tau isoforms expressed in different neuronal populations could lead to different pathologies (Biochim. Biophys. Acta 2005, 1739(2) 240-250). Neurodegenerative diseases characterized by pathological tau accumulation are termed 'tauopathies' (Ann. Rev. Neurosci. 2001, 24, 1121-1159). Besides AD and FTD, other tauopathies include progressive supranuclear palsy (PSP), 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 ~~present application~~embodiments disclosed herein 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.

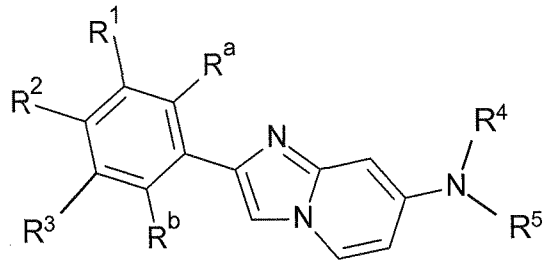
A further object of the embodiments disclosed herein ~~present invention~~ is a method of imaging tau-aggregate deposits, comprising

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

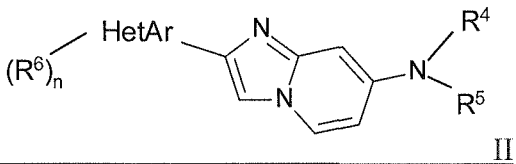
- detecting the compound associated with one or more tau-aggregate deposits.

A further object of the embodiments disclosed herein ~~present invention~~ is a pharmaceutical composition, containing compounds of formula I or II and pharmaceutical acceptable carriers, which may be used for identifying potential patients.

In one aspect, there is provided a compound of formula



I or



II

wherein

R^1 is hydrogen, lower alkyl, lower alkoxy, halogen, S-lower alkyl, lower alkoxy substituted by halogen, di-lower alkyl amino, C(O)O-lower alkyl, lower alkyl substituted by hydroxy or hydroxy;

R^2 is hydrogen, lower alkyl, halogen, lower alkoxy, S-lower alkyl, lower alkoxy substituted by halogen, $O(CH_2)_2$-lower alkoxy substituted by halogen, di-lower alkyl amino, alkyl amino, NH-lower alkyl substituted by halogen, N(lower alkyl)-benzyl, lower alkyl substituted by hydroxy, heterocycloalkyl optionally substituted by halogen, CH_2-lower alkoxy, CH_2-lower alkoxy substituted by halogen or hydroxy; or

R^1 and R^2 form together with the carbon atoms to which they are attached a ring containing

$-OCH_2CH_2O-$, OCH_2O-, $OCH_2CH_2CH_2O-$ or $-NHC(O)CH_2O-$;

R^3 is hydrogen or lower alkoxy;

R^4 is hydrogen or lower alkyl;

R^5 is lower alkyl, cycloalkyl, lower alkyl substituted by hydroxy or lower alkyl substituted by halogen; or

R^4 and R^5 form together with the nitrogen atom to which they are attached a ring containing

$-CH_2CH_2CHRCH_2CH_2-$, $-CH_2CHRCH_2CH_2-$, $-CH_2CH_2OCH_2CH_2-$, $-CH_2CH_2NR'CH_2CH_2-$, CH_2CHR- or $-CH_2CH_2CH_2-$; wherein

R is hydrogen, halogen, lower alkyl, lower alkoxy or lower alkyl substituted by halogen;

R' is lower alkyl substituted by halogen;

R^a is hydrogen or ^3H;

R^b is hydrogen, hydroxy or ^3H;

R^6 is hydrogen, halogen or lower alkyl;

HetAr is selected from the group consisting of thiophenyl, furanyl, thiozolyl, benzofuranyl, pyrazolyl, benzoimidazolyl or pyridinyl;

n is 1 or 2;

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 or II as defined herein for use in binding and imaging tau aggregates, beta-amyloid aggregates or alpha-synuclein aggregates.

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

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

In another aspect, there is provided a method of imaging tau-aggregate deposits, comprising detecting a compound of formula I or II that has associated with one or more tau-aggregate deposits, wherein the compound of formula I or II was from a detectable quantity of a composition as defined herein that had been introduced into a mammal.

In another aspect, there is provided the use of a compound as defined herein in the manufacture of a diagnostic imaging agent for diagnostic imaging of tau-aggregate deposits in the brain of a mammal.

The following definitions of the general terms used in the present description apply irrespective of whether the terms in question appear alone or in combination.

As used herein, the term "lower alkyl" denotes a saturated, i.e. aliphatic hydrocarbon group including a straight or branched carbon chain with 1 – 7 carbon atoms. Examples for “alkyl” are methyl, ethyl, n-propyl, and isopropyl.

The term “cycloalkyl” denotes a non aromatic hydrocarbon ring, containing from 3 to 6 carbon atoms.

The term “alkoxy” denotes a group -O-R’ wherein R’ is lower alkyl as defined above.

The term “halogen” denotes chlorine, bromine, fluorine or iodine.

The term “lower alkyl substituted by halogen” denotes an alkyl group as defined above, wherein at least one hydrogen atom is replaced by a halogen atom.

The term “lower alkyl substituted by hydroxy” denotes an alkyl group as defined above, wherein at least one hydrogen atom is replaced by a hydroxy group.

The term “lower alkoxy substituted by halogen” denotes an alkoxy group as defined above, wherein at least one hydrogen atom is replaced by a halogen atom.

The term heterocycloalkyl denotes a saturated ring, containing one or more heteroatoms selected from N, O or S, which rings are selected from pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl.

The term "pharmaceutically acceptable salt" or “pharmaceutically acceptable acid addition salt” embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane-sulfonic acid, p-toluenesulfonic acid and the like.

It has been found that the compounds of formula I or II may be used for binding and imaging tau aggregates and related b-sheet aggregates including besides others beta-amyloid aggregates or alpha-synuclein aggregates.

One object of the present invention are compounds of formula

17. A pharmaceutical preparation comprising a compound of formula I or II according to any one of claims 1 – 12 and a pharmaceutical acceptable carrier.

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

~~- introducing into a mammal a detectable quantity of a composition according to claim 17;~~

~~- allowing sufficient time for the compound of formula I or II to be associated with tau-aggregate deposits, and~~

- detecting ~~the~~ a compound of formula I or II that has associated with one or more tau-aggregate deposits, wherein the compound of formula I or II was from a detectable quantity of a composition according to claim 17 that had been introduced into a mammal.

19. The use of a compound as defined in any one of claims 1 – 12 in the manufacture of a diagnostic imaging agent for diagnostic imaging of tau-aggregate deposits in the brain of a mammal.

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