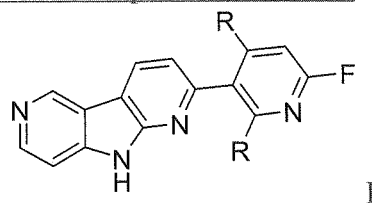


The object of the ~~present application~~ embodiments disclosed herein is to find an imaging tool which will improve diagnosis by identifying potential patients with excess of tau aggregates in the brain, which may be likely to develop Alzheimer's disease. It will also be useful to monitor the progression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

In the first aspect, there is provided a compound of formula



wherein

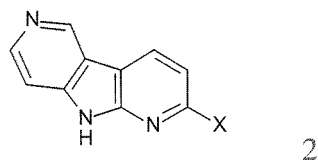
R is hydrogen or tritium;

10 F is fluoro or ¹⁸fluoro;

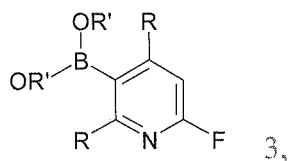
or a pharmaceutically acceptable acid addition salt.

In another aspect, there is provided a process for the manufacture of a compound of formula I as defined herein, which process comprises

a) coupling a compound of formula 2 (X = Cl, Br)

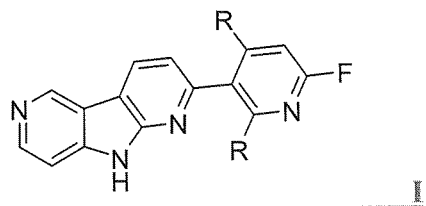


with suitable boronic acids or boronic acid esters of formula 3



wherein R' is hydrogen or lower alkyl,

to afford compounds of formula I

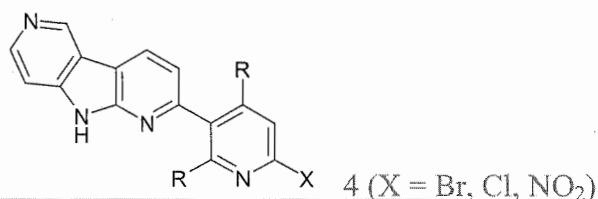


wherein R is hydrogen,

and, if desired, converting the obtained compound into pharmaceutically acceptable acid addition salts or into a compound of formula I, wherein R is tritium;

or

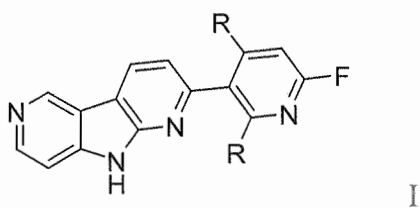
b) coupling a compound of formula 4



with suitable fluorinating reagents selected from potassium fluoride or

5 tetrabutylammonium fluoride,

to afford compounds of formula I

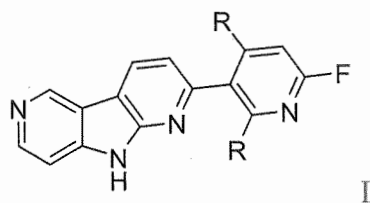


wherein the substituent R is hydrogen

and, if desired, converting the compound obtained into pharmaceutically acceptable acid addition

10 salts or into compounds of formula I, wherein R is tritium

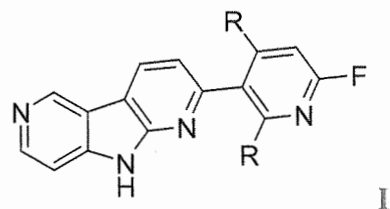
c) reacting a compound of formula I



wherein R is hydrogen, with tritium gas in the presence of a iridium, ruthenium, rhodium

or palladium catalyst in a suitable solvent, selected from dichloromethane, chlorobenzene, DMF,

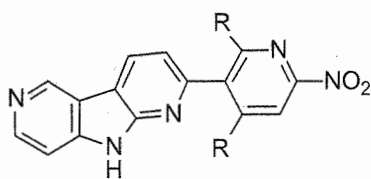
15 DMSO or mixtures thereof to afford compound of formula I



wherein R is tritium, and, if desired, converting the compounds obtained into

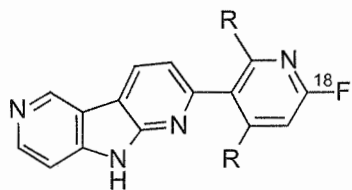
pharmaceutically acceptable acid addition salts or

d) dissolving a compound of formula 10



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in dimethylsulfoxide and sonicate prior to end of bombardment with aqueous [¹⁸F]fluoride ion to a compound of formula



I

5 and, if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

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.

10 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.

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.

15 ~~A further object of the present invention~~ In another aspect, there is provided 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 to be associated with tau-aggregate deposits, and
- 20 - detecting the compound associated with one or more tau-aggregate deposits.

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

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

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.

^3H denotes a tritium atom.

F denotes a fluoro atom or a ^{18}F fluoro atom.

The term "leaving group" denotes halogen or sulfonate. Examples of sulfonate are tosylate, mesylate, triflate, nosylate or brosylate.

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 may be used for binding and imaging tau aggregates and related beta-sheet aggregates including besides others beta-amyloid aggregates or alpha-synuclein aggregates.

One embodiment of the present invention are compounds of formula I which compounds are 2-(6-fluoro-pyridin-3-yl)-9H-dipyrido[2,3-b;3',4'-d]pyrrole, ^3H -2-(6-fluoro-pyridin-3-yl)-9H-

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

- introducing into a mammal a detectable quantity of a preparation according to claim 8;
- 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.

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~~10. The use of a compound as defined in any one of claims 1 or 2 for diagnostic imaging of tau-aggregate deposits in the brain of a mammal.~~

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