

INHIBITING MONOACYLGLYCEROL LIPASE (MAGL)

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This patent application claims the benefit under 35 U.S.C. §119(e) of U.S. Provisional Patent Application No. 63/294,747 filed December 29, 2021, which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

[0002] The present disclosure relates to compounds and methods for inhibiting monoacylglycerol lipase (MAGL), including compounds and methods for reversible inhibition of MAGL.

BACKGROUND

[0003] MAGL is the principal enzyme responsible for the *in vivo* degradation of 2-arachidonoyl glycerol (2-AG), an endogenous ligand of the cannabinoid receptors (e.g., CB1 and CB2). MAGL inhibition increases accumulation of the CB1/2 receptor agonist 2-arachidonoyl glycerol (2-AG), and reduces arachidonic acid (AA) and prostaglandin levels in the brain and peripheral tissues. Irreversible MAGL inhibitor compounds, such as JZL-184, increase brain and peripheral 2-AG and reduce brain AA, however tolerance can develop with chronic irreversible MAGL inhibition. Covalent interactions with MAGL could lead to irreversible enzymatic inhibition, with potential for immune-mediated toxicity.

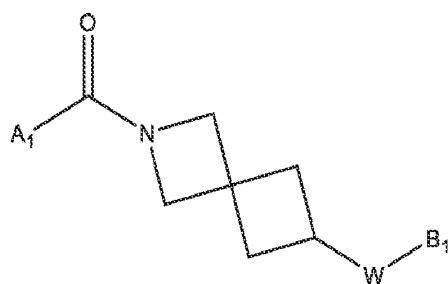
[0004] There remains a need for reversible MAGL inhibitors useful for the treatment of MAGL-mediated diseases or disorders, including the development of therapeutic compounds with improved control of dose and exposure. Such compounds can be developed through clinical trials as analgesic compounds for the treatment of pain management and/or treatment of various MAGL-mediated conditions.

[0005] Thus, there is a need in the art for compounds that can potently, selectively and reversibly inhibit MAGL and for means for treating conditions or disorders that are associated with or linked to endocannabinoid signaling activities. The present disclosure addresses these and other unfulfilled needs in the art.

SUMMARY

[0006] The inventors have discovered *inter alia* compounds to inhibit monoacylglycerol lipase (MAGL), including compounds that reversibly inhibit MAGL. Accordingly, in another aspect, the disclosure provides compounds and methods for inhibiting monoacylglycerol lipase (MAGL).

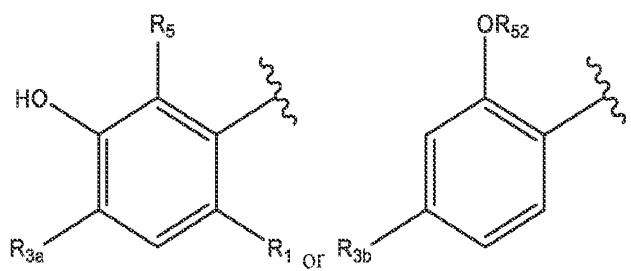
[0007] In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof:



Formula (I),

wherein

A₁ is



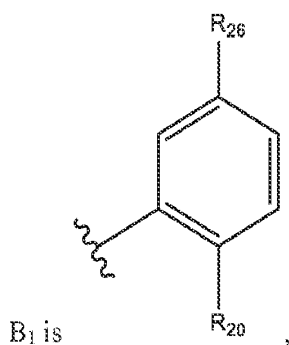
R₁ is hydrogen, halogen, or cyano;

R_{3a} and R₅ are each independently hydrogen, halogen, or lower alkyl;

R₅₂ is lower alkyl, lower cycloalkyl or lower haloalkyl;

R_{3b} is halogen;

W is a diazole optionally substituted with lower alkyl, lower cycloalkyl, or lower haloalkyl;



R₂₀ is hydrogen, halogen, lower alkyl, or lower haloalkyl; and

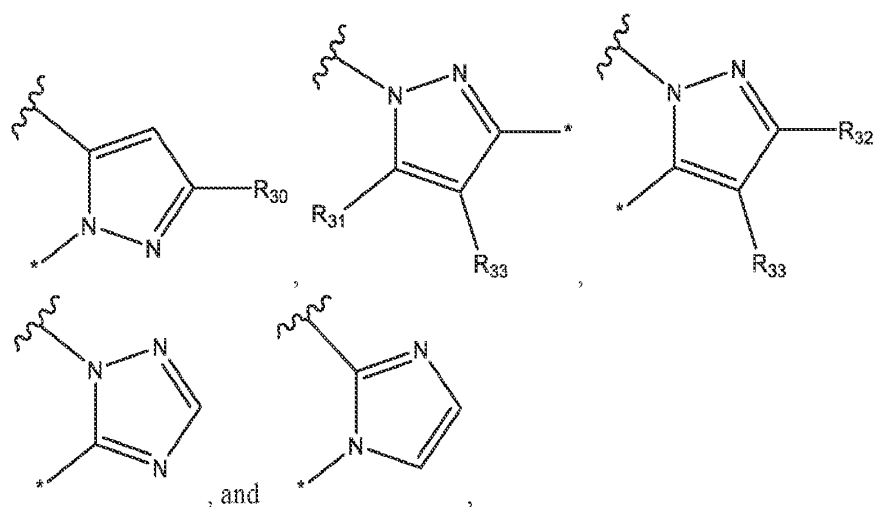
R₂₆ is hydrogen, or halogen, provided the compound is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone.

[0008] In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein R₁ is hydrogen, fluoro, or cyano; and R_{3a} and R₅ are each independently hydrogen, fluoro, or methyl. In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein R₁ is fluoro; and R_{3a} and R₅ are each independently hydrogen. In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein R₁ is hydrogen, fluoro, or cyano; R_{3a} is hydrogen, fluoro, or methyl; and R₅ is hydrogen. In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein R₁ is hydrogen or fluoro; R_{3a} is hydrogen, fluoro, or methyl; and R₅ is hydrogen.

[0009] In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein R₅₂ is lower alkyl, cyclopropyl or lower haloalkyl; and R_{3b} is fluoro. In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein R₅₂ is lower alkyl and R_{3b} is fluoro. In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein R₅₂ is lower haloalkyl and R_{3b} is fluoro. In

some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein R_{52} is lower alkyl optionally substituted with one or more fluoro and R_{3b} is fluoro. In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein R_{52} is cyclopropyl, and R_{3b} is fluoro.

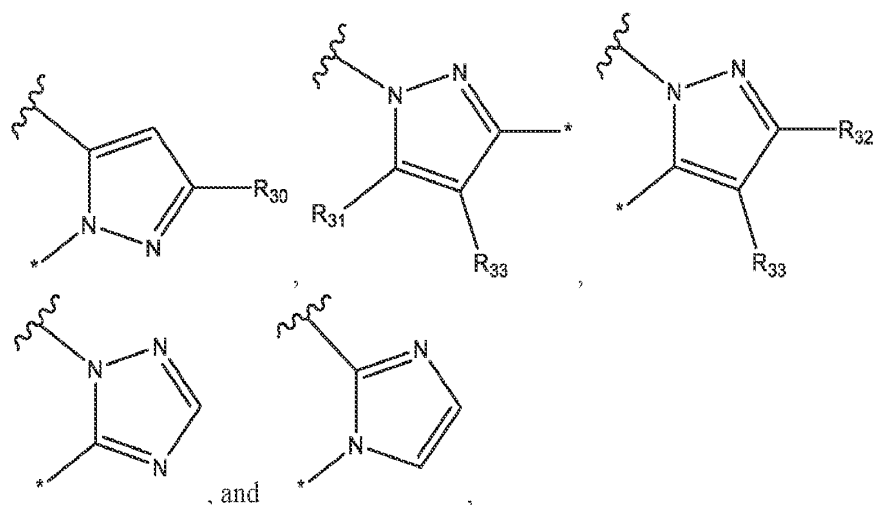
[00010] In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein W is selected from the group consisting of:



wherein * indicates a covalent bond to B_1 ; and

R_{30} , R_{31} , R_{32} and R_{33} are each independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl, provided that at least one of R_{31} and R_{33} and at least one of R_{32} and R_{33} is not hydrogen.

[00011] In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein W is selected from the group consisting of:



wherein * indicates a covalent bond to B₁; and

R₃₀, R₃₁, R₃₂ and R₃₃ are each independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl, provided that at least one of R₃₁ and R₃₃ and at least one of R₃₂ and R₃₃ is not hydrogen.

[00012] In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein R₃₀, R₃₁, R₃₂ and R₃₃ are each independently hydrogen, methyl, CF₃, or cyclopropyl, provided that at least one of R₃₁ and R₃₃ and at least one of R₃₂ and R₃₃ is not hydrogen. In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein R₃₀ is methyl. In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein R₃₃ is hydrogen, methyl, CF₃, or cyclopropyl, provided that at least one of R₃₁ and R₃₃ and at least one of R₃₂ and R₃₃ is not hydrogen. In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein R₃₂ is hydrogen and R₃₃ is methyl, CF₃ or cyclopropyl; or R₃₂ is methyl, CF₃ or cyclopropyl, and R₃₃ is hydrogen. In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein R₃₁ is hydrogen and R₃₃ is methyl, CF₃ or cyclopropyl; or R₃₁ is methyl, CF₃ or cyclopropyl, and R₃₃ is hydrogen.

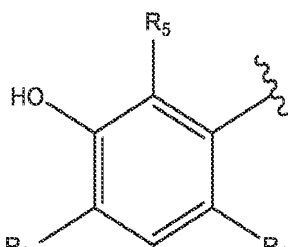
[00013] In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein R₂₀ is hydrogen, fluoro, chloro, methyl, or CF₃;

and R₂₆ is hydrogen, or fluoro. In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein R₂₀ is fluoro, chloro, methyl, or CF₃; and R₂₆ is hydrogen, or fluoro. In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein R₂₀ is methyl, or CF₃; and R₂₆ is hydrogen, or fluoro. In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein R₂₀ is fluoro or chloro, or CF₃; and R₂₆ is hydrogen, or fluoro.

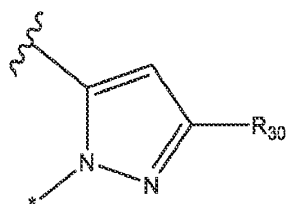
[00014] In some embodiments, the disclosure provides a compound of Formula (I) a pharmaceutically acceptable salt thereof, wherein the compound is not (2-fluoro-5-hydroxyphenyl){6-[3-methyl-1-(o-tolyl)-5-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone.

[00015] In some embodiments, the disclosure provides a compound of Formula (I) a pharmaceutically acceptable salt thereof, wherein the compound is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone.

[00016] In some embodiments, the disclosure provides a compound of Formula (I) or a

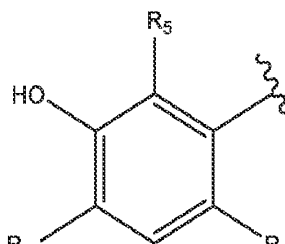


pharmaceutically acceptable salt thereof, wherein A₁ is R_{3a}; R₁ is hydrogen, F, or cyano; R_{3a} and R₅ are each independently hydrogen, F, or methyl; W is

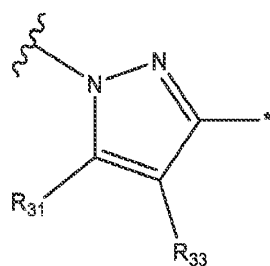


, wherein * indicates a covalent bond to B₁; R₃₀ is hydrogen, methyl, CF₃, or cyclopropyl; and R₂₀ is hydrogen, F, Cl, methyl, or CF₃; and R₂₆ is hydrogen, or F; provided that the compound is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone.

[00017] In some embodiments, the disclosure provides a compound of Formula (I) or a

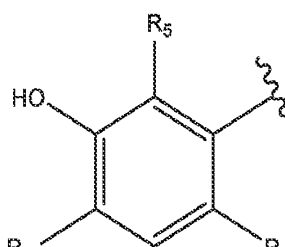


pharmaceutically acceptable salt thereof, wherein A₁ is R_{3a}; R₁ is hydrogen, F, or cyano; R_{3a} and R₅ are each independently hydrogen, F, or methyl; W is

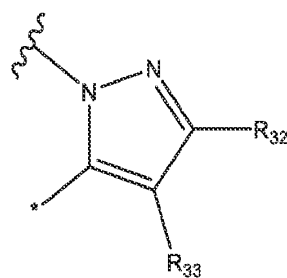


, wherein * indicates a covalent bond to B₁; R₃₁ and R₃₃ are each independently hydrogen, methyl, CF₃, or cyclopropyl, provided that at least one of R₃₁ and R₃₃ is hydrogen; R₂₀ is hydrogen, F, Cl, methyl, or CF₃; and R₂₆ is hydrogen, or F.

[00018] In some embodiments, the disclosure provides a compound of Formula (I) or a

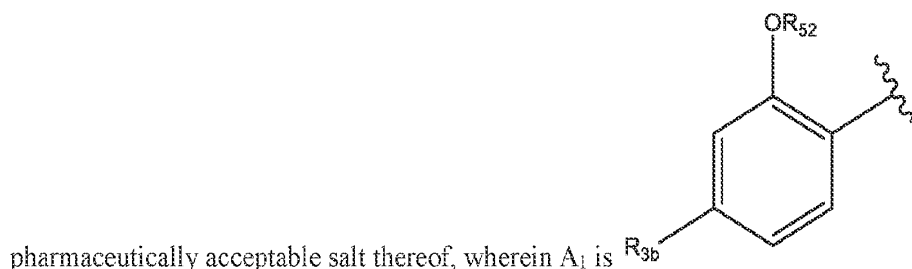


pharmaceutically acceptable salt thereof, wherein A₁ is R_{3a}; R₁ is hydrogen, F, or cyano; R_{3a} and R₅ are each independently hydrogen, F, or methyl; W is

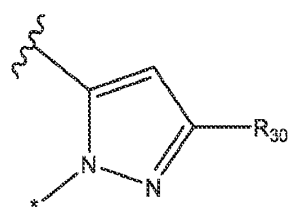


, wherein * indicates a covalent bond to B₁; R₃₂ and R₃₃ are each independently hydrogen, methyl, CF₃, or cyclopropyl, provided that at least one of R₃₂ and R₃₃ is hydrogen; R₂₀ is hydrogen, F, Cl, methyl, or CF₃; and R₂₆ is hydrogen, or F.

[00019] In some embodiments, the disclosure provides a compound of Formula (I) or a

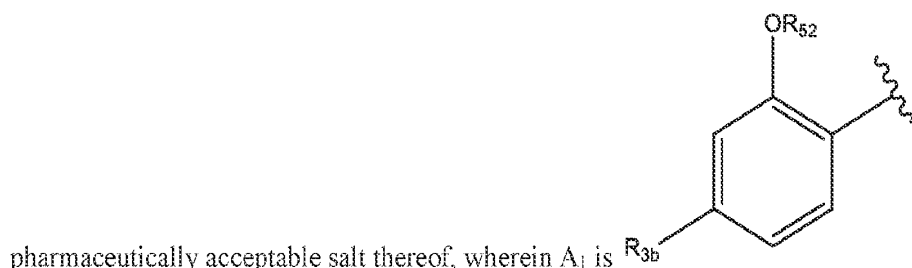


pharmaceutically acceptable salt thereof, wherein A_1 is R_{3b} ; R_{3b} is F; R_{52} is lower alkyl optionally substituted with one or more F, or cyclopropyl; W is

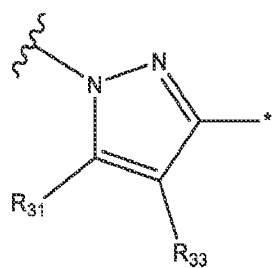


, wherein * indicates a covalent bond to B_1 ; R_{30} is hydrogen, methyl, CF_3 , or cyclopropyl; R_{20} is hydrogen, F, Cl, methyl, or CF_3 ; and R_{26} is hydrogen, or F.

[00020] In some embodiments, the disclosure provides a compound of Formula (I) or a

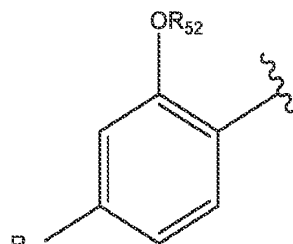


pharmaceutically acceptable salt thereof, wherein A_1 is R_{3b} ; R_{3b} is F; R_{52} is lower alkyl optionally substituted with one or more F, or cyclopropyl; W is

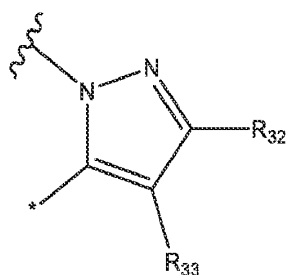


, wherein * indicates a covalent bond to B_1 ; R_{31} and R_{33} are each independently hydrogen, methyl, CF_3 , or cyclopropyl, provided that at least one of R_{31} and R_{33} is hydrogen; R_{20} is hydrogen, F, Cl, methyl, or CF_3 ; and R_{26} is hydrogen, or F.

[00021] In some embodiments, the disclosure provides a compound of Formula (I) or a



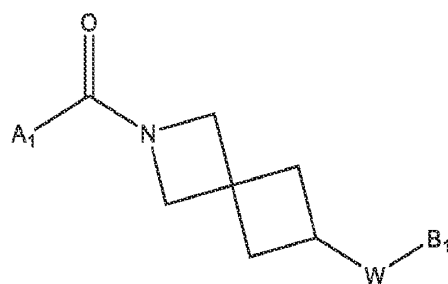
pharmaceutically acceptable salt thereof, wherein A₁ is R_{3b} ; R_{3b} is F; R_{52} is lower alkyl optionally substituted with one or more F, or cyclopropyl; W is



, wherein * indicates a covalent bond to B₁; R_{32} and R_{33} are each independently hydrogen, methyl, CF₃, or cyclopropyl, provided that at least one of R_{32} and R_{33} is hydrogen; R_{20} is hydrogen, F, Cl, methyl, or CF₃; and R_{26} is hydrogen, or F.

[00022] Generally, methods disclosed herein include administering a compound described by a chemical formula disclosed herein to inhibit MAGL. In some embodiments, the compounds described by the chemical formulae disclosed herein can be used by contacting a compound with a cell (e.g., a cell expressing MAGL) to reversibly inhibit MAGL in the cell. In still another aspect, the disclosure provides a method for treating a monoglycerol lipase mediated disease or disorder. Without limitations, administering to the cell can be in vitro or in vivo. In some embodiments, the method comprises administering to a subject in need thereof a therapeutically effective amount of a compound described by a chemical formula disclosed herein. For example, an effective amount of a compound disclosed herein can be administered to a subject to treat a condition responsive to the reversible inhibition of MAGL.

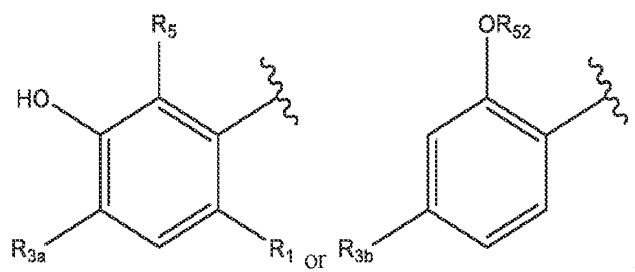
[00023] In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof,



Formula (I),

wherein:

A₁ is



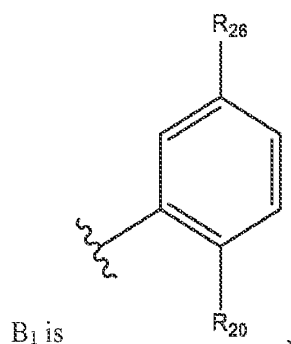
R₁ is halogen, hydrogen, or cyano;

R_{3a} and R₅ are each independently hydrogen, halogen, or lower alkyl;

R₅₂ is lower alkyl, lower cycloalkyl or lower haloalkyl;

R_{3b} is halogen;

W is a diazole optionally substituted with lower alkyl, lower cycloalkyl, or lower haloalkyl;



B₁ is

R₂₀ is halogen, hydrogen, lower alkyl, or lower haloalkyl; and

R₂₆ is hydrogen, or halogen;

provided the compound is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone.

[00024] In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein

R₁ is hydrogen, fluoro, or cyano;

R_{3a} and R₅ are each independently hydrogen, halogen, or methyl;

R₅₂ is lower alkyl, cyclopropyl or lower haloalkyl;

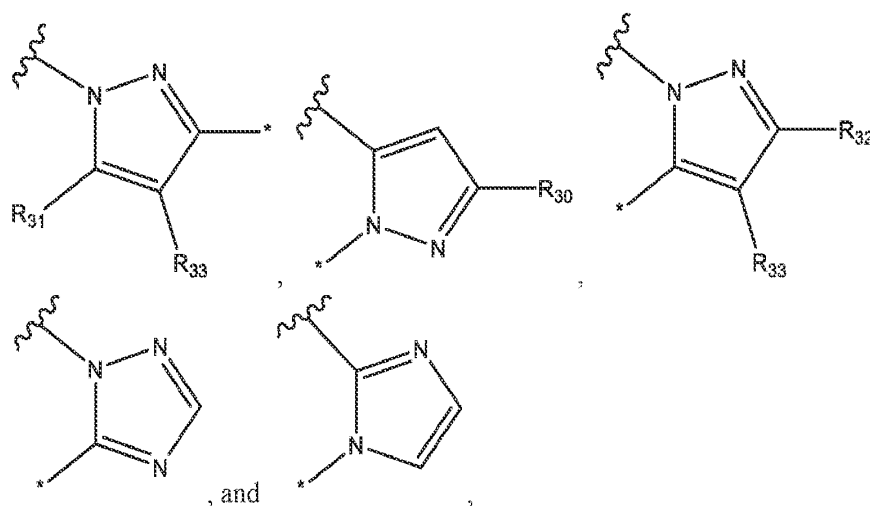
R_{3b} is fluoro;

W is a diazole optionally substituted with one of methyl, cyclopropyl, or CF₃;

R₂₀ is fluoro or chloro, methyl, or CF₃; and

R₂₆ is hydrogen, fluoro or chloro.

[00025] In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein W is selected from the group consisting of:

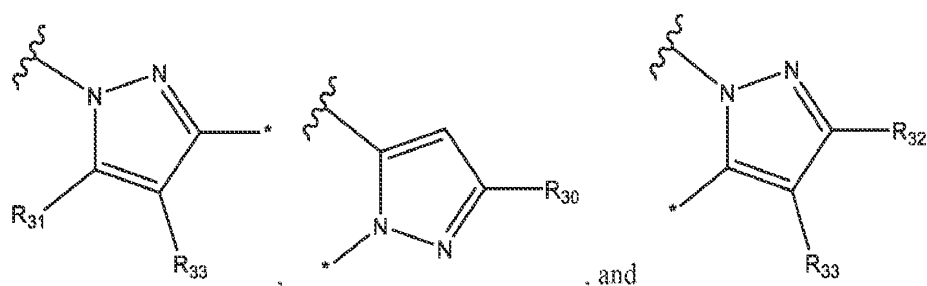


wherein * indicates a covalent bond to B₁; and

R_{30} , R_{31} , R_{32} and R_{33} are each independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl, provided that at least one of R_{31} and R_{33} and at least one of R_{32} and R_{33} is not hydrogen.

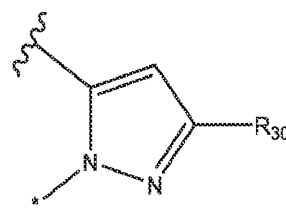
[00026] In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein R_{30} , R_{31} , R_{32} and R_{33} are each independently hydrogen, methyl, CF_3 , or cyclopropyl, provided that at least one of R_{31} and R_{33} and at least one of R_{32} and R_{33} is not hydrogen.

[00027] In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein W is selected from the group consisting of:



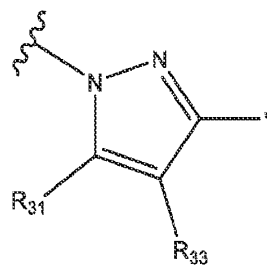
wherein * indicates a covalent bond to B_1 .

[00028] In some embodiments, the disclosure provides a compound of Formula (I) or a



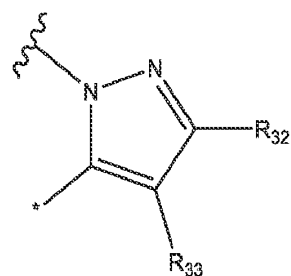
pharmaceutically acceptable salt thereof, wherein W is
wherein * indicates a covalent bond to B_1 , and R_{30} is methyl.

[00029] In some embodiments, the disclosure provides a compound of Formula (I) or a



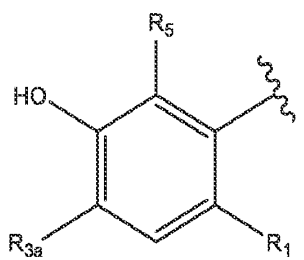
pharmaceutically acceptable salt thereof, wherein W is
* indicates a covalent bond to B₁, and R₃₁ and R₃₃ are each independently hydrogen, methyl, CF₃, or cyclopropyl, provided that one of R₃₁ and R₃₃ is hydrogen.

[00030] In some embodiments, the disclosure provides a compound of Formula (I) or a



pharmaceutically acceptable salt thereof, wherein W is
wherein * indicates a covalent bond to B₁, and R₃₂ and R₃₃ are each independently hydrogen, methyl, CF₃, or cyclopropyl, provided that one of R₃₂ and R₃₃ is hydrogen.

[00031] In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein A₁ is



[00032] In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein R₅ is hydrogen.

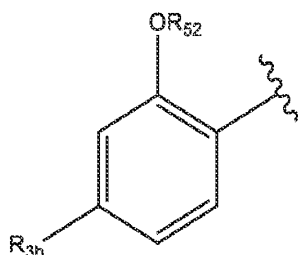
[00033] In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein R_1 is fluoro.

[00034] In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein R_{3a} is hydrogen, fluoro, or methyl.

[00035] In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein R_{3a} is hydrogen.

[00036] In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein R_{20} is methyl, and R_{26} is hydrogen or fluoro; or R_{20} is chloro, fluoro or CF_3 , and R_{26} is hydrogen.

[00037] In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein A_1 is



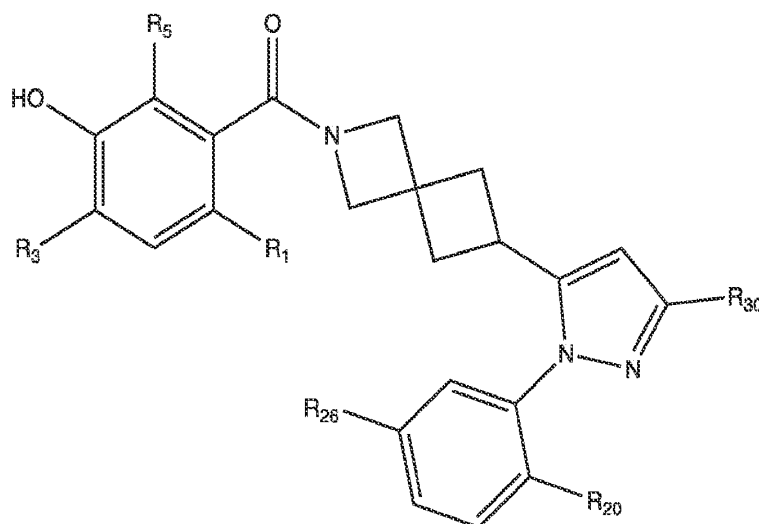
[00038] In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein R_{52} is lower alkyl optionally substituted with one or more fluoro and cyclopropyl.

[00039] In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein R_{3b} is fluoro.

[00040] In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein R_{20} is methyl, and R_{26} is hydrogen or fluoro; or

R₂₀ is fluoro or CF₃, and R₂₆ is hydrogen.

[00041] In some embodiments, the disclosure provides a compound of Formula (II-B) or a pharmaceutically acceptable salt thereof:



Formula (II-B),

wherein

R₁ is halogen or cyano;

R₃ is hydrogen, lower alkyl, or halogen;

R₅ is hydrogen, halogen or lower alkyl;

R₂₀ is halogen or lower alkyl optionally substituted with one or more halogen;

R₂₆ is halogen or hydrogen; and

R₃₀ is hydrogen or lower alkyl optionally substituted with one or more halogen, provided the compound is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone.

[00042] In some embodiments, the disclosure provides a compound of Formula (II-B) or a pharmaceutically acceptable salt thereof, wherein

R₁ is F or cyano;

R₃ is hydrogen, methyl, or F;

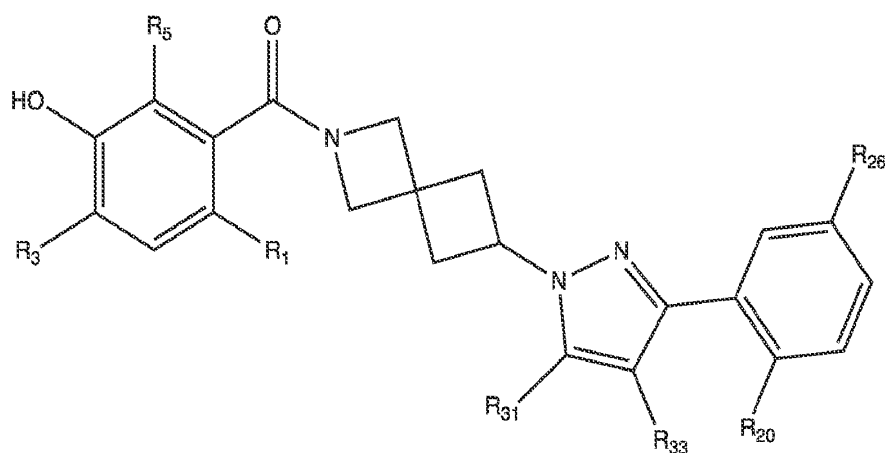
R₅ is hydrogen, F or methyl;

R₂₀ is F, methyl, or CF₃;

R₂₆ is hydrogen or F; and

R₃₀ is hydrogen, methyl or CF₃, provided the compound is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone.

[00043] In some embodiments, the disclosure provides a compound of Formula (II-C) or a pharmaceutically acceptable salt thereof:



Formula (II-C),

wherein

R₁ is halogen or cyano;

R₃ is hydrogen, lower alkyl, or halogen;

R₅ is hydrogen, halogen or lower alkyl;

R₂₀ is halogen or lower alkyl optionally substituted with one or more halogen;

R₂₆ is hydrogen or halogen; and

R₃₁ and R₃₃ are each independently hydrogen or lower alkyl optionally substituted with one or more halogen, provided that one of R₃₁ and R₃₃ is hydrogen.

[00044] In some embodiments, the disclosure provides a compound of Formula (II-C) or a pharmaceutically acceptable salt thereof, wherein

R₁ is F or cyano;

R₃ is hydrogen, methyl, or F;

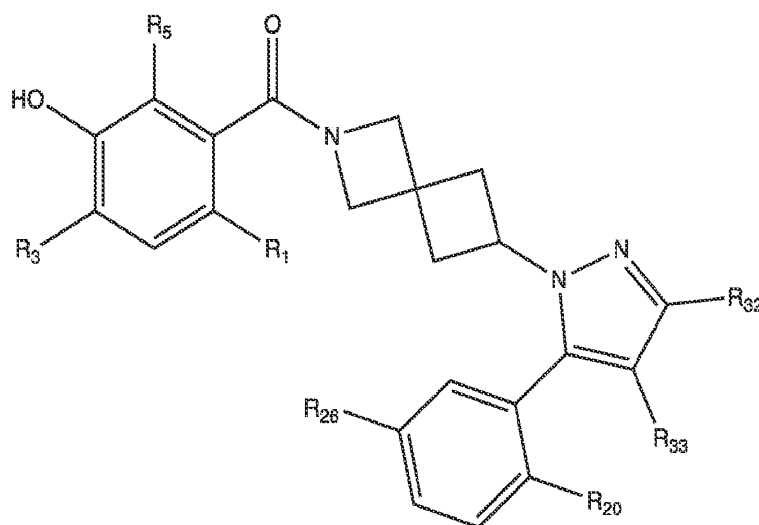
R₅ is hydrogen, F or methyl;

R₂₀ is F, methyl, or CF₃;

R₂₆ is hydrogen or F; and

R₃₁ and R₃₃ are each independently hydrogen, methyl or CF₃.

[00045] In some embodiments, the disclosure provides a compound of Formula (II-D) or a pharmaceutically acceptable salt thereof:



wherein

R₁ is halogen or cyano;

R₃ is hydrogen, lower alkyl, or halogen;

R₅ is hydrogen, halogen or lower alkyl;

R₆ is hydrogen;

R₂₀ is halogen or lower alkyl optionally substituted with one or more halogen;

R₂₆ is halogen or hydrogen; and

R₃₂ and R₃₃ are each independently hydrogen or lower alkyl optionally substituted with one or more halogen, provided that one of R₃₂ and R₃₃ is hydrogen.

[00046] In some embodiments, the disclosure provides a compound of Formula (II-D) or a pharmaceutically acceptable salt thereof, wherein

R₁ is F or cyano;

R₃ is hydrogen, F or methyl;

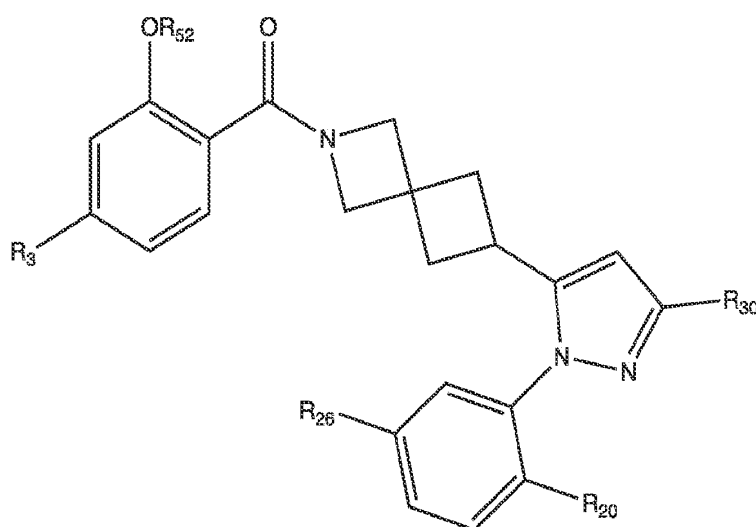
R₅ is hydrogen, F or methyl;

R₂₀ is F or methyl, or CF₃;

R₂₆ is hydrogen or F; and

R₃₂ and R₃₃ are each independently hydrogen, methyl or, CF₃ provided that one of R₃₂ and R₃₃ is hydrogen.

[00047] In some embodiments, the disclosure provides a compound of Formula (III-B) or a pharmaceutically acceptable salt thereof:



Formula (III-B)

wherein

R₃ is halogen;

R₅₂ is lower alkyl or lower cycloalkyl, each optionally substituted with halogen,

R₃₀ is lower alkyl;

R₂₀ is lower alkyl; and

R₂₆ is hydrogen or halogen.

[00048] In some embodiments, the disclosure provides a compound of Formula (III-B) or a pharmaceutically acceptable salt thereof, wherein

R₃ is F;

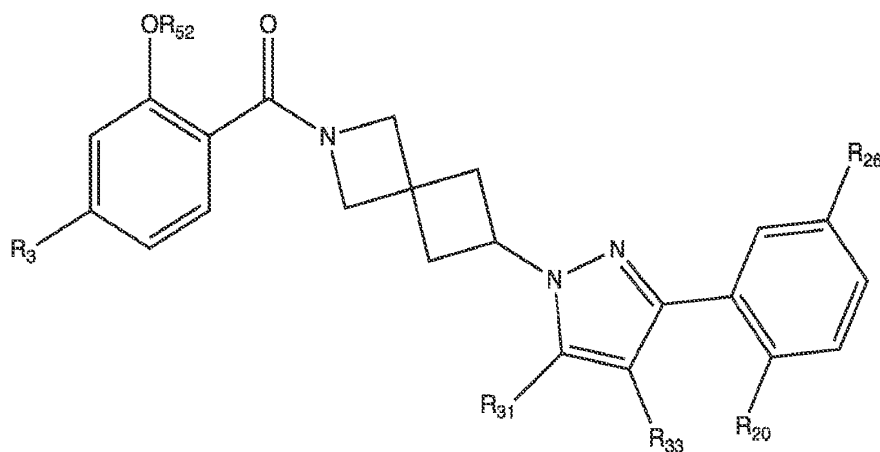
R₅₂ is lower alkyl optionally substituted with one or more F or cyclopropyl;

R₃₀ is methyl;

R₂₀ is methyl; and

R₂₆ is hydrogen or F.

[00049] In some embodiments, the disclosure provides a compound of Formula (III-C) or a pharmaceutically acceptable salt thereof:



wherein

R₃ is halogen;

R₅₂ is lower alkyl or lower cycloalkyl, each optionally substituted with halogen,

R₃₁ and R₃₃ are each independently hydrogen or lower alkyl optionally substituted with one or more halogen, provided that one of R₃₁ and R₃₃ is hydrogen.

R₂₀ is lower alkyl optionally substituted with halogen; and

R₂₆ is hydrogen or halogen.

[00050] In some embodiments, the disclosure provides a compound of Formula (III-C) or a pharmaceutically acceptable salt thereof, wherein

R₃ is F;

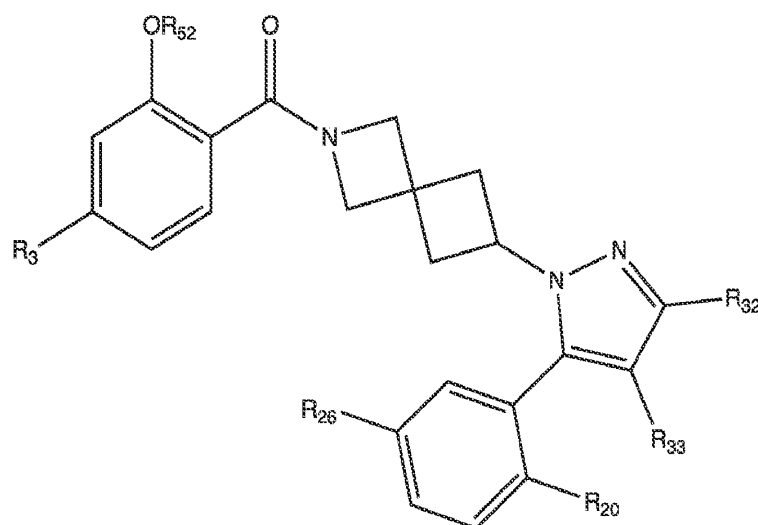
R₅₂ is lower alkyl optionally substituted with one or more F; or cyclopropyl;

R₃₁ and R₃₃ are each independently hydrogen, methyl or CF₃, provided that one of R₃₁ and R₃₃ is hydrogen;

R₂₀ is methyl or CF₃; and

R₂₆ is hydrogen or F.

[00051] In some embodiments, the disclosure provides a compound of Formula (III-D) or a pharmaceutically acceptable salt thereof:



Formula (III-D)

wherein

R₃ is halogen;

R₅₂ is lower alkyl or lower cycloalkyl, each optionally substituted with halogen,

R₃₂ and R₃₃ are each independently hydrogen or lower alkyl optionally substituted with one or more halogen, provided that one of R₃₂ and R₃₃ is hydrogen.

R₂₀ is lower alkyl optionally substituted with halogen; and

R₂₆ is hydrogen or halogen.

[00052] In some embodiments, the disclosure provides a compound of Formula (III-D) or a pharmaceutically acceptable salt thereof, wherein

R₃ is F;

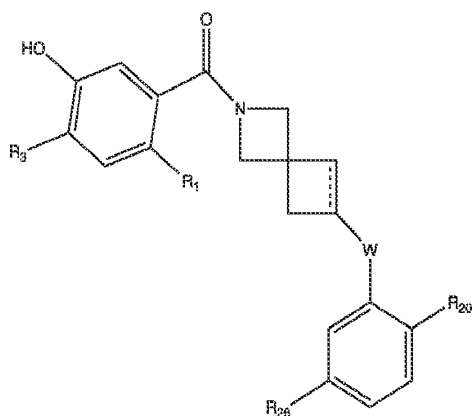
R₅₂ is lower alkyl optionally substituted with one or more F, or cyclopropyl,

R₃₂ and R₃₃ are each independently hydrogen, methyl or CF₃, provided that one of R₃₂ and R₃₃ is hydrogen;

R₂₀ is methyl or CF₃; and

R₂₆ is hydrogen or F.

[00053] In some embodiments, the disclosure provides a compound of Formula (II), or a pharmaceutically acceptable salt thereof,



Formula (II),

wherein

the dashed line represents an optional double bond;

R₁ is halogen;

R₃ is hydrogen;

W is A;

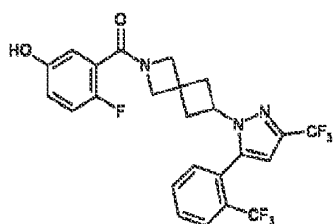
A is a 5-member heteroaryl ring optionally substituted with one or more R₃₀;

R₂₀ is halogen or lower alkyl optionally substituted with one or more halogen;

R₃₀ is lower alkyl optionally substituted with one or more halogen; and

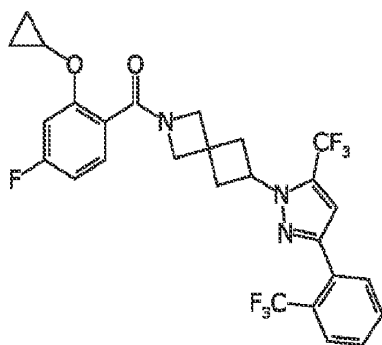
R₂₆ is halogen or hydrogen, provided the compound is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone.

[00054] In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein the compound is



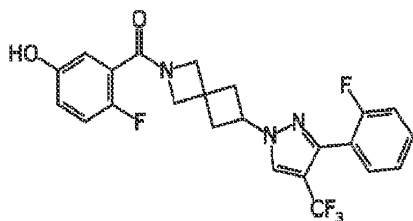
, or a pharmaceutically acceptable salt thereof.

[00055] In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein the compound is



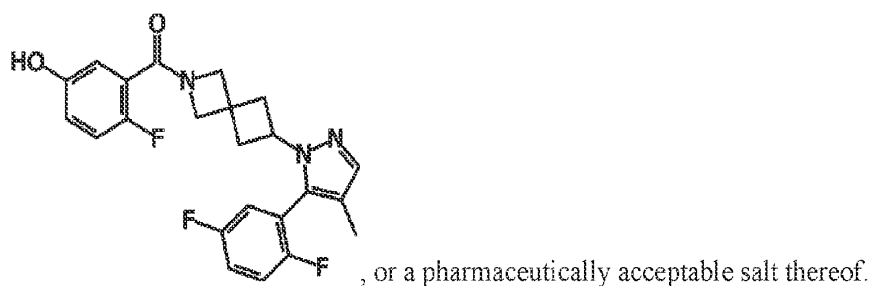
, or a pharmaceutically acceptable salt thereof.

[00056] In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein the compound is

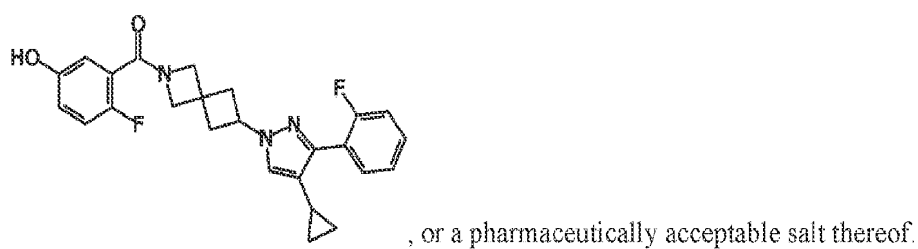


, or a pharmaceutically acceptable salt thereof.

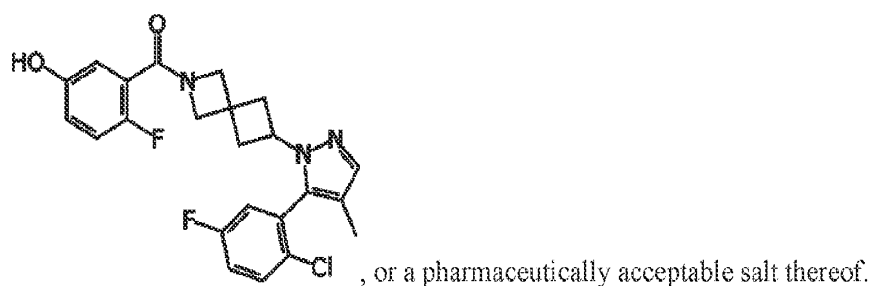
[00057] In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein the compound is



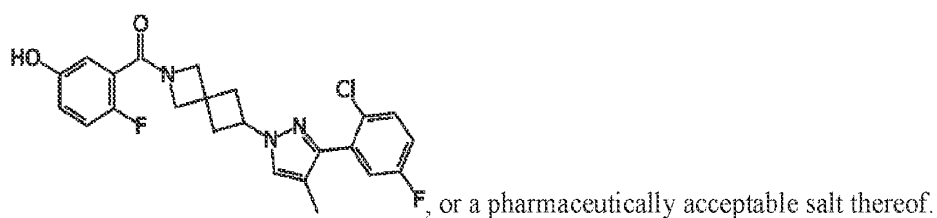
[00058] In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein the compound is



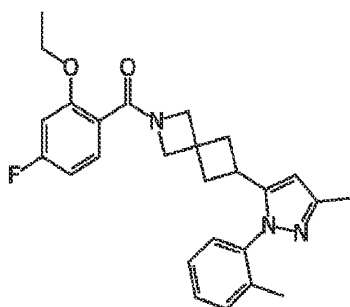
[00059] In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein the compound is



[00060] In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein the compound is

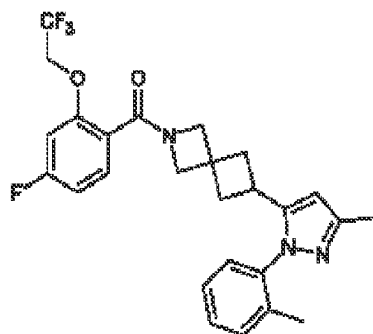


[00061] In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein the compound is



, or a pharmaceutically acceptable salt thereof.

[00062] In some embodiments, the disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein the compound is



, or a pharmaceutically acceptable salt thereof.

[00063] In some embodiments, the disclosure provides a pharmaceutical composition comprising a compound defined herein, or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient (API), provided the compound is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone.

[00064] In some embodiments, the disclosure provides a method of inhibiting monoacylglycerol lipase (MAGL) in a subject comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound defined herein.

[00065] In some embodiments, the disclosure provides a method of reversibly inhibiting monoacylglycerol lipase (MAGL) comprising the step of contacting a compound defined herein with a cell expressing MAGL.

[00066] The disclosure also provides a pharmaceutical composition comprising a compound defined herein as a Reversible MAGL Inhibitor Compound and/or Selective MAGL Inhibitor Compound disclosed herein, and a pharmaceutically acceptable carrier or excipient.

BRIEF DESCRIPTION OF THE FIGURES

[00067] No Figures are included in the disclosure.

DETAILED DESCRIPTION

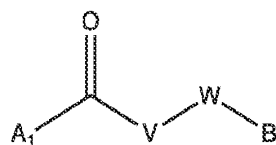
[00068] Applicants have discovered chemical compounds that are Reversible MAGL Inhibitor Compounds and Selective MAGL Inhibitor Compounds. In some embodiments, the compound is a Reversible MAGL Inhibitor Compound. In some embodiments, the compound is a Selective MAGL Inhibitor Compound. In some embodiments, the compound is both a Reversible MAGL Inhibitor Compound and a Selective MAGL Inhibitor Compound.

[00069] In some embodiments, the compound is a reversible MAGL Inhibitor Compound that is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone. In some embodiments, the compound is a Reversible MAGL Inhibitor Compound and a Selective MAGL Inhibitor Compound that is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone.

Compounds

[00070] In some embodiments, the disclosure provides certain compounds that are both a Selective MAGL Inhibitor Compound and a Reversible MAGL Inhibitor Compound as defined herein, or a pharmaceutically acceptable salt thereof.

[00071] In some embodiments, the disclosure provides certain compounds of Formula (I-A) that are both a Selective MAGL Inhibitor Compound and a Reversible MAGL Inhibitor Compound as defined herein, or a pharmaceutically acceptable salt thereof.



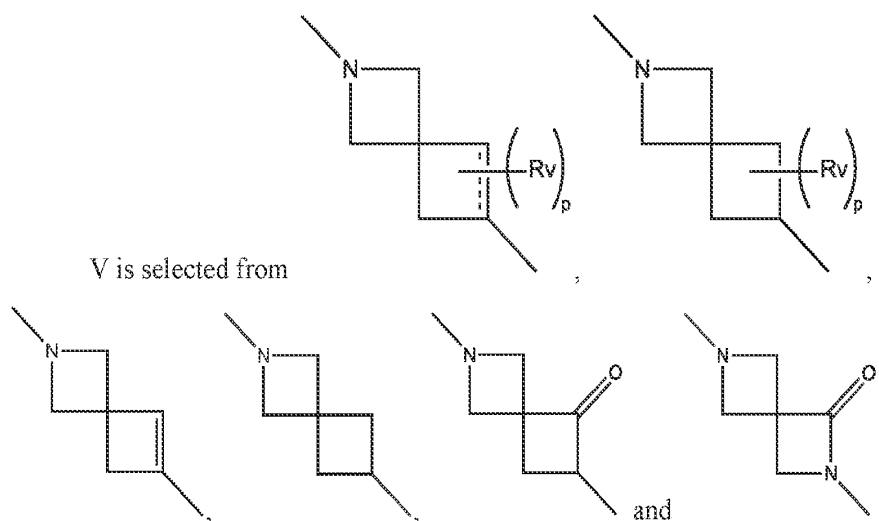
Formula (I-A),

wherein

A_1 is an aryl or heteroaryl optionally substituted with one or more R_a ;

each R_a is independently halogen, cyano, lower alkyl optionally substituted with one or more halogen, cycloalkyl, aminoalkyl, carboxy, carboxamide, or $-OR_6$;

R_6 is hydrogen, lower alkyl or lower cycloalkyl optionally substituted with one or more halogen;



each p is independently 0, 1, 2, 3 or 4;

each R_v is independently hydrogen, halogen, or alkyl optionally substituted with one or more halogen;

W is $-A_2-$, $-C(O)-$, $C(O)-A_2-$, $-C(O)N(R_{10})-$ and $-C(O)N(R_{10})-A_2-$;

A_2 is a 5-member heteroaryl ring optionally substituted with one or more R_{30} ;

each R_{30} is lower alkyl;

R_{10} is hydrogen or lower alkyl;

B is 5- or 6-member aryl or heteroaryl optionally substituted with one or more R_b or $-OR_b$; and

each R_b is independently halogen, cyano, lower alkyl optionally substituted with one or more halogen, cycloalkyl, aminoalkyl, carboxy, or carboxamide; and

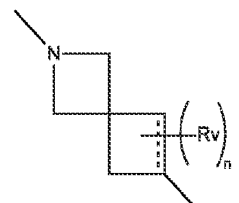
provided that the compound of Formula (I-A) is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone.

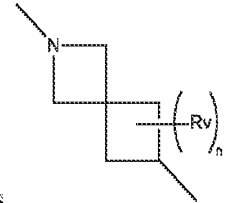
[00072] In some embodiments, a compound is both a Selective MAGL Inhibitor Compound and a Reversible MAGL Inhibitor Compound of Formula (I-A) that is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone, wherein A₁ is a 6-member aryl or heteroaryl ring comprising at least one nitrogen; A₂ is a 5-member heteroaryl ring comprising at least one nitrogen heteroatom, and B is a 5- or 6- member aryl or B is a 5- or 6- member heteroaryl ring comprising at least one nitrogen atom, wherein each heteroaryl ring in A₁, A₂ and B comprises one or more heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur.

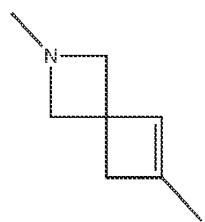
[00073] In some embodiments, A₁ in Formula (I-A) is a 6-member aryl or heteroaryl optionally substituted with one or more R_a. In some embodiments, A₁ in Formula (I-A) is phenyl optionally substituted with one or more R_a. In some embodiments, A₁ in Formula (I-A) is pyridine optionally substituted with one or more R_a. In some embodiments, A₁ in Formula (I-A) is phenyl optionally substituted with one or more R_a.

[00074] Each R_a substitution of A₁ of Formula (I-A) can be the same or different. Each R_a in Formula (I-A) is independently halogen, cyano, lower alkyl optionally substituted with one or more halogen, cycloalkyl, aminoalkyl, carboxy, carboxamide, or -OR₆; and each R₆ in Formula (I-A) is independently hydrogen, lower alkyl or lower cycloalkyl optionally substituted with one or more halogen. In some embodiments, the halogen in R_a in Formula (I-A) is F or Cl. In some embodiments, the halogen in R_a in Formula (I-A) is F. In some embodiments, the halogen in R_a in Formula (I-A) is F or Cl. In some embodiments, the lower alkyl in R_a in Formula (I-A) is (C₁-C₄) alkyl. In some embodiments, the lower alkyl in R_a in Formula (I-A) is methyl optionally substituted with one or more F. In some embodiments, R_a in Formula (I-A) is CHF₂, CH₂F, CF₃, - cyclopropyl, aminoalkyl (including azridinyl), carboxy, carboxamide, formamide, and amide. In some embodiments, cycloalkyl in R_a in Formula (I-A) is cyclopropyl. In some embodiments, R_a in Formula (I-A) is -NR_xCOR_y or -CONR_x or NR_xCO, wherein R_x and R_y are each independently hydrogen or lower alkyl. In some embodiments, R_a in Formula (I-A) is -NR_xCOR_y or -CONR_x or NR_xCO, wherein R_x and R_y are each independently (C₁-C₄) alkyl or

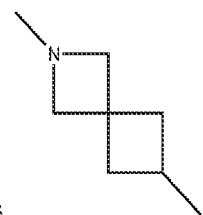
hydrogen. In some embodiments, R_a in Formula (I-A) is $-NR_xCOR_y$ or $-CONR_x$ or NR_xCO , wherein R_x and R_y are each independently methyl. In some embodiments, R_a in Formula (I-A) is $-NR_xCOR_y$ or $-CONR_x$ or NR_xCO , wherein R_x and R_y are each independently hydrogen.

[00075] In some embodiments, V in Formula (I-A) is , where n and each

R_v is as defined above. In some embodiments, V in Formula (I-A) is , where n and each R_v is as defined above. In some embodiments, V in Formula (I-A) is

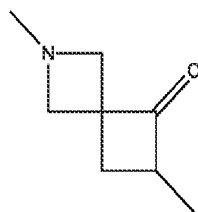


In some embodiments, V in Formula (I-A) is

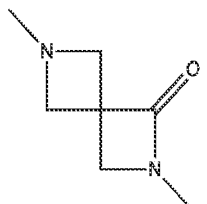


In some

embodiments, V in Formula (I-A) is



In some embodiments, V in Formula (I-

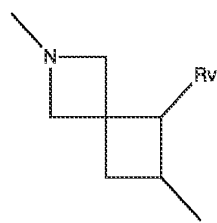
A) is . In some embodiments, V in Formula (I-A) is wherein R_v is as defined herein with respect to Formula (I-A).

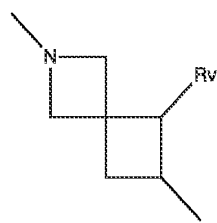
[00076] In some embodiments, each R_v in Formula (I-A) is independently hydrogen, halogen, or alkyl optionally substituted with one or more halogen. In some embodiments, one or more R_v in Formula (I-A) is hydrogen. In some embodiments, one or more R_v in Formula (I-A)

is F or Cl. In some embodiments, one or more R_v in Formula (I-A) is F. In some embodiments, one or more R_v in Formula (I-A) is alkyl optionally substituted with one or more F. In some embodiments, one or more R_v in Formula (I-A) is lower alkyl optionally substituted with one or more F. In some embodiments, one or more R_v in Formula (I-A) is (C₁-C₄) alkyl optionally substituted with one or more F. In some embodiments, one or more R_v in Formula (I-A) is CF₃. In some embodiments, each R_v in Formula (I-A) is -O-R_{v2} where R_{v2} is hydrogen or alkyl optionally substituted with one or more halogen. In some embodiments, each R_v in Formula (I-A) is -O-R_{v2} where R_{v2} is hydrogen or lower alkyl optionally substituted with one or more halogen. In some embodiments, each R_v in Formula (I-A) is -O-R_{v2} where R_{v2} is hydrogen or lower alkyl optionally substituted with one or more F. In some embodiments, each R_v in Formula (I-A) is -O-R_{v2} where R_{v2} is hydrogen. In some embodiments, each R_v in Formula (I-A) is -O-R_{v2} where R_{v2} is lower alkyl optionally substituted with one or more halogen. In some embodiments, each R_v in Formula (I-A) is F. In some embodiments, each R_v in Formula (I-A) is methyl optionally substituted with one or more F. In some embodiments, each R_v in Formula (I-A) is methyl.

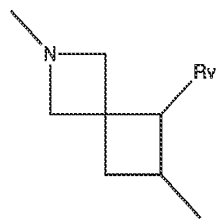
[00077] In some embodiments, each R_v in Formula (I-A) is -O-R_{v2} where R_{v2} is (C₁-C₄) alkyl optionally substituted with one or more halogen. In some embodiments, each R_v in Formula (I-A) is -O-R_{v2} where R_{v2} is (C₁-C₄) alkyl optionally substituted with one or more F. In some embodiments, each R_v in Formula (I-A) is -O-R_{v2} where R_{v2} is methyl optionally substituted with one or more F.

[00078] In some embodiments, each n with respect to R_v in Formula (I-A) is 0, 1, 2, 3 or 4. In some embodiments, each n with respect to R_v in Formula (I-A) is 0. In some embodiments, each n with respect to R_v in Formula (I-A) is 1. In some embodiments, each n with respect to R_v in Formula (I-A) is 2. In some embodiments, each n with respect to R_v in Formula (I-A) is 3. In some embodiments, each n with respect to R_v in Formula (I-A) is 4.

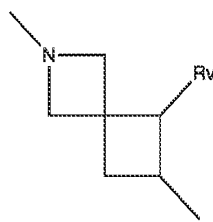


[00079] In some embodiments, V in Formula (I-A) is , wherein R_v is halogen, lower alkyl optionally substituted with one or more halogen, or -O-R_{v2} where R_{v2} is

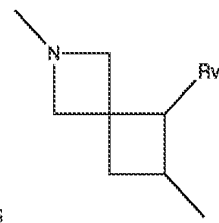
(C₁-C₄) alkyl optionally substituted with one or more halogen. In some embodiments, V in



Formula (I-A) is , wherein R_v is F, (C₁-C₄) alkyl optionally substituted with one or more F, or -O-R_{v2} where R_{v2} is methyl optionally substituted with one or more halogen.



In some embodiments, V in Formula (I-A) is , wherein R_v is F, methyl optionally substituted with one or more F, or -O-R_{v2} where R_{v2} is methyl optionally substituted

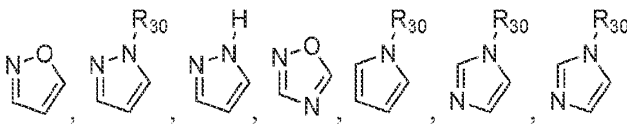


with one or more halogen. In some embodiments, V in Formula (I-A) is , wherein R_v is F, methyl, ethyl, -CF₃, or -O-R_{v2} where R_{v2} is methyl optionally substituted with one or more halogen.

[00080] In some embodiments, W in Formula (I-A) is A₂, wherein A₂ is as defined above. In some embodiments, W in Formula (I-A) is -C(O)- or -C(O)N(R₁₀)-, wherein R₁₀ is as defined above with respect to Formula (I-A). In some embodiments, W in Formula (I-A) is -C(O)-. In some embodiments, W in Formula (I-A) is -C(O)N(R₁₀)-, wherein R₁₀ is as defined above with respect to Formula (I-A).

[00081] In some embodiments, W in Formula (I-A) is A₂, and W in Formula (I-B) is A, wherein A or A₂ is a 5-member heteroaryl comprising one or more heteroatoms selected from nitrogen, oxygen and sulfur, and optionally substituted with one or more R₃₀ as defined above. In some W in Formula (I-A) or Formula (I-B) is a 5-member heteroaryl comprising one or more nitrogen heteroatoms and optionally further comprising one or more additional heteroatoms selected from nitrogen, oxygen and sulfur, and optionally substituted with one or more R₃₀ as defined above. In some W in Formula (I-A) or Formula (I-B) is a 5-member heteroaryl

comprising one or more nitrogen heteroatoms and optionally further comprising one or two additional heteroatoms selected from nitrogen, oxygen and sulfur, and optionally substituted with one or more R_{30} as defined above. In some W in Formula (I-A) or Formula (I-B) is

selected from the group consisting of: ,

and , wherein R_{30} is as defined herein.

[00082] In some embodiments, A_2 in Formula (I-A) is a 5-member heteroaryl ring optionally substituted with one or more R_{30} , wherein R_{30} is (C₁-C₄) alkyl. In some embodiments, A_2 in Formula (I-A) is a 5-member heteroaryl ring optionally substituted with one or more R_{30} , wherein R_{30} is methyl.

[00083] In some embodiments, each R_{10} in Formula (I-A) can be the same or different. In some embodiments, each R_{10} in Formula I-A is hydrogen or (C₁-C₄) alkyl. In some embodiments, one or more R_{10} in Formula I-A is hydrogen. In some embodiments, one or more R_{10} in Formula I-A is (C₁-C₄) alkyl. In some embodiments, one or more R_{10} in Formula I-A is methyl.

[00084] In some embodiments, B in Formula (I-A) is 5- or 6-member aryl or heteroaryl optionally substituted with one or more R_b ; and each R_b is independently halogen, cyano, lower alkyl optionally substituted with one or more halogen, cycloalkyl, aminoalkyl, carboxy, carboxamide, or -OR₆; and R_6 is hydrogen, lower alkyl or lower cycloalkyl optionally substituted with one or more halogen.

[00085] In some embodiments, B in Formula (I-A) is phenyl or 5- or 6-member heteroaryl comprising one or more heteroatoms selected from N, O and S, wherein the B group is optionally substituted with one or more R_b ; and each R_b is independently halogen, cyano, (C₁-C₄) alkyl optionally substituted with one or more halogen, (C₃-C₆)cycloalkyl, 3-6 member heterocycloalkyl, aminoalkyl, carboxy, carboxamide, or -OR₆; and R_6 is hydrogen, (C₁-C₄)alkyl or (C₃-C₆)cycloalkyl optionally substituted with one or more halogen. In some embodiments, any one or more halogen within the B group in Formula (I-A) is F.

[00086] In some embodiments, B in Formula (I-A) is phenyl optionally substituted with one or more R_b ; and each R_b is independently F, Cl, cyano, (C₁-C₄) alkyl optionally substituted with

one or more F or Cl, (C₃-C₆)cycloalkyl, 3-6 member heterocycloalkyl, aminoalkyl, carboxy, carboxamide, or -OR₆; and R₆ is hydrogen, (C₁-C₄)alkyl or (C₃-C₆)cycloalkyl optionally substituted with one or more F or Cl.

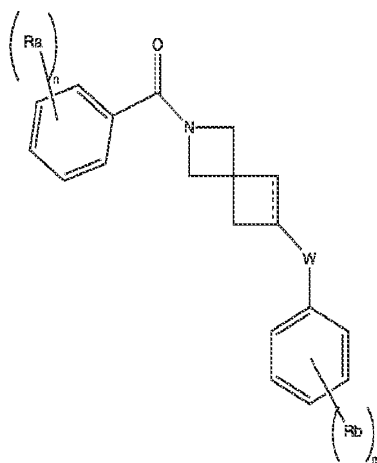
[00087] In some embodiments, B in Formula (I-A) is 5-member heteroaryl comprising one or more heteroatoms selected from N, O and S, optionally substituted with one or more R_b; and each R_b is independently F, Cl, cyano, (C₁-C₄) alkyl optionally substituted with one or more F or Cl, (C₃-C₆)cycloalkyl, 3-6 member heterocycloalkyl, aminoalkyl, carboxy, carboxamide, or -OR₆; and R₆ is hydrogen, (C₁-C₄)alkyl or (C₃-C₆)cycloalkyl optionally substituted with one or more F or Cl. In some embodiments, B in Formula (I-A) is 5-member heteroaryl comprising nitrogen and 0, 1 or 2 additional heteroatoms selected from N, O and S, optionally substituted with one or more R_b; and each R_b is independently F, Cl, cyano, (C₁-C₄) alkyl optionally substituted with one or more F or Cl, (C₃-C₆)cycloalkyl, 3-6 member heterocycloalkyl, aminoalkyl, carboxy, carboxamide, or -OR₆; and R₆ is hydrogen, (C₁-C₄)alkyl or (C₃-C₆)cycloalkyl optionally substituted with one or more F or Cl.

[00088] In some embodiments, B in Formula (I-A) is 6-member heteroaryl comprising one or more heteroatoms selected from N, O and S, optionally substituted with one or more R_b; and each R_b is independently F, Cl, cyano, (C₁-C₄) alkyl optionally substituted with one or more F or Cl, (C₃-C₆)cycloalkyl, 3-6 member heterocycloalkyl, aminoalkyl, carboxy, carboxamide, or -OR₆; and R₆ is hydrogen, (C₁-C₄)alkyl or (C₃-C₆)cycloalkyl optionally substituted with one or more F or Cl. In some embodiments, B in Formula (I-A) is 6-member heteroaryl comprising nitrogen and 0, 1 or 2 additional heteroatoms selected from N, O and S, optionally substituted with one or more R_b; and each R_b is independently F, Cl, cyano, (C₁-C₄) alkyl optionally substituted with one or more F or Cl, (C₃-C₆)cycloalkyl, 3-6 member heterocycloalkyl, aminoalkyl, carboxy, carboxamide, or -OR₆; and R₆ is hydrogen, (C₁-C₄)alkyl or (C₃-C₆)cycloalkyl optionally substituted with one or more F or Cl.

[00089] In some embodiments, B in Formula (I-A) is substituted with 0, 1, 2, 3, 4 or 4 R_b that are each the same or different from each other. In some embodiments, one or more R_b in Formula (I-A) is F. In some embodiments, one or more R_b in Formula (I-A) is Cl. In some embodiments, one or more R_b in Formula (I-A) is -CN. In some embodiments, one or more R_b in Formula (I-A) is (C₁-C₄) alkyl optionally substituted with one or more F or Cl. In some embodiments, one or more R_b in Formula (I-A) is (C₁-C₄) alkyl optionally substituted with one

or more F. In some embodiments, one or more R_b in Formula (I-A) is methyl optionally substituted with one or more F or Cl. In some embodiments, one or more R_b in Formula (I-A) is methyl optionally substituted with one or more F. In some embodiments, one or more R_b in Formula (I-A) is (C_3-C_6) cycloalkyl. In some embodiments, one or more R_b in Formula (I-A) is cyclopropyl. In some embodiments, one or more R_b in Formula (I-A) is cyclobutyl. In some embodiments, one or more R_b in Formula (I-A) is cyclohexyl. In some embodiments, one or more R_b in Formula (I-A) is a 3-member heterocycloalkyl group comprising an O, N or S heteroatom. In some embodiments, one or more R_b in Formula (I-A) is a 4-member heterocycloalkyl group comprising one or more O, N or S heteroatoms. In some embodiments, one or more R_b in Formula (I-A) is a 5-member heterocycloalkyl group comprising one or more O, N or S heteroatoms. In some embodiments, one or more R_b in Formula (I-A) is a 6-member heterocycloalkyl group comprising one or more O, N or S heteroatoms. In some embodiments, one or more R_b in Formula (I-A) is an aminoalkyl. In some embodiments, one or more R_b in Formula (I-A) is carboxy group. In some embodiments, one or more R_b in Formula (I-A) is OR_6 , and R_6 is hydrogen, (C_1-C_4) alkyl or (C_3-C_6) cycloalkyl optionally substituted with one or more F or Cl.

[00090] In some embodiments, the disclosure provides a compound of Formula (I-B) or a pharmaceutically acceptable salt thereof:



Formula (I-B),

wherein

n is 1, 2, 3, 4 or 5;

each R_a is independently halogen, cyano, lower alkyl optionally substituted with one or more halogen, -OR₆, amine, amide, or ester,

R₆ is hydrogen, lower alkyl or cycloalkyl optionally substituted with one or more halogen;

W is A, -C(O)-, or -C(O)N(R₁₀)-;

A is aryl or heteroaryl each optionally substituted with one or more R₃₀;

each R₃₀ is independently lower alkyl optionally substituted with one or more halogen;

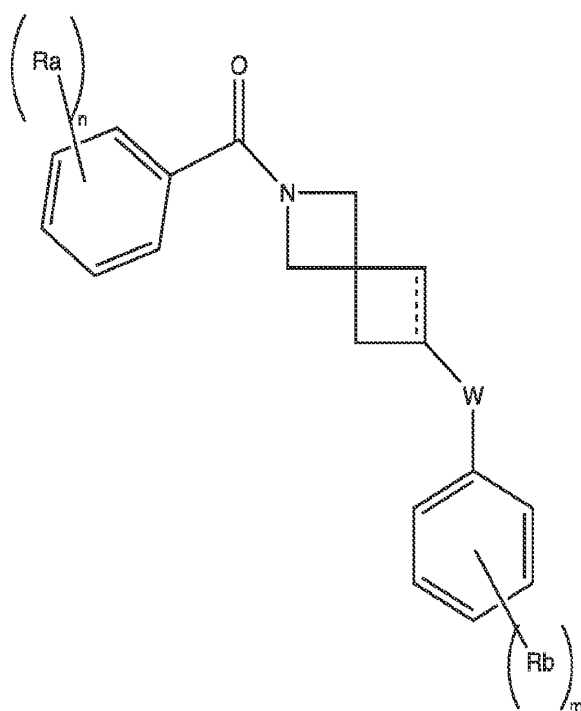
R₁₀ is hydrogen or lower alkyl;

m is 1, 2, 3, 4 or 5, and

each R_b is independently halogen, or lower alkyl optionally substituted with one or more halogen.

[00091] In some embodiments, compounds can be a compound of Formula (I-B), wherein n is 1, 2 or 3 and each R_a is independently halogen, cyano, lower alkyl optionally substituted with one or more halogen, or -OR₆; R₆ is hydrogen, lower alkyl or cycloalkyl optionally substituted with one or more halogen. In compounds of Formula (I-B), n is 1, 2 or 3 and each R_a is independently F or Cl, cyano, (C₁-C₄)alkyl optionally substituted with one or more F, or -OR₆; R₆ is hydrogen, (C₁-C₄)alkyl or cyclopropyl optionally substituted with one or more F.

[00092] In some embodiments, the disclosure provides a compound of Formula (I-B) or a pharmaceutically acceptable salt thereof:



Formula (I-B),

wherein

n is 1, 2, or 3;

each Ra is independently halogen, cyano, lower alkyl optionally substituted with one or more halogen, or -OR₆;

R₆ is hydrogen, lower alkyl or lower cycloalkyl optionally substituted with one or more halogen;

W is A, -C(O)-, -C(O)-A-, or -C(O)N(R₁₀)-;

R₁₀ is hydrogen or lower alkyl;

A is a 5-member heteroaryl ring optionally substituted with one or more R₃₀;

R₃₀ is lower alkyl;

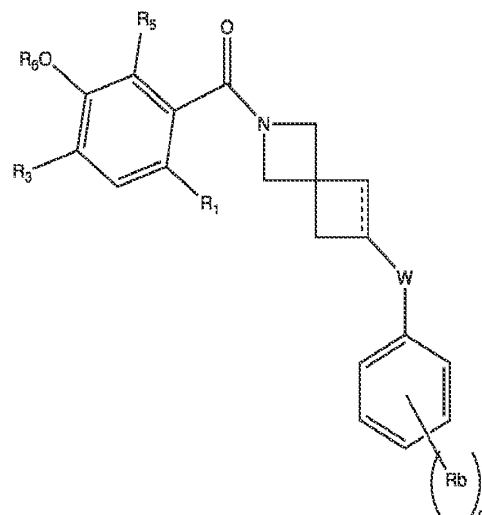
m is 1, or 2; and

each R_b is independently halogen, or lower alkyl optionally substituted with one or more halogen;

provided that the compound of Formula (I-B) is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone.

In compounds of Formula (I-B), W is a 5-member heteroaryl ring comprising at least one nitrogen, such as a triazole, imidazole, pyrazole, or an oxadiazole. In some embodiments, one or more of the lower alkyl groups in R_a, R_v, R₆, R₁₀, R₃₀ and R_b can independently be methyl. In some embodiments, a compound is a compound of Formula (I-B), wherein each R_a is independently Cl, F, CN, cyano, methyl, or -OR₆; R₆ is hydrogen, (C₁-C₄)alkyl optionally substituted with one or more F or cyclopropyl; W is -A-, -C(O)-, or -C(O)N(R₁₀)-; R₁₀ is hydrogen or methyl; A is a 5-member heteroaryl ring optionally substituted with one or more R₃₀; R₃₀ is (C₁-C₄)alkyl; m is 1, or 2; and each R_b is independently halogen, or (C₁-C₄)alkyl optionally substituted with one or more F. In some embodiments, a compound is a compound of Formula (I-B) wherein R₃₀ is methyl; and each R_b is independently halogen, or methyl optionally substituted with one or more F. In some embodiments, a compound is a compound of Formula (I-B) wherein A is pyrazole, imidazole, or triazole, each optionally substituted with one methyl. In some embodiments, a compound is a compound of Formula (I-B) wherein A is oxadiazole. In some embodiments, a compound is a compound of Formula (I-B), wherein A is pyrazole substituted with one methyl. In some embodiments, a compound is a compound of Formula (I-B), wherein one R_a is -OR₆.

[00093] In some embodiments, compounds of Formula (I-A) of Formula (I-B) can be a compound of Formula (I-B-1), or pharmaceutically acceptable salt thereof:



Formula (I-B-1),

wherein

R₁ is hydrogen or halogen;

R₃ is hydrogen, halogen, or lower alkyl optionally substituted with one or more halogen;

R₅ is hydrogen, halogen, lower alkoxy or lower alkyl each optionally substituted with one or more halogen;

R₆ is hydrogen, lower alkyl or cycloalkyl optionally substituted with one or more halogen; and

W is A, -C(O)-, or -C(O)N(R₁₀)-;

A is aryl or heteroaryl each optionally substituted with one or more R₃₀;

each R₃₀ is independently lower alkyl optionally substituted with one or more halogen;

R₁₀ is hydrogen or lower alkyl; and

m is 1, 2, 3, 4 or 5; and

each R₈ is independently halogen, or lower alkyl optionally substituted with one or more halogen;

provided that the compound of Formula (I-B-1) is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone.

[00094] In some embodiments, a compound is a compound of Formula (I-B-1) wherein R₁ is hydrogen, -CN, Cl or F. In some embodiments, R₆ is hydrogen, (C₁-C₄)alkyl or cyclopropyl optionally substituted with one or more F. In some embodiments, a compound is a compound of Formula (I-B-1) wherein R₁ is hydrogen, -CN, Cl or F and R₆ is hydrogen, (C₁-C₄)alkyl or cyclopropyl optionally substituted with one or more F. In some embodiments, R₃ is hydrogen, F, or methyl optionally substituted with one or more halogen. In some embodiments, a compound is a compound of Formula (I-B-1) wherein R₁ is hydrogen, -CN, Cl or F; R₆ is hydrogen, (C₁-C₄)alkyl or cyclopropyl optionally substituted with one or more F; and R₃ is hydrogen, F, or methyl optionally substituted with one or more halogen. In some embodiments, a compound is a compound of Formula (I-B-1) wherein R₁ is hydrogen, -CN, Cl or F; R₆ is hydrogen, (C₁-C₄)alkyl or cyclopropyl optionally substituted with one or more F; R₃ is hydrogen, F, or methyl optionally substituted with one or more halogen; and R₅ is hydrogen.

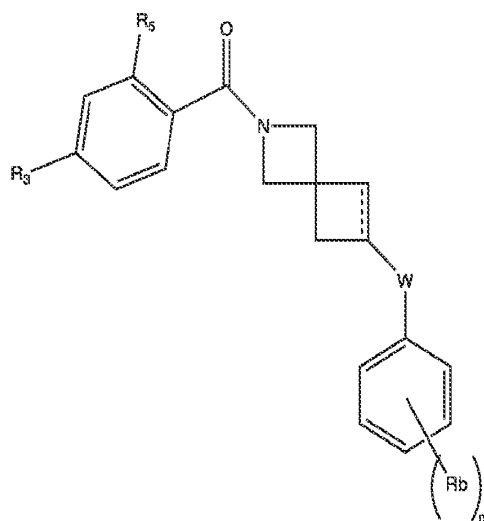
[00095] In some embodiments, a compound is a compound of Formula (I-B-1) wherein R₁ is Cl, F or -CN and R₆ is hydrogen. In some embodiments, a compound is a compound of Formula

(I-B-1) wherein R_1 is F. In some embodiments, a compound is a compound of Formula (I-B-1) wherein R_1 is Cl, F or -CN and R_3 , R_5 and R_6 are each hydrogen. In some embodiments, a compound is a compound of Formula (I-B-1) wherein R_1 is Cl, F or -CN; R_3 is hydrogen, methyl or F; R_5 is hydrogen, methyl or F; and R_6 is hydrogen. In some embodiments, a compound is a compound of Formula (I-B-1) wherein R_1 is F; R_3 is hydrogen, methyl or F; R_5 is hydrogen; and R_6 is hydrogen. In some embodiments, a compound is a compound of Formula (I-B-1) wherein R_1 is F; R_3 is hydrogen; R_5 is hydrogen or F; and R_6 is hydrogen. In some embodiments, a compound is a compound of Formula (I-B-1) wherein R_1 is hydrogen; R_3 is hydrogen or F; R_5 is hydrogen; and R_6 is hydrogen. In some embodiments, a compound is a compound of Formula (I-B-1) wherein R_1 is F or -CN; R_3 is hydrogen or F; R_5 is hydrogen; and R_6 is hydrogen. In some embodiments, a compound is a compound of Formula (I-B-1) wherein R_1 and R_6 are each hydrogen.

[00096] In some embodiments, a compound is a compound of Formula (I-B-1) wherein R_1 is F and R_6 is hydrogen. In some embodiments, a compound is a compound of Formula (I-B-1) wherein R_1 is F, R_6 is hydrogen and at least one of R_3 and R_5 is hydrogen. In some embodiments, a compound is a compound of Formula (I-B-1) wherein R_1 is F, R_6 is hydrogen, and R_3 and R_5 are each hydrogen. In some embodiments, a compound is a compound of Formula (I-B-1) wherein R_1 is F, R_6 is hydrogen and at least one of R_3 and R_5 is hydrogen and at least one of R_3 and R_5 is F or methyl.

[00097] In some embodiments, a compound is a compound of Formula (I-B-1) wherein W is A and A is 5-member aryl or 5-member heteroaryl wherein each A is optionally substituted with one or more R_{30} ; and each R_{30} is independently lower alkyl optionally substituted with one or more halogen. In some embodiments, a compound is a compound of Formula (I-B-1) wherein W is A and A is 5-member heteroaryl comprising at least one nitrogen heteroatom wherein each A is optionally substituted with one or more R_{30} ; and each R_{30} is independently (C₁-C₄) alkyl optionally substituted with one or more halogen. In some embodiments, a compound is a compound of Formula (I-B-1) wherein W is A and A is 5-member heteroaryl comprising at least one nitrogen heteroatom wherein each A is optionally substituted with one or more R_{30} ; and each R_{30} is independently F or methyl optionally substituted with one or more F.

[00098] In some embodiments, compounds of Formula (I-A) or Formula (I-B) can be a compound of Formula (I-B-2), or pharmaceutically acceptable salt thereof.



Formula (I-B-2),

wherein

R_3 is hydrogen or halogen;

R_5 is $-O-R_{52}$;

R_{52} is lower alkyl or cycloalkyl, each optionally substituted with halogen,

W is A, $-C(O)-$, or $-C(O)N(R_{10})-$;

A is aryl or heteroaryl each optionally substituted with one or more R_{30} ;

each R_{30} is independently lower alkyl optionally substituted with one or more halogen;

R_{10} is hydrogen or lower alkyl; and

m is 1, 2, 3, 4 or 5; and

each R_b is independently halogen, or lower alkyl optionally substituted with one or more halogen.

[00099] In some embodiments, a compound is a compound of Formula (I-B-2) wherein R_3 is hydrogen, Cl or F. In some embodiments, a compound is a compound of Formula (I-B-2) wherein R_3 is F. In some embodiments, a compound is a compound of Formula (I-B-2) wherein R_{52} is (C_1-C_4) alkyl optionally substituted with one or more halogen, or cyclopropyl. In some embodiments, a compound is a compound of Formula (I-B-2) wherein R_3 is F and R_{52} is (C_1-C_4) alkyl optionally substituted with one or more halogen, or cyclopropyl. In some embodiments, a compound is a compound of Formula (I-B-2) wherein R_{52} is (C_1-C_4) alkyl optionally substituted with one or more F, or cyclopropyl. In some embodiments, a compound is a compound of

Formula (I-B-2) wherein R_3 is F and R_{52} is (C₁-C₄)alkyl optionally substituted with one or more F, or cyclopropyl.

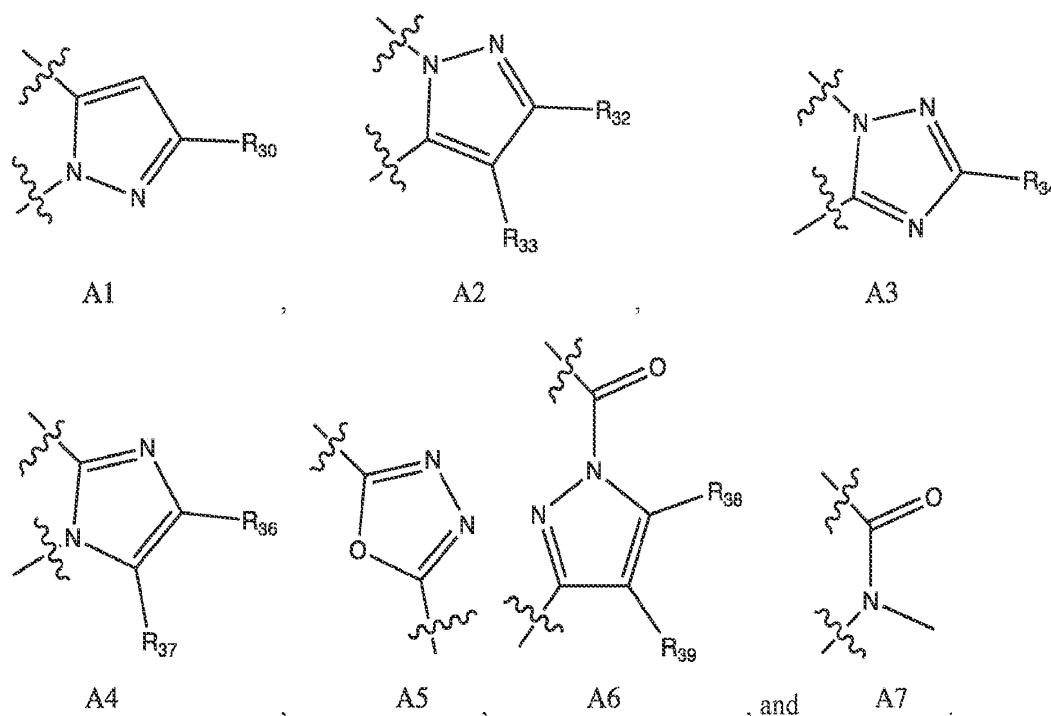
[000100] In some embodiments, a compound is a compound of Formula (I-B-2) wherein R_{52} is selected from the group consisting of: methyl, ethyl, propyl optionally substituted with one or more F. In some embodiments, a compound is a compound of Formula (I-B-2) wherein R_3 is F and R_{52} is selected from the group consisting of: methyl, ethyl, propyl optionally substituted with one or more F. In some embodiments, a compound is a compound of Formula (I-B-2) wherein R_{52} is selected from the group consisting of: methyl, ethyl, isopropyl, -CH₂-CF₃ and cyclopropyl. In some embodiments, a compound is a compound of Formula (I-B-2) wherein R_3 is F and R_{52} is selected from the group consisting of: methyl, ethyl, isopropyl, -CH₂-CF₃ and cyclopropyl.

[000101] In some embodiments, a compound is a compound of Formula (I-B-2) wherein W is A and A is 5-member aryl or 5-member heteroaryl wherein each A is optionally substituted with one or more R_{30} ; and each R_{30} is independently lower alkyl optionally substituted with one or more halogen. In some embodiments, a compound is a compound of Formula (I-B-2) wherein W is A and A is 5-member heteroaryl comprising at least one nitrogen heteroatom wherein each A is optionally substituted with one or more R_{30} ; and each R_{30} is independently (C₁-C₄) alkyl optionally substituted with one or more halogen. In some embodiments, a compound is a compound of Formula (I-B-2) wherein W is A and A is 5-member heteroaryl comprising at least one nitrogen heteroatom wherein each A is optionally substituted with one or more R_{30} ; and each R_{30} is independently F or methyl optionally substituted with one or more F.

[000102] In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein W is A, and A is an aryl or heteroaryl optionally substituted with one or more R_{30} , and R_{30} is (C₁-C₄)alkyl optionally substituted with one or more halogen. In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein A is a 5-member heteroaryl optionally substituted with one or more (C₁-C₄)alkyl optionally substituted with one or more halogen. In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein A is a 5-member heteroaryl comprising one or more nitrogen heteroatoms and optionally substituted with one or more methyl.

[000103] In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein W is selected from the group consisting of:

imidazole, prazole, triazole and oxadiazole each optionally substituted with one or more lower alkyl. In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein W is selected from the group consisting of: imidazole, prazole, triazole and oxadiazole each optionally substituted with one or more methyl. In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein W is selected from the group consisting of A1, A2, A3, A4, A5, A6 and A7 as shown below, wherein R₃₀, R₃₂, R₃₃, R₃₄, R₃₆, R₃₇, R₃₈ and R₃₉ are each independently hydrogen or lower alkyl:



[000104] In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein W is selected from the group consisting of A1, A2, A3, A4, A5, and A6 as shown above, wherein R₃₀, R₃₂, R₃₃, R₃₄, R₃₆, R₃₇, R₃₈ and R₃₉ are each independently hydrogen or methyl. In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein W is selected from the group consisting of A1, A2, A3, A4, A5, and A6 as shown above, wherein R₃₀, R₃₂, R₃₃, R₃₄, R₃₆, R₃₇, R₃₈ and R₃₉ are each independently hydrogen or methyl.

[000105] In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein W is A1 and R₃₀ is hydrogen or methyl. In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein W is A1 and R₃₀ is hydrogen. In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein W is A1 and R₃₀ is methyl. In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein W is A2 and R₃₂ and R₃₃ is hydrogen or methyl.

[000106] In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein W is A2 and one of R₃₂ and R₃₃ is hydrogen and one of R₃₂ and R₃₃ is methyl. In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein W is A2 and R₃₂ is methyl and R₃₃ is hydrogen. In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein W is A2 and R₃₂ is hydrogen and R₃₃ is methyl. In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein W is A2 and R₃₂ is hydrogen and R₃₃ is hydrogen.

[000107] In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein W is A3 and R₃₄ is hydrogen or methyl. In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein W is A3 and R₃₄ is hydrogen. In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein W is A1 and R₃₄ is methyl.

[000108] In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein W is A4 and one of R₃₆ and R₃₇ is hydrogen and one of R₃₆ and R₃₇ is methyl. In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein W is A4 and R₃₆ is methyl and R₃₇ is hydrogen. In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein W is A4 and R₃₆ is hydrogen and R₃₇ is methyl. In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein W is A4 and R₃₆ is hydrogen and R₃₇ is hydrogen.

[000109] In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein W is A5.

[000110] In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein W is A6 and one of R₃₈ and R₃₉ is hydrogen and one of R₃₈ and R₃₉ is methyl. In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein W is A6 and R₃₈ is methyl and R₃₉ is hydrogen. In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein W is A6 and R₃₈ is hydrogen and R₃₉ is methyl. In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein W is A6 and R₃₈ is hydrogen and R₃₉ is hydrogen.

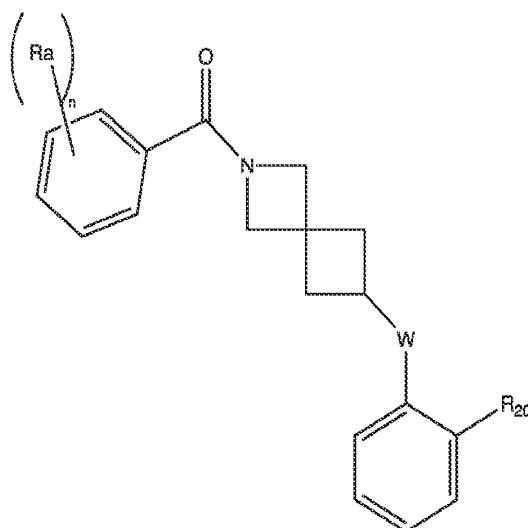
[000111] In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein at least one of R_a is hydroxyl or (C₁-C₄)alkoxy optionally substituted with one or more halogen, and n is 1, 2 or 3. In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein at least one of R_a is hydroxyl or (C₁-C₄)alkoxy optionally substituted with one or more F, and n is 1, 2 or 3. In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein at least one of R_a is hydroxyl, (C₁-C₄)alkoxy or -O-(C₁-C₆)cycloalkyl each optionally substituted with one or more F, with the remaining R_a selected from the group consisting of halogen, methyl, and cyano; and n is 1, 2 or 3. In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein at least one of R_a is hydroxyl, (C₁-C₄)alkoxy or -O-(cyclopropyl) each optionally substituted with one or more F, with the remaining R_a selected from the group consisting of halogen, methyl, and cyano; and n is 1, 2 or 3. In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein at least one of R_a is hydroxyl, (C₁-C₄)alkoxy or -O-(cyclopropyl) each optionally substituted with one or more F, with the remaining R_a selected from the group consisting of Cl, F, methyl, and cyano; and n is 1, 2 or 3.

[000112] In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein W is A7.

[000113] In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein W is -C(O)-.

[000114] In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein W is -C(O)N(R₁₀)-, and -R₁₀ is hydrogen. In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein W is -C(O)N(R₁₀)-, and -R₁₀ is methyl. In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein W is -C(O)N(R₁₀)-, and -R₁₀ is (C₁-C₄) alkyl optionally substituted with F. In some embodiments, a compound is a compound of Formula (I-A), Formula (I-B), Formula (I-B-1) or Formula (I-B-2), wherein W is -C(O)N(R₁₀)-, and -R₁₀ is lower alkyl optionally substituted with halogen.

[000115] In some embodiments, compounds of Formula (I-A) or Formula (I-B) can be a compound of Formula (I-C), or pharmaceutically acceptable salt thereof:



Formula (I-C)

wherein:

R₂₀ is lower alkyl;

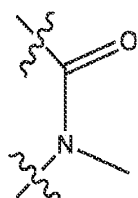
n is 1, 2, or 3;

each R_a is independently halogen, cyano, lower alkyl optionally substituted with one or more halogen, or -OR₆; and

R₆ is hydrogen, lower alkyl or lower cycloalkyl optionally substituted with one or more halogen; and

W is as defined above for Formula (I-A) or Formula (I-B).

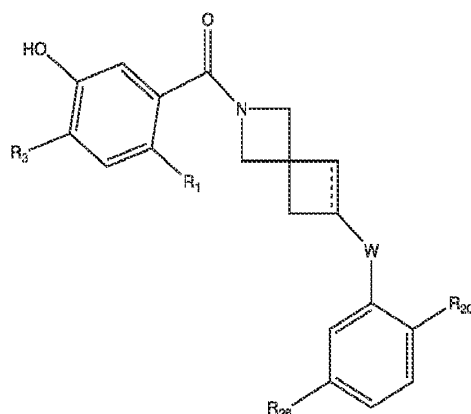
[000116] In some embodiments, a compound is a compound of Formula (I-C), wherein R_{20} is (C_1-C_4) alkyl. In some embodiments, a compound is a compound of Formula (I-C), wherein R_{20} is methyl. In some embodiments, a compound is a compound of Formula (I-C), wherein W is A7



A7 and R_{20} is methyl, each R_a is independently F, Cl, -CN, (C_1-C_4) alkyl optionally substituted with one or more F or Cl, or -OR₆ and R₆ is hydrogen, (C_1-C_4) alkyl or cyclopropyl optionally substituted with one or more F or Cl. In some embodiments, a compound is a compound of Formula (I-C), wherein n is 1, 2 or 3, W is A7 and R_{20} is methyl, each R_a is independently F, Cl, -CN, methyl, or -OH. In some embodiments, a compound is a compound of Formula (I-C), wherein n is 2, W is A7 and R_{20} is methyl, each R_a is independently F or -OH.

[000117] In some embodiments, a compound is a compound of Formula (I-C), wherein at least one of R_a is hydroxyl or (C_1-C_4) alkoxy optionally substituted with one or more halogen, and n is 1, 2 or 3. In some embodiments, a compound is a compound of Formula (I-C), wherein at least one of R_a is hydroxyl or (C_1-C_4) alkoxy optionally substituted with one or more F, and n is 1, 2 or 3. In some embodiments, a compound is a compound of Formula (I-C), wherein at least one of R_a is hydroxyl, (C_1-C_4) alkoxy or -O-(C_1-C_6)cycloalkyl each optionally substituted with one or more F, with the remaining R_a selected from the group consisting of halogen, methyl, and cyano; and n is 1, 2 or 3. In some embodiments, a compound is a compound of Formula (I-C), wherein at least one of R_a is hydroxyl, (C_1-C_4) alkoxy or -O-(cyclopropyl) each optionally substituted with one or more F, with the remaining R_a selected from the group consisting of halogen, methyl, and cyano; and n is 1, 2 or 3. In some embodiments, a compound is a compound of Formula (I-C), wherein at least one of R_a is hydroxyl, (C_1-C_4) alkoxy or -O-(cyclopropyl) each optionally substituted with one or more F, with the remaining R_a selected from the group consisting of Cl, F, methyl, and cyano; and n is 2 or 3. In some embodiments, a compound is a compound of Formula (I-C), wherein at least one of R_a is hydroxyl, with the remaining R_a selected from the group consisting of F, methyl, and cyano; and n is 2 or 3.

[000118] In some embodiments, the disclosure provides a compound of Formula (I-A) or Formula (I-B) that are also compounds of Formula (II) or a pharmaceutically acceptable salt thereof.



Formula (II),

wherein

R₁ is halogen or cyano;

R₃ is hydrogen, lower alkyl, or halogen;

W is -C(O)-A, -C(O)N(R₁₀)-A, and A;

R₁₀ is hydrogen or lower alkyl;

A is a 5-member heteroaryl ring optionally substituted with one or more R₃₀;

R₂₀ is halogen or lower alkyl optionally substituted with one or more halogen;

R₃₀ is lower alkyl optionally substituted with one or more halogen; and

R₂₆ is halogen or hydrogen.

[000119] In some embodiments, a compound of Formula (I-A) or Formula (I-B) can be a compound of Formula (II) wherein R₁ is Cl, F or cyano; R₃ is hydrogen, F or methyl; R₁₀ is hydrogen or methyl; R₂₀ and R₃₀ are each independently methyl; and R₂₆ is F or hydrogen. In some embodiments, a compound of Formula (I) can be a compound of Formula (II) wherein R₁ is Cl, F or cyano; R₃ is hydrogen, F or methyl; R₁₀ is hydrogen or methyl; R₂₀ and R₃₀ are each independently methyl; and R₂₆ is hydrogen. In some embodiments, a compound of Formula (I) can be a compound of Formula (II) wherein W is -C(O)N(R₁₀)-A, and A wherein R₁₀ is hydrogen or methyl and A is a 5-member heteroaryl ring comprising at least one nitrogen optionally substituted with one or more lower alkyl, the lower alkyl being optionally substituted with one or more halogen; and R₂₆ is hydrogen. In some embodiments, a compound of Formula (I) can be a

compound of Formula (II) wherein R_{20} and R_{30} are each independently lower alkyl optionally substituted with one or more F and R_{26} is hydrogen. In some embodiments, a compound of Formula (I) can be a compound of Formula (II) wherein R_{20} is halogen or lower alkyl optionally substituted with one or more F; R_{30} is lower alkyl optionally substituted with one or more F; and R_{26} is hydrogen. In some embodiments, a compound of Formula (I) can be a compound of Formula (II) wherein R_{20} is Cl, F or methyl optionally substituted with one or more F; R_{30} is methyl optionally substituted with one or more F; and R_{26} is hydrogen.

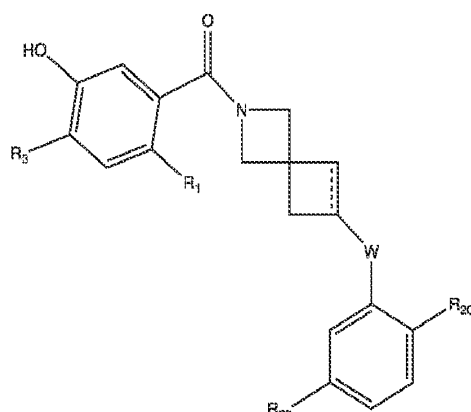
[000120] In some embodiments, a compound of Formula (I-A) or Formula (I-B) can be a compound of Formula (II) wherein W is an amide optionally substituted with lower alkyl, carboxyl or 5-member heteroaryl ring comprising at least one nitrogen, such as a pyrazole, imidazole, triazole or oxadiazole, each optionally substituted with lower alkyl. In some embodiments, R_1 is Cl, F or CN in Formula (II); and R_{26} is hydrogen. In some embodiments, R_3 is methyl; and R_{26} is hydrogen. In some embodiments, R_3 is hydrogen; and R_{26} is hydrogen. In some embodiments, R_3 is F; and R_{26} is hydrogen. In some embodiments, a compound can be a compound of Formula (II) wherein W is pyrazole, imidazole, triazole or oxadiazole, each optionally substituted with methyl; R_1 is Cl, F or CN; R_3 is hydrogen, methyl or F; and R_{26} is hydrogen.

[000121] In some embodiments, a compound of Formula (I-A) or Formula (I-B) can be a compound of Formula (II) wherein the lower alkyl in R_1 , R_3 , and R_{20} is methyl; and R_{26} is hydrogen. In some embodiments, a compound of Formula (I) can be a compound of Formula (II) wherein R_{10} is methyl; A is pyrazole, imidazole, triazole or oxadiazole each optionally substituted with methyl; and R_{20} is methyl; and R_{26} is hydrogen. In some embodiments, a compound of Formula (I) can be a compound of Formula (II) wherein W is pyrazole optionally substituted with one or more methyl; R_1 is the F; R_3 is H or F and R_{20} is methyl; and R_{26} is hydrogen. In some embodiments, a compound of Formula (I) can be a compound of Formula (II) wherein W is pyrazole optionally substituted with one or more methyl, R_1 is the F, R_3 is H and R_{20} is methyl and R_{26} is hydrogen.

[000122] In some embodiments, a compound of Formula (I-A) or Formula (I-B) can be a compound of Formula (II) wherein the lower alkyl in R_1 , R_3 , and R_{20} is methyl; and R_{26} is F. In some embodiments, a compound of Formula (I) can be a compound of Formula (II) wherein R_{10} is methyl; A is pyrazole, imidazole, triazole or oxadiazole each optionally substituted with methyl;

and R₂₀ is methyl; and R₂₆ is F. In some embodiments, a compound of Formula (I) can be a compound of Formula (II) wherein W is pyrazole optionally substituted with one or more methyl; R₁ is the F; R₃ is H or F and R₂₀ is methyl; and R₂₆ is F. In some embodiments, a compound of Formula (I) can be a compound of Formula (II) wherein W is pyrazole optionally substituted with one or more methyl, R₁ is the F, R₃ is H and R₂₀ is methyl and R₂₆ is F.

[000123] In some embodiments, the disclosure provides a compound of Formula (I-A) or Formula (I-B) that are also compounds of Formula (II) or a pharmaceutically acceptable salt thereof:



Formula (II),

wherein

R₁ is halogen or cyano;

R₃ is hydrogen or halogen;

W is A, -C(O)-, or -C(O)N(R₁₀)-;

R₁₀ is hydrogen or lower alkyl;

A is a 5-member heteroaryl ring optionally substituted with one or more R₃₀; and

R₂₀ and R₃₀ are each independently lower alkyl; and

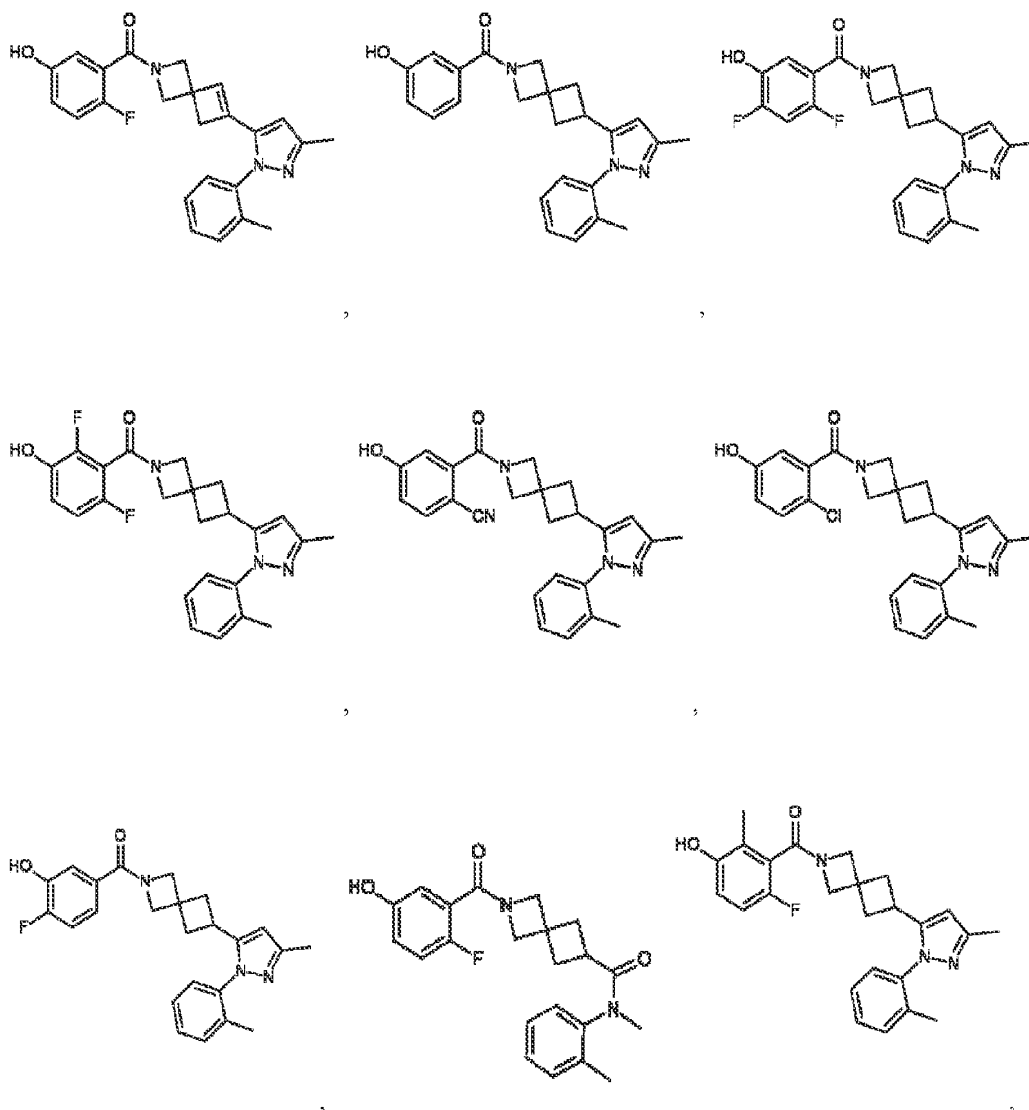
R₂₆ is as defined herein for Formula (I-A) or Formula (I-B);

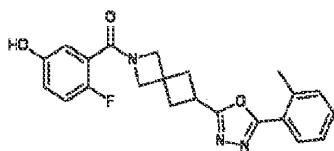
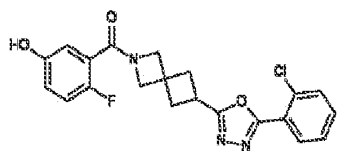
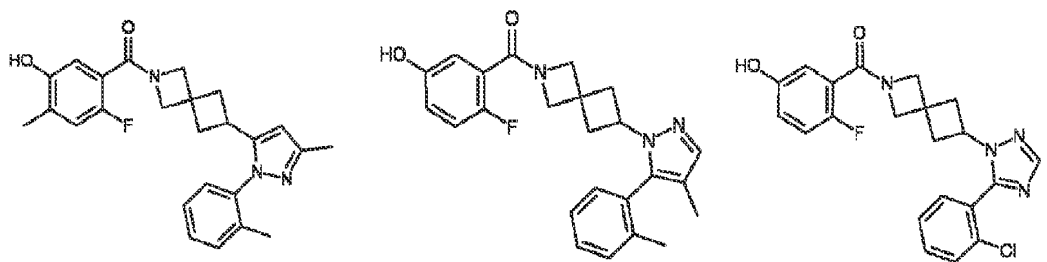
provided that the compound of Formula (II) is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone.

[000124] In compounds of Formula (II), W is a 5-member heteroaryl ring comprising at least one nitrogen, such as a pyrazole. In some embodiments, R₁ is Cl, F or CN. In some embodiments, R₃ is H. In some embodiments, R₃ is F. In some embodiments, the lower alkyl in each of R_a, R₆, R₁₀, R₃₀ and R_b can independently be methyl. In some embodiments, W is pyrazole optionally

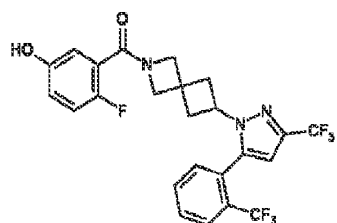
substituted with one or more methyl, R₁ is the F, R₃ is H or F and each of R_a, R₆, R₁₀, R₃₀ and R_b is methyl in a compound of Formula (II). In some embodiments, W is pyrazole optionally substituted with one or more methyl, R₁ is the F, R₃ is H and each of R_a, R₆, R₁₀, R₃₀ and R_b is methyl in a compound of Formula (II).

[000125] In some embodiments, the compound of Formula (II) is selected from the group consisting of:



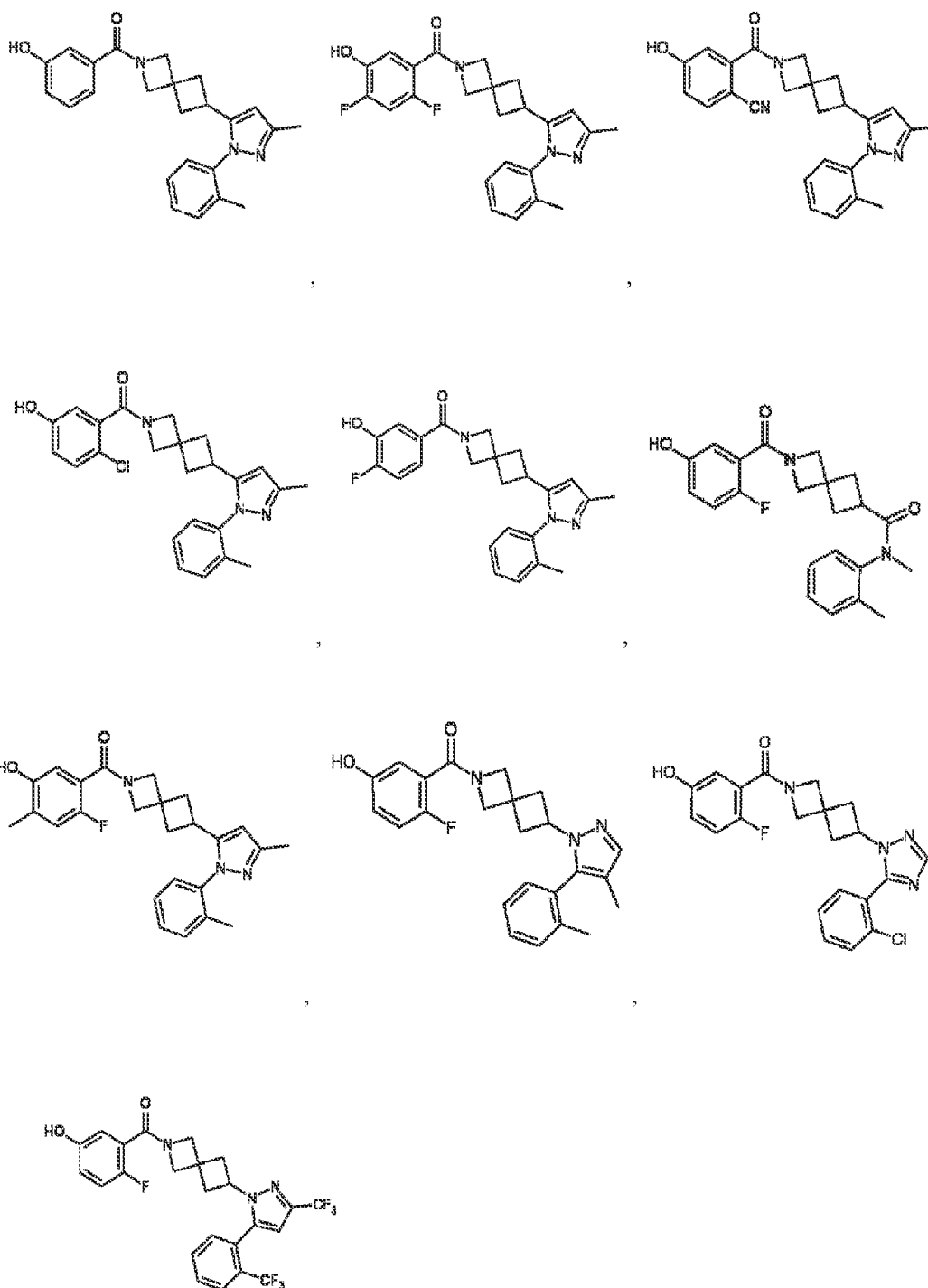


, and



or a pharmaceutically acceptable salt thereof.

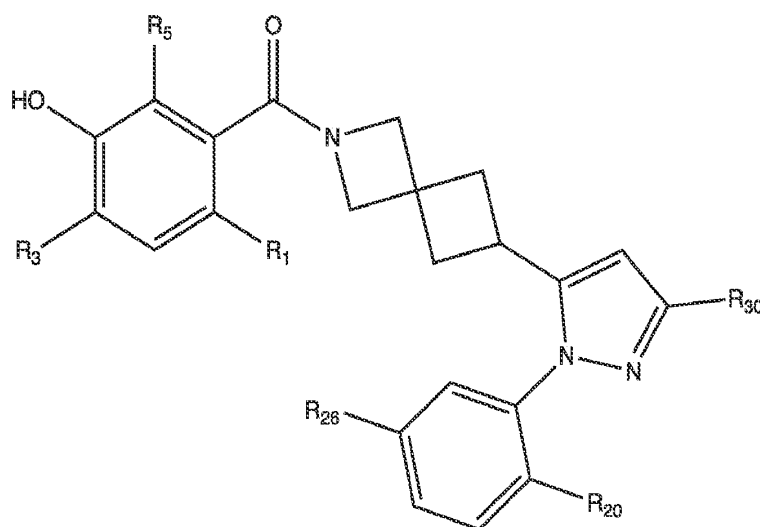
[000126] In some embodiments, the compound of Formula (II) is selected from the group consisting of:



and

or a pharmaceutically acceptable salt thereof.

[000127] In some embodiments, the disclosure provides a compound of Formula (II-B) or a pharmaceutically acceptable salt thereof:



Formula (II-B),

wherein

R₁ is halogen or cyano;

R₃ is hydrogen, lower alkyl, or halogen;

R₅ is hydrogen, halogen or lower alkyl;

R₂₀ is halogen or lower alkyl optionally substituted with one or more halogen;

R₂₆ is halogen or hydrogen; and

R₃₀ is hydrogen or lower alkyl optionally substituted with one or more halogen.

[000128] In some embodiments, the disclosure provides a compound of Formula (II-B) or a pharmaceutically acceptable salt thereof, wherein the compound is not (2-fluoro-5-hydroxyphenyl){6-[3-methyl-1-(o-tolyl)-5-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone.

[000129] In some embodiments, the disclosure provides a compound of Formula (II-B) or a pharmaceutically acceptable salt thereof, wherein the compound is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone.

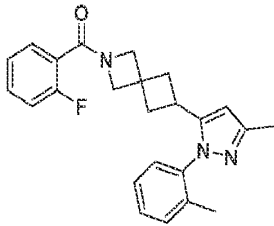
[000130] In some embodiments, the disclosure provides a compound of Formula (II-B) or a pharmaceutically acceptable salt thereof, wherein when R₁ is fluoro, R₃ and R₅ are both hydrogen, and R₃₀ is methyl, then R₂₆ is not hydrogen.

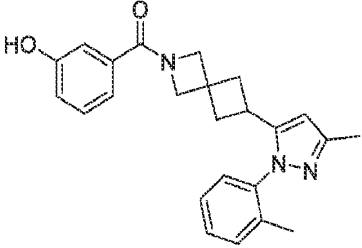
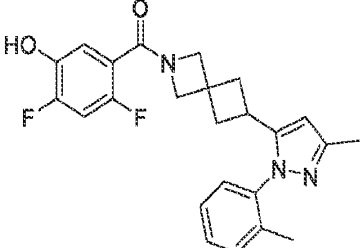
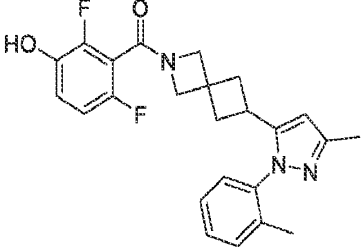
General procedure for acid amine coupling for Preparing Compounds of Formula (II-B)

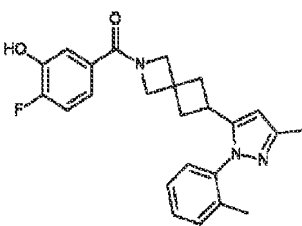
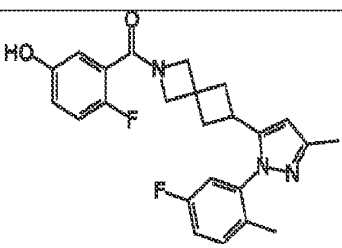
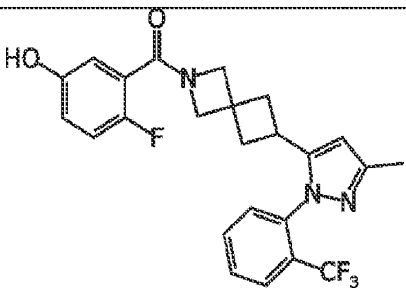
[000131] In general, analogs of formula of II-B can be made by following a modified version of synthetic scheme for PSY05-00367 (Compound 367). 2-(*tert*-butoxycarbonyl)-2-azaspiro[3.3]heptane-6-carboxylic acid, **Int-1**, is treated with methoxyamine hydrochloride to generate Weinreb amide, **Int-2**, which undergoes Grignard addition with methylmagnesium bromide (CH₃MgBr) to yield methyl ketone intermediate **Int-3**. Treating **Int-3** with *N,N*-dimethylacetamide dimethyl acetal (DMA-DMA) yields spirocyclic-substituted 3-(dimethylamino)but-2-en-1-one intermediate, **Int-4**. 1,3-dipolar cycloaddition of **Int-4** with various phenyl hydrazines yields desired variation of 3-methylpyrazole intermediate, **Int-5**. Boc deprotection of **Int-5** with trifluoroacetic acid yields corresponding trifluoroacetate salt of **Int-5**, **Int-6**, which then couples with various substituted benzoic acids to yield final analog.

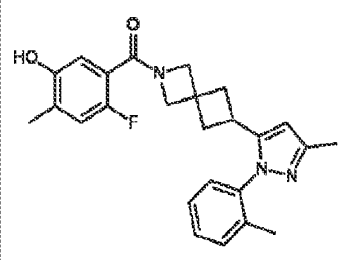
[000132] To a stirred solution of 6-(3-methyl-1-(*o*-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptane 2,2,2-trifluoroacetate (1 eq.) and 2-fluoro-benzoic acid (1.5 eq.) in DMF (10 V) at 0 °C, was added DIPEA (5 eq.) and stirred for 15 min. To this reaction mixture T₃P (50% solution in ethyl acetate) (1.5 eq.) was added. The resulting mixture was stirred at room temperature for 2h. The reaction mixture was quenched by the addition of ice cold water (10 mL) and extracted by ethyl acetate (3x25 mL). The organic layer was dried over sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography using 5 % MeOH in DCM.

Table 1

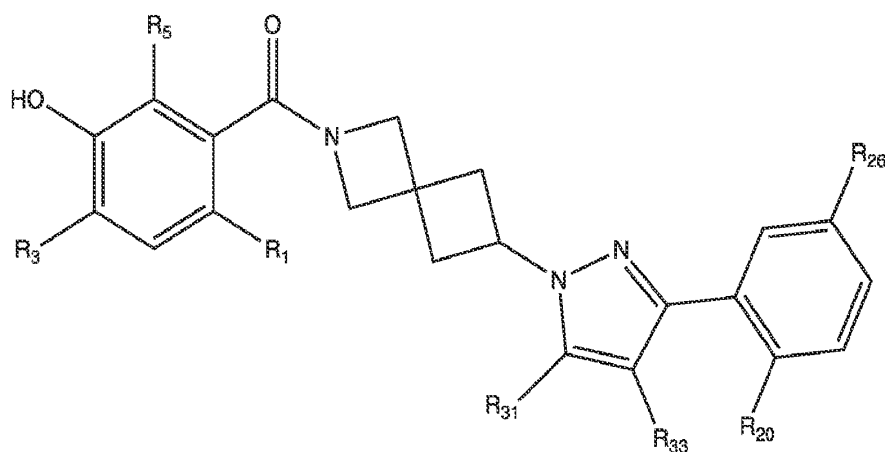
Structure	Description
 PSY-05-00122	Compound 122 by followed the general procedure given above from 70 mg of 6-(3-methyl-1-(<i>o</i>-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptane 2,2,2-trifluoroacetate (1 eq.) to obtain (2-fluorophenyl)(6-(3-methyl-1-(<i>o</i>-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone (20 mg, 28%) as a white solid. Compound can be prepared by reacting Int-4 with <i>o</i>-tolylhydrazine hydrochloride, then reacting Int-6 with 2-fluorobenzoic acid.

Structure	Description
 PSY-05-00125	Compound-125 was prepared by followed the general procedure given above from 70 mg of 6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptane 2,2,2-trifluoroacetate (1 eq.) to obtain (3-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone (15 mg, 21%) as a white solid. Compound can be prepared by reacting Int-4 with <i>o</i>-tolylhydrazine hydrochloride, then reacting Int-6 with 3-(benzyloxy)benzoic acid, which then undergoes Pd/C hydrogenolysis to liberate free hydroxyl group.
 PSY-05-00126	Compound-126 was prepared by followed the general procedure given above from 100 mg of 6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptane 2,2,2-trifluoroacetate (1 eq.) to obtain (2,4-difluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone (50 mg, 21%) as a white solid. Compound can be prepared by reacting Int-4 with <i>o</i>-tolylhydrazine hydrochloride, then reacting Int-6 with 5-(benzyloxy)-2,4-difluorobenzoic acid, which then undergoes Pd/C hydrogenolysis to liberate free hydroxyl group. 5-(benzyloxy)-2,4-difluorobenzoic acid is prepared by reacting 2,4-difluoro-5-hydroxybenzoic acid with benzyl bromide, then performing sodium hydroxide-catalyzed ester hydrolysis to liberate the free acid.
 PSY-05-00127	Compound-00127 was prepared by followed the general procedure given above from 100 mg of 6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptane 2,2,2-trifluoroacetate (1 eq.) to obtain (2,6-difluoro-3-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone (20 mg, 18%) as a white solid. Compound can be prepared by reacting Int-4 with <i>o</i>-tolylhydrazine hydrochloride, then reacting Int-6 with 3-(benzyloxy)-2,6-difluorobenzoic acid, which then undergoes Pd/C hydrogenolysis to liberate free hydroxyl group. 3-(benzyloxy)-2,6-difluorobenzoic acid is prepared by reacting 2,6-difluoro-3-hydroxybenzoic acid with benzyl bromide, then performing sodium hydroxide-catalyzed ester hydrolysis to liberate the free acid.

Structure	Description
 Compound 141	Compound-00141-001 was prepared by followed the general procedure given above from 120 mg of 6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro [3.3] heptane 2,2,2-trifluoroacetate (1 eq.) to obtain (4-fluoro-3-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone (19 mg, 100.49%) as a white solid. Compound can be prepared by reacting Int-4 with <i>o</i>-tolylhydrazine hydrochloride, then reacting Int-6 with 3-(benzyloxy)-4-fluorobenzoic acid, which then undergoes Pd/C hydrogenolysis to liberate free hydroxyl group. 3-(benzyloxy)-4-fluorobenzoic acid is prepared by reacting 4-fluoro-3-hydroxybenzoic acid with benzyl bromide, then performing sodium hydroxide-catalyzed ester hydrolysis to liberate the free acid.
 Compound 365	Compound can be prepared by reacting Int-4 with (5-fluoro-2-methylphenyl)hydrazine hydrochloride, then reacting Int-6 with 5-(benzyloxy)-2-fluorobenzoic acid, which then undergoes Pd/C hydrogenolysis to liberate free hydroxyl group. 5-(benzyloxy)-2-fluorobenzoic acid is prepared by reacting 2-fluoro-5-hydroxybenzoic acid with benzyl bromide, then performing sodium hydroxide-catalyzed ester hydrolysis to liberate the free acid.
 Compound 366	Compound can be prepared by reacting Int-4 with (2-(trifluoromethyl)phenyl)hydrazine hydrochloride, then reacting Int-6 with 5-(benzyloxy)-2-fluorobenzoic acid, which then undergoes Pd/C hydrogenolysis to liberate free hydroxyl group. 5-(benzyloxy)-2-fluorobenzoic acid is prepared by reacting 2-fluoro-5-hydroxybenzoic acid with benzyl bromide, then performing sodium hydroxide-catalyzed ester hydrolysis to liberate the free acid.

Structure	Description
 Compound 371	Compound can be prepared by reacting Int-4 with <i>o</i>-tolylhydrazine hydrochloride, then reacting Int-6 with 5-(benzyloxy)-2-fluoro-4-methylbenzoic acid, which then undergoes Pd/C hydrogenolysis to liberate free hydroxyl group. 5-(benzyloxy)-2-fluoro-4-methylbenzoic acid is prepared by reacting 2-fluoro-5-hydroxy-4-methylbenzoic acid with benzyl bromide, then performing sodium hydroxide-catalyzed ester hydrolysis to liberate the free acid.

[000133] In some embodiments, the disclosure provides a compound of Formula (II-C) or a pharmaceutically acceptable salt thereof:



Formula (II-C),

wherein

R₁ is halogen or cyano;

R₃ is hydrogen, lower alkyl, or halogen;

R₅ is hydrogen, halogen or lower alkyl;

R₂₀ is halogen or lower alkyl optionally substituted with one or more halogen;

R₂₆ is halogen or hydrogen; and

R₃₁ and R₃₃ are each independently hydrogen or lower alkyl optionally substituted with one or more halogen, provided that one of R₃₁ and R₃₃ is hydrogen.

General procedure for Preparing Compounds of Formula (II-C)

[000134] Analogs with a 1-(4-methyl)pyrazolyl warhead (W) can be made by following the synthetic scheme for PSY-05-00519-001 (Compound 519). Substituted propiophenone intermediate (**Int-1**) is treated with *N,N*-dimethylformamide dimethyl acetal (DMF-DMA) to yield phenyl-substituted 3-(dimethylamino)prop-2-en-1-one intermediate, **Int-2**, which subsequently undergoes 1,3-dipolar cycloaddition with hydrazine (NH₂NH₂) to yield 5-aryl-4-methylpyrrole intermediate, **Int-3**. Simultaneous synthesis of *tert*-butyl 6-((methylsulfonyl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate, **Int-C**, is performed by reacting *tert*-butyl 6-hydroxy-2-azaspiro[3.3]heptane-2-carboxylate with methanesulfonyl chloride. *N*-alkylation of **Int-3** with **Int-C** yields a mixture of two regioisomers: 1,4,5-trisubstituted pyrrole product, **Int-4**, and 1,3,4-trisubstituted pyrrole product **Int-4A**. Both **Int-4** and **Int-4A** are subjected to *N*-Boc-deprotection with trifluoroacetic acid to yield corresponding trifluoroacetate salts, **Int-5** and **Int-5A**, respectively. Amidation of 2,fluoro-5-hydroxybenzoic acid with either **Int-5** or **Int-5A** yields either 1-(5-aryl-4-methyl)pyrazolyl or 1-(3-aryl-4-methyl)pyrazolyl analogs, respectively.

[000135] Analogs with a 1-(4-trifluoromethyl)pyrazole warhead can be made by following the synthetic scheme for PSY-05-00475-001 (Compound 475). Substituted iodobenzene, **Int-A**, undergoes Sonogashira coupling with ethyl propiolate to generate phenyl-substituted propiolate intermediate, **Int-B**. Sodium hydroxide-catalyzed ester hydrolysis of **Int-B** yields the propiolic acid intermediate, **Int-1**, which then undergoes a unique copper-mediated decarboxylative trifluoromethylation with Togni's reagent to generate the α -trifluoromethyl ketone intermediate, **Int-2**. Treatment of **Int-2** with *N,N*-dimethylformamide dimethyl acetal (DMF-DMA) affords the 3-(dimethylamino)-2-(trifluoromethyl)prop-2-en-1-one intermediate, **Int-3**, which undergoes 1,3-dipolar cycloaddition with hydrazine to yield 2-aryl-4-(trifluoromethyl)pyrazole intermediate, **Int-4**. Treatment of **Int-4** with spirocyclic mesylate intermediate described previously, **Int-C**, yields a mixture of two regioisomers: 1,4,5-trisubstituted pyrrole product, **Int-5**, and 1,3,4-trisubstituted pyrrole product **Int-5A**. Both **Int-5** and **Int-5A** are subjected to *N*-Boc-deprotection with trifluoroacetic acid to yield corresponding trifluoroacetate salts, **Int-6** and **Int-6A**, respectively. Amidation of 2,fluoro-5-hydroxybenzoic acid with either **Int-6** or **Int-6A** yields

either 1-(5-aryl-4-trifluoromethyl)pyrazolyl or 1-(3-aryl-4-trifluoromethyl)pyrazolyl analogs, respectively.

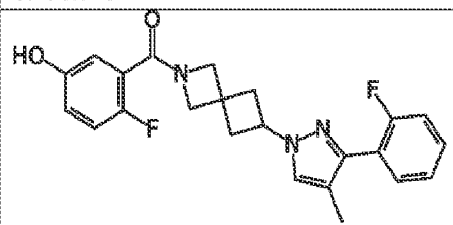
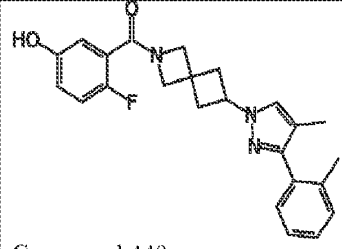
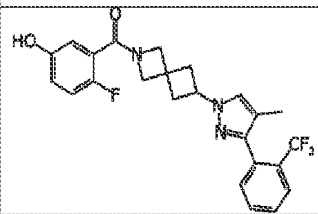
[000136] Similar to the synthesis of Compound 525, the syntheses of 1-(4-cyclopropyl)pyrazole warhead analogs begins with treating substituted acetophenone, **Int-1**, with *N,N*-dimethylformamide dimethyl acetal (DMF-DMA) to form 3-(dimethylamino)prop-2-en-1-one intermediate, **Int-2**, which subsequently undergoes 1,3-dipolar cycloaddition with hydrazine to form 2-arylpyrazole intermediate, **Int-3**. 4-iodination of **Int-3** forms **Int-4** which subsequently undergoes *N*-PMB protection to form **Int-5**. Suzuki coupling of **Int-5** with cyclopropylboronic acid affords the 2-aryl-4-cyclopropylpyrazole intermediate, **Int-6**, which undergoes PMB-deprotection to liberate the free *N*-H pyrazole intermediate, **Int-7**. Treatment of **Int-7** with spirocyclic mesylate intermediate described previously, **Int-C**, yields a mixture of two regioisomers: 1,4,5-trisubstituted pyrazole product, **Int-8**, and 1,3,4-trisubstituted pyrazole product **Int-8A**. Both **Int-8** and **Int-8A** are subjected to *N*-Boc-deprotection with trifluoroacetic acid to yield corresponding trifluoroacetate salts, **Int-9** and **Int-9A**, respectively. Amidation of 2,fluoro-5-hydroxybenzoic acid with either **Int-9** or **Int-9A** yields either 1-(5-aryl-4-cyclopropyl)pyrazolyl or 1-(3-aryl-4-cyclopropyl)pyrazolyl analogs, respectively.

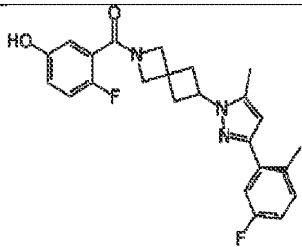
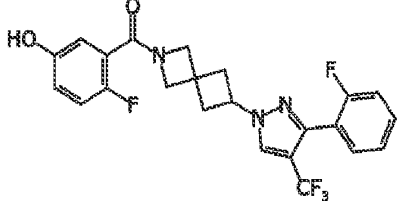
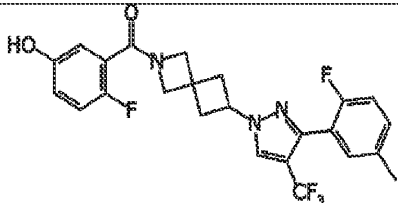
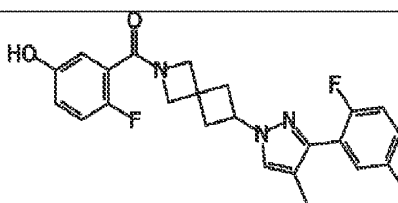
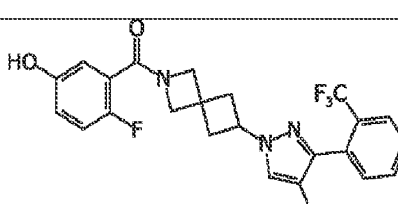
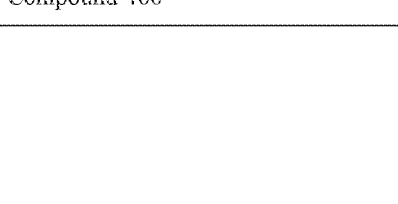
[000137] For analogs with a 5-(1-aryl-3-methyl)pyrazolyl warhead, the first two steps are identical to the steps provided for the syntheses of analogs in Formula (II-B). Beginning with **Int-3** from Formula (II-B), Claisen-type condensation is performed with ethyl acetate to yield the 1,3-dicarbonyl intermediate, **Int-4**.

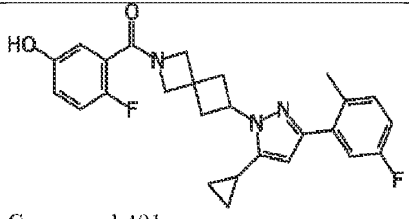
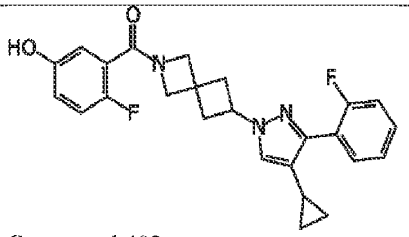
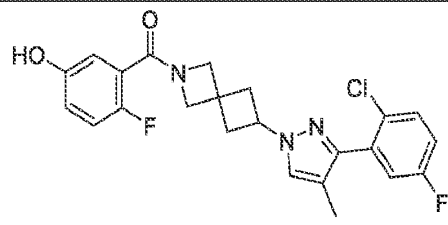
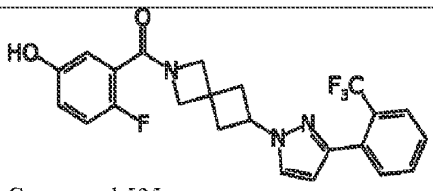
[000138] For analogs with a 1-(5-aryl-3-cyclopropyl)pyrazolyl or 1-(3-aryl-5-cyclopropyl)pyrazolyl warhead, substituted acetophenone, **Int-1**, undergoes a Claisen-type condensation with ethyl cyclopropanecarboxylate to yield the 1,3-dicarbonyl intermediate, **Int-2**. Cyclization of **Int-2** with substituted hydrazine hydrate affords the 5-aryl-3-cyclopropylpyrazole intermediate, **Int-3**, which undergoes *N*-alkylation with spirocyclic mesylate intermediate, **Int-C**, to form two trisubstituted regioisomers: 1-(5-aryl-3-cyclopropyl)pyrazolyl intermediate, **Int-4**, and 1-(3-aryl-5-cyclopropyl)pyrazolyl intermediate, **Int-4a**. Both **Int-4** and **Int-4A** are subjected to *N*-Boc-deprotection with trifluoroacetic acid to yield corresponding trifluoroacetate salts, **Int-5** and **Int-5A**, respectively. Amidation of 2,fluoro-5-hydroxybenzoic acid with either **Int-5** or **Int-5A** yields either 1-(5-aryl-3-cyclopropyl)pyrazolyl or 1-(3-aryl-5-cyclopropyl)pyrazolyl analogs, respectively.

[000139] The synthesis of 1-(5-aryl-3-cyclopropyl)pyrazolyl and 1-(3-aryl-5-cyclopropyl)pyrazolyl warhead analogs pertains to the synthesis of the following analogs: 1-(5-aryl-3-methyl)pyrazolyl warhead analogs, and 1-(3-aryl-5-methyl)pyrazolyl warhead analogs. For these two types of analogs, replace ethyl cyclopropanecarboxylate with ethyl acetate in step 1. For 1-(5-aryl-3-trifluoromethyl)pyrazolyl warhead analogs and 1-(3-aryl-5-trifluoromethyl)pyrazolyl warhead analogs, replace ethyl cyclopropanecarboxylate with ethyl 2,2,2-trifluoroacetate.

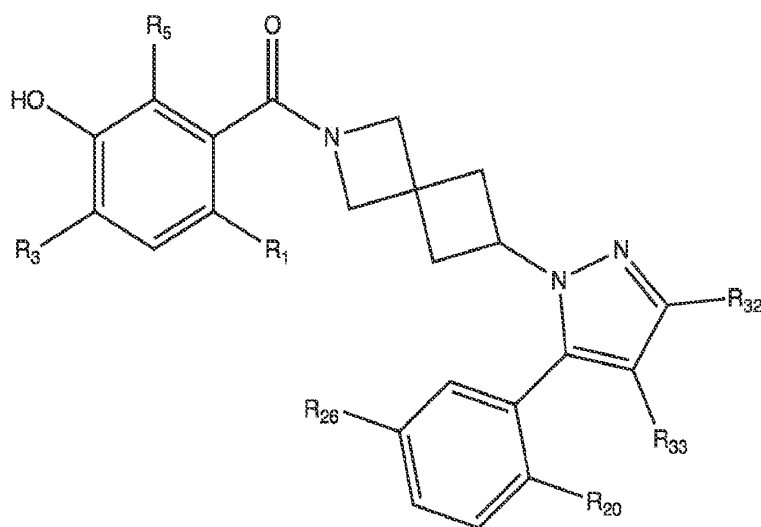
Table 2

Structure	Description
 Compound 417	Compound-## was prepared by followed the general procedure given above from 70 mg of 6-(3-methyl-1-(<i>o</i>-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptane 2,2,2-trifluoroacetate (1 eq.) to obtain (2-fluoro-5-methoxyphenyl)(6-(3-methyl-1-(<i>o</i>-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone (25 mg, 15%) as a white solid. LCMS: ## <i>m/z</i> [M+H]⁺. ¹H NMR (400 MHz, Methanol-<i>d</i>₄) δ ### Analog is prepared by following method for preparation of 1-(4-methyl)pyrazolyl warhead (W) analogs. Compound can be prepared by reacting 1-(2-fluorophenyl)propan-1-one with DMF-DMA to form Int-1. Int-4A is selectively advanced for <i>N</i>-Boc-deprotection and subsequent amide coupling to yield final compound.
 Compound 440	Analog is prepared by following method for preparation of 1-(4-methyl)pyrazolyl warhead (W) analogs. Compound can be prepared by reacting 1-(<i>o</i>-tolyl)propan-1-one with DMF-DMA to form Int-1. Int-4A is selectively advanced for <i>N</i>-Boc-deprotection and subsequent amide coupling to yield final compound.
	Analog is prepared by following method for preparation of 1-(4-methyl)pyrazolyl warhead (W) analogs. Compound can be prepared by reacting 1-(2-(trifluoromethyl)phenyl)propan-1-one with DMF-DMA to form Int-1. Int-4A is selectively

Structure	Description
Compound 444	advanced for <i>N</i> -Boc-deprotection and subsequent amide coupling to yield final compound.
	Synthesis of compound follows synthesis for 1-(3-aryl-5-methyl)pyrazolyl warhead analogs. 1-(5-fluoro-2-methylphenyl)ethan-1-one is used as Int-1 . Int-4A is selectively advanced for <i>N</i> -Boc-deprotection and subsequent amide coupling to yield final compound.
	Compound 446
	Compound 473
	Compound 475
	Compound 477
	Compound 488

Structure	Description
 Compound 491	Analog is prepared by following method describing synthesis for analogs with a 1-(3-aryl-5-cyclopropyl)pyrazolyl warhead. 1-(5-fluoro-2-methylphenyl)ethan-1-one is used as Int-1. Int-4A is selectively advanced for <i>N</i>-Boc-deprotection and subsequent amide coupling to yield final compound.
 Compound 493	Analog is prepared by following method for preparation of 1-(4-cyclopropyl)pyrazolyl warhead (W) analogs. Compound can be prepared by using 1-(2-fluorophenyl)ethan-1-one as Int-1. Int-9A is selectively advanced for <i>N</i>-Boc-deprotection and subsequent amide coupling to yield final compound.
 Compound 520	Analog is prepared by following method for preparation of 1-(4-methyl)pyrazolyl warhead (W) analogs. Compound can be prepared by reacting 1-(2-chloro-5-fluorophenyl)propan-1-one with DMF-DMA to form Int-1. Int-4A is selectively advanced for <i>N</i>-Boc-deprotection and subsequent amide coupling to yield final compound.
 Compound 525	Analog is prepared by following method for preparation of 1-(4-methyl)pyrazolyl warhead (W) analogs. Compound can be prepared by reacting 1-(2-(trifluoromethyl)phenyl)ethan-1-one with DMF-DMA to form Int-1. Int-4A is selectively advanced for <i>N</i>-Boc-deprotection and subsequent amide coupling to yield final compound.

[000140] In some embodiments, the disclosure provides a compound of Formula (II-D) or a pharmaceutically acceptable salt thereof:



Formula (II-D),

wherein

R₁ is halogen or cyano;

R₃ is hydrogen, lower alkyl, or halogen;

R₅ is hydrogen, halogen or lower alkyl;

R₆ is hydrogen;

R₂₀ is halogen or lower alkyl optionally substituted with one or more halogen;

R₂₆ is halogen or hydrogen; and

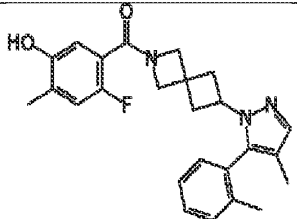
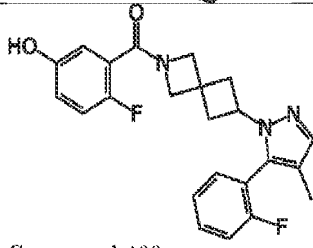
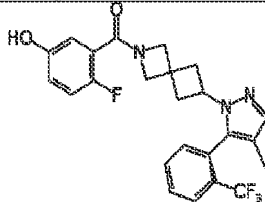
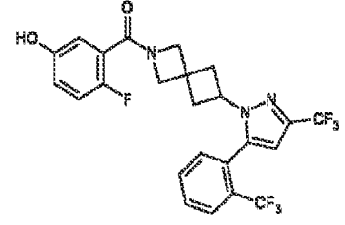
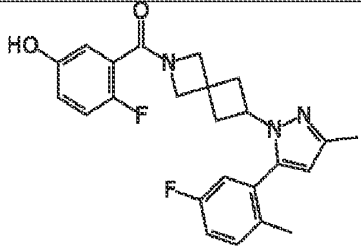
R₃₂ and R₃₃ are each independently hydrogen or lower alkyl optionally substituted with one or more halogen, provided that one of R₃₂ and R₃₃ is hydrogen.

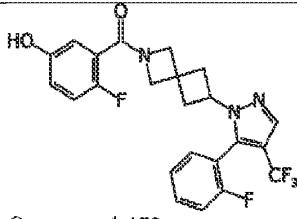
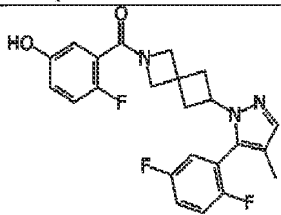
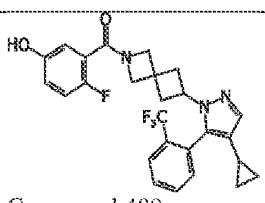
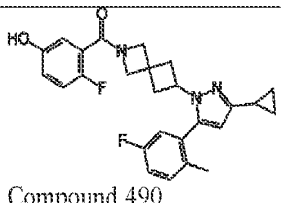
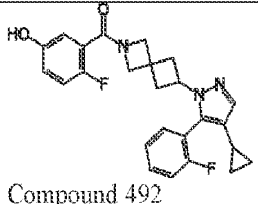
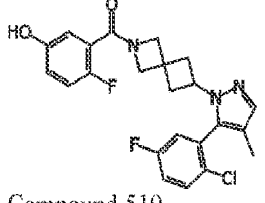
General procedure for Preparing Compounds of Formula (II-D)

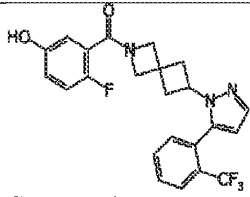
[000141] Syntheses of analogs can be performed by following methods provided in Formula (II-C).

Table 3

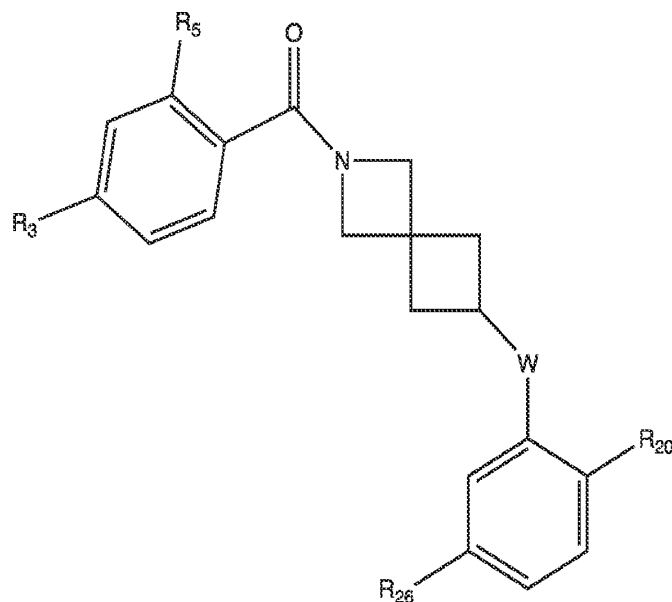
Structure	Description
PSY-05-407	Compound-## was prepared by followed the general procedure given above from 70 mg of 6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptane 2,2,2-trifluoroacetate (1 eq.) to obtain (2-fluoro-5-

Structure	Description
	methoxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone (25 mg, 15%) as a white solid. LCMS: ## m/z $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ ###
 Compound 408	Analog is prepared by following method for preparation of 1-(4-methyl)pyrazolyl warhead (W) analogs. Compound can be prepared by reacting 1-(2-fluorophenyl)propan-1-one with DMF-DMA to form Int-1 . Int-4 is selectively advanced for <i>N</i> -Boc-deprotection and subsequent amide coupling to yield final compound.
 Compound 410	Analog is prepared by following method for preparation of 1-(4-methyl)pyrazolyl warhead (W) analogs. Compound can be prepared by reacting 1-(2-(trifluoromethyl)phenyl)propan-1-one with DMF-DMA to form Int-1 . Int-4 is selectively advanced for <i>N</i> -Boc-deprotection and subsequent amide coupling to yield final compound.
 Compound 414	Analog is prepared by following synthesis for 1-(5-aryl-3-trifluoromethyl)pyrazolyl warhead analogs. Compound can be synthesized by using 1-(2-(trifluoromethyl)phenyl)ethan-1-one as Int-1 . Int-4 is selectively advanced for <i>N</i> -Boc-deprotection and subsequent amide coupling to yield final compound.
 Compound 415	Analog is prepared by following synthesis for 1-(5-aryl-3-methyl)pyrazolyl warhead analogs. Compound can be synthesized by using 1-(5-fluoro-2-methylphenyl)ethan-1-one is used as Int-1 . Int-4 is selectively advanced for <i>N</i> -Boc-deprotection and subsequent amide coupling to yield final compound.

Structure	Description
 Compound 472	Analog is prepared by following method for preparation of 1-(4-(trifluoromethyl)pyrazolyl) warhead (W) analogs. 1-fluoro-2-iodobenzene is used as Int-A for generating propiolic acid Int-1 . Int-5 is selectively advanced for <i>N</i> -Boc-deprotection and subsequent amide coupling to yield final compound.
 Compound 476	Analog is prepared by following method for preparation of 1-(4-methyl)pyrazolyl warhead (W) analogs. Compound can be prepared by reacting 1-(2,5-difluorophenyl)propan-1-one with DMF-DMA to form Int-1 . Int-4 is selectively advanced for <i>N</i> -Boc-deprotection and subsequent amide coupling to yield final compound.
 Compound 489	Analog is prepared by following method for preparation of 1-(4-cyclopropyl)pyrazolyl warhead (W) analogs. Compound can be prepared by using 1-(2-(trifluoromethyl)phenyl)ethan-1-one as Int-1 . Int-9 is selectively advanced for <i>N</i> -Boc-deprotection and subsequent amide coupling to yield final compound.
 Compound 490	Analog is prepared by following method for preparation of 1-(5-aryl-3-cyclopropyl)pyrazolyl analogs. Compound can be synthesized by using 1-(5-fluoro-2-methylphenyl)ethan-1-one as Int-1 . Int-4 is selectively advanced for <i>N</i> -Boc-deprotection and subsequent amide coupling to yield final compound.
 Compound 492	Analog is prepared by following method for preparation of 1-(4-cyclopropyl)pyrazolyl warhead (W) analogs. Compound can be prepared by using 1-(2-fluorophenyl)ethan-1-one as Int-1 . Int-9 is selectively advanced for <i>N</i> -Boc-deprotection and subsequent amide coupling to yield final compound.
 Compound 519	Analog is prepared by following method for preparation of 1-(4-methyl)pyrazolyl warhead (W) analogs. Compound can be prepared by reacting 1-(2-chloro-5-fluorophenyl)propan-1-one with DMF-DMA to form Int-1 . Int-4 is selectively advanced for <i>N</i> -Boc-deprotection and subsequent amide coupling to yield final compound.

Structure	Description
 Compound 526	Analog is prepared by following method for preparation of 1-(4-methyl)pyrazolyl warhead (W) analogs. Compound can be prepared by reacting 1-(2-(trifluoromethyl)phenyl)ethan-1-one with DMF-DMA to form Int-1. Int-4 is selectively advanced for <i>N</i>-Boc-deprotection and subsequent amide coupling to yield final compound.

[000142] In some embodiments, the disclosure provides a compound of Formula (III) or a pharmaceutically acceptable salt thereof:



Formula (III)

wherein

R_3 is halogen;

R_5 is $-O-R_{52}$;

R_{52} is lower alkyl or cycloalkyl, each optionally substituted with halogen,

W is a 5-member heteroaryl ring optionally substituted with one or more R_{30} ;

R_{30} is lower alkyl;

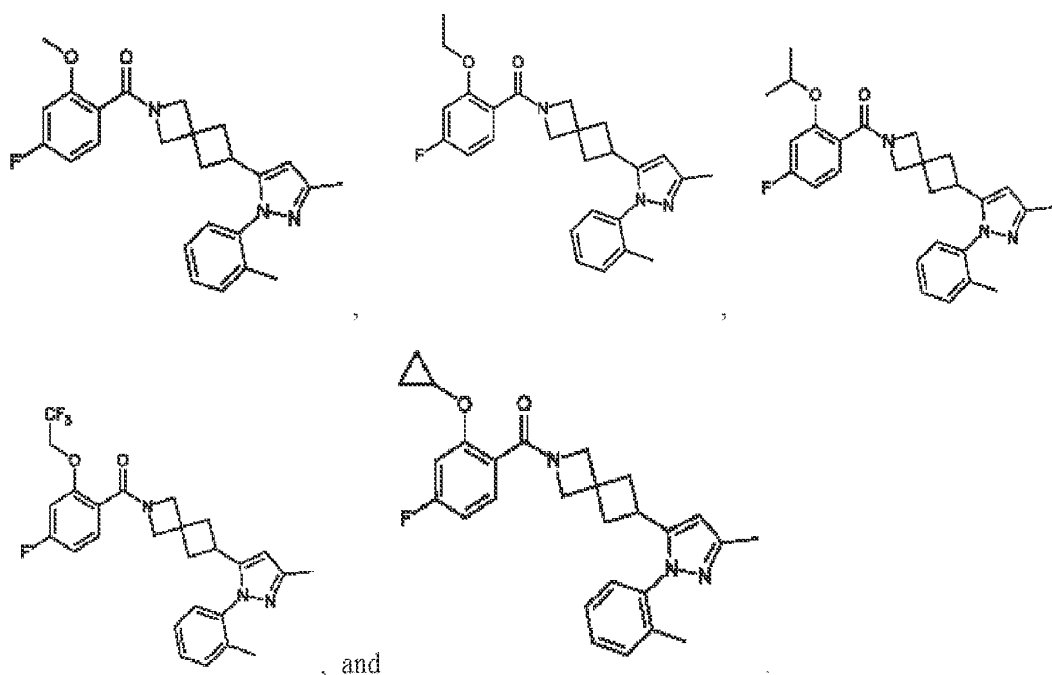
R_{20} is lower alkyl; and

R_{26} is hydrogen or halogen.

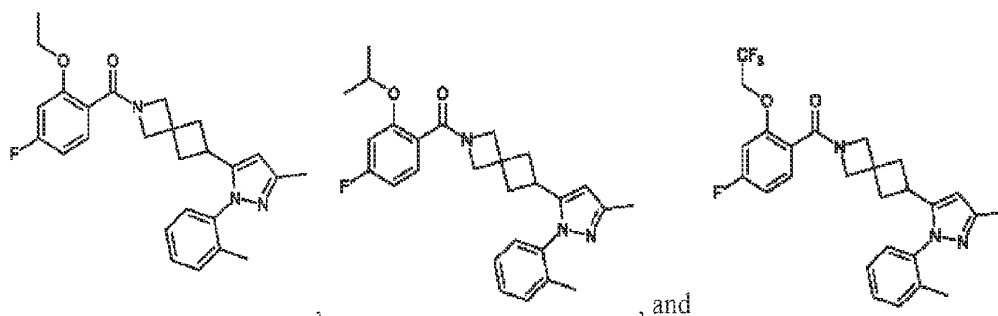
[000143] In some embodiments, R_{20} is methyl and R_{26} is hydrogen or F in compounds of Formula (III). In some embodiments, R_{20} is methyl and R_{26} is hydrogen in compounds of Formula (III). In some embodiments, R_{20} is methyl and R_{26} is F.

[000144] In compounds of Formula (III), W is a 5-member heteroaryl ring comprising at least one nitrogen, such as a pyrazole. In some embodiments, R_3 is F. In some embodiments, R_{62} is lower alkyl or cycloalkyl. In some embodiments, the lower alkyl in R_{20} , R_{30} and R_{62} can be methyl. In some embodiments, W is pyrazole optionally substituted with one or more methyl, and R_3 is the F. In some embodiments, W is pyrazole optionally substituted with one or more methyl, and R_3 is the F, R_{62} is methyl, ethyl, propyl or cyclopropyl each optionally substituted with one or more F, and R_{20} is methyl in a compound of Formula (III).

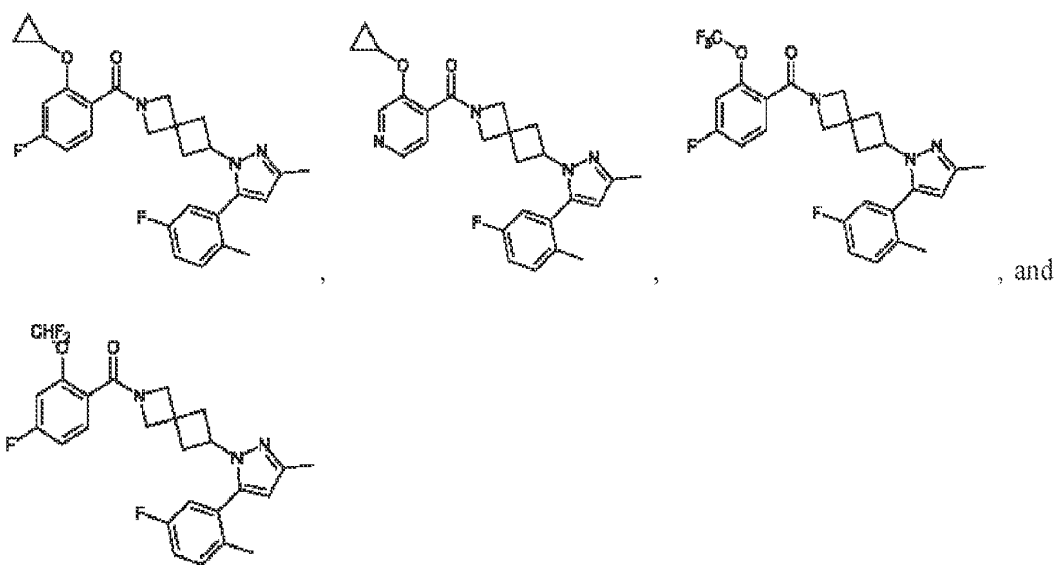
[000145] In some embodiments, the compound of Formula (III) is selected from the group consisting of:



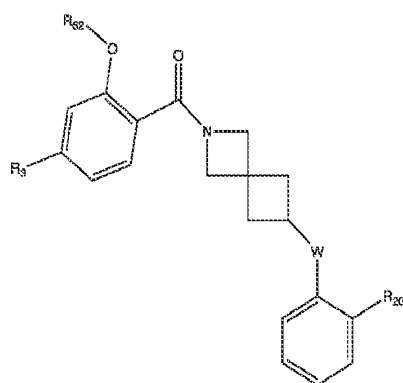
[000146] In some embodiments, the compound of Formula (III) is selected from the group consisting of:



[000147] In some embodiments, the compound is selected from the group consisting of:



[000148] In some embodiments, the disclosure provides a compound of Formula (III) or a pharmaceutically acceptable salt thereof:



Formula (III-A)

wherein

R₃ is halogen;

R₆₂ is lower alkyl or cycloalkyl, each optionally substituted with halogen,

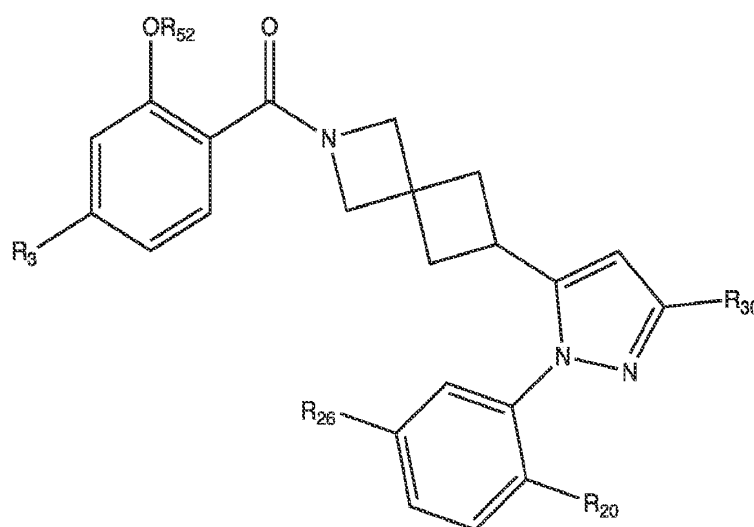
W is a 5-member heteroaryl ring optionally substituted with one or more R₃₀;

R₃₀ is lower alkyl; and

R₂₀ is lower alkyl.

[000149] In compounds of Formula (III-A), W is a 5-member heteroaryl ring comprising at least one nitrogen, such as a pyrazole. In some embodiments, R₃ is F. In some embodiments, R₆₂ is lower alkyl or cycloalkyl. In some embodiments, the lower alkyl in R₂₀, R₃₀ and R₆₂ can be methyl. In some embodiments, W is pyrazole optionally substituted with one or more methyl, and R₃ is the F. In some embodiments, W is pyrazole optionally substituted with one or more methyl, and R₃ is the F, R₆₂ is methyl, ethyl, propyl or cyclopropyl each optionally substituted with one or more F, and R₂₀ is methyl in a compound of Formula (III-A).

[000150] In some embodiments, the disclosure provides a compound of Formula (III-B) or a pharmaceutically acceptable salt thereof.



Formula (III-B)

wherein

R₃ is halogen;

R₅₂ is lower alkyl or lower cycloalkyl, each optionally substituted with halogen,

R₃₀ is lower alkyl;

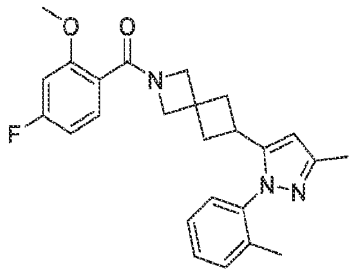
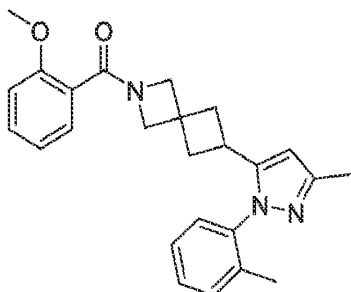
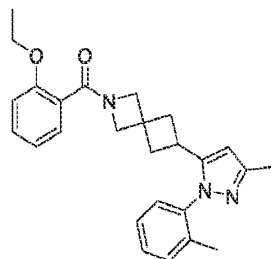
R₂₀ is lower alkyl; and

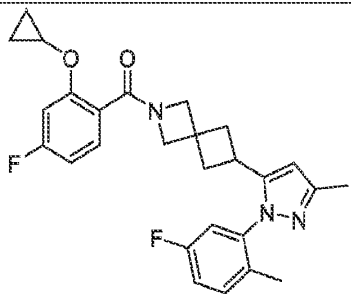
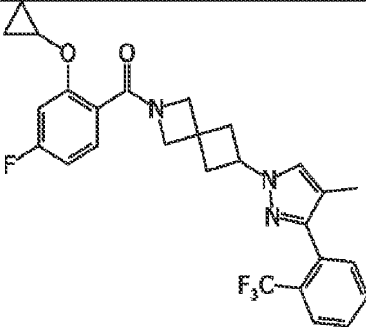
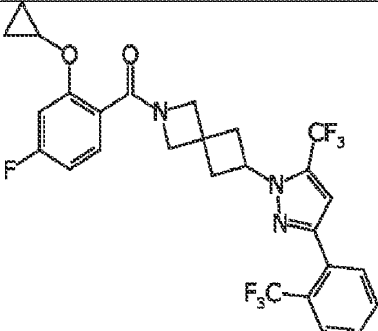
R₂₆ is hydrogen or halogen.

General procedure for Preparing Compounds of Formula (III-B)

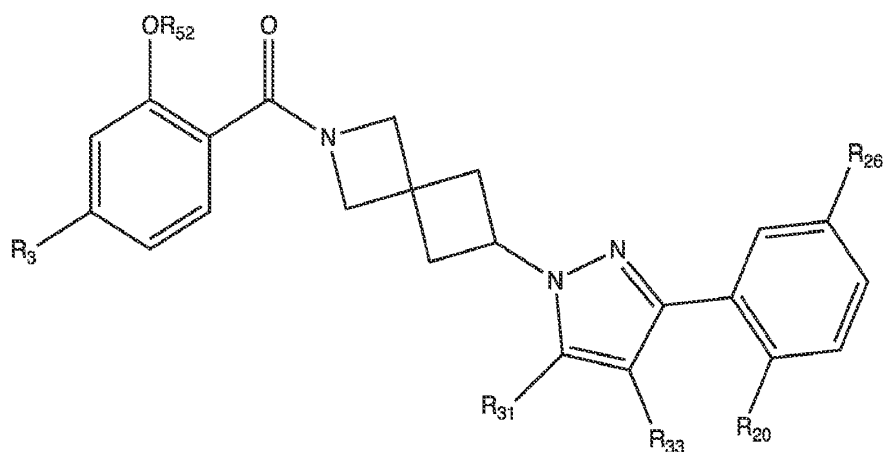
[000151] Syntheses of analogs is performed by following methods provided in Formulas (II-B) and (II-C).

Table 4

Structure	Description
 PSY-05-00142-001	Compound 00142-001 was prepared by followed the general procedure given above from 120 mg of 6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptane 2,2,2-trifluoroacetate (1 eq.) to obtain (4-fluoro-2-methoxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3] heptan-2-yl)methanone (35 mg, 19.44%) as a white solid. Compound can be made by following synthetic methodology provided in Formula (II-B). Int-4 is reacted with <i>o</i>-tolylhydrazine hydrochloride, then Int-6 is reacted with 4-fluoro-2-methoxybenzoic acid to yield the final analog.
 PSY-05-00143-001	Compound-00143-001 was prepared by followed the general procedure given above from 80 mg of 6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptane 2,2,2-trifluoroacetate (1 eq.) to obtain (2-methoxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3] heptan-2-yl)methanone (25 mg, 20.83%) as a white solid. Compound can be made by following synthetic methodology provided in Formula (II-B). Int-4 is reacted with <i>o</i>-tolylhydrazine hydrochloride, then Int-6 is reacted with 2-methoxybenzoic acid to yield the final analog.
 PSY-05-00145-001	Compound-00145-001 was prepared by followed the general procedure given above from 80 mg of 6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptane 2,2,2-trifluoroacetate (1 eq.) to obtain (2-ethoxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone (30 mg, 24.19%) as a white solid. Compound can be made by following synthetic methodology provided in Formula (II-B). Int-4 is reacted

	with <i>o</i> -tolylhydrazine hydrochloride, then Int-6 is reacted with 2-ethoxybenzoic acid to yield the final analog.
 PSY-05-418	Compound can be made by following synthetic methodology provided in Formula (II-B). Int-4 is reacted with (5-fluoro-2-methylphenyl)hydrazine hydrochloride, then Int-6 is reacted with 2-cyclopropoxy-4-fluorobenzoic acid to yield the final analog.
 PSY-05-448	Analog is prepared by following method for preparation of 1-(4-methyl)pyrazolyl warhead analogs. Compound can be prepared by reacting 1-(2-(trifluoromethyl)phenyl)propan-1-one with DMF-DMA to form Int-1 . Int-4A is selectively advanced for <i>N</i> -Boc-deprotection and subsequent amide coupling with 2-cyclopropoxy-4-fluorobenzoic acid to yield final compound.
 PSY-05-451	Analog is prepared by following synthesis for 1-(3-aryl-5-trifluoromethyl)pyrazolyl warhead analogs. Compound can be synthesized by using 1-(2-(trifluoromethyl)phenyl)ethan-1-one as Int-1 . Int-4A is selectively advanced for <i>N</i> -Boc-deprotection and subsequent amide coupling with 2-cyclopropoxy-4-fluorobenzoic acid to yield final compound.

[000152] In some embodiments, the disclosure provides a compound of Formula (III-C) or a pharmaceutically acceptable salt thereof.



Formula (III-C)

wherein

R₃ is halogen;

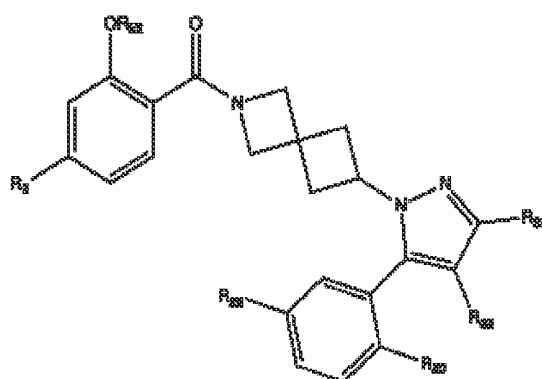
R₅₂ is lower alkyl or lower cycloalkyl, each optionally substituted with halogen,

R₃₁ and R₃₃ are each independently hydrogen or lower alkyl optionally substituted with one or more halogen, provided that one of R₃₁ and R₃₃ is hydrogen.

R₂₀ is lower alkyl optionally substituted with halogen; and

R₂₆ is hydrogen or halogen.

[000153] In some embodiments, the disclosure provides a compound of Formula (III-D) or a pharmaceutically acceptable salt thereof:



Formula (III-D)

wherein

R₃ is halogen;

R₅₂ is lower alkyl or lower cycloalkyl, each optionally substituted with halogen,

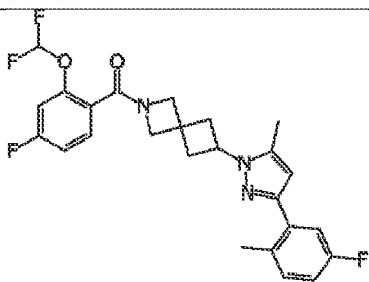
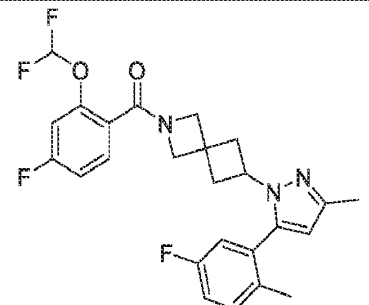
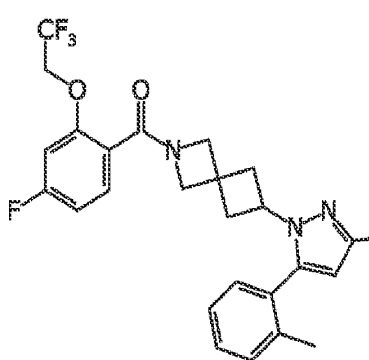
R₃₂ and R₃₃ are each independently hydrogen or lower alkyl optionally substituted with one or more halogen, provided that one of R₃₂ and R₃₃ is hydrogen.

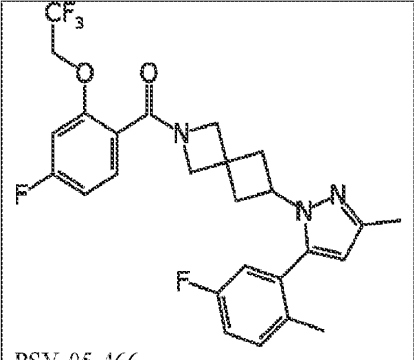
R₂₀ is lower alkyl optionally substituted with halogen; and

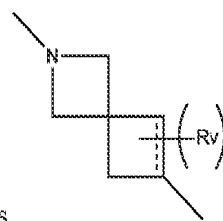
R₂₆ is hydrogen or halogen.

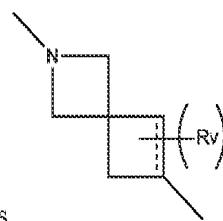
General procedure for Preparing Compounds of Formula (III-D)

Table 5

Structure	Description
 PSY-05-455	Analog can be prepared by following synthesis for 1-(3-aryl-5-methyl)pyrazolyl warhead analogs. 1-(5-fluoro-2-methylphenyl)ethan-1-one is used as Int-1. Int-4A is selectively advanced for <i>N</i>-Boc-deprotection and subsequent amide coupling with 2-(difluoromethoxy)-4-fluorobenzoic acid to yield final compound.
 PSY-05-428	Analog can be prepared by following synthesis for 1-(5-aryl-3-methyl)pyrazolyl warhead analogs. 1-(5-fluoro-2-methylphenyl)ethan-1-one is used as Int-1. Int-4 is selectively advanced for <i>N</i>-Boc-deprotection and subsequent amide coupling with 2-(difluoromethoxy)-4-fluorobenzoic acid to yield final compound.
 PSY-05-464	Analog can be prepared by following synthesis for 1-(5-aryl-3-methyl)pyrazolyl warhead analogs. 1-(o-tolyl)ethan-1-one is used as Int-1. Int-4 is selectively advanced for <i>N</i>-Boc-deprotection and subsequent amide coupling with 4-fluoro-2-(2,2,2-trifluoroethoxy)benzoic acid to yield final compound. 4-fluoro-2-(2,2,2-trifluoroethoxy)benzoic acid is prepared by reacting methyl 2,4-difluorobenzoate with 2,2,2-trifluoroethanol, then performing sodium hydroxide-catalyzed ester hydrolysis to liberate the free acid.

	Analog can be prepared by following synthesis for 1-(5-aryl-3-methyl)pyrazolyl warhead analogs. 1-(5-fluoro-2-methylphenyl)ethan-1-one is used as Int-1. Int-4 is selectively advanced for <i>N</i>-Boc-deprotection and subsequent amide coupling with 4-fluoro-2-(2,2,2-trifluoroethoxy)benzoic acid to yield final compound. 4-fluoro-2-(2,2,2-trifluoroethoxy)benzoic acid is prepared by reacting methyl 2,4-difluorobenzoate with 2,2,2-trifluoroethanol, than performing sodium hydroxide-catalyzed ester hydrolysis to liberate the free acid.
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[000154] In some embodiments, V in Formula (I-A) is , where n and each Rv is as defined above, and the dashed line represents an optional double bond. In some embodiments, in Formula (I-B) the dashed line represents an optional double bond. In some embodiments, in Formula (I-B-1) the dashed line represents an optional double bond. In some embodiments, in Formula (I-B-2) the dashed line represents an optional double bond. In some embodiments, in Formula (II) the dashed line represents an optional double bond.

[000155] The compounds described herein can exist as salts, such as with pharmaceutically acceptable acids. Accordingly, such salts of the compounds described herein are included. The term “pharmaceutically acceptable salt” is meant to include salts of the active compounds that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those

derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, oxalic, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge et al., "Pharmaceutical Salts", *Journal of Pharmaceutical Science*, 1977, 66, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[000156] The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents.

Pharmaceutical Compositions

[000157] In certain embodiments, the present application is directed to a pharmaceutical composition comprising an active pharmaceutical ingredient. In certain embodiments, the pharmaceutical composition comprises a compound as disclosed herein as the active pharmaceutical ingredient (API) and a pharmaceutically acceptable carrier comprising one or more excipients. In some embodiments, the pharmaceutical composition optionally further comprises an additional therapeutic compound (i.e., agent) with the pharmaceutically acceptable carrier. The pharmaceutical composition can be a medicament.

[000158] Pharmaceutically acceptable carriers include those known in the art. The choice of a pharmaceutically acceptable carrier can depend, for example, on the desired route of administration of the composition. A pharmaceutical composition (preparation) can be administered to a subject by any of a number of routes of administration including, for example, parenteral administration (e.g. intravenously, subcutaneously, or intramuscularly), oral administration (for example, tablets, and capsules); absorption through the oral mucosa (e.g., sublingually) or transdermally (for example as a patch applied to the skin) or topically (for example, as a cream, ointment or spray applied to the skin).

[000159] In some embodiments, pharmaceutical compositions comprising compounds of Formula (I) or pharmaceutically acceptable salts thereof can be formulated for oral administration. For example, a compound provided herein can be combined with suitable compendial excipients to form an oral unit dosage form, such as a capsule or tablet, containing a target dose of a compound of Formula (I). The drug product can be prepared by first manufacturing the compound of Formula (I) as an active pharmaceutical ingredient (API), followed by roller compaction/milling with intragranular excipients and blending with extra granular excipients. A Drug Product can contain the selected compound of Formula (I) as the API and excipient components in a tablet in a desired dosage strength of Compound 1. The blended material can be compressed to form tablets and then film coated. The excipients can be selected from materials appropriate for inclusion in a pharmaceutical composition for an intended purpose and route of delivery including providing a desired manufacturing and stability properties and/or desired in vivo characteristics or other properties to the pharmaceutical composition. In some embodiments, the pharmaceutical composition can include a compound of Formula (I) as the API in combination with a filler (e.g., a form of microcrystalline cellulose), a dry binder or disintegrant (e.g., a cross-linked polymer), a glidant (e.g., colloidal silicon dioxide) and/or a lubricant (e.g., magnesium stearate). In some embodiments, the pharmaceutical composition can comprise a material such as an extended release or disintegrant involved in carrying or transporting the API pharmaceutical agent from one organ, or portion of the body, to another organ, or portion of the body of a subject, including materials to desirable control the absorption of the API in the intestine.

[000160] The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration. The amount of active ingredient that can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. For use in the methods of this invention, active compounds can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

[000161] Methods of preparing these formulations or compositions include the step of bringing into association an active compound, such as a compound of the invention, with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[000162] To prepare solid dosage forms for oral administration, the active ingredient is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, (2) binders, (3) humectants, (4) disintegrating agents, (5) solution retarding agents, (6) absorption accelerators, (7) wetting agents, (8) absorbents, (9) lubricants, (10) complexing agents, and (11) coloring agents. In the case of capsules (including sprinkle capsules and gelatin capsules), tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using suitable excipients. The pharmaceutical compositions according to the present invention may contain conventional pharmaceutical carriers and/or auxiliary agents. In some embodiments, the pharmaceutical compositions according to the present invention may contain conventional carrier agents including a binder, a lubricant and/or a glidant selected from those products and materials generally used in pharmaceutical industry for preparation of pharmaceutical compositions for an intended route of administration.

[000163] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[000164] Liquid dosage forms useful for oral administration include pharmaceutically acceptable carriers and the active ingredient provided as a solid form for reconstitution prior to administration or as a liquid (e.g., solutions, suspensions, or emulsions). In addition to the active ingredient, a liquid dosage form may contain inert diluents commonly used in the art. For example, formulations of pharmaceutically acceptable compositions for injection can include aqueous solutions such as water or physiologically buffered saline or other solvents or vehicles

suitable for the intended route of administration. In some embodiments, the pharmaceutical composition is formulated for parenteral administration.

[000165] The therapeutically effective amount of a pharmaceutical composition can be determined by human clinical trials to determine the safe and effective dose for a patient with a relevant diagnosis. It is generally understood that the effective amount of the compound may vary according to the weight, sex, age, and medical history of the subject. Other factors which influence the effective amount may include, but are not limited to, the severity of the patient's condition, the disorder being treated, the stability of the compound, and, if desired, another type of therapeutic agent being administered with the compound of the invention. A larger total dose can be delivered by multiple administrations of the pharmaceutical composition at a dose and dose interval determined to be safe and effective for the patient.

[000166] The present disclosure includes the use of pharmaceutically acceptable salts of compounds of the invention in the compositions and methods of the present invention. Pharmaceutically-acceptable salts include, for example, acid-addition salts and base-addition salts. The acid that is added to a compound to form an acid-addition salt can be an organic acid or an inorganic acid. A base that is added to a compound to form a base-addition salt can be an organic base or an inorganic base. In some embodiments, a pharmaceutically-acceptable salt is a metal salt, in some embodiments, a pharmaceutically-acceptable salt is an ammonium salt. For example, a pharmaceutically acceptable acid addition salt can exist as various solvates, such as with water, methanol, ethanol, dimethylformamide, and the like. Mixtures of such solvates can also be prepared. The source of such solvate can be from the solvent of crystallization, inherent in the solvent of preparation or crystallization, or adventitious to such solvent.

Methods of use

[000167] The compounds described herein can modulate activity of monoacylglycerol lipase. For example, the compounds described herein can inhibit MAGL. Accordingly, in one aspect the disclosure provides a method for inhibiting MAGL, e.g., in a cell expressing MAGL. Generally, the method comprises administering to the cell a compound of Formula (I) described herein. It is noted that the inhibition can be reversible or irreversible. In some embodiments, the compounds are capable of reversibly inhibiting MAGL. As used herein, "reversible inhibition" means MAGL retains its activity once the compound is taken away or MAGL is no longer in contact with the

compound. In other words, the activity of MAGL returns to the same level it was prior to use of the compound.

[000168] The compound can be administered to the cell, e.g. cell expressing MAGL *in vitro* or *ex vivo*. As used herein, administering the compound to the cell means contacting the cell with the compound so that the compound is taken up by the cell. Generally, the cell can be contacted with the compound in a cell culture e.g., *in vitro* or *ex vivo*, or the compound can be administered to a subject, e.g., *in vivo*. The term “contacting” or “contact” as used herein in connection with contacting a cell includes subjecting the cells to an appropriate culture media, which comprises a compound of Formula (I). Where the cell is *in vivo*, “contacting” or “contact” includes administering the compound, e.g., in a pharmaceutical composition to a subject via an appropriate administration route such that the compound contacts the cell *in vivo*.

[000169] As described herein, the compound of Formula (I) can be administered to a cell *in vivo* for modulating MAGL, e.g., inhibiting MAGL. Accordingly, in some embodiments, a therapeutically effective amount of a compound of Formula (I) can be administered to a subject for inhibiting monoacylglycerol lipase. For example, a therapeutically effective amount of a compound of Formula (I) can be administered to a subject for treating a monoglycerol lipase mediated disease or disorder.

[000170] By a MAGL-mediated disease or disorder is meant a disease or disorder wherein activity of MAGL is a cause of the disease or disorder. Non-limiting example, of MAGL-mediated diseases or disorders include neurodegenerative diseases, neuropsychiatric disorders, pain and chronic inflammatory diseases, cancer and other conditions that can be treated with a reversible MAGL inhibitor of Formula (I).

[000171] In some embodiments, a compound of Formula (I) is useful for evaluation as a drug candidate for the treatment of neurodegenerative diseases such as Parkinson’s disease, amyotrophic lateral sclerosis, Alzheimer’s disease or Huntington’s disease. In some embodiments, a compound of Formula (I) is useful for evaluation as a drug candidate for the treatment of neuropsychiatric disorders such as head injury, epilepsy, cerebral ischemia and anxiety and/or depression. In some embodiments, a compound of Formula (I) is useful for evaluation as a drug candidate for the treatment of pain and inflammatory diseases or conditions. In some embodiments, a compound of Formula (I) is useful for evaluation as a drug candidate for the treatment of forms of cancer treatable by increasing 2-AG. In some embodiments, a compound

of Formula (I) is useful for evaluation as a drug candidate for the treatment of obesity, fibrosis, emesis, asthma, fever and osteoporosis. In some embodiments, a compound of Formula (I) is useful for evaluation as a drug candidate for increasing levels of 2-AG in a subject in need thereof.

[000172] A subject can be one who has been previously diagnosed with or identified as suffering from or having a condition in need of treatment a MAGL-mediated disease or disorder or one or more complications related to such a condition, and optionally, have already undergone treatment for such a disease or disorder. Alternatively, a subject can also be one who has not been previously diagnosed as having a MAGL-mediated disease or disorder or one or more complications related to such a disease or disorder. A “subject in need” of treatment for a particular condition can be a subject having that condition, diagnosed as having that condition, or at risk of developing that condition.

[000173] In one embodiment, the subject is human. In another embodiment, the subject is an experimental animal or animal substitute as a disease model.

[000174] It is noted that the terms “administered” and “subjected” are used interchangeably in the context of treatment of a disease or disorder. In jurisdictions that forbid the patenting of methods that are practiced on the human body, the meaning of “administering” of a composition to a human subject shall be restricted to prescribing a controlled substance that a human subject will be administer to the subject by any technique (e.g., orally, inhalation, topical application, injection, insertion, etc.). The broadest reasonable interpretation that is consistent with laws or regulations defining patentable subject matter is intended. In jurisdictions that do not forbid the patenting of methods that are practiced on the human body, the “administering” of compositions includes both methods practiced on the human body and also the foregoing activities.

[000175] As used herein, the term “administer” refers to the placement of a composition into a subject by a method or route which results in at least partial localization of the composition at a desired site such that desired effect is produced. A compound or composition described herein can be administered by any appropriate route known in the art including, but not limited to, oral or parenteral routes, including intravenous, intramuscular, subcutaneous, transdermal, airway (aerosol), pulmonary, nasal, rectal, and topical (including buccal and sublingual) administration.

[000176] Exemplary modes of administration include, but are not limited to, injection, infusion, instillation, inhalation, or ingestion. “Injection” includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intraventricular, intracapsular, intraorbital, intracardiac,

intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, sub capsular, subarachnoid, intraspinal, intracerebro spinal, and intrasternal injection and infusion. In some embodiments, administration will generally be local rather than systemic.

[000177] In preferred embodiments, the compositions are orally administered. Without limitations, oral administration can be in the form of solutions, suspensions, tablets, pills, capsules, sustained-release formulations, oral rinses, powders and the like.

[000178] The phrase “therapeutically-effective amount” as used herein means that amount of a compound, material, or composition comprising a compound described herein which is effective for producing some desired therapeutic effect in at least a sub-population of cells, e.g., modulate or inhibit activity of MAGL in a subject at a reasonable benefit/risk ratio applicable to any medical treatment. Thus, “therapeutically effective amount” means that amount which, when administered to a subject for treating a disease, is sufficient to affect such treatment for the disease.

[000179] Depending on the route of administration, effective doses can be calculated according to the body weight, body surface area, or organ size of the subject to be treated. Optimization of the appropriate dosages can readily be made by one skilled in the art in light of pharmacokinetic data observed in human clinical trials. Alternatively, or additionally, the dosage to be administered can be determined from studies using animal models for the particular type of condition to be treated, and/or from animal or human data obtained from agents which are known to exhibit similar pharmacological activities. The final dosage regimen will be determined by the attending surgeon or physician, considering various factors which modify the action of active agent, e.g., the agent’s specific activity, the agent’s specific half-life *in vivo*, the severity of the condition and the responsiveness of the patient, the age, condition, body weight, sex and diet of the patient, the severity of any present infection, time of administration, the use (or not) of other concomitant therapies, and other clinical factors.

[000180] The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the IC_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of use or administration utilized. The effective dose can be estimated initially from cell culture assays. A dose can be formulated in animal models to achieve a circulating plasma concentration range that includes the IC_{50} (i.e., the concentration of the therapeutic which achieves a half-maximal

inhibition of symptoms) as determined in cell culture. Levels in plasma can be measured, for example, by high performance liquid chromatography. The effects of any particular dosage can be monitored by a suitable bioassay.

[000181] It will be appreciated that methods of treatment of the present invention can be employed in combination with additional therapies. For example, a treatment according to the present disclosure can be co-administered with one or more desired therapeutics or medical procedures for treating a MAGL-mediated disease or disorder.

Definitions

[000182] Unless otherwise defined herein, scientific and technical terms used in this application shall have the meanings that are commonly understood by those of ordinary skill in the art.

[000183] For convenience, certain terms employed herein, in the specification, examples and appended claims are collected herein. Unless stated otherwise, or implicit from context, the following terms and phrases include the meanings provided below. Unless explicitly stated otherwise, or apparent from context, the terms and phrases below do not exclude the meaning that the term or phrase has acquired in the art to which it pertains. The definitions are provided to aid in describing particular embodiments, and are not intended to limit the claimed invention, because the scope of the invention is limited only by the claims. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular.

[000184] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as those commonly understood to one of ordinary skill in the art to which this invention pertains. Although any known methods, devices, and materials may be used in the practice or testing of the invention, the methods, devices, and materials in this regard are described herein.

[000185] As used herein, the term “Selective MAGL Inhibitor Compound” refers to a compound that selectively inhibits MAGL with an IC_{50} that is at least 10 times the IC_{50} for its inhibition of fatty acid amide hydrolase (FAAH), and that has an IC_{50} of 100nM or less for MAGL inhibition (according to the MAGL Potency assay of Example 22 and the FAAH potency assay of Example 15).

[000186] As used herein, the term “Reversible MAGL Inhibitor Compound” the percent inhibition after dilution to the IC_{50} concentration is $50 \pm 15\%$ in the assay described for “determining MAGL reversible inhibition” section of Example 16 below.

[000187] As used herein, the term “Reversible Selective MAGL Inhibitor Compound” refers to a compound that is both a Selective MAGL Inhibitor Compound and a Reversible MAGL Inhibitor Compound, or a pharmaceutically acceptable salt thereof.

[000188] As used herein, the term “alkyl” refers to an aliphatic hydrocarbon group which can be straight or branched having 1 to about 10 carbon atoms in the chain, and which preferably have about 1 to about 6 carbons in the chain. “Lower alkyl” refers to an alkyl group having 1 to about 4 carbon atoms. “Higher alkyl” refers to an alkyl group having about 5 to about 10 carbon atoms. The alkyl group can be optionally substituted with one or more alkyl group substituents which can be the same or different, where “alkyl group substituent” includes halo, amino, aryl, hydroxy, alkoxy, aryloxy, alkylthio, arylthio, aralkyloxy, aralkylthio, carboxy, alkoxycarbonyl, oxo and cycloalkyl. “Branched” refers to an alkyl group in which a lower alkyl group, such as methyl, ethyl or propyl, is attached to a linear alkyl chain. Exemplary alkyl groups include methyl, ethyl, i-propyl, n-butyl, t-butyl, n-pentyl, heptyl, octyl, decyl, dodecyl, tridecyl, tetradecyl, pentadecyl and hexadecyl. Useful alkyl groups include branched or straight chain alkyl groups of 6 to 50 carbon, and also include the lower alkyl groups of 1 to about 4 carbons and the higher alkyl groups of about 12 to about 16 carbons.

[000189] As used herein, the term “cycloalkyl” refers to a non-aromatic mono- or multicyclic ring system of about 3 to about 12 carbon atoms. Representative monocyclic cycloalkyl rings include cyclopropyl, cyclobutyl, and cyclohexyl. Useful multicyclic cycloalkyl rings include adamantyl. “Lower cycloalkyl” refers to an alkyl group having 3 to about 6 carbon atoms in the cycloalkyl ring, optionally substituted with halogen, alkyl, alkoxy or other substituents disclosed herein. “Higher alkyl” refers to an alkyl group having about 5 to about 10 carbon atoms.

[000190] “Aryl” refers to an aromatic carbocyclic radical containing about 3 to about 10 carbon atoms. The aryl group can be optionally substituted with one or more substituents, which can be the same or different, where “aryl group substituent” includes alkyl, alkenyl, alkynyl, hydroxy, alkoxy, carboxy, halo, nitro, trihalomethyl, cyano, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, acyloxy, acylamino, aroylamino, carbamoyl, alkylcarbamoyl,

dialkylcarbamoyl, arylthio, alkylthio, and alkylene. Exemplary aryl groups include substituted or unsubstituted phenyl.

[000191] “Heterocyclyl” refers to a nonaromatic 3-8 membered monocyclic, or 8-12 membered bicyclic ring systems having 1-3 heteroatoms if monocyclic, or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S (*e.g.*, carbon atoms and 1-3, or 1-6 heteroatoms of N, O, or S if monocyclic, or bicyclic, respectively). C_xheterocyclyl and C_x-C_yheterocyclyl are typically used where X and Y indicate the number of carbon atoms in the ring system. In some embodiments, 1, 2 or 3 hydrogen atoms of each ring can be substituted by a substituent. Exemplary heterocyclyl groups include, but are not limited to piperazinyl, pyrrolidinyl, dioxanyl, morpholinyl, tetrahydrofuranyl, piperidyl, 4-morpholyl, 4-piperazinyl, pyrrolidinyl, perhydropyrroliziny, 1,4-diazaperhydroepinyl, 1,3-dioxanyl, 1,4-dioxanyl and the like.

[000192] “Heteroaryl” refers to an aromatic 3-8 membered monocyclic, or 8-12 membered fused bicyclic ring system having 1-3 heteroatoms if monocyclic, or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S (*e.g.*, carbon atoms and 1-3, 1-6, or 1-9 heteroatoms of N, O, or S if monocyclic, bicyclic, or tricyclic, respectively).

[000193] Exemplary aryls and heteroaryls include, but are not limited to, phenyl, pyridinyl, pyrimidinyl, furanyl, thienyl, imidazolyl, thiazolyl, pyrazolyl, pyridazinyl, pyrazinyl, triazinyl, tetrazolyl, indolyl, benzyl, naphthyl, anthracenyl, azulenyl, fluorenyl, indanyl, indenyl, naphthyl, tetrahydronaphthyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazoliny, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazoliny, carbazolyl, 4aH carbazolyl, carboliny, chromanyl, chromenyl, cinnoliny, decahydroquinoliny, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3 b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazoliny, imidazolyl, 1H-indazolyl, indolenyl, indoliny, indoliziny, indolyl, 3H-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindoliny, isoindolyl, isoquinoliny, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholiny, naphthyridiny, octahydroisoquinoliny, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxindolyl, pyrimidinyl, phenanthridiny, phenanthroliny, phenazinyl, phenothiazinyl, phenoxathiny, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, puriny, pyranyl, pyrazinyl, pyrazolidinyl, pyrazoliny, pyrazolyl,

pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinoliziny, quinoxaliny, quinuclidiny, tetrahydrofurany, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl or xanthenyl, each of which can be optionally substituted.

[000194] As used herein, the term “halogen” or “halo” refers to an atom selected from fluorine, chlorine, bromine and iodine. The term “halogen radioisotope” or “halo isotope” refers to a radionuclide of an atom selected from fluorine, chlorine, bromine and iodine.

[000195] A “halogen-substituted moiety” or “halo-substituted moiety”, as an isolated group or part of a larger group, means an aliphatic, alicyclic, or aromatic moiety, as described herein, substituted by one or more “halo” atoms, as such terms are defined in this application.

[000196] The term “haloalkyl” as used herein refers to an alkyl structure with at least one substituent of fluorine, chlorine, bromine or iodine, or with combinations thereof. Exemplary halo-substituted alkyl includes haloalkyl, dihaloalkyl, trihaloalkyl, perhaloalkyl and the like (e.g. halosubstituted (C₁-C₃)alkyl includes chloromethyl, dichloromethyl, difluoromethyl, trifluoromethyl (CF₃), perfluoroethyl, 2,2,2-trifluoroethyl, 2,2,2-trifluoro-1,1-dichloroethyl, and the like).

[000197] As used herein, the term “amino” means -NH₂ or -NH₃⁺ where one or more hydrogens are optionally substituted with alkyl, and the alkyl is optionally further substituted with one or more halogen or other substituents disclosed herein. The term “alkylamino” means a nitrogen moiety having one straight or branched unsaturated aliphatic, cyclyl, or heterocyclyl radicals attached to the nitrogen, e.g., -NH(alkyl). The term “dialkylamino” means a nitrogen moiety having at two straight or branched unsaturated aliphatic, cyclyl, or heterocyclyl radicals attached to the nitrogen, e.g., -N(alkyl)(alkyl). The term “alkylamino” includes “alkenylamino,” “alkynylamino,” “cyclylamino,” and “heterocyclylamino.” The term “arylamino” means a nitrogen moiety having at least one aryl radical attached to the nitrogen. For example, -NHaryl, and —N(aryl)₂. The term “heteroarylamino” means a nitrogen moiety having at least one heteroaryl radical attached to the nitrogen. For example —NHheteroaryl, and —N(heteroaryl)₂. Optionally, two substituents together with the nitrogen can also form a ring. Unless indicated otherwise, the compounds described herein containing amino moieties can include protected

derivatives thereof. Suitable protecting groups for amino moieties include acetyl, tertbutoxycarbonyl, benzyloxycarbonyl, and the like. Exemplary alkylamino includes, but is not limited to, $\text{NH}(\text{C}_1\text{-C}_{10}\text{alkyl})$, such as ---NHCH_3 , $\text{---NHCH}_2\text{CH}_3$, $\text{---NHCH}_2\text{CH}_2\text{CH}_3$, and $\text{---NHCH}(\text{CH}_3)_2$. Exemplary dialkylamino includes, but is not limited to, $\text{---N}(\text{C}_1\text{-C}_{10}\text{alkyl})_2$, such as $\text{---N}(\text{CH}_3)_2$, $\text{---N}(\text{CH}_2\text{CH}_3)_2$, $\text{---N}(\text{CH}_2\text{CH}_2\text{CH}_3)_2$, and $\text{---N}(\text{CH}(\text{CH}_3)_2)_2$.

[000198] The term “aminoalkyl” means an alkyl, alkenyl, and alkynyl as defined above, except where one or more substituted or unsubstituted nitrogen atoms (---N---) are positioned between carbon atoms of the alkyl, alkenyl, or alkynyl. For example, an ($\text{C}_2\text{-C}_6$) aminoalkyl refers to a chain comprising between 2 and 6 carbons and one or more nitrogen atoms positioned between the carbon atoms.

[000199] The terms “hydroxy” and “hydroxyl” mean the radical ---OH .

[000200] The terms “alkoxyl” or “alkoxy” as used herein refers to an alkyl group, as defined above, having an oxygen radical attached thereto, and can be represented by one of ---O-alkyl , ---O-alkenyl , and ---O-alkynyl . Aroxy can be represented by ---O-aryl or ---O-heteroaryl , wherein aryl and heteroaryl are as defined herein. The alkoxy and aroxy groups can be substituted as described above for alkyl. Exemplary alkoxy groups include, but are not limited to O-methyl , O-ethyl , $\text{O-}n\text{-propyl}$, O-isopropyl , $\text{O-}n\text{-butyl}$, O-isobutyl , $\text{O-}sec\text{-butyl}$, $\text{O-}tert\text{-butyl}$, O-pentyl , O-hexyl , O-cyclopropyl , O-cyclobutyl , O-cyclopentyl , O-cyclohexyl and the like.

[000201] As used herein, the term “carbonyl” means the radical ---C(O)--- . It is noted that the carbonyl radical can be further substituted with a variety of substituents to form different carbonyl groups including acids, acid halides, amides, esters, ketones, and the like.

[000202] The term “carboxy” means the radical ---C(O)O--- . It is noted that compounds described herein containing carboxy moieties can include protected derivatives thereof, i.e., where the oxygen is substituted with a protecting group. Suitable protecting groups for carboxy moieties include benzyl, tert-butyl, and the like. As used herein, a carboxy group includes ---COOH , i.e., carboxyl group.

[000203] The term “cyano” means the radical ---CN .

[000204] The term “nitro” means the radical ---NO_2 .

[000205] The term, “heteroatom” refers to an atom that is not a carbon atom. Particular examples of heteroatoms include, but are not limited to nitrogen, oxygen, sulfur and halogens. A “heteroatom moiety” includes a moiety where the atom by which the moiety is attached is not a

carbon. Examples of heteroatom moieties include ---N= , $\text{---NR}^{\text{N}}\text{---}$, $\text{---N}^+(\text{O}^-)=$, ---O--- , ---S--- or $\text{---S(O)}_2\text{---}$, $\text{---OS(O)}_2\text{---}$, and ---SS--- , wherein R^{N} is H or a further substituent.

[000206] “Acyl” refers to an alkyl-CO— group, wherein alkyl is as previously described. Exemplary acyl groups comprise alkyl of 1 to about 30 carbon atoms. Exemplary acyl groups also include acetyl, propanoyl, 2-methylpropanoyl, butanoyl and palmitoyl.

[000207] “Alkoxycarbonyl” refers to an alkyl-O—CO— group. Exemplary alkoxycarbonyl groups include methoxycarbonyl, ethoxycarbonyl, butyloxycarbonyl, and t-butyloxycarbonyl.

[000208] “Carbamoyl” refers to an $\text{H}_2\text{N—CO—}$ group.

[000209] “Alkylcarbamoyl” refers to a $\text{R}^{\text{R}}\text{R}^{\text{N}}\text{—CO—}$ group, wherein one of R and R' is hydrogen and the other of R and R' is alkyl as previously described.

[000210] “Dialkylcarbamoyl” refers to $\text{R}^{\text{R}}\text{R}^{\text{N}}\text{—CO—}$ group, wherein each of R and R' is independently alkyl as previously described.

[000211] The term “optionally substituted” means that the specified group or moiety is unsubstituted or is substituted with one or more (typically 1, 2, 3, 4, 5 or 6 substituents) independently selected from the group of substituents listed below in the definition for “substituents” or otherwise specified. The term “substituents” refers to a group “substituted” on a substituted group at any atom of the substituted group. Suitable substituents include, without limitation, halogen, hydroxy, carboxy, oxo, nitro, haloalkyl, alkyl, alkenyl, alkynyl, alkaryl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, alkoxy, aryloxy, amino, acylamino, alkylcarbanoyl, arylcarbanoyl, aminoalkyl, alkoxycarbonyl, carboxy, hydroxyalkyl, alkanesulfonyl, arenesulfonyl, alkanesulfonamido, arenesulfonamido, aralkylsulfonamido, alkylcarbonyl, acyloxy, cyano or ureido. In some cases, two substituents, together with the carbons to which they are attached to can form a ring.

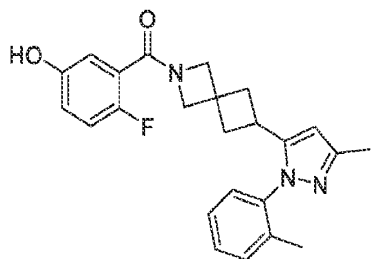
[000212] For example, any alkyl, alkenyl, cycloalkyl, heterocyclyl, heteroaryl or aryl is optionally substituted with 1, 2, 3, 4 or 5 groups selected from OH, CN, SH, SO_2NH_2 , $\text{SO}_2(\text{C}_1\text{--C}_4)\text{alkyl}$, $\text{SO}_2\text{NH}(\text{C}_1\text{--C}_4)\text{alkyl}$, halogen, carbonyl, thiol, cyano, NH_2 , $\text{NH}(\text{C}_1\text{--C}_4)\text{alkyl}$, $\text{N}[(\text{C}_1\text{--C}_4)\text{alkyl}]_2$, C(O)NH_2 , COOH, COOMe, acetyl, $(\text{C}_1\text{--C}_8)\text{alkyl}$, $\text{O}(\text{C}_1\text{--C}_8)\text{alkyl}$, $\text{O}(\text{C}_1\text{--C}_8)\text{haloalkyl}$, $(\text{C}_2\text{--C}_8)\text{alkenyl}$, $(\text{C}_2\text{--C}_8)\text{alkynyl}$, haloalkyl, thioalkyl, cyanomethylene, alkylaminyl, aryl, heteroaryl, substituted aryl, $\text{NH}_2\text{—C(O)—alkylene}$, $\text{NH(Me)—C(O)—alkylene}$, $\text{CH}_2\text{—C(O)—alkyl}$, C(O)—alkyl , alkylcarbonylaminy, $\text{CH}_2\text{—[CH(OH)]}_m\text{—(CH}_2)_p\text{—OH}$, $\text{CH}_2\text{—[CH(OH)]}_m\text{—}$

$(\text{CH}_2)_p\text{---NH}_2$ or $\text{CH}_2\text{---aryl---alkoxy}$; or wherein any alkyl, cycloalkyl or heterocyclyl is optionally substituted with oxo; “m” and “p” are independently 1, 2, 3, 4, 5 or 6.

[000213] In some embodiments, an optionally substituted group is substituted with 1 substituent. In some other embodiments, an optionally substituted group is substituted with 2 independently selected substituents, which can be same or different. In some other embodiments, an optionally substituted group is substituted with 3 independently selected substituents, which can be same, different or any combination of same and different. In still some other embodiments, an optionally substituted group is substituted with 4 independently selected substituents, which can be same, different or any combination of same and different. In yet some other embodiments, an optionally substituted group is substituted with 5 independently selected substituents, which can be same, different or any combination of same and different.

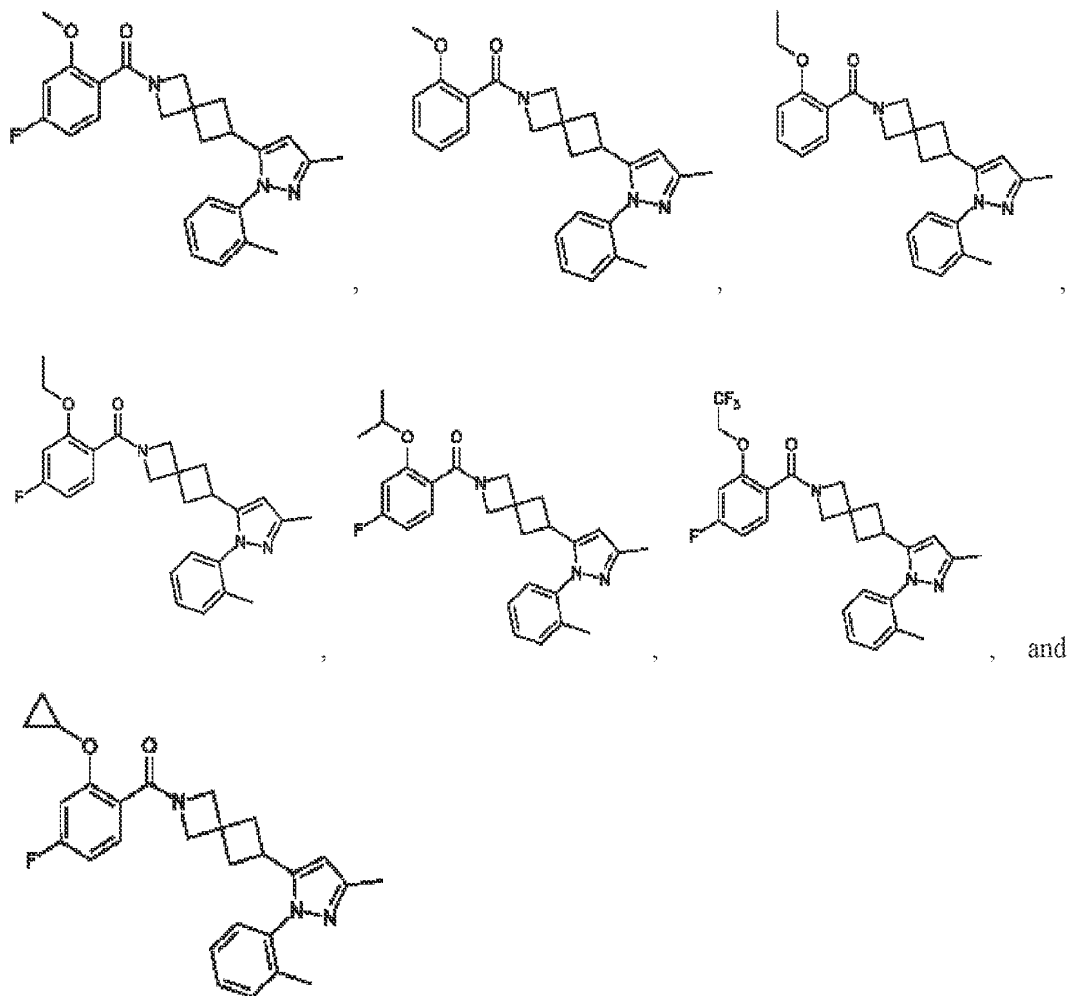
[000214] As used herein, the compound designation terms “Compound #”, “PSY-#” and “PSY-05-#” (where # indicates any number having one or more digits) are synonymous with each other, unless otherwise indicated (e.g., “Compound 1” refers to a compound alternatively designated as “PSY-05-0001” or “PSY-1”).

[000215] As used herein, Compound (PSY-05-00074) (alternatively designated as Compound 74) is:

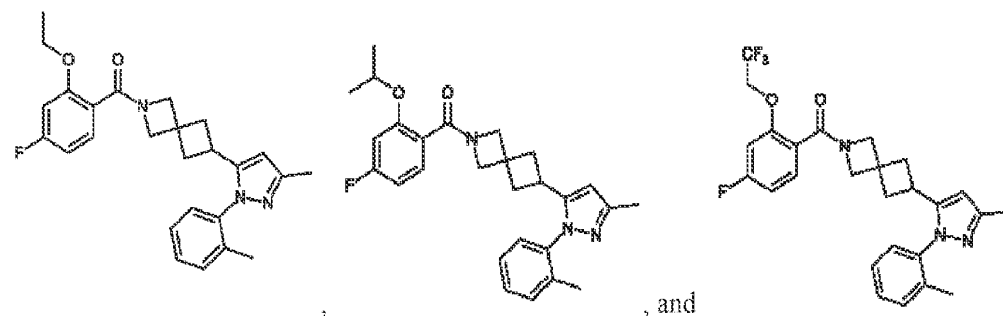


Compound (PSY-05-00074) is referred to by name as (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone, or (2-fluoro-5-hydroxyphenyl){6-[3-methyl-1-(o-tolyl)-5-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone. Either name may be used interchangeably herein to refer to Compound (PSY-05-00074).

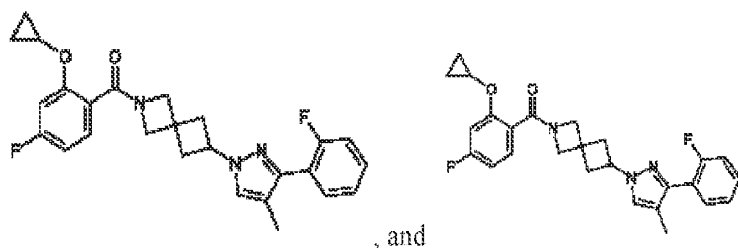
[000216] In some embodiments, the compound is selected from the group consisting of:



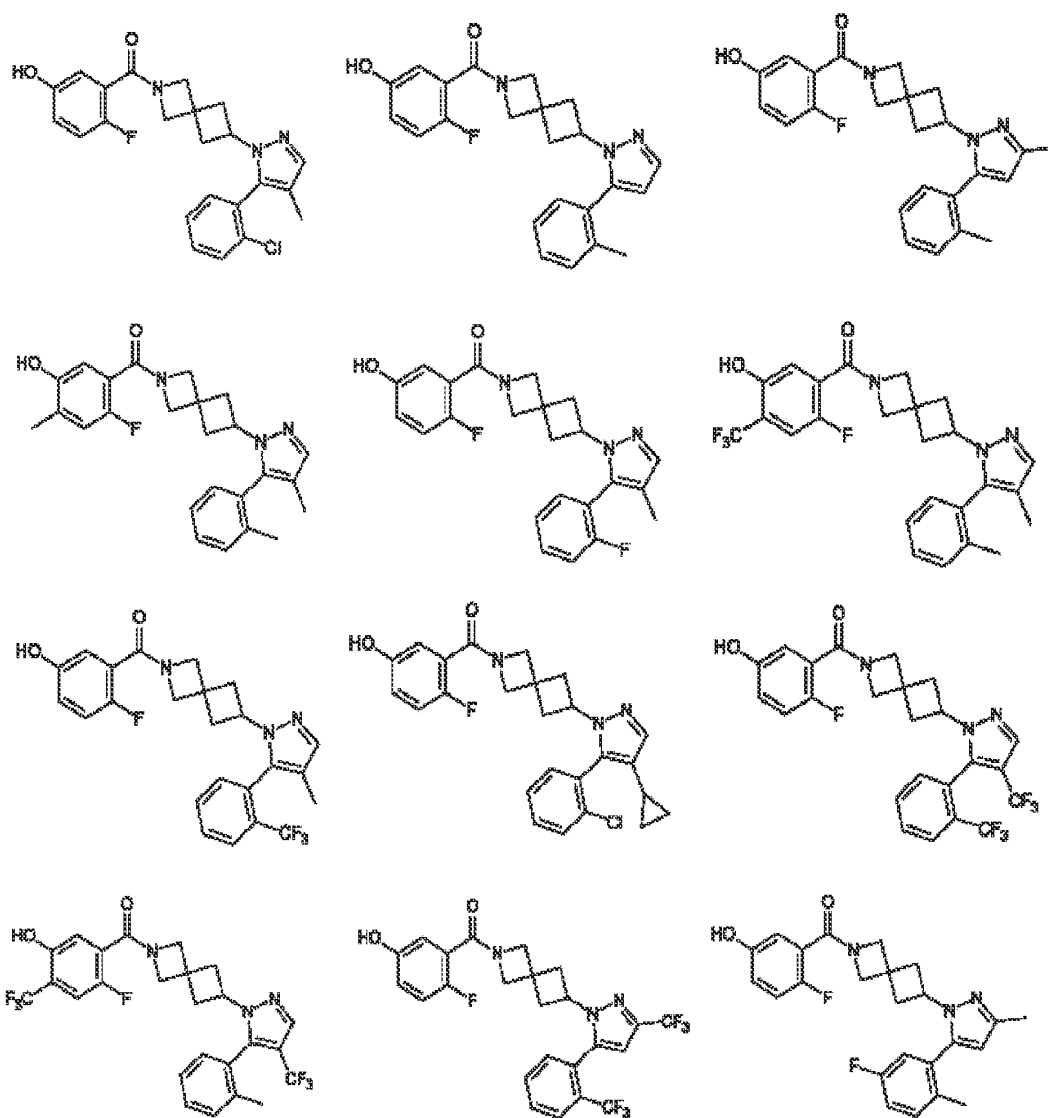
[000217] In some embodiments, the compound is selected from the group consisting of:

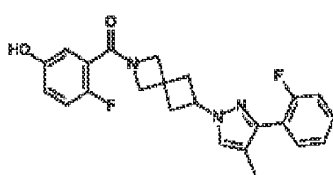
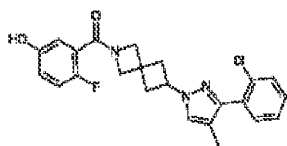


[000218] In some embodiments, the compound is selected from the group consisting of:

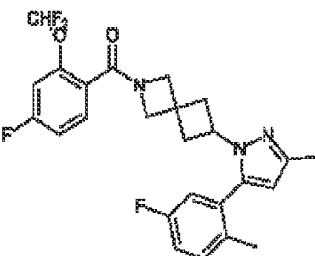
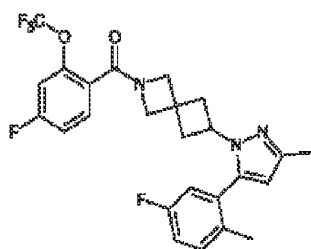
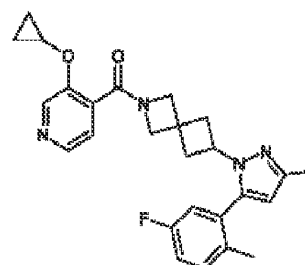
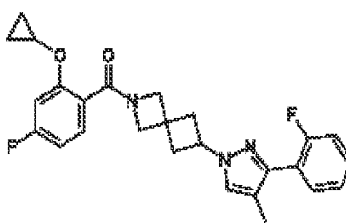
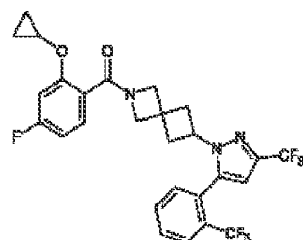
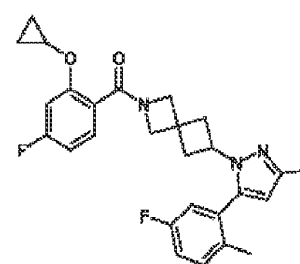
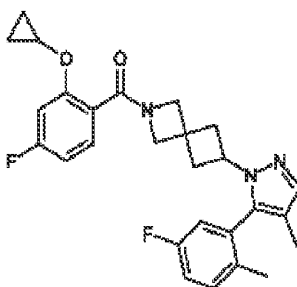
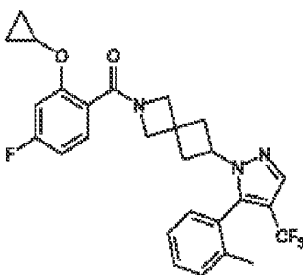
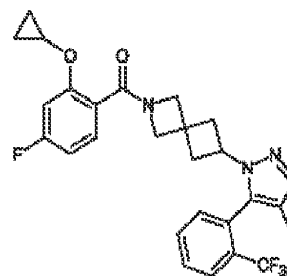
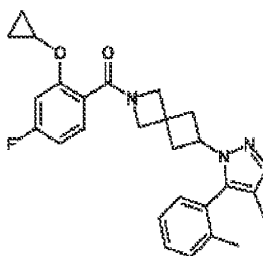
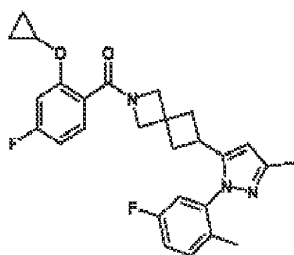


[000219] Other compounds include the compounds shown below that are Selective MAGL Inhibitors and Reversible MAGL Inhibitors:





[000220] Other compounds include compounds shown below:

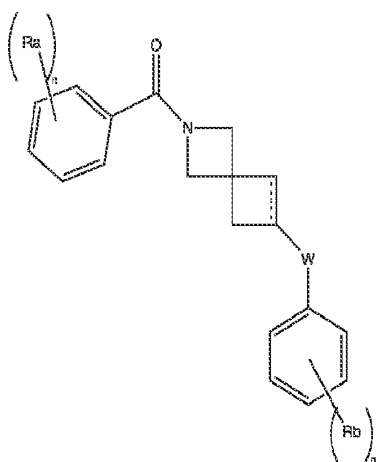


Additional Embodiments

[000221] Further, although preferred embodiments have been depicted and described in detail herein, it will be apparent to those skilled in the relevant art that various modifications, additions, substitutions, and the like can be made without departing from the spirit of the invention and these are therefore considered to be within the scope of the invention as defined in the claims which follow. Further, to the extent not already indicated, it will be understood by those of ordinary skill in the art that any one of the various embodiments herein described and illustrated can be further modified to incorporate features shown in any of the other embodiments disclosed herein.

[000222] The Additional Embodiments include those listed below:

1. A Reversible and Selective MAGL Inhibitor Compound of Formula (I) or a pharmaceutically acceptable salt thereof,



Formula (I-B),

wherein

n is 1, 2, or 3;

each Ra is independently halogen, cyano, lower alkyl optionally substituted with one or more halogen, or -OR₆;

R₆ is hydrogen, lower alkyl or lower cycloalkyl optionally substituted with one or more halogen;

W is A, -C(O)-, or -C(O)N(R₁₀)-;

R₁₀ is hydrogen or lower alkyl;

A is a 5-member heteroaryl ring optionally substituted with one or more R₃₀;

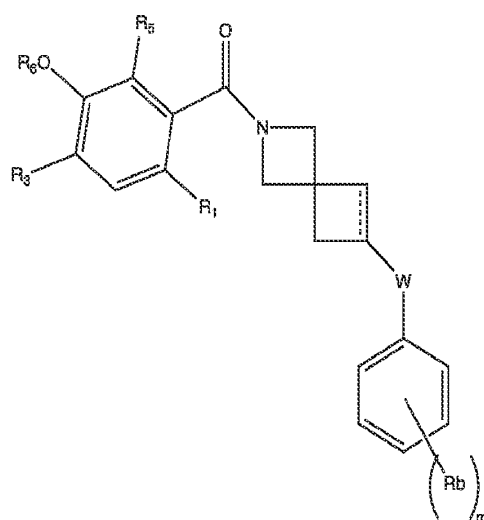
R₃₀ is lower alkyl;

m is 1, or 2; and

each R_b is independently halogen, or lower alkyl optionally substituted with one or more halogen,

provided that the compound is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone.

2. The compound of embodiment 1, wherein
 - a. each R_a is independently Cl, F, CN, cyano, methyl, or -OR₆;
 - b. R₆ is hydrogen, (C₁-C₄)alkyl optionally substituted with one or more F or cyclopropyl;
 - c. W is A;
 - d. R₁₀ is hydrogen or methyl;
 - e. A is a 5-member heteroaryl ring optionally substituted with one or more R₃₀;
 - f. R₃₀ is (C₁-C₄)alkyl;
 - g. m is 1, or 2; and
 - h. each R_b is independently halogen, or (C₁-C₄)alkyl optionally substituted with one or more F.
3. The compound of embodiment 2, wherein R₃₀ is methyl; and each R_b is independently halogen, or methyl optionally substituted with one or more F.
4. The compound of embodiment 3, wherein A is selected from the group consisting of
 - a. pyrazole, imidazole, or triazole, each optionally substituted with one methyl; and
 - b. oxadiazole.
5. The compound of embodiment 4, wherein A is pyrazole substituted with one methyl.
6. The compound of any one of embodiments 1-5, wherein one R_a is -OR₆.
7. The compound of embodiment 6, wherein one R_b is methyl.
8. The compound of embodiment 1, of Formula (I-B-1):



Formula (I-B-1),

wherein

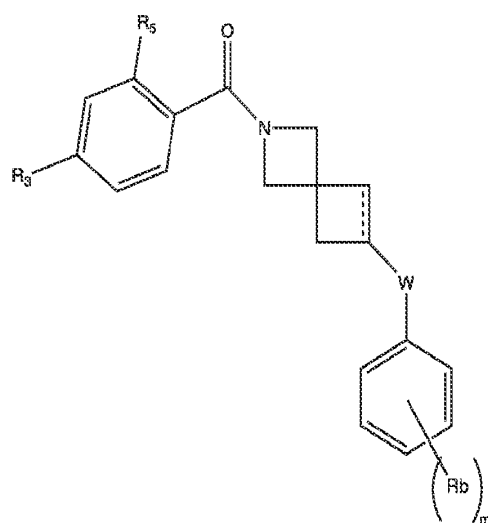
R_1 is hydrogen or halogen;

R_3 is hydrogen, halogen, or lower alkyl optionally substituted with one or more halogen;

R_5 is hydrogen, halogen, lower alkoxy or lower alkyl each optionally substituted with one or more halogen; and

R_6 is hydrogen, lower alkyl or cycloalkyl optionally substituted with one or more halogen.

9. The compound of embodiment 1, of Formula (I-B-2),



Formula (I-B-2),

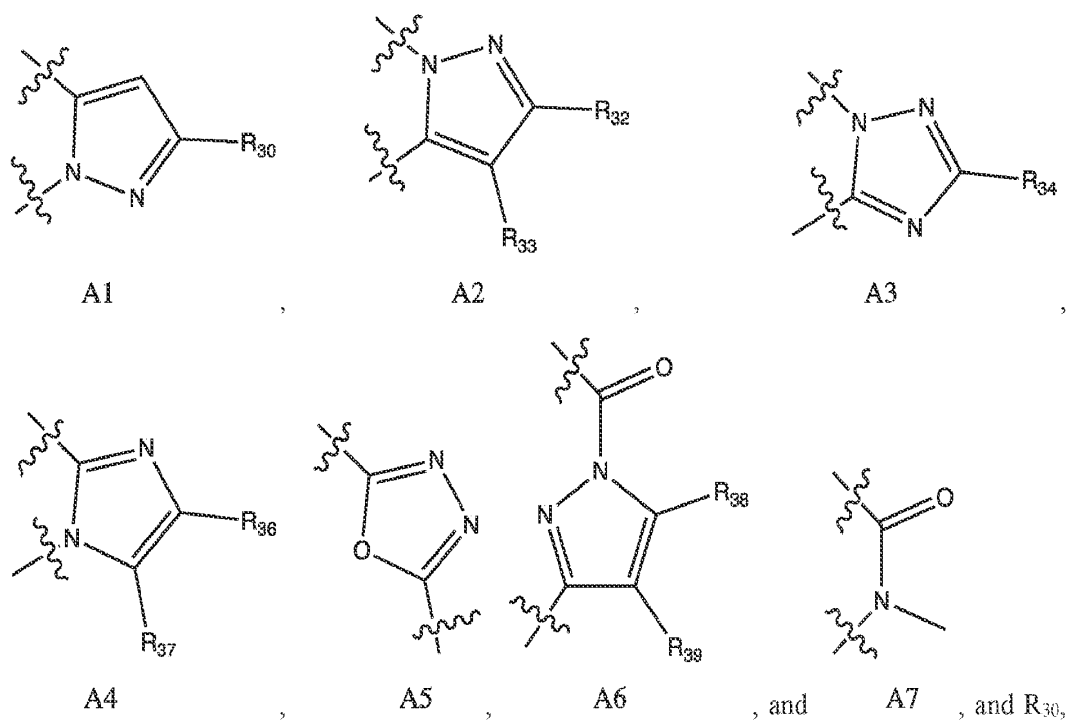
wherein

R_3 is hydrogen or halogen;

R_5 is $-O-R_{52}$; and

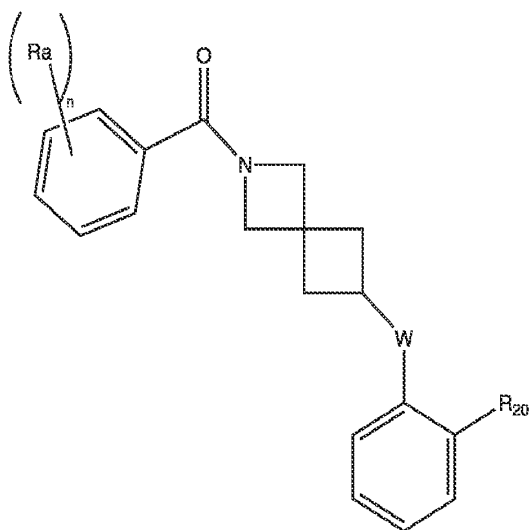
R_{52} is lower alkyl or cycloalkyl, each optionally substituted with halogen

10. The compound of any one of embodiments 1, 8 or 9, wherein W is selected from the group consisting of A1, A2, A3, A4, A5, A6 and A7,



R₃₂, R₃₃, R₃₄, R₃₆, R₃₇, R₃₈ and R₃₉ are each independently hydrogen or lower alkyl.

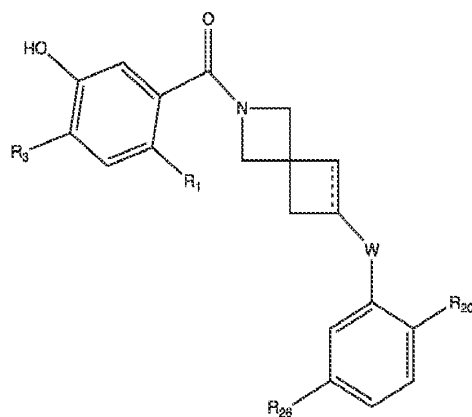
11. The compound of embodiment 10, wherein R₃₀, R₃₂, R₃₃, R₃₄, R₃₆, R₃₇, R₃₈ and R₃₉ are each independently hydrogen or methyl.
12. The compound of embodiment 10, wherein W is A1 and R₃₀ is methyl.
13. The compound of embodiment 10, wherein W is A2 and R₃₂ is hydrogen and R₃₃ is methyl.
14. The compound of embodiment 10, wherein W is A7 and R_b is methyl.
15. The compound of embodiment 1, of Formula (I-C),



Formula (I-C)

wherein R_{20} is lower alkyl; and R_a , n , and W are as defined above with respect to Formula (I).

16. The compound of embodiment 15, wherein R_{20} is methyl optionally substituted with one or more F.
17. A Reversible and Selective MAGL Inhibitor Compound of Formula (II), or a pharmaceutically acceptable salt thereof,



Formula (II),

wherein

R_1 is halogen or cyano;

R_3 is hydrogen or halogen;

W is A, $-C(O)-$, $-C(O)N(R_{10})-$;

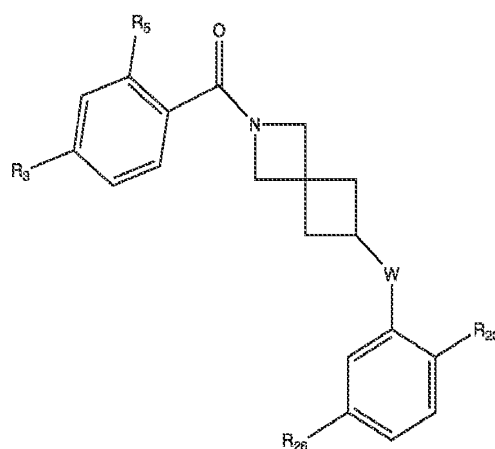
R₁₀ is hydrogen or lower alkyl;

A is a 5-member heteroaryl ring optionally substituted with one or more R₃₀; and

R₂₀ and R₃₀ are each independently lower alkyl,

provided that the compound is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone.

18. A Reversible and Selective MAGL Inhibitor Compound of Formula (III), or a pharmaceutically acceptable salt thereof,



Formula (III)

wherein

R₃ is halogen;

R₅ is -O-R₅₂;

R₅₂ is lower alkyl or cycloalkyl, each optionally substituted with halogen,

W is a 5-member heteroaryl ring optionally substituted with one or more R₃₀;

R₃₀ is lower alkyl;

R₂₀ is lower alkyl; and

R₂₆ is hydrogen or halogen.

19. The compound of embodiment 18, wherein

R₃ is F;

R₅₂ is methyl optionally substituted with halogen, or cyclopropyl;

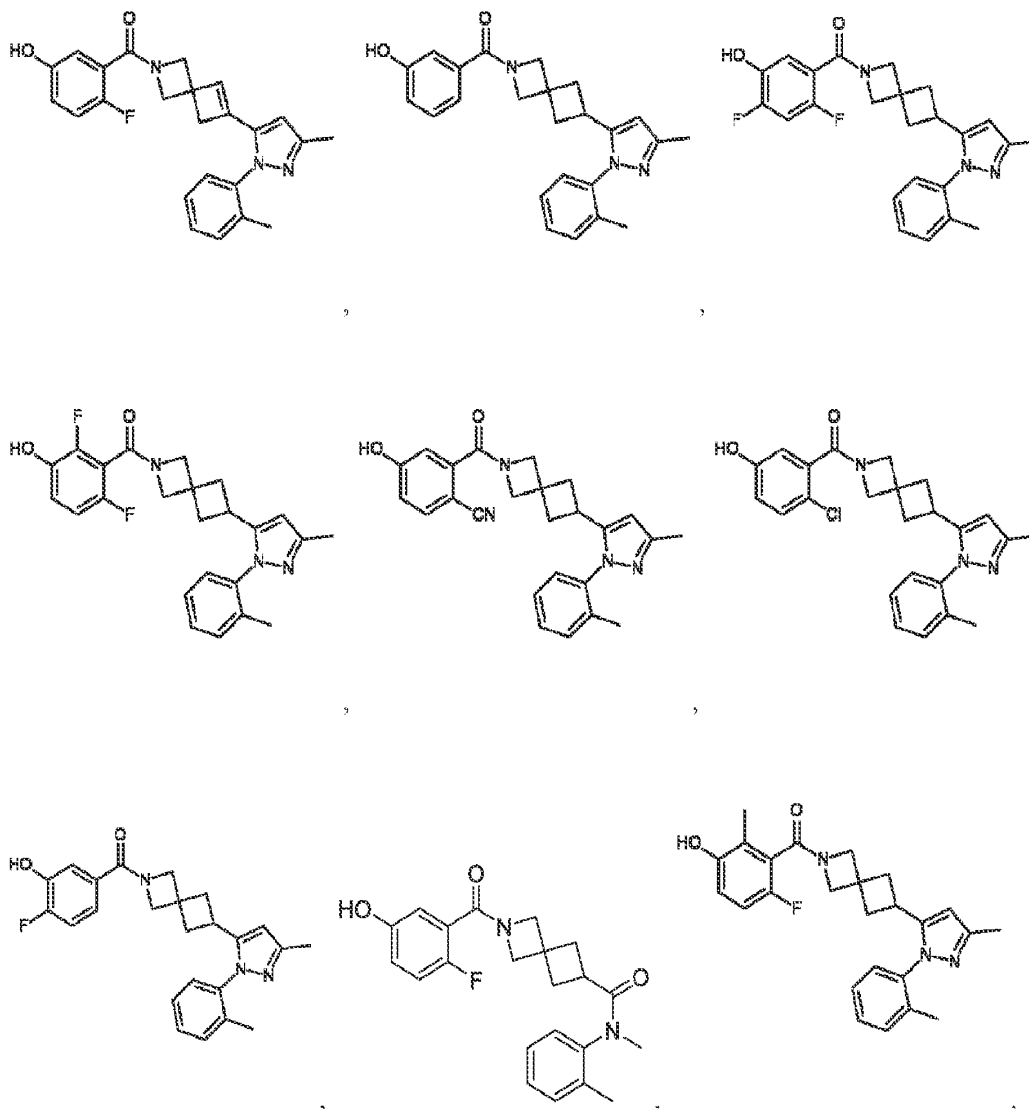
W is a 5-member heteroaryl ring comprising at least one nitrogen atom and optionally substituted with one or more R₃₀;

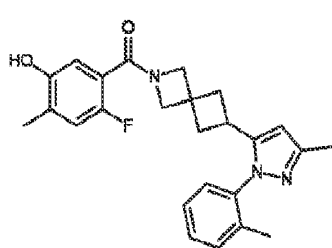
R₃₀ is methyl;

R₂₀ is methyl; and

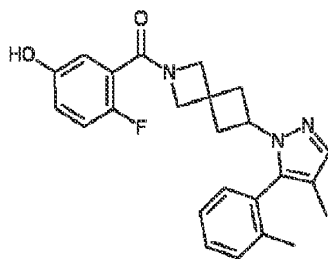
R₂₆ is hydrogen, or F.

20. A compound selected from the group consisting of:

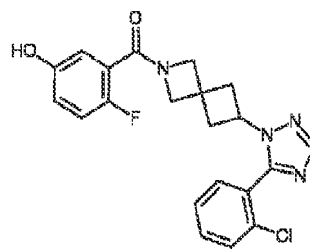




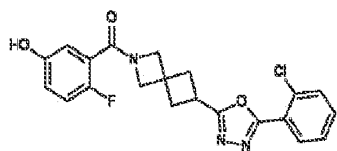
,



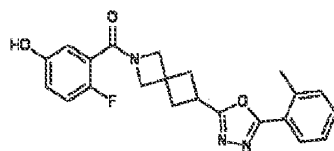
,



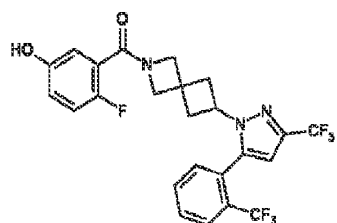
,



,

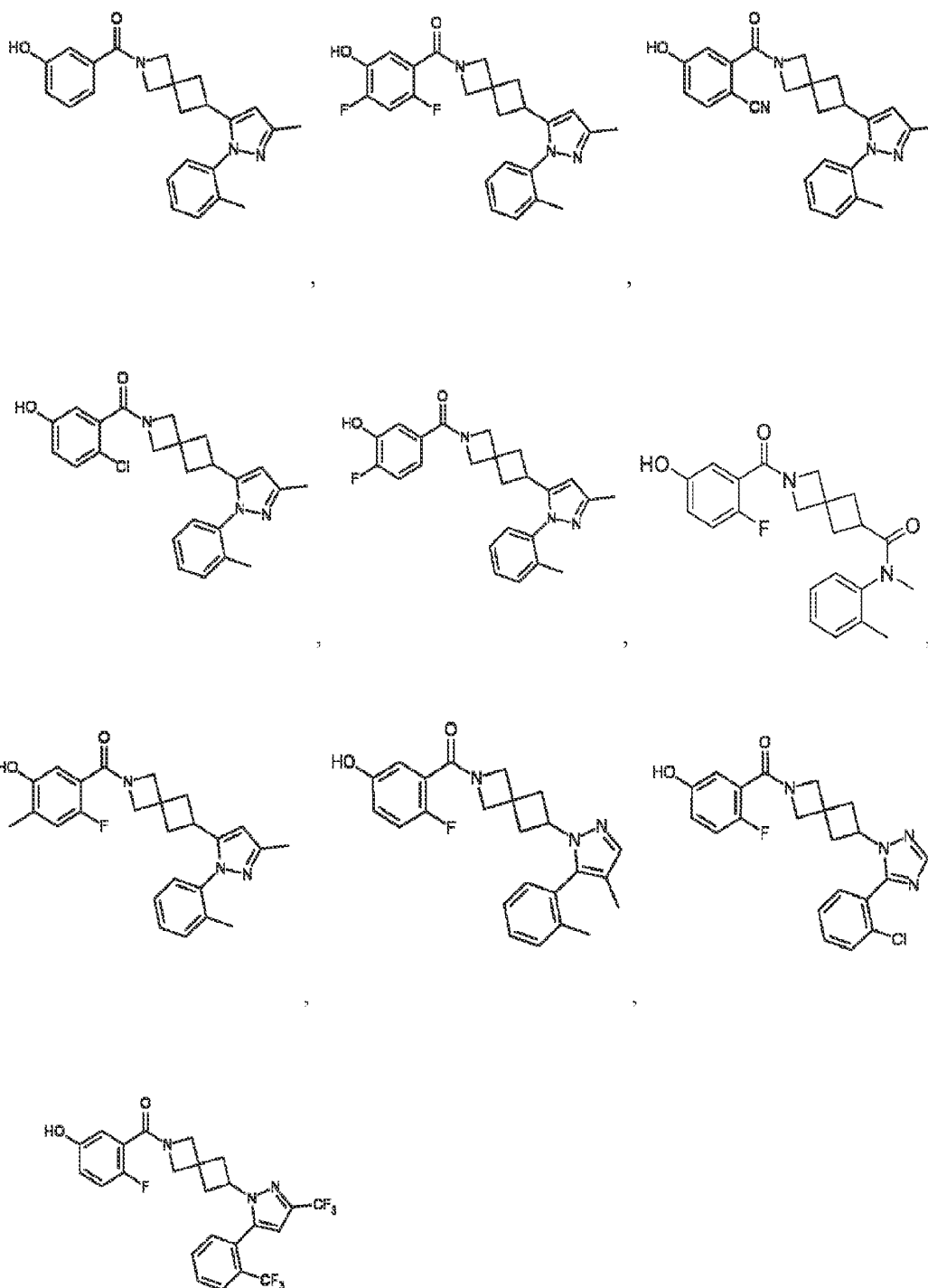


, and



or a pharmaceutically acceptable salt thereof.

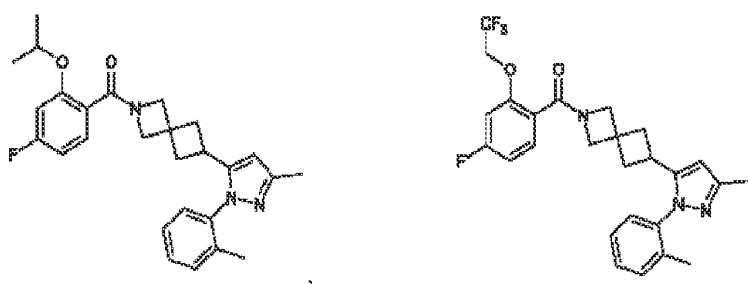
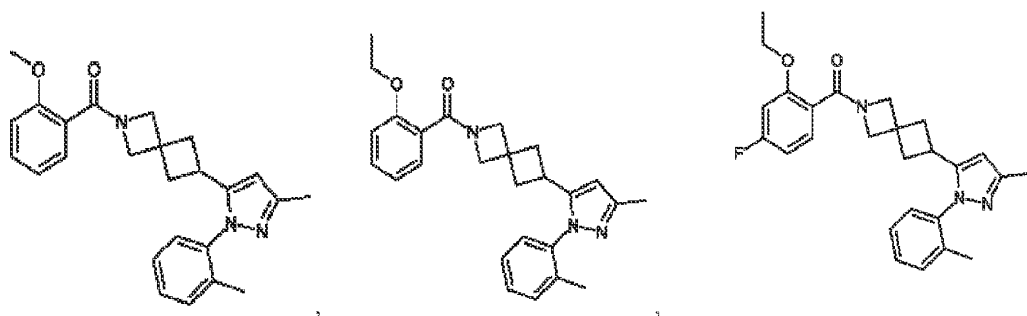
21. A compound selected from the group consisting of:



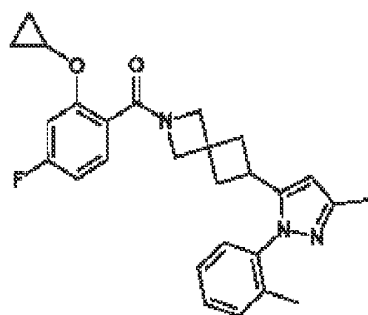
and

or a pharmaceutically acceptable salt thereof.

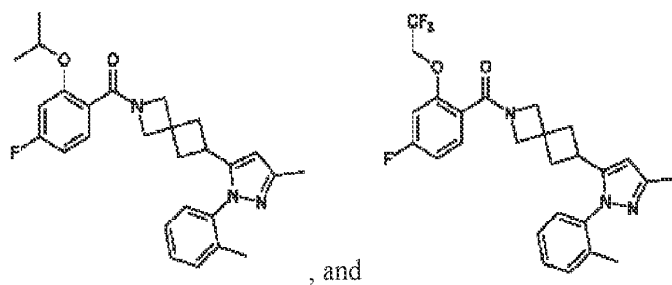
22. A compound selected from the group consisting of:



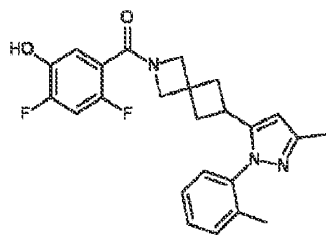
and



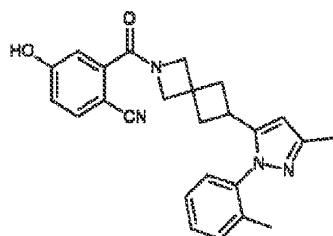
23. A compound selected from the group consisting of:



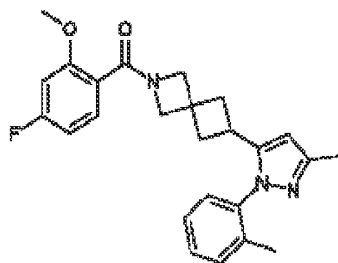
, and



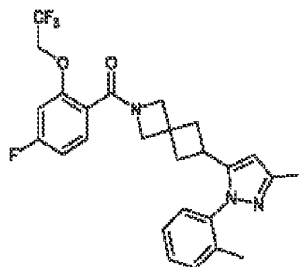
24. The compound or a pharmaceutically acceptable salt thereof.



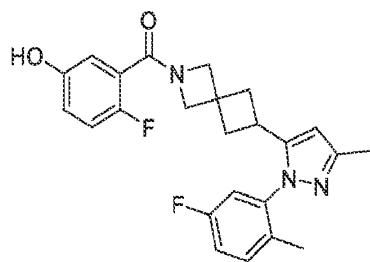
25. The compound or a pharmaceutically acceptable salt thereof.



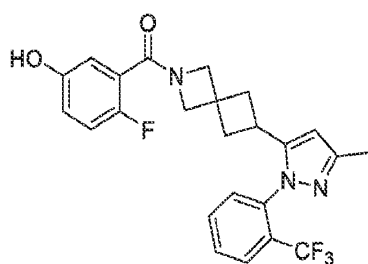
26. The compound or a pharmaceutically acceptable salt thereof.



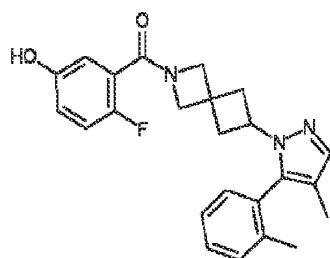
27. The compound or a pharmaceutically acceptable salt thereof.



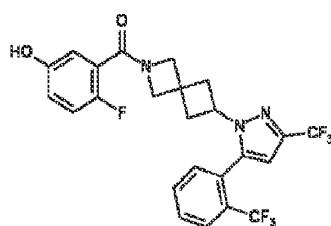
28. The compound thereof. or a pharmaceutically acceptable salt



29. The compound thereof. or a pharmaceutically acceptable salt

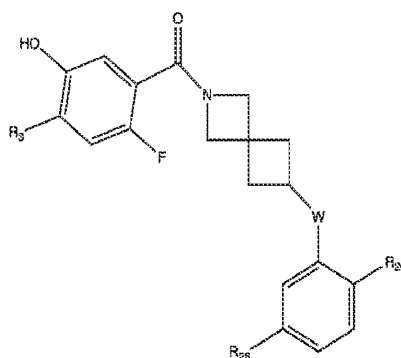


30. The compound thereof. or a pharmaceutically acceptable salt



31. The compound thereof. or a pharmaceutically acceptable salt

32. The compound of embodiment 17, wherein W is -C(O)N(R₁₀)- and R₁₀ is methyl; and R₂₀ is methyl.
33. The compound of embodiment 32, wherein R₂₆ is hydrogen.
34. The compound of any one of embodiments 32-33, wherein R₁ is F.
35. The compound of embodiment 34, wherein R₃ is hydrogen.
36. The compound of embodiment 18, wherein W is -C(O)N(R₁₀)- and R₁₀ is methyl; and R₂₀ is methyl.
37. The compound of embodiment 36, wherein R₂₆ is hydrogen.
38. The compound of any one of embodiments 36-37, wherein R₅ is -O-R₅₂; and R₅₂ is (C₁-C₄)alkyl.
39. The compound of embodiment 34, wherein R₃ is F.
40. The compound of any one of embodiments 1, 8, 9, 15, or 17, wherein W is A.
41. A compound of Formula (II-A), or a pharmaceutically acceptable salt thereof:



Formula (II-A),

wherein

R₃ is hydrogen, methyl optionally substituted with one or more F, or F;

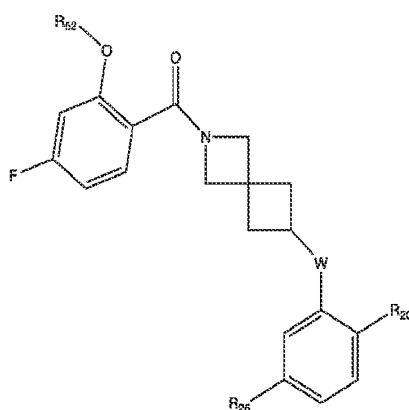
W is a 5-member heteroaryl ring comprising at least one nitrogen heteroatom optionally substituted with one methyl optionally substituted with one or more F; or cyclopropyl;

R₂₀ is methyl optionally substituted with one or more F, Cl or F;

R₂₆ is hydrogen or F; and

provided that the compound of Formula (II) is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone.

42. A compound of Formula (III-A), or a pharmaceutically acceptable salt thereof,



Formula (III-A)

wherein

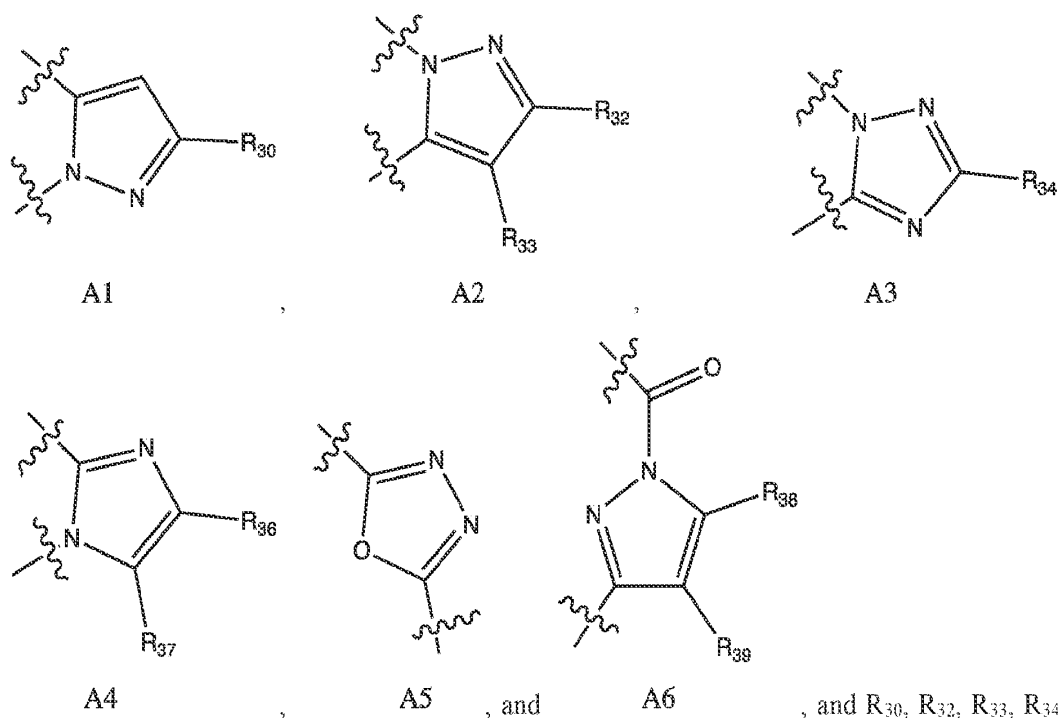
R_{52} is cyclopropyl or (C₁-C₄) alkyl optionally substituted with one or more F;

W is C(O)N(R₁₀)- and R₁₀ is methyl; or W is a 5-member heteroaryl ring comprising at least one nitrogen heteroatom and optionally substituted with one methyl;

R_{20} is (C₁-C₄) alkyl; and

R_{26} is hydrogen or F.

43. The compound of embodiment 42, wherein R_{52} is ethyl or methyl.
44. The compound of embodiment 42, wherein R_{52} is cyclopropyl.
45. The compound of any one of embodiments 42-44, wherein R_{20} is methyl.
46. The compound of any one of embodiments 42-44, wherein R_{20} is -CF₃.
47. The compound of any one of embodiments 42-46, wherein R_{26} is hydrogen.
48. The compound of any one of embodiments 1, 2, 3, 6-11, 15-19, or 41-47, wherein W is selected from the group consisting of A1, A2, A3, A4, A5, and A6,



R₃₆, R₃₇, R₃₈ and R₃₉ are each independently hydrogen or methyl.

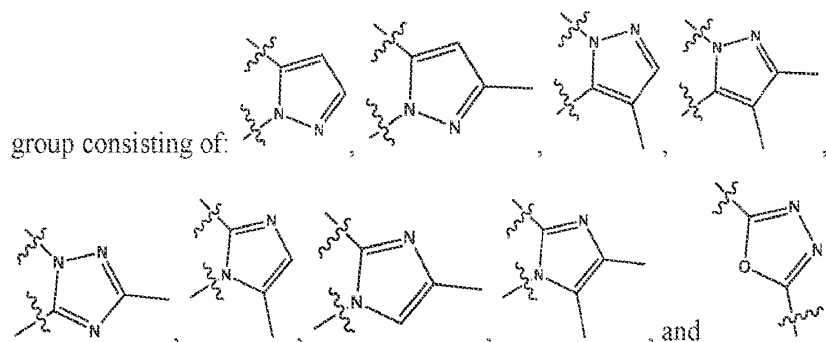
49. The compound of embodiment 48, wherein R₃₀, R₃₂, R₃₃, and R₃₄ are each independently methyl.

50. The compound of embodiment 49, wherein

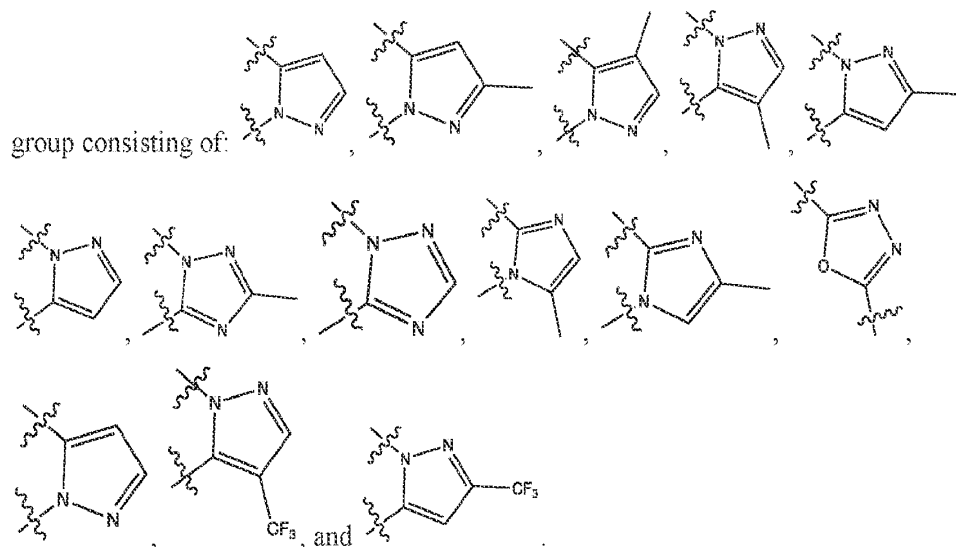
- a. one of R₃₆ and R₃₇ is methyl and the other is hydrogen; and
- b. one of R₃₈ and R₃₉ is methyl and the other is hydrogen.

51. The compound of any one of embodiments 48-50, wherein W is selected from the group consisting of A1, A2, A3, A4, and A5.

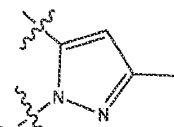
52. The compound of any one of embodiments 1-19 or 32-52, wherein W is selected from the



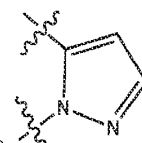
53. The compound of any one of embodiments 1-19 or 32-52, wherein W is selected from the



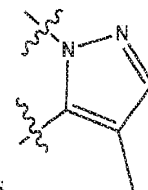
54. The compound of any one of embodiments 1-19 or 32-52, wherein W is



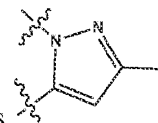
55. The compound of any one of embodiments 1-19 or 32-52, wherein W is



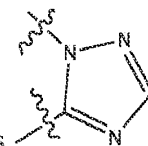
56. The compound of any one of embodiments 1-19 or 32-52, wherein W is



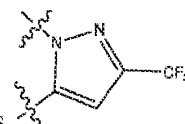
57. The compound of any one of embodiments 1-19 or 32-52, wherein W is

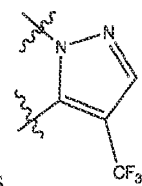


58. The compound of any one of embodiments 1-19 or 32-52, wherein W is



59. The compound of any one of embodiments 1-19 or 32-52, wherein W is





60. The compound of any one of embodiments 1-19 or 32-52, wherein W is

61. A Reversible Selective MAGL Inhibitor Compound that is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone.

[000223] The Additional Embodiments include those listed below:

1. A compound selected from the group consisting of:

(2,4-difluoro-5-hydroxyphenyl){6-[3-methyl-1-(o-tolyl)-5-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone (Compound 126);

4-hydroxy-2-({6-[3-methyl-1-(o-tolyl)-5-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}carbonyl)benzonitrile (Compound 128);

(2-fluoro-5-hydroxyphenyl){6-[1-(5-fluoro-2-tolyl)-3-methyl-5-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone (Compound 365);

(2-fluoro-5-hydroxyphenyl)(6-{3-methyl-1-[o-(trifluoromethyl)phenyl]-5-pyrazolyl}-2-aza-2-spiro[3.3]heptyl)methanone (Compound 366);

(2-fluoro-5-hydroxyphenyl)(6-{5-(trifluoromethyl)-3-[o-(trifluoromethyl)phenyl]-1-pyrazolyl}-2-aza-2-spiro[3.3]heptyl)methanone (Compound 414);

(2-fluoro-5-hydroxyphenyl){6-[3-(o-fluorophenyl)-4-methyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone (Compound 417);

(2-fluoro-5-hydroxyphenyl){6-[4-methyl-3-(o-tolyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone (Compound 440);

(2-fluoro-5-hydroxyphenyl)(6-{4-methyl-3-[o-(trifluoromethyl)phenyl]-1-pyrazolyl}-2-aza-2-spiro[3.3]heptyl)methanone (Compound 444);

(2-fluoro-5-hydroxyphenyl){6-[3-(5-fluoro-2-tolyl)-5-methyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone (Compound 446);

(2-fluoro-5-hydroxyphenyl){6-[3-(o-fluorophenyl)-4-(trifluoromethyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone (Compound 473);

(2-fluoro-5-hydroxyphenyl){6-[3-(2-fluoro-5-tolyl)-4-(trifluoromethyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone (Compound 475);

{6-[3-(2,5-difluorophenyl)-4-methyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}(2-fluoro-5-hydroxyphenyl)methanone (Compound 477);

(6-{4-cyclopropyl-3-[o-(trifluoromethyl)phenyl]-1-pyrazolyl}-2-aza-2-spiro[3.3]heptyl)(2-fluoro-5-hydroxyphenyl)methanone (Compound 488);

{6-[5-cyclopropyl-3-(5-fluoro-2-tolyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}(2-fluoro-5-hydroxyphenyl)methanone (Compound 491);

{6-[4-cyclopropyl-3-(o-fluorophenyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}(2-fluoro-5-hydroxyphenyl)methanone (Compound 493);

{6-[3-(2-chloro-5-fluorophenyl)-4-methyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}(2-fluoro-5-hydroxyphenyl)methanone (Compound 520);

(2-fluoro-5-hydroxyphenyl)(6-{3-[o-(trifluoromethyl)phenyl]-1-pyrazolyl}-2-aza-2-spiro[3.3]heptyl)methanone (Compound 525);

(2-ethoxy-4-fluorophenyl){6-[3-methyl-1-(o-tolyl)-5-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone (Compound 146); and

[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]{6-[3-methyl-1-(o-tolyl)-5-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone (Compound 178), or a pharmaceutically acceptable salt thereof.

2. The compound of embodiment 1, wherein the compound is (2,4-difluoro-5-hydroxyphenyl){6-[3-methyl-1-(o-tolyl)-5-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone (Compound 126), or a pharmaceutically acceptable salt thereof.

3. The compound of embodiment 1, wherein the compound is 4-hydroxy-2-({6-[3-methyl-1-(o-tolyl)-5-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}carbonyl)benzonitrile (Compound 128), or a pharmaceutically acceptable salt thereof.

4. The compound of embodiment 1, wherein the compound is (2-fluoro-5-hydroxyphenyl){6-[1-(5-fluoro-2-tolyl)-3-methyl-5-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone (Compound 365), or a pharmaceutically acceptable salt thereof.
5. The compound of embodiment 1, wherein the compound is (2-fluoro-5-hydroxyphenyl)(6-{3-methyl-1-[o-(trifluoromethyl)phenyl]-5-pyrazolyl}-2-aza-2-spiro[3.3]heptyl)methanone (Compound 366), or a pharmaceutically acceptable salt thereof.
6. The compound of embodiment 1, wherein the compound is (2-fluoro-5-hydroxyphenyl)(6-{5-(trifluoromethyl)-3-[o-(trifluoromethyl)phenyl]-1-pyrazolyl}-2-aza-2-spiro[3.3]heptyl)methanone (Compound 414), or a pharmaceutically acceptable salt thereof.
7. The compound of embodiment 1, wherein the compound is (2-fluoro-5-hydroxyphenyl){6-[3-(o-fluorophenyl)-4-methyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone (Compound 417), or a pharmaceutically acceptable salt thereof.
8. The compound of embodiment 1, wherein the compound is (2-fluoro-5-hydroxyphenyl){6-[4-methyl-3-(o-tolyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone (Compound 440), or a pharmaceutically acceptable salt thereof.
9. The compound of embodiment 1, wherein the compound is (2-fluoro-5-hydroxyphenyl)(6-{4-methyl-3-[o-(trifluoromethyl)phenyl]-1-pyrazolyl}-2-aza-2-spiro[3.3]heptyl)methanone (Compound 444), or a pharmaceutically acceptable salt thereof.
10. The compound of embodiment 1, wherein the compound is (2-fluoro-5-hydroxyphenyl){6-[3-(5-fluoro-2-tolyl)-5-methyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone (Compound 446), or a pharmaceutically acceptable salt thereof.
11. The compound of embodiment 1, wherein the compound is (2-fluoro-5-hydroxyphenyl){6-[3-(o-fluorophenyl)-4-(trifluoromethyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone (Compound 473), or a pharmaceutically acceptable salt thereof.

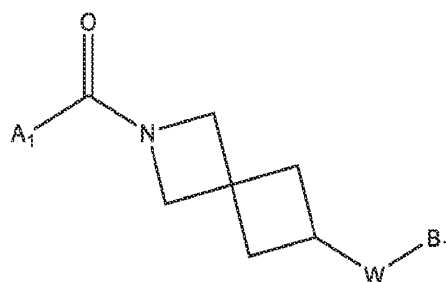
12. The compound of embodiment 1, wherein the compound is (2-fluoro-5-hydroxyphenyl){6-[3-(2-fluoro-5-tolyl)-4-(trifluoromethyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone (Compound 475), or a pharmaceutically acceptable salt thereof.
13. The compound of embodiment 1, wherein the compound is {6-[3-(2,5-difluorophenyl)-4-methyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}(2-fluoro-5-hydroxyphenyl)methanone (Compound 477), or a pharmaceutically acceptable salt thereof.
14. The compound of embodiment 1, wherein the compound is (6-{4-cyclopropyl-3-[o-(trifluoromethyl)phenyl]-1-pyrazolyl}-2-aza-2-spiro[3.3]heptyl)(2-fluoro-5-hydroxyphenyl)methanone (Compound 488), or a pharmaceutically acceptable salt thereof.
15. The compound of embodiment 1, wherein the compound is {6-[5-cyclopropyl-3-(5-fluoro-2-tolyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}(2-fluoro-5-hydroxyphenyl)methanone (Compound 491), or a pharmaceutically acceptable salt thereof.
16. The compound of embodiment 1, wherein the compound is {6-[4-cyclopropyl-3-(o-fluorophenyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}(2-fluoro-5-hydroxyphenyl)methanone (Compound 493), or a pharmaceutically acceptable salt thereof.
17. The compound of embodiment 1, wherein the compound is {6-[3-(2-chloro-5-fluorophenyl)-4-methyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}(2-fluoro-5-hydroxyphenyl)methanone (Compound 520), or a pharmaceutically acceptable salt thereof.
18. The compound of embodiment 1, wherein the compound is (2-fluoro-5-hydroxyphenyl)(6-{3-[o-(trifluoromethyl)phenyl]-1-pyrazolyl}-2-aza-2-spiro[3.3]heptyl)methanone (Compound 525), or a pharmaceutically acceptable salt thereof.

19. The compound of embodiment 1, wherein the compound is (2-ethoxy-4-fluorophenyl){6-[3-methyl-1-(o-tolyl)-5-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone (Compound 146), or a pharmaceutically acceptable salt thereof.

20. The compound of embodiment 1, wherein the compound is [4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]{6-[3-methyl-1-(o-tolyl)-5-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone (Compound 178), or a pharmaceutically acceptable salt thereof.

[000224] Additional Embodiments include those listed below:

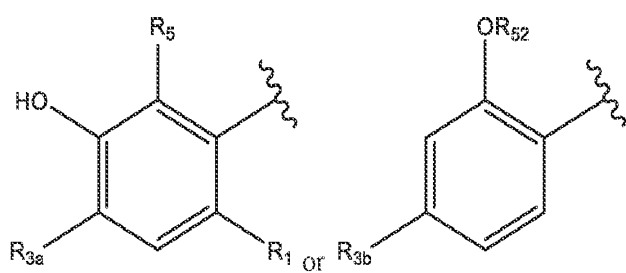
1. A compound of Formula (I) or a pharmaceutically acceptable salt thereof,



Formula (I),

wherein:

A₁ is



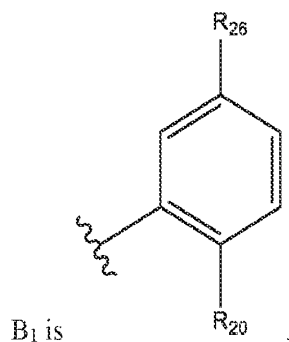
R₁ is hydrogen, halogen, or cyano;

R_{3a} and R₅ are each independently hydrogen, halogen, or lower alkyl;

R₅₂ is lower alkyl, lower cycloalkyl or lower haloalkyl;

R_{3b} is halogen;

W is a diazole optionally substituted with lower alkyl, lower cycloalkyl, or lower haloalkyl;



R₂₀ is hydrogen, halogen, lower alkyl, or lower haloalkyl; and

R₂₆ is hydrogen, or halogen;

provided the compound is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone.

2. The compound of embodiment 1, wherein

R₁ is hydrogen, fluoro, or cyano;

R_{3a} and R₅ are each independently hydrogen, halogen, or methyl;

R₅₂ is lower alkyl, cyclopropyl or lower haloalkyl;

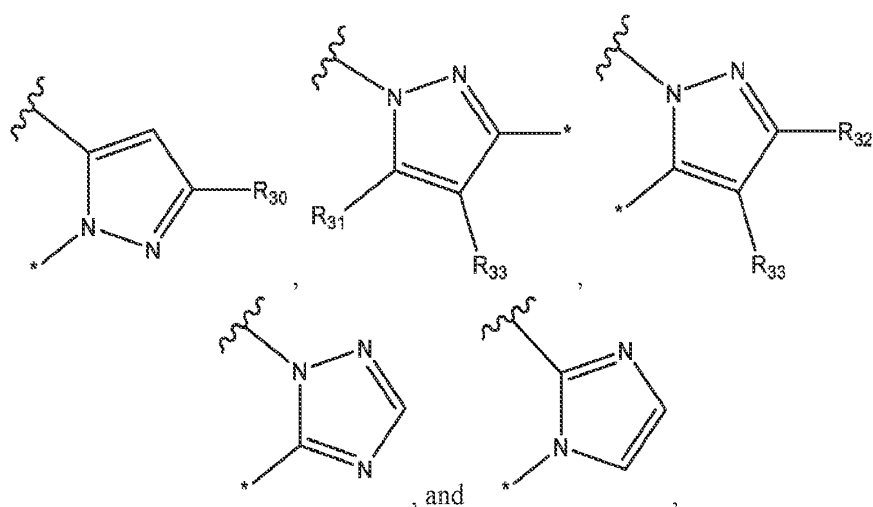
R_{3b} is fluoro;

W is a diazole optionally substituted with one of methyl, cyclopropyl, or CF₃;

R₂₀ is fluoro or chloro, methyl, or CF₃; and

R₂₆ is hydrogen, fluoro or chloro.

3. The compound of embodiment 2, wherein W is selected from the group consisting of:

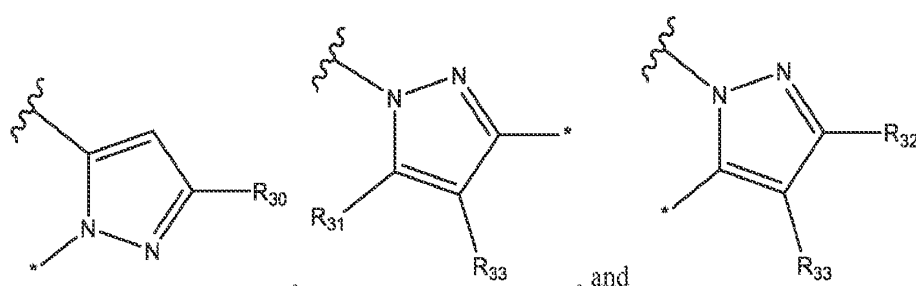


wherein * indicates a covalent bond to B₁; and

R₃₀, R₃₁, R₃₂ and R₃₃ are each independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl, provided that at least one of R₃₁ and R₃₃ and at least one of R₃₂ and R₃₃ is not hydrogen.

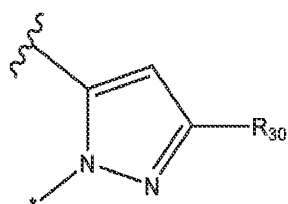
4. The compound of embodiment 3, wherein R₃₀, R₃₁, R₃₂ and R₃₃ are each independently hydrogen, methyl, CF₃, or cyclopropyl, provided that at least one of R₃₁ and R₃₃ and at least one of R₃₂ and R₃₃ is not hydrogen.

5. The compound of embodiment 4, wherein W is selected from the group consisting of:



wherein * indicates a covalent bond to B₁.

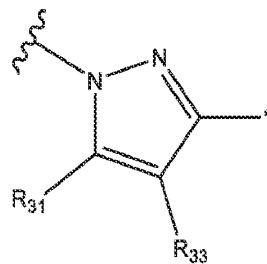
6. The compound of embodiment 5, wherein W is



, wherein *

indicates a covalent bond to B₁, and R₃₀ is methyl.

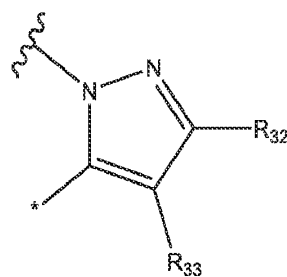
7. The compound of embodiment 5, wherein W is



, wherein *

indicates a covalent bond to B₁, and R₃₁ and R₃₃ are each independently hydrogen, methyl, CF₃, or cyclopropyl, provided that one of R₃₁ and R₃₃ is hydrogen.

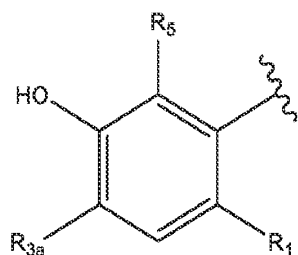
8. The compound of embodiment 5, wherein W is



, wherein *

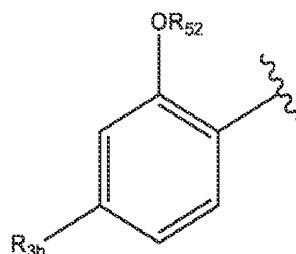
indicates a covalent bond to B₁, and R₃₂ and R₃₃ are each independently hydrogen, methyl, CF₃, or cyclopropyl, provided that one of R₃₂ and R₃₃ is hydrogen.

9. The compound of any one of embodiments 4-8, wherein A₁ is

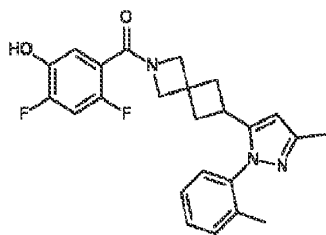


10. The compound of embodiment 9, wherein R₅ is hydrogen.

11. The compound of embodiment 10, wherein R_1 is fluoro.
12. The compound of embodiment 11, wherein R_{3a} is hydrogen, fluoro, or methyl.
13. The compound of embodiment 12, wherein R_{3a} is hydrogen.
14. The compound of embodiment 13, wherein R_{20} is methyl, and R_{26} is hydrogen or fluoro; or R_{20} is chloro, fluoro or CF_3 , and R_{26} is hydrogen.
15. The compound of any one of embodiments 4-8, wherein A_1 is

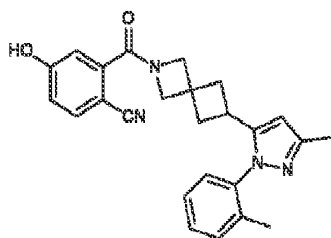


16. The compound of embodiment 15, wherein R_{52} is lower alkyl optionally substituted with one or more fluoro and cyclopropyl.
17. The compound of embodiment 16, wherein R_{3b} is fluoro.
18. The compound of embodiment 17, wherein
 R_{20} is methyl, and R_{26} is hydrogen or fluoro; or
 R_{20} is fluoro or CF_3 , and R_{26} is hydrogen.
19. The compound of embodiment 1, wherein the compound is



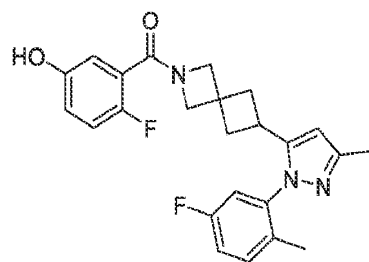
, or a pharmaceutically acceptable salt thereof.

20. The compound of embodiment 1, wherein the compound is



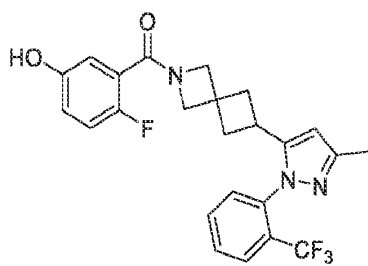
, or a pharmaceutically acceptable salt thereof.

21. The compound of embodiment 1, wherein the compound is



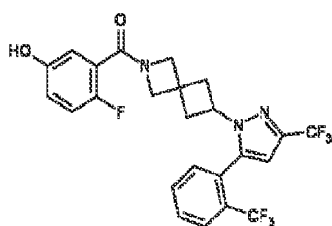
, or a pharmaceutically acceptable salt thereof.

22. The compound of embodiment 1, wherein the compound is



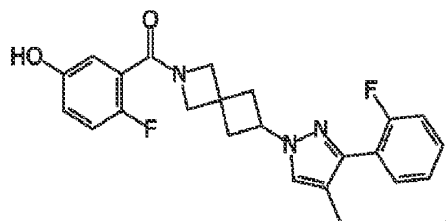
, or a pharmaceutically acceptable salt thereof.

23. The compound of embodiment 1, wherein the compound is



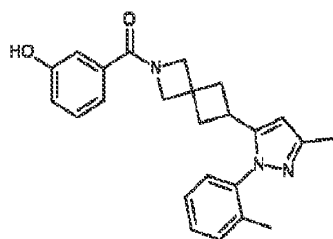
, or a pharmaceutically acceptable salt thereof.

24. The compound of embodiment 1, wherein the compound is



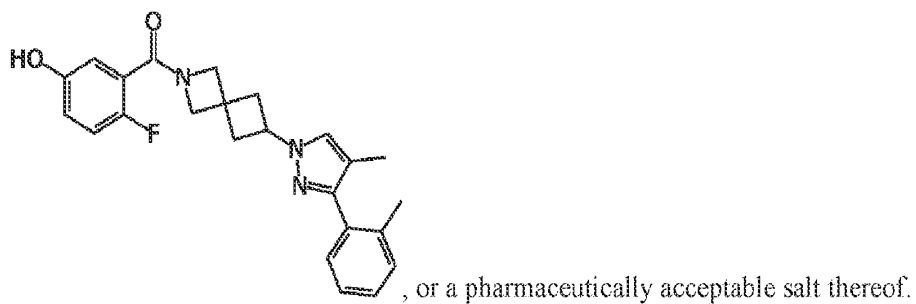
, or a pharmaceutically acceptable salt thereof.

25. The compound of embodiment 1, wherein the compound is ,

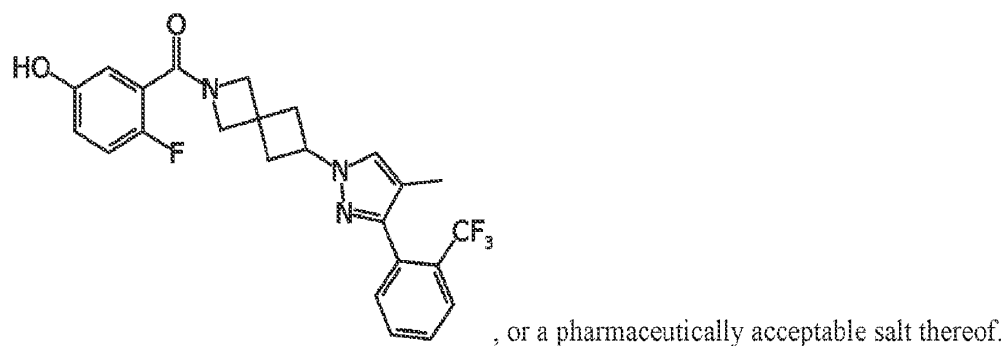


or a pharmaceutically acceptable salt thereof.

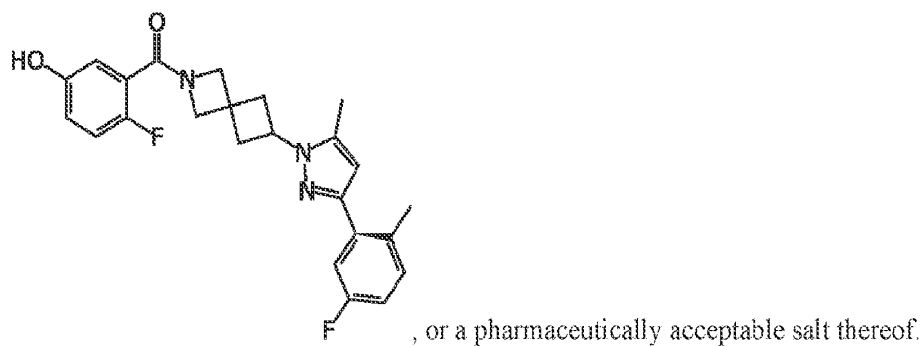
26. The compound of embodiment 1, wherein the compound is



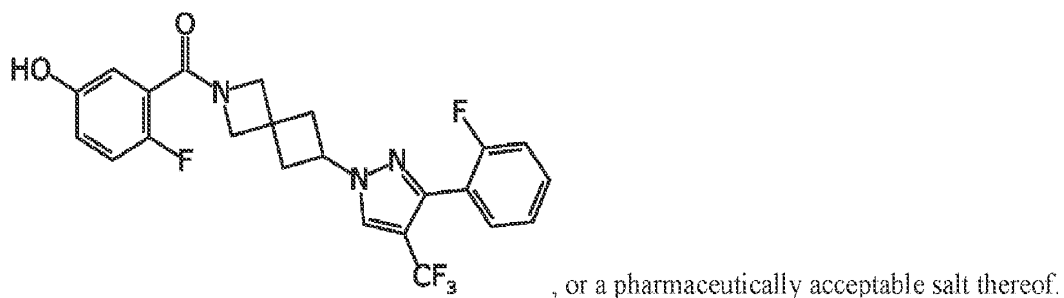
27. The compound of embodiment 1, wherein the compound is



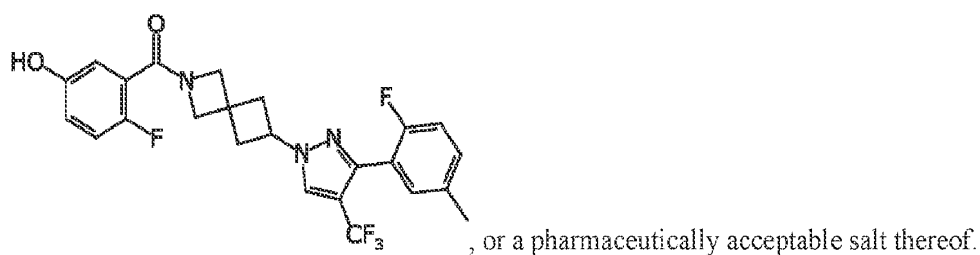
28. The compound of embodiment 1, wherein the compound is



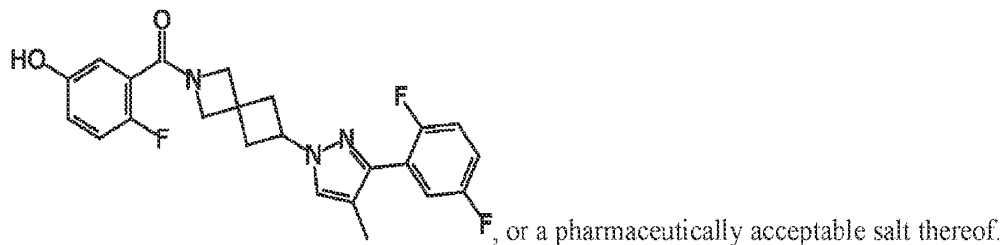
29. The compound of embodiment 1, wherein the compound is



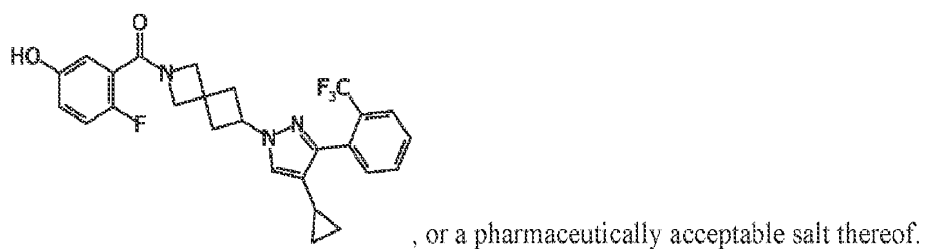
30. The compound of embodiment 1, wherein the compound is



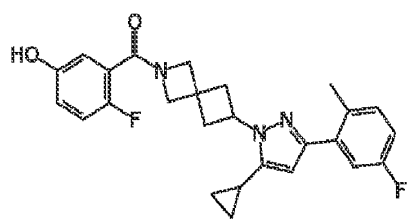
31. The compound of embodiment 1, wherein the compound is



32. The compound of embodiment 1, wherein the compound is

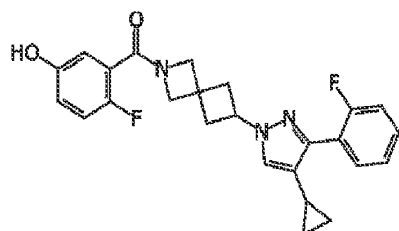


33. The compound of embodiment 1, wherein the compound is



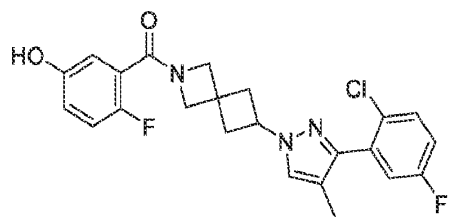
, or a pharmaceutically acceptable salt thereof.

34. The compound of embodiment 1, wherein the compound is



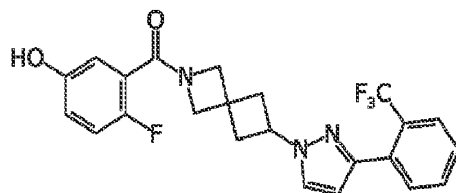
, or a pharmaceutically acceptable salt thereof.

35. The compound of embodiment 1, wherein the compound is



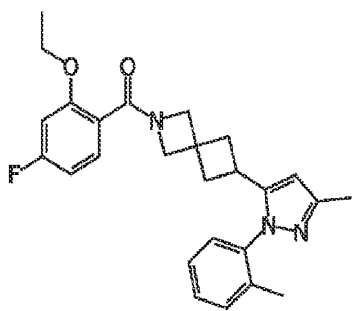
, or a pharmaceutically acceptable salt thereof.

36. The compound of embodiment 1, wherein the compound is



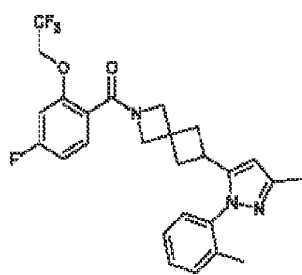
, or a pharmaceutically acceptable salt thereof.

37. The compound of embodiment 1, wherein the compound is



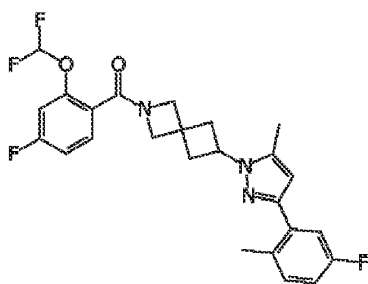
, or a pharmaceutically acceptable salt thereof.

38. The compound of embodiment 1, wherein the compound is



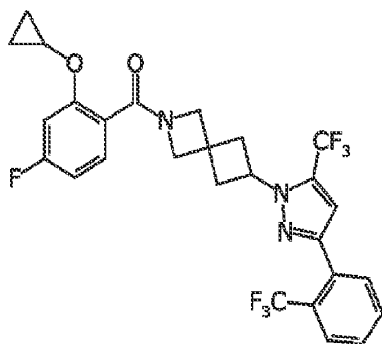
, or a pharmaceutically acceptable salt thereof.

39. The compound of embodiment 1, wherein the compound is



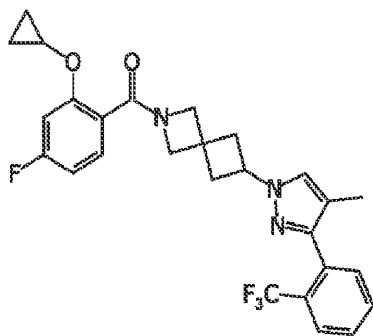
, or a pharmaceutically acceptable salt thereof.

40. The compound of embodiment 1, wherein the compound is



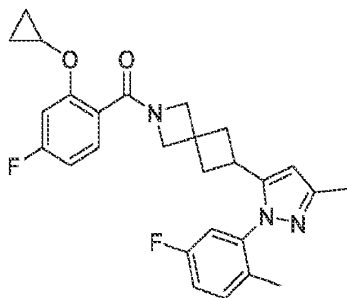
, or a pharmaceutically acceptable salt thereof.

41. The compound of embodiment 1, wherein the compound is



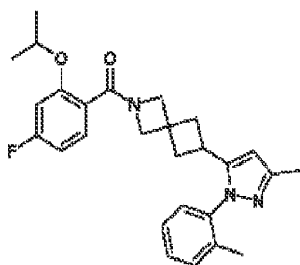
, or a pharmaceutically acceptable salt thereof.

42. The compound of embodiment 1, wherein the compound is



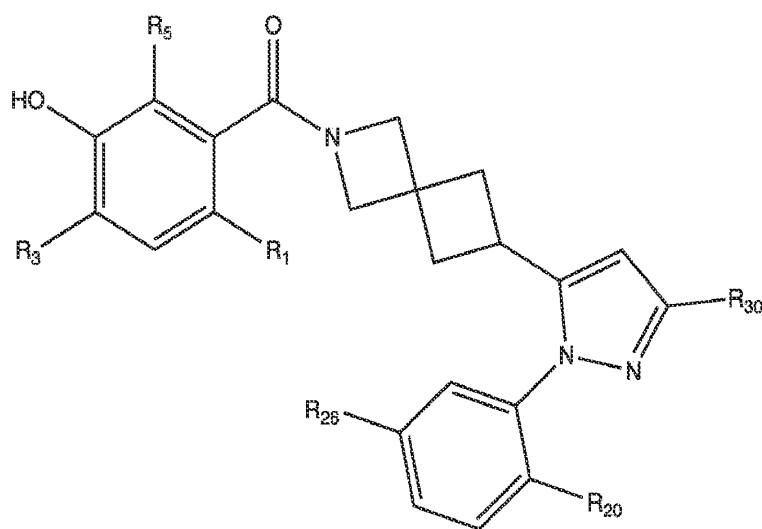
, or a pharmaceutically acceptable salt thereof.

43. The compound of embodiment 1, wherein the compound is



, or a pharmaceutically acceptable salt thereof.

44. A compound of Formula (II-B) or a pharmaceutically acceptable salt thereof:



Formula (II-B),

wherein

R₁ is halogen or cyano;

R₃ is hydrogen, lower alkyl, or halogen;

R₅ is hydrogen, halogen or lower alkyl;

R₂₀ is halogen or lower alkyl optionally substituted with one or more halogen;

R₂₆ is halogen or hydrogen; and

R₃₀ is hydrogen or lower alkyl optionally substituted with one or more halogen, provided the compound is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone.

45. The compound of embodiment 44, wherein

R₁ is F or cyano;

R₃ is hydrogen, methyl, or F;

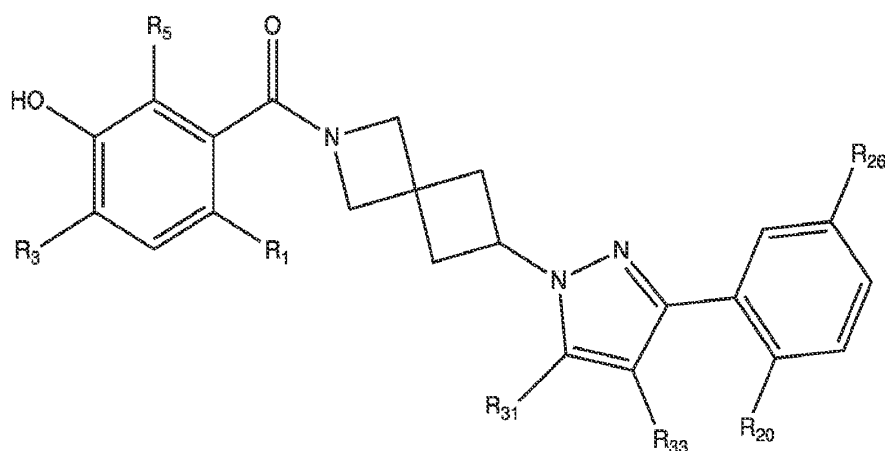
R₅ is hydrogen, F or methyl;

R₂₀ is F, methyl, or CF₃;

R₂₆ is hydrogen or F; and

R₃₀ is hydrogen, methyl or CF₃, provided the compound is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone.

46. A compound of Formula (II-C) or a pharmaceutically acceptable salt thereof:



Formula (II-C),

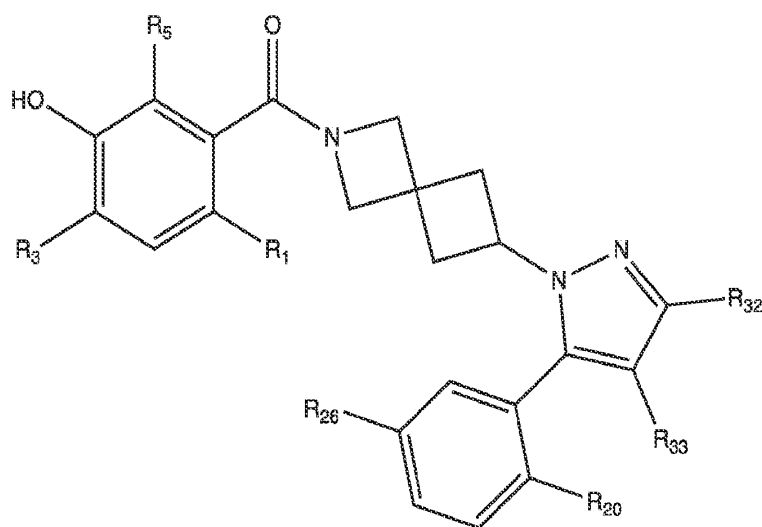
wherein

- R₁ is halogen or cyano;
- R₃ is hydrogen, lower alkyl, or halogen;
- R₅ is hydrogen, halogen or lower alkyl;
- R₂₀ is halogen or lower alkyl optionally substituted with one or more halogen;
- R₂₆ is hydrogen or halogen; and
- R₃₁ and R₃₃ are each independently hydrogen or lower alkyl optionally substituted with one or more halogen, provided that one of R₃₁ and R₃₃ is hydrogen.

47. The compound of embodiment 46, wherein

- R₁ is F or cyano;
- R₃ is hydrogen, methyl, or F;
- R₅ is hydrogen, F or methyl;
- R₂₀ is F, methyl, or CF₃;
- R₂₆ is hydrogen or F; and
- R₃₁ and R₃₃ are each independently hydrogen, methyl or CF₃.

48. A compound of Formula (II-D) or a pharmaceutically acceptable salt thereof:



wherein

R₁ is halogen or cyano;

R₃ is hydrogen, lower alkyl, or halogen;

R₅ is hydrogen, halogen or lower alkyl;

R₆ is hydrogen;

R₂₀ is halogen or lower alkyl optionally substituted with one or more halogen;

R₂₆ is halogen or hydrogen; and

R₃₂ and R₃₃ are each independently hydrogen or lower alkyl optionally substituted with one or more halogen, provided that one of R₃₂ and R₃₃ is hydrogen.

49. The compound of embodiment 48, wherein

R₁ is F or cyano;

R₃ is hydrogen, F or methyl;

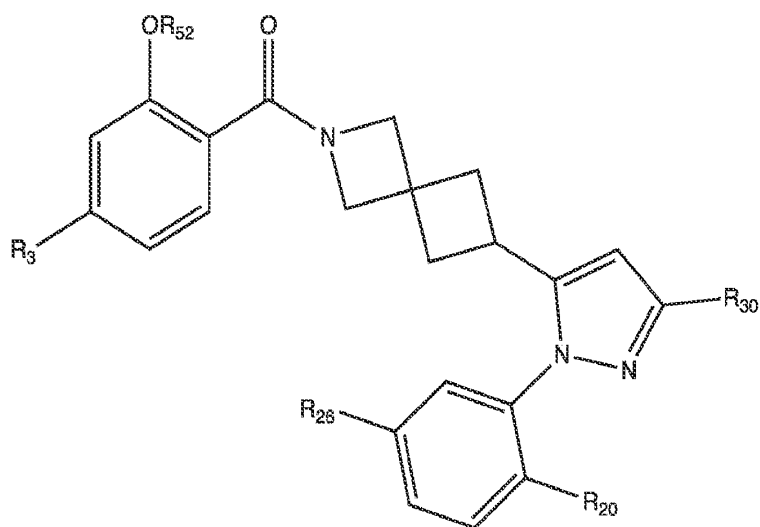
R₅ is hydrogen, F or methyl;

R₂₀ is F or methyl, or CF₃;

R₂₆ is hydrogen or F; and

R₃₂ and R₃₃ are each independently hydrogen, methyl or, CF₃ provided that one of R₃₂ and R₃₃ is hydrogen.

50. A compound of Formula (III-B) or a pharmaceutically acceptable salt thereof:



Formula (III-B)

wherein

R_3 is halogen;

R_{52} is lower alkyl or lower cycloalkyl, each optionally substituted with halogen,

R_{30} is lower alkyl;

R_{20} is lower alkyl; and

R_{26} is hydrogen or halogen.

51. The compound of embodiment 50, wherein

R_3 is F;

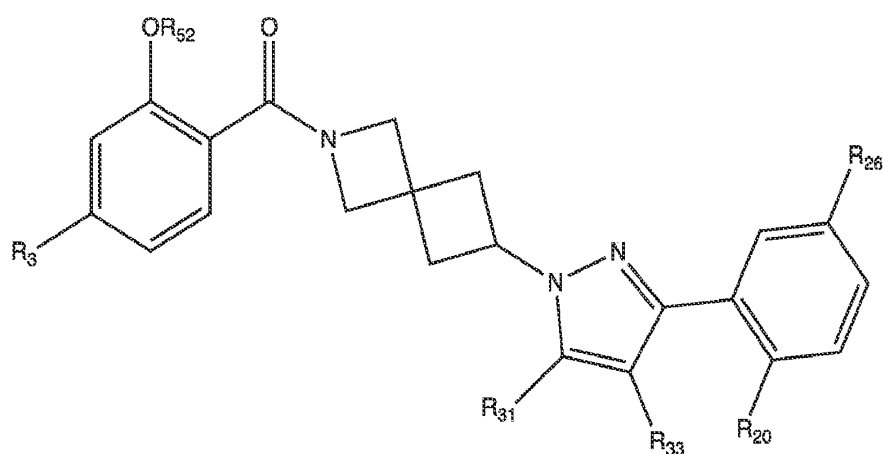
R_{52} is lower alkyl optionally substituted with one or more F or cyclopropyl;

R_{30} is methyl;

R_{20} is methyl; and

R_{26} is hydrogen or F.

52. A compound of Formula (III-C) or a pharmaceutically acceptable salt thereof.



wherein

R_3 is halogen;

R_{52} is lower alkyl or lower cycloalkyl, each optionally substituted with halogen,

R_{31} and R_{33} are each independently hydrogen or lower alkyl optionally substituted with one or more halogen, provided that one of R_{31} and R_{33} is hydrogen.

R_{20} is lower alkyl optionally substituted with halogen; and

R_{26} is hydrogen or halogen.

53. The compound of embodiment 52, wherein

R_3 is F;

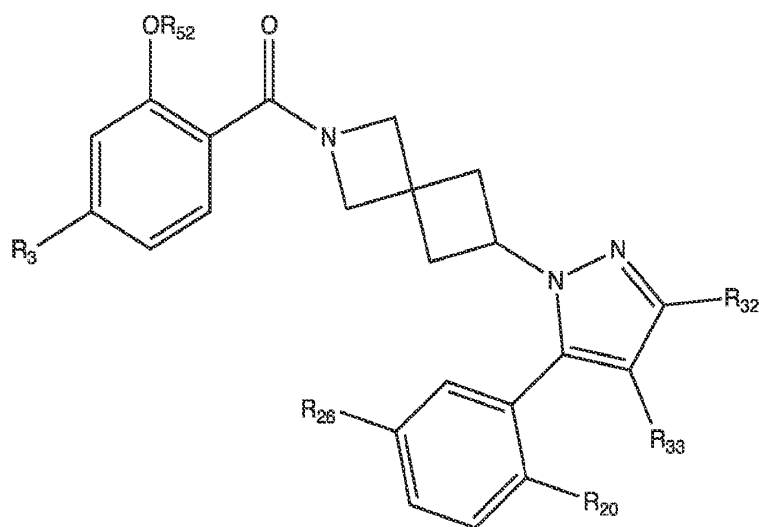
R_{52} is lower alkyl optionally substituted with one or more F; or cyclopropyl;

R_{31} and R_{33} are each independently hydrogen, methyl or CF_3 , provided that one of R_{31} and R_{33} is hydrogen;

R_{20} is methyl or CF_3 ; and

R_{26} is hydrogen or F.

54. A compound of Formula (III-D) or a pharmaceutically acceptable salt thereof:



Formula (III-D)

wherein

R_3 is halogen;

R_{52} is lower alkyl or lower cycloalkyl, each optionally substituted with halogen,

R_{32} and R_{33} are each independently hydrogen or lower alkyl optionally substituted with one or more halogen, provided that one of R_{32} and R_{33} is hydrogen.

R_{20} is lower alkyl optionally substituted with halogen; and

R_{26} is hydrogen or halogen.

55. The compound of embodiment 54, wherein

R_3 is F;

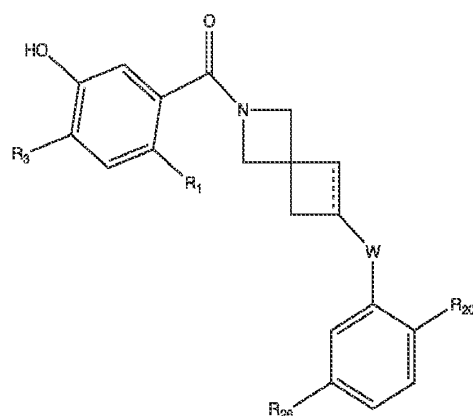
R_{52} is lower alkyl optionally substituted with one or more F, or cyclopropyl;

R_{32} and R_{33} are each independently hydrogen, methyl or CF_3 , provided that one of R_{32} and R_{33} is hydrogen;

R_{20} is methyl or CF_3 ; and

R_{26} is hydrogen or F.

56. A compound of Formula (II), or a pharmaceutically acceptable salt thereof,



Formula (II),

wherein

the dashed line represents an optional double bond;

R₁ is halogen;

R₃ is hydrogen;

W is A;

A is a 5-member heteroaryl ring optionally substituted with one or more R₃₀;

R₂₀ is halogen or lower alkyl optionally substituted with one or more halogen;

R₃₀ is lower alkyl optionally substituted with one or more halogen; and

R₂₆ is halogen or hydrogen, provided the compound is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone.

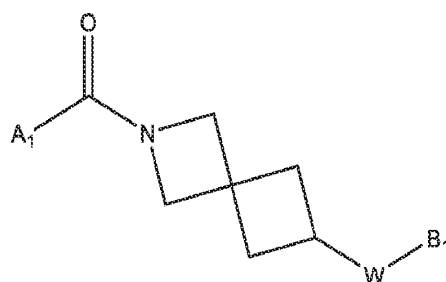
57. A pharmaceutical composition comprising a compound of any one of embodiments 1-56, or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient (API), provided the compound is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone.

58. A method of inhibiting monoacylglycerol lipase (MAGL) in a subject comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound of any one of embodiments 1-56.

59. A method of reversibly inhibiting monoacylglycerol lipase (MAGL) comprising the step of contacting a compound of any one of embodiments 1-56 with a cell expressing MAGL.

[000225] Additional Embodiments include those listed below:

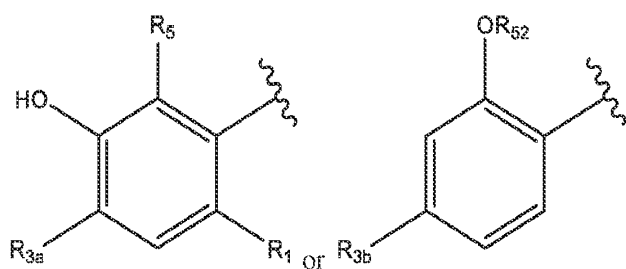
1. A compound of Formula (I) or a pharmaceutically acceptable salt thereof,



Formula (I),

wherein:

A₁ is



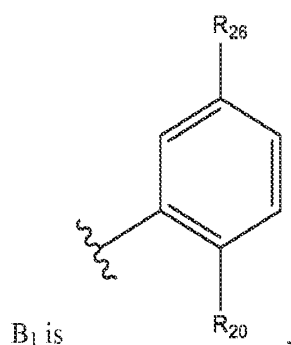
R₁ is halogen, hydrogen, or cyano;

R_{3a} and R₅ are each independently hydrogen, halogen, or lower alkyl;

R₅₂ is lower alkyl, lower cycloalkyl or lower haloalkyl;

R_{3b} is halogen;

W is a diazole optionally substituted with lower alkyl, lower cycloalkyl, or lower haloalkyl;



R₂₀ is halogen, hydrogen, lower alkyl, or lower haloalkyl; and

R₂₆ is hydrogen, or halogen;

provided the compound is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone.

2. The compound of embodiment 1, wherein

R₁ is hydrogen, fluoro, or cyano;

R_{3a} and R₅ are each independently hydrogen, halogen, or methyl;

R₅₂ is lower alkyl, cyclopropyl or lower haloalkyl;

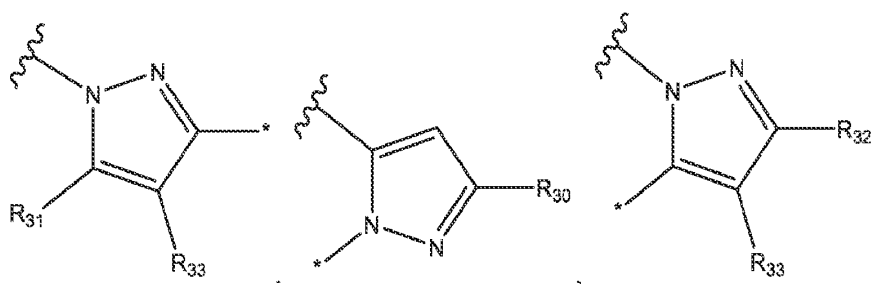
R_{3b} is fluoro;

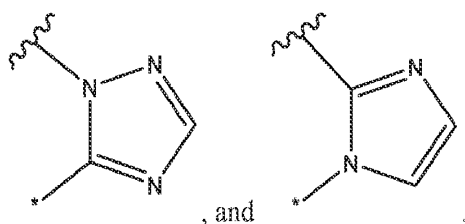
W is a diazole optionally substituted with one of methyl, cyclopropyl, or CF₃;

R₂₀ is fluoro or chloro, methyl, or CF₃; and

R₂₆ is hydrogen, fluoro or chloro.

3. The compound of embodiment 2, wherein W is selected from the group consisting of:



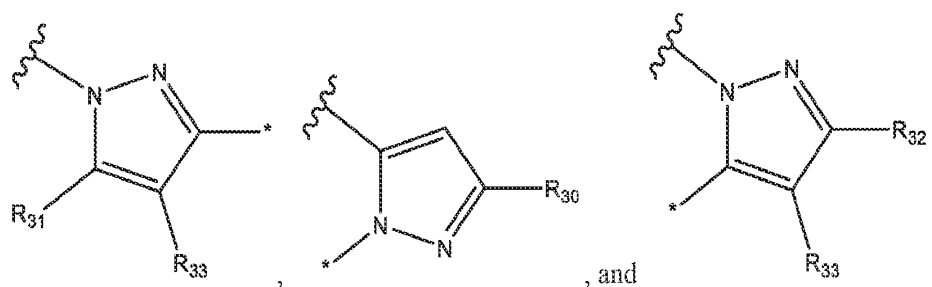


wherein * indicates a covalent bond to B₁; and

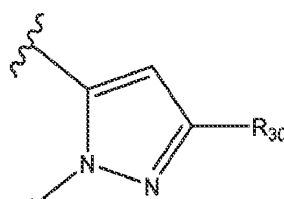
R₃₀, R₃₁, R₃₂ and R₃₃ are each independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl, provided that at least one of R₃₁ and R₃₃ and at least one of R₃₂ and R₃₃ is not hydrogen.

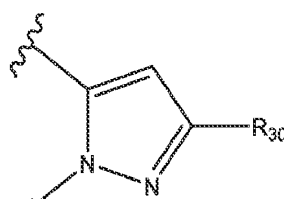
4. The compound of embodiment 3, wherein R₃₀, R₃₁, R₃₂ and R₃₃ are each independently hydrogen, methyl, CF₃, or cyclopropyl, provided that at least one of R₃₁ and R₃₃ and at least one of R₃₂ and R₃₃ is not hydrogen.

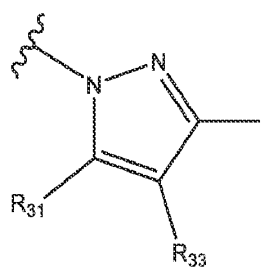
5. The compound of embodiment 4, wherein W is selected from the group consisting of:

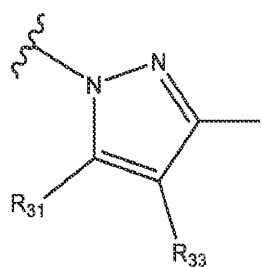


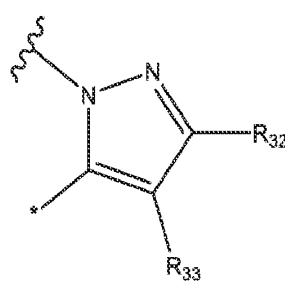
wherein * indicates a covalent bond to B₁.

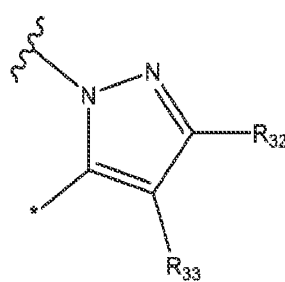


6. The compound of embodiment 5, wherein W is , wherein * indicates a covalent bond to B₁, and R₃₀ is methyl.

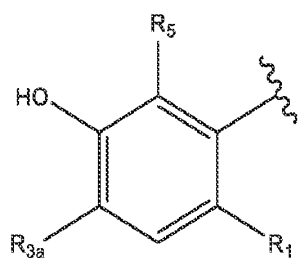


7. The compound of embodiment 5, wherein W is , wherein * indicates a covalent bond to B₁, and R₃₁ and R₃₃ are each independently hydrogen, methyl, CF₃, or cyclopropyl, provided that one of R₃₁ and R₃₃ is hydrogen.



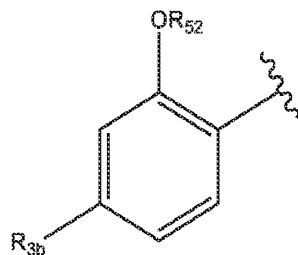
8. The compound of embodiment 5, wherein W is , wherein * indicates a covalent bond to B₁, and R₃₂ and R₃₃ are each independently hydrogen, methyl, CF₃, or cyclopropyl, provided that one of R₃₂ and R₃₃ is hydrogen.

9. The compound of any one of embodiments 4-8, wherein A₁ is

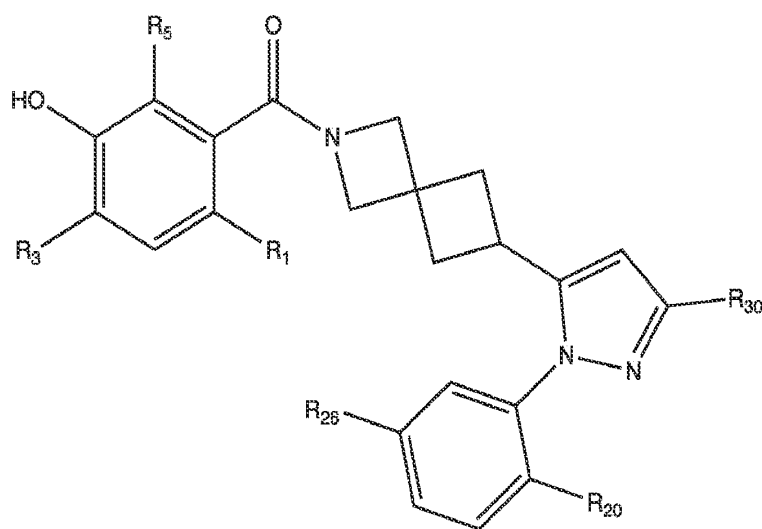


10. The compound of embodiment 9, wherein R₅ is hydrogen.
11. The compound of embodiment 10, wherein R₁ is fluoro.
12. The compound of embodiment 11, wherein R_{3a} is hydrogen, fluoro, or methyl.

13. The compound of embodiment 12, wherein R_{3a} is hydrogen.
14. The compound of embodiment 13, wherein R_{20} is methyl, and R_{26} is hydrogen or fluoro; or R_{20} is chloro, fluoro or CF_3 , and R_{26} is hydrogen.
15. The compound of any one of embodiments 4-8, wherein A_1 is



16. The compound of embodiment 15, wherein R_{52} is lower alkyl optionally substituted with one or more fluoro and cyclopropyl.
17. The compound of embodiment 16, wherein R_{3b} is fluoro.
18. The compound of embodiment 17, wherein
 R_{20} is methyl, and R_{26} is hydrogen or fluoro; or
 R_{20} is fluoro or CF_3 , and R_{26} is hydrogen.
19. A compound of Formula (II-B) or a pharmaceutically acceptable salt thereof.



Formula (II-B),

wherein

R₁ is halogen or cyano;

R₃ is hydrogen, lower alkyl, or halogen;

R₅ is hydrogen, halogen or lower alkyl;

R₂₀ is halogen or lower alkyl optionally substituted with one or more halogen;

R₂₆ is halogen or hydrogen; and

R₃₀ is hydrogen or lower alkyl optionally substituted with one or more halogen, provided the compound is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone.

20. The compound of embodiment 19, wherein

R₁ is F or cyano;

R₃ is hydrogen, methyl, or F;

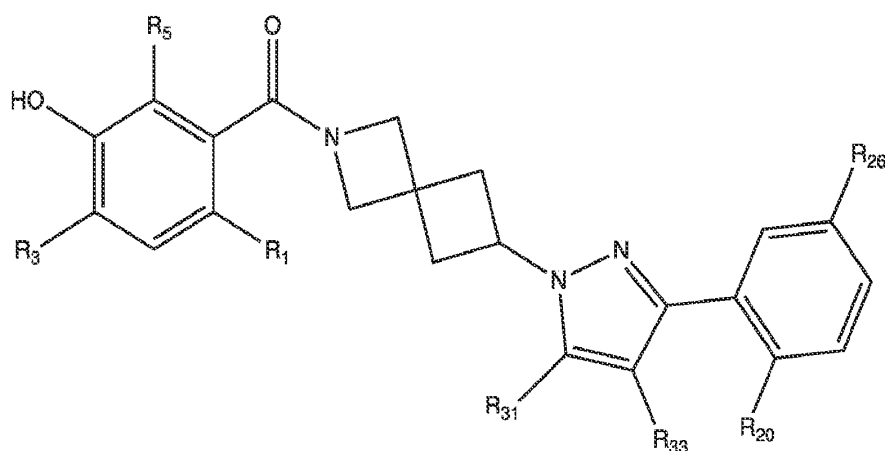
R₅ is hydrogen, F or methyl;

R₂₀ is F, methyl, or CF₃;

R₂₆ is hydrogen or F; and

R₃₀ is hydrogen, methyl or CF₃, provided the compound is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone.

21. A compound of Formula (II-C) or a pharmaceutically acceptable salt thereof:



Formula (II-C),

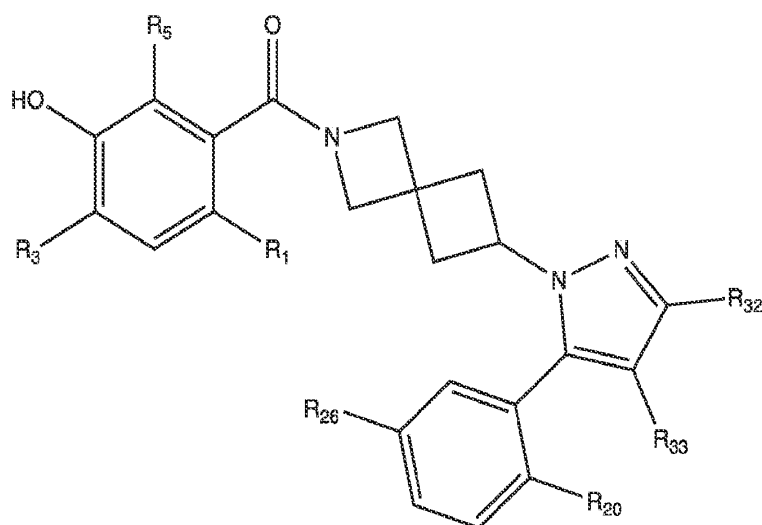
wherein

- R₁ is halogen or cyano;
- R₃ is hydrogen, lower alkyl, or halogen;
- R₅ is hydrogen, halogen or lower alkyl;
- R₂₀ is halogen or lower alkyl optionally substituted with one or more halogen;
- R₂₆ is hydrogen or halogen; and
- R₃₁ and R₃₃ are each independently hydrogen or lower alkyl optionally substituted with one or more halogen, provided that one of R₃₁ and R₃₃ is hydrogen.

22. The compound of embodiment 21, wherein

- R₁ is F or cyano;
- R₃ is hydrogen, methyl, or F;
- R₅ is hydrogen, F or methyl;
- R₂₀ is F, methyl, or CF₃;
- R₂₆ is hydrogen or F; and
- R₃₁ and R₃₃ are each independently hydrogen, methyl or CF₃.

23. A compound of Formula (II-D) or a pharmaceutically acceptable salt thereof:



wherein

R₁ is halogen or cyano;

R₃ is hydrogen, lower alkyl, or halogen;

R₅ is hydrogen, halogen or lower alkyl;

R₆ is hydrogen;

R₂₀ is halogen or lower alkyl optionally substituted with one or more halogen;

R₂₆ is halogen or hydrogen; and

R₃₂ and R₃₃ are each independently hydrogen or lower alkyl optionally substituted with one or more halogen, provided that one of R₃₂ and R₃₃ is hydrogen.

24. The compound of embodiment 23, wherein

R₁ is F or cyano;

R₃ is hydrogen, F or methyl;

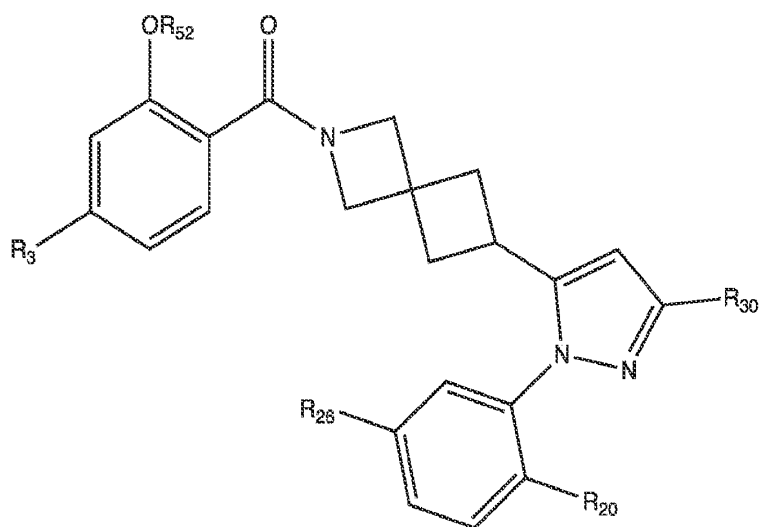
R₅ is hydrogen, F or methyl;

R₂₀ is F or methyl, or CF₃;

R₂₆ is hydrogen or F; and

R₃₂ and R₃₃ are each independently hydrogen, methyl or, CF₃ provided that one of R₃₂ and R₃₃ is hydrogen.

25. A compound of Formula (III-B) or a pharmaceutically acceptable salt thereof:



Formula (III-B)

wherein

R_3 is halogen;

R_{52} is lower alkyl or lower cycloalkyl, each optionally substituted with halogen,

R_{30} is lower alkyl;

R_{20} is lower alkyl; and

R_{26} is hydrogen or halogen.

26. The compound of embodiment 25, wherein

R_3 is F;

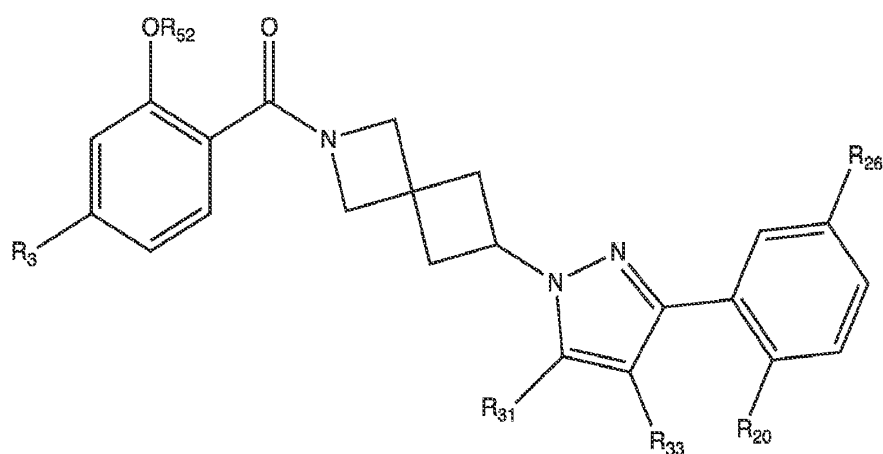
R_{52} is lower alkyl optionally substituted with one or more F or cyclopropyl;

R_{30} is methyl;

R_{20} is methyl; and

R_{26} is hydrogen or F.

27. A compound of Formula (III-C) or a pharmaceutically acceptable salt thereof.



wherein

R_3 is halogen;

R_{52} is lower alkyl or lower cycloalkyl, each optionally substituted with halogen,

R_{31} and R_{33} are each independently hydrogen or lower alkyl optionally substituted with one or more halogen, provided that one of R_{31} and R_{33} is hydrogen.

R_{20} is lower alkyl optionally substituted with halogen; and

R_{26} is hydrogen or halogen.

28. The compound of embodiment 27, wherein

R_3 is F;

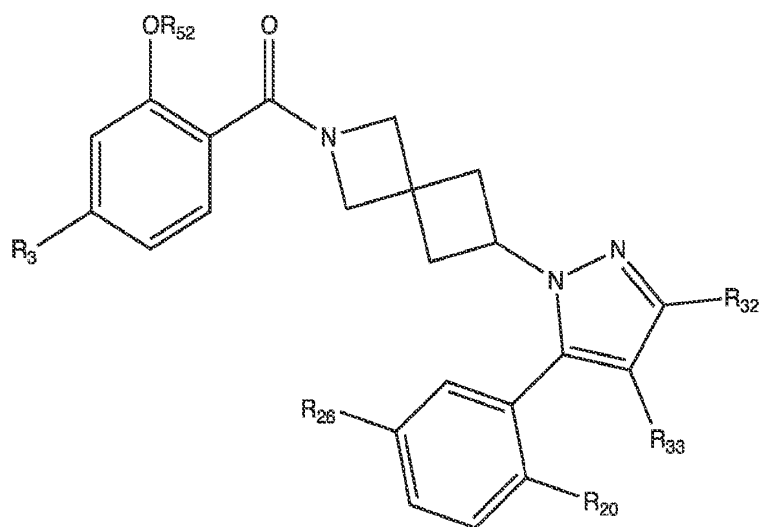
R_{52} is lower alkyl optionally substituted with one or more F; or cyclopropyl;

R_{31} and R_{33} are each independently hydrogen, methyl or CF_3 , provided that one of R_{31} and R_{33} is hydrogen;

R_{20} is methyl or CF_3 ; and

R_{26} is hydrogen or F.

29. A compound of Formula (III-D) or a pharmaceutically acceptable salt thereof:



Formula (III-D)

wherein

R_3 is halogen;

R_{52} is lower alkyl or lower cycloalkyl, each optionally substituted with halogen,

R_{32} and R_{33} are each independently hydrogen or lower alkyl optionally substituted with one or more halogen, provided that one of R_{32} and R_{33} is hydrogen.

R_{20} is lower alkyl optionally substituted with halogen; and

R_{26} is hydrogen or halogen.

30. The compound of embodiment 29, wherein

R_3 is F;

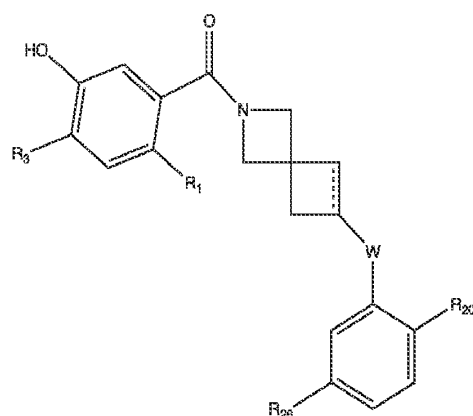
R_{52} is lower alkyl optionally substituted with one or more F, or cyclopropyl;

R_{32} and R_{33} are each independently hydrogen, methyl or CF_3 , provided that one of R_{32} and R_{33} is hydrogen;

R_{20} is methyl or CF_3 ; and

R_{26} is hydrogen or F.

31. A compound of Formula (II), or a pharmaceutically acceptable salt thereof,



Formula (II),

wherein

the dashed line represents an optional double bond;

R₁ is halogen;

R₃ is hydrogen;

W is A;

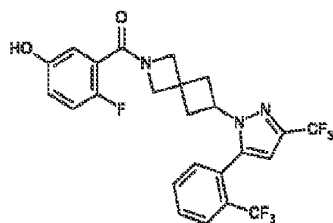
A is a 5-member heteroaryl ring optionally substituted with one or more R₃₀;

R₂₀ is halogen or lower alkyl optionally substituted with one or more halogen;

R₃₀ is lower alkyl optionally substituted with one or more halogen; and

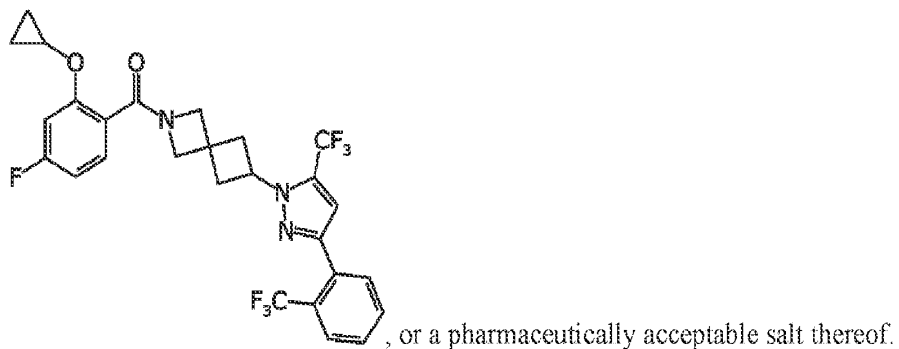
R₂₆ is halogen or hydrogen, provided the compound is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone.

32. The compound of embodiment 1, wherein the compound is

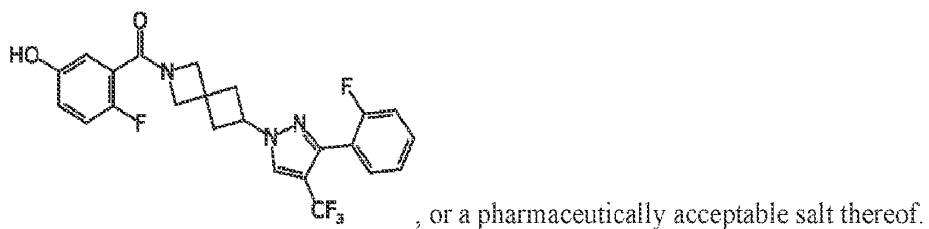


, or a pharmaceutically acceptable salt thereof.

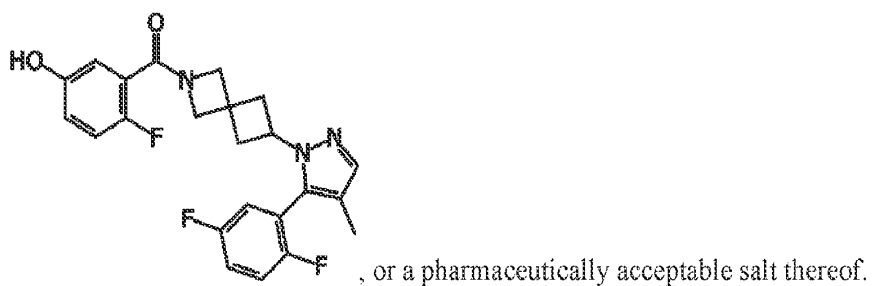
33. The compound of embodiment 1, wherein the compound is



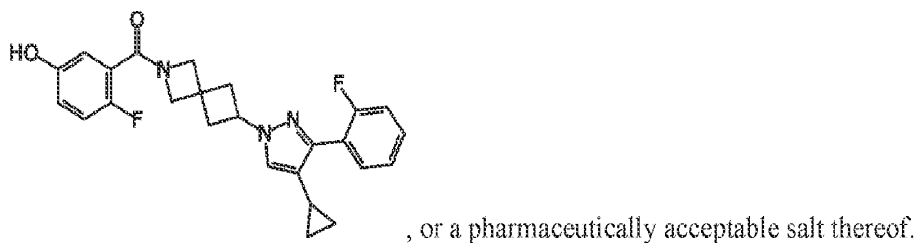
34. The compound of embodiment 1, wherein the compound is



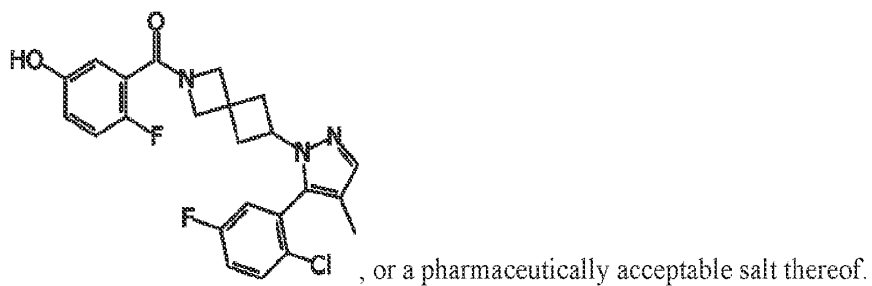
35. The compound of embodiment 1, wherein the compound is



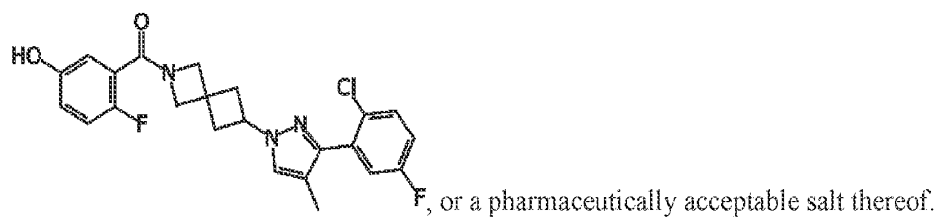
36. The compound of embodiment 1, wherein the compound is



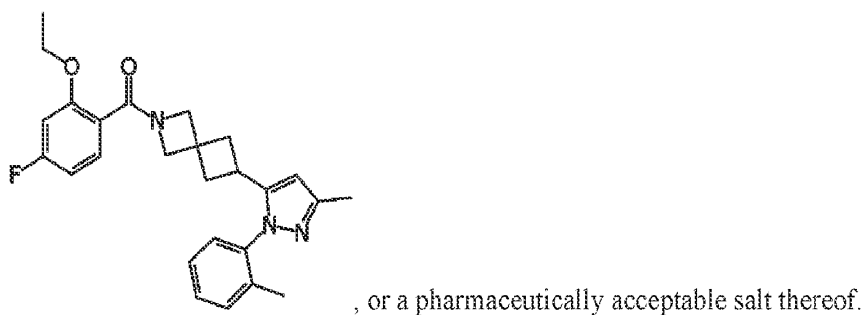
37. The compound of embodiment 1, wherein the compound is



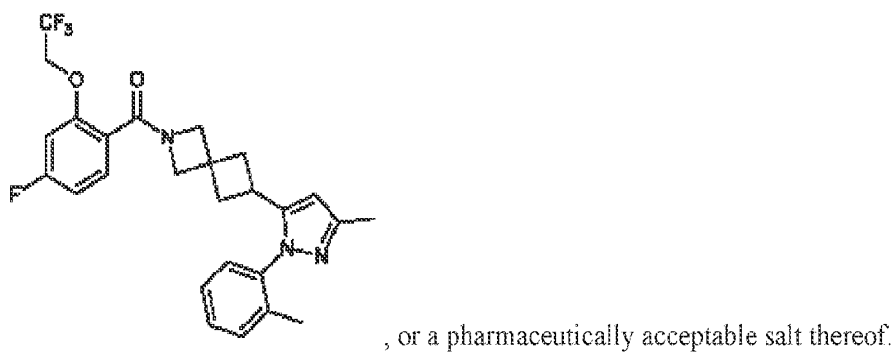
38. The compound of embodiment 1, wherein the compound is



39. The compound of embodiment 1, wherein the compound is



40. The compound of embodiment 1, wherein the compound is



41. A pharmaceutical composition comprising a compound of any one of embodiments 1-40, or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient (API), provided the compound is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone.

42. A method of inhibiting monoacylglycerol lipase (MAGL) in a subject comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound of any one of embodiments 1-40.

43. A method of reversibly inhibiting monoacylglycerol lipase (MAGL) comprising the step of contacting a compound of any one of embodiments 1-40 with a cell expressing MAGL.

EXAMPLES

[000226] The following examples illustrate some embodiments and aspects of the invention. It will be apparent to those skilled in the relevant art that various modifications, additions, substitutions, and the like can be performed without altering the spirit or scope of the invention, and such modifications and variations are encompassed within the scope of the invention as defined in the claims which follow. The following examples do not in any way limit the invention.

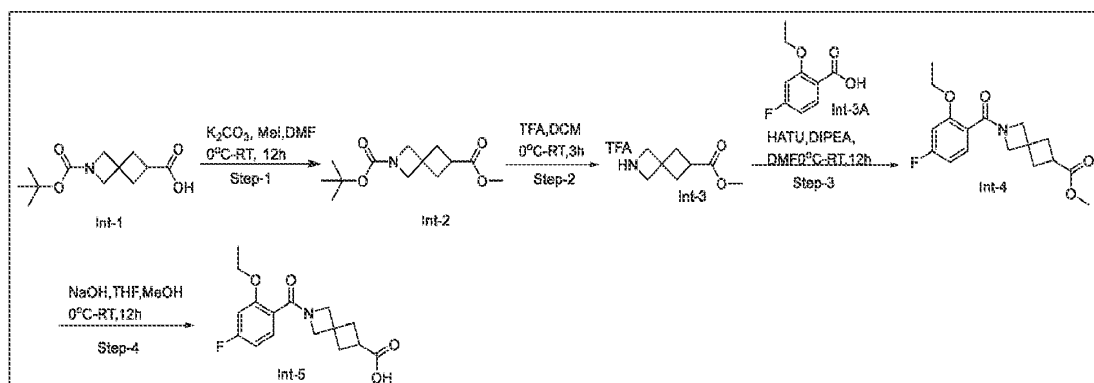
[000227] LC/MS...

Table of Abbreviations

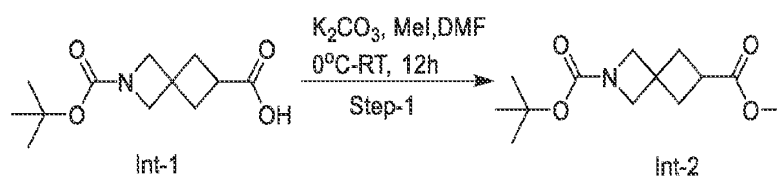
Example 1: Preparation of Synthetic Intermediates

Intermediate-5: 2-(2-ethoxy-4-fluorobenzoyl)-2-azaspiro [3.3] heptane-6-carboxylic acid

Synthetic scheme:

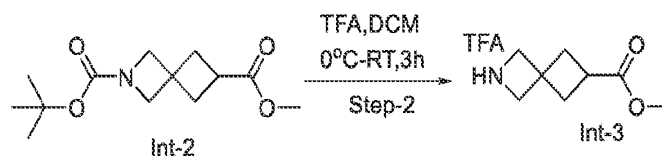


Step-1: Synthesis of 2-(tert-butyl) 6-methyl 2-azaspiro [3.3] heptane-2,6-dicarboxylate (Int-2)



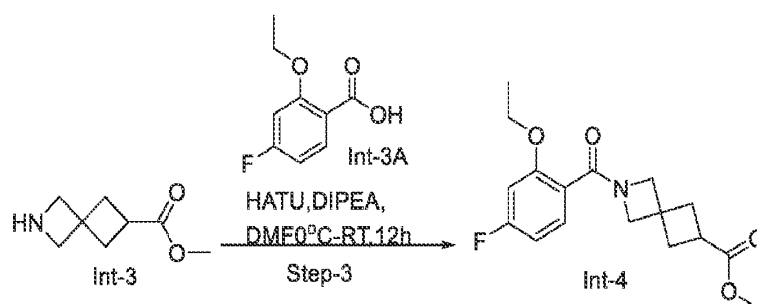
To a stirred solution of 2-(tert-butoxycarbonyl)-2-azaspiro [3.3] heptane-6-carboxylic acid (3.0 gm, 12.44 mmol, 1.0 eq.) in N,N-Dimethyl formamide (30 mL), was added potassium carbonate (2.061 gm, 14.93 mmol, 1.2 eq.) at 0°C. The reaction was stirred at 0°C for 10 min. Methyl Iodide (2.12 gm, 14.93 mmol, 1.2 eq.) was added dropwise and stirred the reaction mass at room temperature for 12 hrs. After completion of reaction as monitored by TLC, the reaction mixture was diluted with Ice cold water (30 mL) and extracted with Ethyl acetate (3 x 30mL). The combined organic layer was washed with brine solution, dried over sodium sulfate and concentrated to obtain crude product, which was purified by combiflash using 30% Ethyl acetate in Hexane as eluent to afford 2-(tert-butyl) 6-methyl 2-azaspiro[3.3]heptane-2,6-dicarboxylate (Int-2) 3.10 gm, (Yield-97.79%). LCMS: 200.2/z [M-56]⁺

Step-2: Synthesis of methyl 2-azaspiro [3.3] heptane-6-carboxylate (Int-3)



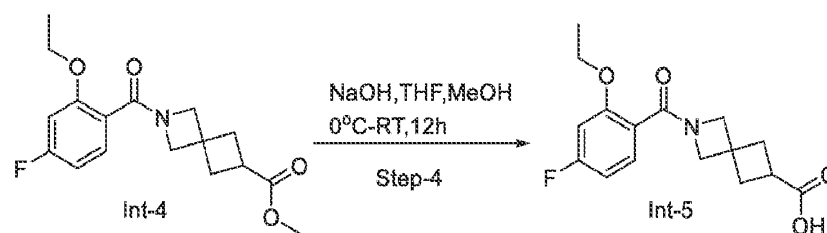
To a stirred solution of 2-(tert-butyl) 6-methyl 2-azaspiro[3.3]heptane-2,6-dicarboxylate (Int-2) (3.0 gm, 8.0 mmol, 1.0 eq.) in Dichloromethane (30 mL) was added Trifluoroacetic acid (3.0 mL) at 0°C and allowed to stirred the reaction at Room temperature for 3 hr; the progress of the reaction of the was monitored by TLC. After completion of reaction, the reaction mixture was evaporated under vacuum and basified with bicarbonate solution (15mL) extracted with Ethyl acetate(3*30 mL) Ethyl acetate layer separated dried over sodium sulfate and concentrated to obtain crude product methyl 2-azaspiro[3.3]heptane-6-carboxylate (Int-3) 2.50 gm (Yield: quantitative); LCMS: 155.90/z [M+1]⁺

Step-3: Synthesis of methyl 2-(2-ethoxy-4-fluorobenzoyl)-2-azaspiro [3.3] heptane-6-carboxylate (Int-4).



To a stirred solution of 2-ethoxy-4-fluorobenzoic acid (2.0 gm, 10.86 mmol, 1 eq.) in N,N-Dimethyl formamide (20 mL) were added HATU (6.19 gm, 16.30 mmol, 1.5eq.) DIPEA (4.20 gm, 32.6mmol, 3.0 eq.) followed by methyl 2-azaspiro [3.3] heptane-6-carboxylate (Int-3) (1.33 gm, 10.86 mmol, 1.0 eq.) at 0°C and allowed to stirred the reaction at room temperature for 12 hr; the progress of the reaction of was monitored by TLC. After completion of reaction, the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 X 30 mL), washed with brine. The organic layer was dried over sodium sulphate and concentrated under vacuum to get crude material; which was purified by Combi-flash by using 70% Ethyl acetate in n Hexane as mobile phase to give desired product 2-(2-ethoxy-4-fluorobenzoyl)-2-azaspiro[3.3]heptane-6-carboxylic acid (Int-4) 2.4gm (Yield: 73.52%); LCMS: 322.3m/z [M+1]⁺

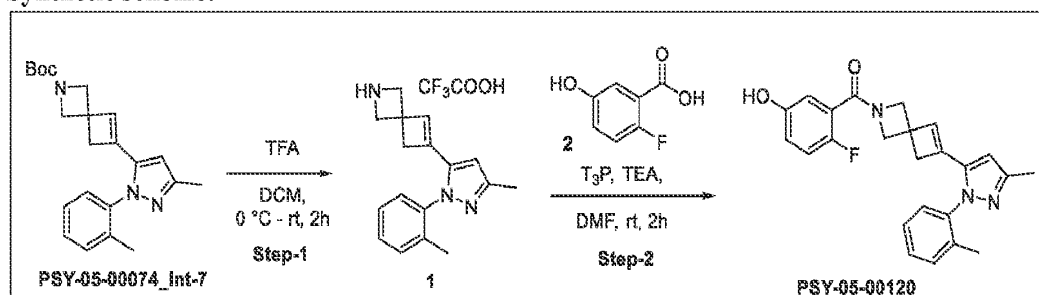
Step-4: Synthesis of 2-(2-ethoxy-4-fluorobenzoyl)-2-azaspiro [3.3] heptane-6-carboxylic acid (Int-5)



To a stirred solution of methyl 2-(2-ethoxy-4-fluorobenzoyl)-2-azaspiro [3.3] heptane-6-carboxylate (Int-4) (1.0 gm, 3.11 mmol, 1.0 eq.) in Tetrahydrofuran (10 mL), Methanol (5 mL), Water (10 mL) was added Sodium Hydroxide [NaOH] (0.13 gm, 6.23 mmol, 2.0 eq.) at 0°C. The reaction mixture was stirred at Room temperature for next 12 hr. The progress of the reaction was monitored by TLC; after completion of reaction, the reaction mixture was evaporated under vacuum. The crude product was acidified with 2N HCL (PH~4) The white solid was precipitated out which was filtered through Buchner funnel and dried under vacuum to give 2-(2-ethoxy-4-fluorobenzoyl)-2-azaspiro[3.3]heptane-6-carboxylic acid (Int-5), 0.75gm (Yield: 72.11%); LCMS: 308.3 m/z $[M+1]^+$

Example 2: Synthesis of (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]hept-5-en-2-yl)methanone. [Compound 120]

Synthetic scheme:



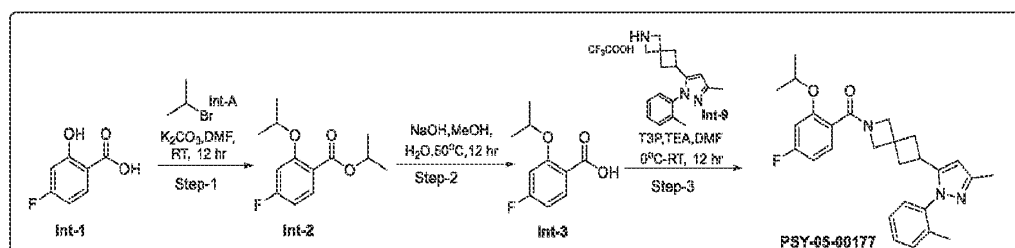
Methanol-d₄) δ : 7.51-7.47 (m, 1H), 7.44-7.36 (m, 2H), 7.28 (d, J = 7.6 Hz, 1H), 6.38 (s, 1H), 5.36 (s, 1H), 4.19-4.13 (m, 4H), 2.88-2.86 (m, 2H), 2.31 (s, 3H), 2.01 (s, 3H).

Step-2: ((2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]hept-5-en-2-yl)methanone

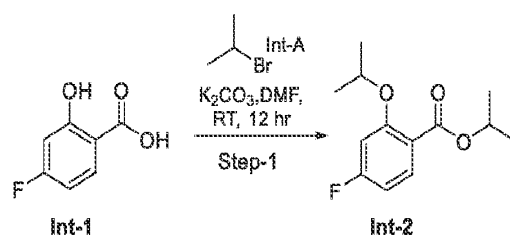
[000229] To a stirred solution of 6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]hept-5-ene 2,2,2-trifluoroacetate (0.11 g, 0.421 mmol) in DMF (1 mL) were added 2-fluoro-5-hydroxybenzoic acid (0.054g, 0.506 mmol), TEA (0.088g, 1.26 mmol) and T3P (0.111g, 0.506 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 2h. After completion of reaction as monitored by TLC, the reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (3*50 mL). The organic layer was washed with brine (3*25 mL), dried over sodium sulphate and concentrated under vacuum to get crude material which was purified by combiflash using 3% MeOH in DCM as eluent to get ((2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]hept-5-en-2-yl)methanone) PSY-05-00120 (0.03 g, 27%) as white solid. LCMS: 473.7 m/z [M+H]⁺; ¹H NMR (400 MHz, Methanol-d₄) δ 7.51 – 7.33 (m, 3H), 7.28 (d, J = 7.9 Hz, 1H), 7.00 (t, J = 9.2 Hz, 1H), 6.92 – 6.78 (m, 2H), 6.35 (s, 1H), 5.39 (s, 1H), 4.29 – 4.09 (m, 4H), 2.78 (d, J = 5.6 Hz, 2H), 2.30 (s, 3H), 2.00 (s, 3H).

Example 3: Synthesis of (4-fluoro-2-isopropoxyphenyl) (6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro [3.3] heptan-2-yl) methanone. [Compound 177]

Synthetic scheme:

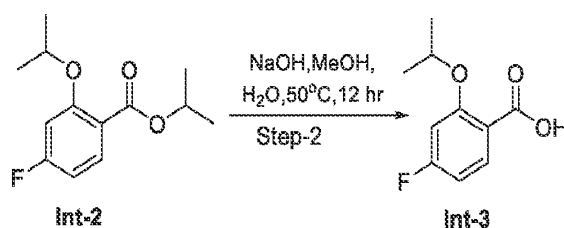


Step-1: Synthesis of isopropyl 4-fluoro-2-isopropoxybenzoate (Int-2).



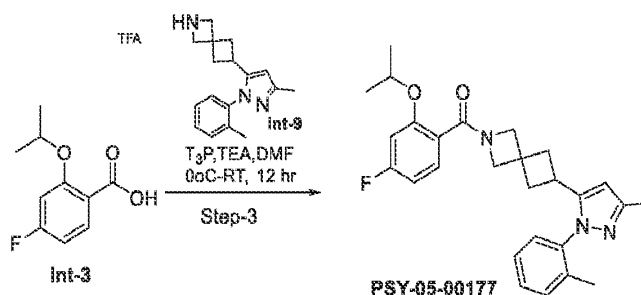
To a stirred solution of 4-fluoro-2-hydroxybenzoic acid (2.0 gm, 12.820 mmol, 1 eq.) in N,N-Dimethyl formamide (20 mL) were added Potassium carbonate (17.07 gm, 51.282 mmol, 4.0eq.) followed by dropwise addition of Isopropyl iodide (8.88 gm, 51.282 mmol, 4.0 eq.) at 0°C and allowed to stirred the reaction at room temperature for 12 hr; the progress of the reaction of the was monitored by TLC. After completion of reaction, the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 X 50 mL), washed with brine. The organic layer was dried over sodium sulphate and concentrated under vacuum to get crude material; which was purified by combi-flash by using 20% Ethyl acetate in hexane as mobile phase to give desired product 4-fluoro-2-isopropoxybenzoic acid 2.0 gm (Yield: 65.14%); ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.65 (dd, *J* = 8.7, 7.0 Hz, 1H), 7.08 (dd, *J* = 11.8, 2.4 Hz, 1H), 6.82 (td, *J* = 8.4, 2.4 Hz, 1H), 5.09 (hept, *J* = 6.2 Hz, 1H), 4.72 (p, *J* = 6.0 Hz, 1H), 3.18 (d, *J* = 5.2 Hz, 1H), 1.29 (dd, *J* = 6.1, 2.7 Hz, 12H).

Step-2: Synthesis of 4-fluoro-2-isopropoxybenzoic acid carbonate (Int-3).



To a stirred solution of isopropyl 4-fluoro-2-isopropoxybenzoate (Int-2) (1.60 gm, 6.66 mmol, 1.0 eq.) in Tetrahydrofuran (10 mL), Methanol (10 mL), Water (10 mL) was added Sodium Hydroxide [NaOH] (0.53 gm, 13.33 mmol, 2.0 eq.) at 0°C. The reaction mixture was stirred at 50°C for next 12 hr. The progress of the reaction was monitored by TLC; after completion of reaction, the reaction mixture was evaporated under vacuum. The crude product was acidified with 2N HCL (PH~4) The white solid was precipitated out which was filtered through Buchner funnel and dried under vacuum to give isopropyl 4-fluoro-2-isopropoxybenzoic acid (Int-3) 1.20 gm (Yield: 91%); ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.53 (s, 1H), 7.69 (t, *J* = 7.9 Hz, 1H), 7.05 (dd, *J* = 11.9, 2.5 Hz, 1H), 6.80 (td, *J* = 8.4, 2.5 Hz, 1H), 4.69 (hept, *J* = 6.0 Hz, 1H), 1.27 (d, *J* = 6.0 Hz, 6H).

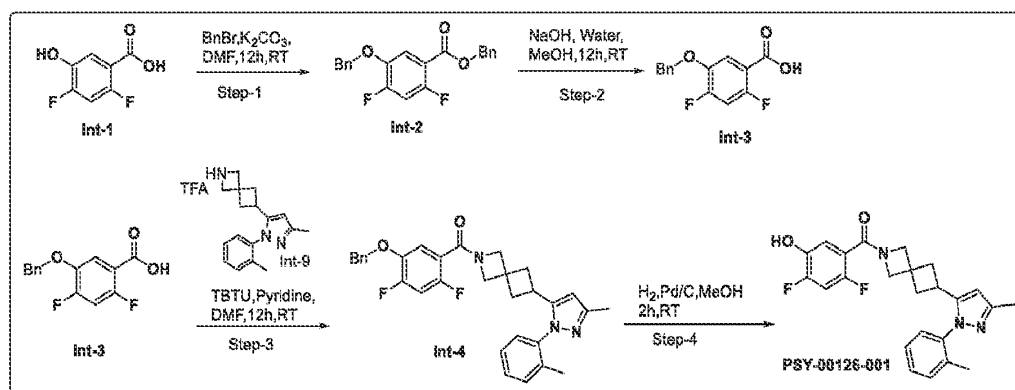
Step-3: Synthesis of (4-fluoro-2-isopropoxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone (Compound-00177).



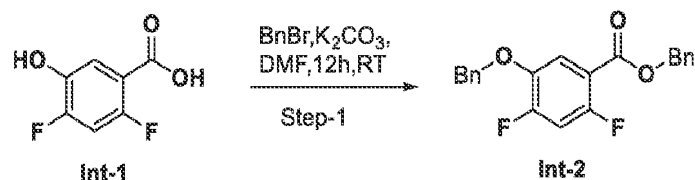
To a stirred solution of 6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro [3.3] heptane 2,2,2-trifluoroacetate (0.150gm, 0.56 mmol 1.0 eq.) in N,N-Dimethyl formamide (3 mL) were added 4-fluoro-2-isopropoxybenzoic acid (0.133gm, 0.674 mmol, 1.2 eq.), TEA (0.170gm, 1.68mmol, 3.0 eq.) and T₃P (50% in ethyl acetate) (0.214 gm, 0.674 mmol, 1.2 eq.) at 0 °C. The resulting reaction mixture was stirred at room temperature for 12h. After completion of reaction as monitored by TLC, the reaction mixture was diluted with water (10 ml) and extracted with ethyl acetate (3*20 ml). The organic layer was washed with brine (10ml), dried over sodium sulphate and concentrated under vacuum to get crude material which was purified by combiflash using 50% Ethyl acetate in hexane as eluent to get PSY-05-00177 as white solid (0.040. (Yield: 16%); LCMS: 448.5 *m/z* [M+H]⁺. HPLC: 98.35%; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.38 (t, *J* = 8.3 Hz, 2H), 7.33 – 7.22 (m, 2H), 7.15 (dd, *J* = 7.9, 4.2 Hz, 1H), 6.97 (dd, *J* = 11.6, 8.5 Hz, 1H), 6.75 (q, *J* = 7.6 Hz, 1H), 6.13 (d, *J* = 17.6 Hz, 1H), 4.70 – 4.60 (m, 1H), 3.93 (s, 1H), 3.85 (d, *J* = 15.1 Hz, 2H), 3.78 (s, 1H), 3.00 (dt, *J* = 18.8, 8.5 Hz, 1H), 2.34 – 2.16 (m, 4H), 2.16 (s, 3H), 1.93 (s, 3H), 1.24 (dd, *J* = 11.5, 6.1 Hz, 6H).

Example 4: Synthesis of (2,4-difluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone. [Compound 126]

Synthetic scheme:

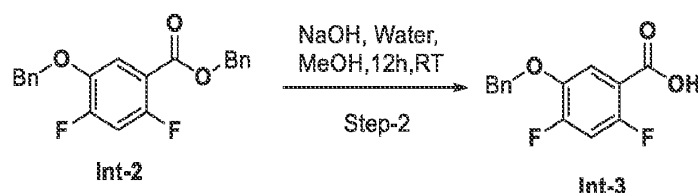


Step-1: Synthesis of benzyl 5-(benzyloxy)-2,4-difluorobenzoate (Int-2)



To a stirred solution of 2,4-difluoro-5-hydroxybenzoic acid (0.40 gm, 2.13mmol, 1.0 eq.) in N,N-Dimethyl formamide (5.0 mL) were added Potassium carbonate (0.88 gm, 6.38 mmol, 3.0 eq.) Benzyl bromide (1.09 gm, 6.38 mmol, 3.0 eq.) at 0°C and allowed to stirred the reaction at room temperature for 12 hr; the progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 X 20 mL), washed with brine. The organic layer was dried over sodium sulphate and concentrated under vacuum to get crude material; which was purified by combi-flash by using 35% Ethyl acetate in n-Hexane as mobile phase to give desired product benzyl 5-(benzyloxy)-2,4-difluorobenzoate (Int-2) 0.560 gm (Yield: 69.13%); ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.68 (dd, *J* = 9.4, 6.8 Hz, 1H), 7.52 (t, *J* = 10.9 Hz, 1H), 7.47 (d, *J* = 1.9 Hz, 2H), 7.47 – 7.31 (m, 8H), 5.36 (s, 2H), 5.24 (s, 2H).

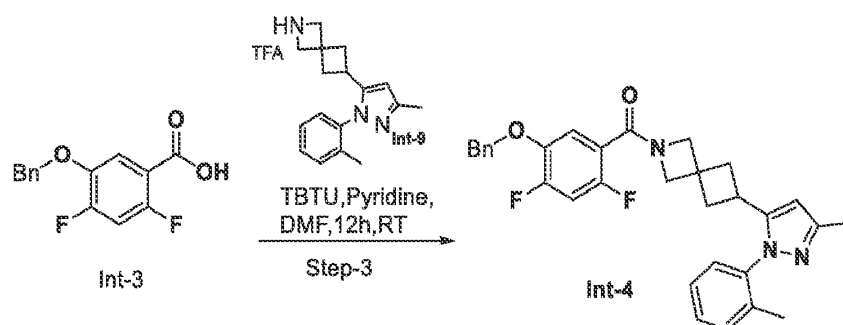
Step-2: 5-(benzyloxy)-2,4-difluorobenzoic acid (Int-3).



To a stirred solution of benzyl 5-(benzyloxy)-2,4-difluorobenzoate (Int-2) (0.50 gm, 1.44 mmol, 1.0 eq.) in Tetrahydrofuran (5.0 mL), Methanol (5.0 mL), Water (5.0 mL) was added Sodium Hydroxide [NaOH]

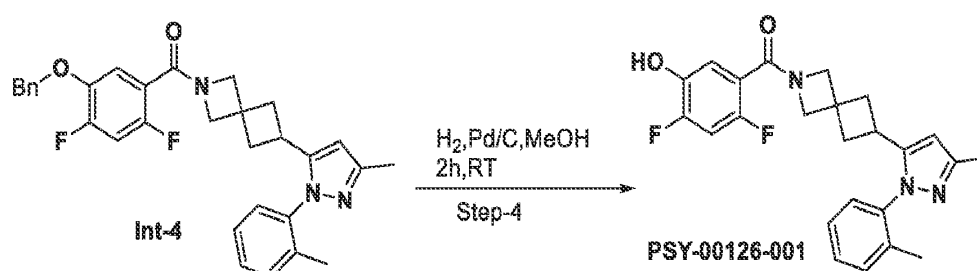
(0.11 gm, 2.89 mmol, 2.0 eq.) at 0°C. The reaction mixture was stirred at Room temperature for next 12 hr. The progress of the reaction was monitored by TLC; after completion of reaction, the reaction mixture was evaporated under vacuum. The crude product was acidified with 2N HCL (PH~4) The white solid was precipitated out which was filtered through Buchner funnel and dried under vacuum to give 5-(benzyloxy)-2,4-difluorobenzoic acid (Int-3), 0.35 gm (Yield: 94.59%); ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.42 (s, 1H), 7.65 (dd, *J* = 9.5, 6.9 Hz, 1H), 7.52 – 7.29 (m, 5H), 5.23 (s, 2H).

Step-3: Synthesis of (5-(benzyloxy)-2,4-difluorophenyl)(6-(3-methyl-1-(*o*-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone (Int-4).



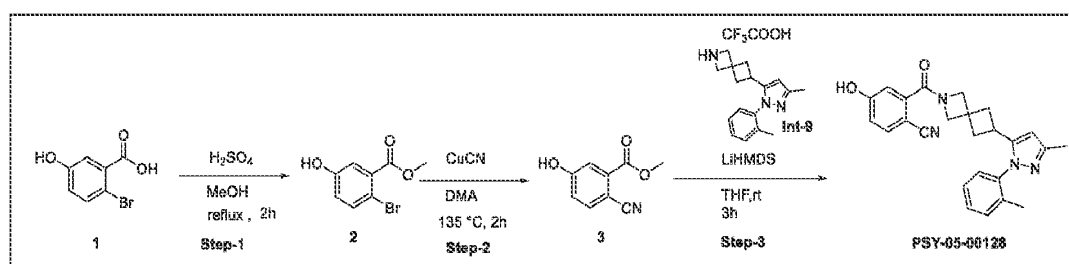
To a stirred solution of 2-(5-(benzyloxy)-2-fluorobenzoyl)-2-azaspiro[3.3]heptane-6-carboxylic acid (0.25 gm, 0.677 mmol, 1.0 eq.) in *N,N*-Dimethyl formamide (10.0 mL) were added TBTU (0.326 gm, 1.01 mmol, 1.5 eq.) Pyridine (0.15 gm, 2.03 mmol, 3.0 eq.) followed by addition of 5-(benzyloxy)-2,4-difluorobenzoic acid (Int-3) (0.16 gm, 0.677 mmol, 1.0 eq.) at 0°C and allowed to stirred the reaction at room temperature for 12 hr; the progress of the reaction of the was monitored by TLC. After completion of reaction, the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 X 20 mL), washed with brine. The organic layer was dried over sodium sulphate and concentrated under vacuum to get crude material; which was purified by combi-flash by using 80% Ethyl acetate in Hexane as mobile phase to give desired product (5-(benzyloxy)-2,4-difluorophenyl)(6-(3-methyl-1-(*o*-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone (Int-4) 0.25 gm (Yield: 52.08%); LCMS: 514.05 *m/z* [*M*⁺].

Step-4: Synthesis of (2,4-difluoro-5-hydroxyphenyl)(6-(3-methyl-1-(*o*-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone (Compound-00126).



To a stirred solution (5-(benzyloxy)-2,4-difluorophenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone (Int-4) (0.20 gm, 0.400 mmol, 1.0 eq.) was dissolved in Methanol (10 mL). 10% Pd/C (with 50% moisture) 0.050gm was added at Room Temperature and Reaction mixture was allowed to stir for 2 hr. under Hydrogen atmosphere. Reaction was monitored by TLC. After completion of the reaction, Reaction mixture was filtered through celite bed, washed with Methanol (50 mL) and concentrated to get crude compound, which was purified by column chromatography using 60-120 mesh size silica gel and 80% Ethyl acetate in Hexane as mobile phase to give the desired product (2,4-difluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl) methanone (PSY-05-00126) as a white solid, 0.080 gm, (Yield: 48.78%); LCMS: 424.4 m/z $[M+1]^+$ ^1H NMR (400 MHz, DMSO- d_6) δ 10.30 (s, 1H), 7.38 (t, $J = 7.7$ Hz, 3H), 7.33 – 7.23 (m, 1H), 7.15 (t, $J = 6.7$ Hz, 1H), 7.02 – 6.93 (m, 1H), 6.14 (d, $J = 18.3$ Hz, 1H), 3.97 (d, $J = 3.4$ Hz, 2H), 3.91 (s, 2H), 2.98 (dt, $J = 18.5, 8.8$ Hz, 1H), 2.45 (s, 1H), 2.34 – 2.22 (m, 1H), 2.19 (t, $J = 11.7$ Hz, 3H), 1.93 (s, 3H).

Example 5: Synthesis of 4-hydroxy-2-(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptane-2-carbonyl)benzonitrile [Compound 128]



Step-1: Methyl 2-bromo-5-hydroxybenzoate (2):

[000230] To stirred solution of 2-bromo-5-hydroxybenzoic acid (0.5g, 2.325 mmol), in MeOH, Con. H₂SO₄ (2 mL) was added dropwise. The reaction mixture was heated to 90 °C and stirred at same temperature for 2h. After completed reaction RM was concentrated, diluted with ethylacetate, washed with aq. NaHCO₃ solution (3x15 mL), dried over Na₂SO₄, and evaporated. The crude material was purified by combiflash using 30 % ethylacetate in hexane to give methyl 2-bromo-5-hydroxybenzoate (300 mg, 56%) as colorless liquid. LCMS: 229.9 *m/z* [M+H]⁺.

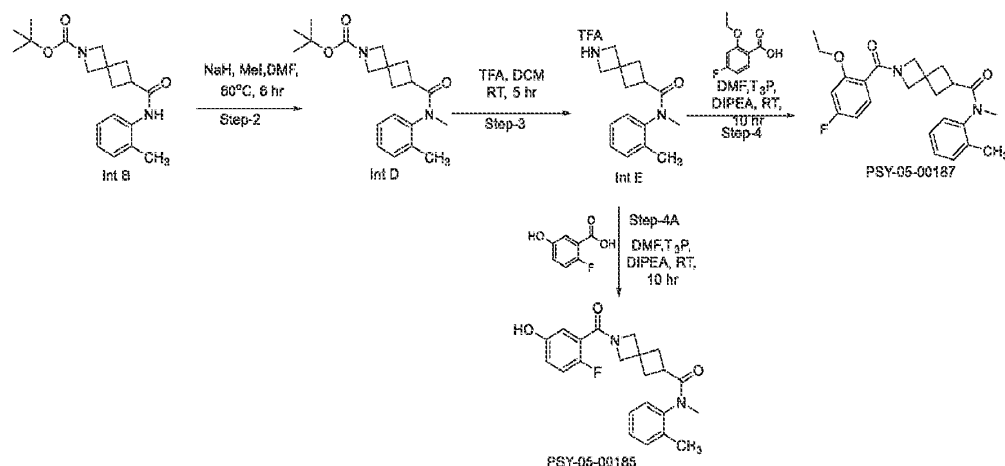
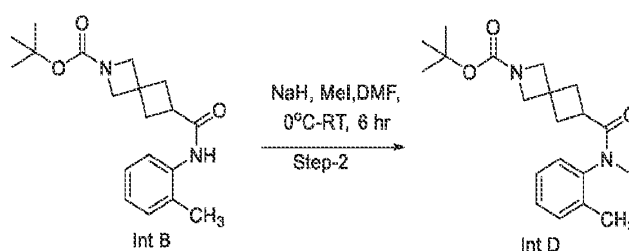
Step-2: Methyl 2-cyano-5-hydroxybenzoate (3):

[000231] To stirred solution of methyl 2-bromo-5-hydroxybenzoate (0.3 g, 1.31 mmol) in DMA, was added CuCN (0.174g, 1.89 mmol) and stirred at 135 °C for 2h. The reaction was quenched by the addition of cold water (50 mL) and extracted with ethyl acetate (3x25 mL). The organic layer was concentrated and purified by combiflash using 30 % ethylacetate in hexane to give methyl 2-cyano-5-hydroxybenzoate (140 mg, 61%) as a white solid. ¹H NMR (400 MHz, CD₃Cl) δ 7.71 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 2 Hz, 1H), 7.13-7.10 (m, 1H), 6.31 (s, 1H), 4.01 (s, 3H).

Step-3: (4-hydroxy-2-(6-(3-methyl-1-(*o*-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptane-2-carbonyl)benzonitrile) (Compound-00128):

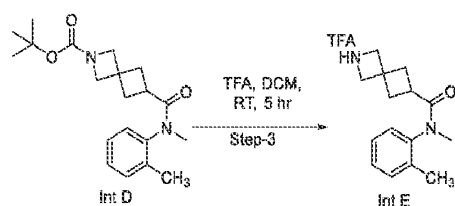
[000232] To stirred solution of 6-(3-methyl-1-(*o*-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptane 2,2,2-trifluoroacetate (0.120 g, 0.449 mmol) and methyl 2-cyano-5-hydroxybenzoate (0.0795 g, 0.449 mmol) in THF at -78 °C, was added LiHMDS (1.35 mL, 1.347 mmol; 1 M solution in THF) for 15 min then it stirred at rt for 3h. The reaction mass was quenched by the addition of water (50 mL) and extracted by ethyl acetate (3x30 mL). The organic layer was concentrated under reduced pressure and purified by combiflash using 5 % MeOH in DCM to give (4-hydroxy-2-(6-(3-methyl-1-(*o*-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptane-2-carbonyl)benzonitrile) (60 mg 21%) as a white solid. LCMS: 413.4 *m/z* [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.68 (t, *J* = 7.8 Hz, 1H), 7.43 – 7.26 (m, 3H), 7.15 (dd, *J* = 7.8, 3.9 Hz, 1H), 6.98 – 6.85 (m, 2H), 6.13 (d, *J* = 19.6 Hz, 1H), 3.99 (dd, *J* = 24.0, 13.9 Hz, 4H), 2.99 (dt, *J* = 22.2, 8.4 Hz, 1H), 2.39 – 2.28 (m, 2H), 2.23 (dd, *J* = 12.7, 9.0 Hz, 2H), 2.17 (d, *J* = 8.5 Hz, 3H), 1.92 (s, 3H).

Example 6: Synthesis of 2-(2-Fluoro-5-hydroxybenzoyl)-N-Methyl-N-(o-tolyl)-2-azaspiro [3.3] heptane-6-carboxamide [Compound 185] and 2-(2-Ethoxy-4-fluorobenzoyl)-N-Methyl-N-(o-tolyl)-2-azaspiro [3.3] heptane-6-carboxamide [Compound 187]

Reaction Scheme:Step-1: - Synthesis of Tert-butyl 6-(methyl(o-tolyl) carbamoyl)-2-azaspiro [3.3] heptane-2-carboxylate (Int-D)

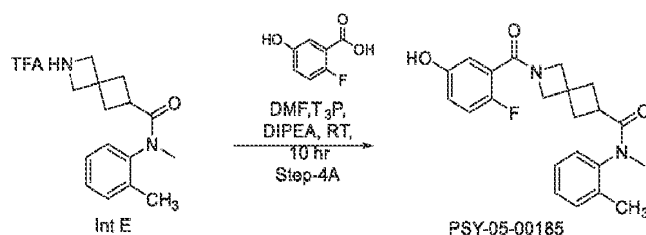
[000233] Tert-butyl 6-(o-tolylcarbamoyl)-2-azaspiro [3.3] heptane-2-carboxylate 0.5 g (1.5151 mmol, 1 eq.) dissolved in Dimethylformamide 5 mL. Sodium hydride 0.08 g (1.9696 mmol, 1.3 eq.) was added, stirred reaction mixture at room temperature for 15 min followed by Methyl Iodide 0.25 g (1.818 mmol, 1.2 eq.) added stirred reaction mixture at 60°C for 6 hr. Reaction monitored on TLC. After completion of the reaction, the reaction mixture diluted with water. Product extracted with Ethyl Acetate (3*25 mL), combined organics concentrated to obtain crude product. Crude purified by column chromatography using Ethyl acetate: Hexanes as solvent system to get desired product. Tert-butyl 6-(methyl(o-tolyl) carbamoyl)-2-azaspiro [3.3] heptane-2-carboxylate. 0.51 g (Solid) (yield-98%) m/z 345.4 [M+1]⁺. NMR (400 MHz, Chloroform-d) δ 7.35-7.20 (m, 3H), 7.05 (d, J = 7.6 Hz, 1H), 3.91 – 3.76 (m, 4H), 3.20 (s, 3H), 2.70 (q, J = 8.3 Hz, 1H), 2.57 – 2.47 (m, 1H), 2.49 – 2.39 (m, 1H), 2.22 (s, 3H), 2.05 – 1.95 (m, 2H), 1.43 (s, 9H).

Step-2: - Synthesis of N-Methyl-N-(o-tolyl)-2-azaspiro [3.3] heptane-6-carboxamide (Int-E)



[000234] Tert-butyl 6-(methyl(o-tolyl) carbamoyl)-2-azaspiro [3.3] heptane-2-carboxylate 0.5 g was taken in Dichloromethane 50mL, cooled it to 0oC, Trifluoroacetic acid 0.8 mL was added, stirred reaction mixture at room temperature for 5 hr. Reaction was monitored on TLC. After completion of the reaction it was concentrated completed was triturated with diethyl ether to get desired product as N-Methyl-N-(o-tolyl)-2-azaspiro [3.3] heptane-6-carboxamide 0.5 g (Solid) (yield-92%) m/z 245.4 [M+1] +.

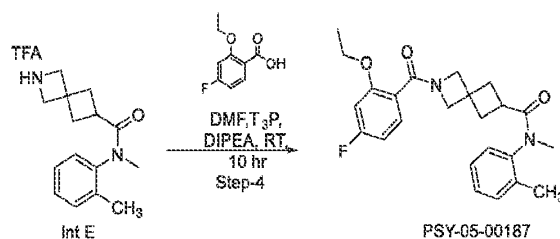
Step-3: - Synthesis of 2-(2-Fluoro-5-hydroxybenzoyl)-N-Methyl-N-(o-tolyl)-2-azaspiro [3.3] heptane-6-carboxamide (Compound-00185)



[000235] To a solution of 2-Fluoro-4-hydroxy benzoic acid 0.1 g (0.676 mmol, 1.1 eq.) in Dimethylformamide 2 mL. TFA salt of N-Methyl-N-(o-tolyl)-2-azaspiro [3.3] heptane-6-carboxamide 0.15 g (0.6147 mmol, 1 eq.) added and stir for 10min. DIPEA 0.4 mL (2.459 mmol, 4 eq.), stirred reaction mixture for 10 min. T3P 0.4 mL (0.7377 mmol, 1.2 eq.) was added and stir, reaction mixture at room temperature for 10 hr. Reaction monitored on TLC. After completion of the reaction, it diluted with water. Product extracted with Ethyl acetate (3*15 mL), combined organics washed with water and dried over anhydrous Sodium sulphate. Organic layer concentrated to get crude compound. Crude gum, which purified by column chromatography using Ethyl acetate: Hexanes as solvent system. Desired product obtained as 2-(2-Fluoro-5-hydroxybenzoyl)-N-Methyl-N-(o-tolyl)-2-azaspiro [3.3] heptane-6-carboxamide 0.05 g (Solid). (yield-22.22%) m/z 383.35 [M+1]+ 1H NMR (400 MHz, DMSO-d6) δ 9.62 (d, J = 13.5 Hz, 1H), 7.40 – 7.23 (m, 3H), 7.16 (s, 1H), 7.17 – 6.98 (m, 1H), 6.83 (ddt, J = 12.9, 8.7, 3.7 Hz, 1H), 6.78

– 6.69 (m, 1H), 3.97 – 3.80 (m, 4H), 3.05 (d, J = 6.1 Hz, 3H), 2.62 (td, J = 15.6, 7.7 Hz, 1H), 2.39 – 2.23 (m, 2H), 2.22 – 2.05 (m, 3H), 2.00 – 1.90 (m, 2H).

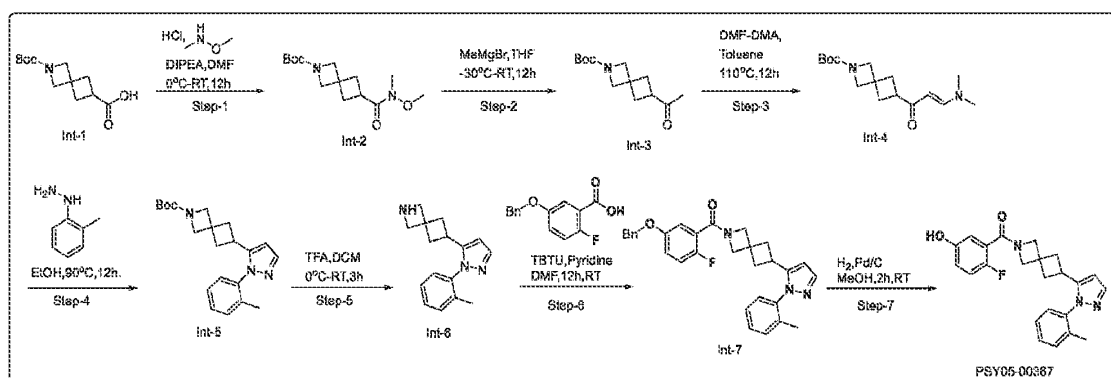
Step-4: - Synthesis of 2-(2-Ethoxy-4-fluorobenzoyl)-N-Methyl-N-(o-tolyl)-2-azaspiro [3.3] heptane-6-carboxamide (Compound-00187)



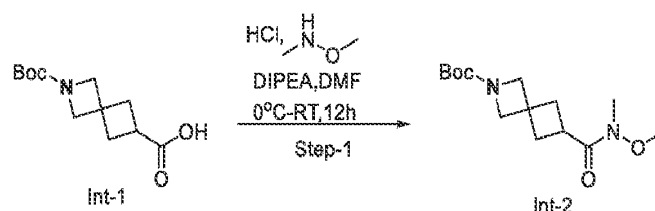
[000236] To a solution of 2-Ethoxy-4-fluorobenzoic acid 0.15 g (0.676 mmol, 1.1 eq.) in Dimethyl formamide 2 mL. TFA salt of N-Methyl-N-(o-tolyl)-2-azaspiro [3.3] heptane-6-carboxamide 0.15 g (0.6147 mmol, 1 eq.) was added followed by Di-isopropyl ethyl amine 0.4 mL (2.459 mmol, 4 eq.), stirred reaction mixture for 10 min. T3P 0.4 mL (0.7377 mmol, 1.2 eq.) was added, stirred reaction mixture at room temperature for 10 hr. Reaction was monitored on TLC. Reaction mixture diluted with water and extracted with Ethyl acetate (3*15 mL). Organic layer combined, concentrated to obtained crude. Crude compound as gum, which purified by column chromatography using EtOAc: Hexanes as solvent system to get desired product. 2-(2-Ethoxy-4-fluorobenzoyl)-N-Methyl-N-(o-tolyl)-2-azaspiro [3.3] heptane-6-carboxamide 0.05 g (Solid) (yield-21.22%) m/z 411.4 [M+1]⁺ 1H NMR (400 MHz, Methanol-d₄) δ 7.42-7.22 (dq, J = 27.9, 7.8 Hz, 4H), 7.14 (d, J = 7.5 Hz, 1H), 6.91 – 6.66 (m, 2H), 4.18 – 3.89 (m, 5H), 3.87 (s, 1H), 3.17 (d, J = 5.4 Hz, 3H), 2.79 (dp, J = 24.3, 8.0 Hz, 1H), 2.43 (ddt, J = 27.5, 19.5, 9.9 Hz, 2H), 2.20 (s, 3H), 2.17 – 1.98 (m, 2H), 1.41 (dt, J = 18.6, 7.0 Hz, 3H).

Example 7: Synthesis of (2-fluoro-5-hydroxyphenyl)(6-(1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro [3.3] heptan-2-yl) methanone [Compound 367]

Synthetic scheme:

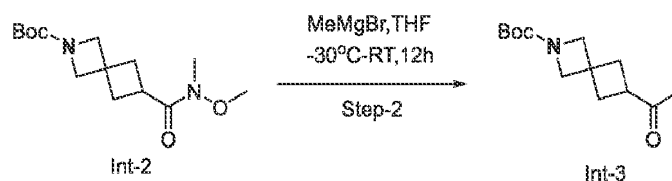


Step-1: Synthesis of tert-butyl 6-(methoxy (methyl) carbamoyl) -2-azaspiro [3.3] heptane-2-carboxylate (Int-2).



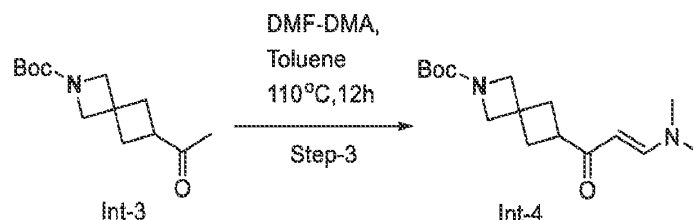
[000237] To a stirred solution of 2-(tert-butoxycarbonyl)-2-azaspiro[3.3]heptane-6-carboxylic acid (2.0 gm, 8.298 mmol, 1.0 eq.) in N,N-Dimethyl formamide (20 mL) were added HATU (3.15 gm, 8.29 mmol, 1.5 eq.), DIPEA (3.21 gm, 24.89 mmol, 3.0 eq.) followed by addition of N,O-Dimethylhydroxylamine Hydrochloride (1.00 gm, 10.37 mmol, 1.25 eq.) at 0°C and allowed to stirred the reaction at room temperature for 12 hr; the progress of the reaction of the was monitored by TLC. After completion of reaction, the reaction mixture was diluted with water (25 mL) and extracted with ethyl acetate (3 X 30 mL), washed with brine. The organic layer was dried over sodium sulphate and concentrated under vacuum to get crude material; which was purified by combi-flash by using 100% Ethyl acetate as mobile phase to give desired product tert-butyl 6-(methoxy(methyl)carbamoyl)-2-azaspiro[3.3]heptane-2-carboxylate (Int-2) 1.50 gm (Yield: 63.82%), ¹H NMR (400 MHz, DMSO-d₆) δ 3.89 (s, 2H), 3.73 (s, 2H), 3.62 (s, 3H), 3.08 (s, 3H), 2.30 (dt, J = 8.1, 2.1 Hz, 4H), 1.37 (s, 9H).

Step-2: Synthesis of tert-butyl 6-acetyl-2-azaspiro [3.3] heptane-2-carboxylate (Int-3)



[000238] To a stirred solution of tert-butyl 6-(methoxy (methyl) carbamoyl)-2-azaspiro [3.3] heptane-2-carboxylate (Int-2) (1.7gm, 5.98 mmol, 1.0 eq.) in THF was added Methyl magnesium bromide (3M in THF) (5.98 mL, 17.95 mmol, 3.0 eq.) under inert atmosphere at -30°C . The reaction mixture was stirred at Room temperature for next 12 hr. The progress of the reaction was monitored by TLC; after completion of reaction, the reaction mixture was cooled to 0°C and quenched with saturated ammonium chloride solution (10mL) further diluted with water (30mL) and extracted with ethyl acetate (3 X 30 mL), washed with brine. The organic layer was dried over sodium sulphate and concentrated under vacuum to get crude material; which was purified by combi-flash by using 80% Ethyl acetate in Hexane as mobile phase to give desired product tert-butyl 6-acetyl-2-azaspiro [3.3] heptane-2-carboxylate (Int-3) 1.30 gm (Yield: 90.90%); ^1H NMR (400 MHz, Chloroform- d) δ 3.98 (s, 2H), 3.85 (s, 2H), 3.16 (p, $J = 8.3$ Hz, 1H), 2.46 – 2.32 (m, 4H), 2.14 (s, 3H), 1.47 (s, 9H).

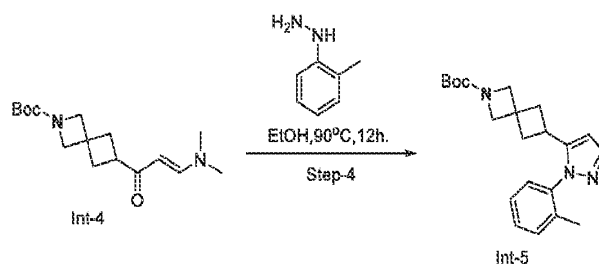
Step-3: Synthesis of tert-butyl (E)-6-(3-(dimethylamino) acryloyl)-2-azaspiro [3.3] heptane-2-carboxylate (Int-4).



[000239] To a stirred solution of tert-butyl 6-acetyl-2-azaspiro[3.3]heptane-2-carboxylate (Int-3) (0.050 gm, 0.209 mmol, 1.0 eq.) in Toluene (1 mL) was added DMF-DMA (0.074 gm, 0.627 mmol, 3.0 eq.) and allowed to stirred the reaction at 100°C for 12 hr; the progress of the reaction of the was monitored by TLC. After completion of reaction, the reaction mixture was diluted with water (3 mL) and extracted with ethyl acetate (3 X 5 mL), washed with brine. The organic layer was dried over sodium sulphate and concentrated under vacuum to get crude material; which was purified by combi-flash by using 90% Ethyl acetate in Hexane as mobile phase to give desired

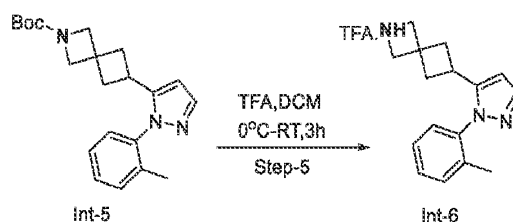
product tert-butyl (E)-6-(3 (dimethylamino) acryloyl) -2-azaspiro [3.3] heptane-2-carboxylate (Int-4) 0.040 gm (Yield: 65.04%); LCMS: 295.3m/z [M+1] +

Step-4: Synthesis of tert-butyl 6-(1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro [3.3] heptane-2-carboxylate (Int-5)



[000240] To a stirred solution of tert-butyl (E)-6-(3 (dimethylamino) acryloyl)-2-azaspiro [3.3] heptane-2-carboxylate (Int-4) (0.30 gm, 0.020 mmol, 1.0 eq.) in Ethanol (9 mL) was added o-tolylhydrazine (0.177 gm, 1.122 mmol, 1.1 eq.) and allowed to stirred the reaction at 90°C for 12 hr; the progress of the reaction of the was monitored by TLC. After completion of reaction, the reaction mixture was evaporated under vacuum to get crude compound which was absorbed on silica gel and purified by combi-flash by using 100% Ethyl acetate as mobile phase to give desired product tert-butyl 6-(1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptane-2-carboxylate (Int-5) 0.340 gm (Yield: 94.44%); LCMS: 354.3m/z [M+1]+

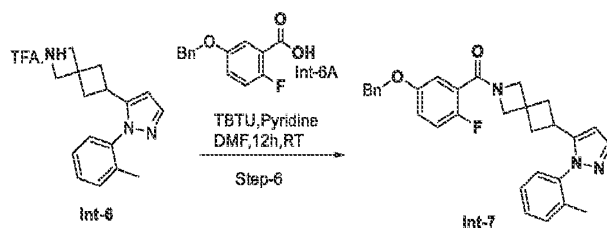
Step-5: Synthesis of 6-(1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro [3.3] heptane (Int-6)



[000241] To a stirred solution of tert-butyl 6-(1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro [3.3] heptane-2-carboxylate (Int-5) (0.30 gm, 0.84mmol, 1.0 eq.) in Dichloromethane (10 mL) was added Trifluoroacetic acid (1.0 mL) at 0°C and allowed to stirred the reaction at Room temperature for 3 hr; the progress of the reaction of the was monitored by TLC. After completion of reaction, the reaction mixture was evaporated under vacuum and triturated with pentane to

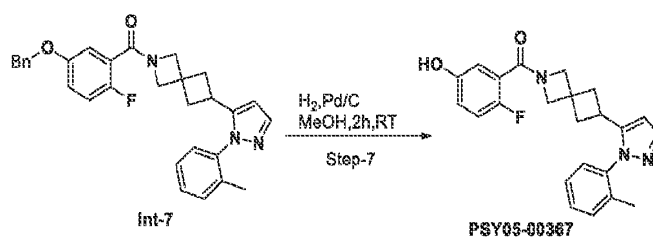
afford crude compound 6-(1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptane (Int-6) 0.30 gm (Yield: quantitative); LCMS: 254.2m/z [M+1]⁺

Step-6: Synthesis of (5-(benzyloxy)-2-fluorophenyl) (6-(1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro [3.3] heptan-2-yl) methanone (Int-7)



[000242] To a stirred solution of 5-(benzyloxy)-2-fluorobenzoic acid 6-(1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro [3.3] heptane (Int-6A) (0.25 gm, 1.016 mmol, 1.0 eq.) in N,N-Dimethyl formamide (10 mL) were added TBTU (0.58 gm, 1.52 mmol, 1.5 eq.) Pyridine (0.24 gm, 3.04 mmol, 3.0 eq.) followed by addition of 6-(1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro [3.3] heptane (Int-6) (0.30 gm, 1.21 mmol, 1.2 eq.) at 0°C and allowed to stirred the reaction at room temperature for 12 hr; the progress of the reaction of the was monitored by TLC. After completion of reaction, the reaction mixture was diluted with water (15 mL) and extracted with ethyl acetate (3 X 20 mL), washed with brine. The organic layer was dried over sodium sulphate and concentrated under vacuum to get crude material; which was purified by combi-flash by using 90% Ethyl acetate in Hexane as mobile phase to give desired product (5-(benzyloxy)-2-fluorophenyl)(6-(1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone (Int-7), 0.250 gm (Yield: 51.22%); LCMS: 482.3m/z [M+1]⁺

Step-7: Synthesis of (2-fluoro-5-hydroxyphenyl) (6-(1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro [3.3] heptan-2-yl) methanone (Compound-00367)

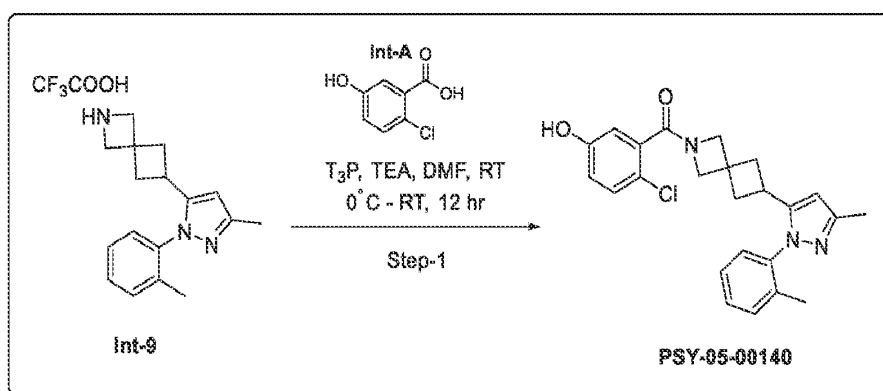


[000243] To a stirred solution of (5-(benzyloxy)-2-fluorophenyl) (6-(1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro [3.3] heptan-2-yl) methanone (Int-7) (0.20 gm, 0.415 mmol, 1.0 eq.) was dissolved

in Methanol (10 mL). 10% Pd/C (with 50% moisture) 0.050gm was added at Room Temperature and Reaction mixture was allowed to stir for 2 hr. under Hydrogen atmosphere. Reaction was monitored by TLC. After completion of the reaction, Reaction mixture was filtered through celite bed, washed with Methanol (50 mL) and concentrated to get crude compound, which was purified by column chromatography using 60-120 mesh size silica gel and 80% Ethyl acetate in Hexane as mobile phase to give the desired product (2-fluoro-5-hydroxyphenyl)(6-(1-(*o*-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone (PSY-05-00367) as a white solid, 0.120 gm, (Yield: 74.07%); LCMS: 392.1 m/z [M+]⁺ 1H NMR (400 MHz, DMSO-d₆) δ 9.63 (dd, J = 8.3, 2.5 Hz, 1H), 7.56 (d, J = 9.5 Hz, 1H), 7.41 (t, J = 8.5 Hz, 2H), 7.32 (d, J = 8.7 Hz, 1H), 7.19 (t, J = 7.4 Hz, 1H), 7.05 (tt, J = 9.2, 5.3 Hz, 1H), 6.83 (s, 1H), 6.74 (dd, J = 5.5, 2.7 Hz, 1H), 6.36 (d, J = 18.6 Hz, 1H), 3.94 (dd, J = 25.2, 10.5 Hz, 3H), 3.05 (dt, J = 18.8, 8.4 Hz, 1H), 2.34 (q, J = 12.2, 11.5 Hz, 2H), 2.24 (q, J = 10.5, 9.9 Hz, 2H), 1.91 (d, J = 2.4 Hz, 3H).

Example 8: Synthesis of [(2-chloro-5-hydroxyphenyl) (6-(3-methyl-1-(*o*-tolyl)-1H-pyrazol-5-yl)-2-azaspiro [3.3] heptan-2-yl) methanone] [Compound 140]

Synthetic scheme:



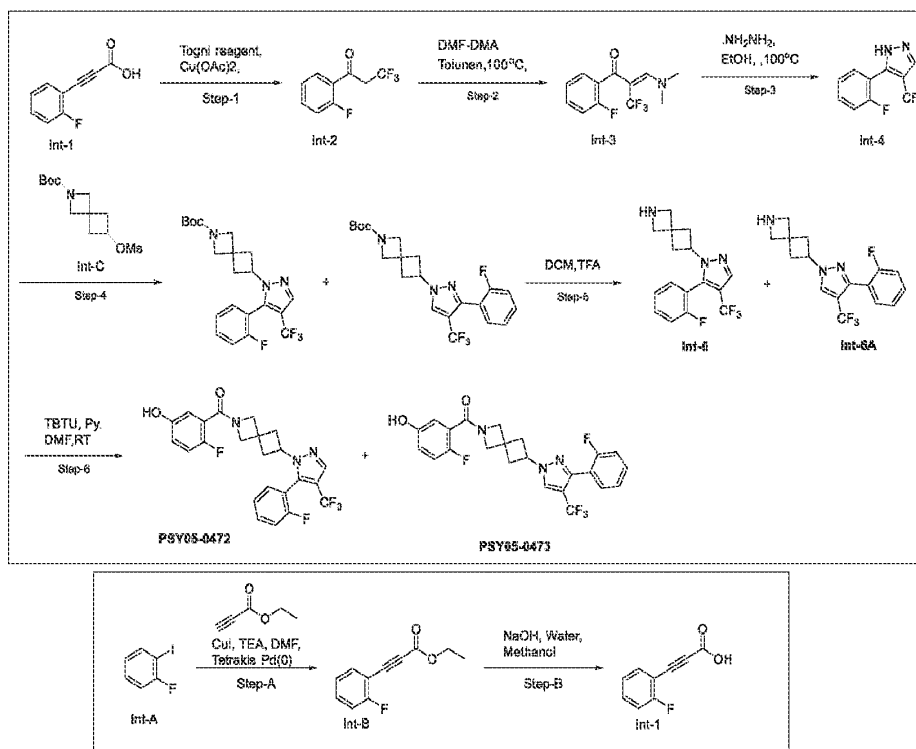
Step-1: Synthesis of [(2-chloro-5-hydroxyphenyl) (6-(3-methyl-1-(*o*-tolyl)-1H-pyrazol-5-yl)-2-azaspiro [3.3] heptan-2-yl) methanone] [Compound-00140]

[000244] To a stirred solution of 6-(3-methyl-1-(*o*-tolyl)-1H-pyrazol-5-yl)-2-azaspiro [3.3] hept-5-ene 2,2,2-trifluoroacetate (0.100 gm, 0.2624 mmol) in DMF (5.0 mL) were added 2-

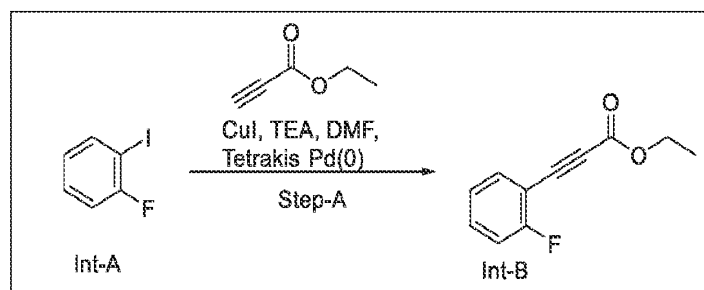
chloro-5-hydroxybenzoic acid (0.054 gm, 0.314 mmol), Triethylamine (0.106 gm, 1.049 mmol) and Propanephosphonic acid anhydride [T3P, 50 wt. % in ethyl acetate] (0.125 gm, 0.393 mmol) at 0°C. The resulting reaction mixture was stirred at room temperature for next 12 hr. The progress of the reaction was monitored by TLC; After completion of reaction, the reaction mixture was diluted with water (10 mL) and extracted with Ethyl acetate (3*50mL), The organic layer was washed with brine, dried over sodium sulphate and concentrated under vacuum to get crude material; which was purified by Prep HPLC using 0.1% Formic acid in water-100% Acetonitrile as mobile phase to give desired compound as [(2-chloro-5-hydroxyphenyl) (6-(3-methyl-1-(*o*-tolyl)-1*H*-pyrazol-5-yl)-2-azaspiro [3.3] heptan-2-yl) methanone] (PSY-05-0140) 0.028 gm (Yield: 26%) m/z 422.6 $[M+1]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 9.95 (s, 1H), 7.43 – 7.1 (m, 4H), 7.15 (t, $J = 7.7$ Hz, 1H), 6.80 (t, 1H), 6.67 (d, $J = 2.8$ Hz, 1H), 6.16-6.10 (s, 1H), 3.98 (s, 1H), 3.92 (s, 1H), 3.82 (s, 1H), 3.76 (s, 1H), 2.99 (dt, $J = 20.8, 8.4$ Hz, 1H), 2.32 – 2.19 (m, 2H), 2.17 (d, $J = 10.7$ Hz, 2H), 2.09 (s, 3H), 1.93 (d, $J = 2.2$ Hz, 3H).

*Example 9: Synthesis of (2-fluoro-5-hydroxyphenyl)(6-(5-(2-fluorophenyl)-4-(trifluoromethyl)-1*H*-pyrazol-1-yl)-2-azaspiro[3.3]heptan-2-yl)methanone [Compound 472] and (2-fluoro-5-hydroxyphenyl)(6-(3-(2-fluorophenyl)-4-(trifluoromethyl)-1*H*-pyrazol-1-yl)-2-azaspiro[3.3]heptan-2-yl)methanone [Compound 473].*

Synthetic scheme:



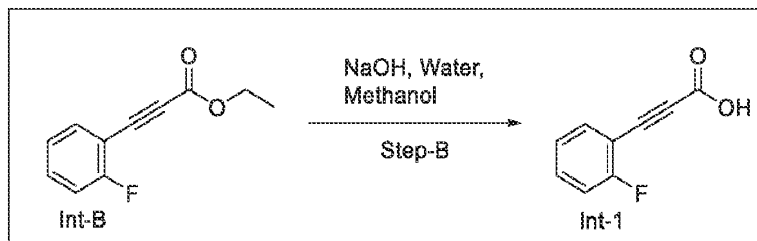
Step-A: ethyl 3-(2-fluorophenyl) propiolate (Int-B).



[000245] A mixture of the 1-fluoro-2-iodo-benzene (**Int-A**) (11.3 g, 56.06 mmol, 1.1 eq.), *Tetrakis* (Triphenyl phosphine) palladium (0) (5.8 g, 5.096 mmol, 0.1 eq.), and CuI (copper (I) iodide) (1.0 g, 5.096 mmol, 0.1 eq.) in **Triethylamine** (50 ml) was purged with nitrogen and treated with the **ethyl propiolate** (5.0 g, 50.96 mmol, 1.0 eq.). The resultant mixture was stirred at room temperature overnight. The reaction mixture was poured into sat aq. NaHCO₃ Solⁿ and extracted with ethyl acetate. The organic layer was washed with brine, dried sodium sulphate,

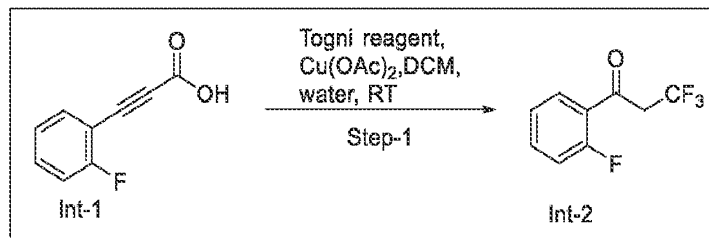
decanted, concentrated, and purified by flash chromatography (0-20% ethyl acetate in n-hexane) to get desired product ethyl 3-(2-fluoro-phenyl)propiolate (**Int-B**) as a clear oil. (2.0 g, 20.44 %).

Step-B: 3-(2-fluoro-phenyl) propiolic acid (Int-1).



[000246] To a solution of the ethyl 3-(2-fluoro-phenyl) propiolate (**Int-B**) (2.0 g, 10.42 mmol, 1.0 eq.) in Methanol (5 mL) and H₂O (15 mL) was added NaOH (0.916 g, 22.91 mmol, 2.2 eq.). The mixture stirred at room temperature for 16 h, then concentrated in vacuum. The crude was diluted with water (100 mL) and acidified with an aq. solution of 2M HCl. This aq mixture was extracted with ethyl acetate (2 x 200 mL) and the combined organic extracts were washed with brine (400 mL), dried over sodium sulphate and concentrated in vacuum to provide to product of 3-(2-fluoro-phenyl) propiolic acid (**Int-1**) as solid. (1.6 g, 93.63 %).

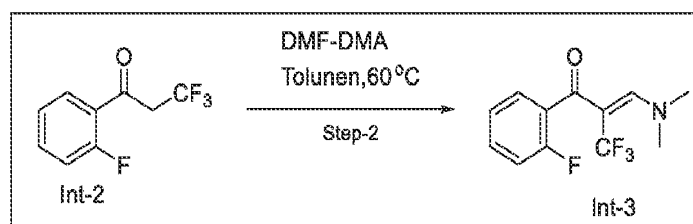
Step-1: 3,3,3-trifluoro-1-(2-fluoro-phenyl)propan-1-one (Int-2).



[000247] A Sealed test tube with a magnetic stirring bar was charged with 3-(2-fluoro-phenyl) propiolic acid (1.6 g, 9.816 mmol, 1.0 eq.) Togni-(II) (6.4g, 19.632 mmol, 2.0 eq.) Cu(OAc)₂·H₂O (3.56g, 19.632mmol, 2.0eq), TMEDA (3.6mL, 24.54 mmol, 2.5eq.), followed by dichloromethane (16 mL) and H₂O (24 mL). The reaction mixture was stirred at room temperature. After stirring for 24 h, the reaction mixture was extracted with dichloromethane (15 mL×3), dried over sodium sulphate, filtered and concentrated. The residue was purified with silica gel chromatography to

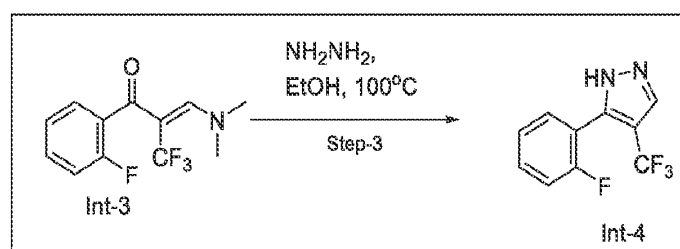
provide pure product of 3,3,3-trifluoro-1-(2-fluoro-phenyl) propan-1-one (**Int-2**) as solid (0.200 g, 9.95 %).

Step-2: (Z)-3-(dimethylamino)-1-(2-fluorophenyl)-2-(trifluoromethyl) prop-2-en-1-one (Int-3).



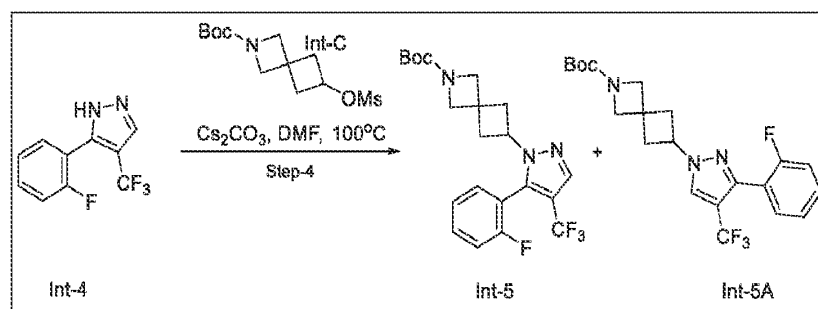
[000248] To a stirred solution of 3,3,3-trifluoro-1-(2-fluoro-phenyl)propan-1-one (Int-2) (1.5 g, 7.28 mmol, 1.0 eq.) in Toluene (10 mL) was added N,N-Dimethylformamide dimethyl-acetal (2.6 g, 21.84 mmol, 3.0 eq.) the reaction mass was heated at 60 °C for 16h. After completion of reaction as monitored by TLC, the reaction mixture was poured in ice cold water (100mL) and extracted with ethyl acetate (50 mL*3). The organic layer was washed with brine (100 mL), dried over sodium sulphate and concentrated under reduce pressure to get residue. The residue was purified by combiflash using 15-20% ethyl acetate in n-hexane as eluent to get (Z)-3-(dimethylamino)-1-(2-fluorophenyl)-2-(trifluoromethyl) prop-2-en-1-one (**Int-3**) (1.5 g, 78.91 %).

Step-3: 5-(2-fluorophenyl)-4-(trifluoromethyl)-1H-pyrazole (Int-4).



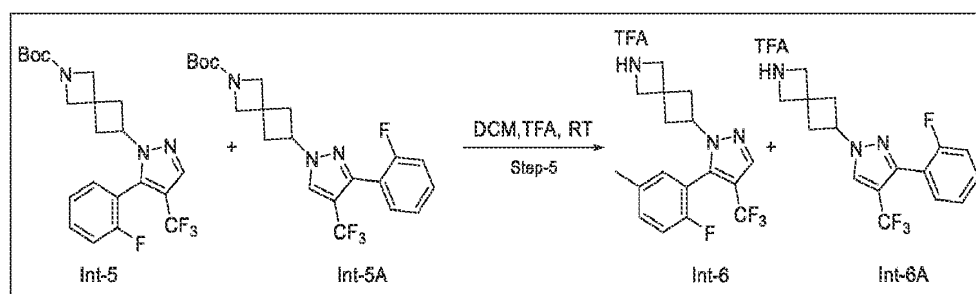
[000249] To a stirred solution of (Z)-3-(dimethylamino)-1-(2-fluorophenyl)-2-(trifluoromethyl)prop-2-en-1-one (1.5 g, 6.95 mmol, 1.0 eq.) in isopropyl alcohol (10 mL) was added hydrazine hydrate (0.38 g, 7.65 mmol, 1.1 eq.) the reaction mass was heated at 80 °C for 16hr. After completion of reaction as monitored by TLC, the reaction mixture was concentrated to get residue. The residue was purified by combiflash using 15-20% ethyl acetate in n-hexane as eluent to get 5-(2-fluorophenyl)-4-(trifluoromethyl)-1H-pyrazole (**Int-4**) (0.90 g, 68.01%).

Step-4: Tert-butyl 6-(5-(2-fluoro-phenyl)-4-(trifluoromethyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptane-2-carboxylate (**Int-5**) and
tert-butyl 6-(3-(2-fluoro-phenyl)-4-(trifluoromethyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptane-2-carboxylate (**Int-5A**)



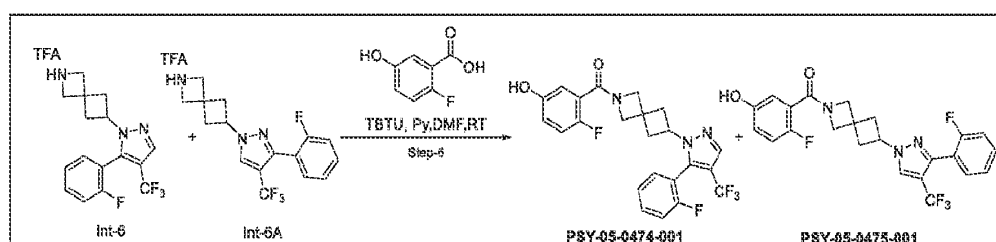
[000250] To a solution of 5-(2-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-pyrazole (**Int-4**) (0.900 g, 3.9121 mmol, 1.0 eq.) in N,N-Dimethylformamide (10 mL), tert-butyl 6-((methylsulfonyl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (**Int-C**) (1.37g, 4.694 mmol, 1.2 eq.) and cesium carbonate (2.54 g, 7.824 mmol, 2.0 eq.) were added, and the reaction mixture was heated at 100°C for 16hr. After cooling to room temperature, the reaction mixture was poured into water (20 mL), and the solution was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel with ethyl acetate and n-hexane to get two regio isomers of tert-butyl 6-(5-(2-fluoro-phenyl)-4-(trifluoromethyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate (**Int-5**) and tert-butyl 6-(3-(2-fluoro-phenyl)-4-(trifluoromethyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate (**Int-5A**) (1.0 g, 60.11%).

Step-5: 6-(5-(2-fluoro-phenyl)-4-(trifluoromethyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptane (**Int-6**) and
6-(3-(2-fluoro-5phenyl)-4-(trifluoromethyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptane (**Int-6A**).



[000251] To a stirred solution of tert-butyl 6-(5-(2-fluorophenyl)-4-(trifluoromethyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptane-2-carboxylate (Int-5) and tert-butyl 6-(3-(2-fluorophenyl)-4-(trifluoromethyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate (Int-5A) (1.0 g, 0.6605 mmol, 1.0 eq.) in dichloromethane (10 ml) was added Trifluoroacetic acid (2.5 mL, 2.5 v) at 0 °C. The reaction was stirred at room temperature for 16 hr. After completion of reaction as monitored by TLC, the reaction mixture was concentrated and triturated with mixture of diethyl ether and hexane (1:1, 10 ml*3) to get two regio-isomers. 6-(5-(5-fluorophenyl)-3-methyl-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptane (**Int-6**) and 6-(3-(5-fluorophenyl)-5-methyl-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptane (**Int-6A**) (1.5 g (TFA salt).

Step-6: 2-fluoro-5-hydroxyphenyl(6-(5-(2-fluorophenyl)-4-(trifluoromethyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptan-2-yl)methanone (PSY-05-00474-001) and 2-fluoro-5-hydroxyphenyl(6-(3-(2-fluorophenyl)-4-(trifluoromethyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptan-2-yl)methanone (PSY-05-00475-001).



[000252] To a stirred solution of 6-(5-(5-fluorophenyl)-3-methyl-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane (INT-5) & 6-(3-(5-fluorophenyl)-5-methyl-1H-pyrazol-1-yl)-2-

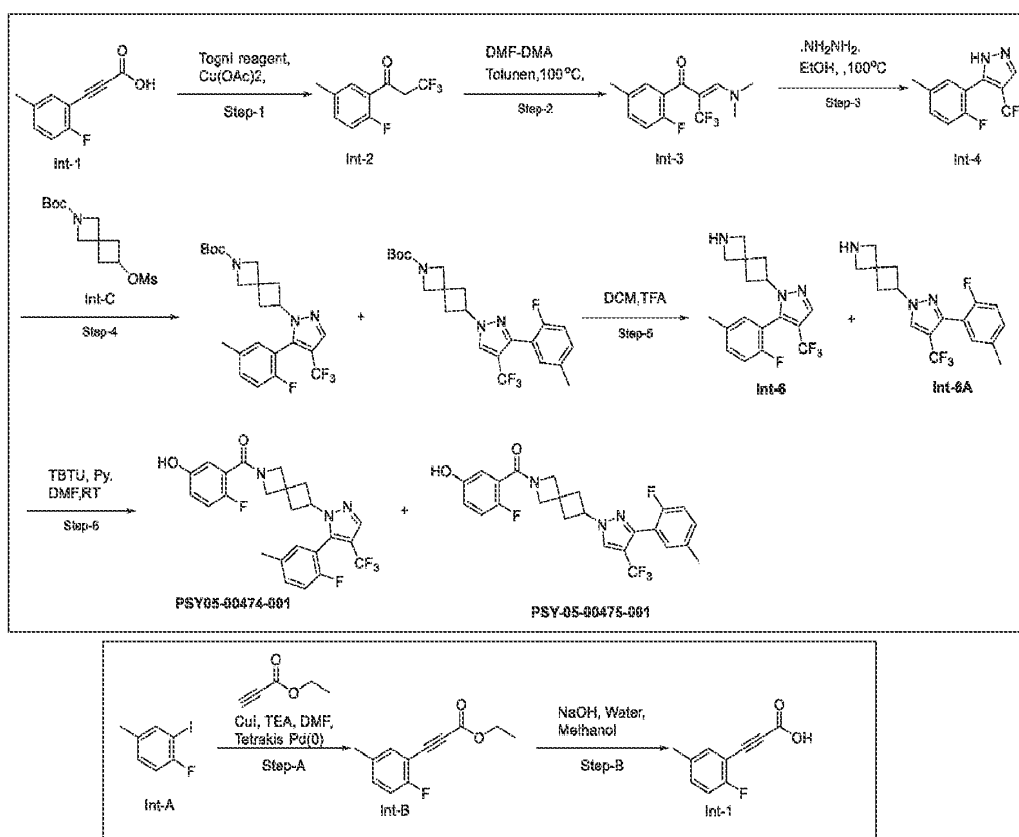
azaspiro[3.3]heptane) (Int-5A) (0.500 g, 1.537 mmol, 1.0 eq.) in N,N-Dimethylformamide (5.0 mL) were added, pyridine (1.07 g, 15.37 mmol, 10.0 eq.), TBTU (0.740 g, 0.2306 mmol, 1.5 eq.) at 0 °C. Reaction to stirred for 15 min. then to add a 2-fluoro-5-hydroxybenzoic acid (0.359 g, 2.306 mmol, 1.5 eq.) at 0 °C. The resulting reaction mixture was stirred at room temperature for 16hr. After completion of reaction as monitored by TLC, the reaction mixture was diluted with water (15 ml) and extracted with ethyl acetate (3*20 ml) and again washed with sat. NaHCO₃ solution. The organic layer was dried over sodium sulphate and concentrated under vacuum to get crude material which was purified by using reverse phase Prep-HPLC. To get two fraction.

[000253] Fraction-1: (2-fluoro-5-hydroxyphenyl)(6-(3-(2-fluorophenyl)-4-(trifluoromethyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptan-2-yl)methanone (**PSY-05-00473-001**) (0.012 g 1.68 %). LCMS: m/z 464.01 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.68 (s, 1H), 8.12 (d, J = 9.7 Hz, 1H), 7.63 - 7.43 (dq, J = 19.3, 9.9, 7.4 Hz, 4H), 7.08 (q, J = 9.5 Hz, 1H), 6.85 (s, 1H), 6.77 (s, 1H), 4.50 (dt, J = 14.3, 7.5 Hz, 1H), 4.03 (d, J = 9.0 Hz, 4H), 2.79 - 2.63 (m, 4H).

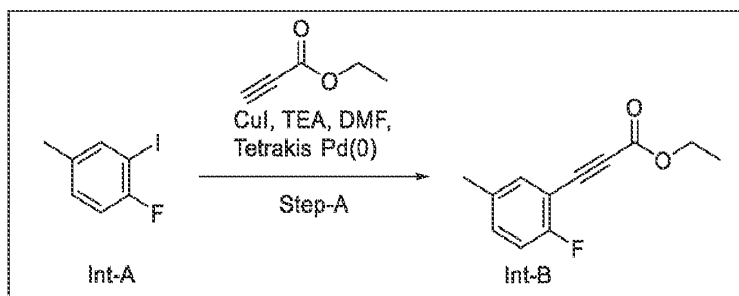
[000254] Fraction-2: 2-fluoro-5-hydroxyphenyl)(6-(5-(2-fluorophenyl)-4-(trifluoromethyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptan-2-yl)methanone (**PSY-05-00472-001**) (0.031 g 4.35%). LCMS: m/z 464.41 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.69 (d, J = 5.5 Hz, 1H), 8.62 (d, J = 9.6 Hz, 1H), 7.53 (s, 1H), 7.51 - 7.42 (m, 1H), 7.39 - 7.25 (m, 2H), 7.10 (q, J = 9.0 Hz, 1H), 6.89 - 6.84 (m, 1H), 6.81 (s, 1H), 4.90 (dt, J = 23.7, 7.9 Hz, 1H), 4.16 (d, J = 10.3 Hz, 2H), 4.06 (d, J = 8.1 Hz, 2H), 2.74 (dd, J = 24.9, 10.1 Hz, 4H).

Example 10: Synthesis of (2-fluoro-5-hydroxyphenyl)(6-(3-(2-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptan-2-yl)methanone [Compound 474]; and (2-fluoro-5-hydroxyphenyl)(6-(5-(2-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptan-2-yl)methanone [Compound 475]

Synthetic scheme:



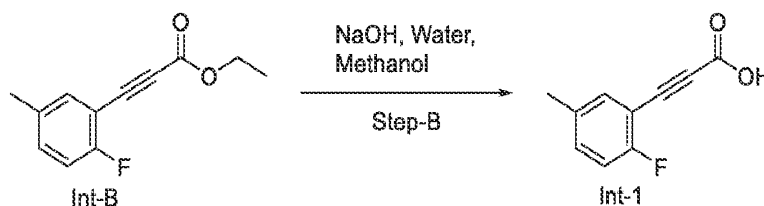
Step-A: ethyl 3-(2-fluoro-5-methylphenyl) propiolate (Int-A).



[000255] A mixture of the 4-fluoro-2-iodo-1-methylbenzene (Int-A) (5.0 g, 21.19 mmol, 1.0 eq.), *Tetrakis* (Triphenyl phosphine) palladium (0) (2.4 g, 2.119 mmol, 0.1 eq.) and CuI (0.403 g, 2.119 mmol, 0.1 eq.) in **Triethylamine (30 mL)** was purged with nitrogen and treated with the **ethyl propiolate** (2.28 g, 23.30 mmol, 1.1 eq.). The resultant mixture was stirred at room temperature overnight. The reaction mixture was poured into sat aq NaHCO_3 (Sodium bicarbonate) and extracted with Ethyl acetate. The organic layer was washed with brine, dried

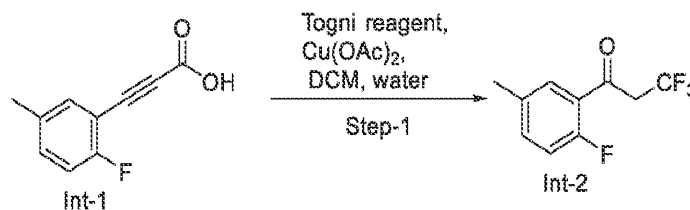
over sodium sulfate, concentrated, and purified by flash chromatography (0-20% Ethyl acetate/hexane) to get desired product Ethyl 3-(2-fluoro-5-methylphenyl) propiolate (**Int-B**) as a clear oil. (1.0 g, 22.89 %).

Step-B: 3-(2-fluoro-5-methylphenyl) propiolic acid (Int-1).



[000256] To a solution of the ethyl 3-(2-fluoro-5-methylphenyl) propiolate (1.0 g, 4.854 mmol, 1.0 eq.) in Methanol (5 mL) and H₂O (15 mL) was added NaOH (Sodium hydroxide) (0.388 g, 9.7086 mmol, 2.0eq.). The mixture stirred at room temperature for 16 h, then concentrated in vacuum. The crude was diluted with H₂O (100 mL) and acidified with an aq solution of 2M HCl (Hydrochloric acid). This aq mixture was extracted with Ethyl acetate (2 x 200 mL) and the combined org extracts were washed with brine (400 mL), dried (MgSO₄), and concentrated *in vacuum* to provide to product of 3-(2-fluoro-5-methylphenyl) propiolic acid (**Int-1**) as a solid. (0.500 g, 57.87 %)

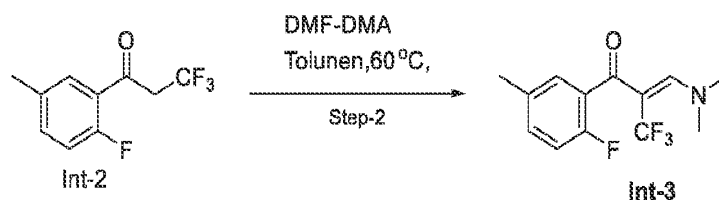
Step-1: 3,3,3-trifluoro-1-(2-fluoro-5-methylphenyl)propan-1-one (Int-2).



[000257] A Sealed test tube with a magnetic stirring bar was charged with 3-(2-fluoro-5-methylphenyl) propiolic acid (1.0 g, 5.6179 mmol, 1.0 eq.) Togni (II) (1.77 g, 5.6179 mmol, 1.0 eq.) Cu(OAc)₂·H₂O (Cupric acetate hydrate) (2.04 g, 11.24 mmol, 2.0 eq.), TMEDA (1,2-Bis(dimethylamino)ethane) (1.306 g, 11.24 mmol, 2.0 eq.), followed by Dichloromethane (10 mL) and H₂O (10.5 mL). The reaction mixture was stirred at room temperature. After stirring for 24 hr., the reaction mixture was extracted with Dichloromethane (15 mL x 3), dried over sodium

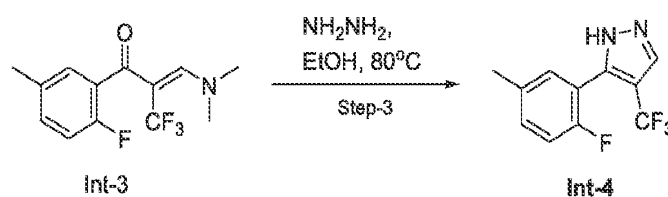
sulphate and concentrated. The residue was purified with silica gel chromatography to provide pure product of 3,3,3-trifluoro-1-(2-fluoro-5-methylphenyl)propan-1-one (**Int-2**) as solid (0.350 g, 28.32 %).

Step-2: (Z)-3-(dimethylamino)-1-(2-fluoro-5-methylphenyl)-2-(trifluoromethyl) prop-2-en-1-one (Int-3).



[000258] To a stirred solution of 3,3,3-trifluoro-1-(2-fluoro-5-methylphenyl)propan-1-one (0.90 g, 4.12 mmol, 1.0 eq.) in Toluene (10 mL) was added N,N-Dimethylformamide dimethylacetal (1.47 g, 12.38 mmol, 3.0 eq.) the reaction mass was heated at 60 °C for 16h. After completion of reaction as monitored by TLC, the reaction mixture was poured in ice cold water (100mL) and extracted with ethyl acetate (50 mL*3). The organic layer was washed with brine (100 mL), dried over Na₂SO₄ and concentrated under reduce pressure to get residue. The residue was purified by combiflash using 15-20% ethyl acetate in hexane as eluent to get (Z)-3-(dimethylamino)-1-(2-fluoro-5-methylphenyl)-2-(trifluoromethyl) prop-2-en-1-one (**Int-3**) (0.47 g, 41.77 %).

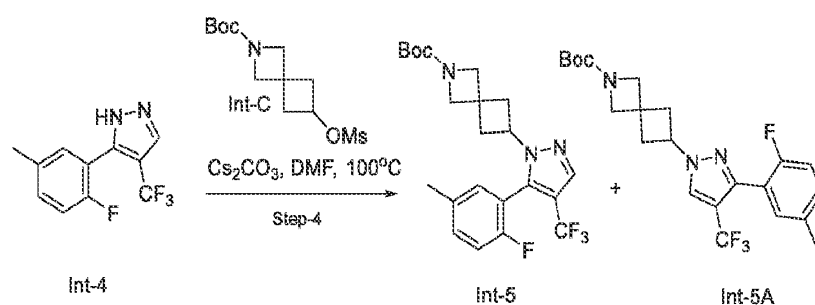
Step-3: 5-(2-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-pyrazole (Int-4).



[000259] To a stirred solution of (Z)-3-(dimethylamino)-1-(2-fluoro-5-methylphenyl)-2-(trifluoromethyl)prop-2-en-1-one (0.47 g, 1.70 mmol, 1.0 eq.) in Isopropyl alcohol (5 mL) was added hydrazine hydrate (0.128 g, 2.56 mmol, 1.5 eq.) the reaction mass was heated at 80 °C for 16hr. After completion of reaction as monitored by TLC, the reaction mixture was concentrated

to get residue. The residue was purified by combiflash using 15-20% ethyl acetate in n-hexane as eluent to get 5-(2-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-pyrazole (**Int-4**) (0.290 g, 69.55%).

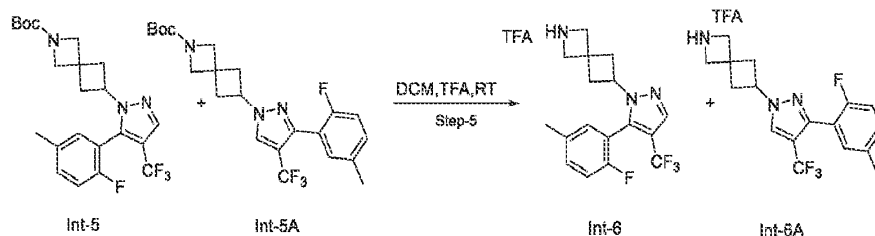
Step-4: Tert-butyl 6-(5-(2-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptane-2-carboxylate (**Int-5**) and tert-butyl 6-(3-(2-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate (**Int-5A**).



[000260] To a solution of 5-(2-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-pyrazole (**Int-4**) (0.270 g, 1.1065 mmol, 1.0eq.) in N,N-Dimethylformamide (4.8 mL), tert-butyl 6-((methylsulfonyl)oxy)-2-azaspiro [3.3] heptane-2-carboxylate (**Int-C**) (0.386 g, 1.328 mmol, 1.2eq.) and cesium carbonate (0.719 g, 2.213 mmol, 2.0 eq.) were added. The reaction mixture was heated at 100 °C for 16 h. After cooling to room temperature. The reaction mixture was poured into water (20 mL), and the solution was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel with n-hexane and ethyl acetate to get two region isomers of tert-butyl 6-(5-(2-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptane-2-carboxylate (**Int-5**) and tert-butyl 6-(3-(2-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate (**Int-5A**) (0.450 g, 92.61 %).

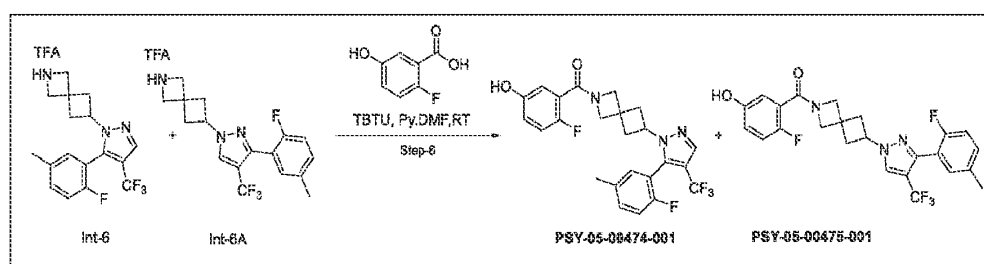
Step-5: 6-(5-(2-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptane (**Int-6**) and

6-(3-(2-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptane (Int-6A). [3.3]



[000261] To a stirred solution of tert-butyl 6-(5-(2-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate (Int-5) and tert-butyl 6-(3-(2-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate (Int-5A) (0.290 g, 0.6605 mmol, 1.0 eq.) in dichloromethane (3.0 mL) was added Trifluoroacetic acid (0.725 mL, 2.5 v) at 0 °C. The reaction was stirred at room temperature for 16 hr. After completion of reaction as monitored by TLC, the reaction mixture was concentrated and triturated with mixture of diethyl ether and n-hexane (1:1, 10 mL*3) to get two regio-isomers. 6-(5-(5-fluoro-2-methylphenyl)-3-methyl-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptane (Int-6) 6-(3-(5-fluoro-2-methylphenyl)-5-methyl-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptane (Int-6A) as a TFA salt (0.210 g, crude).

Step-6: 2-fluoro-5-hydroxyphenyl(6-(5-(2-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptan-2-yl)methanone (PSY-05-00474-001) & 2-fluoro-5-hydroxyphenyl(6-(3-(2-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptan-2-yl)methanone (PSY-05-00475-001).



[000262] To a stirred solution of 6-(5-(5-fluoro-2-methylphenyl)-3-methyl-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane (Int-6) 6-(3-(5-fluoro-2-methylphenyl)-5-methyl-1H-pyrazol-1-yl)-2-

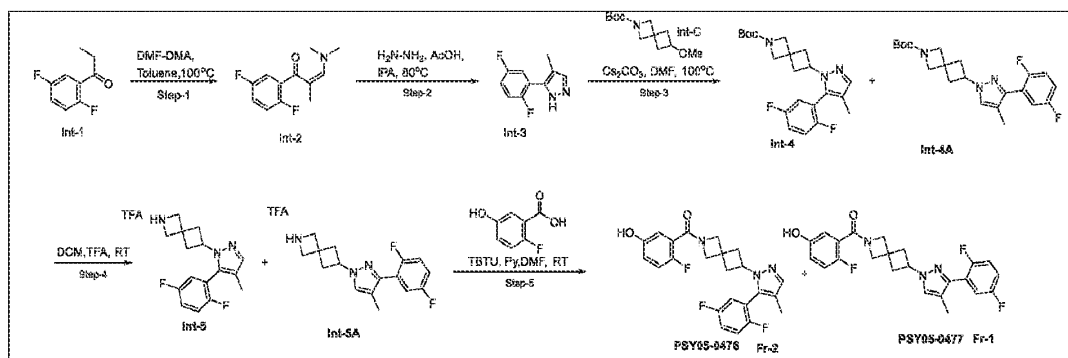
azaspiro[3.3]heptane)(Int-6A) (0.210 g, 0.6192 mmol, 1.0 eq.) in N,N-Dimethylformamide (2.0 mL) were added pyridine (0.247 g, 6.192 mmol, 10.0 eq.), 2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetra fluoroborate (TBTU) (0.298 g, 0.9288 mmol, 1.5 eq.) at 0°C and stirred for 15 mins. Then to added 2-fluoro-5-hydroxybenzoic acid (0.144g, 0.9288 mmol, 1.5 eq.) at 0 °C. The resulting reaction mixture was stirred at room temperature for 16h. After completion of reaction as monitored by TLC, the reaction mixture was diluted with water (15 mL) and extracted with ethyl acetate (3*20 mL) and washed with sat. Sodium carbonate (NaHCO₃) solution. The organic layer was dried over sodium sulphate and concentrated under vacuum to get crude material which was purified by using Prep-HPLC using 1% formic acid in water: acetonitrile. To get two fractions.

[000263] Fraction-1: (2-fluoro-5-hydroxyphenyl)(6-(3-(2-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptan-2-yl)methanone (**PSY-05-00475-001**) (0.023 g 8.2 %). LCMS: 478.41 *m/z* [M+1]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.67 (s, 1H), 8.11 (d, *J* = 9.9 Hz, 1H), 7.45 (s, 1H), 7.39 – 7.18 (m, 2H), 7.08 (q, *J* = 9.6 Hz, 1H), 6.85 (s, 1H), 6.77 (s, 1H), 4.49 (dt, *J* = 14.5, 7.7 Hz, 1H), 4.03 (d, *J* = 8.7 Hz, 4H), 2.68 (ddt, *J* = 51.2, 19.7, 8.6 Hz, 2H), 2.47 (m, 2H), 2.35 (d, *J* = 9.5 Hz, 3H).

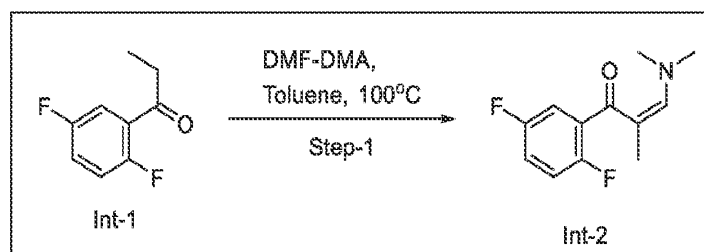
[000264] Fraction-2: (2-fluoro-5-hydroxyphenyl)(6-(5-(2-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptan-2-yl)methanone (**PSY-05-00474-001**) (0.011 g 3.9 %). LCMS: *m/z* 478.40 [M+1]⁺ ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.67 (s, 1H), 8.1 (d, *J* = 9.9 Hz, 1H), 7.29-7.20 (m, 3H), 7.09 (q, *J* = 9.6 Hz, 1H), 6.84 (s, 1H), 6.79 (s, 1H), 4.88 (dt, *J* = 14.5, 7.7 Hz, 1H), 4.03 (d, *J* = 8.7 Hz, 4H), 2.74 (ddt, *J* = 51.2, 19.7, 8.6 Hz, 4H), 2.35 (d, *J* = 9.5 Hz, 3H).

Example 11: Synthesis of (6-(5-(2,5-Difluorophenyl)-4-methyl-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl) (2-fluoro-5-hydroxyphenyl) methanone [Compound 476] and (6-(3-(2,5-Difluorophenyl)-4-methyl-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl) (2-fluoro-5-hydroxyphenyl) methanone [Compound 477]

Synthetic scheme:

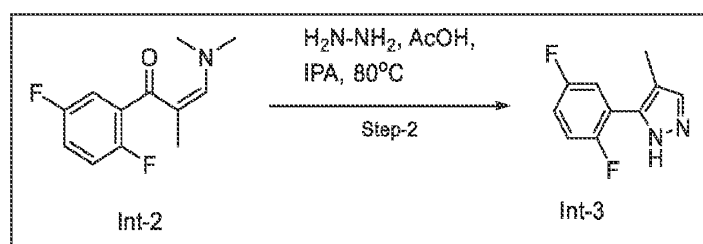


Step-1: Synthesis of (Z)-1-(2, 5-Difluorophenyl)-3-(dimethyl amino)-2-methylprop-2-en-1-one (Int-2).



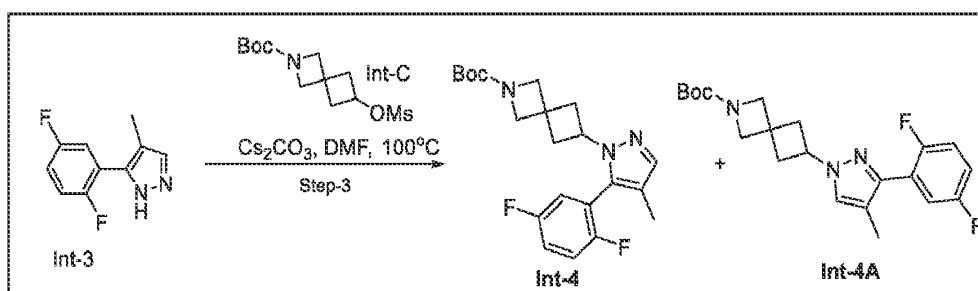
[000265] To a stirred solution of 1-(2,5-Difluorophenyl)propan-1-one (1.0 g, 5.8768 mmol, 1.0 eq.) in **Toluene** (10 mL) was added N,N-Dimethylformamide dimethylacetal (3.0 mL, 29.384 mmol, 5.0 eq.) the reaction mass was heated at 100 °C for 16h. After completion of reaction as monitored by TLC and LCMS. After completion, reaction mixture was poured in ice cold water (50 mL) and extracted with ethyl acetate (20mL*3). The organic layer was washed with brine (50 mL), dried over Sodium sulphate and concentrated under reduce pressure to get residue. The residue was purified by combi flash using 30-40% ethyl acetate in hexane as eluent to (Z)-1-(2, 5-Difluorophenyl)-3-(dimethyl amino)-2-methylprop-2-en-1-one (Int-2) (1.1 g, 84.61%).

Step-2: Synthesis of 5-(2,5-Difluorophenyl)-4-methyl-1H-pyrazole (Int-3)



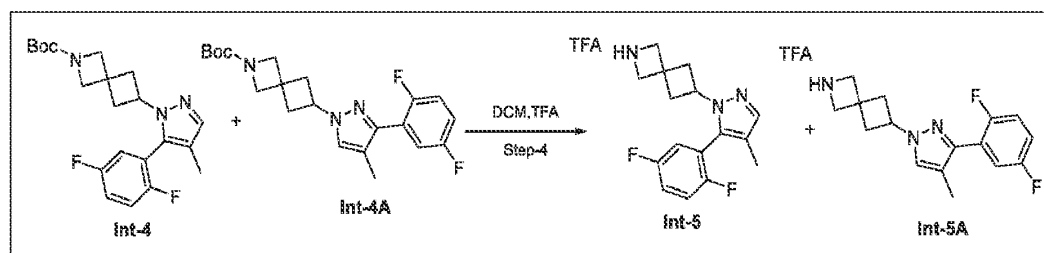
[000266] To a stirred solution of (Z)-1-(2,5-Difluorophenyl)-3-(dimethylamino)-2-methylprop-2-en-1-one (1.1 g, 4.88 mmol, 1.0 eq.) in Isopropyl alcohol (20 mL) was added hydrazine hydrate (0.36 mL, 7.33 mmol, 1.5 eq.) the reaction mass was heated at 80 °C for 16h. After completion of reaction as monitored by TLC and LCMS, the reaction mixture was concentrated to get residue. The residue was purified by combi flash using 20-30% ethyl acetate in hexane as eluent to get 5-(2,5-Difluorophenyl)-4-methyl-1H-pyrazole (**Int-3**) (0.80 g, 84.38%).

Step-3: Synthesis of Tert-butyl 6-(5-(pyridin-3-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate and Tert-butyl 6-(3-(pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate (mix of Int-4 and Int-4A)



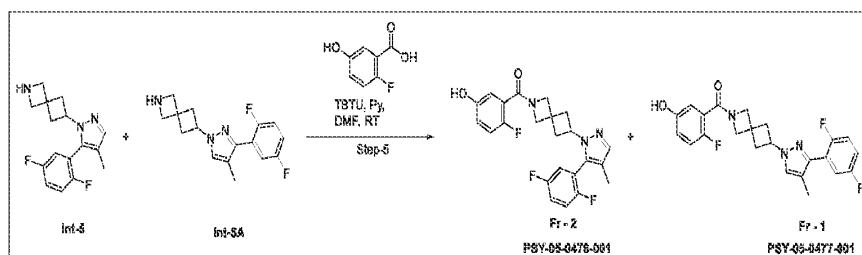
[000267] To a well stirred reaction mixture of 3-(3-(Trifluoromethyl)-1H-pyrazol-5-yl)pyridine (0.800 g, 4.12 mmol, 1.0 eq.), CS_2CO_3 (2.01 g, 6.18 mmol, 1.5 eq.) in N,N-dimethylformamide (10 mL) was added Tert-butyl 6-((methylsulfonyl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (1.44 g, 4.94 mmol, 1.2 eq.). The reaction was heated at 100 °C for 12 h. After completion of reaction as monitored by TLC, the reaction mixture was poured in water (100 mL) and extracted with ethyl acetate (50 mL*3). The organic layer was washed with brine (100 mL), dried over Sodium sulphate and concentrated under reduce pressure to get residue. The residue was purified by combi flash using 30-50% ethyl acetate in hexane as eluent to get to mixture of **Int-4** and **Int-4A** (1.0 g, 62.5%).

Step-4: Synthesis of 6-(5-(2,5-difluorophenyl)-4-methyl-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane TFA salt (Int-5) and 6-(3-(2,5-difluorophenyl)-4-methyl-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane TFA salt (Int-5A).



[000268] To a well stirred reaction mixture of Int-4 and Int-4A (1.0 g, 2.5706 mmol, 1.0 eq.) in dichloromethane (10 mL) was added TFA (2.0 mL) dropwise at 0 °C. After completion of reaction as monitored by TLC and LCMS, the reaction mixture was concentrated to get TFA salt of Int-5 and Int-5A (1.1 g).

Step-5: Synthesis of (6-(5-(2,5-Difluorophenyl)-4-methyl-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl) (2-fluoro-5-hydroxyphenyl) methanone and (6-(3-(2,5-Difluorophenyl)-4-methyl-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl) (2-fluoro-5-hydroxyphenyl) methanone (PSY-05-00476-001 and PSY-05-00477-001).



[000269] To a well stirred reaction mixture of Int-5 and Int-5A (1.13 g, 2.9230 mmol, 1.2 eq.), Pyridine (0.98 mL, 12.1794 mmol, 5.0 eq.), 2-Fluoro-5-hydroxybenzoic acid (0.38 g, 2.4358 mmol, 1.0 eq.) in N,N-dimethyl formamide (5 mL) was added TBTU (0.321 g, 3.6538 mmol, 1.5 eq.) at 0°C. The reaction mass was stirred at room temperature for 3-4 hr. After completion of reaction as monitored by TLC and LCMS, the reaction mixture was poured in water (100 mL) and extracted with ethyl acetate (50 mL*3). The organic layer was washed with saturated solution of sodium carbonate (50 mL) and brine (100 mL), dried over sodium sulphate (Na₂SO₄)

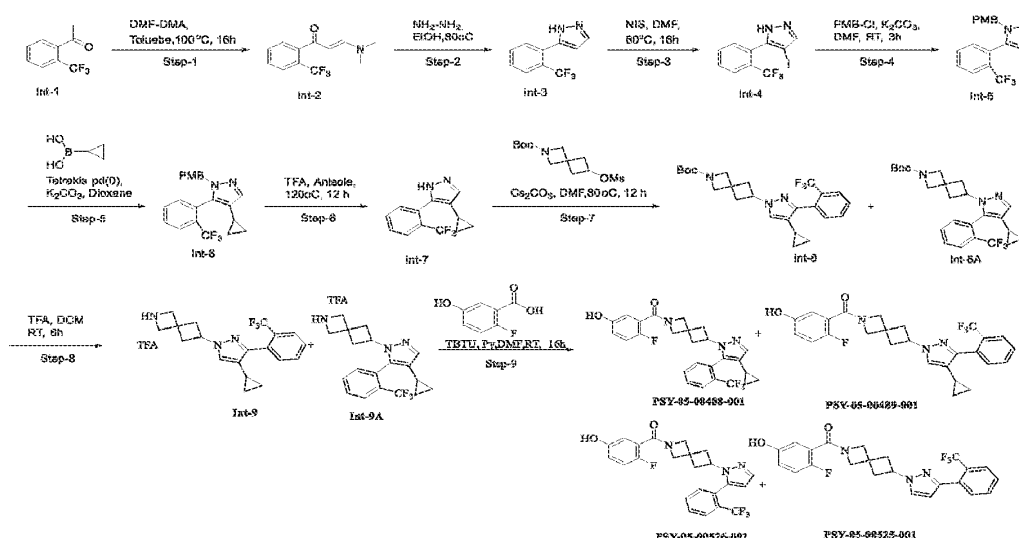
and concentrated under reduce pressure to get residue. The residue was purified by combi flash using 40-50% ethyl acetate in hexane as eluent. The crude was submitted to prep-HPLC for purification. (PSY-05-00476-001-FR-2: 0.308 g, 20.95%) (PSY-05-00477-001-FR-1: 0.096 g, 6.53%).

[000270] Fraction-1: (6-(3-(2,5-Difluorophenyl)-4-methyl-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl) (2-fluoro-5-hydroxyphenyl) methanone (PSY-05-0477-001 Fr-1). LCMS: m/z 428.03 $[M+1]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 7.52 – 7.40 (m, 3H), 7.30 (dd, J = 5.4, 2.8 Hz, 1H), 7.08 (q, J = 8.9 Hz, 1H), 6.85 (d, J = 3.9 Hz, 1H), 6.81 – 6.75 (m, 1H), 4.47 (dt, J = 15.6, 7.8 Hz, 1H), 4.07 (dd, J = 24.5, 5.0 Hz, 4H), 2.60 (dd, J = 20.2, 8.3 Hz, 4H), 1.90 (s, 3H).

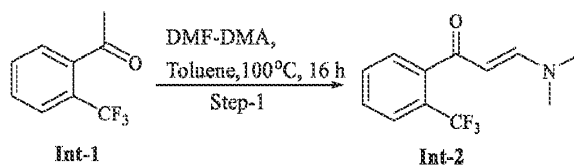
[000271] Fraction-2: (6-(5-(2,5-Difluorophenyl)-4-methyl-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl) (2-fluoro-5-hydroxyphenyl) methanone (PSY-05-00476-001 Fr-2). LCMS: m/z 428.3 $[M+1]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 9.69 (s, 1H), 7.72 (d, J = 5.9 Hz, 1H), 7.39 – 7.26 (m, 3H), 7.10 (q, J = 9.1 Hz, 1H), 6.82 – 6.87 (q, J = 9.1 Hz, 1H), 6.74 – 6.79 (q, J = 9.1 Hz, 1H), 4.76 (dt, J = 23.3, 7.9 Hz, 1H), 4.15 (d, J = 11.2 Hz, 2H), 4.05 (d, J = 8.7 Hz, 2H), 2.76 – 2.60 (m, 4H), 1.99 (s, 3H).

Example 12: Synthesis of (6-(4-Cyclopropyl-5-(2-(trifluoromethyl) phenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl) (2-fluoro-5-hydroxyphenyl) methanone (PSY-05-00488-001); (6-(4-Cyclopropyl-3-(2-(trifluoromethyl) phenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl) (2-fluoro-5-hydroxyphenyl) methanone (PSY-05-00489-001); (2-fluoro-5-hydroxyphenyl)(6-(3-(2-(trifluoro methyl) phenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl)methanone (PSY-05-00525-001); and (2-fluoro-5-hydroxyphenyl)(6-(5-(2-(trifluoro methyl) phenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl)methanone (PSY-05-00526-001).

Synthetic scheme:

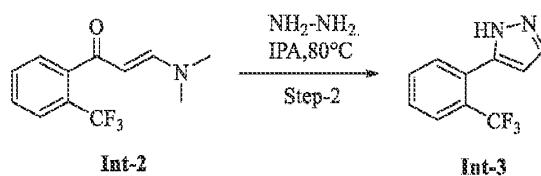


Step-1: Synthesis of (E)-3-(Dimethyl amino)-1-(2-(trifluoromethyl) phenyl) prop-2-en-1-one (Int-2).



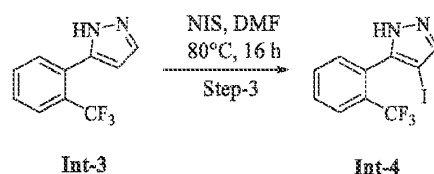
[000272] To a stirred solution of 1-(2-(Trifluoromethyl) phenyl) ethan-1-one (10.0 g, 53.19 mmol, 1.0 eq.) in Toluene (100mL) was added N, N-Dimethylformamide dimethyl acetal (20.56 mL, 265.95 mmol, 5.0 eq.). The reaction mass was heated at 100 °C for 16h. After completion of reaction as monitored by TLC and LCMS, reaction mixture was poured in ice cold water (50 mL) and extracted with ethyl acetate (75 mL*3). The organic layer was washed with brine (100 mL), dried over Na₂SO₄ and concentrated under reduce pressure to get residue. The residue was purified by combi flash using 30-40% ethyl acetate in n-hexane as eluent to (E)-3-(Dimethyl amino)-1-(2-(trifluoromethyl) phenyl) prop-2-en-1-one (Int-2) (11.12 g, 86.06%).

Step-2: Synthesis of 5-(2-(Trifluoromethyl) phenyl)-1H-pyrazole (Int-3).



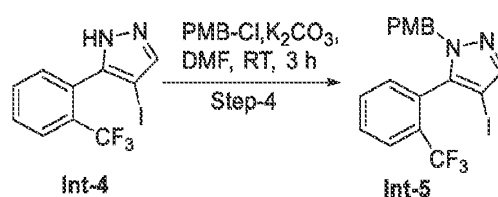
[000273] To a stirred solution of (E)-3-(Dimethyl amino)-1-(2-(trifluoromethyl) phenyl) prop-2-en-1-one (11.12 g, 45.7613 mmol, 1.0 eq.) in Isopropanol (100 mL) was added hydrazine hydrate (2.19 mL, 68.64 mmol, 1.5 eq.). The reaction mass was heated at 80 °C for 16h. After completion of reaction as monitored by TLC and LCMS, the reaction mixture was concentrated to get residue. The residue was purified by combi flash using 20-30% ethyl acetate in n-hexane as eluent to get 5-(2-(Trifluoromethyl) phenyl)-1H-pyrazole (**Int-3**) (8.67 g, 89.38 %).

Step-3: Synthesis of 4-Iodo-5-(2-(trifluoromethyl) phenyl)-1H-pyrazole (Int-4).



[000274] To a well stirred solution of 5-(2-(Trifluoromethyl) phenyl)-1H-pyrazole (8.67 g, 40.86 mmol, 1.0 eq.) in N,N-dimethyl formamide (90 mL) was added N-Iodo succinamide (10.11 g, 44.94 mmol, 1.1 eq.) in reaction mixture. The reaction was heated at 80 °C for 16 h. After completion of reaction as monitored by TLC, the reaction mixture was poured in ice water (100 mL) and extracted with ethyl acetate (100 mL*3). The organic layer was washed with brine (100 mL), dried over Na₂SO₄ and concentrated under reduce pressure to get residue. The residue was purified by combi flash using 30-50% ethyl acetate in n-hexane as eluent to get to 4-Iodo-5-(2-(trifluoromethyl) phenyl)-1H-pyrazole (**Int-4**) (9.2 g, 66.6 %).

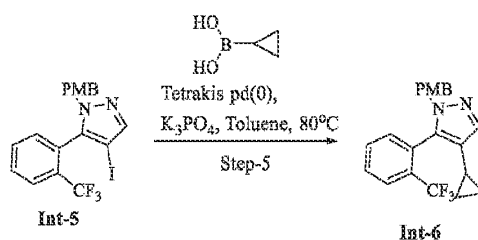
Step-4: Synthesis of 4-Iodo-1-(4-methoxybenzyl)-5-(2-(trifluoromethyl) phenyl)-1H-pyrazole (Int-5).



[000275] To a well stirred solution of 4-Iodo-5-(2-(trifluoromethyl) phenyl)-1H-pyrazole (9.2 g, 27.21 mmol, 1.0 eq.), Cs₂CO₃ (13.26 g, 40.82 mmol, 1.5 eq.) in N,N-dimethyl formamide (100 mL) was added 4-Metoxybenzyl chloride (4.44 mL, 32.66 mmol, 1.2 eq.). The reaction was stirred at room temperature for 2-3 h. After completion of reaction as monitored by TLC

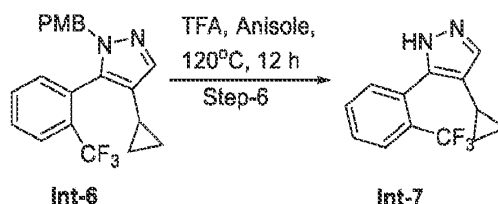
and LCMS, the reaction mixture was poured in ice water (100 mL) and extracted with ethyl acetate (100 mL*3). The organic layer was washed with brine (100 mL), dried over Na₂SO₄ and concentrated under reduce pressure to get residue. The residue was purified by combi flash using 30-50% ethyl acetate in n-hexane as eluent to get 4-Iodo-1-(4-methoxybenzyl)-5-(2-(trifluoromethyl) phenyl)-1H-pyrazole (**Int-5**) (10.10 g, 81.0 %).

Step-5: Synthesis of 4-Cyclopropyl-1-(4-methoxybenzyl)-5-(2-(trifluoromethyl) phenyl)-1H-pyrazole (Int-6**).**



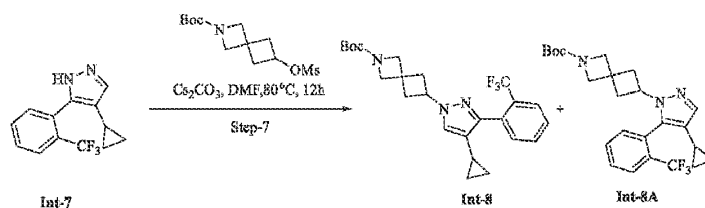
[000276] To a well stirred reaction mixture of 4-Iodo-1-(4-methoxybenzyl)-5-(2-(trifluoromethyl) phenyl)-1H-pyrazole (10.10 g, 22.05 mmol, 1.0 eq.), Cyclopropyl boronic acid (3.78 g, 44.10 mmol, 2.0 eq.), potassium phosphate (K₃PO₄) (14.04 g, 66.15 mmol, 3.0 eq.) in Toluene (100 mL). N_{2(g)} was purged for 20 min, after that Tetrakis Pd(0) (1.27 g, 1.102 mmol, 1.2 eq.) was added and heated the reaction mixture for 80 °C for 48 h. After completion of reaction as monitored by TLC and LCMS, the reaction mixture was filtered through cellite bed, washed with ethyl acetate (3 * 15 mL). Filtrate was diluted in water (100 mL) and extracted with ethyl acetate (100 mL*3). The organic layer was washed with brine (100 mL), dried over Na₂SO₄ and concentrated under reduce pressure to get residue. The residue was purified by combi flash using 0-50% ethyl acetate in n-hexane as eluent to get to 4-Cyclopropyl-1-(4-methoxybenzyl)-5-(2-(trifluoromethyl) phenyl)-1H-pyrazole (**Int-6**) (4.5 g, 54.82 %).

Step-6: Synthesis of 4-Cyclopropyl-5-(2-(trifluoromethyl) phenyl)-1H-pyrazole (Int-7**).**



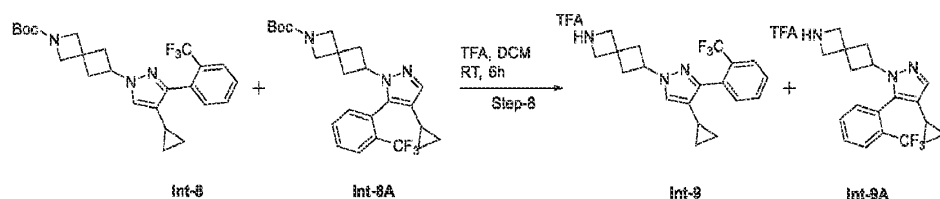
[000277] To a well stirred reaction mixture of 4-cyclopropyl-5-(2-fluorophenyl)-1-(4-methoxybenzyl)-1H-pyrazole (4.5 g, 12.06 mmol, 1.0 eq.) in 40 mL Anisole, was added 4.5 mL Trifluoro acetic acid (TFA). The reaction mixture was heated at 120 °C for 12 h. After completion of reaction as monitored by TLC and LCMS, the reaction mixture was poured in water (100 mL) and extracted with ethyl acetate (50 mL*3). The organic layer was washed with brine (100 mL), dried over Na₂SO₄ and concentrated under reduce pressure to get residue. The residue was purified by combi flash using 30-80% ethyl acetate in n-hexane as eluent to get to 4-Cyclopropyl-5-(2-(trifluoromethyl) phenyl)-1H-pyrazole (**Int-7**) (1.67 g, 54.79 %).

Step-7: Synthesis of tert-butyl 6-(4-cyclopropyl-3-(2-(trifluoromethyl) phenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptane-2-carboxylate (Int-8**) and Tert-butyl 6-(4-cyclopropyl-5-(2-(trifluoromethyl) phenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptane-2-carboxylate (**Int-8A**).**



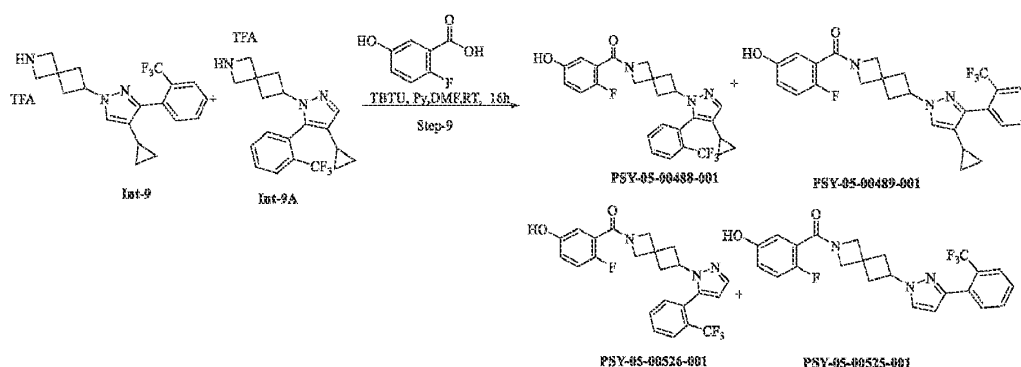
[000278] To a well stirred reaction mixture of 4-cyclopropyl-5-(2-fluorophenyl)-1H-pyrazole (1.67 g, 6.62 mmol, 1.0 eq.) Cs₂CO₃ (3.2 g, 9.94 mmol, 1.5 eq.) in N,N-dimethyl formamide (15 mL) was added Tert-butyl 6-((methyl sulfonyl)oxy)-2-azaspiro [3.3] heptane-2-carboxylate (1.92 g, 6.62 mmol, 1.0 eq.). The reaction was heated at 80 °C for 12 h. After completion of reaction as monitored by TLC and LCMS, the reaction mixture was poured in water (50 mL) and extracted with ethyl acetate (50 mL*3). The organic layer was washed with brine (50 mL), dried over Na₂SO₄ and concentrated under reduce pressure to get residue. The residue was purified by combi flash using 30-50% ethyl acetate in n-hexane as eluent to get to mixture of two regio isomer tert-butyl 6-(4-cyclopropyl-3-(2-(trifluoromethyl)phenyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate (**Int-8**) and tert-butyl 6-(4-cyclopropyl-5-(2-(trifluoromethyl)phenyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate (**Int-8A**) (1.5 g, 50.63 %).

Step-8: Synthesis of 6-(4-cyclopropyl-3-(2-(trifluoromethyl)phenyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane (**Int-9**) and 6-(4-cyclopropyl-5-(2-(trifluoromethyl)phenyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane (**Int-9A**).



[000279] To a well stirred reaction mixture of tert-butyl 6-(4-cyclopropyl-3-(2-(trifluoromethyl)phenyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate (**Int-8**) and tert-butyl 6-(4-cyclopropyl-5-(2-(trifluoromethyl)phenyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate (**Int-8A**) (1.5 g, 2.57 mmol, 1.0 eq.) in dichloromethane (10 mL) was added trifluoroacetic acid (TFA) (2.0 mL) dropwise at 0°C and stirred for 2-3 h.. After completion of reaction as monitored by TLC and LCMS, the reaction mixture was concentrated to get TFA salt of 6-(4-cyclopropyl-3-(2-(trifluoromethyl)phenyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane (**Int-9**) and 6-(4-cyclopropyl-5-(2-(trifluoromethyl)phenyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane (**Int-9A**) (1.7 g).

[000280] **Step-9:** Synthesis of (6-(4-Cyclopropyl-5-(2-(trifluoromethyl) phenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl) (2-fluoro-5-hydroxyphenyl) methanone (PSY-05-00488-001) and (6-(4-Cyclopropyl-3-(2-(trifluoromethyl) phenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl) (2-fluoro-5-hydroxyphenyl) methanone (PSY-05-00489-001). (2-fluoro-5-hydroxyphenyl)(6-(3-(2-(trifluoromethyl)phenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl)methanone (PSY-05-00525-001) and (2-fluoro-5-hydroxyphenyl)(6-(5-(2-(trifluoromethyl)phenyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptan-2-yl)methanone (PSY-05-00526-001).



[000281] To a well stirred reaction mixture of TFA salt of 6-(4-cyclopropyl-3-(2-(trifluoromethyl)phenyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane (**Int-9**) and 6-(4-cyclopropyl-5-(2-(trifluoromethyl)phenyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane (**Int-9A**) (1.7 g, 4.92 mmol, 1.2 eq.), Pyridine (1.65 mL, 20.51 mmol, 5.0 eq.), 2-Fluoro-5-hydroxybenzoic acid (0.640 g, 4.10 mmol, 1.0 eq.) in N,N dimethyl formamide (5 mL) was added TBTU (1.97 g, 6.1538 mmol, 1.5 eq.) at 0°C. The reaction mass was stirred at room temperature for 16 h. After completion of reaction as monitored by TLC and LCMS, the reaction mixture was poured in water (50 mL) and extracted with ethyl acetate (50 mL*3). The organic layer was washed with saturated solution of sodium carbonate (50 mL) and brine (100 mL), dried over Na₂SO₄ and concentrated under reduce pressure to get residue. The residue was purified by combi flash using 0-100 % ethyl acetate in n-hexane as eluent to get crude product. Which was purified by prep- HPLC to obtained two fractions.

[000282] **Fraction-1:** (6-(4-Cyclopropyl-5-(2-(trifluoromethyl) phenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl) (2-fluoro-5-hydroxyphenyl) methanone (**PSY-05-00488-001**) (0.026 g, 1.11 %). LCMS: *m/z* 486.33 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.73 (s, 1H), 7.91 (dd, *J* = 12.6, 8.1 Hz, 1H), 7.83 – 7.69 (m, 2H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 10.1 Hz, 1H), 7.04 (dt, *J* = 17.3, 9.2 Hz, 1H), 6.74 (s, 2H), 4.09 (dd, *J* = 14.2, 6.8 Hz, 1H), 4.01 – 3.91 (m, 4H), 2.63 (s, 2H), 2.54 (s, 2H), 1.18 (m, 1H), 0.59 (s, 2H), 0.39 (d, *J* = 15.1 Hz, 2H).

[000283] **Fraction-2:** (6-(4-Cyclopropyl-3-(2-(trifluoromethyl) phenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl) (2-fluoro-5-hydroxyphenyl) methanone (**PSY-05-00489-001**) (0.07613 g, 3.20 %). LCMS: *m/z* 486.33[M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.67 (s, 1H), 7.83 (s, 1H), 7.72 (d, *J* = 5.2 Hz, 1H), 7.63 (s, 1H), 7.53 (s, 2H), 7.09 (d, *J* = 8.9 Hz, 1H), 6.85 (s, 2H), 4.70

(d, $J = 7.4$ Hz, 1H), 4.12 (d, $J = 10.2$ Hz, 2H), 4.00 (d, $J = 8.5$ Hz, 2H), 2.65 (dd, $J = 19.9, 11.1$ Hz, 4H), 1.29 (m, 1H), 0.67 (d, $J = 6.9$ Hz, 2H), 0.41 (s, 2H).

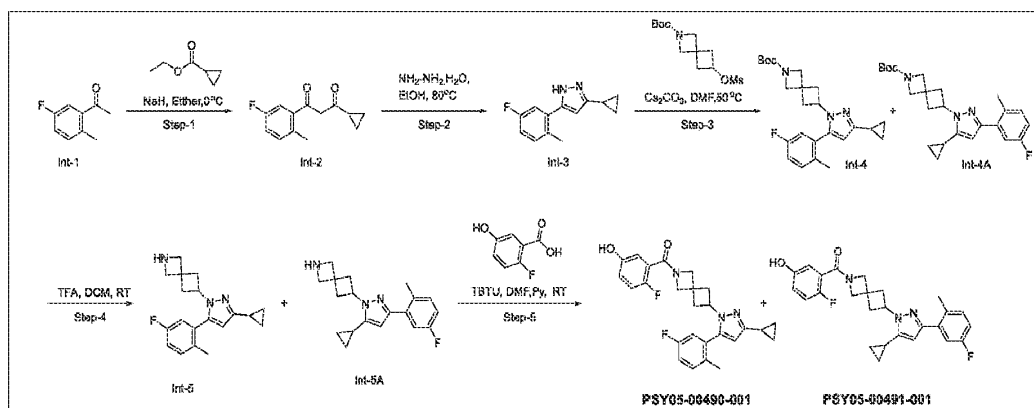
[000284] (NOTE: In Suzuki coupling reaction, dess-iodo of Int-5 observe along with Int-6 product. There was no separation on TLC, LCMS. We used this mixture for next several steps. In Last Prep-HPLC purification, we had isolated Product as dess-CF₃ product of PSY-05-00488-001.)

[000285] **Fraction-3:** (2-fluoro-5-hydroxyphenyl)(6-(3-(2-(trifluoromethyl)phenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl)methanone (**PSY-05-00525-001**) (0.028 g, 1.18 %). LCMS: m/z 446.30 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.64 (s, 1H), 7.89 (s, 1H), 7.78 – 7.71 (m, 2H), 7.58 (d, $J = 9.1$ Hz, 1H), 7.42 (s, 1H), 7.03 (s, 1H), 6.82 (s, 1H), 6.75 (s, 1H), 6.28 (s, 1H), 4.26 (s, 1H), 3.99 (d, $J = 19.2$ Hz, 4H), 2.78 (s, 4H).

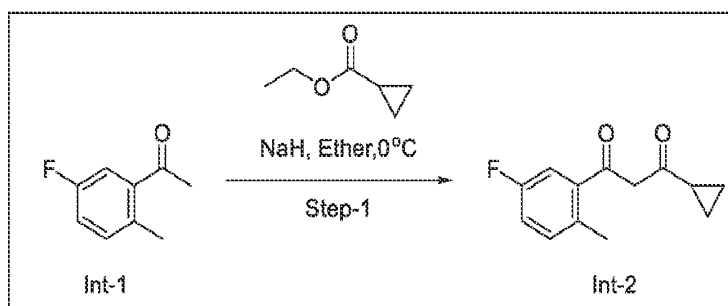
[000286] **Fraction-4:** (2-fluoro-5-hydroxyphenyl)(6-(5-(2-(trifluoromethyl)phenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl)methanone (**PSY-05-00526-001**) (0.19 g, 8.25 %). LCMS: m/z 446.20 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.66 (d, $J = 7.4$ Hz, 1H), 7.82 (dd, $J = 16.3, 9.0$ Hz, 2H), 7.73 – 7.54 (m, 3H), 7.08 (q, $J = 8.8$ Hz, 1H), 6.88 – 6.82 (m, 1H), 6.79 (s, 1H), 6.42 (s, 1H), 4.82 (dt, $J = 23.6, 7.9$ Hz, 1H), 4.14 (d, $J = 10.1$ Hz, 2H), 4.04 (d, $J = 7.9$ Hz, 2H), 2.71 (dt, $J = 17.5, 10.4$ Hz, 4H).

Example 13: Synthesis of (6-(3-cyclopropyl-5-(5-fluoro-2-methylphenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl)(2-fluoro-5-hydroxyphenyl)methanone [Compound 490]; and (6-(5-cyclopropyl-3-(5-fluoro-2-methylphenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl)(2-fluoro-5-hydroxyphenyl)methanone [Compound 491].

Synthetic scheme:

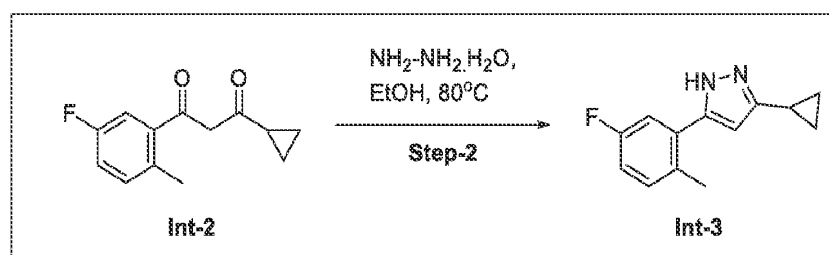


Step-1: 1-cyclopropyl-3-(5-fluoro-2-methylphenyl) propane-1,3-dione (Int-2):



[000287] To a stirred solution of 1-(5-fluoro-2-methylphenyl)ethan-1-one (2.0 g, 13.15 mmol, 1.0 eq.) in Diethyl ether (10 mL) was added NaH 60% (2.1 g, 52.63 mmol, 4.0 eq.) at 0 °C, followed by the dropwise addition of ethyl cyclopropane carboxylate (7.5 g, 65.78 mmol, 5.0 eq.). The reaction mass was stirred at room temperature for 4-5 hr. After completion of reaction as monitored by TLC. The reaction mixture was poured in water (100 mL), acidified with 10% dilute HCl and extracted with ethyl acetate (50 mL*3). The organic layer was washed with brine (100 mL), dried over Na₂SO₄ and concentrated under reduce pressure to get residue. The residue was purified by combiflash using 2-5% ethyl acetate in n-hexane as eluent to obtain cyclopropyl-3-(5-fluoro-2-methylphenyl)propane-1,3-dione (**Int-2**) (2.7 g, 93.27%).

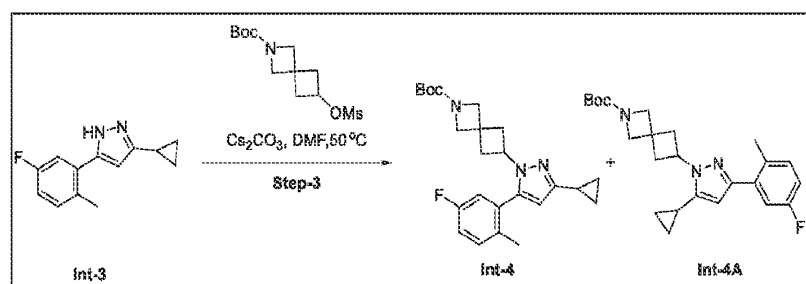
PSY-05-00490 Int-3 3-cyclopropyl-5-(5-fluoro-2-methylphenyl)-1H-pyrazole:



[000288] To a stirred solution of obtain 1-cyclopropyl-3-(5-fluoro-2-methylphenyl)propane-1,3-dione (Int-2) (2.7 g, 12.44 mmol, 1.0 eq.) in Isopropyl alcohol (30 mL) was added hydrazine hydrate (0.93 g, 18.66 mmol, 1.5 eq.) the reaction mass was heated at 80 °C for 16 hr. After completion of reaction as monitored by TLC, the reaction mixture was concentrated to get residue. The residue was purified by combiflash using 15-20% ethyl acetate in n-hexane as eluent to 3-cyclopropyl-5-(5-fluoro-2-methylphenyl)-1H-pyrazole (2.4 g, 90.53 %).

Step-3: Tert-butyl 6-(3-cyclopropyl-5-(5-fluoro-2-methylphenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptane-2-carboxylate (Int-4) and

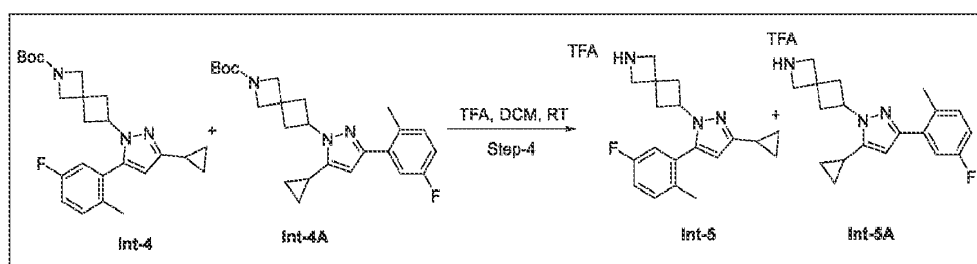
Tert-butyl 6-(5-cyclopropyl-3-(5-fluoro-2-methylphenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptane-2-carboxylate (Int-4A).



[000289] To a well stirred reaction mixture of 3-cyclopropyl-5-(5-fluoro-2-methylphenyl)-1H-pyrazole (Int-3) (1.3 g, 5.99 mmol, 1.0 eq.), Cs_2CO_3 (2.9 g, 8.98 mmol, 1.5 eq.) in N,N-dimethyl formamide (10 mL) was added tert-butyl 6-((methyl sulfonyl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (1.74 g, 5.99 mmol, 1.0 eq.). The reaction was heated at 100 °C for 12 hr. After completion of reaction as monitored by TLC, the reaction mixture was poured in water (100 mL) and extracted with ethyl acetate (50 mL*3). The organic layer was washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduce pressure to get residue. The residue was purified by combiflash using 30-35% ethyl acetate in n-hexane as eluent to get the mixture of tert-butyl 6-(3-cyclopropyl-5-(5-fluoro-2-methylphenyl)-1H-

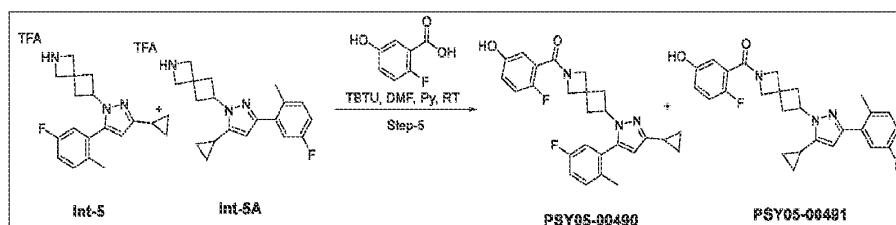
pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate (**int-4**) and tert-butyl 6-(5-cyclopropyl-3-(5-fluoro-2-methylphenyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate (**int-4A**) (0.80 g, 32.34 %).

Step-4: 6-(3-cyclopropyl-5-(5-fluoro-2-methylphenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptane (**Int- 5**) and 6-(5-cyclopropyl-3-(5-fluoro-2-methylphenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptane (**Int-5A**).



[000290] To a well stirred reaction mixture of tert-butyl 6-(3-cyclopropyl-5-(5-fluoro-2-methylphenyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate (**int-4**) and tert-butyl 6-(5-cyclopropyl-3-(5-fluoro-2-methylphenyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate (**int-4A**) (0.8 g, 1.94 mmol, 1.0 eq.) in dichloromethane (5 mL) was added Trifluoroacetic acid (1.2 mL) dropwise at 0 °C. After completion of reaction as monitored by TLC, the reaction mixture was concentrated to get the mixture of 6-(3-cyclopropyl-5-(5-fluoro-2-methylphenyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane (**int-5**) and 6-(5-cyclopropyl-3-(5-fluoro-2-methylphenyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane (**int-5A**) (0.98 g, crude).

Step-5: (6-(3-cyclopropyl-5-(5-fluoro-2-methylphenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl)(2-fluoro-5-hydroxyphenyl) methanone (PSY-05-00490-001 Fr-2) and (6-(5-cyclopropyl-3-(5-fluoro-2-methylphenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl)(2-fluoro-5-hydroxyphenyl) methanone (PSY-05-00491-001 Fr-1).



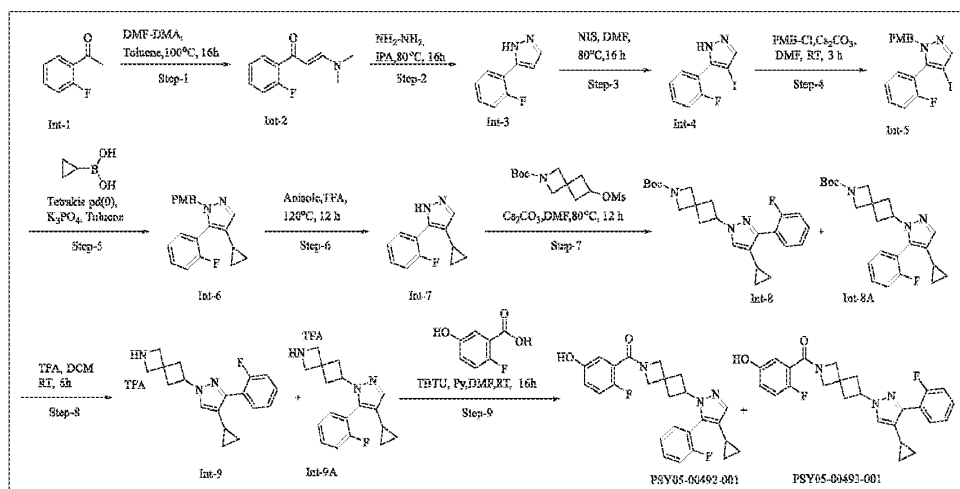
[000291] To a well stirred reaction mixture of 6-(3-cyclopropyl-5-(5-fluoro-2-methylphenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptane (int-5) and 6-(5-cyclopropyl-3-(5-fluoro-2-methylphenyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane (int-5A) (1.0 g, 3.52 mmol, 1.0 eq.), Pyridine (1.23 g, 17.62 mmol, 5.0 eq.), carboxylic acid (0.66 g, 4.23 mmol, 1.2 eq.) in N,N-dimethyl formamide (5 mL) was added TBTU (1.7 g, 5.28 mmol, 1.5 eq.) at 0°C. The reaction mass was stirred at room temperature for 3-4 hr. After completion of reaction as monitored by TLC, the reaction mixture was poured in water (100 mL) and extracted with ethyl acetate (50 mL*3). The organic layer was washed with saturated solution of sodium carbonate (50 mL) and brine (100 mL), dried over Na₂SO₄ and concentrated under reduce pressure to get residue. The residue was purified by combiflash using 30-35% ethyl acetate in n-hexane as eluent. The crude was submitted to prep HPLC for purification. Two Fraction was collected.

[000292] **Fraction-1:** (6-(5-cyclopropyl-3-(5-fluoro-2-methylphenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl)(2-fluoro-5-hydroxyphenyl) methanone (PSY-05-00491-001 Fr-1) (0.075 g, 1.64 %). LCMS: *m/z* 449.5 [M+1]⁺. NMR: ¹H NMR (400 MHz, DMSO-d₆) δ 9.65 (d, J = 7.5 Hz, 1H), 7.36 (d, J = 5.7 Hz, 1H), 7.21 (d, J = 9.3 Hz, 0H), 7.10 – 7.00 (m, 1H), 6.99 (d, J = 9.0 Hz, 1H), 6.84 (s, 1H), 6.76 (s, 1H), 5.93 (s, 1H), 4.28 – 4.19 (m, 1H), 4.01 (d, J = 9.4 Hz, 4H), 2.67 (s, 4H), 2.01 (s, 3H), 1.90 (s, 1H), 0.87 (s, 2H), 0.66 (d, J = 14.9 Hz, 2H).

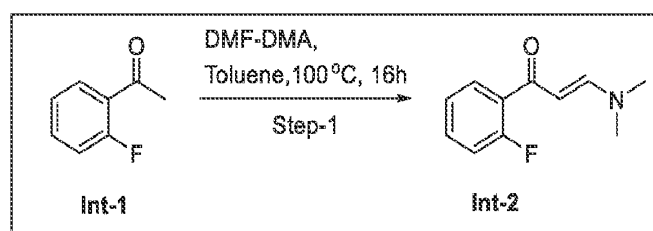
[000293] **Fraction-2:** (6-(3-cyclopropyl-5-(5-fluoro-2-methylphenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl) (2-fluoro-5-hydroxyphenyl) methanone (PSY-05-00490-001 Fr-2) (0.041 g, 0.89 %). LCMS: *m/z* 449.5 [M+1]⁺. NMR: ¹H NMR (400 MHz, DMSO-d₆) δ 9.67 (d, J = 8.4 Hz, 1H), 7.37 – 7.26 (m, 2H), 7.13 – 6.98 (m, 2H), 6.85 (s, 1H), 6.80 (s, 1H), 6.24 (s, 1H), 4.16 (d, J = 9.1 Hz, 2H), 4.07 (s, 2H), 2.75 (s, 4H), 2.41 (d, J = 17.2 Hz, 3H), 1.85 (s, 1H), 0.94 (s, 2H), 0.65 (s, 2H).

Example 14: Synthesis of (6-(4-Cyclopropyl-5-(2-fluorophenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl) (2-fluoro-5-hydroxyphenyl) methanone [Compound 492]; and (6-(4-Cyclopropyl-3-(2-fluorophenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl) (2-fluoro-5-hydroxyphenyl) methanone [Compound 493].

Synthetic scheme:

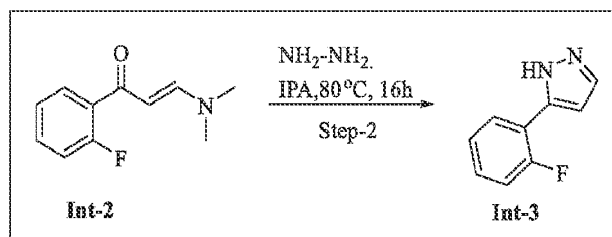


Step-1: Synthesis of (E)-3-(dimethyl amino)-1-(2-fluorophenyl) prop-2-en-1-one (Int-2).



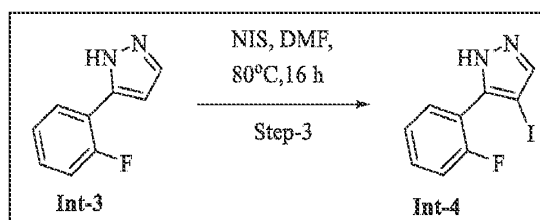
[000294] To a stirred solution of 1-(2-fluorophenyl) ethan-1-one (10.0 g, 5.8768 mmol, 1.0 eq.) in Toluene (10 mL) was added N, N-Dimethylformamide dimethyl acetal (3.0 mL, 29.3841 mmol, 5.0 eq.). The reaction mass was heated at 100 °C for 16h. After completion of reaction as monitored by TLC and LCMS. The reaction mixture was poured in ice cold water (50 mL) and extracted with ethyl acetate (20 mL*3). The organic layer was washed with brine (50 mL), dried over Na₂SO₄ and concentrated under reduce pressure to get residue. The residue was purified by combi flash using 30-40% ethyl acetate in n-hexane as eluent to (Z)-1-(2, 5-Difluorophenyl)-3-(dimethyl amino)-2-methylprop-2-en-1-one (**Int-2**) (10.5 g, 75.0 %).

Step-2: Synthesis of 5-(2-Fluorophenyl)-1H-pyrazole (Int-3).



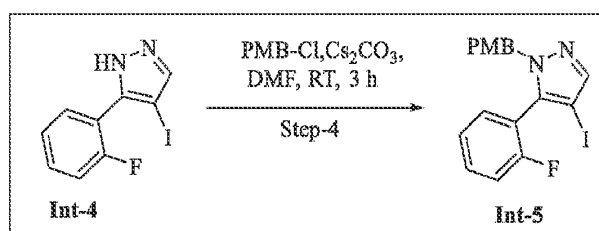
[000295] To a stirred solution of (E)-3-(dimethyl amino)-1-(2-fluorophenyl) prop-2-en-1-one (10.0 g, 51.81 mmol, 1.0 eq.) in Isopropyl alcohol (100 mL) was added hydrazine hydrate (2.49 mL, 77.72 mmol, 1.5 eq.). The reaction mass was heated at 80 °C for 16h. After completion of reaction as monitored by TLC and LCMS, the reaction mixture was concentrated to get residue. The residue was purified by combi flash using 20-30% ethyl acetate in n-hexane as eluent to get 5-(2-Fluorophenyl)-1H-pyrazole (**Int-3**) (7.0 g, 83.40 %).

Step-3: Synthesis of 5-(2-fluorophenyl)-4-iodo-1H-pyrazole (Int-4).



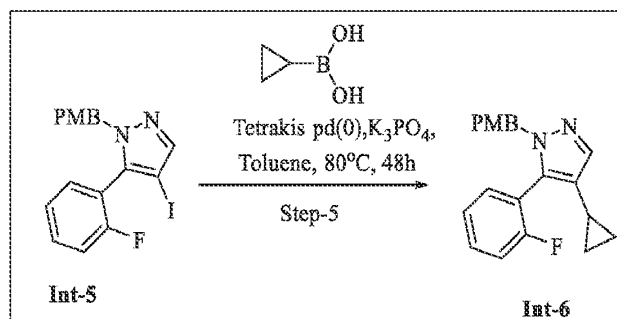
[000296] To a well stirred solution of 5-(2-fluorophenyl)-1H-pyrazole (7.0 g, 43.15 mmol, 1.0 eq.) in N,N-dimethyl formamide (10 mL) was added N-iodo succinamide (10.68 g, 47.4722 mmol, 1.1 eq.). The reaction was heated at 80°C for 16 h. After completion of reaction as monitored by TLC, the reaction mixture was poured in ice water (100 mL) and extracted with ethyl acetate (50 mL*3). The organic layer was washed with brine (50 mL), dried over Na₂SO₄ and concentrated under reduce pressure to get residue. The residue was purified by combi flash using 30-50% ethyl acetate in n-hexane as eluent to get to 5-(2-Fluorophenyl)-4-iodo-1H-pyrazole (**Int-4**) (7.56 g, 60.80 %).

Step-4: Synthesis of 5-(2-Fluorophenyl)-4-iodo-1-(4-methoxybenzyl)-1H-pyrazole (Int-5).



[000297] To a well stirred solution of 5-(2-fluorophenyl)-4-iodo-1H-pyrazole (7.56 g, 26.25 mmol, 1.0 eq.), Cs_2CO_3 (12.79 g, 39.37 mmol, 1.5 eq.) in N,N-dimethyl formamide (75 mL) was added 4-Methoxybenzyl chloride (4.28 mL, 31.500 mmol, 1.2 eq.). The reaction was stirred at room temperature for 2-3 h. After completion of reaction as monitored by TLC, the reaction mixture was poured in ice water (100 mL) and extracted with ethyl acetate (50 mL*3). The organic layer was washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduce pressure to get residue. The residue was purified by combi flash using 30-50% ethyl acetate in hexane as eluent to get 5-(2-Fluorophenyl)-4-iodo-1-(4-methoxybenzyl)-1H-pyrazole (**Int-5**) (8.25 g, 77.01%).

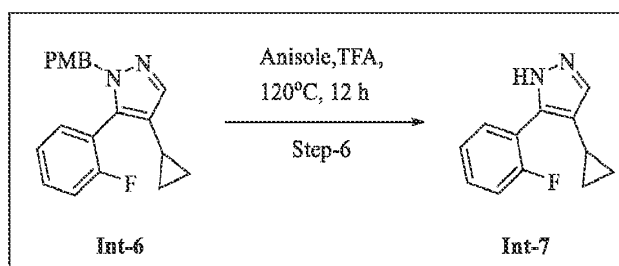
Step-5: Synthesis of 4-cyclopropyl-5-(2-fluorophenyl)-1-(4-methoxybenzyl)-1H-spyrazole (Int-6).



[000298] To a well stirred reaction mixture of 5-(2-fluorophenyl)-4-iodo-1-(4-methoxybenzyl)-1H-pyrazole (8.0 g, 19.60 mmol, 1.0 eq.), Cyclopropyl boronic acid (3.36 g, 39.21 mmol, 2.0 eq.), potassium phosphate (12.48 g, 58.80 mmol, 3.0 eq.) in Toluene (80 mL). $\text{N}_2(g)$ was purged for 20 min, after that Tetrakis (1.13 g, 0.98 mmol, 0.05 eq.) was added and heated the reaction mixture for 80 °C for 48h. After completion of reaction as monitored by TLC, the reaction mixture was filtered through celite bed, celite bed was washed with ethyl acetate. Filtrate was diluted in water (100 mL) and extracted with ethyl acetate (50 mL*3). The organic layer was washed with brine (100 mL), dried over Na_2SO_4 and concentrated under

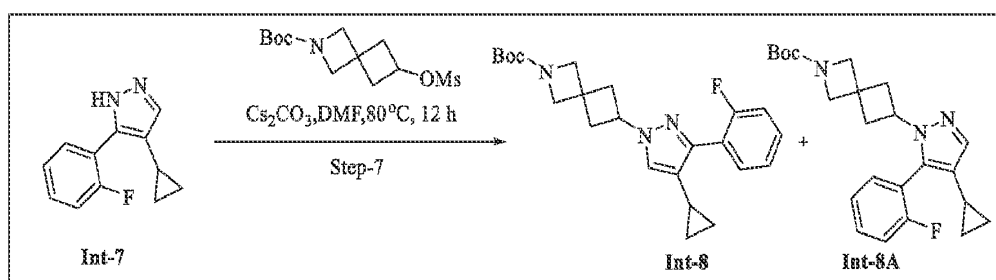
reduce pressure to get residue. The residue was purified by combi flash using 0-50% ethyl acetate in n-hexane as eluent to get to 4-Cyclopropyl-5-(2-fluorophenyl)-1-(4-methoxybenzyl)-1H-pyrazole (**Int-6**) (1.2 g, 18.99 %).

Step-6: Synthesis of 4-cyclopropyl-5-(2-fluorophenyl)-1H-pyrazole (Int-7).



[000299] To a well stirred reaction mixture of 4-cyclopropyl-5-(2-fluorophenyl)-1-(4-methoxybenzyl)-1H-pyrazole (1.2 g, 3.7267 mmol, 1.0 eq.) in 10 mL Anisole, was added 1 mL trifluoro acetic acid. The reaction mixture was heated at 120 °C for 12 h. After completion of reaction as monitored by TLC, the reaction mixture was poured in water (100 mL) and extracted with ethyl acetate (50 mL*3). The organic layer was washed with brine (100 mL), dried over Na₂SO₄ and concentrated under reduce pressure to get residue. The residue was purified by combi flash using 30-50% ethyl acetate in n-hexane as eluent to get to 4-Cyclopropyl-5-(2-fluorophenyl)-1H-pyrazole (**Int-7**) (0.680 g, 90.33 %).

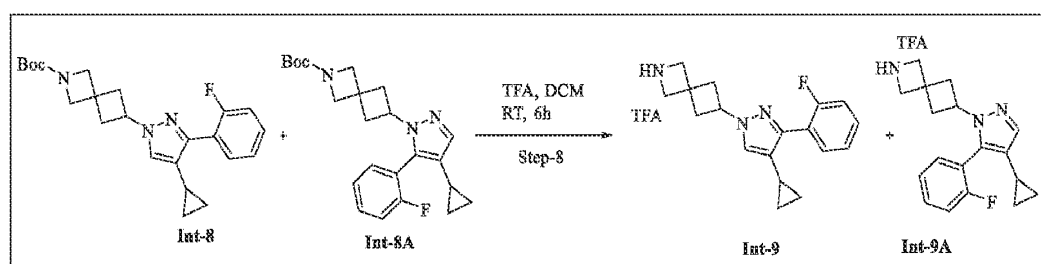
Step-7: Synthesis of Tert-butyl 6-(4-cyclopropyl-3-(2-fluorophenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptane-2-carboxylate (Int-8) and tert-butyl 6-(4-cyclopropyl-5-(2-fluorophenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptane-2-carboxylate (Int-8A).



[000300] To a well stirred reaction mixture of 4-cyclopropyl-5-(2-fluorophenyl)-1H-pyrazole (0.80 g, 3.96 mmol, 1.0 eq.), Cs₂CO₃ (1.93 g, 5.94 mmol, 1.5 eq.) in N,N-dimethyl formamide (10 mL) was added Tert-butyl 6-((methyl sulfonyl)oxy)-2-azaspiro [3.3] heptane-2-carboxylate

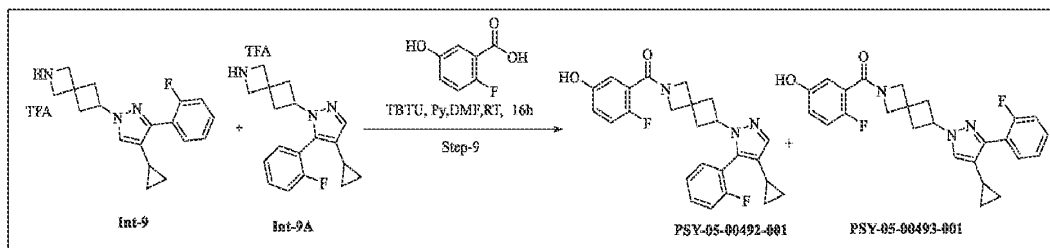
(1.15 g, 3.96 mmol, 1.0 eq.). The reaction was heated at 80 °C for 12 h. After completion of reaction as monitored by TLC and LCMS, the reaction mixture was poured in water (50 mL) and extracted with ethyl acetate (50 mL*3). The organic layer was washed with brine (50 mL), dried over Na₂SO₄ and concentrated under reduce pressure to get residue. The residue was purified by combi flash using 30-50% ethyl acetate in n-hexane as eluent to get to mixture of two regio isomer, tert-butyl 6-(4-cyclopropyl-3-(2-fluorophenyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate (**Int-8**) and tert-butyl 6-(4-cyclopropyl-5-(2-fluorophenyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate (**Int-8A**) (1.0 g, 63.60 %).

[000301] Step-8: Synthesis of 6-(4-cyclopropyl-3-(2-fluorophenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptane (**Int-9**) and 6-(4-cyclopropyl-5-(2-fluorophenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptane (**Int-9A**).



[000302] To a well stirred reaction mixture of tert-butyl 6-(4-cyclopropyl-3-(2-fluorophenyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate (**Int-8**) and tert-butyl 6-(4-cyclopropyl-5-(2-fluorophenyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate (**Int-8A**) (1.0 g, 2.5706 mmol, 1.0 eq.) in dichloromethane (10 mL), was added trifluoro acetic acid (2.0 mL) dropwise at 0 °C for 6 h. After completion of reaction as monitored by TLC and LCMS, the reaction mixture was concentrated to get TFA salt of 6-(4-cyclopropyl-3-(2-fluorophenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptane (**Int-9**) and 6-(4-cyclopropyl-5-(2-fluorophenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptane (**Int-9A**) (1.13 g).

[000303] Step-9: Synthesis of (6-(4-Cyclopropyl-5-(2-fluorophenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl) (2-fluoro-5-hydroxyphenyl) methanone (PSY-05-00492-001) and (6-(4-Cyclopropyl-3-(2-fluorophenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl) (2-fluoro-5-hydroxyphenyl) methanone (PSY-05-00493-001).



[000304] To a well stirred reaction mixture of TFA salt of 6-(4-cyclopropyl-3-(2-fluorophenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptane (**Int-9**) and 6-(4-cyclopropyl-5-(2-fluorophenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptane (**Int-9A**) (0.868 g, 2.92 mmol, 1.2 eq.), Pyridine (0.98 mL, 12.17 mmol, 5.0 eq.), 2-Fluoro-5-hydroxybenzoic acid (0.38 g, 2.43 mmol, 1.0 eq.) in N,N-dimethyl formamide (5 mL) was added TBTU (1.17 g, 3.65 mmol, 1.5 eq.) at 0°C. The reaction mass was stirred at room temperature for 16 h. After completion of reaction as monitored by TLC and LCMS, the reaction mixture was poured in water (100 mL) and extracted with ethyl acetate (50 mL*3). The organic layer was washed with saturated solution of sodium carbonate (50 mL) and brine (100 mL), dried over Na₂SO₄ and concentrated under reduce pressure to get residue. The residue was purified by combi flash using 0-100% ethyl acetate in n-hexane as eluent to get mixture of two regio isomer. Which was purified by prep-HPLC purification to obtained two fractions.

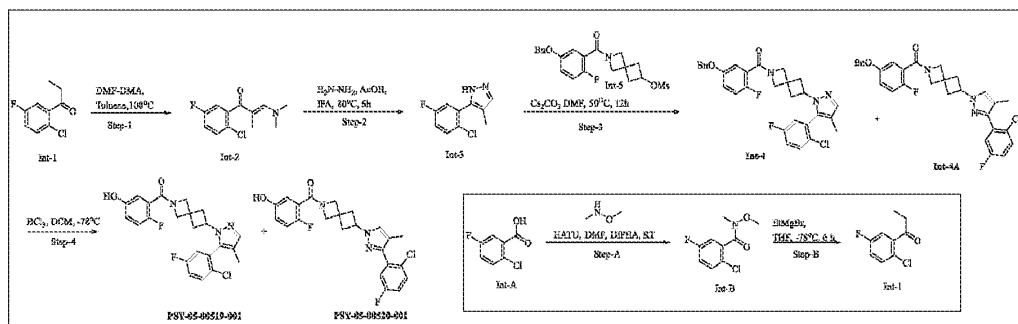
[000305] Fraction-1: (6-(4-Cyclopropyl-3-(2-fluorophenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl) (2-fluoro-5-hydroxyphenyl) methanone (**PSY-05-00493-001**) (0.027 g, 1.61 %). LCMS: *m/z* 436.22 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.64 (s, 1H), 7.36 (dd, *J* = 26.7, 8.4 Hz, 4H), 7.08 (d, *J* = 9.0 Hz, 1H), 6.77 (s, 2H), 4.41 (s, 1H), 4.02 (s, 4H), 2.70 (s, 4H), 1.40 (s, 1H), 0.69 (s, 2H), 0.46 (s, 2H).

[000306] Fraction-2: (6-(4-Cyclopropyl-5-(2-fluorophenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl) (2-fluoro-5-hydroxyphenyl) methanone (**PSY-05-00492-001**) (0.087 gm, 5.15 %). LCMS: *m/z* 436.20 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.69 (s, 1H), 7.56 (dd, *J* = 20.5, 7.4 Hz, 3H), 7.33 – 7.24 (m, 2H), 6.81 (s, 2H), 4.76 – 4.66 (m, 1H), 4.15 (d, *J* = 10.4 Hz, 2H), 4.04 (d, *J* = 8.4 Hz, 2H), 2.72 – 2.62 (m, 4H), 1.56 (s, 1H), 0.76 (s, 2H), 0.44 (s, 2H).

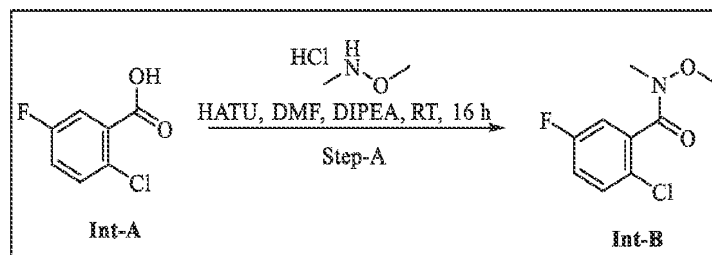
Example 15: Synthesis of (6-(5-(2-chloro-5-fluorophenyl)-4-methyl-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl) (2-fluoro-5-hydroxyphenyl) methanone [Compound 519], and (6-(3-

(2-chloro-5-fluorophenyl)-4-methyl-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl)(2-fluoro-5-hydroxyphenyl)methanone [Compound 520]

Synthetic scheme:

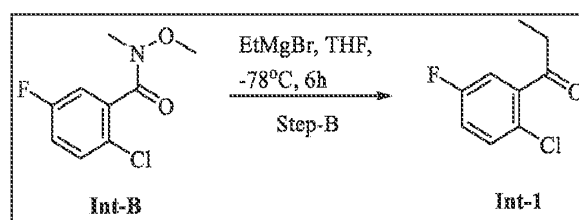


Step-A: 2-chloro-5-fluoro-N-methoxy-N-methylbenzamide (Int-B).



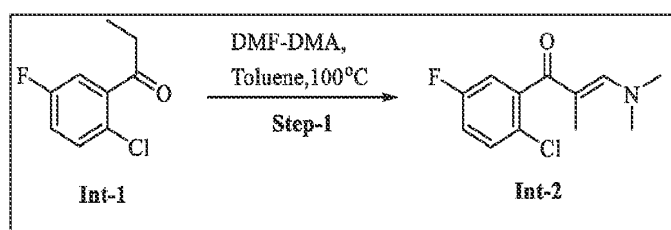
[000307] To a stirred solution of 2-chloro-5-fluorobenzoic acid (10.0 g, 57.27 mmol, 1.0 eq.), N,N-di-isopropyl ethylamine (29.4 mL, 171.82 mmol, 3.0 eq.), N,O-dimethyl hydroxylamine hydrochloride (6.142 g, 63.0 mmol, 1.1 eq.) in N,N-Dimethylformamide (50 mL) was added HATU (32.66 g, 85.91 mmol, 1.5 eq.) at 0 °C. Stir the reaction at room temperature for 16 h. After completion of reaction as monitored by TLC, the reaction mixture was poured in ice cold water (100 mL) and extracted with ethyl acetate (50 mL*3). The organic layer was dried over Sodium sulfate and concentrated under reduce pressure to get residue. The residue was purified by combiflash using 25% Ethyl acetate in n-hexane as eluent to get 2-chloro-5-fluoro-N-methoxy-N-methylbenzamide (**Int-B**) (10.9 g, 87.3%).

Step-B: 1-(2-chloro-5-fluorophenyl) propan-1-one (Int-1).



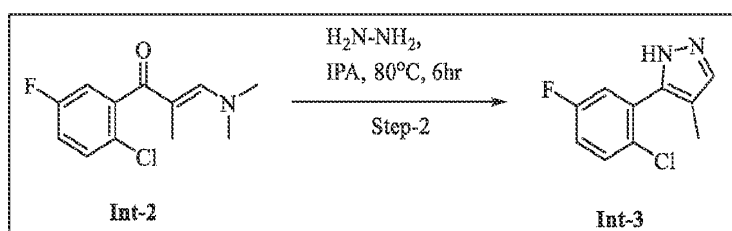
[000308] To a stirred solution of 2-chloro-5-fluoro-N-methoxy-N-methylbenzamide (10.9 g, 50.25 mmol, 1.0 eq.) in tetrahydrofuran (50 mL), was slowly added Ethyl magnesium bromide 3M solⁿ in Tetrahydrofuran (25.13 mL, 75.38 mmol, 1.5 eq.) at -78 °C. Stir the reaction at room temperature for 6 h. After completion of reaction as monitored by TLC, the reaction mixture was poured in ice cold water (100 mL) and extracted with ethyl acetate (50 mL*3). The organic layer was dried over Sodium sulfate and concentrated under reduce pressure to get residue. The residue was purified by combiflash using 20-25% Ethyl acetate in n-hexane as eluent to get 1-(2-chloro-5-fluorophenyl) propan-1-one (**Int-1**) (5.28 g, 56.49 %).

Step-1: (E)-1-(2-chloro-5-fluorophenyl)-3-(dimethylamino)-2-methylprop-2-en-1-one (Int-2).



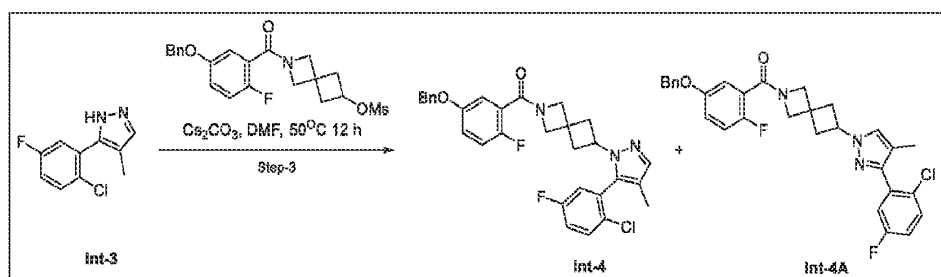
[000309] To a stirred solution of 1-(2-chloro-5-fluorophenyl)propan-1-one (5.28 g, 28.29 mmol, 1.0 eq.) in Toluene (15 mL) was added N,N-Dimethylformamide dimethyl acetal (23.60 g, 198.06 mmol, 7.0 eq.) the reaction mass was heated at 100 °C for 16h. After completion of reaction as monitored by TLC, the reaction mixture was poured in ice cold water (100 mL) and extracted with ethyl acetate (50 mL*3). The organic layer was washed with brine (100 mL), dried over Sodium sulfate and concentrated under reduce pressure to get residue. The residue was purified by combiflash using 25-30% ethyl acetate in hexane as eluent to get (E)-1-(2-chloro-5-fluorophenyl)-3-(dimethylamino)-2-methylprop-2-en-1-one (**Int-2**) (5.65 g, 82.62 %).

Step-2: 5-(2-chloro-5-fluorophenyl)-4-methyl-1H-pyrazole (Int-3).



[000310] To a stirred solution of (E)-1-(2-chloro-5-fluorophenyl)-3-(dimethylamino)-2-methylprop-2-en-1-one (5.65 g, 23.44 mmol, 1.0 eq.) in Isopropyl alcohol (30 mL) was added hydrazine hydrate (2.0 g, 35.16 mmol, 1.5 eq.) the reaction mass was heated at 80 °C for 16h. After completion of reaction as monitored by TLC, the reaction mixture was concentrated to get residue. The residue was purified by combiflash using 15-20% ethyl acetate in hexane as eluent to get 5-(2-chloro-5-fluorophenyl)-4-methyl-1H-pyrazole (**Int-3**) (4.3 g, 87.33%).

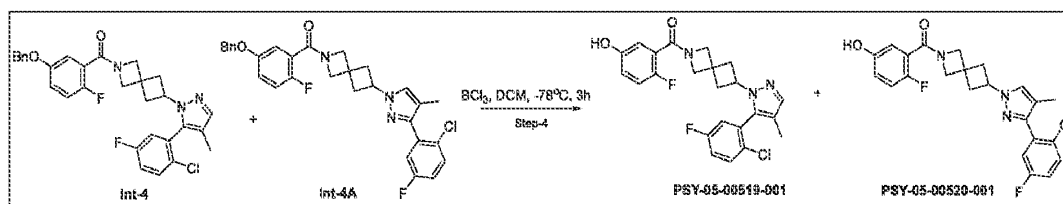
[000311] Step-3: (5-(benzyloxy)-2-fluorophenyl)(6-(5-(2-chloro-5-fluorophenyl)-4-methyl-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl) methanone (**Int- 4**) and (5-(benzyloxy)-2-fluorophenyl)(6-(3-(2-chloro-5-fluorophenyl)-4-methyl-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl) methanone (**Int- 4A**).



[000312] To a well stirred reaction mixture of 5-(2-chloro-5-fluorophenyl)-4-methyl-1H-pyrazole (0.2 g, 0.094 mmol, 1.0 eq.), Cesium carbonate (0.46 g, 1.42 mmol, 1.5 eq.) in N,N-Dimethylformamide (5 mL) was added 2-(5-(benzyloxy)-2-fluorobenzoyl)-2-azaspiro[3.3]heptan-6-yl methane sulfonate (0.43 g, 1.04 mmol, 1.3 eq.). The reaction was heated at 50 °C for 12 h. After completion of reaction as monitored by TLC, the reaction mixture was poured in water (30 mL) and extracted with ethyl acetate (50 mL). The organic layer was washed with brine (30 mL), dried over Sodium sulfate and concentrated under reduce pressure to get residue. The residue was purified by combiflash using 35-40% ethyl acetate in n-hexane as eluent to get mixture of two regio isomers (5-(benzyloxy)-2-fluorophenyl)(6-(5-(2-

chloro-5-fluorophenyl)-4-methyl-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptan-2-yl)methanone (**Int-4**) and (5-(benzyloxy)-2-fluorophenyl)(6-(3-(2-chloro-5-fluorophenyl)-4-methyl-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptan-2-yl)methanone (**Int-4A**) (0.9 g, 97.63%).

[000313] Step-4: (6-(5-(2-chloro-5-fluorophenyl)-4-methyl-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptan-2-yl)(2-fluoro-5-hydroxyphenyl)methanone (PSY-05-00519-001) and (6-(3-(2-chloro-5-fluorophenyl)-4-methyl-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptan-2-yl)(2-fluoro-5-hydroxyphenyl)methanone (PSY-05-00520-001).



[000314] To a stirred solution of (5-(benzyloxy)-2-fluorophenyl)(6-(5-(2-chloro-5-fluorophenyl)-4-methyl-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptan-2-yl)methanone and (5-(benzyloxy)-2-fluorophenyl)(6-(3-(2-chloro-5-fluorophenyl)-4-methyl-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptan-2-yl)methanone (0.5 g, 0.93 mmol, 1.0 eq.) in dichloromethane (5 mL) was cooled to -78°C , was added BCl_3 1.0 M Solⁿ. in dichloromethane (2.8 mL, 2.80 mmol, 3.0 eq.), then the resulting reaction mixture was stirred at -78°C for next 2-3 h. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was quenched with Triethylamine (2 mL) and concentrated under vacuum to get crude. The crude was purified by prep-HPLC to get two fractions.

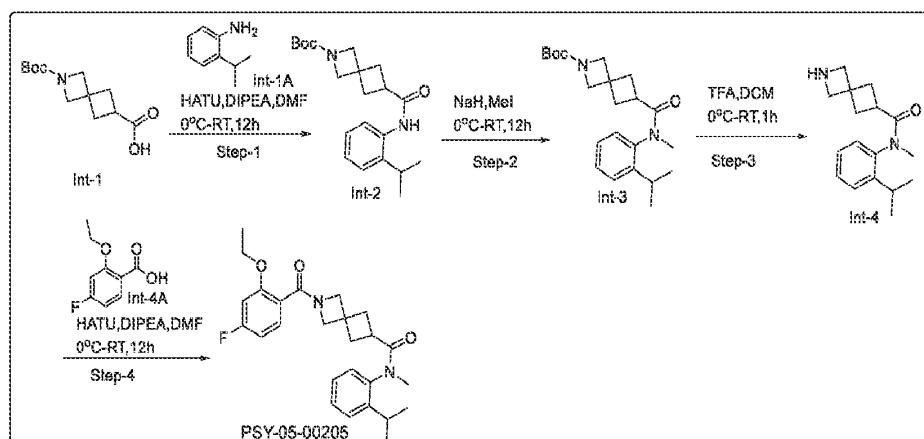
[000315] Fraction-1: (6-(5-(2-chloro-5-fluorophenyl)-4-methyl-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptan-2-yl)(2-fluoro-5-hydroxyphenyl)methanone (**PSY-05-00519-001**) (0.062 g, 15.01 %). LCMS: m/z 444.40 $[\text{M}+1]^+$. NMR: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.70 (s, 1H), 7.68 (d, J = 5.0 Hz, 1H), 7.58 (dt, J = 8.8, 5.6 Hz, 2H), 7.35 – 7.17 (m, 1H), 7.08 (q, J = 9.1 Hz, 1H), 6.85 – 6.71 (m, 2H), 4.32 (dq, J = 24.0, 7.9 Hz, 1H), 4.03 (d, J = 10.7 Hz, 4H), 2.68 (q, J = 15.2, 13.3 Hz, 4H), 1.81 (d, J = 2.6 Hz, 3H).

[000316] Fraction-2: (6-(3-(2-chloro-5-fluorophenyl)-4-methyl-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptan-2-yl)(2-fluoro-5-hydroxyphenyl)methanone (**PSY-05-00520-001**) (0.019 g, 4.76 %). LCMS: m/z 444.40 $[\text{M}+1]^+$. NMR: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.80 (s, 1H), 7.68 (d, J = 5.0 Hz, 1H), 7.58 (dt, J = 8.8, 5.6 Hz, 1H), 7.35 – 7.17 (m, 2H), 7.08 (q, J = 9.1 Hz, 1H), 6.87 – 6.74 (m,

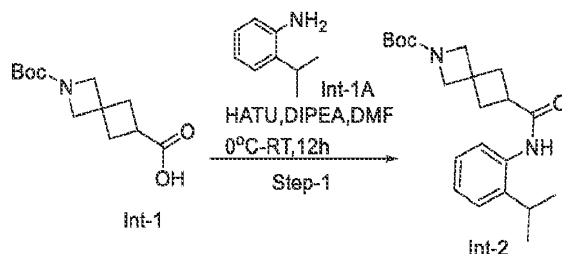
2H), 4.72 (dq, $J = 24.0, 7.9$ Hz, 1H), 4.13 (d, $J = 10.7$ Hz, 2H), 4.02 (d, $J = 9.4$ Hz, 2H), 2.68 (q, $J = 15.2, 13.3$ Hz, 4H), 1.91 (d, $J = 2.6$ Hz, 3H).

Example 16: Synthesis of 2-(2-ethoxy-4-fluorobenzoyl)-N-(2-isopropylphenyl)-N-methyl-2-azaspiro [3.3] heptane -6-carboxamide [Compound 205]

Synthetic scheme:



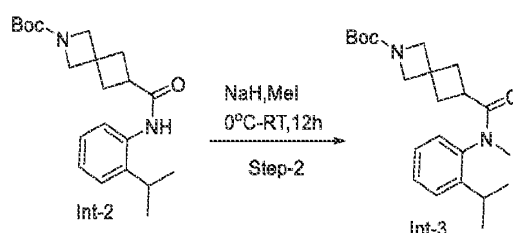
Step-1: Synthesis of tert-butyl 6-((2-isopropylphenyl)carbamoyl)-2-azaspiro[3.3]heptane-2-carboxylate (Int-2).



[000317] To a stirred solution of 2-(tert-butoxycarbonyl)-2-azaspiro [3.3] heptane-6-carboxylic acid (0.30 gm, 1.24 mmol, 1 eq.) in N,N-Dimethyl formamide (5 mL) were added HATU (0.70 gm, 1.86 mmol, 1.5 eq.) DIPEA (0.802 gm, 6.22 mmol, 5.0 eq.) followed by addition of 2-isopropylaniline (Int-1A) (0.21 gm, 1.24 mmol, 1.0 eq.) at 0°C and allowed to stirred the reaction at room temperature for 12 hr, the progress of the reaction of was monitored by TLC. After completion of reaction, the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 X 20 mL), washed with brine. The organic layer was dried over

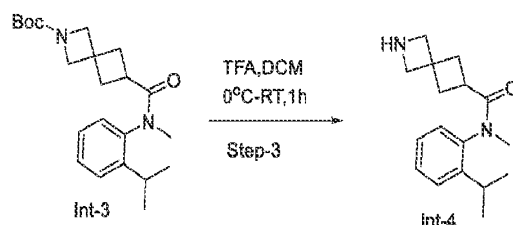
sodium sulphate and concentrated under vacuum to get crude material; which was purified by combi-flash by using 30% Ethyl acetate in n Hexane as mobile phase to give desired product tert-butyl 6-((2-isopropylphenyl)carbamoyl)-2-azaspiro [3.3] heptane-2-carboxylate (Int-2) 0.280 gm (Yield: 63.63%); LCMS: 359.6m/z [M+1]⁺

Step-2: Synthesis tert-butyl 6-((2-isopropylphenyl)(methyl)carbamoyl)-2-azaspiro [3.3] heptane-2-carboxylate (Int-3).



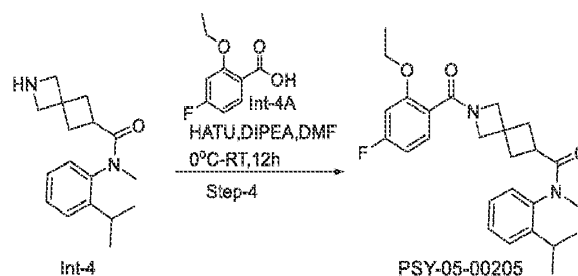
[000318] To a stirred solution of tert-butyl 6-((2-isopropylphenyl)carbamoyl)-2-azaspiro [3.3] heptane-2-carboxylate (0.4 gm, 1.11 mmol, 1.0 eq.) in N,N-Dimethyl formamide (5 mL), was added Sodium hydride (0.031 gm, 1.33 mmol, 1.2 eq.) at 0°C. The reaction was stirred at 0°C for 10 min. Methyl Iodide (0.187 gm, 1.33mmol, 1.2 eq.) was added dropwise and stirred the reaction mass at room temperature for 12 hrs. After completion of reaction as monitored by TLC, the reaction mixture was diluted with Ice cold water (10 mL) and extracted with Ethyl acetate (2 x 30mL). The combined organic layer was washed with brine solution, dried over sodium sulfate and concentrated to obtain crude product, which was purified by combiflash using 30% Ethyl acetate in Hexane as eluent to afford tert-butyl 6-((2-isopropylphenyl)(methyl)carbamoyl)-2-azaspiro[3.3]heptane-2-carboxylate (Int-3) 0.31 gm, (Yield-75.60%). LCMS: 373.4m/z [M⁺]

Step-3: Synthesis of N-(2-isopropylphenyl)-N-methyl-2-azaspiro [3.3] heptane-6-carboxamide (Int-4).



[000319] To a stirred solution tert-butyl 6-((2-isopropylphenyl)(methyl)carbamoyl)-2-azaspiro [3.3] heptane-2-carboxylate (Int-3) (0.50 gm, 1.33 mmol, 1.0 eq.) in Dichloromethane (10 mL) was added Trifluoroacetic acid (1.0 mL) at 0°C and allowed to stirred the reaction at Room temperature for 3 hr; the progress of the reaction of the was monitored by TLC. After completion of reaction, the reaction mixture was evaporated under vacuum and basified with bicarbonate solution (5 mL) extracted with Ethyl acetate. Ethyl acetate layer separated dried over sodium sulfate and concentrated to obtain crude product N-(2-isopropylphenyl)-N-methyl-2-azaspiro [3.3] heptane-6-carboxamide (Int-4) 0.350 gm (Yield: quantitative); LCMS: 273.4m/z [M+1]⁺

Step-4: Synthesis of 2-(2-ethoxy-4-fluorobenzoyl)-N-(2-isopropylphenyl)-N-methyl-2-azaspiro[3.3]heptane-6-carboxamide (Compound-00205)

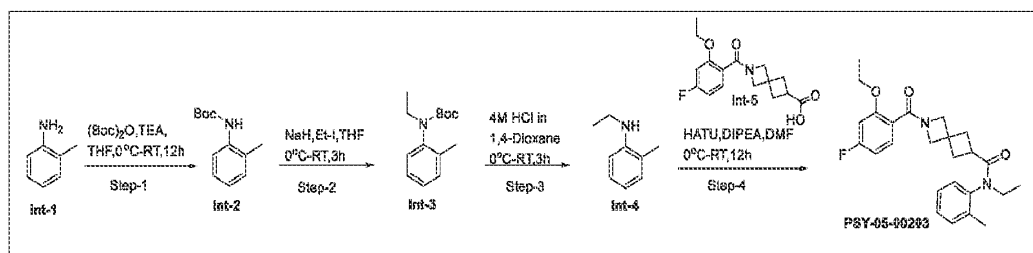


[000320] To a stirred solution of 2-ethoxy-4-fluorobenzoic acid (Int-4A), (0.150 gm, 0.815 mmol 1.0 eq.) in N,N-Dimethyl formamide (3 ml) were added N-(2-isopropylphenyl)-N-methyl-2-azaspiro [3.3] heptane-6-carboxamide (0.221 gm, 0.815 mmol, 1 eq.), DIPEA (0.31 gm, 2.445 mmol, 3.0 eq.), HATU (0.10 gm, 1.222 mmol, 1.5 eq.) at 0 °C. The resulting reaction mixture was stirred at room temperature for 12h. After completion of reaction as monitored by TLC, the reaction mixture was diluted with water (10 ml) and extracted with ethyl acetate (3*20 ml). The organic layer was washed with brine (10ml), dried over sodium sulphate and concentrated under vacuum to get crude material which was purified by combi-flash using 10% Methanol in Dichloromethane as eluent to get 2-(2-ethoxy-4-fluorobenzoyl)-N-(2-isopropylphenyl)-N-methyl-2-azaspiro [3.3] heptane-6-carboxamide (PSY-05-00205) as white solid 0.070gm (Yield: 20%); LCMS: 439.7 m/z ¹H NMR (400 MHz, DMSO-d₆) δ 7.51 – 7.38 (m, 1H), 7.42 – 7.25 (m, 1H), 7.26 (dd, J = 7.9, 4.7 Hz, 1H), 6.95 (ddd, J = 19.4, 11.6, 2.4 Hz, 1H), 6.84 – 6.71 (m, 1H), 4.08 (dq, J = 21.4, 6.8 Hz, 2H), 3.82 (t, J = 4.8 Hz, 3H), 3.75 (dq, J =

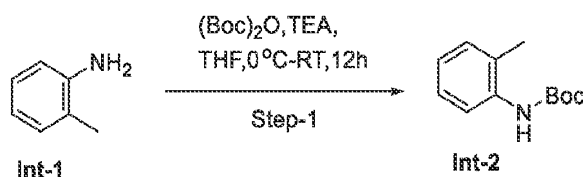
14.6, 8.9, 6.8 Hz, 1H), 3.16 – 3.01 (m, 3H), 2.83 (p, J = 6.8 Hz, 1H), 2.68 – 2.53 (m, 1H), 2.35 – 2.20 (m, 2H), 2.00 (ddd, J = 30.9, 12.2, 8.7 Hz, 2H), 1.31 (dt, J = 21.4, 7.0 Hz, 3H), 1.21 – 1.09 (m, 6H).

Example 17: Synthesis of 2-(2-ethoxy-4-fluorobenzoyl)-N-ethyl-N-(o-tolyl)-2-azaspiro [3.3] heptane-6-carboxamide [Compound 203]

Synthetic scheme:

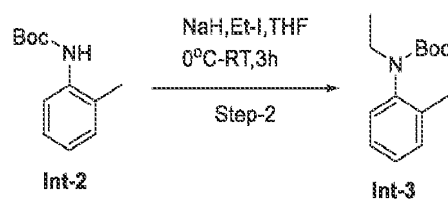


Step-1: Synthesis of tert-butyl o-tolyl carbamate (Int-2).



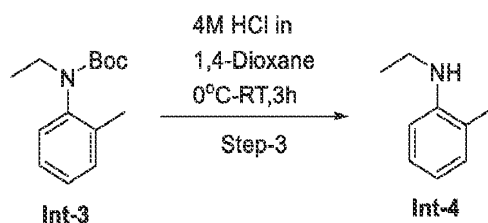
[000321] To a stirred solution of o-toluidine (1.0 gm, 9.34 mmol, 1.0 eq.) in N,N-Dimethyl formamide (10 mL) were added TEA (1.88 gm, 18.69 mmol, 2.0 eq.) followed by addition of Boc anhydride (2.24 gm, 10.288 mmol, 1.0 eq.) at 0°C and allowed to stirred the reaction at room temperature for 12 hr; the progress of the reaction of was monitored by TLC. After completion of reaction, the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 X 20 mL), washed with brine. The organic layer was dried over sodium sulphate and concentrated under vacuum to get crude material; which was purified by combi-flash by using 30% Ethyl acetate in n Hexane as mobile phase to give desired product tert-butyl o-tolylcarbamate (Int-2) 1.1 gm (Yield: 56.99%); LCMS: 208.2m/z [M+1]⁺

Step-2: Synthesis of tert-butyl ethyl (o-tolyl) carbamate (Int-3).



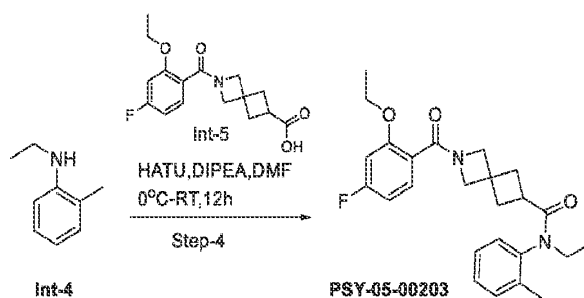
[000322] To a stirred solution of tert-butyl o-tolylcarbamate (0.5 gm, 2.415 mmol, 1.0 eq.) in N,N –Dimethyl formamide (8 mL), was added Sodium hydride (0.069 gm, 2.898 mmol, 1.2 eq.) at 0oC. The reaction was stirred at 0oC for 10 min. Ethyl Iodide (0.741 gm, 2.898 mmol, 1.2 eq.) was added dropwise and stirred the reaction mass at room temperature for 12 hrs. After completion of reaction as monitored by TLC, the reaction mixture was diluted with Ice cold water (10 mL) and extracted with Ethyl acetate (2 x 30mL). The combined organic layer was washed with brine solution, dried over sodium sulfate and concentrated to obtain crude product, which was purified by combiflash using 30% Ethyl acetate in Hexane as eluent to afford tert-butyl ethyl(o-tolyl)carbamate (Int-3) 0.45 gm, (Yield-80.35%). LCMS: 180.1m/z [M-56] +

Step-3: Synthesis of N-ethyl-2-methylaniline (Int-4)



[000323] To a stirred solution of tert-butyl ethyl(o-tolyl)carbamate (Int-3) (0.50 gm, 2.127 mmol, 1.0 eq.) in Dichloromethane (10 mL) was added Trifluoroacetic acid (1.0 mL) at 0oC and allowed to stirred the reaction at Room temperature for 3 hr; the progress of the reaction of the was monitored by TLC. After completion of reaction, the reaction mixture was evaporated under vacuum and basified with bicarbonate solution (5mL) extracted with Ethyl acetate. Ethyl acetate layer separated dried over sodium sulfate and concentrated to obtain crude product N-ethyl-2-methylaniline (Int-4) 0.350 gm (Yield: quantitative); LCMS: 136.1m/z [M+1] +

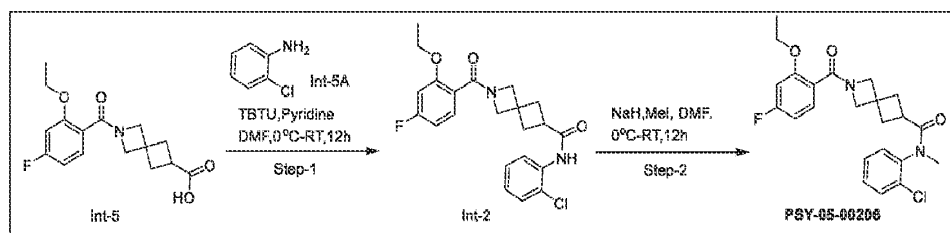
Step-4: Synthesis of 2-(2-ethoxy-4-fluorobenzoyl)-N-ethyl-N-(o-tolyl)-2-azaspiro [3.3] heptane-6-carboxamide (Compound-00203).



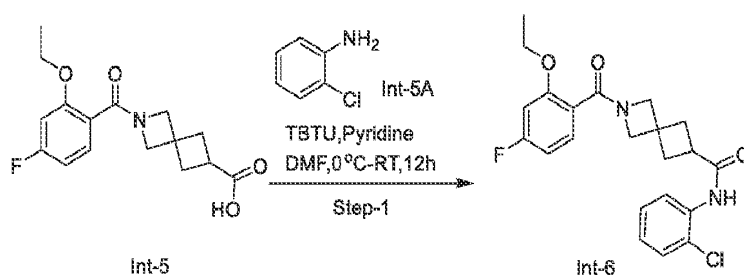
[000324] To a stirred solution of 2-(2-ethoxy-4-fluorobenzoyl)-2-azaspiro[3.3]heptane-6-carboxylic acid (Int-5), (0.20gm, 0.651 mmol 1.eq.) in N,N-Dimethyl formamide (5 ml) were N-ethyl-2-methylaniline (0.096 gm, 0.651 mmol, 1.0 eq.), DIPEA (0.25 gm, 1.954 mmol, 3.0 eq.), HATU (0.371 gm, 0.977 mmol, 1.5 eq.) at 0 °C. The resulting reaction mixture was stirred at room temperature for 12h. After completion of reaction as monitored by TLC, the reaction mixture was diluted with water (10 ml) and extracted with ethyl acetate (3*20 ml). The organic layer was washed with brine (10ml), dried over sodium sulphate and concentrated under vacuum to get crude material which was purified by combiflash using 10% Methanol in Dichloromethane as eluent to get 2-(2-ethoxy-4-fluorobenzoyl)-N-ethyl-N-(o-tolyl)-2-azaspiro[3.3]heptane-6-carboxamide (PSY-05-00203) as white solid 0.10 gm (Yield: 37.03 %); LCMS: 425.7 m/z ¹H NMR (400 MHz, DMSO-d₆) δ 7.33 (s, 2H), 7.33 – 7.20 (m, 2H), 7.09 (d, J = 7.6 Hz, 1H), 6.94 (ddd, J = 17.5, 11.7, 2.4 Hz, 1H), 6.76 (dtd, J = 10.8, 8.4, 2.5 Hz, 1H), 4.08 (dt, J = 13.8, 6.9 Hz, 3H), 4.06 – 3.88 (m, 1H), 3.86 – 3.73 (m, 2H), 3.71 (s, 2H), 3.10 (dt, J = 13.6, 6.8 Hz, 1H), 2.33 – 2.19 (m, 2H), 2.12 (d, J = 1.9 Hz, 3H), 1.92 (s, 1H), 1.93 – 1.82 (m, 1H), 1.30 (dt, J = 21.2, 7.0 Hz, 3H), 0.98 (td, J = 7.1, 5.2 Hz, 3H).

Example 18: *Synthesis of N-(2-chlorophenyl)-2-(2-ethoxy-4-fluorobenzoyl)-N-methyl-2-azaspiro[3.3] heptane -6-carboxamide [Compound 206]*

Synthetic scheme:

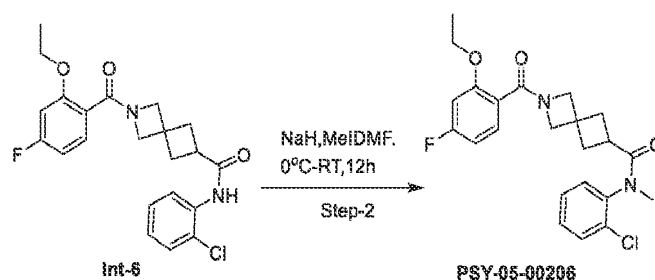


Step-1: Synthesis of N-(2-chlorophenyl)-2-(2-ethoxy-4-fluorobenzoyl)-2-azaspiro [3.3] heptane-6-carboxamide (Int-6).



[000325] To a stirred solution of 2-(2-ethoxy-4-fluorobenzoyl)-2-azaspiro [3.3] heptane-6-carboxylic acid (0.150 gm, 0.488 mmol, 1.0 eq.) in N,N-Dimethyl formamide (5 mL) were added TBTU (0.326 gm, 0.879 mmol, 1.8 eq.) Pyridine (0.154 gm, 1.954 mmol, 5.0 eq.) followed by addition of 2-chloroaniline (Int-5A) (0.082 gm, 0.586 mmol, 1.2 eq.) at 0°C and allowed to stirred the reaction at room temperature for 12 hr; the progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 X 20 mL), washed with brine. The organic layer was dried over sodium sulphate and concentrated under vacuum to get crude material; which was purified by combi-flash by using 5% Methanol in Dichloromethane as mobile phase to give desired product N-(2-chlorophenyl)-2-(2-ethoxy-4-fluorobenzoyl)-2-azaspiro[3.3]heptane-6-carboxamide (Int-6) 0.150 gm (Yield: 75%); LCMS: 417.7m/z [M+]

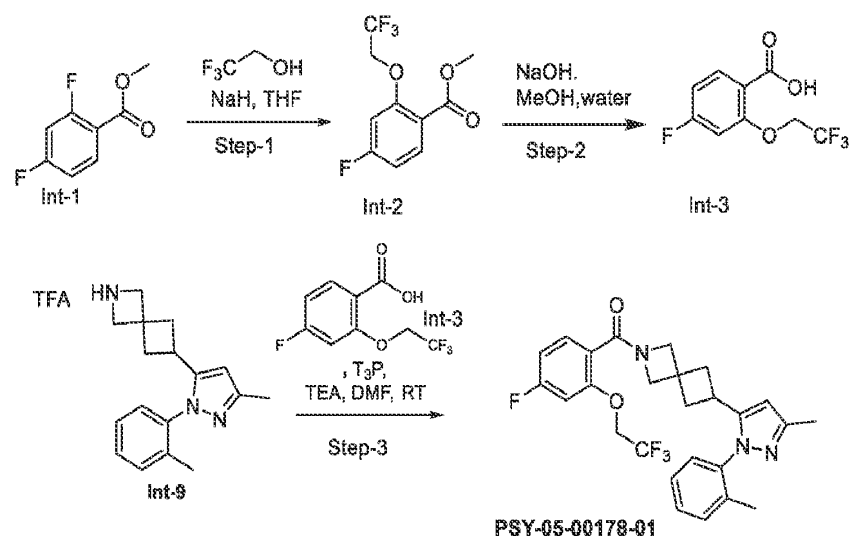
Step-2: Synthesis of N-(2-chlorophenyl)-2-(2-ethoxy-4-fluorobenzoyl)-N-methyl-2-azaspiro [3.3] heptane-6-carboxamide (Compound-00206)



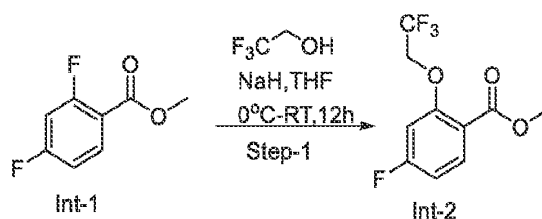
[000326] To a stirred solution of N-(2-chlorophenyl)-2-(2-ethoxy-4-fluorobenzoyl)-2-azaspiro [3.3] heptane-6-carboxamide (0.175 gm, 0.420 mmol, 1 eq.) in N,N-Dimethyl formamide (3 mL), was added Sodium hydride (0.012 gm, 0.504 mmol, 1.2 eq.) at 0°C. The reaction was stirred at 0°C for 10 min. Methyl Iodide (0.071 gm, 0.504 mmol, 1.2 eq.) was added dropwise and stirred the reaction mass at room temperature for 12 hrs. After completion of reaction as monitored by TLC, the reaction mixture was diluted with Ice cold water (10 mL) and extracted with Ethyl acetate (2 x 20mL). The combined organic layer was washed with brine solution, dried over sodium sulfate and concentrated to obtain crude product, which was purified by combiflash using 5% Methanol in Dichloromethane as mobile phase to give desired product N-(2-chlorophenyl)-2-(2-ethoxy-4-fluorobenzoyl) -N-methyl-2-azaspiro [3.3] heptane-6-carboxamide (PSY-05-00206) 0.10 gm, (Yield-55.55%). LCMS: 431.4m/z [M+]⁺ 1H NMR (400 MHz, DMSO-d₆) δ 7.64 (ddd, J = 9.3, 6.6, 3.9 Hz, 1H), 7.46 (ddd, J = 13.8, 6.0, 3.3 Hz, 3H), 7.38 – 7.22 (m, 1H), 6.95 (ddd, J = 15.6, 11.6, 2.4 Hz, 1H), 6.77 (dtd, J = 10.6, 8.4, 2.4 Hz, 1H), 4.11 (q, J = 5.9, 5.1 Hz, 1H), 4.06 (q, J = 6.9, 5.9 Hz, 1H), 3.84 (d, J = 7.1 Hz, 2H), 3.76 (d, J = 14.2 Hz, 2H), 3.07 (d, J = 6.4 Hz, 3H), 2.68 (hept, J = 8.2 Hz, 1H), 2.34 – 2.24 (m, 2H), 2.08 – 1.85 (m, 2H), 1.42 – 1.22 (m, 3H).

Example 19: Synthesis of (4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl) (6-(3-methyl-1-(o-tolyl) -1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl) methanone. [Compound 178]

Synthetic scheme:

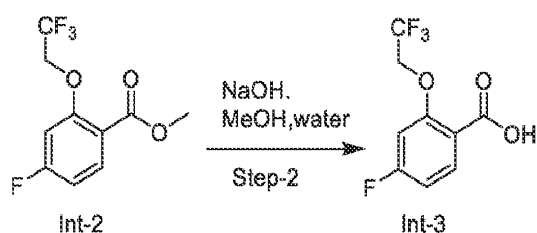


Step-1: Synthesis of methyl 4-fluoro-2-(2, 2, 2-trifluoroethoxy) benzoate (Int-2).



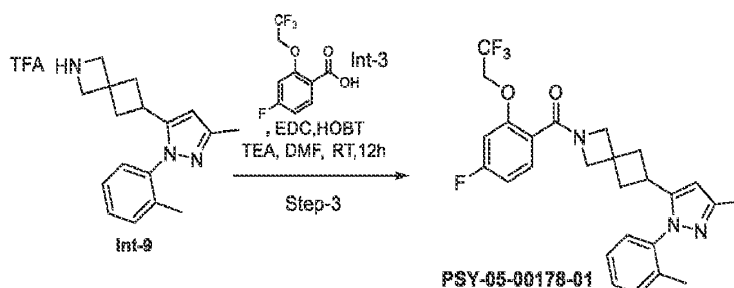
[000327] To a stirred solution of methyl 2,4-difluorobenzoate (0.10 gm, 0.58 mmol, 1.0 eq.) in N,N-Dimethyl formamide (2 mL), was added Sodium hydride (0.016 gm, 0.679 mmol, 1.2 eq.) at 0°C. The reaction was stirred at 0°C for 10 min. 2, 2, 2-trifluoroethan-1-ol (0.081 gm, 0.813 mmol) was added dropwise and stirred the reaction mass at room temperature for 12 hrs. After completion of reaction as monitored by TLC, the reaction mixture was diluted with Ice cold water (5 mL) and extracted with Ethyl acetate (2 x 20mL). The combined organic layer was washed with brine solution, dried over sodium sulfate and concentrated to obtain crude product, which was purified by combiflash using 10% Ethyl acetate in Hexane as eluent to afford methyl 4-fluoro-2-(2,2,2-trifluoroethoxy)benzoate (Int-2) 0.10 gm, (Yield-68%). The compound was containing disubstituted product which was non separable by column chromatography was carried forward as a mixture for next step.

Step-2: Synthesis of 4-fluoro-2-(2,2,2-trifluoroethoxy)benzoic acid (Int-3).



[000328] To a stirred solution of methyl 4-fluoro-2-(2,2,2-trifluoroethoxy)benzoate (Int-2) (1.0 gm, 3.96 mmol, 1 eq.) in THF (10 mL), MeOH (5 mL), Water (5 mL) was added Sodium Hydroxide [NaOH] (0.23 gm, 5.95 mmol, 1.5 eq.) at 0°C. The reaction mixture was stirred at room temperature for next 12 hr. The progress of the reaction was monitored by TLC; after completion of reaction, the reaction mixture was evaporated under vacuum. The crude product was acidified with 2N HCL (PH=4) The white solid was precipitated out which was filtered through Buchner funnel and dried under vacuum to give 4-fluoro-2-(2,2,2-trifluoroethoxy)benzoic acid (Int-3) 0.50gm (Yield: 53%); ¹H NMR (400 MHz, DMSO-d₆) δ 12.83 (s, 1H), 7.77 (dd, J = 8.7, 7.0 Hz, 1H), 7.17 (dd, J = 11.1, 2.4 Hz, 1H), 6.96 (td, J = 8.4, 2.4 Hz, 1H), 4.84 (q, J = 8.8 Hz, 2H).

Step-3: Synthesis of (4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone (Compound-00178-001).

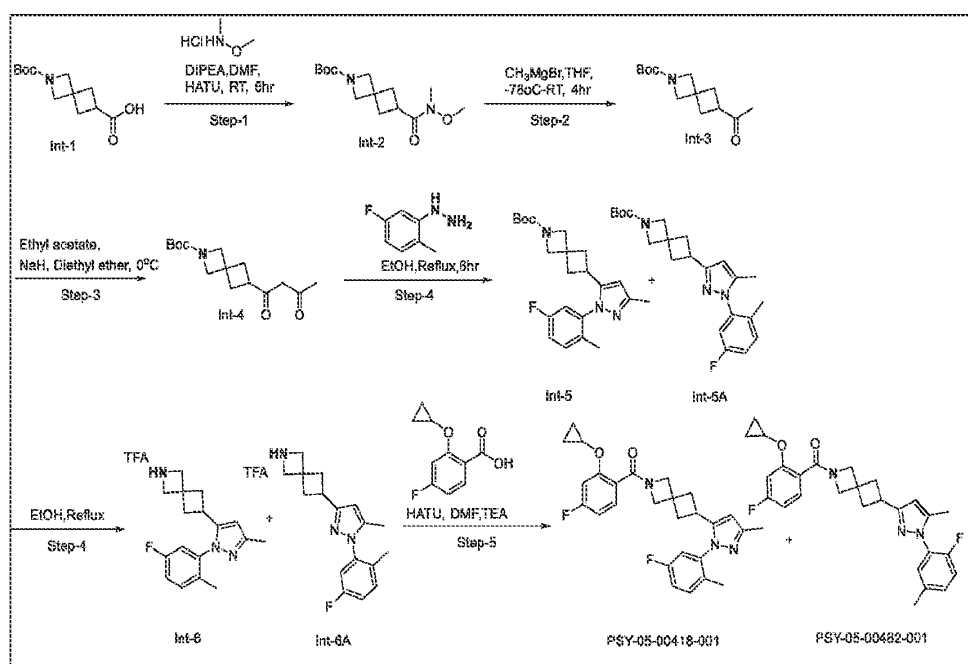


[000329] To a stirred solution of 6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptane 2,2,2-trifluoroacetate (0.10gm, 0.37 mmol 1.eq.) in N,N-Dimethyl formamide (3 ml) were added 4-fluoro-2-(2,2,2-trifluoroethoxy)benzoic acid (0.89 gm, 0.37 mmol, 1.0 eq.), TEA (0.11 gm, 1.12 mmol, 3.0 eq.), EDC-HCl (0.10 gm, 0.56 mmol, 1.5 eq.), and HOBT (0.025 gm, 0.18 mmol, 0.5 eq.) at 0 °C. The resulting reaction mixture was stirred at room temperature for 12h. After completion of reaction as monitored by TLC, the reaction mixture was diluted with water (10 ml) and extracted with ethyl acetate (3*20 ml). The organic layer was washed with

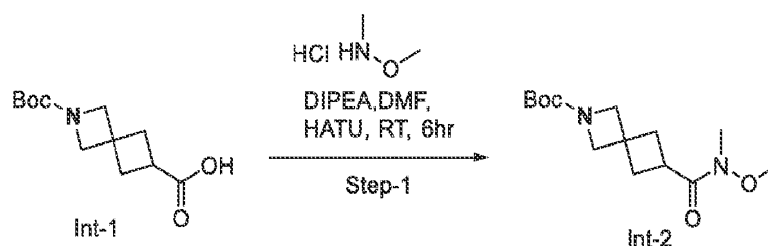
brine (10ml), dried over sodium sulphate and concentrated under vacuum to get crude material which was purified by combiflash using 80% Ethyl acetate in hexane as eluent to get PSY-05-00178 as white solid (0.050. (Yield: 28%); LCMS: 488.5 m/z [M+]⁺ ¹H NMR (400 MHz, DMSO-d₆) δ 7.46 – 7.36 (m, 2H), 7.40 – 7.25 (m, 2H), 7.16 (s, 1H), 7.21 – 7.10 (m, 1H), 6.98 – 6.87 (m, 1H), 6.17 (s, 1H), 4.93 – 4.79 (m, 2H), 3.95 (s, 1H), 3.86 (d, J = 19.9 Hz, 2H), 3.78 (s, 1H), 3.03– 2.92 (m, 1H), 2.33 (t, J = 10.4 Hz, 2H), 2.21 (dd, J = 23.9, 9.2 Hz, 5H), 1.93 (d, J = 2.3 Hz, 3H).

Example 20: Synthesis of (2-cyclopropoxy-4-fluorophenyl)(6-(1-(5-fluoro-2-methylphenyl)-3-methyl-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone [Compound 418]; and (2-cyclopropoxy-4-fluorophenyl)(6-(1-(5-fluoro-2-methylphenyl)-5-methyl-1H-pyrazol-3-yl)-2-azaspiro[3.3]heptan-2-yl)methanone [Compound 482].

Synthetic scheme:

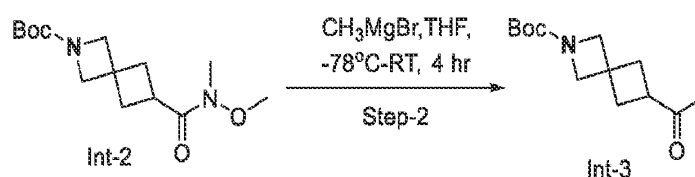


Step-1: Tert-butyl 6-(methoxymethyl)-2-azaspiro[3.3]heptane-2-carboxylate (Int-2).



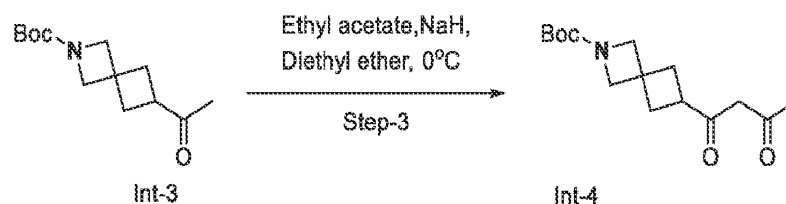
[000330] To a stirred solution of 2-(tert-butoxycarbonyl)-2-azaspiro[3.3]heptane-6-carboxylic acid (5.0 g, 20.72 mmol, 1.0 eq.), Diisopropylethylamine (11 mL, 62.16 mmol, 3.0 eq.), N,O-dimethyl hydroxylamine (3.0 g, 31.08 mmol, 1.5 eq.) in N,N-Dimethylformamide (25 mL), was added HATU (11.8 g, 31.08 mmol, 1.5 eq.) at 0 °C. Stir the reaction at room temperature for 6 hr. After completion of reaction as monitored by TLC, the reaction mixture was poured in ice cold water (100 mL) and extracted with ethyl acetate (50mL*3). The organic layer was dried over Sodium sulfate and concentrated under reduce pressure to get residue. The residue was purified by combiflash using 4-5% Methanol in dichloromethane as eluent to get tert-butyl 6-(methoxy (methyl) carbamoyl)-2-azaspiro [3.3] heptane-2-carboxylate (5.5 g, 93.34%).

Step-2: tert-butyl 6-acetyl-2-azaspiro [3.3] heptane-2-carboxylate (Int-3).



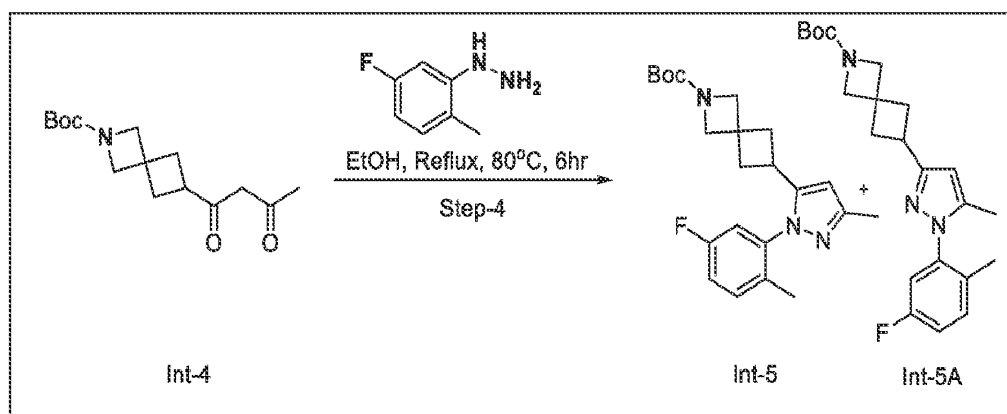
[000331] To a stirred solution of tert-butyl 6-(methoxy (methyl) carbamoyl)-2-azaspiro [3.3] heptane-2-carboxylate (Int-2) (5.5g, 19.34 mmol, 1.0 eq.) in tetrahydrofuran (30 mL), was slowly added Methyl Magnesium Bromide 3M (11.6 mL, 34.81 mmol, 1.5 eq.) at -78 °C. Stir the reaction at RT for 4 hr. After completion of reaction as monitored by TLC, the reaction mixture was poured in ice cold water (100 mL) and extracted with ethyl acetate (50 mL*3). The organic layer was dried over Sodium sulfate and concentrated under reduce pressure to get residue. The residue was purified by combiflash using 12-15% Ethyl acetate in n-hexane as eluent to get tert-butyl 6-acetyl-2-azaspiro [3.3] heptane-2-carboxylate (Int-3) (3.2 g, 69.13%).

Step-3: Tert-butyl 6-(3-oxobutanoyl)-2-azaspiro [3.3] heptane-2-carboxylate (Int-4).



[000332] To a stirred solution of tert-butyl 6-acetyl-2-azaspiro[3.3]heptane-2-carboxylate (Int-3) (2.0 g, 8.36 mmol, 1.0 eq.) in diethyl ether (10 mL) was added Sodium hydride 60% (1.67 g, 41.48 mmol, 5.0 eq.) at 0 °C, followed by the dropwise addition of ethyl acetate (4.9 g, 56.06 mmol, 6.7 eq.). The reaction mass was stirred at room temperature for 4-5 hr. After completion of reaction as monitored by TLC. The reaction mixture was poured in water (100 mL), acidified with 10% dilute HCl and extracted with ethyl acetate (50 mL*3). The organic layer was washed with brine (100 mL), dried over Sodium sulfate and concentrated under reduce pressure to get residue. The residue was purified by combiflash using 10-15% ethyl acetate in n-hexane as eluent to get tert-butyl 6-(3-oxobutanoyl)-2-azaspiro[3.3]heptane-2-carboxylate (Int-4) (2.1 g, 89.3%).

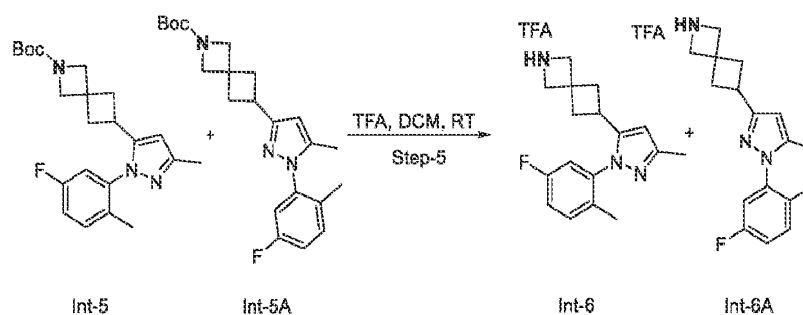
Step-4: Tert-butyl 6-(1-(5-fluoro-2-methylphenyl)-3-methyl-1H-pyrazol-5-yl)-2-azaspiro [3.3] heptane-2-carboxylate (Int- 5) and
Tert-butyl 6-(1-(5-fluoro-2-methylphenyl)-5-methyl-1H-pyrazol-3-yl)-2-azaspiro [3.3] heptane-2-carboxylate (Int-5A).



[000333] To a stirred solution of tert-butyl 6-(3-oxobutanoyl)-2-azaspiro[3.3]heptane-2-carboxylate (1.6 g, 5.69 mmol, 1.0 eq.) in Ethanol (15 mL) was added (5-fluoro-2-

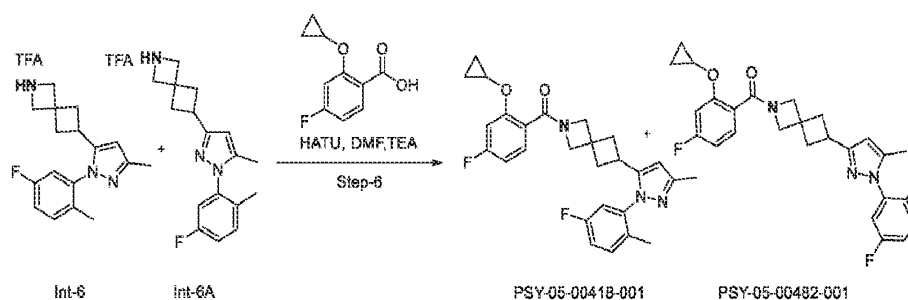
methylphenyl)hydrazine (1.5 g, 8.54 mmol, 1.5 eq.) the reaction mass was heated at 80 °C for 16hr. After completion of reaction as monitored by TLC, the reaction mixture was concentrated to get residue. The residue was purified by combiflash using 80% ethyl acetate in n-hexane as eluent to get mixture of tert-butyl 6-(1-(5-fluoro-2-methylphenyl)-3-methyl-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptane-2-carboxylate (**Int-5**) and tert-butyl 6-(1-(5-fluoro-2-methylphenyl)-5-methyl-1H-pyrazol-3-yl)-2-azaspiro[3.3]heptane-2-carboxylate (**Int-5A**) (2.0g, 91.3%).

Step-5: 6-(1-(5-fluoro-2-methylphenyl)-3-methyl-1H-pyrazol-5-yl)-2-azaspiro [3.3] heptane (Int-6) and 6-(1-(5-fluoro-2-methylphenyl)-5-methyl-1H-pyrazol-3-yl)-2-azaspiro [3.3] heptane (Int-6A).



[000334] To a well stirred reaction mixture of tert-butyl 6-(1-(5-fluoro-2-methylphenyl)-3-methyl-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptane-2-carboxylate (**Int-5**) and tert-butyl 6-(1-(5-fluoro-2-methylphenyl)-5-methyl-1H-pyrazol-3-yl)-2-azaspiro[3.3]heptane-2-carboxylate (**Int-5A**) (2.0 g, 6.99 mmol, 1.0 eq.) in Dichloromethane (10 mL) was added Trifluoroacetic acid (3.0 mL) dropwise at 0 °C. After completion of reaction as monitored by TLC, the reaction mixture was concentrated to get mixture of 6-(1-(5-fluoro-2-methylphenyl)-3-methyl-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptane (**Int-6**) and 6-(1-(5-fluoro-2-methylphenyl)-5-methyl-1H-pyrazol-3-yl)-2-azaspiro[3.3]heptane (**Int-6A**) (0.420 g, 82.58 %).

Step-6: (2-cyclopropoxy-4-fluorophenyl)(6-(1-(5-fluoro-2-methylphenyl)-3-methyl-1H-pyrazol-5-yl)-2-azaspiro [3.3] heptan-2-yl)methanone (PSY-05-00418-001) and (2-cyclopropoxy-4-fluorophenyl)(6-(1-(5-fluoro-2-methylphenyl)-5-methyl-1H-pyrazol-3-yl)-2-azaspiro [3.3] heptan-2-yl) methanone (PSY-05-00482-001).



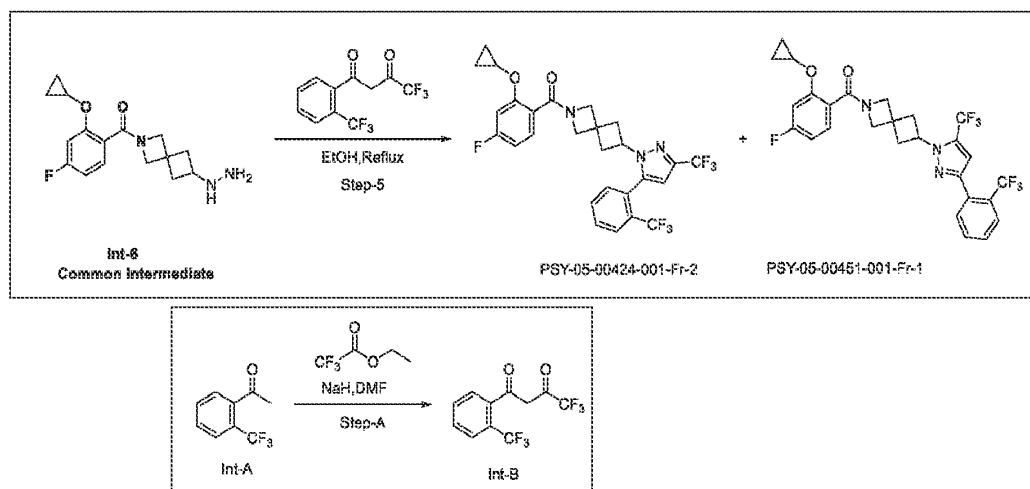
[000335] To a well stirred reaction mixture of 6-(1-(5-fluoro-2-methylphenyl)-3-methyl-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptane (Int-6) and 6-(1-(5-fluoro-2-methylphenyl)-5-methyl-1H-pyrazol-3-yl)-2-azaspiro[3.3]heptane (Int-6A) (0.42 g, 1.56 mmol, 1.2 eq.), N,N-Diisopropylethylamine (0.45 g, 6.50 mmol, 5.0 eq.), Int-D (0.255 g, 1.30 mmol, 1.0 eq.) in N,N-Dimethylformamide (5 mL) was added TBTU (0.63 g, 1.95 mmol, 1.5 eq.) at 0°C. The reaction mass was stirred at room temperature for 3-4 hr. After completion of reaction as monitored by TLC, the reaction mixture was poured in water (100 mL) and extracted with ethyl acetate (50 mL*3). The organic layer was washed with saturated solution of sodium carbonate (50 mL) and brine (100 mL), dried over Sodium sulfate and concentrated under reduce pressure to get residue. The residue was purified by combiflash using 80-90% ethyl acetate in n-hexane as eluent. The crude was submitted to prep HPLC for purification. Two Fraction was collected.

[000336] Fraction-1: (2-cyclopropoxy-4-fluorophenyl)(6-(1-(5-fluoro-2-methylphenyl)-3-methyl-1H-pyrazol-5-yl)-2-azaspiro [3.3] heptan-2-yl)methanone (**PSY-05-00418-001**) (0.027 g, 3.96 %). LCMS: m/z 464.44 $[M+1]^+$. NMR: ^1H NMR (400 MHz, DMSO- d_6) δ 7.42 (q, J = 7.8 Hz, 1H), 7.30 (t, J = 7.6 Hz, 2H), 7.28 – 7.11 (m, 2H), 6.87 – 6.81 (m, 1H), 3.98 – 3.85 (m, 3H), 3.79 (s, 1H), 3.70 (s, 1H), 3.13 – 2.99 (m, 1H), 2.35 (t, J = 10.1 Hz, 1H), 2.22 (dd, J = 23.5, 9.3 Hz, 6H), 1.91 (s, 3H), 0.89 – 0.81 (m, 2H), 0.67 (s, 2H).

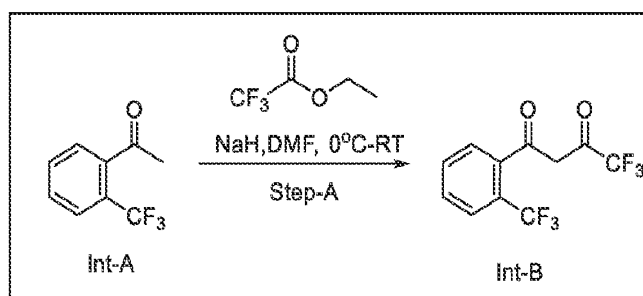
[000337] Fraction-2: (2-cyclopropoxy-4-fluorophenyl)(6-(1-(5-fluoro-2-methylphenyl)-5-methyl-1H-pyrazol-3-yl)-2-azaspiro [3.3] heptan-2-yl) methanone (**PSY-05-00482-001**) (0.050 g, 7.33 %). LCMS: m/z 464.44 $[M+1]^+$. NMR: ^1H NMR (400 MHz, DMSO- d_6) δ 7.43 (d, J = 7.5 Hz, 1H), 7.26 (dq, J = 27.9, 10.5, 9.1 Hz, 4H), 6.82 (d, J = 13.5 Hz, 1H), 6.12 (d, J = 13.5 Hz, 1H), 4.06 (s, 1H), 3.91 (s, 3H), 3.73 (s, 1H), 3.41 (s, 1H), 2.58 -2.41 (d, J = 18.7 Hz, 2H), 2.04 (d, J = 7.3 Hz, 3H), 1.91 (d, J = 16.1 Hz, 3H), 0.89 – 0.80 (m, 2H), 0.72 (s, 2H).

Example 21: Synthesis of (2-cyclopropoxy-4-fluorophenyl)(6-(3-(trifluoromethyl)-5-(2-(trifluoromethyl) phenyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptan-2-yl)methanone (Compound 424); and (2-cyclopropoxy-4-fluorophenyl)(6-(5-(trifluoromethyl)-3-(2-(trifluoromethyl) phenyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptan-2-yl)methanone (Compound 451)

Synthetic scheme:



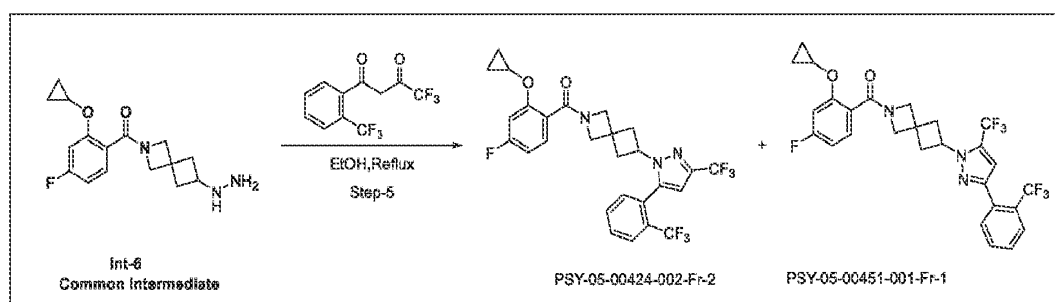
Step-A: 4,4,4-trifluoro-1-(2-(trifluoromethyl)phenyl)butane-1,3-dione (Int-B).



[000338] To a stirred solution of 1-(2-(trifluoromethyl)phenyl)ethan-1-one (3.0 g, 1.59 mmol, 1.0 eq.) in N,N- Dimethylformamide at 0°C under N₂ atmosphere, NaH 60% (0.500 g, 2.393mmol, 1.5eq.) was added and allowed to stir for 30 mins at 0°C. Then added Trifluoroethylacetate (3.50 g, 2.388 mmol, 1.5 eq.) to the reaction mass and stirred the reaction at room temperature for 16 hr. After completion of reaction as monitored by TLC, the reaction mixture was poured in ice cold water (100 mL). Acidified with dil. HCl up to P^H 4.0 and extracted with ethyl acetate (50mL*3). The organic layer was dried over Sodium sulfate and

concentrated under reduce pressure to get residue. The residue was purified by combiflash using 50% ethyl acetate in n-hexane as eluent to get tert-butyl 6-(methoxy (methyl) carbamoyl)-2-azaspiro [3.3] heptane-2-carboxylate (**Int-B**) (2.0 g, 44.15%).

Step-5: (2-cyclopropoxy-4-fluorophenyl)(6-(3-(trifluoromethyl)-5-(2-(trifluoromethyl) phenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl)methanone (PSY-05-00424-001) and (2-cyclopropoxy-4-fluorophenyl)(6-(5-(trifluoromethyl)-3-(2-(trifluoromethyl) phenyl)-1H-pyrazol-1-yl)-2-azaspiro [3.3] heptan-2-yl) methanone (PSY-05-00451-001).



[000339] To a stirred solution of tert-butyl 6-(methoxy (methyl) carbamoyl)-2-azaspiro [3.3] heptane-2-carboxylate (**Int-B**) (0.3 g, 1.05 mmol, 1.0 eq.) in Ethanol (5 mL) was added (2-cyclopropoxy-4-fluorophenyl)(6-hydrazineyl-2-azaspiro[3.3]heptan-2-yl)methanone (Int-6) (0.62 g, 2.10 mmol, 2.0 eq.) the reaction mass was heated at 80 °C for 16hr. After completion of reaction as monitored by TLC, the reaction mixture was concentrated to get residue. The residue was purified by combiflash using 80% ethyl acetate in n-hexane as eluent to get mixture of two region isomers. The crude was submitted to prep HPLC for purification. Two Fraction was collected.

[000340] **Fraction-1:** (2-cyclopropoxy-4-fluorophenyl)(6-(5-(trifluoromethyl)-3-(2-(trifluoromethyl) phenyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptan-2-yl)methanone (**PSY-05-00451-001**) (0.027 g, 4.97 %). LCMS: m/z 553.91 $[M+1]^+$. NMR: ^1H NMR (400 MHz, DMSO- d_6) δ 8.68 (s, 1H), 8.05 – 7.83 (m, 3H), 7.63 (d, J = 7.5 Hz, 1H), 7.30 (dq, J = 27.9, 10.5, 9.1 Hz, 1H), 7.21 – 7.28 (dq, J = 27.9, 10.5, 9.1 Hz, 1H), 6.92 (d, J = 13.5 Hz, 2H), 4.46 (s, 1H), 4.00 – 3.95 (s, 3H), 3.80 (s, 2H), 2.78 -2.70 (d, J = 18.7 Hz, 4H), 0.87 (d, J = 16.1 Hz, 2H), 0.79 – 0.70 (m, 2H).

[000341] **Fraction-2:** (2-cyclopropoxy-4-fluorophenyl)(6-(3-(trifluoromethyl)-5-(2-(trifluoromethyl) phenyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptan-2-yl)methanone (**PSY-05-00424-001**) (0.050 g, 9.20 %). LCMS: m/z 553.91 $[M+1]^+$. NMR: 1H NMR (400 MHz, DMSO- d_6) δ 8.68 (s, 1H), 8.15 – 8.37 (m, 5H), 7.63 (d, $J = 7.5$ Hz, 1H), 7.40 (dq, $J = 27.9, 10.5, 9.1$ Hz, 1H), 6.92 (d, $J = 13.5$ Hz, 1H), 5.52 (d, $J = 13.5$ Hz, 1H), 4.56 (s, 1H), 4.00 (s, 3H), 3.63 (s, 2H), 2.78 -2.70 (d, $J = 18.7$ Hz, 2H), 2.24 (d, $J = 7.3$ Hz, 2H), 0.87 (d, $J = 16.1$ Hz, 2H), 0.79 – 0.70 (m, 2H), 0.72 (s, 2H).

Example 22: Measuring MAGL Inhibition Potency (IC_{50})

[000342] The potency of certain compounds for inhibiting MAGL were obtained using the following assays.

[000343] The monoacylglycerol lipase inhibitor screening assay kit from Cayman Chemical was used to measure the MAGL potency for the compounds in Table 6 and Table 7.

[000344] Cayman's Monoacylglycerol Lipase Inhibitor Screening Assay provides a method for screening human MAGL inhibitors. MAGL hydrolyzes 4-nitrophenylacetate resulting in a yellow product, 4-nitrophenol, with an absorbance of 405-412 nm.

[000345] MAGL Inhibition was measured by the following assay. Monoacylglycerol Lipase (MAGL) inhibition was measured using recombinant MAGL enzyme (aa 2-303 RBC, internal preparation) and the substrate 4-Nitrophenyl acetate (4NPA) (Sigma-Aldrich, N8130).

Hydrolysis of the substrate in the presence of the enzyme was measured by absorbance at 405 nm. 10 μ L of assay buffer (10 mM Tris pH 7.5, 1 mM EDTA, 0.9% DMSO) was added to a black 384-well non-binding plate with clear bottom (Greiner, 781906) for each reaction.

Compounds were dispensed using an acoustic liquid handler (Echo, Beckman) at 45 nL (0.1% DMSO). Test compounds and control for MAGL inhibitor JZL-184 (Caymen Chemical, 13158) were tested in 10-concentration IC_{50} mode with 3-fold serial dilution at a starting concentration of 10 μ M. DMSO control wells were included for reference. A 10.8 nM (1.8X) MAGL mix in assay buffer was prepared, with 25 μ L added to each reaction well, for a final assay concentration of 6 nM. No enzyme wells received 25 μ L of buffer. Plate was incubated at room temperature for 30 minutes. 35 mM solution of 4NPA in methanol was prepared daily. A 4.5x 4NPA substrate solution was prepared in assay buffer and 10 μ L was added to each reaction

well, for a final assay concentration of 0.25 mM. Plate was spun for 1 minute at 1000 rpm before measuring absorbance using a CLARIOstar plate reader (BMG Labtech). A kinetic reading at 405 nm was done every minute for 30 minutes. Data was analyzed using the linear slope of the reaction progress curve and the average of the no-enzyme wells (background) was subtracted from the data. The background-subtracted slope data was converted to % activity using the average of wells with enzyme and DMSO vehicle. IC50s were calculated using GraphPad software (Sigmoidal dose response, variable slope equation).

[000346] Table 6 and Table 7 provide exemplary compounds of Formula (I) and their potency for MAGL inhibition measured using the Potency Assay of Example 22 above, with the following modifications described in Table C below. Table 8 provides potency measurements of MAGL inhibition measured using the Potency Assay of Example 22 above, with the following modifications described in Table C.

Table C. Methods Used to Measure MAGL Inhibition with 4NPA Substrate

Method No.	Name	Modification to Assay of Example 16
1	MAGL (6nM) Reaction Biology Enzyme	Reaction Biology's internal MAGL enzyme prep was used. Concentration of MAGL enzyme in the assay was 6nM.
2	MAGL (10nM) Cayman Chemical Enzyme	Cayman Chemical's MAGL enzyme prep was used. Concentration of MAGL enzyme in the assay was 10nM.
3	MAGL (10nM) Reaction Biology Enzyme	Reaction Biology's internal MAGL enzyme prep was used. Concentration of MAGL enzyme in the assay was 10nM.
4	MAGL (15nM) Cayman Chemical Enzyme	Cayman Chemical's MAGL enzyme prep was used. Concentration of MAGL enzyme in the assay was 15nM.
5	MAGL (25nM) Cayman Chemical Enzyme	Cayman Chemical's MAGL enzyme prep was used. Concentration of MAGL enzyme in the assay was 25nM.
6	MAGL IC50 Enzyme Conc 6, Reaction Biology	Reaction Biology's internal MAGL enzyme prep was used. Concentration of MAGL enzyme in the assay was 6nM.
7	MAGL IC50 Enzyme Conc 10, Reaction Biology	Reaction Biology's internal MAGL enzyme prep was used. Concentration of MAGL enzyme in the assay was 10nM.
8	MAGL IC50 Enzyme Conc 10, Cayman Chemical	Cayman Chemical's MAGL enzyme prep was used. Concentration of MAGL enzyme in the assay was 10nM.
9	MAGL IC50 Enzyme Conc 15, Cayman Chemical	Cayman Chemical's MAGL enzyme prep was used. Concentration of MAGL enzyme in the assay was 15nM.
10	MAGL IC50 Enzyme Conc 25, Cayman Chemical	Cayman Chemical's MAGL enzyme prep was used. Concentration of MAGL enzyme in the assay was 25nM.

Method No.	Name	Modification to Assay of Example 16
11	MAGL IC ₅₀ Enzyme Conc 20, Reaction Biology	Reaction Biology's internal MAGL enzyme prep was used. Concentration of MAGL enzyme in the assay was 25nM.
12	MAGL IC ₅₀ Enzyme Conc 15, Reaction Biology	Reaction Biology's internal MAGL enzyme prep was used. Concentration of MAGL enzyme in the assay was 15nM.
13	MAGL IC ₅₀ Enzyme Conc 12, Reaction Biology	Reaction Biology's internal MAGL enzyme prep was used. Concentration of MAGL enzyme in the assay was 12nM.
14	MAGL IC ₅₀ Enzyme Conc "0", Source "0"	Reaction Biology's internal MAGL enzyme prep was used. Concentration of MAGL enzyme in the assay was 6nM.

[000347] Results of potency measurements in Table 6, Table 7 and Table 8 are expressed as the following ranges: "A" refers to an IC₅₀ measurement of <50 nM, "B" refers to an IC₅₀ measurement of between 50 nM and 150 nM, "C" refers to an IC₅₀ measurement of greater than 150nM and less than 500 nM, "D" refers to an IC₅₀ measurement of 500 nM to 1 micromolar, and "E" refers to an IC₅₀ measurement of greater than 1 micromolar up to 5.1 micromolar. The number after each letter for potency measurement value indicates the Method from Table C that was used to obtain that measurement value (e.g., "A(1)" indicates an IC₅₀ measurement of <50nM obtained from the Method 1 of Example 22 in Table C).

Example 23: Measuring FAAH Inhibition Potency (IC₅₀)

[000348] Comparative compound potency at FAAH can be obtained with the following assay. A "Selective MAGL Inhibitor Compound" refers to a compound that selectively inhibits MAGL with an IC₅₀ that is at least 10x the IC₅₀ for its inhibition of fatty acid amide hydrolase (FAAH), and that has an IC₅₀ of 150 nM or less for MAGL inhibition (according to the MAGL Potency assay of Example 22).

[000349] MAGL inhibitor compounds were also counter-screened for FAAH inhibition potency using the following assay. Assessment of FAAH inhibition was performed using Fatty Acid Amide Hydrolase Inhibitor Screening Assay Kit (Cayman Item No. 10005196) following manufacture's instruction with some modifications. The kit utilizes human recombinant FAAH and the fluorescent substrate, AMC Arachidonoyl amide (AAMCA). 5 µL of assay buffer (125 mM Tris, pH 9.0, 1 mM EDTA, i.e. ethylenediaminetetraacetic acid) was added to a 384-well black plate (Corning, 3573). Test compounds and control inhibitor JZL-195 (Cayman Chemical,

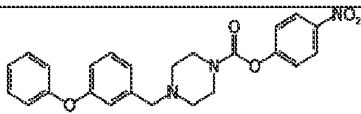
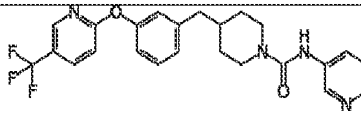
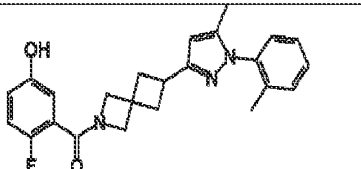
13668) were tested in 10-concentration IC₅₀ mode with 3-fold serial dilution at a starting concentration of 100 μ M and 10 μ M, respectively. 300 nL or 30 nL of test compounds were delivered into a 384-well black plate (Corning, 3573) using a Labcyte Echo, followed by addition of 15 μ L of FAAH enzyme (Cayman, 700302) in assay buffer. After a 5-minute pre-incubation at room temperature, 10 μ L of AAMCA was added in assay buffer to start the reaction. Final concentration of FAAH enzyme is not specified and AAMCA substrate was used at the 20 μ M. After these dilutions, the final concentration of the test compounds ranged from 100 μ M to 5.08 nM or 10 μ M down to 0.508 nM. The reaction was allowed to progress for 60 minutes, while the plate was read on an Envision plate reader at an Ex/Em of 350/460 nm with readings every minute. The data was analyzed in Microsoft Excel, using the slope between 30 and 59 minutes. The average of the no-enzyme wells (background) was subtracted from the data. The background-subtracted slope data was converted to % activity using the average of wells with enzyme and DMSO vehicle. IC₅₀ values were calculated using GraphPad software (Sigmoidal dose response, variable slope equation).

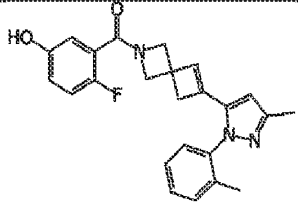
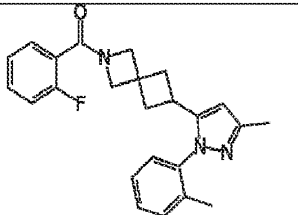
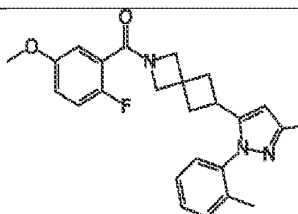
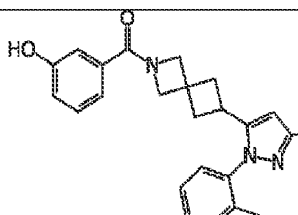
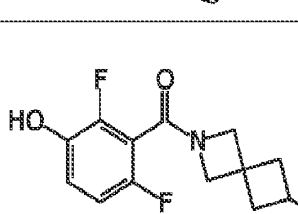
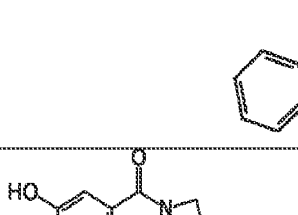
[000350] Compounds listed in Table D2 were tested in the FAAH Counterscreen of Example 23

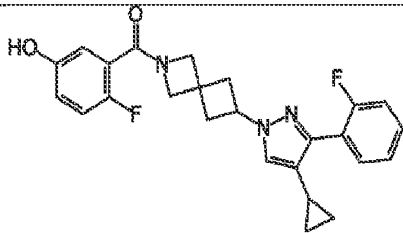
Table D1: Methods Used to Measure FAAH Inhibition

Method	Modification to Assay of Example 23
A	Starting concentration of 100 μ M
B	Starting concentration of 10 μ M

Table D2: FAAH Counter Screen

Method	Compound	Structure	FAAH IC ₅₀ (nM)
A	Comparator		459
A	Comparator		14
A	117		>10,000

Method	Compound	Structure	FAAH IC ₅₀ (nM)
A	120		>10,000
A	122		>10,000
A	123		>10,000
A	125		>10,000
A	127		>10,000
B	473		>10,000

Method	Compound	Structure	FAAH IC ₅₀ (nM)
B	493		>10,000

Example 24: Measuring Reversible MAGL Inhibition (IC₅₀)

[000351] The reversible mechanism of MAGL inhibition of a test compound of Formula (I) can be determined. Flag-tagged MAGL enzyme will be immobilized on anti-Flag beads. Immobilized enzyme will be incubated +/- inhibitor at a dose that produces complete inhibition. Colorimetric substrate (4-NPA) will be added and the reaction monitored on a plate reader for 30 minutes to verify complete inhibition. Immobilized enzyme will then be washed thoroughly to remove the inhibitor, and fresh substrate will be added. The reaction will be monitored for an additional 30 minutes; returning enzymatic activity will indicate reversibility of inhibition.

[000352] To confirm the hypothesized reversible mechanism of inhibition, the effects of dilution and preincubation on the MAGL inhibitory activity of a compound can be evaluated using methods disclosed in *J. Med. Chem.* 2019, 62, 1932–1958, 1942. In the presence of an irreversible mechanism of inhibition, the potency should not decrease after dilution, whereas for a reversible inhibition, the potency level should be strongly reduced after dilution. Therefore, the inhibition produced by incubation with a 4000 nM concentration of a test compound can be measured after a 40× dilution and compared to the potency observed by a 4000 and a 100 nM of the test compound. A reversible mechanism of inhibition can be identified when the inhibition produced by 100 nM of the test compound is similar to that obtained after a 40× dilution and was considerably lower than that produced by the same compound at a concentration of 4000 nM.

[000353] As a second assay to identify or confirm a reversible MAGL inhibitory activity of a test compound, the inhibition activity of a test compound can be measured at different preincubation times with MAGL. The test compound can be preincubated with the enzyme for 0, 30, and 60 min before adding the substrate to start the enzymatic reaction. An irreversible

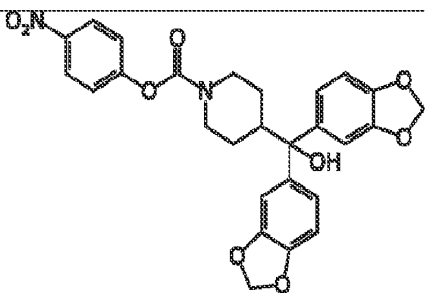
inhibition should produce a higher potency after longer incubation times, whereas a reversible inhibitor should produce a constant inhibition potency over all the different incubation times.

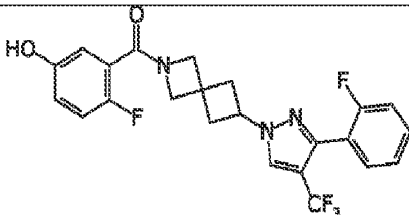
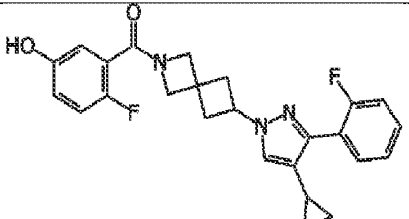
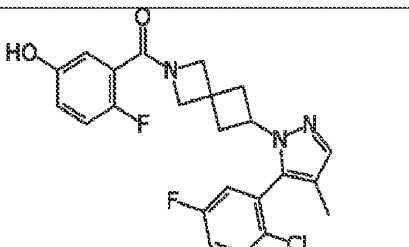
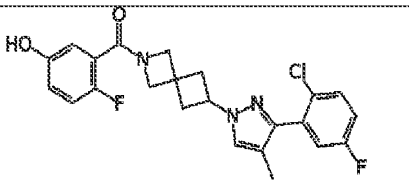
Determining MAGL reversible inhibition:

[000354] MAGL enzyme was incubated for 30 minutes in the presence of 40X the IC₅₀ concentration of inhibitor. Enzyme + inhibitor mix was then diluted 40-fold so that the final concentration of the inhibitor equaled the IC₅₀ concentration. Substrate was added and the reaction was monitored for 30 minutes. For a reversible inhibitor, percent inhibition after dilution to the IC₅₀ concentration should be 50 ± 15%.

[000355] The MAGL reversible inhibition assay of Example 24 above was performed to test reversibility of inhibition by compounds depicted in Table E. Column A shows the degree to which MAGL enzymatic activity returned following washout of test compounds (pre-washout compound concentration: 1 μM), reflecting reversibility of inhibition, as compared to the complete lack of return of MAGL enzymatic activity after washout of the irreversible inhibitor comparator compound JZL-184 (pre-washout compound concentration: 1 μM). Column B shows % MAGL activity returning after washout. % Activity returning after washout represents the amount of MAGL enzymatic activity, relative to control (no inhibitor before washout) reaction amounts, that occurred immediately following a 30 minute washout of the test compound. For some test compounds, % activity returning after washout may be less than 100% if complete compound unbinding takes longer than 30 minutes.

Table E. *Reversible MAGL inhibition*

Compound	Structure	A	B
JZL-184 (comparator)			< 1%

Compound	Structure	A	B
473		41	< 50%
493		47	< 50%
519		155	> 50%
520		100	> 50%

[000356] It should be understood that this disclosure is not limited to the particular methodology, protocols, and reagents, etc., provided herein and as such may vary. The terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present disclosure, which is defined solely by the claims.

Example 25: Pharmacokinetic Study of Compounds in Mice

[000357] Healthy male C57BL/6 mice (8-12 weeks old) weighing between 17 to 35 g were procured from Global, India. Temperature and humidity were maintained at 22 ± 3 °C and 30-70%, respectively and illumination was controlled to give a sequence of 12 hr light and 12 hr dark cycle. Temperature and humidity were recorded by auto-controlled data logger system. All the animals

were provided laboratory rodent diet. Reverse osmosis water treated with ultraviolet light was provided *ad libitum*.

[000358] Protocol A: Twenty-four male mice were divided into two groups as; Group 1: 30 mg/kg/IP; Plasma and brain; Number of animals=12; Animal # 1-12. Group 2: 30 mg/kg/PO; Plasma and brain; Number of animals=12; Animal # 13-24. Animals in Group 1 were administered intraperitoneally with solution formulation of PSY-05-00074-001 in 5% NMP, 5% Solutol HS-15 and 90% normal saline at 30 mg/kg dose. Animals in Group 2 were administered orally with solution formulation of PSY-05-00074-001 in 5% NMP, 5% Solutol HS-15 and 90% normal saline at 30 mg/kg dose. Blood samples (approximately 60 μ L) were collected under light isoflurane anesthesia from retro orbital plexus at 0.25, 0.5, 1, 2, 4 and 8 hr (IP and PO). Plasma samples were separated by centrifugation of whole blood and stored below -70 °C until bioanalysis. Immediately after collection of blood from intraperitoneal and oral group animals, animals were euthanized with excess CO₂ and brain samples were collected from set of two mice at each time point. Brain samples were divided into two parts. Half brain samples were homogenized using ice-cold phosphate buffer saline (pH-7.4) and homogenates were stored below -70 $\pm$ 10 °C until analysis. Total homogenate volume was three times the brain weight. Other part of brain was stored below -70 $\pm$ 10 °C for further analysis. All samples were processed for analysis by protein precipitation using acetonitrile and analyzed with fit-for-purpose LC/MS/MS method (LLOQ – 2.02 ng/mL for plasma and 6.06 ng/g for brain). Pharmacokinetic parameters were calculated using the non-compartmental analysis tool of Phoenix WinNonlin®.

[000359] Protocol B: Thirty six mice were included into the study and divided in to three groups as Group 1 (n=12), Group 2 (n=12) and Group 3 (n=12) with n=2 mice per time-point design. Animals in Group 1 were administered intravenously with solution formulation of PSY-05-00414-001 at 5 mg/kg dose. Animals in Group 2 were administered orally with solution formulation of PSY-05-00414-001 at a dose of 5 mg/kg. Animals in Group 3 were administered intraperitoneally with solution formulation of PSY-05-00414-001 at 5 mg/kg dose. The formulation vehicle for all the three groups was 5% NMP, 5% Solutol HS-15 and 90% normal saline. Blood samples (approximately 60 μ L) were collected under light isoflurane anesthesia from two mice at 0.25, 0.5, 1, 2, 4 and 8 h. Plasma was harvested by centrifugation of blood and stored at -70 $\pm$ 10 °C until analysis. After blood collection, brain was perfused and isolated at 0.25, 0.5, 1, 2, 4 and 8 h. Brain samples were dipped thrice in ice-cold phosphate buffer saline, blotted dry and cut in to two equal

portion. Half -brain samples from each time-point were weighed and homogenized using ice-cold phosphate buffer saline with twice volume of brain weight making the total homogenate three volumes and stored below $-70\pm 10^{\circ}\text{C}$ until analysis. Remaining half-portions of brain samples was snap freeze and kept in $-70\pm 10^{\circ}\text{C}$ until further confirmation from client. Plasma and brain samples were quantified by fit-for-purpose LC-MS/MS method (LLOQ: 1.01 ng/mL for plasma and 2.02 ng/mL for brain).

[000360] Protocol C: Fifty four male mice were included in study and divided in to three groups as Group 1 (n=18), Group 2 (n=18) and Group 3 (n=18) with 3 mice/time point design. Animals from Group 1, Group 2 and Group 3 were administered by intravenous, oral and intraperitoneal route with solution formulation of PSY-05-00451-001 at 5 mg/kg dose, respectively. The formulation vehicle used was 5 % v/v NMP, 5 % v/v Solutol HS-15 and 90 % v/v Normal saline. Blood samples (approximately 60 μL) were collected under light isoflurane anesthesia (Surgivet®) from retro orbital plexus from a set of three mice at 0.25, 0.5, 1, 2, 4 and 8 h. Immediately after blood collection, plasma was harvested by centrifugation at 4000 rpm, 10 min at 4°C and samples were stored at $-70\pm 10^{\circ}\text{C}$ until bioanalysis. Following blood collection, animals were sacrificed followed by vena-cava was cut open and whole body was perfused from heart using 10 mL of normal saline. Brain samples were collected from set of three mice at 0.25, 0.5, 1, 2, 4 and 8 h. After isolation, brain samples were rinsed three times in ice cold normal saline (for 5-10 seconds/rinsed using ~5-10 mL normal saline in disposable petri dish for each rinse), dried on blotting paper and cut in to two equal portion. Half -brain was used for PK estimation and half brain was snap freezed and stored below $-70\pm 10^{\circ}\text{C}$. Half brain (for PK estimation) was weighed and homogenized using ice-cold phosphate buffer saline with twice volume of brain weight making the total homogenate three volumes and stored below $-70\pm 10^{\circ}\text{C}$ until analysis. All samples were processed for analysis by protein precipitation method and analyzed with fit-for-purpose LC-MS/MS method (LLOQ = 2.03 ng/mL for plasma and 1.02 ng/mL for brain). The pharmacokinetic parameters were estimated using non-compartmental analysis tool of Phoenix® WinNonlin software.

[000361] Protocol D: Thirty six male mice were included in study and divided into two groups as Group 1 (n=18) and Group 2 (n=18) with 3 mice/time point as sparse design. Animals from Group 1 and Group 2 were administered by intravenous and oral route with solution formulation of PSY-05-00473-001 at 5 mg/kg dose, respectively. The formulation vehicle used was 5 % v/v

NMP, 5 % v/v Solutol HS-15 and 90 % v/v Normal saline. Blood samples (approximately 60 µL) were collected under light isoflurane anesthesia (Surgivet®) from retro orbital plexus from a set of three mice at 0.25, 0.5, 1, 2, 4 and 8 h. Immediately after blood collection, plasma was harvested by centrifugation at 4000 rpm, 10 min at 4°C and samples were stored at -70±10°C until bioanalysis. Following blood collection, whole body was perfused using 10 mL of normal saline. Brain samples were collected from set of three mice at 0.25, 0.5, 1, 2, 4 and 8 h. After isolation, brain samples were rinsed three times in ice cold normal saline (for 5-10 seconds/rinsed using ~5-10 mL normal saline in disposable petri dish for each rinse), dried on blotting paper and cut in to two equal portion. Half -brain was used for PK estimation and half brain was snap freezed and stored below -70±10 °C. Half brain (for PK estimation) was weighed and homogenized using ice-cold phosphate buffer saline with twice volume of brain weight making the total homogenate to three volumes and stored below -70±10 °C until analysis. All samples were processed for analysis by protein precipitation method and analyzed with fit-for-purpose LC-MS/MS method (LLOQ = 1.01 ng/mL for plasma and 2.01 for brain). The pharmacokinetic parameters were estimated using non-compartmental analysis tool of Phoenix® WinNonlin software.

[000362] Protocol E: Total fifty four male mice were included in study and divided in to three groups as Group 1 (n=18), Group 2 (n=18) and Group 3 (n=18) with 3 mice/time point design. Animals from Group 1, Group 2 and Group 3 were administered by intravenous, oral and intraperitoneal route with solution formulation of PSY-05-00476-001 at 5 mg/kg dose, respectively. The formulation vehicle used was 5 % v/v NMP, 5 % v/v Solutol HS-15 and 90 % v/v Normal saline. Blood samples (approximately 60 µL) were collected under light isoflurane anesthesia (Surgivet®) from retro orbital plexus from a set of three mice at 0.25, 0.5, 1, 2, 4 and 8 h. Immediately after blood collection, plasma was harvested by centrifugation at 4000 rpm, 10 min at 4°C and samples were stored at -70±10°C until bioanalysis. Following blood collection, animals were sacrificed followed by vena-cava was cut open and whole body was perfused from heart using 10 mL of normal saline. Brain samples were collected from set of three mice at 0.25, 0.5, 1, 2, 4 and 8 h. After isolation, brain samples were rinsed three times in ice cold normal saline (for 5-10 seconds/rinsed using ~5-10 mL normal saline in disposable petri dish for each rinse), dried on blotting paper and cut in to two equal portion. Half -brain was used for PK estimation and half brain was snap freezed and stored below -70±10 °C. Half brain (for PK estimation) was weighed and homogenized using ice-cold phosphate buffer saline with twice volume of brain weight

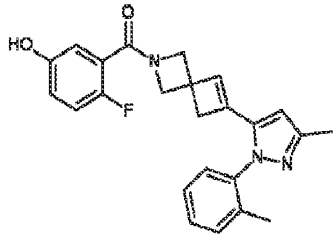
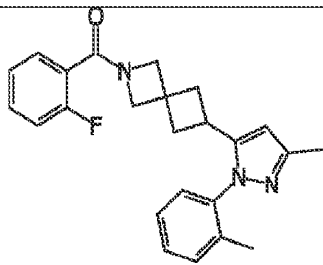
making the total homogenate three volumes and stored below -70 ± 10 °C until analysis. All samples were processed for analysis by protein precipitation method and analyzed with fit-for-purpose LC-MS/MS method (LLOQ = 1.01 ng/mL for plasma and brain). The pharmacokinetic parameters were estimated using non-compartmental analysis tool of Phoenix® WinNonlin software.

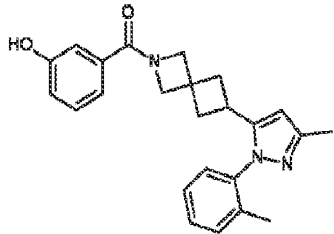
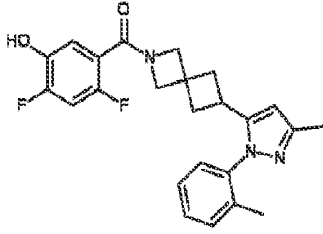
Table F: Data obtained from Pharmacokinetic study of Example 25

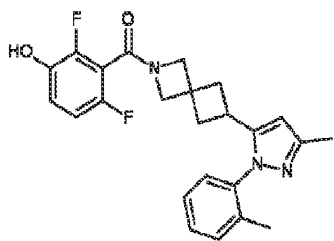
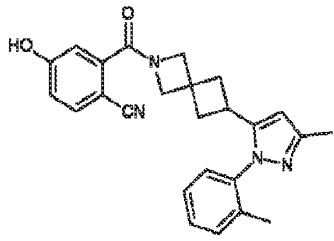
Protocol	Compound	Matrix	Route	Dose (mg/kg)	C _{max} (ng/g)	AUC _{last} (hr*ng/mL)	Brain KP (C _{max})
A	Compound 74	Brain	Oral	30	101.76	116.52	.42
B	Compound 414	Brain	Oral	5	135.83	774.91	1.19
C	Compound 451	Brain	Oral	5	271.39	1204.22	.32
D	Compound 473	Brain	Oral	5	171.59	464.42	1.74
E	Compound 476	Brain	Oral	5	72	223.64	.72

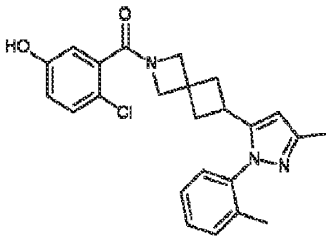
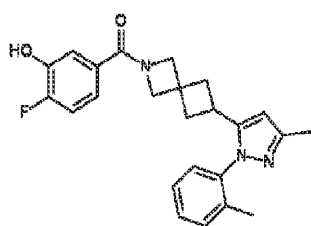
[000363] Referring to the data in Table F, the C_{max} is the peak concentration of a drug observed over time after a dose of the drug has been administered. Data presented in the table above demonstrate the ability of PSY compounds to enter the brain. AUC_{last} is the area under the brain concentration-time curve to the last measured brain concentration. This reflects the total drug exposure over time after a dose has been administered. Brain K_p (C_{max}) is the ratio of the maximum observed concentrations of drug in the brain and plasma. Higher K_p (C_{max}) values indicate more delivery of the drug to the brain.

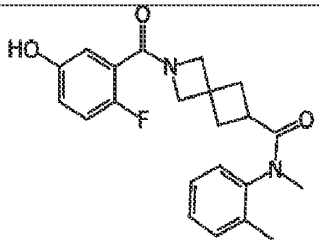
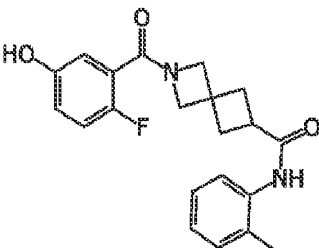
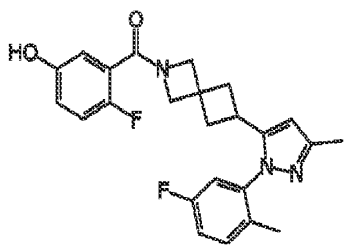
[000364] Table 6 - Compounds of Formula (I), including the value of MAGL inhibition potency measured with a method described in Table C of Example 22.

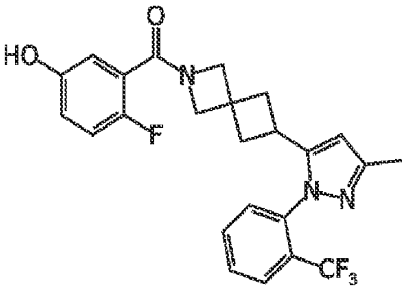
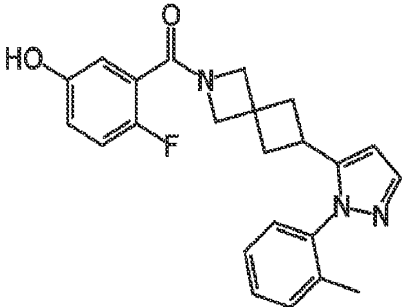
Compound	Structure (IUPAC name)	LCMS / NMR	MAGL Potency (Detection Method)
120	 (2-fluoro-5-hydroxyphenyl){6-[3-methyl-1-(o-tolyl)-5-pyrazolyl]-2-aza-5-spiro[3.3]hepten-2-yl}methanone	LCMS: 473.7 m/z [M+H]⁺; ¹H NMR (400 MHz, Methanol-d₄) δ 7.51 – 7.33 (m, 3H), 7.28 (d, <i>J</i> = 7.9 Hz, 1H), 7.00 (t, <i>J</i> = 9.2 Hz, 1H), 6.92 – 6.78 (m, 2H), 6.35 (s, 1H), 5.39 (s, 1H), 4.29 – 4.09 (m, 4H), 2.78 (d, <i>J</i> = 5.6 Hz, 2H), 2.30 (s, 3H), 2.00 (s, 3H).	C (2)
122	 (o-fluorophenyl){6-[3-methyl-1-(o-tolyl)-5-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: 390.4 m/z [M+H]⁺; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 7.58-7.32 (m, 4H), 7.36-7.21 (m, 3H), 7.16 (t, <i>J</i> = 7.0 Hz, 1H), 6.14 (d, <i>J</i> = 22.8 Hz, 1H), 3.96 (dd, <i>J</i> = 23.5, 17.7 Hz, 4H), 3.00 (m, 1H), 2.39-2.21 (m, 4H), 2.18 (d, <i>J</i> = 10.8 Hz, 3H), 1.93 (s, 3H).	E (2)

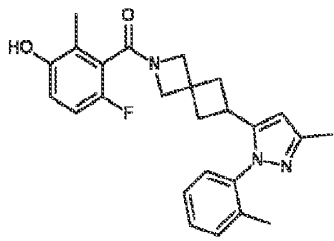
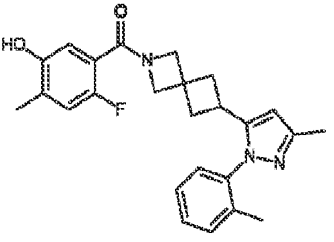
Compound	Structure (IUPAC name)	LCMS / NMR	MAGL Potency (Detection Method)
125	 (m-hydroxyphenyl){6-[3-methyl-1-(o-tolyl)-5-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: 388.4 m/z [M+H]⁺; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.63 (d, <i>J</i> = 13.1 Hz, 1H), 7.44 – 7.26 (m, 3H), 7.17 (dd, <i>J</i> = 19.2, 8.3 Hz, 2H), 6.96 (d, <i>J</i> = 7.6 Hz, 2H), 6.86 (s, 1H), 6.14 (d, <i>J</i> = 12.2 Hz, 1H), 4.19 (d, <i>J</i> = 25.2 Hz, 2H), 3.94 (d, <i>J</i> = 23.0 Hz, 2H), 3.03 – 2.94 (m, 1H), 2.33 (s, 3H), 2.27 – 2.12 (m, 5H), 1.93 (s, 3H).	B (1,2)
126	 (2,4-difluoro-5-hydroxyphenyl){6-[3-methyl-1-(o-tolyl)-5-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: 424.4 m/z [M+H]⁺; ¹H NMR (400 MHz, Methanol-<i>d</i>₄) δ 7.34 (dt, <i>J</i> = 25.4, 8.9 Hz, 3H), 7.18 (t, <i>J</i> = 6.3 Hz, 1H), 7.07 – 6.91 (m, 2H), 6.18 (d, <i>J</i> = 18.4 Hz, 1H), 4.05 (dd, <i>J</i> = 22.8, 7.5 Hz, 4H), 3.13 – 3.02 (m, 1H), 2.36 (td, <i>J</i> = 16.6, 14.9, 9.8 Hz, 4H), 2.26 (d, <i>J</i> = 8.4 Hz, 3H), 1.98 (d, <i>J</i> = 2.3 Hz, 3H).	A (1, 2, 3)

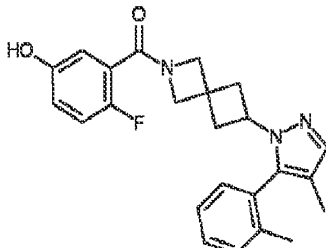
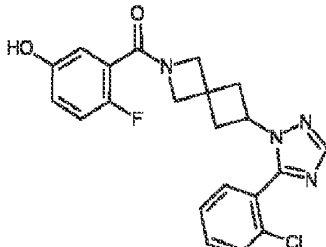
Compound	Structure (IUPAC name)	LCMS / NMR	MAGL Potency (Detection Method)
127	 (2,6-difluoro-3-hydroxyphenyl){6-[3-methyl-1-(o-tolyl)-5-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: 424.7 m/z $[M+H]^+$; 1H NMR (400 MHz, Methanol- d_4) δ 7.50 – 7.25 (m, 3H), 7.18 (dd, J = 7.6, 5.5 Hz, 1H), 6.91 – 6.81 (m, 1H), 6.18 (d, J = 21.0 Hz, 1H), 4.10 (d, J = 22.2 Hz, 2H), 3.96 (d, J = 23.3 Hz, 2H), 3.15 – 3.02 (m, 1H), 2.49 – 2.29 (m, 4H), 2.26 (d, J = 10.5 Hz, 3H), 1.98 (d, J = 2.8 Hz, 3H).	E (2)
128	 4-hydroxy-2-({6-[3-methyl-1-(o-tolyl)-5-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}carbonyl)benzonitrile	LCMS: 413.4 m/z $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 7.68 (t, J = 7.8 Hz, 1H), 7.43 – 7.26 (m, 3H), 7.15 (dd, J = 7.8, 3.9 Hz, 1H), 6.98 – 6.85 (m, 2H), 6.13 (d, J = 19.6 Hz, 1H), 3.99 (dd, J = 24.0, 13.9 Hz, 4H), 2.99 (dt, J = 22.2, 8.4 Hz, 1H), 2.39 – 2.28 (m, 2H), 2.23 (dd, J = 12.7, 9.0 Hz, 2H), 2.17 (d, J = 8.5 Hz, 3H), 1.92 (s, 3H).	A (1, 2)

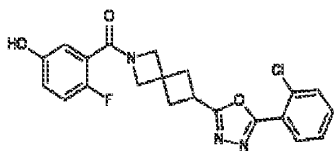
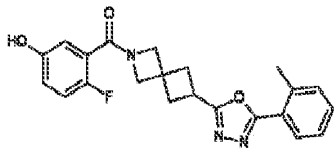
Compound	Structure (IUPAC name)	LCMS / NMR	MAGL Potency (Detection Method)
140	 (2-chloro-5-hydroxyphenyl) (6-[3-methyl-1-(o-tolyl)-5-pyrazolyl]-2-aza-2-spiro[3.3]heptyl)methanone	LCMS: m/z 422.6 [M+1]⁺; NMR: ¹H NMR (400 MHz, DMSO-d₆) δ 9.95 (s, 1H), 7.40 – 7.11 (m, 4H), 7.15 (t, J = 7.7 Hz, 1H), 6.80 (t, 1H), 6.67 (d, J = 2.8 Hz, 1H), 6.16-6.10 (s, 1H), 3.97-3.58 (m, 4H), 3.00-2.93 (m, 1H), 2.33 – 2.15 (m, 7H), 1.91 (s, 3H).	B (2)
141	 (4-fluoro-3-hydroxyphenyl) (6-[3-methyl-1-(o-tolyl)-5-pyrazolyl]-2-aza-2-spiro[3.3]heptyl)methanone	LCMS: 406.3 m/z [M+H]⁺; ¹H NMR (400 MHz, DMSO-d₆) δ 10.16 (s, 1H), 7.38 (s, 2H), 7.30 (d, J = 5.9 Hz, 1H), 7.18 (dd, J = 13.5, 8.4 Hz, 3H), 7.02 (s, 1H), 6.15 (d, J = 10.7 Hz, 1H), 4.25 (s, 1H), 4.19 (s, 1H), 3.97 (s, 1H), 3.92 (s, 1H), 3.04 – 2.94 (m, 1H), 2.23 (d, J = 9.5 Hz, 2H), 2.19 (s, 5H), 1.93 (s, 3H).	B (1) C (2)
185		LCMS: m/z 383.35 [M+1]⁺ NMR: ¹H NMR (400 MHz, DMSO-d₆) δ 9.62 (d, J = 13.5	B (2, 3)

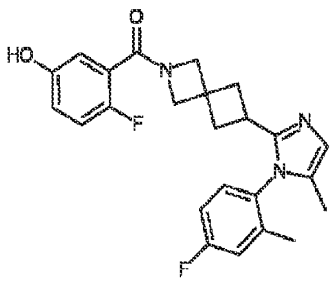
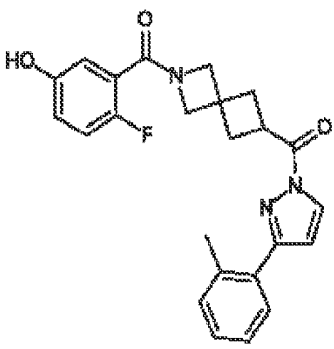
Compound	Structure (IUPAC name)	LCMS / NMR	MAGL Potency (Detection Method)
	 N-methyl-N-o-tolyl-2-(2-fluoro-5-hydroxybenzoyl)- 2-aza-6-spiro[3.3]heptanecarboxamide	Hz, 1H), 7.40 – 7.23 (m, 3H), 7.16 (s, 1H), 7.17 – 6.98 (m, 2H), 6.85–6.81 (m, 1H), 6.78 – 6.69 (m, 1H), 3.97 – 3.80 (m, 4H), 3.05 (d, J = 6.1 Hz, 3H), 2.62 (td, J = 15.6, 7.7 Hz, 1H), 2.39 – 2.23 (m, 2H), 2.22 – 2.05 (m, 3H), 2.00 – 1.90 (m, 2H).	
186	 N-o-tolyl-2-(2-fluoro-5-hydroxybenzoyl)-2-aza-6- spiro[3.3]heptanecarboxamide	LCMS: m/z 369.20 [M+1]⁺ ¹H NMR (400 MHz, DMSO-d₆) δ 9.62 (d, J = 4.8 Hz, 1H), 9.17 (s, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.23 – 7.12 (m, 3H), 7.08 (s, 1H), 6.90 – 6.82 (m, 1H), 6.79 (s, 1H), 4.07 (d, J = 6.6 Hz, 2H), 3.97 (d, J = 6.0 Hz, 2H), 3.16 (dd, J = 17.8, 8.9 Hz, 1H), 2.57 (s, 4H), 2.17 (d, J = 4.0 Hz, 3H).	E (2)
365		LCMS: 424.1 m/z [M+H]⁺ ¹H NMR (400 MHz, DMSO-d₆) δ 9.64 (s, 1H), 7.66 (s, 1H), 7.20 (s, 2H), 7.06 (s, 1H)	A (14)

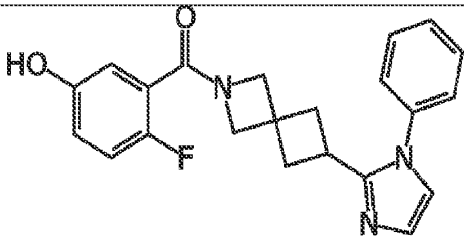
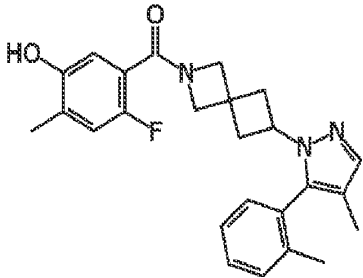
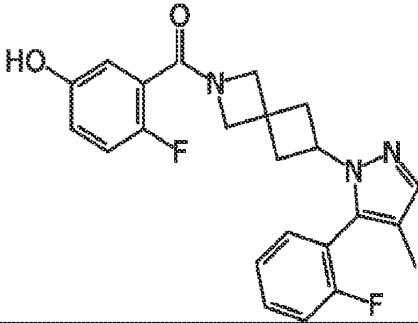
Compound	Structure (IUPAC name)	LCMS / NMR	MAGL Potency (Detection Method)
	(2-fluoro-5-hydroxyphenyl){6-[1-(5-fluoro-2-tolyl)-3-methyl-5-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	6.83 (t, 1H), 6.75 (s, 1H), 6.28 (s, 1H), 3.99 (d, 2H), 3.82 (d, J = 11.5 Hz, 2H), 3.11 (m, 1H), 2.45 (d, 2H), 2.35 (d, 3H), 2.19 (s, 2H), 1.87 (s, 3H).	
366	 (2-fluoro-5-hydroxyphenyl)(6-{3-methyl-1-[o-(trifluoromethyl)phenyl]-5-pyrazolyl}-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: 460.0 $[M+H]^+$ NMR: 1H NMR (400 MHz, DMSO- d_6) δ 9.63 (s, 1H), 7.80 (s, 1H), 7.77 – 7.67 (m, 3H), 7.08 (t, 1H), 7.82 (d, 1H), 6.76 (s, 1H), 6.28 (d, J = 15.4 Hz, 1H), 3.98 (d, 2H), 3.87 (d, J = 9.0 Hz, 2H), 2.96 (m, J = 8.7 Hz, 1H), 2.25 (d, J = 15.6 Hz, 6H)	A (14)
367	 (2-fluoro-5-hydroxyphenyl)(6-{3-methyl-1-phenyl-5-pyrazolyl}-2-aza-2-spiro[3.3]heptyl}methanone	m/z 422.6 $[M+1]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 9.95 (s, 1H), 7.43 – 7.1 (m, 4H), 7.15 (t, J = 7.7 Hz, 1H), 6.80 (t, 1H), 6.67 (d, J = 2.8 Hz, 1H), 6.16-6.10 (s, 1H), 3.98 (s, 1H), 3.92 (s, 1H), 3.82 (s,	B (14)

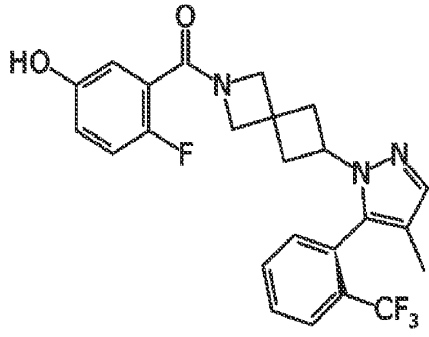
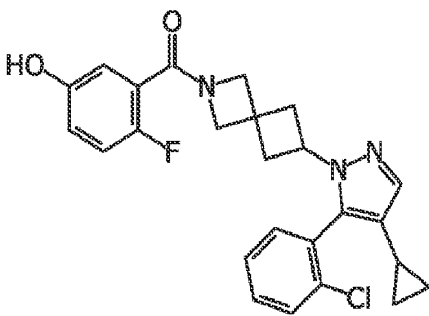
Compound	Structure (IUPAC name)	LCMS / NMR	MAGL Potency (Detection Method)
	(2-fluoro-5-hydroxyphenyl){6-[1-(o-tolyl)-5-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	1H), 3.76 (s, 1H), 2.99 (dt, $J = 20.8$, 8.4 Hz, 1H), 2.32 – 2.19 (m, 2H), 2.17 (d, $J = 10.7$ Hz, 2H), 2.09 (s, 3H), 1.93 (d, $J = 2.2$ Hz, 3H).	
370	 (6-fluoro-3-hydroxy-2-tolyl){6-[3-methyl-1-(o-tolyl)-5-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: 420.6 m/z $[M+H]^+$ NMR: 1H NMR (400 MHz, DMSO- d_6) δ 9.54 (d, $J = 10.5$ Hz, 1H), 7.44 – 7.35 (m, 2H), 7.37 – 7.27 (m, 1H), 7.16 (t, $J = 8.1$ Hz, 1H), 6.84–6.71 (ddd, $J = 36.2, 15.5, 8.7$ Hz, 2H), 6.12 (d, 1H), 4.01 (s, 2H), 3.95 (s, 2H), 3.05–2.94 (m, 1H), 2.37 (d, $J = 12.5$ Hz, 4H), 2.33 – 2.14 (s, 3H), 2.02 – 1.91 (s, 6H).	D (14)
371	 (2-fluoro-5-hydroxy-4-tolyl){6-[3-methyl-1-(o-tolyl)-5-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: 420.23 m/z $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 9.56 (d, $J = 9.0$ Hz, 1H), 7.39 (d, $J = 7.9$ Hz, 2H), 7.31 (d, $J = 7.9$ Hz, 1H), 7.16 (s, $J = 7.9$ Hz, 1H), 6.99 (t, $J = 10.2$ Hz, 1H), 6.78 (d, 1H), 6.15 (d, $J = 19.5$ Hz, 1H), 3.97 (s, 2H), 3.92 (s, 2H), 3.04	B (14)

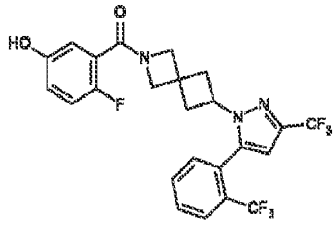
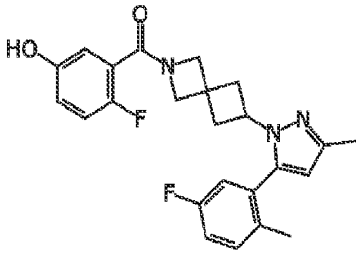
Compound	Structure (IUPAC name)	LCMS / NMR	MAGL Potency (Detection Method)
		– 2.95 (m, 1H), 2.35 (s, 2H), 2.26 – 2.15 (m, 4H), 2.13 (d, J = 4.9 Hz, 3H), 2.20 (d, 3H), 1.94 (s, 3H).	
373	 (2-fluoro-5-hydroxyphenyl){6-[4-methyl-5-(o-tolyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: m/z 406.2 $[M+1]^+$. NMR: ^1H NMR (400 MHz, DMSO- d_6) δ 9.71 (s, 1H), 7.67 (s, 1H), 7.22 – 7.37 (m, 4H), 7.10 (m, 1H), 6.90 – 6.75 (m, 2H), 4.71 (m, 1H), 4.14 (d, J = 5.8 Hz, 2H), 4.04 (m, 2H), 2.64 (m, 4H), 2.20 (m, 3H), 1.9 (s, 3H).	C (14)
376	 {6-[5-(o-chlorophenyl)-1H-1,2,4-triazol-1-yl]-2-aza-2-spiro[3.3]heptyl}(2-fluoro-5-hydroxyphenyl)methanone	LCMS: m/z 413.27 $[M+1]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 9.76 (s, 1H), 8.16–8.14 (d, J=10.0 Hz, 1H), 7.80 – 7.70 (m, 2H), 7.52 (m, 1H), 7.08 – 7.02 (m, 1H), 6.93 (m, 1H), 6.84 (s, 1H), 4.58–4.51 (m, 1H), 4.09 (s, 4H), 2.71 (m, 4H).	B (14)

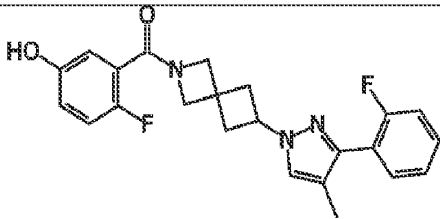
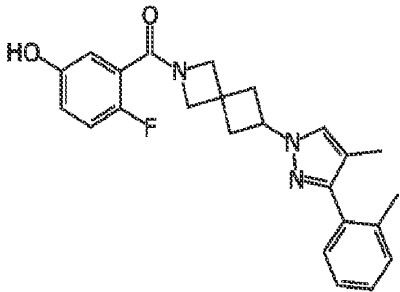
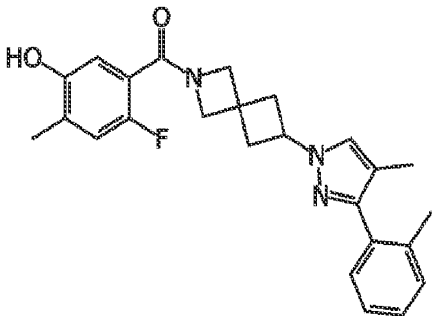
Compound	Structure (IUPAC name)	LCMS / NMR	MAGL Potency (Detection Method)
377	 {6-[5-(o-chlorophenyl)-1,3,4-oxadiazol-2-yl]-2-aza-2-spiro[3.3]heptyl}(2-fluoro-5-hydroxyphenyl)methanone	LCMS: 414.3 m/z $[M+H]^+$ NMR: 1H NMR (400 MHz, DMSO-d_6) δ 9.69 (s, 1H), 7.98-7.93 (m, 1H), 7.62 (m, 3H), 7.02 (td, J = 9.2, 2.9 Hz, 1H), 6.92 – 6.79 (m, 2H), 4.31 (d, J = 5.9 Hz, 2H), 4.07 (d, J = 11.5 Hz, 2H), 3.97 (m, J = 10.4 Hz, 1H), 3.41- 3.71 (q, J = 6.6 Hz, 4H).	D (14)
378	 (2-fluoro-5-hydroxyphenyl){6-[5-(o-tolyl)-1,3,4-oxadiazol-2-yl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: 394.91 m/z $[M+H]^+$ NMR: 1H NMR (400 MHz, DMSO-d_6) δ 9.69 (s, 1H), 7.85 (dd, J = 18.0, 6.8 Hz, 1H), 7.52 – 7.39 (m, 3H), 7.10 (d, 1H) 6.88 (s, 1H), 6.81 (s, 1H), 4.15 (d, J = 5.1 Hz, 2H), 4.08 (s, 2H), 3.76 (m, 1H) 2.74 (d, J = 9.1 Hz, 1H), 2.62 (d, J = 10.9 Hz, 3H), 2.44 (s, 3H).	D (14)

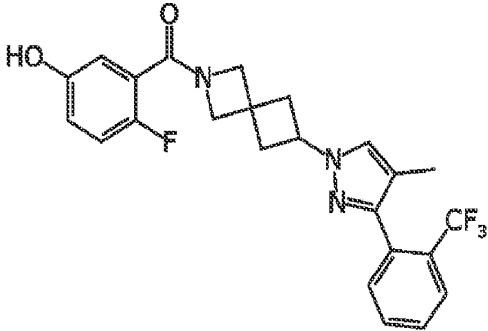
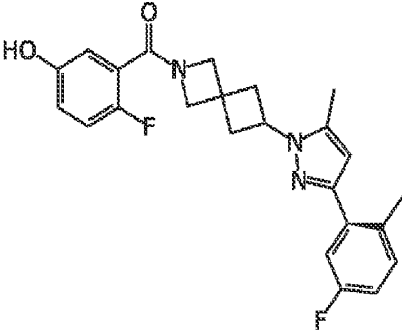
Compound	Structure (IUPAC name)	LCMS / NMR	MAGL Potency (Detection Method)
380	 (2-fluoro-5-hydroxyphenyl){6-[1-(4-fluoro-2-tolyl)-5-methyl-2-imidazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: m/z 424.31 [M+1] ⁺ ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.72 (s, 1H), 7.36-7.29 (m, 3H), 7.07 (q, <i>J</i> = 10.2, 9.8 Hz, 1H), 6.85 (d, <i>J</i> = 6.1 Hz, 1H), 6.79 – 6.69 (m, 2H), 4.00 – 3.90 (m, 4H), 2.91-2.85 (m, 1H), 2.38 (d, <i>J</i> = 7.8 Hz, 2H), 2.34 – 2.24 (m, 2H), 1.89 – 1.80 (m, 6H).	E (14)
381	 {2-(2-fluoro-5-hydroxybenzoyl)-2-aza-6-spiro[3.3]heptyl}[3-(o-tolyl)-1-pyrazolyl]methanone	LCMS: m/z 419.89 [M+1] ⁺ ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.67 (s, 1H), 8.47 (dd, <i>J</i> = 10.0, 2.8 Hz, 1H), 7.64 (d, <i>J</i> = 7.3 Hz, 1H), 7.33 (dd, <i>J</i> = 11.7, 6.1 Hz, 3H), 7.04-7.01 (m, 1H), 7.01 – 6.94 (m, 1H), 6.90 – 6.77 (m, 2H), 4.14 (d, <i>J</i> = 6.2 Hz, 3H), 3.99 (d, <i>J</i> = 8.0 Hz, 2H), 2.64-2.254 (m, 7H).	C (14)
401		LCMS: m/z 419.89 [M+1] ⁺ ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.62 (s, 1H), 7.55 – 7.44 (m, 3H), 7.33 (s, 2H), 7.27 (s, 1H), 7.09	D (14)

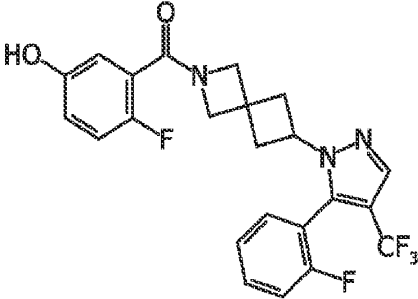
Compound	Structure (IUPAC name)	LCMS / NMR	MAGL Potency (Detection Method)
	 (2-fluoro-5-hydroxyphenyl){6-(1-phenyl-2-imidazolyl)-2-aza-2-spiro[3.3]heptyl}methanone	– 7.03 (m, 1H), 6.96 (d, $J = 10.4$ Hz, 1H), 6.84 (s, 1H), 6.76 (s, 1H), 4.02 (s, 2H), 3.95 (s, 2H), 2.45 (s, 4H).	
407	 (2-fluoro-5-hydroxy-4-tolyl){6-[4-methyl-5-(o-tolyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: m/z 420.30 $[M+1]^+$. NMR: 1H NMR (400 MHz, DMSO-d_6) δ 9.56 (s, 1H), 7.63 (d, $J = 4.5$ Hz, 1H), 7.38 – 7.20 (d, $J = 7.6$ Hz, 4H), 6.93 – 6.78 (m, 2H), 4.72 (dt, $J = 29.9, 7.9$ Hz, 1H), 4.18 (s, 1H), 4.07 (s, 1H), 3.92 (s, 1H), 3.81 (s, 1H), 2.69 (q, $J = 12.3, 9.5$ Hz, 4H), 2.20 (d, $J = 14.3$ Hz, 3H), 2.06 – 1.97 (m, 3H), 1.90 (d, $J = 3.2$ Hz, 3H).	B (6)
408		LCMS: m/z 410.21 $[M+1]^+$. NMR: 1H NMR (400 MHz, DMSO-d_6) δ 9.67 (s, 1H), 7.69 (s, 1H), 7.48 – 7.41 (m, 2H), 7.32 – 7.23 (m, 2H), 7.13 – 7.06 (m, 1H), 6.87 (s, 1H).	B (6)

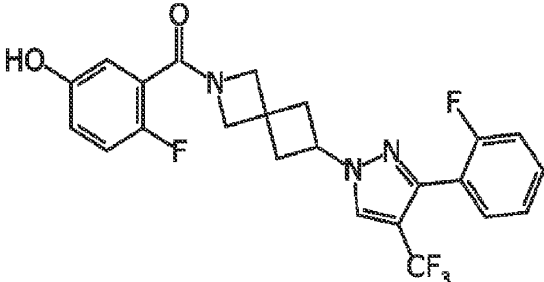
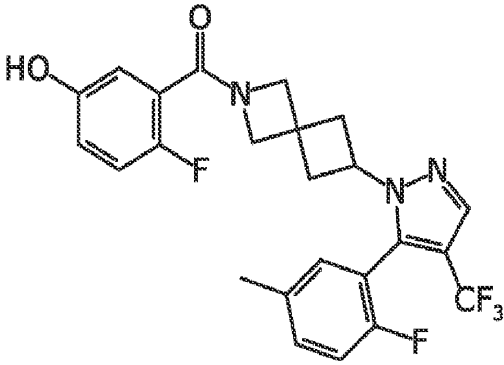
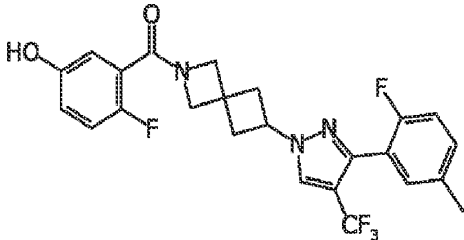
Compound	Structure (IUPAC name)	LCMS / NMR	MAGL Potency (Detection Method)
	(2-fluoro-5-hydroxyphenyl){6-[5-(o-fluorophenyl)-4-methyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	6.81 (s, 1H), 4.75 (dd, $J = 15.0, 7.8$ Hz, 1H), 4.15 (d, $J = 11.0$ Hz, 2H), 4.05 (d, $J = 8.7$ Hz, 2H), 2.67 (dd, $J = 25.9, 9.9$ Hz, 4H), 1.97 (s, 3H).	
410	 4-fluoro-3-{6-[(4M)-4-methyl-5-[2-(trifluoromethyl)phenyl]-1H-pyrazol-1-yl]-2-azaspiro[3.3]heptane-2-carbonyl}phenol	LCMS: m/z 460.44 $[M+1]^+$. NMR: ^1H NMR (400 MHz, DMSO- d_6) δ 9.68 (s, 1H), 7.94 (d, $J = 7.2$ Hz, 1H), 7.81 (s, 1H), 7.75 (s, 1H), 7.64 (s, 1H), 7.38 (s, 1H), 7.08 (s, 1H), 6.86 (s, 1H), 6.76 (s, 1H), 3.84 (d, $J = 12.8$ Hz, 1H), 3.55 (d, $J = 9.2$ Hz, 2H), 3.47 (d, $J = 12.0$ Hz, 2H), 2.5 (s, 2H), 1.87-1.74 (m, 5H).	B (6)
411	 {6-[5-(o-chlorophenyl)-4-cyclopropyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}(2-fluoro-5-hydroxyphenyl)methanone	LCMS: m/z 452.26 $[M+1]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.52-8.42 (m, 3H), 7.80-7.66 (m, 3H), 7.08-7.02 (m, 1H), 6.93 (m, 1H), 6.84 (s, 1H), 5.13 (s, 1H), 4.43 (s, 1H), 4.29 (s, 1H), 3.44 (s, 2H), 2.67-2.61 (m, 2H), 2.1 (d, $J = 9.2$ Hz, 1H),	C (6)

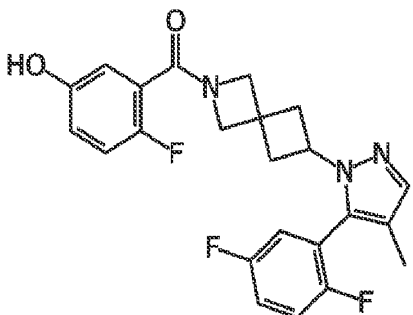
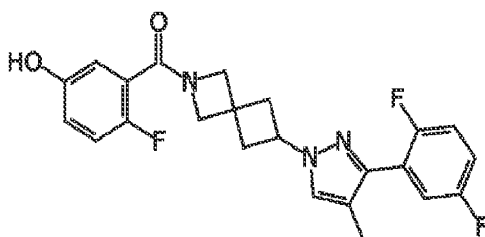
Compound	Structure (IUPAC name)	LCMS / NMR	MAGL Potency (Detection Method)
		1.93 (s, 1H), 1.50 (s, 1H), 0.86 (dd, $J = 11.8, 5.9$ Hz, 2H), 0.70 (s, 2H).	
414	 (2-fluoro-5-hydroxyphenyl)(6-{5-(trifluoromethyl)-3-[o-(trifluoromethyl)phenyl]-1-pyrazolyl}-2-aza-2-spiro[3.3]heptyl)methanone	LCMS: m/z 514.20 $[M+1]^+$. NMR: ^1H NMR (400 MHz, DMSO-d_6) δ 9.67 (d, 1H), 7.95 (t, 1H), 7.85-7.77 (m, 3H), 7.06 (s, 2H), 6.84 (s, 1H), 6.75 (s, 1H), 4.92 (m, 1H), 4.22 (m, 2H), 4.03 (s, 2H), 2.68 (s, 4H).	A (14)
415	 (2-fluoro-5-hydroxyphenyl)(6-[5-(5-fluoro-2-tolyl)-3-methyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl)methanone	LCMS: m/z 424.3 $[M+1]^+$. NMR: ^1H NMR (400 MHz, DMSO-d_6) δ 9.67 (d, 1H), 7.35-7.23 (m, $J=10.8$, 2H), 7.12-7.00 (m, $J=9.6$, 2H), 6.85-6.79 (d, 2H), 6.35 (s, 1H), 4.81-4.72 (m, 1H), 4.14 (d, 2H), 4.06 (d, 2H), 2.73-2.71 (m, 4H), 2.39-2.33 (m, 3H), 2.25 (d, 3H).	B (6)
417		LCMS: m/z 410.35 $[M+1]^+$. NMR: ^1H NMR (400 MHz, DMSO-d_6) δ 9.67 (s, 1H), 7.56 (s, 1H), 7.46 (d, $J=$	A (6)

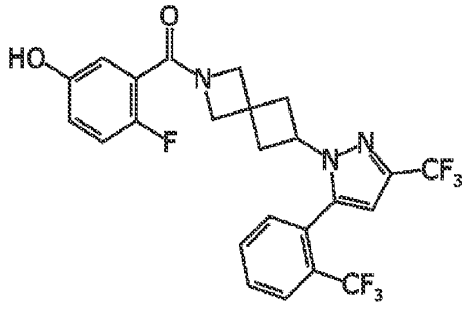
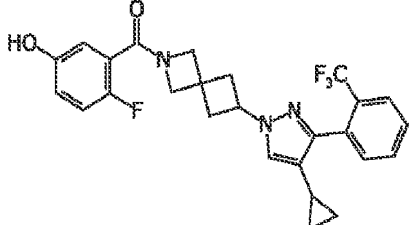
Compound	Structure (IUPAC name)	LCMS / NMR	MAGL Potency (Detection Method)
	 (2-fluoro-5-hydroxyphenyl){6-[3-(o-fluorophenyl)-4-methyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	10.6 Hz, 1H), 7.39 (dd, J = 24.5, 10.1 Hz, 3H), 7.07 (q, J = 9.6, 9.1 Hz, 1H), 6.84 (s, 1H), 6.76 (s, 1H), 4.46 – 4.37 (m, 1H), 4.01 (s, 4H), 2.62 (d, J = 18.8 Hz, 4H), 1.87 (s, 3H).	
440	 (2-fluoro-5-hydroxyphenyl){6-[4-methyl-3-(o-tolyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: m/z 406.20 $[M+1]^+$. NMR: 1H NMR (400 MHz, DMSO-d_6) δ 10.03 (s, 1H), 7.53 – 7.21 (m, 4H), 7.15 – 6.96 (m, 2H), 6.86 – 6.74 (m, 2H), 4.21 (s, 1H), 4.09 – 3.91 (d, J = 12.2 Hz, 4H), 2.67 (dd, J = 26.0, 10.3 Hz, 4H), 2.00 (s, 3H), 1.78 (s, 3H).	A (14)
443	 (2-fluoro-5-hydroxy-4-tolyl){6-[4-methyl-3-(o-tolyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: m/z 420.30 $[M+1]^+$. NMR: 1H NMR (400 MHz, DMSO-d_6) δ 9.55 (s, 1H), 7.42 – 7.23 (dt, J = 23.2, 7.2 Hz, 4H), 7.15 – 7.06 (m, 1H), 6.85 (ddt, J = 26.1, 11.4, 6.6 Hz, 2H), 4.20 (dt, J = 22.6, 7.8 Hz, 1H), 4.04 (s, 2H), 3.74 (d, J = 7.0 Hz, 2H), 2.69	E (6)

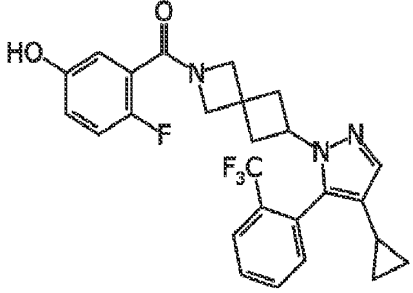
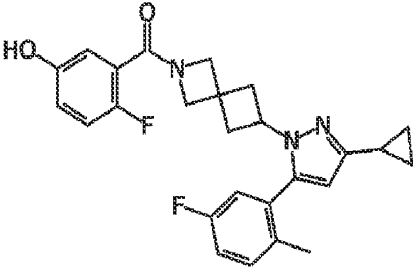
Compound	Structure (IUPAC name)	LCMS / NMR	MAGL Potency (Detection Method)
		(ddd, $J = 34.8$, 17.8, 9.6 Hz, 4H), 1.99 (d, $J =$ 6.3 Hz, 6H), 1.77 (s, 3H).	
444	 (2-fluoro-5-hydroxyphenyl)(6-{4-methyl-3-[o-(trifluoromethyl)phenyl]-1-pyrazolyl}-2-aza-2-spiro[3.3]heptyl)methanone	LCMS: m/z 459.64 $[M+1]^+$. NMR: 1H NMR (400 MHz, DMSO- d_6) δ 9.64 (d, $J = 12.1$ Hz, 1H), 7.98 – 7.88 (m, 1H), 7.80 (s, 2H), 7.47 – 7.36 (m, 2H), 7.09-7.04 (m, 1H), 6.84 (s, 1H), 6.76 (s, 1H), 4.04 – 3.94 (m, 5H), 2.68 – 2.35 (s, 4H), 1.74 (s, 3H).	A (6)
446	 (2-fluoro-5-hydroxyphenyl){6-[3-(5-fluoro-2-tolyl)-5-methyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	Fraction-1: Compound 446- 01 LCMS: m/z 424.3 $[M+1]^+$. NMR: 1H NMR (400 MHz, DMSO- d_6) δ 9.65 (d, 1H), 7.38- 7.33 (dd, $J = 6.4$, 8.6, 1H), 7.21 (t, 1H), 7.10-6.97 (m, $J = 9.2, 11.2$, 2H), 6.85-6.76 (m, 1H), 6.74 (d, 1H), 6.03 (s, 1H), 4.27-4.21 (m, 1H), 4.02 (s, 2H), 4.00 (s, 2H), 2.71 (s, 2H), 2.65 (s, 2H), 2.23 (d, 3H), 2.03 (d, 3H).	A (6)

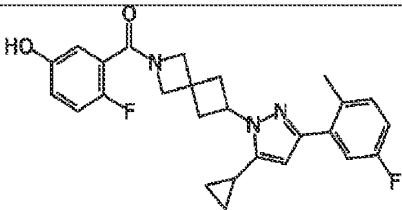
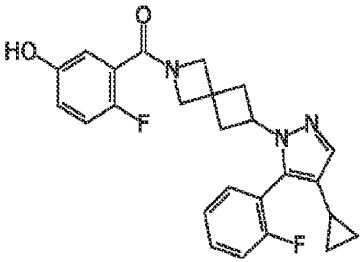
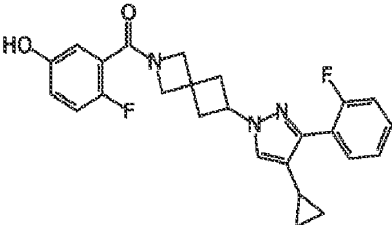
Compound	Structure (IUPAC name)	LCMS / NMR	MAGL Potency (Detection Method)
		Fraction-2: Compound 446-02 LCMS: m/z 424.32 $[M+1]^+$. NMR: ^1H NMR (400 MHz, DMSO- d_6) δ 9.65 (d, 1H), 7.38-7.33 (m, $J=6.4$, 6.8, 7.2, 1H), 7.22-7.20 (dd, 1H), 7.07-6.97 (m, $J=9.2$, 10.8, 9.6, 2H), 6.83 (s, 1H), 6.75 (s, 1H), 6.03 (s, 1H), 4.27-4.21 (m, 1H), 4.00 (d, 4H), 2.69 (d, 4H), 2.19 (d, 3H), 2.03 (d, 3H).	
472	 (2-fluoro-5-hydroxyphenyl){6-[5-(o-fluorophenyl)-4-(trifluoromethyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: m/z 464.41 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 9.69 (d, $J=5.5$ Hz, 1H), 8.62 (d, $J=9.6$ Hz, 1H), 7.53 (s, 1H), 7.51 – 7.42 (m, 1H), 7.39 – 7.25 (m, 2H), 7.10 (q, $J=9.0$ Hz, 1H), 6.89 – 6.84 (m, 1H), 6.81 (s, 1H), 4.90 (dt, $J=23.7$, 7.9 Hz, 1H), 4.16 (d, $J=10.3$ Hz, 2H), 4.06 (d, $J=8.1$ Hz, 2H), 2.74	B (12)

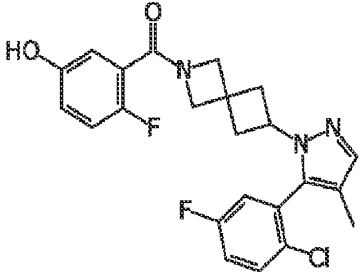
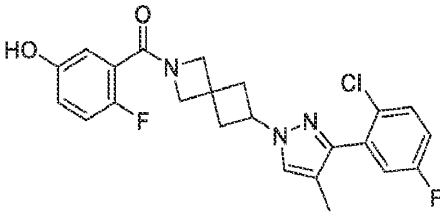
Compound	Structure (IUPAC name)	LCMS / NMR	MAGL Potency (Detection Method)
		(dd, $J = 24.9$, 10.1 Hz, 4H).	
473	 (2-fluoro-5-hydroxyphenyl){6-[3-(o-fluorophenyl)-4-(trifluoromethyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: m/z 464.01 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 9.68 (s, 1H), 8.12 (d, $J = 9.7$ Hz, 1H), 7.63 - 7.43 (dq, $J =$ 19.3, 9.9, 7.4 Hz, 4H), 7.08 (q, $J =$ 9.5 Hz, 1H), 6.85 (s, 1H), 6.77 (s, 1H), 4.50 (dt, $J =$ 14.3, 7.5 Hz, 1H), 4.03 (d, $J =$ 9.0 Hz, 4H), 2.79 - 2.63 (m, 4H).	A (12)
474	 (2-fluoro-5-hydroxyphenyl){6-[5-(2-fluoro-5-tolyl)-4-(trifluoromethyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: m/z 478.40 $[M+1]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 9.67 (s, 1H), 8.1 (d, $J = 9.9$ Hz, 1H), 7.29- 7.20 (m, 3H), 7.09 (q, $J = 9.6$ Hz, 1H), 6.84 (s, 1H), 6.79 (s, 1H), 4.88 (dt, $J = 14.5$, 7.7 Hz, 1H), 4.03 (d, $J = 8.7$ Hz, 4H), 2.74 (ddt, J = 51.2, 19.7, 8.6 Hz, 4H), 2.35 (d, $J = 9.5$ Hz, 3H).	C (12)
475		LCMS: m/z 478.4 $[M+1]^+$. NMR: 1H NMR (400 MHz, DMSO- d_6) δ 9.67 (s, 1H), 8.11 (d, J = 9.9 Hz, 1H),	A (12)

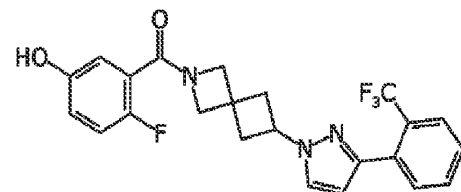
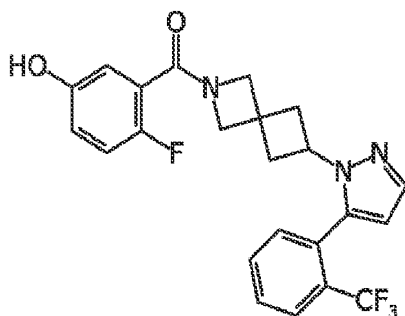
Compound	Structure (IUPAC name)	LCMS / NMR	MAGL Potency (Detection Method)
	(2-fluoro-5-hydroxyphenyl){6-[3-(2-fluoro-5-tolyl)-4-(trifluoromethyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	7.45 (s, 1H), 7.39 – 7.18 (m, 2H), 7.08 (q, $J = 9.6$ Hz, 1H), 6.85 (s, 1H), 6.77 (s, 1H), 4.49 (dt, $J = 14.5$, 7.7 Hz, 1H), 4.03 (d, $J = 18.8$ Hz, 4H), 2.68-2.51 (m, 2H), 2.47 (m, 2H), 2.35 (d, $J = 9.5$ Hz, 3H).	
476	 {6-[5-(2,5-difluorophenyl)-4-methyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}(2-fluoro-5-hydroxyphenyl)methanone	LCMS: m/z 428.3 $[M+1]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 9.69 (s, 1H), 7.72 (d, $J = 5.9$ Hz, 1H), 7.39 – 7.26 (m, 3H), 7.10 (q, $J = 9.1$ Hz, 1H), 6.82 – 6.87 (q, $J = 9.1$ Hz, 1H), 6.74 – 6.79 (q, $J = 9.1$ Hz, 1H), 4.76 (dt, $J = 23.3$, 7.9 Hz, 1H), 4.15 (d, $J = 11.2$ Hz, 2H), 4.05 (d, $J = 8.7$ Hz, 2H), 2.76 – 2.60 (m, 4H), 1.99 (s, 3H).	B (13)
477	 {6-[3-(2,5-difluorophenyl)-4-methyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}(2-fluoro-5-hydroxyphenyl)methanone	LCMS: m/z 428.03 $[M+1]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 7.52 – 7.40 (m, 3H), 7.30 (dd, $J = 5.4$, 2.8 Hz, 1H), 7.08 (q, $J = 8.9$ Hz, 1H), 6.85 (d, $J = 3.9$ Hz, 1H), 6.81 – 6.75 (m, 1H), 4.47 (dt, $J =$	A (13)

Compound	Structure (IUPAC name)	LCMS / NMR	MAGL Potency (Detection Method)
		15.6, 7.8 Hz, 1H), 4.07 (dd, J = 24.5, 5.0 Hz, 4H), 2.60 (dd, J = 20.2, 8.3 Hz, 4H), 1.90 (s, 3H).	
487	 (2-fluoro-5-hydroxyphenyl)(6-{3-(trifluoromethyl)-5-[o-(trifluoromethyl)phenyl]-1-pyrazolyl}-2-aza-2-spiro[3.3]heptyl)methanone	LCMS: m/z 514.20 $[M+1]^+$. NMR: $^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ 9.67 (d, 1H), 7.96 (m, 1H), 7.78-7.67 (m, 2H), 7.63 (m, 1H), 7.08 (s, 2H), 6.84-6.78 (dd, J = 3.6 Hz, 8.4 Hz, 2H), 6.72 (s, 1H), 4.16 (m, 2H), 4.08 – 4.02 (m, 2H), 2.79 (s, 4H).	C (13)
488	 (6-{4-cyclopropyl-3-[o-(trifluoromethyl)phenyl]-1-pyrazolyl}-2-aza-2-spiro[3.3]heptyl)(2-fluoro-5-hydroxyphenyl)methanone	LCMS: m/z 486.33 $[M+H]^+$. NMR: $^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ 9.73 (s, 1H), 7.91 (dd, J = 12.6, 8.1 Hz, 1H), 7.83 – 7.69 (m, 2H), 7.40 (t, J = 8.0 Hz, 1H), 7.26 (d, J = 10.1 Hz, 1H), 7.04 (dt, J = 17.3, 9.2 Hz, 1H), 6.74 (s, 2H), 4.09 (dd, J = 14.2, 6.8 Hz, 1H), 4.01 – 3.91 (m, 4H), 2.63 (s, 2H), 2.54 (s, 2H), 1.18 (m, 1H), 0.59 (s, 2H), 0.39 (d, J = 15.1 Hz, 2H).	A (12)

Compound	Structure (IUPAC name)	LCMS / NMR	MAGL Potency (Detection Method)
489	 (6-{4-cyclopropyl-5-[o-(trifluoromethyl)phenyl]-1-pyrazolyl}-2-aza-2-spiro[3.3]heptyl)(2-fluoro-5-hydroxyphenyl)methanone	LCMS: m/z 486.33[M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.67 (s, 1H), 7.83 (s, 1H), 7.72 (d, J = 5.2 Hz, 1H), 7.63 (s, 1H), 7.53 (s, 2H), 7.09 (d, J = 8.9 Hz, 1H), 6.85 (s, 2H), 4.70 (d, J = 7.4 Hz, 1H), 4.12 (d, J = 10.2 Hz, 2H), 4.00 (d, J = 8.5 Hz, 2H), 2.65 (dd, J = 19.9, 11.1 Hz, 4H), 1.29 (m, 1H), 0.67 (d, J = 6.9 Hz, 2H), 0.41 (s, 2H).	B (12)
490	 {6-[3-cyclopropyl-5-(5-fluoro-2-tolyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}(2-fluoro-5-hydroxyphenyl)methanone	LCMS: m/z 449.5 [M+1]⁺. NMR: ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.67 (d, J = 8.4 Hz, 1H), 7.37 – 7.26 (m, 2H), 7.13 – 6.98 (m, 2H), 6.85 (s, 1H), 6.80 (s, 1H), 6.24 (s, 1H), 4.16 (d, J = 9.1 Hz, 2H), 4.07 (s, 2H), 2.75 (s, 4H), 2.41 (d, J = 17.2 Hz, 3H), 1.85 (s, 1H), 0.94 (s, 2H), 0.65 (s, 2H).	B (13)
491		LCMS: m/z 449.5 [M+1]⁺. NMR: ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.65 (d, J = 7.5 Hz, 1H), 7.36 (d,	A (13)

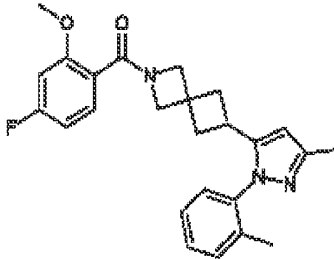
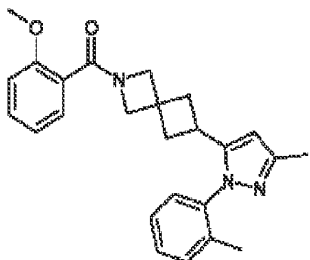
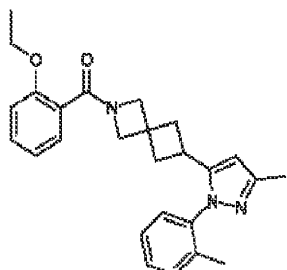
Compound	Structure (IUPAC name)	LCMS / NMR	MAGL Potency (Detection Method)
	 {6-[5-cyclopropyl-3-(5-fluoro-2-tolyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}(2-fluoro-5-hydroxyphenyl)methanone	J = 5.7 Hz, 1H), 7.21 (d, J = 9.3 Hz, 0H), 7.10 – 7.00 (m, 1H), 6.99 (d, J = 9.0 Hz, 1H), 6.84 (s, 1H), 6.76 (s, 1H), 5.93 (s, 1H), 4.28 – 4.19 (m, 1H), 4.01 (d, J = 9.4 Hz, 4H), 2.67 (s, 4H), 2.01 (s, 3H), 1.90 (s, 1H), 0.87 (s, 2H), 0.66 (d, J = 14.9 Hz, 2H).	
492	 {6-[4-cyclopropyl-5-(o-fluorophenyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}(2-fluoro-5-hydroxyphenyl)methanone	LCMS: <i>m/z</i> 436.20 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.69 (s, 1H), 7.56 (dd, J = 20.5, 7.4 Hz, 3H), 7.33 – 7.24 (m, 2H), 6.81 (s, 2H), 4.76 – 4.66 (m, 1H), 4.15 (d, J = 10.4 Hz, 2H), 4.04 (d, J = 8.4 Hz, 2H), 2.72 – 2.62 (m, 4H), 1.56 (s, 1H), 0.76 (s, 2H), 0.44 (s, 2H).	B (12)
493	 {6-[4-cyclopropyl-3-(o-fluorophenyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}(2-fluoro-5-hydroxyphenyl)methanone	LCMS: <i>m/z</i> 436.22 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.64 (s, 1H), 7.36 (dd, J = 26.7, 8.4 Hz, 4H), 7.08 (d, J = 9.0 Hz, 1H), 6.77 (s, 2H), 4.41 (s, 1H), 4.02 (s, 4H), 2.70 (s, 4H), 1.40	A (12)

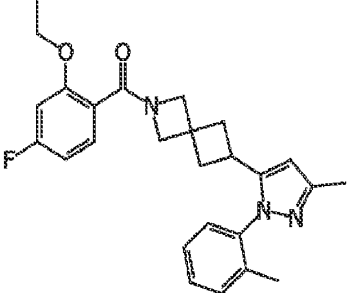
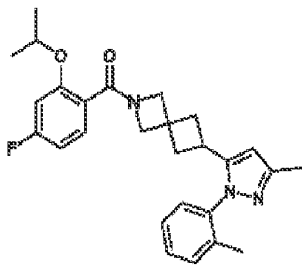
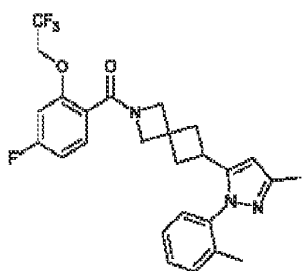
Compound	Structure (IUPAC name)	LCMS / NMR	MAGL Potency (Detection Method)
		(s, 1H), 0.69 (s, 2H), 0.46 (s, 2H).	
519	 {6-[5-(2-chloro-5-fluorophenyl)-4-methyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}(2-fluoro-5-hydroxyphenyl)methanone	LCMS: <i>m/z</i> 444.40 [M+1]⁺. NMR: ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.80 (s, 1H), 7.68 (d, <i>J</i> = 5.0 Hz, 1H), 7.58 (dt, <i>J</i> = 8.8, 5.6 Hz, 1H), 7.35 – 7.17 (m, 2H), 7.08 (q, <i>J</i> = 9.1 Hz, 1H), 6.87 – 6.74 (m, 2H), 4.72 (dq, <i>J</i> = 24.0, 7.9 Hz, 1H), 4.13 (d, <i>J</i> = 10.7 Hz, 2H), 4.02 (d, <i>J</i> = 9.4 Hz, 2H), 2.68 (q, <i>J</i> = 15.2, 13.3 Hz, 4H), 1.91 (d, <i>J</i> = 2.6 Hz, 3H).	B (12)
520	 {6-[3-(2-chloro-5-fluorophenyl)-4-methyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}(2-fluoro-5-hydroxyphenyl)methanone	LCMS: <i>m/z</i> 444.40 [M+1]⁺. NMR: ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.70 (s, 1H), 7.68 (d, <i>J</i> = 5.0 Hz, 1H), 7.58 (dt, <i>J</i> = 8.8, 5.6 Hz, 2H), 7.35 – 7.17 (m, 1H), 7.08 (q, <i>J</i> = 9.1 Hz, 1H), 6.85 – 6.71 (m, 2H), 4.32 (dq, <i>J</i> = 24.0, 7.9 Hz, 1H), 4.03 (d, <i>J</i> = 10.7 Hz, 4H), 2.68 (q, <i>J</i> = 15.2, 13.3 Hz, 4H), 1.81 (d, <i>J</i> = 2.6 Hz, 3H).	A (12)

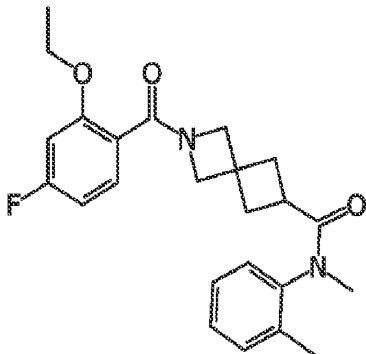
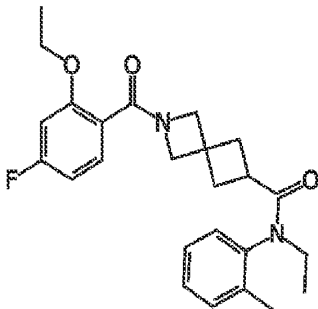
Compound	Structure (IUPAC name)	LCMS / NMR	MAGL Potency (Detection Method)
525	 (2-fluoro-5-hydroxyphenyl)(6-{3-[o-(trifluoromethyl)phenyl]-1-pyrazolyl}-2-aza-2-spiro[3.3]heptyl)methanone	LCMS: m/z 446.30 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 9.64 (s, 1H), 7.89 (s, 1H), 7.78 – 7.71 (m, 2H), 7.58 (d, J = 9.1 Hz, 1H), 7.42 (s, 1H), 7.03 (s, 1H), 6.82 (s, 1H), 6.75 (s, 1H), 6.28 (s, 1H), 4.26 (s, 1H), 3.99 (d, J = 19.2 Hz, 4H), 2.78 (s, 4H).	A (12)
526	 (2-fluoro-5-hydroxyphenyl)(6-{5-[o-(trifluoromethyl)phenyl]-1-pyrazolyl}-2-aza-2-spiro[3.3]heptyl)methanone	LCMS: m/z 446.20 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 9.66 (d, J = 7.4 Hz, 1H), 7.82 (dd, J = 16.3, 9.0 Hz, 2H), 7.73 – 7.54 (m, 3H), 7.08 (q, J = 8.8 Hz, 1H), 6.88 – 6.82 (m, 1H), 6.79 (s, 1H), 6.42 (s, 1H), 4.82 (dt, J = 23.6, 7.9 Hz, 1H), 4.14 (d, J = 10.1 Hz, 2H), 4.04 (d, J = 7.9 Hz, 2H), 2.71 (dt, J = 17.5, 10.4 Hz, 4H).	B (12)

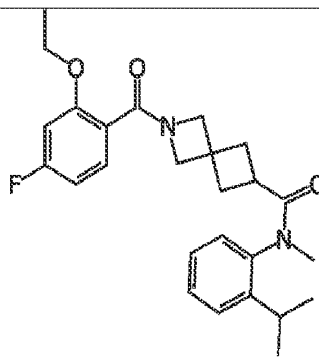
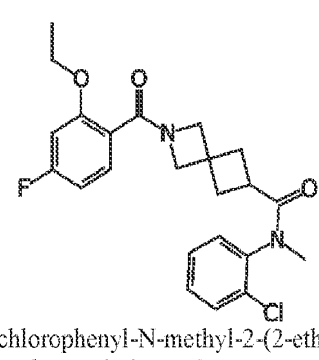
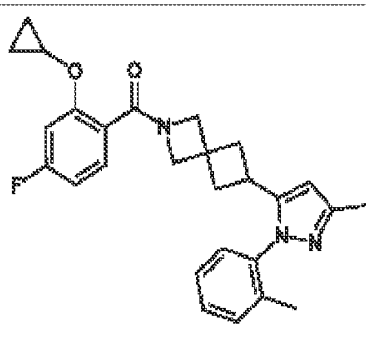
[000365] Table 7 - Compounds of Formula (I), including the value of MAGL inhibition potency measured with a method described in Table C of Example 22.

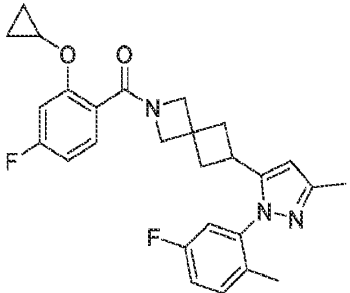
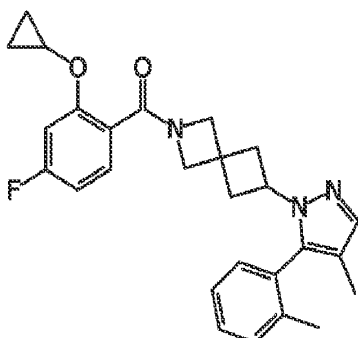
Compound	Structure (IUPAC name)	LCMS / NMR	MAGL Potency (Detection Method)
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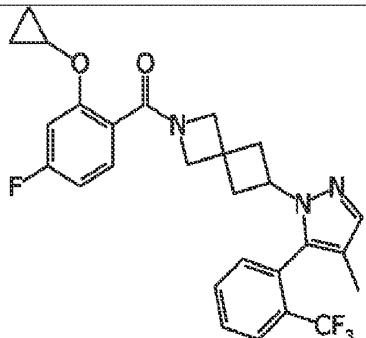
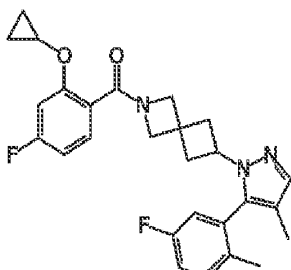
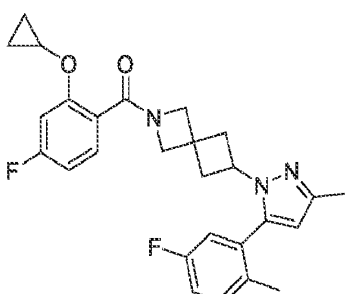
142	 (4-fluoro-2-methoxyphenyl){6-[3-methyl-1-(o-tolyl)-5-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: 420.41 m/z [M+H]⁺; ¹H NMR (400 MHz, DMSO-d₆) δ 7.44 – 7.25 (m, 4H), 7.16 (t, J = 6.5 Hz, 1H), 6.98 (s, 1H), 6.85 – 6.74 (m, 1H), 6.17 (s, 1H), 3.95 (s, 1H), 3.89 (s, 1H), 3.86 – 3.75 (m, 5H), 2.99 (dt, J = 25.9, 8.5 Hz, 1H), 2.26 – 2.43 (m, 3H), 2.26 – 2.14 (m, 4H), 1.94 (d, J = 2.2 Hz, 3H).	D (2)
143	 (o-methoxyphenyl){6-[3-methyl-1-(o-tolyl)-5-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: 401.8 m/z [M]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 7.50 – 7.17 (m, 5H), 7.17 – 6.96 (m, 3H), 6.23 – 6.17 (s, 1H), 4.11 (s, 1H), 4.05 (s, 1H), 3.97 (s, 1H), 3.93 – 3.84 (m, 4H), 3.08 (dq, J = 29.0, 8.5 Hz, 1H), 2.48 – 2.35 (m, 3H), 2.32 (dd, J = 27.0, 12.1 Hz, 4H), 2.01 (d, J = 3.1 Hz, 3H).	E (2)
145	 (o-ethoxyphenyl){6-[3-methyl-1-(o-tolyl)-5-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: 416.74 m/z [M+H]⁺; ¹H NMR (400 MHz, DMSO-d₆) δ 7.45 – 7.24 (m, 3H), 7.20 (d, J = 7.5 Hz, 1H), 7.14 (q, J = 8.1, 7.2 Hz, 1H), 7.08 – 6.89 (m, 2H), 6.17 – 6.07 (s, 1H), 4.06 (dq, J = 9.9, 6.9 Hz, 2H), 3.94 (s, 1H), 3.88 (s, 1H), 3.83 (s, 1H), 3.77 (s, 1H), 2.98 (dq, J = 25.0, 8.4 Hz, 1H), 2.39 – 2.14 (m, 7H), 1.93 (d, J = 1.9 Hz, 3H), 1.30 (dt, J = 9.8, 6.9 Hz, 3H).	E (2)
146		LCMS: m/z 433.8 [M+1]⁺ ¹H NMR (400 MHz, DMSO-d₆) δ 7.43 – 7.22 (m, 4H), 7.15 (dd, J = 7.6, 4.7 Hz, 1H), 6.95	C(2) A (3)

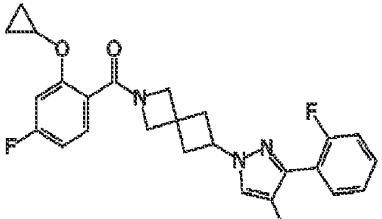
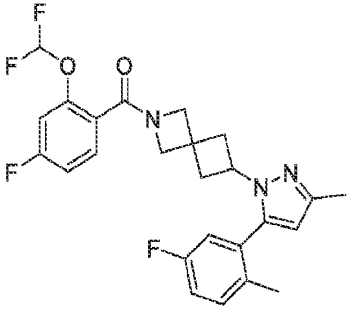
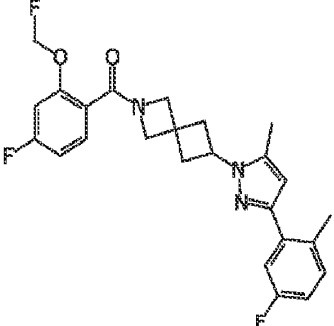
	 (2-ethoxy-4-fluorophenyl){6-[3-methyl-1-(o-tolyl)-5-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	(s, 1H), 6.79-6.74 (m, 1H), 6.11 (d, 1H), 4.10-4.07 (m, 2H), 3.94 (s, 1H), 3.86 (d, $J = 14.0$ Hz, 2H), 3.78 (s, 1H), 3.04-2.96 (m, 1H), 2.33 (s, 1H), 2.32-2.25 (m, 2H), 2.22 (dd, $J = 35.1, 9.2$ Hz, 4H), 1.93 (d, $J = 1.8$ Hz, 3H), 1.30 (dt, $J = 9.8, 6.9$ Hz, 3H).	
177	 (4-fluoro-2-isopropoxyphenyl){6-[3-methyl-1-(o-tolyl)-5-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: 448.5 m/z $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ 7.38 (t, $J = 8.3$ Hz, 2H), 7.33 – 7.22 (m, 2H), 7.15 (dd, $J = 7.9, 4.2$ Hz, 1H), 6.97 (dd, $J = 11.6, 8.5$ Hz, 1H), 6.75 (q, $J = 7.6$ Hz, 1H), 6.13 (d, $J = 17.6$ Hz, 1H), 4.70 – 4.60 (m, 1H), 3.93 (s, 1H), 3.85 (d, $J = 15.1$ Hz, 2H), 3.78 (s, 1H), 3.00 (dt, $J = 18.8, 8.5$ Hz, 1H), 2.34 – 2.16 (m, 4H), 2.16 (s, 3H), 1.93 (s, 3H), 1.24 (dd, $J = 11.5, 6.1$ Hz, 6H).	B (2)
178	 [4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]{6-[3-methyl-1-(o-tolyl)-5-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: 488.5 m/z $[M+]$ 1H NMR (400 MHz, DMSO-d_6) δ 7.46 – 7.36 (m, 2H), 7.40 – 7.25 (m, 2H), 7.16 (s, 1H), 7.21 – 7.10 (m, 1H), 6.98 – 6.87 (m, 1H), 6.17 (s, 1H), 4.93 – 4.79 (m, 2H), 3.95 (s, 1H), 3.86 (d, $J = 19.9$ Hz,	A (2, 3, 5)

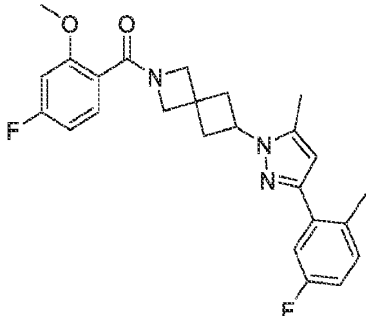
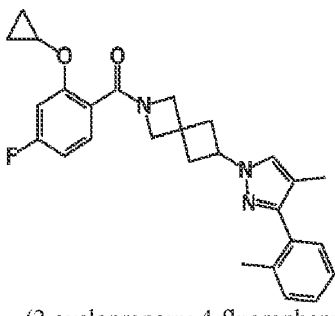
		2H), 3.78 (s, 1H), 3.03–2.92 (m, 1H), 2.33 (t, J = 10.4 Hz, 2H), 2.21 (dd, J = 23.9, 9.2 Hz, 5H), 1.93 (d, J = 2.3 Hz, 3H).	
187	 N-methyl-N-o-tolyl-2-(2-ethoxy-4-fluorobenzoyl)-2-aza-6-spiro[3.3]heptanecarboxamide	m/z 411.4 [M+1]⁺ ¹H NMR (400 MHz, Methanol-d₄) δ 7.42–7.22 (dq, J = 27.9, 7.8 Hz, 4H), 7.14 (d, J = 7.5 Hz, 1H), 6.91–6.66 (m, 2H), 4.18–3.89 (m, 5H), 3.87 (s, 1H), 3.17 (d, J = 5.4 Hz, 3H), 2.79 (dp, J = 24.3, 8.0 Hz, 1H), 2.43 (ddt, J = 27.5, 19.5, 9.9 Hz, 2H), 2.20 (s, 3H), 2.17–1.98 (m, 2H), 1.41 (dt, J = 18.6, 7.0 Hz, 3H).	C (2) E (2, 3)
203	 N-ethyl-N-o-tolyl-2-(2-ethoxy-4-fluorobenzoyl)-2-aza-6-spiro[3.3]heptanecarboxamide	LCMS: 425.7 m/z ¹H NMR (400 MHz, DMSO-d₆) δ 7.33 (s, 2H), 7.33–7.20 (m, 2H), 7.09 (d, J = 7.6 Hz, 1H), 6.94 (ddd, J = 17.5, 11.7, 2.4 Hz, 1H), 6.76 (ddt, J = 10.8, 8.4, 2.5 Hz, 1H), 4.08 (dt, J = 13.8, 6.9 Hz, 3H), 4.06–3.88 (m, 1H), 3.86–3.73 (m, 2H), 3.71 (s, 2H), 3.10 (dt, J = 13.6, 6.8 Hz, 1H), 2.33–2.19 (m, 2H), 2.12 (d, J = 1.9 Hz, 3H), 1.92 (s, 1H), 1.93–1.82 (m, 1H), 1.30 (dt, J = 21.2, 7.0 Hz, 3H), 0.98 (td, J = 7.1, 5.2 Hz, 3H).	C (4)
205		LCMS: 439.7 m/z ¹H NMR (400 MHz, DMSO-d₆) δ 7.51–7.38 (m, 1H), 7.42–7.25 (m, 1H), 7.26 (dd, J = 7.9, 4.7 Hz, 1H), 6.95 (ddd, J = 19.4, 11.6, 2.4 Hz, 1H), 6.84–6.71 (m, 1H), 4.08	D (4)

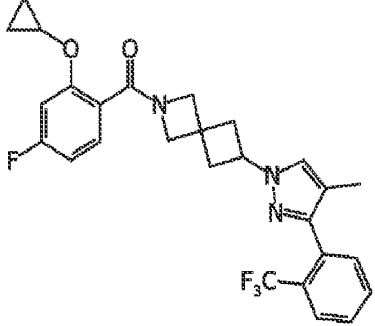
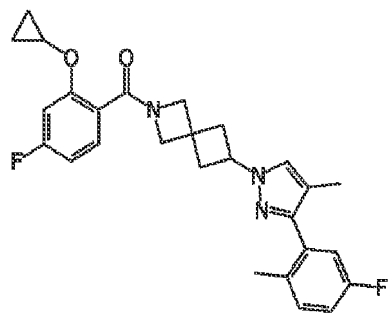
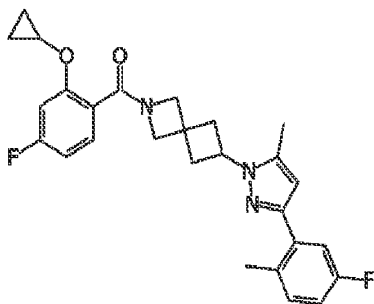
	 N-o-cumenyl-N-methyl-2-(2-ethoxy-4-fluorobenzoyl)-2-aza-6-spiro[3.3]heptanecarboxamide	(dq, J = 21.4, 6.8 Hz, 2H), 3.82 (t, J = 4.8 Hz, 3H), 3.75 (dq, J = 14.6, 8.9, 6.8 Hz, 1H), 3.16 – 3.01 (m, 3H), 2.83 (p, J = 6.8 Hz, 1H), 2.68 – 2.53 (m, 1H), 2.35 – 2.20 (m, 2H), 2.00 (ddd, J = 30.9, 12.2, 8.7 Hz, 2H), 1.31 (dt, J = 21.4, 7.0 Hz, 3H), 1.21 – 1.09 (m, 6H).	
206	 N-o-chlorophenyl-N-methyl-2-(2-ethoxy-4-fluorobenzoyl)-2-aza-6-spiro[3.3]heptanecarboxamide	LCMS: 431.4m/z [M+] ¹ H NMR (400 MHz, DMSO-d ₆) δ 7.64 (ddd, J = 9.3, 6.6, 3.9 Hz, 1H), 7.46 (ddd, J = 13.8, 6.0, 3.3 Hz, 3H), 7.38 – 7.22 (m, 1H), 6.95 (ddd, J = 15.6, 11.6, 2.4 Hz, 1H), 6.77 (dtd, J = 10.6, 8.4, 2.4 Hz, 1H), 4.11 (q, J = 5.9, 5.1 Hz, 1H), 4.06 (q, J = 6.9, 5.9 Hz, 1H), 3.84 (d, J = 7.1 Hz, 2H), 3.76 (d, J = 14.2 Hz, 2H), 3.07 (d, J = 6.4 Hz, 3H), 2.68 (hept, J = 8.2 Hz, 1H), 2.34 – 2.24 (m, 2H), 2.08 – 1.85 (m, 2H), 1.42 – 1.22 (m, 3H).	E (4)
374	 (2-cyclopropoxy-4-fluorophenyl){6-[3-methyl-1-(o-tolyl)-5-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: m/z 446.3 [M+] ⁺ . ¹ H NMR (400 MHz, Chloroform-d) δ 7.36 (m, 4H), 7.18 (dd, 1H), 7.07 – 6.97 (t, 1H), 6.72 (d, J = 7.7 Hz, 1H), 6.07-6.00 (s, 1H), 4.10 (dt, J = 18.6 Hz, 2H), 3.91 (s, 1H), 3.84 (s, 1H), 3.76 (m, 1H), 3.11 – 2.96 (m, J = 8.5 Hz, 1H),	C (14)

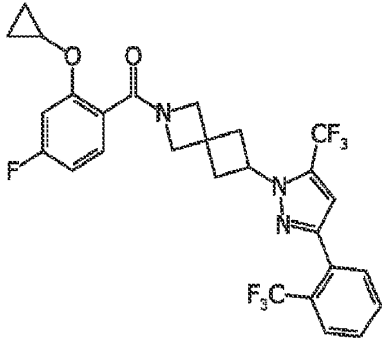
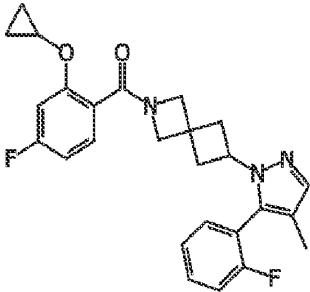
		2.44 (d, 1H), 2.34 (d, $J = 6.2$ Hz, 5H), 2.25 (d, $J = 11.0$ Hz, 1H), 2.06 (s, $J = 3.1$ Hz, 3H), 0.85 (d, $J = 13.3$ Hz, 4H).	
418	 (2-cyclopropoxy-4-fluorophenyl){6-[1-(5-fluoro-2-tolyl)-3-methyl-5-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: m/z 464.44 $[M+1]^+$. NMR: 1H NMR (400 MHz, DMSO-d_6) δ 7.42 (q, $J = 7.8$ Hz, 1H), 7.30 (t, $J = 7.6$ Hz, 2H), 7.28 – 7.11 (m, 2H), 6.87 – 6.81 (m, 1H), 3.98 – 3.85 (m, 3H), 3.79 (s, 1H), 3.70 (s, 1H), 3.13 – 2.99 (m, 1H), 2.35 (t, $J = 10.1$ Hz, 1H), 2.22 (dd, $J = 23.5, 9.3$ Hz, 6H), 1.91 (s, 3H), 0.89 – 0.81 (m, 2H), 0.67 (s, 2H).	B (12)
419	 (2-cyclopropoxy-4-fluorophenyl){6-[4-methyl-5-(o-tolyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: m/z 446.39 $[M+1]^+$. 1H NMR (400 MHz, DMSO-d_6) δ 7.64 (s, 1H), 7.38–7.28 (m, 3H), 7.22 – 7.16 (m, 3H), 6.81 (m, 1H), 4.77 (m, 1H), 4.11 (s, 1H), 4.05 (s, 1H), 3.97 (s, 2H), 3.85 (s, 1H), 2.74–2.68 (m, 4H), 2.20 (d, $J = 8.0$ Hz, 3H), 1.92 (s, 3H), 0.89–0.84 (m, 2H), 0.70 (s, 2H).	E (6)
420		LCMS: m/z 500.2 $[M+1]^+$. NMR: 1H NMR (400 MHz, DMSO-d_6) δ 7.83 (t, $J = 7.6$ Hz, 1H), 7.71 (d, $J = 6.6$ Hz, 1H), 7.62 (s, 2H), 7.45 – 7.37 (m, 1H), 7.36 – 7.27	E (6)

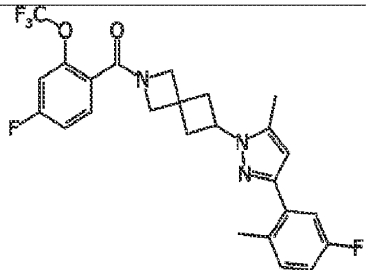
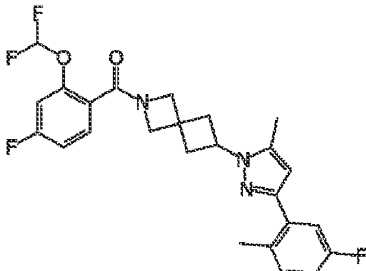
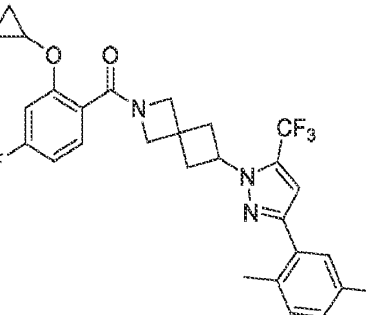
	 (2-cyclopropoxy-4-fluorophenyl)(6-{4-methyl-5-[o-(trifluoromethyl)phenyl]-1-pyrazolyl}-2-aza-2-spiro[3.3]heptyl)methanone	(m, 1H), 7.21 (t, $J = 11.7$ Hz, 1H), 6.86 (d, $J = 7.5$ Hz, 1H), 4.70 (dd, $J = 20.2$, 7.8 Hz, 1H), 4.09 (s, 1H), 3.95 (d, $J = 17.4$ Hz, 3H), 3.80 (s, 1H), 2.71 (s, 2H), 2.64 (d, $J = 7.7$ Hz, 2H), 1.84 (s, 3H), 0.89 – 0.83 (m, 2H), 0.72 (s, 1H), 0.66 (s, 1H).	
422	 (2-cyclopropoxy-4-fluorophenyl){6-[5-(5-fluoro-2-tolyl)-4-methyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl)methanone	LCMS: m/z 464.30 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.67 – 7.67 (d, $J = 2.4$ Hz, 1H), 7.38 – 7.20 (m, 3H), 7.12 (s, 1H), 7.03 (s, 1H), 6.86 (d, $J = 6.4$ Hz, 1H), 4.78 (m, 1H), 4.11 (s, 1H), 4.05 (s, 1H), 3.94 (s, 2H), 3.84 (s, 1H), 2.68 (m, 4H), 2.20 (d, $J = 6.0$ Hz, 3H), 1.92 (s, 3H), 0.86 (dd, $J = 11.8$, 5.9 Hz, 2H), 0.70 (s, 2H).	E (6)
423	 (2-cyclopropoxy-4-fluorophenyl){6-[5-(5-fluoro-2-tolyl)-3-methyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl)methanone	LCMS: m/z 464.34 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.43 – 7.33 (m, 2H), 7.28 (dd, $J = 24.8$, 11.2 Hz, 2H), 7.08 (d, $J = 8.6$ Hz, 1H), 6.90 (d, $J = 8.1$ Hz, 1H), 6.40 (s, 1H), 4.81 (dt, $J = 22.3$, 7.4 Hz, 1H), 4.16 (s, 1H), 4.06 (s, 1H), 4.00 (s, 2H), 3.92 (s, 1H), 2.67 (d, $J = 17.7$ Hz, 4H), 2.59-2.44 (m, 3H), 2.30 (d, $J = 9.7$ Hz,	E (6)

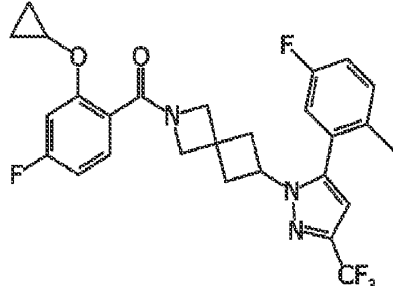
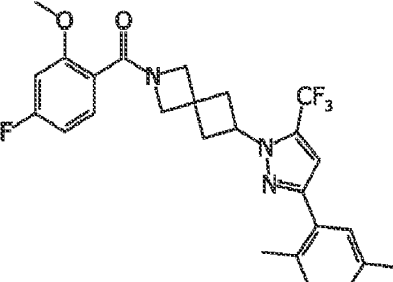
		3H), 0.94 – 0.86 (m, 2H), 0.76 (d, $J = 18.2$ Hz, 2H).	
425	 (2-cyclopropoxy-4-fluorophenyl){6-[3-(o-fluorophenyl)-4-methyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: m/z 449.9 $[M+1]^+$ 1H NMR (400 MHz, DMSO-d_6) δ 7.56 (s, 1H), 7.44 (dd, $J = 17.5, 10.9$ Hz, 1H), 7.34 (dq, $J = 15.5, 8.3, 7.9$ Hz, 4H), 7.25 – 7.15 (m, 1H), 6.85 (s, 1H), 4.41 (dt, $J = 16.5, 7.8$ Hz, 1H), 4.01 – 3.95 (m, 4H), 3.82 (s, 2H), 2.74 – 2.55 (m, 3H), 1.87 (s, 3H), 0.84 (s, 2H), 0.69 (s, 2H).	C (6)
428	 (2-difluoromethoxy-4-fluorophenyl){6-[5-(5-fluoro-2-tolyl)-3-methyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: m/z 474.23 $[M]^+$ NMR: 1H NMR (400 MHz, DMSO-d_6) δ 7.58-7.49 (m, 1H), 7.35-7.02 (m, 6H), 6.36 (s, 1H), 4.82-4.72 (m, 1H), 4.17 (s, 1H), 4.07 (d, $J = 4.4$ Hz, 2H), 3.99 (s, 1H), 2.77 – 2.66 (m, 4H), 2.42 (d, $J = 19.1$ Hz, 3H), 2.26 (d, $J = 11.6$ Hz, 3H).	C (6)
437	 (2-(2-fluoromethoxy)-4-fluorophenyl){6-[5-(5-fluoro-2-tolyl)-3-methyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: m/z 456.34 $[M+1]^+$ 1H NMR (400 MHz, DMSO-d_6) δ 7.43 – 7.32 (m, 2H), 7.29 – 7.11 (m, 2H), 7.01 (t, $J = 9.1$ Hz, 2H), 6.08 – 5.98 (m, 3H), 4.26 (dt, $J = 25.0, 7.9$ Hz, 1H), 4.03 (s, 2H), 3.92 (d,	E (11)

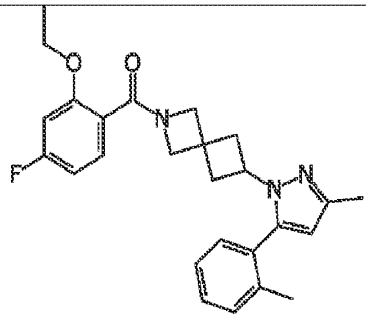
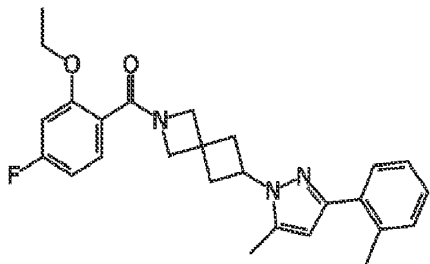
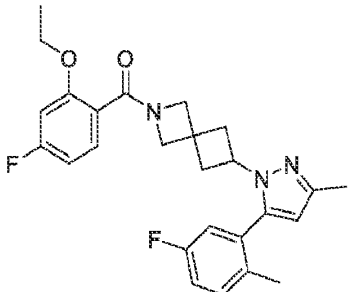
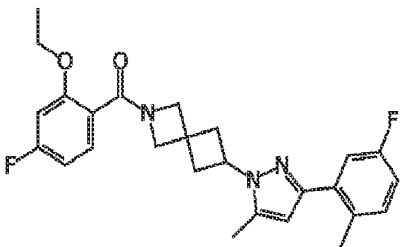
	(4-fluoro-2-fluoromethoxyphenyl){6-[3-(5-fluoro-2-tolyl)-5-methyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	$J = 6.8$ Hz, 2H), 2.70 (dd, $J = 20.4, 10.5$ Hz, 4H), 2.23 (d, $J = 15.1$ Hz, 3H), 2.04 (d, $J = 8.0$ Hz, 3H).	
439	 (4-fluoro-2-methoxyphenyl){6-[3-(5-fluoro-2-tolyl)-5-methyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: m/z 438.20 $[M+1]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 7.43 – 7.16 (m, 3H), 7.04 – 6.94 (m, 2H), 6.79 (q, $J = 6.5$ Hz, 1H), 6.05 (s, 1H), 4.24 (dt, $J = 24.2, 7.9$ Hz, 1H), 3.99 (s, 2H), 3.88 (d, $J = 4.0$ Hz, 2H), 3.82 (d, $J = 10.0$ Hz, 3H), 2.70 (dt, $J = 21.5, 11.0$ Hz, 2H), 2.55 (s, 2H), 2.21 (d, $J = 14.1$ Hz, 3H), 2.02 (d, $J = 7.5$ Hz, 3H)	E (6)
447	 (2-cyclopropoxy-4-fluorophenyl){6-[4-methyl-3-(o-tolyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: m/z 446.40 $[M+1]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 7.48 – 7.28 (m, 5H), 7.26 – 7.08 (m, 2H), 6.81 (m, 1H), 4.21 (dt, $J = 16.1, 7.9$ Hz, 1H), 3.97 (s, 2H), 3.91 (s, 1H), 3.82 (d, $J = 6.0$ Hz, 2H), 2.68 (ddt, $J = 26.0, 18.1, 9.5$ Hz, 4H), 2.00 (d, $J = 6.0$ Hz, 3H), 1.79 (s, 3H), 0.86 (dd, $J = 11.8, 5.9$ Hz, 2H), 0.70 (s, 2H).	C (6)
448		LCMS: m/z 500.2 $[M+1]^+$	B (6)

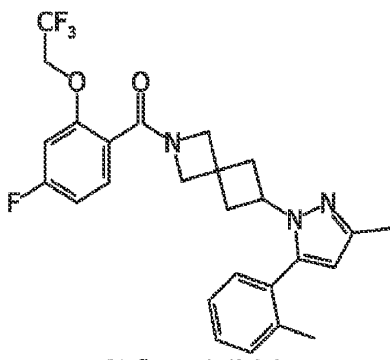
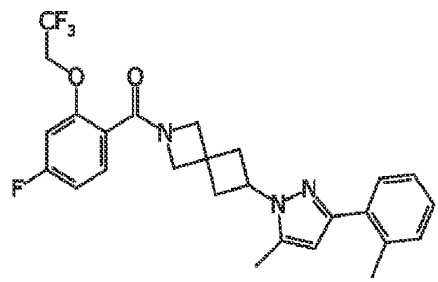
	 (2-cyclopropoxy-4-fluorophenyl)(6-{4-methyl-3-[o-(trifluoromethyl)phenyl]-1-pyrazolyl}-2-aza-2-spiro[3.3]heptyl)methanone	NMR: ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 7.97 – 7.87 (m, 1H), 7.83 (d, <i>J</i> = 7.1 Hz, 2H), 7.76-7.70 (m, 2H), 7.47 – 7.35 (m, 1H), 7.38 – 7.24 (m, 1H), 6.87-6.81 (m, 1H), 4.16-4.08 (m, 1H), 3.92 (t, <i>J</i> = 17.8 Hz, 3H), 3.84 – 3.73 (m, 2H), 2.77 – 2.57 (m, 2H), 2.45-2.40 (m, 2H), 1.73 (s, 3H), 0.87-0.82 (m, 2H), 0.69-0.66 (m, 2H).	
449	 (2-cyclopropoxy-4-fluorophenyl){6-[3-(5-fluoro-2-tolyl)-4-methyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl)methanone	LCMS: <i>m/z</i> 464.35 [M+1]⁺ ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 7.46– 7.43 (m, 2H), 7.28 – 7.18 (m, 3H), 7.02 (s, 1H), 6.84 (m, 1H), 4.26 (m, 1H), 3.97 (s, 3H), 3.82 (s, 2H), 2.78-2.68 (m, 3H), 1.97 (d, <i>J</i> = 6.0 Hz, 3H), 1.79 (s, 3H), 0.86 (dd, <i>J</i> = 11.8, 5.9 Hz, 2H), 0.70 (s, 2H).	C (6)
450	 (2-cyclopropoxy-4-fluorophenyl){6-[3-(5-fluoro-2-tolyl)-5-methyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl)methanone	LCMS: <i>m/z</i> 463.7 [M+1]⁺ ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 7.56-7.35 (m, 2H), 7.24 (t, <i>J</i> = 9.7 Hz, 2H), 7.04 (t, <i>J</i> = 9.7 Hz, 1H), 6.88 (d, <i>J</i> = 7.4 Hz, 1H), 6.09 (s, 1H), 4.30 (dt, <i>J</i> = 15.9, 8.0 Hz, 1H), 4.02 (s, 3H), 3.86 (s, 2H), 2.79 – 2.69 (m, 4H), 2.26	C (6)

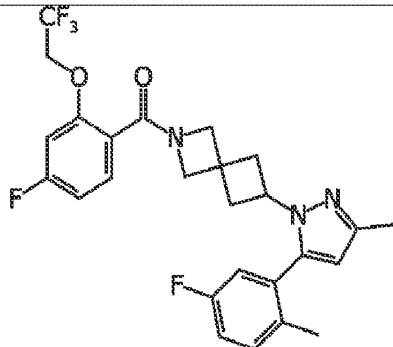
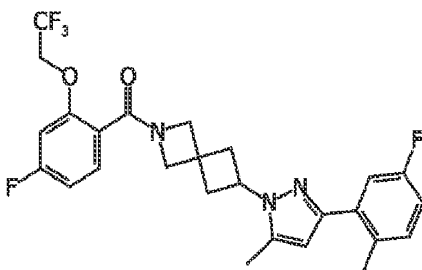
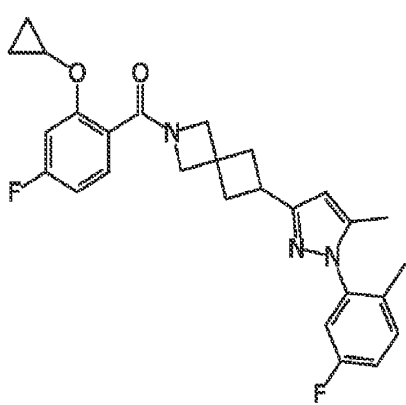
		(d, $J = 12.5$ Hz, 3H), 2.07 (d, $J = 6.0$ Hz, 3H), 0.93 – 0.84 (m, 2H), 0.73 (s, 2H).	
451	 (2-cyclopropoxy-4-fluorophenyl)(6-{5-(trifluoromethyl)-3-[o-(trifluoromethyl)phenyl]-1-pyrazolyl}-2-aza-2-spiro[3.3]heptyl)methanone	LCMS: m/z 553.91 $[M+1]^+$. NMR: ^1H NMR (400 MHz, DMSO-d_6) δ 8.68 (s, 1H), 8.05 – 7.83 (m, 3H), 7.63 (d, $J = 7.5$ Hz, 1H), 7.30 (dq, $J = 27.9, 10.5, 9.1$ Hz, 1H), 7.21 – 7.28 (dq, $J = 27.9, 10.5, 9.1$ Hz, 1H), 6.92 (d, $J = 13.5$ Hz, 2H), 4.46 (s, 1H), 4.00 – 3.95 (s, 3H), 3.80 (s, 2H), 2.78 – 2.70 (d, $J = 18.7$ Hz, 4H), 0.87 (d, $J = 16.1$ Hz, 2H), 0.79 – 0.70 (m, 2H).	B (6)
452	 (2-cyclopropoxy-4-fluorophenyl){6-[5-(o-fluorophenyl)-4-methyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl)methanone	LCMS: m/z 450.41 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.69 (s, 1H), 7.48 – 7.41 (m, 2H), 7.31 – 7.13 (m, 4H), 6.85 (s, 1H), 4.73 (m, 1H), 4.11 (s, 1H), 4.01 (s, 1H), 3.95 (s, 2H), 3.85 (s, 1H), 2.64 (dd, $J = 21.4, 9.3$ Hz, 4H), 1.97 (s, 3H), 0.90 – 0.84 (m, 2H), 0.73 (d, $J = 14.9$ Hz, 2H).	E (6)
454		LCMS: m/z 492.31 $[M+1]^+$. NMR: ^1H NMR (400 MHz, DMSO-d_6) δ 7.65 (d, $J = 6.0$ Hz, 1H), 7.49 (d, $J = 8.3$ Hz, 1H), 7.38 (dd, $J = 12.8, 6.5$ Hz, 2H), 7.23 (dt, $J = 14.3,$	E (11)

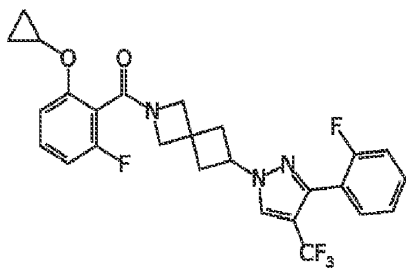
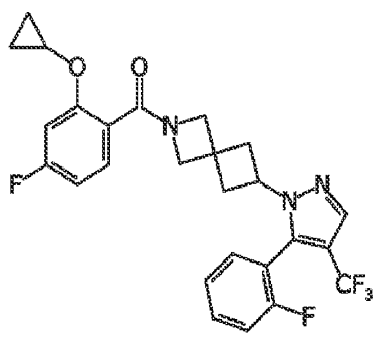
	 {6-[3-(5-fluoro-2-tolyl)-5-methyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}(4-fluoro-2-trifluoromethoxyphenyl)methanone	7.5 Hz, 1H), 7.01 (t, $J = 9.1$ Hz, 1H), 6.06 (s, 1H), 4.28 (dt, $J = 22.1, 7.9$ Hz, 1H), 4.06 (s, 2H), 3.96 (d, $J = 3.9$ Hz, 2H), 2.70 (dd, $J = 25.2, 10.0$ Hz, 4H), 2.23 (d, $J = 15.5$ Hz, 3H), 2.04 (d, $J = 7.4$ Hz, 3H).	
455	 (2-difluoromethoxy-4-fluorophenyl){6-[3-(5-fluoro-2-tolyl)-5-methyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: m/z 474.23 $[M+1]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 7.50 (d, $J = 18.0$ Hz, 1H), 7.38 (dd, $J = 14.4, 6.2$ Hz, 1H), 7.28 (dd, $J = 20.8, 10.0$ Hz, 2H), 7.24 – 7.09 (m, 2H), 7.02 (t, $J = 8.7$ Hz, 1H), 6.06 (s, 1H), 4.27 (dt, $J = 24.5, 7.8$ Hz, 1H), 4.05 (s, 2H), 3.95 (d, $J = 5.6$ Hz, 2H), 2.77 – 2.66 (m, 4H), 2.23 (d, $J = 14.9$ Hz, 3H), 2.04 (d, $J = 7.1$ Hz, 3H).	B (6)
456	 (2-cyclopropoxy-4-fluorophenyl){6-[3-(5-fluoro-2-tolyl)-5-(trifluoromethyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: m/z 518.45 $[M+1]^+$. NMR: 1H NMR (400 MHz, DMSO- d_6) δ 7.44 (dd, $J = 15.7, 9.9$ Hz, 1H), 7.32 (t, $J = 8.3$ Hz, 2H), 7.30 – 7.14 (m, 2H), 6.85 (m, 2H), 4.51 (dt, $J = 16.6, 7.9$ Hz, 1H), 4.00 (dd, 2H), 3.98-3.84 (dd, $J = 6.6$ Hz, 3H), 2.77 – 2.67 (m, 2H), 2.62 (d, $J = 6.4$ Hz, 2H), 2.06 (d, $J = 5.1$ Hz, 3H), 0.90 – 0.82 (m, 2H), 0.68 74 (d, $J = 6.5$ Hz, 2H).	D (11)

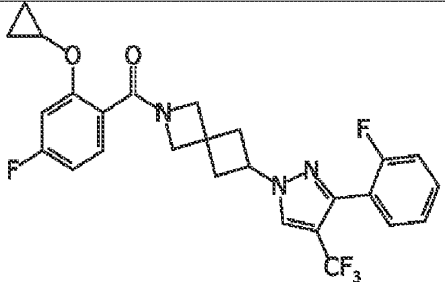
457	 (2-cyclopropoxy-4-fluorophenyl){6-[5-(5-fluoro-2-tolyl)-3-(trifluoromethyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: 518.45 m/z $[M]^{-1}$ NMR: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.44 (dd, J = 19.6, 10.1 Hz, 1H), 7.38 – 7.29 (m, 2H), 7.31 – 7.11 (m, 3H), 6.86 (d, J = 7.5 Hz, 1H), 4.93 (dt, J = 16.0, 7.7 Hz, 1H), 4.12 (s, 1H), 4.04 (s, 1H), 3.96 (s, 2H), 3.89 (s, 1H), 2.78 (dd, J = 21.8, 8.8 Hz, 4H), 2.47 (s, 3H), 0.86 (dd, J = 11.9, 6.0 Hz, 2H), 0.74 (m, 1H), 0.69 (d, 1H).	E (11)
458	 (4-fluoro-2-methoxyphenyl){6-[3-(5-fluoro-2-tolyl)-5-(trifluoromethyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: m/z 492.4 $[M+1]^{+1}$ NMR: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.43 (dt, J = 13.7, 8.2 Hz, 1H), 7.31 (dd, J = 10.5, 5.0 Hz, 2H), 7.18 (t, J = 10.3 Hz, 1H), 6.99 (t, J = 10.1 Hz, 1H), 6.86 – 6.77 (m, 2H), 4.49 (dt, J = 26.5, 7.9 Hz, 1H), 4.01 (s, 2H), 3.90 (d, J = 6.2 Hz, 2H), 3.82 (d, J = 7.2 Hz, 3H), 2.77 – 2.66 (m, 1H), 2.68 – 2.58 (m, 1H), 2.55 (s, 2H), 2.04 (d, J = 6.9 Hz, 3H).	E (11)
460		LCMS: m/z 434.44 $[M+1]^{+1}$ ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.54-7.50 (m, 1H), 7.16 – 7.40 (m, 4H), 7.03-6.98 (m, 1H), 6.76 – 6.88 (m, 1H), 6.29 (s, 1H),	E (11)

	 (2-ethoxy-4-fluorophenyl){6-[3-methyl-5-(o-tolyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	4.75 (m, 1H), 4.13 (q, J = 7.5, 6.2 Hz, 2H), 4.05 (d, J = 3.4 Hz, 2H), 3.97 (s, 1H), 2.74-2.67 (m, 4H), 2.27 (d, J = 10.4 Hz, 3H), 2.44 (d, J = 17.6 Hz, 3H), 1.40-1.33 (m, 3H),	
461	 (2-ethoxy-4-fluorophenyl){6-[5-methyl-3-(o-tolyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: 434.44 m/z, ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.39-7.26 (m, 4H), 7.15 (m, 1H), 7.00-6.78 (m, 2H), 6.02 (s, 1H), 4.11 – 4.31 (m, 1H), 4.03 – 4.14 (m, 2H), 4.00 (d, J = 4.9 Hz, 2H), 3.91 (d, J = 9.8 Hz, 2H), 2.75 (t, J = 10.5 Hz, 4H), 2.23 (d, J = 13.6 Hz, 3H), 2.08 (d, J = 7.3 Hz, 3H), 1.33 (q, J = 7.5 Hz, 3H),	D (11)
462	 (2-ethoxy-4-fluorophenyl){6-[5-(5-fluoro-2-tolyl)-3-methyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: m/z 452.4 [M+1] ⁺ ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.35-7.23 (m, 3H), 7.06-6.96 (m, 2H), 6.81 (q, J = 8.2 Hz, 1H), 6.35 (s, 1H), 4.8 (dt, J = 25.1, 7.7 Hz, 1H), 4.13 (m, 3H), 4.03 (s, 2H), 3.91 (s, 1H), 2.70 (dd, J = 18.6, 8.1 Hz, 4H), 2.42 (d, J = 17.3 Hz, 3H), 2.26 (d, J = 10.4 Hz, 3H), 1.36 (dt, J = 13.9, 6.9 Hz, 3H).	E (11)
463	 (2-ethoxy-4-fluorophenyl){6-[5-(5-fluoro-2-tolyl)-3-methyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: m/z 452.4 [M+1] ⁺ ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.41 – 7.3 (m, 2H), 7.05 (m, 1H), 6.98 (q, J = 11.6, 10.7 Hz, 2H), 6.74 (m, 1H), 6.0 (s, 1H), 4.26 (dt, J = 19.9, 7.9 Hz, 1H), 4.08 (dt, J = 13.6, 6.8 Hz, 2H), 3.99 (s, 2H), 3.90 (d, J = 4.1 Hz, 2H), 2.70 (dt, J = 20.7, 10.5 Hz, 4H),	D (11)

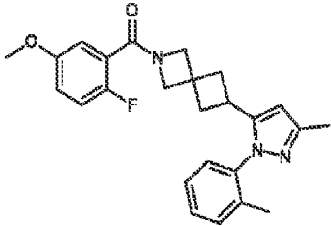
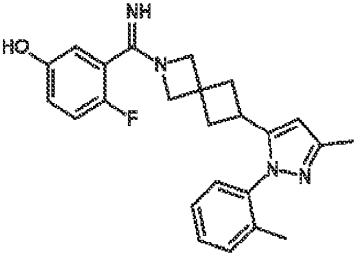
	(2-ethoxy-4-fluorophenyl){6-[3-(5-fluoro-2-tolyl)-5-methyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	2.21 (d, $J = 13.5$ Hz, 3H), 2.03 (d, $J = 6.5$ Hz, 3H), 1.32 (q, $J = 6.7$ Hz, 3H).	
464	 [4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]{6-[3-methyl-5-(o-tolyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: m/z 488.4 $[M+1]^{+1}$ NMR: ^1H NMR (400 MHz, DMSO- d_6) δ 7.53 – 7.37 (m, 2H), 7.22–7.18(m, 4H), 6.99–6.96 (m, 1H), 6.26 (s 1H), 4.92 (d, $J = 8.9$ Hz, 2H), 4.66 – 4.91 (m, 1H), 4.15 (s, 1H), 4.04 (d, $J = 8.1$ Hz, 2H), 3.94 (s, 1H), 2.70 (ddd, $J = 20.2$, 12.6, 8.6 Hz, 4H), 2.44 (d, $J = 19.3$ Hz, 3H), 2.27 (d, $J = 12.5$ Hz, 3H),	D (11)
465	 [4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]{6-[5-methyl-3-(o-tolyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: m/z 488.4 $[M+1]^{+1}$ ^1H NMR (400 MHz, DMSO- d_6) δ 8.50 (s, 1H), 7.33 (ddt, $J = 23.2$, 15.4, 7.3 Hz, 4H), 7.09 – 7.22 (m, 2H), 6.88 – 7.00 (m, 1H), 6.01 (d, $J = 2.6$ Hz, 1H), 4.88 (dq, $J = 17.3$, 8.8 Hz, 2H), 4.22 (dt, $J = 35.6$, 8.0 Hz, 1H), 4.00 (d, $J = 5.5$ Hz, 2H), 3.89 (d, $J = 10.3$ Hz, 2H), 2.76 (d, $J = 11.0$ Hz, 1H), 2.67 (d, $J = 12.5$ Hz, 1H), 2.45 (t, $J = 10.4$ Hz, 2H), 2.23 (d, $J = 14.5$ Hz, 3H), 2.08 (d, $J = 8.4$ Hz, 3H),	C (11)
466		LCMS: m/z 506.41 $[M]^{+}$	D (11)

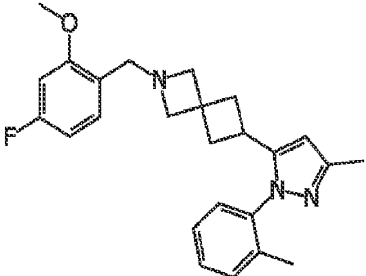
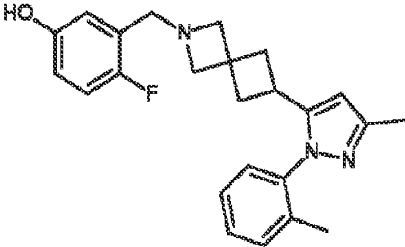
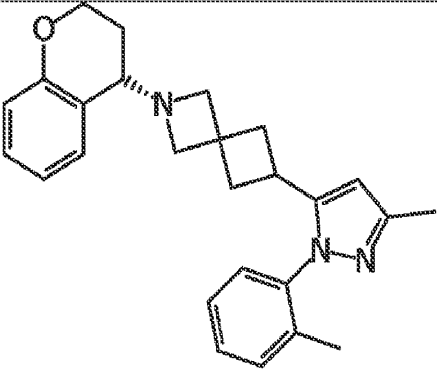
	 {6-[5-(5-fluoro-2-tolyl)-3-methyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]methanone	NMR: ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 7.43-7.01 (m, 4H), 7.05-6.95 (m, 2H), 6.37 (s, 1H), 4.92 (q, <i>J</i> = 8.9 Hz, 2H), 4.83 – 4.69 (m, 1H), 4.15 (s, 1H), 4.05 (d, <i>J</i> = 10.2 Hz, 2H), 3.95 (s, 1H), 2.75-2.63 (m, 4H), 2.43 (d, <i>J</i> = 19.1 Hz, 3H), 2.27 (d, <i>J</i> = 12.2 Hz, 3H).	
467	 {6-[3-(5-fluoro-2-tolyl)-5-methyl-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]methanone	LCMS: <i>m/z</i> 506.4 [M]⁺ ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 7.41 – 7.32 (m, 2H), 7.29 – 7.13 (m, 2H), 7.06 – 6.91 (m, 2H), 6.03 (s, 1H), 4.88 (dq, <i>J</i> = 17.9, 8.9 Hz, 2H), 4.26 (dt, <i>J</i> = 34.0, 7.9 Hz, 1H), 4.02 (d, <i>J</i> = 10.2 Hz, 2H), 3.89 (d, <i>J</i> = 5.1 Hz, 2H), 2.76-2.54 (m, 2H), 2.46 (s, 2H), 2.24 (t, <i>J</i> = 12.5 Hz, 3H), 2.04 (d, <i>J</i> = 6.4 Hz, 3H).	C (11)
482	 (2-cyclopropoxy-4-fluorophenyl){6-[1-(5-fluoro-2-tolyl)-5-methyl-3-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: <i>m/z</i> 464.44 [M+1]⁺ NMR: ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 7.43 (d, <i>J</i> = 7.5 Hz, 1H), 7.26 (dq, <i>J</i> = 27.9, 10.5, 9.1 Hz, 4H), 6.82 (d, <i>J</i> = 13.5 Hz, 1H), 6.12 (d, <i>J</i> = 13.5 Hz, 1H), 4.06 (s, 1H), 3.91 (s, 3H), 3.73 (s, 1H), 2.58-2.41 (d, <i>J</i> = 18.7 Hz, 5H), 2.04 (d, <i>J</i> = 7.3 Hz, 3H), 1.91 (d, <i>J</i> = 7.3 Hz, 3H).	D (12)

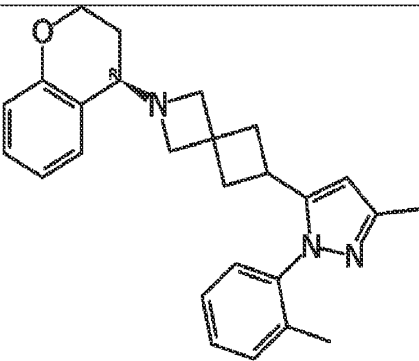
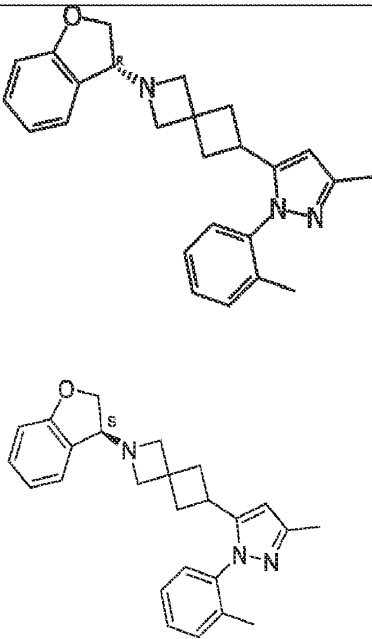
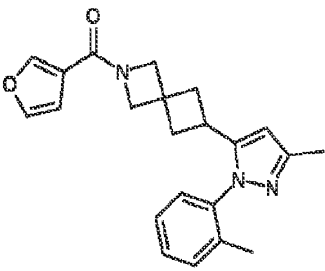
		16.1 Hz, 3H), 0.89 – 0.80 (m, 2H), 0.72 (s, 2H).	
522	 (2-cyclopropoxy-6-fluorophenyl){6-[3-(o-fluorophenyl)-4-(trifluoromethyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: m/z 504.60 $[M+1]^+$. NMR: ^1H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, J = 12.9 Hz, 1H), 7.60-7.35 (dt, J = 14.0, 7.7 Hz, 5H), 7.18 (t, J = 8.1 Hz, 1H), 6.92 – 6.83 (m, 1H), 4.53 – 4.43 (m, 1H), 4.03 (d, J = 19.0 Hz, 2H), 3.95 – 3.73 (m, 3H), 2.62-2.55 (s, 4H), 0.80 (s, 2H), 0.63 (s, 2H).	E (12)
523	 (2-cyclopropoxy-4-fluorophenyl){6-[5-(o-fluorophenyl)-4-(trifluoromethyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	LCMS: m/z 504.50 $[M+1]^+$. NMR: ^1H NMR (400 MHz, DMSO-d_6) δ 8.58 (d, J = 6.5 Hz, 1H), 7.44 (d, J = 19.5 Hz, 2H), 7.31 (dd, J = 19.0, 7.7 Hz, 3H), 7.19 (d, J = 10.9 Hz, 1H), 6.85 (d, J = 7.7 Hz, 1H), 4.90 (s, 1H), 4.10 (s, 1H), 4.02-3.99 (s, 1H), 3.94 (s, 2H), 3.81 (d, J = 19.8 Hz, 1H), 2.72 (dt, J = 19.7, 9.9 Hz, 4H), 0.85 (s, 2H), 0.70 (d, J = 17.1 Hz, 2H).	E (12)
524		LCMS: m/z 504.50 $[M+1]^+$. NMR: ^1H NMR (400 MHz, DMSO-d_6) δ 8.07 (dd, J = 20.1, 11.5 Hz, 1H),	C (12)

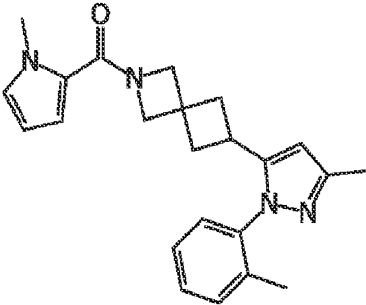
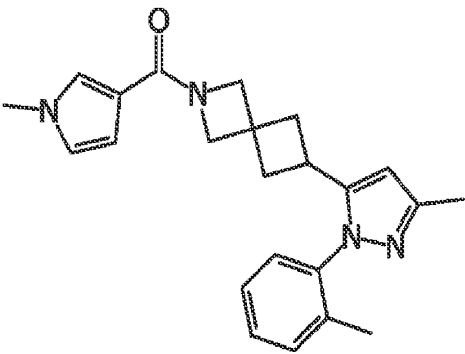
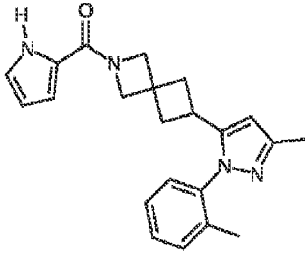
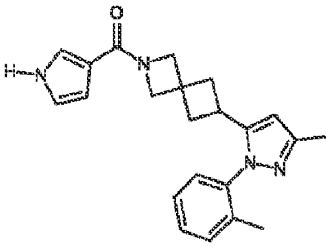
	 (2-cyclopropoxy-4-fluorophenyl){6-[3-(o-fluorophenyl)-4-(trifluoromethyl)-1-pyrazolyl]-2-aza-2-spiro[3.3]heptyl}methanone	7.62 (dt, $J = 19.5, 10.9$ Hz, 1H), 7.48 – 7.26 (m, 4H), 7.21 (dt, $J = 17.6, 8.0$ Hz, 1H), 6.86 – 6.79 (m, 1H), 4.48 (dt, $J = 16.3, 7.4$ Hz, 1H), 4.05 – 3.73 (m, 5H), 2.58 (d, $J = 18.8$ Hz, 4H), 0.88 – 0.80 (m, 2H), 0.71 (d, $J = 19.9$ Hz, 2H).	
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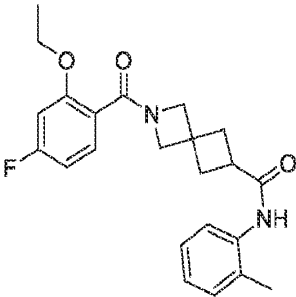
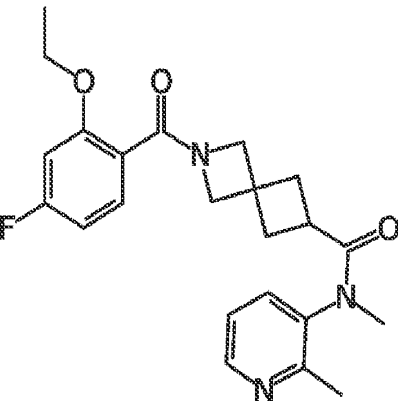
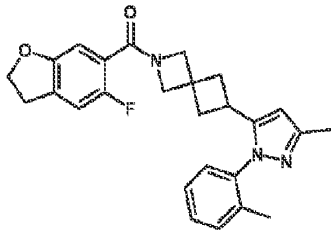
[000366] Table 8 - Compounds

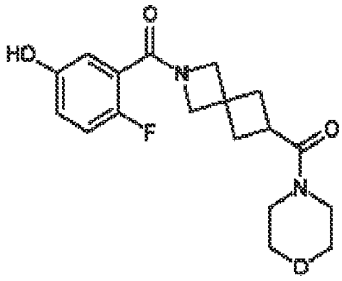
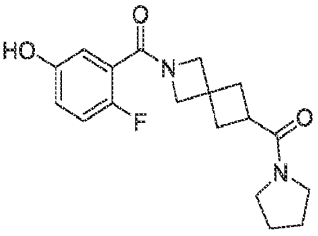
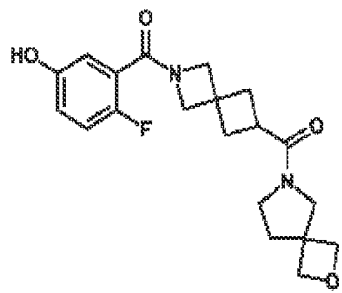
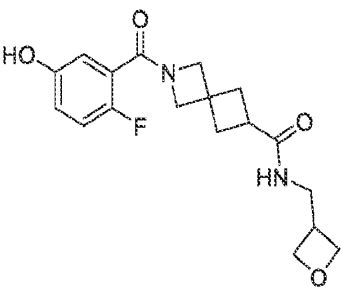
Comparator	Structure	Potency
123		>10,000 nM (2)
144		>10,000 nM (2)

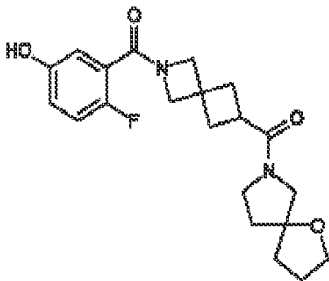
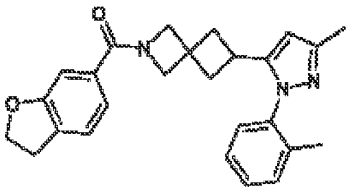
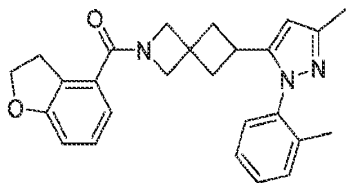
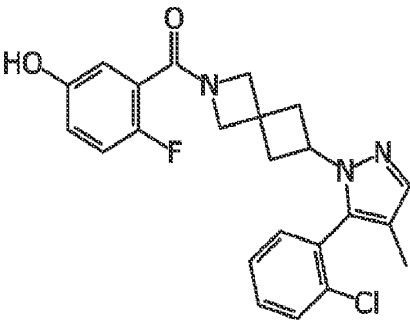
Comparator	Structure	Potency
149		>10,000 nM (2)
150		>10,000 nM
152, 153		>10,000 nM (2)

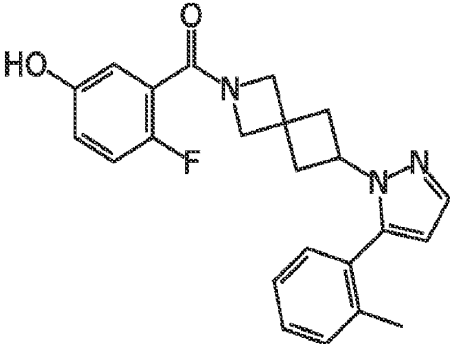
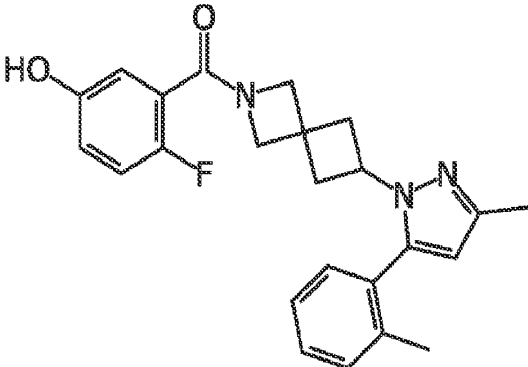
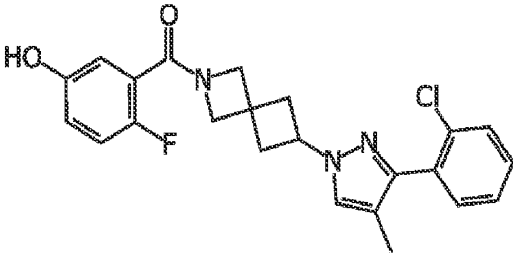
Comparator	Structure	Potency
		
154, 155		>10,000 nM (2)
179		>10,000 nM (2)

Comparator	Structure	Potency
181		>10,000 nM (2)
182		>10,000 nM (2)
183		>10,000 nM (2)
184		>10,000 nM (2)

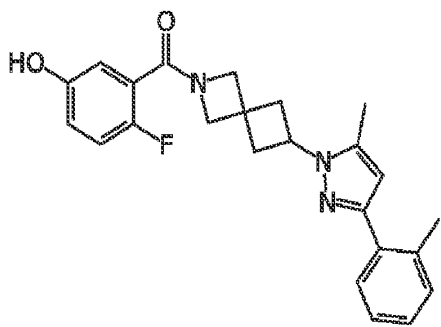
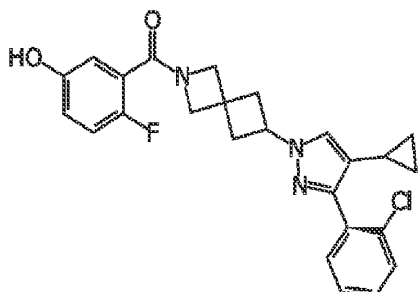
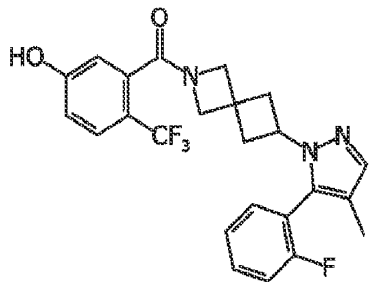
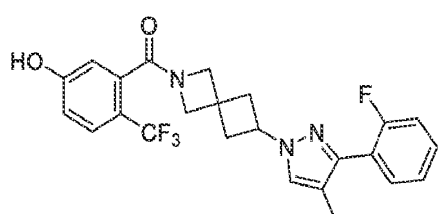
Comparator	Structure	Potency
188		>10,000 nM (2)
198		>10,000 nM (4)
368		>10,000 nM (14)

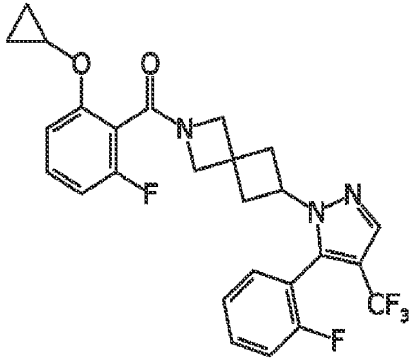
Comparator	Structure	Potency
384		>10,000 nM (14)
388		>10,000 nM (14)
391		>10,000 nM (14)
395		>10,000 nM (14)

Comparator	Structure	Potency
400		>10,000 nM (14)
402		>10,000 nM (14)
403		>10,000 nM (14)
404		>10,000 nM (6)

Comparator	Structure	Potency
405		>10,000 nM (6)
406		>10,000 nM (6)
416		>10,000 nM (6)

Comparator	Structure	Potency
424		>10,000 nM (6)
427		>10,000 nM (11)
441		>10,000 nM (6)

Comparator	Structure	Potency
442		>10,000 nM (6)
445		>10,000 nM (6)
494		>10,000 nM (12)
495		>10,000 nM (12)

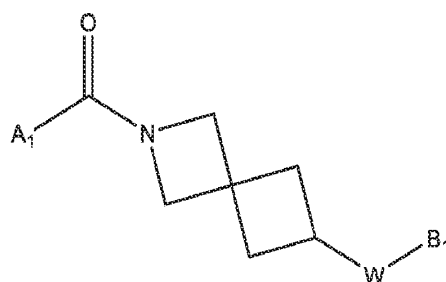
Comparator	Structure	Potency
521		>10,000 nM (12)

[000367] Further, although preferred embodiments have been depicted and described in detail herein, it will be apparent to those skilled in the relevant art that various modifications, additions, substitutions, and the like can be made without departing from the spirit of the invention and these are therefore considered to be within the scope of the invention as defined in the claims which follow. Further, to the extent not already indicated, it will be understood by those of ordinary skill in the art that any one of the various embodiments herein described and illustrated can be further modified to incorporate features shown in any of the other embodiments disclosed herein.

CLAIMS

What is claimed is:

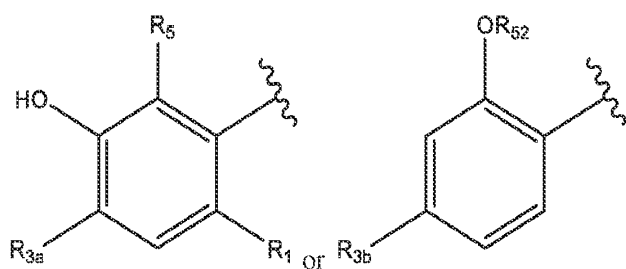
1. A compound of Formula (I) or a pharmaceutically acceptable salt thereof,



Formula (I),

wherein:

A₁ is



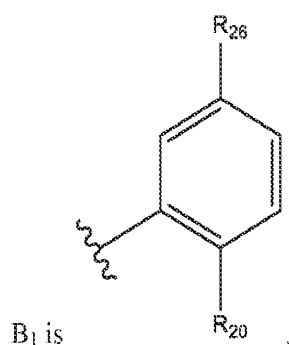
R₁ is halogen, hydrogen, or cyano;

R_{3a} and R₅ are each independently hydrogen, halogen, or lower alkyl;

R₅₂ is lower alkyl, lower cycloalkyl or lower haloalkyl;

R_{3b} is halogen;

W is a diazole optionally substituted with lower alkyl, lower cycloalkyl, or lower haloalkyl;



R₂₀ is halogen, hydrogen, lower alkyl, or lower haloalkyl; and

R₂₆ is hydrogen, or halogen;

provided the compound is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone.

2. The compound of claim 1, wherein

R₁ is hydrogen, fluoro, or cyano;

R_{3a} and R₅ are each independently hydrogen, halogen, or methyl;

R₅₂ is lower alkyl, cyclopropyl or lower haloalkyl;

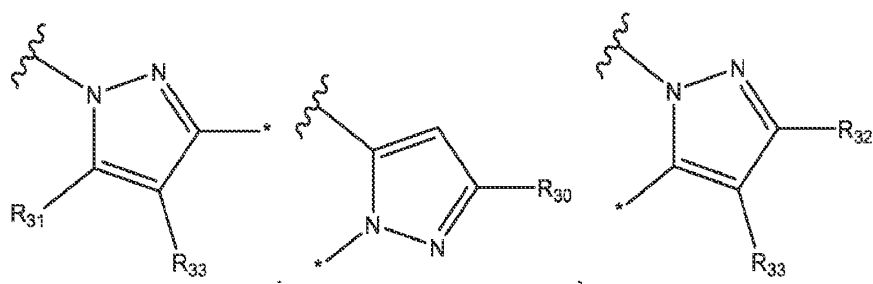
R_{3b} is fluoro;

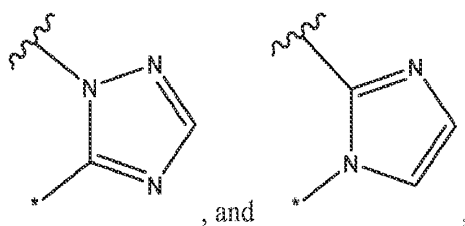
W is a diazole optionally substituted with one of methyl, cyclopropyl, or CF₃;

R₂₀ is fluoro or chloro, methyl, or CF₃; and

R₂₆ is hydrogen, fluoro or chloro.

3. The compound of claim 2, wherein W is selected from the group consisting of:



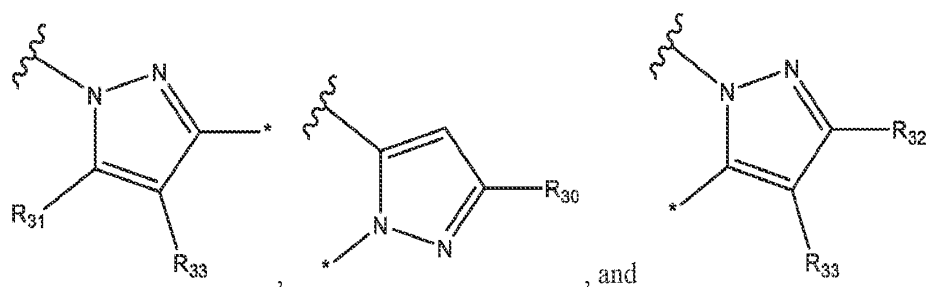


wherein * indicates a covalent bond to B₁; and

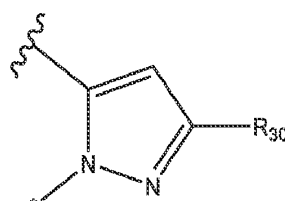
R₃₀, R₃₁, R₃₂ and R₃₃ are each independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl, provided that at least one of R₃₁ and R₃₃ and at least one of R₃₂ and R₃₃ is not hydrogen.

4. The compound of claim 3, wherein R₃₀, R₃₁, R₃₂ and R₃₃ are each independently hydrogen, methyl, CF₃, or cyclopropyl, provided that at least one of R₃₁ and R₃₃ and at least one of R₃₂ and R₃₃ is not hydrogen.

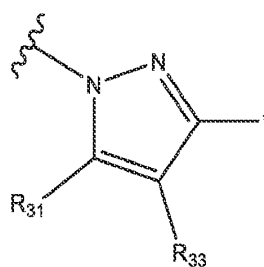
5. The compound of claim 4, wherein W is selected from the group consisting of:

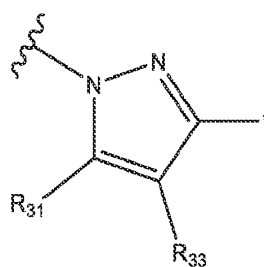


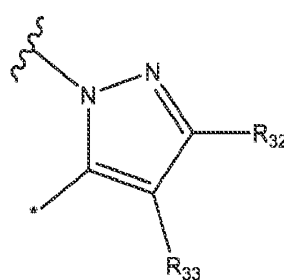
wherein * indicates a covalent bond to B₁.

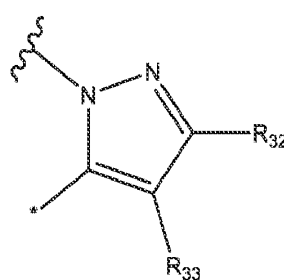


6. The compound of claim 5, wherein W is , wherein * indicates a covalent bond to B₁, and R₃₀ is methyl.

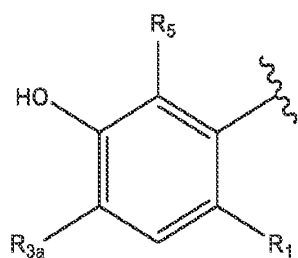


7. The compound of claim 5, wherein W is , wherein * indicates a covalent bond to B₁, and R₃₁ and R₃₃ are each independently hydrogen, methyl, CF₃, or cyclopropyl, provided that one of R₃₁ and R₃₃ is hydrogen.



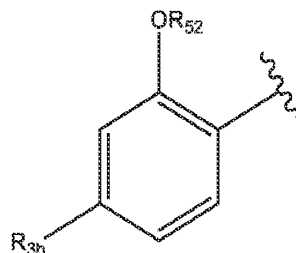
8. The compound of claim 5, wherein W is , wherein * indicates a covalent bond to B₁, and R₃₂ and R₃₃ are each independently hydrogen, methyl, CF₃, or cyclopropyl, provided that one of R₃₂ and R₃₃ is hydrogen.

9. The compound of any one of claims 4-8, wherein A₁ is

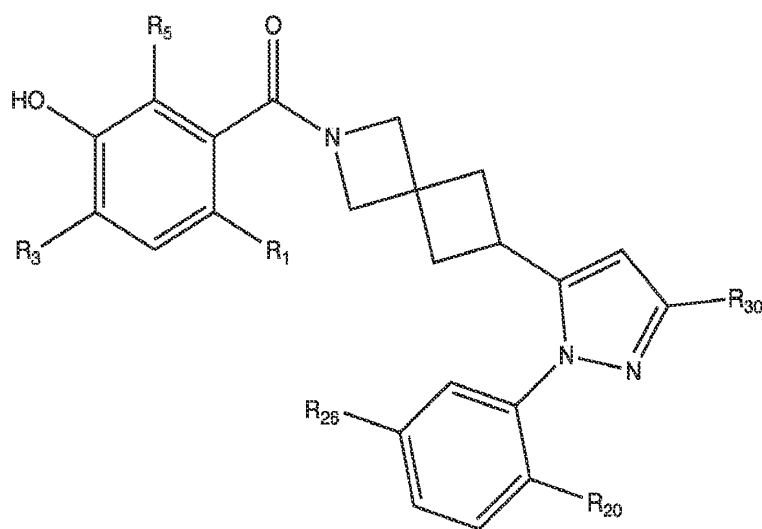


10. The compound of claim 9, wherein R₅ is hydrogen.
11. The compound of claim 10, wherein R₁ is fluoro.
12. The compound of claim 11, wherein R_{3a} is hydrogen, fluoro, or methyl.

13. The compound of claim 12, wherein R_{3a} is hydrogen.
14. The compound of claim 13, wherein R_{20} is methyl, and R_{26} is hydrogen or fluoro; or R_{20} is chloro, fluoro or CF_3 , and R_{26} is hydrogen.
15. The compound of any one of claims 4-8, wherein A_1 is



16. The compound of claim 15, wherein R_{52} is lower alkyl optionally substituted with one or more fluoro and cyclopropyl.
17. The compound of claim 16, wherein R_{3b} is fluoro.
18. The compound of claim 17, wherein
 R_{20} is methyl, and R_{26} is hydrogen or fluoro; or
 R_{20} is fluoro or CF_3 , and R_{26} is hydrogen.
19. A compound of Formula (II-B) or a pharmaceutically acceptable salt thereof.



Formula (II-B),

wherein

R₁ is halogen or cyano;

R₃ is hydrogen, lower alkyl, or halogen;

R₅ is hydrogen, halogen or lower alkyl;

R₂₀ is halogen or lower alkyl optionally substituted with one or more halogen;

R₂₆ is halogen or hydrogen; and

R₃₀ is hydrogen or lower alkyl optionally substituted with one or more halogen, provided the compound is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone.

20. The compound of claim 19, wherein

R₁ is F or cyano;

R₃ is hydrogen, methyl, or F;

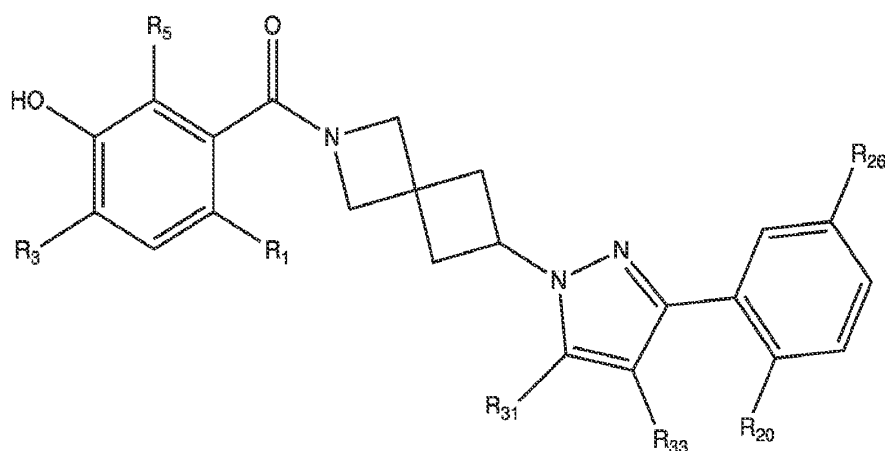
R₅ is hydrogen, F or methyl;

R₂₀ is F, methyl, or CF₃;

R₂₆ is hydrogen or F; and

R₃₀ is hydrogen, methyl or CF₃, provided the compound is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone.

21. A compound of Formula (II-C) or a pharmaceutically acceptable salt thereof:



Formula (II-C),

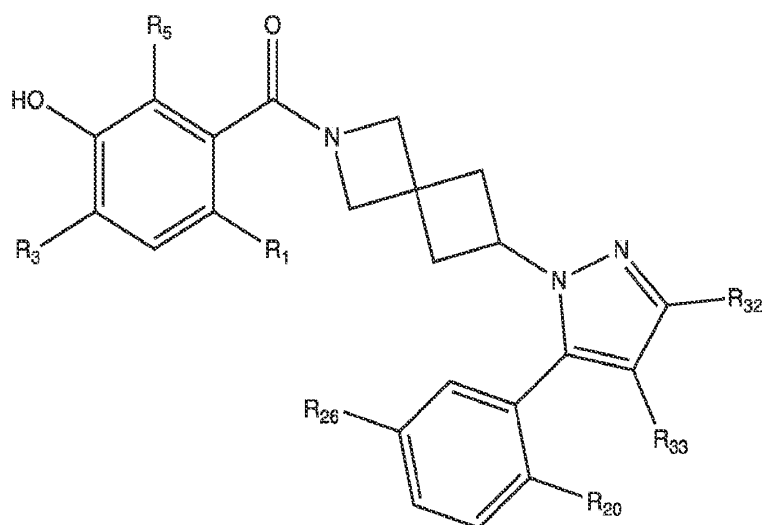
wherein

- R₁ is halogen or cyano;
- R₃ is hydrogen, lower alkyl, or halogen;
- R₅ is hydrogen, halogen or lower alkyl;
- R₂₀ is halogen or lower alkyl optionally substituted with one or more halogen;
- R₂₆ is hydrogen or halogen; and
- R₃₁ and R₃₃ are each independently hydrogen or lower alkyl optionally substituted with one or more halogen, provided that one of R₃₁ and R₃₃ is hydrogen.

22. The compound of claim 21, wherein

- R₁ is F or cyano;
- R₃ is hydrogen, methyl, or F;
- R₅ is hydrogen, F or methyl;
- R₂₀ is F, methyl, or CF₃;
- R₂₆ is hydrogen or F; and
- R₃₁ and R₃₃ are each independently hydrogen, methyl or CF₃.

23. A compound of Formula (II-D) or a pharmaceutically acceptable salt thereof:



wherein

R_1 is halogen or cyano;

R_3 is hydrogen, lower alkyl, or halogen;

R_5 is hydrogen, halogen or lower alkyl;

R_6 is hydrogen;

R_{20} is halogen or lower alkyl optionally substituted with one or more halogen;

R_{26} is halogen or hydrogen; and

R_{32} and R_{33} are each independently hydrogen or lower alkyl optionally substituted with one or more halogen, provided that one of R_{32} and R_{33} is hydrogen.

24. The compound of claim 23, wherein

R_1 is F or cyano;

R_3 is hydrogen, F or methyl;

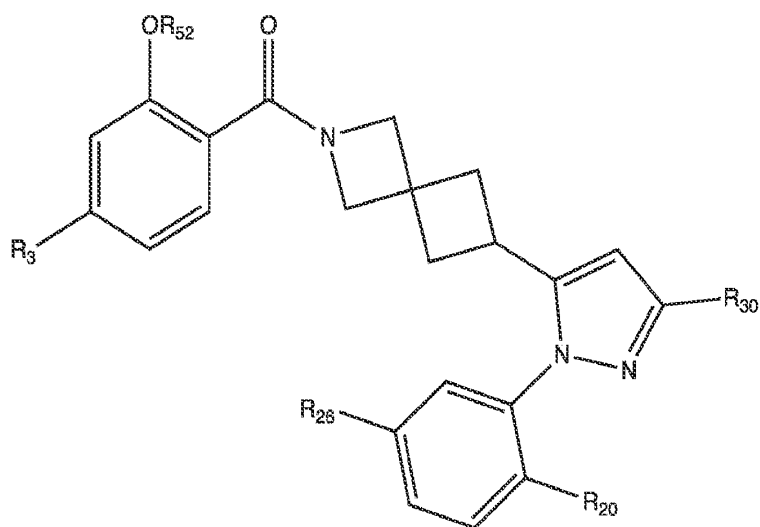
R_5 is hydrogen, F or methyl;

R_{20} is F or methyl, or CF_3 ;

R_{26} is hydrogen or F; and

R_{32} and R_{33} are each independently hydrogen, methyl or, CF_3 provided that one of R_{32} and R_{33} is hydrogen.

25. A compound of Formula (III-B) or a pharmaceutically acceptable salt thereof.



Formula (III-B)

wherein

R_3 is halogen;

R_{52} is lower alkyl or lower cycloalkyl, each optionally substituted with halogen,

R_{30} is lower alkyl;

R_{20} is lower alkyl; and

R_{26} is hydrogen or halogen.

26. The compound of claim 25, wherein

R_3 is F;

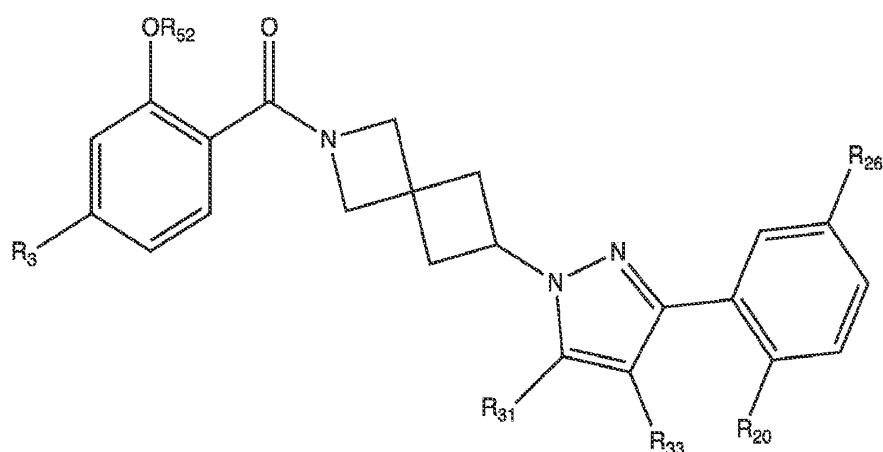
R_{52} is lower alkyl optionally substituted with one or more F or cyclopropyl;

R_{30} is methyl;

R_{20} is methyl; and

R_{26} is hydrogen or F.

27. A compound of Formula (III-C) or a pharmaceutically acceptable salt thereof.



wherein

R_3 is halogen;

R_{52} is lower alkyl or lower cycloalkyl, each optionally substituted with halogen,

R_{31} and R_{33} are each independently hydrogen or lower alkyl optionally substituted with one or more halogen, provided that one of R_{31} and R_{33} is hydrogen.

R_{20} is lower alkyl optionally substituted with halogen; and

R_{26} is hydrogen or halogen.

28. The compound of claim 27, wherein

R_3 is F;

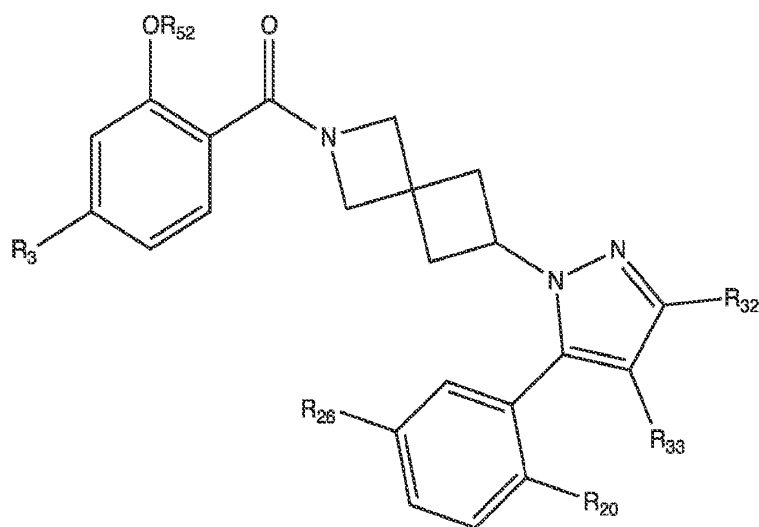
R_{52} is lower alkyl optionally substituted with one or more F; or cyclopropyl;

R_{31} and R_{33} are each independently hydrogen, methyl or CF_3 , provided that one of R_{31} and R_{33} is hydrogen;

R_{20} is methyl or CF_3 ; and

R_{26} is hydrogen or F.

29. A compound of Formula (III-D) or a pharmaceutically acceptable salt thereof:



Formula (III-D)

wherein

R_3 is halogen;

R_{52} is lower alkyl or lower cycloalkyl, each optionally substituted with halogen,

R_{32} and R_{33} are each independently hydrogen or lower alkyl optionally substituted with one or more halogen, provided that one of R_{32} and R_{33} is hydrogen.

R_{20} is lower alkyl optionally substituted with halogen; and

R_{26} is hydrogen or halogen.

30. The compound of claim 29, wherein

R_3 is F;

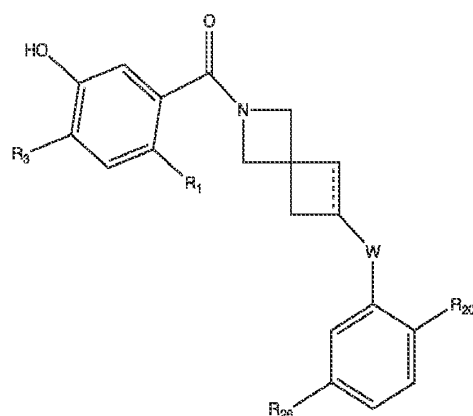
R_{52} is lower alkyl optionally substituted with one or more F, or cyclopropyl;

R_{32} and R_{33} are each independently hydrogen, methyl or CF_3 , provided that one of R_{32} and R_{33} is hydrogen;

R_{20} is methyl or CF_3 ; and

R_{26} is hydrogen or F.

31. A compound of Formula (II), or a pharmaceutically acceptable salt thereof,



Formula (II),

wherein

the dashed line represents an optional double bond;

R₁ is halogen;

R₃ is hydrogen;

W is A;

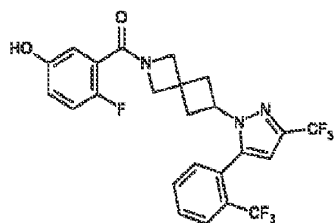
A is a 5-member heteroaryl ring optionally substituted with one or more R₃₀;

R₂₀ is halogen or lower alkyl optionally substituted with one or more halogen;

R₃₀ is lower alkyl optionally substituted with one or more halogen; and

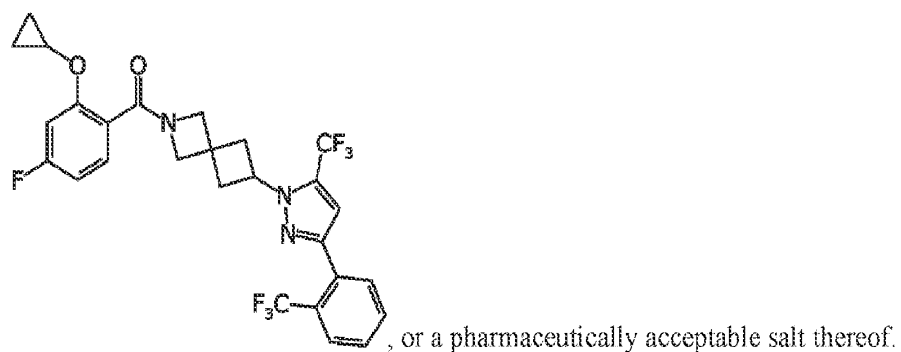
R₂₆ is halogen or hydrogen, provided the compound is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone.

32. The compound of claim 1, wherein the compound is

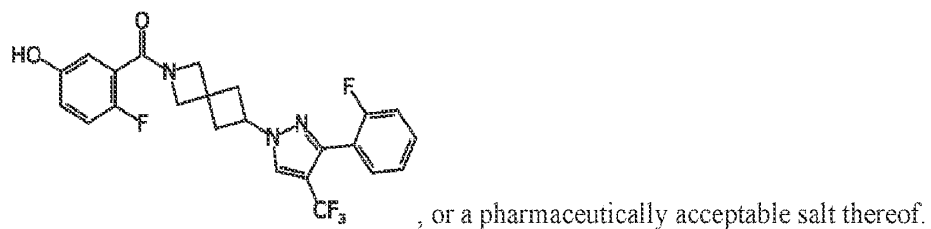


, or a pharmaceutically acceptable salt thereof.

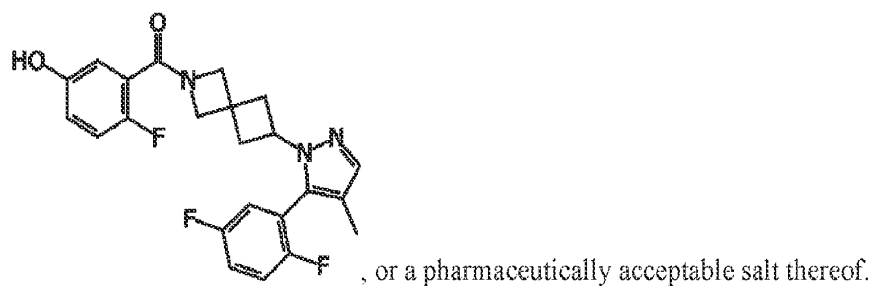
33. The compound of claim 1, wherein the compound is



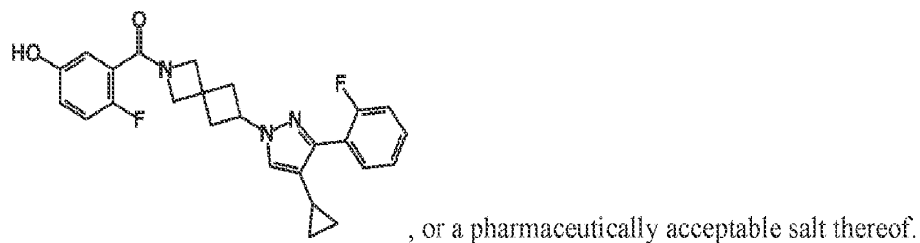
34. The compound of claim 1, wherein the compound is



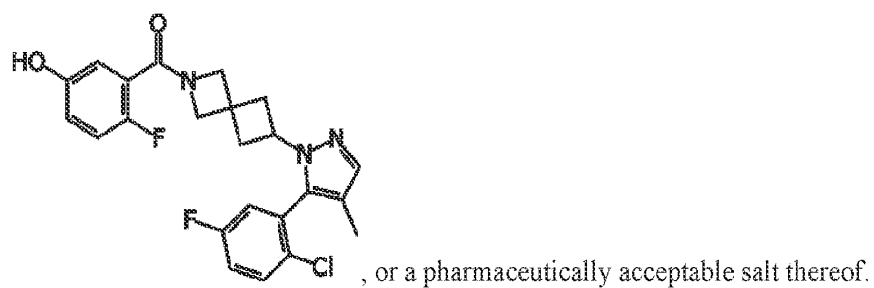
35. The compound of claim 1, wherein the compound is



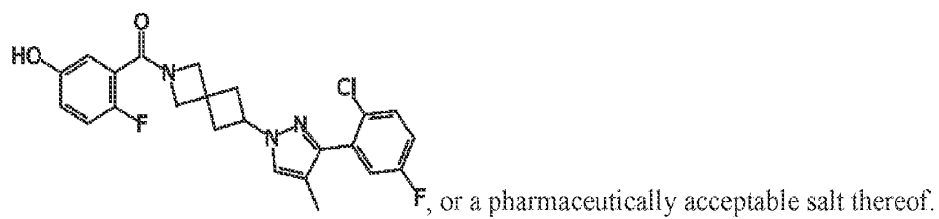
36. The compound of claim 1, wherein the compound is



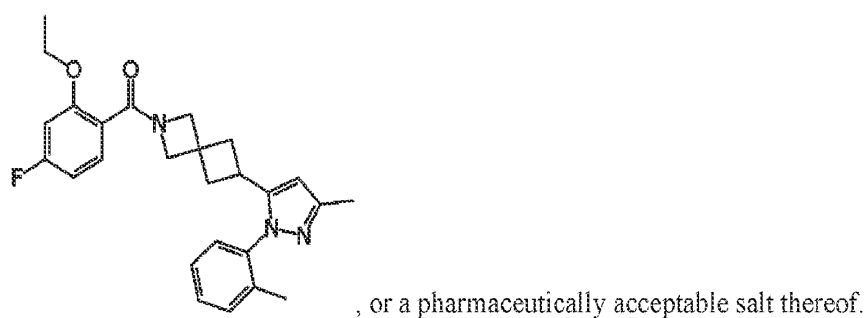
37. The compound of claim 1, wherein the compound is



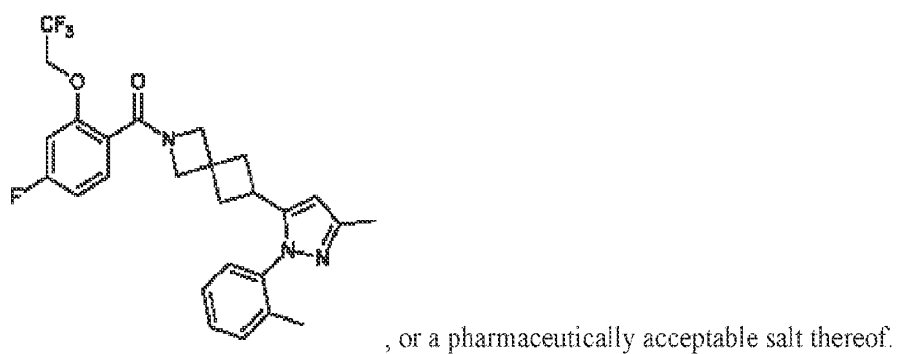
38. The compound of claim 1, wherein the compound is



39. The compound of claim 1, wherein the compound is



40. The compound of claim 1, wherein the compound is



41. A pharmaceutical composition comprising a compound of any one of claims 1-40, or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient (API), provided the compound is not (2-fluoro-5-hydroxyphenyl)(6-(3-methyl-1-(o-tolyl)-1H-pyrazol-5-yl)-2-azaspiro[3.3]heptan-2-yl)methanone.
42. A method of inhibiting monoacylglycerol lipase (MAGL) in a subject comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-40.
43. A method of reversibly inhibiting monoacylglycerol lipase (MAGL) comprising the step of contacting a compound of any one of claims 1-40 with a cell expressing MAGL.