

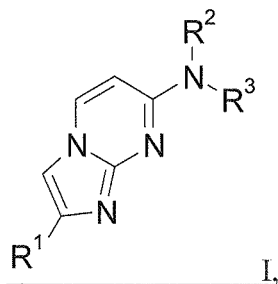
tangle-predominant dementia, Pick's disease, frontotemporal lobar degeneration (FTLD), Down's syndrome and others.

A direct correlation has been established between the progressive involvement of neocortical areas and the increasing severity of dementia, suggesting that pathological tau aggregates such as NFTs are a reliable marker of the neurodegenerative process. The degree of NFT involvement in AD is defined by Braak stages (Acta Neuropathol. 1991, 82, 239-259). Braak stages I and II are defined when NFT involvement is confined mainly to the transentorhinal region of the brain, stages III and IV are diagnosed when limbic regions such as the hippocampus are involved, and stages V and VI when extensive neocortical involvement is found.

Presently, detection of tau aggregates is only possible by histological analysis of biopsy or autopsy materials. *In vivo* imaging of tau pathology would provide novel insights into deposition of tau aggregates in the human brain and allow to non-invasively examine the degree of tau pathology, quantify changes in tau deposition over time, assess its correlation with cognition and analyze the efficacy of an anti-tau therapy. Potential ligands for detecting tau aggregates in the living brain must cross the blood-brain barrier and possess high affinity and specificity for tau aggregates. To this end, successful neuroimaging radiotracers must have appropriate lipophilicity (logD 1-3) and low molecular weight (<450), show rapid clearance from blood and low non-specific binding.

The object of the ~~embodiments disclosed herein present application~~ is to find an imaging tool which will improve diagnosis by identifying potential patients with excess of tau aggregates in the brain, which may be likely to develop Alzheimer's disease. It will also be useful to monitor the progression of the disease. When an anti-tau aggregate drug become available, imaging tau tangles in the brain may provide an essential tool for monitoring treatment.

In one aspect, there is provided a compound of formula



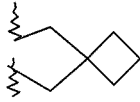
wherein

R^1 is phenyl, optionally substituted by one or two substituents, selected from ^3H , halogen, lower alkyl, di-methyl-amino, $NHC(O)$ -lower alkyl, $C(O)O$ -lower alkyl, lower alkoxy, $OC(^3H)_3$, $O^{11}CH_3$, $OCH_2CH_2^{18}F$, lower alkoxy substituted by halogen, hydroxy, lower alkyl substituted by hydroxy, S-lower alkyl, or by a heterocyclyl group; or is benzo[d][1,3]dioxol-5-yl, 2,3-dihydrobenzo[b][1,4]dioxin-6-yl, indolin-2-one, or is heteroaryl, selected from the group consisting of thiophenyl, benzofuranyl, benzothiophenyl, pyrazinyl, or benzothiazolyl;

R^2 is hydrogen, lower alkyl or lower alkyl substituted by halogen;

10 R^3 is lower alkyl, $C(^3H)_3$, $^{11}CH_3$, lower alkyl substituted by halogen, $-(CH_2)_2-O$ -lower alkyl substituted by halogen or cycloalkyl; or

R^2 and R^3 form together with the N-atom to which they are attach a ring containing $-CH_2CH_2CHRCH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2-NR-CH_2CH_2-$,

$-CH_2CH_2-O-CH_2CH_2-$, $-CH_2CH_2CHRCH_2-$, $-CH_2CHRCH_2-$ or  ;

15 R is hydrogen, halogen, lower alkyl substituted by halogen or lower alkoxy; or a pharmaceutically acceptable acid addition salt, a racemic mixture or its corresponding enantiomer and/or optical isomers thereof.

In another aspect, there is provided a compound of formula I as defined herein for use in binding and imaging tau aggregates, beta-amyloid aggregates or alpha-synuclein aggregates.

20 In another aspect, there is provided a compound of formula I as defined herein for use in binding and imaging tau aggregates in Alzheimer patients.

In another aspect, there is provided a compound of formula I as defined herein for use in a tau-binding study.

25 In another aspect, there is provided a compound of formula I as defined herein for use in diagnostic imaging of tau-aggregates in the brain of a mammal.

In another aspect, there is provided a pharmaceutical composition comprising a compound of formula I as defined herein and a pharmaceutical acceptable carrier.

~~A further object of the present invention also relates to~~ is a method of imaging tau-aggregate deposits, comprising

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- introducing into a mammal a detectable quantity of a composition
 - allowing sufficient time for the compound of formula I to be associated with tau-aggregate deposits, and
 - detecting the compound associated with one or more tau-aggregate deposits.

In another aspect, there is provided a method of imaging tau-aggregate deposits, comprising detecting a compound of formula I that has associated with one or more tau-aggregate deposits after a detectable quantity of a composition as defined herein has been introduced into a mammal and allowed to associate with the tau-aggregate deposits.

- 5 In another aspect, there is provided the use of a compound as defined herein for diagnostic imaging of tau-aggregate deposits in the brain of a mammal.
- A further ~~object embodiment~~ of the present ~~invention~~ disclosure is a pharmaceutical composition, containing compounds of formula I and pharmaceutical acceptable carriers, which may be used for identifying potential patients.

9. A compound of formula I according to any one of claims 1 – 7 for use in binding and imaging tau aggregates in Alzheimer patients.

5 10. A compound of formula I according to any one of claims 1 – 7 for use in a tau-binding study.

11. A compound of formula I according to any one of claims 1 – 7 for use in diagnostic imaging of tau-aggregates in the brain of a mammal.

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12. A pharmaceutical composition comprising a compound of formula I according to any one of claims 1 – 7 and a pharmaceutical acceptable carrier.

13. A method of imaging tau-aggregate deposits, comprising

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~~– introducing into a mammal a detectable quantity of a composition according to claim 12;~~
~~– allowing sufficient time for the compound of formula I to be associated with tau-~~
~~aggregate deposits, and~~

- detecting the a compound of formula I that has associated with one or more tau-aggregate deposits after a detectable quantity of a composition according to claim 12 has been introduced
20 into a mammal and allowed to associate with the tau-aggregate deposits.

14. The use of a compound as defined in any one of claims 1 – 7 for diagnostic imaging of tau-aggregate deposits in the brain of a mammal.

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