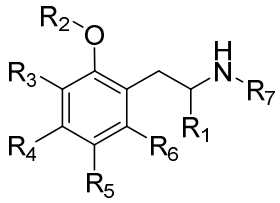
CLAIMS

1. A compound of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof,

wherein:

R_1 is H, methyl, ethyl, -CH_2-OH, -CH_2-O-(methyl) , -CH_2F, or -CH_2CH_2F;

R_2 is H, C1-C5 alkyl, C3-C5 cycloalkyl, C3-C5 alkenyl, or C3-C5 alkynyl, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F;

R_3 is H, C1-C3 alkyl, cyclopropyl, or F, wherein alkyl and cyclopropyl are optionally substituted with one or more F;

R_6 is H, C1-C3 alkyl, cyclopropyl, or F, wherein alkyl and cyclopropyl are optionally substituted with one or more F;

R_4 is C2-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C3-C8 cycloalkyl, -(C1-C5 alkyl)-(C3-C6 cycloalkyl), -S-(C1-C8 alkyl), -S-(C3-C8 alkenyl), -S-(C3-C8 alkynyl), -S-(C3-C8 cycloalkyl), -S-(C1-C5 alkyl)-(C3-C6 cycloalkyl), Cl, Br, I, CF_3, NO_2, or SF_5, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl, or

R_4 is C2 alkyl substituted with one or more F, C3-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C3-C8 cycloalkyl, -(C1-C5 alkyl)-(C3-C6 cycloalkyl), -S-(C1-C8 alkyl), -S-(C3-C8 alkenyl), -S-(C3-C8 alkynyl), -S-(C3-C8 cycloalkyl), -S-(C1-C5 alkyl)-(C3-C6 cycloalkyl), NO_2, or SF_5, wherein alkyl, alkenyl, and alkynyl are optionally substituted with one or more F, wherein cycloalkyl is optionally substituted with one or more F, C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl, and wherein R4 is not isopropyl;

R_5 is C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, C3-C5 cycloalkyl, -S(O)(O)-(C1-C5 alkyl), NH_2, NH(C1-C5 alkyl), or $N(C1\text{-}C5\ alkyl)_2$, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, or

R_5 is F, Cl, Br, I, -S-(C1-C5 alkyl), CN, or NO_2, wherein alkyl is optionally substituted with one or more F;

with the provisos that when R_5 is C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, C3-C5 cycloalkyl, -S(O)(O)-(C1-C5 alkyl), NH_2, NH(C1-C5 alkyl), or $N(C1\text{-}C5\ alkyl)_2$, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, then R_4 is C2-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C3-C8 cycloalkyl, -(C1-C5 alkyl)-(C3-C6 cycloalkyl), -S-(C1-C8 alkyl), -S-(C3-C8 alkenyl), -S-(C3-C8 alkynyl), -S-(C3-C8 cycloalkyl), -S-(C1-C5 alkyl)-(C3-C6 cycloalkyl), Cl, Br, I, CF_3, NO_2, or SF_5, wherein alkyl, alkenyl, and alkynyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more F, C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl, or

when R_5 is F, Cl, Br, I, -S-(C1-C5 alkyl), CN, or NO_2, wherein alkyl is optionally substituted with one or more F, then R_4 is C2 alkyl substituted with one or more F, C3-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C3-C8 cycloalkyl, -(C1-C5 alkyl)-(C3-C6 cycloalkyl), -S-(C1-C8 alkyl), -S-(C3-C8 alkenyl), -S-(C3-C8 alkynyl), -S-(C3-C8 cycloalkyl), -S-(C1-C5 alkyl)-(C3-C6 cycloalkyl), NO_2, or SF_5, wherein alkyl, alkenyl, and alkynyl are optionally substituted with one or more F, wherein cycloalkyl is optionally substituted with one or more F, C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl, and wherein R4 is not isopropyl;

R_7 is H, $-CH_2$-(aryl), or $-CH_2$-(heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH_2, NO_2, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, C3-C5 cycloalkyl, -O-(C1-C5 alkyl), -O-(C3-C5 alkenyl), -O-(C3-C5 alkynyl), -O-(C3-C5 cycloalkyl), -S-(C1-C5 alkyl), -S-(C3-C5 alkenyl), -S-(C3-C5 alkynyl), and -S-(C3-C5 cycloalkyl), wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 4-6-membered ring optionally interrupted by 1-3 heteroatoms selected from O, N, and S;

with the further provisos that:

(a) when R_2 is methyl, R_3 is methyl, R_4 is Cl or Br, R_5 is methyl, R_6 is H, and R_7 is H, then R_1 is not H or methyl;

(b) when R_1 is H or methyl, R_2 is H or methyl, R_3 is H, R_5 is methyl, R_6 is H, and R_7 is H, then R_4 is not Cl;

(c) when R_1 is H, R_2 is methyl, R_3 is H, R_5 is CF_3, R_6 is H, and R_7 is ortho-methoxybenzyl, then R_4 is not Br;

(d) when R_1 is H, R_2 is H, R_3 is H, R_5 is Cl, R_6 is H, and R_7 is H or benzyl, then R_4 is not cyclohexyl; and

(e) when R1 is methyl, R2 is H, R3 is H, R5 is NH_2, R6 is H, and R7 is H, then R4 is not Cl.

2. The compound of claim 1, wherein:

R_2 is H, C1-C3 alkyl, cyclopropyl, C3 alkenyl, or C3 alkynyl,

wherein alkyl, alkenyl, alkynyl, and cyclopropyl are optionally substituted with one or more F;

R_3 is H, methyl, ethyl, or F, wherein methyl and ethyl are optionally substituted with one or more F;

R_6 is H, methyl, ethyl, or F, wherein methyl and ethyl are optionally substituted with one or more F;

R_5 is C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, C3-C5 cycloalkyl, or -S(O)(O)-(C1-C5 alkyl), wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F,

and then R_4 is C2-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C3-C8 cycloalkyl, -(C1-C5 alkyl)-(C3-C6 cycloalkyl), -S-(C1-C8 alkyl), -S-(C3-C8 alkenyl), -S-(C3-C8 alkynyl), -S-(C3-C8 cycloalkyl), -S-(C1-C5 alkyl)-(C3-C6 cycloalkyl), Cl, Br, I, CF_3, NO_2, or SF_5, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl;

or R_5 is F, Cl, Br, I, -S-(C1-C5 alkyl), CN, or NO_2, wherein alkyl is optionally substituted with one or more F,

and then R_4 is C2 alkyl substituted with one or more F, C3-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C3-C8 cycloalkyl, -(C1-C5 alkyl)-(C3-C6 cycloalkyl), -S-(C1-C8 alkyl), -S-(C3-C8 alkenyl), -S-(C3-C8 alkynyl), -S-(C3-C8 cycloalkyl), -S-(C1-C5 alkyl)-(C3-C6 cycloalkyl), NO_2,

or SF_5, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, wherein cycloalkyl is optionally substituted with one or more C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl, and wherein R4 is not isopropyl;

R_7 is H, -CH_2-(6-membered aryl), or -CH_2-(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH_2, NO_2, C1-C3 alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C5 cycloalkyl, -O-(C1-C3 alkyl), -O-(C3 alkenyl), -O-(C3 alkynyl), -O-(C3-C5 cycloalkyl), -S-(C1-C3 alkyl), -S-(C3 alkenyl), -S-(C3 alkynyl), and -S-(C3-C5 cycloalkyl), wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S; or wherein

R_2 is H, methyl, or ethyl, wherein methyl and ethyl are optionally substituted with one or more F;

R_3 is H or F;

R_6 is H or F;

R_5 is C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, C3-C5 cycloalkyl, or -S(O)(O)-(C1-C5 alkyl), wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F,

and then R_4 is C2-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, -(C1-C3 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C6 alkyl), -S-(C3-C6 alkenyl), -S-(C3-C6 alkynyl), -S-(C3-C6 cycloalkyl), -S-(C1-C3 alkyl)-(C3-C5 cycloalkyl), Cl, Br, I, CF_3, NO_2, or SF_5, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl;

or R_5 is F, Cl, Br, I, -S-(C1-C5 alkyl), CN, or NO_2, wherein alkyl is optionally substituted with one or more F,

and then R_4 is C2 alkyl substituted with one or more F, C3-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, -(C1-C3 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C6 alkyl), -S-(C3-C6 alkenyl), -S-(C3-C6 alkynyl), -S-(C3-C6 cycloalkyl), -S-(C1-C3 alkyl)-(C3-C5 cycloalkyl), NO_2, or SF_5, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or

more F, wherein cycloalkyl is optionally substituted with one or more C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl, and wherein R4 is not isopropyl;

R_7 is H, -CH_2-(6-membered aryl), or -CH_2-(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH_2, NO_2, C1-C3 alkyl, C2-C3 alkenyl, C2-C3 alkynyl, cyclopropyl, -O-(C1-C3 alkyl), -O-(C3 alkenyl), -O-(C3 alkynyl), -O-(cyclopropyl), -S-(C1-C3 alkyl), -S-(C3 alkenyl), -S-(C3 alkynyl), and -S-(cyclopropyl), wherein alkyl, alkenyl, alkynyl, and cyclopropyl are optionally substituted with one or more F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S.

3. The compound of any one of claims 1-3, wherein R_2 is methyl; or wherein R_3 and R_6 are both H; or wherein R_2 is methyl and R_3 and R_6 are both H.

4. The compound of any one of claims 1-3, wherein:

R_5 is C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, or C3-C5 cycloalkyl, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F,

and then R_4 is C2-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, -(C1-C3 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C6 alkyl), -S-(C3-C6 alkenyl), -S-(C3-C6 alkynyl), -S-(C3-C6 cycloalkyl), -S-(C1-C3 alkyl)-(C3-C5 cycloalkyl), Cl, Br, I, CF_3, NO_2, or SF_5, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one to three F, and wherein cycloalkyl is optionally substituted with one or more C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl;

or R_5 is F, Cl, Br, I, -S-(C1-C5 alkyl), or CN, wherein alkyl is optionally substituted with one or more F,

and then R_4 is C2 alkyl substituted with one or more F, C3-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, -(C1-C3 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C6 alkyl), -S-(C3-C6 alkenyl), -S-(C3-C6 alkynyl), -S-(C3-C6 cycloalkyl), -S-(C1-C3 alkyl)-(C3-C5 cycloalkyl), NO_2, or SF_5, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one to three F, wherein cycloalkyl is optionally substituted with one or more C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl, and wherein R_4 is not isopropyl; or wherein

R_5 is C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, or C3-C5 cycloalkyl, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F,

and then R_4 is C2-C4 alkyl, C2-C4 alkenyl, C2-C4 alkynyl, C3-C5 cycloalkyl, -(C1-C2 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C4 alkyl), -S-(C3-C4 alkenyl), -S-(C3-C4 alkynyl), -S-(C3-C5 cycloalkyl), -S-(C1-C2 alkyl)-(C3-C5 cycloalkyl), Cl, Br, I, CF_3, NO_2, or SF_5, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one to three F, and wherein cycloalkyl is optionally substituted with one or more C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl;

or R_5 is F, Cl, Br, I, -S-(C1-C5 alkyl), or CN, wherein alkyl is optionally substituted with one or more F,

and then R_4 is C2 alkyl substituted with one or more F, C3-C4 alkyl, C2-C4 alkenyl, C2-C4 alkynyl, C3-C5 cycloalkyl, -(C1-C2 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C4 alkyl), -S-(C3-C4 alkenyl), -S-(C3-C4 alkynyl), -S-(C3-C5 cycloalkyl), -S-(C1-C2 alkyl)-(C3-C5 cycloalkyl), NO_2, or SF_5, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one to three F, wherein cycloalkyl is optionally substituted with one or more C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl, and wherein R_4 is not isopropyl.

5. The compound of any one of claims 1-4, wherein R_7 is H; or wherein

R_7 is -CH_2-(6-membered aryl) or -CH_2-(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH_2, NO_2, C1-C3 alkyl, cyclopropyl, -O-(C1-C3 alkyl), -O-(cyclopropyl), -S-(C1-C3 alkyl), and -S-(cyclopropyl), wherein alkyl and cyclopropyl are optionally substituted with one to three F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S; or wherein

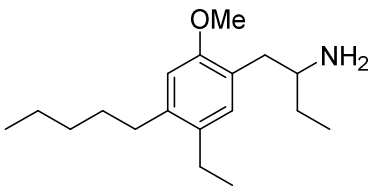
R_7 is -CH_2-(6-membered aryl) or -CH_2-(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, C1-C3 alkyl, cyclopropyl, -O-(C1-C3 alkyl), and -O-(cyclopropyl), wherein alkyl and cyclopropyl are optionally substituted with one to three F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which

they are connected, form a 5-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S; or wherein

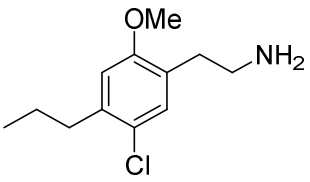
R_7 is -CH_2-(6-membered aryl) or -CH_2-(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, methyl, and -O-(methyl), wherein methyl is optionally substituted with one to three F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a methylenedioxy ring or wherein R_7 is -CH_2-(6-membered aryl), wherein aryl is optionally substituted at the ortho position with one F, OH, or -O-(methyl), or with a methylenedioxy ring linking the ortho and meta positions.

6. The compound of any one of claims 1-5, wherein R_1 is H , methyl, ethyl, -CH_2-OH, or -CH_2-O-(methyl).

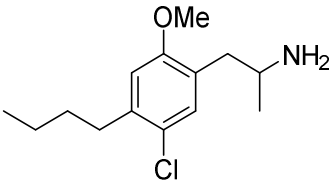
7. The compound of claim 1, selected from the group consisting of:



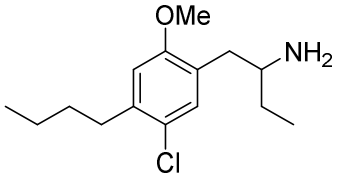
1 ,



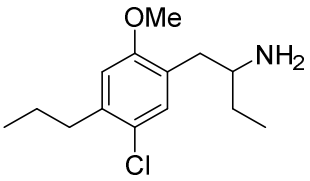
2 ,



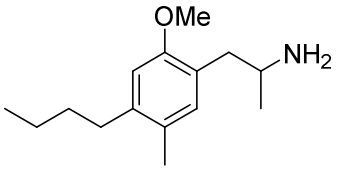
3 ,



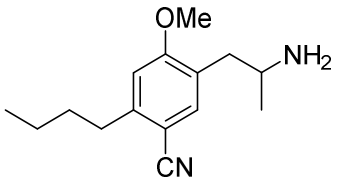
4 ,



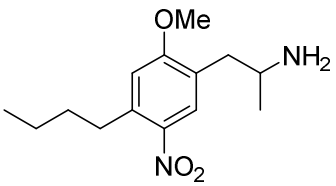
5 ,



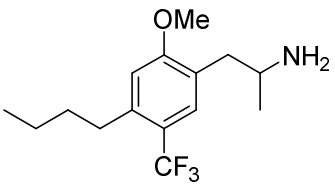
6 ,



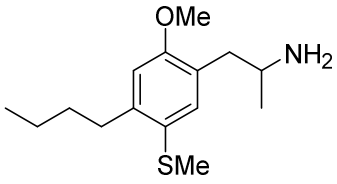
7 ,



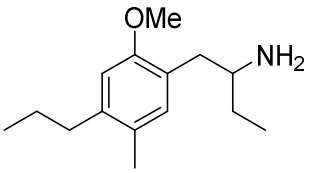
8 ,



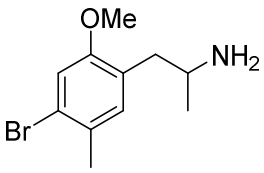
9 ,



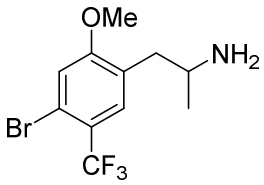
10,



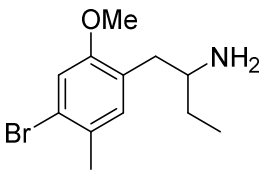
11,



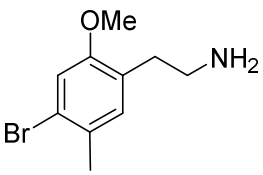
14,



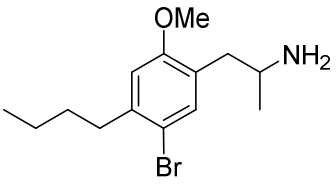
17,



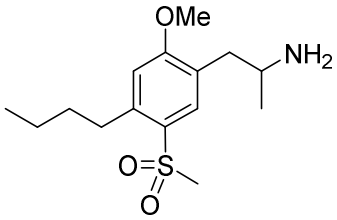
19,



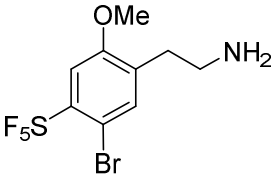
20,



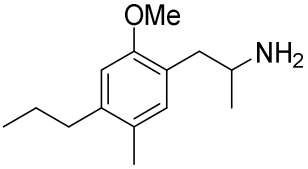
21,



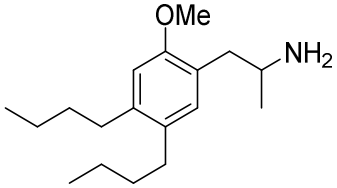
22,



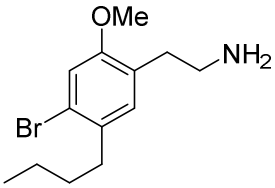
23,



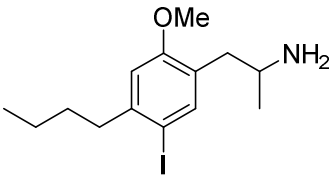
24,



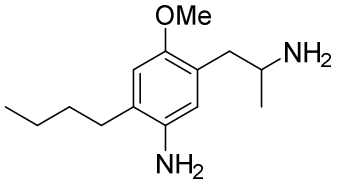
25,



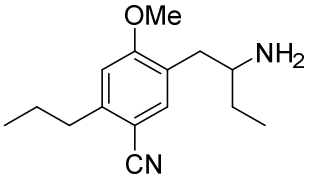
27,



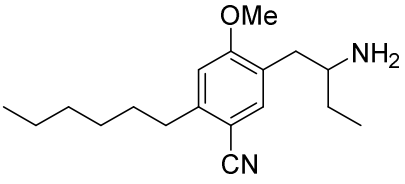
28,



29,



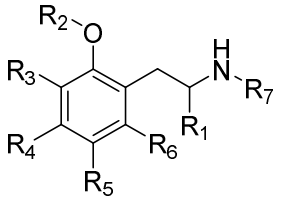
30, and



32,

or a pharmaceutically acceptable salt thereof.

8. A compound of Formula (I)



(I),

or a pharmaceutically acceptable salt thereof,

wherein:

R_1 is $-CH_2$-OH, $-CH_2$-O-(methyl), $-CH_2F$, or $-CH_2CH_2F$;

R_2 is C1-C5 alkyl, C3-C5 cycloalkyl, C3-C5 alkenyl, or C3-C5 alkynyl,

wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F;

R_3 is H, C1-C3 alkyl, cyclopropyl, or F, wherein alkyl and cyclopropyl are optionally substituted with one or more F;

R_4 is C1-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C3-C8 cycloalkyl, -(C1-C5 alkyl)-(C3-C6 cycloalkyl), -S-(C1-C8 alkyl), -S-(C3-C8 alkenyl), -S-(C3-C8 alkynyl), -S-(C3-C8 cycloalkyl), -S-(C1-C5 alkyl)-(C3-C6 cycloalkyl), F, Cl, Br, I, CN, NO_2, or SF_5, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl;

R_5 is -O-(C1-C5 alkyl), -O-(C3-C5 alkenyl), -O-(C3-C5 alkynyl), -O-(C3-C5 cycloalkyl), -O-(C1-C5 alkyl)-(C3-C5 cycloalkyl), CF_3, CN, Br, or I, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl;

R_6 is H, C1-C3 alkyl, cyclopropyl, or F, wherein alkyl and cyclopropyl are optionally substituted with one or more F;

R_7 is H, $-CH_2$-(aryl), or $-CH_2$-(heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH_2, NO_2, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, C3-C5 cycloalkyl, -O-(C1-C5 alkyl), -O-(C3-C5 alkenyl), -O-(C3-C5 alkynyl), -O-(C3-C5 cycloalkyl), -S-(C1-C5 alkyl), -S-(C3-C5 alkenyl), -S-(C3-C5 alkynyl), and -S-(C3-C5 cycloalkyl), wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein any

two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 4-6-membered ring optionally interrupted by 1-3 heteroatoms selected from O, N, and S;

with the provisos that:

(a) when R_1 is -CH_2-OH, R_2 is methyl, R_3 is H, R_5 is -O-(methyl), R_6 is H, and R_7 is H, then R_4 is not methyl, -S-(methyl), or n-butyl;

(b) when R1 is -CH_2-OH, R2 is methyl, R3 is methyl, R5 is -O-(methyl), R6 is H, and R7 is H, then R4 is not methyl;

(c) when R_1 is -CH_2CH_2F, R_2 is methyl, R_3 is H, R_5 is -O-(methyl), R_6 is H, and R_7 is H, then R_4 is not methyl; and

(d) when R_1 is -CH_2-OH, R_2 is methyl, R_3 is methyl, R_5 is Br, R_6 is methyl, and R_7 is H, then R_4 is not methyl.

9. The compound of claim 8, wherein:

R_2 is C1-C3 alkyl, cyclopropyl, C3 alkenyl, or C3 alkynyl, wherein alkyl, alkenyl, alkynyl, and cyclopropyl are optionally substituted with one or more F;

R_3 is H, methyl, ethyl, or F, wherein methyl and ethyl are optionally substituted with one or more F;

R_5 is -O-(C1-C3 alkyl), -O-(C3 alkenyl), -O-(C3 alkynyl), -O-(cyclopropyl), -O-(C1-C3 alkyl)-(cyclopropyl), CF_3, or CN, wherein alkyl, alkenyl, alkynyl, and cyclopropyl are optionally substituted with one or more F, and wherein cyclopropyl is optionally substituted with one or more C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl;

R_6 is H, methyl, ethyl, or F, wherein methyl and ethyl are optionally substituted with one or more F;

R_7 is H, -CH_2-(6-membered aryl), or -CH_2-(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH_2, NO_2, C1-C3 alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C5 cycloalkyl, -O-(C1-C3 alkyl), -O-(C3 alkenyl), -O-(C3 alkynyl), -O-(C3-C5 cycloalkyl), -S-(C1-C3 alkyl), -S-(C3 alkenyl), -S-(C3 alkynyl), and -S-(C3-C5 cycloalkyl), wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are

connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S; or wherein

R_2 is methyl or ethyl, wherein methyl and ethyl are optionally substituted with one or more F;

R_3 is H or F;

R_4 is C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, -(C1-C3 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C6 alkyl), -S-(C3-C6 alkenyl), -S-(C3-C6 alkynyl), -S-(C3-C6 cycloalkyl), -S-(C1-C3 alkyl)-(C3-C5 cycloalkyl), F, Cl, Br, I, CN, NO_2, or SF_5, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl;

R_5 is -O-(methyl), -O-(ethyl), or CN, wherein methyl and ethyl are optionally substituted with one or more F;

R_6 is H or F;

R_7 is H, -CH_2-(6-membered aryl), or -CH_2-(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH_2, NO_2, C1-C3 alkyl, C2-C3 alkenyl, C2-C3 alkynyl, cyclopropyl, -O-(C1-C3 alkyl), -O-(C3 alkenyl), -O-(C3 alkynyl), -O-(cyclopropyl), -S-(C1-C3 alkyl), -S-(C3 alkenyl), -S-(C3 alkynyl), and -S-(cyclopropyl), wherein alkyl, alkenyl, alkynyl, and cyclopropyl are optionally substituted with one or more F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S.

10. The compound of claim 8 or 9, wherein R_2 is methyl and R_5 is -O-(methyl),

R_3 and R_6 are both H, or R_2 is methyl and R_5 is -O-(methyl), and R_3 and R_6 are both H.

11. The compound of any one of claims 8-10, wherein R_4 is C1-C4 alkyl, C2-C4 alkenyl, C2-C4 alkynyl, C3-C5 cycloalkyl, -(C1-C2 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C4 alkyl), -S-(C3-C4 alkenyl), -S-(C3-C4 alkynyl), -S-(C3-C5 cycloalkyl), -S-(C1-C2 alkyl)-(C3-C5 cycloalkyl), F, Cl, Br, I, CN, NO_2, or SF_5, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally

substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl; or wherein

R_4 is C1-C4 alkyl, C2-C4 alkenyl, C2-C4 alkynyl, C3-C5 cycloalkyl, -(C1-C2 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C4 alkyl), -S-(C3-C4 alkenyl), -S-(C3-C4 alkynyl), -S-(C3-C5 cycloalkyl), -S-(C1-C2 alkyl)-(C3-C5 cycloalkyl), Cl, Br, I, or SF_5, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one to three F, and wherein cycloalkyl is optionally substituted with one to three C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl.

12. The compound of any one of claims 8-11, wherein R_7 is H; or wherein

R_7 is -CH_2-(6-membered aryl) or -CH_2-(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH_2, NO_2, C1-C3 alkyl, cyclopropyl, -O-(C1-C3 alkyl), -O-(cyclopropyl), -S-(C1-C3 alkyl), and -S-(cyclopropyl), wherein alkyl and cyclopropyl are optionally substituted with one to three F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S; or wherein

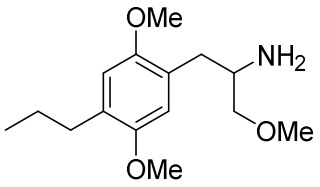
R_7 is -CH_2-(6-membered aryl) or -CH_2-(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, C1-C3 alkyl, cyclopropyl, -O-(C1-C3 alkyl), and -O-(cyclopropyl), wherein alkyl and cyclopropyl are optionally substituted with one to three F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S; or wherein

R_7 is -CH_2-(6-membered aryl) or -CH_2-(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, methyl, and -O-(methyl), wherein methyl is optionally substituted with one to three F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a methylenedioxy ring; or wherein

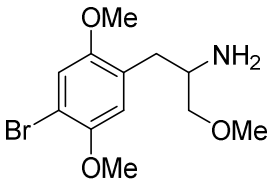
R_7 is -CH_2-(6-membered aryl), wherein aryl is optionally substituted at the ortho position with one F, OH, or -O-(methyl), or with a methylenedioxy ring linking the ortho and meta positions.

13. The compound of any one of claims 8-12, wherein R_1 is -CH_2-OH, -CH_2-O-(methyl),-CH_2F, or -CH_2CH_2F.

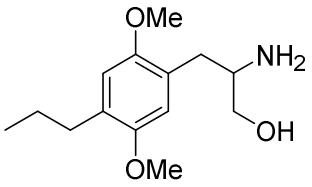
14. The compound of claim 8, selected from the group consisting of:



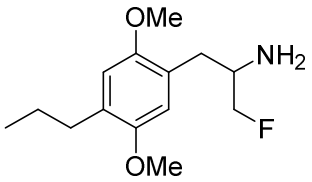
1A,



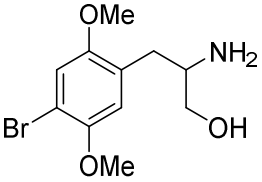
2A,



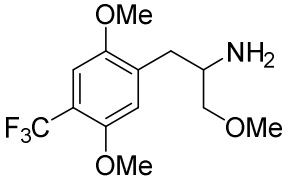
3A,



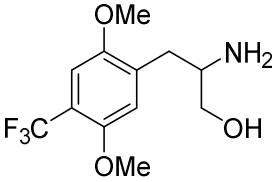
4A,



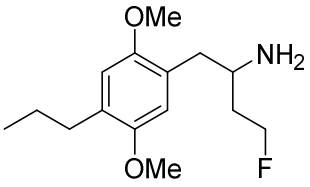
5A,



6A,



7A,

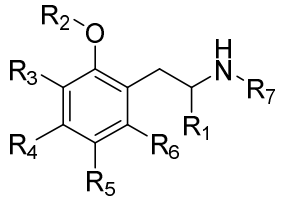


8A

and ,

or a pharmaceutically acceptable salt thereof.

15. A compound of Formula (I)



(I),

or a pharmaceutically acceptable salt thereof,

wherein:

R_1 is H, methyl, ethyl, n-propyl, -CH_2-OH, -CH_2-O-(methyl), -CH_2F, or -CH_2CH_2F;

R_2 is C1-C5 alkyl, C3-C5 cycloalkyl, C3-C5 alkenyl, or C3-C5 alkynyl,

wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F;

R_3 is H, C1-C3 alkyl, cyclopropyl, or F, wherein alkyl and cyclopropyl are optionally substituted with one or more F;

R_4 is C1-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C3-C8 cycloalkyl, -(C1-C5 alkyl)-(C3-C6 cycloalkyl), -S-(C1-C8 alkyl), -S-(C3-C8 alkenyl), -S-(C3-C8 alkynyl), -S-(C3-C8 cycloalkyl), -S-(C1-C5 alkyl)-(C3-C6 cycloalkyl), F, Cl, Br, I, CN, NO_2, or SF_5, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl;

R_5 is C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, C3-C5 cycloalkyl, -S-(C1-C5 alkyl), -S-(C3-C5 alkenyl), -S-(C3-C5 alkynyl), -S-(C3-C5 cycloalkyl), -S-(C1-C5 alkyl)-(C3-C5 cycloalkyl), -S(O)(O)-(C1-C5 alkyl), -S(O)(O)-(C3-C5 alkenyl), -S(O)(O)-(C3-C5 alkynyl), -S(O)(O)-(C3-C5 cycloalkyl), -S(O)(O)-(C1-C5 alkyl)-(C3-C5 cycloalkyl), -O-(C1-C5 alkyl), -O-(C3-C5 alkenyl), -O-(C3-C5 alkynyl), -O-(C3-C5 cycloalkyl), -O-(C1-C5 alkyl)-(C3-C5 cycloalkyl), NH_2, NH(C1-C5 alkyl), or $N(C1\text{-}C5\ alkyl)_2$, F, Cl, Br, I, CN, or NO_2, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl;

R_6 is F;

R_7 is H, $-CH_2$-(aryl), or $-CH_2$-(heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH_2, NO_2, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, C3-C5 cycloalkyl, -O-(C1-C5 alkyl), -O-(C3-C5 alkenyl), -O-(C3-C5 alkynyl), -O-(C3-C5 cycloalkyl), -S-(C1-C5 alkyl), -S-(C3-C5 alkenyl), -S-(C3-C5 alkynyl), and -S-(C3-C5 cycloalkyl), wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 4-6-membered ring optionally interrupted by 1-3 heteroatoms selected from O, N, and S;

with the proviso that when R_1 is H, R_2 is methyl, R_3 is H, R_4 is F, and R_7 is H, then R_5 is not Cl or Br.

16. The compound of claim 15, wherein:

R_2 is C1-C3 alkyl, cyclopropyl, C3 alkenyl, or C3 alkynyl, wherein alkyl, alkenyl, alkynyl, and cyclopropyl are optionally substituted with one or more F;

R_3 is H, methyl, ethyl, or F, wherein methyl and ethyl are optionally substituted with one or more F;

R_5 is -O-(C1-C3 alkyl), -O-(C3 alkenyl), -O-(C3 alkynyl), -O-(cyclopropyl), -O-(C1-C3 alkyl)-(cyclopropyl), or CN, wherein alkyl, alkenyl, alkynyl, and cyclopropyl are optionally substituted with one or more F, and wherein cyclopropyl is optionally substituted with one or more C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl;

R_7 is H, -CH_2-(6-membered aryl), or -CH_2-(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH_2, NO_2, C1-C3 alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C5 cycloalkyl, -O-(C1-C3 alkyl), -O-(C3 alkenyl), -O-(C3 alkynyl), -O-(C3-C5 cycloalkyl), -S-(C1-C3 alkyl), -S-(C3 alkenyl), -S-(C3 alkynyl), and -S-(C3-C5 cycloalkyl), wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S; or wherein

R_2 is methyl or ethyl, wherein methyl and ethyl are optionally substituted with one or more F;

R_3 is H or F;

R_4 is C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, -(C1-C3 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C6 alkyl), -S-(C3-C6 alkenyl), -S-(C3-C6 alkynyl), -S-(C3-C6 cycloalkyl), -S-(C1-C3 alkyl)-(C3-C5 cycloalkyl), F, Cl, Br, I, CN, NO_2, or SF_5, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl;

R_5 is -O-(methyl), -O-(ethyl), or CN, wherein methyl and ethyl are optionally substituted with one or more F;

R_7 is H, -CH_2-(6-membered aryl), or -CH_2-(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from

the group consisting of halo, CN, OH, NH_2, NO_2, C1-C3 alkyl, C2-C3 alkenyl, C2-C3 alkynyl, cyclopropyl, -O-(C1-C3 alkyl), -O-(C3 alkenyl), -O-(C3 alkynyl), -O-(cyclopropyl), -S-(C1-C3 alkyl), -S-(C3 alkenyl), -S-(C3 alkynyl), and -S-(cyclopropyl), wherein alkyl, alkenyl, alkynyl, and cyclopropyl are optionally substituted with one or more F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S.

17. The compound of any one of claims 15-16, wherein R_2 is methyl, R_5 is -O-(methyl), or R_3 is H, or wherein R_2 is methyl, R_5 is -O-(methyl), and R_3 is H.

18. The compound of any one of claims 15-17, wherein R_4 is C1-C4 alkyl, C2-C4 alkenyl, C2-C4 alkynyl, C3-C5 cycloalkyl, -(C1-C2 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C4 alkyl), -S-(C3-C4 alkenyl), -S-(C3-C4 alkynyl), -S-(C3-C5 cycloalkyl), -S-(C1-C2 alkyl)-(C3-C5 cycloalkyl), F, Cl, Br, I, CN, NO_2, or SF_5, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl; or wherein

R_4 is C1-C4 alkyl, C2-C4 alkenyl, C2-C4 alkynyl, C3-C5 cycloalkyl, -(C1-C2 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C4 alkyl), -S-(C3-C4 alkenyl), -S-(C3-C4 alkynyl), -S-(C3-C5 cycloalkyl), -S-(C1-C2 alkyl)-(C3-C5 cycloalkyl), Cl, Br, I, or SF_5, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one to three F, and wherein cycloalkyl is optionally substituted with one to three C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl.

19. The compound of any one of claims 15-18, wherein R_7 is H; or wherein

R_7 is -CH_2-(6-membered aryl) or -CH_2-(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH_2, NO_2, C1-C3 alkyl, cyclopropyl, -O-(C1-C3 alkyl), -O-(cyclopropyl), -S-(C1-C3 alkyl), and -S-(cyclopropyl), wherein alkyl and cyclopropyl are optionally substituted with one to three F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S; or wherein

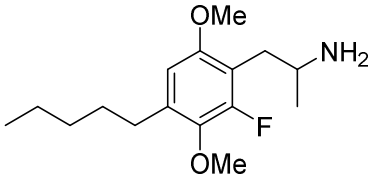
R_7 is -CH_2-(6-membered aryl) or -CH_2-(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, C1-C3 alkyl, cyclopropyl, -O-(C1-C3 alkyl), and -O-(cyclopropyl), wherein alkyl and cyclopropyl are optionally substituted with one to three F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S or wherein

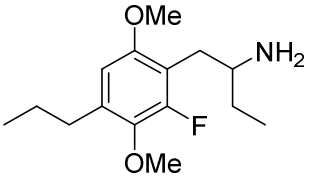
R_7 is -CH_2-(6-membered aryl) or -CH_2-(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, methyl, and -O-(methyl), wherein methyl is optionally substituted with one to three F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a methylenedioxy ring; or wherein

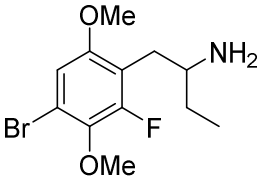
R_7 is -CH_2-(6-membered aryl), wherein aryl is optionally substituted at the ortho position with one F, OH, or -O-(methyl), or with a methylenedioxy ring linking the ortho and meta positions.

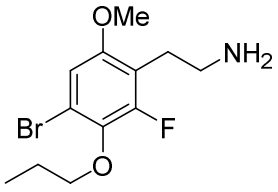
20. The compound of any one of claims 15-19, wherein R_1 is H , Me, ethyl, n-propyl, -CH_2-OH, -CH_2-O-(methyl), -CH_2F, or -CH_2CH_2F.

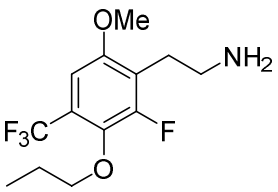
21. The compound of claim 15, selected from the group consisting of:



1B ,


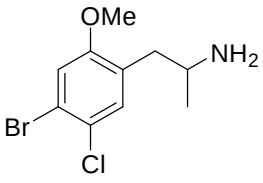
2B ,


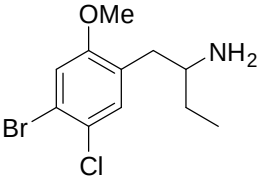
3B ,


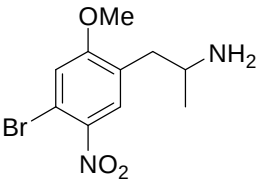
4B , and


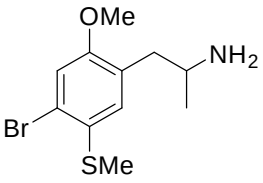
5B ,
or a pharmaceutically acceptable salt thereof.

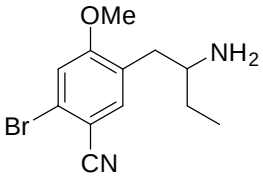
22. A compound selected from the group consisting of:

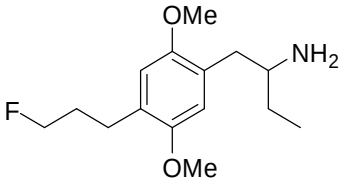


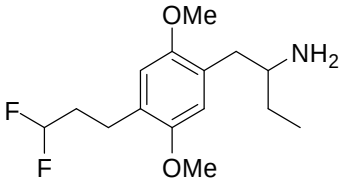
12, 

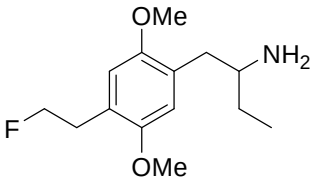
13, 

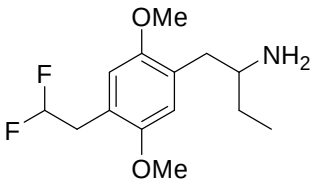
16, 

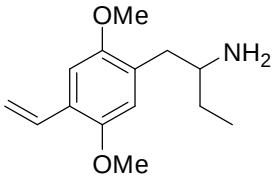
18, and 

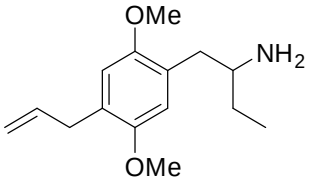
31, 

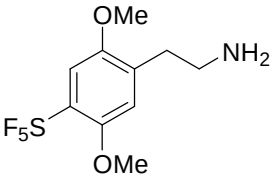
1C, 

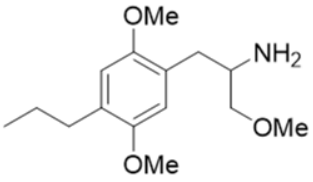
2C, 

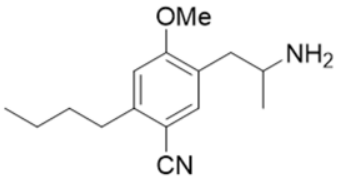
3C, 

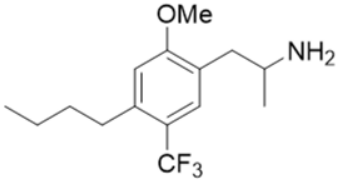
4C, 

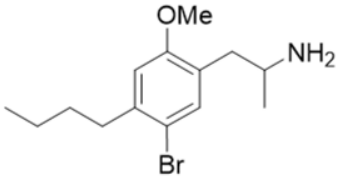
5C, and 

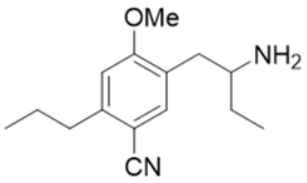
6C, 

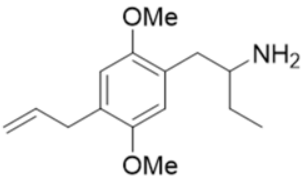
1D, 

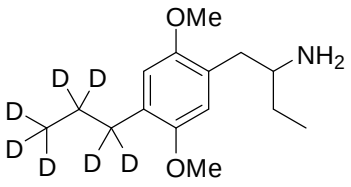
1A, 

7, 

9, 

21, 

30, 

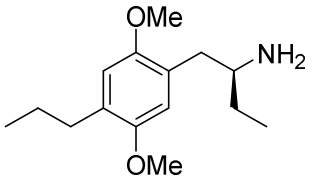
6C, or 

2D, wherein each deuterium-enriched H-site is greater than 0.02%, 90%, or 95% deuterium, or a pharmaceutically acceptable salt thereof.

23. The compound of any one of claims 1 to 22 in the S-enantiomeric form or the R-enantiomeric form., which optionally includes the compound of the opposite enantiomeric form, provided the compound contains >50% of the indicated enantiomeric form and <50% of the opposite enantiomeric form.

24. The compound of claim 23, wherein the compound is substantially enantiomerically pure.

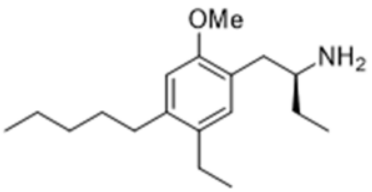
25. A composition comprising the following S-enantiomeric compound:



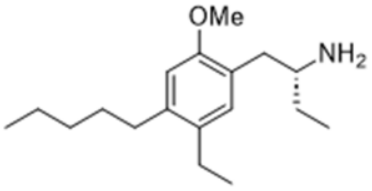
3DS ,

which optionally includes the R-enantiomeric form of the same compound, provided that the composition contains greater than 50% ,90%, or 95% of the S-enantiomeric form.

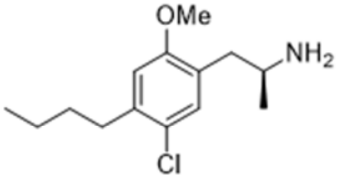
26. A compound selected from the group consisting of:



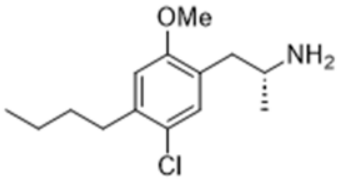
1S



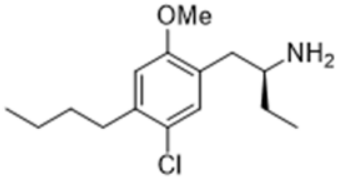
1R



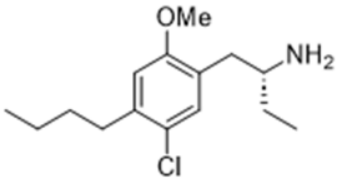
3S



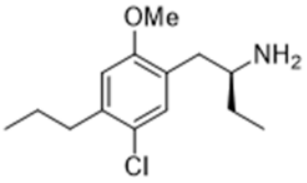
3R



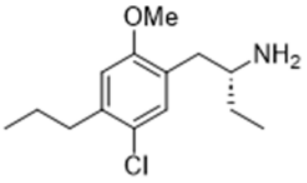
4S



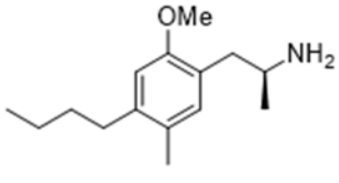
4R



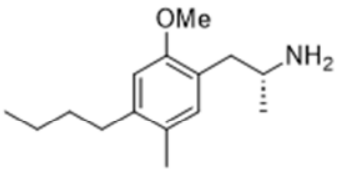
5S



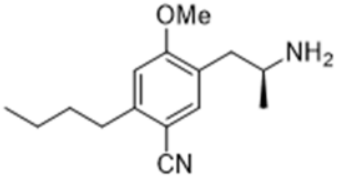
5R



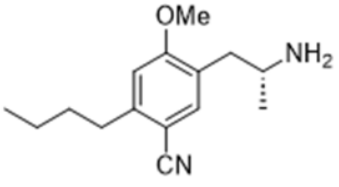
6S



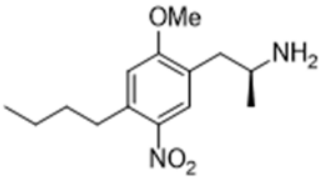
6R



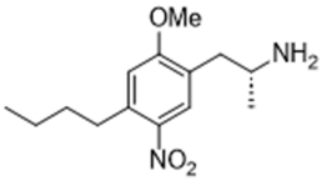
7S



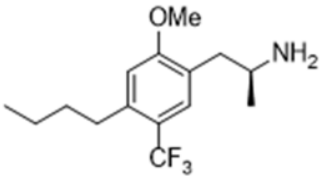
7R



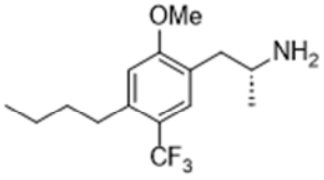
8S



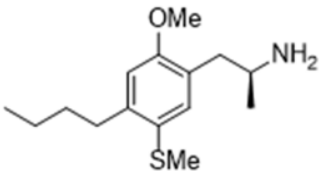
8R



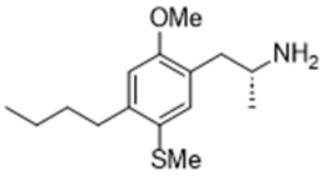
9S



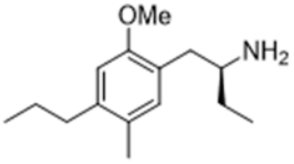
9R



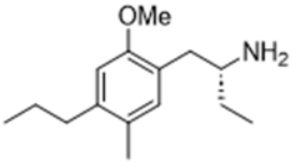
10S



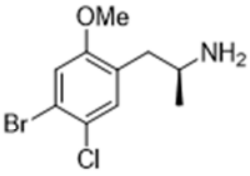
10R



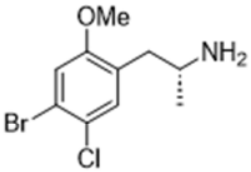
11S



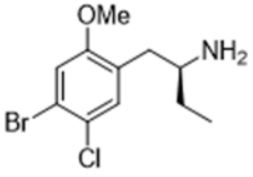
11R



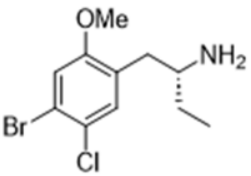
12S



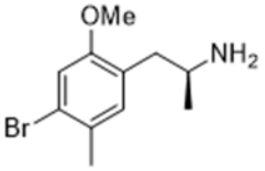
12R



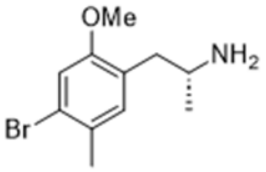
13S



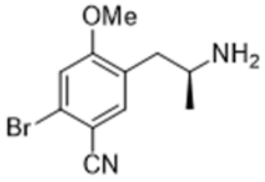
13R



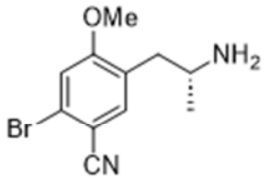
14S



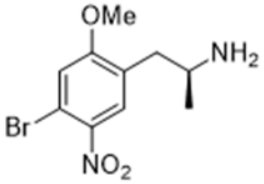
14R



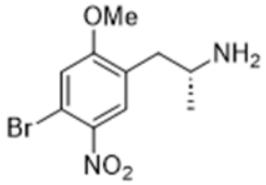
15S



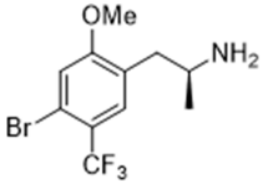
15R



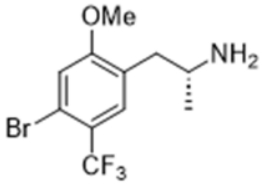
16S



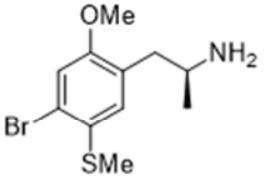
16R



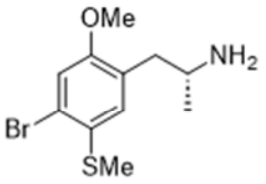
17S



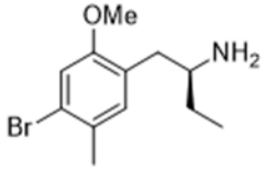
17R



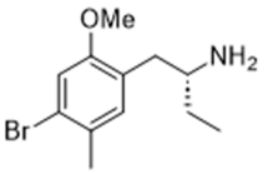
18S



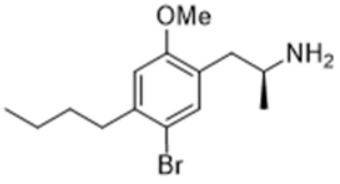
18R



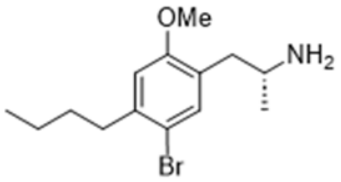
19S



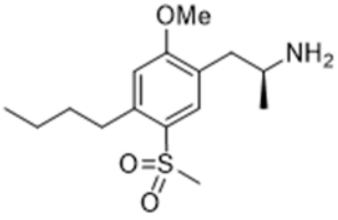
19R



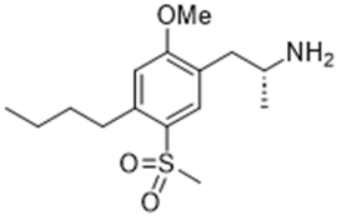
21S



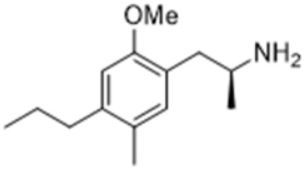
21R



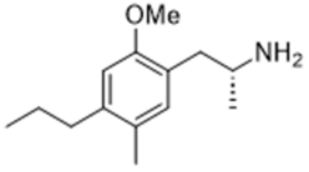
22S



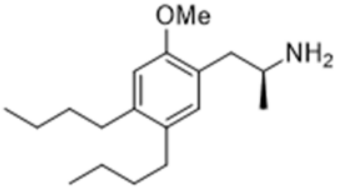
22R



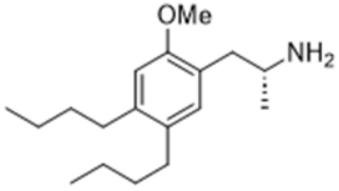
24S



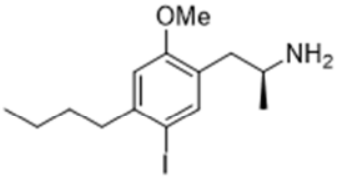
24R



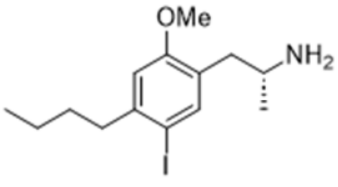
25S



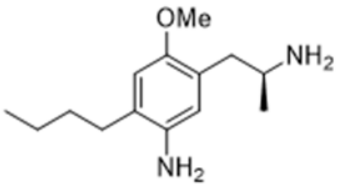
25R



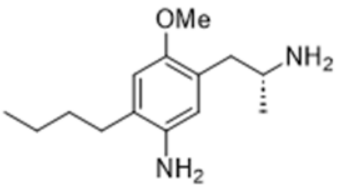
28S



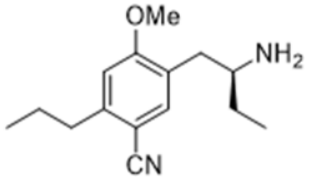
28R



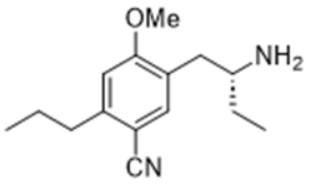
29S



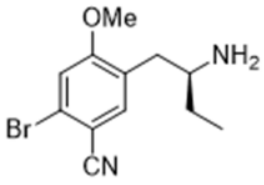
29R



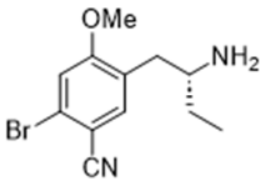
30S



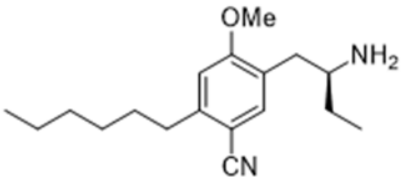
30R



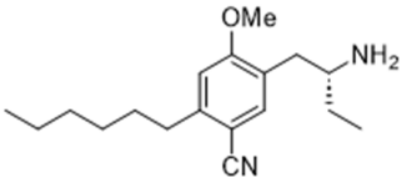
31S



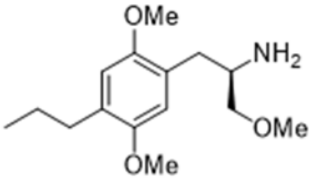
31R



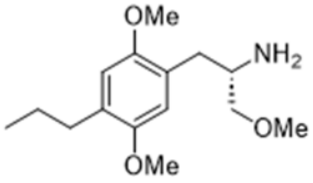
32S



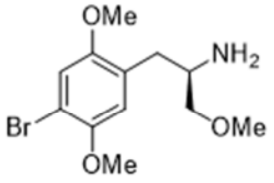
32R



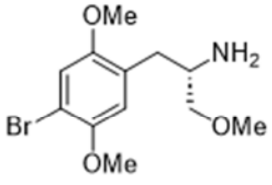
1AR



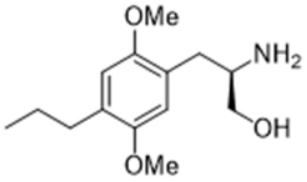
1AS



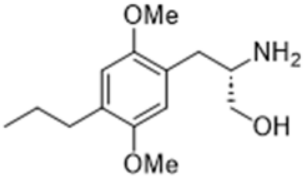
2AR



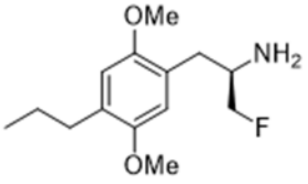
2AS



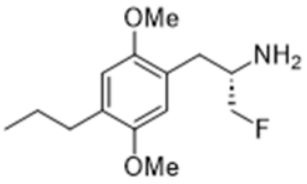
3AR



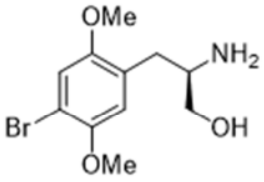
3AS



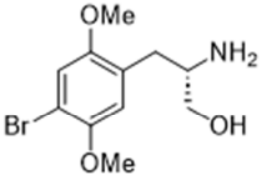
4AR



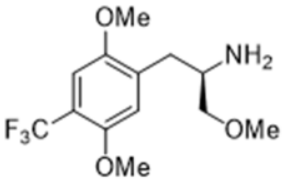
4AS



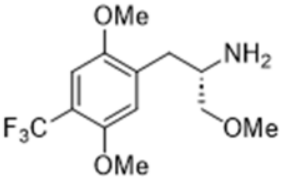
5AR



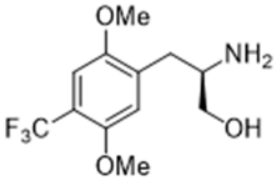
5AS



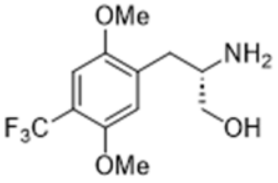
6AR



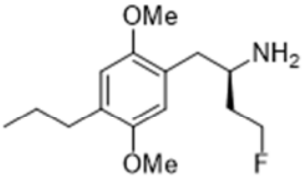
6AS



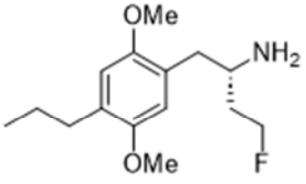
7AR



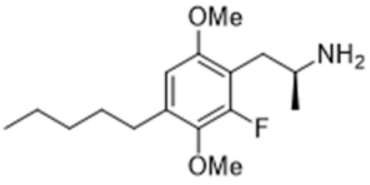
7AS



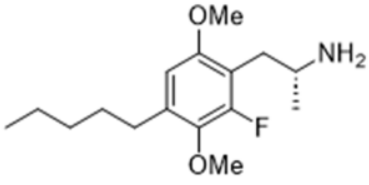
8AR



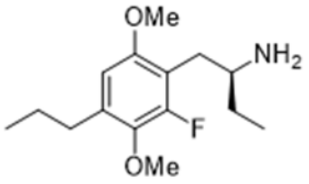
8AS



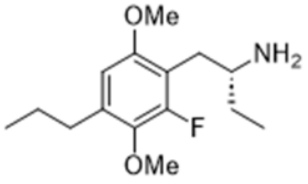
1BS



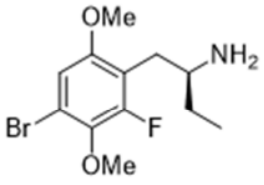
1BR



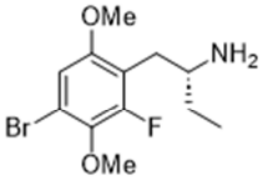
2BS



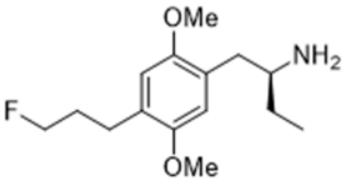
2BR



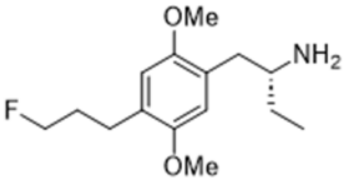
3BS



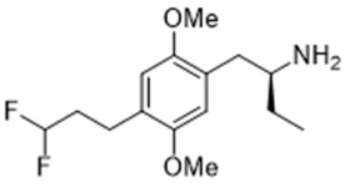
3BR



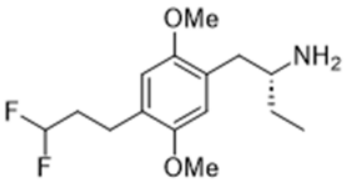
1CS



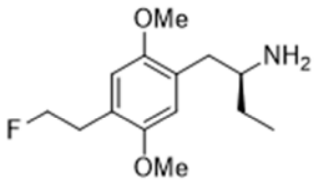
1CR



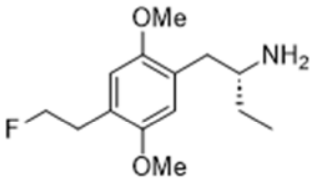
2CS



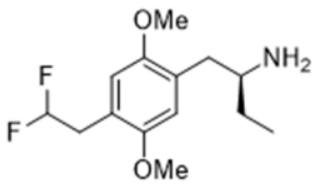
2CR



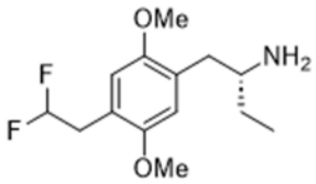
3CS



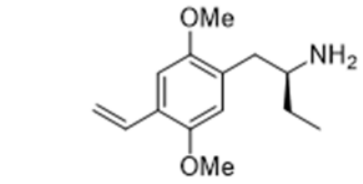
3CR



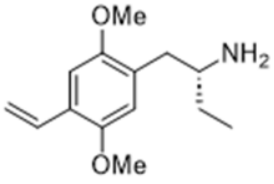
4CS



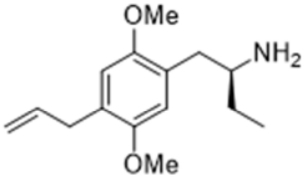
4CR



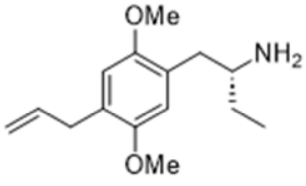
5CS



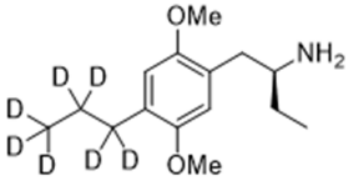
5CR



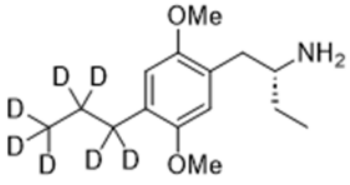
6CS



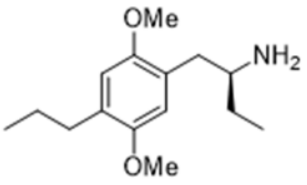
6CR



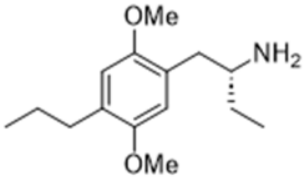
2DS



2DR



3DS



3DR

.

27. A pharmaceutical composition comprising the compound of any one of claims 1-24 or 26 or the composition of claim 25, and a pharmaceutically acceptable carrier.

28. Use of the compound of any one of claims 1-24 or 26 or the composition of claim 25 in the manufacture of a pharmaceutical composition for treating a psychiatric disease or disorder, or a headache or headache disorder or inflammatory disease or disorder or high intraocular pressure,

wherein the psychiatric disease or disorder is selected from the group consisting of depressive disorders and bipolar disorders,

a depressive disorder,

a treatment-resistant depressive disorder,

major depressive disorder, persistent depressive disorder, postpartum depression, premenstrual dysphoric disorder, seasonal affective disorder, psychotic depression, disruptive mood dysregulation disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition,

bipolar disorder I, bipolar disorder II, cyclothymic disorder, substance/medication-induced bipolar and related disorder, ,bipolar and related disorder due to another medical condition,

a substance-related disorder,

a substance-use disorder,

an anxiety disorder,

obsessive-compulsive and related disorders, trauma- and stressor-related disorders, feeding and eating disorders, borderline personality disorder, attention-deficit/hyperactivity disorder, and autism spectrum disorder.