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(54) **Title:** DIAGNOSTIC AGENTS FOR AMYLOID BETA IMAGING

(57) **Abstract:** This invention relates to compounds suitable for labeling or already labeled by F-18, methods of preparing such a compound, compositions comprising such compounds, kits comprising such compounds or compositions and uses of such compounds, compositions or kits for diagnostic imaging.

Diagnostic agents for amyloid beta imaging

Field of Invention

This invention relates to compounds suitable for labeling or already labeled by F-18, methods of preparing such a compound, compositions comprising such compounds, kits comprising such compounds or compositions and uses of such compounds, compositions or kits for diagnostic imaging.

Background

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder marked by loss of memory, cognition, and behavioral stability. AD is defined pathologically by extracellular senile plaques comprised of fibrillar deposits of the beta-amyloid peptide (Aβ) and neurofibrillary tangles comprised of paired helical filaments of hyperphosphorylated tau. The 39 - 43 amino acids comprising Aβ peptides are derived from the larger amyloid precursor protein (APP). In the amyloidogenic pathway, Aβ peptides are cleaved from APP by the sequential proteolysis by beta- and gamma-secretases. Aβ peptides are released as soluble proteins and are detected at low level in the cerebrospinal fluid (CSF) in normal aging brain. During the progress of AD the Aβ peptides aggregate and form amyloid deposits in the parenchyma and vasculature of the brain, which can be detected post mortem as diffuse and senile plaques and vascular amyloid during histological examination (for a recent review see: Blennow et al. Lancet. 2006 Jul 29;368(9533):387-403).

Alzheimers disease (AD) is becoming a great health and social economical problem all over the world. There are great efforts to develop techniques and methods for the early detection and effective treatment of the disease. Currently, diagnosis of AD in an academic memory-disorders clinic setting is approximately 85-90% accurate (Petrella JR et al. Radiology. 2003 226:315-36). It is based on the exclusion of a variety of diseases causing similar symptoms and the careful neurological and psychiatric examination, as well as neuropsychological testing.

Molecular imaging has the potential to detect disease progression or therapeutic effectiveness earlier than most conventional methods in the fields of neurology, oncology and cardiology. Among the several promising molecular imaging technologies, such as optical imaging, MRI, SPECT and PET, PET is of particular interest for drug development because of its high sensitivity and ability to provide quantitative and kinetic data.

For example positron emitting isotopes include e.g. carbon, iodine, nitrogen, and oxygen. These isotopes can replace their non-radioactive counterparts in target compounds to produce PET tracers that have similar biological properties. Among these isotopes F-18 is a preferred labeling isotope due to its half life of 110 min, which permits the preparation of diagnostic tracers and subsequent study of biochemical processes. In addition, its low β+ energy (634 keV) is also advantageous.

The nucleophilic aromatic and aliphatic [F-18]fluoro-fluorination reaction is of great importance for [F-18]fluoro-labeled radiopharmaceuticals which are used as *in vivo* imaging agents for diseases. The half-life of F-18 is about 110 minutes, which demands quick preparation and administration of the radioactive compound.

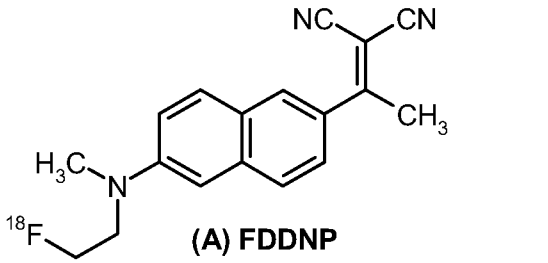
A couple of methods are known to introduce F-18 e.g. to an aromatic ring (Coenen, Fluorine-18 Labeling Methods: Features and Possibilities of Basic Reactions, (2006), in: Schubiger P.A., Friebe M., Lehmann L , (eds), PET-Chemistry - The Driving Force in Molecular Imaging. Springer, Berlin Heidelberg, pp.15-50). One of the later discoveries is the replacement of an iodonium leaving group with [F-18]fluoride (compare also e.g. WO2005061415(A1), WO2005097713(A1), WO2007010534(A2), WO2007073200(A1) and WO2007141529(A1)).

Post-mortem histological examination of the brain is still the only definite diagnosis of Alzheimer ' s disease. Thus, the *in vivo* detection of one pathological feature of the disease - the amyloid aggregate deposition in the brain - is thought to have a strong impact on the early detection of AD and differentiating it from other forms of dementia. Additionally, most disease modifying therapies which are in development are aiming at lowering of the amyloid load in the brain.

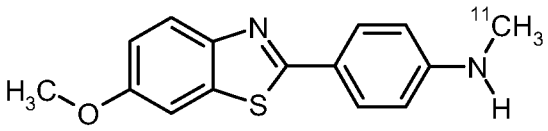
Thus, imaging the amyloid load in the brain may provide an essential tool for patient stratification and treatment monitoring (for a recent review see: Nordberg. Eur J Nucl Med Mol Imaging. 2008 Mar;35 Suppl 1:S46-50).

In addition, amyloid deposits are also known to play a role in amyloidoses, in which amyloid proteins (e.g. tau) are abnormally deposited in different organs and/or tissues, causing disease. For a recent review see Chiti et al. Annu Rev Biochem. 2006;75:333-66.

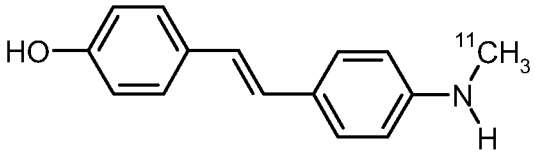
Potential ligands for visualizing amyloid aggregates in the brain must show a high binding affinity to amyloid aggregates and must cross the blood brain barrier. PET tracers which were already investigated in humans regarding their accumulation in the brain of AD patients are e.g. [F-18]FDDNP **(A)** (Shoghi-Jadid et al., Am J Geriatr Psychiatry 2002; 10:24-35), [C-11]PIB **(B)** (Klunk et al. Ann Neurol. 2004 55:306-319), [C-11]SB-13 **(C)** (Verhoeff et al., Am J Geriatr Psychiatry 2004; 12:584-595, [C-11]BF227 (Kudo et al., J Nucl. Med 2007; 49:554-561), and [F-18]PIB (Farrar et al. Turku PET Symposium, Abstract 49).



(A) FDDNP



(B) C-11 PIB

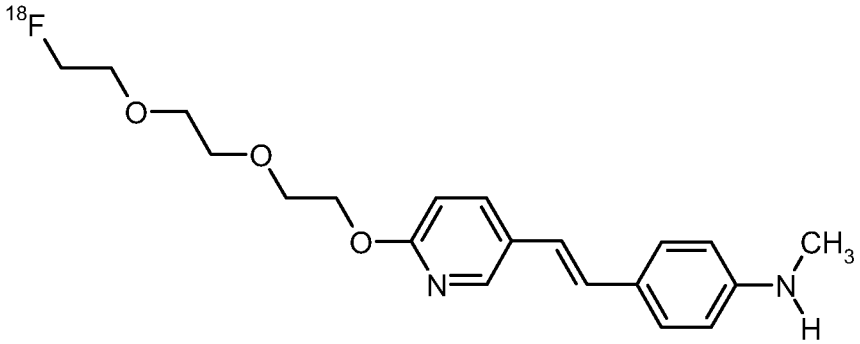


(C) C-11, SB-13

It is an important goal for the design of a suitable CNS-PET tracer that the brain pharmacokinetics are optimized. Thus, the PET ligand should enter the brain

rapidly in sufficient amounts. A fraction of tracer molecules should then bind specifically to the target. Subsequently, those molecules which have not bound should be eliminated rapidly from the surrounding area ("wash-out" from the brain) in order to achieve an image with a high signal to background ratio.

Styrylpyridine derivatives **(D)** have also been labeled with PET isotopes and are covered by patent application WO2007126733 and members of the corresponding patent families.



AV-45 (D)

Reports in the literature (Zhang et al., Nucl Med Biol. 2007 Jan;34(1):89-97; Stephenson et al., Bioconjug Chem. 2007 Jan-Feb;18(1):238-46) describe the advantages of fluoropegylated tracers for detection of Aβ plaques. In healthy mice, AV-45 shows a only a moderate brain wash out ratio ([%ID/g at 2min] / [%ID/g at 60min]) of 3.9 (Choi et al., J Nucl Med. 2009 Nov;50(11):1887-94). Surprisingly, non-fluoropegylated styrylpyridine derivative described herein (e.g. **1a)** showed excellent brain uptake and higher brain wash out ratios (18.6) in healthy mice, indicating a lower background signal, which is advantageous for high contrast imaging of amyloid beta.

Summary of the Invention

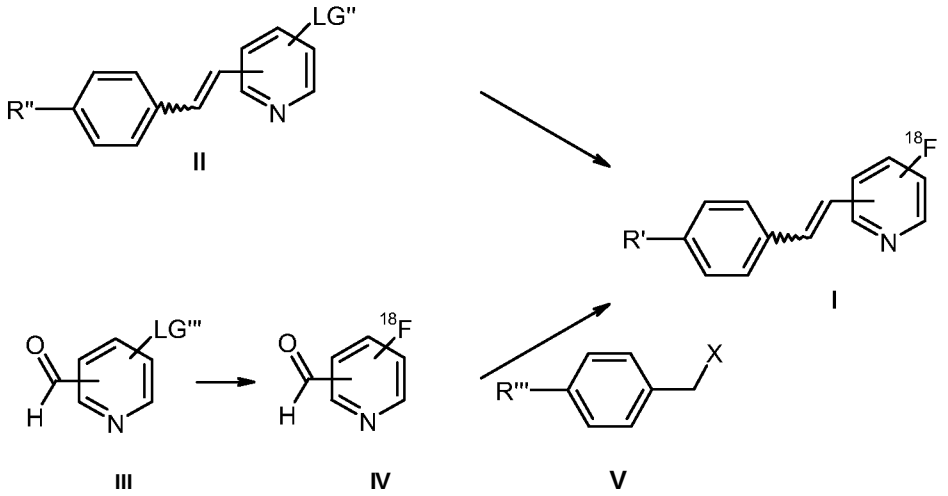


figure 1: overview on aspects of the present invention

- The present invention provides novel compounds of Formulae I and II encompassing single isomers and mixtures thereof, or pharmaceutically acceptable salts of an inorganic or organic acid thereof, hydrates, complexes, esters, amides, solvates and prodrugs thereof.

- The present invention also provides pharmaceutical compositions comprising a radiolabeled compound of Formula I or pharmaceutically acceptable salts of an inorganic or organic acid thereof, hydrates, complexes, esters, amides, solvates and prodrugs thereof and optionally a pharmaceutically acceptable carrier, diluent, adjuvant or excipient.

- The present invention provides a compound of Formula II which is a precursor (starting material) for PET-isotope labeling compounds of Formula I.

- The present invention provides a method of imaging or diagnosing diseases, the method comprising introducing into a patient a detectable quantity of a labeled compound of Formula I or pharmaceutically acceptable salts of an inorganic or organic acid thereof, hydrates, complexes, esters, amides, solvates and prodrugs thereof.

- A preferred method of imaging or diagnosing a disease is imaging or diagnosing Alzheimer's disease.

- The present invention is directed to the use of compounds of Formula I for the manufacture of a pharmaceutical for imaging.

- The present invention provides the compounds of Formula I for use as medicament.

- The present invention also provides methods for producing compounds of Formula I by reacting

  a) compounds of Formula II with [F-18]fluoride, optionally including a subsequent deprotection step;

  b) compounds of Formula IV, being generated from compounds of Formula III, with compounds of Formula V optionally including a subsequent deprotection step.

- The present invention also provides a kit for preparing a radiopharmaceutical preparation, said kit comprising a sealed vial containing a predetermined quantity of

  a) the compound of Formula II;

  b) the compounds of Formula III and V;

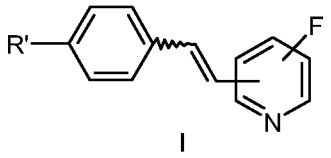
- A further aspect of this invention is directed to methods and intermediates useful for producing the imaging compound of Formula I. More specifically the compound of this invention is useful for the imaging of diseases including but not limited to Alzheimer's disease, other forms of dementias (e.g. Lewy body dementia) and/or amyloidoses. The invention, therefore,

also relates to the use of imaging compounds for diagnosing these diseases as well as for stratification of therapy and therapy monitoring.

- The present invention also relates to a method of imaging amyloid aggregates using radioactively labeled compounds of the invention.

Description of the Invention:

In a ***first aspect*** the present invention is directed to compounds of Formula **I**



I

or pharmaceutically acceptable salts of an inorganic or organic acid thereof, hydrates, complexes, esters, amides, solvates or prodrugs thereof, encompassing also single isomers and mixtures thereof,

wherein

F is a fluorine atom, preferably, **F** is a [F-18]fluorine atom.

R' is selected from the group comprising:

a) **0-R^A,**

b) **NR^BR^C**

R^A, R^B, R^C are selected from the group comprising:

a) hydrogen,

b) branched or non-branched (C1-C5)alkyl,

c) branched or non-branched (C3-C5)alkenyl, with the proviso that R^A ,R'^3 and R^C are not attached to O or N with a sp2 hybridized carbon atom,

d) branched or non-branched (C3-C5)alkynyl, with the proviso that R^A ,R'^3 and R^C are not attached to O or N with a sp hybridized carbon atom,

e) (C1 -C5)alkyl-[0-(C1 -C5)alkyl]$_n$

wherein n is 1-5,

or R^B and R^C together are a group that is selected from groups comprising:

a) -$(CH_2)_m$-,

b) -$(CH_2)_2$-0-$(CH_2)_2$-,

c) -$(CH_2)_2$-NR^A-$(CH_2)_2$-.

wherein m is 2-5.

in a preferred embodiment R' is selected from the group comprising:

a) Hydroxyl,

b) OMe,

c) NH_2,

d) NHMe,

e) NMe_2.

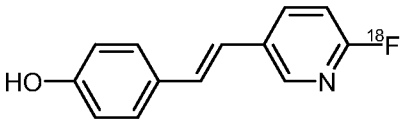
in a more preferred embodiment R' is selected from the group comprising:

a) OMe,

b) NHMe,

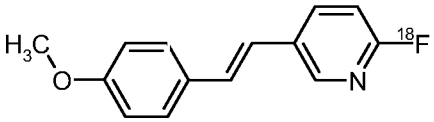
c) NMe_2.

A preferred compounds is:



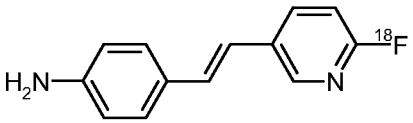
4-{(E)-2-[6-(F-18)fluoropyridin-3-yl]vinyl}phenol

Another preferred compounds is:



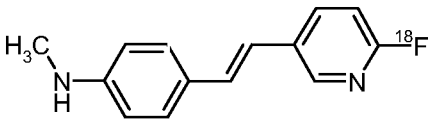
2-(F-18)fluoro-5-[(E)-2-(4-methoxyphenyl)vinyl]pyridine

Another preferred compounds is:



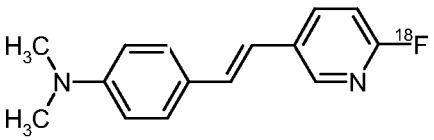
4-{(E)-2-[6-(F-1 8)fluoropyridin-3-yl]vinyl}aniline

Another preferred compounds is:



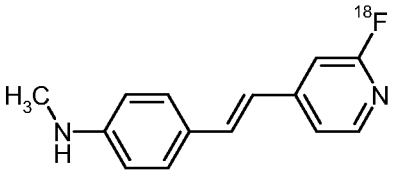
4-{(E)-2-[6-(F-18)fluoropyridin-3-yl]vinyl}-N-methylaniline

Another preferred compounds is:



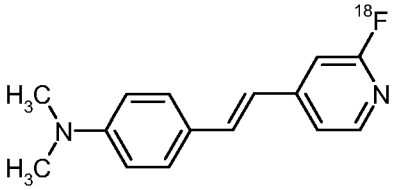
4-{(E)-2-[6-(F-18)fluoropyridin-3-yl]vinyl}-N,N-dimethylaniline

Another preferred compounds is:



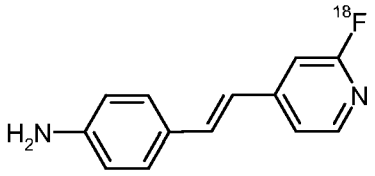
4-{(E)-2-[2-(F-18)fluoropyridin-4-yl]vinyl}-N-methylaniline

Another preferred compounds is:



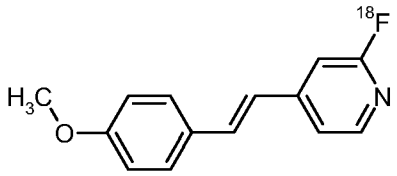
4-{(E)-2-[2-(F-18)fluoropyridin-4-yl]vinyl}-N,N-dimethylaniline

Another preferred compounds is:



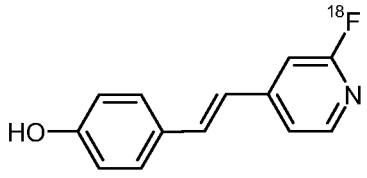
4-{(E)-2-[2-(F-18)fluoropyridin-4-yl]vinyl}aniline

Another preferred compounds is:



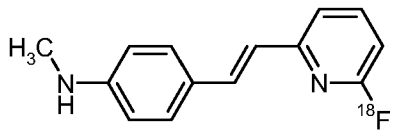
2-(F-18)fluoro-4-[(E)-2-(4-methoxyphenyl)vinyl]pyridine

Another preferred compounds is:



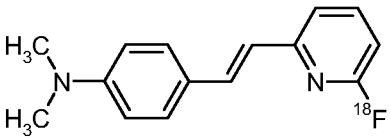
4-{(E)-2-[2-(F-18)fluoropyridin-4-yl]vinyl}phenol

Another preferred compounds is:



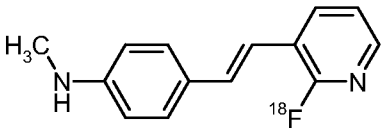
4-{(E)-2-[6-(F-18)fluoropyridin-2-yl]vinyl}-N-methylaniline

Another preferred compounds is:



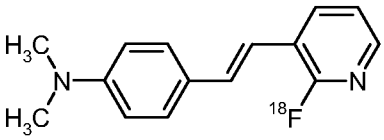
4-{(E)-2-[6-(F-18)fluoropyridin-2-yl]vinyl}-N,N-dimethylaniline

Another preferred compounds is:



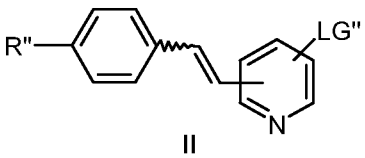
4-{(E)-2-[2-(F-18)fluoropyridin-3-yl]vinyl}-N-methylaniline

Another preferred compounds is:



4-{(E)-2-[2-(F-18)fluoropyridin-3-yl]vinyl}-N,N-dimethylaniline

In ***second aspect*** *the* present invention is directed to compounds of Formula **II**



II

or pharmaceutically acceptable salts of an inorganic or organic acid thereof, hydrates, complexes, esters, amides, solvates or prodrugs thereof, encompassing also single isomers and mixtures thereof,

wherein:

(R'' is 0-A^{1A} and LG is a halogen) or;

(R'' is 0-A^{1A} and LG is a nitro group) or;

(R'' is 0-A^{1A} and LG is a trialkylammonium group) or;

(R'' is 0-A^{1A} and LG is a aryl iodonium group) or;

(R'' is 0-A^{1A} and LG is a diaryl sulfonium group) or;

(R'' is $NA^{1B}A^{1C}$ and LG is a halogen) or;

(R'' is $NA^{1B}A^{1C}$ and LG is a nitro group) or;

(R'' is $NA^{1B}A^{1C}$ and LG is a trialkylammonium group) or;

(R'' is $NA^{1B}A^{1C}$ and LG is a aryl iodonium group) or;

(R'' is $NA^{1B}A^{1C}$ and LG is a diaryl sulfonium group).

A^{1A}, A^{1B}, A^{1C} are selected from the group comprising:

a) hydrogen,

b) branched or non-branched (C1-C5)alkyl,

c) branched or non-branched (C3-C5)alkenyl, with the proviso that A^{1A}, A^{1B}, A^{1C} are not attached to O or N with a sp2 hybridized carbon atom,

d) branched or non-branched (C3-C5)alkynyl, with the proviso that A^{1A}, A^{1B}, A^{1C} are not attached to O or N with a sp hybridized carbon atom,

e) PG

f) (C1-C5)alkyl-[0-(C1-C5)alkyl]n

wherein n is 1-5

Or A^{1B} and A^{1C} together are group that is selected from groups comprising:

d) $-(CH_2)_m-$,

e) $-(CH_2)_2-O-(CH_2)_2-$,

f) $-(CH_2)_2-NA^{1A}-(CH_2)_2-$.

wherein m is 2-5.

PG is a protecting group which is known or obvious to someone skilled in the art, which is chosen from but not limited to a class of protecting groups namely ethers, benzyl ethers, silyl ethers, esters, carbonates, sulfonates, acetals, ketals, ortho esters and boronates and which is chosen from but not limited to those described in the textbook Greene and Wuts, Protecting groups in Organic Synthesis, third edition, page 17-245, included herewith by reference.

In a preferred embodiment, PG is selected from the group comprising:

a) Boc,

b) Methoxymethyl,

c) Acetyl,

d) Trityl,

e) Fmoc.

In a preferred embodiment compounds of Formula **II** are selected from group consisting of:

a) ((R" is OPG) and (LG is chloro, iodo or bromo)) or;

b) ((R" is OMe) and (LG is chloro, iodo)) or;

c) 2-bromo-6-[(E)-2-(4-methoxyphenyl)vinyl]pyridine or;

d) 2-bromo-3-[(E)-2-(4-methoxyphenyl)vinyl]pyridine or;

e) 2-bromo-5-[(E)-2-(4-methoxyphenyl)vinyl]pyridine or;

f) ((R" is OPG or OMe) and (LG is a nitro group)) or;

g) ((R" is OPG or OMe) and (LG is a trimethylammonium group)) or;

h) ((R" is OPG or OMe) and (LG is a aryl iodonium group)) or;

i) ((R" is OPG or OMe) and (LG is a diaryl sulfonium group)) or;

j) ((R" is NPGH) and (LG is chloro, iodo or bromo)) or;

k) ((R" is NPGH) and (LG is a nitro group)) or;

l) ((R" is NPGH) and (LG is a trimethylammonium group)) or;

m) ((R" is NPGH) and (LG is a aryl iodonium group)) or;

n) ((R" is NPGH) and (LG is a diaryl sulfonium group)) or;

o) ((R" is NPG_2) and (LG is chloro, iodo or bromo)) or;

P) ((R" is NPG_2) and (LG is a nitro group)) or;

q) ((R" is NPG_2) and (LG is a trimethylammonium group)) or;

r) ((R" is NPG_2) and (LG is a aryl iodonium group)) or;

s) ((R" is NPG_2) and (LG is a diaryl sulfonium group)) or;

t) ((R" is NPGMe) and (LG is chloro, iodo or bromo)) or;

u) ((R" is NPGMe) and (LG is a nitro group)) or;

v) ((R" is NPGMe) and (LG is a trimethylammonium group)) or;

w) ((R" is NPGMe) and (LG is a aryl iodonium group)) or;

x) ((R" is NPGMe) and (LG is a diaryl sulfonium group)) or;

y) ((R" is NMe_2) and (LG is chloro, iodo or bromo)) or;

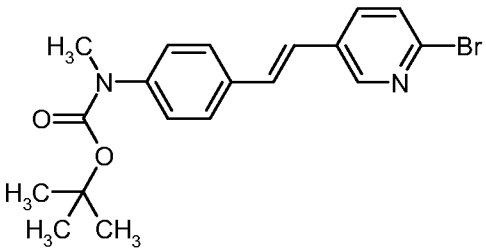
z) ((R" is NMe_2) and (LG is a nitro group)) or;

aa) ((R" is NMe_2) and (LG is a trimethylammonium group)) or;

bb) ((R" is NMe_2) and (LG is a aryl iodonium group)) or;

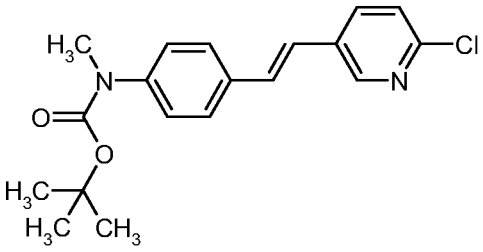
cc) ((R" is NMe_2) and (LG is a diaryl sulfonium group)).

A preferred compounds is:



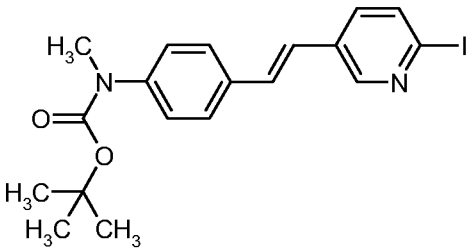
tert-butyl {4-[(E)-2-(6-bromopyridin-3-yl)vinyl]phenyl}methylcarbamate

Another preferred compounds is:



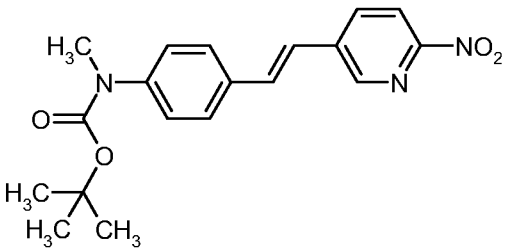
tert-butyl {4-[(E)-2-(6-chloropyridin-3-yl)vinyl]phenyl}methylcarbamate

Another preferred compounds is:

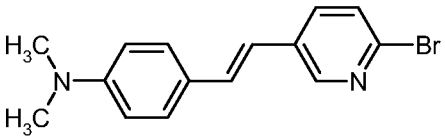


tert-butyl {4-[(E)-2-(6-iodopyridin-3-yl)vinyl]phenyl}methylcarbamate

Another preferred compounds is:

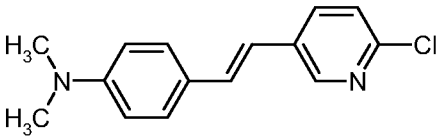


tert-butyl {4-[(E)-2-(6nitropyridin-3-yl)vinyl]phenyl}methylcarbamate



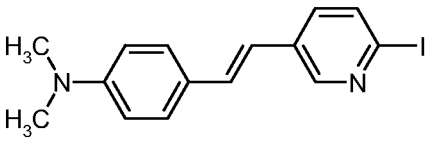
N,N-dimethyl-4-[(E)-2-(6-bromopyridin-3-yl)vinyl]aniline

Another preferred compounds is:



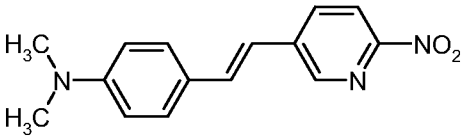
N,N-dimethyl-4-[(E)-2-(6-chloropyridin-3-yl)vinyl]aniline

Another preferred compounds is:



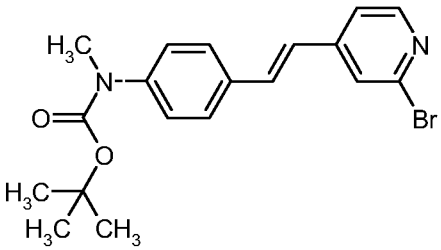
N,N-dimethyl-4-[(E)-2-(6-iodopyridin-3-yl)vinyl]aniline

Another preferred compounds is:



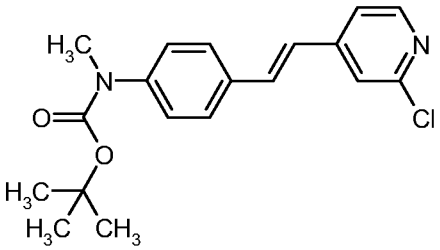
N,N-dimethyl-4-[(E)-2-(6-nitropyridin-3-yl)vinyl]aniline

Another preferred compounds is:



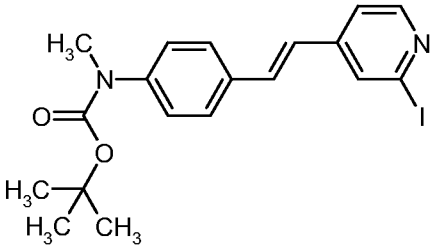
tert-butyl {4-[(E)-2-(2-bromopyridin-4-yl)vinyl]phenyl}methylcarbamate

Another preferred compounds is:



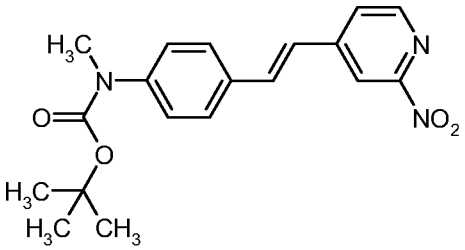
tert-butyl {4-[(E)-2-(2-chloropyridin-4-yl)vinyl]phenyl}methylcarbamate

Another preferred compounds is:



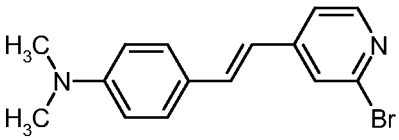
tert-butyl {4-[(E)-2-(2-iodopyridin-4-yl)vinyl]phenyl}methylcarbamate

Another preferred compounds is:



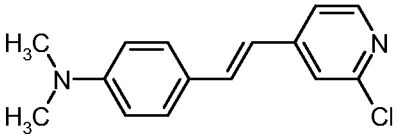
tert-butyl {4-[(E)-2-(2-nitropyridin-4-yl)vinyl]phenyl}methylcarbamate

Another preferred compounds is:



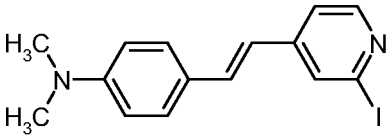
4-[(E)-2-(2-bromopyridin-4-yl)vinyl]-N,N-dimethylaniline

Another preferred compounds is:



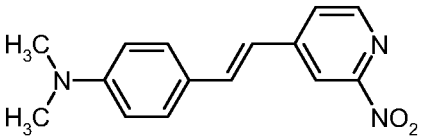
4-[(E)-2-(2-chloropyridin-4-yl)vinyl]-N,N-dimethylaniline

Another preferred compounds is:



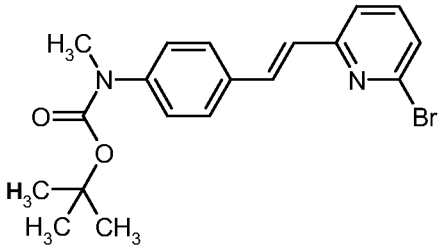
4-[(E)-2-(2-iodopyridin-4-yl)vinyl]-N,N-dimethylaniline

Another preferred compounds is:



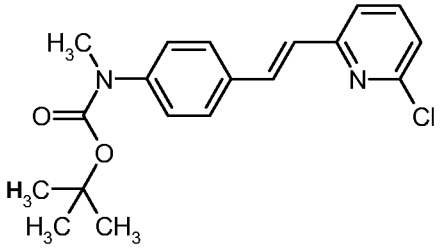
4-[(E)-2-(2-nitropyridin-4-yl)vinyl]-N,N-dimethylaniline

Another preferred compounds is:



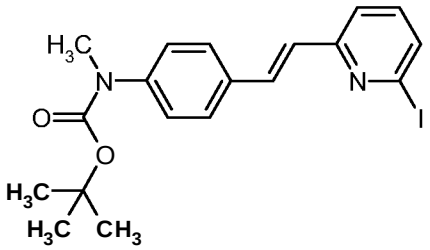
tert-butyl {4-[(E)-2-(6-bromopyridin-2-yl)vinyl]phenyl}methylcarbamate

Another preferred compounds is:



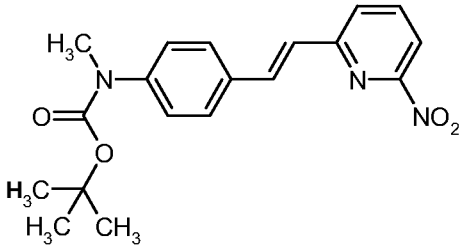
tert-butyl {4-[(E)-2-(6-chloropyridin-2-yl)vinyl]phenyl}methylcarbamate

Another preferred compounds is:



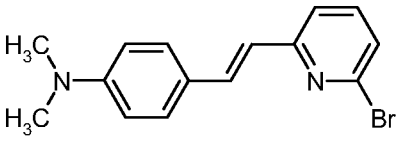
tert-butyl {4-[(E)-2-(6-iodopyridin-2-yl)vinyl]phenyl}methylcarbamate

Another preferred compounds is:



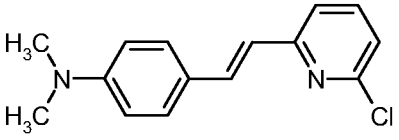
tert-butyl {4-[(E)-2-(6-nitropyridin-2-yl)vinyl]phenyl}methylcarbamate

Another preferred compounds is:



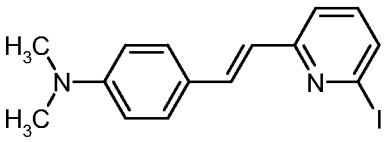
4-[(E)-2-(6-bromopyridin-2-yl)vinyl]-N,N-dimethylaniline

Another preferred compounds is:



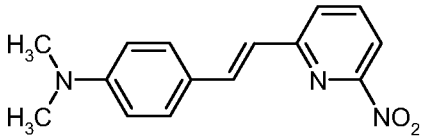
4-[(E)-2-(6-chloropyridin-2-yl)vinyl]-N,N-dimethylaniline

Another preferred compounds is:



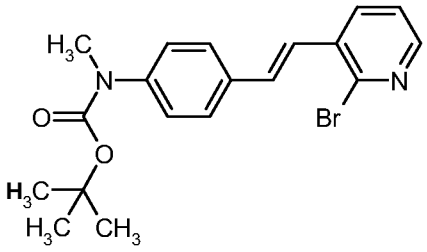
4-[(E)-2-(6-iodopyridin-2-yl)vinyl]-N,N-dimethylaniline

Another preferred compounds is:



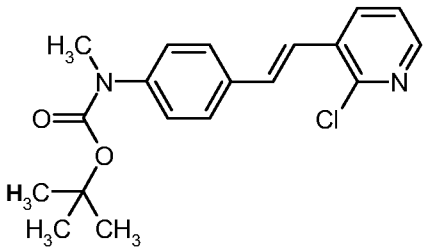
4-[(E)-2-(6-nitropyridin-2-yl)vinyl]-N,N-dimethylaniline

Another preferred compounds is:



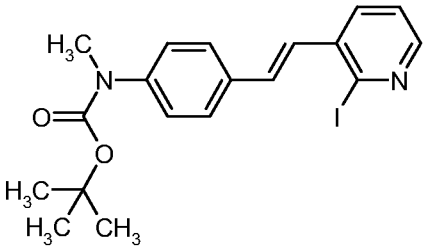
tert-butyl {4-[(E)-2-(2-bromopyridin-3-yl)vinyl]phenyl}methylcarbamate

Another preferred compounds is:



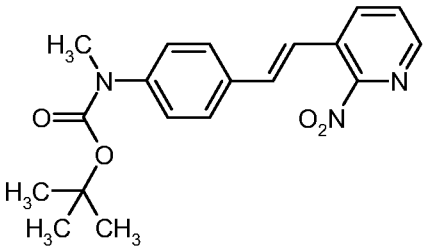
tert-butyl {4-[(E)-2-(2-chloropyridin-3-yl)vinyl]phenyl}methylcarbamate

Another preferred compounds is:



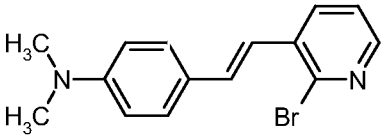
tert-butyl {4-[(E)-2-(2-iodopyridin-3-yl)vinyl]phenyl}methylcarbamate

Another preferred compounds is:



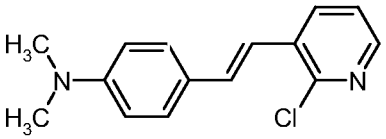
tert-butyl {4-[(E)-2-(2-nitropyridin-3-yl)vinyl]phenyl}methylcarbamate

Another preferred compounds is:



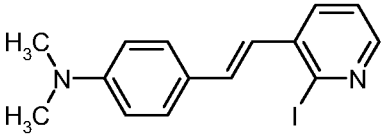
4-[(E)-2-(2-bromopyridin-3-yl)vinyl]-N,N-dimethylaniline

Another preferred compounds is:



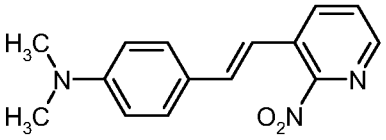
4-[(E)-2-(2-chloropyridin-3-yl)vinyl]-N,N-dimethylaniline

Another preferred compounds is:



4-[(E)-2-(2-iodopyridin-3-yl)vinyl]-N,N-dimethylaniline

Another preferred compounds is:



4-[(E)-2-(2-nitropyridin-3-yl)vinyl]-N,N-dimethylaniline

In a **third aspect** of the invention is directed to a method for obtaining compounds of Formula **I**, are as defined above. This includes in particular all preferred embodiments mentioned above.

Two methods have been identified for obtaining compounds of Formula **I**.

The first method comprises a straight forward fluoro labeling reaction i.e. one-step method from compounds of Formula **II**, as described above, for obtaining compound of Formula **I**.

The radiolabeling method for obtaining compound of Formula **I** comprises the step of:

- Reacting a compound of Formula **II** with a fluorinating agent for obtaining a compound of Formula **I**.
- Optionally, a subsequent deprotection leads to compound of Formula **I** after reacting a compound of Formula **II** with a fluorinating agent.

Wherein compound of Formula **II** is described above.

In a preferred embodiment, the fluorination agent is a fluorine radioactive isotope derivative.

More preferably the fluorine radioactive isotope derivative is a F-18 derivative. More preferably, the F-18 radioactive isotope derivative is 4,7,13,16,21,24-Hexaoxa-1,10-diazabicyclo[8.8.8]-hexacosane K[F-18]F (crownether salt Kryptofix K[F-18]F), K[F-18]F, H[F-18]F, $KH[F\text{-}18]F_2$, Cs[F-18]F, Na[F-18]F or tetraalkylammonium salt of F-18 (e.g. [F-18] tetrabutylammonium fluoride). More preferably, the fluorination agent is K[F-18]F, H[F-18]F, or $KH[F\text{-}18]F_2$, [F-18] tetrabutylammonium fluoride, most preferably K[F-18]F.

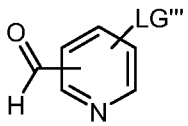
The second method comprises a straight forward radioisotope labeling reaction i.e. one-step method from compounds of Formula **III** using [F-18]fluoride anions and subsequent reaction of F-18 labeled compound of Formula IV with compound of Formula V.

The method for obtaining compound of Formula I comprises the steps of:

- Reacting a compound of Formula III with fluorination agent to obtain compound of Formula IV.
- Reacting of compound of Formula IV with compound of Formula V.
- Optionally, a deprotection reaction.

The fluorination agent is defined as above.

The compound of Formula III is:



III

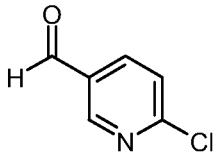
or salts of an inorganic or organic acid thereof, wherein

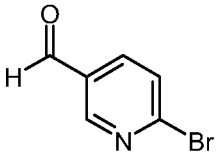
LG''' is a leaving group.

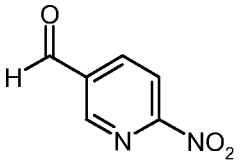
In a preferred embodiment LG''' is selected from the group comprising:

a) halogen,
b) nitro,
c) trimethylammonium,
d) diaryl-sulfonium,
e) aryl-iodonium.

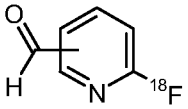
Preferred compounds are:







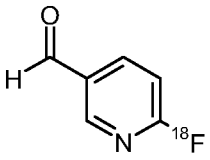
The compound of Formula IV is:



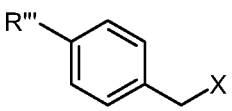
IV

or salts of an inorganic or organic acid thereof, wherein

Preferred compound are:



The compound of Formula V is:



V

or pharmaceutically acceptable salts of an inorganic or organic acid thereof, hydrates, complexes, esters, amides, solvates or prodrugs thereof,

wherein

LG''' is selected from the group comprising:

a) 0-A^{3A},

b) $NA^{3B}A^{3C}$

A^{3A}, A^{3B}, A^{3C} are selected from the group comprising:

a) hydrogen,

b) branched or non-branched (C1-C5)alkyl,

c) branched or non-branched (C3-C5)alkenyl, with the proviso that A^{1A}, A^{1B}, A^{1C} are not attached to O or N with a sp2 hybridized carbon atom,

d) branched or non-branched (C3-C5)alkynyl, with the proviso that A^{1A}, A^{1B}, A^{1C} are not attached to O or N with a sp hybridized carbon atom,

e) PG

f) (C1-C5)alkyl-[0-(C1-C5)alkyl]$_n$

wherein n is 1-5

in a preferred embodiment A^1 is selected from the group comprising:

a) hydroxyl

b) O-PG,

c) OMe,

d) NHPG,

e) $N(PG)_2$,

f) NHMe,

g) NMePG,

h) NMe_2.

PG is a protecting group which is known or obvious to someone skilled in the art, which is chosen from but not limited to a class of protecting groups namely

ethers, benzyl ethers, silyl ethers, esters, carbonates, sulfonates, acetals, ketals, ortho esters and boronates and which is chosen from but not limited to those described in the textbook Greene and Wuts, Protecting groups in Organic Synthesis, third edition, page 17-245, included herewith by reference;

in a preferred embodiment, PG is selected from the group comprising:

a) Boc,
b) Methoxymethyl,
c) Acetyl,
d) Trityl,
e) Fmoc.

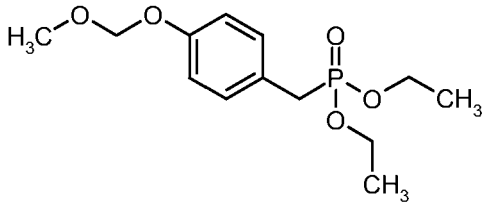
in a more preferred embodiment $\mathbf{A^3}$ is selected from the group comprising:

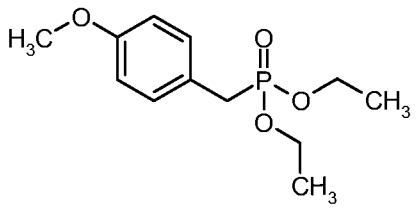
a) OMe,
b) NHMe,
c) NMePG,
d) NMe_2.

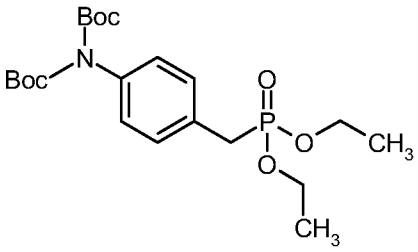
X is selected from the group comprising:

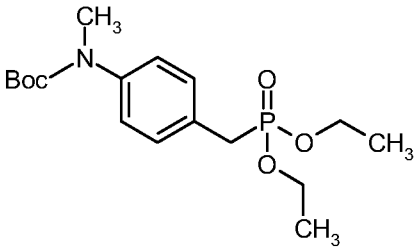
a) $P(O)(O\text{-}[C1\text{-}C5]alkyl)_2$,
b) $P^+(aryl)_3$.

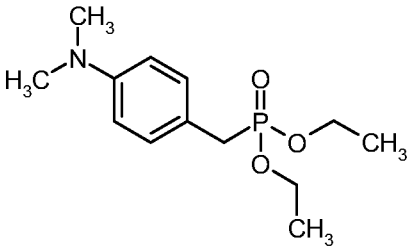
Preferred compound are:











In a ***fourth aspect*** of the invention compounds according to Formula **I** are provided as medicament or pharmaceutical.

The invention relates also to the use of compound of Formula **I** for the manufacture of medicament or pharmaceutical for treatment.

In a ***fifth aspect*** of the invention, compounds according to Formula **I** are provided as diagnostic imaging agent or imaging agent, preferably as imaging agent for PET applications.

The invention relates also to the use of compound of Formula for the manufacture of imaging agent.

In a more preferred embodiment the use concerns the imaging of CNS diseases. CNS diseases include but are not limited to Alzheimer's disease,

dementia with Lewy bodies, frontotemporal dementia, amyloidoses and diseases of unidentified cause.

The present invention is also directed to a method of imaging comprising the step of introducing into a patient a detectable quantity of an F-18 labeled compound of Formula I and imaging said patient.

The compounds as described above and herein are, in a preferred embodiment of the invention, bound to Aβ.

The compounds as described above and herein are, in a preferred embodiment of the invention, bound to a tau filament or tangle.

Another aspect of the invention is the use of a compound of Formula I as described above and herein for diagnosing and/or treating Alzheimer's disease and/or amyloidoses in a patient, in particular in a mammal, such as a human.

Preferably, the use of a compound of the invention in the diagnosis is performed using positron emission tomography (PET).

Another aspect of the invention is directed to a method of imaging amyloid deposits. Such a method comprises a) administering to a mammal a compound as described above and herein containing a detectable label, and b) detecting the signal stemming from the compound that is specifically bound to the amyloid deposits. The specific binding is a result of the high binding affinity of the compounds of the present invention to the amyloid deposits.

In a further aspect, the invention is directed to a method of diagnosing a patient with Alzheimer's disease or amyloidoses. This method comprises a) administering to a human in need of such diagnosis a compound of the invention with a detectable label for detecting the compound in the human as described above and herein, and b) measuring the signal from the detectable label arising

from the administration of the compound to the human, preferably by positron emission tomography (PET).

A further embodiment of the invention includes a diagnostic method for other neurological disorders than Alzheimer's disease comprising the exclusion of Alzheimer's disease in a patient, that method comprising administering a compound of the invention to a patient and applying an imaging method of the invention.

In a ***sixt aspect,*** the invention is directed to a kit comprising one vial or more than one vial comprising a predetermined quantity of a compound having any one of the following general chemical Formulae or mixture thereof

a) compounds of Formula **II** or Formula **Ma;**
b) compounds of Formula **III** and **V.**

Further, according to this aspect of the present invention the kit comprises a compound having general chemical Formula as disclosed above along with an acceptable carrier, diluent, excipient or adjuvant or mixture thereof.

Definitions

The term "alkyl" refers to a linear or branched chain monovalent or divalent radical consisting of solely carbon and hydrogen, containing no unsaturation and having the specified number of carbons, such as methyl **(Ci),** ethyl **(C2),** n-propyl **(C3),** 1-methlyethyl **((C3)** iso-propyl), n-butyl **(C_4),** n-pentyl **(C5)** and the like. More preferably alkyl is **Ci-C_4** alkyl.

The term "Alkenyl" is similarly defined as for alkyl, but contains at least one carbon-carbon double bond, respectively. More preferably alkenyl is **C2-C_4** alkenyl.

The term "Alkynyl" is similarly defined as for alkyl, but contain at least one carbon-carbon triple bond, respectively. More preferably alkynyl is C_2-C_4 alkynyl.

The term "aryl" as employed herein by itself or as part of another group refers to monocyclic or bicyclic aromatic or heteroaromatic groups containing from 5-10 atoms (C, N, S) in the ring portion, such as phenyl, naphthyl, thiophenyl or tetrahydronaphthyl.

The term halogen or halo refers to Cl, Br, F or I.

The term "alkyloxy" or "alkoxy" refers to alkyl groups respectively linked by an oxygen atom, with the alkyl being as defined above.

As used hereinafter in the description of the invention and in the claims, the term "prodrug" means any covalently bonded compound, which releases the active parent pharmaceutical according to Formula II.

The term "prodrug" as used throughout this text means the pharmacologically acceptable derivatives such as esters, amides and phosphates, such that the resulting in vivo biotransformation product of the derivative is the active drug as defined in the compounds of Formula (!}. The reference by Goodman and GiSman (The Pharmaco- logical Basis of Therapeutics, 8 ed, McGraw- HiM, Int. Ed. 1992,"Biotransformation of Drugs", p 13-15) describing prodrugs generally is hereby incorporated. Prodrugs of a compound of the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compound. Prodrugs of the compounds of the present invention include those compounds wherein for instance a hydroxy group, such as the hydroxy group on the asymmetric carbon atom, or an amino group is bonded to any group that, when the prodrug is administered to a patient, cleaves to form a free hydroxyl or free amino, respectively.

Typical examples of prodrugs are described for instance in WO 99/33795, WO 99/33815, WO 99/33793 and WO 99/33792 all incorporated herein by reference.

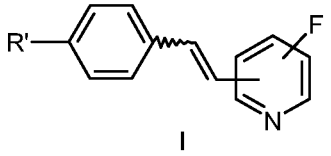
Prodrugs are characterized by excellent aqueous solubility, increased bioavailability and are readily metabolized into the active inhibitors in vivo.

As used hereinafter in the description of the invention and in the claims, the terms "salts of inorganic or organic acids", "inorganic acid" and "organic acid" refer to mineral acids, including, but not being limited to: acids such as carbonic, nitric, phosphoric, hydrochloric, perchloric or sulphuric acid or the acidic salts thereof such as potassium hydrogen sulphate, or to appropriate organic acids which include, but are not limited to: acids such as aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulphonic acids, examples of which are formic, acetic, trifluoracetic, propionic, succinic, glycolic, gluconic, lactic, malic, fumaric, pyruvic, benzoic, anthranilic, mesylic, fumaric, salicylic, phenylacetic, mandelic, embonic, methansulfonic, ethanesulfonic, benzenesulfonic, phantothenic, toluenesulfonic, trifluormethansulfonic and sulfanilic acid, respectively.

As used hereinafter in the description of the invention and in the claims, the term "pharmaceutically acceptable salt" relates to salts of inorganic and organic acids, such as mineral acids, including, but not limited to, acids such as carbonic, nitric or sulfuric acid, or organic acids, including, but not limited to, acids such as aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulphonic acids, examples of which are formic, acetic, trifluoroacetic, propionic, succinic, glycolic, gluconic, lactic, malic, fumaric, pyruvic, benzoic, anthranilic, mesylic, salicylic, phenylacetic, mandelic, embonic, methansulfonic, ethanesulfonic, benzenesulfonic, phantothenic, toluenesulfonic and sulfanilic acid.

In particular, the invention relates to

1. A compound according to formula I



I

or pharmaceutically acceptable salts of an inorganic or organic acid thereof, hydrates, complexes, esters, amides, solvates or prodrugs thereof, encompassing also single isomers and mixtures thereof,

wherein

R' is selected from the group comprising:

a) 0-R^A,

b) NR^BR^C

and wherein

R^A, R^B, R^c are selected from the group comprising:

a) hydrogen,

b) branched or non-branched (C1-C5)alkyl,

c) branched or non-branched (C3-C5)alkenyl, with the proviso that R^A ,R'^3 and R^c are not attached to O or N with a sp2 hybridized carbon atom,

d) branched or non-branched (C3-C5)alkynyl, with the proviso that R^A ,R'^3 and R^c are not attached to O or N with a sp hybridized carbon atom,

e) (C1 -C5)alkyl-[0-(C1 -C5)alkyl]$_n$

wherein n is 1-5,

or R^B and R^c together are a group that is selected from groups comprising:

a) -$(CH_2)_m$-,

b) $-(CH_2)_2-O-(CH_2)_2-$,

c) $-(CH_2)_2-NR^A-(CH_2)_2-$.

wherein m is 2-5.

2. A compound according to count 1,

wherein R' is selected from the group comprising:

a) Hydroxyl,
b) OMe,
c) NH_2,
d) NHMe,
e) NMe_2.

3. A compound according to count 1,

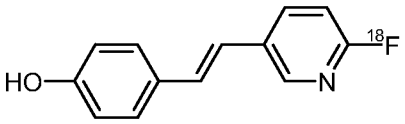
wherein R' is selected from the group comprising:

a) OMe,
b) NHMe,
c) NMe_2.

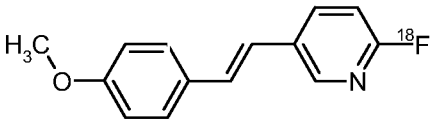
4. A compound according to counts 1-3,

wherein F has the meaning of ^{18}F.

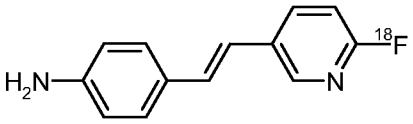
5. A compound according to count 1 selected from the group of compounds consisting of:



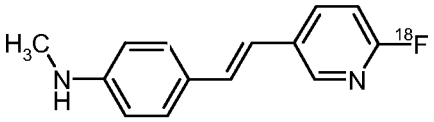
4-{(E)-2-[6-(F-18)fluoropyridin-3-yl]vinyl}phenol,



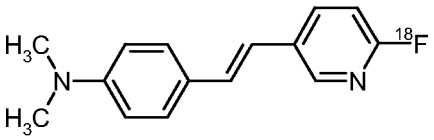
2-(F-1 8)fluoro-5-[(E)-2-(4-methoxyphenyl)vinyl]pyridine,



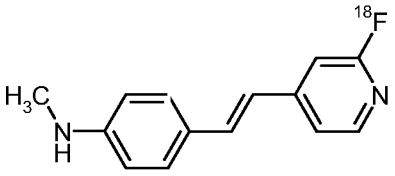
4-{(E)-2-[6-(F-18)fluoropyridin-3-yl]vinyl}aniline,



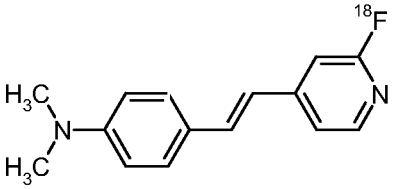
4-{(E)-2-[6-(F-18)fluoropyridin-3-yl]vinyl}-N-methylaniline,



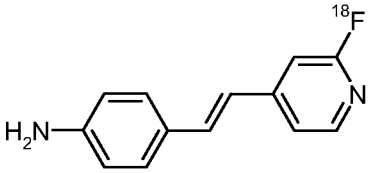
4-{(E)-2-[6-(F-18)fluoropyridin-3-yl]vinyl}-N,N-dimethylaniline,



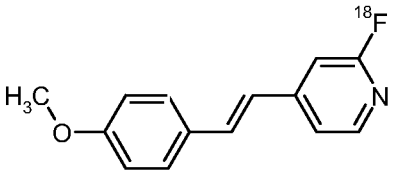
4-{(E)-2-[2-(F-18)fluoropyridin-4-yl]vinyl}-N-methylaniline,



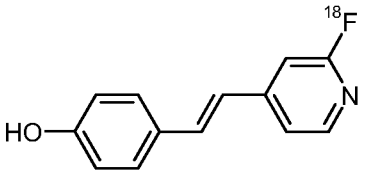
4-{(E)-2-[2-(F-18)fluoropyridin-4-yl]vinyl}-N,N-dimethylaniline,



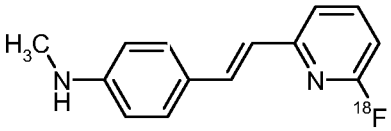
4-{(E)-2-[2-(F-18)fluoropyridin-4-yl]vinyl}aniline,



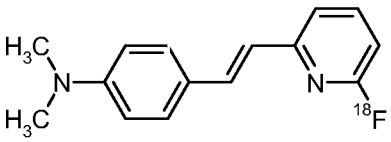
2-(F-18)fluoro-4-[(E)-2-(4-methoxyphenyl)vinyl]pyridine,



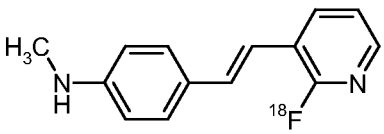
4-{(E)-2-[2-(F-1 8)fluoropyridin-4-yl]vinyl}phenol,



4-{(E)-2-[6-(F-18)fluoropyridin-2-yl]vinyl}-N-methylaniline,

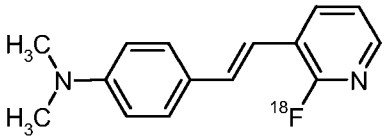


4-{(E)-2-[6-(F-18)fluoropyridin-2-yl]vinyl}-N,N-dimethylaniline,



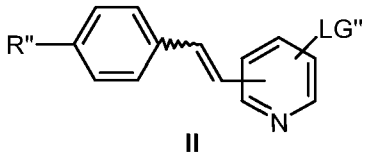
4-{(E)-2-[2-(F-18)fluoropyridin-3-yl]vinyl}-N-methylaniline,

and



4-{(E)-2-[2-(F-18)fluoropyridin-3-yl]vinyl}-N,N-dimethylaniline.

6. A compound according to formula II



II

or pharmaceutically acceptable salts of an inorganic or organic acid thereof, hydrates, complexes, esters, amides, solvates or prodrugs thereof, encompassing also single isomers and mixtures thereof,

wherein:

(R" is O-A^{1A} and LG is a halogen), or

(R" is 0-A^{1A} and LG is a nitro group), or

(R" is O-A^{1A} and LG is a trialkylammonium group), or

(R" is 0-A^{1A} and LG is a aryl iodonium group), or

(R" is 0-A^{1A} and LG is a diaryl sulfonium group), or

(R" is $NA^{1B}A^{1C}$ and LG is a halogen), or

(R" is $NA^{1B}A^{1C}$ and LG is a nitro group), or

(R" is $NA^{1B}A^{1C}$ and LG is a trialkylammonium group), or

(R" is $NA^{1B}A^{1C}$ and LG is a aryl iodonium group), or

(R'' is $NA^{1B}A^{1C}$ and LG is a diaryl sulfonium group);

and wherein

A^{1A}, A^{1B}, A^{1C} are selected from the group consisting of:

a) hydrogen,

b) branched or non-branched (C1-C5)alkyl,

c) branched or non-branched (C3-C5)alkenyl, with the proviso that A^{1A}, A^{1B}, A^{1C} are not attached to O or N with a sp2 hybridized carbon atom,

d) branched or non-branched (C3-C5)alkynyl, with the proviso that R^A ,R^B and R^c are not attached to O or N with a sp hybridized carbon atom,

e) PG, being a protecting group,

f) (C1 -C5)alkyl-[0-(C1 -C5)alkyl]$_n$,

wherein n is 1-5;

or A^{1B} and A^{1C} together are group that is selected from groups comprising:

a) -$(CH_2)_m$-,

b) -$(CH_2)_2$-0-$(CH_2)_2$-,

c) -$(CH_2)_2$-NA^{1A}-$(CH_2)_2$-.

wherein m is 2-5.

7. A compound according to count 6, wherein:

a) ((R'' is OPG) and (LG is chloro, iodo or bromo)) or;

b) ((R'' is OMe) and (LG is chloro, iodo)) or;

c) the compound is 2-bromo-6-[(E)-2-(4-methoxyphenyl)vinyl]pyridine or;

d) the compound is 2-bromo-3-[(E)-2-(4-methoxyphenyl)vinyl]pyridine or;

e) the compound is 2-bromo-5-[(E)-2-(4-methoxyphenyl)vinyl]pyridine or;

f) ((R" is OPG or OMe) and (LG is a nitro group)) or;

g) ((R" is OPG or OMe) and (LG is a trimethylammonium group)) or;

h) ((R" is OPG or OMe) and (LG is a aryl iodonium group)) or;

i) ((R" is OPG or OMe) and (LG is a diaryl sulfonium group)) or;

j) ((R" is NPGH) and (LG is chloro, iodo or bromo)) or;

k) ((R" is NPGH) and (LG is a nitro group)) or;

l) ((R" is NPGH) and (LG is a trimethylammonium group)) or;

m) ((R" is NPGH) and (LG is a aryl iodonium group)) or;

n) ((R" is NPGH) and (LG is a diaryl sulfonium group)) or;

o) ((R" is NPG_2) and (LG is chloro, iodo or bromo)) or;

p) ((R" is NPG_2) and (LG is a nitro group)) or;

q) ((R" is NPG_2) and (LG is a trimethylammonium group)) or;

r) ((R" is NPG_2) and (LG is a aryl iodonium group)) or;

s) ((R" is NPG_2) and (LG is a diaryl sulfonium group)) or;

t) ((R" is NPGMe) and (LG is chloro, iodo or bromo)) or;

u) ((R" is NPGMe) and (LG is a nitro group)) or;

v) ((R" is NPGMe) and (LG is a trimethylammonium group)) or;

w) ((R" is NPGMe) and (LG is a aryl iodonium group)) or;

x) ((R" is NPGMe) and (LG is a diaryl sulfonium group)) or;

y) ((R" is NMe_2) and (LG is chloro, iodo or bromo)) or;

z ((R" is NMe_2) and (LG is a nitro group)) or;

aa) ((R" is NMe_2) and (LG is a trimethylammonium group)) or;

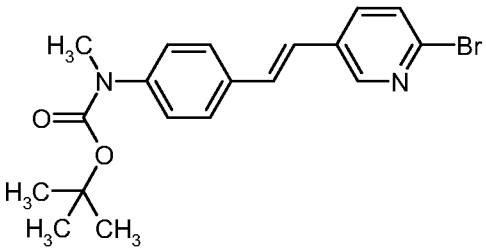
bb) ((R" is NMe_2) and (LG is a aryl iodonium group)) or;

cc) ((R" is NMe_2) and (LG is a diaryl sulfonium group)).

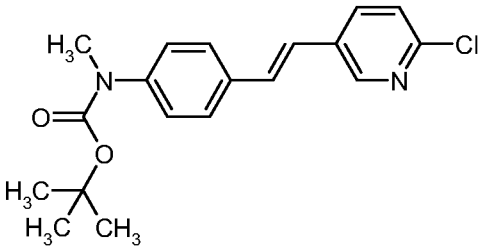
8. A compound according to count 6 or 7, wherein PG is selected from the group comprising:

a) Boc,
b) Methoxymethyl,
c) Acetyl,
d) Trityl,
e) Fmoc.

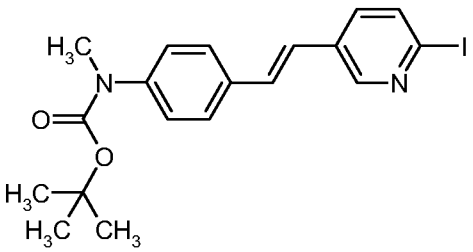
9. A compound according to count 6, selected from the group of compounds consisting of



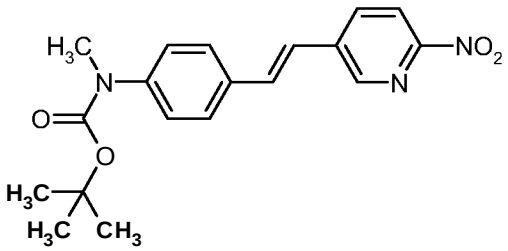
tert-butyl {4-[(E)-2-(6-bromopyridin-3-yl)vinyl]phenyl}methylcarbamate,



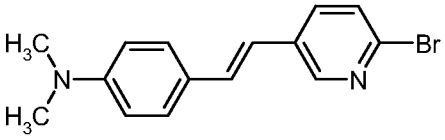
tert-butyl {4-[(E)-2-(6-chloropyridin-3-yl)vinyl]phenyl}methylcarbamate,



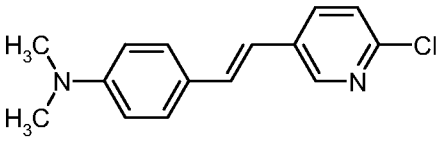
tert-butyl {4-[(E)-2-(6-iodopyridin-3-yl)vinyl]phenyl}methylcarbamate,



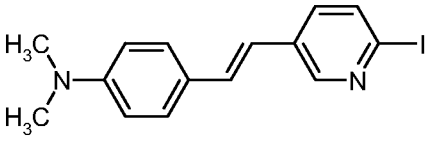
tert-butyl {4-[(E)-2-(6nitropyridin-3-yl)vinyl]phenyl}methylcarbamate,



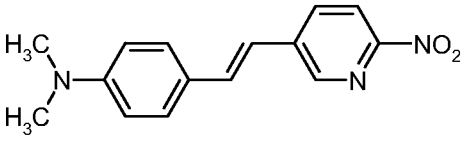
N,N-dimethyl-4-[(E)-2-(6-bromopyridin-3-yl)vinyl]aniline,



N,N-dimethyl-4-[(E)-2-(6-chloropyridin-3-yl)vinyl]aniline,



N,N-dimethyl-4-[(E)-2-(6-iodopyridin-3-yl)vinyl]aniline,



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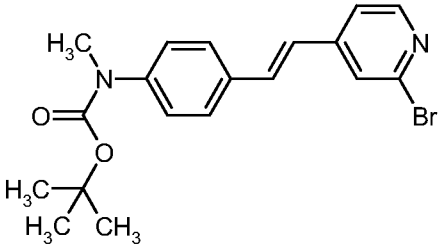
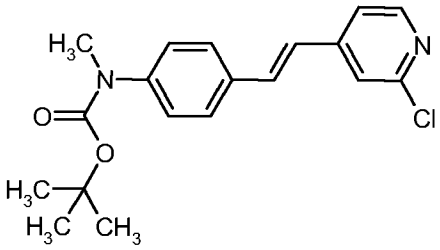
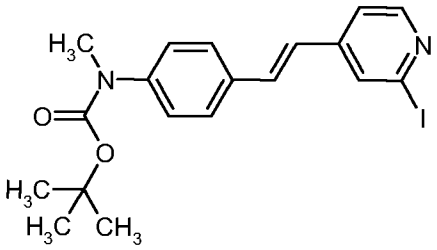


tert-butyl {4-[(E)-2-(2-bromopyridin-4-yl)vinyl]phenyl}methylcarbamate,



tert-butyl {4-[(E)-2-(2-chloropyridin-4-yl)vinyl]phenyl}methylcarbamate,



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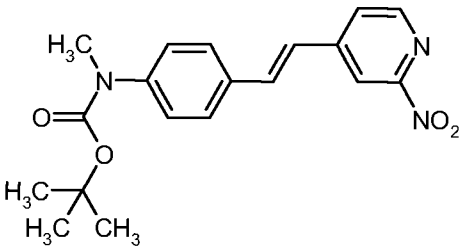
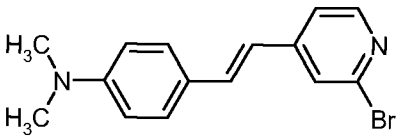
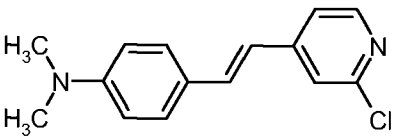


tert-butyl {4-[(E)-2-(2-nitropyridin-4-yl)vinyl]phenyl}methylcarbamate,



4-[(E)-2-(2-bromopyridin-4-yl)vinyl]-N,N-dimethylaniline,



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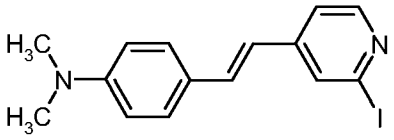

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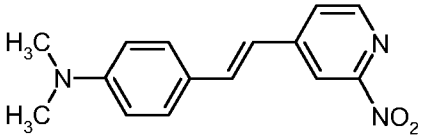

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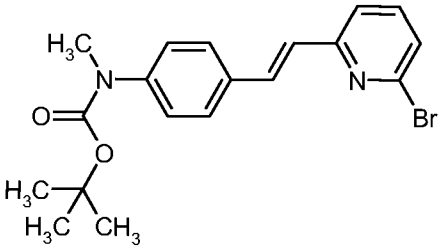
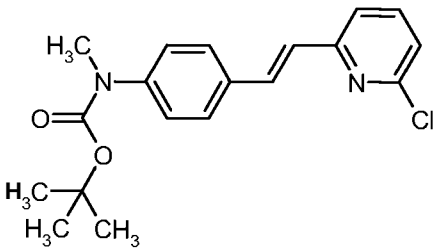


tert-butyl {4-[(E)-2-(6-bromopyridin-2-yl)vinyl]phenyl}methylcarbamate,



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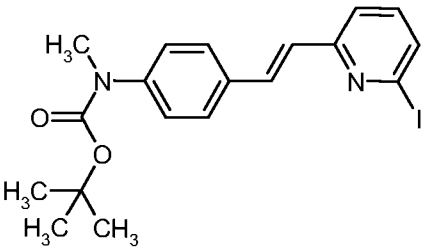

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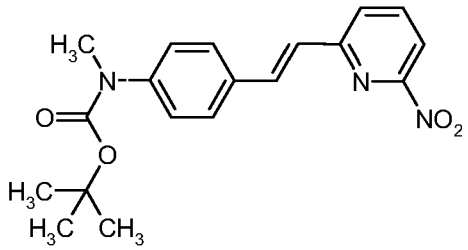

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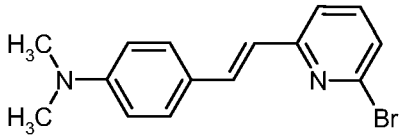
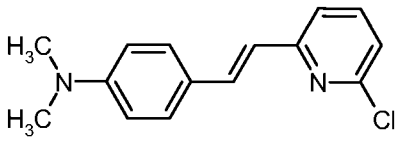


4-[(E)-2-(6-bromopyridin-2-yl)vinyl]-N,N-dimethylaniline,



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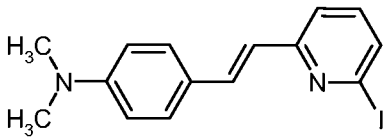

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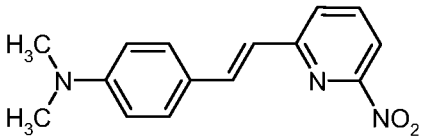

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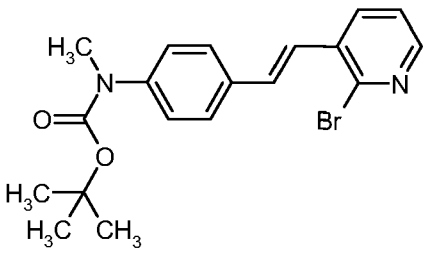
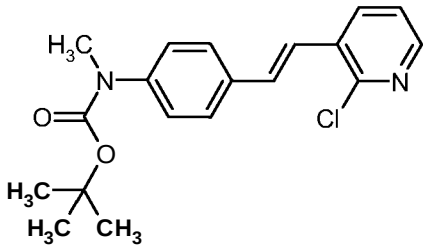
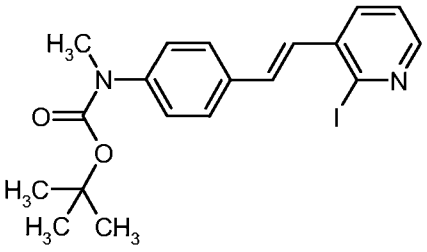


tert-butyl {4-[(E)-2-(2-bromopyridin-3-yl)vinyl]phenyl}methylcarbamate,



tert-butyl {4-[(E)-2-(2-chloropyridin-3-yl)vinyl]phenyl}methylcarbamate,



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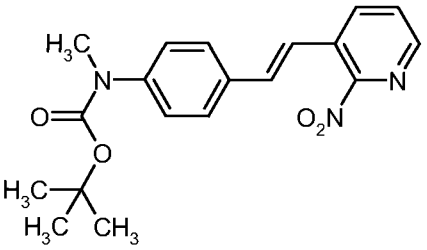
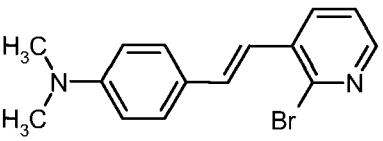
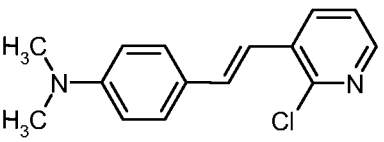


tert-butyl {4-[(E)-2-(2-nitropyridin-3-yl)vinyl]phenyl}methylcarbamate,



4-[(E)-2-(2-bromopyridin-3-yl)vinyl]-N,N-dimethylaniline,



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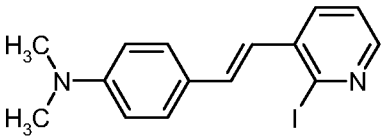
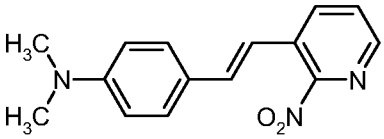


4-[(E)-2-(2-iodopyridin-3-yl)vinyl]-N,N-dimethylaniline,
and



4-[(E)-2-(2-nitropyridin-3-yl)vinyl]-N,N-dimethylaniline.

10. A method of manufacturing a compound of count 4 or 5, wherein a suitable precursor compound of counts 6-9 is reacted with a ^{18}F fluorination agent.

11. A method according to count 10, wherein a compound of count 5 is prepared by reacting a suitable precursor compound of count 9 with a ^{18}F fluorination agent.

12. A compound according to counts 4 or 5 as a diagnostic compound.

13. A compound according to counts 4 or 5 as a diagnostic compound for diagnosing Alzheimer's disease.

14. A kit comprising at least one sealed vial comprising a compound according to counts 6 - 9.

15. A kit according to count 14, comprising at least one sealed vial comprising a compound according to count 9.

16. A pharmaceutical or diagnostic composition, comprising a compound according to counts 4 or 5.

17. A diagnostic composition according to count 16 for the imaging and/or diagnosis of amyloidoses, preferably Alzheimer's disease.

18. Use of a compound according to claims 4 or 5 in a method for manufacturing a diagnostic composition useful for imaging or diagnosing an amyloidodsis, preferably Alzheimer's disease.

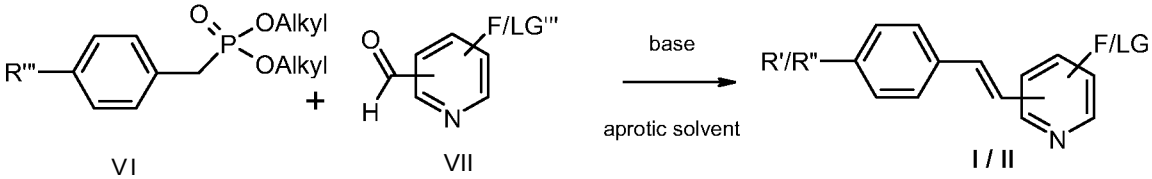
Brief description of the figures

Figure 1: Analytical HPLC: top: **[F-18]1a** (gamma), bottom: co-injection of reference **1a** (UV).

Figure 2: Autoradiographical analysis of binding of compound [F-18]1a to brain sections from cortex of Alzheimer's disease patients (AD) and controls without Aβ plaques (HC) (healthy control). Blocking of specific signals was performed with an excess of cold compound. Arrows point to plaque-specific signals.

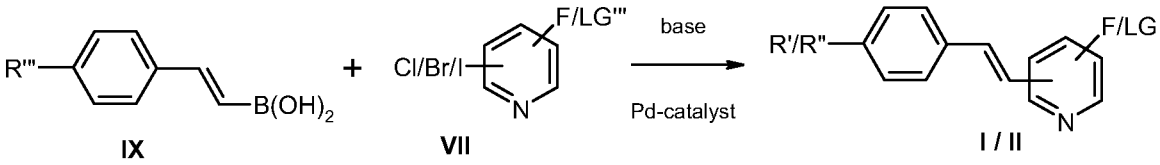
General synthetic access

Compounds of the general formula **I** or **II** are synthetically accessible via a Horner-Wadsworth-Emmons reaction reaction (Kelly, S. E. *Comp. Org. Syn.* **1991 ,** *1,* 729-817; B. E. Maryanoff, Reitz, A. B. *Chem. Rev.* **1989,** *89,* 863-927) of a pyridyl aldehyde like compound of formula **VII** with a benzyl phosphonate of formula **VI** in the presence of a base known to the expert in the field like lithium hydroxide, sodium hydride, butyl lithium or preferably potassium tert. butylate.



VI VII I / II

Compounds of the general formula **I** or **II** are generally accessible via a Suzuki reaction (Miyaura, N.; Suzuki, A *Chem Rev.* **1995,** *95,* 2457-2483) of a pyridyl halogenid like compound of formula **VIII** with a vinyl boronic acid of formula **IX** in the presence of a catalyst known to the expert in the field like tetrakis triphenylphosphin palladium and a base known to the expert in the field like potassium carbonate.



IX **VII** **I / II**

Experimental part

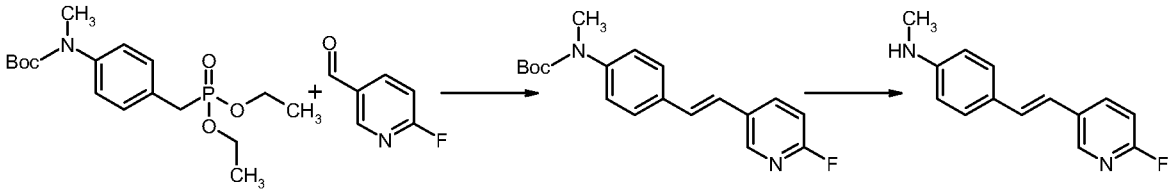
Abbreviations

d	doublet
dd	doublet of doublet
DMF	*N*,/V-dimethylformamide
DMSO	dimethyl sulphoxide
dt	doublet of triplet
EtOH	ethanol
HCL	hydrochloric acid
MS	mass spectrometry
m	multiplet
MeCN	acetonitrile
NaOH	sodium hydroxide
NMR	nuclear magnetic resonance spectroscopy : chemical shifts (δ) are given in ppm.
s	singlet
t	triplet
THF	tetrahydrofurane

Examples

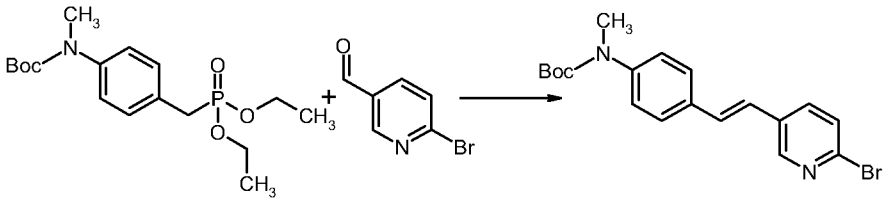
Example 1 Synthesis of 4-[(E)-2-(6-fluoropyridin-3-yl)vinyl]-N-methylaniline (1a)

Compound **1a** was synthesized by Horner-Wadsworth-Emmons reaction and subsequent acidic cleavage of the Boc-protecting group.



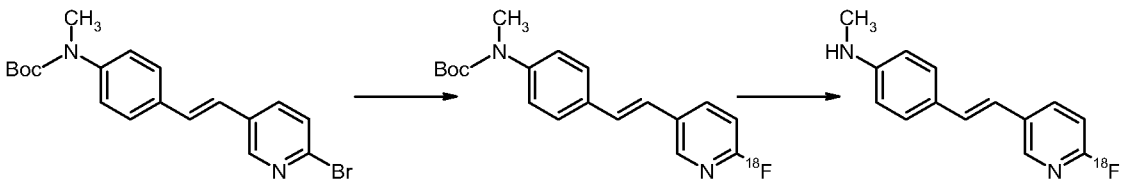
3 **4** **1a'** **1a**

Labeling precursor **2a** was synthesized from bromo derivative **5** and phosphonate **3**.



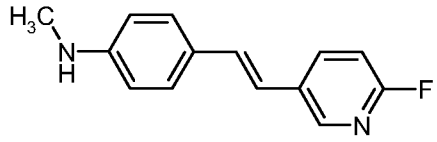
3 **5** **2a**

Compound **2a** is radiofluorinated with [F-18]fluoride, potassium carbonate and crown ether (kryptofix) in dimethyl formamide or dimethyl sulfoxide to obtain compound **[F-18]1a'.** This radiofluorination can carried by a single operator by "hand" or on a module (see above) by automated or semi-automated methods (Krasikowa 2006). Compound **[F-18]1a'** is deprotected using acid, preferably mineral acid, more preferably hydrogen chloride, perchloric acid or sulfuric acid. After deprotection of compound **[F-18]1a'** compound **[F-18]1a** is obtained which is typically purified using cartridges or HPLC-columns.



2a **[F-18]1a'** **[F-18]1a**

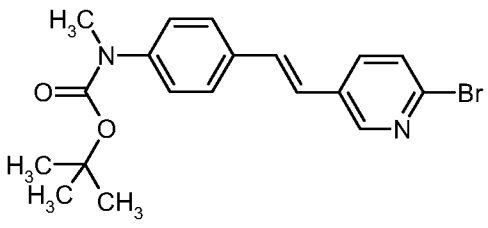
Synthesis of 4-[(E)-2-(6-fluoropyridin-3-vnvinyll-N-methylaniline **(1a)**



To a solution of diethyl {4-[(tertbutoxycarbonyl)(methyl)amino]benzyl} phosphonate (520 mg, 1.45 mmol) and 6-fluoronicotinaldehyde (200 mg, 1.60 mmol) in DMF (14.5 mL) was added to a solution of potassium tert.butylat (408 mg, 3.63 mmol) in DMF (36 mL). After stirring for one hour the reaction mixture was quenched with ice water, extracted with dichloromethane, washed with brine and dried over sodium sulfate. The residue was purified by chromatography on silica gel (ethyl acetate in hexane 5 to 10%) to yield 153 mg tert-butyl {4-[(E)-2-(6-fluoropyridin-3-yl)vinyl]phenyl}methylcarbamate, which was solved in trifluoroacetic acid (1.9 mL) and stirred for 20 min at room temperature. The solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane and extracted with brine and water. The organic layer was dried over sodium sulphate, filtrated and concentrated. The crude product was purified by chromatography on silica gel (ethyl acetate in hexane 0 to 20%) followed by thin layer chromatography on silica gel yield (10% ethyl acetate in hexane) to yield 66 mg of the title compound.

^{1}H-NMR (300 MHz, CHLOROFORM-d) δ = 2.88 (s, 3H), 6.61 (d, 2H), 6.83 (d, 1H), 6.90 (dd, 1H), 7.00 (d, 1H), 7.37 (d, 2H), 7.90 (td, 1H), 8.23 (m, 1H) ppm. ^{19}F-NMR (376 MHz, CHLOROFORM-d) δ = -70.96 (s, 1F) ppm. MS ES+ m/z = 229 (M+1).

Synthesis of tert-butyl {4-[(E)-2-(6-bromopyridin-3-yl)vinyl1phenyl) methyl-carbamate **(2a)**

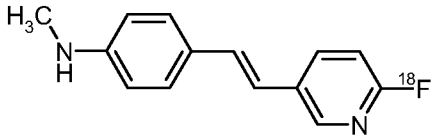


To a solution of diethyl {4-[(tert-butoxycarbonyl)(methyl)amino]benzyl} phosphonate (250 mg, 0.70 mmol) and 6-bromopyridine-3-carbaldehyde (130 mg, 0.70 mmol) in DMF (2 mL) was

added a solution of potassium tert.butylat (196 mg, 1.75 mmol) in DMF (8 ml_). After stirring for one hour the reaction mixture was quenched with saturated aqueous ammonium chloride solution, extracted with dichloromethane, washed with brine and dried over sodium sulfate. The residue was purified by chromatography on silica gel (ethyl acetate in hexane 0 to 25%) to yield 197 mg (72 %) of the title compound.

^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.48 (s, 9H), 3.29 (s, 3H), 6.97 (d, 1H), 7.13 (d, 1H), 7.27 (d, 2H), 7.47 (d, 1H), 7.48 (d, 2H), 7.70 (dd, 1 H), 8.45 (d, 1H) ppm. LC/MS ES+ m/z = 388 / 390 (M+1).

Radiolabeling of 4-[(E)-2-(6-[F-1 81fluoropyridin-3-v0vinyll-N-methylaniline



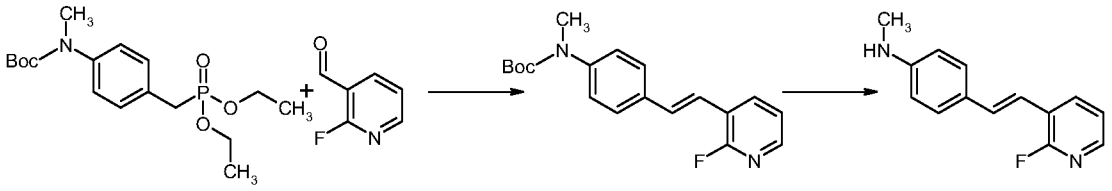
([F-18]1a)

Aqueous [^{18}F]Fluoride (15410 MBq) was trapped on a QMA cartridge (Waters) and eluted with 1.5 ml_ Kryptofix solution (5 mg K2.2.2 in 0.95ml_ MeCN + 1 mg K2CO3 in 50µI_ water) into the reactor. The solvent was removed by heating at 120°C for 10 min under a stream of nitrogen. Anhydrous MeCN (1 ml_) was added and evaporated as before. A solution of 3 mg precursor **2a** in 400 µI anhydrous DMSO was added. After heating at 180°C for 20 min the crude reaction mixture was cooled down to 50°C and to cleave the protective group a mixture of 1ml_ MeCN and 1ml_ 2M HCI was added and heated for 5 more min at 80°C. After cooling to room temperature the crude reaction mixture was diluted with a mixture of 1.5 ml_ 0.1 M ammonium formate + 1 ml_ 2M NaOH + 10mg sodium ascorbate and purified by preparative HPLC: ACE 5-C18 250mmx10mm; 5µηι Advanced Chromatography Technologies; Cat.No.: ACE 121-2510; isocratic, 0.1 M ammonium formate in H_20 /MeCN= 56 / 44, flow: 4 mL/min; t_R~26.5 min. The collected HPLC fraction was diluted with 40ml water and immobilized on a Sep-Pak plus short tC18 cartridge (Waters), which was washed with 10mL 20% EtOH in H_2O and eluted with 1mL EtOH to deliver 3678 MBq of the F-18 labeled product (45% rc. yield, corrected for decay; >96% TLC, >95% HPLC) in a overall synthesis time of -100 min. The desired F-18 labeled

product was analyzed using analytical HPLC: ACE3-C18 50 mm x 4,6 mm; ACE-1 11-0546; S /N: A56904, Advanced Chromatography Technologies; solvent gradient: start 5% acetonitrile - 95% acetonitrile in 0.1 % trifluoroacetic acid in 7 min., flow: 2 mL/min and confirmed by co-injection with the corresponding non-radioactive F-19 fluoro-standard **1a** on the analytical HPLC (t_R=2.8 min), see figure 1.

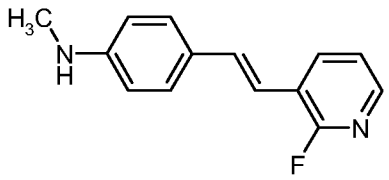
Example 2 Synthesis of 4-[(E)-2-(2-fluoropyridin-3-yl)vinyl]-N-methyl-aniline (1b)

Compound **1b** was synthesized by Horner-Wadsworth-Emmons reaction and subsequent acidic cleavage of the Boc-protecting group.



3 6 lb- 1b

Synthesis of 4-[(E)-2-(2-fluoropyridin-3-vnvinyll-N-methylaniline **(1b)**



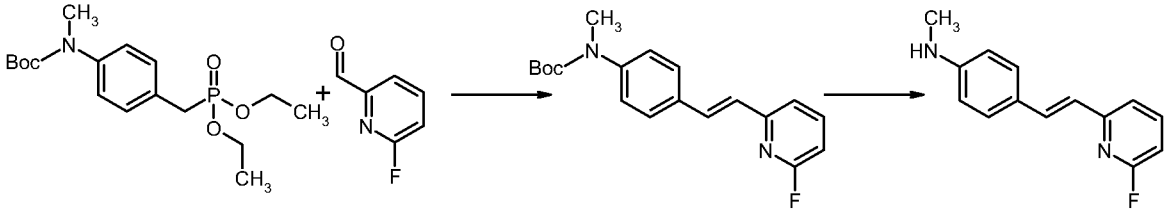
To a solution of diethyl {4-[(tertbutoxycarbonyl)(methyl)amino]benzyl} phosphonate (520 mg, 1.45 mmol) and 2-fluoronicotinaldehyde (200 mg, 1.60 mmol) in DMF (14.5 ml_) was added to a solution of potassium tert.butylat (408 mg, 3.63 mmol) in DMF (36 ml_). After stirring for one hour the reaction mixture was quenched with ice water, extracted with dichloromethane, washed with brine and dried over sodium sulfate. The residue was purified by chromatography on silica gel (ethyl acetate in hexane 5 to 10%) to yield 121 mg tert-butyl {4-[(E)-2-(2-fluoropyridin-3-yl)vinyl]phenyl}methylcarbamate, which was solved in trifluoroacetic acid (1.5 ml_) and stirred for 25 min at room temperature. The solvent was removed under reduced pressure, and the residue was

dissolved in dichloromethane and extracted with brine and water. The organic layer was dried over sodium sulphate, filtrated and concentrated. The crude product was purified by chromatography on silica gel (ethyl acetate in hexane 0 to 20%) followed by thin layer chromatography on silica gel yield (10% ethyl acetate in hexane) to yield 47 mg of the title compound.

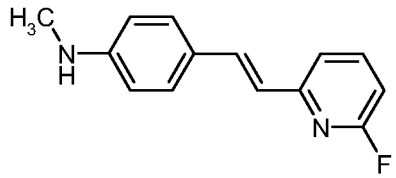
^{1}H-NMR (300 MHz, CHLOROFORM-d) δ = 2.88 (s, 3H), 6.61 (d, 2H), 6.93 (d, 1H), 7.15 (m, 2H), 7.40 (d, 2H), 7.94 (m, 1H), 8.02 (m, 1H) ppm. ^{19}F-NMR (376 MHz, CHLOROFORM-d) δ = -72.0 (s, 1F) ppm. MS ES+ m/z = 229 (M+1).

Example 3 Synthesis of 4-[(E)-2-(6-fluoropyridin-2-yl)vinyl]-N-methyl-aniline (1c)

Compound **1c** was synthesized by Horner-Wadsworth-Emmons reaction and subsequent acidic cleavage of the Boc-protecting group.



Synthesis of 4-[(E)-2-(6-fluoropyridin-2-vnvinyll-N-methylaniline **(1c)**



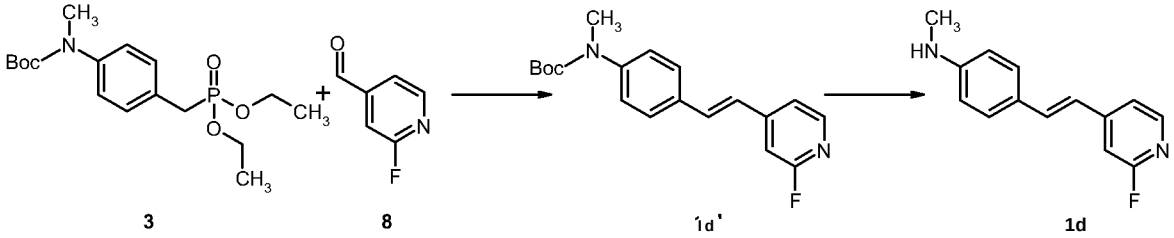
To a solution of diethyl {4-[(tertbutoxycarbonyl)(methyl)amino]benzyl} phosphonate (480 mg, 1.34 mmol) and 6-fluoropyridine-2-carbaldehyde (185 mg, 1.48 mmol) in DMF (10 mL) was added to a solution of potassium tert.butylat (377 mg, 3.36 mmol) in DMF (20 mL). After stirring for one hour the reaction mixture was quenched with ice water, extracted with dichloromethane, washed with brine and dried over sodium sulfate. The residue was purified by chromatography on silica gel (ethyl acetate in hexane 5 to 10%) to yield tert-butyl {4-[(E)-2-(6-fluoropyridin-2-yl)vinyl]phenyl}methylcarbamate, which was solved in trifluoroacetic acid (1.5 mL) and stirred for 25 min at room temperature. The solvent was removed under reduced pressure, and the residue was

dissolved in dichloromethane and extracted with brine and water. The organic layer was dried over sodium sulphate, filtrated and concentrated. The crude product was purified by chromatography on silica gel (ethyl acetate in hexane 0 to 20%) followed by thin layer chromatography on silica gel yield (10% ethyl acetate in hexane) to yield 10 mg of the title compound.

^{1}H-NMR (300 MHz, CHLOROFORM-d) δ = 2.87 (s, 3H), 6.60 (d, 2H), 6.69 (dd, 1H), 6.87 (d, 1H), 7.13 (m, 1H), 7.94 (m, 1H), 7.43 (d, 2H), 7.60 (d, 1H), 7.68 (q, 1H) ppm. ^{19}F-NMR (376 MHz, CHLOROFORM-d) δ = -66.9 (s, 1F) ppm.

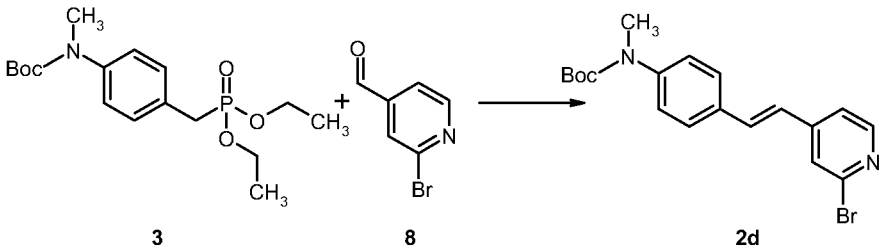
Example 4 Synthesis of 4-[(E)-2-(2-fluoropyridin-4-yl)vinyl]-N-methyl-aniline (1d)

Compound **1d** was synthesized by Horner-Wadsworth-Emmons reaction and subsequent acidic cleavage of the Boc-protecting group.



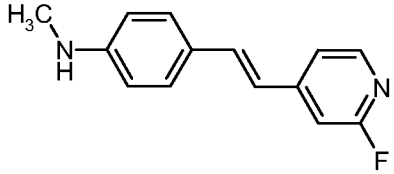
3 8 1d' 1d

Labeling precursor **2d** was synthesized from bromo derivative **8** and phosphonate **3**.



3 8 2d

Synthesis of 4-[(E)-2-(2-fluoropyridin-4-yl)vinyll-N-methylaniline **(1d)**

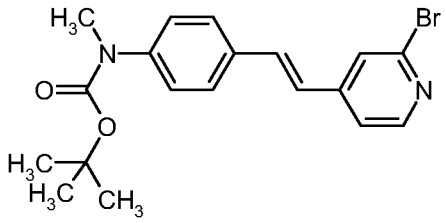


To a solution of diethyl {4-[(tertbutoxycarbonyl)(methyl)amino]benzyl} phosphonate (250 mg, 0.70 mmol) and 2-fluoropyridine-4-carbaldehyde (88 mg,

0.70 mmol) in DMF (2 mL) was added a solution of potassium tert.butylat (196 mg, 1.75 mmol) in DMF (8 mL). After stirring for one hour the reaction mixture was quenched with saturated aqueous ammonium chloride solution, extracted with dichloromethane, washed with brine and dried over sodium sulfate. The residue was purified by chromatography on silica gel (ethyl acetate in hexane 0 to 50%) to yield 60 mg tert-butyl {4-[(E)-2-(2-fluoropyridin-4-yl)vinyl]phenyl}methylcarbamate, which was solved in dichloromethane (3 mL) and treated with a 4 M HCl in dioxane (180 µL) for 72 hours at room temperature. The residue was purified by chromatography on silica gel (methanol in dichloromethane 0 to 20%) followed by thin layer chromatography on silica gel yield (30% ethyl acetate in hexane) to yield 13.9 mg of the title compound.

^{1}H-NMR (300 MHz, DMSO-d$_6$) δ = 2.87 (s, 3H), 6.93 (d, 1H), 7.34 (d, 2H), 7.43 (m, 2H), 7.54 (d, 1H), 7.66 (d, 1H), 7.74 (d, 2H), 8.21 (d, 1H) ppm. ^{19}F-NMR (376 MHz, CHLOROFORM-d) δ = -70.06 (s, 1F) ppm. LC/MS ES+ m/z = 228.9 (M+1).

Synthesis of tert-butyl {4-[(E)-2-(2-bromopyridin-4-yl)vinyllphenyl)methyl-



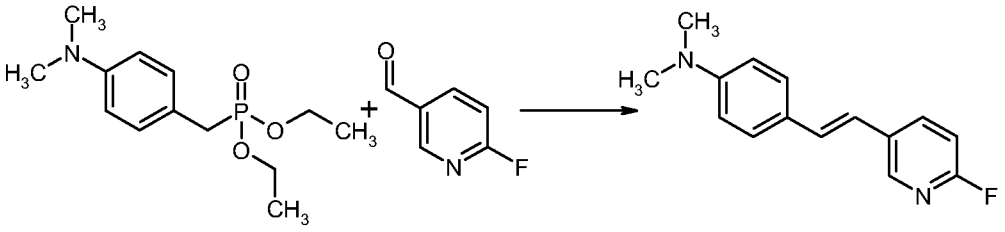
carbamate **(2d)**

To a solution of diethyl diethyl {4-[(tert-butoxycarbonyl)(methyl)amino]benzyl} phosphonate (384 mg, 1.08 mmol) in THF (4.4 mL) was added a 1 M solution of potassium tert.butylat (1.6 mL, 1.6 mmol) in THF at 0°C. After stirring for 15 minutes at 0°C 2-bromopyridine-4-carbaldehyde (200 mg, 1.08 mmol) in THF (3.5 mL) was added and stirring was continued for 30 minutes at 0°C. The reaction mixture was quenched with saturated aqueous ammonium chloride solution, extracted with diethyl ether, washed with brine and dried over sodium sulfate. The residue was purified by chromatography on silica gel (ethyl acetate in hexane 0 to 20%) to yield 41 mg (9.8%) of the title compound and 42 mg of the Z isomer.

^{1}H-NMR (300 MHz, CDCl3) δ = 1.48 (s, 9H), 3.30 (s, 3H), 6.90 (d, 1H), 7.25 - 7.35 (m, 4H), 7.50 (d, 1H), 7.56 (d, 2H), 8.32 (d, 1H) ppm. MS ES+ m/z = 388 / 390 (M+1).

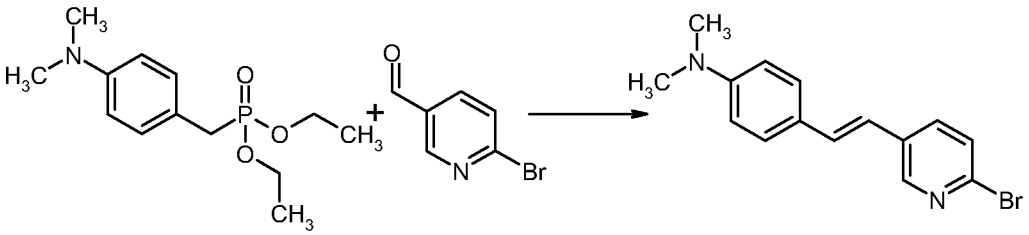
Example 5 Synthesis of 4-[(E)-2-(6-fluoropyridin-3-yl)vinyl]-N,N-dimethyl-aniline (1e)

Compound **1c** was synthesized by Horner-Wadsworth-Emmons reaction using phosphanate **9** and aldehyde **4**.



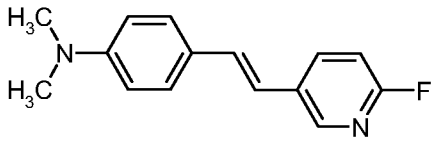
9 **4** **1e**

Labeling precursor **2d** was synthesized from bromo derivative **8** and phosphonate **3**.



9 **5** **2e**

Synthesis of 4-[(E)-2-(6-fluoropyridin-3-yl)vinyl1-N,N-dimethylaniline **(1e)**

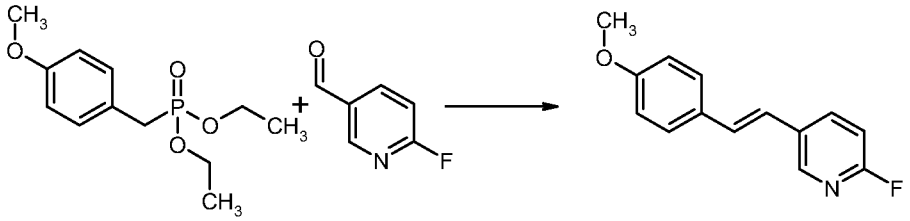


To a solution of diethyl [4-(dimethylamino)benzyl]phosphonate (208 mg, 0.77 mmol) and 6-fluoropyridine-3-carbaldehyde (96 mg, 0.77 mmol) in DMF (2 mL) was added a solution of potassium tert.butylat (215.1 mg, 1.92 mmol) in DMF (8 mL). After stirring for one hour the reaction mixture was quenched with saturated aqueous ammonium chloride solution, extracted with dichloromethane, washed with brine and dried over sodium sulfate. The residue was purified by

chromatography on silica gel (ethyl acetate in hexane 0 to 50%) to yield 6 mg (3%) of the title compound. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 3.02 (s, 6H), 6.78 (br. , 2H), 6.87 (d, 1H), 6.91 (dd, 1H), 7.02 (d, 1H), 7.43 (d, 2H), 7.92 (ddd, 1H), 8.25 (d, 1H) ppm. ^{19}F NMR (400 MHz, CHLOROFORM-d) δ = -71 .06 (s, 1F). MS ES+ m/z = 243.14 (M+1).

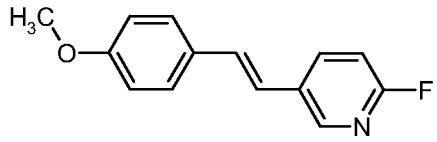
Example 6 Synthesis of 2-fluoro-5-[(E)-2-(4-methoxyphenyl)vinyl]pyridine (1f)

Compound **1f** was synthesized by Horner-Wadsworth-Emmons.



10 **4** **1f**

Synthesis of 2-fluoro-5-[(E)-2-(4-methoxyphenyl)vinyl1pyridine **(1f)**



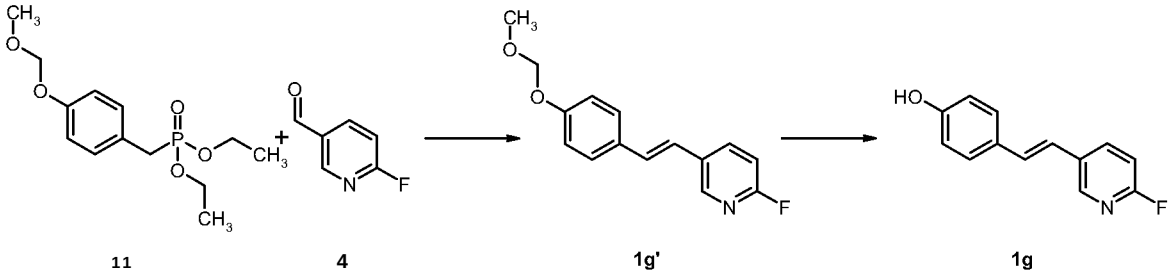
To a solution of diethyl [4-(meththoxy)benzyl]phosphonate (500 mg, 1.94 mmol) and 6-fluoropyridine-3-carbaldehyde (242 mg, 1.94 mmol) in DMF (4 mL) was added a solution of potassium tert.butylat (543 mg, 4.8 mmol) in DMF (16 mL). After stirring for one hour the reaction mixture was quenched with saturated aqueous ammonium chloride solution, extracted with dichloromethane, washed with brine and dried over sodium sulfate. The residue was purified by chromatography on silica gel (ethyl acetate in hexane 0 to 50%) to yield 50.6 mg (10.3%) of the title compound.

^{1}H-NMR (400 MHz, CHLOROFORM-d) d = 3.85 (s, 3H), 6.92 (d, 1H), 6.92 (dd, 1H), 6.93 (d, 2H), 7.05 (d, 1H), 7.46 (d, 2H), 7.93 (ddd, 1H), 8.28 (d, 1H) ppm.

^{19}F-NMR (376 MHz, CHLOROFORM-d) δ = -70.13 (d, 1F) ppm. MS ES+ m/z = 230.13 (M+1).

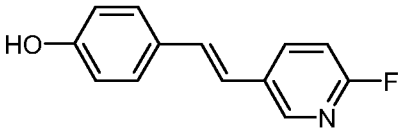
Example 7 Synthesis of 4-[(E)-2-(6-fluoropyridin-3-yl)vinyl]phenol (1g)

Compound **1d** was synthesized by Horner-Wadsworth-Emmons reaction and subsequent acidic cleavage of the Mom-protecting group.



11 4 1g' 1g

Synthesis of 4-[(E)-2-(6-fluoropyridin-3-yl)vinyl1phenol **(1g)**

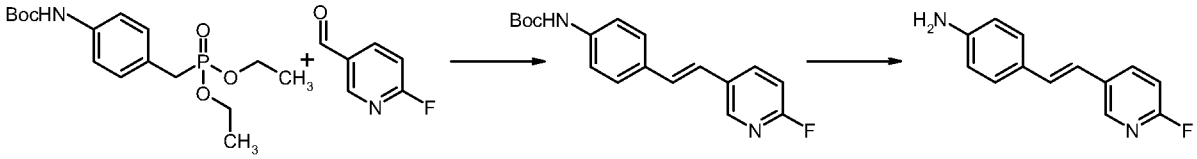


To a solution of diethyl [4-(methoxymethoxy)benzyl]phosphonate (250 mg, 0.87 mmol) and 6-fluoropyridine-3-carbaldehyde (108.5 mg, 0.87 mmol) in DMF (2 ml_) was added a solution of potassium tert.butylat (243 mg, 2.17 mmol) in DMF (8 ml_). After stirring for one hour the reaction mixture was quenched with saturated aqueous ammonium chloride solution, extracted with dichloromethane, washed with brine and dried over sodium sulfate. The residue was purified by chromatography on silica gel (ethyl acetate in hexane 0 to 50%) to yield 32.8 mg 2-fluoro-5-{(E)-2-[4-(methoxymethoxy)phenyl]vinyl}pyridine, which was solved in THF (2 ml_) and treated with aqueous 18.5% HCl (182 µl_) at 50°C for one hour. The solution was concentrated under reduced pressure to yield 25.4 mg of the title compound as a yellow solid.

^{1}H-NMR (400 MHz, DMSO-d_6) δ = 6.79 (d, 2H), 7.05 (d, 1H), 7.18 (dd, 1H), 7.24 (d, 1H), 7.43 (d, 2H), 8.20 (ddd, 1 H), 8.34 (d, 1 H) ppm. ^{19}F-NMR (376 MHz, CHLOROFORM-d) δ = -71 .20 (d, 1 F) ppm. LC/MS ES+ m/z = (M+1).

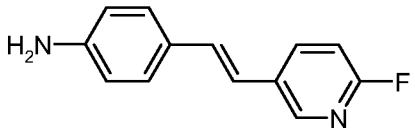
Example 8 Synthesis of 4-[(E)-2-(6-fluoropyridin-3-yl)vinyl]aniline (1h)

Compound **1h** was synthesized by Horner-Wadsworth-Emmons reaction and subsequent acidic cleavage of the Boc-protecting group.



12 4 1h' 1h

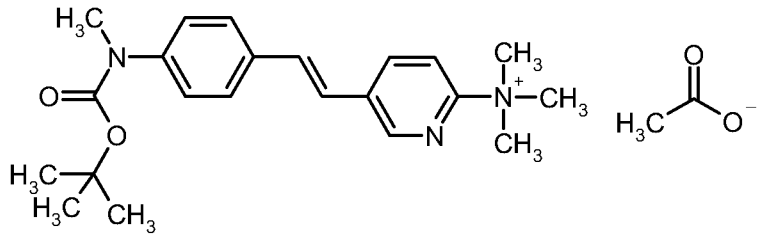
Synthesis of 4-[(E)-2-(6-fluoropyridin-3-yl)vinyl1aniline **(1h)**



To a solution of diethyl diethyl {4-[(tert-butoxycarbonyl)amino]benzyl} phosphonate (272 mg, 0.79 mmol) and 6-fluoropyridine-3-carbaldehyde (99 mg, 0.79 mmol) in DMF (2 mL) was added a solution of potassium tert.butylat (196 mg, 1.75 mmol) in DMF (8 mL). After stirring for one hour the reaction mixture was quenched with saturated aqueous ammonium chloride solution, extracted with dichloromethane, washed with brine and dried over sodium sulfate. The residue was purified by chromatography on silica gel (ethyl acetate in hexane 0 to 50%) to yield 21mg of tert-butyl {4-[(E)-2-(6-fluoropyridin-3-yl)vinyl]phenyl} carbamate, which was solved in dichloromethane (1 mL) and treated with a 4 M HCl in dioxane (68 µL) for 24 under reflux. The solution was concentrated under reduced pressure and purified by thin layer chromatography on silica gel (30% ethyl acetate in hexane) to yield 9 mg of the title compound.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 3.81 (br., 2H), 6.69 (d, 2H), 6.86 (d, 1H), 6.91 (dd, 1H), 7.00 (d, 1H), 7.34 (d, 2H), 7.91 (ddd, 1H), 8.25 (d, 1H) ppm. ^{19}F-NMR (376 MHz, CHLOROFORM-d) δ = -70.70 (d, 1F) ppm. MS ES+ m/z = 214.9 (M+1).

Synthesis of 5-[(E)-2-{4-[(tert-butoxycarbonyl)(methyl)aminolphenyl)vinyl1-N,N,N-trimethylpyridin-2-aminium acetate **(2i)**



To a solution of diethyl {4-[(tert-butoxycarbonyl)(methyl)amino]benzyl} phosphonate (1.5 g, 4.2 mmol) and 6-fluoropyridine-3-carbaldehyde (525 mg, 4.2 mmol) in DMF (20 ml_) was added a solution of potassium tert.butylat (1.18 mg, 10.5 mmol) in DMF (40 ml_). After stirring for 6 hours the reaction mixture was quenched with saturated aqueous ammonium chloride solution, extracted with diethyl ether, washed with brine and dried over sodium sulfate. The residue was purified by chromatography on silica gel (ethyl acetate in hexane 0 to 25%) to yield 800 mg of tert-butyl (4-{(E)-2-[6-(dimethylamino)pyridin-3-yl]vinyl}phenyl)methylcarbamate, which (100 mg, 0.28 mmol) was suspended in toluene (3 ml_) and treated with methyl trifluormethansulfonate (31 µ, 0.28 mmol). Stirred for 20 hours while the methyl trifluormethansulfonate addition was repeated after 4 hours.The mixture was filtered, the filtrate concentrated and purified by HPLC on a XBrigde C18 5µηι 150x19 mm column (methanol in 0.1 M ammonium acetate / acetic acid buffer pH 5.8 hexane 40 to 90%) to yield 26 mg of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.38 (s, 9H), 1.71 (s, 3H), 3.17 (s, 3H), 3.55 (s, 9H), 7.32 (d, 2H), 7.33 (d, 1H), 7.53 (d, 1H), 7.58 (d, 2H), 8.06 (d, 1H), 8.41 (dd, 1H), 8.78 (d, 1H) ppm. MS ES+ m/z = 368.1 (M - $COOCH_3$).

Example 9 Biological evaluation of compounds 1a, 1d, 1e, 1f

Binding studies using human brain homogenate

A competition assay with a tritiated amyloid ligand was performed in 96-well plates (Greiner bio-one; Cat. 651201 ; Lot. 06260130) using brain homogenate from AD patients.

Homogenates were prepared by homogenizing (Ultra-Turrax, setting 2, 30 s, 24000 rpm) dissected frontal cortex containing grey matter and white matter from AD patients in phosphate buffered saline (PBS, pH 7.4). The homogenate with a concentration of 100 mg wet tissue/ml was divided into aliquots of 300 µI and stored at -80°C.

Varying concentrations of the unlabeled test substances were incubated with 100 µg/ml homogenate and 10 nM of the tritiated ligand in PBS, 0.1 % BSA (final

volume 200 µl) for 3 h at room temperature. Subsequently the binding mixture was filtered through Whatman GF/B filters (wetted with PBS, 0.1 % BSA) using a Filtermate 196 harvester (Packard). Filters were then washed twice with PBS, 0.1% BSA and 40 µl scintillator was added to each well before the bound radioactivity was measured in a TopCount devise (Perkin Elmer). Non-specific binding was assessed by adding an excess of 1000x of the reference ligand to the reaction mixture. Finally IC50 values were calculated with the help of appropriate analysis software.

Table 1 **IC50 to AD brain homagenate**

Compound	**IC_{50} [nM]**
4-[(E)-2-(6-fluoropyridin-3-yl)vinyl]-N-methylaniline **(1a)**	31
4-[(E)-2-(2-fluoropyridin-4-yl)vinyl]-N-methylaniline **(1d)**	40
4-[(E)-2-(6-fluoropyridin-3-yl)vinyl]-N,N-dimethylaniline **(1e)**	31
2-fluoro-5-[(E)-2-(4-methoxyphenyl)vinyl]pyridine **(1f)**	88
4-[(E)-2-(6-fluoropyridin-3-yl)vinyl]phenol **(1g)**	108

Autoradiographical analysis

Fresh frozen as well as paraffin embedded sections of the frontal lobe from Alzheimer's dementia patients (AD) and age matched controls (HC) were used for the study.

Frozen sections, sliced at 18 µm thickness on a cryostate (Leica, Germany) and paraffin sections, sliced on a sliding microtom (Leica) at a thickness of 6 µm, were mounted onto glass slides (Superfrost Plus, Fa.Menzel, Braunschweig Germany). Frozen sections were allowed to adhere to the slides for several nights at -20°C. The paraffin sections were deparaffinized using routine histological methods. For binding studies sections were incubated with the F-18 labeled test compound at 10 Bq/µl diluted in 25mM Hepes buffer, pH 7.4, 0,1 %

(BSA) (200-300 µl/slide) for 1,5 hour at room temperature in a humidified chamber. For blocking experiments an excess of the unlabeled test substance was added to the incubation mixture. After hybridization, sections were washed four times with Hepes buffer, 0.1 % BSA (or alternatively two times with 40% ethanol) and finally dipped two times into dest. water for 10 sec. The air-dried sections were exposed to imaging plates and signals were detected by a phosphoimager device (Fuji BAS5000).

Biodistribution experiments in mice

Biodistribution and excretion studies were performed in male NMRI mice (body weight approx. 30 g; 3 animals per time point). During an acclimation period of at least 3 days before the beginning of the study, animals were clinically examined to ascertain the absence of abnormal clinical signs.

At 2, 5, 30, 60, 240 min post intravenous injection via the tail vein of ca. 150 kBq of the test compound (ca. 100 µl), urine and feces were quantitatively collected. At the same time points, animals were sacrificed by decapitation and under isoflurane anaesthesia and organs and tissues of interest were removed for the determination of radioactivity using a gamma-counter. For analysis the decay corrected percentage of the injected dose per tissue weight (%ID/g ± standard deviation) was calculated.

Table 2 Brain uptake of compound [F-18]1a in % of injected dose per gram tissue [%ID/g]. Distribution of F-18 signal after administration of compound [F-18]1a in mice at 2 min and 60 min after compound administration

Compound	Brain uptake at 2 min [%ID/g]	Brain uptake at 60 min [%ID/g]	Brain wash-out ratio [%ID/g at 2min] / [%ID/g at 60min]
1a	5.6	0.3	18.6

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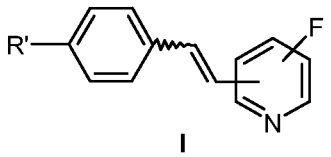
Claims

1. A compound according to formula I



I

or pharmaceutically acceptable salts of an inorganic or organic acid thereof, hydrates, complexes, esters, amides, solvates or prodrugs thereof, encompassing single isomers and mixtures thereof,

wherein

R' is selected from the group comprising:

a) **0-R^A,**

b) **NR^BR^C**

and wherein

R^A, R^B, R^c are selected from the group comprising:

a) hydrogen,

b) branched or non-branched (C1-C5)alkyl,

c) branched or non-branched (C3-C5)alkenyl, with the proviso that **R^A ,R^B** and **R^c** are not attached to O or **N** with a sp2 hybridized carbon atom,

d) branched or non-branched (C3-C5)alkynyl, with the proviso that **R^A ,R^B** and **R^c** are not attached to O or **N** with a sp hybridized carbon atom,

e) (C1 -C5)alkyl-[0-(C1 -C5)alkyl]$_n$

wherein n is 1-5,

or R^B and R^C together are group that is selected from groups comprising:

a) $-(CH_2)m-$,

b) $-(CH_2)2-0-(CH_2)2-$,

c) $-(CH_2)2-NR^A-(CH_2)2-$.

wherein m is 2-5.

2. A compound according to claim 1,

wherein R' is selected from the group comprising:

a) Hydroxyl,

b) OMe,

c) NH_2,

d) NHMe,

e) NMe_2.

3. A compound according to claim 1,

wherein R' is selected from the group comprising:

a) OMe,

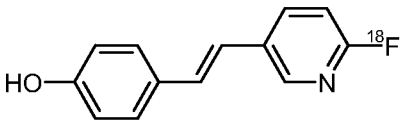
b) NHMe,

c) NMe_2.

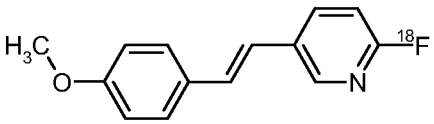
4. A compound according to claims 1-3,

wherein F has the meaning of ^{18}F.

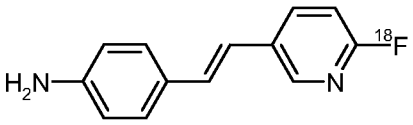
5. A compound according to claim 1 selected from the group of compounds consisting of:



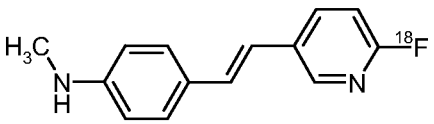
4-{(E)-2-[6-(F-18)fluoropyridin-3-yl]vinyl}phenol,



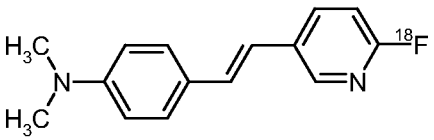
2-(F-18)fluoro-5-[(E)-2-(4-methoxyphenyl)vinyl]pyridine,



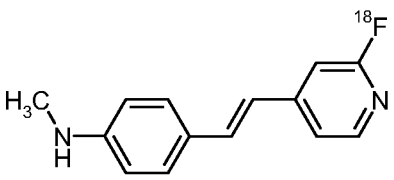
4-{(E)-2-[6-(F-18)fluoropyridin-3-yl]vinyl}aniline,



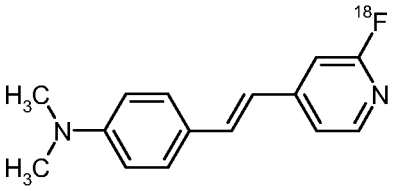
4-{(E)-2-[6-(F-1 8)fluoropyridin-3-yl]vinyl}-N-methylaniline,



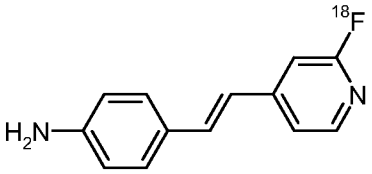
4-{(E)-2-[6-(F-18)fluoropyridin-3-yl]vinyl}-N,N-dimethylaniline,



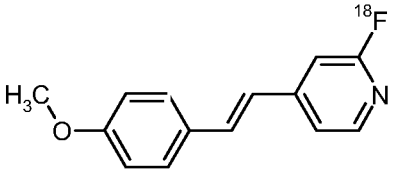
4-{(E)-2-[2-(F-18)fluoropyridin-4-yl]vinyl}-N-methylaniline,



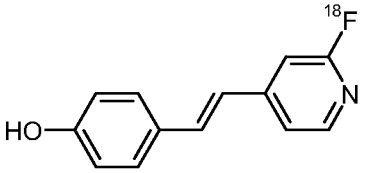
4-{(E)-2-[2-(F-18)fluoropyridin-4-yl]vinyl}-N,N-dimethylaniline,



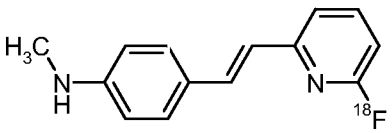
4-{(E)-2-[2-(F-18)fluoropyridin-4-yl]vinyl}aniline,



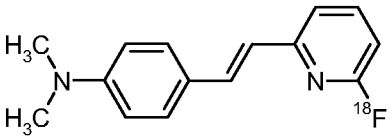
2-(F-18)fluoro-4-[(E)-2-(4-methoxyphenyl)vinyl]pyridine,



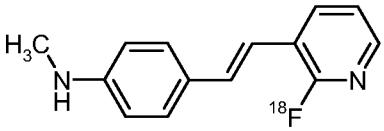
4-{(E)-2-[2-(F-18)fluoropyridin-4-yl]vinyl}phenol,



4-{(E)-2-[6-(F-1 8)fluoropyridin-2-yl]vinyl}-N-methylaniline,

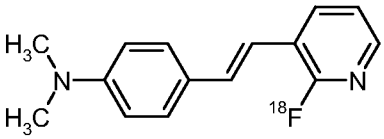


4-{(E)-2-[6-(F-18)fluoropyridin-2-yl]vinyl}-N,N-dimethylaniline,



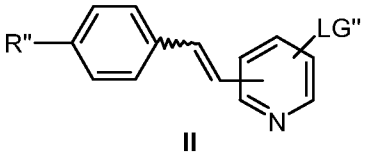
4-{(E)-2-[2-(F-18)fluoropyridin-3-yl]vinyl}-N-methylaniline,

and



4-{(E)-2-[2-(F-18)fluoropyridin-3-yl]vinyl}-N,N-dimethylaniline.

6. A compound according to formula II



II

or pharmaceutically acceptable salts of an inorganic or organic acid thereof, hydrates, complexes, esters, amides, solvates or prodrugs thereof, encompassing single isomers and mixtures thereof,

wherein:

(R" is 0-A ^{1A} and LG is a halogen), or

(R" is 0-A ^{1A} and LG is a nitro group), or

(R" is 0-A ^{1A} and LG is a trialkylammonium group), or

(R" is 0-A ^{1A} and LG is a aryl iodonium group), or

(R" is 0-A ^{1A} and LG is a diaryl sulfonium group), or

(R" is $NA^{1B}A^{1C}$ and **LG** is a halogen), or

(R" is $NA^{1B}A^{1C}$ and **LG** is a nitro group), or

(R" is $NA^{1B}A^{1C}$ and **LG** is a trialkylammonium group), or

(R" is $NA^{1B}A^{1C}$ and **LG** is a aryl iodonium group), or

(R" is $NA^{1B}A^{1C}$ and **LG** is a diaryl sulfonium group);

and wherein

A^{1A}, A^{1B}, A^{1C} are selected from the group consisting of:

a) hydrogen,

b) branched or non-branched (C1-C5)alkyl,

c) branched or non-branched (C3-C5)alkenyl, with the proviso that A^{1A}, A^{1B}, A^{1C} are not attached to **O** or N with a sp2 hybridized carbon atom,

d) branched or non-branched (C3-C5)alkynyl, with the proviso that A^{1A}, A^{1B}, A^{1C} are not attached to **O** or N with a sp hybridized carbon atom,

e) PG, being a protecting group,

f) (C1 -C5)alkyl-[0-(C1 -C5)alkyl]$_n$,

wherein n is 1-5;

or A^{1B} and A^{1C} together are group that is selected from groups comprising:

a) -$(CH_2)_m$-,

b) -$(CH_2)_2$-0-$(CH_2)_2$-,

c) -$(CH_2)_2$-NA^{1A}-$(CH_2)_2$-.

wherein m is 2-5.

7. A compound according to claim 6, wherein:

((R" is **OPG)** and **(LG** is chloro, iodo or bromo)), or

((R" is OMe) and (LG is chloro, iodo)), or

the compound is 2-bromo-6-[(E)-2-(4-methoxyphenyl)vinyl]pyridine, or

the compound is 2-bromo-3-[(E)-2-(4-methoxyphenyl)vinyl]pyridine, or

the compound is 2-bromo-5-[(E)-2-(4-methoxyphenyl)vinyl]pyridine, or

((R'' is OPG or OMe) and (LG is a nitro group)), or

((R" is OPG or OMe) and (LG is a trimethylammonium group)), or

((R" is OPG or OMe) and (LG is a aryl iodonium group)), or

((R" is OPG or OMe) and (LG is a diaryl sulfonium group)), or

((R" is NPGH) and (LG is chloro, iodo or bromo)), or

((R" is NPGH) and (LG is a nitro group)), or

((R" is NPGH) and (LG is a trimethylammonium group)), or

((R" is NPGH) and (LG is a aryl iodonium group)), or

((R" is NPGH) and (LG is a diaryl sulfonium group)), or

((R" is NPG_2) and (LG is chloro, iodo or bromo)), or

((R" is NPG_2) and (LG is a nitro group)), or

((R" is NPG_2) and (LG is a trimethylammonium group)), or

((R" is NPG_2) and (LG is a aryl iodonium group)), or

((R" is NPG_2) and (LG is a diaryl sulfonium group)), or

((R" is NPGMe) and (LG is chloro, iodo or bromo)), or

((R" is NPGMe) and (LG is a nitro group)), or

((R" is NPGMe) and (LG is a trimethylammonium group)), or

((R" is NPGMe) and (LG is a aryl iodonium group)), or

((R" is NPGMe) and (LG is a diaryl sulfonium group)), or

((R" is NMe_2) and (LG is chloro, iodo or bromo)), or

((R" is NMe_2) and (LG is a nitro group)), or

((R" is NMe_2) and (LG is a trimethylammonium group)), or

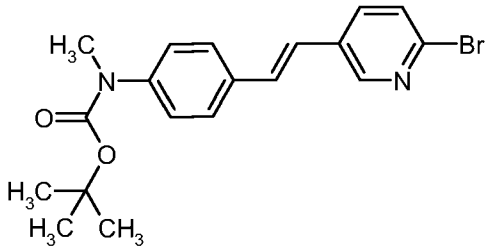
((R" is $NM\theta_2$) and (LG is a aryl iodonium group)), or

((R" is NMe_2) and (LG is a diaryl sulfonium group)).

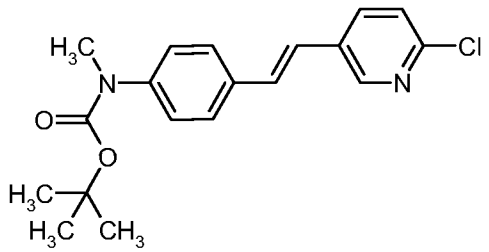
8. A compound according to claim 6 or 7, wherein PG is selected from the group comprising:

a) Boc,
b) Methoxymethyl,
c) Acetyl,
d) Trityl,
e) Fmoc.

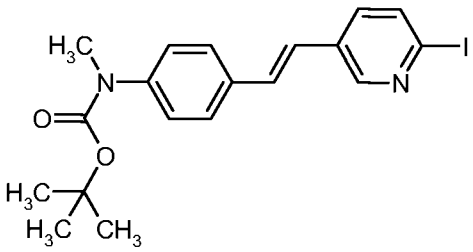
9. A compound according to claim 6, selected from the group of compounds consisting of



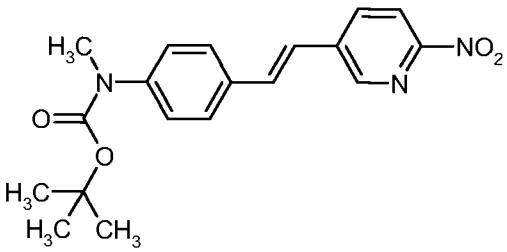
tert-butyl {4-[(E)-2-(6-bromopyridin-3-yl)vinyl]phenyl}methylcarbamate,



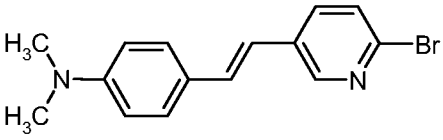
tert-butyl {4-[(E)-2-(6-chloropyridin-3-yl)vinyl]phenyl}methylcarbamate,



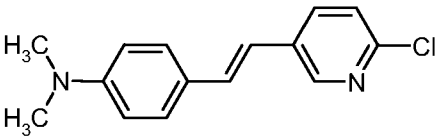
tert-butyl {4-[(E)-2-(6-iodopyridin-3-yl)vinyl]phenyl}methylcarbamate,



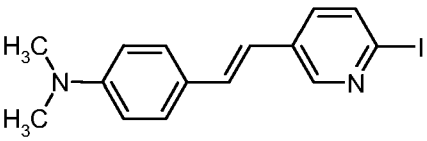
tert-butyl {4-[(E)-2-(6nitropyridin-3-yl)vinyl]phenyl}methylcarbamate,



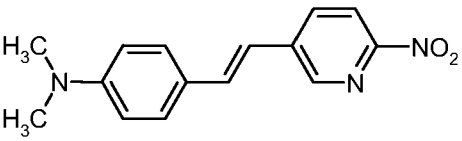
N,N-dimethyl-4-[(E)-2-(6-bromopyridin-3-yl)vinyl]aniline,



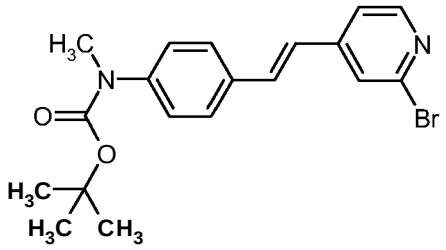
N,N-dimethyl-4-[(E)-2-(6-chloropyridin-3-yl)vinyl]aniline,



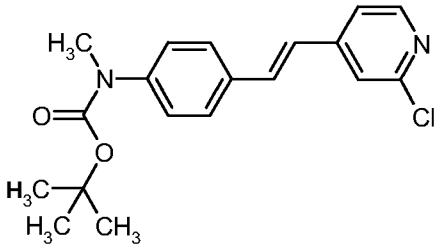
N,N-dimethyl-4-[(E)-2-(6-iodopyridin-3-yl)vinyl]aniline,



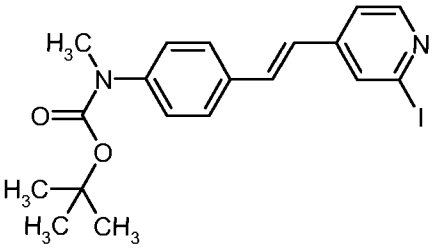
N,N-dimethyl-4-[(E)-2-(6-nitropyridin-3-yl)vinyl]aniline,



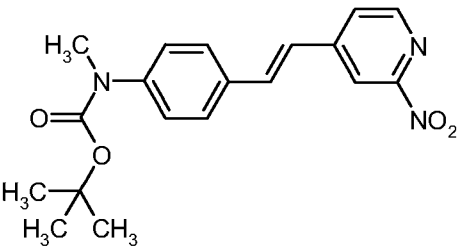
tert-butyl {4-[(E)-2-(2-bromopyridin-4-yl)vinyl]phenyl}methylcarbamate,



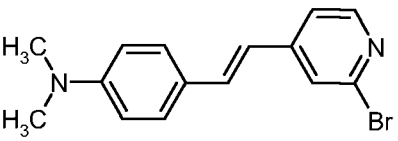
tert-butyl {4-[(E)-2-(2-chloropyridin-4-yl)vinyl]phenyl}methylcarbamate,



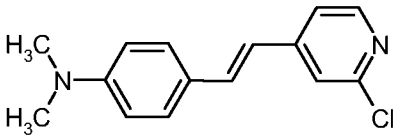
tert-butyl {4-[(E)-2-(2-iodopyridin-4-yl)vinyl]phenyl}methylcarbamate,



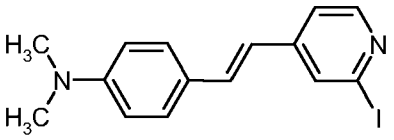
tert-butyl {4-[(E)-2-(2-nitropyridin-4-yl)vinyl]phenyl}methylcarbamate,



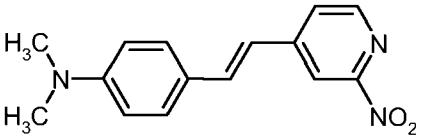
4-[(E)-2-(2-bromopyridin-4-yl)vinyl]-N,N-dimethylaniline,



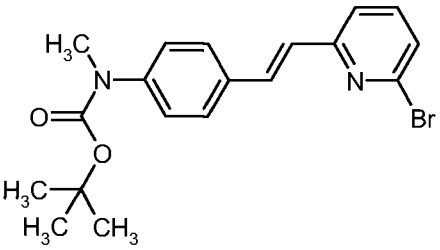
4-[(E)-2-(2-chloropyridin-4-yl)vinyl]-N,N-dimethylaniline,



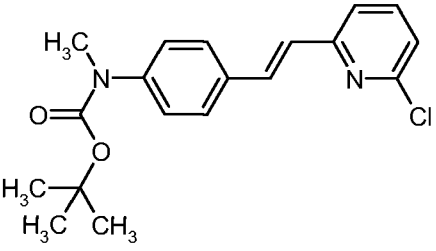
4-[(E)-2-(2-iodopyridin-4-yl)vinyl]-N,N-dimethylaniline,



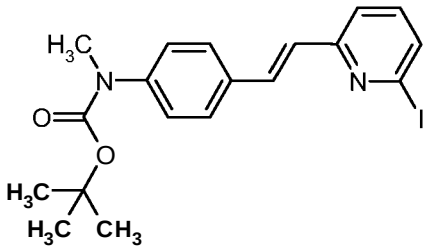
4-[(E)-2-(2-nitropyridin-4-yl)vinyl]-N,N-dimethylaniline,



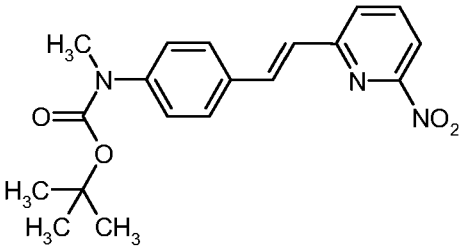
tert-butyl {4-[(E)-2-(6-bromopyridin-2-yl)vinyl]phenyl}methylcarbamate,



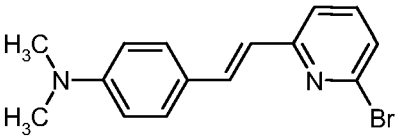
tert-butyl {4-[(E)-2-(6-chloropyridin-2-yl)vinyl]phenyl}methylcarbamate,



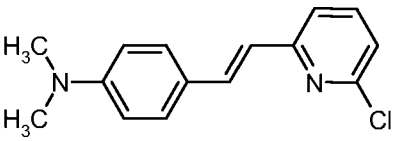
tert-butyl {4-[(E)-2-(6-iodopyridin-2-yl)vinyl]phenyl}methylcarbamate,



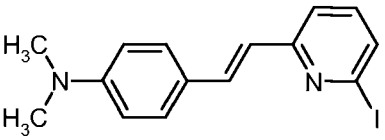
tert-butyl {4-[(E)-2-(6-nitropyridin-2-yl)vinyl]phenyl}methylcarbamate,



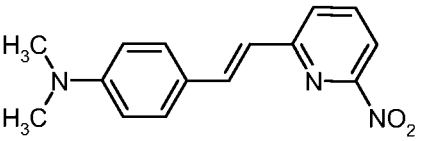
4-[(E)-2-(6-bromopyridiri-2-yl)vinyl]-N,N-dimethylaniline,



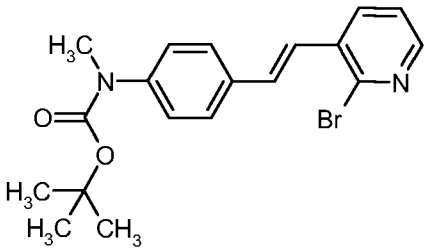
4-[(E)-2-(6-chloropyridin-2-yl)vinyl]-N,N-dimethylaniline,



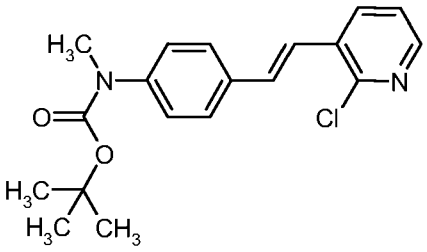
4-[(E)-2-(6-iodopyridin-2-yl)vinyl]-N,N-dimethylaniline,



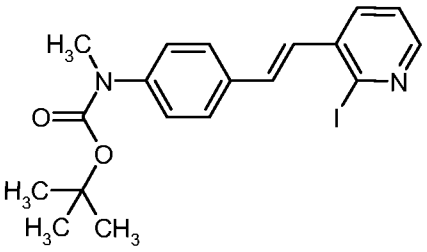
4-[(E)-2-(6-nitropyridin-2-yl)vinyl]-N,N-dimethylaniline,



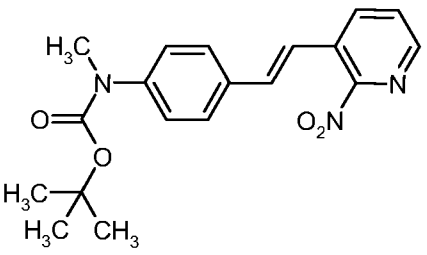
tert-butyl {4-[(E)-2-(2-bromopyridin-3-yl)vinyl]phenyl}methylcarbamate,



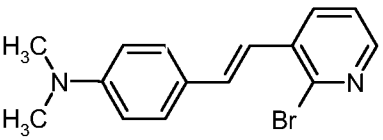
tert-butyl {4-[(E)-2-(2-chloropyridin-3-yl)vinyl]phenyl}methylcarbamate,



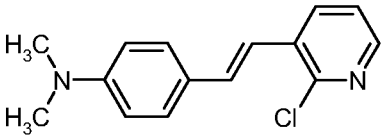
tert-butyl {4-[(E)-2-(2-iodopyridin-3-yl)vinyl]phenyl}methylcarbamate,



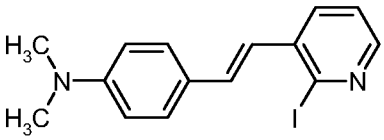
tert-butyl {4-[(E)-2-(2-nitropyridin-3-yl)vinyl]phenyl}methylcarbamate,



4-[(E)-2-(2-bromopyridin-3-yl)vinyl]-N,N-dimethylaniline,

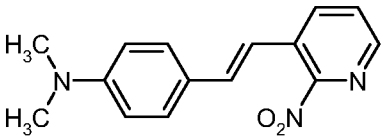


4-[(E)-2-(2-chloropyridin-3-yl)vinyl]-N,N-dimethylaniline,



4-[(E)-2-(2-iodopyridin-3-yl)vinyl]-N,N-dimethylaniline,

and



4-[(E)-2-(2-nitropyridin-3-yl)vinyl]-N,N-dimethylaniline.

10. A method of manufacturing a compound of claim 4 or 5, wherein a suitable precursor compound of claims 6-9 is reacted with a ^{18}F fluorination agent.

11. A method according to claim 10, wherein a compound of claim 5 is prepared by reacting a suitable precursor compound of claim 9 with a ^{18}F fluorination agent.

12. A compound according to claims 4 or 5 as a diagnostic compound.

13. A compound according to claims 4 or 5 as a diagnostic compound for diagnosing Alzheimer's disease.

14. A kit comprising at least one sealed vial comprising a compound according to claims 6 - 9.

15. A kit according to claim 14, comprising at least one sealed vial comprising a compound according to claim 9.

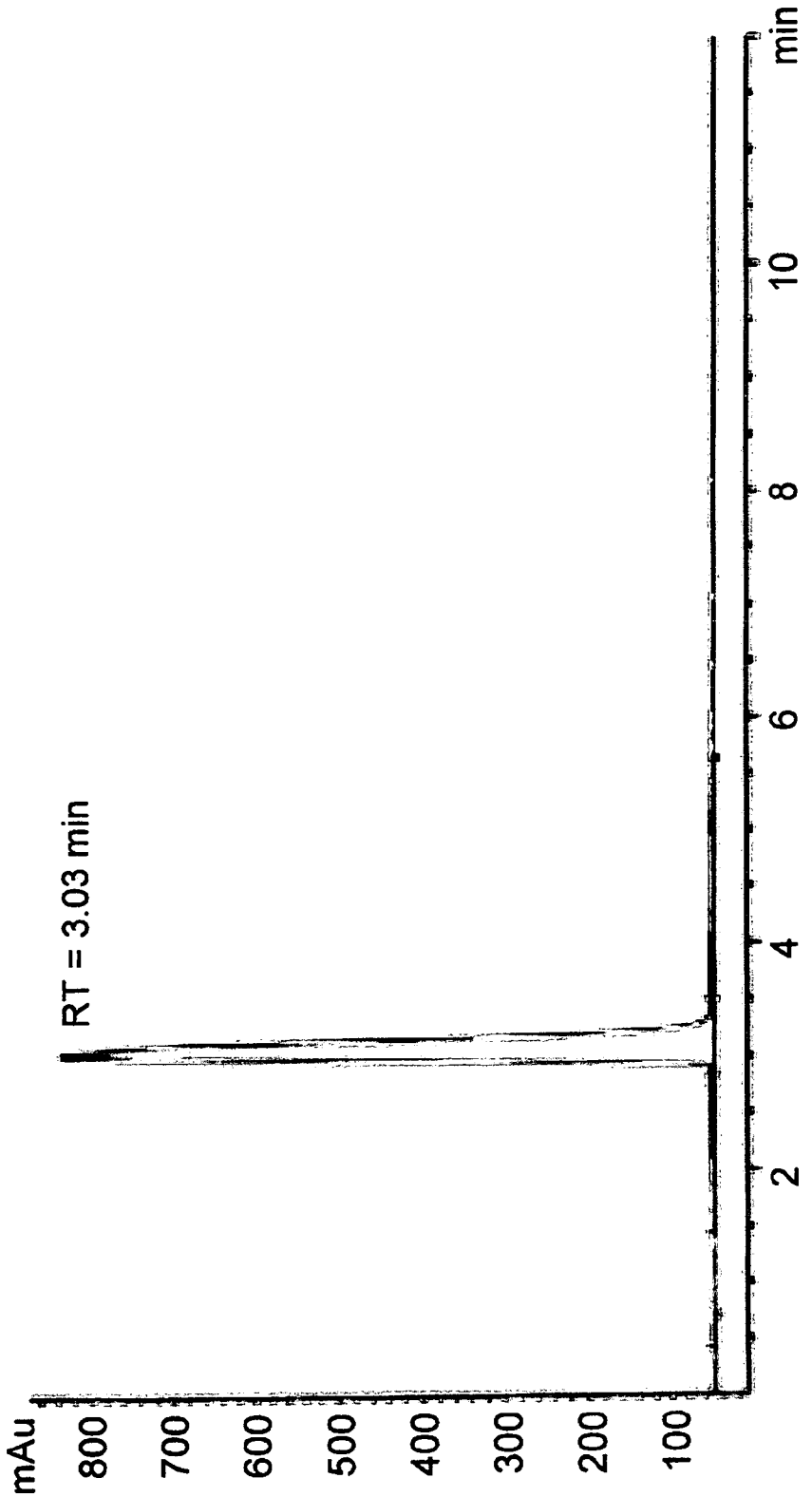


Figure 1

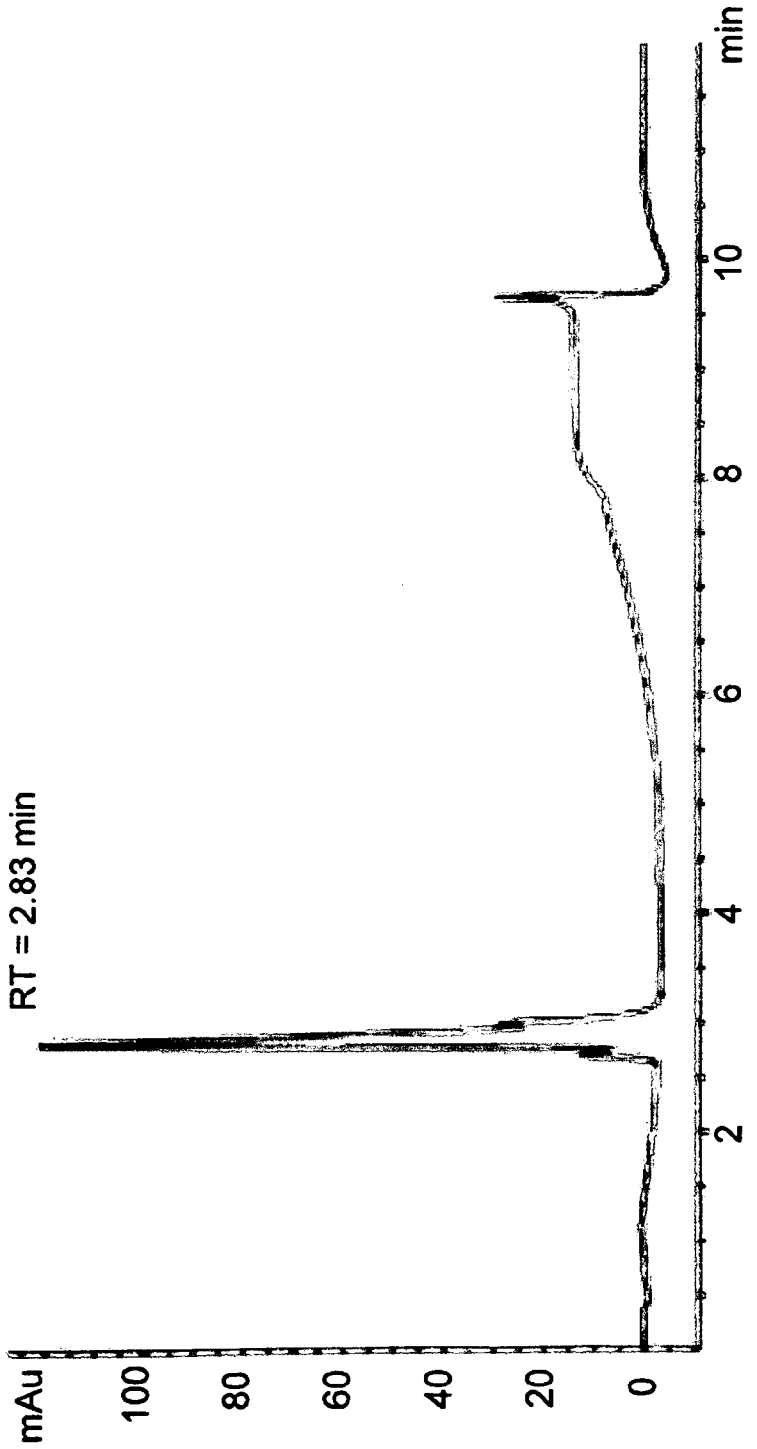


Figure 1, continued

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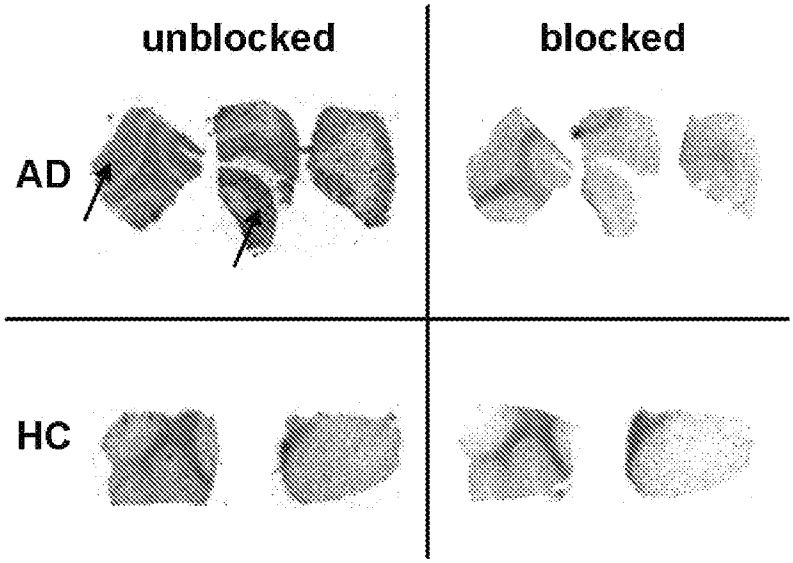

Fig. 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/057630

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/61 C07D213/72 A61K51/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal , CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	the whole document	1-15

-/- ·

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 July 2011	08/08/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Guspanova, Jana

1

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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X	M. HOOPER ET AL: "Preparation and antibacterial activity of isatogens and related compounds" , JOURNAL OF PHARMACY AND PHARMACOLOGY, vol . 17, no. 11, 1 November 1965 (1965-11-01) , pages 734-741 , XP55002988, ISSN: 0022-3573 , DOI: 10. 1111/j .2042-7158. 1965 .tb07596.x compounds VI and VII on page 735	6,7
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 8 May 2009 (2009-05-08) , Ko et al: "Production of ruthenium complex amphipathic compound as dye for dye-sensitized solar cell", XP002651244, retrieved from STN Database accession no. 2010: 1450746 abstract	6,7

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Information on patent family members

International application No
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