ISOTOPICALLY-LABELLED TRAPIDIL DERIVATIVES

CROSS-REFERENCE

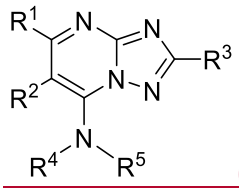
[0001] This application claims the benefit of U. S. Provisional Application Serial No. 63/000,347 filed March 26, 2020 and U. S. Provisional Application Serial No. 63/063,846 filed August 10, 2020 which are hereby incorporated by reference in their entirety.

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;

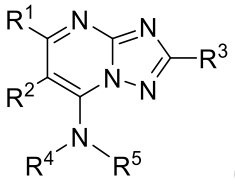
R^4 is hydrogen, $-CH_2CH_3$; $-CD_2CD_3$; $-CD_2CH_3$; $-CH_2CD_3$; $-CDHCH_3$; $-CH_2CDH_2$; $-CH_2CD_2H$; $-CD_2CDH_2$; $-CD_2CD_2H$; $-CDHCD_3$; $-CDHCDH_2$; or $-CDHCD_2H$;

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 ~~embodiment~~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;

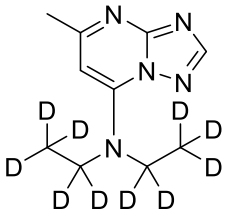
R^3 is hydrogen or -D;

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

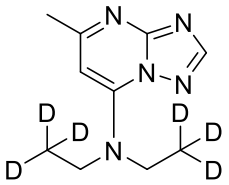
wherein at least one of R^1, R^2, R^3, R^4, or R^5, comprises at least one deuterium atom.

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

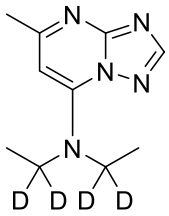


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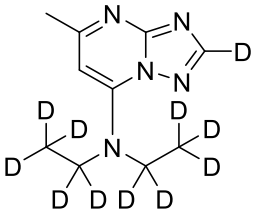
[0005] Provided herein, in certain ~~embodiment~~examples, is a compound or a pharmaceutically acceptable salt, co-crystal or solvate thereof, that is:



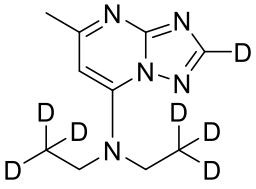
[0006] Provided herein, in certain ~~embodiment~~examples, is a compound or a pharmaceutically acceptable salt, co-crystal or solvate thereof, that is:



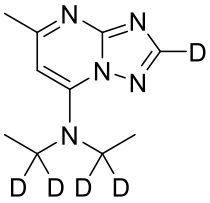
[0007] Provided herein, in certain ~~embodiment~~examples, is a compound or a pharmaceutically acceptable salt, co-crystal or solvate thereof, that is:



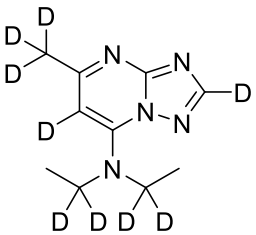
[0008] Provided herein, in certain ~~embodiment~~examples, is a compound or a pharmaceutically acceptable salt, co-crystal or solvate thereof, that is:



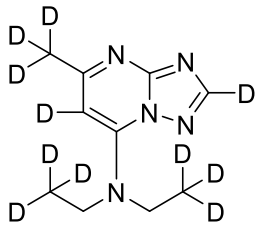
[0009] Provided herein, in certain ~~embodiment~~examples, is a compound or a pharmaceutically acceptable salt, co-crystal or solvate thereof, that is:



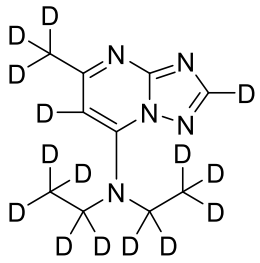
[0010] Provided herein, in certain ~~embodiment~~examples, is a compound or a pharmaceutically acceptable salt, co-crystal or solvate thereof, that is:



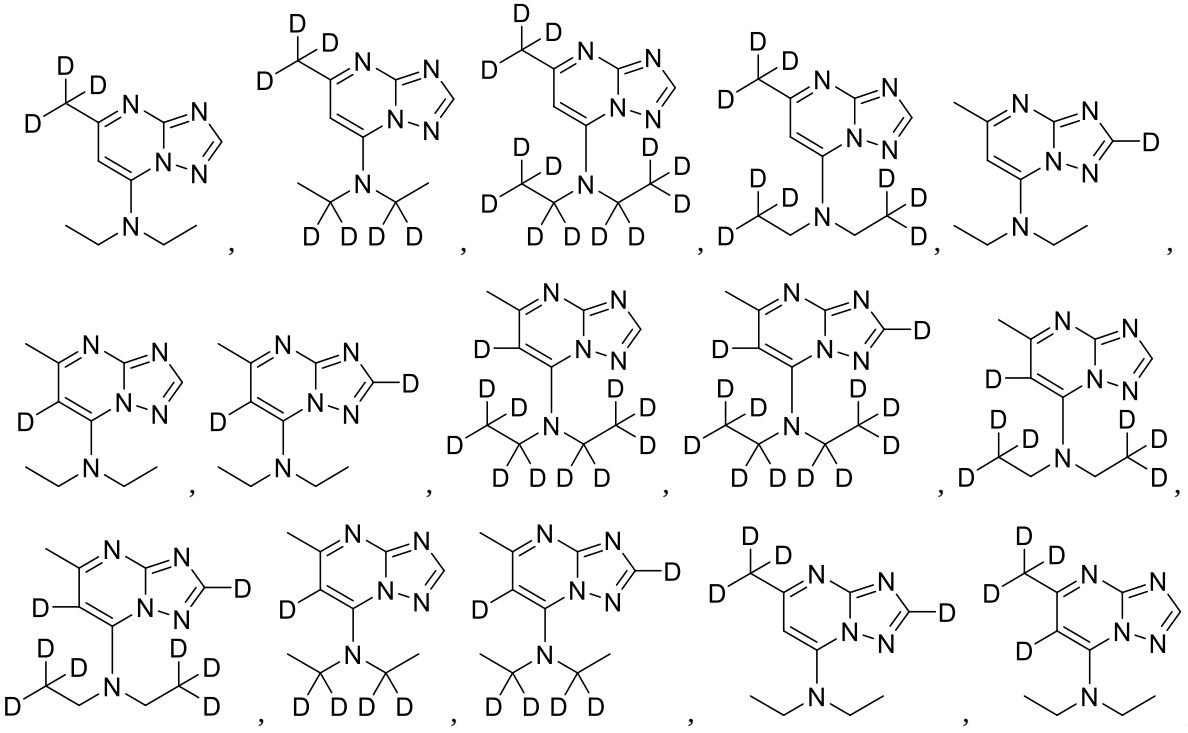
[0011] Provided herein, in certain ~~embodiment~~examples, is a compound or a pharmaceutically acceptable salt, co-crystal or solvate thereof, that is:

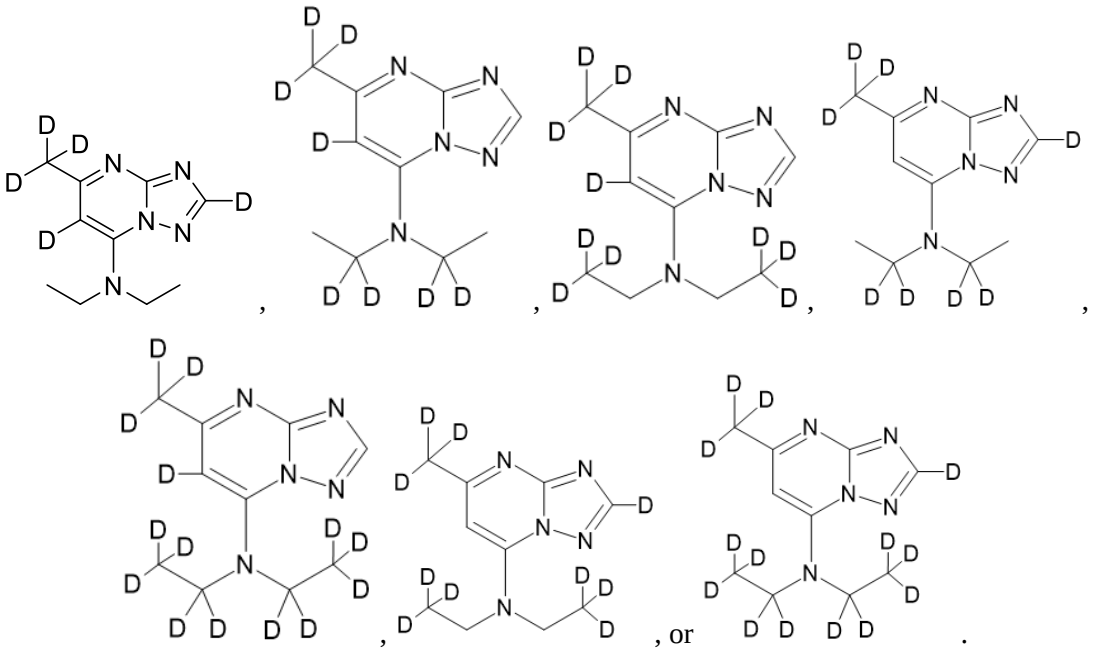


[0012] Provided herein, in certain ~~embodiment~~examples, is a compound or a pharmaceutically acceptable salt, co-crystal or solvate thereof, that is:



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





[0014] In some ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~examples, the additional therapeutic agent is a dopamine precursor. In some ~~embodiment~~examples, the dopamine precursor is levodopa. In some ~~embodiment~~examples, the additional therapeutic agent is a dopamine agonist. In some ~~embodiment~~examples, the dopamine agonist is pramipexole, ropinirole, rotigotine, pergolide, bromocriptine, piribedile, lisuride, or apomorphine, or a combination thereof. In some ~~embodiment~~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 ~~embodiment~~examples, the additional therapeutic agent is a Catechol O-methyl transferase (COMT) inhibitor. In some ~~embodiment~~examples, the COMT inhibitor is entacapone or tolcapone. In some ~~embodiment~~examples, the COMT inhibitor is entacapone, tolcapone, or opicapone. In some ~~embodiment~~examples, the additional therapeutic agent is a Catechol O-methyl transferase (COMT) inhibitor comprising entacapone, tolcapone, or opicapone. In some ~~embodiment~~examples, the additional therapeutic agent is a monoamine oxidase B (MAOB) inhibitor. In some ~~embodiment~~examples, the MAOB inhibitor is selegiline or rasagiline. In some ~~embodiment~~examples, the additional therapeutic agent is a monoamine oxidase B (MAOB) inhibitor comprising selegiline or rasagiline. In some ~~embodiment~~examples, the additional therapeutic agent is a dopa decarboxylase inhibitor. In some ~~embodiment~~examples, the dopa decarboxylase inhibitor is carbidopa or benserazide. In some ~~embodiment~~examples, the additional therapeutic agent is a dopa decarboxylase inhibitor comprising carbidopa or benserazide. In some ~~embodiment~~examples, in any of the methods provided herein, the movement disorder to be treated is dyskinesia. In some ~~embodiment~~examples, the dyskinesia is levodopa-induced dyskinesia (LID), diphasic dyskinesia, or peak-dose dyskinesia.

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

[0019] Provided herein, in certain ~~embodiment~~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 ~~embodiment~~examples, the additional therapeutic agent is a dopamine precursor. In some ~~embodiment~~examples, the dopamine precursor is levodopa. In some ~~embodiment~~examples, the additional therapeutic agent is a dopamine agonist. In some ~~embodiment~~examples, the dopamine agonist is pramipexole, ropinirole, rotigotine, pergolide, bromocriptine, piribedile, lisuride, or apomorphine. In some ~~embodiment~~examples, the additional therapeutic agent is a dopamine agonist comprising pramipexole, ropinirole, rotigotine, pergolide, bromocriptine, piribedile, lisuride, or apomorphine. In some ~~embodiment~~examples, the additional therapeutic agent is a Catechol O-methyl transferase (COMT) inhibitor. In some ~~embodiment~~examples, the COMT inhibitor is entacapone or tolcapone. In some ~~embodiment~~examples, the COMT inhibitor is entacapone, tolcapone, or opicapone. In some ~~embodiment~~examples, the additional therapeutic agent is a Catechol O-methyl transferase (COMT) inhibitor. In some ~~embodiment~~examples comprising entacapone, tolcapone, or opicapone. In some ~~embodiment~~examples, the additional therapeutic agent is a monoamine oxidase B (MAOB) inhibitor. In some ~~embodiment~~examples, the MAOB inhibitor is selegiline or rasagiline. In some ~~embodiment~~examples, the additional therapeutic agent is a monoamine oxidase B (MAOB) inhibitor comprising selegiline or rasagiline. In some ~~embodiment~~examples, the additional therapeutic agent is a dopa decarboxylase inhibitor. In some ~~embodiment~~examples, the dopa

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

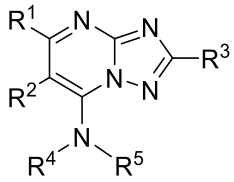
[0024] Provided herein, in certain embodiments, are Trapidil derivatives for treating Parkinson's disease and movement disorders associated with Parkinson's disease in a subject in need thereof. In some embodiments, the Trapidil derivative is isotopically-labelled. In some embodiments, the Trapidil-derivative 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;

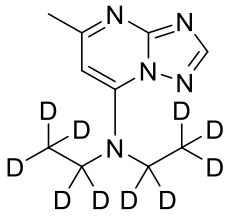
R^3 is hydrogen or -D;

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

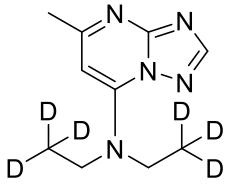
wherein at least one of R^1, R^2, R^3, R^4, or R^5, comprises at least one deuterium atom.

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



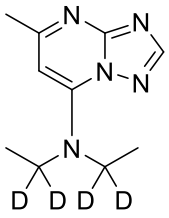
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3. The compound of claim 1, wherein the~~A~~ compound or the~~a~~ pharmaceutically acceptable salt, co-crystal or solvate thereof~~, that~~ is:

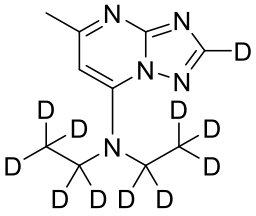


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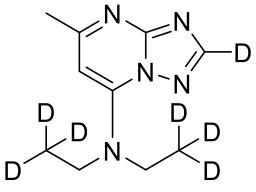
4. The compound of claim 1, wherein the~~A~~ compound or the~~a~~ pharmaceutically acceptable salt, co-crystal or solvate thereof~~, that~~ is:



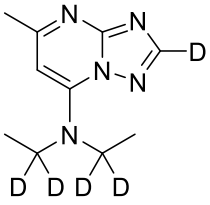
5. The compound of claim 1, wherein the~~A~~ compound or the~~a~~ pharmaceutically acceptable salt, co-crystal or solvate thereof~~, that~~ is:



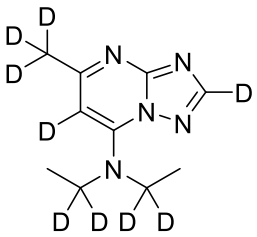
6. The compound of claim 1, wherein the~~A~~ compound or the~~a~~ pharmaceutically acceptable salt, co-crystal or solvate thereof~~, that~~ is:



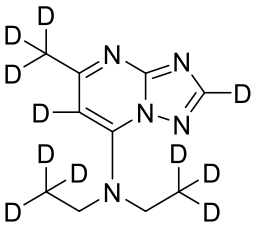
7. The compound of claim 1, wherein the~~A~~ compound or the~~a~~ pharmaceutically acceptable salt, co-crystal or solvate thereof~~, that~~ is:



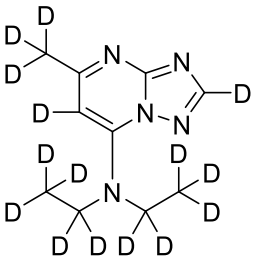
8. The compound of claim 1, wherein the~~A~~ compound or the~~a~~ pharmaceutically acceptable salt, co-crystal or solvate thereof~~, that~~ is:



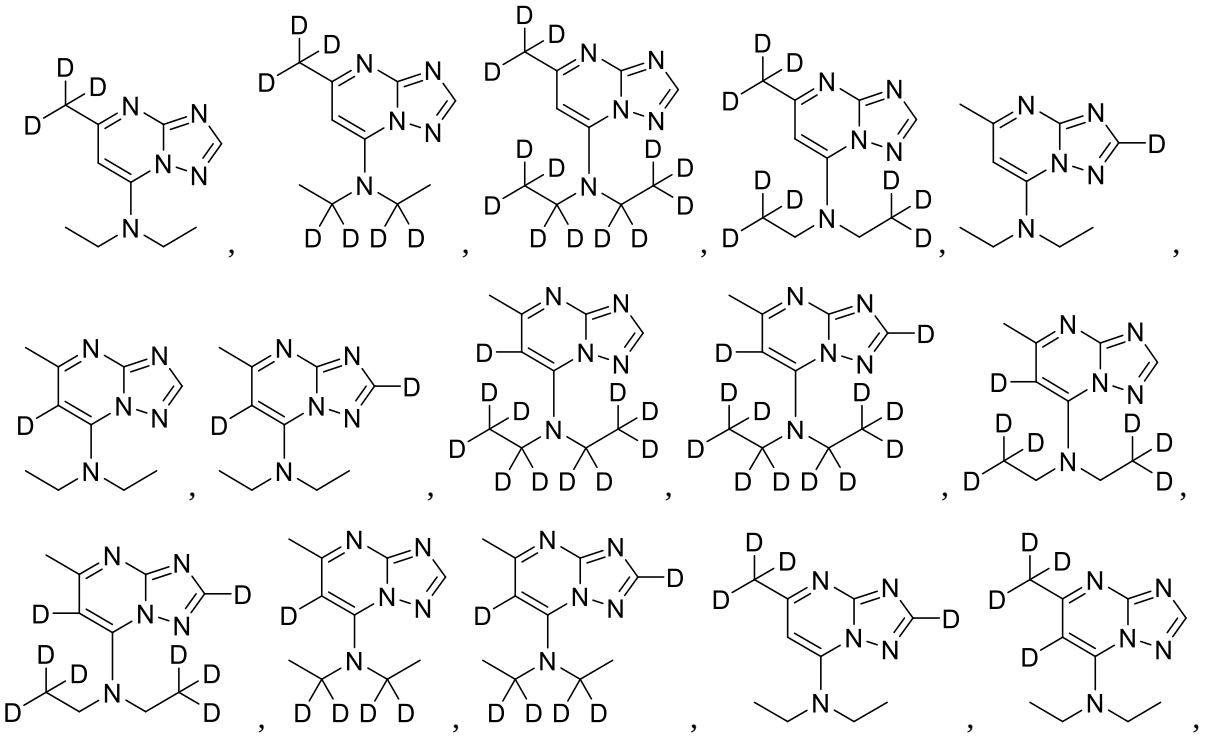
9. The compound of claim 1, wherein the~~A~~ compound or the~~a~~ pharmaceutically acceptable salt, co-crystal or solvate thereof~~, that~~ is:

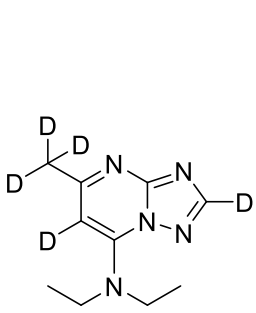
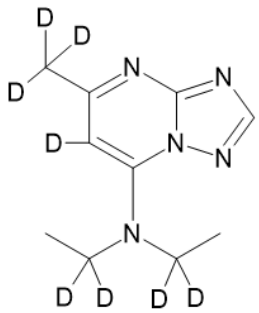
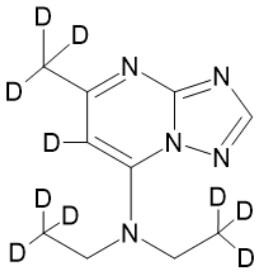
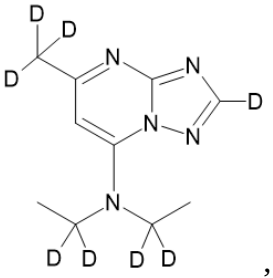
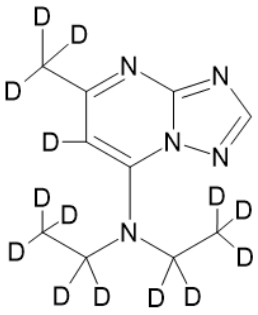
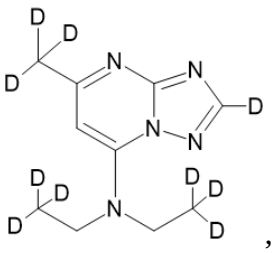
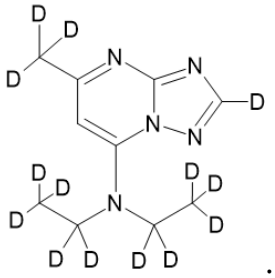


10. The compound of claim 1, wherein the~~A~~ compound or the~~a~~ pharmaceutically acceptable salt, co-crystal or solvate thereof~~, that~~ is:



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



, , , , , , or .

12. The compound of any one of claims 1-11, wherein positions represented as D of the compound or thea pharmaceutically acceptable salt, co-crystal or solvate thereof~~, wherein the positions represented as D~~ 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 thea pharmaceutically acceptable salt, co-crystal or solvate thereof~~, wherein the positions represented as D~~ 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.

~~15. 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 the compound of any one of claims 1-13 or the pharmaceutical composition of claim 14.~~

~~16. 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) the compound of any one of claims 1-13 or the pharmaceutical composition of claim 14, and (b) an additional therapeutic agent.~~

~~17. The method of claim 16, wherein the additional therapeutic agent is a dopamine precursor.~~

~~18. The method of claim 17, wherein the dopamine precursor is levodopa.~~

~~19. The method of claim 16, wherein the additional therapeutic agent is a dopamine agonist comprising pramipexole, ropinirole, rotigotine, pergolide, bromocriptine, piribedile, lisuride, or apomorphine, or a combination thereof.~~

20. The method of claim 16, wherein the additional therapeutic agent is a Catechol O-methyl transferase (COMT) inhibitor comprising entacapone, tolcapone, or opicapone.

21. The method of claim 16, wherein the additional therapeutic agent is a monoamine oxidase B (MAOB) inhibitor comprising selegiline or rasagiline.

22. The method of claim 16, wherein the additional therapeutic agent is a dopa decarboxylase inhibitor comprising carbidopa or benserazide.

23. The method of claim 15 or 16, wherein the movement disorder is dyskinesia.

24. The method of claim 23, wherein the dyskinesia is levodopa-induced dyskinesia (LID), diphasic dyskinesia, or peak-dose dyskinesia.

25. The method of claim 15 or 16, wherein the movement disorder is dystonia.

26. The method of claim 25, wherein the dystonia is generalized dystonia, focal dystonia, segmental dystonia, or acute dystonia.

27. The method of claim 15 or 16, wherein the movement disorder is akathisia.

28. The method of claim 27, wherein the akathisia is acute akathisia, chronic akathisia, pseudoakathisia, or withdrawal akathisia.

29. The method of claim 15 or 16, wherein the subject is diagnosed with Parkinson's disease.

30. 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) a compound of any one of claims 1-13 or the pharmaceutical composition of claim 14; and

    (b) an additional therapeutic agent for treating Parkinson's disease.

31. The pharmaceutical combination of claim 30, wherein the additional therapeutic agent is a dopamine precursor.

32. The pharmaceutical combination of claim 31, wherein the dopamine precursor is levodopa.

33. The pharmaceutical combination of claim 30, wherein the additional therapeutic agent is a dopamine agonist comprising pramipexole, ropinirole, rotigotine, pergolide, bromocriptine, piribedile, lisuride, or apomorphine.

34. The pharmaceutical combination of claim 30, wherein the additional therapeutic agent is a Catechol O-methyl transferase (COMT) inhibitor comprising entacapone, tolcapone, or opicapone.

35. The pharmaceutical combination of claim 30, wherein the additional therapeutic agent is a monoamine oxidase B (MAOB) inhibitor comprising selegiline or rasagiline.

~~36. The pharmaceutical combination of claim 30, wherein the additional therapeutic agent is a dopa decarboxylase inhibitor comprising carbidopa or benserazide.~~

~~37. The pharmaceutical combination of claim 30, wherein the movement disorder is dyskinesia.~~

~~38. The pharmaceutical combination of claim 37, wherein the dyskinesia is levodopa-induced dyskinesia (LID), diphasic dyskinesia, or peak-dose dyskinesia.~~

~~39. The pharmaceutical combination of claim 30, wherein the movement disorder is dystonia.~~

~~40. The pharmaceutical combination of claim 39, wherein the dystonia is generalized dystonia, focal dystonia, segmental dystonia, or acute dystonia.~~

~~41. The pharmaceutical combination of claim 30, wherein the movement disorder is akathisia.~~

~~42. The pharmaceutical combination of claim 41, wherein the akathisia is acute akathisia, chronic akathisia, pseudoakathisia, or withdrawal akathisia.~~

~~43. The pharmaceutical combination of claim 30, wherein the subject is diagnosed with Parkinson's disease.~~