ISOTOPICALLY-LABELLED TRAPIDIL DERIVATIVES

CROSS-REFERENCE

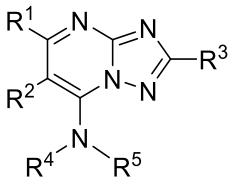
[0001] This application claims the benefit of U. S. Provisional Application Serial No. 63/000,347 filed March 26, 2020 and U. S. Provisional Application Serial No. 63/063,846 filed August 10, 2020 which are hereby incorporated by reference in their entirety.

STATEMENT AS TO FEDERALLY SPONSORED RESEARCH

[0002] This invention was made with government support under R44GM121117 awarded by the National Institutes of Health. The government has certain rights in the invention.

SUMMARY

[0002a] In an aspect of the present disclosure, there is provided a compound of Formula (I) or a pharmaceutically salt, co-crystal or solvate thereof:



(I)

wherein:

R^1 is $-CH_3$, $-CD_3$, $-CHD_2$, or $-CH_2D$;

R^2 is hydrogen or -D;

R^3 is hydrogen or -D;

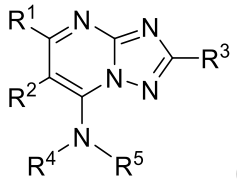
R^4 is hydrogen, $-CH_2CH_3$; $-CD_2CD_3$; $-CD_2CH_3$; $-CH_2CD_3$; $-CDHCH_3$; $-CH_2CDH_2$; $-CH_2CD_2H$; $-CD_2CDH_2$; $-CD_2CD_2H$; $-CDHCD_3$; $-CDHCDH_2$; or $-CDHCD_2H$;

R^5 is hydrogen, $-CH_2CH_3$; $-CD_2CD_3$; $-CD_2CH_3$; $-CH_2CD_3$; $-CDHCH_3$; $-CH_2CDH_2$; $-CH_2CD_2H$; $-CD_2CDH_2$; $-CD_2CD_2H$; $-CDHCD_3$; $-CDHCDH_2$; or $-CDHCD_2H$; and

wherein at least one of R^1, R^2, R^3, R^4, or R^5, comprises at least one deuterium atom.

[0002b] In another aspect of the present disclosure, there is provided a pharmaceutical composition, comprising: a compound disclosed herein, or a pharmaceutically acceptable salt, co-crystal or solvate thereof, and a pharmaceutically acceptable carrier.

[0003] Provided herein, in certain examples, is a compound of Formula (I) or a pharmaceutically salt, co-crystal or solvate thereof:



(I)

wherein:

R^1 is $-CH_3$, $-CD_3$, $-CHD_2$, or $-CH_2D$;

R^2 is hydrogen or -D;

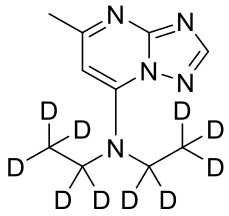
R^3 is hydrogen or -D;

R^4 is hydrogen, $-CH_2CH_3$; $-CD_2CD_3$; $-CD_2CH_3$; $-CH_2CD_3$; $-CDHCH_3$; $-CH_2CDH_2$; $-CH_2CD_2H$; $-CD_2CDH_2$; $-CD_2CD_2H$; $-CDHCD_3$; $-CDHCDH_2$; or $-CDHCD_2H$;

R^5 is hydrogen, $-CH_2CH_3$; $-CD_2CD_3$; $-CD_2CH_3$; $-CH_2CD_3$; $-CDHCH_3$; $-CH_2CDH_2$; $-CH_2CD_2H$; $-CD_2CDH_2$; $-CD_2CD_2H$; $-CDHCD_3$; $-CDHCDH_2$; or $-CDHCD_2H$; and

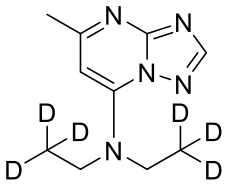
wherein at least one of R^1, R^2, R^3, R^4, or R^5, comprises at least one deuterium atom.

[0004] Provided herein, in certain examples, is a compound or a pharmaceutically acceptable salt, co-crystal or solvate thereof, that is:

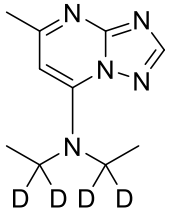


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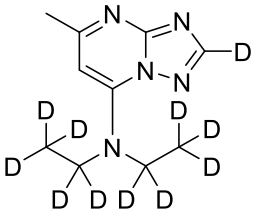
[0005] Provided herein, in certain examples, is a compound or a pharmaceutically acceptable salt, co-crystal or solvate thereof, that is:



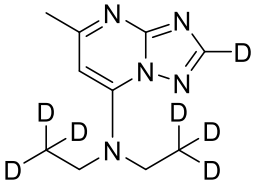
[0006] Provided herein, in certain examples, is a compound or a pharmaceutically acceptable salt, co-crystal or solvate thereof, that is:



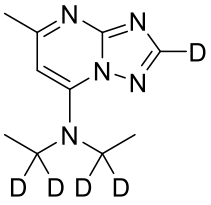
[0007] Provided herein, in certain examples, is a compound or a pharmaceutically acceptable salt, co-crystal or solvate thereof, that is:



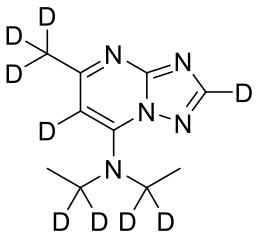
[0008] Provided herein, in certain examples, is a compound or a pharmaceutically acceptable salt, co-crystal or solvate thereof, that is:



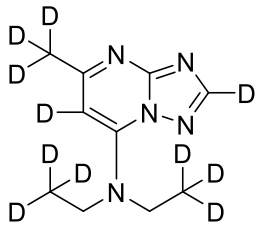
[0009] Provided herein, in certain examples, is a compound or a pharmaceutically acceptable salt, co-crystal or solvate thereof, that is:



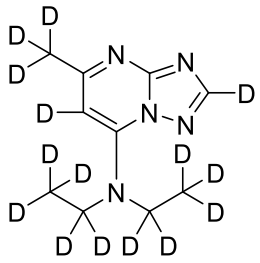
[0010] Provided herein, in certain examples, is a compound or a pharmaceutically acceptable salt, co-crystal or solvate thereof, that is:



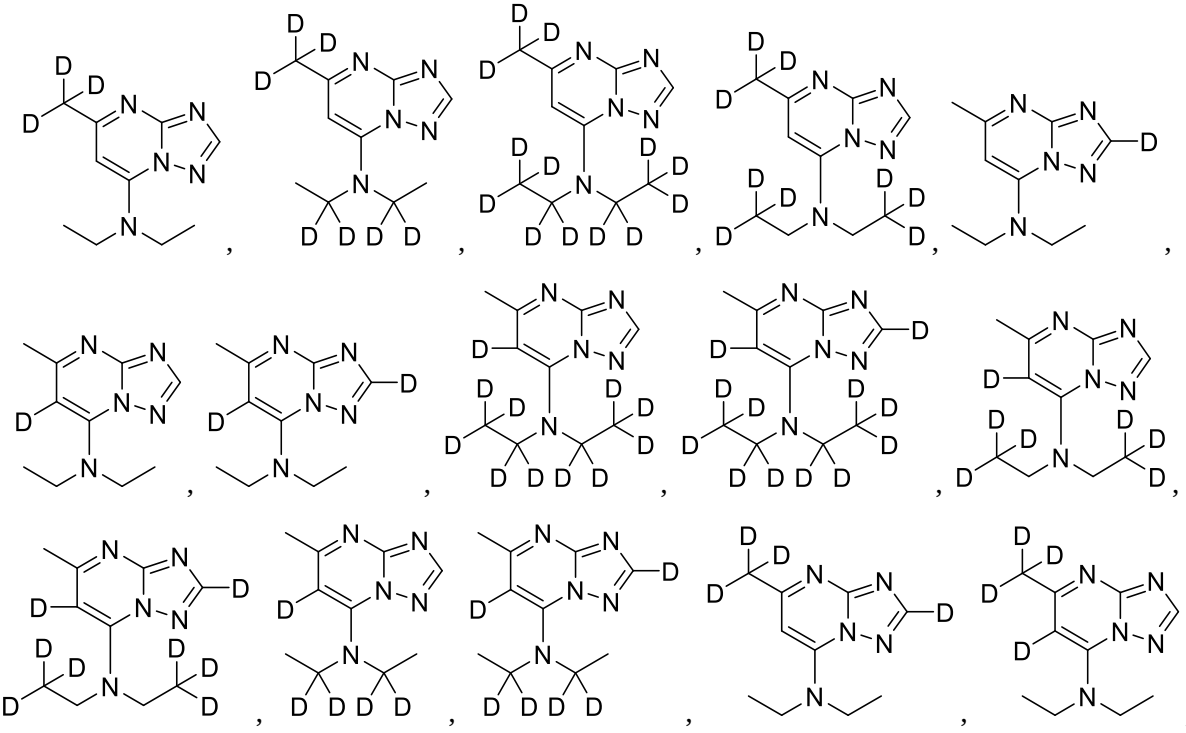
[0011] Provided herein, in certain examples, is a compound or a pharmaceutically acceptable salt, co-crystal or solvate thereof, that is:

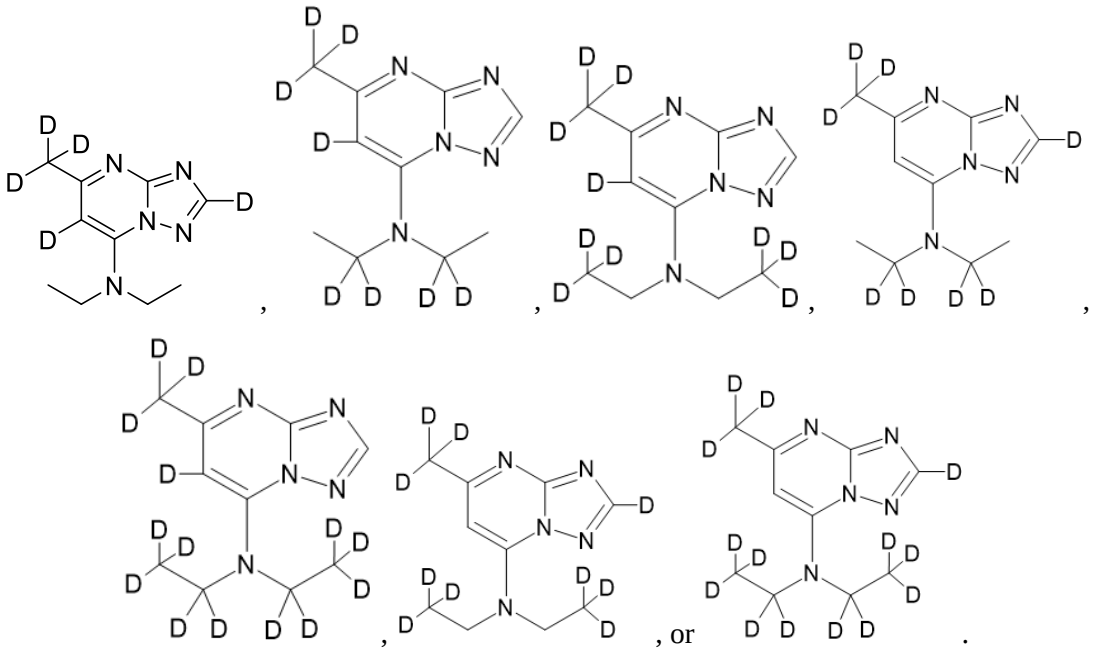


[0012] Provided herein, in certain examples, is a compound or a pharmaceutically acceptable salt, co-crystal or solvate thereof, that is:



[0013] Provided herein, in certain examples, is a compound or a pharmaceutically acceptable salt, co-crystal or solvate thereof, that is:





[0014] In some examples, in any one of the compounds disclosed herein, or in pharmaceutically acceptable salts, co-crystals or solvates thereof, the positions represented as D have deuterium enrichment of at least 98%. In some examples, in any one of the compounds disclosed herein, or in pharmaceutically acceptable salts, co-crystals or solvates thereof, the positions represented as D have deuterium enrichment of at least 90%. In some examples, in any one of the compounds disclosed herein, or in pharmaceutically acceptable salts, co-crystals or solvates thereof, the positions represented as D have deuterium enrichment of at least 50%. In some examples, in any one of the compounds disclosed herein, or in pharmaceutically acceptable salts, co-crystals or solvates thereof, the positions represented as D have deuterium enrichment of at least 10%.

[0015] Provided herein, in certain examples, is a pharmaceutical composition comprising any one of the compounds disclosed herein, or a pharmaceutically acceptable salt, co-crystal or solvate thereof, and a pharmaceutically acceptable carrier.

[0016] Provided herein, in certain examples, is a method of treating Parkinson's disease or a movement disorder associated with Parkinson's disease in a subject in need thereof, comprising administering to the subject any one of the compounds disclosed herein or a pharmaceutical composition disclosed herein.

[0017] Provided herein, in certain examples, is a method of treating Parkinson's disease or a movement disorder associated with Parkinson's disease in a subject in need thereof, comprising administering to the subject a therapeutically effective combination of (a) any one of the compounds disclosed herein or a pharmaceutical composition disclosed herein, and (b) an additional therapeutic agent. In some examples, the additional therapeutic agent is a dopamine precursor. In some examples, the dopamine precursor is levodopa. In some examples, the additional therapeutic agent is a dopamine agonist. In some examples, the dopamine agonist is pramipexole, ropinirole, rotigotine, pergolide, bromocriptine, piribedile, lisuride, or apomorphine, or a combination thereof. In some examples, the additional therapeutic agent is a dopamine agonist comprising pramipexole, ropinirole, rotigotine, pergolide,

bromocriptine, piribedile, lisuride, or apomorphine, or a combination thereof. In some examples, the additional therapeutic agent is a Catechol O-methyl transferase (COMT) inhibitor. In some examples, the COMT inhibitor is entacapone or tolcapone. In some examples, the COMT inhibitor is entacapone, tolcapone, or opicapone. In some examples, the additional therapeutic agent is a Catechol O-methyl transferase (COMT) inhibitor comprising entacapone, tolcapone, or opicapone. In some examples, the additional therapeutic agent is a monoamine oxidase B (MAOB) inhibitor. In some examples, the MAOB inhibitor is selegiline or rasagiline. In some examples, the additional therapeutic agent is a monoamine oxidase B (MAOB) inhibitor comprising selegiline or rasagiline. In some examples, the additional therapeutic agent is a dopa decarboxylase inhibitor. In some examples, the dopa decarboxylase inhibitor is carbidopa or benserazide. In some examples, the additional therapeutic agent is a dopa decarboxylase inhibitor comprising carbidopa or benserazide. In some examples, in any of the methods provided herein, the movement disorder to be treated is dyskinesia. In some examples, the dyskinesia is levodopa-induced dyskinesia (LID), diphasic dyskinesia, or peak-dose dyskinesia.

[0018] In some examples, in any of the methods provided herein, the movement disorder to be treated is dystonia. In some examples, the dystonia is generalized dystonia, focal dystonia, segmental dystonia, or acute dystonia. In some examples, in any of the methods provided herein, the movement disorder to be treated is akathisia. In some examples, the akathisia is acute akathisia, chronic akathisia, pseudoakathisia, or withdrawal akathisia. In some examples, in any of the methods provided herein, the subject to be treated is diagnosed with Parkinson's disease.

[0019] Provided herein, in certain examples, is a pharmaceutical combination for use for the treatment or prevention of Parkinson's disease or a movement disorder associated with Parkinson's disease in a subject in need thereof, comprising: a therapeutic combination of (a) any of the compounds disclosed herein or any of the pharmaceutical compositions disclosed herein; and (b) an additional therapeutic agent for treating Parkinson's disease. In some examples, the additional therapeutic agent is a dopamine precursor. In some examples, the dopamine precursor is levodopa. In some examples, the additional therapeutic agent is a dopamine agonist. In some examples, the dopamine agonist is pramipexole, ropinirole, rotigotine, pergolide, bromocriptine, piribedile, lisuride, or apomorphine. In some examples, the additional therapeutic agent is a dopamine agonist comprising pramipexole, ropinirole, rotigotine, pergolide, bromocriptine, piribedile, lisuride, or apomorphine. In some examples, the additional therapeutic agent is a Catechol O-methyl transferase (COMT) inhibitor. In some examples, the COMT inhibitor is entacapone or tolcapone. In some examples, the COMT inhibitor is entacapone, tolcapone, or opicapone. In some examples, the additional therapeutic agent is a Catechol O-methyl transferase (COMT) inhibitor. In some examples comprising entacapone, tolcapone, or opicapone. In some examples, the additional therapeutic agent is a monoamine oxidase B (MAOB) inhibitor. In some examples, the MAOB inhibitor is selegiline or rasagiline. In some examples, the additional therapeutic agent is a monoamine oxidase B (MAOB) inhibitor comprising selegiline or rasagiline. In some examples, the additional therapeutic agent is a dopa decarboxylase inhibitor. In some examples, the dopa

decarboxylase inhibitor is carbidopa or benserazide. In some examples, the additional therapeutic agent is a dopa decarboxylase inhibitor comprising carbidopa or benserazide. In some examples, the movement disorder is dyskinesia. In some examples, the dyskinesia is levodopa-induced dyskinesia (LID), diphasic dyskinesia, or peak-dose dyskinesia. In some examples, the movement disorder is dystonia. In some examples, the dystonia is generalized dystonia, focal dystonia, segmental dystonia, or acute dystonia. In some examples, the movement disorder is akathisia. In some examples, the akathisia is acute akathisia, chronic akathisia, pseudoakathisia, or withdrawal akathisia. In some examples, the subject is diagnosed with Parkinson's disease.

BRIEF DESCRIPTION OF THE FIGURES

[0020] **FIG. 1** shows a plasma concentration (ng/mL, linear scale) time profile of male Sprague Dawley rats following oral administration of Trapidil (diamond), Example 3-1 (square), 3-2 (triangle) and 3-3 (circle).

[0021] **FIG. 2** shows the same results as FIG. 1 in logarithmic scale.

[0022] **FIG. 3** shows a plasma concentration (ng/mL, linear scale) time profile of male Sprague Dawley rats following intravenous administration of Trapidil (diamond), Example 3-1 (square), 3-2 (triangle) and 3-3 (circle).

[0023] **FIG. 4** shows the same results as FIG. 3 in logarithmic scale.

DETAILED DESCRIPTION

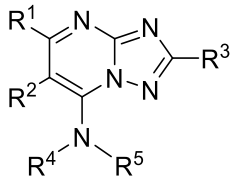
[0024] Provided herein, in certain embodiments, are Trapidil derivatives for treating Parkinson's disease and movement disorders associated with Parkinson's disease in a subject in need thereof. In some embodiments, the Trapidil derivative is isotopically-labelled. In some embodiments, the Trapidil-derivative is deuterated. In some embodiments, the movement disorder is an adverse drug reaction to a therapeutic agent used to treat Parkinson's disease. In some embodiments, the Trapidil derivatives of the present disclosure are administered to a subject in need alone, or in combination with an additional therapeutic agent. In some embodiments, the additional therapeutic agent is a dopamine precursor, dopamine agonist, Catechol O-methyl transferase (COMT) inhibitor, monoamine oxidase B (MAOB) inhibitor, or dopa decarboxylase inhibitor.

[0025] Parkinson's disease is the second most common neurodegenerative disorder. Parkinson's disease is associated with severe motor, cognitive, and emotional disturbances. Although the mechanism(s) underlying Parkinson's disease neurodegeneration remains unclear, the loss of dopaminergic terminals in the neostriatum and neuronal cell bodies underlie the motor symptoms. Parkinson's disease has pharmacological treatments primarily for motor symptoms and typically increase activation of the two dopamine receptors type: Dopamine 1 receptors (D1, D5) and Dopamine 2 receptors (D2-D4). Dopamine 1 receptors (D1R) are located on striatonigral neurons in the striatum and are activated by dopamine. Dopamine 2 receptors (D2R) are located on striatopallidal neurons in the striatum and are inhibited by dopamine. Pharmacological

CLAIMS

WHAT IS CLAIMED:

1. A compound of Formula (I) or a pharmaceutically salt, co-crystal or solvate thereof:



(I)

wherein:

R^1 is $-CH_3$, $-CD_3$, $-CHD_2$, or $-CH_2D$;

R^2 is hydrogen or -D;

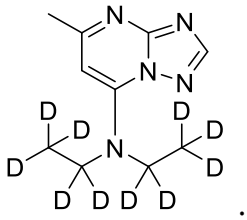
R^3 is hydrogen or -D;

R^4 is hydrogen, $-CH_2CH_3$; $-CD_2CD_3$; $-CD_2CH_3$; $-CH_2CD_3$; $-CDHCH_3$; $-CH_2CDH_2$; $-CH_2CD_2H$; $-CD_2CDH_2$; $-CD_2CD_2H$; $-CDHCD_3$; $-CDHCDH_2$; or $-CDHCD_2H$;

R^5 is hydrogen, $-CH_2CH_3$; $-CD_2CD_3$; $-CD_2CH_3$; $-CH_2CD_3$; $-CDHCH_3$; $-CH_2CDH_2$; $-CH_2CD_2H$; $-CD_2CDH_2$; $-CD_2CD_2H$; $-CDHCD_3$; $-CDHCDH_2$; or $-CDHCD_2H$; and

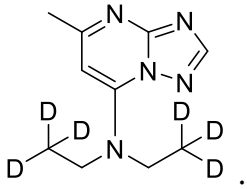
wherein at least one of R^1, R^2, R^3, R^4, or R^5, comprises at least one deuterium atom.

2. The compound of claim 1, wherein the compound or the pharmaceutically acceptable salt, co-crystal or solvate thereof is:



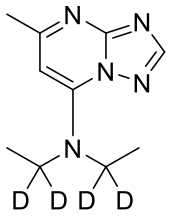
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3. The compound of claim 1, wherein the compound or the pharmaceutically acceptable salt, co-crystal or solvate thereof is:



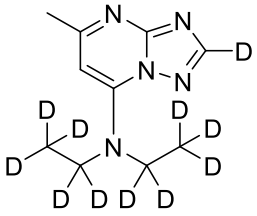
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4. The compound of claim 1, wherein the compound or the pharmaceutically acceptable salt, co-crystal or solvate thereof is:



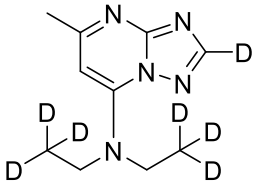
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5. The compound of claim 1, wherein the compound or the pharmaceutically acceptable salt, co-crystal or solvate thereof is:



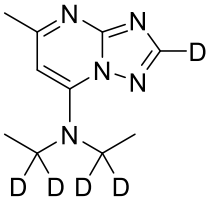
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6. The compound of claim 1, wherein the compound or the pharmaceutically acceptable salt, co-crystal or solvate thereof is:



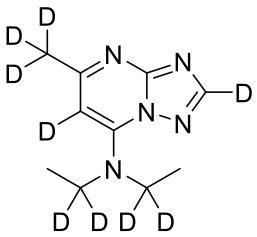
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7. The compound of claim 1, wherein the compound or the pharmaceutically acceptable salt, co-crystal or solvate thereof is:



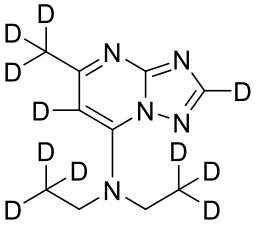
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8. The compound of claim 1, wherein the compound or the pharmaceutically acceptable salt, co-crystal or solvate thereof is:



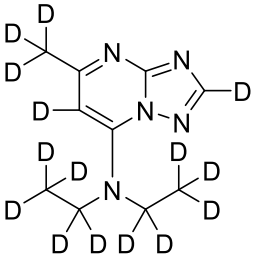
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9. The compound of claim 1, wherein the compound or <u>the</u> pharmaceutically acceptable salt, co-crystal or solvate thereof is:



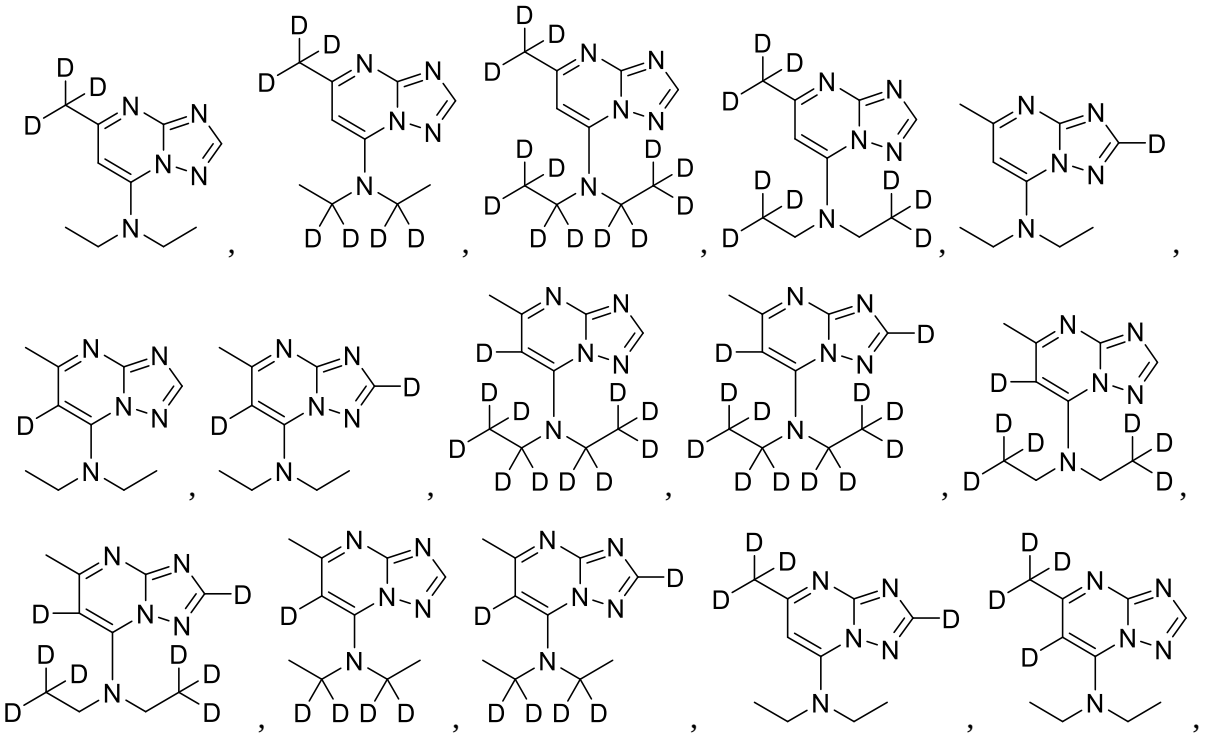
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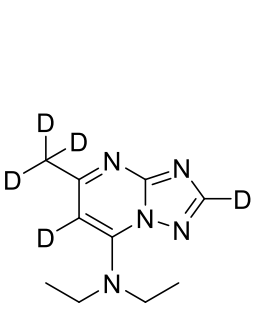
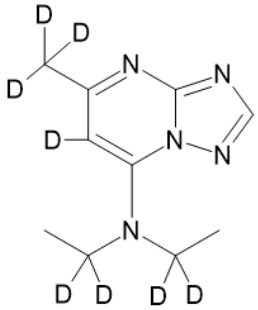
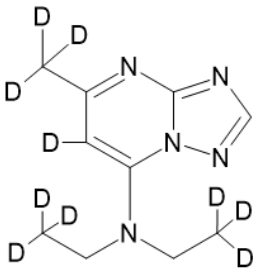
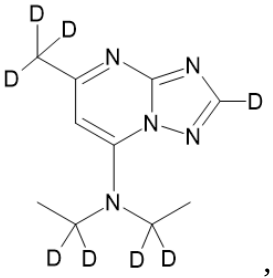
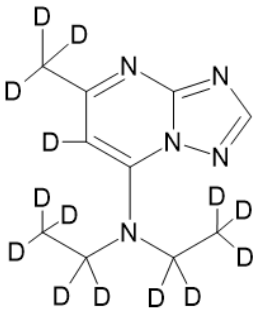
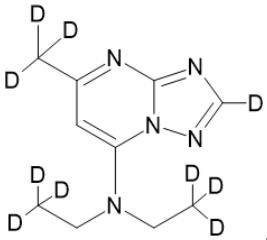
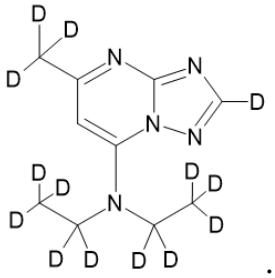
10. The compound of claim 1, wherein the compound or the pharmaceutically acceptable salt, co-crystal or solvate thereof is:



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11. The compound of claim 1, wherein the compound or the pharmaceutically acceptable salt, co-crystal or solvate thereof is:



, , , , , , or .

12. The compound of any one of claims 1-11, wherein positions represented as D of the compound or the pharmaceutically acceptable salt, co-crystal or solvate thereof have deuterium enrichment of at least 98%.
13. The compound of any one of claims 1-11, wherein positions represented as D of the compound or the pharmaceutically acceptable salt, co-crystal or solvate thereof have deuterium enrichment of at least 90%.
14. A pharmaceutical composition, comprising: a compound of any one of claims 1-13, or a pharmaceutically acceptable salt, co-crystal or solvate thereof, and a pharmaceutically acceptable carrier.