

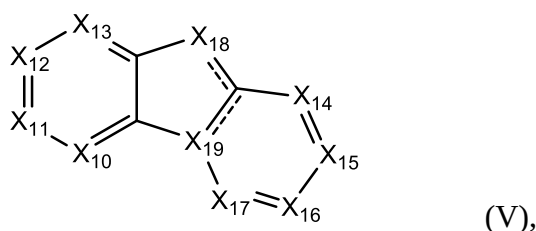
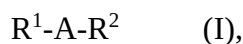
potentially interfere with quantification of cortical uptake of the tracer. See Xia, C. F., et al., *Alzheimer's Dement.* **2013** 9 (6), 666-76; Zhang, W., et al., *J. Alzheimer's Disease:JAD* **2012** 31 (3), 601-12; Chien, D. T., et al., *J. Alzheimer's Disease:JAD* **2013** 34 (2), 457-68; and Chien,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



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;

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

5 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.

10 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.

15 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.

20 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.

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

25 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.

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

30 The disclosure includes a deuterated 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.

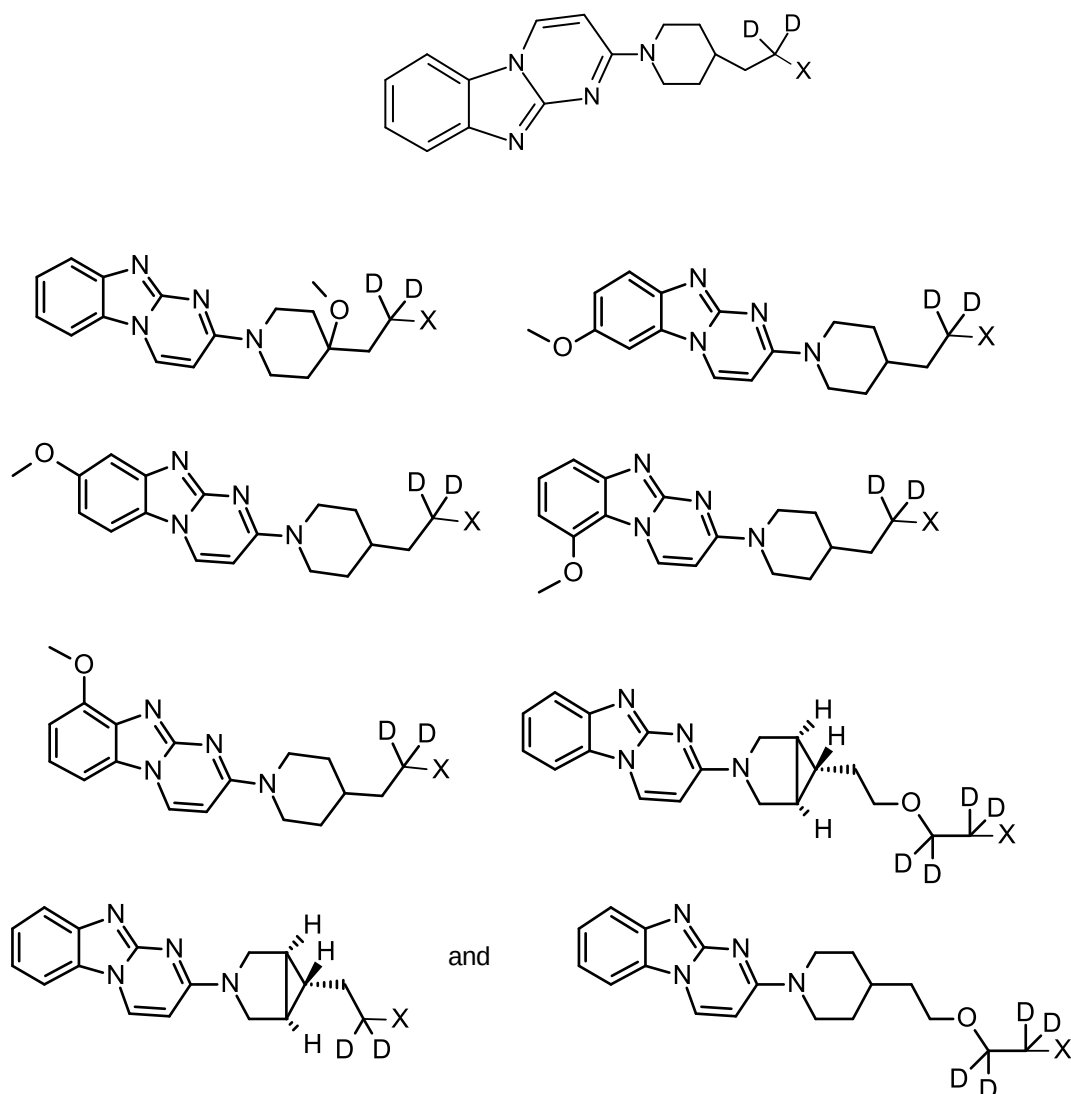
The disclosure includes the use of a deuterated compound as described herein, or a pharmaceutically acceptable salt thereof, to prepare a medicament for detecting a neurological disorder in an animal.

5 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.

10 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.

15 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.

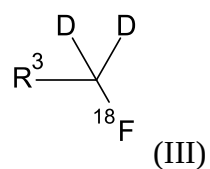
In one aspect, the disclosure includes a compound selected from:



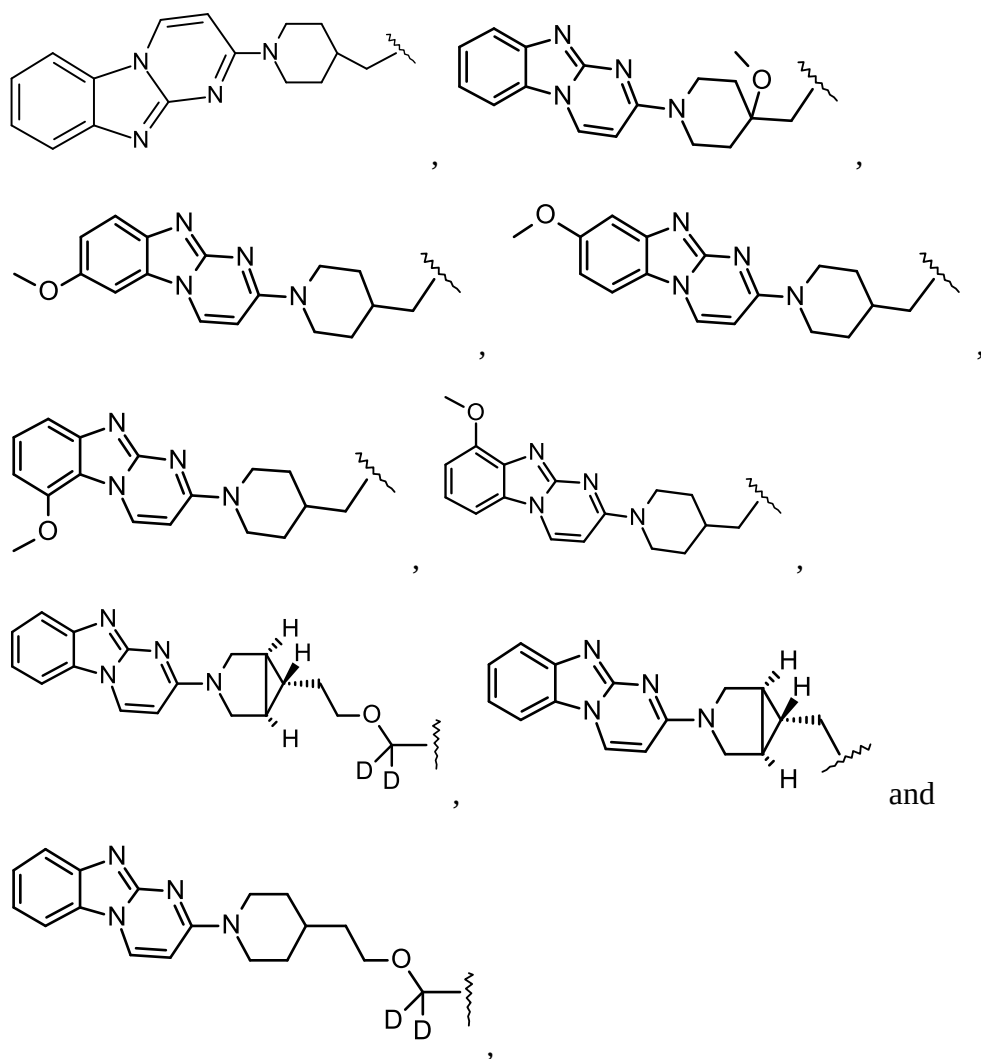
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wherein X is bromine, hydroxy or a toluenesulfonyl group, and salts thereof.

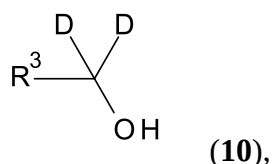
In another aspect, the disclosure includes a method for the preparation of a compound of formula (III)



10 wherein R^3 is a group selected from



the method comprising the ^{18}F fluorination of a compound of formula (10)



and optionally converting the compound obtained into a salt thereof.

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**].

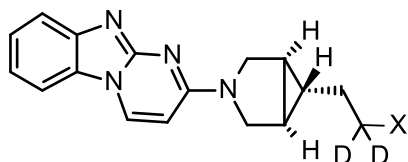
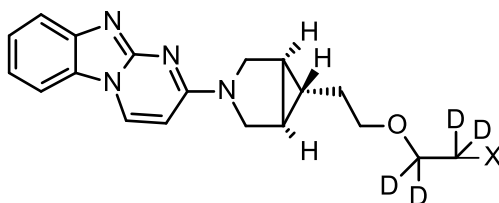
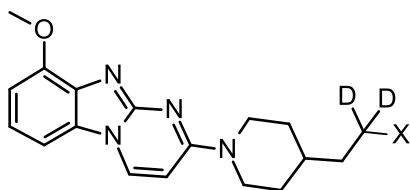
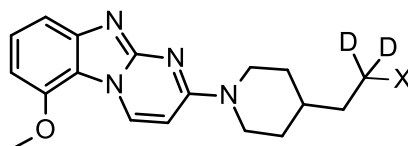
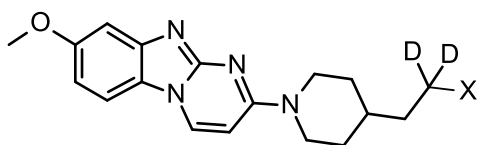
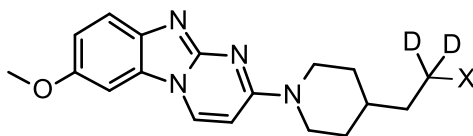
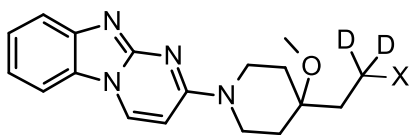
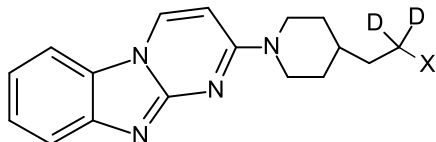
5 **Figures 7A-7F:** In vitro assessment of metabolic stability of [^{18}F][**A**]-d2 and [^{18}F][**A**] (n = 3) using human, rhesus or mouse liver microsomes. The formation of [^{18}F]fluoride (**7A-7C**) and amount of remaining parent compound were measured (**7D-7F**) at 5, 15 and 45 min.

10 **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

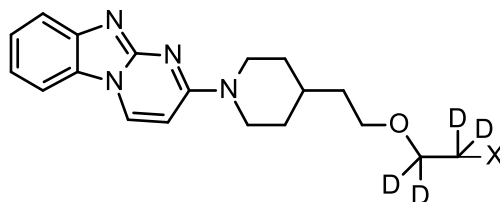
CLAIMS

We claim:

- 5 1. A compound selected from:



and

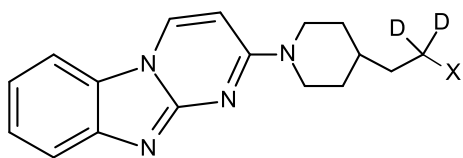


- 10 wherein X is bromine, hydroxy or a toluenesulfonyl group, and salts thereof.

2. A compound according to claim 1, wherein X is bromine or hydroxy, and salts thereof.

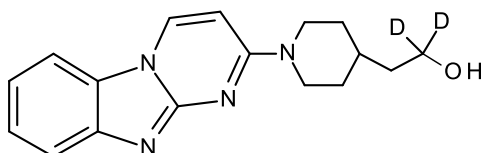
- 15 3. A compound according to claim 1, wherein X is hydroxy, and salts thereof.

4. A compound according to claim 1, which is



wherein X is bromine or hydroxy, and salts thereof.

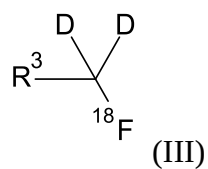
5. A compound according to claim 1, which is



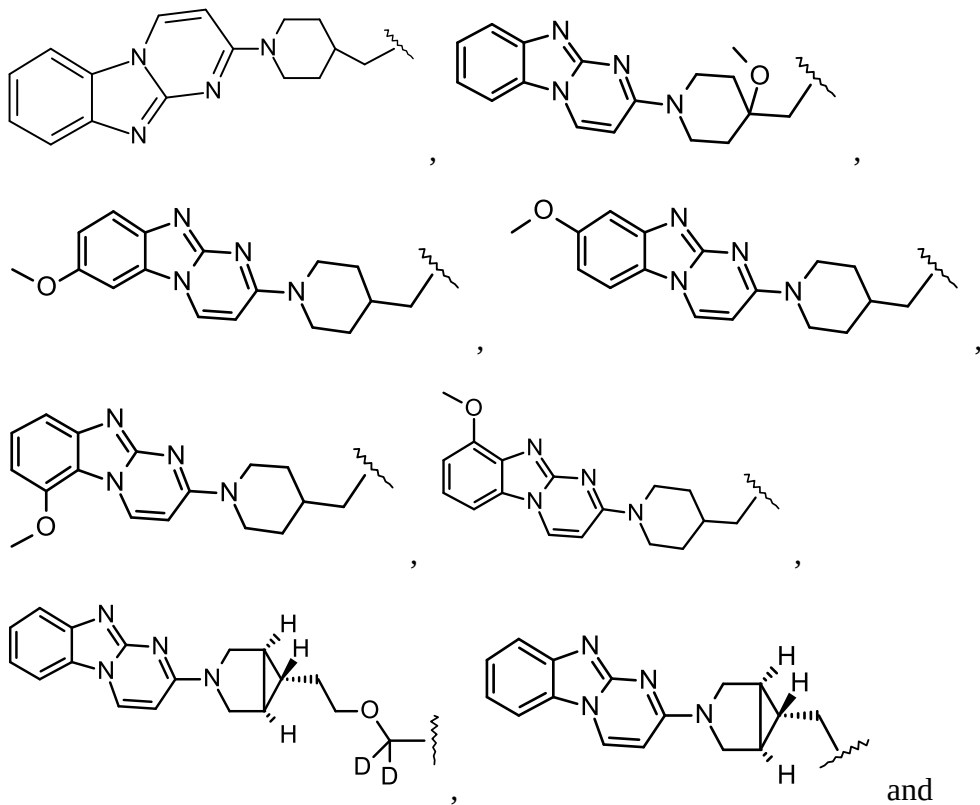
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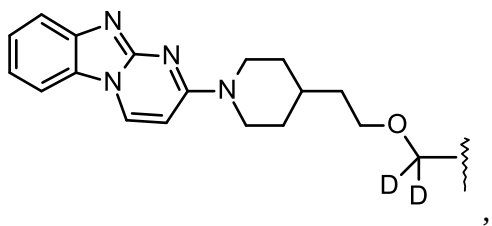
and salts thereof.

6. A method for the preparation of a compound of formula (III)

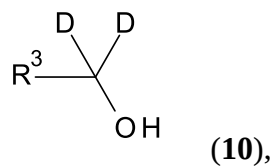


10 wherein R³ is a group selected from





the method comprising the ^{18}F fluorination of a compound of formula **(10)**



and optionally converting the compound obtained into a salt thereof.

5

7. The method according to claim 6, wherein R^3 is

