, 0.01 mmol), LiOH (0.93 mg, 0.04 mmol), water (1 mL) and THF (4
mL) at rt. The resulting mixture was stirred at rt for 2 h under nitrogen atmosphere. The
resulting mixture was acidified to pH 3 with 2 N aq. HCl solution and concentrated. The
10 residue was purified by Chiral-Prep-HPLC with the following conditions: Column: CHIRAL
ART Amylose-C NEO, 3*25 cm, 5 μ m; Mobile Phase A: Hex (0.1% FA)-HPLC, Mobile
Phase B: IPA-HPLC; Flow rate: 35 mL/min; Gradient: 30% B to 30% B in 15 min; Wave
Length: 220/254 nm; RT1(min): 0.82; Sample Solvent: IPA: CAN = 3: 1; Injection Volume:
0.8 mL; The collected solution was concentrated under vacuum to remove ACN and resulting
15 solution was dried by lyophilization to give **Example 26** (2.5 mg, 32.7%) as a white solid.
MS (ESI): calcd. for $C_{27}H_{37}F_3N_2O_5S_2$: 590.2; Found: 591.2 $[M + 1]^+$. 1H NMR (400 MHz,
 CD_3OD): δ 7.26 (s, 1H), 7.06 (s, 1H), 4.35 – 4.14 (m, 2H), 3.89 (s, 1H), 2.59 (dd, J = 16.0,
10.4 Hz, 1H), 2.46 (s, 3H), 2.34 (s, 3H), 2.18 (d, J = 11.2 Hz, 3H), 2.03 (s, 2H), 1.94 – 1.87
(m, 9H), 1.77 – 1.51 (m, 6H), 1.32 (s, 2H), 1.13 (s, 2H) ppm.

20

Synthesis of methyl (R)-2-(bromomethyl)-5,5-difluorohexanoate (**27-9**)



Scheme 27

Step 1. Synthesis of (R)-1-(4-benzyl-2-oxooxazolidin-3-yl)hexane-1,5-dione (27-2). Into a 50 L 4-necked round-bottom flask were added 5-oxohexanoic acid (**27-1**) (1.113 kg, 8.56 mol), THF (24 L) and TEA (0.95 kg, 9.40 mol) at room temperature. To the above mixture was added pivaloyl chloride (1.14 kg, 9.40 mol) dropwise at 5 °C over 2 h. The resulting mixture was stirred for an additional 2 h at room temperature. Into a 20 L 4-necked round-bottom flasks were added (4R)-4-benzyl-1,3-oxazolidin-2-one (1.44 kg, 8.12 mol) and THF (16 L) at room temperature. To the above mixture was added n-BuLi (3.25 L, 8.12 mol) dropwise at -50°C over 4 h. The resulting mixture was stirred at -50 °C for an additional 1 h. Then the lithium reagent was transferred to the mixed anhydride via cannula, with the 50 L flasks under reduced pressure. The resulting mixture was stirred at -20°C for 4 h under nitrogen atmosphere. The resulting mixture was diluted with EtOAc (50 L). The resulting mixture was washed with aq. NaHCO₃ solution (20 L x 2) and brine (20 L x 2), dried over anhydrous Na₂SO₄, and concentrated. The residue was triturated PE/EA = 20/1 (v/v) (60 L) three times. The precipitate was collected and dried in vacuo to give **27-2** (1.7 kg, 68.7%) as a white solid. MS (ESI): calcd. for C₁₆H₁₉NO₄: 289.1; Found: 290.1 [M + 1]⁺.

Step 2. Synthesis of (R)-4-benzyl-3-(5,5-difluorohexanoyl)oxazolidin-2-one (27-3). Into a 2 L 3-necked round-bottom flask were added (R)-1-(4-benzyl-2-oxooxazolidin-3-yl)hexane-1,5-dione (**27-2**) (200 g, 691.25 mol) and DCE (600 mL) at room temperature. To the above mixture was added BAST (382.33 g, 1728.13 mol) at room temperature. The resulting

mixture was stirred at 70 °C for an additional 6 h. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with DCM (1 L). The reaction was slowly poured into sat. aq. NaHCO₃ solution. The resulting mixture was extracted with DCM (1 L x 2). The combined organic layers were washed with brine (1 L), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/THF (10:1 (v/v)) to give **27-3** (153 g, 71.1%) as a brown oil. MS (ESI): calcd. for C₁₆H₁₉F₂NO₃: 311.1; Found: 312.1 [M + 1]⁺. ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.38 – 7.16 (m, 5H), 4.66 (t, *J* = 7.8, 3.1 Hz, 1H), 4.33 (t, *J* = 8.5 Hz, 1H), 4.19 (dd, *J* = 8.8, 2.9 Hz, 1H), 3.09 – 2.76 (m, 4H), 2.05 – 1.83 (m, 2H), 1.83 – 1.70 (m, 2H), 1.62 (t, *J* = 18.9 Hz, 3H) ppm.

Step 3. Synthesis of (R)-4-benzyl-3-((S)-2-((benzyloxy)methyl)-5,5-difluorohexanoyl)oxazolidin-2-one (27-4). A solution of (R)-4-benzyl-3-(5,5-difluorohexanoyl)oxazolidin-2-one (**27-3**) (1015 g, 3.26 mol) in DCM (9.1 L) was treated with TiCl₄ (649.28 g, 3.42 mol) at 0°C under nitrogen atmosphere. The mixture was stirred for 30 min at 0° C. The solution was treated with TEA (362.90 g, 3.59 mol) dropwise at 0°C under nitrogen atmosphere, then stirred at 0°C for 2 h. The mixture was followed by the addition of ((chloromethoxy)methyl)benzene (1021 g, 6.52 mol) dropwise at 0°C and stirred at 0°C for 2 h. The reaction was quenched with sat. aq. NH₄Cl solution (3.5 L) at 0°C. The resulting mixture was separated, and the aqueous layer was extracted with DCM (2 L x 2). The combined organic layers were washed with sat. aq. NaHCO₃ (5 L x 2) solution and brine (5 L), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by trituration with PE/EA = 30/1 (v/v) (60 L x 3). The precipitate was collected and dried in vacuo to give **27-4** (1160 g) as a light brown solid, which was used in the next step directly without further purification. MS (ESI): calcd. for C₂₄H₂₇F₂NO₄: 431.2; Found: 432.2[M + 1]⁺. ¹H NMR (400 MHz, CDCl₃): δ 7.43 – 7.17 (m, 10H), 4.75 (ddt, *J* = 9.3, 7.9, 3.3 Hz, 1H), 4.57 (s, 2H), 4.29 – 4.17 (m, 2H), 4.16 (dd, *J* = 9.1, 3.2 Hz, 1H), 3.80 (dd, *J* = 9.2, 7.1 Hz, 1H), 3.71 (dd, *J* = 9.2, 5.3 Hz, 1H), 3.25 (dd, *J* = 13.5, 3.4 Hz, 1H), 2.70 (dd, *J* = 13.5, 9.3 Hz, 1H), 2.07 – 1.92 (m, 1H), 1.96 – 1.86 (m, 1H), 1.89 – 1.72 (m, 1H), 1.61 (t, *J* = 18.4 Hz, 3H) ppm.

Step 4. Synthesis of (S)-2-((benzyloxy)methyl)-5,5-difluorohexanoic acid (27-5). A solution of (R)-4-benzyl-3-((S)-2-((benzyloxy)methyl)-5,5-difluorohexanoyl)oxazolidin-2-one (**27-4**) (1000 g, 2.32 mol) in THF (12 L) and H₂O (2 L) was treated with H₂O₂ (1051 g, 9.27 mol, 30%) dropwise at 0°C for 30 min under nitrogen atmosphere. The mixture was stirred at 0°C for 30 min, then treated with LiOH·H₂O (194.49 g, 4.64 mol) in H₂O (2 L) dropwise at 0°C. The resulting mixture was stirred at 0°C for 2 h. The reaction was quenched by the addition of Na₂SO₃ (5 L) at 0°C, then concentrated under vacuum. The resulting solution was adjusted to pH = 12 with 1 N aq. NaOH solution and extracted with DCM (5 L x 3). The water layer was adjusted to pH = 2 with sat. aq. HCl solution (4 M). The resulting solution was extracted with EtOAc (6 L x 4). The combined organic extracts were washed with brine (15 L), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give **27-5** (600 g) as a light-yellow oil, which was used in the next step directly without further purification. MS (ESI): calcd. for C₁₄H₁₈F₂O₃: 272.1; Found: 273.1 [M + 1]⁺.

Step 5. Synthesis of methyl (S)-2-((benzyloxy)methyl)-5,5-difluorohexanoate (27-6). A solution of (S)-2-((benzyloxy)methyl)-5,5-difluorohexanoic acid (**27-5**) (1.80 kg, 6.6 mol) in MeOH (9 L) was treated with SOCl₂ (1.65 kg, 13.88 mol) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred at room temperature for an additional 4 h. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (10:1 (v/v)) to give **27-6** (1.5 kg, 81.4%) as a brown oil. MS (ESI): calcd. for C₁₅H₂₀F₂O₃: 286.1; Found: 287.1 [M + 1]⁺.

Step 6. Synthesis of methyl (S)-5,5-difluoro-2-(hydroxymethyl)hexanoate (27-7). Into a 20 L autoclave were added a solution of methyl (S)-2-((benzyloxy)methyl)-5,5-difluorohexanoate (**27-6**) (750 g, 2619.5 mmol) in MeOH (15 L) and Pd/C (111.50 g, 10%, wet.) at room temperature. The resulting mixture was stirred at 60° C for 18 h under hydrogen atmosphere (30 atm). The resulting mixture was filtered, and the filter cake was washed with MeOH (1 L x 4). The filtrate was concentrated, and the residue was dried in

vacuo to give **27-7** (460 g, 89.5%) as a light-yellow oil. MS (ESI): calcd. for C₈H₁₄F₂O₃: 196.1; Found: 197.1 [M + 1]⁺.

Step 7. Synthesis of methyl (S)-5,5-difluoro-2-(((methylsulfonyl)oxy)methyl)hexanoate

5 **(27-8)**. A solution of methyl (S)-5,5-difluoro-2-(hydroxymethyl)hexanoate (**27-7**) (441 g, 2.25 mol) and TEA (455 g, 4.50 mol) in DCM (5 L) was treated with MsCl (309 g, 2.70 mol) at 0°C under nitrogen atmosphere. The mixture was stirred at room temperature for 2 h under nitrogen atmosphere. The reaction was quenched with water at 0°C, then extracted with DCM (1 L x 3). The combined organic layers were washed with brine (4 L), dried over anhydrous
10 Na₂SO₄, and concentrated. The residue was dried in vacuo to give **27-8** (575 g) as a light-brown liquid, which was used for the next step without further purification.

Step 8. Synthesis of methyl (R)-2-(bromomethyl)-5,5-difluorohexanoate (27-9). The

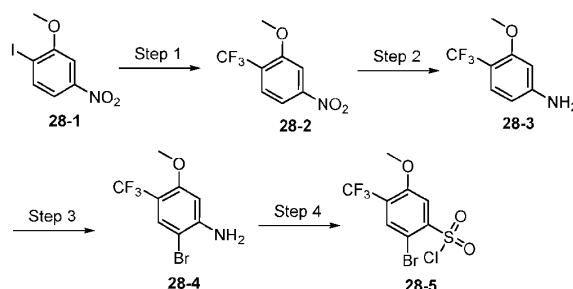
solution of methyl (S)-5,5-difluoro-2-(((methylsulfonyl)oxy)methyl)hexanoate (**27-8**) (1150
15 g, 4.38 mol) and LiBr (1.52 kg, 17.50 mol) in Acetone (12 L) was stirred at 60°C for 3 h. The mixture was allowed to cool down to room temperature and concentrated under vacuum. The resulting organic mixture was diluted with EtOAc (10 L), washed with water (4 L x 3) and brine (5 L), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give **27-9** (1020 g, 88.2%) as a light-brown liquid, which was used in the next step directly
20 without further purification. ¹H NMR (300 MHz, CD₃OD): δ 3.75 (s, 3H), 3.64 (dd, J = 6.0, 1.8 Hz, 2H), 2.96 – 2.85 (m, 1H), 2.00 – 1.77 (m, 4H), 1.61 (t, J = 18.6 Hz, 3H) ppm.

Following the same procedure for **151-8a cis-racemate** by replacing methyl 2-

(bromomethyl)-5,5,5-trifluoropentanoate (**151-7**) with methyl (R)-2-(bromomethyl)-5,5-

25 difluorohexanoate (**27-9**), (2S,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-8-hydroxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (**Example 10b**) was obtained as a single diastereomer.

Synthesis of 2-bromo-5-methoxy-4-(trifluoromethyl)benzenesulfonyl chloride (**28-5**)



Scheme 28

Step 1. Synthesis of 2-methoxy-4-nitro-1-(trifluoromethyl)benzene (28-2). To a solution of iodocopper (15.96 g, 84.07 mmol) in tetramethylene sulfone was added cesium fluoride (33.2 g, 218.6 mmol) and 2-methoxy-1-iodo-4-nitrobenzene (**28-1**) (24.0 g, 84.1 mmol). The resulting solution was stirred at 45°C. Then trimethyl(trifluoromethyl)silane (31.05 g, 218.6 mmol) was added dropwise at 45°C and stirred at room temperature overnight. Subsequently, the mixture was diluted with water and the resulting mixture was extracted with MTBE (100 mL x 3). The combined organic extracts were washed with brine (100 mL), dried over Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography using EtOAc/hexanes as eluent to give **28-2** (8 g, 43%) as a yellow solid.

Step 2. Synthesis of 3-methoxy-4-(trifluoromethyl)aniline (28-3). To a solution of 2-methoxy-4-nitro-1-(trifluoromethyl)benzene (**28-2**) (8.0 g, 35.85 mmol) in MeOH was added palladium (379.68 mg, 3.59 mmol). The resulting mixture was hydrogenated at ambient pressure and ambient temperature for 4 h. The mixture was filtered, and the filtrate was concentrated. The residue was dried in vacuo to give **28-3** (5 g, 73%), which was used in the next step without further purification.

Step 3. Synthesis of 2-bromo-5-methoxy-4-(trifluoromethyl)aniline (28-4). To a solution of 3-methoxy-4-(trifluoromethyl)aniline (**28-3**) (5.0 g, 26.17 mmol) in ACN (100 mL) was added 1-bromopyrrolidine-2,5-dione (4.63 g, 26.17 mmol) at -20°C. After stirring at rt overnight, the reaction mixture was concentrated. The residue was diluted with EtOAc (100 mL). The mixture was washed with water (25 mL) and brine (25 mL), dried over anhydrous

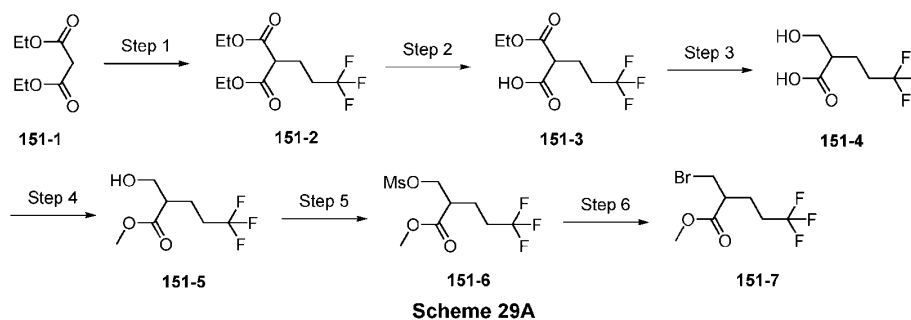
Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography to give **28-4** (6 g, 85%) as a yellow solid.

Step 4. Synthesis of 2-bromo-5-methoxy-4-(trifluoromethyl)benzene-1-sulfonyl chloride

- 5 **(28-5)**. A mixture of 2-bromo-5-methoxy-4-(trifluoromethyl)aniline (**28-4**) (6.0 g, 22.31 mmol) in sat. aq. HCl solution (8.03 g, 223.09 mmol) and water (100 mL) was added a solution of sodium nitrite (1.85 g, 26.77 mmol) in water (5 mL) at -10°C. After stirring at rt for 1 h, the mixture was added to a mixture of sulfuryl dichloride (26.3 g, 223.09 mmol) and copper chloride (218.4 mg, 2.23 mmol) in water (200 mL) at 0 °C. The resulting mixture was stirred at rt for 2 h and diluted with DCM (50 mL). The aqueous layer was extracted with DCM (50 mL x 3). The combined organic extracts were washed with water (50 mL) and saturated aqueous NaHCO₃ (50 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography to give **28-5** (3 g, 38%).

- 15 Examples 151a and 151b. 3-(((2S,3R)-5-(4,4-difluorocyclohexyl)-2-fluoro-1,1-dioxido-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid (151a) and 3-(((2R,3S)-5-(4,4-difluorocyclohexyl)-2-fluoro-1,1-dioxido-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid (151b)

20



Step 1. Synthesis of diethyl 2-(3,3,3-trifluoropropyl)malonate (151-2). Into a 500 mL 3-necked round-bottom flask were added diethyl malonate (25 g, 156.08 mmol) and

tetrahydrofuran (250 mL) at 0°C. To the above mixture was added NaH (60% in oil, 3.12 g, 78.04 mmol) in portions at 0 °C over 10 min. The resulting mixture was stirred for an additional 30 min at rt. To the above mixture was added 1,1,1-trifluoro-3-iodopropane (17.48 g, 78.04 mmol) dropwise at rt over 5 min. The resulting mixture was stirred at 80 °C for 24 h.

5 The reaction was monitored by LC-MS. The mixture was allowed to cool down to rt. The resulting mixture was extracted with EtOAc (300 mL x 2). The combined organic layers were washed with brine (450 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA (40:1 (v/v)) to give **151-2** (30 g, 75.2%) as a colorless oil. ¹H NMR (300 MHz, CDCl₃): δ 4.29 – 4.13 (m, 4H),

10 3.39 (t, *J* = 6.6 Hz, 1H), 2.27 – 2.07 (m, 4H), 1.27 (t, *J* = 7.2 Hz, 6H) ppm.

Step 2. Synthesis of 2-(ethoxycarbonyl)-5,5,5-trifluoropentanoic acid (151-3). Into a 500 mL 3-necked round-bottom flask were added diethyl 2-(3,3,3-trifluoropropyl)malonate (**151-2**) (25 g, 97.57 mmol), EtOH (250 mL) and KOH (6.02 g, 107.33 mmol) at rt. The resulting

15 mixture was stirred at rt for 8 h under nitrogen atmosphere. The reaction was monitored by LC-MS. The mixture was acidified to pH = 2 with aq. HCl solution (2 M). The resulting mixture was extracted with EtOAc (150 mL x 4). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with CH₂Cl₂/MeOH (9:1 (v/v)) to give

20 **151-3** (21 g, 94.3%) as a colorless liquid. ¹H NMR (300 MHz, CDCl₃): δ 8.65 (br.s, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.48 (t, *J* = 6.7 Hz, 1H), 2.39 – 2.06 (m, 4H), 1.30 (t, *J* = 7.0 Hz, 3H) ppm.

Step 3. Synthesis of 5,5,5-trifluoro-2-(hydroxymethyl)pentanoic acid (151-4). To a stirred

25 solution of 2-(ethoxycarbonyl)-5,5,5-trifluoropentanoic acid (**151-3**) (20 g, 87.66 mmol) in *i*-PrOH (200 mL) was added LiBH₄ (2 M in THF, 87.70 mL, 175.40 mmol) in portions at 0°C under nitrogen atmosphere. The resulting mixture was stirred at rt for 3 h under nitrogen atmosphere. The reaction was monitored by LC-MS. The mixture was acidified to pH = 2 with aq. HCl solution (2 N). The resulting mixture was extracted with EtOAc (200 mL x 5).

30 The combined organic layers were washed with brine (200 mL), dried over anhydrous

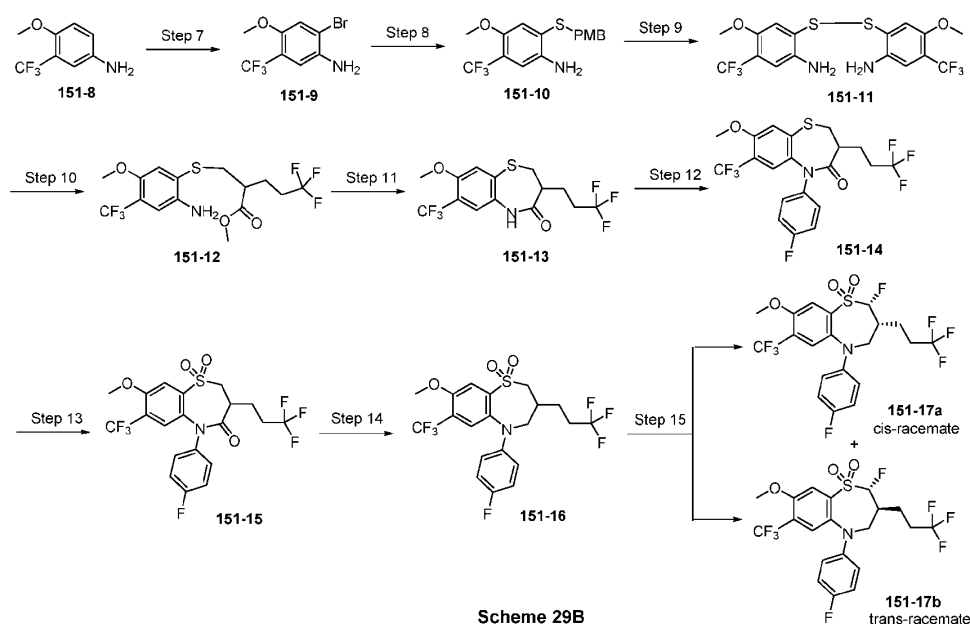
Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with CH₂Cl₂/MeOH (4:1 (v/v)) to give **151-4** (15 g, 91.9%) as a colorless liquid. ¹H NMR (300 MHz, CDCl₃): δ 6.38 (br.s, 2H), 3.93 – 3.77 (m, 2H), 2.74 – 2.59 (m, 1H), 2.37 – 2.07 (m, 2H), 2.06 – 1.75 (m, 2H) ppm.

5

Step 4. Synthesis of methyl 5,5,5-trifluoro-2-(hydroxymethyl)pentanoate (151-5). Into a 500 mL 3-necked round-bottom flask were added 5,5,5-trifluoro-2-(hydroxymethyl)pentanoic acid (**151-4**) (20 g, 107.45 mmol), H₂SO₄ (6.32 g, 64.47 mmol) and MeOH (200 mL) at rt. The resulting mixture was stirred at 60 °C for 4 h under nitrogen atmosphere. The reaction was monitored by LC-MS. The mixture was allowed to cool down to rt. The resulting mixture was concentrated under reduced pressure. The resulting mixture was extracted with EtOAc (150 mL x 3). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA = 4/1 (v/v) to **151-5** (21 g, 97.6%) as a yellow liquid. ¹H NMR (300 MHz, CDCl₃): δ 3.80 (dd, J = 5.4, 2.7 Hz, 2H), 3.75 (s, 3H), 2.70 – 2.56 (m, 1H), 2.28 – 2.11 (m, 2H), 2.06 (br.s, 1H), 2.02 – 1.77 (m, 2H) ppm.

Step 5. Synthesis of methyl 5,5,5-trifluoro-2-(((methylsulfonyl)oxy)methyl)pentanoate (151-6). To a stirred mixture of methyl 5,5,5-trifluoro-2-(hydroxymethyl)pentanoate (**151-5**) (15 g, 74.94 mmol) and TEA (22.75 g, 224.82 mmol) in DCM (150 mL) was added MsCl (10.30 g, 89.93 mmol) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 0°C for 2 h under nitrogen atmosphere. The reaction was monitored by GC-MS. The resulting mixture was extracted with CH₂Cl₂ (150 mL x 3). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (4:1 (v/v)) to give **151-6** (17 g, 81.5%) as a colorless liquid. ¹H NMR (300 MHz, CDCl₃): δ 4.45 – 4.31 (m, 2H), 3.76 (s, 3H), 3.03 (s, 3H), 2.94 – 2.79 (m, 1H), 2.32 – 2.07 (m, 2H), 2.06 – 1.79 (m, 2H) ppm.

Step 6. Synthesis of methyl 2-(bromomethyl)-5,5,5-trifluoropentanoate (151-7). Into a 250 mL 3-necked round-bottom flask were added methyl 5,5,5-trifluoro-2-(((methylsulfonyl)oxy)methyl)pentanoate (**151-6**) (15 g, 53.91 mmol), LiBr (14.04 g, 161.73 mmol) and acetone (150 mL) at rt. The resulting mixture was stirred at 60°C for 3 h under nitrogen atmosphere. The reaction was monitored by GC-MS. The mixture was allowed to cool down to rt. The resulting mixture was extracted with EtOAc (150 mL x 3). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/THF (9:1 (v/v)) to give **151-7** (11 g, 77.6%) as a colorless liquid. ¹H NMR (300 MHz, CDCl₃): δ 3.76 (s, 3H), 3.61 – 3.48 (m, 2H), 2.94 – 2.80 (m, 1H), 2.29 – 2.09 (m, 2H), 2.08 – 1.84 (m, 2H) ppm.



Step 7. Synthesis of 2-bromo-4-methoxy-5-(trifluoromethyl)aniline (151-9). Into a 50 L 4-necked round-bottom flask were added 4-methoxy-3-(trifluoromethyl)aniline (1100 g, 5.75 mol) and THF (22 L). To the above mixture was added NBS (1057.56 g, 5.75 mol) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred at 10°C for 2 h

under nitrogen atmosphere. After completion of the reaction (monitored by LC-MS), the reaction was quenched with sat. aq. Na_2SO_3 solution (25 L) at 5 °C. The resulting mixture was concentrated under reduced pressure. The resulting mixture was extracted with EtOAc (25 L x 3). The combined organic layers were washed with brine (25 L x 2), dried over
5 anhydrous Na_2SO_4 , and concentrated. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (15:1 (v/v)) to give **151-9** (1067 g, 68.6%) as a yellow solid. MS (ESI): calcd. for $\text{C}_8\text{H}_7\text{BrF}_3\text{NO}$: 269.0; Found: 311.0 $[\text{M} + \text{ACN} + 1]^+$.

10 **Step 8. Synthesis of 4-methoxy-2-((4-methoxybenzyl)thio)-5-(trifluoromethyl)aniline (151-10).** Into a 20 L 4-necked round-bottom flask were added 2-bromo-4-methoxy-5-(trifluoromethyl)aniline (**151-9**) (1000 g, 3.95 mol), dioxane (10 L), PMBSH (913.79 g, 5.92 mol), DIEA (1.53 kg, 11.85 mol), $\text{Pd}_2(\text{dba})_3$ (85.04 g, 0.093 mol) and Xantphos (107.43 g, 0.186 mol) at room temperature. The resulting mixture was stirred at 120 °C for 24 h under
15 nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was filtered, the filter cake was washed with EtOAc (5 L x 2). The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography, eluted with PE/EA/DCM (5/1/0.1 (v/v/v)) to give crude **151-10** (1167 g, containing some ligands) as a brown oil, which was directly used in the next step without
20 further purification. MS (ESI): calcd. for $\text{C}_{16}\text{H}_{16}\text{F}_3\text{NO}_2\text{S}$: 343.1; Found: 344.1 $[\text{M} + 1]^+$.

Step 9. Synthesis of 6,6'-disulfanediylbis(4-methoxy-3-(trifluoromethyl)aniline) (151-11). Into a 20 L 4-necked round-bottom flask were added 4-methoxy-2-((4-methoxybenzyl)thio)-5-(trifluoromethyl)aniline (**151-10**) (1160 g, 3.40 mol), TFA (4 L) and
25 MsOH (1.2 L) at room temperature. The resulting mixture was stirred at room temperature for 16 h. The mixture was concentrated under reduced pressure and diluted with EtOAc (15 L). The mixture was acidified to pH = 9 with saturated aq. NaHCO_3 solution. The resulting solution was stirred at rt for 16 h under oxygen atmosphere. The resulting mixture was separated, and the aqueous layer was extracted with EtOAc (8 L x 2). The combined organic
30 layers were washed with brine (10 L x 2), dried over anhydrous Na_2SO_4 , and concentrated.

The residue was purified by silica gel column chromatography, eluted with PE/EA (3:1 (v/v)) to give **151-11** (500 g, 33.1%) as a light brown solid. MS (ESI): calcd. for $C_{16}H_{14}F_6N_2O_2S_2$: 444.0; Found: 445.0 $[M + 1]^+$.

- 5 **Step 10. Synthesis of methyl 2-(((2-amino-5-methoxy-4-(trifluoromethyl)phenyl)thio)methyl)-5,5,5-trifluoropentanoate (151-12).** A solution of 6,6'-disulfanediybis(4-methoxy-3-(trifluoromethyl)aniline) (**151-11**) (20.27 g, 45.6 mmol), Cs_2CO_3 (55.72 g, 171 mmol), and sodium dithionite (29.77 g, 171 mmol) in DMF (280 mL) was stirred for 20 min, then the mixture was treated with methyl 2-(bromomethyl)-5,5,5-trifluoropentanoate (**151-7**) (15 g, 57 mmol) in DMF (57 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The solution was diluted with H_2O (400 mL) and extracted with EtOAc (300 mL x 3). The combined organic layers were washed with brine (500 mL), dried over anhydrous Na_2SO_4 , and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA = 6/1 (v/v) to give **151-12** (11.2 g, 48.6%) as a light brown oil. MS (ESI): calcd. for $C_{15}H_{17}F_6NO_3S$: 405.1; Found: 406.1 $[M + 1]^+$.

- Step 11. Synthesis of 8-methoxy-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (151-13).** A solution of methyl 2-(((2-amino-5-methoxy-4-(trifluoromethyl)phenyl)thio)methyl)-5,5,5-trifluoropentanoate (**151-12**) (10.22 g, 25.21 mmol) in THF (100 mL) was treated with LiHMDS (50.41 mL, 50.41 mmol) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 2 h. The reaction was quenched with sat. aq. NH_4Cl solution at room temperature, then the mixture was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4 , and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA (4:1 (v/v)) to give **151-13** (8.6 g, 91.4%) as an off-white solid. MS (ESI): calcd. for $C_{14}H_{13}F_6NO_2S$: 373.1; Found: 374.1 $[M + 1]^+$.

Step 12. Synthesis of 5-(4-fluorophenyl)-8-methoxy-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (151-14). A solution of 8-methoxy-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (**151-13**) (8.56 g, 22.93 mmol), (4-fluorophenyl)boronic acid (9.63 g, 68.79 mmol) and TEA (9.28 g, 91.72 mmol) in DMF (86 mL) was treated with Cu(OAc)₂ (6.25 g, 34.40 mmol) at room temperature under oxygen atmosphere. The resulting mixture was stirred at 80°C for 16 h under oxygen atmosphere. The mixture was allowed to cool down to room temperature and diluted with sat. aq. NH₄Cl solution (200 mL). The resulting solution was extracted with EtOAc (150 mL x 3). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA (6:1 (v/v)) to give **151-14** (10.6 g, 92.8%) as a yellow solid. MS (ESI): calcd. C₂₀H₁₆F₇NO₂S: 467.1; Found: 468.1 [M + 1]⁺.

Step 13. Synthesis of 5-(4-fluorophenyl)-8-methoxy-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one 1,1-dioxide (151-15). A solution of 5-(4-fluorophenyl)-8-methoxy-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (**151-14**) (10.62 g, 22.72 mmol) and oxone (104.74 g, 170.40 mmol) in THF (200 mL) and H₂O (100 mL) was stirred at room temperature for 16 h. The resulting mixture was filtered, and the filter cake was washed with EtOAc (150 mL x 3). The mixture was acidified to PH = 8 with sat. aq. NaHCO₃ solution. The resulting mixture was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA = 5/1 (v/v) to give **151-15** (10.6 g, 93.4%) as a yellow solid. MS (ESI): calcd. for C₂₀H₁₆F₇NO₄S: 499.1; Found: 500.2 [M + 1]⁺.

Step 14. Synthesis of 5-(4-fluorophenyl)-8-methoxy-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepine 1,1-dioxide (151-16). A solution of 5-(4-fluorophenyl)-8-methoxy-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one 1,1-dioxide (**151-15**) (4 g, 8.0 mmol) and

BH₃·Me₂S (8 mL, 80 mmol) in THF (40 mL) was stirred at 60°C for 16 h. After the reaction was completed, the mixture was allowed to cool to 0°C with ice-water. The mixture was quenched with MeOH (8 mL) (dropwise) at 0°C, then concentrated under reduced pressure. The residue was dissolved in water (50 mL) and the mixture was extracted with EtOAc (70 mL x 3). The combined organic layers were washed with brine (150 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA (4:1 (v/v)) to give **151-16** (3.6 g, 93.6%) as a white solid. MS (ESI): calcd. for C₂₀H₁₈F₇NO₃S: 485.1; Found: 486.1 [M + 1]⁺.

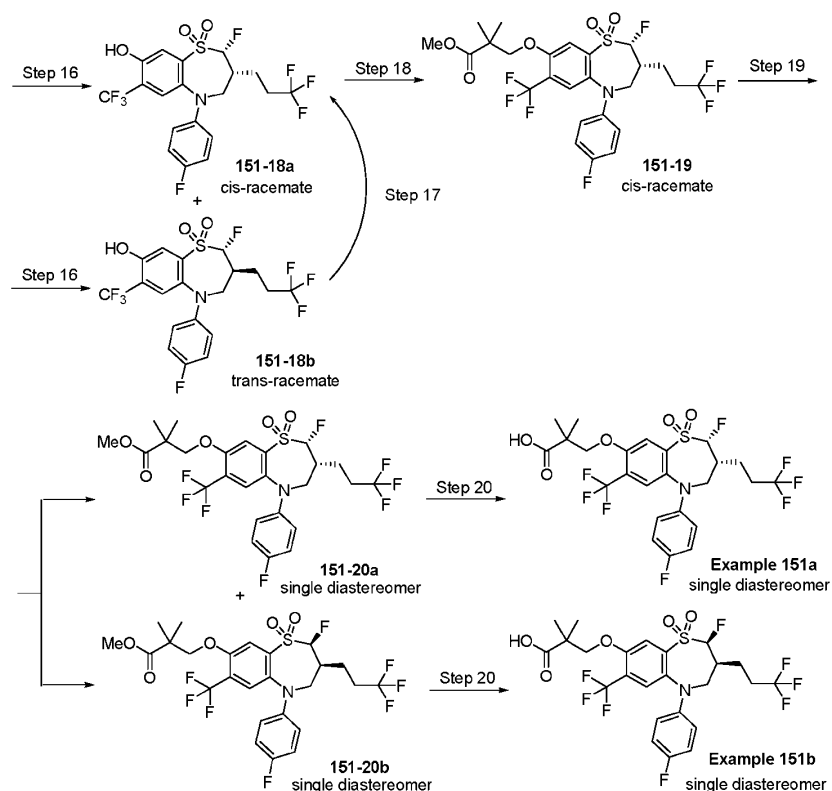
Step 15. Synthesis of rac-cis-2-fluoro-5-(4-fluorophenyl)-8-methoxy-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (151-17a) and rac-trans-2-fluoro-5-(4-fluorophenyl)-8-methoxy-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (151-17b). A solution of 5-(4-fluorophenyl)-8-methoxy-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (**151-16**) (3.6 g, 7.42 mmol) in THF (60 mL) was treated with LiHMDS (8.9 mL, 8.9 mmol) at -78 °C for 10 min under nitrogen atmosphere. The mixture was stirred for 30 min, followed by the addition of a solution of NFSI (2.11 g, 6.68 mmol) in THF (35 mL) dropwise at -78°C. The resulting mixture was stirred at -78 °C for 3 h under nitrogen atmosphere. The reaction was quenched by the addition of sat. aq. NH₄Cl solution (100 mL) at 0°C, then the mixture was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (150 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA (4:1 (v/v)) to give **151-17a** (cis-racemate, 498 mg) as a yellow solid and **151-17b** (trans-racemate, 1.92 g) as a yellow solid.

151-17a (cis-racemate): MS (ESI): calcd. for C₂₀H₁₇F₈NO₃S: 503.1; Found: 504.2 [M + 1]⁺.

¹H NMR (300 MHz, CDCl₃): δ 7.72 (s, 1H), 7.50 (s, 1H), 7.03 – 6.91 (m, 2H), 6.69 – 6.58 (m, 2H), 5.27 (d, *J* = 45.9 Hz, 1H), 4.10 – 4.04 (m, 1H), 4.03 (s, 3H), 3.34 (dd, *J* = 15.9, 11.4 Hz, 1H), 2.91 – 2.65 (m, 1H), 2.39 – 2.18 (m, 2H), 1.91 – 1.66 (m, 2H) ppm. **151-17b** (trans-

racemate): MS (ESI): calcd. for C₂₀H₁₇F₈NO₃S: 503.1; Found: 504.2 [M + 1]⁺. ¹H NMR (300

MHz, CDCl₃): δ 7.68 (s, 1H), 7.25 (s, 1H), 7.10 – 6.89 (m, 4H), 5.23 (dd, J = 44.7, 4.8 Hz, 1H), 4.17 – 4.03 (m, 1H), 3.99 (s, 3H), 3.61 (d, J = 15.3 Hz, 1H), 2.52 – 2.30 (m, 1H), 2.24 – 2.04 (m, 2H), 2.06 – 1.85 (m, 2H) ppm.



Scheme 29C

- 5
- Step 16. Synthesis of rac-cis-2-fluoro-5-(4-fluorophenyl)-8-hydroxy-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepine 1,1-dioxide (151-18a) and rac-trans-2-fluoro-5-(4-fluorophenyl)-8-hydroxy-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepine 1,1-dioxide (151-18b).** Into a 40 mL vial were added rac-cis-2-fluoro-5-(4-fluorophenyl)-8-methoxy-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepine 1,1-dioxide (151-17a) (490 mg, 0.97 mmol), LiCl (822.4 mg, 19.4 mmol) and DMSO (4.9 mL) at room temperature. The resulting mixture was stirred at 140 °C for 16 h under nitrogen atmosphere. The reaction was

monitored by LC-MS. After the reaction was completed, the mixture was allowed to cool down to room temperature. The reaction was quenched with water at room temperature. The resulting mixture was extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (3 x 70 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA (5:1 (v/v)) to give **151-18a** (cis-racemate, 414 mg, 87.0%) as a light-yellow solid. MS (ESI): calcd. for C₁₉H₁₅F₈NO₃S: 489.1; Found: 490.3 [M + 1]⁺. ¹H NMR (300 MHz, CD₃OD): δ 7.66 (s, 1H), 7.49 (s, 1H), 7.06 – 6.82 (m, 2H), 6.79 – 6.49 (m, 2H), 5.68 (d, *J* = 44.7 Hz, 1H), 4.18 (d, *J* = 16.2 Hz, 1H), 3.31 – 3.21 (m, 1H), 2.94 – 2.60 (m, 1H), 2.59 – 2.33 (m, 2H), 1.95 – 1.66 (m, 2H) ppm.

Following the same procedure for preparing **151-18a** by replacing **151-17a** with **151-17b** (1.9 g, 3.77 mmol), **151-18b** (trans-racemate, 1.6 g, 86.5%) was obtained as a light-yellow solid. MS (ESI): calcd. for C₁₉H₁₅F₈NO₃S: 489.1; Found: 490.2 [M + 1]⁺. ¹H NMR (300 MHz, CD₃OD): δ 7.63 (s, 1H), 7.27 (s, 1H), 7.09 – 6.84 (m, 4H), 5.56 (dd, *J* = 43.8, 6.3 Hz, 1H), 4.25 – 3.90 (m, 1H), 3.85 – 3.52 (m, 1H), 2.58 – 2.38 (m, 1H), 2.38 – 2.15 (m, 2H), 2.04 – 1.73 (m, 2H) ppm.

Step 17. Conversion of rac-trans-2-fluoro-5-(4-fluorophenyl)-8-hydroxy-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepine 1,1-dioxide (151-18b) to rac-cis-2-fluoro-5-(4-fluorophenyl)-8-hydroxy-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepine 1,1-dioxide (151-18a). A solution of rac-trans-2-fluoro-5-(4-fluorophenyl)-8-methoxy-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepine 1,1-dioxide (**151-18b**) (1.6 g, 3.27 mmol) in THF (16 mL) was treated with LiHMDS (1 mol/L, 3.27 mL, 3.27 mmol) at -78°C for 10 min under nitrogen atmosphere. The resulting mixture was stirred at -40°C for 1 h under nitrogen atmosphere. The reaction was quenched with sat. aq. NH₄Cl solution (20 mL) at -40°C and diluted with water (20 mL). The resulting mixture was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica

gel column chromatography, eluted with PE/EA (3/1 (v/v)) to give **151-18a** (1.4 g, 87.5%) as a yellow solid.

Step 18. Synthesis of rac-methyl 3-(((2*R*,3*S*)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoate (151-19). A solution of rac-(2*R*,3*S*)-2-fluoro-5-(4-fluorophenyl)-8-hydroxy-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepine 1,1-dioxide (**151-18a**) (1 g, 2.04 mmol), methyl 3-hydroxy-2,2-dimethylpropanoate (1.08 g, 8.17 mmol) and PPh₃ (2.14 g, 8.17 mmol) in THF (15 mL) was stirred under nitrogen atmosphere for 10 min. The solution was treated with DIAD (1.65 g, 8.17 mmol) at room temperature under nitrogen atmosphere, then stirred at 110 °C for 6 h under nitrogen atmosphere. The mixture was allowed to cool down to room temperature and diluted with water (50 mL). The resulting mixture was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA (5:1 (v/v)) to give **151-19** (1.1 g, 89.2%) as yellow semi-solid. MS (ESI): calcd. for C₂₅H₂₆F₇NO₅S: 603.5; Found: 604.2 [M + 1]⁺. ¹H NMR (400 MHz, CDCl₃): δ 7.69 (s, 1H), 7.48 (s, 1H), 7.00 – 6.92 (m, 2H), 6.67 – 6.60 (m, 2H), 5.27 (d, *J* = 46.0 Hz, 1H), 4.16 (s, 2H), 4.08 – 4.00 (m, 1H), 3.71 (s, 3H), 3.33 (dd, *J* = 15.8, 11.2 Hz, 1H), 2.89 – 2.68 (m, 1H), 2.37 – 2.20 (m, 2H), 1.91 – 1.67 (m, 2H), 1.36 (s, 6H) ppm.

Step 19. Synthesis of methyl 3-(((2*S*,3*R*)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoate (151-20a) and methyl 3-(((2*R*,3*S*)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoate (151-20b). The racemic methyl 3-(((2*R*,3*S*)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoate (**151-19**) (1.1 g, 1.82 mmol) was purified by SFC (Condition: Column: XA-(R, R)-WHELK-O, 3*25 cm, 5 μm; Mobile Phase A: CO₂, Mobile Phase B: MeOH;

Flow rate: 80 mL/min; Gradient: isocratic 25% B; Column Temperature: 35 °C; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 3.03; RT2(min): 4.26; Sample Solvent: MeOH: DCM = 4: 1 (v/v); Injection Volume: 5 mL) to give **151-20a** (single diastereomer, 480 mg, 43.6%) and **151-20b** (single diastereomer, 475 mg, 43.2%) as a yellow semi-solid, respectively. MS (ESI): calcd. for C₂₅H₂₆F₇NO₅S: 603.5; Found: 604.2 [M + 1]⁺.

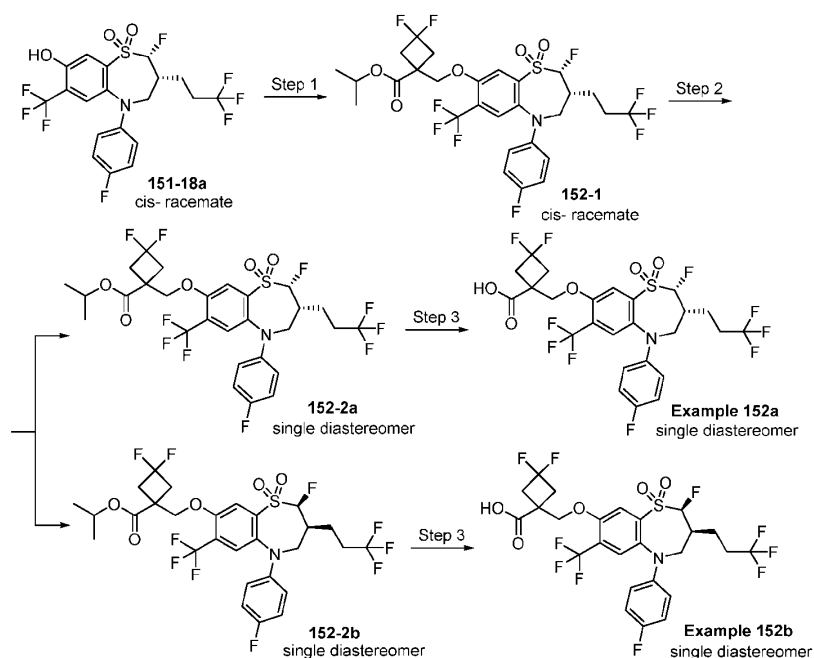
Step 20. Synthesis of 3-(((2*S*,3*R*)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid (Example 151a) and 3-(((2*R*,3*S*)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid (Example 151b). Into a 40 mL vial were added methyl 3-(((2*S*,3*R*)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoate (**151-20a**) (480 mg, 0.80 mmol), LiOH (76.64 mg, 3.2 mmol), H₂O (2 mL) and dioxane (8 mL) at room temperature. The resulting mixture was stirred at 40°C for 16 h under nitrogen atmosphere. The reaction was monitored by LC-MS. After the reaction was completed, the mixture was allowed to cool down to room temperature. The mixture was acidified to pH = 2 with aq. HCl solution (2 M). The resulting mixture was extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated. The crude product (475 mg) was purified by Prep-HPLC (Condition: Column: Sunfire Prep C18 OBD Column, 19*150 mm, 5 µm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 30 mL/min; Gradient: 40% B to 75% B in 8 min; Wavelength: 254 nm/220 nm; RT1(min): 7.28) to give **Example 151a** (single diastereomer, 303 mg, 64.6%) as a yellow solid. MS (ESI): calcd. for C₂₄H₂₃F₈NO₅S: 589.1; Found: 588.1 [M - 1]⁻. ¹H NMR (300 MHz, CD₃OD): δ 7.79 (s, 1H), 7.57 (s, 1H), 7.05 – 6.93 (m, 2H), 6.78 – 6.68 (m, 2H), 5.75 (d, *J* = 45.0 Hz, 1H), 4.33 – 4.15 (m, 3H), 3.41 – 3.34 (m, 1H), 2.90 – 2.65 (m, 1H), 2.60 – 2.34 (m, 2H), 1.94 – 1.70 (m, 2H), 1.37 (s, 6H) ppm.

- Following the same procedure for preparing **Example 151a** by replacing **151-20a** with **151-20b** (475 mg, 0.79 mmol), **Example 151b** was obtained (single diastereomer, 272 mg, 58.6%) as a yellow solid. Chiral HPLC condition: Column: Sunfire Prep C18 OBD Column, 19*150 mm, 5 μ m; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN;
- 5 Flow rate: 30 mL/min; Gradient: 40% B to 75% B in 8 min; Wavelength: 254 nm/220 nm; RT1(min): 7.28. MS (ESI): calcd. for C₂₄H₂₃F₈NO₅S: 589.1; Found: 588.1 [M - 1]⁻. ¹H NMR (300 MHz, CD₃OD): δ 7.79 (s, 1H), 7.57 (s, 1H), 7.05 – 6.93 (m, 2H), 6.78 – 6.68 (m, 2H), 5.75 (d, *J* = 45.0 Hz, 1H), 4.33 – 4.15 (m, 3H), 3.41 – 3.34 (m, 1H), 2.90 – 2.65 (m, 1H), 2.60 – 2.34 (m, 2H), 1.94 – 1.70 (m, 2H), 1.37 (s, 6H) ppm.

10

Examples 152a and 152b. 3,3-difluoro-1-((((2S,3R)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclobutane-1-carboxylic acid (152a) and 3,3-difluoro-1-((((2R,3S)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-

tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclobutane-1-carboxylic acid (**152b**)



Scheme 30

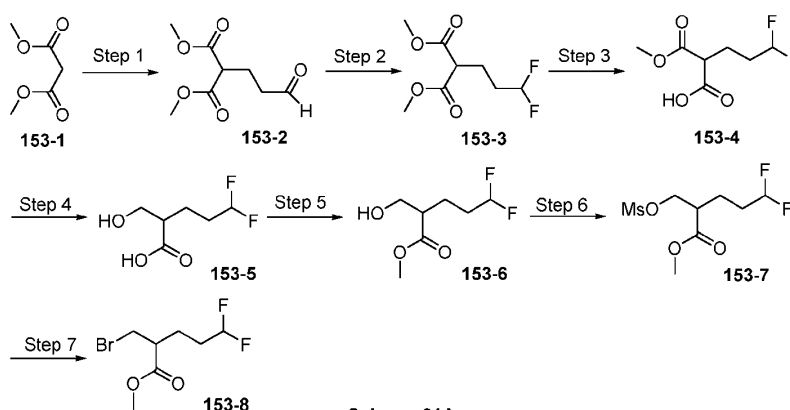
- 5 **Step 1. Synthesis of rac-isopropyl 3,3-difluoro-1-(((2S,3R)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-**
tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclobutane-1-carboxylate (152-1**).** A
 solution of rac-(2S,3R)-2-fluoro-5-(4-fluorophenyl)-8-hydroxy-7-(trifluoromethyl)-3-(3,3,3-
 10 trifluoropropyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (**151-18a**) (105 mg,
 0.215 mmol), isopropyl 3,3-difluoro-1-((tosyloxy)methyl)cyclobutane-1-carboxylate (116.63
 mg, 0.323 mmol), Cs₂CO₃ (209.72 mg, 0.645 mmol) and KI (35.62 mg, 0.215 mmol) in DMF
 (5 mL) was stirred at 80 °C for 18 h. The mixture was allowed to cool down to room
 temperature, then diluted with water (20 mL). The resulting mixture was extracted
 with EtOAc (15 mL x 3). The combined organic layers were washed with water (20 mL x 5)
 15 and brine (20 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified
 by silica gel column chromatography, eluted with PE/EA (4:1 (v/v)) to give **152-1** (100 mg,
 58.3%) as a brown oil. MS (ESI): calcd. for C₂₈H₂₇F₁₀NO₅S: 679.1; Found: 680.1 [M + 1]⁺.

Step 2. Synthesis of isopropyl 3,3-difluoro-1-(((2S,3R)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclobutane-1-carboxylate (152-2a)
5 **and isopropyl 3,3-difluoro-1-(((2R,3S)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclobutane-1-carboxylate (152-2b).** The racemic isopropyl 3,3-difluoro-1-(((2S,3R)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclobutane-1-
10 carboxylate (100 mg, 0.147 mmol, 1 equiv) was purified by Prep-CHIRAL-HPLC (Condition: Column: XA-(R, R)-WHELK-O, 2.11*25 cm, 5 µm; Mobile Phase A: HEX:DCM = 3:1 (v/v) , Mobile Phase B: EtOH; Flow rate: 25 mL/min; Gradient: isocratic 15; Wave Length: 254 nm) to give **152-2a** (RT = 1.577 min, single diastereomer, 43 mg, 40.9%) as a yellow oil, MS (ESI): calcd. for C₂₈H₂₇F₁₀NO₅S: 679.1; Found: 680.1 [M + 1]⁺
15 and **152-2b** (RT = 1.846 min, single diastereomer, 38 mg, 36.1%) as a yellow oil, MS (ESI): calcd. for C₂₈H₂₇F₁₀NO₅S: 679.1; Found: 680.1 [M + 1]⁺.

Step 3. Synthesis of 3,3-difluoro-1-(((2S,3R)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclobutane-1-carboxylic acid (Example 152a) and 3,3-difluoro-1-(((2R,3S)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclobutane-1-carboxylic acid (Example 152b). A solution of isopropyl 3,3-difluoro-1-(((2S,3R)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)cyclobutane-1-carboxylate (**152-2a**) (43
25 mg, 0.063 mmol) and LiOH (4.55 mg, 0.189 mmol) in Dioxane (5 mL) and H₂O (1 mL) was stirred at 40 °C for 16 h. The resulting mixture was diluted with water (20 mL), then extracted with EtOAc (5 mL x 2). The aqueous phase was acidified to pH 3 with aq. HCl solution (2M), then extracted with EtOAc (10 mL x 3). The combined organic layers were
30 washed with brine (10 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue (40

mg) was purified by Prep-HPLC (Condition: Column: Sunfire Prep C18 OBD Column, 19*150mm, 5 μ m; Mobile Phase A: Water(0.1% FA), Mobile Phase B: ACN; Flow rate: 30 mL/min; Gradient: 45% B to 75 % B in 8 min; Wavelength: 254 nm/220 nm) to give

- Example 152a** (RT = 1.813 min, single diastereomer, 15.2 mg, 37.6%) as a light yellow solid. MS (ESI): calcd. for C₂₅H₂₁F₁₀NO₅S: 637.1; Found: 638.1 [M + 1]⁺. ¹H NMR (400 MHz, CDCl₃): δ 7.73 (s, 1H), 7.48 (s, 1H), 6.95 - 7.00 (m, 2H), 6.65 - 6.68 (m, 2H), 5.28 (d, *J* = 46.0 Hz, 1H), 4.45 - 4.51 (m, 2H), 4.06 (d, *J* = 14.8 Hz, 1H), 3.34 (dd, *J* = 15.6, 10.8 Hz, 1H), 3.15 - 3.25 (m, 2H), 2.71 - 2.89 (m, 3H), 2.22 - 2.34 (m, 2H), 1.71 - 1.87 (m, 2H) ppm.
- Following the same procedure for preparing **Example 152a** by replacing **152-2a** with **152-2b** (38 mg, 0.056 mmol), **Example 152b** (RT = 2.328 min, single diastereomer, 12.3 mg, 33.9%) was obtained a light-yellow solid. Chiral HPLC condition: Column: Sunfire Prep C18 OBD Column, 19*150mm, 5 μ m; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 30 mL/min; Gradient: 45% B to 75 % B in 8 min; Wavelength: 254 nm/220 nm).
- MS (ESI): calcd. for C₂₅H₂₁F₁₀NO₅S: 637.1; Found: 638.1 [M + 1]⁺. ¹H NMR (400 MHz, CDCl₃): δ 7.73 (s, 1H), 7.52 (s, 1H), 6.95 - 7.00 (m, 2H), 6.65 - 6.68 (m, 2H), 5.28 (d, *J* = 46.0 Hz, 1H), 4.45 - 4.51 (m, 2H), 4.06 (d, *J* = 15.2 Hz, 1H), 3.34 (dd, *J* = 16.0, 11.2 Hz, 1H), 3.15 - 3.24 (m, 2H), 2.71 - 2.88 (m, 3H), 2.22 - 2.34 (m, 2H), 1.71 - 1.87 (m, 2H) ppm.
- Examples 153a and 153b. 3-(((2S,3R)-3-(3,3-difluoropropyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid (153a) and 3-(((2R,3S)-3-(3,3-difluoropropyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid (153b)



Step 1. Synthesis of dimethyl 2-(3-oxopropyl)malonate (153-2). A solution of dimethyl malonate (**153-1**) (100 g, 756.92 mmol) in MeOH (1 L) was treated with sodium methoxide (4.09 g, 75.69 mmol) for 2 min at room temperature under nitrogen atmosphere, followed by the addition of acrolein (55.17 g, 983.99 mmol) dropwise at 0 °C. The resulting mixture was stirred at room temperature for 16 h. The resulting mixture was concentrated under reduced pressure. The resulting mixture was extracted with EtOAc (1 L x 2). The combined organic layers were washed with brine (1 L), dried over anhydrous Na₂SO₄, and concentrated. The crude product was purified by distillation under reduced pressure and the fraction was collected at room temperature to give **153-2** (65 g, 45.6%) as a colorless liquid. MS (ESI): calcd. for C₈H₁₂O₅: 188.1; Found: 189.1 [M + 1]⁺.

Step 2. Synthesis of dimethyl 2-(3,3-difluoropropyl)malonate (153-3). A solution of dimethyl 2-(3-oxopropyl)malonate (**153-2**) (65 g, 345.42 mmol) and BAST (152.84 g, 690.83 mmol) in DCE (650 mL) was stirred at 70 °C for 16 h. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with CH₂Cl₂ (200 mL). The mixture was adjusted to pH = 9 with saturated aq. NaHCO₃ solution. The resulting mixture was extracted with CH₂Cl₂ (1 L x 2). The combined organic layers were washed with brine (1 L), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with CH₂Cl₂/MeOH (7/1 (v/v)) to give **153-3** (25 g, 34.4%) as a colorless liquid. MS (ESI): calcd. for C₈H₁₂F₂O₄: 210.1; Found: 211.1 [M + 1]⁺.

Step 3. Synthesis of 5,5-difluoro-2-(methoxycarbonyl)pentanoic acid (153-4). A solution of dimethyl 2-(3,3-difluoropropyl)malonate (**153-3**) (25 g, 118.95 mmol) and potassium hydroxide (8.01 g, 142.74 mmol) in MeOH (250 mL) was stirred at room temperature for 8 h. The mixture was acidified to pH = 2 with aq. HCl solution (2 N). The resulting mixture was extracted with EtOAc (200 mL x 2). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried to give **153-4** (18 g, 77.2%) as a colorless liquid. MS (ESI): calcd. for C₇H₁₀F₂O₄: 196.1; Found: 197.1 [M + 1]⁺.

Step 4. Synthesis of 5,5-difluoro-2-(hydroxymethyl)pentanoic acid (153-5). A solution of 5,5-difluoro-2-(methoxycarbonyl)pentanoic acid (**153-4**) (25 g, 127.45 mmol) and LiBH₄ (5.55 g, 254.91 mmol) in i-PrOH (250 mL) was stirred at room temperature for 3 h. The mixture was acidified to pH = 3 with conc. aq. HCl solution. The resulting mixture was extracted with EtOAc (250 mL x 2). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give **153-5** (20 g, 93.3%) as a colorless liquid, which was used in the next step without further purification. MS (ESI): calcd. for C₆H₁₀F₂O₃: 168.1; Found: 169.1 [M + 1]⁺.

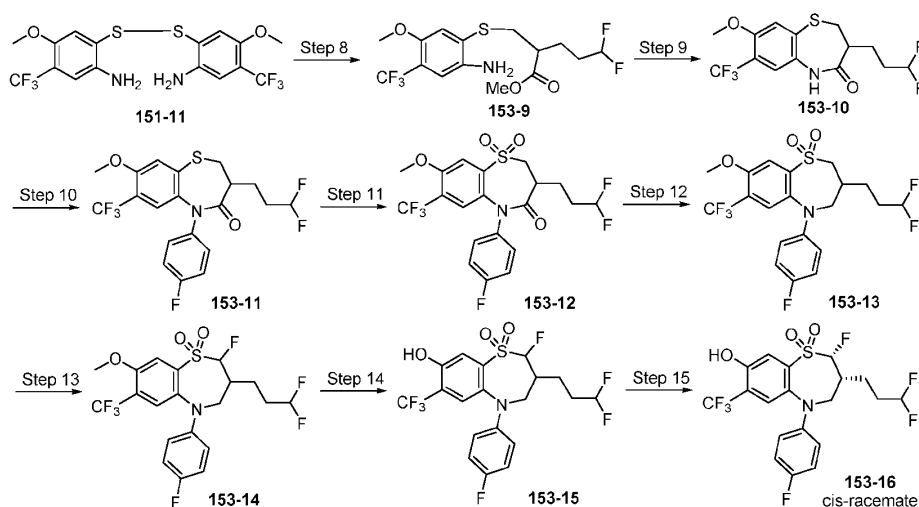
Step 5. Synthesis of methyl 5,5-difluoro-2-(hydroxymethyl)pentanoate (153-6). A solution of 5,5-difluoro-2-(hydroxymethyl)pentanoic acid (**153-5**) (20 g, 118.95 mmol) and H₂SO₄ (3.5 mL, 118.95 mmol) in MeOH (200 mL) was stirred at 60 °C for 4 h. The mixture was allowed to cool down to room temperature. The reaction was quenched with water at room temperature. The resulting mixture was extracted with EtOAc (200 mL x 4). The combined organic layers were washed with brine (1 L), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give **153-6** (18 g, 83.1%) as a colorless liquid, which was used in the next step without further purification. MS (ESI): calcd. for C₇H₁₂F₂O₃: 182.1; Found: 183.1 [M + 1]⁺.

Step 6. Synthesis of methyl 5,5-difluoro-2-(((methylsulfonyl)oxy)methyl)pentanoate

(**153-7**). A solution of methyl 5,5-difluoro-2-(hydroxymethyl)pentanoate (**153-6**) (18 g, 98.81 mmol) in DCM (180 mL) was treated with TEA (30.00 g, 296.43 mmol) for 5 mins at 0 °C under nitrogen atmosphere, followed by the addition of MsCl (14.71 g, 128.45 mmol) in portions at 0 °C. The resulting mixture was stirred at room temperature for 2 h. The reaction was quenched with water at room temperature. The resulting mixture was extracted with CH₂Cl₂ (200 mL x 2). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give **153-7** (20 g, 77.8%) as a yellow oil, which was used in the next step without further purification. MS (ESI): calcd. for C₈H₁₄F₂O₅S: 260.1; Found: 261.1 [M + 1]⁺.

Step 7. Synthesis of methyl 2-(bromomethyl)-5,5-difluoropentanoate (153-8).

A solution of methyl 5,5-difluoro-2-(((methylsulfonyl)oxy)methyl)pentanoate (**153-7**) (20 g, 76.85 mmol) and LiBr (20.02 g, 230.55 mmol) in acetone (200 mL) was stirred at 60 °C for 3 h. The mixture was allowed to cool down to room temperature. The reaction was quenched with water (100 mL) at room temperature and then concentrated to remove the organic solvent. The resulting mixture was extracted with EtOAc (200 mL x 2). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give **153-8** (15 g, 79.7%) as a yellow oil, which was used in the next step without further purification. MS (ESI): calcd. for C₇H₁₁BrF₂O₂: 244.0; Found: 245.0 [M + 1]⁺.



Scheme 31B

Step 8. Synthesis of methyl 2-(((2-amino-5-methoxy-4-(trifluoromethyl)phenyl)thio)methyl)-5,5-difluoropentanoate (153-9). A solution of 6,6'-disulfanedibis(4-methoxy-3-(trifluoromethyl)aniline) (**151-11**) (15 g, 33.75 mmol) in DMF (150 mL) was treated with Cs_2CO_3 (32.99 g, 101.26 mmol) for 2 mins at room temperature under nitrogen atmosphere followed by the addition of $\text{Na}_2\text{S}_2\text{O}_4$ (23.51 g, 135.01 mmol) dropwise at room temperature. The resulting mixture was stirred at room temperature for 1 h. To the above mixture was added methyl 2-((bromomethyl)-5,5-difluoropentanoate (**153-8**) (8.27 g, 33.75 mmol) dropwise at room temperature over 10 mins. The resulting mixture was stirred at room temperature for an additional 3 h. The reaction was quenched with water at room temperature. The resulting mixture was extracted with EtOAc (150 mL x 2). The combined organic layers were washed with brine (150 mL), dried over anhydrous Na_2SO_4 , and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA (10:1 (v/v)) to give **153-9** (10.7 g, 81.8%) as a white solid. MS (ESI): calcd. for $\text{C}_{15}\text{H}_{18}\text{F}_5\text{NO}_3\text{S}$: 387.1; Found: 388.1 $[\text{M} + 1]^+$.

Step 9. Synthesis of 3-(3,3-difluoropropyl)-8-methoxy-7-(trifluoromethyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (153-10). Into a 500 mL 3-necked round-bottom

flask were added methyl 2-(((2-amino-5-methoxy-4-(trifluoromethyl)phenyl)thio)methyl)-5,5-difluoropentanoate (**153-9**) (10.7 g, 27.62 mmol) and THF (110 mL) at room temperature. To the above mixture was added LiHMDS (50 mL, 55.24 mmol) dropwise at 0 °C over 30 min. The resulting mixture was stirred at room temperature for an additional 2

5 h. The reaction was quenched with sat. aq. NH₄Cl solution at room temperature. The resulting mixture was extracted with EtOAc (100 mL x 2). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA (10:1 (v/v)) to give **153-10** (6 g, 61.1%) as a white solid. MS (ESI): calcd. for C₁₄H₁₄F₅NO₂S: 355.1; Found: 356.0 [M + 1]⁺.

10

Step 10. Synthesis of 3-(3,3-difluoropropyl)-5-(4-fluorophenyl)-8-methoxy-7-(trifluoromethyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (153-11). To a stirred solution of 3-(3,3-difluoropropyl)-8-methoxy-7-(trifluoromethyl)-2,3-

15 dihydrobenzo[b][1,4]thiazepin-4(5H)-one (**153-10**) (6 g, 16.89 mmol) and TEA (6.84 g, 67.54 mmol) in DMF (60 mL) were added Cu(OAc)₂ (4.60 g, 25.33 mmol) and 4-fluorophenylboronic acid (7.09 g, 50.66 mmol) dropwise at room temperature. The resulting mixture was stirred at 80 °C for 16 h under O₂ atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was filtered, the filter cake was washed

20 with EtOAc (50 mL x 3). The filtrate was concentrated under reduced pressure. The resulting mixture was extracted with EtOAc (100 mL x 2). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA (10:1 (v/v)) to **153-11** (7 g, 92.2%) as a white solid. MS (ESI): calcd. for C₂₀H₁₇F₆NO₂S: 449.1; Found: 450.1 [M + 1]⁺.

25

Step 11. Synthesis of 3-(3,3-difluoropropyl)-5-(4-fluorophenyl)-8-methoxy-7-(trifluoromethyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one 1,1-dioxide (153-12). A solution of 3-(3,3-difluoropropyl)-5-(4-fluorophenyl)-8-methoxy-7-(trifluoromethyl)-2,3-

dihydrobenzo[b][1,4]thiazepin-4(5H)-one (**153-11**) (7.5 g, 16.69 mmol) and Oxone® (56.13 g, 333.78 mmol) in THF (75 mL) was stirred at room temperature for 16 hr. The resulting mixture was filtered, the filter cake was washed with EtOAc (50 mL x 3). The filtrate was concentrated under reduced pressure. The resulting mixture was extracted with EtOAc (100 mL x 2). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give **153-12** (7 g, 87.1%) as a yellow solid, which was used in the next step without further purification. MS (ESI): calcd. for C₂₀H₁₇F₆NO₄S: 481.1; Found: 482.1 [M + 1]⁺.

Step 12. Synthesis of 3-(3,3-difluoropropyl)-5-(4-fluorophenyl)-8-methoxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (153-13). A solution of 3-(3,3-difluoropropyl)-5-(4-fluorophenyl)-8-methoxy-7-(trifluoromethyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one 1,1-dioxide (**153-12**) (7 g, 14.54 mmol) and BH₃·THF (6.96 mL, 72.71 mmol) in THF (70 mL) was stirred at 60 °C for 16 hr. The mixture was allowed to cool down to room temperature. The reaction was quenched with water at room temperature. The resulting mixture was extracted with EtOAc (70 mL x 2). The combined organic layers were washed with brine (70 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA (10:1 (v/v)) to give **153-13** (5 g, 73.6%) as a white solid. MS (ESI): calcd. for C₂₀H₁₉F₆NO₃S: 467.1; Found: 468.1 [M + 1]⁺.

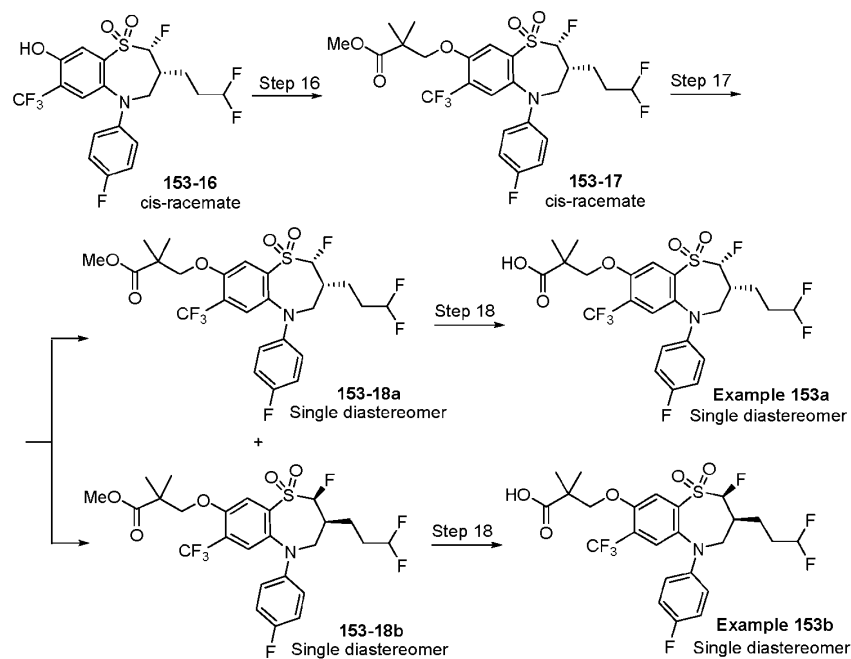
Step 13. Synthesis of 3-(3,3-difluoropropyl)-2-fluoro-5-(4-fluorophenyl)-8-methoxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (153-14). Into a 250 mL 3-necked round-bottom flask were added 3-(3,3-difluoropropyl)-5-(4-fluorophenyl)-8-methoxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (**153-13**) (6.5 g, 13.91 mmol) and THF (130 mL) at room temperature. To the above mixture was added LiHMDS (2.79 g, 16.69 mmol) dropwise at -78 °C over 0.5 hr. The resulting mixture was stirred at -78 °C for an additional 30 min. To the above mixture was added NFSI (3.95 g,

12.52 mmol) dropwise at -78 °C over 1 hr. The resulting mixture was stirred at -78 °C for an additional 30 min. The reaction was quenched with sat. aq. NH₄Cl solution at room temperature. The resulting mixture was extracted with EtOAc (250 mL x 2). The combined organic layers were washed with brine (250 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA (10:1 (v/v)) to **153-14** (2.6 g, 38.5%) as a yellow solid. MS (ESI): calcd. for C₂₀H₁₈F₇NO₃S: 485.1; Found: 486.1 [M + 1]⁺.

Step 14. Synthesis of 3-(3,3-difluoropropyl)-2-fluoro-5-(4-fluorophenyl)-8-hydroxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (153-15). A solution of 3-(3,3-difluoropropyl)-2-fluoro-5-(4-fluorophenyl)-8-methoxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (**153-14**) (2.4 g, 4.94 mmol) and LiCl (4.19 g, 98.88 mmol) in DMSO (24 mL) was stirred at 140 °C for 16 hr. The mixture was allowed to cool down to room temperature. The reaction was quenched with Water at room temperature. The resulting mixture was extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA (10:1 (v/v)) to give **153-15** (1.8 g, 77.2%) as a yellow solid. MS (ESI): calcd. for C₁₉H₁₆F₇NO₃S: 471.1; Found: 472.0 [M + 1]⁺.

Step 15. Synthesis of rac-(2R,3S)-3-(3,3-difluoropropyl)-2-fluoro-5-(4-fluorophenyl)-8-hydroxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (153-16). Into a 50 mL 3-necked round-bottom flask were added 3-(3,3-difluoropropyl)-2-fluoro-5-(4-fluorophenyl)-8-hydroxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (**153-15**) (1.8 g, 3.82 mmol) and THF (18 mL) at room temperature. To the above mixture was added LiHMDS (13.2 mL, 19.09 mmol) dropwise at -40 °C over 10 min. The resulting mixture was stirred at -40 °C for an additional 30 min. The reaction was quenched with water at room temperature. The resulting mixture was extracted with EtOAc (20 mL x

2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 , and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA (10:1 (v/v)) to give **153-16** (cis- racemate, 730 mg, 40.6%) as a yellow solid. MS (ESI): calcd. for $\text{C}_{19}\text{H}_{16}\text{F}_7\text{NO}_3\text{S}$: 471.1; Found: 472.0 $[\text{M} + 1]^+$.



Scheme 31C

Step 16. Synthesis of rac-methyl 3-(((2R,3S)-3-(3,3-difluoropropyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoate (153-17**).** To a stirred solution of rac-(2R,3S)-3-(3,3-difluoropropyl)-2-fluoro-5-(4-fluorophenyl)-8-hydroxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (**153-16**) (730 mg, 1.55 mmol) and DIAD (1.25 g, 6.20 mmol) in THF (7.3 mL) were added PPh_3 (1.62 g, 6.20 mmol) and methyl 3-hydroxy-2,2-dimethylpropanoate (409.33 mg, 3.10 mmol) dropwise at room temperature. The resulting mixture was stirred at 110 °C for 16 h under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched with water at room temperature. The resulting mixture was extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , and

concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA (10:1 (v/v)) to give **153-17** (750 mg, 82.7%) as a yellow solid. MS (ESI): calcd. for $C_{25}H_{26}F_7NO_5S$: 585.1; Found: 586.1 $[M + 1]^+$.

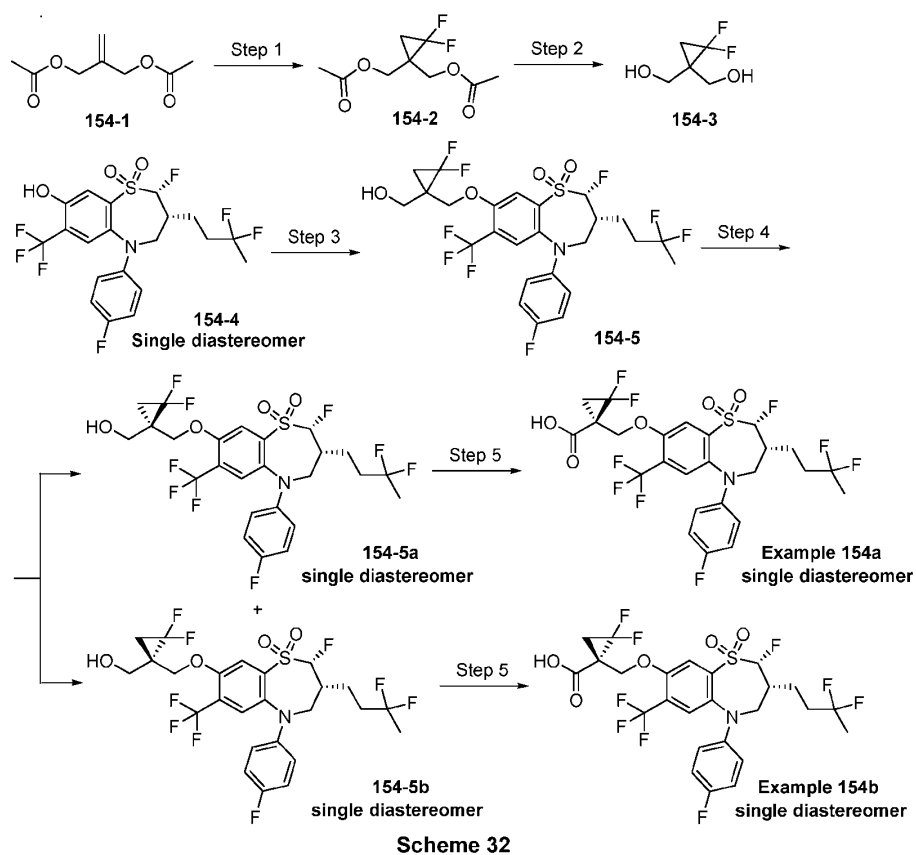
5 **Step 17. Synthesis of methyl 3-(((2S,3R)-3-(3,3-difluoropropyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoate (153-18a) and methyl 3-(((2R,3S)-3-(3,3-difluoropropyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoate (153-18b).** The
10 racemic methyl 3-(((2R,3S)-3-(3,3-difluoropropyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoate (**153-17**) (750 mg) was purified by prep-SFC (condition:
(2#SHIMADZU (SFC-150), Column: XA-(R, R)-WHELK-O, 2.11*25 cm, 5 μ m; Mobile
Phase A: HEX:DCM = 3:1 (v/v), Mobile Phase B: EtOH; Flow rate: 25 mL/min; Gradient:
15 isocratic 30; Wavelength: 220 nm; RT1 (min): 4.8; RT2 (min): 6.0; Sample Solvent: EtOH:
DCM = 1: 1 (v/v); Injection Volume: 5 mL) to give **153-18a** (310 mg, 82.7%, single
diastereomer) and **153-18b** (320 mg, 91.4%, single diastereomer) as a white solid,
respectively. MS (ESI): calcd. for $C_{25}H_{26}F_7NO_5S$: 585.1; Found: 586.1 $[M + 1]^+$.

20 **Step 18. Synthesis of 3-(((2S,3R)-3-(3,3-difluoropropyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid (Example 153a) and 3-(((2R,3S)-3-(3,3-difluoropropyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid (Example**
25 **153b).** A solution of methyl 3-(((2S,3R)-3-(3,3-difluoropropyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoate (**153-18a**) (310 mg, 0.57 mmol) and LiOH (16.02 mg, 0.5mmol) in 1,4-dioxane (4 mL) and H₂O (1 mL) was stirred for 12 h at rt. The mixture was acidified to pH =

4 with aq. HCl (2 M). The resulting mixture was extracted with EA (10 mL x 2). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue (300 mg) was purified by Prep-HPLC (condition: Column: Sunfire Prep C18 OBD Column, 19*150 mm, 5 µm; Mobile Phase A: Water (0.1% FA), Mobile
5 Phase B: ACN; Flow rate: 30 mL/min; Gradient: 50% B to 80 % B in 8 min; Wavelength: 254 nm/220 nm; RT1(min): 7.26) to give **Example 153a** (285 mg, 94.4% single diastereomer) as a white solid. MS (ESI): calcd. for C₂₄H₂₄F₇NO₅S: 571.1; Found: 572.1 [M + 1]⁺. ¹H NMR (300 MHz, CD₃OD): δ 7.79 (s, 1H), 7.57 (s, 1H), 6.98 (t, J = 8.7 Hz, 2H), 6.74 - 6.69 (m, 2H), 6.17 - 5.63 (m, 2H), 4.29 - 4.18 (m, 3H), 3.32 - 3.27 (m, 1H), 2.86 -
10 2.57 (m, 1H), 2.21 - 1.98 (m, 2H), 1.83 - 1.58 (m, 2H), 1.37 (s, 6H) ppm.

Following the same procedure for preparing **Example 153a** by replacing **153-18a** with **153-18b** (320 mg, 0.59 mmol), **Example 153b** (282 mg, 90.4%, single diastereomer) was obtained as a white solid. Prep-HPLC condition: Column: Sunfire Prep C18 OBD Column,
15 19*150 mm, 5 µm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 30 mL/min; Gradient: 50% B to 80 % B in 8 min; Wavelength: 254 nm/220 nm; RT1(min): 7.26. MS (ESI): calcd. for C₂₄H₂₄F₇NO₅S: 571.1; Found: 572.1 [M + 1]⁺. ¹H NMR (300 MHz, CD₃OD): δ 7.79 (s, 1H), 7.57 (s, 1H), 6.98 (t, J = 8.7 Hz, 2H), 6.74 - 6.69 (m, 2H), 6.16 - 5.63 (m, 2H), 4.32 - 4.15 (m, 3H), 3.32 - 3.27 (m, 1H), 2.83 - 2.61 (m, 1H), 2.21 -
20 1.97 (m, 2H), 1.83 - 1.58 (m, 2H), 1.37 (s, 6H) ppm.

Examples 154a and 154b. (S)-1-(((2S,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)-2,2-difluorocyclopropane-1-carboxylic acid (154a) and (R)-1-(((2S,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)-2,2-difluorocyclopropane-1-carboxylic acid (154b)
25



Step 1. Synthesis of (2,2-difluorocyclopropane-1,1-diyl)bis(methylene) diacetate (**154-2**).

Into a 1000 mL 3-necked round-bottom flask were added 2-methylenepropane-1,3-diyl diacetate (**154-1**) (20 g, 116.2 mmol) and DME (100 mL) at room temperature. To the above mixture was added $\text{ClCF}_2\text{CO}_2\text{Na}$ (106.26 g, 697 mmol) in 400 mL THF dropwise at 80°C over 5 h. The resulting mixture was stirred at 80°C for an additional 1 h. The mixture was allowed to cool down to room temperature. The resulting mixture was extracted with PE (200 mL x 2). The combined organic extracts were washed with brine (100 mL x 4), dried over anhydrous Na_2SO_4 , and concentrated. The residue was dried in vacuo to give **154-2** (15 g, 58.1%) as a colorless oil.

Step 2. Synthesis of (2,2-difluorocyclopropane-1,1-diyl)dimethanol (154-3). Into a 250 mL 3-necked round-bottom flask were added (2,2-difluorocyclopropane-1,1-diyl)bis(methylene) diacetate (**154-2**) (15 g, 67.5 mmol), methanol (150 mL) and K₂CO₃ (28.19 g, 202.5 mmol) at room temperature. The resulting mixture was stirred at room temperature for 3 h under nitrogen atmosphere. The resulting mixture was diluted with water (300 mL). The resulting mixture was extracted with EtOAc (300 mL x 2). The combined organic extracts were washed with brine (200 mL x 2), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA (1:1 (v/v)) to give **154-3** (5 g, 53.6%) as a colorless oil.

¹H NMR (400 MHz, CDCl₃): δ 3.99 – 3.82 (m, 4H), 1.36 (t, *J* = 8.4 Hz, 2H) ppm.

Step 3. Synthesis of rac-(2S,3R)-8-((2,2-difluoro-1-(hydroxymethyl)cyclopropyl)methoxy)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (154-5). Into a 8 mL vial were added rac-(2S,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-8-hydroxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide (**154-4**) (single diastereomer, 140 mg, 0.29 mmol), THF (4 mL), (2,2-difluorocyclopropane-1,1-diyl)dimethanol (**154-3**) (47.80 mg, 0.35 mmol), PPh₃ (98.34 mg, 0.37 mmol) and DIAD (75.82 mg, 0.37 mmol) at room temperature. The resulting mixture was stirred at 55°C for 2 h under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of water (10 mL) at room temperature. The resulting mixture was extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (10 mL x 2), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA (1:1 (v/v)) to give **154-5** (100 mg, 57.3%) as a yellow solid. MS (ESI): calcd. for C₂₅H₂₄F₉NO₄S: 605.1; Found: 606.1 [M + 1]⁺.

Step 4. Synthesis of (2S,3R)-8-(((R)-2,2-difluoro-1-(hydroxymethyl)cyclopropyl)methoxy)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine 1,1-dioxide

(**154-5a**) and (2S,3R)-8-(((S)-2,2-difluoro-1-(hydroxymethyl)cyclopropyl)methoxy)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine **1,1-dioxide (154-5b)**. The crude rac-(2S,3R)-8-((2,2-difluoro-1-(hydroxymethyl)cyclopropyl)methoxy)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine **1,1-dioxide (154-5)** (100 mg) was purified by Prep-HPLC ((2#SHIMADZU (HPLC-01)), Column: CHIRAL ART Amylose-C NEO, 3*25 cm, 5 μ m; Mobile Phase A: Hex (0.1% FA)-HPLC, Mobile Phase B: IPA-HPLC; Flow rate: 35 mL/min; Gradient: 30% B to 30% B in 15 min; Wavelength: 220/254 nm; RT1(min): 10; RT2(min): 12; Sample Solvent: IPA:CAN = 3:1 (v/v); Injection Volume: 0.8 mL) to give **154-5a** (40 mg, single diastereomer, the stereochemistry was arbitrarily assigned) and **154-5b** (42 mg, single diastereomer, the stereochemistry was arbitrarily assigned) as yellow solid, respectively.

Step 5. Synthesis of (S)-1-(((2S,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)-2,2-difluorocyclopropane-1-carboxylic acid (Example 154a) and (R)-1-(((2S,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)methyl)-2,2-difluorocyclopropane-1-carboxylic acid (Example 154b). Into a 8 mL vial were added (2S,3R)-8-(((R)-2,2-difluoro-1-(hydroxymethyl)cyclopropyl)methoxy)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine **1,1-dioxide (154-5a)** (40 mg, 0.07 mmol), dioxane (4 mL), water (2 mL), NaOH (5.29 mg, 0.13 mmol) and KMnO₄ (36.56 mg, 0.23 mmol) at room temperature. The resulting mixture was stirred at room temperature for 4 hr under nitrogen atmosphere. The precipitate was collected by filtration and washed with water (40 mL x 2). The filtrate was acidified to pH = 3 with 2 N aq. HCl solution. The resulting mixture was extracted with EtOAc (30 mL x 2). The combined organic extracts were washed with brine (30 mL x 2), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by Prep-HPLC (Column: Sunfire Prep C18 OBD Column, 19*150 mm, 5 μ m; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 30 mL/min;

Gradient: 55% B to 70 % B in 8 min; Wavelength: 254 nm/220 nm; RT1(min): 7.42) to give

Example 154a (14 mg, 34.8%, single diastereomer, the stereochemistry is arbitrarily assigned) as yellow solid. MS (ESI): calcd. for $C_{25}H_{22}F_9NO_5S$: 619.1; Found: 618.2 [M - 1].

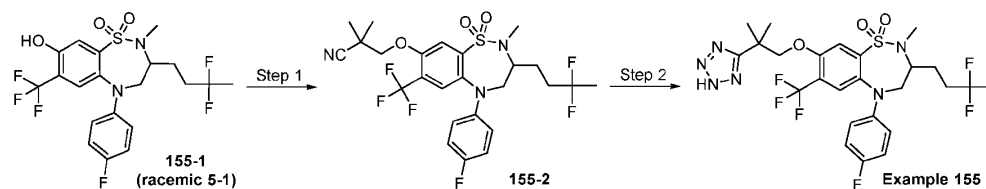
1H NMR (400 MHz, CD_3OD): δ 7.81 (s, 1H), 7.55 (s, 1H), 7.02 – 6.92 (m, 2H), 6.75 – 6.67

(m, 2H), 5.69 (d, J = 45.2 Hz, 1H), 4.84 – 4.80 (m, 1H), 4.38 (d, J = 10.0 Hz, 1H), 4.19 (d, J = 16.0 Hz, 1H), 3.33 – 3.29 (m, 1H), 2.80 – 2.59 (m, 1H), 2.45 – 2.34 (m, 1H), 2.21 – 1.96 (m, 2H), 1.82 – 1.53 (m, 5H) ppm.

Following the same procedure for preparing **Example 154a** by replacing 154-5a with 154-5b

(single diastereomer, 42 mg), **Example 154b** was obtained (14 mg, 33.1%, single diastereomer, the stereochemistry is arbitrarily assigned) as a yellow solid. Prep-HPLC condition: Column: Sunfire Prep C18 OBD Column, 19*150 mm, 5 μ m; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 30 mL/min; Gradient: 55% B to 70 % B in 8 min; Wavelength: 254 nm/220 nm; RT1 (min): 7.58. MS (ESI): calcd. for $C_{25}H_{22}F_9NO_5S$: 619.1; Found: 618.2 [M - 1]. 1H NMR (400 MHz, CD_3OD): δ 7.82 (s, 1H), 7.55 (s, 1H), 7.02 – 6.92 (m, 2H), 6.76 – 6.67 (m, 2H), 5.69 (d, J = 45.2 Hz, 1H), 4.92 – 4.90 (m, 1H), 4.34 (d, J = 10.0 Hz, 1H), 4.19 (d, J = 15.6 Hz, 1H), 3.29 - 3.25 (m, 1H), 2.79 – 2.60 (m, 1H), 2.44 – 2.33 (m, 1H), 2.24 – 2.04 (m, 2H), 2.04 – 1.93 (m, 1H), 1.83 – 1.48 (m, 5H) ppm.

Example 155. 3-(3,3-Difluorobutyl)-5-(4-fluorophenyl)-2-methyl-8-(2-methyl-2-(2H-tetrazol-5-yl)prooxy)-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide

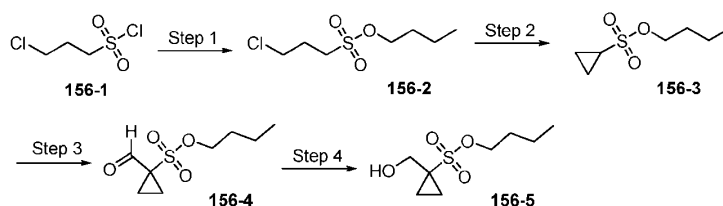


Scheme 33

Step 1. Synthesis of 3-((3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)-2,2-dimethylpropanenitrile (155-2). To a solution of 3-(3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-8-hydroxy-2-methyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (**155-1**) (0.1 g, 0.2 mmol) in DMF (5 mL), 3-bromo-2,2-dimethylpropanenitrile and Cs₂CO₃ (0.16 g, 0.5 mmol) were added. The reaction vessel was tightly sealed, and the reaction mixture was stirred and heated at 100 °C for 24 h. After completion of the reaction the crude product was isolated and purified by HPLC to give **155-2** (79 mg, 70%) as an off-white solid. MS (ESI): calcd. for C₂₅H₂₇F₆N₃O₃S: 563.2; Found: 562.2 [M - 1]⁺.

Step 2. Synthesis of 3-(3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-2-methyl-8-(2-methyl-2-(2H-tetrazol-5-yl)propoxy)-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (Example 155). To a solution of 3-(3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)-2,2-dimethylpropanenitrile (**155-2**) (79 mg, 0.14 mmol) in toluene (15 mL), Bu₂Sn(OAc)₂ (2 eq.) and TMSN₃ (0.086 g, 0.56 mmol) were added. The reaction vessel was tightly sealed, and the reaction mixture was stirred and heated at 150 °C microwave irradiation for 72 h. After completion of the reaction the crude product was isolated and purified by HPLC to give **Example 155** (4 mg, 4%) as an off-white solid. MS (ESI): calcd. for C₂₅H₂₈F₆N₆O₃S: 606.2; Found: 605.2 [M - 1]⁺. ¹H NMR (500 MHz, CD₃CN): δ 7.62 (s, 1H), 7.49 (s, 1H), 6.97 (t, *J* = 8.9 Hz, 2H), 6.69 (t, *J* = 6.5 Hz, 2H), 4.47 – 4.39 (m, 2H), 4.12 – 3.80 (m, 3H), 3.34 (d, *J* = 2.6 Hz, 1H), 2.58 (s, 3H), 1.99 (s, 3H), 1.65 (t, *J* = 18.8 Hz, 3H), 1.59 (d, *J* = 3.1 Hz, 6H) ppm.

Example 156. 1-(((3-(3,3-Difluorobutyl)-5-(4-fluorophenyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)methyl)cyclopropane-1-sulfonic acid



Scheme 34A

Step 1. Synthesis of butyl 3-chloropropyl sulfonate (156-2). A solution of 3-chloropropyl sulfonate (156-1) (15.0 g, 85.25 mmol) in DCM (75 mL) was added dropwise to a mixture of n-butanol (6.95 g, 93.80 mmol) and trimethylamine (11.21 g, 11.08 mmol) in DCM (70 mL) at 0 °C, and the reaction mixture was stirred at rt for 4 h. Upon completion of the reaction, the reaction mixture was diluted with DCM (100 mL), washed with water (75 mL x 3) and brine (75 mL), dried over Na₂SO₄, and concentrated. The residue was dried in vacuo to give **156-2** (17.3 g, 94.5%) as a yellow oil, which was used in the next step without further purification.

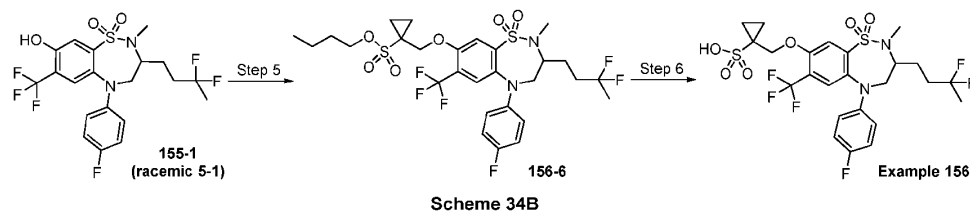
Step 2. Synthesis of butyl cyclopropanesulfonate (156-3). Butyl 3-chloropropyl sulfonate (156-2) (8.0 g, 37.4 mmol) in THF (40 mL) and n-butyllithium (23% in hexanes) (16.85 mL, 41.12 mmol) were added dropwise simultaneously to a cooled THF (-78 °C) (160 mL), while maintaining the temperature below -70 °C during the addition. The reaction mixture was stirred at -78 °C for 3 h and then warmed up to 0 °C. Subsequently, sat. aq. NH₄Cl solution (100 mL) was added to quench the reaction, and the resulting mixture was then separated into phases. The aqueous phase was further extracted with EtOAc (75 mL x 2). Then the combined organic extracts were evaporated to dryness. The residue was dissolved in EtOAc (250 mL), washed with water (50 mL x 2) and brine (50 mL), dried over Na₂SO₄, and concentrated. The residue was purified by flash chromatography to give **156-3** (5.0 g, 75.0%) as a yellow oil, which was used in the next step without further purification.

Step 3. Synthesis of butyl 1-formylcyclopropane-1-sulfonate (156-4). N-butyllithium (23% in hexanes) (6.32 mL, 15.45 mmol) was added dropwise to a solution of butyl

cyclopropanesulfonate (**156-3**) (2.5 g, 14.03 mmol) in THF (50 mL) at -78°C. After stirring at -78°C for 45 min, a solution of anhydrous DMF (2.17 mL, 28.04 mmol) in THF (5 mL) was added dropwise to the reaction mixture and the resulting mixture was warmed to room temperature for 4 h. Subsequently, the reaction mixture was quenched with sat. aq. NH₄Cl solution, and the phases were subsequently separated. The aqueous phase was further extracted with EtOAc (30 mL), and then the combined organic extracts were concentrated. The residue was dissolved in EtOAc (75 mL), washed with water (20 mL x 2) and brine (20 mL), dried over Na₂SO₄, and concentrated. and the solvent was removed in vacuum. The residue was dried in vacuo to give crude **156-4** (1.8 g, 20% purity per HNMR), which was used in the next step without further purification.

Step 4. Synthesis of butyl 1-(hydroxymethyl)cyclopropane-1-sulfonate (156-5). Butyl 1-formylcyclopropane-1-sulfonate (**156-5**) (1.8 g) was dissolved in methanol (18 mL) and cooled to 0°C. Sodium borohydride (133 mg, 3.5 mmol) was added to the reaction mixture in portions, and the resulting mixture was stirred at rt for 3 h. Upon completion of the reaction, the reaction mixture was concentrated, and the residue was diluted with DCM (30 mL). The mixture was washed with water (10 mL x 3) and brine (10 mL), dried over Na₂SO₄, and concentrated. The residue was purified by flash chromatography to give **156-5** (120 mg, 33.0%) as a yellow oil.

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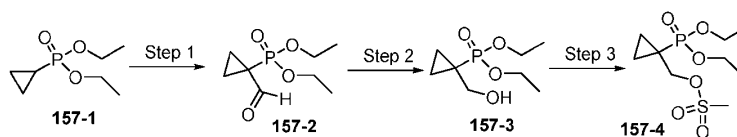


Step 5. Synthesis of butyl 1-(((3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)methyl)cyclopropane-1-sulfonate (156-6). Triphenylphosphine (54.6 mg, 0.21 mmol), butyl 1-(hydroxymethyl)cyclopropane-1-sulfonate (**156-5**) (43.4 mg, 0.21 mmol) and

- DIAD (42.1 mg, 2.1 mmol) were added sequentially to an ice-cooled solution of 3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-8-hydroxy-2-methyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (**155-1**) (50 mg, 0.1 mmol) in THF (2.5 mL). The reaction mixture was stirred at room temperature overnight and then concentrated.
- 5 The residue was purified by prep-HPLC to give **156-6** (33 mg, 47.1%) as an off-white solid. MS (ESI): calcd. for C₂₈H₃₄F₆N₂O₆S₂: 672.2; Found: 671.2 [M - 1].

- Step 6. Synthesis of 1-(((3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)methyl)cyclopropane-1-sulfonic acid (Example 156).** Potassium thiocyanate (5 mg, 51.55 μmol) was added to a stirred mixture of butyl 1-(((3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)methyl)cyclopropane-1-sulfonate (**156-6**) (33 mg, 49.1 μmol) in DCE (0.25 mL) and water (0.25 mL). The reaction vessel was tightly
- 15 sealed, and the reaction mixture was allowed to react at 95°C overnight. Upon completion of the reaction, the reaction mixture was cooled to room temperature and 1 N aq. HCl solution was added. The crude product was purified by prep-HPLC to give **Example 156** (9.3 mg, 30.8%) as an off-white solid. MS (ESI): calcd. for C₂₄H₂₆F₆N₂O₆S₂: 616.1; Found: 615.2 [M - 1]. ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.54 (s, 1H), 7.50 (s, 1H), 7.00 (t, *J* = 8.7 Hz, 2H),
- 20 6.67 (s, 2H), 4.57 – 4.47 (m, 2H), 4.07 (d, *J* = 16.2 Hz, 1H), 3.80 (s, 1H), 3.29 (s, 2H), 2.53 (s, 3H), 2.03 – 1.92 (m, 2H), 1.81 (d, *J* = 7.8 Hz, 1H), 1.62 (t, *J* = 18.9 Hz, 4H), 0.93 (dt, *J* = 4.3, 2.2 Hz, 2H), 0.76 (d, *J* = 2.8 Hz, 2H) ppm.

- Example 157. 1-(((3-(3,3-Difluorobutyl)-5-(4-fluorophenyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)methyl)cyclopropane-1-sulfonic acid
- 25



Scheme 35A

Step 1. Synthesis of diethyl (1-formylcyclopropyl)phosphonate (157-2).

N-butyllithium (23% in hexanes) (2.54 mL, 6.20 mmol) was added dropwise to a solution of diethyl

cyclopropylphosphonate (**157-1**) (1.0 g, 5.64 mmol) in THF (10 mL) at -78°C , and the reaction mixture was allowed to react for 45 min at this temperature. Then a solution of ethyl formate (0.68 mL, 8.46 mmol) in THF (3.5 mL) was added dropwise to the reaction mixture, and the resulting mixture was warmed up to room temperature and stirred for 4 h.

Subsequently, the reaction mixture was quenched by the addition of sat. aq. NH_4Cl (5 mL).

The aqueous phase was further extracted with EtOAc (10 mL), and the combined organic extracts were combined and concentrated. The residue was dissolved in EtOAc (25 mL), washed with water (5 mL x 2) and brine (10 mL), dried over Na_2SO_4 , and concentrated. The residue was dried in vacuo to give crude **157-2** (0.7 g, 70% purity per HNMR) as a light-brown oil, which was used in the next step without further purification.

Step 2. Synthesis of ethyl (1-(hydroxymethyl)cyclopropyl)(propyl)phosphinate (157-3).

Diethyl (1-formylcyclopropyl)phosphonate (**157-2**) (0.7 g 70% purity, 1.75 mmol) was

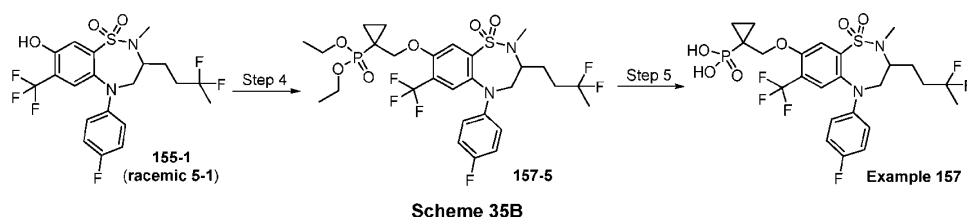
dissolved in methanol (7 mL) and cooled to 0°C . Sodium borohydride (258 mg, 6.78 mmol) was added to the reaction mixture in portions. After stirring at rt for 3 h, the reaction mixture

was concentrated. The residue was dissolved in DCM (20 mL), and the mixture was washed with water (5 mL x 3) and brine (5 mL), dried over anhydrous Na_2SO_4 , and concentrated. The residue was purified by prep-HPLC to give **157-3** (90 mg, 13.0%) as a yellow oil.

Step 3. Synthesis of (1-(diethoxyphosphoryl)cyclopropyl)methyl methanesulfonate (157-4).

To a solution of ethyl (1-(hydroxymethyl)cyclopropyl)(propyl)phosphinate (**157-3**) (90 mg, 0.45 mmol) in DCM (2 mL) and triethylamine (54 mg, 0.54 mmol) at 0°C , mesyl chloride (56 mg, 0.5 mmol) was added dropwise, and the reaction mixture was stirred at

room temperature for 4 hours. After completion of the reaction, the reaction mixture was concentrated under vacuum and the resulting residue was dissolved in EtOAc (3 mL). The organic layer was washed with water (1 mL x 2) and brine (1 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give **157-4** (85 mg, 69.1%,
 5 95 % NMR purity) as a yellow oil, which was used in the next step without further purification.



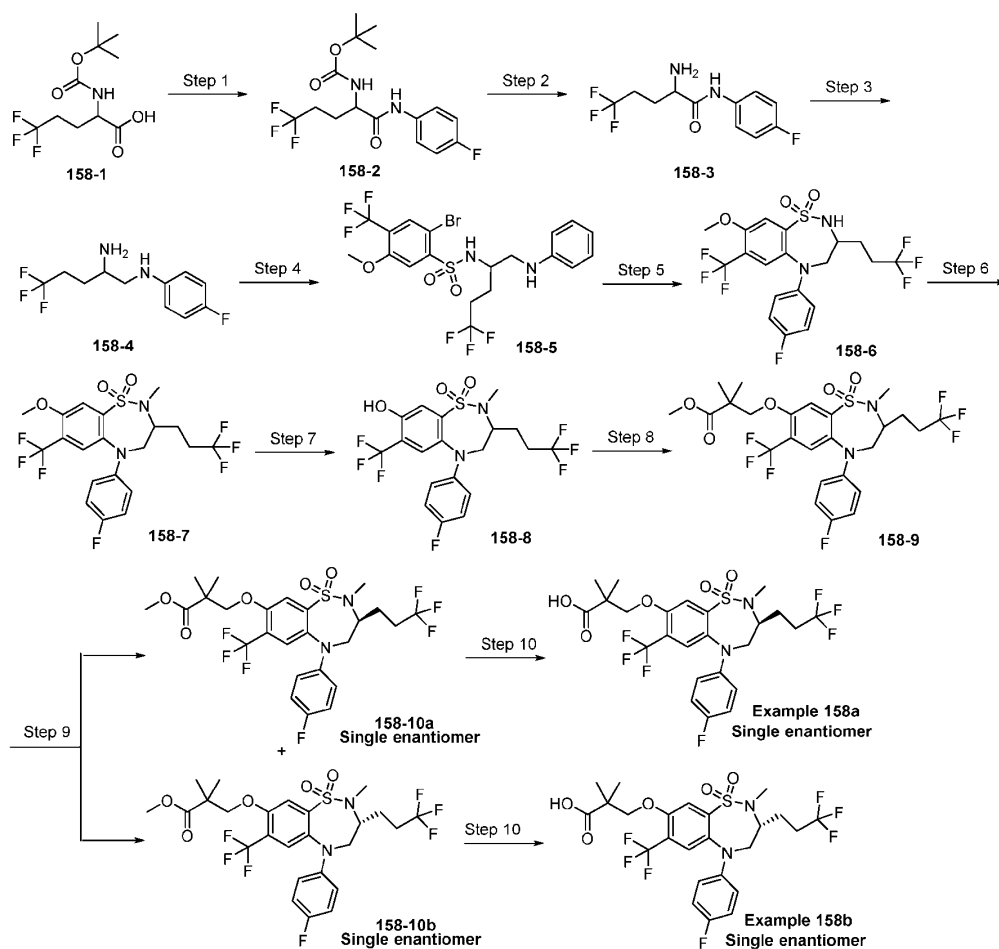
10 **Step 4. Synthesis of diethyl (1-(((3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)methyl)cyclopropyl)phosphonate (**157-5**)**. 3-(3,3-Difluorobutyl)-5-(4-fluorophenyl)-8-hydroxy-2-methyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (**155-1**) (58.9 mg, 0.12 mmol), cesium carbonate (119 mg, 0.37 mmol), and (1-
 15 (diethoxyphosphoryl)cyclopropyl)methyl methanesulfonate (**157-4**) (70 mg, 0.24 mmol) were mixed in DMF (2 mL). After stirring at 75°C for 16 h, the reaction mixture was cooled to rt and filtered through a cotton plug. The filtrate was purified by prep-HPLC to give **157-5** (46 mg, 56.0%) as an off-white solid. MS (ESI): calcd. for C₂₈H₃₅F₆N₂O₆PS: 672.2; Found 671.2 [M-1]⁻.

20

Step 5. Synthesis of (1-(((3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)methyl)cyclopropyl)phosphonic acid (Example 157). To a solution of diethyl (1-
 25 (((3-(3,3-difluorobutyl)-5-(4-fluorophenyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)methyl)cyclopropyl)phosphonate (**157-5**) (46 mg, 68.39 μmol) in anhydrous DCM (2 mL), pyridine (54.7 mg, 0.69 mmol) and TMSBr

- (210.5 mg, 1.39 mmol) were respectively added and the reaction mixture was stirred at rt overnight. Subsequently, the resulting solution was acidified with 3 N aq. HCl solution to pH ~2, diluted with DMSO (3 mL) and purified by prep-HPLC to give **Example 157** (23.2 mg, 54.3%) as an off-white solid. MS (ESI): calcd. for C₂₄H₂₇F₆N₂O₆PS: 616.1; Found 615.1 [M-1]. ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.51 (d, *J* = 6.4 Hz, 2H), 7.01 (t, *J* = 8.6 Hz, 2H), 6.68 (s, 2H), 4.42 – 4.23 (m, 2H), 4.08 (d, *J* = 16.1 Hz, 1H), 3.78 (d, *J* = 19.2 Hz, 1H), 3.49 (s, 1H), 2.53 (d, *J* = 3.0 Hz, 3H), 1.98 (dt, *J* = 17.0, 9.0 Hz, 2H), 1.89 – 1.74 (m, 1H), 1.62 (t, *J* = 18.9 Hz, 4H), 0.99 – 0.88 (m, 2H), 0.88 – 0.81 (m, 2H) ppm.
- 10 Examples 158a and 158b. (S)-3-((5-(4-fluorophenyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid (158a) and (R)-3-((5-(4-fluorophenyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid (158b)

15



Scheme 36

Step 1. Synthesis of tert-butyl N-4,4,4-trifluoro-1-[(4-fluorophenyl)carbamoyl]butylcarbamate (158-2**).** To a reactor containing a solution of 2-[(tert-butoxy)carbonyl]amino-5,5,5-trifluoropentanoic acid (**158-1**) (10.0 g, 36.89 mmol) in DCM (100 mL) was added 1H-1,2,3-benzotriazol-1-ol (5.48 g, 40.57 mmol) and (3-[(ethylimino)methylidene]aminopropyl)dimethylamine hydrochloride (8.46 g, 44.26 mmol). After stirring at rt for 20 min, the mixture was cooled to 0°C and triethylamine (9.32 g, 92.22 mmol) and 4-fluoroaniline (4.1 g, 36.89 mmol) were added. Subsequently, the mixture was stirred at rt overnight and then concentrated. The residue was diluted with MTBE (250 mL) and the resulting mixture was washed with brine (30 mL), dried over anhydrous Na₂SO₄, and

concentrated. The residue was dried in vacuo to give **158-2** (9 g, 90 %) as a brown solid, which was used in the next step without further purification. MS (ESI): calcd. for $C_{16}H_{20}F_4N_2O_3$: 364.1; Found: 363.1 [M-1]⁻.

5 **Step 2. Synthesis of 2-amino-5,5,5-trifluoro-N-(4-fluorophenyl)pentanamide (158-3).** To a solution tert-butyl N-4,4,4-trifluoro-1-[(4-fluorophenyl)carbamoyl]butylcarbamate (**158-2**) (9.0 g, 24.7 mmol) in DCM (20 mL) at 0 °C, a solution of 4 M HCl in 1,4-dioxane (10 mL) was added and the reaction mixture was stirred at room temperature for 16 hours. After completion of the reaction, the reaction mixture was concentrated under vacuum and the
10 residue was quenched with saturated aq. $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (200 mL x 2). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4 , and concentrated. The residue was dried in vacuo to give crude **158-3** (6.2 g, 68.9 %) as a brown solid, which was used in the next step without further purification. MS (ESI): calcd. for $C_{11}H_{12}F_4N_2O$: 264.1; Found: 263.1 [M-1]⁻.

15

Step 3. Synthesis of 5,5,5-trifluoro-N1-(4-fluorophenyl)pentane-1,2-diamine (158-4). To a solution of 2-amino-5,5,5-trifluoro-N-(4-fluorophenyl)pentanamide (**158-3**) (6.2 g, 23.47 mmol) in THF (100 mL) at 0 °C was added (methylsulfanyl)methane borane (17.85 g, 117.33 mL) and the reaction mixture was heated at 75°C for 16 h. The reaction mixture was cooled
20 to 0°C and added methanol (25 mL). After stirring at rt for 30 min, the mixture was concentrated. The residue was treated with 3 N aq. HCl solution (10 mL). The mixture was then adjusted to pH 10 with saturated aq. NaOH solution. The aqueous layer was extracted with EtOAc (100 mL x 2). The combined organic extracts were washed with brine (20 mL x 2), and dried over anhydrous Na_2SO_4 , and concentrated. The residue was dried in vacuo to
25 give crude **158-4** (4 g, 64.5%) as a brown solid, which was used in the next step without further purification. MS (ESI): calcd. for $C_{11}H_{14}F_4N_2$: 250.1; Found: 249.1 [M-1]⁻.

Step 4. Synthesis of 2-bromo-5-methoxy-N-5,5,5-trifluoro-1-[(4-fluorophenyl)amino]pentan-2-yl-4-(trifluoromethyl)benzene-1-sulfonamide (158-5). To a
30 solution of 5,5,5-trifluoro-N1-(4-fluorophenyl)pentane-1,2-diamine (**158-4**) (4.7 g, 18.78

mmol) in THF at 0°C were added 2-bromo-5-methoxy-4-(trifluoromethyl)benzene-1-sulfonyl chloride (6.61 g, 18.78 mmol) and triethylamine (3.8 g, 37.56 mmol). After stirring at rt for 4 h, the reaction mixture was concentrated. The residue was diluted with EtOAc (100 mL), and the mixture was washed with water 25 mL) and brine (25 mL), dried over anhydrous Na₂SO₄,
5 and concentrated. The residue was dried in vacuo to give crude **158-5** (4.6 g, 97.8 %) as a brown solid, which was used in the next step without further purification. MS (ESI): calcd. for C₁₉H₁₉BrF₆N₂O₃S: 548.0; Found: 547.0 [M-1]⁻. ¹H NMR (500 MHz, CDCl₃): δ 7.79 (s, 1H), 7.53 (s, 1H), 6.77 (t, *J* = 8.8 Hz, 2H), 6.15 (m, 2H), 5.3 (d, *J* = 8.5 Hz, 1H), 3.83 (s, 3H), 3.59 (m, 1H), 3.52 (m, 1H), 3.16 (m, 1H), 3.03 (m, 1H), 2.39 (m, 1H), 2.24 (m, 1H), 1.90 (m,
10 1H), 1.72 (m, 1H) ppm.

Step 5. Synthesis of 5-(4-fluorophenyl)-8-methoxy-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydro-1λ⁶,2,5-benzothiadiazepine-1,1-dione (158-6).

To a solution of 2-bromo-5-methoxy-N-5,5,5-trifluoro-1-[(4-fluorophenyl)amino]pentan-2-yl-4-(trifluoromethyl)benzene-1-sulfonamide (**158-5**) (4.5 g, 7.93 mmol) in DMF were added
15 copper iodide (301.14 mg, 1.59 mmol), pyridine-2-carboxylic acid (195.17 mg, 1.59 mmol) and dipotassium carbonate (3.28 g, 23.8 mmol). The reaction mixture was degassed for 5 minutes under Ar and the reaction mixture was then stirred at 90°C overnight. After completion of the reaction, the reaction mixture was quenched with ice cold water and the
20 aqueous layer was extracted with MTBE. The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give crude **158-6** (3 g, 65.2%), which was used in the next step without further purification. MS (ESI): calcd. for C₁₉H₁₇F₇N₂O₃S: 486.1; Found: 485.1 [M - H]⁻.

25

Step 6. Synthesis of 5-(4-fluorophenyl)-8-methoxy-2-methyl-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydro-1λ⁶,2,5-benzothiadiazepine-1,1-dione (158-7).

Cesium carbonate (6.03 g, 18.51 mmol) and iodomethane (2.63 g, 18.51 mmol) were added to a solution of 5-(4-fluorophenyl)-8-methoxy-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-
30 2,3,4,5-tetrahydro-1λ⁶,2,5-benzothiadiazepine-1,1-dione (**158-6**) (3.0 g, 6.17 mmol) in

DMF. The resulting solution was stirred at 60°C overnight. After completion of the reaction, the reaction mixture was concentrated under vacuum. The residue was purified by prep-HPLC to give **158-7** (3 g, 96.8%) as an off-white solid. MS (ESI): calcd. for C₂₀H₁₉F₇N₂O₃S: 500.1; Found: 505.1 [M + 1]⁺.

5

Step 7. Synthesis of 5-(4-fluorophenyl)-8-hydroxy-2-methyl-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydro-1lambda6,2,5-benzothiadiazepine-1,1-dione (158-8).

To a solution of 5-(4-fluorophenyl)-8-methoxy-2-methyl-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydro-1lambda6,2,5-benzothiadiazepine-1,1-dione (**158-7**) (3.0 g, 5.99 mmol) in DMF was added sodium hydride (1.01 g, 41.97 mmol) (under argon atmosphere). Then methanethiol (2.94 g, 41.97 mmol) was bubbled until the precipitate was dissolved and the resulting mixture was stirred at 40°C overnight. Subsequently, sat. aq. citric acid solution (50 mL) was added, the precipitate was collected and purified by silica gel column chromatography to give **158-8** (1.5 g, 50%). MS (ESI): calcd. for C₁₉H₁₇F₇N₂O₃S: 486.1; Found: 485.1 [M - 1]⁻. ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.43 (s, 1H), 7.54 (s, 1H), 7.45 (s, 1H), 7.00 (t, *J* = 8.7 Hz, 2H), 6.65 (m, 2H), 4.10 (m, 1H), 3.88 (m, 1H), 3.36 (m, 1H), 2.54 (s, 3H), 2.40 (m, 1H), 2.34 (m, 1H), 1.91 (m, 1H), 1.70 (m, 1H) ppm.

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Step 8. Synthesis of methyl 3-[5-(4-fluorophenyl)-2-methyl-1,1-dioxo-7-

(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydro-1lambda6,2,5-benzothiadiazepin-8-yl]oxy-2,2-dimethylpropanoate (158-9). To a solution of 5-(4-Fluorophenyl)-8-hydroxy-2-methyl-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydro-1lambda6,2,5-benzothiadiazepine-1,1-dione (**158-8**) (250.0 mg, 513.98 μmol) in DMF was added cesium carbonate (502.9 mg, 1.54 mmol) and methyl 3-bromo-2,2-dimethylpropanoate (299.45 mg, 1.54 mmol) at rt. The resulting solution was stirred at 60°C overnight. After completion of the reaction, the reaction mixture was concentrated under vacuum. The crude product was purified by prep-HPLC to give **158-9** (125 mg, 50%). MS (ESI): calcd. for C₂₅H₂₇F₇N₂O₅S: 600.2; Found: 599.2 [M - 1]⁻. ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.49 (s, 1H), 7.32 (s, 1H), 6.95 (t, *J* = 7.8 Hz, 2H), 6.74 (m, 2H), 4.09 (m, 2H), 3.9

25

(m, 2H), 3.69 (s, 3H), 3.55 (m, 1H), 2.33 (m, 1H), 2.22 (m, 1H), 1.91 (m, 1H), 1.74 (m, 1H), 1.33 (s, 6H) ppm.

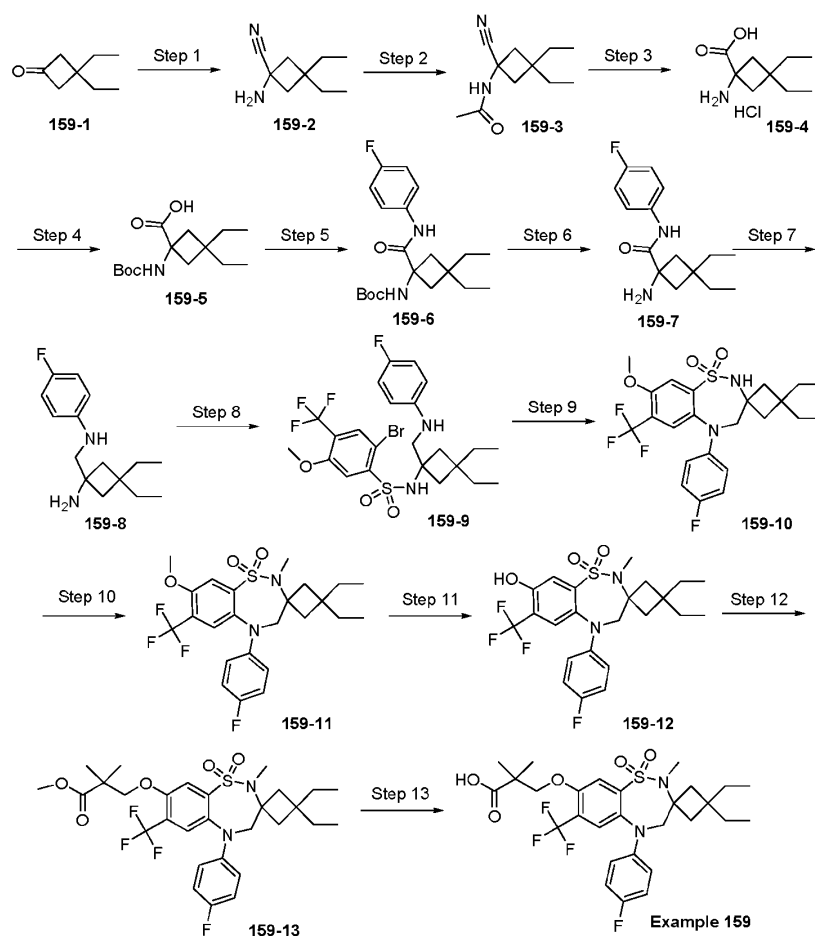
Steps 9 and 10. Synthesis of (S)-3-((5-(4-fluorophenyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid (Example 158a) and (R)-3-((5-(4-fluorophenyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid (Example 158b). Chiral separation (**Step 9**) of methyl 3-[5-(4-fluorophenyl)-2-methyl-1,1-dioxo-7-(trifluoromethyl)-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydro-1λ⁶,2,5-benzothiadiazepin-8-yl]oxy-2,2-dimethylpropanoate (**158-9**) (Condition: Column: CHIRALCEL OD-H (250×20 mm, 5 μm)-OD11_2020_RMK-RMK; Mobile Phase: Hexane/IPA/MeOH = 80/10/10 (v/v/v); Flow Rate: 12 mL/min), followed by saponification (**Step 10**) with LiOH in dioxane/water = 5/1 (v/v) to give **Example 158a** (single enantiomer, 14.1 mg, 36.1%) and **Example 158b** (single enantiomer, 17.7 mg, 45.3%), respectively

Example 158a: Analytic chiral HPLC method: Column: Chiralpak AD-H (250×4.6 mm, 5 μm)-ADH0CE-BO021-14; Mobile Phase: Hexane (0.1%TFA)/IPA = 80/20 (v/v); Flow Rate: 0.6 mL/min; RT (min): 17.01; Purity: 100%. MS (ESI): calcd. for C₂₄H₂₅F₇N₂O₅S: 586.1; Found: 587.2 [M + H]⁺. ¹H NMR (500 MHz, CD₃CN): δ 7.61 (s, 1H), 7.52 (s, 1H), 6.99 (t, J = 8.7 Hz, 2H), 6.72 (dd, J = 9.2, 4.6 Hz, 2H), 4.26 – 4.18 (m, 2H), 3.98 (s, 2H), 3.47 (d, J = 82.4 Hz, 1H), 2.60 (s, 3H), 2.37 (dtp, J = 21.3, 10.3, 6.1, 5.3 Hz, 2H), 1.92 – 1.80 (m, 2H), 1.32 (d, J = 2.2 Hz, 6H) ppm.

Example 158b: Analytic chiral HPLC method: Column: Chiralpak AD-H (250×4.6 mm, 5 μm)-ADH0CE-BO021-14; Mobile Phase: Hexane (0.1%TFA)/IPA = 80/20 (v/v); Flow Rate: 0.6 mL/min; RT (min): 11.48; Purity: 98.93 %. MS (ESI): calcd. for C₂₄H₂₅F₇N₂O₅S: 586.1; Found: 587.2 [M + H]⁺. ¹H NMR (500 MHz, CD₃CN): δ 7.62 (s, 1H), 7.52 (s, 1H), 6.99 (t, J

= 8.8 Hz, 2H), 6.72 (dd, J = 9.2, 4.5 Hz, 2H), 4.26 – 4.16 (m, 2H), 3.99 (s, 2H), 3.40 (s, 1H), 2.36 (ddq, J = 19.8, 8.9, 5.7, 4.6 Hz, 2H), 1.92 – 1.76 (m, 2H), 1.32 (d, J = 2.3 Hz, 6H) ppm.

Example 159. 3-((3',3'-Diethyl-5-(4-fluorophenyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-4,5-dihydro-2H-spiro[benzo[f][1,2,5]thiadiazepine-3,1'-cyclobutan]-8-yl)oxy)-2,2-dimethylpropanoic acid



Scheme 37

10 **Step 1. Synthesis of 1-amino-3,3-diethylcyclobutane-1-carbonitrile (159-2).** To a solution of 3,3-diethylcyclobutan-1-one (**159-1**) (10.0 g, 79.3 mmol) in methanol/water (1:1 (v/v))

(100 mL) was added potassium iminomethanide (15.46 g, 237.89 mmol), followed by ammonium chloride (12.61 g, 237.89 mmol). After stirring at rt for 2 days, the reaction mixture was concentrated to remove organic solvent and the residue was extracted with DCM (50 mL x 3). The combined organic extracts were dried over anhydrous Na₂SO₄ and
5 concentrated. The residue was dried in vacuo to give **159-2** (10.5g, 87.0%) as a brown oil, which was used in next step without further purification.

Step 2. Synthesis of N-(1-cyano-3,3-diethylcyclobutyl)acetamide (159-3). To a solution of 1-amino-3,3-diethylcyclobutane-1-carbonitrile (**159-2**) (10.5 g, 69.02 mmol) and
10 triethylamine (16.75 g, 165.65 mmol) in DCM (150 mL) was added acetyl anhydride (10.56 g, 103.53 mmol) at -30°C. After stirring at rt overnight, the mixture was diluted with water (50 mL). The organic layer was washed with sat. aq. NaHSO₄ solution, dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give crude **159-3** (12 g, 89.5%) as a brown oil, which was used in the next step without further purification.

15 **Step 3. Synthesis of 1-carboxy-3,3-diethylcyclobutan-1-aminium chloride (159-4).** A solution of N-(1-cyano-3,3-diethylcyclobutyl)acetamide (**159-3**) (12.0 g, 61.8 mmol) in methanol (150 mL) was added acetyl chloride (48.2 g, 618.1 mmol) at -30°C. After stirring at rt overnight, the reaction mixture was concentrated. The residue was diluted with sat. aq.
20 HCl solution and the resulting mixture was refluxed for 5 h. Subsequently, the mixture was concentrated to give **159-4** (8.0 g, 62.3%) as a brown oil, which was used in the next step without further purification.

Step 4. Synthesis of 1-[(tert-butoxy)carbonyl]amino-3,3-diethylcyclobutane-1-carboxylic acid (159-5). To a solution of sodium hydroxide (7.72 g, 193.14 mmol) in water/THF
25 (150 mL/150 mL), 1-amino-3,3-diethylcyclobutane-1-carboxylic acid hydrochloride (**159-4**) (8.0 g, 38.63 mmol) was added, followed by di-tert-butyl dicarbonate (10.11 g, 46.35 mmol) at 0 °C. After stirring at rt overnight, the reaction mixture was diluted with water. The aqueous layer was extracted with EtOAc (100 mL x 3). The combined organic extracts were

dried over anhydrous Na_2SO_4 and concentrated. The residue was dried in vacuo to give **159-5** (5 g, 47.7%) as a brown oil, which was used in the next step without further purification.

Step 5. Synthesis of tert-butyl N-3,3-diethyl-1-[(4-

5 **fluorophenyl)carbamoyl]cyclobutylcarbamate (159-6).** To a solution of 1-[(tert-butoxy)carbonyl]amino-3,3-diethylcyclobutane-1-carboxylic acid (**159-5**) (7.6 g, 28.0 mmol) in DCM (150 mL) was added 1H-1,2,3-benzotriazol-1-ol (4.16 g, 30.8 mmol) and 4-fluoroaniline (3.11 g, 28.0 mmol) at rt. After stirring at rt for 15 min, the mixture was cooled to -30°C , followed by adding (3-[(ethylimino)methylidene]aminopropyl)dimethylamine
10 hydrochloride (6.43 g, 33.6 mmol) and triethylamine (7.08 g, 70.1 mmol). The resulting mixture was stirred at rt overnight and then washed with sat. aq. NH_4Cl solution (50 mL x 2) and brine (50 mL), dried over anhydrous Na_2SO_4 , and concentrated. The residue was purified by silica gel column chromatography to give **159-6** (8.1 g, 79.3%) as an off-white solid. MS (ESI): calcd. for $\text{C}_{20}\text{H}_{29}\text{FN}_2\text{O}_3$: 364.2; Found: 263.2 [M - Boc - 1].

15

Step 6. Synthesis of 1-amino-3,3-diethyl-N-(4-fluorophenyl)cyclobutane-1-carboxamide (159-7). To a solution of tert-butyl N-3,3-diethyl-1-[(4-

fluorophenyl)carbamoyl]cyclobutylcarbamate (**159-6**) (8.1 g, 22.23 mmol) in DCM (50 mL) at 0°C was added 4N HCl in 1,4-dioxane (10 mL) at rt. After stirring at rt for 16 h, the
20 reaction mixture was concentrated. The residue was diluted with saturated aq. NaHCO_3 solution (100 mL). The mixture was extracted with EtOAc (100 mL x 3). The combined organic layer extracts were washed brine (50 mL), dried over anhydrous Na_2SO_4 , and concentrated. The residue was dried in vacuo to give **159-7** (4.4 g, 74.9%) as a brown solid, which was used in the next step without further purification. MS (ESI): calcd. for
25 $\text{C}_{15}\text{H}_{21}\text{FN}_2\text{O}$: 264.2; Found: 263.2 [M - 1].

Step 7. Synthesis of N-[(1-amino-3,3-diethylcyclobutyl)methyl]-4-fluoroaniline (159-8).

To a solution of 1-amino-3,3-diethyl-N-(4-fluorophenyl)cyclobutane-1-carboxamide (**159-7**) (4.4 g, 16.65 mmol) in THF (150 mL) at 0°C was added (methylsulfanyl)methane borane
30 (12.66 g, 83.22 mL) at rt. After stirring at 75°C for 16 h, the reaction mixture was cooled to

0 °C, followed by adding methanol (50 mL). The mixture was stirred at rt for 30 min and then concentrated. The residue was added 3 N aq. HCl solution (20 mL) and then adjusted to pH 9 with saturated aq. NaOH solution. The aqueous layer was extracted with EtOAc (100 mL x 3). The combined organic extracts were washed brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give crude **159-8** (3g, 72%) as a brown solid, which was used in the next step without further purification. MS (ESI): calcd. for C₁₅H₂₃FN₂: 250.2; Found: 249.2 [M - 1]⁻.

Step 8. Synthesis of 2-bromo-N-(3,3-diethyl-1-[(4-fluorophenyl)amino]methylcyclobutyl)-5-methoxy-4-(trifluoromethyl)benzene-1-sulfonamide (159-9). To a solution of N-[(1-amino-3,3-diethylcyclobutyl)methyl]-4-fluoroaniline (**159-8**) (3.0 g, 11.98 mmol) in THF (50 mL) at 0 °C were added 2-bromo-5-methoxy-4-(trifluoromethyl)benzene-1-sulfonyl chloride (4.22 g, 11.98 mmol) and triethylamine (1.45 g, 14.38 mmol) at rt. After stirring at rt for 4 h, the reaction mixture was concentrated. The residue was dissolved in EtOAc (100 mL) and the mixture was washed with sat. aq. NH₄Cl solution (25 mL), sat. aq. NaHCO₃ solution (25 mL), and brine (25mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography to give **159-9** (1.8 g, 26.5%). MS (ESI): calcd. for C₂₃H₂₇BrF₄N₂O₃S: 566.1; Found: 565.1 [M - 1]⁻.

Step 9. Synthesis of 3',3'-diethyl-5-(4-fluorophenyl)-8-methoxy-7-(trifluoromethyl)-4,5-dihydro-2H-spiro[11lambda6,2,5-benzothiadiazepine-3,1'-cyclobutane]-1,1-dione (159-10). To a solution of 2-bromo-N-(3,3-diethyl-1-[(4-fluorophenyl)amino]methylcyclobutyl)-5-methoxy-4-(trifluoromethyl)benzene-1-sulfonamide (**159-9**) (1.8 g, 3.17 mmol) in DMF, copper (199.58 mg, 3.17 mmol) and dipotassium carbonate (874.77 mg, 6.34 mmol) were added. The reaction mixture was degassed for 5 min under Ar atmosphere and the reaction mixture was then heated at 100°C overnight. After completion of the reaction, the reaction mixture was quenched with ice-cold water (50 mL) and the aqueous layer was extracted with MTBE (100 mL x 2). The combined organic layer was washed with brine (30 mL), dried over anhydrous Na₂SO₄ and concentrated. The residue was dried in vacuo to give crude **159-10**

(1.5 g, 97.3%), which was used in the next step without further purification. MS (ESI): calcd. for $C_{23}H_{26}F_4N_2O_3S$: 486.2; Found: 485.2 [M - 1]⁻.

Step 10. Synthesis of 3',3'-diethyl-5-(4-fluorophenyl)-8-methoxy-2-methyl-7-

5 **(trifluoromethyl)-4,5-dihydro-2H-spiro[11lambda6,2,5-benzothiadiazepine-3,1'-cyclobutane]-1,1-dione (159-11).** 3',3'-Diethyl-5-(4-fluorophenyl)-8-methoxy-7-(trifluoromethyl)-4,5-dihydro-2H-spiro[11lambda6,2,5-benzothiadiazepine-3,1'-cyclobutane]-1,1-dione (**159-10**) (1.5 g, 3.08 mmol) was dissolved in DMF, then dipotassium carbonate (1.28 g, 9.25 mmol) and iodomethane (1.31 g, 9.25 mmol) were added. After stirring at 65°C overnight, the reaction mixture was concentrated. The residue was purified by prep-HPLC to give **159-11** (1 g, 64.9%) as an off-white solid. MS (ESI): calcd. for $C_{24}H_{28}F_4N_2O_3S$: 500.2; Found: 499.2 [M - 1]⁻.

Step 11. Synthesis of 3',3'-diethyl-5-(4-fluorophenyl)-8-hydroxy-2-methyl-7-

15 **(trifluoromethyl)-4,5-dihydro-2H-spiro[11lambda6,2,5-benzothiadiazepine-3,1'-cyclobutane]-1,1-dione (159-12).** To a reactor containing a solution of 3',3'-diethyl-5-(4-fluorophenyl)-8-methoxy-2-methyl-7-(trifluoromethyl)-4,5-dihydro-2H-spiro[11lambda6,2,5-benzothiadiazepine-3,1'-cyclobutane]-1,1-dione (**159-11**) (150.0 mg, 299.67 μmol) in NMP (1 mL) was added lithium iodide (401.88 mg, 3.0 mmol). After stirring at 130 °C overnight, the mixture was purified by prep-HPLC to give **159-12** (49 mg, 33.6%). MS (ESI): calcd. for $C_{23}H_{26}F_4N_2O_3S$: 486.2; Found: 485.2 [M - 1]⁻.

Step 12. Synthesis of methyl 3-[3',3'-diethyl-5-(4-fluorophenyl)-2-methyl-1,1-dioxo-7-

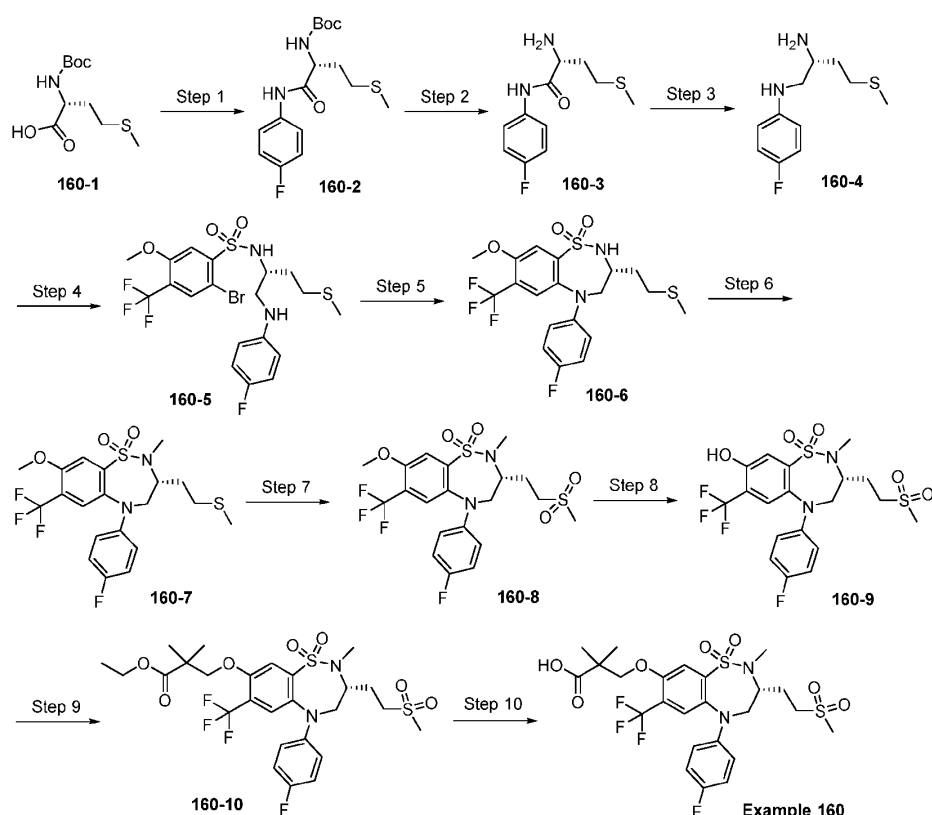
25 **(trifluoromethyl)-4,5-dihydro-2H-spiro[11lambda6,2,5-benzothiadiazepine-3,1'-cyclobutan]-8-yloxy]-2,2-dimethylpropanoate (159-13).** To a reactor containing a solution of 3',3'-diethyl-5-(4-fluorophenyl)-8-hydroxy-2-methyl-7-(trifluoromethyl)-4,5-dihydro-2H-spiro[11lambda6,2,5-benzothiadiazepine-3,1'-cyclobutane]-1,1-dione (**159-12**) (49.0 mg, 100.71 μmol) in DMF (1 mL) was added methyl 3-bromo-2,2-dimethylpropanoate (29.31 mg, 151.08 μmol), followed by dicesium carbonate (49.22 mg, 151.08 μmol). After stirring at rt overnight, the mixture was purified by prep-HPLC to give **159-13** (21 mg,

35.0%) as an off-white solid. MS (ESI): calcd. for $C_{29}H_{36}F_4N_2O_5S$: 600.2; Found: 599.2 $[M - 1]^-$.

Step 13. Synthesis of (3-[3',3'-diethyl-5-(4-fluorophenyl)-2-methyl-1,1-dioxo-7-(trifluoromethyl)-4,5-dihydro-2H-spiro[1lambda6,2,5-benzothiadiazepine-3,1'-cyclobutan]-8-yloxy]-2,2-dimethylpropanoic acid (Example 159). To a stirred solution of methyl 3-[3',3'-diethyl-5-(4-fluorophenyl)-2-methyl-1,1-dioxo-7-(trifluoromethyl)-4,5-dihydro-2H-spiro[1lambda6,2,5-benzothiadiazepine-3,1'-cyclobutan]-8-yloxy]-2,2-dimethylpropanoate (**159-13**) (21.0 mg, 34.96 μ mol) in a mixture of 1,4-dioxane and water (1 mL, 5:1 (v/v)), lithium hydrate hydroxide (2.94 mg, 69.89 μ mol) was added. After stirring at rt for 12 h, the mixture was added several drops of 2 N aq. HCl solution. The resulting mixture was purified by prep-HPLC to give **Example 159** (15.6 mg, 88.6%). MS (ESI): calcd. for $C_{28}H_{34}F_4N_2O_5S$: 586.2; Found: 587.0 $[M+1]^+$. 1H NMR (500 MHz, $CDCl_3$): δ 7.50 (s, 1H), 6.96 (d, J = 6.4 Hz, 5H), 4.10 (s, 2H), 2.56 (s, 3H), 2.34 (s, 1H), 1.99 (s, 2H), 1.70 (s, 1H), 1.66 – 1.40 (m, 6H), 1.38 (s, 6H), 0.72 (t, J = 7.3 Hz, 3H), 0.67 (t, J = 7.3 Hz, 3H) ppm.

Example 160. (R)-3-((5-(4-Fluorophenyl)-2-methyl-3-(2-(methylsulfonyl)ethyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid

20



Scheme 38

Example 160

Step 1. Synthesis of (R)-tert-butyl 1-(4-fluorophenylamino)-4-(methylthio)-1-oxobutan-2-ylcarbamate (160-2). A stirred solution of (R)-2-(tert-butoxycarbonylamino)-4-(methylthio)butanoic acid (**160-1**) (5 g, 20 mmol), 4-fluoroaniline (3.4 g, 30 mmol) and TEA (4 g, 40 mmol) in THF (50 mL) was added HATU (9.2 g, 24 mmol). The reaction was stirred at room temperature for 3 hours. After completion of the reaction (monitored by LCMS), the reaction was quenched with water (100 mL) and extracted with EA (100 mL x 3). The combined organic extracts were washed with brine (40 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography (20% EA/PE) to give **160-2** (6.5 g, 95%) as a white solid. TLC: 20% EA/PE (v/v) (R_f: 0.3). MS (ESI): calcd. for C₁₆H₂₃FN₂O₃S: 342.1; Found: 287.1 [M -56+ 1]⁺.

Step 2. Synthesis of (R)-2-amino-N-(4-fluorophenyl)-4-(methylthio)butanamide (160-3).

To a stirred solution of (R)-tert-butyl 1-(4-fluorophenylamino)-4-(methylthio)-1-oxobutan-2-ylcarbamate (**160-2**) (6.5 g, 19 mmol) in DCM (30 ml), TFA (15 ml) was added dropwise at 0 °C. The resulting reaction was stirred at room temperature for 2 h. After completion of the reaction (monitored by LCMS), the reaction mixture was concentrated under vacuum to
5 remove DCM and TFA. The residue was dissolved with EA (50 ml) and diluted with H₂O (20 ml). Then saturated aq. NaHCO₃ solution was added dropwise until pH > 7, and the aqueous layer was extracted with EA (50 mL x 3). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography (3% MeOH/DCM (v/v)) to give **160-3** (3.4 g, 74%) as a
10 colorless oil. TLC: 3% MeOH/DCM (v/v) (R_f: 0.2). MS (ESI): calcd. for C₁₁H₁₅FN₂O₅: 242.1; Found: 243.3 [M + 1]⁺.

Step 3. Synthesis of (R)-N1-(4-fluorophenyl)-4-(methylthio)butane-1,2-diamine (160-4).

To a stirred solution of (R)-2-amino-N-(4-fluorophenyl)-4-(methylthio)butanamide (**160-3**)
15 (3.4 g, 14 mmol) in anhydrous THF (34 mL) was added LiAlH₄ (1.6 g, 42 mmol) portion-wise below 10 °C under Ar atmosphere. After stirring at 65 °C for 4 hr under an Ar atmosphere, the reaction mixture was quenched with ice-cold water (1.6 mL) and 15% NaOH (1.6 ml). The mixture was dried over anhydrous Na₂SO₄ and filtered through a Celite[®] pad. The filtrate was concentrated, and the residue was dried in vacuo to give crude **160-4** (3.2 g,
20 100%) as colorless oil, which was used in the next step without further purification. TLC: 5% MeOH/DCM (v/v) (R_f: 0.2). MS (ESI): calcd. for C₁₁H₁₇FN₂S: 228.1; Found: 229.2 [M + 1]⁺.

Step 4. Synthesis of (R)-2-bromo-N-(1-(4-fluorophenylamino)-4-(methylthio)butan-2-yl)-5-methoxy-4-(trifluoromethyl)benzenesulfonamide (160-5).

To a stirred solution of (R)-N1-(4-fluorophenyl)-4-(methylthio)butane-1,2-diamine (**160-4**) (3.2 g, 14 mmol) and TEA (2.8 g, 28 mmol) in anhydrous DCM (32 mL) was added a solution of 2-bromo-5-methoxy-4-(trifluoromethyl)benzene-1-sulfonyl chloride (5.9 g, 16.8 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 3 hours. After completion of the reaction (monitored by LCMS), the reaction mixture was quenched with ice-cold water
30 (50 mL) and the aqueous layer was extracted with DCM (50 mL x 3). The combined organic

extracts were washed with brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography (18% EA/PE (v/v)) to afford **160-5** (7.0 g, 88%) as a yellow solid. TLC: 20% EA/PE (v/v) (R_f: 0.3). MS (ESI): calcd. for C₁₉H₂₁BrF₄N₂O₃S₂: 544.0; Found: 545.0 [M + 1]⁺.

5

Step 5. Synthesis of ethyl (R)-5-(4-fluorophenyl)-8-methoxy-3-(2-(methylthio)ethyl)-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (160-6).

To a stirred solution of (R)-2-bromo-N-(1-(4-fluorophenylamino)-4-(methylthio)butan-2-yl)-5-methoxy-4-(trifluoromethyl)benzenesulfonamide (**160-5**) (7.0 g, 12.9 mmol) and K₂CO₃ (3.6 g, 25.8 mmol) in DMF (35 mL) was added Cu (826 mg, 12.9 mmol). After stirring at 115 °C for 16 h, the reaction mixture was diluted with saturated NH₄Cl (30 mL), and the aqueous layer was extracted with EA (50 mL x 3). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give crude **160-6** (5.0 g) as a yellow solid, which was used in the next step without further purification. TLC: 20% EA/PE (v/v) (R_f: 0.2). MS (ESI): calcd. for C₁₉H₂₀F₄N₂O₃S₂: 464.1; Found: 465.0 [M + 1]⁺.

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Step 6. Synthesis of (R)-5-(4-fluorophenyl)-8-methoxy-2-methyl-3-(2-(methylthio)ethyl)-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (160-7):

To a stirred solution of (R)-5-(4-fluorophenyl)-8-methoxy-3-(2-(methylthio)ethyl)-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (**160-6**) (5.0 g, crude product, 10.8 mmol) and Cs₂CO₃ (7.0 g, 21.6 mmol) in DMF (30 mL) was added MeI (3.0 g, 21.6 mmol), and the reaction was stirred at room temperature for 5 hours. After completion of the reaction (monitored by LCMS), the reaction was quenched with ice-cold water (50 ml) and the aqueous layer was extracted with EA (50 mL x 3). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography (20% EA/PE (v/v)) to give **160-7** (500 mg, 10%) as a yellow solid. TLC: 20% EA/PE (v/v) (R_f: 0.2). MS (ESI): calcd. for C₂₀H₂₂F₄N₂O₃S₂: 478.1; Found: 479.0 [M + 1]⁺.

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Step 7. Synthesis of (R)-5-(4-fluorophenyl)-8-methoxy-2-methyl-3-(2-**(methylsulfonyl)ethyl)-7-(trifluoromethyl)-2,3,4,5-****tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (160-8).** To a stirred solution of (R)-5-

(4-fluorophenyl)-8-methoxy-2-methyl-3-(2-(methylthio)ethyl)-7-(trifluoromethyl)-2,3,4,5-

5 tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (**160-7**) (400 mg, 0.84 mmol) in

anhydrous DCM (4 mL) was added 3-chlorobenzoperoxoic acid (m-CPBA) (433 mg, 2.5

mmol) at 0°C. The reaction was stirred at room temperature for 3 hours. After completion of the reaction (monitored by LCMS), the reaction was quenched with 10% aq. Na₂S₂O₃

solution, and the aqueous layer was extracted with DCM (30 mL x 3). The combined organic

10 extracts were dried over anhydrous Na₂SO₄ and concentrated. The residue was purified bysilica gel column chromatography (50% EA/PE (v/v)) to give **160-8** (306 mg, 72%) as abrown solid. TLC: 50% EA/PE (v/v) (R_f: 0.3). MS (ESI): calcd. for C₂₀H₂₂F₄N₂O₅S₂: 510.1;Found: 511.0 [M + 1]⁺.15 **Step 8. Synthesis of (R)-5-(4-fluorophenyl)-8-hydroxy-2-methyl-3-(2-****(methylsulfonyl)ethyl)-7-(trifluoromethyl)-2,3,4,5-****tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (160-9).** To a stirred solution of (R)-5-

(4-fluorophenyl)-8-methoxy-2-methyl-3-(2-(methylsulfonyl)ethyl)-7-(trifluoromethyl)-

2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (**160-8**) (306 mg, 0.6 mmol) in

20 DMF (5 mL) was added LiCl (504 mg, 12 mmol) and the reaction was heated at 130 °C for

16 hours. After completion of the reaction (monitored by LCMS), the reaction mixture was

quenched with ice water (20 mL) and the aqueous layer was extracted with EA (30 mL x 3).

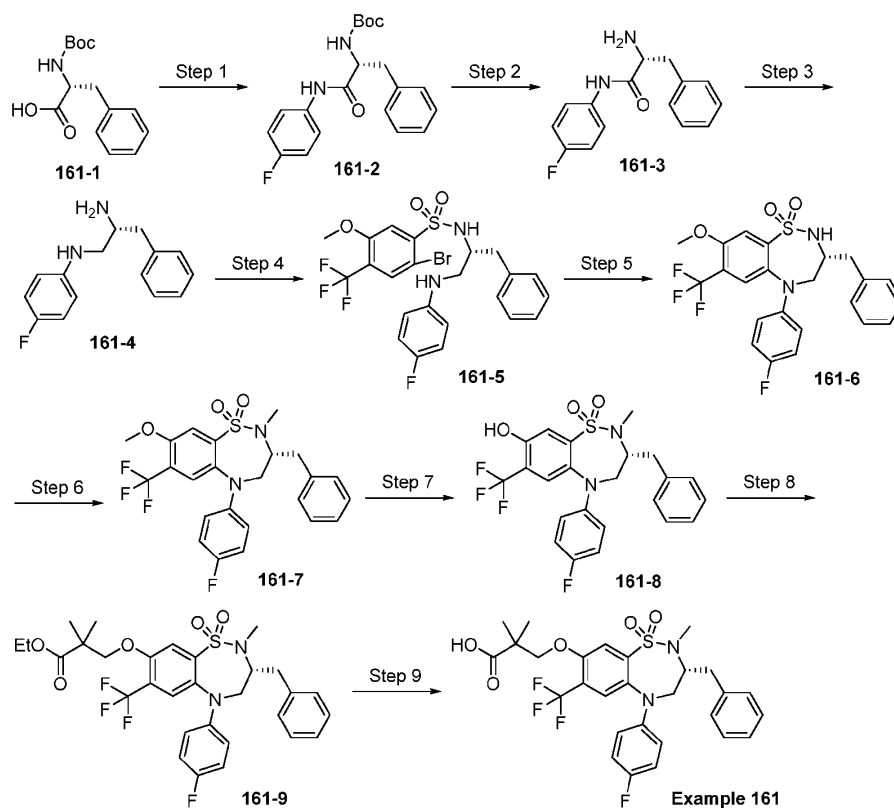
The combined organic extracts were washed with water (30 mL) and brine (30 mL), dried

over anhydrous Na₂SO₄, and concentrated. The residue was purified by Isolera column25 chromatography (50% EA/PE (v/v)) to **160-9** (170 mg, 57%) as a yellow solid. TLC: 50%EA/PE (v/v) (R_f: 0.3). MS (ESI): calcd. for C₁₉H₂₀F₄N₂O₅S₂: 496.1; Found: 514.0 [M + 18]⁺.**Step 9. Synthesis of (R)-ethyl 3-((5-(4-fluorophenyl)-2-methyl-3-(2-****(methylsulfonyl)ethyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-**30 **tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)-2,2-dimethylpropanoate (160-10).** To a

stirred solution of (R)-5-(4-fluorophenyl)-8-hydroxy-2-methyl-3-(2-(methylsulfonyl)ethyl)-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (**160-9**) (170 mg, 0.34 mmol) and Cs₂CO₃ (166 mg, 0.51 mmol) in DMF (2 mL) was added ethyl 2,2-dimethyl-3-(((trifluoromethyl)sulfonyl)oxy)propanoate (142 mg, 0.51 mmol). The reaction was stirred at 100 °C for 3 hr. After completion of the reaction (monitored by LCMS), the reaction was poured into water (10 mL) and extracted with EA (15 mL x 3). The combined organic layer was washed with water (10 mL x 3), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by prep-TLC (30% EA/PE (v/v)) to give **160-10** (170 mg, 80%) as a white solid. TLC: 30% EA/PE (v/v) (R_f: 0.3). MS (ESI): calcd. for C₂₆H₃₂F₄N₂O₇S₂: 624.2; Found: 625.2 [M + 1]⁺.

Step 10. Synthesis of (R)-3-((5-(4-fluorophenyl)-2-methyl-3-(2-(methylsulfonyl)ethyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid (Example 160). To a stirred solution of (R)-ethyl 3-((5-(4-fluorophenyl)-2-methyl-3-(2-(methylsulfonyl)ethyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)-2,2-dimethylpropanoate (**160-10**) (170 mg, 0.27 mmol) in dioxane/H₂O (1.2 mL/0.4 mL) was added LiOH (34 mg, 0.82 mmol). After stirring at rt for 16 hr, the reaction mixture was added several drops of 2N aq. HCl solution. The resulting mixture was purified by prep-HPLC to give **Example 160** (110 mg, 68%) as a white solid. MS (ESI): calcd. for C₂₄H₂₈F₄N₂O₇S₂: 596.1; Found: 597.0 [M + 1]⁺. ¹H NMR (500 MHz, DMSO-d₆): δ 7.57 – 7.53 (m, 2H), 7.05 – 7.01 (m, 2H), 6.74 – 6.70 (m, 2H), 4.24 – 4.19 (m, 3H), 3.91 (s, 1H), 3.43 – 3.18 (m, 3H), 3.03 (s, 3H), 2.59 (s, 3H), 2.16 – 2.10 (m, 1H), 1.99 – 1.89 (m, 1H), 1.25 (s, 6H) ppm

Example 161. (R)-3-((3-benzyl-5-(4-fluorophenyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid



Step 1. Synthesis of (R)-tert-butyl 1-((4-fluorophenyl)amino)-1-oxo-3-phenylpropan-2-ylcarbamate (161-2). To a stirred solution of (R)-2-((tert-butoxycarbonyl)amino)-3-phenylpropanoic acid (**161-1**) (5 g, 18.9 mmol) and DIEA (3.7 g, 28.7 mmol) in DMF (50 mL) was added 4-fluoroaniline (2.6 g, 23.4 mmol) and HATU (9.3 g, 24.5 mmol). The reaction mixture was stirred at room temperature overnight. After the completion of the reaction (monitored by LCMS), the reaction mixture was quenched with water (50 mL) and the aqueous phase was extracted with EA (50 mL x 3). The combined organic extracts were washed with sat. aq. LiCl solution (50 mL x 2) and brine (50 mL x 3), dried over anhydrous Na_2SO_4 , and concentrated. The residue was purified by silica gel column chromatography (30% EA/PE (v/v)) to give **161-2** (6.8 g, quantitative) as a white solid. TLC: 30% EA/PE (v/v) (R_f : 0.7). MS (ESI): calcd. for $\text{C}_{20}\text{H}_{23}\text{FN}_2\text{O}_3$: 358.2, Found: 303.1 [$\text{M} - 56 + 1$] $^+$.

Step 2. Synthesis of (R)-2-amino-N-(4-fluorophenyl)-3-phenylpropanamide (161-3). To a stirred solution of (R)-tert-butyl (1-((4-fluorophenyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (**161-2**) (6.8 g, 19 mmol) in DCM (50 mL) was added TFA (25 mL). The reaction was stirred at room temperature for 3 h. After the completion of the reaction

5 (monitored by LCMS), the reaction mixture was concentrated, and the residue was added water (50 mL) and neutralized with 15% NaOH solution. The aqueous phase was extracted with DCM (50 mL x 3). The combined organic extracts were washed with brine (50 mL), and dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel chromatography (20% EA/PE (v/v)) to give crude **161-3** (4.9 g, quantitative) as a yellow

10 solid. TLC: 10% MeOH/DCM (v/v) (R_f: 0.6); MS (ESI): calcd. for C₁₅H₁₅FN₂O: 258.1; Found: 259.1 [M+1]⁺.

Step 3. Synthesis of (R)-N¹-(4-fluorophenyl)-3-phenylpropane-1,2-diamine (161-4). A solution of (R)-2-amino-N-(4-fluorophenyl)-3-phenylpropanamide (**161-3**) (2 g, 7.8 mmol) in

15 THF (40 mL), was added LAH (2.3 g, 60.6 mmol) at 0°C. The reaction was stirred at 60°C overnight. After the completion of the reaction (monitored by LCMS), the reaction was diluted with MTBE (40 mL) and quenched with water (10 mL) and 15% NaOH solution (3 mL) at 0°C. Anhydrous Na₂SO₄ was added to the solution and the mixture was stirred for 30 min. The mixture was filtered, and the filtrate was concentrated in vacuo to give crude **161-4**

20 (1.2 g, 63%) as yellow oil, which was used in the next step without further purification. MS (ESI): calcd. for C₁₅H₁₇FN₂: 244.1; Found: 245.2 [M+1]⁺.

Step 4. (R)-2-bromo-N-(1-((4-fluorophenyl)amino)-3-phenylpropan-2-yl)-5-methoxy-4-(trifluoromethyl)benzenesulfonamide (161-5). To a solution of (R)-N¹-(4-fluorophenyl)-3-phenylpropane-1,2-diamine (**161-4**) (600 mg, 2.45 mmol) and TEA (750 mg, 7.41 mmol) in

25 THF (10 mL) was added 2-bromo-5-methoxy-4-(trifluoromethyl)benzene-1-sulfonyl chloride (1 g, 2.80 mmol) at room temperature. The reaction was stirred at room temperature overnight. After the completion of the reaction, the reaction was quenched with water (30 mL). The aqueous phase was extracted with EA (30 mL x 3). The combined organic extracts

30 were washed with brine (30 mL), dried over anhydrous Na₂SO₄, and concentrated. The

residue was purified by silica gel column chromatography (25% EA/PE (v/v)) to give **161-5** (700 mg, 51.0%) as a yellow solid. TLC: 20% EA/PE (v/v) (R_f : 0.7). MS (ESI): calcd. for $C_{23}H_{21}BrF_4N_2O_3S$: 560.0; Found: 561.0 $[M+1]^+$.

5 **Step 5. Synthesis of (R)-3-benzyl-5-(4-fluorophenyl)-8-methoxy-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (161-6).** A solution of (R)-2-bromo-N-(1-((4-fluorophenyl)amino)-3-phenylpropan-2-yl)-5-methoxy-4-(trifluoromethyl)benzenesulfonamide (**161-5**) (700 mg 1.25 mmol) in DMF (10 mL) was added K_2CO_3 (350 mg, 2.5 mmol) and Cu (80 mg, 1.26 mmol). The reaction mixture was
10 heated at 110°C and stirred overnight. After the completion of the reaction (monitored by LCMS) the reaction was quenched with water (30 mL). The aqueous layer was extracted with EA (20 mL x 3). The combined organic extracts were washed with sat. aq. LiCl solution (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4 , and concentrated. The residue was dried in vacuo to give crude **161-6** (600 mg) as a brown solid, which was used in the next
15 step without further purification. MS (ESI): calcd. for $C_{23}H_{20}F_4N_2O_3S$: 480.1; Found: 481.0 $[M+1]^+$.

Step 6. Synthesis of (R)-3-benzyl-5-(4-fluorophenyl)-8-methoxy-2-methyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide(161-7). A
20 solution of (R)-3-benzyl-5-(4-fluorophenyl)-8-methoxy-2-methyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (**161-6**) (600 mg 1.25 mmol) in DMF (10 mL) was added K_2CO_3 (350 mg, 2.5 mmol) and MeI (1.8 g, 12.7 mmol). The reaction mixture was stirred at room temperature for 2 h. After the completion of the reaction (monitored by LCMS), the reaction was quenched with water (20 mL). The aqueous phase
25 was extracted with EA (20 mL x 3). The combined organic extracts were washed with sat. aq. LiCl solution (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4 , and concentrated. The residue was purified by silica gel column chromatography (20% EA/PE (v/v)) to give **161-7** (618 mg, quantitative) as a yellow solid. TLC: 20% EA/PE (v/v) (R_f : 0.8). MS (ESI): calcd. for $C_{24}H_{22}F_4N_2O_3S$: 494.1; Found: 495.0 $[M+1]^+$.

Step 7. Synthesis of (R)-3-benzyl-5-(4-fluorophenyl)-8-hydroxy-2-methyl-7-**(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (161-8).** To

a solution of (R)-3-benzyl-5-(4-fluorophenyl)-8-methoxy-2-methyl-7-(trifluoromethyl)-

2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (**161-7**) (618 mg, 1.25 mmol) in

5 DMF (10 mL) was added LiCl (1.8 g, 42 mmol). The reaction was stirred at 110°C overnight.

After the completion of the reaction (monitored by LCMS), the reaction was quenched with

water (20 mL). The aqueous phase was extracted with EA (20 mL x 3). The combined

organic extracts were washed with sat. aq. LiCl solution (20 mL) and brine (20 mL), dried

over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column10 chromatography (20% EA/PE (v/v)) to give **161-8** (350 mg, 58.3%) as a yellow solid. TLC:20% EA/PE (v/v) (R_f: 0.7). MS (ESI): calcd. for C₂₃H₂₀F₄N₂O₃S: 480.1; Found: 481.0[M+1]⁺.**Step 8. Synthesis of (R)-ethyl 3-((3-benzyl-5-(4-fluorophenyl)-2-methyl-1,1-dioxido-7-**15 **(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)-2,2-****dimethylpropanoate (161-9).** A solution of (R)-3-benzyl-5-(4-fluorophenyl)-8-hydroxy-2-methyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (**161-****8**) (350 mg, 0.73 mmol) and Cs₂CO₃ (475 mg, 1.45 mmol) in DMF (6 mL) was added ethyl

2,2-dimethyl-3-((methylsulfonyl)oxy)propanoate (653 mg, 2.92 mmol). The reaction was

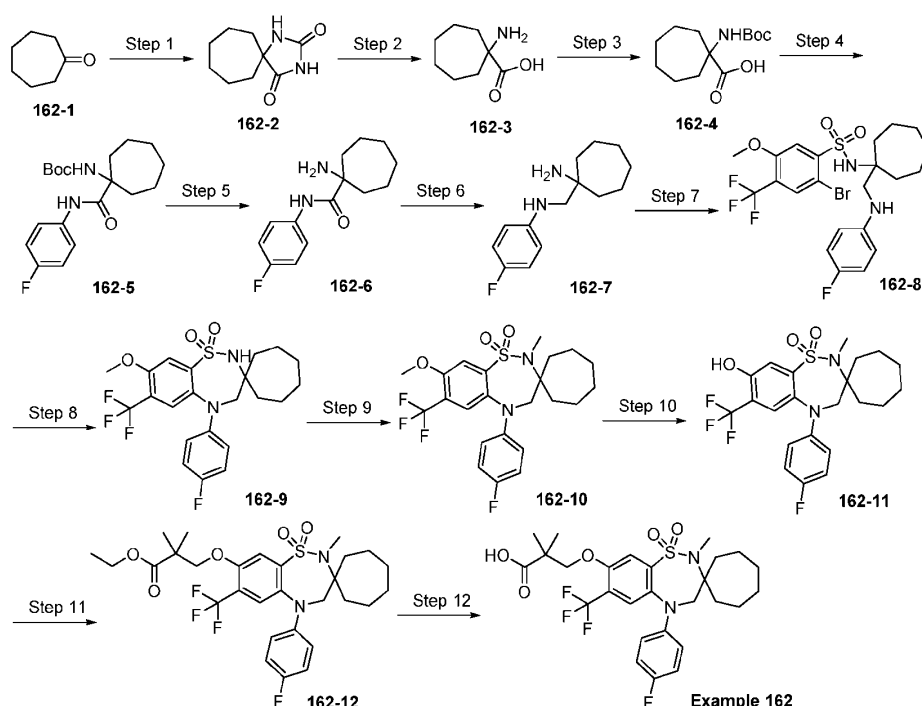
20 stirred at 110°C overnight. After the completion of the reaction (monitored by LCMS), the

reaction was quenched with water (20 mL). The aqueous phase was extracted with EA. The

combined organic extracts were washed with sat. aq. LiCl solution (15 mL) and brine (15

mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gelcolumn chromatography (20% EA/PE (v/v)) to give **161-9** (200 mg, 45.1%) as a yellow solid.25 TLC: 20% EA/PE (v/v) (R_f: 0.9). MS (ESI): calcd. for C₃₀H₃₂F₄N₂O₅S: 608.2; Found: 609.1[M+1]⁺.**Step 9. Synthesis of (R)-3-((3-benzyl-5-(4-fluorophenyl)-2-methyl-1,1-dioxido-7-****(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][(R)-ethyl 3-((3-benzyl-5-(4-fluorophenyl)-**30 **2-methyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-**

- 8-yl)oxy)-2,2-dimethylpropanoate 1,2,5]thiadiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid (Example 161).** A solution of (R)-ethyl 3-((3-benzyl-5-(4-fluorophenyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)-2,2-dimethylpropanoate (**161-9**) (200 mg) in water and dioxane was added LiOH. The reaction mixture was stirred at room temperature overnight. After the completion of the reaction, the reaction was quenched with water. The aqueous phase was neutralized with sat. aq. KHSO₄ aqueous solution and extracted with EA (25 mL x 3). The combined organic extracts were washed with brine (25 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by prep-HPLC to give **Example 161** (100 mg, 52.4%) as a white solid. MS (ESI): calcd. for C₂₈H₂₈F₄N₂O₅S: 580.2; Found: 581.0 [M+1]⁺. ¹H NMR (400 MHz, CD₃OD): δ 7.63 (s, 1H), 7.49 – 7.32 (m, 6H), 6.84 (t, J = 8.6 Hz, 2H), 6.39 (s, 2H), 4.21 – 4.04 (m, 4H), 3.48 (s, 1H), 3.07 – 3.02 (m, 1H), 2.92 – 2.87 (m, 1H), 2.67 (s, 3H), 2.16 – 1.96 (m, 2H), 1.36 (s, 6H) ppm.
- Example 162. 3-((5-(4-Fluorophenyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-4,5-dihydro-2H-spiro[benzo[f][1,2,5]thiadiazepine-3,1'-cycloheptan]-8-yl)oxy)-2,2-dimethylpropanoic acid



Scheme 40

Step 1. Synthesis of 1,3-diazaspiro[4.6]undecane-2,4-dione (162-2). Cycloheptanone (**162-1**) (5 g, 44.6 mmol), TMSCN (6.62 g, 66.9 mmol), CsF (10.2 g, 66.9 mmol), and (NH₄)₂CO₃ (12.8 g, 133.8 mmol) were mixed in EtOH/H₂O (1:1 (v/v), 100 mL) and the reaction was stirred at 50 °C overnight. The reaction was poured into water and extracted with EA (80 mL x 3). The combined organic extracts were washed with brine (80 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give crude **162-2** as an off-white solid, which was used in the next step without further purification. MS (ESI): calcd. for C₉H₁₄N₂O₂: 181.2; Found: 182.2 [M+1]⁺.

Step 2. Synthesis of 1-aminocycloheptane-1-carboxylic acid (162-3). Crude 1,3-diazaspiro[4.6]undecane-2,4-dione (**162-2**) was suspended in aqueous NaOH solution (10 N aqueous solution)/ethylene glycol (1:1 (v/v), 100 mL) and the reaction was refluxed for 3 days. After completion of the reaction (monitored by LCMS), the reaction mixture was

cooled to room temperature. The pH value was adjusted to 2~3 with 6 N aq. HCl solution and the mixture was used to the next step without further purification.

Step 3. Synthesis of 1-((tert-butoxycarbonyl)amino)cycloheptane-1-carboxylic acid (162-4).

5 4). To the above solution was added K₂CO₃ (18.6 g, 133.6 mmol), followed by a solution of Boc₂O (14.5 g, 66.3 mmol) in ethanol (50 mL). The resulting mixture was stirred at room temperature overnight and then neutralized to pH = 2~3 with 3 N aq. HCl solution. The mixture was extracted with EA (100 mL x 3). The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by silica gel column chromatography using EA/PE as eluent to give **162-4** (4.7 g, 41% over 3 steps) as an off-white solid. MS (ESI): calcd. for C₁₃H₂₃NO₄: 257.2; Found: 202.2 [M -56 +1]⁺.

Step 4. Synthesis of tert-butyl (1-((4-fluorophenyl)carbamoyl)cycloheptyl)carbamate (162-5).

15 (162-4) (4.7 g, 18.3 mmol) in DCM (60 mL) were added TEA (2.8 g, 27.5 mmol) and HATU (9 g, 23.8 mmol), followed by a solution of 4-fluoroaniline (2.44 g, 22 mmol) in DCM (5 mL) at 0°C. The resulting mixture was stirred at room temperature overnight and then diluted with water. The aqueous phase was extracted with DCM (50 mL x 3). The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by silica gel column chromatography using EA/PE as eluent to give **162-5** (4.8 g, 75%) as an off-white solid. MS (ESI): calcd. for C₁₉H₂₇FN₂O₃: 350.2; Found: 351.2 [M+1]⁺.

Step 5. Synthesis of 1-amino-N-(4-fluorophenyl)cycloheptane-1-carboxamide (162-6).

25 a solution of tert-butyl (1-((4-fluorophenyl)carbamoyl)cycloheptyl)carbamate (**162-5**) (4.8 g, 13.7 mmol) in DCM (60 mL) was added TFA (30 mL) dropwise. After stirring at room temperature for 2 hours, the reaction mixture was concentrated. The residue was diluted with EA, and the resulting mixture was added sat. aq. K₂CO₃ solution to adjust pH ~ 9. Next, the mixture was extracted with DCM (100 mL x 3) and the combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated. The residue was dried in vacuo to give crude **162-**

6 (2.3 g, 67.6%) as a brown solid. MS (ESI): calcd. for $C_{14}H_{19}FN_2O$: 250.1; Found: 251.1 [M+1]⁺.

Step 6. Synthesis of 1-(((4-fluorophenyl)amino)methyl)cycloheptan-1-amine (162-7). To

5 a solution of 1-amino-N-(4-fluorophenyl)cycloheptane-1-carboxamide (**162-6**) (2.3 g, 9.2 mmol) in THF (40 mL) was added LAH (2.1 g, 55.2 mmol) and the reaction mixture was refluxed overnight. After cooling to room temperature, the reaction was added 15% aqueous NaOH solution and H₂O. The mixture was diluted with tert-butyl methyl ether and then filtered. The filtrate was concentrated, and the residue was purified by silica gel column
10 chromatography using EA/PE as eluent to give **162-7** (1.3 g, 60%) as a yellow oil. MS (ESI): calcd. for $C_{14}H_{21}FN_2$: 236.2; Found: 237.2 [M+1]⁺.

Step 7. Synthesis of 2-bromo-N-(1-(((4-fluorophenyl)amino)methyl)cycloheptyl)-5-methoxy-4-(trifluoromethyl)benzenesulfonamide (162-8). To a solution of 1-(((4-

15 fluorophenyl)amino)methyl)cycloheptan-1-amine (**162-7**) (950 mg, 4 mmol) in DCM (15 mL) was added TEA (1.2 g, 8 mmol), followed by a solution of 2-bromo-5-methoxy-4-(trifluoromethyl)benzenesulfonyl chloride (1.83 g, 5.2 mmol) in DCM (5 mL). After completion of the reaction, the reaction mixture was diluted with water and extracted with DCM (50 mL x 3). The combined organic extracts were dried over anhydrous Na₂SO₄ and
20 concentrated. The residue was purified by silica gel column chromatography using EA/PE as eluent to give **162-8** (1.3 g, 59%) as a yellow solid. MS (ESI): calcd. for $C_{22}H_{25}BrF_4N_2O_3S$: 552.1; Found: 553.1 [M+1]⁺.

Step 8. Synthesis of 5-(4-fluorophenyl)-8-methoxy-7-(trifluoromethyl)-4,5-dihydro-2H-

25 **spiro[benzo[f][1,2,5]thiadiazepine-3,1'-cycloheptane] 1,1-dioxide (162-9).** To a solution of 2-bromo-N-(1-(((4-fluorophenyl)amino)methyl)cycloheptyl)-5-methoxy-4-(trifluoromethyl)benzenesulfonamide (**162-8**) (1.2 g, 2.2 mmol) in DMF (10 mL) were added Cu powder (140 mg, 2.2 mmol) and K₂CO₃ (607 mg, 4.4 mmol). The resulting mixture was stirred at 110°C overnight and then quenched with water. The mixture was extracted with EA
30 (50 mL x 3). The combined organic extracts were washed with sat. aq. LiCl solution and

concentrated. The residue was dried in vacuo to give crude **162-9** (2 g) as a brown solid, which was used in the next step without further purification. MS (ESI): calcd. for $C_{22}H_{24}F_4N_2O_3S$: 472.1; Found: 473.1 $[M+1]^+$.

5 **Step 9. Synthesis of 5-(4-fluorophenyl)-8-methoxy-2-methyl-7-(trifluoromethyl)-4,5-dihydro-2H-spiro[benzo[f][1,2,5]thiadiazepine-3,1'-cycloheptane] 1,1-dioxide (162-10).**

To a solution of crude 5-(4-fluorophenyl)-8-methoxy-7-(trifluoromethyl)-4,5-dihydro-2H-spiro[benzo[f][1,2,5]thiadiazepine-3,1'-cycloheptane] 1,1-dioxide (**162-9**) (2 g) in DMF (15 mL) was added MeI (3.12 g, 22 mmol), followed by K_2CO_3 (607 mg, 4.4 mmol). After
10 stirring at rt overnight, the reaction mixture was diluted with water (50 mL). The mixture was extracted with EA (50 mL x 3). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated. The residue was purified by silica gel column chromatography using EA/PE as eluent to give **162-10** (900 mg, 85% over 2 steps) as a yellow solid. MS (ESI): calcd. for $C_{23}H_{26}F_4N_2O_3S$: 486.2; Found: 487.2 $[M+1]^+$.

15

Step 10. Synthesis of 5-(4-fluorophenyl)-8-hydroxy-2-methyl-7-(trifluoromethyl)-4,5-dihydro-2H-spiro[benzo[f][1,2,5]thiadiazepine-3,1'-cycloheptane] 1,1-dioxide (162-11).

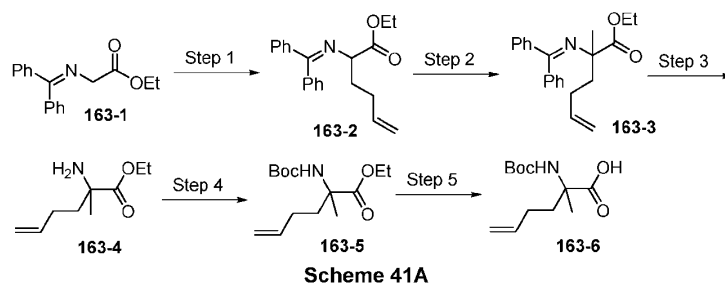
To a solution of 5-(4-fluorophenyl)-8-methoxy-2-methyl-7-(trifluoromethyl)-4,5-dihydro-2H-spiro[benzo[f][1,2,5]thiadiazepine-3,1'-cycloheptane] 1,1-dioxide (**162-10**) (800 mg, 1.6
20 mmol) in NMP (10 mL) was added LiCl (2.08 g, 50 mmol). After stirring at 130°C overnight, the mixture was cooled to rt and diluted with water (25 mL). The resulting mixture was extracted with EA (25 mL x 3). The combined organic extracts were washed with brine (25 mL), dried over anhydrous Na_2SO_4 , and concentrated. The residue was purified by silica gel column chromatography using EA/PE as eluent to give **162-11** (500 mg, 64%) as a yellow
25 solid. MS (ESI): calcd. for $C_{22}H_{24}F_4N_2O_3S$: 472.1; Found: 473.1 $[M+1]^+$.

Step 11. Synthesis of ethyl 3-((5-(4-fluorophenyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-4,5-dihydro-2H-spiro[benzo[f][1,2,5]thiadiazepine-3,1'-cycloheptan]-8-yl)oxy)-2,2-dimethylpropanoate (162-12). To a solution of 5-(4-fluorophenyl)-8-hydroxy-
30 2-methyl-7-(trifluoromethyl)-4,5-dihydro-2H-spiro[benzo[f][1,2,5]thiadiazepine-3,1'-

cycloheptane] 1,1-dioxide (**162-11**) (150 mg, 0.32 mmol) and Cs₂CO₃ (209 mg, 0.64 mmol) in DMF (3 mL) was added ethyl 2,2-dimethyl-3-(((trifluoromethyl)sulfonyl)oxy)propanoate (178 mg, 0.64 mmol) at rt. After stirring at 110 °C for 2 hr, the reaction mixture was cooled to rt and diluted with water (20 mL). The resulting mixture was extracted with EA (30 mL x 3). The combined organic extracts were washed with sat. aq. LiCl solution, dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give crude **162-12** (200 mg) as a brown solid, which was used in the next step without further purification. MS (ESI): calcd. for C₂₉H₃₆F₄N₂O₅S: 600.2; Found: 601.2 [M+1]⁺.

Step 12. Synthesis of 3-((5-(4-fluorophenyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-4,5-dihydro-2H-spiro[benzo[f][1,2,5]thiadiazepine-3,1'-cycloheptan]-8-yl)oxy)-2,2-dimethylpropanoic acid (Example 162). To a solution of crude ethyl 3-((5-(4-fluorophenyl)-2-methyl-1,1-dioxido-7-(trifluoromethyl)-4,5-dihydro-2H-spiro[benzo[f][1,2,5]thiadiazepine-3,1'-cycloheptan]-8-yl)oxy)-2,2-dimethylpropanoate (**162-12**) (200 mg, crude) in dioxane/H₂O (1:1 (v/v), 12 mL) was added LiOH·H₂O (384 mg, 6.4 mmol) at rt. After stirring at rt overnight, the reaction mixture was diluted with water (10 mL) and adjusted to pH = 3~4 with sat. aq. KHSO₄ solution. The reaction was extracted with EA (20 mL x 3). The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by prep-HPLC to give **Example 162** (30 mg, 16%). MS (ESI): calcd. for C₂₇H₃₂F₄N₂O₅S: 572.2; Found: 573.2 [M+1]⁺. ¹H NMR (400 MHz, CD₃OD): δ 7.54 (s, 1H), 7.14 – 7.00 (m, 5H), 4.13 (m, 4H), 3.60 – 3.48 (m, 1H), 2.85 – 2.80 (s, 3H), 2.19 – 2.16 (m, 2H), 1.63 – 1.46 (m, 10H), 1.32 (s, 6H) ppm.

Example 163. 3-((3-(3,3-Fifluoropropyl)-5-(4-fluorophenyl)-2,3-dimethyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid



Step 1. Synthesis of ethyl 2-((diphenylmethylene)amino)hex-5-enoate (163-2). To a solution of ethyl 2-((diphenylmethylene)amino)acetate (**163-1**) (10.0 g, 37.4 mmol), K_2CO_3 (15.5 g, 112.2 mmol), and TBAB (1.2 g, 3.74 mmol) in CH_3CN (100 mL) was added 4-bromobut-1-ene (7.5 g, 56.2 mmol). The resulting reaction was refluxed overnight. After completion of the reaction (monitored by LCMS), the reaction mixture was filtered through a Celite[®]545 pad. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography (5% EA/PE (v/v)) to give **163-2** (10.3 g, 82%) as a colorless oil. TLC: 5% EA/PE (v/v) (R_f : 0.3). MS (ESI): calcd. for $C_{21}H_{23}NO_2$: 321.2; Found: 322.2 $[M + 1]^+$.

Step 2. Synthesis of ethyl 2-((diphenylmethylene)amino)-2-methylhex-5-enoate (163-3). A stirred solution of **163-2** (10.3 g, 32.0 mmol) in anhydrous THF (103 mL) was added *t*-BuOK (128 mL of 1.0 M solution in THF, 128.0 mmol) via syringe under Ar. After stirring at 0°C for 20 mins, the reaction mixture was added MeI (18.2 g, 128 mmol). The resulting mixture was stirred at rt for 2 h. After completion of the reaction (monitored by LCMS), the reaction mixture was filtered through a Celite[®]545 pad. The filtrate was concentrated, and the residue was dried in vacuo to give crude **163-3** (10.5 g, 100%) as yellow oil, which was used in the next step without further purification. TLC: 5% EA/PE (v/v) (R_f : 0.2). MS (ESI): calcd. for $C_{22}H_{25}NO_2$: 335.2; Found: 336.2 $[M + 1]^+$.

Step 3. Synthesis of ethyl 2-amino-2-methylhex-5-enoate (163-4). To a solution of **163-3** (9.0 g, crude product, 26.9 mmol) in MTBE (100 mL) was added 1 N aq. HCl solution (80 mL, 80.6 mmol). The resulting mixture was stirred overnight at room temperature. After

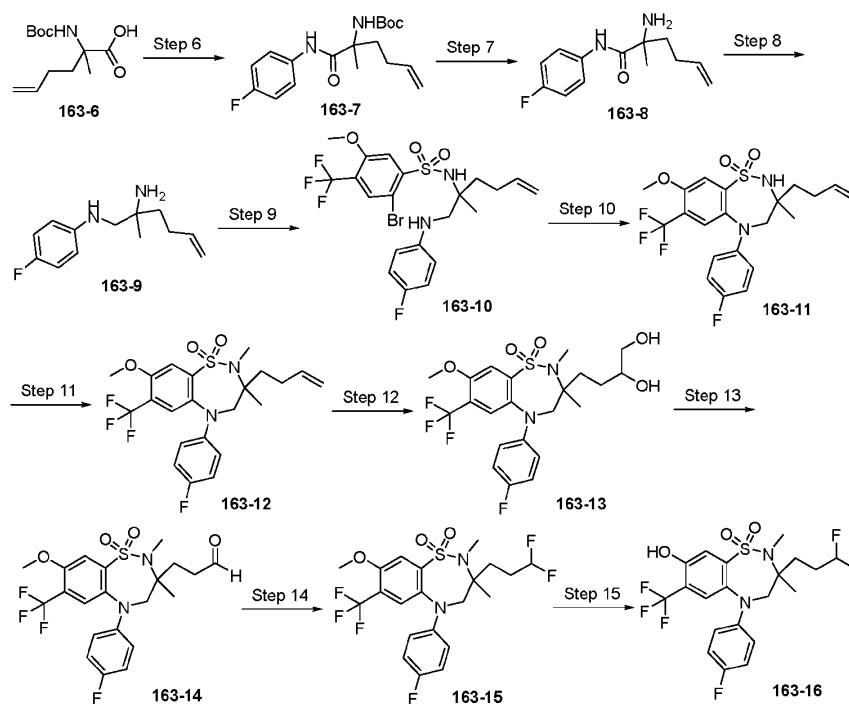
completion of the reaction (monitored by LCMS), the reaction mixture was extracted with MTBE (100 mL x 2). The combined organic extracts were washed with saturated aq. NaHCO₃ solution, dried with anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give crude **163-4** (4.6 g) as a brown oil, which was used in the next step without further purification. MS (ESI): calcd. for C₉H₁₇NO₂: 171.1; Found: 172.2 [M + 1]⁺.

Step 4. Synthesis of ethyl 2-((tert-butoxycarbonyl)amino)-2-methylhex-5-enoate (163-5).

A stirred solution of **163-4** (4.6 g, 26.9 mmol) and K₂CO₃ (18.6 g, 134.5 mmol) in dioxane/H₂O (200 mL, 1/1 (v/v)) was added (Boc)₂O (6.5 g, 29.6 mmol) dropwise below 10 °C, and the reaction mixture was stirred overnight at room temperature. After completion of the reaction (monitored by LCMS), the reaction mixture was extracted with EA (100 mL x 3). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give crude **163-5** (7.2 g, 100%) as yellow oil, which was directly used in the next step without further purification. MS (ESI): calcd. for C₁₄H₂₅NO₄: 271.2; Found: 172.3 [M – Boc + 1]⁺.

Step 5. Synthesis of 2-((tert-butoxycarbonyl)amino)-2-methylhex-5-enoic acid (163-6).

To a solution of **163-5** (9.0 g, crude product, 26.9 mmol) in EtOH (40 mL) was added 4 N aq. NaOH solution (40 mL). The reaction mixture was stirred at room temperature overnight. After completion of the reaction (monitored by LCMS), the reaction mixture was extracted with PE (50 mL x 2). The aq. phase was adjusted to pH 2.0 with 1N aq. HCl solution. Subsequently, the mixture was extracted with EA (100 mL x 4). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give crude **163-6** (6.2 g, 96%) as yellow oil, which was used in the next step without further purification. MS (ESI): calcd. for C₁₂H₂₁NO₄: 243.2; Found: 144.2 [M – Boc + 1]⁺.



Scheme 41B

Step 6. Synthesis of tert-butyl (1-((4-fluorophenyl)amino)-2-methyl-1-oxohex-5-en-2-yl)carbamate (163-7). To a solution of **163-6** (6.2 g, 25.5 mmol), 4-fluoroaniline (3.4 g, 30.6 mmol), and TEA (5.2 g, 51.0 mmol) in THF (60 mL) was added HATU (11.6 g, 30.6 mmol). The resulting reaction was stirred for 3 hr at room temperature. After completion of the reaction (monitored by LCMS), the reaction mixture was diluted with water (100 mL) and the aqueous layer was extracted with EA (100 mL x 3). The combined organic extracts were washed with brine (40 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography (20% EA/PE (v/v)) to give **163-7** (6.9 g, 81%) as a white solid. TLC: 15% EA/PE (v/v) (R_f: 0.2). MS (ESI): calcd. for C₁₈H₂₅FN₂O₃: 336.2; Found: 281.2 [M - 56 + 1]⁺.

Step 7. Synthesis of 2-amino-N-(4-fluorophenyl)-2-methylhex-5-enamide (163-8). To a solution of **163-7** (6.9 g, 20.5 mmol) in DCM (90 mL), TFA (45 mL) was added dropwise at 0

°C. The resulting reaction was stirred at room temperature for 3 hours. After completion of the reaction (monitored by LCMS), the reaction mixture was concentrated under vacuum to remove extra TFA. The mixture was dissolved with EA (50 ml) and diluted with H₂O (20 ml). Then saturated aq. NaHCO₃ was added dropwise until pH > 7. The aqueous layer was
5 extracted with EA (100 mL x 3). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give crude **163-8** (5.5 g, 100%) as a yellow oil, which was used in the next step without further purification. MS (ESI): calcd. for C₁₃H₁₇FN₂O: 236.1; Found: 237.1 [M + 1]⁺.

10 **Step 8. Synthesis of N1-(4-fluorophenyl)-2-methylhex-5-ene-1,2-diamine (163-9).** To a solution of **163-8** (5.8 g, 26.1 mmol) in anhydrous THF (60 mL) was carefully added LiAlH₄ (3.0 g, 78.4 mmol) portion-wise below 10 °C under Ar atmosphere. The reaction was stirred at 65 °C for 4 hr under an Ar atmosphere. After completion of the reaction (monitored by LCMS), the reaction mixture was added ice-cold water (3.0 mL) and 15% aq. NaOH (3.0
15 mL). The mixture was filtered through a Celite®545 pad. The filtrate was dried over anhydrous Na₂SO₄ and concentrated. The residue was dried in vacuo to give crude **163-9** (4.1 g, 71%) as a colorless oil, which was used in the next step without further purification. MS (ESI): calcd. for C₁₃H₁₉FN₂: 222.2; Found: 223.2 [M + 1]⁺.

20 **Step 9. Synthesis of 2-bromo-N-(1-((4-fluorophenyl)amino)-2-methylhex-5-en-2-yl)-5-methoxy-4-(trifluoromethyl)benzenesulfonamide (163-10).** To a solution of **163-9** (4.1 g, 18.5 mmol) and TEA (4.7 g, 46.2 mmol) in anhydrous DCM (40 mL) was added 2-bromo-5-methoxy-4-(trifluoromethyl)benzene-1-sulfonyl chloride (8.4 g, 24.0 mmol) at 0 °C. The resulting reaction was stirred at room temperature for 3 hr. After completion of the reaction
25 (monitored by LCMS), the reaction mixture was added ice-cold water (50 mL), and the aqueous layer was extracted with DCM (50 mL x 3). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography (10% EA/PE (v/v)) to give **163-10** (6.2 g, 62%) as a white solid. TLC: 15% EA/PE (v/v) (R_f: 0.3). MS (ESI): calcd. for C₂₁H₂₃BrF₄N₂O₃S:
30 538.1; Found: 539.1 [M + 1]⁺.

Step 10. Synthesis of 3-(but-3-en-1-yl)-5-(4-fluorophenyl)-8-methoxy-3-methyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (163-11). To a solution of **163-10** (6.2 g, 11.5 mmol) and K₂CO₃ (3.2 g, 23.0 mmol) in DMF (40 mL) was added Cu (738 mg, 11.5 mmol). The mixture was stirred at 115 °C for 16 hr. After completion of the reaction (monitored by LCMS), the reaction mixture was quenched with saturated aq. NH₄Cl (30 mL). The aqueous layer was extracted with EA (50 mL x 3). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give crude **163-11** (5.2 g, 100%) as brown oil, which was used in the next step without further purification. TLC: 20% EA/PE (v/v) (R_f: 0.2). MS (ESI): calcd. for C₂₁H₂₂F₄N₂O₃S: 458.1; Found: 459.1 [M + 1]⁺.

Step 11. Synthesis of 3-(but-3-en-1-yl)-5-(4-fluorophenyl)-8-methoxy-2,3-dimethyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (163-12). To a solution of **163-11** (5.2 g, crude product, 11.3 mmol) and Cs₂CO₃ (7.4 g, 22.7 mmol) in DMF (40 mL) was added MeI (3.2 g, 22.7 mmol). The reaction mixture was stirred at room temperature for 5 hr. After completion of the reaction (monitored by LCMS), the reaction mixture was added ice-cold water (50 mL) and the aqueous layer was extracted with EA (50 mL x 3). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography (15% EA/PE (v/v)) to give **163-12** (5.0 g, 94%) as yellow oil. TLC: 15% EA/PE (v/v) (R_f: 0.2). MS (ESI): calcd. for C₂₂H₂₄F₄N₂O₃S: 472.1; Found: 473.1 [M + 1]⁺.

Step 12. Synthesis of 3-(3,4-dihydroxybutyl)-5-(4-fluorophenyl)-8-methoxy-2,3-dimethyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (163-13). A stirred solution of **163-12** (5.0 g, 10.6 mmol), AD-mix-beta (578 mg, 0.74 mmol), K₂OsO₄ (144 mg, 0.4 mmol) and methanesulfonamide (2.0 g, 21.2 mmol) in t-BuOH (25 mL) was added a solution of K₂CO₃ (5.2 g, 37.1 mmol) and K₃Fe(CN)₆ (10.5 g, 31.8

mmol) in H₂O (25 mL). The resulting reaction was stirred at room temperature overnight. After completion of the reaction (monitored by LCMS), the reaction mixture was added sat. aq. Na₂S₂O₃ and the mixture was extracted with EA (50 mL x 3). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated.

- 5 The residue was dried in vacuo to give crude **163-13** (5.3 g, 95%) as a yellow oil, which was used in the next step without further purification. TLC: 20% EA/PE (v/v) (R_f: 0.3). MS (ESI): calcd. for. C₂₂H₂₆F₄N₂O₅S: 506.2; Found: 507.2 [M + 1]⁺.

Step 13. Synthesis of 3-(5-(4-fluorophenyl)-8-methoxy-2,3-dimethyl-1,1-dioxido-7-

- 10 **(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-3-yl)propanal (163-14).**

To a solution of **163-13** (5.3 g, 10.5 mmol) in EtOH/H₂O (54 mL, 2/1 (v/v)) was added NaIO₄ (4.5 g, 21.0 mmol) below 10 °C. The reaction mixture was stirred at rt for 2 hr. After completion of the reaction (monitored by LCMS), the reaction mixture was added aq. Na₂S₂O₃, and the mixture was extracted with EA (50 mL x 3). The combined organic extracts
15 were washed with brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was dried in vacuo to give **163-14** (5.0 g, 100%) as brown oil, which was used in the next step without further purification. TLC: 15% EA/PE (v/v) (R_f: 0.3). MS (ESI): calcd. for. C₂₁H₂₂F₄N₂O₄S: 474.1; Found: 475.1 [M + 1]⁺.

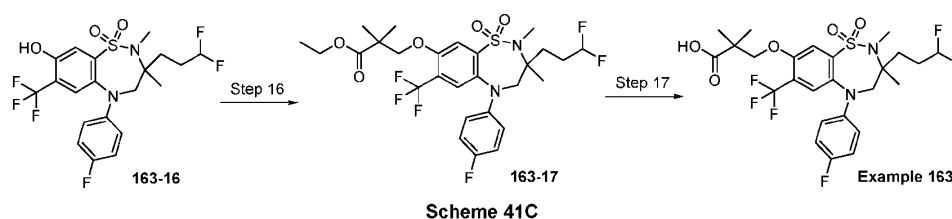
- 20 **Step 14. Synthesis of 3-(3,3-difluoropropyl)-5-(4-fluorophenyl)-8-methoxy-2,3-dimethyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (163-15).**

To a solution of **163-14** (5.0 g, 10.5 mmol) in DCM (50 mL) was added BAST (7.0 g, 31.5 mmol) dropwise at 0 °C. The resulting reaction was stirred at room temperature for 3 hours. After completion of the reaction (monitored by LCMS), the reaction mixture was quenched
25 with sat. aq. NaHCO₃, and the mixture was extracted with EA (50 mL x 3). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography (20% EA/PE (v/v)) to give **163-15** (1.9 g, 32%) as brown oil. TLC: 20% EA/PE (v/v) (R_f: 0.2). MS (ESI): calcd. for C₂₁H₂₂F₆N₂O₃S: 496.1; Found: 497.0 [M + 1]⁺.

Step 15. Synthesis of 3-(3,3-difluoropropyl)-5-(4-fluorophenyl)-8-hydroxy-2,3-dimethyl-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (**163-16**). To a solution of **163-15** (900 mg, 1.8 mmol) in NMP (9 mL) was added LiCl (3.8 g, 54.0 mmol). The reaction mixture was heated at 130 °C for 16 hr. After completion of the reaction

5 (monitored by LCMS), the reaction mixture was added with ice water (20 mL), and the aqueous layer was extracted with EA (30 mL x 3). The combined organic extracts were washed with water (30 mL) and brine (30 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography (25% EA/PE (v/v)) to give **163-16** (220 mg, 25%) as yellow oil. TLC: 25% EA/PE (v/v) (R_f: 0.3); MS

10 (ESI): calcd. for C₂₀H₂₀F₆N₂O₃S: 482.1; Found: 483.1 [M + 1]⁺.



Step 16. Synthesis of ethyl 3-((3-(3,3-difluoropropyl)-5-(4-fluorophenyl)-2,3-dimethyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)-2,2-dimethylpropanoate (**163-17**). A stirred solution of **163-16** (110 mg, 0.23 mmol) and Cs₂CO₃ (150 mg, 0.46 mmol) in DMF (1 mL) was added ethyl 2,2-dimethyl-3-(((trifluoromethyl)sulfonyl)oxy)propanoate (95 mg, 0.34 mmol). The reaction mixture was stirred at 100 °C for 3 hr. After completion of the reaction (monitored by LCMS), the reaction

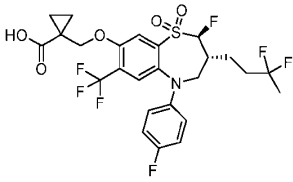
20 mixture was poured into water (10 mL) and extracted with EA (30 mL x 3). The combined organic extracts were washed with water (30 mL) and brine (30 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography (15% EA/PE (v/v)) to give **163-17** (140 mg, 99%) as yellow oil. TLC: 15% EA/PE (v/v) (R_f: 0.2). MS (ESI): calcd. for C₂₇H₃₂F₆N₂O₅S: 610.2; Found: 611.2 [M + 1]⁺.

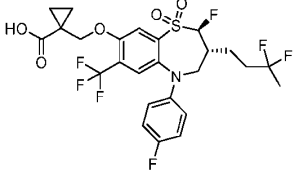
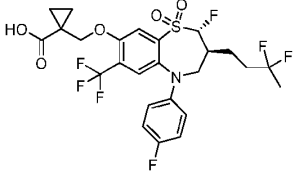
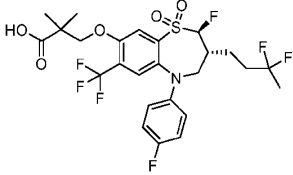
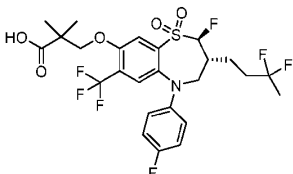
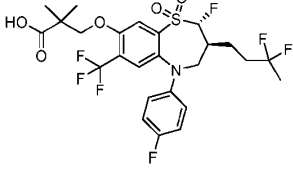
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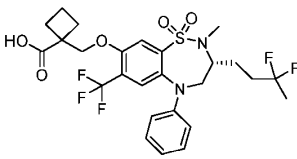
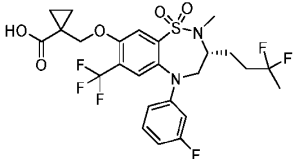
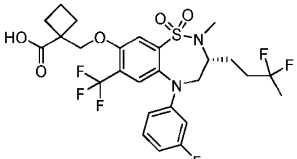
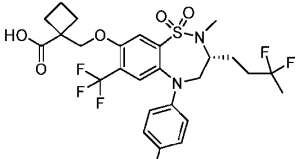
Step 17. Synthesis of 3-((3-(3,3-difluoropropyl)-5-(4-fluorophenyl)-2,3-dimethyl-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid (**Example 163**). A solution of **163-17** (50 mg, 0.08 mmol) in Dioxane/H₂O (v/v = 0.3 mL/0.1 mL) was added LiOH (10 mg, 0.24 mmol), and the reaction mixture was stirred at rt for 18 hr. After completion of the reaction (monitored by LCMS), the reaction was neutralized with saturated aq. KHSO₄ solution. The aqueous layer was extracted with EA (20 mL x 3). The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by prep-HPLC to give **Example 163** (15 mg, 32%) as a white solid. MS (ESI): calcd. for C₂₅H₂₈F₆N₂O₅S: 582.2; Found: 583.2 [M + 1]⁺. ¹H NMR (400 MHz, CD₃OD): δ 7.53 (s, 1H), 7.25 – 7.06 (m, 5H), 5.80 (t, J = 57.2 Hz, 1H), 4.30 – 4.22 (m, 1H), 4.12 (s, 2H), 3.77 – 3.62 (m, 1H), 2.89 (s, 3H), 2.50 – 2.33 (m, 1H), 2.10 – 1.83 (m, 2H), 1.41 – 1.31 (m, 10H) ppm

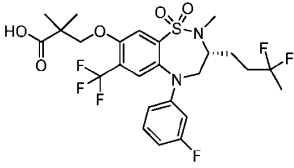
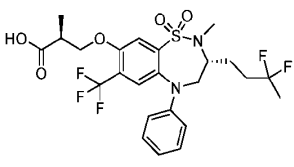
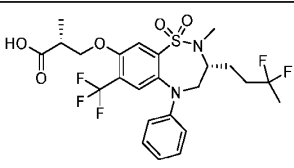
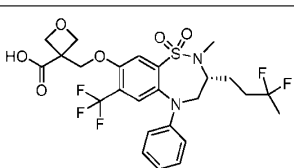
TABLE 4 shows structures and analytical data for representative Examples of the present invention. These compounds can be prepared according to the synthetic schemes described above and using procedures known to those of ordinary skill in the art.

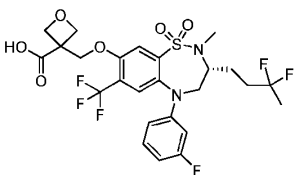
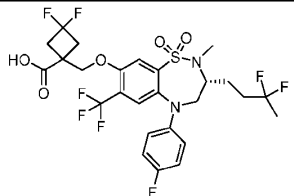
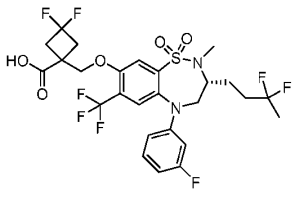
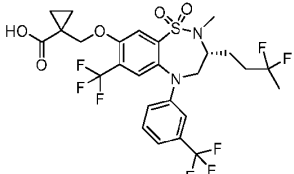
TABLE 4: Representative Examples of the present invention

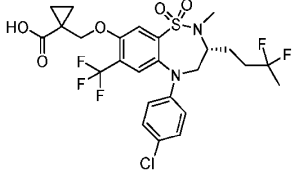
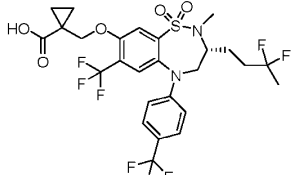
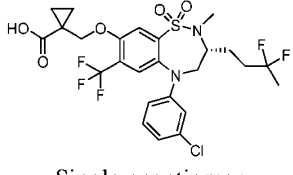
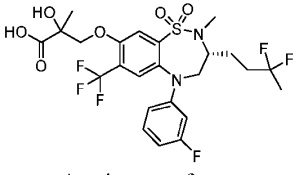
Example	Structure	MS [M+1] ⁺	¹ H NMR
9c/d	 trans- racemate	584.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.75 (s, 1H), 7.30 (s, 1H), 7.07 – 7.01 (m, 4H), 5.56 (dd, J = 44.4, 5.8 Hz, 1H), 4.41 - 4.33 (m, 2H), 4.19 – 4.09 (m, 1H), 4.00 (s, 1H), 2.46 – 2.42 (m, 1H), 2.03 – 1.77 (m, 4H), 1.43 (t, J = 18.6Hz, 3H), 1.35 – 1.34 (m, 2H), 1.13 – 1.07 (m, 2H) ppm.

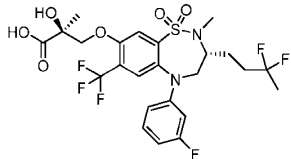
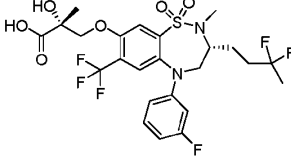
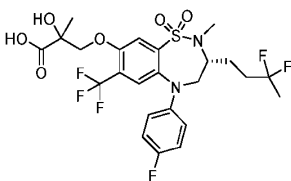
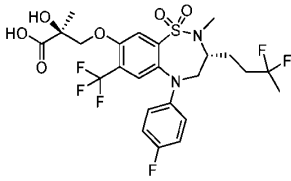
9c	 Single diastereomer	584.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.75 (s, 1H), 7.30 (s, 1H), 7.07 – 7.01 (m, 4H), 5.56 (dd, J = 44.1, 6.0 Hz, 1H), 4.40 – 4.32 (m, 2H), 4.14 – 4.12 (m, 1H), 3.72 – 3.66 (m, 1H), 2.42 – 2.40 (m, 1H), 2.03 – 1.75 (m, 4H), 1.43 (t, J = 18.6 Hz, 3H), 1.35 – 1.34 (m, 2H), 1.16 – 1.07 (m, 2H) ppm
9d	 Single diastereomer	584.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.78 (s, 1H), 7.32 (s, 1H), 7.09 – 7.03 (m, 4H), 5.58 (dd, J = 44.1, 6.0 Hz, 1H), 4.43 – 4.35 (m, 2H), 4.19 – 4.12 (m, 1H), 3.74 – 3.69 (m, 1H), 2.44 – 2.43 (m, 1H), 2.05 – 1.78 (m, 4H), 1.45 (t, J = 18.3 Hz, 3H), 1.37 – 1.31 (m, 2H), 1.21 – 1.12 (m, 2H) ppm
10c/d	 trans- racemate	586.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.75 (s, 1H), 7.33 (s, 1H), 7.09 – 7.04 (m, 4H), 5.59 (dd, J = 44.1, 5.8 Hz, 1H), 4.26 – 4.13 (m, 3H), 3.74 – 3.69 (m, 1H), 2.45 – 2.41 (m, 1H), 2.05 – 1.78 (m, 4H), 1.45 (t, J = 18.3 Hz, 3H), 1.36 (s, 6H) ppm
10c	 Single diastereomer	586.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.75 (s, 1H), 7.33 (s, 1H), 7.09 – 7.04 (m, 4H), 5.59 (dd, J = 44.1, 6.0 Hz, 1H), 4.26 – 4.10 (m, 3H), 3.73 – 3.59 (m, 1H), 2.45 – 2.44 (m, 1H), 2.05 – 1.75 (m, 4H), 1.45 (t, J = 18.3 Hz, 3H), 1.36 (s, 6H) ppm
10d	 Single diastereomer	586.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.75 (s, 1H), 7.33 (s, 1H), 7.09 – 7.04 (m, 4H), 5.59 (dd, J = 44.1, 6.0 Hz, 1H), 4.26 – 4.23 (m, 2H), 4.20 – 4.11 (m, 1H), 3.74 – 3.70 (m, 1H), 2.46 – 2.44 (m, 1H), 2.05 – 1.80 (m, 4H), 1.45 (t, J = 18.3 Hz, 3H), 1.36 (s, 6H) ppm

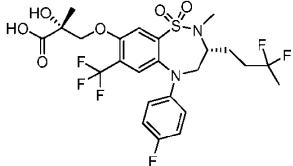
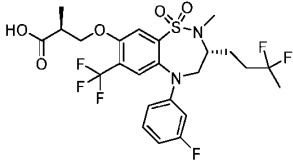
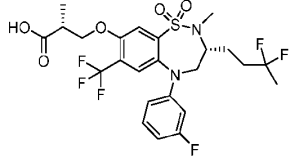
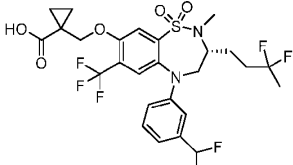
27	 Single enantiomer	577.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.68 (s, 1H), 7.47 (s, 1H), 6.83 (t, J = 8.4 Hz, 2H), 6.83 (t, J = 7.2 Hz, 1H), 6.74 (d, J = 7.6 Hz, 2H), 4.42 (s, 2H), 4.20 – 3.87 (m, 2H), 3.41 – 3.33 (m, 1H), 2.65 (s, 3H), 2.55 – 2.47 (m, 2H), 2.26 – 2.17 (m, 2H), 2.12 – 1.95 (m, 4H), 1.85 – 1.76 (m, 2H), 1.62 (t, J = 18.4 Hz, 3H) ppm
28	 Single enantiomer	581.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.68 (s, 1H), 7.56 (s, 1H), 7.17 (q, J = 8.0 Hz, 1H), 6.52 – 6.47 (m, 1H), 6.42 – 6.33 (m, 2H), 4.44 – 4.34 (m, 2H), 4.13 – 3.96 (m, 2H), 3.42 – 3.33 (m, 1H), 2.59 (s, 3H), 2.10 – 2.00 (m, 2H), 1.97 – 1.82 (m, 2H), 1.63 (t, J = 18.4 Hz, 3H), 1.35 – 1.34 (m, 2H), 1.12 – 1.11 (m, 2H) ppm
29	 Single enantiomer	595.0	¹ H NMR (400 MHz, d ₆ -DMSO): δ 7.67 (s, 1H), 7.61 (s, 1H), 7.19 (dd, J = 16.0, 8.0 Hz, 1H), 6.54 (dd, J = 16.0, 8.0 Hz, 2H), 6.35 (d, J = 6.8 Hz, 1H), 4.31 (s, 2H), 4.14 (d, J = 13.6 Hz, 1H), 3.90 (s, 1H), 3.34 (s, 1H), 2.50 (s, 3H), 2.49 – 2.32 (m, 2H), 2.09 – 1.83 (m, 6H), 1.69 (t, J = 18.8 Hz, 4H), 1.20 – 1.16 (m, 1H) ppm
30	 Single enantiomer	595.0	¹ H NMR (400 MHz, d ₆ -DMSO): δ 7.59 (s, 1H), 7.55 (s, 1H), 7.04 (t, J = 8.8 Hz, 2H), 6.68 (s, 2H), 4.29 (s, 2H), 4.13 (d, J = 14.8 Hz, 1H), 3.83 (s, 1H), 3.33 (s, 1H), 2.54 (s, 3H), 2.35 – 2.32 (m, 2H), 2.08 – 1.83 (m, 7H), 1.68 (t, J = 18.8 Hz, 4H) ppm

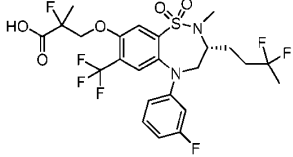
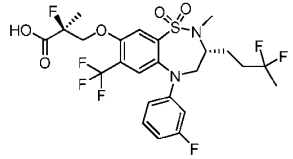
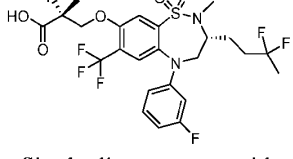
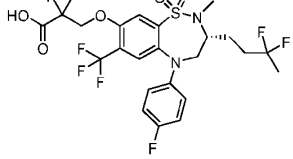
31	 Single enantiomer	583.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.66 (s, 1H), 7.56 (s, 1H), 7.19 – 7.14 (m, 1H), 6.52 – 6.32 (m, 3H), 4.22 (s, 2H), 4.11 – 4.00 (m, 2H), 3.33 – 3.31 (m, 1H), 2.59 (s, 3H), 2.10 – 1.75 (m, 4H), 1.63 (t, J = 18.4 Hz, 3H), 1.35 (s, 6H) ppm
32a	 Single diastereomer	551.2	¹ H NMR (400 MHz, CD ₃ OD): 7.65 (s, 1H), 7.47 (s, 1H), 7.23 – 7.19 (m, 2H), 6.84 – 6.81 (m, 1H), 6.74 – 6.72 (m, 2H), 4.39 – 4.35 (m, 1H), 4.24 – 4.12 (m, 2H), 4.01 – 3.82 (m, 1H), 3.49 – 3.40 (m, 1H), 2.96 – 2.85 (m, 1H), 2.64 (s, 3H), 2.10 – 1.93 (m, 2H), 1.84 – 1.78 (m, 2H), 1.62 (t, J = 18.8 Hz, 3H), 1.32 (d, J = 6.8 Hz, 3H) ppm
32b	 Single diastereomer	551.2	¹ H NMR (400 MHz, CD ₃ OD): 7.64 (s, 1H), 7.47 (s, 1H), 7.24 – 7.20 (m, 2H), 6.85 – 6.81 (m, 1H), 6.75 – 6.73 (m, 2H), 4.37 – 4.25 (m, 2H), 4.15 – 4.12 (m, 1H), 3.94 – 3.92 (m, 1H), 3.48 – 3.47 (m, 1H), 2.98 – 2.93 (m, 1H), 2.64 (s, 3H), 2.08 – 1.93 (m, 2H), 1.84 – 1.78 (m, 2H), 1.62 (t, J = 18.4 Hz, 3H), 1.32 (d, J = 7.2 Hz, 3H) ppm
33	 Single enantiomer	597.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.71 (s, 1H), 7.43 (s, 1H), 7.02 – 6.94 (m, 2H), 6.83 – 6.75 (m, 2H), 4.96 (dd, J = 6.4, 1.6 Hz, 2H), 4.73 (d, J = 6.0 Hz, 2H), 4.59 (s, 2H), 4.15 – 4.00 (m, 1H), 3.98 – 3.80 (m, 1H), 3.65 – 3.40 (m, 1H), 2.66 (s, 3H), 2.15 – 1.88 (m, 2H), 1.88 – 1.73 (m, 2H), 1.61 (t, J = 18.4 Hz, 3H) ppm

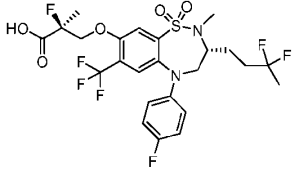
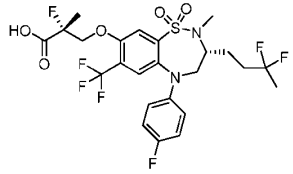
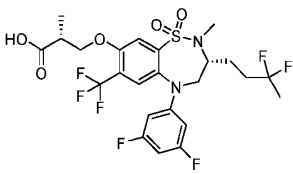
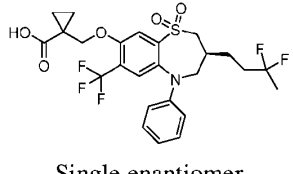
34	 Single enantiomer	597.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.76 (s, 1H), 7.59 (s, 1H), 7.18 (dd, <i>J</i> = 15.2, 8.4 Hz, 1H), 6.55 – 6.47 (m, 1H), 6.46 – 6.33 (m, 2H), 4.98 (dd, <i>J</i> = 6.0, 3.6 Hz, 2H), 4.75 (d, <i>J</i> = 6.0 Hz, 2H), 4.62 (s, 2H), 4.20 – 3.95 (m, 2H), 3.50 – 3.33 (m, 1H), 2.61 (s, 2H), 2.15 – 1.92 (m, 2H), 1.92 – 1.71 (m, 2H), 1.63 (t, <i>J</i> = 18.4 Hz, 3H) ppm
35	 Single enantiomer	631.0	¹ H NMR (400 MHz, CD ₃ OD): δ 7.66 (s, 1H), 7.41 (s, 1H), 7.03 – 6.92 (m, 2H), 6.85 – 6.72 (m, 2H), 4.46 (s, 2H), 4.15 – 3.98 (m, 1H), 3.97 – 3.79 (m, 1H), 3.60 – 3.40 (m, 1H), 3.15 – 2.99 (m, 2H), 2.90 – 2.73 (m, 2H), 2.65 (s, 3H), 2.15 – 1.90 (m, 2H), 1.86 – 1.72 (m, 2H), 1.61 (t, <i>J</i> = 18.4 Hz, 3H) ppm
36	 Single enantiomer	631.0	¹ H NMR (400 MHz, CD ₃ OD): δ 7.41 (s, 1H), 7.57 (s, 1H), 7.21 – 7.13 (m, 1H), 6.54 – 6.47 (m, 1H), 6.46 – 6.31 (m, 2H), 4.51 (s, 2H), 4.18 – 3.90 (m, 2H), 3.46 – 3.33 (m, 1H), 3.16 – 3.00 (m, 2H), 2.90 – 2.76 (m, 2H), 2.60 (s, 3H), 2.12 – 1.94 (m, 2H), 1.92 – 1.71 (m, 2H), 1.62 (t, <i>J</i> = 18.8 Hz, 3H) ppm
37	 Single enantiomer	631.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.71 (s, 1H), 7.57 (s, 1H), 7.36 (t, <i>J</i> = 8.0 Hz, 1H), 7.04 (d, <i>J</i> = 7.2 Hz, 1H), 6.86 (d, <i>J</i> = 9.2 Hz, 1H), 6.81 (s, 1H), 4.47 – 4.34 (m, 2H), 4.19 – 4.00 (m, 2H), 3.33 – 3.31 (m, 1H), 2.60 (s, 3H), 2.08 – 1.98 (m, 2H), 1.89 – 1.77 (m, 2H), 1.63 (t, <i>J</i> = 18.4 Hz, 3H), 1.33 – 1.30 (m, 2H), 1.10 – 1.08 (m, 2H) ppm

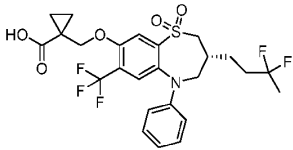
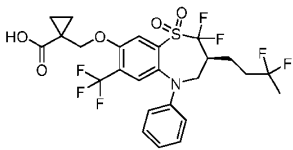
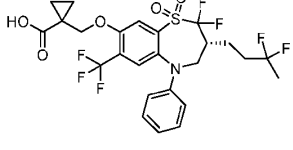
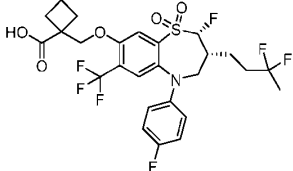
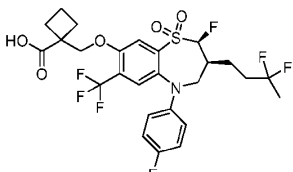
38	 Single enantiomer	597.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.67 (s, 1H), 7.52 (s, 1H), 7.17 (d, J = 9.2 Hz, 2H), 6.64 (d, J = 8.4 Hz, 2H), 4.42 – 4.34 (m, 2H), 4.11 – 3.97 (m, 2H), 3.32 – 3.31 (m, 1H), 2.60 (s, 3H), 2.06 – 1.96 (m, 2H), 1.83 – 1.80 (m, 2H), 1.33 (t, J = 4.0 Hz, 3H), 1.34 – 1.31 (m, 2H), 1.10 – 1.08 (m, 2H) ppm
39	 Single enantiomer	631.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.71 (s, 1H), 7.62 (s, 1H), 7.45 (d, J = 8.8 Hz, 2H), 6.70 (s, 2H), 4.45 – 4.36 (m, 2H), 4.20 – 4.06 (m, 2H), 3.38 – 3.33 (m, 1H), 2.58 (s, 3H), 2.11 – 2.00 (m, 2H), 1.94 – 1.75 (m, 2H), 1.64 (t, J = 18.4 Hz, 3H), 1.35 – 1.32 (m, 2H), 1.13 – 1.10 (m, 2H) ppm
40	 Single enantiomer	597.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.69 (s, 1H), 7.55 (s, 1H), 7.15 (t, J = 8.0 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.70 – 6.50 (m, 2H), 4.44 (d, J = 9.6 Hz, 1H), 4.35 (d, J = 9.6 Hz, 1H), 4.20 – 3.91 (m, 2H), 3.52 – 3.45 (m, 1H), 2.59 (s, 3H), 2.14 – 1.93 (m, 2H), 1.85 (s, 2H), 1.63 (t, J = 18.4 Hz, 3H), 1.34 (d, J = 2.8 Hz, 2H), 1.16 – 1.14 (m, 1H), 1.11 (d, J = 2.8 Hz, 2H) ppm
41a/b	 A mixture of two diastereomers	585.2	¹ H NMR (400 MHz, CD ₃ OD): 7.70 (s, 1H), 7.56 (s, 1H), 7.19 – 7.14 (m, 1H), 6.51 – 6.47 (m, 1H), 6.42 – 6.34 (m, 2H), 4.38 – 4.29 (m, 2H), 4.10 – 3.98 (m, 2H), 3.47 – 3.33 (m, 1H), 2.59 (s, 3H), 2.08 – 1.96 (m, 2H), 1.88 – 1.78 (m, 2H), 1.62 (t, J = 18.4 Hz, 3H), 1.52 (s, 3H) ppm

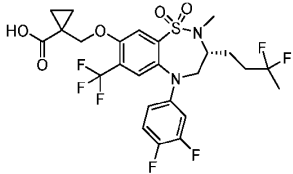
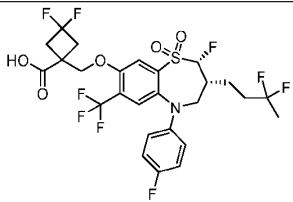
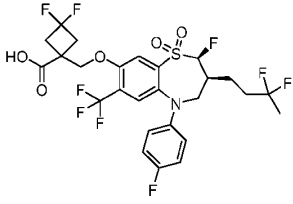
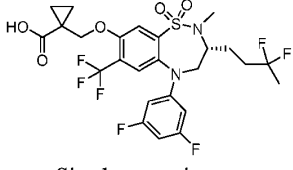
41a	 Single diastereomer with arbitrarily assigned stereochemistry of the 2-hydroxy-2-methyl-3-hydroxy-propionic acid moiety	585.2	¹ H NMR (400 MHz, CD ₃ OD): 7.70 (s, 1H), 7.56 (s, 1H), 7.19 – 7.14 (m, 1H), 6.51 – 6.34 (m, 3H), 4.38 – 4.29 (m, 2H), 4.10 – 3.99 (m, 2H), 3.32 – 3.31 (m, 1H), 2.59 (s, 3H), 2.08 – 1.98 (m, 2H), 1.86 – 1.78 (m, 2H), 1.63 (t, <i>J</i> = 18.4 Hz, 3H), 1.52 (s, 3H) ppm
41b	 Single diastereomer with arbitrarily assigned stereochemistry of the 2-hydroxy-2-methyl-3-hydroxy-propionic acid moiety	585.2	¹ H NMR (400 MHz, CD ₃ OD): 7.70 (s, 1H), 7.56 (s, 1H), 7.19 – 7.14 (m, 1H), 6.51 – 6.34 (m, 3H), 4.37 – 4.30 (m, 2H), 4.10 – 3.99 (m, 2H), 3.47 – 3.32 (m, 1H), 2.59 (s, 3H), 2.10 – 1.96 (m, 2H), 1.90 – 1.77 (m, 2H), 1.62 (t, <i>J</i> = 18.4 Hz, 3H), 1.52 (s, 3H) ppm
42a/b	 A mixture of two diastereomers	585.3	¹ H NMR (400 MHz, CD ₃ OD): δ 7.65 (s, 1H), 7.40 (s, 1H), 7.00 – 6.93 (m, 2H), 6.81 – 6.73 (m, 2H), 4.29 (dd, <i>J</i> = 23.2, 9.6 Hz, 2H), 4.06 (d, <i>J</i> = 15.6 Hz, 1H), 3.96 – 3.82 (m, 1H), 3.60 – 3.37 (m, 1H), 2.64 (s, 3H), 2.15 – 1.90 (m, 2H), 1.85 – 1.72 (m, 2H), 1.61 (t, <i>J</i> = 18.4 Hz, 3H), 1.51 (s, 3H) ppm
42a	 Single diastereomer with arbitrarily assigned stereochemistry of the 2-hydroxy-2-methyl-3-hydroxy-propionic acid moiety	585.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.65 (s, 1H), 7.40 (s, 1H), 7.00 – 6.93 (m, 2H), 6.80 – 6.73 (m, 2H), 4.29 (dd, <i>J</i> = 24.4, 9.6 Hz, 2H), 4.06 (d, <i>J</i> = 14.8 Hz, 1H), 3.95 – 3.82 (m, 1H), 3.56 – 3.35 (m, 1H), 2.64 (s, 3H), 2.15 – 1.88 (m, 2H), 1.85 – 1.72 (m, 2H), 1.61 (t, <i>J</i> = 18.4 Hz, 3H), 1.51 (s, 3H) ppm

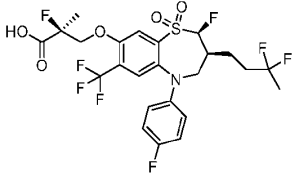
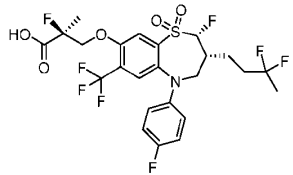
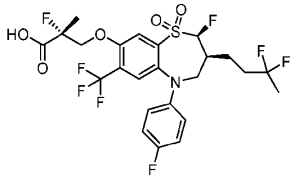
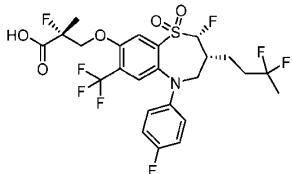
42b	 Single diastereomer with arbitrarily assigned stereochemistry of the 2-hydroxy-2-methyl-3-hydroxy-propionic acid moiety	585.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.65 (s, 1H), 7.41 (s, 1H), 7.00 – 6.93 (m, 2H), 6.80 – 6.73 (m, 2H), 4.29 (dd, <i>J</i> = 20.8, 9.2 Hz, 2H), 4.06 (d, <i>J</i> = 16.0 Hz, 1H), 3.95 – 3.82 (m, 1H), 3.60 – 3.35 (m, 1H), 2.64 (s, 3H), 2.15 – 1.88 (m, 2H), 1.85 – 1.72 (m, 2H), 1.61 (t, <i>J</i> = 18.4 Hz, 3H), 1.51 (s, 3H) ppm
43a	 Single diastereomer	569.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.67 (s, 1H), 7.56 (s, 1H), 7.19 – 7.13 (m, 1H), 6.51 – 6.47 (m, 1H), 6.42 – 6.34 (m, 2H), 4.40 – 4.36 (m, 1H), 4.30 – 4.26 (m, 1H), 4.10 – 4.02 (m, 2H), 3.47 – 3.33 (m, 1H), 2.98 – 2.93 (m, 1H), 2.59 (s, 3H), 2.10 – 1.96 (m, 2H), 1.88 – 1.78 (m, 2H), 1.62 (t, <i>J</i> = 18.4 Hz, 3H), 1.32 (d, <i>J</i> = 7.2 Hz, 3H) ppm
43b	 Single diastereomer	569.2	¹ H NMR (400 MHz, CD ₃ OD): 7.68 (s, 1H), 7.56 (s, 1H), 7.19 – 7.13 (m, 1H), 6.51 – 6.47 (m, 1H), 6.41 – 6.33 (m, 2H), 4.39 – 4.35 (m, 1H), 4.29 – 4.25 (m, 1H), 4.10 – 4.02 (m, 2H), 3.32 – 3.30 (m, 1H), 2.98 – 2.92 (m, 1H), 2.59 (s, 3H), 2.06 – 1.98 (m, 2H), 1.86 – 1.78 (m, 2H), 1.63 (t, <i>J</i> = 18.4 Hz, 3H), 1.31 (d, <i>J</i> = 7.2 Hz, 3H) ppm
44	 Single enantiomer	613.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.68 (s, 1H), 7.54 (s, 1H), 7.29 (t, <i>J</i> = 8.0 Hz, 1H), 6.96 – 6.94 (m, 1H), 6.78 – 6.76 (m, 2H), 6.56 (d, <i>J</i> = 56.4 Hz, 1H), 4.43 – 4.33 (m, 2H), 4.16 – 3.98 (m, 2H), 3.41 – 3.30 (m, 1H), 2.60 (s, 3H), 2.06 – 1.81 (m, 4H), 1.62 (t, <i>J</i>

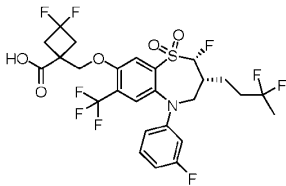
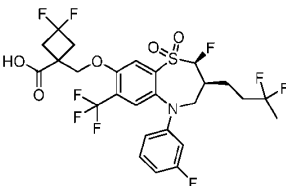
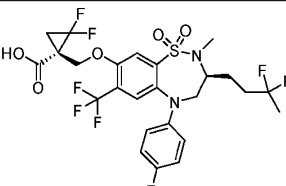
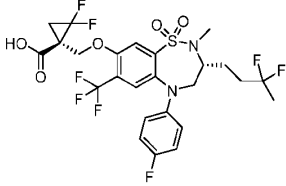
			= 18.8 Hz, 3H), 1.34 – 1.33 (m, 2H), 1.12 – 1.11 (m, 2H) ppm
45a/b	 A mixture of two diastereomers	587.1	¹ H NMR (400 MHz, CD ₃ OD): 7.70 (s, 1H), 7.57 (s, 1H), 7.20 – 7.14 (m, 1H), 6.53 – 6.36 (m, 3H), 4.63 – 4.49 (m, 2H), 4.11 – 4.01 (m, 2H), 3.47 – 3.34 (m, 1H), 2.59 (s, 3H), 2.10 – 1.93 (m, 2H), 1.90 – 1.78 (m, 2H), 1.70 – 1.58 (m, 6H) ppm
45a	 Single diastereomer with arbitrarily assigned stereochemistry of the 2-fluoro-2-methyl-3-hydroxypropionic acid moiety	587.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.70 (s, 1H), 7.58 (s, 1H), 7.22 – 7.14 (m, 1H), 6.55 – 6.47 (m, 1H), 6.47 – 6.33 (m, 2H), 4.64 – 4.48 (m, 2H), 4.15 – 3.92 (m, 2H), 3.50 – 3.32 (m, 1H), 2.60 (s, 3H), 2.15 – 1.95 (m, 2H), 1.92 – 1.72 (m, 2H), 1.68 (d, <i>J</i> = 21.2 Hz, 3H), 1.63 (t, <i>J</i> = 18.4 Hz, 3H) ppm
45b	 Single diastereomer with arbitrarily assigned stereochemistry of the 2-fluoro-2-methyl-3-hydroxypropionic acid moiety	587.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.71 (s, 1H), 7.58 (s, 1H), 7.22 – 7.14 (m, 1H), 6.55 – 6.47 (m, 1H), 6.47 – 6.33 (m, 2H), 4.65 – 4.48 (m, 2H), 4.15 – 3.92 (m, 2H), 3.50 – 3.32 (m, 1H), 2.60 (s, 3H), 2.15 – 1.92 (m, 2H), 1.92 – 1.72 (m, 2H), 1.68 (d, <i>J</i> = 20.8 Hz, 3H), 1.63 (t, <i>J</i> = 18.4 Hz, 3H) ppm
46a/b	 A mixture of two diastereomers	587.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.65 (s, 1H), 7.41 (s, 1H), 7.02 – 6.93 (m, 2H), 6.83 – 6.73 (m, 2H), 4.60 – 4.43 (m, 2H), 4.07 (d, <i>J</i> = 15.6 Hz, 1H), 3.95 – 3.82 (m, 1H), 3.60 – 3.37 (m, 1H), 2.65 (s, 3H), 2.15 – 1.90 (m, 2H), 1.87 – 1.72 (m, 2H), 1.66 (d, <i>J</i> = 20.8 Hz, 3H), 1.61 (t, <i>J</i> = 18.4 Hz, 3H) ppm

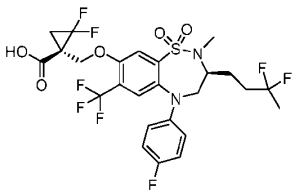
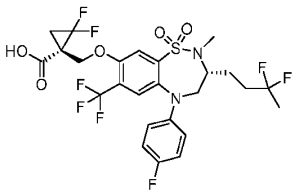
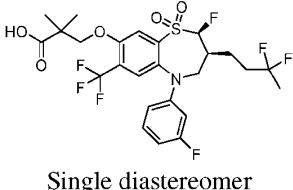
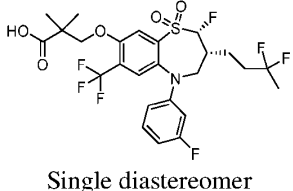
46a	 Single diastereomer with arbitrarily assigned stereochemistry of the 2-fluoro-2-methyl-3-hydroxypropionic acid moiety	587.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.65 (s, 1H), 7.41 (s, 1H), 7.02 – 6.93 (m, 2H), 6.83 – 6.74 (m, 2H), 4.60 – 4.43 (m, 2H), 4.07 (d, <i>J</i> = 14.4 Hz, 1H), 3.95 – 3.82 (m, 1H), 3.60 – 3.40 (m, 1H), 2.65 (s, 3H), 2.15 – 1.90 (m, 2H), 1.85 – 1.73 (m, 2H), 1.66 (d, <i>J</i> = 20.8 Hz, 3H), 1.61 (t, <i>J</i> = 18.4 Hz, 3H) ppm
46b	 Single diastereomer with arbitrarily assigned stereochemistry of the 2-fluoro-2-methyl-3-hydroxypropionic acid moiety	587.3	¹ H NMR (400 MHz, CD ₃ OD): δ 7.65 (s, 1H), 7.41 (s, 1H), 7.02 – 6.93 (m, 2H), 6.83 – 6.74 (m, 2H), 4.60 – 4.43 (m, 2H), 4.07 (d, <i>J</i> = 12.8 Hz, 1H), 3.97 – 3.80 (m, 1H), 3.60 – 3.40 (m, 1H), 2.65 (s, 3H), 2.15 – 1.90 (m, 2H), 1.88 – 1.72 (m, 2H), 1.66 (d, <i>J</i> = 20.8 Hz, 3H), 1.61 (t, <i>J</i> = 18.8 Hz, 3H) ppm
47	 Single diastereomer	587.2	¹ H NMR (400 MHz, CD ₃ OD): δ 8.10 (s, 1H), 7.15 (s, 1H), 6.40 (t, <i>J</i> = 8.1 Hz, 3H), 4.15 (ddd, <i>J</i> = 77.0, 39.9, 34.1 Hz, 4H), 3.48 (s, 1H), 2.85 (dd, <i>J</i> = 13.5, 6.5 Hz, 1H), 2.59 (s, 3H), 2.01 (ddd, <i>J</i> = 70.8, 39.2, 31.3 Hz, 4H), 1.63 (t, <i>J</i> = 18.5 Hz, 3H), 1.26 (d, <i>J</i> = 7.1 Hz, 3H) ppm
48a	 Single enantiomer	548.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.75 (s, 1H), 7.50 (s, 1H), 7.23 – 7.18 (m, 2H), 6.80 (t, <i>J</i> = 7.2 Hz, 1H), 6.70 (d, <i>J</i> = 8.1 Hz, 2H), 4.43 – 4.29 (m, 3H), 3.56 – 3.50 (m, 1H), 3.29 – 3.22 (m, 2H), 2.46 – 2.41 (m, 1H), 2.08 – 1.95 (m, 2H), 1.68 – 1.53 (m, 5H), 1.36 – 1.33 (m, 2H), 1.13 – 1.11 (m, 2H) ppm

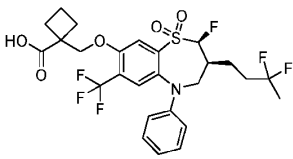
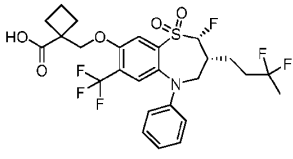
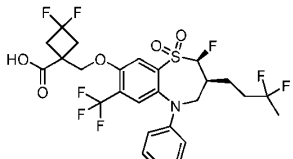
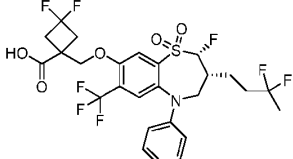
48b	 Single enantiomer	548.2	^1H NMR (300 MHz, CD_3CN): δ 7.75 (s, 1H), 7.50 (s, 1H), 7.23 – 7.18 (m, 2H), 6.80 (t, J = 7.2 Hz, 1H), 6.70 (d, J = 8.1 Hz, 2H), 4.84 – 4.29 (m, 3H), 3.56 – 3.50 (m, 1H), 3.30 – 3.19 (m, 2H), 2.46 – 2.42 (m, 1H), 2.08 – 1.95 (m, 2H), 1.68 – 1.53 (m, 5H), 1.36 – 1.32 (m, 2H), 1.12 – 1.11 (m, 2H) ppm
49a	 Single enantiomer	584.1	^1H NMR (300 MHz, CD_3CN): δ 7.79 (s, 1H), 7.65 (s, 1H), 7.30 – 7.19 (m, 2H), 6.85 (t, J = 7.2 Hz, 1H), 6.69 (d, J = 8.1 Hz, 2H), 4.37 (s, 2H), 4.33 – 4.27 (m, 1H), 3.52 – 3.38 (m, 1H), 3.03 – 2.94 (m, 1H), 2.16 – 2.10 (m, 2H), 1.75 – 1.48 (m, 5H), 1.37 – 1.30 (m, 2H), 1.13 – 1.06 (m, 2H) ppm
49b	 Single enantiomer	584.1	^1H NMR (300 MHz, CD_3CN): δ 7.79 (s, 1H), 7.65 (s, 1H), 7.27 – 7.21 (m, 2H), 6.85 (t, J = 7.2 Hz, 1H), 6.69 (d, J = 8.1 Hz, 2H), 4.37 (s, 2H), 4.34 – 4.26 (m, 1H), 3.55 – 3.28 (m, 1H), 3.09 – 2.90 (m, 1H), 2.10 – 2.02 (m, 2H), 1.80 – 1.45 (m, 5H), 1.39 – 1.23 (m, 2H), 1.15 – 1.04 (m, 2H) ppm
50a	 Single diastereomer	598.2	^1H NMR (300 MHz, CD_3OD): δ 7.82 (s, 1H), 7.55 (s, 1H), 6.97 (t, J = 8.7 Hz, 2H), 6.73 – 6.68 (m, 2H), 5.68 (d, J = 45.3 Hz, 1H), 4.50 – 4.43 (m, 2H), 4.19 (d, J = 16.2 Hz, 1H), 3.29 – 3.23 (m, 1H), 2.79 – 2.60 (m, 1H), 2.58 – 2.48 (m, 2H), 2.28 – 1.99 (m, 6H), 1.82 – 1.57 (m, 5H) ppm
50b		598.2	^1H NMR (300 MHz, CD_3OD): δ 7.82 (s, 1H), 7.55 (s, 1H), 6.97 (t, J = 8.7 Hz, 2H), 6.73 – 6.68 (m, 2H), 5.68 (d, J = 45.3 Hz, 1H), 4.50 – 4.43 (m, 2H), 4.19 (d, J = 16.2 Hz, 1H), 3.29 –

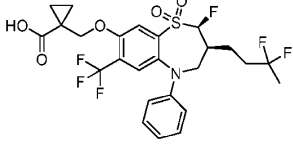
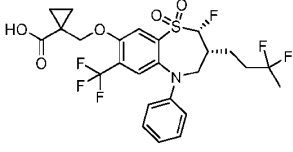
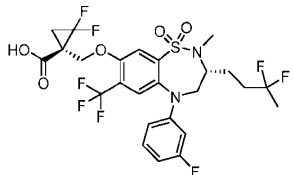
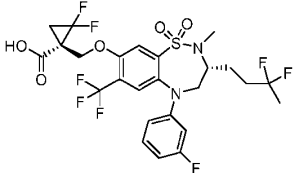
	Single diastereomer		3.23 (m, 1H), 2.78 – 2.64 (m, 1H), 2.58 – 2.48 (m, 2H), 2.27 – 2.01 (m, 6H), 1.77 – 1.57 (m, 5H) ppm
60	 Single enantiomer	599.1	¹ H NMR (400 MHz, CDCl ₃): δ 7.60 (s, 1H), 7.48 (s, 1H), 7.08 – 7.01 (m, 1H), 6.47 – 6.45 (m, 1H), 6.35 – 6.31 (m, 1H), 4.45 – 4.43 (m, 1H), 4.29 – 4.27 (m, 1H), 4.02 – 3.89 (m, 2H), 2.62 (s, 3H), 2.14 – 1.95 (m, 2H), 1.82 – 1.78 (m, 2H), 1.72 (s, 1H), 1.63 (s, 1H), 1.57 – 1.51 (m, 2H), 1.27 – 1.21 (m, 2H) ppm
61a	 Single diastereomer	634.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.83 (s, 1H), 7.56 (s, 1H), 7.00 – 6.94 (m, 2H), 6.74 – 6.69 (m, 2H), 5.69 (d, J = 45.3 Hz, 1H), 4.56 – 4.48 (m, 2H), 4.19 (d, J = 15.6 Hz, 1H), 3.28 – 3.24 (m, 1H), 3.16 – 2.90 (m, 2H), 2.86 – 2.63 (m, 3H), 2.19 – 2.03 (m, 2H), 1.77 – 1.57 (m, 5H) ppm
61b	 Single diastereomer	634.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.83 (s, 1H), 7.56 (s, 1H), 7.00 – 6.94 (m, 2H), 6.74 – 6.69 (m, 2H), 5.69 (d, J = 45.3 Hz, 1H), 4.52 – 4.48 (m, 2H), 4.19 (d, J = 15.6 Hz, 1H), 3.28 – 3.24 (m, 1H), 3.15 – 2.89 (m, 2H), 2.85 – 2.60 (m, 3H), 2.18 – 2.05 (m, 2H), 1.79 – 1.57 (m, 5H) ppm
62	 Single enantiomer	599.7	¹ H NMR (400 MHz, CDCl ₃): δ 7.61 (s, 1H), 7.53 (d, J = 8.7 Hz, 1H), 6.28 (t, J = 8.7 Hz, 1H), 6.01 (s, 2H), 4.47 (d, J = 9.6 Hz, 1H), 4.24 (d, J = 9.7 Hz, 1H), 4.12 (d, J = 7.3 Hz, 1H), 3.87 (d, J = 15.8 Hz, 1H), 3.19 (s, 1H), 2.56 (s, 3H), 2.02 (ddd, J = 24.3, 19.0, 7.6 Hz, 2H), 1.79 (d, J = 4.6 Hz, 2H), 1.66 (t, J = 18.4 Hz, 3H), 1.52 (t,

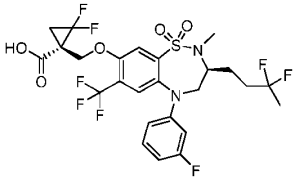
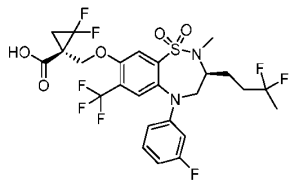
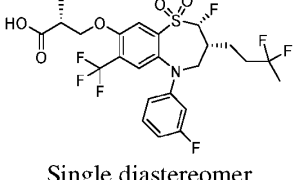
			J = 3.8 Hz, 2H), 1.22 (s, 1H), 0.93 – 0.79 (m, 1H) ppm
63a	 Single diastereomer I with arbitrarily assigned stereochemistry	590.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.83 (s, 1H), 7.57 (s, 1H), 6.99 (t, J = 8.7 Hz, 2H), 6.76 – 6.75 (m, 2H), 5.69 (d, J = 45.3 Hz, 1H), 4.61 – 4.53 (m, 2H), 4.20 (d, J = 16.2 Hz, 1H), 3.30 – 3.23 (m, 1H), 2.79 – 2.65 (m, 1H), 2.19 – 2.06 (m, 2H), 1.73 – 1.59 (m, 8H) ppm
63b	 Single diastereomer II with arbitrarily assigned stereochemistry	590.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.83 (s, 1H), 7.57 (s, 1H), 6.99 (t, J = 8.7 Hz, 2H), 6.76 – 6.75 (m, 2H), 5.69 (d, J = 45.3 Hz, 1H), 4.68 – 4.48 (m, 2H), 4.20 (d, J = 16.2 Hz, 1H), 3.15 – 3.05 (m, 1H), 2.88 – 2.65 (m, 1H), 2.19 – 2.06 (m, 2H), 1.79 – 1.59 (m, 8H) ppm,
63c	 Single diastereomer III with arbitrarily assigned stereochemistry	590.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.83 (s, 1H), 7.57 (s, 1H), 6.99 (t, J = 8.7 Hz, 2H), 6.76 – 6.75 (m, 2H), 5.69 (d, J = 45.3 Hz, 1H), 4.67 – 4.51 (m, 2H), 4.20 (d, J = 16.2 Hz, 1H), 3.37 – 3.33 (m, 1H), 2.79 – 2.65 (m, 1H), 2.19 – 2.06 (m, 2H), 1.79 – 1.55 (m, 8H) ppm
63d	 Single diastereomer IV with arbitrarily assigned stereochemistry	590.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.83 (s, 1H), 7.58 (s, 1H), 6.99 (t, J = 8.7 Hz, 2H), 6.76 – 6.75 (m, 2H), 5.69 (d, J = 45.3 Hz, 1H), 4.66 – 4.48 (m, 2H), 4.20 (d, J = 16.2 Hz, 1H), 3.27 – 3.20 (m, 1H), 2.82 – 2.65 (m, 1H), 2.16 – 2.05 (m, 2H), 1.79 – 1.59 (m, 8H) ppm

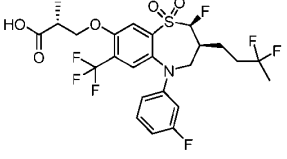
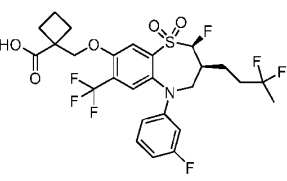
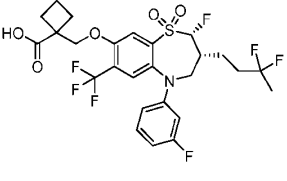
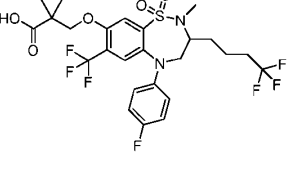
64a	 Single diastereomer	634.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.86 (s, 1H), 7.66 (s, 1H), 7.23 - 7.15 (m, 1H), 6.54 - 6.48 (m, 1H), 6.43 - 6.40 (m, 1H), 6.36 - 6.32 (m, 1H), 5.70 (d, J = 45.3 Hz, 1H), 4.54 (s, 2H), 4.19 (d, J = 15.9 Hz, 1H), 3.43 - 3.35 (m, 1H), 3.19 - 3.01 (m, 2H), 2.88 - 2.81 (m, 3H), 2.21 - 2.08 (m, 2H), 1.78 - 1.65 (m, 2H), 1.65 (t, J = 18.3 Hz, 3H) ppm
64b	 Single diastereomer	634.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.87 (s, 1H), 7.66 (s, 1H), 7.23 - 7.15 (m, 1H), 6.54 - 6.49 (m, 1H), 6.43 - 6.41 (m, 1H), 6.36 - 6.32 (m, 1H), 5.70 (d, J = 45.0 Hz, 1H), 4.54 (s, 2H), 4.20 (d, J = 16.2 Hz, 1H), 3.30 (s, 1H), 3.11 - 3.07 (m, 2H), 2.84 - 2.71 (m, 3H), 2.19 - 2.09 (m, 2H), 1.78 - 1.65 (m, 2H), 1.65 (t, J = 18.6 Hz, 3H) ppm
65a	 Single diastereomer I with arbitrarily assigned stereochemistry	615.2 [M-1] ⁻	¹ H NMR (500 MHz, CD ₃ CN): δ 7.66 (s, 1H), 7.52 (s, 1H), 7.03 - 6.93 (m, 2H), 6.80 - 6.64 (m, 2H), 4.80 (d, J = 10.3 Hz, 1H), 4.37 (d, J = 10.2 Hz, 1H), 4.01 (d, J = 16.5 Hz, 1H), 3.93 (s, 1H), 3.35 (s, 1H), 2.59 (s, 3H), 2.34 (dd, J = 12.3, 6.8 Hz, 1H), 2.07 (d, J = 16.2 Hz, 2H), 1.92 - 1.73 (m, 4H), 1.65 (t, J = 18.8 Hz, 3H) ppm
65b	 Single diastereomer II with arbitrarily assigned stereochemistry	615.2 [M-1] ⁻	¹ H NMR (500 MHz, CD ₃ CN): δ 7.67 (s, 1H), 7.53 (s, 1H), 6.98 (t, J = 8.7 Hz, 2H), 6.71 (d, J = 5.7 Hz, 2H), 4.85 (d, J = 10.4 Hz, 1H), 4.33 (d, J = 10.3 Hz, 1H), 4.00 (d, J = 16.2 Hz, 1H), 3.95 (s, 1H), 3.32 (s, 1H), 2.59 (s, 3H), 2.37 - 2.30 (m, 1H), 2.05 (s, 2H), 1.92 - 1.71 (m, 4H), 1.65 (t, J = 18.8 Hz, 3H) ppm

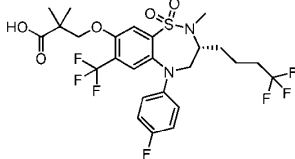
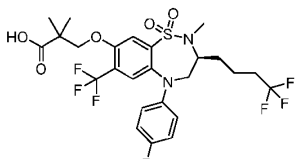
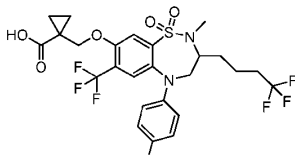
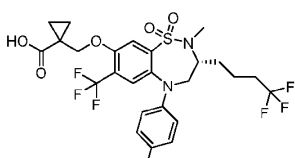
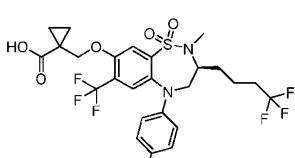
65c	 Single diastereomer III with arbitrarily assigned stereochemistry	615.2 [M-1] ⁻	¹ H NMR (500 MHz, CD ₃ CN): δ 7.67 (s, 1H), 7.53 (s, 1H), 7.01 – 6.95 (m, 2H), 6.70 (t, <i>J</i> = 6.5 Hz, 2H), 4.85 (d, <i>J</i> = 10.2 Hz, 1H), 4.34 (d, <i>J</i> = 10.3 Hz, 1H), 4.00 (d, <i>J</i> = 16.8 Hz, 1H), 3.95 (s, 1H), 3.34 (s, 1H), 2.59 (s, 3H), 2.34 (dt, <i>J</i> = 13.7, 7.4 Hz, 1H), 2.08 (s, 2H), 1.92 – 1.73 (m, 4H), 1.65 (t, <i>J</i> = 18.8 Hz, 3H) ppm
65d	 Single diastereomer IV with arbitrarily assigned stereochemistry	615.2 [M-1] ⁻	¹ H NMR (500 MHz, CD ₃ CN): δ 7.66 (s, 1H), 7.52 (s, 1H), 6.98 (t, <i>J</i> = 8.8 Hz, 2H), 6.72 (d, <i>J</i> = 7.2 Hz, 2H), 4.80 (d, <i>J</i> = 10.4 Hz, 1H), 4.37 (d, <i>J</i> = 10.2 Hz, 1H), 4.01 (d, <i>J</i> = 16.3 Hz, 1H), 3.94 (s, 1H), 3.36 (s, 1H), 2.59 (s, 3H), 2.33 (d, <i>J</i> = 11.2 Hz, 1H), 2.12 – 2.03 (m, 2H), 1.92 – 1.72 (m, 4H), 1.65 (t, <i>J</i> = 18.8 Hz, 3H) ppm
66a	 Single diastereomer	586.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.80 (s, 1H), 7.65 (s, 1H), 7.23 – 7.15 (m, 1H), 6.54 – 6.50 (m, 1H), 6.48 – 6.39 (m, 1H), 6.36 – 6.31 (m, 1H), 5.69 (d, <i>J</i> = 45.3 Hz, 1H), 4.30 – 4.22 (m, 2H), 4.16 (s, 1H), 3.30 – 3.27 (m, 1H), 3.07 – 2.65 (m, 1H), 2.22 – 2.08 (m, 2H), 1.78 – 1.73 (m, 2H), 1.65 (t, <i>J</i> = 18.6 Hz, 3H), 1.36 (s, 6H) ppm
66b	 Single diastereomer	586.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.80 (s, 1H), 7.65 (s, 1H), 7.23 – 7.15 (m, 1H), 6.54 – 6.50 (m, 1H), 6.48 – 6.39 (m, 1H), 6.36 – 6.31 (m, 1H), 5.69 (d, <i>J</i> = 45.0 Hz, 1H), 4.27 – 4.23 (m, 2H), 4.16 (s, 1H), 3.30 – 3.27 (m, 1H), 2.84 – 2.70 (m, 1H), 2.22 – 2.08 (m, 2H), 1.78 – 1.73 (m, 2H), 1.65 (t, <i>J</i> = 18.6 Hz, 3H), 1.36 (s, 6H) ppm

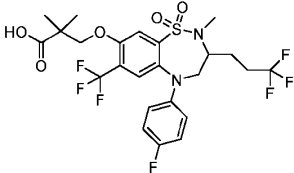
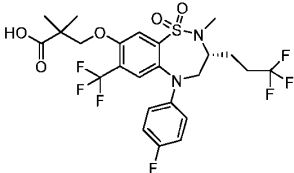
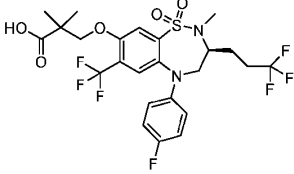
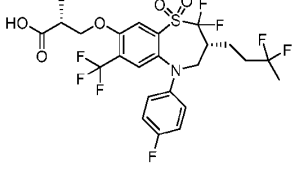
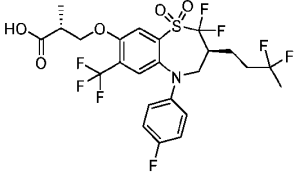
67a	 Single diastereomer	580.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.83 (s, 1H), 7.59 (s, 1H), 7.24 – 7.19 (m, 2H), 6.84 – 6.79 (m, 1H), 6.70 – 6.67 (m, 2H), 5.68 (d, J = 45.0 Hz, 1H), 4.51 – 4.43 (m, 2H), 4.24 (d, J = 15.6 Hz, 1H), 3.30 – 3.25 (m, 1H), 2.85 – 2.60 (m, 1H), 2.53 – 2.51 (m, 2H), 2.28 – 2.03 (m, 6H), 1.77 – 1.58 (m, 5H) ppm
67b	 Single diastereomer	580.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.83 (s, 1H), 7.59 (s, 1H), 7.24 – 7.19 (m, 2H), 6.84 – 6.79 (m, 1H), 6.69 – 6.67 (m, 2H), 5.68 (d, J = 45.0 Hz, 1H), 4.51 – 4.43 (m, 2H), 4.24 (d, J = 15.9 Hz, 1H), 3.30 – 3.25 (m, 1H), 2.85 – 2.60 (m, 1H), 2.52 – 2.49 (m, 2H), 2.28 – 2.03 (m, 6H), 1.77 – 1.58 (m, 5H) ppm
68a	 Single diastereomer	616.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.86 (s, 1H), 7.62 (s, 1H), 7.27 – 7.22 (m, 2H), 6.87 – 6.82 (m, 1H), 6.73 – 6.70 (m, 2H), 5.71 (d, J = 45.0 Hz, 1H), 4.59 – 4.51 (m, 2H), 4.26 (d, J = 15.4 Hz, 1H), 3.30 – 3.27 (m, 1H), 3.18 – 3.05 (m, 2H), 2.93 – 2.71 (m, 3H), 2.22 – 2.05 (m, 2H), 1.81 – 1.73 (m, 2H), 1.66 (t, J = 18.5 Hz, 3H) ppm
68b	 Single diastereomer	616.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.86 (s, 1H), 7.62 (s, 1H), 7.27 – 7.22 (m, 2H), 6.87 – 6.82 (m, 1H), 6.73 – 6.70 (m, 2H), 5.71 (d, J = 45.0 Hz, 1H), 4.59 – 4.51 (m, 2H), 4.26 (d, J = 15.3 Hz, 1H), 3.32 – 3.27 (m, 1H), 3.18 – 3.05 (m, 2H), 2.93 – 2.80 (m, 3H), 2.23 – 2.09 (m, 2H), 1.81 – 1.73 (m, 2H), 1.66 (t, J = 18.6 Hz, 3H) ppm

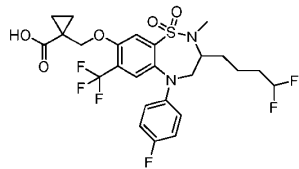
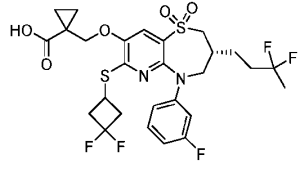
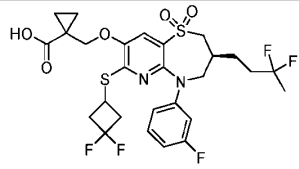
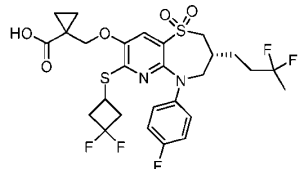
69a	 Single diastereomer	566.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.80 (s, 1H), 7.58 (s, 1H), 7.24 – 7.19 (m, 2H), 6.83 (t, J = 7.2 Hz, 1H), 6.69 – 6.66 (m, 2H), 5.74 – 5.59 (m, 1H), 4.44 – 4.40 (m, 2H), 4.23 (d, J = 15.9 Hz, 1H), 3.30 – 3.24 (m, 1H), 2.80 – 2.67 (m, 1H), 2.21 – 2.07 (m, 2H), 1.78 – 1.70 (m, 2H), 1.64 (t, J = 18.6 Hz, 3H), 1.38 – 1.34 (m, 2H), 1.16 – 1.12 (m, 2H) ppm
69b	 Single diastereomer	566.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.80 (s, 1H), 7.58 (s, 1H), 7.24 – 7.19 (m, 2H), 6.81 (t, J = 7.5 Hz, 1H), 6.78 – 6.66 (m, 2H), 5.66 (d, J = 45.3 Hz, 1H), 4.44 – 4.36 (m, 2H), 4.23 (d, J = 15.9 Hz, 1H), 3.30 – 3.24 (m, 1H), 2.69 (s, 1H), 2.21 – 2.03 (m, 2H), 1.78 – 1.70 (m, 2H), 1.64 (t, J = 18.6 Hz, 3H), 1.38 – 1.34 (m, 2H), 1.16 – 1.12 (m, 2H) ppm
70a	 Single diastereomer I with arbitrarily assigned stereochemistry	615.2 [M-H] ⁻	¹ H NMR (500 MHz, CD ₃ CN): δ 7.66 (d, J = 17.0 Hz, 2H), 7.19 (td, J = 8.3, 6.9 Hz, 1H), 6.53 (td, J = 8.4, 2.4 Hz, 1H), 6.47 – 6.32 (m, 2H), 4.83 (dd, J = 10.3, 2.4 Hz, 1H), 4.38 (d, J = 10.3 Hz, 1H), 4.00 (d, J = 17.1 Hz, 2H), 3.27 (s, 1H), 2.38 (dt, J = 12.5, 7.8 Hz, 1H), 2.05 (ddd, J = 15.7, 11.0, 5.2 Hz, 2H), 1.98 (d, J = 3.6 Hz, 3H), 1.87 (td, J = 9.2, 4.9 Hz, 2H), 1.66 (t, J = 18.8 Hz, 4H) ppm
70b		615.2 [M-1] ⁻	¹ H NMR (500 MHz, CD ₃ CN): δ 7.66 (d, J = 22.0 Hz, 2H), 7.18 (q, J = 8.0 Hz, 1H), 6.53 (td, J = 8.4, 2.3 Hz, 1H), 6.41 (t, J = 9.9 Hz, 2H), 4.80 (dd, J = 10.3, 2.4 Hz, 1H), 4.41 (d, J = 10.3 Hz, 1H), 4.01 (d, J = 19.3 Hz, 2H), 3.28 (s, 1H), 2.37 (dt, J = 12.4,

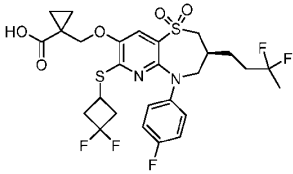
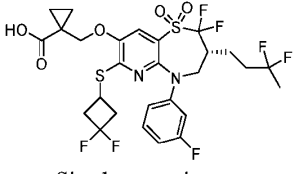
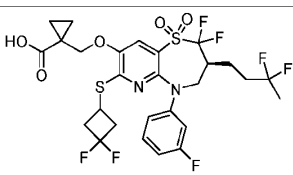
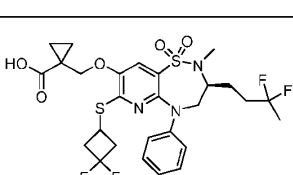
	Single diastereomer II with arbitrarily assigned stereochemistry		7.7 Hz, 1H), 2.05 (dt, $J = 11.2, 6.0$ Hz, 2H), 1.98 (d, $J = 3.4$ Hz, 3H), 1.91 – 1.80 (m, 2H), 1.66 (t, $J = 18.8$ Hz, 4H) ppm
70c	 Single diastereomer III with arbitrarily assigned stereochemistry	615.2 [M-1] ⁻	¹ H NMR (500 MHz, CD ₃ CN): δ 7.69 (s, 1H), 7.64 (s, 1H), 7.19 (td, $J = 8.2, 6.9$ Hz, 1H), 6.53 (td, $J = 8.4, 2.3$ Hz, 1H), 6.39 (dd, $J = 18.0, 10.7$ Hz, 2H), 4.87 (d, $J = 10.1$ Hz, 1H), 4.36 (d, $J = 9.9$ Hz, 1H), 4.00 (d, $J = 17.0$ Hz, 2H), 3.28 (s, 1H), 2.55 (s, 3H), 2.36 (s, 1H), 2.06 (dd, $J = 10.6, 5.4$ Hz, 2H), 1.98 (d, $J = 3.6$ Hz, 3H), 1.66 (t, $J = 18.9$ Hz, 4H) ppm
70d	 Single diastereomer IV with arbitrarily assigned stereochemistry	615.2 [M-1] ⁻	¹ H NMR (500 MHz, CD ₃ CN): δ 7.68 (s, 1H), 7.64 (s, 1H), 7.19 (td, $J = 8.3, 5.7$ Hz, 1H), 6.53 (td, $J = 8.5, 8.1, 2.3$ Hz, 1H), 6.40 (d, $J = 13.0$ Hz, 2H), 4.78 (dd, $J = 10.4, 2.4$ Hz, 1H), 4.42 (d, $J = 10.3$ Hz, 1H), 4.01 (d, $J = 18.6$ Hz, 2H), 3.28 (s, 1H), 2.55 (s, 3H), 2.38 (dt, $J = 12.5, 7.7$ Hz, 1H), 2.05 (ddd, $J = 15.7, 10.7, 4.9$ Hz, 2H), 1.98 (d, $J = 3.6$ Hz, 3H), 1.66 (t, $J = 18.8$ Hz, 4H) ppm
80a	 Single diastereomer	572.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.82 (s, 1H), 7.64 (s, 1H), 7.22 – 7.15 (m, 1H), 6.53 – 6.50 (m, 1H), 6.48 – 6.31 (m, 2H), 5.69 (d, $J = 45.0$ Hz, 1H), 4.44 – 4.41 (m, 1H), 4.39 – 4.29 (m, 1H), 4.24 (d, $J = 18.3$ Hz, 1H), 3.29 (s, 1H), 2.97 – 2.92 (m, 1H), 2.85 – 2.69 (m, 1H), 2.24 – 2.11 (m, 2H), 1.78 – 1.71 (m, 2H), 1.64 (d, $J = 18.6$ Hz, 3H), 1.35 (d, $J = 7.2$ Hz, 3H) ppm

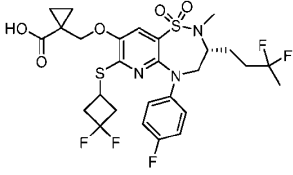
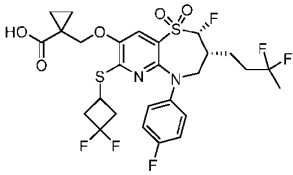
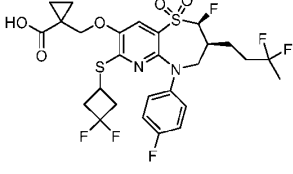
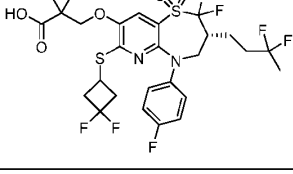
80b	 Single diastereomer	572.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.83 (s, 1H), 7.64 (s, 1H), 7.22 – 7.14 (m, 1H), 6.53 – 6.50 (m, 1H), 6.46 – 6.30 (m, 2H), 5.68 (d, J = 45.0 Hz, 1H), 4.49 – 4.41 (m, 1H), 4.25 – 4.16 (m, 2H), 3.29 (s, 1H), 2.91 – 2.86 (m, 1H), 2.85 – 2.69 (m, 1H), 2.19 – 2.08 (m, 2H), 1.78 – 1.71 (m, 2H), 1.64 (d, J = 18.6 Hz, 3H), 1.34 (d, J = 7.2 Hz, 3H) ppm
81a	 Single diastereomer	598.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.86 (s, 1H), 7.65 (s, 1H), 7.23 – 7.15 (m, 1H), 6.54 – 6.48 (m, 1H), 6.43 – 6.31 (m, 2H), 5.70 (d, J = 45.0 Hz, 1H), 4.52 – 4.45 (m, 2H), 4.22 – 4.17 (m, 1H), 3.36 – 3.32 (m, 1H), 2.92 – 2.67 (m, 1H), 2.55 – 2.49 (m, 2H), 2.26 – 2.06 (m, 6H), 1.78 – 1.59 (m, 5H) ppm
81b	 Single diastereomer	598.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.86 (s, 1H), 7.65 (s, 1H), 7.23 – 7.15 (m, 1H), 6.54 – 6.50 (m, 1H), 6.43 – 6.32 (m, 2H), 5.70 (d, J = 45.0 Hz, 1H), 4.52 – 4.45 (m, 2H), 4.19 (d, J = 16.2 Hz, 1H), 3.36 – 3.32 (m, 1H), 2.90 – 2.66 (m, 1H), 2.55 – 2.49 (m, 2H), 2.26 – 2.03 (m, 6H), 1.78 – 1.59 (m, 5H) ppm
82a/b		601.2	¹ H NMR (500 MHz, d ₆ -DMSO): δ 12.47 (s, 1H), 7.54 (s, 1H), 7.50 (s, 1H), 7.01 (t, J = 8.9 Hz, 2H), 6.66 (d, J = 8.4 Hz, 2H), 4.19 (s, 2H), 4.02 (d, J = 16.2 Hz, 1H), 3.80 (s, 1H), 3.26 (s, 1H), 2.54 (s, 3H), 2.27 (s, 2H), 1.61 (dd, J = 46.3, 9.8 Hz, 4H), 1.23 (s, 6H) ppm

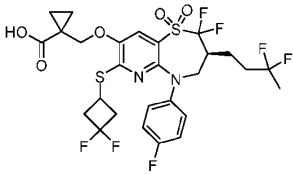
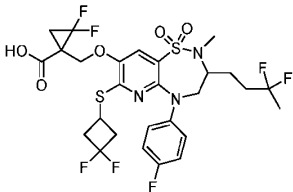
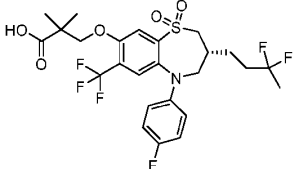
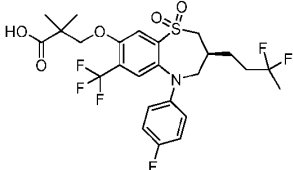
82a	 Single enantiomer with arbitrarily assigned stereochemistry	601.2	¹ H NMR (500 MHz, d ₆ -DMSO): δ 12.47 (s, 1H), 7.54 (s, 1H), 7.50 (s, 1H), 7.06 – 6.95 (m, 2H), 6.67 (s, 2H), 4.19 (s, 2H), 4.02 (d, <i>J</i> = 16.2 Hz, 1H), 3.80 (s, 1H), 3.36 (s, 1H), 2.54 (s, 3H), 2.27 (s, 2H), 1.63 (d, <i>J</i> = 47.5 Hz, 4H), 1.23 (s, 6H) ppm
82b	 Single enantiomer with arbitrarily assigned stereochemistry	601.2	¹ H NMR (500 MHz, d ₆ -DMSO): δ 12.47 (s, 1H), 7.54 (s, 1H), 7.50 (s, 1H), 7.01 (t, <i>J</i> = 8.6 Hz, 2H), 6.67 (s, 2H), 4.19 (s, 2H), 4.03 (d, <i>J</i> = 16.2 Hz, 1H), 3.80 (s, 1H), 3.36 (s, 1H), 2.54 (s, 3H), 2.27 (s, 2H), 1.72 – 1.49 (m, 4H), 1.23 (s, 6H) ppm
83a/b		597.2 [M-1] ⁻	¹ H NMR (500 MHz, d ₆ -DMSO): δ 12.45 (s, 1H), 7.54 (s, 1H), 7.49 (s, 1H), 7.01 (t, <i>J</i> = 8.7 Hz, 2H), 6.66 (s, 2H), 4.40 – 4.26 (m, 2H), 4.02 (d, <i>J</i> = 16.2 Hz, 1H), 3.80 (s, 1H), 3.20 (s, 1H), 2.53 (s, 3H), 2.28 (s, 2H), 1.73 – 1.47 (m, 4H), 1.20 (q, <i>J</i> = 3.7 Hz, 2H), 1.04 (q, <i>J</i> = 3.6 Hz, 2H) ppm
83a	 Single enantiomer with arbitrarily assigned stereochemistry	597.0 [M-1] ⁻	¹ H NMR (500 MHz, d ₆ -DMSO): δ 12.45 (s, 1H), 7.54 (s, 1H), 7.49 (s, 1H), 7.01 (t, <i>J</i> = 8.7 Hz, 2H), 6.65 (d, <i>J</i> = 8.5 Hz, 2H), 4.39 – 4.27 (m, 2H), 4.02 (d, <i>J</i> = 16.2 Hz, 1H), 3.80 (s, 1H), 3.37 (s, 1H), 2.54 (s, 3H), 2.28 (s, 2H), 1.73 – 1.48 (m, 4H), 1.20 (q, <i>J</i> = 3.7 Hz, 2H), 1.04 (q, <i>J</i> = 3.6 Hz, 2H) ppm
83b		597.0 [M-1] ⁻	¹ H NMR (500 MHz, d ₆ -DMSO): δ 12.46 (s, 1H), 7.54 (s, 1H), 7.49 (s, 1H), 7.01 (t, <i>J</i> = 8.5 Hz, 2H), 6.66 (s, 2H), 4.41 – 4.22 (m, 2H), 4.02 (d, <i>J</i> = 16.0 Hz, 1H), 3.80 (s, 1H), 3.36 (s, 1H), 2.53 (s, 3H), 2.27 (s, 2H), 1.62 (d,

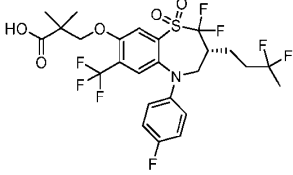
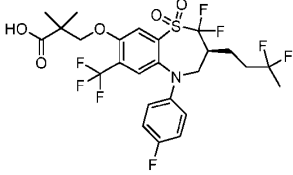
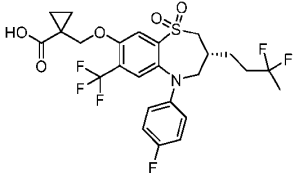
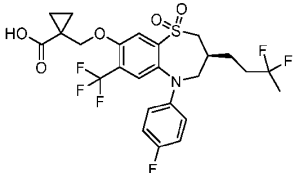
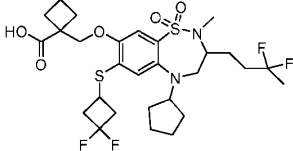
	Single enantiomer with arbitrarily assigned stereochemistry		$J = 49.7$ Hz, 4H), 1.19 (q, $J = 3.8$, 3.3 Hz, 2H), 1.04 (t, $J = 3.4$ Hz, 2H) ppm
84a/b		587.2	^1H NMR (500 MHz, CD_3CN): δ 7.61 (s, 1H), 7.52 (s, 1H), 6.99 (t, $J = 8.8$ Hz, 2H), 6.72 (dd, $J = 9.1$, 4.5 Hz, 2H), 4.26 – 4.18 (m, 2H), 3.99 (s, 2H), 3.43 (d, $J = 34.7$ Hz, 1H), 2.60 (s, 3H), 2.37 (dq, $J = 21.6$, 10.8, 5.5 Hz, 2H), 1.90 – 1.76 (m, 2H), 1.32 (d, $J = 2.3$ Hz, 6H) ppm
84a	 Single enantiomer with arbitrarily assigned stereochemistry	587.2	^1H NMR (500 MHz, CD_3CN): δ 7.61 (s, 1H), 7.52 (s, 1H), 6.99 (t, $J = 8.7$ Hz, 2H), 6.72 (dd, $J = 9.2$, 4.6 Hz, 2H), 4.26 – 4.18 (m, 2H), 3.98 (s, 2H), 3.47 (d, $J = 82.4$ Hz, 1H), 2.60 (s, 3H), 2.37 (dtp, $J = 21.3$, 10.3, 6.1, 5.3 Hz, 2H), 1.92 – 1.80 (m, 2H), 1.32 (d, $J = 2.2$ Hz, 6H) ppm
84b	 Single enantiomer with arbitrarily assigned stereochemistry	587.2	^1H NMR (500 MHz, CD_3CN): δ 7.62 (s, 1H), 7.52 (s, 1H), 6.99 (t, $J = 8.8$ Hz, 2H), 6.72 (dd, $J = 9.2$, 4.5 Hz, 2H), 4.26 – 4.16 (m, 2H), 3.99 (s, 2H), 3.40 (s, 1H), 2.36 (ddq, $J = 19.8$, 8.9, 5.7, 4.6 Hz, 2H), 1.92 – 1.76 (m, 2H), 1.32 (d, $J = 2.3$ Hz, 6H) ppm
85a	 Single diastereomer	590.2	^1H NMR (400 MHz, CD_3OD): δ 7.82 (s, 1H), 7.52 (s, 1H), 7.00 (t, $J = 8.8$ Hz, 2H), 6.78 (s, 2H), 4.41 – 4.37 (m, 1H), 4.34 – 4.31 (m, 2H), 3.57 – 3.47 (m, 1H), 2.97 – 2.94 (m, 2H), 2.17 – 1.93 (m, 3H), 1.60 (t, $J = 18.4$ Hz, 4H), 1.33 (d, $J = 7.2$ Hz, 3H) ppm
85b		590.2	^1H NMR (400 MHz, CD_3OD): δ 7.82 (s, 1H), 7.52 (s, 1H), 7.01 (t, $J = 8.8$ Hz, 2H), 6.78 (s, 2H), 4.42 – 4.38 (m, 1H), 4.33 – 4.30 (m, 2H), 3.65 – 3.51 (m, 1H), 2.99 – 2.89 (m, 2H), 2.22 –

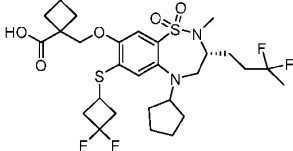
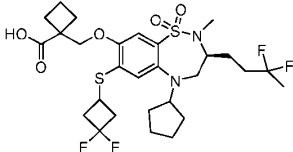
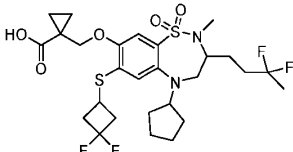
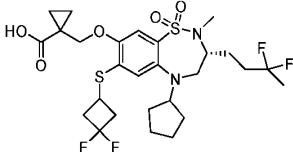
	Single diastereomer		1.93 (m, 3H), 1.60 (t, $J = 18.4$ Hz, 4H), 1.3 (d, $J = 7.2$ Hz, 3H) ppm
86		579.2 [M-1] ⁻	¹ H NMR (500 MHz, CD ₃ CN): δ 7.62 (s, 1H), 7.53 (s, 1H), 7.01 – 6.95 (m, 2H), 6.67 (dd, $J = 9.2, 4.5$ Hz, 2H), 5.95 (tt, $J = 56.9, 4.4$ Hz, 1H), 4.39 (d, $J = 9.9$ Hz, 1H), 4.30 (d, $J = 9.9$ Hz, 1H), 3.97 (d, $J = 17.4$ Hz, 3H), 3.29 (s, 1H), 2.57 (s, 3H), 1.89 (dd, $J = 8.3, 4.3$ Hz, 2H), 1.63 (d, $J = 5.4$ Hz, 3H), 1.59 – 1.52 (m, 1H), 1.34 (d, $J = 3.9$ Hz, 2H), 1.10 (q, $J = 4.5$ Hz, 2H) ppm
87a	 Single enantiomer	621.2	¹ H NMR (300 MHz, DMSO-d ₆): δ 12.49 – 12.44 (m, 1H), 7.59 (s, 1H), 7.25 (q, $J = 6.9$ Hz, 1H), 6.72 – 6.66 (m, 3H), 4.29 – 4.21 (m, 3H), 3.66 (d, $J = 10.5$ Hz, 2H), 3.45 – 3.36 (m, 3H), 2.94 – 2.83 (m, 1H), 2.80 – 2.67 (m, 2H), 2.33 – 2.28 (m, 1H), 2.10 – 2.02 (m, 2H), 1.63 – 1.51 (m, 5H), 1.22 (s, 2H), 1.05 (s, 2H) ppm
87b	 Single enantiomer	621.2	¹ H NMR (300 MHz, DMSO-d ₆): δ 7.58 (s, 1H), 7.25 (q, $J = 7.8$ Hz, 1H), 6.76 – 6.65 (m, 3H), 4.32 – 4.19 (m, 3H), 3.66 (d, $J = 11.1$ Hz, 2H), 3.45 – 3.39 (m, 3H), 2.89 – 2.83 (m, 1H), 2.73 – 2.59 (m, 2H), 2.33 – 2.28 (m, 1H), 2.10 – 1.94 (m, 2H), 1.63 – 1.47 (m, 5H), 1.21 (s, 2H), 1.04 (s, 2H) ppm
88a	 Single enantiomer	621.2	¹ H NMR (300 MHz, CD ₃ CN): δ 7.45 (s, 1H), 7.02 – 7.00 (m, 4H), 4.13 – 4.04 (m, 3H), 3.56 (dd, $J = 15.3, 7.5$ Hz, 1H), 3.45 – 3.38 (m, 2H), 3.18 (dd, $J = 14.7, 9.9$ Hz, 1H), 2.56 – 2.43 (m, 1H), 2.42 – 2.41 (m, 1H), 2.39 – 2.21 (m, 3H), 1.87 – 1.74 (m,

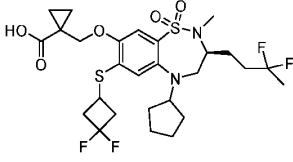
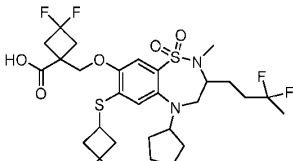
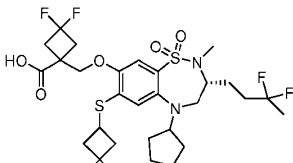
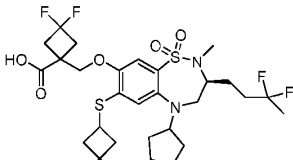
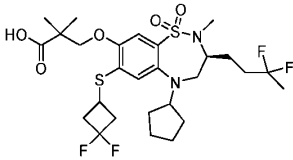
			2H), 1.53 – 1.36 (m, 5H), 1.23 – 1.18 (m, 2H), 0.97 – 0.94 (m, 2H) ppm
88b	 Single enantiomer	621.1	¹ H NMR (300 MHz, CD ₃ CN): δ 7.57 (s, 1H), 7.14 – 7.11 (m, 4H), 4.23 – 4.16 (m, 3H), 3.58 (dd, J = 15.3, 7.5 Hz, 1H), 3.51 – 3.34 (m, 2H), 3.28 (dd, J = 14.7, 9.9 Hz, 1H), 2.76 – 2.64 (m, 1H), 2.61 – 2.55 (m, 1H), 2.51 – 2.45 (m, 3H), 1.98 – 1.86 (m, 2H), 1.65 – 1.48 (m, 5H), 1.33 – 1.30 (m, 2H), 1.07 – 1.06 (m, 2H) ppm
89a	 Single enantiomer	657.1	¹ H NMR (400 MHz, CDCl ₃): δ 7.61 (s, 1H), 7.32 (t, J = 8.0 Hz, 1H), 6.81 (t, J = 8.4 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 6.65 (d, J = 10.8 Hz, 1H), 4.33 – 4.29 (m, 2H), 4.14 (d, J = 15.2 Hz, 1H), 3.74 – 3.62 (m, 2H), 2.93 (s, 1H), 2.87 – 2.65 (m, 2H), 2.54 – 2.32 (m, 2H), 2.12 – 1.97 (m, 3H), 1.70 – 1.58 (m, 6H), 1.28 (s, 2H) ppm
89b	 Single enantiomer	657.1	¹ H NMR (400 MHz, CDCl ₃): δ 7.61 (s, 1H), 7.32 (t, J = 8.0 Hz, 1H), 6.81 (t, J = 8.4 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 6.65 (d, J = 10.8 Hz, 1H), 4.28 dd, J = 24.8, 10.0 Hz, 2H), 4.14 (d, J = 16.4 Hz, 1H), 3.74 – 3.62 (m, 2H), 2.92 (s, 1H), 2.77 – 2.64 (m, 2H), 2.52 – 2.36 (m, 2H), 2.10 – 1.97 (m, 3H), 1.70 – 1.56 (m, 6H), 1.22 (s, 2H) ppm
90a	 Single enantiomer	634.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ 12.39 (s, 1H), 7.41 (s, 1H), 7.17 (d, J = 6.7 Hz, 4H), 4.19 – 4.11 (m, 2H), 4.11 – 3.92 (m, 2H), 3.67 (s, 1H), 3.35 (s, 1H), 2.82 (s, 3H), 2.47 – 2.36 (m, 4H), 1.98 (d, J = 13.8 Hz, 2H), 1.76 (s, 1H), 1.59 (t, J = 19.0 Hz, 4H), 1.17 (q, J = 3.9 Hz, 2H), 1.00 (q, J = 4.1 Hz, 2H) ppm

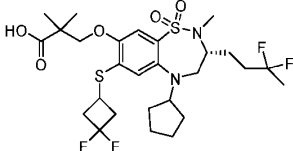
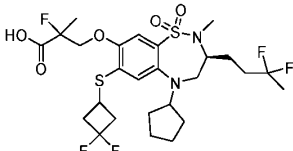
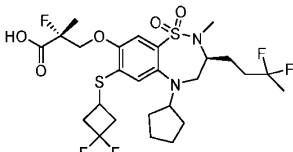
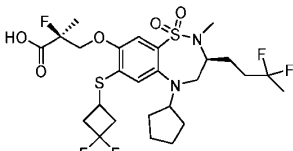
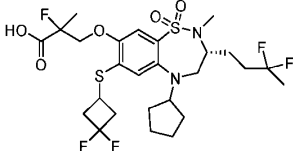
90b	 Single enantiomer	634.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ 12.39 (s, 1H), 7.41 (s, 1H), 7.17 (d, <i>J</i> = 6.8 Hz, 4H), 4.19 – 4.11 (m, 2H), 4.02 (t, <i>J</i> = 18.1 Hz, 2H), 3.67 (s, 1H), 3.35 (s, 1H), 2.82 (s, 3H), 2.47 – 2.37 (m, 4H), 1.99 (dd, <i>J</i> = 16.1, 8.1 Hz, 2H), 1.76 (s, 1H), 1.59 (t, <i>J</i> = 18.9 Hz, 4H), 1.17 (q, <i>J</i> = 3.9 Hz, 2H), 1.00 (q, <i>J</i> = 3.9 Hz, 2H) ppm
91a	 Single diastereomer I with arbitrarily assigned stereochemistry of the 3-(3,3-difluorobutyl)-2-fluoro-2,3,4,5-tetrahydropyrido[3,2-b][1,4]thiazepine 1,1-dioxide moiety	639.1	¹ H NMR (300 MHz, CDCl ₃): δ 7.58 (s, 1H), 7.28 – 7.05 (m, 4H), 5.31 (d, <i>J</i> = 46.8 Hz, 1H), 4.30 (d, <i>J</i> = 9.9 Hz, 1H), 4.21 (d, <i>J</i> = 9.9 Hz, 1H), 3.93 (d, <i>J</i> = 13.8 Hz, 1H), 3.55 – 3.47 (m, 2H), 2.86 – 2.70 (m, 2H), 2.54 – 2.20 (m, 3H), 2.06 – 1.80 (m, 2H), 1.78 – 1.54 (m, 5H), 1.53 – 1.51 (m, 2H), 1.21 – 1.16 (m, 2H) ppm
91b	 Single diastereomer II with arbitrarily assigned stereochemistry of the 3-(3,3-difluorobutyl)-2-fluoro-2,3,4,5-tetrahydropyrido[3,2-b][1,4]thiazepine 1,1-dioxide moiety	639.1	¹ H NMR (300 MHz, CDCl ₃): δ 7.58 (s, 1H), 7.28 – 7.05 (m, 4H), 5.31 (d, <i>J</i> = 46.8 Hz, 1H), 4.30 (d, <i>J</i> = 9.9 Hz, 1H), 4.21 (d, <i>J</i> = 9.9 Hz, 1H), 3.93 (d, <i>J</i> = 14.1 Hz, 1H), 3.55 – 3.47 (m, 2H), 2.89 – 2.70 (m, 2H), 2.58 – 2.20 (m, 3H), 2.16 – 1.91 (m, 2H), 1.83 – 1.54 (m, 5H), 1.53 – 1.47 (m, 2H), 1.21 – 1.20 (m, 2H) ppm
92a		657.1	¹ H NMR (300 MHz, CDCl ₃): δ 7.57 (s, 1H), 7.20 (d, <i>J</i> = 46.8 Hz, 4H), 4.27 (s, 2H), 4.08 (d, <i>J</i> = 14.7 Hz, 1H), 3.93 – 3.85 (m, 1H), 3.45 – 3.40 (m, 1H), 2.84 – 2.76 (m, 1H), 2.60 – 2.27 (m,

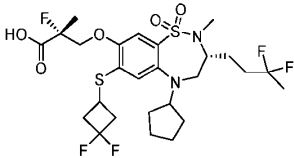
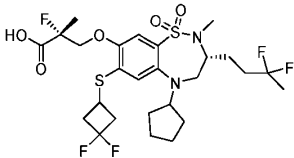
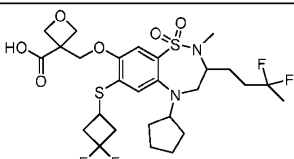
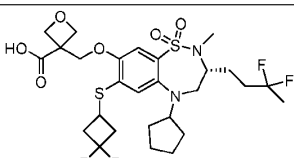
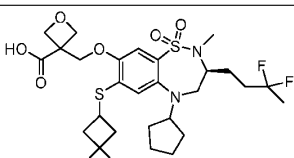
	Single enantiomer		4H), 2.07 – 1.90 (m, 3H), 1.80 – 1.72 (m, 1H), 1.69 – 1.53 (m, 5H), 1.21 – 1.14 (m, 2H) ppm
92b	 Single enantiomer	657.1	¹ H NMR (300 MHz, CDCl ₃): δ 7.57 (s, 1H), 7.20 (d, J = 46.8 Hz, 4H), 4.24 (s, 2H), 4.08 (d, J = 14.4 Hz, 1H), 3.93 – 3.85 (m, 1H), 3.42 (s, 1H), 2.85 – 2.80 (m, 1H), 2.66 – 2.31 (m, 4H), 2.10 – 1.90 (m, 3H), 1.80 – 1.69 (m, 1H), 1.65 – 1.53 (m, 5H), 1.23 – 1.17 (m, 2H) ppm
93		670.2 [M-1] ⁺	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆): δ 13.44 (s, 1H), 7.50 (d, J = 3.4 Hz, 1H), 7.19 (t, J = 7.4 Hz, 4H), 4.54 (dd, J = 28.5, 10.3 Hz, 1H), 4.20 (dd, J = 25.8, 10.3 Hz, 1H), 4.11 (s, 1H), 4.01 (s, 1H), 3.67 (s, 1H), 3.25 (s, 1H), 2.83 (d, J = 6.4 Hz, 3H), 2.52 (d, J = 7.8 Hz, 1H), 2.46 – 2.30 (m, 3H), 2.29 – 2.24 (m, 1H), 2.11 – 2.03 (m, 1H), 2.04 – 1.92 (m, 2H), 1.76 (s, 1H), 1.59 (t, J = 18.9 Hz, 4H) ppm
94a	 Single enantiomer	568.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.74 (s, 1H), 7.48 (s, 1H), 6.98 (t, J = 8.8 Hz, 2H), 6.76 – 6.72 (m, 2H), 4.31 – 4.23 (m, 3H), 3.56 (dd, J = 19.2, 3.2 Hz, 1H), 3.32 – 3.17 (m, 2H), 2.45 – 2.42 (m, 1H), 2.11 – 1.96 (m, 2H), 1.71 – 1.61 (m, 5H), 1.36 (s, 6H) ppm
94b	 Single enantiomer	568.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.74 (s, 1H), 7.48 (s, 1H), 6.98 (t, J = 8.8 Hz, 2H), 6.76 – 6.73 (m, 2H), 4.31 – 4.23 (m, 3H), 3.56 (d, J = 19.6 Hz, 1H), 3.32 – 3.23 (m, 2H), 2.43 – 2.41 (m, 1H), 2.12 – 1.95 (m, 2H), 1.69 – 1.55 (m, 5H), 1.36 (s, 6H) ppm

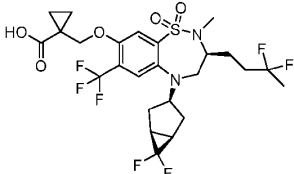
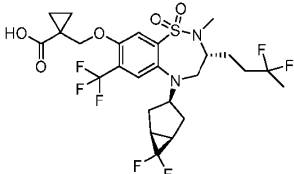
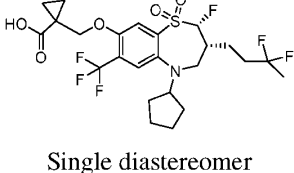
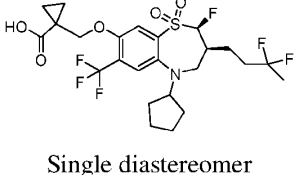
95a	 Single enantiomer	602.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.81 (s, 1H), 7.52 (s, 1H), 7.04 – 6.98 (m, 2H), 6.90 – 6.70 (m, 2H), 4.30 – 4.22 (m, 3H), 3.56 – 3.54 (m, 1H), 2.97 – 2.86 (m, 1H), 2.20 – 2.03 (m, 2H), 1.98 – 1.94 (m, 1H), 1.66 – 1.54 (m, 4H), 1.34 (s, 6H) ppm
95b	 Single enantiomer	602.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.81 (s, 1H), 7.52 (s, 1H), 7.04 – 6.98 (m, 2H), 6.85 – 6.70 (m, 2H), 4.30 – 4.22 (m, 3H), 3.56 – 3.53 (m, 1H), 2.97 – 2.91 (m, 1H), 2.16 – 1.94 (m, 3H), 1.66 – 1.54 (m, 4H), 1.35 (s, 6H) ppm
96a	 Single enantiomer	566.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.74 (s, 1H), 7.45 (s, 1H), 6.96 (t, J = 8.4 Hz, 2H), 6.73 (t, J = 4.0 Hz, 2H), 4.37 (dd, J = 12.0, 22.0 Hz, 2H), 4.26 (d, J = 16.4 Hz, 1H), 3.55 – 3.48 (m, 1H), 3.30 – 3.13 (m, 2H), 2.41 – 2.39 (m, 1H), 2.07 – 1.95 (m, 2H), 1.70 – 1.59 (m, 5H), 1.37 (q, J = 4.0 Hz, 2H), 1.15 (q, J = 4.0 Hz, 2H) ppm
96b	 Single enantiomer	566.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.74 (s, 1H), 7.45 (s, 1H), 6.96 (t, J = 8.4 Hz, 2H), 6.73 (t, J = 4.0 Hz, 2H), 4.37 (dd, J = 12.0, 22.0 Hz, 2H), 4.25 (d, J = 15.6 Hz, 1H), 3.55 – 3.48 (m, 1H), 3.30 – 3.13 (m, 2H), 2.41 – 2.39 (m, 1H), 2.07 – 1.95 (m, 2H), 1.70 – 1.54 (m, 5H), 1.38 (q, J = 4.0 Hz, 2H), 1.15 (q, J = 4.0 Hz, 2H) ppm
97a/b		623.2	¹ H NMR (500 MHz, CD ₃ CN): δ 7.30 (s, 1H), 6.77 (s, 1H), 4.28 (s, 2H), 3.93 (d, J = 8.7 Hz, 1H), 3.83 (dtd, J = 8.7, 5.8, 2.9 Hz, 1H), 3.28 – 3.11 (m, 4H), 2.61 (dtd, J = 17.9, 13.3, 5.9 Hz, 4H), 2.54 – 2.43 (m, 3H), 2.17 – 1.99 (m, 8H), 1.93 (s, 2H), 1.78 – 1.70 (m, 3H),

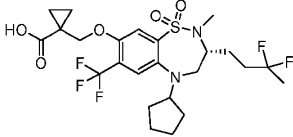
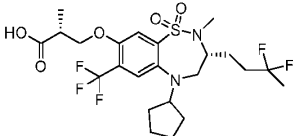
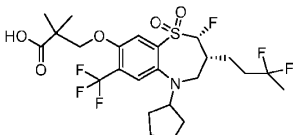
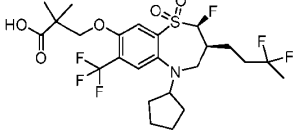
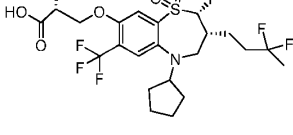
			1.65 (t, $J = 18.8$ Hz, 5H), 1.54 (s, 2H) ppm
97a	 Single enantiomer	623.2	^1H NMR (500 MHz, DMSO- d_6): δ 12.43 (s, 1H), 7.18 (s, 1H), 6.65 (s, 1H), 4.19 (s, 2H), 3.91 (s, 2H), 3.64 (s, 1H), 3.19 (q, $J = 16.9, 13.7$ Hz, 3H), 2.58 (q, $J = 19.0$ Hz, 3H), 2.41 – 2.27 (m, 3H), 2.07 – 1.91 (m, 6H), 1.85 (dq, $J = 10.6, 5.1, 4.6$ Hz, 2H), 1.62 (t, $J = 18.9$ Hz, 8H), 1.46 (s, 3H) ppm
97b	 Single enantiomer	623.2	^1H NMR (500 MHz, DMSO- d_6): δ 12.41 (s, 1H), 7.18 (s, 1H), 6.65 (s, 1H), 4.19 (s, 2H), 3.91 (q, $J = 8.5, 7.0$ Hz, 2H), 3.19 (d, $J = 36.7$ Hz, 3H), 2.65 – 2.53 (m, 4H), 2.35 (td, $J = 9.9, 8.7, 5.9$ Hz, 3H), 2.14 – 1.90 (m, 7H), 1.85 (tt, $J = 10.4, 4.8$ Hz, 2H), 1.77 – 1.31 (m, 12H) ppm
98a/b		607.2 [M-1] ⁻	^1H NMR (500 MHz, DMSO- d_6): δ 12.40 (s, 1H), 7.12 (s, 1H), 6.66 (s, 1H), 4.07 (d, $J = 11.1$ Hz, 2H), 3.91 (s, 2H), 3.62 (s, 1H), 3.30 (s, 37H), 3.19 (d, $J = 11.4$ Hz, 2H), 2.61 (d, $J = 10.5$ Hz, 3H), 2.52 (s, 3H), 2.05 – 1.90 (m, 3H), 1.85 (s, 1H), 1.62 (t, $J = 18.9$ Hz, 8H), 1.45 (d, $J = 16.2$ Hz, 3H), 1.16 (d, $J = 3.0$ Hz, 2H), 1.01 (d, $J = 2.9$ Hz, 2H) ppm
98a	 Single enantiomer	607.2 [M-1] ⁻	^1H NMR (500 MHz, CD ₃ CN): δ 7.24 (s, 1H), 6.77 (s, 1H), 4.18 (d, $J = 9.0$ Hz, 1H), 4.10 (d, $J = 9.8$ Hz, 1H), 3.93 (s, 1H), 3.85 (dq, $J = 6.0, 4.2, 2.9$ Hz, 1H), 3.29 – 3.16 (m, 3H), 2.62 (ddt, $J = 18.6, 13.3, 6.5$ Hz, 6H), 2.08 – 1.99 (m, 4H), 1.67 (q, $J = 18.8, 18.1$ Hz, 10H), 1.54 (s, 2H), 1.29 (dt, $J = 5.0, 2.6$ Hz, 2H), 1.06 (t, $J = 3.8$ Hz, 2H) ppm

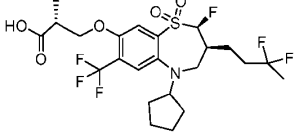
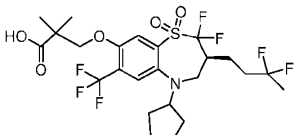
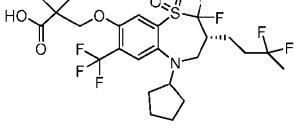
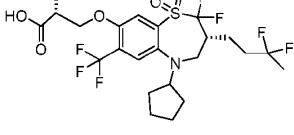
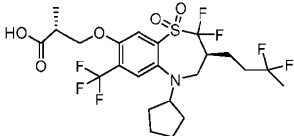
98b	 Single enantiomer	607.2 [M-1] ⁺	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆): δ 7.12 (s, 1H), 6.66 (s, 1H), 4.13 – 4.05 (m, 2H), 3.96 – 3.88 (m, 2H), 3.50 (d, <i>J</i> = 16.0 Hz, 2H), 3.20 (s, 3H), 2.60 (s, 6H), 2.04 – 1.89 (m, 3H), 1.85 (s, 1H), 1.62 (dd, <i>J</i> = 22.6, 15.1 Hz, 8H), 1.54 (s, 1H), 1.49 – 1.44 (m, 1H), 1.15 – 1.07 (m, 2H), 0.94 (s, 2H) ppm
99a/b	 Single enantiomer	657.2 [M-1] ⁺	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ 13.07 (s, 1H), 7.20 (s, 1H), 6.65 (s, 1H), 4.23 (s, 2H), 3.91 (s, 2H), 3.61 (s, 2H), 3.23 (s, 3H), 2.99 (q, <i>J</i> = 13.4 Hz, 2H), 2.82 (q, <i>J</i> = 12.9 Hz, 2H), 2.58 (q, <i>J</i> = 19.2, 15.1 Hz, 3H), 2.49 (s, 2H), 2.06 – 1.89 (m, 3H), 1.85 (s, 1H), 1.73 – 1.44 (m, 11H) ppm
99a	 Single enantiomer	657.2 [M-1] ⁺	¹ H NMR (500 MHz, CD ₃ CN): δ 7.40 (s, 1H), 6.86 (s, 1H), 4.40 (s, 2H), 4.04 (s, 1H), 3.93 (dtt, <i>J</i> = 8.8, 5.9, 2.8 Hz, 1H), 3.90 (s, 1H), 3.44 – 3.24 (m, 3H), 3.22 – 3.12 (m, 2H), 2.96 – 2.87 (m, 2H), 2.86 – 2.47 (m, 5H), 2.28 – 2.10 (m, 3H), 2.08 (d, <i>J</i> = 3.6 Hz, 3H), 1.88 – 1.57 (m, 11H) ppm
99b	 Single enantiomer	657.0 [M-1] ⁺	¹ H NMR (500 MHz, Acetone- <i>d</i> ₆): δ 7.40 (s, 1H), 6.86 (s, 1H), 4.40 (s, 2H), 4.04 (s, 1H), 3.93 (s, 1H), 3.31 (s, 3H), 3.16 (s, 2H), 2.91 (q, <i>J</i> = 13.8 Hz, 2H), 2.81 – 2.57 (m, 5H), 2.13 (s, 3H), 1.89 – 1.55 (m, 14H) ppm
100a	 Single enantiomer	611.2	¹ H NMR (500 MHz, CD ₃ CN): δ 7.24 (s, 1H), 6.75 (s, 1H), 4.26 (d, <i>J</i> = 74.4 Hz, 1H), 4.08 – 4.01 (m, 2H), 3.93 (s, 1H), 3.83 (dtt, <i>J</i> = 11.5, 5.7, 2.8 Hz, 1H), 3.60 (s, 1H), 3.47 – 2.84 (m, 4H), 2.75 – 2.36 (m, 5H), 2.22 – 2.00 (m, 3H), 1.67 (q, <i>J</i> = 18.8, 18.4 Hz, 9H),

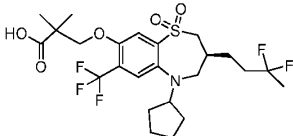
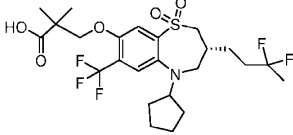
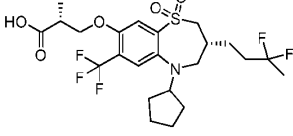
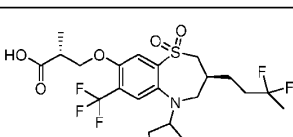
			1.54 (s, 2H), 1.31 (d, $J = 3.3$ Hz, 6H) ppm
100b	 Single enantiomer	611.2	^1H NMR (500 MHz, CD_3CN): δ 7.24 (s, 1H), 6.75 (s, 1H), 4.18 (d, $J = 2.9$ Hz, 1H), 4.08 – 4.00 (m, 2H), 3.93 (s, 1H), 3.84 (dt, $J = 8.9, 5.9, 3.0$ Hz, 1H), 3.69 (s, 1H), 3.42 – 2.80 (m, 4H), 2.80 – 2.42 (m, 5H), 2.21 – 1.99 (m, 3H), 1.67 (q, $J = 18.8, 17.8$ Hz, 9H), 1.54 (s, 2H), 1.31 (dd, $J = 3.3, 1.3$ Hz, 6H) ppm
101a/b	 A mixture of two diastereomers	613.2 [M-1] ⁻	^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 13.51 (s, 1H), 7.18 (s, 1H), 6.65 (s, 1H), 4.30 (dd, $J = 30.4, 16.2$ Hz, 2H), 3.93 (s, 2H), 3.22 (s, 4H), 2.58 (s, 3H), 2.02 (dd, $J = 47.8, 20.8$ Hz, 4H), 1.85 (s, 1H), 1.74 – 1.50 (m, 14H), 1.46 (s, 2H) ppm
101a	 Single diastereomer with arbitrarily assigned stereochemistry	613.2 [M-1] ⁻	^1H NMR (500 MHz, $\text{Acetone}-d_6$): δ 7.37 (s, 1H), 6.87 (s, 1H), 4.49 (dd, $J = 27.4, 10.8$ Hz, 1H), 4.39 (dd, $J = 15.7, 10.7$ Hz, 1H), 4.03 (s, 1H), 3.95 (dtq, $J = 8.9, 5.9, 2.8$ Hz, 1H), 3.86 (d, $J = 56.4$ Hz, 1H), 3.53 – 2.87 (m, 4H), 2.88 – 2.48 (m, 5H), 2.22 – 2.09 (m, 3H), 1.90 – 1.60 (m, 15H) ppm
101b	 Single diastereomer with arbitrarily assigned stereochemistry	613.2 [M-1] ⁻	^1H NMR (500 MHz, CD_3CN): δ 7.27 (s, 1H), 6.76 (s, 1H), 4.38 (d, $J = 25.3$ Hz, 1H), 4.28 (s, 1H), 3.93 (s, 1H), 3.85 (s, 1H), 3.67 (s, 1H), 3.21 (s, 4H), 2.77 – 2.45 (m, 5H), 2.09 – 1.99 (m, 3H), 1.67 (q, $J = 19.5, 18.8$ Hz, 15H) ppm
101c/d		613.2 [M-1] ⁻	^1H NMR (500 MHz, CD_3CN): δ 7.27 (s, 1H), 6.77 (s, 1H), 4.37 (dd, $J = 23.8, 10.7$ Hz, 1H), 4.24 (dd, $J = 19.0, 10.9$ Hz, 1H), 3.93 (s, 1H), 3.87 (s, 1H), 3.22 (s, 3H), 2.64 (dt, $J = 25.4,$

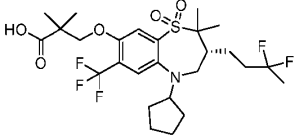
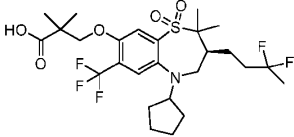
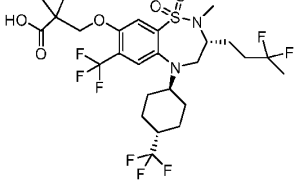
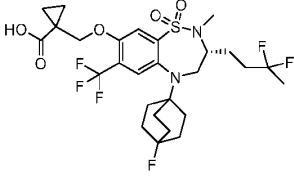
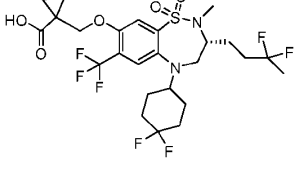
	A mixture of two diastereomers		14.9 Hz, 5H), 2.52 (d, $J = 13.5$ Hz, 2H), 2.03 (s, 3H), 1.72 (s, 3H), 1.70 – 1.55 (m, 12H) ppm
101c	 Single diastereomer with arbitrarily assigned stereochemistry	613.2 [M-1] ⁻	¹ H NMR (500 MHz, CD ₃ CN): δ 7.28 (s, 1H), 6.76 (s, 1H), 4.40 (dd, $J = 27.1, 10.8$ Hz, 1H), 4.28 (dd, $J = 16.0, 10.8$ Hz, 1H), 3.94 (s, 1H), 3.85 (dtq, $J = 8.7, 5.8, 2.9$ Hz, 1H), 3.77 (d, $J = 48.2$ Hz, 1H), 3.47 – 2.78 (m, 4H), 2.78 – 2.28 (m, 5H), 2.00 (d, $J = 13.7$ Hz, 3H), 1.80 – 1.46 (m, 15H) ppm
101d	 Single diastereomer with arbitrarily assigned stereochemistry	613.2 [M-1] ⁻	¹ H NMR (500 MHz, CD ₃ CN): δ 7.27 (s, 1H), 6.77 (s, 1H), 4.39 (dd, $J = 26.7, 10.6$ Hz, 1H), 4.27 (t, $J = 13.5$ Hz, 1H), 3.93 (s, 1H), 3.89 – 3.83 (m, 1H), 3.61 (s, 1H), 3.32 – 2.97 (m, 4H), 2.76 – 2.33 (m, 5H), 2.06 – 1.99 (m, 3H), 1.79 – 1.43 (m, 15H) ppm
102a/b		623.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ 13.11 (s, 1H), 7.23 (s, 1H), 6.66 (s, 1H), 4.76 (d, $J = 6.1$ Hz, 2H), 4.58 (d, $J = 6.1$ Hz, 2H), 4.40 (s, 2H), 3.92 (s, 2H), 3.61 (s, 2H), 3.21 (t, $J = 10.9$ Hz, 4H), 2.71 – 2.52 (m, 4H), 2.05 – 1.90 (m, 3H), 1.85 (s, 1H), 1.76 – 1.43 (m, 11H) ppm
102a	 Single enantiomer	623.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ 13.10 (s, 1H), 7.23 (s, 1H), 6.65 (s, 1H), 4.76 (d, $J = 6.1$ Hz, 2H), 4.58 (d, $J = 6.1$ Hz, 2H), 4.40 (s, 2H), 3.92 (s, 2H), 3.62 (s, 1H), 3.29 – 3.24 (m, 2H), 3.21 (s, 3H), 2.65 – 2.55 (m, 3H), 2.54 – 2.50 (m, 1H), 2.06 – 1.90 (m, 3H), 1.85 (s, 1H), 1.74 – 1.41 (m, 11H) ppm
102b		623.0 [M-1] ⁻	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ 13.10 (s, 1H), 7.23 (s, 1H), 6.65 (s, 1H), 4.76 (d, $J = 6.1$ Hz, 2H), 4.58 (d, $J = 6.1$ Hz, 2H), 4.40 (s, 2H), 3.92 (s,

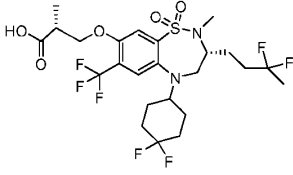
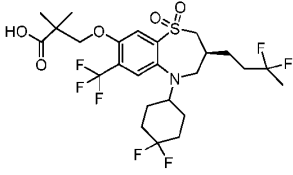
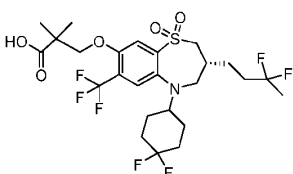
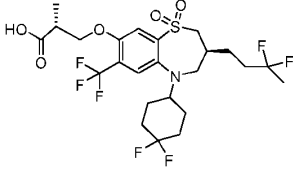
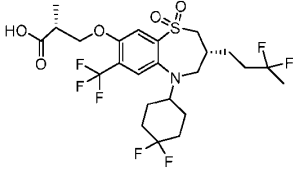
	Single enantiomer		2H), 3.61 (s, 1H), 3.27 (s, 2H), 3.26 – 3.07 (m, 3H), 2.59 (d, $J = 17.7$ Hz, 3H), 2.53 (d, $J = 7.8$ Hz, 1H), 2.06 – 1.91 (m, 3H), 1.85 (s, 1H), 1.74 – 1.43 (m, 11H) ppm
103a	 Single diastereomer	601.2 [M-1] ⁺	¹ H NMR (500 MHz, CD ₃ CN): δ 7.49 (s, 1H), 7.36 (s, 1H), 4.27 (s, 2H), 4.19 (d, $J = 9.8$ Hz, 1H), 3.04 (d, $J = 74.4$ Hz, 5H), 2.50 – 2.27 (m, 3H), 2.18 – 2.12 (m, 1H), 2.07 – 2.00 (m, 3H), 1.65 (t, $J = 18.8$ Hz, 7H), 1.30 (q, $J = 3.2$ Hz, 2H), 1.07 (t, $J = 3.7$ Hz, 2H) ppm
103b	 Single diastereomer	601.2 [M-1] ⁺	¹ H NMR (500 MHz, CD ₃ CN): δ 7.48 (s, 1H), 7.37 (s, 1H), 4.31 (d, $J = 41.9$ Hz, 2H), 4.19 (d, $J = 9.8$ Hz, 1H), 3.12 (s, 1H), 2.56 (s, 4H), 2.38 (d, $J = 8.8$ Hz, 3H), 2.14 (d, $J = 15.1$ Hz, 1H), 2.06 – 1.99 (m, 3H), 1.65 (t, $J = 18.9$ Hz, 7H), 1.30 (d, $J = 4.0$ Hz, 2H), 1.07 (d, $J = 3.0$ Hz, 2H) ppm
104a	 Single diastereomer	558.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.68 (s, 1H), 7.54 (s, 1H), 5.60 (d, $J = 46.0$ Hz, 1H), 4.32 (s, 2H), 3.92 (t, $J = 7.2$ Hz, 1H), 3.22 (d, $J = 14.6$ Hz, 1H), 2.84 – 2.73 (m, 1H), 2.61 – 2.43 (m, 1H), 2.19 – 1.89 (m, 4H), 1.84 – 1.57 (m, 10H), 1.46 – 1.43 (m, 1H), 1.36 – 1.33 (m, 2H), 1.14 – 1.11 (m, 2H) ppm
104b	 Single diastereomer	558.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.69 (s, 1H), 7.55 (s, 1H), 5.60 (d, $J = 46.0$ Hz, 1H), 4.33 (s, 2H), 3.92 (t, $J = 7.2$ Hz, 1H), 3.26 – 3.18 (m, 1H), 2.84 – 2.73 (m, 1H), 2.62 – 2.44 (m, 1H), 2.17 – 1.89 (m, 4H), 1.84 – 1.57 (m, 10H), 1.48 – 1.40 (m, 1H), 1.36 – 1.33 (m, 2H), 1.14 – 1.11 (m, 2H) ppm

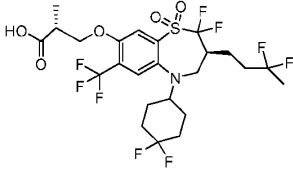
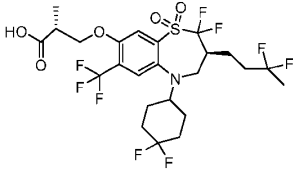
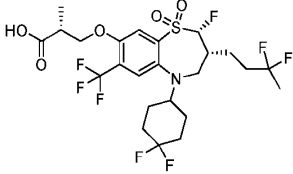
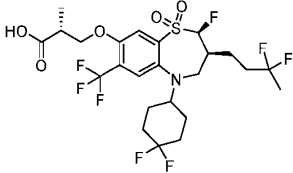
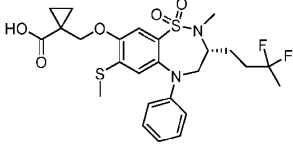
105	 Single enantiomer	555.2	¹ H NMR (400 MHz, DMSO-d ₆): δ 7.41 (s, 1H), 7.30 (s, 1H), 4.19 (d, J = 9.8 Hz, 2H), 3.93 (s, 1H), 3.65 (s, 1H), 2.67 (s, 2H), 2.49 – 2.37 (m, 2H), 2.16 – 1.78 (m, 5H), 1.60 (dd, J = 51.7, 32.7 Hz, 1H), 1.14 (d, J = 2.8 Hz, 2H), 0.97 (d, J = 2.7 Hz, 2H) ppm
106	 Single diastereomer	543.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.50 (s, 1H), 7.36 (s, 1H), 4.19 (ddd, J = 14.5, 8.8, 6.3 Hz, 2H), 3.85 (d, J = 68.6 Hz, 2H), 2.91 (dt, J = 13.6, 6.8 Hz, 2H), 2.68 (s, 3H), 2.05 (dt, J = 30.3, 11.5 Hz, 4H), 1.68 (dt, J = 37.0, 12.4 Hz, 1H), 1.29 (d, J = 7.1 Hz, 3H) ppm
107a	 Single diastereomer	560.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.66 (s, 1H), 7.56 (s, 1H), 5.61 (d, J = 46.0 Hz, 1H), 4.20 – 4.11 (m, 2H), 3.93 (t, J = 6.8 Hz, 1H), 3.22 (d, J = 14.8 Hz, 1H), 2.85 – 2.74 (m, 1H), 2.64 – 2.43 (m, 1H), 2.17 – 1.88 (m, 4H), 1.88 – 1.65 (m, 6H), 1.64 – 1.62 (m, 2H), 1.61 – 1.52 (m, 2H), 1.50 – 1.42 (m, 1H), 1.35 (s, 6H) ppm
107b	 Single diastereomer	560.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.66 (s, 1H), 7.56 (s, 1H), 5.61 (d, J = 46.0 Hz, 1H), 4.20 – 4.11 (m, 2H), 3.93 (t, J = 6.8 Hz, 1H), 3.22 (d, J = 14.8 Hz, 1H), 2.85 – 2.74 (m, 1H), 2.64 – 2.43 (m, 1H), 2.17 – 1.88 (m, 4H), 1.88 – 1.65 (m, 6H), 1.64 – 1.62 (m, 2H), 1.61 – 1.52 (m, 2H), 1.50 – 1.42 (m, 1H), 1.35 (s, 6H) ppm
108a	 Single diastereomer	546.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.66 (s, 1H), 7.53 (s, 1H), 5.59 (d, J = 46.0 Hz, 1H), 4.33 – 4.25 (m, 1H), 4.23 – 4.17 (m, 1H), 3.94 – 3.86 (m, 1H), 3.20 (d, J = 14.4 Hz, 1H), 2.92 (q, J = 6.8 Hz, 1H), 2.82 – 2.71 (m, 1H), 2.57 – 2.42 (m, 1H), 2.15 – 1.85 (m, 4H),

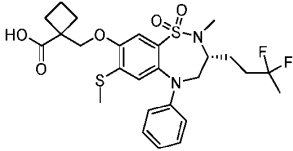
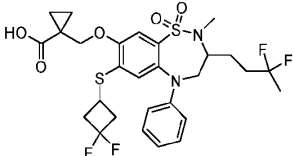
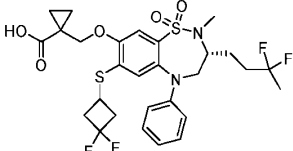
			1.84 – 1.50 (m, 10H), 1.48 – 1.38 (m, 1H), 1.30 (d, J = 7.2 Hz, 3H) ppm
108b	 Single diastereomer	546.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.66 (s, 1H), 7.53 (s, 1H), 5.58 (d, J = 46.4 Hz, 1H), 4.30 (t, J = 7.4 Hz, 1H), 4.19 (t, J = 7.4 Hz, 1H), 3.94 – 3.86 (m, 1H), 3.20 (d, J = 14.8 Hz, 1H), 2.96 – 2.88 (m, 1H), 2.83 – 2.71 (m, 1H), 2.60 – 2.42 (m, 1H), 2.15 – 1.86 (m, 4H), 1.84 – 1.50 (m, 10H), 1.48 – 1.39 (m, 1H), 1.30 (d, J = 7.2 Hz, 3H) ppm
109a	 Single enantiomer	578.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.67 (s, 1H), 7.57 (s, 1H), 4.15 (s, 2H), 3.93 – 3.90 (m, 1H), 3.42 (d, J = 16.0 Hz, 1H), 2.97 – 2.85 (m, 1H), 2.83 – 2.75 (m, 1H), 2.13 – 1.84 (m, 5H), 1.83 – 1.51 (m, 8H), 1.50 – 1.36 (m, 2H), 1.32 (s, 6H) ppm
109b	 Single enantiomer	578.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.67 (s, 1H), 7.57 (s, 1H), 4.15 (s, 2H), 3.93 – 3.90 (m, 1H), 3.42 (d, J = 16.0 Hz, 1H), 2.97 – 2.85 (m, 1H), 2.82 – 2.70 (m, 1H), 2.15 – 1.84 (m, 5H), 1.83 – 1.52 (m, 8H), 1.50 – 1.36 (m, 2H), 1.32 (s, 6H) ppm
110a	 Single diastereomer	564.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.69 (s, 1H), 7.57 (s, 1H), 4.37 – 4.29 (m, 1H), 4.18 (t, J = 7.6 Hz, 1H), 3.96 – 3.88 (m, 1H), 3.42 (d, J = 14.8 Hz, 1H), 2.97 – 2.86 (m, 2H), 2.77 (s, 1H), 2.18 – 1.86 (m, 5H), 1.85 – 1.52 (m, 8H), 1.53 – 1.35 (m, 2H), 1.30 (d, J = 7.2 Hz, 3H) ppm
110b	 Single diastereomer	564.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.72 (s, 1H), 7.59 (s, 1H), 4.41 – 4.33 (m, 1H), 4.17 (t, J = 7.6 Hz, 1H), 3.98 – 3.88 (m, 1H), 3.44 (d, J = 15.2 Hz, 1H), 2.99 – 2.72 (m, 3H), 2.15 – 1.86

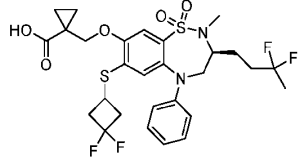
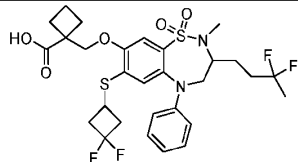
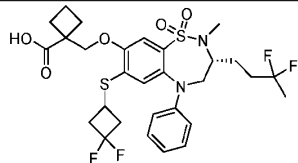
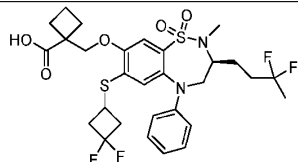
			(m, 5H), 1.87 – 1.55 (m, 8H), 1.52 – 1.38 (m, 2H), 1.32 (d, J = 7.2 Hz, 3H) ppm
111a	 Single enantiomer	542.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.60 (s, 1H), 7.50 (s, 1H), 4.83 (s, 2H), 3.93 – 3.86 (m, 1H), 3.53 – 3.47 (m, 1H), 3.31 – 3.30 (m, 1H), 3.15 – 3.06 (m, 1H), 2.66 – 2.57 (m, 1H), 2.21 – 2.17 (m, 1H), 2.00 – 1.90 (m, 4H), 1.89 – 1.52 (m, 11H), 1.35 – 1.29 (m, 6H) ppm
111b	 Single enantiomer	542.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.60 (s, 1H), 7.50 (s, 1H), 4.83 (s, 2H), 3.90 – 3.86 (m, 1H), 3.53 – 3.47 (m, 1H), 3.31 – 3.30 (m, 1H), 3.15 – 3.06 (m, 1H), 2.66 – 2.57 (m, 1H), 2.17 – 2.12 (m, 1H), 2.00 – 1.90 (m, 4H), 1.89 – 1.59 (m, 11H), 1.35 – 1.29 (m, 6H) ppm
112a	 Single diastereomer	528.2	¹ H NMR (300 MHz, Methanol-d ₄) δ 7.63 (s, 1H), 7.49 (s, 1H), 4.39 – 4.28 (m, 1H), 4.16 – 4.11 (m, 1H), 3.90 – 3.86 (m, 1H), 3.51 – 3.47 (m, 1H), 3.40 – 3.31 (m, 1H), 3.14 – 3.06 (m, 1H), 2.90 – 2.83 (m, 1H), 2.65 – 2.57 (m, 1H), 2.20 – 2.14 (m, 1H), 2.05 – 1.85 (m, 4H), 1.80 – 1.39 (m, 11H), 1.28(d, J = 6.9 Hz, 3H).
112b	 Single diastereomer	528.2	¹ H NMR (300 MHz, Methanol-d ₄) δ 7.63 (s, 1H), 7.49 (s, 1H), 4.36 – 4.31 (m, 1H), 4.12 – 4.07 (m, 1H), 3.90 – 3.86 (m, 1H), 3.54 – 3.46 (m, 1H), 3.40 – 3.31 (m, 1H), 3.10 – 3.07 (m, 1H), 2.90 – 2.84 (m, 1H), 2.65 – 2.57 (m, 1H), 2.20 – 2.15 (m, 1H), 2.05 – 1.83 (m, 4H), 1.85 – 1.35 (m, 11H), 1.28(d, J = 6.9 Hz, 3H).

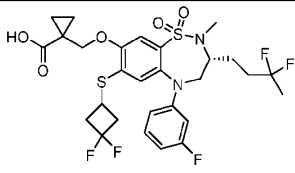
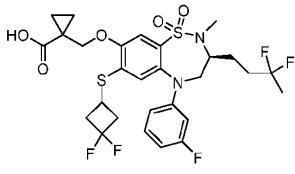
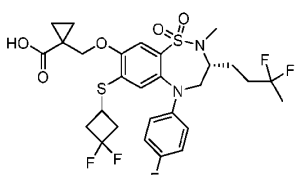
113a	 Single enantiomer	570.3	¹ H NMR (400 MHz, CD ₃ OD): δ 7.62 (s, 1H), 7.43 (s, 1H), 4.10 (s, 2H), 3.96 – 3.88 (m, 1H), 3.36 (s, 1H), 2.69 (t, J = 13.8 Hz, 1H), 2.25 – 1.88 (m, 5H), 1.85 – 1.73 (m, 2H), 1.76 – 1.55 (m, 10H), 1.48 – 1.38 (m, 1H), 1.32 (s, 6H), 1.08 (s, 4H) ppm
113b	 Single enantiomer	570.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.62 (s, 1H), 7.43 (s, 1H), 4.10 (s, 2H), 3.96 – 3.88 (m, 1H), 3.38 – 3.32 (m, 1H), 2.69 (t, J = 13.8 Hz, 1H), 2.25 – 1.87 (m, 5H), 1.87 – 1.77 (m, 2H), 1.76 – 1.52 (m, 10H), 1.49 – 1.37 (m, 1H), 1.32 (s, 6H), 1.08 (s, 4H) ppm
114	 Single diastereomer	637.3	¹ H NMR (400 MHz, DMSO-d ₆): δ 12.33-12.06 (m, 1H), 7.37 (s, 1H), 7.18 (s, 1H), 4.18 (s, 2H), 3.52 – 3.37 (m, 3H), 2.70 – 2.52 (m, 3H), 2.30 – 2.27 (m, 1H), 2.05 – 1.81 (m, 4H), 1.72 – 1.13 (m, 13H), 0.98 (s, 2H), 0.84 (t, J = 6.4 Hz, 1H) ppm
115	 Single enantiomer	613.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.54 (d, J = 7.6 Hz, 2H), 4.36 (d, J = 10.0 Hz, 1H), 4.27 (d, J = 9.6 Hz, 1H), 4.01 – 3.85 (m, 1H), 3.38 (d, J = 15.6 Hz, 1H), 2.60 (dd, J = 16.0, 10.4 Hz, 1H), 2.39 (s, 3H), 2.22 – 1.97 (m, 5H), 1.95 – 1.80 (m, 9H), 1.79 – 1.72 (m, 1H), 1.66 (t, J = 18.4 Hz, 4H), 1.39 – 1.29 (m, 2H), 1.15 – 1.05 (m, 2H) ppm
116	 Single enantiomer	605.2	¹ H NMR (400 MHz, CDCl ₃): δ 7.49 (s, 1H), 7.26 (s, 4H), 4.32 (s, 1H), 4.20 (d, J = 9.4 Hz, 1H), 3.41 (s, 1H), 3.16 (s, 1H), 2.82 (s, 6H), 2.27 – 2.05 (m, 4H), 2.03 – 1.76 (m, 5H), 1.66 (t, J = 18.4 Hz, 3H), 1.46 (q, J = 4.7 Hz, 2H), 1.18 (q, J = 4.8 Hz, 2H) ppm

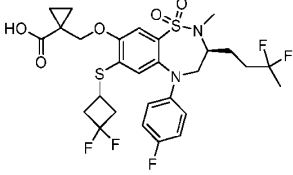
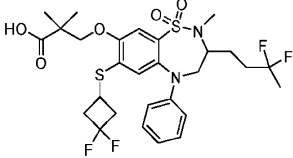
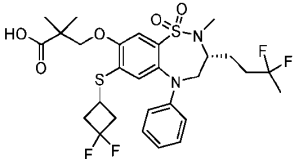
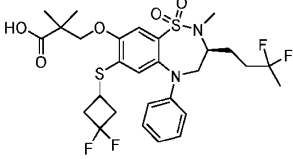
117	 Single diastereomer	593.2	¹ H NMR (400 MHz, CDCl ₃): δ 7.49 (s, 1H), 7.26 (s, 1H), 4.30 – 4.21 (m, 1H), 4.15 (dd, J = 8.7, 5.8 Hz, 1H), 3.42 (s, 1H), 3.16 (s, 2H), 3.03 (dd, J = 13.2, 6.6 Hz, 2H), 2.64 (s, 2H), 2.27 – 2.04 (m, 4H), 1.88 (m, 6H), 1.66 (t, J = 18.4 Hz, 5H), 1.36 (d, J = 7.1 Hz, 3H) ppm
118a	 Single enantiomer	592.3	¹ H NMR (300 MHz, CD ₃ OD): δ 7.62 (s, 1H), 7.50 (s, 1H), 4.13 (s, 2H), 3.55 – 3.41 (m, 3H), 3.15 – 3.06 (m, 1H), 2.71 – 2.62 (m, 1H), 2.19 – 1.82 (m, 11H), 1.79 – 1.65 (m, 5H), 1.32 (s, 6H) ppm
118b	 Single enantiomer	592.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.62 (s, 1H), 7.50 (s, 1H), 4.13 (s, 2H), 3.55 – 3.41 (m, 3H), 3.15 – 3.06 (m, 1H), 2.71 – 2.62 (m, 1H), 2.19 – 1.77 (m, 11H), 1.65 – 1.52 (m, 5H), 1.32 (s, 6H) ppm
119a	 Single enantiomer	578.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.64 (s, 1H), 7.50 (s, 1H), 4.33 – 4.28 (m, 1H), 4.19 – 4.14 (m, 1H), 3.55 – 3.41 (m, 3H), 3.14 – 3.06 (m, 1H), 2.94 – 2.87 (m, 1H), 2.71 – 2.62 (m, 1H), 2.18 – 1.76 (m, 11H), 1.65 – 1.50 (m, 5H), 1.29 (d, J = 7.2 Hz, 3H) ppm
119b	 Single enantiomer	578.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.64 (s, 1H), 7.50 (s, 1H), 4.32 – 4.27 (m, 1H), 4.20 – 4.15 (m, 1H), 3.54 – 3.42 (m, 3H), 3.14 – 3.06 (m, 1H), 2.92 – 2.87 (m, 1H), 2.70 – 2.62 (m, 1H), 2.19 – 1.75 (m, 11H), 1.65 – 1.50 (m, 5H), 1.29 (d, J = 7.2 Hz, 3H) ppm

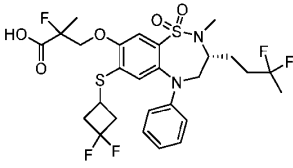
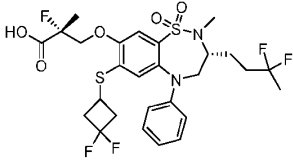
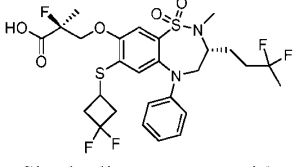
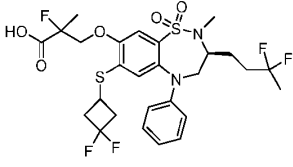
120a	 Single diastereomer	614.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.71 (s, 1H), 7.58 (s, 1H), 4.35 – 4.30 (m, 1H), 4.22 – 4.17 (m, 1H), 3.53 (d, J = 12.6 Hz, 2H), 3.07 – 2.87 (m, 2H), 2.83 – 2.75 (m, 1H), 2.17 – 1.89 (m, 10H), 1.77 – 1.68 (m, 1H), 1.62 (t, J = 18.6 Hz, 3H), 1.53 – 1.40 (m, 1H), 1.30 (d, J = 7.2 Hz, 3H) ppm
120b	 Single diastereomer	614.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.71 (s, 1H), 7.58 (s, 1H), 4.37 – 4.32 (m, 1H), 4.20 – 4.15 (m, 1H), 3.53 (d, J = 12.6 Hz, 2H), 3.07 – 2.67 (m, 3H), 2.17 – 1.68 (m, 11H), 1.62 (t, J = 18.6 Hz, 3H), 1.53 – 1.40 (m, 1H), 1.30 (d, J = 7.2 Hz, 3H) ppm
121a	 Single diastereomer	596.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.67 (s, 1H), 7.55 (s, 1H), 5.61 (d, J = 46.2 Hz, 1H), 4.33 – 4.20 (m, 2H), 3.60 – 3.50 (m, 1H), 3.40 – 3.33 (m, 1H), 3.07 – 2.91 (m, 1H), 2.86 – 2.82 (m, 1H), 2.77 – 2.43 (m, 1H), 2.28 – 1.83 (m, 9H), 1.77 – 1.51 (m, 6H), 1.31 (d, J = 7.2 Hz, 3H) ppm
121b	 Single diastereomer	596.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.67 (s, 1H), 7.55 (s, 1H), 5.61 (d, J = 46.2 Hz, 1H), 4.32 – 4.22 (m, 2H), 3.54 – 3.53 (m, 1H), 3.31 – 3.30 (m, 1H), 3.08 – 2.91 (m, 1H), 2.86 – 2.77 (m, 1H), 2.55 – 2.43 (m, 1H), 2.15 – 1.83 (m, 9H), 1.77 – 1.53 (m, 6H), 1.31 (d, J = 7.2 Hz, 3H) ppm
122	 Single enantiomer	541.30	¹ H NMR (400 MHz, CD ₃ OD): δ 7.37 (s, 1H), 7.19 – 7.15 (m, 2H), 7.02 (s, 1H), 6.75 (t, J = 7.2 Hz, 1H), 6.67 (d, J = 7.6 Hz, 2H), 4.29 (q, J = 10.0 Hz, 2H), 4.12 – 3.91 (m, 2H), 3.42 – 3.33 (m, 1H), 2.57 (s, 3H), 2.31 (s, 3H), 2.10 – 1.94 (m, 2H), 1.84 – 1.76 (m,

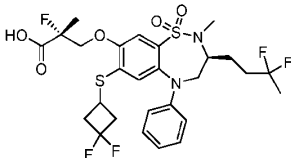
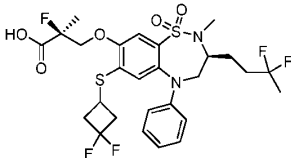
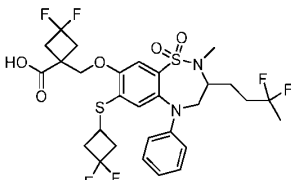
			2H), 1.62 (t, J = 18.4 Hz, 3H), 1.36 – 1.33 (m, 2H), 1.17 – 1.14 (m, 2H) ppm
123	 Single enantiomer	555.30	¹ H NMR (400 MHz, CD ₃ OD): δ 7.40 (s, 1H), 7.20 – 7.16 (m, 2H), 7.02 (s, 1H), 6.76 (t, J = 7.2 Hz, 1H), 6.68 (d, J = 8.0 Hz, 2H), 4.35 (s, 2H), 4.13 – 3.93 (m, 2H), 3.40 – 3.31 (m, 1H), 2.60 – 2.48 (m, 5H), 2.30 (s, 3H), 2.28 – 2.23 (m, 9H), 2.17 – 1.95 (m, 9H), 1.85 – 1.79 (m, 2H), 1.62 (t, J = 18.4 Hz, 3H) ppm
124a/b		615.0 [M-1] ⁺	¹ H NMR (500 MHz, DMSO-d ₆): δ 12.44 (s, 1H), 7.27 (d, J = 2.9 Hz, 1H), 7.14 (t, J = 7.8 Hz, 2H), 6.95 (s, 1H), 6.71 (t, J = 7.4 Hz, 1H), 6.63 (d, J = 8.0 Hz, 2H), 4.22 (q, J = 9.9 Hz, 2H), 4.06 (d, J = 16.1 Hz, 1H), 3.82 (s, 2H), 3.13 (s, 1H), 2.97 (d, J = 12.1 Hz, 1H), 2.57 (d, J = 16.8 Hz, 2H), 2.47 (s, 3H), 2.05 (d, J = 2.7 Hz, 1H), 1.98 (tt, J = 16.4, 8.5 Hz, 2H), 1.89 – 1.79 (m, 1H), 1.63 (t, J = 18.8 Hz, 4H), 1.21 (q, J = 4.1 Hz, 2H), 1.06 (q, J = 3.4 Hz, 2H) ppm
124a	 Single enantiomer	615.0 [M-1] ⁺	¹ H NMR (500 MHz, DMSO-d ₆): δ 12.45 (s, 1H), 7.27 (s, 1H), 7.14 (t, J = 7.8 Hz, 2H), 6.95 (s, 1H), 6.70 (t, J = 7.3 Hz, 1H), 6.63 (d, J = 8.1 Hz, 2H), 4.21 (q, J = 9.8 Hz, 2H), 4.06 (d, J = 16.0 Hz, 1H), 3.82 (s, 2H), 3.13 (s, 1H), 2.99 (d, J = 12.4 Hz, 1H), 2.64 – 2.50 (m, 2H), 2.47 (s, 3H), 1.98 (tt, J = 16.3, 8.2 Hz, 2H), 1.83 (t, J = 7.0 Hz, 1H), 1.63 (t, J = 18.9 Hz, 4H), 1.20 (t, J = 3.5 Hz, 2H), 1.06 (q, J = 3.3 Hz, 2H) ppm

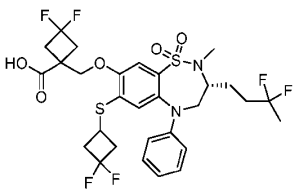
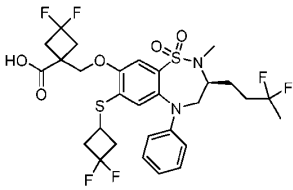
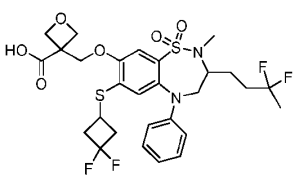
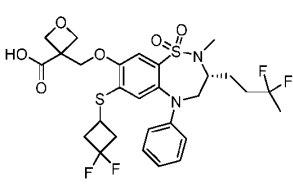
124b	 Single enantiomer	615.0 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 12.45 (s, 1H), 7.27 (s, 1H), 7.14 (t, J = 7.8 Hz, 2H), 6.95 (s, 1H), 6.70 (t, J = 7.3 Hz, 1H), 6.63 (d, J = 8.1 Hz, 2H), 4.21 (q, J = 9.8 Hz, 2H), 4.06 (d, J = 15.9 Hz, 1H), 3.82 (s, 2H), 3.26 (s, 1H), 3.13 (s, 1H), 2.98 (s, 1H), 2.64 – 2.50 (m, 2H), 2.47 (s, 3H), 1.98 (tt, J = 16.2, 8.0 Hz, 2H), 1.83 (d, J = 8.4 Hz, 1H), 1.63 (t, J = 18.9 Hz, 4H), 1.21 (d, J = 3.0 Hz, 2H), 1.06 (s, 2H) ppm
125a/b		629.2 [M-1] ⁻	¹ H NMR (500 MHz, CD ₃ CN): δ 7.46 (s, 1H), 7.21 (t, J = 7.7 Hz, 2H), 6.98 (s, 1H), 6.79 (t, J = 7.2 Hz, 1H), 6.67 (d, J = 8.1 Hz, 2H), 4.41 (s, 2H), 4.01 (d, J = 15.0 Hz, 1H), 3.71 (s, 1H), 3.31 (s, 1H), 3.13 (s, 1H), 3.03 (d, J = 12.1 Hz, 1H), 2.61 – 2.46 (m, 8H), 2.15 (t, J = 14.2 Hz, 6H), 1.74 (s, 1H), 1.66 (t, J = 18.8 Hz, 4H) ppm
125a	 Single enantiomer	629.2 [[M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 12.48 (s, 1H), 7.35 (s, 1H), 7.18 – 7.12 (m, 2H), 6.95 (s, 1H), 6.71 (t, J = 7.3 Hz, 1H), 6.64 (d, J = 8.1 Hz, 2H), 4.34 (s, 2H), 4.06 (d, J = 15.9 Hz, 1H), 3.80 (s, 2H), 3.23 (d, J = 16.3 Hz, 1H), 3.13 (s, 1H), 2.97 (s, 1H), 2.53 (d, J = 11.8 Hz, 2H), 2.44 (s, 3H), 2.39 (d, J = 8.3 Hz, 2H), 2.13 – 1.93 (m, 5H), 1.91 – 1.81 (m, 2H), 1.63 (t, J = 18.9 Hz, 4H) ppm
125b	 Single enantiomer	629.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 12.48 (s, 1H), 7.35 (s, 1H), 7.19 – 7.11 (m, 2H), 6.95 (s, 1H), 6.71 (t, J = 7.3 Hz, 1H), 6.64 (d, J = 8.1 Hz, 2H), 4.34 (s, 2H), 4.06 (d, J = 16.0 Hz, 1H), 3.83 (d, J = 25.6 Hz, 2H), 3.26 (s, 1H), 3.12 (s, 1H), 2.96 (d, J = 13.4 Hz, 1H), 2.53

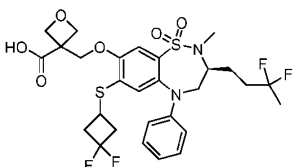
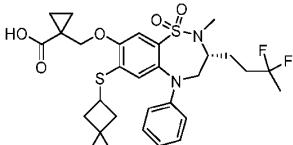
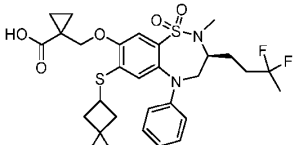
			(d, J = 9.7 Hz, 2H), 2.44 (s, 3H), 2.42 – 2.36 (m, 2H), 2.13 – 1.94 (m, 5H), 1.86 (td, J = 13.9, 11.7, 6.5 Hz, 2H), 1.63 (t, J = 18.9 Hz, 4H) ppm
126a	 Single enantiomer	633.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 12.43 (s, 1H), 7.29 (s, 1H), 7.12 (q, J = 7.9 Hz, 1H), 7.03 (s, 1H), 6.45 (dt, J = 22.1, 10.5 Hz, 2H), 6.33 (d, J = 8.4 Hz, 1H), 4.26 (d, J = 9.8 Hz, 1H), 4.21 (d, J = 9.7 Hz, 1H), 4.04 (d, J = 16.4 Hz, 1H), 3.87 (s, 2H), 3.18 (s, 2H), 3.10 – 3.00 (m, 1H), 2.61 – 2.50 (m, 2H), 2.44 (s, 3H), 2.07 – 1.85 (m, 3H), 1.64 (t, J = 18.9 Hz, 4H), 1.24 – 1.17 (m, 2H), 1.07 (t, J = 3.5 Hz, 2H) ppm
126b	 Single enantiomer	633.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 12.44 (s, 1H), 7.29 (s, 1H), 7.12 (q, J = 7.8 Hz, 1H), 7.03 (s, 1H), 6.45 (dt, J = 21.9, 10.9 Hz, 2H), 6.33 (d, J = 8.4 Hz, 1H), 4.29 – 4.17 (m, 2H), 4.04 (d, J = 16.1 Hz, 1H), 3.86 (d, J = 8.6 Hz, 2H), 3.18 (s, 2H), 3.05 (t, J = 11.6 Hz, 1H), 2.57 (s, 2H), 2.44 (s, 3H), 2.06 – 1.84 (m, 3H), 1.64 (t, J = 18.9 Hz, 4H), 1.25 – 1.16 (m, 2H), 1.06 (d, J = 5.1 Hz, 2H) ppm
127a	 Single enantiomer	633.0 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 12.43 (s, 1H), 7.26 (d, J = 1.7 Hz, 1H), 7.02 – 6.94 (m, 2H), 6.91 (s, 1H), 6.63 (s, 2H), 4.27 – 4.15 (m, 2H), 4.03 (d, J = 16.0 Hz, 1H), 3.81 (s, 2H), 3.13 (s, 2H), 2.98 (s, 1H), 2.57 (s, 2H), 2.47 (s, 3H), 1.97 (tt, J = 16.6, 8.3 Hz, 2H), 1.87 – 1.75 (m, 1H), 1.62 (t, J = 18.8 Hz, 4H), 1.20 (p, J = 2.9 Hz, 2H), 1.10 – 0.99 (m, 2H) ppm

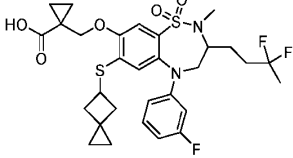
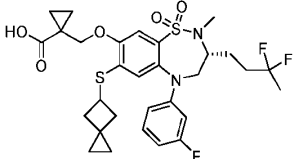
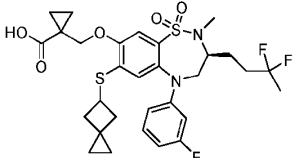
127b	 Single enantiomer	633.0 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 12.43 (s, 1H), 7.26 (s, 1H), 6.98 (t, J = 8.6 Hz, 2H), 6.91 (s, 1H), 6.64 (t, J = 6.6 Hz, 2H), 4.21 (q, J = 9.8 Hz, 2H), 4.02 (d, J = 16.2 Hz, 1H), 3.81 (s, 2H), 3.13 (s, 2H), 2.98 (s, 1H), 2.57 (s, 2H), 2.47 (s, 3H), 1.97 (tt, J = 16.3, 8.1 Hz, 2H), 1.82 (d, J = 7.4 Hz, 1H), 1.62 (t, J = 18.9 Hz, 4H), 1.21 (q, J = 3.8 Hz, 2H), 1.06 (q, J = 3.3 Hz, 2H) ppm
128a/b		619.2	¹ H NMR (500 MHz, DMSO-d ₆): δ 12.46 (s, 1H), 7.28 (s, 1H), 7.14 (t, J = 7.8 Hz, 2H), 6.94 (s, 1H), 6.71 (t, J = 7.2 Hz, 1H), 6.63 (d, J = 7.9 Hz, 2H), 4.10 (s, 2H), 4.05 (s, 1H), 3.82 (s, 2H), 3.28 – 3.20 (m, 3H), 3.14 (s, 1H), 2.98 (s, 1H), 2.52 (s, 3H), 1.98 (dt, J = 16.2, 8.4 Hz, 2H), 1.83 (s, 1H), 1.63 (t, J = 18.9 Hz, 4H), 1.25 (d, J = 2.5 Hz, 6H) ppm
128a	 Single enantiomer	619.2	¹ H NMR (500 MHz, DMSO-d ₆): δ 12.47 (s, 1H), 7.28 (s, 1H), 7.14 (t, J = 7.9 Hz, 2H), 6.94 (s, 1H), 6.71 (t, J = 7.3 Hz, 1H), 6.64 (d, J = 8.0 Hz, 2H), 4.10 (s, 2H), 3.82 (s, 2H), 3.07 (d, J = 91.5 Hz, 2H), 2.52 (s, 7H), 2.06 – 1.93 (m, 2H), 1.83 (s, 1H), 1.63 (t, J = 18.8 Hz, 4H), 1.25 (d, J = 2.5 Hz, 6H) ppm
128b	 Single enantiomer	619.0	¹ H NMR (600 MHz, DMSO-d ₆): δ 12.43 (s, 1H), 7.28 (s, 1H), 7.14 (t, J = 7.8 Hz, 2H), 6.94 (s, 1H), 6.71 (t, J = 7.3 Hz, 1H), 6.63 (d, J = 8.0 Hz, 2H), 4.09 (s, 2H), 3.81 (s, 2H), 3.16 (s, 1H), 2.98 (s, 1H), 2.52 (s, 4H), 2.50 (d, J = 2.1 Hz, 3H), 1.98 (tt, J = 16.5, 8.3 Hz, 2H), 1.83 (d, J = 8.1 Hz, 1H), 1.63 (t, J = 18.9 Hz, 4H), 1.24 (d, J = 2.4 Hz, 6H) ppm

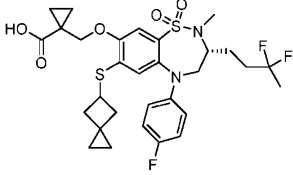
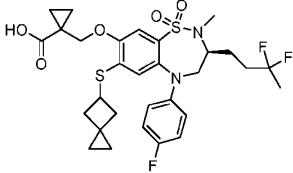
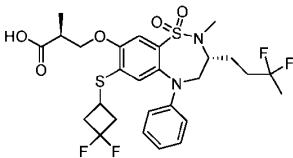
129a/b	 A mixture of two diastereomers	621.2 [M-1] ⁻	¹ H NMR (500 MHz, CD ₃ CN): δ 7.42 (d, J = 1.7 Hz, 1H), 7.21 (td, J = 8.0, 7.3, 1.5 Hz, 2H), 6.99 (s, 1H), 6.79 (t, J = 7.3 Hz, 1H), 6.68 (d, J = 8.1 Hz, 2H), 4.53 (ddd, J = 27.1, 10.9, 3.6 Hz, 1H), 4.42 (dd, J = 15.8, 10.8 Hz, 1H), 4.01 (d, J = 15.6 Hz, 2H), 3.72 (d, J = 8.0 Hz, 1H), 3.31 (s, 1H), 3.13 (d, J = 11.4 Hz, 1H), 3.07 – 2.96 (m, 1H), 2.65 – 2.55 (m, 2H), 2.54 (s, 3H), 2.06 (ddd, J = 16.2, 11.0, 5.3 Hz, 2H), 1.84 (dq, J = 15.9, 5.4 Hz, 1H), 1.65 (dd, J = 19.9, 18.1 Hz, 7H) ppm
129a	 Single diastereomer with arbitrarily assigned stereochemistry	621.2 [M-1] ⁻	¹ H NMR (600 MHz, DMSO-d ₆): δ 13.49 (s, 1H), 7.34 (s, 1H), 7.15 (t, J = 7.8 Hz, 2H), 6.95 (s, 1H), 6.72 (t, J = 7.3 Hz, 1H), 6.64 (d, J = 8.1 Hz, 2H), 4.56 – 4.37 (m, 2H), 4.06 (d, J = 16.1 Hz, 1H), 3.83 (s, 2H), 3.14 (s, 2H), 2.98 (s, 1H), 2.54 (s, 2H), 2.50 (d, J = 3.9 Hz, 3H), 1.98 (tt, J = 16.4, 8.2 Hz, 2H), 1.83 (d, J = 13.8 Hz, 1H), 1.67 – 1.55 (m, 7H) ppm
129b	 Single diastereomer with arbitrarily assigned stereochemistry	621.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 13.56 (s, 1H), 7.35 (s, 1H), 7.15 (t, J = 7.8 Hz, 2H), 6.96 (s, 1H), 6.72 (t, J = 7.3 Hz, 1H), 6.64 (d, J = 8.1 Hz, 2H), 4.56 – 4.39 (m, 2H), 4.06 (d, J = 15.5 Hz, 1H), 3.83 (s, 2H), 3.14 (s, 2H), 2.98 (s, 1H), 2.54 (d, J = 13.9 Hz, 2H), 2.49 (s, 3H), 1.98 (tt, J = 16.0, 8.0 Hz, 2H), 1.83 (s, 1H), 1.68 – 1.55 (m, 7H) ppm
129c/d		621.2 [M-1] ⁻	¹ H NMR (500 MHz, CD ₃ CN): δ 7.42 (d, J = 1.7 Hz, 1H), 7.24 – 7.18 (m, 2H), 6.99 (s, 1H), 6.79 (t, J = 7.3 Hz, 1H), 6.68 (d, J = 8.1 Hz, 2H), 4.53 (ddd, J = 26.9, 10.8, 3.6 Hz, 1H), 4.41

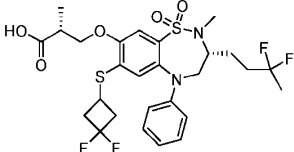
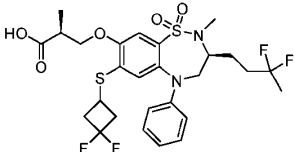
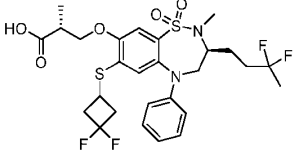
	A mixture of two diastereomers		(dd, J = 16.2, 10.8 Hz, 1H), 4.05 – 3.93 (m, 2H), 3.72 (d, J = 9.0 Hz, 1H), 3.31 (s, 1H), 3.11 (s, 1H), 3.07 – 2.95 (m, 1H), 2.63 – 2.55 (m, 2H), 2.54 (s, 3H), 2.14 – 2.01 (m, 2H), 1.86 – 1.80 (m, 1H), 1.74 (s, 1H), 1.65 (dd, J = 20.1, 17.1 Hz, 6H) ppm
129c	 Single diastereomer with arbitrarily assigned stereochemistry	621.2 [M-1] ⁻	¹ H NMR (600 MHz, DMSO-d ₆): δ 13.54 (s, 1H), 7.35 (s, 1H), 7.15 (t, J = 7.8 Hz, 2H), 6.96 (s, 1H), 6.72 (t, J = 7.3 Hz, 1H), 6.64 (d, J = 8.1 Hz, 2H), 4.54 – 4.36 (m, 2H), 4.05 (s, 1H), 3.83 (s, 2H), 3.15 (s, 2H), 2.98 (s, 1H), 2.52 (s, 2H), 2.50 (d, J = 2.3 Hz, 3H), 1.98 (tt, J = 16.3, 8.3 Hz, 2H), 1.87 – 1.79 (m, 1H), 1.67 – 1.55 (m, 7H) ppm
129d	 Single diastereomer with arbitrarily assigned stereochemistry	621.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 13.56 (s, 1H), 7.35 (s, 1H), 7.15 (t, J = 7.8 Hz, 2H), 6.96 (s, 1H), 6.72 (t, J = 7.4 Hz, 1H), 6.64 (d, J = 8.1 Hz, 2H), 4.55 – 4.37 (m, 2H), 4.08 (s, 1H), 3.83 (s, 2H), 3.14 (s, 2H), 2.97 (s, 1H), 2.52 (s, 2H), 2.49 (s, 3H), 1.98 (dt, J = 16.5, 8.1 Hz, 2H), 1.83 (s, 1H), 1.68 – 1.56 (m, 7H) ppm
130a/b		665.2 [M-1] ⁻	¹ H NMR (500 MHz, CD ₃ CN): δ 7.45 (s, 1H), 7.23 – 7.18 (m, 2H), 6.98 (s, 1H), 6.79 (t, J = 7.3 Hz, 1H), 6.67 (d, J = 8.2 Hz, 2H), 4.44 (s, 2H), 4.01 (d, J = 16.0 Hz, 2H), 3.70 (qd, J = 6.0, 3.0 Hz, 2H), 3.32 (s, 1H), 3.11 (p, J = 12.6 Hz, 3H), 3.04 – 2.95 (m, 1H), 2.84 (td, J = 14.6, 10.3 Hz, 2H), 2.55 (s, 3H), 2.51 (d, J = 14.6 Hz, 1H), 2.05 (dt, J = 16.3, 5.6 Hz, 2H), 1.89 – 1.80 (m, 1H), 1.73 (d, J = 10.9 Hz, 1H), 1.66 (t, J = 18.8 Hz, 3H) ppm

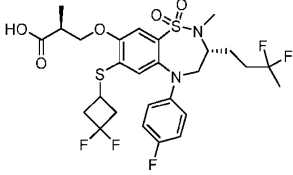
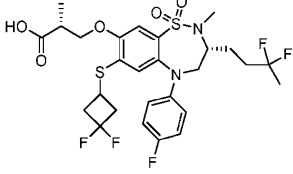
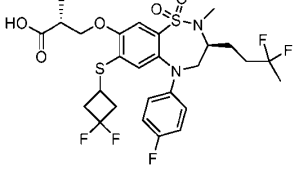
130a	 Single enantiomer	665.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 13.13 (s, 1H), 7.36 (s, 1H), 7.15 (t, J = 7.8 Hz, 2H), 6.95 (s, 1H), 6.72 (t, J = 7.2 Hz, 1H), 6.65 (d, J = 8.0 Hz, 2H), 4.37 (s, 2H), 4.06 (s, 1H), 3.81 (s, 2H), 3.28 – 3.20 (m, 2H), 3.13 (s, 1H), 3.02 (q, J = 14.1 Hz, 3H), 2.86 (d, J = 12.9 Hz, 2H), 2.57 – 2.49 (m, 3H), 2.44 (s, 1H), 1.98 (dq, J = 16.3, 8.1 Hz, 2H), 1.84 (s, 1H), 1.63 (t, J = 18.8 Hz, 4H) ppm
130b	 Single enantiomer	665.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 13.12 (s, 1H), 7.36 (s, 1H), 7.15 (t, J = 7.8 Hz, 2H), 6.95 (s, 1H), 6.72 (t, J = 7.3 Hz, 1H), 6.65 (d, J = 7.8 Hz, 2H), 4.38 (s, 2H), 4.07 (s, 1H), 3.81 (s, 2H), 3.24 (d, J = 7.2 Hz, 2H), 3.13 (s, 1H), 3.06 – 2.94 (m, 3H), 2.86 (d, J = 13.2 Hz, 2H), 2.52 (s, 3H), 2.43 (d, J = 6.7 Hz, 1H), 1.98 (dt, J = 16.3, 8.1 Hz, 2H), 1.83 (s, 1H), 1.63 (t, J = 18.9 Hz, 4H) ppm
131a/b	 Single enantiomer	631.0 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 7.37 (s, 1H), 7.15 (t, J = 7.8 Hz, 2H), 6.96 (s, 1H), 6.71 (t, J = 7.3 Hz, 1H), 6.65 (d, J = 8.1 Hz, 2H), 4.76 (d, J = 5.8 Hz, 2H), 4.58 (d, J = 5.8 Hz, 2H), 4.46 (s, 2H), 4.05 (s, 1H), 3.83 (s, 2H), 3.37 (s, 1H), 3.23 (s, 2H), 3.13 (s, 1H), 2.97 (s, 1H), 2.52 (s, 3H), 1.98 (td, J = 16.3, 7.9 Hz, 2H), 1.83 (s, 1H), 1.63 (t, J = 18.9 Hz, 4H) ppm
131a	 Single enantiomer	631.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 13.20 (s, 1H), 7.39 (s, 1H), 7.15 (t, J = 7.7 Hz, 2H), 6.96 (s, 1H), 6.72 (t, J = 7.3 Hz, 1H), 6.65 (d, J = 8.1 Hz, 2H), 4.78 (dd, J = 6.1, 2.0 Hz, 2H), 4.61 (dd, J = 6.0, 2.4 Hz, 2H), 4.53 (s, 2H),

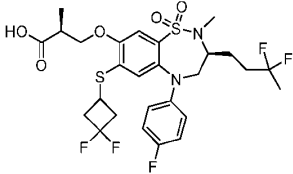
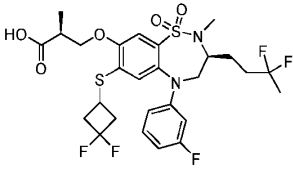
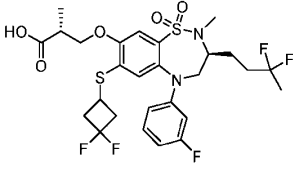
			4.06 (s, 1H), 3.82 (s, 2H), 3.24 (s, 1H), 3.13 (s, 1H), 2.97 (s, 1H), 2.52 (s, 3H), 2.50 (s, 2H), 1.99 (tt, J = 16.4, 8.2 Hz, 2H), 1.83 (s, 1H), 1.63 (t, J = 18.9 Hz, 4H) ppm
131b	 Single enantiomer	631.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 13.24 (s, 1H), 7.37 (s, 1H), 7.15 (t, J = 7.8 Hz, 2H), 6.96 (s, 1H), 6.71 (t, J = 7.1 Hz, 1H), 6.65 (d, J = 8.1 Hz, 2H), 4.77 (d, J = 5.8 Hz, 2H), 4.58 (d, J = 5.8 Hz, 2H), 4.46 (s, 2H), 4.06 (s, 1H), 3.86 (d, J = 31.3 Hz, 2H), 3.26 (s, 1H), 3.13 (s, 1H), 2.97 (s, 1H), 2.52 (s, 3H), 2.52 (s, 2H), 1.99 (dt, J = 16.1, 8.3 Hz, 2H), 1.84 (s, 1H), 1.63 (t, J = 18.9 Hz, 4H) ppm
132a	 Single enantiomer	605.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 12.43 (s, 1H), 7.24 (s, 1H), 7.12 (dd, J = 8.5, 7.1 Hz, 2H), 6.84 (s, 1H), 6.69 (t, J = 7.2 Hz, 1H), 6.61 (d, J = 8.0 Hz, 2H), 4.25 – 4.16 (m, 2H), 4.05 (d, J = 16.1 Hz, 1H), 3.95 (p, J = 7.3 Hz, 1H), 3.84 (s, 1H), 3.26 (s, 1H), 2.50 (s, 1H), 2.46 (s, 3H), 2.41 (dd, J = 11.7, 8.0 Hz, 1H), 2.15 – 1.92 (m, 4H), 1.82 (d, J = 8.0 Hz, 1H), 1.63 (t, J = 18.9 Hz, 4H), 1.20 (t, J = 3.6 Hz, 2H), 1.07 (dt, J = 4.9, 2.2 Hz, 2H), 0.40 (d, J = 11.8 Hz, 4H) ppm
132b	 Single enantiomer	605.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 12.43 (s, 1H), 7.24 (s, 1H), 7.12 (t, J = 7.8 Hz, 2H), 6.84 (s, 1H), 6.69 (t, J = 7.3 Hz, 1H), 6.61 (d, J = 8.1 Hz, 2H), 4.25 – 4.17 (m, 2H), 4.10 – 3.97 (m, 1H), 3.95 (q, J = 7.4 Hz, 1H), 3.84 (s, 1H), 3.23 (s, 1H), 2.52 (s, 1H), 2.47 – 2.45 (m, 3H), 2.43 – 2.39 (m, 1H), 2.08 (ddd, J = 33.3, 12.0, 6.4 Hz, 2H),

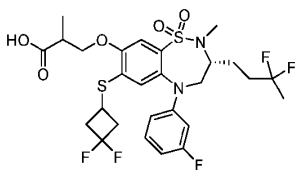
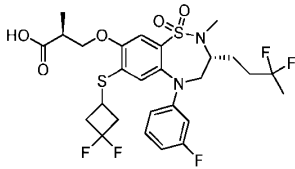
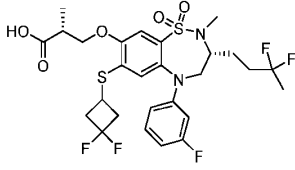
			1.97 (dq, J = 16.5, 8.2 Hz, 2H), 1.87 – 1.77 (m, 1H), 1.63 (t, J = 18.9 Hz, 4H), 1.20 (t, J = 3.7 Hz, 2H), 1.07 (dt, J = 5.0, 2.2 Hz, 2H), 0.40 (d, J = 12.3 Hz, 4H) ppm
133a/b		623.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 12.42 (s, 1H), 7.26 (s, 1H), 7.10 (q, J = 7.9 Hz, 1H), 6.90 (s, 1H), 6.46 (t, J = 8.3 Hz, 1H), 6.39 (d, J = 12.8 Hz, 1H), 6.32 (d, J = 8.4 Hz, 1H), 4.23 (q, J = 9.8 Hz, 2H), 4.03 (dd, J = 14.4, 6.8 Hz, 2H), 3.89 (s, 1H), 2.55 (d, J = 10.6 Hz, 2H), 2.43 (s, 4H), 2.09 (ddd, J = 32.3, 11.9, 6.2 Hz, 2H), 1.94 (dd, J = 33.2, 16.5 Hz, 3H), 1.63 (t, J = 18.9 Hz, 4H), 1.21 (t, J = 3.8 Hz, 2H), 1.08 (q, J = 4.3, 3.5 Hz, 2H), 0.42 (d, J = 7.4 Hz, 4H) ppm
133a	 Single enantiomer	623.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 12.44 (s, 1H), 7.26 (s, 1H), 7.10 (q, J = 8.0 Hz, 1H), 6.90 (s, 1H), 6.50 – 6.42 (m, 1H), 6.39 (d, J = 12.7 Hz, 1H), 6.32 (d, J = 8.6 Hz, 1H), 4.23 (q, J = 9.8 Hz, 2H), 4.10 – 3.95 (m, 2H), 3.89 (s, 1H), 3.23 (s, 1H), 2.54 (t, J = 10.7 Hz, 1H), 2.46 – 2.44 (m, 1H), 2.43 (s, 3H), 2.13 (dd, J = 11.8, 6.4 Hz, 1H), 2.06 (dd, J = 11.7, 6.1 Hz, 1H), 2.03 – 1.85 (m, 3H), 1.63 (t, J = 18.9 Hz, 4H), 1.21 (t, J = 3.8 Hz, 2H), 1.12 – 1.03 (m, 2H), 0.42 (d, J = 7.5 Hz, 4H) ppm
133b	 Single enantiomer	623.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 12.43 (s, 1H), 7.26 (s, 1H), 7.10 (q, J = 8.0 Hz, 1H), 6.90 (s, 1H), 6.49 – 6.43 (m, 1H), 6.39 (d, J = 12.6 Hz, 1H), 6.32 (d, J = 8.4 Hz, 1H), 4.23 (q, J = 9.8 Hz, 2H), 4.12 – 3.94 (m, 2H),

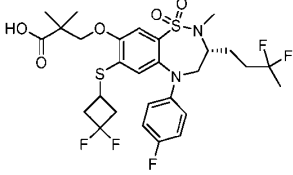
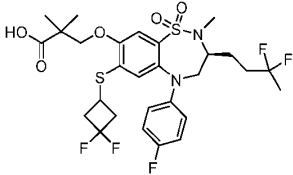
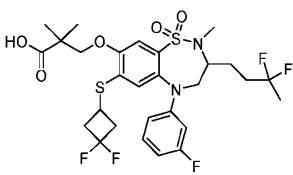
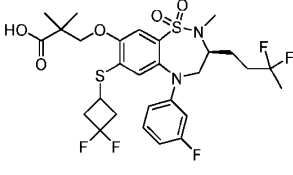
			3.89 (s, 1H), 3.22 (s, 1H), 2.55 (d, J = 10.3 Hz, 1H), 2.45 (s, 1H), 2.43 (s, 3H), 2.13 (dd, J = 12.0, 6.3 Hz, 1H), 2.06 (dd, J = 11.9, 6.2 Hz, 1H), 2.04 – 1.79 (m, 3H), 1.63 (t, J = 18.9 Hz, 4H), 1.26 – 1.17 (m, 2H), 1.12 – 1.01 (m, 2H), 0.42 (d, J = 7.5 Hz, 4H) ppm
134a	 Single enantiomer	623.2 [M-1] ⁺	¹ H NMR (500 MHz, DMSO-d ₆): δ 12.43 (s, 1H), 7.23 (s, 1H), 6.97 (t, J = 8.7 Hz, 2H), 6.79 (s, 1H), 6.62 (s, 2H), 4.25 – 4.15 (m, 2H), 4.00 (t, J = 14.3 Hz, 1H), 3.94 (t, J = 7.2 Hz, 1H), 3.81 (s, 1H), 3.27 (s, 1H), 2.52 (s, 1H), 2.46 (s, 3H), 2.40 (t, J = 10.1 Hz, 1H), 2.11 (dd, J = 11.9, 6.3 Hz, 1H), 2.04 (dd, J = 11.8, 6.2 Hz, 1H), 1.96 (dq, J = 16.4, 8.2 Hz, 2H), 1.80 (d, J = 10.1 Hz, 1H), 1.62 (t, J = 18.9 Hz, 4H), 1.20 (t, J = 3.5 Hz, 2H), 1.07 (d, J = 3.2 Hz, 2H), 0.41 (d, J = 7.5 Hz, 4H) ppm
134b	 Single enantiomer	623.2 [M-1] ⁺	¹ H NMR (500 MHz, DMSO-d ₆): δ 12.42 (s, 1H), 7.23 (s, 1H), 6.97 (t, J = 8.8 Hz, 2H), 6.79 (s, 1H), 6.63 (d, J = 5.3 Hz, 2H), 4.24 – 4.16 (m, 2H), 4.09 – 3.96 (m, 1H), 3.93 (q, J = 7.3 Hz, 1H), 3.82 (s, 1H), 3.26 (s, 1H), 2.52 (s, 1H), 2.46 (s, 3H), 2.40 (dd, J = 11.8, 8.1 Hz, 1H), 2.11 (dd, J = 11.9, 6.3 Hz, 1H), 2.04 (dd, J = 11.9, 6.2 Hz, 1H), 1.96 (dq, J = 16.3, 8.0 Hz, 2H), 1.80 (d, J = 8.0 Hz, 1H), 1.62 (t, J = 18.9 Hz, 4H), 1.20 (t, J = 3.5 Hz, 2H), 1.11 – 1.03 (m, 2H), 0.41 (d, J = 7.7 Hz, 4H) ppm
135a		605.2	¹ H NMR (500 MHz, CD ₃ CN): δ 7.40 (s, 1H), 7.20 (dd, J = 8.6, 7.0 Hz, 2H), 6.97 (s, 1H), 6.78 (t, J = 7.3 Hz, 1H), 6.66 (d, J = 8.1 Hz, 2H), 4.30 (t, J =

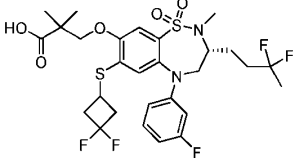
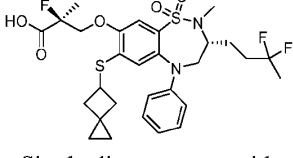
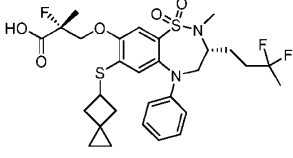
	Single diastereomer with arbitrarily assigned stereochemistry		8.0 Hz, 1H), 4.23 (d, J = 6.9 Hz, 1H), 4.01 (d, J = 15.1 Hz, 2H), 3.71 (s, 1H), 3.30 (s, 2H), 3.14 (s, 1H), 3.02 (td, J = 9.0, 4.2 Hz, 2H), 2.57 (s, 1H), 2.54 (s, 3H), 2.06 (dt, J = 10.8, 5.6 Hz, 2H), 1.88 – 1.83 (m, 1H), 1.73 (s, 1H), 1.66 (t, J = 18.8 Hz, 3H), 1.29 (d, J = 6.8 Hz, 3H) ppm
135b	 Single diastereomer with arbitrarily assigned stereochemistry	605.2	¹ H NMR (500 MHz, CD ₃ CN): δ 7.40 (s, 1H), 7.20 (dd, J = 8.5, 7.0 Hz, 2H), 6.97 (s, 1H), 6.78 (t, J = 7.3 Hz, 1H), 6.66 (d, J = 8.1 Hz, 2H), 4.31 (dd, J = 9.1, 6.6 Hz, 1H), 4.23 (dd, J = 9.1, 5.4 Hz, 1H), 4.01 (d, J = 14.9 Hz, 2H), 3.71 (s, 1H), 3.30 (s, 1H), 3.14 (s, 2H), 3.02 (td, J = 9.3, 4.5 Hz, 1H), 2.94 (q, J = 6.6 Hz, 1H), 2.58 (d, J = 5.1 Hz, 1H), 2.54 (s, 3H), 2.10 – 2.04 (m, 2H), 1.86 – 1.70 (m, 2H), 1.66 (t, J = 18.8 Hz, 3H), 1.30 (d, J = 7.0 Hz, 3H) ppm
135c	 Single diastereomer with arbitrarily assigned stereochemistry	605.2	¹ H NMR (500 MHz, CD ₃ CN): δ 7.40 (s, 1H), 7.26 – 7.14 (m, 2H), 6.98 (s, 1H), 6.78 (t, J = 7.3 Hz, 1H), 6.66 (d, J = 8.1 Hz, 2H), 4.29 (dd, J = 9.2, 6.9 Hz, 1H), 4.24 (dd, J = 9.1, 5.2 Hz, 1H), 4.01 (d, J = 15.3 Hz, 2H), 3.76 – 3.66 (m, 1H), 3.30 (s, 1H), 3.14 (d, J = 4.1 Hz, 1H), 3.00 (dtd, J = 25.9, 8.0, 7.4, 4.9 Hz, 2H), 2.54 (d, J = 4.0 Hz, 5H), 2.05 (dt, J = 16.3, 5.6 Hz, 2H), 1.98 (d, J = 3.6 Hz, 3H), 1.77 (d, J = 34.8 Hz, 1H), 1.66 (t, J = 18.8 Hz, 3H), 1.30 (d, J = 7.1 Hz, 3H) ppm
135d		605.2	¹ H NMR (500 MHz, CD ₃ CN): δ 7.40 (s, 1H), 7.27 – 7.15 (m, 2H), 6.98 (s, 1H), 6.78 (t, J = 7.3 Hz, 1H), 6.66 (d, J = 8.1 Hz, 2H), 4.30 (dd, J = 9.2, 6.5 Hz, 1H), 4.25 (dd, J = 9.2, 5.2 Hz, 1H),

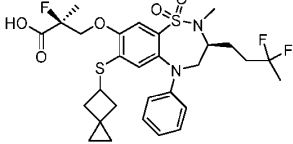
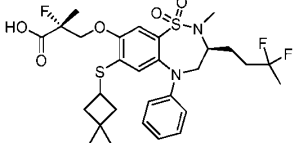
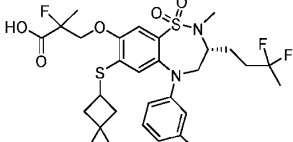
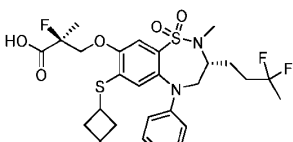
	Single diastereomer with arbitrarily assigned stereochemistry		4.01 (d, J = 14.8 Hz, 2H), 3.71 (dt, J = 10.4, 7.6, 3.8 Hz, 1H), 3.30 (s, 1H), 3.14 (t, J = 11.6 Hz, 1H), 3.08 – 2.90 (m, 2H), 2.54 (d, J = 4.5 Hz, 5H), 2.14 – 2.02 (m, 2H), 1.98 (d, J = 3.7 Hz, 3H), 1.74 (s, 1H), 1.66 (t, J = 18.8 Hz, 3H), 1.31 (d, J = 7.0 Hz, 3H) ppm
136a	 Single diastereomer with arbitrarily assigned stereochemistry	621.0 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 12.46 (s, 1H), 7.28 (s, 1H), 6.98 (t, J = 8.7 Hz, 2H), 6.91 (s, 1H), 6.64 (s, 2H), 4.22 (dd, J = 9.1, 6.6 Hz, 1H), 4.16 (dd, J = 9.0, 5.4 Hz, 1H), 4.03 (d, J = 15.8 Hz, 1H), 3.81 (s, 2H), 3.26 (s, 1H), 3.14 (s, 1H), 2.98 (s, 1H), 2.85 (q, J = 6.5 Hz, 1H), 2.52 (s, 1H), 2.49 (s, 3H), 2.44 (s, 1H), 1.98 (dq, J = 16.9, 8.8, 8.3 Hz, 2H), 1.87 – 1.76 (m, 1H), 1.63 (t, J = 18.9 Hz, 4H), 1.21 (d, J = 7.1 Hz, 3H) ppm
136b	 Single diastereomer with arbitrarily assigned stereochemistry	621.2 [M-1] ⁻	¹ H NMR (500 MHz, CD ₃ CN): δ 7.39 (s, 1H), 7.01 – 6.94 (m, 2H), 6.92 (s, 1H), 6.67 (dd, J = 9.3, 4.2 Hz, 2H), 4.29 (dd, J = 9.2, 6.6 Hz, 1H), 4.24 (dd, J = 9.1, 5.3 Hz, 1H), 3.95 (d, J = 15.2 Hz, 2H), 3.72 – 3.66 (m, 1H), 3.33 (s, 1H), 3.13 (d, J = 12.1 Hz, 1H), 3.06 – 2.90 (m, 2H), 2.54 (s, 5H), 1.99 (s, 3H), 1.74 (t, J = 16.5 Hz, 1H), 1.65 (t, J = 18.8 Hz, 3H), 1.30 (d, J = 7.1 Hz, 3H) ppm
136c	 Single diastereomer with arbitrarily assigned stereochemistry	623.2	¹ H NMR (500 MHz, CD ₃ CN): δ 7.39 (s, 1H), 6.97 (t, J = 8.8 Hz, 2H), 6.92 (s, 1H), 6.66 (dd, J = 9.3, 4.4 Hz, 2H), 4.35 – 4.16 (m, 2H), 3.95 (d, J = 15.7 Hz, 2H), 3.69 (dt, J = 8.9, 6.0, 2.9 Hz, 1H), 3.32 (s, 1H), 3.22 – 3.07 (m, 1H), 3.01 (dddd, J = 22.3, 13.5, 8.9, 3.8 Hz, 2H), 2.54 (s, 5H), 2.00 – 1.97 (m, 3H),

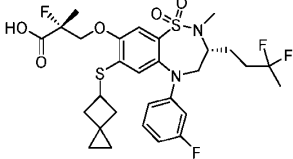
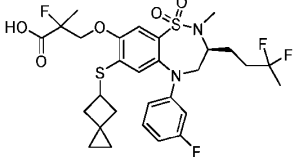
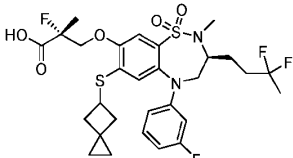
			1.65 (t, J = 18.8 Hz, 4H), 1.30 (d, J = 6.9 Hz, 3H) ppm
136d	 Single diastereomer with arbitrarily assigned stereochemistry	623.2	¹ H NMR (500 MHz, CD ₃ CN): δ 7.39 (s, 1H), 7.02 – 6.93 (m, 2H), 6.92 (s, 1H), 6.67 (dd, J = 9.3, 4.4 Hz, 2H), 4.29 (dd, J = 9.2, 6.6 Hz, 1H), 4.24 (dd, J = 9.1, 5.2 Hz, 1H), 3.95 (d, J = 15.2 Hz, 2H), 3.69 (ddh, J = 11.6, 5.8, 2.8 Hz, 1H), 3.33 (s, 1H), 3.15 (d, J = 13.4 Hz, 1H), 3.08 – 2.91 (m, 2H), 2.54 (s, 5H), 1.98 (d, J = 3.5 Hz, 3H), 1.65 (t, J = 18.8 Hz, 4H), 1.31 (d, J = 7.2 Hz, 3H) ppm
137a	 Single diastereomer with arbitrarily assigned stereochemistry	623.2	¹ H NMR (600 MHz, DMSO-d ₆): δ 12.51 (s, 1H), 7.31 (s, 1H), 7.12 (q, J = 8.0 Hz, 1H), 7.03 (s, 1H), 6.53 – 6.38 (m, 2H), 6.33 (d, J = 7.7 Hz, 1H), 4.26 (dd, J = 9.1, 6.2 Hz, 1H), 4.16 (dd, J = 9.3, 5.9 Hz, 1H), 4.04 (d, J = 16.2 Hz, 1H), 3.87 (s, 2H), 3.19 (s, 2H), 3.04 (d, J = 13.3 Hz, 1H), 2.81 (s, 1H), 2.61 – 2.50 (m, 2H), 2.45 (s, 3H), 2.05 – 1.87 (m, 3H), 1.64 (t, J = 18.9 Hz, 4H), 1.21 (d, J = 7.2 Hz, 3H) ppm
137b	 Single diastereomer with arbitrarily assigned stereochemistry	623.2	¹ H NMR (600 MHz, DMSO-d ₆): δ 12.47 (s, 1H), 7.31 (s, 1H), 7.13 (q, J = 8.0 Hz, 1H), 7.03 (s, 1H), 6.48 (td, J = 8.1, 2.1 Hz, 1H), 6.43 (d, J = 12.4 Hz, 1H), 6.34 (d, J = 8.4 Hz, 1H), 4.24 (dd, J = 9.0, 6.7 Hz, 1H), 4.19 (dd, J = 9.0, 5.5 Hz, 1H), 4.04 (d, J = 16.4 Hz, 1H), 3.87 (s, 2H), 3.19 (s, 2H), 3.04 (d, J = 12.5 Hz, 1H), 2.85 (q, J = 6.6 Hz, 1H), 2.61 – 2.50 (m, 2H), 2.45 (s, 3H), 2.03 – 1.95 (m, 2H), 1.91 (d, J = 15.3 Hz, 1H), 1.64 (t, J = 18.9 Hz, 4H), 1.21 (d, J = 7.1 Hz, 3H) ppm

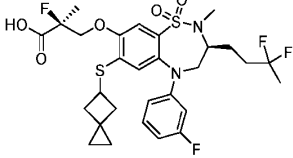
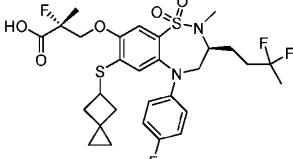
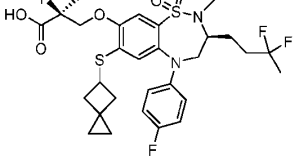
137c/d	 A mixture of two diastereomers	621.2 [M-1] ⁻	¹ H NMR (600 MHz, DMSO-d ₆): δ 12.54 (s, 1H), 7.31 (s, 1H), 7.12 (q, J = 7.9 Hz, 1H), 7.03 (s, 1H), 6.48 (dt, J = 10.1, 5.0 Hz, 1H), 6.43 (d, J = 11.5 Hz, 1H), 6.39 – 6.25 (m, 1H), 4.30 – 4.20 (m, 1H), 4.16 (dd, J = 9.0, 5.8 Hz, 1H), 4.04 (d, J = 16.0 Hz, 1H), 3.87 (s, 2H), 3.24 – 3.15 (m, 2H), 3.16 – 2.91 (m, 2H), 2.82 (p, J = 6.6 Hz, 1H), 2.55 (d, J = 14.1 Hz, 1H), 2.45 (s, 3H), 1.98 (dt, J = 16.2, 8.7 Hz, 2H), 1.90 (s, 1H), 1.64 (t, J = 18.9 Hz, 4H), 1.21 (dd, J = 7.2, 3.5 Hz, 3H) ppm
137c	 Single diastereomer with arbitrarily assigned stereochemistry	623.2	¹ H NMR (500 MHz, CD ₃ CN): δ 7.41 (s, 1H), 7.17 (q, J = 8.0 Hz, 1H), 7.02 (s, 1H), 6.49 (td, J = 8.4, 2.4 Hz, 1H), 6.38 (t, J = 12.8 Hz, 2H), 4.32 (dd, J = 9.2, 6.4 Hz, 1H), 4.26 (dd, J = 9.1, 5.2 Hz, 1H), 4.06 (s, 1H), 3.94 (d, J = 16.2 Hz, 1H), 3.80 – 3.69 (m, 1H), 3.28 (s, 1H), 3.15 (d, J = 13.2 Hz, 1H), 3.13 – 3.03 (m, 1H), 2.98 (q, J = 6.6 Hz, 1H), 2.64 – 2.52 (m, 2H), 2.51 (s, 3H), 2.04 (dt, J = 10.1, 5.1 Hz, 1H), 1.98 (d, J = 3.6 Hz, 3H), 1.66 (t, J = 18.8 Hz, 4H), 1.31 (d, J = 7.1 Hz, 3H) ppm
137d	 Single diastereomer with arbitrarily assigned stereochemistry	621.0 [M-1] ⁻	¹ H NMR (500 MHz, CD ₃ CN): δ 7.41 (s, 1H), 7.17 (q, J = 7.9 Hz, 1H), 7.02 (s, 1H), 6.49 (td, J = 8.3, 2.4 Hz, 1H), 6.44 – 6.28 (m, 2H), 4.31 (t, J = 8.0 Hz, 1H), 4.24 (dd, J = 9.2, 5.1 Hz, 1H), 4.06 (s, 1H), 3.94 (d, J = 16.2 Hz, 1H), 3.79 – 3.71 (m, 1H), 3.28 (s, 1H), 3.18 (s, 1H), 3.13 – 3.03 (m, 1H), 2.98 (s, 1H), 2.61 – 2.53 (m, 2H), 2.51 (s, 3H), 2.05 (d, J = 5.5 Hz, 1H), 1.99 (s, 3H), 1.66 (t, J = 18.8 Hz, 4H), 1.30 (d, J = 6.9 Hz, 3H) ppm

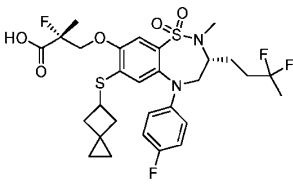
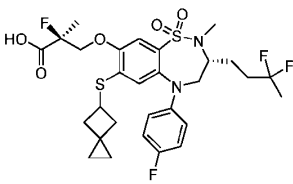
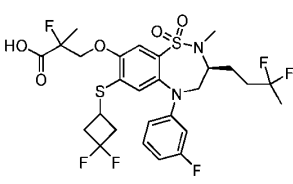
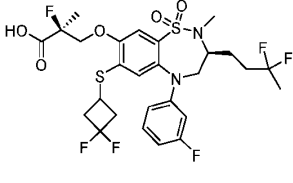
138a	 Single enantiomer	637.2	¹ H NMR (600 MHz, DMSO-d ₆): δ 12.59 (s, 1H), 7.26 (s, 1H), 6.98 (t, J = 8.6 Hz, 2H), 6.90 (s, 1H), 6.65 (d, J = 6.8 Hz, 2H), 4.11 – 3.93 (m, 3H), 3.81 (s, 2H), 3.24 (s, 1H), 3.14 (s, 1H), 2.98 (d, J = 13.1 Hz, 1H), 2.54 (d, J = 19.7 Hz, 2H), 2.44 (s, 3H), 1.98 (tt, J = 16.5, 8.2 Hz, 2H), 1.86 – 1.78 (m, 1H), 1.63 (t, J = 18.9 Hz, 4H), 1.21 (s, 6H) ppm
138b	 Single enantiomer	637.0	¹ H NMR (600 MHz, DMSO-d ₆): δ 12.48 (s, 1H), 7.27 (s, 1H), 6.98 (t, J = 8.6 Hz, 2H), 6.90 (s, 1H), 6.65 (s, 2H), 4.08 (s, 2H), 4.03 (d, J = 13.4 Hz, 1H), 3.80 (s, 2H), 3.24 (s, 1H), 3.14 (s, 1H), 2.99 (d, J = 13.6 Hz, 1H), 2.53 (d, J = 13.4 Hz, 2H), 2.43 (s, 3H), 1.98 (tt, J = 16.4, 8.2 Hz, 2H), 1.86 – 1.76 (m, 1H), 1.63 (t, J = 18.9 Hz, 4H), 1.24 (d, J = 2.2 Hz, 6H) ppm
139a/b	 Single enantiomer	635.0 [M-1] ⁺	¹ H NMR (500 MHz, DMSO-d ₆): δ 12.45 (s, 1H), 7.29 (s, 1H), 7.12 (q, J = 7.9 Hz, 1H), 7.02 (s, 1H), 6.54 – 6.36 (m, 2H), 6.34 (s, 1H), 4.11 (s, 2H), 4.04 (d, J = 15.9 Hz, 1H), 3.87 (s, 2H), 3.24 (d, J = 39.7 Hz, 2H), 3.05 (s, 1H), 2.54 (s, 2H), 2.45 (s, 3H), 2.04 – 1.86 (m, 3H), 1.64 (t, J = 18.9 Hz, 4H), 1.25 (d, J = 3.1 Hz, 6H) ppm
139a	 Single enantiomer	637.2	¹ H NMR (600 MHz, DMSO-d ₆): δ 12.46 (s, 1H), 7.30 (s, 1H), 7.12 (q, J = 7.9 Hz, 1H), 7.02 (s, 1H), 6.52 – 6.39 (m, 2H), 6.34 (d, J = 8.4 Hz, 1H), 4.11 (s, 2H), 4.04 (d, J = 16.2 Hz, 1H), 3.86 (s, 2H), 3.19 (s, 2H), 3.04 (d, J = 11.3 Hz, 1H), 2.61 – 2.50 (m, 2H), 2.45 (s, 3H), 2.04 – 1.86 (m, 3H), 1.64

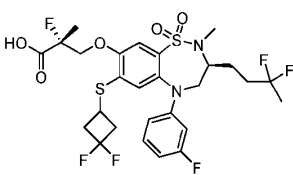
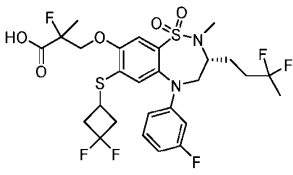
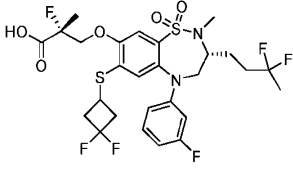
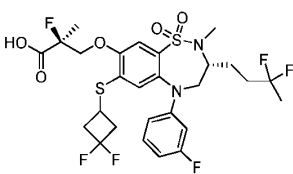
			(t, J = 18.9 Hz, 4H), 1.25 (d, J = 3.5 Hz, 6H) ppm
139b	 Single enantiomer	637.2	¹ H NMR (600 MHz, DMSO-d ₆): δ 12.46 (s, 1H), 7.30 (s, 1H), 7.12 (q, J = 7.9 Hz, 1H), 7.02 (s, 1H), 6.46 (dt, J = 21.9, 10.1 Hz, 2H), 6.34 (s, 1H), 4.11 (s, 2H), 4.04 (d, J = 15.7 Hz, 1H), 3.86 (d, J = 9.3 Hz, 2H), 3.19 (s, 2H), 3.04 (d, J = 12.1 Hz, 1H), 2.53 (d, J = 8.7 Hz, 2H), 2.45 (s, 3H), 2.04 – 1.87 (m, 3H), 1.64 (t, J = 18.9 Hz, 4H), 1.25 (d, J = 3.5 Hz, 6H) ppm
140a	 Single diastereomer with arbitrarily assigned stereochemistry	611.2 [M-1] ⁻	¹ H NMR (600 MHz, DMSO-d ₆): δ 13.55 (s, 1H), 7.31 (s, 1H), 7.13 (t, J = 7.8 Hz, 2H), 6.85 (s, 1H), 6.70 (t, J = 7.2 Hz, 1H), 6.62 (d, J = 8.1 Hz, 2H), 4.52 – 4.35 (m, 2H), 4.05 (d, J = 15.8 Hz, 1H), 3.96 (p, J = 7.1 Hz, 1H), 3.84 (s, 1H), 3.21 (s, 1H), 2.50 (s, 1H), 2.47 (s, 3H), 2.41 (dd, J = 11.8, 8.1 Hz, 1H), 2.10 (dd, J = 11.8, 6.3 Hz, 1H), 2.03 (dd, J = 11.8, 6.1 Hz, 1H), 1.97 (dq, J = 16.4, 8.1 Hz, 2H), 1.81 (d, J = 13.5 Hz, 1H), 1.68 – 1.57 (m, 7H), 0.45 – 0.36 (m, 4H) ppm
140b	 Single diastereomer with arbitrarily assigned stereochemistry	611.2 [M-1] ⁻	¹ H NMR (600 MHz, DMSO-d ₆): δ 13.57 (s, 1H), 7.32 (s, 1H), 7.15 – 7.09 (m, 2H), 6.85 (s, 1H), 6.70 (t, J = 7.3 Hz, 1H), 6.62 (d, J = 8.1 Hz, 2H), 4.53 – 4.36 (m, 2H), 4.12 – 3.98 (m, 1H), 3.95 (q, J = 7.2 Hz, 1H), 3.84 (s, 1H), 3.21 (s, 1H), 2.51 (s, 1H), 2.47 (s, 3H), 2.41 (dd, J = 11.8, 8.1 Hz, 1H), 2.10 (dd, J = 11.8, 6.3 Hz, 1H), 2.04 (dd, J = 11.8, 6.2 Hz, 1H), 1.97 (dq, J = 16.4, 8.0 Hz, 2H), 1.81 (d, J = 13.9 Hz, 1H), 1.67 – 1.56 (m, 7H), 0.45 – 0.36 (m, 4H) ppm

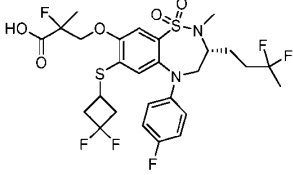
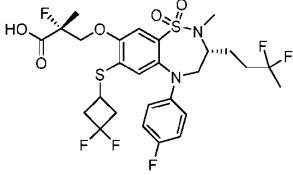
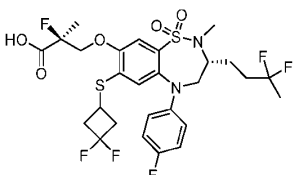
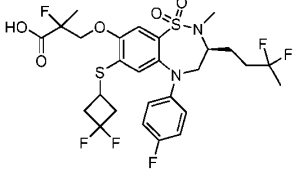
140c	 Single diastereomer with arbitrarily assigned stereochemistry	611.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 13.58 (s, 1H), 7.31 (s, 1H), 7.13 (t, J = 7.8 Hz, 2H), 6.85 (s, 1H), 6.70 (t, J = 7.4 Hz, 1H), 6.62 (d, J = 8.2 Hz, 2H), 4.44 (dq, J = 19.6, 11.1 Hz, 2H), 4.04 (s, 1H), 4.01 – 3.93 (m, 1H), 3.84 (s, 1H), 3.19 (s, 1H), 2.47 (s, 3H), 2.41 (t, J = 10.1 Hz, 1H), 2.27 – 1.71 (m, 6H), 1.69 – 1.53 (m, 7H), 0.40 (d, J = 12.9 Hz, 4H) ppm
140d	 Single diastereomer with arbitrarily assigned stereochemistry	611.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 13.46 (s, 1H), 7.32 (d, J = 2.4 Hz, 1H), 7.14 (t, J = 7.8 Hz, 2H), 6.84 (s, 1H), 6.71 (d, J = 7.4 Hz, 1H), 6.69 – 6.59 (m, 2H), 4.54 – 4.34 (m, 2H), 4.04 (d, J = 16.1 Hz, 1H), 3.94 (q, J = 7.3 Hz, 1H), 3.83 (s, 1H), 3.32 (s, 1H), 2.47 (s, 3H), 2.40 (t, J = 10.0 Hz, 1H), 2.17 – 1.83 (m, 5H), 1.87 – 1.76 (m, 1H), 1.69 – 1.55 (m, 7H), 0.41 (d, J = 12.2 Hz, 4H) ppm
141a/b	 A mixture of two diastereomers	629.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 13.56 (s, 1H), 7.33 (d, J = 1.7 Hz, 1H), 7.11 (dt, J = 8.3, 6.3 Hz, 1H), 6.92 (s, 1H), 6.46 (td, J = 8.4, 2.3 Hz, 1H), 6.40 (d, J = 12.8 Hz, 1H), 6.33 (s, 1H), 4.56 – 4.37 (m, 2H), 4.09 – 3.98 (m, 2H), 3.89 (s, 1H), 2.96 (s, 2H), 2.58 – 2.52 (m, 1H), 2.44 (s, 3H), 2.11 (dd, J = 11.9, 6.3 Hz, 1H), 2.09 – 2.03 (m, 1H), 2.03 – 1.93 (m, 2H), 1.93 – 1.85 (m, 1H), 1.68 – 1.56 (m, 7H), 0.42 (h, J = 3.3, 2.5 Hz, 4H) ppm
141a		629.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 13.58 (s, 1H), 7.34 (s, 1H), 7.11 (q, J = 7.9 Hz, 1H), 6.92 (s, 1H), 6.46 (td, J = 8.4, 2.3 Hz, 1H), 6.40 (d, J = 12.9 Hz, 1H), 6.37 – 6.26 (m, 1H), 4.56 –

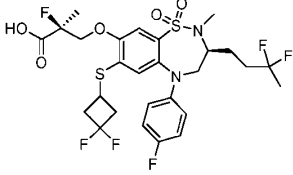
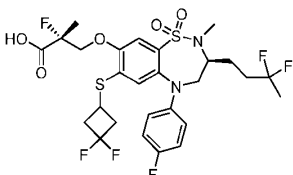
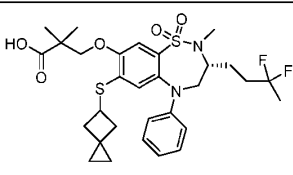
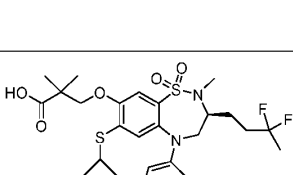
	Single diastereomer with arbitrarily assigned stereochemistry		4.37 (m, 2H), 4.09 – 3.97 (m, 2H), 3.89 (s, 1H), 3.20 (s, 1H), 2.55 (t, J = 10.1 Hz, 1H), 2.46 (d, J = 8.2 Hz, 1H), 2.44 (s, 3H), 2.11 (dd, J = 11.8, 6.4 Hz, 1H), 2.07 – 2.04 (m, 1H), 2.03 – 1.93 (m, 2H), 1.92 – 1.85 (m, 1H), 1.68 – 1.55 (m, 7H), 0.42 (d, J = 8.6 Hz, 4H) ppm
141b	 Single diastereomer with arbitrarily assigned stereochemistry	629.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 13.56 (s, 1H), 7.33 (s, 1H), 7.11 (q, J = 7.9 Hz, 1H), 6.92 (s, 1H), 6.46 (td, J = 8.3, 2.3 Hz, 1H), 6.39 (d, J = 12.6 Hz, 1H), 6.37 – 6.30 (m, 1H), 4.54 – 4.40 (m, 2H), 4.03 (p, J = 7.4, 6.9 Hz, 2H), 3.89 (s, 1H), 3.20 (s, 1H), 2.55 (t, J = 10.3 Hz, 1H), 2.47 (s, 1H), 2.44 (s, 3H), 2.11 (dd, J = 11.9, 6.3 Hz, 1H), 2.07 – 2.03 (m, 1H), 2.02 – 1.93 (m, 2H), 1.90 (d, J = 13.3 Hz, 1H), 1.67 – 1.55 (m, 7H), 0.42 (dd, J = 10.0, 2.2 Hz, 4H) ppm
141c/d	 A mixture of two diastereomers	629.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 7.33 – 7.16 (m, 1H), 7.10 (q, J = 7.8 Hz, 1H), 6.90 (s, 1H), 6.52 – 6.42 (m, 1H), 6.39 (d, J = 12.5 Hz, 1H), 6.32 (s, 1H), 4.29 (s, 1H), 4.25 (d, J = 4.9 Hz, 1H), 4.02 (d, J = 15.3 Hz, 2H), 3.89 (s, 1H), 3.21 (s, 1H), 2.55 (dd, J = 20.1, 10.0 Hz, 2H), 2.43 (s, 3H), 2.18 – 2.05 (m, 2H), 2.02 – 1.91 (m, 2H), 1.88 (s, 1H), 1.63 (t, J = 18.9 Hz, 4H), 1.44 (dd, J = 21.0, 5.5 Hz, 3H), 0.42 (d, J = 9.4 Hz, 4H) ppm
141c		629.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 13.59 (s, 1H), 7.33 (s, 1H), 7.10 (q, J = 8.0 Hz, 1H), 6.92 (s, 1H), 6.46 (t, J = 8.4 Hz, 1H), 6.40 (d, J = 12.8 Hz, 1H), 6.31 (s, 1H), 4.58 – 4.37 (m, 2H),

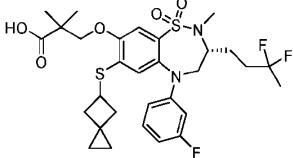
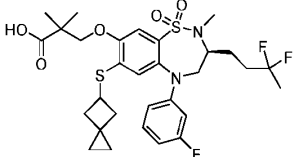
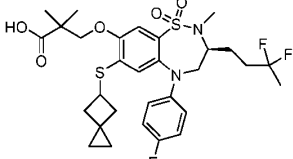
	Single diastereomer with arbitrarily assigned stereochemistry		4.09 – 3.94 (m, 2H), 3.89 (s, 1H), 3.20 (s, 1H), 2.55 (t, J = 11.6 Hz, 1H), 2.44 (d, J = 6.3 Hz, 3H), 2.19 – 1.80 (m, 6H), 1.69 – 1.54 (m, 7H), 0.42 (d, J = 6.5 Hz, 4H) ppm
141d	 Single diastereomer with arbitrarily assigned stereochemistry	629.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 13.55 (s, 1H), 7.33 (s, 1H), 7.11 (q, J = 7.9 Hz, 1H), 6.92 (s, 1H), 6.47 (td, J = 8.3, 2.3 Hz, 1H), 6.40 (d, J = 12.6 Hz, 1H), 6.33 (d, J = 8.4 Hz, 1H), 4.54 – 4.37 (m, 2H), 4.11 – 3.96 (m, 2H), 3.89 (s, 1H), 3.20 (s, 1H), 2.59 – 2.52 (m, 1H), 2.47 (s, 1H), 2.44 (s, 3H), 2.11 (dd, J = 11.8, 6.3 Hz, 1H), 2.05 (dd, J = 12.0, 6.0 Hz, 1H), 2.02 – 1.92 (m, 2H), 1.89 (q, J = 11.4, 9.8 Hz, 1H), 1.67 – 1.54 (m, 7H), 0.47 – 0.39 (m, 4H) ppm
142a	 Single diastereomer with arbitrarily assigned stereochemistry	629.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 13.55 (s, 1H), 7.30 (s, 1H), 6.97 (t, J = 8.6 Hz, 2H), 6.79 (s, 1H), 6.63 (d, J = 8.4 Hz, 2H), 4.54 – 4.28 (m, 2H), 4.08 – 3.85 (m, 2H), 3.81 (s, 1H), 3.25 (s, 1H), 2.47 (s, 3H), 2.39 (t, J = 10.0 Hz, 1H), 2.21 – 1.84 (m, 5H), 1.86 – 1.75 (m, 1H), 1.69 – 1.54 (m, 7H), 0.41 (d, J = 8.4 Hz, 4H) ppm
142b	 Single diastereomer with arbitrarily assigned stereochemistry	629.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 13.54 (s, 1H), 7.30 (s, 1H), 6.98 (t, J = 8.7 Hz, 2H), 6.80 (s, 1H), 6.64 (s, 2H), 4.55 – 4.33 (m, 2H), 4.12 – 3.88 (m, 2H), 3.81 (s, 1H), 3.23 (s, 1H), 2.47 (s, 3H), 2.40 (dd, J = 11.7, 8.2 Hz, 1H), 2.21 – 1.84 (m, 5H), 1.87 – 1.73 (m, 1H), 1.67 – 1.51 (m, 7H), 0.41 (d, J = 8.0 Hz, 4H) ppm

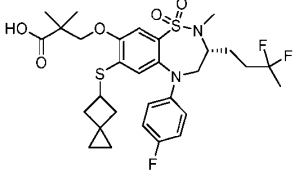
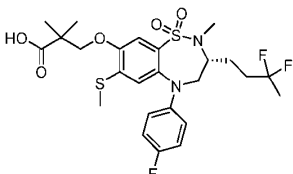
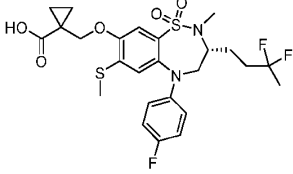
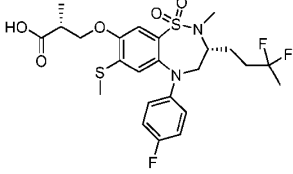
142c	 Single diastereomer with arbitrarily assigned stereochemistry	629.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 13.55 (s, 1H), 7.30 (s, 1H), 6.97 (t, J = 8.6 Hz, 2H), 6.79 (s, 1H), 6.64 (s, 2H), 4.55 – 4.29 (m, 2H), 4.08 – 3.86 (m, 2H), 3.81 (s, 1H), 3.25 (s, 1H), 2.47 (s, 3H), 2.39 (t, J = 10.0 Hz, 1H), 2.24 – 1.85 (m, 5H), 1.76 (d, J = 29.1 Hz, 1H), 1.68 – 1.55 (m, 7H), 0.41 (d, J = 8.2 Hz, 4H) ppm
142d	 Single diastereomer with arbitrarily assigned stereochemistry	629.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 13.53 (s, 1H), 7.30 (s, 1H), 6.98 (t, J = 8.6 Hz, 2H), 6.80 (s, 1H), 6.63 (d, J = 8.4 Hz, 2H), 4.56 – 4.31 (m, 2H), 4.08 – 3.87 (m, 2H), 3.81 (s, 1H), 3.24 (s, 1H), 2.47 (s, 3H), 2.39 (t, J = 9.9 Hz, 1H), 2.27 – 1.83 (m, 5H), 1.80 (d, J = 10.0 Hz, 1H), 1.68 – 1.55 (m, 7H), 0.41 (d, J = 8.3 Hz, 4H) ppm
143a/b	 A mixture of two diastereomers	639.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 13.55 (s, 1H), 7.37 (s, 1H), 7.13 (q, J = 7.3 Hz, 1H), 7.05 (s, 1H), 6.53 – 6.39 (m, 2H), 6.35 (s, 1H), 4.59 – 4.38 (m, 2H), 4.04 (d, J = 15.8 Hz, 1H), 3.88 (s, 2H), 3.19 (s, 2H), 3.05 (s, 1H), 2.52 (s, 1H), 2.45 (s, 3H), 2.14 – 1.80 (m, 4H), 1.69 – 1.55 (m, 7H) ppm
143a	 Single diastereomer with arbitrarily assigned stereochemistry	639.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 7.28 (s, 1H), 7.12 (q, J = 7.9 Hz, 1H), 7.03 (s, 1H), 6.45 (q, J = 14.4, 11.3 Hz, 2H), 6.33 (d, J = 8.3 Hz, 1H), 4.35 – 4.23 (m, 2H), 4.03 (d, J = 16.1 Hz, 1H), 3.89 (s, 2H), 3.27 – 3.13 (m, 2H), 3.05 (d, J = 10.7 Hz, 1H), 2.52 (s, 2H), 2.44 (s, 3H), 1.94 (d, J = 37.6 Hz, 3H), 1.64 (t, J = 18.9 Hz, 4H), 1.44 (d, J = 21.0 Hz, 3H) ppm

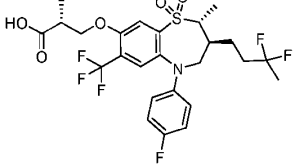
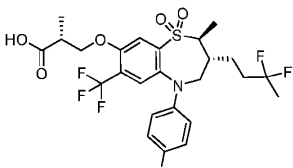
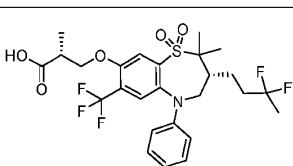
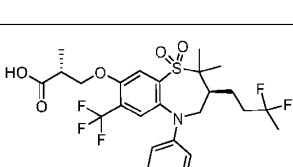
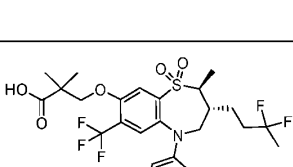
143b	 Single diastereomer with arbitrarily assigned stereochemistry	639.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 7.27 (s, 1H), 7.12 (q, J = 8.0 Hz, 1H), 7.02 (s, 1H), 6.46 (t, J = 8.5 Hz, 2H), 6.33 (s, 1H), 4.33 – 4.21 (m, 2H), 4.03 (d, J = 16.1 Hz, 1H), 3.89 (s, 2H), 3.20 (s, 2H), 3.05 (s, 1H), 2.52 (s, 2H), 2.43 (s, 3H), 1.93 (d, J = 38.4 Hz, 3H), 1.63 (t, J = 18.9 Hz, 4H), 1.43 (d, J = 21.1 Hz, 3H) ppm
143c/d	 A mixture of two diastereomers	639.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 13.60 (s, 1H), 7.36 (s, 1H), 7.13 (qd, J = 8.1, 2.4 Hz, 1H), 7.05 (s, 1H), 6.53 – 6.38 (m, 2H), 6.34 (s, 1H), 4.59 – 4.31 (m, 2H), 4.04 (d, J = 16.2 Hz, 1H), 3.88 (s, 2H), 3.19 (s, 2H), 3.05 (s, 1H), 2.53 (dd, J = 20.0, 11.7 Hz, 2H), 2.45 (s, 3H), 2.04 – 1.86 (m, 3H), 1.69 – 1.54 (m, 7H) ppm
143c	 Single diastereomer with arbitrarily assigned stereochemistry	639.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 13.61 (s, 1H), 7.36 (s, 1H), 7.12 (q, J = 7.9 Hz, 1H), 7.05 (s, 1H), 6.54 – 6.37 (m, 2H), 6.33 (d, J = 8.0 Hz, 1H), 4.57 – 4.39 (m, 2H), 4.05 (d, J = 16.2 Hz, 1H), 3.96 – 3.76 (m, 2H), 3.20 (s, 2H), 3.05 (td, J = 9.7, 4.7 Hz, 1H), 2.53 (dd, J = 15.8, 10.3 Hz, 2H), 2.45 (s, 3H), 2.03 – 1.86 (m, 3H), 1.69 – 1.54 (m, 7H) ppm
143d	 Single diastereomer with arbitrarily assigned stereochemistry	639.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 13.59 (s, 1H), 7.36 (s, 1H), 7.13 (q, J = 7.9 Hz, 1H), 7.05 (s, 1H), 6.48 (td, J = 8.4, 2.2 Hz, 1H), 6.44 (s, 1H), 6.34 (s, 1H), 4.55 – 4.40 (m, 2H), 4.05 (d, J = 15.9 Hz, 1H), 3.88 (s, 2H), 3.19 (s, 2H), 3.04 (d, J = 12.4 Hz, 1H), 2.61 – 2.50 (m, 2H), 2.45 (s, 3H), 2.04 – 1.86 (m, 3H), 1.69 – 1.52 (m, 7H) ppm

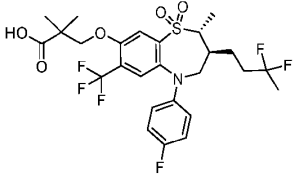
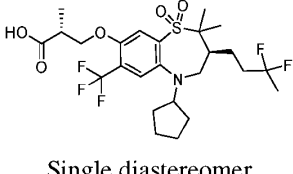
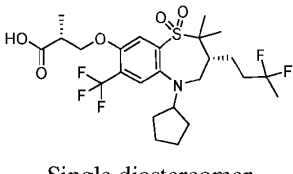
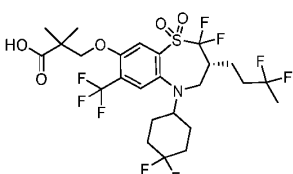
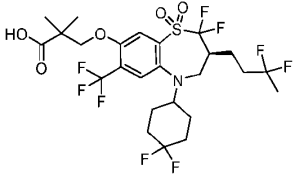
144a/b	 A mixture of two diastereomers	639.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 13.54 (s, 1H), 7.34 (s, 1H), 6.99 (td, J = 8.8, 2.2 Hz, 2H), 6.91 (s, 1H), 6.66 (s, 2H), 4.54 – 4.36 (m, 2H), 4.03 (d, J = 15.9 Hz, 1H), 3.81 (s, 2H), 3.14 (s, 1H), 2.98 (s, 1H), 2.52 (s, 6H), 1.98 (tt, J = 16.4, 8.3 Hz, 2H), 1.81 (d, J = 8.1 Hz, 1H), 1.67 – 1.55 (m, 7H) ppm
144a	 Single diastereomer with arbitrarily assigned stereochemistry	639.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 13.59 (s, 1H), 7.34 (s, 1H), 6.98 (t, J = 8.5 Hz, 2H), 6.91 (s, 1H), 6.66 (d, J = 8.0 Hz, 2H), 4.56 – 4.33 (m, 2H), 4.02 (d, J = 16.1 Hz, 1H), 3.81 (s, 2H), 3.14 (s, 2H), 3.05 – 2.91 (m, 1H), 2.52 (d, J = 1.6 Hz, 1H), 2.47 (s, 3H), 2.17 – 1.85 (m, 3H), 1.81 (s, 1H), 1.69 – 1.53 (m, 7H) ppm
144b	 Single diastereomer with arbitrarily assigned stereochemistry	639.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 13.57 (s, 1H), 7.34 (s, 1H), 6.99 (t, J = 8.6 Hz, 2H), 6.91 (s, 1H), 6.66 (s, 2H), 4.57 – 4.35 (m, 2H), 4.03 (d, J = 16.0 Hz, 1H), 3.81 (s, 2H), 3.14 (s, 2H), 2.98 (d, J = 3.3 Hz, 1H), 2.52 (d, J = 1.7 Hz, 1H), 2.45 (s, 3H), 2.10 – 1.89 (m, 3H), 1.81 (s, 1H), 1.69 – 1.54 (m, 7H) ppm
144c/d	 A mixture of two diastereomers	639.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 13.54 (s, 1H), 7.34 (s, 1H), 7.04 – 6.95 (m, 2H), 6.91 (s, 1H), 6.65 (d, J = 8.3 Hz, 2H), 4.55 – 4.36 (m, 2H), 4.03 (d, J = 16.1 Hz, 1H), 3.81 (s, 2H), 3.14 (s, 1H), 2.98 (s, 1H), 2.53 (t, J = 6.4 Hz, 6H), 1.98 (tt, J = 16.4, 8.2 Hz, 2H), 1.87 – 1.76 (m, 1H), 1.68 – 1.55 (m, 7H) ppm

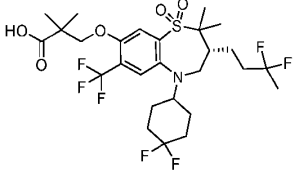
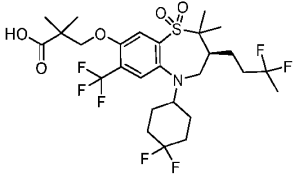
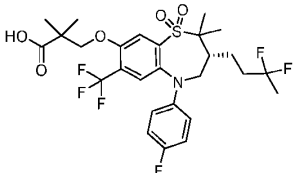
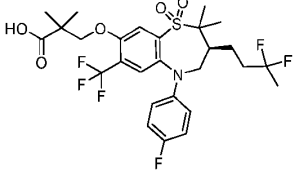
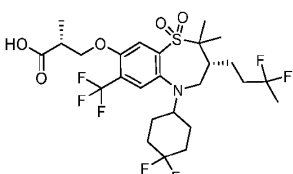
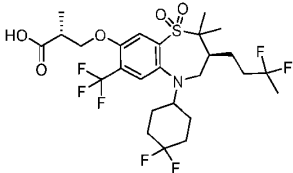
144c	 Single diastereomer with arbitrarily assigned stereochemistry	639.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 13.58 (s, 1H), 7.33 (s, 1H), 6.99 (t, J = 8.6 Hz, 2H), 6.92 (s, 1H), 6.66 (d, J = 8.0 Hz, 2H), 4.56 – 4.33 (m, 2H), 4.03 (d, J = 14.8 Hz, 1H), 3.82 (s, 2H), 3.14 (s, 2H), 2.97 (d, J = 12.3 Hz, 1H), 2.56 – 2.51 (m, 1H), 2.46 (s, 3H), 2.21 – 1.85 (m, 3H), 1.81 (d, J = 8.3 Hz, 1H), 1.66 – 1.55 (m, 7H) ppm
144d	 Single diastereomer with arbitrarily assigned stereochemistry	639.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 13.60 (s, 1H), 7.34 (s, 1H), 6.98 (t, J = 8.7 Hz, 2H), 6.92 (s, 1H), 6.66 (d, J = 6.4 Hz, 2H), 4.54 – 4.35 (m, 2H), 4.03 (d, J = 14.9 Hz, 1H), 3.81 (d, J = 9.5 Hz, 2H), 3.13 (d, J = 13.1 Hz, 2H), 2.97 (d, J = 12.4 Hz, 1H), 2.54 – 2.51 (m, 1H), 2.44 (s, 3H), 2.38 – 1.67 (m, 4H), 1.67 – 1.54 (m, 7H) ppm
145a	 Single enantiomer	609.4	¹ H NMR (500 MHz, DMSO-d ₆): δ 12.46 (s, 1H), 7.25 (s, 1H), 7.17 – 7.06 (m, 2H), 6.84 (s, 1H), 6.69 (t, J = 7.3 Hz, 1H), 6.61 (d, J = 8.1 Hz, 2H), 4.08 (s, 3H), 3.96 (q, J = 7.3 Hz, 1H), 3.84 (s, 1H), 3.25 (s, 1H), 2.52 (s, 1H), 2.46 (s, 3H), 2.44 – 2.39 (m, 1H), 2.14 – 1.92 (m, 4H), 1.82 (d, J = 8.0 Hz, 1H), 1.63 (t, J = 18.9 Hz, 4H), 1.25 (d, J = 2.6 Hz, 6H), 0.46 – 0.34 (m, 4H) ppm
145b	 Single enantiomer	609.4	¹ H NMR (500 MHz, DMSO-d ₆): δ 12.47 (s, 1H), 7.25 (s, 1H), 7.12 (t, J = 7.8 Hz, 2H), 6.84 (s, 1H), 6.69 (t, J = 7.3 Hz, 1H), 6.61 (d, J = 8.2 Hz, 2H), 4.08 (s, 3H), 3.96 (t, J = 7.4 Hz, 1H), 3.84 (s, 1H), 3.25 (s, 1H), 2.52 (s, 1H), 2.46 (s, 3H), 2.41 (t, J = 10.0 Hz, 1H), 2.10 (dd, J = 11.8, 6.4 Hz, 1H), 2.07 – 1.91 (m, 3H), 1.82 (s, 1H), 1.63 (t, J =

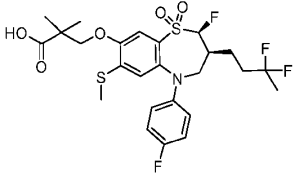
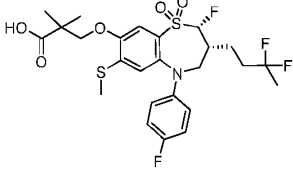
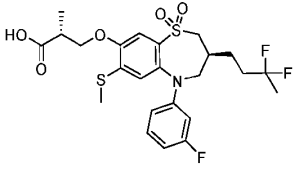
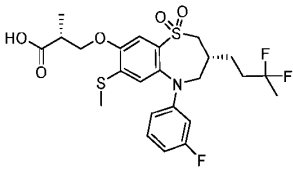
			18.9 Hz, 4H), 1.25 (d, J = 2.5 Hz, 6H), 0.40 (d, J = 11.4 Hz, 4H) ppm
146a	 Single enantiomer	626.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO-d ₆): δ 12.45 (s, 1H), 7.27 (s, 1H), 7.10 (q, J = 7.9 Hz, 1H), 6.90 (s, 1H), 6.46 (t, J = 8.4 Hz, 1H), 6.39 (d, J = 12.5 Hz, 1H), 6.32 (d, J = 8.2 Hz, 1H), 4.10 (s, 2H), 4.03 (d, J = 7.8 Hz, 2H), 3.89 (s, 1H), 3.22 (s, 1H), 2.55 (d, J = 10.6 Hz, 2H), 2.44 (s, 3H), 2.12 (dd, J = 11.7, 6.5 Hz, 1H), 2.06 (dd, J = 11.6, 6.5 Hz, 1H), 1.97 (s, 3H), 1.63 (t, J = 19.0 Hz, 4H), 1.26 (d, J = 3.2 Hz, 6H), 0.42 (s, 4H) ppm
146b	 Single enantiomer	627.2	¹ H NMR (500 MHz, DMSO-d ₆): δ 12.45 (s, 1H), 7.27 (s, 1H), 7.10 (q, J = 8.0 Hz, 1H), 6.90 (s, 1H), 6.46 (t, J = 8.1 Hz, 1H), 6.39 (d, J = 12.6 Hz, 1H), 6.32 (d, J = 8.5 Hz, 1H), 4.10 (s, 2H), 4.07 – 3.95 (m, 2H), 3.89 (s, 1H), 3.22 (s, 1H), 2.58 – 2.51 (m, 2H), 2.44 (s, 3H), 2.12 (dd, J = 11.8, 6.6 Hz, 1H), 2.08 – 2.04 (m, 1H), 1.93 (d, J = 42.2 Hz, 3H), 1.63 (t, J = 18.9 Hz, 4H), 1.26 (d, J = 3.2 Hz, 6H), 0.42 (d, J = 5.6 Hz, 4H) ppm
147a	 Single enantiomer	627.2	¹ H NMR (500 MHz, DMSO-d ₆): δ 12.43 (s, 1H), 7.24 (d, J = 2.4 Hz, 1H), 6.97 (t, J = 8.7 Hz, 2H), 6.79 (s, 1H), 6.62 (d, J = 8.6 Hz, 2H), 4.08 (d, J = 2.5 Hz, 2H), 4.06 – 3.96 (m, 1H), 3.94 (s, 1H), 3.81 (s, 1H), 3.16 (s, 1H), 2.53 (s, 2H), 2.40 (dd, J = 11.6, 8.2 Hz, 3H), 2.14 – 2.06 (m, 1H), 2.06 – 1.92 (m, 3H), 1.80 (s, 1H), 1.62 (t, J = 18.8 Hz, 4H), 1.25 (d, J = 2.4 Hz, 6H), 0.46 – 0.37 (m, 4H) ppm

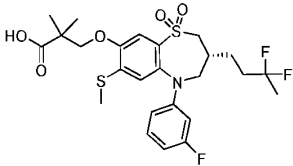
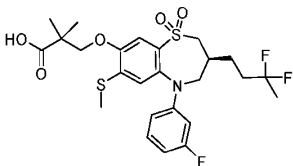
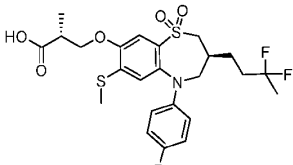
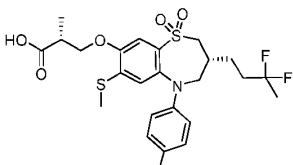
147b	 Single enantiomer	627.2	¹ H NMR (500 MHz, DMSO-d ₆): δ 12.41 (s, 1H), 7.24 (s, 1H), 6.97 (t, J = 8.7 Hz, 2H), 6.79 (s, 1H), 6.64 (s, 2H), 4.07 (s, 2H), 4.01 (d, J = 16.8 Hz, 1H), 3.97 – 3.90 (m, 1H), 3.81 (s, 1H), 3.24 (d, J = 12.9 Hz, 1H), 2.53 (s, 2H), 2.38 (d, J = 10.0 Hz, 3H), 2.13 – 1.93 (m, 4H), 1.80 (d, J = 9.7 Hz, 1H), 1.62 (t, J = 18.9 Hz, 4H), 1.25 (d, J = 2.0 Hz, 6H), 0.41 (d, J = 7.1 Hz, 4H) ppm
148	 Single enantiomer	561.2	¹ H NMR (400 MHz, DMSO-d ₆): δ 7.27 (s, 1H), 7.03 – 6.96 (m, 3H), 6.63 – 6.61 (m, 2H), 4.11 – 4.04 (m, 3H), 3.85–3.82 (m, 1H), 3.34 (s, 3H), 2.46 (s, 3H), 2.32 (s, 3H), 2.04 – 1.92 (m, 2H), 1.88 – 1.79 (m, 1H), 1.64 (m, 3H), 1.26 (s, 6H) ppm
149	 Single enantiomer	559.1	¹ H NMR (400 MHz, DMSO-d ₆): δ 7.27 (s, 1H), 7.01 – 6.96 (m, 3H), 6.63 – 6.61 (m, 2H), 4.24 (q, J = 14.8, 9.6 Hz, 2H), 4.07 – 3.99 (m, 1H), 3.86 – 3.81 (m, 1H), 3.46 – 3.37 (m, 3H), 2.46 (s, 3H), 2.33 (s, 3H), 2.05 – 1.92 (m, 2H), 1.88 – 1.79 (m, 1H), 1.69 – 1.59 (m, 3H), 1.18 – 1.17 (m, 2H), 1.04 – 1.02 (m, 2H) ppm
150	 Single diastereomer	547.1	¹ H NMR (400 MHz, DMSO-d ₆): δ 7.27 (s, 1H), 7.02 – 6.96 (m, 3H), 6.61 – 6.60 (m, 2H), 4.26 – 4.23 (m, 1H), 4.16 – 4.12 (m, 1H), 4.07 – 4.03 (m, 1H), 3.85 – 3.83 (m, 1H), 3.23 – 3.21 (m, 2H), 2.83 – 2.78 (m, 1H), 2.46 (s, 3H), 2.32 (s, 3H), 2.03 – 1.93 (m, 2H), 1.86 – 1.81 (m, 1H), 1.64 (m, 4H), 1.22 (d, J = 7.2 Hz, 3H) ppm

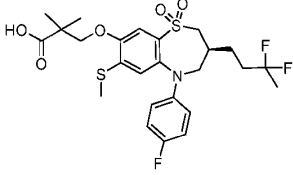
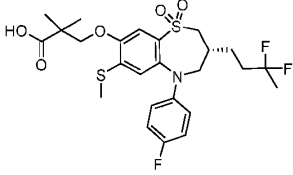
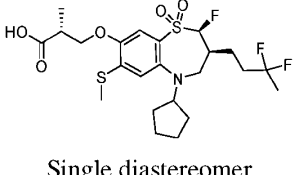
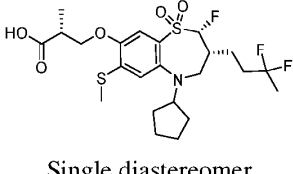
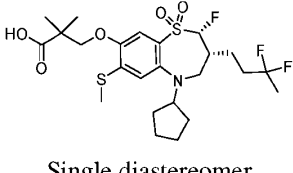
164	 Single diastereomer	568.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.75 (s, 1H), 7.32 (s, 1H), 7.07 - 6.97 (m, 4H), 4.84 - 4.30 (m, 1H), 4.28 - 4.25 (m, 1H), 4.21 - 3.66 (m, 2H), 3.39 (t, J = 6.6 Hz, 1H), 3.04 - 2.87 (m, 1H), 2.08 (s, 1H), 2.00 - 1.74 (m, 4H), 1.59 - 1.43 (m, 6H), 1.23 (d, J = 4.5 Hz, 3H) ppm
165	 Single diastereomer	568.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.75 (s, 1H), 7.32 (s, 1H), 7.07 - 6.89 (m, 4H), 4.36 (t, J = 8.1 Hz, 1H), 4.29 - 4.25 (m, 1H), 4.09 - 3.71 (m, 2H), 3.40 (d, J = 7.2 Hz, 1H), 3.09 - 2.84 (m, 1H), 2.08 (s, 1H), 2.00 - 1.87 (m, 3H), 1.76 - 1.63 (m, 1H), 1.55 - 1.43 (m, 6H), 1.34 (d, J = 7.2 Hz, 3H) ppm
166	 Single diastereomer	582.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.76 (s, 1H), 7.48 - 7.43 (m, 1H), 7.03 - 6.97 (m, 2H), 6.79 - 6.73 (m, 2H), 4.38 - 4.35 (m, 1H), 4.30 - 4.24 (m, 2H), 2.99 - 2.93 (m, 1H), 2.40 - 2.21 (m, 2H), 2.11 - 1.95 (m, 1H), 1.80 - 1.46 (m, 8H), 1.34 (d, J = 6.9 Hz, 3H), 1.21 (s, 4H) ppm
167	 Single diastereomer	582.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.76 (s, 1H), 7.48-7.40 (m, 1H), 7.03 - 6.97 (m, 2H), 6.89 - 6.76 (m, 2H), 4.41 - 4.34 (m, 1H), 4.27 - 4.16 (m, 2H), 3.09 - 2.98 (m, 1H), 2.33 - 2.12 (m, 2H), 2.08 - 2.00 (m, 1H), 1.84 - 1.44 (m, 8H), 1.35 (d, J = 5.7 Hz, 3H), 1.21 (s, 4H) ppm
168	 Single diastereomer	582.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.73 (s, 1H), 7.33 (s, 1H), 7.07 - 6.97 (m, 4H), 4.20 (s, 2H), 4.04 - 3.84 (m, 2H), 3.41 (t, J = 7.5 Hz, 1H), 3.86 (s, 1H), 3.39 (t, J = 7.0 Hz, 1H), 2.07 (d, J = 9.9 Hz, 1H), 2.00 - 1.87 (m, 3H),

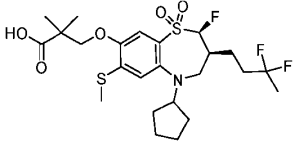
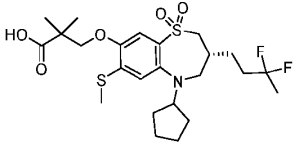
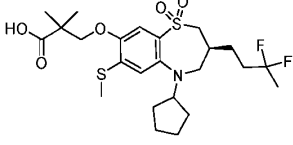
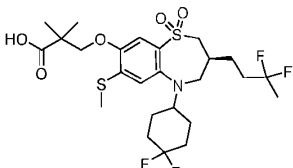
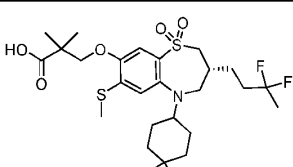
			1.76 - 1.63 (m, 1H), 1.55 - 1.43 (m, 6H), 1.36 (s, 6H) ppm
169	 Single diastereomer	582.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.73 (s, 1H), 7.33 (s, 1H), 7.07 - 6.97 (m, 2H), 6.97 (s, 2H), 4.20 (s, 2H), 4.01 - 3.84 (m, 2H), 3.39 (t, J = 7.2 Hz, 1H), 2.08 (s, 1H), 2.05 - 1.64 (m, 4H), 1.55 - 1.48 (m, 6H), 1.43 (s, 6H) ppm
170	 Single diastereomer	556.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.65 (s, 1H), 7.43 (s, 1H), 4.30 - 4.15 (m, 2H), 3.99 - 3.88 (m, 1H), 3.36 (s, 1H), 2.93 (q, J = 6.6 Hz, 1H), 2.72 - 2.63 (m, 1H), 2.26 - 1.89 (m, 5H), 1.86 - 1.51 (m, 12H), 1.49 - 1.38 (m, 1H), 1.31 (d, J = 7.2 Hz, 3H), 1.16 - 1.00 (m, 4H) ppm
171	 Single diastereomer	556.3	¹ H NMR (400 MHz, CD ₃ OD): δ 7.64 (s, 1H), 7.43 (s, 1H), 4.29 - 4.14 (m, 2H), 3.99 - 3.88 (m, 1H), 3.36 (s, 1H), 2.93 (q, J = 6.6 Hz, 1H), 2.74 - 2.63 (m, 1H), 2.27 - 1.89 (m, 5H), 1.87 - 1.47 (m, 12H), 1.48 - 1.38 (m, 1H), 1.30 (d, J = 7.2 Hz, 3H), 1.14 - 0.97 (m, 4H) ppm
172	 Single enantiomer	628.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.68 (s, 1H), 7.59 (s, 1H), 4.19 (s, 2H), 3.54 (d, J = 12.0 Hz, 2H), 3.08 - 2.92 (m, 1H), 2.75 (s, 1H), 2.23 - 1.85 (m, 10H), 1.75 (d, J = 9.0 Hz, 1H), 1.731.64 (t, J = 18.6 Hz, 3H), 1.55 - 1.45 (m, 1H), 1.35 (s, 6H) ppm
173	 Single enantiomer	628.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.68 (s, 1H), 7.59 (s, 1H), 4.19 (s, 2H), 3.55 (d, J = 12.0 Hz, 2H), 3.08 - 2.92 (m, 1H), 2.80 (s, 1H), 2.26 - 1.85 (m, 10H), 1.78 (d, J = 9.3 Hz, 1H), 1.64 (t, J = 18.6 Hz, 3H), 1.55 - 1.45 (m, 1H), 1.35 (s, 6H) ppm

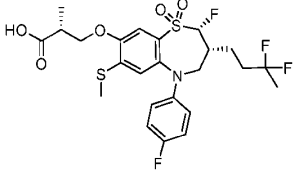
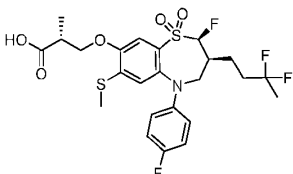
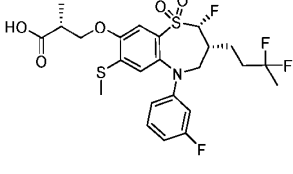
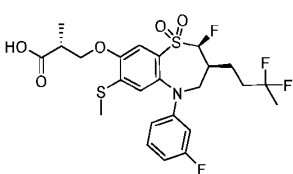
174	 Single enantiomer	620.3	¹ H NMR (300 MHz, CD ₃ OD): δ 7.62 (s, 1H), 7.43 (s, 1H), 4.12 (s, 2H), 3.67 – 3.43 (m, 3H), 2.88 – 2.65 (m, 1H), 2.30 – 1.91 (m, 9H), 1.86 – 1.55 (m, 8H), 1.32 (s, 7H), 1.12 (s, 3H) ppm
175	 Single enantiomer	620.3	¹ H NMR (300 MHz, CD ₃ OD): δ 7.62 (s, 1H), 7.43 (s, 1H), 4.12 (s, 2H), 3.67 – 3.43 (m, 3H), 2.88 – 2.65 (m, 1H), 2.32 – 1.91 (m, 9H), 1.86 – 1.55 (m, 8H), 1.34 (s, 7H), 1.12 (s, 3H) ppm
176	 Single enantiomer	596.3	¹ H NMR (300 MHz, CDCl ₃): δ 7.68 (s, 1H), 7.42 (s, 1H), 6.98 (t, J = 8.7 Hz, 2H), 6.70 (s, 2H), 4.20 – 4.10 (m, 3H), 3.19 (s, 1H), 2.26 (s, 1H), 2.14 – 1.88 (m, 2H), 1.88 – 1.68 (m, 4H), 1.62 (s, 3H), 1.42 (s, 6H), 1.33 – 1.27 (m, 4H) ppm
177	 Single enantiomer	596.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.72 (s, 1H), 7.47 (s, 1H), 6.98 (t, J = 8.4 Hz, 2H), 6.73 (s, 2H), 4.26 – 4.19 (m, 3H), 3.30 – 3.07 (m, 1H), 2.24 – 2.03 (m, 2H), 2.02 – 1.99 (m, 1H), 1.74 – 1.56 (m, 7H), 1.34 (s, 7H), 1.18 (s, 3H) ppm
178	 Single diastereomer	606.3	¹ H NMR (300 MHz, CD ₃ OD): δ 7.64 (s, 1H), 7.43 (s, 1H), 4.35 – 4.13 (m, 2H), 3.65 – 3.40 (m, 2H), 2.95 (q, J = 6.6 Hz, 1H), 2.84 – 2.66 (m, 1H), 2.31 – 1.88 (m, 10H), 1.83 – 1.56 (m, 8H), 1.48 – 1.36 (m, 1H), 1.30 (d, J = 7.2 Hz, 3H), 1.12 (s, 3H) ppm
179	 Single diastereomer	606.3	¹ H NMR (300 MHz, CD ₃ OD): δ 7.64 (s, 1H), 7.43 (s, 1H), 4.39 – 4.14 (m, 2H), 3.67 – 3.44 (m, 2H), 2.95 (q, J = 6.6 Hz, 1H), 2.83 – 2.64 (m, 1H), 2.32 – 1.85 (m, 10H), 1.83 – 1.53 (m,

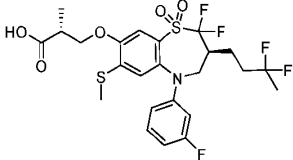
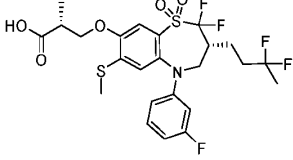
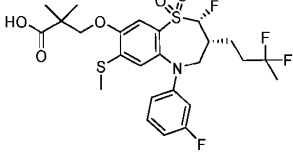
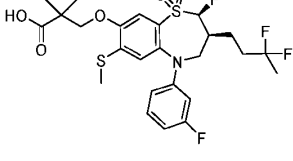
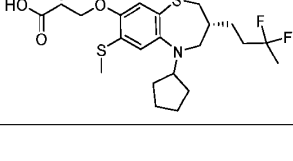
	Single diastereomer		8H), 1.48 – 1.36 (m, 1H), 1.33 (d, J = 7.2 Hz, 3H), 1.12 (s, 3H) ppm
180	 Single diastereomer	564.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.45 (s, 1H), 7.05 (s, 1H), 6.98 – 6.89 (m, 2H), 6.69 – 6.61 (m, 2H), 5.55 (d, J = 45.6 Hz, 1H), 4.21 – 4.07 (m, 3H), 3.28 – 3.26 (m, 1H), 2.80 – 2.59 (m, 1H), 2.34 (s, 3H), 2.21 – 2.01 (m, 2H), 1.79 – 1.56 (m, 5H), 1.37 (s, 6H) ppm
181	 Single diastereomer	564.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.48 (s, 1H), 7.08 (s, 1H), 7.00 – 6.91 (m, 2H), 6.72 – 6.63 (m, 2H), 5.57 (d, J = 45.6 Hz, 1H), 4.23 – 4.12 (m, 3H), 3.24 – 3.28 (m, 1H), 2.82 – 2.62 (m, 1H), 2.37 (s, 3H), 2.21 – 2.06 (m, 2H), 1.79 – 1.58 (m, 5H), 1.39 (s, 6H) ppm
182	 Single diastereomer	532.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.48 (s, 1H), 7.18 – 7.10 (m, 1H), 7.08 (s, 1H), 6.46 – 6.40 (m, 2H), 6.31 – 6.27 (m, 1H), 4.37 – 4.20 (m, 3H), 3.47 – 3.43 (m, 1H), 3.22 – 3.13 (m, 2H), 2.99 – 2.97 (m, 1H), 2.58 – 2.42 (m, 1H), 2.36 (s, 3H), 2.10 – 2.00 (m, 2H), 1.68 – 1.57 (m, 5H), 1.35 (d, J = 7.2 Hz, 3H) ppm
183	 Single diastereomer	532.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.48 (s, 1H), 7.15 – 7.10 (m, 1H), 7.08 (s, 1H), 6.46 – 6.35 (m, 2H), 6.30 – 6.26 (m, 1H), 4.32 – 4.23 (m, 3H), 3.48 – 3.43 (m, 1H), 3.22 – 3.13 (m, 2H), 3.00 – 2.98 (m, 1H), 2.52 – 2.42 (m, 1H), 2.36 (s, 3H), 2.07 – 2.03 (m, 2H), 1.68 – 1.56 (m, 5H), 1.33 (d, J = 7.2 Hz, 3H) ppm

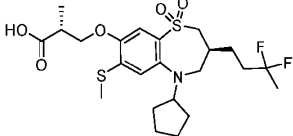
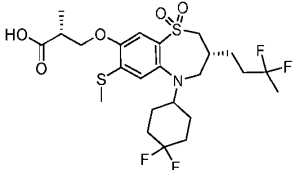
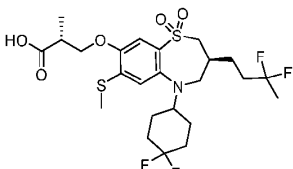
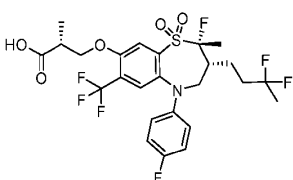
184	 Single enantiomer	546.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.46 (s, 1H), 7.18 - 7.10 (m, 1H), 7.08 (s, 1H), 6.46 - 6.40 (m, 2H), 6.29 (d, J = 12.6 Hz, 1H), 4.28 (d, J = 15.3 Hz, 1H), 4.17 (s, 2H), 3.54 - 3.47 (m, 1H), 3.21 - 3.09 (m, 2H), 2.51 - 2.48 (m, 1H), 2.36 (s, 3H), 2.12 - 1.97 (m, 2H), 1.73 - 1.62 (m, 5H), 1.37 (s, 6H) ppm
185	 Single enantiomer	546.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.46 (s, 1H), 7.18 - 7.10 (m, 1H), 7.08 (s, 1H), 6.46 - 6.39 (m, 2H), 6.29 (d, J = 12.3 Hz, 1H), 4.28 (d, J = 15.3 Hz, 1H), 4.17 (s, 2H), 3.31 - 3.30 (m, 1H), 3.18 - 3.09 (m, 2H), 2.53 - 2.51 (m, 1H), 2.36 (s, 3H), 2.14 - 1.97 (m, 2H), 1.73 - 1.65 (m, 5H), 1.37 (s, 6H) ppm
186	 Single diastereomer	532.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.45 (s, 1H), 7.00 (s, 1H), 6.92 (t, J = 8.7 Hz, 2H), 6.66 (dd, J = 9.0, 4.2 Hz, 2H), 4.37 - 4.13 (m, 3H), 3.51 - 3.40 (m, 1H), 3.25 - 3.10 (m, 2H), 3.04 - 2.97 (s, 1H), 2.45 - 2.39 (m, 1H), 2.31 (s, 3H), 2.11 - 1.92 (m, 2H), 1.72 - 1.48 (m, 5H), 1.34 (d, J = 6.9 Hz, 3H) ppm
187	 Single diastereomer	532.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.46 (s, 1H), 7.04 - 6.86 (m, 3H), 6.69 - 6.67 (m, 2H), 4.36 - 4.15 (m, 3H), 3.51 - 3.40 (m, 1H), 3.36 - 3.29 (m, 2H), 3.00 - 2.94 (m, 1H), 2.46 - 2.40 (m, 1H), 2.31 (s, 3H), 2.08 - 1.96 (m, 2H), 1.74 - 1.44 (m, 5H), 1.34 (d, J = 6.9 Hz, 3H) ppm

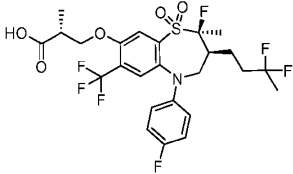
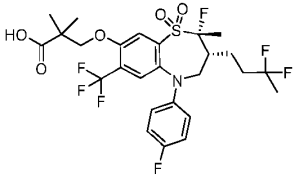
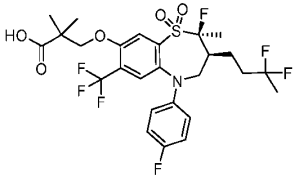
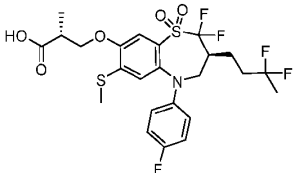
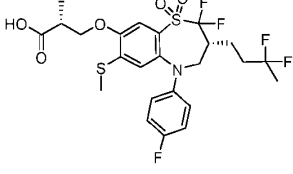
188	 Single enantiomer	546.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.43 (s, 1H), 7.00 (s, 1H), 6.92 (t, J = 8.7 Hz, 2H), 6.68 – 6.65 (m, 2H), 4.32 – 4.29 (m, 1H), 4.14 (s, 2H), 3.51 – 3.40 (m, 1H), 3.25 – 3.10 (m, 2H), 2.52 – 2.35 (m, 1H), 2.31 (s, 3H), 2.11 – 1.91 (m, 2H), 1.73 – 1.46 (m, 5H), 1.35 (s, 6H) ppm
189	 Single enantiomer	546.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.43 (s, 1H), 7.00 (s, 1H), 6.92 (t, J = 8.7 Hz, 2H), 6.68 – 6.64 (m, 2H), 4.26 (d, J = 18.0 Hz, 1H), 4.14 (s, 2H), 3.51 – 3.40 (m, 1H), 3.25 – 3.10 (m, 2H), 2.50 – 2.40 (m, 1H), 2.31 (s, 3H), 2.13 – 1.91 (m, 2H), 1.75 – 1.47 (m, 5H), 1.35 (s, 6H) ppm
190	 Single diastereomer	524.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.34 (s, 1H), 7.02 (s, 1H), 5.47 (d, J = 46.5 Hz, 1H), 4.22 (s, 1H), 4.12 (s, 1H), 3.93 (s, 1H), 3.07 (s, 1H), 2.96 – 2.90 (m, 1H), 2.82 – 2.62 (m, 1H), 2.45 (s, 3H), 2.14 – 1.85 (m, 4H), 1.81 – 1.39 (m, 12H), 1.32 (d, J = 6.9 Hz, 3H) ppm
191	 Single diastereomer	524.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.34 (s, 1H), 7.02 (s, 1H), 5.46 (d, J = 46.2 Hz, 1H), 4.34 – 4.10 (m, 1H), 4.10 – 3.98 (m, 1H), 3.97 – 3.84 (m, 1H), 3.12 – 3.00 (m, 2H), 2.84 – 2.61 (m, 1H), 2.44 (s, 3H), 2.13 – 1.86 (m, 4H), 1.81 – 1.42 (m, 12H), 1.31 (d, J = 7.2 Hz, 3H) ppm
192	 Single diastereomer	538.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.32 (s, 1H), 7.02 (s, 1H), 5.48 (d, J = 46.2 Hz, 1H), 4.06 (s, 2H), 3.93 (t, J = 6.9 Hz, 1H), 3.23 – 3.12 (m, 1H), 2.81 – 2.67 (m, 1H), 2.60 – 2.35 (m, 4H),

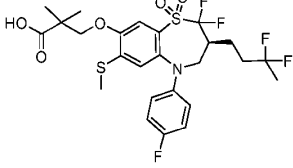
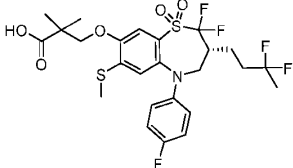
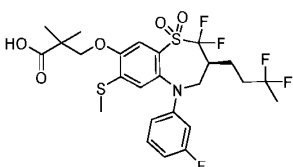
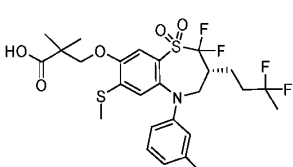
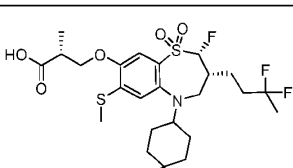
			2.13 – 1.87 (m, 4H), 1.83 – 1.40 (m, 11H), 1.34 (s, 6H) ppm
193	 Single diastereomer	538.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.31 (s, 1H), 7.02 (s, 1H), 5.48 (d, J = 46.5 Hz, 1H), 4.06 (s, 2H), 3.98 – 3.88 (m, 1H), 3.23 – 3.12 (m, 1H), 2.81 – 2.67 (m, 1H), 2.60 – 2.36 (m, 4H), 2.17 – 1.86 (m, 4H), 1.83 – 1.39 (m, 11H), 1.34 (s, 6H) ppm
194	 Single enantiomer	520.3	¹ H NMR (400 MHz, CD ₃ OD): δ 7.30 (s, 1H), 7.01 (s, 1H), 4.04 (s, 2H), 3.95 – 3.87 (m, 1H), 3.47 – 3.38 (m, 2H), 3.30 – 3.23 (m, 1H), 3.06 – 2.95 (m, 1H), 2.62 – 2.52 (m, 1H), 2.43 (s, 3H), 2.19 – 2.09 (m, 1H), 2.04 – 1.89 (m, 4H), 1.85 – 1.64 (m, 4H), 1.64 – 1.46 (m, 7H), 1.33 (s, 6H) ppm
195	 Single enantiomer	520.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.31 (s, 1H), 7.01 (s, 1H), 4.04 (s, 2H), 3.91 (t, J = 6.8 Hz, 1H), 3.50 – 3.38 (m, 1H), 3.29 – 3.25 (m, 1H), 3.06 – 2.95 (m, 1H), 2.63 – 2.52 (m, 1H), 2.43 (s, 3H), 2.20 – 2.08 (m, 1H), 2.04 – 1.88 (m, 4H), 1.84 – 1.64 (m, 4H), 1.64 – 1.47 (m, 7H), 1.33 (s, 6H) ppm
196	 Single enantiomer	570.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.32 (s, 1H), 7.01 (s, 1H), 4.05 (s, 2H), 3.54 – 3.37 (m, 3H), 3.05 – 2.97 (m, 1H), 2.68 – 2.60 (m, 1H), 2.44 (s, 3H), 2.16 – 1.80 (m, 11H), 1.65 – 1.55 (m, 5H), 1.33 (s, 6H) ppm
197	 Single enantiomer	570.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.32 (s, 1H), 7.01 (s, 1H), 4.05 (s, 2H), 3.54 – 3.37 (m, 3H), 3.05 – 2.97 (m, 1H), 2.68 – 2.59 (m, 1H), 2.43 (s, 3H), 2.20 – 1.80 (m, 11H), 1.65 – 1.43 (m, 5H), 1.33 (s, 6H) ppm

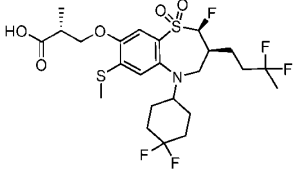
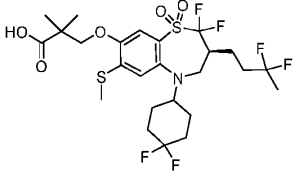
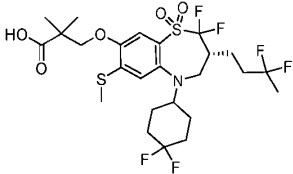
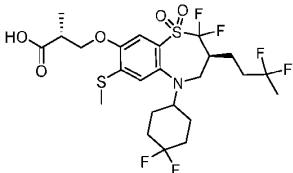
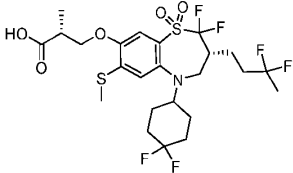
198	 Single diastereomer	550.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.47 (s, 1H), 7.05 (s, 1H), 6.98 - 6.89 (m, 2H), 6.65 (dd, J = 9.2, 4.2 Hz, 2H), 5.55 (d, J = 45.6 Hz, 1H), 4.33 (t, J = 7.6 Hz, 1H), 4.25 - 4.19 (m, 1H), 4.14 (d, J = 15.6 Hz, 1H), 3.27 - 3.23 (m, 1H), 3.03 - 2.93 (m, 1H), 2.80 - 2.62 (m, 1H), 2.34 (s, 3H), 2.17 - 2.05 (m, 2H), 1.79 - 1.55 (m, 5H), 1.35 (d, J = 7.2 Hz, 3H) ppm
199	 Single diastereomer	550.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.47 (s, 1H), 7.05 (s, 1H), 6.93 (t, J = 8.8 Hz, 2H), 6.69 - 6.61 (m, 2H), 5.55 (d, J = 45.6 Hz, 1H), 4.35 - 4.20 (m, 2H), 4.14 (d, J = 15.6 Hz, 1H), 3.28 - 3.24 (m, 1H), 3.03 - 2.95 (m, 1H), 2.80 - 2.59 (m, 1H), 2.34 (s, 3H), 2.22 - 2.02 (m, 2H), 1.77 - 1.57 (m, 5H), 1.35 (d, J = 7.2 Hz, 3H) ppm
200	 Single diastereomer	550.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.52 (s, 1H), 7.26 - 7.07 (m, 2H), 6.52 - 6.40 (m, 2H), 6.32 (dt, J = 12.6, 2.3 Hz, 1H), 5.59 (d, J = 45.3 Hz, 1H), 4.40 - 4.24 (m, 2H), 4.16 (d, J = 15.8 Hz, 1H), 3.41 - 3.33 (m, 1H), 3.06 - 2.97 (m, 1H), 2.90 - 2.66 (m, 1H), 2.40 (s, 3H), 2.27 - 2.06 (m, 2H), 1.82 - 1.57 (m, 5H), 1.38 (d, J = 7.1 Hz, 3H) ppm
201	 Single diastereomer	548.1 [M-1] ⁻	¹ H NMR (300 MHz, CD ₃ OD): δ 7.52 (s, 1H), 7.24 - 7.12 (m, 2H), 6.52 - 6.40 (m, 2H), 6.37 - 6.27 (m, 1H), 5.59 (d, J = 45.4 Hz, 1H), 4.42 - 4.32 (m, 1H), 4.30 - 4.22 (m, 1H), 4.20 - 4.11 (m, 1H), 3.38 - 3.35 (m, 1H), 3.07 - 2.96 (m, 1H), 2.91 - 2.68 (m, 1H), 2.40 (s, 3H), 2.29 - 2.05 (m,

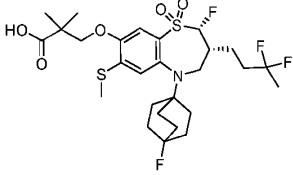
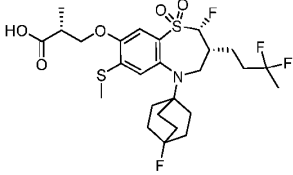
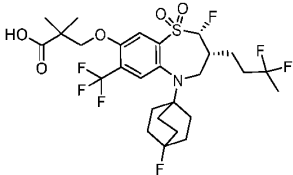
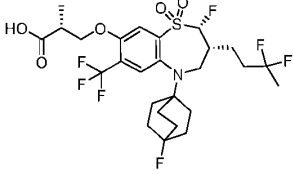
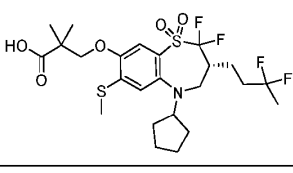
			2H), 1.81 - 1.57 (m, 5H), 1.38 (d, J = 7.1 Hz, 3H) ppm
202	 Single diastereomer	568.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.52 (s, 1H), 7.23 - 7.13 (m, 2H), 6.52 - 6.43 (m, 2H), 6.38 - 6.28 (m, 1H), 4.38 - 4.24 (m, 3H), 3.45 - 3.39 (m, 1H), 3.02 - 2.96 (m, 2H), 2.38 (s, 3H), 2.28 - 1.85 (m, 3H), 1.65 (t, J = 18.6 Hz, 4H), 1.35 (d, J = 7.2 Hz, 3H) ppm
203	 Single diastereomer	568.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.52 (s, 1H), 7.20 - 7.13 (m, 2H), 6.50 - 6.43 (m, 2H), 6.37 - 6.27 (m, 1H), 4.33 - 4.29 (m, 3H), 3.44 - 3.38 (m, 1H), 3.00 - 2.98 (m, 2H), 2.38 (s, 3H), 2.32 - 1.92 (m, 3H), 1.65 (t, J = 18.6 Hz, 4H), 1.35 (d, J = 7.2 Hz, 3H) ppm
204	 Single diastereomer	564.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.50 (s, 1H), 7.23 - 7.11 (m, 2H), 6.52 - 6.39 (m, 2H), 6.32 (d, J = 12.3 Hz, 1H), 5.58 (d, J = 45.3 Hz, 1H), 4.25 - 4.10 (m, 3H), 3.40 - 3.35 (m, 1H), 2.92 - 2.66 (m, 1H), 2.40 (s, 3H), 2.27 - 2.06 (m, 2H), 1.82 - 1.58 (m, 5H), 1.40 (s, 6H) ppm
205	 Single diastereomer	564.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.50 (s, 1H), 7.27 - 7.10 (m, 2H), 6.55 - 6.39 (m, 2H), 6.32 (dt, J = 12.3, 2.4 Hz, 1H), 5.58 (d, J = 45.4 Hz, 1H), 4.27 - 4.07 (m, 3H), 3.41 - 3.35 (m, 1H), 2.93 - 2.66 (m, 1H), 2.40 (s, 3H), 2.30 - 2.04 (m, 2H), 1.85 - 1.55 (m, 5H), 1.41 (s, 6H) ppm
206		506.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.33 (s, 1H), 7.01 (s, 1H), 4.21 (t, J = 7.6 Hz, 1H), 4.14 - 4.08 (m, 1H), 3.95 - 3.87 (m, 1H), 3.46 - 3.38 (m, 1H),

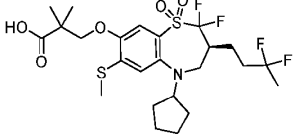
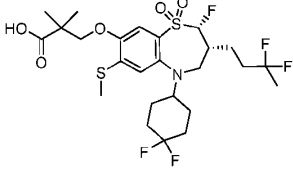
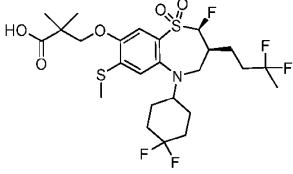
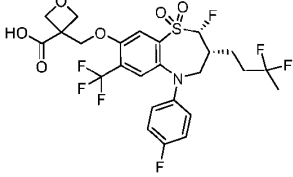
	Single diastereomer		3.29 - 3.25 (m, 1H), 3.06 - 2.96 (m, 1H), 2.95 - 2.89 (m, 1H), 2.63 - 2.52 (m, 1H), 2.43 (s, 3H), 2.20 - 2.08 (m, 1H), 2.04 - 1.89 (m, 4H), 1.85 - 1.65 (m, 4H), 1.64 - 1.45 (m, 7H), 1.31 (s, 3H) ppm
207	 Single diastereomer	506.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.33 (s, 1H), 7.01 (s, 1H), 4.23 (t, J = 7.6 Hz, 1H), 4.14 - 4.07 (m, 1H), 3.96 - 3.86 (m, 1H), 3.42 (dd, J = 12.0, 4.0 Hz, 1H), 3.30 - 3.23 (m, 1H), 3.06 - 2.95 (m, 1H), 2.94 - 2.89 (m, 1H), 2.62 - 2.53 (m, 1H), 2.43 (s, 3H), 2.20 - 2.08 (m, 1H), 2.05 - 1.88 (m, 4H), 1.84 - 1.65 (m, 4H), 1.64 - 1.45 (m, 7H), 1.31 (s, 3H) ppm
208	 Single diastereomer	556.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.34 (s, 1H), 7.01 (s, 1H), 4.30 - 4.18 (m, 1H), 4.15 - 4.05 (m, 1H), 3.54 - 3.46 (m, 1H), 3.42 - 3.38 (m, 2H), 3.05 - 3.00 (m, 1H), 2.98 - 2.96 (m, 1H), 2.71 - 2.56 (m, 1H), 2.44 (s, 3H), 2.16 - 1.80 (m, 11H), 1.65 - 1.43 (m, 5H), 1.31 (d, J = 6.9 Hz, 3H) ppm.
209	 Single diastereomer	556.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.34 (s, 1H), 7.01 (s, 1H), 4.22 - 4.19 (m, 1H), 4.14 - 4.12 (m, 1H), 3.54 - 3.52 (m, 1H), 3.47 - 3.41 (m, 2H), 3.08 - 3.01 (m, 1H), 2.96 - 2.90 (m, 1H), 2.71 - 2.56 (m, 1H), 2.44 (s, 3H), 2.17 - 1.80 (m, 11H), 1.65 - 1.43 (m, 5H), 1.31 (d, J = 7.2 Hz, 3H) ppm
210	 Single diastereomer	586.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.80 (s, 1H), 7.52 (s, 1H), 6.98 (t, J = 9.0 Hz, 2H), 6.74 (dd, J = 9.0, 4.5 Hz, 2H), 4.87 - 4.24 (m, 3H), 3.54 - 3.30 (m, 1H), 2.97 (s, 1H), 2.69 - 2.57 (m, 1H), 2.22 - 1.85 (m, 6H), 1.63 (t, J =

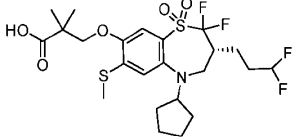
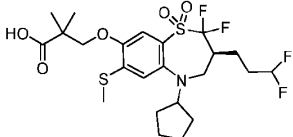
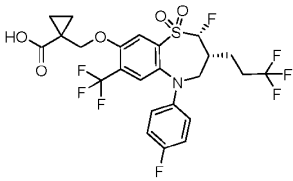
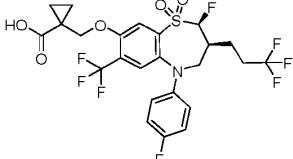
			21.6 Hz, 4H), 1.33 (d, J = 7.2 Hz, 3H) ppm
211	 Single diastereomer	586.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.80 (s, 1H), 7.52 (s, 1H), 6.98 (t, J = 17.4 Hz, 2H), 6.76 - 6.72 (m, 2H), 4.38 - 4.25 (m, 3H), 3.54 - 3.30 (m, 1H), 2.99 (s, 1H), 2.70 - 2.54 (m, 1H), 2.22 - 1.88 (m, 6H), 1.57 (t, J = 18.6 Hz, 4H), 1.33 (d, J = 7.2 Hz, 3H) ppm
212	 Single diastereomer	600.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.79 (s, 1H), 7.53 (s, 1H), 6.98 (t, J = 9.0 Hz, 2H), 6.76 - 6.72 (m, 2H), 4.30 - 4.18 (m, 3H), 3.56 - 3.31 (m, 1H), 2.64 - 2.54 (m, 1H), 2.23 - 1.88 (m, 6H), 1.63 (t, J = 18.3 Hz, 4H), 1.35 (s, 6H) ppm
213	 Single diastereomer	600.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.79 (s, 1H), 7.53 (s, 1H), 6.98 (t, J = 8.7 Hz, 2H), 6.76 - 6.72 (m, 2H), 4.30 - 4.18 (m, 3H), 3.45 - 3.30 (m, 1H), 2.69 - 2.54 (m, 1H), 2.23 - 1.88 (m, 6H), 1.63 (t, J = 18.3 Hz, 4H), 1.35 (s, 6H) ppm
214	 Single diastereomer	568.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.50 (s, 1H), 7.07 - 6.91 (m, 3H), 6.70 (s, 2H), 4.40 - 4.17 (m, 3H), 3.12 - 2.82 (m, 2H), 2.33 (s, 3H), 2.25 - 1.77 (m, 4H), 1.62 (t, J = 18.6 Hz, 4H), 1.34 (d, J = 7.2 Hz, 3H) ppm
215	 Single diastereomer	568.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.50 (s, 1H), 6.97 (t, J = 8.7 Hz, 3H), 6.70 (s, 2H), 4.35 - 4.24 (m, 3H), 3.10 - 2.79 (m, 2H), 2.33 (s, 3H), 2.26 - 1.82 (m, 4H), 1.62 (t, J = 18.6 Hz, 4H), 1.34 (d, J = 6.9 Hz, 3H) ppm

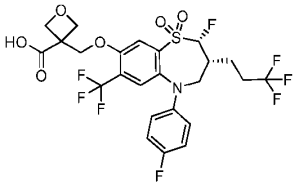
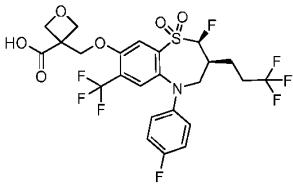
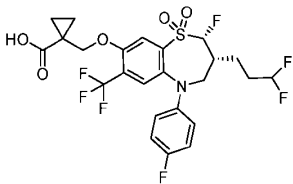
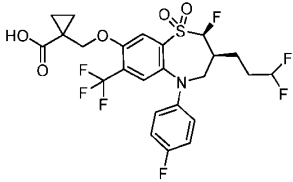
216	 Single enantiomer	582.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.48 (s, 1H), 7.04 (s, 1H), 6.97 (t, J = 8.7 Hz, 2H), 6.71 (s, 2H), 4.17 (s, 3H), 3.57 – 3.51 (m, 1H), 2.92 – 2.87 (m, 1H), 2.33 (s, 3H), 2.26 – 1.89 (m, 3H), 1.62 (t, J = 18.6 Hz, 4H), 1.36 (s, 6H) ppm
217	 Single enantiomer	582.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.48 (s, 1H), 7.04 (s, 1H), 6.97 (t, J = 8.7 Hz, 2H), 6.71 (s, 2H), 4.30 – 4.17 (m, 3H), 3.56 – 3.51 (m, 1H), 3.07 – 2.93 (m, 1H), 2.33 (s, 3H), 2.26 – 1.90 (m, 3H), 1.62 (t, J = 18.3 Hz, 4H), 1.36 (s, 6H) ppm
218	 Single enantiomer	582.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.53 (s, 1H), 7.25 – 7.15 (m, 2H), 6.55 – 6.33 (m, 3H), 4.39 – 4.35 (m, 1H), 4.25 – 4.18 (m, 2H), 3.56 – 3.34 (m, 1H), 3.10 – 3.01 (m, 1H), 2.40 (s, 3H), 2.33 – 1.99 (m, 3H), 1.67 (t, J = 18.6 Hz, 4H), 1.39 (s, 6H) ppm
219	 Single enantiomer	582.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.53 (s, 1H), 7.25 – 7.15 (m, 2H), 6.55 – 6.33 (m, 3H), 4.39 – 4.34 (m, 1H), 4.25 – 4.18 (m, 2H), 3.56 – 3.34 (m, 1H), 3.10 – 2.97 (m, 1H), 2.40 (s, 3H), 2.33 – 1.99 (m, 3H), 1.67 (t, J = 18.6 Hz, 4H), 1.39 (s, 6H) ppm
220	 Single diastereomer	574.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.37 (s, 1H), 7.05 (s, 1H), 5.52 (d, J = 46.5 Hz, 1H), 4.21 (d, J = 23.7 Hz, 2H), 3.56 (s, 1H), 3.32 (s, 1H), 3.01 – 2.88 (m, 1H), 2.86 – 2.77 (m, 1H), 2.56 – 2.47 (m, 4H), 2.22 – 1.96 (m, 8H), 1.88 – 1.73 (m, 2H), 1.64 (t, J = 12.0 Hz, 5H), 1.34 (d, J = 6.9 Hz, 3H) ppm

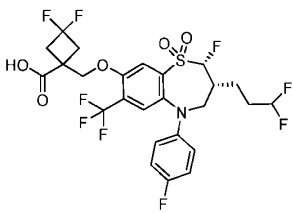
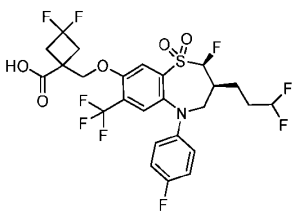
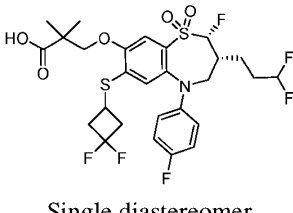
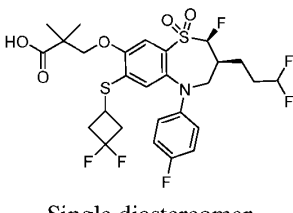
221	 Single diastereomer	574.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.37 (s, 1H), 7.05 (s, 1H), 5.52 (d, J = 46.5 Hz, 1H), 4.21 (d, J = 36.0 Hz, 2H), 3.56 (s, 1H), 3.33 (s, 1H), 3.02 – 2.88 (m, 1H), 2.86 - 2.77 (m, 1H), 2.55 - 2.47 (m, 4H), 2.24 - 1.88 (m, 8H), 1.85 - 1.76 (m, 2H), 1.64 (t, J = 12.0 Hz, 5H), 1.34 (d, J = 6.9 Hz, 3H) ppm
222	 Single enantiomer	606.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.35 (s, 1H), 7.05 (s, 1H), 4.08 (s, 2H), 3.53 (s, 2H), 2.90 (s, 1H), 2.86 - 2.71 (m, 1H), 2.46 (s, 3H), 2.17 (s, 1H), 2.07 (s, 4H), 1.99 - 1.84 (m, 4H), 1.78 (s, 2H), 1.62 (t, J = 18.4 Hz, 3H), 1.46 (s, 1H), 1.34 (s, 6H) ppm
223	 Single enantiomer	606.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.35 (s, 1H), 7.05 (s, 1H), 4.08 (s, 2H), 3.54 (s, 2H), 2.90 (s, 1H), 2.86 - 2.71 (m, 1H), 2.46 (s, 3H), 2.20 - 1.86 (m, 9H), 1.77 (s, 2H), 1.62 (t, J = 18.4 Hz, 3H), 1.46 (s, 1H), 1.34 (s, 6H) ppm
224	 Single diastereomer	592.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.37 (s, 1H), 7.05 (s, 1H), 4.25 (s, 1H), 4.13 (s, 1H), 3.53 (s, 2H), 2.93 (s, 2H), 2.86 - 2.69 (m, 1H), 2.45 (s, 3H), 2.23 - 2.07 (m, 5H), 2.03 - 1.89 (m, 4H), 1.77 (s, 2H), 1.62 (t, J = 18.4 Hz, 3H), 1.46 (s, 1H), 1.31 (s, 3H) ppm
225	 Single diastereomer	592.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.37 (s, 1H), 7.05 (s, 1H), 4.26 (s, 1H), 4.12 (s, 1H), 3.53 (s, 2H), 2.89 (s, 2H), 2.86 - 2.72 (m, 1H), 2.45 (s, 3H), 2.21 - 1.88 (m, 9H), 1.85 (s, 2H), 1.62 (t, J = 10.4 Hz, 3H), 1.46 (s, 1H), 1.32 (s, 3H) ppm

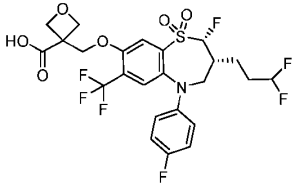
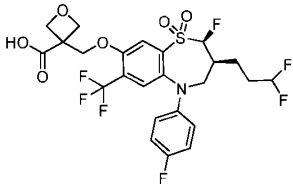
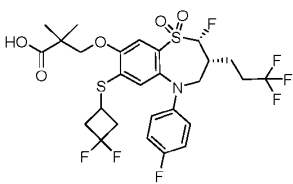
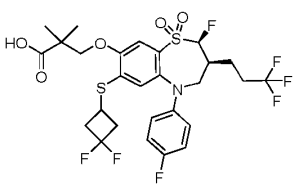
226	 Single diastereomer	596.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.23 (s, 1H), 7.05 (s, 1H), 4.06 (s, 2H), 3.93 - 3.85 (m, 1H), 3.33 - 3.28 (m, 1H), 2.59 (dd, J = 15.9, 10.2 Hz, 1H), 2.44 (s, 3H), 2.33 (s, 3H), 2.29 - 2.16 (m, 3H), 2.15 - 1.96 (m, 2H), 1.96 - 1.89 (m, 9H), 1.77 - 1.56 (m, 5H), 1.35 (s, 6H) ppm
227	 Single diastereomer	579.2	¹ H NMR (400 MHz, CDCl ₃): δ 7.26 (s, 1H), 6.93 (s, 1H), 4.28 - 4.25 (m, 1H), 4.13 - 4.09 (m, 1H), 3.94 - 3.84 (m, 1H), 3.16 (d, J = 15.2 Hz, 1H), 3.10 - 3.05 (m, 1H), 2.65 - 2.49 (m, 1H), 2.42 (s, 3H), 2.32 (s, 3H), 2.20 - 2.07 (m, 4H), 2.06 - 1.97 (m, 1H), 1.96 - 1.75 (m, 11H), 1.65 (t, J = 8.8 Hz, 3H), 1.38 (d, J = 7.2 Hz, 3H) ppm
228	 Single diastereomer	618.2	¹ H NMR (300 MHz, CDCl ₃): δ 7.47 (s, 1H), 7.45 (s, 1H), 4.15 (d, J = 8.4 Hz, 1H), 4.06 (d, J = 8.4 Hz, 1H), 3.95 - 3.84 (m, 1H), 3.23 (d, J = 15.0 Hz, 1H), 2.64 - 2.50 (m, 1H), 2.38 (s, 3H), 2.19 - 2.06 (m, 4H), 1.97 - 1.79 (m, 10H), 1.78 - 1.61 (m, 5H), 1.54 - 1.49 (m, 1H) ppm
229	 Single diastereomer	604.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.62 - 7.54 (m, 2H), 4.31 - 4.22 (m, 2H), 3.96 - 3.91 (m, 1H), 3.45 - 3.41 (m, 1H), 3.10 - 2.72 (m, 1H), 2.64 - 2.55 (m, 1H), 2.39 (s, 3H), 2.17 - 2.12 (m, 3H), 2.10 - 1.99 (m, 2H), 1.92 - 1.81 (m, 9H), 1.79 - 1.57 (m, 5H), 1.33 (d, J = 6.6 Hz, 3H) ppm
230	 Single diastereomer	556.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.33 (s, 1H), 7.05 (s, 1H), 4.07 (s, 2H), 3.99 - 3.89 (m, 1H), 3.46 - 3.35 (m, 1H), 3.04 - 2.66 (m, 2H), 2.45 (s,

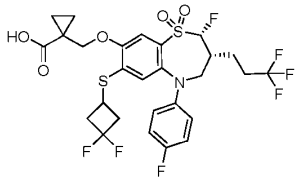
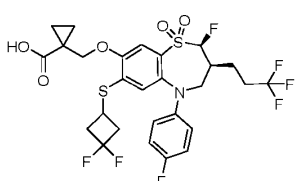
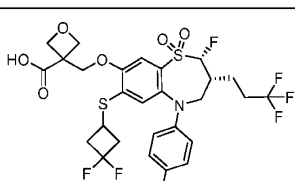
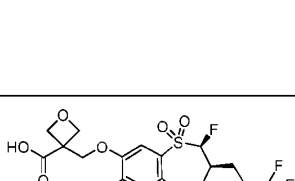
	Single enantiomer		3H), 2.25 – 1.87 (m, 5H), 1.85 – 1.67 (m, 4H), 1.64 – 1.53 (m, 4H), 1.50 – 1.37 (m, 2H), 1.34 – 1.22 (m, 6H) ppm
231	 Single enantiomer	556.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.34 (s, 1H), 7.05 (s, 1H), 4.07 (s, 2H), 3.99 – 3.89 (m, 1H), 3.46 – 3.35 (m, 1H), 2.95 – 2.62 (m, 2H), 2.45 (s, 3H), 2.19 – 1.87 (m, 5H), 1.84 – 1.64 (m, 4H), 1.62 – 1.50 (m, 4H), 1.47 – 1.35 (m, 2H), 1.34 (s, 6H) ppm
232	 Single diastereomer	588.4	¹ H NMR (300 MHz, CD ₃ OD): δ 7.33 (s, 1H), 7.03 (s, 1H), 5.50 (d, J = 46.2 Hz, 1H), 4.07 (s, 2H), 3.60 – 3.47 (m, 1H), 3.30 – 3.20 (m, 1H), 2.87 – 2.72 (m, 1H), 2.63 – 2.29 (m, 4H), 2.27 – 2.00 (m, 5H), 1.98 – 1.83 (m, 3H), 1.80 – 1.75 (m, 2H), 1.70 – 1.48 (m, 5H), 1.34 (s, 6H) ppm
233	 Single diastereomer	588.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.32 (s, 1H), 7.03 (s, 1H), 5.50 (d, J = 46.5 Hz, 1H), 4.07 (s, 2H), 3.59 – 3.46 (m, 1H), 3.30 – 3.18 (m, 1H), 2.87 – 2.72 (m, 1H), 2.65 – 2.33 (m, 4H), 2.25 – 2.00 (m, 5H), 1.98 – 1.92 (m, 3H), 1.80 – 1.74 (m, 2H), 1.73 – 1.47 (m, 5H), 1.34 (s, 6H) ppm
234	 Single diastereomer	600.3	¹ H NMR (400 MHz, CD ₃ OD): δ 7.87 (s, 1H), 7.57 (s, 1H), 7.02 – 6.93 (m, 2H), 6.75 – 6.70 (m, 2H), 5.69 (d, J = 45.2 Hz, 1H), 4.97 (d, J = 6.2 Hz, 2H), 4.74 – 4.66 (m, 4H), 4.19 (d, J = 15.6 Hz, 1H), 3.34 – 3.31 (m, 1H), 2.79 – 2.61 (m, 1H), 2.20 – 2.05 (m, 2H), 1.81 – 1.68 (m, 2H), 1.67 – 1.57 (m, 3H) ppm

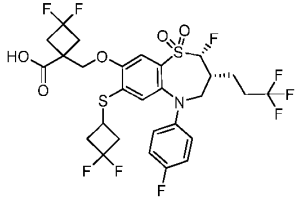
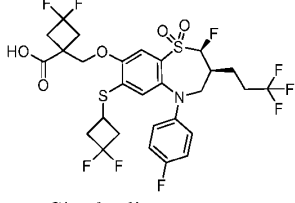
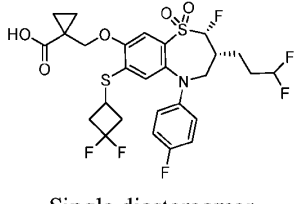
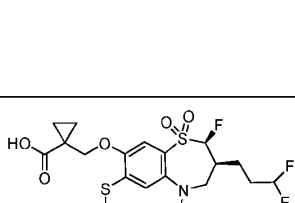
235	 Single enantiomer	542.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.38 (s, 1H), 7.06 (s, 1H), 4.33 – 4.21 (m, 1H), 4.19 – 4.11 (m, 1H), 3.97 – 3.93 (m, 1H), 3.42 (d, <i>J</i> = 13.8 Hz, 1H), 2.99 – 2.85 (m, 2H), 2.82 – 2.67 (m, 1H), 2.47 (s, 3H), 2.18 – 1.90 (m, 5H), 1.86 – 1.73 (m, 3H), 1.63 (t, <i>J</i> = 18.6 Hz, 5H), 1.54 – 1.41 (m, 2H), 1.32 (d, <i>J</i> = 6.9 Hz, 3H) ppm
236	 Single enantiomer	542.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.38 (s, 1H), 7.06 (s, 1H), 4.33 – 4.21 (m, 1H), 4.19 – 4.11 (m, 1H), 3.97 – 3.93 (m, 1H), 3.42 (d, <i>J</i> = 13.8 Hz, 1H), 2.99 – 2.85 (m, 2H), 2.82 – 2.67 (m, 1H), 2.47 (s, 3H), 2.18 – 1.90 (m, 5H), 1.86 – 1.73 (m, 3H), 1.63 (t, <i>J</i> = 18.6 Hz, 5H), 1.54 – 1.41 (m, 2H), 1.32 (d, <i>J</i> = 6.9 Hz, 3H) ppm
237	 Single diastereomer	588.1	¹ H NMR (400 MHz, CDCl ₃): δ 7.71 (s, 1H), 7.49 (s, 1H), 6.94 – 7.00 (m, 2H), 6.62 – 6.65 (m, 2H), 5.26 (d, <i>J</i> = 46.0 Hz, 1H), 4.34 – 4.39 (m, 2H), 4.04 (d, <i>J</i> = 14.8 Hz, 1H), 3.36 (dd, <i>J</i> = 12.8, 9.6 Hz, 1H), 2.73 – 2.83 (m, 1H), 2.22 – 2.34 (m, 2H), 1.73 – 1.85 (m, 2H), 1.51 (q, <i>J</i> = 4.4 Hz, 2H), 1.21 (q, <i>J</i> = 4.4 Hz, 2H) ppm
238	 Single diastereomer	588.1	¹ H NMR (400 MHz, CDCl ₃): δ 7.71 (s, 1H), 7.49 (s, 1H), 6.95 – 7.00 (m, 2H), 6.62 – 6.65 (m, 2H), 5.27 (d, <i>J</i> = 46.0 Hz, 1H), 4.33 – 4.39 (m, 2H), 4.04 (d, <i>J</i> = 15.2 Hz, 1H), 3.33 (dd, <i>J</i> = 15.6, 11.2 Hz, 1H), 2.73 – 2.83 (m, 1H), 2.22 – 2.31 (m, 2H), 1.73 – 1.85 (m, 2H), 1.51 (q, <i>J</i> = 4.4 Hz, 2H), 1.21 (q, <i>J</i> = 4.4 Hz, 2H) ppm

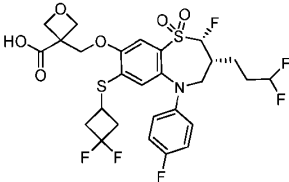
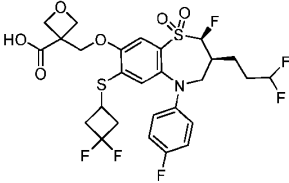
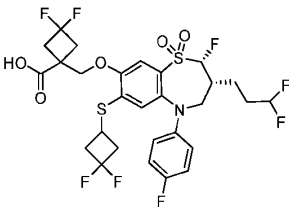
239	 Single diastereomer	604.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.87 (s, 1H), 7.57 (s, 1H), 7.03 - 6.92 (m, 2H), 6.77 - 6.69 (m, 2H), 5.74 (d, J = 45.2 Hz, 1H), 4.97 (d, J = 6.4 Hz, 2H), 4.78 - 4.60 (m, 4H), 4.26 - 4.17 (m, 1H), 3.36 - 3.32 (m, 1H), 2.83 - 2.67 (m, 1H), 2.54 - 2.37 (m, 2H), 1.88 - 1.72 (m, 2H) ppm
240	 Single diastereomer	604.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.87 (s, 1H), 7.57 (s, 1H), 7.03 - 6.92 (m, 2H), 6.77 - 6.69 (m, 2H), 5.75 (d, J = 44.8 Hz, 1H), 4.97 (d, J = 6.4 Hz, 2H), 4.77 - 4.67 (m, 4H), 4.21 (d, J = 15.6 Hz, 1H), 3.37 - 3.32 (m, 1H), 2.87 - 2.66 (m, 1H), 2.55 - 2.36 (m, 2H), 1.89 - 1.71 (m, 2H) ppm
241	 Single diastereomer	568.1 [M-1] ⁻	¹ H NMR (300 MHz, CD ₃ OD): δ 7.81 (s, 1H), 7.56 (s, 1H), 6.98 (t, J = 8.7 Hz, 2H), 6.73 - 6.69 (m, 2H), 5.97 - 5.62 (m, 2H), 4.42 - 4.40 (m, 2H), 4.20 (d, J = 16.5 Hz, 1H), 3.27 - 3.25 (m, 1H), 2.85 - 2.61 (m, 1H), 2.11 - 2.07 (m, 2H), 1.73 - 1.68 (m, 2H), 1.39 - 1.35 (m, 2H), 1.16 - 1.12 (m, 2H) ppm
242	 Single diastereomer	568.1 [M-1] ⁻	¹ H NMR (300 MHz, CD ₃ OD): δ 7.81 (s, 1H), 7.56 (s, 1H), 6.98 (t, J = 8.7 Hz, 2H), 6.73 - 6.69 (m, 2H), 6.20 - 5.62 (m, 2H), 4.42 - 4.40 (m, 2H), 4.20 (d, J = 15.6 Hz, 1H), 3.30 - 3.27 (m, 1H), 2.84 - 2.62 (m, 1H), 2.21 - 1.98 (m, 2H), 1.81 - 1.70 (m, 2H), 1.37 - 1.35 (m, 2H), 1.16 - 1.14 (m, 2H) ppm

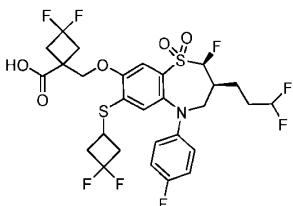
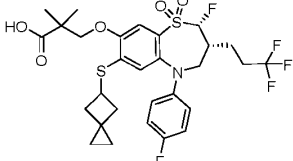
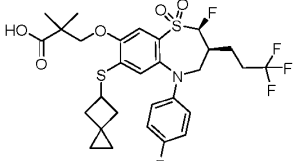
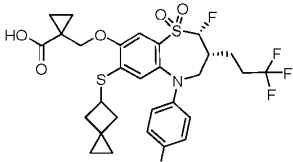
243	 Single diastereomer	620.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.85 (s, 1H), 7.59 (s, 1H), 7.30 - 6.97 (m, 2H), 6.76 - 6.72 (m, 2H), 6.18 - 5.65 (m, 2H), 4.58 - 4.50 (m, 2H), 4.22 (d, J = 15.9 Hz, 1H), 3.33 - 3.28 (m, 1H), 3.18 - 3.04 (m, 2H), 2.92 - 2.69 (m, 3H), 2.22 - 2.03 (m, 2H), 1.79 - 1.66 (m, 2H) ppm
244	 Single diastereomer	620.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.85 (s, 1H), 7.59 (s, 1H), 7.00 (t, J = 8.7 Hz, 2H), 6.76 - 6.72 (m, 2H), 6.16 - 5.65 (m, 2H), 4.59 - 4.51 (m, 2H), 4.22 (d, J = 15.9 Hz, 1H), 3.33 - 3.28 (m, 1H), 3.18 - 3.01 (m, 2H), 2.92 - 2.67 (m, 3H), 2.19 - 2.03 (m, 2H), 1.79 - 1.64 (m, 2H) ppm
245	 Single diastereomer	624.1 [M-1] ⁻	¹ H NMR (300 MHz, CD ₃ OD): δ 7.50 (s, 1H), 7.05 - 6.90 (m, 3H), 6.74 - 6.63 (m, 2H), 5.97 (tt, J = 56.7, 4.2 Hz, 1H), 5.59 (d, J = 45.6 Hz, 1H), 4.23 - 4.09 (m, 3H), 3.83 - 3.65 (m, 1H), 3.31 - 3.24 (m, 1H), 3.21 - 2.90 (m, 2H), 2.83 - 2.63 (m, 1H), 2.62 - 2.39 (m, 2H), 2.23 - 1.96 (m, 2H), 1.80 - 1.58 (m, 2H), 1.38 (s, 6H) ppm
246	 Single diastereomer	624.1 [M-1] ⁻	¹ H NMR (300 MHz, CD ₃ OD): δ 7.50 (s, 1H), 7.05 - 6.90 (m, 3H), 6.74 - 6.63 (m, 2H), 5.97 (tt, J = 56.7, 4.2 Hz, 1H), 5.59 (d, J = 45.6 Hz, 1H), 4.23 - 4.09 (m, 3H), 3.83 - 3.65 (m, 1H), 3.31 - 3.24 (m, 1H), 3.21 - 2.90 (m, 2H), 2.83 - 2.63 (m, 1H), 2.62 - 2.39 (m, 2H), 2.23 - 1.96 (m, 2H), 1.80 - 1.58 (m, 2H), 1.38 (s, 6H) ppm

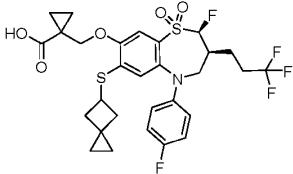
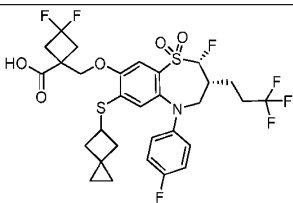
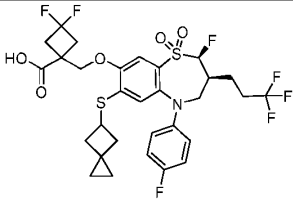
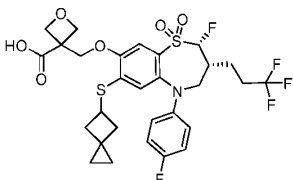
247	 Single diastereomer	586.1	¹ H NMR (400 MHz, CDCl ₃): δ 7.78 (s, 1H), 7.49 (s, 1H), 7.00 – 6.95 (m, 2H), 6.68 – 6.65 (m, 2H), 5.91 (t, <i>J</i> = 56.0 Hz, 1H), 5.30 (d, <i>J</i> = 46.0 Hz, 1H), 5.07 (dd, <i>J</i> = 6.4, 2.4 Hz, 2H), 4.71 – 4.66 (m, 4H), 4.06 (d, <i>J</i> = 14.8 Hz, 1H), 3.33 (dd, <i>J</i> = 15.6, 11.2 Hz, 1H), 2.81 – 2.71 (m, 1H), 2.08 – 1.96 (m, 2H), 1.74 – 1.66 (m, 2H) ppm
248	 Single diastereomer	586.1	¹ H NMR (400 MHz, CDCl ₃): δ 7.78 (s, 1H), 7.49 (s, 1H), 6.99 – 6.95 (m, 2H), 6.68 – 6.66 (m, 2H), 5.91 (t, <i>J</i> = 56.0 Hz, 1H), 5.30 (d, <i>J</i> = 46.0 Hz, 1H), 5.07 (dd, <i>J</i> = 6.4, 2.4 Hz, 2H), 4.71 – 4.66 (m, 4H), 4.06 (d, <i>J</i> = 14.8 Hz, 1H), 3.33 (dd, <i>J</i> = 15.6, 11.2 Hz, 1H), 2.81 – 2.71 (m, 1H), 2.10 – 1.96 (m, 2H), 1.74 – 1.65 (m, 2H) ppm
249	 Single diastereomer	644.1	¹ H NMR (300 MHz, CDCl ₃): δ 7.50 (s, 1H), 7.00 - 6.95 (m, 2H), 6.79 (s, 1H), 6.65 - 6.61 (m, 2H), 5.25 (d, <i>J</i> = 46.2 Hz, 1H), 4.27 - 4.17 (m, 2H), 4.03 (d, <i>J</i> = 16.2 Hz, 1H), 3.68 - 3.50 (m, 1H), 3.41 - 3.26 (m, 1H), 3.19 - 2.45 (m, 5H), 2.51 - 2.22 (m, 2H), 1.88 - 1.73 (m, 2H), 1.44 (s, 6H) ppm.
250	 Single diastereomer	644.1	¹ H NMR (300 MHz, CDCl ₃): δ 7.50 (s, 1H), 7.00 - 6.95 (m, 2H), 6.79 (s, 1H), 6.65 - 6.60 (m, 2H), 5.25 (d, <i>J</i> = 46.5 Hz, 1H), 4.20 - 4.14 (m, 2H), 4.02 (d, <i>J</i> = 14.7 Hz, 1H), 3.63 - 3.48 (m, 1H), 3.46 - 3.26 (m, 1H), 3.16 - 2.51 (m, 5H), 2.38 - 2.21 (m, 2H), 1.92 - 1.71 (m, 2H), 1.45 (s, 6H) ppm

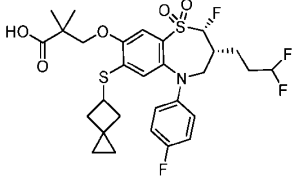
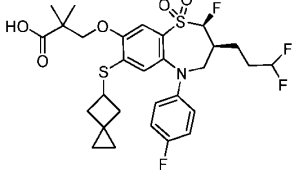
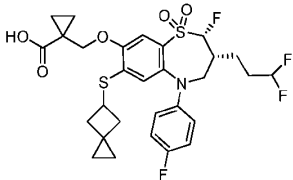
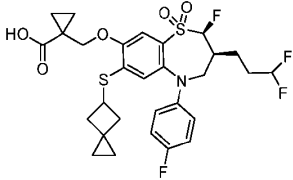
251	 Single diastereomer	642.1	¹ H NMR (300 MHz, CDCl ₃): δ 7.50 (s, 1H), 7.00 - 6.95 (m, 2H), 6.80 (s, 1H), 6.66 - 6.56 (m, 2H), 5.24 (d, J = 46.2 Hz, 1H), 4.43 - 4.23 (m, 2H), 4.02 (d, J = 15.3 Hz, 1H), 3.65 - 3.56 (m, 1H), 3.42 - 3.31 (m, 1H), 3.14 - 2.57 (m, 5H), 2.41 - 2.21 (m, 2H), 1.95 - 1.71 (m, 2H), 1.63 - 1.51 (m, 2H), 1.35 - 1.14 (m, 2H) ppm
252	 Single diastereomer	642.1	¹ H NMR (300 MHz, CDCl ₃): δ 7.50 (s, 1H), 7.00 - 6.95 (m, 2H), 6.80 (s, 1H), 6.64 - 6.60 (m, 2H), 5.24 (d, J = 46.5 Hz, 1H), 4.38 - 4.27 (m, 2H), 4.02 (d, J = 15.3 Hz, 1H), 3.65 - 3.56 (m, 1H), 3.42 - 3.30 (m, 1H), 3.14 - 2.63 (m, 5H), 2.39 - 2.21 (m, 2H), 1.94 - 1.70 (m, 2H), 1.62 - 1.52 (m, 2H), 1.29 - 1.18 (m, 2H) ppm
253	 Single diastereomer	658.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.60 (s, 1H), 7.02 - 6.91 (m, 3H), 6.74 - 6.66 (m, 2H), 5.63 (d, J = 45.6 Hz, 1H), 5.02 - 4.95 (m, 2H), 4.77 (dd, J = 6.0, 2.4 Hz, 2H), 4.60 (d, J = 2.0 Hz, 2H), 4.16 (d, J = 16.0 Hz, 1H), 3.78 - 3.70 (m, 1H), 3.34 - 3.32 (m, 1H), 3.19 - 3.05 (m, 1H), 3.03 - 2.91 (m, 1H), 2.84 - 2.66 (m, 1H), 2.62 - 2.36 (m, 4H), 1.87 - 1.71 (m, 2H) ppm
254	 Single diastereomer	658.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.60 (s, 1H), 7.01 - 6.92 (m, 3H), 6.74 - 6.66 (m, 2H), 5.63 (d, J = 45.6 Hz, 1H), 5.02 - 4.95 (m, 2H), 4.77 (dd, J = 6.0, 2.4 Hz, 2H), 4.64 - 4.58 (m, 2H), 4.16 (d, J = 16.0 Hz, 1H), 3.78 - 3.68 (m, 1H), 3.35 - 3.32 (m, 1H), 3.16 - 3.06 (m, 1H), 3.02 - 2.92 (m, 1H)

			1H), 2.86 - 2.65 (m, 1H), 2.60 - 2.39 (m, 4H), 1.87 - 1.71 (m, 2H) ppm
255	 Single diastereomer	692.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.57 (s, 1H), 7.00 - 6.95 (m, 3H), 6.77 - 6.68 (m, 2H), 5.65 (d, <i>J</i> = 45.6 Hz, 1H), 4.46 (s, 2H), 4.17 (d, <i>J</i> = 15.9 Hz, 1H), 3.81 - 3.69 (m, 1H), 3.31 - 3.28 (m, 1H), 3.21 - 2.78 (m, 6H), 2.75 - 2.66 (m, 1H), 2.62 - 2.37 (m, 4H), 1.89 - 1.73 (m, 2H) ppm.
256	 Single diastereomer	692.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.57 (s, 1H), 7.00 - 6.95 (m, 3H), 6.78 - 6.66 (m, 2H), 5.65 (d, <i>J</i> = 45.6 Hz, 1H), 4.46 (s, 2H), 4.17 (d, <i>J</i> = 15.9 Hz, 1H), 3.82 - 3.69 (m, 1H), 3.28 (s, 1H), 3.20 - 2.79 (m, 6H), 2.75 - 2.66 (m, 1H), 2.62 - 2.37 (m, 4H), 1.89 - 1.73 (m, 2H) ppm
257	 Single diastereomer	624.1	¹ H NMR (300 MHz, CDCl ₃): δ 7.50 (s, 1H), 6.97 (t, <i>J</i> = 9.0 Hz, 2H), 6.81 (s, 1H), 6.60 - 6.64 (m, 2H), 5.93 (tt, <i>J</i> = 56.1, 3.9 Hz, 1H), 5.25 (d, <i>J</i> = 46.2 Hz, 1H), 4.30 (q, <i>J</i> = 9.9 Hz, 2H), 4.02 (d, <i>J</i> = 15.3 Hz, 1H), 3.58 - 3.61 (m, 1H), 3.30 - 3.39 (m, 1H), 2.99 - 3.10 (m, 2H), 2.57 - 2.68 (m, 3H), 2.02 - 2.09 (m, 2H), 1.69 - 1.75 (m, 2H), 1.56 (q, <i>J</i> = 4.2 Hz, 2H), 1.24 (q, <i>J</i> = 4.2 Hz, 2H) ppm
258	 Single diastereomer	624.1	¹ H NMR (300 MHz, CDCl ₃): δ 7.50 (s, 1H), 6.97 (t, <i>J</i> = 8.7 Hz, 2H), 6.81 (s, 1H), 6.60 - 6.64 (m, 2H), 5.93 (tt, <i>J</i> = 56.1, 3.9 Hz, 1H), 5.25 (d, <i>J</i> = 46.2 Hz, 1H), 4.31 (q, <i>J</i> = 9.9 Hz, 2H), 4.03 (d, <i>J</i> = 15.3 Hz, 1H), 3.58 - 3.61 (m, 1H), 3.30 - 3.39 (m, 1H), 2.98 - 3.12 (m, 2H), 2.57 - 2.88 (m, 3H), 2.03 - 2.09 (m, 2H), 1.68 - 1.73

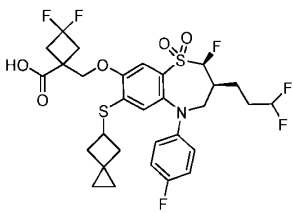
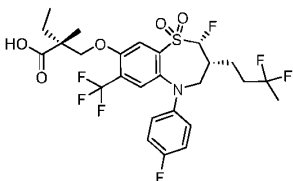
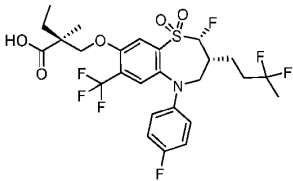
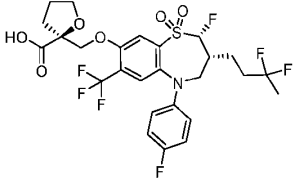
			(m, 2H), 1.56 (q, $J = 4.2$ Hz, 2H), 1.24 (d, $J = 3.3$ Hz, 2H) ppm
259	 Single diastereomer	640.1	^1H NMR (300 MHz, CDCl_3): δ 7.59 (s, 1H), 6.98 (t, $J = 8.7$ Hz, 2H), 6.80 (s, 1H), 6.63 – 6.67 (m, 2H), 5.93 (tt, $J = 56.1, 3.9$ Hz, 1H), 5.28 (d, $J = 46.8$ Hz, 1H), 5.10 (d, $J = 6.6$ Hz, 2H), 4.77 (d, $J = 6.6$ Hz, 2H), 4.64 (s, 2H), 4.05 (d, $J = 16.8$ Hz, 1H), 3.55 – 3.57 (m, 1H), 3.31 – 3.40 (m, 1H), 2.83 – 3.13 (m, 3H), 2.53 – 2.71 (m, 2H), 2.02 – 2.08 (m, 2H), 1.67 – 1.76 (m, 2H) ppm
260	 Single diastereomer	640.1	^1H NMR (300 MHz, CDCl_3): δ 7.59 (s, 1H), 6.98 (t, $J = 8.7$ Hz, 2H), 6.80 (s, 1H), 6.63 – 6.66 (m, 2H), 5.93 (tt, $J = 56.1, 3.9$ Hz, 1H), 5.28 (d, $J = 46.8$ Hz, 1H), 5.10 (d, $J = 6.6$ Hz, 2H), 4.77 (d, $J = 6.6$ Hz, 2H), 4.64 (s, 2H), 4.05 (d, $J = 16.8$ Hz, 1H), 3.55 – 3.58 (m, 1H), 3.31 – 3.40 (m, 1H), 2.94 – 3.20 (m, 2H), 2.43 – 2.87 (m, 3H), 2.04 – 2.06 (m, 2H), 1.69 – 1.74 (m, 2H) ppm
261	 Single diastereomer	674.1	^1H NMR (300 MHz, CDCl_3): δ 7.55 (s, 1H), 6.98 (t, $J = 8.7$ Hz, 2H), 6.79 (s, 1H), 6.63 – 6.67 (m, 2H), 5.93 (tt, $J = 56.1, 3.6$ Hz, 1H), 5.28 (d, $J = 45.6$ Hz, 1H), 4.46 (s, 2H), 4.04 (d, $J = 15.0$ Hz, 1H), 3.53 – 3.57 (m, 1H), 3.09 – 3.39 (m, 4H), 2.84 – 3.07 (m, 3H), 2.52 – 2.71 (m, 3H), 2.02 – 2.09 (m, 2H), 1.69 – 1.76 (m, 2H) ppm

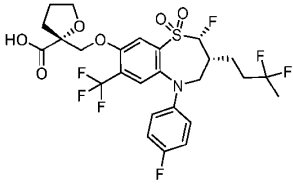
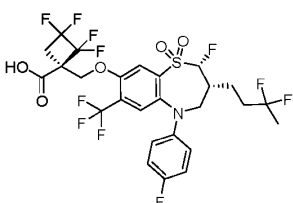
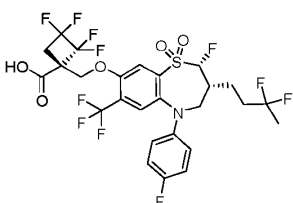
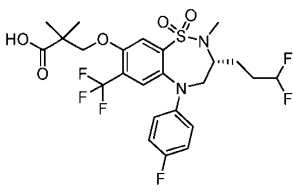
262	 Single diastereomer	674.1	¹ H NMR (300 MHz, CDCl ₃): δ 7.55 (s, 1H), 6.98 (t, <i>J</i> = 8.7 Hz, 2H), 6.79 (s, 1H), 6.63 – 6.67 (m, 2H), 5.93 (t, <i>J</i> = 56.1, 3.6 Hz, 1H), 5.28 (d, <i>J</i> = 45.6 Hz, 1H), 4.46 (s, 2H), 4.04 (d, <i>J</i> = 15.6 Hz, 1H), 3.54 – 3.57 (m, 1H), 3.02 – 3.39 (m, 4H), 2.84 – 3.00 (m, 3H), 2.52 – 2.71 (m, 3H), 2.01 – 2.90 (m, 2H), 1.69 – 1.76 (m, 2H) ppm
263	 Single diastereomer	634.2	¹ H NMR (300 MHz, CDCl ₃): δ 7.47 (s, 1H), 6.98 – 6.89 (m, 2H), 6.82 (s, 1H), 6.69 – 6.56 (m, 2H), 5.23 (d, <i>J</i> = 46.5 Hz, 1H), 4.24 – 4.11 (m, 2H), 4.00 (d, <i>J</i> = 15.3 Hz, 1H), 3.97 – 3.80 (m, 1H), 3.43 – 3.32 (m, 1H), 2.89 – 2.74 (m, 1H), 2.64 – 2.50 (m, 1H), 2.49 – 2.40 (m, 1H), 2.39 – 2.18 (m, 4H), 1.93 – 1.64 (m, 2H), 1.46 (s, 6H), 0.49 (s, 4H) ppm
264	 Single diastereomer	634.2	¹ H NMR (300 MHz, CDCl ₃): δ 7.47 (s, 1H), 6.98 – 6.90 (m, 2H), 6.81 (s, 1H), 6.68 – 6.53 (m, 2H), 5.23 (d, <i>J</i> = 46.5 Hz, 1H), 4.23 – 4.13 (m, 2H), 4.00 (d, <i>J</i> = 15.3 Hz, 1H), 3.96 – 3.82 (m, 1H), 3.45 – 3.32 (m, 1H), 2.90 – 2.79 (m, 1H), 2.61 – 2.53 (m, 1H), 2.49 – 2.39 (m, 1H), 2.38 – 2.20 (m, 4H), 1.90 – 1.72 (m, 2H), 1.47 (s, 6H), 0.49 (s, 4H) ppm
265	 Single diastereomer	632.1	¹ H NMR (300 MHz, CDCl ₃): δ 7.47 (s, 1H), 6.98 – 6.87 (m, 2H), 6.81 (s, 1H), 6.71 – 6.54 (m, 2H), 5.22 (d, <i>J</i> = 45.9 Hz, 1H), 4.48 – 4.20 (m, 2H), 3.98 (d, <i>J</i> = 15.0 Hz, 1H), 3.98 – 3.82 (m, 1H), 3.45 – 3.31 (m, 1H), 2.84 – 2.79 (m, 1H), 2.61 – 2.52 (m, 1H), 2.51 – 2.43 (m, 1H), 2.39 – 2.19 (m, 4H), 1.89 – 1.72 (m, 2H), 1.62 – 1.48

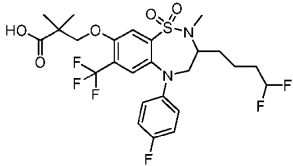
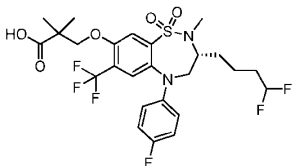
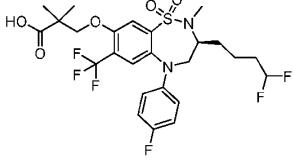
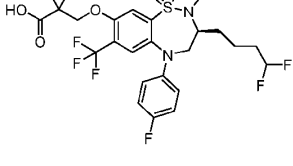
			(m, 2H), 1.35 - 1.19 (m, 2H), 0.49 (s, 4H) ppm
266	 Single diastereomer	632.1	¹ H NMR (300 MHz, CDCl ₃): δ 7.47 (s, 1H), 7.08 - 6.90 (m, 2H), 6.81 (s, 1H), 6.68 - 6.55 (m, 2H), 5.22 (d, J = 47.1 Hz, 1H), 4.45 - 4.25 (m, 2H), 4.00 (d, J = 15.3 Hz, 1H), 3.96 - 3.85 (m, 1H), 3.43 - 3.32 (m, 1H), 2.90 - 2.74 (m, 1H), 2.62 - 2.41 (m, 2H), 2.40 - 2.16 (m, 4H), 1.94 - 1.71 (m, 2H), 1.63 - 1.49 (m, 2H), 1.33 - 1.18 (m, 2H), 0.49 (s, 4H) ppm
267	 Single diastereomer	682.1	¹ H NMR (300 MHz, CDCl ₃): δ 7.51 (s, 1H), 7.09 - 6.89 (m, 2H), 6.82 (s, 1H), 6.73 - 6.59 (m, 2H), 5.25 (d, J = 46.5 Hz, 1H), 4.45 (s, 2H), 4.01 (d, J = 15.9 Hz, 1H), 3.96 - 3.83 (m, 1H), 3.41 - 3.31 (m, 1H), 3.30 - 3.19 (m, 2H), 3.00 - 2.89 (m, 2H), 2.84 - 2.69 (m, 1H), 2.63 - 2.40 (m, 2H), 2.39 - 2.13 (m, 4H), 1.93 - 1.70 (m, 2H), 0.49 (s, 4H) ppm
268	 Single diastereomer	682.1	¹ H NMR (300 MHz, CDCl ₃): δ 7.51 (s, 1H), 7.08 - 6.90 (m, 2H), 6.82 (s, 1H), 6.75 - 6.57 (m, 2H), 5.25 (d, J = 46.5 Hz, 1H), 4.45 (s, 2H), 4.01 (d, J = 16.5 Hz, 1H), 3.96 - 3.82 (m, 1H), 3.45 - 3.32 (m, 1H), 3.31 - 3.28 (m, 2H), 3.00 - 2.72 (m, 3H), 2.61 - 2.49 (m, 1H), 2.48 - 2.37 (m, 1H), 2.36 - 2.14 (m, 4H), 1.93 - 1.66 (m, 2H), 0.49 (s, 4H) ppm
269	 Single diastereomer	648.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.58 (s, 1H), 6.99 - 6.93 (m, 3H), 6.74 - 6.69 (m, 2H), 5.64 (d, J = 45.6 Hz, 1H), 5.02 - 5.00 (m, 2H), 4.86 - 4.82 (m, 2H), 4.81 - 4.61 (m, 2H), 4.19 - 4.14 (m, 1H), 3.99 - 3.94 (m, 1H),

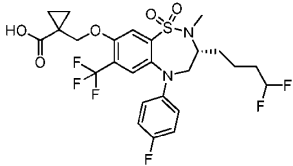
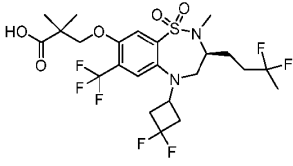
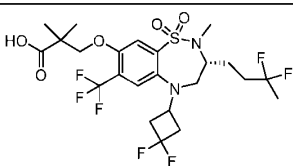
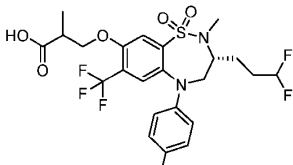
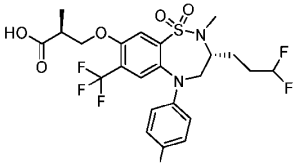
			3.37 - 3.34 (m, 1H), 2.87 - 2.65 (m, 1H), 2.61 - 2.43 (m, 4H), 2.25 - 2.19 (m, 2H), 1.85 - 1.80 (m, 2H), 0.48 (s, 4H) ppm
270	 Single diastereomer	616.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.47 (s, 1H), 6.98 - 6.91 (m, 3H), 6.71 - 6.66 (m, 2H), 6.16 - 5.79 (m, 1H), 5.58 (d, J = 45.6 Hz, 1H), 4.20 - 4.12 (m, 3H), 3.99 - 3.94 (m, 1H), 3.33 - 3.25 (m, 1H), 2.61 - 2.44 (m, 3H), 2.25 - 2.07 (m, 4H), 1.72 - 1.67 (m, 2H), 1.40 (s, 6H), 0.48 (s, 4H) ppm
271	 Single diastereomer	616.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.47 (s, 1H), 6.98 - 6.91 (m, 3H), 6.71 - 6.66 (m, 2H), 6.16 - 5.79 (m, 1H), 5.58 (d, J = 45.6 Hz, 1H), 4.20 - 4.11 (m, 3H), 3.99 - 3.94 (m, 1H), 3.33 - 3.25 (m, 1H), 2.61 - 2.44 (m, 3H), 2.25 - 2.07 (m, 4H), 1.75 - 1.67 (m, 2H), 1.40 (s, 6H), 0.48 - 0.47 (m, 4H) ppm
272	 Single diastereomer	614.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.48 (s, 1H), 6.97 - 6.90 (m, 3H), 6.74 - 6.62 (m, 2H), 5.97 (tt, J = 56.7, 4.2 Hz, 1H), 5.57 (d, J = 45.6 Hz, 1H), 4.32 (s, 2H), 4.13 (d, J = 15.6 Hz, 1H), 4.01 - 3.91 (m, 1H), 3.32 - 3.24 (m, 1H), 2.82 - 2.64 (m, 1H), 2.62 - 2.43 (m, 2H), 2.28 - 2.01 (m, 4H), 1.77 - 1.61 (m, 2H), 1.43 - 1.33 (m, 2H), 1.23 - 1.13 (m, 2H), 0.47 (s, 4H) ppm
273	 Single diastereomer	614.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.48 (s, 1H), 7.01 - 6.87 (m, 3H), 6.73 - 6.62 (m, 2H), 5.97 (tt, J = 56.7, 4.2 Hz, 1H), 5.57 (d, J = 45.6 Hz, 1H), 4.32 (s, 2H), 4.13 (d, J = 15.9 Hz, 1H), 4.02 - 3.90 (m, 1H), 3.32 - 3.24

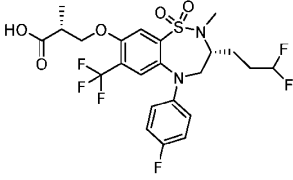
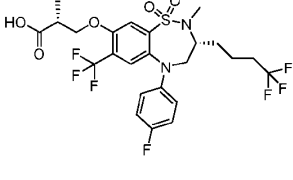
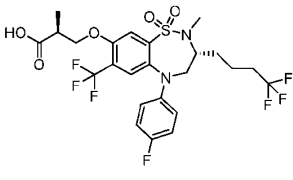
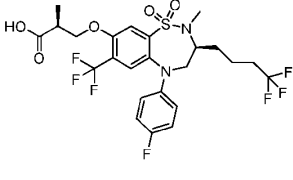
			(m, 1H), 2.82 - 2.64 (m, 1H), 2.62 - 2.43 (m, 2H), 2.28 - 2.01 (m, 4H), 1.77 - 1.61 (m, 2H), 1.45 - 1.33 (m, 2H), 1.23 - 1.13 (m, 2H), 0.47 (s, 4H) ppm
274	Single diastereomer	630.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.58 (s, 1H), 6.99 - 6.93 (m, 3H), 6.73 - 6.68 (m, 2H), 6.18 - 5.79 (m, 1H), 5.60 (d, J = 45.6 Hz, 1H), 5.02 - 5.01 (m, 2H), 4.83 - 4.81 (m, 2H), 4.60 (s, 2H), 4.18 - 4.13 (m, 1H), 4.00 - 3.95 (m, 1H), 3.33 - 3.26 (m, 1H), 2.80 - 2.66 (m, 1H), 2.61 - 2.44 (m, 2H), 2.25 - 2.07 (m, 4H), 1.75 - 1.65 (m, 2H), 0.48 (s, 4H) ppm
275	Single diastereomer	630.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.58 (s, 1H), 6.99 - 6.93 (m, 3H), 6.72 - 6.68 (m, 2H), 6.17 - 5.78 (m, 1H), 5.59 (d, J = 45.6 Hz, 1H), 5.10 - 5.01 (m, 2H), 4.89 - 4.84 (m, 2H), 4.55 (s, 2H), 4.18 - 4.13 (m, 1H), 4.00 - 3.95 (m, 1H), 3.33 - 3.26 (m, 1H), 2.78 - 2.68 (m, 1H), 2.62 - 2.57 (m, 1H), 2.55 - 2.44 (m, 1H), 2.25 - 2.03 (m, 4H), 1.73 - 1.71 (m, 2H), 0.48 (s, 4H) ppm
276	Single diastereomer	664.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.53 (s, 1H), 7.01 - 6.87 (m, 3H), 6.76 - 6.64 (m, 2H), 6.19 - 5.77 (m, 1H), 5.58 (d, J = 45.6 Hz, 1H), 4.44 (t, J = 2.5 Hz, 2H), 4.14 (d, J = 15.6 Hz, 1H), 4.02 - 3.90 (m, 1H), 3.32 - 3.25 (m, 1H), 3.20 - 3.02 (m, 2H), 2.99 - 2.65 (m, 3H), 2.62 - 2.39 (m, 2H), 2.29 - 1.98 (m, 4H), 1.78 - 1.59 (m, 2H), 0.47 (s, 4H) ppm.

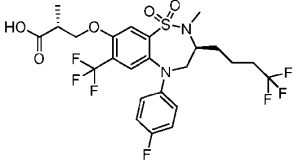
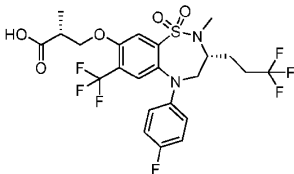
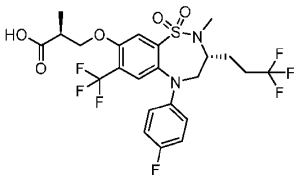
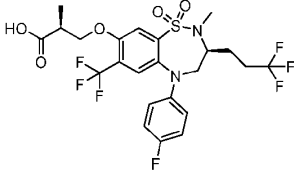
277	 Single diastereomer	664.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.53 (s, 1H), 7.00 - 6.88 (m, 3H), 6.76 - 6.64 (m, 2H), 6.19 - 5.77 (m, 1H), 5.58 (d, J = 45.6 Hz, 1H), 4.44 (s, 2H), 4.14 (d, J = 15.6 Hz, 1H), 4.03 - 3.89 (m, 1H), 3.32 - 3.25 (m, 1H), 3.18 - 3.03 (m, 2H), 2.99 - 2.65 (m, 3H), 2.62 - 2.39 (m, 2H), 2.26 - 1.99 (m, 4H), 1.77 - 1.61 (m, 2H), 0.47 (s, 4H) ppm
278	 Single diastereomer with arbitrarily assigned stereochemistry	600.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.79 (s, 1H), 7.57 (s, 1H), 6.99 (t, J = 8.7 Hz, 2H), 6.79 - 6.65 (m, 2H), 5.70 (d, J = 45.3 Hz, 1H), 4.32 (d, J = 8.7 Hz, 1H), 4.27 - 4.17 (m, 2H), 3.32 - 3.27 (m, 1H), 2.84 - 2.61 (m, 1H), 2.26 - 2.03 (m, 2H), 1.89 - 1.74 (m, 4H), 1.65 (t, J = 18.6 Hz, 3H), 1.35 (s, 3H), 0.96 (t, J = 7.5 Hz, 3H) ppm
279	 Single diastereomer with arbitrarily assigned stereochemistry	600.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.79 (s, 1H), 7.57 (s, 1H), 6.98 (t, J = 8.7 Hz, 2H), 6.79 - 6.65 (m, 2H), 5.70 (d, J = 45.3 Hz, 1H), 4.35 (d, J = 8.7 Hz, 1H), 4.20 (d, J = 10.8 Hz, 2H), 3.27 (s, 1H), 2.84 - 2.61 (m, 1H), 2.26 - 2.01 (m, 2H), 1.89 - 1.74 (m, 4H), 1.65 (t, J = 18.6 Hz, 3H), 1.35 (s, 3H), 0.96 (t, J = 7.5 Hz, 3H).
280	 Single diastereomer with arbitrarily assigned stereochemistry	614.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.87 (s, 1H), 7.57 (s, 1H), 7.05 - 6.94 (m, 2H), 6.78 - 6.68 (m, 2H), 5.70 (d, J = 45.2 Hz, 1H), 4.49 (q, J = 10.0 Hz, 2H), 4.25 - 4.17 (m, 1H), 4.14 - 4.01 (m, 2H), 3.31 - 3.26 (m, 1H), 2.83 - 2.62 (m, 1H), 2.39 - 2.21 (m, 2H), 2.21 - 1.95 (m, 4H), 1.84 - 1.71 (m, 2H), 1.66 (t, J = 18.4 Hz, 3H) ppm

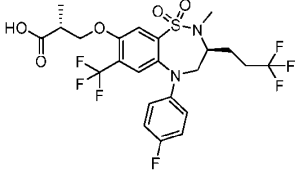
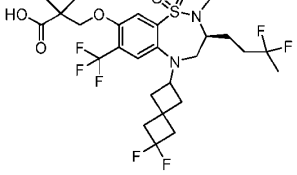
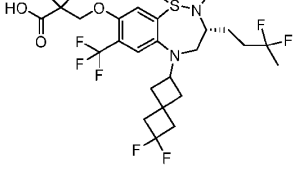
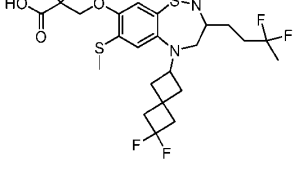
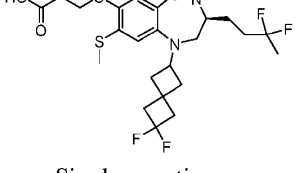
281	 Single diastereomer with arbitrarily assigned stereochemistry	614.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.86 (s, 1H), 7.57 (s, 1H), 7.05 - 6.94 (m, 2H), 6.77 - 6.68 (m, 2H), 5.70 (d, J = 45.2 Hz, 1H), 4.54 (d, J = 10.0 Hz, 1H), 4.44 (d, J = 10.0 Hz, 1H), 4.21 (d, J = 16.0 Hz, 1H), 4.14 - 4.00 (m, 2H), 3.32 - 3.26 (m, 1H), 2.81 - 2.61 (m, 1H), 2.38 - 2.22 (m, 2H), 2.22 - 1.97 (m, 4H), 1.84 - 1.67 (m, 2H), 1.66 (t, J = 18.4 Hz, 3H) ppm
282	 Single diastereomer with arbitrarily assigned stereochemistry	668.1 [M-1] ⁻	¹ H NMR (300 MHz, CD ₃ OD): δ 7.82 (s, 1H), 7.56 (s, 1H), 7.04 - 6.91 (m, 2H), 6.79 - 6.66 (m, 2H), 5.70 (d, J = 45.0 Hz, 1H), 4.85 - 4.77 (m, 1H), 4.52 (d, J = 9.3 Hz, 1H), 4.19 (d, J = 15.9 Hz, 1H), 3.40 - 3.32 (m, 1H), 3.29 - 3.22 (m, 1H), 2.99 - 2.82 (m, 1H), 2.82 - 2.59 (m, 1H), 2.25 - 2.00 (m, 2H), 1.83 - 1.52 (m, 5H) ppm
283	 Single diastereomer with arbitrarily assigned stereochemistry	668.1 [M-1] ⁻	¹ H NMR (300 MHz, CD ₃ OD): δ 7.82 (s, 1H), 7.56 (s, 1H), 7.04 - 6.91 (m, 2H), 6.80 - 6.67 (m, 2H), 5.70 (d, J = 45.0 Hz, 1H), 4.80 (d, J = 9.3 Hz, 1H), 4.55 (d, J = 9.0 Hz, 1H), 4.19 (d, J = 15.6 Hz, 1H), 3.42 - 3.33 (m, 1H), 3.29 - 3.21 (m, 1H), 3.00 - 2.83 (m, 1H), 2.82 - 2.59 (m, 1H), 2.24 - 2.00 (m, 2H), 1.83 - 1.53 (m, 5H) ppm
284	 Single enantiomer	567.1 [M-1] ⁻	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ 12.46 (s, 1H), 7.54 (s, 1H), 7.50 (s, 1H), 7.01 (t, J = 8.7 Hz, 2H), 6.69 (s, 2H), 6.10 (t, J = 56.7 Hz, 1H), 4.19 (s, 2H), 4.07 (s, 1H), 3.81 (s, 1H), 3.39 (s, 1H), 2.55 (s, 3H), 1.92 (s, 2H), 1.76 (s, 1H), 1.62 (s, 1H), 1.23 (s, 6H) ppm

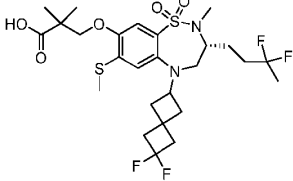
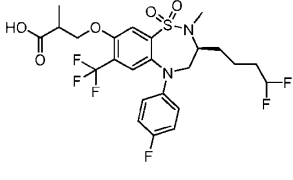
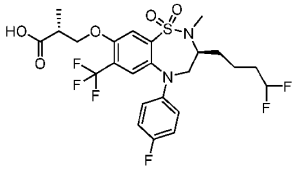
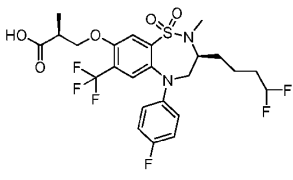
285		581.2 [M-H] ⁻	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆): δ 12.48 (s, 1H), 7.53 (d, <i>J</i> = 20.8 Hz, 2H), 7.00 (t, <i>J</i> = 8.7 Hz, 2H), 6.65 (d, <i>J</i> = 8.3 Hz, 2H), 6.09 (tt, <i>J</i> = 56.8, 4.4 Hz, 1H), 4.19 (s, 2H), 4.01 (d, <i>J</i> = 16.2 Hz, 1H), 3.80 (s, 1H), 3.33 (s, 1H), 2.53 (s, 3H), 1.83 (s, 2H), 1.64 (d, <i>J</i> = 10.1 Hz, 1H), 1.61 – 1.47 (m, 2H), 1.44 (dt, <i>J</i> = 14.1, 7.1 Hz, 1H), 1.23 (s, 6H) ppm
286	 Single enantiomer	583.2	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ 12.47 (s, 1H), 7.55 (s, 1H), 7.51 (s, 1H), 7.00 (t, <i>J</i> = 8.6 Hz, 2H), 6.65 (s, 2H), 6.22 – 5.95 (m, 1H), 4.20 (s, 2H), 4.01 (d, <i>J</i> = 16.2 Hz, 1H), 3.80 (s, 1H), 3.27 (s, 1H), 2.53 (s, 3H), 1.83 (s, 2H), 1.65 (s, 1H), 1.60 – 1.47 (m, 2H), 1.47 – 1.38 (m, 1H), 1.23 (s, 6H) ppm
287	 Single enantiomer	583.2	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ 12.47 (s, 1H), 7.55 (s, 1H), 7.52 (s, 1H), 7.00 (t, <i>J</i> = 8.6 Hz, 2H), 6.65 (s, 2H), 6.25 – 5.94 (m, 1H), 4.20 (s, 2H), 4.01 (d, <i>J</i> = 16.4 Hz, 1H), 3.80 (s, 1H), 3.25 (s, 1H), 2.53 (s, 3H), 1.83 (s, 2H), 1.64 (d, <i>J</i> = 8.7 Hz, 1H), 1.54 (dd, <i>J</i> = 22.2, 10.8 Hz, 2H), 1.43 (s, 1H), 1.23 (s, 6H) ppm
288	 Single enantiomer	579.1 [M-1] ⁻	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ 12.50 (s, 1H), 7.55 (s, 1H), 7.50 (s, 1H), 7.00 (t, <i>J</i> = 8.8 Hz, 2H), 6.64 (s, 2H), 6.24 – 5.95 (m, 1H), 4.41 – 4.26 (m, 2H), 4.01 (d, <i>J</i> = 16.1 Hz, 1H), 3.80 (s, 1H), 3.22 (s, 1H), 2.52 (s, 3H), 1.83 (s, 2H), 1.64 (s, 1H), 1.54 (d, <i>J</i> = 25.1 Hz, 2H), 1.44 (d, <i>J</i> = 11.5 Hz, 1H), 1.16 (s, 2H), 1.00 (s, 2H) ppm

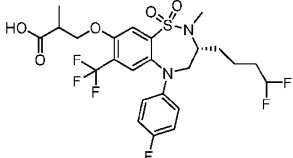
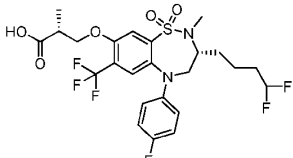
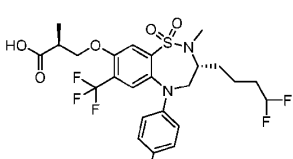
289	 Single enantiomer	579.1 [M-1] ⁻	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ 12.44 (s, 1H), 7.54 (s, 1H), 7.51 (s, 1H), 7.00 (t, <i>J</i> = 8.7 Hz, 2H), 6.64 (s, 2H), 6.28 – 5.90 (m, 1H), 4.40 – 4.26 (m, 2H), 4.01 (d, <i>J</i> = 15.8 Hz, 1H), 3.80 (s, 1H), 3.25 (s, 1H), 2.52 (s, 3H), 1.83 (s, 2H), 1.64 (d, <i>J</i> = 8.9 Hz, 1H), 1.60 – 1.48 (m, 2H), 1.44 (d, <i>J</i> = 9.5 Hz, 1H), 1.20 (d, <i>J</i> = 3.2 Hz, 2H), 1.08 – 1.01 (m, 2H) ppm
290	 Single enantiomer	579.2	¹ H NMR (500 MHz, CD ₃ OD): δ 7.57 (s, 1H), 7.22 (s, 1H), 4.81 (s, 1H), 4.10 (dq, <i>J</i> = 13.0, 6.5, 4.5 Hz, 4H), 3.08 – 2.73 (m, 4H), 2.70 – 2.27 (m, 4H), 2.25 – 1.94 (m, 3H), 1.73 (s, 1H), 1.63 (t, <i>J</i> = 18.5 Hz, 3H), 1.32 (s, 6H) ppm
291	 Single enantiomer	579.2	¹ H NMR (500 MHz, CD ₃ OD): δ 7.57 (s, 1H), 7.21 (s, 1H), 4.73 (s, 1H), 4.17 – 3.64 (m, 4H), 2.88 (d, <i>J</i> = 51.1 Hz, 4H), 2.54 (d, <i>J</i> = 111.2 Hz, 4H), 2.26 – 1.89 (m, 3H), 1.73 (s, 1H), 1.63 (t, <i>J</i> = 18.5 Hz, 3H), 1.31 (d, <i>J</i> = 3.9 Hz, 6H) ppm
292		553.1 [M-1] ⁻	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ 12.47 (s, 1H), 7.56 (s, 1H), 7.49 (s, 1H), 7.07 – 6.97 (m, 2H), 6.69 (s, 2H), 6.10 (t, <i>J</i> = 56.8 Hz, 1H), 4.31 (d, <i>J</i> = 6.4 Hz, 2H), 4.08 (s, 1H), 3.81 (s, 1H), 3.40 (s, 1H), 2.86 (q, <i>J</i> = 6.8 Hz, 1H), 2.55 (s, 3H), 1.92 (s, 2H), 1.75 (s, 1H), 1.62 (s, 1H), 1.20 (dd, <i>J</i> = 7.2, 1.9 Hz, 3H) ppm
293		555.1	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ 12.47 (s, 1H), 7.56 (s, 1H), 7.50 (s, 1H), 7.01 (t, <i>J</i> = 8.6 Hz, 2H), 6.69 (s, 2H), 6.26 – 5.93 (m, 1H), 4.30 (q, <i>J</i> = 9.1, 7.5 Hz, 2H), 4.08 (s, 1H), 3.81 (s,

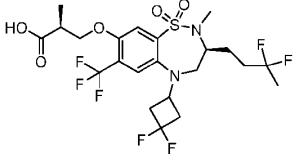
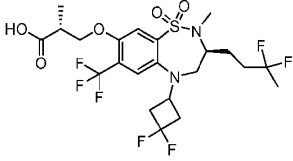
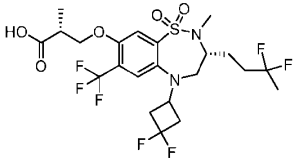
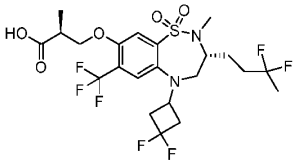
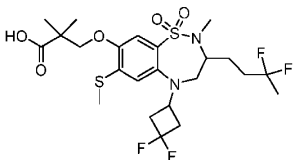
	Single diastereomer		1H), 3.21 (s, 1H), 2.86 (q, $J = 6.5$ Hz, 1H), 2.49 (d, $J = 1.9$ Hz, 3H), 1.92 (s, 2H), 1.75 (s, 1H), 1.62 (s, 1H), 1.20 (d, $J = 7.1$ Hz, 3H) ppm
294	 Single diastereomer	555.1	^1H NMR (500 MHz, DMSO- d_6): δ 12.47 (s, 1H), 7.56 (s, 1H), 7.49 (s, 1H), 7.01 (t, $J = 8.5$ Hz, 2H), 6.70 (s, 2H), 6.10 (t, $J = 57.0$ Hz, 1H), 4.31 (d, $J = 5.9$ Hz, 2H), 4.07 (s, 1H), 3.81 (s, 1H), 3.21 (s, 1H), 2.86 (q, $J = 6.6$ Hz, 1H), 2.48 (s, 3H), 1.92 (s, 2H), 1.81 – 1.71 (m, 1H), 1.62 (s, 1H), 1.20 (d, $J = 7.0$ Hz, 3H) ppm
295	 Single diastereomer	587.1	^1H NMR (500 MHz, DMSO- d_6): δ 12.46 (s, 1H), 7.56 (s, 1H), 7.49 (s, 1H), 7.01 (t, $J = 8.7$ Hz, 2H), 6.67 (s, 2H), 4.30 (dd, $J = 6.2, 2.7$ Hz, 2H), 4.02 (d, $J = 15.7$ Hz, 1H), 3.80 (s, 1H), 3.26 (s, 1H), 2.86 (q, $J = 6.3$ Hz, 1H), 2.54 (s, 3H), 2.27 (s, 2H), 1.74 – 1.50 (m, 4H), 1.20 (d, $J = 7.1$ Hz, 3H) ppm
296	 Single diastereomer	587.1	^1H NMR (500 MHz, CD_3CN): δ 7.63 (s, 1H), 7.53 (s, 1H), 7.04 – 6.93 (m, 2H), 6.69 (dd, $J = 9.1, 4.4$ Hz, 2H), 4.39 – 4.30 (m, 2H), 3.98 (d, $J = 19.1$ Hz, 2H), 3.31 (s, 1H), 2.98 (dt, $J = 13.2, 6.8$ Hz, 1H), 2.33 – 2.16 (m, 2H), 1.70 (dd, $J = 30.1, 7.4$ Hz, 4H), 1.30 (d, $J = 7.1$ Hz, 3H) ppm
297	 Single diastereomer	587.1	^1H NMR (500 MHz, CD_3CN): δ 7.63 (s, 1H), 7.52 (s, 1H), 7.03 – 6.91 (m, 2H), 6.69 (dd, $J = 9.3, 4.4$ Hz, 2H), 4.34 (qd, $J = 9.1, 5.8$ Hz, 2H), 3.98 (d, $J = 17.0$ Hz, 2H), 3.32 (s, 1H), 2.99 (dt, $J = 13.1, 6.7$ Hz, 1H), 2.59 (s, 3H), 2.24 (dd, $J = 14.8, 9.7$ Hz,

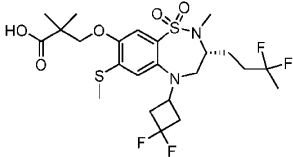
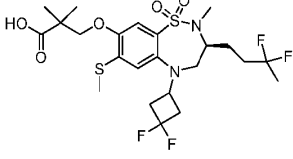
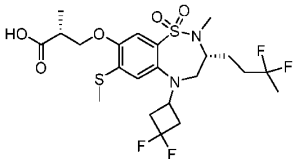
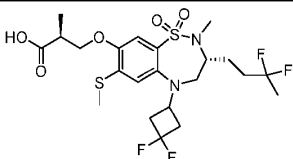
			2H), 1.77 – 1.64 (m, 4H), 1.30 (d, $J = 7.1$ Hz, 3H) ppm
298	 Single diastereomer	587.1	^1H NMR (500 MHz, CD_3CN): δ 7.63 (s, 1H), 7.53 (s, 1H), 6.98 (t, $J = 8.8$ Hz, 2H), 6.69 (dd, $J = 9.3, 4.4$ Hz, 2H), 4.33 (qd, $J = 9.0, 5.8$ Hz, 2H), 3.98 (d, $J = 17.0$ Hz, 2H), 3.31 (s, 1H), 2.98 (q, $J = 6.7$ Hz, 1H), 2.58 (s, 3H), 2.23 (tq, $J = 11.2, 6.1, 5.2$ Hz, 2H), 1.77 – 1.63 (m, 4H), 1.29 (d, $J = 7.1$ Hz, 3H) ppm
299	 Single diastereomer	571.1 [M-1] ⁻	^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 12.47 (s, 1H), 7.56 (s, 1H), 7.49 (s, 1H), 7.02 (t, $J = 8.7$ Hz, 2H), 6.72 (s, 2H), 4.30 (qd, $J = 9.1, 5.9$ Hz, 2H), 4.12 (s, 1H), 3.84 (s, 1H), 3.26 (s, 1H), 2.85 (q, $J = 6.5$ Hz, 1H), 2.57 (s, 3H), 2.39 (d, $J = 34.6$ Hz, 2H), 1.89 (s, 1H), 1.73 (s, 1H), 1.19 (d, $J = 7.1$ Hz, 3H) ppm
300	 Single diastereomer	571.1 [M-1] ⁻	^1H NMR (500 MHz, CD_3CN): δ 7.63 (s, 1H), 7.52 (s, 1H), 7.02 – 6.95 (m, 2H), 6.73 (s, 2H), 4.39 – 4.30 (m, 2H), 3.98 (s, 2H), 3.39 (s, 1H), 2.98 (dt, $J = 13.2, 6.7$ Hz, 1H), 2.60 (s, 3H), 2.37 (dt, $J = 16.9, 11.0$ Hz, 2H), 1.86 (d, $J = 15.6$ Hz, 3H), 1.30 (d, $J = 7.2$ Hz, 3H) ppm
301	 Single diastereomer	573.1	^1H NMR (500 MHz, CD_3CN): δ 7.63 (s, 1H), 7.52 (s, 1H), 7.03 – 6.94 (m, 2H), 6.79 – 6.65 (m, 2H), 4.41 – 4.28 (m, 2H), 3.98 (s, 2H), 3.40 (s, 1H), 2.98 (h, $J = 6.8$ Hz, 1H), 2.61 (s, 3H), 2.37 (dq, $J = 20.2, 9.9, 9.2, 5.8$ Hz, 2H), 1.94 – 1.82 (m, 2H), 1.30 (d, $J = 7.2$ Hz, 3H) ppm

302	 Single diastereomer	573.1	¹ H NMR (500 MHz, CD ₃ CN): δ 7.63 (s, 1H), 7.52 (s, 1H), 6.99 (t, <i>J</i> = 8.9 Hz, 2H), 6.73 (d, <i>J</i> = 4.9 Hz, 2H), 4.33 (qd, <i>J</i> = 9.1, 5.9 Hz, 2H), 3.98 (s, 2H), 3.39 (s, 1H), 2.97 (q, <i>J</i> = 6.6 Hz, 2H), 2.37 (dt, <i>J</i> = 16.9, 10.9 Hz, 2H), 1.99 (s, 3H), 1.89 (s, 2H), 1.29 (d, <i>J</i> = 7.2 Hz, 3H) ppm
303	 Single enantiomer	619.2	¹ H NMR (500 MHz, CD ₃ OD): δ 7.53 (s, 1H), 7.14 (s, 1H), 4.11 – 3.46 (m, 4H), 3.06 (s, 2H), 2.84 – 2.61 (m, 4H), 2.62 – 2.35 (m, 6H), 2.23 (t, <i>J</i> = 9.2 Hz, 1H), 2.16 – 2.06 (m, 1H), 2.06 – 1.98 (m, 1H), 1.90 (d, <i>J</i> = 26.2 Hz, 1H), 1.72 (s, 1H), 1.63 (t, <i>J</i> = 18.5 Hz, 3H), 1.31 (s, 6H) ppm
304	 Single enantiomer	619.2	¹ H NMR (500 MHz, CD ₃ OD): δ 7.53 (s, 1H), 7.14 (s, 1H), 4.17 – 3.52 (m, 4H), 3.02 (s, 2H), 2.78 – 2.61 (m, 4H), 2.61 – 2.37 (m, 6H), 2.23 (s, 1H), 2.09 (d, <i>J</i> = 18.0 Hz, 1H), 2.06 – 1.98 (m, 1H), 1.86 (d, <i>J</i> = 29.5 Hz, 1H), 1.72 (s, 1H), 1.63 (t, <i>J</i> = 18.5 Hz, 3H), 1.31 (s, 6H) ppm
305		597.2	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ 12.37 (s, 1H), 7.11 (s, 1H), 6.58 (s, 1H), 4.02 (t, <i>J</i> = 7.4 Hz, 1H), 3.96 (t, <i>J</i> = 7.3 Hz, 2H), 3.67 (s, 1H), 3.04 – 2.51 (m, 8H), 2.52 (s, 3H), 2.40 (s, 3H), 2.15 (s, 1H), 2.00 (d, <i>J</i> = 6.3 Hz, 2H), 1.81 (s, 1H), 1.63 (t, <i>J</i> = 18.9 Hz, 5H), 1.21 (s, 6H) ppm
306	 Single enantiomer	597.2	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ 12.37 (s, 1H), 7.11 (s, 1H), 6.58 (s, 1H), 4.02 (t, <i>J</i> = 7.4 Hz, 1H), 3.99 – 3.92 (m, 2H), 3.70 (s, 1H), 2.61 (dt, <i>J</i> = 56.0, 12.8 Hz, 8H), 2.45 – 2.42 (m, 3H), 2.41 (s, 3H), 2.15 (s, 1H), 1.99

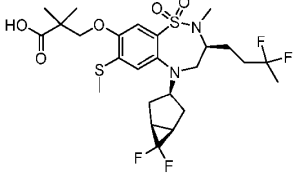
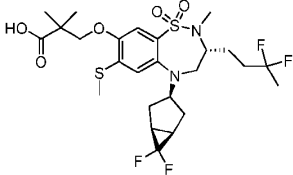
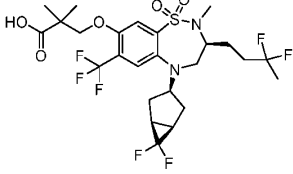
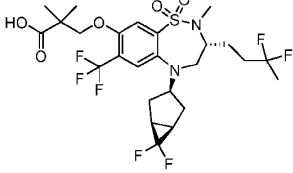
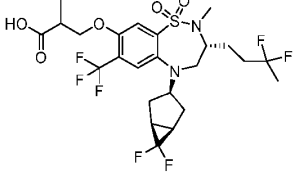
			(d, $J = 15.3$ Hz, 2H), 1.81 (s, 1H), 1.63 (t, $J = 18.9$ Hz, 5H), 1.21 (s, 6H) ppm
307	 Single enantiomer	597.2	^1H NMR (500 MHz, DMSO- d_6): δ 12.37 (s, 1H), 7.11 (s, 1H), 6.58 (s, 1H), 4.02 (t, $J = 7.4$ Hz, 1H), 3.99 – 3.92 (m, 2H), 3.69 (s, 1H), 3.05 – 2.51 (m, 8H), 2.44 (s, 3H), 2.41 (s, 3H), 2.15 (s, 1H), 1.99 (d, $J = 17.5$ Hz, 2H), 1.81 (s, 1H), 1.63 (t, $J = 18.9$ Hz, 5H), 1.21 (s, 6H) ppm
308	 Single enantiomer	569.1	^1H NMR (500 MHz, CD $_3$ CN): δ 7.63 (s, 1H), 7.53 (s, 1H), 6.98 (t, $J = 8.8$ Hz, 2H), 6.68 (dd, $J = 9.2, 4.4$ Hz, 2H), 5.95 (tt, $J = 56.9, 4.4$ Hz, 1H), 4.34 (ddt, $J = 13.9, 11.3, 4.5$ Hz, 2H), 3.98 (d, $J = 16.7$ Hz, 2H), 3.29 (s, 1H), 3.04 – 2.92 (m, 1H), 1.98 (d, $J = 3.6$ Hz, 3H), 1.93 – 1.85 (m, 2H), 1.67 – 1.54 (m, 4H), 1.29 (dd, $J = 7.1, 2.8$ Hz, 3H) ppm
309	 Single diastereomer	569.1	^1H NMR (500 MHz, DMSO- d_6): δ 12.47 (s, 1H), 7.56 (s, 1H), 7.51 (s, 1H), 7.01 (t, $J = 8.7$ Hz, 2H), 6.65 (s, 2H), 6.24 – 5.95 (m, 1H), 4.30 (d, $J = 6.2$ Hz, 2H), 4.01 (d, $J = 16.4$ Hz, 1H), 3.80 (s, 1H), 3.28 (s, 1H), 2.86 (q, $J = 6.4$ Hz, 1H), 2.53 (s, 3H), 1.83 (s, 2H), 1.64 (s, 1H), 1.60 – 1.48 (m, 2H), 1.43 (s, 1H), 1.20 (d, $J = 7.2$ Hz, 3H) ppm
310	 Single diastereomer	569.1	^1H NMR (600 MHz, DMSO- d_6): δ 12.47 (s, 1H), 7.56 (s, 1H), 7.51 (s, 1H), 7.01 (t, $J = 8.8$ Hz, 2H), 6.65 (dd, $J = 8.4, 4.5$ Hz, 2H), 6.09 (tt, $J = 56.8, 4.4$ Hz, 1H), 4.36 – 4.27 (m, 2H), 4.01 (d, $J = 16.2$ Hz, 1H), 3.80 (s, 1H), 3.24 (s, 1H), 2.86 (h, $J = 6.8$

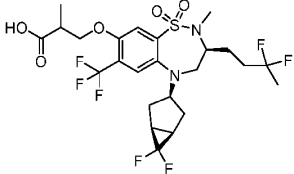
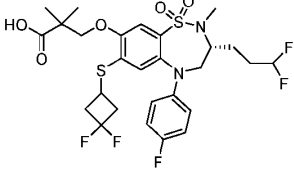
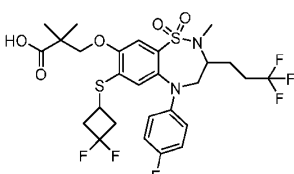
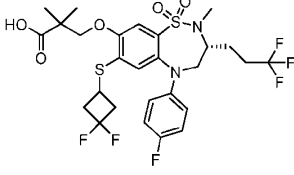
			Hz, 1H), 2.53 (s, 3H), 1.82 (t, J = 13.8 Hz, 2H), 1.69 – 1.61 (m, 1H), 1.53 (ddd, J = 29.5, 16.2, 9.7 Hz, 2H), 1.47 – 1.39 (m, 1H), 1.20 (d, J = 7.1 Hz, 3H) ppm
311		569.1	^1H NMR (500 MHz, DMSO- d_6): δ 12.47 (s, 1H), 7.56 (s, 1H), 7.51 (s, 1H), 7.01 (t, J = 8.4 Hz, 2H), 6.65 (s, 2H), 6.09 (t, J = 56.8 Hz, 1H), 4.30 (s, 2H), 4.01 (d, J = 15.9 Hz, 1H), 3.80 (s, 1H), 3.24 (s, 1H), 2.86 (d, J = 8.4 Hz, 1H), 2.53 (s, 3H), 1.83 (s, 2H), 1.64 (s, 1H), 1.61 – 1.48 (m, 2H), 1.43 (s, 1H), 1.20 (d, J = 7.0 Hz, 3H) ppm
312	 Single diastereomer	569.1	^1H NMR (600 MHz, DMSO- d_6): δ 12.50 (s, 1H), 7.56 (s, 1H), 7.51 (s, 1H), 7.01 (t, J = 8.8 Hz, 2H), 6.65 (dd, J = 9.1, 4.4 Hz, 2H), 6.09 (tt, J = 56.9, 4.4 Hz, 1H), 4.35 – 4.24 (m, 2H), 4.01 (d, J = 16.2 Hz, 1H), 3.80 (s, 1H), 3.27 – 3.19 (m, 1H), 2.84 (q, J = 6.5 Hz, 1H), 2.53 (s, 3H), 1.83 (s, 2H), 1.69 – 1.61 (m, 1H), 1.53 (tdd, J = 21.6, 14.0, 8.2 Hz, 2H), 1.42 (tq, J = 13.2, 7.2 Hz, 1H), 1.19 (d, J = 7.1 Hz, 3H) ppm
313	 Single diastereomer	569.1	^1H NMR (500 MHz, DMSO- d_6): δ 12.50 (s, 1H), 7.56 (s, 1H), 7.51 (s, 1H), 7.00 (t, J = 8.7 Hz, 2H), 6.64 (d, J = 8.5 Hz, 2H), 6.09 (tt, J = 56.9, 4.5 Hz, 1H), 4.35 – 4.26 (m, 2H), 4.01 (d, J = 16.0 Hz, 1H), 3.80 (s, 1H), 3.24 (s, 1H), 2.85 (q, J = 6.4 Hz, 1H), 2.53 (s, 3H), 1.89 – 1.76 (m, 2H), 1.63 (d, J = 8.7 Hz, 1H), 1.54 (dd, J = 21.6, 10.4 Hz, 2H), 1.43 (q, J = 7.9 Hz, 1H), 1.20 (d, J = 7.1 Hz, 3H) ppm

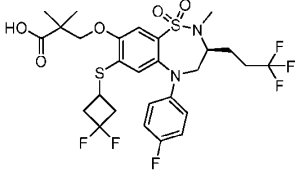
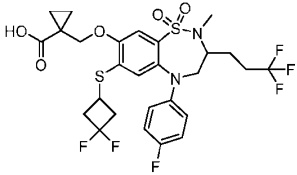
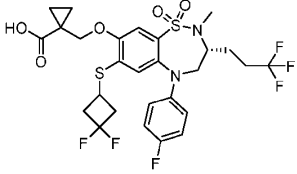
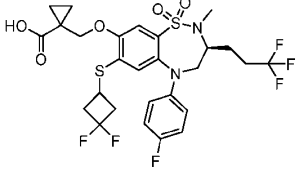
314	 Single diastereomer	565.2	¹ H NMR (500 MHz, CD ₃ OD): δ 7.59 (s, 1H), 7.21 (s, 1H), 4.82 (s, 1H), 4.26 (dd, <i>J</i> = 8.9, 6.5 Hz, 1H), 4.20 (dd, <i>J</i> = 8.9, 5.4 Hz, 1H), 4.14 – 3.41 (m, 2H), 3.13 – 2.73 (m, 5H), 2.64 (d, <i>J</i> = 16.3 Hz, 4H), 2.22 – 1.92 (m, 3H), 1.74 (d, <i>J</i> = 14.2 Hz, 1H), 1.63 (t, <i>J</i> = 18.5 Hz, 3H), 1.30 (d, <i>J</i> = 7.1 Hz, 3H) ppm
315	 Single diastereomer	565.2	¹ H NMR (500 MHz, CD ₃ OD): δ 7.59 (s, 1H), 7.21 (s, 1H), 4.81 (s, 1H), 4.30 – 4.17 (m, 2H), 4.09 (qd, <i>J</i> = 7.0, 2.6 Hz, 2H), 3.11 – 2.72 (m, 5H), 2.71 – 2.22 (m, 4H), 2.21 – 1.94 (m, 3H), 1.73 (s, 1H), 1.63 (t, <i>J</i> = 18.5 Hz, 3H), 1.30 (d, <i>J</i> = 7.9 Hz, 3H) ppm
316	 Single diastereomer	565.2	¹ H NMR (500 MHz, CD ₃ OD): δ 7.59 (s, 1H), 7.21 (s, 1H), 4.83 (s, 1H), 4.26 (dd, <i>J</i> = 8.9, 6.5 Hz, 1H), 4.20 (dd, <i>J</i> = 8.9, 5.4 Hz, 1H), 4.08 (ddt, <i>J</i> = 10.1, 7.2, 2.8 Hz, 2H), 3.14 – 2.74 (m, 5H), 2.73 – 2.24 (m, 4H), 2.23 – 1.96 (m, 3H), 1.74 (d, <i>J</i> = 13.8 Hz, 1H), 1.63 (t, <i>J</i> = 18.5 Hz, 3H), 1.30 (d, <i>J</i> = 7.1 Hz, 3H) ppm
317	 Single diastereomer	565.2	¹ H NMR (500 MHz, CD ₃ OD): δ 7.59 (s, 1H), 7.21 (s, 1H), 4.80 (s, 1H), 4.33 – 4.18 (m, 2H), 4.08 (qt, <i>J</i> = 9.2, 4.5 Hz, 2H), 3.13 – 2.75 (m, 5H), 2.64 (d, <i>J</i> = 16.0 Hz, 4H), 2.20 – 1.93 (m, 3H), 1.73 (s, 1H), 1.63 (t, <i>J</i> = 18.5 Hz, 3H), 1.30 (d, <i>J</i> = 7.1 Hz, 3H) ppm
318	 Single diastereomer	557.2	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ 12.40 (s, 1H), 7.14 (s, 1H), 6.65 (s, 1H), 4.20 – 4.07 (m, 1H), 3.97 (q, <i>J</i> = 8.5 Hz, 2H), 3.86 (s, 1H), 2.95 (d, <i>J</i> =

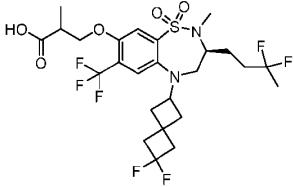
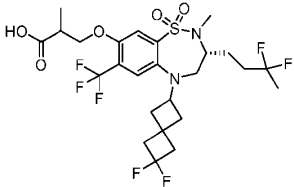
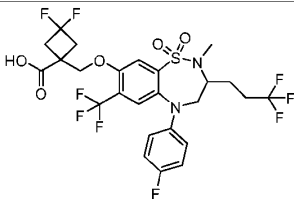
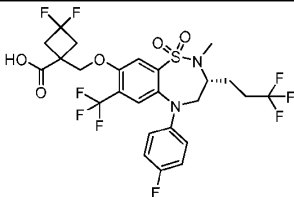
			5.7 Hz, 3H), 2.52 (s, 3H), 2.42 (s, 3H), 2.39 – 1.93 (m, 5H), 1.63 (t, $J = 18.9$ Hz, 4H), 1.48 (s, 1H), 1.21 (s, 6H) ppm
319	 Single enantiomer	557.2	^1H NMR (500 MHz, DMSO- d_6): δ 12.38 (s, 1H), 7.14 (s, 1H), 6.66 (s, 1H), 4.13 (s, 1H), 3.97 (q, $J = 8.4$ Hz, 3H), 2.93 (s, 3H), 2.55 (s, 3H), 2.42 (s, 3H), 2.01 (s, 5H), 1.63 (t, $J = 18.9$ Hz, 5H), 1.22 (s, 6H) ppm
320	 Single enantiomer	557.2	^1H NMR (500 MHz, DMSO- d_6): δ 12.37 (s, 1H), 7.11 (s, 1H), 6.58 (s, 1H), 4.02 (t, $J = 7.4$ Hz, 1H), 3.99 – 3.92 (m, 2H), 3.70 (s, 1H), 2.61 (dt, $J = 56.0, 12.8$ Hz, 8H), 2.45 – 2.42 (m, 3H), 2.41 (s, 3H), 2.15 (s, 1H), 1.99 (d, $J = 15.3$ Hz, 2H), 1.81 (s, 1H), 1.63 (t, $J = 18.9$ Hz, 5H), 1.21 (s, 6H) ppm
321	 Single diastereomer	541.2 [M-1] ⁻	^1H NMR (600 MHz, DMSO- d_6): δ 12.32 (s, 1H), 7.16 (s, 1H), 6.66 (s, 1H), 4.13 (dd, $J = 9.0, 6.3$ Hz, 2H), 4.01 (t, $J = 7.5$ Hz, 1H), 3.86 (s, 1H), 3.39 (s, 1H), 2.94 (s, 3H), 2.76 (d, $J = 6.7$ Hz, 2H), 2.54 (s, 3H), 2.42 (s, 3H), 2.17 – 1.91 (m, 3H), 1.63 (t, $J = 18.9$ Hz, 5H), 1.17 (d, $J = 7.1$ Hz, 3H) ppm
322	 Single diastereomer	541.2 [M-1] ⁻	^1H NMR (600 MHz, DMSO- d_6): δ 12.45 (s, 1H), 7.16 (s, 1H), 6.65 (s, 1H), 4.11 (q, $J = 8.4, 7.3$ Hz, 2H), 4.04 (dd, $J = 9.1, 5.8$ Hz, 1H), 3.98 – 3.41 (m, 1H), 3.40 (s, 1H), 3.02 – 2.86 (m, 3H), 2.77 (d, $J = 6.5$ Hz, 2H), 2.55 (s, 3H), 2.42 (s, 3H), 2.21 – 1.94 (m, 3H), 1.63 (t, $J = 18.9$ Hz, 5H), 1.18 (d, $J = 7.1$ Hz, 3H) ppm

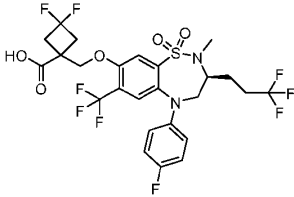
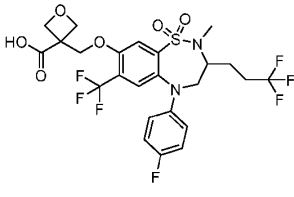
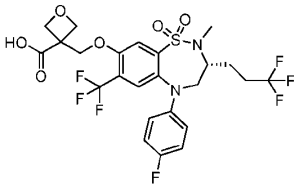
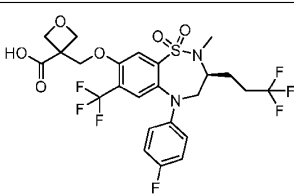
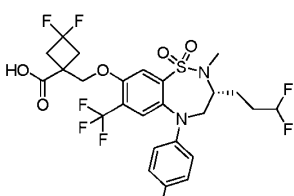
323	Single diastereomer	541.2	¹ H NMR (500 MHz, CD ₃ CN): δ 7.29 (s, 1H), 6.69 (s, 1H), 4.23 – 4.08 (m, 3H), 4.00 (s, 1H), 2.92 (d, <i>J</i> = 6.4 Hz, 4H), 2.78 (s, 1H), 2.60 (dd, <i>J</i> = 35.2, 20.6 Hz, 2H), 2.45 (d, <i>J</i> = 4.4 Hz, 5H), 1.98 (d, <i>J</i> = 3.6 Hz, 3H), 1.65 (td, <i>J</i> = 18.8, 4.7 Hz, 5H), 1.27 (d, <i>J</i> = 6.9 Hz, 3H) ppm
324	Single diastereomer	541.2	¹ H NMR (500 MHz, CD ₃ CN): δ 7.28 (s, 1H), 6.69 (s, 1H), 4.20 (dd, <i>J</i> = 9.0, 6.8 Hz, 1H), 4.12 (ddt, <i>J</i> = 14.5, 7.1, 4.1 Hz, 2H), 4.01 (s, 1H), 2.92 (q, <i>J</i> = 7.7, 6.8 Hz, 4H), 2.79 (s, 1H), 2.64 (d, <i>J</i> = 14.7 Hz, 2H), 2.45 (d, <i>J</i> = 3.9 Hz, 5H), 1.99 (s, 3H), 1.65 (td, <i>J</i> = 18.7, 4.1 Hz, 5H), 1.27 (d, <i>J</i> = 7.1 Hz, 3H) ppm
325		569.2	¹ H NMR (500 MHz, CD ₃ CN): δ 7.21 (s, 1H), 6.86 (s, 1H), 4.51 – 3.75 (m, 3H), 3.05 (s, 2H), 2.47 (s, 3H), 2.40 (s, 2H), 2.18 – 2.11 (m, 1H), 2.03 (s, 3H), 1.87 (s, 4H), 1.77 (s, 2H), 1.65 (t, <i>J</i> = 18.8 Hz, 6H), 1.27 (dd, <i>J</i> = 7.1, 3.2 Hz, 3H) ppm
326		569.2	¹ H NMR (500 MHz, CD ₃ CN): δ 7.21 (s, 1H), 6.86 (s, 1H), 4.54 – 4.27 (m, 1H), 4.16 (dd, <i>J</i> = 16.1, 8.9 Hz, 2H), 4.00 – 3.60 (m, 1H), 3.05 (s, 2H), 2.92 (dd, <i>J</i> = 13.6, 6.8 Hz, 2H), 2.47 (s, 3H), 2.37 (d, <i>J</i> = 14.4 Hz, 2H), 2.14 (d, <i>J</i> = 4.0 Hz, 1H), 2.03 (s, 3H), 1.89 (s, 4H), 1.76 (s, 1H), 1.65 (t, <i>J</i> = 18.8 Hz, 6H), 1.27 (dd, <i>J</i> = 7.1, 3.2 Hz, 3H) ppm

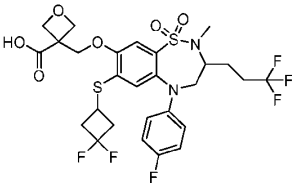
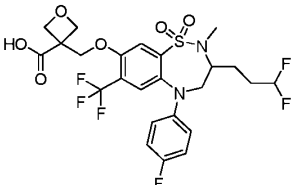
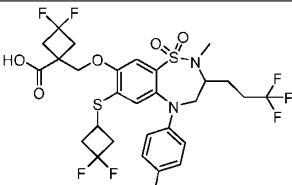
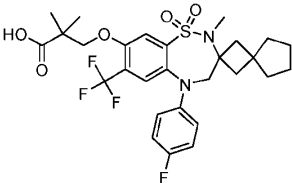
327	 Single diastereomer	583.2	¹ H NMR (500 MHz, CD ₃ CN): δ 7.20 (s, 1H), 6.86 (s, 1H), 4.38 (s, 1H), 4.07 – 4.02 (m, 2H), 3.82 (d, <i>J</i> = 32.4 Hz, 1H), 3.06 (s, 1H), 2.58 (d, <i>J</i> = 30.2 Hz, 2H), 2.47 (s, 3H), 2.37 (d, <i>J</i> = 11.2 Hz, 3H), 2.19 – 2.08 (m, 2H), 2.02 (dd, <i>J</i> = 16.3, 7.6 Hz, 3H), 1.76 (s, 1H), 1.65 (t, <i>J</i> = 18.8 Hz, 6H), 1.30 (d, <i>J</i> = 3.8 Hz, 6H) ppm
328	 Single diastereomer	583.2	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ 12.37 (s, 1H), 7.08 (s, 1H), 6.78 (s, 1H), 4.37 (s, 1H), 3.96 (s, 2H), 3.72 (s, 1H), 3.28 (s, 1H), 2.96 (s, 1H), 2.52 (s, 3H), 2.44 (s, 3H), 2.36 (d, <i>J</i> = 37.2 Hz, 3H), 2.18 (s, 1H), 2.12 – 1.87 (m, 3H), 1.61 (q, <i>J</i> = 18.6 Hz, 6H), 1.21 (s, 6H) ppm
329	 Single diastereomer	605.2	¹ H NMR (600 MHz, CD ₃ OD): δ 7.49 (s, 1H), 7.37 (s, 1H), 4.36 (s, 1H), 4.09 (s, 2H), 3.87 (s, 1H), 3.14 (s, 1H), 3.00 – 2.45 (m, 4H), 2.39 (s, 2H), 2.20 – 1.93 (m, 4H), 1.77 (s, 2H), 1.70 – 1.58 (m, 4H), 1.31 (d, <i>J</i> = 1.8 Hz, 6H) ppm
330	 Single diastereomer	605.2	¹ H NMR (600 MHz, CD ₃ OD): δ 7.49 (s, 1H), 7.37 (s, 1H), 4.36 (s, 1H), 4.09 (s, 2H), 4.01 – 3.60 (m, 1H), 3.14 (s, 1H), 2.57 (dd, <i>J</i> = 138.6, 65.6 Hz, 6H), 2.16 – 1.96 (m, 4H), 1.92 – 1.69 (m, 2H), 1.70 – 1.52 (m, 5H), 1.31 (d, <i>J</i> = 1.9 Hz, 6H) ppm
331	 Single diastereomer	589.2 [M-1] ⁻	¹ H NMR (500 MHz, CD ₃ CN): δ 7.49 (s, 1H), 7.37 (s, 1H), 4.36 (s, 1H), 4.22 (d, <i>J</i> = 29.3 Hz, 2H), 3.18 – 2.86 (m, 1H), 2.56 (d, <i>J</i> = 35.8 Hz, 1H), 2.39 (s, 2H), 2.11 – 2.08 (m, 3H), 2.06 – 2.03 (m, 1H), 1.83 (dp, <i>J</i> = 7.4, 2.9 Hz, 4H), 1.75 (s, 2H), 1.66 (t,

			$J = 18.8 \text{ Hz, 6H}$), 1.25 (dd, $J = 7.1$, 1.9 Hz, 3H) ppm
332	 Single enantiomer	591.2	$^1\text{H NMR}$ (500 MHz, CD_3CN): δ 7.49 (s, 1H), 7.37 (s, 1H), 4.36 (s, 1H), 4.22 (d, $J = 34.0 \text{ Hz, 2H}$), 2.89 (q, $J = 6.5 \text{ Hz, 1H}$), 2.52 (s, 1H), 2.42 – 2.32 (m, 2H), 2.18 (s, 1H), 2.16 – 2.07 (m, 3H), 1.85 – 1.80 (m, 4H), 1.76 (s, 2H), 1.66 (t, $J = 18.8 \text{ Hz, 6H}$), 1.25 (dd, $J = 7.2$, 1.9 Hz, 3H) ppm
333	 Single enantiomer	621.2 [M-1] ⁻	$^1\text{H NMR}$ (500 MHz, $\text{DMSO-}d_6$): δ 12.46 (s, 1H), 7.27 (s, 1H), 6.98 (t, $J = 8.6 \text{ Hz, 2H}$), 6.89 (s, 1H), 6.65 (s, 2H), 6.25 – 5.95 (m, 1H), 4.09 (s, 2H), 4.01 (s, 1H), 3.80 (s, 2H), 3.36 (s, 2H), 3.25 (s, 2H), 3.14 (s, 1H), 2.98 (s, 1H), 2.52 (s, 3H), 1.91 (d, $J = 10.0 \text{ Hz, 2H}$), 1.76 (d, $J = 8.9 \text{ Hz, 1H}$), 1.61 (s, 1H), 1.24 (d, $J = 2.2 \text{ Hz, 6H}$) ppm
334	 Single enantiomer	639.2 [M-1] ⁻	$^1\text{H NMR}$ (500 MHz, CD_3OD): δ 7.35 (s, 1H), 6.97 (t, $J = 8.8 \text{ Hz, 2H}$), 6.81 (s, 3H), 4.11 (d, $J = 1.4 \text{ Hz, 2H}$), 3.96 (d, $J = 52.2 \text{ Hz, 2H}$), 3.69 – 3.41 (m, 2H), 3.03 (s, 1H), 2.97 – 2.84 (m, 1H), 2.64 (s, 3H), 2.54 – 2.26 (m, 4H), 1.86 (s, 2H), 1.35 (d, $J = 2.0 \text{ Hz, 6H}$) ppm
335	 Single enantiomer	639.2 [M-1] ⁻	$^1\text{H NMR}$ (500 MHz, $\text{DMSO-}d_6$): δ 12.45 (s, 1H), 7.26 (s, 1H), 6.99 (t, $J = 8.7 \text{ Hz, 2H}$), 6.89 (s, 1H), 6.68 (s, 2H), 4.09 (d, $J = 1.9 \text{ Hz, 3H}$), 3.87 (s, 1H), 3.79 (s, 1H), 3.25 (s, 1H), 3.13 (s, 1H), 2.97 (s, 1H), 2.52 (s, 3H), 2.39 (s, 4H), 1.91 (s, 1H), 1.72 (s, 1H), 1.24 (d, $J = 1.9 \text{ Hz, 6H}$) ppm

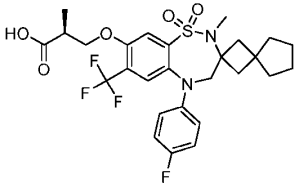
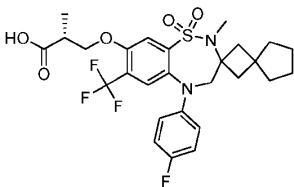
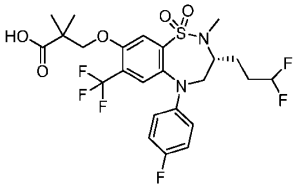
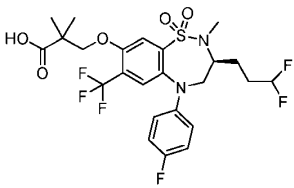
336	 Single enantiomer	639.2 [M-1] ⁻	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ 12.45 (s, 1H), 7.26 (s, 1H), 6.99 (t, <i>J</i> = 8.7 Hz, 2H), 6.89 (s, 1H), 6.68 (s, 2H), 4.09 (d, <i>J</i> = 1.9 Hz, 3H), 3.87 (s, 1H), 3.79 (s, 1H), 3.25 (s, 1H), 3.13 (s, 1H), 2.97 (s, 1H), 2.52 (s, 3H), 2.47 – 2.38 (m, 4H), 1.90 (s, 1H), 1.72 (s, 1H), 1.24 (d, <i>J</i> = 1.8 Hz, 6H) ppm
337	 Single enantiomer	637.1 [M-1] ⁻	¹ H NMR (500 MHz, CD ₃ OD): δ 7.37 (s, 1H), 6.97 (t, <i>J</i> = 8.6 Hz, 2H), 6.83 (s, 1H), 6.78 (s, 2H), 4.32 – 4.20 (m, 2H), 3.96 (d, <i>J</i> = 52.0 Hz, 2H), 3.66 (s, 1H), 3.03 (s, 1H), 2.92 (s, 1H), 2.63 (s, 3H), 2.50 (d, <i>J</i> = 21.7 Hz, 2H), 2.31 (d, <i>J</i> = 20.6 Hz, 2H), 2.03 (s, 3H), 1.86 (s, 1H), 1.36 (q, <i>J</i> = 4.0 Hz, 2H), 1.14 (q, <i>J</i> = 4.0 Hz, 2H) ppm
338	 Single enantiomer	637.1 [M-1] ⁻	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ 12.43 (s, 1H), 7.26 (s, 1H), 6.99 (t, <i>J</i> = 8.7 Hz, 2H), 6.89 (s, 1H), 6.67 (s, 2H), 4.21 (q, <i>J</i> = 9.8 Hz, 2H), 4.05 (s, 1H), 3.83 (d, <i>J</i> = 37.8 Hz, 2H), 3.23 (s, 1H), 3.12 (s, 1H), 2.97 (s, 1H), 2.55 (d, <i>J</i> = 27.2 Hz, 3H), 2.47 – 2.36 (m, 4H), 1.90 (s, 1H), 1.71 (s, 1H), 1.20 (q, <i>J</i> = 3.8 Hz, 2H), 1.06 (q, <i>J</i> = 3.5 Hz, 2H) ppm
339	 Single enantiomer	637.1 [M-1] ⁻	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ 12.44 (s, 1H), 7.26 (s, 1H), 6.99 (t, <i>J</i> = 8.7 Hz, 2H), 6.89 (s, 1H), 6.67 (s, 2H), 4.21 (q, <i>J</i> = 9.8 Hz, 2H), 4.05 (s, 1H), 3.83 (d, <i>J</i> = 36.1 Hz, 2H), 3.25 (s, 1H), 3.12 (s, 1H), 2.96 (d, <i>J</i> = 13.0 Hz, 1H), 2.52 (s, 3H), 2.47 – 2.35 (m, 4H), 1.90 (s, 1H), 1.71 (s, 1H), 1.20

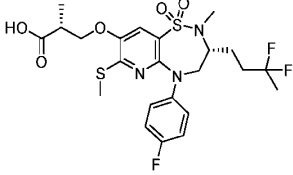
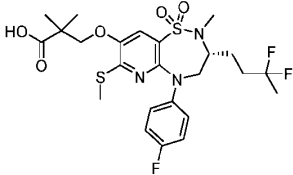
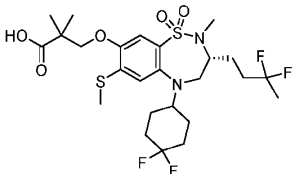
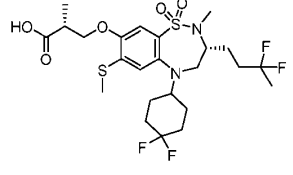
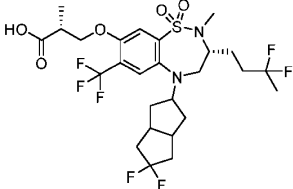
			(d, $J = 3.1$ Hz, 2H), 1.06 (q, $J = 3.5$ Hz, 2H) ppm
340		603.2 [M-1] ⁻	¹ H NMR (500 MHz, CD ₃ CN): δ 7.25 (s, 1H), 6.66 (s, 1H), 4.25 – 4.12 (m, 1H), 4.07 (dt, $J = 15.2, 8.0$ Hz, 2H), 2.85 (d, $J = 7.0$ Hz, 1H), 2.69 (t, $J = 12.5$ Hz, 3H), 2.61 – 2.53 (m, 5H), 2.45 (s, 9H), 2.24 (d, $J = 9.6$ Hz, 1H), 1.66 (t, $J = 18.8$ Hz, 6H), 1.25 (dd, $J = 7.1, 2.4$ Hz, 3H) ppm
341		603.2 [M-1] ⁻	¹ H NMR (500 MHz, CD ₃ CN): δ 7.25 (s, 1H), 6.65 (s, 1H), 4.18 (t, $J = 7.9$ Hz, 1H), 4.14 – 4.09 (m, 1H), 4.06 (t, $J = 7.5$ Hz, 1H), 2.94 – 2.87 (m, 2H), 2.69 (t, $J = 12.5$ Hz, 4H), 2.61 – 2.53 (m, 4H), 2.49 (dd, $J = 11.7, 4.6$ Hz, 3H), 2.45 (s, 3H), 2.23 (t, $J = 9.6$ Hz, 1H), 2.01 (s, 2H), 1.66 (t, $J = 18.8$ Hz, 5H), 1.26 (dd, $J = 7.1, 2.5$ Hz, 3H) ppm
342		633.1 [M-H] ⁻	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ 7.59 (s, 1H), 7.49 (s, 1H), 7.02 (t, $J = 8.6$ Hz, 2H), 6.73 (s, 2H), 4.40 (d, $J = 6.6$ Hz, 2H), 4.10 (s, 1H), 3.84 (s, 1H), 3.21 (s, 1H), 2.99 – 2.90 (m, 2H), 2.73 (d, $J = 13.5$ Hz, 2H), 2.57 (s, 3H), 2.45 – 2.37 (m, 2H), 1.89 (s, 1H), 1.73 (s, 1H) ppm
343	 Single enantiomer	633.1 [M-1] ⁻	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ 13.14 (s, 1H), 7.61 (s, 1H), 7.49 (s, 1H), 7.02 (t, $J = 8.6$ Hz, 2H), 6.74 (s, 2H), 4.46 (t, $J = 7.0$ Hz, 2H), 4.13 (s, 1H), 3.84 (s, 1H), 3.44 (s, 1H), 3.00 (q, $J = 13.2$ Hz, 2H), 2.83 (q, $J = 13.0$ Hz, 2H), 2.57 (s, 3H), 2.40 (s, 2H), 1.89 (s, 1H), 1.73 (s, 1H) ppm

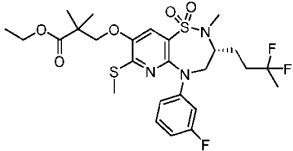
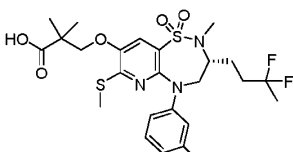
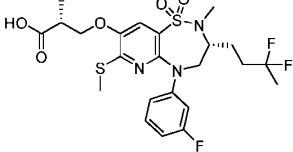
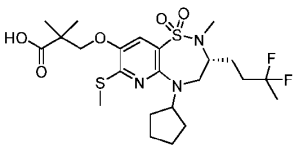
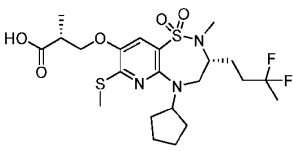
344	 Single enantiomer	633.1 [M-1] ⁻	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ 13.13 (s, 1H), 7.61 (s, 1H), 7.49 (s, 1H), 7.02 (t, <i>J</i> = 8.6 Hz, 2H), 6.74 (s, 2H), 4.53 – 4.44 (m, 2H), 4.12 (s, 1H), 3.84 (s, 1H), 3.40 (s, 1H), 3.01 (q, <i>J</i> = 13.3 Hz, 2H), 2.84 (q, <i>J</i> = 13.0 Hz, 2H), 2.58 (s, 3H), 2.41 (s, 2H), 1.89 (s, 1H), 1.78 – 1.68 (m, 1H) ppm
345		599.1 [M-H] ⁻	¹ H NMR (600 MHz, CD ₃ CN): δ 7.68 (s, 1H), 7.51 (s, 1H), 6.97 (t, <i>J</i> = 8.6 Hz, 2H), 6.72 (s, 2H), 4.89 – 4.59 (m, 4H), 3.97 (s, 2H), 2.59 (s, 2H), 2.53 (s, 3H), 2.41 (s, 1H), 2.35 (d, <i>J</i> = 13.8 Hz, 2H), 1.88 (d, <i>J</i> = 11.3 Hz, 2H) ppm
346	 Single enantiomer	599.1 [M-1] ⁻	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ 13.15 (s, 1H), 7.64 (s, 1H), 7.50 (s, 1H), 7.02 (t, <i>J</i> = 8.7 Hz, 2H), 6.74 (s, 2H), 4.78 (d, <i>J</i> = 6.2 Hz, 2H), 4.68 – 4.62 (m, 2H), 4.59 (dd, <i>J</i> = 6.2, 2.5 Hz, 2H), 4.13 (s, 1H), 3.84 (s, 1H), 3.41 (s, 1H), 2.58 (s, 3H), 2.39 (s, 2H), 1.89 (s, 1H), 1.74 (d, <i>J</i> = 9.4 Hz, 1H) ppm
347	 Single enantiomer	599.1 [M-1] ⁻	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ 13.16 (s, 1H), 7.64 (s, 1H), 7.50 (s, 1H), 7.02 (t, <i>J</i> = 8.6 Hz, 2H), 6.74 (s, 2H), 4.77 (d, <i>J</i> = 6.1 Hz, 2H), 4.65 (d, <i>J</i> = 3.4 Hz, 2H), 4.58 (dd, <i>J</i> = 6.0, 2.5 Hz, 2H), 4.13 (s, 1H), 3.84 (s, 1H), 3.40 (s, 1H), 2.58 (s, 3H), 2.39 (s, 2H), 1.89 (s, 1H), 1.73 (s, 1H) ppm
348		615.1 [M-1] ⁻	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ 13.14 (s, 1H), 7.61 (s, 1H), 7.50 (s, 1H), 7.01 (t, <i>J</i> = 8.6 Hz, 2H), 6.71 (d, <i>J</i> = 6.9 Hz, 2H), 6.24 – 5.97 (m, 1H), 4.46 (s, 2H), 4.09 (s, 1H), 3.80 (s, 1H), 3.19 (s, 1H), 3.00 (q, <i>J</i> = 13.3

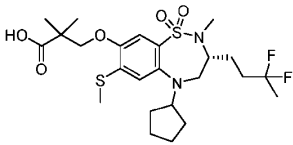
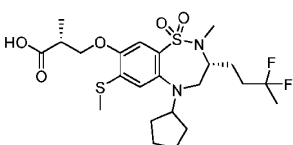
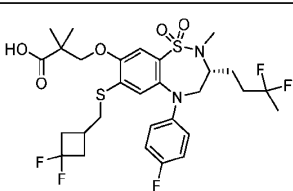
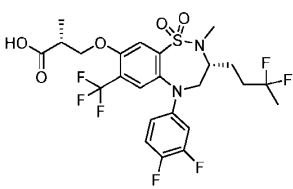
	Single enantiomer		H _z , 2H), 2.82 (q, <i>J</i> = 13.5, 13.1 Hz, 2H), 2.56 (s, 3H), 1.93 (d, <i>J</i> = 9.1 Hz, 2H), 1.80 – 1.72 (m, 1H), 1.62 (s, 1H) ppm
349		653.2 [M-1] ⁻	¹ H NMR (500 MHz, CD ₃ CN): δ 12.17 (s, 1H), 7.43 (s, 1H), 6.95 (t, <i>J</i> = 8.6 Hz, 2H), 6.88 (s, 1H), 6.67 (s, 2H), 4.82 (d, <i>J</i> = 246.1 Hz, 3H), 4.06 – 3.31 (m, 3H), 3.08 (s, 2H), 2.54 (s, 5H), 2.35 (s, 3H), 2.12 (s, 3H), 1.87 (s, 2H) ppm
350		581.0 [M-1] ⁻	¹ H NMR (500 MHz, CD ₃ CN): δ 7.70 (s, 1H), 7.53 (s, 1H), 7.01 – 6.96 (m, 2H), 6.71 (dd, <i>J</i> = 9.2, 4.4 Hz, 2H), 5.99 (tt, <i>J</i> = 56.7, 4.3 Hz, 1H), 4.90 (t, <i>J</i> = 5.3 Hz, 2H), 4.67 – 4.63 (m, 4H), 4.04 – 3.93 (m, 2H), 3.48 (d, <i>J</i> = 114.5 Hz, 4H), 2.60 (s, 3H), 1.77 (td, <i>J</i> = 13.3, 12.0, 7.7 Hz, 2H) ppm
351		687.0 [M-1] ⁻	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ 7.34 (s, 1H), 6.99 (t, <i>J</i> = 8.6 Hz, 2H), 6.89 (s, 1H), 6.69 (s, 2H), 4.39 – 4.32 (m, 2H), 4.07 (s, 1H), 3.82 (d, <i>J</i> = 41.0 Hz, 2H), 3.12 (s, 2H), 3.00 (q, <i>J</i> = 13.8 Hz, 3H), 2.82 (q, <i>J</i> = 13.5, 13.1 Hz, 2H), 2.51 (s, 3H), 2.38 (s, 2H), 1.90 (s, 1H), 1.72 (s, 1H), 1.38 (s, 2H), 0.95 – 0.80 (m, 2H) ppm
352		585.2	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ 12.45 (s, 1H), 7.48 (s, 1H), 7.22 (s, 1H), 7.09 (t, <i>J</i> = 8.6 Hz, 2H), 7.01 (s, 2H), 4.48 (s, 1H), 4.14 (s, 2H), 3.22 (s, 1H), 2.46 (s, 3H), 2.23 (s, 2H), 1.88 (d, <i>J</i> = 38.9 Hz, 3H), 1.57 – 1.36 (m, 7H), 1.21 (s, 6H) ppm

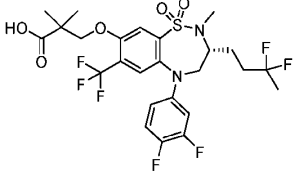
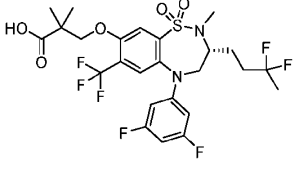
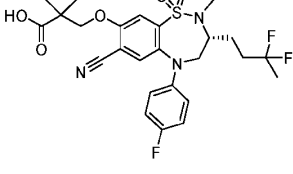
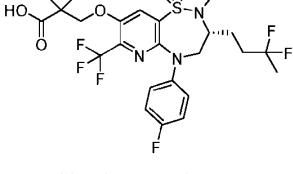
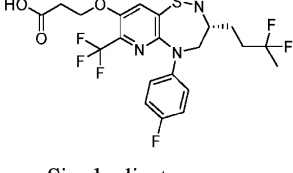
353		573.2	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ 12.45 (s, 1H), 7.50 (s, 1H), 7.23 (s, 1H), 7.08 (t, <i>J</i> = 8.6 Hz, 2H), 7.00 (s, 2H), 4.42 (s, 1H), 4.26 (d, <i>J</i> = 5.5 Hz, 2H), 3.22 (s, 1H), 2.84 (q, <i>J</i> = 6.4 Hz, 1H), 2.45 (s, 3H), 2.18 – 1.93 (m, 2H), 1.73 (s, 2H), 1.43 (d, <i>J</i> = 7.4 Hz, 2H), 1.37 (d, <i>J</i> = 7.6 Hz, 2H), 1.18 (d, <i>J</i> = 7.1 Hz, 3H), 0.67 (t, <i>J</i> = 7.3 Hz, 3H), 0.61 (t, <i>J</i> = 7.3 Hz, 3H) ppm
354	Single enantiomer	573.2	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ 12.44 (s, 1H), 7.50 (s, 1H), 7.23 (s, 1H), 7.08 (t, <i>J</i> = 8.6 Hz, 2H), 7.00 (s, 2H), 4.42 (s, 1H), 4.26 (d, <i>J</i> = 5.6 Hz, 2H), 3.17 (s, 1H), 2.84 (q, <i>J</i> = 6.5 Hz, 1H), 2.50 (d, <i>J</i> = 2.1 Hz, 3H), 2.14 – 1.94 (m, 2H), 1.74 (s, 2H), 1.43 (d, <i>J</i> = 7.6 Hz, 2H), 1.37 (d, <i>J</i> = 7.4 Hz, 2H), 1.18 (d, <i>J</i> = 7.1 Hz, 3H), 0.67 (t, <i>J</i> = 7.3 Hz, 3H), 0.60 (t, <i>J</i> = 7.3 Hz, 3H) ppm
355	Single enantiomer	573.2	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ 12.44 (s, 1H), 7.50 (s, 1H), 7.23 (s, 1H), 7.08 (t, <i>J</i> = 8.6 Hz, 2H), 7.00 (d, <i>J</i> = 6.1 Hz, 2H), 4.42 (s, 1H), 4.26 (d, <i>J</i> = 5.7 Hz, 2H), 3.21 (s, 1H), 2.84 (q, <i>J</i> = 6.4 Hz, 1H), 2.54 (s, 3H), 2.15 – 1.94 (m, 2H), 1.74 (s, 2H), 1.43 (d, <i>J</i> = 7.7 Hz, 2H), 1.37 (q, <i>J</i> = 7.3 Hz, 2H), 1.18 (d, <i>J</i> = 7.1 Hz, 3H), 0.67 (t, <i>J</i> = 7.4 Hz, 3H), 0.60 (t, <i>J</i> = 7.3 Hz, 3H) ppm
356		571.1	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ 12.44 (s, 1H), 7.50 (s, 1H), 7.22 (s, 1H), 7.09 (t, <i>J</i> = 8.6 Hz, 2H), 7.01 (s, 2H), 4.46 (s, 1H), 4.31 – 4.21 (m, 2H), 3.17 (s, 1H), 2.83 (q, <i>J</i> = 6.4 Hz, 1H), 2.46 (s, 3H), 2.23 (s, 2H), 1.77

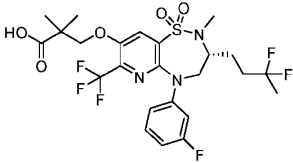
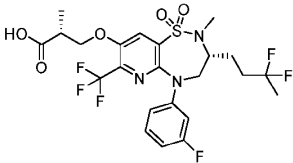
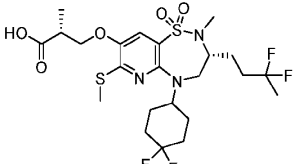
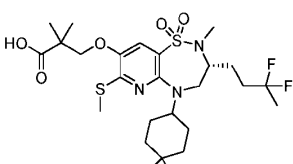
			(s, 3H), 1.60 – 1.37 (m, 7H), 1.18 (d, $J = 7.1$ Hz, 3H) ppm
357	 Single enantiomer	571.2	^1H NMR (600 MHz, DMSO- d_6): δ 12.44 (s, 1H), 7.50 (s, 1H), 7.22 (s, 1H), 7.09 (t, $J = 8.5$ Hz, 2H), 7.01 (d, $J = 5.7$ Hz, 2H), 4.46 (s, 1H), 4.25 (q, $J = 8.8, 7.3$ Hz, 2H), 3.27 (s, 2H), 3.20 (s, 1H), 2.84 (q, $J = 6.6$ Hz, 1H), 2.47 – 2.46 (m, 3H), 2.23 (s, 1H), 1.99 – 1.72 (m, 3H), 1.57 – 1.39 (m, 6H), 1.18 (d, $J = 7.1$ Hz, 3H) ppm
358	 Single enantiomer	571.2	^1H NMR (600 MHz, DMSO- d_6): δ 12.43 (s, 1H), 7.50 (s, 1H), 7.22 (s, 1H), 7.09 (t, $J = 8.6$ Hz, 2H), 7.01 (s, 2H), 4.55 – 4.31 (m, 1H), 4.29 – 4.23 (m, 2H), 3.27 (s, 2H), 3.21 (s, 1H), 2.85 (p, $J = 6.5$ Hz, 1H), 2.47 (s, 3H), 2.24 (s, 1H), 1.82 (d, $J = 50.5$ Hz, 3H), 1.55 (s, 2H), 1.47 (s, 2H), 1.42 – 1.38 (m, 2H), 1.18 (d, $J = 7.0$ Hz, 3H) ppm
359	 Single enantiomer	569.1	^1H NMR (400 MHz, CD $_3$ OD): δ 7.64 (s, 1H), 7.44 (s, 1H), 7.04 – 6.95 (m, 2H), 6.84 – 6.76 (m, 2H), 6.14 – 5.80 (m, 1H), 4.21 (s, 2H), 4.15 – 4.02 (m, 1H), 4.00 – 3.87 (m, 1H), 3.62 – 3.43 (m, 1H), 2.68 (s, 3H), 2.13 – 1.90 (m, 2H), 1.87 – 1.71 (m, 2H), 1.36 (s, 6H) ppm
360	 Single enantiomer	569.1	^1H NMR (400 MHz, CD $_3$ OD): δ 7.64 (s, 1H), 7.44 (s, 1H), 7.04 – 6.95 (m, 2H), 6.84 – 6.76 (m, 2H), 6.14 – 5.80 (m, 1H), 4.21 (s, 2H), 4.15 – 4.02 (m, 1H), 4.00 – 3.87 (m, 1H), 3.62 – 3.43 (m, 1H), 2.68 (s, 3H), 2.13 – 1.90 (m, 2H), 1.87 – 1.71 (m, 2H), 1.36 (s, 6H) ppm

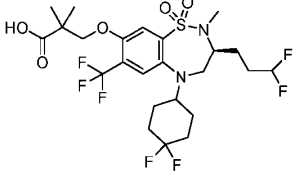
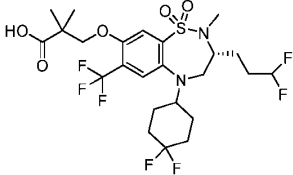
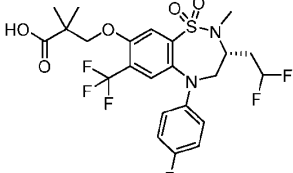
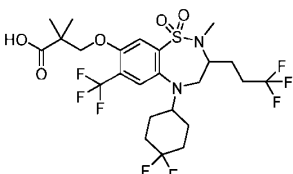
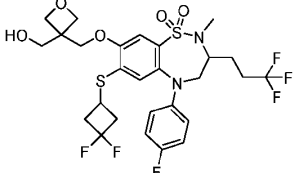
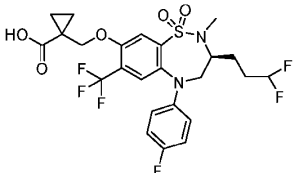
361	 Single diastereomer	548.2	¹ H NMR (400 MHz, d ₆ -DMSO): δ 7.42 (s, 1H), 7.20 – 7.12 (m, 2H), 7.11 – 7.02 (m, 2H), 4.30 – 4.18 (m, 2H), 4.12 – 4.05 (m, 1H), 4.02 – 3.94 (m, 1H), 3.89 – 3.69 (m, 1H), 2.91 (s, 3H), 2.89 – 2.84 (m, 1H), 2.16 – 2.00 (m, 1H), 1.98 (s, 3H), 1.97 – 1.86 (m, 2H), 1.73 – 1.65 (m, 1H), 1.59 (t, J = 18.4 Hz, 3H), 1.29 (d, J = 3.6 Hz, 3H) ppm.
362	 Single enantiomer	562.2	¹ H NMR (400 MHz, d ₆ -DMSO): δ 7.43 (s, 1H), 7.22 – 7.14 (m, 2H), 7.12 – 7.05 (m, 2H), 4.32 – 4.18 (m, 1H), 4.07 (d, J = 1.6 Hz, 2H), 4.05 – 3.95 (m, 1H), 3.83 – 3.70 (m, 1H), 2.92 (s, 3H), 2.20 – 2.05 (m, 2H), 2.01 (s, 3H), 1.99 – 1.87 (m, 1H), 1.77 – 1.67 (m, 1H), 1.62 (t, J = 18.8 Hz, 3H), 1.33 (s, 6H) ppm.
363	 Single enantiomer	585.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.24 (s, 1H), 6.90 (brs, 1H), 4.04 (s, 2H), 3.93 – 3.45 (m, 2H), 3.32 – 3.13 (m, 2H), 2.86 – 2.35 (m, 6H), 2.14 – 1.61 (m, 15H), 1.33 (s, 6H) ppm
364	 Single diastereomer	571.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.23 (s, 1H), 6.88 (brs, 1H), 4.19 (dd, J = 8.4, 6.8 Hz, 1H), 4.06 (dd, J = 8.8, 6.0 Hz, 1H), 3.87 – 3.45 (m, 2H), 3.30 – 3.13 (m, 2H), 2.96 – 2.86 (m, 1H), 2.75 – 2.25 (m, 6H), 2.12 – 1.56 (m, 15 H), 1.30 (d, J = 7.2 Hz, 3H) ppm
365		619.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.55 (s, 1H), 7.45 – 7.39 (m, 1H), 4.33 – 4.32 (m, 1H), 4.21 – 4.16 (m, 1H), 4.09 – 4.03 (m, 1H), 3.36 – 3.33 (m,

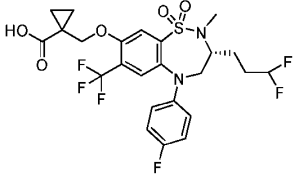
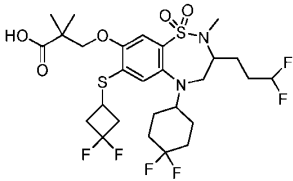
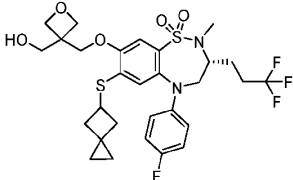
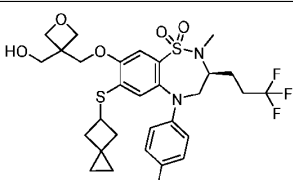
	Single diastereomer		¹ H), 2.85 – 2.32 (m, 9H), 2.29-1.60 (m, 14H), 1.30 – 1.28 (m, 3H) ppm
366	 Single enantiomer	590.3	¹ H NMR (400 MHz, CD ₃ OD): δ 7.49 (s, 1H), 7.31 – 7.24 (m, 1H), 6.83 – 6.67 (m, 3H), 4.22 – 4.05 (m, 5H), 4.00 – 3.80 (m, 2H), 2.80 (s, 3H), 2.18 (s, 3H), 2.17 – 1.85 (m, 3H), 1.85 – 1.73 (m, 1H), 1.63 (t, <i>J</i> = 18.6 Hz, 3H), 1.35 (s, 6H), 1.25 (t, <i>J</i> = 7.2 Hz, 3H) ppm
367	 Single enantiomer	562.3	¹ H NMR (400 MHz, CD ₃ OD): δ 7.50 (s, 1H), 7.31 – 7.22 (m, 1H), 6.81 – 6.65 (m, 3H), 4.18 – 4.07 (m, 3H), 3.96 – 3.81 (m, 2H), 2.78 (s, 3H), 2.20 (s, 3H), 2.17 – 1.96 (m, 2H), 1.96 – 1.73 (m, 2H), 1.64 (t, <i>J</i> = 18.4 Hz, 3H), 1.36 (s, 6H) ppm
368	 Single diastereomer	548.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.52 (s, 1H), 7.31 – 7.23 (m, 1H), 6.81 – 6.65 (m, 3H), 4.30 (dd, <i>J</i> = 9.2, 6.4 Hz, 1H), 4.18 (dd, <i>J</i> = 9.2, 5.8 Hz, 1H), 4.21 – 4.05 (m, 1H), 3.96 – 3.80 (m, 2H), 3.00 – 2.89 (m, 1H), 2.79 (s, 3H), 2.19 (s, 3H), 2.16 – 1.85 (m, 3H), 1.84 – 1.73 (m, 1H), 1.63 (t, <i>J</i> = 18.4 Hz, 3H), 1.33 (d, <i>J</i> = 7.2 Hz, 3H) ppm
369	 Single enantiomer	536.3	¹ H NMR (400 MHz, CD ₃ OD): δ 7.36 (s, 1H), 4.85 – 4.73 (m, 1H), 4.01 (s, 2H), 3.85 – 3.73 (m, 1H), 3.60 – 3.50 (m, 1H), 3.49 – 3.40 (m, 1H), 2.89 (s, 3H), 2.49 (s, 3H), 2.24 – 1.91 (m, 5H), 1.86 – 1.56 (m, 9H), 1.51 – 1.39 (m, 1H), 1.33 (s, 6H) ppm
370		522.3	¹ H NMR (400 MHz, CD ₃ OD): δ 7.39 (s, 1H), 4.85 – 4.74 (m, 1H), 4.21 – 4.15 (m, 1H), 4.09 – 4.03 (m, 1H), 3.85 – 3.74 (m, 1H), 3.60 – 3.40 (m,

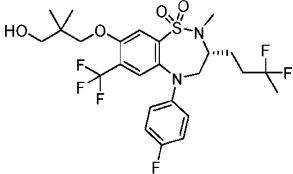
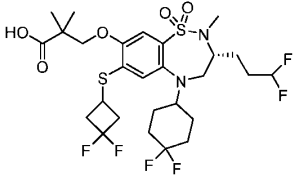
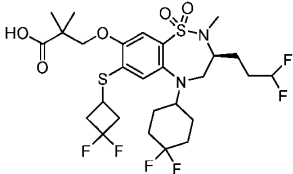
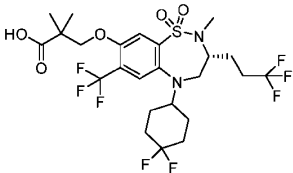
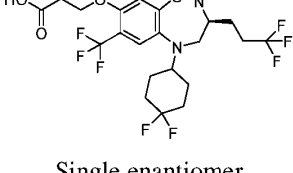
	Single diastereomer		2H), 2.95 – 2.84 (m, 4H), 2.49 (s, 3H), 2.25 – 2.06 (m, 2H), 2.05 – 1.92 (m, 3H), 1.86 – 1.55 (m, 9H), 1.52 – 1.39 (m, 1H), 1.31 (d, $J = 7.2$ Hz, 3H) ppm
371	 Single enantiomer	535.2	^1H NMR (400 MHz, CD_3OD): δ 7.23 (s, 1H), 6.92 – 6.89 (m, 1H), 4.03 (s, 2H), 4.01 – 3.97 (s, 1H), 3.27 – 3.14 (m, 1H), 2.67 – 2.53 (m, 2H), 2.14 – 1.98 (m, 5H), 1.93 – 1.50 (m, 12H), 1.42 – 1.19 (m, 10H) ppm.
372	 Single diastereomer	521.2	^1H NMR (400 MHz, d_6 -DMSO): δ 7.11 (s, 1H), 6.81 – 6.77 (m, 1H), 4.12 – 3.92 (m, 3H), 3.71 – 3.51 (m, 2H), 3.15 – 2.58 (m, 4H), 2.45 (s, 3H), 2.04 – 1.41 (m, 16H), 1.19 (d, $J = 6.8$ Hz, 3H) ppm.
373	 Single enantiomer	651.2	^1H NMR (400 MHz, CD_3OD): δ 7.39 (s, 1H), 7.07 (s, 1H), 6.95 (t, $J = 9.2$ Hz, 2H), 6.73 – 6.72 (m, 2H), 4.14 (s, 2H), 4.06 – 3.93 (m, 2H), 3.49 – 3.42 (m, 1H), 3.03 – 2.99 (m, 2H), 2.61 (s, 5H), 2.32 – 2.27 (m, 3H), 2.11 – 1.94 (m, 2H), 1.82 – 1.79 (m, 2H), 1.63 (t, $J = 18.4$ Hz, 3H), 1.37 (s, 6H) ppm
374	 Single diastereomer	587.1	^1H NMR (400 MHz, d_6 -DMSO): δ 7.64 (s, 1H), 7.59 (s, 1H), 7.19 (q, $J = 10.0$ Hz, 1H), 6.82 – 6.79 (m, 1H), 6.29 – 6.27 (m, 1H), 4.38 – 4.27 (m, 2H), 4.10 (d, $J = 16.8$ Hz, 1H), 3.87 (s, 1H), 3.42 (s, 1H), 2.84 (q, $J = 6.0$ Hz, 1H), 2.52 (s, 3H), 2.07 – 1.91 (m, 3H), 1.70 – 1.60 (m, 4H), 1.21 (d, $J = 7.2$ Hz, 3H) ppm

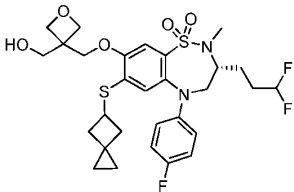
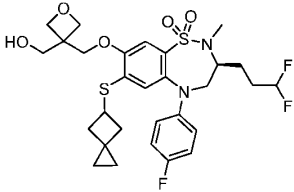
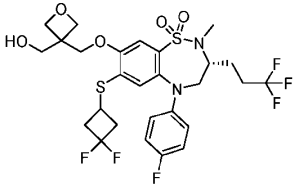
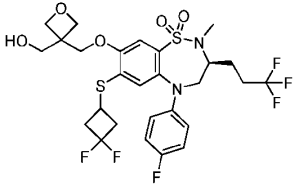
375	 Single enantiomer	601.1	¹ H NMR (400 MHz, d ₆ -DMSO): δ 7.65 (s, 1H), 7.58 (s, 1H), 7.19 (q, J = 9.6 Hz, 1H), 6.81 – 6.80 (m, 1H), 6.29 – 6.28 (m, 1H), 4.23 (s, 2H), 4.10 (q, J = 16.0 Hz, 1H), 3.87 (s, 1H), 3.33 (s, 1H), 2.52 (s, 3H), 2.03 – 1.89 (m, 3H), 1.70 – 1.60 (m, 4H), 1.25 (s, 6H) ppm
376	 Single enantiomer	601.3	¹ H NMR (400 MHz, CD ₃ OD): δ 7.68 (s, 1H), 7.56 (s, 1H), 7.14 – 7.05 (m, 1H), 6.63 – 6.54 (m, 1H), 6.40 (d, J = 7.6 Hz, 1H), 4.24 (s, 2H), 4.12 – 3.95 (m, 2H), 3.50 – 3.35 (m, 1H), 2.62 (s, 3H), 2.13 – 1.95 (m, 2H), 1.93 – 1.72 (m, 2H), 1.65 (t, J = 18.4 Hz, 3H), 1.36 (s, 6H) ppm
377	 Single enantiomer	540.2	¹ H NMR (400 MHz, d ₆ -DMSO): δ 7.84 (s, 1H), 7.54 (s, 1H), 7.01 (t, J = 8.8 Hz, 2H), 6.71 – 6.63 (m, 2H), 4.23 (s, 2H), 4.15 – 4.05 (m, 1H), 3.87 – 3.75 (m, 1H), 2.53 (s, 3H), 2.22 – 2.13 (m, 2H), 2.03 – 1.93 (m, 2H), 1.88 – 1.83 (m, 1H), 1.64 (t, J = 18.8 Hz, 4H), 1.25 (s, 6H) ppm
378	 Single enantiomer	584.2	¹ H NMR (400 MHz, CD ₃ OD): δ 8.00 (s, 1H), 7.20 – 7.13 (m, 2H), 7.12 – 7.05 (m, 2H), 4.31 – 4.19 (m, 1H), 4.17 (s, 2H), 4.11 – 3.99 (m, 1H), 3.87 – 3.73 (m, 1H), 2.95 (s, 3H), 2.18 – 1.85 (m, 3H), 1.78 – 1.68 (m, 1H), 1.62 (t, J = 18.4 Hz, 3H), 1.33 (s, 6H) ppm
379	 Single diastereomer	570.1	¹ H NMR (400 MHz, CD ₃ OD): δ 8.02 (s, 1H), 7.22 – 7.13 (m, 2H), 7.12 – 7.04 (m, 2H), 4.36 – 4.29 (m, 1H), 4.28 – 4.21 (m, 1H), 4.10 – 3.96 (m, 1H), 3.86 – 3.73 (m, 2H), 2.95 (s, 3H), 2.94 – 2.86 (m, 1H), 2.20 – 1.85

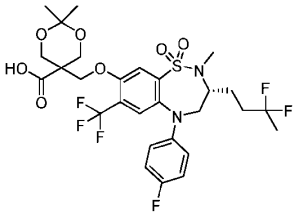
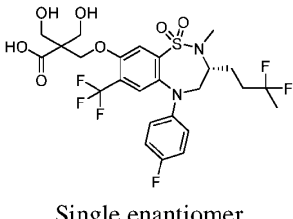
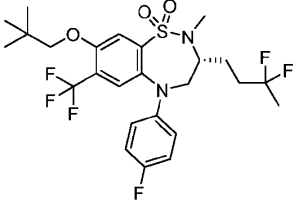
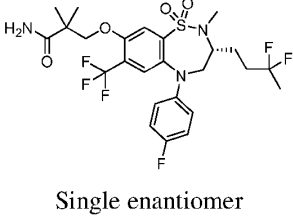
			(m, 3H), 1.79 – 1.69 (m, 1H), 1.62 (t, $J = 18.4$ Hz, 3H), 1.31 (d, $J = 7.2$ Hz, 3H) ppm
380	 Single enantiomer	584.2	^1H NMR (400 MHz, CD_3OD): δ 8.08 (s, 1H), 7.31 – 7.24 (m, 1H), 6.79 – 6.67 (m, 3H), 4.25 (s, 2H), 4.22 – 4.09 (m, 1H), 3.98 – 3.82 (m, 2H), 2.82 (s, 3H), 2.20 – 1.75 (m, 4H), 1.64 (t, $J = 18.8$ Hz, 3H), 1.35 (s, 6H) ppm
381	 Single diastereomer	570.1	^1H NMR (400 MHz, CD_3OD): δ 8.09 (s, 1H), 7.32 – 7.24 (m, 1H), 6.80 – 6.68 (m, 3H), 4.39 (dd, $J = 8.8, 6.8$ Hz, 1H), 4.31 (dd, $J = 8.8, 5.6$ Hz, 1H), 4.22 – 4.10 (m, 1H), 3.97 – 3.84 (m, 2H), 3.02 – 2.91 (m, 1H), 2.82 (s, 3H), 2.20 – 1.75 (m, 4H), 1.64 (t, $J = 18.4$ Hz, 3H), 1.34 (d, $J = 7.2$ Hz, 3H) ppm
382	 Single diastereomer	571.2	^1H NMR (400 MHz, CD_3OD): δ 7.40 (s, 1H), 4.55 – 4.40 (m, 1H), 4.22 – 4.15 (m, 1H), 4.10 – 4.03 (m, 1H), 3.90 – 3.75 (m, 1H), 3.60 – 3.43 (m, 2H), 2.91 (s, 3H), 2.91 – 2.85 (m, 1H), 2.51 (s, 3H), 2.26 – 1.92 (m, 10H), 1.88 – 1.71 (m, 2H), 1.64 (t, $J = 18.4$ Hz, 3H), 1.31 (d, $J = 7.2$ Hz, 3H) ppm.
383	 Single enantiomer	586.2	^1H NMR (400 MHz, CD_3OD): δ 7.38 (s, 1H), 4.55 – 4.40 (m, 1H), 4.01 (s, 2H), 3.90 – 3.75 (m, 1H), 3.58 – 3.42 (m, 2H), 2.91 (s, 3H), 2.51 (s, 3H), 2.26 – 1.88 (m, 10H), 1.86 – 1.70 (m, 2H), 1.64 (t, $J = 18.4$ Hz, 3H), 1.34 (s, 6H) ppm

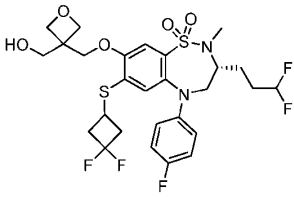
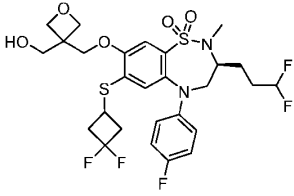
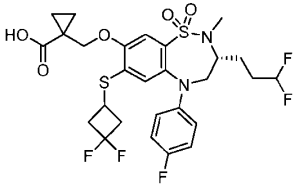
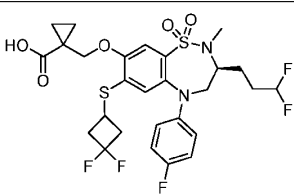
384	 Single enantiomer	593.3	¹ H NMR (400 MHz, d ₆ -DMSO): δ 7.46 (s, 1H), 6.19 – 7.23 (m, 1H), 6.08 – 5.78 (m, 1H), 4.10 – 4.04 (m, 2H), 3.44 – 3.17 (m, 3H), 2.82 – 2.49 (m, 4H), 2.21 – 1.67 (m, 12H), 1.37 – 1.36 (m, 6H) ppm
385	 Single enantiomer	593.3	¹ H NMR (400 MHz, d ₆ -DMSO): δ 7.46 (s, 1H), 6.99 – 7.23 (m, 1H), 6.08 – 5.78 (m, 1H), 4.10 – 4.04 (m, 2H), 3.43 – 3.17 (m, 3H), 2.95 – 2.46 (m, 4H), 2.21 – 1.68 (m, 12H), 1.37 – 1.36 (m, 6H) ppm
386	 Single enantiomer	555.1	¹ H NMR (400 MHz, d ₆ -DMSO): δ 7.62 (s, 1H), 7.40 (s, 1H), 7.05 – 7.01 (m, 2H), 6.88 (s, 2H), 6.27 – 5.96 (m, 1H), 4.22 – 3.22 (m, 5H), 2.78 (s, 3H), 2.40 (s, 1H), 2.18 – 2.11 (m, 1H), 1.36 (s, 6H) ppm
387		611.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.40 (s, 1H), 7.23 (s, 1H), 3.99 (s, 2H), 3.52 – 3.20 (m, 3H), 2.76 – 2.23 (m, 6H), 2.02 – 1.21 (m, 10H), 1.21 (s, 6H) ppm
388		641.3	¹ H NMR (400 MHz, CD ₃ OD): δ 7.47 (s, 1H), 7.01 (t, J = 8.4 Hz, 2H), 6.89 – 6.78 (m, 3H), 4.74 – 4.67 (m, 2H), 4.62 – 4.57 (m, 2H), 4.34 (s, 2H), 4.13 – 3.99 (m, 1H), 3.96 (s, 2H), 3.96 – 3.85 (m, 1H), 3.74 – 3.50 (m, 2H), 3.14 – 2.88 (m, 2H), 2.67 (s, 3H), 2.60 – 2.30 (m, 4H), 2.00 – 1.80 (m, 2H) ppm
389	 Single enantiomer	567.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.66 (s, 1H), 7.43 (s, 1H), 7.03 – 6.95 (m, 2H), 6.83 – 6.75 (m, 2H), 6.14 – 5.80 (m, 1H), 4.38 (dd, J = 19.2, 10.0 Hz, 2H), 4.15 – 4.01 (m, 1H), 4.01 – 3.85 (m, 1H), 3.64 – 3.40 (m, 1H), 2.68 (s,

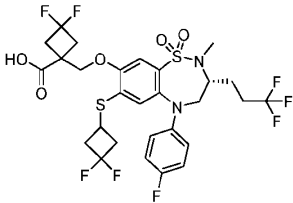
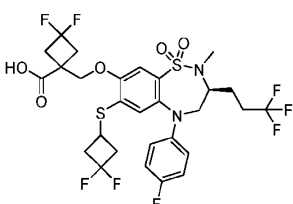
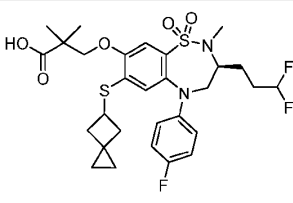
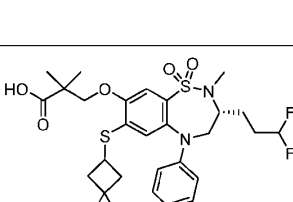
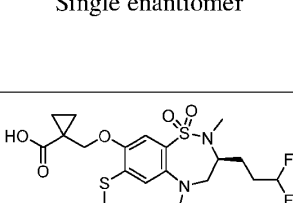
			3H), 2.15 – 1.88 (m, 2H), 1.88 – 1.71 (m, 2H), 1.35 (dd, $J=7.0$, 3.8 Hz, 2H), 1.13 (dd, $J=7.0$, 4.2 Hz, 2H) ppm
390	 Single enantiomer	567.2	^1H NMR (400 MHz, CD_3OD): δ 7.66 (s, 1H), 7.43 (s, 1H), 7.03 – 6.95 (m, 2H), 6.83 – 6.75 (m, 2H), 6.14 – 5.80 (m, 1H), 4.38 (dd, $J=18.0$, 10.0 Hz, 2H), 4.15 – 4.01 (m, 1H), 4.01 – 3.85 (m, 1H), 3.64 – 3.40 (m, 1H), 2.68 (s, 3H), 2.15 – 1.88 (m, 2H), 1.88 – 1.71 (m, 2H), 1.36 (dd, $J=7.0$, 4.2 Hz, 2H), 1.14 (dd, $J=7.0$, 3.8 Hz, 2H) ppm
391	 Single enantiomer	647.2	^1H NMR (400 MHz, CDCl_3): δ 7.27 (s, 1H), 6.83 (s, 1H), 6.14 – 5.83 (m, 1H), 4.81 – 4.87 (m, 1H), 4.05 (s, 2H), 3.90 – 3.77 (m, 1H), 3.63 – 3.48 (m, 1H), 3.26 – 3.10 (m, 3H), 2.64 – 2.54 (m, 4H), 2.14 – 1.69 (m, 14H), 1.35 (m, 6H) ppm
392	 Single enantiomer	631.2	^1H NMR (400 MHz, CD_3OD): δ 7.43 (s, 1H), 6.98 (t, $J=9.2$ Hz, 2H), 6.87 – 6.76 (m, 3H), 4.74 – 4.70 (m, 2H), 4.62 – 4.58 (m, 2H), 4.33 (s, 2H), 4.10 – 3.99 (m, 1H), 3.97 (s, 2H), 3.95 – 3.84 (m, 1H), 3.64 – 3.37 (m, 1H), 2.68 (s, 3H), 2.55 – 2.26 (m, 4H), 2.22 – 2.07 (m, 2H), 1.98 – 1.80 (m, 2H), 0.55 – 0.40 (m, 4H) ppm
393	 Single enantiomer	631.2	^1H NMR (400 MHz, CD_3OD): δ 7.43 (s, 1H), 6.98 (t, $J=9.2$ Hz, 2H), 6.87 – 6.76 (m, 3H), 4.74 – 4.70 (m, 2H), 4.62 – 4.58 (m, 2H), 4.33 (s, 2H), 4.10 – 3.99 (m, 1H), 3.97 (s, 2H), 3.95 – 3.84 (m, 1H), 3.64 – 3.37 (m, 1H), 2.66 (s, 3H), 2.55 – 2.30 (m,

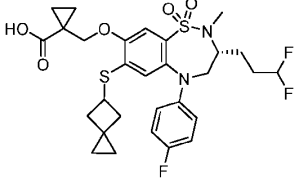
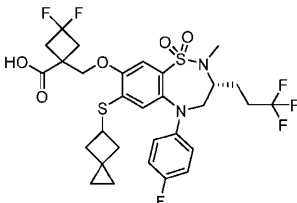
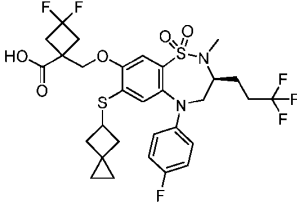
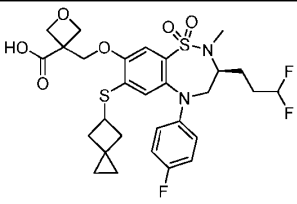
			4H), 2.21 – 2.07 (m, 2H), 1.98 – 1.80 (m, 2H), 0.52 – 0.42 (m, 4H) ppm
394	 Single enantiomer	569.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.63 (s, 1H), 7.45 (s, 1H), 6.99 (t, J = 8.8 Hz, 2H), 6.79 – 6.75 (m, 2H), 4.10 – 4.02 (m, 1H), 3.96 (s, 3H), 3.49 (s, 2H), 2.66 (s, 3H), 2.12 – 1.96 (m, 2H), 1.84 – 1.78 (m, 2H), 1.68 – 1.59 (m, 3H), 1.06 (s, 6H) ppm
395	 Single enantiomer	647.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.31 (s, 1H), 6.83 (brs, 1H), 6.14 – 5.83 (m, 1H), 4.06 – 4.02 (m, 2H), 3.90 – 3.83 (m, 1H), 3.55 – 3.49 (m, 1H), 3.26 – 3.12 (m, 3H), 2.65 – 2.54 (m, 5H), 2.22 – 1.69 (m, 14H), 1.35 – 1.34 (m, 6H) ppm
396	 Single enantiomer	647.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.28 (s, 1H), 6.83 (brs, 1H), 6.14 – 5.83 (m, 1H), 4.07 – 4.02 (m, 2H), 3.90 – 3.83 (m, 1H), 3.54 – 3.49 (m, 1H), 3.26 – 3.12 (m, 3H), 2.65 – 2.54 (m, 5H), 2.22 – 1.69 (m, 14H), 1.35 – 1.34 (m, 6H) ppm
397	 Single enantiomer	611.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.51 (s, 1H), 7.35 (s, 1H), 4.11 (s, 2H), 3.64 – 3.33 (m, 3H), 2.76 – 2.72 (m, 3H), 2.44 – 1.83 (m, 13H), 1.34 (s, 6H) ppm
398	 Single enantiomer	611.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.56 (s, 1H), 7.39 (s, 1H), 4.15 (s, 2H), 3.68 – 3.37 (m, 3H), 2.92 – 2.69 (m, 3H), 2.48 – 1.88 (m, 13H), 1.38 (s, 6H) ppm

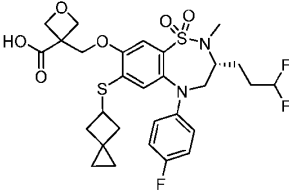
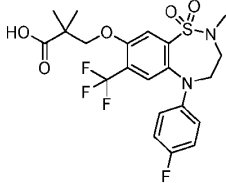
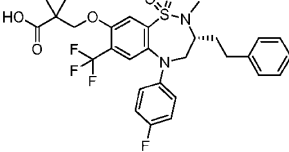
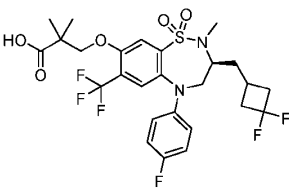
399	 Single enantiomer	613.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.41 (s, 1H), 6.98 – 6.90 (m, 2H), 6.79 (s, 1H), 6.78 – 6.71 (m, 2H), 6.11 – 5.78 (m, 1H), 4.69 (d, <i>J</i> = 6.0 Hz, 2H), 4.58 (d, <i>J</i> = 6.0 Hz, 2H), 4.31 (s, 2H), 4.05 – 3.82 (m, 5H), 3.55 – 3.39 (m, 1H), 2.61 (s, 3H), 2.54 – 2.45 (m, 1H), 2.43 – 2.35 (m, 1H), 2.20 – 2.12 (m, 1H), 2.11 – 2.04 (m, 1H), 2.04 – 1.85 (m, 2H), 1.82 – 1.68 (m, 2H), 0.48 – 0.41 (m, 4H) ppm
400	 Single enantiomer	613.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.41 (s, 1H), 6.98 – 6.90 (m, 2H), 6.79 (s, 1H), 6.78 – 6.71 (m, 2H), 6.11 – 5.78 (m, 1H), 4.69 (d, <i>J</i> = 6.0 Hz, 2H), 4.58 (d, <i>J</i> = 6.0 Hz, 2H), 4.31 (s, 2H), 4.05 – 3.82 (m, 5H), 3.55 – 3.39 (m, 1H), 2.61 (s, 3H), 2.54 – 2.45 (m, 1H), 2.43 – 2.35 (m, 1H), 2.20 – 2.12 (m, 1H), 2.11 – 2.04 (m, 1H), 2.04 – 1.85 (m, 2H), 1.82 – 1.68 (m, 2H), 0.48 – 0.41 (m, 4H) ppm
401	 Single enantiomer	641.3	¹ H NMR (400 MHz, CD ₃ OD): δ 7.47 (s, 1H), 7.01 (t, <i>J</i> = 8.4 Hz, 2H), 6.85 – 6.83 (m, 3H), 4.71 – 4.64 (m, 2H), 4.60 – 4.59 (m, 2H), 4.34 (s, 2H), 4.13 – 3.99 (m, 1H), 3.96 (s, 2H), 3.96 – 3.82 (m, 1H), 3.70 – 3.64 (m, 2H), 3.07 – 2.92 (m, 2H), 2.67 (s, 3H), 2.60 – 2.30 (m, 4H), 2.00 – 1.85 (m, 2H) ppm
402	 Single enantiomer	641.3	¹ H NMR (400 MHz, CD ₃ OD): δ 7.47 (s, 1H), 7.01 (t, <i>J</i> = 8.4 Hz, 2H), 6.85 – 6.83 (m, 3H), 4.71 – 4.69 (m, 2H), 4.60 – 4.59 (m, 2H), 4.34 (s, 2H), 4.13 – 4.01 (m, 1H), 3.96 (s, 2H), 3.96 – 3.86 (m, 1H), 3.70 – 3.53 (m, 2H), 3.15 – 2.89 (m, 2H), 2.67 (s,

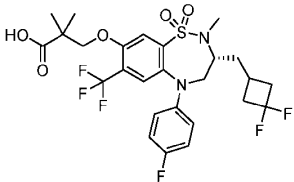
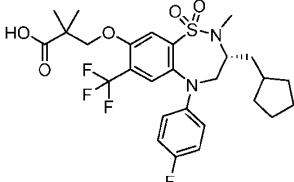
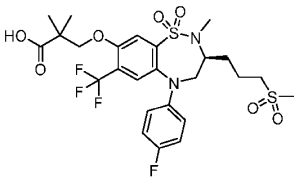
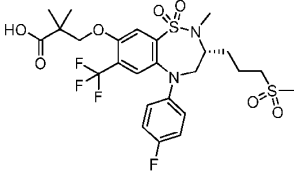
			3H), 2.58 – 2.28 (m, 4H), 1.97 – 1.84 (m, 2H) ppm
403	 Single enantiomer	655.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.71 (s, 1H), 7.44 (s, 1H), 7.02 – 6.98 (m, 2H), 6.82 – 6.79 (m, 2H), 4.57 (s, 2H), 4.30 (dd, J = 12.0, 2.4 Hz, 2H), 4.11 – 3.92 (m, 4H), 3.52 – 3.49 (m, 1H), 2.68 (s, 3H), 2.13 – 1.97 (m, 2H), 1.85 – 1.79 (m, 2H), 1.64 (t, J = 18.4 Hz, 3H), 1.50 (s, 3H), 1.42 (s, 3H) ppm
404	 Single enantiomer	615.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.70 (s, 1H), 7.43 (s, 1H), 6.96 (t, J = 8.8 Hz, 2H), 6.77 – 6.74 (m, 2H), 4.42 (s, 2H), 4.08 – 3.81 (m, 6H), 3.48 – 3.47 (m, 1H), 2.64 (s, 3H), 2.10 – 1.92 (m, 2H), 1.92 – 1.77 (m, 2H), 1.61 (t, J = 18.4 Hz, 3H) ppm
405	 Single enantiomer	553.3	¹ H NMR (400 MHz, CD ₃ OD): δ 7.59 (s, 1H), 7.45 (s, 1H), 7.00 – 6.96 (m, 2H), 6.79 – 6.75 (m, 2H), 6.78 – 6.75 (m, 2H), 4.10 – 3.92 (m, 1H), 3.92 (s, 2H), 3.33 – 3.31 (m, 1H), 2.63 (s, 3H), 2.09 – 1.96 (m, 2H), 1.84 – 1.78 (m, 2H), 1.68 – 1.58 (m, 3H), 1.04 (s, 6H) ppm
406	 Single enantiomer	582.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.62 (s, 1H), 7.41 (s, 1H), 6.97 (t, J = 8.8 Hz, 2H), 6.78 – 6.75 (m, 2H), 4.20 – 4.15 (m, 2H), 4.08 – 4.04 (m, 1H), 3.91 – 3.87 (m, 1H), 3.48 – 3.47 (m, 1H), 2.65 (s, 3H), 2.06 – 1.94 (m, 2H), 1.82 – 1.76 (m, 2H), 1.65 – 1.56 (m, 3H), 1.34 (d, J = 2.4 Hz, 6H) ppm

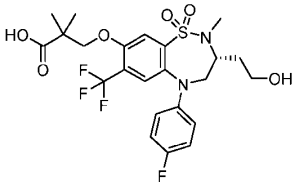
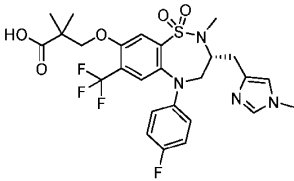
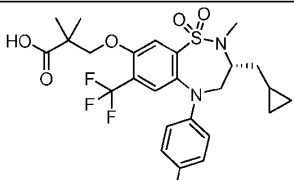
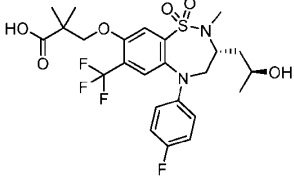
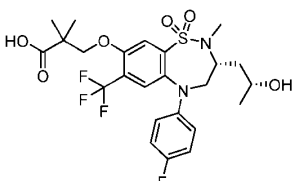
407	 Single enantiomer	623.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.47 (s, 1H), 7.03 – 6.95 (m, 2H), 6.86 (s, 1H), 6.82 – 6.74 (m, 2H), 6.13 – 5.81 (m, 1H), 4.70 (dd, <i>J</i> = 6.0, 1.6 Hz, 2H), 4.59 (d, <i>J</i> = 6.0 Hz, 2H), 4.34 (s, 2H), 4.12–3.99 (m, 1H), 3.99 – 3.88 (m, 3H), 3.75 – 3.63 (m, 1H), 3.60 – 3.40 (m, 1H), 3.16 – 3.02 (m, 1H), 3.02 – 2.88 (m, 1H), 2.64 (s, 3H), 2.60 – 2.38 (m, 2H), 2.13 – 1.88 (m, 2H), 1.85 – 1.70 (m, 2H) ppm
408	 Single enantiomer	623.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.47 (s, 1H), 7.03 – 6.95 (m, 2H), 6.86 (s, 1H), 6.82 – 6.74 (m, 2H), 6.13 – 5.81 (m, 1H), 4.70 (dd, <i>J</i> = 6.4, 1.6 Hz, 2H), 4.59 (d, <i>J</i> = 6.4 Hz, 2H), 4.34 (s, 2H), 4.12–3.99 (m, 1H), 3.99 – 3.88 (m, 3H), 3.75 – 3.63 (m, 1H), 3.60 – 3.40 (m, 1H), 3.16 – 3.02 (m, 1H), 3.02 – 2.88 (m, 1H), 2.64 (s, 3H), 2.60 – 2.38 (m, 2H), 2.13 – 1.88 (m, 2H), 1.85 – 1.70 (m, 2H) ppm
409	 Single enantiomer	621.2	¹ H NMR (400 MHz, d ₆ -DMSO): δ 7.28 (s, 1H), 7.02 – 6.98 (m, 2H), 6.92 (s, 1H), 6.67 – 6.66 (m, 2H), 6.26 – 5.98 (m, 1H), 4.26 – 4.19 (m, 2H), 4.05 – 4.02 (m, 1H), 3.84 – 3.82 (m, 2H), 3.32 – 2.97 (m, 3H), 2.60 – 2.50 (m, 5H), 2.01 – 1.59 (m, 4H), 1.24 – 1.20 (m, 2H), 1.06 – 1.05 (m, 2H) ppm
410	 Single enantiomer	621.2	¹ H NMR (400 MHz, d ₆ -DMSO): δ 7.28 (s, 1H), 7.02 – 6.98 (m, 2H), 6.92 (s, 1H), 6.66 – 6.65 (m, 2H), 6.27 – 5.97 (m, 1H), 4.26 – 4.19 (m, 2H), 4.05 – 4.01 (m, 1H), 3.84 – 3.82 (m, 2H), 3.32 – 2.94 (m, 3H), 2.67 – 2.50 (m, 5H), 1.99 – 1.63 (m, 4H),

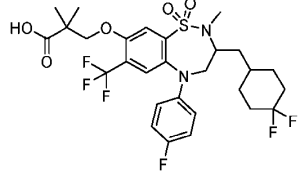
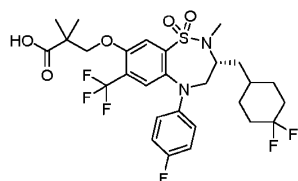
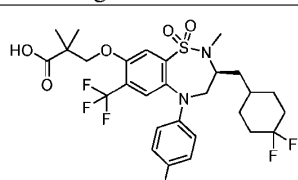
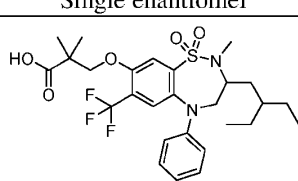
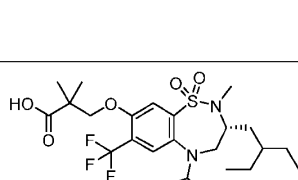
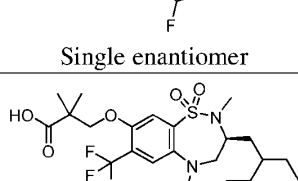
			1.23 – 1.20 (m, 2H), 1.05 – 1.04 (m, 2H) ppm
411	 Single enantiomer	689.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.44 (s, 1H), 7.01 (t, J = 8.8 Hz, 2H), 6.81 – 6.84 (m, 3H), 4.43 (s, 2H), 4.06 – 3.92 (m, 2H), 3.66 – 3.59 (m, 2H), 3.15 – 3.05 (m, 3H), 2.98 – 2.80 (m, 3H), 2.68 (s, 3H), 2.53 – 2.31 (m, 4H), 1.91 – 1.87 (m, 2H) ppm
412	 Single enantiomer	689.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.44 (s, 1H), 7.00 (t, J = 8.8 Hz, 2H), 6.81 – 6.84 (m, 3H), 4.41 (s, 2H), 4.06 – 3.92 (m, 2H), 3.68 – 3.59 (m, 2H), 3.15 – 3.01 (m, 3H), 2.98 – 2.80 (m, 3H), 2.67 (s, 3H), 2.52 – 2.31 (m, 4H), 1.91 – 1.87 (m, 2H) ppm
413	 Single enantiomer	613.2	¹ H NMR (400 MHz, d ₆ -DMSO): δ 12.35 (s, 1H), 7.25 (s, 1H), 6.99 (t, J = 8.8 Hz, 2H), 6.80 (s, 1H), 6.66 – 6.65 (m, 2H), 6.27 – 5.97 (m, 1H), 4.09 (s, 2H), 4.04 – 3.84 (m, 3H), 3.32 (s, 1H), 2.50 – 2.39 (m, 4H), 2.13 – 1.56 (m, 6H), 1.27 – 1.24 (m, 7H), 0.43 – 0.39 (m, 4H) ppm
414	 Single enantiomer	613.2	¹ H NMR (400 MHz, d ₆ -DMSO): δ 12.42 (s, 1H), 7.26 (s, 1H), 6.99 (t, J = 5.2 Hz, 2H), 6.80 (s, 1H), 6.67 – 6.65 (m, 2H), 6.27 – 5.97 (m, 1H), 4.09 (s, 2H), 4.04 – 3.84 (m, 3H), 3.31 (s, 1H), 2.50 – 2.39 (m, 4H), 2.13 – 1.62 (m, 6H), 1.27 – 1.23 (m, 7H), 0.43 – 0.39 (m, 4H) ppm
415	 Single enantiomer	611.2	¹ H NMR (400 MHz, d ₆ -DMSO): δ 12.41 (s, 1H), 7.25 (s, 1H), 6.99 (t, J = 5.2 Hz, 2H), 6.80 (s, 1H), 6.65 – 6.64 (m, 2H), 6.27 – 5.97 (m, 1H), 4.22 (s, 2H), 4.04 – 3.84 (m, 3H), 3.31 (s, 1H), 2.50 – 2.39 (m, 4H),

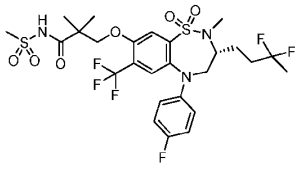
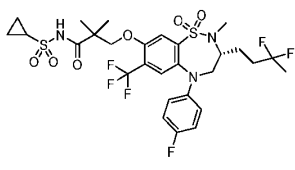
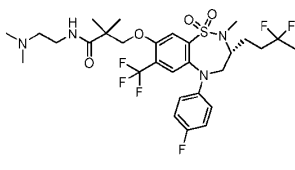
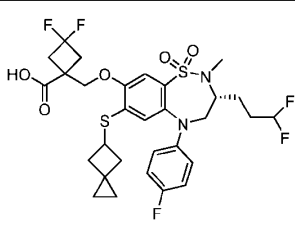
			2.14 – 1.63 (m, 6H), 1.23 – 1.22 (m, 3H), 1.09 – 1.08 (m, 2H), 0.43 – 0.39 (m, 4H) ppm
416	 Single enantiomer	611.2	¹ H NMR (400 MHz, d ₆ -DMSO): δ 12.40 (s, 1H), 7.25 (s, 1H), 6.99 (t, J = 8.8 Hz, 2H), 6.80 (s, 1H), 6.65 – 6.64 (m, 2H), 6.27 – 5.97 (m, 1H), 4.25 – 4.19 (m, 2H), 4.04 – 3.84 (m, 3H), 3.31 (s, 1H), 2.50 – 2.39 (m, 4H), 2.14 – 1.62 (m, 6H), 1.24 – 1.22 (m, 3H), 1.11 – 1.08 (m, 2H), 0.46 – 0.42 (m, 4H) ppm
417	 Single enantiomer	679.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.40 (s, 1H), 7.00 – 6.96 (m, 2H), 6.84 – 6.78 (m, 3H), 4.38 (s, 2H), 4.03 – 3.82 (m, 3H), 3.64 – 3.50 (m, 1H), 3.16 – 3.04 (m, 2H), 2.91 – 2.81 (m, 2H), 2.66 (s, 3H), 2.51 – 2.31 (m, 4H), 2.18 – 2.07 (m, 2H), 2.01 – 1.83 (m, 2H), 0.49 – 0.43 (m, 4H) ppm
418	 Single enantiomer	679.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.40 (s, 1H), 7.00 – 6.95 (m, 2H), 6.84 – 6.78 (m, 3H), 4.38 (s, 2H), 4.03 – 3.82 (m, 3H), 3.62 – 3.50 (m, 1H), 3.15 – 3.04 (m, 2H), 2.91 – 2.81 (m, 2H), 2.66 (s, 3H), 2.51 – 2.31 (m, 4H), 2.18 – 2.07 (m, 2H), 2.01 – 1.83 (m, 2H), 0.49 – 0.43 (m, 4H) ppm
419	 Single enantiomer	627.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.45 (s, 1H), 7.01 – 6.93 (m, 2H), 6.81 (s, 1H), 6.80 – 6.73 (m, 2H), 6.13 – 5.81 (m, 1H), 5.01 (dd, J = 6.0, 2.4 Hz, 2H), 4.81 (d, J = 6.0 Hz, 2H), 4.52 (s, 2H), 4.07 – 3.84 (m, 3H), 3.57 – 3.40 (m, 1H), 2.64 (s, 3H), 2.55 – 2.45 (m, 1H), 2.44 – 2.36 (m, 1H), 2.22 – 2.14 (m, 1H), 2.14 – 2.07 (m, 1H), 2.07 –

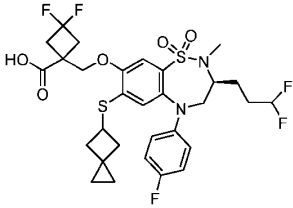
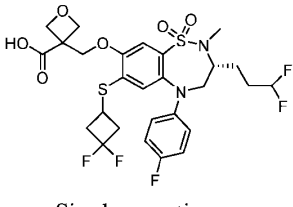
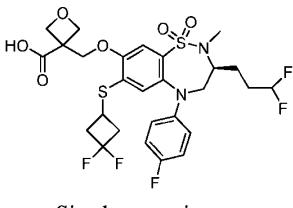
			1.87 (m, 2H), 1.85 – 1.70 (m, 2H), 0.50 – 0.43 (m, 4H) ppm
420	 Single enantiomer	627.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.45 (s, 1H), 7.01 – 6.93 (m, 2H), 6.81 (s, 1H), 6.80 – 6.73 (m, 2H), 6.13 – 5.81 (m, 1H), 5.01 (dd, <i>J</i> = 6.0, 2.4 Hz, 2H), 4.81 (d, <i>J</i> = 6.0 Hz, 2H), 4.51 (s, 2H), 4.07 – 3.84 (m, 3H), 3.57 – 3.40 (m, 1H), 2.64 (s, 3H), 2.55 – 2.45 (m, 1H), 2.44 – 2.36 (m, 1H), 2.22 – 2.14 (m, 1H), 2.14 – 2.07 (m, 1H), 2.06 – 1.87 (m, 2H), 1.85 – 1.70 (m, 2H), 0.50 – 0.40 (m, 4H) ppm
421		491.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.66 (s, 1H), 7.52 (s, 1H), 6.96 (t, <i>J</i> = 8.8 Hz, 2H), 6.74 – 6.70 (m, 2H), 4.22 (s, 2H), 3.88 – 3.82 (m, 1H), 3.64 – 3.50 (m, 2H), 3.37 – 3.33 (m, 1H), 2.81 (s, 3H), 1.36 (s, 6H) ppm
422	 Single enantiomer	595.3	¹ H NMR (400 MHz, d ₆ -DMSO): δ 12.47 (s, 1H), 7.57 (s, 1H), 7.53 (s, 1H), 7.31 – 7.26 (m, 4H), 7.21 – 7.16 (m, 1H), 7.03 (t, <i>J</i> = 8.8 Hz, 2H), 6.66 – 6.65 (m, 2H), 4.22 – 4.20 (m, 2H), 4.11 – 4.01 (m, 1H), 3.85 – 3.82 (m, 1H), 3.35 – 3.31 (m, 1H), 2.73 – 2.65 (m, 2H), 2.61 (s, 3H), 1.96 – 1.92 (m, 1H), 1.83 – 1.80 (m, 1H), 1.25 (s, 6H) ppm
423	 Single enantiomer	595.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.63 (s, 1H), 7.42 (s, 1H), 7.01 (t, <i>J</i> = 8.4 Hz, 2H), 6.81 – 6.78 (m, 2H), 4.21 (m, 2H), 4.09 – 4.05 (m, 1H), 3.86 – 3.85 (m, 1H), 3.51 – 3.50 (m, 1H), 2.75 – 2.69 (m, 5H), 2.34 – 2.24 (m, 3H), 2.00 – 1.94 (m, 1H), 1.75 – 1.70 (m, 1H), 1.36 (s, 6H) ppm.

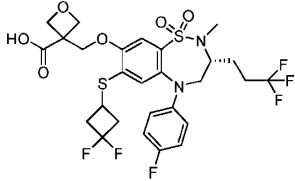
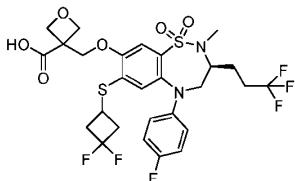
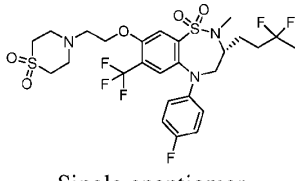
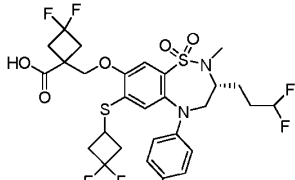
424	 Single enantiomer	595.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.62 (s, 1H), 7.42 (s, 1H), 7.01 (t, J = 8.4 Hz, 2H), 6.81 – 6.78 (m, 2H), 4.21 (m, 2H), 4.09 – 4.05 (m, 1H), 3.86 – 3.85 (m, 1H), 3.51 – 3.50 (m, 1H), 2.76 – 2.68 (m, 5H), 2.34 – 2.21 (m, 3H), 2.00 – 1.95 (m, 1H), 1.75 – 1.68 (m, 1H), 1.36 (s, 6H) ppm.
425	 Single enantiomer	573.2	¹ H NMR (400 MHz, d ₆ -DMSO): δ 8.97 (s, 1H), 8.33 – 8.29 (m, 1H), 7.85 – 7.80 (m, 3H), 7.53 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 5.6 Hz, 1H), 5.10 (s, 1H), 4.56 (d, J = 6.0 Hz, 2H), 4.41 – 4.36 (m, 1H), 4.10 – 4.03 (m, 1H), 3.92 – 3.89 (m, 1H), 3.63 – 3.58 (m, 1H), 3.16 – 3.13 (m, 1H), 3.08 – 2.92 (m, 4H), 2.19 – 2.15 (m, 1H), 1.97 – 1.94 (m, 1H), 1.79 – 1.68 (m, 2H) ppm.
426	 Single enantiomer	611.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.65 (s, 1H), 7.45 (s, 1H), 7.03 – 6.95 (m, 2H), 6.82 – 6.73 (m, 2H), 4.22 (s, 2H), 4.13 – 3.90 (m, 2H), 3.57 – 3.40 (m, 1H), 3.27 – 3.13 (m, 2H), 2.99 (s, 3H), 2.69 (s, 3H), 2.12 – 1.98 (m, 1H), 1.98 – 1.72 (m, 3H), 1.36 (s, 6H) ppm
427	 Single enantiomer	611.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.65 (s, 1H), 7.45 (s, 1H), 7.03 – 6.95 (m, 2H), 6.82 – 6.73 (m, 2H), 4.22 (s, 2H), 4.13 – 3.90 (m, 2H), 3.57 – 3.40 (m, 1H), 3.27 – 3.13 (m, 2H), 2.99 (s, 3H), 2.69 (s, 3H), 2.12 – 1.98 (m, 1H), 1.98 – 1.72 (m, 3H), 1.37 (s, 6H) ppm

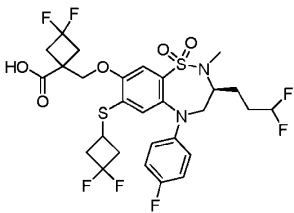
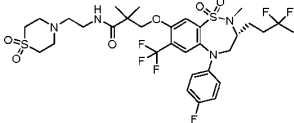
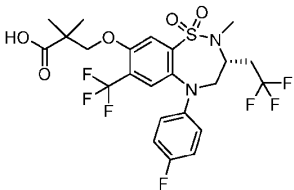
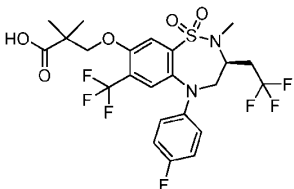
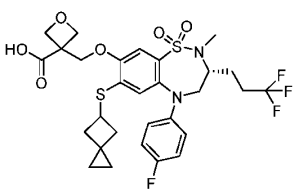
428	 Single enantiomer	534.2	¹ H NMR (400 MHz, d ₆ -DMSO): δ 7.54 (d, J = 10.8 Hz, 2H), 7.04 – 7.00 (m, 2H), 6.70 (s, 2H), 4.70 – 4.67 (m, 1H), 4.20 – 4.01 (m, 4H), 3.60 – 3.51 (m, 3H), 2.57 (s, 3H), 1.71 – 1.70 (m, 2H), 1.24 (s, 6H) ppm
429	 Single enantiomer	585.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.61 (s, 2H), 7.43 (s, 1H), 6.97 (s, 1H), 6.90 (t, J = 8.8 Hz, 2H), 6.60 – 6.56 (m, 2H), 4.19 – 4.16 (m, 4H), 3.73 (s, 3H), 3.54 – 3.46 (m, 1H), 2.99 – 2.76 (m, 2H), 2.67 (m, 3H), 1.33 – 1.31 (m, 6H) ppm.
430	 Single enantiomer	545.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.61 (s, 1H), 7.43 (s, 1H), 6.99 – 6.94 (m, 2H), 6.76 – 6.73 (m, 2H), 4.19 – 4.16 (m, 3H), 4.04 – 4.00 (m, 1H), 3.43 – 3.30 (m, 1H), 2.68 (s, 3H), 1.80 – 1.73 (m, 1H), 1.31 – 1.26 (m, 7H), 0.90 – 0.83 (m, 1H), 0.62 – 0.54 (m, 2H), 0.21 – 0.14 (m, 2H) ppm.
431	 Single diastereomer	549.3	¹ H NMR (400 MHz, d ₆ -DMSO): δ 7.54 (d, J = 12.4 Hz, 2H), 7.03 (t, J = 8.8 Hz, 2H), 6.72 (s, 2H), 4.72 (s, 1H), 4.23 – 4.07 (m, 4H), 3.76 – 3.33 (m, 2H), 2.57 (s, 3H), 1.64 – 1.61 (m, 1H), 1.52 – 1.46 (m, 1H), 1.25 (s, 6H), 1.12 (d, J = 6.0 Hz, 3H) ppm
432	 Single diastereomer	549.3	¹ H NMR (400 MHz, d ₆ -DMSO): δ 7.55 (d, J = 5.6 Hz, 2H), 7.03 – 6.99 (m, 2H), 6.89 – 6.65 (m, 2H), 4.70 (s, 1H), 4.21 – 4.08 (m, 4H), 3.82 – 3.78 (m, 2H), 2.56 (s, 3H), 1.66 – 1.56 (m, 2H), 1.25 (s, 6H), 1.12 (d, J = 6.0 Hz, 3H) ppm

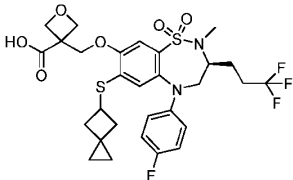
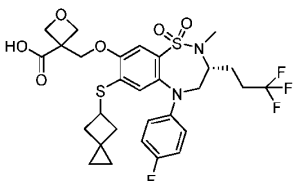
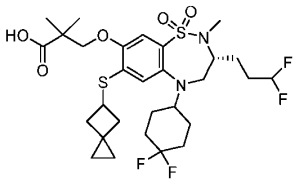
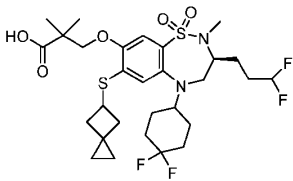
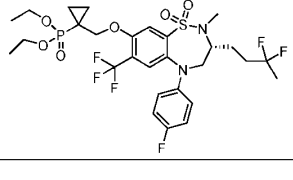
433		623.3	^1H NMR (400 MHz, CD_3OD): δ 7.66 (s, 1H), 7.46 (s, 1H), 6.98 (t, J = 8.8 Hz, 2H), 6.74 – 6.71 (m, 2H), 4.21 (s, 2H), 4.11 – 4.01 (m, 2H), 3.40 – 3.37 (m, 1H), 2.64 (s, 3H), 2.06 – 1.57 (m, 9H), 1.48 – 1.20 (m, 9H) ppm
434	 Single enantiomer	623.3	^1H NMR (400 MHz, CD_3OD): δ 7.65 (s, 1H), 7.46 (s, 1H), 6.98 (t, J = 9.2 Hz, 2H), 6.75 – 6.72 (m, 2H), 4.22 (s, 2H), 4.11 – 4.01 (m, 2H), 3.37 – 3.34 (m, 1H), 2.65 (s, 3H), 2.08 – 1.60 (m, 9H), 1.48 – 1.25 (m, 9H) ppm
435	 Single enantiomer	623.3	^1H NMR (400 MHz, CD_3OD): δ 7.65 (s, 1H), 7.46 (s, 1H), 6.98 (t, J = 8.8 Hz, 2H), 6.75 – 6.72 (m, 2H), 4.22 (s, 2H), 4.09 – 4.01 (m, 2H), 3.37 – 3.34 (m, 1H), 2.65 (s, 3H), 2.06 – 1.61 (m, 9H), 1.48 – 1.25 (m, 9H) ppm
436		575.2	^1H NMR (400 MHz, d_6 -DMSO): δ 7.65 (s, 1H), 7.48 (s, 1H), 6.98 (t, J = 8.8 Hz, 2H), 6.73 – 6.69 (m, 2H), 4.22 (s, 2H), 4.10 – 4.02 (m, 2H), 3.37 – 3.34 (m, 1H), 2.63 (s, 3H), 1.63 – 1.30 (m, 13H), 0.96 – 0.89 (m, 6H) ppm
437	 Single enantiomer	575.2	^1H NMR (400 MHz, CD_3OD): δ 7.65 (s, 1H), 7.47 (s, 1H), 6.98 (t, J = 8.8 Hz, 2H), 6.73 – 6.69 (m, 2H), 4.22 (s, 2H), 4.10 – 4.02 (m, 2H), 3.38 – 3.34 (m, 1H), 2.63 (s, 3H), 1.63 – 1.30 (m, 13H), 0.96 – 0.89 (m, 6H) ppm
438	 Single enantiomer	575.2	^1H NMR (400 MHz, CD_3OD): δ 7.65 (s, 1H), 7.47 (s, 1H), 6.98 (t, J = 8.8 Hz, 2H), 6.73 – 6.69 (m, 2H), 4.22 (s, 2H), 4.10 – 4.02 (m, 2H), 3.37 – 3.34 (m, 1H), 2.63 (s, 3H), 1.66 – 1.32 (m, 13H), 0.96 – 0.89 (m, 6H) ppm

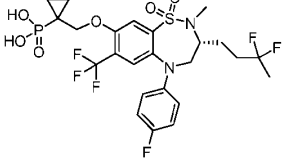
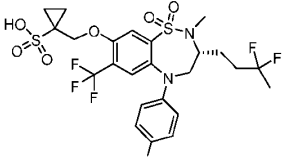
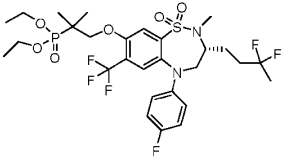
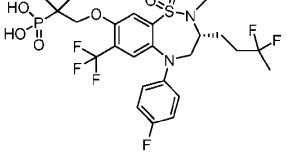
439	 Single enantiomer	660.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.65–7.63 (m, 1H), 7.43 (s, 1H), 7.00 (t, <i>J</i> = 8.8 Hz, 2H), 6.81–6.80 (m, 2H), 4.29 (s, 2H), 4.11–4.05 (m, 1H), 3.92–3.87 (m, 1H), 3.63–3.49 (m, 1H), 3.36–3.33 (m, 1H), 3.21 (s, 2H), 3.19–3.14 (m, 1H), 2.68 (s, 3H), 2.12–1.96 (m, 2H), 1.84–1.81 (m, 2H), 1.39–1.36 (m, 6H) ppm
440	 Single enantiomer	686.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.66–7.63 (m, 1H), 7.43–7.42 (m, 1H), 7.00 (t, <i>J</i> = 8.8 Hz, 2H), 6.82–6.79 (m, 2H), 4.27 (s, 2H), 4.11–4.07 (m, 1H), 3.91–3.86 (m, 1H), 3.53–3.49 (m, 1H), 3.36–3.33 (m, 1H), 3.03–2.96 (m, 1H), 2.68 (s, 3H), 2.12–1.95 (m, 2H), 1.84–1.72 (m, 2H), 1.68–1.59 (m, 3H), 1.39–1.36 (m, 6H), 1.24–1.18 (m, 2H), 1.08–1.03 (m, 2H) ppm
441	 Single enantiomer	653.3	¹ H NMR (400 MHz, CD ₃ OD): δ 7.63 (s, 1H), 7.43 (s, 1H), 6.99 (t, <i>J</i> = 8.8 Hz, 2H), 6.80–6.78 (m, 2H), 4.19 (s, 2H), 4.10–4.06 (m, 1H), 3.91–3.90 (m, 1H), 3.50–3.49 (m, 1H), 3.37–3.35 (m, 2H), 3.29–3.30 (m, 1H), 2.66 (s, 3H), 2.49–2.45 (m, 2H), 2.29 (m, 6H), 2.12–1.96 (m, 2H), 1.84–1.78 (m, 2H), 1.68–1.58 (m, 3H), 1.35 (d, <i>J</i> = 2.4 Hz, 6H) ppm
442	 Single enantiomer	661.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.38 (s, 1H), 6.99–6.90 (m, 2H), 6.80–6.72 (m, 3H), 6.11–5.78 (m, 1H), 4.37 (s, 2H), 4.05–3.80 (m, 3H), 3.57–3.36 (m, 1H), 3.15–2.98 (m, 2H), 2.91–2.77 (m, 2H), 2.61 (s, 3H), 2.52–2.43 (m, 1H), 2.41–2.33 (m, 1H), 2.18–2.11 (m, 1H), 2.11–

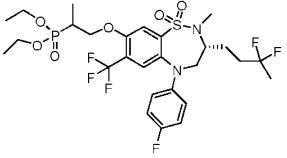
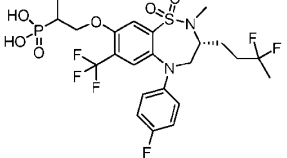
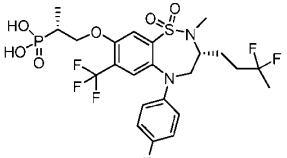
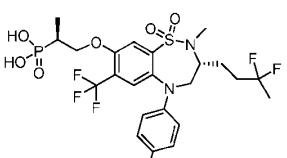
			2.04 (m, 1H), 2.04 – 1.84 (m, 2H), 1.83 – 1.68 (m, 2H), 0.47 – 0.40 (m, 4H) ppm
443	 Single enantiomer	661.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.38 (s, 1H), 6.99 – 6.90 (m, 2H), 6.80 – 6.72 (m, 3H), 6.11 – 5.78 (m, 1H), 4.37 (s, 2H), 4.05 – 3.80 (m, 3H), 3.57 – 3.36 (m, 1H), 3.15 – 2.98 (m, 2H), 2.91 – 2.77 (m, 2H), 2.62 (s, 3H), 2.52 – 2.43 (m, 1H), 2.41 – 2.33 (m, 1H), 2.18 – 2.11 (m, 1H), 2.11 – 2.04 (m, 1H), 2.04 – 1.84 (m, 2H), 1.83 – 1.68 (m, 2H), 0.47 – 0.40 (m, 4H) ppm
444	 Single enantiomer	637.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.47 (s, 1H), 7.01 – 6.93 (m, 2H), 6.85 (s, 1H), 6.81 – 6.74 (m, 2H), 6.11 – 5.79 (m, 1H), 4.98 (dd, <i>J</i> = 6.4, 1.6 Hz, 2H), 4.76 (d, <i>J</i> = 6.0 Hz, 2H), 4.55 (s, 2H), 4.10 – 3.85 (m, 2H), 3.71 – 3.60 (m, 1H), 3.60 – 3.39 (m, 1H), 3.11 – 2.96 (m, 1H), 2.96 – 2.84 (m, 1H), 2.63 (s, 3H), 2.58 – 2.35 (m, 2H), 2.10 – 1.85 (m, 2H), 1.85 – 1.69 (m, 2H) ppm
445	 Single enantiomer	637.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.47 (s, 1H), 7.01 – 6.93 (m, 2H), 6.85 (s, 1H), 6.81 – 6.74 (m, 2H), 6.11 – 5.79 (m, 1H), 4.98 (dd, <i>J</i> = 6.0, 2.0 Hz, 2H), 4.76 (d, <i>J</i> = 6.0 Hz, 2H), 4.54 (s, 2H), 4.10 – 3.85 (m, 2H), 3.71 – 3.60 (m, 1H), 3.60 – 3.39 (m, 1H), 3.11 – 2.96 (m, 1H), 2.96 – 2.84 (m, 1H), 2.63 (s, 3H), 2.58 – 2.35 (m, 2H), 2.10 – 1.85 (m, 2H), 1.84 – 1.69 (m, 2H) ppm

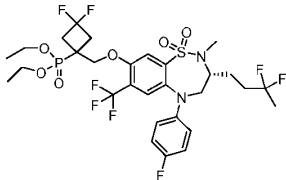
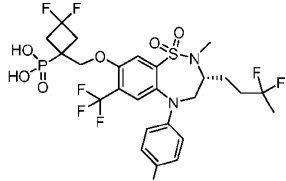
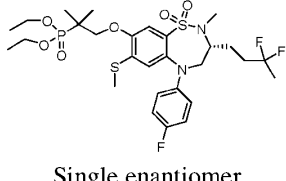
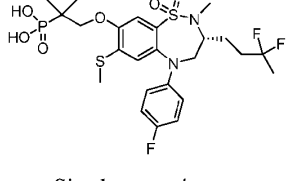
446	 Single enantiomer	655.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.46 (s, 1H), 6.98 (t, J = 8.8 Hz, 2H), 6.88 – 6.74 (m, 3H), 4.98 (dd, J = 6.4, 1.6 Hz, 2H), 4.75 (d, J = 6.0 Hz, 2H), 4.53 (s, 2H), 4.12 – 3.80 (m, 2H), 3.72 – 3.42 (m, 2H), 3.14 – 2.08 (m, 2H), 2.65 (s, 3H), 2.55 – 2.25 (m, 4H), 2.03 – 1.75 (m, 2H) ppm
447	 Single enantiomer	655.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.46 (s, 1H), 6.98 (t, J = 8.8 Hz, 2H), 6.88 – 6.74 (m, 3H), 4.98 (dd, J = 6.0, 0.8 Hz, 2H), 4.75 (d, J = 6.0 Hz, 2H), 4.55 (s, 2H), 4.12 – 3.80 (m, 2H), 3.72 – 3.42 (m, 2H), 3.14 – 2.08 (m, 2H), 2.65 (s, 3H), 2.55 – 2.25 (m, 4H), 2.03 – 1.75 (m, 2H) ppm
448	 Single enantiomer	644.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.73 (s, 1H), 7.43 (s, 1H), 7.03 – 6.97 (m, 2H), 6.82 – 6.79 (m, 2H), 4.38 – 4.28 (m, 2H), 4.11 – 4.07 (m, 1H), 3.90 – 3.85 (m, 1H), 3.63 – 3.43 (m, 1H), 3.20 – 3.17 (m, 4H), 3.15 – 3.10 (m, 4H), 3.09 – 3.06 (m, 2H), 2.68 (s, 3H), 2.10 – 1.96 (m, 2H), 1.84 – 1.78 (m, 2H), 1.68 – 1.58 (m, 3H) ppm
449	 Single enantiomer	671.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.43 (s, 1H), 7.01 – 6.93 (m, 2H), 6.84 (s, 1H), 6.81 – 6.73 (m, 2H), 6.11 – 5.78 (m, 1H), 4.38 (s, 2H), 4.08 – 3.85 (m, 2H), 3.70 – 3.60 (m, 1H), 3.57 – 3.40 (m, 1H), 3.15 – 2.98 (m, 3H), 2.98 – 2.75 (m, 3H), 2.62 (s, 3H), 2.56 – 2.34 (m, 2H), 2.10 – 1.85 (m, 2H), 1.85 – 1.68 (m, 2H) ppm

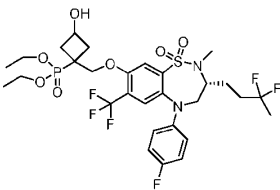
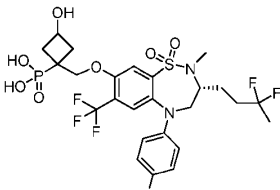
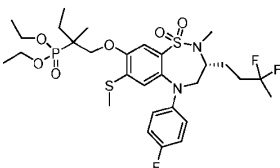
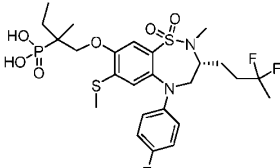
450	 Single enantiomer	671.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.42 (s, 1H), 7.01 – 6.93 (m, 2H), 6.84 (s, 1H), 6.81 – 6.73 (m, 2H), 6.11 – 5.78 (m, 1H), 4.37 (s, 2H), 4.08 – 3.85 (m, 2H), 3.70 – 3.60 (m, 1H), 3.57 – 3.40 (m, 1H), 3.15 – 2.98 (m, 3H), 2.98 – 2.75 (m, 3H), 2.62 (s, 3H), 2.56 – 2.34 (m, 2H), 2.10 – 1.85 (m, 2H), 1.85 – 1.68 (m, 2H) ppm
451	 Single enantiomer	743.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.63 (s, 1H), 7.41 (s, 1H), 6.97 (t, J = 8.8Hz, 2H), 6.81 – 6.78 (m, 2H), 4.21 – 4.16 (m, 2H), 4.08 – 4.05 (m, 1H), 3.87 – 3.80 (m, 1H), 3.53 – 3.47 (m, 4H), 3.34 – 3.31 (m, 2H), 3.29 – 3.30 (m, 1H), 3.00 (s, 8H), 2.70 – 2.62 (m, 5H), 2.09 – 1.91 (m, 2H), 1.80 – 1.74(m, 2H), 1.65 – 1.56 (m, 3H), 1.33 (d, J= 2.8 Hz, 6H) ppm
452	 Single enantiomer	573.1	¹ H NMR (400 MHz, d ₆ -DMSO): δ 12.37 (s, 1H), 7.56 – 7.53 (m, 2H), 7.06 (t, J = 8.8 Hz, 2H), 6.74 (s, 2H), 4.23 – 4.13 (m, 4H), 3.65 – 3.32 (m, 1H), 2.87 – 2.82 (m, 2H), 2.67 (s, 3H), 1.24 (s, 6H) ppm
453	 Single enantiomer	573.1	¹ H NMR (400 MHz, d ₆ -DMSO): δ 12.36 (s, 1H), 7.56 – 7.53 (m, 2H), 7.08 – 7.04 (m, 2H), 6.74 (s, 2H), 4.23 – 4.13 (m, 4H), 3.68 – 3.50 (m, 1H), 2.87 – 2.82 (m, 2H), 2.64 (s, 3H), 1.24 (s, 6H) ppm
454	 Single enantiomer	645.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.42 (s, 1H), 6.96 (t, J = 9.2 Hz, 2H), 6.85 – 6.72 (m, 3H), 4.98 (dd, J = 6.0, 1.2 Hz, 2H), 4.78 (d, J = 6.0 Hz, 2H), 4.52 (s, 2H), 4.08–3.72 (m, 3H), 3.66 – 3.43 (m, 1H), 2.64 (s, 3H), 2.52 – 2.24 (m, 4H), 2.17 – 2.01 (m,

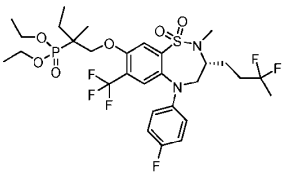
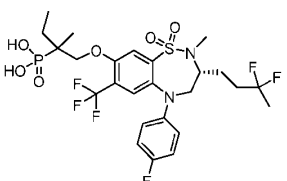
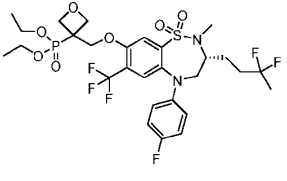
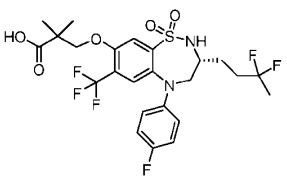
			2H), 1.98 – 1.76 (m, 2H), 0.48 – 0.37 (m, 4H) ppm
455	 Single enantiomer	645.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.42 (s, 1H), 6.96 (t, <i>J</i> = 8.8 Hz, 2H), 6.85 – 6.72 (m, 3H), 4.98 (dd, <i>J</i> = 6.0, 0.8 Hz, 2H), 4.78 (d, <i>J</i> = 6.0 Hz, 2H), 4.52 (s, 2H), 4.11 – 3.80 (m, 3H), 3.67 – 3.52 (m, 1H), 2.64 (s, 3H), 2.52–2.25 (m, 4H), 2.20 – 2.02 (m, 2H), 1.99 – 1.77 (m, 2H), 0.48 – 0.38 (m, 4H) ppm
456	 Single enantiomer	559.2 [M-H ₂ O+1]	¹ H NMR (400 MHz, CD ₃ OD): δ 7.66 (s, 1H), 7.43 (s, 1H), 6.94 (t, <i>J</i> = 8.8 Hz, 2H), 6.71 – 6.68 (m, 2H), 4.20 – 4.16 (m, 2H), 4.08 – 4.04 (m, 1H), 3.93 – 3.85 (m, 1H), 3.34 – 3.32 (m, 1H), 2.61 (s, 3H), 1.70 – 1.53 (m, 4H), 1.29 (s, 6H), 1.22 (s, 6H) ppm
457	 Single enantiomer	637.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.21 (s, 1H), 6.75 (s, 1H), 6.11 – 5.81 (m, 1H), 4.10 – 4.02 (m, 1H), 4.01 (s, 2H), 3.82 – 3.59 (m, 1H), 3.48 – 3.47 (m, 1H), 3.25 – 3.06 (m, 1H), 2.69 – 2.40 (m, 5H), 2.43 – 1.57 (m, 15H), 1.33 (d, <i>J</i> = 1.2 Hz, 6H), 0.56 – 0.47 (m, 4H) ppm
458	 Single enantiomer	637.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.21 (s, 1H), 6.75 (s, 1H), 6.11 – 5.81 (m, 1H), 4.10 – 4.02 (m, 1H), 4.01 (s, 2H), 3.97 – 3.61 (m, 1H), 3.48 – 3.36 (m, 1H), 3.25 – 3.06 (m, 1H), 2.69 – 2.40 (m, 5H), 2.26 – 1.66 (m, 15H), 1.33 (d, <i>J</i> = 1.6 Hz, 6H), 0.56 – 0.42 (m, 4H) ppm
459		673.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.61 (s, 1H), 7.41 (s, 1H), 7.02 – 6.94 (m, 2H), 6.84 – 6.75 (m, 2H), 4.32 – 4.21 (m, 2H), 4.20 – 4.12 (m, 4H), 4.11 –

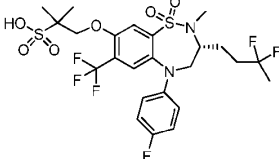
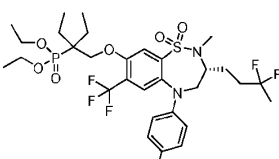
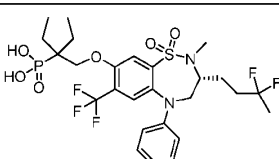
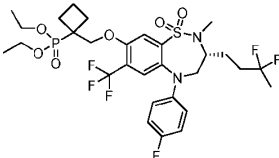
	Single enantiomer		4.00 (m, 1H), 3.95 – 3.82 (m, 1H), 3.62 – 3.40 (m, 1H), 2.66 (s, 3H), 2.15 – 1.89 (m, 2H), 1.87 – 1.71 (m, 2H), 1.61 (t, $J = 18.6$ Hz, 3H), 1.33 (td, $J = 7.2, 1.6$ Hz, 6H), 1.26 – 1.18 (m, 2H), 1.12 – 1.04 (m, 2H) ppm
460	 Single enantiomer	634.1 [M + 18] ⁺	¹ H NMR (400 MHz, CD ₃ OD): δ 7.61 (s, 1H), 7.41 (s, 1H), 7.01 – 6.93 (m, 2H), 6.82 – 6.73 (m, 2H), 4.35 (d, $J = 10.4$ Hz, 2H), 4.14 – 4.00 (m, 1H), 3.97 – 3.82 (m, 1H), 3.60 – 3.40 (m, 1H), 2.65 (s, 3H), 2.15 – 1.88 (m, 2H), 1.85 – 1.73 (m, 2H), 1.61 (t, $J = 18.4$ Hz, 3H), 1.17 – 1.08 (m, 2H), 1.07 – 0.98 (m, 2H) ppm
461	 Single enantiomer	617.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.68 (s, 1H), 7.41 (s, 1H), 7.01 – 6.93 (m, 2H), 6.80 – 6.73 (m, 2H), 4.68 – 4.59 (m, 2H), 4.13 – 4.00 (m, 1H), 3.95 – 3.83 (m, 1H), 3.57 – 3.39 (m, 1H), 2.64 (s, 3H), 2.15 – 1.87 (m, 2H), 1.85 – 1.73 (m, 2H), 1.61 (t, $J = 18.4$ Hz, 3H), 1.31 – 1.25 (m, 2H), 1.10 – 1.05 (m, 2H) ppm
462	 Single enantiomer	675.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.60 (s, 1H), 7.43 (s, 1H), 7.01 – 6.95 (m, 2H), 6.81 – 6.78 (m, 2H), 4.22 – 4.14 (m, 6H), 4.06 – 4.03 (m, 1H), 3.88 – 3.84 (m, 1H), 3.54 – 3.47 (m, 1H), 2.67 (s, 3H), 2.10 – 1.94 (m, 2H), 1.84 – 1.75 (m, 2H), 1.61 (t, $J = 18.4$ Hz, 3H), 1.37 – 1.28 (m, 12H) ppm
463	 Single enantiomer	636.1 [M + 18] ⁺	¹ H NMR (400 MHz, CD ₃ OD): δ 7.60 (s, 1H), 7.44 (s, 1H), 6.98 (t, $J = 8.8$ Hz, 2H), 6.80 – 6.76 (m, 2H), 4.21 (d, $J = 6.0$ Hz, 2H), 4.12 – 4.04 (m, 1H), 3.94 – 3.85 (m, 1H), 3.59 – 3.45 (m, 1H), 2.65 (s, 3H), 2.10 – 1.92 (m,

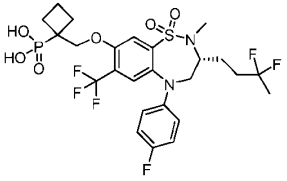
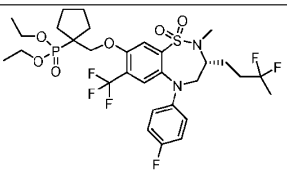
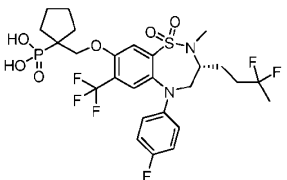
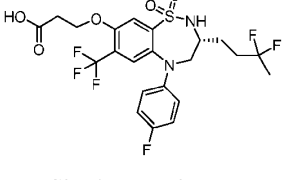
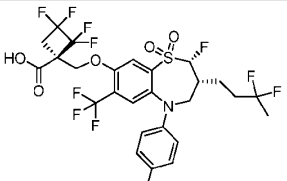
			2H), 1.82 – 1.75 (m, 2H), 1.61 (t, J = 18.4 Hz, 3H), 1.35 (dd, J = 16.0 Hz, 4.0Hz, 6H) ppm
464	 A mixture of diastereomers	661.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.62 (s, 1H), 7.42 (s, 1H), 7.01 – 6.95 (m, 2H), 6.82 – 6.79 (m, 2H), 4.47 – 4.40 (m, 1H), 4.24 – 4.19 (m, 5H), 4.09 – 4.05 (m, 1H), 3.88 – 3.85 (m, 1H), 3.54 – 3.47 (m, 1H), 2.67 (s, 3H), 2.57 – 2.47 (m, 1H), 2.10 – 1.94 (m, 2H), 1.83 – 1.76 (m, 2H), 1.61 (t, J = 18.4 Hz, 3H), 1.40 – 1.33 (m, 9H) ppm
465	 A mixture of diastereomers	622.1 [M + 18] ⁺	¹ H NMR (400 MHz, CD ₃ OD): δ 7.63 (s, 1H), 7.43 (s, 1H), 6.97 (m, J = 8.8 Hz, 2H), 6.79 – 6.76 (m, 2H), 4.60 – 4.52 (m, 1H), 4.08 – 4.05 (m, 2H), 3.89 – 3.85 (m, 1H), 3.50 – 3.45 (m, 1H), 2.65 (s, 3H), 2.36 – 2.31 (m, 1H), 2.10 – 1.93 (m, 2H), 1.82 – 1.78 (m, 2H), 1.61 (t, J = 18.4 Hz, 3H), 1.37 – 1.28 (m, 3H) ppm
466	 Single diastereomer	622.1 [M + 18] ⁺	¹ H NMR (400 MHz, CD ₃ OD): δ 7.62 (s, 1H), 7.43 (s, 1H), 6.98 (t, J = 9.2 Hz, 2H), 6.80 – 6.77 (m, 2H), 4.55 – 4.50 (m, 1H), 4.12 – 4.06 (m, 2H), 3.94 – 3.85 (m, 1H), 3.58 – 3.46 (m, 1H), 2.66 (s, 3H), 2.42 – 2.32 (m, 1H), 2.10 – 1.93 (m, 2H), 1.82 – 1.74 (m, 2H), 1.61 (t, J = 18.8 Hz, 3H), 1.40 – 1.29 (m, 3H) ppm
467	 Single diastereomer	622.1 [M + 18] ⁺	¹ H NMR (400 MHz, CD ₃ OD): δ 7.63 (s, 1H), 7.43 (s, 1H), 6.97 (t, J = 9.2 Hz, 2H), 6.79 – 6.76 (m, 2H), 4.59 – 4.51 (m, 1H), 4.11 – 4.02 (m, 2H), 3.94 – 3.86 (m, 1H), 3.55 – 3.43 (m, 1H), 2.65 (s, 3H), 2.42 – 2.30 (m, 1H), 2.10 – 1.92 (m, 2H), 1.82 – 1.79

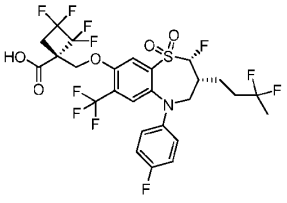
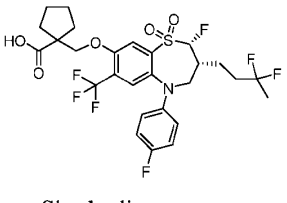
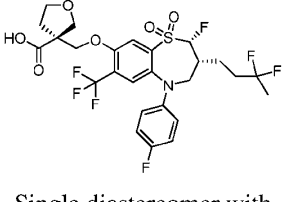
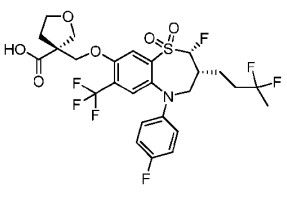
			(m, 2H), 1.61 (t, J = 18.4 Hz, 3H), 1.37 – 1.29 (m, 3H) ppm
468	 Single enantiomer	723.2	¹ H NMR (400 MHz, CDCl ₃): δ 7.57 (s, 1H), 7.37 (s, 1H), 7.01 – 6.95 (m, 2H), 6.78 – 6.72 (m, 2H), 4.35 – 4.31 (m, 2H), 4.26 – 4.17 (m, 4H), 3.97 – 3.82 (m, 2H), 3.56 – 3.43 (m, 1H), 3.14 – 2.98 (m, 2H), 2.97 – 2.85 (m, 2H), 2.70 (s, 3H), 2.13 – 1.91 (m, 2H), 1.90 – 1.71 (m, 2H), 1.64 (t, J = 16.0 Hz, 3H), 1.39 – 1.35 (m, 6H) ppm
469	 Single enantiomer	684.1 [M + 18] ⁺	¹ H NMR (400 MHz, CD ₃ OD): δ 7.67 (s, 1H), 7.44 (s, 1H), 6.99 (t, J = 8.4 Hz, 2H), 6.81 (m, 2H), 4.44 (d, J = 8.4 Hz, 2H), 4.10 – 3.89 (m, 2H), 3.53 – 3.46 (m, 1H), 3.04 – 2.90 (m, 4H), 2.66 (s, 3H), 2.10 – 1.93 (m, 2H), 1.82 – 1.79 (m, 2H), 1.61 (t, J = 16.0 Hz, 3H) ppm.
470	 Single enantiomer	653.7	¹ H NMR (400 MHz, CD ₃ OD): δ 7.33 (s, 1H), 6.98 – 6.90 (m, 3H), 6.72 – 6.69 (m, 2H), 4.24 – 3.93 (m, 8H), 3.48 – 3.34 (m, 1H), 2.58 (s, 3H), 2.32 (s, 3H), 2.10 – 1.94 (m, 2H), 1.81 – 1.77 (m, 2H), 1.62 (t, J = 18.8 Hz, 3H), 1.39 – 1.34 (m, 12H) ppm
471	 Single enantiomer	597.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.33 (s, 1H), 6.98 – 6.90 (m, 3H), 6.69 (s, 2H), 4.14 (d, J = 6.4 Hz, 2H), 4.04 – 3.95 (m, 2H), 3.48 – 3.35 (m, 1H), 2.57 (s, 3H), 2.32 (s, 3H), 2.10 – 1.94 (m, 2H), 1.79 – 1.77 (m, 2H), 1.62 (t, J = 18.4 Hz, 3H), 1.38 (dd, J = 16.0 Hz, 4.0 Hz, 6H) ppm

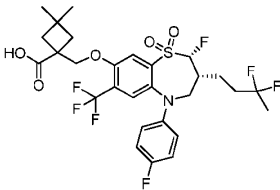
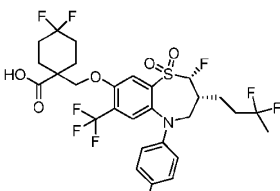
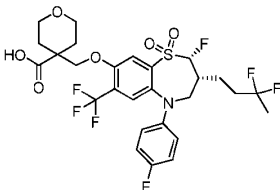
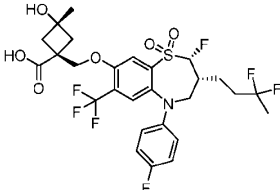
472	 A mixture of two diastereomers	703.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.67 (s, 1H), 7.44 (s, 1H), 6.98 (t, J = 8.4 Hz, 2H), 6.82 (m, 2H), 4.59 – 4.54 (m, 1H), 4.36 (d, J = 12.0 Hz, 2H), 4.23 – 4.17 (m, 4H), 4.09 – 4.06 (m, 1H), 3.89 – 3.85 (m, 1H), 2.67 (s, 3H), 2.60 – 2.44 (m, 4H), 2.21 – 1.94 (m, 2H), 1.82 – 1.76 (m, 2H), 1.61 (t, J = 20.0 Hz, 3H), 1.35 (t, J = 4.0 Hz, 6H) ppm
473	 A mixture of two diastereomers	647.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.70 – 7.68 (m, 1H), 7.46 (s, 1H), 6.99 – 6.95 (m, 2H), 6.82 – 6.71 (m, 2H), 4.54 – 4.41 (m, 1H), 4.37 – 4.24 (m, 2H), 4.10 – 3.90 (m, 2H), 3.48 – 3.46 (m, 1H), 2.63 (s, 3H), 2.56 – 2.36 (m, 4H), 2.08 – 1.94 (m, 2H), 1.82 – 1.76 (m, 2H), 1.61 (t, J = 20.0 Hz, 3H) ppm
474	 A mixture of two diastereomers	667.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.35 (s, 1H), 6.97 – 6.90 (m, 3H), 6.73 – 6.67 (m, 2H), 4.25 – 3.94 (m, 8H), 3.48 – 3.34 (m, 1H), 2.58 (s, 3H), 2.31 (s, 3H), 2.08 – 1.77 (m, 6H), 1.62 (t, J = 18.4 Hz, 3H), 1.36 – 1.30 (m, 9H), 1.03 (t, J = 7.6 Hz, 3H) ppm
475	 A mixture of two diastereomers	611.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.35 (s, 1H), 7.00 – 6.90 (m, 3H), 6.71 – 6.67 (m, 2H), 4.30 – 4.25 (m, 1H), 4.14 – 3.95 (m, 3H), 3.42 – 3.33 (m, 1H), 2.57 (s, 3H), 2.32 (s, 3H), 2.10 – 1.77 (m, 6H), 1.62 (t, J = 18.4 Hz, 3H), 1.35 (dd, J = 16.0, 3.2 Hz, 3H), 1.09 – 1.04 (m, 3H) ppm

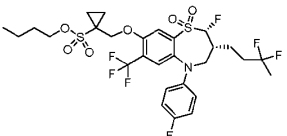
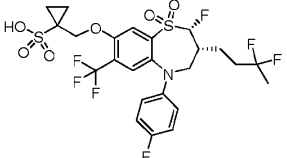
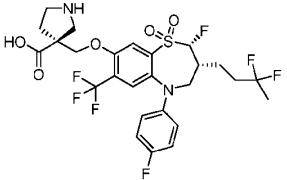
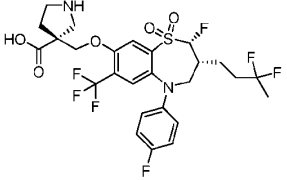
476	 A mixture of two diastereomers	689.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.62 (s, 1H), 7.43 (s, 1H), 6.98 (t, J = 8.8 Hz, 2H), 6.82 – 6.76 (m, 2H), 4.30 (t, J = 9.2 Hz, 1H), 4.21 – 4.10 (m, 6H), 3.93 – 3.84 (m, 1H), 3.56 – 3.46 (m, 1H), 2.67 (s, 3H), 2.08 – 1.75 (m, 5H), 1.61 (t, J = 18.4 Hz, 3H), 1.36 – 1.28 (m, 10H), 1.02 (t, J = 7.6 Hz, 3H) ppm
477	 A mixture of two diastereomers	633.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.62 (s, 1H), 7.44 (s, 1H), 7.00 – 6.95 (m, 2H), 6.80 – 6.75 (m, 2H), 4.37 – 4.32 (m, 1H), 4.19 – 4.05 (m, 2H), 3.96 – 3.85 (m, 1H), 2.65 (s, 3H), 2.08 – 1.75 (m, 6H), 1.61 (t, J = 18.4 Hz, 3H), 1.32 (dd, J = 16.4, 3.4 Hz, 3H), 1.07 – 1.02 (m, 3H) ppm
478	 Single enantiomer	689.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.69 (s, 1H), 7.45 (s, 1H), 6.99 (t, J = 8.8 Hz, 2H), 6.83 – 6.82 (m, 2H), 4.95 – 4.93 (m, 2H), 4.86 – 4.80 (m, 2H), 4.52 (d, J = 10.8 Hz, 2H), 4.29 – 4.21 (m, 4H), 4.10 – 4.06 (m, 1H), 3.89 – 3.88 (m, 1H), 3.53 – 3.47 (m, 1H), 2.67 (s, 3H), 2.10 – 1.94 (m, 2H), 1.82 – 1.78 (m, 2H), 1.61 (t, J = 18.4 Hz, 3H), 1.37 (t, J = 7.2 Hz, 6H) ppm.
479	 Single enantiomer	569.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.66 (s, 1H), 7.45 (s, 1H), 6.91 – 6.93 (m, 2H), 6.73 – 6.70 (m, 2H), 4.00 – 4.32 (m, 1H), 4.18 (s, 2H), 3.58 – 3.52 (m, 1H), 3.05 (m, 1H), 2.21 – 2.14 (m, 1H), 2.04 – 1.96 (m, 1H), 1.94 – 1.77 (m, 1H), 1.65 – 1.56 (m, 4H), 1.33 (s, 6H) ppm.

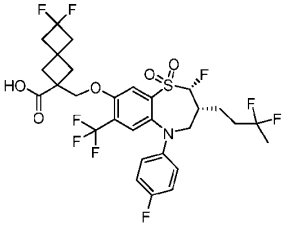
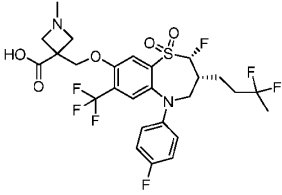
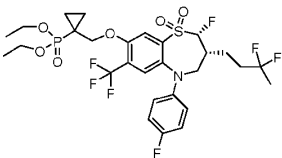
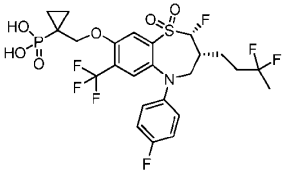
480	 Single enantiomer	619.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.62 (s, 1H), 7.44 (s, 1H), 6.97 (t, J = 8.8 Hz, 1H), 6.82–6.70 (m, 1H), 4.34 (s, 2H), 4.20 – 3.80 (m, 2H), 3.60 – 3.36 (m, 1H), 2.64 (s, 3H), 2.15 – 1.90 (m, 2H), 1.87 – 1.70 (m, 2H), 1.61 (t, J = 18.4 Hz, 3H), 1.48 (s, 3H), 1.46 (s, 3H), ppm
481	 Single enantiomer	703.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.64 (s, 1H), 7.43 (s, 1H), 6.98 (t, J = 8.8 Hz, 2H), 6.82 – 6.77 (m, 2H), 4.26 (d, J = 13.2 Hz, 2H), 4.20 – 4.10 (m, 4H), 3.90 – 3.86 (m, 1H), 3.58 – 3.46 (m, 1H), 2.67 (s, 3H), 2.08 – 1.80 (m, 5H), 1.61 (t, J = 18.4 Hz, 3H), 1.36 – 1.29 (m, 10H), 1.06 – 1.02 (m, 6H) ppm
482	 Single enantiomer	647.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.64 (s, 1H), 7.44 (s, 1H), 7.00 – 6.94 (m, 2H), 6.80 – 6.77 (m, 2H), 4.29 (d, J = 7.6 Hz, 2H), 4.10 – 4.06 (m, 1H), 3.94 – 3.83 (m, 1H), 3.52 – 3.45 (m, 1H), 2.66 (s, 3H), 2.10 – 1.74 (m, 8H), 1.61 (t, J = 18.4 Hz, 3H), 1.08 – 1.03 (m, 6H) ppm
483	 Single enantiomer	687.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.63 (s, 1H), 7.45 (s, 1H), 6.98 (t, J = 8.8 Hz, 2H), 6.81 – 6.78 (m, 2H), 4.30 (d, J = 10.4 Hz, 2H), 4.23 – 4.16 (m, 4H), 4.10 – 4.07 (m, 2H), 3.56 – 3.45 (m, 1H), 2.66 (s, 3H), 2.55 – 2.31 (m, 4H), 2.18 – 1.93 (m, 4H), 1.82 – 1.75 (m, 2H), 1.61 (t, J = 18.4 Hz, 3H), 1.36 (t, J = 7.2 Hz, 6H) ppm.

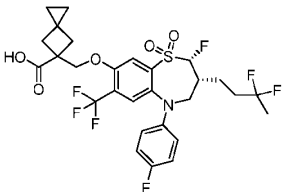
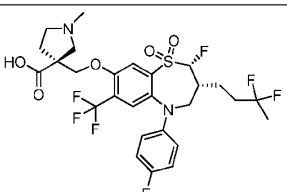
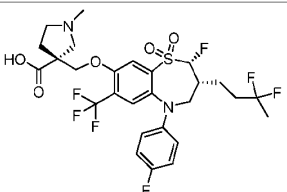
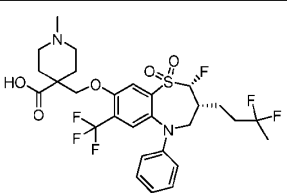
484	 Single enantiomer	631.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.64 (s, 1H), 7.47 (s, 1H), 6.98 (t, J = 8.8 Hz, 2H), 6.81 – 6.78 (m, 2H), 4.25 (d, J = 5.6 Hz, 2H), 4.10 – 3.91 (m, 2H), 3.56 – 3.46 (m, 1H), 2.64 (s, 3H), 2.48 – 2.40 (m, 4H), 2.10 – 1.93 (m, 4H), 1.82 – 1.77 (m, 2H), 1.61 (t, J = 18.8 Hz, 3H) ppm
485	 Single enantiomer	701.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.62 (s, 1H), 7.43 (s, 1H), 6.98 (t, J = 8.8 Hz, 2H), 6.79 (s, 2H), 4.22 – 4.14 (m, 6H), 4.10 – 3.38 (m, 3H), 2.66 (s, 3H), 2.15 – 1.75 (m, 12H), 1.61 (t, J = 18.4 Hz, 3H), 1.34 (t, J = 7.2 Hz, 6H) ppm
486	 Single enantiomer	645.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.62 (s, 1H), 7.44 (s, 1H), 6.97 (t, J = 8.8 Hz, 2H), 6.78 – 6.77 (m, 2H), 4.27 (d, J = 7.6 Hz, 2H), 4.12 – 3.47 (m, 3H), 2.64 (s, 3H), 2.18 – 1.75 (m, 12H), 1.61 (t, J = 18.4 Hz, 3H) ppm
487	 Single enantiomer	541.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.71 (s, 1H), 7.43 (s, 1H), 6.94 (t, J = 8.4 Hz, 2H), 6.72 – 6.68 (m, 2H), 4.43 – 4.36 (m, 3H), 3.58 – 3.52 (m, 1H), 3.13 – 2.99 (m, 1H), 2.71 (t, J = 6.4 Hz, 2H), 2.22 – 1.96 (m, 2H), 1.85 – 1.76 (m, 1H), 1.68 – 1.65 (m, 1H), 1.61 (t, J = 18.4 Hz, 3H) ppm
488	 Single diastereomer with arbitrarily assigned stereochemistry	668.1 [M - 1] ⁺	¹ H NMR (300 MHz, CD ₃ OD): δ 7.82 (s, 1H), 7.56 (s, 1H), 7.04 – 6.91 (m, 2H), 6.79 – 6.66 (m, 2H), 5.70 (d, J = 45.0 Hz, 1H), 4.85 – 4.77 (m, 1H), 4.52 (d, J = 9.3 Hz, 1H), 4.19 (d, J = 15.9 Hz, 1H), 3.40 – 3.32 (m, 1H), 3.29 – 3.22 (m, 1H), 2.99 – 2.82 (m, 1H), 2.82 – 2.59 (m, 1H), 2.25 –

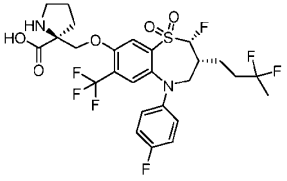
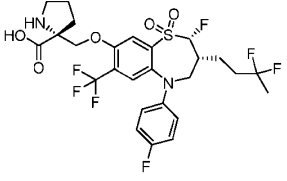
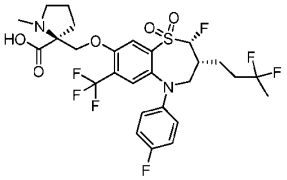
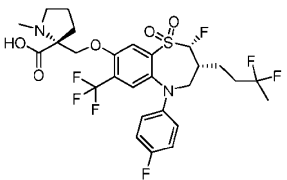
			2.00 (m, 2H), 1.83 – 1.52 (m, 5H) ppm
489	 Single diastereomer with arbitrarily assigned stereochemistry	668.1 [M - 1] ⁻	¹ H NMR (300 MHz, CD ₃ OD): δ 7.82 (s, 1H), 7.56 (s, 1H), 7.04 – 6.91 (m, 2H), 6.80 – 6.67 (m, 2H), 5.70 (d, J = 45.0 Hz, 1H), 4.80 (d, J = 9.3 Hz, 1H), 4.55 (d, J = 9.0 Hz, 1H), 4.19 (d, J = 15.6 Hz, 1H), 3.42 – 3.33 (m, 1H), 3.29 – 3.21 (m, 1H), 3.00 – 2.83 (m, 1H), 2.82 – 2.59 (m, 1H), 2.24 – 2.00 (m, 2H), 1.83 – 1.53 (m, 5H) ppm
490	 Single diastereomer	610.1 [M - 1] ⁻	¹ H NMR (300 MHz, CD ₃ OD): δ 7.80 (s, 1H), 7.57 (s, 1H), 7.05 – 6.92 (m, 2H), 6.85 – 6.59 (m, 2H), 5.70 (d, J = 45.0 Hz, 1H), 4.38 – 4.28 (m, 2H), 4.21 (d, J = 15.3 Hz, 1H), 3.31 – 3.25 (m, 1H), 2.86 – 2.59 (m, 1H), 2.29 – 2.01 (m, 4H), 1.93 – 1.55 (m, 11H) ppm
491	 Single diastereomer with arbitrarily assigned stereochemistry	614.0	¹ H NMR (300 MHz, CD ₃ OD): δ 7.83 (s, 1H), 7.57 (s, 1H), 7.01 – 6.96 (m, 2H), 6.74 – 6.70 (m, 2H), 5.70 (d, J = 45.3 Hz, 1H), 4.51 – 4.48 (m, 1H), 4.41 – 4.38 (m, 1H), 4.23 – 4.16 (m, 2H), 3.99 – 3.92 (m, 3H), 3.32 – 3.26 (m, 1H), 2.80 – 2.65 (m, 1H), 2.47 – 2.41 (m, 1H), 2.19 – 2.10 (m, 3H), 1.78 – 1.65 (m, 5H) ppm
492	 Single diastereomer with arbitrarily assigned stereochemistry	614.0	¹ H NMR (300 MHz, CD ₃ OD): δ 7.83 (s, 1H), 7.58 (s, 1H), 7.02 – 6.96 (m, 2H), 6.75 – 6.71 (m, 2H), 5.71 (d, J = 45.3 Hz, 1H), 4.49 – 4.42 (m, 2H), 4.24 – 4.17 (m, 2H), 3.99 – 3.93 (m, 3H), 3.33 – 3.27 (m, 1H), 2.83 – 2.62 (m, 1H), 2.50 – 2.41 (m, 1H), 2.19 – 2.10 (m, 3H), 1.79 – 1.66 (m, 5H) ppm

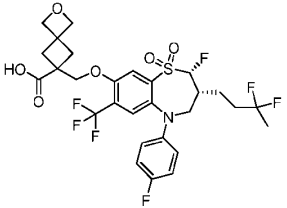
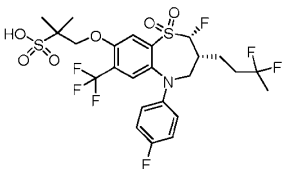
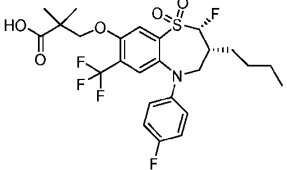
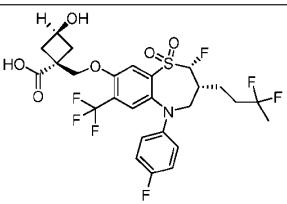
493	 Single diastereomer	624.2 [M - 1] ⁺	¹ H NMR (300 MHz, CDCl ₃): δ 7.74 (s, 1H), 7.50 (s, 1H), 7.00 – 6.95 (m, 2H), 6.67 – 6.63 (m, 2H), 5.31 (d, J = 45.9 Hz, 1H), 4.41 (s, 2H), 4.06 (d, J = 15.6 Hz, 1H), 3.37 – 3.28 (m, 1H), 2.84 – 2.73 (m, 1H), 2.46 (d, J = 13.2 Hz, 2H), 2.11 – 1.97 (m, 4H), 1.78 – 1.62 (m, 5H), 1.26 – 1.23 (m, 6H) ppm
494	 Single diastereomer	660.2 [M - 1] ⁺	¹ H NMR (300 MHz, CDCl ₃): δ 7.68 (s, 1H), 7.48 (s, 1H), 7.00 – 6.93 (m, 2H), 6.68 – 6.64 (m, 2H), 5.31 (d, J = 45.9 Hz, 1H), 4.32 – 4.18 (m, 2H), 4.06 (d, J = 15.9 Hz, 1H), 3.31 (dd, J = 15.9, 11.4 Hz, 1H), 2.83 – 2.74 (m, 1H), 2.49 – 2.37 (m, 2H), 2.14 – 1.96 (m, 6H), 1.83 – 1.62 (m, 7H) ppm
495	 Single diastereomer	628.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.79 (s, 1H), 7.57 (s, 1H), 7.02 – 6.96 (m, 2H), 6.75 – 6.70 (m, 2H), 5.71 (d, J = 45.3 Hz, 1H), 4.36 – 4.29 (m, 2H), 4.23 – 4.18 (m, 1H), 3.91 – 3.87 (m, 2H), 3.73 – 3.66 (m, 2H), 3.33 – 3.27 (m, 1H), 2.88 – 2.62 (m, 1H), 2.22 – 2.01 (m, 4H), 1.85 – 1.59 (m, 7H) ppm
496	 Single diastereomer	626.2 [M - 1] ⁺	¹ H NMR (300 MHz, CDCl ₃): δ 7.78 (s, 1H), 7.53 (s, 1H), 7.01–6.93 (m, 2H), 6.69–6.65 (m, 2H), 5.32 (d, J = 45.9 Hz, 1H), 4.37 (s, 2H), 4.07 (d, J = 15.6 Hz, 1H), 3.38 – 3.29 (m, 1H), 3.15–3.11 (m, 1H), 2.84 – 2.81 (m, 1H), 2.79 – 2.55 (m, 4H), 2.02 – 2.02 (m, 2H), 1.97 – 1.74 (m, 2H), 1.68–1.62 (m, 3H), 1.49 (s, 3H) ppm

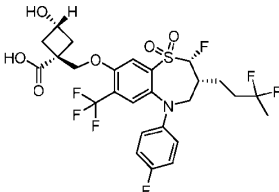
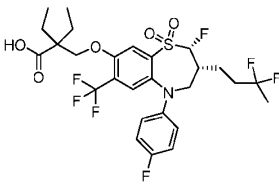
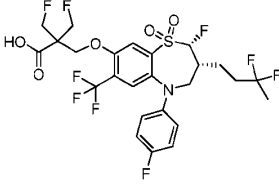
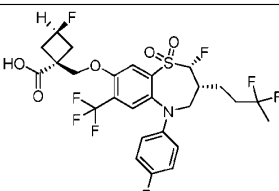
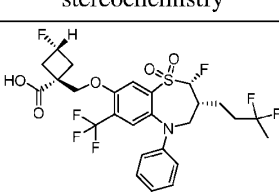
497	 Single diastereomer	676.3	¹ H NMR (400 MHz, CDCl ₃): δ 7.71 (s, 1H), 7.50 (s, 1H), 7.03 – 6.90 (m, 2H), 6.71 – 6.61 (m, 2H), 5.30 (d, J = 46.0 Hz, 1H), 4.58 (d, J = 10.4 Hz, 1H), 4.51 (d, J = 10.4 Hz, 1H), 4.31 (t, J = 6.6 Hz, 2H), 4.05 (d, J = 15.6 Hz, 1H), 3.31 (dd, J = 15.8, 11.2 Hz, 1H), 2.89 – 2.52 (m, 1H), 2.15 – 1.90 (m, 2H), 1.79 – 1.71 (m, 4H), 1.71 – 1.60 (m, 5H), 1.52 – 1.35 (m, 2H), 1.36 – 1.29 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H) ppm
498	 Single diastereomer	620.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.83 (s, 1H), 7.54 (s, 1H), 7.05 – 6.90 (m, 2H), 6.76 – 6.65 (m, 2H), 5.67 (d, J = 45.2 Hz, 1H), 4.74 – 4.60 (m, 2H), 4.17 (d, J = 14.8 Hz, 1H), 3.30 – 3.25 (m, 1H), 2.82 – 2.56 (m, 1H), 2.25 – 2.00 (m, 2H), 1.85 – 1.50 (m, 5H), 1.35 – 1.23 (m, 2H), 1.15 – 1.03 (m, 2H) ppm
499	 Single diastereomer with arbitrarily assigned stereochemistry	613.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.85 (s, 1H), 7.56 (s, 1H), 6.97 (t, J = 8.8 Hz, 2H), 6.74 – 6.67 (m, 2H), 5.68 (d, J = 45.2 Hz, 1H), 4.62 (d, J = 9.2 Hz, 1H), 4.36 (d, J = 8.8 Hz, 1H), 4.19 (d, J = 16 Hz, 1H), 3.88 (d, J = 11.6 Hz, 1H), 3.55 – 3.46 (m, 1H), 3.45 – 3.36 (m, 1H), 3.30 – 3.23 (m, 2H), 2.79 – 2.61 (m, 1H), 2.42 – 2.31 (m, 1H), 2.29 – 2.17 (m, 1H), 2.19 – 2.02 (m, 3H), 1.80 – 1.56 (m, 5H) ppm
500		613.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.85 (s, 1H), 7.56 (s, 1H), 6.97 (t, J = 8.4 Hz, 2H), 6.74 – 6.68 (m, 2H), 5.68 (d, J = 45.2 Hz, 1H), 4.62 (d, J = 9.2 Hz, 1H), 4.36 (d, J = 9.2 Hz, 1H), 4.19 (d, J = 15.6 Hz, 1H), 3.88 (d, J = 11.6

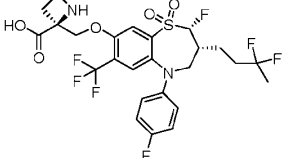
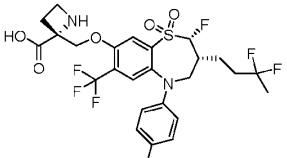
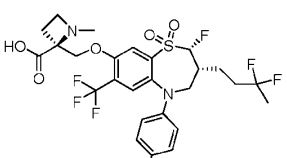
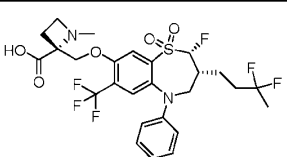
	Single diastereomer with arbitrarily assigned stereochemistry		Hz, 1H), 3.54 – 3.45 (m, 1H), 3.44 – 3.34 (m, 1H), 3.30 – 3.20 (m, 2H), 2.79 – 2.60 (m, 1H), 2.42 – 2.31 (m, 1H), 2.30 – 2.03 (m, 3H), 1.81 – 1.55 (m, 5H) ppm
501	 Single enantiomer	674.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.82 (s, 1H), 7.58 (s, 1H), 7.06 – 6.92 (m, 2H), 6.77 – 6.67 (m, 2H), 5.71 (d, J = 45.3 Hz, 1H), 4.48 – 4.34 (m, 2H), 4.21 (d, J = 14.4 Hz, 1H), 3.27 (s, 1H), 2.85 – 2.56 (m, 7H), 2.50 (d, J = 12.9 Hz, 2H), 2.26 – 2.08 (m, 2H), 1.84 – 1.55 (m, 5H) ppm
502	 Single enantiomer	613.1	¹ H NMR (300 MHz, CDCl ₃): δ 7.86 (s, 1H), 7.55 (s, 1H), 6.99 (t, J = 8.1 Hz, 2H), 6.84 – 6.55 (m, 2H), 5.35 (d, J = 45.6 Hz, 1H), 5.14 – 4.71 (m, 2H), 4.62 – 4.30 (m, 2H), 4.29 – 3.95 (m, 3H), 3.40 – 3.29 (m, 1H), 2.98 (s, 3H), 2.86 – 2.66 (m, 1H), 2.18 – 1.91 (m, 2H), 1.80 – 1.57 (m, 5H) ppm
503	 Single diastereomer	676.1	¹ H NMR (300 MHz, CDCl ₃): δ 7.71 (s, 1H), 7.51 (s, 1H), 7.01 – 6.93 (m, 2H), 6.78 – 6.63 (m, 2H), 5.31 (d, J = 45.9 Hz, 1H), 4.31–4.2 (m, 6H), 4.07 (d, J = 14.7 Hz, 1H), 3.37 – 3.28 (m, 1H), 2.87 – 2.70 (m, 1H), 2.12 – 1.97 (m, 2H), 1.83–1.74 (m, 2H), 1.72 – 1.62 (m, 3H), 1.40 – 1.35 (m, 8H), 1.07 (s, 2H) ppm
504	 Single diastereomer	620.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.80 (s, 1H), 7.54 (s, 1H), 6.99 – 6.93 (m, 2H), 6.70 – 6.66 (m, 2H), 5.66 (d, J = 44.7 Hz, 1H), 4.51 (d, J = 3.6 Hz, 2H), 4.20 – 4.15 (m, 1H), 3.27 – 3.20 (m, 1H), 2.65 – 2.17 (m, 1H), 2.14 – 2.07 (m, 2H), 1.76 – 1.57 (m, 5H), 1.05 – 0.92 (m, 4H) ppm

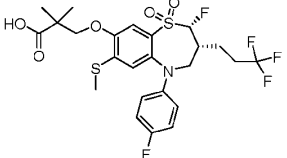
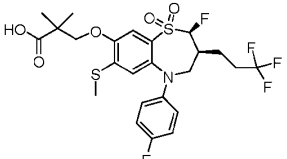
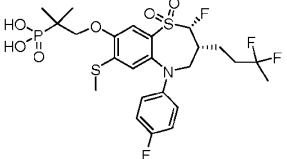
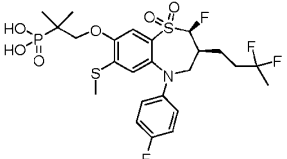
505	 Single diastereomer	624.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.86 (s, 1H), 7.57 (s, 1H), 7.06 – 6.93 (m, 2H), 6.79 – 6.67 (m, 2H), 5.71 (d, J = 45.3 Hz, 1H), 4.66 – 4.53 (m, 2H), 4.21 (d, J = 15.6 Hz, 1H), 3.31 – 3.25 (s, 1H), 2.85 – 2.60 (m, 3H), 2.29 – 2.04 (m, 4H), 1.85 – 1.55 (m, 5H), 0.64 – 0.43 (m, 4H) ppm
506	 Single diastereomer with arbitrarily assigned stereochemistry	627.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.85 (s, 1H), 7.56 (s, 1H), 6.97 (t, J = 8.4 Hz, 2H), 6.75 – 6.67 (m, 2H), 5.68 (d, J = 45.2 Hz, 1H), 4.60 (d, J = 8.8 Hz, 1H), 4.35 (d, J = 8.8 Hz, 1H), 4.19 (d, J = 15.6 Hz, 1H), 4.02 (d, J = 11.2 Hz, 1H), 3.70 – 3.65 (m, 1H), 3.34 – 3.28 (m, 2H), 3.28 – 3.23 (m, 1H), 2.97 (s, 3H), 2.80 – 2.61 (m, 1H), 2.43 – 2.32 (m, 2H), 2.21 – 2.03 (m, 2H), 1.82 – 1.54 (m, 5H) ppm
507	 Single diastereomer with arbitrarily assigned stereochemistry	627.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.85 (s, 1H), 7.56 (s, 1H), 6.97 (t, J = 8.4 Hz, 2H), 6.75 – 6.67 (m, 2H), 5.68 (d, J = 45.2 Hz, 1H), 4.60 (d, J = 8.8 Hz, 1H), 4.37 (d, J = 9.2 Hz, 1H), 4.19 (d, J = 16 Hz, 1H), 4.03 (d, J = 11.6 Hz, 1H), 3.70 – 3.66 (m, 1H), 3.36 – 3.28 (m, 2H), 3.27 – 3.23 (m, 1H), 2.98 (s, 3H), 2.82 – 2.60 (m, 1H), 2.42 – 2.34 (m, 2H), 2.21 – 2.01 (m, 2H), 1.84 – 1.53 (m, 5H) ppm
508	 Single diastereomer	641.1	¹ H NMR (300 MHz, CDCl ₃): δ 7.74 (s, 1H), 7.49 (s, 1H), 6.95 (t, J = 8.4 Hz, 2H), 6.73 – 6.54 (m, 2H), 5.29 (d, J = 45.9 Hz, 1H), 4.49 – 4.12 (m, 2H), 4.03 (d, J = 15.0 Hz, 1H), 3.59 – 2.95 (m, 5H), 2.82 – 2.63 (m, 4H), 2.47 – 2.32 (m, 2H), 2.22 – 1.97 (m, 4H), 1.77 – 1.59 (m, 5H) ppm

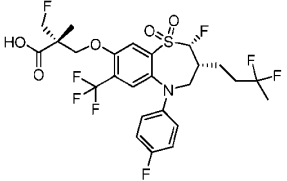
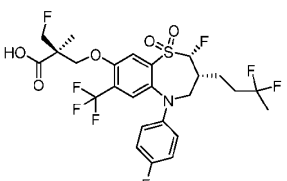
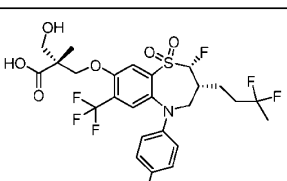
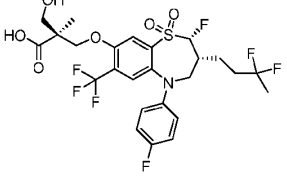
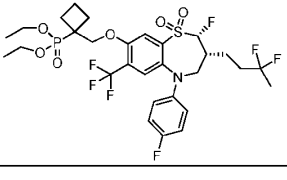
509	 Single diastereomer with arbitrarily assigned stereochemistry	613.0	¹ H NMR (400 MHz, CD ₃ OD): δ 7.84 (s, 1H), 7.58 (s, 1H), 6.98 (t, J = 8.6 Hz, 2H), 6.76 – 6.68 (m, 2H), 5.70 (d, J = 45.2 Hz, 1H), 4.75 (d, J = 10.0 Hz, 1H), 4.46 (d, J = 10.4 Hz, 1H), 4.19 (d, J = 16.0 Hz, 1H), 3.61 – 3.45 (m, 1H), 3.30 (s, 1H), 3.25 (s, 1H), 2.79 – 2.62 (m, 1H), 2.41 – 2.34 (m, 1H), 2.31 – 2.19 (m, 1H), 2.18 – 1.95 (m, 4H), 1.80 – 1.53 (m, 5H) ppm
510	 Single diastereomer with arbitrarily assigned stereochemistry	613.0	¹ H NMR (400 MHz, CD ₃ OD): δ 7.83 (s, 1H), 7.58 (s, 1H), 6.98 (t, J = 8.4 Hz, 2H), 6.76 – 6.69 (m, 2H), 5.69 (d, J = 45.2 Hz, 1H), 4.73 (d, J = 10.4 Hz, 1H), 4.47 (d, J = 10.0 Hz, 1H), 4.20 (d, J = 16.0 Hz, 1H), 3.64 – 3.52 (m, 1H), 3.30 (s, 1H), 3.25 (s, 1H), 2.82 – 2.60 (m, 1H), 2.46 – 2.32 (m, 1H), 2.28 – 2.24 (m, 1H), 2.20 – 1.96 (m, 4H), 1.84 – 1.52 (m, 5H) ppm
511	 Single diastereomer with arbitrarily assigned stereochemistry	627.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.90 (s, 1H), 7.59 (s, 1H), 6.98 (t, J = 8.7 Hz, 2H), 6.78 – 6.70 (m, 2H), 5.71 (d, J = 45.0 Hz, 1H), 4.83 – 4.71 (m, 2H), 4.20 (d, J = 16.0 Hz, 1H), 3.78 (t, J = 9.2 Hz, 1H), 3.29 – 3.22 (m, 2H), 2.98 (s, 3H), 2.80 – 2.61 (m, 1H), 2.47 – 2.37 (m, 2H), 2.17 – 2.03 (m, 3H), 2.00 – 1.96 (m, 1H), 1.82 – 1.52 (m, 5H) ppm
512	 Single diastereomer with arbitrarily assigned stereochemistry	627.0	¹ H NMR (400 MHz, CD ₃ OD): δ 7.91 (s, 1H), 7.60 (s, 1H), 6.98 (t, J = 8.8 Hz, 2H), 6.77 – 6.69 (m, 2H), 5.71 (d, J = 45.2 Hz, 1H), 4.82 (s, 1H), 4.73 (d, J = 11.6 Hz, 1H), 4.20 (d, J = 16.0 Hz, 1H), 3.78 (t, J = 9.2 Hz, 1H), 3.31 – 3.24 (m, 2H), 2.98 (s, 3H),

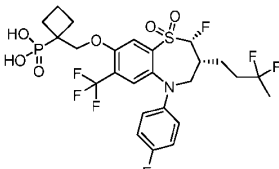
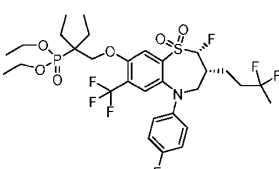
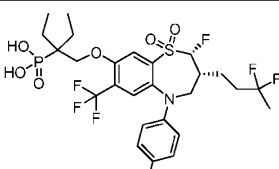
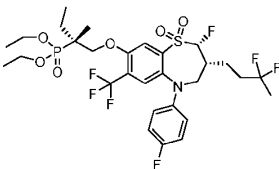
	Single diastereomer with arbitrarily assigned stereochemistry		2.79 – 2.61 (m, 1H), 2.46 – 2.37 (m, 2H), 2.17 – 2.03 (m, 3H), 2.00 – 1.96 (m, 1H), 1.81 – 1.56 (m, 5H) ppm
513	 Single diastereomer	640.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.79 (s, 1H), 7.55 (s, 1H), 7.03 – 6.91 (m, 2H), 6.76 – 6.65 (m, 2H), 5.68 (d, J = 45.3 Hz, 1H), 4.78 (s, 2H), 4.67 (s, 2H), 4.39 – 4.26 (m, 2H), 4.19 (d, J = 14.4 Hz, 1H), 3.29 – 3.23 (m, 1H), 2.85 – 2.48 (m, 5H), 2.26 – 1.97 (m, 2H), 1.85 – 1.53 (m, 5H) ppm
514	 Single diastereomer	620.1 [M - 1] ⁻	¹ H NMR (300 MHz, CD ₃ OD): δ 7.80 (s, 1H), 7.57 (s, 1H), 7.01 – 6.95 (m, 2H), 6.73 – 6.69 (m, 2H), 5.67 (d, J = 45.9 Hz, 1H), 4.31 (s, 2H), 4.22 – 4.17 (m, 1H), 3.32 – 3.20 (m, 1H), 2.84 – 2.20 (m, 1H), 2.19 – 1.95 (m, 2H), 1.79 – 1.59 (m, 5H), 1.38 – 1.32 (m, 6H) ppm
515	 Single diastereomer	550.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.72 (s, 1H), 7.52 (s, 1H), 6.97 (t, J = 8.7 Hz, 2H), 6.66 – 6.61 (m, 2H), 5.32 (d, J = 46.2 Hz, 1H), 4.21 (s, 2H), 4.05 (d, J = 16.5 Hz, 1H), 3.32 – 3.23 (m, 1H), 2.78 – 2.65 (m, 1H), 1.59 – 1.28 (m, 12H), 1.00 – 0.96 (m, 3H) ppm
516	 Single diastereomer with arbitrarily assigned stereochemistry	614.0	¹ H NMR (300 MHz, CD ₃ OD): δ 7.82 (s, 1H), 7.57 (s, 1H), 6.99 (t, J = 8.7 Hz, 2H), 6.75 – 6.70 (m, 2H), 5.71 (d, J = 44.7 Hz, 1H), 4.53 – 4.40 (m, 3H), 4.21 (d, J = 15.9 Hz, 1H), 3.33 – 3.31 (m, 1H), 2.84 – 2.58 (m, 3H), 2.24 – 2.00 (m, 4H), 1.82 – 1.56 (m, 5H) ppm

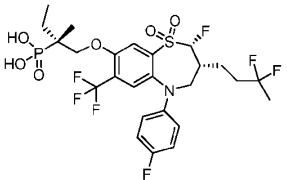
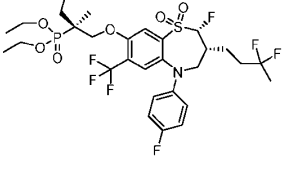
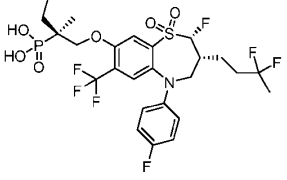
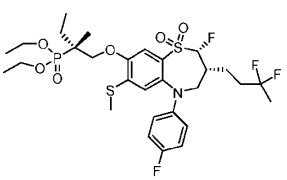
517	 Single diastereomer with arbitrarily assigned stereochemistry	614.0	¹ H NMR (300 MHz, CD ₃ OD): δ 7.84 (s, 1H), 7.58 (s, 1H), 6.99 (t, J = 9.0 Hz, 2H), 6.78 – 6.67 (m, 2H), 5.71 (d, J = 45.0 Hz, 1H), 4.53 – 4.34 (m, 3H), 4.21 (d, J = 16.2 Hz, 1H), 3.33 – 3.27 (m, 1H), 2.83 – 2.65 (m, 1H), 2.63 – 2.43 (m, 4H), 2.25 – 2.01 (m, 1H), 1.85 – 1.51 (m, 5H) ppm
518	 Single diastereomer	614.1	¹ H NMR (300 MHz, CDCl ₃): δ 7.76 (s, 1H), 7.50 (s, 1H), 6.99 – 6.91 (m, 2H), 6.67 – 6.62 (m, 2H), 5.30 (d, J = 45.9 Hz, 1H), 4.26 (s, 2H), 4.05 (d, J = 15.9 Hz, 1H), 3.37 – 3.20 (m, 1H), 2.85 – 2.66 (m, 1H), 2.11 – 1.95 (m, 2H), 1.89 – 1.80 (m, 4H), 1.76 – 1.60 (m, 5H), 0.95 – 0.90 (m, 6H) ppm
519	 Single diastereomer	622.1	¹ H NMR (300 MHz, CDCl ₃): δ 7.76 (s, 1H), 7.51 (s, 1H), 7.01 – 6.93 (m, 2H), 6.71 – 6.67 (m, 2H), 5.32 (d, J = 45.6 Hz, 1H), 4.87 (d, J = 45.9 Hz, 4H), 4.45 (s, 2H), 4.07 (d, J = 16.2 Hz, 1H), 3.38 – 3.29 (m, 1H), 2.84 – 2.69 (m, 1H), 2.10 – 1.96 (m, 2H), 1.73 – 1.58 (m, 5H) ppm
520	 Single diastereomer with arbitrarily assigned stereochemistry	616.0	¹ H NMR (300 MHz, CD ₃ OD): δ 7.83 (s, 1H), 7.58 (s, 1H), 7.02 – 6.97 (m, 2H), 6.76 – 6.71 (m, 2H), 5.70 (d, J = 45.3 Hz, 1H), 5.34 – 5.13 (m, 1H), 4.50 – 4.42 (m, 2H), 4.21 (d, J = 15.9 Hz, 1H), 3.33 – 3.28 (m, 1H), 2.87 – 2.49 (m, 5H), 2.20 – 2.11 (m, 2H), 1.79 – 1.59 (m, 5H) ppm
521		616.0	¹ H NMR (300 MHz, CD ₃ OD): δ 7.84 (s, 1H), 7.59 (s, 1H), 7.02 – 6.97 (m, 2H), 6.76 – 6.71 (m, 2H), 5.71 (d, J = 45.3 Hz, 1H), 5.32 – 5.07 (m, 1H), 4.49 – 4.42 (m, 2H), 4.21 (d, J = 15.9 Hz, 1H), 3.33 – 3.27 (m, 1H), 2.79 –

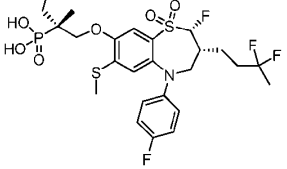
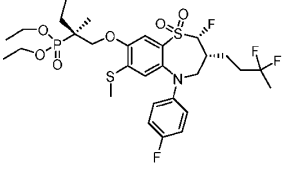
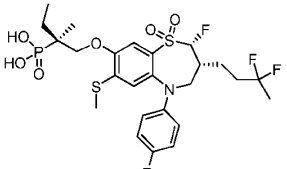
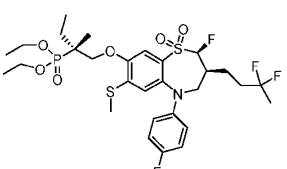
	Single diastereomer with arbitrarily assigned stereochemistry		2.63 (m, 5H), 2.22 – 2.05 (m, 2H), 1.84 – 1.59 (m, 5H) ppm
522	 Single diastereomer with arbitrarily assigned stereochemistry	599.0	¹ H NMR (400 MHz, CD ₃ OD): δ 7.87 (s, 1H), 7.61 (s, 1H), 6.98 (t, J = 8.4 Hz, 2H), 6.76 – 6.73 (m, 2H), 5.71 (d, J = 45.2 Hz, 1H), 4.68 (s, 2H), 4.21 (d, J = 15.2 Hz, 1H), 4.10 – 3.89 (m, 2H), 3.31 – 3.23 (m, 1H), 2.93 – 2.81 (m, 1H), 2.80 – 2.61 (m, 2H), 2.29 – 1.99 (m, 2H), 1.84 – 1.54 (m, 5H) ppm
523	 Single diastereomer with arbitrarily assigned stereochemistry	599.0	¹ H NMR (400 MHz, CD ₃ OD): δ 7.87 (s, 1H), 7.62 (s, 1H), 6.98 (t, J = 8.8 Hz, 2H), 6.75 – 6.72 (m, 2H), 5.71 (d, J = 45.2 Hz, 1H), 4.67 (q, J = 10.08 Hz, 22.8 Hz, 2H), 4.21 (d, J = 15.6 Hz, 1H), 4.10 – 3.87 (m, 2H), 3.36 – 3.32 (m, 1H), 2.91 – 2.82 (m, 1H), 2.81 – 2.60 (m, 2H), 2.25 – 2.00 (m, 2H), 1.84 – 1.53 (m, 5H) ppm
524	 Single diastereomer with arbitrarily assigned stereochemistry	613.0	¹ H NMR (300 MHz, CDCl ₃): δ 7.92 (s, 1H), 7.56 (s, 1H), 7.00 (t, J = 9.0 Hz, 2H), 6.74 – 6.70 (m, 2H), 5.38 (d, J = 45.6 Hz, 1H), 4.89 (s, 2H), 4.44 (s, 1H), 4.08 (d, J = 15.0 Hz, 1H), 3.94 – 3.83 (m, 1H), 3.45 – 3.27 (m, 1H), 3.02 (s, 4H), 2.92 – 2.83 (m, 1H), 2.82 – 2.62 (m, 1H), 2.18 – 1.94 (m, 2H), 1.67 (t, J = 18.3 Hz, 5H) ppm
525	 Single diastereomer with arbitrarily assigned stereochemistry	613.0	¹ H NMR (300 MHz, CDCl ₃): δ 7.89 (s, 1H), 7.56 (s, 1H), 7.00 (t, J = 8.4 Hz, 2H), 6.89 – 6.61 (m, 2H), 5.37 (d, J = 45.3 Hz, 1H), 4.89 (s, 2H), 4.44 (s, 1H), 4.06 (d, J = 15.0 Hz, 1H), 3.95 – 3.79 (m, 1H), 3.42 – 3.28 (m, 1H), 3.01 (s, 4H), 2.92 – 2.83 (m, 1H), 2.82 – 2.58 (m, 1H), 2.17 – 1.91 (m, 2H), 1.67 (t, J = 18.3 Hz, 5H) ppm

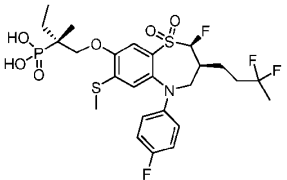
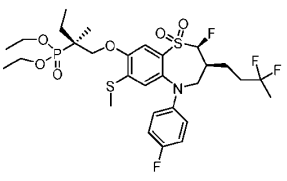
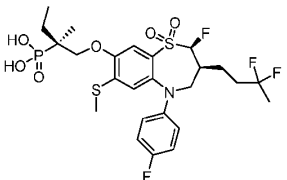
			(m, 2H), 1.66 (t, J = 18.6 Hz, 5H) ppm
526	 Single diastereomer	568.1	¹ H NMR (300 MHz, CDCl ₃): δ 7.48 (s, 1H), 7.03 – 6.87 (m, 3H), 6.72 – 6.54 (m, 2H), 5.23 (d, J = 46.5 Hz, 1H), 4.19 (s, 2H), 4.03 (d, J = 15.3 Hz, 1H), 3.45 – 3.31 (m, 1H), 2.98 – 2.64 (m, 1H), 2.38 (s, 3H), 2.35 – 2.23 (m, 2H), 1.92 – 1.70 (m, 2H), 1.45 (s, 6H) ppm
527	 Single diastereomer	568.1	¹ H NMR (300 MHz, CDCl ₃): δ 7.48 (s, 1H), 7.07 – 6.88 (m, 3H), 6.72 – 6.57 (m, 2H), 5.23 (d, J = 45.9 Hz, 1H), 4.17 (s, 2H), 4.03 (d, J = 15.9 Hz, 1H), 3.49 – 3.24 (m, 1H), 2.95 – 2.67 (m, 1H), 2.39 (s, 3H), 2.35 – 2.23 (m, 2H), 1.92 – 1.74 (m, 2H), 1.45 (s, 6H) ppm
528	 Single diastereomer	600.0	¹ H NMR (300 MHz, CD ₃ OD): δ 7.48 (s, 1H), 7.07 (s, 1H), 6.94 (t, J = 8.7 Hz, 2H), 6.72 – 6.64 (m, 2H), 5.53 (d, J = 45.6 Hz, 1H), 4.24 – 4.23 (m, 2H), 4.14 (d, J = 15.6 Hz, 1H), 3.32 – 3.26 (m, 1H), 2.84 – 2.61 (m, 1H), 2.38 (s, 3H), 2.25 – 2.05 (m, 2H), 1.65 (t, J = 18.6 Hz, 5H), 1.40 (d, J = 3.6 Hz, 3H), 1.35 (d, J = 3.7 Hz, 3H) ppm
529	 Single diastereomer	600.0	¹ H NMR (300 MHz, CD ₃ OD): δ 7.48 (s, 1H), 7.07 (s, 1H), 6.94 (t, J = 8.7 Hz, 2H), 6.68 – 6.64 (m, 2H), 5.53 (d, J = 45.7 Hz, 1H), 4.29 – 4.22 (m, 2H), 4.15 (d, J = 15.9 Hz, 1H), 3.32 – 3.26 (m, 1H), 2.84 – 2.61 (m, 1H), 2.38 (s, 3H), 2.22 – 2.03 (m, 2H), 1.65 (t, J = 18.6 Hz, 5H), 1.40 (d, J = 3.9 Hz, 3H), 1.35 (d, J = 3.9 Hz, 3H) ppm

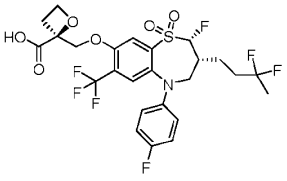
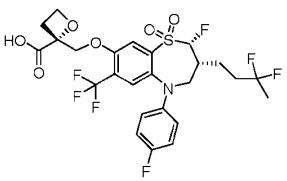
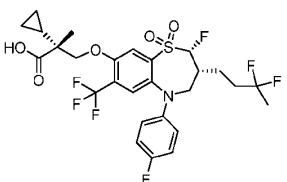
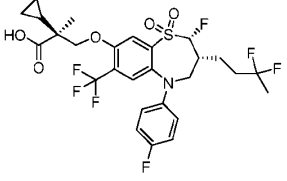
530	 Single diastereomer with arbitrarily assigned stereochemistry	604.0	¹ H NMR (300 MHz, CD ₃ OD): δ 7.82 (s, 1H), 7.59 (s, 1H), 6.99 (t, J = 8.7 Hz, 2H), 6.75 – 6.71 (m, 2H), 5.71 (d, J = 45.0 Hz, 1H), 4.88 – 4.56 (m, 2H), 4.45 (d, J = 9.0 Hz, 1H), 4.32 (d, J = 9.0 Hz, 1H), 4.21 (d, J = 15.6 Hz, 1H), 3.33 – 3.22 (m, 1H), 2.81 – 2.63 (m, 1H), 2.23 – 2.05 (m, 2H), 1.77 – 1.59 (m, 5H), 1.38 (s, 3H) ppm
531	 Single diastereomer with arbitrarily assigned stereochemistry	604.0	¹ H NMR (300 MHz, CD ₃ OD): δ 7.82 (s, 1H), 7.59 (s, 1H), 6.99 (t, J = 8.7 Hz, 2H), 6.75 – 6.71 (m, 2H), 5.71 (d, J = 45.0 Hz, 1H), 4.88 – 4.56 (m, 2H), 4.39 (q, J = 9.0 Hz, 2H), 4.21 (d, J = 15.9 Hz, 1H), 3.33 – 3.27 (m, 1H), 2.82 – 2.63 (m, 1H), 2.22 – 2.05 (m, 2H), 1.76 – 1.59 (m, 5H), 1.38 (s, 3H) ppm
532	 Single diastereomer with arbitrarily assigned stereochemistry	602.0	¹ H NMR (300 MHz, CD ₃ OD): δ 7.83 (s, 1H), 7.58 (s, 1H), 6.98 (t, J = 8.7 Hz, 2H), 6.77 – 6.69 (m, 2H), 5.70 (d, J = 45.0 Hz, 1H), 4.42 – 4.30 (m, 2H), 4.21 (d, J = 15.9 Hz, 1H), 3.88 – 3.76 (m, 2H), 3.27 (s, 1H), 2.84 – 2.63 (m, 1H), 2.23 – 2.06 (m, 2H), 1.76 – 1.59 (m, 5H), 1.33 (s, 3H) ppm
533	 Single diastereomer with arbitrarily assigned stereochemistry	602.0	¹ H NMR (300 MHz, CD ₃ OD): δ 7.83 (s, 1H), 7.58 (s, 1H), 6.98 (t, J = 8.7 Hz, 2H), 6.74 – 6.69 (m, 2H), 5.70 (d, J = 45.0 Hz, 1H), 4.37 (t, J = 1.8 Hz, 2H), 4.20 (d, J = 15.9 Hz, 1H), 3.88 – 3.75 (m, 2H), 3.26 (s, 1H), 2.80 – 2.61 (m, 1H), 2.25 – 2.04 (m, 2H), 1.80 – 1.58 (m, 5H), 1.33 (s, 3H) ppm
534	 Single diastereomer with arbitrarily assigned stereochemistry	690.0	¹ H NMR (300 MHz, CD ₃ OD): δ 7.82 (s, 1H), 7.62 (s, 1H), 7.03 – 6.97 (m, 2H), 6.77 – 6.72 (m, 2H), 5.72 (d, J = 45.3 Hz, 1H), 4.40 – 4.36 (m, 2H),

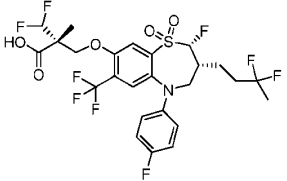
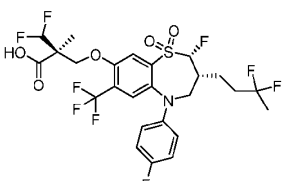
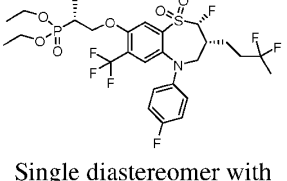
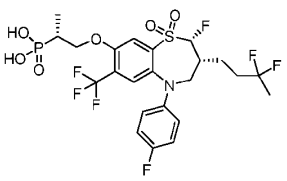
	Single diastereomer		4.27 – 4.17 (m, 5H), 3.32 – 3.28 (m, 1H), 2.66 – 2.55 (m, 1H), 2.51 – 2.37 (m, 4H), 2.22 – 2.10 (m, 4H), 1.80 – 1.72 (m, 2H), 1.66 (t, J = 18.6 Hz, 3H), 1.40 – 1.35 (m, 6H) ppm
535	 Single diastereomer	632.1 [M - 1] ⁻	¹ H NMR (300 MHz, CD ₃ OD): δ 7.84 (s, 1H), 7.61 (s, 1H), 6.99 (t, J = 8.7 Hz, 2H), 6.75 – 6.71 (m, 2H), 5.68 (d, J = 45.0 Hz, 1H), 4.38 – 4.29 (m, 2H), 4.24 – 4.18 (m, 1H), 3.55 – 3.32 (m, 1H), 2.80 – 2.66 (m, 1H), 2.50 – 2.33 (m, 4H), 2.17 – 2.02 (m, 4H), 1.82 – 1.56 (m, 5H) ppm
536	 Single diastereomer	706.3	¹ H NMR (300 MHz, CDCl ₃): δ 7.77 (s, 1H), 7.53 (s, 1H), 7.02 – 6.96 (m, 2H), 6.68 – 6.64 (m, 2H), 5.32 (d, J = 45.9 Hz, 1H), 4.29 – 4.23 (m, 2H), 4.21 – 4.13 (m, 4H), 4.10 – 4.04 (m, 1H), 3.40 – 3.31 (m, 1H), 2.85 – 2.71 (m, 1H), 2.13 – 1.97 (m, 2H), 1.94 – 1.77 (m, 4H), 1.75 – 1.62 (m, 5H), 1.39 – 1.35 (m, 6H), 1.08 – 1.03 (m, 6H) ppm
537	 Single diastereomer	648.2 [M - 1] ⁻	¹ H NMR (300 MHz, CD ₃ OD): δ 7.87 (s, 1H), 7.57 (s, 1H), 7.01 – 6.96 (m, 2H), 6.73 – 6.69 (m, 2H), 5.68 (d, J = 45.3 Hz, 1H), 4.47 – 4.38 (m, 2H), 4.20 (d, J = 15.3 Hz, 1H), 3.38 – 3.24 (m, 1H), 2.79 – 2.65 (m, 1H), 2.20 – 2.01 (m, 2H), 1.96 – 1.55 (m, 6H), 1.70 – 1.49 (m, 3H), 1.13 – 1.06 (m, 6H) ppm
538		692.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.76 (s, 1H), 7.52 (s, 1H), 7.01 – 6.96 (m, 2H), 6.68 – 6.64 (m, 2H), 5.32 (d, J = 46.5 Hz, 1H), 4.37 – 4.29 (m, 1H), 4.27 – 4.11 (m, 5H), 4.09 – 4.04 (m, 1H), 3.39 – 3.30 (m, 1H), 2.88 – 2.66

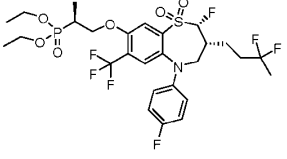
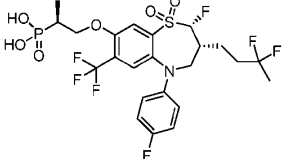
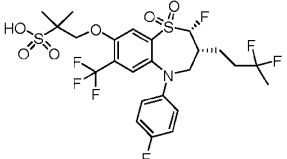
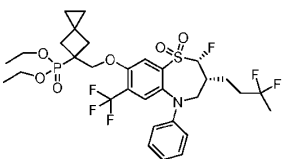
	Single diastereomer with arbitrarily assigned stereochemistry		(m, 1H), 2.13 – 1.77 (m, 4H), 1.74 – 1.62 (m, 5H), 1.40 – 1.29 (m, 9H), 1.09 – 0.99 (m, 3H) ppm
539	 Single diastereomer with arbitrarily assigned stereochemistry	634.2 [M -1] ⁺	¹ H NMR (300 MHz, CD ₃ OD): δ 7.84 (s, 1H), 7.58 (s, 1H), 7.01 – 6.96 (m, 2H), 6.74 – 6.69 (m, 2H), 5.68 (d, J = 45.0 Hz, 1H), 4.46 – 4.42 (m, 1H), 4.34 – 4.26 (m, 1H), 4.20 (d, J = 16.5 Hz, 1H), 3.31 – 3.24 (m, 1H), 2.80 – 2.65 (m, 1H), 2.20 – 2.02 (m, 2H), 1.97 – 1.71 (m, 4H), 1.66 (t, J = 18.0 Hz, 3H), 1.34 (d, J = 15.0 Hz, 3H), 1.07 (t, J = 7.5 Hz, 3H) ppm
540	 Single diastereomer with arbitrarily assigned stereochemistry	692.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.76 (s, 1H), 7.52 (s, 1H), 7.01 – 6.96 (m, 2H), 6.68 – 6.64 (m, 2H), 5.32 (d, J = 46.2 Hz, 1H), 4.37 – 4.29 (m, 1H), 4.26 – 4.11 (m, 5H), 4.10 – 4.04 (m, 1H), 3.39 – 3.30 (m, 1H), 2.87 – 2.66 (m, 1H), 2.13 – 1.81 (m, 4H), 1.79 – 1.58 (m, 5H), 1.42 – 1.27 (m, 9H), 1.09 – 1.00 (m, 3H) ppm
541	 Single diastereomer with arbitrarily assigned stereochemistry	634.2 [M -1] ⁺	¹ H NMR (300 MHz, CD ₃ OD): δ 7.83 (s, 1H), 7.58 (s, 1H), 7.01 – 6.96 (m, 2H), 6.74 – 6.69 (m, 2H), 5.68 (d, J = 45.6 Hz, 1H), 4.49 – 4.44 (m, 1H), 4.37 – 4.13 (m, 2H), 3.31 – 3.20 (m, 1H), 2.85 – 2.60 (m, 1H), 2.27 – 2.03 (m, 2H), 1.98 – 1.70 (m, 4H), 1.66 (t, J = 18.0 Hz, 3H), 1.33 (d, J = 15.0 Hz, 3H), 1.09 (t, J = 9.0 Hz, 3H) ppm
542	 Single diastereomer with arbitrarily assigned stereochemistry	670.4	¹ H NMR (400 MHz, CDCl ₃): δ 7.47 (s, 1H), 6.95 – 6.91 (m, 3H), 6.59 – 6.57 (m, 2H), 5.22 (d, J = 46.0 Hz, 1H), 4.26 – 3.98 (m, 7H), 3.33 (dd, J = 16.0, 11.6 Hz, 1H), 2.81 – 2.73 (m, 1H), 2.34 (s, 3H), 1.99 – 1.85 (m,

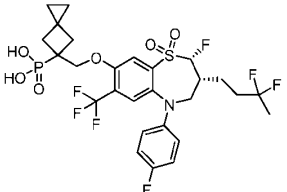
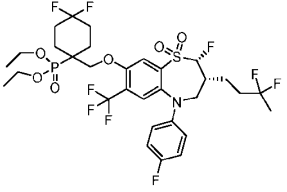
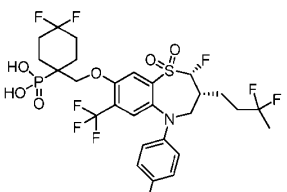
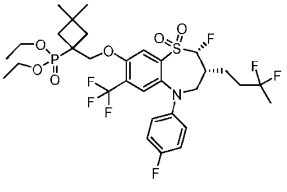
	Single diastereomer with arbitrarily assigned stereochemistry		4H), 1.74 – 1.61 (m, 5H), 1.37 – 1.33 (m, 9H), 1.04 (t, J = 7.6 Hz, 3H) ppm
543	 Single diastereomer with arbitrarily assigned stereochemistry	612.2 [M - 1] ⁻	¹ H NMR (300 MHz, CD ₃ OD): δ 7.51 (s, 1H), 7.07 (s, 1H), 6.95 (t, J = 9.0 Hz, 2H), 6.67 (dd, J = 9.3, 4.5 Hz, 2H), 5.54 (d, J = 45.3 Hz, 1H), 4.40 – 4.36 (m, 1H), 4.23 – 4.13 (m, 2H), 3.33 – 3.32 (m, 1H), 2.80 – 2.65 (m, 1H), 2.38 (s, 3H), 2.22 – 2.07 (m, 2H), 2.00 – 1.83 (m, 2H), 1.77 – 1.60 (m, 5H), 1.36 (d, J = 15.3 Hz, 3H), 1.11 (t, J = 7.5 Hz, 3H) ppm
544	 Single diastereomer with arbitrarily assigned stereochemistry	670.4	¹ H NMR (400 MHz, CDCl ₃): δ 7.47 (s, 1H), 6.95 – 6.91 (m, 3H), 6.60 – 6.57 (m, 2H), 5.23 (d, J = 46.0 Hz, 1H), 4.28 – 4.14 (m, 5H), 4.14 – 3.98 (m, 2H), 3.34 (dd, J = 16.0, 11.6 Hz, 1H), 2.88 – 2.71 (m, 1H), 2.34 (s, 3H), 1.99 – 1.82 (m, 4H), 1.72 – 1.61 (m, 5H), 1.37 – 1.32 (m, 9H), 1.04 (t, J = 7.6 Hz, 3H) ppm
545	 Single diastereomer with arbitrarily assigned stereochemistry	612.1 [M - 1] ⁻	¹ H NMR (300 MHz, CD ₃ OD): δ 7.51 (s, 1H), 7.07 (s, 1H), 6.95 (t, J = 9.0 Hz, 2H), 6.67 (dd, J = 9.3, 4.2 Hz, 2H), 5.54 (d, J = 45.9 Hz, 1H), 4.37 – 4.33 (m, 1H), 4.25 – 4.12 (m, 2H), 3.33 – 3.27 (m, 1H), 2.80 – 2.65 (m, 1H), 2.38 (s, 3H), 2.19 – 2.07 (m, 2H), 2.00 – 1.80 (m, 2H), 1.77 – 1.60 (m, 5H), 1.36 (d, J = 15.3 Hz, 3H), 1.09 (t, J = 7.5 Hz, 3H) ppm
546		670.0	¹ H NMR (300 MHz, CDCl ₃): δ 7.49 (s, 1H), 6.99 – 6.93 (m, 3H), 6.61 (dd, J = 9.2, 4.2 Hz, 2H), 5.25 (d, J = 46.2 Hz, 1H), 4.31 – 4.25 (m, 1H), 4.25 – 4.15 (m, 4H), 4.15 – 4.08 (m, 1H), 4.08 – 4.01 (m, 1H), 3.37 (dd, J = 15.6, 11.4 Hz, 1H), 2.86 – 2.72 (m,

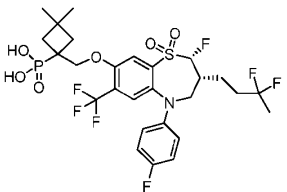
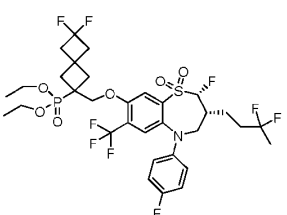
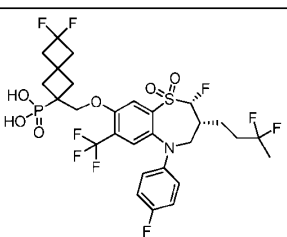
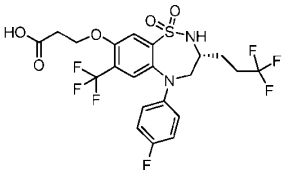
	Single diastereomer with arbitrarily assigned stereochemistry		1H), 2.36 (s, 3H), 2.13 – 1.83 (m, 4H), 1.77 – 1.62 (m, 5H), 1.40 – 1.28 (m, 9H), 1.06 (t, J = 7.5 Hz, 3H) ppm
547	 Single diastereomer with arbitrarily assigned stereochemistry	612.1 [M - 1] ⁻	¹ H NMR (300 MHz, CD ₃ OD): δ 7.52 (s, 1H), 7.07 (s, 1H), 6.95 (t, J = 9.0 Hz, 2H), 6.67 (dd, J = 9.3, 4.5 Hz, 2H), 5.54 (d, J = 45.6 Hz, 1H), 4.39 – 4.34 (m, 1H), 4.27 – 4.22 (m, 1H), 4.18 – 4.12 (m, 1H), 3.33 – 3.27 (m, 1H), 2.80 – 2.65 (m, 1H), 2.38 (s, 3H), 2.20 – 2.07 (m, 2H), 2.00 – 1.81 (m, 2H), 1.79 – 1.59 (m, 5H), 1.36 (d, J = 15.0 Hz, 3H), 1.09 (t, J = 7.5 Hz, 3H) ppm
548	 Single diastereomer with arbitrarily assigned stereochemistry	670.0	¹ H NMR (300 MHz, CDCl ₃): δ 7.49 (s, 1H), 6.99 – 6.93 (m, 3H), 6.61 (dd, J = 9.0, 4.2 Hz, 2H), 5.25 (d, J = 46.2 Hz, 1H), 4.29 – 4.18 (m, 5H), 4.15 – 4.11 (m, 1H), 4.08 – 4.00 (m, 1H), 3.36 (dd, J = 15.6, 11.4 Hz, 1H), 2.90 – 2.68 (m, 1H), 2.36 (s, 3H), 2.11 – 1.84 (m, 4H), 1.78 – 1.62 (m, 5H), 1.40 – 1.34 (m, 9H), 1.07 (t, J = 7.5 Hz, 3H) ppm
549	 Single diastereomer with arbitrarily assigned stereochemistry	612.1 [M - 1] ⁻	¹ H NMR (300 MHz, CD ₃ OD): δ 7.49 (s, 1H), 7.04 (s, 1H), 6.93 (t, J = 9.0 Hz, 2H), 6.64 (dd, J = 9.3, 4.5 Hz, 2H), 5.52 (d, J = 45.6 Hz, 1H), 4.39 – 4.34 (m, 1H), 4.23 – 4.10 (m, 2H), 3.30 – 3.25 (m, 1H), 2.78 – 2.63 (m, 1H), 2.36 (s, 3H), 2.20 – 2.04 (m, 2H), 1.97 – 1.80 (m, 2H), 1.77 – 1.57 (m, 5H), 1.33 (d, J = 15.0 Hz, 3H), 1.08 (t, J = 7.5 Hz, 3H) ppm

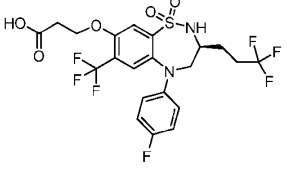
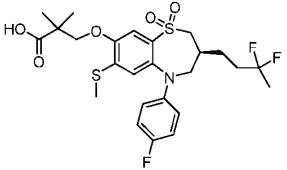
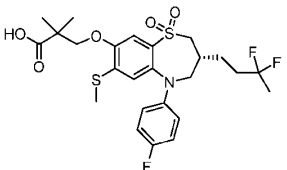
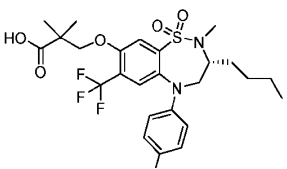
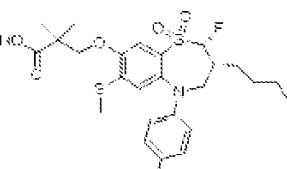
550	 Single diastereomer with arbitrarily assigned stereochemistry	600.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.87 (s, 1H), 7.57 (s, 1H), 6.97 (t, J = 8.8 Hz, 2H), 6.72 (dd, J = 9.2, 4.0 Hz, 2H), 5.68 (d, J = 45.2 Hz, 1H), 4.76 – 4.54 (m, 3H), 4.49 – 4.45 (m, 1H), 4.19 (d, J = 16.0 Hz, 1H), 3.30 – 3.27 (m, 1H), 3.13 – 3.07 (m, 1H), 2.90 – 2.87 (m, 1H), 2.75 – 2.65 (m, 1H), 2.19 – 2.03 (m, 2H), 1.79 – 1.59 (m, 5H) ppm
551	 Single diastereomer with arbitrarily assigned stereochemistry	600.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.87 (s, 1H), 7.58 (s, 1H), 6.97 (t, J = 8.8 Hz, 2H), 6.72 (dd, J = 9.2, 4.4 Hz, 2H), 5.68 (d, J = 45.2 Hz, 1H), 4.74 – 4.61 (m, 3H), 4.56 – 4.49 (m, 1H), 4.19 (d, J = 15.6 Hz, 1H), 3.30 – 3.27 (m, 1H), 3.13 – 3.05 (m, 1H), 2.90 – 2.87 (m, 1H), 2.76 – 2.65 (m, 1H), 2.19 – 2.03 (m, 2H), 1.79 – 1.59 (m, 5H) ppm
552	 Single diastereomer with arbitrarily assigned stereochemistry	612.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.80 (s, 1H), 7.58 (s, 1H), 6.99 (t, J = 8.7 Hz, 2H), 6.74 – 6.70 (m, 2H), 5.71 (d, J = 45.0 Hz, 1H), 4.48 – 4.46 (m, 1H), 4.23 – 4.18 (m, 2H), 3.33 – 3.27 (m, 1H), 2.80 – 2.66 (m, 1H), 2.23 – 2.07 (m, 2H), 1.82 – 1.60 (m, 5H), 1.26 – 1.13 (m, 4H), 0.57 – 0.44 (m, 4H) ppm
553	 Single diastereomer with arbitrarily assigned stereochemistry	612.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.81 (s, 1H), 7.58 (s, 1H), 6.99 (t, J = 8.7 Hz, 2H), 6.74 – 6.70 (m, 2H), 5.71 (d, J = 45.3 Hz, 1H), 4.52 – 4.49 (m, 1H), 4.24 – 4.18 (m, 2H), 3.33 – 3.27 (m, 1H), 2.80 – 2.63 (m, 1H), 2.23 – 2.07 (m, 2H), 1.82 – 1.66 (m, 5H), 1.24 – 1.14 (m, 4H), 0.62 – 0.44 (m, 4H) ppm.

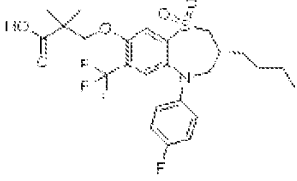
554	 Single diastereomer with arbitrarily assigned stereochemistry	622.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.80 (s, 1H), 7.58 (s, 1H), 6.99 (t, J = 8.7 Hz, 2H), 6.75 – 6.72 (m, 2H), 6.29 (t, J = 55.8 Hz, 1H), 5.71 (d, J = 45.0 Hz, 1H), 4.48 – 4.43 (m, 2H), 4.20 (d, J = 15.6 Hz, 1H), 3.32 – 3.21 (m, 1H), 2.83 – 2.60 (m, 1H), 2.25 – 2.02 (m, 2H), 1.76 – 1.59 (m, 5H), 1.42 (s, 3H) ppm
555	 Single diastereomer with arbitrarily assigned stereochemistry	622.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.80 (s, 1H), 7.58 (s, 1H), 6.99 (t, J = 8.7 Hz, 2H), 6.76 – 6.71 (m, 2H), 6.29 (t, J = 55.8 Hz, 1H), 5.71 (d, J = 45.3 Hz, 1H), 4.45 (s, 2H), 4.21 (d, J = 15.9 Hz, 1H), 3.32 – 3.21 (m, 1H), 2.83 – 2.60 (m, 1H), 2.25 – 2.02 (m, 2H), 1.82 – 1.56 (m, 5H), 1.43 (s, 3H) ppm
556	 Single diastereomer with arbitrarily assigned stereochemistry	664.1	¹ H NMR (300 MHz, CDCl ₃): δ 7.74 (s, 1H), 7.52 (s, 1H), 7.01 – 6.96 (m, 2H), 6.68 – 6.64 (m, 2H), 5.31 (d, J = 45.6 Hz, 1H), 4.29 – 4.23 (m, 1H), 4.25 – 4.11 (m, 5H), 4.09 – 4.04 (m, 1H), 3.39 – 3.30 (m, 1H), 2.90 – 2.64 (m, 1H), 2.60 – 2.37 (m, 1H), 2.13 – 1.97 (m, 2H), 1.79 – 1.60 (m, 5H), 1.46 – 1.42 (m, 3H), 1.38 – 1.32 (m, 6H) ppm
557	 Single diastereomer with arbitrarily assigned stereochemistry	606.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.82 (s, 1H), 7.57 (s, 1H), 7.01 – 6.96 (m, 2H), 6.74 – 6.69 (m, 2H), 5.68 (d, J = 45.0 Hz, 1H), 4.71 – 4.61 (m, 1H), 4.26 – 4.02 (m, 2H), 3.31 – 3.24 (m, 1H), 2.84 – 2.62 (m, 1H), 2.38 – 2.05 (m, 3H), 1.83 – 1.70 (m, 2H), 1.69 – 1.53 (m, 3H), 1.44 – 1.30 (m, 3H) ppm

558	 Single diastereomer with arbitrarily assigned stereochemistry	664.1	¹ H NMR (300 MHz, CDCl ₃): δ 7.74 (s, 1H), 7.52 (s, 1H), 7.01 – 6.96 (m, 2H), 6.68 – 6.64 (m, 2H), 5.31 (d, J = 45.9 Hz, 1H), 4.53 – 4.46 (m, 1H), 4.25 – 4.12 (m, 5H), 4.09 – 4.04 (m, 1H), 3.38 – 3.29 (m, 1H), 2.89 – 2.65 (m, 1H), 2.61 – 2.38 (m, 1H), 2.13 – 1.97 (m, 2H), 1.76 – 1.61 (m, 5H), 1.45 – 1.29 (m, 9H) ppm
559	 Single diastereomer with arbitrarily assigned stereochemistry	606.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.82 (s, 1H), 7.58 (s, 1H), 7.01 – 6.96 (m, 2H), 6.74 – 6.69 (m, 2H), 5.68 (d, J = 45.0 Hz, 1H), 4.74 – 4.61 (m, 1H), 4.27 – 4.15 (m, 1H), 4.15 – 4.02 (m, 1H), 3.31 – 3.24 (m, 1H), 2.84 – 2.59 (m, 1H), 2.41 – 2.26 (m, 1H), 2.24 – 2.08 (m, 2H), 1.78 – 1.70 (m, 2H), 1.70 – 1.51 (m, 3H), 1.43 – 1.29 (m, 3H) ppm
560	 Single diastereomer	620.1 [M - 1] ⁻	¹ H NMR (300 MHz, CD ₃ OD): δ 7.80 (s, 1H), 7.59 (s, 1H), 6.99 (t, J = 6.0 Hz, 2H), 6.80 – 6.69 (dd, J = 6.3, 4.2 Hz, 2H), 5.69 (d, J = 46.2 Hz, 1H), 4.47 – 4.34 (m, 2H), 4.20 (d, J = 17.4 Hz, 1H), 3.46 (s, 1H), 2.90 – 2.59 (m, 1H), 2.33 – 2.03 (m, 2H), 1.80 – 1.60 (m, 5H), 1.51 (d, J = 4.5 Hz, 6H) ppm
561	 Single diastereomer	716.3	¹ H NMR (300 MHz, CDCl ₃): δ 7.80 (s, 1H), 7.55 (s, 1H), 6.99 (t, J = 9.0 Hz, 2H), 6.69 – 6.65 (m, 2H), 5.32 (d, J = 45.9 Hz, 1H), 4.40 (d, J = 10.2 Hz, 2H), 4.32 – 4.20 (m, 4H), 4.08 (d, J = 15.9 Hz, 1H), 3.45 – 3.27 (m, 1H), 2.94 – 2.73 (m, 1H), 2.72 – 2.61 (m, 2H), 2.44 (t, J = 12.9 Hz, 2H), 2.19 – 1.94 (m, 2H), 1.83 – 1.61 (m, 5H), 1.39 (t, J = 6.0 Hz, 6H), 0.55 (s, 4H) ppm

562	 Single diastereomer	658.1 [M - 1] ⁻	¹ H NMR (300 MHz, CD ₃ OD): δ 7.88 (s, 1H), 7.60 (s, 1H), 6.99 (t, J = 9.0 Hz, 2H), 6.74 – 6.70 (m, 2H), 5.67 (d, J = 45.3 Hz, 1H), 4.52 – 4.35 (m, 2H), 4.20 (d, J = 15.9 Hz, 1H), 3.37 – 3.33 (m, 1H), 2.87 – 2.72 (m, 1H), 2.64 – 2.36 (m, 4H), 2.29 – 2.03 (m, 2H), 1.87 – 1.73 (m, 2H), 1.72 – 1.55 (m, 3H), 0.61 – 0.49 (m, 2H), 0.48 – 0.38 (m, 2H) ppm
563	 Single diastereomer	754.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.86 (s, 1H), 7.60 (s, 1H), 7.02 – 6.97 (m, 2H), 6.76 – 6.72 (m, 2H), 5.72 (d, J = 45.3 Hz, 1H), 4.45 – 4.39 (m, 2H), 4.25 – 4.15 (m, 5H), 3.27 – 3.10 (m, 1H), 2.79 – 2.65 (m, 1H), 2.26 – 1.98 (m, 10H), 1.82 – 1.72 (m, 2H), 1.69 – 1.59 (m, 3H), 1.37 – 1.32 (m, 6H) ppm
564	 Single diastereomer	696.3 [M - 1] ⁻	¹ H NMR (300 MHz, CD ₃ OD): δ 7.85 (s, 1H), 7.58 (s, 1H), 6.98 (t, J = 8.7 Hz, 2H), 6.74 – 6.69 (m, 2H), 5.67 (d, J = 45.3 Hz, 1H), 4.40 – 4.37 (m, 2H), 4.20 (d, J = 15.9 Hz, 1H), 3.26 (s, 1H), 2.85 – 2.62 (m, 1H), 2.50 – 2.42 (m, 2H), 2.16 – 2.05 (m, 6H), 1.97 – 1.94 (m, 2H), 1.78 – 1.59 (m, 5H) ppm
565	 Single diastereomer	718.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.87 (s, 1H), 7.60 (s, 1H), 7.01 (d, J = 7.2 Hz, 2H), 6.76 (d, J = 2.7 Hz, 2H), 5.72 (d, J = 60.6 Hz, 1H), 4.62 – 4.41 (m, 2H), 4.40 – 4.00 (m, 5H), 3.51 – 3.39 (m, 1H), 2.73 (d, J = 35.4 Hz, 1H), 2.52 – 2.29 (m, 2H), 2.12 (t, J = 13.2 Hz, 4H), 1.87 – 1.51 (m, 5H), 1.47 – 1.16 (m, 13H) ppm

566	 Single diastereomer	662.1	¹ H NMR (300 MHz, CD ₃ OD): δ 7.73 (s, 1H), 7.67 (s, 1H), 7.04 (t, J = 9.0 Hz, 3H), 6.72 – 6.62 (dd, J = 9.3, 4.5 Hz, 2H), 6.07 (d, J = 44.4 Hz, 1H), 4.31 – 4.13 (m, 3H), 3.19 (s, 1H), 2.78 – 2.59 (m, 1H), 2.31 – 2.08 (m, 4H), 1.99 (t, J = 13.2 Hz, 2H), 1.63 (t, J = 18.9 Hz, 5H), 1.25 (s, 3H), 1.11 (s, 3H) ppm
567	 Single diastereomer	766.3	¹ H NMR (300 MHz, CD ₃ OD): δ 7.81 (s, 1H), 7.62 (s, 1H), 6.99 (t, J = 8.4 Hz, 2H), 6.84 – 6.61 (dd, J = 9.3, 4.2 Hz, 2H), 5.72 (d, J = 45.0 Hz, 1H), 4.37 – 4.30 (m, 2H), 4.29 – 4.17 (m, 4H), 3.36 (s, 1H), 2.90 – 2.40 (m, 9H), 2.30 – 1.98 (m, 2H), 1.82 – 1.73 (m, 1H), 1.65 (t, J = 18.6 Hz, 4H), 1.38 (t, J = 6.9 Hz, 6H) ppm
568	 Single diastereomer	708.2 [M - 1] ⁺	¹ H NMR (300 MHz, CD ₃ OD): δ 7.85 (s, 1H), 7.62 (s, 1H), 6.99 (t, J = 8.4 Hz, 2H), 6.84 – 6.61 (dd, J = 9.3, 4.2 Hz, 2H), 5.72 (d, J = 45.0 Hz, 1H), 4.31 (s, 2H), 4.21 (d, J = 23.7 Hz, 4H), 3.36 (s, 1H), 2.80 – 2.60 (m, 3H), 2.60 – 2.40 (m, 6H), 2.30 – 1.98 (m, 2H), 1.82 – 1.73 (m, 2H), 1.65 (t, J = 18.6 Hz, 3H) ppm
569	 Single enantiomer	545.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.69 (s, 1H), 7.44 (s, 1H), 6.95 (t, J = 8.8 Hz, 2H), 6.80 – 6.65 (dd, J = 4 Hz, 8.8 Hz, 2H), 4.50 – 4.25 (m, 3H), 3.65 – 3.53 (m, 1H), 3.21 – 2.95 (m, 1H), 2.80 (t, J = 6.0 Hz, 2H), 2.55 – 2.20 (m, 2H), 1.98 – 1.82 (m, 1H), 1.78 – 1.62 (m, 1H) ppm

570	 Single enantiomer	545.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.69 (s, 1H), 7.43 (s, 1H), 6.95 (t, <i>J</i> = 9.2 Hz, 2H), 6.78 – 6.66 (dd, <i>J</i> = 4.8 Hz, 9.2 Hz, 2H), 4.47 – 4.33 (m, 3H), 3.65 – 3.55 (m, 1H), 3.17 – 2.95 (m, 1H), 2.79 (t, <i>J</i> = 6.0 Hz, 2H), 2.52 – 2.28 (m, 2H), 1.96 – 1.82 (m, 1H), 1.78 – 1.64 (m, 1H) ppm
571	 Single enantiomer	546.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.43 (s, 1H), 7.00 (s, 1H), 6.92 (t, <i>J</i> = 8.7 Hz, 2H), 6.68 – 6.65 (m, 2H), 4.32 – 4.29 (m, 1H), 4.14 (s, 2H), 3.51 – 3.40 (m, 1H), 3.25 – 3.10 (m, 2H), 2.52 – 2.35 (m, 1H), 2.31 (s, 3H), 2.11 – 1.91 (m, 2H), 1.73 – 1.46 (m, 5H), 1.35 (s, 6H) ppm
572	 Single enantiomer	546.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.43 (s, 1H), 7.00 (s, 1H), 6.92 (t, <i>J</i> = 8.7 Hz, 2H), 6.68 – 6.64 (m, 2H), 4.26 (d, <i>J</i> = 18.0 Hz, 1H), 4.14 (s, 2H), 3.51 – 3.40 (m, 1H), 3.25 – 3.10 (m, 2H), 2.50 – 2.40 (m, 1H), 2.31 (s, 3H), 2.13 – 1.91 (m, 2H), 1.75 – 1.47 (m, 5H), 1.35 (s, 6H) ppm
573	 Single enantiomer	547.2	¹ H NMR (400 MHz, CD ₃ OD): δ 7.64 (s, 1H), 7.46 (s, 1H), 6.97 (t, <i>J</i> = 8.8 Hz, 2H), 6.73 – 6.70 (m, 2H), 4.21 (s, 2H), 4.08 – 4.04 (m, 1H), 3.94 (m, 1H), 2.63 (s, 3H), 1.61 – 1.56 (m, 2H), 1.51 – 1.29 (m, 4H), 1.37 (s, 6H), 1.39 – 1.31 (m, 1H), 0.99 – 0.92 (m, 3H) ppm
574		528.2	¹ H NMR (300 MHz, CD ₃ OD): δ 7.47 (s, 1H), 7.07 (s, 1H), 6.95 (t, <i>J</i> = 8.7 Hz, 2H), 6.72 – 6.59 (m, 2H), 5.49 (d, <i>J</i> = 45.6 Hz, 1H), 4.22 – 3.99 (m, 3H), 3.31 – 3.19 (m, 1H), 2.79 – 2.54 (dd, <i>J</i> = 33.6, 9.6 Hz, 1H), 2.36 (s, 3H), 1.65 –

	Single diastereomer		1.41 (m, 6H), 1.39 (s, 6H), 1.00 (t, J = 6.9 Hz, 3H) ppm
575		532.1	¹ H NMR (400 MHz, CD ₃ OD): δ 7.72 (s, 1H), 7.46 (s, 1H), 6.95 (t, J = 8.8 Hz, 2H), 6.72 – 6.68 (m, 2H), 4.34 – 4.15 (m, 3H), 3.57 – 3.46 (m, 1H), 3.28 – 3.20 (m, 1H), 3.19 – 3.12 (m, 1H), 2.37 (s, 1H), 1.51 – 1.36 (m, 6H), 1.34 (s, 6H), 0.94 (t, J = 7.2 Hz, 3H) ppm
	Single enantiomer		

VI. Biological Data

HepG2-NTCP HBV infection protocol

HepG2 cells stably expressing the sodium taurocholate cotransporting polypeptide (HepG2-NTCP) were maintained in culture using DMEM (HyClone, Cat# SH30243.02) supplemented with 10% FBS, 150 µg/mL G418 (Alfa Aesar, Cat# J62671), 50 U/mL penicillin-streptomycin (Invitrogen, Cat# 15140-122), and 0.5 µg/mL blasticidin (Sigma, Cat# 15205). Prior to infection, the cells were washed twice with 1× DPBS (Invitrogen, Cat# 14190-136) and treated with 3 mL of 0.05% trypsin (Invitrogen, Cat# 25200-056) to dissociate the cells. Following dissociation, 10 mL of HepG2-NTCP growth medium was added to the cells to neutralize the trypsin and the cells were then counted and centrifuged at 1,300 rpm for 5 minutes. Following centrifugation, the cells were resuspended in DMEM supplemented with 5% FBS, 50 U/mL penicillin-streptomycin, 4% PEG-8000 (Hamilton Research, Cat# HR2-515), and 1% DMSO (Sigma, Cat# D4540) to a density of 8 × 10⁵ cells/mL and infected with HBV at an MOI of 50. Immediately after infection, 50 µL of the cell/HBV mixture was added to a 96-well plate containing 50 µL of compound and incubated at 37°C for 24 hours (2% final DMSO concentration). After the incubation, the infection media was removed and replaced with DMEM supplemented with 5% FBS, 50 U/mL penicillin-streptomycin, and 1% DMSO and incubated for an additional 72 hours. At the end of the incubation, the plates were spun at 1,800 rpm for 8 minutes and the supernatant was removed for HBeAg quantification using electrochemiluminescence enzyme-linked immunosorbent assays (ECL-ELISA).

To conduct the HBeAg ECL-ELISA, Lumitrack high-binding 96-well plates (Greiner, Cat# 655074) were treated with 625 ng/mL HBeAg mAb (Biocheck, Cat# 70426) in 1× DPBS for 2 hours at 25°C with shaking. The HBeAg mAb solution was then removed and the plates treated with 1× DPBS containing 0.5% bovine serum albumin (BSA) (Sigma, Cat# A7030-100g) for 2 hours at 25°C with shaking. The HBeAg-coated plates were then washed 4 times with 1× DPBS containing 0.05% Tween 20 (DPBS-T) (Thermo Fisher Scientific, Cat# J61544-K2). Following the wash, 90 µL of HRP-conjugated antibody (Fitzgerald, Cat# 61-H10K), diluted 1:8,000 in 1× DPBS-T containing 0.5% BSA, was added to the HBeAg-coated plates along with 15 µL of each sample. The plates were then incubated for 2 hours at 25 °C with shaking. Following the incubation, the sample was then removed and 200 µL of 1× PBS-T was added and the plates were incubated for 10 minutes at 25°C with shaking. The plates were then washed 6 times with 1× PBS-T and blotted dry. 80 µL of ECL substrate (Millipore, Cat# WBKLS0500) was then added to the plate and the luminescence was measured using a Tecan M1000 Pro plate reader.

Other assays are known in the art, see for example, Lempp *et al.*, Nature Communications, 2019, 10:2265, <https://doi.org/10.1038/s41467-019-10211-2>, Grosser *et al.*, Frontiers in Molecular Biosciences, 2021, 8: doi: 10.3389/fmolb.2021.689757.

TABLE 5 shows assay data for exemplified compounds of the invention following the described HepG2-NTCP HBV infection protocol, grouped in the following ranges: **A** indicates EC₅₀ < 10 nM; **B** indicates 10 nM ≤ EC₅₀ < 100 nM; **C** indicates 100 nM ≤ EC₅₀ < 500 nM; and **D** indicates EC₅₀ of ≥500 nM.

TABLE 5: assay data for exemplified compounds of the invention following the described HepG2-NTCP HBV infection protocol.

Example	HBeAg EC ₅₀ (nM)
1	A
2	B
3	B
4	A
5	B
6a	B
6b	B

7	A
8a	D
8b	B
9a	D
9b	B
9c/d	B
9c	B
9d	C
10a	D
10b	A
10c/d	B
10c	B
10d	B
11a	D
11b	A
12a	B
12b	D
13a	C
13b	B
14	C
15	B
16	C
17a	D
17b	B
18a	D
18b	B
19a	D
19b	B
20a	D
20b	B
21	B
22	B
23	B
24a	A
24b	B
25	B
26	B
27	A
28	A
29	B
30	B
31	A
32a	B

32b	B
33	A
34	B
35	B
36	B
37	B
38	B
39	B
40	A
41a/b	B
41a	C
41b	B
42a/b	D
42a	D
42b	D
43a	B
43b	A
44	A
45a/b	A
45a	A
45b	A
46a/b	B
46a	A
46b	B
47	D
48a	D
48b	B
49a	D
49b	B
50a	A
50b	C
60	C
61a	A
61b	C
62	A
63a	D
63b	B
63c	D
63d	A
64a	A
64b	C
65a	D
65b	A

65c	D
65d	B
66a	D
66b	A
67a	D
67b	A
68a	D
68b	A
69a	D
69b	B
70a	B
70b	C
70c	A
70d	A
80a	A
80b	C
81a	C
81b	A
82a/b	B
82a	B
82b	D
83a/b	B
83a	B
83b	D
84a/b	B
84a	D
84b	B
85a	B
85b	D
86	C
87a	B
87b	C
88a	B
88b	C
89a	D
89b	C
90a	C
90b	D
91a	B
91b	D
92a	B
92b	D
93	B

94a	B
94b	C
95a	D
95b	A
96a	B
96b	D
97a/b	B
97a	B
97b	D
98a/b	B
98a	B
98b	C
99a/b	B
99a	A
99b	C
100a	C
100b	B
101a/b	D
101a	D
101b	D
101c/d	B
101c	B
101d	B
102a/b	C
102a	B
102b	D
103a	C
103b	B
104a	B
104b	D
105	C
106	A
107a	C
107b	B
108a	D
108b	D
109a	C
109b	A
110a	B
110b	D
111a	B
111b	D
112a	D

112b	B
113a	D
113b	C
114	C
115	B
116	C
117	B
118a	D
118b	B
119a	D
119b	C
120a	B
120b	D
121a	D
121b	B
122	B
123	A
124a/b	B
124a	C
124b	B
125a/b	N/A
125a	C
125b	B
126a	B
126b	C
127a	B
127b	C
128a/b	B
128a	C
128b	B
129a/b	B
129a	C
129b	B
129c/d	D
129c	D
129d	D
130a/b	B
130a	B
130b	C
131a/b	C
131a	C
131b	D
132a	A

132b	C
133a/b	B
133a	A
133b	C
134a	B
134b	C
135a	B
135b	B
135c	D
135d	D
136a	B
136b	B
136c	C
136d	D
137a	D
137b	D
137c/d	B
137c	B
137d	B
138a	B
138b	D
139a/b	B
139a	D
139b	C
140a	B
140b	B
140c	D
140d	D
141a/b	B
141a	A
141b	A
141c/d	D
141c	D
141d	D
142a	D
142b	D
142c	B
142d	A
143a/b	D
143a	D
143b	D
143c/d	B
143c	B

143d	B
144a/b	B
144a	B
144b	B
144c/d	C
144c	D
144d	D
145a	B
145b	C
146a	A
146b	B
147a	D
147b	B
148	B
149	B
150	B
151a	A
151b	D
152a	A
152b	D
153a	A
153b	D
154a	A
154b	B
155	C
156	A
157	A
158a	D
158b	B
159	B
160	B
161	B
162	C
163	C
164	D
165	B
166	C
167	D
168	B
169	D
170	D
171	B
172	B

173	D
174	B
175	D
176	B
177	C
178	B
179	D
180	D
181	B
182	D
183	C
184	D
185	C
186	D
187	C
188	D
189	B
190	D
191	B
192	B
193	C
194	C
195	D
196	D
197	B
198	B
199	D
200	A
201	D
202	D
203	A
204	B
205	D
206	D
207	D
208	D
209	C
210	A
211	D
212	A
213	C
214	D
215	B

216	C
217	A
218	C
219	A
220	B
221	D
222	D
223	B
224	D
225	A
226	B
227	C
228	B
229	B
230	B
231	C
232	B
233	D
234	A
235	D
236	A
237	B
238	D
239	C
240	D
241	B
242	D
243	A
244	D
245	A
246	D
247	B
248	D
249	A
250	D
251	B
252	D
253	B
254	D
255	B
256	D
257	B
258	D

259	B
260	D
261	A
262	D
263	A
264	C
265	B
266	C
267	A
268	C
269	B
270	A
271	D
272	B
273	D
274	B
275	C
276	A
277	D
278	A
279	B
280	B
281	B
282	B
283	A
284	B
285	B
286	B
287	A
288	C
289	B
290	D
291	A
292	B
293	B
294	B
295	A
296	B
297	D
298	C
299	B
300	B
301	D

302	D
303	D
304	B
305	B
306	D
307	B
308	B
309	D
310	D
311	A
312	B
313	B
314	D
315	C
316	B
317	D
318	C
319	B
320	D
321	C
322	D
323	D
324	D
325	C
326	D
327	D
328	B
329	D
330	C
331	C
332	D
333	B
334	B
335	B
336	C
337	A
338	B
339	C
340	D
341	C
342	B
343	C
344	A

345	C
346	B
347	D
348	B
349	D
350	C
351	B
352	B
353	B
354	B
355	B
356	B
357	B
358	B
359	B
360	D
361	C
362	B
363	B
364	B
365	B
366	B
367	B
368	B
369	B
370	B
371	B
372	B
373	B
374	A
375	A
376	A
377	B
378	B
379	B
380	B
381	B
382	D
383	B
384	D
385	B
386	C
387	C

388	D
389	D
390	B
391	C
392	D
393	D
394	D
395	D
396	A
397	D
398	B
399	D
400	D
401	D
402	D
403	A
404	C
405	D
406	D
407	D
408	D
409	B
410	B
411	B
412	B
413	D
414	B
415	D
416	B
417	C
418	A
419	C
420	B
421	D
422	C
423	D
424	B
425	B
426	D
427	B
428	D
429	D
430	B

431	B
432	C
433	D
434	D
435	B
436	B
437	D
438	B
439	B
440	B
441	D
442	B
443	A
444	D
445	B
446	B
447	C
448	D
449	C
450	B
451	D
452	D
453	C
454	C
455	B
456	B
457	C
458	B
459	D
460	A
461	A
462	D
463	A
464	D
465	A
466	A
467	B
468	C
469	A
470	D
471	A
472	C
473	C

474	D
475	A
476	D
477	A
478	D
479	A
480	A
481	C
482	A
483	D
484	A
485	D
486	A
487	C
488	B
489	A
490	A
491	B
492	B
493	A
494	A
495	B
496	B
497	B
498	A
499	D
500	D
501	A
502	D
503	D
504	A
505	A
506	D
507	D
508	D
509	D
510	D
511	D
512	D
513	B
514	A
515	A
516	D

517	C
518	B
519	A
520	B
521	A
522	D
523	D
524	D
525	D
526	D
527	B
528	A
529	D
530	A
531	A
532	B
533	A
534	D
535	A
536	D
537	B
538	D
539	A
540	C
541	A
542	D
543	A
544	D
545	A
546	D
547	D
548	D
549	D
550	B
551	B
552	A
553	B
554	A
555	A
556	C
557	A
558	D
559	B

560	A
561	D
562	A
563	D
564	A
565	D
566	B
567	N/A
568	N/A
569	N/A
570	N/A
571	D
572	B
573	A
574	N/A
575	N/A

HepG2-NTCP HDV infection protocol

- HepG2 cells stably expressing the sodium taurocholate cotransporting polypeptide (HepG2-NTCP) were maintained in culture in DMEM (HyClone, Cat# SH30243.02)
- 5 supplemented with 10% FBS, 150 µg/mL G418 (Alfa Aesar, Cat# J62671), 50 U/mL penicillin-streptomycin (Invitrogen, Cat# 15140-122), and 0.5 µg/mL blasticidin (Sigma, Cat# 15205). 10,000 HepG2-NTCP cells were seeded in 96-well plate in 50 µL DMEM supplemented with 5% FBS, 50U/mL penicillin-streptomycin, 4% PEG-8000 (Hamilton Research, Cat# HR2-515), and 1% DMSO (Sigma, Cat# D4540). After cell seeding,
- 10 compounds were dispensed using a Tecan D300e dispenser in the wells in a serial dilution (4-fold, 8 doses) followed by infection with 50 µL HDV inoculum at an MOI of 20 vge/cell. Cells were then incubated at 37 °C in 5% CO₂ for 24 hrs. After the incubation, the infection media was removed and replaced with DMEM supplemented with 5% FBS, 50 U/mL penicillin-streptomycin, and 1% DMSO and incubated for an additional 96 hrs. To conduct
- 15 an HDAg in-cell ELISA, at the end of the incubation, the supernatant was removed, cells washed with PBS, fixed for 30 minutes at room temperature, washed with PBS, and permeabilized for 15 minutes at room temperature followed by a PBS wash and blocking for 45 minutes at room temperature. After aspiration of the supernatant, a primary mouse anti-HDAg antibody was added, incubated at 4 °C overnight followed by multiple PBS-T washes

and addition of a secondary anti-mouse IRDye800CW antibody. After 1 hr incubation at room temperature, cells were washed multiple times with PBS-T prior to readout. For HDAg readout, the plates were scanned on the LiCoR Odyssey CLX infrared scanner. Bulevirtide and DMSO treated cells were used as positive and negative controls in the assay, respectively.

TABLE 6 shows assay data for exemplified compounds of the invention following the described HepG2-NTCP HDV infection protocol, grouped in the following ranges: **A** indicates $EC_{50} < 10 \text{ nM}$; **B** indicates $10 \text{ nM} \leq EC_{50} < 100 \text{ nM}$; **C** indicates $100 \text{ nM} \leq EC_{50} < 500 \text{ nM}$; and **D** indicates $EC_{50} \geq 500 \text{ nM}$.

TABLE 6: assay data for exemplified compounds of the invention following the described HepG2-NTCP HDV infection protocol.

Example	HDAg EC ₅₀ (nM)
2	B
6a	B
7	B
10b	B
11b	B
20b	B
21	B
28	B
80a	A
151a	B
158b	B
284	B

NTCP assay protocol

50,000 HEK293 cells were seeded in 96-well plate in 100 μL Eagle’s Minimum Essential Medium (EMEM) supplemented with 10% FBS and a transfection mix (Lipofectamine 3000) containing human NTCP-expression DNA plasmids. The cells were incubated at 37 °C in 5% CO₂ for 24 h. After incubation, compounds were dispensed to the wells using a Tecan D300e dispenser in a serial dilution (4-fold, 8 doses) and the cells were

incubated at 37 °C in 5% CO₂ for 1 h. After incubation, 2 µM bile acid 3- α -nitrobenzoxadiazole (NBD)-Taurocholic acid (TCA) was added to each well and incubated at 37 °C in 5% CO₂ for 50 minutes, followed by aspiration of supernatants from the wells and reading the plates in a Tecan M1000 plate reader to measure the NBD (490ex/520em) fluorescence intensity. Bulevirtide and DMSO treated cells were used positive and negative controls, respectively.

Statistical Analysis

Percentage inhibitions were calculated with respect to the assay controls. Further data analysis was performed using validated statistical software (GraphPad Prism) to calculate the average EC₅₀ or IC₅₀ value from X experiments for the test compound.

ASBT assay protocol

20,000 HEK293T cells stably overexpressing human apical sodium-dependent bile salt transporter (ASBT) were seeded in a 96- well plate in 100 µL DMEM/High glucose with L-glutamine medium supplemented with 10% FBS containing puromycin (0.9 mg/mL) and incubated at 37 °C in 5% CO₂ in the presence of serially diluted compounds (3-fold serial dilution in DMSO, 8 concentrations) in DMEM (with 10% FBS) for 30 minutes. After incubation, 2 µM bile acid 3- α -nitrobenzoxadiazole (NBD)-Taurocholic acid (TCA) was added and incubated 2 minutes at 37 °C in 5% CO₂ followed by centrifugation at 500 RCF for 5 minutes at room temperature. After centrifugation, supernatant was carefully aspirated and 100 µL PBS/well added. Subsequently, plates were centrifuged at 500 RCF for 5 minutes at room temperature, followed by supernatant removal and adding 175 µL PBS/well and cells were resuspended thoroughly. For analysis, an Attune NxT Flow Cytometer (Invitrogen) was used, and NBD's fluorescence intensity was measured at 488 nm excitation. Linerixibat and DMSO treated cells were used as positive and negative controls, respectively.

Statistical Analysis

Percentage inhibitions were calculated cells respect to the assay controls. Further data analysis was performed using validated statistical software (GraphPad Prism) to calculate the average EC₅₀ or IC₅₀ value from X experiments for the test compound.

5 **Study design of pharmacokinetics**

Non-human primates (NHPs) were dosed with **Example 10b** via oral gavage at single dose levels ranging between 3 to 30 mg/kg.

Group No.	Frequency	Dose (mg/kg)	Volume (mL/kg)	Route	No. of Animals	Timepoint post-dose (hr)
1	Single	3	2	p.o.	3	0.25, 0.5, 1, 2, 4, 6, 8, 24, 48, 72
2	Single	10	2	p.o.	3	0.25, 0.5, 1, 2, 4, 6, 8, 24, 48, 72
3	Single	30	2	p.o.	3	0.25, 0.5, 1, 2, 4, 6, 8, 24, 48, 72

10 *Blood sampling pharmacokinetic phase*

Fifty microliters (50 µL) of blood were collected via cephalic and saphenous vein from all animals into EDTA-k2 tubes and stored under chilled conditions until centrifugation at 4 °C to obtain plasma. Plasma samples were labeled and stored at -80 °C until analysis.

15 *Bioanalysis*

Example 10b plasma concentrations were assessed via liquid chromatography-tandem mass spectrometry. The lower limit of quantitation was 3 ng/mL.

Reference: J Pharmacol. Exp. Ther. 2013, 344, 673–685.

20 **VII. Stereochemistry of Examples**

A crystal with size of 0.07 x 0.07 x 0.05 mm of 3-(((2S,3R)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid (**Example 10b**), which was synthesized through an asymmetric approach using methyl (R)-2-(bromomethyl)-

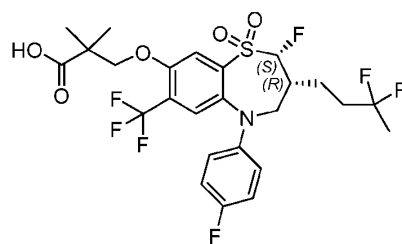
5,5-difluorohexanoate as a starting material (Scheme 27), was obtained from CHCl_3 /hexane (1/1.2 (v/v)) after 14 days of volatilization and was used for X-ray diffraction data collection. The data were collected on a Bruker D8 Venture diffractometer at 213.00 K using $\text{GaK}\alpha$ ($\lambda = 1.34139$) radiation. 38713 reflections were collected, of which 10215 reflections were unique
 5 (R(int) = 0.0615).

The crystal belongs to the monoclinic crystal system, with a space group P 1 21 1. The unit cell parameters were as follows: $a = 16.0606(2)$ Å, $b = 6.80110(10)$ Å, $c = 25.4318(4)$ Å, $\alpha = \gamma = 90.0^\circ$, $\beta = 103.3150(10)^\circ$, $V = 2703.23(7)$ Å³, $Z = 4$.

The structure was solved by direct methods and all the non-H atoms were refined
 10 against F^2 by full-matrix least-squares methods using the SHELXT structure solution program. Using the intrinsic phase method and using the SHELXL refinement package minimized by the least squares method for refinement. Multi-scans absorption correction method was used, and the maximum and minimum transmission parameters were 0.7508 and 0.5846, respectively. The final R , wR_2 , GOF are 0.0494 ($I > 2\sigma(I)$), 0.1317 and 1.053,
 15 respectively.

There is one $\text{C}_{25}\text{H}_{26}\text{F}_7\text{NO}_5\text{S}$ molecule in the asymmetric unit.

The ORTEP plot for Example 10b is presented in Figure. 1. The stereochemistry of Example 10b is shown below. The depictions of stereochemistry in the chemical structures of related examples are based on this assignment.



Stereochemistry of Example 10b based on ORTEP plot assignments.

A crystal with size of 0.07 x 0.07 x 0.05 mm of (R)-3-(((2R,3S)-3-(3,3-difluorobutyl)-2-fluoro-5-(4-fluorophenyl)-1,1-dioxido-7-(trifluoromethyl)-2,3,4,5-
 25 tetrahydrobenzo[b][1,4]thiazepin-8-yl)oxy)-2-methylpropanoic acid (Example 11a), which

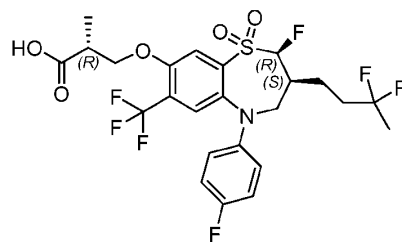
was synthesized using methyl (R)-3-hydroxy-2-methylpropanoate as a starting material (Scheme 11), was obtained from CHCl₃/hexane (1/1.2 (v/v)) after 5 days of volatilization and was used for X-ray diffraction data collection. The data were collected on a Bruker D8 Venture diffractometer at 213.00 K using GaK α (λ = 1.34139) radiation. 46833 reflections were collected, of which 10244 reflections were unique (R(int) = 0.1160).

The crystal belongs to orthorhombic crystal system, with a space group P2₁2₁2₁. The unit cell parameters were as follows: a = 9.4371(6) Å, b = 16.6833(9) Å, c = 34.123(2) Å, α = β = γ = 90.0°, V = 5372.4(6) Å³, Z = 8.

The structure was solved by direct methods and all the non-H atoms were refined against F^2 by full-matrix least-squares methods using the SHELXT structure solution program. Using the intrinsic phase method and using the SHELXL refinement package minimized by the least squares method for refinement. Multi-scans absorption correction method was used, and the maximum and minimum transmission parameters were 0.7508 and 0.3680, respectively. The final R , wR_2 , GOF are 0.0685 ($I > 2\sigma(I)$), 0.1650 and 1.015, respectively.

There are two C₂₄H₂₄F₇NO₅S molecules in the asymmetric unit.

The ORTEP plot for Example 11a is presented in Figure. 2. The stereochemistry of Example 11a is shown below. The depictions of stereochemistry in the chemical structures of related examples are based on this assignment.



Stereochemistry of Example 11a based on ORTEP plot assignments.

EQUIVALENTS

While specific embodiments of the subject disclosure have been discussed, the above specification is illustrative and not restrictive. Many variations of the disclosure will

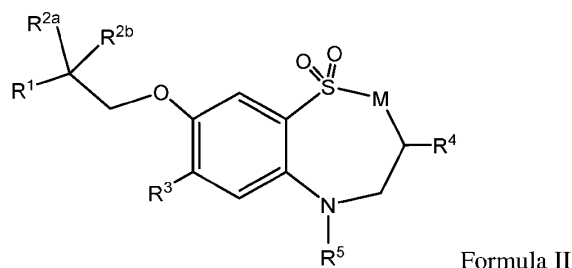
become apparent to those skilled in the art upon review of this specification. The full scope of the disclosure should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction
5 conditions, and so forth used in the specification and claims are to be understood as being
modified in all instances by the term “about.” Accordingly, unless indicated to the contrary,
the numerical parameters set forth in this specification and attached claims are
approximations that may vary depending upon the desired properties sought to be obtained by
the present disclosure.

10

CLAIMS:

1. A compound of Formula II

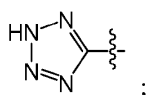


, or a pharmaceutically acceptable salt thereof, wherein:

5 M is -CHF-, -CH(CH₃)-, -CF(CH₃)-, -CF₂-, or -C(CH₃)₂-;

R^a, R^b and R^c are independently selected for each occurrence from the group consisting of hydrogen, C₁₋₆alkyl, haloC₁₋₆alkyl and C₃₋₆monocycloalkyl;

R¹ is OH, CH₃, -C(O)NH₂, -C(O)OH, -C(O)OC₁₋₆alkyl, -P(O)(OH)₂, -S(O)₂OH or



10 R^{2a} and R^{2b} are independently selected from the group consisting of hydrogen, halo, OH, methyl, ethyl and CH₂OH; or R^{2a} and R^{2b} together with the carbon atom to which they are attached form a C=CH₂, C₃₋₆monocycloalkyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl or 1,3-dioxanyl group, wherein the C₃₋₆monocycloalkyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl or 1,3-dioxanyl group is optionally substituted with 1 to
15 3 independently selected from halo and methyl groups;

R³ is selected from the group consisting of hydrogen, halogen, cyano, R^aR^bN-, C₁₋₄alkyl, haloC₁₋₄alkyl, C₁₋₄alkoxy, haloC₁₋₄alkoxy, C₁₋₄alkylthio, haloC₁₋₄alkylthio, C₃₋₇monocycloalkyl, C₃₋₇monocycloalkyloxy, C₃₋₇monocycloalkylthio, C₃₋₇monocycloalkyl-CH₂-thio, and C₅₋₁₂bicycloalkylthio, wherein the C₃₋₇monocycloalkyl, C₃₋₇monocycloalkyloxy, C₃₋₇monocycloalkylthio, C₃₋₇monocycloalkyl-CH₂-thio, and C₅₋₁₂bicycloalkylthio group is optionally substituted with 1 to 3 halo groups;

R⁴ is haloC₃₋₄alkyl;

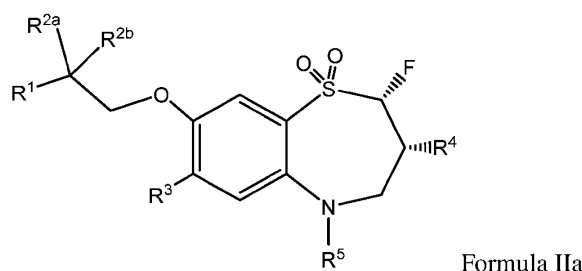
R⁵ is phenyl, C₃₋₇monocycloalkyl or C₅₋₁₂bicycloalkyl, wherein the phenyl, C₃₋₇monocycloalkyl or C₅₋₁₂bicycloalkyl is optionally substituted with one to six substituents

independently selected from the group consisting of halo, OH, CN, HOC(O)-, R^aR^bN -,
 $R^aR^bNS(O)_{q-}$, $C_{1-4}alkyl$, $C_{2-4}alkenyl$, $C_{2-4}alkynyl$, $haloC_{1-4}alkyl$, $hydroxyC_{1-4}alkyl$ -, $R^aR^bNC_{1-4}alkyl$ -,
 $C_{1-4}alkoxy$, $haloC_{1-4}alkoxy$, $hydroxyC_{1-4}alkoxy$ -, $R^aR^bNC_{1-4}alkoxy$ -, $C_{1-3}alkoxyC_{1-4}alkyl$ -,
 $haloC_{1-3}alkoxyC_{1-4}alkyl$ -, $R^aR^bNC(O)$ -, $C_{1-4}alkylC(O)$ -, $C_{1-4}alkoxyC(O)$ -, $C_{1-4}alkylC(O)O$ -,
 $C_{1-4}alkylS(O)_{q-}$, $C_{1-4}alkylS(O)_{q-}NR^c$ -, $C_{1-6}alkylS(O)_qC_{1-4}alkyl$ -, $C_{1-4}alkylC(O)C_{1-6}alkyl$ -, and $C_{1-6}alkylC(O)OC_{1-4}alkyl$ -, and

q is independently selected for each occurrence from the group consisting of 0, 1 and 2.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein M is $-CHF-$.

3. The compound of claim 1 or 2, wherein Formula II is of Formula IIa



, or a pharmaceutically acceptable salt thereof.

4. The compound according to any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein R^1 is $-C(O)OH$.

5. The compound according to any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein R^1 is $-S(O)_2OH$.

6. The compound according to any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein R^1 is $-P(O)(OH)_2$,

7. The compound according to any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^{2a} and R^{2b} are independently selected from the group consisting of hydrogen, halo, OH and methyl.

5 8. The compound according to any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^{2a} and R^{2b} are methyl.

9. The compound according to any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^{2a} is hydrogen and R^{2b} are methyl.

10

10. The compound according to any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^{2a} and R^{2b} together with the carbon atom to which they are attached form a $C=CH_2$, cyclopropyl, cyclobutyl, or oxetanyl group, wherein the cyclopropyl or cyclobutyl group is optionally substituted with 1-3 halo groups.

15

11. The compound of claim 10, or a pharmaceutically acceptable salt thereof, wherein R^{2a} and R^{2b} together with the carbon atom to which they are attached form a $C=CH_2$, cyclopropyl, cyclobutyl, or oxetanyl group.

20 12. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein R^{2a} and R^{2b} together with the carbon atom to which they are attached form a cyclopropyl group.

25 13. The compound according to any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein R^3 is halo C_{1-2} alkyl.

14. The compound of claim 13, or a pharmaceutically acceptable salt thereof, wherein R^3 is CF_3 .

15. The compound according to any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein R^3 is C_{5-12} bicycloalkylthio.

16. The compound according to any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein R^3 is $haloC_{3-7}$ monocycloalkylthio.

17. The compound according to any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein R^4 is n-butyl substituted with 1 to 6 halo atoms.

18. The compound of claim 17, or a pharmaceutically acceptable salt thereof, wherein R^4 is n-butyl substituted with 1 to 6 F atoms.

19. The compound of claim 18, or a pharmaceutically acceptable salt thereof, wherein R^4 is $-CH_2CH_2CF_2CH_3$.

20. The compound according to any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein R^4 is n-propyl substituted with 1 to 6 halo atoms.

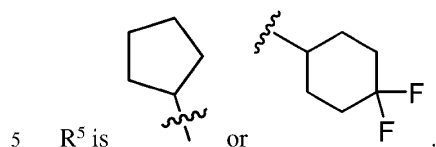
21. The compound of claim 20, or a pharmaceutically acceptable salt thereof, wherein R^4 is n-propyl substituted with 1 to 6 F atoms.

22. The compound of claim 21, or a pharmaceutically acceptable salt thereof, wherein R^4 is $-CH_2CH_2CF_3$.

23. The compound according to any one of claims 1-22, or a pharmaceutically acceptable salt thereof, wherein R^5 is C_{3-7} monocycloalkyl optionally substituted with one to six substituents independently selected from the group consisting of halo, OH, CN, $HOC(O)-$, R^aR^bN- , $R^aR^bNS(O)_q-$, $C_{1-4}alkyl$, $C_{2-4}alkenyl$, $C_{2-4}alkynyl$, $haloC_{1-4}alkyl$, $hydroxyC_{1-4}alkyl-$, $R^aR^bNC_{1-4}alkyl-$, $C_{1-4}alkoxy$, $haloC_{1-4}alkoxy$, $hydroxyC_{1-4}alkoxy-$, $R^aR^bNC_{1-4}alkoxy-$, $C_{1-4}alkoxyC_{1-4}alkyl-$, $haloC_{1-3}alkoxyC_{1-4}alkyl-$, $R^aR^bNC(O)-$, $C_{1-4}alkylC(O)-$, $C_{1-4}alkoxyC(O)-$,

C₁₋₄alkylC(O)O-, C₁₋₄alkylS(O)_q-, C₁₋₄alkylS(O)_qNR^c-, C₁₋₆alkylS(O)_qC₁₋₄alkyl-, C₁₋₄alkylC(O)C₁₋₆alkyl-, and C₁₋₆alkylC(O)OC₁₋₄alkyl-.

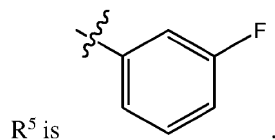
24. The compound of claim 23, or a pharmaceutically acceptable salt thereof, wherein



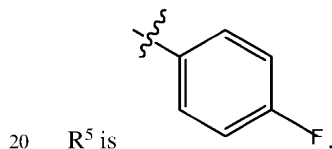
25. The compound according to an one of claims 1- 22, or a pharmaceutically acceptable salt thereof, wherein In certain embodiments, R⁵ is phenyl optionally substituted with one to six substituents independently selected form the group consisting of halo, OH, CN, HOC(O)-, R^aR^bN-, R^aR^bNS(O)_q-, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, haloC₁₋₄alkyl, hydroxyC₁₋₄alkyl-, R^aR^bNC₁₋₄alkyl-, C₁₋₄alkoxy, haloC₁₋₄alkoxy, hydroxyC₁₋₄alkoxy-, R^aR^bNC₁₋₄alkoxy-, C₁₋₃alkoxyC₁₋₄alkyl-, haloC₁₋₃alkoxyC₁₋₄alkyl-, R^aR^bNC(O)-, C₁₋₄alkylC(O)-, C₁₋₄alkoxyC(O)-, C₁₋₄alkylC(O)O-, C₁₋₄alkylS(O)_q-, C₁₋₄alkylS(O)_qNR^c-, C₁₋₆alkylS(O)_qC₁₋₄alkyl-, C₁₋₄alkylC(O)C₁₋₆alkyl-, and C₁₋₆alkylC(O)OC₁₋₄alkyl-.

15

26. The compound of claim 25, or a pharmaceutically acceptable salt thereof, wherein



27. The compound of claim 25, or a pharmaceutically acceptable salt thereof, wherein



28. A pharmaceutical composition comprising a compound according to any one of claims 1-27, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

5 29. A method of treating Hepatitis B (HBV) infection in a subject in need thereof, the method comprising: administering to the subject a therapeutically effective amount of a compound according to any one of claims 1-27, or a pharmaceutically acceptable salt thereof.

 30. A method of treating Hepatitis B (HBV) infection in a subject in need thereof, the
10 method comprising: administering to the subject a therapeutically effective amount of a pharmaceutical composition of claim 28.

 31. A method of treating Hepatitis D (HDV) infection in a subject in need thereof, the
15 method comprising: administering to the subject a therapeutically effective amount of a compound according to any one of claims 1-27, or a pharmaceutically acceptable salt thereof.

 32. A method of treating Hepatitis D (HDV) infection in a subject in need thereof, the
20 method comprising: administering to the subject a therapeutically effective amount of a pharmaceutical composition of claim 28.

 33. A compound according to any one of claims 1-27, or a pharmaceutically acceptable salt thereof, for use in therapy.

 34. A compound according to any one of claims 1-27, or a pharmaceutically
25 acceptable salt thereof, for use as a medicament.