potentially interfere with quantification of cortical uptake of the tracer. See Xia, C. F., et al., *Alzheimer's Dement.* **2013** *9* (6), 666-76; Zhang, W., et al., *J. Alzheimer's Disease:JAD* **2012** *31* (3), 601-12; Chien, D. T., et al., *J. Alzheimer's Disease:JAD* **2013** *34* (2), 457-68; and Chien, D. T., et al., *J. Alzheimer's Disease:JAD* **2014** *38* (1), 171-84.

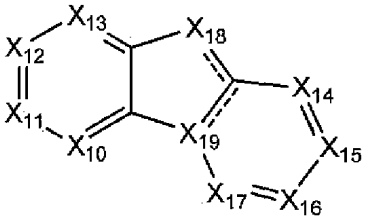
Currently there is a need for additional detectable compounds that bind to tau. In particular, there is a need for detectable compounds with improved *in vivo* properties, such as improved metabolism characteristics.

SUMMARY

The disclosure includes a deuterated detectable compound, or salt thereof, that binds to a tau protein.

The disclosure includes a compound of formula (I) or formula (V):

$$R^1\text{-}A\text{-}R^2 \qquad (I),$$



(V),

or a salt thereof, wherein:

R^1 is phenyl, naphthyl, 6-membered heteroaryl, 9- or 10-membered bicyclic heterocyclyl, 12-13 membered tricyclic carbocyclyl, or 12-13 membered tricyclic heterocyclyl, wherein R^1 is optionally substituted with one or more groups R^a, wherein R^1 is attached to the remainder of the compound of formula (I) at any synthetically feasible position;

A is absent, C_{1-4}alkylene, C_{3-6}cycloalkylene, C_{2-4}alkenylene, or C_{2-4}alkynylene;

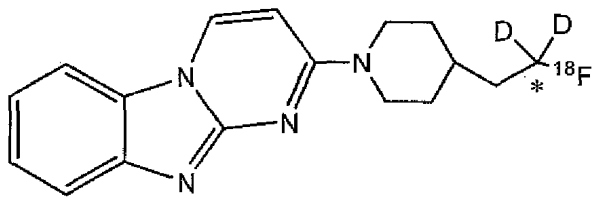
R^2 is 6-, 9-, or 10-membered carbocyclyl or a 5-, 6-, 9-, or 10-membered heterocyclyl, which carbocyclyl and heterocyclyl is optionally substituted with one or more groups R^b, wherein R^2 is attached to the remainder of the compound of formula (I) at any synthetically feasible position;

each X_{10}-X_{17} is independently CH or N;

X_{18} is CH, N, O, or S; and

X_{19} is CH, C, or N;

One aspect includes a deuterated compound having the formula (Ie):

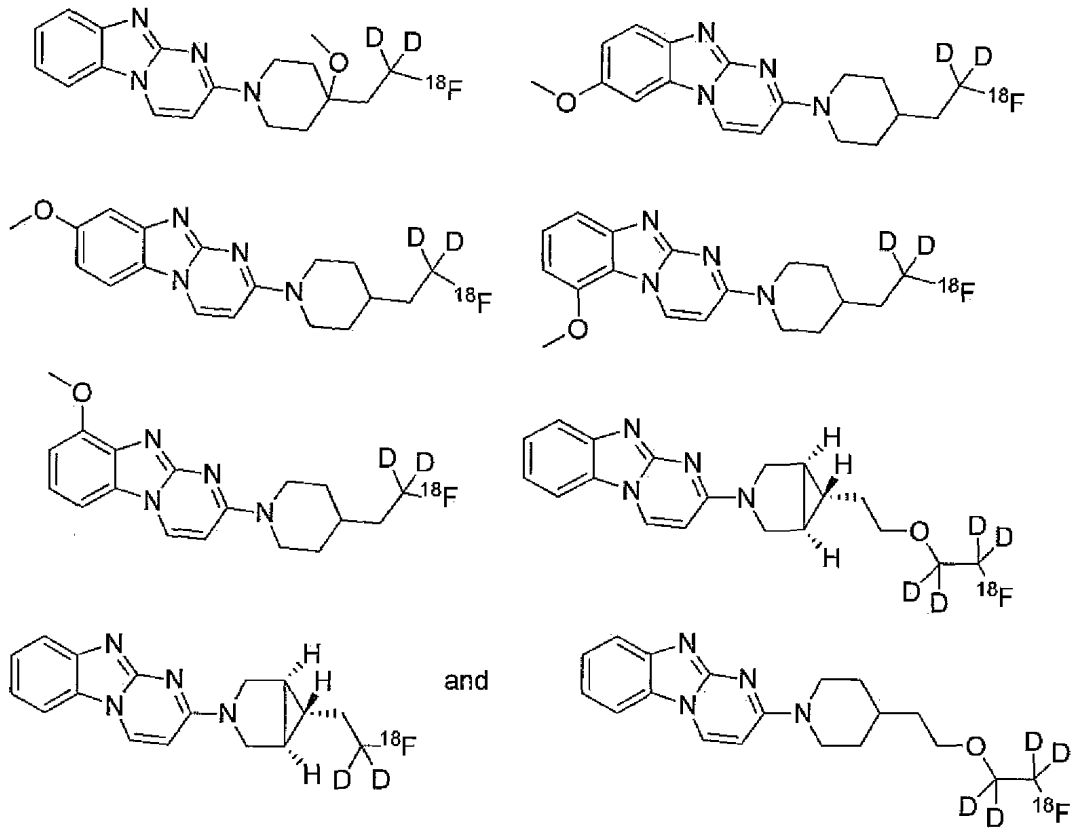


(Ie)

or a salt thereof,

wherein the carbon marked * has a deuterium isotopic enrichment factor of at least 3500.

Another aspect includes a deuterated compound, which is a compound selected from:



and

or a salt thereof.

Another aspect includes a pharmaceutical composition comprising a deuterated compound as described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier.

The disclosure includes a method for detecting neurofibrillary tangles and/or senile plaques in an animal comprising administering a deuterated compound comprising an imaging isotope as described herein, or a pharmaceutically acceptable salt thereof, to the animal, and measuring the radioactive signal of the compound. Another aspect includes a method for detecting neurofibrillary tangles and/or senile plaques in an animal comprising measuring the radioactive signal of a compound as described herein, or a pharmaceutically acceptable salt thereof, that had been administered to the animal.

The disclosure includes a method of detecting a neurological disorder associated with amyloid plaque and/or tau protein aggregation in an animal comprising administering a deuterated compound comprising an imaging isotope as described herein, or a pharmaceutically acceptable salt thereof, to the animal, and measuring the radioactive signal of the compound, which is associated with amyloid deposits and/or tau protein aggregates. Another aspect includes a method of detecting a neurological disorder associated with amyloid plaque and/or tau protein aggregation in an animal comprising measuring the radioactive signal of a compound as described herein, or a pharmaceutically acceptable salt thereof which is associated with amyloid deposits and/or tau protein aggregates.

The disclosure includes a method of detecting Alzheimer's disease associated with amyloid plaque and/or tau protein aggregation in an animal comprising administering a deuterated compound comprising an imaging isotope as described herein, or a pharmaceutically acceptable salt thereof, to the animal, and measuring the radioactive signal of the compound associated with amyloid deposits and/or tau protein aggregates. Another aspect includes a detecting Alzheimer's disease associated with amyloid plaque and/or tau protein aggregation in an animal comprising measuring the radioactive signal of a compound as described herein, or a pharmaceutically acceptable salt thereof, which is associated with amyloid deposits and/or tau protein aggregates.

The disclosure includes a method of detecting Alzheimer's disease associated with tau protein aggregation comprising administering a deuterated compound comprising an imaging isotope as described herein, or a pharmaceutically acceptable salt thereof, to the animal, and measuring the radioactive signal of the compound associated with tau protein aggregates. Another aspect includes a method of detecting Alzheimer's disease associated with tau protein aggregation comprising measuring the radioactive signal of a

compound as described herein, or a pharmaceutically acceptable salt thereof, which is associated with tau protein aggregates.

The disclosure includes a deuterated compound as described herein, or a pharmaceutically acceptable salt thereof, for use in medical diagnosis or treatment. Another aspect includes a compound as described herein, or a pharmaceutically acceptable salt thereof, for use in medical diagnosis or treatment.

The disclosure includes a deuterated compound as described herein, or a pharmaceutically acceptable salt thereof, for use in detecting neurofibrillary tangles and/or senile plaques. Another aspect includes a compound as described herein, or a pharmaceutically acceptable salt thereof, for use in detecting neurofibrillary tangles and/or senile plaques.

The disclosure includes a deuterated compound as described herein, or a pharmaceutically acceptable salt thereof, for use in detecting a neurological disorder. Another aspect includes a compound as described herein, or a pharmaceutically acceptable salt thereof, for use in detecting a neurological disorder.

The disclosure includes a deuterated compound as described herein, or a pharmaceutically acceptable salt thereof, for use in detecting Alzheimer's disease. Another aspect includes a compound as described herein, or a pharmaceutically acceptable salt thereof, for use in detecting Alzheimer's disease.

The disclosure includes the use of a deuterated compound as described herein, or a pharmaceutically acceptable salt thereof, to prepare a medicament for detecting neurofibrillary tangles and/or senile plaques in an animal. Another aspect includes a use of a compound as described herein, or a pharmaceutically acceptable salt thereof, to prepare a medicament for detecting neurofibrillary tangles and/or senile plaques in an animal.

The disclosure includes the use of a deuterated compound as described herein, or a pharmaceutically acceptable salt thereof, to prepare a medicament for detecting a neurological disorder in an animal. Another aspect includes a use of a compound as described herein, or a pharmaceutically acceptable salt thereof, to prepare a medicament for detecting a neurological disorder in an animal.

The disclosure includes the use of a deuterated compound as described herein, or a pharmaceutically acceptable salt thereof, to prepare a medicament for detecting Alzheimer's disease in an animal. Another aspect includes a use of a compound as described herein, or a pharmaceutically acceptable salt thereof, to prepare a medicament for detecting Alzheimer's disease in an animal.

The disclosure includes a method of detecting progressive supranuclear palsy associated with amyloid plaque and/or tau protein aggregation in an animal, comprising administering a deuterated compound comprising an imaging isotope as described herein, or a pharmaceutically acceptable salt thereof, to the animal, and measuring the radioactive signal of the compound associated with amyloid deposits and/or tau protein aggregates. Another aspect includes a method of detecting progressive supranuclear palsy associated with amyloid plaque and/or tau protein aggregation in an animal, comprising measuring the radioactive signal of a compound as described herein, or a pharmaceutically acceptable salt thereof, which is associated with amyloid deposits and/or tau protein aggregates.

The disclosure includes a method of detecting progressive supranuclear palsy associated with tau protein aggregation, comprising administering a deuterated compound comprising an imaging isotope as described herein, or a pharmaceutically acceptable salt thereof, to the animal, and measuring the radioactive signal of the compound associated with tau protein aggregates. Another aspect includes a method of detecting progressive supranuclear palsy associated with tau protein aggregation, comprising measuring the radioactive signal of a compound as described herein, or a pharmaceutically acceptable salt thereof, which is associated with tau protein aggregates.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: Autoradiographic evaluation of binding properties of [**A**] and [**A**]-d2 using human brain tissues.

Figure 2: In vitro assessment of metabolic stability of [^{18}F][**A**]-d2 and [^{18}F][**A**] using mouse and human liver microsomes. The formation of [^{18}F]fluoride (**2A** and **2B**) and amount of remaining parent compound were measured (**2C** and **2D**) at 5, 15 and 45 min.

Figure 3: Human and mouse liver microsome assay performed with non-radiolabeled **[A]** and **[A]**-d2 showed higher stability of [**A**]-d2 and slower metabolism of both compounds in presence of human liver microsomes.

Figure 4: Pre-clinical PET imaging in mice from Example 6 below.

Figure 5: Radio-HPLC chromatogram of purified [^{18}F][**A**]-d2.

Figure 6: Radio-HPLC chromatogram of purified [^{18}F][**A**].

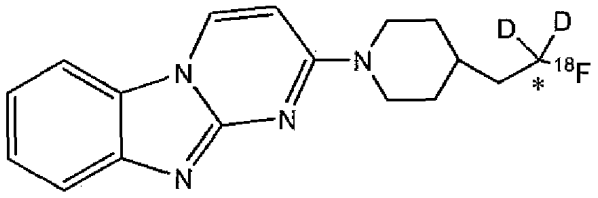
Figures 7A-7F: In vitro assessment of metabolic stability of [^{18}F][**A**]-d2 and [^{18}F][**A**] (n = 3) using human, rhesus or mouse liver microsomes. The formation of [^{18}F]fluoride (**7A-7C**) and amount of remaining parent compound were measured (**7D-7F**) at 5, 15 and 45 min.

Figures 8A, 8B: [^{18}F][**A**]-d2, [^{18}F][**A**] or ^{18}F T807 (370 MBq (10 mCi)) was intravenous bolus injected into an anesthetized rhesus, and dynamic PET data acquired over 240 minutes. Standard Uptake Values ([Radioactivity]/(injected dose/body weight)) were measured in the indicated structures from the reconstructed PET data. Data was collected

CLAIMS

We claim:

1. A deuterated compound having the formula (Ie):

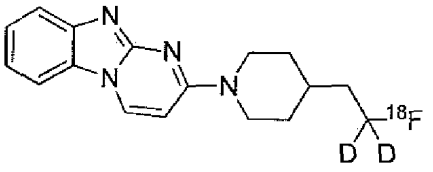


(Ie)

or a salt thereof,

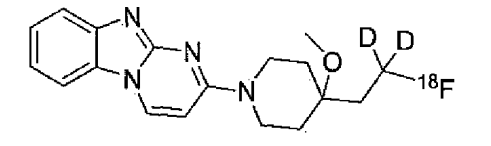
wherein the carbon marked * has a deuterium isotopic enrichment factor of at least 3500.

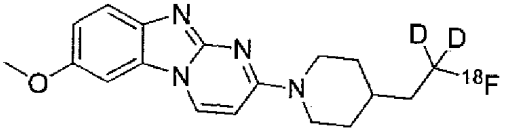
2. The deuterated compound of claim 1 which is the compound:

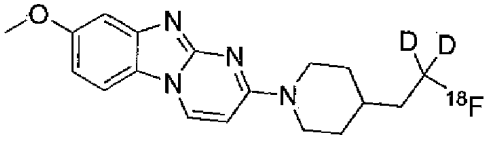


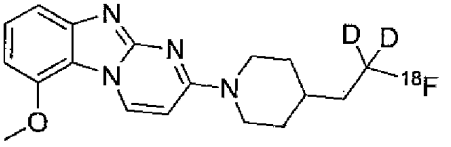
or a salt thereof.

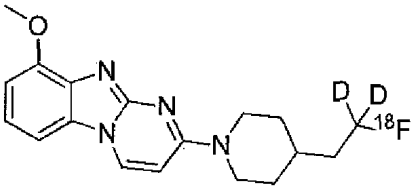
3. A deuterated compound, which is a compound selected from:

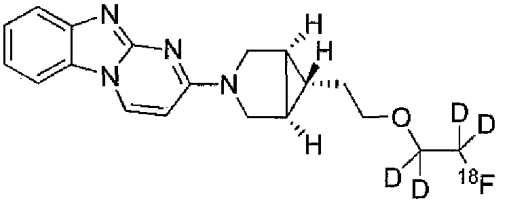


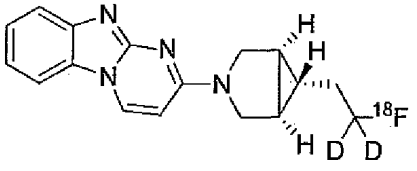




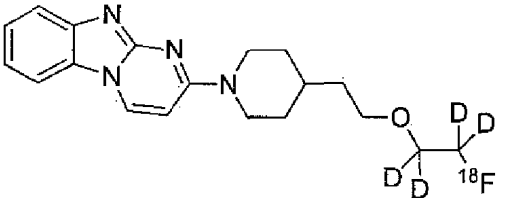








and



or a salt thereof.

4. A pharmaceutical composition comprising a deuterated compound as described in any one of claims 1-3, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier.

5. A method for detecting neurofibrillary tangles and/or senile plaques in an animal comprising measuring the radioactive signal of a compound as described

in any one of claims 1-3, or a pharmaceutically acceptable salt thereof, that had been administered to the animal.

6. The method of claim 5 wherein the detection is by gamma imaging.

7. A method of detecting a neurological disorder associated with amyloid plaque and/or tau protein aggregation in an animal comprising measuring the radioactive signal of a compound as described in any one of claims 1-3, or a pharmaceutically acceptable salt thereof which is associated with amyloid deposits and/or tau protein aggregates.

8. A method of detecting Alzheimer's disease associated with amyloid plaque and/or tau protein aggregation in an animal comprising measuring the radioactive signal of a compound as described in any one of claims 1-3, or a pharmaceutically acceptable salt thereof, which is associated with amyloid deposits and/or tau protein aggregates.

9. A method of detecting Alzheimer's disease associated with tau protein aggregation comprising measuring the radioactive signal of a compound as described in any one of claims 1-3, or a pharmaceutically acceptable salt thereof, which is associated with tau protein aggregates.

10. A compound as described in any one of claims 1-3, or a pharmaceutically acceptable salt thereof, for use in medical diagnosis or treatment.

11. A compound as described in any one of claims 1-3, or a pharmaceutically acceptable salt thereof, for use in detecting neurofibrillary tangles and/or senile plaques.

12. A compound as described in any one of claims 1-3, or a pharmaceutically acceptable salt thereof, for use in detecting a neurological disorder.

13. A compound as described in any one of claims 1-3, or a pharmaceutically acceptable salt thereof, for use in detecting Alzheimer's disease.

14. The use of a compound as described in any one of claims 1-3, or a pharmaceutically acceptable salt thereof, to prepare a medicament for detecting neurofibrillary tangles and/or senile plaques in an animal.

15. The use of a compound as described in any one of claims 1-3, or a pharmaceutically acceptable salt thereof, to prepare a medicament for detecting a neurological disorder in an animal.

16. The use of a compound as described in any one of claims 1-3, or a pharmaceutically acceptable salt thereof, to prepare a medicament for detecting Alzheimer's disease in an animal.

17. A method of detecting progressive supranuclear palsy associated with amyloid plaque and/or tau protein aggregation in an animal, comprising measuring the radioactive signal of a compound as described in any one of claims 1-3, or a pharmaceutically acceptable salt thereof, which is associated with amyloid deposits and/or tau protein aggregates.

18. A method of detecting progressive supranuclear palsy associated with tau protein aggregation, comprising measuring the radioactive signal of a compound as described in any one of claims 1-3, or a pharmaceutically acceptable salt thereof, which is associated with tau protein aggregates.