

The present invention relates to novel compounds useful for binding and imaging amyloid deposits and their use in detecting or treating Alzheimer's disease and amyloidoses.

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Background of the Invention

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 (A β) and neurofibrillary tangles comprised of paired helical filaments of hyperphosphorylated tau. The 39 to 43 amino acids comprising A β peptides are derived from the larger amyloid precursor protein (APP). In the amyloidogenic pathway, A β peptides are cleaved from APP by the sequential proteolysis of β - and γ -secretases. A β peptides are released as soluble proteins and can be detected at low levels in the cerebrospinal fluid (CSF) in normal aging brains. During the progress of AD the A β 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).

Alzheimer's disease is becoming a great health and social economical problem all over the world. There are great efforts being made to develop techniques and methods for the early detection and effective treatment of the disease. Currently, diagnosis of AD in an academic setting of memory-disorder clinics 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. However, post mortem histological examination of the brain is still the only definite diagnosis of this disease. Thus the *in vivo* detection of one pathological feature of the disease – the deposition of amyloid aggregates in the brain – is thought to have a big impact on the early detection of AD and differentiation from other dementias. Additionally, most disease modifying therapies that are under development are aiming at lowering 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.

In addition, amyloid deposits are also known to play a role in amyloidoses, in which amyloid proteins 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 and must cross the blood brain barrier. PET tracers that have been already investigated in humans regarding their binding patterns in brains of AD patients are [F-18]FDDNP (Shoghi-Jadid et. al, Am J Geriatr Psychiatry 2002; 10:24-35), [C-11]PIB (Klunk e. al, Ann Neurol. 2004 55:306-319), [C-11]SB-13 (Verhoeff et. al, Am J Geriatr Psychiatry 2004; 12:584-595, [F-18]Bay 94-9172 (Rowe et al. Lancet Neurol 2008, 7:129-135), [C-11]BF227 (Kudo et. al, J Nucl. Med 2007; 49:554-561), and [F-18]PIB (Farrar et. al Turku PET Symposium 2007, Abstract 49). For recent reviews see Lockhardt, Drug Discov Today, 2006 11:1093-1099, Henriksen et al., Eur. J. Nucl. Med. Mol. Imaging 2007, Cohen, Mol. Imaging Biol. 2007 9:204-216, Nordberg, Curr. Opin Biol. 2007, 20:398-402, Small et al., Neurology 2008 7:161-172, Nordberg, Eur. J. Nucl. Med. Mol. Imaging 2008, 35, S46-S50.

Besides their specific binding to amyloid deposits in the brain, the currently most promising PET tracers show a disadvantageous non-specific accumulation, especially in white matter brain regions in AD patients as well as in HC. Generally, non-specific background binding interferes with the image quality and could e.g. impair the quantification of amyloid and the diagnosis of very early stages of the disease.

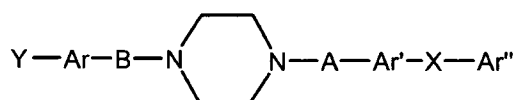
Accordingly, the problem underlying the present invention was to provide compounds suited for detecting amyloid deposits in patients with amyloid-related diseases with high specificity at an early stage of the disease.

The present invention solves this problem by providing novel tracers with high affinity for amyloid β and rapid elimination of non-specific signals from the brain.

Description of the invention

The present invention is directed to compounds that bind to amyloid deposits and are able to pass through the blood-brain barrier, and are therefore useful in diagnosing Alzheimer's disease and amyloidoses in a patient, preferably at an early stage of the disease.

Accordingly, in one aspect, the invention is directed to compounds according to formula I



Formula I

and to pharmaceutically acceptable salts or prodrugs thereof,
wherein

- Y is selected from the group consisting of:

F, Cl, Br, I, H,

detectable labels, such as ^{18}F , ^{19}F , ^{76}Br , ^{123}I , ^{125}I , ^{11}C , ^3H , ^{13}N , ^{15}O ;

5 leaving groups, such as tosyl, brosyl, nosyl, triflate, sulfonate, substituted sulfonate, mesylate, and nonaflate; and if directly bound to an aromatic C-atom iodonium-aryl I^+ -aryl, trialkylammonium, preferred trimethylammonium, and NO_2 ;

Ar is selected from the group consisting of:

10 mono-, bi- or tricyclic aromatic or heteroaromatic ring systems, optionally substituted by one or two alkyl, alkylen, alkynesubstituents and/or alkoxy substituents,

wherein the alkyl, alkylen, alkynesubstituents and/or alkoxy substituents optionally are substituted, wherein the substituent is preferably selected from oxo or hydroxyl,

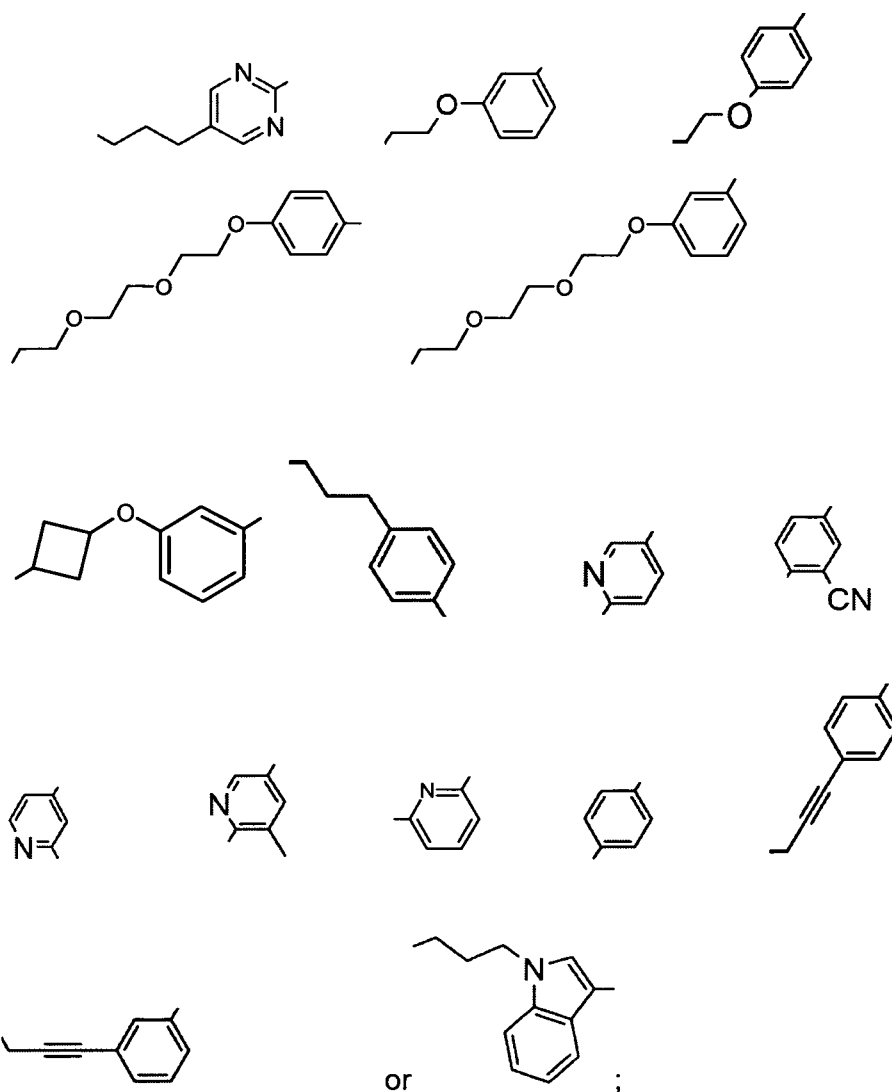
15 and wherein further the alkyl, alkylen, alkynesubstituents and/or alkoxy substituents may be interrupted by 1 – 5 oxygen atoms, $-\text{SO}-$ or $-\text{SO}_2-$ groups, preferably the substituents are polyethylenglycol-moieties,

20 and wherein further the alkyl, alkylen, alkynesubstituents and/or alkoxy substituents may comprise C_3 - C_6 cycloalkyl moieties,

25 and wherein the mono-, bi- or tricyclic aromatic or heteroaromatic ring systems may be further substituted by electron withdrawing groups directly bound to an aromatic C-atom,

wherein preferred electron withdrawing groups are $-\text{CN}$ or $-\text{CF}_3$;

30 Ar is preferably selected from the group consisting of: phenyl, 2, 3, or 4 pyridyl, pyrimidyl, pyrazyl, propylpyrimidin-2-yl, ethoxyphenyl, $(\text{CH}_2\text{CH}_2\text{O})_3$ phenyl, alkylphenyl, alkoxyphenyl, N-alkylindolyl, and alkylpyridyl, and is in an even more preferred embodiment



- B is selected from the group consisting of:

direct bond, a branched or non-branched alkyl or alkyl chain comprised of 1-10 C-atoms wherein the alkyl chain may comprise 1 or 2 unsaturated bonds,

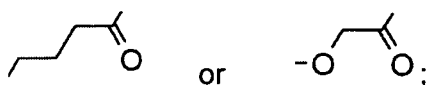
and wherein the alkyl or alkyl chain is optionally interrupted by N, S, SO, SO₂ or O,

and wherein the alkyl or alkyl chain is optionally substituted by oxo or -OH;

Preferably, B is selected from the group consisting of

direct bond, CONH-CH₂CO, CO-(CH₂)₂CO, (CH₂)_nCO, O(CH₂)_nCO with n=1 to 10, and (CH=CH)CO,

and is even more preferably



- A is selected from the group consisting of:
a direct bond, and CO-NH, CS-NH;

- Ar' is selected from the group consisting of:

mono-, or bi-cyclic aromatic or heteroaromatic ring systems, optionally substituted by one or two alkyl, alkylen, alkynesubstituents and/or alkoxy substituents,

wherein the alkyl, alkylen, alkynesubstituents and/or alkoxy substituents optionally are substituted, wherein the substituent is preferably selected from oxo or hydroxyl,

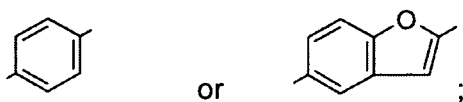
and wherein further the alkyl, alkylen, alkynesubstituents and/or alkoxy substituents may be interrupted by 1 – 5 oxygen atoms, preferably the substituents are poly-ethylenglycol-moieties,

and wherein further the alkyl, alkylen, alkynesubstituents and/or alkoxy substituents may comprise C₃-C₆ cycloalkyl moieties;

Ar' is preferably selected from the group consisting of: phenyl, 2, 3, or 4 pyridyl, pyrimidyl, pyrazyl, propylpyrimidin-2-yl, ethoxyphenyl, (CH₂CH₂O)₃phenyl, alkyl-phenyl, alkoxyphenyl, N-alkylindolyl, phenyl, benzofuranyl, indolyl and alkylpyridyl,

More preferred, Ar' is selected from the group consisting of phenyl, benzofuranyl, and indolyl,

and is even more preferably



Ar' is mostly preferred phenyl;

X is selected from the group consisting of:

a direct bond or

a C₁-C₃ alkyl chain, optionally substituted by 1 or 2 substituents that are preferably but not limited to oxo or thio,

and wherein the alkyl chain may be interrupted by 1 to 2 O, N, S, SO or SO₂ groups;

Preferably, X is selected from the group consisting of

direct bond, OCH₂, NHCO, CH₂O, CONH, NHCS, or CSNH;

Ar'' is selected from the group consisting of:

mono-, or bi-cyclic aromatic or heteroaromatic ring systems, optionally substituted by one or two alkyl, alkylen, alkynesubstituents and/or alkoxy substituents,

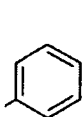
wherein the alkyl, alkylen, alkynesubstituents and/or alkoxy substituents optionally are substituted, wherein the substituent is preferably selected from oxo or hydroxyl,

and wherein further the alkyl, alkylen, alkynesubstituents and/or alkoxy substituents may be interrupted by 1 – 5 oxygen atoms, preferably the substituents are poly-ethylenglycol-moieties,

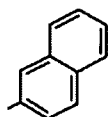
and wherein further the alkyl, alkylen, alkynesubstituents and/or alkoxy substituents may comprise C₃-C₆ cycloalkyl moieties.

More preferably. Ar'' is selected from the group consisting of

phenyl, 1-phenyl, 1-naphthyl, 2-naphthyl, and all respective heterocycles thereof, and is even more preferably



or



Ar' as well as Ar'' can optionally also be substituted by F, Cl, Br, I, H, detectable labels, such as ¹⁸F, ¹⁹F, ⁷⁶Br, ¹²³I, ¹²⁵I, ¹¹C, ³H, ¹³N, ¹⁵O;

leaving groups, such as tosyl, brosyl, nosyl, triflate, sulfonate, substituted sulfonate, mesylate, and nonaflate; and if directly bound to an aromatic C-atom iodonium-aryl I^+ -aryl, trialkylammonium, preferred trimethylammonium, and NO_2

- 5 For diagnostic purposes, both *in vitro* and *in vivo*, those compound of formula I are preferred that comprise or contain a detectable label, such as a radioactive nuclide or a fluorescent label. For *in vitro* use, histological sections such as fresh frozen samples or paraffin samples can be analyzed.
- 10 Preferred embodiments of the compounds of formula I are given below and are designated compounds 1d/e, 2d/e, 3g/h, 4f/g, 5b/c, 6f, 7d, 8g, 9d/e, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21 and 22. These preferred embodiments also exemplify the different groups which can be represented by the letters Y, Ar, B, A, Ar', X, and Ar'' of formula I.
- 15 "Alkyl" refers to a straight or branched chain group consisting solely of carbon and hydrogen, containing no unsaturation and having from one to eight carbon atoms, e.g., methyl, ethyl, n-propyl, 1-methylethyl (iso-propyl), n-butyl, n-pentyl, 1,1-dimethylethyl (t-butyl), n-heptyl, and the like. "Alkoxy" refers to a group of the formula -Oalkyl where alkyl is as defined above.
- 20 In the context of the present invention, preferred salts are pharmaceutically acceptable salts of the compounds according to the invention. The invention also comprises salts which for their part are not suitable for pharmaceutical applications, but which can be used, for example, for isolating or purifying the compounds according to the invention.
- Pharmaceutically acceptable salts of the compounds according to the invention include acid
- 25 addition salts of mineral acids, carboxylic acids and sulphonic acids, for example salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, naphthalene disulphonic acid, acetic acid, trifluoroacetic acid, propionic acid, lactic acid, tartaric acid, malic acid, citric acid, fumaric acid, maleic acid and benzoic acid.
- 30 Pharmaceutically acceptable salts of the compounds according to the invention also include salts of customary bases, such as, by way of example and by way of preference, alkali metal salts (for example sodium salts and potassium salts), alkaline earth metal salts (for example calcium salts and magnesium salts) and ammonium salts, derived from ammonia or organic amines having 1 to 16 carbon atoms, such as, by way of example and by way of preference,
- 35 ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, dietha-

nolamine, triethanolamine, dicyclohexylamine, dimethylaminoethanol, procaine, dibenzylamine, N-methylmorpholine, arginine, lysine, ethylenediamine and N-methylpiperidine.

Moreover, the present invention also comprises prodrugs of the compounds according to the invention. The term "prodrugs" includes compounds which for their part may be biologically
5 active or inactive but which, during the time they spend in the body, are converted into compounds according to the invention (for example metabolically or hydrolytically).

In particular, the present invention also comprises hydrolyzable ester derivatives of the carboxylic acids of the formula (I). These are to be understood as being esters which can be hydrolyzed in physiological media and in particular *in vivo* by enzymatical or chemical means to
10 give the free carboxylic acids. Such esters are preferably straight-chain or branched (C₁-C₆)-alkyl esters in which the alkyl group may be substituted by hydroxyl, (C₁-C₄)-alkoxy, amino, mono-(C₁-C₄)-alkylamino and/or di-(C₁-C₄)-alkylamino. Particular preference is given to the methyl or ethyl esters of the compounds of the formula (I).

In the context of the present invention, unless specified otherwise, the substituents have the
15 following meanings:

In the context of the invention, alkyl represents a straight-chain or branched alkyl radical having the number of carbon atoms stated in each case. The following radicals may be mentioned by way of example and by way of preference: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, 1-methylpropyl, tert-butyl, n-pentyl, isopentyl, 1-ethylpropyl, 1-methylbutyl, 2-
20 methylbutyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,4-dimethylpentyl, 4,4-dimethylpentyl and 1,4,4-trimethylpentyl.

In the context of the invention, cycloalkyl represents a monocyclic saturated alkyl radical having 3 to 7 carbon atoms. The following radicals may be mentioned by way of example and by
25 way of preference: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

In the context of the invention, alkoxy represents a straight-chain or branched alkoxy radical having 1 to 4 carbon atoms. The following radicals may be mentioned by way of example and by way of preference: methoxy, ethoxy, n-propoxy, isopropoxy, 1-methylpropoxy, n-butoxy, isobutoxy and tert-butoxy.

In the context of the invention, halogen includes fluorine, chlorine, bromine and iodine. Preference is given to fluorine.
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If radicals in the compounds according to the invention are substituted, the radicals can, unless specified otherwise, be mono- or polysubstituted. In the context of the present invention, the meanings of all radicals which occur more than once are independent of one another.
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other. Substitution with one, two or three identical or different substituents is preferred. Very particular preference is given to substitution with one substituent.

5 The compounds of the invention, or their pharmaceutically acceptable salts, may have asymmetric carbon atoms in their structure. The compounds of the invention and their pharmaceutically acceptable salts may therefore exist as single enantiomers, diastereoisomers, racemates, and mixtures of enantiomers and diastereoisomers. All such single enantiomers, diastereoisomers, racemates, and mixtures thereof are within the scope of this invention.

10 The compounds as described above and herein are, in a preferred embodiment of the invention, bound to an A β peptide.

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.

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The treatment of a patient with Alzheimer's disease and/or amyloidoses can preferably be performed with a compound of the invention according to formula I that does not bear a radioactive label, but in which Y is e.g. hydrogen.

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Preferably, the use of a compound of the invention in the diagnosis is performed using positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetic resonance (MR)-spectroscopy or tomography.

25 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.

30 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

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by using a gamma camera, by positron emission tomography (PET), or by single photon emission computed tomography (SPECT).

5 A further embodiment of the invention includes a diagnostic method for other neurological disorders as 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.

10 A further aspect of the invention refers to a diagnostic composition for imaging amyloid deposits, comprising a radiolabeled compound according to formula I.

The diagnostic methods of the invention can also be used as post-mortem diagnostic methods.

15 Furthermore, the diagnostic methods of the invention can also be used for monitoring the therapy of Alzheimer's disease, a neurodegenerative disorder or an amyloidoses.

20 Furthermore, the diagnostic methods of the invention can also be used in diagnosing neurological disorders other than Alzheimer's disease by excluding Alzheimer's disease.

In a further aspect of the invention, the invention comprises a method of treating or preventing amyloidoses or Alzheimer's disease comprising administering to a human in need of such a treatment a compound of formula I as described herein.

25 A further aspect of the invention refers to a pharmaceutical composition which comprises a compound of the invention as described herein, optionally together with a suitable carrier and/or additive.

30 Furthermore, the compounds of the invention can also be used as tools in screening, for example high throughput screening methods and in vitro assays.

The invention also refers to a method for synthesizing a compound of the invention according to formula I as described herein. The general synthetic methods of the compounds of the invention are as follows.

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F-18 radiolabeling

A further aspect of the invention refers to a method of radiofluorination of a compound of formula I for the manufacture of radiolabeled compound of formula I comprising the step of reacting a compound of formula I with a fluorination agent. Useful Radiofluorination methods are well known to the person skilled in the art.

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In a preferred embodiment, the fluorination agent is 4,7,13,16,21,24-Hexaoxa-1,10 diazabicyclo[8.8.8]-hexacosane $K^{18}F$ (crownether salt Kryptofix $K^{18}F$), $K^{18}F$, $H^{18}F$, $KH^{18}F_2$ or tetraalkylammonium salt of ^{18}F . More preferably, fluorination agent is $K^{18}F$, $H^{18}F$, or $KH^{18}F_2$.

10 The solvents used can be Dimethylformamide, DMF, Dimethylsulfoxide, DMSO, Acetonitrile, MeCN, Dimethylacetamide, DMA, DMAA etc., preferably DMSO, MeCN or DMF. The solvents can also be a mixture of solvents as indicated above.

[F-18] radiolabeling procedures are well known to the person skilled in the art. For example, radiolabeling can be performed as described in the following.

[F-18]Fluoride can be produced by proton bombardment in a cyclotron using a silver target (1 mL) filled with [O-18] water for the $^{18}O(p,n)^{18}F$ reaction. The aqueous [F-18]fluoride can be passed through a cartridge (e.g. QMA-resin cartridge Waters, Sep Pak Light QMA Part.No.: WAT023525). The trapped [F-18]fluoride can then be eluted from the cartridge by adding e.g. a Kryptofix K2.2.2/ K_2CO_3 solution (Kryptofix is 4,7,13,16,21,24-Hexaoxa-1,10-diazabicyclo[8.8.8]-hexacosane). The nucleophilic substitution of the precursor works preferably in the presence of a base such as NBu_4OH , $(NBu_4)_2CO_3$, K_2CO_3 etc. and at elevated temperatures. The addition of crown ethers such as Kryptofix (K2.2.2) can influence the reaction positively, especially in the presence of K_2CO_3 as the base.

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The potassium fluoride Kryptofix complex is preferably dried by repeated azeotropic distillation with sequential addition of acetonitrile. Solvents such as acetonitrile, DMF, DMSO etc. can be used as a reaction solvent. The labeling product can be purified by solid phase extraction using cartridges. Preferred cartridges are Sep-Pak Plus C18 cartridge (Waters, WAT020515). The cartridge can be rinsed with water and the compound can be eluted with acetonitrile. The eluted compound can be diluted with water and can then be subjected to preparative HPLC purification. Preferred HPLC columns are reversed phase columns such as Gemini 5 μ C 18 110 Å, 250 * 10 mm (Phenomenex, 00G-4435-N0). Mixtures of buffer solution, acids, water etc. with organic solvents such as acetonitrile, methanol, ethanol etc. can be used as mobile.

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The solution can then be diluted with e.g. water to be passed through a cartridge for concentration and solvent change.

General synthesis of F-18 compounds: alkyl-F and (hetero)aryl-F

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Precursors for alkyl-F-18 compounds of general formula I (formula I with Y = ^{18}F) are e.g. tosylates, brosylates, nosylates, mesylates, triflates, nonaflates etc. (formula I with Y = leaving group) which can be synthesized from the respective hydroxy compounds according to methods known in the art (J. March, Advanced Organic Chemistry, 4th ed. 1992, John Wiley & Sons, pp 352ff). An additional method is described in Examples 3f, 4e and 5a and comprises the synthesis by suitable bis(tosylates) and the like, e.g. $\text{TsO}-(\text{CH}_2)_n\text{-OTs}$.

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Other precursors for alkyl-F-18 compounds of general formula I (formula I with Y = ^{18}F) are e.g. iodides and bromides and the like whose conversion to the respective fluorides is also known in the art (J. March, see above).

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Precursors for aryl-F-18 compounds of general formula I are e.g. aryl or heteroaryl bromides, nitro compounds, trialkyl ammonium, arylodonium which can be converted to the respective F-18 compounds of this invention by methods known in the art (L. Cai, S. Lu, V. Pike, Eur. J. Org. Chem 2008, 2853-2873). Starting materials for these precursors are commercially available or can be synthesized by methods known in the art (R.C. Larock, Comprehensive Organic Transformations, VCH Publishers 1989).

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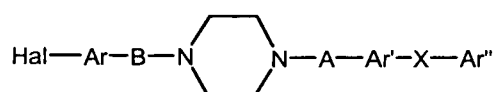
The synthesis of hydroxy compounds as starting materials for tosylates, brosylates, nosylates, mesylates, triflates, nonaflates etc. comprises

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- the deprotection of OH-protecting groups. As one of the very versatile protecting groups might be mentioned the acetyl protecting group. Many others are known in the art, see e.g. T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 3rd ed, 1999, John Wiley & Sons, pp 17ff), see also e.g. Examples 3d and 4c

or

- the introduction of the hydroxyalkyl group by Pd catalyzed substitution of



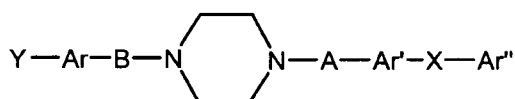
with Hal = Br, I as described in Examples 1b and 2b

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or

- as in Example 6d, where the hydroxy compound HO-Ar-B' with the meaning of B' as -CO-(CH₂)_n-COOH can be synthesized by Friedel Crafts Acylation.

Compounds of the general formula I



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with Y = Br, I, HO, Protecting Group-O- can be synthesized by

- an amide coupling to establish -CO-NH- groups in any position and sequence order or

- optionally by reaction of a piperazine derivative with a suitable amino component by use of phosgene or an equivalent to phosgene to build a urea bond (-NH-CO-NH-) as described in Examples 1a and 2a.

Aryl-piperazines are commercially available or can be synthesized according to the literature, e.g. according to *Klapars et al., Journal of the American Chemical Society 2002, 124, 7421-28 and literature cited herein*.

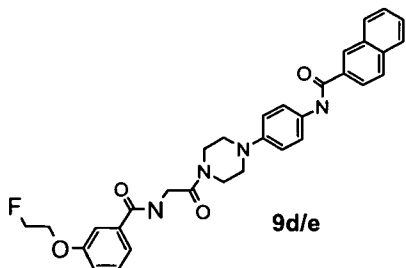
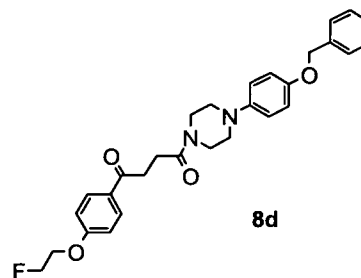
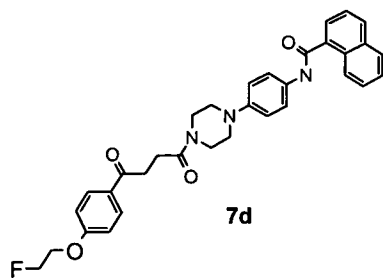
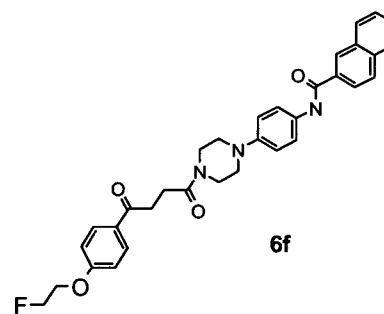
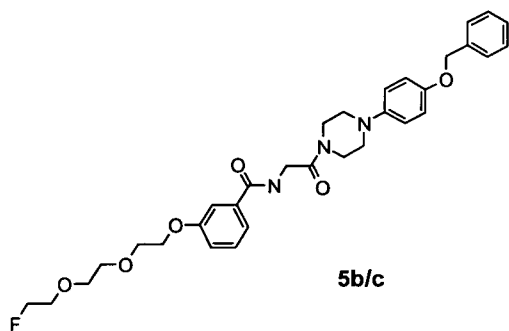
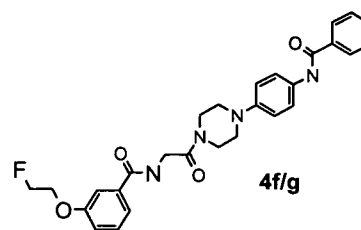
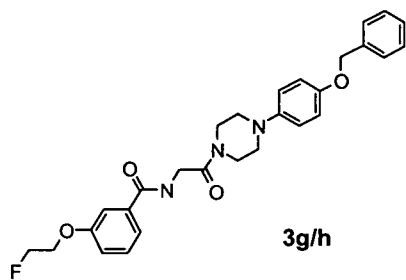
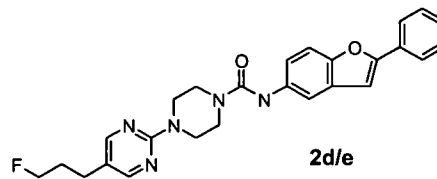
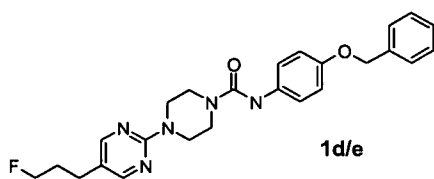
A further aspect of the invention refers to a kit comprising a non-radiolabeled compound of the invention, the compound optionally being in a dry condition or having an inert, pharmaceutically acceptable carrier and/or solvent and/or auxiliary substances added. In a preferred embodiment the kit comprises one or more sealed containers which comprise the compounds of the kit. In a preferred embodiment the kit comprises a compound of formula I as described herein, in which Y is a leaving group, such as tosyl, brosyl, nosyl, triflate, sulfonate, substituted sulfonate, mesylate, nonaflate, iodonium-aryl I⁺-aryl, trialkylammonium, trimethylammonium, or NO₂.

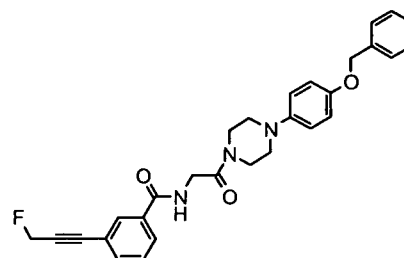
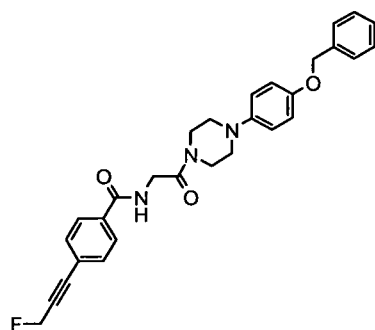
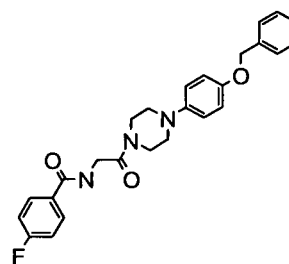
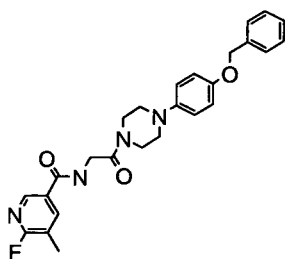
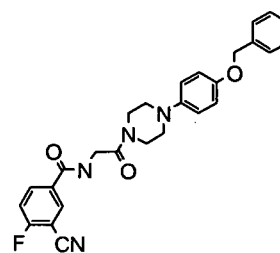
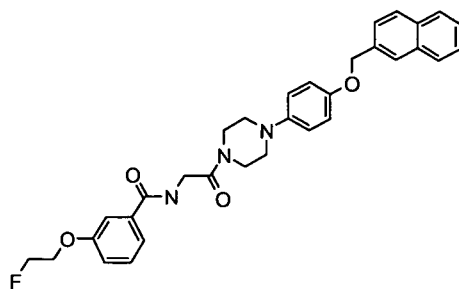
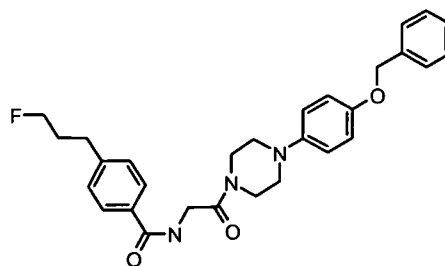
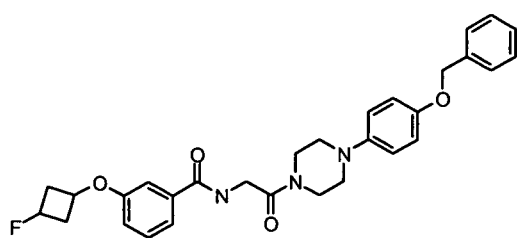
Yet another aspect of the invention refers to a method of inhibiting the formation of amyloid or modulating the pathogenicity of amyloid in a mammal. This method comprises administering a compound of formula I as described herein in an amount that is effective to inhibit the formation of amyloid or to modulate the pathogenicity of amyloid.

Preferred Compounds of the Invention

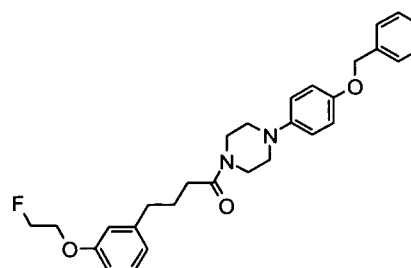
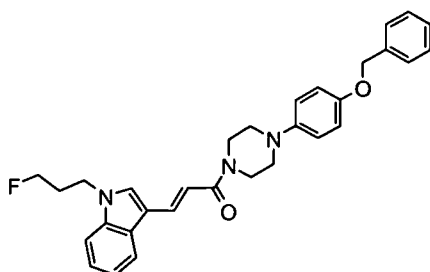
Of the various aspects of the invention, certain compounds of formula I are preferred. Such preferred compounds are given below, wherein those compounds are named with a figure

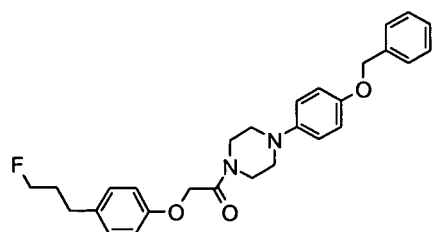
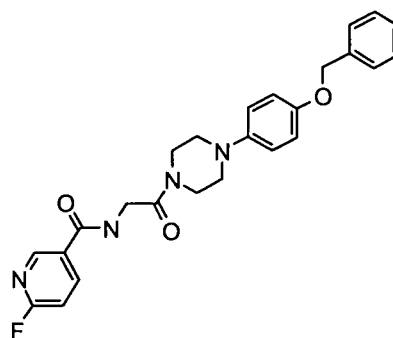
together with a letter which refer to the examples given below describing the synthesis of these compounds.



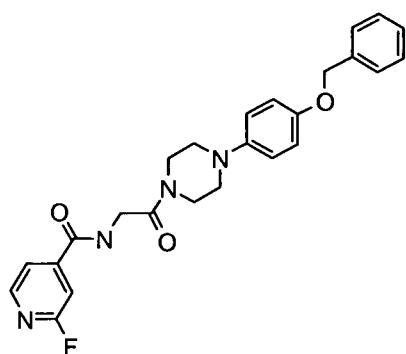
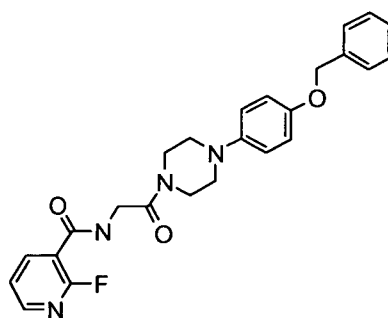


5



**10d/e**

5

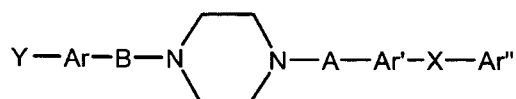
**11b/c****12b/c**

10 Even more preferred embodiments of the invention are the respective F-18 compounds.

The compounds of the invention represent novel tracers with high affinity for amyloid β and rapid elimination of non-specific signals from the brain.

15 In particular, the invention relates to

1. A compound of formula I



20 Formula I

or a pharmaceutically acceptable salt or a prodrug thereof,
wherein

5

- Y is selected from the group consisting of:

F, Cl, Br, I, H, ^{18}F , ^{19}F , ^{76}Br , ^{123}I , ^{125}I , ^{11}C , ^3H , ^{13}N , ^{15}O ;

a leaving group, tosyl, brosyl, nosyl, triflate, sulfonate, substituted sulfonate, mesy-
late, and nonaflate; and if directly bound to an aromatic C-atom iodonium-aryl I^+ -aryl,
trialkylammonium, preferred trimethylammonium, and NO_2 ;

10

- Ar is selected from the group consisting of:

substituted or non-substituted mono-, bi- or tricyclic aromatic or heteroaromatic ring
systems;

15

- B is selected from the group consisting of:

direct bond, a branched or non-branched alkyl or alkyl chain comprised of 1-10 C-
atoms;

20

- A is selected from the group consisting of:

a direct bond, and CO-NH, CS-NH;

- Ar' is selected from the group consisting of:

substituted or non-substituted mono-, or bi-cyclic aromatic or heteroaromatic ring sys-
tems;

25

- X is selected from the group consisting of:

a direct bond or a substituted or non-substituted C_1 - C_3 alkyl chain;

30

- Ar'' is selected from the group consisting of:

substituted or non-substituted mono-, or bi-cyclic aromatic or heteroaromatic ring sys-
tems.

35

2. A compound according to count 1, wherein

- the heteroaromatic or aromatic ring systems of Ar are optionally substituted by one or two alkyl, alkylen, alkynesubstituents and/or alkoxy substituents, and wherein

- the mono-, bi- or tricyclic aromatic or heteroaromatic ring systems may be further substituted by electron withdrawing groups directly bound to an aromatic C-atom; and wherein

- the alkyl chain of B may comprise 1 or 2 unsaturated bondings, and wherein the alkyl or alkyl chain is optionally interrupted by N, S, SO, SO₂ or O, and wherein the alkyl or alkyl chain is optionally substituted by oxo or -OH;

and wherein

- the heteroaromatic or aromatic ring systems of Ar' are optionally substituted by one or two alkyl, alkylen, alkynesubstituents and/or alkoxy substituents and wherein the mono-, bi- or tricyclic aromatic or heteroaromatic ring systems may be further substituted by electron withdrawing groups directly bound to an aromatic C-atom;

and wherein

- the C₁-C₃ alkyl chain of X is optionally substituted by 1 or 2 substituents that may be oxo or thio, and wherein the alkyl chain may be interrupted by 1 to 2 O, N, S, SO or SO₂ groups;

and wherein

- the heteroaromatic or aromatic ring systems of Ar'' are optionally substituted by one or two alkyl, alkylen, alkynesubstituents and/or alkoxy substituents and wherein the mono-, bi- or tricyclic aromatic or heteroaromatic ring systems may be further substituted by electron withdrawing groups directly bound to an aromatic C-atom.

3. A compound according to count 1 or 2, wherein

- the optional alkyl, alkylen, alkynesubstituents and/or alkoxy substituents of Ar, Ar' and Ar'' are selected from the group consisting of oxo or hydroxyl,

and wherein the alkyl, alkylen, alkynesubstituents and/or alkoxy substituents of Ar, Ar' and Ar'' may be interrupted by 1 – 5 oxygen atoms, preferably the substituents are polyethylenglycol-moieties,

and wherein further the alkyl, alkylen, alkynesubstituents and/or alkoxy substituents of Ar, Ar' and Ar'' may comprise C₃-C₆ cycloalkyl moieties, and wherein the optional electron withdrawing groups of Ar, Ar' and Ar'' are selected from the group consisting of -CN or CF₃;

and wherein

- B is optionally selected from the group consisting of direct bond, CONH-CH₂CO, CO-(CH₂)₂CO, (CH₂)_nCO, O(CH₂)_nCO with n=1 to 10, (CH=CH)CO,



5

and wherein

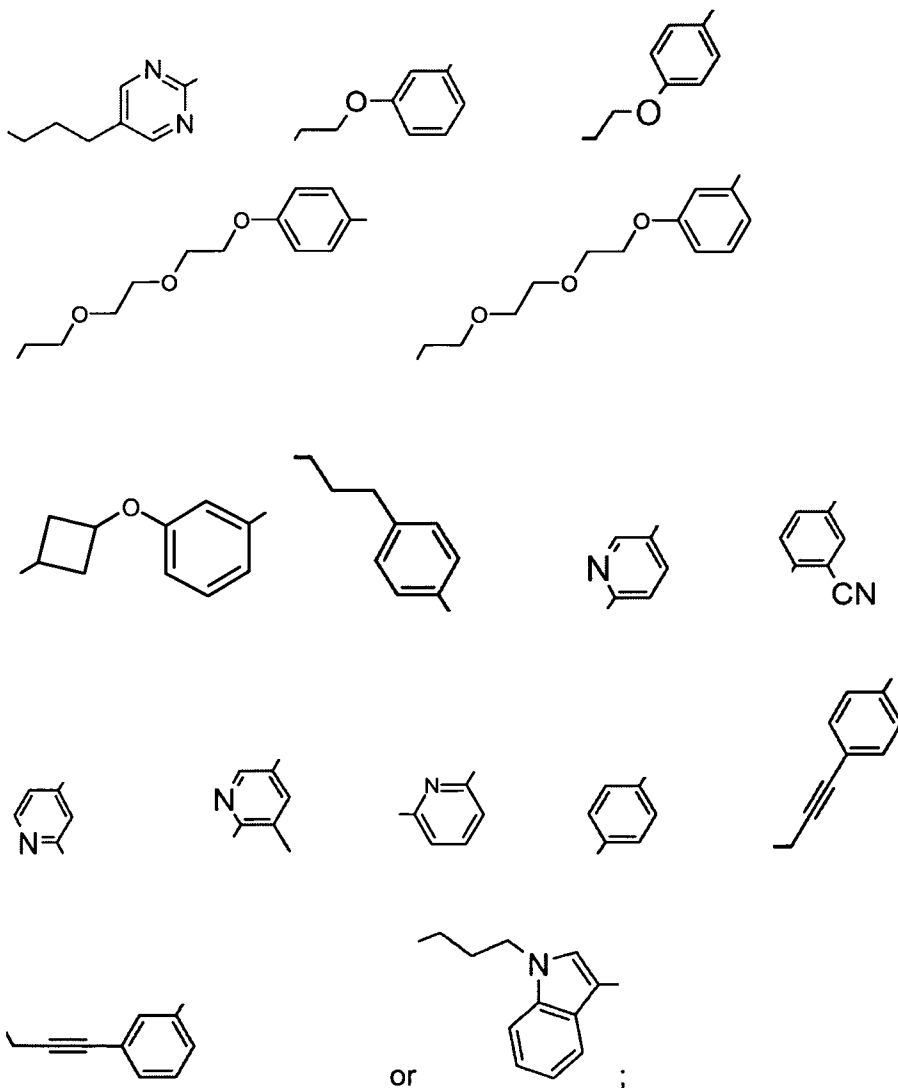
- X is optionally selected from the group consisting of direct bond, OCH₂, NHCO, CH₂O, CONH, NHCS, or CSNH.

10

4. A compound according to counts 1 – 3, wherein

- Ar is optionally selected from the group consisting of propylpyrimidin-2-yl, ethoxyphenyl, (CH₂CH₂O)₃phenyl, alkylphenyl, alkoxyphenyl, N-alkylindolyl, and alkylpyridyl,

15



20

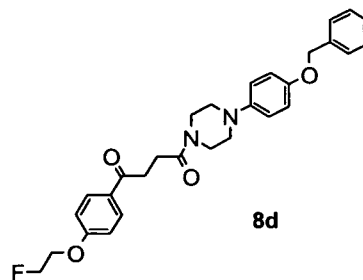
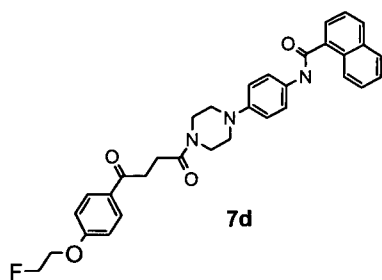
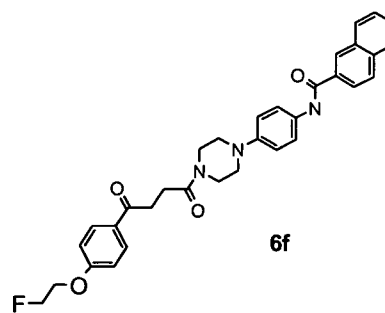
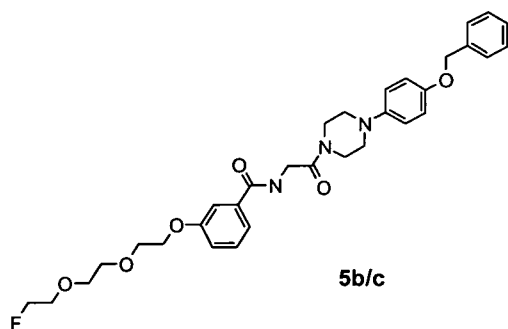
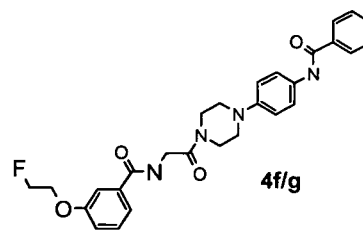
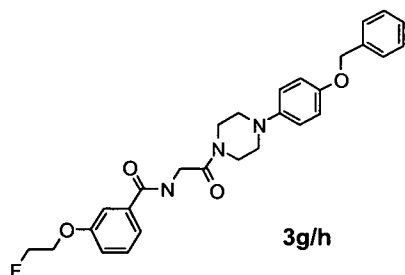
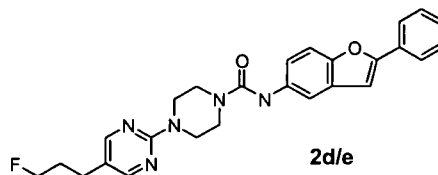
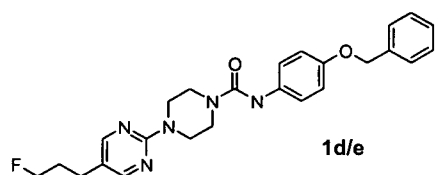
and wherein

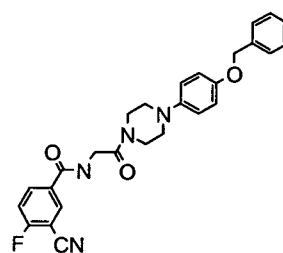
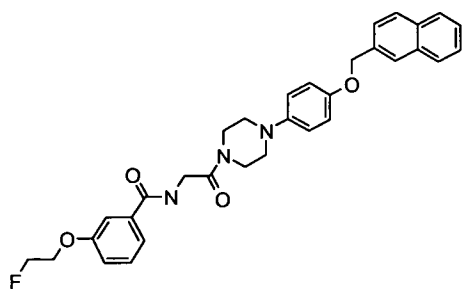
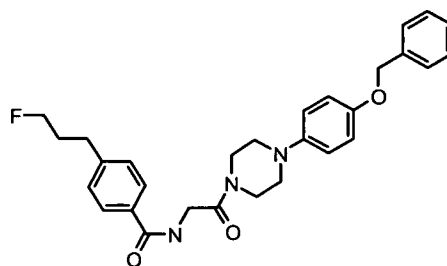
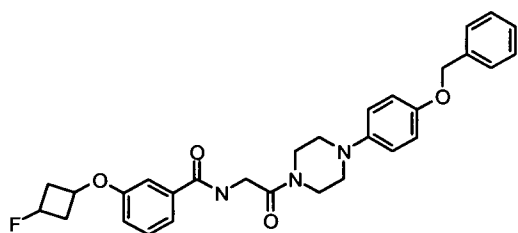
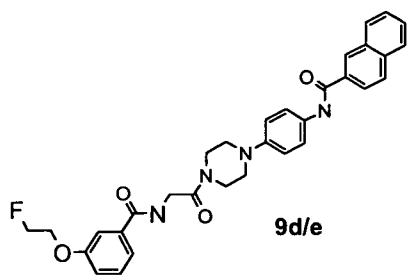
- Ar' is optionally selected from the group consisting of
propylpyrimidin-2-yl, ethoxyphenyl, (CH₂CH₂O)₃phenyl, alkylphenyl, alkoxyphenyl, N-
alkylindolyl, phenyl, benzofuranyl, indolyl and alkylpyridyl;

and wherein

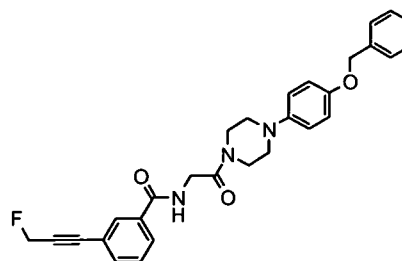
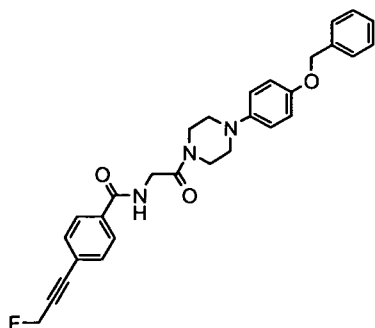
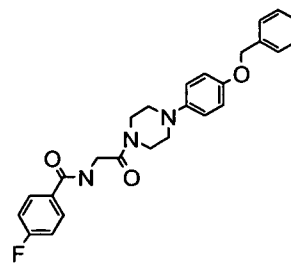
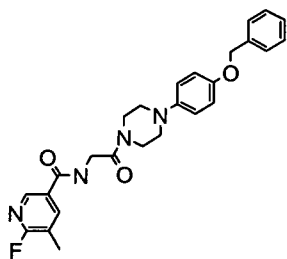
- Ar'' is optionally selected from the group consisting of
phenyl, 1-phenyl, 1-naphthyl, 2-naphthyl, and all respective heterocycles thereof.

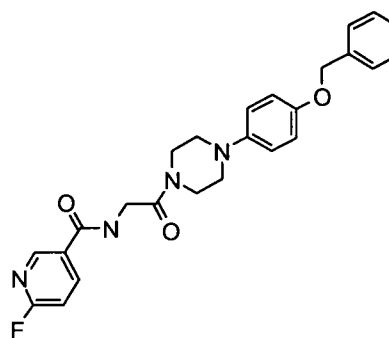
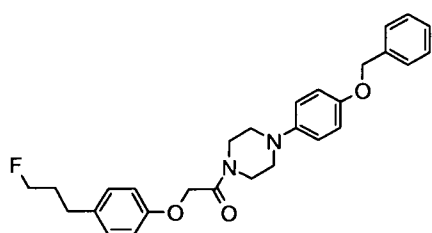
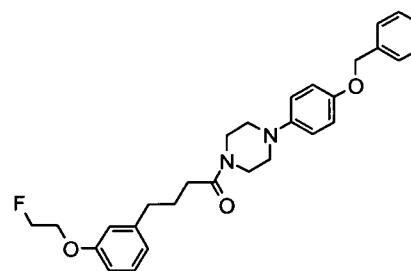
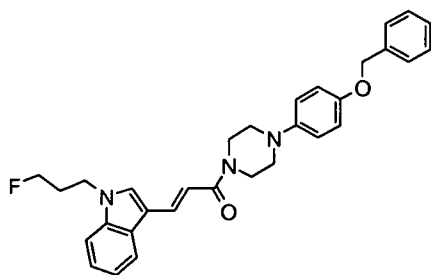
5. A compound, selected from the group consisting of



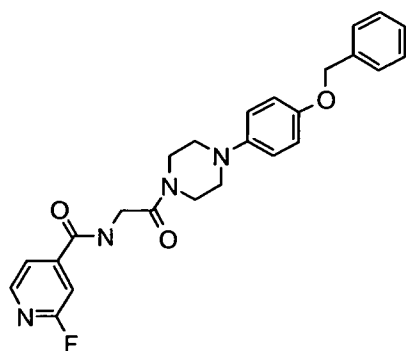
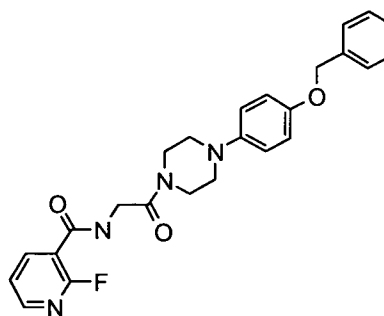


5



**10d/e**

5

**11b/c****12b/c.**

10

6. A compound according to count 5, wherein F has the meaning of ^{18}F .

15 7. A compound according to count 1, 2, 3 or 4 containing a detectable label, such as a radioactive nuclide or a fluorescent label.

8. A compound according to count 7, wherein the detectable label is ^{18}F .
9. A compound according to counts 1 – 8 as a diagnostic compound.
- 5 10. A compound according to counts 1 – 5 or 7 as a medicament.
11. A compound according to count 8, as a diagnostic compound for a disease selected from the group consisting of Alzheimer's disease, a neurodegenerative disorder, or an amyloidosis.
- 10 12. A compound according to count 10 as a medicament for treating a disease selected from the group consisting of Alzheimer's disease, a neurodegenerative disorder, or an amyloidosis.
- 15 13. A method for the preparation of a fluorinated compound according to counts 1 – 8, the method comprising reacting a suitable precursor molecule with a fluorinating agent.
14. A method for treating or preventing a disorder selected from the group consisting of Alzheimer's disease, a neurodegenerative disorder, or an amyloidosis in a mammal, this method comprising administering a therapeutically effective amount of a compound according to counts 1 – 5 or 7 to said mammal.
- 20 15. Use of a compound according to counts 1 – 5 or 7 in the treatment of a disease selected from the group consisting of Alzheimer's disease, a neurodegenerative disorder, or an amyloidosis in a mammal, wherein a therapeutically effective amount of said compound is administered to said mammal.
- 25 16. A method for diagnosing a disease in a mammal selected from the group consisting of Alzheimer's disease, a neurodegenerative disorder, or an amyloidosis, this method comprising administering to said mammal a compound according to count 6 or 8.
- 30 17. The method of count 16, this method comprising imaging of said mammal and detecting the imaging signal.
- 35 18. The method of count 17, where said imaging is performed using an imaging method selected from the group consisting of PET, SPECT, MR-spectroscopy, and MR-tomography.

19. A method according to counts 16 – 18, wherein the effect of a therapy is monitored.

20. A method for diagnosing or therapy monitoring of a disease selected from the group consisting of Alzheimer's disease, a neurodegenerative disorder, or an amyloidosis in a mammal, said method comprising analyzing *in vitro* a sample of said mammal, wherein said mammal or sample has been treated with a compound according to counts 6 or 8.

21. The method of count 20, wherein the sample is cerebrospinal fluid.

22. A kit comprising a compound according to counts 1 - 8.

The kit may contain one or more sealed vials comprising the compounds according to counts 1 – 8.

The invention further relates to pharmaceutical or diagnostic compositions comprising a compound according to counts 1 – 8, preferred are such compositions comprising radiolabeled compounds, even more preferred are such compositions comprising the compounds labeled with F-18.

The invention further relates to a compound according to count 1, with the proviso that if A and B are direct bonds Ar and Ar' are six ring membered aromatic systems.

The invention further relates to a compound according to count 1, with the proviso that if A or B are direct bonds Ar and Ar' are six ring membered aromatic systems.

The invention further relates to a compound according to count 1, with the proviso that if A or B are direct bonds the directly bound residue Ar or Ar' is a six ring membered aromatic system.

The radiolabeled compounds and diagnostic compositions of the invention are useful for beta-amyloid imaging.

Brief description of the Figures

Fig. 1 shows the autoradiographical analysis of binding of 3g to cryosections from cortex of Alzheimer's disease patients (AD) and controls without A β plaques (HC/FTD) (healthy control/ frontotemporal dementia). Specific binding in plaque-rich regions of AD samples is indicated by arrows.

Fig. 2 shows the autoradiographical analysis of binding of example 10e to cryosections from cortex of Alzheimer's disease patients (AD) and controls without A β plaques (HC/FTD) (healthy control/ frontotemporal dementia). Specific binding in plaque-rich regions of AD samples is indicated by arrows.

Fig. 3 shows the Autoradiographical analysis of binding of example 11c to cryosections from cortex of Alzheimer's disease patients (AD) and controls without A β plaques (HC/FTD) (healthy control/ frontotemporal dementia). Specific binding in plaque-rich regions of AD samples is indicated by arrows.

Fig. 4 shows the autoradiographical analysis of binding of example 12c to cryosections from cortex of Alzheimer's disease patients (AD) and controls without A β plaques (HC/FTD) (healthy control/ frontotemporal dementia). Specific binding in plaque-rich regions of AD samples is indicated by arrows.

Fig. 5 shows IC₅₀ values in [nM] of selected compounds measured in a competition assay using brain homogenate from AD patients.

Fig. 6 A and Fig. 6 B show HPLC analyses of compounds of example 14.

Fig. 7 A and Fig. 7 B show HPLC analyses of compounds of example 15.

Fig. 8 shows the autoradiographical analysis of binding of 14f to cryosections from cortex of Alzheimer's disease patients (AD) and healthy controls (HC). Specific binding in plaque-rich regions of AD samples is indicated by arrows.

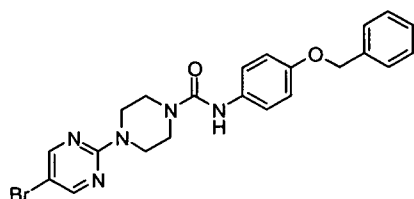
Fig. 9 shows shows IC₅₀ values in [nM] of selected compounds measured in a competition assay using brain homogenate from AD patients.

Examples

The methods for synthesizing and labeling these compositions are more fully illustrated in the following Examples. These Examples illustrate certain aspects of the above-described method and advantageous results and are shown by way of illustration and not by way of limitation.

Example 1

- 10 a) 4-(5-Bromo-pyrimidin-2-yl)-piperazine-1-carboxylic acid (4-benzyloxy-phenyl)-amide



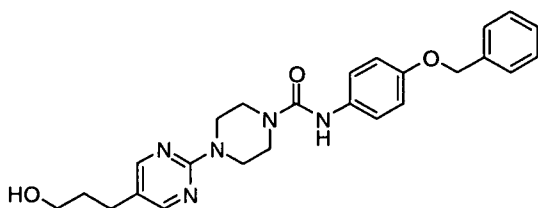
- 15 A solution of 707 mg (3 mmol) of 4-benzyloxy-phenylamine hydrochloride (Aldrich) and 1.13 mL (6.6 mmol) of N,N-ethyl diisopropylamine in 10 mL of dichloromethane are added dropwise to a solution of 297 mg (1 mmol) of triphosgene in 10 mL of dichloromethane at 0°C. The reaction mixture is stirred for 15 minutes at 0°C, then a mixture of 0.73 g (3 mmol) of 5-bromo-2-piperazin-1-yl-pyrimidine and 1.13 mL (6.6 mmol) of N,N-ethyl diisopropylamine in 10 mL of dichloromethane are added. After 30 min at 0°C and overnight at room temperature, the solvent is evaporated and the residue is chromatographed on silica gel using a dichloromethane/ethyl acetate gradient.
- 20

Yield: 0.93 g (66 %)

Elemental analysis:

- | | | | | |
|-----------|---------|--------|----------|---------|
| calcd.: | C 56.42 | H 4.73 | Br 17.06 | N 14.95 |
| 25 found: | C 56.11 | H 4.83 | Br 16.94 | N 14.77 |

- b) 4-[5-(3-Hydroxy-propyl)-pyrimidin-2-yl]-piperazine-1-carboxylic acid (4-benzyloxyphenyl)-amide



To a solution of 0.21 mL (3 mmol) of allyl alcohol in 9 mL of dry tetrahydrofuran (THF) are added at 0°C 18 mL (9 mmol) of a 0.5 M solution of 9-borabicyclo-(3.3.1)-nonane in THF. This mixture is stirred at 0°C for additional 15 min and 5 h at room temperature (= Solution A).

0.70 g (1.5 mmol) of the bromo derivative compound 1a are suspended in 10 mL dry DMF and 0.35 g (0.3 mmol) of tetrakis(triphenyl phosphine) palladium(0) and 4 mL (12 mmol) 3 M aqueous potassium carbonate solution are added (= Suspension B).

Solution A is added to suspension B and stirred overnight at 65°C. After evaporation of the solvents the residue is chromatographed on silica gel using a dichloromethane/methanol gradient.

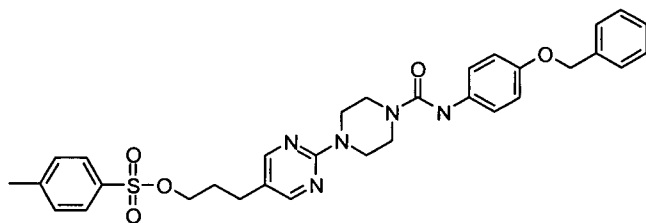
Yield: 110 mg (16 %)

Elemental analysis:

calcd.: C 67.10 H 6.53 N 15.65

found: C 66.92 H 6.41 N 15.88

c) Toluene-4-sulfonic acid 3-{2-[4-(4-benzyloxy-phenylcarbamoyl)-piperazin-1-yl]-pyrimidin-5-yl}-propyl ester



To a suspension of 0.45 g (1 mmol) of the hydroxy derivative 1b in 3 mL of dry pyridine is added dropwise at 0°C a solution of 0.25 g (1.3 mmol) of p-toluenesulfonyl chloride in 2 mL of dry pyridine. After stirring for 30 min the mixture is evaporated to dryness and the residue is chromatographed on silica gel using a dichloromethane/hexane gradient.

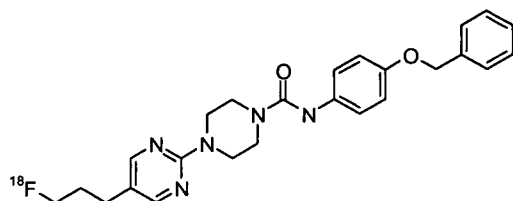
Yield: 379 mg (63 %)

Elemental analysis:

calcd.: C 63.88 H 5.86 N 11.64 S 5.33

found: C 63.67 H 5.97 N 11.48 S 5.02

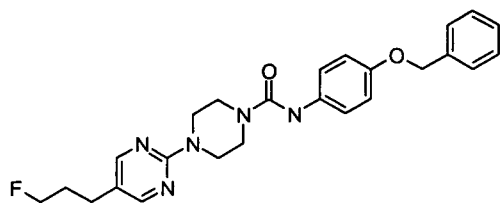
- d) 4-[5-(3-[F-18]Fluoro-propyl)-pyrimidin-2-yl]-piperazine-1-carboxylic acid (4-benzyloxy-phenyl)-amide



- 5 [F-18]Fluoride was produced by proton bombardment in a cyclotron using a low volume, low pressure silver target (1 mL) filled with [O-18] water for the $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$ reaction. The aqueous [F-18]fluoride (app. 1 mL) was passed through a QMA-resin cartridge (Waters, Sep Pak Light QMA Part.No.: WAT023525). The trapped [F-18]fluoride was eluted from the cartridge by adding a Kryptofix K2.2.2/ K_2CO_3 solution (5 mg K2.2.2/ 1.5 mL acetonitrile + 1 mg K_2CO_3 /
- 10 0.5 mL water). The mixture was dried by repeated (2 x) azeotropic distillation with sequential addition of 1 mL of acetonitrile. The tosylate precursor 1c was dissolved in dry dimethylformamide (100 μL) and acetonitrile (400 μL) and added to the dry potassium/ Kryptofix/ fluoride complex. The solution was heated to 110 $^\circ\text{C}$ for 6 min and then allowed to cool to room temperature for 5 min. The solution was diluted with water to give a final volume of 10 mL and
- 15 was passed through a Sep-Pak Plus C18 cartridge (Waters, WAT020515). The cartridge was rinsed with water (20 ml) and the compound was eluted with acetonitrile (3 mL). The eluted compound was diluted with water to yield 5 mL and was subjected to preparative HPLC purification. A Gemini 5 μC 18 110 $\text{\AA}$, 250 * 10 mm (Phenomenex, 00G-4435-N0) was used as a stationary phase. A water (A)/ acetonitrile (B) 3 / 7 mixture was used as a mobile phase with
- 20 a flow rate of 3 mL/ min.

- The solution was diluted with water to give a final volume of 20 mL and was passed through a Sep-Pak light C18 cartridge (Waters, WAT023501). The cartridge was rinsed with water (10 ml) and the compound was eluted with ethanol (0.5 mL). The final product was characterized by HPLC on a Gemini 5 μC 18 110 $\text{\AA}$, 250 * 4,6 mm (Phenomenex, 00G-4435-E0)
- 25 HPLC column with an isocratic water/ acetonitrile (2/8; v/v) mixture at a flow rate of 1 mL/ min. Retention time (t_R): 4.8 min. Radiochemical yield (RCY) decay corrected (d.c.) at end of bombardment: 44 %. Radiochemical purity (RCP): 98 %.

- 30 e) 4-[5-(3-Fluoro-propyl)-pyrimidin-2-yl]-piperazine-1-carboxylic acid (4-benzyloxy-phenyl)-amide (HPLC standard)



To 67 mg (0.15 mmol) of hydroxy derivative compound 1b in 10 mL dichloromethane were added 48 mg (0.3 mmol) of diethylamino sulfur trifluoride (DAST) at 0°C. After 30 min at 0°C, water was added, the organic phase was dried over sodium sulfate and after evaporation of the organic solvent, the residue was chromatographed on silica gel using a dichloromethane/ethyl acetate gradient.

Yield: 40 mg (60 %)

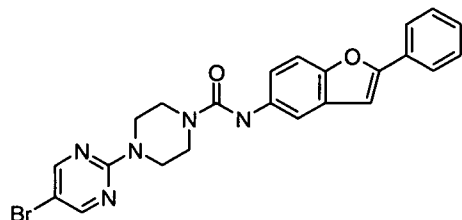
10 Elemental analysis:

calcd.:	C 66.80	H 6.28	F 4.23	N 15.58
found:	C 66.54	H 6.49	F 4.06	N 15.77

Example 2

a) 4-(5-Bromo-pyrimidin-2-yl)-piperazine-1-carboxylic acid (2-phenyl-benzofuran-5-yl)-amide

5



A solution of 628 mg (3 mmol) of 2-phenyl-benzofuran-5-ylamine hydrochloride (ChemBridge Corp., San Diego, USA) and 1.13 mL (6.6 mmol) of N,N-ethyl diisopropylamine in 20 mL of dichloromethane are added dropwise to a solution of 297 mg (1 mmol) of triphosgene in 10 mL of dichloromethane at 0°C. The reaction mixture is stirred for 30 minutes at 0°C, then a mixture of 0.73 g (3 mmol) of 5-bromo-2-piperazin-1-yl-pyrimidine and 0.56 mL, 3.3 mmol) of N,N-ethyl diisopropylamine in 20 mL of dichloromethane are added. After 1 h at 0°C and overnight at room temperature, the solvent is evaporated and the residue is chromatographed on silica gel using a dichloromethane/ethyl acetate gradient.

15 Yield: 0.81 g (56 %)

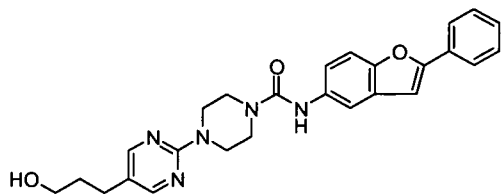
Elemental analysis:

ber.: C 57.75 H 4.21 Br 16.70 N 14.64

gef.: C 57.43 H 4.37 Br 16.11 N 14.45

20

b) 4-[5-(3-Hydroxy-propyl)-pyrimidin-2-yl]-piperazine-1-carboxylic acid (2-phenyl-benzofuran-5-yl)-amide



25

To a solution of 0.21 mL (3 mmol) of allyl alcohol in 9 mL of dry tetrahydrofuran (THF) are added at 0°C 18 mL (9 mmol) of a 0.5 M solution of 9-borabicyclo-(3.3.1)-nonane in THF. This mixture is stirred at 0°C for additional 15 min and 5 h at room temperature (= Solution A).

0.72 g (1.5 mmol) of compound 2a are suspended in 10 mL dry DMF and 0.35 g (0.3 mmol) of tetrakis(triphenyl phosphine) palladium(0) and 4 mL (12 mmol) 3 M aqueous potassium carbonate solution are added (= Suspension B).

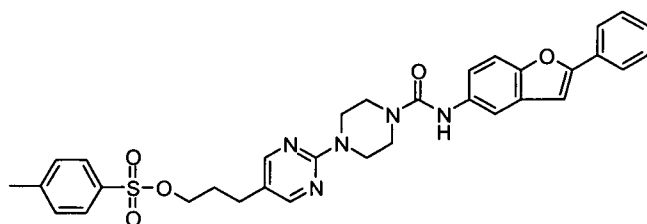
Solution A is added to suspension B and stirred overnight at 65°C. After evaporation of the solvents the residue is chromatographed on silica gel using a dichloromethane/methanol gradient.

Yield: 85 mg (12 %)

Elemental analysis:

calcd.:	C 68.25	H 5.95	N 15.31
found:	C 68.05	H 6.12	N 15.20

c) Toluene-4-sulfonic acid 3-{2-[4-(2-phenyl-benzofuran-5-ylcarbamoyl)-piperazin-1-yl]-pyrimidin-5-yl}-propyl ester



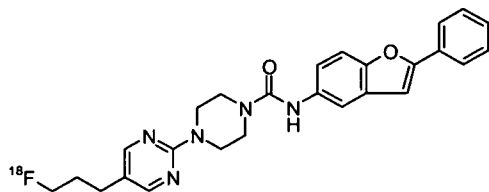
To a suspension of 0.46 g (1 mmol) of the hydroxy derivative 2b in 3 mL of dry pyridine is added dropwise at 0°C a solution of 0.25 g (1.3 mmol) of p-toluenesulfonyl chloride in 2 mL of dry pyridine. After stirring for 30 min the mixture is evaporated to dryness and the residue is chromatographed on silica gel using a dichloromethane/hexane gradient.

Yield: 434 mg (71 %)

Elemental analysis:

calcd.:	C 64.80	H 5.44	N 11.45	S 5.24
found:	C 64.66	H 5.23	N 11.74	S 4.97

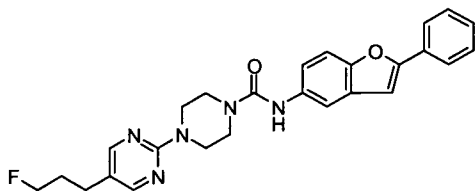
d) 4-[5-(3-[F-18]Fluoro-propyl)-pyrimidin-2-yl]-piperazine-1-carboxylic acid (2-phenyl-benzofuran-5-yl)-amide



The tosylate precursor 2c was dissolved in dry dimethylformamide (100 μ L) and acetonitrile (400 μ L) and added to the dry potassium/ Kryptofix/ fluoride complex (vide supra). The solution was heated to 110 $^{\circ}$ C for 6 min and then allowed to cool to room temperature for 5 min. The solution was diluted with water to give a final volume of 10 mL and was passed through a Sep-Pak Plus C18 cartridge (Waters, WAT020515). The cartridge was rinsed with water (20 ml) and the compound was eluted with acetonitrile (3 mL). The eluted compound was diluted with water to yield 5 mL and was subjected to preparative HPLC purification. A Gemini 5 μ C 18 110 $\text{\AA}$, 250 * 10 mm (Phenomenex, 00G-4435-N0) was used as a stationary phase. A water (A)/ acetonitrile (B) 3 / 7 mixture was used as a mobile phase with a flow rate of 3 mL/ min.

The solution was diluted with water to give a final volume of 20 mL and was passed through a Sep-Pak light C18 cartridge (Waters, WAT023501). The cartridge was rinsed with water (10 ml) and the compound was eluted with ethanol (0.5 mL). The final product was characterized by HPLC on a Gemini 5 μ C 18 110 $\text{\AA}$, 250 * 4,6 mm (Phenomenex, 00G-4435-E0) HPLC column with an isocratic water/ acetonitrile (2/8; v/v) mixture at a flow rate of 1 mL/ min. Retention time (t_R): 4.1 min. RCY (d.c.): 38 %. RCP: 97 %.

e) 4-[5-(3-Fluoro-propyl)-pyrimidin-2-yl]-piperazine-1-carboxylic acid (2-phenyl-benzofuran-5-yl)-amide (HPLC standard)



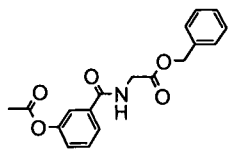
To 69 mg (0.15 mmol) of hydroxy derivative compound 2b in 10 mL dichloromethane were added 48 mg (0.3 mmol) of diethylamino sulfur trifluoride (DAST) at 0 $^{\circ}$ C. After 30 min at 0 $^{\circ}$ C, water was added, the organic phase was dried over sodium sulfate and after evaporation of the organic solvent, the residue was chromatographed on silica gel using a dichloromethane/ethyl acetate gradient.

Yield: 15 mg (22 %)

Elemental analysis:

calcd.:	C 67.96	H 5.70	F 4.13	N 15.24
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found:	C 67.67	H 5.96	F 3.96	N 15.22
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Example 3**a) (3-Acetoxy-benzoylamino)-acetic acid benzyl ester**

5

30.4 g (90 mmol) Glycine benzylester p-toluene sulfonate salt are solved in the two phase system dichloromethane and aqueous saturated sodium hydrogencarbonate solution. The organic phase is dried over magnesium sulfate and then evaporated.

10 13.09 g (79.25 mmol) of free amine is obtained which is used in the subsequent coupling reaction without further purification.

To a solution of 14.28 g (79.25 mmol) 3-Acetoxy-benzoic acid in 150 mL THF and 11 mL triethyl amine (79.25 mmol) at -15°C , 11.39 mL (87.2 mmol) isobutyl chloroformate are added dropwise and the solution is maintained at this temperature for another 15 min. Then,

15 13.09 g of glycine benzyl ester and 11 mL triethyl amine (79.25 mmol) in 50 mL THF and 50 mL dichloromethane are added slowly to this cold solution, the temperature is kept below 10°C for another 15 min and is then allowed to reach room temperature. After stirring overnight the solvent is evaporated and the residue is chromatographed on silica gel using an ethyl acetate/ethanol gradient.

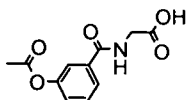
20 Yield: 24.6 g (95 %).

Elemental analysis:

calcd.: C 66.05 H 5.23 N 4.28

found: C 65.84 H 5.43 N 4.16

25

b) (3-Acetoxy-benzoylamino)-acetic acid

30 To a solution of 19.64 g (60 mmol) of benzyl ester 3a in 300 mL methanol are added 3 g Pd on charcoal (10%) and the suspension is stirred under hydrogen overnight at room temperature. The catalyst is filtered off and the solvent evaporated.

Yield: 14.2 g (quantitative).

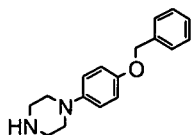
Elemental analysis:

calcd.: C 55.70 H 4.67 N 5.90

found: C 55.66 H 4.49 N 5.77

5

c) 1-(4-Benzyloxy-phenyl)-piperazine



10 All glassware is dried at 100°C. To a solution of 4.32 g (50.16 mmol) of piperazine in 60 mL toluene is added 459 mg (0.5 mmol) of tris(dibenzylidene acetone) dipalladium(0) and 423 mg (0.68 mmol) of BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl). Then, a solution of 12 g (45.6 mmol) of 4-Benzyloxy-bromobenzene in 40 mL THF is added followed by a suspension of 6.56 g (68.27 mmol) of sodium t-butyrate in THF.

15 The reaction mixture is refluxed for 3 h and stirred at room temperature overnight. After evaporation of the solvents the residue is chromatographed on silica gel using a dichloromethane/methanol gradient.

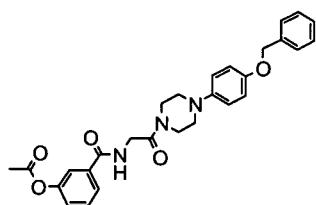
Yield: 12.2 g (45.7 %).

20 Elemental analysis:

calcd.: C 76.09 H 7.51 N 10.44

found: C 75.91 H 7.76 N 10.20

25 d) Acetic acid 3-{2-[4-(4-benzyloxy-phenyl)-piperazin-1-yl]-2-oxo-ethylcarbamoyl}-phenyl ester



To a solution of 654 mg (2.76 mmol) (3-Acetoxy-benzoylamino)-acetic acid 3b in 70 mL THF
30 and 0.40 mL triethyl amine (2.87 mmol) at -15°C, 0.396 mL (3.03 mmol) isobutyl chloroformate are added dropwise and the solution is maintained at this temperature for another 15

min. Then, 740 mg of 1-(4-benzyloxy-phenyl)-piperazine 3c and 1.7 mL triethyl amine (12.25 mmol) in 30 mL THF and 30 mL dichloromethane are added slowly to this cold solution, the temperature is kept below 10°C for another 15 min and is then allowed to reach room temperature. After stirring overnight the solvent is evaporated and the residue is chromatographed on silica gel using a hexane/ethyl acetate gradient.

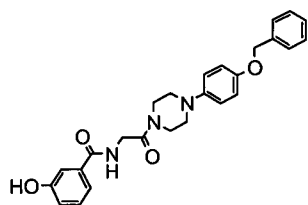
Yield: 390 mg (30 %).

Elemental analysis:

calcd.: C 68.98 H 6.00 N 8.62

found: C 69.09 H 5.81 N 8.42

e) N-{2-[4-(4-Benzyloxy-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-3-hydroxy-benzamide



230 mg (0.47 mmol) of the acetate 3d are solved in 30 mL of ethanol and cooled to 0°C. After addition of 1.5 mL 3N NaOH the solution is stirred for 1 h, glacial acetic acid is added until the pH is below pH 7 and the solvents are evaporated. The raw product is crystallized from ethanol.

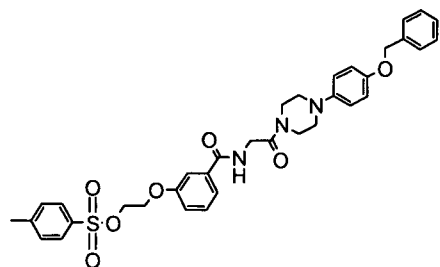
Yield: 200 mg (95 %).

Elemental analysis:

calcd.: C 70.10 H 6.11 N 9.43

found: C 69.88 H 6.27 N 9.20

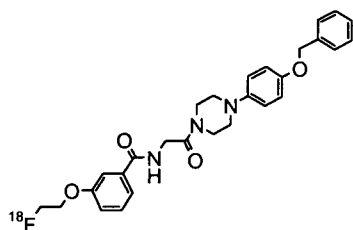
f) Toluene-4-sulfonic acid 2-(3-{2-[4-(4-benzyloxy-phenyl)-piperazin-1-yl]-2-oxo-ethylcarbamoyl}-phenoxy)-ethyl ester



To a solution of 80 mg (0.18 mmol) of N-{2-[4-(4-Benzoyloxy-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-3-hydroxy-benzamide (**3e**) in 10 mL DMF are added 62 mg (0.45 mmol) of potassium carbonate and 100 mg (0.27 mmol) of 1,2 bis(tosyloxy)ethane (Aldrich) . The mixture is heated to 60°C for 3 h. After stirring overnight at room temperature the solvent is evaporated and the residue is chromatographed on silica gel using an ethyl acetate/hexane gradient. Yield: 56 mg (48 %).

The compound has a purity >95% according to HPLC and is suitable as a precursor of the F-18 labelling.

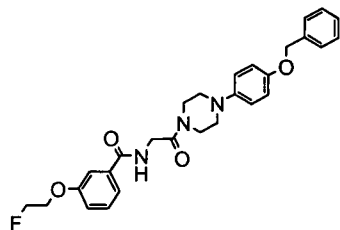
g) N-{2-[4-(4-Benzoyloxy-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-3-(2-[F-18]fluoro-ethoxy)-benzamide



The tosylate precursor **3f** was dissolved in dry dimethylformamide (100 µL) and acetonitrile (400 µL) and added to the dry potassium/ Kryptofix/ fluoride complex (vide supra). The solution was heated to 110 °C for 6 min and then allowed to cool to room temperature for 5 min. The solution was diluted with water to give a final volume of 10 mL and was passed through a Sep-Pak Plus C18 cartridge (Waters, WAT020515). The cartridge was rinsed with water (20 ml) and the compound was eluted with acetonitrile (3 mL). The eluted compound was diluted with water to yield 5 mL and was subjected to preparative HPLC purification. A Gemini 5 µ C 18 110 Å, 250 * 10 mm (Phenomenex, 00G-4435-N0) was used as a stationary phase. A water (A)/ acetonitrile (B) 3 / 7 mixture was used as a mobile phase with a flow rate of 3 mL/ min.

The solution was diluted with water to give a final volume of 20 mL and was passed through a Sep-Pak light C18 cartridge (Waters, WAT023501). The cartridge was rinsed with water (10 ml) and the compound was eluted with ethanol (0.5 mL). The final product was characterized by HPLC on a Gemini 5 µ C 18 110 Å, 250 * 4,6 mm (Phenomenex, 00G-4435-E0) HPLC column with an isocratic water/ acetonitrile (2/8; v/v) mixture at a flow rate of 1 mL/ min. Retention time (t_R): 4.3 min. RCY (d.c.): 38 %. RCP: 99 %.

- h) N-{2-[4-(4-Benzyloxy-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-3-(2-fluoro-ethoxy)-benzamide
(HPLC standard)



To a solution of 50 mg (0.11 mmol) of N-{2-[4-(4-Benzyloxy-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-3-hydroxy-benzamide (**3e**) in 5 mL DMF are added 34 mg (0.25 mmol) of potassium carbonate and 10 μ L (0.13 mmol) of 1-fluoro-2-bromoethane (ABCR, Germany). The mixture is heated to 60°C for 3 h. The solvent is evaporated and the residue is chromatographed on silica gel using an ethyl acetate/hexane gradient.

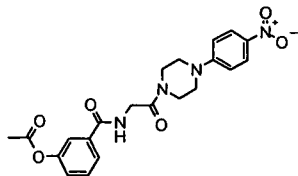
Yield: 30 mg (54 %).

Elemental analysis:

calcd.:	C 68.42	H 6.15	F 3.86	N 8.55
found:	C 68.17	H 6.28	F 3.64	N 8.71

Example 4

a) Acetic acid 3-{2-[4-(4-nitrophenyl)-piperazin-1-yl]-2-oxo-ethylcarbamoyl}-phenyl ester



To a solution of 3.43 g (14.5 mmol) of (3-Acetoxy-benzoylamino)-acetic acid (**3b**) and 2.0 g (9.65 mmol) of 1-(4-Nitrophenyl)piperazine (Aldrich) in 100 mL DMF are added 5.0 g (9.65 mmol) PyBOP ((Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate) and 5 mL N-ethyl-N,N-diisopropylamine and the reaction mixture is stirred overnight at room temperature. After evaporation of the solvents the residue is chromatographed on silica gel using an ethyl acetate/ethanol gradient.

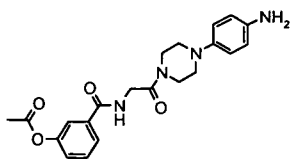
Yield: 1.2 g (29.2 %).

Elemental analysis:

calcd.: C 59.15 H 5.20 N 13.14

found: C 59.38 H 5.01 N 13.25

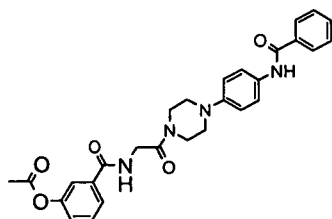
b) Acetic acid 3-{2-[4-(4-amino-phenyl)-piperazin-1-yl]-2-oxo-ethylcarbamoyl}-phenyl ester



To a solution of 853 mg (2 mmol) of nitro compound **4a** in 50 mL methanol/dichloromethane (1:1) is added a catalytic amount of Pd on charcoal (10%) and the suspension is stirred under hydrogen overnight at room temperature. The catalyst is filtered off and the solvent evaporated.

Yield: 795 mg (quantitative). The product is used in the next step without further purification.

c) Acetic acid 3-{2-[4-(4-benzoylamino-phenyl)-piperazin-1-yl]-2-oxo-ethylcarbamoyl}-phenyl ester



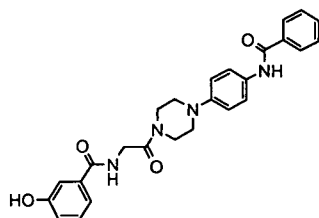
To a solution of 396 mg (1 mmol) acetic acid 3-{2-[4-(4-amino-phenyl)-piperazin-1-yl]-2-oxo-ethylcarbamoyl}-phenyl ester (**4b**) and 134 mg (1.1 mmol) of benzoic acid in 20 mL DMF are added 590 mg (1.14 mmol) of PyBOP and 0.35 mL (2 mmol) of N-ethyl-N,N-diisopropylamine and the reaction mixture is stirred at room temperature. After 4h the solvents are evaporated and the residue is chromatographed on silica gel using an dichloromethane/hexane gradient. Yield: 0.31 g (62.1 %).

10 Elemental analysis:

calcd.: C 67.19 H 5.64 N 11.19

found: C 66.94 H 5.88 N 11.02

15 d) N-{2-[4-(4-Benzoylamino-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-3-hydroxy-benzamide



235 mg (0.47 mmol) of the acetate **4c** are solved in 30 mL of ethanol and cooled to 0°C. After addition of 1.5 mL 3N NaOH the solution is stirred for 1 h, glacial acetic acid is added until the pH is below pH 7 and the solvents are evaporated. The raw product is crystallized from ethanol.

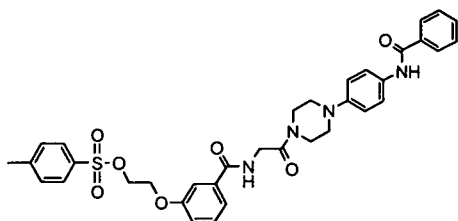
Yield: 177 mg (82 %).

Elemental analysis:

calcd.: C 68.11 H 5.72 N 12.22

found: C 67.91 H 5.60 N 12.00

- e) Toluene-4-sulfonic acid 2-(3-{2-[4-(4-benzoylamino-phenyl)-piperazin-1-yl]-2-oxo-ethyl-carbamoyl}-phenoxy)-ethyl ester

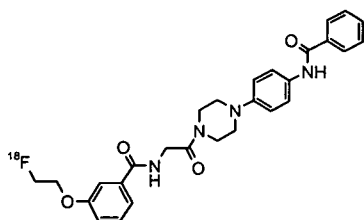


- 5 To a solution of 83 mg (0.18 mmol) of N-{2-[4-(4-Benzoylamino-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-3-hydroxy-benzamide (**4d**) in 10 mL DMF are added 62 mg (0.45 mmol) of potassium carbonate and 100 mg (0.27 mmol) of 1,2 bis(tosyloxy)ethane (Aldrich). The mixture is heated to 60°C for 3 h. After stirring overnight at room temperature the solvent is evaporated and the residue is chromatographed on silica gel using an ethyl acetate/hexane gradient.
- 10 Yield: 60 mg (51 %).

The compound has a purity >95% according to HPLC and is suitable as a precursor of the F-18 labelling.

15

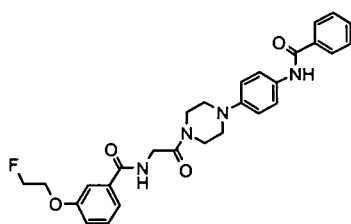
- f) N-{2-[4-(4-Benzoylamino-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-3-(2-[F-18]fluoro-ethoxy)-benzamide



- 20 The tosylate precursor **4e** was dissolved in dry dimethylformamide (100 µL) and acetonitrile (400 µL) and added to the dry potassium/ Kryptofix/ fluoride complex (vide supra). The solution was heated to 110 °C for 6 min and then allowed to cool to room temperature for 5 min. The solution was diluted with water to give a final volume of 10 mL and was passed through a Sep-Pak Plus C18 cartridge (Waters, WAT020515). The cartridge was rinsed with water
- 25 (20 ml) and the compound was eluted with acetonitrile (3 mL). The eluted compound was diluted with water to yield 5 mL and was subjected to preparative HPLC purification. A Gemini 5 µ C 18 110 Å, 250 * 10 mm (Phenomenex, 00G-4435-N0) was used as a stationary phase. A water (A)/ acetonitrile (B) 3 / 7 mixture was used as a mobile phase with a flow rate of 3 mL/ min.

The solution was diluted with water to give a final volume of 20 mL and was passed through a Sep-Pak light C18 cartridge (Waters, WAT023501). The cartridge was rinsed with water (10 ml) and the compound was eluted with ethanol (0.5 mL). The final product was characterized by HPLC on a Gemini 5 μ C 18 110 Å, 250 * 4,6 mm (Phenomenex, 00G-4435-E0) HPLC column with an isocratic water/ acetonitrile (2/8; v/v) mixture at a flow rate of 1 mL/min. Retention time (t_R): 4.1 min. RCY (d.c.): 32 %. RCP: 99 %.

g) N-{2-[4-(4-Benzoylamino-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-3-(2-fluoro-ethoxy)-benzamide (HPLC standard)



To a solution of 50 mg (0.11 mmol) of N-{2-[4-(4-Benzoylamino-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-3-hydroxy-benzamide (**4d**) in 5 mL DMF are added 34 mg (0.25 mmol) of potassium carbonate and 10 μ L (0.13 mmol) of 1-fluoro-2-bromoethane (ABCR, Germany). The mixture is heated to 60°C for 3 h. The solvent is evaporated and the residue is chromatographed on silica gel using an ethyl acetate/hexane gradient.

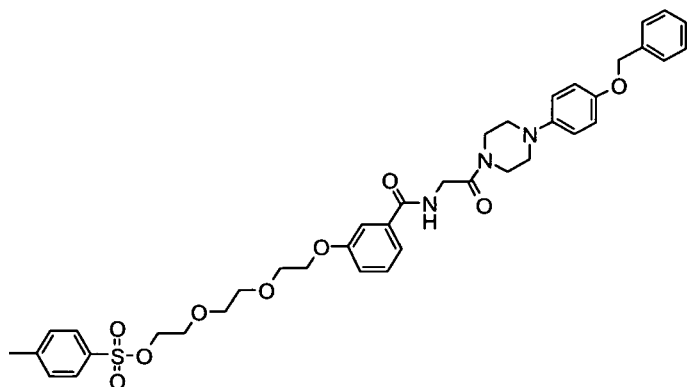
Yield: 34 mg (62 %).

Elemental analysis:

calcd.:	C 66.65	H 5.79	F 3.77	N 11.10
found:	C 66.43	H 5.89	F 3.41	N 11.31

Example 5

- 5 a) Toluene-4-sulfonic acid 2-{2-[2-(3-{2-[4-(4-benzyloxy-phenyl)-piperazin-1-yl]-2-oxo-ethylcarbamoyl}-phenoxy)-ethoxy]-ethoxy}-ethyl ester



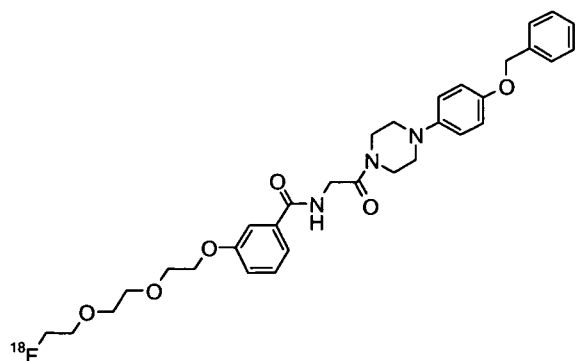
10 To a solution of 80 mg (0.18 mmol) of N-{2-[4-(4-Benzyloxy-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-3-hydroxy-benzamide (**3e**) in 10 mL DMF are added 62 mg (0.45 mmol) of potassium carbonate and 124 mg (0.27 mmol) of tri(ethylene glycol) di-p-toluenesulfonate (Aldrich). The mixture is heated to 60°C for 3 h. After stirring overnight at room temperature the solvent is evaporated and the residue is chromatographed on silica gel using an ethyl acetate/hexane gradient.

Yield: 54 mg (41 %).

15

The compound has a purity >95% according to HPLC and is suitable as a precursor of the F-18 labelling.

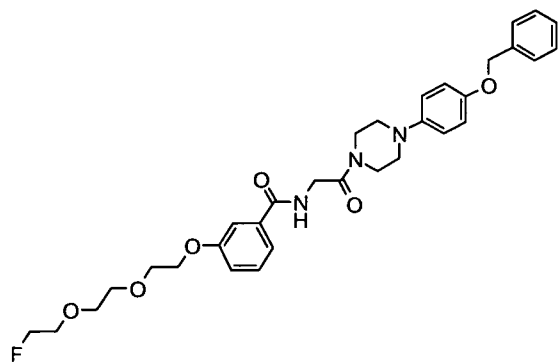
- 20 b) N-{2-[4-(4-Benzyloxy-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-3-{2-[2-(2-[F-18]fluoro-ethoxy)-ethoxy]-ethoxy}-benzamide



The tosylate precursor 5a was dissolved in dry dimethylformamide (100 μ L) and acetonitrile (400 μ L) and added to the dry potassium/ Kryptofix/ fluoride complex (vide supra). The solution was heated to 110 °C for 6 min and then allowed to cool to room temperature for 5 min. The solution was diluted with water to give a final volume of 10 mL and was passed through a Sep-Pak Plus C18 cartridge (Waters, WAT020515). The cartridge was rinsed with water (20 ml) and the compound was eluted with acetonitrile (3 mL). The eluted compound was diluted with water to yield 5 mL and was subjected to preparative HPLC purification. A Gemini 5 μ C 18 110 Å, 250 * 10 mm (Phenomenex, 00G-4435-N0) was used as a stationary phase. A water (A)/ acetonitrile (B) 3 / 7 mixture was used as a mobile phase with a flow rate of 3 mL/ min.

The solution was diluted with water to give a final volume of 20 mL and was passed through a Sep-Pak light C18 cartridge (Waters, WAT023501). The cartridge was rinsed with water (10 ml) and the compound was eluted with ethanol (0.5 mL). The final product was characterized by HPLC on a Gemini 5 μ C 18 110 Å, 250 * 4,6 mm (Phenomenex, 00G-4435-E0) HPLC column with an isocratic water/ acetonitrile (2/8; v/v) mixture at a flow rate of 1 mL/ min. Retention time (t_R): 4.2 min. RCY (d.c.): 42 %. RCP: 99 %.

c) N-{2-[4-(4-Benzoyloxy-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-3-{2-[2-(2-fluoro-ethoxy)-ethoxy]-ethoxy}-benzamide (HPLC standard)



73 mg (0.10 mmol) of the tosylate precursor 5a are dissolved in 2mL acetonitrile. 6.8 mg (0.12 mmol) potassium fluoride and 44.4 mg Kryptofix in 1 mL acetonitrile are added and incubated for 10 min at 100°C. The reaction is checked by analytical HPLC. After completion of the reaction, the mixture is evaporated and the residue is chromatographed on silica gel using an ethyl acetate/hexane gradient.

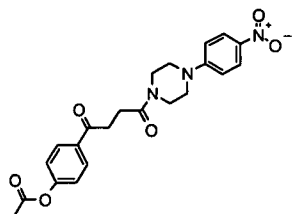
Yield: 28 mg (49 %).

Elemental analysis:

calcd.:	C 66.31	H 6.61	F 3.28	N 7.25
found:	C 66.07	H 6.73	F 3.11	N 7.38

Example 6

a) Acetic acid 4-{4-[4-(4-nitrophenyl)-piperazin-1-yl]-4-oxo-butyl}-phenyl ester



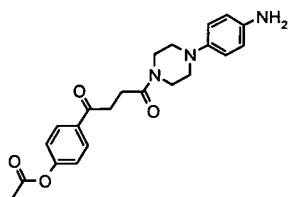
5

To a solution of 1.18 g (5 mmol) of 4-(4-acetoxycarbonylphenyl)-4-oxobutanoic acid (Arch. Pharm. (Weinheim, Germany) **284**; 292 (1951)) and 1.04 g (5 mmol) of 1-(4-nitrophenyl)piperazine (Aldrich) in 20 mL DMF are added 1.71 mL (10 mmol) of N-ethyl-N,N-diisopropylamine and 1.9 g (5 mmol) of 2-(1H-benzotriazol-1-yl)-tetramethyluronium hexafluorophosphate (HBTU). The reaction mixture is stirred at room temperature for 4h, then the solvents are evaporated and the residue is chromatographed on silica gel using an ethyl acetate/ethanol gradient. Yield: 1.53 g (72 %).

15 Elemental analysis:

calcd.:	C 62.11	H 5.45	N 9.88
found:	C 61.89	H 5.54	N 9.61

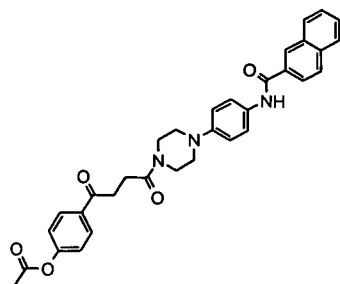
20 b) Acetic acid 4-{4-[4-(4-amino-phenyl)-piperazin-1-yl]-4-oxo-butyl}-phenyl ester



To a solution of 851 mg (2 mmol) of nitro compound **6a** in 50 mL methanol/DMF (3:1) is added a catalytic amount of Pd on charcoal (10%) and the suspension is stirred under hydrogen overnight at room temperature. The catalyst is filtered off and the solvent evaporated. Yield: 791 mg (quantitative). The product is used in the next step without further purification.

c) Acetic acid 4-[4-(4-{4-[(naphthalene-2-carbonyl)-amino]-phenyl}-piperazin-1-yl)-4-oxo-butyl]-phenyl ester

30



To a solution of 395 mg (1 mmol) acetic acid 4-{4-[4-(4-amino-phenyl)-piperazin-1-yl]-4-oxo-butyl}-phenyl ester (6b) and 190 mg (1.1 mmol) of 2-naphthalene carboxylic acid (Aldrich) in 20 mL DMF are added 590 mg (1.14 mmol) of PyBOP and 0.35 mL (2 mmol) of N-ethyl-N,N-diisopropylamine and the reaction mixture is stirred at room temperature. After 4h the solvents are evaporated and the residue is chromatographed on silica gel using an dichloromethane/hexane gradient.

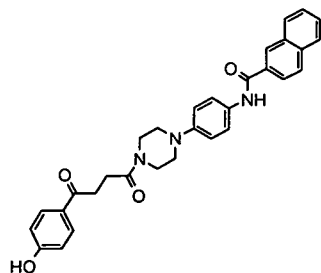
Yield: 374 mg (68 %).

Elemental analysis:

calcd.: C 72.12 H 5.69 N 7.65

found: C 72.30 H 5.61 N 7.42

d) Naphthalene-2-carboxylic acid (4-{4-[4-(4-hydroxy-phenyl)-4-oxo-butyl]-piperazin-1-yl}-phenyl)-amide



242 mg (0.44 mmol) of the acetate 6c are solved in 30 mL of ethanol/DMF (1:1) and cooled to 0°C. After addition of 2.2 mL 2N NaOH the solution is stirred for 30 min, glacial acetic acid is then added until the pH is below pH 7 and the solvents are evaporated. The raw product is crystallized from water and dried at 40°C in vacuo.

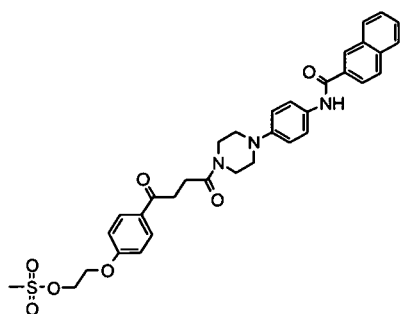
Yield: 223 mg (quantitative).

Elemental analysis:

calcd.: C 73.35 H 5.76 N 8.28

found: C 73.10 H 5.91 N 8.25

- 5 e) Toluene-4-sulfonic acid 2-{4-[4-(4-{[(naphthalene-2-carbonyl)-amino]-phenyl}-piperazin-1-yl)-4-oxo-butyl]-phenoxy}-ethyl ester

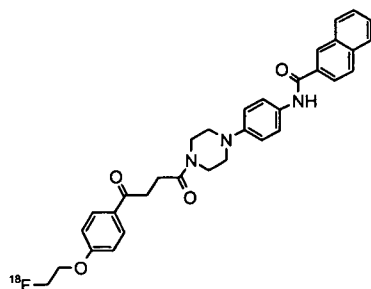


- 10 To a solution of 91 mg (0.18 mmol) of naphthalene-2-carboxylic acid (4-{4-[4-(4-hydroxy-phenyl)-4-oxo-butyl]-piperazin-1-yl}-phenyl)-amide (6d) in 10 mL DMF are added 62 mg (0.45 mmol) of potassium carbonate and 100 mg (0.27 mmol) of 1,2 bis(tosyloxy)ethane (Aldrich). The mixture is heated to 60°C for 3 h. After stirring overnight at room temperature the solvent is evaporated and the residue is chromatographed on silica gel using an ethyl acetate/hexane gradient.
- 15 Yield: 57 mg (46 %).

The compound has a purity >95% according to HPLC and is suitable as a precursor of the F-18 labelling.

20

- f) Naphthalene-2-carboxylic acid [4-(4-{4-[4-(2-[F-18]fluoro-ethoxy)-phenyl]-4-oxo-butyl]-piperazin-1-yl)-phenyl]-amide



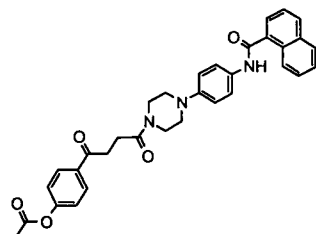
- 25 The tosylate precursor 6e was dissolved in dry dimethylformamide (100 µL) and acetonitrile (400 µL) and added to the dry potassium/ Kryptofix/ fluoride complex (vide supra). The solu-

tion was heated to 110 °C for 6 min and then allowed to cool to room temperature for 5 min. The solution was diluted with water to give a final volume of 10 mL and was passed through a Sep-Pak Plus C18 cartridge (Waters, WAT020515). The cartridge was rinsed with water (20 ml) and the compound was eluted with acetonitrile (3 mL). The eluted compound was diluted with water to yield 5 mL and was subjected to preparative HPLC purification. A Gemini 5 μ C 18 110 Å, 250 * 10 mm (Phenomenex, 00G-4435-N0) was used as a stationary phase. A water (A)/ acetonitrile (B) 3 / 7 mixture was used as a mobile phase with a flow rate of 3 mL/ min.

The solution was diluted with water to give a final volume of 20 mL and was passed through a Sep-Pak light C18 cartridge (Waters, WAT023501). The cartridge was rinsed with water (10 ml) and the compound was eluted with ethanol (0.5 mL). The final product was characterized by HPLC on a Gemini 5 μ C 18 110 Å, 250 * 4,6 mm (Phenomenex, 00G-4435-E0) HPLC column with an isocratic water/ acetonitrile (2/8; v/v) mixture at a flow rate of 1 mL/ min. Retention time (t_R): 5.6 min. RCY (d.c.): 35 %. RCP: 98 %.

Example 7

- a) Acetic acid 4-[4-(4-[4-[(naphthalene-1-carbonyl)-amino]-phenyl]-piperazin-1-yl)-4-oxo-buteryl]-phenyl ester



To a solution of 395 mg (1 mmol) acetic acid 4-{4-[4-(4-amino-phenyl)-piperazin-1-yl]-4-oxo-buteryl}-phenyl ester (**6b**) and 190 mg (1.1 mmol) of 1-naphthalene carboxylic acid (Aldrich) in 20 mL DMF are added 590 mg (1.14 mmol) of PyBOP and 0.35 mL (2 mmol) of N-ethyl-N,N-diisopropylamine and the reaction mixture is stirred at room temperature. After 4h the solvents are evaporated and the residue is chromatographed on silica gel using an dichloro-methane/hexane gradient.

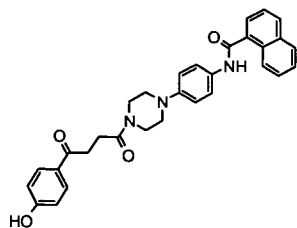
Yield: 336 mg (61 %).

Elemental analysis:

calcd.: C 72.12 H 5.69 N 7.65

found: C 71.94 H 5.77 N 7.59

- b) Naphthalene-1-carboxylic acid (4-{4-[4-(4-hydroxy-phenyl)-4-oxo-buteryl]-piperazin-1-yl}-phenyl)-amide



242 mg (0.44 mmol) of the acetate **7a** are solved in 30 mL of ethanol/DMF (1:1) and cooled to 0°C. After addition of 2.2 mL 2N NaOH the solution is stirred for 30 min, glacial acetic acid is then added until the pH is below pH 7 and the solvents are evaporated. The raw product is crystallized from water and dried at 40°C in vacuo.

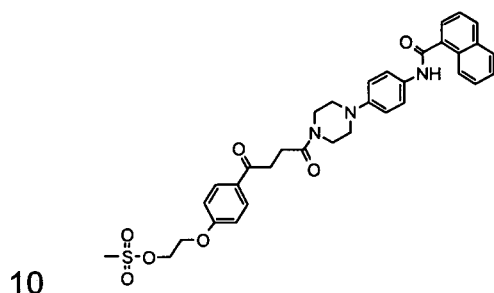
Yield: 223 mg (quantitative).

Elemental analysis:

calcd.: C 73.35 H 5.76 N 8.28

5 found: C 73.21 H 5.62 N 8.11

c) Toluene-4-sulfonic acid 2-{4-[4-(4-{[(naphthalene-1-carbonyl)-amino]-phenyl}-piperazin-1-yl)-4-oxo-butyl]-phenoxy}-ethyl ester



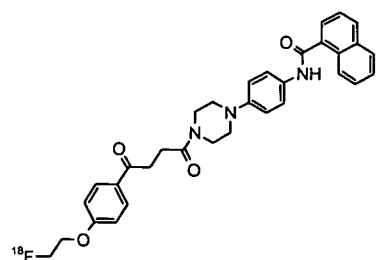
To a solution of 91 mg (0.18 mmol) of naphthalene-1-carboxylic acid (4-{4-[4-(4-hydroxy-phenyl)-4-oxo-butyl]-piperazin-1-yl]-phenyl)-amide (**7b**) in 10 mL DMF are added 62 mg (0.45 mmol) of potassium carbonate and 100 mg (0.27 mmol) of 1,2 bis(tosyloxy)ethane (Aldrich). The mixture is heated to 60°C for 3 h. After stirring overnight at room temperature the solvent is evaporated and the residue is chromatographed on silica gel using an ethyl acetate/hexane gradient.

Yield: 63 mg (51 %).

20 The compound has a purity >95% according to HPLC and is suitable as a precursor of the F-18 labelling.

d) Naphthalene-1-carboxylic acid [4-(4-{4-[4-(2-[F-18]fluoro-ethoxy)-phenyl]-4-oxo-butyl]-piperazin-1-yl)-phenyl]-amide

25



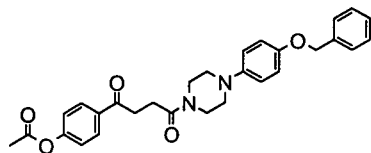
The tosylate precursor 7c was dissolved in dry dimethylformamide (100 μ L) and acetonitrile (400 μ L) and added to the dry potassium/ Kryptofix/ fluoride complex (vide supra). The solution was heated to 110 °C for 6 min and then allowed to cool to room temperature for 5 min. The solution was diluted with water to give a final volume of 10 mL and was passed through a Sep-Pak Plus C18 cartridge (Waters, WAT020515). The cartridge was rinsed with water (20 ml) and the compound was eluted with acetonitrile (3 mL). The eluted compound was diluted with water to yield 5 mL and was subjected to preparative HPLC purification. A Gemini 5 μ C 18 110 Å, 250 * 10 mm (Phenomenex, 00G-4435-N0) was used as a stationary phase. A water (A)/ acetonitrile (B) 3 / 7 mixture was used as a mobile phase with a flow rate of 3 mL/ min.

The solution was diluted with water to give a final volume of 20 mL and was passed through a Sep-Pak light C18 cartridge (Waters, WAT023501). The cartridge was rinsed with water (10 ml) and the compound was eluted with ethanol (0.5 mL). The final product was characterized by HPLC on a Gemini 5 μ C 18 110 Å, 250 * 4,6 mm (Phenomenex, 00G-4435-E0) HPLC column with an isocratic water/ acetonitrile (2/8; v/v) mixture at a flow rate of 1 mL/ min. Retention time (t_R): 6.0 min. RCY (d.c.): 32 %. RCP: 97 %.

Example 8

a) Acetic acid 4-{4-[4-(4-benzyloxy-phenyl)-piperazin-1-yl]-4-oxobutyl}-phenyl ester

5



To a solution of 652 mg (2.76 mmol) of 4-(4-acetoxyphe-nyl)-4-oxobutyric acid (Arch. Pharm. (Weinheim, Germany) 284; 292 (1951)) in 70 mL THF and 0.40 mL triethyl amine (2.87 mmol) at -15°C, 0.396 mL (3.03 mmol) isobutyl chloroformate are added dropwise and the solution is maintained at this temperature for another 15 min. Then, 740 mg of 1-(4-benzyloxy-phenyl)-piperazine 3c and 1.7 mL triethyl amine (12.25 mmol) in 30 mL THF and 30 mL dichloromethane are added slowly to this cold solution, the temperature is kept below 10°C for another 15 min and is then allowed to reach room temperature. After stirring over-night the solvent is evaporated and the residue is chromatographed on silica gel using a hexane/ethyl acetate gradient.

15

Yield: 219 mg (45 %).

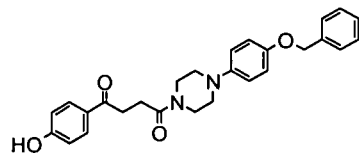
Elemental analysis:

calcd.: C 71.59 H 6.21 N 5.76

20

found: C 71.33 H 6.46 N 5.60

b) 1-[4-(4-Benzyloxy-phenyl)-piperazin-1-yl]-4-(4-hydroxyphenyl)-butane-1,4-dione



25

229 mg (0.47 mmol) of the acetate 8a are solved in 30 mL of ethanol and cooled to 0°C. After addition of 1.5 mL 3N NaOH the solution is stirred for 1 h, glacial acetic acid is added until the pH is below pH 7 and the solvents are evaporated. The raw product is crystallized from ethanol.

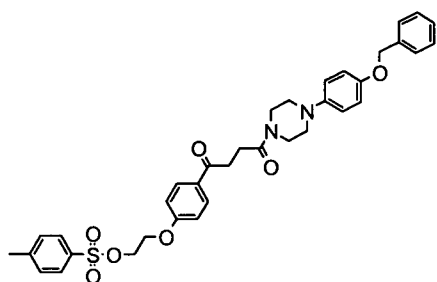
30

Yield: 186 mg (89 %).

Elemental analysis:

calcd.: C 72.95 H 6.35 N 6.30
 found: C 72.78 H 6.27 N 6.41

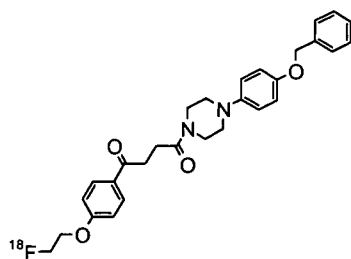
- 5 c) Toluene-4-sulfonic acid 2-(4-{4-[4-(4-benzyloxy-phenyl)-piperazin-1-yl]-4-oxobutyl}-phenoxy)-ethyl ester



To a solution of 80 mg (0.18 mmol) of 1-[4-(4-Benzyloxy-phenyl)-piperazin-1-yl]-4-(4-hydroxyphenyl)-butane-1,4-dione (**8b**) in 10 mL DMF are added 62 mg (0.45 mmol) of potassium carbonate and 100 mg (0.27 mmol) of 1,2 bis(tosyloxy)ethane (Aldrich). The mixture is heated to 60°C for 3 h. After stirring overnight at room temperature the solvent is evaporated and the residue is chromatographed on silica gel using an ethyl acetate/hexane gradient.
 Yield: 60 mg (52 %).

15 The compound has a purity >95% according to HPLC and is suitable as a precursor of the F-18 labelling.

- 20 d) 1-[4-(4-Benzyloxy-phenyl)-piperazin-1-yl]-4-[4-(2-[F-18]fluoro-ethoxy)-phenyl]-butane-1,4-dione



The tosylate precursor **8c** was dissolved in dry dimethylformamide (100 µL) and acetonitrile (400 µL) and added to the dry potassium/ Kryptofix/ fluoride complex (vide supra). The solution was heated to 110 °C for 6 min and then allowed to cool to room temperature for 5 min. The solution was diluted with water to give a final volume of 10 mL and was passed through

a Sep-Pak Plus C18 cartridge (Waters, WAT020515). The cartridge was rinsed with water (20 ml) and the compound was eluted with acetonitrile (3 mL). The eluted compound was diluted with water to yield 5 mL and was subjected to preparative HPLC purification. A Gemini 5 μ C 18 110 Å, 250 * 10 mm (Phenomenex, 00G-4435-N0) was used as a stationary phase.

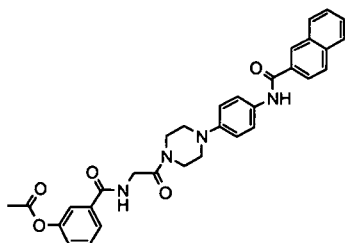
5 A water (A)/ acetonitrile (B) 3 / 7 mixture was used as a mobile phase with a flow rate of 3 mL/ min.

The solution was diluted with water to give a final volume of 20 mL and was passed through a Sep-Pak light C18 cartridge (Waters, WAT023501). The cartridge was rinsed with water (10 ml) and the compound was eluted with ethanol (0.5 mL). The final product was character-

10 ized by HPLC on a Gemini 5 μ C 18 110 Å, 250 * 4,6 mm (Phenomenex, 00G-4435-E0) HPLC column with an isocratic water/ acetonitrile (2/8; v/v) mixture at a flow rate of 1 mL/ min. Retention time (t_R): 4.7 min. RCY (d.c.): 45 %. RCP: 99 %.

Example 9

- a) Acetic acid 3-[2-(4-{4-[(naphthalene-2-carbonyl)-amino]-phenyl}-piperazin-1-yl)-2-oxo-ethylcarbamoyl]-phenyl ester



To a solution of 396 mg (1 mmol) acetic acid 3-{2-[4-(4-amino-phenyl)-piperazin-1-yl]-2-oxo-ethylcarbamoyl}-phenyl ester (**4b**) and 190 mg (1.1 mmol) of 2-naphthalene carboxylic acid (Aldrich) in 20 mL DMF are added 590 mg (1.14 mmol) of PyBOP and 0.35 mL (2 mmol) of N-ethyl-N,N-diisopropylamine and the reaction mixture is stirred at room temperature. After 4h the solvents are evaporated and the residue is chromatographed on silica gel using an dichloromethane/hexane gradient.

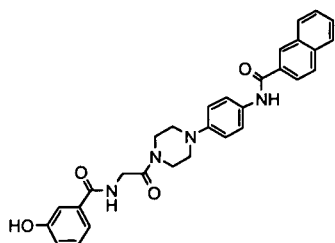
Yield: 0.25 g (43.9 %).

Elemental analysis:

calcd.: C 69.80 H 5.49 N 10.18

found: C 69.55 H 5.61 N 10.03

- b) Naphthalene-2-carboxylic acid (4-{4-[2-(3-hydroxy-benzoylamino)-acetyl]-piperazin-1-yl}-phenyl)-amide



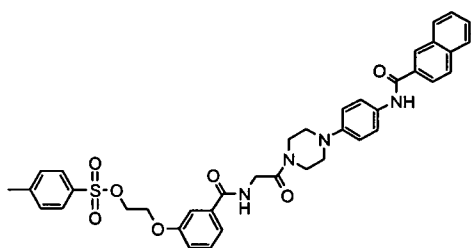
240 mg (0.44 mmol) of the acetate **9a** are solved in 30 mL of ethanol/DMF (1:1) and cooled to 0°C. After addition of 2.2 mL 2N NaOH the solution is stirred for 30 min, glacial acetic acid is then added until the pH is below pH 7 and the solvents are evaporated. The raw product is crystallized from water and dried at 40°C *in vacuo*.

Yield: 220 mg (quantitative).

Elemental analysis:

5 calcd.: C 70.85 H 5.55 N 11.02
found: C 70.53 H 5.77 N 10.85

- 10 c) Toluene-4-sulfonic acid 2-{3-[2-(4-{4-[(naphthalene-2-carbonyl)-amino]-phenyl)-piperazin-1-yl]-2-oxo-ethylcarbamoyl]-phenoxy}-ethyl ester



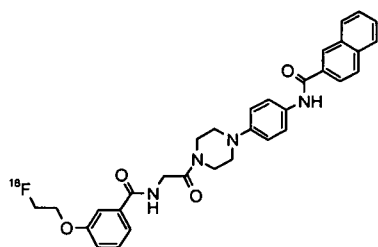
15 To a solution of 92 mg (0.18 mmol) of Naphthalene-2-carboxylic acid (4-{4-[2-(3-hydroxy-benzoylamino)-acetyl]-piperazin-1-yl}-phenyl)-amide (**9b**) in 10 mL DMF are added 62 mg (0.45 mmol) of potassium carbonate and 100 mg (0.27 mmol) of 1,2 bis(tosyloxy)ethane (Aldrich). The mixture is heated to 60°C for 3 h. After stirring overnight at room temperature the solvent is evaporated and the residue is chromatographed on silica gel using an ethyl acetate/hexane gradient.

Yield: 58 mg (46 %).

20

The compound has a purity >95% according to HPLC and is suitable as a precursor of the F-18 labelling.

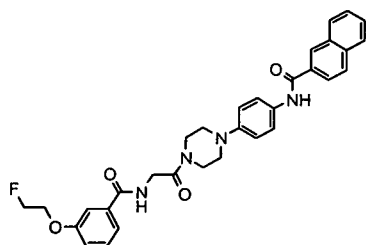
- 25 d) Naphthalene-2-carboxylic acid [4-(4-{2-[3-(2-[F-18]fluoro-ethoxy)-benzoylamino]-acetyl]-piperazin-1-yl)-phenyl]-amide



The tosylate precursor 9c was dissolved in dry dimethylformamide (100 μ L) and acetonitrile (400 μ L) and added to the dry potassium/ Kryptofix/ fluoride complex (vide supra). The solution was heated to 110 $^{\circ}$ C for 6 min and then allowed to cool to room temperature for 5 min. The solution was diluted with water to give a final volume of 10 mL and was passed through a Sep-Pak Plus C18 cartridge (Waters, WAT020515). The cartridge was rinsed with water (20 ml) and the compound was eluted with acetonitrile (3 mL). The eluted compound was diluted with water to yield 5 mL and was subjected to preparative HPLC purification. A Gemini 5 μ C 18 110 $\text{\AA}$, 250 * 10 mm (Phenomenex, 00G-4435-N0) was used as a stationary phase. A water (A)/ acetonitrile (B) 3 / 7 mixture was used as a mobile phase with a flow rate of 3 mL/ min.

The solution was diluted with water to give a final volume of 20 mL and was passed through a Sep-Pak light C18 cartridge (Waters, WAT023501). The cartridge was rinsed with water (10 ml) and the compound was eluted with ethanol (0.5 mL). The final product was characterized by HPLC on a Gemini 5 μ C 18 110 $\text{\AA}$, 250 * 4,6 mm (Phenomenex, 00G-4435-E0) HPLC column with an isocratic water/ acetonitrile (2/8; v/v) mixture at a flow rate of 1 mL/ min. Retention time (t_R): 4.6 min. RCY (d.c.): 39 %. RCP: 99 %.

e) Naphthalene-2-carboxylic acid [4-(4-{2-[3-(2-fluoro-ethoxy)-benzoylamino]-acetyl}-piperazin-1-yl)-phenyl]-amide (HPLC-Standard)



To a solution of 56 mg (0.11 mmol) of Naphthalene-2-carboxylic acid (4-{4-[2-(3-hydroxy-benzoylamino)-acetyl]-piperazin-1-yl}-phenyl)-amide (**9b**) in 5 mL DMF are added 34 mg (0.25 mmol) of potassium carbonate and 10 μ L (0.13 mmol) of 1-fluoro-2-bromoethane (ABCR, Germany). The mixture is heated to 60 $^{\circ}$ C for 3 h. The solvent is evaporated and the residue taken up in dimethyl sulfoxide and chromatographed twice on RP-18 using a water/acetonitrile gradient.

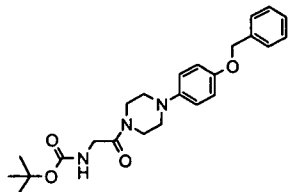
Yield: 24 mg (40 %).

Elemental analysis:

calcd.: C 69.30	H 5.63	F 3.43	N 10.10
found: C 69.15	H 5.81	F 3.22	N 10.28

Example 10

a) {2-[4-(4-Benzyloxy-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-carbamic acid tert-butyl ester



To a solution of 7.7 g (43.97 mmol) *t*-Butoxycarbonyl-glycine (Aldrich) in 800 mL THF and 8 mL triethyl amine (57.71 mmol) at -15°C , 5.75 mL (43.97 mmol) isobutyl chloroformate are added dropwise and the solution is maintained at this temperature for another 15 min. Then, 11.8 g of 1-(4-benzyloxyphenyl)-piperazine (**3c**) and 29 mL triethyl amine (210 mmol) in 300 mL THF/dichloromethane (1:1) are added slowly to this cold solution, the temperature is kept below 10°C for another 15 min and is then allowed to reach room temperature. After stirring overnight the solvent is evaporated and the residue is taken up in ethyl acetate. This solution is washed successively with aqueous sodium carbonate, water, 1 M aqueous HCl solution, saturated aqueous sodium chloride solution, finally dried over magnesium sulfate and then evaporated. This residue is chromatographed on silica gel using a hexane/ethyl acetate gradient.

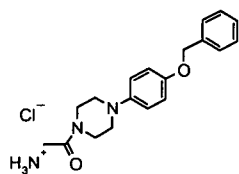
Yield: 15.51 g (82.9 %).

Elemental analysis:

calcd.: C 67.74 H 7.34 N 9.87

found: C 67.33 H 7.47 N 9.62

b) 2-[4-(4-Benzyloxy-phenyl)-piperazin-1-yl]-2-oxo-ethyl-ammonium chloride



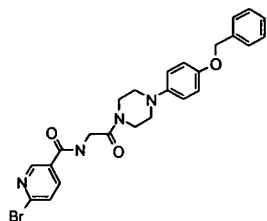
17.0 g (39.95 mmol) of {2-[4-(4-Benzyloxy-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-carbamic acid tert-butyl ester (**10a**) are suspended in 300 mL 2N HCl in diethyl ether and stirred overnight

at room temperature. The precipitate is filtered off and washed with ether and dried at 40°C *in vacuo*.

Yield: 14.5 g (quantitative). The product is used in the next step without further purification.

5

c) N-{2-[4-(4-Benzyloxy-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-6-bromo-nicotinamide



10 To a solution of 202 mg (1 mmol) of 2-bromo-5-pyridinecarboxylic acid (Aldrich) and 398 mg (1.1 mmol) of 2-[4-(4-benzyloxyphenyl)-piperazin-1-yl]-2-oxoethyl-ammonium chloride (10b) in 20 mL DMF are added 624 mg (1.2 mmol) PyBOP and 0.61 mL N-ethyl-N,N-diisopropylamine and the reaction mixture is stirred overnight at room temperature. After evaporation of the solvent the residue is chromatographed on silica gel using an ethyl acetate/ethanol gradient.

15 Yield: 183 mg (35.9 %).

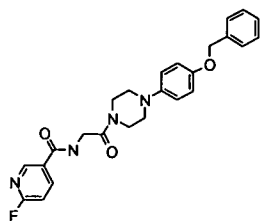
Elemental analysis:

calcd.: C 58.95 H 4.95 Br 15.69 N 11.00

found: C 58.66 H 5.18 Br 15.20 N 11.36

20 The compound has a purity >95% according to HPLC and is suitable as a precursor for the F-18 labelling.

d) N-{2-[4-(4-Benzyloxy-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-6-fluoro-nicotinamide



25

To a solution of 141 mg (1 mmol) of 2-fluoro-5-pyridinecarboxylic acid (Aldrich) and 398 mg (1.1 mmol) of 2-[4-(4-benzyloxyphenyl)-piperazin-1-yl]-2-oxoethyl-ammonium chloride (10b)

in 20 mL DMF are added 624 mg (1.2 mmol) PyBOP and 0.61 mL N-ethyl-N,N-diisopropylamine and the reaction mixture is stirred overnight at room temperature. After evaporation of the solvent the residue is chromatographed on silica gel using an ethyl acetate/ethanol gradient.

5 Yield: 302 mg (67.3 %).

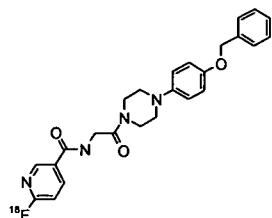
Elemental analysis:

calcd.: C 66.95 H 5.62 F 4.24 N 12.49

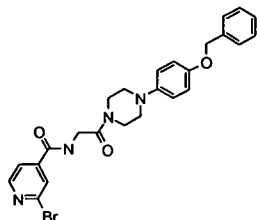
found: C 66.84 H 5.97 F 3.95 N 12.52

10

e) N-{2-[4-(4-Benzyloxy-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-6-[F-18]-fluoro-nicotinamide



15 Aqueous [¹⁸F]Fluoride (5.1 GBq) was trapped on a QMA cartridge (Waters, Sep Pak Light QMA Part.No.: WAT023525) and eluted with 5mg K_{2.2.2} in 0,95ml MeCN +1mg K₂CO₃ in 50μl water into a Wheaton vial (5ml). 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 precursor **10c** (5 mg) in 700 μl anhydrous DMSO was added. After heating at
20 180°C for 30 min the crude reaction mixture was diluted with water to a total volume and purified by preparative HPLC: ACE 5-C18-HL 250mmx10mm, Advanced Chromatography Technologies; Cat.No.: ACE 321-2510; isocratic, 35% acetonitrile in 0.1% trifluoroacetic acid, flow: 4 ml/min; t_R=18min. The collected HPLC fraction was diluted with 40ml water and immobilized on a Sep-Pak light C18 cartridge (Waters, WAT023501), which was washed with
25 5ml water and eluted with 1ml ethanol to deliver 1015 MBq of the product (36%, corrected for decay; radiochemical purity >99%). The desired product was characterized by co-injection with the non-radioactive F-19 fluoro standard on the analytical HPLC: Agilent ZORBAX 300SB-C18 250*4.6 mm ; 5 μm Agilent; PN 880995-902; A): Water + 0,1% TFA, B): MeCN + 0,1% TFA, 0 to 10 min, 35% B; 10 to 10:30 min, 35% B to 100%B; 1mL/min (t_R=7.6min),
30 RCP: 99 %(HPLC).

Example 11**a) N-{2-[4-(4-Benzyloxy-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-2-bromo-isonicotinamide**

To a solution of 202 mg (1 mmol) of 2-bromo-4-pyridinecarboxylic acid (Alfa) and 398 mg (1.1 mmol) of 2-[4-(4-benzyloxyphenyl)-piperazin-1-yl]-2-oxoethyl-ammonium chloride (**10b**) in 20 mL DMF are added 624 mg (1.2 mmol) PyBOP and 0.61 mL N-ethyl-N,N-diisopropylamine and the reaction mixture is stirred overnight at room temperature. After evaporation of the solvent the residue is chromatographed on silica gel using an ethyl acetate/ethanol gradient. The product containing fractions are collected and recrystallized from ethyl acetate.

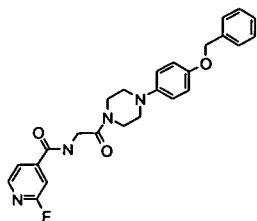
Yield: 165 mg (32.4 %).

Elemental analysis:

calcd.: C 58.95 H 4.95 Br 15.69 N 11.00

found: C 58.32 H 5.09 Br 15.11 N 10.73

The compound has a purity >95% according to HPLC and is suitable as a precursor for the F-18 labelling.

b) N-{2-[4-(4-Benzyloxy-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-2-fluoro-isonicotinamide

To a solution of 141 mg (1 mmol) of 2-fluoro-4-pyridinecarboxylic acid (Aldrich) and 398 mg (1.1 mmol) of 2-[4-(4-benzyloxyphenyl)-piperazin-1-yl]-2-oxoethyl-ammonium chloride (**10b**) in 20 mL DMF are added 624 mg (1.2 mmol) PyBOP and 0.61 mL N-ethyl-N,N-diisopropylamine and the reaction mixture is stirred overnight at room temperature. After

evaporation of the solvent the residue is chromatographed on silica gel using an ethyl acetate/ethanol gradient.

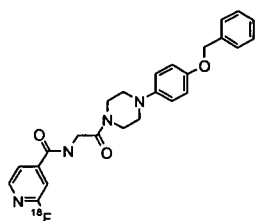
Yield: 326 mg (72.7 %).

5 Elemental analysis:

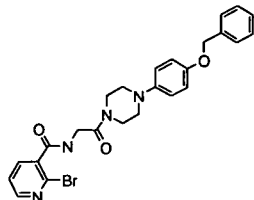
calcd.: C 66.95 H 5.62 F 4.24 N 12.49

found: C 66.58 H 5.81 F 4.03 N 12.68

10 c) N-{2-[4-(4-Benzoyloxy-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-2-[F-18]-fluoro-isonicotinamide



Aqueous [¹⁸F]Fluoride (4,9 GBq) was trapped on a QMA cartridge (Waters, Sep Pak Light QMA Part.No.: WAT023525) and eluted with 5mg K_{2.2.2} in 0,95ml MeCN +1mg K₂CO₃ in 50μl water into a Wheaton vial (5ml). 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 precursor **11a** (5 mg) in 700 μl anhydrous DMSO was added. After heating at 180°C for 30 min the crude reaction mixture was diluted with water to a total volume of 5mL and purified by preparative HPLC: ACE 5-C18-HL 250mmx10mm, Advanced Chromatography Technologies; Cat.No.: ACE 321-2510; isocratic, 35% acetonitrile in 0.1% trifluoroacetic acid, flow: 4 ml/min; t_R=18min. The collected HPLC fraction was diluted with 40ml water and immobilized on a Sep-Pak light C18 cartridge (Waters, WAT023501), which was washed with 5ml water and eluted with 1ml ethanol to deliver 1293 MBq of the product (44%, corrected for decay) which was characterized and reconfirmed by co-injection with the non-radioactive F-19 fluoro standard using analytical HPLC: Agilent ZORBAX 300SB-C18 50*4.6 mm ; 5 μm Agilent; PN 880995-902, A): Water + 0,1% TFA, B): MeCN + 0,1% TFA, 0 to 10 min, 35% B; 10 to 10:30 min, 35% B to 100%B; 1mL/min, (t_R=7.5min), RCP: >99 %(HPLC).

Example 12**a) N-{2-[4-(4-Benzyloxy-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-2-bromo-nicotinamide**

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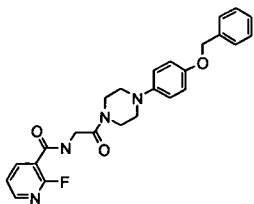
To a solution of 202 mg (1 mmol) of 2-bromo-nicotinic acid (Aldrich) and 398 mg (1.1 mmol) of 2-[4-(4-benzyloxyphenyl)-piperazin-1-yl]-2-oxoethyl-ammonium chloride (**10b**) in 20 mL DMF are added 624 mg (1.2 mmol) PyBOP and 0.61 mL N-ethyl-N,N-diisopropylamine and the reaction mixture is stirred overnight at room temperature. After evaporation of the solvent the residue is chromatographed on silica gel using an ethyl acetate/ethanol gradient. Yield: 210 mg (41.2 %).

Elemental analysis:

15	calcd.: C 58.95	H 4.95	Br 15.69	N 11.00
	found: C 59.11	H 4.75	Br 15.39	N 11.03

The compound has a purity >95% according to HPLC and is suitable as a precursor for the F-18 labelling.

20

b) N-{2-[4-(4-Benzyloxy-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-2-fluoro-nicotinamide

To a solution of 141 mg (1 mmol) of 2-fluoro-nicotinic acid (Aldrich) and 398 mg (1.1 mmol) of 2-[4-(4-benzyloxyphenyl)-piperazin-1-yl]-2-oxoethyl-ammonium chloride (**10b**) in 20 mL DMF are added 624 mg (1.2 mmol) PyBOP and 0.61 mL N-ethyl-N,N-diisopropylamine and the reaction mixture is stirred overnight at room temperature. After evaporation of the solvent the residue is chromatographed on silica gel using an ethyl acetate/ethanol gradient.

25

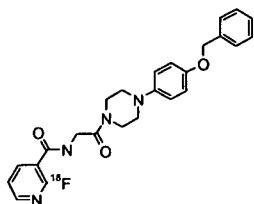
Yield: 326 mg (72.7 %).

Elemental analysis:

calcd.: C 66.95 H 5.62 F 4.24 N 12.49

5 found: C 66.71 H 5.79 F 3.88 N 12.30

c) N-{2-[4-(4-Benzyloxy-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-2-[F-18]-fluoro-nicotinamide



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Aqueous [¹⁸F]Fluoride (7 GBq) was trapped on a QMA cartridge (Waters, Sep Pak Light QMA Part.No.: WAT023525) and eluted with 5mg K_{2.2.2} in 0,95ml MeCN +1mg K₂CO₃ in 50μl water into a Wheaton vial (5ml). 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.

15 A solution of precursor **12a** (5 mg) in 700 μl anhydrous DMSO was added. After heating at

180°C for 30 min the crude reaction mixture was diluted with water to a total volume of 5mL and purified by preparative HPLC: ACE 5-C18-HL 250mmx10mm, Advanced Chromatography Technologies; Cat.No.: ACE 321-2510; isocratic, 35% acetonitrile in 0.1% trifluoroacetic acid, flow: 4 ml/min; t_R=19min. The collected HPLC fraction was diluted with 40ml water and

20 immobilized on a Sep-Pak light C18 cartridge (Waters, WAT023501), which was washed with

5ml water and eluted with 1ml ethanol to deliver 2015 MBq of the product (49%, corrected for decay) which was characterized and reconfirmed by co-injection with the non-radioactive F-19 fluoro standard using analytical HPLC: Agilent ZORBAX 300SB-C18 50*4.6 mm ; 5 μm Agilent; PN 880995-902, A): Water + 0,1% TFA, B): MeCN + 0,1% TFA, 0 to 10 min, 35% B;

25 10 to 10:30 min, 35% B to 100%B; 1mL/min, (t_R=7.8min), RCP: >99 %(HPLC).

Example 13: Biological data

a) Methods

5

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.

10 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 µl and stored at -80°C.

15 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
20 binding was assessed by adding an excess of 1000x of the tritiated ligand to the reaction mixture. Finally IC50 values were calculated with the help of appropriate analysis software.

Autoradiographical analysis

25 Fresh frozen as well as paraffin embedded sections of the frontal lobe from Alzheimer's dementia patients, frontotemporal dementia patients and age matched controls were used for the study.

Frozen sections, sliced at 18 µm thickness on a cryostat (Leica, Germany) and paraffin sections, sliced on a sliding microtome (Leica) at a thickness of 6 µm, were mounted onto glass slides (Superfrost Plus, Fa.Menzel, Braunschweig Germany). Frozen sections were allowed
30 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 a 1000-fold excess of the unlabeled test substance was added to the incubation mixture.
35 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).

5 Biodistribution

Biodistribution and excretion studies were performed in male NMRI mice (body weight app. 30 g; 3 animals per time point). The animals were kept under normal laboratory conditions at a temperature of $22 \pm 2^\circ\text{C}$ and a dark/light rhythm of 12 hours. Food and water were provided ad libitum. 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 in 100 μl of the test compound, urine and feces were quantitatively collected. At the same time points, animals were sacrificed by decapitation and under isoflurane anaesthesia and the following organs and tissues were removed for the determination of radioactivity using a gamma-counter: spleen, liver, kidney, lung, femur, heart, brain, fat, thyroid, muscle, skin, blood, tail, stomach (without content), testicle, intestine (with content), pancreas, adrenals, and the remaining body. For analysis the decay corrected percentage of the injected dose per tissue weight ($\%ID/g \pm$ standard deviation) was calculated.

b) Results

Organ distribution of F-18 signal of 3g in mice

%ID/g		2min		5min		30min		60min		240min	
timepoint		%ID/g	S.D.	%ID/g	S.D.	%ID/g	S.D.	%ID/g	S.D.	%ID/g	S.D.
spleen		1,73	0,28	2,22	0,13	1,28	0,09	0,86	0,10	0,36	0,08
liver		6,35	1,12	13,36	2,37	8,75	0,75	5,04	1,07	1,44	0,13
kidney		15,52	0,74	14,38	0,46	11,43	1,95	7,70	3,56	1,05	0,12
lung		5,58	0,82	4,05	0,51	2,55	0,07	1,66	0,43	0,59	0,13
femur		1,95	0,22	1,79	0,12	1,05	0,08	1,11	0,11	3,06	0,78
heart		15,57	3,77	8,25	1,31	3,47	0,09	2,07	0,40	0,61	0,04
brain		5,15	0,33	4,14	0,56	1,88	0,02	0,93	0,12	0,42	0,03
fat		1,97	0,29	2,44	1,14	4,26	3,05	2,38	1,61	0,34	0,09
thyroid		3,87	0,88	3,67	1,08	1,78	0,19	1,04	0,13	0,56	0,14
muscle		3,95	1,47	3,17	0,31	1,95	0,39	1,31	0,50	0,30	0,07
skin		1,72	0,22	2,15	0,15	1,93	0,03	1,29	0,22	0,42	0,06
blood		1,72	0,09	2,12	0,09	1,85	0,15	1,32	0,25	0,57	0,06
tail		8,94	3,00	9,06	5,33	4,73	2,49	2,57	0,51	1,98	1,08
stomach		4,78	0,88	4,49	0,46	2,20	0,34	1,53	0,28	0,82	0,29
testicle		1,19	0,24	1,58	0,19	1,44	0,23	1,84	0,65	0,38	0,07
intestine		1,93	0,11	1,87	0,23	4,58	0,27	6,47	1,14	8,50	1,85
pancreas		4,96	0,46	4,26	0,09	2,21	0,24	1,22	0,22	0,32	0,09
adrenals		7,57	2,04	10,67	4,23	4,49	2,77	1,77	0,25	1,03	0,32

Autoradiography

Fig. 1 shows the autoradiographical analysis of binding of 3g to cryosections from cortex of Alzheimer's disease patients (AD) and controls without A β plaques (HC/FTD) (healthy control/ frontotemporal dementia). Specific binding in plaque-rich regions of AD samples is indicated by arrows.

10

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Organ distribution of F-18 signal of 10e in mice

%ID/g		2min		5min		30min		60min		240min	
timepoint		%ID/g	S.D.	%ID/g	S.D.	%ID/g	S.D.	%ID/g	S.D.	%ID/g	S.D.
spleen		1,96	0,26	1,99	0,11	1,08	0,12	0,35	0,05	0,06	0,03
liver		7,44	1,69	12,02	0,72	9,60	0,42	5,27	1,00	2,29	0,41
kidney		8,58	0,72	7,92	0,80	6,29	0,18	2,61	0,31	0,50	0,02
lung		4,31	0,27	3,86	0,09	1,93	0,15	0,89	0,22	0,10	0,00
femur		1,44	0,14	1,53	0,11	1,15	0,10	1,43	0,35	1,75	0,15
heart		5,18	0,15	4,49	0,50	1,85	0,11	0,69	0,05	0,11	0,01
brain		4,99	1,22	4,33	0,55	1,44	0,27	0,44	0,04	0,04	0,01
fat		1,79	0,99	2,66	0,24	1,95	0,09	0,67	0,07	0,15	0,06
thyroid		2,51	0,32	2,62	0,22	1,26	0,12	0,56	0,18	0,35	0,11
muscle		2,40	0,10	2,07	0,13	1,16	0,37	0,34	0,02	0,06	0,02
skin		1,37	0,11	1,76	0,07	1,39	0,11	0,51	0,01	0,08	0,02
blood		2,01	0,22	1,98	0,12	1,38	0,04	0,55	0,02	0,09	0,01
tail		8,65	2,47	6,65	1,67	1,86	0,75	1,00	0,22	0,69	0,31
stomach		3,69	0,21	2,84	0,25	2,40	1,18	1,09	0,25	0,50	0,52
testicle		1,53	0,04	1,81	0,20	1,28	0,11	0,52	0,10	0,06	0,00
intestine		2,13	0,30	2,40	0,10	8,20	0,17	10,63	0,82	6,90	0,59
pancreas		4,59	0,40	4,54	0,72	2,27	0,15	0,92	0,17	1,07	0,85
adrenals		7,86	2,13	6,20	0,43	2,36	0,68	0,67	0,22	0,43	0,25

Autoradiography

Fig. 2 shows the autoradiographical analysis of binding of example 10e to cryosections from
5 cortex of Alzheimer's disease patients (AD) and controls without A β plaques (HC/FTD)
(healthy control/ frontotemporal dementia). Specific binding in plaque-rich regions of AD
samples is indicated by arrows.

Organ distribution of F-18 signal of 11c in mice

%ID/g		2 min		5 min		30 min		60 min		240 min	
timepoint		%ID/g	S.D.	%ID/g	S.D.	%ID/g	S.D.	%ID/g	S.D.	%ID/g	S.D.
spleen		1,47	0,39	2,01	0,54	0,93	0,09	0,37	0,07	0,09	0,01
liver		7,17	1,92	12,14	2,51	9,41	1,98	4,72	0,75	2,09	0,19
kidney		7,68	1,21	8,07	1,53	7,83	1,58	4,37	0,54	1,12	0,22
lung		4,14	0,23	3,76	0,46	1,65	0,26	0,69	0,08	0,31	0,17
femur		1,53	0,06	1,54	0,42	0,68	0,10	0,38	0,03	0,16	0,04
heart		4,68	1,05	4,36	1,06	1,54	0,24	0,54	0,08	0,13	0,03
brain		5,54	0,32	4,73	1,38	1,00	0,09	0,34	0,07	0,05	0,01
fat		1,52	0,58	1,84	1,02	1,94	0,19	0,80	0,33	0,08	0,03
thyroid		3,11	0,56	2,41	0,55	1,08	0,19	0,50	0,07	0,19	0,07
muscle		2,38	0,13	2,54	0,70	1,03	0,10	0,38	0,07	0,07	0,01
skin		1,22	0,07	1,80	0,26	1,43	0,21	0,66	0,31	0,10	0,02
blood		1,70	0,16	1,78	0,32	1,13	0,16	0,49	0,06	0,12	0,03
tail		8,55	1,68	5,41	3,33	3,21	0,09	0,87	0,23	0,39	0,20
stomach		3,46	0,37	3,07	0,52	3,10	0,60	1,13	0,47	0,34	0,10
testicle		1,36	0,28	1,70	0,36	1,13	0,17	0,65	0,15	0,15	0,01
intestine		2,14	0,13	2,66	0,26	10,01	0,75	14,79	1,58	13,00	2,12
pancreas		4,44	0,33	3,97	0,79	2,20	0,55	0,77	0,22	0,18	0,05
adrenals		9,24	3,42	5,60	3,03	2,41	0,73	2,45	1,49	0,30	0,24

Autoradiography

Fig. 3 shows the Autoradiographical analysis of binding of example 11c to cryosections from
5 cortex of Alzheimer's disease patients (AD) and controls without A β plaques (HC/FTD)
(healthy control/ frontotemporal dementia). Specific binding in plaque-rich regions of AD
samples is indicated by arrows.

Organ distribution of F-18 signal of 12c in mice

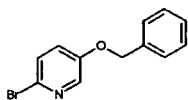
%ID/g										
timepoint	2 min			5 min			30 min			240 min
	%ID/g	S.D.	%ID/g	%ID/g	S.D.	%ID/g	%ID/g	S.D.	%ID/g	S.D.
spleen	1,32	0,37	2,08	0,16	0,87	0,04	0,42	0,04	0,06	0,01
liver	5,84	1,96	8,93	1,76	8,20	0,44	6,01	0,80	2,40	0,11
kidney	7,70	1,04	7,76	0,50	7,88	1,44	3,63	0,34	0,58	0,05
lung	3,52	0,34	3,73	0,07	1,78	0,33	0,79	0,15	0,15	0,01
femur	1,70	0,24	1,63	0,05	5,55	0,89	7,65	0,92	7,96	1,25
heart	4,76	0,98	4,28	0,20	1,52	0,04	0,69	0,08	0,08	0,00
brain	5,37	0,88	4,60	0,10	1,28	0,03	0,60	0,11	0,07	0,01
fat	1,00	0,16	1,92	0,38	1,89	0,13	1,29	0,04	0,11	0,08
thyroid	3,59	0,46	3,10	0,58	1,92	0,24	1,27	0,33	0,41	0,04
muscle	2,48	0,44	17,41	25,71	0,88	0,04	0,47	0,07	0,06	0,05
skin	1,25	0,03	1,23	0,99	1,51	0,04	0,66	0,10	0,08	0,00
blood	1,78	0,19	1,90	0,16	1,30	0,02	0,70	0,15	0,09	0,01
tail	12,72	8,59	6,80	3,78	2,72	0,91	3,08	0,64	1,30	0,24
stomach	3,14	0,22	3,52	0,06	1,91	0,45	1,89	0,70	0,71	0,13
testicle	1,21	0,45	1,79	0,17	1,09	0,04	0,58	0,10	0,08	0,00
intestine	1,78	0,33	2,44	0,29	6,62	0,87	8,88	1,22	10,54	3,63
pancreas	3,58	0,26	4,30	0,28	1,55	0,25	0,75	0,09	0,12	0,01
adrenals	6,60	1,76	10,38	6,50	2,77	1,44	1,55	0,61	0,40	0,25

Autoradiography

5 Fig. 4 shows the autoradiographical analysis of binding of example 12c to cryosections from cortex of Alzheimer's disease patients (AD) and controls without A β plaques (HC/FTD) (healthy control/ frontotemporal dementia). Specific binding in plaque-rich regions of AD samples is indicated by arrows.

10 IC50 values of selected compounds

Fig. 5 shows IC₅₀ values in [nM] of selected compounds measured in a competition assay using brain homogenate from AD patients.

Example 14**a) 5-Benzyloxy-2-bromo-pyridine**

5

To a solution of 10.0 g (57.47 mmol) of 2-bromo-5-hydroxypyridine in 400 mL DMF was added 14.75 g (86.21 mmol) of benzyl bromide and 23.82 g (172.4 mmol) of potassium carbonate. The mixture was stirred for 6 h at 60°C and overnight at room temperature. The suspension was filtered off and after evaporation of the solvent the residue was chromatographed on silica gel using a dichloromethane/methanol gradient.

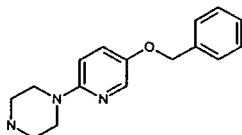
10

Yield: 14.82 g (96.7 %).

MS (ESIpos): m/z = 264, 266 $[M+H]^+$

$^1\text{H-NMR}$ (300MHz, CHLOROFORM- d): δ [ppm]= 5.10 (s, 2H), 7.16 (dd, 1H), 7.32 - 7.47 (m, 6H), 8.14 (d, 1H).

15

b) 1-(5-Benzyloxy-pyridin-2-yl)-piperazine

20

All glassware was dried at 100°C. To a solution of 5.27 g (61.22 mmol) of piperazine in 180 mL toluene was added 561 mg (0.61 mmol) of tris(dibenzylidene acetone) dipalladium(0) and 520 mg (0.83 mmol) of BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl). Then, a solution of 14.7 g (55.66 mmol) of 5-benzyloxy-2-bromo-pyridine (example 14a) in THF was added followed by a suspension of 8.02 g (83.48 mmol) of sodium t-butyrate in THF.

25

The reaction mixture was refluxed for 6 h and stirred at room temperature overnight. After evaporation of the solvents the residue was chromatographed on silica gel using a dichloromethane/methanol gradient.

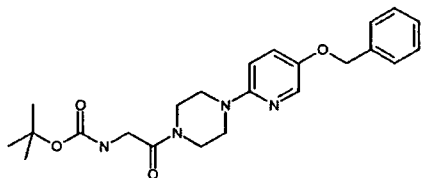
Yield: 7.12 g (47.0 %).

30

MS (ESIpos): m/z = 270 $[M+H]^+$

¹H-NMR (300MHz, CHLOROFORM-d): δ [ppm]= 2.97 - 3.07 (m, 4H), 3.36 - 3.46 (m, 4H), 5.04 (s, 2H), 6.63 (d, 1H), 7.21 (dd, 1H), 7.29 - 7.48 (m, 5H), 8.00 (d, 1H).

5 c) tert-butyl (2-{4-[5-(benzyloxy)pyridin-2-yl]piperazin-1-yl}-2-oxoethyl)carbamate



To a solution of 4.63 g (26.43 mmol) *t*-Butoxycarbonyl-glycine (Aldrich) in 500 mL THF and 5 mL triethyl amine (35.87 mmol) at -15°C, 3.43 mL (26.43 mmol) isobutyl chloroformate were added dropwise and the solution was maintained at this temperature for another 15 min.

10 Then, 7.12 g of 1-(5-Benzyloxy-pyridin-2-yl)-piperazine (14b) and 18 mL triethyl amine (129 mmol) in 200 mL THF/dichloromethane (1:1) were added slowly to this cold solution, the temperature was kept below -10°C for another 15 min and was then allowed to reach room temperature. After stirring overnight the solvent was evaporated and the residue was taken up in ethyl acetate. This solution was washed successively with aqueous sodium carbonate,

15 water, 1 M aqueous HCl solution, saturated aqueous sodium chloride solution, finally dried over magnesium sulfate and then evaporated. This residue was chromatographed on silica gel using a hexane/ethyl acetate gradient.

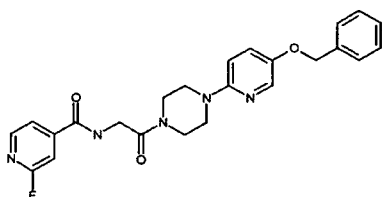
Yield: 8.04 g (70.6 %).

20 MS (ESIpos): $m/z = 427 [M+H]^+$

¹H-NMR (300MHz, CHLOROFORM-d): δ [ppm]= 1.46 (s, 9H), 3.36 - 3.45 (m, 2H), 3.51 (br. s., 4H), 3.70 - 3.81 (m, 2H), 4.02 (d, 2H), 5.05 (s, 2H), 5.53 (br. s., 1H), 6.65 (d, 1H), 7.23 (dd, 1H), 7.30 - 7.48 (m, 5H), 8.00 (d, 1H).

25

d) N-(2-{4-[5-(benzyloxy)pyridin-2-yl]piperazin-1-yl}-2-oxoethyl)-2-fluoropyridine-4-carboxamide



8.0 g (18.76 mmol) of tert-butyl (2-{4-[5-(benzyloxy)pyridin-2-yl]piperazin-1-yl}-2-oxoethyl) carbamate (**14c**) were suspended in 160 mL 2N HCl in diethyl ether and stirred overnight at room temperature. The precipitate was filtered off and washed with ether and dried at 40°C *in vacuo*.

- 5 Yield: 7.4 g (quantitative). The product was used in the next step without further purification.

MS (ESIpos): $m/z = 327$ $[M+H]^+$

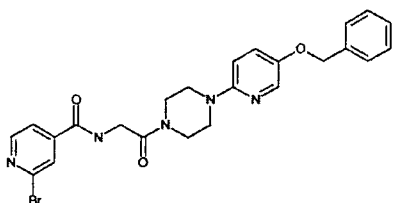
To a solution of 177 mg (1.25 mmol) of 2-fluoropyridine-4-carboxylic acid (Aldrich) and 501 mg (1.38 mmol) of hydrochloride prepared above in 40 mL DMF were added 784 mg (1.5 mmol) PyBOP and 0.80 mL N-ethyl-N,N-diisopropylamine and the reaction mixture was stirred overnight at room temperature. After evaporation of the solvent the residue was chromatographed on silica gel using an ethyl acetate/ethanol gradient.

- 10 Yield: 315 mg (50.2 %).

MS (ESIpos): $m/z = 449$ $[M+H]^+$

- 15 $^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 3.37 (br. s., 2H), 3.44 (br. s., 2H), 3.52 - 3.66 (m, 4H), 4.22 (d, 2H), 5.07 (s, 2H), 6.83 (d, 1H), 7.27 - 7.47 (m, 6H), 7.53 (s, 1H), 7.70 - 7.81 (m, 1H), 7.95 (d, 1H), 8.39 (d, 1H), 9.01 (t, 1H).

- 20 e) N-(2-{4-[5-(benzyloxy)pyridin-2-yl]piperazin-1-yl}-2-oxoethyl)-2-bromopyridine-4-carboxamide



8.0 g (18.76 mmol) of tert-butyl (2-{4-[5-(benzyloxy)pyridin-2-yl]piperazin-1-yl}-2-oxoethyl) carbamate (**14c**) were suspended in 160 mL 2N HCl in diethyl ether and stirred overnight at room temperature. The precipitate was filtered off and washed with ether and dried at 40°C *in vacuo*.

Yield: 7.4 g (quantitative). The product was used in the next step without further purification.

MS (ESIpos): $m/z = 327$ $[M+H]^+$

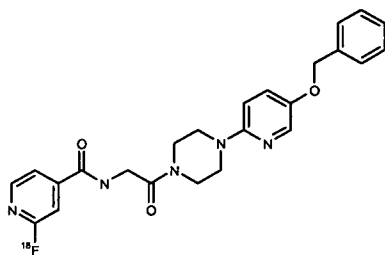
To a solution of 1.01 g (5.01 mmol) of 2-bromopyridine-4-carboxylic acid (Aldrich) and 2.0 g (5.51 mmol) of hydrochloride prepared above in 160 mL DMF were added 3.13 g (6.0 mmol) PyBOP and 2.75 mL N-ethyl-N,N-diisopropylamine and the reaction mixture was stirred overnight at room temperature. After evaporation of the solvent the residue was chromatographed on silica gel using an ethyl acetate/ethanol gradient.

- 30 Yield: 739 mg (27.7 %).

MS (ESIpos): m/z = 510, 512 $[M+H]^+$

$^1\text{H-NMR}$ (400MHz, DMSO-d_6): δ [ppm]= 2.72 (s, 1H), 2.88 (s, 1H), 3.40 - 3.48 (m, 2H), 3.51 - 3.64 (m, 4H), 4.21 (d, 2H), 5.07 (s, 2H), 6.86 (d, 1H), 7.25 - 7.48 (m, 6H), 7.81 (dd, 1H), 7.95 (d, 1H), 8.02 (s, 1H), 8.56 (d, 1H), 9.06 (s, 1H).

f) $[^{18}\text{F}]\text{-N-(2-{4-[5-(benzyloxy)pyridin-2-yl]piperazin-1-yl}-2-oxoethyl)-2-fluoropyridine-4-carboxamide}$

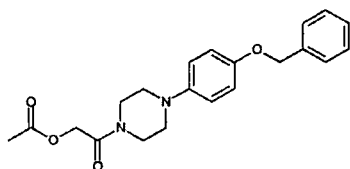


Aqueous $[^{18}\text{F}]\text{Fluoride}$ 38.7GBq was trapped on a QMA cartridge (Waters) and eluted with 2mL of a TBAOH solution (1.5mL MeCN, 0.3 mL H_2O + 8 μL TBAOH sol. (40%)) into the reactor. The solvent was removed by heating at 120°C for 10 min under a stream of nitrogen. Anhydrous MeCN (1 mL) was added and evaporated as before. A solution of precursor **14e** (5 mg) in 500 μL anhydrous DMSO was added. After heating at 180 °C for 20 min the crude reaction mixture was diluted with 4 mL water/MeCN (50:50) and purified by preparative HPLC: ACE 5-C18-HL 250mmx10mm; isocratic, 25% acetonitrile in water with 0.1% trifluoroacetic acid, flow: 4 mL/min; t_R ~22 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 5mL water and eluted with 1mL ethanol to deliver the 3.5 GBq of the F-18 labeled product (15.5 % rc. yield, corrected for decay; >96% HPLC) in 1000 μL EtOH in a overall synthesis time of ~80 min. The desired F-18 labeled product **14f** (t_R =3.2 min) was analyzed using analytical HPLC: ACE3-C18 50 mm x 4,6 mm; solvent gradient: start 5 % acetonitrile – 95 % acetonitrile in 0.1% trifluoroacetic acid in 7 min., flow: 2mL/min and confirmed by co-injection with the corresponding non-radioactive F-19 fluoro-standard **14d** on the analytical HPLC (t_R =3.1 min).

HPLC analysis is shown in Fig. 6 A and Fig. 6 B.

Example 15**a) 2-{4-[4-(Benzyloxy)phenyl]piperazin-1-yl}-2-oxoethyl acetate**

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To a solution of 1.42 g (12 mmol) acetoxyacetic acid (Aldrich) in 300 mL THF and 7.5 mL triethyl amine (54.3 mmol) at -15°C , 1.73 mL (13.23 mmol) isobutyl chloroformate were added dropwise and the solution was maintained at this temperature for another 15 min.

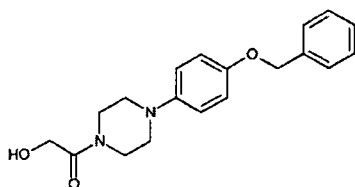
10 Then, 3.23 g (12 mmol) of 1-(4-benzyloxyphenyl)-piperazine (3c) and 1.74 mL triethyl amine (12.5 mmol) in 240 mL THF/dichloromethane (1:1) were added slowly to this cold solution, the temperature was kept below -10°C for another 15 min and was then allowed to reach room temperature. After stirring overnight the solvent was evaporated and the residue was taken up in ethyl acetate. This solution was washed successively with aqueous sodium carbonate, water, 1 M aqueous HCl solution, saturated aqueous sodium chloride solution, finally

15 dried over magnesium sulfate and then evaporated. This residue was chromatographed on silica gel using a hexane/ethyl acetate gradient.

Yield: 1.12 g (25.2 %).

20 MS (ESIpos): $m/z = 369$ $[\text{M}+\text{H}]^{+}$

$^1\text{H-NMR}$ (300MHz, CHLOROFORM-d): δ [ppm]= 2.21 (s, 3H), 3.02 - 3.14 (m, 4H), 3.55 (br. s., 2H), 3.78 (br. s., 2H), 4.78 (s, 2H), 5.03 (s, 2H), 6.83 - 7.00 (m, 4H), 7.29 - 7.48 (m, 5H).

25 b) 1-[4-(4-Benzyloxy-phenyl)-piperazin-1-yl]-2-hydroxy-ethanone

246 mg (0.67 mmol) of the acetate 15a were solved in 40 mL of ethanol and cooled to 0°C . After addition of 2.1 mL 3N NaOH the solution was stirred for 1 h, glacial acetic acid was added until the pH was below pH 7 and the solvents were evaporated. The raw product was

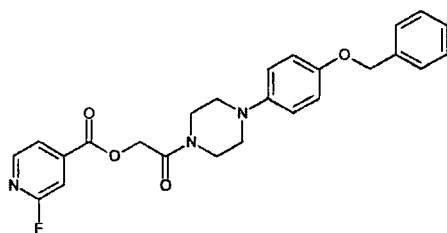
30 crystallized from ethanol.

Yield: 116 mg (52.7 %).

MS (ESIpos): $m/z = 327 [M+H]^+$

$^1\text{H-NMR}$ (300MHz, CHLOROFORM- d): δ [ppm]= 3.01 - 3.14 (m, 4H), 3.37 - 3.49 (m, 2H), 3.63 (t, 1H), 3.78 - 3.88 (m, 2H), 4.22 (d, 2H), 5.04 (s, 2H), 6.83 - 7.00 (m, 4H), 7.29 - 7.49 (m, 5H).

c) 2-{4-[4-(benzyloxy)phenyl]piperazin-1-yl}-2-oxoethyl 2-fluoropyridine-4-carboxylate



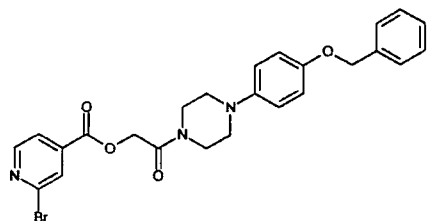
10 To a solution of 28.2 mg (0.2 mmol) 2-fluoropyridine-4-carboxylic acid (Aldrich) in 5 mL THF and 29 μL (microliter) triethyl amine (0.2 mmol) at -15°C , 31.6 μL (0.22 mmol) isobutyl chloroformate were added dropwise and the solution was maintained at this temperature for another 15 min. Then, 65.28 mg (0.2 mmol) of 1-[4-(4-Benzyloxy-phenyl)-piperazin-1-yl]-2-hydroxy-ethanone (15b) and 125 μL triethyl amine (0.9 mmol) in 5 mL THF/dichloromethane
15 (1:1) were added slowly to this cold solution, the temperature was kept below -10°C for another 15 min and was then allowed to reach room temperature. After stirring overnight the solvent was evaporated and the residue was taken up in ethyl acetate. This solution was washed successively with aqueous sodium carbonate, water, 1 M aqueous HCl solution, saturated aqueous sodium chloride solution, finally dried over magnesium sulfate and then
20 evaporated. This residue was chromatographed on silica gel using a hexane/ethyl acetate gradient.

Yield: 30 mg (33.4 %).

MS (ESIpos): $m/z = 450 [M+H]^+$

25 $^1\text{H-NMR}$ (400MHz, CHLOROFORM- d): δ [ppm]= 3.03 - 3.18 (m, 4H), 3.61 (br. s., 2H), 3.81 (br. s., 2H), 5.06 (d, 4H), 6.87 - 6.99 (m, 4H), 7.29 - 7.47 (m, 5H), 7.55 - 7.62 (m, 1H), 7.83 (dt, 1H), 8.40 (d, 1H).

30 d) 2-{4-[4-(Benzyloxy)phenyl]piperazin-1-yl}-2-oxoethyl 2-bromopyridine-4-carboxylate



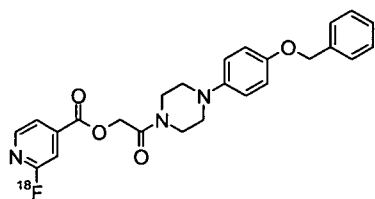
To a solution of 185.7 mg (0.92 mmol) 2-bromopyridine-4-carboxylic acid (Aldrich) in 25 mL THF and 0.2 mL triethyl amine (1.44 mmol) at -15°C , 132.3 μL (1.01 mmol) isobutyl chloroformate were added dropwise and the solution was maintained at this temperature for another 15 min. Then, 300 mg (0.92 mmol) of 1-[4-(4-Benzyloxy-phenyl)-piperazin-1-yl]-2-hydroxy-ethanone (**15b**) and 0.6 mL triethyl amine (4.3 mmol) in 24 mL THF/dichloromethane (1:1) were added slowly to this cold solution, the temperature was kept below -10°C for another 15 min and was then allowed to reach room temperature. After stirring overnight the solvent was evaporated and the residue was taken up in ethyl acetate. This solution was washed successively with aqueous sodium carbonate, water, 1 M aqueous HCl solution, saturated aqueous sodium chloride solution, finally dried over magnesium sulfate and then evaporated. This residue was chromatographed on silica gel using a hexane/ethyl acetate gradient.

Yield: 145 mg (30.6 %).

MS (ESIpos): $m/z = 510, 512 [M+H]^+$

$^1\text{H-NMR}$ (400MHz, CHLOROFORM-d): δ [ppm]= 3.11 (d, 4H), 3.60 (br. s., 2H), 3.80 (br. s., 2H), 5.05 (d, 4H), 6.86 - 6.99 (m, 4H), 7.29 - 7.48 (m, 5H), 7.89 (dd, 1H), 8.13 (s, 1H), 8.56 (d, 1H).

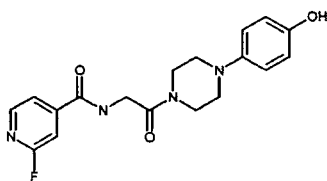
e) [^{18}F]-2-{4-[4-(benzyloxy)phenyl]piperazin-1-yl}-2-oxoethyl 2-fluoropyridine-4-carboxylate



Aqueous [^{18}F]Fluoride 19 GBq was trapped on a QMA cartridge (Waters) and eluted with 2mL of a TBAOH solution (1.5mL MeCN, 0.3 mL H_2O + 8 μL TBAOH sol. (40%)) 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 precursor **15d** (5 mg) in 500 μL anhydrous DMSO was added. After heating at 180°C for 20 min the crude

reaction mixture was diluted with 4 mL water/MeCN (50:50) and purified by preparative HPLC: ACE 5-C18-HL 250mmx10mm; isocratic, 40% acetonitrile in water with 0.1% trifluoroacetic acid, flow: 4 mL/min; t_R ~24 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 5mL water and eluted with 1mL ethanol to deliver the 0.2 GBq of the F-18 labeled product **15e** (2 % rc. yield, corrected for decay; >98% HPLC) in 1000µl EtOH in a overall synthesis time of ~80 min. The desired F-18 labeled product **15e** (t_R =4.3 min) was analyzed using analytical HPLC: ACE3-C18 50 mm x 4,6 mm; solvent gradient: start 5 % acetonitrile – 95 % acetonitrile in 0.1% trifluoroacetic acid in 7 min., flow: 2mL/min and confirmed by co-injection with the corresponding non-radioactive F-19 fluoro-standard **15c** on the analytical HPLC (t_R =4.2 min).

HPLC analyses are shown in Fig. 7 A and Fig. 7 B.

Example 16**a) 2-Fluoro-N-{2-[4-(4-hydroxyphenyl)piperazin-1-yl]-2-oxoethyl}pyridine-4-carboxamide**

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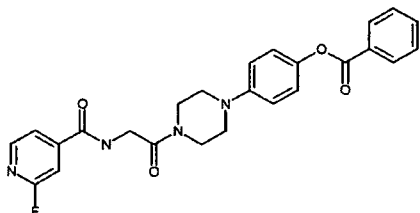
To a solution of 280 mg (0.62 mmol) of N-{2-[4-(4-Benzyloxy-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-2-fluoro-isonicotinamide (**11b**) in 70 mL of methanol was added 100 mg of palladium on activated carbon (10%) and the suspension was stirred under hydrogen atmosphere overnight at room temperature. It was then filtered off from the catalyst and the solution was

10

evaporated *in vacuo*. The product was used in the next step without further purification.

Yield: 175 mg (54.8%).

MS (ESIpos): $m/z = 359 [M+H]^+$

15 b) 4-(4-{N-[(2-fluoropyridin-4-yl)carbonyl]glycyl}piperazin-1-yl)phenyl benzoate

To a solution of 57.9 mg (0.47 mmol) benzoic acid in 10 mL THF and 90 μ L (0.65 mmol) triethyl amine at -15°C , 62.06 μ L (0.47 mmol) isobutyl chloroformate were added dropwise and the solution was maintained at this temperature for another 15 min. Then, 170 mg (0.47 mmol) of example **16a**, prepared above, and 0.4 mL triethyl amine (2.87 mmol) in 20 mL THF/dichloromethane (1:1) were added slowly to this cold solution, the temperature was kept below -10°C for another 15 min and was then allowed to reach room temperature. After stirring overnight the solvent was evaporated and the residue was taken up in ethyl acetate. This solution was washed successively with aqueous sodium carbonate, water, 1 M aqueous

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HCl solution, saturated aqueous sodium chloride solution, finally dried over magnesium sulfate and then evaporated. This residue was chromatographed on silica gel using a hexane/ethyl acetate gradient.

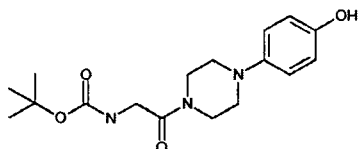
Yield: 23 mg (9.5 %).

MS (ESIpos): $m/z = 463 [M+H]^+$

$^1\text{H-NMR}$ (400MHz, DMSO-d_6): δ [ppm]= 3.15 (br. s., 2H), 3.22 (br. s., 2H), 3.66 (br. s., 4H), 4.24 (d, 2H), 7.00 - 7.11 (m, 2H), 7.11 - 7.21 (m, 2H), 7.50 - 7.66 (m, 3H), 7.68 - 7.82 (m, 2H), 8.12 (d, 2H), 8.41 (d, 1H), 9.03 (t, 1H).

5

c) tert-butyl {2-[4-(4-hydroxyphenyl)piperazin-1-yl]-2-oxoethyl}carbamate

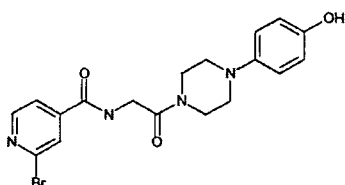


To a solution of 2.5 g (5.88 mmol) of {2-[4-(4-Benzyloxy-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-carbamic acid tert-butyl ester (10a) in 100 mL of methanol was added 1 g of palladium on activated carbon (10%) and the suspension was stirred under hydrogen atmosphere overnight at room temperature. It was then filtered off from the catalyst and the solution was evaporated *in vacuo*. The product was used in the next step without further purification.

Yield: 1.92 g (95.9%).

15 MS (ESIpos): $m/z = 336 [M+H]^+$

d) 2-Bromo-N-{2-[4-(4-hydroxyphenyl)piperazin-1-yl]-2-oxoethyl}pyridine-4-carboxamide



20 1.8 g (5.37 mmol) of tert-butyl {2-[4-(4-hydroxyphenyl)piperazin-1-yl]-2-oxoethyl}carbamate (16c) were suspended in 60 mL 2N HCl in diethyl ether and stirred overnight at room temperature. The precipitate was filtered off and washed with ether and dried at 40°C *in vacuo*. Yield: 1.8 g (quantitative). The product was used in the next step without further purification.

25 To a solution of 338 mg (1.67 mmol) of 2-bromo-4-pyridinecarboxylic acid (Alfa) and 500 mg (1.84 mmol) of the hydrochloride prepared above in 60 mL DMF were added 1.045 g (2 mmol) PyBOP and 2.86 mL (16.73 mmol) of N-ethyl-N,N-diisopropylamine and the reaction mixture was stirred overnight at room temperature. After evaporation of the solvent the residue was chromatographed on silica gel using an ethyl acetate/ethanol gradient. The product

30 containing fractions were collected and recrystallized from ethyl acetate.

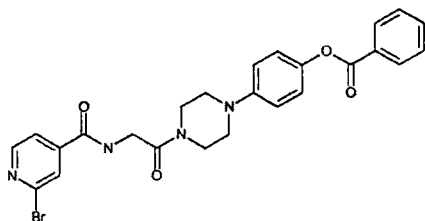
Yield: 284 mg (40.5 %).

MS (ESIpos): $m/z = 419, 421 [M+H]^+$

$^1\text{H-NMR}$ (300MHz, METHANOL- d_4): δ [ppm]= 1.49 (dt, 4H), 2.17 (dt, 4H), 2.76 (s, 2H), 5.11 - 5.22 (m, 2H), 5.29 - 5.40 (m, 2H), 6.23 (dd, 1H), 6.43 - 6.50 (m, 1H), 6.89 - 6.98 (m, 1H).

5

e) 4-(4-{N-[(2-bromopyridin-4-yl)carbonyl]glycyl}piperazin-1-yl)phenyl benzoate



To a solution of 218 mg (0.52 mmol) of 2-Bromo-N-[2-[4-(4-hydroxyphenyl)piperazin-1-yl]-2-oxoethyl]pyridine-4-carboxamide (**16d**) in 45 mL DMF were added 214.56 mg (1.04 mmol) of 1.3-dicyclohexyl carbodiimide and 20 mg of 4-dimethyl aminopyridine (DMAP) and stirred for 40 min at room temperature. Then, 127 mg (1.04 mmol) of benzoic acid were added and the reaction mixture was stirred for 3d at this temperature. The solvent was evaporated and the residue was chromatographed on silica gel using a ethyl acetate / ethanol gradient.

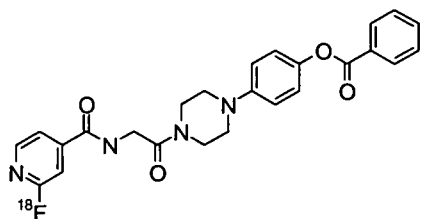
Yield: 222 mg (81.6 %).

MS (ESIpos): $m/z = 523, 525 [M+H]^+$

$^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 3.25 (br. s., 4H), 3.65 (br. s., 4H), 4.23 (d, 2H), 6.99 - 7.10 (m, 2H), 7.10 - 7.21 (m, 2H), 7.53 - 7.65 (m, 2H), 7.67 - 7.77 (m, 1H), 7.83 (dd, 1H), 7.99 - 8.06 (m, 1H), 8.06 - 8.17 (m, 2H), 8.55 (d, 1H), 9.05 (t, 1H).

20

f) [^{18}F]-4-(4-{N-[(2-fluoropyridin-4-yl)carbonyl]glycyl}piperazin-1-yl)phenyl benzoate



25

Aqueous [^{18}F]Fluoride 1 GBq was trapped on a QMA cartridge (Waters) and eluted with 2mL of a TBAOH solution (1.5mL MeCN, 0.3 mL H_2O + 8 μL TBAOH sol. (40%)) into the reactor. The solvent was removed by heating at 120°C for 10 min under a stream of nitrogen. Anhy-

drous MeCN (1 mL) was added and evaporated as before. A solution of precursor **16e** (5 mg) in 500 µl anhydrous DMSO was added. After heating at 180 °C for 20 min the crude reaction mixture was analyzed using analytical HPLC: ACE3-C18 50 mm x 4,6 mm; solvent gradient: start 5 % acetonitrile – 95 % acetonitrile in 0.1% trifluoroacetic acid in 7 min., flow: 2mL/min and confirmed by co-injection with the corresponding non-radioactive F-19 fluoro-standard **15c** on the analytical HPLC (t_R = 3.7 min). The crude product may be purified by preparative HPLC: ACE 5-C18-HL 250mmx10mm; isocratic, 35% acetonitrile in water with 0.1% trifluoroacetic acid, flow: 4 mL/min.

Example 17: Biological data

5 Biological data of compounds of examples 14 and 15 were obtained as described in example 13.

Fig. 8 shows the autoradiographical analysis of binding of 14f to cryosections from cortex of Alzheimer's disease patients (AD) and healthy controls (HC). Specific binding in plaque-rich regions of AD samples is indicated by arrows.

10

Fig. 9 shows shows IC₅₀ values in [nM] of selected compounds measured in a competition assay using brain homogenate from AD patients.

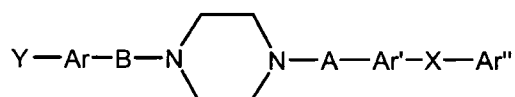
Organ distribution of F-18 signal of 14f in mice

%ID/g timepoint	2 min		5 min		30 min		60 min		240 min	
	%ID/g	S.D.	%ID/g	S.D.	%ID/g	S.D.	%ID/g	S.D.	%ID/g	S.D.
spleen	1,67	0,03	2,25	0,13	0,78	0,16	0,12	0,01	0,04	0,01
liver	8,19	1,28	13,46	0,36	5,20	1,26	1,87	0,27	0,90	0,39
kidneys	7,60	0,53	8,59	0,50	7,84	0,86	2,86	1,11	0,79	0,62
lung	3,63	0,23	3,93	0,14	1,27	0,10	0,42	0,15	0,12	0,04
femur	1,44	0,07	1,38	0,09	0,55	0,04	0,24	0,10	0,13	0,06
heart	3,67	0,13	3,81	0,21	0,93	0,08	0,20	0,03	0,06	0,01
brain	3,87	0,07	3,14	0,40	0,52	0,07	0,13	0,01	0,02	0,00
fat	1,05	0,08	2,17	1,42	1,02	0,38	0,59	0,78	0,02	0,01
thyroid	3,00	0,81	2,94	0,29	0,94	0,22	0,30	0,01	0,16	0,10
muscle	1,94	0,25	2,14	0,12	0,62	0,05	0,26	0,15	0,03	0,01
skin	1,12	0,05	1,84	0,06	1,17	0,17	0,43	0,08	0,06	0,01
blood	2,05	0,07	2,36	0,12	1,30	0,20	0,33	0,05	0,08	0,01
tail	5,14	1,89	4,06	2,06	2,28	0,44	0,67	0,13	0,31	0,09
stomach	3,81	0,79	3,68	0,12	2,88	0,57	2,07	1,99	0,46	0,21
testicle	1,42	0,13	1,73	0,06	0,79	0,12	0,27	0,07	0,04	0,01
intestine	2,27	0,14	2,90	0,29	11,37	0,48	13,11	0,99	13,53	1,48
pancreas	4,49	0,64	4,49	0,21	1,64	0,93	0,32	0,08	0,11	0,03
adrenals	16,31	11,87	6,14	1,92	1,57	0,44	1,35	0,72	0,23	n.d.

Claims

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1. A diagnostic composition comprising a compound of formula I



Formula I

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or a pharmaceutically acceptable salt or a prodrug thereof,
wherein

15

- Y is selected from the group consisting of:

F, Cl, Br, I, H, ^{18}F , ^{19}F , ^{76}Br , ^{123}I , ^{125}I , ^{11}C , ^3H , ^{13}N , ^{15}O ;

a leaving group, tosyl, brosyl, nosyl, triflate, sulfonate, substituted sulfonate, mesy-
late, and nonaflate; and if directly bound to an aromatic C-atom iodonium-aryl I^+ -aryl,
trialkylammonium, preferred trimethylammonium, and NO_2 ;

20

- Ar is selected from the group consisting of:

substituted or non-substituted mono-, bi- or tricyclic aromatic or heteroaromatic ring
systems;

25

- B is selected from the group consisting of:

direct bond, a branched or non-branched alkyl or alkyl chain comprised of 1-10 C-
atoms;

30

- A is selected from the group consisting of:

a direct bond, and CO-NH , CS-NH ;

- Ar' is selected from the group consisting of:

substituted or non-substituted mono-, or bi-cyclic aromatic or heteroaromatic ring sys-
tems;

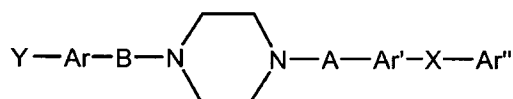
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- X is selected from the group consisting of:
a direct bond or a substituted or non-substituted C₁-C₃ alkyl chain;

- Ar'' is selected from the group consisting of:
substituted or non-substituted mono-, or bi-cyclic aromatic or heteroaromatic ring systems.

2. The composition according to claim 1, wherein Y is ¹⁸F.

3. A compound of formula I



Formula I

or a pharmaceutically acceptable salt or a prodrug thereof,
wherein

- Y is selected from the group consisting of:
F, Cl, Br, I, H, ¹⁸F, ¹⁹F, ⁷⁶Br, ¹²³I, ¹²⁵I, ¹¹C, ³H, ¹³N, ¹⁵O;

a leaving group, tosyl, brosyl, nosyl, triflate, sulfonate, substituted sulfonate, mesylate, and nonaflate; and if directly bound to an aromatic C-atom iodonium-aryl I⁺-aryl, trialkylammonium, preferred trimethylammonium, and NO₂;

- Ar is selected from the group consisting of:
substituted or non-substituted mono-, bi- or tricyclic aromatic or heteroaromatic ring systems;

- B is selected from the group consisting of:
direct bond, a branched or non-branched alkyl or alkyl chain comprised of 1-10 C-atoms;

- A is selected from the group consisting of:
a direct bond, and CO-NH, CS-NH;

- Ar' is selected from the group consisting of:

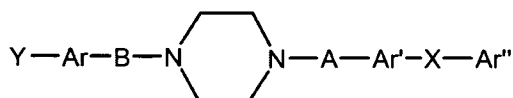
substituted or non-substituted mono-, or bi-cyclic aromatic or heteroaromatic ring systems;

- 5 - X is selected from the group consisting of:
a direct bond or a substituted or non-substituted C₁-C₃ alkyl chain;

- Ar'' is selected from the group consisting of:
substituted or non-substituted mono-, or bi-cyclic aromatic or heteroaromatic ring systems,
10

with the proviso that if A and/or B are direct bonds the directly bound residue Ar or Ar' is a six ring membered aromatic system.

- 15 4. A compound of formula I



Formula I

- 20 or a pharmaceutically acceptable salt or a prodrug thereof,
wherein

- Y is selected from the group consisting of:
F, Cl, Br, I, H, ¹⁸F, ¹⁹F, ⁷⁶Br, ¹²³I, ¹²⁵I, ¹¹C, ³H, ¹³N, ¹⁵O;
25 a leaving group, tosyl, brosyl, nosyl, triflate, sulfonate, substituted sulfonate, mesylate, and nonaflate; and if directly bound to an aromatic C-atom iodonium-aryl I⁺-aryl, trialkylammonium, preferred trimethylammonium, and NO₂;

- Ar is selected from the group consisting of:
30 mono-, bi- or tricyclic aromatic or heteroaromatic ring systems substituted by one or two alkyl, alkylen, alkynesubstituents and/or alkoxy substituents,

- B is selected from the group consisting of:

direct bond, a branched or non-branched alkyl or alkyl chain comprised of 1-10 C-atoms;

- A is selected from the group consisting of:

a direct bond, and CO-NH, CS-NH;

- Ar' is selected from the group consisting of:

mono-, or bi-cyclic aromatic or heteroaromatic ring systems which are substituted by one or two alkyl, alkyl, alkyne substituents and/or alkoxy substituents and wherein the mono-, bi- or tricyclic aromatic or heteroaromatic ring systems are further substituted by electron withdrawing groups directly bound to an aromatic C-atom;

- X is selected from the group consisting of:

a direct bond or a substituted or non-substituted C₁-C₃ alkyl chain;

- Ar'' is selected from the group consisting of:

substituted or non-substituted mono-, or bi-cyclic aromatic or heteroaromatic ring systems.

5. A compound according to claim 3 or 4, wherein

- the alkyl, alkyl, alkyne substituents and/or alkoxy substituents of Ar, Ar' and Ar'' are selected from the group consisting of oxo or hydroxyl,

and wherein the alkyl, alkyl, alkyne substituents and/or alkoxy substituents of Ar, Ar' and Ar'' are interrupted by 1 – 5 oxygen atoms, preferably the substituents are poly-ethylenglycol-moieties,

and wherein further the alkyl, alkyl, alkyne substituents and/or alkoxy substituents of Ar, Ar' and Ar'' comprise C₃-C₆ cycloalkyl moieties, and wherein the optional electron withdrawing groups of Ar, Ar' and Ar'' are selected from the group consisting of –CN or CF₃;

and wherein

- B is selected from the group consisting of direct bond, CONH-CH₂CO, CO-(CH₂)₂CO, (CH₂)_nCO, O(CH₂)_nCO with n=1 to 10, (CH=CH)CO,



and wherein

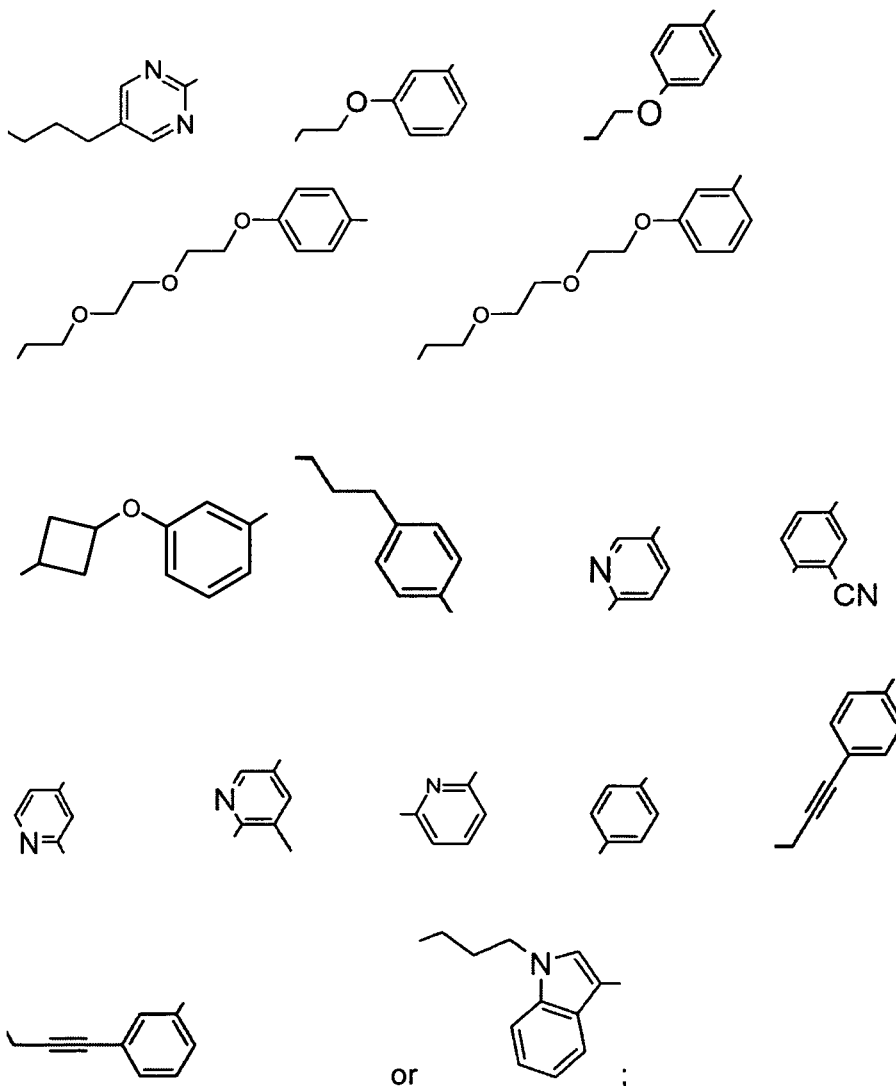
- X is selected from the group consisting of direct bond, OCH₂, NHCO, CH₂O, CONH, NHCS, or CSNH.

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6. A compound according to claims 3 – 5, wherein

- Ar is selected from the group consisting of propylpyrimidin-2-yl, ethoxyphenyl, (CH₂CH₂O)₃phenyl, alkylphenyl, alkoxyphenyl, N-alkylindolyl, and alkylpyridyl,

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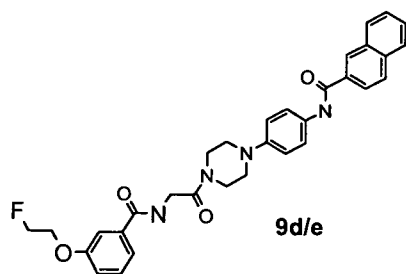
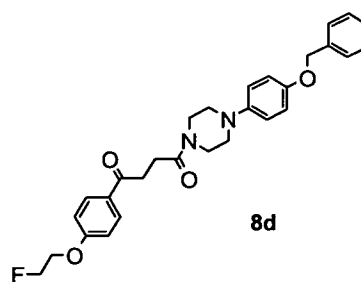
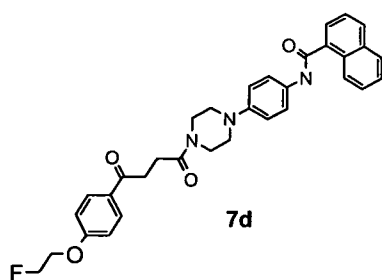
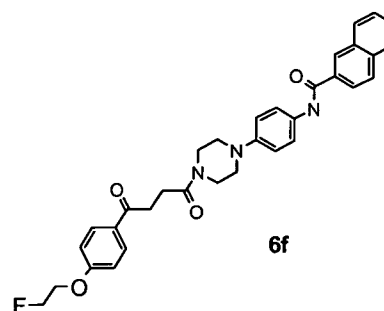
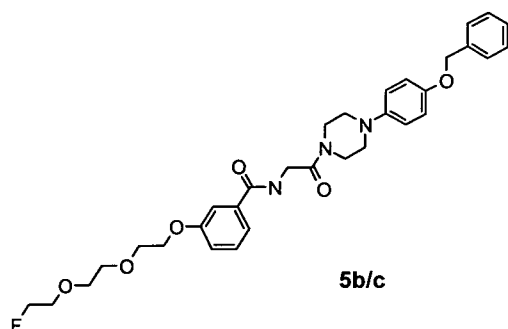
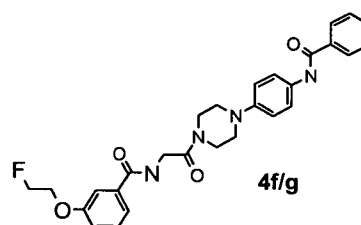
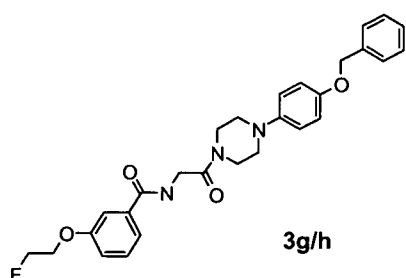
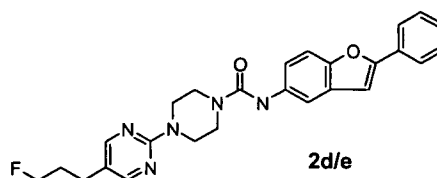
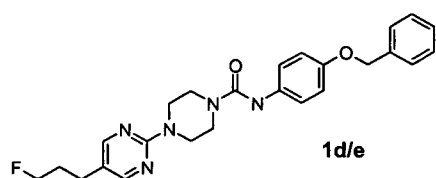
and wherein

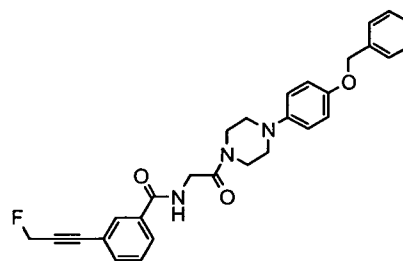
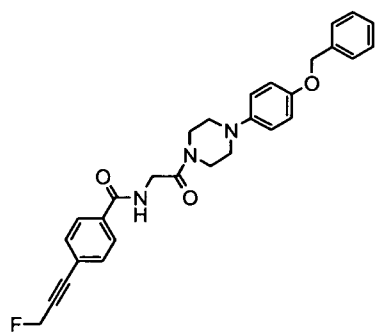
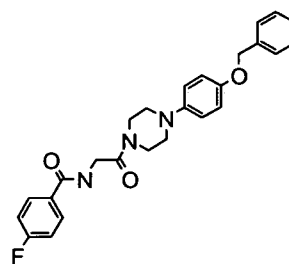
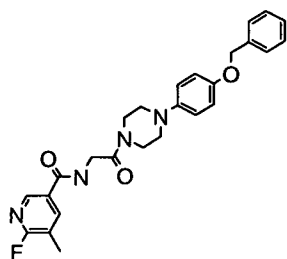
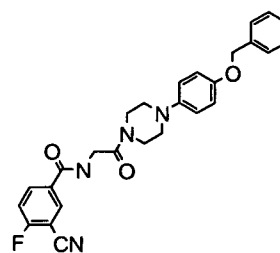
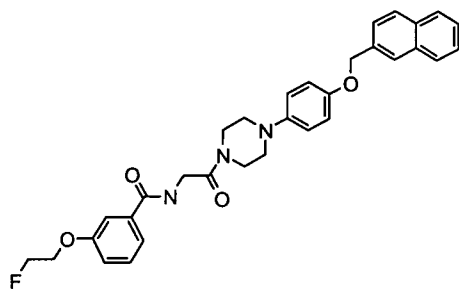
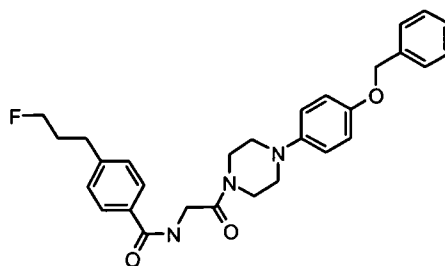
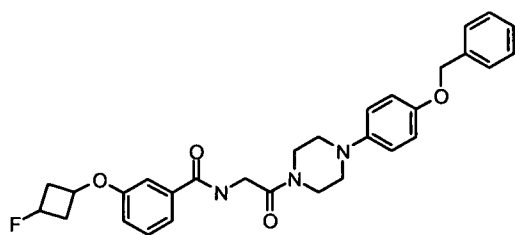
- Ar' is selected from the group consisting of propylpyrimidin-2-yl, ethoxyphenyl, (CH₂CH₂O)₃phenyl, alkylphenyl, alkoxyphenyl, N-alkylindolyl, phenyl, benzofuranyl, indolyl and alkylpyridyl;

and wherein

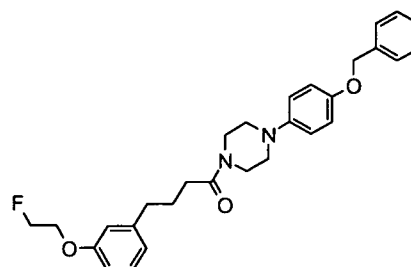
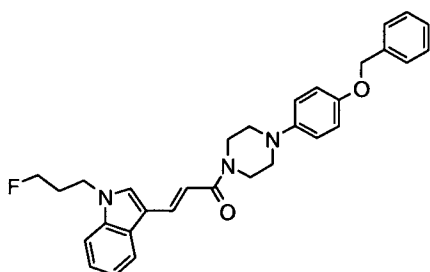
- Ar'' is selected from the group consisting of phenyl, 1-phenyl, 1-naphthyl, 2-naphthyl, and all respective heterocycles thereof.

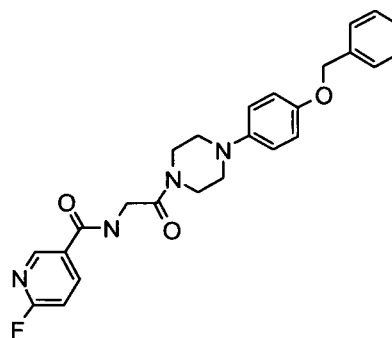
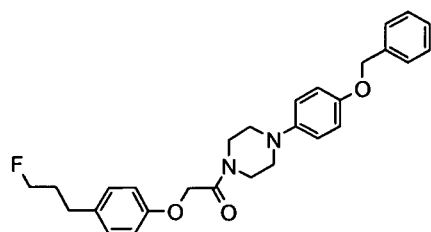
5 7. A compound, selected from the group consisting of





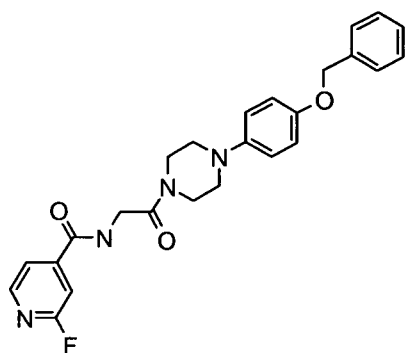
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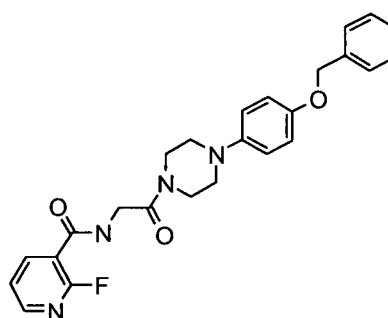


10d/e

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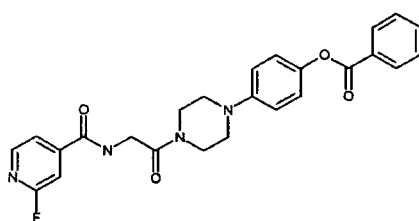
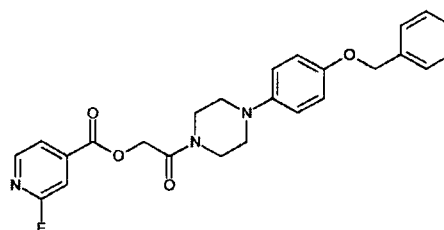
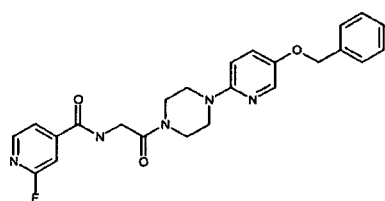


11b/c



12b/c.

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8. A compound according to claim 7, wherein F has the meaning of ^{18}F .
9. A compound according to claim 3, 4, 5 or 6 containing a detectable label, such as a radioactive nuclide or a fluorescent label.
- 5 10. A compound according to claim 9, wherein the detectable label is ^{18}F .
11. A compound according to claims 3 – 10 as a diagnostic compound.
- 10 12. A compound according to claims 3 – 7 as a medicament.
13. A compound according to claim 8, 9, or 10 as a diagnostic compound for a disease selected from the group consisting of Alzheimer's disease, a neurodegenerative disorder, or an amyloidosis.
- 15 14. A compound according to claim 12 as a medicament for treating a disease selected from the group consisting of Alzheimer's disease, a neurodegenerative disorder, or an amyloidosis.
- 20 15. A method for the preparation of a fluorinated compound according to claims 3 – 10 or a compound as defined by claim 1 or 2 used in the composition of claim 1 or 2, the method comprising reacting a suitable precursor molecule with a fluorinating agent.
- 25 16. A method for treating or preventing a disorder selected from the group consisting of Alzheimer's disease, a neurodegenerative disorder, or an amyloidosis in a mammal, this method comprising administering a therapeutically effective amount of a compound according to claims 3 – 7 or 12 to said mammal.
- 30 17. Use of a compound according to claims 3 – 7 or 12 in the treatment of a disease selected from the group consisting of Alzheimer's disease, a neurodegenerative disorder, or an amyloidosis in a mammal, wherein a therapeutically effective amount of said compound is administered to said mammal.
- 35 18. A method for diagnosing a disease in a mammal selected from the group consisting of Alzheimer's disease, a neurodegenerative disorder, or an amyloidosis, this method comprising administering to said mammal a compound according to claim 8 to 11, or a composition according to claims 1 or 2.

19. The method of claim 18, this method comprising imaging of said mammal and detecting the imaging signal.
- 5 20. The method of claim 19, where said imaging is performed using an imaging method selected from the group consisting of PET, SPECT, MR-spectroscopy, and MR-tomography.
- 10 21. A method according to claims 18 – 20, wherein the effect of a therapy is monitored.
22. A method for diagnosing or therapy monitoring of a disease selected from the group consisting of Alzheimer's disease, a neurodegenerative disorder, or an amyloidosis in a mammal, said method comprising analyzing *in vitro* a sample of said mammal, wherein said mammal or sample has been treated with a compound according to
15 claims 3 – 11 or a composition according to claim 1 or 2.
23. The method of claim 22, wherein the sample is cerebrospinal fluid.
- 20 24. A kit comprising a compound according to claims 3 – 14 or a composition of claims 1 or 2 in a sealed vial.
25. A compound according claim 7, wherein F is replaced by a leaving group.
- 25 26. A compound according to claim 25, wherein the leaving group is selected from the group consisting of tosyl, brosyl, nosyl, triflate, sulfonate, substituted sulfonate, mesylate, nonaflate; and if directly bound to an aromatic C-atom iodonium-aryl I⁺-aryl, trialkylammonium, trimethylammonium, and NO₂.
- 30 27. A method of preparing a compound according to claim 7 or 8, comprising reacting the corresponding compound of claim 25 or 26 with a fluorinating agent.