

HEPATITIS B CORE PROTEIN ALLOSTERIC MODULATORS

STATEMENT OF GOVERNMENT SUPPORT

[0001] This invention was made with government support under AI067417 awarded by the National Institutes of Health. The government has certain rights in the invention.

RELATED APPLICATIONS

[0002] This application claims the benefit of and priority to United States Provisional Patent Applications serial nos. 61/952,467, filed March 13, 2014, and 62/010,025, filed June 10, 2014, the contents of each of which are hereby incorporated by reference.

BACKGROUND

[0003] Hepatitis B (HBV) causes viral Hepatitis that can further lead to chronic liver disease and increase the risk of liver cirrhosis and liver cancer (hepatocellular carcinoma). Worldwide, about 2 billion people have been infected with HBV, around 360 million people are chronically infected, and every year HBV infection causes more than one half million deaths (2009; WHO, 2009). HBV can be spread by body fluids: from mother to child, by sex, and via blood products. Children born to HBV -positive mothers may also be infected, unless vaccinated at birth.

[0004] The virus particle is composed of a lipid enveloped studded with surface protein (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 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 assembly, P reverse transcribes the pgRNA to rcDNA within the confines of the capsid to generate the DNA-filled viral core. For convenience, we divide the assembly process at the point of capsid assembly and pgRNA-packaging. Steps preceding this event are “upstream”; steps following RNA-packaging are “downstream”.

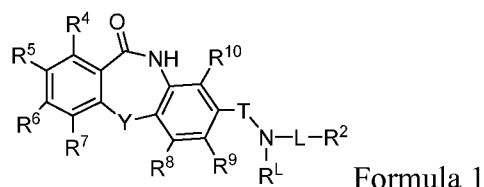
[0005] At present, chronic HBV is primarily treated with nucleos(t)ide analogs (e.g. entecavir) that suppress the virus while the patient remains on treatment but do not eliminate the infection, even after many years of treatment. Once a patient starts taking nucleotide analogs most must continue taking them or risk the possibility of a life threatening immune response to viral rebound. Further, nucleos(t)ide therapy may lead to the emergence of antiviral drug resistance (Deres and Rubsamen-Waigmann, 1999; Tennant et al., 1998; Zhang et al., 2003) and – in rare patients- adverse events have been reported (Ayoub and Keeffe , 2011).

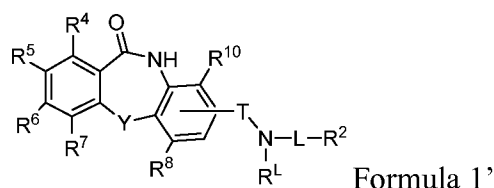
[0006] The only FDA approved alternative to nucleos(t)ide analogs is treatment with interferon α or pegylated interferon α . Unfortunately, the adverse event incidence and profile of interferon α can result in poor tolerability, and many patients are unable to complete therapy. Moreover, only a small percentage of patients are considered appropriate for interferon therapy, as only a small subset of patients are likely to have asustained 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 for treatment.

[0007] Thus, current HBV treatments can range from palliative to watchful waiting. Nucleos(t)ide analogs suppress virus production, treating the symptom, but leave the infection 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.

SUMMARY

[0008] Provided herein are compounds that can have properties such as those described below, where the compounds in some embodiments may be represented by:





wherein R^2 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^L , Y, T, and L are defined herein. Also provided herein are methods of treating viral infections, such as hepatitis B, comprising administering to patient a disclosed compound.

[0009] For example, the present disclosure is directed in part to compounds having allosteric effector properties against Hepatitis B virus Cp, a protein found as a dimer, a multimer, and as the protein shell of the HBV core. Without being bound by theory, disclosed compounds may ultimately target multimerization of viral core proteins, which is central to HBV infection, where the core protein multimerizes into shell, or capsid, and/or disclosed compounds may for example, ultimately target interaction of viral core proteins with other macromolecules, such as host or viral nucleic acid, host proteins, or other viral proteins. For example, disclosed compounds may be considered in some embodiments CpAM -- core protein allosteric modifiers. CpAM interaction with core protein can allosterically favor an assembly-active form of Cp dimer and lead to viral capsid assembly at an inappropriate time or place or lead to non-standard intersubunit interactions, all resulting in defective capsids. CpAMs may additionally or alternatively affect steps of “upstream” of capsid assembly by altering the concentrations or nature of Cp available as dimer as compared to capsid or other multimeric forms. Disclosed compounds or CpAMs may, in some embodiments, noticeably affect functions upstream of viral assembly such as modulation of cccDNA transcription, RNA stability and/or protein-protein interactions.

BRIEF DESCRIPTION OF THE FIGURES

[00010] Figure 1 illustrates synthetic scheme 1.

[00011] Figure 2 illustrates synthetic scheme 2.

DETAILED DESCRIPTION

[00012] The features and other details of the disclosure will now be more particularly described. Before further description of the present invention, certain terms employed in the 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.

Definitions

[00013] As intended herein, the terms "a" and "an" include singular as well as plural references unless the context clearly dictates otherwise. For example, the term "an assembly effector" can include one or more such effectors.

[00014] 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, 1-4, or 1-3 carbon atoms, referred to herein as C₁₋₆alkyl, C₁₋₄alkyl, and C₁₋₃alkyl, respectively. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, 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, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, etc.

[00015] 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 or 3-4 carbon atoms, referred to herein as C₂₋₆alkenyl, and C₃₋₄alkenyl, respectively. Exemplary alkenyl groups include, but are not limited to, vinyl, allyl, butenyl, pentenyl, etc.

[00016] The term "alkoxy" as used herein refers to a straight or branched alkyl group attached to oxygen (alkyl-O-). Exemplary alkoxy groups include, but are not limited to, alkoxy groups of 1-6 or 2-6 carbon atoms, referred to herein as C₁₋₆alkoxy, and C₂₋₆alkoxy, respectively. Exemplary alkoxy groups include, but are not limited to methoxy, ethoxy, isopropoxy, etc.

[00017] 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, or 3-6 carbon atoms, referred to herein as C₂₋₆alkynyl, and C₃₋₆alkynyl, respectively. Exemplary alkynyl groups include, but are not limited to, ethynyl, propynyl, butynyl, pentynyl, hexynyl, methylpropynyl, etc.

[00018] The terms “cycloalkyl” or a “carbocyclic group” as used herein refers to a saturated or partially unsaturated hydrocarbon group of, for example, 3-6, or 4-6 carbons, referred to herein as C₃₋₆cycloalkyl or C₄₋₆cycloalkyl, respectively. Exemplary cycloalkyl groups include, but are not limited to, cyclohexyl, cyclopentyl, cyclopentenyl, cyclobutyl or cyclopropyl.

[00019] The terms “halo” or “halogen” as used herein refer to F, Cl, Br, or I.

[00020] The terms “heteroaryl” or “heteroaromatic group” as used herein refers to a monocyclic aromatic 5-6 membered ring system containing one or more heteroatoms, for example one to three heteroatoms, such as nitrogen, oxygen, and sulfur. Where possible, said heteroaryl ring may be linked to the adjacent radical through carbon or nitrogen. Examples of heteroaryl rings include but are not limited to furan, thiophene, pyrrole, thiazole, oxazole, isothiazole, isoxazole, imidazole, pyrazole, triazole, pyridine or pyrimidine etc.

[00021] The terms “heterocyclyl” or “heterocyclic group” are art-recognized and refer to saturated or partially unsaturated 4-7 membered ring structures, whose ring structures include one to three heteroatoms, such as nitrogen, oxygen, and sulfur. Where possible, heterocyclyl rings may be linked to the adjacent radical through carbon or nitrogen. Examples of heterocyclyl groups include, but are not limited to, pyrrolidine, piperidine, morpholine, thiomorpholine, piperazine, oxetane, azetidine, tetrahydrofuran or dihydrofuran etc

[00022] The terms “hydroxy” and “hydroxyl” as used herein refers to the radical –OH.

[00023] "Treatment" as used herein includes the alleviation, prevention, reversal, amelioration or control of a pathology, disease, disorder, process, condition or event, including viral infection. In this context, the term "treatment" is further to be understood as embracing the use of a drug to inhibit, block, reverse, restrict or control progression of viral infection.

[00024] As used herein, the term “pharmaceutical composition” refers to compositions of matter comprising at least one pharmaceutical compound and optionally a pharmaceutically acceptable carrier.

[00025] As used herein, the term “pharmaceutical compound” or “drug” refers to a free compound, its therapeutically suitable salts, solvates such as hydrates, specific crystal forms of the compound or its salts, or therapeutically suitable prodrugs of the compound.

[00026] Pharmaceutically or pharmacologically 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 sterility, pyrogenicity, and general safety and purity standards as required by FDA Office of Biologics standards.

[00027] 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, and the like, that are compatible with pharmaceutical 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.

[00028] 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 invention 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.

[00029] 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 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.

[00030] Compounds of the disclosure may contain a carbocyclic or heterocyclic ring and 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 a carbocyclic or heterocyclic rings 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*.”

[00031] Individual enantiomers and diastereomers of compounds of the present invention 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, 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 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 enantio- and diastereoselective transformations, and may involve the use of chiral auxiliaries. For examples, see Carreira and Kvaerno, *Classics in Stereoselective Synthesis*, Wiley-VCH: Weinheim, 2009.

[00032] 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 intended that the invention 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.

[00033] The invention also embraces isotopically labeled compounds of the invention which 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 invention 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 , respectively. For example, a compound of the invention may have one or more H atom replaced with deuterium.

[00034] 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 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 invention can generally be prepared by following procedures analogous to those disclosed in the examples herein by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

[00035] The term "therapeutically suitable salt," refers to salts or zwitterions of pharmaceutical compounds which are water or oil-soluble or dispersible, suitable for treatment of disorders and effective for their intended use. The salts may be prepared, for instance, during the final isolation and purification of the compounds or separately by reacting an amino group of

the compounds with a suitable acid. For example, a compound may be dissolved in a suitable solvent, such as but not limited to methanol and water, and treated with at least one equivalent of an acid, for instance hydrochloric acid. The resulting salt may precipitate out and be isolated by filtration and dried under reduced pressure. Alternatively, the solvent and excess acid may be removed under reduced pressure to provide the salt. Representative salts include acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, formate, isethionate, fumarate, lactate, maleate, methanesulfonate, naphthylenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, oxalate, maleate, pivalate, propionate, succinate, tartrate, trichloroacetate, trifluoroacetate, glutamate, para-toluenesulfonate, undecanoate, hydrochloric, hydrobromic, sulfuric, phosphoric, and the like. The amino groups of a compound may also be quaternized with alkyl chlorides, bromides, and iodides such as methyl, ethyl, propyl, isopropyl, butyl, lauryl, myristyl, stearyl, and the like.

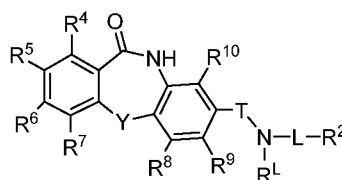
[00036] Basic addition salts may be prepared, for instance, during the final isolation and purification of pharmaceutical compounds by reaction of a carboxyl group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation such as lithium, sodium, potassium, calcium, magnesium, or aluminum, or an organic primary, secondary, or tertiary amine. Quaternary amine salts may be derived, for example, from methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, N,N-dibenzylphenethylamine, 1-phenamine, and N,N'-dibenzylethylenediamine, ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine, and the like.

[00037] The term “therapeutically suitable prodrug,” refers to those prodrugs or zwitterions which are suitable for use in contact with the tissues of subjects and are effective for their intended use. The term “prodrug” refers to compounds that are transformed in vivo to a pharmaceutical compound, for example, by hydrolysis in blood. The term “prodrug,” refers to compounds that contain, but are not limited to, substituents known as “therapeutically suitable esters.” The term “therapeutically suitable ester,” refers to alkoxycarbonyl groups appended to the parent molecule on an available carbon atom. More specifically, a “therapeutically suitable

ester,” refers to alkoxycarbonyl groups appended to the parent molecule on one or more available aryl, cycloalkyl and/or heterocycle groups. Compounds containing therapeutically suitable esters are an example, but are not intended to limit the scope of compounds considered to be prodrugs. Examples of prodrug ester groups include pivaloyloxymethyl, acetoxymethyl, phthalidyl, indanyl and methoxymethyl, as well as other such groups known in the art. Other examples of prodrug ester groups are found in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems*, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

[00038] The terms "pharmaceutically effective amount" and "effective amount", as used herein, refer to an amount of a pharmaceutical formulation that will elicit the desired therapeutic effect or response when administered in accordance with the desired treatment regimen. US2011/0144086 describes the use of some diabenzothiazepine molecules (DBTs) as anti-malarial "inhibitors of the plasmodial surface anion channel." However, no study of DBT molecules as anti-virals has yet been reported.

1. Disclosed compounds contemplated herein may in some embodiments be represented by Formula 1:



Formula 1

wherein:

T is selected from the group consisting of $-C(O)-$, $-CH_2-C(O)-$, $-N(C(O)-CH_3)-$, $-NH-$, $-O-$, and $-S(O)_z-$, where z is 0, 1 or 2;

Y is $C(R^{11})_2$, $S(O)_y$, NR_Y and O wherein y is 0, 1, or 2;

R_Y is selected from the group consisting of H, methyl, ethyl, propyl, phenyl and benzyl;

R_L is selected from the group consisting of H, methyl, and $-C(O)-C_{1-3}alkyl$;

L is a bond or C_{1-4} straight chain alkylene optionally substituted by one or two substituents each independently selected from the group consisting of methyl (optionally substituted by halogen or hydroxyl), ethenyl, hydroxyl, $NR'R''$, phenyl, heterocycle, and halogen and wherein the C_{1-4} straight chain alkylene may be interrupted by an $-O-$;

R^2 is selected from the group consisting of H,

phenyl or naphthyl (wherein the phenyl or naphthyl may be optionally substituted with one, two, three or more substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano, carboxy, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{1-6}alkoxy$, $NR'R''$, $-C(O)-NR'R''$, $-C(O)-C_{1-6}alkyl$, $-C(O)-C_{1-6}alkoxy$, phenyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of halogen, hydroxyl, cyano, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{1-6}alkoxy$, $NR'R''$, $C(O)-NR'R''$, $-C(O)-C_{1-6}alkyl$, $-C(O)-C_{1-6}alkoxy$, $-S(O)_w-C_{1-6}alkyl$ (where w is 1, 2 or 3), $S(O)_w-NR'R''$ (where w is 1, 2 or 3), $-NR'-S(O)_w$, and $-S(O)_w-NR'R''$ (where w is 1, 2 or 3)), heteroaryl (optionally substituted by one, two or three substituents each independently selected from the group consisting of halogen, hydroxyl, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{1-6}alkoxy$, $NR'R''$, $C(O)-NR'R''$, $-C(O)-C_{1-6}alkyl$, $-C(O)-C_{1-6}alkoxy$, $-S(O)_w-C_{1-6}alkyl$ (where w is 1, 2 or 3), $NR'-S(O)_w$, and $-S(O)_w-NR'R''$ (where w is 1, 2 or 3)), $C_{3-6}cycloalkyl$, $-S(O)_w-C_{1-6}alkyl$ (where w is 1, 2 or 3), $-S(O)_w-NR'R''$ (where w is 1, 2 or 3), and $-NR'-S(O)_w$ (where w is 1, 2 or 3)),

5-6 membered heteroaryl having one, two, or three heteroatoms each independently selected from O, N and S (wherein the 5-6 membered heteroaryl may be optionally substituted on a carbon with one, two, three or more substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano, carboxy, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{1-6}alkoxy$, phenyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of halogen, hydroxyl, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{1-6}alkoxy$, $NR'R''$, $C(O)-NR'R''$, $-C(O)-C_{1-6}alkyl$, $-C(O)-OH$, $-C(O)-C_{1-6}alkoxy$, $-S(O)_w-C_{1-6}alkyl$ (where w is 1, 2 or 3), $-NR'-S(O)_w$, and $-S(O)_w-NR'R''$ (where w is 1, 2 or 3)), heteroaryl, heterocycle, $NR'R''$, $-C(O)-NR'R''$, $-C(O)-C_{1-6}alkyl$, $-C(O)-C_{1-6}alkoxy$, $-S(O)_w-C_{1-6}alkyl$ (where w is 1, 2 or 3), $-NR'-S(O)_w$, and $-S(O)_w-NR'R''$ (where w is 1, 2 or 3), and on a nitrogen by R'),

C₁₋₆alkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₃₋₁₀cycloalkyl (optionally substituted with one, two, three or more substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano, carboxy, NR'R'', -C(O)-NR'R'', =CNR', C₁₋₆alkyl, C₁₋₆alkoxy, -C(O)-C₁₋₆alkyl, and -C(O)-C₁₋₆alkoxy, and wherein the C₃₋₁₀cycloalkyl may optionally be a bridged cycloalkyl)), and a 4-6 membered heterocycloalkyl having one or two heteroatoms each independently selected from O, N and S (wherein the 4-6 membered heterocycloalkyl may be optionally substituted with one, two, three or more substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano, carboxy, NR'R'', -C(O)-NR'R'', C₁₋₆alkyl, C₁₋₆alkoxy, -C(O)-C₁₋₆alkyl, and -C(O)-C₁₋₆alkoxy);

R' is selected, independently for each occurrence, from H, methyl, ethyl, propyl, phenyl, and benzyl;

R'' is selected, independently for each occurrence, from H, methyl, ethyl, propyl, butyl, carboxybenzyl, -C(O)-methyl and -C(O)-ethyl, or R' and R'' taken together may form a 4-6 membered heterocycle;

each of moieties R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, and R¹¹ are independently selected for each occurrence from the group consisting of hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, halogen, hydroxyl, nitro, cyano, NR'R'', -C(O)-NR'R'', -S(O)_w-C₁₋₆alkyl (where w is 1, 2 or 3), -NR'-S(O)_w, and -S(O)_w-NR'R'' (where w is 0, 1 or 2), C₁₋₆alkoxy, -C(O)-OH, -C(O)-C₁₋₆alkyl, and -C(O)-C₁₋₆alkoxy;

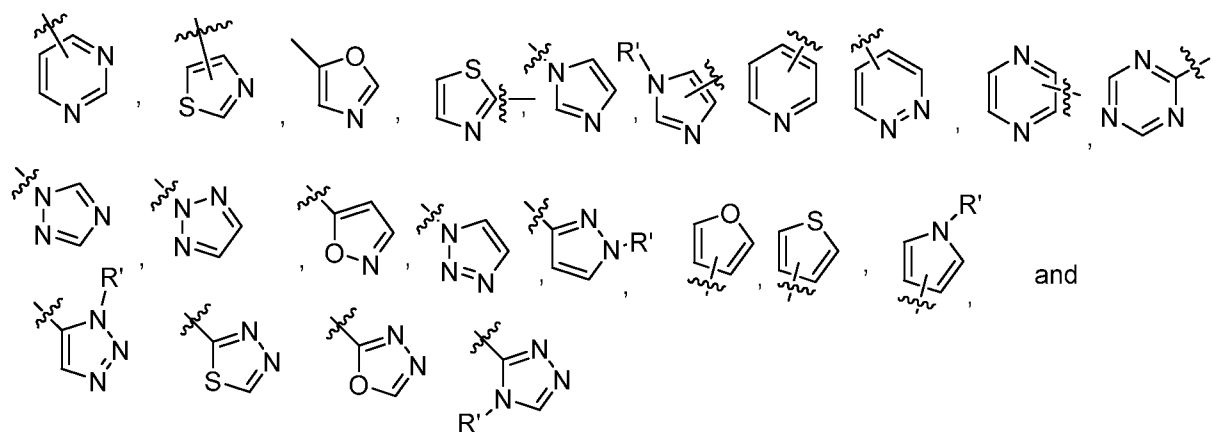
wherein for each occurrence, C₁₋₆alkyl may be optionally substituted with one, two, three or more substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano, carboxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, phenyl, NR'R'', -C(O)-NR'R'', S(O)_w-methyl (where w is 1, 2 or 3), -NR'-S(O)_w, and S(O)_w-NR'R'' (where w is 0, 1 or 2); C₁₋₆alkoxy may be optionally substituted with one, two, three or more substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano, carboxy, C₁₋₆alkyl, phenyl, NR'R'', -C(O)-NR'R'', S(O)_w-C₁₋₆alkyl (where w is 1, 2 or 3), -NR'-S(O)_w, and S(O)_w-NR'R'' (where w is 0, 1 or 2); and C₃₋₆cycloalkyl may be optionally substituted with one, two, three or more substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano, carboxy, C₁₋₆alkyl, C₁₋

₆alkoxy, -C(O)-C₁₋₆alkyl, -C(O)-C₁₋₆alkoxy, and NR'R''; and pharmaceutically acceptable salts thereof.

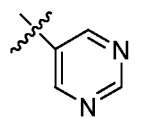
[00039] For example, in certain embodiments, L may be selected from the group consisting of a bond, -CH₂-, -CH₂-CH₂-, or CH₂(CH₂)-CH₂-. For example, in certain embodiments, L is C₂₋₃alkylene, or in other embodiments, L is selected from the group consisting of -CH₂-CH₂-, -CH₂(CH₂)-CH₂-, -CH₂-CH₂(OH)-, -CH₂-CH₂(CH₃OH)-, and -CH₂-CH₂(OH)-CH₂-. L may be a bond, or for example, L may be C₂₋₃alkylene-O-. For example, L may be -O-CH₂-CH₂(OH)-, -CH₂-CH₂(CH₃OH)-, or -CH₂-CH₂(OH)-CH₂-. In other embodiments, L is -O-.

[00040] Y, in certain embodiments, may be S(O)_y (where y is 0, 1 or 2), or NR_Y. In certain embodiments y is 0 or 2, for example, Y may be S.

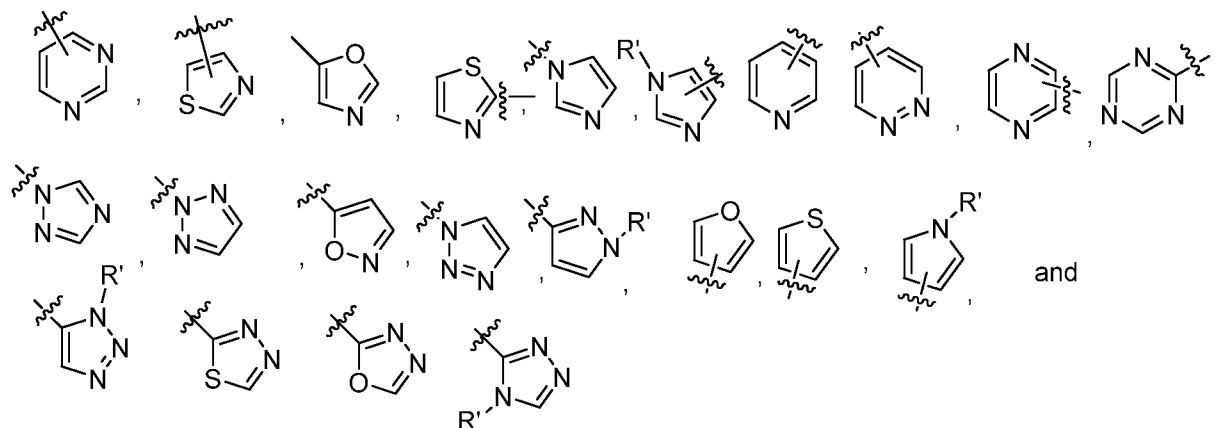
[00041] In certain other embodiments, R² is phenyl, for example, R² may be phenyl substituted by C₁₋₆alkyl or C₁₋₆alkoxy. In other embodiments, R² is phenyl substituted by one or two substituents each selected from the group consisting of fluorine, chlorine, C₁₋₆alkyl (optionally substituted by one, two or three fluorines), C₁₋₆alkoxy (optionally substituted by one, two or three fluorines), hydroxyl, NR'R'', -S(O)₂-NR'R'', heteroaryl, and phenyl (optionally substituted by halogen or hydroxyl). For example, R² may be phenyl substituted by an 5-6 membered heteroaryl selected from the group consisting of:



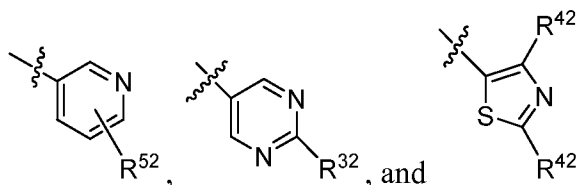
In an exemplary embodiment R² is phenyl substituted by



[00042] In other embodiments, R^2 may be a 5-6 membered heteroaryl, for example, R^2 may be selected from the group consisting of:



[00043] In another embodiment, R^2 may be a 4-6 membered heterocycloalkyl, which may be optionally substituted as described above. For example, R^2 may be selected from the group consisting of:

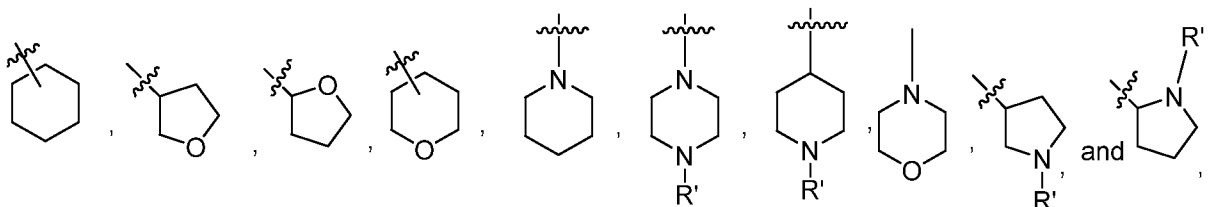


wherein R^{32} is selected from the group consisting of H, halogen, phenyl, and C_{1-6} alkyl (optionally substituted by one, two or three halogens); R^{52} is selected from the group consisting of H, halogen, phenyl, and C_{1-6} alkyl (optionally substituted by one, two or three halogens); and R^{42} is selected from the group consisting of H, halogen, phenyl, C_{1-6} alkyl (optionally substituted by one, two or three halogens), C_{1-6} alkoxy (optionally substituted by one, two or three halogens), NH_2 , $-OCH_3$, $NHCH_3$, and $N(CH_3)_2$.

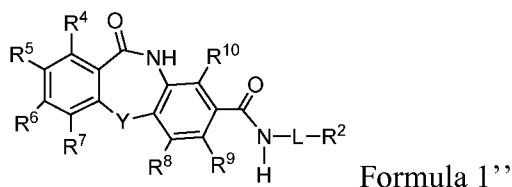
[00044] R^{42} , in some embodiments, may be independently selected for each occurrence from the group consisting of H, methyl, ethyl, propyl, $-CF_3$, $-CH_2CH_3$, Cl, F, phenyl, $-NH_2$, $-OCH_3$, $NHCH_3$, and $N(CH_3)_2$.

[00045] In other embodiments, e.g. when R^2 is a heteroaryl, R^2 may be optionally substituted on a carbon by one or two substituents each selected from the group consisting of fluorine, chlorine, phenyl, $-NH_2$, NH C_{1-6} alkyl, and $N(C_{1-6}alkyl)_2$, C_{1-6} alkyl, and C_{1-6} alkoxy. In certain embodiments, R^{11} is CH_2 or $-CH_2(CH_3)-$

[00046] Also contemplated herein is a compound of formula 1 or 1' wherein R^2 is a 4-6 membered heterocycloalkyl or C_{4-6} cycloalkyl, for example, R^2 is selected from the group of: tetrahydropyranyl, tetrahydrofuran, cyclopentane, cyclohexane, and cyclobutane. In an embodiment, R^2 is selected from the group consisting of:



[00047] A compound represented by:



is also contemplated herein, wherein

Y is $S(O)_y$, wherein y is 0, 1, 2;

L is a bond or C_{1-4} straight chain alkylene optionally substituted by one or two substituents each independently selected from the group consisting of methyl (optionally substituted by halogen or hydroxyl), hydroxyl and halogen;

R^2 is selected from phenyl optionally substituted with one, two, three or more substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano, carboxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, $NR'R''$, $-C(O)-NR'R''$, $-C(O)-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkoxy, phenyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of halogen, hydroxyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, $NR'R''$, $C(O)-NR'R''$, $-C(O)-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkoxy, $-S(O)_w-C_{1-6}$ alkyl (where w is 1, 2 or 3), $NR'-S(O)_w$, and $-S(O)_w-NR'R''$ (where w is 1, 2 or 3)), 5-6 membered heteroaryl having one, two, or three heteroatoms each independently selected from O, N and S (optionally substituted by one, two or three substituents each independently selected from the group

consisting of halogen, hydroxyl, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, NR'R'', C(O)-NR'R'', -C(O)-C₁₋₆alkyl, -C(O)-C₁₋₆alkoxy, -S(O)_w-C₁₋₆alkyl (where w is 1, 2 or 3), -NR'-S(O)_w, and -S(O)_w-NR'R'' (where w is 1, 2 or 3)), C₃₋₆cycloalkyl, -S(O)_w-C₁₋₆alkyl (where w is 1, 2 or 3), S(O)_w-NR'R'' (where w is 1, 2 or 3), and -NR'-S(O)_w, (where w is 1, 2 or 3)), and a 5-6 membered heteroaryl having one, two, or three heteroatoms each independently selected from O, N and S (wherein the 5-6 membered heteroaryl may be optionally substituted on a carbon with one, two, three or more substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano, carboxy, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, phenyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, NR'R'', C(O)-NR'R'', -C(O)-C₁₋₆alkyl, -C(O)-C₁₋₆alkoxy, -S(O)_w-C₁₋₆alkyl (where w is 1, 2 or 3), S(O)_w-NR'R'' (where w is 1, 2 or 3), -NR'-S(O)_w, and -S(O)_w-NR'R'' (where w is 1, 2 or 3)), heteroaryl, heterocycle, NR'R'', -C(O)-NR'R'', -C(O)-C₁₋₆alkyl, -C(O)-C₁₋₆alkoxy, -S(O)_w-C₁₋₆alkyl (where w is 1, 2 or 3), -NR'-S(O)_w, and -S(O)_w-NR'R'' (where w is 1, 2 or 3), and on a nitrogen by R');

R' is selected, independently for each occurrence, from H, methyl, ethyl, and propyl,

R'' is selected, independently for each occurrence, from H, methyl, ethyl, propyl, butyl, -C(O)-methyl and -C(O)-ethyl, or R' and R'' taken together may form a 4-6 membered heterocycle;

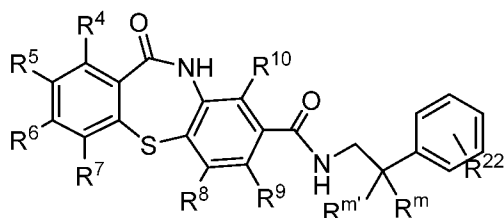
each of moieties R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, and R¹¹ are independently selected for each occurrence from the group consisting of hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, halogen, hydroxyl, nitro, cyano, NR'R'', -C(O)-NR'R'', -S(O)_w-C₁₋₆alkyl (where w is 1, 2 or 3), NR'-S(O)_w, and S(O)_w-NR'R'' (where w is 0, 1 or 2), C₁₋₆alkoxy, -C(O)-OH, -C(O)-C₁₋₆alkyl, and -C(O)-C₁₋₆alkoxy;

wherein for each occurrence, C₁₋₆alkyl may be optionally substituted with one, two, three or more substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano, carboxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, phenyl, NR'R'', -C(O)-NR'R'', S(O)_w-methyl (where w is 1, 2 or 3), -NR'-S(O)_w, and S(O)_w-NR'R'' (where w is 0, 1 or 2); C₁₋₆alkoxy may be optionally substituted with one, two, three or more substituents selected from the group

consisting of halogen, hydroxyl, nitro, cyano, carboxy, C₁₋₆alkyl, phenyl, NR'R'', -C(O)-NR'R'', S(O)_w-C₁₋₆alkyl (where w is 1, 2 or 3), -NR'-S(O)_w, and S(O)_w-NR'R'' (where w is 0, 1 or 2); and C₃₋₆cycloalkyl may be optionally substituted with one, two, three or more substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano, carboxy, C₁₋₆alkyl, C₁₋₆alkoxy, -C(O)-C₁₋₆alkyl, -C(O)-C₁₋₆alkoxy, and NR'R'' and pharmaceutically acceptable salts thereof.

[00048] In some embodiments, compounds of Formula 1, 1' and/or 1'' may have R⁷ selected from H and F; and/or R⁶ is selected from H and F; and/or R⁵ is selected from H and F. In some embodiments, compounds of Formula 1, 1' and/or 1'' may have R¹⁰ selected from the group consisting of H, methyl and F and/or R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, and/or R¹¹ may be H.

[00049] In another embodiment, a compound represented by Formula 2 is provided:



wherein

R^{m'} and R^m are each independently selected from the group consisting of H, halogen, C₁₋₆alkyl (optionally substituted by one, two or three substituents each independently selected from halogen and hydroxyl), NR'R'', and hydroxyl;

R²² is selected for each occurrence from the group consisting of H, halogen, hydroxyl, nitro, cyano, carboxy, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, NR'R'', -C(O)-C₁₋₆alkyl, -C(O)-C₁₋₆alkoxy, phenyl, heteroaryl, C₃₋₆cycloalkyl, -S(O)_w-C₁₋₆alkyl (where w is 1, 2 or 3), -S(O)_w-NR'R'' (where w is 1, 2 or 3), and -NR'-S(O)_w, (where w is 1, 2 or 3));

R' is selected, independently for each occurrence, from H, methyl, ethyl, and propyl;

R'' is selected, independently for each occurrence, from H, methyl, ethyl, propyl, butyl, -C(O)-methyl and -C(O)-ethyl, or R' and R'' taken together with the nitrogen to which they are attached may form a 4-6 membered heterocycle;

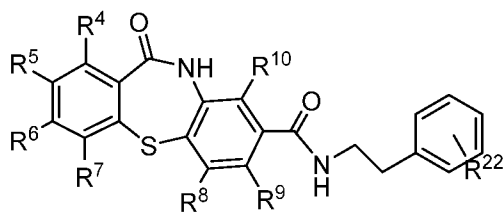
each of moieties R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , and R^{10} is independently selected for each occurrence from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{2-6} alkenyl, halogen, hydroxyl, nitro, cyano, and $NR'R''$;

wherein for each occurrence, C_{1-6} alkyl may be optionally substituted with one, two, three or more substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano, carboxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, $NR'R''$, $-NR'-S(O)_w$, and $S(O)_w-NR'R''$; C_{1-6} alkoxy may be optionally substituted with one, two, three or more substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano, carboxy, C_{1-6} alkyl, $NR'R''$, $-NR'-S(O)_w$, and $S(O)_w-NR'R''$; C_{3-6} cycloalkyl may be optionally substituted with one, two, three or more substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-6} alkoxy, $-C(O)-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkoxy, and $NR'R''$; phenyl may be optionally substituted by one, two or three substituents each independently selected from the group consisting of halogen, hydroxyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, $NR'R''$, $C(O)-NR'R''$, $-C(O)-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkoxy, $-S(O)_w-C_{1-6}$ alkyl (where w is 1, 2 or 3), $NR'-S(O)_w$, and $-S(O)_w-NR'R''$ (where w is 1, 2 or 3), and heteroaryl may be optionally substituted by one, two or three substituents each independently selected from the group consisting of halogen, hydroxyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, C_{2-6} alkynyl, C_{1-6} alkoxy, $NR'R''$, $C(O)-NR'R''$, $-C(O)-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkoxy, $-S(O)_w-C_{1-6}$ alkyl (where w is 1, 2 or 3), $NR'-S(O)_w$, and $-S(O)_w-NR'R''$ (where w is 1, 2 or 3)), C_{3-6} cycloalkyl; and

pharmaceutically acceptable salts thereof.

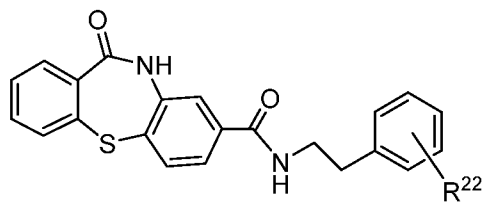
[00050] For example, a compound of Formula 2 may have R^7 is selected from H and F; and/or R^6 is selected from H and F; and/or R^5 is selected from H and F; and/or R^{10} is selected from the group consisting of H, methyl and F; and/or each of R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , and R^{11} may be H.

[00051] For example, provided herein is a compound represented by

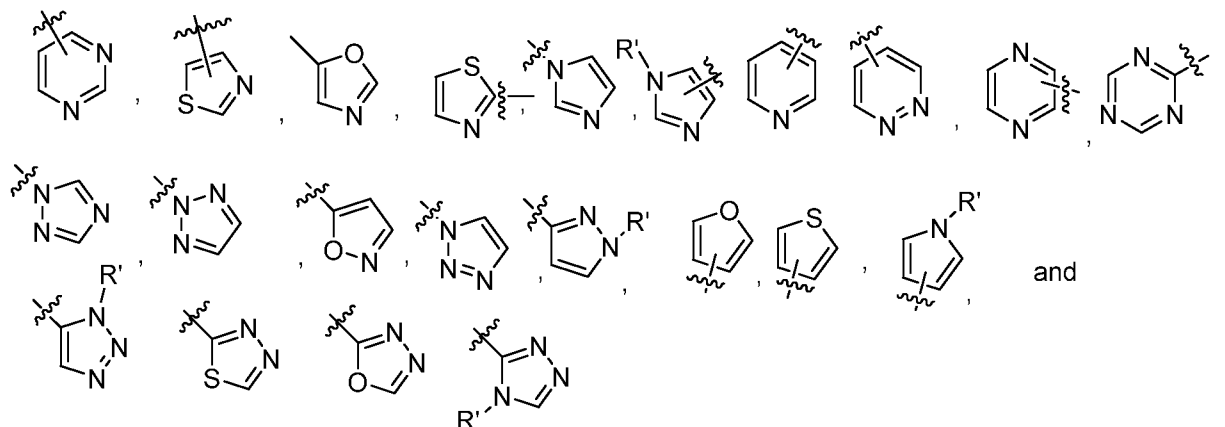


[00052] , wherein the R moieties are described above.

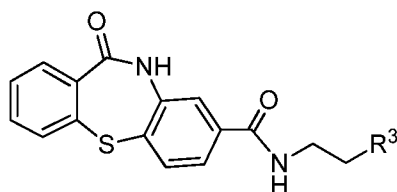
For example, in an embodiment, provided herein is a compound represented by:



wherein R^{22} for example, is selected from the group consisting of:



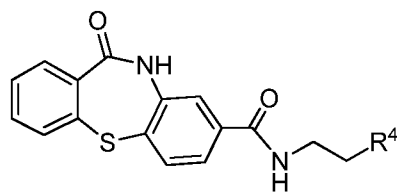
[00053] Also provided are compounds of Formula 3:



Formula 3

wherein the moiety R³ is selected from the group consisting of phenyl and naphthyl. R³ is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, cyano, carboxy, alkoxy, amino-cycloalkyl, phenyl, carbonyl-alkoxy, sulfonyl-alkyl, sulfonyl-amino, and sulfonyl-amino-alkyl.

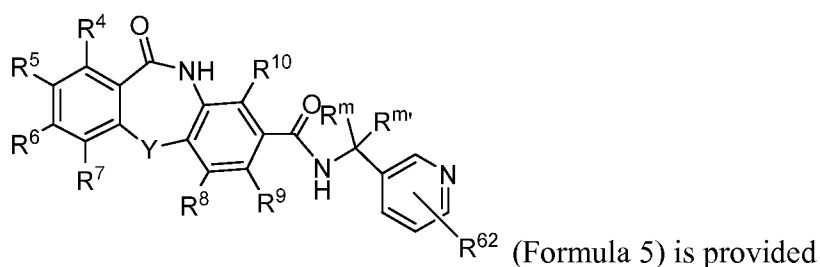
[00054] In addition, compounds of Formula 4 are provided:



Formula 4

wherein moiety R^4 is selected from the group consisting of pyridinyl, pyrimidinyl, thiazolyl, oxazolyl, piperidinyl, and piperazinyl. R^4 may be optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, cyano, carboxy, alkoxy, amino-cycloalkyl, phenyl, carbonyl-alkoxy, sulfonyl-alkyl, sulfonyl-amino, and sulfonylamino-alkyl.

[00055] In another embodiment, a compound represented by:



wherein

Y is $C(R^{11})_2$, $S(O)_y$, NR_Y and O wherein y is 0, 1, or 2;

R_Y is selected from the group consisting of H, methyl, ethyl, propyl, phenyl and benzyl;

$R^{m'}$ and R^m are each independently selected from the group consisting of H, halogen, C_{1-6} alkyl (optionally substituted by one, two or three substituents each independently selected from halogen and hydroxyl), C_{2-6} alkenyl (optionally substituted by one, two or three substituents each independently selected from halogen and hydroxyl), $NR'R''$, and hydroxyl (e.g., $R^{m'}$ and R^m may each be H in certain embodiments);

R^{62} is selected for each occurrence from the group consisting of H, halogen, hydroxyl, nitro, cyano, carboxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, $NR'R''$, $-C(O)-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkoxy, phenyl, heteroaryl, C_{3-6} cycloalkyl, $-S(O)_w-C_{1-6}$ alkyl (where w is 1, 2 or 3), $-S(O)_w-NR'R''$ (where w is 1, 2 or 3), and $-NR'-S(O)_w$ (where w is 1, 2 or 3));

R' is selected, independently for each occurrence, from H, methyl, ethyl, and propyl;

R'' is selected, independently for each occurrence, from H, methyl, ethyl, propyl, butyl, –C(O)-methyl and –C(O)-ethyl, or R' and R'' taken together with the nitrogen to which they are attached may form a 4-6 membered heterocycle;

each of moieties R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, and R¹⁰ is independently selected for each occurrence from the group consisting of hydrogen, C₁₋₆alkyl, C₂₋₆alkynyl, C₂₋₆alkenyl, halogen, hydroxyl, nitro, cyano, and NR'R'';

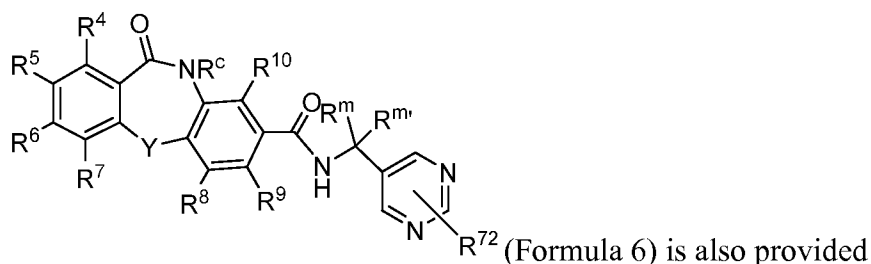
wherein for each occurrence, C₁₋₆alkyl may be optionally substituted with one, two, three or more substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano, carboxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, NR'R'', –NR'-S(O)_w, and S(O)_w-NR'R''; C₁₋₆alkoxy may be optionally substituted with one, two, three or more substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano, carboxy, C₁₋₆alkyl, NR'R'', –NR'-S(O)_w, and S(O)_w-NR'R''; C₃₋₆cycloalkyl may be optionally substituted with one, two, three or more substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano, carboxy, C₁₋₆alkyl, C₁₋₆alkoxy, –C(O)-C₁₋₆alkyl, –C(O)-C₁₋₆alkoxy, and NR'R''; phenyl may be optionally substituted by one, two or three substituents each independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, NR'R'', C(O)-NR'R'', –C(O)-C₁₋₆alkyl, –C(O)-C₁₋₆alkoxy, –S(O)_w-C₁₋₆alkyl (where w is 1, 2 or 3), NR'-S(O)_w, and –S(O)_w-NR'R'' (where w is 1, 2 or 3), and heteroaryl may be optionally substituted by one, two or three substituents each independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, NR'R'', C(O)-NR'R'', –C(O)-C₁₋₆alkyl, –C(O)-C₁₋₆alkoxy, –S(O)_w-C₁₋₆alkyl (where w is 1, 2 or 3), NR'-S(O)_w, and –S(O)_w-NR'R'' (where w is 1, 2 or 3), and C₃₋₆cycloalkyl; and

pharmaceutically acceptable salts thereof.

In an embodiment, a compound of Formula 5 may have R⁷ selected from H and F and/or R⁶ is selected from H and F and/or R⁵ may be selected from H and F; and/or R¹⁰ may be selected from the group consisting of H, methyl and F; and/or R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, and R¹¹ may be H.

[00056] In some embodiments, Y of Formula 5 may be S.

[00057] A compound represented by:



wherein

Y is $C(R^{11})_2$, $S(O)_y$, NR_Y and O wherein y is 0, 1, or 2;

R_Y is selected from the group consisting of H, methyl, ethyl, propyl, phenyl and benzyl;

$R^{m'}$ and R^m are each independently selected from the group consisting of H, halogen, C_{1-6} alkyl (optionally substituted by one, two or three substituents each independently selected from halogen and hydroxyl), C_{2-6} alkenyl (optionally substituted by one, two or three substituents each independently selected from halogen and hydroxyl), $NR'R''$, and hydroxyl (e.g., $R^{m'}$ and R^m may each be H in certain embodiments);

R^c is H or C_{1-6} alkyl;

R^{72} is selected for each occurrence from the group consisting of H, halogen, hydroxyl, nitro, cyano, carboxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, $NR'R''$, $-C(O)-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkoxy, phenyl, heteroaryl, C_{3-6} cycloalkyl, $-S(O)_w-C_{1-6}$ alkyl (where w is 1, 2 or 3), $-S(O)_w-NR'R''$ (where w is 1, 2 or 3), and $-NR'-S(O)_w$ (where w is 1, 2 or 3));

R' is selected, independently for each occurrence, from H, methyl, ethyl, and propyl;

R'' is selected, independently for each occurrence, from H, methyl, ethyl, propyl, butyl, $-C(O)-methyl$ and $-C(O)-ethyl$, or R' and R'' taken together with the nitrogen to which they are attached may form a 4-6 membered heterocycle;

each of moieties R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , and R^{10} is independently selected for each occurrence from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{2-6} alkenyl, halogen, hydroxyl, nitro, cyano, and $NR'R''$;

wherein for each occurrence, C_{1-6} alkyl may be optionally substituted with one, two, three or more substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano,

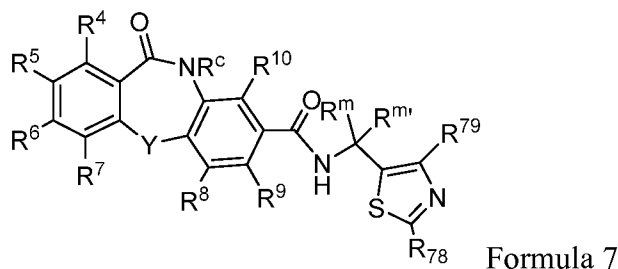
carboxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, NR'R'', -NR'-S(O)_w, and S(O)_w-NR'R''; C₁₋₆alkoxy may be optionally substituted with one, two, three or more substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano, carboxy, C₁₋₆alkyl, NR'R'', -NR'-S(O)_w, and S(O)_w-NR'R''; C₃₋₆cycloalkyl may be optionally substituted with one, two, three or more substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano, carboxy, C₁₋₆alkyl, C₁₋₆alkoxy, -C(O)-C₁₋₆alkyl, -C(O)-C₁₋₆alkoxy, and NR'R''; phenyl may be optionally substituted by one, two or three substituents each independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, NR'R'', C(O)-NR'R'', -C(O)-C₁₋₆alkyl, -C(O)-C₁₋₆alkoxy, -S(O)_w-C₁₋₆alkyl (where w is 1, 2 or 3), NR'-S(O)_w, and -S(O)_w-NR'R'' (where w is 1, 2 or 3), and heteroaryl may be optionally substituted by one, two or three substituents each independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, NR'R'', C(O)-NR'R'', -C(O)-C₁₋₆alkyl, -C(O)-C₁₋₆alkoxy, -S(O)_w-C₁₋₆alkyl (where w is 1, 2 or 3), NR'-S(O)_w, -S(O)_w-NR'R'' (where w is 1, 2 or 3), and C₃₋₆cycloalkyl, and

pharmaceutically acceptable salts thereof.

[00058] In some embodiments, R^c of a compound of formula 6 may be H or methyl, e.g., H; and/or R⁷ may be selected from H and F; and/or R⁶ may be selected from H and F; and/or R⁵ may be selected from H and F; and/or R¹⁰ may be selected from the group consisting of H, methyl and F; and/or R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, and R¹¹ may be H.

[00059] In certain embodiments, the Y moiety of Formula 6 is S.

[00060] Provided herein, in certain embodiments, is a compound represented by:



wherein

Y is C(R¹¹)₂, S(O)_y, NR_Y and O wherein y is 0, 1, or 2;

R_Y is selected from the group consisting of H, methyl, ethyl, propyl, phenyl and benzyl;

$R^{m'}$ and R^m are each independently selected from the group consisting of H, halogen, C_{1-6} alkyl (optionally substituted by one, two or three substituents each independently selected from halogen and hydroxyl), C_{2-6} alkenyl (optionally substituted by one, two or three substituents each independently selected from halogen and hydroxyl), $NR'R''$, and hydroxyl (e.g., $R^{m'}$ and R^m may each be H in certain embodiments);

R^c is H or C_{1-6} alkyl;

R^{78} is selected from the group consisting of H, halogen, hydroxyl, nitro, cyano, carboxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, $NR'R''$, $-C(O)-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkoxy, phenyl, heteroaryl, C_{3-6} cycloalkyl, $-S(O)_w-C_{1-6}$ alkyl (where w is 1, 2 or 3), $-S(O)_w-NR'R''$ (where w is 1, 2 or 3), and $-NR'-S(O)_w$, (where w is 1, 2 or 3));

R^{79} is selected from the group consisting of H, halogen, hydroxyl, nitro, cyano, carboxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, $NR'R''$, $-C(O)-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkoxy, phenyl, heteroaryl, C_{3-6} cycloalkyl, $-S(O)_w-C_{1-6}$ alkyl (where w is 1, 2 or 3), $-S(O)_w-NR'R''$ (where w is 1, 2 or 3), and $-NR'-S(O)_w$, (where w is 1, 2 or 3));

R' is selected, independently for each occurrence, from H, methyl, ethyl, and propyl;

R'' is selected, independently for each occurrence, from H, methyl, ethyl, propyl, butyl, $-C(O)$ -methyl and $-C(O)$ -ethyl, or R' and R'' taken together with the nitrogen to which they are attached may form a 4-6 membered heterocycle;

each of moieties R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , and R^{10} is independently selected for each occurrence from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{2-6} alkenyl, halogen, hydroxyl, nitro, cyano, and $NR'R''$;

wherein for each occurrence, C_{1-6} alkyl may be optionally substituted with one, two, three or more substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano, carboxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, $NR'R''$, $-NR'-S(O)_w$, and $S(O)_w-NR'R''$; C_{1-6} alkoxy may be optionally substituted with one, two, three or more substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano, carboxy, C_{1-6} alkyl, $NR'R''$, $-NR'-S(O)_w$, and $S(O)_w-NR'R''$; C_{3-6} cycloalkyl may be optionally substituted with one, two, three or more

substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano, carboxy, C₁₋₆alkyl, C₁₋₆alkoxy, -C(O)-C₁₋₆alkyl, -C(O)-C₁₋₆alkoxy, and NR'R''; phenyl may be optionally substituted by one, two or three substituents each independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, NR'R'', C(O)-NR'R'', -C(O)-C₁₋₆alkyl, -C(O)-C₁₋₆alkoxy, -S(O)_w-C₁₋₆alkyl (where w is 1, 2 or 3), NR'-S(O)_w, and -S(O)_w-NR'R'' (where w is 1, 2 or 3), and heteroaryl may be optionally substituted by one, two or three substituents each independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₁₋₆alkoxy, NR'R'', C(O)-NR'R'', -C(O)-C₁₋₆alkyl, -C(O)-C₁₋₆alkoxy, -S(O)_w-C₁₋₆alkyl (where w is 1, 2 or 3), NR'-S(O)_w, and -S(O)_w-NR'R'' (where w is 1, 2 or 3), and pharmaceutically acceptable salts thereof.

R^c is H or methyl.

[00061] In certain embodiments, compound of formula 7 may have R^c as H; and/or R⁷ may be selected from H and F; and/or R⁶ may be selected from H and F; and/or R⁵ may be selected from H and F; and/or R¹⁰ may be selected from the group consisting of H, methyl and F; and/or each of R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, and R¹¹ may be H.

[00062] For example, the present disclosure also provides, in part, a compound selected from the group consisting a compound of Table 1, 2, 3, 4, 5, 6 and 7. Also contemplated herein are compounds: N-((2-methylthiazol-5-yl)methyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide, N-((2-aminothiazol-5-yl)methyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide, N-((2-methylthiazol-5-yl)methyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5,5-dioxide, N-((2-aminothiazol-5-yl)methyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5,5-dioxide, 11-oxo-N-(2-phenylbutyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5,5-dioxide, N-(2-(4,4-difluorocyclohexyl)ethyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5,5-dioxide, 3'-(5,5-dioxido-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamido)-[1,1'-biphenyl]-2-carboxylic acid, 9-methyl-N-((2-methylthiazol-5-yl)methyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide, N-(2-(4'-fluoro-[1,1'-biphenyl]-4-yl)ethyl)-11-oxo-10,11-

dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5,5-dioxide, N-((2-aminothiazol-5-yl)methyl)-9-methyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide, 11-oxo-N-(pyrimidin-5-ylmethyl)-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepine-8-carboxamide, 11-oxo-N-(2-(pyridin-2-yl)ethyl)-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepine-8-carboxamide, 11-oxo-N-(2-(pyridin-3-yl)ethyl)-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepine-8-carboxamide, 11-oxo-N-(pyridin-3-ylmethyl)-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepine-8-carboxamide, N-(2-([1,1'-biphenyl]-4-yl)ethyl)-11-oxo-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepine-8-carboxamide, 11-oxo-N-(pyridin-4-yl)-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepine-8-carboxamide, N-(4-(N,N-dimethylsulfamoyl)phenethyl)-11-oxo-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepine-8-carboxamide, N-([1,1'-biphenyl]-3-yl)-11-oxo-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepine-8-carboxamide, (Z)-N-((3-(methylinino)prop-1-en-2-yl)oxy)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide, 11-oxo-N-(pyrimidin-5-yloxy)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide, 11-oxo-N-(4-(pyrimidin-5-yl)benzyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide, N-(2-(4'-fluoro-[1,1'-biphenyl]-4-yl)ethyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide, 2-chloro-N-((2-methylthiazol-5-yl)methyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide, 2-chloro-11-oxo-N-(pyridin-3-ylmethyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide, 2-chloro-11-oxo-N-(pyrimidin-5-ylmethyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide, 3-chloro-N-((2-methylthiazol-5-yl)methyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide, 3-chloro-11-oxo-N-(pyridin-3-ylmethyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide, 3-chloro-11-oxo-N-(pyrimidin-5-ylmethyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide, 11-methyl-N-((2-methylthiazol-5-yl)methyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepine-3-carboxamide, 11-methyl-6-oxo-N-(pyridin-3-ylmethyl)-6,11-dihydro-5H-dibenzo[b,e]azepine-3-carboxamide, 11-methyl-6-oxo-N-(pyrimidin-5-ylmethyl)-6,11-dihydro-5H-dibenzo[b,e]azepine-3-carboxamide, 2-chloro-11-oxo-N-(thiazol-5-ylmethyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide, 3-chloro-11-oxo-N-(thiazol-5-ylmethyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide, 11-methyl-6-oxo-N-(thiazol-5-ylmethyl)-6,11-dihydro-5H-dibenzo[b,e]azepine-3-carboxamide, and 11-oxo-N-(2-(thiazol-5-yl)propan-2-yl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide;

or a pharmaceutically acceptable salt thereof.

[00063] In a second aspect, a method for the synthesis of disclosed compounds is provided. The method follows Synthetic Scheme 1, as illustrated in FIG. 1. A first mixture comprising reagents **1** and **2** is formed for synthetic step **A** to yield synthetic intermediate **3**. Synthetic step **A** may be conducted in an organic solvent, for instance a polar aprotic solvent such as dimethyl sulfoxide (DMSO), dimethylformamide (DMF), dioxane, hexamethylphosphorotriamide, and tetrahydrofuran. The reaction may be conducted in the presence of a base, for example a carbonate such as Li_2CO_3 , Na_2CO_3 , K_2CO_3 , Rb_2CO_3 , Cs_2CO_3 , MgCO_3 , CaCO_3 , SrCO_3 , and BaCO_3 .

[00064] In reagent **1**, moiety $-\text{YH}$ is selected from the group consisting of $-\text{SH}$, $-\text{OH}$, and $-\text{N}(\text{R}^{12})\text{H}$, wherein R^{12} is selected from the group consisting of hydrogen and alkyl. In intermediates **3**, **4**, **5**, and in product **6**, moiety $-\text{Y}-$ is selected from the group consisting of $-\text{S}-$, $-\text{O}-$, and $-\text{N}(\text{R}^{12})-$. Moieties P^1 and P^2 are independently selected carboxyl protecting groups, such as methoxyl or ethoxyl groups. In some cases, at least one of P^3 and P^4 is an amino protecting group, for example selected from the group consisting of carbobenzyloxy (Cbz), *p*-methoxybenzyl-carbonyl (Moz or MeOZ), *tert*-butyloxycarbonyl (BOC), 9-fluorenylmethyloxycarbonyl (Fmoc), acetyl (Ac), benzoyl (Bz), benzyl (Bn), carbamate group, *p*-Methoxybenzyl (PMB), 3,4-dimethoxybenzyl (DMPM), *p*-methoxyphenyl (PMP), tosyl (Ts), sulfonamides (Nosyl and Nps). Alternatively, moiety $-\text{N}(\text{P}^3)(\text{P}^4)$ may be a group that can be transformed in an amino group by appropriate chemical reactions. By way of example, moiety $-\text{N}(\text{P}^3)(\text{P}^4)$ may be an $-\text{NO}_2$ group that is transformed into an amino ($-\text{NH}_2$) moiety by reaction with a reductant.

[00065] In synthetic step **B**, protecting groups P^1 and P^2 are removed to yield carboxyl moieties. In instances where P^1 and P^2 are alkoxy groups, this may be achieved by hydrolysis, for example in the presence of a base or acid. Group $-\text{N}(\text{P}^3)(\text{P}^4)$ is transformed into an amino moiety, as exemplified above, to yield intermediate **4**. In synthetic step **C**, the amino group of intermediate **4** is reacted with the carboxy group on the other phenyl moiety, forming the 1,4-thiazepan-5-one moiety of intermediate **5**. The formation of this amide bond may be speeded up by the addition of activators. Example activators include carbodiimides, such as $\text{N,N}'$ -

dicyclohexylcarbodiimide (DCC), N,N'-diisopropylcarbodiimide (DIC), and carbonyl diimidazole (CDI); and triazolols, such as 1-hydroxy-benzotriazole (HOBt) and 1-hydroxy-7-aza-benzotriazole (HOAt). Other activators include HBTU, HATU, HCTU, TBTU, and PyBOP.

[00066] In synthetic step **D**, intermediate **5** is reacted with a molecule of formula R^2NH_2 to create an amide bond and yield products of Formula **6**. As with synthetic step **C**, the formation of the amide bond may be speeded up with an activator. An exemplary Synthetic Scheme is illustrated in FIG. 2.

[00067] 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, and 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 pharmaceutical composition comprising a disclosed compound, or two or more disclosed compounds.

[00068] For use in accordance with this aspect, the appropriate dosage is expected to vary depending on, for example, the particular 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 $\mu\text{g/kg}$ body weight. In some cases, the administration dose of the compound may be less than 400 $\mu\text{g/kg}$ body weight. In other cases, the administration dose may be less than 200 $\mu\text{g/kg}$ body weight. In yet other cases, the administration dose may be in the range between about 0.1 to about 100 $\mu\text{g/kg}$ 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.

[00069] A compound may be administered by any conventional 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 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).

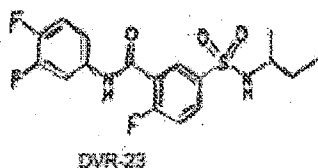
[00070] For oral administration, pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); 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. 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, 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.

[00071] 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.

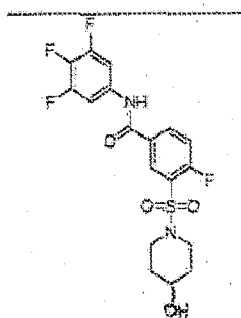
[00072] A disclosed compound may also be formulated for parenteral administration by injection e.g. by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may 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 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.

[00073] 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 patient suffering from hepatitis B comprising administering to a subject 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: another HBV caspid assembly promoter (such as certain compounds disclosed herein or for example, GLS4, BAY 41-4109, AT-130, DVR-23 (e.g., as depicted below),

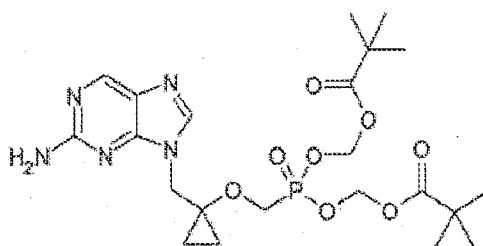


NVR 3-778, NVR1221 (by code); and N890 (as depicted below):

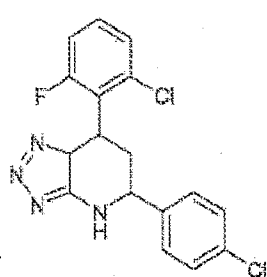


other CpAMs such as those disclosed in the following patent applications hereby incorporated by reference: WO2014037480, WO2014184328, WO2013006394, WO2014089296, WO2014106019, WO2013102655, WO2014184350, WO2014184365, WO2014161888, WO2014131847, WO2014033176, WO2014033167, and WO2014033170; Nucleoside analogs interfering with viral polymerase, such as entecavir (Baraclude), Lamivudine, (Epivir-HBV), Telbivudine (Tyzeka, Sebivo), Adefovir dipivoxil (Hepsera), Tenofovir (Viread), Tenofovir

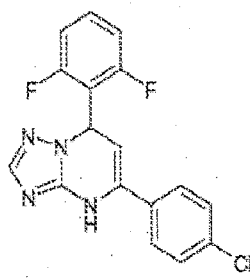
alafenamide fumarate (TAF), prodrugs of tenofavir (e.g. AGX-1009), L-FMAU (Clevudine), LB80380 (Besifovir) and:



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: :

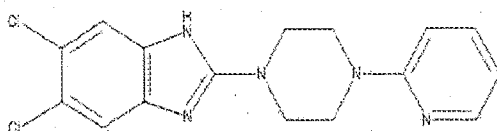


22: HBF-0529

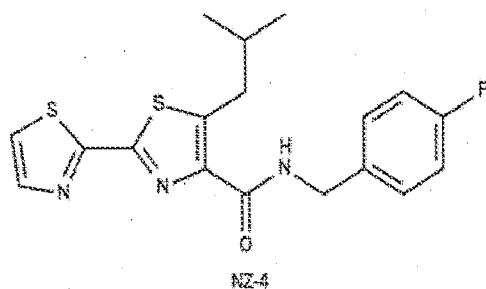


23: PBHBV-2-15

and BM601 as depicted below:

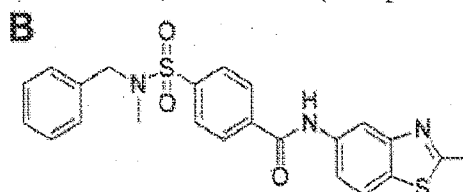
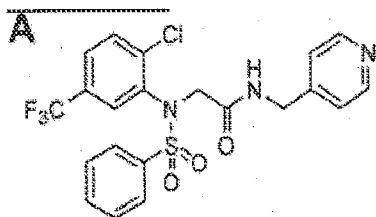


disruptors of nucleocapsid formation or integrity such as NZ-4/W28F:



NZ-4

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



HBc 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](http://dx.doi.org/10.1016/j.intimp.2015.01.028); antiviral 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 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; 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 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, and biologics directed against viral components or interacting host proteins.

[00074] 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-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

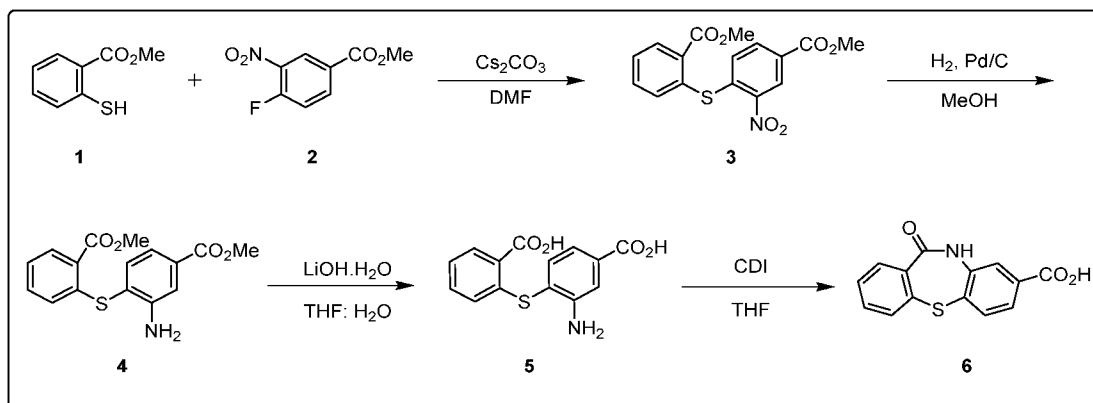
days or weeks prior to initiation of administration of the antiviral. Moreover, additional drugs may be given in conjunction with the above combination therapy.

[00075] 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, 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 AlexaFluor® 488 (Invitrogen) and BODIPY FL (Invitrogen), as well as fluorescein, rhodamine, cyanine, indocarbocyanine, anthraquinones, fluorescent proteins, aminocoumarin, methoxycoumarin, hydrooxycoumarin, 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 new compounds for biological activity.

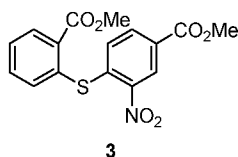
EXAMPLES

[00076] 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 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 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.

Example 1: Synthesis of 11-oxo-10, 11-dihydrodibenzo [b, f] [1, 4] thiazepine-8-carboxylic acid (6) - a common intermediate

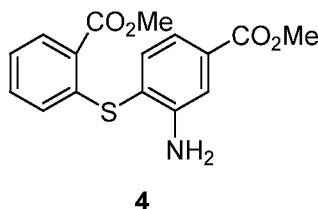


Synthesis of methyl 4-((2-(methoxycarbonyl) phenyl) thio)-3-nitrobenzoate (3):



[00077] To a stirred solution of methyl 4-fluoro-3-nitrobenzoate **2** (30 g, 150.67 mmol) in DMF (300 mL) under inert atmosphere were added cesium carbonate (58.76 g, 180.8 mmol) and methyl 2-mercaptobenzoate **1** (22.6 mL, 165.47 mmol) at RT; heated to 55-60 °C and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (1500 mL) and the precipitated solid was filtered to obtain the crude. The crude was washed with water (500 mL), hexane (200 mL) and dried *in vacuo* to afford compound **3** (48.8 g, 93%) as yellow solid. **TLC**: 20% EtOAc/ hexanes (*R_f*: 0.4); **¹H NMR** (CDCl₃, 400 MHz): δ 8.85 (s, 1H), 7.99-7.92 (m, 2H), 7.66-7.56 (m, 3H), 6.93 (d, *J* = 8.6 Hz, 1H), 3.94 (s, 3H), 3.79 (s, 3H).

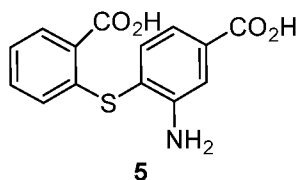
Synthesis of methyl 3-amino-4-((2-(methoxycarbonyl) phenyl) thio) benzoate (4):



[00078] To a stirred solution of compound **3** (48 g, 138.32 mmol) in MeOH (1000 mL) under

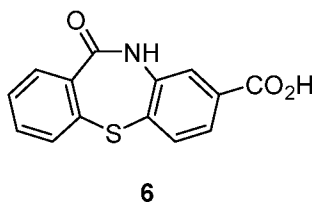
inert atmosphere was added 10% Pd/C (20 g, wet) at RT under hydrogen atmosphere in an autoclave (100 psi pressure) and stirred for 24 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered through celite, washed with 50% MeOH/ CH₂Cl₂ (500 mL). The filtrate was removed *in vacuo* to obtain the crude which as triturated with diethyl ether (200 mL), washed with hexane (200 mL) and dried *in vacuo* to afford compound **4** (40 g, 91%) as yellow solid. **TLC:** 10% EtOAc/ hexanes (*R_f*: 0.3); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 7.95 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.48-7.35 (m, 3H), 7.23 (td, *J* = 7.5, 1.1 Hz, 1H), 7.15 (dd, *J* = 8.0, 1.8 Hz, 1H), 6.66 (dd, *J* = 8.2, 0.8 Hz, 1H), 5.67 (br s, 2H), 3.88 (s, 3H), 3.84 (s, 3H).

Synthesis of 3-amino-4-((2-carboxyphenyl) thio) benzoic acid (5):



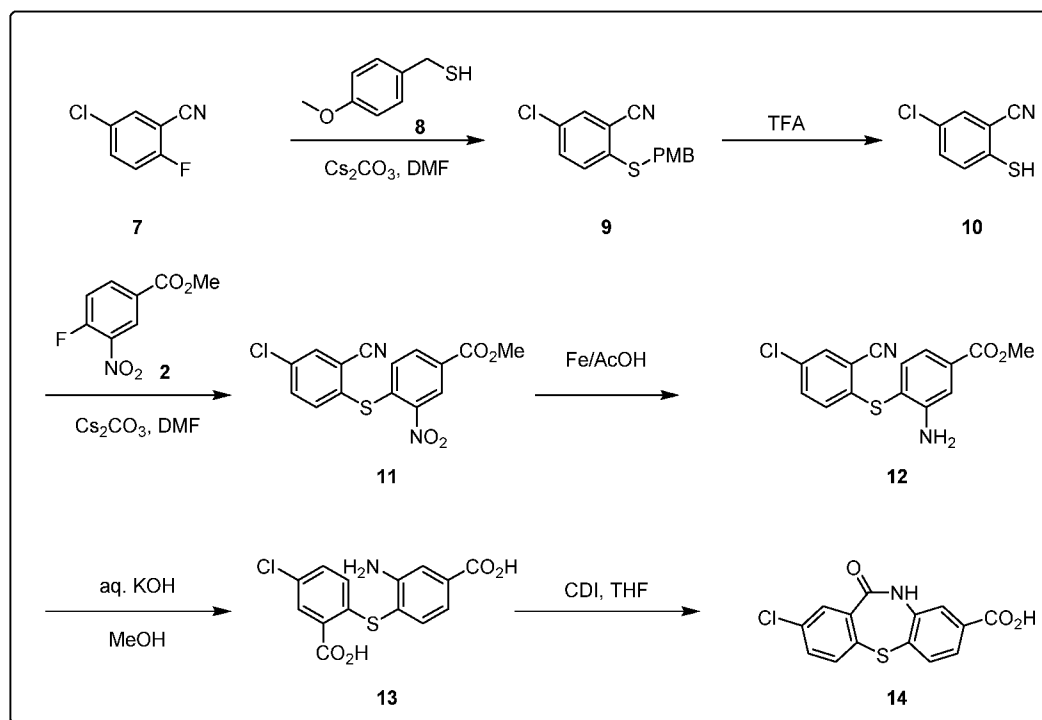
[00079] To a stirred solution of compound **4** (40 g, 126.18 mmol) in THF: H₂O (5: 1, 400 mL) was added lithium hydroxide monohydrate (26 g, 619.0 mmol) at 0 °C; warmed to RT and stirred for 48 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The pH of the residue was acidified with 2 N HCl to ~2. The precipitated solid was filtered and dried *in vacuo* to afford compound **5** (34.6 g, 95%) as an off-white solid. **TLC:** 30% EtOAc/ hexanes (*R_f*: 0.1); **¹H NMR (DMSO-*d*₆, 500 MHz):** δ 13.00 (br s, 2H), 7.93 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.42 (s, 1H), 7.40-7.31 (m, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.13 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.61 (d, *J* = 7.8 Hz, 1H), 5.55 (br s, 2H).

Synthesis of 11-oxo-10, 11-dihydrodibenzo [b, f] [1, 4] thiazepine-8-carboxylic acid (6):

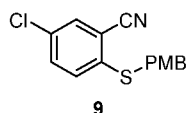


[00080] To a stirred solution of compound **5** (31 g, 107.26 mmol) in THF (600 mL) under inert atmosphere was added CDI (86.88 g, 536.29 mmol) at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was acidified with 2 N HCl to pH~4. The obtained solid was filtered and further dried by using toluene (2 x 200 mL) to afford compound **6** (26 g, 90%) as white solid. **TLC**: 10% MeOH/CH₂Cl₂ (*R_f*: 0.3); **¹H NMR (DMSO-*d*₆, 400 MHz)**: δ 13.22 (br s, 1H), 10.81 (s, 1H), 7.78 (s, 1H), 7.72-7.64 (m, 3H), 7.57-7.44 (m, 3H).

Example 2: Synthesis of 2-chloro-11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxylic acid (14) - a common intermediate



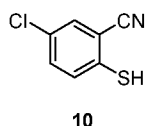
Synthesis of 5-chloro-2-((4-methoxybenzyl) thio) benzonitrile (9):



[00081] To a stirred solution of 5-chloro-2-fluorobenzonitrile **7** (1 g, 6.41 mmol) in DMF (10 mL) under inert atmosphere was added cesium carbonate (2.30 g, 7.05 mmol) at RT; heated to

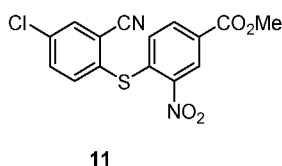
40 °C and to this was added (4-methoxyphenyl) methanethiol **8** (1.08 g, 7.05 mmol); heated to 60 °C and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 25 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 3-5% EtOAc/ hexanes to afford compound **9** (1 g, 54%) as white solid. **TLC:** 10% EtOAc/ hexanes (R_f : 0.6); **¹H-NMR (CDCl₃, 500 MHz):** δ 7.57 (s, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.28-7.27 (m, 1H), 7.20 (d, J = 9.0 Hz, 2H), 6.81 (d, J = 9.0 Hz, 2H), 4.15 (s, 2H), 3.78 (s, 3H).

Synthesis of 5-chloro-2-mercaptobenzonitrile (**10**):



[00082] A stirred solution of compound **9** (1 g, 3.47 mmol) in trifluoro acetic acid (10 mL) under inert atmosphere was stirred at 70 °C for 5 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude compound **10** (590 mg) which was carried to the next step without further purification. **TLC:** 30% EtOAc/ hexanes (R_f : 0.2); **¹H-NMR (CDCl₃, 500 MHz):** δ 7.57 (s, 1H), 7.41 (d, J = 9.0 Hz, 1H), 7.34 (d, J = 9.0 Hz, 1H), 4.08 (s, 1H).

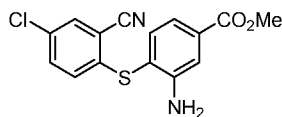
Synthesis of methyl 4-((4-chloro-2-cyanophenyl) thio)-3-nitrobenzoate (**11**):



[00083] To a stirred solution of compound **10** (620 mg, 3.11 mmol) in DMF (10 mL) under inert atmosphere was added cesium carbonate (1.1 g, 3.42 mmol) at RT; heated to 40 °C and stirred for 10 min. To this was added methyl 4-fluoro-3-nitrobenzoate **2** (582 mg, 3.42 mmol) at 60 °C and stirred for 3 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to

obtain the crude. The crude was purified through silica gel column chromatography using 25% EtOAc/ hexanes to afford compound **11** (600 mg, 55%) as pale yellow solid. **TLC:** 30% EtOAc/ hexanes (R_f : 0.4); **$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz):** δ 8.66 (s, 1H), 8.33 (s, 1H), 8.05-8.03 (m, 1H), 7.98-7.92 (m, 2H), 7.02 (d, J = 8.4 Hz, 1H), 3.86 (s, 3H).

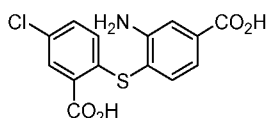
Synthesis of methyl 3-amino-4-((4-chloro-2-cyanophenyl) thio) benzoate (12):



12

[00084] To a stirred solution of compound **11** (450 mg, 1.29 mmol) in acetic acid (15 mL) under inert atmosphere was added iron powder (724 mg, 12.9 mmol) at RT; heated to 90 °C and stirred for 3 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was basified with saturated NaHCO_3 solution (15 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was triturated with 3% EtOAc/ hexanes (2 x 5 mL) to afford compound **12** (290 mg, 70%) as pale yellow solid. **TLC:** 20% MeOH/ CH_2Cl_2 (R_f : 0.7); **$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz):** δ 8.05 (s, 1H), 7.63-7.60 (m, 1H), 7.48 (s, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.14 (d, J = 8.8 Hz, 1H), 6.75 (d, J = 8.8 Hz, 1H), 5.88 (s, 2H), 3.84 (s, 3H).

Synthesis of 2-((2-amino-4-carboxyphenyl) thio)-5-chlorobenzoic acid (13):

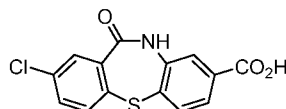


13

[00085] To a stirred solution of compound **12** (450 mg, 1.41 mmol) in MeOH (10 mL) was added potassium hydroxide (792 mg, 14.1 mmol) in water (3 mL) at 0 °C; heated to 90 °C and stirred for 9 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was acidified with 1 N HCl to pH~4.0. The obtained solid was filtered, washed with ether (2 x 5 mL) and dried *in vacuo* to afford compound **13** (350 mg, 76%) as an off-white solid. **TLC:** 20% MeOH/ CH_2Cl_2 (R_f : 0.3); **$^1\text{H-NMR}$**

(DMSO-*d*₆, 400 MHz): δ 12.92 (br s, 2H), 7.89 (s, 1H), 7.44-7.38 (m, 3H), 7.14 (d, J = 8.8 Hz, 1H), 6.60 (d, J = 8.8 Hz, 1H), 5.64 (br s, 2H).

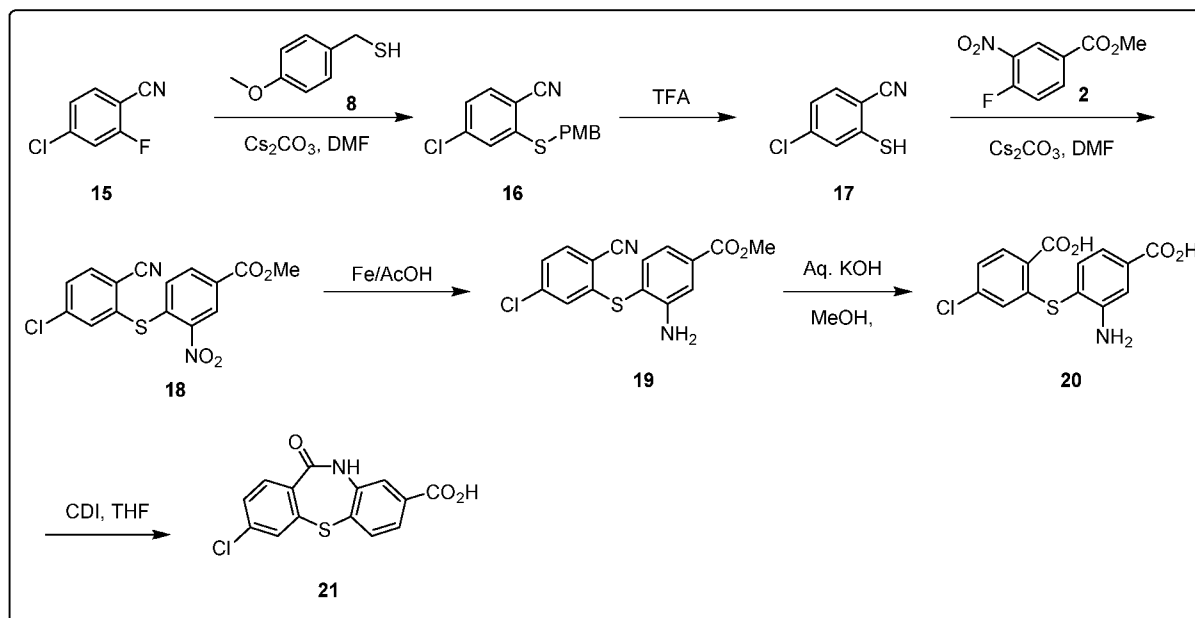
[00086] Synthesis of 2-chloro-11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxylic acid (14):

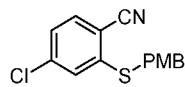


14

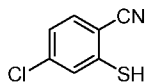
[00087] To a stirred solution of compound **13** (30 mg, 0.09 mmol) in THF (2 mL) under inert atmosphere was added CDI (45 mg, 0.27 mmol) at RT and stirred for 7 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was acidified with 2 N HCl to pH~4.0. The obtained solid was filtered, washed with ether (2 x 3 mL) and dried *in vacuo* to afford compound **14** (15 mg, 53%) as an off-white solid. TLC: 15% MeOH/ CH₂Cl₂ (R_f : 0.5); ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 13.05 (br s, 1H), 10.98 (s, 1H), 7.80 (s, 1H), 7.72-7.70 (m, 3H), 7.64 (s, 2H).

Example 3: Synthesis of 3-chloro-11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxylic acid (21) - a common intermediate

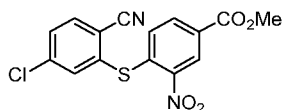


Synthesis of 4-chloro-2-((4-methoxybenzyl) thio) benzonitrile (16):**16**

[00088] To a stirred solution of 4-chloro-2-fluorobenzonitrile **15** (1 g, 6.41 mmol) in DMF (25 mL) under inert atmosphere was added cesium carbonate (2.30 g, 7.05 mmol) at RT; heated to 40 °C and to this was added (4-methoxyphenyl) methanethiol **8** (1.08 g, 7.05 mmol); heated to 60 °C and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 25 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 4% EtOAc/ hexanes to afford compound **16** (900 mg, 48%) as white solid. **TLC:** 10% EtOAc/ hexanes (R_f : 0.6); **¹H-NMR (CDCl₃, 400 MHz):** δ 7.51 (d, J = 8.4 Hz, 1H), 7.33 (s, 1H), 7.23-7.20 (m, 3H), 6.84 (d, J = 8.4 Hz, 2H), 4.19 (s, 2H), 3.79 (s, 3H).

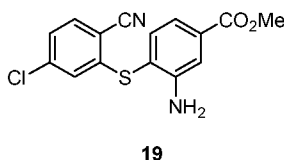
Synthesis of 4-chloro-2-mercaptobenzonitrile (17):**17**

[00089] A stirred solution of compound **16** (900 mg, 3.11 mmol) in trifluoro acetic acid (10 mL) under inert atmosphere at RT was heated to 70 °C and stirred for 4 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude compound **17** (527 mg) as brown solid. The crude was carried to the next step without further purification. **TLC:** 5% MeOH/ CH₂Cl₂ (R_f : 0.1); **¹H-NMR (CDCl₃, 400 MHz):** δ 7.52 (d, J = 8.4 Hz, 1H), 7.41 (s, 1H), 7.22-7.19 (m, 1H), 4.13 (s, 1H).

Synthesis of methyl 4-((5-chloro-2-cyanophenyl) thio)-3-nitrobenzoate (18):**18**

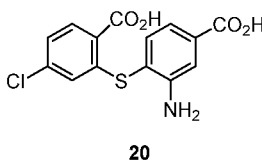
[00090] To a stirred solution of compound **17** (550 mg, 2.76 mmol) in DMF (15 mL) under inert atmosphere was added cesium carbonate (988 mg, 3.04 mmol) at RT; heated to 40 °C and stirred for 10 min. To this was added methyl 4-fluoro-3-nitrobenzoate **2** (515 mg, 3.04 mmol) at 60 °C and stirred for 3 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (20 mL). The obtained solid was filtered, washed with 15% EtOAc/ hexanes (2 x 5 mL) and dried *in vacuo* to afford compound **18** (700 mg, 73%) as yellow solid. **TLC:** 20% EtOAc/ hexanes (R_f : 0.3); **¹H-NMR (DMSO-*d*₆, 500 MHz):** δ 8.69 (s, 1H), 8.18-8.15 (m, 2H), 8.10 (d, J = 8.5 Hz, 1H), 7.92 (d, J = 8.5 Hz, 1H), 7.10 (d, J = 9.0 Hz, 1H), 3.90 (s, 3H).

Synthesis of methyl 3-amino-4-((5-chloro-2-cyanophenyl) thio) benzoate (19):



[00091] To a stirred solution of compound **18** (700 mg, 2.01 mmol) in acetic acid (15 mL) under inert atmosphere was added iron powder (1.12 g, 20.11 mmol) at RT; heated to 90 °C and stirred for 5 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was basified with 10% NaHCO₃ solution (20 mL) and extracted with CH₂Cl₂ (2 x 30 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 20% EtOAc/ hexanes to afford compound **19** (500 mg, 78%) as yellow solid. **TLC:** 30% EtOAc/ hexanes (R_f : 0.8); **¹H-NMR (DMSO-*d*₆, 500 MHz):** δ 7.92 (d, J = 7.5 Hz, 1H), 7.51-7.43 (m, 3H), 7.17 (d, J = 8.0 Hz, 1H), 6.66 (s, 1H), 5.96 (s, 2H), 3.86 (s, 3H).

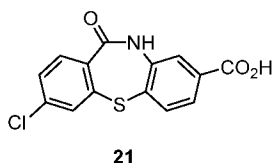
Synthesis of 2-((2-amino-4-carboxyphenyl) thio)-4-chlorobenzoic acid (20):



[00092] To a stirred solution of compound **19** (500 mg, 1.57 mmol) in MeOH (6 mL) was

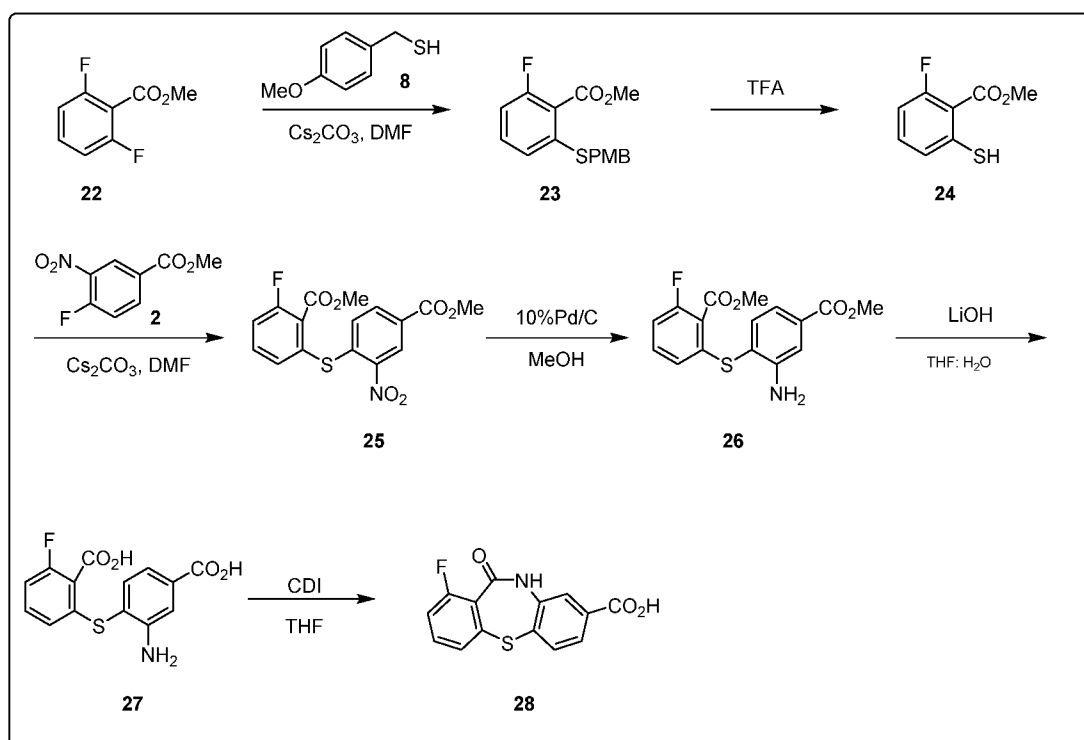
added potassium hydroxide (1.32 mg, 23.5 mmol) in water (6 mL) at 0 °C; heated to 90 °C and stirred for 24 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with water (20 mL) and extracted with EtOAc (2 x 25 mL). The aqueous layer was acidified with 1 N HCl to pH~6.0. The obtained solid was filtered, washed with ether (2 x 7 mL) and dried *in vacuo* to afford compound **20** (375 mg, 74%) as an off-white solid. **TLC:** 20% MeOH/ CH₂Cl₂ (*R_f*: 0.2); **¹H-NMR (CDCl₃, 400 MHz):** δ 8.05 (d, *J* = 8.4 Hz, 1H), 7.55-7.47 (m, 3H), 7.17-7.14 (m, 1H), 6.67 (s, 1H).

Synthesis of 3-chloro-11-oxo-10, 11-dihydrodibenzo [*b, f*] [1, 4] thiazepine-8-carboxylic acid (21):

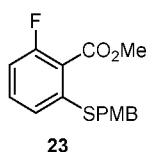


[00093] To a stirred solution of compound **20** (375 mg, 1.16 mmol) in THF (10 mL) under inert atmosphere was added CDI (564 mg, 3.48 mmol) at RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with water (15 mL) and acidified with 6 N HCl to pH~1.0. The obtained solid was filtered, washed with ether (2 x 5 mL) and dried *in vacuo* to afford compound **21** (285 mg, 81%) as an off-white solid. **TLC:** 20% MeOH/ CH₂Cl₂ (*R_f*: 0.4); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 14.56 (br s, 2H), 10.90 (s, 1H), 9.11 (s, 1H), 7.71-7.65 (m, 4H).

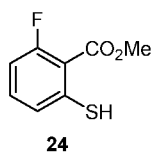
Example 4: Synthesis of 1-fluoro-11-oxo-10, 11-dihydrodibenzo [*b, f*] [1, 4] thiazepine-8-carboxylic acid (28) - a common intermediate



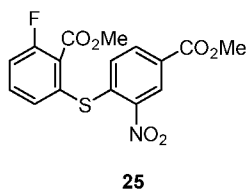
Synthesis of methyl 2-fluoro-6-((4-methoxybenzyl) thio) benzoate (23):



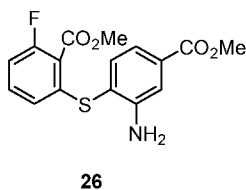
[00094] To a stirred solution of methyl 2, 6-difluorobenzoate **22** (10 g, 58.13 mmol) in DMF (100 mL) under inert atmosphere were added (4-methoxyphenyl) methanethiol **8** (8.96 g, 58.13 mmol), cesium carbonate (20.8 g, 63.95 mmol) at 0 °C; warmed to 10 °C and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (200 mL) and extracted with EtOAc (2 x 800 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 10-15% EtOAc/hexanes to afford compound **23** (7.5 g, 42%) as white solid. **TLC:** 10% EtOAc/ hexanes (R_f : 0.3); **^1H NMR (DMSO- d_6 , 400 MHz)** δ 7.53-7.44 (m, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.26 (d, J = 8.6 Hz, 2H), 7.15 (t, J = 9.0 Hz, 1H), 6.86 (d, J = 8.7 Hz, 2H), 4.22 (s, 2H), 3.72 (s, 3H), 3.33 (s, 3H).

Synthesis of methyl 2-fluoro-6-mercaptobenzoate (24):

[00095] A stirred solution of compound **23** (7.5 g, 24.5 mmol) in trifluoro acetic acid (100 mL) at RT under inert atmosphere was heated to 60-65 °C and stirred for 5 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed and dried *in vacuo* to obtain compound **24** (4.6 g) as brown syrup. The crude was carried forward for next step without further purification. **TLC:** 10% EtOAc/ hexanes (R_f : 0.7).

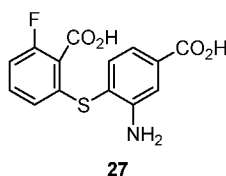
Synthesis of methyl 2-fluoro-6-((4-(methoxycarbonyl)-2-nitrophenyl) thio) benzoate (25):

[00096] To a stirred solution of methyl 4-fluoro-3-nitrobenzoate **2** (4.5 g, 22.61 mmol) in DMF (100 mL) under inert atmosphere were added compound **24** (4.6 g, crude), cesium carbonate (11 g, 33.91 mmol) at RT; heated to 60-65 °C and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (600 mL) and stirred for 1 h. The precipitated solid was filtered, titrated with 10% EtOAc/ hexanes(2 x 20 mL) and dried *in vacuo* to afford compound **25** (7 g, 85%) as yellow solid. **TLC:** 20% EtOAc/ hexanes (R_f : 0.3); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 8.65 (s, 1H), 8.08 (dd, J = 8.6, 1.9 Hz, 1H), 7.79-7.72 (m, 1H), 7.67-7.61 (m, 2H), 7.01 (d, J = 8.6 Hz, 1H), 3.88 (s, 3H), 3.72 (s, 3H).

Synthesis of methyl 2-((2-amino-4-(methoxycarbonyl) phenyl) thio)-6-fluorobenzoate (26):

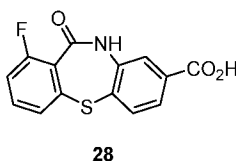
[00097] To a stirred solution of compound **25** (7.09 g, 19.17 mmol) in MeOH (200 mL) under inert atmosphere was added 10% Pd/ C (3.5 g) at RT and stirred under hydrogen at 80 psi for 16 h in an autoclave. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered through celite and washed with 40% MeOH/ CH₂Cl₂ (3 x 500 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude compound was triturated with 20% EtOAc/ hexanes (200 mL) and dried *in vacuo* to afford compound **26** (5 g, 78%) as an off-white solid. **TLC:** 20% EtOAc/ hexanes (*R_f*: 0.4); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 7.45-7.36 (m, 3H), 7.19-7.11 (m, 2H), 6.68 (d, *J* = 7.7 Hz, 1H), 5.71 (s, 2H), 3.90 (s, 3H), 3.83 (s, 3H).

Synthesis of 2-((2-amino-4-carboxyphenyl) thio)-6-fluorobenzoic acid (27):



[00098] To a stirred solution of compound **26** (5 g, 14.92 mmol) in THF: H₂O (5: 1, 90 mL) was added lithium hydroxide monohydrate (3.13 g, 74.62 mmol) at RT and stirred for 16 h and heated to 80 °C for 5 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with water (200 mL) and acidified with 2 N HCl to pH~4. The precipitated solid was filtered and dried *in vacuo* to afford compound **27** (4 g, 87%) as an off-white solid. **TLC:** 30% EtOAc/ hexanes (*R_f*: 0.1); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 12.89 (br s, 1H), 7.42-7.36 (m, 2H), 7.35-7.31 (m, 1H), 7.14 -7.08 (m, 2H), 6.63 (d, *J* = 8.0 Hz, 1H), 5.75 (br s, 2H).

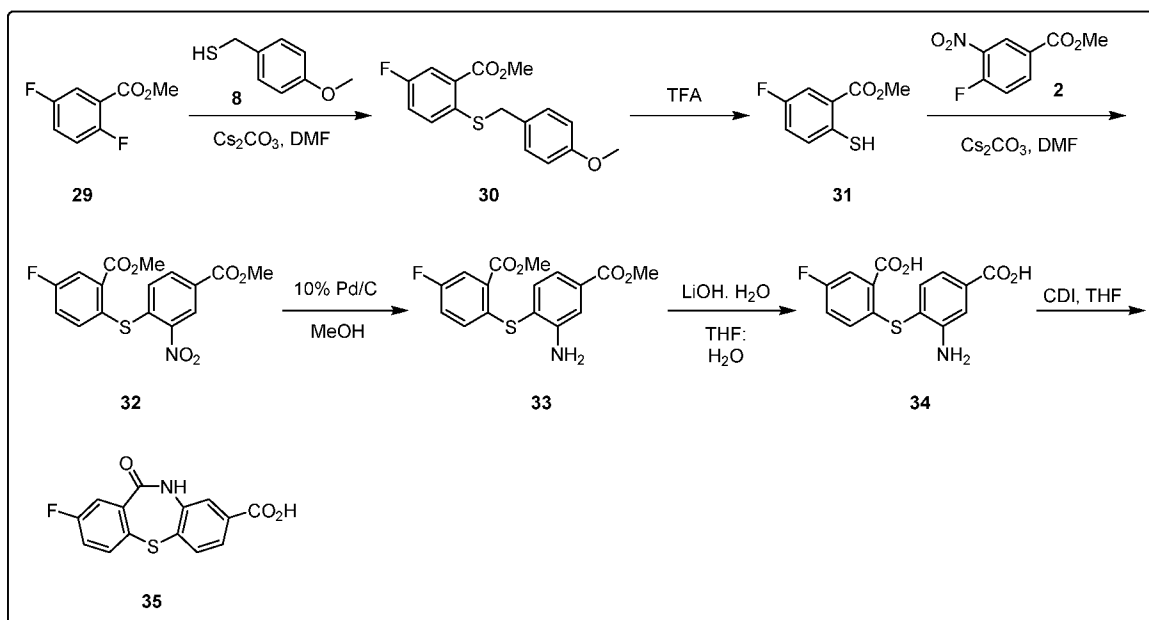
Synthesis of 1-fluoro-11-oxo-10, 11-dihydrodibenzo [b, f] [1, 4] thiazepine-8-carboxylic acid (28):



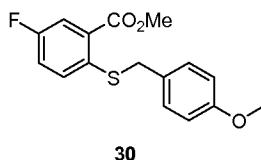
[00099] To a stirred solution of compound **27** (4 g, 13.02 mmol) in THF (100 mL) under inert

atmosphere was added CDI (10.56 g, 65.1 mmol) at RT and stirred for 26 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with ice cold water (80 mL) and acidified with 2 N HCl to pH~4. The precipitated solid was filtered and dried *in vacuo* to afford compound **28** (3.3 g, 88%) as an off-white solid. **TLC**: 15% MeOH/ CH₂Cl₂ (*R_f*: 0.2); **¹H NMR (DMSO-*d*₆, 400 MHz)**: δ 13.33 (br s, 2H), 11.00 (s, 1H), 7.77 (s, 1H), 7.69-7.67 (m, 2H), 7.53-7.47 (m, 1H), 7.42-7.39 (m, 1H), 7.35-7.29 (m, 1H).

Example 5: Synthesis of 2-fluoro-11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxylic acid (35) - a common intermediate



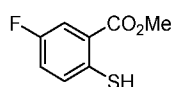
Synthesis of methyl-5-fluoro-2-((4-methoxybenzyl) thio) benzoate (30):



[000100] To a stirred solution of methyl 2, 5-difluorobenzoate **29** (1 g, 5.80 mmol) in DMF (20 mL) under argon atmosphere were added (4-methoxyphenyl) methanethiol **8** (985 mg, 6.39 mmol), cesium carbonate (2.07 g, 6.39 mmol) at RT and stirred for 3 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water

(30 mL) and extracted with CH₂Cl₂ (2 x 30 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 5-7% EtOAc/ hexanes to afford compound **30** (700 mg, 40%) as white solid. **TLC:** 10% EtOAc/ hexanes (*R_f*: 0.3); **¹H-NMR (CDCl₃, 400 MHz):** δ 7.64-7.61 (m, 1H), 7.32-7.29 (m, 3H), 7.17-7.09 (m, 1H), 6.86-6.82 (m, 2H), 4.09 (s, 2H), 3.90 (s, 3H), 3.79 (s, 3H).

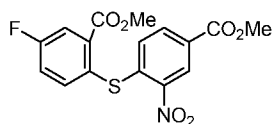
Synthesis of methyl 5-fluoro-2-mercaptobenzoate (31):



31

[000101] A stirred solution of compound **30** (700 mg, 2.28 mmol) in trifluoro acetic acid (7 mL) at RT under argon atmosphere was heated to 60-65 °C and stirred for 5 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed and dried *in vacuo* to obtain compound **31** (380 mg, 89%) as brown syrup. **TLC:** 10% EtOAc/ hexanes (*R_f*: 0.7); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 7.70-7.58 (m, 2H), 7.42-7.35 (m, 1H), 5.42 (s, 1H), 3.86 (s, 3H).

Synthesis of methyl 5-fluoro-2-((4-(methoxycarbonyl)-2-nitrophenyl) thio) benzoate (32):

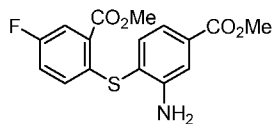


32

[000102] To a stirred solution of methyl 4-fluoro-3-nitrobenzoate **2** (350 mg, 1.75 mmol) in DMF (10 mL) under argon atmosphere were added compound **31** (360 mg, 1.93 mmol), cesium carbonate (1.14 g, 3.51 mmol) at RT; heated to 60-65 °C and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (30 mL) and extracted with CH₂Cl₂ (2 x 40 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 7-10% EtOAc/ hexanes to afford compound **32** (500 mg, 78%) as yellow solid. **TLC:** 10% EtOAc/ hexanes (*R_f*: 0.3); **¹H-NMR (DMSO-*d*₆, 400**

MHz): δ 8.64 (s, 1H), 8.04-8.02 (m, 1H), 7.83-7.79 (m, 2H), 7.64-7.59 (m, 1H), 7.01 (d, J = 8.4 Hz, 1H), 3.88 (s, 3H), 3.71 (s, 3H).

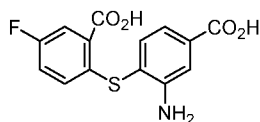
Synthesis of methyl 2-((2-amino-4-(methoxycarbonyl) phenyl) thio)-5-fluorobenzoate (33):



33

[000103] To a stirred solution of compound **32** (500 mg, 1.36 mmol) in MeOH (10 mL) under argon atmosphere was added 10% Pd/ C (300 mg) at RT and stirred under hydrogen atmosphere (balloon pressure) for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered through celite and washed with 20% MeOH/ CH₂Cl₂ (2 x 30 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 8-10% EtOAc/ hexanes to afford compound **33** (300 mg, 66%) as pale yellow solid. **TLC:** 30% EtOAc/ hexanes (R_f : 0.5); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 7.78 (d, J = 9.6 Hz, 1H), 7.45-7.41 (m, 2H), 7.35-7.30 (m, 1H), 7.14 (d, J = 9.6 Hz, 1H), 6.68-6.65 (m, 1H), 5.70 (s, 2H), 3.89 (s, 3H), 3.83 (s, 3H).

Synthesis of 2-((2-amino-4-carboxyphenyl) thio)-5-fluorobenzoic acid (34):

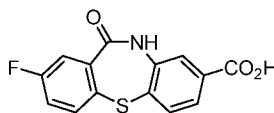


34

[000104] To a stirred solution of compound **33** (300 mg, 0.89 mmol) in THF: H₂O (5: 1, 6 mL) under argon atmosphere was added lithium hydroxide monohydrate (188 mg, 4.47 mmol) at RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with water (15 mL) and acidified with 6 N HCl to pH~4. The precipitated solid was filtered and dried *in vacuo* to afford compound **34** (180 mg, 66%) as white solid. **TLC:** 50% EtOAc/ hexanes (R_f : 0.2); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 12.99-12.96 (m, 2H), 7.69 (d, J = 6.8 Hz, 1H), 7.40 (t, J = 7.2 Hz, 2H), 7.29 (t, J = 7.2

Hz, 1H), 7.13 (d, $J = 7.2$ Hz, 1H), 6.64-6.61 (m, 1H), 5.64-5.61 (m, 2H).

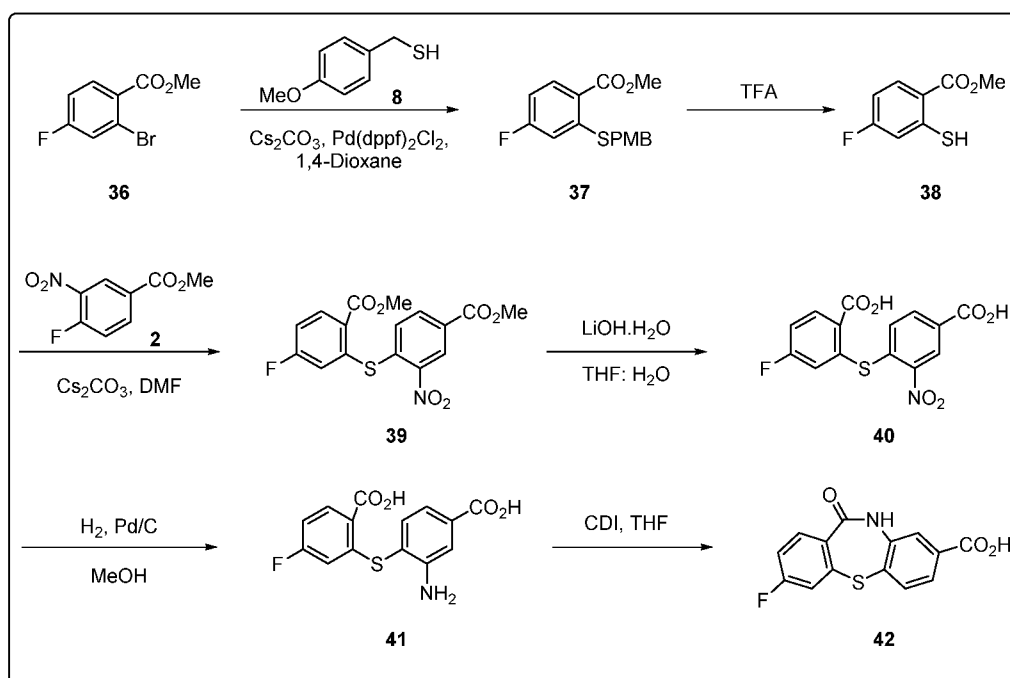
Synthesis of 2-fluoro-11-oxo-10, 11-dihydrodibenzo [*b, f*] [1, 4] thiazepine-8-carboxylic acid (35):



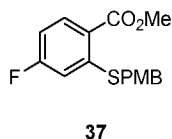
35

[000105] To a stirred solution of compound **34** (180 mg, 0.58 mmol) in THF (10 mL) under argon atmosphere was added CDI (284 mg, 1.75 mmol) at RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with ice cold water (10 mL) and acidified with 6 N HCl to pH~4. The precipitated solid was filtered and dried *in vacuo* to afford compound **35** (80 mg, 47%) as an off-white solid. **TLC:** 10% MeOH/ CH₂Cl₂ (R_f : 0.2); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 13.30 (br s, 1H), 10.93 (s, 1H), 7.70 (s, 1H), 7.67 (d, $J = 7.6$ Hz, 2H), 7.59 (t, $J = 7.6$ Hz, 1H), 7.48 (t, $J = 7.6$ Hz, 1H), 7.40-7.35 (m, 1H).

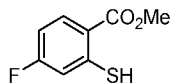
Example 6: Synthesis of 3-fluoro-11-oxo-10, 11-dihydrodibenzo [*b, f*] [1, 4] thiazepine-8-carboxylic acid (42) - a common intermediate



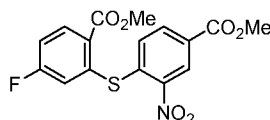
Synthesis of methyl 4-fluoro-2-((4-methoxybenzyl) thio) benzoate (37):



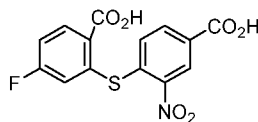
[000106] To a stirred solution of methyl 2-bromo-4-fluorobenzoate **36** (2 g, 8.58 mmol) in 1,4-dioxane (50 mL) under inert atmosphere were added (4-methoxyphenyl) methanethiol **8** (1.58 g, 10.25 mmol), cesium carbonate (4.18 g, 12.80 mmol) at RT and purged under argon atmosphere for 30 min. To this was added Pd(dppf)₂Cl₂ (306 mg, 0.42 mmol); heated to 120 °C and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 250 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 7% EtOAc/hexanes to afford compound **37** (1.6 g, 61%) as an off-white solid. **TLC:** 10% EtOAc/hexanes (*R_f*: 0.4); **¹H NMR (CDCl₃, 400 MHz):** δ 8.01 (dd, *J* = 8.7, 6.2 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 2H), 7.04 (dd, *J* = 10.3, 2.4 Hz, 1H), 6.88-6.80 (m, 3H), 4.09 (s, 2H), 3.88 (s, 3H), 3.80 (s, 3H).

Synthesis of methyl 4-fluoro-2-mercaptobenzoate (38):**38**

[000107] A stirred solution of compound **37** (2.2 g, 7.18 mmol) in trifluoro acetic acid (30 mL) at RT under inert atmosphere was heated to 90 °C and stirred for 3 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain compound **38** (1.33 g, crude) as brown syrup. The crude was carried forward for next step without further purification. **TLC:** 10% EtOAc/ hexanes (R_f : 0.8).

Synthesis of methyl 4-fluoro-2-((4-(methoxycarbonyl)-2-nitrophenyl) thio) benzoate (39):**39**

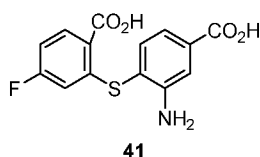
[000108] To a stirred solution of methyl 4-fluoro-3-nitrobenzoate **2** (1.29 g, 6.93 mmol) in DMF (50 mL) under inert atmosphere were added cesium carbonate (2.93 g, 9.01 mmol) and compound **38** (1.2 g, 6.03 mmol) at RT; heated to 55-60 °C and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (20 mL), the precipitated solid was filtered to obtain the crude. The crude was washed with pentane (2 x 20 mL) and dried *in vacuo* to afford compound **39** (1.5 g, 68%) as yellow solid. **TLC:** 10% EtOAc/ hexanes (R_f : 0.3); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 8.63 (s, 1H), 8.13-8.04 (m, 2H), 7.53-7.46 (m, 2H), 7.24 (d, J = 8.4 Hz, 1H), 3.89 (s, 3H), 3.72 (s, 3H).

Synthesis of 2-((4-carboxy-2-nitrophenyl) thio)-4-fluorobenzoic acid (40):**40**

[000109] To a stirred solution of compound **39** (1.5 g, 4.10 mmol) in THF: H₂O (4: 1, 20 mL) was added lithium hydroxide monohydrate (690 mg, 16.4 mmol) at RT, heated to 80 °C and

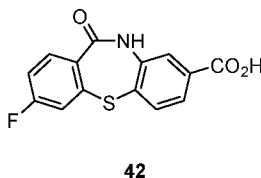
stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The pH of the residue was acidified with 2 N HCl to ~6. The precipitated solid was filtered and dried *in vacuo* to afford compound **40** (1.2 g, 86%) as an off-white solid. **TLC:** 5% MeOH/ CH₂Cl₂ (*R_f*: 0.2); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 13.46 (br s, 2H), 8.58 (s, 1H), 8.08-8.01 (m, 2H), 7.45-7.40 (m, 1H), 7.38-7.35 (m, 1H), 7.29 (d, *J* = 8.4 Hz, 1H).

Synthesis of 2-((2-amino-4-carboxyphenyl) thio)-4-fluorobenzoic acid (41):



[000110] To a stirred solution of compound **40** (1.2 g, 3.56 mmol) in MeOH (50 mL) under inert atmosphere was added 10% Pd/ C (300 mg) at RT and stirred under hydrogen atmosphere (balloon pressure) for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered through celite, washed with MeOH (20 mL). The filtrate was removed *in vacuo* to obtain the crude which was triturated with 10% EtOAc/ *n*-pentane (50 mL) to afford compound **41** (1 g, 91%) as an off-white solid. **TLC:** 10% MeOH/ CH₂Cl₂ (*R_f*: 0.3); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 12.96 (br s, 2H), 8.06-8.02 (m, 1H), 7.46 (s, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 7.07-7.02 (m, 1H), 6.24 (d, *J* = 8.0 Hz, 1H), 5.67 (br s, 2H).

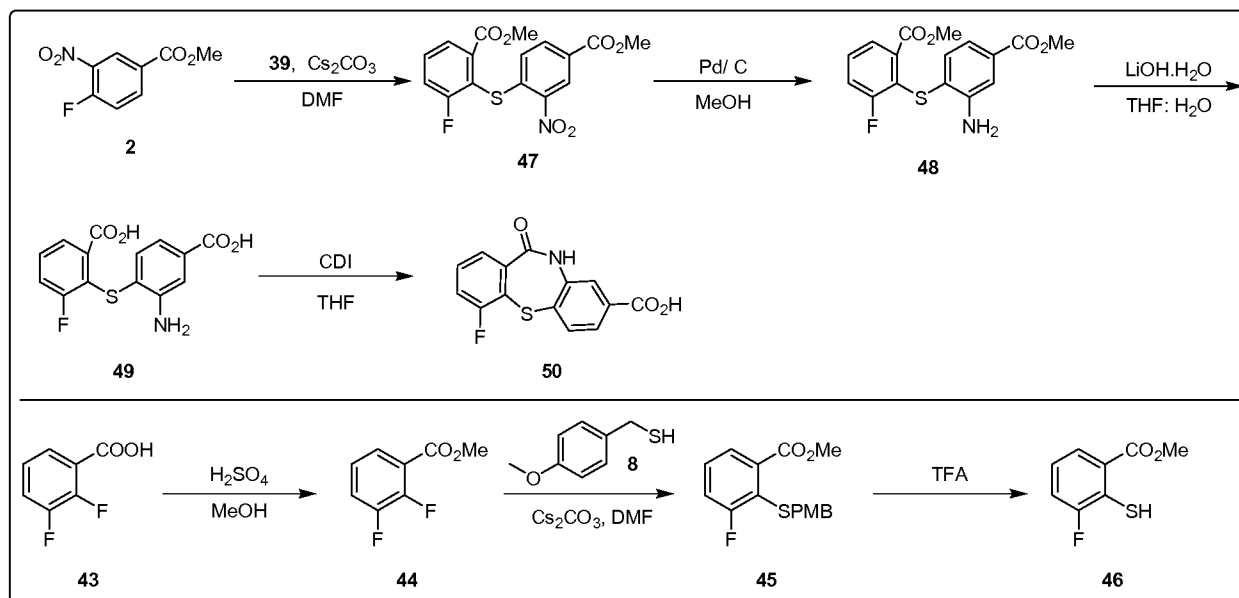
Synthesis of 3-fluoro-11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxylic acid (42):



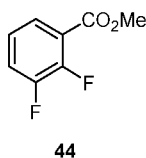
[000111] To a stirred solution of compound **41** (1 g, 3.25 mmol) in THF (30 mL) under inert atmosphere was added CDI (1.61 g, 9.77 mmol) at RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was acidified with 2 N HCl to pH~4. The obtained solid was filtered, washed with water (20 mL), ether (2 x 5 mL) and

dried *in vacuo* to afford compound **42** (760 mg, 80%) as white solid. **TLC:** 10% MeOH/ CH₂Cl₂ (*R_f*: 0.3); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 13.24 (br s, 1H), 10.83 (s, 1H), 7.78-7.74 (m, 2H), 7.69-7.66 (m, 2H), 7.47-7.44 (m, 1H), 7.35-7.30 (m, 1H).

Example 7: Synthesis of 4-fluoro-11-oxo-10, 11-dihydrodibenzo [b, f] [1, 4] thiazepine-8-carboxylic acid (50) - a common intermediate



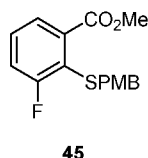
Synthesis of methyl 2, 3-difluorobenzoate (44):



[000112] To a stirred solution of 2, 3-difluorobenzoic acid **43** (1 g, 6.28 mmol) in MeOH (10 mL) under inert atmosphere was added Conc. H₂SO₄ (5 mL) at 0 °C and heated to reflux for 36 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with water (25 mL) and pH adjusted to ~8 with saturated sodium bicarbonate solution (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 20% EtOAc/ hexanes to afford compound **44** (800 mg, 74%) as an off-white solid. **TLC:** 40% EtOAc/

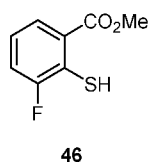
hexanes (R_f : 0.8); ^1H NMR (DMSO- d_6 , 500 MHz) δ 7.80 - 7.65 (m, 2H), 7.41-7.23 (m, 1H), 3.88 (s, 3H).

Synthesis of methyl 3-fluoro-2-((4-methoxybenzyl) thio) benzoate (45):



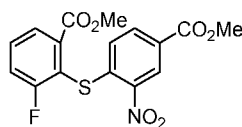
[000113] To a stirred solution of compound **44** (800 mg, 4.65 mmol) in DMF (10 mL) under inert atmosphere were added (4-methoxyphenyl) methanethiol **8** (282 mg, 5.11 mmol), cesium carbonate (1.66 g, 5.11 mmol) at RT and stirred for 6 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted water (25 mL) and extracted with ether (2 x 40 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 20% EtOAc/ hexanes to afford compound **45** (750 mg, 53%) as an off-white solid. **TLC:** 20% EtOAc/ hexanes (R_f : 0.4); ^1H NMR (DMSO- d_6 , 500 MHz): δ 7.49-7.36 (m, 3H), 7.10 (d, J = 8.9 Hz, 2H), 6.79 (d, J = 8.9 Hz, 2H), 4.06 (s, 2H), 3.81 (s, 3H), 3.70 (s, 3H);

Synthesis of methyl 3-fluoro-2-mercaptobenzoate (46):



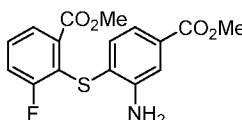
[000114] A stirred solution of compound **45** (750 mg, 2.45 mmol) in trifluoro acetic acid (7 mL) at RT under inert atmosphere was heated to 70 °C and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain compound **46** (1.1 g, crude) as colorless liquid. The crude was carried forward for next step. **TLC:** 30% EtOAc/ hexanes (R_f : 0.8).

Synthesis of methyl 3-fluoro-2-((4-(methoxycarbonyl)-2-nitrophenyl) thio) benzoate (47):

**47**

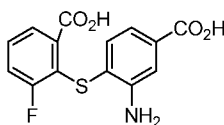
[000115] To a stirred solution of compound **46** (5.96 g, 3.20 mmol) in DMF (100 mL) under inert atmosphere were added methyl 4-fluoro-3-nitrobenzoate **2** (5.8 g, 2.91 mmol), cesium carbonate (10.41 g, 3.20 mmol) at RT; heated to 80 °C and stirred for 4 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with ice cold water (25 mL). The obtained solid was filtered, washed with hexane (2 x 10 mL) and dried *in vacuo* to afford compound **47** (7.8 g, 73%) as a pale yellow solid. **TLC:** 30% EtOAc/hexanes (R_f : 0.5); **¹H NMR (DMSO-*d*₆, 500 MHz):** δ 8.67 (s, 1H), 8.05 (dd, J = 8.7, 1.7 Hz, 1H), 7.94-7.75 (m, 2H), 7.73-7.67 (m, 1H), 7.00 (d, J = 8.4 Hz, 1H), 3.88 (s, 3H), 3.77-3.64 (m, 3H).

Synthesis of methyl 2-((2-amino-4-(methoxycarbonyl) phenyl) thio)-3-fluorobenzoate (48**):**

**48**

[000116] To a stirred solution of compound **47** (670 mg, 1.83 mmol) in MeOH (10 mL) under inert atmosphere was added 10% Pd/C (150 mg) at RT and stirred under hydrogen atmosphere (balloon pressure) for 12 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered through celite and the filtrate was concentrated *in vacuo* to afford compound **48** (500 mg, 81%) as an off-white solid. **TLC:** 30% EtOAc/hexanes (R_f : 0.4); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 7.58-7.50 (m, 2H), 7.48-7.41 (m, 1H), 7.33 (s, 1H), 7.04 (s, 2H), 5.59 (br s, 2H), 3.82 (s, 3H), 3.79 (s, 3H).

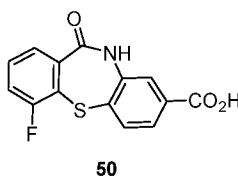
Synthesis of 2-((2-amino-4-carboxyphenyl) thio)-3-fluorobenzoic acid (49**):**

**49**

[000117] To a stirred solution of compound **48** (500 mg, 1.49 mmol) in THF: H₂O (4: 1, 20

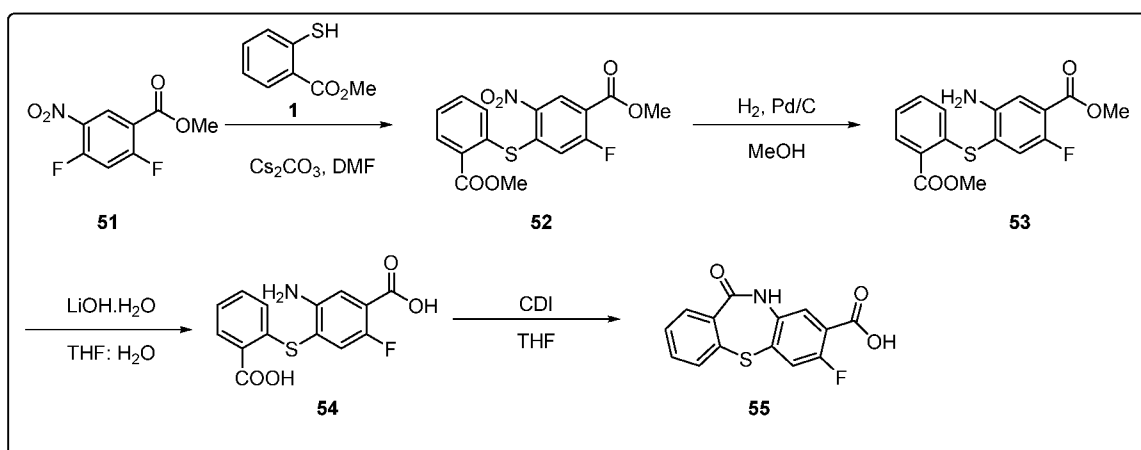
mL) was added lithium hydroxide monohydrate (376 mg, 8.95 mmol) at RT; heated to 80 °C and stirred for 3 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with water (25 mL) and washed with diethyl ether (2 x 25 mL). The aqueous layer was acidified with 2 N HCl to pH~4 and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude which was washed with diethyl ether (2 x 5 mL) and dried *in vacuo* to afford compound **49** (300 mg, 65%) as an off-white solid. **TLC:** 10% MeOH/ CH₂Cl₂ (*R_f*: 0.2); **¹H NMR (DMSO-*d*₆, 500 MHz):** δ 12.68 (br s, 2H), 7.54-7.45 (m, 2H), 7.39-7.32 (m, 1H), 7.28 (s, 1H), 7.09-7.06 (m, 1H), 7.02-6.96 (m, 1H), 5.56 (br s, 2H);

Synthesis of 4-fluoro-11-oxo-10, 11-dihydrodibenzo [*b, f*] [1, 4] thiazepine-8-carboxylic acid (50):

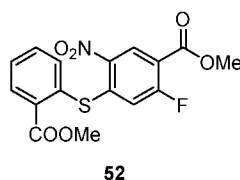


[000118] To a stirred solution of compound **49** (300 mg, 0.97 mmol) in THF (15 mL) under inert atmosphere was added CDI (474 mg, 2.92 mmol) at RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The pH of the residue was acidified with 4 N HCl to ~2. The obtained solid was filtered, washed with diethyl ether (2 x 5 mL) and dried *in vacuo* to afford compound **50** (150 mg, 53%) as an off-white solid. **TLC:** 15% MeOH/ CH₂Cl₂ (*R_f*: 0.5); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 13.38 (br s, 1H), 10.92 (s, 1H), 7.79 (s, 1H), 7.75-7.66 (m, 2H), 7.55-7.46 (m, 3H).

Example 8: Synthesis of 7-fluoro-11-oxo-10, 11-dihydrodibenzo [*b, f*] [1, 4] thiazepine-8-carboxylic acid (55) - a common intermediate

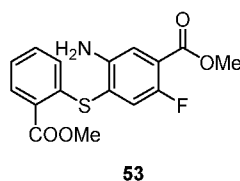


Synthesis of methyl 2-fluoro-4-((2-(methoxycarbonyl) phenyl) thio)-5-nitrobenzoate (52):



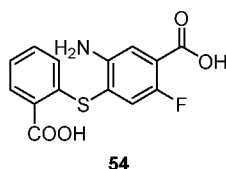
[000119] To a stirred solution of methyl 2, 4-difluoro-5-nitrobenzoate **51** (9.0 g, 41.45 mmol) in DMF (100 mL) under inert atmosphere were added methyl 2-mercaptobenzoate **1** (6.97 g, 41.45 mmol), cesium carbonate (14.82 g, 45.60 mmol) at 0 °C; warmed to 10 °C and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (800 mL) and extracted with EtOAc (2 x 500 mL). The combined organic extracts were dried under sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 10% EtOAc/ hexanes to afford compound **52** (11 g, 73%) as an off-white solid. **TLC:** 10% EtOAc/ hexanes (*R_f*: 0.4); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 8.69 (d, *J* = 6.8 Hz, 1H), 8.04-7.92 (m, 1H), 7.81-7.69 (m, 3H), 6.60 (d, *J* = 11.5 Hz, 1H), 3.88 (s, 3H), 3.73 (s, 3H).

Synthesis of methyl 5-amino-2-fluoro-4-((2-(methoxycarbonyl) phenyl) thio) benzoate (53):



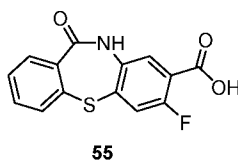
[000120] To a stirred solution of compound **52** (11 g, 30.13 mmol) in MeOH (400 mL) under inert atmosphere was added 10% Pd/ C (5 g) at RT and stirred under hydrogen atmosphere (balloon pressure) for 24 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered through celite, washed with 30% MeOH/ CH₂Cl₂ (3 x 60 mL). The filtrate was removed *in vacuo* to afford compound **53** (6.5 g, 64%) as an off-white solid. **TLC:** 20% EtOAc/ hexanes (*R_f*: 0.4); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 8.01-7.88 (m, 1H), 7.45-7.40 (m, 1H), 7.34-7.24 (m, 3H), 6.72 (dd, *J* = 8.2, 0.8 Hz, 1H), 5.51 (s, 2H), 3.88 (s, 3H), 3.85 (s, 3H).

Synthesis of 5-amino-4-((2-carboxyphenyl) thio)-2-fluorobenzoic acid (54):



[000121] To a stirred solution of compound **53** (6.5 g, 19.4 mmol) in THF: H₂O (4: 1, 90 mL) was added lithium hydroxide monohydrate (4 g, 97.01 mmol) at RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The pH of the residue was acidified with 2 N HCl to ~4. The precipitated solid was filtered and dried *in vacuo* to afford compound **54** (4.5 g, 75.6%) as an off-white solid. **TLC:** 30% EtOAc/ hexane (*R_f*: 0.2); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 13.19 (br s, 2H), 7.96 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.30 (d, *J* = 6.6 Hz, 1H), 7.27-7.20 (m, 2H), 6.68 (dd, *J* = 8.2, 0.7 Hz, 1H), 5.42 (br s, 2H).

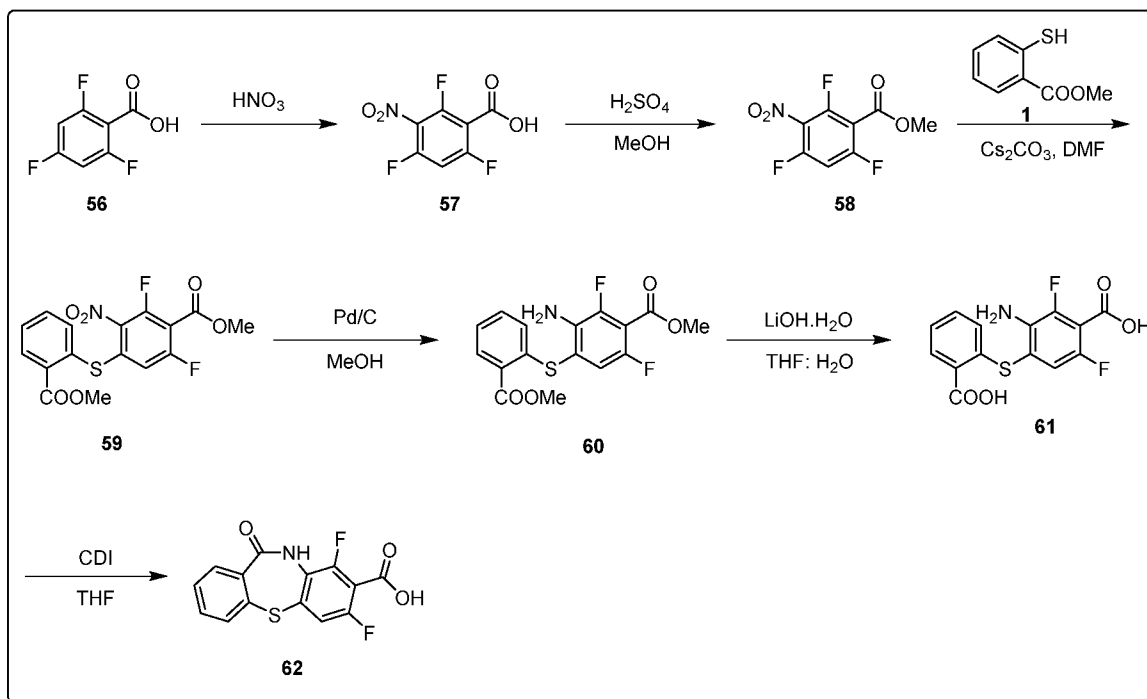
Synthesis of 7-fluoro-11-oxo-10, 11-dihydrodibenzo [b, f] [1, 4] thiazepine-8-carboxylic acid (55):



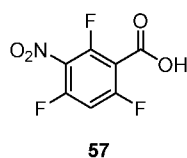
[000122] To a stirred solution of compound **54** (4.5 g, 14.65 mmol) in THF (100 mL) under inert atmosphere was added CDI (11.88 g, 73.28 mmol) at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture

was quenched with 2 N HCl to pH~4; the precipitated solid was filtered, dried *in vacuo* to afford compound **55** (3.5 g, 83%) as an off-white solid. **TLC**: 15% MeOH/ CH₂Cl₂ (*R_f*: 0.2); **¹H NMR (DMSO-*d*₆, 400 MHz)**: δ 13.61 (br s, 1H), 10.75 (s, 1H), 7.74-7.65 (m, 2H), 7.59-7.45 (m, 4H).

Example 9: Synthesis of 7, 9-difluoro-11-oxo-10, 11-dihydrodibenzo [b, f] [1, 4] thiazepine-8-carboxylic acid (62) - a Common Intermediate



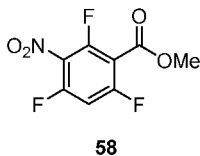
Synthesis of 2, 4, 6-trifluoro-3-nitrobenzoic acid (57):



[000123] To 2, 4, 6-trifluorobenzoic acid **56** (15 g, 85.22 mmol) at 0 °C, fuming nitric acid (20 mL) was added dropwise for 10 min; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with ice cold water (500 mL) and extracted with EtOAc (2 x 200 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford compound **57** (20 g) as pale yellow liquid. **TLC**: 5% MeOH/ CH₂Cl₂ + 0.05 mL CH₃COOH (*R_f*: 0.2); **¹H NMR**

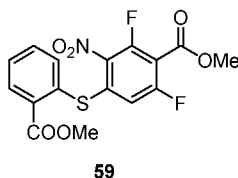
(DMSO-*d*₆, 400 MHz): δ 14.12 (br s, 1H), 7.83 (td, J = 10.5, 2.1 Hz, 1H).

Synthesis of methyl 2, 4, 6-trifluoro-3-nitrobenzoate (58):



[000124] To a stirred solution of compound **57** (20 g) in MeOH (200 mL) under argon atmosphere was added concentrated sulfuric acid (20 mL) dropwise for 20 min at 0 °C and heated to reflux for 48 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with water (500 mL) and extracted with EtOAc (4 x 200 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 5-8% EtOAc/ hexanes to afford compound **58** (14 g, 70% for 2 steps) as pale yellow syrup. **TLC:** 20% EtOAc/ hexane (R_f : 0.8); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 7.88 (td, J = 10.6, 2.2 Hz, 1H), 3.93 (s, 3H).

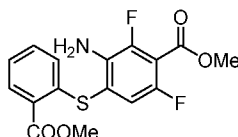
Synthesis of methyl 2, 6-difluoro-4-((2-(methoxycarbonyl) phenyl) thio)-3-nitrobenzoate (59):



[000125] To a stirred solution of compounds **58** (14 g, 59.57 mmol) in DMF (300 mL) under inert atmosphere were added methyl 2-mercaptobenzoate **1** (11.1 g, 66.07 mmol), cesium carbonate (38.77 g, 119.14 mmol) at 0 °C; warmed to RT and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with ice cold water (200 mL) and extracted with EtOAc (3 x 300 mL). The combined organic extracts were washed with water (200 mL), brine (200 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography to afford compound **59** (14.5 g, 64%) as yellow syrup. **TLC:** 10% EtOAc/

hexanes (R_f : 0.2); $^1\text{H NMR}$ ($\text{DMSO}-d_6$, 500 MHz): δ 7.98 (dd, $J = 7.7, 1.3$ Hz, 1H), 7.66-7.61 (m, 1H), 7.59-7.55 (m, 1H), 7.46 (d, $J = 7.8$ Hz, 1H), 7.19 (d, $J = 9.3$ Hz, 1H), 3.93 (s, 3H), 3.81 (s, 3H).

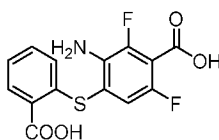
Synthesis of methyl 3-amino-2, 6-difluoro-4-((2-(methoxycarbonyl) phenyl) thio) benzoate (60):



60

[000126] To a stirred solution of compound **59** (18 g, 46.99) in MeOH (400 mL) under inert atmosphere was added Pd/C (9 g, 50% wet) at RT and stirred under hydrogen atmosphere in an autoclave (5 kg/cm² pressure) for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered through celite, washed with MeOH (500 mL). The filtrate was concentrated *in vacuo* to afford compound **60** (15.1 g, 91%) as colorless semi solid. **TLC**: 20% EtOAc/ hexanes (R_f : 0.5); $^1\text{H NMR}$ ($\text{DMSO}-d_6$, 500 MHz): δ 8.00-7.93 (m, 1H), 7.48-7.42 (m, 1H), 7.31-7.21 (m, 2H), 6.76-6.64 (m, 1H), 5.54-5.47 (m, 2H), 3.91 (s, 3H), 3.89 (s, 3H).

Synthesis of 3-amino-4-((2-carboxyphenyl) thio)-2, 6-difluorobenzoic acid (61):

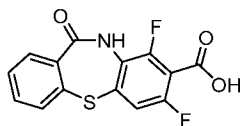


61

[000127] To a stirred solution of compound **60** (15.1 g, 39.42 mmol) in THF: H₂O (4: 1, 250 mL) was added lithium hydroxide monohydrate (8.3 g, 197.61 mmol) at RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*, diluted with water (100 mL) and washed with EtOAc (2 x 100 mL). The pH of the aqueous layer was acidified with 4 N HCl to ~4. The precipitated solid was filtered, washed with water (100 mL), pentane (100 mL). The obtained solid was further dried using toluene (150 mL) to afford compound **61** (11 g, 79%) as an off-white solid. **TLC**: 20% EtOAc/

hexanes (R_f : 0.2); ^1H NMR (DMSO- d_6 , 400 MHz): δ 13.24 (br s, 1H), 7.97 (dd, J = 7.7, 1.4 Hz, 1H), 7.46-7.39 (m, 1H), 7.28-7.19 (m, 2H), 6.66 (d, J = 8.2 Hz, 1H), 5.39 (br s, 2H).

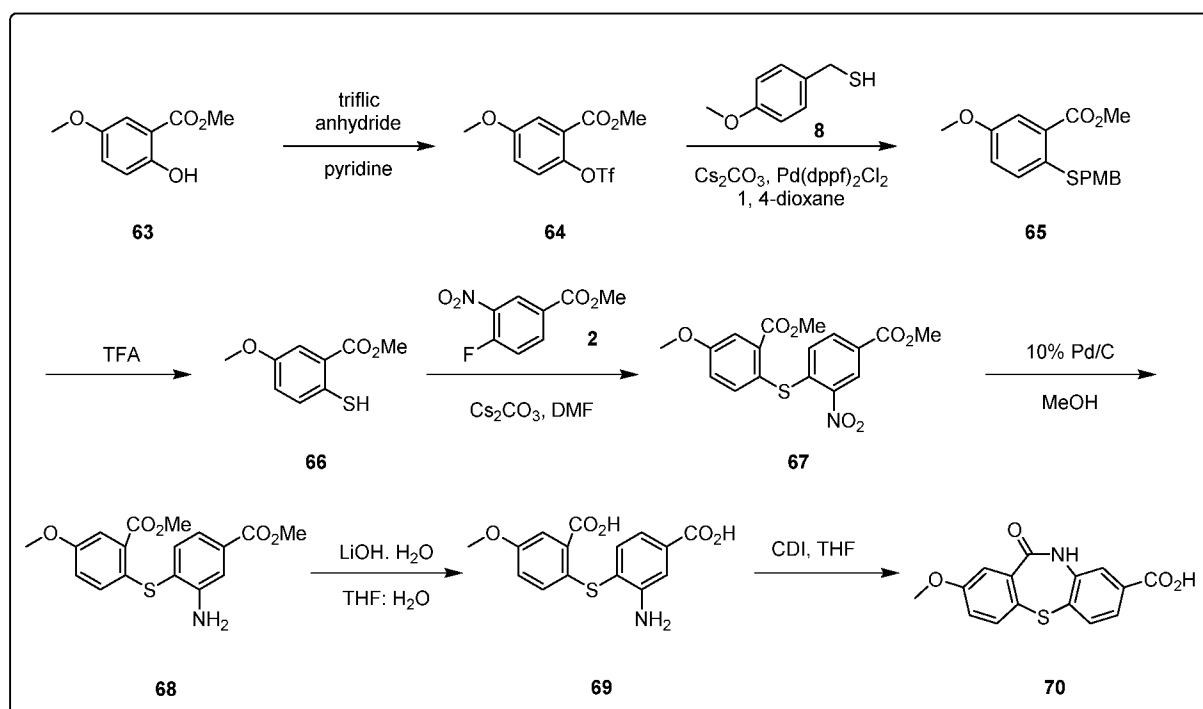
Synthesis of 7, 9-difluoro-11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxylic acid (62):



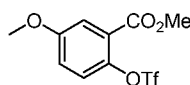
62

[000128] To a stirred solution of compound **61** (10 g, 30.76 mmol) in THF (200 mL) under argon atmosphere was added CDI (14.9 g, 81.97 mmol) at RT and stirred for 24 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with water (300 mL) and the pH was adjusted to ~3 with 2 N HCl. The obtained solid was filtered, washed with water (100 mL), pentane (50 mL) and diethyl ether (150 mL) and dried *in vacuo* to obtain compound **62** (2.83 g, 30%) as brick red solid. **TLC**: 15% MeOH/ CH₂Cl₂ (R_f : 0.3); ^1H NMR (DMSO- d_6 , 500 MHz): δ 14.19 (br s, 1H), 10.64 (s, 1H), 7.73-7.66 (m, 2H), 7.58- 7.48 (m, 3H).

Example 10: 2-methoxy-11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxylic acid (70) - a common intermediate

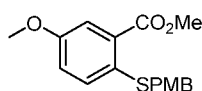


Synthesis of methyl 5-methoxy-2-(((trifluoromethyl) sulfonyl) oxy) benzoate (**64**):

**64**

[000129] To a stirred solution of methyl 2-hydroxy-5-methoxybenzoate **63** (2 g, 10.97 mmol) in pyridine (8 mL) under inert atmosphere was added triflic anhydride (3.56 g, 12.62 mmol) at 0 °C; warmed to RT and stirred for 2 h; heated to 40 °C and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with water (40 mL) and extracted with ether (3 x 40 mL). The combined organic extracts were washed with 1 N HCl (40 mL), water (40 mL), brine (40 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 5-10% EtOAc/ hexanes to afford compound **64** (2.9 g, 85%) as colorless liquid. **TLC**: 10% EtOAc/ hexanes (R_f : 0.6); **$^1\text{H-NMR}$ (CDCl_3 , 500 MHz)**: δ 7.50 (s, 1H), 7.09 (d, J = 7.5 Hz, 1H), 7.03 (d, J = 7.5 Hz, 1H), 3.94 (s, 3H), 3.84 (s, 3H).

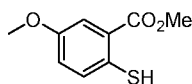
Synthesis of methyl-5-methoxy-2-((4-methoxybenzyl) thio) benzoate (**65**):



65

[000130] To a stirred solution of compound **64** (500 mg, 1.59 mmol) in 1, 4-dioxane (10 mL) under inert atmosphere were added (4-methoxyphenyl) methanethiol **8** (270 mg, 1.75 mmol), cesium carbonate (1.035 g, 3.18 mmol) at RT and degassed for 20 min. To this was added Pd(dppf)₂Cl₂ (29.1 mg, 0.039 mmol); heated to 110 °C and stirred for 10 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 30 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 10-15% EtOAc/ hexanes to afford compound **65** (280 mg, 55%) as pale yellow solid. **TLC:** 10% EtOAc/ hexanes (*R_f*: 0.4); **¹H-NMR (CDCl₃, 500 MHz):** δ 7.42 (s, 1H), 7.28-7.25 (m, 3H), 6.98 (d, *J* = 8.5 Hz, 1H), 6.84 (d, *J* = 8.5 Hz, 2H), 4.08 (s, 2H), 3.93 (s, 3H), 3.83 (s, 3H), 3.81 (s, 3H).

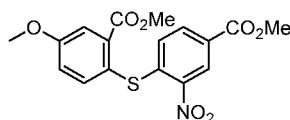
Synthesis of methyl 2-mercapto-5-methoxybenzoate (66):



66

[000131] A stirred solution of compound **65** (280 mg, 0.88 mmol) in trifluoro acetic acid (10 mL) at RT under inert atmosphere was heated to 70 °C and stirred for 4 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain compound **66** (170 mg, crude) as brown syrup. **TLC:** 10% MeOH/ CH₂Cl₂ (*R_f*: 0.8); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 7.68 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 7.2 Hz, 1H), 7.39 (s, 1H), 5.13 (s, 1H), 3.88 (s, 3H), 3.84 (s, 3H).

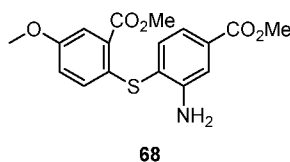
Synthesis of methyl 5-methoxy-2-((4-(methoxycarbonyl)-2-nitrophenyl) thio) benzoate (67):



67

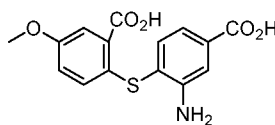
[000132] To a stirred solution of compound **66** (150 mg, 0.75 mmol) in DMF (5 mL) under inert atmosphere were added methyl 4-fluoro-3-nitrobenzoate **2** (164 mg, 0.82 mmol), cesium carbonate (490 mg, 1.50 mmol) at RT; heated to 55-60 °C and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (20 mL) and extracted with CH₂Cl₂ (2 x 30 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 15-25% EtOAc/ hexanes (*R_f*: 0.3); ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 8.64 (s, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.59-7.54 (m, 1H), 7.31 (d, *J* = 8.8 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.68 (s, 3H).

Synthesis of methyl 2-((2-amino-4-(methoxycarbonyl) phenyl) thio)-5-methoxybenzoate (68):



[000133] To a stirred solution of compound **67** (200 mg, 0.53 mmol) in MeOH (10 mL) under inert atmosphere was added 10% Pd/ C (100 mg) at RT and stirred under hydrogen atmosphere (balloon pressure) for 26 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered through celite and washed with 50% CH₂Cl₂/ MeOH (2 x 25 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 15-20% EtOAc/ hexanes to afford compound **68** (120 mg, 65%) as yellow solid. TLC: 30% EtOAc/ hexanes (*R_f*: 0.6); ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 7.42 (s, 2H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.66 (d, *J* = 8.8 Hz, 1H), 5.61 (s, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 3.75 (s, 3H).

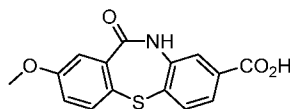
Synthesis of 2-((2-amino-4-carboxyphenyl) thio)-5-methoxybenzoic acid (69):



69

[000134] To a stirred solution of compound **68** (120 mg, 0.34 mmol) in THF: H₂O (4: 1, 5 mL) was added lithium hydroxide monohydrate (72.5 mg, 1.72 mmol) at RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with water (10 mL) and acidified with 6 N HCl to pH~4. The precipitated solid was filtered and dried *in vacuo* to afford compound **69** (80 mg, 73%) as an off-white solid. **TLC:** 40% EtOAc/ hexanes (*R_f*: 0.2); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 12.99 (br s, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 8.8 Hz, 1H), 6.61 (d, *J* = 8.8 Hz, 1H), 5.54 (br s, 2H), 3.74 (s, 3H).

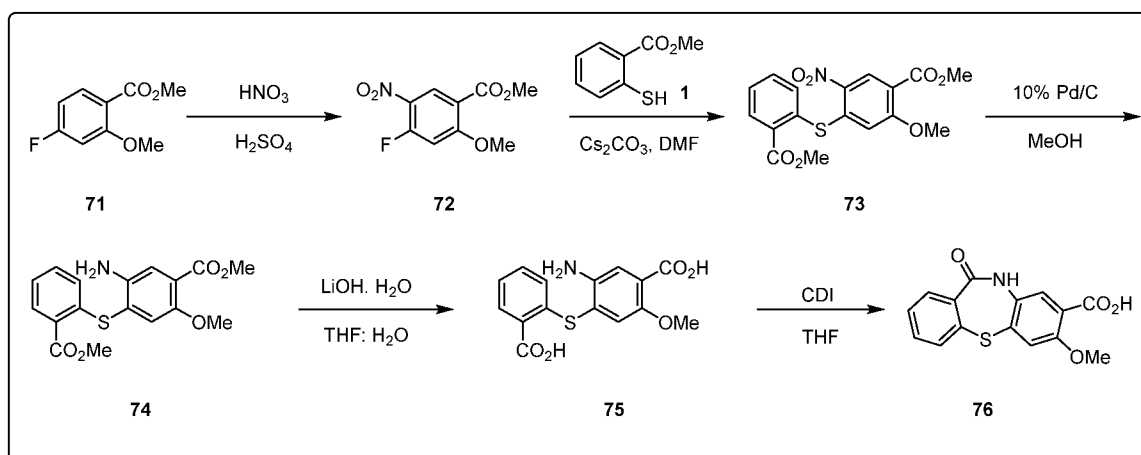
Synthesis of 2-methoxy-11-oxo-10,11-dihydrodibenzo [b, f] [1, 4] thiazepine-8-carboxylic acid (70):



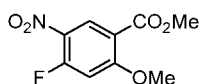
70

[000135] To a stirred solution of compound **69** (80 mg, 0.25 mmol) in THF (5 mL) under inert atmosphere was added CDI (122 mg, 0.75 mmol) at RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with water (10 mL) and acidified with 6 N HCl to pH~4. The precipitated solid was filtered and dried *in vacuo* to afford compound **70** (40 mg, 53%) as an off-white solid. **TLC:** 10% MeOH/ CH₂Cl₂ (*R_f*: 0.4); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 13.15 (br s, 1H), 10.79 (s, 1H), 7.78 (s, 1H), 7.69-7.66 (m, 2H), 7.44-7.42 (m, 1H), 7.20-7.19 (m, 1H), 7.08-7.05 (m, 1H), 3.77 (s, 3H).

Example 11: 7-methoxy-11-oxo-10,11-dihydrodibenzo [b, f] [1, 4] thiazepine-8-carboxylic acid (76) - a common intermediate



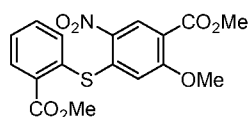
Synthesis of methyl 4-fluoro-2-methoxy-5-nitrobenzoate (72):



72

[000136] To a stirred solution of methyl 4-fluoro-2-methoxybenzoate **71** (500 mg, 2.50 mmol) in sulfuric acid (1 mL) under inert atmosphere was added the mixture of nitric acid (0.125 mL), sulfuric acid (0.5 mL) at -5°C and stirred for 10 min. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (25 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were washed with 10% NaHCO_3 solution (20 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was triturated with diethyl ether (2 x 5 mL) to afford compound **72** (200 mg, 33%) as an off-white solid. **TLC:** 20% EtOAc/ hexanes (R_f : 0.4); **$^1\text{H-NMR}$ (CDCl_3 , 400 MHz):** δ 8.69 (d, $J = 8.8$ Hz, 1H), 6.83 (d, $J = 12.8$ Hz, 1H), 4.01 (s, 3H), 3.92 (s, 3H).

Synthesis of methyl 2-methoxy-4-((2-(methoxycarbonyl) phenyl) thio)-5-nitrobenzoate (73):

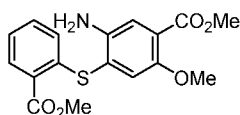


73

[000137] To a stirred solution of compound **72** (200 mg, 0.81 mmol) in DMF (4 mL) under

inert atmosphere were added methyl 2-mercaptobenzoate **1** (151 mg, 0.89 mmol), cesium carbonate (318 mg, 0.97 mmol) at RT; heated to 80 °C and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with ice water (20 mL) and extracted with EtOAc (2 x 35 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 15% EtOAc/ hexanes to afford compound **73** (200 mg, 61%) as yellow solid. **TLC:** 20% EtOAc/ hexanes (R_f : 0.4); **$^1\text{H-NMR}$ (CDCl_3 , 400 MHz):** δ 8.80 (s, 1H), 7.94-7.92 (m, 1H), 7.70 (t, J = 8.0 Hz, 1H), 7.61-7.59 (m, 2H), 6.30 (s, 1H), 3.90 (s, 3H), 3.82 (s, 3H), 3.52 (s, 3H).

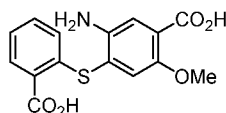
Synthesis of methyl 5-amino-2-methoxy-4-((2-(methoxycarbonyl) phenyl) thio) benzoate (74):



74

[000138] To a stirred solution of compound **73** (200 mg, 0.53 mmol) in MeOH (15 mL) under inert atmosphere was added 10% Pd/C (100 mg) at RT and stirred under hydrogen atmosphere (balloon pressure) for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered through celite and the filtrate was concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 15% EtOAc/ hexanes to afford compound **74** (110 mg, 60%) as yellow sticky solid. **TLC:** 20% EtOAc/ hexanes (R_f : 0.6); **$^1\text{H-NMR}$ (CDCl_3 , 400 MHz):** δ 7.99 (d, J = 8.0 Hz, 1H), 7.54 (s, 1H), 7.34-7.31 (m, 1H), 7.20 (t, J = 8.0 Hz, 1H), 7.12 (s, 1H), 6.80 (d, J = 8.4 Hz, 1H), 3.96 (s, 3H), 3.88 (s, 3H), 3.80 (s, 3H).

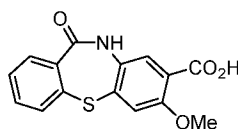
Synthesis of 5-amino-4-((2-carboxyphenyl) thio)-2-methoxybenzoic acid (75):



75

[000139] To a stirred solution of compound **74** (110 mg, 0.31 mmol) in THF: H₂O (5: 1, 3 mL) was added lithium hydroxide monohydrate (66 mg, 1.58 mmol) at RT; heated to 70 °C and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (15 mL) and extracted with EtOAc (2 x 25 mL). The aqueous layer was acidified to pH~2 with 6 N HCl, the obtained solid was filtered, washed with *n*-hexane (2 x 5 mL) and dried *in vacuo* to afford compound **75** (70 mg, 70%) as an off-white solid. **TLC:** 10% MeOH/ CH₂Cl₂ (*R_f*: 0.2); **¹H-NMR (DMSO-*d*₆, 500 MHz):** δ 12.78 (br s, 2H), 7.94 (d, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.13 (s, 1H), 7.05 (s, 1H), 6.67 (d, *J* = 8.5 Hz, 1H), 5.11 (br s, 2H), 3.68 (s, 3H).

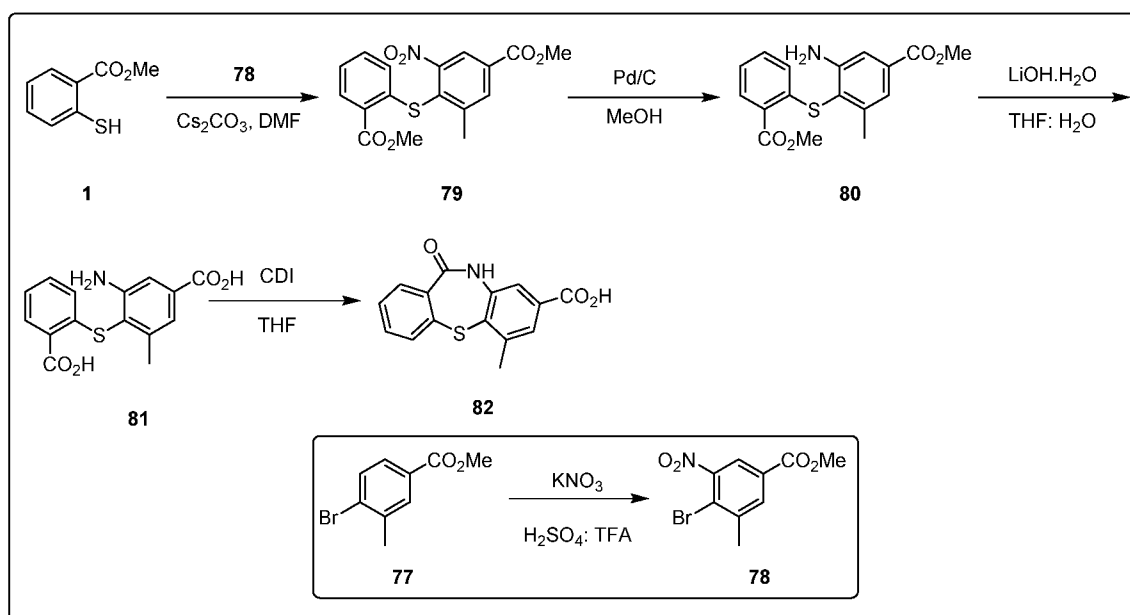
Synthesis of 7-methoxy-11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxylic acid (76**):**



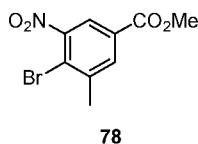
76

[000140] To a stirred solution of compound **75** (70 mg, 0.21 mmol) in THF (2 mL) under inert atmosphere was added CDI (106 mg, 0.65 mmol) at RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*, diluted with ice water (15 mL), acidified with 6 N HCl, the obtained solid was filtered, washed with 20% EtOAc/ hexanes and dried *in vacuo* to afford compound **76** (40 mg, 61%) as an off-white solid. **TLC:** 5% MeOH/ CH₂Cl₂ (*R_f*: 0.3); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 12.88 (br s, 1H), 10.64 (s, 1H), 7.71-7.69 (m, 1H), 7.58-7.42 (m, 4H), 7.28 (s, 1H), 3.81 (s, 3H).

Example 12: Synthesis of 6-methyl-11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxylic acid (82**) - a common intermediate**

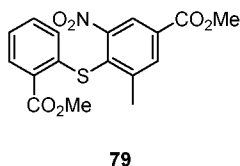


Synthesis of methyl 4-bromo-3-methyl-5-nitrobenzoate (78):



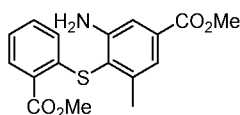
[000141] To a stirred solution of methyl 4-bromo-3-methylbenzoate **77** (500 mg, 2.18 mmol) in sulfuric acid: trifluoro acetic acid (1: 0.1, 6.6 mL) under inert atmosphere was added potassium nitrate (231 mg, 2.29 mmol) at 0 °C; warmed to RT and stirred for 4 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was quenched with ice water (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford crude compound **78** (540 mg, 95%) as yellow oil. **TLC:** 10% EtOAc/ hexanes (*R_f*: 0.4); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 8.25 (s, 1H), 8.17 (s, 1H), 3.89 (s, 3H), 2.53 (s, 3H).

Synthesis of methyl 4-((2-(methoxycarbonyl) phenyl) thio)-3-methyl-5-nitrobenzoate (79):



[000142] To a stirred solution of methyl 2-mercaptobenzoate **1** (575 mg, 2.18 mmol) in DMF (6 mL) under inert atmosphere were added cesium carbonate (1.42 g, 4.37 mmol), compound **78** (385 mg, 2.29 mmol) at RT; heated to 65 °C and stirred for 4 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 25 mL). The combined organic extracts were washed with water (15 mL), brine (15 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to afford the crude. The crude was recrystallized using CH₂Cl₂: *n*-pentane (1: 4, 5 mL) to afford compound **79** (120 mg, 16%) as yellow solid. **TLC**: 20% EtOAc/ hexanes (*R_f*: 0.4); **¹H-NMR (DMSO-*d*₆, 400 MHz)**: δ 8.32 (s, 1H), 8.24 (s, 1H), 7.63-7.59 (m, 1H), 7.49-7.45 (m, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 2.35 (s, 3H).

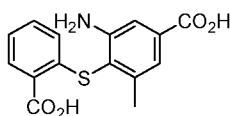
Synthesis of methyl 3-amino-4-((2-(methoxycarbonyl) phenyl) thio)-5-methylbenzoate (80**):**



80

[000143] To a stirred solution of compound **79** (200 mg, 0.55 mmol) in MeOH (5 mL) under inert atmosphere was added Pd/C (70 mg) at RT and stirred under hydrogen atmosphere for 6 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude compound **80** (175 mg, 96%) as yellow solid. **TLC**: 30% EtOAc/ hexanes (*R_f*: 0.7); **¹H-NMR (DMSO-*d*₆, 400 MHz)**: δ 7.96 (d, *J* = 7.6 Hz, 1H), 7.38-7.31 (m, 2H), 7.24-7.20 (m, 1H), 7.14 (s, 1H), 6.56 (d, *J* = 8.0 Hz, 1H), 5.67 (s, 2H), 3.89 (s, 3H), 3.83 (s, 3H), 2.25 (s, 3H).

Synthesis of 3-amino-4-((2-carboxyphenyl) thio)-5-methylbenzoic acid (81**):**

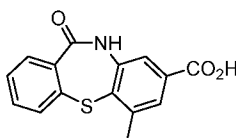


81

[000144] To a stirred solution of compound **80** (160 mg, 0.48 mmol) in THF: H₂O (3: 1.5, 4.5 mL) was added lithium hydroxide (118 mg, 2.90 mmol) at RT and stirred for 24 h; heated to reflux and stirred for 12 h. The reaction was monitored by TLC; after completion of the reaction,

the volatiles were removed *in vacuo*. The residue was diluted with water (15 mL), filtered the precipitated solid and dried *in vacuo* to afford the crude compound **81** (140 mg, 96%) as an off-white solid. **TLC:** 30% EtOAc/ hexanes (R_f : 0.2); **$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz):** δ 13.00 (br s, 2H), 7.95 (d, $J = 8.0$ Hz, 1H), 7.35-7.29 (m, 2H), 7.19 (t, $J = 7.6$ Hz, 1H), 7.13 (s, 1H), 6.54 (d, $J = 8.0$ Hz, 1H), 5.30 (br s, 2H), 2.25 (s, 3H).

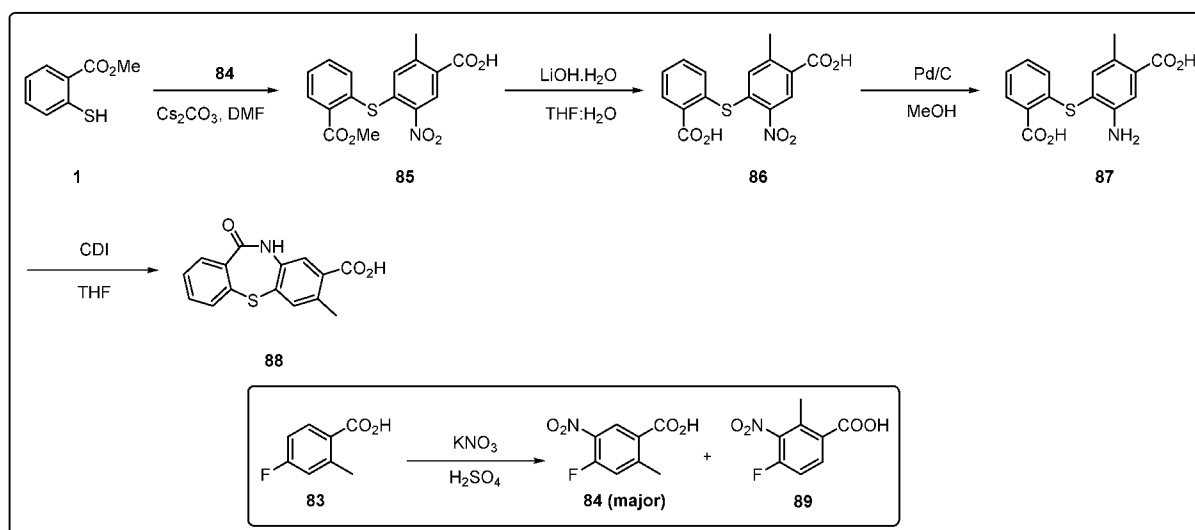
Synthesis of 6-methyl-11-oxo-10, 11-dihydrodibenzo [b, f] [1, 4] thiazepine-8-carboxylic acid (82):



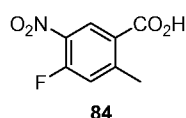
82

[000145] To a stirred solution of compound **81** (140 mg, 0.46 mmol) in THF (5 mL) under inert atmosphere was added CDI (375 mg, 2.31 mmol) at RT and stirred for 24 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* and neutralized with 1 N HCl, filtered the precipitated solid and dried *in vacuo* to afford the crude compound **82** (120 mg, 91%) as an off-white solid. **TLC:** 10% MeOH/ CH_2Cl_2 (R_f : 0.4); **$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz):** δ 13.05 (br s, 1H), 10.73 (s, 1H), 7.69-7.58 (m, 4H), 7.51-7.44 (m, 2H), 2.56 (s, 3H).

Example 13: Synthesis of 7-methyl-11-oxo-10, 11-dihydrodibenzo [b, f] [1, 4] thiazepine-8-carboxylic acid (88) - a common intermediate

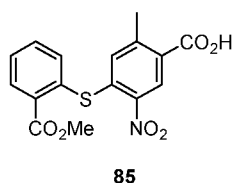


Synthesis of 4-fluoro-2-methyl-5-nitrobenzoic acid (84):



[000146] To a stirred solution of 4-fluoro-2-methylbenzoic acid **83** (500 mg, 3.24 mmol) in concentrated sulfuric acid (2.5 mL) under inert atmosphere was added potassium nitrate (655 mg, 6.49 mmol) at 0 °C; warmed to RT and stirred for 6 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was quenched with ice water (20 mL), filtered the precipitated solid and dried *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 5% MeOH/ CH₂Cl₂ to afford compound **84** (300 mg, 60%) as brown syrup. **TLC:** 10% MeOH/ CH₂Cl₂ (*R_f*: 0.3); **¹H-NMR (DMSO-*d*₆, 500 MHz):** δ 13.56 (br s, 1H), 8.52 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 12.5 Hz, 1H), 2.63 (s, 3H).

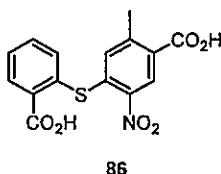
Synthesis of 4-((2-(methoxycarbonyl) phenyl) thio)-2-methyl-5-nitrobenzoic acid (85):



[000147] To a stirred solution of methyl 2-mercaptobenzoate **1** (514 mg, 3.08 mmol) in DMF (10 mL) under inert atmosphere were added cesium carbonate (1.81 g, 5.57 mmol), compound

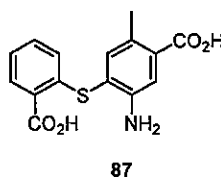
84 (560 mg, 2.78 mmol) at RT; heated to 60 °C and stirred for 4 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed under reduced pressure. The residue was diluted with water (20 mL) and pH was adjusted to ~2 with 1 N HCl, filtered the precipitated solid and dried *in vacuo* to afford compound **85** (500 mg, 52%) as an off-white solid. **TLC:** 5% MeOH/ CH₂Cl₂ (*R_f*: 0.4); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 13.47 (br s, 1H), 8.59 (s, 1H), 7.94 (d, *J* = 7.2 Hz, 1H), 7.68-7.60 (m, 3H), 6.83 (s, 1H), 3.72 (s, 3H), 2.40 (s, 3H).

Synthesis of 4-((2-carboxyphenyl)thio)-2-methyl-5-nitrobenzoic acid (86):



[000148] To a stirred solution of compound **85** (500 mg, 1.45 mmol) in THF: H₂O (2:1, 15 mL) was added lithium hydroxide monohydrate (300 mg, 7.31 mmol) at RT and stirred for 8 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with water (15 mL), and pH was adjusted to ~2 with 1 N HCl, filtered the precipitated solid and dried *in vacuo* to afford crude compound **86** (500 mg) as an off-white solid. **TLC:** 5% MeOH/ CH₂Cl₂ (*R_f*: 0.1); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 13.51 (br s, 2H), 8.57 (s, 1H), 7.92 (d, *J* = 7.2 Hz, 1H), 7.64-7.58 (m, 2H), 7.53 (t, *J* = 8.0 Hz, 1H), 6.89 (s, 1H), 2.41 (s, 3H).

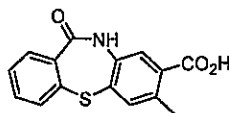
Synthesis of 5-amino-4-((2-carboxyphenyl) thio)-2-methylbenzoic acid (87):



[000149] To a stirred solution of compound **86** (500 mg) in MeOH (15 mL) under inert atmosphere was added Pd/ C (250 mg) at RT and stirred under hydrogen atmosphere for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to afford crude compound **87** (430 mg) as an off-white solid. **TLC:** MeOH/ CH₂Cl₂ (*R_f*: 0.1); **LC-MS:** 84.24%; 304.5 (M⁺+1); (column; X-Select CSH C-18, (50 × 3.0 mm,

3.5 μ m); RT 3.75 min. 0.05% TFA (Aq): ACN; 0.8 mL/min).

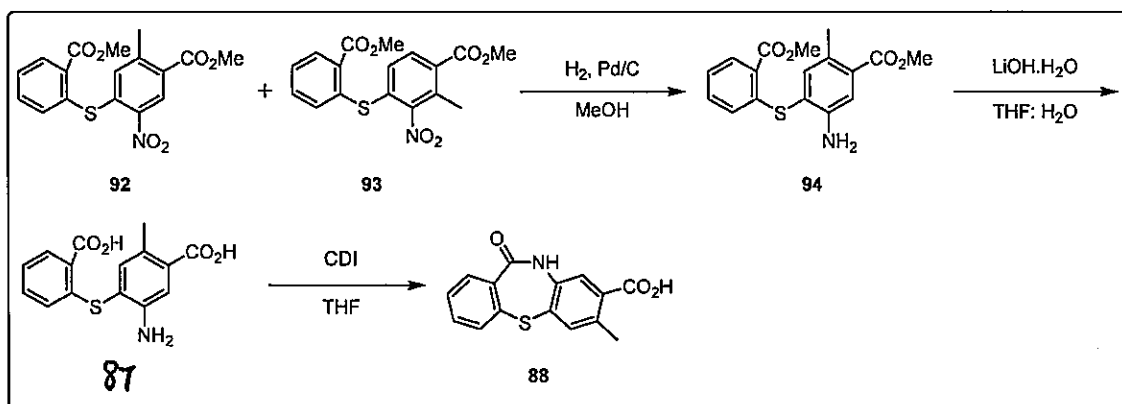
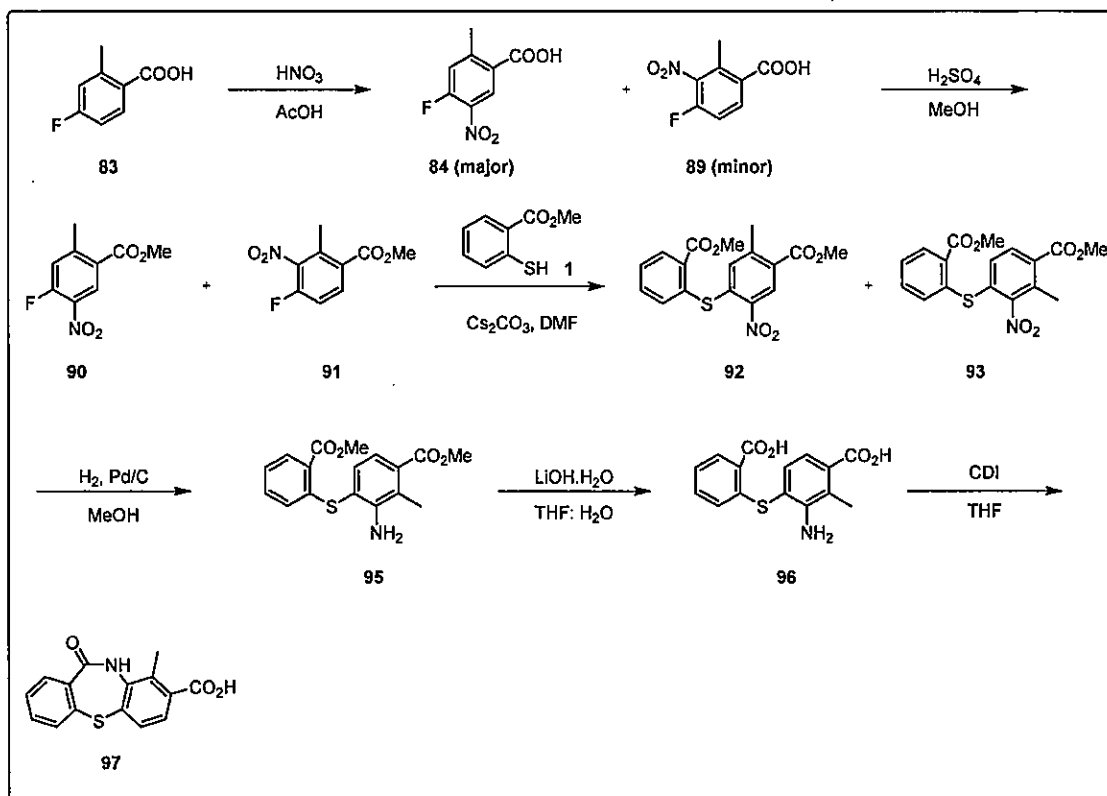
Synthesis of 7-methyl-11-oxo-10, 11-dihydrodibenzo [b, f] [1, 4] thiazepine-8-carboxylic acid (88):



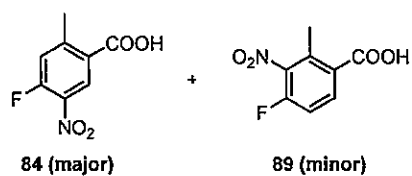
88

[000150] To a stirred solution of compound **87** (430 mg) in THF (20 mL) under inert atmosphere was added CDI (1.15 g, 7.09 mmol) at RT and stirred for 18 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* and neutralized with 1 N HCl, filtered the precipitated solid and dried *in vacuo* to afford the crude compound **88** (290 mg) as an off-white solid. TLC: 10% MeOH/ CH₂Cl₂ (*R_f*: 0.5); ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 13.15 (br s, 1H), 10.68 (s, 1H), 7.69-7.68 (m, 2H), 7.67-7.44 (m, 4H), 2.44 (s, 3H).

Example 14: 9-methyl-11-oxo-10, 11-dihydrodibenzo [b, f] [1, 4] thiazepine-8-carboxylic acid (97) - a common intermediate and Synthesis of 7-methyl-11-oxo-10, 11-dihydrodibenzo [b, f] [1, 4] thiazepine-8-carboxylic acid (88) a common intermediate - Alternate Approach

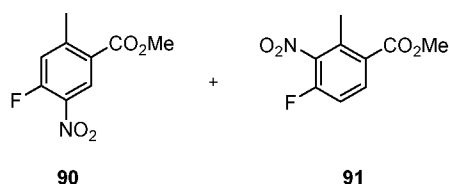


Synthesis of mixture of 4-fluoro-2-methyl-3-nitrobenzoic acid (89) and 4-fluoro-2-methyl-5-nitrobenzoic acid (84):



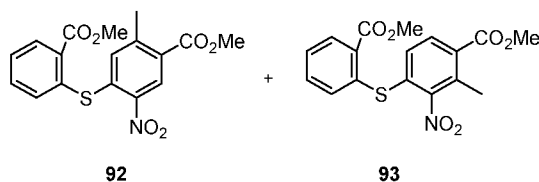
[000151] To a stirred solution of 4-fluoro-2-methylbenzoic acid **83** (10 g, 64.51 mmol) in acetic acid (50 mL) under inert atmosphere was added fuming nitric acid (50 mL) at RT and heated to 80 °C for 6 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with ice cold water (100 mL). The precipitate was filtered and dried *in vacuo* to afford mixture of compounds **84** and **89** (5.3 g, 40%) as white solid. **TLC:** 70% EtOAc/ hexanes (*R_f*: 0.4); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 13.30 (br s, 2H), 8.52 (d, *J* = 8.0 Hz, 2H), 8.10 (dd, *J* = 8.9 5.9, Hz, 1H), 7.60 (d, *J* = 12.5 Hz, 2H), 7.56 (t, *J* = 9.3 Hz, 1H), 2.63 (s, 6H), 2.48 (s, 3H); (¹H NMR showed mixture of compounds **84** and **89** in the ratio of 2: 1).

Synthesis of methyl 4-fluoro-2-methyl-3-nitrobenzoate (91) and methyl 4-fluoro-2-methyl-5-nitrobenzoate (90):



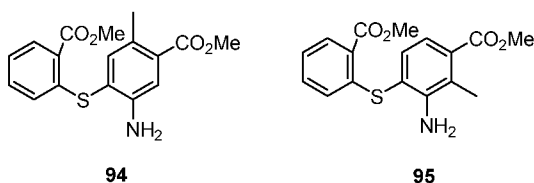
[000152] To a stirred solution of compound **84** and **89** (10 g) in MeOH (100 mL) under argon atmosphere was conc. sulfuric acid (20 mL) at 0 °C and heated to reflux for 48 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford mixture of compounds **90** & **91** (6 g) as colorless thick syrup. **TLC:** 30% EtOAc/ hexane (*R_f*: 0.5); **¹H NMR (DMSO-*d*₆, 500 MHz):** δ 8.51 (d, *J*=7.8 Hz, 1H), 8.09 (dd, *J*= 8.8, 5.6 Hz, 0.5H), 7.63 (d, *J*= 12.4 Hz, 1H), 7.58 (t, *J*= 9.1 Hz, 0.5H), 3.87 (s, 4.5H), 2.62 (s, 3H), 2.45 (s, 1.5H); (¹H NMR showed mixture of compounds **90: 91** in the ratio of 2: 1).

Synthesis of methyl 4-((2-(methoxycarbonyl) phenyl) thio)-2-methyl-3-nitrobenzoate (93) and methyl 4-((2-(methoxycarbonyl) phenyl) thio)-2-methyl-5-nitrobenzoate (92):

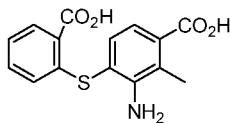


[000153] To a stirred solution of compounds **90** and **91** (11 g) in DMF (100 mL) under inert atmosphere were added methyl 2-mercaptobenzoate **1** (10.4 g, 61.97 mmol), cesium carbonate (18.5 g, 56.81 mmol) at 0 °C; heated to 80 °C and stirred for 4 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with ice cold water (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with water (200 mL), brine (200 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a mixture of compounds **93** and **92** (12 g) as a yellow solid. **TLC**: 20% EtOAc/ hexanes (R_f : 0.2); **LC-MS**: 12.57% + 81.14%; 370.8 ($M^+ + 1$); (column; X-Select CSH C18, (50 × 3.0 mm, 3.5 μm); RT 2.77 min. 0.05% Aq. TFA: ACN; 0.8 mL/min); RT 4.05, 4.14 min.

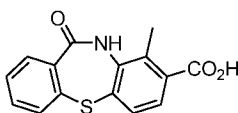
Synthesis of methyl 3-amino-4-((2-(methoxycarbonyl) phenyl) thio)-2-methylbenzoate (95) and Synthesis of methyl 5-amino-4-((2-(methoxycarbonyl) phenyl) thio)-2-methylbenzoate (94):



[000154] To a stirred solution of compound **93** and **92** (14 g, crude) in MeOH (500 mL) under inert atmosphere was added Pd/C (1.4 g, 50% wet) at RT and stirred under hydrogen atmosphere in an autoclave (6 kg/ cm² pressure) for 18 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered through celite, washed with MeOH (100 mL). The filtrate was concentrated *in vacuo* to obtain the crude. The crude was recrystallized with EtOH (20 mL) and further purified through silica gel column chromatography column chromatography using 10% EtOAc/ hexanes to afford compound **95** (3 g, 30%) and **94** (8 g, 63%) as sticky off-white solids. **TLC**: 30% EtOAc/ hexanes (R_f : 0.4); **¹H NMR (DMSO-*d*₆, 400 MHz) (95)**: δ 7.94 (d, J = 7.1 Hz, 1H), 7.40 (t, J = 7.3 Hz, 1H), 7.33-7.26 (m, 2H), 7.22 (dt, J = 7.6, 1.1 Hz, 1H), 6.67 (dd, J = 8.2, 0.8 Hz, 1H), 5.41 (s, 2H), 3.89 (s, 3H), 3.83 (s, 3H), 2.33 (s, 3H). **¹H NMR (DMSO-*d*₆, 400 MHz) (94)**: δ 7.94 (dd, J = 7.8, 1.4 Hz, 1H), 7.42-7.38 (m, 1H), 7.32 (s, 1H), 7.26 (s, 1H), 7.22 (td, J = 7.5, 1.0 Hz, 1H), 6.67 (dd, J = 8.1, 0.8 Hz, 1H), 5.41 (s, 2H), 3.88 (s, 2H), 3.82 (s, 3H), 2.33 (s, 3H).

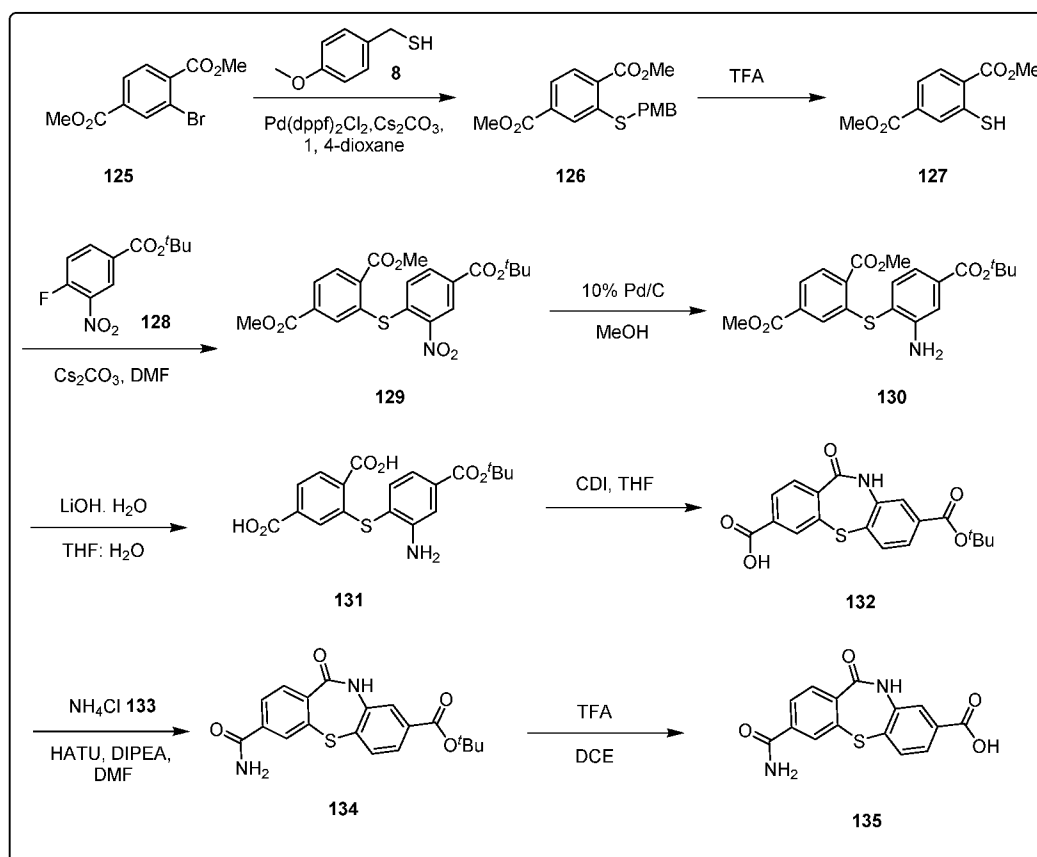
Synthesis of 3-amino-4-((2-carboxyphenyl) thio)-2-methylbenzoic acid (96):**96**

[000155] To a stirred solution of compound **95** (2 g, 6.04 mmol) in THF: H₂O (4: 1, 50 mL) was added lithium hydroxide monohydrate (2.5 g, 10.0 mmol) at 0 °C; warmed to RT and stirred for 48 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with water (10 mL) and washed with diethyl ether (2 x 50 mL). The pH of the aqueous layer was acidified with 4 N HCl to ~1. The precipitated solid was filtered and dried *in vacuo* to afford compound **96** (1.2 g, 66%) as white solid. **TLC:** 20% MeOH/ CH₂Cl₂ (*R_f*: 0.2); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 13.01 (br s, 2H), 7.94 (d, *J* = 7.4 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.20 (dt, *J* = 7.4, 6.3 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.61 (d, *J* = 7.4 Hz, 1H), 5.25 (br s, 2H), 2.27 (s, 3H).

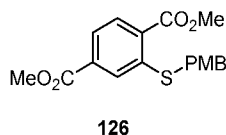
Synthesis of 9-methyl-11-oxo-10, 11-dihydrodibenzo [b, f] [1, 4] thiazepine-8-carboxylic acid (97):**97**

[000156] To a stirred solution of compound **96** (2.6 g, 4.30 mmol) in THF (30 mL) under argon atmosphere was added CDI (3.5 g, 21.50 mmol) at RT; heated to 80 °C and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with water (20 mL) and pH was adjusted with 4 N HCl to ~2. The obtained solid was filtered, washed with diethyl ether and dried *in vacuo* to obtain compound **97** (1.6 g, 67%) as an off white solid. **TLC:** 15% MeOH/ CH₂Cl₂ (*R_f*: 0.2); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 13.20 (br s, 1H), 10.23 (s, 1H), 7.74-7.60 (m, 1H), 7.56-7.51 (m, 2H), 7.50-7.42 (m, 3H), 2.47 (s, 3H).

Example 15: Synthesis of 3-carbamoyl-11-oxo-10, 11-dihydrodibenzo [b, f] [1, 4] thiazepine-8-carboxylic acid (135) - a common intermediate



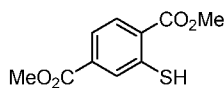
Synthesis of dimethyl 2-((4-methoxybenzyl) thio) terephthalate (126):



[000157] To a stirred solution of dimethyl 2-bromoterephthalate **125** (1 g, 3.66 mmol) in 1, 4-dioxane (50 mL) under inert atmosphere were added (4-methoxyphenyl) methanethiol **8** (620 mg, 4.02 mmol), cesium carbonate (2.38 g, 7.32 mmol), Pd(dppf)₂Cl₂ (67 mg, 0.09 mmol) at RT and stirred under argon for 30 min; heated to 110 °C and stirred for 20 h in a sealed tube. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (50 mL) and extracted with EtOAc (2 x 75 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 10% EtOAc/ hexanes to afford compound **126** (680 mg, 54%) as an off-white solid. **TLC:** 10% EtOAc/ hexanes (*R_f*: 0.3); **¹H-NMR (CDCl₃, 500 MHz):** δ 8.06 (s, 1H), 7.99 (d, *J* = 8.5 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H),

7.34 (d, $J = 8.5$ Hz, 2H), 6.85 (d, $J = 8.5$ Hz, 2H), 4.18 (s, 2H), 3.93 (s, 3H), 3.91 (s, 3H), 3.79 (s, 3H).

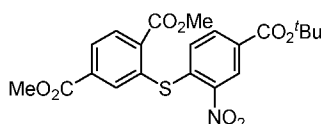
Synthesis of dimethyl 2-mercaptoterephthalate (127):



127

[000158] A stirred solution of compound **126** (1.47 g, 4.24 mmol) in trifluoro acetic acid (25 mL) under inert atmosphere at RT was heated to 80 °C and stirred for 5 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude compound **127** (950 mg) as pale green semi-solid which was carried to the next step without any purification. **TLC:** 15% EtOAc/ hexanes (R_f : 0.7).

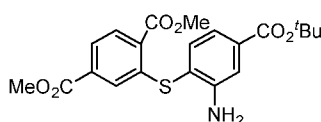
Synthesis of dimethyl 2-((4-(*tert*-butoxycarbonyl)-2-nitrophenyl) thio) terephthalate (129):



129

[000159] To a stirred solution of *tert*-butyl 4-fluoro-3-nitrobenzoate **128** (400 mg, 1.65 mmol) in DMF (20 mL) under inert atmosphere were added compound **127** (525 mg, crude), cesium carbonate (1.07 g, 3.31 mmol) at RT; heated to 60 °C and stirred for 1 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted water (25 mL) and extracted with EtOAc (2 x 40 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 5-7% EtOAc/ hexanes to afford compound **129** (400 mg, 54%) as yellow solid. **TLC:** 10% EtOAc/ hexanes (R_f : 0.4); **$^1\text{H-NMR}$ (CDCl_3 , 400 MHz):** δ 8.76 (s, 1H), 8.25 (s, 1H), 8.20-8.17 (m, 1H), 7.98 (d, $J = 8.4$ Hz, 1H), 7.92 (d, $J = 8.4$ Hz, 1H), 6.91 (d, $J = 8.4$ Hz, 1H), 3.93 (s, 3H), 3.82 (s, 3H), 1.58 (s, 9H).

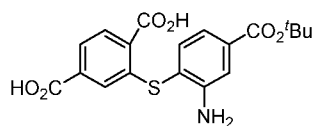
Synthesis of dimethyl 2-((2-amino-4-(*tert*-butoxycarbonyl) phenyl) thio) terephthalate (130):



130

[000160] To a stirred solution of compound **129** (1 g, 2.23 mmol) in MeOH (50 mL) under inert atmosphere was added 10% Pd/C (500 mg) at RT and stirred under hydrogen atmosphere (balloon pressure) for 24 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered through celite and the filtrate was concentrated *in vacuo* to obtain the crude. The crude was triturated with 2% EtOAc/ *n*-pentane (2 x 5 mL) and dried *in vacuo* to afford compound **130** (800 mg, 86%) as an off-white solid. **TLC:** 15% EtOAc/ hexanes (*R_f*: 0.4); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 8.05 (d, *J* = 8.0 Hz, 1H), 7.76-7.73 (m, 1H), 7.43-7.40 (m, 2H), 7.27 (s, 1H), 7.13-7.10 (m, 1H), 5.68 (br s, 2H), 3.91 (s, 3H), 3.75 (s, 3H), 1.55 (s, 9H).

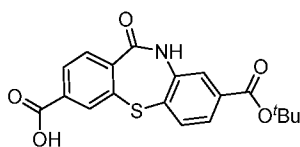
Synthesis of 2-((2-amino-4-(*tert*-butoxycarbonyl) phenyl) thio) terephthalic acid (131):



131

[000161] To a stirred solution of compound **130** (250 mg, 0.59 mmol) in THF: H₂O (4: 1, 10 mL) under inert atmosphere was added lithium hydroxide monohydrate (123 mg, 2.99 mmol) at RT and stirred for 5 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with water (25 mL) and extracted with diethyl ether (2 x 25 mL). The aqueous layer was acidified with 2 N HCl to pH~6. The obtained solid was filtered and dried *in vacuo* to afford compound **131** (180 mg, 77%) as yellow solid. **TLC:** 10% MeOH/ CH₂Cl₂ (*R_f*: 0.2); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 13.16 (br s, 2H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.44-7.40 (m, 2H), 7.16 (s, 1H), 7.13-7.09 (m, 1H), 5.64 (br s, 2H), 1.55 (s, 9H).

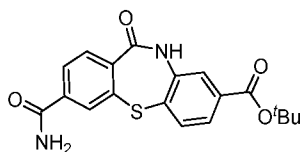
Synthesis of 8-(*tert*-butoxycarbonyl)-11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-3-carboxylic acid (132):



132

[000162] To a stirred solution of compound **131** (180 mg, 0.46 mmol) in THF (9 mL) under inert atmosphere was added CDI (225 mg, 1.39 mmol) at RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with water (15 mL) and acidified with HCl. The obtained solid was filtered and dried *in vacuo* to afford compound **132** (150 mg, 87%) as an off-white solid. **TLC:** 7% MeOH/ CH₂Cl₂ (*R_f*: 0.2); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 13.32 (br s, 1H), 10.93 (s, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.97-7.94 (m, 1H), 7.81-7.77 (m, 2H), 7.71-7.62 (m, 1H), 7.43-7.42 (m, 1H), 1.55-1.51 (m, 9H).

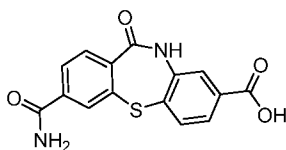
Synthesis of *tert*-butyl 3-carbamoyl-11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxylate (134**):**



134

[000163] To a stirred solution of compound **132** (150 mg, 0.40 mmol) in DMF (9 mL) under inert atmosphere were added HATU (307 mg, 0.80 mmol), ammonium chloride **133** (43 mg, 0.80 mmol), diisopropyl ethyl amine (0.3 mL, 1.60 mmol) at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (20 mL). The obtained solid was filtered, triturated with 10% EtOAc/ hexanes (2 x 5 mL) and dried *in vacuo* to afford compound **134** (95 mg, 63%) as white solid. **TLC:** 7% MeOH/ CH₂Cl₂ (*R_f*: 0.6); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 10.89 (s, 1H), 8.15 (s, 1H), 8.00 (s, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.77-7.76 (m, 2H), 7.74-7.69 (m, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.58 (br s, 1H), 1.52 (s, 9H).

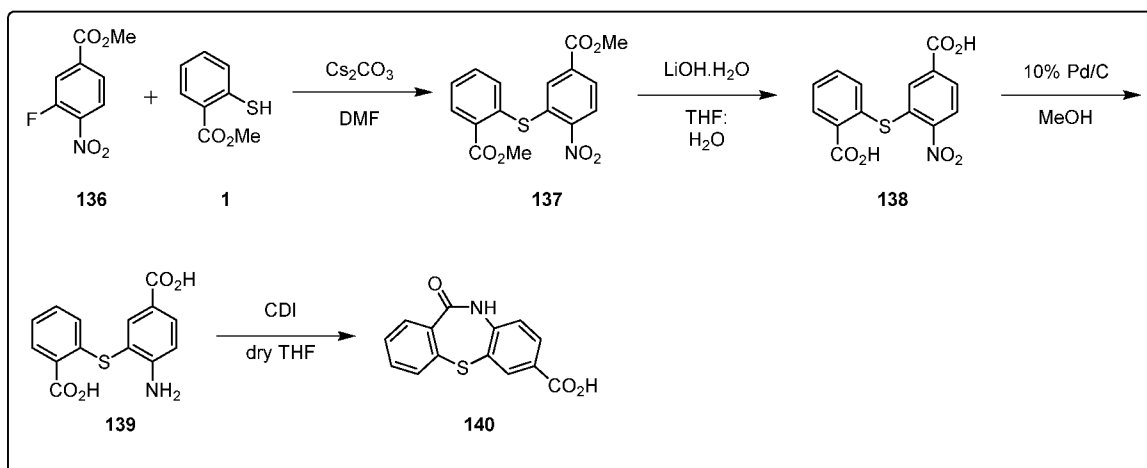
Synthesis of 3-carbamoyl-11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxylic acid (135**):**



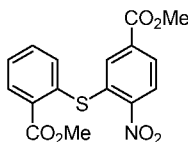
135

[000164] To a stirred solution of compound **134** (95 mg, 0.25 mmol) in EDC (10 mL) under inert atmosphere was added trifluoroacetic acid (293 mg, 2.56 mmol) at RT; heated to 80 °C and stirred for 5 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered. The obtained solid was triturated with 5% CH₂Cl₂ (2 x 5 mL) and dried *in vacuo* to afford compound **135** (70 mg, 87%) as white solid. **TLC:** 10% MeOH/ CH₂Cl₂ (*R_f*: 0.2); **¹H-NMR (DMSO-*d*₆, 500 MHz):** δ 10.93 (s, 1H), 8.16 (s, 1H), 8.01 (s, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.81-7.76 (m, 2H), 7.72-7.68 (m, 2H), 7.59 (s, 1H).

Example 16: 11-oxo-10, 11-dihydrodibenzo [b, f] [1, 4] thiazepine-7-carboxylic acid (140) - a common intermediate



Synthesis of methyl 3-((2-(methoxycarbonyl) phenyl) thio)-4-nitrobenzoate (137):

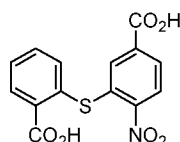


137

[000165] To a stirred solution of methyl 3-fluoro-4-nitrobenzoate **136** (100 mg, 0.50 mmol) in DMF (3 mL) under argon atmosphere was added cesium carbonate (180 mg, 0.55 mmol) at RT

and heated to 40 °C. To this was added methyl 2-mercaptobenzoate **1** (93 mg, 0.55 mmol) in DMF (1 mL) drop wise for 3 min and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude. The crude was diluted with water (30 mL) and extracted with CH₂Cl₂ (2 x 30 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford compound **137** (120 mg, 69%) as yellow crystalline solid. **TLC:** 20% EtOAc/ hexanes (*R_f*: 0.3); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 8.30 (d, *J* = 8.4 Hz, 1H), 7.99-7.93 (m, 2H), 7.65-7.60 (m, 3H), 7.49 (d, *J* = 7.6 Hz, 1H), 3.80 (s, 3H), 3.74 (s, 3H).

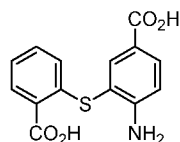
Synthesis of 3-((2-carboxyphenyl) thio)-4-nitrobenzoic acid (138):



138

[000166] To a stirred solution of compound **137** (100 mg, 0.26 mmol) in THF (7 mL) under argon atmosphere was added lithium hydroxide monohydrate (28 mg, 0.66 mmol) in water (3 mL) at RT; heated to reflux and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*, diluted with water (20 mL) and pH was adjusted to ~2 with 1 N HCl. The obtained solid was filtered and dried *in vacuo* to afford compound **138** (72 mg, 85%) as yellow solid. **TLC:** 10% MeOH/ CH₂Cl₂ (*R_f*: 0.2); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 13.49 (br s, 2H), 8.25 (d, *J* = 8.4 Hz, 1H), 7.96-7.91 (m, 2H), 7.66 (s, 1H), 7.60-7.54 (m, 2H), 7.40 (d, *J* = 7.6 Hz, 1H).

Synthesis of 4-amino-3-((2-carboxyphenyl) thio) benzoic acid (139):

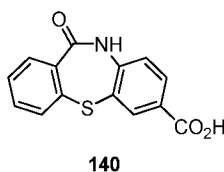


139

[000167] To a stirred solution of compound **138** (70 mg, 0.20 mmol) in MeOH (5 mL) under argon atmosphere was added 10% Pd/C (10 mg) and stirred under hydrogen atmosphere (balloon pressure) for 24 h. The reaction was monitored by TLC; after completion of the reaction, the

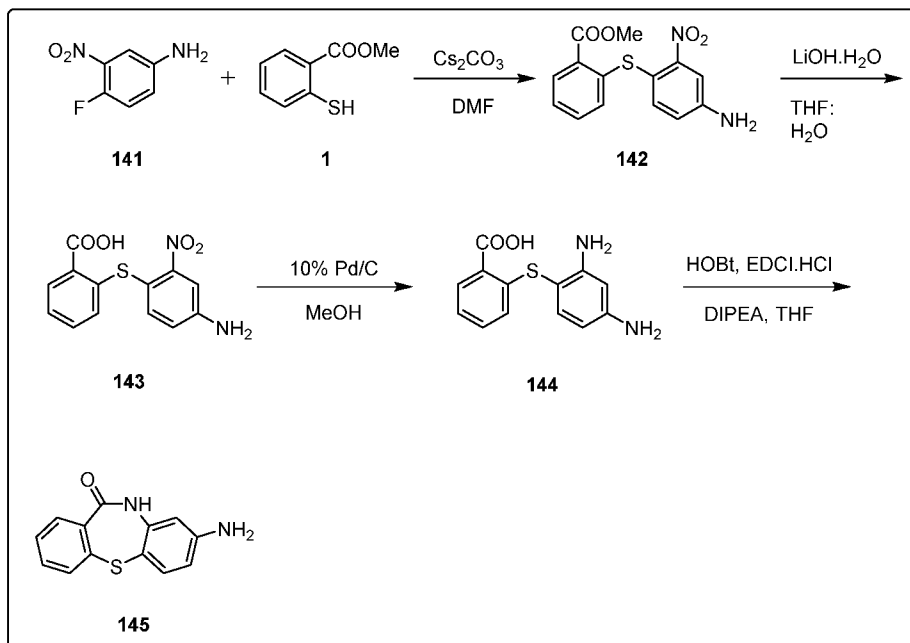
reaction mixture was filtered through celite, washed with MeOH (2 x 5 mL) and the filtrate was concentrated *in vacuo* to afford compound **139** (53 mg, 90%) as an off-white solid. **TLC:** 20% MeOH/ CH₂Cl₂ (*R_f*: 0.3); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 12.91 (br s, 2H), 7.94 (d, *J* = 6.4 Hz, 1H), 7.86 (s, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 8.8 Hz, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 6.14 (br s, 2H).

Synthesis of 11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-7-carboxylic acid (140):

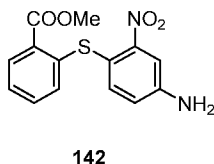


[000168] To a stirred solution of compound **139** (50 mg, 0.17 mmol) in dry THF (3 mL) under argon atmosphere was added CDI (84 mg, 0.51 mmol) at 0 °C; warmed to RT and stirred for 12 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was quenched with 1 N HCl (3 mL), water (10 mL). The obtained solid was filtered, washed with ether (2 x 5 mL) and dried *in vacuo* to afford compound **140** (28 mg, 61%) as white solid. **TLC:** 20% MeOH/ CH₂Cl₂ (*R_f*: 0.5); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 13.10 (br s, 1H), 10.97 (s, 1H), 8.05 (s, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.53-7.44 (m, 2H), 7.31 (d, *J* = 8.4 Hz, 1H).

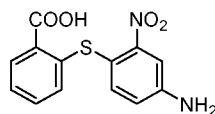
Example 17: Synthesis of 8-aminodibenzo [*b*, *f*] [1, 4] thiazepin-11 (10*H*)-one (145) - a common intermediate



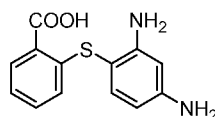
Synthesis of methyl 2-((4-amino-2-nitrophenyl)thio) benzoate (142):



[000169] To a stirred solution of 4-fluoro-3-nitroaniline **141** (500 mg, 3.20 mmol) in DMF (6 mL) under inert atmosphere was added cesium carbonate (1.14 g, 3.50 mmol) at RT and heated to 40 °C. To this was added methyl 2-mercaptobenzoate **1** (592 mg, 3.50 mmol) in DMF (1 mL) drop wise for 3 min and stirred for 3 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (35 mL) and extracted with CH₂Cl₂ (2 x 35 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 15% EtOAc/ hexanes to afford compound **142** (600 mg, 62%) as brown syrup. **TLC:** 30% EtOAc/ hexanes (*R_f*: 0.5); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 7.91 (d, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.30-7.20 (m, 2H), 7.10 (s, 1H), 6.87-6.84 (m, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.24 (s, 2H), 3.84 (s, 3H).

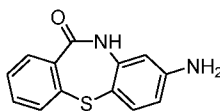
Synthesis of 2-((4-amino-2-nitrophenyl) thio) benzoic acid (143):**143**

[000170] To a stirred solution of compound **142** (600 mg, 1.98 mmol) in THF: H₂O (10: 3, 13 mL) under inert atmosphere was added lithium hydroxide monohydrate (406 mg, 9.90 mmol) at RT; heated to 60 °C and stirred for 5 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). The aqueous layer was acidified with HCl to pH~2. The obtained solid was filtered and dried *in vacuo* to afford compound **143** (350 mg, 61%) as orange solid. **TLC:** 10% MeOH/ CH₂Cl₂ (*R_f*: 0.3); **¹H-NMR (DMSO-*d*₆, 500 MHz):** δ 13.18 (s, 1H), 7.89 (d, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 7.0 Hz, 1H), 7.28 (d, *J* = 9.0 Hz, 1H), 7.19 (t, *J* = 8.0 Hz, 1H), 7.07 (s, 1H), 6.84 (d, *J* = 8.5 Hz, 1H), 6.71 (d, *J* = 8.5 Hz, 1H), 6.23 (s, 2H).

Synthesis of 2-((2, 4-diaminophenyl) thio) benzoic acid (144):**144**

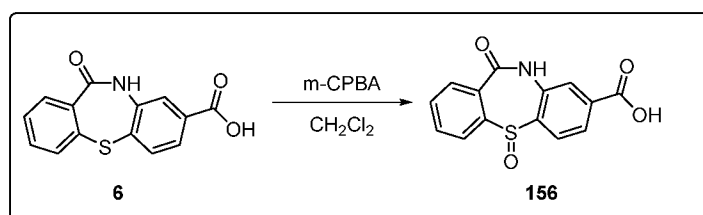
[000171] To a stirred solution of compound **143** (350 mg, 1.20 mmol) in MeOH (10 mL) under inert atmosphere was added 10% Pd/C (100 mg) at RT and stirred under hydrogen atmosphere (balloon pressure) for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered and the filtrate was concentrated *in vacuo* to obtain the crude. The crude was washed with *n*-pentane (2 x 10 mL) and dried *in vacuo* to afford compound **144** (250 mg, 80%) as white solid. **TLC:** 10% MeOH/ CH₂Cl₂ (*R_f*: 0.3); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 12.60 (br s, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 8.4 Hz, 1H), 7.12 (t, *J* = 6.8 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 6.02 (s, 1H), 5.93 (d, *J* = 8.4 Hz, 1H), 5.02-4.98 (m, 4H).

Synthesis of 8-aminodibenzo [*b*, *f*] [1, 4] thiazepin-11 (10*H*)-one (145):

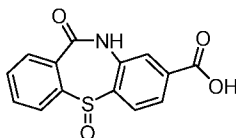
**145**

[000172] To a stirred solution of compound **144** (150 mg, 0.57 mmol) in DMF (4 mL) under inert atmosphere were added HOBt (233 mg, 1.73 mmol), EDCI.HCl (330 mg, 5.19 mmol), diisopropyl ethyl amine (0.5 mL, 2.87 mmol) at 0 °C; warmed to RT and stirred for 6 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with ice cold water (30 mL). The obtained solid was filtered, washed with hexanes (2 x 10 mL) and dried *in vacuo* to afford compound **145** (80 mg, 57%) as an off-white solid. **TLC:** 5% MeOH/ CH₂Cl₂ (*R_f*: 0.5); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 10.40 (s, 1H), 7.63 (d, *J* = 6.8 Hz, 1H), 7.45-7.37 (m, 3H), 7.12 (d, *J* = 8.4 Hz, 1H), 6.39 (s, 1H), 6.31 (d, *J* = 8.4 Hz, 1H), 5.46 (s, 2H).

Example 18: Synthesis of 11-oxo-10, 11-dihydrodibenzo [b, f] [1, 4] thiazepine-8-carboxylic acid 5-oxide (156) - a common intermediate



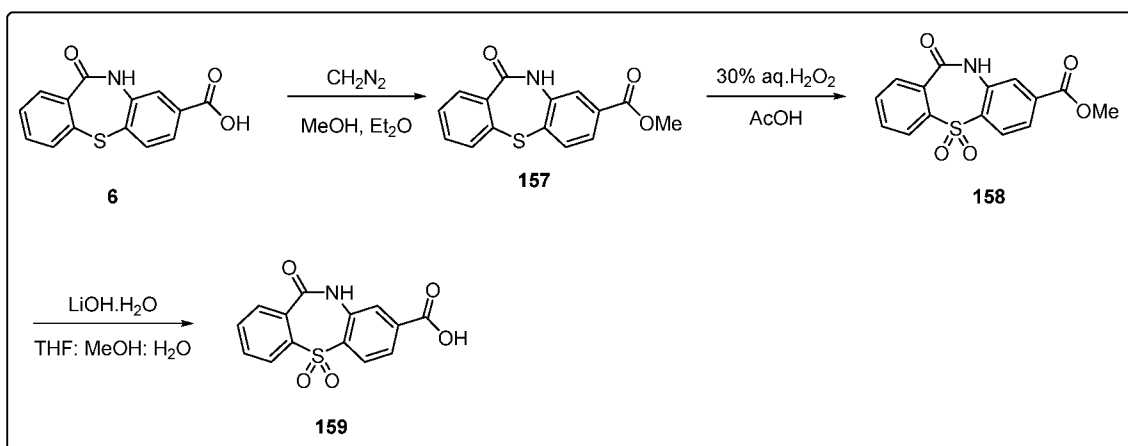
Synthesis of 11-oxo-10, 11-dihydrodibenzo [b, f] [1, 4] thiazepine-8-carboxylic acid 5-oxide (156):

**156**

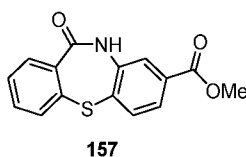
[000173] To a stirred solution of **6** (2.5 g, 9.21 mmol) in CH₂Cl₂ (50 mL) under inert atmosphere was added *m*-chloro perbenzoic acid (1.59 g, 9.21 mmol) at RT and stirred for 48 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was

the volatiles were removed *in vacuo* to obtain the crude. The crude was triturated with 10% MeOH/ CH₂Cl₂ (2 x 5 mL), isopropanol (10 mL) to afford compound **156** (2.3 g, 87%) as white solid. **TLC**: 10% MeOH/ CH₂Cl₂ + 0.05 mL CH₃COOH (*R_f*: 0.4); **¹H NMR (DMSO-*d*₆, 500 MHz)**: δ 13.36 (br s, 1H), 11.08 (s, 1H), 7.96 (d, *J* = 7.8 Hz, 1H), 7.92-7.87 (m, 1H), 7.85-7.66 (m, 3H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H);

Example 19: Synthesis of 11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxylic acid 5, 5-dioxide (159) - a common intermediate

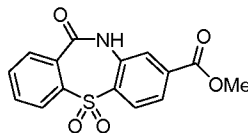


Synthesis of methyl 11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxylate (157):



[000174] To a stirred solution of **6** (500 mg, 1.84 mmol) in MeOH: CH₂Cl₂ (1: 1, 20 mL) under argon atmosphere was added CH₂N₂ (prepared *in situ* using *N*-nitrosomethyl urea (0.95 g, 9.2 mmol) + KOH (0.51 g, 9.22 mmol) at 0 °C; warmed to RT and stirred for 1 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 20% EtOAc/ hexanes to afford compound **157** (450 mg, 86%) as white solid. **TLC**: 30% EtOAc/ hexanes (*R_f*: 0.5); **¹H-NMR (DMSO-*d*₆, 500 MHz)**: δ 10.82 (s, 1H), 7.82 (s, 1H), 7.75-7.69 (m, 3H), 7.58-7.63 (m, 3H), 3.82 (s, 3H).

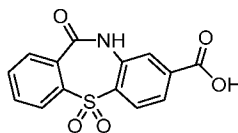
Synthesis of methyl 11-oxo-10, 11-dihydrodibenzo [b, f] [1, 4] thiazepine-8-carboxylate 5, 5-dioxide (158):



158

[000175] To a stirred solution of **157** (5 g, 17.54 mmol) in acetic acid (25 mL) was added 30% aqueous hydrogen peroxide (100 mL) at 0 °C; warmed to 50 °C and stirred for 72 h. The reaction was monitored by TLC; after completion of the reaction, the obtained solid was filtered, washed with water (100 mL), 10% EtOAc/ hexanes (100 mL) and dried *in vacuo* to afford compound **158** (3.5 g, 64%) as white solid. **TLC:** 5% MeOH/ CH₂Cl₂ (*R_f*: 0.3); **¹H NMR (DMSO-*d*₆, 500 MHz):** δ 11.58 (s, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 8.01-7.95 (m, 3H), 7.93-7.83 (m, 3H), 3.88 (s, 3H).

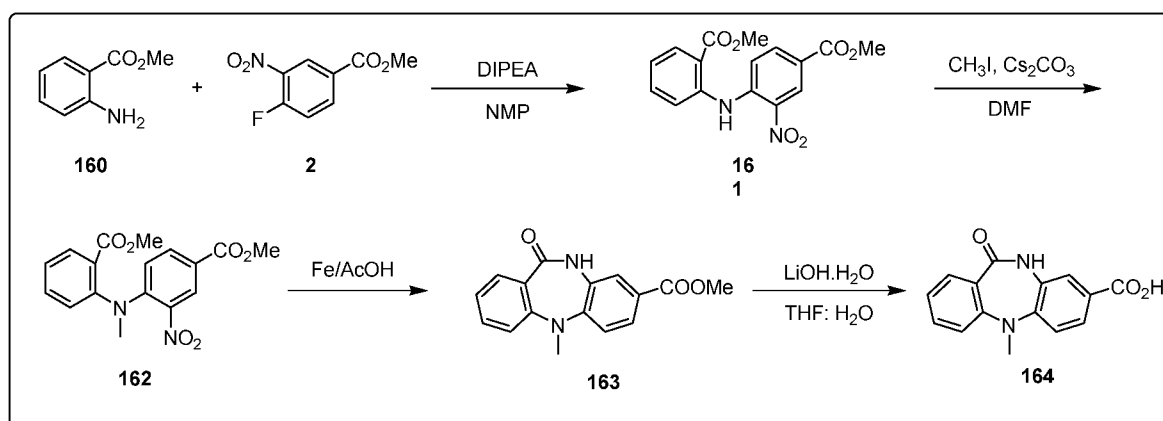
Synthesis of 11-oxo-10, 11-dihydrodibenzo [b, f] [1, 4] thiazepine-8-carboxylic acid 5, 5-dioxide (159):



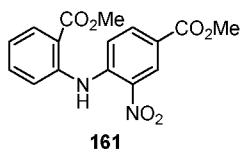
159

[000176] To a stirred solution of compound **158** (3.5 g, 11.04 mmol) in a mixture of THF: MeOH: H₂O (2: 2: 1, 25 mL) was added lithium hydroxide monohydrate (1.3 g, 33.12 mmol) portion wise for 10 min at 0 °C; warmed to RT and stirred for 3 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with water (20 mL) and acidified with 1 N HCl to pH~2. The obtained solid was filtered, washed with isopropyl alcohol (15 mL) and dried *in vacuo* to obtain compound **159** (2.8 g, 84%) as white solid. **TLC:** 5% MeOH/ CH₂Cl₂ (*R_f*: 0.1); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 13.65 (br s, 1H), 11.55 (s, 1H), 8.07 (d, *J* = 8.3 Hz, 1H), 8.03-7.82 (m, 6H).

Example 20: Synthesis of 5-methyl-11-oxo-10, 11-dihydro-5H-dibenzo [b, e] [1, 4] diazepine-8-carboxylic acid (164) - a common intermediate

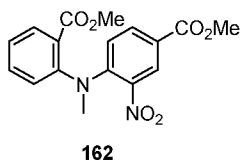


Synthesis of methyl 4-((2-(methoxycarbonyl) phenyl) amino)-3-nitrobenzoate (161):



[000177] To a stirred solution of methyl 2-aminobenzoate **160** (5 g, 33.07 mmol) in NMP (13 mL) under inert atmosphere were added diisopropylethylamine (18 mL, 103.46 mmol), methyl 4-fluoro-3-nitrobenzoate **2** (9.87 g, 49.61 mmol) at RT; heated to 120 °C in a sealed tube and stirred for 24 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with diethyl ether (50 mL) and stirred for 1 h. The obtained solid was filtered, washed with diethyl ether (10 mL) and dried *in vacuo* to afford compound **161** (3.2 g, 29%) as yellow solid. **TLC:** 20% EtOAc/ hexanes (*R_f*: 0.4); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 11.13 (s, 1H), 8.67 (s, 1H), 8.11-7.94 (m, 2H), 7.70-7.62 (m, 2H), 7.58 (d, *J* = 9.0 Hz, 1H), 7.32-7.27 (m, 1H), 3.87 (s, 6H).

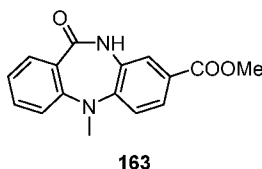
Synthesis of methyl 4-((2-(methoxycarbonyl) phenyl) (methyl) amino)-3-nitrobenzoate (162):



[000178] To a stirred solution of compound **161** (3 g, 9.09 mmol) in DMF (30 mL) under inert atmosphere were added cesium carbonate (5.9 g, 18.15 mmol), methyl iodide (0.84 mL, 13.59

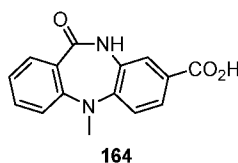
mmol) at RT and stirred for 6 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with ice-cold water (60 mL) and extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 20% EtOAc/ hexanes to afford compound **162** (2.73 g, 88%) as yellow solid. **TLC:** 30% EtOAc/ hexanes (R_f : 0.4); **^1H NMR (DMSO- d_6 , 400 MHz):** δ 8.07 (s, 1H), 8.06 (d, $J = 7.8$ Hz, 1H), 7.71 (dd, $J = 7.8, 1.5$ Hz, 1H), 7.62 (t, $J = 7.3$ Hz, 1H), 7.40-7.26 (m, 3H), 3.84 (s, 3H), 3.53 (s, 3H), 3.38 (s, 3H).

Synthesis of methyl 5-methyl-11-oxo-10, 11-dihydro-5H-dibenzo [b, e] [1, 4] diazepine-8-carboxylate (163):



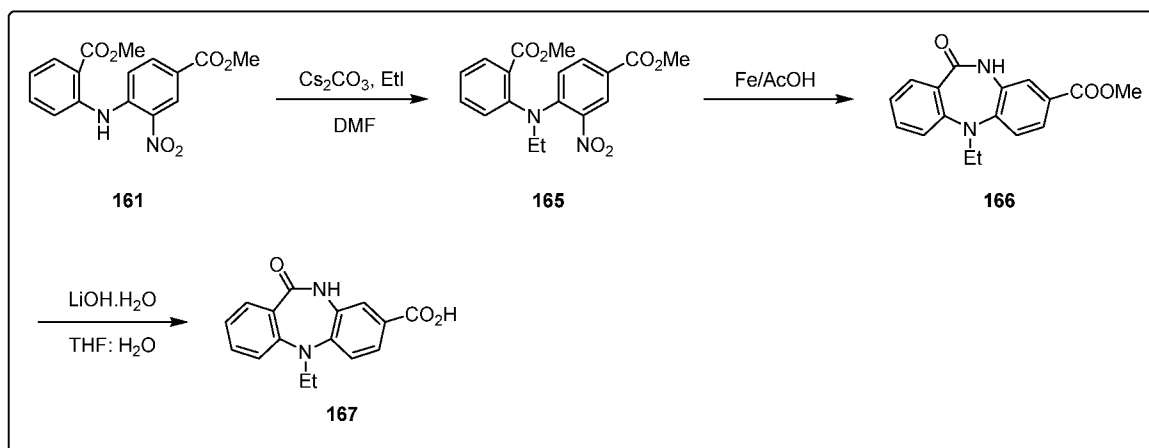
[000179] To a stirred solution of compound **162** (2.73 g, 7.93 mmol) in acetic acid (36 mL) under inert atmosphere was added iron powder (7 g, 127.2 mmol) at RT; heated to 80 °C and stirred for 4 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with CH_2Cl_2 (50 mL), stirred for 2 h and filtered through celite and the filtrate was concentrated *in vacuo* to obtain the crude. The crude was dissolved in CH_2Cl_2 (200 mL), washed with saturated aqueous NaHCO_3 solution (100 mL), brine (100 mL). The organic extract was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford compound **163** (2 g, 91%) as an off-white solid. **TLC:** 30% EtOAc/ hexanes (R_f : 0.4); **^1H NMR (DMSO- d_6 , 500 MHz):** δ 10.33 (s, 1H), 7.68 (dd, $J = 8.5, 1.9$ Hz, 1H), 7.65-7.61 (m, 2H), 7.50 (t, $J = 7.8$ Hz, 1H), 7.28 (d, $J = 8.4$ Hz, 1H), 7.21 (d, $J = 8.1$ Hz, 1H), 7.10 (t, $J = 7.4$ Hz, 1H), 3.80 (s, 3H), 3.33 (s, 3H).

Synthesis of 5-methyl-11-oxo-10, 11-dihydro-5H-dibenzo [b, e] [1, 4] diazepine-8-carboxylic acid (164):

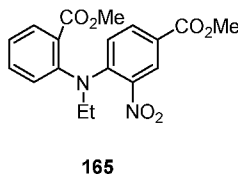


[000180] To a stirred solution of compound **163** (2 g, 7.09 mmol) in THF: H₂O (1: 1, 80 mL) was added lithium hydroxide monohydrate (900 mg, 21.42 mmol) at RT and stirred for 12 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The pH of the residue was adjusted to ~2 with 2 N HCl. The precipitated solid was filtered and dried *in vacuo* to afford compound **164** (1.7 g, 89%) as an off-white solid. **TLC:** 40% EtOAc/ hexanes (*R_f*: 0.2); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 12.82 (br s, 1H), 10.33 (s, 1H), 7.70-7.60 (m, 3H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 8.5 Hz, 1H), 7.21 (d, *J* = 7.8 Hz, 1H), 7.11 (t, *J* = 7.2 Hz, 1H), 3.32 (s, 3H).

Example 21: Synthesis of 5-ethyl-11-oxo-10, 11-dihydro-5H-dibenzo [b, e] [1, 4] diazepine-8-carboxylic acid (167) - a common intermediate



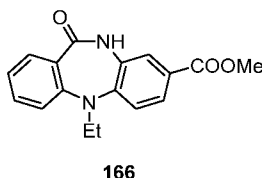
Synthesis of methyl 4-(ethyl (2-(methoxycarbonyl) phenyl) amino)-3-nitrobenzoate (165):



[000181] To a stirred solution of compound **161** (2.9 g, 8.78 mmol) in DMF (40 mL) under inert atmosphere were added cesium carbonate (6 g, 18.46 mmol), ethyl iodide (1.06 mL, 12.82

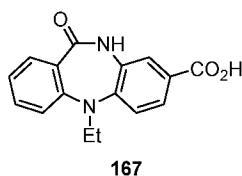
mmol) at RT and stirred for 5 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with ice-cold water (60 mL), extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude which was titrated with *n*-pentane (20 mL) to afford compound **165** (2.8 g, 89%) as pale yellow solid. **TLC:** 30% EtOAc/ hexanes (R_f : 0.5); **^1H NMR (DMSO- d_6 , 500 MHz):** δ 8.05 (dd, J = 9.0, 2.0 Hz, 1H), 8.02 (s, 1H), 7.62-7.57 (m, 2H), 7.45 (d, J = 9.0 Hz, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.28 (t, J = 7.5 Hz, 1H), 3.94 (q, J = 7.1 Hz, 2H), 3.82 (s, 3H), 3.44 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H).

Synthesis of methyl 5-ethyl-11-oxo-10, 11-dihydro-5H-dibenzo [b, e] [1, 4] diazepine-8-carboxylate (166):



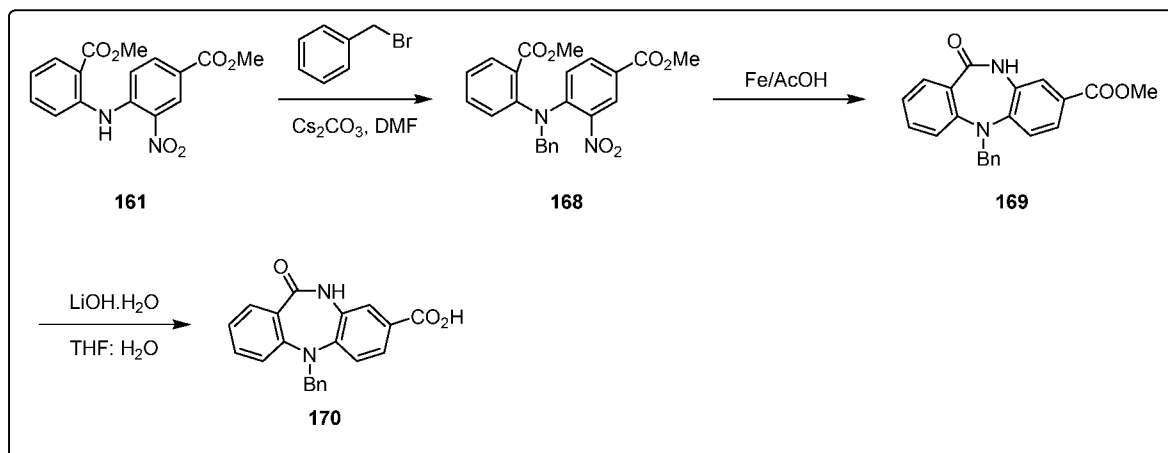
[000182] To a stirred solution of compound **165** (2.8 g, 7.82 mmol) in acetic acid (40 mL) under inert atmosphere was added iron powder (6.8 g, 125.1 mmol) at RT; heated to 80 °C and stirred for 4 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with CH_2Cl_2 (50 mL), stirred for 2 h and filtered through celite. The filtrate was concentrated *in vacuo* to obtain the crude. The crude was diluted with CH_2Cl_2 (200 mL), washed with saturated aqueous sodium bicarbonate solution (100 mL) and brine (100 mL). The organic extract was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford compound **166** (2.2 g, 96%) as an off-white solid. **TLC:** 30% EtOAc/ hexanes (R_f : 0.3); **^1H NMR (DMSO- d_6 , 500 MHz):** δ 10.35 (br s, 1H), 7.70 (dd, J = 8.5, 1.9 Hz, 1H), 7.67 (s, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.51 (t, J = 8.1 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.22 (d, J = 8.1 Hz, 1H), 7.12 (t, J = 7.4 Hz, 1H), 3.31 (s, 5H), 1.11 (t, J = 6.9 Hz, 3H).

Synthesis of 5-ethyl-11-oxo-10, 11-dihydro-5H-dibenzo [b, e] [1, 4] diazepine-8-carboxylic acid (167):

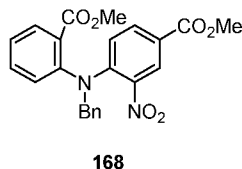


[000183] To a stirred solution of compound **166** (2.1 g, 7.09 mmol) in THF: H₂O (1: 1, 60 mL) was added lithium hydroxide monohydrate (890 mg, 21.26 mmol) at RT and stirred for 12 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The pH of the residue was acidified to ~2 with 2 N HCl. The precipitated solid was filtered, washed with water (50 mL) and dried *in vacuo* to afford compound **167** (1.6 g, 80%) as an off-white solid. **TLC:** 30% EtOAc/ hexanes (*R_f*: 0.2); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 12.82 (br s, 1H), 10.33 (s, 1H), 7.69-7.59 (m, 3H), 7.53-7.48 (m, 1H), 7.24 (dd, *J* = 19.7, 8.2 Hz, 2H), 7.12 (t, *J* = 7.5 Hz, 1H), 3.79 (br s, 2H), 1.12 (t, *J* = 7.0 Hz, 3H).

Example 22: Synthesis of 5-benzyl-11-oxo-10, 11-dihydro-5H-dibenzo [b, e] [1, 4] diazepine-8-carboxylic acid (170) - a common intermediate



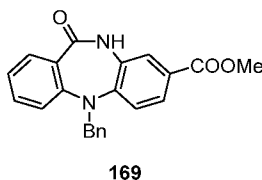
Synthesis of methyl 4-(benzyl (2-(methoxycarbonyl) phenyl) amino)-3-nitrobenzoate (168):



[000184] To a stirred solution of compound **161** (2.5 g, 7.57 mmol) in DMF (40 mL) under inert atmosphere were added cesium carbonate (4.92 g, 15.15 mmol), benzyl bromide (1.34 mL,

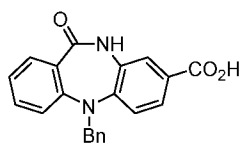
11.36 mmol) at RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with ice-cold water (60 mL) and extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 10% EtOAc/ hexanes to afford compound **168** (3 g, 91%) as colorless thick syrup. **TLC:** 20% EtOAc/ hexanes (R_f : 0.4); **^1H NMR (DMSO- d_6 , 500 MHz):** δ 8.04 (s, 1H), 7.97 (dd, J = 8.8, 1.9 Hz, 1H), 7.61-7.57 (m, 1H), 7.56- 7.50 (m, 3H), 7.40 (t, J = 8.2 Hz, 2H), 7.34 (t, J = 7.7 Hz, 2H), 7.28-7.23 (m, 2H), 5.20 (s, 2H), 3.81 (s, 3H), 3.39 (s, 3H).

Synthesis of methyl 5-benzyl-11-oxo-10, 11-dihydro-5H-dibenzo [b, e] [1, 4] diazepine-8-carboxylate (169):



[000185] To a stirred solution of compound **168** (950 mg, 2.26 mmol) in acetic acid (10 mL) under inert atmosphere was added iron powder (2 g, 36.36 mmol) at RT; heated to 80 °C and stirred for 4 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with CH_2Cl_2 (50 mL), filtered through celite and the filtrate was concentrated *in vacuo* to obtain the crude. The crude was dissolved in CH_2Cl_2 (200 mL), washed with saturated aqueous sodium bicarbonate solution (100 mL) and brine (100 mL). The organic extract was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford compound **169** (800 mg, 98%) as an off-white solid. **TLC:** 20% EtOAc/ hexanes (R_f : 0.4); **^1H NMR (DMSO- d_6 , 500 MHz):** δ 10.42 (s, 1H), 7.66 (s, 1H), 7.62 (d, J = 8.1 Hz, 2H), 7.48- 7.34 (m, 4H), 7.33-7.21 (m, 3H), 7.15 (t, J = 7.2 Hz, 1H), 7.09 (t, J = 7.4 Hz, 1H), 5.04 (br s, 2H), 3.79 (s, 3H).

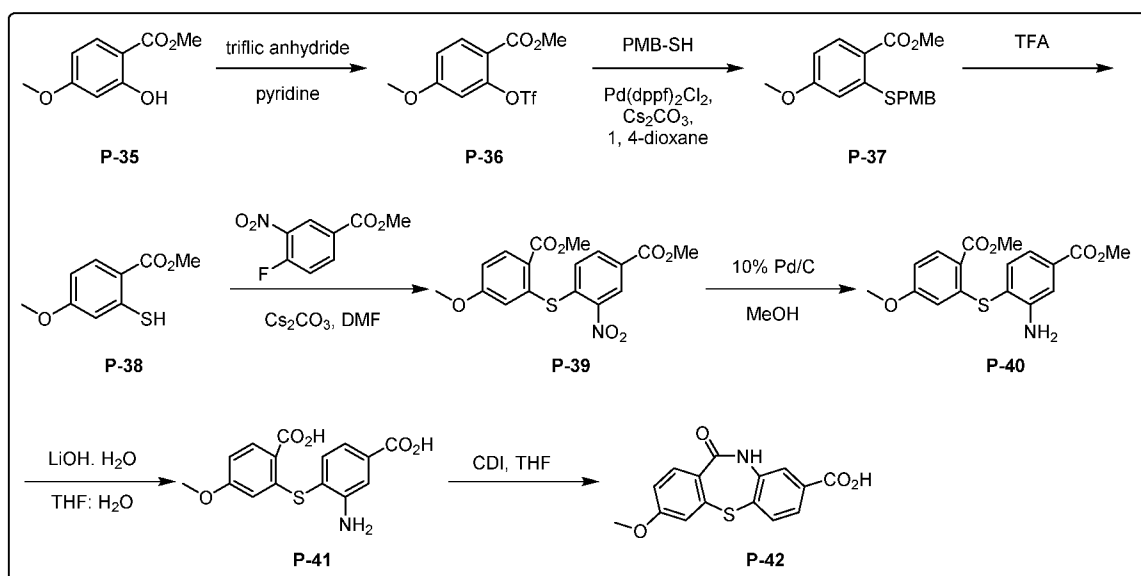
Synthesis of 5-benzyl-11-oxo-10, 11-dihydro-5H-dibenzo [b, e] [1, 4] diazepine-8-carboxylic acid (170):



170

[000186] To a stirred solution of compound **169** (2 g, 5.58 mmol) in THF: H₂O (1: 1, 80 mL) was added lithium hydroxide monohydrate (703 mg, 16.73 mmol) at RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The pH of the residue was acidified with 6 N HCl to pH ~2 and stirred for 1 h. The precipitated solid was filtered and dried *in vacuo* to afford compound **170** (1.5 g, 78%) as an off-white solid. **TLC**: 50% EtOAc/ hexanes (*R_f*: 0.2); **¹H NMR (DMSO-*d*₆, 500 MHz)**: δ 12.87 (br s, 1H), 10.39 (s, 1H), 7.65-7.55 (m, 3H), 7.47- 7.21 (m, 7H), 7.16-7.04 (m, 2H), 5.02 (br s, 2H).

Example 23: Synthesis of 3-methoxy-11-oxo-10, 11-dihydrodibenzo [b, f] [1, 4] thiazepine-8-carboxylic acid (P-42)



[000187] **Synthesis of methyl 4-methoxy-2-(((trifluoromethyl) sulfonyl) oxy) benzoate (P-36):** To a stirred solution of methyl 2-hydroxy-4-methoxybenzoate **P-35** (1 g, 5.49 mmol) in pyridine (5 mL) under argon atmosphere was added triflic anhydride (1 mL, 6.31 mmol) drop wise at 0 °C; warmed to RT and stirred for 2 h; heated to 40 °C and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with water (25 mL) and extracted with diethyl ether (2 x 30 mL). The

combined organic extracts were washed with 1 N HCl (15 mL), water (15 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 10% EtOAc/ hexanes to afford compound **P-36** (1.58 g, 92%) as colorless syrup. **TLC:** 10% EtOAc/ hexanes (R_f : 0.6); **$^1\text{H-NMR}$ (CDCl_3 , 500 MHz):** δ 8.06 (d, J = 9.0 Hz, 1H), 6.95 (d, J = 8.5 Hz, 1H), 6.78 (s, 1H), 3.93 (s, 3H), 3.88 (s, 3H).

[000188] Synthesis of methyl-4-methoxy-2-((4-methoxybenzyl) thio) benzoate (P-37): To a stirred solution of compound **P-36** (1 g, 3.18 mmol) in 1, 4-dioxane (15 mL) under argon atmosphere were added (4-methoxyphenyl) methanethiol (539 mg, 3.50 mmol), cesium carbonate (2 g, 6.36 mmol) at RT and degassed under argon for 20 min. To this was added $\text{Pd(dppf)}_2\text{Cl}_2$ (233 mg, 0.31 mmol); heated to 80 °C and stirred for 8 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 35 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 5-7% EtOAc/ hexanes to afford compound **P-37** (340 mg, 30%) as an off-white solid. **TLC:** 10% EtOAc/ hexanes (R_f : 0.4); **$^1\text{H-NMR}$ (CDCl_3 , 500 MHz):** δ 7.96 (d, J = 8.5 Hz, 1H), 7.38-7.37 (m, 1H), 7.35 (d, J = 9.0 Hz, 1H), 6.85 (d, J = 8.0 Hz, 2H), 6.82 (s, 1H), 6.64 (d, J = 8.5 Hz, 1H), 4.10 (s, 2H), 3.86 (s, 3H), 3.79 (s, 6H).

[000189] Synthesis of methyl 2-mercapto-4-methoxybenzoate (P-38): A stirred solution of compound **P-37** (330 mg, 1.03 mmol) in trifluoroacetic acid (5 mL) under argon atmosphere was heated to reflux and stirred for 6 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude compound **P-38** (340 mg) as brown syrup which was carried to the next step without any further purification. **TLC:** 10% EtOAc/ hexanes (R_f : 0.7).

[000190] Synthesis of methyl 4-methoxy-2-((4-(methoxycarbonyl)-2-nitrophenyl) thio) benzoate (P-39): To a stirred solution of compound **P-38** (200 mg, 1.01 mmol) in DMF (5 mL) under argon atmosphere were added methyl 4-fluoro-3-nitrobenzoate (201 mg, 1.01 mmol), cesium carbonate (656 mg, 2.02 mmol) at RT; heated to 40 °C and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*.

The residue was diluted with water (20 mL) and extracted with EtOAc (2 x 25 mL). The combined organic extracts were washed with water (20 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 15% EtOAc/ hexanes to afford compound **P-39** (280 mg, 74%) as yellow solid. **TLC:** 20% EtOAc/ hexanes (R_f : 0.4); **$^1\text{H-NMR}$ (CDCl_3 , 400 MHz):** δ 8.84 (d, J = 7.2 Hz, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.96-7.92 (m, 1H), 7.78 (s, 1H), 7.17-7.12 (m, 1H), 7.08-6.93 (m, 1H), 3.96-3.93 (m, 3H), 3.85 (s, 3H), 3.80-3.74 (m, 3H).

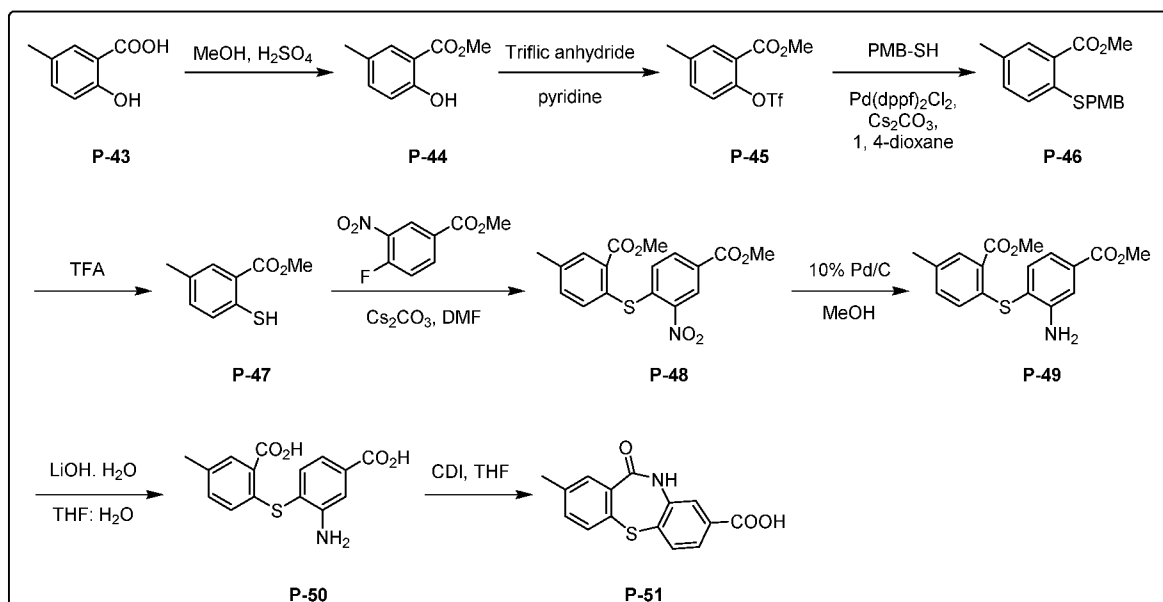
[000191] Synthesis of methyl 2-((2-amino-4-(methoxycarbonyl) phenyl) thio)-4-methoxybenzoate (P-40): To a stirred solution of compound **P-39** (270 mg, 0.71 mmol) in MeOH (10 mL) under argon atmosphere was added 10% Pd/C (80 mg) at RT and stirred under hydrogen atmosphere (balloon pressure) for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered through celite, washed with CH_2Cl_2 (2 x 25 mL) and the filtrate was concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 15% EtOAc/ hexanes to afford compound **P-40** (180 mg, 79%) as colorless syrup. **TLC:** 20% EtOAc/ hexanes (R_f : 0.5); **$^1\text{H-NMR}$ (CDCl_3 , 400 MHz):** δ 8.03 (d, J = 8.8 Hz, 1H), 7.54-7.40 (m, 1H), 7.08 (d, J = 8.8 Hz, 1H), 6.79-6.72 (m, 1H), 6.66-6.63 (m, 1H), 6.21-6.14 (m, 1H), 3.95-3.88 (m, 5H), 3.85 (s, 3H), 3.65 (s, 3H).

[000192] Synthesis of 2-((2-amino-4-carboxyphenyl) thio)-4-methoxybenzoic acid (P-41): To a stirred solution of compound **P-40** (160 mg, 0.46 mmol) in THF: H_2O (2: 1, 6 mL) under argon atmosphere was added lithium hydroxide monohydrate (96 mg, 2.30 mmol) at RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*, diluted with water (20 mL), acidified with 1 N HCl to pH~6. The obtained precipitate was filtered and dried *in vacuo* to afford compound **P-41** (85 mg, crude) as an off-white solid. **TLC:** 50% EtOAc/ hexanes (R_f : 0.2); **$^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz):** δ 12.84 (br s, 2H), 7.95 (d, J = 8.8 Hz, 1H), 7.44 (s, 1H), 7.40 (d, J = 8.0 Hz, 1H), 6.13 (s, 1H), 5.58 (br s, 2H), 3.80-3.69 (m, 2H), 3.60 (s, 3H).

[000193] Synthesis of 3-methoxy-11-oxo-10, 11-dihydrodibenzo [*b, f*] [1, 4] thiazepine-8-carboxylic acid (P-42): To a stirred solution of compound **41** (80 mg, 0.25 mmol) in THF (8

mL) under argon atmosphere was added CDI (203 mg, 1.25 mmol) at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*, diluted with water (20 mL), acidified with dilute HCl. The obtained precipitate was filtered and dried *in vacuo* to afford compound **P-42** (50 mg, crude) as an off-white solid. **TLC:** 5% MeOH/ CH₂Cl₂ (*R_f*: 0.3); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 13.18 (br s, 1H), 10.64 (s, 1H), 7.77 (s, 1H), 7.66 (s, 2H), 7.16-7.07 (m, 1H), 7.01 (d, *J* = 8.8 Hz, 1H), 6.82-6.79 (m, 1H), 3.80 (s, 3H).

Example 24: Synthesis of 2-methyl-11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxylic acid (P-51)



[000194] Synthesis of methyl 2-hydroxy-5-methylbenzoate (P-44): To a stirred solution of 2-hydroxy-5-methylbenzoic acid **P-43** (2 g, 13.15 mmol) in MeOH (65 mL) under argon atmosphere was added sulphuric acid (0.65 mL) at RT; heated to reflux and stirred for 20 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with ice water (50 mL) and extracted with ether (3 x 40 mL). The combined organic extracts were washed with 10% aqueous NaHCO₃ solution (until the pH becomes neutral), dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain compound **P-44** (2 g, 92%) as colorless liquid. **TLC:** 10% EtOAc/ hexanes (*R_f*: 0.7); **¹H-NMR (CDCl₃, 500 MHz):** δ 10.57 (s, 1H), 7.65 (s, 1H), 7.29 (d, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 8.0 Hz,

1H), 3.96 (s, 3H), 2.30 (s, 3H).

[000195] Synthesis of methyl 5-methyl-2-(((trifluoromethyl) sulfonyl) oxy) benzoate (P-45): To a stirred solution of compound **P-44** (2 g, 12.04 mmol) in pyridine (8 mL) under argon atmosphere was added trifluoro methane sulfonic anhydride (2.3 mL, 13.85 mmol) at 0 °C; warmed to RT and stirred for 2 h; heated to 40 °C and stirred for 8 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with water (50 mL) and extracted with ether (3 x 50 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL), 1 N HCl (40 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 3-5% EtOAc/ hexanes to afford compound **P-45** (2.6 g, 72%) as colorless liquid. **TLC:** 7% EtOAc/ hexanes (*R_f*: 0.6); **¹H-NMR (CDCl₃, 500 MHz):** δ 7.88 (s, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 3.96 (s, 3H), 2.42 (s, 3H).

[000196] Synthesis of methyl 2-((4-methoxybenzyl) thio)-5-methylbenzoate (P-46): To a stirred solution of compound **P-45** (1 g, 3.35 mmol) in 1, 4-dioxane (15 mL) under argon atmosphere were added (4-methoxyphenyl) methanethiol (568 mg, 3.69 mmol), cesium carbonate (2.18 g, 6.71 mmol) at RT and degassed for 20 min. To this was added Pd(dppf)₂Cl₂ (61.4 mg, 0.083 mmol); heated to 110 °C and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (30 mL) and extracted with EtOAc (2 x 40 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 3-5% EtOAc/ hexanes to afford compound **P-46** (290 mg, 29%) as yellow solid. **TLC:** 10% EtOAc/ hexanes (*R_f*: 0.5); **¹H-NMR (CDCl₃, 400 MHz):** δ 7.75 (s, 1H), 7.30 (d, *J* = 8.8 Hz, 2H), 7.22-7.21 (m, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 4.09 (s, 2H), 3.89 (s, 3H), 3.79 (s, 3H), 2.32 (s, 3H).

[000197] Synthesis of methyl 2-mercapto-5-methylbenzoate (P-47): A stirred solution of compound **P-46** (200 mg, 0.66 mmol) in trifluoro acetic acid (10 mL) at RT under argon atmosphere was heated to 70-75 °C and stirred for 4 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to afford compound **P-47** (100 mg, crude) as yellow syrup. **TLC:** 10% EtOAc/ hexanes (*R_f*: 0.7); **¹H-NMR (DMSO-*d*₆, 500**

MHz): δ 7.74 (s, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.26 (d, J = 7.5 Hz, 1H), 5.20 (s, 1H), 3.82 (s, 3H), 2.28 (s, 3H).

[000198] Synthesis of methyl 2-((4-(methoxycarbonyl)-2-nitrophenyl) thio)-5-

methylbenzoate (P-48): To a stirred solution of compound **P-47** (100 mg, 0.50 mmol) in DMF (5 mL) under argon atmosphere were added methyl 4-fluoro-3-nitrobenzoate (100 mg, 0.55 mmol), cesium carbonate (326 mg, 1.00 mmol) at RT; heated to 60 °C and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with water (30 mL) and extracted with CH₂Cl₂ (2 x 30 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 10% EtOAc/ hexanes to afford compound **P-48** (100 mg, 55%) as yellow solid. **TLC:** 10% EtOAc/ hexanes (R_f : 0.3); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 8.63 (s, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.78 (s, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.55-7.53 (m, 1H), 6.99 (d, J = 8.4 Hz, 1H), 3.87 (s, 3H), 3.68 (s, 3H), 2.43 (s, 3H).

[000199] Synthesis of methyl 2-((2-amino-4-(methoxycarbonyl) phenyl) thio)-5-

methylbenzoate (P-49): To a stirred solution of compound **P-48** (400 mg, 1.10 mmol) in MeOH (20 mL) under argon atmosphere was added 10% Pd/ C (200 mg) at RT and stirred under hydrogen atmosphere (balloon pressure) for 24 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered through celite and washed with 50% MeOH/ CH₂Cl₂ (2 x 25 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 7-10% EtOAc/ hexanes to afford compound **P-49** (220 mg, 60%) as pale yellow solid. **TLC:** 20% EtOAc/ hexanes (R_f : 0.5); **¹H-NMR (DMSO-*d*₆, 500 MHz):** δ 7.77 (s, 1H), 7.44 (s, 1H), 7.40 (d, J = 7.5 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.16-7.14 (m, 1H), 6.57 (d, J = 8.5 Hz, 1H), 5.63 (br s, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 2.27 (s, 3H).

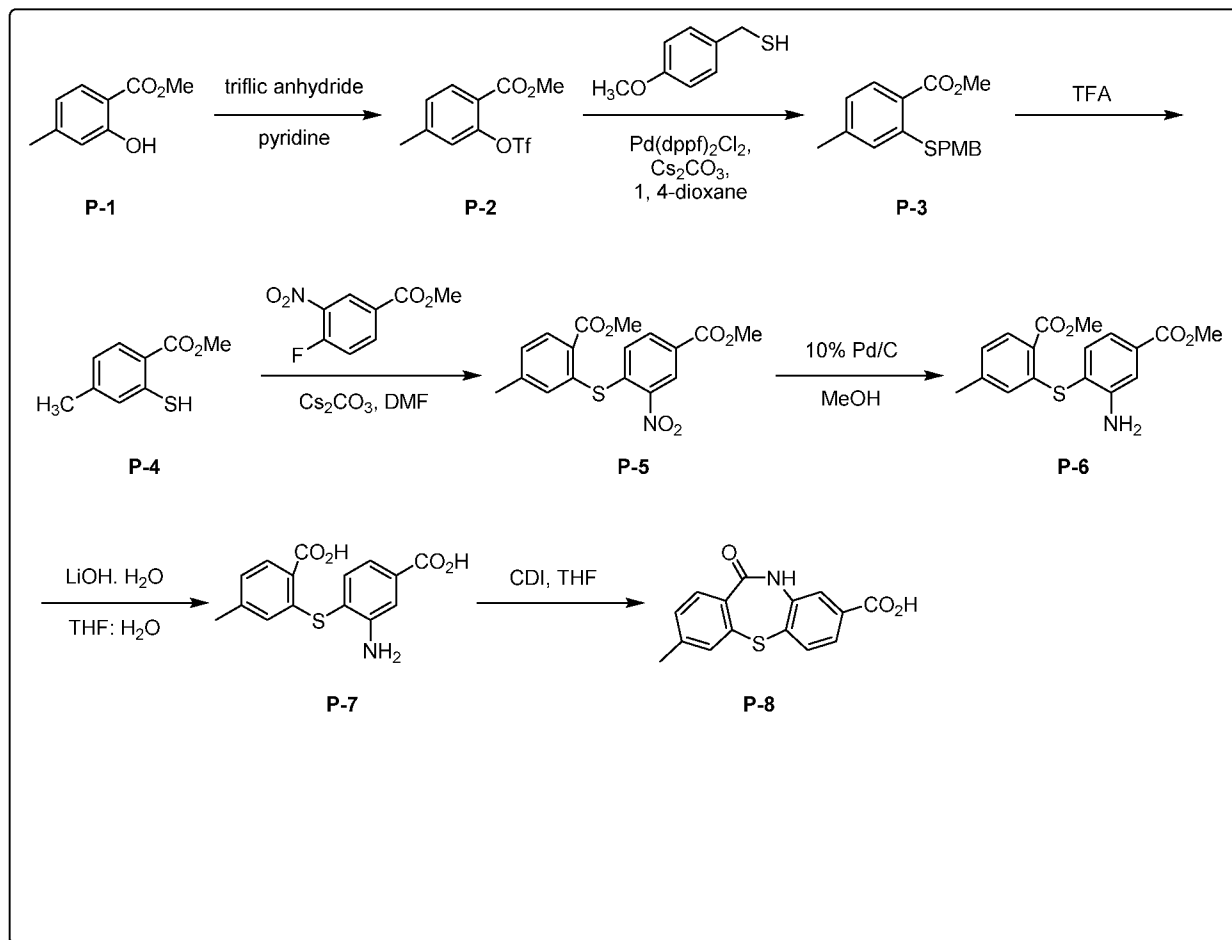
[000200] Synthesis of 2-((2-amino-4-carboxyphenyl) thio)-5-methylbenzoic acid (P-50): To

a stirred solution of compound **P-49** (220 mg, 0.66 mmol) in THF: H₂O (5: 1, 6 mL) under argon atmosphere was added lithium hydroxide monohydrate (139 mg, 3.32 mmol) at RT and stirred for 20 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were

removed *in vacuo*. The residue was diluted with water (15 mL) and acidified with 6 N HCl to pH~4. The precipitated solid was filtered and dried *in vacuo* to afford compound **P-50** (110 mg, 55%) as an off-white solid. **TLC:** 20% EtOAc/ hexanes (R_f : 0.2); **$^1\text{H-NMR}$ (DMSO- d_6 , 500 MHz):** δ 12.96 (br s, 2H), 7.76 (s, 1H), 7.42 (s, 1H), 7.37 (d, $J = 8.0$ Hz, 1H), 7.18 (d, $J = 8.0$ Hz, 1H), 7.15-7.13 (m, 1H), 6.54 (d, $J = 8.0$ Hz, 1H), 5.54 (br s, 2H), 2.26 (s, 3H).

[000201] Synthesis of 2-methyl-11-oxo-10, 11-dihydrodibenzo [b, f] [1, 4] thiazepine-8-carboxylic acid (P-51): To a stirred solution of compound **P-50** (110 mg, 0.36 mmol) in THF (10 mL) under argon atmosphere was added CDI (176 mg, 1.08 mmol) at RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with ice cold water (20 mL) and acidified with 6 N HCl to pH~4. The precipitated solid was filtered and dried *in vacuo* to afford compound **P-51** (60 mg, 58%) as white solid. **TLC:** 10% MeOH/ CH_2Cl_2 (R_f : 0.6); **$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz):** δ 13.21 (br s, 1H), 10.76 (s, 1H), 7.76 (s, 1H), 7.65 (s, 2H), 7.50 (s, 1H), 7.41 (d, $J = 8.0$ Hz, 1H), 7.30 (d, $J = 8.0$ Hz, 1H), 2.29 (s, 3H).

Example 25: Synthesis of 3-methyl-11-oxo-10, 11-dihydrodibenzo [b, f] [1, 4] thiazepine-8-carboxylic acid (P-8)



[000202] Synthesis of methyl 4-methyl-2-(((trifluoromethyl) sulfonyl) oxy) benzoate (P-2):

To a stirred solution of methyl 2-hydroxy-4-methylbenzoate **P-1** (950 mg, 5.70 mmol) in pyridine (9.5 mL) under argon atmosphere was added triflic anhydride (1.05 mL, 6.20 mmol) drop wise at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was acidified with 6 N HCl and extracted with diethyl ether (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 2% EtOAc/ hexanes to afford compound **P-2** (1.2 g, 71%) as colorless liquid. **TLC:** 10% EtOAc/ hexanes (R_f : 0.7); **$^1\text{H-NMR}$ (CDCl_3 , 400 MHz):** δ 7.98 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.09 (s, 1H), 3.94 (s, 3H), 2.45 (s, 3H).

[000203] Synthesis of methyl 2-((4-methoxybenzyl) thio)-4-methylbenzoate (P-3): To a stirred solution of compound **2** (600 mg, 2.01 mmol) in 1, 4-dioxane (12 mL) under argon atmosphere were added (4-methoxyphenyl) methanethiol (341 mg, 2.21 mmol), cesium carbonate (1.3 g, 4.02 mmol) at RT and degassed under argon for 20 min. To this was added Pd(dppf)₂Cl₂ (36.8 mg, 0.05 mmol); heated to 100 °C and stirred for 48 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (25 mL) and extracted with EtOAc (2 x 35 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 3% EtOAc/ hexanes to afford compound **3** (200 mg, 33%) as sticky solid. **TLC:** 10% EtOAc/ hexanes (*R_f*: 0.4); **¹H-NMR (CDCl₃, 500 MHz):** δ 7.85 (d, *J* = 8.5 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.14 (s, 1H), 6.94 (d, *J* = 8.5 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 2H), 4.10 (s, 2H), 3.86 (s, 3H), 3.78 (s, 3H), 2.34 (s, 3H).

[000204] Synthesis of methyl 2-mercapto-4-methylbenzoate (P-4): A stirred solution of compound **P-3** (200 mg, 0.65 mmol) in trifluoro acetic acid (4 mL) under argon atmosphere at RT was heated to 80 °C and stirred for 4 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude compound **P-4** (115 mg) which was carried to the next step without any further purification. **TLC:** 10% EtOAc/ hexanes (*R_f*: 0.8).

[000205] Synthesis of methyl 2-((4-(methoxycarbonyl)-2-nitrophenyl) thio)-4-methylbenzoate (P-5): To a stirred solution of methyl 4-fluoro-3-nitrobenzoate (120 mg, 0.60 mmol) in DMF (4 mL) under argon atmosphere were added compound **P-4** (115 mg, crude), cesium carbonate (392 mg, 1.20 mmol) at RT; heated to 60 °C and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 35 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 10% EtOAc/ hexanes to afford compound **P-5** (120 mg, 55%) as yellow solid. **TLC:** 15% EtOAc/ hexanes (*R_f*: 0.7); **¹H-NMR (CDCl₃, 400 MHz):** δ 8.85 (s, 1H), 7.95-7.89 (m, 2H), 7.46 (s, 1H), 7.38 (d, *J* = 8.8 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 3.93 (s, 3H), 3.76 (s, 3H), 2.42 (s, 3H).

[000206] Synthesis of methyl 2-((2-amino-4-(methoxycarbonyl) phenyl) thio)-4-

methylbenzoate (P-6): To a stirred solution of compound **P-5** (120 mg, 0.33 mmol) in MeOH (10 mL) under argon atmosphere was added 10% Pd/C (60 mg) at RT and stirred under hydrogen atmosphere (balloon pressure) for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered through celite, washed with *n*-pentane (2 x 5 mL) and dried *in vacuo* to afford compound **P-6** (90 mg, 82%) as yellow sticky solid. **TLC:** 15% EtOAc/ hexanes (*R_f*: 0.5); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 7.86 (d, *J* = 8.0 Hz, 1H), 7.45 (s, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.44 (s, 1H), 5.65 (br s, 2H), 3.85-3.84 (m, 6H), 2.13 (s, 3H).

[000207] Synthesis of 2-((2-amino-4-carboxyphenyl) thio)-4-methylbenzoic acid (P-7):

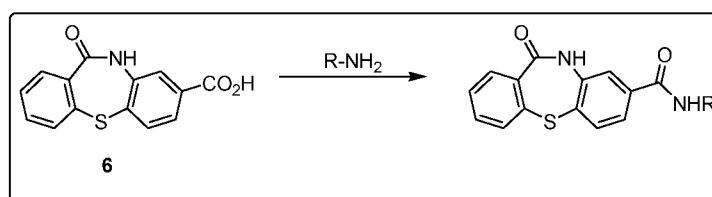
To a stirred solution of compound **P-6** (90 mg, 0.27 mmol) in THF: H₂O (2: 1, 3 mL) under argon atmosphere was added lithium hydroxide monohydrate (56 mg, 1.35 mmol) at RT and stirred for 5 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (15 mL) and extracted with EtOAc (2 x 20 mL). The aqueous layer was acidified with 2 N HCl, the obtained solid was filtered, washed with *n*-hexane (2 x 5 mL) and dried *in vacuo* to afford compound **P-7** (60 mg, 73%) as an off-white solid. **TLC:** 10% MeOH/ CH₂Cl₂ (*R_f*: 0.2); **¹H-NMR (DMSO-*d*₆, 500 MHz):** δ 12.95 (br s, 2H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.44 (s, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.15 (d, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.42 (s, 1H), 5.57 (br s, 2H), 2.13 (s, 3H).

[000208] Synthesis of 3-methyl-11-oxo-10, 11-dihydrodibenzo [*b*,*f*] [1, 4] thiazepine-8-

carboxylic acid (P-8): To a stirred solution of compound **P-7** (60 mg, 0.19 mmol) in THF (4 mL) under argon atmosphere was added CDI (96 mg, 0.59 mmol) at RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*, diluted with water (20 mL), acidified with dil. HCl to pH~ 3. The obtained precipitate was filtered and dried *in vacuo* to afford compound **P-8** (45 mg, 80%) as an off-white solid. **TLC:** 10% MeOH/ CH₂Cl₂ (*R_f*: 0.3); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 13.12 (br s, 1H), 10.72 (s, 1H), 7.76 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.37 (s, 1H), 7.26 (s, 1H), 2.30 (s, 3H).

Example 26: Preparation of Compounds

[000209] Acids similar to compound **6** (compounds **14**, **21**, **28**, **35**, **42**, **50**, **55**, **62**, **70**, **76**, **82**, **88**, **97**, **135**, **140**, **145**, **150**, **155**, **156**, **159**, **164**, **167**, **170**, **P-8**, **P-42**, **P-51**) were synthesized as mentioned above and converted to final products either using commercially available amines or by using prepared amines employing Procedures A, B, C, D, E, F, G, H and the results are captured in Table 1.

**Procedure A:**

[000210] To a stirred solution of **6** (50 mg, 0.18 mmol) in DMF (3 mL) under argon atmosphere were added EDCI.HCl (50 mg, 0.22 mmol), HOBT (35 mg, 0.22 mmol), 2-(5-methyl-1,3,4-thiadiazol-2-yl)ethan-1-amine hydrochloride **187** (50 mg, 0.22 mmol) and diisopropyl ethyl amine (0.1 mL, 0.55 mmol) at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (20 mL) and stirred for 1 h. The crude was extracted with EtOAc or the precipitated material was either directly dried *in vacuo* or triturated or purified through silica gel column chromatography to afford the desired compound.

Procedure B:

[000211] To a stirred solution of **6** (40 mg, 0.14 mmol) in DMF (4 mL) under argon atmosphere were added pyridin-3-amine **182** (15 mg, 0.16 mmol), HATU (84 mg, 0.22 mmol), diisopropyl ethyl amine (0.05 mL, 0.29 mmol) at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with ice cold water (15 mL), the obtained precipitate was filtered, or extracted with EtOAc (2 x 30 mL). The combined organic extracts were dried over sodium sulfate, filtered, concentrated *in vacuo* to obtain the crude. The crude was extracted with EtOAc or the precipitated material was directly dried *in vacuo*, triturated or purified through silica gel column

chromatography to afford the desired compound.

Procedure C:

[000212] To a stirred solution of compound **35** (50 mg, 0.17 mmol) in CH₂Cl₂ (5 mL) were added oxalyl chloride (0.03 mL, 0.34 mmol) or (0.06 mL, 0.69 mmol), DMF (0.01 mL) under argon atmosphere at 0 °C; warmed to 10 °C and stirred for 2-3 h. After completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude. The crude was carried to the next step without further purification.

[000213] To a stirred solution of crude acid chloride (70 mg, crude) in CH₂Cl₂ (5 mL) under argon atmosphere were added 2-chloro-4-fluoroaniline **184** (25 mg, 0.17 mmol) and pyridine (0.07 mL, 0.86 mmol) at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (20 mL) and extracted with CH₂Cl₂ (2 x 30 mL). The combined organic extracts were washed with 1 N HCl (20 mL), 10% NaHCO₃ solution (30 mL), brine (15 mL) dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain crude. The precipitated material was either directly dried *in vacuo* or triturated or purified through silica gel column chromatography /preparative HPLC or by acid-base treatment to afford the desired compound.

Procedure D:

[000214] To a stirred solution of **6** (40 mg, 0.14 mmol) in DMF (3 mL) under argon atmosphere was added CDI (71.7 mg, 0.17 mmol) at 0 °C; warmed to RT and stirred for 2 h. To this were added (4-(trifluoromethoxy) phenyl) methanamine **172** (33.8 mg, 0.17 mmol), and diisopropyl ethyl amine (0.05 mL, 0.29 mmol) and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mass was diluted with water (15 mL) and stirred for 1 h. The precipitate was filtered or extracted with EtOAc or CH₂Cl₂ and the obtained solid was dried *in vacuo* or purified by column chromatography or triturated to afford the desired product.

Procedure E:

[000215] A stirred solution of **6** (40 mg, 0.14 mmol) in thionyl chloride (1 mL) under argon atmosphere was heated to 90 °C and stirred for 1 h. The reaction was monitored by TLC; after

completion of the reaction, the volatiles were removed *in vacuo* to obtain acid chloride (50 mg, crude) which was carried to the next step without further purification. To a stirred solution of 2-amino pyridine **181** (15 mg, 0.16 mmol) in CH₂Cl₂ (5 mL) under argon atmosphere were added pyridine (0.035 mL), acid chloride (50 mg, crude) at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude which was purified through silica gel column chromatography using 2% MeOH/ CH₂Cl₂ to afford the desired product.

Procedure F:

[000216] To a stirred solution of compound **35** (50 mg, 0.17 mmol) in CH₂Cl₂ (5 mL) under argon atmosphere were added ethyl 2-amino-2-(pyridin-2-yl) acetate hydrochloride **249** (26 mg, 0.17 mmol), propylphosphonic anhydride (~50% solution in EtOAc, 0.22 mL, 0.34 mmol), NMM (0.037 mL, 0.34 mmol) at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* and diluted with water (20 mL) or the pH of the reaction mixture was adjusted to ~8 and extracted with CH₂Cl₂ (2 x 30 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified either through silica gel column chromatography or triturated to afford the desired product.

Procedure G:

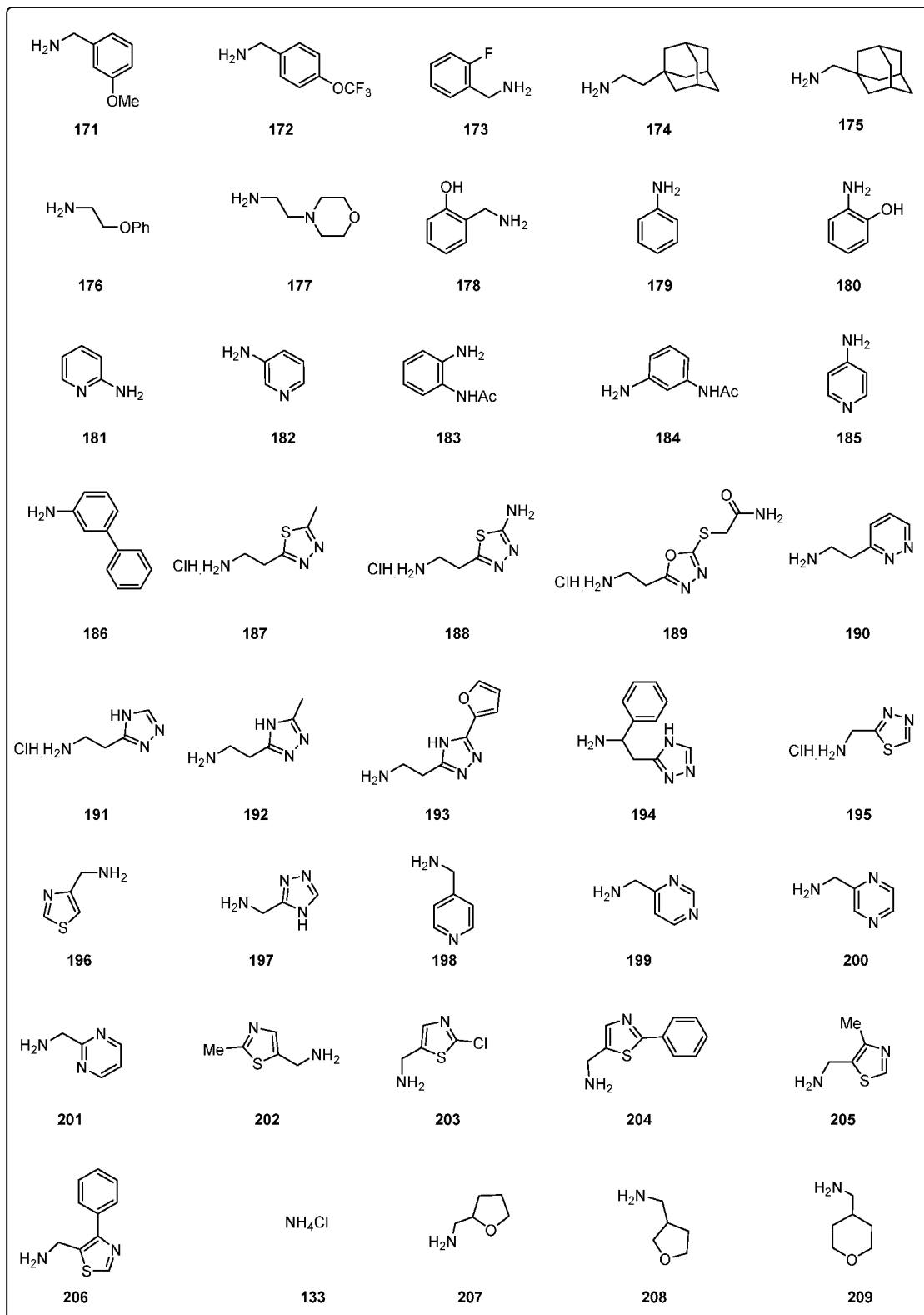
[000217] To a stirred solution of compound **159** (100 mg, 0.33 mmol) in CH₃CN (2 mL) under argon atmosphere was added thiazol-2-amine **231** (36 mg, 0.36 mmol), propylphosphonic anhydride (~50% solution in EtOAc, 0.8 mL, 1.32 mmol) and NMM (0.14 mL, 1.32 mmol) at RT in a microwave vial and heated at 100 °C and stirred for 1 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* and diluted with water (20 mL) and the precipitated solid was filtered. The obtained solid was either directly dried *in vacuo* or titrated or purified by column chromatography to afford the desired product.

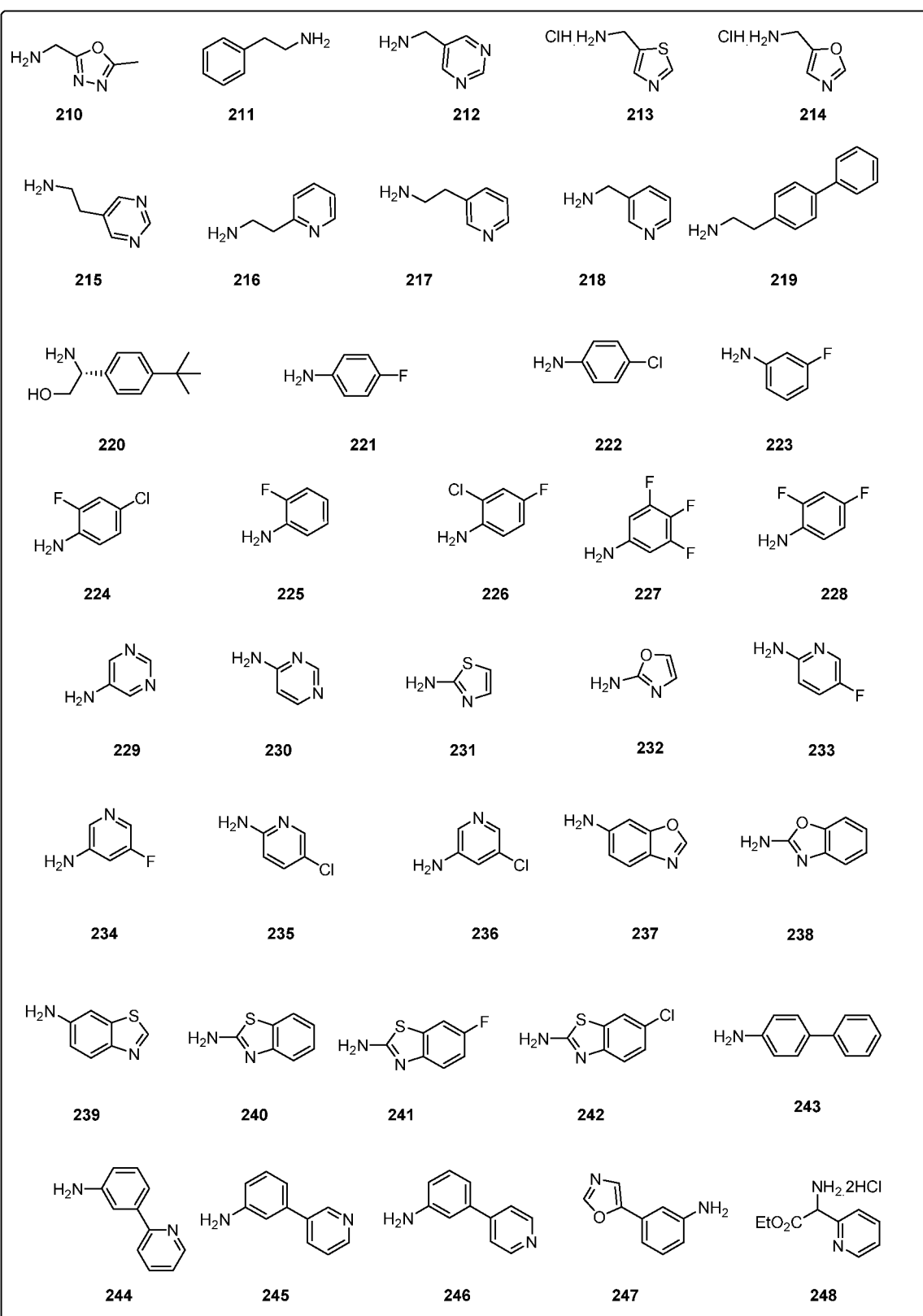
Procedure H:

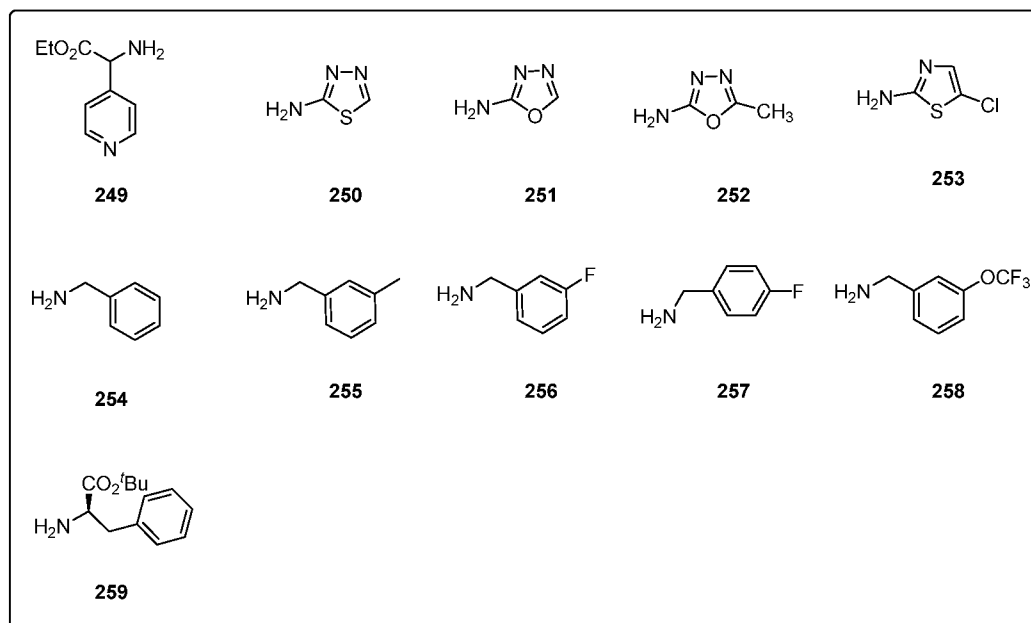
[000218] To a stirred solution of compound **159** (100 mg, 0.33 mmol) in CH₂Cl₂ (12 mL) under argon atmosphere were added EDCI.HCl (188.8 mg, 0.98 mmol), 6-fluorobenzo [*d*]

thiazol-2-amine **241** (61 mg, 0.36 mmol) and DMAP (120.7 mg, 0.98 mmol) at RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the precipitated solid was filtered washed with water and titrated to afford the desired product.

Representative Commercially Available Amines Used for Synthesis

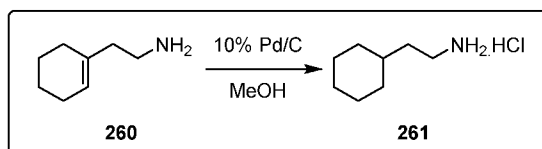






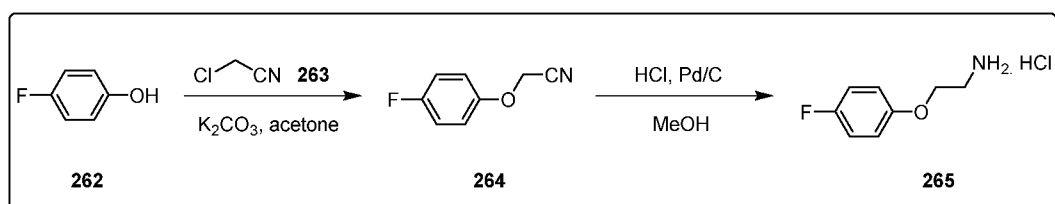
Preparation of amines for compound synthesis

Synthesis of 2-cyclohexylethanamine hydrochloride (261):



[000219] To a stirred solution of 2-(cyclohex-1-en-1-yl) ethanamine **260** (500 mg, 4.00 mmol) in MeOH (10 mL) under argon atmosphere was added 10% Pd/C (50 mg) at RT and stirred under hydrogen atmosphere (balloon pressure) for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered through celite, washed with MeOH (2 x 5 mL) and the filtrate was concentrated *in vacuo*. The residue was triturated with CH₂Cl₂: EtOAc (1: 1, 2 mL), diethyl ether in 1 N HCl (4 mL) to afford compound **261** (250 mg, 38%) as white solid. **TLC**: 20% EtOAc/ hexanes (*R_f*: 0.3); **¹H-NMR (DMSO-*d*₆, 500 MHz)**: δ 7.79 (br s, 2H), 2.77 (t, *J* = 7.5 Hz, 2H), 1.66-1.59 (m, 5H), 1.45-1.41 (m, 2H), 1.32-1.28 (m, 1H), 1.23-1.11 (m, 3H), 0.91-0.84 (m, 2H).

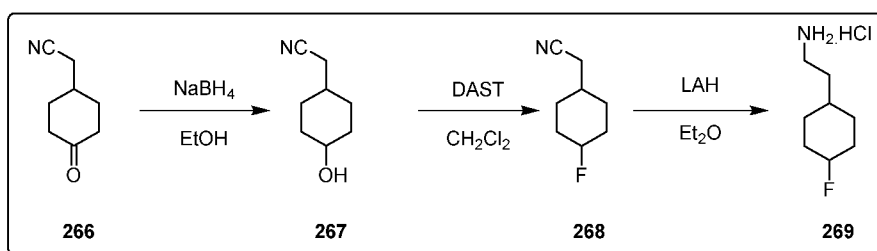
Synthesis of 2-(4-fluorophenoxy) ethan-1-amine hydrochloride (265)



[000220] Synthesis of 2-(4-fluorophenoxy) acetonitrile (264): To a stirred solution of 4-fluorophenol **262** (1.74 mL, 18.96 mmol) in acetone (50 mL) under argon atmosphere were added potassium carbonate (6.5 g, 47.40 mmol), chloro acetonitrile **263** (1 mL, 15.80 mmol) at RT; heated to reflux and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was extracted with diethyl ether (3 x 40 mL). The combined organic extracts were washed with NaOH solution (30 mL), water (30 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to afford compound **264** (2.4 g, 90%) as brown syrup. **TLC:** 10% EtOAc/hexanes (R_f : 0.3); **1H -NMR ($CDCl_3$, 400 MHz):** δ 7.06-7.01 (m, 2H), 6.98-6.89 (m, 2H), 4.73 (s, 2H).

[000221] Synthesis of 2-(4-fluorophenoxy) ethan-1-amine hydrochloride (265): To a stirred solution of compound **264** (200 mg, 1.32 mmol) in MeOH (10 mL) under argon atmosphere were added HCl (0.3 mL), Pd/C (90 mg) and stirred under hydrogen atmosphere (balloon pressure) at RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with saturated sodium potassium tartrate solution (20 mL) and extracted with diethyl ether (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford compound **265** (130 mg, 65%) as an off-white solid. **TLC:** 10% EtOAc/ hexanes (R_f : 0.2); **1H -NMR ($DMSO-d_6$, 400 MHz):** δ 8.31-8.28 (m, 2H), 7.17-7.12 (m, 2H), 7.02-6.98 (m, 2H), 4.16 (t, J = 5.2 Hz, 2H), 3.17 (t, J = 5.2 Hz, 2H).

Synthesis of 2-(4-fluorocyclohexyl) ethan-1-amine hydrochloride (269)



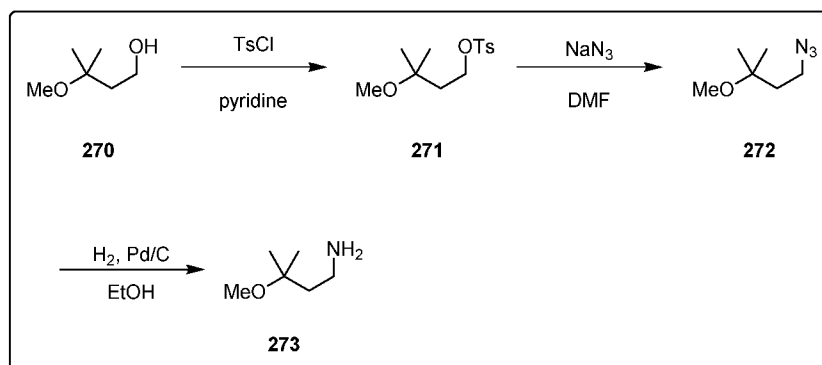
[000222] Synthesis of 2-(4-hydroxycyclohexyl) acetonitrile (267): To a stirred solution of 2-(4-oxocyclohexyl) acetonitrile **266** (200 mg, 1.45 mmol) in EtOH (10 mL) under argon atmosphere was added sodium borohydride (82.7 mg, 2.18 mmol) at 0°C ; warmed to $10\text{--}15^\circ\text{C}$ and stirred for 1 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was quenched with ice cold water (2 mL) and the volatiles were removed *in vacuo*. The residue was diluted with water (20 mL) and extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford compound **267** (180 mg, 89%) as colorless syrup. **TLC:** 50% EtOAc / hexanes (R_f : 0.4); **$^1\text{H-NMR}$ (CDCl_3 , 400 MHz):** δ 3.62-3.55 (m, 1H), 2.30-2.24 (m, 2H), 2.06-2.01 (m, 2H), 1.92-1.88 (m, 2H), 1.80-1.78 (m, 1H), 1.70-1.63 (m, 2H), 1.59-1.56 (m, 1H), 1.40-1.16 (m, 2H).

[000223] Synthesis of 2-(4-fluorocyclohexyl) acetonitrile (268): To a stirred solution of compound **267** (180 mg, 1.29 mmol) in CH_2Cl_2 (5 mL) under argon atmosphere was added DAST (313 mg, 1.94 mmol) at -20°C ; warmed to RT and stirred for 6 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was quenched with ice cold water (20 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 5-7% EtOAc / hexanes to afford compound **268** (35 mg, 19%) as colorless syrup. **TLC:** 20% EtOAc / hexanes (R_f : 0.4); **$^1\text{H-NMR}$ (CDCl_3 , 500 MHz):** δ 4.88-4.79 (m, 1H), 2.27 (d, $J = 7.0$ Hz, 2H), 2.10-2.08 (m, 2H), 1.77-1.70 (m, 3H), 1.57-1.33 (m, 4H).

[000224] Synthesis of 2-(4-fluorocyclohexyl) ethan-1-amine hydrochloride (269): To a stirred solution of compound **268** (35 mg, 0.24 mmol) in ether (5 mL) under argon atmosphere was added lithium aluminium hydride (18.8 mg, 0.49 mmol) at 0°C ; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction

mixture was quenched with saturated sodium potassium tartrate solution (10 mL) at 0-5 °C and extracted with ether (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was dissolved in ether (3 mL), slowly added 2 N HCl in ether (10 mL) and stirred for 1 h. The precipitated solid was filtered and dried *in vacuo* to afford compound **269** (12 mg, 33%) as pale yellow solid. **TLC:** 30% EtOAc/ hexanes (R_f : 0.2); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 7.81 (br s, 2H), 4.87 (br s, 1H), 4.75 (br s, 1H), 2.82-2.77 (m, 2H), 1.89-1.84 (m, 2H), 1.59-1.40 (m, 6H), 1.20 (t, J = 10.0 Hz, 2H).

Synthesis of 3-methoxy-3-methylbutan-1-amine (273)



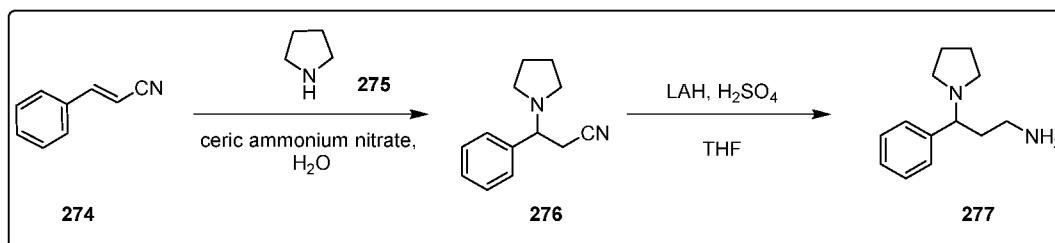
[000225] Synthesis of 3-methoxy-3-methylbutyl 4-methylbenzenesulfonate (271): To a stirred solution of 3-methoxy-3-methylbutan-1-ol **270** (1 g, 8.46 mmol) in pyridine (15 mL) under argon atmosphere was added tosyl chloride (1.6 g, 8.46 mmol) at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was quenched with saturated NaHCO₃ solution (20 mL) and extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried over sodium sulphate, filtered and concentrated *in vacuo* to afford compound **271** (1.8 g, 78%) as colorless syrup. **TLC:** 30% EtOAc/ hexanes (R_f : 0.7); **¹H-NMR (CDCl₃, 400 MHz):** δ 7.79 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 7.6 Hz, 2H), 4.13 (t, J = 7.2 Hz, 2H), 3.10 (s, 3H), 2.45 (s, 3H), 1.87 (t, J = 7.6 Hz, 2H), 1.12 (s, 6H).

[000226] Synthesis of 1-azido-3-methoxy-3-methylbutane (272): To a stirred solution of compound **271** (1 g, 3.67 mmol) in DMF (10 mL) under argon atmosphere was added sodium azide (478 mg, 7.34 mmol) at 0 °C; warmed to RT and stirred for 16 h. The reaction was

monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (30 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over sodium sulphate, filtered and concentrated *in vacuo* to afford compound 272 (525 mg, 76%) as white solid. **TLC:** 30% EtOAc/ hexanes (R_f : 0.7); **$^1\text{H-NMR}$ (CDCl_3 , 400 MHz):** δ 3.34 (t, J = 7.6 Hz, 2H), 3.18 (s, 3H), 1.78 (t, J = 8.0 Hz, 2H), 1.18 (s, 6H).

[000227] Synthesis of 3-methoxy-3-methylbutan-1-amine (273): To a stirred solution of compound 272 (400 mg, 2.79 mmol) in EtOH (5 mL) under argon atmosphere was added 10% Pd/C (250 mg) at RT and stirred under hydrogen atmosphere (balloon pressure) for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered through celite and the filtrate was concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 80% EtOAc/ hexanes to afford compound 273 (320 mg, 33%) as colorless syrup. **TLC:** 70% EtOAc/ hexanes (R_f : 0.3); **$^1\text{H-NMR}$ (CDCl_3 , 400 MHz):** δ 3.18 (s, 3H), 2.80 (t, J = 8.0 Hz, 0.5 H), 2.70 (t, J = 7.6 Hz, 1H), 2.49 (t, J = 8.0 Hz, 0.5H), 1.71 (t, J = 7.6 Hz, 2H), 1.56 (s, 6H).

Synthesis of 3-phenyl-3-(pyrrolidin-1-yl) propan-1-amine (277)

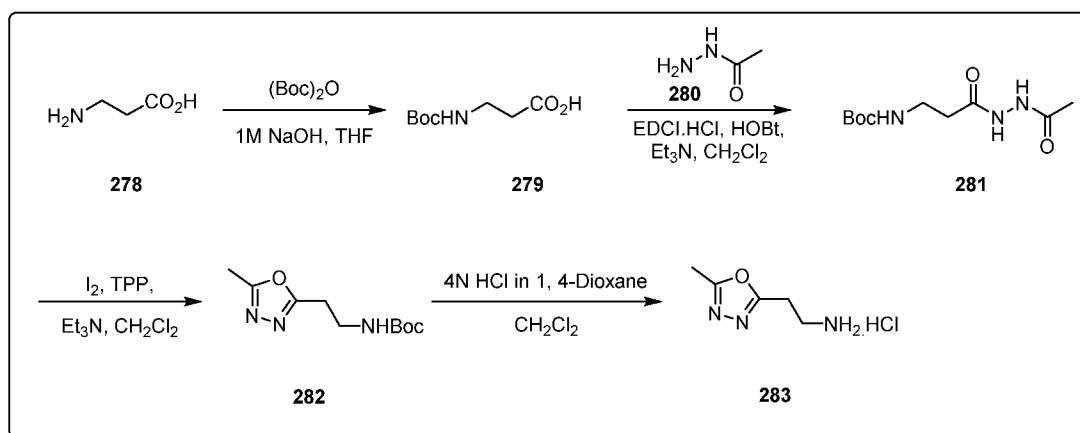


[000228] Synthesis of 3-phenyl-3-(pyrrolidin-1-yl) propanenitrile (276): To a stirred solution of cinnamionitrile 274 (500 mg, 3.87 mmol) in H₂O (15 mL) were added pyrrolidine 275 (412 mg, 5.80 mmol), ceric ammonium nitrate (2.1 g, 3.87 mmol) at RT, heated to 60 °C and stirred for 4 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 30 mL). The combined organic extracts were dried over sodium sulphate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 25% EtOAc/ hexanes to afford compound 276 (300 mg, 39%) as colorless syrup. **TLC:** 30% EtOAc/ hexanes (R_f : 0.5); **$^1\text{H-NMR}$ (CDCl_3 , 400 MHz):** δ 7.39-7.31 (m, 5H), 3.50-3.35 (m, 1H), 2.80-2.70 (m,

2H), 2.60-2.45 (m, 4H), 1.89-1.72 (m, 4H).

[000229] Synthesis of 3-phenyl-3-(pyrrolidin-1-yl) propan-1-amine (277): To a stirred solution of compound **276** (150 mg, 0.75 mmol) in THF (10 mL) under argon atmosphere were added lithium aluminium hydride (57 mg, 1.50 mmol), H₂SO₄ (0.04 mL, 0.75 mmol) at 0 °C; warmed to RT and stirred for 5 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was quenched with saturated sodium sulphate and the reaction mixture was filtered through celite, washed with EtOAc (2 x 5 mL). The volatiles were removed *in vacuo* to afford compound **277** (100 mg, 65%) as an off-white solid. **TLC:** 10% MeOH/EtOAc (*R_f*: 0.3); **¹H-NMR (CDCl₃, 400 MHz):** δ 7.31-7.30 (m, 5H), 3.26-3.22 (m, 1H), 2.59-2.40 (m, 4H), 2.39-2.37 (m, 2H), 2.14-2.10 (m, 1H), 2.10 -2.04 (m, 1H), 1.98-1.72 (m, 6H).

Synthesis of 2-(5-methyl-1, 3, 4-oxadiazol-2-yl) ethan-1-amine hydrochloride (283)



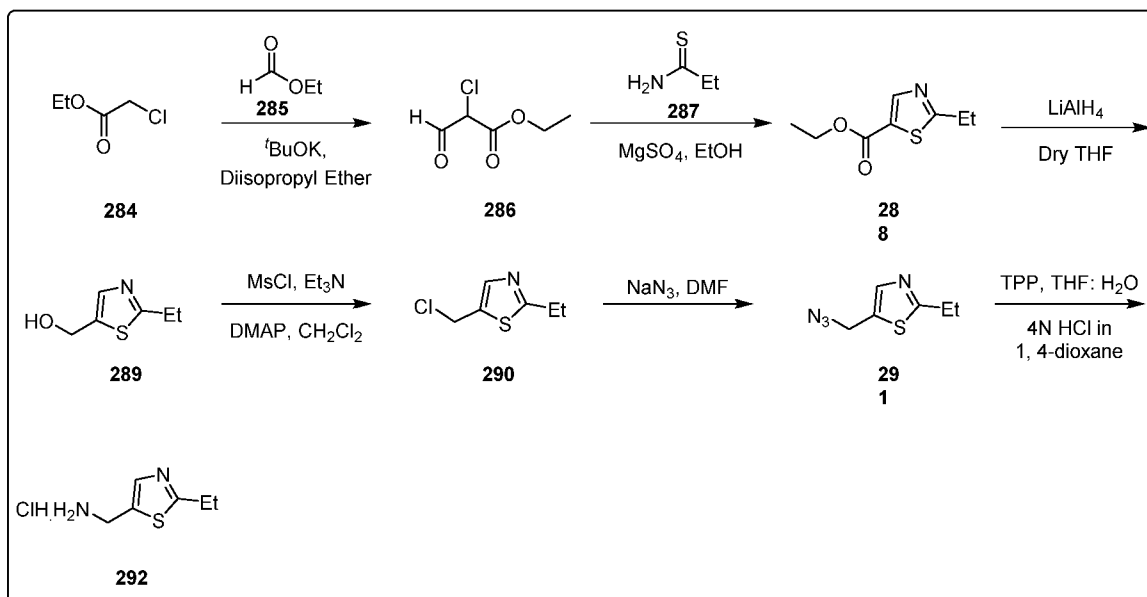
[000230] Synthesis of 3-((tert-butoxycarbonyl) amino) propanoic acid (279): To a stirred solution of 3-aminopropanoic acid **278** (5 g, 51.02 mmol) in THF (50 mL) were added 1 M aqueous sodium hydroxide solution (25 mL) and Boc-anhydride (11.3 mL, 51.02 mmol) at 0 °C; warmed to RT and stirred for 12 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The aqueous layer was washed with diethyl ether (2 x 50 mL) and the pH was adjusted to ~6 with 4 M HCl and extracted with diethyl ether (4 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried over sodium sulphate, filtered and concentrated *in vacuo* to obtain compound **279** (8 g, 79%) as an off-white solid. **TLC:** 50% EtOAc/ hexanes (*R_f*: 0.3); **¹H-NMR (DMSO-*d*₆, 500 MHz):** δ 12.18 (br s, 1H), 6.81 (t, *J* = 4.8 Hz, 1H), 3.11 (q, *J* = 6.9 Hz, 2H), 2.34 (t, *J* = 7.1 Hz, 2H), 1.36 (s, 9H).

[000231] Synthesis of *tert*-butyl (3-(2-acetylhydrazinyl)-3-oxopropyl) carbamate (281) To a stirred solution of compound **279** (1 g, 5.29 mmol) in CH₂Cl₂ (15 mL) under argon atmosphere were added EDCI.HCl (1.3 g, 6.87 mmol), HOBt (714 mg, 5.29 mmol), triethyl amine (0.99 mL, 6.87 mmol), acetic acid hydrazide **280** (430 mg, 5.82 mmol) at 0 °C; warmed to RT and stirred for 1.5 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with ice cold water (5 mL) and extracted with CH₂Cl₂ (4 x 20 mL). The combined organic extracts were dried over sodium sulphate, filtered and concentrated *in vacuo* to obtain crude. The crude was purified through silica gel column chromatography using 10% EtOAc/ hexanes to afford compound **281** (610 mg, 50%) as an off white solid. **TLC:** 10% EtOAc/ hexanes (*R_f*: 0.3); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 9.70 (s, 2H), 6.73 (t, *J* = 4.7 Hz, 1H), 3.13 (q, *J* = 6.6 Hz, 2H), 2.27 (t, *J* = 7.4 Hz, 2H), 1.83 (s, 3H), 1.37 (s, 9H).

[000232] Synthesis of *tert*-butyl (2-(5-methyl-1, 3, 4-oxadiazol-2-yl) ethyl) carbamate (282): To a stirred solution of triphenyl phosphine (428 mg, 1.63 mmol) in CH₂Cl₂ (5 mL) under argon atmosphere were added iodine (414 mg, 1.63 mmol) and stirred for 15 min. To this were added triethyl amine (0.47 mL, 3.26 mmol), compound **281** (200 mg, 0.81 mmol) at RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 4% EtOAc/ hexanes to afford crude compound **282** (360 mg) as an off-white solid. **TLC:** 10% EtOAc/ hexanes (*R_f*: 0.7); **¹H NMR** shows mixture of compound and TPPO as major impurity. **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 7.68-7.49 (m, 48H-TPPO as impurity), 6.97 (t, *J* = 5.0 Hz, 1H), 3.27 (q, *J* = 6.5 Hz, 2H), 2.89 (t, *J* = 6.7 Hz, 2H), 2.43 (s, 3H), 1.35 (s, 9H).

[000233] Synthesis of 2-(5-methyl-1, 3, 4-oxadiazol-2-yl) ethan-1-amine hydrochloride (283): To a stirred solution of compound **282** (350 mg) in CH₂Cl₂ (5 mL) under argon atmosphere was added 4 N HCl in 1, 4-dioxane (4 mL) at 0 °C; warmed to RT and stirred for 4 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude. The crude was titrated with CH₂Cl₂ (2 mL), diethyl ether (5 mL) and *n*-pentane (5 mL) and dried *in vacuo* to afford crude compound **283** (60 mg) as brown solid. **TLC:** 10% EtOAc/ hexanes (*R_f*: 0.1).

Synthesis of (2-ethylthiazol-5-yl) methanamine hydrochloride (292)



[000234] Synthesis of ethyl 2-chloro-3-oxopropanoate (286): To a stirred solution of ethyl 2-chloroacetate **284** (5 g, 40.98 mmol) and **285** (3.03 g, 40.98 mmol) in diisopropyl ether (100 mL) under argon atmosphere was added potassium *tert*-butoxide (5.49 g, 45.08 mmol) portion wise for 10 min at 0 °C; warmed to RT and stirred for 24 h. The reaction was monitored by TLC; after completion of the reaction, the pH of the reaction mixture was adjusted to ~ 6 using 5 N HCl. The obtained solid was filtered, washed with diethyl ether (200 mL) and dried *in vacuo* to afford compound **286** (6 g) as pale brown syrup. **TLC:** 30% EtOAc/ hexanes (R_f : 0.2); **LC-MS:** 21.49% + 75.58%; 149.0 ($\text{M}^+ - 1$); (column; X-Select C-18, (50 × 3.0 mm, 3.5 μm); RT 0.56 min, 0.77 min. 5 Mm Aq. NH_4OAc : ACN 0.8 mL/min).

[000235] Synthesis of ethyl 2-ethylthiazole-5-carboxylate (288): To a stirred solution of compound **286** (1 g) in ethanol (25 mL) under argon atmosphere were added propanethioamide **287** (594 mg, 6.67 mmol), dry magnesium sulfate (4 g) at RT and heated to reflux for 24 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*, diluted with EtOAc (2 × 100 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution (2 × 100 mL), brine (50 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through flash column chromatography using 6% EtOAc/ hexanes to afford compound **288** (330 mg, 27%) as

brown syrup. **TLC:** 10% EtOAc/ hexanes (R_f : 0.4); **$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz):** δ 8.29 (s, 1H), 4.30 (q, $J = 7.1$ Hz, 2H), 3.04 (q, $J = 7.5$ Hz, 2H), 1.31 (t, $J = 7.3$ Hz, 3H), 1.29 (t, $J = 7.3$ Hz, 3H).

[000236] Synthesis of (2-ethylthiazol-5-yl) methanol (289) (SAP-MA1426-31): To a stirred suspension of lithium aluminium hydride (205 mg, 5.40 mmol) in dry THF (15 mL) under inert atmosphere was added compound **288** (500 mg, 2.70 mmol) at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was cooled to 0 °C, quenched with 20% aqueous sodium hydroxide solution (3 mL), filtered through celite and washed with EtOAc (3 x 100 mL). The filtrate was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford compound **289** (310 mg, 80%) as pale yellow solid. **TLC:** 50% EtOAc/ hexanes (R_f : 0.4). **$^1\text{H-NMR}$ (CDCl₃, 400 MHz):** δ 7.51 (s, 1H), 4.82 (s, 2H), 3.01 (q, $J = 7.5$ Hz, 2H), 1.38 (t, $J = 7.6$ Hz, 3H).

[000237] Synthesis of 5-(chloromethyl)-2-ethylthiazole (290) (SAP-MA1426-34): To a stirred solution of compound **289** (300 mg, 2.09 mmol) in CH₂Cl₂ (15 mL) under inert atmosphere were added triethyl amine (0.6 mL, 4.20 mmol), DMAP (25.6 mg, 0.21 mmol) and mesyl chloride (0.19 mL, 2.51 mmol) at 0 °C; warmed to RT and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (50 mL) and extracted with CH₂Cl₂ (3 x 100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford compound **290** (500 mg, crude) as pale yellow syrup. **TLC:** 30% EtOAc/ hexanes (R_f : 0.8); **LC-MS:** 30.71%; 162.0 ($M^+ + 1$); (column; Ascentis Express C18, (50 x 3.0 mm, 2.7 μm); RT 2.14 min. 0.025% Aq. TFA + 5% ACN: ACN + 5% 0.025% Aq. TFA, 1.2 mL/min).

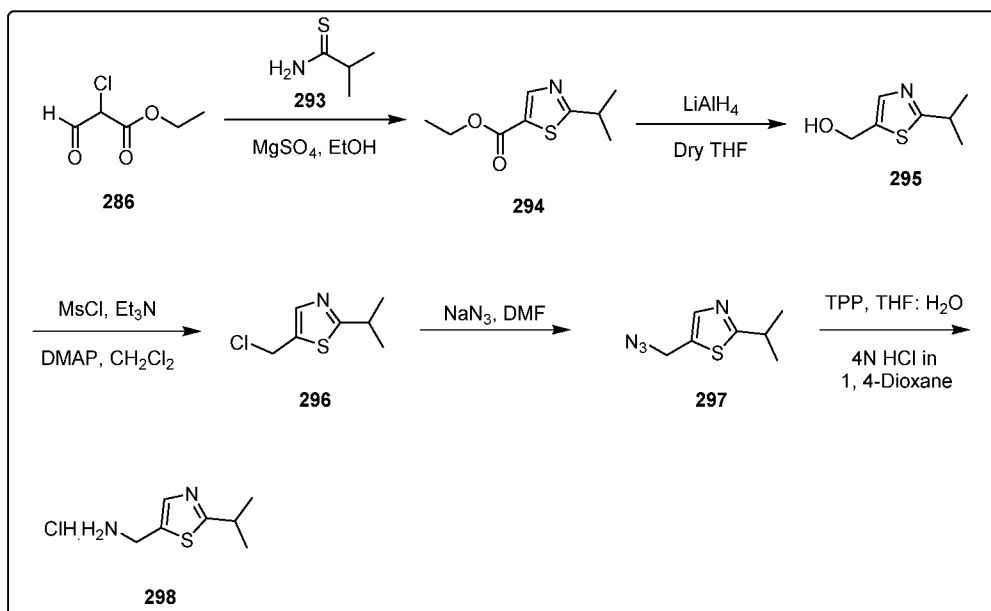
[000238] Synthesis of 5-(azidomethyl)-2-ethylthiazole (291) (SAP-MA1426-35): To a stirred solution of compound **290** (500 mg, 2.26 mmol) in DMF (20 mL) under inert atmosphere was added sodium azide (294 mg, 4.52 mmol) at RT and heated to 80 °C for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with ice cold water (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through flash column chromatography using 15% EtOAc/ hexanes to afford

compound **291** (250 mg, 71%) as pale yellow syrup. **TLC:** 20% EtOAc/ hexanes (R_f : 0.4); **$^1\text{H-NMR}$ (CDCl_3 , 400 MHz):** δ 7.56 (s, 1H), 4.49 (s, 2H), 3.03 (q, J = 7.6 Hz, 2H), 1.40 (t, J = 7.6 Hz, 3H);

[000239] Synthesis of (2-ethylthiazol-5-yl) methanamine hydrochloride (**292**): To a stirred solution of compound **291** (250 mg, 1.48 mmol) in THF: H_2O (5:1, 12 mL) was added triphenyl phosphine (780 mg, 2.97 mmol) at RT and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude. The obtained solid was further dried using toluene (2 x 5 mL) to obtain the crude amine.

[000240] The above compound was dissolved in CH_2Cl_2 (5 mL) added 4 N HCl in 1, 4-dioxane (4 mL) under inert atmosphere at 0 °C and stirred for 30 min. The volatiles were removed *in vacuo* to obtain the crude, which was titrated with EtOAc (2 mL), diethyl ether (2 mL) and pentane (5 mL) to afford compound **292** (180 mg, 68%) as an off-white solid. **TLC:** 5% MeOH/ CH_2Cl_2 (R_f : 0.2); **$^1\text{H NMR}$ ($\text{DMSO}-d_6$, 500 MHz):** δ 8.48 (br s, 3H), 7.74 (s, 1H), 4.25 (q, J = 5.5 Hz, 2H), 2.98 (q, J = 7.5 Hz, 2H), 1.28 (t, J = 7.5 Hz, 3H);

Synthesis of (2-isopropylthiazol-5-yl) methanamine hydrochloride (**298**)



[000241] Synthesis of ethyl 2-isopropylthiazole-5-carboxylate (**294**): To a stirred solution of compound **286** (3.05 g) in ethanol (60 mL) under argon atmosphere were added 2-

methylpropanethioamide **293** (1.5 g, 14.56 mmol), dry magnesium sulfate (5 g) at RT and heated to reflux for 24 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with saturated sodium bicarbonate solution (100 mL), extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through flash column chromatography using 2% EtOAc/ hexanes to afford compound **294** (550 mg, 17%) as brown syrup. **TLC:** 10% EtOAc/ hexanes (*R_f*: 0.5); **¹H NMR (500 MHz, DMSO-*d*₆)** δ 8.31 (s, 1H), 4.30 (q, *J* = 7.0 Hz, 2H), 3.36-3.29 (m, 1H), 1.34 (d, *J* = 6.9 Hz, 6H), 1.29 (t, *J* = 7.1 Hz, 3H).

[000242] Synthesis of (2-isopropylthiazol-5-yl) methanol (295): To a stirred solution of compound **294** (550 mg, 2.76 mmol) in dry THF (10 mL) under inert atmosphere was added lithium aluminium hydride (210 mg, 5.52 mmol) at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was cooled to 0 °C, quenched with 15% aqueous sodium hydroxide solution (3 mL), filtered through celite and washed with EtOAc (100 mL). The filtrate was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford compound **295** (360 mg, 83%) as pale yellow syrup. **TLC:** 50% EtOAc/ hexanes (*R_f*: 0.3). **¹H NMR (400MHz, DMSO-*d*₆)** δ 7.47 (s, 1H), 5.43 (t, *J* = 5.7 Hz, 1H), 4.61 (dd, *J* = 5.6, 0.6 Hz, 2H), 3.26-3.19 (m, 1H), 1.30 (d, *J* = 6.9 Hz, 6H).

[000243] Synthesis of 5-(chloromethyl)-2-isopropylthiazole (296): To a stirred solution of compound **295** (350 mg, 2.23 mmol) in CH₂Cl₂ (20 mL) under inert atmosphere were added triethyl amine (0.64 mL, 4.45 mmol), DMAP (27.2 mg, 0.22 mmol) and mesyl chloride (0.2 mL, 2.67 mmol) at 0 °C; warmed to RT and stirred for 3 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (50 mL) and extracted with CH₂Cl₂ (2 x 100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford compound **296** (500 mg, crude) as pale yellow syrup. **TLC:** 40% EtOAc/ hexanes (*R_f*: 0.8); **LC-MS:** 70.54%; 175.8 (M⁺+1); (column; Ascentis Express C18, (50 × 3.0 mm, 2.7 μm); RT 2.34 min. 0.025% Aq. TFA + 5% ACN: ACN + 5% 0.025% Aq. TFA, 1.2 mL/min).

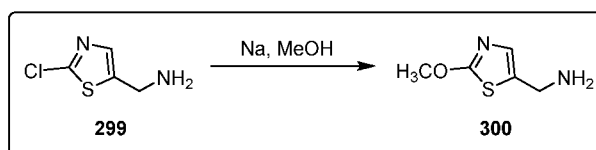
[000244] Synthesis of 5-(azidomethyl)-2-isopropylthiazole (297): To a stirred solution of

compound **296** (500 mg, 2.26 mmol) in DMF (20 mL) under inert atmosphere was added sodium azide (445 mg, 6.85 mmol) at RT and heated to 80 °C for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with ice cold water (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through column chromatography using 8% EtOAc/ hexanes to afford compound **297** (255 mg, 63%) as colorless liquid. **TLC:** 10% EtOAc/ hexanes (R_f : 0.4); **^1H NMR (500 MHz, DMSO- d_6):** δ = 7.67 (s, 1H), 4.69 (s, 2H), 3.29-3.24 (m, 1H), 1.32 (d, J = 6.9 Hz, 8H).

[000245] Synthesis of (2-isopropylthiazol-5-yl) methanamine hydrochloride (298): To a stirred solution of compound **297** (250 mg, 1.37 mmol) in THF: H₂O (5:1, 12 mL) was added triphenyl phosphine (720 mg, 2.74 mmol) at RT and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude. The obtained solid was further dried using toluene (2 x 5 mL) to obtain the crude amine.

[000246] The above crude compound was dissolved in CH₂Cl₂ (5 mL) added 4 N HCl in 1, 4-dioxane (10 mL) under inert atmosphere at 0 °C and stirred for 30 min. The volatiles were removed *in vacuo* to obtain the crude, which was titrated with EtOAc (2 mL), diethyl ether (2 mL) and pentane (5 mL) to afford compound **298** (170 mg, 65%) as low melting hygroscopic solid. **TLC:** 5% MeOH/ CH₂Cl₂ (R_f : 0.2); **^1H NMR (500 MHz, DMSO- d_6):** δ 8.29 (br s, 2H), 7.72 (s, 1H), 4.25 (d, J = 5.8 Hz, 2H), 3.29-3.24 (m, 1H), 1.30 (d, J = 6.9 Hz, 6H)

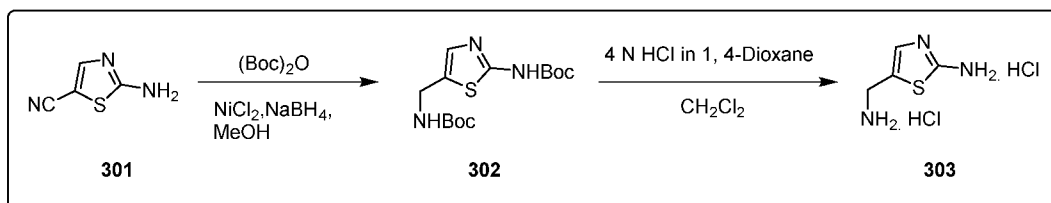
Synthesis of (2-methoxythiazol-5-yl) methanamine (300)



[000247] Synthesis of (2-methoxythiazol-5-yl) methanamine (300): Sodium metal (46.6 mg, 2.02 mmol) was added slowly to MeOH (5 mL) under argon atmosphere and stirred for 15 min in a sealed tube. To this was added (2-chlorothiazol-5-yl) methanamine **299** (100 mg, 0.67 mmol) and the reaction mixture was heated to 80 °C for 3 h. The reaction was monitored by TLC; after completion the reaction, the reaction mixture was extracted with 20% MeOH/ CH₂Cl₂ (3 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and

concentrated *in vacuo* to obtain the crude compound **300** (32 mg, 33%). The crude was carried forward for next step without purification. **TLC**: 5% MeOH/ CH₂Cl₂ (*R_f*: 0.2); **LC-MS**: 90.34%; 145.0 (*M*⁺+1); (column; X-Select CSH C18, (50 × 3.0 mm, 3.5 μm); RT 0.88 min. 2.5 mM Aq.NH₄OOCH + 5% ACN: ACN + 5% 2.5 mM Aq. NH₄OOCH; 1.2 mL/min).

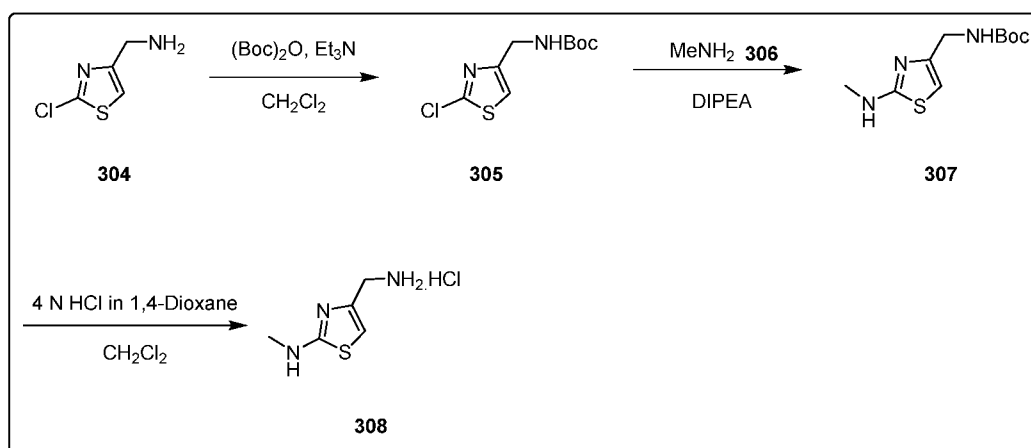
Synthesis of 5-(aminomethyl) thiazol-2-amine dihydrochloride (**303**)



[000248] Synthesis of *tert*-butyl ((2-((*tert*-butoxycarbonyl) amino) thiazol-5-yl) methyl) carbamate (302**):** To a stirred solution of 2-aminothiazole-5-carbonitrile **301** (300 mg, 2.40 mmol) in MeOH (50 mL) were added Boc-anhydride (1.5 mL, 7.20 mmol), nickel(II) chloride (571 mg, 2.40 mmol) at 0 °C. To this was added sodium borohydride (638 mg, 16.80 mmol) portion wise for 10 min at 0 °C; warmed to RT and stirred for 18 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with EtOAc (100 mL) and water (75 mL), filtered through celite. The organic layer was dried over sodium sulphate, filtered and concentrated *in vacuo* to obtain compound **302** (300 mg) as colorless syrup. **TLC**: 10% MeOH/ CH₂Cl₂ (*R_f*: 0.5); **¹H NMR (DMSO-*d*₆, 500 MHz)**: δ 11.24 (br s, 1H), 7.38 (br s, 1H), 7.11 (s, 1H), 4.17 (d, *J* = 5.5 Hz, 2H), 1.39 (s, 9H), 1.37 (s, 9H).

[000249] Synthesis of 5-(aminomethyl) thiazol-2-amine dihydrochloride (303**):** To a stirred solution of compound **302** (300 mg) in CH₂Cl₂ (10 mL) was added 4 N HCl in 1, 4-dioxane (5 mL) under argon atmosphere at 0-5 °C; warmed to RT and stirred for 4 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed under reduced pressure. The obtained solid was washed with CH₂Cl₂ (5 mL), EtOAc (5 mL) and dried *in vacuo* to afford compound **303** (120 mg, HCl salt) as yellow solid. **TLC**: 10% MeOH/ CH₂Cl₂ (*R_f*: 0.2); **¹H NMR (DMSO-*d*₆, 500 MHz)**: δ 9.31 (br s, 1H), 8.53 (br s, 2H), 8.14 (br s, 1H), 7.37 (br s, 1H), 7.27 (br s, 1H), 7.17 (br s, 1H), 4.07 (d, *J* = 5.5 Hz, 2H).

Synthesis of 4-(aminomethyl)-*N*-methylthiazol-2-amine hydrochloride (**308**)



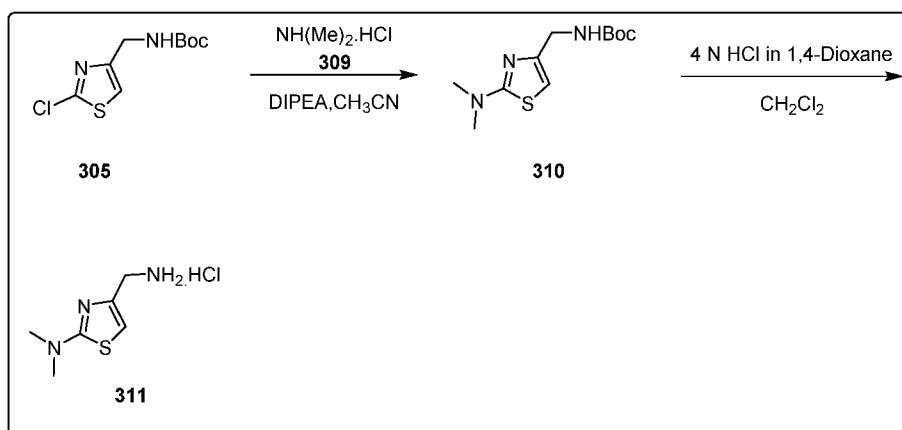
[000250] Synthesis of *tert*-butyl ((2-chlorothiazol-4-yl) methyl) carbamate (305): To a stirred solution of (2-chlorothiazol-4-yl) methanamine **304** (200 mg, 1.35 mmol) in CH_2Cl_2 (10 mL) were added triethylamine (0.6 mL, 4.14 mmol) and Boc-anhydride (0.6 mL, 2.7 mmol) at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The aqueous layer was washed with CH_2Cl_2 (50 mL), washed with water (50 mL). The organic extract was dried over sodium sulphate, filtered and concentrated *in vacuo* to obtain compound **305** (200 mg, 60%) as pale yellow sticky solid. **TLC:** 5% MeOH/ CH_2Cl_2 (R_f : 0.4); **^1H NMR (DMSO- d_6 , 400 MHz):** δ 7.56 (br s, 1H), 7.49 (s, 1H), 4.24 (d, J = 5.9 Hz, 3H), 1.39 (s, 9H).

[000251] Synthesis of *tert*-butyl ((2-(methylamino) thiazol-4-yl) methyl) carbamate (307): A mixture of compound **305** (100 mg, 0.41 mmol) and methyl amine **306** (5 mL, 33% solution in EtOH) in a sealed tube under argon atmosphere was added diisopropyl ethylamine (0.2 mL, 1.21 mmol) under argon atmosphere at RT and heated to 120 °C for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The crude was purified through silica gel column chromatography using 70% EtOAc/ hexanes to afford compound **307** (90 mg, 92%) as colorless sticky solid. **TLC:** 50% EtOAc/ hexanes (R_f : 0.2); **^1H NMR (DMSO- d_6 , 400 MHz):** δ 7.26 (d, J = 5.6 Hz, 2H), 6.77 (s, 1H), 4.05 (d, J = 5.7 Hz, 2H), 2.76 (d, J = 4.8 Hz, 3H), 1.38 (s, 9H).

[000252] Synthesis of 4-(aminomethyl)-*N*-methylthiazol-2-amine hydrochloride (308) To a stirred solution of compound **307** (90 mg, 0.37 mmol) in CH_2Cl_2 (3 mL) under argon atmosphere was added 4 N HCl in 1, 4-dioxane (3 mL) at 0 °C; warmed to RT and stirred for 4 h. The

reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The crude was titrated with diethyl ether (5 mL) and dried *in vacuo* to afford compound **308** (70 mg, HCl salt) as brown solid. **TLC**: 30% EtOAc/ hexanes (R_f : 0.1); **^1H NMR (DMSO- d_6 , 400 MHz)**: δ 9.73-9.27 (m, 1H), 8.39 (br s, 3H), 7.35 (s, 1H), 4.08 (q, J = 5.3 Hz, 2H), 2.95 (s, 3H).

Synthesis of 4-(aminomethyl)-*N,N*-dimethylthiazol-2-amine hydrochloride (310)

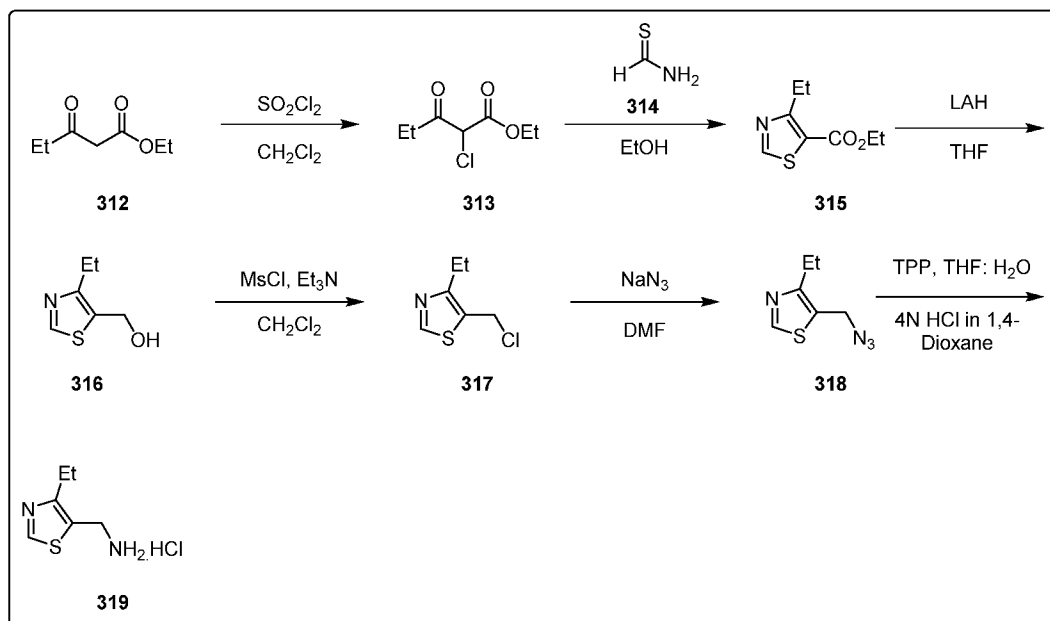


[000253] Synthesis of *tert*-butyl ((2-(dimethylamino) thiazol-4-yl) methyl) carbamate (310): To a stirred solution of compound **305** (100 mg, 0.41 mmol) in CH_3CN (3 mL) under argon atmosphere were added dimethyl amine hydrochloride **310** (648 mg, 8.06 mmol) and diisopropyl ethylamine (0.2 mL, 1.21 mmol) in a sealed tube at RT and heated to 120 °C for 54 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with EtOAc (2 x 50 mL) washed with water (20 mL). The organic extract was dried over sodium sulphate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 20% EtOAc/ hexanes to afford compound **310** (80 mg, 77%) as an off-white solid. **TLC**: 30% EtOAc/ hexanes (R_f : 0.2); **^1H NMR (DMSO- d_6 , 400 MHz)**: δ 7.29 (t, J = 4.8 Hz, 1H), 6.89 (s, 1H), 4.08 (d, J = 5.9 Hz, 2H), 2.97 (s, 6H), 1.38 (s, 9H).

[000254] Synthesis of 4-(aminomethyl)-*N,N*-dimethylthiazol-2-amine hydrochloride (311): To a stirred solution of compound **310** (100 mg, 0.38 mmol) in CH_2Cl_2 (3 mL) under argon atmosphere was added 4 N HCl in 1, 4-dioxane (3 mL) at 0 °C; warmed to RT and stirred for 4 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were

removed *in vacuo*. The crude was titrated with diethyl ether (5 mL) and dried *in vacuo* to afford compound **311** (75 mg, HCl salt) as an off-white solid. **TLC**: 50% EtOAc/ hexanes (R_f : 0.1); **^1H NMR (DMSO- d_6 , 400 MHz)**: δ 8.44 (br s, 3H), 7.38 (s, 1H), 4.10 (q, J = 5.6 Hz, 2H), 3.14 (s, 6H).

Synthesis of (4-ethylthiazol-5-yl) methanamine hydrochloride (**319**)



[000255] Synthesis of ethyl 2-chloro-3-oxopentanoate (313): To a stirred solution of ethyl 3-oxopentanoate **312** (1 g, 6.94 mmol) in CH_2Cl_2 (20 mL) under argon atmosphere was added sulfuryl chloride (0.56 mL, 6.94 mmol) at 0 °C; warmed to RT and stirred for 6 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to afford compound crude **313** (1 g) as colorless liquid. **TLC**: 10% EtOAc/ hexanes (R_f : 0.5); **^1H NMR (DMSO- d_6 , 400 MHz)**: δ 5.66-5.55 (m, 1H), 5.66-5.55 (m, 1H), 4.22 (q, J = 7.1 Hz, 3H), 2.73-2.67 (m, 2H), 1.22 (t, J = 7.1 Hz, 3H), 0.99 (t, J = 7.2 Hz, 3H).

[000256] Synthesis of ethyl 4-ethylthiazole-5-carboxylate (315): To a stirred solution of compound **313** (1 g, crude) in EtOH (10 mL) under inert atmosphere was added thioformamide **314** (3.3 g, 55.55 mmol) at RT; heated at 80 °C and stirred for 24 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude. The crude was purified through column chromatography using 40% EtOAc/ hexanes to

afford compound **315** (300 mg, 30%) as yellow solid. **TLC**: 20% EtOAc/ hexanes (R_f : 0.4); **LC-MS**: 51.18%; 185.9 ($M^+ + 1$); (column; Ascentis Express C18, (50 × 3.0 mm, 2.7 μ m); RT 2.24 min. 0.025% Aq. TFA + 5% ACN: ACN + 5% 0.025% Aq. TFA, 1.2 mL/min).

[000257] Synthesis of (4-ethylthiazol-5-yl) methanol (316): To a stirred solution of compound **315** (300 mg, 1.62 mmol) in THF (10 mL) under inert atmosphere was added lithium aluminium hydride (123 mg, 3.24 mmol) at 0 °C; warmed to RT and stirred for 1 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was quenched with saturated 10% NaOH solution (1 mL), filtered through celite. The filtrate was concentrated *in vacuo* to obtain the crude. The crude was purified through column chromatography using 30% EtOAc/ hexanes to afford compound **316** (200 mg, 86%) as yellow solid. **TLC**: 30% EtOAc/ hexanes (R_f : 0.4); **^1H NMR (DMSO- d_6 , 400 MHz)**: δ 8.86 (s, 1H), 5.45 (t, J = 5.5 Hz, 1H), 4.62 (d, J = 5.5 Hz, 2H), 2.67 (q, J = 7.5 Hz, 2H), 1.17 (t, J = 7.5 Hz, 3H).

[000258] Synthesis of 5-(chloromethyl)-4-ethylthiazole (317): To a stirred solution of compound **316** (200 mg, 1.39 mmol) in CH_2Cl_2 (10 mL) under inert atmosphere were added triethyl amine (0.4 mL, 4.17 mmol), mesyl chloride (0.3 mL, 2.79 mmol) at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was quenched with saturated NaHCO_3 solution (5 mL). The organic extract was dried over sodium sulphate, filtered and concentrated *in vacuo* to obtain compound **317** (200 mg, crude) as yellow solid. **TLC**: 30% EtOAc/ hexanes (R_f : 0.7); **^1H NMR (DMSO- d_6 , 400 MHz)**: δ 9.01 (s, 1H), 5.08 (s, 2H), 2.76 (q, J = 7.5 Hz, 2H), 1.20 (t, J = 7.5 Hz, 3H).

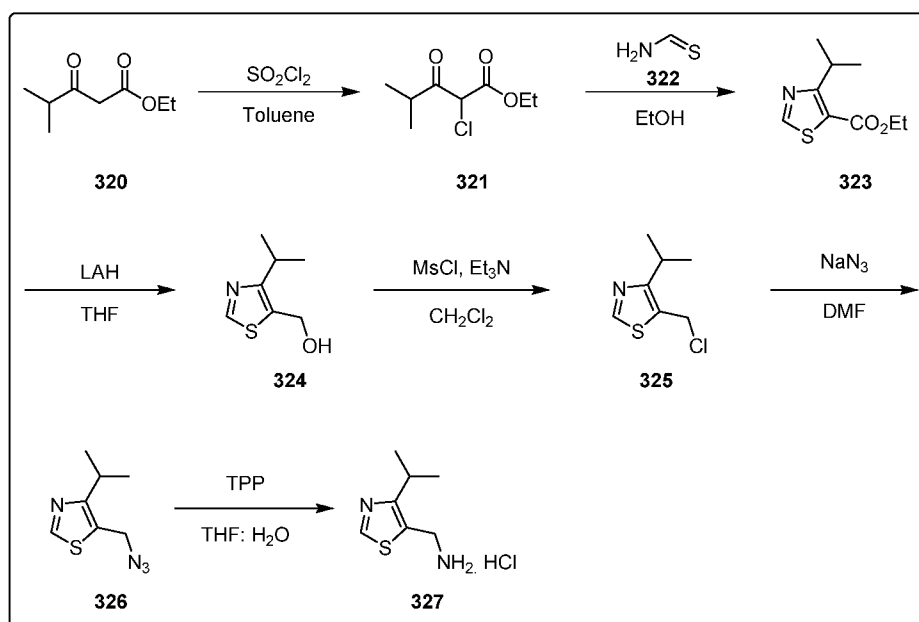
[000259] Synthesis of 5-(azidomethyl)-4-ethylthiazole (318): To a stirred solution of compound **317** (400 mg, 2.48 mmol) in DMF (10 mL) under argon atmosphere was added sodium azide (322 mg, 4.96 mmol) at RT; warmed to 80 °C and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was quenched with ice-cold water (100 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulphate, filtered and concentrated *in vacuo* to afford crude compound **318** (350 mg) as yellow liquid. The crude was carried forward for next step without further purification. **TLC**: 20% EtOAc/ hexanes (R_f : 0.5).

[000260] Synthesis of (4-ethylthiazol-5-yl) methanamine hydrochloride (319): To a stirred

solution of compound **318** (350 mg) in THF: H₂O (4: 1, 20 mL) was added triphenyl phosphine (1.3 g, 5.20 mmol) at RT and stirred for 3 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude.

[000261] The crude was diluted with CH₂Cl₂ (2 mL) cooled to 0 °C; added 4 N HCl 1, 4-dioxane (5 mL) under argon atmosphere and stirred for 1 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude which was titrated with diethyl ether (2 x 5 mL) dried *in vacuo* to afford compound **319** (136 mg) as an off-white solid. **TLC**: 40% EtOAc/ hexanes (*R_f*: 0.2); **LC-MS**: 89.95%; 142.9 (M⁺+1); (column; Ascentis Express C18, (50 × 3.0 mm, 2.7 μm); RT 1.29 min. 0.025% Aq. TFA + 5% ACN: ACN + 5% 0.025% Aq. TFA, 1.2 mL/min).

Synthesis of (4-isopropylthiazol-5-yl) methanamine hydrochloride (**327**)



[000262] **Synthesis of ethyl 2-chloro-4-methyl-3-oxopentanoate (321)**: To a stirred solution of ethyl 4-methyl-3-oxopentanoate **320** (5 g, 31.64 mmol) in Toluene (50 mL) under argon atmosphere was added sulfuryl chloride (4.26 g, 31.64 mmol) at 0 °C; warmed to RT and stirred for 24 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to afford compound crude **321** (6 g) as brown syrup. **TLC**: 10% EtOAc/ hexanes (*R_f*: 0.8).

[000263] Synthesis of ethyl 4-isopropylthiazole-5-carboxylate (323): To a stirred solution of compound **321** (2.1 g) in ethanol (30 mL) under argon atmosphere was added thioformamide **322** (0.667 g, 10.93 mmol) at RT and heated to reflux for 30 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with EtOAc (200 mL), washed with saturated sodium bicarbonate solution (100 mL). The organic extract was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford crude compound **323** (230 mg, 11%) as brown syrup. **TLC:** 10% EtOAc/ hexanes (R_f : 0.5); **LC-MS:** 93.64%; 199.9 ($M^+ + 1$); (column; Ascentis Express C18, (50 × 3.0 mm, 2.7 μ m); RT 2.49 min. 0.025% Aq. TFA + 5% ACN: ACN + 5% 0.025% Aq. TFA, 1.2 mL/min).

[000264] Synthesis of (4-isopropylthiazol-5-yl) methanol (324): To a stirred solution of compound **323** (230 mg, 1.15 mmol) in THF (10 mL) under inert atmosphere was added lithium aluminium hydride (87 mg, 2.28 mmol) at 0 °C; warmed to RT and stirred for 4 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was cooled to 0 °C, quenched with ice-cold water (10 mL), 15% aqueous sodium hydroxide solution (5 mL), filtered through celite and washed with EtOAc (100 mL). The filtrate was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford crude compound **324** (112 mg) as an off-white solid. **TLC:** 20% EtOAc/ hexanes (R_f : 0.2). **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 8.85 (s, 1H), 5.45 (t, J = 5.5 Hz, 1H), 4.64 (d, J = 5.5 Hz, 2H), 3.14-3.07 (m, 1H), 1.19 (d, J = 6.8 Hz, 6H).

[000265] Synthesis of 5-(chloromethyl)-4-isopropylthiazole (325): To a stirred solution of compound **324** (112 mg) in CH₂Cl₂ (10 mL) under inert atmosphere were added triethyl amine (0.21 mL, 2.13 mmol), mesyl chloride (0.08 mL, 0.97 mmol) at 0 °C; warmed to RT and stirred for 5 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with CH₂Cl₂ (50 mL) washed with NaHCO₃ solution (50 mL), brine (50 mL). The organic extract was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford compound **325** (126 mg) as brown thick syrup. **TLC:** 30% EtOAc/ hexanes (R_f : 0.8); **LC-MS:** 87.83%; 175.8 ($M^+ + 1$); (column; Ascentis Express C18, (50 × 3.0 mm, 2.7 μ m); RT 2.30 min. 0.025% Aq. TFA + 5% ACN: ACN + 5% 0.025% Aq. TFA, 1.2 mL/min).

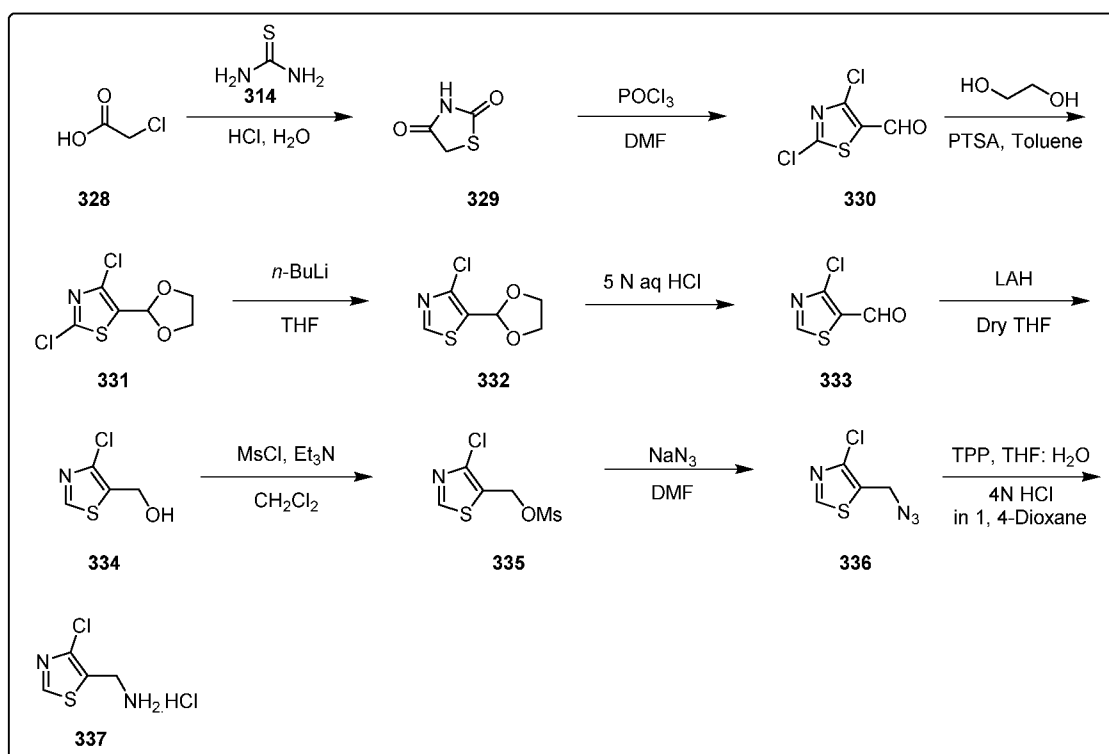
[000266] Synthesis of 5-(azidomethyl)-4-isopropylthiazole (326): To a stirred solution of compound **325** (126 mg, 0.53 mmol) in DMF (10 mL) under inert atmosphere was added sodium

azide (70 mg, 1.07 mmol) at RT and heated to 80 °C for 4 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with EtOAc (75 mL) washed with water (50 mL). The organic extract were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford crude compound **326** (82 mg, 63%) as thick syrup. **TLC:** 30% EtOAc/ hexanes (*R_f*: 0.7); **¹H NMR (DMSO-*d*₆, 500 MHz):** δ 9.01 (s, 1H), 4.74 (s, 2H), 3.30-3.21 (m, 1H), 1.21 (d, *J* = 6.8 Hz, 6H);

[000267] Synthesis of (4-isopropylthiazol-5-yl) methanamine hydrochloride (327): To a stirred solution of compound **326** (80 mg, 0.43 mmol) in THF: H₂O (4: 1, 10 mL) was added triphenyl phosphine (230 mg, 0.87 mmol) at RT and stirred for 4 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude. The obtained solid was further dried using toluene (2 x 5 mL) to obtain the crude.

[000268] The crude compound was dissolved in CH₂Cl₂ (3 mL) added 4 N HCl in 1, 4-dioxane (2 mL) under inert atmosphere at 0 °C and stirred for 1 h. The volatiles were removed *in vacuo* to obtain the crude, which was washed with diethyl ether (2 mL) to afford compound **327** (42 mg, 50%) as an off-white solid. **TLC:** 10% MeOH/ CH₂Cl₂ (*R_f*: 0.2); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 9.02 (s, 1H), 8.26 (br s, 2H), 4.24 (q, *J* = 5.6 Hz, 2H), 3.24-3.17 (m, 1H), 1.19 (d, *J* = 6.8 Hz, 6H).

Synthesis of (4-chlorothiazol-5-yl) methanamine hydrochloride (337)



[000269] Synthesis of thiazolidine-2, 4-dione (329): To a stirred solution of 2-chloroacetic acid **328** (5 g, 52.9 mmol) in H₂O (10 mL) was added thiourea **314** (3.80 g, 52.9 mmol) at 0 °C stirred for 30 min added concentrated HCl (6 mL) dropwise for 15 min; heated at 110 °C and stirred for 24 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was cooled to 0 °C and stirred for 30 min. The precipitated solid was filtered and dried *in vacuo* to afford compound **329** (3.2 g, 47%) as white solid. **TLC:** 30% EtOAc/hexanes (*R_f*: 0.2); **¹H NMR (400 MHz, DMSO-*d*₆):** δ 12.01 (br s, 1H), 4.15 (s, 2H).

[000270] Synthesis of 2, 4-dichlorothiazole-5-carbaldehyde (330): A mixture of compound **329** (2.7 g, 23.07 mmol) in DMF (1.23 mL, 15.98 mmol) at 0 °C under argon atmosphere was added phosphorous oxychloride (8.15 mL, 87.17 mmol) dropwise for 15 min at 0 °C; warmed to RT and stirred for 1 h; heated to 120 °C and stirred for 4 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was poured into ice cold water slowly and extracted with CH₂Cl₂ (3 x 100 mL). The combined organic extracts were washed with saturated NaHCO₃ solution (100 mL), water (100 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through column chromatography using 5% EtOAc/ hexanes to afford compound **330** (1.4 g, 33%) as brown color

oil. **TLC:** 30% EtOAc/ hexanes (R_f : 0.8); **^1H NMR (500 MHz, DMSO- d_6):** δ 9.87 (s, 1H).

[000271] Synthesis of 2,4-dichloro-5-(1, 3-dioxolan-2-yl) thiazole (331): To a stirred solution of compound **330** (1.4 g, 7.73 mmol) in Toluene (20 mL) under argon atmosphere was added ethane-1, 2-diol (1.43 g, 23.20 mmol), *p*-toluenesulfonic acid (133 mg, 0.77mmol) at 0 °C; heated at 110 °C and stirred for 5 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was quenched with 10% aqueous NaHCO_3 solution (50 mL) and extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through column chromatography using 10% EtOAc/ hexanes to afford compound **331** (1.7 g, 98%) as yellow oil. **TLC:** 10% EtOAc/ hexanes (R_f : 0.2); **^1H NMR (400 MHz, CDCl_3):** δ 6.04 (s, 1H), 4.14-4.07 (m, 2H), 4.06-4.00 (m, 2H).

[000272] Synthesis of 4-chloro-5-(1, 3-dioxolan-2-yl) thiazole (332): To a stirred solution of compound **331** (1.7 g, 7.55 mmol) in THF (20 ML) under argon atmosphere was added *n*-butyl lithium (3.9 mL, 9.82 mmol, 2.5 M solution in THF) dropwise for 10 min at -78 °C and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was quenched with ice cold water (50 mL) and extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through column chromatography using 5% EtOAc/ hexanes to afford compound **332** (1.1 g, 76%) as yellow oil. **TLC:** 10% EtOAc/ hexanes (R_f : 0.2); **^1H NMR (CDCl_3 , 500 MHz):** δ 8.74 (s, 1H), 6.16 (s, 1H), 4.19-4.15 (m, 2H), 4.08-4.04 (m, 2H).

[000273] Synthesis of 4-chlorothiazole-5-carbaldehyde (333): To a stirred solution of compound **332** (1.1 g, 5.75 mmol) in THF (10 mL) was added 5 N aqueous HCl in 1, 4-dioxane (6 mL) at 0 °C; warmed to RT and stirred for 3 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was poured into brine (20 mL) extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with saturated sodium bicarbonate (100 mL) dried over sodium sulfate, filtered and concentrated *in vacuo* to afford compound **333** (800 mg, 95%) as yellow oil. **TLC:** 10% EtOAc/ hexanes (R_f : 0.3); **^1H NMR (CDCl_3 , 500 MHz):** δ 10.11 (s, 1H), 9.00 (s, 1H).

[000274] Synthesis of (4-chlorothiazol-5-yl) methanol (334): To a stirred solution of compound **333** (750 mg, 5.10 mmol) in dry THF (20 mL) under inert atmosphere was added lithium aluminium hydride (193 mg, 5.10 mmol) at 0 °C; warmed to RT and stirred for 3 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was cooled to 0 °C, quenched with 30% aqueous sodium hydroxide solution (3 mL) extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford compound **334** (520 mg, 68%) as yellow oil. **TLC:** 10% EtOAc/hexanes (*R_f*: 0.3); **¹H NMR (CDCl₃, 500 MHz):** δ 8.69 (m, 1H), 4.88 (s, 2H).

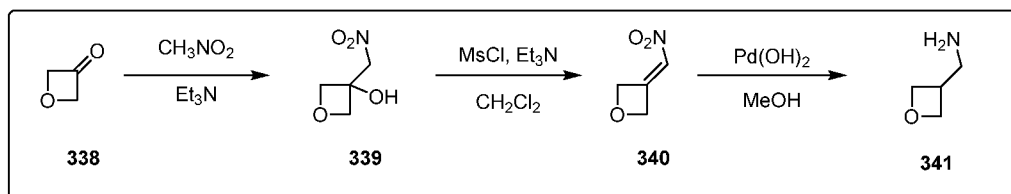
[000275] Synthesis of (4-chlorothiazol-5-yl) methyl methanesulfonate (335): To a stirred solution of compound **334** (520 mg, 3.48 mmol) in CH₂Cl₂ (15 mL) under inert atmosphere were added triethyl amine (1.23 mL, 8.71 mmol) and mesyl chloride (0.34 mL, 4.18 mmol) at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (50 mL) and extracted with CH₂Cl₂ (2 x 50 mL). The combined organic extracts were washed with saturated NaHCO₃ (50 mL) dried over sodium sulfate, filtered and concentrated *in vacuo* to afford compound **335** (600 mg, crude) as brown liquid. **TLC:** 10% EtOAc/ hexanes (*R_f*: 0.8); **¹H NMR (CDCl₃, 500 MHz):** δ 8.74 (s, 1H), 4.79 (s, 2H), 1.44 (s, 3H).

[000276] Synthesis of 5-(azidomethyl)-4-chlorothiazole (336): To a stirred solution of compound **335** (600 mg, 2.64 mmol) in DMF (10 mL) under inert atmosphere was added sodium azide (343 mg, 5.28 mmol) at RT and heated to 100 °C for 4 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with ice cold water (100 mL) and extracted with diethyl ether (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford compound **336** (250 mg, 54%) as yellow oil. **TLC:** 8% EtOAc/ hexanes (*R_f*: 0.5); **¹H NMR (CDCl₃, 400 MHz)** δ 8.74 (s, 1H), 4.58 (s, 2H).

[000277] Synthesis of (4-chlorothiazol-5-yl) methanamine hydrochloride (337): To a stirred solution of compound **336** (250 mg, 1.43 mmol) in THF: H₂O (3:1, 13 ML) was added triphenyl phosphine (752 mg, 2.87 mmol) at RT and stirred for 4 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* and the residue was

acidified with 4 N HCl in 1, 4-dioxane (2 mL) at 0 °C. The volatiles were removed *in vacuo* and the obtained solid was washed with EtOAc (2 mL), diethyl ether (2 mL) to afford compound **337** (110 mg) as yellow solid. **TLC:** 5% MeOH/ CH₂Cl₂ (*R_f*: 0.2); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 9.19 (s, 1H), 8.52 (br s, 3H), 4.24 (q, *J* = 5.6 Hz, 2H);

Synthesis of oxetan-3-ylmethanamine (341)



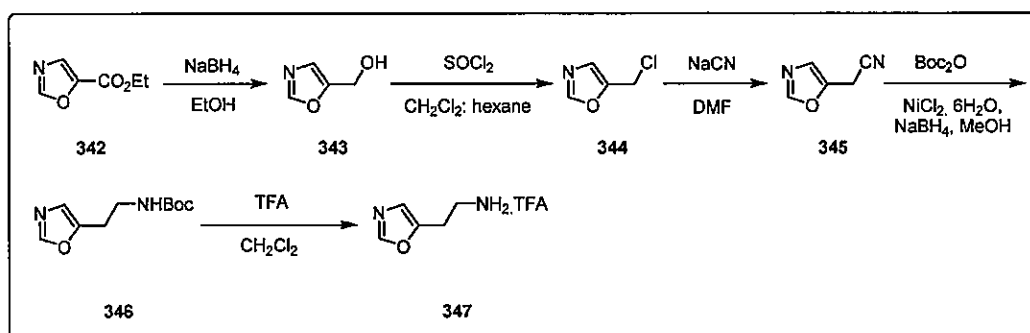
[000278] Synthesis of 3-(nitromethyl) oxetan-3-ol (339): To a stirred solution of oxetan-3-one **338** (500 mg, 0.69 mmol) in nitromethane (1.25 mL) under argon atmosphere was added triethyl amine (0.25 mL) at RT and stirred for 12 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain crude. The crude was purified through silica gel column chromatography using 25% EtOAc/ hexanes to afford compound **339** (750 mg, 81%) as an off white solid. **TLC:** 30% EtOAc/ hexanes (*R_f*: 0.3); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 6.47 (s, 1H), 4.93 (s, 2H), 4.64 (d, *J* = 7.5 Hz, 2H), 4.49 (d, *J* = 7.3 Hz, 2H).

[000279] Synthesis of 3-(nitromethylene) oxetane (340): To a stirred solution of compound **339** (750 mg, 5.63 mmol) in CH₂Cl₂ (10 mL) under inert atmosphere were added triethyl amine (3.17 mL, 22.55 mmol), mesyl chloride (1.20 mL, 15.50 mmol), at 0 °C; cooled -78 °C and stirred for 1 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain crude. The crude was purified through silica gel column chromatography using 25% EtOAc/ hexanes to afford compound **340** (380 mg, 58%) as an off white solid. **TLC:** 10% EtOAc/ hexanes (*R_f*: 0.5); **¹H NMR (CDCl₃, 400 MHz):** δ 6.94-6.92 (m, 1H), 5.68-5.64 (m, 2H), 5.41-5.36 (m, 2H).

[000280] Synthesis of oxetan-3-ylmethanamine (341): To a stirred solution of compound **340** (500 mg, 4.34 mmol) in MeOH (10 mL) under inert atmosphere was added Pd(OH)₂ (100 mg) at RT; heated at 45 °C stirred under hydrogen atmosphere (balloon pressure) for 5 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered

through celite and washed with MeOH (20 mL). The filtrate was evaporated *in vacuo* to obtain the crude which was triturated with diethyl ether (2 x 10 mL) to afford crude compound **341** (100 mg) as pale brown solid. TLC: 10% MeOH / CH₂Cl₂ (*R_f*: 0.2); Mass (*m/z*) (Agilent 6310 Ion Trap): 88.5 (*M*⁺+1).

[000281] Synthesis of 2-(oxazol-5-yl)ethan-1-amine, TFA salt (347)



[000282] Synthesis of oxazol-5-ylmethanol (343): To a stirred solution of ethyl oxazole-5-carboxylate **342** (2 g, 14.18 mmol) in EtOH (20 mL) under argon atmosphere was added sodium borohydride (1.07 g, 28.36 mmol) at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was quenched with saturated ammonium chloride solution (25 mL) and extracted with 5% MeOH/ CH₂Cl₂ (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 5% MeOH/ CH₂Cl₂ to afford compound **343** (810 mg, 58%) as colorless syrup. TLC: 5% MeOH/ CH₂Cl₂ (*R_f*: 0.3); ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 8.28 (s, 1H), 7.04 (s, 1H), 5.36 (t, *J* = 6.0 Hz, 1H), 4.47 (d, *J* = 6.0 Hz, 2H).

[000283] Synthesis of 5-(chloromethyl) oxazole (344): To a stirred solution of compound **343** (800 mg, 8.08 mmol) in CH₂Cl₂: *n*-hexane (1: 1, 10 mL) under argon atmosphere was added thionyl chloride (1.2 mL, 16.16 mmol) at 0 °C; heated to reflux and stirred for 3 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was neutralized with saturated NaHCO₃ solution (20 mL) and extracted with ether (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the

crude compound **344** (700 mg) as colorless syrup. **TLC:** 40% EtOAc/ hexanes (R_f : 0.5); **^1H -NMR (CDCl_3 , 400 MHz):** δ 7.89 (s, 1H), 7.10 (s, 1H), 4.62 (s, 2H).

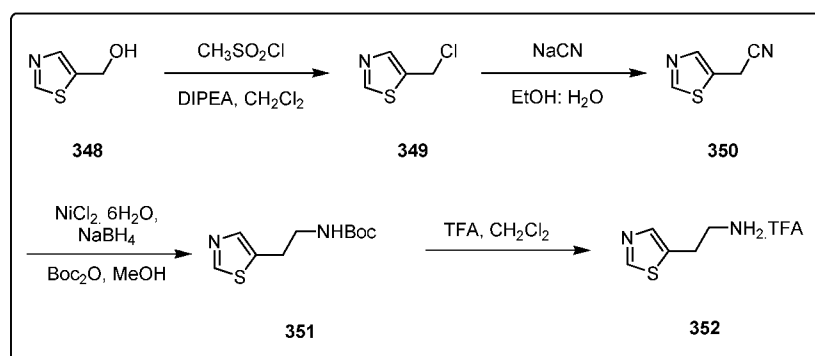
[000284] Synthesis of 2-(oxazol-5-yl) acetonitrile (345): To a stirred solution of compound **344** (700 mg, 5.95 mmol) in DMF (8 mL) under argon atmosphere was added sodium cyanide (1.02 g, 20.85 mmol) at RT; heated to 70 °C and stirred for 4 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (20 mL) and extracted with ether (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude compound **345** (650 mg) as colorless syrup. **TLC:** 40% EtOAc/ hexanes (R_f : 0.3); **^1H -NMR (CDCl_3 , 400 MHz):** δ 7.89 (s, 1H), 7.10 (s, 1H), 3.84 (s, 2H).

[000285] Synthesis of *tert*-butyl (2-(oxazol-5-yl) ethyl) carbamate (346): To a stirred solution of compound **345** (50 mg, 0.46 mmol) in MeOH (3 mL) under argon atmosphere were added Boc-anhydride (0.21 mL, 0.92 mmol), nickel chloride hexahydrate (11 mg, 0.04 mmol), sodium borohydride (122 mg, 3.24 mmol) portion wise for 5 min at 0 °C; warmed to RT and stirred for 6 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with MeOH (10 mL), filtered through celite and the filtrate was concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 30% EtOAc/ hexanes to afford compound **346** (68 mg, 71%) as colorless syrup. **TLC:** 50% EtOAc/ hexanes (R_f : 0.5); **^1H -NMR (CDCl_3 , 400 MHz):** δ 7.82 (s, 1H), 6.85 (s, 1H), 4.64 (br s, 1H), 3.42-3.40 (m, 2H), 2.89 (t, J = 6.4 Hz, 2H), 1.43 (s, 9H).

[000286] Synthesis of 2-(oxazol-5-yl)ethan-1-amine, TFA salt (347):

To a stirred solution of compound **346** (65 mg, 0.30 mmol) in CH_2Cl_2 (3 mL) under argon atmosphere was added trifluoro acetic acid (0.14 mL, 1.83 mmol) at 0 °C; warmed to RT and stirred for 4 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude compound **347** (50 mg) as colorless syrup. **TLC:** 60% EtOAc/ hexanes (R_f : 0.2); **^1H -NMR ($\text{DMSO}-d_6$, 500 MHz):** δ 8.30 (s, 1H), 7.85-7.79 (m, 2H), 7.02 (s, 1H), 3.10-3.05 (m, 2H), 2.98 (t, J = 7.5 Hz, 2H).

Synthesis of 2-(thiazol-5-yl)ethan-1-amine, TFA salt (352)



[000287] Synthesis of 5-(chloromethyl) thiazole (349): To a stirred solution of thiazol-5-ylmethanol **348** (1 g, 8.69 mmol) in CH_2Cl_2 (50 mL) under argon atmosphere were added mesyl chloride (1.09 g, 9.56 mmol) drop wise for 15 min, diisopropyl ethyl amine (1.23 g, 9.56 mmol) at 0-5 °C; warmed to RT and stirred for 4 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude. The crude was washed with saturated NaHCO_3 solution (20 mL) and purified through silica gel column chromatography using 50% EtOAc/ hexanes to afford compound **349** (650 mg, 57%) as yellow liquid. **TLC:** 5% MeOH/ CH_2Cl_2 (R_f : 0.7); **$^1\text{H-NMR}$ (CDCl_3 , 500 MHz):** δ 8.84 (s, 1H), 7.86 (s, 1H), 4.84 (s, 2H).

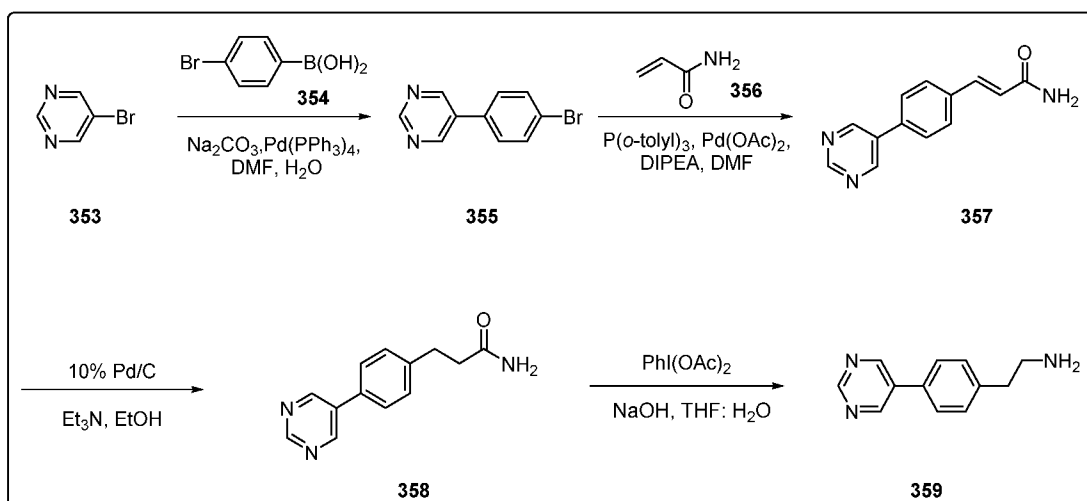
[000288] Synthesis of 2-(thiazol-5-yl) acetonitrile (350): To a stirred solution of compound **349** (650 mg, 4.92 mmol) in EtOH: H_2O (4: 1, 10 mL) under argon atmosphere was added sodium cyanide (361 mg, 7.38 mmol) at RT; heated to 80 °C and stirred for 4 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with water (20 mL) and extracted with EtOAc (2 x 25 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 70% EtOAc/ hexanes to afford compound **350** (250 mg, 41%) as colorless semi-solid. **TLC:** 70% EtOAc/ hexanes (R_f : 0.4); **$^1\text{H-NMR}$ (CDCl_3 , 500 MHz):** δ 8.81 (s, 1H), 7.85 (s, 1H), 3.84 (s, 2H).

[000289] Synthesis of tert-butyl (2-(thiazol-5-yl) ethyl) carbamate (351): To a stirred solution of compound **350** (50 mg, 0.40 mmol) in MeOH (3 mL) under argon atmosphere were added Boc-anhydride (175 mg, 0.80 mmol), nickel chloride hexahydrate (9.75 mg, 0.04 mmol), sodium borohydride (107 mg, 2.82 mmol) portion wise for 5 min at 0-5 °C; warmed to RT and

stirred for 4 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered, washed with EtOAc (2 x 10 mL) and the filtrate was concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 50% EtOAc/ hexanes to afford compound **351** (20 mg, 22%) as brown solid. **TLC:** 70% EtOAc/ hexanes (R_f : 0.6); **$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz):** δ 8.92 (s, 1H), 7.65 (s, 1H), 6.98-6.96 (m, 1H), 3.15 (q, 2H), 2.95 (t, J = 6.8 Hz, 2H), 1.39 (s, 9H).

[000290] Synthesis of 2-(thiazol-5-yl) ethan-1-amine (352): To a stirred solution of compound **351** (20 mg, 0.08 mmol) in CH_2Cl_2 (3 mL) under argon atmosphere was added trifluoro acetic acid (60 mg, 0.53 mmol) at 0-5 °C; warmed to RT and stirred for 4 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude compound **352** (10 mg) as colorless liquid. The crude was carried to the next step without any further purification. **TLC:** 70% EtOAc/ hexanes (R_f : 0.2); **$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz):** δ 9.01 (s, 1H), 7.95-7.89 (m, 2H), 7.76 (s, 1H), 3.16-3.10 (m, 4H).

Synthesis of 2-(4-(pyrimidin-5-yl) phenyl) ethan-1-amine (359)



[000291] Synthesis of 5-(4-bromophenyl) pyrimidine (355): To a stirred solution of 5-bromopyrimidine **353** (1 g, 6.32 mmol) in DMF: H_2O (4: 1, 25 mL) were added sodium carbonate (1 g, 9.43 mmol) and (4-bromophenyl) boronic acid **354** (1.26 g, 6.32 mmol), purged under argon atmosphere for 30 min. To this was added $\text{Pd}(\text{PPh}_3)_4$ (731 mg, 0.63 mmol) at RT; heated to 80 °C and stirred for 2.5 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mass was filtered through celite; the filtrate was diluted with water (100

mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 15% EtOAc/ hexanes to afford compound **355** (1 g, 67%) as white solid. **TLC:** 30% EtOAc/ hexanes (R_f : 0.3); **$^1\text{H-NMR}$ (DMSO- d_6 , 500 MHz):** δ 9.20 (s, 1H), 9.15 (s, 2H), 7.93 (d, J = 8.5 Hz, 2H), 7.74 (d, J = 9.0 Hz, 2H).

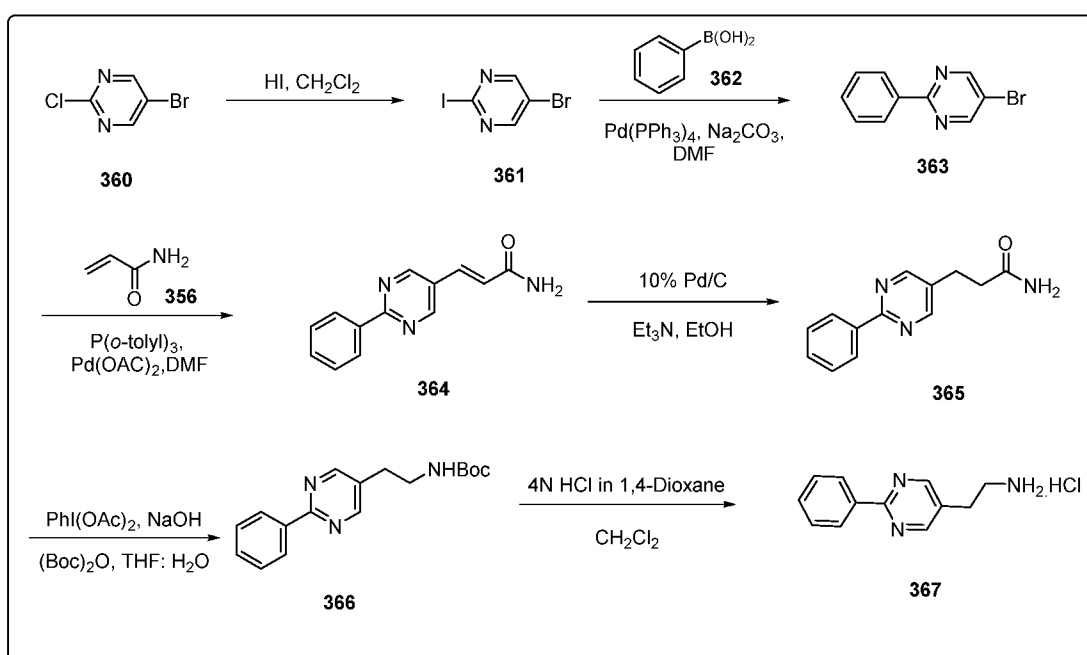
[000292] Synthesis of (E)-3-(4-(pyrimidin-5-yl) phenyl) acrylamide (357): To a stirred solution of 5-(4-bromophenyl) pyrimidine **355** (1 g, 4.27 mmol) in DMF (10 mL) under inert atmosphere was added acrylamide **356** (364 mg, 5.12 mmol) at RT and purged under argon for 10 min. To this were added *o*-tolyl phosphine (142 mg, 0.47 mmol), $\text{Pd}(\text{OAc})_2$ (4.78 mg, 0.021 mmol), and diisopropyl ethyl amine (0.9 mL, 7.32 mmol) at RT; heated to 130 °C and stirred for 5 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered through celite washed with 50% MeOH/ CH_2Cl_2 (2 x 10 mL), the filtrate was concentrated under reduced pressure to afford the crude. The crude was washed with 50% MeOH/ CH_2Cl_2 (2 x 15 mL), dried *in vacuo* to afford compound **357** (600 mg, 62%) as white solid. **TLC:** 40% EtOAc/ hexanes (R_f : 0.2); **$^1\text{H NMR}$ (400MHz, DMSO- d_6)** δ 9.23-9.16 (m, 3H), 7.88 (d, J = 8.3 Hz, 2H), 7.72 (d, J = 8.3 Hz, 2H), 7.56 (br s, 1H), 7.48 (d, J = 15.9 Hz, 1H), 7.14 (br s, 1H), 6.70 (d, J = 15.9 Hz, 1H).

[000293] Synthesis of 3-(4-(pyrimidin-5-yl) phenyl) propanamide (358): To a stirred solution of compound **357** (150 mg, 0.64 mmol) in EtOH (4 mL) under inert atmosphere were added 10% Pd/ C (50 mg) and triethylamine (0.092 mL, 0.64 mmol) at RT and stirred under H_2 (balloon pressure) for 4 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered through celite. The filtrate was concentrated *in vacuo* to obtain the crude which was purified by silicagel column chromatography using 3% MeOH/ CH_2Cl_2 to afford compound **358** (65 mg, 43%) as white solid. **TLC:** 30% EtOAc/ hexanes (R_f : 0.2); **$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz):** δ 9.16 (s, 1H), 9.12 (s, 2H), 7.72 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.29 (br s, 1H), 6.76 (br s, 1H), 2.87 (t, J = 8.0 Hz, 2H), 2.39 (t, J = 8.0 Hz, 2H).

[000294] Synthesis of 2-(4-(pyrimidin-5-yl) phenyl) ethan-1-amine (359): To a stirred solution of compound **358** (65 mg, 0.28 mmol) in THF: H_2O (1:1, 3 mL) were added NaOH (128 mg, 0.91 mmol), phenyl- λ^3 -iodanediyl diacetate (92 mg, 0.28 mmol) at 0 °C and stirred for 1 h.

The reaction was monitored by TLC; after completion of the reaction, the pH of the reaction mixture was adjusted to ~ 2 using 3 N HCl and extracted with CH_2Cl_2 (2 x 50 mL). The pH of the aqueous layer was basified to ~ 8 with 3 N NaOH, extracted with THF (2 x 100 mL). The combined organic extracts were dried over sodium sulphate, filtered and concentrated *in vacuo* to afford crude compound **359** (40 mg) as white solid. **TLC**: 10% MeOH/ CH_2Cl_2 (R_f : 0.3); **^1H -NMR (DMSO- d_6 , 400 MHz)**: δ 9.16 (s, 1H), 9.11 (s, 2H), 7.72 (d, $J = 8.4$ Hz, 2H), 7.37 (d, $J = 8.0$ Hz, 2H), 2.81-2.66 (m, 2H), 1.78-1.69 (m, 2H).

Synthesis of 2-(2-phenylpyrimidin-5-yl) ethan-1-amine hydrochloride (**366**)



[000295] Synthesis of 5-bromo-2-iodopyrimidine (361**)**: To a stirred solution of 5-bromo-2-chloropyrimidine **360** (1 g, 5.16 mmol) in CH_2Cl_2 (10 mL) was added hydrogen iodide (5 mL, 57% aqueous solution) at -10°C ; warmed to 0°C and stirred for 5 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was quenched with solid K_2CO_3 (2 g), diluted with water (100 mL) and extracted with CH_2Cl_2 (2 x 100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain crude compound **361** (1.4 g, 94%) as yellow solid. **TLC**: 10% EtOAc/ hexanes (R_f : 0.7); **^1H -NMR (DMSO- d_6 , 400 MHz)**: δ 8.55 (s, 2H).

[000296] Synthesis of 5-bromo-2-phenylpyrimidine (363**)**: To a stirred solution of compound

361 (1.4 g) in DMF: H₂O (4:1, 20 mL) were added sodium carbonate (783 mg, 7.39 mmol) and phenylboronic acid **362** (451 mg, 3.69 mmol), purged under argon for 30 min. To this was added Pd(PPh₃)₄ (570 mg, 0.49 mmol) at RT; heated to 80 °C and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mass was filtered through celite; the filtrate was diluted with water (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried over sodium sulfate, filtered, concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 2% EtOAc/ hexanes to afford compound **363** (400 mg, 35%) as white solid. **TLC:** 10% EtOAc/ hexanes (*R_f*: 0.9); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 8.83 (s, 2H), 8.41-8.39 (m, 2H), 7.50-7.48 (m, 3H).

[000297] **Synthesis of (*E*)-3-(2-phenylpyrimidin-5-yl) acrylamide (364):** To a stirred solution of compound **363** (300 mg, 1.28 mmol) in DMF (20 mL) under inert atmosphere was added acrylamide **356** (109 mg, 1.53 mmol) at RT and purged under argon for 10 min. To this were added *o*-tolyl phosphine (42 mg, 0.07 mmol), palladium acetate (15.7 mg, 0.07 mmol), and diisopropyl ethyl amine (0.28 mL, 1.53 mmol) at RT; heated to 140 °C and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted water (100 mL) and extracted with 10% MeOH/ CH₂Cl₂ (2 x 50 mL). The combined organic extracts were dried over sodium sulphate, filtered and concentrated *in vacuo* to obtain the crude. The crude compound was triturated with 50% EtOAc/ hexanes (10 mL) and dried *in vacuo* to afford compound **364** (50 mg, 17%) as an off-white solid. **TLC:** 70% EtOAc/ hexanes (*R_f*: 0.2); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 9.10 (s, 2H), 8.43-8.41 (m, 2H), 7.64 (br s, 1H), 7.55-7.54 (m, 3H), 7.47 (d, *J* = 16.0 Hz, 1H), 7.22 (br s, 1H), 6.85 (d, *J* = 16.0 Hz, 1H).

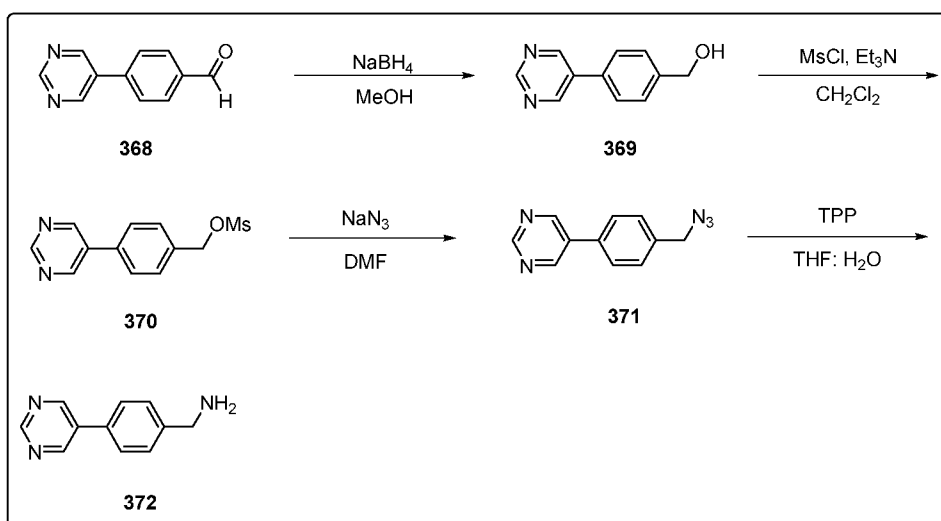
[000298] **Synthesis of 3-(2-phenylpyrimidin-5-yl) propanamide (365):** To a stirred solution of compound **364** (50 mg, 0.22 mmol) in EtOH (2 mL) under inert atmosphere were added triethyl amine (0.032 mL, 0.22 mmol), 10% Pd/ C (17 mg, dry) at RT and stirred under hydrogen atmosphere (balloon pressure) for 4 h. The reaction was monitored by LC-MS; after completion of the reaction, the reaction mixture was filtered through celite and the filtrate was concentrated *in vacuo* to obtain the crude which was triturated with 10% EtOAc/ *n*-pentane (2 x 5 mL) and dried *in vacuo* to afford compound **365** (30 mg, 60%) as an off-white solid. **TLC:** 5% MeOH/ CH₂Cl₂ (*R_f*: 0.5); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 8.76 (s, 2H), 8.37-8.35 (m, 2H), 7.52-7.50

(m, 3H), 7.31 (br s, 1H), 6.80 (br s, 1H), 2.85 (t, $J = 7.2$ Hz, 2H), 2.46 (t, $J = 7.2$ Hz, 2H).

[000299] Synthesis of *tert*-butyl (2-(2-phenylpyrimidin-5-yl) ethyl) carbamate (366): To a stirred solution of compound **365** (15 mg, 0.06 mmol) in THF (2 mL) were added sodium hydroxide (8 mg, 0.2 mmol) in water (0.5 mL), phenyl- λ^3 -iodanediyl diacetate (21 mg, 0.06 mmol) at 0 °C and stirred for 30 min. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with water (25 mL) and extracted with EtOAc (2 x 25 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 20% EtOAc/ hexanes to afford compound **366** (10 mg, 51%) as sticky solid. **TLC:** 50% EtOAc/ hexanes (R_f : 0.9); **$^1\text{H-NMR}$ (CDCl_3 , 400 MHz):** δ 8.65 (s, 2H), 8.42-8.40 (m, 2H), 7.49-7.47 (m, 3H), 4.62 (br s, 1H), 3.43-3.38 (m, 2H), 2.84 (t, $J = 7.2$ Hz, 2H), 1.43 (s, 9H).

[000300] Synthesis of 2-(2-phenylpyrimidin-5-yl) ethan-1-amine hydrochloride (367): To a stirred solution of compound **366** (80 mg, 0.35 mmol) in CH_2Cl_2 (3 ML) was added 4N HCl in 1, 4-Dioxane (0.7 mL) under argon atmosphere at 0 °C; warmed to RT and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude and was washed with 20% CH_2Cl_2 / *n*-pentane (2 x 5 mL) and dried *in vacuo* to afford compound **367** (50 mg, HCl salt) as white solid. **TLC:** 10% MeOH/ CH_2Cl_2 (R_f : 0.1); **$^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz):** δ 8.84 (s, 2H), 8.40-8.37 (m, 2H), 8.07 (br s, 2H), 7.54-7.52 (m, 3H), 3.19-3.14 (m, 2H), 2.97 (t, $J = 7.2$ Hz, 2H).

Synthesis of (4-(pyrimidin-5-yl) phenyl) methanamine (372)



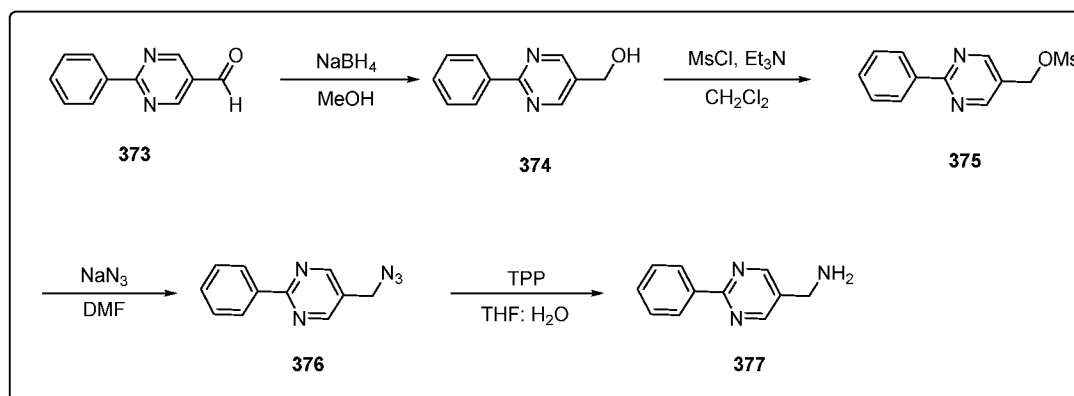
[000301] Synthesis of 4-(pyrimidin-5-yl) phenyl) methanol (369): To a stirred solution of 4-(pyrimidin-5-yl) benzaldehyde **368** (500 mg, 2.71 mmol) in MeOH (20 mL) under argon atmosphere and sodium borohydride (155 mg, 39.99 mmol) at 0°C ; warmed to RT and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, volatiles were removed *in vacuo*. The residue was diluted with brine solution (100 mL), extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulphate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 5% $\text{MeOH}/\text{CH}_2\text{Cl}_2$ to afford compound **369** (260 mg, 51%) as white solid. **TLC:** 20% $\text{EtOAc}/\text{hexanes}$ (R_f : 0.4); **$^1\text{H-NMR}$ (CDCl_3 , 500 MHz):** δ 9.20 (s, 1H), 8.93 (s, 2H), 7.58 (d, $J = 8.5$ Hz, 2H), 7.53 (d, $J = 8.0$ Hz, 2H), 4.79 (s, 2H).

[000302] Synthesis of 4-(pyrimidin-5-yl) benzyl methanesulfonate (370): To a stirred solution of compound **369** (260 mg, 1.39 mmol) in CH_2Cl_2 (10 mL) under argon atmosphere were added triethyl amine (0.3 mL, 2.09 mmol), methane sulfonyl chloride (0.16 mL, 2.09 mmol) at 0°C ; warmed to RT and stirred for 14 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (20 mL), washed with 10% NaHCO_3 solution (30 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain crude compound **370** (300 mg) as thick syrup. The crude was carried to the next step without further purification. **TLC:** 5% $\text{MeOH}/\text{CH}_2\text{Cl}_2$ (R_f : 0.4).

[000303] Synthesis of 5-(4-(azidomethyl) phenyl) pyrimidine (371): To a stirred solution of compound **370** (300 mg, crude) in DMF (6 mL) under argon atmosphere was added sodium azide (74 mg, 1.13 mmol) at RT; heated to 60 °C and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with ice water (20 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain crude. The crude was purified through silica gel column chromatography using 20% EtOAc/ hexanes to afford compound **371** (45 mg) as colorless thick syrup. TLC: 30% EtOAc/ hexanes (*R_f*: 0.6); ¹H-NMR (CDCl₃, 400 MHz): δ 9.22 (s, 1H), 8.96 (s, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 4.43 (s, 2H).

[000304] Synthesis of (4-(pyrimidin-5-yl) phenyl) methanamine (372): To a stirred solution of compound **371** (40 mg, 0.18 mmol) in THF: H₂O (9:1, 2 mL) was added triphenyl phosphine (74 mg, 0.28 mmol) at RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 10% MeOH/ CH₂Cl₂ to afford compound **372** (23 mg, 66%) as an off-white solid. TLC: 10% MeOH/ CH₂Cl₂ (*R_f*: 0.2); ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 9.21 (s, 1H), 9.17 (s, 2H), 8.27 (br s, 2H), 7.87 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 4.07 (s, 2H).

Synthesis of (2-phenylpyrimidin-5-yl) methanamine (377)



[000305] Synthesis of (2-phenylpyrimidin-5-yl) methanol (374): To a stirred solution of 2-phenylpyrimidine-5-carbaldehyde **373** (200 mg, 1.08 mmol) in MeOH (20 mL) under argon

atmosphere was added sodium borohydride (74 mg, 2.17 mmol) at 0 °C; warmed to RT and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with ice cold water (50 mL), extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulphate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 5% MeOH/ CH₂Cl₂ to afford compound **374** (135 mg, 65%) as colorless solid. **TLC:** 40% EtOAc/ MeOH (*R_f*: 0.3); **¹H-NMR (DMSO-*d*₆, 500 MHz):** δ 8.83 (s, 2H), 8.40-8.38 (m, 2H), 7.53-7.51 (m, 3H), 5.45 (t, *J* = 5.5 Hz, 1H), 4.58 (d, *J* = 5.5 Hz, 2H).

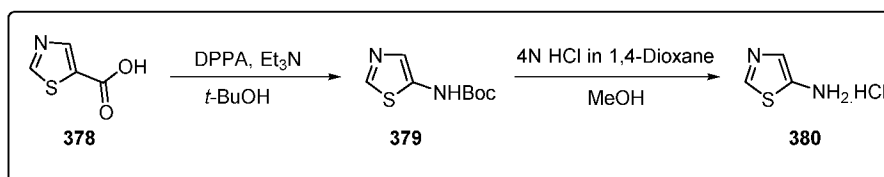
[000306] Synthesis of (2-phenylpyrimidin-5-yl) methyl methanesulfonate (375): To a stirred solution of compound **374** (130 mg, 0.69 mmol) in CH₂Cl₂ (5 mL) under argon atmosphere were added triethyl amine (0.4 mL, 2.09 mmol) and methane sulfonyl chloride (0.07 mL, 0.84 mmol) at 0 °C; warmed to RT and stirred for 30 min. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted CH₂Cl₂ (50 mL), washed with water (2 x 20 mL). The organic extract was dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain crude compound **375** (150 mg) as yellow oil. The crude was carried to the next step without further purification. **TLC:** 50% EtOAc/ hexanes (*R_f*: 0.5); **¹H-NMR (DMSO-*d*₆, 500 MHz):** 9.00 (t, *J* = 10.0 Hz, 2H), 8.42-8.41 (m, 2H), 7.56-7.55 (m, 3H), 5.40 (s, 2H), 3.32 (s, 3H).

[000307] Synthesis of 5-(azidomethyl)-2-phenylpyrimidine (376): To a stirred solution of compound **375** (150 mg) in DMF (6 mL) under argon atmosphere was added sodium azide (56 mg, 0.76 mmol) at RT; heated to 60 °C and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with ice water (20 mL) and extracted with diethyl ether (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain crude. The crude was purified through silica gel column chromatography using 20% EtOAc/ hexanes to afford compound **376** (60 mg, 49%) as colorless syrup. **TLC:** 40% EtOAc/ hexanes (*R_f*: 0.9); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 8.94 (s, 2H), 8.41 (dd, *J* = 6.8, 3.0 Hz, 2H), 7.56-7.53 (m, 3H), 4.63 (s, 2H).

[000308] Synthesis of (2-phenylpyrimidin-5-yl) methanamine (377): To a stirred solution of compound **376** (90 mg, 0.42 mmol) in THF: H₂O (9:1, 4 mL) was added triphenyl phosphine

(167 mg, 0.63 mmol) at RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 10% MeOH/ CH₂Cl₂ to afford compound **377** (30 mg, 38%) as yellow solid. TLC: 10% MeOH/ CH₂Cl₂ (*R_f*: 0.2); ¹H NMR (DMSO-*d*₆, 500 MHz): δ 8.96 (s, 2H), 8.40 (d, *J* = 3.9 Hz, 2H), 7.59-7.45 (m, 3H), 6.84 (br s, 2H), 4.01 (s, 2H).

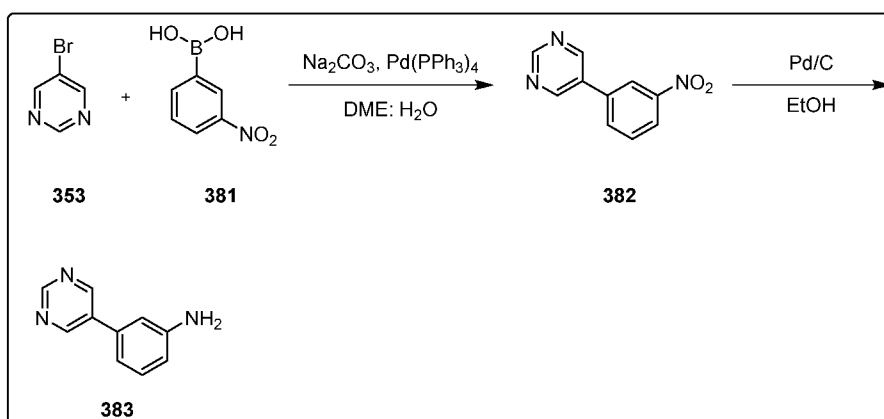
Synthesis of thiazol-5-amine hydrochloride (**380**)



[000309] **Synthesis of *tert*-butyl thiazol-5-ylcarbamate (**379**):** To a stirred solution of thiazole-5-carboxylic acid **378** (400 mg, 3.1 mmol) in *t*-butanol (6 mL) were added diphenylphosphonic azide (1.34 mL, 6.18 mmol) and triethyl amine (0.89 mL, 6.18 mmol) at RT and heated to 100 °C for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 30% EtOAc/ hexanes to afford compound **379** (300 mg, 48%) as white solid. TLC: 50% EtOAc/ hexanes (*R_f*: 0.8); ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 10.60 (br s, 1H), 8.51 (s, 1H), 8.40 (s, 1H), 1.49 (s, 9H).

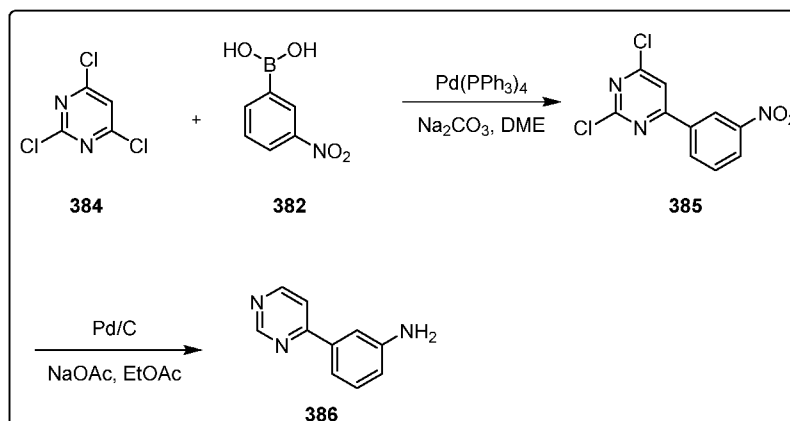
[000310] **Synthesis of thiazol-5-amine hydrochloride (**380**):** To a stirred solution of compound **379** (300 mg, 1.5 mmol) in MeOH (5 mL) was added 4 N HCl in 1, 4-Dioxane (5 mL) under argon atmosphere at 0 °C; warmed to RT and stirred for 3 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude. The crude was washed with *n*-pentane (2 x 5 mL) and dried *in vacuo* to afford compound **380** (150 mg, HCl salt) as pale yellow solid. TLC: 50% EtOAc/ hexanes (*R_f*: 0.1); ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 9.10 (s, 1H), 7.22 (s, 1H).

Synthesis of 3-(pyrimidin-5-yl) aniline (**383**)



[000311] Synthesis of 5-(3-nitrophenyl) pyrimidine (382): To a stirred solution of 5-bromopyrimidine **353** (2 g, 12.58 mmol) and (3-nitrophenyl) boronic acid **381** (2.3 g, 13.84 mmol) in 1, 2-dimethoxy ethane: H₂O (4:1, 20 mL) under inert atmosphere were added sodium carbonate (2.66 g, 25.17 mmol) at RT and purged under argon atmosphere for 20 min. To this was added Pd(PPh₃)₄ (726 mg, 0.62 mmol) and heated to 110 °C for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The obtained solid was filtered, dried *in vacuo* to obtain the crude which was purified through silicagel column chromatography in 50% EtOAc/ hexanes to afford compound **382** (2.5 g, 68%) as an off-white solid. **TLC:** 60% EtOAc/ hexanes (*R_f*: 0.3); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 9.27 (s, 3H), 8.66-8.63 (m, 1H), 8.37-8.25 (m, 2H), 7.84 (t, *J* = 8.0 Hz, 1H).

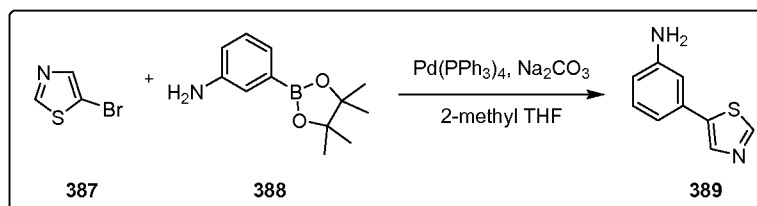
[000312] Synthesis of 3-(pyrimidin-5-yl) aniline (383): To a stirred solution of compound **382** (1.7 g, 8.45 mmol) in EtOH (30 mL) under inert atmosphere was added 10% Pd/C (500 mg) under argon atmosphere and stirred under H₂ atmosphere (balloon pressure) for 5 h. After completion of the reaction, the reaction mixture was filtered through celite, washed with 5% MeOH/ CH₂Cl₂ (50 mL). The filtrate was concentrated *in vacuo* to obtain the crude which was triturated with mixture of ether: pentane (1:1, 10 ML) and dried *in vacuo* to afford compound **383** (1.2 g, 86%) as an off-white solid. **TLC:** 70% % EtOAc/ hexanes (*R_f*: 0.2); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 9.15 (s, 1H), 9.00 (s, 2H), 7.17 (t, *J* = 7.8 Hz, 1H), 6.91 – 6.86 (m, 2H), 6.69-6.64 (m, 1H), 5.27 (s, 3H).

Synthesis of 3-(pyrimidin-4-yl) aniline (386)

[000313] Synthesis of 2, 4-dichloro-6-(3-nitrophenyl) pyrimidine (385): To a stirred solution of 2, 4, 6-trichloropyrimidine **384** (500 mg, 2.76 mmol) and (3-nitrophenyl) boronic acid **382** (594 mg, 2.76 mmol) in 1, 2-dimethoxy ethane (10 mL) under inert atmosphere were added sodium carbonate (878 mg, 8.28 mmol) at RT and purged under argon atmosphere for 20 min. To this was added $\text{Pd(PPh}_3)_4$ (159 mg, 0.13 mmol) and heated to 80 °C for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered through celite and the filtrate was concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 10% EtOAc/ hexanes to afford crude compound **385** (200 mg) as yellow solid which was carried forward for next step. **TLC:** 10% EtOAc/ hexanes (R_f : 0.7).

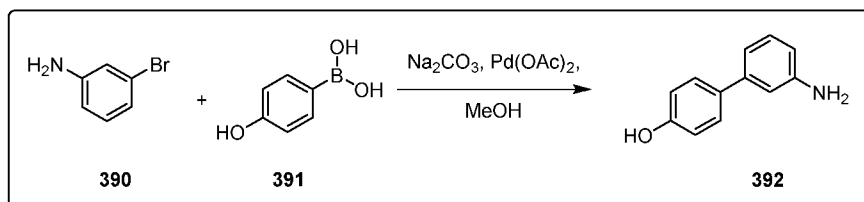
[000314] Synthesis of 3-(pyrimidin-4-yl) aniline (386): To a stirred solution of compound **385** (200 mg, crude) in EtOAc (50 mL) under inert atmosphere were added sodium acetate (304 mg, 3.71 mmol), 10% Pd/C (100 mg, wet) under argon atmosphere and stirred under H_2 atmosphere (balloon pressure) for 6 h. After completion of the reaction, the reaction mixture was filtered through celite, washed with 50% MeOH/ CH_2Cl_2 (50 mL). The filtrate was concentrated *in vacuo* to obtain the crude which was purified through silicagel column chromatography in 90% EtOAc/ hexanes to afford compound **386** (100 mg, 78%) as an off-white solid. **TLC:** 70% EtOAc/ hexanes (R_f : 0.4); **$^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$):** δ 9.19 (s, 1H), 8.80 (d, $J = 5.4$ Hz, 1H), 7.91 (dd, $J = 5.4, 1.4$ Hz, 1H), 7.45-7.43 (m, 1H), 7.30 (d, $J = 7.7$ Hz, 1H), 7.18 (t, $J = 7.8$ Hz, 1H), 6.74 (d, $J = 7.5$ Hz, 1H), 5.31 (s, 2H).

Synthesis of 3-(thiazol-5-yl) aniline (389)



[000315] To a stirred solution of 5-bromothiazole **387** (350 mg, 2.13 mmol) in 2-methyl THF (5 mL) under inert atmosphere were added 3-aminophenylboronic acid pinacol ester **388** (600 mg, 2.35 mmol), sodium carbonate (565 mg, 5.33 mmol), at RT and stirred under argon atmosphere for 20 min. To this was added $\text{Pd(dppf)}_2\text{Cl}_2$ (78 mg, 0.106 mmol) and heated to 110 °C and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered through celite and the filtrate was concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 80% EtOAc/hexanes to afford compound **389** (200 mg, 52%) as yellow syrup. **TLC**: 70% EtOAc/ hexanes (R_f : 0.4); **LC-MS**: 84.49%; 176.8 ($\text{M}^+ + 1$); (column; Ascentis Express C18, (50 × 3.0 mm, 2.7 μm); RT 1.40 min. 0.025% Aq. TFA + 5% ACN: ACN + 5% 0.025% Aq. TFA, 1.2 mL/min).

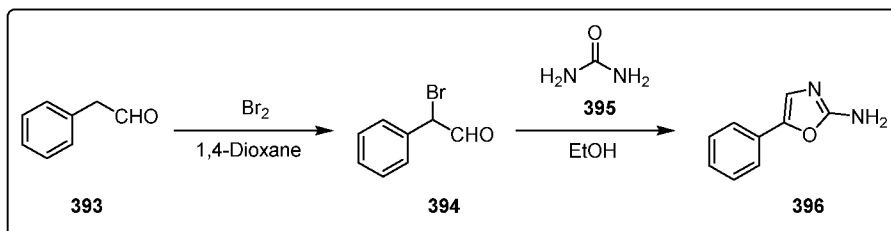
Synthesis of 3'-amino-[1, 1'-biphenyl]-4-ol (392)



[000316] To a stirred solution of 3-bromoaniline **390** (400 mg, 2.32 mmol) and (4-hydroxyphenyl) boronic acid **391** (353 mg, 2.55 mmol) in MeOH (4 mL) under inert atmosphere were added sodium carbonate (493 mg, 4.65 mmol) at RT and purged under argon atmosphere for 20 min. To this was added Pd(OAc)_2 (156 mg, 0.23 mmol) and heated to 80 °C for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered through celite, washed with MeOH (20 mL). The filtrate was concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography in 20% EtOAc/ hexanes to afford compound **392** (160 mg) as brick red solid. **TLC**: 30% EtOAc/

hexanes (R_f : 0.4); **LC-MS**: 67.89%; 185.9 ($M^+ + 1$); (column; Ascentis Express C18, (50 × 3.0 mm, 2.7 μ m); RT 2.10 min. 0.025% Aq. TFA + 5% ACN: ACN + 5% 0.025% Aq. TFA, 1.2 mL/min).

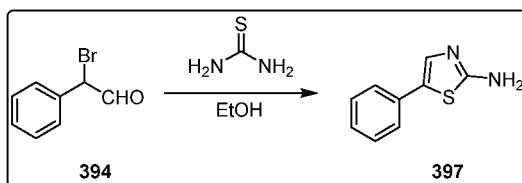
Synthesis of 5-phenyloxazol-2-amine (396)



[000317] Synthesis of 2-bromo-2-phenylacetaldehyde (394): To a stirred solution of 2-phenylacetaldehyde **393** (500 mg, 4.16 mmol) in 1, 4-Dioxane (2 mL) under inert atmosphere was added bromine (0.27 mL, 4.99 mmol) at 0 °C and stirred for 20 min; warmed to RT and stirred for 1 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to afford crude compound **394** (800 mg) as green syrup. The crude was carried forward for next step without further purification. **TLC**: 10% EtOAc/ hexanes (R_f : 0.7);

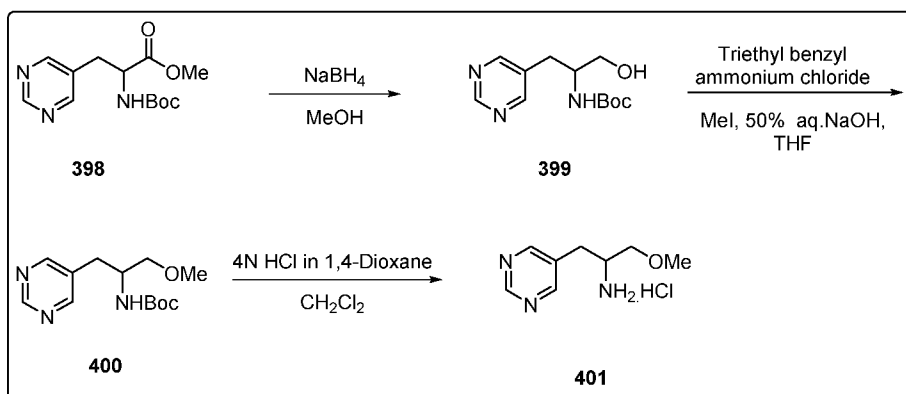
[000318] Synthesis of 5-phenyloxazol-2-amine (396): To a stirred solution of compound **394** (800 mg, crude) in EtOH (10 mL) under inert atmosphere was added urea **395** (482 mg, 8.04 mmol) at RT; heated at 80 °C and stirred for 6 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* and the residue was diluted with water (60 mL). The pH was neutralized with 10% aqueous NaHCO_3 solution (10 mL) and extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through flash column chromatography using 2-3% MeOH/ CH_2Cl_2 to afford compound **396** (200 mg, 32%) as an off-white solid. **TLC**: 5% MeOH/ CH_2Cl_2 (R_f : 0.5); **^1H NMR (400 MHz, DMSO- d_6)**: δ 7.45 (d, J = 7.2 Hz, 2H), 7.36 (t, J = 7.8 Hz, 2H), 7.21-7.16 (m, 2H), 6.81 (s, 2H);

Synthesis of 5-phenylthiazol-2-amine (397)



[000319] Synthesis of 5-phenylthiazol-2-amine (397): To a stirred solution of 2-bromo-2-phenylacetaldehyde **394** (860 mg, crude) in EtOH (20 mL) under inert atmosphere was added thiourea (658 mg, 8.64 mmol) at RT; heated at 80 °C and stirred for 8 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude. The pH of the residue was neutralized with 10% aqueous NaHCO₃ solution (10 mL) and extracted with EtOAc (2 x 200 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through flash column chromatography using 2-3% MeOH/ CH₂Cl₂ to afford compound **397** (500 mg, 66%) as an off-white solid. **TLC:** 5% MeOH/ CH₂Cl₂ (*R_f*: 0.6); **¹H NMR (400 MHz, DMSO-*d*₆):** δ 7.43-7.38 (m, 3H), 7.32 (t, *J* = 7.8 Hz, 2H), 7.17 (tt, *J* = 7.5, 0.9 Hz, 1H), 7.12 (s, 2H).

Synthesis of 1-methoxy-3-(pyrimidin-5-yl) propan-2-amine hydrochloride (401)



[000320] Synthesis of *tert*-butyl (1-hydroxy-3-(pyrimidin-5-yl) propan-2-yl) carbamate (399): To a stirred solution of methyl 2-((*tert*-butoxycarbonyl) amino)-3-(pyrimidin-5-yl) propanoate **398** (200 mg, 0.71 mmol) in MeOH (5 mL) under inert atmosphere was added sodium borohydride (105 mg, 2.84 mmol) at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (25 mL) and extracted with 10% MeOH/ CH₂Cl₂ (5 x 25 mL). The combined

organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 8% MeOH/ CH₂Cl₂ to afford compound **399** (110 mg, 61%) as an off-white solid. **TLC:** 10% MeOH/ CH₂Cl₂ (*R_f*: 0.4); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 8.99 (s, 1H), 8.61 (s, 2H), 6.70 (d, *J* = 9.0 Hz, 1H), 4.82 (t, *J* = 5.4 Hz, 1H), 3.61 (br s, 2H), 3.45-3.34 (m, 2H), 2.93-2.82 (m, 1H), 1.26 (s, 9H)

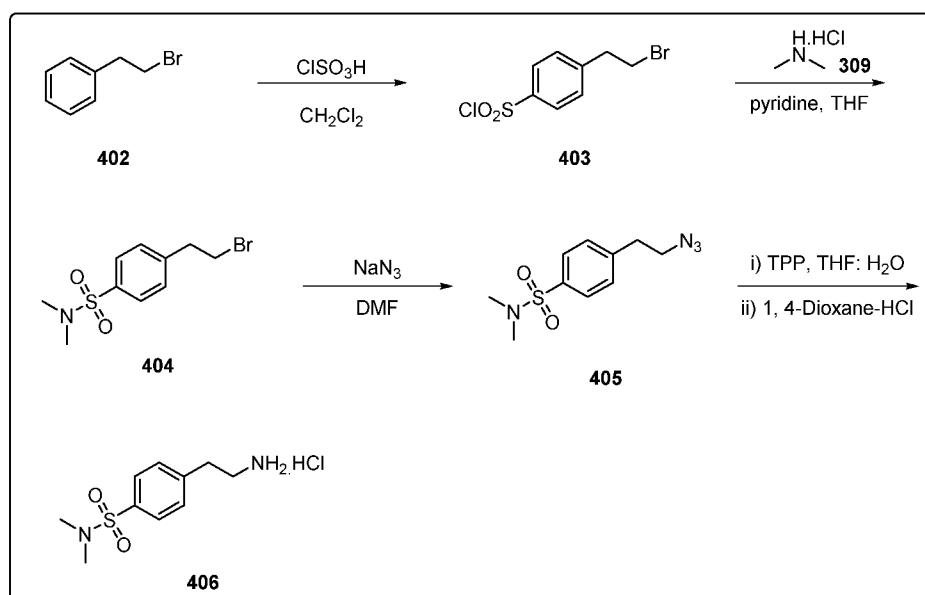
[000321] Synthesis of *tert*-butyl (1-methoxy-3-(pyrimidin-5-yl) propan-2-yl) carbamate

(400): To a stirred solution of compound **399** (100 mg, 0.39 mmol) in THF (10 mL) were added triethyl benzyl ammonium chloride (9 mg, 0.03 mmol), 50% aqueous sodium hydroxide solution (3.5 mL) and methyl iodide (0.02 mL, 0.39 mmol) at 0 °C; warmed to RT and stirred for 24 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (25 mL) and extracted with EtOAc (3 x 25 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 3% MeOH/ CH₂Cl₂ to afford compound **400** (70 mg, 67%) as colorless syrup. **TLC:** 5% MeOH/ CH₂Cl₂ (*R_f*: 0.5); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 9.00 (s, 1H), 8.62 (s, 2H), 6.84 (d, *J* = 8.8 Hz, 1H), 3.78 (brs, 2H), 3.29-3.23 (m, 5H), 2.85 (dd, *J* = 13.8, 4.1 Hz, 1H), 1.28-1.21 (m, 9H).

[000322] Synthesis of 1-methoxy-3-(pyrimidin-5-yl) propan-2-amine hydrochloride (401):

To a stirred solution of compound **400** (60 mg, 0.22 mmol) in CH₂Cl₂ (3 mL) was added 4 N HCl in 1, 4-Dioxane (1 mL) under argon atmosphere at 0 °C; warmed to RT and stirred for 3 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude. The crude was washed with *n*-pentane (2 x 5 mL) and dried *in vacuo* to afford compound **401** (40 mg, HCl salt) as brown solid. **TLC:** 5% MeOH/ CH₂Cl₂ (*R_f*: 0.1); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 9.11 (s, 1H), 8.75 (s, 2H), 8.24 (br s, 2H), 3.68-3.59 (m, 1H), 3.53-3.48 (m, 1H), 3.39 (dd, *J* = 10.5, 5.7 Hz, 1H), 3.30 (s, 3H), 2.95 (t, *J* = 7.3 Hz, 2H).

Synthesis of 4-(2-aminoethyl)-*N*, *N*-dimethylbenzenesulfonamide hydrochloride (406)



[000323] Synthesis of 4-(2-bromoethyl) benzenesulfonyl chloride (403): To a stirred solution of (2-bromoethyl) benzene **402** (5 g, 27.02 mmol) in CH_2Cl_2 (15 mL) under argon atmosphere was added chlorosulfonic acid (5.4 mL, 81.08 mmol) at 0°C ; warmed to RT and stirred for 3 h. The reaction was monitored by TLC; after completion the reaction, the reaction mixture was poured into ice-cold water (100 mL) extracted with CH_2Cl_2 (2 x 150 mL). The combined organic extracts were washed with brine (100 mL), separated dried over sodium sulfate, filtered and concentrated *in vacuo* to afford crude compound **403** (5 g) as colorless thick syrup. TLC: 10% EtOAc/ hexanes (R_f : 0.6); ^1H -NMR (DMSO- d_6 , 400 MHz): δ 8.00 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.8 Hz, 2H), 3.62 (t, J = 7.2 Hz, 2H), 3.30 (t, J = 7.2 Hz, 2H).

[000324] Synthesis of 4-(2-bromoethyl)-N,N-dimethylbenzenesulfonamide (404): To a stirred solution of compound **403** (5 g, crude) in THF (100 mL) under argon atmosphere were added pyridine (14.37 mL, 176.05 mmol), dimethylamine hydrochloride **309** (7.1 g, 88.02 mmol) at 0°C ; warmed to RT and stirred for 1 h. The reaction was monitored by TLC; after completion the reaction, the volatiles were removed *in vacuo*. The residue was diluted with CH_2Cl_2 (500 mL) and washed with 1 N HCl (15 mL). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain crude. The crude was titrated with pentane (30 mL) and dried *in vacuo* to afford compound **404** (3.5 g, 68%) as an off-white solid. TLC: 20% EtOAc/ hexane (R_f : 0.5); ^1H NMR (CDCl_3 , 400 MHz): δ 7.74 (d, J = 8.4 Hz, 2H), 7.39 (d, J =

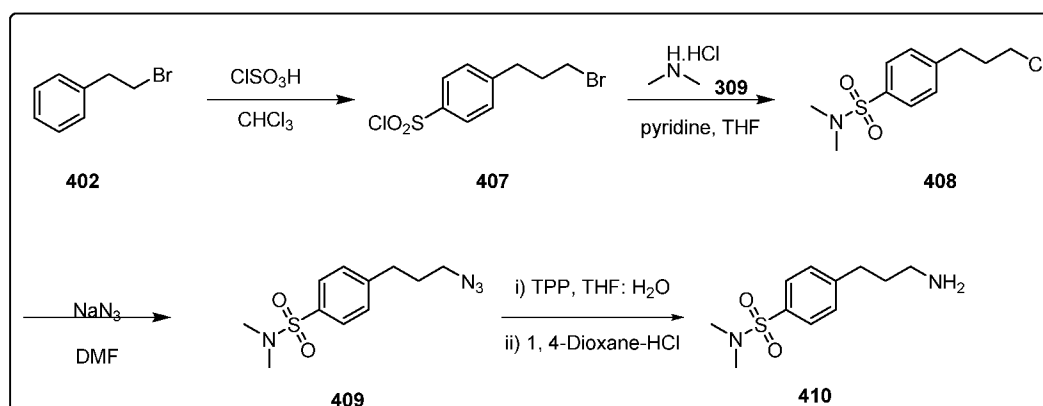
8.5 Hz, 2H), 3.60 (t, $J = 7.2$ Hz, 2H), 3.25 (t, $J = 7.3$ Hz, 2H), 2.72 (s, 6H).

[000325] Synthesis of 4-(2-azidoethyl)-*N,N*-dimethylbenzenesulfonamide (405): To a stirred solution of compound **404** (500 mg, 1.71 mmol) in DMF (10 mL) under inert atmosphere was added sodium azide (335 mg, 5.15 mmol) at RT and heated to 80 °C for 2 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with ice-cold water (20 mL) and extracted with CH₂Cl₂ (2 x 200 mL). The combined organic extracts were dried under sodium sulfate, filtered and concentrated *in vacuo* to afford compound **405** (350 mg, 80%) as thick syrup. TLC: 20% EtOAc/ hexane (R_f : 0.6); ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 7.73 (d, $J = 8.4$ Hz, 2H), 7.40 (d, $J = 6.8$ Hz, 2H), 3.56 (t, $J = 6.8$ Hz, 2H), 2.97 (t, $J = 6.8$ Hz, 2H), 2.71 (s, 6H).

[000326] Synthesis of 4-(2-aminoethyl)-*N,N*-dimethylbenzenesulfonamide hydrochloride (406): To a stirred solution of compound **405** (350 mg, 1.37 mmol) in a mixture of THF: H₂O (4:1, 10 mL) was added triphenyl phosphine (1.08 g, 4.13 mmol) at RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 3-5% MeOH/ CH₂Cl₂ to afford free amine (200 mg) as thick syrup.

[000327] To a stirred solution of the free amine (200 mg) in CH₂Cl₂ (2 mL) under argon atmosphere was added 4 N HCl in 1, 4-dioxane (0.5 mL) at 0 °C and stirred for 10 min. The volatiles were removed *in vacuo* to obtain the crude which was washed with diethyl ether (2 x 5 mL) and dried *in vacuo* to afford compound **406** (125 mg, 35%) as white solid. TLC: 10% MeOH/ CH₂Cl₂ (R_f : 0.2); ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 8.04 (br s, 2H), 7.70 (d, $J = 8.4$ Hz, 2H), 7.54 (d, $J = 8.4$ Hz, 2H), 3.15-3.05 (m, 2H), 3.01-2.98 (m, 2H), 2.60 (s, 6H).

Synthesis of 4-(3-aminopropyl)-*N,N*-dimethylbenzenesulfonamide hydrochloride (410)



[000328] Synthesis of 4-(3-bromopropyl) benzenesulfonyl chloride (407): To a stirred solution of (2-bromoethyl) benzene **402** (5 g, 27.02 mmol) in CHCl_3 (15 mL) under argon atmosphere was added chlorosulfonic acid (5.4 mL, 81.08 mmol) at 0°C ; warmed to RT and stirred for 3 h. The reaction was monitored by TLC; after completion the reaction, the reaction mixture was poured into ice-cold water (100 mL) extracted with CH_2Cl_2 (2 x 100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford crude compound **407** (5 g) as colorless thick syrup. **TLC:** 10% EtOAc/ hexanes (R_f : 0.4); **^1H NMR (CDCl_3 , 400 MHz):** δ 7.97 (d, J = 8.8 Hz, 2H), 7.45 (d, J = 8.8 Hz, 2H), 3.40 (t, J = 6.4 Hz, 2H), 2.93 (t, J = 7.2 Hz, 2H), 2.24-2.17 (m, 2H).

[000329] Synthesis of 4-(3-chloropropyl)-N,N-dimethylbenzenesulfonamide (408): To a stirred solution of compound **407** (5 g, crude) in THF (100 mL) under argon atmosphere were added pyridine (14.42 mL, 176.6 mmol), dimethylamine hydrochloride **309** (7.2 g, 88.33 mmol) at 0°C ; warmed to RT and stirred for 1 h. The reaction was monitored by TLC; after completion the reaction, the volatiles were removed the *in vacuo*. The residue was diluted with water (100 mL) and extracted with CH_2Cl_2 (2 x 100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 20% EtOAc/ hexanes to afford compound **408** (3 g) as white sticky solid. **TLC:** 20% EtOAc/ hexanes (R_f : 0.5); **^1H NMR (CDCl_3 , 400 MHz):** δ 7.71 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 3.53 (t, J = 6.4 Hz, 1H), 3.40 (t, J = 6.4 Hz, 1H), 2.87 (t, J = 7.2 Hz, 2H), 2.71 (s, 6H), 2.23-2.08 (m, 2H).

[000330] Synthesis of 4-(3-azidopropyl)-N,N-dimethylbenzenesulfonamide (409): To a stirred solution of compound **408** (3 g, 9.83 mmol) in DMF (50 mL) under inert atmosphere was

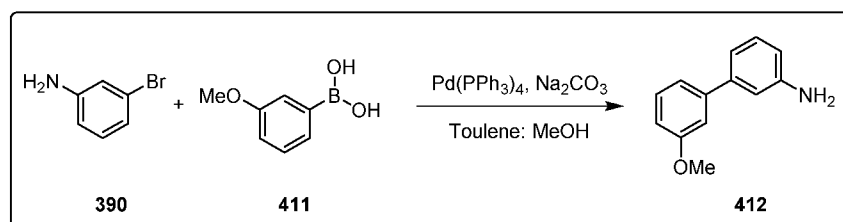
added sodium azide (1.91 g, 29.50 mmol) at RT and heated to 70-80 °C for 2 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with ice-cold water (20 mL) and extracted with EtOAc (2 x 150 mL). The combined organic extracts were dried under sodium sulfate, filtered and concentrated *in vacuo* to afford compound **409** (2 g, 76%) as colorless thick syrup. **TLC:** 20% EtOAc/ hexane (R_f : 0.6); **^1H NMR (CDCl_3 , 500 MHz):** δ 7.71 (d, J = 8.1 Hz, 2H), 7.36 (d, J = 8.1 Hz, 2H), 3.32 (t, J = 6.7 Hz, 2H), 2.82-2.77 (m, 2H), 2.71 (s, 6H), 1.98-1.91 (m, 2H).

[000331] Synthesis of 4-(3-aminopropyl)-N, N-dimethylbenzenesulfonamide

hydrochloride (410): To a stirred solution of compound **409** (2.35 g, 8.76 mmol) in a mixture of THF: H_2O (4: 1, 100 mL) was added triphenyl phosphine (6.89 g, 26.30 mmol) at RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 15% MeOH/ CH_2Cl_2 to afford free amine (2 g) as thick syrup.

[000332] To a stirred solution of the above compound (2 g) in CH_2Cl_2 (20 mL) under argon atmosphere was added 4 N HCl in 1, 4-dioxane (10 mL) at 0 °C and stirred for 10 min. The solvent was decanted and the obtained solid was dried *in vacuo* to afford compound **410** (1.5 g, 70%) as white solid. **TLC:** 10% MeOH/ CH_2Cl_2 (R_f : 0.2); **^1H -NMR ($\text{DMSO}-d_6$, 400 MHz):** δ 8.08 (br s, 3H), 7.68 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 2.81-2.75 (m, 4H), 2.59 (s, 6H), 1.94-1.86 (m, 2H).

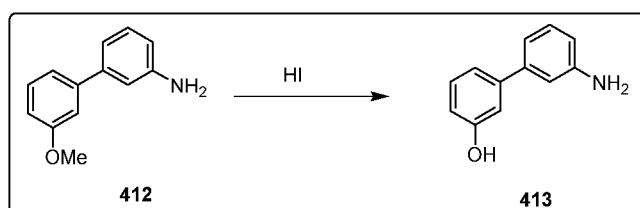
[000333] Synthesis of 3'-methoxy-[1, 1'-biphenyl]-3-amine (412)



[000334] To a stirred solution of 3-bromoaniline **390** (1 g, 5.81 mmol) and (3-methoxyphenyl) boronic acid **411** (883 mg, 5.81 mmol) in Toluene: MeOH (1:1, 20 mL) under inert atmosphere were added sodium carbonate (2.15 g, 20.34 mmol in 10 mL of H_2O) at RT and purged under argon atmosphere for 20 min. To this was added $\text{Pd}(\text{PPh}_3)_4$ (335 mg, 0.28 mmol) and heated to

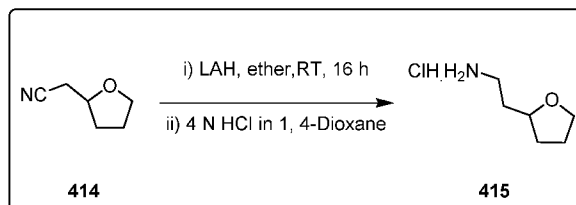
100 °C for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered through celite, washed with 50% MeOH/ CH₂Cl₂ (150 mL). The filtrate was evaporated *in vacuo* to obtain the crude which was purified through silica gel column chromatography in 70% EtOAc/ hexanes to afford compound **412** (500 mg, 54%) as yellow thick syrup. **TLC:** 70% EtOAc/ hexanes (*R_f*: 0.5); **¹H NMR (400 MHz, CDCl₃):** δ 7.35-7.30 (m, 1H), 7.25-7.19 (m, 1H), 7.17-7.13 (m, 1H), 7.10-7.08 (m, 1H), 7.00-6.96 (m, 1H), 6.92-6.85 (m, 2H), 6.68-6.65 (m, 1H), 3.85 (s, 3H), 3.72 (br s, 2H);

Synthesis of 3'-amino-[1, 1'-biphenyl]-3-ol (**413**)



[000335] A mixture of compound **412** (400 mg, 2.01 mmol) in hydrogen iodide (5 mL, 57% aqueous solution) was refluxed for 5 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was quenched with ice-cold water and the pH was neutralized with 10% sodium bicarbonate solution (5 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The obtained solid was filtered, dried *in vacuo* to obtain the crude which was purified through silicagel column chromatography in 80% EtOAc/ hexanes to afford compound **413** (200 mg, 54%) as an off-white solid. **TLC:** 50% EtOAc/ hexanes (*R_f*: 0.4); **¹H NMR (400 MHz, DMSO-*d*₆):** δ 9.41 (s, 1H), 7.20 (t, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 7.8 Hz, 1H), 6.99-6.88 (m, 2H), 6.78-6.76 (m, 1H), 6.73-6.68 (m, 2H), 6.55-6.52 (m, 1H), 5.12 (s, 2H).

Synthesis of 2-(tetrahydrofuran-2-yl) ethan-1-amine hydrochloride (**415**)

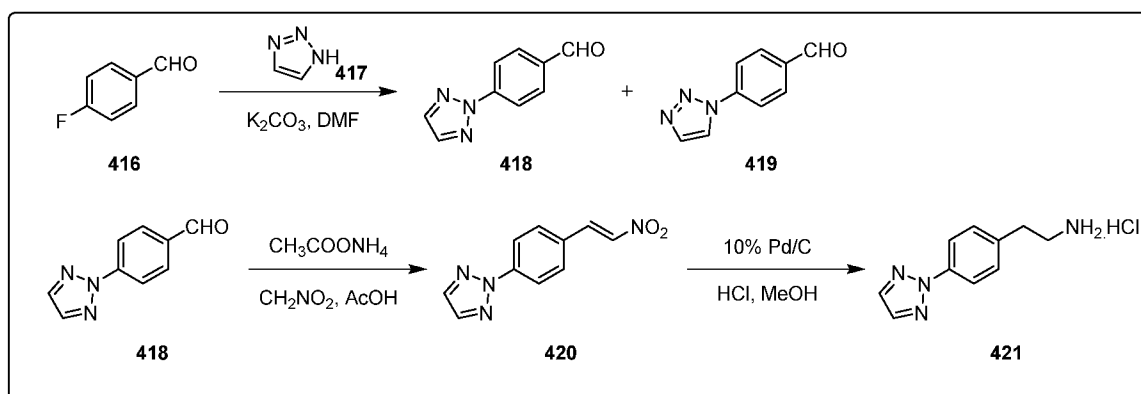


[000336] To a stirred solution of 2-(tetrahydrofuran-2-yl) acetonitrile **414** (2 g, 17.99 mmol) in

ether (20 mL) under argon atmosphere was added lithium aluminium hydride (1.36 g, 35.83 mmol) at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was quenched with saturated sodium potassium tartrate solution (30 mL) at 0-5 °C and extracted with ether (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude.

[000337] The crude was dissolved in CH₂Cl₂ (5 mL) cooled to 0 °C and added 4 N HCl in 1, 4-dioxane (10 mL) under argon atmosphere and stirred at the same temperature for 30 min. The volatiles were removed *in vacuo*. The obtained solid was titrated with CH₂Cl₂ (2 x 5 mL) and *in vacuo* to afford compound **415** (500 mg, HCl salt) as sticky solid. **TLC:** 10% MeOH/ CH₂Cl₂ (*R_f*: 0.2).

Synthesis of 2-(4-(2*H*-1, 2, 3-triazol-2-yl) phenyl) ethan-1-amine hydrochloride (**421**)



[000338] **Synthesis of 4-(2*H*-1, 2, 3-triazol-2-yl) benzaldehyde & 4-(1*H*-1, 2, 3-triazol-1-yl) benzaldehyde (**418** & **419**):** To a stirred solution of 4-fluorobenzaldehyde **417** (2 g, 16 mmol) in DMF (50 mL) under argon atmosphere were added 1*H*-1, 2, 3-triazole **417** (1.32 g, 19.2 mmol), potassium carbonate (3.3 g, 24 mmol) at RT; heated to 100 °C and stirred for 5 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with ice cold water (35 mL) and extracted with EtOAc (2 x 40 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 20% EtOAc/ hexanes to afford compound **418** (800 mg, 29%) and using 40% EtOAc/ hexanes to afford compound **419** (1 g, 36%) as yellow solids.

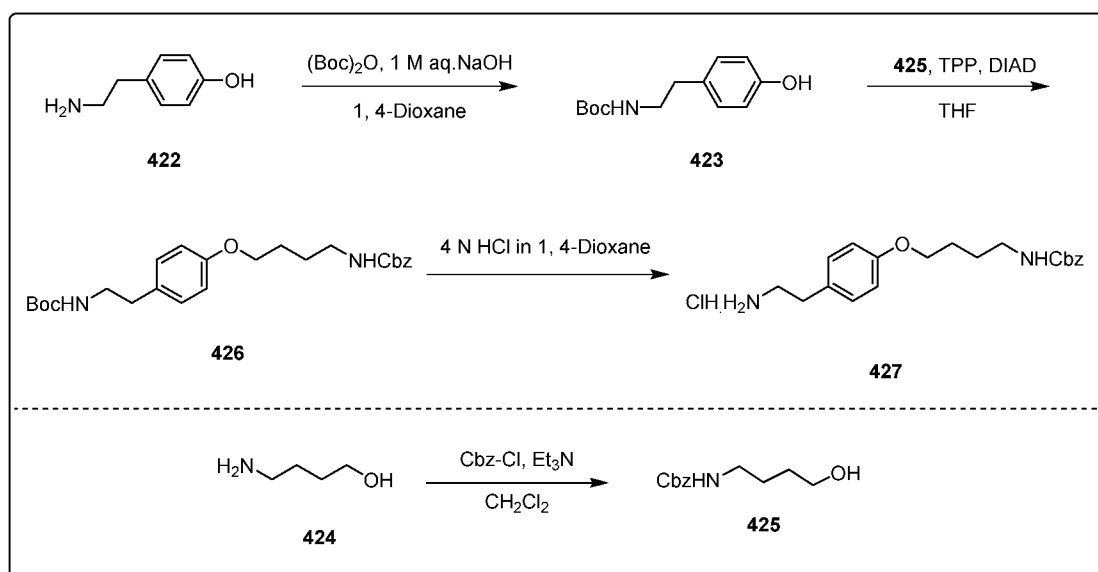
[000339] **Compound 418 analytical data:** TLC: 20% EtOAc/ hexanes (R_f : 0.8); $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ 10.05 (s, 1H), 8.27 (s, 2H), 8.25 (d, $J = 8.8$ Hz, 2H), 8.11 (d, $J = 8.8$ Hz, 2H).

[000340] **Compound 419 analytical data:** TLC: 20% EtOAc/ hexanes (R_f : 0.3); $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ 10.07 (s, 1H), 8.98 (s, 1H), 8.19 (d, $J = 8.8$ Hz, 2H), 8.13 (d, $J = 8.8$ Hz, 2H), 8.04 (s, 1H).

[000341] **Synthesis of (*E*)-2-(4-(2-nitrovinyl) phenyl)-2*H*-1, 2, 3-triazole (420):** To a stirred solution of compound **418** (400 mg, 2.31 mmol) in AcOH (10 mL) under argon atmosphere were added nitromethane (1.41 mL, 23.12 mmol), ammonium acetate (267 mg, 3.46 mmol) at RT; heated to 100 °C and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* and diluted with water (20 mL). The obtained solid was filtered, washed with *n*-hexane and dried *in vacuo* to afford compound **420** (400 mg, 80%) as yellow solid. TLC: 20% EtOAc/ hexanes (R_f : 0.3); $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ 8.29-8.18 (m, 4H), 8.13-8.05 (m, 4H).

[000342] **Synthesis of 2-(4-(2*H*-1, 2, 3-triazol-2-yl) phenyl) ethan-1-amine hydrochloride (421):** To a stirred solution of compound **420** (200 mg, 0.92 mmol) in MeOH (10 mL) under argon atmosphere were added 10% Pd/C (100 mg), HCl (0.2 mL) at RT and stirred under hydrogen atmosphere (balloon pressure) for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered through celite and the filtrate was concentrated *in vacuo* to obtain the crude. The crude was triturated with 2 M HCl in Et₂O (2 x 5 mL) and dried *in vacuo* to afford compound **421** (100 mg, 48%) as an off-white solid. TLC: 30% EtOAc/ hexanes (R_f : 0.2); $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ 8.16 (s, 2H), 8.12 (br s, 2H), 7.98 (d, $J = 8.4$ Hz, 2H), 7.46 (d, $J = 8.4$ Hz, 2H), 3.10-3.05 (m, 2H), 2.96 (t, $J = 8.4$ Hz, 2H).

Synthesis of benzyl (4-(4-(2-aminoethyl) phenoxy) butyl) carbamate hydrochloride (427)



[000343] Synthesis of *tert*-butyl (4-hydroxyphenethyl) carbamate (423): To a stirred solution of 4-(2-aminoethyl) phenol **422** (1 g, 7.29 mmol) in 1, 4-dioxane: H₂O (1: 1, 30 mL) were added 2 M aqueous sodium hydroxide solution (2 mL) and Boc-anhydride (1.9 mL, 8.25 mmol) at 0 °C; warmed to RT and stirred for 3 h. The reaction was monitored by TLC; after completion of the reaction, the pH of the reaction mixture cooled to 0 °C, acidified with 1 M HCl to ~3 and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulphate, filtered and concentrated *in vacuo* to afford compound **423** (1.5 g, 87%) as an off-white solid. **TLC:** 50% EtOAc/ hexanes (*R_f*: 0.8); **¹H NMR (DMSO-*d*₆, 500 MHz):** δ 9.15 (s, 1H), 6.95 (d, *J* = 8.4 Hz, 2H), 6.83 (t, *J* = 5.4 Hz, 1H), 6.64 (d, *J* = 8.1 Hz, 2H), 3.09-3.00 (m, 2H), 2.56-2.51 (m, 2H), 1.35 (s, 9H).

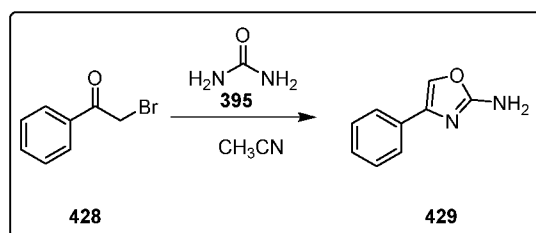
[000344] Synthesis of benzyl (4-hydroxybutyl) carbamate (425): To a stirred solution of 4-aminobutan-1-ol **424** (1.0 g, 11.23 mmol) in CH₂Cl₂ (15 mL) under argon atmosphere were added triethyl amine (1.78 mL, 12.35 mmol) and benzyl chloroformate (1.76 mL, 12.35 mmol, 50% solution in toluene) at 0 °C; warmed to RT and stirred for 6 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with saturated ammonium chloride (50 mL) at 0 °C. The organic layer was washed with brine (50 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to afford compound **425** (2.1 g, 84%) as colorless liquid. **TLC:** 50% EtOAc/ hexanes (*R_f*: 0.5); **¹H NMR (DMSO-*d*₆, 500 MHz):** δ 7.40-7.22 (m, 6H), 4.98 (s, 2H), 4.37 (t, *J* = 5.1 Hz, 1H), 3.36 (q, *J* = 5.8 Hz, 2H), 2.97 (q, *J* = 6.3 Hz,

2H), 1.51-1.28 (m, 4H).

[000345] Synthesis of *tert*-butyl (4-(4-(((benzyloxy) carbonyl) amino) butoxy) phenethyl) carbamate (426): To a stirred solution of compound **423** (1.5 g, 6.32 mmol) and compound **425** (1.4 g, 6.32 mmol) in THF (50 mL) under argon atmosphere at 0 °C were added triphenyl phosphine (1.65 g, 6.32 mmol), diisopropyl azodicarboxylate (1.4 mL, 6.96 mmol) at 0 °C; warmed to RT and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude. The crude was dissolved in 10% EtOAc/ hexanes (5 mL) and the precipitated solid was filtered, washed with hexane (20 mL), dried *in vacuo* to afford compound **426** (1.9 g, 68%) as an off-white solid. **TLC:** 5% MeOH/ CH₂Cl₂ (*R_f*: 0.7); **¹H NMR (DMSO-*d*₆, 500 MHz):** δ 8.89 (s, 1H), 7.68-7.51 (m, 5H), 7.40-7.24 (m, 2H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.88-6.78 (m, 2H), 5.00 (s, 2H), 4.80-4.73 (m, 2H), 3.91 (t, *J* = 6.4 Hz, 2H), 3.11-3.02 (m, 2H), 2.60 (t, *J* = 7.5 Hz, 2H), 1.72-1.64 (m, 2H), 1.56-1.52 (m, 2H), 1.18 (d, *J* = 6.1 Hz, 9H).

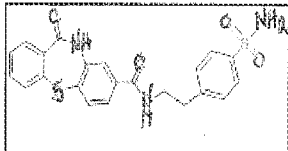
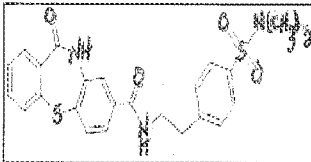
[000346] Synthesis of benzyl (4-(4-(2-aminoethyl) phenoxy) butyl) carbamate hydrochloride (427): To a stirred solution of compound **426** (500 mg, 1.13 mmol) in CH₂Cl₂ (5 mL) was added 4 N HCl in 1, 4-dioxane (3 mL) under argon atmosphere at 0-5 °C; warmed to RT and stirred for 3 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed under reduced pressure. The obtained solid was washed with diethyl ether (10 mL), *n*-pentane (10 mL) and dried *in vacuo* to afford compound **427** (200 mg, 47%) as white solid. **TLC:** 5% MeOH/ CH₂Cl₂ (*R_f*: 0.4); **¹H NMR (DMSO-*d*₆, 500 MHz):** δ 7.88 (br s, 3H), 7.39-7.28 (m, 5H), 7.15 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.00 (s, 2H), 3.93 (t, *J* = 6.4 Hz, 2H), 3.04 (q, *J* = 6.7 Hz, 2H), 2.97 (d, *J* = 6.4 Hz, 2H), 2.81-2.76 (m, 2H), 1.73-1.65 (m, 2H), 1.57-1.51 (m, 2H).

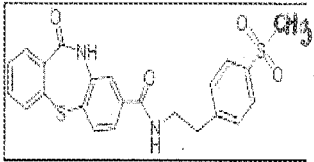
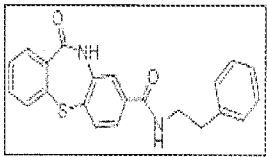
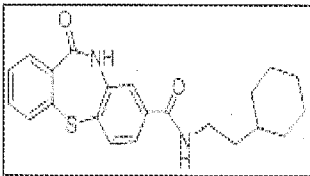
Synthesis of 4-phenyloxazol-2-amine (429)

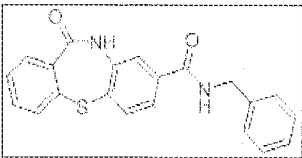
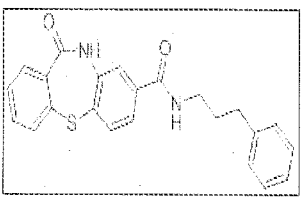
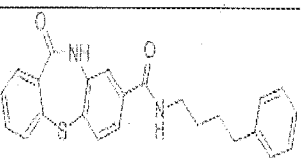
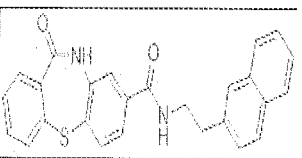


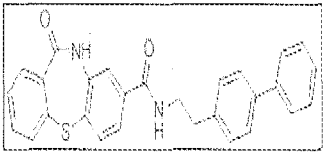
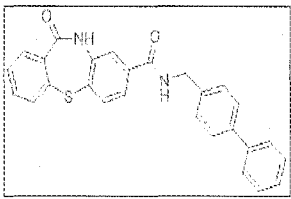
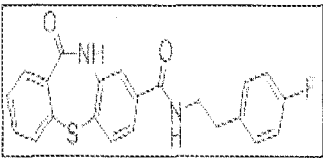
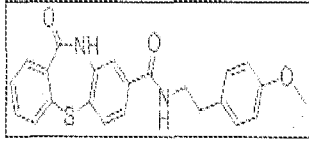
[000347] **Synthesis of 4-phenyloxazol-2-amine (429):** To a stirred solution of 2-bromo-1-phenylethan-1-one **428** (100 mg, 0.50 mmol) in CH₃CN (5 ml) under inert atmosphere was added urea **395** (301 mg, 5.02 mmol) at RT; heated at 80 °C and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude. The crude was purified through flash column chromatography using 30% EtOAc/ hexanes to afford compound **429** (50 mg, 63%) as an off-white solid. **TLC:** 50% EtOAc/ hexanes (*R_f*: 0.6); **¹H NMR** (400 MHz, DMSO-*d*₆): δ 7.86 (s, 1H), 7.63 (d, *J* = 7.0 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.26-7.22 (m, 1H), 6.70 (s, 2H).

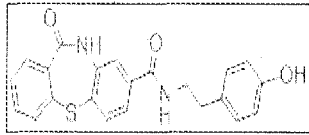
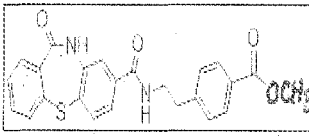
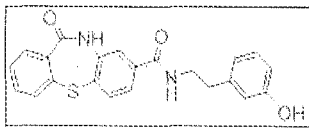
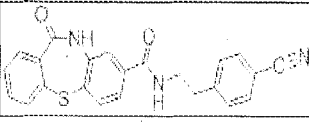
Table 1: Synthesis of compounds from compounds 6, 14, 21, 28, 35, 42, 50, 55, 62, 70, 76, 82, 88, 97, 103, 112, 118, 124, 135, 140, 145, 150, 155, 156, 159, 164, 167, 170, P-42 and various amines

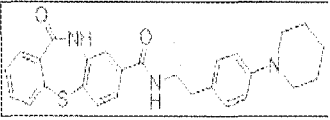
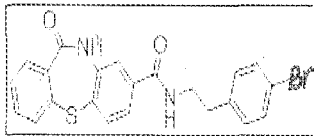
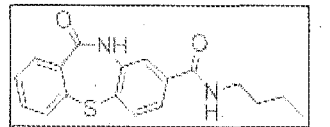
No.	Structure	Procedure, Intermediate, Amine	Rx Yield (%)	Mass Spec. Found	Mass Spec. Calculated	¹ H-NMR
1101		D, 6	52	476.0701	476.0715 for C ₂₂ H ₁₉ N ₃ O ₄ S ₂ Na (M+Na)+	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.78 (s, 1H), 8.62 (t, <i>J</i> = 5.6 Hz, 1H), 7.76 – 7.59 (m, 5H), 7.57 – 7.35 (m, 6H), 7.26 (s, 2H), 3.47 (t, <i>J</i> = 6.6 Hz, 2H), 2.88 (t, <i>J</i> = 7.1 Hz, 2H).
1102		D, 6	51	504.1048	504.1028 for C ₂₄ H ₂₃ N ₃ O ₄ S ₂ Na (M+Na)+	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.78 (s, 1H), 8.60 (t, <i>J</i> = 5.6 Hz, 1H), 7.71 – 7.57 (m, 5H), 7.55 – 7.40 (m, 6H), 3.50 (q, <i>J</i> = 6.8 Hz, 2H), 2.91 (t, <i>J</i> = 7.1 Hz, 2H), 2.52 (s, 6H).

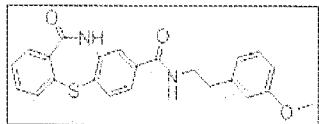
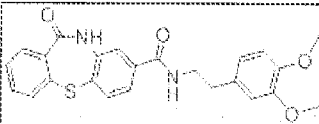
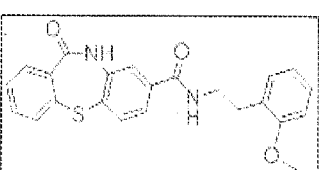
1103		D, 6	83	453.0936	453.0943 for $C_{23}H_{21}N_2O_4S_2$ (M+H) ⁺	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.78 (s, 1H), 8.60 (t, <i>J</i> = 5.5 Hz, 1H), 7.71 – 7.59 (m, 3H), 7.53 (d, <i>J</i> = 8.3 Hz, 1H), 7.51 – 7.42 (m, 2H), 7.27 (t, <i>J</i> = 7.3 Hz, 2H), 7.18 (dd, <i>J</i> = 15.9, 7.3 Hz, 3H), 3.44 (q, <i>J</i> = 6.9 Hz, 2H), 2.80 (t, <i>J</i> = 7.4 Hz, 2H).
1104		D, 6	63	373.0999	373.1016 for $C_{22}H_{17}N_2O_2S$ (M-H) ⁻	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.78 (s, 1H), 8.60 (t, <i>J</i> = 5.5 Hz, 1H), 7.71 – 7.59 (m, 3H), 7.53 (d, <i>J</i> = 8.3 Hz, 1H), 7.51 – 7.42 (m, 2H), 7.27 (t, <i>J</i> = 7.3 Hz, 2H), 7.18 (dd, <i>J</i> = 15.9, 7.3 Hz, 3H), 3.44 (q, <i>J</i> = 6.9 Hz, 2H), 2.80 (t, <i>J</i> = 7.4 Hz, 2H).
1105		D, 6	80	381.1633	381.1637 for $C_{22}H_{25}N_2O_2S$ (M+H) ⁺	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.76 (s, 1H), 8.43 (t, <i>J</i> = 5.6 Hz, 1H), 7.71 – 7.59 (m, 3H), 7.58 – 7.40 (m, 4H), 3.28 – 3.17 (m, 2H), 1.73 – 1.53 (m, 6H), 1.37 (q, <i>J</i> = 7.0 Hz, 2H), 1.32 – 1.03 (m, 3H), 0.87 (tt, <i>J</i> = 11.5, 6.1 Hz, 2H).

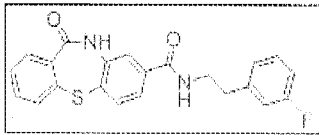
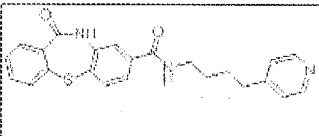
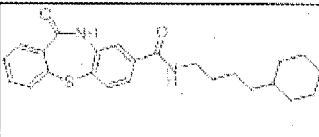
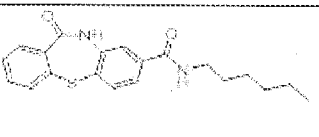
1107		D, 6	79	361.1001	361.1011 for $C_{21}H_{17}N_2O_2S$ (M+H) ⁺	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.77 (s, 1H), 9.08 (t, J = 6.0 Hz, 1H), 7.74 – 7.58 (m, 4H), 7.57 – 7.40 (m, 3H), 7.35 – 7.19 (m, 5H), 4.43 (d, J = 6.0 Hz, 2H).
1108		D, 6	71	389.1307	389.1324 for $C_{23}H_{21}N_2O_2S$ (M+H) ⁺	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.76 (s, 1H), 8.52 (t, J = 5.6 Hz, 1H), 7.71 – 7.60 (m, 3H), 7.60 – 7.42 (m, 4H), 7.30 – 7.13 (m, 5H), 3.23 (q, J = 6.6 Hz, 2H), 2.59 (t, J = 7.7 Hz, 2H), 1.83 – 1.74 (m, 2H).
1109		D, 6	81	403.1496	403.1480 for $C_{24}H_{23}N_2O_2S$ (M+H) ⁺	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.75 (s, 1H), 8.48 (t, J = 5.6 Hz, 1H), 7.71 – 7.59 (m, 3H), 7.58 – 7.40 (m, 4H), 7.29 – 7.09 (m, 5H), 3.23 (q, J = 6.5 Hz, 2H), 2.57 (t, J = 7.4 Hz, 2H), 1.63 – 1.44 (m, 4H).
1110		D, 6	65	447.1162	447.1143 for $C_{26}H_{20}N_2O_2SNa$ (M+Na) ⁺	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.77 (s, 1H), 8.65 (t, J = 5.6 Hz, 1H), 7.83 (t, J = 8.5 Hz, 3H), 7.78 – 7.59 (m, 4H), 7.57 – 7.35 (m, 7H), 3.55 (q, J = 6.8 Hz, 2H), 2.97 (t, J = 7.3 Hz, 2H).

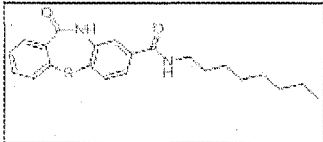
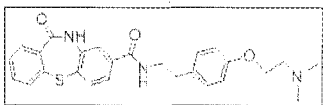
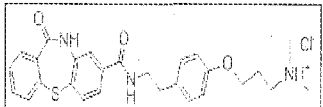
1111		D, 6	36	473.1319	473.1300 for $C_{28}H_{22}N_2O$ $_2SNa$ $(M+Na)^+$	1H NMR (400 MHz, DMSO- d_6) δ 10.78 (s, 1H), 8.63 (t, J = 5.7 Hz, 1H), 7.71–7.39 (m, 13H), 7.32 (dd, J = 13.3, 7.5 Hz, 3H), 3.48 (q, J = 6.7 Hz, 2H), 2.85 (t, J = 7.2 Hz, 2H).
1112		D, 6	82	459.1154	459.1143 for $C_{27}H_{20}N_2O$ $_2SNa$ $(M+Na)^+$	1H NMR (400 MHz, DMSO- d_6) δ 10.78 (s, 1H), 9.12 (t, J = 6.0 Hz, 1H), 7.76–7.29 (m, 16H), 4.48 (d, J = 5.9 Hz, 2H).
1113		D, 6	83	415.0894	415.0892 for $C_{22}H_{17}N_2O$ $_2SFNa$ $(M+Na)^+$	1H NMR (400 MHz, DMSO- d_6) δ 10.78 (s, 1H), 8.57 (t, J = 5.7 Hz, 1H), 7.65 (ddd, J = 17.4, 6.5, 2.8 Hz, 3H), 7.57–7.40 (m, 4H), 7.23 (dd, J = 8.4, 5.6 Hz, 2H), 7.08 (t, J = 8.8 Hz, 2H), 3.43 (q, J = 6.8 Hz, 2H), 2.79 (t, J = 7.2 Hz, 2H).
1114		D, 6	78	427.109	427.1092 for $C_{23}H_{20}N_2O$ $_3SNa$ $(M+Na)^+$	1H NMR (400 MHz, DMSO- d_6) δ 10.78 (s, 1H), 8.57 (t, J = 5.6 Hz, 1H), 7.72–7.60 (m, 3H), 7.57–7.40 (m, 4H), 7.15–7.08 (m, 2H), 6.87–6.79 (m, 2H), 3.70 (s, 3H), 3.45–3.35 (m, 2H), 2.73 (t, J = 7.4 Hz, 2H).

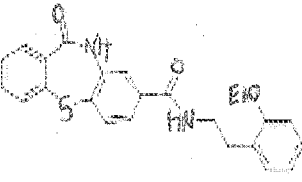
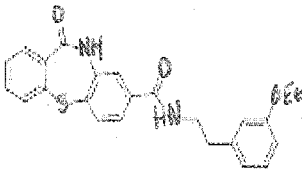
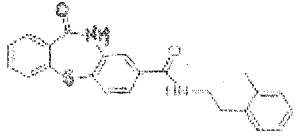
1115		D, 6	63	391.1121	391.1116 for $C_{22}H_{19}N_2O_3S$ (M+H) ⁺	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.78 (s, 1H), 9.14 (s, 1H), 8.55 (t, J = 5.6 Hz, 1H), 7.71 – 7.60 (m, 3H), 7.58 – 7.40 (m, 4H), 6.99 (d, J = 8.2 Hz, 2H), 6.65 (d, J = 8.2 Hz, 2H), 3.37 (q, J = 6.8 Hz, 2H), 2.74 – 2.63 (m, 2H).
1117		D, 6	81	455.1049	455.1041 for $C_{24}H_{20}N_2O_4$ (M+Na) ⁺	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.78 (s, 1H), 8.60 (t, J = 5.7 Hz, 1H), 7.86 (d, J = 8.1 Hz, 2H), 7.71 – 7.60 (m, 3H), 7.57 – 7.40 (m, 4H), 7.36 (d, J = 8.0 Hz, 2H), 3.81 (s, 3H), 3.48 (q, J = 6.7 Hz, 2H), 2.88 (t, J = 7.1 Hz, 2H).
1118		D, 6	76	413.0937	413.0936 for $C_{22}H_{18}N_2O_3S$ (M+Na) ⁺	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.78 (s, 1H), 9.23 (s, 1H), 8.59 (t, J = 5.6 Hz, 1H), 7.71 – 7.59 (m, 3H), 7.58 – 7.40 (m, 4H), 7.05 (t, J = 7.7 Hz, 1H), 6.59 (td, J = 9.0, 6.9 Hz, 3H), 3.40 (q, J = 6.8 Hz, 2H), 2.70 (t, J = 7.5 Hz, 2H).
1120		D, 6	13	422.1	422.1 (M+Na) ⁺	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.78 (s, 1H), 8.59 (t, J = 5.6 Hz, 1H),

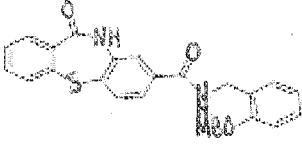
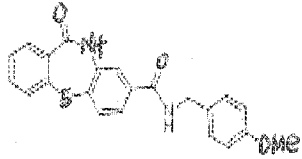
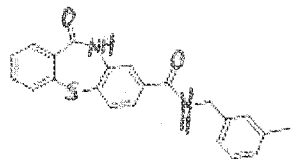
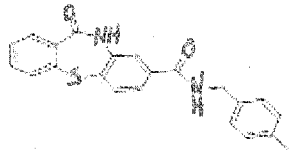
						7.83 – 7.33 (m, 1H), 3.47 (dd, J = 7.8, 5.1 Hz, 2H), 2.90 (t, J = 7.0 Hz, 2H).
1121		D, 6	32	458.2	458.2 (M+H) ⁺	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.78 (s, 1H), 8.57 (t, J = 5.6 Hz, 1H), 7.71 – 7.60 (m, 3H), 7.58 – 7.40 (m, 4H), 7.06 – 6.96 (m, 2H), 6.87 – 6.78 (m, 2H), 3.42 – 3.32 (m, 2H), 3.04 (t, J = 5.4 Hz, 4H), 2.68 (t, J = 7.5 Hz, 2H), 1.63 – 1.43 (m, 6H).
1122		D, 6	49	486.9872	486.9883 for C ₂₂ H ₁₇ N ₂ O 2SClBr (M+Cl) ⁺	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.78 (s, 1H), 8.58 (t, J = 5.6 Hz, 1H), 7.65 (ddd, J = 17.0, 5.8, 2.1 Hz, 3H), 7.57 – 7.40 (m, 6H), 7.17 (d, J = 8.3 Hz, 2H), 3.43 (q, J = 6.7 Hz, 2H), 2.77 (t, J = 7.1 Hz, 2H).
1123		D, 6	37	361.078	361.0778 for C ₁₈ H ₁₈ N ₂ O 2SCl (M+Cl) ⁺	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.75 (s, 1H), 8.45 (d, J = 5.7 Hz, 1H), 7.71 – 7.59 (m, 3H), 7.59 – 7.40 (m, 4H), 3.21 (q, J = 6.7 Hz, 2H), 1.45 (p, J = 7.5 Hz, 2H), 1.27 (dt, J = 20.8, 10.6 Hz, 2H), 0.86 (td, J = 7.2, 2.4 Hz, 3H).

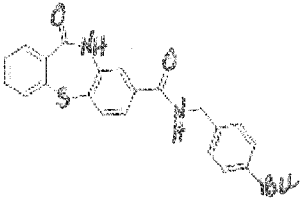
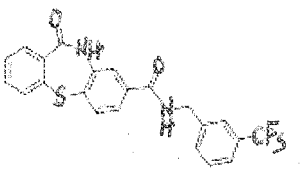
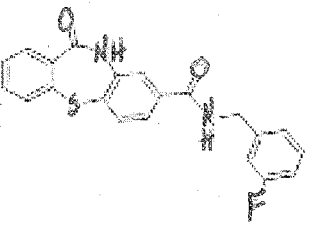
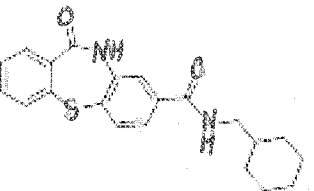
1124		D, 6	48	439.2	439.2 (M+Cl) ⁻	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.78 (s, 1H), 8.59 (t, J = 5.6 Hz, 1H), 7.72 – 7.61 (m, 3H), 7.58 – 7.40 (m, 4H), 7.18 (t, J = 8.0 Hz, 1H), 6.81 – 6.71 (m, 3H), 3.70 (s, 3H), 3.44 (q, J = 7.1 Hz, 2H), 2.78 (t, J = 7.4 Hz, 2H).
1125		D, 6	59	433.1206	433.1222 for C ₂₄ H ₂₁ N ₂ O 4S	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.78 (s, 1H), 8.56 (t, J = 5.6 Hz, 1H), 7.71 – 7.60 (m, 3H), 7.58 – 7.40 (m, 4H), 6.89 – 6.76 (m, 2H), 6.70 (dd, J = 8.2, 2.0 Hz, 1H), 3.68 (d, J = 2.0 Hz, 6H), 3.16 (d, J = 5.2 Hz, 2H), 2.73 (t, J = 7.3 Hz, 2H).
1127		D, 6	49	405.1269	405.1273 for C ₂₃ H ₂₁ N ₂ O 3S (M+H) ⁺	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.78 (s, 1H), 8.55 (d, J = 6.3 Hz, 1H), 7.71 – 7.59 (m, 3H), 7.57 – 7.40 (m, 4H), 7.22 – 7.07 (m, 2H), 6.94 (d, J = 8.3 Hz, 1H), 6.84 (t, J = 7.6 Hz, 1H), 3.76 (d, J = 2.1 Hz, 3H), 3.40 (q, J = 7.0 Hz, 2H), 2.82 – 2.74 (m, 2H).

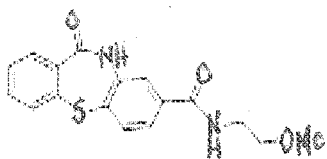
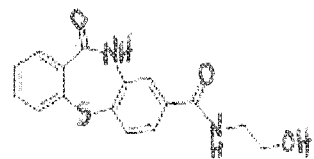
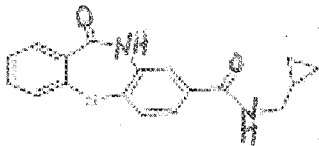
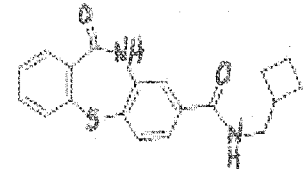
1130		D, 6	41	391.091	391.0917 for $C_{22}H_{16}N_2O_2FS$	1H NMR (400 MHz, DMSO- d_6) δ 10.78 (s, 1H), 8.60 (t, J = 5.6 Hz, 1H), 7.75 – 7.57 (m, 3H), 7.57 – 7.39 (m, 4H), 7.30 (td, J = 8.0, 6.2 Hz, 1H), 7.09 – 6.95 (m, 3H), 3.46 (q, J = 6.7 Hz, 2H), 2.83 (t, J = 7.2 Hz, 2H).
1149		D, 6	28	404.1438	404.1433 for $C_{23}H_{22}N_3O_2S$	1H NMR (400 MHz, DMSO- d_6) δ 10.75 (s, 1H), 8.49 (t, J = 5.7 Hz, 1H), 8.42 (d, J = 5.1 Hz, 2H), 7.71 – 7.40 (m, 7H), 7.20 (d, J = 5.4 Hz, 2H), 3.24 (q, J = 6.5 Hz, 2H), 2.49 (q, J = 2.8, 1.7 Hz, 2H), 1.54 (dp, J = 41.6, 7.1 Hz, 4H).
1150		D, 6	75	409.1961	409.1950 for $C_{24}H_{29}N_2O_2S$	1H NMR (400 MHz, DMSO- d_6) δ 10.76 (s, 1H), 8.46 (t, J = 5.7 Hz, 1H), 7.71 – 7.40 (m, 7H), 3.19 (q, J = 6.6 Hz, 2H), 1.68 – 1.54 (m, 5H), 1.44 (p, J = 7.2 Hz, 2H), 1.33 – 1.03 (m, 8H), 0.83 (t, J = 11.1 Hz, 2H).
1151		D, 6	74	355.1477	355.1480 for $C_{20}H_{23}N_2O_2S$	1H NMR (400 MHz, DMSO- d_6) δ 10.75 (s, 1H), 8.46 (t, J = 5.7 Hz, 1H), 7.71 – 7.40 (m, 7H), 3.20 (q, J

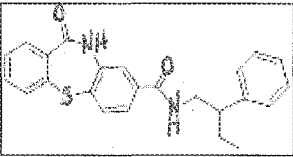
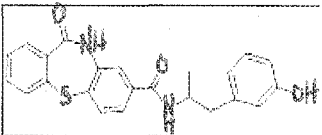
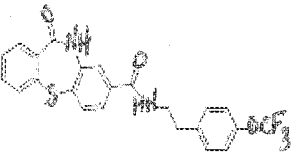
						= 6.6 Hz, 2H), 1.46 (p, J = 6.9 Hz, 2H), 1.32 – 1.20 (m, 6H), 0.88 – 0.80 (m, 3H).
1152		D, 6	59	383.1802	383.1793 for $C_{22}H_{27}N_2O_2S$	1H NMR (400 MHz, DMSO- d_6) δ 10.75 (s, 1H), 8.46 (t, J = 5.7 Hz, 1H), 7.71 – 7.40 (m, 7H), 3.19 (q, J = 6.6 Hz, 2H), 1.50 – 1.42 (m, 2H), 1.23 (q, J = 4.6, 4.0 Hz, 10H), 0.83 (t, J = 6.6 Hz, 3H).
1154		D, 6	38	462.186	462.1851 for $C_{26}H_{28}N_3O_3S$	1H NMR (400 MHz, DMSO- d_6) δ 10.78 (s, 1H), 8.57 (t, J = 5.6 Hz, 1H), 7.71 – 7.60 (m, 3H), 7.57 – 7.40 (m, 4H), 7.10 (d, J = 8.3 Hz, 2H), 6.83 (d, J = 8.2 Hz, 2H), 3.98 (t, J = 5.8 Hz, 2H), 3.44 – 3.34 (m, 2H), 2.72 (t, J = 7.4 Hz, 2H), 2.58 (t, J = 5.8 Hz, 2H), 2.19 (s, 6H).
1155		D, 6	40	476.2007	476.2008 for $C_{27}H_{30}N_3O_3S$	1H NMR (400 MHz, DMSO- d_6) δ 10.79 (s, 1H), 10.43 (s, 1H), 8.60 (t, J = 5.6 Hz, 1H), 7.71 – 7.40 (m, 7H), 7.13 (d, J = 8.2 Hz, 2H), 6.84 (d, J = 8.2 Hz, 2H), 3.99 (t, J = 6.1 Hz, 2H), 3.40 (q, J = 6.8 Hz, 2H),

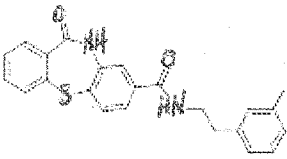
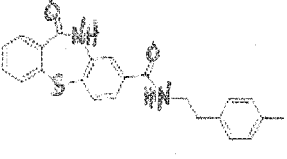
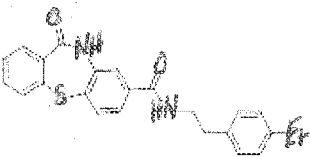
						3.16 (dt, $J = 13.2, 5.4$ Hz, 2H), 2.75 (d, $J = 5.0$ Hz, 8H), 2.10 (dq, $J = 12.2, 6.1$ Hz, 2H).
1156		D, 6	59	419.2 (M+1) ⁺		(DMSO- <i>d</i> ₆ , 400 MHz): δ 10.76 (br s, 1H), 8.54 (br s, 1H), 7.69-7.62 (m, 3H), 7.55-7.45 (m, 4H), 7.17-7.10 (m, 2H), 6.93 (d, $J = 8.4$ Hz, 1H), 6.82 (t, $J = 7.2$ Hz, 1H), 4.03-3.99 (m, 2H), 3.43 (d, $J = 6.8$ Hz, 2H), 2.78 (t, $J = 6.8$ Hz, 2H), 1.32 (t, $J = 6.8$ Hz, 3H);
1157		D, 6	49	419.2 (M+1) ⁺		¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.79 (br s, 1H), 8.59-8.58 (m, 1H), 7.69-7.63 (m, 3H), 7.55-7.44 (m, 4H), 7.16 (t, $J = 8.0$ Hz, 1H), 6.75 (t, $J = 8.0$ Hz, 3H), 3.95 (q, 2H), 3.46-3.43 (m, 2H), 2.76 (t, $J = 7.6$ Hz, 2H), 1.26 (t, $J = 6.8$ Hz, 3H)
1158		D, 6	52	389.2 (M+1) ⁺		(DMSO- <i>d</i> ₆ , 500 MHz): δ 10.76 (s, 1H), 8.64 (t, $J = 5.5$ Hz, 1H), 7.67-7.62 (m, 3H), 7.55-7.42 (m, 4H), 7.12-7.06 (m, 4H), 3.40-3.36 (m, 2H), 2.77 (t, $J =$

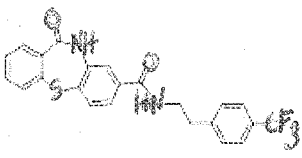
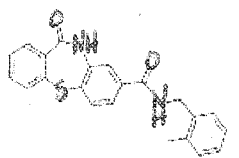
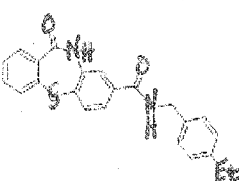
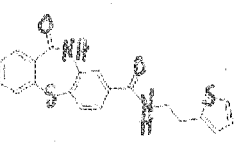
						8.0 Hz, 2H), 2.28 (s, 3H);
1159		D, 6	35	391.3 (M+1) ⁺ ;		(DMSO-d ₆ , 400 MHz): δ 10.76 (s, 1H), 8.88- 8.87 (m, 1H), 7.72-7.63 (m, 4H), 7.55-7.43 (m, 3H), 7.22 (t, J = 7.2 Hz, 1H), 7.13 (d, J = 7.6 Hz, 1H), 6.98 (d, J = 7.2 Hz, 1H), 6.87 (t, J = 7.2 Hz, 1H), 4.40 (d, J = 4.8 Hz, 2H), 3.80 (s, 3H);
1161		D, 6	43	391.2 (M+1) ⁺ ;		(DMSO-d ₆ , 400 MHz): δ 10.76 (s, 1H), 8.99 (t, J = 4.4 Hz, 1H), 7.69-7.59 (m, 4H), 7.54-7.43 (m, 3H), 7.20 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 4.36 (d, J = 5.6 Hz, 2H), 3.71 (s, 3H);
1163		A, 6	36	375.0 (M+1) ⁺ ;		(DMSO-d ₆ , 400 MHz): δ 10.76 (s, 1H), 9.04 (t, J = 6.0 Hz, 1H), 7.71-7.61 (m, 4H), 7.55-7.43 (m, 3H), 7.18 (t, J = 7.2 Hz, 1H), 7.08-7.03 (m, 3H), 4.40 (d, J = 6.0 Hz, 2H), 2.26 (s, 3H)
1164		D, 6	64	375.3 (M+1) ⁺ ;		(DMSO-d ₆ , 400 MHz): δ 10.77 (s, 1H), 9.03- 9.02 (m, 1H), 7.70-7.60 (m, 4H), 7.55-7.45 (m, 3H), 7.16 (d, J = 8.0 Hz, 2H), 7.10 (d, J

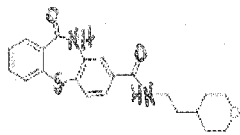
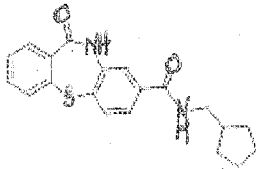
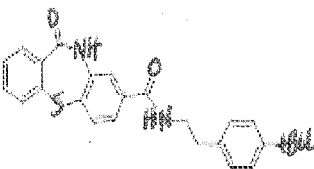
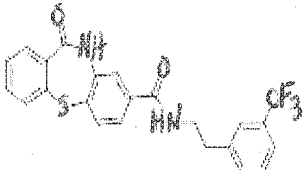
						= 8.0 Hz, 2H), 4.38 (d, J = 6.0 Hz, 2H), 2.25 (s, 3H)
1165		A, 6	65	417.4 (M+1) ⁺		(DMSO- d_6 , 400 MHz): δ 10.76 (br s, 1H), 9.02 (t, J = 6.0 Hz, 1H), 7.71-7.60 (m, 4H), 7.55-7.43 (m, 3H), 7.32 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 4.39 (d, J = 6.0 Hz, 2H), 1.24 (s, 9H);
1166		D, 6	48	429.4 (M+1) ⁺		(DMSO- d_6 , 400 MHz): δ 10.77 (s, 1H), 9.17 (t, J = 4.8 Hz, 1H), 7.72-7.67 (m, 3H), 7.64-7.59 (m, 6H), 7.57-7.43 (m, 2H), 4.52 (d, J = 4.8 Hz, 2H);
1168		A, 6	62	379.1 (M+1) ⁺		(DMSO- d_6 , 400 MHz): δ 10.77 (s, 1H), 9.11 (t, J = 6.0 Hz, 1H), 7.72-7.62 (m, 4H), 7.55-7.44 (m, 3H), 7.36 (t, J = 8.0 Hz, 1H), 7.13-7.04 (m, 3H), 4.45 (d, J = 6.0 Hz, 2H);
1169		D, 6	56	367.3 (M+1) ⁺		(DMSO- d_6 , 400 MHz): δ 10.75 (s, 1H), 8.46 (t, J = 6.0 Hz, 1H), 7.69-7.62 (m, 3H), 7.57-7.51 (m, 2H), 7.49-7.43 (m, 2H), 3.07-3.04 (m, 2H), 1.67-1.60 (m, 4H), 1.50-1.48 (m, 2H), 1.17-1.12 (m, 3H), 0.93-0.87

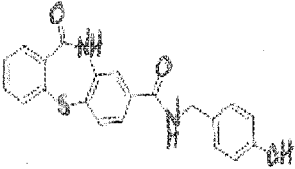
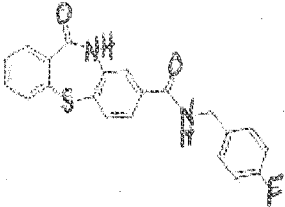
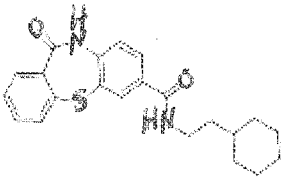
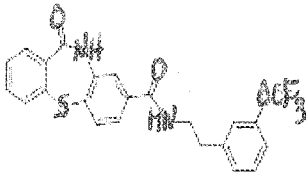
						(m, 2H);
1171		A, 6	40	329.1 (M+1) ⁺ ;		(DMSO-d ₆ , 400 MHz): δ 10.76 (s, 1H), 8.58 (t, J = 6.8 Hz, 1H), 7.72-7.69 (m, 3H), 7.56-7.52 (m, 2H), 7.48-7.44 (m, 2H), 3.44-3.38 (m, 4H), 3.24 (s, 3H);
1172		D, 6	82	315 (M+1) ⁺ ;		(DMSO-d ₆ , 400 MHz): δ 10.73 (s, 1H), 8.43 (t, J = 4.8 Hz, 1H), 7.66-7.56 (m, 3H), 7.54-7.40 (m, 4H), 4.65 (t, J = 4.8 Hz, 1H), 3.46-3.41 (m, 2H), 3.25-3.23 (m, 2H);
1173		D, 6	52	325.2 (M+1) ⁺ ;		(DMSO-d ₆ , 400 MHz): δ 10.75 (s, 1H), 8.58 (t, J = 4.8 Hz, 1H), 7.69-7.59 (m, 4H), 7.57-7.55 (m, 3H), 7.53-7.43 (m, 2H), 3.10 (t, J = 6.4 Hz, 2H), 1.01-0.97 (m, 1H), 0.43-0.38 (m, 2H), 0.21-0.19 (m, 2H);
1174		A, 6	54	339.1 (M+1) ⁺ ;		(DMSO-d ₆ , 400 MHz): δ 10.75 (s, 1H), 8.48-8.46 (m, 1H), 7.69-7.63 (m, 3H), 7.57-7.43 (m, 4H), 3.26-3.23 (m, 2H), 2.50-2.49 (m, 1H), 1.97-1.91 (m, 2H), 1.82-1.76 (m, 2H), 1.71-1.65 (m, 2H);

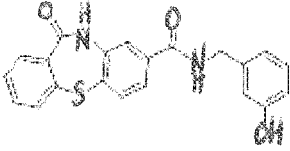
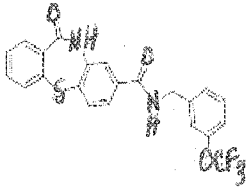
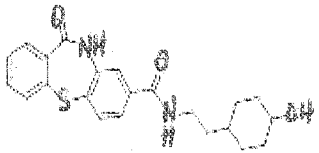
1176		D, 6	39	403.1 (M+1) ⁺	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.75 (s, 1H), 8.47 (t, J = 5.8 Hz, 1H), 7.64 (ddd, J = 24.5, 5.6, 1.9 Hz, 3H), 7.56 – 7.39 (m, 4H), 7.27 (t, J = 7.6 Hz, 2H), 7.18 (d, J = 7.3 Hz, 3H), 3.40 (ddt, J = 24.8, 13.3, 6.4 Hz, 2H), 2.76 (dt, J = 11.9, 5.8 Hz, 1H), 1.72 (ddd, J = 13.0, 7.1, 4.9 Hz, 1H), 1.52 (ddd, J = 16.5, 14.1, 7.7 Hz, 1H), 0.69 (t, J = 7.3 Hz, 3H).
1177		D, 6	92	405.0 (M+1) ⁺	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.75 (s, 1H), 9.19 (s, 1H), 8.32 (d, J = 8.2 Hz, 1H), 7.65 (dd, J = 18.8, 7.5 Hz, 3H), 7.49 (dt, J = 23.9, 8.6 Hz, 4H), 7.02 (t, J = 7.9 Hz, 1H), 6.60 (d, J = 7.6 Hz, 2H), 4.17 – 4.07 (m, 1H), 2.76 (dd, J = 13.1, 7.3 Hz, 1H), 2.56 (dd, J = 12.9, 6.7 Hz, 1H), 1.08 (d, J = 6.5 Hz, 3H).
1182		A, 6	46	459.2 (M ⁺ +1) ⁺	(DMSO-d ₆ , 500 MHz): δ 10.76 (s, 1H), 8.59–8.58 (m, 1H), 7.66 (d, J = 7.0 Hz, 1H), 7.62 (d, J = 7.5 Hz, 2H), 7.51–7.42

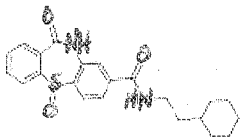
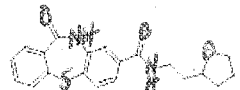
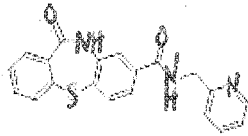
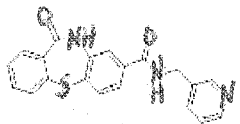
						(m, 4H), 7.32 (d, $J = 8.0$ Hz, 2H), 7.24 (d, $J = 8.0$ Hz, 2H), 3.43 (t, $J = 6.5$ Hz, 2H), 2.82 (t, $J = 7.0$ Hz, 2H);
1183		A, 6	43	389.2 (M+1) ⁺		(DMSO- <i>d</i> ₆ , 400 MHz): δ 10.76 (s, 1H), 9.04 (t, $J = 6.0$ Hz, 1H), 7.71-7.61 (m, 4H), 7.55-7.43 (m, 3H), 7.18 (t, $J = 7.2$ Hz, 1H), 7.08-7.03 (m, 3H), 4.40 (d, $J = 6.0$ Hz, 2H), 2.72 (t, $J = 6.0$ Hz, 2H), 2.26 (s, 3H);
1184		A, 6	43	389.2 (M+1) ⁺		(DMSO- <i>d</i> ₆ , 400 MHz): δ 10.77 (s, 1H), 8.58-8.57 (m, 1H), 7.69-7.63 (m, 3H), 7.55-7.45 (m, 4H), 7.09-7.07 (m, 4H), 3.44-3.39 (m, 2H), 2.75 (t, $J = 7.6$ Hz, 2H), 2.24 (s, 3H);
1185		A, 6	42	403.2 (M+1) ⁺		(DMSO- <i>d</i> ₆ , 400 MHz): δ 10.76 (s, 1H), 8.58-8.57 (m, 1H), 7.67-7.61 (m, 3H), 7.53-7.41 (m, 4H), 7.10-7.08 (m, 4H), 3.42-3.37 (m, 2H), 2.74 (t, $J = 7.2$ Hz, 2H), 2.55-2.51 (m, 2H), 1.12 (t, $J = 7.6$ Hz, 3H);

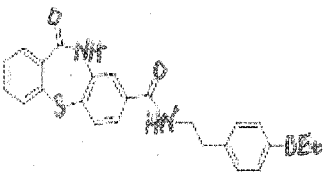
1186		A, 6	28	443.2 (M ⁺ +1);	(DMSO- <i>d</i> ₆ , 400 MHz): δ 10.78 (s, 1H), 8.59 (t, <i>J</i> = 5.6 Hz, 1H), 7.69-7.62 (m, 5H), 7.55-7.43 (m, 6H), 3.49 (q, 2H), 2.91 (t, <i>J</i> = 7.2 Hz, 2H);
1187		D, 6	36	375.2 (M+1) ⁺ ;	NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.75 (br s, 1H), 8.92 (br s, 1H), 7.72-7.65 (m, 4H), 7.53-7.45 (m, 3H), 7.19-7.14 (m, 4H), 4.42 (br s, 2H), 2.29 (s, 3H);
1188		A, 6	56	389.1 (M+1) ⁺ ;	(DMSO- <i>d</i> ₆ , 400 MHz): δ 10.76 (s, 1H), 9.02 (t, <i>J</i> = 6.0 Hz, 1H), 7.71-7.60 (m, 4H), 7.55-7.43 (m, 3H), 7.19 (d, <i>J</i> = 8.0 Hz, 2H), 7.13 (d, <i>J</i> = 8.0 Hz, 2H), 4.39 (d, <i>J</i> = 6.0 Hz, 2H), 2.58-2.54 (m, 2H), 1.14 (t, <i>J</i> = 7.6 Hz, 3H);
1190		D, 6	52	381.1 (M+1) ⁺ ;	(CDCl ₃ , 400 MHz): δ 10.79 (s, 1H), 8.67-8.66 (m, 1H), 7.69-7.64 (m, 3H), 7.57-7.45 (m, 4H), 7.31 (d, <i>J</i> = 4.8 Hz, 1H), 6.94-6.89 (m, 2H), 3.48-3.46 (m, 2H), 3.04-3.01 (m, 2H);

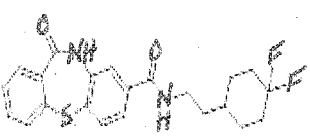
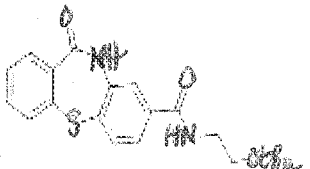
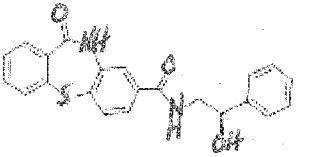
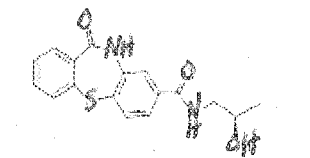
1191		A, 6	46	383.2 (M ⁺ +1);	(DMSO-d ₆ , 400 MHz): δ 10.77 (s, 1H), 8.48-8.47 (m, 1H), 7.69-7.63 (m, 3H), 7.57-7.43 (m, 4H), 3.82-3.78 (m, 2H), 3.26-3.20 (m, 4H), 1.57 (d, J = 9.6 Hz, 2H), 1.45-1.40 (m, 3H), 1.18-1.09 (m, 2H);
1193		A, 6	52	353.1 (M ⁺ +1);	(CDCl ₃ , 400 MHz): δ 10.75 (s, 1H), 8.50-8.49 (m, 1H), 7.69-7.63 (m, 3H), 7.57-7.43 (m, 4H), 3.14 (t, J = 6.8 Hz, 2H), 2.13-2.06 (m, 1H), 1.66-1.60 (m, 2H), 1.56-1.45 (m, 4H), 1.25-1.17 (m, 2H);
1194		A, 6	22	431.3 (M ⁺ +1);	(DMSO-d ₆ , 400 MHz): δ 10.78 (s, 1H), 8.61-8.60 (m, 1H), 7.69-7.63 (m, 3H), 7.56-7.53 (m, 2H), 7.51-7.45 (m, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 3.45-3.41 (m, 2H), 2.78-2.74 (m, 2H), 1.24 (s, 9H);
1195		A, 6	58	443.7 (M+1) ⁺	(DMSO-d ₆ , 500 MHz): δ 10.77 (s, 1H), 8.59 (t, J = 6.0 Hz, 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.62 (d, J = 8.0 Hz, 2H), 7.56-7.42 (m, 8H), 3.50-

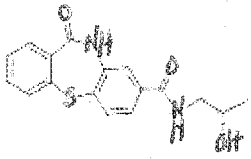
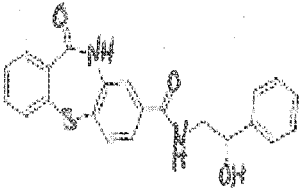
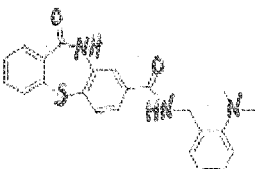
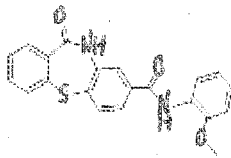
						3.46 (m, 2H), 2.92-2.87 (m, 2H);
1196		A, 6	43	377.0 (M+1) ⁺ ;		(DMSO- <i>d</i> ₆ , 500 MHz): δ 10.78 (s, 1H), 9.26 (br s, 1H), 8.96 (t, <i>J</i> = 6.0 Hz, 1H), 7.72-7.64 (m, 4H), 7.56-7.44 (m, 3H), 7.08 (d, <i>J</i> = 8.5 Hz, 2H), 6.66 (d, <i>J</i> = 8.5 Hz, 2H), 4.31-4.29 (m, 2H);
1197		A, 6	36	379.2 (M+1) ⁺ ;		(DMSO- <i>d</i> ₆ , 400 MHz): δ 10.76 (s, 1H), 9.08 (t, <i>J</i> = 5.6 Hz, 1H), 7.71-7.61 (m, 4H), 7.55-7.43 (m, 3H), 7.32 (t, <i>J</i> = 6.0 Hz, 2H), 7.15-7.10 (m, 2H), 4.41 (d, <i>J</i> = 6.0 Hz, 2H);
1199		A, 6	54	380.9 (M ⁺ +1)		(DMSO- <i>d</i> ₆ , 500 MHz): δ 10.85 (s, 1H), 8.43 (t, <i>J</i> = 5.5 Hz, 1H), 8.02 (s, 1H), 7.78 (d, <i>J</i> = 8.5 Hz, 1H), 7.67 (d, <i>J</i> = 7.5 Hz, 1H), 7.55-7.43 (m, 3H), 7.25 (d, <i>J</i> = 8.0 Hz, 1H), 3.25-3.21 (m, 2H), 1.69- 1.57 (m, 5H), 1.40-1.36 (m, 2H), 1.18-1.09 (m, 4H), 0.90- 0.83 (m, 2H);
1201		A, 6	60	459.2 (M ⁺ +1);		(DMSO- <i>d</i> ₆ , 400 MHz): δ 10.76 (s, 1H), 8.59- 8.58 (m, 1H), 7.69-7.64 (m, 3H), 7.53-7.38 (m, 5H), 7.26-

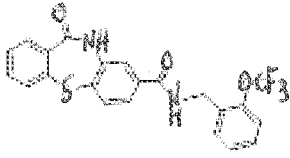
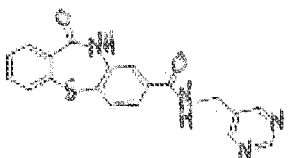
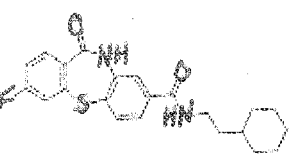
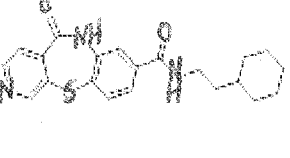
						7.16 (m, 3H), 3.48-3.47 (m, 2H), 2.89-2.87 (m, 2H);
1202		A, 6	36	377.1 (M ⁺ +1);		(DMSO- <i>d</i> ₆ , 500 MHz); δ 10.79 (s, 1H), 9.29 (s, 1H), 9.03 (t, <i>J</i> = 5.5 Hz, 1H), 7.72-7.62 (m, 4H), 7.55-7.45 (m, 3H), 7.08 (t, <i>J</i> = 8.0 Hz, 1H), 6.68 (d, <i>J</i> = 12.0 Hz, 2H), 6.60 (d, <i>J</i> = 8.5 Hz, 1H), 4.35 (d, <i>J</i> = 6.0 Hz, 2H);
1203		A, 6	45	445.1 (M+1) ⁺ ;		(DMSO- <i>d</i> ₆ , 400 MHz); δ 10.77 (s, 1H), 9.15 (t, <i>J</i> = 4.8 Hz, 1H), 7.71-7.61 (m, 4H), 7.55-7.43 (m, 4H), 7.31 (d, <i>J</i> = 8.0 Hz, 1H), 7.23 (d, <i>J</i> = 8.4 Hz, 2H), 4.48 (d, <i>J</i> = 6.0 Hz, 2H);
1204		A, 6	34	397.2 (M ⁺ +1);		(DMSO- <i>d</i> ₆ , 400 MHz); δ 10.74 (s, 1H), 8.46 (t, <i>J</i> = 6.0 Hz, 1H), 7.74-7.64 (m, 3H), 7.54-7.42 (m, 4H), 4.40 (d, <i>J</i> = 5.2 Hz, 1H), 3.26-3.20 (m, 2H), 1.77 (d, <i>J</i> = 11.2 Hz, 2H), 1.68 (d, <i>J</i> = 11.2 Hz, 2H), 1.39-1.34 (m, 3H), 1.18-1.12 (m, 2H), 0.93- 0.84 (m, 2H);

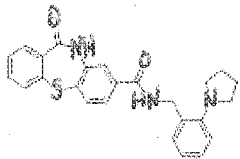
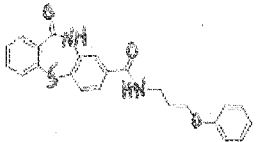
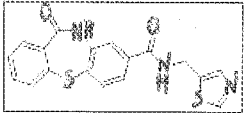
1205		A, 156	50	459.2 (M ⁺ +1);	(DMSO- <i>d</i> ₆ , 400 MHz): δ 11.05-11.04 (m, 1H), 8.54-8.53 (m, 1H), 7.81-7.73 (m, 3H), 7.68-7.60 (m, 4H), 3.26-3.25 (m, 3H), 1.70-1.62 (m, 6H), 1.39-1.37 (m, 2H), 1.23-1.14 (m, 2H), 0.88-0.85 (m, 2H);
1209		A, 6	56	369.1 (M ⁺ +1);	(DMSO- <i>d</i> ₆ , 400 MHz): δ 10.75 (s, 1H), 8.49 (t, <i>J</i> = 5.6 Hz, 1H), 7.69-7.63 (m, 3H), 7.56-7.45 (m, 4H), 3.77-3.70 (m, 2H), 3.59-3.54 (m, 1H), 3.26-3.24 (m, 2H), 1.98-1.90 (m, 1H), 1.83-1.76 (m, 2H), 1.69-1.63 (m, 2H), 1.43-1.34 (m, 1H);
1210		A, 6	56	362.4 (M ⁺ +1);	(DMSO- <i>d</i> ₆ , 500 MHz): δ 10.78 (s, 1H), 9.14 (t, <i>J</i> = 6.0 Hz, 1H), 8.49 (s, 1H), 7.74-7.65 (m, 5H), 7.55-7.44 (m, 3H), 7.28-7.23 (m, 2H), 4.53 (d, <i>J</i> = 5.5 Hz, 2H);
1211		A, 6	66	362.1 (M ⁺ +1);	(DMSO- <i>d</i> ₆ , 500 MHz): δ 10.76 (s, 1H), 9.12 (t, <i>J</i> = 6.0 Hz, 1H), 8.52 (s, 1H), 8.45-8.44 (m, 1H), 7.70 (d, <i>J</i> = 10.0 Hz, 1H), 7.67-7.60 (m, 4H), 7.55-7.44 (m, 3H), 7.33 (t,

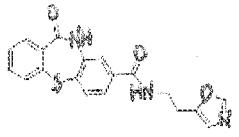
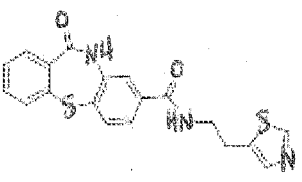
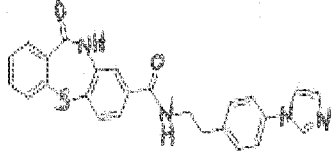
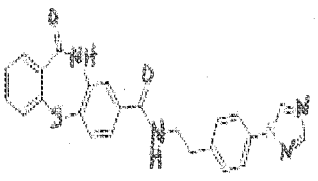
						$J = 6.5 \text{ Hz, 1H}$), 4.46 (d, $J = 5.5$ Hz, 2H);
1212		D, 6	44	389.1 ($M+1$) ⁺		¹ H NMR (400 MHz, DMSO- d ₆) δ 10.76 (s, 1H), 8.54 (t, $J =$ 5.8 Hz, 1H), 7.71 – 7.58 (m, 3H), 7.48 (tt, J = 15.3, 7.6 Hz, 4H), 7.23 (ddd, $J = 25.3, 16.4,$ 7.3 Hz, 5H), 3.45 – 3.26 (m, 2H), 3.01 (q, J = 7.1 Hz, 1H), 1.19 (d, $J = 6.9$ Hz, 3H).
1213		D, 6	54	403.1 ($M+1$) ⁺		¹ H NMR (400 MHz, DMSO- d ₆) δ 10.74 (s, 1H), 8.28 (t, $J =$ 6.4 Hz, 1H), 7.71 – 7.58 (m, 3H), 7.57 – 7.35 (m, 6H), 7.29 (t, $J = 7.6 \text{ Hz, 2H}$), 7.17 (t, $J = 7.3$ Hz, 1H), 3.41 (d, $J = 6.3 \text{ Hz,}$ 2H), 1.26 (s, 6H).
1214		D, 6	60	419.5 ($M+1$) ⁺		NMR (DMSO- d ₆ , 400 MHz): δ 10.77 (s, 1H), 8.56 (t, $J = 4.8$ Hz, 1H), 7.69- 7.63 (m, 3H), 7.55-7.43 (m, 4H), 7.10 (d, J = 8.8 Hz, 2H), 6.81 (d, $J = 8.4$ Hz, 2H), 3.96 (q, 2H), 3.42- 3.37 (m, 2H), 2.72 (t, $J = 7.2$ Hz, 2H), 1.30- 1.23 (m, 3H);

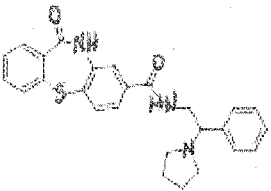
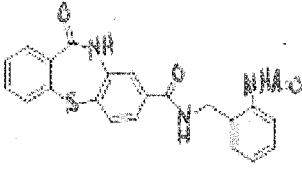
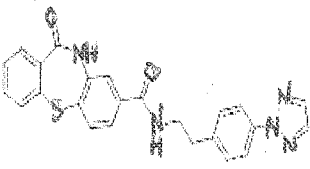
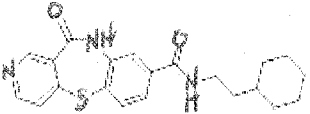
1216		A, 6	30	417.3 (M ⁺ +1);	(DMSO-d ₆ , 400 MHz): δ 10.76 (s, 1H), 8.47 (t, J = 5.6 Hz, 1H), 7.69-7.63 (m, 3H), 7.57-7.45 (m, 4H), 3.30-3.25 (m, 2H), 2.00-1.93 (m, 2H), 1.78-1.76 (m, 4H), 1.45-1.43 (m, 3H), 1.18-1.10 (m, 2H);
1218		A, 6	75	371.2 (M ⁺ +1);	(DMSO-d ₆ , 400 MHz): δ 10.77 (s, 1H), 8.50 (t, J = 5.6 Hz, 1H), 7.69-7.63 (m, 3H), 7.58-7.43 (m, 4H), 3.40-3.37 (m, 2H), 3.28 (s, 2H), 1.10 (s, 9H);
1220		A, 6	74	391.4 (M ⁺ +1);	(DMSO-d ₆ , 400 MHz): δ 10.77 (s, 1H), 8.53 (t, J = 6.8 Hz, 1H), 7.69-7.63 (m, 3H), 7.57-7.43 (m, 4H), 7.35-7.29 (m, 4H), 7.23 (t, J = 6.8 Hz, 1H), 5.46 (d, J = 4.8 Hz, 1H), 4.76-4.71 (m, 1H), 3.47-3.41 (m, 1H);
1221		A, 6	62	329.1 (M ⁺ +1);	(DMSO-d ₆ , 400 MHz): δ 10.74 (s, 1H), 8.40 (t, J = 5.6 Hz, 1H), 7.69-7.43 (m, 7H), 4.68 (d, J = 4.8 Hz, 1H), 3.77-3.71 (m, 1H), 3.16 (t, J = 6.0 Hz, 2H), 1.03 (d, J = 6.4 Hz, 3H);

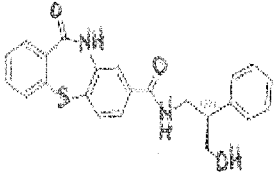
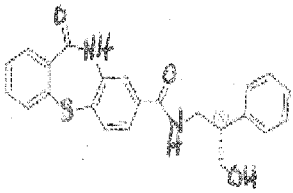
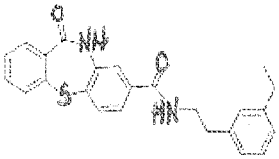
1222		A, 6	41	329.2 (M ⁺ +1);	(DMSO-d ₆ , 400 MHz): δ 10.74 (s, 1H), 8.40 (t, J = 5.6 Hz, 1H), 7.69-7.58 (m, 4H), 7.55-7.45 (m, 3H), 4.68 (d, J = 4.8 Hz, 1H), 3.77-3.71 (m, 1H), 3.16 (t, J = 6.0 Hz, 2H), 1.03 (d, J = 6.4 Hz, 3H);
1226		A, 6	75	391.6 (M ⁺ +1);	(DMSO-d ₆ , 400 MHz): δ 10.78 (s, 1H), 8.54 (t, J = 6.4 Hz, 1H), 7.69-7.63 (m, 3H), 7.57-7.43 (m, 4H), 7.35-7.29 (m, 4H), 7.23 (t, J = 7.2 Hz, 1H), 5.46 (d, J = 4.8 Hz, 1H), 4.75-4.71 (m, 1H), 3.47-3.41 (m, 1H);
1227		A, 6	83	404.4 (M ⁺ +1);	(DMSO-d ₆ , 400 MHz): δ 10.77 (s, 1H), 8.97 (t, J = 6.0 Hz, 1H), 7.73 (s, 1H), 7.70-7.63 (m, 3H), 7.56-7.43 (m, 3H), 7.21-7.16 (m, 2H), 7.11 (d, J = 7.6 Hz, 1H), 6.97 (t, J = 7.2 Hz, 1H), 4.53 (d, J = 5.6 Hz, 2H), 2.64 (s, 6H);
1228		A, 6	27	376.4 (M ⁺ +1);	(DMSO-d ₆ , 400 MHz): δ 10.80 (s, 1H), 9.49 (s, 1H), 7.75 (s, 1H), 7.73-7.70 (m, 3H), 7.55-7.46 (m, 3H), 7.16 (t, J = 7.6 Hz, 1H), 7.08 (d, J = 7.2 Hz,

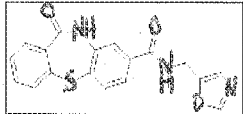
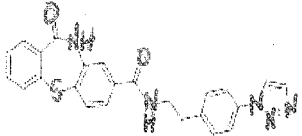
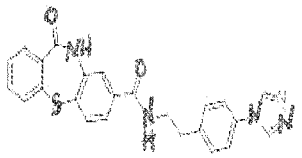
						¹ H, 6.95 (t, <i>J</i> = 7.6 Hz, 1H), 3.81 (s, 3H);
1232		D, 6	50	445.1 (M+1) ⁺		¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.79 (s, 1H), 9.08 (t, <i>J</i> = 5.9 Hz, 1H), 7.74–7.59 (m, 4H), 7.58–7.25 (m, 7H), 4.50 (d, <i>J</i> = 5.7 Hz, 2H).
1233		D, 6	83	363.1 (M+1) ⁺		¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.77 (s, 1H), 9.15 (t, <i>J</i> = 5.9 Hz, 1H), 9.07 (s, 1H), 8.73 (s, 2H), 7.72–7.40 (m, 7H), 4.46 (d, <i>J</i> = 5.7 Hz, 2H).
1234		A, 6	57	399.5 (M ⁺ +1);		(DMSO- <i>d</i> ₆ , 400 MHz): δ 10.79 (br s, 1H), 8.45 (t, <i>J</i> = 5.6 Hz, 1H), 7.67–7.73 (m, 1H), 7.66–7.63 (m, 2H), 7.58–7.56 (m, 1H), 7.46–7.43 (m, 1H), 7.35–7.30 (m, 1H), 3.27–3.22 (m, 2H), 1.70–1.58 (m, 5H), 1.41–1.35 (m, 2H), 1.27–1.09 (m, 4H), 0.95–0.83 (m, 2H);
1237		A, 6	71	382.3 (M ⁺ +1);		(DMSO- <i>d</i> ₆ , 400 MHz): δ 11.04 (br s, 1H), 8.72 (s, 1H), 8.65 (d, <i>J</i> = 4.8 Hz, 1H), 8.46 (t, <i>J</i> = 5.6 Hz, 1H), 7.69–7.67 (m, 2H), 7.63–7.58 (m, 2H), 3.27–3.22 (m, 2H), 1.70–

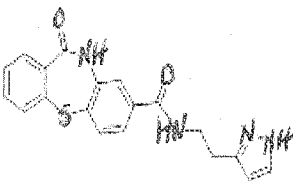
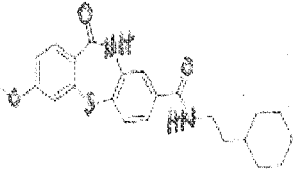
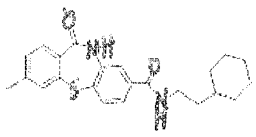
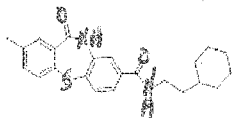
						1.58 (m, 4H), 1.41-1.35 (m, 2H), 1.27-1.14 (m, 4H), 0.93- 0.83 (m, 3H); LC-MS: 93.50%; 382.3 (M ⁺ +1);
1240		A, 6	25	430.4 (M ⁺ +1);		(DMSO-d ₆ , 400 MHz): δ 10.77 (s, 1H), 8.92 (t, J = 5.2 Hz, 1H), 7.73 (s, 1H), 7.70-7.62 (m, 3H), 7.56-7.43 (m, 3H), 7.12 (t, J = 7.6 Hz, 2H), 6.96 (d, J = 8.0 Hz, 1H), 6.84 (t, J = 6.8 Hz, 1H), 4.46 (d, J = 5.6 Hz, 2H), 3.10 (t, J = 6.0 Hz, 4H), 1.87 (t, J = 6.0 Hz, 4H);
1241		A, 6	33	405.4 (M ⁺ +1);		(DMSO-d ₆ , 500 MHz): δ 10.75 (s, 1H), 8.58 (t, J = 6.0 Hz, 1H), 7.67-7.45 (m, 7H), 7.26 (t, J = 7.5 Hz, 2H), 6.91-6.89 (m, 3H), 3.99 (t, J = 6.0 Hz, 2H), 3.41-3.30 (m, 2H), 1.94 (t, J = 6.5 Hz, 2H);
1245		D, 6	54	368.1 (M+1) ⁺		¹ H NMR (400 MHz, DMSO- d ₆) δ 10.77 (s, 1H), 9.23 (t, J = 5.9 Hz, 1H), 8.95 (s, 1H), 7.79 (s, 1H), 7.71-7.40 (m, 7H), 4.64 (d, J = 5.8 Hz, 2H).

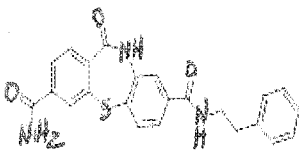
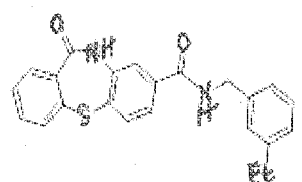
1246		A, 6	75	366.2 (M ⁺ +1);	(DMSO- <i>d</i> ₆ , 400 MHz): δ 10.78 (s, 1H), 8.65 (t, <i>J</i> = 6.0 Hz, 1H), 8.21 (s, 1H), 7.69-7.64 (m, 3H), 7.54-7.43 (m, 4H), 6.91 (s, 1H), 3.48 (q, 2H), 2.90 (t, <i>J</i> = 6.8 Hz, 2H);
1247		A, 6	40	382.2 (M ⁺ +1);	(DMSO- <i>d</i> ₆ , 400 MHz): δ 10.79 (s, 1H), 8.90 (s, 1H), 8.69-8.68 (m, 1H), 7.68-7.65 (m, 4H), 7.56-7.45 (m, 4H), 3.47 (q, 2H), 3.09 (t, <i>J</i> = 6.8 Hz, 2H);
1248		A, 6	28	441.4 (M ⁺ +1);	(DMSO- <i>d</i> ₆ , 400 MHz): δ 10.77 (s, 1H), 8.60 (t, <i>J</i> = 6.4 Hz, 1H), 8.19 (s, 1H), 7.69-7.65 (m, 4H), 7.55-7.43 (m, 6H), 7.34 (d, <i>J</i> = 7.6 Hz, 2H), 7.08 (s, 1H), 3.51-3.46 (m, 2H), 2.86 (t, <i>J</i> = 7.6 Hz, 2H);
1249		A, 6	50	442.4 (M ⁺ +1);	(DMSO- <i>d</i> ₆ , 400 MHz): δ 10.78 (s, 1H), 9.22 (s, 1H), 8.62-8.61 (m, 1H), 8.20 (s, 1H), 7.75 (d, <i>J</i> = 8.4 Hz, 2H), 7.69-7.63 (m, 3H), 7.55-7.38 (m, 6H), 3.52-3.47 (m, 2H), 2.87 (t, <i>J</i> = 6.0 Hz, 2H);

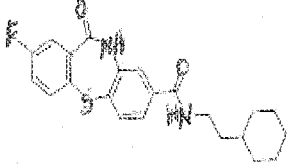
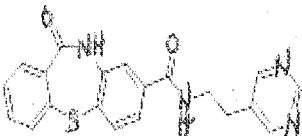
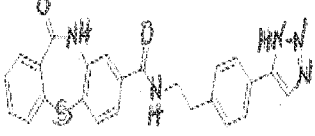
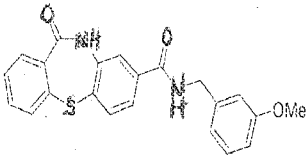
1251		A, 6	33	444.4 (M ⁺ +1);	(CDCl ₃ + CD ₃ OD, 400 MHz); δ 7.71 (d, <i>J</i> = 8.0 Hz, 1H), 7.56 (d, <i>J</i> = 8.0 Hz, 1H), 7.51-7.40 (m, 4H), 7.34-7.28 (m, 6H), 4.01 (dd, <i>J</i> = 13.2, 4.8 Hz, 1H), 3.70-3.66 (m, 1H), 3.60-3.55 (m, 1H), 2.85- 2.78 (m, 2H), 2.63-2.50 (m, 2H), 1.83 (t, <i>J</i> = 6.4 Hz, 4H);
1253		A, 6	34	418.3 (M ⁺ +1);	(DMSO- <i>d</i> ₆ , 400 MHz); δ 10.76 (s, 1H), 9.69 (s, 1H), 9.09 (t, <i>J</i> = 6.0 Hz, 1H), 7.72 (s, 1H), 7.68-7.66 (m, 2H), 7.62 (d, <i>J</i> = 8.0 Hz, 1H), 7.55-7.51 (m, 2H), 7.50-7.43 (m, 2H), 7.25- 7.20 (m, 2H), 7.10 (t, <i>J</i> = 7.2 Hz, 1H), 4.41 (d, <i>J</i> = 5.6 Hz, 2H), 2.08 (s, 3H);
1256		A, 6	46	442.3 (M ⁺ +1);	(DMSO- <i>d</i> ₆ , 400 MHz); δ 10.78 (br s, 1H), 8.62 (br s, 1H), 8.08 (br s, 2H), 7.92 (d, <i>J</i> = 7.2 Hz, 2H), 7.69-7.65 (m, 3H), 7.54- 7.40 (m, 6H), 3.50-3.49 (m, 2H), 2.88-2.87 (m, 2H);
1257		A, 6	22	381.9 (M ⁺ +1);	(DMSO- <i>d</i> ₆ , 400 MHz); δ 10.96 (s, 1H), 8.77 (s, 1H), 8.61 (d, <i>J</i>

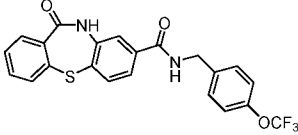
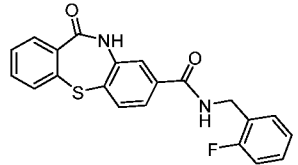
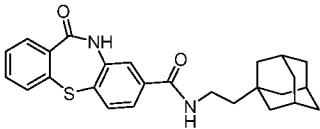
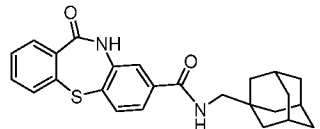
						= 5.2 Hz, 1H), 8.47 (t, J = 5.2 Hz, 1H), 7.70 (s, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.60-7.56 (m, 2H), 3.27-3.24 (m, 2H), 1.71-1.58 (m, 5H), 1.41-1.36 (m, 2H), 1.29-1.09 (m, 4H), 0.91-0.83 (m, 2H);
1258		A, 6	42	404.9 (M^+ +1);		(DMSO- d_6 , 400 MHz): δ 10.75 (s, 1H), 8.45 (t, J = 5.6 Hz, 1H), 7.68 (d, J = 7.2 Hz, 1H), 7.61 (d, J = 8.0 Hz, 2H), 7.54-7.42 (m, 4H), 7.28-7.15 (m, 5H), 4.67 (t, J = 5.2 Hz, 1H), 3.61-3.57 (m, 2H), 3.55-3.48 (m, 2H), 3.10-2.98 (m, 1H);
1259		A, 6	34	404.9 (M^+ +1);		(DMSO- d_6 , 400 MHz): δ 10.74 (s, 1H), 8.43 (t, J = 5.6 Hz, 1H), 7.67 (d, J = 6.0 Hz, 1H), 7.61 (d, J = 8.0 Hz, 2H), 7.54-7.42 (m, 4H), 7.28-7.15 (m, 5H), 4.65 (t, J = 5.2 Hz, 1H), 3.62-3.57 (m, 2H), 3.55-3.45 (m, 2H), 3.06-2.99 (m, 1H);
1260		A, 6	59	403.5 (M^+ +1);		(CD_3OD + $CDCl_3$, 400 MHz): δ 7.73 (d, J = 7.6 Hz, 1H), 7.62 (d, J = 8.0 Hz, 2H), 7.59-7.41 (m,

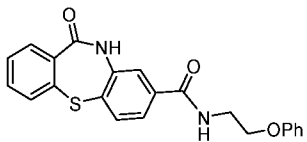
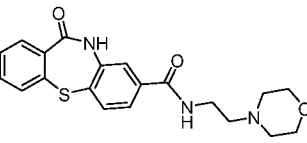
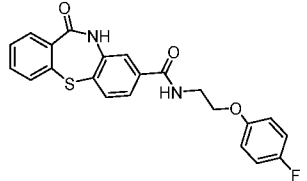
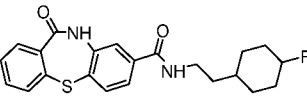
						4H), 7.17 (t, $J = 7.2$ Hz, 1H), 7.03 (t, $J = 7.6$ Hz, 2H), 3.55 (t, $J = 7.6$ Hz, 2H), 2.86 (t, $J = 7.6$ Hz, 2H), 2.58 (q, 2H), 1.16 (t, $J = 7.6$ Hz, 3H);
1264		D, 6	73	352.1 ($M+1$) ⁺		¹ H NMR (400 MHz, DMSO- d_6) δ 10.74 (s, 1H), 9.04 (t, $J = 5.6$ Hz, 1H), 8.24 (s, 1H), 7.68–7.59 (m, 3H), 7.56 (dd, $J = 8.2, 1.9$ Hz, 1H), 7.53–7.38 (m, 3H), 7.00 (s, 1H), 4.47 (d, $J = 5.5$ Hz, 2H).
1266		A, 6	41	442.5 ($M+1$) ⁺		(DMSO- d_6 , 400 MHz): δ 10.78 (s, 1H), 8.76 (s, 1H), 8.62 (t, $J = 5.6$ Hz, 1H), 7.94 (s, 1H), 7.80 (d, $J = 8.0$ Hz, 2H), 7.69–7.63 (m, 3H), 7.55–7.42 (m, 6H), 3.51 (q, 2H), 2.90 (t, $J = 6.8$ Hz, 2H);
1267		A, 6	43	442.5 ($M+1$) ⁺		(DMSO- d_6 , 400 MHz): δ 10.80 (s, 1H), 9.10 (s, 2H), 8.63–8.61 (m, 1H), 7.74–7.57 (m, 6H), 7.56–7.36 (m, 5H), 3.52–3.46 (m, 2H), 2.91–2.89 (m, 2H);

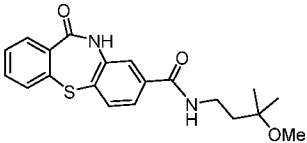
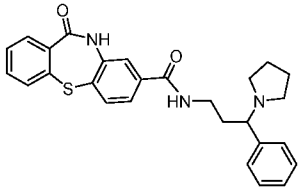
1270		A, 6	41	365.3 ($M^+ + 1$);	(DMSO- d_6 , 400 MHz): δ 12.50-12.36 (m, 1H), 10.77 (s, 1H), 8.60 (br s, 1H), 7.69-7.63 (m, 3H), 7.57-7.34 (m, 5H), 6.06 (br s, 1H), 3.49-3.44 (m, 2H), 2.82-2.78 (m, 2H);
1271		A, P-42	28	411.8 ($M^+ + 1$);	(DMSO- d_6 , 400 MHz): δ 10.59 (s, 1H), 8.43 (t, $J = 5.6$ Hz, 1H), 7.65-7.59 (m, 3H), 7.55 (d, $J = 8.4$ Hz, 1H), 7.06 (s, 1H), 7.01 (d, $J = 8.8$ Hz, 1H), 3.80 (s, 3H), 3.26-3.23 (m, 2H), 1.71-1.58 (m, 5H), 1.41-1.36 (m, 2H), 1.29-1.23 (m, 1H), 1.19-1.09 (m, 3H), 0.91-0.83 (m, 2H);
1273		A, P-8	29	395.9 ($M^+ + 1$);	(DMSO- d_6 , 400 MHz): δ 10.66 (br s, 1H), 8.43 (t, $J = 5.6$ Hz, 1H), 7.64-7.53 (m, 4H), 7.36 (s, 1H), 7.26 (d, $J = 7.6$ Hz, 1H), 3.26-3.21 (m, 2H), 2.30 (s, 3H), 1.70-1.58 (m, 5H), 1.41-1.35 (m, 2H), 1.28-1.14 (m, 4H), 0.91-0.83 (m, 2H);
1274		A, P-51	55	395.5 ($M^+ + 1$);	(DMSO- d_6 , 400 MHz): δ 10.70 (br s, 1H), 8.42 (t, $J = 5.2$ Hz, 1H), 7.62 (t, $J =$

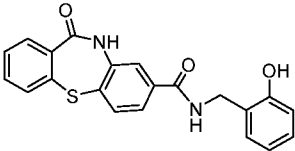
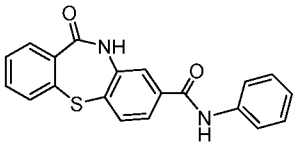
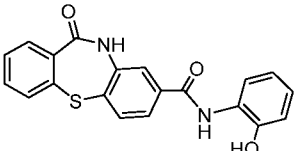
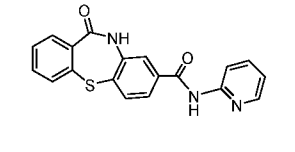
						5.6 Hz, 2H), 7.54 (d, $J = 7.2$ Hz, 1H), 7.49 (s, 1H), 7.40 (d, $J = 7.6$ Hz, 1H), 7.29 (d, $J = 7.6$ Hz, 1H), 3.26-3.21 (m, 2H), 2.29 (s, 3H), 1.70-1.62 (m, 5H), 1.40-1.35 (m, 2H), 1.26-1.09 (m, 4H), 0.95-0.83 (m, 2H);
1279		A, 135	50	418.8 ($M^+ + 1$)		(DMSO- d_6 , 500 MHz): δ 10.89 (s, 1H), 8.62-8.61 (m, 1H), 8.14 (s, 1H), 8.00 (s, 1H), 7.89 (d, $J = 8.0$ Hz, 1H), 7.75 (d, $J = 8.0$ Hz, 1H), 7.66 (d, $J = 7.0$ Hz, 2H), 7.55 (d, $J = 7.5$ Hz, 2H), 7.29-7.26 (m, 2H), 7.22-7.17 (m, 3H), 3.47-3.43 (m, 2H), 2.80 (t, $J = 7.5$ Hz, 2H);
1283		A, 6	35	389.5 ($M^+ + 1$);		(DMSO- d_6 , 400 MHz): δ 10.77 (s, 1H), 9.04 (t, $J = 5.6$ Hz, 1H), 7.71-7.61 (m, 4H), 7.55-7.43 (m, 3H), 7.21 (t, $J = 7.6$ Hz, 1H), 7.12-7.08 (m, 3H), 4.41 (d, $J = 5.6$ Hz, 2H), 2.59-2.55 (m, 2H), 1.15 (t, $J = 7.6$ Hz, 3H);

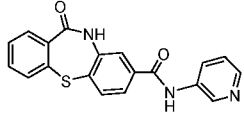
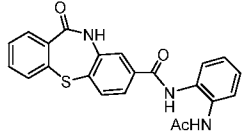
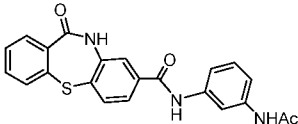
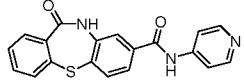
1285		A, 35	55	399.7 (M ⁺ +1);		(DMSO- <i>d</i> ₆ , 400 MHz): δ 10.88 (s, 1H), 8.46 (t, <i>J</i> = 6.8 Hz, 1H), 7.66-7.62 (m, 2H), 7.58-7.55 (m, 2H), 7.46 (d, <i>J</i> = 7.2 Hz, 1H), 7.38 (t, <i>J</i> = 7.2 Hz, 1H), 3.28-3.24 (m, 2H), 1.74-1.56 (m, 5H), 1.42-1.38 (m, 2H), 1.28-1.26 (m, 1H), 1.22-1.08 (m, 3H), 0.94-0.85 (m, 2H);
1290		A, 6	29	377.5 (M ⁺ +1);		(DMSO- <i>d</i> ₆ , 500 MHz): δ 10.77 (s, 1H), 9.01 (s, 1H), 8.66 (s, 2H), 7.69-7.62 (m, 4H), 7.55-7.44 (m, 4H), 3.54-3.51 (m, 2H), 2.85 (t, <i>J</i> = 5.6 Hz, 2H);
1291		A, 6	60	442.6 (M ⁺ +1);		(DMSO- <i>d</i> ₆ , 400 MHz): δ 15.01 (br s, 1H), 10.77 (s, 1H), 8.61 (t, <i>J</i> = 5.6 Hz, 1H), 8.25 (br s, 1H), 7.76 (d, <i>J</i> = 8.0 Hz, 2H), 7.69-7.63 (m, 3H), 7.55-7.43 (m, 4H), 7.30 (d, <i>J</i> = 8.4 Hz, 2H), 3.50-3.45 (m, 2H), 2.84 (t, <i>J</i> = 7.2 Hz, 2H);
1160		A ^a , 6, 171 (a = solvent DMF; CH ₂ Cl ₂ 1:1)	52	391.3 (M ⁺ +1);	390.10 for C ₂₂ H ₁₈ N ₂ O ₃ S	¹ H-NMR DMSO- <i>d</i> ₆ , 400 MHz): δ 10.77 (s, 1H), 9.05 (t, <i>J</i> = 5.6 Hz, 1H), 7.71-7.61 (m, 4H), 7.55-7.45 (m, 3H), 7.21 (t,

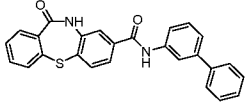
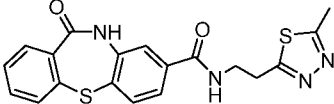
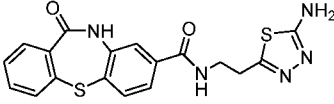
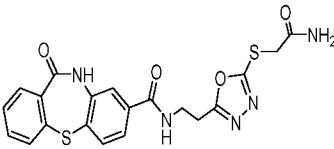
						$J = 8.0$ Hz, 1H), 6.85-6.79 (m, 3H), 4.41 (d, $J = 5.6$ Hz, 2H), 3.71 (s, 3H);
1162		D, 6, 172	55	445.4 ($M^{+}+1$)	444.08 for $C_{22}H_{15}F_3N_2O_3$	1H -NMR DMSO- d_6 , 400 MHz): δ 10.78 (s, 1H), 9.13 (t, $J = 6.0$ Hz, 1H), 7.72-7.61 (m, 4H), 7.55-7.39 (m, 5H), 7.30 (d, $J = 8.0$ Hz, 2H), 4.46 (d, $J = 6.0$ Hz, 2H);
1167		A, 6, 173	54	379.3 ($M^{+}+1$);	378.08 for $C_{21}H_{15}FN_2O_2S$	1H -NMR DMSO- d_6 , 400 MHz): δ 10.76 (s, 1H), 9.07-9.04 (m, 1H), 7.71-7.61 (m, 4H), 7.55-7.43 (m, 3H), 7.34-7.27 (m, 2H), 7.19-7.12 (m, 2H), 4.47 (d, $J = 4.8$ Hz, 2H);
1170		A, 6, 174	63	433.3 ($M^{+}+1$);	432.19 for $C_{26}H_{28}N_2O_2S$	1H -NMR DMSO- d_6 , 400 MHz): δ 10.77 (br s, 1H), 8.40 (t, $J = 4.8$ Hz, 1H), 7.69-7.62 (m, 3H), 7.55-7.43 (m, 4H), 3.25-3.20 (m, 2H), 1.91-1.90 (m, 3H), 1.67-1.58 (m, 6H), 1.49-1.47 (m, 6H), 1.30-1.26 (m, 2H);
1189		A, 6, 175	40	419.2 ($M^{+}+1$);	418.17 for $C_{25}H_{26}N_2O_2S$	1H -NMR DMSO- d_6 , 400 MHz): δ 10.74 (s, 1H), 8.29 (t, $J = 6.0$ Hz, 1H), 7.69-7.63 (m, 3H), 7.59-7.43 (m, 4H), 2.94 (d, $J = 6.4$ Hz,

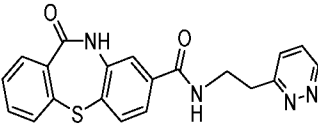
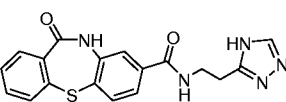
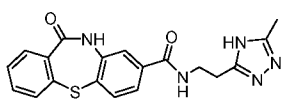
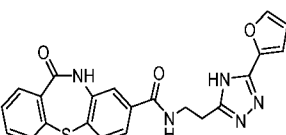
						2H), 1.93-1.91 (m, 3H), 1.66-1.56 (m, 6H), 1.46 (s, 6H);
1192		A, 6, 176	35	391.2 (M ⁺ +1);	390.10 for C ₂₂ H ₁₈ N ₂ O ₃ S	¹ H-NMR DMSO-d ₆ , 400 MHz): δ 10.77 (s, 1H), 8.74 (t, J = 6.0 Hz, 1H), 7.69-7.64 (m, 3H), 7.60-7.58 (m, 1H), 7.54-7.43 (m, 3H), 7.28 (t, J = 8.4 Hz, 2H), 6.92 (t, J = 8.4 Hz, 3H), 4.07 (t, J = 6.0 Hz, 2H), 3.59 (q, 2H);
1175		D, 6, 177	59	384.3 (M ⁺ +1);	383.13 for C ₂₀ H ₂₁ N ₃ O ₃ S	¹ H-NMR DMSO-d ₆ , 400 MHz): δ 10.77 (s, 1H), 8.43 (t, J = 4.8 Hz, 1H), 7.69-7.64 (m, 3H), 7.56-7.43 (m, 4H), 3.55-3.53 (m, 4H), 3.35-3.33 (m, 2H), 2.50 (s, 2H), 2.44-2.38 (m, 4H);
1208		A, 6, 265	33	409.1 (M ⁺ +1);	408.09 for C ₂₂ H ₁₇ FN ₂ O ₃ S	¹ H-NMR DMSO-d ₆ , 400 MHz): δ 10.77 (s, 1H), 8.72 (t, J = 5.2 Hz, 1H), 7.69-7.58 (m, 3H), 7.55 (s, 1H), 7.53-7.45 (m, 3H), 7.09 (t, J = 8.8 Hz, 2H), 6.96-6.93 (m, 2H), 4.06 (t, J = 5.2 Hz, 2H), 3.58 (d, J = 5.6 Hz, 2H);
1217		A, 6, 269	28	399.3 (M ⁺ +1);	398.15 for C ₂₂ H ₂₃ FN ₂	¹ H-NMR (DMSO-d ₆ , 400 MHz): δ 10.76 (s, 1H), 8.45 (t, J = 5.6 Hz, 1H),

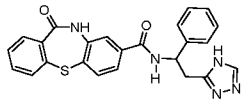
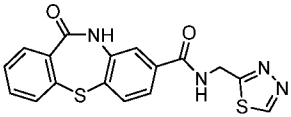
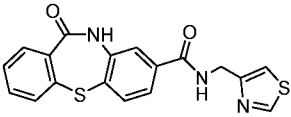
					O ₂ S	7.65-7.63 (m, 3H), 7.56-7.45 (m, 4H), 4.84-4.72 (m, 1H), 3.30-3.29 (m, 2H), 1.87-1.78 (m, 3H), 1.54-1.51 (m, 2H), 1.42-1.41 (m, 4H), 1.21-1.18 (m, 2H);
1238		A, 6, 273	37	371.2 (M ⁺ +1);	370.14 for C ₂₀ H ₂₂ N ₂ O ₃ S	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.74 (s, 1H), 8.41 (t, <i>J</i> = 5.6 Hz, 1H), 7.69-7.63 (m, 3H), 7.55-7.41 (m, 4H), 3.28-3.22 (m, 2H), 3.10 (s, 3H), 1.66 (t, <i>J</i> = 8.4 Hz, 2H), 1.11 (s, 6H);
1252		A, 6, 277	22	458.4 (M ⁺ +1);	457.18 for C ₂₇ H ₂₇ N ₃ O ₂ S	¹ H-NMR (CDCl ₃ + CD ₃ OD, 400 MHz): δ 7.73 (d, <i>J</i> = 7.6 Hz, 1H), 7.61 (d, 8.0 Hz, 1H), 7.52 (d, <i>J</i> = 8.4 Hz, 2H), 7.48-7.46 (m, 3H), 7.45-7.31 (m, 4H), 7.26 (d, <i>J</i> = 6.8 Hz, 1H), 3.31-3.30 (m, 1H), 3.25-3.17 (m, 1H), 3.06-3.00 (m, 1H), 2.68-2.67 (m, 2H), 2.44-2.42 (m, 2H), 2.36-2.28 (m, 1H), 2.13-2.04 (m, 1H), 1.78 (t, <i>J</i> = 6.4 Hz, 4H);

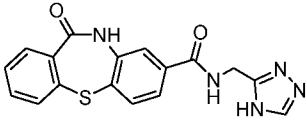
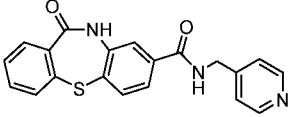
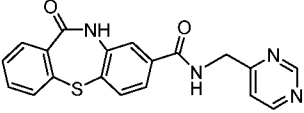
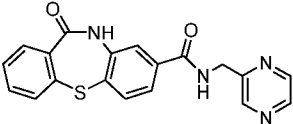
1219		A, 6, 178	59	376.9 (M ⁺ +1)	C ₂₁ H ₁₆ N ₂ O 3S 376.09	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.75 (s, 1H), 9.50 (s, 1H), 8.91(t, <i>J</i> = 6.0Hz, 1H), 7.72-7.65 (m, 4H), 7.55-7.43 (m, 3H), 7.08- 7.03 (m, 2H), 6.79 (d, <i>J</i> =7.6 Hz, 1H), 6.72 (t, <i>J</i> =7.2 Hz, 1H), 4.38 (d, <i>J</i> =5.6 Hz, 2H);
1223		A, 6, 179	59	347.2 (M ⁺ +1);	C ₂₀ H ₁₄ N ₂ O 2S 346.08	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.80 (s, 1H), 10.25 (s, 1H), 7.75-7.71 (m, 6H), 7.55 (br s, 1H), 7.49 (t, <i>J</i> =8.8 Hz, 2H), 7.32 (t, <i>J</i> = 6.8Hz, 2H), 7.10 (t, <i>J</i> =7.2 Hz, 1H);
1229		D, 6, 180	34	363.5 (M ⁺ +1)	C ₂₀ H ₁₄ N ₂ O 3S 362.07	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.81 (s, 1H), 9.71 (br s, 1H), 9.51 (br s, 1H), 7.76 (s, 1H), 7.71 (s, 3H), 7.64 (d, <i>J</i> =8.4 Hz, 1H), 7.57-7.45 (m, 3H), 7.02 (t, <i>J</i> = 6.8 Hz, 1H), 6.90 (d, <i>J</i> =7.2 Hz, 1H), 6.81 (t, <i>J</i> =8.0 Hz, 1H);
1230		E, 6, 181	35	348.4 (M ⁺ +1)	C ₁₉ H ₁₃ N ₃ O 2S 347.07	¹ H-NMR (DMSO- <i>d</i> ₆ , 500 MHz): δ 10.85- 10.82 (m, 2H), 8.38 (br s, 1H), 8.14 (d, <i>J</i> =8.0 Hz, 1H), 7.83- 7.67 (m, 5H), 7.57-7.47 (m,

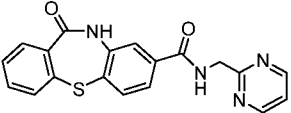
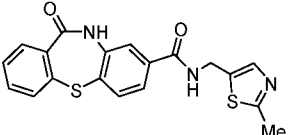
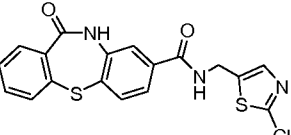
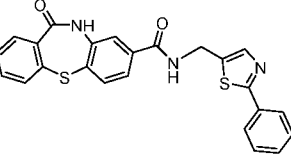
						3H), 7.16 (t, J = 7.5 Hz, 1H);
1231		B, 6, 182	61	348.2 ($M^{+}+1$);	$C_{19}H_{13}N_3O_2S$ 347.07	1H -NMR (DMSO- d_6 , 400 MHz): δ 10.85 (s, 1H), 10.48 (s, 1H), 8.88 (s, 1H), 8.31 (s, 1H), 8.15 (d, J = 8.4 Hz, 1H), 7.78-7.70 (m, 4H), 7.57-7.45 (m, 3H), 7.40-7.37 (m, 1H);
1242		A, 6, 183	28	404.2 ($M^{+}+1$);	$C_{22}H_{17}N_3O_3S$ 403.10	1H -NMR (DMSO- d_6 , 400 MHz): δ 10.85 (s, 1H), 9.85 (s, 1H), 9.61 (s, 1H), 7.76-7.68 (m, 4H), 7.57 (t, J = 6.8 Hz, 2H), 7.53-7.47 (m, 3H), 7.19 (t, J = 4.4 Hz, 2H), 2.05 (s, 3H);
1243		A, 6, 184	51	404.3 ($M^{+}+1$);	$C_{22}H_{17}N_3O_3S$ 403.10	1H -NMR (DMSO- d_6 , 400 MHz): δ 10.82 (br s, 1H), 10.29 (br s, 1H), 9.95 (br s, 1H), 8.06 (s, 1H), 7.75-7.70 (m, 4H), 7.57-7.47 (m, 3H), 7.37 (d, J = 7.6 Hz, 1H), 7.32 (d, J = 7.2 Hz, 1H), 7.23 (t, J = 7.6 Hz, 1H), 2.03 (s, 3H);
1444		A, 6, 185	32	347.9 ($M^{+}+1$);	$C_{19}H_{13}N_3O_2S$ 347.07	1H -NMR (DMSO- d_6 , 400 MHz): δ 10.85 (s, 1H), 10.62 (s, 1H), 8.48 (d, J = 6.1 Hz, 2H), 7.79-7.69 (m, 6H), 7.60-7.45 (m, 3H);

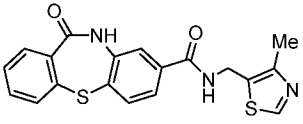
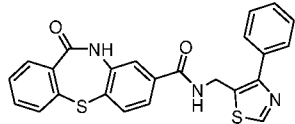
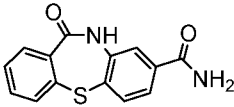
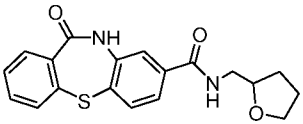
1445		A, 6, 186	25	423.1 (M ⁺ +1);	C ₂₆ H ₁₈ N ₂ O S 422.11	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.85 (s, 1H), 10.36 (s, 1H), 8.07- 8.04 (m, 1H), 7.80-7.70 (m, 5H), 7.65-7.61 (m, 2H), 7.57 (dd, <i>J</i> = 7.7, 1.6 Hz, 1H), 7.54- 7.35 (m, 7H);
1567		A, 6, 187	44	396.9 (M ⁺ +1);	C ₁₉ H ₁₆ N ₄ O S ₂ 396.07	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.79 (s, 1H), 8.72 (t, <i>J</i> = 5.3 Hz, 1H), 7.71-7.63 (m, 3H), 7.59-7.41 (m, 4H), 3.59 (q, <i>J</i> = 6.3 Hz, 2H), 3.29-3.25 (m, 2H), 2.66 (s, 3H);
1568		A, 6, 188	55	398.0 (M ⁺ +1)	C ₁₈ H ₁₅ N ₅ O S ₂ 397.07	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.78 (s, 1H), 8.69 (t, <i>J</i> = 5.4 Hz, 1H), 7.74-7.63 (m, 3H), 7.60-7.43 (m, 4H), 6.97 (s, 2H), 3.51 (q, <i>J</i> = 6.6 Hz, 2H), 3.03 (t, <i>J</i> = 6.7 Hz, 2H);
1582		B, 6, 189	63	456.1 (M ⁺ +1);	C ₂₀ H ₁₇ N ₅ O S ₂ 455.07	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.78 (s, 1H), 8.71 (t, <i>J</i> = 5.4 Hz, 1H), 7.74-7.62 (m, 4H), 7.56-7.41 (m, 4H), 7.32 (br s, 1H), 3.99 (s, 2H), 3.58 (q, <i>J</i> = 6.5 Hz, 2H), 3.06 (t, <i>J</i> = 6.6 Hz, 2H);

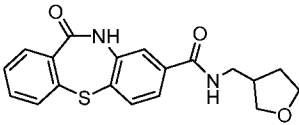
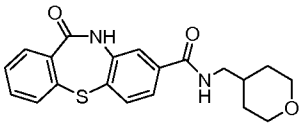
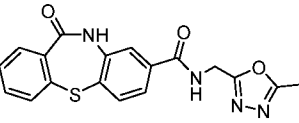
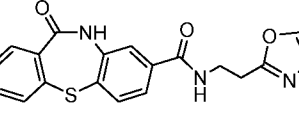
1569		A, 6, 190	75	377.1 (M ⁺ +1)	C ₂₀ H ₁₆ N ₄ O 2S 376.10	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.76 (s, 1H), 9.07 (dd, <i>J</i> = 4.4, 2.0 Hz, 1H), 8.64 (t, <i>J</i> = 5.5 Hz, 1H), 7.71-7.41 (m, 9H), 3.68- 3.62 (m, 2H), 3.14 (t, <i>J</i> = 7.0 Hz, 2H);
1551		A, 6, 191	22	366.0 (M ⁺ +1);	C ₁₈ H ₁₅ N ₅ O 2S 365.09	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 13.67 (br s, 1H), 10.77 (s, 1H), 8.64 (br s, 1H), 8.42 (br s, 0.4H), 7.82 (br s, 0.6H), 7.71- 7.62 (m, 3H), 7.58-7.42 (m, 4H), 3.55 (q, <i>J</i> = 6.7 Hz, 2H), 3.00-2.82 (m, 2H);
1583		B ^a , 6, 192 (a = RT 8 h)	51	380.1 (M ⁺ +1);	C ₁₉ H ₁₇ N ₅ O 2S 379.11	¹ H-NMR (DMSO- <i>d</i> ₆ , 500 MHz): δ 13.24 (d, <i>J</i> = 9.8 Hz, 1H), 10.77 (br s, 1H), 8.69- 8.57 (m, 1H), 7.71-7.63 (m, 3H), 7.58-7.43 (m, 4H), 3.56- 3.47 (m, 2H), 2.87 (t, <i>J</i> = 7.1 Hz, 1H), 2.76 (t, <i>J</i> = 7.5 Hz, 1H), 2.31-2.16 (s, 3H);
1570		A, 6, 193	46	432.0 (M ⁺ +1);	C ₂₂ H ₁₇ N ₅ O 3S 431.11	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 13.80 (br s, 1H), 10.77 (s, 1H), 8.69 (br s, 1H), 7.74 (br s, 1H), 7.70-7.65 (m, 2H), 7.64 (s,

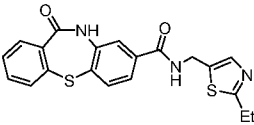
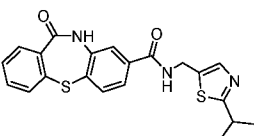
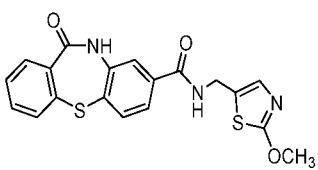
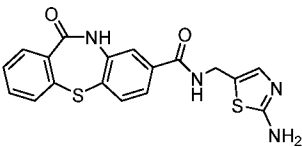
						1H), 7.58-7.43 (m, 4H), 6.84 (br s, 1H), 6.59 (br s, 1H), 3.62-3.55 (m, 2H), 3.00-2.91 (m, 2H);
1552		A, 6, 194	31	442.1 (M ⁺ +1);	C ₂₄ H ₁₉ N ₅ O ₂ S 441.13	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 13.62 (br s, 1H), 10.75 (s, 1H), 9.01 (br s, 1H), 8.38 (br s, 0.5H), 7.77 (br s, 0.5H), 7.71-7.62 (m, 3H), 7.60-7.42 (m, 4H), 7.37-7.32 (m, 2H), 7.27 (t, <i>J</i> = 7.5 Hz, 2H), 7.22-7.17 (m, 1H), 5.47 (q, <i>J</i> = 7.7 Hz, 1H), 3.39-3.33 (m, 1H), 3.27-3.17 (m, 1H);
1571		A, 6, 195	86	369.0 (M ⁺ +1);	C ₁₇ H ₁₂ N ₄ O ₂ S ₂ 368.04	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.79 (s, 1H), 9.53-9.48 (m, 2H), 7.73-7.67 (m, 3H), 7.62 (dd, <i>J</i> = 8.0, 1.8 Hz, 1H), 7.57-7.43 (m, 3H), 4.86 (d, <i>J</i> = 5.9 Hz, 2H);
1584		A, 6, 196	54	367.9 (M ⁺ +1);	C ₁₈ H ₁₃ N ₃ O ₂ S ₂ 367.04	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.77 (s, 1H), 9.10 (t, <i>J</i> = 5.7 Hz, 1H), 9.04 (s, 1H), 7.74-7.62 (m, 4H), 7.57-7.42 (m, 4H), 4.58 (d, <i>J</i> = 5.6 Hz, 2H);

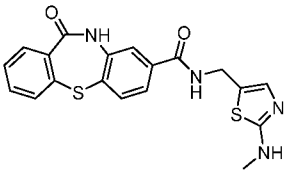
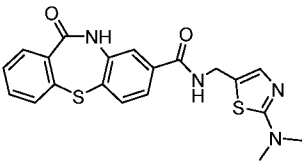
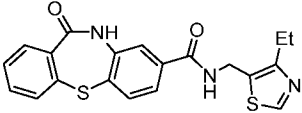
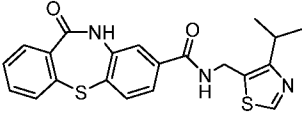
1599		A, 6, 197	23	352.1 (M ⁺ +1);	C ₁₇ H ₁₃ N ₃ O S 351.08	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 13.77 (br s, 1H), 10.79 (br s, 1H), 9.06 (br s, 1H), 8.33 (br s, 1H), 7.74-7.60 (m, 4H), 7.57- 7.42 (m, 3H), 4.51 (d, <i>J</i> = 4.8 Hz, 2H);
1572		A, 6, 198	50	361.9 (M ⁺ +1);	C ₂₀ H ₁₅ N ₃ O S 361.09	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.78 (s, 1H), 9.16 (t, <i>J</i> = 5.9 Hz, 1H), 8.48 (d, <i>J</i> = 5.9 Hz, 2H), 7.76- 7.63 (m, 4H), 7.57-7.42 (m, 3H), 7.27 (d, <i>J</i> = 5.5 Hz, 2H), 4.46 (d, <i>J</i> = 5.7 Hz, 2H);
1585		A, 6, 199	64	362.9 (M ⁺ +1);	C ₁₉ H ₁₄ N ₄ O S 362.08	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.79 (s, 1H), 9.22 (t, <i>J</i> = 5.3 Hz, 1H), 9.09 (s, 1H), 8.71 (d, <i>J</i> = 5.2 Hz, 1H), 7.74 (s, 1H), 7.72- 7.65 (m, 3H), 7.57-7.44 (m, 3H), 7.39 (d, <i>J</i> = 4.9 Hz, 1H), 4.52 (d, <i>J</i> = 5.9 Hz, 2H);
1586		A, 6, 200	60	362.9 (M ⁺ +1);	C ₁₉ H ₁₄ N ₄ O S 362.08	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.78 (s, 1H), 9.22 (t, <i>J</i> = 5.7 Hz, 1H), 8.61 (s, 1H), 8.58- 8.56 (m, 1H), 8.54-8.51 (m, 1H), 7.73 (s, 1H), 7.71- 7.63 (m, 3H), 7.57-7.43 (m,

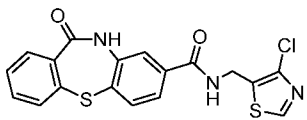
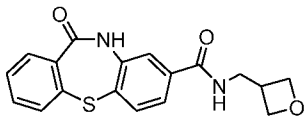
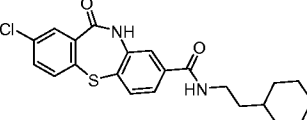
						3H), 4.59 (d, J = 5.7 Hz, 2H);
1587		A, 6, 201	67	362.9 ($M^{+}+1$);	$C_{19}H_{14}N_4O$ $_2S$ 362.08	1H -NMR (DMSO- d_6 , 400 MHz): δ 10.80 (s, 1H), 9.10 (t, J = 5.8 Hz, 1H), 8.74 (d, J = 4.9 Hz, 2H), 7.73 (s, 1H), 7.71-7.65 (m, 3H), 7.57-7.43 (m, 3H), 7.38 (t, J = 4.9 Hz, 1H), 4.63 (d, J = 5.9 Hz, 2H);
1588		A, 6, 202	71	381.9 ($M^{+}+1$);	$C_{19}H_{15}N_3O$ $_2S_2$ 381.06	1H -NMR (DMSO- d_6 , 400 MHz): δ 10.77 (s, 1H), 9.17 (t, J = 5.7 Hz, 1H), 7.71-7.64 (m, 3H), 7.59-7.42 (m, 5H), 4.55 (d, J = 5.6 Hz, 2H), 2.57 (s, 3H);
1589		A, 6, 203	72	401.9 ($M^{+}+1$);	$C_{18}H_{12}ClN$ $_3O_2S_2$ 401.01	1H -NMR (DMSO- d_6 , 400 MHz): δ 10.77 (s, 1H), 9.28 (t, J = 5.7 Hz, 1H), 7.72-7.64 (m, 3H), 7.61-7.42 (m, 5H), 4.55 (d, J = 5.4 Hz, 2H);
1590		A, 6, 204	65	443.9 ($M^{+}+1$);	$C_{24}H_{17}N_3O$ $_2S_2$ 443.08	1H -NMR (DMSO- d_6 , 400 MHz): δ 10.78 (s, 1H), 9.28 (t, J = 5.7 Hz, 1H), 7.90-7.86 (m, 2H), 7.79 (s, 1H), 7.73-7.66 (m, 3H), 7.61 (dd, J = 8.2, 1.8 Hz, 1H), 7.56-7.42 (m, 6H), 4.66 (d, J = 5.6 Hz, 2H);

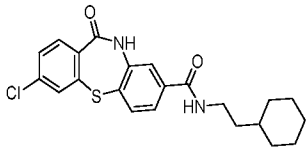
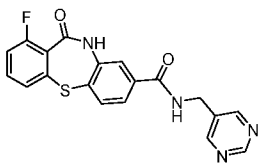
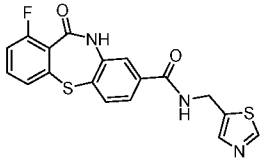
1600		A, 6, 205	28	382.0 (M ⁺ +1);	C ₁₉ H ₁₅ N ₃ O 2S ₂ 381.06	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.76 (s, 1H), 9.15 (t, <i>J</i> = 5.7 Hz, 1H), 8.83 (s, 1H), 7.70-7.64 (m, 3H), 7.59-7.43 (m, 4H), 4.55 (d, <i>J</i> = 5.7 Hz, 2H), 2.39 (s, 3H);
1605		A ^b , 6, 206 <i>b</i> = 24 h RT	32	443.9 (M ⁺ +1);	C ₂₄ H ₁₇ N ₃ O 2S ₂ 443.08	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.78 (s, 1H), 9.34 (t, <i>J</i> = 5.5 Hz, 1H), 9.02 (s, 1H), 7.74-7.66 (m, 5H), 7.60 (dd, <i>J</i> = 8.1, 1.8 Hz, 1H), 7.56-7.39 (m, 6H), 4.74 (d, <i>J</i> = 5.5 Hz, 2H);
1525		B, 6, 133	73	270.8 (M ⁺ +1);	C ₁₄ H ₁₀ N ₂ O 2S 270.05	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.77 (s, 1H), 7.99 (br s, 1H), 7.72- 7.58 (m, 4H), 7.56-7.43 (m, 4H);
1592		A, 6, 207	23	354.9 (M ⁺ +1)	C ₁₉ H ₁₈ N ₂ O 3S 354.10	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.75 (br s, 1H), 8.55 (t, <i>J</i> = 5.4 Hz, 1H), 7.71-7.62 (m, 3H), 7.60- 7.43 (m, 4H), 3.98-3.89 (m, 1H), 3.79-3.72 (m, 1H), 3.65- 3.57 (m, 1H), 3.29-3.25 (m, 2H), 1.93-1.73 (m, 3H), 1.61- 1.49 (m, 1H);

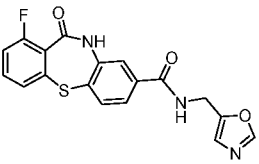
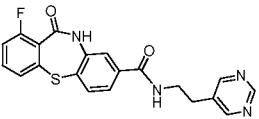
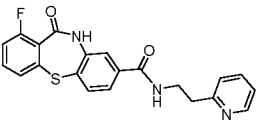
1606		A, 6, 208	23	354.9 (M ⁺ +1);	C ₁₉ H ₁₈ N ₂ O S 354.10	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.75 (br s, 1H), 8.60 (t, <i>J</i> = 5.5 Hz, 1H), 7.71-7.63 (m, 3H), 7.59 - 7.43 (m, 4H), 3.76-3.56 (m, 3H), 3.43 (dd, <i>J</i> = 8.5, 5.4 Hz, 1H), 3.26-3.14 (m, 2H), 2.47- 2.38 (m, 1H), 1.96-1.86 (m, 1H), 1.63-1.51 (m, 1H);
1607		A, 6, 209	22	354.9 (M ⁺ +1);	C ₂₀ H ₂₀ N ₂ O S 368.12	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.75 (s, 1H), 8.51 (t, <i>J</i> = 5.6 Hz, 1H), 7.71-7.62 (m, 3H), 7.60-7.43 (m, 4H), 3.82 (dd, <i>J</i> = 11.2, 2.5 Hz, 2H), 3.27-3.20 (m, 2H), 3.12 (t, <i>J</i> = 6.3 Hz, 2H), 1.81-1.69 (m, 1H), 1.61 - 1.51 (m, 2H), 1.24- 1.10 (m, 2H);
1578		A, 6, 210	30	367.0 (M ⁺ +1);	C ₁₈ H ₁₄ N ₄ O S 366.08	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.79 (s, 1H), 9.26 (t, <i>J</i> = 5.7 Hz, 1H), 7.72-7.67 (m, 3H), 7.62 (dd, <i>J</i> = 7.9, 1.8 Hz, 1H), 7.57-7.43 (m, 3H), 4.63 (d, <i>J</i> = 5.6 Hz, 2H), 2.45 (s, 3H);
1603		A, 6, 283	70	381.0 (M ⁺ +1);	C ₁₉ H ₁₆ N ₄ O S 380.09	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.78 (s, 1H), 8.69 (t, <i>J</i> = 5.7 Hz, 1H),

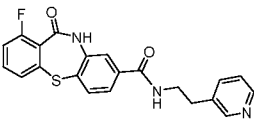
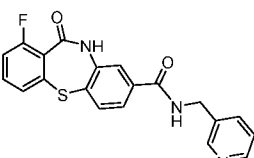
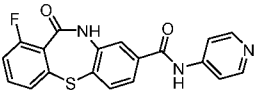
						7.70-7.62 (m, 3H), 7.56-7.42 (m, 4H), 3.58 (q, $J = 6.6$ Hz, 2H), 3.03 (t, $J = 6.8$ Hz, 2H), 2.43 (s, 3H);
1604		B, 6, 292	89	395.9 ($M^{+}+1$);	$C_{20}H_{17}N_3O_2S_2$ 395.08	1H -NMR (CDCl ₃ , 400 MHz): δ 10.77 (s, 1H), 9.18 (t, $J = 5.7$ Hz, 1H), 7.71-7.64 (m, 3H), 7.60-7.43 (m, 5H), 4.56 (d, $J = 5.6$ Hz, 2H), 2.90 (q, $J = 7.5$ Hz, 2H), 1.24 (t, $J = 7.5$ Hz, 3H);
1611		B, 6, 298	73	410.0 ($M^{+}+1$);	$C_{21}H_{19}N_3O_2S_2$ 409.09	1H NMR (DMSO- d_6 , 400 MHz): δ 10.77 (s, 1H), 9.18 (t, $J = 5.7$ Hz, 1H), 7.72-7.64 (m, 3H), 7.61-7.42 (m, 5H), 4.57 (d, $J = 5.6$ Hz, 2H), 3.22-3.15 (m, 1H), 1.27 (d, $J = 6.9$ Hz, 6H);
1612		B, 6, 300	59	397.9 ($M^{+}+1$);	$C_{19}H_{15}N_3O_3S_2$ 397.06	1H NMR (DMSO- d_6 , 400 MHz): δ 10.76 (s, 1H), 9.15 (t, $J = 5.6$ Hz, 1H), 7.71-7.63 (m, 3H), 7.60-7.42 (m, 4H), 7.06 (s, 1H), 4.44 (d, $J = 5.6$ Hz, 2H), 3.95 (s, 3H);
1613		A, 6, 303	23	382.9 ($M^{+}+1$);	$C_{18}H_{14}N_4O_2S_2$ 382.06	1H NMR (DMSO- d_6 , 400 MHz): δ 10.76 (s, 1H), 9.00 (t, $J = 5.5$ Hz, 1H), 7.72-7.42 (m, 7H), 6.88 (br s, 2H), 6.81 (s,

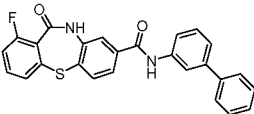
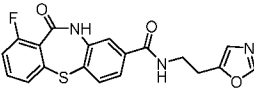
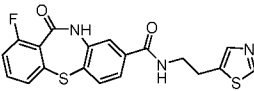
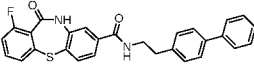
						1H), 4.35 (d, J = 5.5 Hz, 2H);
1638		A, 6, 308	53	396.9 ($M^{+}+1$);	$C_{19}H_{16}N_4O$ $_2S_2$ 396.07	1H NMR (DMSO- d_6 , 500 MHz): δ 10.77 (s, 1H), 9.03 (t, J = 5.6 Hz, 1H), 7.69-7.62 (m, 3H), 7.59-7.42 (m, 4H), 7.34- 7.30 (m, 1H), 6.87 (s, 1H), 4.36 (d, J = 5.8 Hz, 2H), 2.72 (d, J = 4.9 Hz, 3H);
1639		A, 6, 311	61	411.0 ($M^{+}+1$);	$C_{20}H_{18}N_4O$ $_2S_2$ 410.09	1H NMR (DMSO- d_6 , 400 MHz): δ 10.75 (s, 1H), 9.05 (t, J = 5.7 Hz, 1H), 7.72-7.62 (m, 3H), 7.59-7.42 (m, 4H), 6.99 (s, 1H), 4.41 (d, J = 5.5 Hz, 2H), 2.95 (s, 6H);
1631		A, 6, 319	15	395.9 ($M^{+}+1$);	$C_{20}H_{17}N_3O$ $_2S_2$ 395.08	1H -NMR (DMSO- d_6 , 400 MHz): δ 10.78 (s, 1H), 8.69 (t, J = 5.7 Hz, 1H), 7.70-7.62 (m, 3H), 7.56-7.42 (m, 4H), 3.58 (q, J = 6.6 Hz, 2H), 3.03 (t, J = 6.8 Hz, 2H), 2.43 (s, 3H);
1614		A, 6, 327 (Reaction time 24h)	27	409.9 ($M^{+}+1$);	$C_{21}H_{19}N_3O$ $_2S_2$ 409.09	1H NMR (DMSO- d_6 , 400 MHz): δ 10.77 (s, 1H), 9.15 (t, J = 5.8 Hz, 1H), 8.84 (s, 1H), 7.70-7.64 (m, 3H), 7.59-7.42 (m, 4H), 4.58 (d, J = 5.9 Hz, 2H), 3.32-3.29 (m, 1H), 1.21 (d, J = 6.8 Hz,

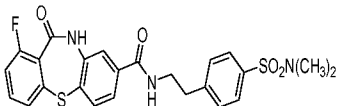
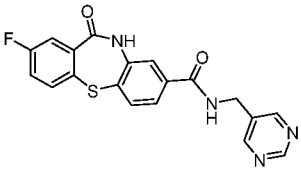
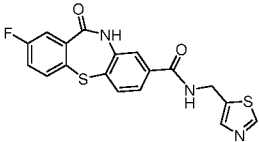
						6H);
1632		A, 6, 337	33	401.9 ($M^{+}+1$);	$C_{18}H_{12}ClN$ $_3O_2S_2$ 401.01	1H NMR (DMSO- d_6 , 400 MHz): δ 10.77 (s, 1H), 9.31 (t, $J = 5.5$ Hz, 1H), 9.01 (s, 1H), 7.73-7.65 (m, 3H), 7.59 (dd, J $= 7.9, 1.8$ Hz, 1H), 7.56-7.42 (m, 3H), 4.57 (d, $J = 5.7$ Hz, 2H);
1640		A, 6, 341 (Reaction time 12 h)	16	341.0 ($M^{+}+1$);	$C_{18}H_{16}N_2O$ $_3S$ 340.09	1H NMR (DMSO- d_6 , 400 MHz): δ 10.75 (s, 1H), 8.62 (t, $J = 5.5$ Hz, 1H), 7.70-7.63 (m, 3H), 7.59-7.43 (m, 4H), 4.60 (dd, $J = 7.8, 6.0$ Hz, 2H), 4.31 (t, $J = 6.0$ Hz, 2H), 3.50 (dd, J $= 7.8, 6.0$ Hz, 2H), 3.17-3.09 (m, 1H).
1235		A, 14, 261	45	415.4 ($M^{+}+1$);	$C_{22}H_{23}ClN$ $_2O_2S$ 414.12	1H -NMR ($CDCl_3$, 400 MHz): δ 8.16 (br s, 1H), 7.81 (s, 1H), 7.61 (d, $J = 8.0$ Hz, 1H), 7.57 (s, 1H), 7.45-7.42 (m, 2H), 7.39-7.36 (m, 1H), 5.99- 5.98 (m, 1H), 3.48-3.43 (m, 2H), 1.75-1.67 (m, 5H), 1.57- 1.46 (m, 2H), 1.34-1.31 (m, 1H), 1.27-1.16 (m, 3H), 0.98- 0.92 (m, 2H);

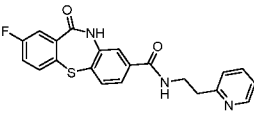
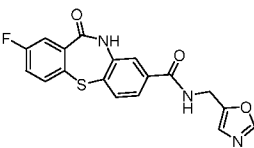
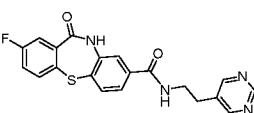
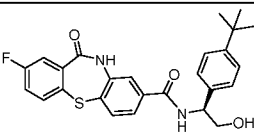
1250		A, 21, 261 (285 mg)	45	415.5 (M ⁺ +1)	C ₂₂ H ₂₃ ClN O ₂ S 414.12	¹ H-NMR (CDCl ₃ , 400 MHz): δ 8.70 (s, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.63-7.60 (m, 2H), 7.51 (s, 1H), 7.45 (d, J = 9.6 Hz, 1H), 7.35 (d, J = 10.0 Hz, 1H), 6.07 (t, J = 6.0 Hz, 1H), 3.48- 3.43 (m, 2H), 1.73-1.45 (m, 8H), 1.30-1.14 (m, 3H), 1.00- 0.91 (m, 2H);
1540		A, 28, 212 (75 mg)	15	381.0 (M ⁺ +1);	C ₁₉ H ₁₃ FN ₄ O ₂ S 380.07	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.94 (br s, 1H), 9.20 (t, J = 5.7 Hz, 1H), 9.08 (s, 1H), 8.75 (s, 2H), 7.75-7.60 (m, 3H), 7.53- 7.46 (m, 1H), 7.41 (dd, J = 7.8, 0.9 Hz, 1H), 7.32-7.28 (m, 1H), 4.47 (d, J = 5.6 Hz, 2H);
1541		A, 28, 213	22	385.9 (M ⁺ +1);	C ₁₈ H ₁₂ FN ₃ O ₂ S ₂ 385.04	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.95 (s, 1H), 9.25 (t, J = 5.7 Hz, 1H), 8.96 (s, 1H), 7.80 (s, 1H), 7.71-7.65 (m, 2H), 7.60 (dd, J = 8.0, 2.0 Hz, 1H), 7.52-7.46 (m, 1H), 7.40 (d, J = 7.7 Hz, 1H), 7.34-7.28 (m, 1H), 4.65 (d, J = 5.7 Hz, 2H);

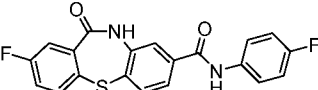
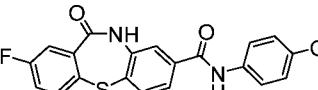
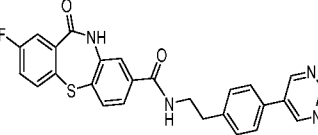
1542		A, 28, 214	31	370.0 (M ⁺ +1);	C ₁₈ H ₁₂ FN ₃ O ₃ S 369.06	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.95 (s, 1H), 9.09 (t, <i>J</i> = 5.4 Hz, 1H), 8.27 (s, 1H), 7.72-7.65 (m, 2H), 7.61 (dd, <i>J</i> = 8.0, 1.9 Hz, 1H), 7.53-7.46 (m, 1H), 7.40 (d, <i>J</i> = 7.2 Hz, 1H), 7.34-7.27 (m, 1H), 7.03 (s, 1H), 4.51 (d, <i>J</i> = 5.4 Hz, 2H);
1543		A, 28, 215	22	370.0 (M ⁺ +1);	C ₂₀ H ₁₅ FN ₄ O ₂ S 394.09	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.96 (s, 1H), 9.01 (s, 1H), 8.69-8.60 (m, 3H), 7.66 (d, <i>J</i> = 8.0 Hz, 1H), 7.62 (s, 1H), 7.51 (dd, <i>J</i> = 8.2, 2.0 Hz, 1H), 7.49-7.46 (m, 1H), 7.40 (d, <i>J</i> = 7.8 Hz, 1H), 7.28-7.33 (m, 1H), 3.53 (q, <i>J</i> = 6.4 Hz, 2H), 2.84 (t, <i>J</i> = 6.6 Hz, 2H);
1471		A, 28, 216	22	393.9 (M ⁺ +1);	C ₂₁ H ₁₆ FN ₃ O ₂ S 393.09	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.96 (s, 1H), 8.63 (t, <i>J</i> = 5.5 Hz, 1H), 8.52-8.47 (m, 1H), 7.71-7.64 (m, 3H), 7.55 (dd, <i>J</i> = 8.2, 1.8 Hz, 1H), 7.51- 7.49 (m, 1H), 7.40 (d, <i>J</i> = 7.4 Hz, 1H), 7.31 (t, <i>J</i> = 9.2 Hz, 1H), 7.25 (d, <i>J</i> = 7.7 Hz, 1H), 7.23-7.19 (m, 1H), 3.59 (q, <i>J</i> = 6.8 Hz, 2H),

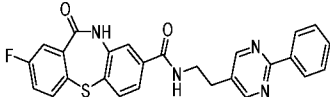
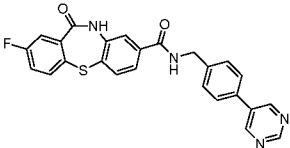
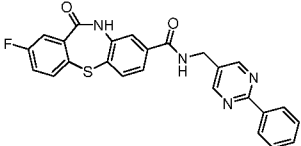
						2.96 (t, $J = 7.3$ Hz, 2H);
1555		A, 28, 217	20	393.9 ($M^{+}+1$);	$C_{21}H_{16}FN_3O_2S$ 393.09	1H NMR (DMSO- d_6 , 400 MHz): δ 10.97 (s, 1H), 8.64 (t, $J = 5.5$ Hz, 1H), 8.43 (s, 1H), 8.40 (dd, $J = 4.8, 1.6$ Hz, 1H), 7.68-7.61 (m, 3H), 7.53 (dd, $J = 8.0, 2.0$ Hz, 1H), 7.51-7.46 (m, 1H), 7.40 (d, $J = 7.8$ Hz, 1H), 7.34-7.27 (m, 2H), 3.49 (q, $J = 7.0$ Hz, 2H), 2.84 (t, $J = 7.0$ Hz, 2H);
1490		A, 28, 218	27	393.9 ($M^{+}+1$);	$C_{20}H_{14}FN_3O_2S$ 379.08	1H NMR (DMSO- d_6 , 400 MHz): δ 10.96 (s, 1H), 9.15 (t, $J = 5.7$ Hz, 1H), 8.52 (s, 1H), 8.45 (dd, $J = 4.7, 1.4$ Hz, 1H), 7.73-7.66 (m, 3H), 7.63 (dd, $J = 8.2, 1.8$ Hz, 1H), 7.54-7.44 (m, 1H), 7.40 (d, $J = 7.3$ Hz, 1H), 7.36-7.28 (m, 2H), 4.46 (d, $J = 5.6$ Hz, 2H);
1463		A, 28, 185	39	365.9 ($M^{+}+1$);	$C_{19}H_{12}FN_3O_2S$ 365.06	1H NMR (DMSO- d_6 , 400 MHz): δ 11.04 (s, 1H), 10.63 (s, 1H), 8.48 (d, $J = 6.0$ Hz, 2H), 7.80-7.69 (m, 5H), 7.43 (d, $J = 7.6$ Hz, 2H), 7.33 (t, $J = 9.1$ Hz, 1H);

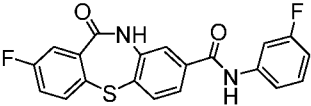
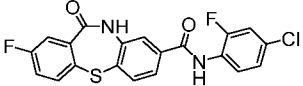
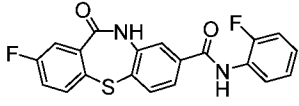
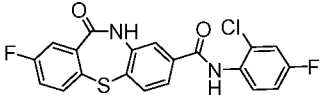
1472		A, 28, 186	13	440.9 (M ⁺ +1);	C ₂₆ H ₁₇ FN ₂ O ₂ S 440.10	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 11.04 (s, 1H), 10.38 (s, 1H), 8.07- 8.04 (m, 1H), 7.82-7.72 (m, 4H), 7.67-7.61 (m, 2H), 7.55- 7.30 (m, 8H);
1580		A, 28, 347	9	384.0 (M ⁺ +1);	C ₁₉ H ₁₄ FN ₃ O ₃ S 383.07	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.98 (s, 1H), 8.68 (t, <i>J</i> = 5.6 Hz, 1H), 8.22 (s, 1H), 7.69-7.64 (m, 2H), 7.55 (dd, <i>J</i> = 8.0, 1.9 Hz, 1H), 7.53-7.46 (m, 1H), 7.40 (dd, <i>J</i> = 7.6, 0.9 Hz, 1H), 7.36- 7.28 (m, 1H), 6.92 (s, 1H), 3.49 (q, <i>J</i> = 6.2 Hz, 2H), 2.90 (t, <i>J</i> = 6.7 Hz, 2H);
1598		A, 28, 352	29	399.9 (M ⁺ +1);	C ₁₉ H ₁₄ FN ₃ O ₂ S ₂ 399.05	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.98 (br s, 1H), 8.91 (s, 1H), 8.70 (t, <i>J</i> = 5.6 Hz, 1H), 7.68 (d, <i>J</i> = 7.9 Hz, 3H), 7.57 (dd, <i>J</i> = 8.0, 1.9 Hz, 1H), 7.53- 7.47 (m, 1H), 7.41 (d, <i>J</i> = 7.1 Hz, 1H), 7.35- 7.29 (m, 1H), 3.48 (q, <i>J</i> = 5.9 Hz, 2H), 3.10 (t, <i>J</i> = 6.7 Hz, 2H);
1465		A, 28, 219	30	469.0 (M ⁺ +1);	C ₂₈ H ₂₁ FN ₂ O ₂ S 468.13	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.97 (s, 1H), 8.66 (t, <i>J</i> = 5.3 Hz, 1H),

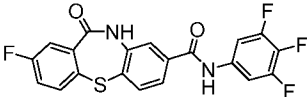
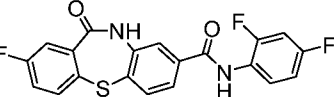
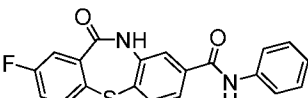
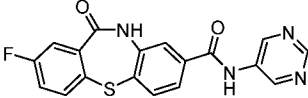
						7.77-7.24 (m, 15H), 3.50 (q, $J = 7.0$ Hz, 2H), 2.86 (t, $J = 7.0$ Hz, 2H);
1477		A, 28, 406	12	500.1 ($M^{+}+1$);	$C_{24}H_{22}FN_3$ O_4S_2 499.10	1H NMR (DMSO- d_6 , 400 MHz): δ 10.97 (s, 1H), 8.63 (t, $J = 5.5$ Hz, 1H), 7.69-7.61 (m, 4H), 7.54-7.46 (m, 4H), 7.40 (d, $J = 7.0$ Hz, 1H), 7.34-7.28 (m, 1H), 3.56-3.46 (m, 2H), 2.93 (t, $J = 7.0$ Hz, 2H), 2.54 (s, 6H);
1308		A, 35, 212	39	380.9 ($M^{+}+1$);	$C_{19}H_{13}FN_4$ O_2S 380.07	1H -NMR (DMSO- d_6 , 400 MHz): δ 10.89 (s, 1H), 9.16 (t, $J = 5.6$ Hz, 1H), 9.07 (s, 1H), 8.74 (s, 2H), 7.71-7.66 (m, 2H), 7.64-7.58 (m, 2H), 7.47 (dd, $J = 9.2, 2.8$ Hz, 1H), 7.37 (dt, $J = 11.6, 3.2$ Hz, 1H), 4.47 (d, $J = 5.6$ Hz, 2H);
1309		B, 35, 213	21	385.9 ($M^{+}+1$);	$C_{18}H_{12}FN_3$ O_2S_2 385.04	1H -NMR (DMSO- d_6 , 400 MHz): δ 10.89 (br s, 1H), 9.24 (t, $J = 5.6$ Hz, 1H), 8.95 (br s, 1H), 7.80 (br s, 1H), 7.70-7.65 (m, 2H), 7.61-7.57 (m, 2H), 7.47 (d, $J = 6.4$ Hz, 1H), 7.39-7.37 (m, 1H), 4.64 (d, $J = 5.6$ Hz, 2H);

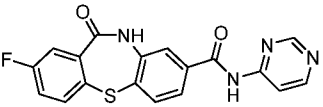
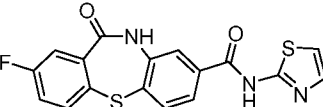
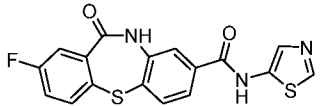
1310		A, 35, 216	44	393.9 (M ⁺ +1);	C ₂₁ H ₁₆ FN ₃ O ₂ S 393.09	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.89 (s, 1H), 8.62 (t, <i>J</i> = 5.6 Hz, 1H), 8.47 (d, <i>J</i> = 8.0 Hz, 1H), 7.70- 7.61 (m, 3H), 7.59-7.54 (m, 2H), 7.48 (dd, <i>J</i> = 9.2, 2.8 Hz, 1H), 7.36 (dt, <i>J</i> = 11.6, 3.2 Hz, 1H), 7.24 (d, <i>J</i> = 8.0 Hz, 1H), 7.22-7.19 (m, 1H), 3.61-3.50 (m, 2H), 2.96 (t, <i>J</i> = 7.2 Hz, 2H);
1311		A, 35, 214	35	369.9 (M ⁺ +1);	C ₁₈ H ₁₂ FN ₃ O ₃ S 369.06	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.89 (br s, 1H), 9.07 (t, <i>J</i> = 5.2 Hz, 1H), 8.27 (s, 1H), 7.70 (s, 1H), 7.66 (d, <i>J</i> = 8.0 Hz, 1H), 7.62-7.57 (m, 2H), 7.48 (dd, <i>J</i> = 9.2, 2.8 Hz, 1H), 7.37 (dt, <i>J</i> = 11.6, 3.2 Hz, 1H), 7.03 (s, 1H), 4.50 (d, <i>J</i> = 5.2 Hz, 2H);
1312		A, 35, 215	11	395.2 (M ⁺ +1);	C ₂₀ H ₁₅ FN ₄ O ₂ S 394.09	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.89 (br s, 1H), 9.01 (s, 1H), 8.65- 8.62 (m, 3H), 7.65-7.35 (m, 6H), 3.52 (t, <i>J</i> = 6.4 Hz, 2H), 2.84 (t, <i>J</i> = 6.4 Hz, 2H);
1313		A, 35, 220	69	465.2 (M ⁺ +1);	C ₂₆ H ₂₅ FN ₂ O ₃ S 464.16	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.88 (s, 1H), 8.72 (d, <i>J</i> = 8.0 Hz, 1H),

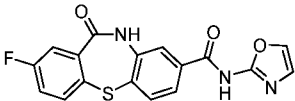
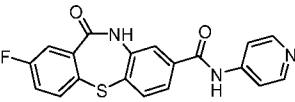
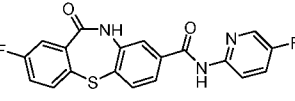
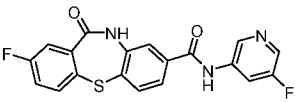
						7.70 (s, 1H), 7.66 (s, 2H), 7.62-7.58 (m, 1H), 7.47 (dd, J = 8.8, 2.8 Hz, 1H), 7.37 (dt, J = 11.6, 3.2 Hz, 1H), 7.32-7.25 (m, 4H), 5.01- 4.95 (m, 1H), 4.86 (t, J = 6.0 Hz, 1H), 3.68- 3.57 (m, 2H), 1.24 (s, 9H);
1316		A, 35, 221	50	382.8 ($M^{+}+1$)	$C_{20}H_{12}F_2N_2O_2S$ 382.06	1H -NMR (DMSO- d_6 , 400 MHz): δ 10.96 (s, 1H), 10.35 (s, 1H), 7.76- 7.72 (m, 5H), 7.63-7.60 (m, 1H), 7.50 (dd, J = 9.2, 2.8 Hz, 1H), 7.41-7.36 (m, 1H), 7.19 (t, J = 8.8 Hz, 2H);
1321		A, 35, 222	51	398.9 ($M^{+}+1$)	$C_{20}H_{12}ClF N_2O_2S$ 398.03	1H -NMR (DMSO- d_6 , 400 MHz): δ 10.94 (s, 1H), 10.40 (s, 1H), 7.78- 7.70 (m, 5H), 7.63-7.60 (m, 1H), 7.50 (dd, J = 9.2, 3.2 Hz, 1H), 7.41-7.37 (m, 3H);
1320		A, 35, 359	7	471.0 ($M^{+}+1$)	$C_{26}H_{19}FN_4O_2S$ 470.12	1H -NMR (DMSO- d_6 , 400 MHz): δ 10.90 (s, 1H), 9.15 (s, 1H), 9.11 (s, 1H), 8.64 (t, J = 5.2 Hz, 1H), 7.73 (d, J = 8.0 Hz, 2H), 7.67- 7.61 (m, 2H), 7.59-7.55 (m, 2H), 7.48 (dd, J = 9.2, 2.8 Hz, 1H), 7.40-7.34 (m, 2H), 3.50

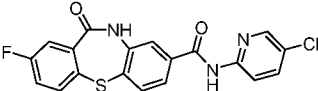
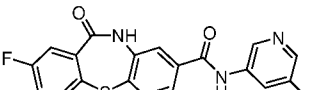
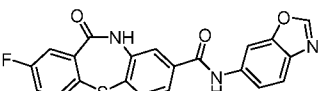
						(q, 2H), 2.89 (t, $J = 7.2$ Hz, 2H);
1343		A, 35, 367	49	471.4 ($M^{+}+1$);	$C_{26}H_{19}FN_4$ O_2S 470.12	1H -NMR (DMSO- d_6 , 400 MHz): δ 10.88 (s, 1H), 8.75 (s, 2H), 8.64 (t, $J = 6.0$ Hz, 1H), 8.36-8.34 (m, 2H), 7.65-7.63 (m, 2H), 7.60-7.57 (m, 2H), 7.55-7.45 (m, 4H), 7.39-7.34 (m, 1H), 3.56 (q, $J = 6.4$ Hz, 2H), 2.88 (t, $J = 6.8$ Hz, 2H);
1314		A, 35, 372	13	457.0 ($M^{+}+1$)	$C_{25}H_{17}FN_4$ O_2S 456.11	1H -NMR (DMSO- d_6 , 400 MHz): δ 10.91 (s, 1H), 9.20 (t, $J = 6.0$ Hz, 1H), 9.17 (s, 1H), 9.11 (s, 2H), 7.77-7.74 (m, 3H), 7.67 (s, 2H), 7.62-7.58 (m, 1H), 7.50-7.40 (m, 3H), 7.38 (td, $J = 11.6, 3.2$ Hz, 1H), 4.50 (d, $J = 6.0$ Hz, 2H);
1315		A, 35, 377	32	456.9 ($M^{+}+1$);	$C_{25}H_{17}FN_4$ O_2S 456.11	1H -NMR (DMSO- d_6 , 400 MHz): δ 10.89 (s, 1H), 9.17 (t, $J = 5.6$ Hz, 1H), 8.84 (s, 2H), 8.38-8.35 (m, 2H), 7.72 (s, 1H), 7.69-7.60 (m, 2H), 7.59-7.58 (m, 1H), 7.52-7.51 (m, 3H), 7.49-7.46 (m, 1H), 7.37 (td, $J = 11.6, 2.8$ Hz, 1H), 4.50 (d, $J = 6.0$ Hz, 2H);

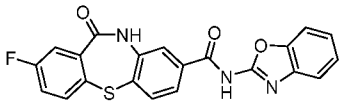
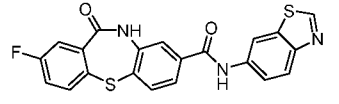
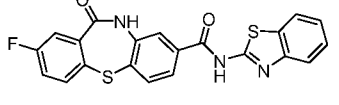
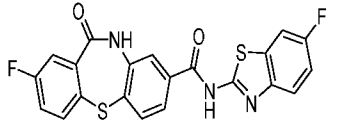
1317		A, 35, 223	30	382.9 (M ⁺ +1);	C ₂₀ H ₁₂ F ₂ N 2O ₂ S 382.06	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.96 (s, 1H), 10.46 (s, 1H), 7.76- 7.68 (m, 4H), 7.64-7.60 (m, 1H), 7.52-7.49 (m, 2H), 7.41- 7.35 (m, 2H), 6.93 (dt, <i>J</i> = 10.0, 1.6 Hz, 1H);
1334		A, 35, 224	14	417.6 (M ⁺ +1);	C ₂₀ H ₁₁ ClF ₂ N ₂ O ₂ S 416.02	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.94 (s, 1H), 10.26 (s, 1H), 7.78 (s, 1H), 7.75-7.70 (m, 2H), 7.64- 7.60 (m, 2H), 7.54-7.51 (m, 2H), 7.39 (dt, <i>J</i> = 11.6, 3.2 Hz, 1H), 7.31 (dd, <i>J</i> = 8.8, 1.2 Hz, 1H);
1322		A, 35, 225	15	382.9 (M ⁺ +1);	C ₂₀ H ₁₂ F ₂ N 2O ₂ S 382.06	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.94 (s, 1H), 10.18 (s, 1H), 7.78 (s, 1H), 7.75-7.74 (m, 2H), 7.64- 7.55 (m, 2H), 7.50 (dd, <i>J</i> = 9.2, 2.8 Hz, 1H), 7.39 (dt, <i>J</i> = 8.8, 2.8 Hz, 1H), 7.31-7.26 (m, 2H), 7.24- 7.19 (m, 1H);
1323		C, 35, 226	21	417.7 (M ⁺ +1)	C ₂₀ H ₁₁ ClF ₂ N ₂ O ₂ S 416.02	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.94 (s, 1H), 10.16 (s, 1H), 7.80 (s, 1H), 7.77-7.72 (m, 2H), 7.63- 7.60 (m, 1H), 7.57-7.53 (m, 2H), 7.50 (dd, <i>J</i>

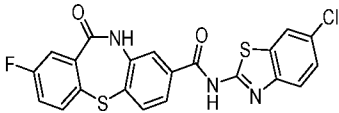
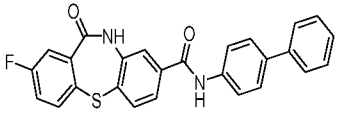
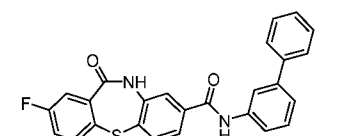
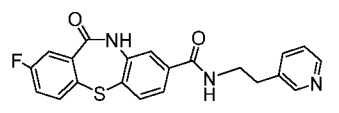
						= 9.2, 2.8 Hz, 1H), 7.39 (td, J = 11.2, 2.8 Hz, 1H), 7.27 (td, J = 11.2, 2.8 Hz, 1H);
1324		A, 35, 227	7	419.2 ($M^{+}+1$)	$C_{20}H_{10}F_4N_2O_2S$ 418.04	1H -NMR (DMSO- d_6 , 400 MHz): δ 10.98 (br s, 1H), 10.60 (br s, 1H), 7.77-7.66 (m, 5H), 7.63-7.60 (m, 1H), 7.51 (dd, J = 9.2, 2.8 Hz, 1H), 7.41-7.37 (m, 1H);
1318		A, 35, 228	67	401.2 ($M^{+}+1$),	$C_{20}H_{11}F_3N_2O_2S$ 400.05	1H -NMR (DMSO- d_6 , 400 MHz): δ 10.93 (s, 1H), 10.19 (s, 1H), 7.78 (s, 1H), 7.73 (s, 2H), 7.63-7.48 (m, 3H), 7.41-7.32 (m, 2H), 7.11 (t, J = 8.8 Hz, 1H);
1319		A, 35, 179	53	364.9 ($M^{+}+1$);	$C_{20}H_{13}FN_2O_2S$ 364.07	1H -NMR (DMSO- d_6 , 400 MHz): δ 10.95 (s, 1H), 10.29 (s, 1H), 7.76 (s, 1H), 7.73-7.72 (m, 4H), 7.64-7.60 (m, 1H), 7.51 (dd, J = 9.2, 2.8 Hz, 1H), 7.40 (dd, J = 8.4, 2.8 Hz, 1H), 7.37-7.32 (m, 2H), 7.10 (t, J = 7.6 Hz, 1H);
1328		A, 35, 229	5	366.9 ($M^{+}+1$),	$C_{18}H_{11}FN_4O_2S$ 366.06	1H -NMR (DMSO- d_6 , 400 MHz): δ 10.99 (s, 1H), 10.69 (s, 1H), 9.13 (s, 2H), 8.93 (s, 1H), 7.80 (s, 1H), 7.77 (s,

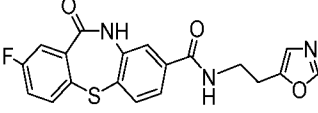
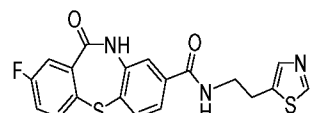
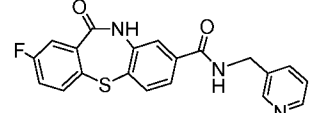
						2H), 7.64-7.60 (m, 1H), 7.51 (dd, $J = 9.2, 3.2$ Hz, 1H), 7.39 (dt, $J = 11.2, 2.8$ Hz, 1H);
1344		C, 35, 230	8	367.5 ($M^{+}+1$);	$C_{18}H_{11}FN_4$ O_2S 366.06	1H NMR (DMSO- d_6 , 400 MHz): δ 11.29 (s, 1H), 10.94 (s, 1H), 8.95 (s, 1H), 8.72 (d, $J = 5.8$ Hz, 1H), 8.17 (d, $J = 5.7$ Hz, 1H), 7.83-7.76 (m, 2H), 7.75-7.67 (m, 1H), 7.62 (dd, $J = 8.5, 5.1$ Hz, 1H), 7.51 (dd, $J = 9.1, 2.8$ Hz, 1H), 7.39 (t, $J = 8.0$ Hz, 1H);
1329		A, 35, 231	28	371.9 ($M^{+}+1$);	$C_{17}H_{10}FN_3$ O_2S_2 371.02	1H -NMR (DMSO- d_6 , 400 MHz): δ 12.70 (br s, 1H), 10.98 (s, 1H), 7.87-7.86 (m, 2H), 7.72 (d, $J = 8.4$ Hz, 1H), 7.63-7.60 (m, 1H), 7.51 (dt, $J = 9.2, 2.8$ Hz, 2H), 7.41-7.37 (m, 1H), 7.28-7.25 (m, 1H);
1335		A, 35, 380	17	371.8 ($M^{+}+1$);	$C_{17}H_{10}FN_3$ O_2S_2 371.02	1H -NMR (DMSO- d_6 , 400 MHz): δ 11.79 (br s, 1H), 10.98 (s, 1H), 8.62 (s, 1H), 7.79-7.73 (m, 2H), 7.61-7.58 (m, 2H), 7.50-7.47 (m, 1H), 7.47 (d, $J = 9.2, 2.8$ Hz, 1H), 7.37 (td, $J = 11.2, 3.2$ Hz, 1H);

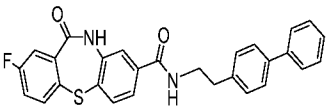
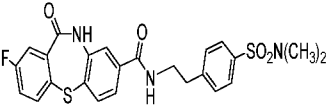
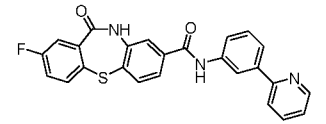
1353		A, 35, 232	4	355.8 ($M^{+}+1$),	$C_{17}H_{10}FN_3$ O_3S 355.04	1H -NMR (DMSO- d_6 , 400 MHz): δ 11.62 (br s, 1H), 10.94 (br s, 1H), 7.95-7.85 (m, 1H), 7.81- 7.69 (m, 3H), 7.63-7.59 (m, 1H), 7.50 (d, J = 6.4 Hz, 1H), 7.40-7.37 (m, 1H), 7.20 (br s, 1H);
1330		C, 35, 185	20	365.8 ($M^{+}+1$),	$C_{19}H_{12}FN_3$ O_2S 365.06	1H -NMR (DMSO- d_6 , 400 MHz): δ 10.97 (s, 1H), 10.63 (s, 1H), 8.48- 8.47 (m, 2H), 7.77-7.73 (m, 5H), 7.64-7.60 (m, 1H), 7.51 (dd, J = 9.2, 2.8 Hz, 1H), 7.39 (td, J = 11.2, 2.8 Hz, 1H);
1336		C, 35, 233	30	383.9 ($M^{+}+1$) $^{+}$,	$C_{19}H_{11}F_2$ N_3O_2S 383.05	1H -NMR (DMSO- d_6 , 400 MHz): δ 10.98 (s, 1H), 10.93 (s, 1H), 8.39- 8.35 (m, 1H), 8.17 (dd, J = 9.2, 4.0 Hz, 1H), 7.82-7.77 (m, 3H), 7.69 (d, J = 8.0 Hz, 1H), 7.63-7.60 (m, 1H), 7.50 (dd, J = 9.2, 2.8 Hz, 1H), 7.38 (td, J = 11.6, 3.2 Hz, 1H);
1337		B, 35, 234	14	383.9 ($M^{+}+1$),	$C_{19}H_{11}F_2N$ $_3O_2S$ 383.05	1H -NMR (DMSO- d_6 , 400 MHz): δ 10.98 (br s, 1H), 10.73 (br s, 1H), 8.74 (s, 1H), 8.34 (s, 1H), 8.16 (d, J

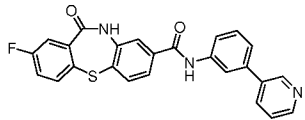
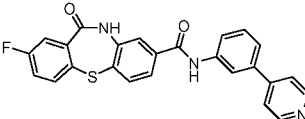
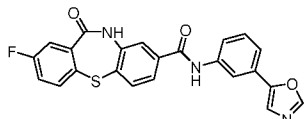
						= 9.2 Hz, 1H), 7.78 (s, 1H), 7.76 (s, 2H), 7.64-7.60 (m, 1H), 7.51 (dd, J = 9.2, 3.2 Hz, 1H), 7.39 (dt, J = 11.6, 3.2 Hz, 1H);
1338		C, 35, 235	12	400.5 ($M+1$) ⁺ ,	C ₁₉ H ₁₁ ClF N ₃ O ₂ S 399.02	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 11.01 (br s, 2H), 8.43 (br s, 1H), 8.18 (d, J = 8.8 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.80-7.77 (m, 2H), 7.69 (d, J = 7.6 Hz, 1H), 7.61-7.60 (m, 1H), 7.50 (d, J = 9.2 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H);
1345		C, 35, 236	6	400.5 (M^++1),	C ₁₉ H ₁₁ ClF N ₃ O ₂ S 399.02	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.97 (br s, 1H), 10.71 (br s, 1H), 8.82 (br s, 1H), 8.36 (d, J = 7.6 Hz, 2H), 7.78-7.76 (m, 3H), 7.62 (t, J = 7.6 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.39 (t, J = 7.2 Hz, 1H);
1331		A, 35, 237	21	406.6 (M^++1),	C ₂₁ H ₁₂ FN ₃ O ₃ S 405.06	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.97 (s, 1H), 10.55 (s, 1H), 8.68 (s, 1H), 8.31 (s, 1H), 7.79-7.75 (m, 4H), 7.60-7.61 (m, 2H), 7.51 (dd, J = 9.2, 2.8 Hz, 1H), 7.39 (dt, J

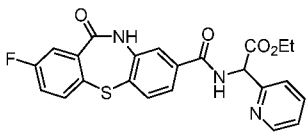
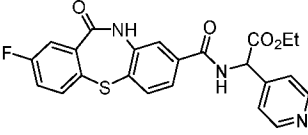
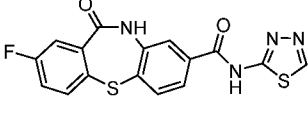
						= 11.6, 3.2 Hz, 1H);
1354		C ^a , 35, 238 (a= Et ₃ N, DMAP)	14	405.9 (M ⁺ +1),	C ₂₁ H ₁₂ FN ₃ O ₃ S 405.06	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 12.44 (br s, 1H), 10.94 (s, 1H), 7.92 (br s, 1H), 7.86-7.84 (m, 1H), 7.72 (d, <i>J</i> = 8.0 Hz, 1H), 7.62-7.60 (m, 2H), 7.55-7.49 (m, 2H), 7.40-7.30 (m, 3H);
1325		A, 35, 239	25	422.0 (M ⁺ +1);	C ₂₁ H ₁₂ FN ₃ O ₂ S ₂ 421.04	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.97 (s, 1H), 10.56 (s, 1H), 9.30 (s, 1H), 8.65 (s, 1H), 8.05 (d, <i>J</i> = 8.8 Hz, 1H), 7.79-7.73 (m, 4H), 7.64-7.61 (m, 1H), 7.51 (dd, <i>J</i> = 9.2, 2.8 Hz, 1H), 7.39 (dt, <i>J</i> = 11.2, 2.8 Hz, 1H);
1339		A, 35, 240	28	422.3 (M ⁺ +1),	C ₂₁ H ₁₂ FN ₃ O ₂ S ₂ 421.04	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 12.09 (br s, 1H), 10.98 (s, 1H), 8.00 (d, <i>J</i> = 8.0 Hz, 1H), 7.93-7.91 (m, 2H), 7.79-7.74 (m, 2H), 7.64-7.60 (m, 1H), 7.53-7.44 (m, 2H), 7.41-7.32 (m, 2H);
1332		C, 35, 241	13	439.9 (M ⁺ +1) ⁺ ,	C ₂₁ H ₁₁ F ₂ N O ₃ S ₂ 439.03	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 12.91 (br s, 1H), 10.96 (s, 1H), 7.93-7.90 (m, 2H), 7.78 (d, <i>J</i> = 6.8 Hz, 1H),

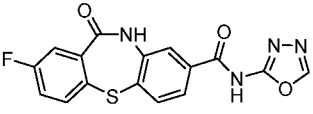
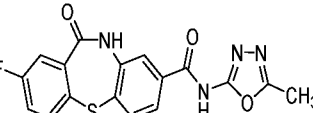
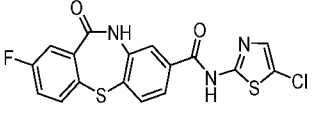
						7.68-7.59 (m, 3H), 7.50 (dd, $J = 9.2, 2.8$ Hz, 1H), 7.38 (td, $J = 11.6, 3.2$ Hz, 1H), 7.23-7.17 (m, 1H);
1340		C, 35, 242	5	455.9 ($M^{+}+1$)	$C_{21}H_{11}ClF$ $N_3O_2S_2$ 455.00	1H -NMR (DMSO- d_6 , 400 MHz): δ 13.01 (br s, 1H), 11.00 (s, 1H), 8.16 (s, 1H), 7.91 (d, $J = 8.0$ Hz, 2H), 7.79-7.70 (m, 2H), 7.64-7.60 (m, 1H), 7.53-7.47 (m, 2H), 7.39 (td, $J = 8.4, 3.2$ Hz, 1H);
1326		A, 35, 243	46	441.5 ($M^{+}+1$);	$C_{26}H_{17}FN_2$ O_2S 440.10	1H -NMR (DMSO- d_6 , 400 MHz): δ 10.96 (s, 1H), 10.39 (s, 1H), 7.84 (d, $J = 8.8$ Hz, 2H), 7.78 (s, 1H), 7.74 (s, 2H), 7.68-7.61 (m, 4H), 7.51 (dd, $J = 9.2, 2.8$ Hz, 1H), 7.47-7.45 (m, 1H), 7.43-7.32 (m, 4H);
1333		A, 35, 186	46	441.4 ($M^{+}+1$);	$C_{26}H_{17}FN_2$ O_2S 440.10	1H NMR (400 MHz, DMSO- d_6) δ 10.97 (s, 1H), 10.38 (s, 1H), 8.05 (s, 1H), 7.83 – 7.73 (m, 4H), 7.68 – 7.61 (m, 3H), 7.52 – 7.37 (m, 7H);
1376		A, 35, 217	59	393.9 ($M^{+}+1$);	$C_{21}H_{16}FN_3$ O_2S 393.09	1H NMR (DMSO- d_6 , 400 MHz): δ 10.91 (s, 1H), 8.62 (t, $J = 5.5$ Hz, 1H), 8.44-8.38 (m, 2H), 7.67-7.57

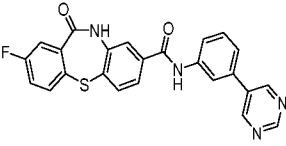
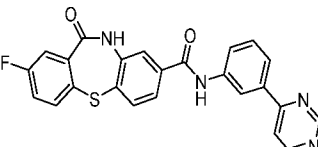
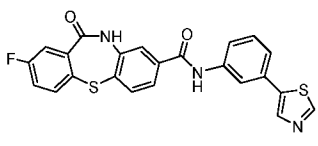
						(m, 4H), 7.54 (dd, $J = 8.2, 1.8$ Hz, 1H), 7.48 (dd, $J = 9.2, 2.9$ Hz, 1H), 7.37 (dt, $J = 8.5, 2.9$ Hz, 1H), 7.29 (dd, $J = 7.7, 4.8$ Hz, 1H), 3.54-3.44 (m, 2H), 2.84 (t, $J = 7.0$ Hz, 2H);
1417		B, 35, 347	12	383.9 ($M^{+}+1$);	$C_{19}H_{14}FN_3O_3S$ 383.07	1H NMR (DMSO- d_6 , 400 MHz): δ 10.90 (br s, 1H), 8.66 (t, $J = 5.5$ Hz, 1H), 8.21 (s, 1H), 7.68-7.63 (m, 2H), 7.60 (dd, $J = 8.6, 5.3$ Hz, 1H), 7.55 (dd, $J = 8.2, 1.7$ Hz, 1H), 7.48 (dd, $J = 9.2, 2.9$ Hz, 1H), 7.37 (dt, $J = 8.5, 3.0$ Hz, 1H), 6.92 (s, 1H), 3.49 (q, 2H), 2.90 (t, $J = 6.7$ Hz, 2H);
1418		B, 35, 352	36	399.9 ($M^{+}+1$);	$C_{19}H_{14}FN_3O_2S_2$ 399.05	1H NMR (DMSO- d_6 , 400 MHz): δ 10.92 (br s, 1H), 8.91 (br s, 1H), 8.70 (br s, 1H), 7.73-7.54 (m, 5H), 7.49 (d, $J = 7.2$ Hz, 1H), 7.42-7.36 (m, 1H), 3.52-3.45 (m, 2H), 3.13-3.10 (m, 2H);
1364		A, 35, 218	38	380.0 ($M^{++}+1$);	$C_{20}H_{14}FN_3O_2S$ 379.08	1H NMR (400 MHz, DMSO- d_6): δ 10.89 (s, 1H), 9.15 (t, $J = 5.4$ Hz, 1H), 8.52 (s, 1H), 8.45 (dd, $J = 4.8, 1.5$ Hz,

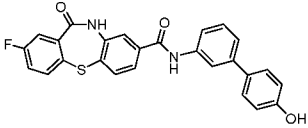
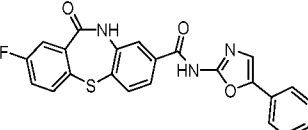
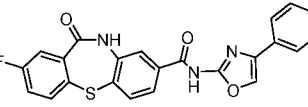
						1H), 7.73-7.57 (m, 5H), 7.48 (dd, J = 9.2, 2.9 Hz, 1H), 7.41-7.36 (m, 1H), 7.34 (dd, J = 7.9, 4.9 Hz, 1H), 4.46 (d, J = 5.9 Hz, 2H);
1370		A, 35, 219	31	469.7 (M++1);	C ₂₈ H ₂₁ FN ₂ O ₂ S 468.13	¹ H NMR (DMSO-d ₆ , 400 MHz): δ 10.91 (s, 1H), 8.65 (t, J = 5.4 Hz, 1H), 7.69-7.53 (m, 8H), 7.50-7.41 (m, 3H), 7.40-7.28 (m, 4H), 3.50 (q, J = 6.7 Hz, 2H), 2.86 (t, J = 7.2 Hz, 2H);
1384		A, 35, 406	29	499.9 (M++1)	C ₂₄ H ₂₂ FN ₃ O ₄ S ₂ 499.10	¹ H NMR (DMSO-d ₆ , 400 MHz): δ 10.91 (br s, 1H), 8.62 (t, J = 5.6 Hz, 1H), 7.67-7.62 (m, 4H), 7.59 (dd, J = 8.6, 5.3 Hz, 1H), 7.53 (dd, J = 8.2, 1.7 Hz, 1H), 7.51-7.46 (m, 3H), 7.37 (td, J = 8.5, 3.0 Hz, 1H), 3.51 (q, J = 6.6 Hz, 2H), 2.93 (t, J = 7.0 Hz, 2H), 2.54 (s, 6H);
1385		A, 35, 244	40	441.9 (M++1);	C ₂₅ H ₁₆ FN ₃ O ₂ S 441.09	¹ H NMR (400 MHz, DMSO-d ₆): δ 10.98 (br s, 1H), 10.44 (s, 1H), 8.68 (d, J = 5.1 Hz, 1H), 8.50 (s, 1H), 7.94-7.89 (m, 2H), 7.87-7.84 (m, 1H), 7.83-7.77 (m, 3H),

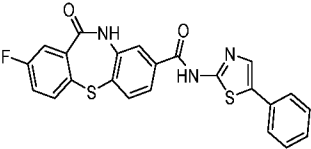
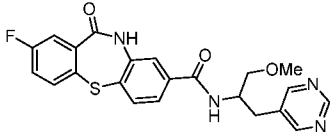
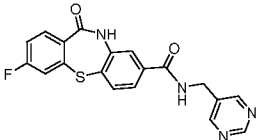
						7.76-7.72 (m, 1H), 7.63 (dd, J = 8.6, 5.3 Hz, 1H), 7.52 (dd, J = 9.1, 2.7 Hz, 1H), 7.47 (t, J = 7.9 Hz, 1H), 7.43-7.35 (m, 2H);
1400		A, 35, 245	21	441.9 (M ⁺⁺ +1);	C ₂₅ H ₁₆ F N ₃ O ₂ S 441.09	¹ H NMR (400 MHz, DMSO-d ₆): δ 10.98 (s, 1H), 10.42 (s, 1H), 8.85 (br s, 1H), 8.59 (d, J = 3.7 Hz, 1H), 8.08 (s, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.85-7.72 (m, 4H), 7.63 (dd, J = 8.5, 5.2 Hz, 1H), 7.54-7.45 (m, 4H), 7.40 (td, J = 8.4, 2.9 Hz, 1H);
1401		A, 35, 246	33	442.0 (M ⁺⁺ +1);	C ₂₅ H ₁₆ F N ₃ O ₂ S 441.09	¹ H NMR (400 MHz, DMSO-d ₆): δ 10.99 (s, 1H), 10.46 (s, 1H), 8.66 (d, J = 6.0 Hz, 2H), 8.18-8.16 (m, 1H), 7.85 (dt, J = 7.6, 1.6 Hz, 1H), 7.81-7.78 (m, 1H), 7.77-7.74 (m, 2H), 7.68-7.61 (m, 3H), 7.56-7.49 (m, 3H), 7.40 (td, J = 8.5, 2.5 Hz, 1H);
1386		A, 35, 247	34	431.9 (M ⁺⁺ +1);	C ₂₃ H ₁₄ FN ₃ O ₃ S 431.07	¹ H NMR (400 MHz, DMSO-d ₆): δ 10.98 (s, 1H), 10.44 (s, 1H), 8.46 (s, 1H), 8.16 (s, 1H), 7.83-7.69 (m, 4H), 7.69-7.59 (m, 2H);

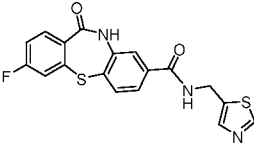
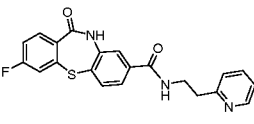
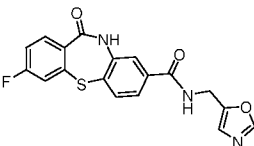
						7.55-7.43 (m, 3H), 7.40 (td, $J = 8.5, 3.0$ Hz, 1H);
1424		F, 35, 248	32	452.0 ($M^{+}+1$);	$C_{23}H_{18}FN_3O_4S$ 451.10	1H NMR (400 MHz, DMSO- d_6): 10.89 (s, 1H), 9.20 (d, $J = 7.3$ Hz, 1H), 8.57-8.54 (m, 1H), 7.84 (td, $J = 7.7, 1.8$ Hz, 1H), 7.74 (s, 1H), 7.70-7.64 (m, 2H), 7.60 (dd, $J = 8.6, 5.3$ Hz, 1H), 7.53 (d, $J = 7.9$ Hz, 1H), 7.48 (dd, $J = 9.2, 2.9$ Hz, 1H), 7.43-7.33 (m, 2H), 5.77 (d, $J = 7.3$ Hz, 1H), 4.16-4.09 (m, 2H), 1.14 (t, $J = 7.1$ Hz, 3H);
1405		F, 35, 249	28	451.9 ($M^{+}+1$);	$C_{23}H_{18}FN_3O_4S$ 451.10	1H NMR (400 MHz, DMSO- d_6): δ 10.90 (s, 1H), 9.38 (d, $J = 7.5$ Hz, 1H), 8.58 (d, $J = 5.0$ Hz, 2H), 7.73 (s, 1H), 7.71-7.65 (m, 2H), 7.61 (dd, $J = 8.6, 5.2$ Hz, 1H), 7.52-7.44 (m, 3H), 7.38 (td, $J = 8.4, 3.0$ Hz, 1H), 5.71 (d, $J = 7.4$ Hz, 1H), 4.19-4.10 (m, 2H), 1.15 (t, $J = 7.1$ Hz, 3H);
1442		F, 35, 250	31	372.8 ($M^{+}+1$);	$C_{16}H_9FN_4O_2S_2$ 372.02	1H NMR (400 MHz, DMSO- d_6): δ 10.91 (s, 1H), 8.87 (br s, 1H), 7.94 (s, 1H), 7.87 (dd, $J = 8.0, 1.7$ Hz,

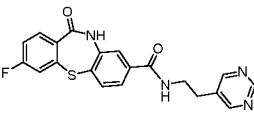
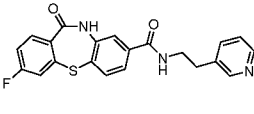
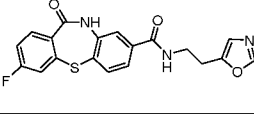
						1H), 7.61 (d, J = 9.0 Hz, 1H), 7.59-7.56 (m, 1H), 7.48 (dd, J = 9.2, 2.9 Hz, 1H), 7.35 (td, J = 8.5, 3.0 Hz, 1H);
1537		F, 35, 251	16	357.0 ($M^{+}+1$);	$C_{16}H_9FN_4O_3S$ 356.04	1H NMR (400 MHz, DMSO- d_6) δ 12.26 (br s, 1H), 10.97 (br s, 1H), 9.02 (s, 1H), 7.84-7.71 (m, 3H), 7.62 (dd, J = 8.4, 5.3 Hz, 1H), 7.51 (dd, J = 9.2, 2.7 Hz, 1H), 7.39 (td, J = 8.4, 2.9 Hz, 1H);
1503		F ^a , 35, 252 (a = Microwave 100 °C temp, 1h)	39	371.0 ($M^{+}+1$);	$C_{17}H_{11}FN_4O_3S$ 370.05	1H NMR (400 MHz, DMSO- d_6): δ 11.95 (br s, 1H), 10.97 (br s, 1H), 7.85-7.70 (m, 3H), 7.62 (dd, J = 8.6, 5.2 Hz, 1H), 7.50 (dd, J = 9.2, 2.8 Hz, 1H), 7.39 (td, J = 8.5, 2.9 Hz, 1H), 2.45 (s, 3H);
1443		F, 35, 253	17	405.9 ($M^{+}+1$);	$C_{17}H_9ClFN_3O_2S_2$ 404.98	1H NMR (400 MHz, DMSO- d_6): δ 12.97 (br s, 1H), 11.00 (br s, 1H), 7.86 (br s, 2H), 7.73 (d, J = 8.2 Hz, 1H), 7.60 (br s, 2H), 7.51 (d, J = 7.7 Hz, 1H), 7.43-7.35 (m, 1H);

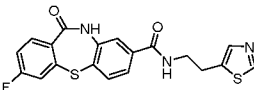
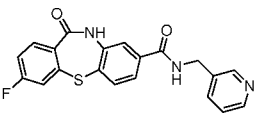
1440		A, 35, 383	34	443.0 ($M^{+}+1$);	$C_{24}H_{15}FN_4$ O_2S 442.09	1H NMR (DMSO- d_6 , 400 MHz): δ 10.99 (s, 1H), 10.47 (s, 1H), 9.21 (s, 1H), 9.09 (s, 2H), 8.13-8.11 (m, 1H), 7.88- 7.85 (m, 1H), 7.80 (s, 1H), 7.77-7.75 (m, 2H), 7.63 (dd, J = 8.6, 5.3 Hz, 1H), 7.56-7.50 (m, 3H), 7.40 (td, J = 8.5, 3.0 Hz, 1H);
1451		A, 35, 386	26	443.0 ($M^{+}+1$);	$C_{24}H_{15}FN_4$ O_2S 442.09	1H NMR (400 MHz, DMSO- d_6): δ 10.99 (s, 1H), 10.52 (s, 1H), 9.27 (s, 1H), 8.88 (d, J = 5.3 Hz, 1H), 8.66-8.63 (m, 1H), 8.04 (dd, J = 5.4, 1.3 Hz, 1H), 7.98-7.91 (m, 2H), 7.83- 7.73 (m, 3H), 7.63 (dd, J = 8.6, 5.3 Hz, 1H), 7.58-7.49 (m, 2H), 7.40 (td, J = 8.5, 3.0 Hz, 1H);
1441		A, 35, 389	32	448.0 ($M^{+}+1$);	$C_{23}H_{14}FN_3$ O_2S_2 447.05	1H NMR (400 MHz, DMSO- d_6): δ 10.99 (s, 1H), 10.42 (s, 1H), 9.10 (s, 1H), 8.27 (s, 1H), 8.06-8.04 (m, 1H), 7.82- 7.71 (m, 4H), 7.63 (dd, J = 8.6, 5.2 Hz, 1H), 7.57-7.35 (m, 4H);

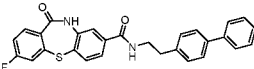
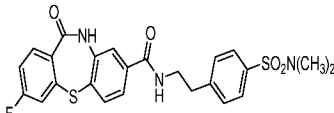
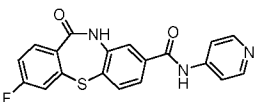
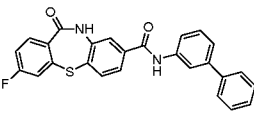
1453		B, 35, 392	10	457.0 (M ⁺ +1);	C ₂₆ H ₁₇ FN ₂ O ₃ S 456.09	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.99 (br s, 1H), 10.33 (s, 1H), 9.57 (s, 1H), 7.96 (s, 1H), 7.79 (s, 1H), 7.75-7.74 (m, 2H), 7.68 (d, <i>J</i> = 8.7 Hz, 1H), 7.63 (dd, <i>J</i> = 8.6, 5.3 Hz, 1H), 7.52 (dd, <i>J</i> = 9.2, 2.9 Hz, 1H), 7.45 (d, <i>J</i> = 8.7 Hz, 2H), 7.43-7.36 (m, 2H), 7.33-7.29 (m, 1H), 6.86 (d, <i>J</i> = 8.7 Hz, 2H);
1480		F ^b , 35, 396 (<i>b</i> = EDC solvent)	32	432.4 (M ⁺ +1)	C ₂₃ H ₁₄ FN ₃ O ₃ S 431.07	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 11.78 (br s, 1H), 10.96 (br s, 1H), 7.90- 7.45 (m, 10H), 7.44-7.33 (m, 2H);
1454		A, 35, 429	37	471.0 (M ⁺ +1);	C ₂₃ H ₁₄ FN ₃ O ₃ S 431.07	¹ H NMR (DMSO- <i>d</i> ₆ , 400MHz): δ 10.98 (s, 1H), 10.37 (s, 1H), 8.02 (s, 1H), 7.83-7.70 (m, 4H), 7.63 (dd, <i>J</i> = 8.6, 5.3 Hz, 1H), 7.52 (dd, <i>J</i> = 9.2, 2.9 Hz, 1H), 7.47-7.36 (m, 4H), 7.20 (d, <i>J</i> = 7.8 Hz, 1H), 7.16-7.14 (m, 1H), 6.96 (dd, <i>J</i> = 8.0, 2.2 Hz, 1H), 3.82 (s, 3H);

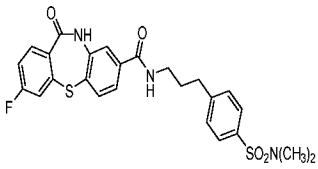
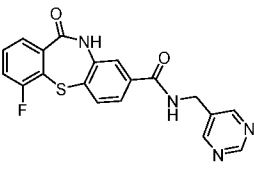
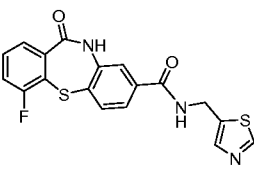
1481		F ^c , 35, 397 (c = CH ₃ CN solvent, Mw, 100 °C, 2h)	43	448.4 (M ⁺ +1)	C ₂₃ H ₁₄ FN ₃ O ₂ S ₂ 447.05	¹ H NMR (400 MHz, DMSO- d ₆): δ 12.82 (br s, 1H), 11.01 (s, 1H), 7.97 (s, 1H), 7.93-7.85 (m, 2H), 7.76- 7.71 (m, 1H), 7.68-7.60 (m, 3H), 7.52 (dd, J = 9.2, 2.9 Hz, 1H), 7.47-7.37 (m, 3H), 7.35- 7.30 (m, 1H);
1397		B, 35, 401 (Reaction time 5 h)	31	439.0 (M ⁺ +1)	C ₂₂ H ₁₉ FN ₄ O ₃ S 438.12	¹ H NMR (DMSO-d ₆ , 400 MHz): δ 10.87 (s, 1H), 8.96 (s, 1H), 8.64 (s, 2H), 8.41 (d, J = 8.7 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.62 - 7.57 (m, 2H), 7.51 (dd, J = 8.1, 1.8 Hz, 1H), 7.47 (dd, J = 9.1, 3.0 Hz, 1H), 7.37 (dt, J = 8.5, 3.0 Hz, 1H), 4.42-4.29 (m, 1H), 3.43 (d, J = 6.1 Hz, 2H), 3.28 (s, 3H), 2.94 (dd, J = 14.0, 4.1 Hz, 1H), 2.74 (dd, J = 14.0, 10.1, Hz, 1H);
1347		A, 42, 212	46	380.9 (M ⁺ +1)	C ₁₉ H ₁₃ FN ₄ O ₂ S 380.07	¹ H NMR (DMSO-d ₆ , 400 MHz): δ 10.81 (s, 1H), 9.17 (t, J = 5.6 Hz, 1H), 9.08 (s, 1H), 8.75 (s, 2H), 7.79-7.59 (m, 4H), 7.45 (dd, J = 8.5 Hz, 2.5 Hz, 1H), 7.32 (td, J = 8.6, 2.6 Hz, 1H), 4.48 (d, J = 5.6 Hz,

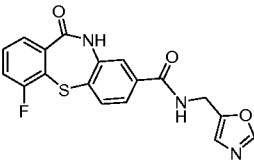
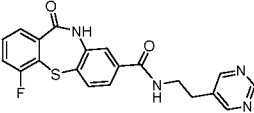
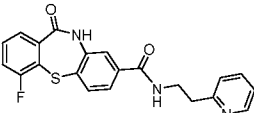
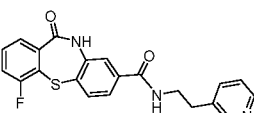
						2H);
1356		F, 42, 213	13	385.8 (M ⁺ +1)	C ₁₈ H ₁₂ FN ₃ O ₂ S ₂ 385.04	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.81 (s, 1H), 9.25 (t, <i>J</i> = 5.9 Hz, 1H), 8.96 (s, 1H), 7.80 (s, 1H), 7.75 (dd, <i>J</i> = 8.7, 5.9 Hz, 1H), 7.71-7.70 (m, 1H), 7.68- 7.65 (m, 1H), 7.63-7.58 (m, 1H), 7.45 (dd, <i>J</i> = 8.5, 2.6 Hz, 1H), 7.32 (td, <i>J</i> = 8.5, 2.6 Hz, 1H), 4.65 (d, <i>J</i> = 5.7 Hz, 2H);
1348		A, 42, 216	41	394.6 (M ⁺ +1)	C ₂₁ H ₁₆ FN ₃ O ₂ S 393.09	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.81 (s, 1H), 8.62 (t, <i>J</i> = 5.5 Hz, 1H), 8.49 (dd, <i>J</i> = 0.8, 4.0 Hz, 1H), 7.75 (dd, <i>J</i> = 8.7, 6.0 Hz, 1H), 7.71-7.61 (m, 3H), 7.55 (dd, <i>J</i> = 1.8, 8.1 Hz, 1H), 7.45 (dd, <i>J</i> = 8.5 Hz, 2.6 Hz, 1H), 7.32 (dt, <i>J</i> = 8.5, 2.6 Hz, 1H), 7.25 (d, <i>J</i> = 7.8 Hz, 1H), 7.22-7.19 (m, 1H), 3.67-3.50 (m, 2H), 2.96 (t, <i>J</i> = 7.3 Hz, 2H);
1349		A, 42, 214	47	369.9 (M ⁺ +1)	C ₁₈ H ₁₂ FN ₃ O ₃ S 369.06	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.79 (br s, 1H), 9.08 (t, <i>J</i> = 5.5 Hz, 1H), 8.27 (s, 1H), 7.91-7.89 (m, 1H), 7.75 (dd, <i>J</i> = 8.7, 6.0

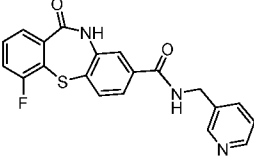
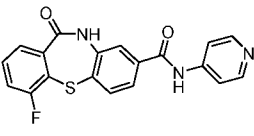
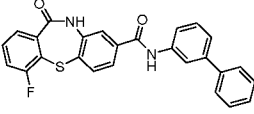
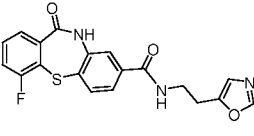
						Hz, 1H), 7.68-7.60 (m, 2H), 7.45 (dd, J = 8.5, 2.5 Hz, 1H), 7.32 (td, J = 8.5, 2.6 Hz, 1H), 7.03 (s, 1H), 4.51 (d, J = 5.4 Hz, 2H);
1362		A, 42, 215	26	395.0 ($M^{+}+1$)	$C_{20}H_{15}FN_4$ O_2S 394.09	1H NMR (DMSO- d_6 , 400 MHz): δ 10.81 (s, 1H), 9.01 (s, 1H), 8.68-8.60 (m, 3H), 7.75 (dd, J = 8.7, 6.0 Hz, 1H), 7.67-7.59 (m, 2H), 7.52 (dd, J = 8.0, 1.8 Hz, 1H), 7.44 (t, J = 6.4 Hz, 1H), 7.32 (dt, J = 8.5, 2.5 Hz, 1H), 3.52 (q, J = 6.4 Hz, 2H), 2.84 (t, J = 6.6 Hz, 2H);
1377		A, 42, 217	34	393.9 ($M^{+}+1$)	$C_{21}H_{16}FN_3$ O_2S 393.09	1H NMR (DMSO- d_6 , 400 MHz): δ 10.82 (s, 1H), 8.62 (t, J = 5.5 Hz, 1H), 8.43-8.42 (m, 1H), 8.40 (d, J = 5.0 Hz, 1H), 7.75 (t, J = 6.7 Hz, 1H), 7.68-7.60 (m, 3H), 7.54 (dd, J = 8.0, 1.8 Hz, 1H), 7.45 (dd, J = 8.6, 2.6 Hz, 1H), 7.38-7.24 (m, 2H), 3.57-3.42 (m, 2H), 2.84 (t, J = 7.0 Hz, 2H);
1402		A, 42, 347	23	383.9 ($M^{+}+1$)	$C_{19}H_{14}FN_3$ O_3S 383.07	1H NMR (DMSO- d_6 , 400MHz): δ 10.82 (s, 1H),

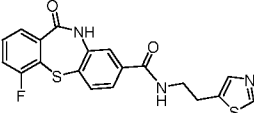
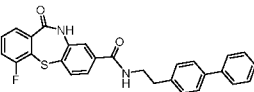
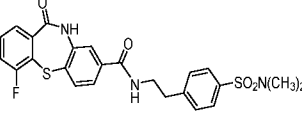
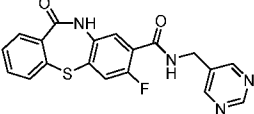
						8.66 (t, $J = 5.6$ Hz, 1H), 8.21 (s, 1H), 7.75 (dd, $J = 8.7, 6.0$ Hz, 1H), 7.69-7.62 (m, 2H), 7.55 (dd, $J = 8.1, 1.7$ Hz, 1H), 7.45 (dd, $J = 8.5, 2.5$ Hz, 1H), 7.32 (td, $J = 8.5, 2.5$ Hz, 1H), 6.92 (s, 1H), 3.58-3.42 (m, 2H), 2.91 (t, $J = 6.7$ Hz, 2H);
1403		A, 42,352	14		$C_{19}H_{14}FN_3$ O_2S_2 399.05	1H NMR (DMSO- d_6 , 400 MHz): δ 10.83 (s, 1H), 8.91 (s, 1H), 8.69 (t, $J = 5.4$ Hz, 1H), 7.76 (dd, $J = 8.6, 5.9$ Hz, 1H), 7.71-7.63 (m, 3H), 7.58 (d, $J = 8.2$ Hz, 1H), 7.45 (dd, $J = 8.5, 2.5$ Hz, 1H), 7.33 (td, $J = 8.6, 2.5$ Hz, 1H), 3.48 (q, $J = 6.4$ Hz, 2H), 3.10 (t, $J = 6.7$ Hz, 2H);
1365		A, 42, 218	53	379.9 ($M^+ + 1$)	$C_{20}H_{14}FN_3$ O_2S 379.08	1H NMR (DMSO- d_6 , 400 MHz): δ 10.81 (s, 1H), 9.15 (t, $J = 6.1$ Hz, 1H), 8.56-8.49 (m, 1H), 8.45 (dd, $J = 4.7, 1.4$ Hz, 1H), 7.78-7.60 (m, 5H), 7.45 (dd, $J = 8.6, 2.5$ Hz, 1H), 7.39-7.27 (m, 2H), 4.47 (d, $J = 5.7$ Hz, 2H);

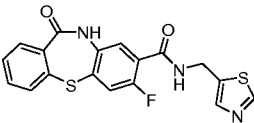
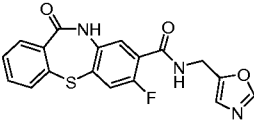
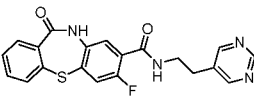
1371		A, 42, 219	25	469.8 (M ⁺ +1);	C ₂₈ H ₂₁ FN ₂ O ₂ S 468.13	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.82 (s, 1H), 8.65 (t, <i>J</i> = 5.5 Hz, 1H), 7.76 (t, <i>J</i> = 6.9 Hz, 1H), 7.69- 7.54 (m, 7H), 7.49-7.39 (m, 3H), 7.38-7.26 (m, 4H), 3.57- 3.35 (m, 2H), 2.86 (t, <i>J</i> = 7.2 Hz, 2H);
1387		A, 42, 406	23	499.9 (M ⁺ +1)	C ₂₄ H ₂₂ FN ₃ O ₄ S ₂ 499.10	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.82 (s, 1H), 8.62 (t, <i>J</i> = 5.6 Hz, 1H), 7.76 (dd, <i>J</i> = 8.7, 6.0 Hz, 1H), 7.66-7.62 (m, 4H), 7.55- 7.43 (m, 4H), 7.33 (td, <i>J</i> = 8.6, 2.6 Hz, 1H), 3.54-3.48 (m, 2H), 2.93 (t, <i>J</i> = 7.1 Hz, 2H), 2.57-2.52 (m, 6H);
1366		A, 42, 185	24	365.9 (M ⁺ +1);	C ₁₉ H ₁₂ FN ₃ O ₂ S 365.06	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.89 (s, 1H), 10.64 (s, 1H), 8.48 (d, <i>J</i> = 5.2 Hz, 2H), 7.84-7.67 (m, 6H), 7.48 (dd, <i>J</i> = 8.5, 2.6 Hz, 1H), 7.34 (t, <i>J</i> = 8.3 Hz, 1H);
1358		A, 42, 186	46	441.6 (M ⁺ +1)	C ₂₆ H ₁₇ FN ₂ O ₂ S 440.10	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.89 (s, 1H), 10.38 (s, 1H), 8.05 (s, 1H), 7.82-7.71 (m, 5H), 7.63 (d, <i>J</i> = 7.2 Hz, 2H), 7.54-7.31 (m, 7H);

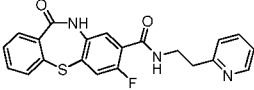
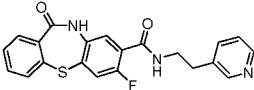
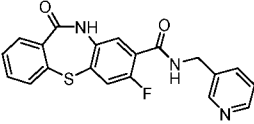
1398		A, 42, 410	20	514.0 (M ⁺ +1);	C ₂₅ H ₂₄ FN ₃ O ₄ S ₂ 513.12	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.81 (s, 1H), 8.55 (t, <i>J</i> = 5.7 Hz, 1H), 7.76 (dd, <i>J</i> = 8.7, 6.0 Hz, 1H), 7.70-7.63 (m, 4H), 7.58 (dd, <i>J</i> = 8.0, 1.7 Hz, 1H), 7.53- 7.42 (m, 3H), 7.33 (td, <i>J</i> = 8.6, 2.6 Hz, 1H), 3.28-3.23 (m, 2H), 2.72 (t, <i>J</i> = 7.6 Hz, 2H), 2.57 (s, 6H), 1.99-1.78 (m, 2H);
1390		A, 50, 212	61	380.9 (M ⁺ +1)	C ₁₉ H ₁₃ FN ₄ O ₂ S 380.07	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.88 (s, 1H), 9.17 (t, <i>J</i> = 5.7 Hz, 1H), 9.08 (s, 1H), 8.74 (s, 2H), 7.71 (dd, <i>J</i> = 4.9 Hz, 3.1 Hz, 2H), 7.67-7.59 (m, 1H), 7.54- 7.43 (m, 3H), 4.47 (d, <i>J</i> = 5.7 Hz, 2H);
1407		A, 50, 213	30	385.9 (M ⁺ +1)	C ₁₈ H ₁₂ FN ₃ O ₂ S ₂ 385.04	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.89 (s, 1H), 9.25 (t, <i>J</i> = 5.7 Hz, 1H), 8.96 (s, 1H), 7.80 (s, 1H), 7.71 (dd, <i>J</i> = 4.8, 3.1 Hz, 2H), 7.60 (dd, <i>J</i> = 8.1, 1.8 Hz, 1H), 7.54-7.45 (m, 3H), 4.65 (d, <i>J</i> = 5.6 Hz, 2H);

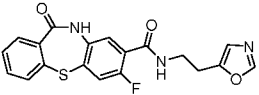
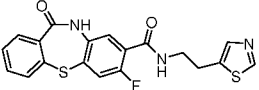
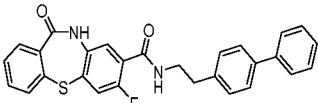
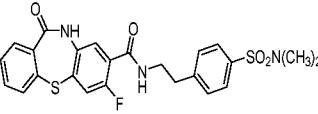
1408		A, 50, 214	23	369.9 (M ⁺ +1)	C ₁₈ H ₁₂ FN ₃ O ₃ S 369.06	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.88 (s, 1H), 9.08 (t, <i>J</i> = 5.5 Hz, 1H), 8.27 (s, 1H), 7.75-7.66 (m, 2H), 7.61 (dd, <i>J</i> = 8.0, 1.5 Hz 1H), 7.54-7.44 (m, 3H), 7.03 (s, 1H), 4.51 (d, <i>J</i> = 5.3 Hz, 2H);
1409		A, 50, 215	29	395.8 (M ⁺ +1);	C ₂₀ H ₁₅ FN ₄ O ₂ S 394.09	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.89 (s, 1H), 9.01 (s, 1H), 8.68-8.61 (m, 3H), 7.69 (d, <i>J</i> = 8.0 Hz, 1H), 7.63 (s, 1H), 7.55-7.45 (m, 4H), 3.55- 3.49 (m, 2H), 2.84 (t, <i>J</i> = 6.6 Hz, 2H);
1383		A, 50, 216	30	393.9 (M ⁺ +1)	C ₂₁ H ₁₆ FN ₃ O ₂ S 393.09	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.89 (s, 1H), 8.63 (t, <i>J</i> = 5.3 Hz, 1H), 8.50-8.47 (m, 1H), 7.72-7.63 (m, 3H), 7.55 (dd, <i>J</i> = 8.1, 1.8 Hz, 1H), 7.53- 7.44 (m, 3H), 7.25 (d, <i>J</i> = 7.8 Hz, 1H), 7.23- 7.18 (m, 1H), 3.62-3.55 (m, 2H), 2.96 (t, <i>J</i> = 7.3 Hz, 2H);
1391		A, 50, 217	44	393.9 (M ⁺ +1)	C ₂₁ H ₁₆ FN ₃ O ₂ S 393.09	¹ H NMR (DMSO- <i>d</i> ₆ , 500 MHz): δ 10.88 (s, 1H), 8.61 (t, <i>J</i> = 5.4 Hz, 1H), 8.44-8.36 (m, 2H), 7.67 (d, <i>J</i> = 8.1 Hz, 1H), 7.65-7.59 (m,

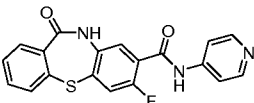
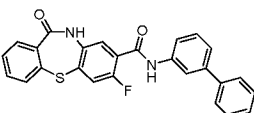
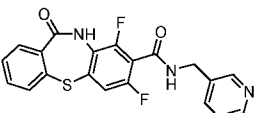
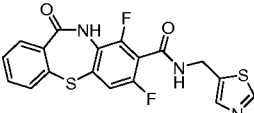
						2H), 7.54-7.43 (m, 4H), 7.28 (dd, $J = 7.4, 5.1$ Hz, 1H), 3.47 (q, $J = 6.7$ Hz, 2H), 2.82 (t, $J = 6.9$ Hz, 2H);
1392		A, 50, 218	22	379.9 ($M^{+}+1$);	$C_{20}H_{14}FN_3$ O_2S 379.08	1H NMR (DMSO- d_6 , 400 MHz): δ 10.88 (s, 1H), 9.15 (t, $J = 5.8$ Hz, 1H), 8.56-8.49 (m, 1H), 8.45 (d, $J = 5.2$ Hz, 1H), 7.74-7.67 (m, 3H), 7.65-7.62 (m, 1H), 7.54-7.43 (m, 3H), 7.34 (dd, $J = 7.7, 4.9$ Hz, 1H), 4.46 (d, $J = 5.7$ Hz, 2H);
1393		A, 50, 185	12	365.9 ($M^{+}+1$)	$C_{19}H_{12}FN_3$ O_2S 365.06	1H NMR (DMSO- d_6 , 400 MHz): δ 10.97 (s, 1H), 10.63 (s, 1H), 8.48 (d, $J = 5.3$ Hz, 2H), 7.82-7.76 (m, 2H), 7.76-7.71 (m, 3H), 7.56-7.47 (m, 3H);
1410		A, 50, 186	19	440.9 ($M^{+}+1$)	$C_{26}H_{17}FN_2$ O_2S 440.10	1H NMR (DMSO- d_6 , 400 MHz): δ 10.97 (s, 1H), 10.38 (s, 1H), 8.05 (s, 1H), 7.85-7.70 (m, 4H), 7.63 (d, $J = 7.2$ Hz, 2H), 7.57-7.36 (m, 8H);
1487		A, 50, 347	22	383.9 ($M^{+}+1$)	$C_{19}H_{14}FN_3$ O_3S 383.07	1H NMR (DMSO- d_6 , 500 MHz): 10.88 (s, 1H), 8.65 (t, $J = 5.5$ Hz, 1H), 8.20 (s, 1H), 7.68 (d, $J = 8.1$ Hz, 1H), 7.64 (s, 1H), 7.57-

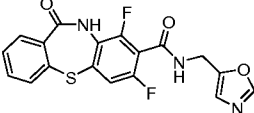
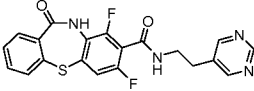
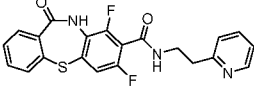
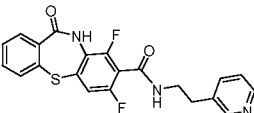
						7.43 (m, 4H), 6.90 (s, 1H), 3.47 (q, $J = 6.7$ Hz, 2H), 2.89 (t, $J = 6.8$ Hz, 2H);
1528		A, 50, 352	43	399.8 ($M^{+}+1$)	$C_{19}H_{14}FN_3$ O_2S_2 399.05	1H NMR (DMSO- d_6 , 400 MHz): δ 10.92 (br s, 1H), 8.91 (s, 1H), 8.71 (t, $J = 5.4$ Hz, 1H), 7.74-7.67 (m, 3H), 7.57 (dd, J $= 8.1, 1.8$ Hz, 1H), 7.54-7.44 (m, 3H), 3.48 (q, $J = 6.5$ Hz, 2H), 3.10 (t, $J =$ 6.7 Hz, 2H);
1466		A, 50, 219	50	469.0 ($M^{+}+1$)	$C_{28}H_{21}FN_2$ O_2S 468.13	1H NMR (DMSO- d_6 , 400 MHz): δ 10.90 (s, 1H), 8.66 (t, $J = 5.6$ Hz, 1H), 7.72-7.67 (m, 2H), 7.65-7.61 (m, 2H), 7.60- 7.56 (m, 3H), 7.54-7.42 (m, 5H), 7.36-7.29 (m, 3H), 3.49 (q, $J = 6.8$ Hz, 2H), 2.86 (t, $J =$ 7.3 Hz, 2H);
1488		A, 50, 406	34	500.0 ($M^{+}+1$)	$C_{24}H_{22}FN_3$ O_4S_2 499.10	1H NMR (DMSO- d_6 , 400 MHz) δ 10.90 (s, 1H), 8.63 (t, $J = 5.6$ Hz, 1H), 7.71-7.61 (m, 4H), 7.56-7.44 (m, 6H), 3.58- 3.45 (m, 2H), 2.92 (t, $J = 7.0$ Hz, 2H), 2.54 (s, 6H);
1428		A, 55, 212	23	381.0 ($M^{+}+1$)	$C_{19}H_{13}FN_4$ O_2S 380.07	1H NMR (DMSO- d_6 , 400 MHz): δ 10.70 (s, 1H), 9.09 (s, 1H), 8.99 (t, $J =$

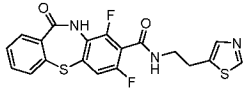
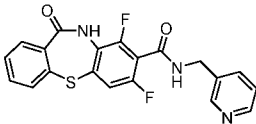
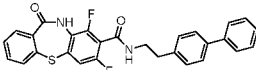
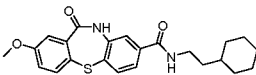
						5.1 Hz, 1H), 8.74 (s, 2H), 7.69 (d, $J = 6.5$ Hz, 1H), 7.59 (d, $J = 9.5$ Hz, 1H), 7.56-7.45 (m, 4H), 4.48 (d, $J = 5.6$ Hz, 2H);
1429		A, 55, 213	30	385.8 ($M^{+}+1$);	$C_{18}H_{12}FN_3O_2S_2$ 385.04	1H NMR (DMSO- d_6 , 400 MHz): δ 10.71 (s, 1H), 9.03 (t, $J = 5.1$ Hz, 1H), 8.98 (s, 1H), 7.79 (s, 1H), 7.69 (dd, $J = 7.4, 1.4$ Hz, 1H), 7.58 (d, $J = 9.5$ Hz, 1H), 7.56-7.47 (m, 3H), 7.46-7.42 (m, 1H), 4.64 (d, $J = 5.7$ Hz, 2H);
1430		A, 55, 214	24	369.9 ($M^{+}+1$);	$C_{18}H_{12}FN_3O_3S$ 369.06	1H NMR (DMSO- d_6 , 400 MHz): δ 10.71 (s, 1H), 8.89 (t, $J = 5.1$ Hz, 1H), 8.29 (s, 1H), 7.69 (dd, $J = 7.4, 1.5$ Hz, 1H), 7.58 (d, $J = 9.4$ Hz, 1H), 7.56-7.45 (m, 3H), 7.43 (d, $J = 6.5$ Hz, 1H), 7.02 (s, 1H), 4.50 (d, $J = 5.5$ Hz, 2H);
1411		A, 55, 215	37	394.9 ($M^{+}+1$);	$C_{20}H_{15}FN_4O_2S$ 394.09	1H NMR (DMSO- d_6 , 400 MHz): δ 10.73 (s, 1H), 9.02 (s, 1H), 8.67 (s, 2H), 8.44 (t, $J = 5.1$ Hz, 1H), 7.69 (d, $J = 6.9$ Hz, 1H), 7.58-7.45 (m, 4H), 7.34 (d, $J = 6.5$

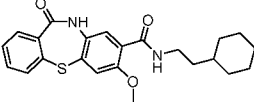
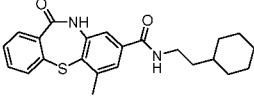
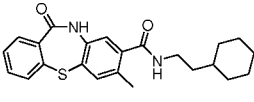
						Hz, 1H), 3.52 (q, 2H), 2.82 (t, $J = 6.6$ Hz, 2H);
1394		A, 55, 216	44	393.9 ($M^{+}+1$)	$C_{21}H_{16}FN_3$ O_2S 393.09	1H NMR (DMSO- d_6 , 400 MHz): δ 10.73 (br s, 1H), 8.53-8.46 (m, 1H), 8.45-8.39 (m, 1H), 7.72-7.67 (m, 2H), 7.57-7.45 (m, 4H), 7.40 (d, $J = 6.6$ Hz, 1H), 7.26 (d, $J = 7.7$ Hz, 1H), 7.24-7.22 (m, 1H), 3.58 (q, 2H), 2.94 (t, $J = 7.2$ Hz, 2H);
1395		A, 55, 217	51	393.9 ($M^{+}+1$)	$C_{21}H_{16}FN_3$ O_2S 393.09	1H NMR (DMSO- d_6 , 400 MHz): δ 10.74 (s, 1H), 8.42 (d, $J = 8.7$ Hz, 3H), 7.69 (d, $J = 7.0$ Hz, 1H), 7.64 (d, $J = 7.8$ Hz, 1H), 7.60-7.44 (m, 4H), 7.36 (d, $J = 6.5$ Hz, 1H), 7.30 (dd, $J = 7.5, 4.9$ Hz, 1H), 3.48 (q, 2H), 2.81 (t, $J = 6.8$ Hz, 2H);
1396		A, 55, 218	46	379.9 ($M^{+}+1$);	$C_{20}H_{14}FN_3$ O_2S 379.08	1H NMR (DMSO- d_6 , 400 MHz): δ 10.70 (br s, 1H), 8.95 (t, $J = 5.1$ Hz, 1H), 8.52 (s, 1H), 8.46 (d, $J = 3.9$ Hz, 1H), 7.75-7.64 (m, 2H), 7.59 (d, $J = 9.5$ Hz, 1H), 7.56-7.44 (m, 4H), 7.35 (dd, $J = 7.7, 4.9$ Hz, 1H), 4.46 (d, J

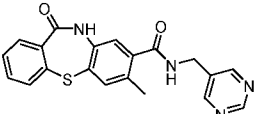
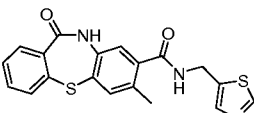
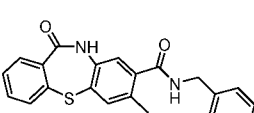
						= 6.0 Hz, 2H);
1557		A, 55, 347	38	383.9 (M ⁺ +1)	C ₁₉ H ₁₄ FN ₃ O ₃ S 383.07	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.73 (s, 1H), 8.46 (t, <i>J</i> = 4.9 Hz, 1H), 8.22 (s, 1H), 7.71-7.67 (m, 1H), 7.58-7.45 (m, 4H), 7.39 (d, <i>J</i> = 6.5 Hz, 1H), 6.92 (s, 1H), 3.48 (q, <i>J</i> = 6.6 Hz, 2H), 2.89 (t, <i>J</i> = 6.7 Hz, 2H);
1558		A, 55, 352	33	400.0 (M ⁺ +1)	C ₁₉ H ₁₄ FN ₃ O ₂ S ₂ 399.05	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.75 (s, 1H), 8.93 (s, 1H), 8.49 (t, <i>J</i> = 4.5 Hz, 1H), 7.72-7.64 (br s, 2H), 7.59-7.44 (m, 4H), 7.41 (d, <i>J</i> = 6.5 Hz, 1H), 3.47 (q, <i>J</i> = 6.4 Hz, 2H), 3.08 (t, <i>J</i> = 6.6 Hz, 2H);
1491		A, 55, 219	87	469.0 (M ⁺ +1);	C ₂₈ H ₂₁ FN ₂ O ₂ S 468.13	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.75 (s, 1H), 8.45 (t, <i>J</i> = 4.5 Hz, 1H), 7.69 (dd, <i>J</i> = 7.4, 1.3 Hz, 1H), 7.64 (d, <i>J</i> = 7.3 Hz, 2H), 7.61-7.42 (m, 8H), 7.40 (d, <i>J</i> = 6.5 Hz, 1H), 7.37-7.30 (m, 3H), 3.48 (q, <i>J</i> = 6.8 Hz, 2H), 2.84 (t, <i>J</i> = 7.2 Hz, 2H)
1507		A, 55, 406	47	499.9 (M ⁺ +1);	C ₂₄ H ₂₂ FN ₃ O ₄ S ₂ 499.10	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.75 (s, 1H), 8.42 (t, <i>J</i> = 5.1 Hz, 1H),

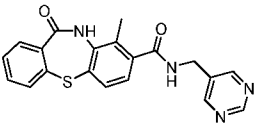
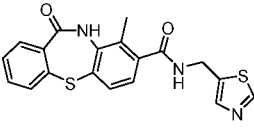
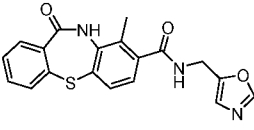
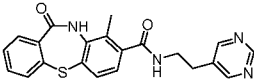
						7.71-7.63 (m, 3H), 7.57-7.45 (m, 6H), 7.35 (d, $J = 6.5$ Hz, 1H), 3.50 (q, $J = 6.7$ Hz, 2H), 2.91 (t, $J = 6.9$ Hz, 2H), 2.56 (s, 6H);
1508		A, 55, 185	32	365.9 ($M^{+}+1$)	$C_{19}H_{12}FN_3$ O_2S 365.06	1H NMR (DMSO- d_6 , 400 MHz): δ 10.79 (s, 2H), 8.48 (d, $J = 6.0$ Hz, 2H), 7.73-7.66 (m, 2H), 7.62 (d, $J = 6.3$ Hz, 2H), 7.59-7.45 (m, 4H);
1509		A, 55, 186	53	441.0 ($M^{+}+1$)	$C_{26}H_{17}FN_2$ O_2S 440.10	1H NMR (DMSO- d_6 , 400 MHz): δ 10.79 (s, 1H), 10.51 (s, 1H), 7.98 (s, 1H), 7.71 (dd, $J = 7.4, 15$ Hz, 1H), 7.68-7.59 (m, 4H), 7.58-7.44 (m, 6H), 7.43-7.35 (m, 3H);
1518		B, 62, 212	39	398.9 ($M^{+}+1$)	$C_{19}H_{12}F_2N$ $4O_2S$ 398.06	1H NMR (DMSO- d_6 , 400 MHz): δ 10.68 (s, 1H), 9.38 (t, $J = 6.0$ Hz, 1H), 9.10 (s, 1H), 8.73 (s, 2H), 7.72-7.68 (m, 1H), 7.59-7.46 (m, 4H), 4.50 (d, $J = 5.9$ Hz, 2H);
1545		B, 62, 213	25	403.9 ($M^{+}+1$)	$C_{18}H_{11}F_2N$ $3O_2S_2$ 403.03	1H NMR (DMSO- d_6 , 400 MHz): δ 10.66 (s, 1H), 9.39 (t, $J = 5.9$ Hz, 1H), 9.00 (s, 1H), 7.79 (s, 1H), 7.72-7.68 (m, 1H), 7.59-7.45

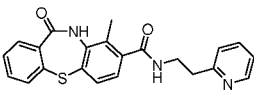
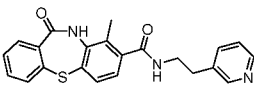
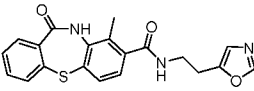
						(m, 4H), 4.66 (d, $J = 5.7$ Hz, 2H);
1530		B, 62, 214	30	387.9 ($M^{+}+1$)	$C_{18}H_{11}F_2N_3O_3S$ 387.05	1H NMR (DMSO- d_6 , 400 MHz): δ 10.66 (s, 1H), 9.26 (t, $J = 5.6$ Hz, 1H), 8.31 (s, 1H), 7.73-7.66 (m, 1H), 7.58-7.46 (m, 4H), 7.02 (s, 1H), 4.51 (d, $J = 5.5$ Hz, 2H);
1562		B, 62, 215	25	413.0 ($M^{+}+1$)	$C_{20}H_{14}F_2N_4O_2S$ 412.08	1H NMR (DMSO- d_6 , 400 MHz): δ 10.66 (s, 1H), 9.03 (s, 1H), 8.80 (t, $J = 5.9$ Hz, 1H), 8.67 (s, 2H), 7.78-7.62 (m, 1H), 7.58-7.43 (m, 4H), 3.53 (q, 2H), 2.81 (t, $J = 6.5$ Hz, 2H);
1519		B, 62, 216	25	411.9 ($M^{+}+1$)	$C_{21}H_{15}F_2N_3O_2S$ 411.09	1H NMR (DMSO- d_6 , 400 MHz): δ 10.64 (s, 1H), 8.78 (t, $J = 5.5$ Hz, 1H), 8.49 (d, $J = 4.2$ Hz, 1H), 7.77-7.62 (m, 2H), 7.59-7.41 (m, 4H), 7.35-7.13 (m, 2H), 3.58 (q, 2H), 2.92 (t, $J = 7.2$ Hz, 2H);
1531		B, 62, 217	57	411.9 ($M^{+}+1$)	$C_{21}H_{15}F_2N_3O_2S$ 411.09	1H NMR (DMSO- d_6 , 400 MHz): δ 10.66 (s, 1H), 8.80 (t, $J = 5.6$ Hz, 1H), 8.51-8.34 (m, 2H), 7.72-7.68 (m, 1H), 7.65 (td, $J = 1.9, 7.8$ Hz, 1H), 7.57-7.45 (m, 4H),

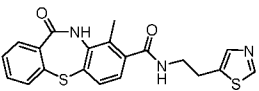
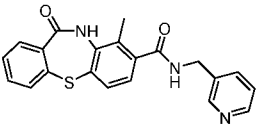
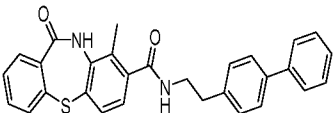
						7.31 (dd, J = 7.7, 4.8 Hz, 1H), 3.49 (q, 2H), 2.80 (t, J = 6.8 Hz, 2H);
1563		B, 62, 352	28	418.0 ($M^{+}+1$)	$C_{19}H_{13}F_2N_3O_2S_2$ 417.04	1H NMR (DMSO- d_6 , 400 MHz): δ 10.66 (s, 1H), 8.94 (s, 1H), 8.88 (t, J = 5.5 Hz, 1H), 7.72-7.69 (m, 1H), 7.68 (s, 1H), 7.58-7.46 (m, 4H), 3.48 (q, 2H), 3.06 (t, J = 6.6 Hz, 2H);
1546		B, 62, 218	46	398.0 ($M^{+}+1$)	$C_{20}H_{13}F_2N_3O_2S$ 397.07	1H NMR (DMSO- d_6 , 400 MHz): δ 10.67 (s, 1H), 9.31 (t, J = 6.0 Hz, 1H), 8.52 (s, 1H), 8.48 (dd, J = 4.8, 1.6 Hz, 1H), 7.74-7.64 (m, 2H), 7.58-7.46 (m, 4H), 7.39-7.36 (m, 1H), 4.48 (d, J = 5.9 Hz, 2H);
1497		B, 62, 219	15	487.0 ($M^{+}+1$);	$C_{28}H_{20}F_2N_2O_2S$ 486.12	1H NMR (DMSO- d_6 , 400 MHz): δ 10.63 (s, 1H), 8.81 (t, J = 5.9 Hz, 1H), 7.71-7.65 (m, 1H), 7.63-7.60 (m, 2H), 7.58-7.50 (m, 3H), 7.50-7.40 (m, 5H), 7.35-7.28 (m, 3H), 3.46 (q, 2H), 2.80 (t, J = 7.1 Hz, 2H);
1272		A, 70, 261	55	412.8 ($M^{+}+1$);	$C_{23}H_{26}N_2O_3S$ 410.17	1H -NMR (DMSO- d_6 , 400 MHz): δ 10.74 (s, 1H), 8.42 (t, J = 6.4 Hz, 1H), 7.64-7.60 (m, 2H), 7.54 (s,

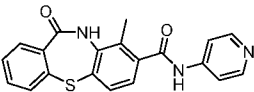
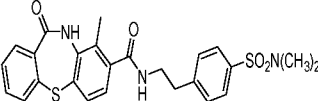
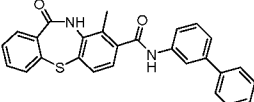
						1H), 7.43 (d, J = 8.8 Hz, 1H), 7.18 (s, 1H), 7.05 (d, J = 8.8 Hz, 1H), 3.76 (s, 3H), 3.24-3.21 (m, 2H), 1.70-1.58 (m, 5H), 1.40-1.35 (m, 2H), 1.26-1.09 (m, 4H), 0.91-0.83 (m, 2H);
1287		A, 76, 261	46	411.9 ($M^{+}+1$);	$C_{23}H_{26}N_2O_3S$ 410.17	1H -NMR (DMSO- d_6 , 400 MHz): δ 10.55 (s, 1H), 8.08 (t, J = 5.6 Hz, 1H), 7.67 (t, J = 5.6 Hz, 1H), 7.54-7.43 (m, 4H), 7.27 (s, 1H), 3.85 (s, 3H), 3.26-3.21 (m, 2H), 1.70-1.59 (m, 5H), 1.39-1.33 (m, 2H), 1.29-1.12 (m, 4H), 0.93-0.85 (m, 2H);
1286		A, 82, 261	20	395.6 ($M^{+}+1$)	$C_{23}H_{26}N_2O_2S$ 394.17	1H -NMR (DMSO- d_6 , 400 MHz): δ 10.69 (s, 1H), 8.37 (t, J = 5.6 Hz, 1H), 7.68-7.59 (m, 3H), 7.53-7.43 (m, 3H), 3.25-3.20 (m, 2H), 2.55 (s, 3H), 1.70-1.58 (m, 5H), 1.40-1.35 (m, 2H), 1.26-1.14 (m, 4H), 0.91-0.85 (m, 2H);
1275		A, 88, 261	35	395.8 ($M^{+}+1$)	$C_{23}H_{26}N_2O_2S$ 394.17	1H -NMR (DMSO- d_6 , 400 MHz): δ 10.66 (br s, 1H), 8.20 (br s, 1H), 7.66 (d, J = 7.2 Hz,

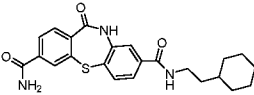
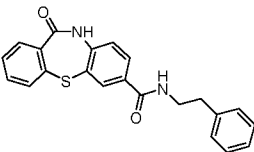
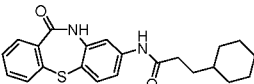
						1H), 7.53-7.44 (m, 4H), 7.10 (s, 1H), 3.22-3.17 (m, 2H), 2.22 (s, 3H), 1.70-1.58 (m, 5H), 1.37-1.09 (m, 6H), 0.90-0.82 (m, 2H);
1641		A, 88, 212	61	377.3 (M ⁺ +1)	C ₂₀ H ₁₆ N ₄ O ₂ S 376.10	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.62 (s, 1H), 9.10 (s, 1H), 8.91 (t, <i>J</i> = 5.7 Hz, 1H), 8.75 (s, 2H), 7.67 (dd, <i>J</i> = 1.6, 7.4, 1.6 Hz, 1H), 7.57-7.42 (m, 4H), 7.23 (s, 1H), 4.44 (d, <i>J</i> = 5.9 Hz, 2H), 2.23 (s, 3H)
1642		A, 88, 213	34	381.9 (M ⁺ +1)	C ₁₉ H ₁₅ N ₃ O ₂ S ₂ 381.06	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.63 (s, 1H), 9.00-8.95 (m, 2H), 7.79 (s, 1H), 7.66 (dd, <i>J</i> = 7.5, 1.5 Hz, 1H), 7.54-7.41 (m, 4H), 7.15 (s, 1H), 4.61 (d, <i>J</i> = 5.7 Hz, 2H), 2.23 (s, 3H);
1643		A, 88, 218	75	376.0 (M ⁺ +1)	C ₂₁ H ₁₇ N ₃ O ₂ S 375.10	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.63 (s, 1H), 8.87 (t, <i>J</i> = 5.9 Hz, 1H), 8.53 (s, 1H), 8.47 (dd, <i>J</i> = 4.8, 1.5 Hz, 1H), 7.74-7.65 (m, 2H), 7.56-7.41 (m, 4H), 7.36 (dd, <i>J</i> = 7.4, 5.1 Hz, 1H), 7.20 (s, 1H), 4.42 (d, <i>J</i>

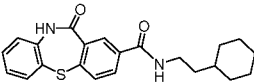
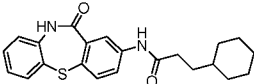
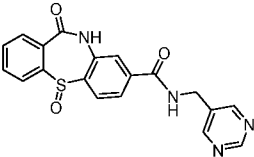
						= 6.0 Hz, 2H), 2.23 (s, 3H)
1478		A, 97, 212 (Reaction time 18 h)	45	376.9 (M ⁺ +1)	C ₂₀ H ₁₆ N ₄ O S 376.10	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.24 (s, 1H), 9.09 (s, 1H), 8.93 (t, <i>J</i> = 5.9 Hz, 1H), 8.75 (s, 2H), 7.69-7.59 (m, 1H), 7.56-7.39 (m, 4H), 7.14 (d, <i>J</i> = 7.9 Hz, 1H), 4.44 (d, <i>J</i> = 5.7 Hz, 2H), 2.26 (s, 3H);
1513		A, 97, 213	28	382.2 (M ⁺ +1)	C ₁₉ H ₁₅ N ₃ O S ₂ 381.06	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.23 (s, 1H), 9.01 (t, <i>J</i> = 5.9 Hz, 1H), 8.98 (s, 1H), 7.79 (s, 1H), 7.71-7.59 (m, 1H), 7.55-7.48 (m, 2H), 7.47- 7.40 (m, 2H), 7.06 (d, <i>J</i> = 7.9 Hz, 1H), 4.61 (d, <i>J</i> = 5.7 Hz, 2H), 2.27 (s, 3H);
1514		B, 97, 214	55	365.8 (M ⁺ +1)	C ₁₉ H ₁₅ N ₃ O S 365.08	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.21 (s, 1H), 8.83 (t, <i>J</i> = 5.7 Hz, 1H), 8.26 (s, 1H), 7.83-7.56 (m, 1H), 7.56-7.36 (m, 4H), 7.06 (d, <i>J</i> = 7.9 Hz, 1H), 7.01 (s, 1H), 4.44 (d, <i>J</i> = 5.6 Hz, 2H), 2.24 (s, 3H);
1529		A, 97, 215	25	390.9 (M ⁺ +1)	C ₂₁ H ₁₈ N ₄ O S 390.12	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.20 (s, 1H), 9.03 (s, 1H), 8.68 (s, 2H), 8.38 (t, <i>J</i> =

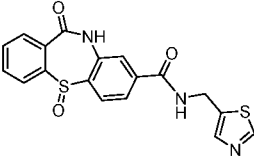
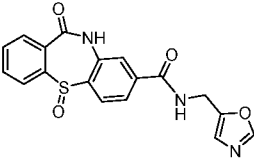
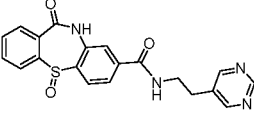
						5.3 Hz, 1H), 7.69-7.60 (m, 1H), 7.53-7.39 (m, 4H), 6.96 (d, $J = 7.9$ Hz, 1H), 3.51 (q, 2H), 2.81 (t, $J = 6.6$ Hz, 2H), 2.13 (s, 3H);
1459		A, 97, 216	58	390.0 ($M^{+}+1$)	$C_{22}H_{19}N_3O$ $_2S$ 389.12	1H NMR (DMSO- d_6 , 400 MHz): δ 10.20 (s, 1H), 8.48 (d, $J = 4.0$ Hz, 1H), 8.34 (br s, 1H), 7.76-7.58 (m, 2H), 7.55-7.35 (m, 4H), 7.26 (d, $J = 7.8$ Hz, 1H), 7.23-7.18 (m, 1H), 7.00 (d, $J = 7.8$ Hz, 1H), 3.55 (d, $J = 5.5$ Hz, 2H), 2.93 (t, $J = 7.1$ Hz, 2H), 2.19 (s, 3H);
1467		A, 97, 217	29	390.0 ($M^{+}+1$)	$C_{22}H_{19}N_3O$ $_2S$ 389.12	1H NMR (DMSO- d_6 , 500 MHz): δ 10.20 (s, 1H), 8.46-8.39 (m, 2H), 8.36 (t, $J = 5.4$ Hz, 1H), 7.65 (td, $J = 6.2, 3.0$ Hz, 2H), 7.58-7.38 (m, 4H), 7.31 (dd, $J = 7.7, 4.8$ Hz, 1H), 6.96 (d, $J = 8.1$ Hz, 1H), 3.47 (d, $J = 5.5$ Hz, 2H), 2.80 (t, $J = 6.8$ Hz, 2H), 2.15 (s, 3H);
1560		A, 97, 347	21	379.9 ($M^{+}+1$)	$C_{20}H_{17}N_3O$ $_3S$ 379.10	1H NMR (DMSO- d_6 , 400 MHz): δ 10.22 (s, 1H), 8.41 (t, $J = 5.7$ Hz, 1H), 8.22 (s, 1H),

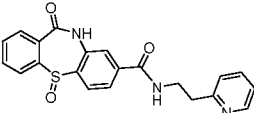
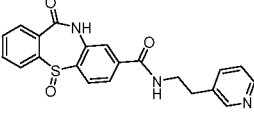
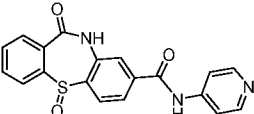
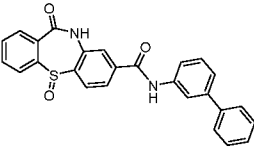
						7.72- 7.58 (m, 1H), 7.56-7.35 (m, 4H), 7.01 (d, $J = 7.9$ Hz, 1H), 6.92 (s, 1H), 3.45 (d, $J = 6.2$ Hz, 2H), 2.98-2.81 (m, 2H), 2.22 (s, 3H);
1561		A, 97, 352	34	396.0 ($M^{+}+1$)	$C_{20}H_{17}N_3O$ $_2S_2$ 395.08	1H NMR (DMSO- d_6 , 400 MHz): δ 10.22 (s, 1H), 8.93 (s, 1H), 8.44 (t, $J = 5.9$ Hz, 1H), 7.68 (s, 1H), 7.67-7.63 (m, 1H), 7.54-7.47 (m, 2H), 7.46-7.42 (m, 2H), 7.02 (d, $J = 7.9$ Hz, 1H), 3.45 (q, 2H), 3.07 (t, $J = 6.6$ Hz, 2H), 2.21 (s, 3H);
1515		A, 97, 218	40	376.0 ($M^{+}+1$)	$C_{21}H_{17}N_3O$ $_2S$ 375.10	1H NMR (DMSO- d_6 , 400 MHz): δ 10.24 (s, 1H), 8.90 (t, $J = 6.1$ Hz, 1H), 8.54-8.51 (m, 1H), 8.46 (d, $J = 5.3$ Hz, 1H), 7.70 (dt, $J = 7.8, 1.9$ Hz, 1H), 7.67-7.63 (m, 1H), 7.54-7.40 (m, 4H), 7.36 (dd, $J = 7.5, 5.1$ Hz, 1H), 7.12 (d, $J = 7.9$ Hz, 1H), 4.42 (d, $J = 6.0$ Hz, 2H), 2.27 (s, 3H);
1495		A, 97, 219	41	465.0 ($M^{+}+1$)	$C_{29}H_{24}N_2O$ $_2S$ 464.16	1H NMR (DMSO- d_6 , 400 MHz): δ 10.20 (s, 1H), 8.37 (t, $J = 5.1$ Hz, 1H), 7.64 (d, $J = 7.2$

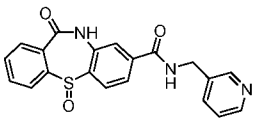
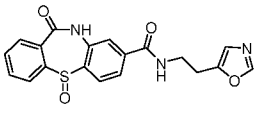
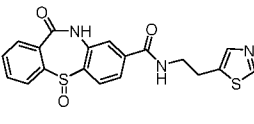
						Hz, 3H), 7.59 (d, $J = 8.0$ Hz, 2H), 7.53-7.40 (m, 6H), 7.39-7.26 (m, 3H), 7.00 (d, $J = 7.9$ Hz, 1H), 3.48 (q, 2H), 2.83 (t, $J = 6.9$ Hz, 2H), 2.19 (s, 3H);
1516		B, 97, 185	34	361.9 ($M^{+}+1$)	$C_{20}H_{15}N_3O$ $_2S$ 361.09	1H NMR (DMSO- d_6 , 400 MHz): δ 10.73 (br s, 1H), 10.34 (br s, 1H), 8.45 (d, $J = 4.6$ Hz, 2H), 7.71-7.53 (m, 5H), 7.50-7.44 (m, 2H), 7.26 (d, $J = 7.9$ Hz, 1H), 2.34 (s, 3H);
1517		B, 97, 406	50	496.0 ($M^{+}+1$)	$C_{25}H_{25}N_3O$ $_4S_2$ 495.13	1H NMR (DMSO- d_6 , 400 MHz): δ 10.21 (s, 1H), 8.36 (t, $J = 5.6$ Hz, 1H), 7.69-7.62 (m, 3H), 7.57-7.40 (m, 6H), 6.96 (d, $J = 7.9$ Hz, 1H), 3.50 (d, $J = 5.3$ Hz, 2H), 2.90 (t, $J = 6.7$ Hz, 2H), 2.58 (s, 6H), 2.14 (s, 3H);
1496		B, 97, 186	37	437.0 ($M^{+}+1$)	$C_{27}H_{20}N_2O$ $_2S$ 436.12	1H NMR (DMSO- d_6 , 400 MHz): δ 10.42 (s, 1H), 10.31 (s, 1H), 8.00 (s, 1H), 7.70-7.63 (m, 2H), 7.62-7.53 (m, 4H), 7.51-7.43 (m, 4H), 7.43-7.35 (m, 3H), 7.26 (d, $J = 7.9$ Hz, 1H), 2.37 (s, 3H);

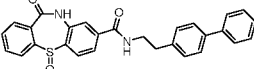
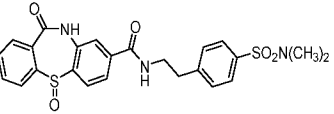
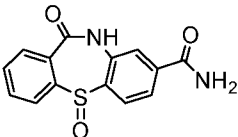
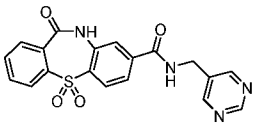
1276		A, 135, 261	40	424.8 ($M^{+}+1$);	$C_{23}H_{25}N_3O$ $_3S$ 423.16	1H -NMR (DMSO- d_6 , 500 MHz): δ 10.86 (br s, 1H), 8.45- 8.44 (m, 1H), 8.14 (s, 1H), 8.00 (s, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.5 Hz, 1H), 7.57 (d, J = 8.5 Hz, 2H), 3.24- 3.23 (m, 2H), 1.70-1.58 (m, 5H), 1.37 (t, J = 6.5 Hz, 2H), 1.18-1.09 (m, 5H), 0.86 (t, J = 6.5 Hz, 2H);
1200		A, 140, 211	73	375.1 ($M^{+}+1$);	$C_{22}H_{18}N_2O$ $_2S$ 374.11	1H -NMR (DMSO- d_6 , 400 MHz): δ 10.85 (s, 1H), 8.60 (t, J = 4.8 Hz, 1H), 8.01 (s, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.54-7.44 (m, 3H), 7.30- 7.17 (m, 6H), 3.47-3.42 (m, 2H), 2.82 (t, J = 7.6 Hz, 2H);
1207		A, 145, 3- cyclohexylp ropanoic acid	35	381.1 ($M^{+}+1$)	$C_{22}H_{24}N_2O$ $_2S$ 380.16	1H -NMR (DMSO- d_6 , 400 MHz): δ 10.67 (s, 1H), 10.03 (s, 1H), 7.66 (d , J = 7.2 Hz, 1H), 7.60 (s, 1H), 7.50-7.40 (m, 4H), 7.31 (d, J = 8.4 Hz, 1H), 2.32-2.27 (m, 2H), 1.69- 1.60 (m, 5H), 1.48-1.43 (m, 2H), 1.18-1.13 (m, 4H), 0.90-

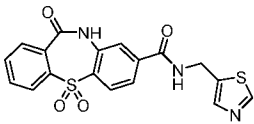
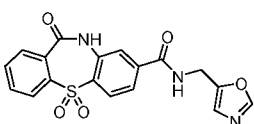
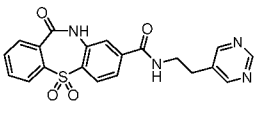
						0.85 (m, 2H);
1644		A, 150, 261	54	381.4 (M ⁺ +1)	C ₂₂ H ₂₄ N ₂ O S 380.16	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.77 (br s, 1H), 8.58- 8.54 (m, 1H), 8.12 (s, 1H), 7.90 (d, <i>J</i> = 8.0 Hz, 1H), 7.62- 7.56 (m, 2H), 7.38-7.34 (m, 1H), 7.23 (d, <i>J</i> = 8.0 Hz, 1H), 7.16 (t, <i>J</i> = 6.8 Hz, 1H), 3.27- 3.24 (m, 2H), 1.72-1.58 (m, 5H), 1.26-1.11 (m, 5H), 0.96- 0.82 (m, 2H);
1645		B, 155, 3- cyclohexylp ropanoic acid	6	381.2 (M ⁺ +1);	C ₂₂ H ₂₄ N ₂ O S 380.16	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.64 (s, 1H), 10.08 (s, 1H), 7.95 (s, 1H), 7.68-7.65 (m, 1H), 7.53 (d, <i>J</i> = 7.2 Hz, 1H), 7.43 (d, <i>J</i> = 8.4 Hz, 1H), 7.34 (t, <i>J</i> = 8.0 Hz, 1H), 7.22 (d, <i>J</i> = 7.2 Hz, 1H), 7.13 (t, <i>J</i> = 7.6 Hz, 1H), 2.32-2.27 (m, 2H), 1.69-1.60 (m, 4H), 1.49- 1.41 (m, 2H), 1.28-1.13 (m, 4H), 0.90-0.85 (m, 3H);
1373		A, 156, 212 (Reaction time 24 h)	21	378.9 (M ⁺ +1)	C ₁₉ H ₁₄ N ₄ O S 378.08	¹ H NMR (DMSO- <i>d</i> ₆ , 500 MHz): δ 11.03 (br s, 1H), 9.21 (t, <i>J</i> = 5.4 Hz, 1H), 9.06 (s, 1H), 8.73 (s, 2H), 7.88 (d, <i>J</i> = 8.1 Hz, 1H), 7.83-7.76 (m,

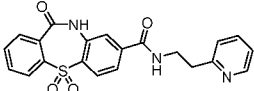
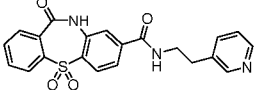
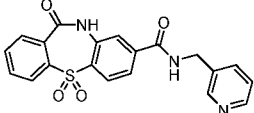
						2H), 7.74-7.67 (m, 3H), 7.63-7.59 (m, 1H), 4.46 (d, $J = 4.9$ Hz, 2H);
1388		A, 156, 213	21	383.9 ($M^{+}+1$)	$C_{18}H_{13}N_3O$ $_3S_2$ 383.04	1H NMR (DMSO- d_6 , 400MHz): δ 11.05 (s, 1H), 9.31 (t, $J = 6.3$ Hz, 1H), 8.96 (s, 1H), 7.88-7.60 (m, 8H), 4.65 (d, $J = 5.6$ Hz, 2H);
1381		A, 156, 214	23	367.9 ($M^{+}+1$)	$C_{18}H_{13}N_3O$ $_4S$ 367.06	1H NMR (DMSO- d_6 , 400 MHz): δ 11.05 (s, 1H), 9.14 (t, $J = 5.6$ Hz, 1H), 8.27 (s, 1H), 7.88 (dd, $J = 8.2, 1.5$ Hz, 1H), 7.84-7.78 (m, 2H), 7.76-7.67 (m, 3H), 7.63 (dd, $J = 7.7, 1.0$ Hz, 1H), 7.04 (s, 1H), 4.51 (d, $J = 5.5$ Hz, 2H);
1423		B, 156, 215	32	393.0 ($M^{+}+1$)	$C_{20}H_{16}N_4O$ $_3S$ 392.09	1H NMR (DMSO- d_6 , 400 MHz): δ 11.06 (s, 1H), 9.01 (s, 1H), 8.69 (t, $J = 5.6$ Hz, 1H), 8.66 (s, 2H), 7.84-7.77 (m, 3H), 7.74 (d, $J = 7.0$ Hz, 1H), 7.67 (d, $J = 8.2$ Hz, 1H), 7.65-7.60 (m, 2H), 3.53 (q, $J = 6.3$ Hz, 2H), 2.84 (t, $J = 6.6$ Hz, 2H);

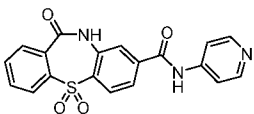
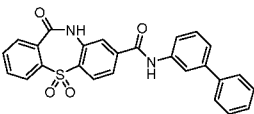
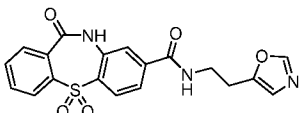
1374		A, 156, 216	44	391.9 (M ⁺ +1)	C ₂₁ H ₁₇ N ₃ O S 391.10	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 11.06 (s, 1H), 8.69 (t, <i>J</i> = 5.6 Hz, 1H), 8.51-8.47 (m, 1H), 7.85-7.78 (m, 3H), 7.74 (d, <i>J</i> = 6.9 Hz, 1H), 7.71-7.60 (m, 4H), 7.25 (d, <i>J</i> = 7.7 Hz, 1H), 7.23-7.18 (m, 1H), 3.59 (q, <i>J</i> = 6.5 Hz, 2H), 2.96 (t, <i>J</i> = 7.3 Hz, 2H);
1389		A, 156, 217	21	391.9 (M ⁺ +1)	C ₂₁ H ₁₇ N ₃ O S 391.10	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 11.06 (s, 1H), 8.69 (t, <i>J</i> = 5.2 Hz, 1H), 8.44-8.37 (m, 2H), 7.84-7.72 (m, 4H), 7.70- 7.60 (m, 4H), 7.29 (dd, <i>J</i> = 7.5, 5.0 Hz, 1H), 3.49 (q, <i>J</i> = 6.5 Hz, 2H), 2.83 (t, <i>J</i> = 7.0 Hz, 2H);
1382		A, 156, 185	8	363.9 (M ⁺ +1)	C ₁₉ H ₁₃ N ₃ O S 363.07	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 11.13 (br s, 1H), 10.69 (s, 1H), 8.53-8.43 (m, 2H), 7.99 (dd, <i>J</i> = 8.1, 1.5 Hz, 1H), 7.86-7.75 (m, 5H), 7.75- 7.70 (m, 2H), 7.67-7.62 (m, 1H);
1375		A, 156, 186	33	439.5 (M ⁺ +1)	C ₂₆ H ₁₈ N ₂ O S 438.10	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 11.13 (s, 1H), 10.44 (s, 1H), 8.07- 7.98 (m, 2H), 7.87-7.72 (m,

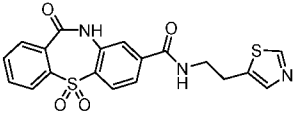
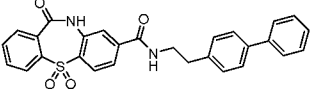
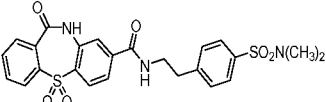
						6H), 7.68-7.60 (m, 3H), 7.52-7.35 (m, 5H);
1427		A, 156, 218	19	377.9 (M ⁺ +1);	C ₂₀ H ₁₅ N ₃ O ₃ S 377.08	¹ H NMR (DMSO-d ₆ , 400 MHz): δ 11.05 (s, 1H), 9.21 (t, J = 5.9 Hz, 1H), 8.53 (s, 1H), 8.45 (dd, J = 4.7, 1.4 Hz, 1H), 7.90 (dd, J = 8.2, 1.5 Hz, 1H), 7.85-7.68 (m, 6H), 7.63 (td, J = 7.5, 1.3 Hz, 1H), 7.34 (dd, J = 7.8, 4.8 Hz, 1H), 4.47 (d, J = 5.2 Hz, 2H);
1485		A, 156, 347	18	381.9 (M ⁺ +1)	C ₁₉ H ₁₅ N ₃ O ₄ S 381.08	¹ H NMR (DMSO-d ₆ , 400 MHz): δ 11.06 (s, 1H), 8.73 (t, J = 5.6 Hz, 1H), 8.21 (s, 1H), 7.85-7.78 (m, 3H), 7.74 (dd, J = 9.5, 2.7 Hz, 1H), 7.68 (d, J = 8.4 Hz, 2H), 7.63 (td, J = 10.1, 1.1 Hz, 1H), 6.92 (s, 1H), 3.53-3.46 (m, 2H), 2.90 (t, J = 6.7 Hz, 2H);
1527		A, 156, 352	24	397.8 (M ⁺ +1)	C ₁₉ H ₁₅ N ₃ O ₃ S ₂ 397.06	¹ H NMR (DMSO-d ₆ , 400 MHz): δ 11.07 (br s, 1H), 8.90 (s, 1H), 8.76 (t, J = 5.5 Hz, 1H), 7.877.78 (m, 3H), 7.75 (d, J = 7.3 Hz, 1H), 7.71-7.67 (m, 3H), 7.66-7.60 (m, 1H), 3.52-3.45 (m, 2H), 3.10 (t, J = 6.7

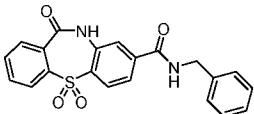
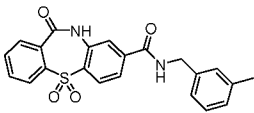
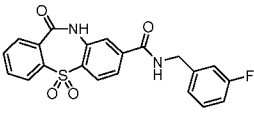
						Hz, 2H);
1476		A, 156, 219	29	467.0 (M ⁺ +1)	C ₂₈ H ₂₂ N ₂ O 3S 466.14	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 11.07 (s, 1H), 8.72 (t, <i>J</i> = 5.4 Hz, 1H), 7.87-7.78 (m, 3H), 7.76-7.73 (m, 1H), 7.71- 7.67 (m, 2H), 7.65-7.60 (m, 3H), 7.58 (d, <i>J</i> = 8.2 Hz, 2H), 7.47-7.41 (m, 2H), 7.36-7.29 (m, 3H), 3.50 (q, <i>J</i> = 6.7 Hz, 2H), 2.86 (t, <i>J</i> = 7.2 Hz, 2H);
1486		A, 156, 406	17	498.0 (M ⁺ +1)	C ₂₄ H ₂₃ N ₃ O 5S ₂ 497.11	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 11.06 (s, 1H), 8.68 (t, <i>J</i> = 5.5 Hz, 1H), 7.85-7.77 (m, 3H), 7.76-7.73 (m, 1H), 7.68- 7.61 (m, 5H), 7.48 (d, <i>J</i> = 8.4 Hz, 2H), 3.61- 3.45 (m, 2H), 2.92 (t, <i>J</i> = 7.0 Hz, 2H), 2.53 (s, 6H);
1575		B, 156, 133	48	286.8 (M ⁺ +1)	C ₁₄ H ₁₀ N ₂ O 3S 286.04	¹ H-NMR DMSO- <i>d</i> ₆ , 400 MHz): δ 11.05 (br s, 1H), 8.06 (br s, 1H), 7.93- 7.58 (m, 7H), 7.52 (br s, 1H);
1446		A, 159, 212	38	395.0 (M ⁺ +1)	C ₁₉ H ₁₄ N ₄ O 4S 394.07	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 11.51 (s, 1H), 9.34 (t, <i>J</i> = 5.8 Hz, 1H), 9.08 (s, 1H), 8.76 (s, 2H), 8.06 (d, <i>J</i> = 8.2 Hz, 1H), 8.01- 7.95 (m, 2H), 7.92-7.80 (m,

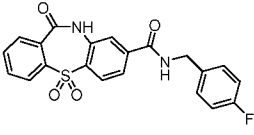
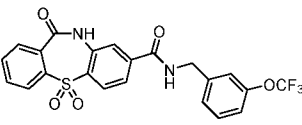
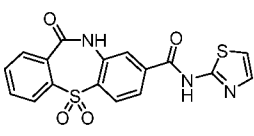
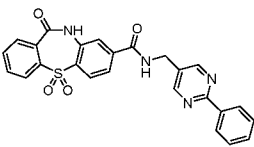
						4H), 4.50 (d, J = 5.6 Hz, 2H);
1455		A, 159, 213	27	399.9 ($M^{+}+1$)	$C_{18}H_{13}N_3O$ 4S_2 399.03	1H NMR (DMSO- d_6 , 400 MHz): δ 11.50 (s, 1H), 9.42 (t, J = 5.9 Hz, 1H), 8.97 (s, 1H), 8.05 (d, J = 8.3 Hz, 1H), 7.98 (td, J = 7.4, 1.1 Hz, 2H), 7.90 (td, J = 7.5, 1.4 Hz, 1H), 7.87-7.77 (m, 4H), 4.67 (d, J = 5.6 Hz, 2H);
1456		A, 159, 214	23	384.0 ($M^{+}+1$)	$C_{18}H_{13}N_3O$ 5S 383.06	1H NMR (DMSO- d_6 , 400 MHz): δ 11.51 (br s, 1H), 9.26 (t, J = 5.6 Hz, 1H), 8.29 (s, 1H), 8.05 (d, J = 8.3 Hz, 1H), 8.01-7.95 (m, 2H), 7.90 (td, J = 7.5, 1.5 Hz, 1H), 7.88-7.78 (m, 3H), 7.06 (s, 1H), 4.53 (d, J = 5.3 Hz, 2H);
1457		A, 159, 215	32	409.0 ($M^{+}+1$)	$C_{20}H_{16}N_4O$ 4S 408.09	1H NMR (DMSO- d_6 , 400 MHz): δ 11.51 (s, 1H), 9.01 (s, 1H), 8.80 (t, J = 5.7 Hz, 1H), 8.67 (s, 2H), 8.03 (d, J = 8.2 Hz, 1H), 8.01-7.96 (m, 2H), 7.94-7.82 (m, 2H), 7.76 (s, 1H), 7.71 (dd, J = 8.3, 1.6 Hz, 1H), 3.55 (q, J = 6.3 Hz, 2H), 2.86 (t, J = 6.6 Hz, 2H);

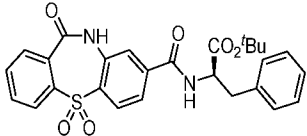
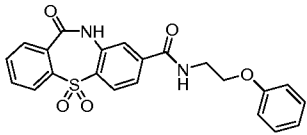
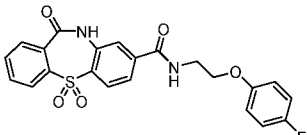
1447		A, 159, 216	30	408.0 (M ⁺ +1)	C ₂₁ H ₁₇ N ₃ O 4S 407.09	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 11.51 (s, 1H), 8.80 (t, <i>J</i> = 5.5 Hz, 1H), 8.51-8.48 (m, 1H), 8.03 (d, <i>J</i> = 8.3 Hz, 1H), 8.00-7.96 (m, 2H), 7.93-7.83 (m, 2H), 7.79- 7.78 (m, 1H), 7.74 (dd, <i>J</i> = 8.3, 1.6 Hz, 1H), 7.69 (td, <i>J</i> = 7.7, 1.8 Hz, 1H), 7.26 (d, <i>J</i> = 7.7 Hz, 1H), 7.23-7.19 (m, 1H), 3.64-3.57 (m, 2H), 2.97 (t, <i>J</i> = 7.3 Hz, 2H);
1448		A, 159, 217	22	407.9 (M ⁺ +1)	C ₂₁ H ₁₇ N ₃ O 4S 407.09	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 11.52 (s, 1H), 8.81 (t, <i>J</i> = 5.6 Hz, 1H), 8.48-8.36 (m, 2H), 8.03 (d, <i>J</i> = 8.3 Hz, 1H), 8.01-7.95 (m, 2H), 7.93-7.83 (m, 2H), 7.79- 7.78 (m, 1H), 7.73 (dd, <i>J</i> = 8.3, 1.5 Hz, 1H), 7.64 (d, <i>J</i> = 7.8 Hz, 1H), 7.29 (dd, <i>J</i> = 7.8, 4.7 Hz, 1H), 3.51 (q, <i>J</i> = 6.5 Hz, 2H), 2.85 (t, <i>J</i> = 7.0 Hz, 2H);
1449		A, 159, 218	15	393.9 (M ⁺ +1)	C ₂₀ H ₁₅ N ₃ O 4S 393.08	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 11.49 (br s, 1H), 9.33 (t, <i>J</i> = 5.5 Hz, 1H), 8.60-8.39 (m, 2H), 8.05 (d, <i>J</i> = 8.2 Hz, 1H), 8.02-7.94

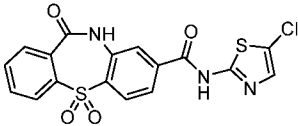
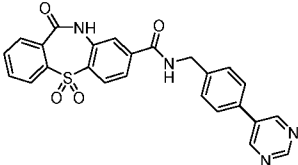
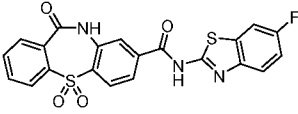
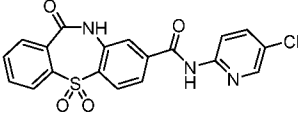
						(m, 2H), 7.93-7.81 (m, 4H), 7.70 (d, $J = 7.7$ Hz, 1H), 7.34 (dd, $J = 7.6, 4.8$ Hz, 1H), 4.49 (d, $J = 5.5$ Hz, 2H);
1462		A, 159, 185	15	379.9 ($M^{+}+1$)	$C_{19}H_{13}N_3O_4S$ 379.06	1H NMR (DMSO- d_6 , 400 MHz): δ 11.60 (s, 1H), 10.80 (s, 1H), 8.50 (d, $J = 6.1$ Hz, 2H), 8.13 (d, $J = 8.2$ Hz, 1H), 8.01 (td, $J = 7.9, 1.0$ Hz, 2H), 7.96-7.84 (m, 4H), 7.73 (d, $J = 6.3$ Hz, 2H);
1458		A, 159, 186	33	455.0 ($M^{+}+1$)	$C_{26}H_{18}N_2O_4S$ 454.10	1H NMR (DMSO- d_6 , 400 MHz): δ 11.57 (s, 1H), 10.53 (s, 1H), 8.10 (d, $J = 8.2$ Hz, 1H), 8.04-7.96 (m, 3H), 7.95-7.82 (m, 4H), 7.73 (d, $J = 7.6$ Hz, 1H), 7.66-7.56 (m, 2H), 7.50-7.33 (m, 5H);
1616		A, 159, 347	9	398.0 ($M^{+}+1$)	$C_{19}H_{15}N_3O_5S$ 397.07	1H NMR (DMSO- d_6 , 400 MHz): δ 11.52 (s, 1H), 8.84 (t, $J = 5.7$ Hz, 1H), 8.22 (s, 1H), 8.04 (d, $J = 8.2$ Hz, 1H), 8.00-7.96 (m, 2H), 7.91 (dd, $J = 7.4, 1.5$ Hz, 1H), 7.89-7.79 (m, 2H), 7.74 (dd, $J = 8.3, 1.5$ Hz, 1H), 6.92 (s, 1H), 3.51 (q, $J = 6.5$ Hz, 2H), 2.92 (t, $J = 6.8$

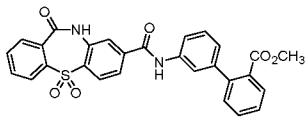
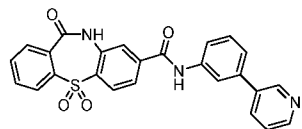
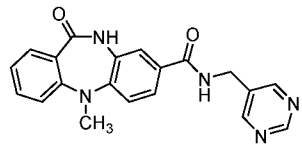
						Hz, 2H).
1617		A, 159, 352	44	414.0 (M ⁺ +1)	C ₁₉ H ₁₅ N ₃ O 4S ₂ 413.05	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 11.53 (s, 1H), 8.91 (s, 1H), 8.87 (t, <i>J</i> = 5.5 Hz, 1H), 8.05 (d, <i>J</i> = 8.3 Hz, 1H), 8.01- 7.96 (m, 2H), 7.92-7.83 (m, 2H), 7.81 (s, 1H), 7.76 (dd, <i>J</i> = 8.3, 1.4 Hz, 1H), 7.69 (s, 1H), 3.50 (q, <i>J</i> = 6.0 Hz, 2H), 3.11 (t, <i>J</i> = 6.6 Hz, 2H);
1618		B, 159, 219 (Reaction time 24 h)	50	481.1 (M ⁺ -1)	C ₂₈ H ₂₂ N ₂ O 4S 482.13	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 11.49 (br s, 1H), 8.83 (t, <i>J</i> = 5.4 Hz, 1H), 8.04 (d, <i>J</i> = 8.3 Hz, 1H), 8.00-7.95 (m, 2H), 7.93-7.80 (m, 3H), 7.76 (dd, <i>J</i> = 8.3, 1.4 Hz, 1H), 7.64- 7.61 (m, 2H), 7.58 (d, <i>J</i> = 8.3 Hz, 2H) 7.44 (t, <i>J</i> = 7.6 Hz, 2H), 7.36-7.30 (m, 3H), 3.52 (q, <i>J</i> = 6.5, 2H), 2.87 (t, <i>J</i> = 7.1 Hz, 2H);
1619		A, 159, 406	25	514.0 (M ⁺ +1)	C ₂₄ H ₂₃ N ₃ O 6S ₂ 513.10	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 11.52 (br s, 1H), 8.80 (t, <i>J</i> = 5.2 Hz, 1H), 8.03 (d, <i>J</i> = 8.2 Hz, 1H), 8.01-7.96 (m, 2H), 7.93-7.82 (m, 2H), 7.77 (s, 1H), 7.72 (d, <i>J</i> = 8.2 Hz, 1H),

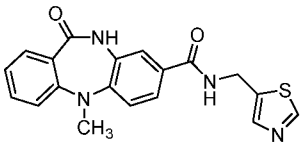
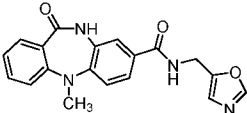
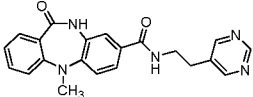
						7.65 (d, $J = 8.2$ Hz, 2H), 7.49 (d, $J = 8.2$ Hz, 2H), 3.59-3.49 (m, 2H), 2.94 (t, $J = 6.8$ Hz, 2H), 2.54 (s, 6H).
1620		A, 159, 254	39	392.9 ($M^{+}+1$)	$C_{21}H_{16}N_2O_4S$ 392.08	1H NMR (DMSO- d_6 , 400 MHz): δ 11.44 (br s, 1H), 9.27 (t, $J = 5.9$ Hz, 1H), 8.05 (d, $J = 8.2$ Hz, 1H), 7.98 (td, $J = 7.7, 1.4$ Hz, 2H), 7.93-7.82 (m, 4H), 7.35-7.28 (m, 4H), 7.27-7.21 (m, 1H), 4.47 (d, $J = 6.1$ Hz, 2H);
1621		A, 159, 255	42	406.9 ($M^{+}+1$)	$C_{22}H_{18}N_2O_4S$ 406.10	1H NMR (DMSO- d_6 , 400 MHz): δ 11.45 (br s, 1H), 9.24 (t, $J = 5.9$ Hz, 1H), 8.05 (d, $J = 8.2$ Hz, 1H), 7.98 (td, $J = 7.7, 1.1$ Hz, 2H), 7.93-7.81 (m, 4H), 7.22-7.18 (m, 1H), 7.13 - 7.04 (m, 3H), 4.43 (d, $J = 5.6$ Hz, 2H), 2.27 (s, 3H);
1622		A, 159, 256	29	411.0 ($M^{+}+1$)	$C_{21}H_{15}FN_2O_4S$ 410.07	1H NMR (DMSO- d_6 , 400 MHz): δ 11.26 (br s, 1H), 9.31 (t, $J = 6.0$ Hz, 1H), 8.06 (d, $J = 8.2$ Hz, 1H), 7.98 (td, $J = 7.8, 1.3$ Hz, 2H), 7.93-7.83 (m, 4H), 7.36 (td, $J = 7.8, 6.3$ Hz, 1H), 7.16-7.04 (m, 3H),

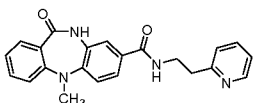
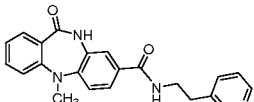
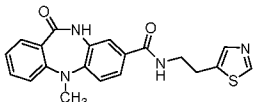
						4.48 (d, $J = 6.0$ Hz, 2H);
1623		A, 159, 257	43	411.0 ($M^{+}+1$)	$C_{21}H_{15}FN_2$ O_4S 410.07	1H NMR (DMSO- d_6 , 400 MHz): δ 11.49 (br s, 1H), 9.26 (t, $J = 5.9$ Hz, 1H), 8.04 (d, $J = 8.3$ Hz, 1H), 8.00-7.94 (m, 2H), 7.92-7.78 (m, 4H), 7.34 (dd, $J = 8.7, 5.6$ Hz, 2H), 7.18-7.10 (m, 2H), 4.44 (d, $J = 5.9$ Hz, 2H);
1624		A, 159, 258	21	476.9 ($M^{+}+1$)	$C_{22}H_{15}F_3N$ $_2O_5S$ 476.07	1H NMR (DMSO- d_6 , 400 MHz): δ 11.52 (s, 1H), 9.34 (t, $J = 5.9$ Hz, 1H), 8.07 (d, $J = 8.2$ Hz, 1H), 8.01-7.96 (m, 2H), 7.93-7.82 (m, 4H), 7.46 (t, $J = 7.9$ Hz, 1H), 7.33 (d, $J = 7.7$ Hz, 1H), 7.30-7.22 (m, 2H), 4.51 (d, $J = 5.9$ Hz, 2H)
1634		G, 159, 231	11	385.8 ($M^{+}+1$)	$C_{17}H_{11}N_3O$ $_4S_2$ 385.02	1H NMR (DMSO- d_6 , 400 MHz): δ 12.90 (br s, 1H), 11.61 (s, 1H), 8.12-7.98 (m, 5H), 7.96-7.84 (m, 2H), 7.58 (d, $J = 3.7$ Hz, 1H), 7.31 (d, $J = 3.0$ Hz, 1H);
1635		A, 159, 377	32	471.0 ($M^{+}+1$)	$C_{25}H_{18}N_4O$ $_4S$ 470.10	1H NMR (DMSO- d_6 , 500 MHz): δ 11.51 (s, 1H), 9.35 (t, $J = 5.7$ Hz, 1H), 8.85 (s, 2H), 8.39-8.35 (m, 2H), 8.06 (d, J

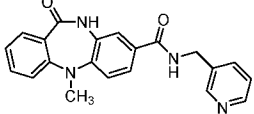
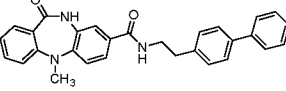
						= 8.2 Hz, 1H), 8.01-7.95 (m, 2H), 7.92-7.81 (m, 4H), 7.54-7.49 (m, 3H), 4.53 (d, $J = 5.5$ Hz, 2H);
1646		A, 159, 259	36	505.3 ($M-1$) ⁺	C ₂₇ H ₂₆ N ₂ O ₆ S 506.15	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 11.52 (s, 1H), 8.99 (br s, 1H), 8.05 (d, $J = 8.5$ Hz, 1H), 8.01-7.96 (m, 2H), 7.93-7.83 (m, 2H), 7.79-7.73 (m, 2H), 7.26 (d, $J = 4.8$ Hz, 4H), 7.21-7.16 (m, 1H), 4.54 (br s, 1H), 3.14-2.98 (m, 2H), 1.34 (s, 9H);
1625		A, 159, 176	18	423.0 ($M^{+}+1$)	C ₂₂ H ₁₈ N ₂ O ₅ S 422.09	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 11.48 (br s, 1H), 8.94 (t, $J = 5.4$ Hz, 1H), 8.04 (d, $J = 8.3$ Hz, 1H), 8.01-7.95 (m, 2H), 7.93-7.78 (m, 4H), 7.31-7.24 (m, 2H), 6.97-6.89 (m, 3H), 4.10 (t, $J = 5.7$ Hz, 2H), 3.63 (q, $J = 5.6$ Hz, 2H);
1647		A, 159, 265	29	440.9 ($M^{+}+1$)	C ₂₂ H ₁₇ FN ₂ O ₅ S 440.08	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 11.51 (s, 1H), 8.92 (s, 1H), 8.04 (d, $J = 8.2$ Hz, 1H), 7.98 (td, $J = 7.5, 0.9$ Hz, 2H), 7.93-7.77 (m, 4H), 7.10 (t, $J = 9.3$ Hz, 2H), 7.00-6.91 (m,

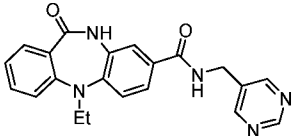
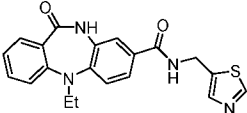
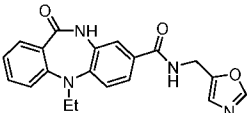
						2H), 4.08 (t, J = 5.5 Hz, 2H), 3.61 (q, J = 5.6 Hz, 2H);
1648		A, 159, 253	18	419.8 ($M^{+}+1$)	$C_{17}H_{10}ClN$ $_3O_4S_2$ 418.98	1H NMR (DMSO- d_6 , 400 MHz): δ 13.19 (br s, 1H), 11.62 (s, 1H), 8.10 (d, J = 8.2 Hz, 1H), 8.07-7.97 (m, 4H), 7.95-7.85 (m, 2H), 7.63 (s, 1H);
1627		A, 159, 372	16	471.0 ($M^{+}+1$)	$C_{25}H_{18}N_4O$ $_4S$ 470.10	1H NMR (DMSO- d_6 , 400 MHz): δ 11.52 (s, 1H), 9.34 (t, J = 5.9 Hz, 1H), 9.17 (s, 1H), 9.12 (s, 2H), 8.07 (d, J = 8.2 Hz, 1H), 7.99 (td, J = 7.8, 1.1 Hz, 2H), 7.94-7.83 (m, 4H), 7.77 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.2 Hz, 2H), 4.53 (d, J = 5.7 Hz, 2H);
1637		H, 159, 241	47	453.9 ($M^{+}+1$)	$C_{21}H_{12}FN_3$ O_4S_2 453.03	1H NMR (DMSO- d_6 , 400 MHz): δ 13.22 (br s, 1H), 11.63 (s, 1H), 8.15-8.08 (m, 2H), 8.06-7.98 (m, 3H), 7.98-7.84 (m, 3H), 7.79 (dd, J = 7.9, 4.8 Hz, 1H), 7.33 (td, J = 8.9, 2.4 Hz, 1H);
1649		C, 159, 235	27	413.8 ($M^{+}+1$)	$C_{19}H_{12}ClN$ $_3O_4S$ 413.02	1H NMR (DMSO- d_6 , 400 MHz): δ 11.56 (br s, 1H), 11.26 (br s, 1H), 8.46 (br s,

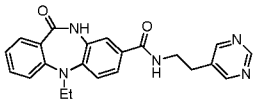
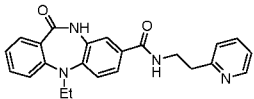
						1H), 8.20 (d, J = 8.7 Hz, 1H), 8.10-7.83 (m, 8H);
1628		A, 159, 519	32	513.0 ($M^{+}+1$)	$C_{28}H_{20}N_2O_6S$ 512.10	1H NMR (DMSO- d_6 , 400 MHz): δ 11.57 (br s, 1H), 10.54 (s, 1H), 8.11 (d, J = 8.3 Hz, 1H), 8.00 (td, J = 9.0, 1.0 Hz, 2H), 7.95-7.84 (m, 4H), 7.76-7.72 (m, 3H), 7.64 (td, J = 9.1, 1.5 Hz, 1H), 7.50 (td, J = 7.6, 1.3 Hz, 1H), 7.46-7.39 (m, 2H), 7.08-7.03 (m, 1H), 3.61 (s, 3H);
1629		A, 159, 246 (Reaction time RT-18 h)	31	455.9 ($M^{+}+1$)	$C_{25}H_{17}N_3O_4S$ 455.09	1H NMR (DMSO- d_6 , 400 MHz): δ 11.60 (s, 1H), 10.60 (s, 1H), 8.86 (br s, 1H), 8.60 (d, J = 3.7 Hz, 1H), 8.13 (d, J = 8.3 Hz, 1H), 8.08 (s, 1H), 8.06-7.98 (m, 3H), 7.97-7.85 (m, 4H), 7.81 (d, J = 6.7 Hz, 1H), 7.55-7.48 (m, 3H);
1520		A, 164, 212	25	360.2 ($M^{+}+1$)	$C_{20}H_{17}N_3O_2$ 359.14	1H NMR (DMSO- d_6 , 400 MHz): δ 10.28 (s, 1H), 9.07 (s, 1H), 9.01 (t, J = 5.7 Hz, 1H), 8.74 (s, 2H), 7.66-7.60 (m, 2H), 7.56 (s, 1H), 7.53-7.47 (m, 1H), 7.26 (d, J = 8.6 Hz, 1H), 7.20 (d, J

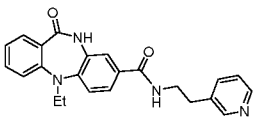
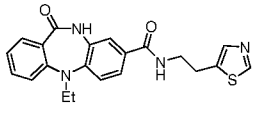
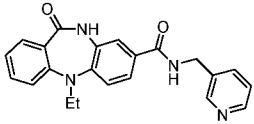
						= 8.0 Hz, 1H), 7.10 (t, J = 7.2 Hz, 1H), 4.47 (d, J = 5.6 Hz, 2H), 3.29 (s, 3H);
1581		A, 164, 213	10	365.0 ($M^{+}+1$)	$C_{19}H_{16}N_4O_2S$ 364.10	1H NMR (DMSO- d_6 , 500 MHz): δ 10.26 (s, 1H), 9.05 (t, J = 5.7 Hz, 1H), 8.93 (s, 1H), 7.77 (s, 1H), 7.66-7.44 (m, 4H), 7.20 (dd, J = 18.1, 8.2 Hz, 2H), 7.08 (t, J = 7.4 Hz, 1H), 4.62 (d, J = 5.6 Hz, 2H), 3.28 (s, 3H);
1547		A, 164, 214	25	348.9 ($M^{+}+1$)	$C_{19}H_{16}N_4O_3$ 348.12	); 1H NMR (DMSO- d_6 , 400 MHz): δ 10.28 (s, 1H), 8.90 (t, J = 5.6 Hz, 1H), 8.27 (s, 1H), 7.66-7.59 (m, 2H), 7.55 (s, 1H), 7.52-7.47 (m, 1H), 7.24 (d, J = 8.5 Hz, 1H), 7.20 (d, J = 7.9 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H), 7.02 (s, 1H), 4.50 (d, J = 5.3 Hz, 2H), 3.30 (s, 3H);
1548		A, 164, 215	29	374.0 ($M^{+}+1$)	$C_{21}H_{19}N_5O$ 373.15	1H NMR (DMSO- d_6 , 400 MHz): δ 10.28 (s, 1H), 9.01 (s, 1H), 8.65 (s, 2H), 8.46 (t, J = 5.7 Hz, 1H), 7.63 (dd, J = 7.7, 1.6 Hz, 1H), 7.53-7.47 (m, 3H), 7.21 (dd, J = 11.2, 8.3 Hz, 2H),

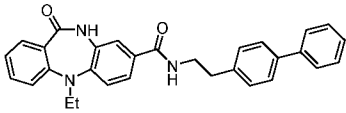
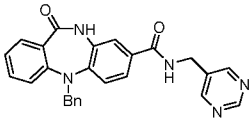
						7.10 (t, $J = 7.5$ Hz, 1H), 3.52 (q, $J = 6.4$ Hz, 2H), 3.29 (s, 3H), 2.85 (t, $J = 6.6$ Hz, 2H);
1498		A, 164, 216	21	373.0 ($M^{+}+1$)	$C_{22}H_{20}N_4O$ 2 372.16	1H NMR (DMSO- d_6 , 400 MHz): δ 10.29 (s, 1H), 8.50 (d, $J = 4.0$ Hz, 1H), 8.46 (t, $J = 5.4$ Hz, 1H), 7.69 (td, $J = 7.6, 1.9$ Hz, 1H), 7.64 (dd, $J = 7.7, 1.7$ Hz, 1H), 7.57-7.47 (m, 3H), 7.27-7.18 (m, 4H), 7.10 (t, $J = 7.2$ Hz, 1H), 3.57 (q, $J = 7.0$ Hz, 2H), 3.30 (s, 3H), 2.96 (t, $J = 7.3$ Hz, 2H);
1549		A, 164, 217	27	373.0 ($M^{+}+1$)	$C_{22}H_{20}N_4O$ 2 372.16	1H NMR (DMSO- d_6 , 400 MHz): δ 10.29 (s, 1H), 8.48-8.42 (m, 2H), 8.40 (dd, $J = 4.7, 1.5$ Hz, 1H), 7.63 (dd, $J = 7.7, 1.6$ Hz, 2H), 7.57-7.45 (m, 3H), 7.29 (dd, $J = 7.7, 4.8$ Hz, 1H), 7.21 (dd, $J = 11.0, 8.4$ Hz, 2H), 7.10 (t, $J = 7.4$ Hz, 1H), 3.48 (q, $J = 7.1$ Hz, 2H), 3.30 (s, 3H), 2.84 (t, $J = 7.0$ Hz, 2H);
1532		A, 164, 352	24	378.0 ($M^{+}+1$);	$C_{20}H_{18}N_4O$ 2S 378.12	1H NMR (DMSO- d_6 , 400 MHz): δ 10.30 (s, 1H), 8.91 (s, 1H), 8.53 (t, $J = 5.7$ Hz, 1H),

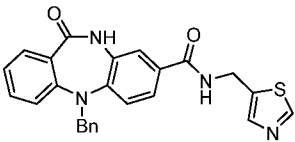
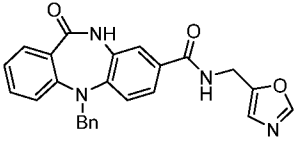
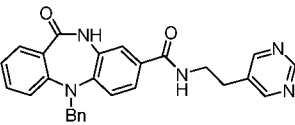
						7.69 (s, 1H), 7.64 (dd, J = 7.7, 1.7 Hz, 1H), 7.57 (dd, J = 8.4, 2.0 Hz, 1H), 7.54-7.47 (m, 2H), 7.22 (dd, J = 16.5, 8.1 Hz, 2H), 7.10 (t, J = 7.1 Hz, 1H), 3.47 (q, J = 6.8 Hz, 2H), 3.31 (s, 3H), 3.10 (t, J = 6.7 Hz, 2H);
1499		A, 164, 218	30	358.9 ($M^{+}+1$)	$C_{21}H_{18}N_4O$ 2 358.14	1H NMR (DMSO- d_6 , 400 MHz): δ 10.29 (s, 1H), 8.98 (t, J = 5.8 Hz, 1H), 8.51 (s, 1H), 8.44 (dd, J = 4.8, 1.6 Hz, 1H), 7.68 (tt, J = 7.9, 1.9 Hz, 1H), 7.63 (tt, J = 8.0, 1.9 Hz, 2H), 7.57 (s, 1H), 7.53-7.47 (m, 1H), 7.34 (dd, J = 7.3, 4.8 Hz, 1H), 7.25 (d, J = 8.5 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.10 (t, J = 7.1 Hz, 1H), 4.46 (d, J = 5.9 Hz, 2H), 3.30 (s, 3H);
1521		A, 164, 219	36	448.1 ($M^{+}+1$)	$C_{29}H_{25}N_3O$ 2 447.19	1H NMR (DMSO- d_6 , 500 MHz): δ 10.28 (s, 1H), 8.47 (t, J = 5.4 Hz, 1H), 7.65-7.54 (m, 6H), 7.52 (s, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.43 (t, J = 7.7 Hz, 2H), 7.35- 7.28 (m, 3H), 7.20 (dd, J =

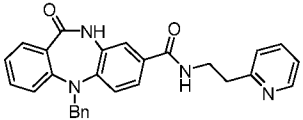
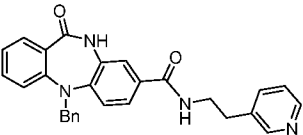
						16.8, 8.4 Hz, 2H), 7.08 (t, J = 7.5 Hz, 1H), 3.47 (q, J = 6.4 Hz, 2H), 3.28 (s, 3H), 2.84 (t, J = 7.2 Hz, 2H);
1533		A^c , 167, 212 (c = Reaction Time 12 h- RT)	19	373.9 ($M^{+}+1$);	$C_{21}H_{19}N_3O$ 2 373.15	1H NMR (DMSO- d_6 , 400 MHz): δ 10.29 (s, 1H), 9.07 (s, 1H), 9.02 (t, J = 5.7 Hz, 1H), 8.74 (s, 2H), 7.65-7.55 (m, 3H), 7.52-7.46 (m, 1H), 7.25 (d, J = 8.5 Hz, 1H), 7.20 (d, J = 8.2 Hz, 1H), 7.11 (t, J = 7.4 Hz, 1H), 4.46 (d, J = 5.6 Hz, 2H), 3.83-3.75 (m, 2H), 1.12 (t, J = 6.9 Hz, 3H);
1534		A^c , 167, 213	22	378.9 ($M^{+}+1$)	$C_{20}H_{18}N_4O$ 2S 378.12	1H NMR (DMSO- d_6 , 400 MHz): δ 10.29 (s, 1H), 9.07 (t, J = 5.9 Hz, 1H), 8.95 (s, 1H), 7.79 (s, 1H), 7.63-7.54 (m, 3H), 7.52-7.46 (m, 1H), 7.24 (d, J = 8.5 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.10 (t, J = 7.2 Hz, 1H), 4.64 (d, J = 5.7 Hz, 2H), 3.84-3.75 (m, 2H), 1.12 (t, J = 7.0 Hz, 3H);
1564		A^c , 167, 214	31	363.0 ($M^{+}+1$)	$C_{20}H_{18}N_4O$ 3 362.14	1H NMR (DMSO- d_6 , 400 MHz): δ 10.29 (s, 1H), 8.90 (t, J = 5.6 Hz, 1H), 8.27 (s, 1H), 7.63-7.55 (m,

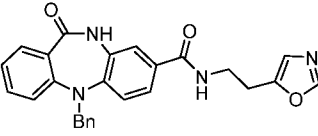
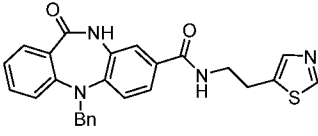
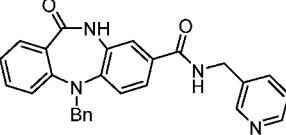
						3H), 7.52-7.47 (m, 1H), 7.24 (d, $J = 8.5$ Hz, 1H), 7.20 (d, $J = 8.2$ Hz, 1H), 7.11 (t, $J = 7.3$ Hz, 1H), 7.01 (s, 1H), 4.50 (d, $J = 5.4$ Hz, 2H), 3.83-3.76 (m, 2H), 1.12 (t, $J = 7.0$ Hz, 3H);
1565		A^c , 167, 215	36	388.0 ($M^{+}+1$)	$C_{22}H_{21}N_5O$ 2 387.17	1H NMR (DMSO- d_6 , 500 MHz): δ 10.27 (s, 1H), 8.99 (s, 1H), 8.64 (s, 1H), 8.44 (t, $J = 5.4$ Hz, 1H), 7.58 (d, $J = 6.7$ Hz, 1H), 7.52-7.45 (m, 3H), 7.19 (dd, $J = 14.6, 8.2$ Hz, 2H), 7.08 (t, $J = 7.5$ Hz, 1H), 3.81-3.72 (m, 2H), 3.50 (q, $J = 6.1$ Hz, 2H), 2.83 (t, $J = 6.7$ Hz, 2H), 1.10 (t, $J = 6.9$ Hz, 3H);
1522		A^c , 167, 216	29	387.0 ($M^{+}+1$)	$C_{23}H_{22}N_4O$ 2 386.17	1H NMR (DMSO- d_6 , 400 MHz): δ 10.29 (s, 1H), 8.49 (d, $J = 4.1$ Hz, 1H), 8.45 (t, $J = 5.3$ Hz, 1H), 7.69 (td, $J = 7.7, 1.8$ Hz, 1H), 7.60 (dd, $J = 7.7, 1.6$ Hz, 1H), 7.57-7.47 (m, 3H), 7.27-7.18 (m, 4H), 7.10 (t, $J = 7.4$ Hz, 1H), 3.83-3.74 (m, 2H), 3.57 (q, $J = 6.9$ Hz, 2H), 2.96 (t, $J = 7.3$ Hz, 2H), 1.12

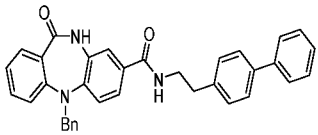
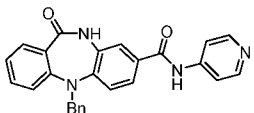
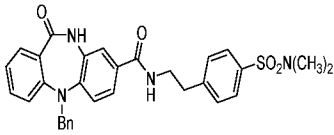
						(t, $J = 6.9$ Hz, 3H);
1523		A ^c , 167, 217	36	387.0 (M ⁺ +1)	C ₂₃ H ₂₂ N ₄ O ₂ 386.17	¹ H NMR (DMSO- <i>d</i> ₆ , 500 MHz): δ 10.28 (s, 1H), 8.47-8.34 (m, 3H), 7.65-7.56 (m, 2H), 7.54-7.45 (m, 3H), 7.28 (dd, $J = 7.5, 4.9$ Hz, 1H), 7.19 (dd, $J = 13.7, 8.2$ Hz, 2H), 7.09 (t, $J = 7.2$ Hz, 1H), 3.76 (br s, 2H), 3.46 (q, $J = 6.7$ Hz, 2H), 2.82 (t, $J = 7.1$ Hz, 2H), 1.10 (t, $J = 6.9$ Hz, 3H);
1566		A ^c , 167, 352	36	393.1 (M ⁺ +1)	C ₂₁ H ₂₀ N ₄ O ₂ S 392.13	¹ H NMR (DMSO- <i>d</i> ₆ , 500 MHz): δ 10.29 (s, 1H), 8.89 (s, 1H), 8.51 (t, $J = 5.4$ Hz, 1H), 7.67 (s, 1H), 7.61-7.43 (m, 4H), 7.22 (d, $J = 8.4$ Hz, 1H), 7.18 (d, $J = 8.1$ Hz, 1H), 7.09 (t, $J = 7.4$ Hz, 1H), 3.82-3.74 (m, 2H), 3.45 (q, $J = 6.5$ Hz, 2H), 3.08 (t, $J = 6.7$ Hz, 2H), 1.11 (t, $J = 6.8$ Hz, 3H);
1550		A ^c , 167, 218	30	373.1 (M ⁺ +1)	C ₂₂ H ₂₀ N ₄ O ₂ 372.16	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.29 (s, 1H), 8.98 (t, $J = 5.9$ Hz, 1H), 8.52 (s, 1H), 8.44 (dd, $J = 4.7, 1.6$ Hz, 1H), 7.68 (dt, $J = 7.9, 1.8$ Hz,

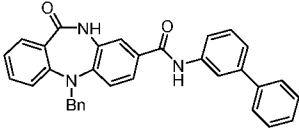
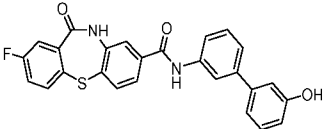
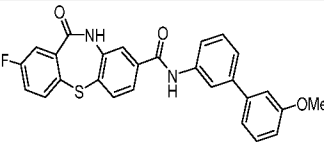
						1H), 7.65-7.56 (m, 3H), 7.49 (td, $J = 7.7, 1.7$ Hz, 1H), 7.36-7.32 (m, 1H), 7.25 (d, $J = 8.5$ Hz, 1H), 7.20 (d, $J = 7.9$ Hz, 1H), 7.10 (td, $J = 7.5, 0.8$ Hz, 1H), 4.46 (d, $J = 5.7$ Hz, 2H), 3.82-3.75 (m, 2H), 1.12 (t, $J = 7.0$ Hz, 3H);
1524		A ^c , 167, 219	15	462.1 (M ⁺ +1)	C ₃₀ H ₂₇ N ₃ O ₂ 461.21	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.30 (s, 1H), 8.48 (t, $J = 5.5$ Hz, 1H), 7.68-7.41 (m, 10H), 7.36-7.29 (m, 3H), 7.21 (dd, $J = 13.5, 8.3$ Hz, 2H), 7.10 (t, $J = 7.5$ Hz, 1H), 3.82-3.75 (m, 2H), 3.48 (q, $J = 6.9$ Hz, 2H), 2.86 (t, $J = 7.2$ Hz, 2H), 1.12 (t, $J = 6.9$ Hz, 3H);
1482		A, 170, 212	36	436.1 (M ⁺ +1)	C ₂₆ H ₂₁ N ₅ O ₂ 435.17	¹ H NMR (DMSO- <i>d</i> ₆ , 500 MHz): δ 10.36 (s, 1H), 9.06 (s, 1H), 8.97 (t, $J = 5.8$ Hz, 1H), 8.72 (s, 2H), 7.61 (dd, $J = 7.7, 1.3$ Hz, 1H), 7.57-7.51 (m, 2H), 7.47-7.39 (m, 3H), 7.33 (d, $J = 8.4$ Hz, 1H), 7.30-7.23 (m, 3H), 7.15 (t, $J = 7.8$ Hz, 1H), 7.08 (t, $J = 7.4$ Hz, 1H), 5.03 (s, 2H), 4.44 (d, J

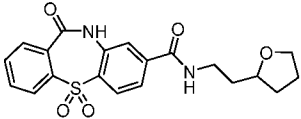
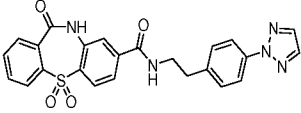
						= 5.5 Hz, 2H);
1510		A, 170, 213	20	441.1 (M ⁺ +1)	C ₂₅ H ₂₀ N ₄ O 2S 440.13	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.37 (s, 1H), 9.04 (t, <i>J</i> = 5.8 Hz, 1H), 8.94 (s, 1H), 7.77 (s, 1H), 7.61 (dd, <i>J</i> = 7.7, 1.6 Hz, 1H), 7.56 (s, 1H), 7.50 (dd, <i>J</i> = 8.5, 1.9 Hz, 1H), 7.47-7.39 (m, 3H), 7.32 (d, <i>J</i> = 8.6 Hz, 1H), 7.29-7.22 (m, 3H), 7.14 (t, <i>J</i> = 7.2 Hz, 1H), 7.08 (t, <i>J</i> = 7.3 Hz, 1H), 5.03 (s, 2H), 4.61 (d, <i>J</i> = 5.6 Hz, 2H);
1492		A, 170, 214	35	425.1 (M ⁺ +1)	C ₂₅ H ₂₀ N ₄ O 3 424.15	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.37 (s, 1H), 8.87 (t, <i>J</i> = 5.6 Hz, 1H), 8.25 (s, 1H), 7.61 (dd, <i>J</i> = 7.7, 1.6 Hz, 1H), 7.55 (s, 1H), 7.51 (dd, <i>J</i> = 8.4, 2.0 Hz, 1H), 7.47-7.39 (m, 3H), 7.32 (d, <i>J</i> = 8.5 Hz, 1H), 7.30-7.23 (m, 3H), 7.17- 7.12 (m, 1H), 7.08 (t, <i>J</i> = 7.2 Hz, 1H), 7.00 (s, 1H), 5.03 (s, 2H), 4.47 (d, <i>J</i> = 5.4 Hz, 2H);
1464		A, 170, 215	16	450.1 (M ⁺ +1)	C ₂₇ H ₂₃ N ₅ O 2 449.19	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.36 (s, 1H), 9.01 (s, 1H), 8.64 (s, 2H), 8.42 (t, <i>J</i> = 5.5 Hz, 1H),

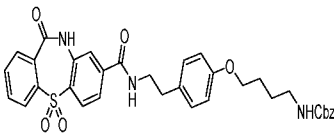
						7.60 (dd, J = 7.7, 1.6 Hz, 1H), 7.49-7.38 (m, 5H), 7.33-7.21 (m, 4H), 7.15 (t, J = 7.1 Hz, 1H), 7.08 (t, J = 7.4 Hz, 1H), 5.02 (s, 2H), 3.49 (q, J = 6.4 Hz, 2H), 2.82 (t, J = 6.7 Hz, 2H);
1474		A, 170, 216	38	449.1 ($M^{+}+1$)	C ₂₈ H ₂₄ N ₄ O ₂ 448.19	¹ H NMR (DMSO- <i>d</i> ₆ , 500 MHz): δ 10.35 (s, 1H), 8.47 (d, J = 3.8 Hz, 1H), 8.41 (t, J = 5.4 Hz, 1H), 7.68-7.64 (m, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.52-7.49 (m, 1H), 7.47-7.37 (m, 4H), 7.31-7.17 (m, 6H), 7.16-7.11 (m, 1H), 7.07 (t, J = 7.2 Hz, 1H), 5.01 (s, 2H), 3.53 (q, J = 6.7 Hz, 2H), 2.92 (t, J = 7.2 Hz, 2H);
1475		A, 170, 217	38	449.1 ($M^{+}+1$)	C ₂₈ H ₂₄ N ₄ O ₂ 448.19	¹ H NMR (DMSO- <i>d</i> ₆ , 500 MHz): δ 10.36 (s, 1H), 8.43-8.39 (m, 2H), 8.37 (dd, J = 4.6, 1.2 Hz, 1H), 7.75-7.54 (m, 2H), 7.49 (s, 1H), 7.46-7.36 (m, 4H), 7.33-7.21 (m, 5H), 7.18-7.10 (m, 1H), 7.06 (t, J = 7.4 Hz, 1H), 5.01 (s, 2H), 3.47-3.41 (m, 2H), 2.80 (t, J =

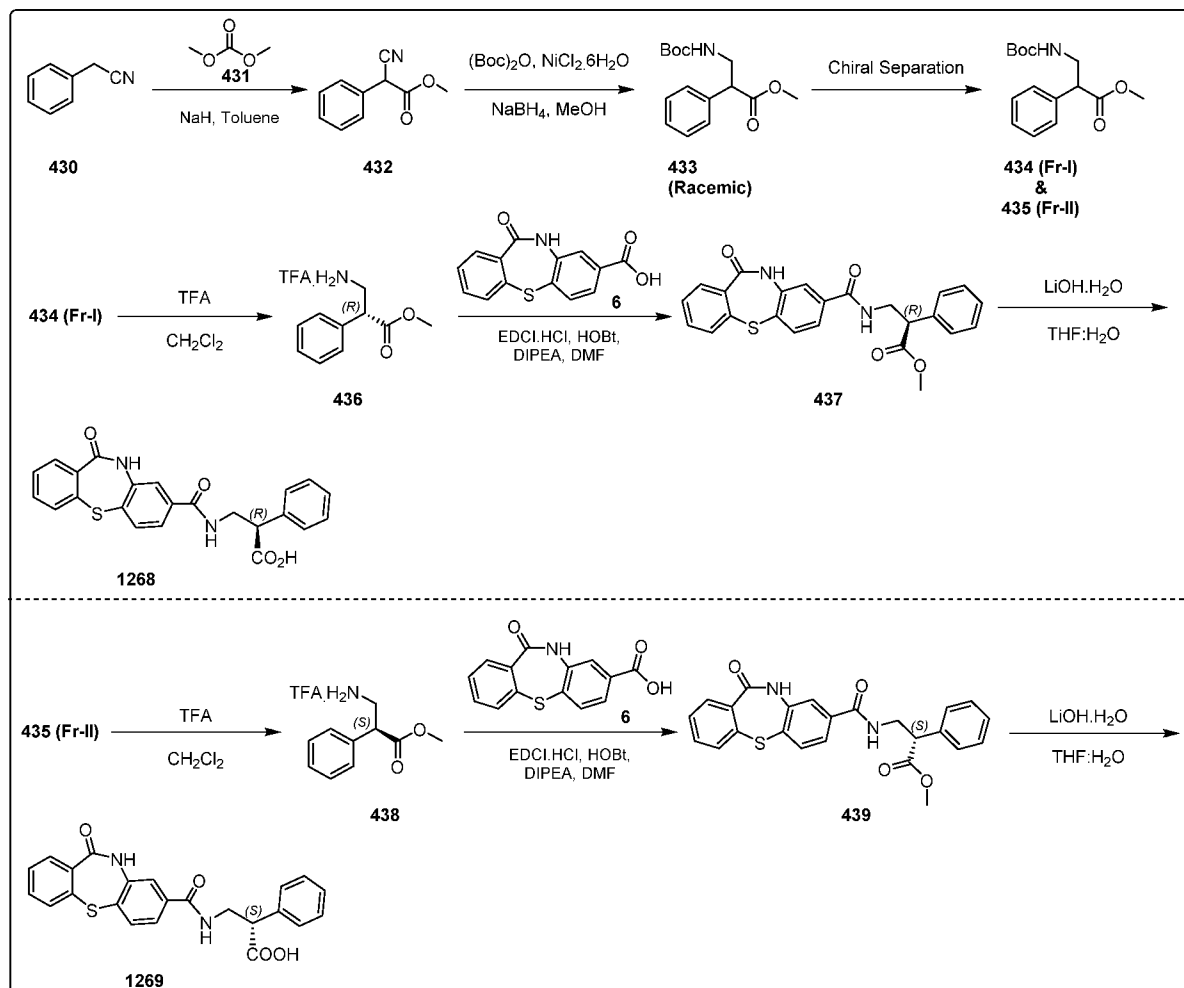
						6.9 Hz, 2H);
1559		A, 170, 347	20	439.1 (M ⁺ +1)	C ₂₆ H ₂₂ N ₄ O 3 438.17	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.37 (s, 1H), 8.47 (t, <i>J</i> = 5.6 Hz, 1H), 8.20 (s, 1H), 7.61 (dd, <i>J</i> = 7.7, 1.6 Hz, 1H), 7.51 (s 1H), 7.47-7.40 (m, 4H), 7.33- 7.23 (m, 4H), 7.18-7.12 (m, 1H), 7.08 (t, <i>J</i> = 7.4 Hz, 1H), 6.90 (s, 1H), 3.46 (q, <i>J</i> = 6.6 Hz, 2H), 2.88 (t, <i>J</i> = 6.8 Hz, 2H);
1511		A, 170, 352	32	455.0 (M ⁺ +1)	C ₂₆ H ₂₂ N ₄ O 2S 454.15	¹ H NMR (DMSO- <i>d</i> ₆ , 500 MHz): δ 10.37 (s, 1H), 8.89 (s, 1H), 8.49 (t, <i>J</i> = 5.5 Hz, 1H), 7.66 (s, 1H), 7.60 (dd, <i>J</i> = 7.7, 1.3 Hz, 1H), 7.52 (s, 1H), 7.49-7.38 (m, 4H), 7.31 (d, <i>J</i> = 8.7 Hz, 1H), 7.28-7.22 (m, 3H), 7.14 (t, <i>J</i> = 7.2 Hz, 1H), 7.07 (t, <i>J</i> = 7.4 Hz, 1H), 5.02 (s, 2H), 3.43 (q, <i>J</i> = 6.5 Hz, 2H), 3.06 (t, <i>J</i> = 6.7 Hz, 2H);
1493		A, 170, 218	16	434.1 (M ⁺ +1)	C ₂₇ H ₂₂ N ₄ O 2 434.17	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.37 (s, 1H), 8.95 (t, <i>J</i> = 5.9 Hz, 1H), 8.51-8.49 (m, 1H), 8.43 (dd, <i>J</i> = 4.8, 1.6 Hz, 1H), 7.66 (td, <i>J</i>

						= 7.5, 1.7 Hz, 1H), 7.61 (dd, J = 7.7, 1.7 Hz, 1H), 7.58-7.52 (m, 2H), 7.47-7.38 (m, 3H), 7.35-7.22 (m, 5H), 7.18-7.12 (m, 1H), 7.08 (t, J = 7.1 Hz, 1H), 5.03 (s, 2H), 4.43 (d, J = 5.7 Hz, 2H);
1483		A, 170, 219	20	524.3 ($M^{+}+1$)	$C_{35}H_{29}N_3O$ 2 523.23	1H NMR (DMSO- d_6 , 500 MHz): δ 10.38 (s, 1H), 8.45 (t, J = 5.5 Hz, 1H), 7.66-7.52 (m, 6H), 7.51-7.39 (m, 6H), 7.37-7.23 (m, 7H), 7.18-7.13 (m, 1H), 7.08 (t, J = 7.4 Hz, 1H), 5.03 (s, 2H), 3.49-3.43 (m, 2H), 2.84 (t, J = 7.2 Hz, 2H);
1494		A, 170, 185	16	421.1 ($M^{+}+1$)	$C_{26}H_{20}N_4O$ 2 420.16	); 1H NMR (DMSO- d_6 , 400 MHz): δ 10.45 (d, J = 4.4 Hz, 2H), 8.53-8.38 (m, 2H), 7.74-7.70 (m, 2H), 7.67-7.62 (m, 3H), 7.50-7.39 (m, 4H), 7.31 (d, J = 8.0 Hz, 1H), 7.27 (t, J = 7.6 Hz, 2H), 7.20-7.08 (m, 2H), 5.07 (s, 2H);
1512		A, 170, 406	18	555.1 ($M^{+}+1$)	$C_{31}H_{30}N_4O$ 4S 554.20	1H NMR (DMSO- d_6 , 400 MHz): δ 10.35 (s, 1H), 8.40 (t, J = 5.6 Hz, 1H), 7.68-7.53 (m, 3H), 7.52-7.36

						(m, 7H), 7.31-7.18 (m, 4H), 7.13 (t, $J = 7.3$ Hz, 1H), 7.06 (t, $J = 7.4$ Hz, 1H), 5.00 (s, 2H), 3.49-3.41 (m, 2H), 2.88 (t, $J = 7.0$ Hz, 2H), 2.51 (s, 6H);
1484		A, 170, 186	7	496.2 ($M^{+}+1$)	$C_{33}H_{25}N_3O$ 2 495.19	1H NMR (DMSO- d_6 , 400 MHz): δ 10.44 (s, 1H), 10.20 (s, 1H), 8.05-8.03 (m, 1H), 7.75 (d, $J = 8.4$ Hz, 1H), 7.69-7.58 (m, 5H), 7.51-7.35 (m, 9H), 7.34-7.24 (m, 3H), 7.17 (t, $J = 7.7$ Hz, 1H), 7.11 (t, $J = 7.5$ Hz, 1H), 5.07 (s, 2H);
1468		A, 35, 413	15	456.9 ($M^{+}+1$)	$C_{26}H_{17}FN_2O_3S$ 456.09	1H NMR (400 MHz, DMSO- d_6): δ 10.97 (s, 1H), 10.36 (s, 1H), 9.53 (s, 1H), 8.03-8.01 (m, 1H), 7.81 - 7.71 (m, 4H), 7.63 (dd, $J = 8.6, 5.3$ Hz, 1H), 7.51 (dd, $J = 9.2, 2.9$ Hz, 1H), 7.45-7.36 (m, 2H), 7.35-7.32 (m, 1H), 7.26 (t, $J = 7.8$ Hz, 1H), 7.06-7.00 (m, 2H), 6.79-6.75 (m, 1H);
1452		A, 35, 412	37	471.0 ($M^{+}+1$)	$C_{27}H_{19}FN_2O_3S$ 470.11	1H NMR (DMSO- d_6 , 400MHz): δ 10.98 (s, 1H), 10.37 (s, 1H), 8.02 (s, 1H),

						7.83-7.70 (m, 4H), 7.63 (dd, $J = 8.6, 5.3$ Hz, 1H), 7.52 (dd, $J = 9.2, 2.9$ Hz, 1H), 7.47-7.36 (m, 4H), 7.20 (d, $J = 7.8$ Hz, 1H), 7.16-7.14 (m, 1H), 6.96 (dd, $J = 8.0, 2.2$ Hz, 1H), 3.82 (s, 3H);
1636		A, 159, 415	50	400.9 ($M^{+}+1$)	$C_{20}H_{20}N_2O_5S$ 400.11	1H NMR (DMSO- d_6 , 400 MHz): δ 11.50 (s, 1H), 8.69 (t, $J = 5.4$ Hz, 1H), 8.03 (d, $J = 8.3$ Hz, 1H), 8.01-7.96 (m, 2H), 7.93-7.82 (m, 2H), 7.80 - 7.76 (m, 2H), 3.81-3.71 (m, 2H), 3.61-3.54 (m, 1H), 3.45-3.40 (m, 1H), 3.29-3.25 (m, 1H), 2.00-1.90 (m, 1H), 1.86-1.73 (m, 2H), 1.68 (q, $J = 7.0$ Hz, 2H), 1.46-1.35 (m, 1H);
1626		A, 159, 421	14	474.0 ($M^{+}+1$)	$C_{24}H_{19}N_5O_4S$ 473.12	1H NMR (DMSO- d_6 , 400 MHz): δ 11.52 (s, 1H), 8.81 (t, $J = 5.5$ Hz, 1H), 8.09 (s, 2H), 8.04 (d, $J = 8.3$ Hz, 1H), 8.00-7.82 (m, 6H), 7.80-7.72 (m, 2H), 7.42 (d, $J = 8.6$ Hz, 2H), 3.57-3.49 (m, 2H), 2.90 (t, $J = 7.0$ Hz, 2H);

1650		A, 159, 427	51	628.1 (M ⁺ +1)	C ₃₄ H ₃₃ N ₃ O ₇ S 627.20	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 11.52 (s, 1H), 8.76 (t, <i>J</i> = 5.5 Hz, 1H), 8.03 (d, <i>J</i> = 8.3 Hz, 1H), 8.00- 7.96 (m, 2H), 7.92-7.83 (m, 2H), 7.79 (s, 1H), 7.75 (dd, <i>J</i> = 8.2, 1.4 Hz, 1H), 7.44-7.22 (m, 6H), 7.11 (d, <i>J</i> = 8.6 Hz, 2H), 6.82 (d, <i>J</i> = 8.5 Hz, 2H), 5.00 (s, 2H), 3.90 (t, <i>J</i> = 6.2 Hz, 2H), 3.43 (q, <i>J</i> = 6.7 Hz, 2H), 3.04 (q, <i>J</i> = 6.7 Hz, 2H), 2.74 (t, <i>J</i> = 7.3 Hz, 2H), 1.71- 1.63 (m, 2H), 1.58-1.49 (m, 2H);
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Example 27: Synthesis of Compounds 1268 and 1269

[000348] Synthesis of methyl 2-cyano-2-phenylacetate (432): To a stirred solution of sodium hydride (60%, 2.5 g, 63.82 mmol) in anhydrous toluene (50 mL) under argon atmosphere was added 2-phenyl acetonitrile **430** (5 g, 42.55 mmol) at 0 °C and stirred for 30 min. To this dimethyl carbonate **431** (5.74 g, 63.82 mmol) in anhydrous toluene (30 mL) was added drop wise for 10 min and stirred at 0 °C for 4 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with saturated ammonium chloride (20 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over sodium sulphate, filtered and concentrated *in vacuo* to obtain the crude. The crude compound was purified through silica gel column chromatography using 20% EtOAc/hexanes to afford compound **432** (4.8 g, 64%) as colorless syrup. **TLC:** 30% EtOAc/ hexanes

(*R_f*: 0.7); ¹H-NMR (CDCl₃, 400 MHz): δ 7.47-7.39 (m, 5H), 4.74 (s, 1H), 3.81 (s, 3H).

[000349] **Synthesis of methyl 3-amino-2-phenylpropanoate (433):** To a stirred solution of compound **432** (1 g, 5.71 mmol) in MeOH (50 mL) under argon atmosphere were added Boc-anhydride (2.49 g, 11.42 mmol), nickel dichloride hexahydrate (135 mg, 0.57 mmol) and sodium borohydride (1.5 g, 39.99 mmol) at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with MeOH (30 mL), filtered through celite and the filtrate was concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 30% EtOAc/Hexanes to afford racemic compound **433** (550 mg, 36%) as an off white solid. TLC: 20% EtOAc/ hexanes (*R_f*: 0.4); ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 7.34 (t, *J* = 7.0 Hz, 2H), 7.30-7.25 (m, 3H), 6.93 (t, *J* = 6.0 Hz, 1H), 3.85 (t, *J* = 7.5 Hz, 1H), 3.60 (s, 3H), 3.28-3.23 (m, 1H), 1.34 (s, 9H). The racemic compound **433** was purified through chiral preparative HPLC to afford compound **434 Fr-I** (120 mg) and compound **435 Fr-II** (90 mg) as off-white solids.

Compound 434 Fr-I analytical data:

[000350] **Chiral HPLC:** 99.27%, *R_t* = 9.58 min (Chiralcel AD-H, 250 x 4.6 mm, 5 μm); mobile phase (A) 0.1% DEA in *n*-Hexane (B) EtOH (A: B: 98: 2); Flow Rate: 1.0 mL/min).

Compound 435 Fr-II analytical data:

[000351] **Chiral HPLC:** 99.29%, *R_t* = 10.87 min (Chiralcel AD-H, 250 x 4.6 mm, 5 μm); mobile phase (A) 0.1% DEA in *n*-Hexane (B) EtOH (A: B: 98: 2); Flow Rate: 1.0 mL/min).

[000352] **Synthesis of methyl (*R*)-2-phenyl-3-((2, 2, 2-trifluoroacetyl)-λ⁴-azanyl)propanoate (436):** To a stirred solution of compound **434** (Fr-I) (50 mg, 0.17 mmol) in CH₂Cl₂ (2 mL) under inert atmosphere was added trifluoroacetic acid (0.026 mL, 0.35 mmol) at 0 °C; warmed to RT and stirred for 3 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude compound **436** (20 mg, TFA salt) as off-white solid. TLC: 70% EtOAc/ hexanes (*R_f*: 0.2); ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 8.10 (br s, 2H), 7.41-7.28 (m, 5H), 4.03 (t, *J* = 6.0 Hz, 1H), 3.63 (s, 3H), 3.48 (t, *J* = 9.2 Hz, 1H), 3.12-3.08 (m, 1H).

[000353] Synthesis of methyl (*R*)-3-(11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxamido)-2-phenylpropanoate (437): To a stirred solution of compound 6 (70 mg, 0.25 mmol) in DMF (5 mL) under argon atmosphere were added EDCI.HCl (73.9 mg, 0.38 mmol), HOBt (30 mg, 0.38 mmol), compound 436 (70 mg, 0.38 mmol), diisopropyl ethyl amine (0.09 mL, 0.51 mmol) at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried over sodium sulphate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 90% EtOAc/ Hexanes to afford compound 437 (70 mg, 63%) as colorless syrup. TLC: 5% MeOH/ CH₂Cl₂ (*R_f*: 0.5); ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 10.75 (s, 1H), 8.65 (t, *J* = 5.6 Hz, 1H), 7.68 (d, *J* = 7.2 Hz, 2H), 7.67-7.60 (m, 4H), 7.54-7.49 (m, 2H), 7.49-7.44 (m, 3H), 7.35-7.25 (m, 1H), 4.02 (t, *J* = 7.2 Hz, 1H), 3.80-3.73 (m, 1H), 3.55 (t, *J* = 6.4 Hz, 1H), 3.47 (s, 3H).

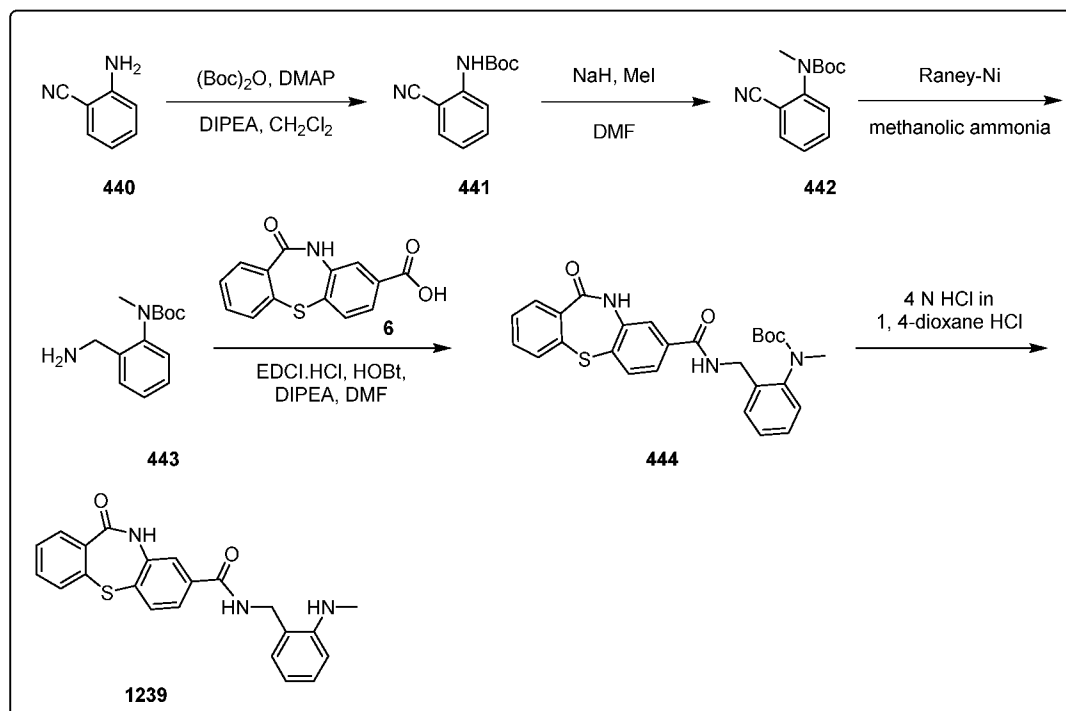
[000354] Synthesis of (*R*)-3-(11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxamido)-2-phenylpropanoic acid (1268): To a stirred solution of compound 437 (40 mg, 0.092 mmol) in THF: H₂O (4: 1, 2.5 mL) was added LiOH.H₂O (7.7 mg, 0.18 mmol) at 0 °C; warmed to RT and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, diluted with water (5 mL), pH was adjusted to ~ 6 using 1 N HCl and extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried over sodium sulphate, filtered and concentrated *in vacuo* to afford 1268 (25 mg, 65%) as white solid. TLC: 10% MeOH/ CH₂Cl₂ (*R_f*: 0.5); ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 12.49 (br s, 1H), 10.76 (s, 1H), 8.62 (t, *J* = 5.6 Hz, 1H), 7.68 (d, *J* = 7.2 Hz, 1H), 7.66-7.61 (m, 2H), 7.54-7.42 (m, 4H), 7.34-7.23 (m, 5H), 3.92 (t, *J* = 7.6 Hz, 1H), 3.77-3.72 (m, 1H), 3.57-3.50 (m, 1H); LC-MS: 90.53%; 419.4 (M⁺+1); (column; X-bridge C-18, (50 x 3.0 mm, 3.5 μm); RT 3.76 min. 0.05% TFA (Aq) : ACN; 0.8 mL/min); UPLC (purity): 93.78%; (column : Acquity BEH C-18 (50 x 2.1 mm, 1.7 μ); RT 2.04 min. ACN : 0.025% TFA (Aq); 0.5 mL/min).

[000355] Synthesis of methyl (*S*)-2-phenyl-3-((2, 2, 2-trifluoroacetyl)-λ⁴-azanyl) propanoate (438): To a stirred solution of compound 435 (Fr-II) (90 mg, 0.32 mmol) in CH₂Cl₂ (3 mL) under inert atmosphere was added trifluoroacetic acid (0.073 mL, 0.64 mmol) at 0 °C; warmed to RT and stirred for 3 h. The reaction was monitored by TLC; after completion of the

reaction, the volatiles were removed *in vacuo* to obtain the crude compound 438 (90 mg, TFA salt) as an off-white solid. **TLC:** 70% EtOAc/ Hexanes (R_f : 0.2); **$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz):** δ 8.10 (br s, 2H), 7.41-7.28 (m, 5H), 4.03 (t, J = 6.0 Hz, 1H), 3.63 (s, 3H), 3.48 (t, J = 9.2 Hz, 1H), 3.12-3.08 (m, 1H).

[000356] Synthesis of methyl (S)-3-(11-oxo-10, 11-dihydrodibenzo [b, f] [1, 4] thiazepine-8-carboxamido)-2-phenylpropanoate (439): To a stirred solution of compound 6 (70 mg, 0.25 mmol) in DMF (5 mL) under argon atmosphere were added EDCI.HCl (73.9 mg, 0.38 mmol), HOBt (52 mg, 0.38 mmol), compound 438 (70 mg, 0.38 mmol), diisopropyl ethyl amine (0.09 mL, 0.51 mmol) at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried over sodium sulphate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 80% EtOAc/ hexanes to afford compound 439 (70mg, 63%) as an off-white solid. **TLC:** 5% MeOH/ CH_2Cl_2 (R_f : 0.5); **$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz):** δ 10.77 (s, 1H), 8.65 (t, J = 5.6 Hz, 1H), 7.69 (d, J = 7.2 Hz, 1H), 7.65-7.61 (m, 2H), 7.55-7.45 (m, 4H), 7.37-7.34 (m, 2H), 7.31-7.27 (m, 3H), 4.02 (t, J = 7.2 Hz, 1H), 3.80-3.74 (m, 1H), 3.59 (s, 3H), 3.56-3.53 (m, 1H).

[000357] Synthesis of (S)-3-(11-oxo-10, 11-dihydrodibenzo [b, f] [1, 4] thiazepine-8-carboxamido)-2-phenylpropanoic acid (1269): To a stirred solution of compound 439 (40 mg, 0.09 mmol) in THF : H_2O (4: 1, 2.5 mL) was added lithium hydroxide monohydrate (7.7 mg, 0.18 mmol) at 0 °C; warmed to RT and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, diluted with water (5 mL), the pH was adjusted to ~ 6 using 1 N HCl and extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried over sodium sulphate, filtered and concentrated *in vacuo* to afford 1269 (25 mg, 65%) as white solid. **TLC:** 10% MeOH/ CH_2Cl_2 (R_f : 0.3); **$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz):** δ 12.51 (br s, 1H), 10.76 (s, 1H), 8.62 (t, J = 5.6 Hz, 1H), 7.68 (d, J = 7.2 Hz, 1H), 7.66-7.61 (m, 2H), 7.54-7.43 (m, 4H), 7.34-7.23 (m, 5H), 3.92 (t, J = 7.6 Hz, 1H), 3.77-3.72 (m, 1H), 3.57-3.50 (m, 1H); **LC-MS:** 96.04%; 417.8 ($\text{M}-1$)⁺; (column; X-select C-18, (50 x 3.0 mm, 3.5 μm); RT 2.38 min. 5.0 mM NH_4OAc : ACN; 0.8 mL/min); **UPLC (purity):** 96.12%; (column : Acquity BEH C-18 (50 x 2.1 mm, 1.7 μm); RT 2.03 min. ACN : 0.025% TFA (Aq); 0.5 mL/min).

Example 28: Synthesis of Compound 1239

[000358] Synthesis of *tert*-butyl (2-cyanophenyl) carbamate (441): To a stirred solution of 2-aminobenzonitrile **440** (1 g, 8.47 mmol) in CH_2Cl_2 (15 mL) under argon atmosphere were added Boc-anhydride (1.84 g, 4.76 mmol) and triethyl amine (0.83 mL, 5.96 mmol), DMAP (0.1 mg, catalytic amount) at 0 °C; warmed to RT and stirred for 5 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 30% EtOAc/ hexanes to afford compound **441** (500 mg, 28%) as white solid. TLC: 30% EtOAc/ hexanes (R_f : 0.8); ^1H -NMR ($\text{DMSO}-d_6$, 400 MHz): δ 9.25 (br s, 1H), 7.85 (d, $J = 7.6$ Hz, 1H), 7.73 (t, $J = 7.6$ Hz, 1H), 7.53 (d, $J = 8.0$ Hz, 1H), 7.45 (t, $J = 7.6$ Hz, 1H), 1.35 (br s, 9H).

[000359] Synthesis of *tert*-butyl (2-cyanophenyl) (methyl) carbamate (442): To a stirred solution of compound **441** (500 mg, 2.29 mmol) in DMF (10 mL) under argon atmosphere were added sodium hydride (60%, 55 mg, 2.29 mmol), methyl iodide (325 mg, 2.29 mmol) at 0 °C; warmed to RT and stirred for 5 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was quenched with ice cold water (10 mL), extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over sodium sulphate, filtered and

concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 40% EtOAc/ hexanes to afford compound **442** (480 mg, 88%) as white solid. TLC: 30% EtOAc/ hexanes (R_f : 0.5); $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ 7.85 (d, J = 7.6 Hz, 1H), 7.73 (t, J = 7.6 Hz, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.45 (t, J = 7.6 Hz, 1H), 3.18 (s, 3H), 1.35 (br s, 9H).

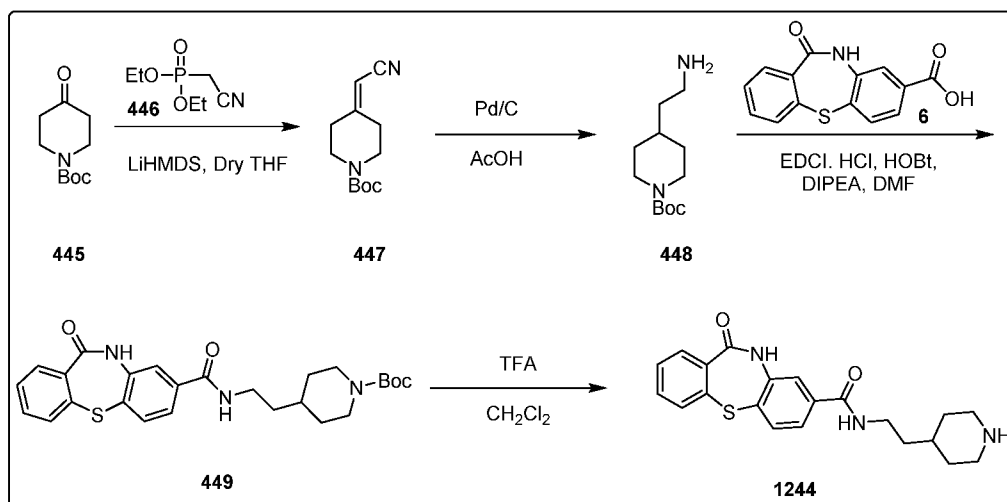
[000360] Synthesis of *tert*-butyl (2-(aminomethyl) phenyl) (methyl) carbamate (443): To a stirred solution of compound **442** (50 mg, 0.21 mmol) in MeOH (3 mL) under argon atmosphere was added Raney Nickel (20 mg), methanolic ammonia (1.5 mL) at RT and stirred under hydrogen atmosphere (balloon pressure) for 6 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered through celite, washed with MeOH (2 x 5 mL) and the filtrate was concentrated *in vacuo* to obtain the crude. The crude was washed with diethyl ether (2 x 10 mL) and dried *in vacuo* to afford compound **443** (40 mg, 80%) as white solid. TLC: 50% EtOAc/ hexanes (R_f : 0.2); $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ 7.52 (d, J = 7.2 Hz, 1H), 7.28-7.20 (m, 2H), 7.12 (t, J = 5.6 Hz, 1H), 3.60-3.57 (m, 2H), 3.14 (br s, 3H), 1.25 (s, 9H).

[000361] Synthesis of *tert*-butyl methyl (2-((11-oxo-10, 11-dihydrodibenzo [*b, f*] [1, 4] thiazepine-8-carboxamido) methyl) phenyl) carbamate (444): To a stirred solution of compound **6** (40 mg, 0.14 mmol) in DMF (3 mL) under argon atmosphere were added EDCI.HCl (42 mg, 0.22 mmol), HOBt (30 mg, 0.22 mmol), compound **443** (37.6 mg, 0.16 mmol), diisopropyl ethyl amine (0.05 mL, 0.29 mmol) at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with ice-cold water (20 mL). The precipitate was filtered and the obtained solid was dried *in vacuo* to afford compound **444** (40 mg, 55%) as white solid. TLC: 5% MeOH/ CH_2Cl_2 (R_f : 0.5); LC-MS: 93.49%; 390.3 (M^+ +1) (Des-Boc).

[000362] Synthesis of *N*-(2-(methylamino) benzyl)-11-oxo-10, 11-dihydrodibenzo [*b, f*] [1, 4] thiazepine-8-carboxamide (1239): A stirred solution of compound **444** (40 mg, 0.08 mmol) in 4 N HCl in 1, 4-dioxane (2 mL) under argon atmosphere at 0-5 °C was stirred for 1 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with saturated NaHCO_3 solution (20 mL) and extracted with EtOAc (2 x 20 mL). The

combined organic extracts were washed with water (15 mL), dried over sodium sulphate, filtered and concentrated *in vacuo* to afford **1239** (10 mg, 32%) as white solid. **TLC**: 5% MeOH/ CH₂Cl₂ (*R_f*: 0.4); **¹H-NMR (DMSO-*d*₆, 400 MHz)**: δ 10.74 (s, 1H), 8.96 (t, *J* = 6.0 Hz, 1H), 7.72-7.60 (m, 4H), 7.55-7.43 (m, 3H), 7.08 (t, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 7.2 Hz, 1H), 6.53 (t, *J* = 7.2 Hz, 2H), 5.38-5.37 (m, 1H), 4.29 (d, *J* = 7.2 Hz, 2H), 2.72 (d, *J* = 4.8 Hz, 3H); **LC-MS**: 93.74%; 390.3 (*M*⁺+1); (column; X-select CSH C-18, (50 x 3.0 mm, 3.5 μm); RT 3.44 min. 0.05% TFA (Aq) : ACN; 0.8 mL/min); **UPLC (purity)**: 94.35%; (column : Acquity UPLC BEH C-18 (2.1 × 50 mm, 1.7 μ); RT 1.87 min. ACN : 0.025% TFA (Aq); 0.5 mL/min).

Example 29: Synthesis of Compound 1244



[000363] Synthesis of tert-butyl 4-(cyanomethylene) piperidine-1-carboxylate (447): To a stirred solution of diethyl (cyanomethyl) phosphonate **445** (978 mg, 5.52 mmol) in anhydrous THF (10 mL) under argon atmosphere was added LiHMDS (1 mL, 5.52 mmol, 1M in THF) was added drop wise for 10 min at -78 °C. To this was added *tert*-butyl 4-oxopiperidine-1-carboxylate **446** (1 g, 5.01 mmol) in THF (2 mL) dropwise for 10 min and stirred for 3 h at the same temperature. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was quenched with saturated ammonium chloride solution (30 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with brine (30 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 15% EtOAc/ hexanes to afford compound **447** (900 mg, 82%) as white solid. **TLC**: 30% EtOAc/ hexanes (*R_f*: 0.5); **¹H NMR**

(CDCl₃, 400 MHz) δ 5.19 (s, 1H), 3.54-3.49 (m, 4H), 2.56 (t, J = 5.8 Hz, 2H), 2.33 (t, J = 5.6 Hz, 2H), 1.48 (s, 9H);

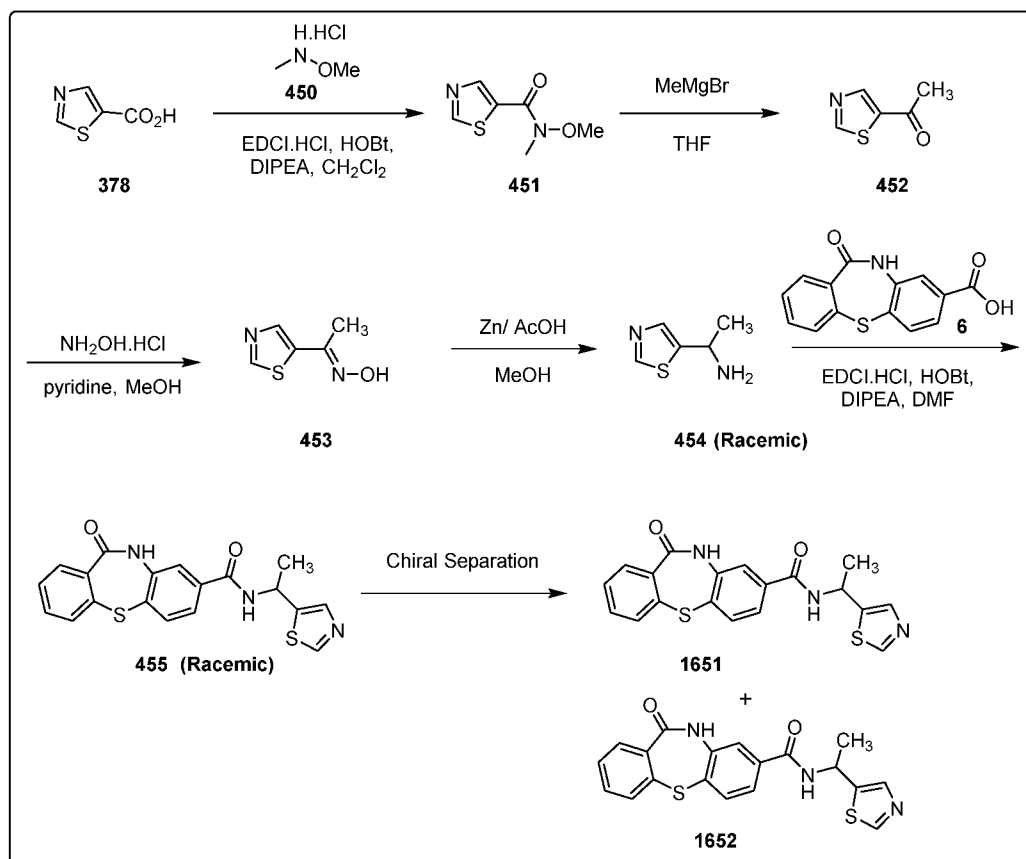
[000364] Synthesis of *tert*-butyl 4-(2-aminoethyl) piperidine-1-carboxylate (448): To a stirred solution of **447** (100 mg, 0.45 mmol) in AcOH (5 mL) under argon atmosphere was added 10% Pd/C (50 mg) at RT and stirred under hydrogen atmosphere (balloon pressure) for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mass was filtered through celite and washed with EtOAc (3 x 15 mL) and the volatiles were removed *in vacuo* to afford compound **448** (70 mg, mixture of isomers) as pale brown syrup. **TLC:** 6% MeOH/CH₂Cl₂ (R_f : 0.2); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 3.89 (d, J = 12.4 Hz, 2H), 2.70-2.68 (m, 2H), 1.68-1.65 (m, 2H), 1.59 (d, J = 12.0 Hz, 1H), 1.38 (s, 9H), 1.33-1.28 (m, 4H), 0.99-0.89 (m, 2H).

[000365] Synthesis of *tert*-butyl 4-(2-(11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxamido) ethyl) piperidine-1-carboxylate (449): To a stirred solution of compound **6** (40 mg, 0.14 mmol) in DMF (3 mL) under argon atmosphere were added EDCI.HCl (42 mg, 0.22 mmol), HOBt (30 mg, 0.22 mmol), compound **448** (40 mg, 0.17 mmol), diisopropyl ethyl amine (0.05 mL, 0.29 mmol) at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude. The crude was triturated with EtOAc: H₂O (1: 5, 12 mL), filtered and the precipitate was dried *in vacuo* to afford compound **449** (36 mg, 51%) as white solid. **TLC:** 7% MeOH/ CH₂Cl₂ (R_f : 0.7); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 10.76 (s, 1H), 8.47 (br s, 1H), 7.69-7.63 (m, 3H), 7.57-7.53 (m, 2H), 7.47 (t, J = 8.8 Hz, 2H), 3.89 (d, J = 10.8 Hz, 2H), 3.26-3.25 (m, 2H), 2.67 (s, 3H), 1.64 (d, J = 10.8 Hz, 2H), 1.42-1.41 (m, 2H), 1.37 (s, 9H), 0.97-0.95 (m, 2H).

[000366] Synthesis of 11-oxo-*N*-(2-(piperidin-4-yl) ethyl)-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxamide (1244): To a stirred solution of compound **449** (36 mg, 0.07 mmol) in CH₂Cl₂ (3 mL) under argon atmosphere was added trifluoro acetic acid (0.03 mL, 0.37 mmol) at 0 °C; warmed to RT and stirred for 4 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude. The crude was neutralized with 10% NaHCO₃ solution (15 mL) and extracted with EtOAc (3 x 15 mL).

The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford **1244** (15 mg, 53%) as an off-white solid. **TLC**: 7% MeOH/ CH₂Cl₂ (*R_f*: 0.2); **¹H-NMR (DMSO-*d*₆, 400 MHz)**: δ 10.77 (br s, 1H), 8.48 (t, *J* = 5.6 Hz, 1H), 7.69-7.64 (m, 3H), 7.57-7.43 (m, 4H), 3.26-3.25 (m, 3H), 3.16-3.12 (m, 2H), 2.68 (t, *J* = 10.0 Hz, 2H), 1.77-1.74 (m, 2H), 1.44 (t, *J* = 6.8 Hz, 3H); 1.23-1.13 (m, 2H); **LC-MS**: 90.01%; 382.4 (*M*⁺+1); (column; X-select CSH C-18, (50 × 3.0 mm, 3.5 μm); RT 2.97 min. 0.05% TFA (Aq) : ACN; 0.8 mL/min); **UPLC (purity)**: 92.90%; (column : Acquity UPLC BEH C-18 (2.1 x 50 mm, 1.7 μ); RT 1.60 min. ACN : 0.025% TFA (Aq); 0.5 mL/min).

Example 30: Synthesis of Compounds 1651 and 1652



[000367] Synthesis of *N*-methoxy-*N*-methylthiazole-5-carboxamide (451**):** To a stirred solution of thiazole-5-carboxylic acid **378** (1.5 g, 11.61 mmol) in CH₂Cl₂ (30 mL) under argon atmosphere were added EDCI.HCl (2.45 g, 12.78 mmol), HOBT (785 mg, 135.13 mmol), *N,O*-dimethyl hydroxylamine hydrochloride **450** (1.36 g, 97.6 mmol) and diisopropyl ethyl amine (10

mL, 58.09 mmol) at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (50 mL) and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic extracts were washed with 1 N HCl (20 mL), saturated NaHCO₃ solution (30 mL), brine (50 mL) and dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through combi flash chromatography using 30-40% EtOAc/ hexanes to afford compound **451** (1.2 g, 60%) as colorless syrup. **TLC:** 5% MeOH/ CH₂Cl₂ (*R_f*: 0.6); **¹H NMR (DMSO-*d*₆, 400 MHz):** 9.32 (s, 1H), 8.52 (s, 1H), 3.77 (s, 3H), 3.30 (s, 3H).

[000368] Synthesis of 1-(thiazol-5-yl) ethan-1-one (452): To a stirred solution of compound **451** (1.2 g, 6.97 mmol) in THF (20 mL) under argon atmosphere was added methyl magnesium bromide (3.2 mL, 10.46 mmol, 3 M solution in Et₂O) dropwise for 10 min at -10 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was quenched with saturated ammonium chloride (30 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through combi flash chromatography using 25-30% EtOAc/ hexanes to afford compound **452** (800 mg, 90%) as white solid. **TLC:** 50% EtOAc/ hexanes (*R_f*: 0.6); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 9.40 (s, 1H), 8.71 (s, 1H), 2.60 (s, 3H).

[000369] Synthesis of 1-(thiazol-5-yl) ethan-1-one oxime (453): To a stirred solution of compound **452** (800 mg, 6.29 mmol) in MeOH (20 mL) under inert atmosphere was added hydroxyl amine hydrochloride (875 mg, 12.59 mmol) and pyridine (2 mL) dropwise for 5 min at 0 °C warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* diluted with water (50 mL) and stirred for 30 min. The precipitated solid was filtered dried *in vacuo* to afford compound **453** (800 mg, 90%) as white solid. **TLC:** 40% EtOAc/ hexanes (*R_f*: 0.4, 0.6); **¹H NMR (DMSO-*d*₆, 400 MHz) (Mixture of E/Z isomers):** δ 11.86 (s, 1H), 11.41 (s, 0.6 H), 9.19 (s, 1H), 9.01 (s, 0.56 H), 8.35 (s, 1H), 8.15 (s, 0.65 H), 2.31 (s, 3H), 2.21 (s, 2H).

[000370] Synthesis of 1-(thiazol-5-yl) ethan-1-amine (454): To a stirred solution of compound **453** (800 mg, 5.63 mmol) in MeOH: acetic acid (1: 1, 20 mL) under inert atmosphere

were zinc powder (2.2 g, 33.80 mmol) at RT; heated at 50 °C and stirred for 4 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered through celite washed with MeOH (3 x 10 mL). The filtrate were removed *in vacuo*, the residue was diluted with water (20 mL), basified with aqueous ammonia (15 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude compound **454 (racemic)** (700 mg, 92%) as brown syrup. **TLC:** 5% MeOH/ CH₂Cl₂ (*R_f*: 0.4, 0.6); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 8.90 (s, 1H), 7.71 (s, 1H), 4.33-4.28 (m, 1H), 3.38 (t, *J* = 6.4 Hz, 1H), 1.87 (s, 3H).

[000371] **Synthesis of 11-oxo-*N*-(1-(thiazol-5-yl) ethyl)-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxamide (455 Racemic):** Using Procedure A the title compound was prepared with **DBT-Acid** (150 mg, 0.55 mmol) and compound **454 racemic** (109 mg, 0.66) to afford compound **455 (Racemic)** (100 mg, 48%); **TLC:** 5% MeOH/ CH₂Cl₂ (*R_f*: 0.5); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 10.87 (br s, 1H), 9.14 (d, *J* = 8.0 Hz, 1H), 8.95 (s, 1H), 7.79 (d, *J* = 3.6 Hz, 2H), 7.70-7.58 (m, 3H), 7.56-7.42 (m, 3H), 5.48-5.41 (m, 1H), 1.60 (s, 3H); **LC-MS:** 98.31%; 381.9 (*M*⁺+1); (column; Ascentis Express C18, (50 × 3.0 mm, 2.7 μm); RT 2.03 min. 0.025% Aq. TFA + 5% ACN: ACN + 5% 0.025% Aq. TFA, 1.2 mL/min); **HPLC (purity):** 97.68%; (column; Eclipse XDB C-18 (150 x 4.6 mm, 5.0 μm); RT 7.58 min. ACN : 0.05% TFA (Aq); 1.0 mL/min) (IP14012554); **Chiral HPLC:** 35.10%, *R_t* = 9.01 min (Chiralpak-IA, 250 x 4.6 mm, 5 μm); mobile phase (A) 0.1% DEA in *n*-Hexane (B) CH₂Cl₂: MeOH (50: 50) (A: B:: 63: 35); Flow Rate: 1.0 mL/min).

[000372] The racemic compound **455** (100 mg) was separated by preparative HPLC using a CHIRALPAK-IC column (250 x 20 mm x 5 μm) (10 mg loading; mobile phase (A) 0.1% DEA in *n*-Hexane (B) CH₂Cl₂: MeOH: DMF (65: 35: 05) (A: B:: 75: 25) to afford **1651** (10 mg) and **1652** (15 mg) as an off-white solids.

Analytical Data of 1651:

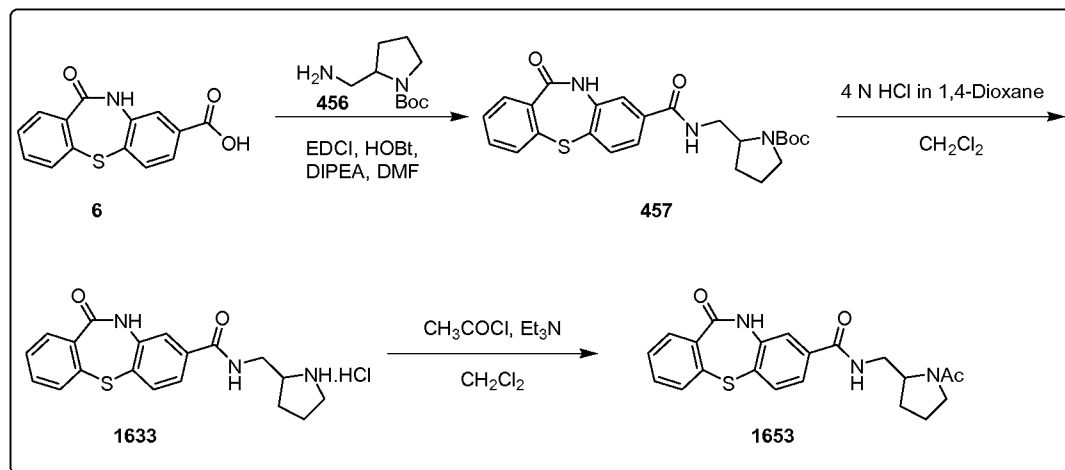
[000373] **TLC:** 5% MeOH/ CH₂Cl₂ (*R_f*: 0.5); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 10.75 (s, 1H), 9.02 (d, *J* = 7.8 Hz, 1H), 8.95 (s, 1H), 7.79 (s, 1H), 7.72-7.64 (m, 3H), 7.62-7.58 (m, 1H), 7.56-7.41 (m, 3H), 5.45 (t, *J* = 7.0 Hz, 1H), 1.57 (d, *J* = 6.8 Hz, 3H); **LC-MS:** 96.06%; 381.8 (*M*⁺+1); (column; Ascentis Express C18, (50 × 3.0 mm, 2.7 μm); RT 2.03 min. 0.025% Aq. TFA + 5%

ACN: ACN + 5% 0.025% Aq. TFA, 1.2 mL/min); **HPLC (purity):** 95.02%; (column; Zorbax SB C-18 (150 x 4.6 mm, 3.5 μ m); RT 7.79 min. ACN : 0.05% TFA (Aq); 1.0 mL/min) (IP15010530); **Chiral HPLC:** 96.24%, R_t = 14.33 min (Chiralpak-IA, 250 x 4.6 mm, 5 μ m); mobile phase (A) 0.1% DEA in *n*-Hexane (B) CH₂Cl₂: MeOH: DMF (65: 35: 05) (A: B:: 75: 25); Flow Rate: 1.0 mL/min). Note: Alternatively the racemic compound **454** was resolved and one fraction had led to **1651**.

Analytical Data of **1652**:

[000374] **TLC:** 5% MeOH/ CH₂Cl₂ (R_f : 0.5); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 10.75 (s, 1H), 9.03 (d, J = 8.3 Hz, 1H), 8.95 (s, 1H), 7.79 (s, 1H), 7.71-7.63 (m, 3H), 7.62-7.58 (m, 1H), 7.56-7.42 (m, 3H), 5.48-5.47(m, 1H), 1.57 (d, J = 6.9 Hz, 3H); **LC-MS:** 96.65%; 381.9 (M^+ +1); (column; Ascentis Express C18, (50 x 3.0 mm, 2.7 μ m); RT 2.68 min. 0.025% Aq. TFA + 5% ACN: ACN + 5% 0.025% Aq. TFA, 1.2 mL/min); **HPLC (purity):** 98.53%; (column; Zorbax SB C-18 (150 x 4.6 mm, 3.5 μ m); RT 7.76 min. ACN : 0.05% TFA (Aq); 1.0 mL/min) (IP15010229). **Chiral HPLC:** 99.87%, R_t = 16.90 min (Chiralpak-IA, 250 x 4.6 mm, 5 μ m); mobile phase (A) 0.1% DEA in *n*-Hexane (B) CH₂Cl₂: MeOH: DMF (65: 35: 05) (A: B:: 75: 25); Flow Rate: 1.0 mL/min).

Example 31: Synthesis of Compounds **1653** and **1633**



[000375] **Synthesis of *tert*-butyl 2-((11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxamido) methyl) pyrrolidine-1-carboxylate (**457**):** Using Procedure A the title compound was prepared with compound **6** (300 mg, 1.10 mmol), *tert*-butyl 2-(aminomethyl)

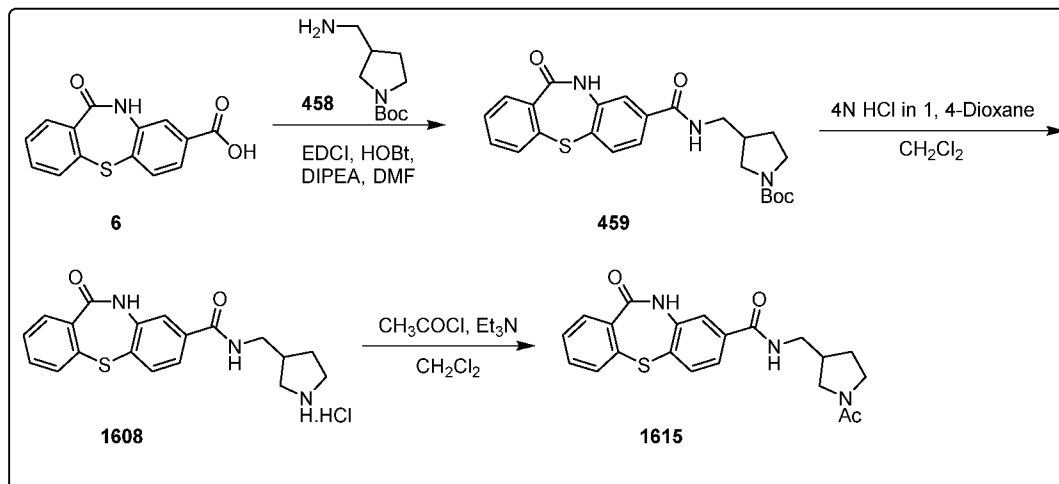
pyrrolidine-1-carboxylate **456** (0.24 mL, 1.21 mmol) and was obtained in 50% yield as an off-white solid; **TLC**: 10% MeOH/ CH₂Cl₂ (*R_f*: 0.7); **¹H NMR (DMSO-*d*₆, 400 MHz)**: δ 10.76 (br s, 1H), 8.53 (t, *J* = 5.5 Hz, 1H), 7.71-7.63 (m, 3H), 7.56-7.43 (m, 4H), 3.95-3.79 (m, 1H), 3.52-3.35 (m, 1H), 3.26-3.19 (m, 3H), 1.86-1.71 (m, 4H), 1.38 (s, 9H).

[000376] Synthesis of 11-oxo-*N*-(pyrrolidin-2-ylmethyl)-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxamide hydrochloride (1633): To a stirred solution of compound **457** (250 mg, 0.55 mmol) in CH₂Cl₂ (5 mL) under argon atmosphere was added 4 N HCl in 1, 4-dioxane (1 mL) at 0 °C; warmed to RT and stirred for 5 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to afford compound **1633** (150 mg, 77%; HCl salt) as an off-white solid. **TLC**: 10% MeOH/ CH₂Cl₂ (*R_f*: 0.1); **¹H NMR (DMSO-*d*₆, 400 MHz)**: δ 10.82 (br s, 1H), 8.88 (br s, 3H), 7.74-7.62 (m, 4H), 7.56-7.43 (m, 3H), 3.67-3.57 (m, 1H), 3.56-3.46 (m, 2H), 3.24-3.07 (m, 2H), 2.07-1.95 (m, 1H), 1.95-1.78 (m, 2H), 1.68-1.59 (m, 1H); **LC-MS**: 96.49%; 354.0 (M⁺+1) (-HCl); (column; Ascentis Express C18, (50 × 3.0 mm, 2.7 μm); RT 1.64 min. 0.025% Aq. TFA + 5% ACN: ACN + 5% 0.025% Aq. TFA, 1.2 mL/min); **HPLC (purity)**: 96.28%; (column; Zorbax SB C-18 (150 × 4.6 mm, 3.5 μm); RT 6.64 min. ACN : 0.05% TFA (Aq); 1.0 mL/min).

[000377] Synthesis of *N*-((1-acetylpyrrolidin-2-yl) methyl)-11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxamide (1653): To a stirred solution of compound **1633** (100 mg, 0.25 mmol) in CH₂Cl₂ (5 mL) under argon atmosphere were added triethylamine (0.12 mL, 0.77 mmol), acetyl chloride (0.02 mL, 0.30 mmol) at 0 °C; warmed to RT, stirred for 12 h. The reaction was monitored by TLC; after completion the reaction, the reaction the volatiles were removed *in vacuo*; the residue was basified with saturated NaHCO₃ solution and extracted with CH₂Cl₂ (2 × 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 5% MeOH/ CH₂Cl₂ to afford **1653** (20 mg, 20%) as an off-white solid. **TLC**: 10% MeOH/ CH₂Cl₂ (*R_f*: 0.6); **¹H NMR (DMSO-*d*₆, 400 MHz)**: δ 10.84-10.73 (m, 1H), 8.87-8.55 (m, 1H), 7.72-7.63 (m, 3H), 7.60-7.43 (m, 4H), 4.17-3.94 (m, 1H), 3.53-3.33 (m, 3H), 3.32-3.30 (m, 0.5H), 3.20-3.09 (m, 0.5H), 2.08-1.92 (m, 3H), 1.88-1.70 (m, 4H); **LC-MS**: 99.36%; 396.4 (M⁺+1); (column; X-Select C-18, (50 × 3.0 mm, 3.5 μm); RT 3.34 min, 0.77 min. 5 mM Aq.NH₄OAc: ACN 0.8 mL/min). **HPLC (purity)**: 98.67%; (column; Eclipse XDB C-18

(150 x 4.6 mm, 5.0 μ m); RT 7.28 min. ACN: 5 mM Aq. NH_4OAc ; 1.0 mL/min).

Example 32: Synthesis of Compounds 1615 and 1608



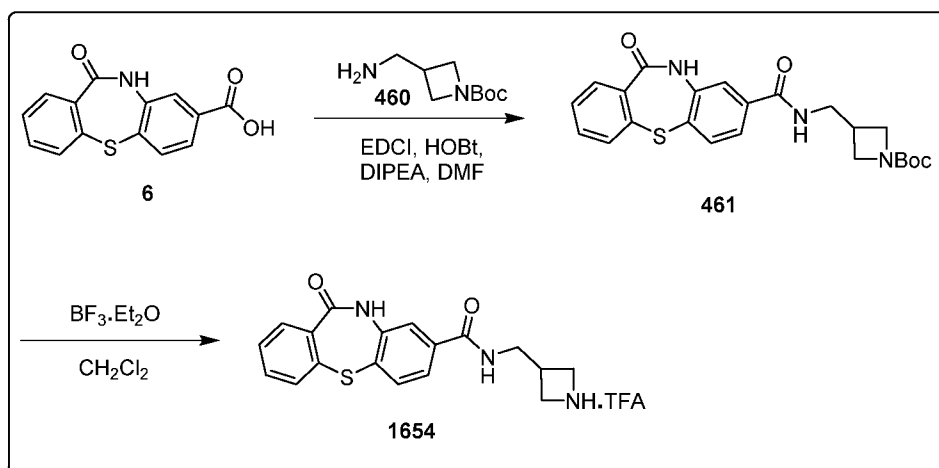
[000378] **Synthesis of *tert*-butyl 3-((11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxamido) methyl) pyrrolidine-1-carboxylate (459):** Using Procedure A the title compound was prepared with **6** (300 mg, 1.10 mmol), *tert*-butyl 3-(aminomethyl) pyrrolidine-1-carboxylate **458** (0.24 mL, 1.21 mmol) and was obtained in 60% yield as an off-white solid; **TLC:** 10% MeOH/ CH_2Cl_2 (R_f : 0.5); **^1H NMR (DMSO- d_6 , 400 MHz):** δ 10.76 (s, 1H), 8.61 (t, J = 5.0 Hz, 1H), 7.72-7.63 (m, 3H), 7.60-7.42 (m, 4H), 3.34-3.18 (m, 1H), 3.28-3.13 (m, 4H), 2.99-2.92 (m, 1H), 2.42-2.34 (m, 1H), 1.94-1.82 (m, 1H), 1.64-1.50 (m, 1H), 1.37 (s, 9H).

[000379] **Synthesis of 11-oxo-*N*-(pyrrolidin-3-ylmethyl)-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxamide hydrochloride (1608):** To a stirred solution of compound **459** (300 mg, 0.66 mmol) in CH_2Cl_2 (5 mL) under argon atmosphere was added 4 N HCl in 1, 4-dioxane (1 mL) at 0 $^\circ\text{C}$; warmed to RT and stirred for 5 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to afford compound **1608** (200 mg, 78%; HCl salt) as an off-white solid. **TLC:** 10% MeOH/ CH_2Cl_2 (R_f : 0.1); **^1H -NMR (DMSO- d_6 , 400 MHz):** δ 10.78 (s, 1H), 8.88 (br s, 2H), 8.70 (t, J = 5.7 Hz, 1H), 7.71-7.65 (m, 3H), 7.59 (dd, J = 8.2, 2.0 Hz, 1H), 7.56-7.43 (m, 3H), 3.27-3.15 (m, 5H), 3.15-3.04 (m, 1H), 2.94-2.80 (m, 1H), 2.04-1.92 (m, 1H), 1.69-1.56 (m, 1H); **LC-MS:** 98.04%; 353.9 ($\text{M}^+ + 1$) (-HCl); (column; Ascentis Express C18, (50 $\times$ 3.0 mm, 2.7 μ m); RT 1.64 min. 0.025% Aq. TFA + 5% ACN: ACN + 5% 0.025% Aq. TFA, 1.2 mL/min); **UPLC (purity):** 97.21%; (column;

Acquity UPLC BEH C-18 (50 x 2.1 mm, 1.7 μ); RT 1.55 min. ACN : 0.025% TFA (Aq); 0.5 mL/min) (IP14120205).

[000380] Synthesis of *N*-((1-acetylpyrrolidin-3-yl) methyl)-11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxamide (1615): To a stirred solution of compound **1608** (100 mg, 0.28 mmol) in CH₂Cl₂ (5 mL) under argon atmosphere were added triethylamine (0.12 mL, 0.84 mmol), acetyl chloride (0.02 mL, 0.33 mmol) at 0 °C; warmed to RT, stirred for 12 h. The reaction was monitored by TLC; after completion the reaction, the reaction the volatiles were removed *in vacuo*; the residue was basified with saturated NaHCO₃ solution and extracted with CH₂Cl₂ (2 x 30 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 5% MeOH/ CH₂Cl₂ to afford **1615** (30 mg, 26%) as an off-white solid. **TLC:** 10% MeOH/ CH₂Cl₂ (*R_f*: 0.6); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 10.71 (m, 1H), 8.69 - 8.58 (m, 1H), 7.72-7.63 (m, 3H), 7.61-7.41 (m, 4H), 3.55-3.34 (m, 3H), 3.29-3.19 (m, 2H), 3.17-3.13 (m, 0.5H), 3.00 (dd, *J* = 11.8, 7.3 Hz, 0.5H), 2.41-2.34 (m, 1H), 2.02-1.84 (m, 4H), 1.73-1.49 (m, 1H); **LC-MS:** 95.89%; 396.0 (*M*⁺+1); (column; Ascentis Express C18, (50 x 3.0 mm, 2.7 μ m); RT 1.87 min. 0.025% Aq. TFA + 5% ACN: ACN + 5% 0.025% Aq. TFA, 1.2 mL/min); **HPLC (purity):** 97.29%; (column; Eclipse XDB C-18 (150 x 4.6 mm, 5.0 μ m); RT 7.05 min. ACN: 5 mM Aq. NH₄OAc; 1.0 mL/min).

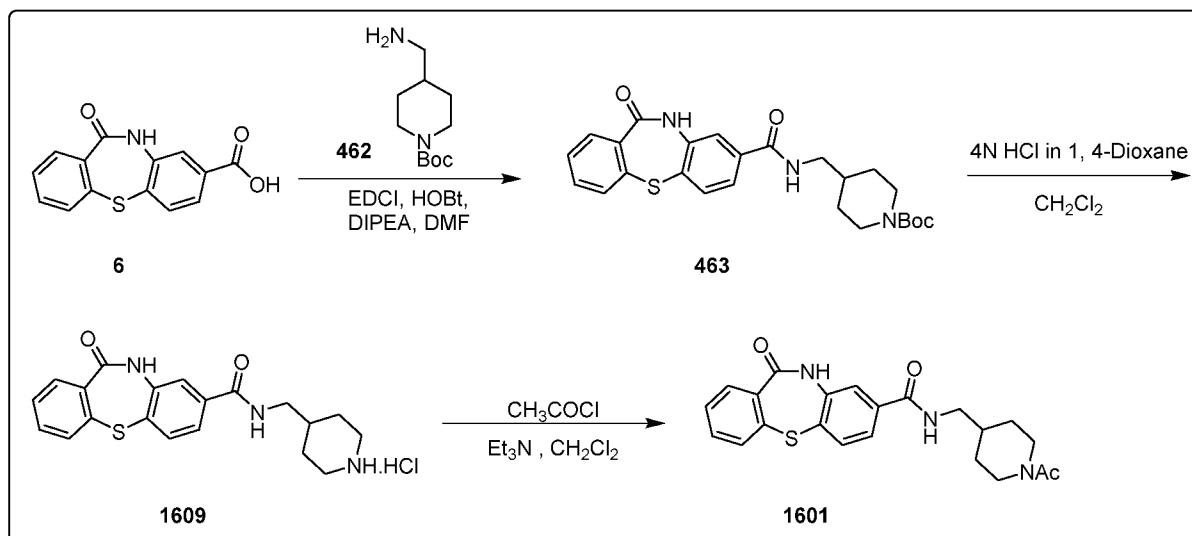
Example 33: Synthesis of Compound 1654



[000381] Synthesis of *tert*-butyl 3-((11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-

carboxamido) methyl) azetidine-1-carboxylate (461): To a stirred solution of compound **6** (600 mg, 2.21 mmol) in DMF (5 mL) under argon atmosphere were added EDCI.HCl (634 mg, 3.32 mmol), HOBt (435 mg, 3.32 mmol), *tert*-butyl 3-(aminomethyl) azetidine-1-carboxylate **460** (453 mg, 2.43 mmol) and diisopropyl ethyl amine (1.14 mL, 6.64 mmol) at RT and stirred for 12 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (25 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 5% MeOH/CH₂Cl₂ to afford compound **461** (600 mg, 61%) as an off-white solid. **TLC:** 10% MeOH/CH₂Cl₂ (*R_f*: 0.6); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 10.76 (s, 1H), 8.64 (t, *J* = 5.6 Hz, 1H), 7.71-7.64 (m, 3H), 7.59-7.43 (m, 4H), 3.84 (t, *J* = 7.0 Hz, 2H), 3.66-3.50 (m, 2H), 3.41 (t, *J* = 6.3 Hz, 2H), 2.72-2.64 (m, 1H), 1.33 (s, 9H).

[000382] **Synthesis of 11-oxo-*N*-((1-(2, 2, 2-trifluoroacetyl)-1*H*-azetidin-3-yl) methyl)-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxamide (1654):** To a stirred solution of **461** (350 mg, 0.79 mmol) in CH₂Cl₂ (10 mL) under argon atmosphere were added BF₃.Et₂O (0.18 mL, 1.59 mmol), molecular sieves (20 mg) at 0 °C; warmed to RT and stirred for 1 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (25 mL) and extracted with CH₂Cl₂ (2 x 25 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified using preparative HPLC purification to afford compound **1654** (20 mg, 7%) as an off-white solid. **TLC:** 10% MeOH/ CH₂Cl₂ (*R_f*: 0.6); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 10.79 (s, 1H), 8.70 (t, *J* = 5.6 Hz, 1H), 8.62-8.39 (m, 1H), 7.73-7.66 (m, 3H), 7.59 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.57-7.43 (m, 3H), 3.99-3.88 (m, 2H), 3.80-3.69 (m, 2H), 3.45 (t, *J* = 6.1 Hz, 2H), 3.04-2.94 (m, 1H); **LC-MS:** 99.41%; 339.9 (M⁺+1); (column; Ascentis Express C18, (50 × 3.0 mm, 2.7 μm); RT 1.70 min. 0.025% Aq. TFA + 5% ACN: ACN + 5% 0.025% Aq. TFA, 1.2 mL/min); **HPLC (purity):** 98.60%; (column; Zorbax SB C-18 (150 x 4.6 mm, 3.5 μm); RT 6.54 min. ACN : 0.05% TFA (Aq); 1.0 mL/min).

Example 34: Synthesis of Compounds 1601 and 1609

[000383] Synthesis of *tert*-butyl 4-((11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxamido) methyl) piperidine-1-carboxylate (463**):** Using Procedure A the title compound was prepared with compound **6** (200 mg, 0.73 mmol), *tert*-butyl 4-(aminomethyl) piperidine-1-carboxylate **462** (0.17 mL, 0.81 mmol) and was obtained in 86% yield as pale brown solid; **TLC**: 5% MeOH/ CH_2Cl_2 (R_f : 0.5); **^1H NMR (DMSO- d_6 , 400 MHz)**: δ 10.75 (br s, 1H), 8.52 (t, $J = 5.6$ Hz, 1H), 7.72-7.61 (m, 3H), 7.60-7.42 (m, 4H), 3.93-3.88 (m, 2H), 3.12 (t, $J = 6.0$ Hz, 2H), 2.71-2.59 (m, 2H), 1.74-1.57 (m, 3H), 1.38 (s, 9H), 1.06-0.92 (m, 2H)

[000384] Synthesis of 11-oxo-*N*-(piperidin-4-ylmethyl)-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxamide hydrochloride (1609**):** To a stirred solution of compound **463** (300 mg, 0.64 mmol) in CH_2Cl_2 (5 mL) under argon atmosphere was added 4 N HCl in 1, 4-dioxane (1 mL) at 0 °C; warmed to RT and stirred for 5 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to afford compound **1609** (200 mg, 85%; HCl salt) as pale brown solid. **TLC**: 5% MeOH/ CH_2Cl_2 (R_f : 0.2); **^1H -NMR (DMSO- d_6 , 400 MHz)**: δ 10.77 (s, 1H), 8.67-8.58 (m, 2H), 8.32 (br s, 1H), 7.71 -7.64 (m, 3H), 7.61-7.43 (m, 4H), 3.27-3.20 (m, 2H), 3.18-3.12 (m, 2H), 2.89-2.76 (m, 2H), 1.82-1.72 (m, 3H), 1.38-1.23 (m, 2H); **LC-MS**: 98.23%; 368.0 ($\text{M}^+ + 1$) (-HCl); (column; Ascentis Express C18, (50 × 3.0 mm, 2.7 μm); RT 1.67 min. 0.025% Aq. TFA + 5% ACN: ACN + 5% 0.025% Aq. TFA, 1.2 mL/min); **UPLC (purity)**: 97.67%; (column; Acquity UPLC BEH C-18 (50 x 2.1 mm, 1.7 μ);

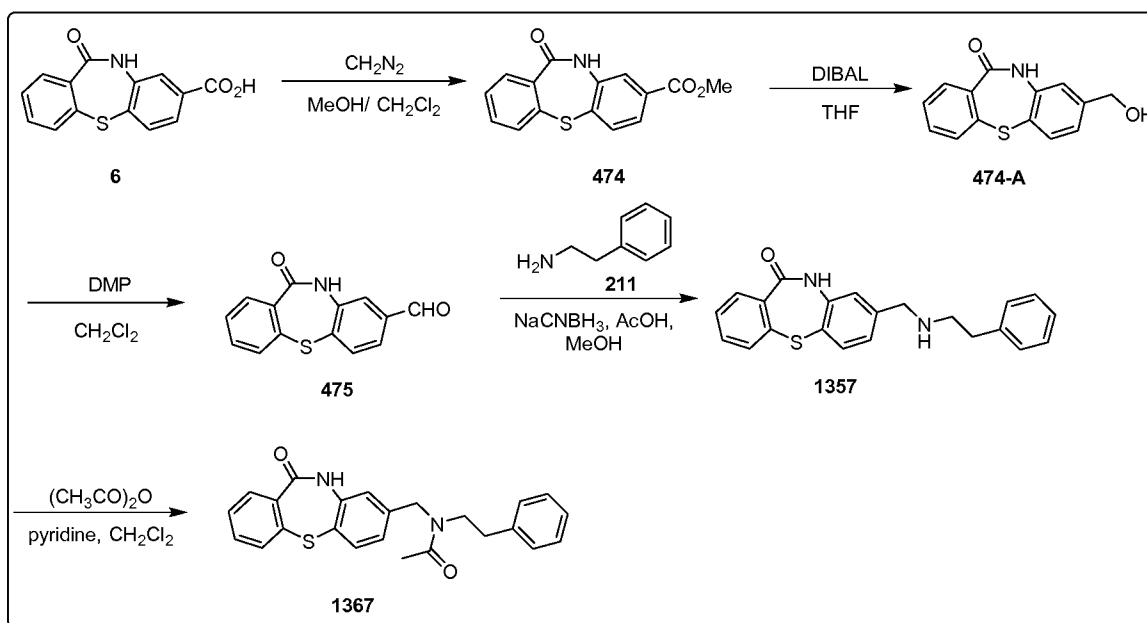
RT 1.59 min. ACN : 0.025% TFA (Aq); 0.5 mL/min).

[000385] Synthesis of *N*-((1-acetylpiperidin-4-yl) methyl)-11-oxo-10, 11-dihydrodibenzo

[*b, f*] [1, 4] thiazepine-8-carboxamide (1601): To a stirred solution of compound **1609** (100 mg, 0.24 mmol) in CH₂Cl₂ (5 mL) under argon atmosphere were added triethylamine (0.1 mL, 0.74 mmol), acetyl chloride (0.02 mL, 0.29 mmol) at 0 °C; warmed to RT, stirred for 12 h. The reaction was monitored by TLC; after completion the reaction, the reaction the volatiles were removed *in vacuo*; the residue was basified with saturated NaHCO₃ solution and extracted with CH₂Cl₂ (2 x 15 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 1% MeOH/ CH₂Cl₂ to afford **1601** (20 mg, 20%) as an off-white solid.

TLC: 10% MeOH/ CH₂Cl₂ (*R_f*: 0.5); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 10.75 (s, 1H), 8.53 (t, *J* = 5.5 Hz, 1H), 7.71-7.63 (m, 3H), 7.61-7.43 (m, 4H), 4.36-4.29 (m, 1H), 3.81-3.73 (m, 1H), 3.19-3.06 (m, 2H), 3.00-2.91 (m, 1H), 2.53-2.46 (m, 1H), 1.96 (s, 3H), 1.82-1.58 (m, 3H), 1.14-0.89 (m, 2H); **LC-MS:** 99.33%; 410.0 (M⁺+1); (column; Ascentis Express C18, (50 × 3.0 mm, 2.7 μm); RT 1.99 min. 0.025% Aq. TFA + 5% ACN: ACN + 5% 0.025% Aq. TFA, 1.2 mL/min); **UPLC (purity):** 99.57%; (column; Acquity UPLC BEH C-18 (50 x 2.1 mm, 1.7 μm); RT 1.79 min. ACN: 0.025% TFA (Aq); 0.5 mL/min).

Example 35: Synthesis of Compounds 1357, 1655, and 1367



[000386] Synthesis of methyl 11-oxo-10, 11-dihydrodibenzo [b, f] [1, 4] thiazepine-8-carboxylate (474): To a stirred solution of compound **6** (500 mg, 1.84 mmol) in MeOH: CH₂Cl₂ (1: 1, 20 mL) under argon atmosphere was added CH₂N₂ (insitu prepared using N-nitrosomethyl urea (0.95 g, 9.2 mmol) + KOH (0.51 g, 9.22 mmol)) at 0 °C; warmed to RT and stirred for 1 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 20% EtOAc/ hexanes to afford compound **474** (450 mg, 86%) as white solid. **TLC:** 30% EtOAc/ hexanes (*R_f*: 0.5); **¹H-NMR (DMSO-*d*₆, 500 MHz):** δ 10.82 (s, 1H), 7.82 (s, 1H), 7.75-7.69 (m, 3H), 7.58-7.63 (m, 3H), 3.82 (s, 3H).

[000387] Synthesis of 8-(hydroxymethyl) dibenzo [b, f] [1, 4] thiazepin-11(10*H*)-one (474-A): To a stirred solution of compound **474** (500 mg, 1.75 mmol) in dry THF (3 mL) under argon atmosphere was added diisobutylaluminium hydride (1 M sol. in Toluene, 5 mL, 5.26 mmol) dropwise for 5 min at -25 °C; warmed to RT and stirred for 3 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was cooled to 0 °C, quenched with saturated sodium potassium tartrate solution (10 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude, which was titrated with MeOH: diethyl ether (1: 4, 5 mL) to afford **474-A** (300 mg, 66%) as an off-white solid. **TLC:** 70% EtOAc/ hexanes (*R_f*: 0.4); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 10.66 (s, 1H), 7.67 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.55-7.38 (m, 4H), 7.19 (s, 1H), 7.07 (dd, *J* = 7.9, 1.7 Hz, 1H), 5.26 (t, *J* = 5.7 Hz, 1H), 4.44 (d, *J* = 5.6 Hz, 2H); **LC-MS:** 97.26%; 257.8 (*M*⁺+1); (column; Ascentis Express C18, (50 × 3.0 mm, 2.7 μm); RT 1.94 min. 0.025% Aq. TFA + 5% ACN: ACN +; 5% 0.025% Aq. TFA, 1.2 mL/min); **UPLC (purity):** 96.65%; (column; Acquity BEH C-18 (50 x 2.1 mm, 1.7 μ); RT 1.80 min. ACN: 0.025% TFA (Aq); 0.5 mL/min).

[000388] Synthesis of 11-oxo-10, 11-dihydrodibenzo [b, f] [1, 4] thiazepine-8-carbaldehyde (475): To a stirred solution of compound **474-A** (60 mg, 0.23 mmol) in CH₂Cl₂ (5 mL) under argon atmosphere was added Dess-Martin periodinane (300 mg, 0.70 mmol) at 0 °C; warmed to RT and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with CH₂Cl₂ (50 mL) and washed with saturated hypo solution (20 mL). The organic extract was dried over sodium sulfate, filtered and concentrated *in vacuo* to

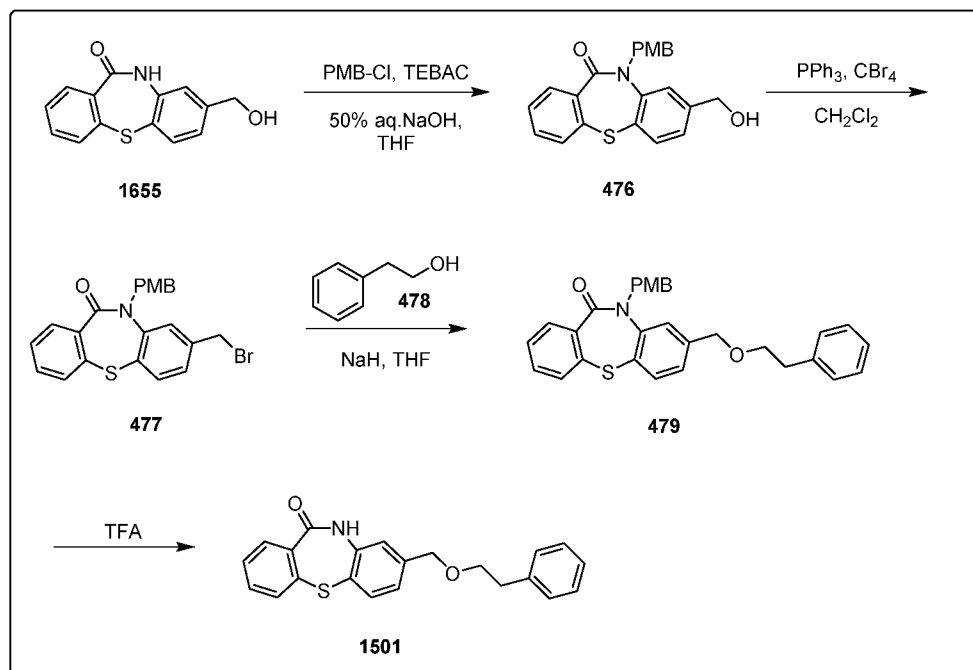
obtain the crude. The crude was purified using silicagel column chromatography using 30% EtOAc/ hexanes to afford compound **475** (41 mg, 68%) as an off-white solid. **TLC:** 70% EtOAc/ hexanes (R_f : 0.8); **^1H NMR (DMSO- d_6 , 400 MHz):** δ 10.89 (s, 1H), 9.96 (s, 1H), 7.81 (d, J = 7.6 Hz, 1H), 7.73-7.66 (m, 3H), 7.59-7.45 (m, 3H).

[000389] Synthesis of 8-((phenethylamino) methyl) dibenzo [*b,f*] [1, 4] thiazepin-11(10*H*)-one (1357): To a stirred solution of compound **475** (100 mg, 0.39 mmol) in MeOH (4 mL) under argon atmosphere were added 2-phenylethan-1-amine **211** (57 mg, 0.47 mmol) and acetic acid (1 mL) at RT and stirred for 1 h. To this was added sodium cyanoborohydride (72 mg, 1.16 mmol) at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with water with EtOAc (100 mL), washed with saturated sodium bicarbonate solution (20 mL) and water (20 mL). The organic extract was dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified using silicagel column chromatography using 2% MeOH/ CH_2Cl_2 to afford compound **1357** (25 mg, 18%) as an off-white solid. **TLC:** 100% EtOAc (R_f : 0.3); **^1H NMR (DMSO- d_6 , 400 MHz):** δ 10.65 (s, 1H), 7.67 (dd, J = 7.4, 1.6 Hz, 1H), 7.54-7.39 (m, 4H), 7.28-7.23 (m, 2H), 7.21-7.14 (m, 4H), 7.10 (d, J = 7.2 Hz, 1H), 3.70 (br s, 2H), 2.72 (br s, 4H); **LC-MS:** 95.70%; 361.0 (M^+ +1); (column; X-select CSH C18, (50 × 3.0 mm, 3.5 μm); RT 2.65 min. 0.05% Aq. TFA: ACN; 0.8 mL/min); **UPLC (purity):** 95.01%; (column; Acquity BEH C-18 (50 × 2.1 mm, 1.7 μm); RT 1.87 min. ACN: 0.025% TFA (Aq); 0.5 mL/min).

[000390] Synthesis of *N*-((11-oxo-10, 11-dihydrodibenzo [*b,f*] [1, 4] thiazepin-8-yl) methyl)-*N*-phenethyl acetamide (1367): To a stirred solution of compound **1357** (40 mg, 0.11 mmol) in CH_2Cl_2 (2 mL) under argon atmosphere were added pyridine (0.013 mL, 0.16 mmol), acetic anhydride (0.011 mL, 0.12 mmol) at 0-5 °C; warmed to RT and stirred for 2 h. The reaction was monitored by TLC; after completion the reaction, the reaction mixture was diluted with CH_2Cl_2 (20 mL) washed with 1 N HCl (5 mL) and brine (10 mL). The organic extract was dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 5% EtOAc/ hexanes to afford **1367** (25 mg, 57%) as an off-white solid. **TLC:** 70% EtOAc/ hexanes (R_f : 0.8); **^1H NMR (DMSO- d_6 , 500 MHz):** δ 10.62-10.60 (m, 1H), 7.67-7.64 (m, 1H), 7.57-7.38 (m, 4H), 7.29-6.94 (m, 7H), 4.45 (d,

$J = 9.8$ Hz, 2H), 3.41-3.35 (m, 2H), 2.82-2.66 (m, 2H), 1.97-1.87 (m, 3H); **LC-MS**: 92.67%; 403.5 ($M^+ + 1$); (column; X-select CSH C18, (50 × 3.0 mm, 3.5 μ m); RT 4.37 min. 5 mM Aq.NH₄OAc: ACN; 0.8 mL/min); **UPLC (purity)**: 93.63%; (column; Acquity BEH C-18 (50 × 2.1 mm, 1.7 μ m); RT 2.41 min. ACN: 0.025% TFA (Aq); 0.5 mL/min).

Example 36: Synthesis of Compound 1501



[000391] Synthesis of 8-(hydroxymethyl)-10-(4-methoxybenzyl) dibenzo [b, f] [1, 4]

thiazepin-11(10H)-one (476): To a stirred solution of **1655** (1 g, 3.89 mmol) in THF (50 mL) were added Benzyltriethylammonium chloride (88 mg, 0.38 mmol), 50% aqueous sodium hydroxide solution (4 mL) at 0-5 °C and stirred for 20 min. To this was added 4-methoxybenzyl chloride (0.52 mL, 3.89 mmol) at 0-5 °C and heated to reflux for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with ice water (40 mL) and extracted with EtOAc (2 × 100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified using silica gel column chromatography using 2% MeOH/ CH₂Cl₂ to afford compound **476** (800 mg, 57%) as white solid. **TLC**: 5% MeOH/ CH₂Cl₂ (R_f : 0.6); **¹H NMR (DMSO-*d*₆, 500 MHz)**: δ 7.64-7.59 (m, 1H), 7.53 (s, 1H), 7.51-7.44 (m, 2H), 7.41-7.35 (m, 2H), 7.22 (d, $J = 8.7$ Hz, 2H), 7.06 (d, $J = 7.8$ Hz, 1H), 6.81 (d, $J = 8.7$ Hz, 2H), 5.67 (d, $J = 15.3$ Hz, 1H), 5.21 (

br s, 1H), 4.85 (d, $J = 15.3$ Hz, 1H), 4.41 (s, 2H), 3.68 (s, 3H).

[000392] Synthesis of 8-(bromomethyl)-10-(4-methoxybenzyl) dibenzo [*b*, *f*] [1, 4] thiazepin-11(10*H*)-one (477):

To a stirred solution of compound **476** (800 mg, 2.12 mmol) in CH_2Cl_2 (20 mL) under argon atmosphere were added triphenyl phosphine (1.1 g, 4.24 mmol), CBr_4 (0.3 mL, 3.18 mmol) at 0 °C; warmed to RT and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 50% EtOAc/ hexanes to afford compound **477** (600 mg, 66%) as an off-white solid. **TLC:** 5% MeOH/ CH_2Cl_2 (R_f : 0.8); **^1H NMR (DMSO- d_6 , 500 MHz):** δ 7.73 (s, 1H), 7.63 (dd, $J = 7.1, 1.9$ Hz, 1H), 7.53-7.44 (m, 2H), 7.43-7.36 (m, 2H), 7.22-7.15 (m, 3H), 6.79 (d, $J = 8.7$ Hz, 2H), 5.77-5.71 (m, 1H), 4.80 (d, $J = 15.0$ Hz, 1H), 4.60 (s, 2H), 3.67 (s, 3H).

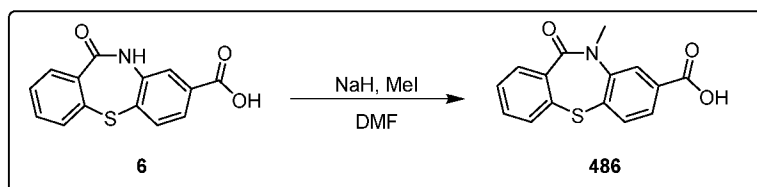
[000393] Synthesis of 10-(4-methoxybenzyl)-8-(phenethoxymethyl)dibenzo [*b*, *f*] [1, 4] thiazepin-11(10*H*)-one (479):

To a stirred solution of 2-phenylethan-1-ol **477** (100 mg, 0.81 mmol) in THF (10 mL) inert atmosphere was added sodium hydride (60%, 49 mg, 2.5 mmol) under portion wise for 5 min at 0 °C; warmed to RT and stirred for 2 h. To this was added compound **478** (359 mg, 0.81 mmol) at RT; heated to 65 °C and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with ice-cold water (20 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude compound **479** (150 mg) as yellow solid. **TLC:** 70% EtOAc/ hexanes (R_f : 0.5); **LC-MS:** 58.75%; 482.0 ($\text{M}^+ + 1$); (column; Ascentis Express C18, (50 x 3.0 mm, 2.7 μm); RT 3.25 min. 0.025% Aq. TFA + 5% ACN: ACN +; 5% 0.025% Aq. TFA, 1.2 mL/min).

[000394] Synthesis of 8-(phenethoxymethyl) dibenzo [*b*, *f*] [1, 4] thiazepin-11(10*H*)-one (1501): A mixture of compound **479** (140 mg, crude) and trifluoro acetic acid (2 mL) under inert atmosphere at RT was heated to 80 °C and stirred for 6 h in a sealed tube. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*, the residue was quenched with 20% aqueous sodium bicarbonate solution (10 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts was dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified using silicagel column

chromatography using 70% EtOAc/ hexanes to afford compound **1501** (35 mg, 33%) as white solid. **TLC:** 70% EtOAc/ hexanes (R_f : 0.4); **^1H NMR (DMSO- d_6 , 400 MHz):** δ 10.65 (s, 1H), 7.67 (dd, J = 7.5, 1.6 Hz, 1H), 7.54-7.40 (m, 4H), 7.29-7.13 (m, 6H), 7.04 (dd, J = 7.9, 1.7 Hz, 1H), 4.44 (s, 2H), 3.63 (t, J = 6.9 Hz, 2H), 2.84 (t, J = 6.9 Hz, 2H); **LC-MS:** 96.49%; 361.9 (M^+ +1); (column; Ascentis Express C18, (50 $\times$ 3.0 mm, 2.7 μm); RT 2.79 min. 0.025% Aq. TFA + 5% ACN: ACN +; 5% 0.025% Aq. TFA, 1.2 mL/min); **HPLC (purity):** 96.59%; (column; Eclipse XDB-C-18 (150 $\times$ 4.6 mm, 5.0 μm); RT 10.25 min. ACN: 0.025% TFA (Aq); 1.0 mL/min).

Example 37: Synthesis of 10-methyl-11-oxo-10, 11-dihydrodibenzo [b, f] [1, 4] thiazepine-8-carboxylic acid (486) - a common intermediate



[000395] To a stirred solution of compound **6** (500 mg, 1.84 mmol) in DMF (10 mL) was added sodium hydride (60%, 442 mg, 18.45 mmol) under inert atmosphere at 0 °C and stirred for 1 h. To this was methyl iodide (1.14 mL, 18.45 mmol) at 0-5 °C, warmed to RT and stirred for 1.5 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (20 mL) and washed with EtOAc (2 $\times$ 20 mL). The aqueous layer was separated and the pH was adjusted to $\sim$ 2 with 4 N HCl. The precipitated solid was filtered, washed with *n*-hexane (10 mL) and dried *in vacuo* to obtain the compound **486** (400 mg, 76%) a white solid. **TLC:** 10% MeOH/ CH_2Cl_2 (R_f : 0.2); **^1H -NMR (DMSO- d_6 , 500 MHz):** δ 13.31 (br s, 1H), 7.99 (s, 1H), 7.75-7.68 (m, 2H), 7.65-7.61 (m, 1H), 7.54-7.49 (m, 1H), 7.44-7.39 (m, 2H), 3.53 (s, 3H).

Example 38: Synthesis of compounds from compound 486 and various commercially available amines

[000396] Compound **486** was converted to final products using commercially available amines or by employing Procedure A and the results are captured in the Table 2:

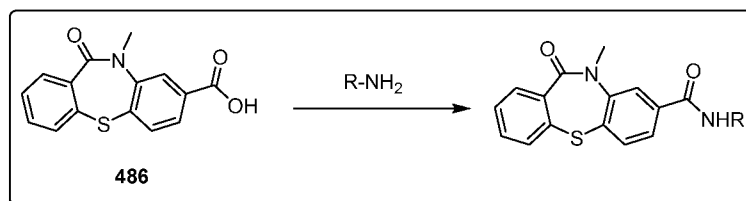
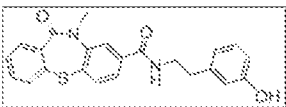
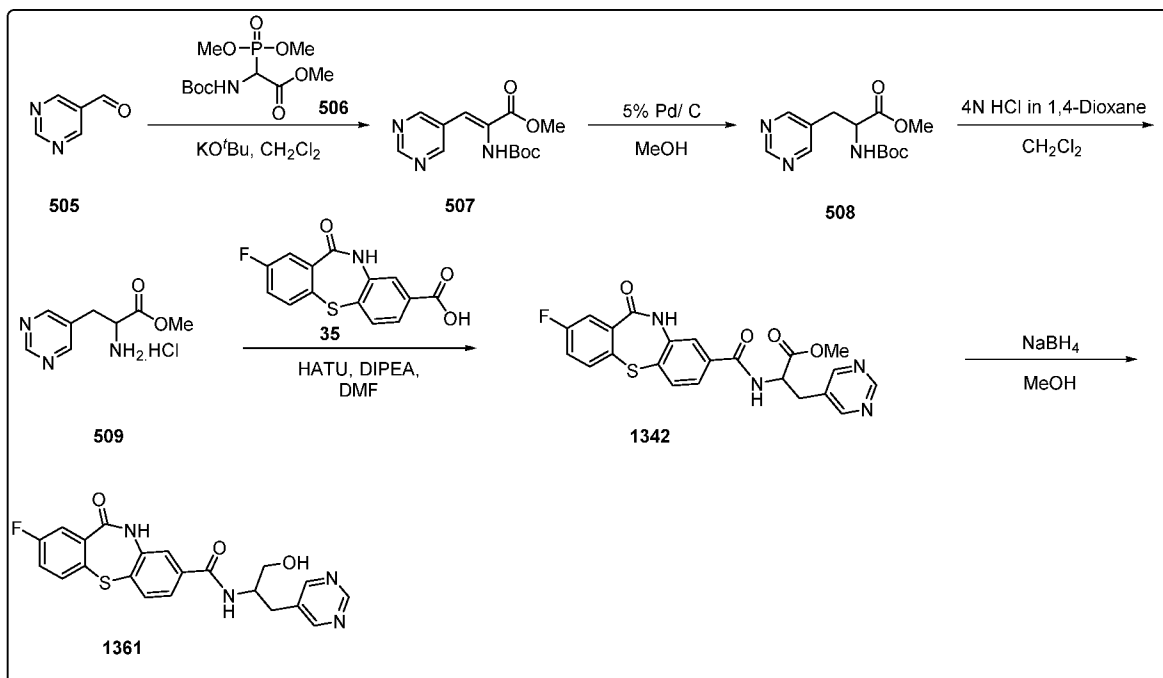


Table 2: Synthesis of compounds from compound 486 and various commercially available amines

No.	Structure	Procedure, Intermediate, Amine	Rx. Yield (%)	Mass Spec. Found	Mass Spec. Calculated	¹ H-NMR
1573		A, 486, 213	36	382.0 (M ⁺ +1)	381.06 for C ₁₉ H ₁₅ N ₃ O ₂ S ₂	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 9.27 (t, <i>J</i> = 5.7 Hz, 1H), 8.96 (s, 1H), 7.96 (s, 1H), 7.82 (s, 1H), 7.74-7.70 (m, 1H), 7.68-7.61 (m, 2H), 7.54-7.49 (m, 1H), 7.45-7.38 (m, 2H), 4.67 (t, <i>J</i> = 5.4 Hz, 2H), 3.54 (s, 3H);
1553		A, 486, 218	30	376.1 (M ⁺ +1)	375.10 for C ₂₁ H ₁₇ N ₃ O ₂ S	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 9.16 (t, <i>J</i> = 5.7 Hz, 1H), 8.54 (s, 1H), 8.45 (dd, <i>J</i> = 4.6, 1.3 Hz, 1H), 7.98 (s, 1H), 7.75-7.61 (m, 4H), 7.55-7.49 (m, 1H), 7.46-7.38 (m, 2H), 7.33 (dd, <i>J</i> = 7.3, 4.8 Hz, 1H), 4.55-4.41 (m, 2H), 3.55 (s, 3H);
1574		A, 486, 212	36	376.9 (M ⁺ +1);	376.10 for C ₂₀ H ₁₆ N ₄ O ₂ S	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 9.19 (t, <i>J</i> = 5.7 Hz, 1H), 9.08 (s, 1H),

						8.76 (s, 2H), 7.98 (s, 1H), 7.73 (d, $J = 8.4$ Hz, 1H), 7.68- 7.60 (m, 2H), 7.55-7.49 (m, 1H), 7.46-7.38 (m, 2H), 4.57 - 4.39 (m, 2H), 3.55 (s, 3H);
1133		D, 486	70	405.127 2	405.1273 for $C_{23}H_{21}N_2O_3$ S	1H NMR (400 MHz, DMSO- d_6) δ 9.25 (s, 1H), 8.63 (t, $J =$ 5.6 Hz, 1H), 7.88 (d, $J = 1.8$ Hz, 1H), 7.73 - 7.56 (m, 3H), 7.55 - 7.47 (m, 1H), 7.47 - 7.36 (m, 2H), 7.05 (t, $J = 7.7$ Hz, 1H), 6.60 (td, $J = 9.2,$ 7.1 Hz, 3H), 3.53 (s, 3H), 3.46 - 3.38 (m, 2H), 2.71 (t, $J =$ 7.4 Hz, 2H).

Example 39: Synthesis of Compounds 1342 and 1361

[000397] Synthesis of methyl (Z)-2-((tert-butoxycarbonyl) amino)-3-(pyrimidin-5-yl)acrylate (507): To a stirred solution of methyl 2-((tert-butoxycarbonyl) amino)-2-(dimethoxyphosphoryl) acetate **506** (3.3 g, 11.11 mmol) in CH_2Cl_2 (15 mL) under inert atmosphere was added potassium *t*-butoxide (13.8 mL, 13.88 mmol, 1M solution in THF), portion wise for 15 min at -30°C . To this was added pyrimidine-5-carbaldehyde **505** (1 g, 9.25 mmol) in CH_2Cl_2 (5 mL) drop wise for 10 min at -30°C , stirred for 2 h; warmed to 0°C and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (50 mL) and extracted with CH_2Cl_2 (2 x 100 mL). The combined organic extracts were washed with water (100 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 50% EtOAc/ hexanes to afford compound **507** (1.8 g, 72%) as an off-white solid. **TLC:** 70% EtOAc/ hexanes (R_f : 0.8); **^1H NMR (500MHz, DMSO- d_6):** δ 9.11 (s, 1H), 9.02 (brs, 1H), 8.98 (s, 2H), 6.46 (s, 1H), 3.76 (s, 3H), 1.42-1.38 (m, 9H).

[000398] Synthesis of methyl 2-((tert-butoxycarbonyl) amino)-3-(pyrimidin-5-yl)propanoate (508): To a stirred solution of compound **507** (1.8 g, 6.45 mmol) in MeOH (25 mL) under inert atmosphere was added 5% Pd/C (500 mg) at RT and stirred under hydrogen

atmosphere (at 100 psi) for 16 h in a steel bomb. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered through celite and washed with 10% MeOH/ CH₂Cl₂ (2 x 50 mL). The filtrate was concentrated *in vacuo* to obtain the crude compound **508** (1.3 g, 72%) as colorless syrup. **TLC:** 5% MeOH/ CH₂Cl₂ (*R_f*: 0.5); **¹H NMR (DMSO-*d*₆, 500 MHz):** δ 9.03 (s, 1H), 8.68 (s, 2H), 7.40 (d, *J* = 7.8 Hz, 1H), 4.33-4.25 (m, 1H), 3.65 (s, 3H), 3.09 (dd, *J* = 14.4, 4.4 Hz, 1H), 2.89-2.81 (m, 1H), 1.33-1.22 (m, 9H).

[000399] Synthesis of methyl 2-amino-3-(pyrimidin-5-yl) propanoate hydrochloride (509):

To a stirred solution of compound **508** (1.3 g, 4.62 mmol) in CH₂Cl₂ (5 mL) under argon atmosphere was added 4 N HCl in 1, 4-dioxane (5 mL) at 0 °C; warmed to RT and stirred for 3.5 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to afford compound **509** (850 mg) as an off-white solid. **TLC:** 5% MeOH/ CH₂Cl₂ (*R_f*: 0.2); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 9.15-9.08 (m, 1H), 8.75 (s, 4H), 4.45-4.44 (m, 1H), 3.73 (s, 3H), 3.22 (dd, *J* = 6.6, 2.4 Hz, 2H).

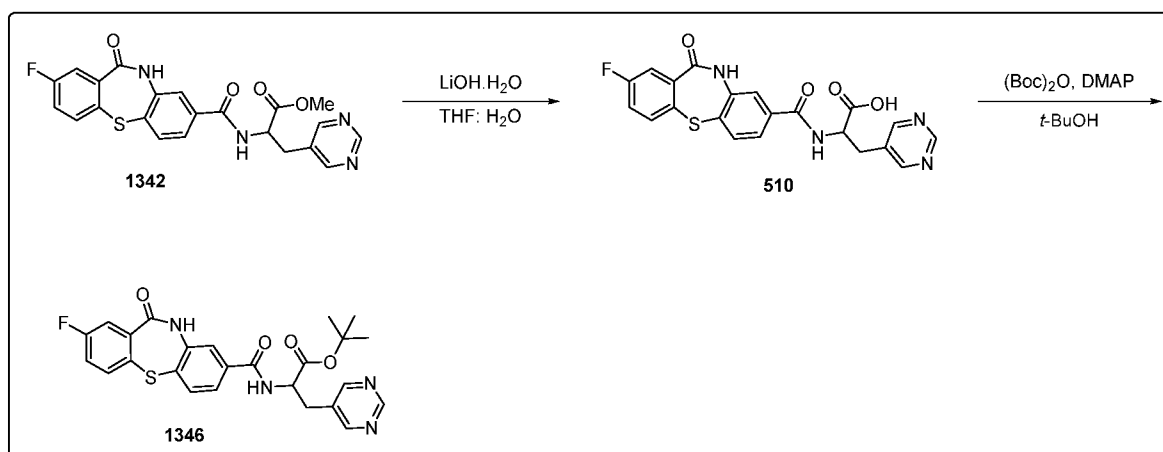
[000400] Synthesis of methyl 2-(2-fluoro-11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4]

thiazepine-8-carboxamido)-3-(pyrimidin-5-yl) propanoate (1342): Using Procedure B the title compound was prepared with compound **35** (200 mg, 0.69 mmol), compound **509** (165 mg, 0.76 mmol) and was obtained in 67% yield as an off-white solid; **TLC:** 5% MeOH/ CH₂Cl₂ (*R_f*: 0.5); **¹H NMR (DMSO-*d*₆, 500 MHz):** δ 10.89 (s, 1H), 8.99 (t, *J* = 4.0 Hz, 2H), 8.69 (s, 2H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.61-7.56 (m, 2H), 7.52 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.46 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.36 (td, *J* = 8.4, 2.9 Hz, 1H), 4.81-4.70 (m, 1H), 3.64 (s, 3H), 3.22 (dd, *J* = 14.2, 4.9 Hz, 1H), 3.05 (dd, *J* = 14.0, 10.6 Hz, 1H); **LC-MS:** 98.59%; 453.4 (M⁺+1); (column; X-select CSH C18, (50 × 3.0 mm, 3.5 μm); RT 3.45 min. 0.05% Aq. TFA: ACN; 0.8 mL/min); **UPLC (purity):** 99.40%; (column; Acquity BEH C-18 (50 x 2.1 mm, 1.7 μ); RT 1.89 min. ACN: 0.025% TFA (Aq); 0.5 mL/min).

[000401] Synthesis of 2-fluoro-*N*-(1-hydroxy-3-(pyrimidin-5-yl) propan-2-yl)-11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxamide (1361): To a stirred solution of **1342** (200 mg, 0.44 mmol) in MeOH (5 mL) under inert atmosphere was added sodium borohydride (65 mg, 1.76 mmol) at 0 °C; warmed to RT and stirred for 6 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was quenched with ice cold water (25

mL) and extracted with 5% MeOH/ CH₂Cl₂ (5 x 25 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 8% MeOH/ CH₂Cl₂ to afford compound **1361** (140 mg, 75%) as an off-white solid. **TLC:** 10% MeOH/ CH₂Cl₂ (*R_f*: 0.4); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 10.87 (s, 1H), 8.96 (s, 1H), 8.64 (s, 2H), 8.30 (d, *J* = 8.7 Hz, 1H), 7.66-7.63 (m, 1H), 7.61-7.57 (m, 2H), 7.53 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.47 (dd, *J* = 9.2, 2.9 Hz, 1H), 7.37 (td, *J* = 8.5, 3.0 Hz, 1H), 4.93 (t, *J* = 5.6 Hz, 1H), 4.22-4.11 (m, 1H), 3.53-3.40 (m, 2H), 2.98 (dd, *J* = 13.9, 4.2 Hz, 1H), 2.73 (dd, *J* = 14.0, 10.1 Hz, 1H); **LC-MS:** 99.82%; 425.4 (*M*⁺+1); (column; X-select CSH C18, (50 × 3.0 mm, 3.5 μm); RT 3.68 min. 0.05% Aq. TFA: ACN; 0.8 mL/min); **UPLC (purity):** 99.77%; (column; Acquity BEH C-18 (50 x 2.1 mm, 1.7 μ); RT 1.65 min. ACN: 0.025% TFA (Aq.); 0.5 mL/min).

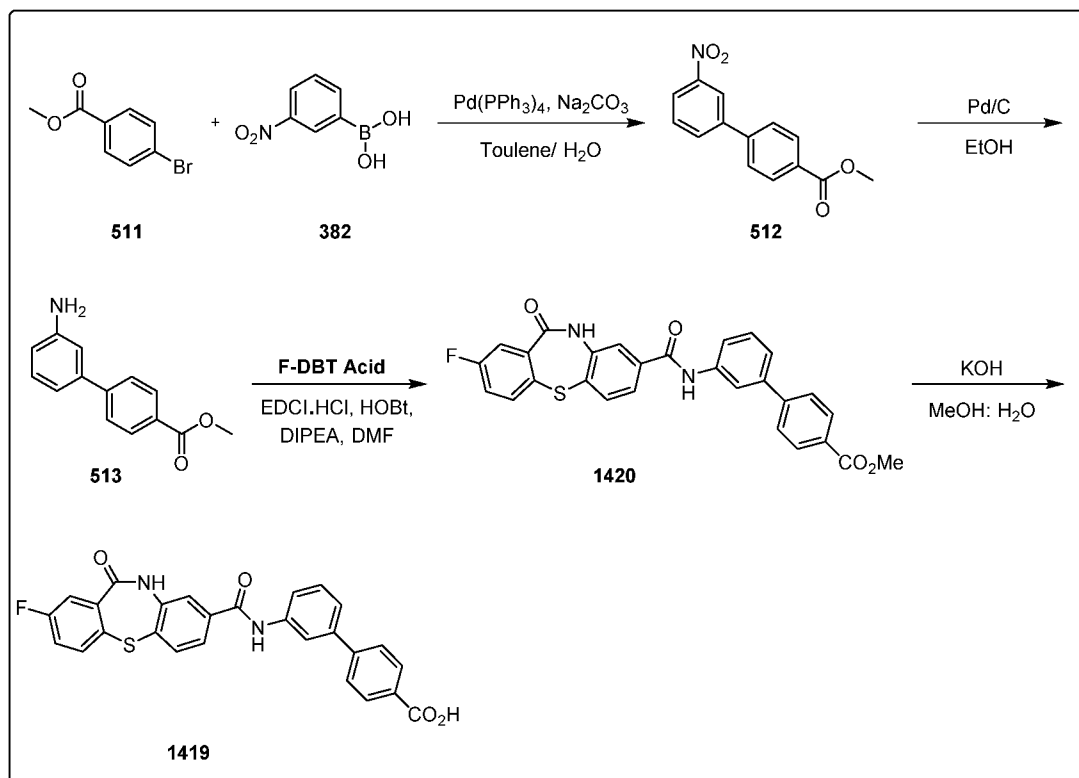
Example 40: Synthesis of Compound 1346



[000402] **Synthesis of 2-(2-fluoro-11-oxo-10,11-dihydrodibenzo [b, f] [1, 4] thiazepine-8-carboxamido)-3-(pyrimidin-5-yl) propanoic acid (510):** To a stirred solution of compound **1342** (150 mg, 0.33 mmol) in a mixture of THF: H₂O (4: 1, 5 mL) was added lithium hydroxide monohydrate (35 mg, 0.82 mmol) at RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with water (3 mL) and the pH was adjusted to ~5 with 1 N HCl. The precipitated solid was filtered and dried *in vacuo* to afford compound **510** (75 mg, 52%) as white solid. **TLC:** 10% MeOH/ CH₂Cl₂ (*R_f*: 0.2); **¹H NMR (DMSO *d*₆, 400 MHz):** δ 10.90 (s, 1H), 8.98 (s, 1H), 8.78 (d, *J* = 7.6 Hz, 1H), 8.68 (s, 2H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.62-7.57 (m, 2H), 7.53 (dd, *J* = 8.1, 1.7

Hz, 1H), 7.47 (dd, $J = 9.2, 2.9$ Hz, 1H), 7.37 (dt, $J = 8.5, 2.9$ Hz, 1H), 7.40-7.34 (m, 1H), 4.69-4.58 (m, 1H), 3.23 (dd, $J = 14.1, 4.6$ Hz, 1H), 3.03 (dd, $J = 14.0, 10.3$ Hz, 1H).

[000403] **Synthesis of *tert*-butyl 2-(2-fluoro-11-oxo-10, 11-dihydrodibenzo [*b, f*] [1, 4] thiazepine-8-carboxamido)-3-(pyrimidin-5-yl) propanoate (1346):** To a stirred solution of compound **510** (70 mg, 0.15 mmol) in *t*-butanol (4 mL) under inert atmosphere were added Boc-anhydride (0.11 mL, 0.47 mmol) and DMAP (30 mg, 0.03 mmol) at 5 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (10 mL) and extracted with CH₂Cl₂ (2 x 25 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through preparative TLC (50% EtOAc/ hexanes) to afford **1346** (25 mg, 32%) as an off-white solid. **TLC:** 70% EtOAc/ hexanes (R_f : 0.4); **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 10.91 (s, 1H), 9.01 (s, 1H), 8.89 (d, $J = 7.8$ Hz, 1H), 8.71 (s, 2H), 7.67 (d, $J = 8.0$ Hz, 1H), 7.64-7.58 (m, 2H), 7.55 (dd, $J = 8.0, 1.9$ Hz, 1H), 7.48 (dd, $J = 9.2, 2.9$ Hz, 1H), 7.38 (td, $J = 8.5, 2.9$ Hz, 1H), 4.65-4.59 (m, 1H), 3.21-3.13 (m, 1H), 3.09-2.99 (m, 1H), 1.39-1.31 (m, 9H); **LC-MS:** 98.60%; 495.6 ($M^+ + 1$); (column; X-select CSH C18, (50 × 3.0 mm, 3.5 μ m); RT 3.91 min. 0.05% Aq. TFA: CAN; 0.8 mL/min); **UPLC (purity):** 98.29%; (column; Acquity BEH C-18 (50 x 2.1 mm, 1.7 μ); RT 2.15 min. CAN: 0.025% TFA (Aq); 0.5 mL/min).

Example 41: Synthesis of Compounds 1420 and 1419

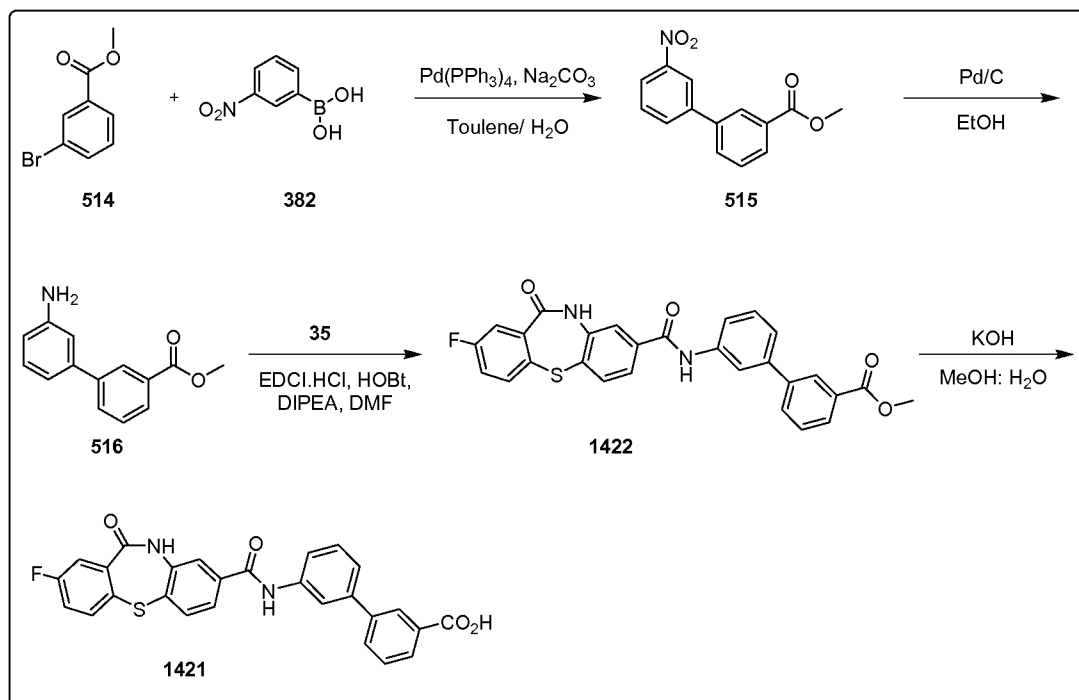
[000404] Synthesis of methyl 3'-nitro-[1, 1'-biphenyl]-4-carboxylate (512): To a stirred solution of methyl 4-bromobenzoate **511** (2.5 g, 14.97 mmol) and (3-nitrophenyl) boronic acid **382** (3.8 g, 17.96 mmol) in Toluene (20 mL) under inert atmosphere were added sodium carbonate (3.17 g, 29.96 mmol in 25 mL of H₂O) at RT and purged under argon atmosphere for 20 min. To this was added $\text{Pd(PPh}_3)_4$ (691 mg, 0.59 mmol) and heated to 80 °C for 5 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with EtOAc (200 mL). The organic extract was dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 10% EtOAc/ hexanes to afford compound **512** (800 mg, 21%) as yellow liquid. **TLC:** 15% EtOAc/ hexanes (R_f : 0.5); **¹H NMR (400 MHz, CD₃OD):** δ 8.54-8.52 (m, 1H), 8.29-8.26 (m, 1H), 8.15 (d, J = 8.7 Hz, 2H), 8.12-8.09 (m, 1H), 7.84 (d, J = 8.6 Hz, 2H), 7.74 (t, J = 8.0 Hz, 1H), 3.94 (s, 3H).

[000405] Synthesis of methyl 3'-amino-[1, 1'-biphenyl]-4-carboxylate (513): To a stirred solution of compound **512** (800 mg, 3.11 mmol) in EtOH (50 mL) under inert atmosphere was

added 10% Pd/C (500 mg, wet) under argon atmosphere and stirred under H₂ atmosphere (balloon pressure) for 5 h. After completion of the reaction, the reaction mixture was filtered through celite, washed with 50% MeOH/ CH₂Cl₂ (150 mL). The filtrate was concentrated *in vacuo* to obtain the crude which was purified through silicagel column chromatography in 5% MeOH/ CH₂Cl₂ to afford compound **513** (600 mg, 67%) as an off-white solid. The crude was carried for next step without further purification. **TLC**: 5% MeOH/ CH₂Cl₂ (*R_f*: 0.4).

[000406] Synthesis of methyl 3'-(2-fluoro-11-oxo-10, 11-dihydrodibenzo [*b, f*] [1, 4] thiazepine-8-carboxamido)-[1, 1'-biphenyl]-4-carboxylate (1420): Using Procedure A the title compound was prepared with **35** (50 mg, 0.17 mmol), compound **513** (43 mg, 0.19 mmol) and was obtained in 58% yield as white solid; **TLC**: 5% MeOH/ CH₂Cl₂ (*R_f*: 0.5); **¹H NMR (DMSO-*d*₆, 400 MHz)**: δ 10.99 (s, 1H), 10.43 (s, 1H), 8.14 (s, 1H), 8.07 (d, *J* = 7.9 Hz, 2H), 7.85-7.72 (m, 6H), 7.63 (dd, *J* = 8.6, 5.3 Hz, 1H), 7.54-7.45 (m, 3H), 7.40 (td, *J* = 8.5, 3.0 Hz, 1H), 3.88 (s, 3H); **LC-MS**: 98.86%; 498.1 (*M*⁺+1); (column; X-select CSH C18, (50 × 3.0 mm, 3.5 μm); RT 4.15 min. 0.05% Aq. TFA: ACN; 0.8 mL/min); **UPLC (purity)**: 95.09%; (column; Acquity BEH C-18 (50 x 2.1 mm, 1.7 μ); RT 2.75 min. ACN : 0.025% TFA (Aq); 0.5 mL/min).

[000407] Synthesis of 3'-(2-fluoro-11-oxo-10, 11-dihydrodibenzo [*b, f*] [1, 4] thiazepine-8-carboxamido)-[1, 1'-biphenyl]-4-carboxylic acid (1419): To a stirred solution of **1420** (50 mg, 0.10 mmol) in MeOH: H₂O (3:1, 8 mL) was added potassium hydroxide (56 mg, 1.00 mmol) at RT in a sealed tube and heated to 90 °C and stirred for 5 h. The reaction was monitored by TLC; after completion of the reaction, the pH of the reaction mixture was acidified with 4 N HCl to pH ~2. The obtained solid was filtered, triturated with 10% EtOAc/ hexanes (10 mL) and dried *in vacuo* and to afford compound **1419** (20 mg, 41%) as an off-white solid. **TLC**: 70% EtOAc/ hexanes (*R_f*: 0.2); **¹H NMR (400 MHz, DMSO-*d*₆)**: δ 12.98 (br s, 1H), 11.00 (s, 1H), 10.51 (s, 1H), 8.15 (s, 1H), 8.04 (d, *J* = 8.4 Hz, 2H), 7.87-7.70 (m, 6H), 7.63 (dd, *J* = 8.6, 5.3 Hz, 1H), 7.54-7.46 (m, 3H), 7.40 (td, *J* = 8.5, 2.9 Hz, 1H); **LC-MS**: 91.15%; 485.0 (*M*⁺+1); (column; Ascentis Express C18, (50 × 3.0 mm, 2.7 μm); RT 2.48 min. 0.025% Aq. TFA + 5% ACN: ACN + 5% 0.025% Aq. TFA, 1.2 mL/min); **UPLC (purity)**: 93.75%; (column; Acquity BEH C-18 (50 x 2.1 mm, 1.7 μ); RT 2.43 min. ACN : 0.025% TFA (Aq); 0.5 mL/min).

Example 42: Synthesis of Compounds 1422 and 1421

[000408] Synthesis of methyl 3'-nitro-[1, 1'-biphenyl]-3-carboxylate (515): To a stirred solution of methyl 3-bromobenzoate **514** (2.5 g, 14.99 mmol) and (3-nitrophenyl) boronic acid **382** (3.8 g, 17.99 mmol) in toluene (20 mL) under inert atmosphere were added sodium carbonate (3.17 g, 29.99 mmol in 20 mL of H₂O) at RT and purged under argon atmosphere for 20 min. To this was added Pd(PPh₃)₄ (693 mg, 0.59 mmol) and heated to 80 °C for 5 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with EtOAc (200 mL). The organic extract was dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 10% EtOAc/ hexanes to afford compound **515** (1 g, 26%) as yellow liquid. **TLC:** 15% EtOAc/ hexanes (*R_f*: 0.5); **¹H NMR (400 MHz, DMSO-*d*₆):** δ 8.48-8.46 (m, 1H), 8.30-8.25 (m, 2H), 8.22-8.18 (m, 1H), 8.11-8.07 (m, 1H), 8.04 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.80 (t, *J* = 8.0 Hz, 1H), 7.69 (t, *J* = 7.8 Hz, 1H), 3.91 (s, 3H).

[000409] Synthesis of methyl 3'-amino-[1, 1'-biphenyl]-3-carboxylate (516): To a stirred solution of compound **515** (1 g, 3.89 mmol) in EtOH (100 mL) under inert atmosphere was added 10% Pd/C (600 mg, wet) under argon atmosphere and stirred under H₂ atmosphere

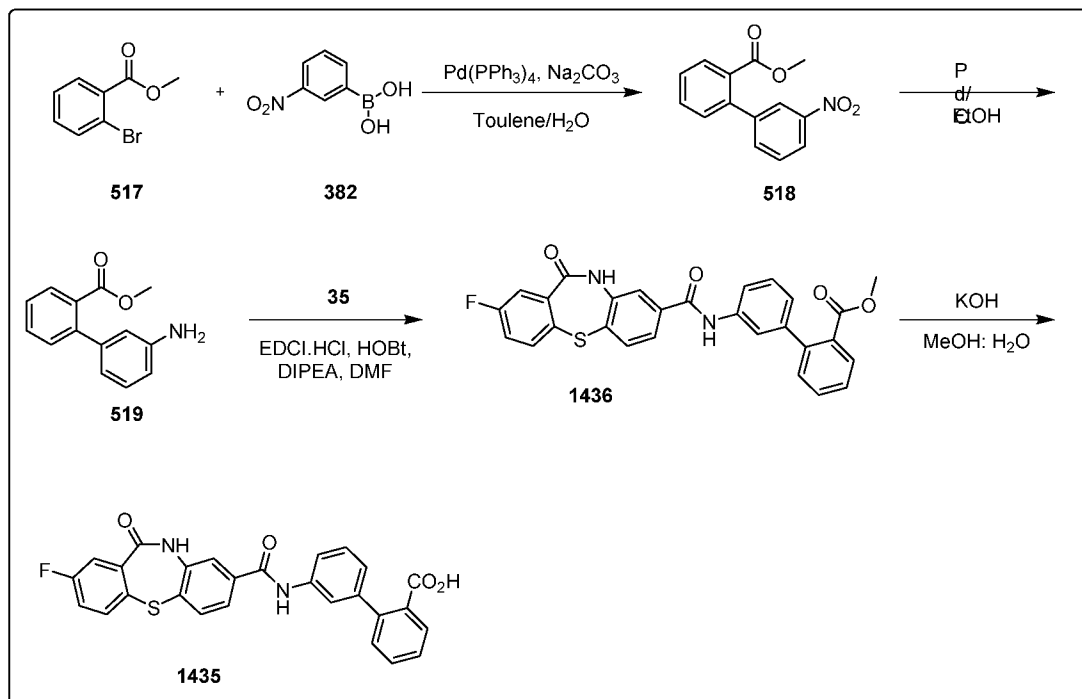
(balloon pressure) for 16 h. After completion of the reaction, the reaction mixture was filtered through celite and the celite pad was washed with 50% MeOH/ CH₂Cl₂ (150 mL). The filtrate was evaporated *in vacuo* to obtain the crude which was purified through silicagel column chromatography in 20% EtOAc/ hexanes to afford compound **516** (600 mg, 67%) as an off-white solid. **TLC:** 40% EtOAc/ hexanes (*R_f*: 0.3); **¹H NMR (400 MHz, DMSO-*d*₆):** δ 8.15- 8.08 (m, 1H), 7.92 (d, *J* = 7.7 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.59 (t, *J* = 7.7 Hz, 1H), 7.13 (t, *J* = 7.8 Hz, 1H), 6.90-6.87 (m, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 6.60 (dd, *J* = 8.0, 1.4 Hz, 1H), 5.22 (s, 2H), 3.32 (s, 3H).

[000410] Synthesis of methyl 3'-(2-fluoro-11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxamido)-[1, 1'-biphenyl]-3-carboxylate (1422): Using Procedure A the title compound was prepared with compound **35** (70 mg, 0.24 mmol), compound **516** (55 mg, 0.24 mmol) and was obtained in 41% yield as white solid; **TLC:** 5% MeOH/ CH₂Cl₂ (*R_f*: 0.5); **¹H NMR (400 MHz, DMSO-*d*₆):** δ 10.99 (s, 1H), 10.43 (s, 1H), 8.12-8.19 (m, 1H), 8.10-8.08 (m, 1H), 7.96 (dd, *J* = 12.8, 7.9 Hz, 2H), 7.85 (dt, *J* = 7.1, 1.8 Hz, 1H), 7.81-7.73 (m, 3H), 7.69-7.59 (m, 2H), 7.54-7.45 (m, 3H), 7.40 (td, *J* = 8.5, 2.9 Hz, 1H), 3.90 (s, 3H); **LC-MS:** 99.82%; 499.0 (M+1)⁺; (column; X-select CSH C18, (50 × 3.0 mm, 3.5 μm); RT 4.10 min. 0.05% Aq. TFA: ACN; 0.8 mL/min); **UPLC (purity):** 98.72%; (column; Acquity BEH C-18 (50 x 2.1 mm, 1.7 μ); RT 2.78 min. ACN : 0.025% TFA (Aq); 0.5 mL/min).

[000411] Synthesis of 3'-(2-fluoro-11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxamido)-[1, 1'-biphenyl]-3-carboxylic acid (1421): To a stirred solution of **1422** (35 mg, 0.07 mmol) in MeOH: H₂O (3:1, 5 mL) under inert atmosphere was added potassium hydroxide (40 mg, 0.70 mmol) at RT in a sealed tube and heated to 80 °C and stirred for 3 h. The reaction was monitored by TLC; after completion of the reaction, the pH of the reaction mixture was acidified with 4 N HCl to pH ~2 and extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The obtained solid was filtered, dried *in vacuo* and triturated with 10% EtOAc/ hexanes (10 mL) to afford compound **1421** (20 mg, 58%) as white solid. **TLC:** 70% EtOAc/ hexanes (*R_f*: 0.2); **¹H NMR (400 MHz, DMSO-*d*₆):** δ 12.99 (br s, 1H), 10.98 (s, 1H), 10.43 (s, 1H), 8.21-8.19 (m, 1H), 8.11-8.09 (m, 1H), 7.96 (d, *J* = 7.7 Hz, 1H), 7.87 (dd, *J* = 19.5, 7.3 Hz, 2H), 7.82-7.73 (m, 3H), 7.66-7.58 (m, 2H), 7.54-7.44 (m, 3H), 7.40 (td, *J* = 8.5, 2.9 Hz, 1H); **LC-MS:** 99.07%;

484.9 ($M^+ + 1$); (column; X-select CSH C18, (50 × 3.0 mm, 3.5 μ m); RT 3.73 min. 0.05% Aq. TFA: ACN; 0.8 mL/min); **UPLC (purity):** 96.90%; (column; Acquity BEH C-18 (50 × 2.1 mm, 1.7 μ); RT 2.46 min. ACN : 0.025% TFA (Aq); 0.5 mL/min).

Example 43: Synthesis of Compounds 1436 and 1435



[000412] Synthesis of methyl 3'-nitro-[1, 1'-biphenyl]-2-carboxylate (518): To a stirred solution of methyl 2-bromobenzoate **517** (2.5 g, 14.97 mmol) and (3-nitrophenyl) boronic acid **382** (3.8 g, 17.96 mmol) in toluene (20 mL) under inert atmosphere were added sodium carbonate (3.17 g, 29.94 mmol in 20 mL of H_2O) at RT and purged under argon atmosphere for 20 min. To this was added $\text{Pd(PPh}_3)_4$ (691 mg, 0.59 mmol) and heated to 80 °C for 6 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with EtOAc (200 mL). The organic extract was dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 15% EtOAc/ hexanes to afford compound **518** (600 mg, 17%) as yellow solid. **TLC:** 30% EtOAc/ hexanes (R_f : 0.6); **$^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$):** δ 8.27-8.23 (m, 1H), 8.11-8.09 (m, 1H), 7.89 (dd, $J = 7.7, 1.3$ Hz, 1H), 7.79-7.67 (m, 3H), 7.59 (td, $J = 7.6, 1.1$ Hz, 1H), 7.52 (dd, $J = 7.6, 0.6$ Hz, 1H), 3.31 (s, 3H).

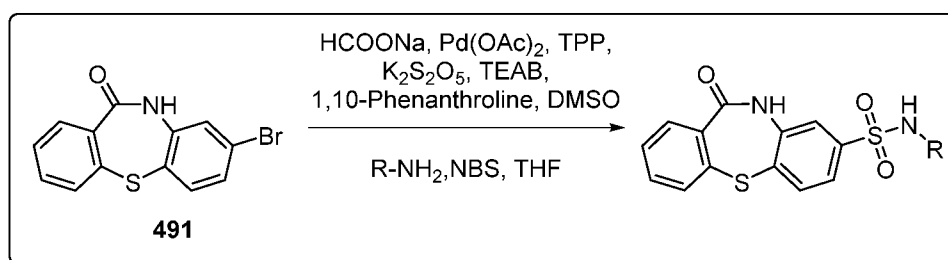
[000413] Synthesis of methyl 3'-amino-[1, 1'-biphenyl]-2-carboxylate (519): To a stirred solution of compound **518** (600 mg, 2.33 mmol) in EtOH (50 mL) under inert atmosphere was added 10% Pd/C (300 mg, wet) under argon atmosphere and stirred under H₂ atmosphere (balloon pressure) for 16 h. After completion of the reaction, the reaction mixture was filtered through celite and the celite pad was washed with 50% MeOH/ CH₂Cl₂ (100 mL). The filtrate was evaporated *in vacuo* to afford compound **519** (500 mg, 87%) as an off-white solid. **TLC:** 30% EtOAc/ hexanes (*R_f*: 0.6); **¹H NMR (400 MHz, DMSO-*d*₆):** δ 7.63 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.56 (td, *J* = 9.0, 1.8 Hz, 1H), 7.43 (td, *J* = 7.6, 1.1 Hz, 1H), 7.37 (dd, *J* = 7.7, 0.8 Hz, 1H), 7.03 (t, *J* = 7.7 Hz, 1H), 6.57-6.52 (m, 1H), 6.52-6.49 (m, 1H), 6.39 (d, *J* = 7.5 Hz, 1H), 5.14 (br s, 2H), 3.59 (s, 3H).

[000414] Synthesis of methyl 3'-(2-fluoro-11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxamido)-[1, 1'-biphenyl]-2-carboxylate (1436): Using Procedure A the title compound was prepared with compound **35** (100 mg, 0.34 mmol), compound **519** (78 mg, 0.34 mmol) and was obtained in 35% yield as white solid; **TLC:** 5% MeOH/ CH₂Cl₂ (*R_f*: 0.5); **¹H NMR (400 MHz, DMSO-*d*₆):** δ 10.97 (s, 1H), 10.37 (s, 1H), 7.78-7.72 (m, 6H), 7.66-7.60 (m, 2H), 7.54-7.48 (m, 2H), 7.46-7.36 (m, 3H), 7.04 (d, *J* = 7.3 Hz, 1H), 3.61 (s, 3H); **LC-MS:** 93.05%; 499.0 (M⁺+1); (column; Ascentis Express C18, (50 × 3.0 mm, 2.7 μm); RT 2.74 min. 0.025% Aq. TFA + 5% ACN: ACN + 5% 0.025% Aq. TFA, 1.2 mL/min); **UPLC (purity):** 91.54%; (column; Acquity BEH C-18 (50 × 2.1 mm, 1.7 μ); RT 2.72 min. ACN : 0.025% TFA (Aq); 0.5 mL/min).

[000415] Synthesis of 3'-(2-fluoro-11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxamido)-[1, 1'-biphenyl]-2-carboxylic acid (1435): To a stirred solution of **1436** (35 mg, 0.07 mmol) in MeOH: H₂O (3:1, 8 mL) was added potassium hydroxide (40 mg, 0.70 mmol) at RT in a sealed tube and heated to 80 °C and stirred for 3 h. The reaction was monitored by TLC; after completion of the reaction, the pH of the reaction mixture was acidified with 4 N HCl to pH ~2 and extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The obtained solid was filtered, triturated with 10% EtOAc/ hexanes (5 mL) and dried *in vacuo* to afford compound **1435** (20 mg, 58%) as white solid. **TLC:** 70% EtOAc/ hexanes (*R_f*: 0.2); **¹H NMR (400 MHz, DMSO-*d*₆):** δ 11.00 (br s, 1H), 10.36 (s, 1H), 7.81-7.69 (m, 5H), 7.67-7.59 (m, 2H), 7.54-7.48

(m, 2H), 7.44-7.31 (m, 4H), 7.07 (d, $J = 7.8$ Hz, 1H); **LC-MS**: 91.40%; 484.9 ($M^+ + 1$); (column; Ascentis Express C18, (50 × 3.0 mm, 2.7 μ m); RT 2.49 min. 0.025% Aq. TFA + 5% ACN: ACN + 5% 0.025% Aq. TFA, 1.2 mL/min); **UPLC (purity)**: 92.47%; (column; Acquity BEH C-18 (50 × 2.1 mm, 1.7 μ); RT 2.36 min. ACN : 0.025% TFA (Aq); 0.5 mL/min).

Example 44: Synthesis of 11-oxo-10, 11-dihydrodibenzo [b, f] [1, 4] thiazepine-8-sulfonamide compounds



[000416] To a stirred solution of compound **491** (80 mg, 0.26 mmol) in DMSO (1.5 mL) under inert atmosphere were added potassium metabisulfate (116 mg, 0.52 mmol), tetraethyl ammonium bromide (60 mg, 0.28 mmol), sodium formate (40 mg, 0.57 mmol), palladium acetate (18 mg, 0.026 mmol) and 1, 10-phenanthroline (14 mg, 0.078 mmol) at RT in a microwave vial and purged under argon atmosphere for 10 min; heated to 90 °C for 4 h. The reaction was monitored by TLC; after completion of the reaction, the crude compound was carried forward to next step. **TLC**: 30% EtOAc/ hexanes (R_f : 0.4).

[000417] The above crude compound and commercially available amines were converted to corresponding sulfonamide employing the Procedure L and the results are captured in the Table 3.

Procedure L:

To a stirred solution of above crude compound (100 mg, crude) in THF (2 mL) under argon atmosphere were added piperidine **521** (0.05 mL, 0.54 mmol) in THF (1 mL), *N*-bromosuccinimide (96 mg, 0.54 mmol) in THF (1 mL) at 0 °C; warmed to RT and stirred for 12 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with brine (20 mL) and extracted with EtOAc (2 × 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude.

The crude was purified through silica gel column chromatography to afford the desired compound.

Commercially available amines used for the preparation of compounds:

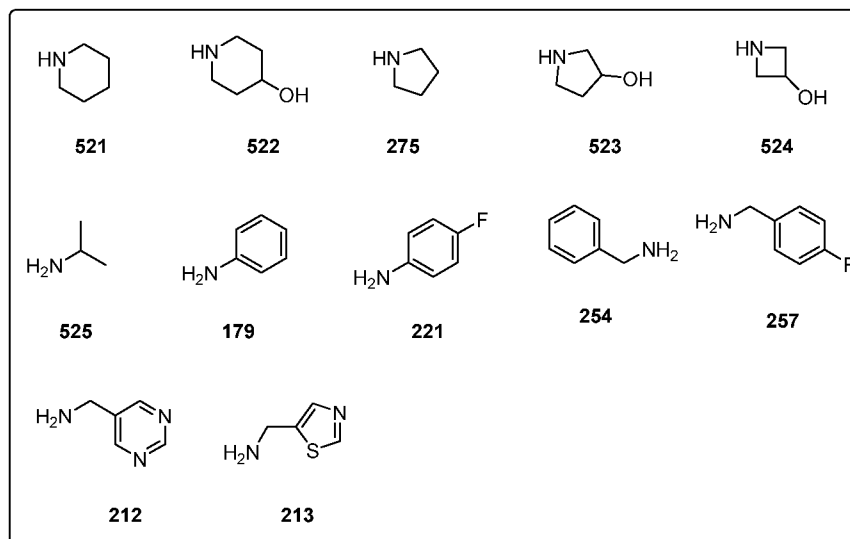
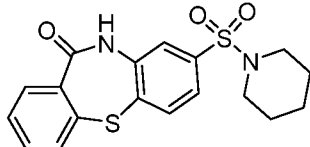
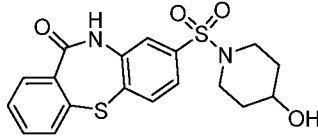
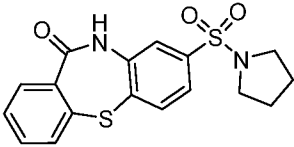
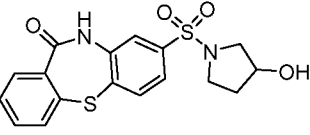
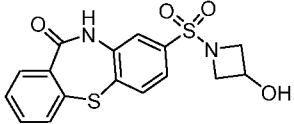
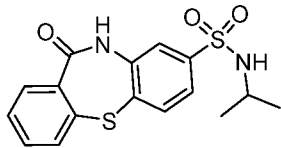
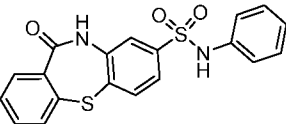
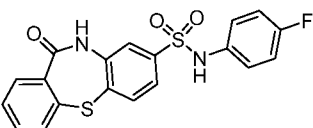
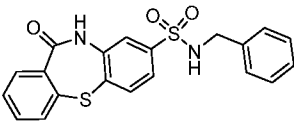
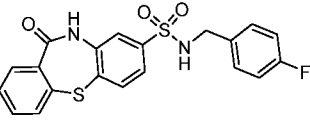
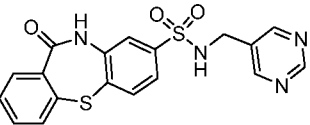


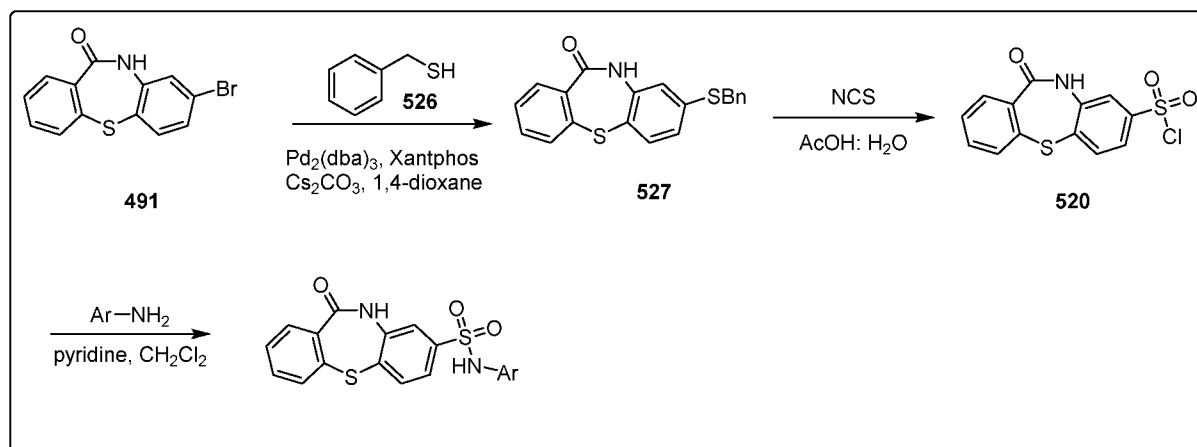
Table 3: Synthesis of compounds from compound 520 and various commercially available amines

No.	Structure	Procedure, Intermediate, Amine	Rx. Yield (%)	Mass Spec. Found	Mass Spec. Calculated	¹ H-NMR
1399		L, 521 (RT 18 h)	15	374.9 (M ⁺ +1)	374.08 for C ₁₈ H ₁₈ N ₂ O 3S ₂	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.86 (s, 1H), 7.80 (d, <i>J</i> = 8.0 Hz, 1H), 7.72 (dd, <i>J</i> = 7.6, 1.4 Hz, 1H), 7.59- 7.55 (m, 2H), 7.54-7.43 (m, 3H), 2.93-2.84 (m, 4H), 1.57- 1.48 (m, 4H), 1.42-1.31 (m, 2H);
1431		L, 522	19	390.9 (M ⁺ +1)	390.07 for C ₁₈ H ₁₈ N ₂ O 4S ₂	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.87 (s, 1H), 7.81 (d, <i>J</i> = 8.2

						Hz, 1H), 7.72 (dd, $J = 7.4, 1.4$ Hz, 1H), 7.60-7.53 (m, 3H), 7.52-7.45 (m, 2H), 4.66 (d, $J = 4.0$ Hz, 1H), 3.53-3.49 (m, 1H), 3.19-3.12 (m, 2H), 2.76-2.69 (m, 2H), 1.77-1.68 (m, 2H), 1.49-1.35 (m, 2H);
1432		L, 275	20	360.8 ($M^+ + 1$)	360.06 for $C_{17}H_{16}N_2O_3S_2$	1H NMR (DMSO- d_6 , 400 MHz): δ 10.85 (s, 1H), 7.79 (d, $J = 8.0$ Hz, 1H), 7.74-7.70 (m, 1H), 7.63 (s, 1H), 7.60-7.45 (m, 4H), 3.16-3.11 (m, 4H), 1.75-1.56 (m, 4H);
1433		L, 523	19	376.9 ($M^+ + 1$)	376.06 for $C_{17}H_{16}N_2O_4S_2$	1H NMR (DMSO- d_6 , 400 MHz): δ 10.83 (s, 1H), 7.78 (d, $J = 8.0$ Hz, 1H), 7.74-7.68 (m, 1H), 7.63 (s, 1H), 7.59-7.45 (m, 4H), 4.86 (d, $J = 3.4$ Hz, 1H), 4.17-4.14 (m, 1H), 3.27-3.18 (m, 3H), 3.10-2.93 (m, 1H), 1.81-1.69 (m, 1H), 1.68-1.58 (m, 1H);
1434		L, 524	20	362.8 ($M^+ + 1$)	362.04 for $C_{16}H_{14}N_2O_4S_2$	1H NMR (DMSO- d_6 , 400 MHz): δ 10.90 (s, 1H), 7.86 (d, $J = 8.2$ Hz, 1H), 7.73 (dd, $J = 7.5, 1.5$ Hz, 1H), 7.64-

						7.62 (m, 1H), 7.60-7.47 (m, 4H), 5.71 (d, $J = 6.3$ Hz, 1H), 4.30-4.22 (m, 1H), 3.89 (dd, $J = 8.5, 6.8$ Hz, 2H), 3.40-3.34 (m, 2H);
1450		L, 525	16	348.9 ($M^{+}+1$)	348.06 for $C_{16}H_{16}N_2O_3S_2$	1H NMR (DMSO- d_6 , 400 MHz): δ 10.89 (s, 1H), 7.77 (d, $J = 8.2$ Hz, 1H), 7.73-7.68 (m, 2H), 7.65-7.63 (m, 1H), 7.57-7.44 (m, 4H), 3.27-3.16 (m, 1H), 0.94 (d, $J = 6.5$ Hz, 6H);
1412		L, 179	15	382.9 ($M^{+}+1$)	382.04 for $C_{19}H_{14}N_2O_3S_2$	1H NMR (DMSO- d_6 , 400 MHz): δ 10.90 (s, 1H), 10.42 (s, 1H), 7.73 (d, $J = 8.2$ Hz, 1H), 7.68 (dd, $J = 6.9, 15.$ Hz, 1H), 7.65-7.63 (m, 1H), 7.55-7.43 (m, 4H), 7.24-7.18 (m, 2H), 7.08-7.04 (m, 2H), 7.01 (t, $J = 7.7$ Hz, 1H);
1413		L, 221	23	400.9 ($M^{+}+1$)	400.04 for $C_{19}H_{13}FN_2O_3S_2$	1H NMR (DMSO- d_6 , 400 MHz): 10.90 (s, 1H), 10.37 (s, 1H), 7.74 (d, $J = 8.3$ Hz, 1H), 7.69 (dd, $J = 6.9, 1.5$ Hz, 1H), 7.60-7.56 (m, 1H), 7.55-7.45 (m, 3H), 7.43 (dd, $J = 8.2, 2.0$ Hz, 1H), 7.09-7.04

						(m, 4H);
1414		L, 254	23	396.9 (M ⁺ +1)	396.06 for C ₂₀ H ₁₆ N ₂ O S ₂	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.83 (s, 1H), 8.28 (t, <i>J</i> = 6.3 Hz, 1H), 7.74 (dd, <i>J</i> = 6.8, 1.5 Hz, 1H), 7.69 (d, <i>J</i> = 8.2 Hz, 1H), 7.59-7.49 (m, 4H), 7.47 (dd, <i>J</i> = 8.2, 2.0 Hz, 1H), 7.15- 7.10 (m, 2H), 7.06 (t, <i>J</i> = 7.4 Hz, 2H), 7.02- 6.96 (m, 1H), 3.99 (d, <i>J</i> = 6.3 Hz, 2H);
1415		L, 257	22	414.9 (M ⁺ +1)	414.05 for C ₂₀ H ₁₅ FN ₂ O ₃ S ₂	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.86 (s, 1H), 8.28 (t, <i>J</i> = 6.2 Hz, 1H), 7.76- 7.67 (m, 2H), 7.63-7.60 (m, 1H), 7.58-7.44 (m, 4H), 7.18 (dd, <i>J</i> = 8.6, 5.6 Hz, 2H), 6.92 (t, <i>J</i> = 8.9 Hz, 2H), 4.04-3.92 (m, 2H);
1473		L, 212	19	399.0 (M ⁺ +1)	398.05 for C ₁₈ H ₁₄ N ₄ O S ₂	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.86 (s, 1H), 8.76 (s, 1H), 8.59 (s, 2H), 8.43 (br s, 1H), 7.78-7.70 (m, 2H), 7.60-7.54 (m, 3H), 7.54- 7.48 (m, 2H), 4.07 (s, 2H);

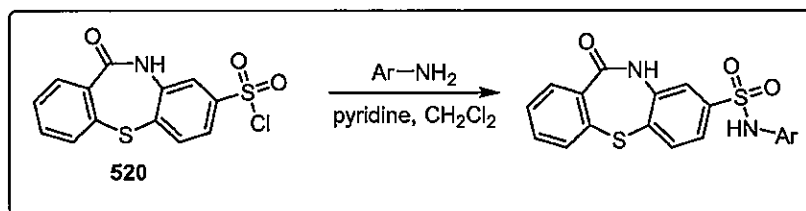
Synthesis of 11-oxo-10, 11-dihydrodibenzo [b, f] [1, 4] thiazepine-8-sulfonyl chloride (520):

[000418] Synthesis of 8-(benzylthio) dibenzo [b, f] [1, 4] thiazepin-11(10H)-one (527): To a stirred solution of compound **491** (1 g, 3.26 mmol) in 1, 4-dioxane (20 mL) under argon atmosphere were added phenylmethanethiol **526** (0.4 mL, 3.59 mmol), CS_2CO_3 (921 mg, 3.92 mmol) at RT, purged under argon atmosphere for 20 min. To this were added $\text{Pd}_2(\text{dba})_3$ (75 mg, 0.081 mmol), Xantphos (94 mg, 1.06 mmol) at RT and heated to 110-120 °C and stirred for 12 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered and the filtrate was removed *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 5-40% EtOAc/ hexanes to afford compound **527** (700 mg, 61%) as pale yellow solid. **TLC:** 30% EtOAc/ hexanes (R_f : 0.4); **^1H NMR (DMSO- d_6 , 400 MHz):** δ 10.63 (s, 1H), 7.68-7.65 (m, 1H), 7.53-7.41 (m, 4H), 7.39-7.34 (m, 2H), 7.32-7.20 (m, 3H), 7.17 (s, 1H), 7.10 (dd, $J = 8.2, 2.1$ Hz, 1H), 4.24 (s, 2H).

[000419] Synthesis of 11-oxo-10, 11-dihydrodibenzo [b, f] [1, 4] thiazepine-8-sulfonyl chloride (520): To a stirred solution of **527** (700 mg, 2.00 mmol) in acetic acid: H_2O (3: 1, 16 mL) under was added *N*-chlorosuccinimide (668 mg, 5.61 mmol) at 0 °C; warmed to RT and stirred for 3 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (100 mL) and extracted with diethyl ether (2 x 100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford crude compound **520** (700 mg) as yellow solid. The crude compound was carried forward for next step without further purification. **TLC:** 20% EtOAc/ hexanes (R_f : 0.6); **LC-MS:** 68.55%; 325.9 ($\text{M}^+ + 1$); column; Ascentis Express C18, (50 x 3.0 mm, 2.7 μm); RT 2.51 min.

0.025% Aq. TFA + 5% ACN: ACN +; 5% 0.025% Aq. TFA, 1.2 mL/min).

Example 45: Synthesis of compounds from compound 520 and various commercially available amines



[000420] Compound **520** and commercially available amines were converted to corresponding sulfonamides employing Procedure M and the results are captured in Table 4.

Procedure M:

[000421] To a stirred solution of 2, 4-difluoroaniline **228** (100 mg, 0.77 mmol) in CH_2Cl_2 (5 mL) under argon atmosphere were added compound **520** (252 mg, crude), pyridine (3.87 mL, 5.26 mmol) at 0 °C; warmed to RT and stirred for 12 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography to afford the desired compound.

Commercially available amines used for the synthesis of compounds

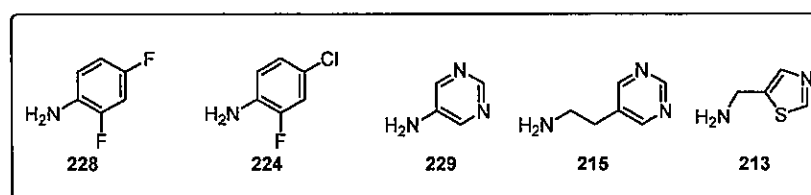
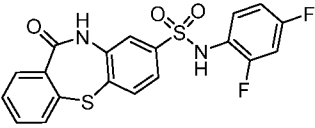
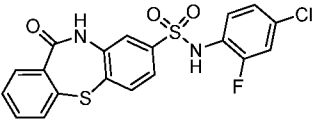
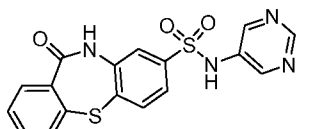
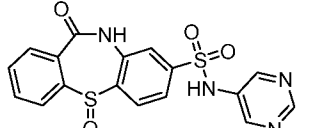
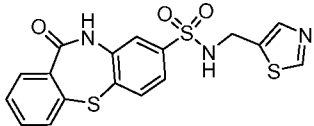
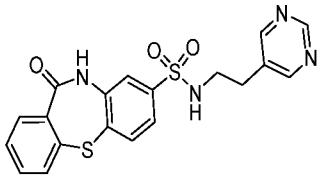
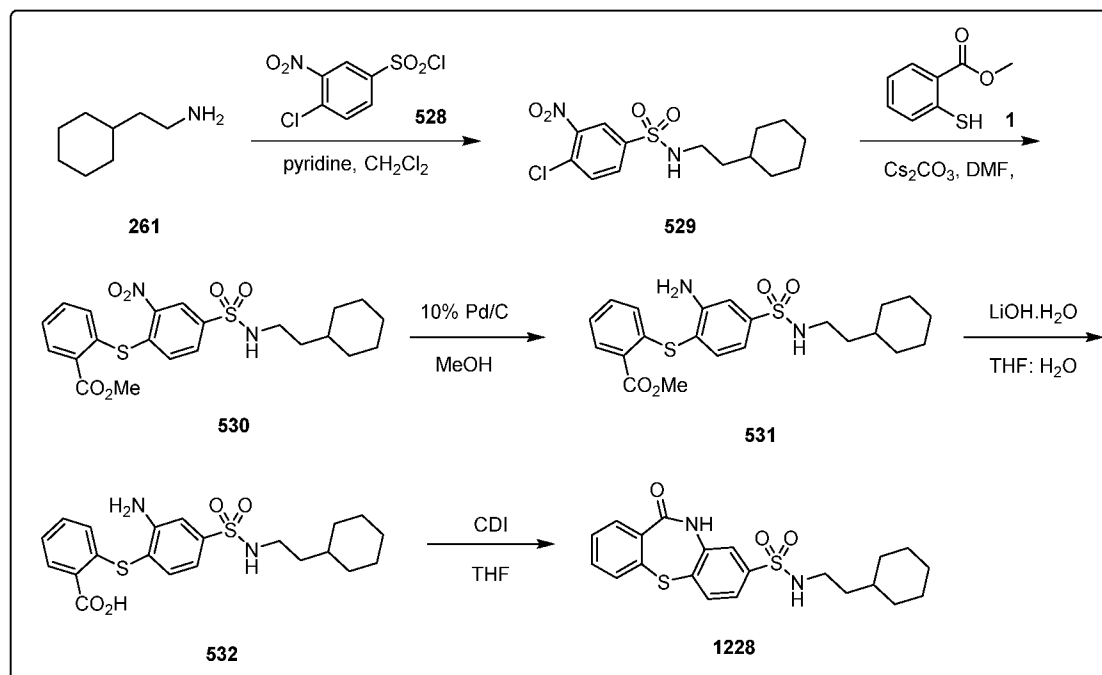


Table 4: Synthesis of compounds from compound 520 and various commercially available amines

No.	Structure	Procedure, Intermediate Amine	Rx. Yield (%)	Mass Spec. Found	Mass Spec. Calculated	¹ H-NMR
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1526		M, 520, 228	8	418.8 (M ⁺ +1)	418.03 for C ₁₉ H ₁₂ F ₂ N ₂ O ₃ S ₂	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.89 (s, 1H), 10.25 (s, 1H), 7.77 (d, <i>J</i> = 8.2 Hz, 1H), 7.70 (dd, <i>J</i> = 7.5, 1.2 Hz, 1H), 7.58- 7.45 (m, 4H), 7.43 (dd, <i>J</i> = 8.2, 2.0 Hz, 1H), 7.25-7.17 (m, 2H), 7.06- 6.98 (m, 1H)
1544		M, 520, 224	10	435.1 (M ⁺ +1)	434.00 for C ₁₉ H ₁₂ ClF N ₂ O ₃ S ₂	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.90 (s, 1H), 10.43 (s, 1H), 7.77 (d, <i>J</i> = 8.2 Hz, 1H), 7.70 (d, <i>J</i> = 7.0 Hz, 1H), 7.61-7.43 (m, 5H), 7.42- 7.37 (m, 1H), 7.26-7.18 (m, 2H);
1505		M, 520, 229	6	385.1 (M ⁺ +1)	384.04 for C ₁₇ H ₁₂ N ₄ O ₃ S ₂	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 11.02 (br s, 1H), 10.90 (s, 1H), 8.90 (s, 1H), 8.52 (s, 2H), 7.78 (d, <i>J</i> = 8.2 Hz, 1H), 7.71-7.64 (m, 2H), 7.57-7.44 (m, 4H);
1506		M, 520, 229 (excess equiv. of NCS)	6	400.8 (M ⁺ +1)	400.03 for C ₁₇ H ₁₂ N ₄ O ₄ S ₂	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 11.15 (s, 1H), 11.08 (br s, 1H), 8.91 (s, 1H), 8.52 (s, 2H), 7.86-7.77 (m, 4H), 7.73 (d, <i>J</i> = 7.0 Hz, 1H), 7.68 (s, 1H), 7.66-7.61

						(m, 1H);
1556		M, 520, 213	9	403.9 (M ⁺ +1)	403.01 for C ₁₇ H ₁₃ N ₃ O S ₃	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.86 (s, 1H), 8.76 (s, 1H), 8.44 (t, <i>J</i> = 6.0 Hz, 1H), 7.76 (d, <i>J</i> = 8.2 Hz, 1H), 7.74-7.71 (m, 1H), 7.66 (s, 1H), 7.62 (s, 1H), 7.59-7.47 (m, 4H), 4.25 (d, <i>J</i> = 5.9 Hz, 2H);
1597		M, 520, 215	5	412.9 (M ⁺ +1)	412.07 for C ₁₉ H ₁₆ N ₄ O S ₂	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.87 (br s, 1H), 8.91 (s, 1H), 8.59 (s, 2H), 7.90-7.85 (m, 1H), 7.78- 7.70 (m, 2H), 7.61-7.44 (m, 5H), 3.10-3.03 (m, 2H), 2.76- 2.63 (m, 2H);

Example 46: Synthesis of Compound 1228

[000422] Synthesis of 4-chloro-N-(2-cyclohexylethyl)-3-nitrobenzenesulfonamide (529): To a stirred solution of 2-cyclohexylethan-1-amine **261** (500 mg, 3.93 mmol) in CH₂Cl₂ (10 mL) under inert atmosphere were added pyridine (0.9 mL), 4-chloro-3-nitrobenzenesulfonyl chloride **528** (1 g, 3.93 mmol) at 0 °C; warmed to RT and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (20 mL) and extracted with CH₂Cl₂ (2 x 30 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 15% EtOAc/ hexanes to afford compound **529** (1.36 g, 52%) as yellow solid. **TLC:** 30% EtOAc/ hexanes (*R_f*: 0.6); **¹H-NMR (CDCl₃, 400 MHz):** δ 8.33 (s, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 4.52 (t, *J* = 5.6 Hz, 1H), 3.03 (q, 2H), 1.69-1.56 (m, 4H), 1.40-1.35 (m, 2H), 1.28-1.08 (m, 5H), 0.89-0.83 (m, 2H).

[000423] Synthesis of methyl 2-((4-(N-(2-cyclohexylethyl) sulfamoyl)-2-nitrophenyl) thio) benzoate (530): To a stirred solution of compound **529** (200 mg, 0.57 mmol) in DMF (4 mL) under inert atmosphere was added cesium carbonate (281 mg, 0.86 mmol) at RT; heated to 40 °C, then added methyl thio salicylate (106 mg, 0.63 mmol) and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water

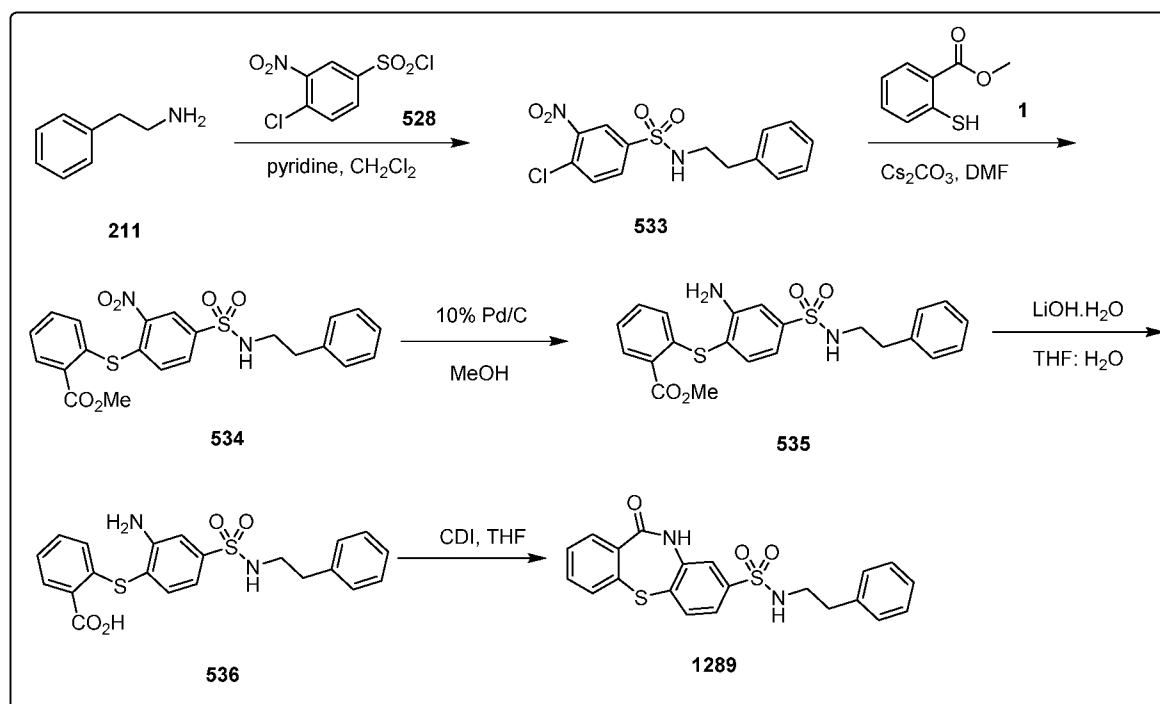
(20 mL) and extracted with EtOAc (2 x 30 mL). The combined organic extracts were washed with water (20 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 20% EtOAc/ hexanes to afford compound **530** (210 mg, 76%) as yellow syrup. **TLC:** 30% EtOAc/ hexanes (R_f : 0.4); **$^1\text{H-NMR}$ (CDCl_3 , 400 MHz):** δ 8.67 (s, 1H), 7.99-7.97 (m, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.65-7.59 (m, 3H), 6.97 (d, J = 8.8 Hz, 1H), 4.44 (t, J = 6.0 Hz, 1H), 3.81 (s, 3H), 3.03-2.98 (m, 2H), 1.67-1.58 (m, 5H), 1.42-1.33 (m, 3H), 1.29-1.09 (m, 3H), 0.91-0.87 (m, 2H).

[000424] Synthesis of methyl 2-((2-amino-4-(*N*-(2-cyclohexylethyl) sulfamoyl) phenyl) thio) benzoate (531): To a stirred solution of compound **530** (200 mg, 0.41 mmol) in MeOH (10 mL) under inert atmosphere was added 10% Pd/ C (60 mg) at RT and stirred under hydrogen atmosphere (balloon pressure) for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered through celite and the filtrate was concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 10% EtOAc/ Hexanes to afford compound **531** (120 mg, 64%) as an off-white solid. **TLC:** 30% EtOAc/ Hexanes (R_f : 0.3); **$^1\text{H-NMR}$ (CDCl_3 , 400 MHz):** δ 8.03 (d, J = 7.6 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.30-7.29 (m, 2H), 7.21-7.16 (m, 2H), 6.71 (d, J = 8.0 Hz, 1H), 4.36 (br s, 1H), 3.97 (s, 3H), 3.04 (t, J = 6.4 Hz, 2H), 1.68-1.61 (m, 5H), 1.39-1.35 (m, 2H), 1.29-1.13 (m, 4H), 0.90-0.84 (m, 2H).

[000425] Synthesis of 2-((2-amino-4-(*N*-(2-cyclohexylethyl) sulfamoyl) phenyl) thio) benzoic acid (532): To a stirred solution of compound **531** (110 mg, 0.24 mmol) in THF: H_2O (2: 1, 6 mL) was added lithium hydroxide monohydrate (20 mg, 0.49 mmol) at RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with water (15 mL), acidified with dil. HCl. The obtained precipitate was filtered, washed with ether (2 x 5 mL) and dried *in vacuo* to afford compound **532** (85 mg, 80%) as white solid. **TLC:** 30% EtOAc/ hexanes (R_f : 0.2); **$^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz):** δ 13.19 (br s, 1H), 7.94 (d, J = 7.6 Hz, 1H), 7.50-7.47 (m, 2H), 7.34 (t, J = 7.2 Hz, 1H), 7.24-7.18 (m, 2H), 6.94 (d, J = 8.0 Hz, 1H), 6.61 (d, J = 8.0 Hz, 1H), 5.82 (br s, 2H), 2.85-2.80 (m, 2H), 1.59-1.52 (m, 5H), 1.27-1.23 (m, 3H), 1.16-1.11 (m, 3H), 0.83-0.78 (m, 2H).

[000426] Synthesis of *N*-(2-cyclohexylethyl)-11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-sulfonamide (1228): To a stirred solution of compound **532** (80 mg, 0.18 mmol) in THF (5 mL) under inert atmosphere was added CDI (89 mg, 0.55 mmol) at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with water (20 mL), acidified with dil.HCl. The obtained precipitate was filtered, washed with ether (2 x 5 mL) and dried *in vacuo* to afford **1228** (35 mg, 46%) as white solid. **TLC:** 5% MeOH/ CH₂Cl₂ (*R_f*: 0.6); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 10.89 (s, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.71-7.69 (m, 1H), 7.64-7.62 (m, 2H), 7.56-7.45 (m, 4H), 2.78-2.73 (m, 2H), 1.48-1.42 (m, 5H), 1.19-1.07 (m, 6H), 0.71-0.66 (m, 2H); **LC-MS:** 98.00%; 417.6 (M⁺+1); (column; X-Select CSH C-18, (50 × 3.0 mm, 3.5 μm); RT 4.76 min. 0.05% TFA (Aq) : ACN; 0.8 mL/min); **UPLC (purity):** 95.34%; (column : Acquity BEH C-18 (50 × 2.1 mm, 1.7 μ); RT 2.74 min. ACN : 0.025% TFA (Aq.); 0.5 mL/min).

Example 47: Synthesis of Compound 1289



[000427] Synthesis of 4-chloro-3-nitro-N-phenethylbenzenesulfonamide (533): To a stirred solution of 2-phenylethan-1-amine **211** (250 mg, 2.06 mmol) in CH₂Cl₂ (5 mL) under inert atmosphere were added 4-chloro-3-nitrobenzenesulfonyl chloride **528** (528 mg, 2.06 mmol),

pyridine (0.5 mL) at 0 °C; warmed to RT and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (20 mL) and extracted with CH₂Cl₂ (2 x 30 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 15% EtOAc/ hexanes to afford compound **533** (410 mg, 58%) as colorless syrup. **TLC:** 30% EtOAc/ hexanes (*R_f*: 0.6); **¹H-NMR (CDCl₃, 400 MHz):** δ 8.21 (s, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.27 (s, 1H), 7.25-7.22 (m, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 4.59 (t, *J* = 6.0 Hz, 1H), 3.32 (q, 2H), 2.81 (t, *J* = 6.8 Hz, 2H).

[000428] Synthesis of methyl 2-((2-nitro-4-(*N*-phenethylsulfamoyl) phenyl) thio) benzoate (534): To a stirred solution of compound **533** (100 mg, 0.29 mmol) in DMF (3 mL) under inert atmosphere were added methyl thio salicylate (54 mg, 0.32 mmol), cesium carbonate (143 mg, 0.44 mmol) at RT; heated to 40 °C and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (15 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with water (20 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 20% EtOAc/ hexanes to afford compound **534** (90 mg, 65%) as yellow solid. **TLC:** 30% EtOAc/ hexanes (*R_f*: 0.4); **¹H-NMR (CDCl₃, 400 MHz):** δ 8.56 (s, 1H), 7.98 (t, *J* = 6.8 Hz, 1H), 7.64-7.60 (m, 4H), 7.23-7.20 (m, 3H), 7.07 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 1H), 4.50 (t, *J* = 6.0 Hz, 1H), 3.80 (s, 3H), 3.28 (q, 2H), 2.79 (t, *J* = 6.8 Hz, 2H).

[000429] Synthesis of methyl 2-((2-amino-4-(*N*-phenethylsulfamoyl) phenyl) thio) benzoate (535): To a stirred solution of compound **534** (330 mg, 0.69 mmol) in MeOH (15 mL) under inert atmosphere was added 10% Pd/ C (100 mg) at RT and stirred under hydrogen atmosphere (balloon pressure) for 12 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered through celite, washed with CH₂Cl₂ (2 x 5 mL) and the filtrate was concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 15% EtOAc/ hexanes to afford compound **535** (210 mg, 68%) as an off-white solid. **TLC:** 30% EtOAc/ hexanes (*R_f*: 0.3); **¹H-NMR (CDCl₃, 400 MHz):** δ 8.03 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 3H), 7.25-7.23 (m, 1H), 7.19-7.11 (m, 5H), 6.69 (d, *J* = 8.0 Hz, 1H), 4.37 (t, *J* = 6.4 Hz, 1H), 4.12 (q, 1H), 3.97 (s, 3H), 3.31

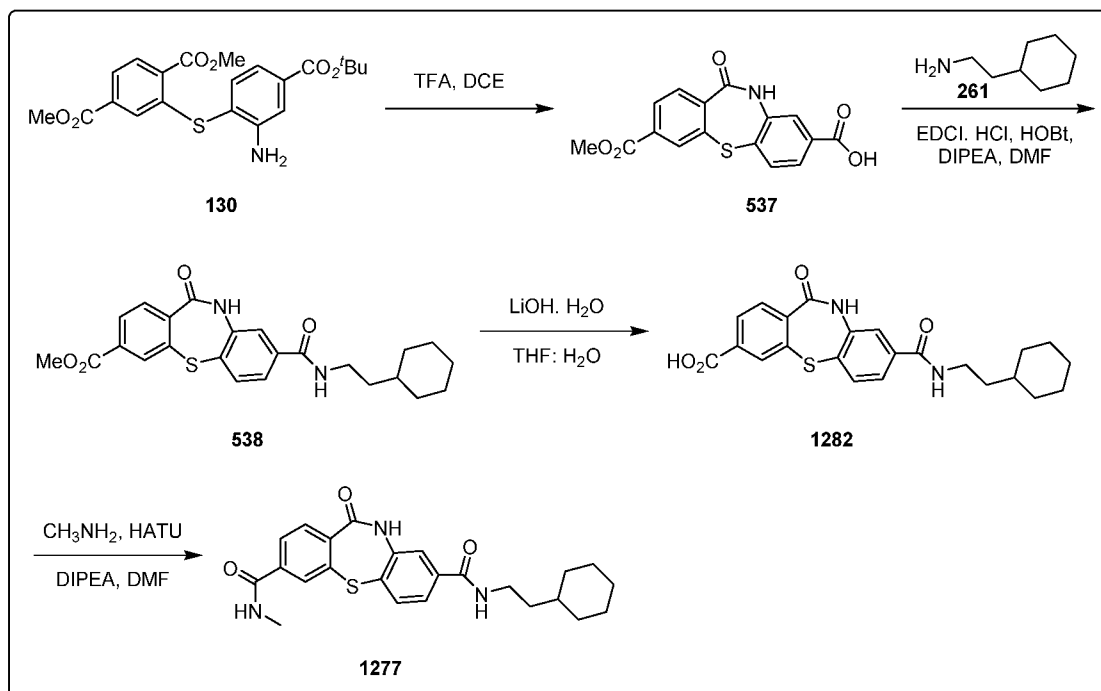
(q, 2H), 2.81 (t, $J = 6.8$ Hz, 2H), 2.04 (s, 1H).

[000430] Synthesis of 2-((2-amino-4-(*N*-phenethylsulfamoyl) phenyl) thio) benzoic acid

(536): To a stirred solution of compound **535** (200 mg, 0.45 mmol) in THF: H₂O (2: 1, 6 mL) was added lithium hydroxide monohydrate (38 mg, 0.90 mmol) at RT and stirred for 16 h; heated to 40 °C and stirred for 3 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with water (15 mL), acidified with dil. HCl. The obtained precipitate was filtered, washed with ether (2 x 5 mL) and dried *in vacuo* to afford compound **536** (130 mg, 67%) as white solid. **TLC:** 40% EtOAc/hexanes (R_f : 0.2); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 7.93 (d, $J = 7.6$ Hz, 1H), 7.68 (t, $J = 6.0$ Hz, 1H), 7.47 (d, $J = 8.0$ Hz, 1H), 7.32-7.25 (m, 4H), 7.21-7.16 (m, 4H), 6.95 (d, $J = 8.0$ Hz, 1H), 6.60 (d, $J = 8.4$ Hz, 1H), 5.81 (br s, 2H), 3.03 (q, 2H), 2.70 (t, $J = 8.0$ Hz, 2H).

[000431] Synthesis of 11-oxo-*N*-phenethyl-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-sulfonamide (1289):

To a stirred solution of compound **536** (100 mg, 0.23 mmol) in THF (5 mL) under inert atmosphere was added CDI (113 mg, 0.70 mmol) at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with water (20 mL), acidified with 1N HCl. The obtained precipitate was filtered, washed with ether (2 x 5 mL) and dried *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 3-5% MeOH/ CH₂Cl₂ to afford **1289** (35 mg, 37%) as white solid. **TLC:** 5% MeOH/ CH₂Cl₂ (R_f : 0.6); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 10.86 (s, 1H), 7.81 (br s, 1H), 7.73 (d, $J = 8.0$ Hz, 2H), 7.71 (s, 1H), 7.59-7.45 (m, 4H), 7.18-7.14 (m, 2H), 7.11-7.07 (m, 3H), 2.97 (q, 2H), 2.64 (t, $J = 7.6$ Hz, 2H); **LC-MS:** 97.83%; 411.5 ($M^+ + 1$); (column: X-Select CSH C-18, (50 × 3.0 mm, 3.5 μ m); RT 4.33 min. 0.05% TFA (Aq): ACN; 0.8 mL/min); **UPLC (purity):** 98.00%; (column: Acquity BEH C-18 (50 × 2.1 mm, 1.7 μ m); RT 2.43 min. ACN: 0.025% TFA (Aq); 0.5 mL/min).

Example 48: Synthesis of Compounds 1277 and 1282

[000432] Synthesis of 3-(methoxycarbonyl)-11-oxo-10,11-dihydrodibenzo[*b,f*] [1,4] thiazepine-8-carboxylic acid (537**):** To a stirred solution of dimethyl 2-((2-amino-4-(tert-butoxycarbonyl)phenyl)thio)terephthalate **130** (200 mg, 0.47 mmol) in 1,2-dichloroethane (10 mL) under inert atmosphere was added trifluoroacetic acid (1.09 g, 9.59 mmol) at RT; heated to 80 °C and stirred for 24 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 6% MeOH/CH₂Cl₂ to afford compound **537** (60 mg, 38%) as an off-white solid. **TLC:** 10% MeOH/CH₂Cl₂ (*R_f*: 0.3); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 13.17 (br s, 1H), 10.99 (s, 1H), 8.02 (s, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.79 (s, 1H), 7.70-7.65 (m, 2H), 3.86 (s, 3H).

[000433] Synthesis of methyl 8-((2-cyclohexylethyl)carbamoyl)-11-oxo-10,11-dihydrodibenzo[*b,f*] [1,4] thiazepine-3-carboxylate (538**):** To a stirred solution of compound **537** (60 mg, 0.18 mmol) in DMF (2.4 mL) under inert atmosphere were added 2-cyclohexylethan-1-amine **261** (28 mg, 0.21 mmol), HOBT (37 mg, 0.27 mmol), EDCI·HCl (52 mg, 0.27 mmol), diisopropyl ethylamine (0.08 mL, 0.36 mmol) at RT and stirred for 16 h. The

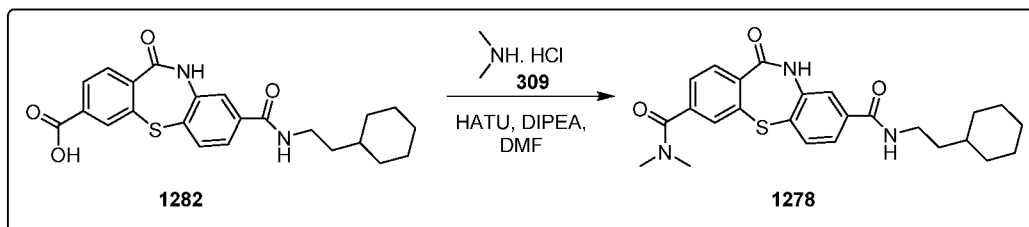
reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (20 mL). The obtained solid was filtered and dried *in vacuo* to afford compound **538** (45 mg, 56%) as an off-white solid. **TLC:** 10% MeOH/ CH₂Cl₂ (*R_f*: 0.6); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 10.94 (s, 1H), 8.46-8.45 (m, 1H), 8.02 (s, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 1H), 3.87 (s, 3H), 3.26-3.21 (m, 2H), 1.70-1.62 (m, 5H), 1.40-1.35 (m, 2H), 1.26-1.09 (m, 4H), 0.91-0.83 (m, 2H).

[000434] Synthesis of 8-((2-cyclohexylethyl) carbamoyl)-11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-3-carboxylic acid (1282): To a stirred solution of compound **538** (125 mg, 0.28 mmol) in THF: H₂O (4: 1, 5 mL) was added lithium hydroxide monohydrate (59.9 mg, 1.42 mmol) at RT and stirred for 5 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude. The crude was diluted with water (20 mL), neutralized with HCl, the obtained solid was filtered and dried *in vacuo* to afford **1282** (90 mg, 74%) as white solid. **TLC:** 10% MeOH/ CH₂Cl₂ (*R_f*: 0.3); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 13.44 (br s, 1H), 10.92 (s, 1H), 8.45 (t, *J* = 5.6 Hz, 1H), 8.00 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.68-7.66 (m, 2H), 7.58-7.56 (m, 1H), 3.26-3.21 (m, 2H), 1.70-1.58 (m, 5H), 1.40-1.35 (m, 2H), 1.30-1.22 (m, 4H), 0.91-0.83 (m, 2H). **LC-MS:** 99.29%; 425.9 (M⁺+1); (column; X-Select CSH C-18, (50 × 3.0 mm, 3.5 μm); RT 4.40 min. 0.05% TFA (Aq) : ACN; 0.8 mL/min); **UPLC (purity):** 98.94%; (column : Acquity BEH C-18 (50 x 2.1 mm, 1.7 μ); RT 2.32 min. ACN : 0.025% TFA (Aq); 0.5 mL/min).

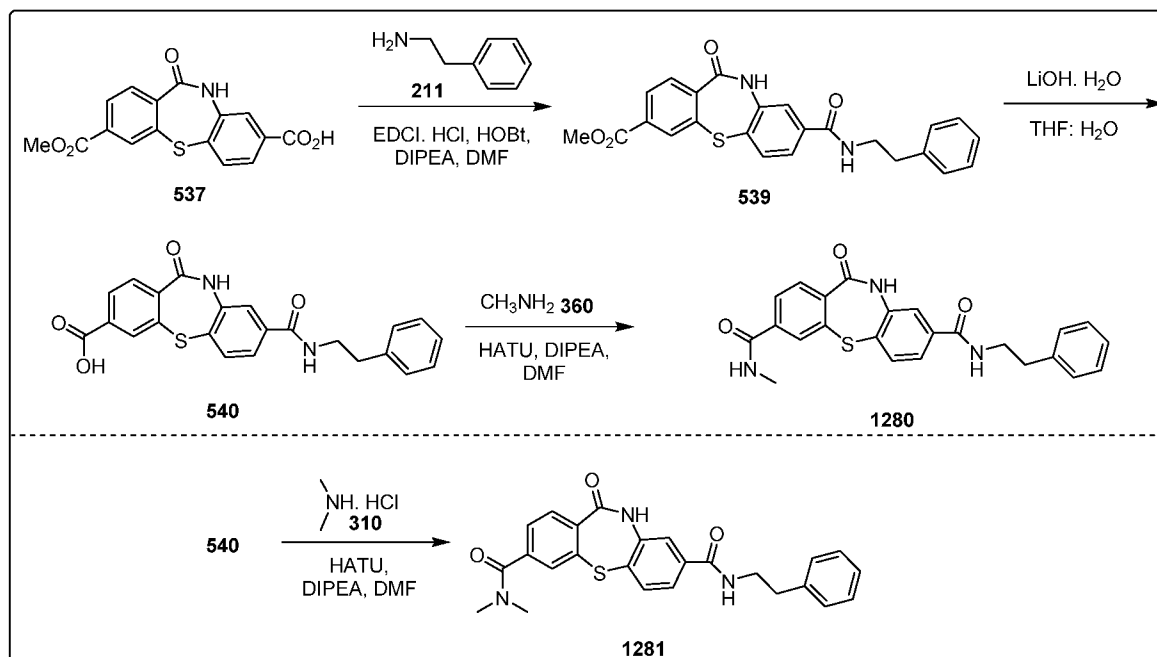
[000435] Synthesis of *N*⁸-(2-cyclohexylethyl)-*N*³-methyl-11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-3, 8-dicarboxamide (1277): To a stirred solution of **1282** (30 mg, 0.07 mmol) in DMF (1.2 mL) under inert atmosphere were added methyl amine **306** (2 M in THF, 0.07 mL, 0.14 mmol), HATU (54.7 mg, 0.14 mmol), diisopropyl ethyl amine (0.05 mL, 0.28 mmol) at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with ice water (10 mL). The obtained solid was filtered, washed with EtOAc (2 x 5 mL) and dried *in vacuo* to afford **1277** (11 mg, 35%) as white solid. **TLC:** 7% MeOH/ CH₂Cl₂ (*R_f*: 0.8); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 10.86 (s, 1H), 8.63-8.62 (m, 1H), 8.44 (t, *J* = 5.2 Hz, 1H), 7.95 (s, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.58-7.55 (m, 1H), 3.26-3.21 (m, 2H), 2.77 (s, 3H), 1.70-1.58 (m, 5H), 1.40-1.35 (m, 2H), 1.26-1.14 (m, 4H), 0.91-0.83 (m, 2H); **LC-**

MS: 94.12%; 438.8 ($M^+ + 1$); (column; X-Select CSH C-18, (50 × 3.0 mm, 3.5 μ m); RT 4.05 min. 0.05% TFA (Aq) : ACN; 0.8 mL/min); **UPLC (purity):** 98.69%; (column : Acquity BEH C-18 (50 x 2.1 mm, 1.7 μ m); RT 2.28 min. ACN : 0.025% TFA (Aq); 0.5 mL/min).

Example 49: Synthesis of Compound 1278



[000436] **Synthesis of N^8 -(2-cyclohexylethyl)- N^3 , N^3 -dimethyl-11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-3, 8-dicarboxamide (1278):** To a stirred solution of **1282** (40 mg, 0.09 mmol) in DMF (2 mL) under inert atmosphere were added dimethylamine hydrochloride (23 mg, 0.28 mmol), HATU (73 mg, 0.18 mmol), diisopropyl ethyl amine (0.09 mL, 0.47 mmol) at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (15 mL). The obtained solid was filtered, triturated with EtOAc (2 x 5 mL) and dried *in vacuo* to afford **1278** (19 mg, 48%) as an off-white solid. **TLC:** 5% MeOH/ CH₂Cl₂ (*R_f*: 0.6); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 10.84 (s, 1H), 8.44 (t, *J* = 5.2 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.67-7.63 (m, 2H), 7.58-7.47 (m, 2H), 7.45 (d, *J* = 8.0 Hz, 1H), 3.27-3.22 (m, 2H), 2.96 (s, 3H), 2.88 (s, 3H), 1.70-1.58 (m, 5H), 1.41-1.35 (m, 2H), 1.28-1.26 (m, 1H), 1.25-1.14 (m, 3H), 0.91-0.83 (m, 2H); **LC-MS:** 98.41%; 452.7 ($M^+ + 1$); (column; X-Select CSH C-18, (50 × 3.0 mm, 3.5 μ m); RT 4.11 min. 0.05% TFA (Aq) : ACN; 0.8 mL/min); **UPLC (purity):** 99.60%; (column : Acquity BEH C-18 (50 x 2.1 mm, 1.7 μ m); RT 2.33 min. ACN : 0.025% TFA (Aq); 0.5 mL/min).

Example 50: Synthesis of Compounds 1280 and 1281

[000437] Synthesis of methyl 11-oxo-8-(phenethylcarbamoyl)-10, 11-dihydrodibenzo [b, f] [1, 4] thiazepine-3-carboxylate (539): To a stirred solution of compound **537** (75 mg, 0.22 mmol) in DMF (3 mL) under inert atmosphere were added 2-phenylethan-1-amine **211** (30 mg, 0.25 mmol), HOBT (46 mg, 0.34 mmol), EDCI. HCl (65 mg, 0.34 mmol), diisopropyl ethyl amine (0.08 mL, 0.45 mmol) at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with ice water (20 mL). The obtained solid was filtered, washed with 20% EtOAc/ Hexanes (2 x 5 mL) and dried *in vacuo* to afford compound **539** (80 mg, 81%) as white solid. **TLC:** 7% MeOH/ CH₂Cl₂ (*R_f*: 0.8); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 10.96 (s, 1H), 8.61 (t, *J* = 5.6 Hz, 1H), 8.02 (s, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.57-7.54 (m, 1H), 7.29-7.25 (m, 2H), 7.22-7.16 (m, 3H), 3.87 (s, 3H), 3.47-3.42 (m, 2H), 2.80 (t, *J* = 7.2 Hz, 2H).

[000438] Synthesis of 11-oxo-8-(phenethylcarbamoyl)-10, 11-dihydrodibenzo [b, f] [1, 4] thiazepine-3-carboxylic acid (540): To a stirred solution of compound **539** (80 mg, 0.18 mmol) in THF: H₂O (4: 1, 3 mL) was added lithium hydroxide monohydrate (39 mg, 0.92 mmol) at RT and stirred for 5 h. The reaction was monitored by TLC; after completion of the reaction, the

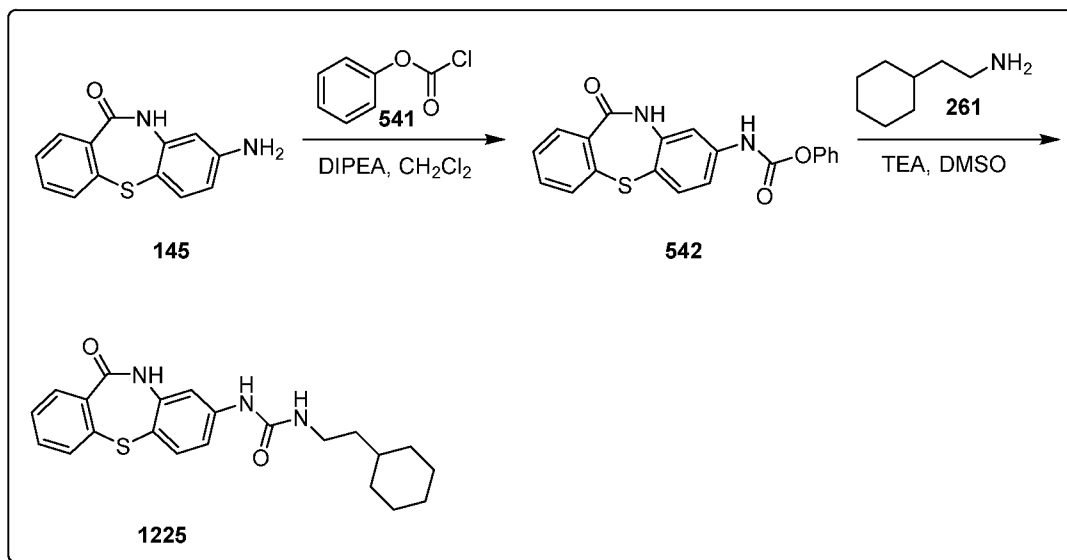
volatiles were removed *in vacuo*. The residue was diluted with water (15 mL), acidified with HCl, the obtained solid was filtered, washed with 20% EtOAc/ hexanes (2 x 5 mL) and dried *in vacuo* to afford compound **540** (65 mg, 84%) as white solid. **TLC:** 10% MeOH/ CH₂Cl₂ (*R_f*: 0.2); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 13.44 (br s, 1H), 10.94 (s, 1H), 8.62 (t, *J* = 5.6 Hz, 1H), 8.00 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.57-7.54 (m, 1H), 7.29-7.25 (m, 2H), 7.22-7.16 (m, 3H), 3.47-3.42 (m, 2H), 2.80 (t, *J* = 7.2 Hz, 2H).

[000439] Synthesis of *N*³-methyl-11-oxo-*N*⁸-phenethyl-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-3, 8-dicarboxamide (1280): To a stirred solution of compound **540** (35 mg, 0.08 mmol) in DMF (2 mL) under inert atmosphere were added methyl amine (2 M in THF, 0.24 mL, 0.50 mmol), HATU (130 mg, 0.32 mmol), diisopropyl ethyl amine (0.10 mL, 0.50 mmol) at 0 °C; warmed to RT and stirred for 44 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with ice water (15 mL). The obtained solid was filtered, washed with EtOAc (2 x 5 mL) and dried *in vacuo* to afford **1280** (12 mg, 28%) as white solid. **TLC:** 10% MeOH/ CH₂Cl₂ (*R_f*: 0.4); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 10.89 (s, 1H), 8.63-8.60 (m, 2H), 7.96 (s, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.66-7.65 (m, 2H), 7.56-7.54 (m, 1H), 7.29-7.26 (m, 2H), 7.22-7.16 (m, 3H), 3.47-3.42 (m, 2H), 2.88-2.73 (m, 5H); **LC-MS:** 95.22%; 432.6 (M⁺+1); (column; X-Select CSH C-18, (50 × 3.0 mm, 3.5 μm); RT 3.61 min. 0.05% TFA (Aq) : ACN; 0.8 mL/min); **UPLC (purity):** 94.66%; (column : Acquity BEH C-18 (50 x 2.1 mm, 1.7 μm); RT 1.97 min. ACN : 0.025% TFA (Aq); 0.5 mL/min).

[000440] Synthesis of *N*³, *N*³-dimethyl-11-oxo-*N*⁸-phenethyl-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-3, 8-dicarboxamide (1281): To a stirred solution of **540** (30 mg, 0.07 mmol) in DMF (2 mL) under inert atmosphere were added dimethyl amine hydrochloride **310** (17.5 mg, 0.21 mmol), HATU (55.5 mg, 0.14 mmol), diisopropyl ethyl amine (0.07 mL, 0.35 mmol) at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (10 mL). The obtained solid was filtered, washed with EtOAc (2 x 5 mL) and dried *in vacuo* to afford **1281** (17 mg, 53%) as an off-white solid. **TLC:** 5% MeOH/ CH₂Cl₂ (*R_f*: 0.6); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 10.86 (s, 1H), 8.61 (t, *J* = 5.2 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.67-7.64 (m, 2H), 7.57-7.53 (m, 2H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.29-7.26 (m, 2H), 7.20-7.16 (m, 3H), 3.48-3.43 (m, 2H), 2.96 (s, 3H), 2.86 (s, 3H), 2.82-2.79 (m, 2H); **LC-MS:** 97.11%; 446.7 (M⁺+1); (column; X-Select CSH C-18,

(50 × 3.0 mm, 3.5 μm); RT 3.68 min. 0.05% TFA (Aq) : ACN; 0.8 mL/min); **UPLC (purity):** 98.02%; (column : Acquity BEH C-18 (50 x 2.1 mm, 1.7 μ); RT 2.03 min. ACN : 0.025% TFA (Aq); 0.5 mL/min).

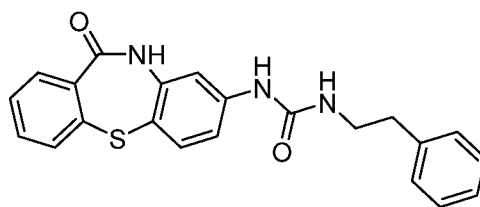
Example 51: Synthesis of Compounds 1225 and 1224



[000441] Synthesis of phenyl (11-oxo-10, 11-dihydrodibenzo [b, f] [1, 4] thiazepin-8-yl) carbamate (542): To a stirred solution of compound **145** (40 mg, 0.16 mmol) in CH₂Cl₂ (3 mL) under inert atmosphere were added diisopropyl ethyl amine (0.06 mL, 0.33 mmol), phenyl carbonochloridate **541** (28 mg, 0.18 mmol) at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (15 mL) and extracted with CH₂Cl₂ (2 x 25 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was triturated with 15% EtOAc/ hexanes to afford compound **542** (50 mg, 83%) as an off-white solid. **TLC:** 70% EtOAc/ Hexanes (*R_f*: 0.8); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 10.73 (s, 1H), 10.45 (s, 1H), 7.68-7.65 (m, 1H), 7.52-7.40 (m, 7H), 7.28-7.24 (m, 2H), 7.21 (d, *J* = 7.6 Hz, 2H).

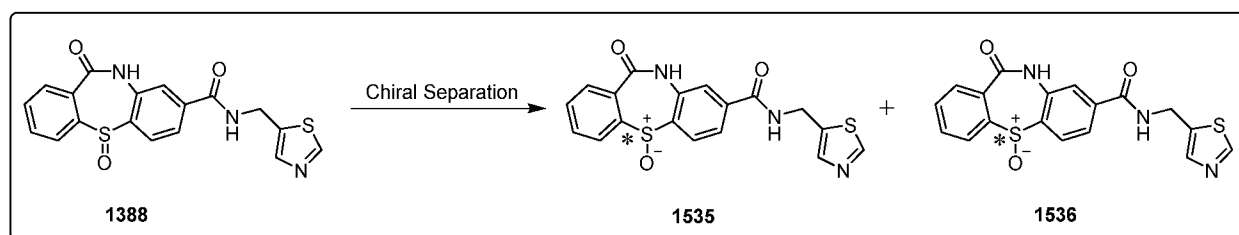
[000442] Synthesis of 1-(2-cyclohexylethyl)-3-(11-oxo-10, 11-dihydrodibenzo [b, f] [1, 4] thiazepin-8-yl) urea (1225): To a stirred solution of compound **542** (50 mg, 0.13 mmol) in DMSO (3 mL) under inert atmosphere were added 2-cyclohexylethan-1-amine **161** (21 mg, 0.16

mmol), triethyl amine (0.04 mL, 0.27 mmol) at 0 °C; warmed to RT and stirred for 5 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (15 mL). The obtained solid was filtered, washed with EtOAc (2 x 5 mL) and dried *in vacuo* to afford **1225** (17 mg, 31%) as white solid. **TLC**: 5% MeOH/ CH₂Cl₂ (*R_f*: 0.5); **¹H-NMR (DMSO-*d*₆, 500 MHz)**: δ 10.58 (s, 1H), 8.58 (s, 1H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.48-7.40 (m, 3H), 7.34 (d, *J* = 7.5 Hz, 2H), 7.13-7.11 (m, 1H), 6.10-6.07 (m, 1H), 3.08-3.04 (m, 2H), 1.67-1.57 (m, 5H), 1.31-1.11 (m, 6H), 0.86-0.84 (m, 2H); **LC-MS**: 95.28%; 396.4 (*M*⁺+1); (column; X-Bridge C-18, (50 × 3.0 mm, 3.5 μm); RT 3.76 min. 0.05% TFA (Aq) : ACN; 0.8 mL/min); **UPLC (purity)**: 96.65%; (column : Acquity UPLC BEH C-18 (2.1 x 50 mm, 1.7 μm); RT 2.65 min. ACN : 0.025% TFA (Aq); 0.5 mL/min).

**1224**

[000443] In a similar manner **1224** (1-(11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepin-8-yl)-3-phenethylurea) was prepared. Yield: 27% **LC-MS**: 390.3 (*M*⁺+1); **¹H-NMR (DMSO-*d*₆, 400 MHz)**: δ 10.59 (s, 1H), 8.69 (s, 1H), 7.65 (d, *J* = 7.2 Hz, 1H), 7.49-7.41 (m, 3H), 7.35 (d, *J* = 7.6 Hz, 2H), 7.29 (d, *J* = 7.2 Hz, 2H), 7.22-7.13 (m, 4H), 6.14 (t, *J* = 6.0 Hz, 1H), 3.30 (s, 2H), 2.73 (t, *J* = 6.8 Hz, 2H).

Example 52: Synthesis of Compounds 1535 and 1536



[000444] The racemic compound of **1388** (18 mg) was separated using a CHIRALPAK-IC column (250 x 20 mm x 5 μm) (10 mg loading; 0.1% DEA in n-hexane: CH₂Cl₂: MeOH (50: 50)

(A: B = 25: 75) as mobile phase) HPLC to afford **1535** (2.5 mg) and **1536** (2.5 mg) as off-white solids.

Compound 1535 analytical data (Fr-I):

[000445] LC-MS: 99.81%; 383.9 ($M^{+}+1$); (column; Ascentis Express C-18, (50 × 3.0 mm, 2.7 μm); RT 1.69 min. 0.025% Aq. TFA + 5% ACN: ACN + 5% 0.025% Aq. TFA, 1.2 mL/min).

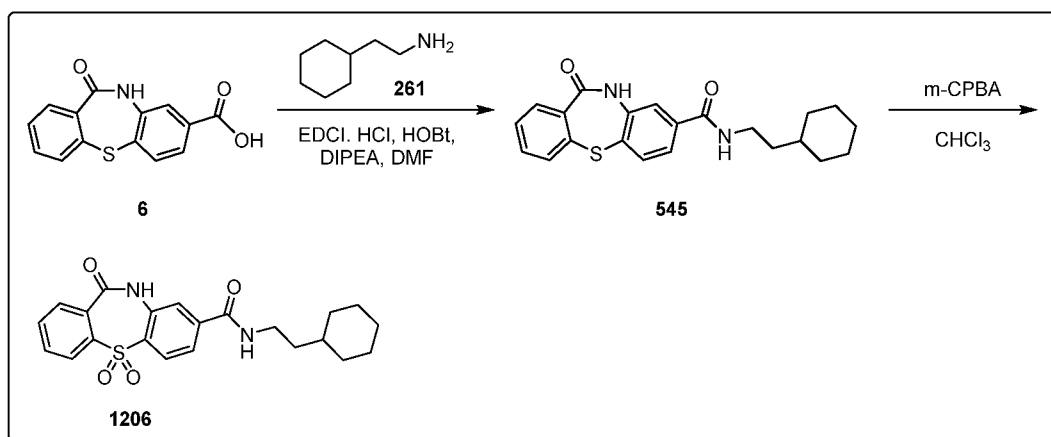
UPLC (purity): 96.76%; (column; Acquity UPLC BEH C-18 (50 x 2.1 mm, 1.7 μm); RT 1.49 min. ACN: 0.025% TFA (Aq); 0.5 mL/min). **Chiral HPLC:** 99.16%, R_t = 99.16 min (Chiralpak-IC, 250 x 4.6 mm, 5 μm); mobile phase (A) 0.1% DEA in *n*-Hexane (B) CH₂Cl₂: MeOH (50: 50) (A: B:: 25: 75); Flow Rate: 1.0 mL/min).

Compound 1536 analytical data (Fr-II):

[000446] LC-MS: 99.39%; 383.9 ($M^{+}+1$); (column; Ascentis Express C-18, (50 × 3.0 mm, 2.7 μm); RT 1.70 min. 0.025% Aq. TFA + 5% ACN: ACN + 5% 0.025% Aq. TFA, 1.2 mL/min).

UPLC (purity): 99.56%; (column; Acquity UPLC BEH C-18 (50 x 2.1 mm, 1.7 μm); RT 1.49 min. ACN: 0.025% TFA (Aq); 0.5 mL/min). **Chiral HPLC:** 98.30%, R_t = 13.33 min (Chiralpak-IC, 250 x 4.6 mm, 5 μm); mobile phase (A) 0.1% DEA in *n*-Hexane (B) CH₂Cl₂: MeOH (50: 50) (A: B:: 25: 75); Flow Rate: 1.0 mL/min).

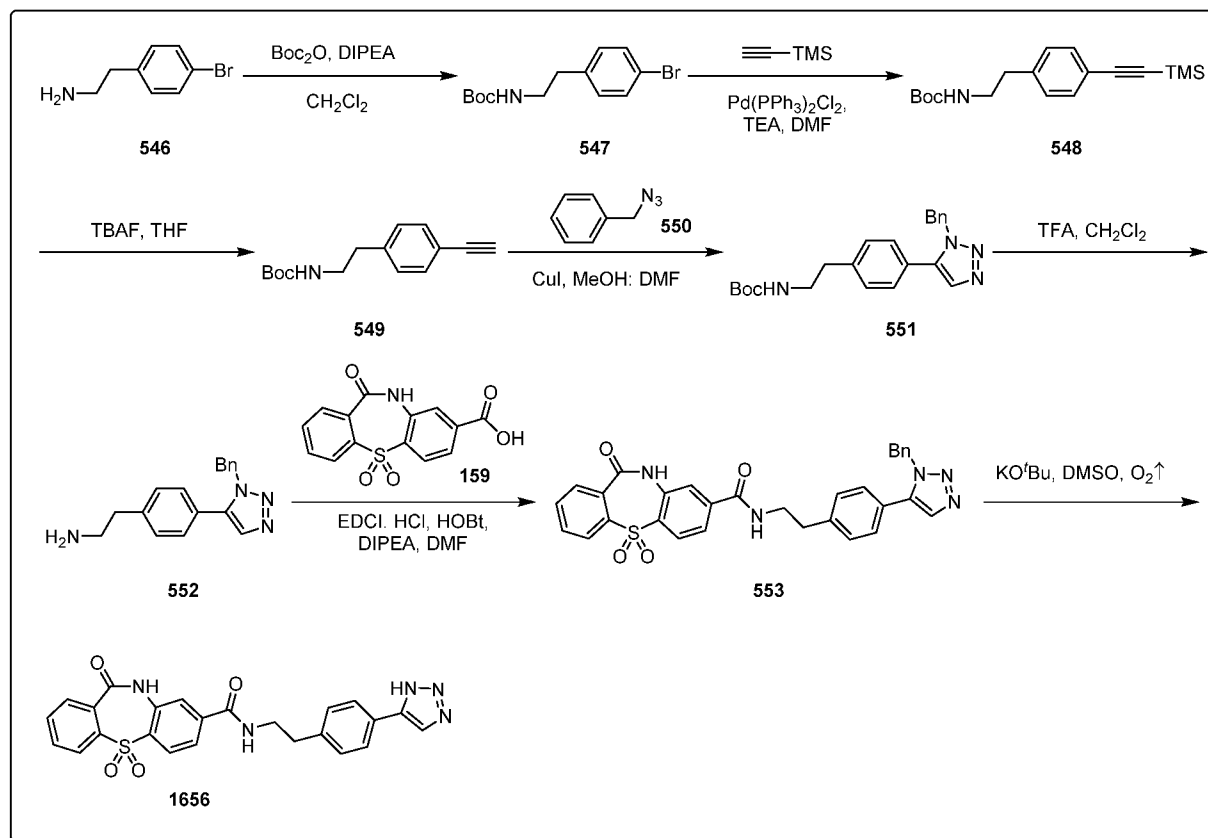
Example 53: Synthesis of Compound 1206



[000447] Synthesis of *N*-(2-cyclohexylethyl)-11-oxo-10,11-dihydrodibenzo[*b,f*] [1, 4] thiazepine-8-carboxamide (545**):** To a stirred solution of **6** (100 mg, 0.36 mmol) in DMF (6 mL) under argon atmosphere were added EDCI.HCl (105 mg, 0.54 mmol), HOBT (74 mg, 0.54

mmol), 2-cyclohexylethan-1-amine **261** (56 mg, 0.44 mmol), and diisopropyl ethyl amine (95 mg, 0.73 mmol) at 0-5 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo*. The residue was diluted with water (20 mL), filtered and washed with water (2 x 5 mL) to obtain the crude. The crude was triturated with EtOAc (2 x 5 mL) to afford **545** (70 mg, 50%) as white solid. **TLC:** 5% MeOH/ CH₂Cl₂ (*R_f*: 0.5); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 10.75 (s, 1H), 8.43 (t, *J* = 5.6 Hz, 1H), 7.69-7.62 (m, 3H), 7.56-7.43 (m, 4H), 3.26-3.21 (m, 2H), 1.70-1.58 (m, 5H), 1.40-1.35 (m, 2H), 1.28-1.09 (m, 4H), 0.91-0.83 (m, 2H).

[000448] Synthesis of *N*-(2-cyclohexylethyl)-11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxamide **5, 5-dioxide (**1206**):** To a stirred solution of **545** (40 mg, 0.10 mmol) in chloroform (20 mL) under inert atmosphere was added *m*-chloro perbenzoic acid (36.3 mg, 0.21 mmol) at RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with saturated sodium bicarbonate solution (15 mL) and extracted with CH₂Cl₂ (2 x 20 mL). The combined organic extracts were washed with water (20 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 30% EtOAc/ hexanes to afford **1206** (16 mg, 37%) as white solid. **TLC:** 5% MeOH/ CH₂Cl₂ (*R_f*: 0.4); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 11.49 (s, 1H), 8.63 (t, *J* = 4.8 Hz, 1H), 8.04-7.96 (m, 3H), 7.91-7.83 (m, 2H), 7.77 (t, *J* = 6.4 Hz, 2H), 3.25-3.24 (m, 2H), 1.71-1.58 (m, 5H), 1.42-1.37 (m, 2H), 1.28-1.14 (m, 4H), 0.92-0.84 (m, 2H); **LC-MS:** 97.31%; 413.2 (*M*⁺+1); (column; X-bridge C-18, (50 × 3.0 mm, 3.5 μm); RT 3.78 min. 0.05% TFA in water: ACN; 0.8 mL/min); **UPLC (purity):** 96.73%; (column : Acquity UPLC BEH C-18 (2.1 x 50 mm, 1.7 μ); RT 2.52 min. ACN : 0.025% TFA (Aq); 0.5 mL/min).

Example 54: Synthesis of Compound 1656

[000449] Synthesis of *tert*-butyl (4-bromophenethyl) carbamate (547): To a stirred solution of 2-(4-bromophenyl) ethan-1-amine **546** (500 mg, 2.50 mmol) in CH₂Cl₂ (5 mL) under argon atmosphere were added Boc-anhydride (594 mg, 2.75 mmol), diisopropyl ethyl amine (1 mL, 7.50 mmol) at RT and stirred for 4 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (25 mL) and extracted with CH₂Cl₂ (2 x 35 mL). The combined organic extracts were washed with water (25 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude was purified through silica gel column chromatography using 5-8% EtOAc/ hexanes to afford compound **547** (500 mg, 65%) as white solid. **TLC:** 10% EtOAc/ hexanes (*R_f*: 0.5); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 7.46 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.86-6.82 (m, 1H), 3.12-3.08 (m, 2H), 2.68-2.64 (m, 2H), 1.32 (s, 9H).

[000450] Synthesis of *tert*-butyl (4-((trimethylsilyl) ethynyl) phenethyl) carbamate (548): To a stirred solution of compound **547** (500 mg, 1.66 mmol) in DMF (10 mL) under argon

atmosphere were added ethynyltrimethylsilane (1.8 mL, 16.66 mmol), triethyl amine (2.32 mL, 16.66 mmol) and purged under argon for 15 min. To this were added Pd(PPh₃)₂Cl₂ (118 mg, 0.16 mmol), copper iodide (33 mg, 0.16 mmol) and purged under argon for 15 min; heated to 70 °C and stirred for 48 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude which was purified through silica gel column chromatography using 10% EtOAc/ hexanes to afford compound **548** (500 mg, 95%) as brown syrup. **TLC:** 10% EtOAc/ hexanes (*R_f*: 0.6); **¹H-NMR (DMSO-*d*₆, 400 MHz):** δ 7.38 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 6.85 (t, *J* = 7.2 Hz, 1H), 3.16-3.11 (m, 2H), 2.70-2.66 (m, 2H), 1.34 (s, 9H), 0.23 (s, 9H).

[000451] Synthesis of *tert*-butyl (4-ethynylphenethyl) carbamate (549): To a stirred solution of compound **548** (500 mg, 1.70 mmol) in THF (5 mL) under argon atmosphere was added TBAF (2.08 mL, 2.08 mmol) in THF (3 mL) at RT and stirred for 4 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude which was purified through silica gel column chromatography using 5-10% EtOAc/ hexanes to afford compound **549** (450 mg, 95%) as brown syrup. **TLC:** 10% EtOAc/ hexanes (*R_f*: 0.4); **¹H-NMR (DMSO-*d*₆, 500 MHz):** δ 7.39 (d, *J* = 7.5 Hz, 2H), 7.20 (d, *J* = 7.5 Hz, 2H), 6.87-6.85 (m, 1H), 4.10 (s, 1H), 3.15-3.12 (m, 2H), 2.71-2.69 (m, 2H), 1.30 (s, 9H).

[000452] Synthesis of *tert*-butyl (4-(1-benzyl-1*H*-1, 2, 3-triazol-5-yl) phenethyl) carbamate (551): To a stirred solution of compound **549** (200 mg, 0.82 mmol) in MeOH: DMF (1: 1, 20 mL) under argon atmosphere were added (azidomethyl) benzene **550** (410 mg, 3.06 mmol), copper iodide (202 mg, 1.02 mmol) at RT; heated to reflux and stirred for 18 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude which was purified through silica gel column chromatography using 30% EtOAc/ hexanes to afford compound **551** (200 mg, 68%) as white solid. **TLC:** 30% EtOAc/ hexanes (*R_f*: 0.3); **¹H-NMR (DMSO-*d*₆, 500 MHz):** δ 8.59 (s, 1H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.41-7.34 (m, 5H), 7.25 (d, *J* = 8.0 Hz, 2H), 6.90-6.88 (m, 1H), 5.64 (s, 2H), 3.17-3.13 (m, 2H), 2.70 (t, *J* = 7.5 Hz, 2H), 1.36 (s, 9H).

[000453] Synthesis of 2-(4-(1-benzyl-1*H*-1, 2, 3-triazol-5-yl) phenyl) ethan-1-amine (552): To a stirred solution of compound **551** (190 mg, 0.50 mmol) in CH₂Cl₂ (4 mL) under argon

atmosphere was added trifluoro acetic acid (1 mL) at RT and stirred for 3 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed *in vacuo* to obtain the crude to obtain compound **552** (180 mg, crude) as dark brown syrup which was carried to the next step without any purification. **TLC:** 100% EtOAc (R_f : 0.2); **$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz):** δ 8.61 (s, 1H), 7.81 (d, J = 8.0 Hz, 2H), 7.78-7.76 (m, 3H), 7.39-7.32 (m, 6H), 5.64 (s, 2H), 3.09-3.04 (m, 2H), 2.87 (t, J = 7.6 Hz, 2H).

[000454] Synthesis of *N*-(4-(1-benzyl-1*H*-1, 2, 3-triazol-5-yl) phenethyl)-11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxamide **5, 5-dioxide (**553**):** To a stirred solution compound **552** (200 mg, 0.66 mmol) in DMF (10 mL) under argon atmosphere were added EDCI. HCl (189 mg, 0.98 mmol), HOBt (189 mg, 0.98 mmol), compound **6** (297 mg, 0.79 mmol), diisopropyl ethyl amine (0.35 mL, 1.98 mmol) at 0 °C; warmed to RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with EtOAc (2 x 50 mL) washed with water (50 mL), brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude compound was purified through column chromatography using 2% MeOH/ CH₂Cl₂ to afford compound **553** (180 mg, 49%) as an off-white solid. **TLC:** 5% MeOH/ CH₂Cl₂ (R_f : 0.5); **$^1\text{H NMR}$ (DMSO- d_6 , 400 MHz):** δ 11.46 (br s, 1H), 8.80 (t, J = 5.5 Hz, 1H), 8.56 (s, 1H), 8.03 (d, J = 8.3 Hz, 1H), 8.00-7.95 (m, 2H), 7.92-7.83 (m, 2H), 7.79 (s, 1H), 7.75 (d, J = 8.2 Hz, 3H), 7.42-7.31 (m, 5H), 7.29 (d, J = 8.3 Hz, 2H), 5.63 (s, 2H), 3.50 (q, J = 6.8 Hz, 2H), 2.85 (t, J = 7.2 Hz, 2H).

[000455] Synthesis of *N*-(4-(1*H*-1, 2, 3-triazol-5-yl) phenethyl)-11-oxo-10, 11-dihydrodibenzo [*b*, *f*] [1, 4] thiazepine-8-carboxamide **5, 5-dioxide (**1656**):** To a stirred solution of compound **553** (180 mg, 0.31 mmol) in DMSO (10 mL) under argon atmosphere was added potassium tertiary butoxide (1 M in THF, 2.5 mL, 2.55 mmol) at RT. The reaction mixture was stirred under oxygen atmosphere (balloon pressure) for 24 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (5 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the crude. The crude compound was purified through column chromatography using 2% MeOH/ CH₂Cl₂, lyophilized and washed EtOAc (5 mL), filtered, washed with *n*-pentane (5 mL) and dried *in vacuo* to afford **1656** (20 mg, 13%) as white solid. **TLC:** 5% MeOH/ CH₂Cl₂ (R_f : 0.3); **$^1\text{H NMR}$ (DMSO- d_6 , 400 MHz):** δ 14.91 (br s,

1H), 11.52 (br s, 1H), 8.81 (t, $J = 5.5$ Hz, 1H), 8.21 (br s, 1H), 8.04 (d, $J = 8.3$ Hz, 1H), 8.01-7.95 (m, 2H), 7.92-7.85 (m, 2H), 7.82-7.73 (m, 4H), 7.31 (d, $J = 7.9$ Hz, 2H), 3.51 (q, $J = 6.6$ Hz, 2H), 2.86 (t, $J = 7.1$ Hz, 2H); **LC-MS**: 96.04%; 473.9 ($M^+ + 1$); (column; Ascentis Express C-18, (50 × 3.0 mm, 2.7 μ m); RT 2.01 min. 0.025% Aq. TFA + 5% ACN: ACN + 5% 0.025% Aq. TFA, 1.2 mL/min). **HPLC (purity)**: 95.54%; (column; Zorbax SB C-18 (150 × 4.6 mm, 3.5 μ m); RT 7.59 min. ACN: 0.05% TFA (Aq); 1.0 mL/min).

Example 55: Synthesis of compounds from compound 575 using various commercially available amines

[000456] Readily available acids similar to **575**, **576** and **577** were converted to the desired compounds using commercially available amines employing Procedures A and B and the results are captured in Tables 5 and 6.

Carbon bridged compounds:

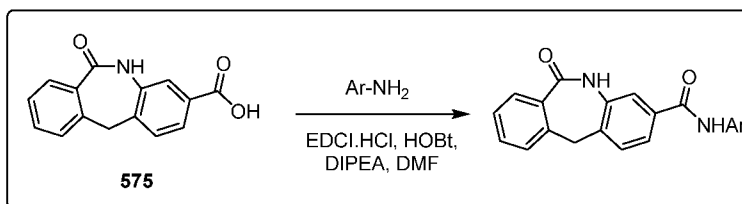
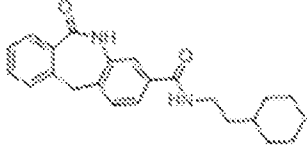


Table 5: Synthesis of compounds from compound 575 using various commercially available amines

No.	Structure	Procedure, Intermediate, Amine	Rx. Yield (%)	Mass Spec. Found	Mass Spec. Calculated	¹ H-NMR
1591		A, 575, 218 (RT 12 h)	44	343.9 ($M^+ + 1$)	343.13 for $C_{21}H_{17}N_3O_2$	¹ H-NMR (DMSO- d_6 , 400 MHz): δ 9.27 (t, $J = 5.7$ Hz, 1H), 8.96 (s, 1H), 7.96 (s, 1H), 7.82 (s, 1H), 7.74-7.70 (m, 1H), 7.68-7.61 (m, 2H), 7.54-7.49 (m, 1H), 7.45-7.38 (m, 2H), 4.67 (t, $J = 5.4$ Hz, 2H), 3.54 (s,

						3H);
1198		A, 575	64	363.2 (M ⁺ +1);		(DMSO- <i>d</i> ₆ , 400 MHz): δ 10.51 (s, 1H), 8.30-8.29 (m, 1H), 7.70 (d, <i>J</i> = 8.0 Hz, 1H), 7.56 (s, 1H), 7.51-7.46 (m, 2H), 7.41-7.31 (m, 3H), 3.94 (s, 2H), 3.23 (d, <i>J</i> = 6.4 Hz, 2H), 1.70-1.62 (m, 5H), 1.39-1.37 (m, 2H), 1.26-1.14 (m, 4H), 0.91-0.86 (m, 2H);
1576		A, 575, 212 (RT 12 h)	44	344.9 (M ⁺ +1)	344.13 for C ₂₀ H ₁₆ N ₄ O ₂	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.52 (s, 1H), 9.10-9.01 (m, 2H), 8.74 (s, 2H), 7.70 (d, <i>J</i> = 7.5 Hz, 1H), 7.62 (s, 1H), 7.57 (d, <i>J</i> = 7.9 Hz, 1H), 7.51-7.43 (m, 2H), 7.38 (d, <i>J</i> = 7.3 Hz, 1H), 7.33 (t, <i>J</i> = 7.5 Hz, 1H), 4.46 (d, <i>J</i> = 5.5 Hz, 2H), 3.96 (s, 2H);
1577		A, 575, 213	26	350.0 (M ⁺ +1)	349.09 for C ₁₉ H ₁₅ N ₃ O ₂ S	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.52 (s, 1H), 9.10 (t, <i>J</i> = 5.8 Hz, 1H), 8.95 (s, 1H), 7.79 (s, 1H), 7.70 (dd, <i>J</i> = 7.7, 1.1 Hz, 1H), 7.61 (s, 1H), 7.54 (dd, <i>J</i> = 7.9, 1.6 Hz, 1H), 7.48 (td, <i>J</i> = 8.8, 1.8 Hz,

						1H), 7.43 (d, J = 7.9 Hz, 1H), 7.38 (d, J = 6.9 Hz, 1H), 7.33 (td, J = 7.6, 1.6 Hz, 1H), 4.64 (d, J = 5.7 Hz, 2H), 3.96 (s, 2H);
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Oxygen-bridged compounds:

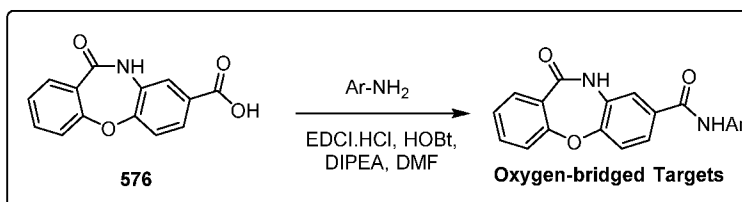
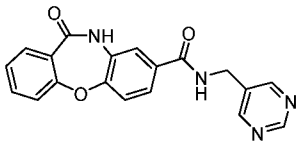
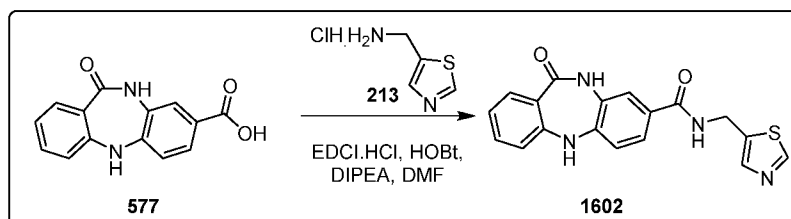


Table 6: Synthesis of compounds from compound 576 and various commercially available amines

No.	Structure	Procedure, Intermediate, Amine	Rx. Yield (%)	Mass Spec. Found	Mass Spec. Calculated	¹ H-NMR
1593		B, 576, 213	38	351.9 (M ⁺ +1)	351.07 for C ₁₈ H ₁₃ N ₃ O ₃ S	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.63 (s, 1H), 9.17 (t, J = 5.8 Hz, 1H), 8.96 (s, 1H), 7.82-7.76 (m, 2H), 7.68 (s, 1H), 7.66-7.59 (m, 2H), 7.42 (d, J = 8.4 Hz, 1H), 7.38-7.31 (m, 2H), 4.65 (d, J = 5.6 Hz, 2H)
1594		A, 576, 218	55	345.9 (M ⁺ +1)	345.11 for C ₂₀ H ₁₅ N ₃ O ₃	¹ H-NMR (DMSO- <i>d</i> ₆ , 400 MHz): δ 10.62 (s, 1H), 9.07 (t, J = 5.8 Hz, 1H), 8.53 (s, 1H), 8.45 (d, J = 4.1 Hz, 1H), 7.78 (dd, J

						= 7.7, 1.6 Hz, 1H), 7.72-7.60 (m, 4H), 7.43 (d, $J = 8.4$ Hz, 1H), 7.39-7.31 (m, 3H), 4.47 (d, $J = 5.7$ Hz, 2H)
1595		A, 576, 212	66	346.9 ($M^+ + 1$)	346.11 for $C_{19}H_{14}N_4O_3$	1H -NMR (DMSO- d_6 , 400 MHz): δ 10.62 (s, 1H), 9.13-9.05 (m, 2H), 8.75 (s, 2H), 7.78 (dd, $J = 7.7, 1.6$ Hz, 1H), 7.68 (s, 1H), 7.66-7.60 (m, 2H), 7.43 (d, $J = 8.4$ Hz, 1H), 7.39-7.30 (m, 2H), 4.48 (d, $J = 5.6$ Hz, 2H)

Nitrogen-bridged compounds:



[000457] Synthesis of 11-oxo-N-(thiazol-5-ylmethyl)-10,11-dihydro-5H-dibenzo [b, e] [1, 4] diazepine-8-carboxamide (1602): Using Procedure A the title compound was prepared using compound **577** (35 mg, 0.13 mmol) and thiazol-5-ylmethanamine hydrochloride **213** (20 mg, 0.13 mmol) and diisopropyl ethyl amine (0.05 mL, 0.27 mmol) and was obtained in 31% yield as an off-white solid; **TLC:** 5% MeOH/ CH_2Cl_2 (R_f : 0.5); **1H -NMR (DMSO- d_6 , 400 MHz):** δ 9.89 (s, 1H), 8.99-8.94 (m, 2H), 8.15 (s, 1H), 7.79 (s, 1H), 7.69 (dd, $J = 7.8, 1.3$ Hz, 1H), 7.50 -7.42 (m, 2H), 7.38-7.32 (m, 1H), 7.00 (dd, $J = 10.9, 8.3$ Hz, 2H), 6.91 (t, $J = 7.4$ Hz, 1H), 4.63 (d, $J = 5.6$ Hz, 2H); **LC-MS:** 93.15%; 351.0 ($M^+ + 1$); column; Ascentis Express C18, (50 $\times$ 3.0 mm, 2.7 μm); RT 1.76 min. 0.025% Aq. TFA + 5% ACN: ACN + 5% 0.025% Aq. TFA, 1.2 mL/min);

UPLC (purity): 93.21%; (column; Acquity BEH C-18 (50 x 2.1 mm, 1.7 μ); RT 1.57 min. ACN: 0.025% TFA (Aq); 0.5 mL/min).

Example 56: Assay Measuring Activity of Compounds on Viral Production in and on Viability of AD38 Cells

[000458] AD38 cells grown in a 175 cm flask with “Growth Medium” (DMEM/F12 (1:1) (cat# SH30023.01, Hyclone, 1X Pen/step (cat#: 30-002-CL, Mediatech, Inc), 10% FBS (cat#: 101, Tissue Culture Biologics), 250 μ g/mL G418 (cat#: 30-234-CR, Mediatech, Inc), 1 μ g/mL Tetracycline (cat#: T3325, Teknova)) were detached with 0.25% trypsin. Tetracycline-free “treatment medium” (15 mL DMEM/F12 (1:1) (cat# SH30023.01, Hyclone, 1x Pen/step (cat#: 30-002-CL, Mediatech, Inc), with 2% FBS, Tet-system approved (cat#: 631106, Clontech) were then added to mix and spun at 1300 rpm for 5 min. Pelleted cells were then re-suspended/washed with 50 mL of 1X PBS 2 times and 10 mL Treatment Medium one time. AD38 cells were then re-suspended with 10 mL of Treatment Medium and counted. Wells of a collagen coated 96-well NUNC microtiter plate were seeded at 50,000/well in 180 μ L of Treatment Medium, and 20 μ L of in treatment media with either 10% DMSO (Control) or a 10X solution of compound in 10% DMSO was added. Plates were incubated for 6 days at 37 °C.

[000459] Viral load production was assayed by quantitative PCR of the core sequence. Briefly, 5 μ L of clarified supernatant was added to a PCR reaction mixture that contained forward primers HBV-f 5'-CTGTGCCTTGGGTGGCTTT-3', Reverse primers HBV-r 5'-AAGGAAAGAAGTCAGAAGGCAAAA-3' and Fluorescent TaqManTM Probes HBV-probe 5'-FAM/AGCTCCAAA/ZEN/TTCTTTATAAGGGTCGATGTCCATG/3IABkFQ -3' in Quanta Biosciences PerfeCTa[®] qPCR Toughmix[®], and was subsequently on an Applied Biosystems ViiA7 in a final volume of 20 μ L. The PCR mixture was incubated at 45 °C for 5 minutes, then 95 °C for 10 min, followed by 40 cycles of 10 seconds at 95 °C and 20 seconds at 60 °C. Viral load was quantitated against known standards by using ViiATM 7 Software. Viral load in the supernatant from wells with treated cells were compared against viral load in supernatant from DMSO control wells (≥ 3 per plate).

[000460] At the end of compound treatment period cell viability was assessed using a Promega CellTiter-Glo protocol. All supernatant was removed the previously treated 96-well microtiter

plate, and 50 μ L Tetracycline-free treatment medium (DMEM/F12 (1:1), 1x Pen/step (cat#: 30-002-CL, Mediatech, Inc), with 2% FBS, Tet-system approved (cat#: 631106, Clontech), and 1% DMSO was added back to each well. Another 50 μ L of CellTiter-Glo reagent solution (Promega, G7573) was then added at room temperature and the contents mixed for 2 minutes on an orbital shaker to induce cell lysis. This was followed by incubation at room temperature for 10 minutes to stabilize the luminescent signal. The luminescence was recorded for 0.2 seconds per well on a Tecan multimode platereader (Infinite M1000 pro). The luminescent signal from each well was normalized against that of untreated (DMSO) control wells. All results were reported percent viability (with controls being 100%).

Table 7

Compound No.	AD38 Viral Load (CpAM/DMSO %) at 10 μ M	AD38 Viability Normalized Result (CPAM/DMSO %) at 10 μ M
1101	15	107
1102	1	100
1103	2	87
1104	1	85
1105	1	101
1107	2	106
1108	1	105
1109	6	99
1110	2	119
1111	2	89
1112	4	73
1113	1	99
1114	1	104
1115	1	106
1117	67	108
1118	61	95

1120	7	94
1121	6	109
1122	21	86
1123	62	95
1124	80	99
1125	20	108
1127	22	94
1130	2	101
1133	94	99
1149	5	118
1150	1	22
1151	1	50
1152	1	45
1154	90	50
1155	18	103
1156	16	106
1157	1	48
1158	37	120
1159	8	92
1160	2	105
1161	1	99
1162	61	99
1163	3	104
1164	27	103
1165	5	82
1166	10	119
1167	57	124
1168	10	117

1169	39	107
1170	1	95
1171	49	103
1172	51	107
1173	39	105
1174	35	109
1175	30	123
1176	2	104
1177	47	118
1182	13	55
1183	2	36
1184	1	0
1185	1	0
1186	1	39
1187	1	73
1188	4	83
1189	1	85
1190	1	70
1191	14	121
1192	3	81
1193	4	90
1194	1	45
1195	0	48
1196	2	95
1197	1	88
1198	3	60
1199	19	109
1200	18	125

1201	1	50
1202	7	107
1203	3	89
1204	2	97
1205	2	89
1206	10	106
1207	24	99
1208	11	103
1209	1	102
1210	25	116
1211	1	106
1212	1	72
1213	2	55
1214	2	94
1216	1	125
1217	1	37
1218	12	104
1219	5	100
1220	2	94
1221	19	106
1222	32	100
1223	2	28
1224	3	65
1225	10	87
1226	1	80
1227	10	92
1228	22	101
1229	45	76

1230	46	102
1231	12	93
1232	42	94
1233	1	93
1234	3	79
1235	6	61
1237	4	66
1238	26	104
1239	33	106
1240	26	92
1241	12	86
1242	91	78
1243	20	118
1244	14	103
1245	1	101
1246	6	96
1247	8	103
1248	3	106
1249	34	108
1250	14	113
1251	8	99
1252	14	94
1253	15	103
1256	1	102
1257	26	113
1258	12	105
1259	11	84
1260	8	100

1264	8	104
1266	1	74
1267	77	93
1268	77	106
1269	63	107
1270	1	94
1271	6	100
1272	24	102
1273	6	96
1274	11	88
1275	3	93
1276	24	89
1277	43	89
1278	3	88
1279	55	84
1280	74	94
1281	29	86
1282	102	105
1283	1	97
1285	3	108
1286	36	114
1287	11	96
1288	5	49
1289	40	96
1290	33	94
1291	1	102
1293	95	97
1308	1	99

1309	1	107
1310	1	89
1311	8	95
1312	5	83
1313	17	108
1314	69	101
1315	4	103
1316	32	89
1317	50	95
1318	14	70
1319	16	83
1320	43	93
1321	15	74
1322	28	94
1323	96	60
1324	10	24
1325	26	90
1326	23	95
1328	54	105
1329	62	109
1330	41	109
1331	43	88
1332	70	103
1333	20	73
1334	33	83
1335	87	104
1336	70	90
1337	77	91

1338	70	118
1339	113	70
1340	64	116
1342	113	95
1343	8	91
1344	96	102
1345	115	93
1346	105	97
1347	3	94
1348	0	107
1349	12	102
1353	50	97
1354	98	70
1356	3	101
1357	39	115
1358	15	72
1361	79	113
1362	19	98
1364	1	102
1365	2	105
1366	12	93
1367	33	88
1370	5	94
1371	6	94
1372	60	103
1373	10	100
1374	1	98
1375	11	89

1376	3	63
1377	5	65
1381	40	93
1382	47	117
1383	1	87
1384	4	79
1385	26	51
1386	61	95
1387	2	78
1388	5	71
1389	15	89
1390	2	92
1391	2	71
1392	2	85
1393	41	87
1394	55	94
1395	64	79
1396	63	95
1397	73	95
1398	5	60
1399	105	92
1400	34	105
1401	31	79
1402	12	81
1403	15	82
1405	14	94
1407	3	103
1408	17	94

1409	4	83
1410	35	50
1411	66	91
1412	48	87
1413	92	78
1414	39	89
1415	27	77
1417	11	75
1418	12	73
1419	113	89
1420	29	86
1421	78	95
1422	64	95
1423	37	91
1424	65	96
1427	7	85
1428	28	93
1429	38	90
1430	56	92
1431	115	92
1432	79	91
1433	82	94
1434	85	96
1435	77	99
1436	10	104
1440	71	91
1441	28	90
1442	65	99

1443	64	95
1444	6	65
1445	24	38
1446	3	84
1447	1	85
1448	3	85
1449	2	86
1450	73	94
1451	30	92
1452	15	62
1453	48	97
1454	27	95
1455	3	89
1456	15	101
1457	28	92
1458	12	49
1459	4	92
1462	35	99
1463	31	97
1464	49	98
1465	39	106
1466	7	88
1467	1	92
1468	76	97
1471	16	97
1472	37	95
1473	81	97
1474	51	101

1475	47	107
1476	1	86
1477	67	16
1478	2	94
1480	72	95
1481	46	100
1482	46	98
1483	65	98
1484	26	100
1485	30	96
1486	53	94
1487	15	96
1488	84	97
1490	7	79
1491	39	80
1492	39	79
1493	51	80
1494	115	60
1495	9	77
1496	2	18
1497	9	49
1498	1	82
1499	2	84
1501	37	71
1503	40	87
1505	81	85
1506	72	85
1507	11	96

1508	31	81
1509	15	29
1510	62	82
1511	38	85
1512	27	99
1513	2	82
1514	13	84
1515	2	82
1516	30	82
1517	2	78
1518	67	85
1519	73	81
1520	1	81
1521	1	22
1522	1	82
1523	1	70
1524	2	18
1525	78	85
1526	57	92
1527	19	116
1528	4	85
1529	12	111
1530	70	93
1531	53	96
1532	17	112
1533	2	105
1534	5	109
1535	108	85

1536	2	120
1537	36	98
1540	12	87
1541	11	117
1542	34	95
1543	72	90
1544	40	97
1545	59	88
1546	65	89
1547	16	90
1548	28	85
1549	7	109
1550	1	87
1551	51	91
1552	64	93
1553	86	93
1555	36	81
1556	67	86
1557	54	86
1558	51	88
1559	68	92
1560	13	92
1561	8	118
1562	25	89
1563	41	93
1564	10	119
1565	4	103
1566	31	91

1567	1	109
1568	1	100
1569	1	114
1570	2	115
1571	35	117
1572	5	116
1573	46	126
1574	78	109
1575	90	108
1576	8	108
1577	6	120
1578	33	100
1580	59	89
1581	3	97
1582	8	112
1583	41	121
1584	52	95
1585	66	87
1586	23	112
1587	78	92
1588	0	98
1589	1	85
1590	1	96
1591	13	111
1592	50	102
1593	3	133
1594	4	109
1595	3	108

1597	64	87
1598	61	93
1599	72	101
1600	12	108
1601	62	106
1602	38	116
1603	6	91
1604	0	105
1605	25	106
1606	7	104
1607	14	93
1608	63	103
1609	68	99
1611	0	130
1612	0	112
1613	0	122
1614	2	45
1615	32	123
1616	5	115
1617	1	118
1618	0	44
1619	12	122
1620	3	111
1621	1	117
1622	0	120
1623	1	128
1624	1	136
1625	2	111

1626	0	118
1627	5	115
1628	17	138
1629	3	95
1631	9	112
1632	2	122
1633	66	124
1634	45	125
1635	1	93
1636	0	111
1637	32	123

INCORPORATION BY REFERENCE

[000461] All publications and patents mentioned herein, including those items listed below, are hereby incorporated by reference in their entirety for all purposes as if each individual publication or patent was specifically and individually incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

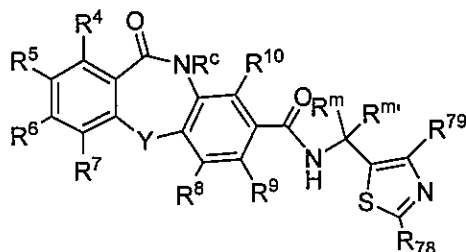
EQUIVALENTS

[000462] While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

[000463] Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction 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 invention.

CLAIMS

1. A compound represented by:



wherein

Y is S(O)_y, wherein y is 2;

R^{m'} and R^m are each independently selected from the group consisting of H, halogen, C₁₋₆ alkyl (optionally substituted by one, two or three substituents each independently selected from halogen and hydroxyl), C₂₋₆ alkenyl (optionally substituted by one, two or three substituents each independently selected from halogen and hydroxyl), NR'R'', and hydroxyl;

R^c is H;

R⁷⁸ is selected from the group consisting of H, halogen, hydroxyl, nitro, cyano, carboxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, NR'R'', -C(O)-C₁₋₆ alkyl, -C(O)-C₁₋₆ alkoxy, phenyl, heteroaryl, C₃₋₆ cycloalkyl, -S(O)_w-C₁₋₆ alkyl (where w is 1, 2 or 3), -S(O)_w-NR'R'' (where w is 1, 2 or 3), and -NR'-S(O)_w, (where w is 1, 2 or 3));

R⁷⁹ is selected from the group consisting of H, halogen, hydroxyl, nitro, cyano, carboxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, NR'R'', -C(O)-C₁₋₆ alkyl, -C(O)-C₁₋₆ alkoxy, phenyl, heteroaryl, C₃₋₆ cycloalkyl, -S(O)_w-C₁₋₆ alkyl (where w is 1, 2 or 3), -S(O)_w-NR'R'' (where w is 1, 2 or 3), and -NR'-S(O)_w, (where w is 1, 2 or 3));

R' is selected, independently for each occurrence, from H, methyl, ethyl, and propyl;

R'' is selected, independently for each occurrence, from H, methyl, ethyl, propyl, butyl, -C(O)-methyl and -C(O)-ethyl, or R' and R'' taken together with the nitrogen to which they are attached may form a 4-6 membered heterocycle;

each of moieties R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , and R^{10} is independently selected for each occurrence from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{2-6} alkenyl, halogen, hydroxyl, nitro, cyano, and $NR'R''$;

wherein for each occurrence, C_{1-6} alkyl may be optionally substituted with one, two, three or more substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano, carboxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, $NR'R''$, $-NR'-S(O)_w$, and $S(O)_w-NR'R''$; C_{1-6} alkoxy may be optionally substituted with one, two, three or more substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano, carboxy, C_{1-6} alkyl, $NR'R''$, $-NR'-S(O)_w$, and $S(O)_w-NR'R''$; C_{3-6} cycloalkyl may be optionally substituted with one, two, three or more substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-6} alkoxy, $-C(O)-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkoxy, and $NR'R''$; phenyl may be optionally substituted by one, two or three substituents each independently selected from the group consisting of halogen, hydroxyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, $NR'R''$, $C(O)-NR'R''$, $-C(O)-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkoxy, $-S(O)_w-C_{1-6}$ alkyl (where w is 1, 2 or 3), $NR'-S(O)_w$, and $-S(O)_w-NR'R''$ (where w is 1, 2 or 3), and heteroaryl may be optionally substituted by one, two or three substituents each independently selected from the group consisting of halogen, hydroxyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, $NR'R''$, $C(O)-NR'R''$, $-C(O)-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkoxy, $-S(O)_w-C_{1-6}$ alkyl (where w is 1, 2 or 3), $NR'-S(O)_w$, and $-S(O)_w-NR'R''$ (where w is 1, 2 or 3), and pharmaceutically acceptable salts thereof.

2. The compound of claim 1, wherein R^7 is selected from H and F.
3. The compound of claim 1, wherein R^6 is selected from H and F.
4. The compound of claim 1, wherein R^5 is selected from H and F.
5. The compound of claim 1, wherein R^{10} is selected from the group consisting of H, methyl and F.
6. The compound of claim 1 wherein each of R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , and R^{10} are H.
7. A pharmaceutically acceptable composition comprising a compound according to any one of claims 1-6, and a pharmaceutically acceptable excipient.
8. The pharmaceutically acceptable composition of claim 7, further comprising one or more additional compounds according to any one of claims 1-6.
9. A compound according to any one of claims 1-6 for use in therapy.

10. A compound according to any one of claims 1-6 for use in the treatment of a hepatitis B infection.
11. A compound according to any one of claims 1-6 and another HBV capsid assembly promoter for use in the treatment of a hepatitis B infection.
12. A first compound selected from any one of claims 1-6, and one or more other 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 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 for use in the treatment of a hepatitis B infection.