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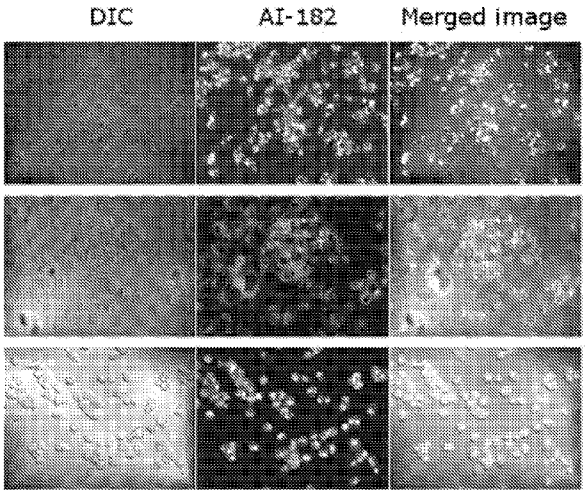
(54) Title: HETEROCYCLIC MOLECULES FOR BIOMEDICAL IMAGING AND THERAPEUTIC APPLICATIONS

FIG.10



(57) Abstract: Probes which target diffuse and fibrillar forms of amyloid beta (Aβ) are described. These probes demonstrate high initial brain penetration and facile clearance from non-targeted regions. The agents can be used to image amyloid quantitatively for monitoring efficacy of Aβ-modifying therapeutics and assist in premortem diagnosis of Alzheimer's disease (AD). Disclosed probes can bind Aβ aggregates of preformed $A\beta_{1-42}$ fibrils in vitro and can be used to image fibrillar and diffuse plaques ex vivo in brain sections. Disclosed probes can be used to determine Aβ burden in early stages of AD. These probes can be used for multimodality imaging of Aβ. F-AI-187(1μM) can detect Aβ plaques in brain sections of APP/PS1 mice. F-AI-187(10μM) can detect Aβ plaques in the frontal lobe in a brain section of a patient with confirmed AD. Some probes can be used for fluorescence imaging of plaque.

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Heterocyclic Molecules for Biomedical Imaging and Therapeutic Applications

CROSS REFERENCE TO RELATED APPLICATION

This application claims priority from U.S. Provisional Application Serial No. 61/885,571 filed October 2, 2013, which is incorporated herein by reference in its entirety.

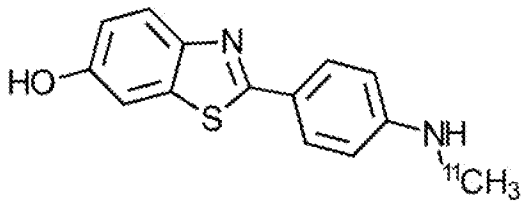
STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

This work received support from NIH Grant AG033328 and NIH Grant AG030498. The government may have certain rights in the invention.

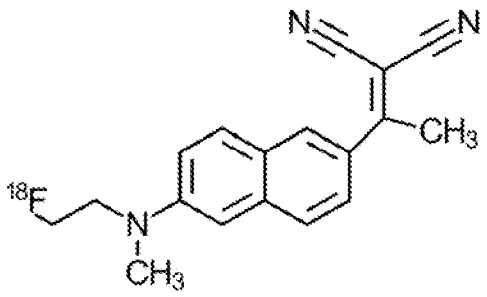
Introduction

Approximately 4 million Americans suffer from Alzheimer's disease (AD), a progressive neurodegenerative disorder with an estimated annual healthcare cost of $100 billion. AD can involve the appearance of distinct abnormal proteinaceous deposits: extracellular amyloid plaques that are characteristic of AD, and intracellular neurofibrillary tangles, which can also be found in other neurodegenerative disorders. Accumulation of amyloid beta (Aβ) can be an initiating event in the pathogenic cascade of AD. An overexpression of amyloid precursor protein (APP) is characteristic of Down Syndrome (DS), and early onset AD has been shown to be present in these patients (Teller, J., Nature Med. 2, 93-95 (1996); Lemere, C., et al. Neurobiol. Disease 3, 16-32, 1996).

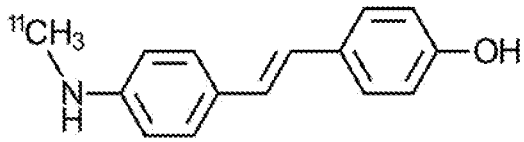
Neuropathological criteria for AD currently rely on densities of senile plaques (SPs) and neurofibrillary tangles (NFTs) to differentiate AD and aging. The presence of SPs and NFTs in non-demented older adults can represent AD at a stage prior to clinical expression (Price, J.L., et al. Neurobiology of Aging 30, 1026-1036, 2009). Amyloid formation can commence prior to the start of a neurodegeneration phase.

Radiopharmaceuticals such as ^{11}C-PIB (2-[p-(Methylamino)phenyl]-3-thia-1-aza-5-indanol, 

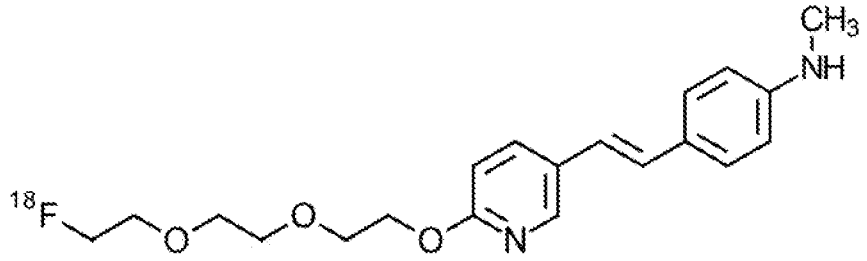
(Rabinovici, G.D., et al., Neurology 68: 1205-1212, 2007); ^{18}F-FDDNP (2-(1-(6-[(2-[18F]fluoroethyl)(methyl)amino]-2-



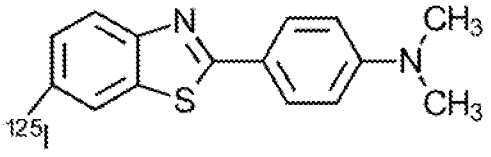
naphthyl)ethylidene)malononitrile, (Shoghi-Jadid, K., et al., Am. J. Geriatr. Psychiatry 10: 24-35, 2002); [^{11}C]-SB-13 ([^{11}C]4-N-methylamino-



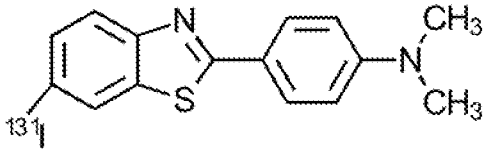
4'-hydroxystilbene, (Verhoeff, N.P., et al., Am. J. Geriatr. Psychiatry 12:584--595, 2004) and ^{18}F-AV-45



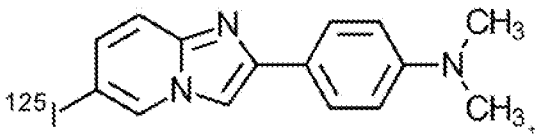
(Hsiao, I.T., et al., Eur. J. Nucl. Med. Mol. Imaging 39, 613-620, 2012) have been investigated in humans as probes for PET imaging of Aβ. In addition, [^{125}I/^{131}I]-TZDM ([^{125}I/^{131}I]2-(4'-



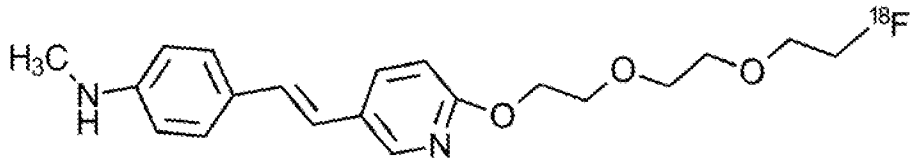
dimethylaminophenyl)-6-iodobenzothiazole, ,



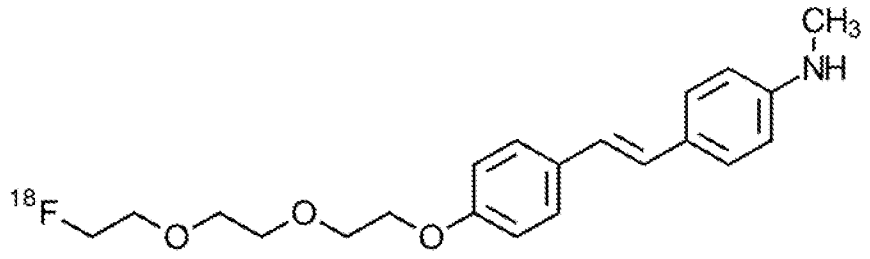
, Zhuang, Z.P., et al, J. Med. Chem. 44:1905-1914, 2001) and ^{125}I-IMPY ([^{125}I] 6-iodo-2-(4'-dimethylamino-)phenyl-imidazo[1,2-a]pyridine,



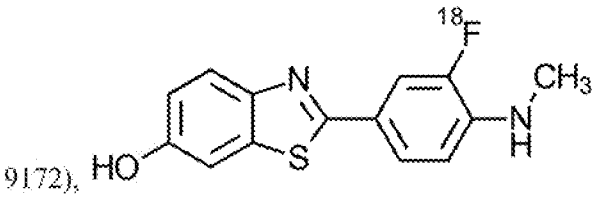
, Kung, M.P., et al., Brain Res. 956:202-210, 2002) have also been investigated for SPECT applications. While ^{11}C-PIB has been most intensely studied, ^{18}F-AV-45 ((E)-4-(2-(6-(2-(2-(2-([18F]-fluoroethoxy)ethoxy)ethoxy)pyridin-3-yl)vinyl)-N-methyl benzenamine,



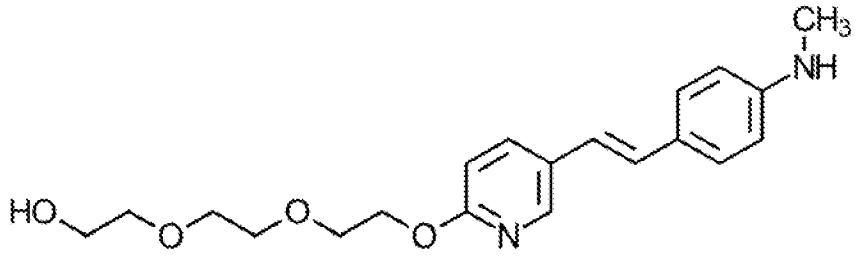
has also been approved by FDA for Aβ imaging. Other examples of ligands for Aβ aggregates include



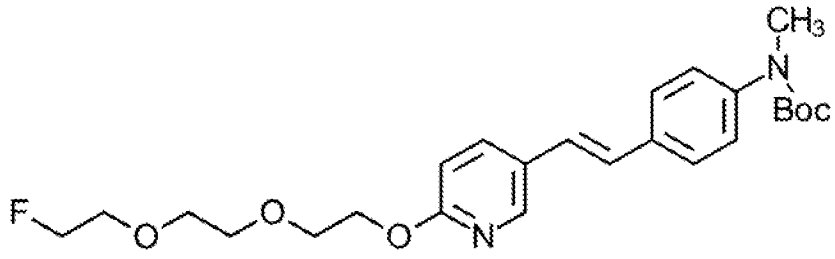
^{18}F-AV-1 (BAY94-9172),



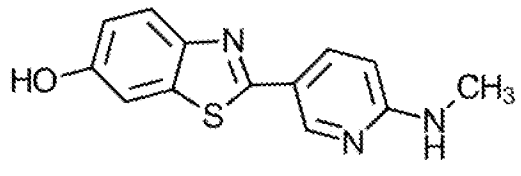
^{18}F-PIB (GE-067),



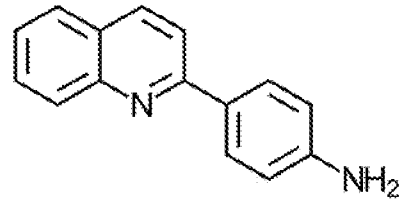
AV-136,



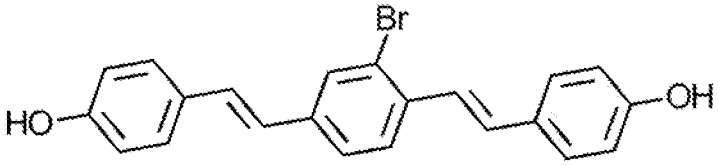
AV-137,



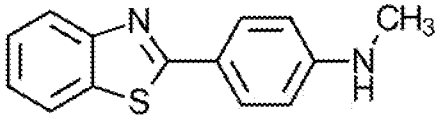
AZD2184,



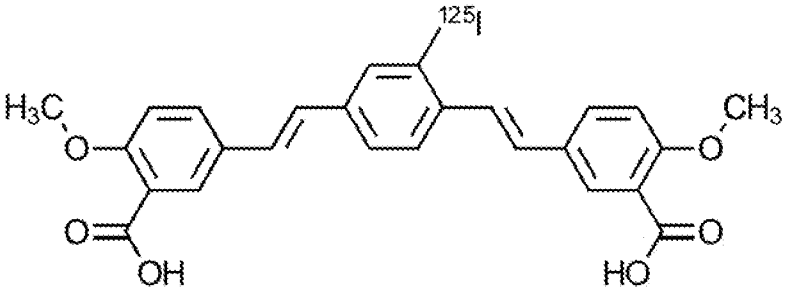
BF-170,



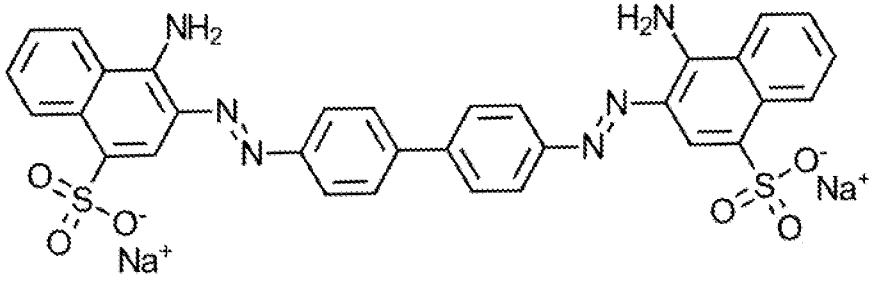
K114,



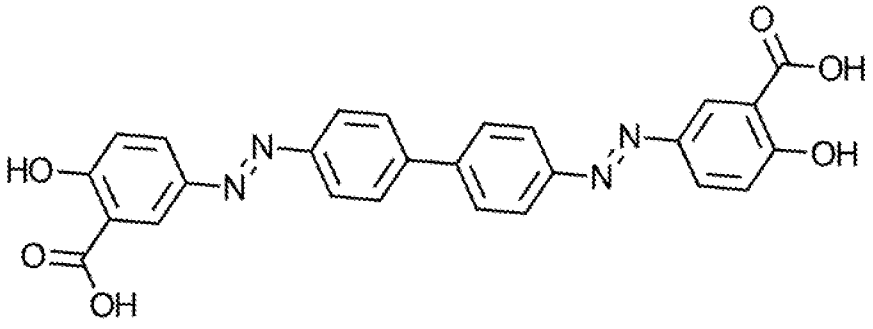
BTA-1;



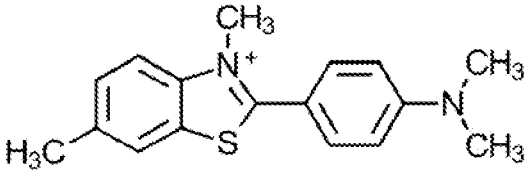
IMSB;



Congo Red;

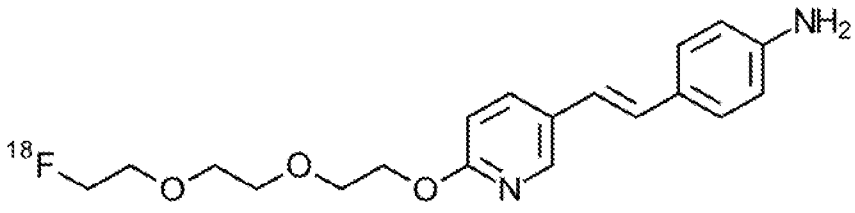


Chrysamine G

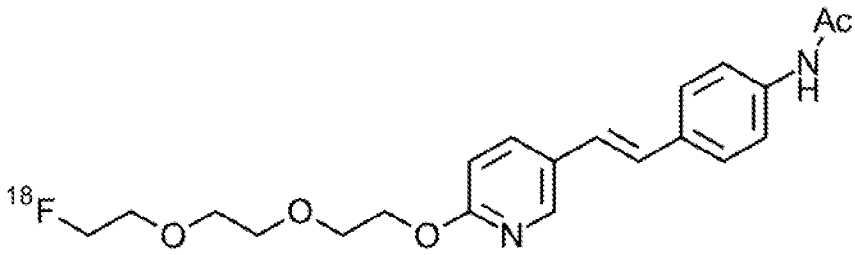


(CG); and Thioflavin T (Choi, S.R., et al., J. Nucl. Med. 50: 1887-1894, 2009; Cui, M., et al., J. Med. Chem. 55, 9283-9296, 2012).

However, each of the established ligands for Aβ aggregates has its drawbacks. For example, ^{11}C-PIB, SB-13, and ^{18}F-AV-45 each exhibit low biological half-life in serum. While metabolites of PIB have been postulated not to penetrate the brain (Nordberg, A. Lancet Neurol. 3, 519-527, 2004; Mathis, C., et al. J. Med. Chem. 46, 2740-2754 2003), two metabolites of ^{18}F-AV-45, i.e.,

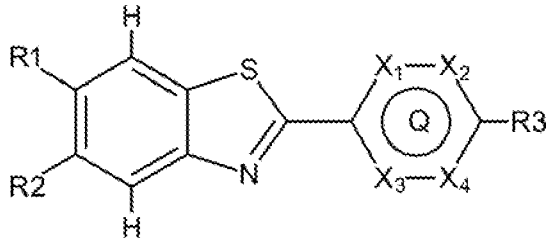


^{18}F-AV-160,; and

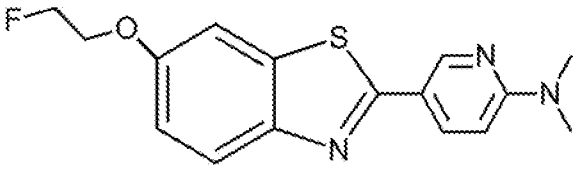


^{18}F-AV-267, have been shown to permeate the brain (4.5% injected dose/gram (ID/g) and 3.3% ID/g respectively, at 2 min in normal mice) thus complicating analysis (Choi, S.R., et al. J. Nucl. Med. 50, 1887-1894, 2009). Systematic investigations of PIB binding (at the tracer concentrations achieved during in vivo imaging scans) to human neuropathological brain specimens indicated PIB binding to classical plaques, neurofibrillary tangles, and cerebrovascular amyloid angiopathy (CAA) that was not displaceable, indicating limited utility of PIB to diagnose and monitor progression of the disease. (Lockhart, A., et al., Brain 130, 2607-2615, 2007). FDDNP has been shown to bind to neurofibrillary tangles and prion plaques in addition to fibrillar Aβ, demonstrating a lack of specificity towards probing AD (Nordberg, A., Lancet Neurol. 3, 519-527, 2004; Agdeppa, E., et al. J. Neurosci. 21, RC189, 2001; Agdeppa, E., et al., Neuroscience 117, 723-730, 2003). FDDNP has been shown to bind both BS1 and BS3 sites with low affinity (Ye, L., et al. J. Biol. Chem. 280, 23599-23604 2005).

US Patent 8,163,928 to Gravenfors, assigned to AstraZeneca, discloses structure



wherein R1 can be, inter alia, C_1-C_6 fluoroalkoxy; R2 can be H; Q is an aromatic ring; X1 can be C; X2 can be N, X3 can be C and X4 can be C; and R3 can be $N(C_{1-3}$ alkyl$)_2$. This patent includes structure



. However, the structure disclosed in US Patent 8,163,928 has only a bond linking the benzothiazole moiety and the pyridine moiety.

^{18}F-agents such as flutemetamol (^{18}F-PIB), florbetaben (BAYER 94-9172) and florbetapir (AV-45) (Choi, S.R., et al., J. Nucl. Med. 50, 1887-1894, 2009; Zhang, W., Nucl. Med. Biol. 34, 89-97, 2007) show high levels of nonspecific white matter retention that can be attributed to high lipophilicity. This high level of nonspecific retention can limit the sensitivity of PET imaging in a prodromal phase of disease when plaque levels are low. Combined with the possibility that these agents could be targeting the same binding site on Aβ, the diagnostic potential of existing imaging agents to segregate patients at earlier stages of the disease to benefit from available therapeutics is debatable. PIB, AV-45, and other agents have been known to bind weakly to amorphous cortical plaques (Ikonomovic, M.D., et al., Brain 131, 1630-1645, 2008; Bacskai, B.J., et al., Arch. Neurol. 64, 431-434, 2007). These agents target fibrillar plaques and interact weakly with diffuse plaques that occur in early stages of the disease prior to clinical manifestation of symptoms.

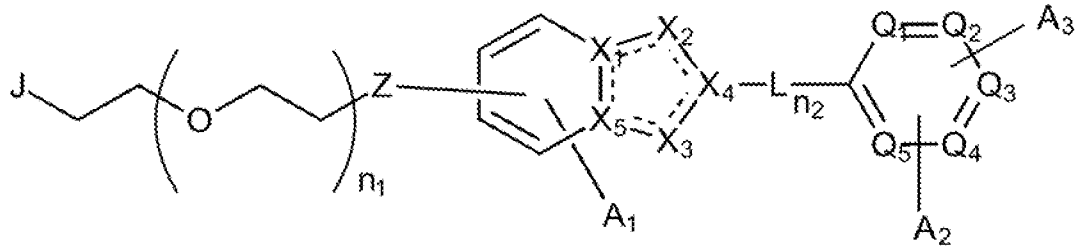
Previous agents have shown white matter binding, which provides a challenge for analysis in early stages of AD. For example, ^{11}C-PIB binding of cerebral Aβ was reported below the level required for detection in a patient (Cairns, N.J., et al., Arch. Neurol. 66, 1557-1562, 2009) thus raising concerns for PIB and other agents in their sensitivity to detect AD variants characterized predominantly by diffuse Aβ plaques. Agents such as PIB and AV-45 have been postulated to bind a high affinity and low dense site on fibrils (Lockhart, A., et al.,

J. Biol. Chem. 280, 7677-7684,2005) thus raising further concerns regarding their diagnostic potential to map early stages of AD. Because the presence of senile plaques in non-demented older adults can represent an early manifestation of AD prior to its clinical expression (Price, J.L., et al., Neurobiology of Aging 30, 1026-1036, 2009; Morris, J.C., et al., Neurology 46, 707-719, 1996; Price, J.L. & Morris, J.C., Annals of Neurology 45, 358-368, 1999; Schmitt, F.A., et al., Neurology 55, 370-376, 2000) the orientation of Aβ binding sites can also be different at earlier stages. Thus, additional ligands for amyloid beta are needed.

Summary

The present inventors have developed tracers for detecting amyloid beta (Aβ). In various embodiments, the tracers can include radionuclides for imaging using known imaging modalities such as PET scanning or SPECT scanning.In various embodiments, the tracers can have fluorescence properties, and can be used for optical imaging. In various embodiments, tracers of the present teachings can possess enhanced specificity (minimal white matter binding) and/or enhanced sensitivity compared to ^{11}C-PIB or ^{18}F-AV-45. In some embodiments, a disclosed tracer can be capable of targeting binding sites different from those targeted by ^{11}C-PIB or ^{18}F-AV-45. In some embodiments, a disclosed tracer can provide diagnostic PET agents for Aβ imaging at earlier stages of Alzheimer's disease compared to tracers such as ^{11}C-PIB or ^{18}F-AV-45. In some embodiments, a disclosed tracer can be used to monitor efficacy of therapeutics. In some embodiments, a disclosed tracer such as, without limitation, ^{18}F-AI-187, can be used for imaging and/or diagnosis of a tumor such as, without limitation, a prolactinoma, a chroid plexus papilloma, a low grade lymphoma, or a pituitary tumor.

In various embodiments, the present teachings include, without limitation, a compound or a pharmaceutically acceptable salt thereof of structure



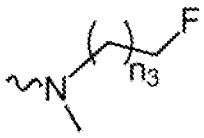
wherein:

J can be selected from the group consisting of a halogen, hydroxy, cyano, $COOR^1$, carboxy, amide, immino, nitro, NR^2R^3 and OR^4;

n_1 can be an integer from 0-4 or an integer from 1-4;

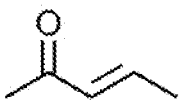
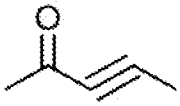
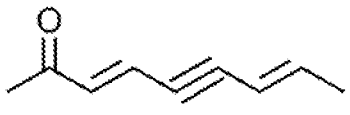
Z can be selected from the group consisting of CH_2, O, NR^5, S and Se;

each of A_1, A_2 and A_3 can be independently selected from the group consisting of H, F, Cl, Br, I, CN, OH, NO_2, NHR^6, NR^7R^8,OR^9, SR^{10}, $COOR^{11}$, COR^{12}, sulfonic acid,



wherein ~ is a bond , 2-ethylidenemalononitrile, (*E*)-2-(but-2-en-1-ylidene)malononitrile, 2-((2E,4E)-hexa-2,4-dien-1-ylidene)malononitrile, acetyl, -$(OCH_2-CH_2)_{n_4}$- and R^{13}; n_3 can be an integer from 0-4; n_4 can be an integer from 0-4; X_1 can be selected from the group consisting of C and N; X_2 can be selected from the group consisting of CH_2,CH, O, NR^{14}, S, Se and N;

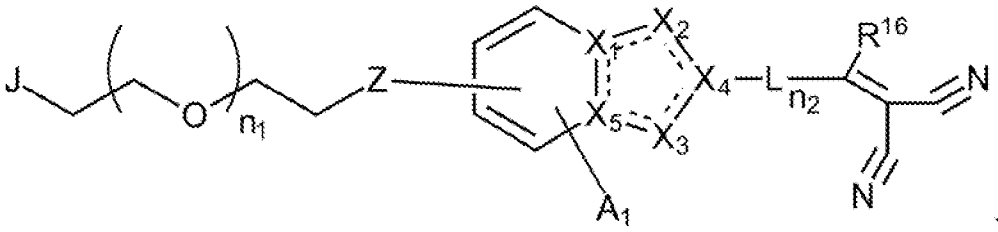
X_3 can be selected from the group consisting of CH_2, CH, O, NR^{15}, S, Se and N;

X_4 isC or CH; X_5 is C, CH or N; wherein X_4 is CH, X_2 and X_4 are linked by a single bond and X_3 and X_4 are linked by a single bond, or X_4 is C, X_2 and X_4 are linked by a single bond and X_3 and X_4 are linked by a double bond, or X_4 is C, X_2 and X_4 are linked by a double bond and X_3 and X_4 are linked by a single bond; wherein when X_1 can be C then X_1 and X_5 are linked by a double bond; wherein when X_1 can be N, then X_1 and X_5 are linked by a single bond; wherein when X_2 can be NR^{14},S, O or Se, then X_2 and X_4 are linked by a single bond; wherein when X_2 can be N, then X_2 and X_4 are linked by a double bond; wherein when X_3 can be NR^{15},S, O or Se, then X_3 and X_4 are linked by a single bond; wherein when X_3 can be N, then X_3 and X_4 are linked by a double bond; wherein when both the X_2 and X_5 are N, then X_1 and X_2 are linked by a double bond, X_2 and X_4 are linked by a single bond, X_3 and X_4 are linked by a double bond, and X_3 and X_5 are linked by a single bond; wherein when both the X_1 and X_2 are N, then X_2 and X_4 are linked by a double bond, X_3 and X_4 are linked by a single bond, X_3 and X_5 are linked by a double bond, and X_1 and X_5 are linked by a single bond; L can be selected from the group consisting of (C_1-C_4) alkyl, (C_3-C_6) cycloalkyl, (C_2-C_8) alkene (straight or branched), (C_2-C_8) alkyne,  ,  and  ;

n_2 can be an integer from 0-4 or an integer from 1-4; each of Q_1, Q_2, Q_3, Q_4 and Q_5 can be independently selected from the group consisting of C and N, with provisos that at least two of Q_1, Q_2, Q_3, Q_4 and Q_5 are C and at least one of Q_1, Q_2, Q_3, Q_4 and Q_5 is N; and each of R^1-R^{15} can be independently selected from the group consisting of H, C_{1-12} linear alkyl, C_{2-12} linear alkene, C_{2-12} linear alkyne, C_{3-12} branched chain alkyl, C_{3-12} branched chain alkene, C_{3-12} branched chain alkyne and C_{3-7} cycloalkyl aryl and a combination thereof.

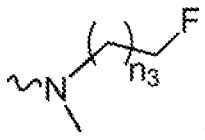
In various aspects of these embodiments, the halogen can be selected from the group consisting of Cl, F, Br and I. In various aspects, the halogen can be selected from the group consisting of F-18, Br-75, Br-76, Br-77, I-123, I-124, I-125 and I-131. In various aspects, R^4 can be or comprise a radionuclide such as a C-11. In various aspects, R^{13} can be or comprise a radionuclide such as a C-11.

In various embodiments, the present teachings include, without limitation, a compound or a pharmaceutically acceptable salt thereof, of structure



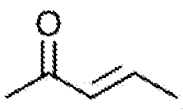
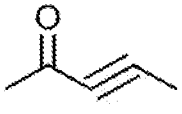
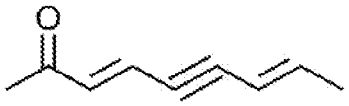
wherein:

J can be selected from the group consisting of a halogen (Cl, F, Br, I) or a radionuclide (such as F-18, Br-75, Br-76, Br-77, I-123, I-124, I-125, I-131), hydroxy, cyano, $COOR^1$, carboxy, amide, immino, nitro, NR^2R^3 and OR^4 (with a radionuclide, such as C-11 or an unlabeled counterpart); n_1 can be an integer from 0-4 or an integer from 1-4; Z can be selected from the group consisting of CH_2, O, NR^5, S and Se; A_1 can be selected from the group consisting of H, F, Cl, Br, I, CN, OH, NO_2, NHR^6, NR^7R^8,OR^9, SR^{10}, $COOR^{11}$, COR^{12}, sulfonic acid,



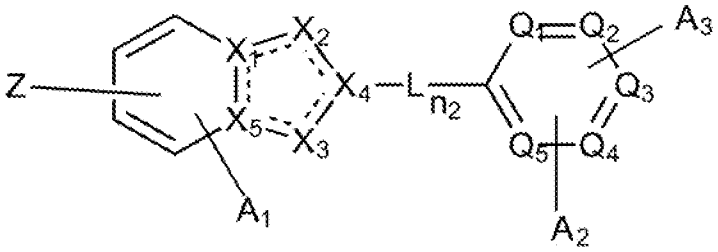
wherein ~ is a bond , 2-ethylidenemalononitrile, (*E*)-2-(but-2-en-1-ylidene)malononitrile, 2-((2E,4E)-hexa-2,4-dien-1-ylidene)malononitrile, acetyl, -$(OCH_2$-$CH_2)_{n_4}$-$(CH_2)_2$-J and R^{13} (including radionuclide); n_3 can be an integer from 0-4; n_4 can be an integer from 0-4;

X_1 can be selected from the group consisting of C and N; X_2 can be selected from the group

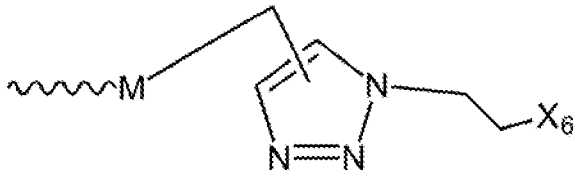
consisting of CH_2, CH, O, NR^{14}, S, Se and N; X_3 can be selected from the group consisting of CH_2,CH, O, NR^{15}, S, Se and N; wherein when X_2 is NR^{14}, S, O or Se, then X_2 and X_4 are linked by a single bond; wherein when X_2 is N, then X_2 and X_4 are linked by a double bond; wherein when X_3 is NR^{15}, S, O or Se, then X_3 and X_4 are linked by a single bond; wherein when X_3 is N, then X_3 and X_4 are linked by a double bond; wherein when both the X_2 and X_5 are N, then X_1 and X_2 are linked by a double bond, X_2 and X_4 are linked by a single bond, X_3 and X_4 are linked by a double bond, and X_3 and X_5 are linked by a single bond; wherein when both the X_1 and X_2 are N, then X_2 and X_4 are linked by a double bond, X_3 and X_4 are linked by a single bond, X_3 and X_5 are linked by a double bond, and X_1 and X_5 are linked by a single bond; L can be selected from the group consisting of aryl, (C_1-C_4) alkyl, (C_3-C_6) cycloalkyl, (C_2-C_8) alkene (straight or branched), (C_2-C_8) alkyne,  ,  and  ; n_2 can be an integer from 0-4 or an integer from 1-4; and each of R^1-R^{16} can be independently selected from the group consisting of H, C_{1-12} linear alkyl, C_{2-12} linear alkene, C_{2-12} linear alkyne, C_{3-12} branched chain alkyl, C_{3-12} branched chain alkene, C_{3-12} branched chain alkyne, C_{3-7} cycloalkyl aryl and a combination thereof.

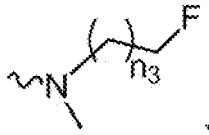
In various aspects, a compound or a pharmaceutically acceptable salt thereof of these embodiments, the halogen can be selected from the group consisting of Cl, F, Br and I, or selected from the group consisting of F-18, Br-75, Br-76, Br-77, I-123, I-124, I-125 and I-131. In some aspects, R^4 can be or can comprise a radionuclide such as, without limitation, a C-11. In some aspects, R^{13} can be or can comprise a radionuclide such as, without limitation, a C-11.

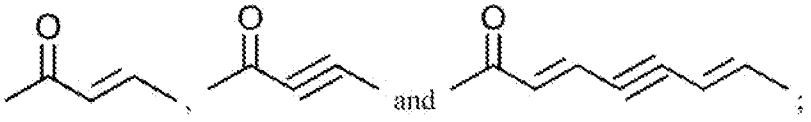
In various embodiments, the present teachings include, without limitation, a compound or a pharmaceutically acceptable salt thereof, of structure



wherein: Z can be selected from the group consisting of CH_2, O, NR^1, S, Se and



wherein ~~~ is a bond; each of A_1, A_2 and A_3 can be independently selected from the group consisting of H, F, Cl, Br, I, CN, OH, NO_2, NHR^2, NR^3R^4,OR^5, SR^6, $COOR^7$, COR^8, sulfonic acid,  wherein ~~~ is a bond , 2-ethylidenemalononitrile, (*E*)-2-(but-2-en-1-ylidene)malononitrile, 2-((2E,4E)-hexa-2,4-dien-1-ylidene)malononitrile, acetyl,-$(OCH_2\text{-}CH_2)_{n4}$ and R^9 (including radionuclide); n_3 can be an integer from 0-4; n_4 can be an integer from 0-4; X_1 can be selected from the group consisting of C and N^+; X_2 can be selected from the group consisting of CH_2, CH, O, NR^{10}, S, Se and N;

X_3 can be selected from the group consisting of CH_2, CH, O, NR^{11}, S, Se and N; wherein when X_2 is NR^{14},S, O or Se, then X_2 and X_4 are linked by a single bond; wherein when X_2 is N, then X_2 and X_4 are linked by a double bond; wherein when X_3 is NR^{15},S, O or Se, then X_3 and X_4 are linked by a single bond; wherein when X_3 is N, then X_3 and X_4 are linked by a double bond; wherein when both the X_2 and X_5 are N, then X_1 and X_2 are linked by a double bond, X_2 and X_4 are linked by a single bond, X_3 and X_4 are linked by a double bond, and X_3 and X_5 are linked by a single bond; wherein when both the X_1 and X_2 are N, then X_2 and X_4 are linked by a double bond, X_3 and X_4 are linked by a single bond, X_3 and X_5 are linked by a double bond, and X_1 and X_5 are linked by a single bond; L can be selected from the group consisting of $(C_1\text{-}C_4)$ alkyl, $(C_3\text{-}C_6)$ cycloalkyl, $(C_2\text{-}C_8)$ alkene (straight or branched), $(C_2\text{-}C_8)$ alkyne,  ;

n_2 can be an integer from 0-4 or an integer from 1-4; each of Q_1, Q_2, Q_3, Q_4 and Q_5 can be independently selected from the group consisting of C and N, with provisos that at least two of Q_1, Q_2, Q_3, Q_4 and Q_5 are C and at least one of Q_1, Q_2, Q_3, Q_4 and Q_5 is N;

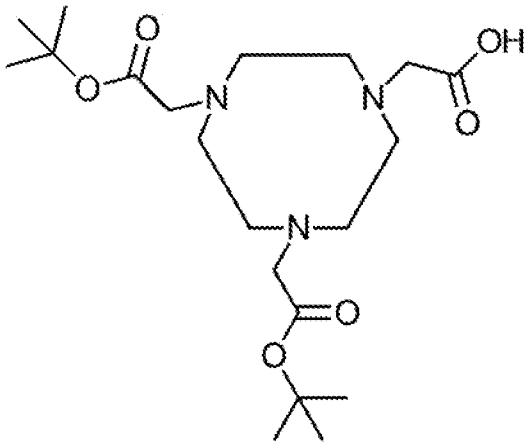
M= O, S, Se, NR^{12}, amide, maleimide, urea, haloalkane, haloalkene, haloalkyne;

X_6 = Halogen, NH_2; NHR^{13} (R^{13}= methyl, ethyl, propyl, or any alkyl straight or branched chain); OR^{14}, $COOR^{15}$, COR^{16}, OH, NHQ (Q =Chelator Core (NOTA, DOTA, DTPA, Triglycine for chelation of metal radionuclide, such as an ion of gallium-67, -gallium-68, an unlabeled gallium, or a paramagnetic metal which includes an ion of gallium-67, an ion of

gallium-68, an ion of an unlabeled gallium, - indium-111 , -iron-52, iron-59, -copper-62, - copper-64, -thallium-201, -technetium-99m, -technetium-94m, -rhenium-188, -rubidium-82, - strontium-92, -yttrium-86 or yttrium-90, -zirconium-86 or zirconium-89, and a paramagnetic metal ion such as, a transition metal (exemplied by iron, manganese, and a cobalt), or a lanthanide metal ion, such as gadolinium); each of R^1-R^{12} and R^{14}-R^{16} can be independently selected from the group consisting of H, C_{1-12} linear alkyl, C_{2-12} linear alkene, C_{2-12} linear alkyne, C_{3-12} branched chain alkyl, C_{3-12} branched chain alkene, C_{3-12} branched chain alkyne and C_{3-7} cycloalkyl aryl. 3a. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 3, wherein the halogen is selected from the group consisting of Cl, F, Br and I.

In some aspects of these embodiments, the halogen can be selected from the group consisting of F-18, Br-75, Br-76, Br-77, I-123, I-124, I-125 and I-131. In some aspects, R^4 can be or can comprise a radionuclide, such as, without limitation, a C-11. In some aspects, R^{13} can be or can comprise a radionuclide, such as, without limitation, a C-11.

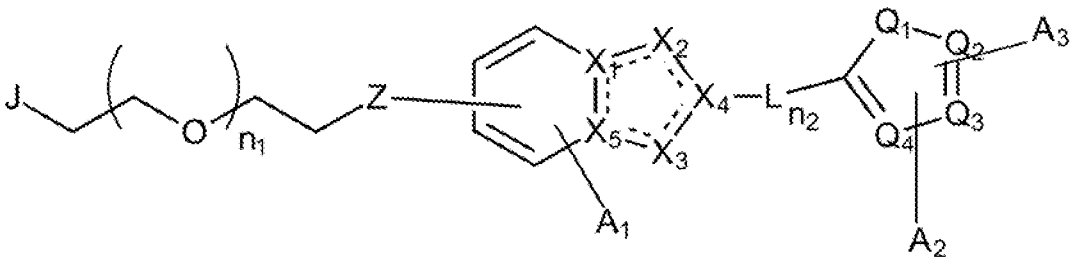
In some aspects of these embodiments, a compound or a pharmaceutically acceptable salt thereof can comprise a chelator core selected from the group consisting of NOTA



, DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), DTPA (Diethylenetriaminepentaacetic acid) and triglycine. In some aspects, a chelator core can chelate a metal radionuclide. In some aspects, metal radionuclide can be an ion selected from the group consisting of an ion of gallium-67and an ion of gallium-68. In some aspects the ion can be selected from the group consisting of an ion of gallium-67, an ion of gallium-68, an ion of an unlabeled gallium, an ion of indium-111 , an ion of iron-52, an ion of iron-59, an ion of copper-62, an ion of copper-64, an ion of thallium-201, an ion of technetium-99m, an ion of technetium-94m, an ion of rhenium-188, an ion of rubidium-82, an ion of strontium-92, an ion of yttrium-86, an ion of yttrium-90, an ion of

zirconium-86, an ion of zirconium-89. In some aspects, the ion can be a paramagnetic metal ion. In some aspects, the ion can be selected from the group consisting of an ion of iron, an ion of manganese and an ion of cobalt. In some aspects, the ion can be a lanthanide metal ion. In some aspects, the ion can be a gadolinium ion.

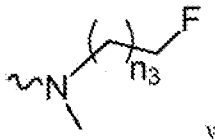
In various embodiments, the present teachings include, without limitation, a compound or a pharmaceutically acceptable salt thereof, of structure



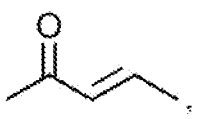
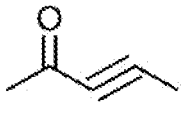
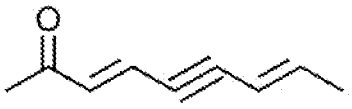
wherein:

J can be selected from the group consisting of Cl, F, Br, I or a radionuclide (such as F-18, Br-75, Br-76, Br-77, I-123, I-124, I-125, I-131), hydroxy, cyano, $COOR^1$, carboxy, amide, immino, nitro, NR^2R^3 and OR^4 (with a radionuclide, such as C-11 or an unlabeled counterpart);

n_1 can be an integer from 0-4 or an integer from 1-4; Z can be selected from the group consisting of CH_2,O, NR^5, S and Se; each of A_1, A_2 and A_3 can be independently selected from the group consisting of H, F, Cl, Br, I, CN, OH, NO_2, NHR^6, NR^7R^8,OR^9, SR^{10},

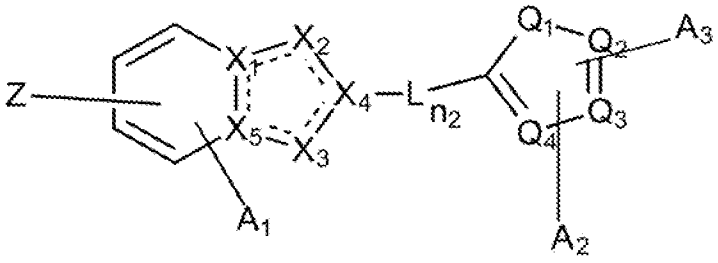


$COOR^{11}$, COR^{12}, sulfonic acid, wherein ~ is a bond, 2-ethylidenemalononitrile, (*E*)-2-(but-2-en-1-ylidene)malononitrile, 2-((2E,4E)-hexa-2,4-dien-1-ylidene)malononitrile, acetyl, $-(OCH_2-CH_2)_{n_4}-(CH_2)_2-J$ and R^{13} (including radionuclide); n_3 can be an integer from 0-4; n_4 can be an integer from 0-4; X_1 can be selected from the group consisting of C and N; X_2 can be selected from the group consisting of CH_2,CH, O, NR^{14}, S, Se and N; X_3 can be selected from the group consisting of CH_2,CH, O, NR^{15}, S, Se and N; wherein when X_2 is NR^{14}, S, O or Se, then X_2 and X_4 are linked by a single bond; wherein when X_2 is N, then X_3 and X_4 are linked by a double bond; wherein when X_3 is NR^{15}, S, O or Se, then X_3 and X_4 are linked by a single bond; wherein when X_3 is N, then X_3 and X_4 are linked by a double bond; wherein when both the X_2 and X_5 are N, then X_1 and X_2 are linked by a double bond, X_2 and X_4 are linked by a single bond, X_3 and X_4 are linked by a double

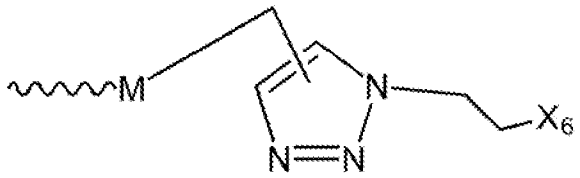
bond, and X_3 and X_5 are linked by a single bond; wherein when both the X_1 and X_2 are N, then X_2 and X_4 are linked by a double bond, X_3 and X_4 are linked by a single bond, X_3 and X_5 are linked by a double bond, and X_1 and X_5 are linked by a single bond; L can be selected from the group consisting of (C_1-C_8) alkyl, (C_3-C_6) cycloalkyl, (C_2-C_8) alkene (straight or branched), (C_2-C_8) alkyne,  ,  and  ; n_2 can be an integer from 0-4 or an integer from 1-4; each of Q_1, Q_2, Q_3 and Q_4 can be independently selected from the group consisting of C and N, with provisos that at least two of Q_1, Q_2, Q_3 andQ_4 are C and at least one of Q_1, Q_2, Q_3 and Q_4 is N; each of R^1-R^{15} can be independently selected from the group consisting of H, $C_{1\text{-}12}$ linear alkyl, $C_{2\text{-}12}$ linear alkene, $C_{2\text{-}12}$ linear alkyne, $C_{3\text{-}12}$ branched chain alkyl, $C_{3\text{-}12}$ branched chain alkene, $C_{3\text{-}12}$ branched chain alkyne and $C_{3\text{-}7}$ cycloalkyl aryl, or a combination thereof.

In various aspects, A compound or a pharmaceutically acceptable salt thereof of these embodiments can comprise a halogen that is selected from the group consisting of Cl, F, Br and I. In various aspects, the halogen can be selected from the group consisting of F-18, Br-75, Br-76, Br-77, I-123, I-124, I-125 and I-131. In various aspects, R^8 can be or can comprise a radionuclide, such as, without limitation, a C-11. In various aspects, R^{13} can be or can comprise a radionuclide, such as, without limitation, a C-11.

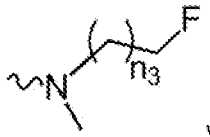
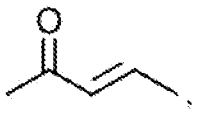
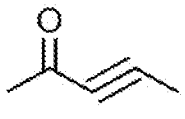
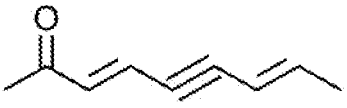
In various embodiments, the present teachings include, without limitation, a pharmaceutically acceptable salt thereof, of structure



, wherein: Z can be selected from the group consisting of CH_2, O, NR^1, S, Se and



wherein  is a bond; each of A_1, A_2

and A_3 can be independently selected from the group consisting of H, F, Cl, Br, I, CN, OH,  NO_2, NHR^2, NR^3R^4,OR^5, SR^6, $COOR^7$, COR^8, sulfonic acid, wherein  is a bond ,2-ethylidenemalononitrile, (*E*)-2-(but-2-en-1-ylidene)malononitrile, 2-((2E,4E)-hexa-2,4-dien-1-ylidene)malononitrile, acetyl-$(OCH_2\text{-}CH_2)_{n4}$-$(CH_2)_2$-J and R^9 (including radionuclide); n_3 can be an integer from 0-4; n_4 can be an integer from 0-4; X_1 can be selected from the group consisting of C and N; X_2 can be selected from the group consisting of CH_2,CH, O, NR^{10}, S, Se and N; X_3 can be selected from the group consisting of CH_2,CH, O, NR^{11}, S, Se and N; when X_2 is NR^{14} ,S, O or Se, then X_2 and X_4 are linked by a single bond; when X_2 is N, then X_2 and X_4 are linked by a double bond; wherein when X_3 is NR^{15} ,S, O or Se, then X_3 and X_4 are linked by a single bond; wherein when X_3 is N, then X_3 and X_4 are linked by a double bond; wherein when both the X_2 and X_5 are N, then X_1 and X_2 are linked by a double bond, X_2 and X_4 are linked by a single bond, X_3 and X_4 are linked by a double bond, and X_3 and X_5 are linked by a single bond; wherein when both the X_1 and X_2 are N, then X_2 and X_4 are linked by a double bond, X_3 and X_4 are linked by a single bond, X_3 and X_5 are linked by a double bond, and X_1 and X_5 are linked by a single bond; L can be selected from the group consisting of $(C_1\text{-}C_4)$ alkyl, $(C_3\text{-}C_6)$ cycloalkyl, $(C_2\text{-}C_8)$ alkene (straight or branched), $(C_2\text{-}C_8)$ alkyne,  ,  and  ; n_2 can be an integer from 0-4 or an integer from 1-4; each of Q_1, Q_2, Q_3 and Q_4 can be independently selected from the group consisting of C and N, with provisos that at least two of Q_1, Q_2, Q_3 and Q_4 are C and at least one of Q_1, Q_2, Q_3 and Q_4 is N; M can be O, S, Se, NR^{12}, amide, maleimide, urea, haloalkane, haloalkene, haloakyne; X_6 can be a halogen, NH_2, NHR^{13}; R^{13} can be methyl, ethyl, propyl, or any alkyl straight or branched chain; OR^{14}, $COOR^{15}$, COR^{16}, OH, NHQ, wherein Q is a chelator core such as NOTA, DOTA, DTPA, Triglycine for chelation of metal radionuclide, which can be, without limitation, an ion of gallium-67, gallium-68, an unlabeled gallium, or a paramagnetic metal which includes an ion of gallium-67, an ion of gallium-68, an ion of an unlabeled gallium, or an ion of indium-111 , an ion of iron-52, an ion of iron-59, an ion of copper-62, an ion of copper-64, an ion of thallium-201, an ion of technetium-99m, an ion of technetium-94m, an

ion of rhenium-188, an ion of rubidium-82, an ion of strontium-92, an ion of yttrium-86 or an ion of yttrium-90, an ion of zirconium-86, an ion of zirconium-89, and a paramagnetic metal ion such as, a transition metal (such as, without limitation, an ion of iron, an ion of manganese, or an ion of cobalt), or a lanthanide metal ion, such as an ion of gadolinium; each of R^1-R^{12} and R^{14}-R^{16} can be independently selected from the group consisting of H, C_{1-12} linear alkyl, C_{2-12} linear alkene, C_{2-12} linear alkyne, C_{3-12} branched chain alkyl, C_{3-12} branched chain alkene, C_{3-12} branched chain alkyne and C_{3-7} cycloalkyl aryl.

In various aspects of these embodiments, a compound or a pharmaceutically acceptable salt thereof can comprise a halogen that can be selected from the group consisting of Cl, F, Br and I, or can be selected from the group consisting of F-18, Br-75, Br-76, Br-77, I-123, I-124, I-125 and I-131. In some aspects, R^4 can comprise a radionuclide such as, without limitation, a C-11. In some aspects, R^{13} can comprise a radionuclide such as, without limitation, a C-11. In various aspects, a compound or a pharmaceutically acceptable salt can comprise a chelator core that can be selected from the group consisting of NOTA, DOTA, DTPA and triglycine. In some aspects, a chelator core of these aspects can chelate a metal radionuclide, which can be, without limitation, an ion of gallium-67and an ion of gallium-68. In some aspects, a chelator core of these embodiments can chelate a metal radionuclide, which can be, without limitation, an ion selected from the group consisting of an ion of gallium-67, an ion of gallium-68, an ion of an unlabeled gallium, an ion of indium-111 , an ion of iron-52, an ion of iron-59, an ion of copper-62, an ion of copper-64, an ion of thallium-201, an ion of technetium-99m, an ion of technetium-94m, an ion of rhenium-188, an ion of rubidium-82, an ion of strontium-92, an ion of yttrium-86, an ion of yttrium-90, an ion of zirconium-86, an ion of zirconium-89. In some aspects, the ion can be a paramagnetic metal ion. In some aspects, the ion can be selected from the group consisting of an ion of iron, an ion of manganese and an ion of cobalt. In some aspects, the ion can be a lanthanide metal ion. In some aspects, the ion can be a gadolinium ion.

In some embodiments, the present teachings include gold nanoparticles which comprise gold conjugated to a compound described herein.

In some embodiments, the present teachings include complexes, wherein a complex comprises a compound or a pharmaceutically acceptable salt thereof described herein, and a gold nanoparticle.

In some embodiments, the present teachings include a gold nanoparticle conjugated to a compound disclosed herein. In some configurations, a gold nanoparticle of the present

teachings can further comprise a linker, such as, without limitation, an aminothiol (Abbas, A., et al., *Langmuir* 2013, 29, 56−64). In various configurations, the aminothiol can be an aminothiophenol. In some configurtions, the aminothiophenol can be a p-aminothiophenol. In various aspects, the gold of a gold nanoparticle can be Au-199 and/or Au-198.

In various embodiments, the present teachings include methods of imaging distribution of amyloid beta in a sample or a subject. In various configurations, these methods can comprise: administering a compound, a pharmaceutically acceptable salt thereof or a gold nanoparticle disclosed herein to the sample or subject wherein the compound pharmaceutically acceptable salt thereof or gold nanoparticle comprises a radionuclide, and subjecting the sample or subject to PET scanning or SPECT scanning. In various configurations, these methods can comprise administering a compound, a pharmaceutically acceptable salt thereof, or a gold nanoparticle disclosed herein to the sample or subject, and applying to the sample or subject electromagnetic radiation visible and/or UV light of wavelength(s) that is/are excitatory for fluorescence of the compound, salt thereof or gold nanoparticle. The methods further include detecting light emitted by fluorescence of the compound, salt thereof or gold nanoparticle by known methods, such as, without limitation, fluorescence microscopy.

In some embodiments, the present teachings include methods of imaging cardiac systemic amyloidosis in a subject. In various configuratons, these methods comprise administering an imaging effective amount of a compound, a pharmaceutically acceptable salt thereof or a gold nanoparticle of the present teachings to the subject, and subjecting the subject to PET or SPECT scanning, or fluorescence imaging.

In some embodiments, the present teachings include methods of inhibiting amyloid beta aggregation. In various aspects, these methods can comprise administering an effective amount of a compound, a pharmaceutically acceptable salt thereof or a gold nanoparticle of the present teachings, wherein the compound or salt thereof comprises at least one Se atom.

In some embodiments, the present teachings include methods of inhibiting diagnosing or monitoring progression of Alzheimer's disease. In various aspects, these methods comprise administering to a subject a compound, a pharmaceutically acceptable salt thereof or a gold nanoparticle of the present teachings, and subjecting the subject to PET or SPECT scanning, or to fluorescence imaging.

In some embodiments, the present teachings include methods of diagnosing or monitoring progression of a neurodegenerative disease. In various aspects, these methods

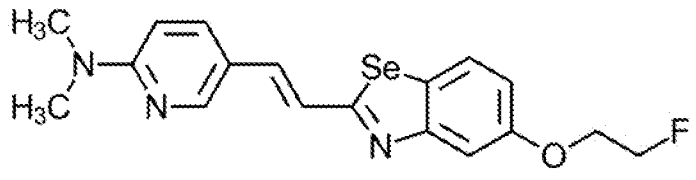
comprise administering to a subject a compound, a pharmaceutically acceptable salt thereof or a gold nanoparticle of the present teachings, and subjecting the subject to PET or SPECT scanning, or to fluorescence imaging.

In some embodiments, the present teachings include methods of diagnosing or monitoring progression of cardiac systemic amyloidosis. In various configurations, these methods include administering to a subject a compound, a pharmaceutically acceptable salt thereof or a gold nanoparticle of the present teachings, and subjecting the subject to PET or SPECT scanning, or to fluorescence imaging.

In some embodiments, the present teachings include methods for detecting or ruling out a meningioma in a subject. In some configurations, these methods can include administering to a subject a compound, a pharmaceutically acceptable salt thereof or a gold nanoparticle of the present teachings. In various aspects, the compound can be targeted to any type of meningioma in the patient. An image can be acquired to detect the presence or absence of any meningioma inside the skull or elsewhere within the patient. In some aspects, the methods can include a step of acquiring the image, which can be performed using an imaging method selected from PET or SPECT scanning with concurrent computed tomography (CT) imaging or magnetic resonance imaging (MRI), SPECT scanning with concurrent computed tomographic imaging, fluorescence imaging, or any combination thereof.

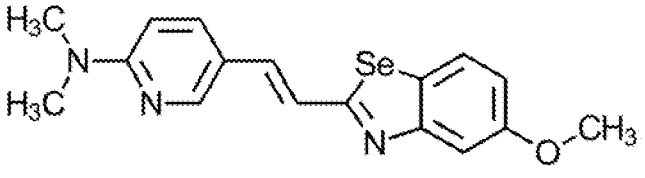
In some embodiments, the present teachings include methods for differentiating the presence of meningiomas from other tumors types via retention of greater activity of a compound, a pharmaceutically acceptable salt thereof or a gold nanoparticle of the present teachings in meningiomas compared with other intracranial tumors, such as pituitary macroadenomas, schwannomas or ependymomas, and metastases.

In some embodiments, the present teachings include a compound of structure



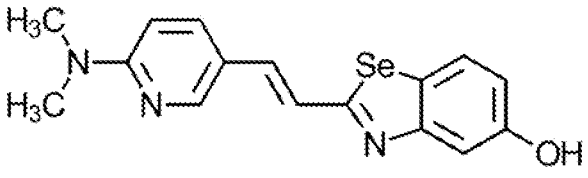
(F-AI-183) or a pharmaceutically acceptable salt thereof.

In some embodiments, the present teachings include a compound of structure



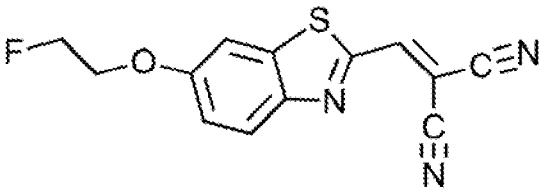
or a pharmaceutically acceptable salt thereof.

In some embodiments, the present teachings include a compound of structure



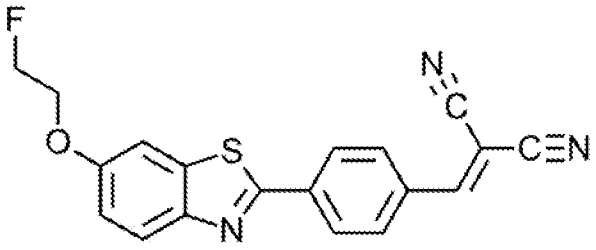
or a pharmaceutically acceptable salt thereof.

In some embodiments, the present teachings include a compound of structure



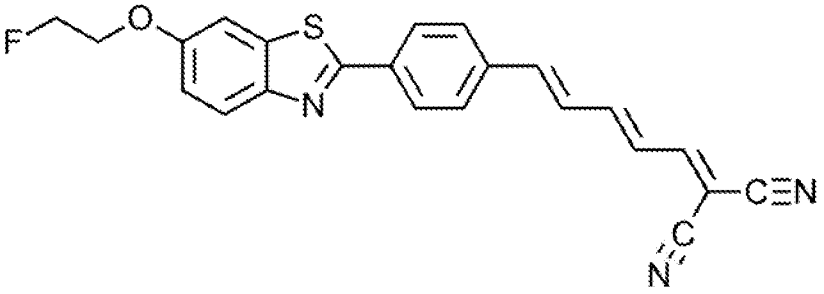
or a pharmaceutically acceptable salt thereof.

In some embodiments, the present teachings include a compound of structure



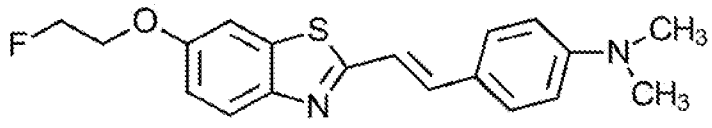
or a pharmaceutically acceptable salt thereof.

In some embodiments, the present teachings include a compound of structure



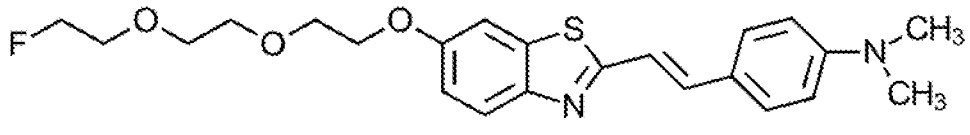
or a pharmaceutically acceptable salt thereof.

In some embodiments, the present teachings include a compound of structure



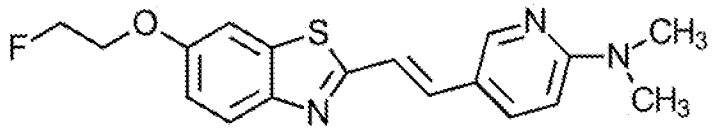
or a pharmaceutically acceptable salt thereof.

In some embodiments, the present teachings include a compound of structure



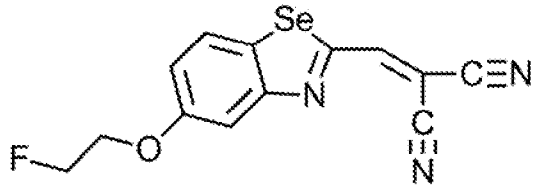
or a pharmaceutically acceptable salt thereof.

In some embodiments, the present teachings include a compound of structure



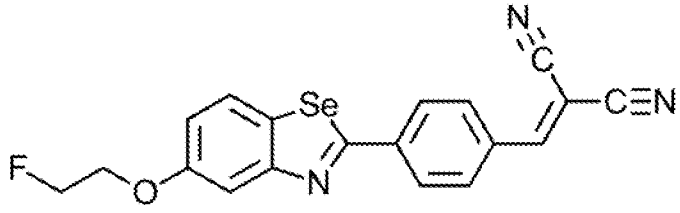
(AI-182) or a pharmaceutically acceptable salt thereof.

In some embodiments, the present teachings include a compound of structure



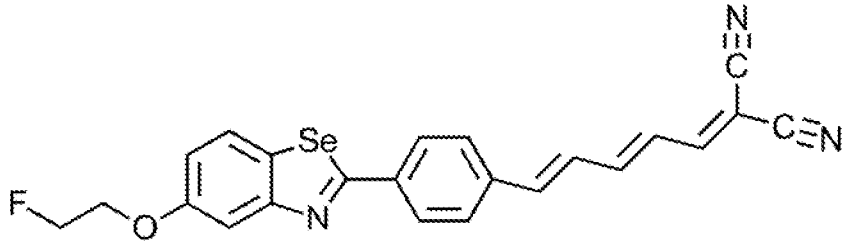
or a pharmaceutically acceptable salt thereof.

In some embodiments, the present teachings include a compound of structure



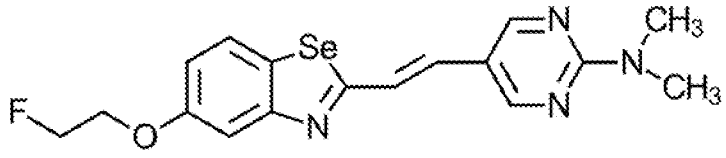
or a pharmaceutically acceptable salt thereof.

In some embodiments, the present teachings include a compound of structure



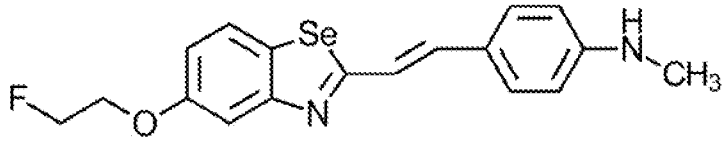
or a pharmaceutically acceptable salt thereof.

In some embodiments, the present teachings include a compound of structure



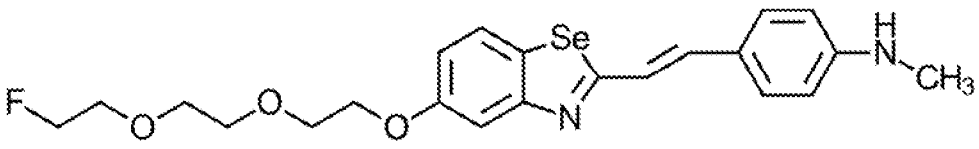
or a pharmaceutically acceptable salt thereof.

In some embodiments, the present teachings include a compound of structure



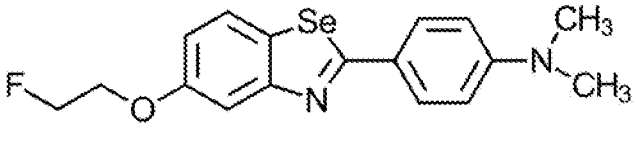
or a pharmaceutically acceptable salt thereof.

In some embodiments, the present teachings include a compound of structure



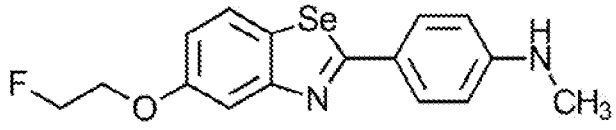
or a pharmaceutically acceptable salt thereof.

In some embodiments, the present teachings include a compound of structure



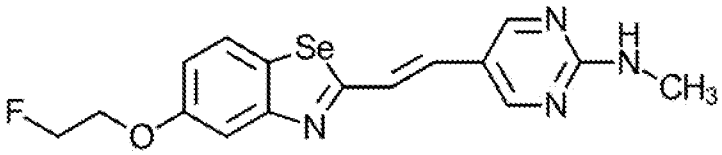
or a pharmaceutically acceptable salt thereof.

In some embodiments, the present teachings include a compound of structure



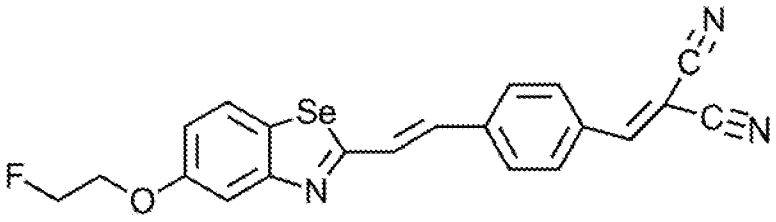
or a pharmaceutically acceptable salt thereof.

In some embodiments, the present teachings include a compound of structure



or a pharmaceutically acceptable salt thereof.

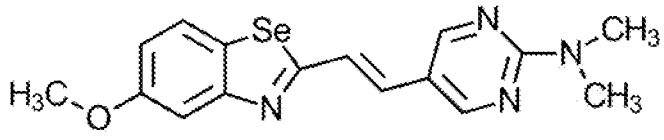
In some embodiments, the present teachings include a compound of structure



or a pharmaceutically acceptable salt thereof.

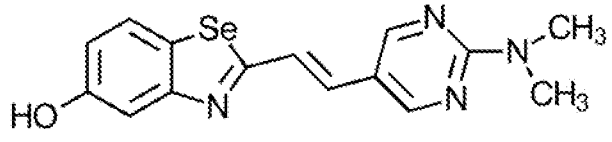
41

In some embodiments, the present teachings include a compound of structure



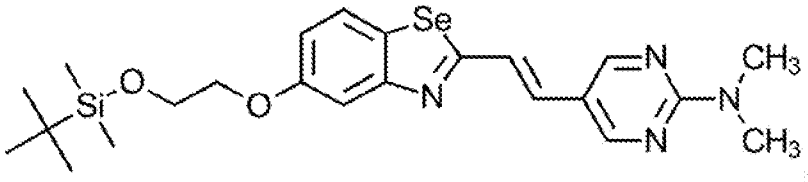
or a pharmaceutically acceptable salt thereof.

In some embodiments, the present teachings include a compound of structure



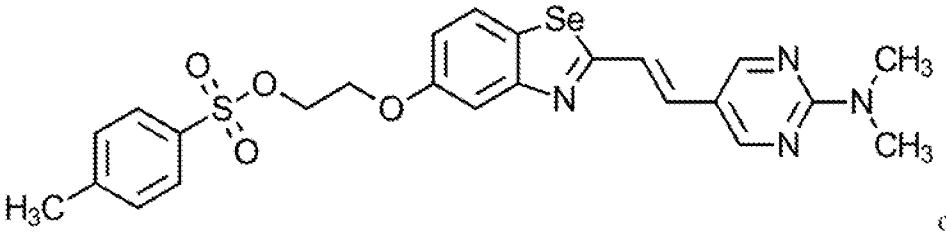
or a pharmaceutically acceptable salt thereof.

In some embodiments, the present teachings include a compound of structure



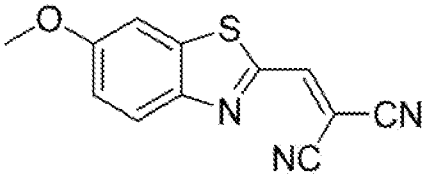
or a pharmaceutically acceptable salt thereof.

In some embodiments, the present teachings include a compound of structure



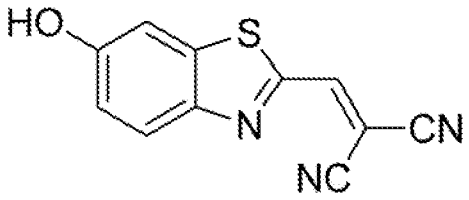
or a pharmaceutically acceptable salt thereof.

In some embodiments, the present teachings include a compound of structure



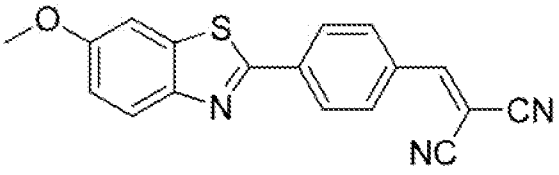
or a pharmaceutically acceptable salt thereof.

In some embodiments, the present teachings include a compound of structure



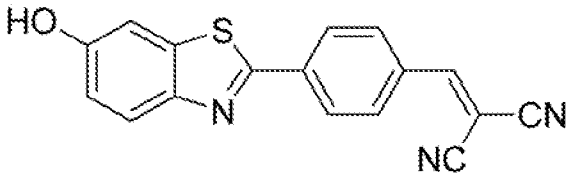
or a pharmaceutically acceptable salt thereof.

In some embodiments, the present teachings include a compound of structure



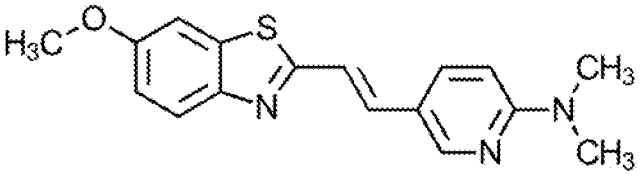
or a pharmaceutically acceptable salt thereof.

In some embodiments, the present teachings include a compound of structure



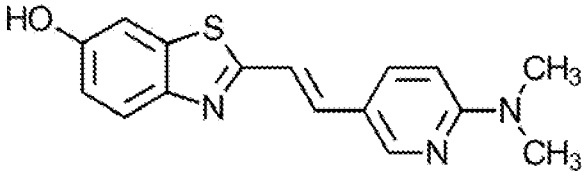
or a pharmaceutically acceptable salt thereof.

In some embodiments, the present teachings include a compound of structure



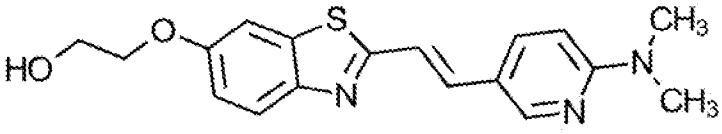
or a pharmaceutically acceptable salt thereof.

In some embodiments, the present teachings include a compound of structure



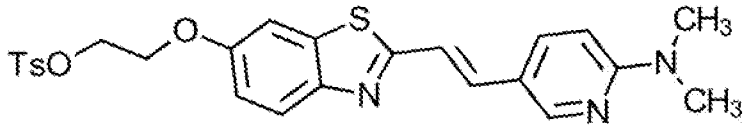
or a pharmaceutically acceptable salt thereof.

In some embodiments, the present teachings include a compound of structure



or a pharmaceutically acceptable salt thereof.

In some embodiments, the present teachings include a compound of structure



or a pharmaceutically acceptable salt thereof.

Brief Description of the Drawings

In drawings based on multi-color originals, gray-scale versions of each color channel (red, green and/or blue) are shown, as well as a composite gray scale that combines all 3 (RGB) color channels.

FIG. 1 illustrates concentration dependent and saturable binding (binding constant, 59±7nM) to preformed Aβ1-42 fibrils of agent F-AI-182, of structure

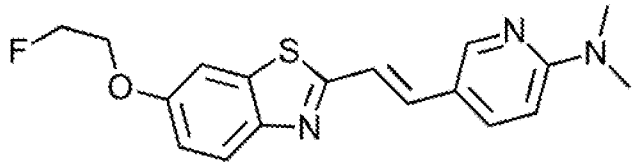
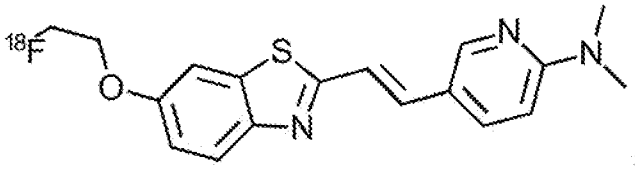
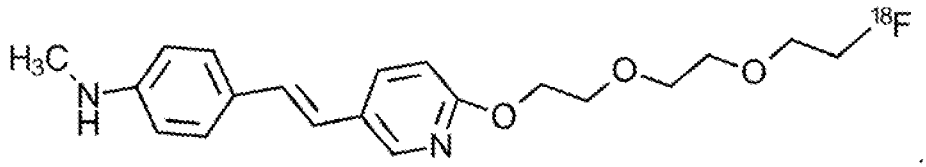


FIG. 2 illustrates staining of both fibrillar and diffuse plaques ex vivo in the hippocampus and cortical region of brain sections in APPsw+/-/PS1 mice using agent F-AI-182. Tissue sections were immunostained with mouse monoclonal antibody and visualized by donkey-anti-mouse Alexa 568 (positive control). Arrows indicate labeling of Aβ plaques (arrows, diffuse; arrow head, fibrillar).

FIG. 3 illustrates a comparative analysis of pharmacokinetics in normal mice for 18F-AI-182 of structure



and ^{18}F-AV-45 of structure



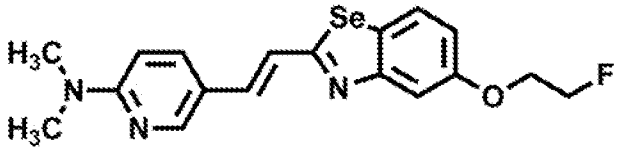
Biodistribution studies with HPLC-purified ^{18}F-AI-182 in normal mice revealed a transient brain uptake value of 7.28± 0.46% ID/g and 1.54 ± 0.06% ID/g, 5 min and 120 min post tail-vein injection, respectively, giving a 5 min/120 min clearance a ratio of 4.73, providing evidence for the ability of ^{18}F-AI-182 to cross the BBB and permeate into brain in vivo. ^{18}F-AV-45 demonstrates brain uptake values of 7.33 ± 1.54 %ID/g and 1.80 ± 0.07 %ID/g at 2 min and 120 min post-injection respectively, thus providing a 2 min/120 min clearance ratio of 4.07 in normal mice that lack target sites. The initial data point for ^{18}F-AI-182 is at 5 min compared with 2 min for ^{18}F-AV-45.

FIG. 4 illustrates that ^{18}F-AI-182 is washed out from blood (25% faster than AV-45) in absence of targeted plaques and remains non-metabolized in human serum. ^{18}F-AI-182 undergoes 25% faster blood clearance from 5 min to 120 min compared with the ^{18}F-AV-45. ^{18}F-AI-182 shows facile penetration of the brain and clearance in normal mice. The initial data point for ^{18}F-AI-182 is at 5 min compared with 2 min for ^{18}F-AV-45.

FIG. 5 illustrates that F-AI-182 can be used to detect both diffuse and compact Aβ plaques in the brain cross-sections of frontal lobe of a 90-year-old female with neuropathologically confirmed Alzheimer's disease: Left. The fluorescent probe (F-AI-182, 50nM) labels both the compact fibrillar amyloid (arrow) and more diffuse beta-amyloid deposits (arrowhead); Right. Aβ (10D5, Eli Lilly) immunohistochemistry reveals similar beta-amyloid plaques in a section from the same tissue block as in (b); bar = 100 μm.

FIG. 6 illustrates real time imaging using F-AI-182: Prior to imaging, dextran-Texas Red was injected for mapping the blood vessels. Following labeling of blood vessels, F- AI-182 (2mg/kg, dissolved in DMSO/PEG; 20:80) was intravenously injected. A z-stack image series was acquired from cortex surface to a depth of approx. 100μm using microscope LSM 510META NLO (Carl-Zeiss Inc). Multi-photon microscopy in live APPsw+/-/PS1 (15 months old) mice demonstrated that F-AI-182 can label plaques in brain parenchyma and blood vessels (CAA), less than 5-min post intravenous administration. The labeling of brain parenchymal plaques was visible within 10 min, indicating facile clearance from non-targeted regions and remained labeled for at-least 30 min.

FIG. 7 illustrates assessment of binding sites of PIB, AV-45, and AI-182. In these studies, we used sitemap to determine binding sites on Aβ1-42, generated a grid, then docked PIB, AV-45, and AI-182 to determine rank order (AV-45 > F-AI-182> PIB) based upon the Glide score. Post docking view of PIB (left), AV-45 (Middle), and F-AI-182 (Right).

FIG. 8 illustrates staining of brain tissue sections from APPsw+/- (24 months old) mice using F-AI-183 of structure 

. Arrows indicate labeling of Aβ plaques (arrows, fibrillar plaques).

FIG. 9 illustrates detection of compact Aβ plaques in the brain cross-sections of frontal lobe of an 88-year-old female with neuropathologically confirmed Alzheimer's disease using F-AI-183. The fluorescent probe (F-AI-183) labels fibrillar amyloid (arrows).

FIG. 10 illustrates fluorescence imaging of tumor cells in vitro, labeled by uptake of fluorescent AI-182.

Detailed Description

Abbreviations

Aβ Amyloid beta

AD Alzheimer's Disease

ADME absorption, distribution, metabolism, and excretion

APP amyloid precursor protein

BBB blood–brain barrier

BS1 binding site 1

BS2 binding site 2

BS3 binding site 3

^{13}C NMR carbon nuclear magnetic resonance

CAA cerebrovascular amyloid angiopathy

CERAD Consortium to Establish a Registry for Alzheimer's Disease

DS Down Syndrome

^{19}F NMR fluorine nuclear magnetic resonance

^{1}H NMR proton nuclear magnetic resonance

HPLC high-performance liquid chromatography

HRMS high-resolution mass spectroscopy

MIRD Medical Internal Radionuclide Dose Committee

NIA-RI National Institute of Aging-Reagan Institute

NFT neurofibrillary tangle

NMR nuclear magnetic resonance

PBS phosphate buffered saline

PET positron emission tomography

SAR Structure-Activity Relationships

SP senile plaque

SPECT single photon emission computed tomography

WT wild type

The present teachings disclose agents that can be used for imaging cancers and neurodegenerative diseases. Reagents described herein also have therapeutic use in neurodegenerative diseases and cardiovascular diseases.

In various embodiments, a flourine-18-based PET probe can be capable of targeting high prevalence sites of Aβ and displaying faster kinetics compared to non-targeted regions, such as white matter. In various embodiments, a flourine-18-based PET probe can be used for quantitative amyloid imaging for monitoring progress of Aβ-modifying treatments in the pre-

symptomatic and symptomatic stages of Alzheimer's disease (AD), and/or premortem diagnosis of AD.

In various embodiments, the present teachings include heterocyclic molecules (exemplified as F-AI-182) that can bind to Aβ aggregates in vitro with concentration dependent and saturable binding. For example and without limitation, binding constants to preformed $A\beta_{1-42}$ fibrils can be F-AI-182, 59±7nM; F-AI-183, 17 nM; F-AI-187, 1.58 nM ± 0.05nM. In various configurations, these probes can stain both fibrillar and diffuse plaques ex vivo in the hippocampus and cortical region of brain sections in $APPsw^{+/-}$/PS1 mice and human tissues. In some aspects, F-AI-182 can incorporate F-18 (^{18}F; $t_{1/2}$ = 110 min), a radionuclide for medical PET imaging (Mahmood, A. & Jones, A. Technetium Radiopharmaceuticals. Handbook of Radiopharmaceuticals. 323-362 (2003); Eckelman, W. The Development of 99mTc Radiopharmaceuticals for Perfusion and Biochemistry: In Technetium and Rhenium in Chemistry and Nuclear Medicine 3. M. Nicolini, G. Bandoli and U. Mazzi (Eds.). Cortina Int., Verona, Italy. pp. 571-580. (1990); Narra, R., et al. A Neutral Tc-99m Complex for Myocardial Imaging. J. Nucl. Med. 30, 1830-1837 (1989); Stadalnik, R., Kudo, M., Eckelman, W. & Vera, D. In vivo functional imaging using receptor-binding radiopharmaceuticals: 99mTc-galactosyl-neoglycoalbumin (TcNGA). Investigative Radiology 28, 64-70 (1993)). In some aspects, F-AI-182 can be used for diagnostic assessment of Aβ burden in earlier stages of AD prior to expression of clinical symptoms. In some aspects, a radiolabeled counterpart ^{18}F-AI-182 can demonstrate a high initial brain penetration (7.28± 0.46% %ID/g) of FVB mice, followed by 25 % faster clearance from the blood pool (compared with AV-45) in normal mice in the absence of targeted plaques. In some aspects, ^{18}F-AI-182 can remain non-metabolized until about 30 min (investigated highest time-point) in human serum. In some aspects, F-AI-182 can demonstrate characteristics that enhance overall signal to background ratios and assist image analysis including lack of metabolites and high first-pass extraction into brain of coupled with fast clearance from the blood pool.

In some embodiments, a tracer of the present teachings can provide high target/background ratios. In some aspects, multiphoton microscopy can demonstrate that an unlabeled counterpart F-AI-182 of the radiolabeled PET agent can label brain parenchymal Aβ plaques as well as tracked cerebrovascular amyloid angiopathy (CAA), indicating its ability to serve as a noninvasive probe for assessment of plaque burden in brain. In some

aspects, these data can illustrate a platform technology for image analysis in biomedical PET imaging, using an F-18 labeled PET agent.

In various embodiments, a functional probe of the present teachings can have hydrophobic characteristics to cross the blood-brain barrier (BBB) and not be retained in non-targeted regions of the brain. In various aspects, a fluorescent molecule of the present teachings can show enhanced fluorescence upon binding to fibrils, can stain both fibrillar and diffuse plaques in brain cross sections of APP/PS1 transgenic mice and human AD tissues, and can show high initial penetration in the normal brain followed by clearance in the absence of targeted plaques. In various aspects, the agent can clear rapidly from other organs, such as liver and kidney, remain non-metabolized in human serum, and display modest hydrophobicity (log P 1.2) for formulation in 2% ethanol and 98% saline for intravenous injections. The scaffold of F-AI-182 can be used for interrogating AD in a prodromal phase.

In some embodiments, heterocyclic small organic molecules of the present teachings can also be used for multimodality imaging of Aβ using PET/Optical imaging in preclinical applications.

In some embodiments, an agent can exhibit enhanced brain penetration, Aβ interaction, and the ability to interact with highly prevalent or more-dense binding sites on Aβ. In some embodiments, an agent can be identified by either the lack of binding or reduced binding to the white matter for enhancing sensitivity of tracers for Aβ detection in human tissues. In some embodiments, an agent of the present teachings can label Aβ plaques in brain parenchyma <5 min post- intravenous administration.

In some embodiments, the specificity of agents can be determined for Aβ compared to other biomarkers prevalent in neurodegenerative disorders (with overlapping symptoms) such as, tau protein, neurofibrillary tangles (NFT) and Lewy body, including further optimization of targeting properties through SAR study. In some embodiments, an agent can exceed or mimic the pharmacokinetic profiles (brain uptake and blood clearance) of ^{18}F-AV-45, an FDA approved agent for imaging Aβ in brain. In an embodiment, ^{18}F-AI-182 showed facile penetration of the blood-brain barrier (BBB) in in vitro targeting of Aβ in a mouse model.

In some embodiments, a compound of the present teachings can be used for noninvasive assessment of Aβ in early stages of AD prior to clinical expression, and can allow therapeutic interventions for disease management. In some embodiments, a compound

of the present teachings can be used for stratification of patients in early phases of AD to allow for therapeutic interventions.

Embodiments of Aβ-targeted agent can include functional components including but not limited to the following examples.

An embodiment of an Aβ-targeted agent can include a benzothiazole moiety without the methyl group on the heterocyclic nitrogen of thioflavinT. This can allow the removal of the positive charge to increase the affinity of the probe to Aβ fibrils and enhance hydrophobicity to facilitate BBB penetration.

An embodiment of an Aβ-targeted agent can include modifications on the 6^{th} position of the benzothiazole ring has been shown to impact affinity of probes for plaques.

An embodiment of an Aβ-targeted agent can include the introduction of an olefin bond between the benzothiazole moiety and the aromatic ring to increase electron density as well as flexibility of the molecule to promote interactions with other binding sites on Aβ plaques.

An embodiment of an Aβ-targeted agent can include substituting a basic dimethylamino group into an aromatic ring at p-position to the olefinic carbon. In some configuraitons, this can allow an increase electron density on nitrogen.

An embodiment of an Aβ-targeted agent can include incorporation of a heteroatom, such as nitrogen in the aromatic ring ortho to the highly basic dimethyl-amino group. In some configuraitons, this can allow better resonance stabilization of the molecule for influencing Pi-Pi interactions and can allow targeting of highly dense and moderate affinity sites on Aβ fibrils.

Methods

Methods and compositions described herein utilize laboratory techniques well-known to skilled artisans. Such technique guidance can be found in laboratory manuals and textbooks such as Spector, D. L. et al., Cells: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1998; Hedrickson et al., Organic Chemistry 3rd edition, McGraw Hill, New York, 1970; Carruthers, W., and Coldham, I., Modern Methods of Organic Synthesis (4th Edition), Cambridge University Press, Cambridge, U.K., 2004; Curati, W.L., Imaging in Oncology, Cambridge University Press, Cambridge, U.K., 1998;

Welch, M.J., and Redvanly, C.S., eds. Handbook of Radiopharmaceuticals: Radiochemistry and Applications, J. Wiley, New York, 2003.

In some embodiments of the present teachings, biochemical characterization of F-AI-182 and other molecules can by performed agents via multiple binding and competitive displacement assays using PIB, AV-45, AZD4694, and BAYER 94-9172 for evaluation of targeted sites on Aβ, phosphorimaging studies in vitro. In vivo, ex vivo binding studies of AD brain homogenates and human AD brain sections can be performed, including specificity for Aβ evaluated compared with other biomarker proteins (tau, prion, TDP43,and α-synclein) prevalent in other neurodegenerative diseases to determine target selectivity, and perform metabolite studies.

In some embodiments of the present teachings, the inventors have biochemically characterized and validated agents via multiple in vitro bioassays to evaluate target sensitivity and specificity. The inventors can evaluate an Aβ-targeted agent of the present teachings to detect Aβ plaques via MicroPET imaging with pharmacokinetic analysis in APP transgenic mice and their WT counterparts. Investigations of the present teachings include a focused Structure-Activity Relationships (SAR) study to discover Aβ-targeted agents. The agents obtained from SAR can be biochemically characterized and evaluated through biodistribution and pharmacokinetic studies. The findings can be used to further characterize Aβ-targeted probes such as ^{18}F-AI-182.

In some embodiments of the present teachings, heterocyclic small organic molecules can be characterized and validated through various analytical steps. In various embodiments, molecules can also be radiolabeled, HPLC purified, and undergo a chemical characterization for developing as either radiopharmaceuticals or optical probes. In some aspects, he HPLC purified organic molecules and their radiolabeled counterparts can be tested for binding affinity. The compounds can be evaluated in animal models using either microPET imaging or multiphoton imaging. The agents that can detect Aβ plaques in mice can also undergo metabolite analysis *in vivo* for interrogating their translational potential. The agents that remain non-metabolized in the targeted tissue (brain) can also be investigated via pharmacokinetic studies in age-matched APP transgenic and control mice for assessing preliminary signal-to-noise ratios.

In some embodiments of the present teachings, binding assays to preformed Aβ fibrils or AD brain homogenates are disclosed.

In some configurations, the present teachings include preparation of Aβ fibrils or AD brain homogenates. In vitro binding assays can be performed to evaluate interactions of radiolabeled peptides with fibrils of $A\beta_{1-40/42}$ or extracts of AD brain homogenates (Choi, S.R., et al. Preclinical properties of ^{18}F-AV-45: a PET agent for Aβ plaques in the brain. J Nucl Med 50, 1887-1894 (2009)) in histopathological core of the Alzheimer's Disease Research Center (ADRC), using standard procedures described in the literature (Zhuang, Z., et al. Structure-activity relationships of imidazo[1,2-a]pyridines as ligands for detecting amyloid plaques in the brain. J Med Chem 46, 237-243 (2003)).

In some embodiments of the present teachings, binding assays to preformed fibrils or AD brain homogenate extracts can be performed using literature procedures (Klunk, W., et al. Uncharged thioflavin-T derivatives bind to amyloid-beta protein with high affinity and readily enter the brain. Life Sci 69, 1471-1484 (2001); Zhen, W., et al. Synthesis and amyloid binding properties of rhenium complexes: preliminary progress towards a reagent for SPECT imaging of Alzheimer's disease brain. J Med Chem 42, 2805-2815 (1999)). Prior to binding assays, the stock solution (2 μM) can be thawed. To aliquots of this stock solution, ^{18}F-AI-182 (also exemplified for either ^{18}F-AI-183 or ^{18}F-AI-187) can be added at various concentrations to a final concentration of 200 nM Aβ fibrils or 200μL of AD brain extracts (20-25μg). The aggregate-bound ^{18}F-AI-182 (or other analogues) can be collected on Whatman GF filters using Brandon M-24R cell harvester, washed, and counted in a γ-counter (Perkin Elmer). Inhibition constants (K_i) can be calculated as described previously (Han, H., Cho, C. & Lansbury, P.J. Technetium complexes for quantification of brain amyloid. J Am Chem Soc 118, 4506-4508 (1996)). Binding assay results can assist in evaluation of target specificity.

Some embodiments of the present teachings include evaluation of binding sites. In some configurations, binding assays can be done as described above in at least Example 8 below. Fixed concentrations of $A\beta_{1-42}$ fibrils and ^{18}F-AI-182 can be incubated in the presence of increasing concentration of cold competitors [thioflavin T (BS1), PIB (BS3 & BS1), FDDNP (BS3 & BS1) and BSB (BS2)]. Cold PIB, BSB, and FDDNP can be synthesized using published procedures. Experiments can also be performed with AV-45, BAYER 94-9172, and AZD4694. Measurements can be performed in triplicate and processed as described in the Examples. Agents competing for sites targeted by ^{18}F-AI-182 can be expected to displace ^{18}F-AI-182. Agents competing for different sites can be expected to have minimal effects. This analysis can identify binding site specificity on Aβ.

Some embodiments of the present teachings include immunohistochemistry and phosphorimaging of labeled probes ex vivo and in vivo.

In various configurations, staining experiments on mice (WT and APP transgenic) brain sections can be performed with either fluorescent Aβ-targeted F-AI-182 (exemplified for other analogues) or highly specific Aβ-targeted HJ3.4 mouse monoclonal antibody conjugated to Alexa 568 (DeMattos, R., O'dell, M., Parsadanian, M., Holtzman, D. & et.al. Clusterin promotes amyloid plaque formation and is critical for neuritic toxicity in a mouse model of Alzheimer's disease. Proc Natl Acad Sci USA 99, 10843-10848 (2002)), and phosphorimaging can also be performed using ^{18}F-AI-182. For in vivo experiments, ^{18}F-AI-182 (exemplified for other analogues) can be intravenously injected. After 2 min and up to 2h, mice (transgenic APP or APP/PS1 or WT) can be sacrificed, brains removed, dissected into two halves, processed and analyzed as described in this disclosure. Stained brain tissue sections of APPsw$^{+/-}$ can serve as positive controls and the non-stained tissue sections from brains of WT mice can provide negative controls. Radioactive brain tissues can be analyzed directly on a phosphorimager. ^{18}F-AI-182 (exemplified for other analogues) showing activity patterns consistent with the staining of unlabeled F-AI-182 or Aβ-targeted HJ3.4 mouse monoclonal antibody-Alexa 568 can be further examined.

In some embodiments, an Aβ-targeted heterocyclic molecule can stain or label Aβ plaques in cortical and hippocampal brain sections of APPsw$^{+/-}$ transgenic mice compared to none or minimal interaction in WT controls. Other embodiments can include labeled heterocyclic molecules that show a correlation between immunohistochemistry, phosphorimaging, and staining using Aβ-targeted HJ3.4 mouse monoclonal antibody-Alexa 568.

Some embodiments of the present teachings include evaluation of target specificity in human brain tissues using F-AI-182 or other Aβ-targeted agents.

In various configurations, specificity of F-AI-182 or other agents can be interrogated. Staining using F-AI-182 or immunohistochemistry can be performed using antibodies such as antibodies against Aβ (10D5, Eli Lilly), phosphorylated tau (PHF-1, Albert Einstein Medical School, Bronx, NY), ubiquitin (Dako, Glostrup, Denmark), α-synuclein (LB-509, Zymed, CA), and TDP-43 (Proteintech, Inc., Chicago, IL) using established methods (e.g., Burack, M.A., et al. In vivo amyloid imaging in autopsy-confirmed Parkinson disease with dementia. Neurology 74, 77-84 (2010)). Sections can be processed and analyzed on a Zeiss LSM 5

PASCAL confocal system coupled to a Zeiss Axiovert 200 microscope. Aβ targeted agents that demonstrate specificity for Aβ in brain sections of diseased subjects consistent with the expected regional distribution of plaques compared to their healthy controls and lack of cross reactivity with histopathological markers (tau, TDP43; and α-synuclein) can thus be investigated.

In some embodiments of the present teachings, metabolic stability of ^{18}F-AI-182 and/or other agents can be evaluated.

In various configurations, identified heterocyclic molecules can be assessed for metabolic stability for use in biomedical imaging applications both in vitro and in vivo using established procedures (e.g., Mathis, C., et al. Synthesis and evaluation of ^{11}C-labeled 6-substituted 2-arylbenzothiazoles as amyloid imaging agents. J Med Chem 46, 2740-2754 (2003); Sharma, V. Radiopharmaceuticals for assessment of multidrug resistance P-glycoprotein-mediated transport activity. Bioconjug .Chem. 15, 1464-1474 (2004)). In some embodiments, ^{18}F-AI-182, another agent, or a combination thereof can be incubated in either serum or human serum albumin at time points corresponding to uptake in vivo (5 min to 2 h) and filtered through filters (30kDa). Free and bound radiotracer can be calculated using previously describe methods (Bartholoma, M.D., et al. Effect of the prosthetic group on the pharmacologic properties of ^{18}F-labeled rhodamine B, a potential myocardial perfusion agent for positron emission tomography (PET). J Med Chem 55, 11004-11012 (2012)), and can be analyzed by radio-TLC scanner and radio-HPLC. For in vivo pharmacokinetics experiments, ^{18}F-AI-182 agent or other agents can be injected into mice via tail-vein, and mice can be sacrificed at the time points corresponding with data of our biodistribution studies (5 min to 2 h). Brain tissues, liver, and kidney can be removed (liver and kidney can be used to evaluate their metabolic stability in more stringent in vivo environments), sonicated, extracted and analyzed through radio-TLC and -HPLC. The ^{18}F-AI-182, other agents, or combinations thereof that demonstrate stability (>95%) at the targeted site through this analysis can be investigated further in nonhuman primates models.

Various embodiments of the present teachings include biodistribution and pharmacokinetic studies of ^{18}F-AI-182 or other agents in normal and transgenic APPsw$^{+/-}$ /PS1 mice.

In various configurations, pharmacokinetic analysis of unlabeled fluorescent small organic molecules, ^{18}F-heterocyclic molecules, and/or their ^{18}F-counterparts via

biodistribution studies in age-matched APPsw$^{+/-}$ transgenic mice and WT mice can be performed to determine target-specificity, and measure the detection of in vivo Aβ plaques, in APPsw$^{+/-}$/PS1 transgenic mice versus control mice, using either multiphoton imaging or microPET/CT imaging system by ^{18}F-heterocyclic small organic molecules.

In various configurations, agents can be evaluated in part by exploring the tissue distribution and kinetics of ^{18}F-AI-182 or other agents in normal mice and transgenic mice. Because these heterocyclic molecules can be labeled with ^{18}F using the methods described herein, biodistribution in normal mice can be determined. In such investigations, BL/6 (control mice; Taconic) or APPsw$^{+/-}$/PS1 (transgenic, Taconic) mice can be anesthetized by isoflurane inhalation and injected with ^{18}F-AI-182 or other agents (20 μCi in 50-100 μl saline) via bolus injection through a tail vein. Animals can be sacrificed by cervical dislocation at 2, 30, 60, and 120 min post-injection (n = 2-4) and data can be quantified into %ID/g as described (Sivapackiam, J., et al. Synthesis, molecular structure, and validation of metalloprobes for assessment of MDR1 P-glycoprotein-mediated functional transport. Dalton Trans 39, 5842-5850 (2010)). The brains can be removed and dissected into cerebellums and remaining whole brain fractions prior to weighing and counting to evaluate regional differences in the location of radiotracer in comparison with transgenic mice.

In some configurations, biodistribution and pharmacokinetic studies can assist in pharmacokinetic analysis, in general, and in evaluation of ^{18}F-AI-182 and/or other agents to permeate the BBB. In the absence of target, radiolabeled heterocyclic molecules can demonstrate uptake in brains of control mice, followed by washout of activity, resulting in low background signals. However, in the presence of plaques in transgenic APPsw$^{+/-}$PS1 mice, enhanced accumulation and retention in brains can allow noninvasive imaging of mice.

Various embodiments of the present teachings include validation and correlation of MicroPET imaging with ^{18}F-AI-182 and/or other agents.

In various configurations, validation and correlation of MicroPET imaging with ^{18}F-AI-182 and/or other agents can be performed in age-matched BL/6 (control) and APPsw$^{+/-}$/PS1 mouse models on MicroPET/CT Focus 220 scanner. Twenty-six frames can be acquired over a 3 hour scan period with the following frame sequences: 5x1 min, 5x2 min, 5x5 min, 8x10 min, and 3x20 min. Frames of the original reconstructed PET data can be summed, and this summed image can be co-registered with CT. Regions of interest can be drawn and

tissue-time activity curves (TAC) can be constructed by plotting the percent injected dose per c.c. tissue (%ID/cc).

From control mice, peak activity in the brain can be detected within the first 5 minutes post bolus injection and rapid clearance can be detected over the subsequent 2 to 3 hours. For APPsw$^{+/-}$/PS1 mice, the early peak can be comparable in magnitude and time, but tracer clearance can be significantly slower, reflecting binding of ^{18}F-AI-182 and/or other agents to Aβ plaques. The differences between normal and APPsw$^{+/-}$/PS1 mice can increase with time. This difference can be correlated with plaque load in a cohort of mice.

Various embodiments of the present teachings include SAR studies to develop agents including but not limited to heterocyclic molecules capable of detecting Aβ plaques in early stages of AD prior to clinical expression.

In various configurations, candidate Aβ-targeted imaging agents can include but are not limited to the following characteristics: a) specific binding to Aβ plaques; b) specific binding to a prevalent binding site on Aβ; c) high first-pass extraction into the brain and region specific binding consistent with pathological localization of Aβ; d) minimal binding to the white matter for sensitivity to detect plaques at earlier stages of the disease to segregate pools of patients likely to benefit from therapeutics, and e) excretion from organs of the body over a time period for MIRD analysis. ^{18}F-AI-182 as an agent demonstrates the above listed characteristics. ^{18}F-AI-182 can offer a scaffold template for further SAR exploration to develop second generation Aβ-targeted agents.

Various embodiments of the present teachings include characterization of molecules via standard analytical tools.

In various configurations, these embodiments can include docking studies that can utilize Glide and ADME calculations using QProp. Molecules can be chemically characterized via standard analytical tools. Binding affinities with other agents, such as PIB, AV-45, and AZD4694 can be compared. Molecules demonstrating different binding sites on Aβ compared to these agents can be identified. Molecules demonstrating high first-pass extraction into brains of transgenic mice and low white matter binding to nonhuman primate or human tissues can be characterized in vivo through biochemical characterization via multiple binding and competitive displacement assays as well as through biodistribution and pharmacokinetic studies.

Examples

The present teachings including descriptions provided in the Examples, are not intended to limit the scope of any claim or aspect. Unless specifically presented in the past tense, an example can be a prophetic or an actual example. The following non-limiting examples are provided to further illustrate the present teachings. Those skilled in the art, in light of the present disclosure, will appreciate that many changes can be made in the specific embodiments that are disclosed and still obtain a like or similar result without departing from the spirit and scope of the present teachings.

Example 1

This example illustrates an Aβ targeted probe of the present teachings.

Utilizing the agent F-AI-182, a heterocyclic molecule was synthesized via multiple steps, purified via chromatography, crystalized in methylene chloride and pentane mixture, and the single crystal structure was determined. F- AI-182 was further characterized via standard analytical tools, including ^{1}H NMR, proton-decoupled ^{11}C-NMR, ^{19}F NMR, high resolution mass spectroscopy (HRMS), and analyzed for uniformity using HPLC (Waters) equipped with a dual λ detector (2487) set to 280 and 364nm on a semi-preparative C-18 column (Vydac).

Example 2

This example illustrates ^{18}F-AI-182 synthesis and testing.

For bioassays described in following sections, ^{18}F-AI-182 was synthesized via standard nucleophilic substitution, employing 2,2,2-kryptofix/^{18}F and AI-182-tosylate analog, purified on a C-18 (Vydac) column employing a gradient eluent mixture of ethanol and water, using radio-HPLC system equipped with a radiodetector (Bioscans). The fraction at R_t= 15 min was collected, concentrated, and resuspended in PBS to 5% ethanol for all radiotracer bioassays. Furthermore, ^{18}F-AI-182 was also characterized by spiking with an analytically characterized sample of an unlabeled F-AI-182 counterpart, prior to injection on the radio-HPLC.

The agent F-AI-182 shows concentration dependent and saturable binding (binding constant, 59±7nM; FIG. 1) to preformed Aβ1-42 fibrils, stains both fibrillar and diffuse

plaques ex vivo in the hippocampus and cortical region of brain sections in APPsw$^{+/-}$/PS1 mice (FIG. 2) and human tissues (FIG. 5), and incorporates F-18 (^{18}F; $t_{1/2}$ =110 min), a radionuclide for medical PET imaging (Mahmood, A. & Jones, A. Technetium Radiopharmaceuticals. Handbook of Radiopharmaceuticals. 323-362 (2003); Eckelman, W. The Development of ^{99m}Tc Radiopharmaceuticals for Perfusion and Biochemistry: In Technetium and Rhenium in Chemistry and Nuclear Medicine 3. M. Nicolini, G. Bandoli and U. Mazzi (Eds.). Cortina Int., Verona, Italy. pp. 571-580. (1990); Narra, R., et al. A Neutral Tc-99m Complex for Myocardial Imaging. J. Nucl. Med. 30, 1830-1837 (1989); Stadalnik, R., Kudo, M., Eckelman, W. & Vera, D. In vivo functional imaging using receptor-binding radiopharmaceuticals: 99mTc-galactosyl-neoglycoalbumin (TcNGA). Investigative Radiology 28, 64-70 (1993)). The radiolabeled counterpart ^{18}F-AI-182 showed a transient high uptake in brains (7.28± 0.46% %ID/g) of FVB mice (FIG. 3), and followed by washout from blood (25% faster than AV-45; FIG. 4) in absence of targeted plaques and remains non-metabolized in human serum. The high first-pass extraction into brain coupled with faster clearance from the blood pool and lack of metabolites offer characteristics that could potentially enhance overall signal to background ratios and assist image analysis. Multi-photon microscopy in live APPsw$^{+/-}$/PS1 (15 months old) mice demonstrated that F-AI-182 labels plaques in brain parenchyma and blood vessels (CAA), by 5-min post intravenous administration (FIG. 6). The F-AI-182 showed facile clearance from non-targeted regions and the plaques remain labeled for investigated time points.

Binding assays of F-AI-182 with preformed $A\beta_{1-42}$ aggregates were performed in PBS. Following excitation at 410nm, fluorescence spectrum of F-AI-182 recorded in PBS containing 1% ethanol showed a broad emission peak 540-610nm with E_{max} at 570nm. Upon incubation with preformed of Aβ(1-42) aggregates, the peak 570 nm showed remarkable enhancement in the fluorescence indicating binding to Aβ aggregates, similar to enhancement in fluorescence of thioflavin T in PBS (a positive control; data not shown). Fluorescence was not observed using Aβ aggregates alone in PBS upon excitation at 410 nm (a negative control). Binding assays of the F-AI-182 with preformed $A\beta_{1-42}$ aggregates indicated a nearly saturable binding with a K_d = 59±7nM (FIG. 1). Comparative analyses can be performed with other compounds such as AV-45, BAYER 94-9172, and AZD4694. An agent can be interacting with either of the two modestly high affinity binding sites (BS1& BS2) or

recognizing an entirely new site on $A\beta_{1-42}$. F-AI-182 can register different complementary binding sites in relation to Aβ-pathophysiology compared to current agents.

Example 3

This example illustrates ex vivo staining studies.

Ex vivo staining studies were performed on brain sections (50 μm) of an APPsw$^{+/-}$/PS1 mouse (24 months old) and a control WT mouse (BL/6; 24 months old) using well-established procedures. As a positive control, HJ3.4 Aβ monoclonal antibody-Alexa 568 was used. Brain sections of APPsw$^{+/-}$ PS1$^{+/-}$mice showed abundant staining of Aβ compared with minimal levels in WT mouse (FIG. 2). Using F-AI-182 (100nM, 60 min), abundant staining of fibrillar and diffuse plaques in the hippocampus and cortical regions of brain sections in APPsw$^{+/-}$ PS1$^{+/-}$mice was observed. By comparison, no staining in WT mice was seen either with F-AI-182 or the antibody indicating the targeting specificity of F-AI-182. The slides were analyzed on a Zeiss LSM 5 PASCAL confocal system coupled to a Zeiss Axiovert 200 microscope.

Example 4

This example illustrates biodistribution studies of ^{18}F-AI-182.

For in vivo imaging of Aβ plaques, the basic pharmacokinetic model in an unaffected normal brain involves high initial penetration of the agent, followed by rapid clearance due to lack of a binding target. However, in AD brains, high initial penetration can be followed by regional retention as the agent binds to Aβ thus leading to differential kinetics. To accomplish this objective, biodistribution studies of ^{18}F-AI-182 were performed in normal FVB mice for assessment of signal to noise ratios and clearance profiles. Brain uptake of ^{18}F-AI-182 was analyzed in terms of percent injected dose per gram of the brain tissue (%ID/g). Biodistribution studies with HPLC purified ^{18}F-AI-182 in normal mice revealed a transient brain uptake value of 7.28± 0.46% ID/g and 1.54 ± 0.06% ID/g, 5 min and 120 min post tail-vein injection, respectively, giving a 5 min/120 min clearance a ratio of 4.73, providing evidence for the ability of ^{18}F-AI-182 to cross the BBB and permeate into brain in vivo (FIG. 3). This initial brain uptake value (5 min) in normal mice is approximately 15-fold high compared with our Aβ-targeted ^{99m}Tc-Peptides (Harpstrite, S.E., Prior, J., Binz, K., Piwnica-Worms, D. & Sharma, V. ^{99m}Tc-Peptide conjugates for imaging β-amyloid in the brain. ACS Med Chem Lett (2013) under review). Additionally, compared to ^{18}F-AV-45 (Liver: 17.0 ± 0.69 (2 min), 4.96 ± 0.90 (120 min); Kidney: 14.19 ± 2.34 (2 min), 2.19 ± 0.36 (120 min),

^{18}F-AI-182 clears rapidly from non-targeted tissues, such as liver and kidney (Liver: 16.32 ± 1.41 (5 min), 2.71 ± 0.21 (120 min); Kidney: 6.76± 1.57 (5 min), 1.57 ± 0.08 (120 min) and these clearance profiles could translate into better MIRD analysis. For comparison, ^{18}F-AV-45 demonstrates brain uptake values of 7.33 ± 1.54 %ID/g and 1.80 ± 0.07 %ID/g at 2 min and 120 min post-injection (Choi, S.R., et al. Preclinical properties of 18F-AV-45: a PET agent for Abeta plaques in the brain. J Nucl Med 50, 1887-1894 (2009)) respectively, thus providing a 2 min/120 min clearance ratio of 4.07 in normal mice that lack target sites (FIG. 3). Net brain uptake of ^{18}F-AI-182 is 1.2- fold higher than that of ^{18}F- AV-45. Our data indicates a 5 min uptake compared with a 2 min data point reported for ^{18}F-AV-45 thus we do expect these 2min/120 min ratios to be much superior, upon comparative analysis at the same time points. ^{18}F-AI-182 undergoes 25% faster blood clearance from 5 min to 120 min compared with the 18F-AV-45 (FIG. 4). Compared with ^{11}C-PIB (Mathis, C., et al. Synthesis and evaluation of ^{11}C-labeled 6-substituted 2-arylbenzothiazoles as amyloid imaging agents. J Med Chem 46, 2740-2754 (2003)) and ^{18}F-AV-45 (Choi, S.R., et al. Preclinical properties of ^{18}F-AV-45: a PET agent for Abeta plaques in the brain. J Nucl Med 50, 1887-1894 (2009)) that undergo facile metabolism in vivo, ^{18}F-AI-182 remains non-metabolized in human serum.

Example 5

This example illustrates staining experiments with an F-AI-182 agent.

Staining experiments were performed with human brain tissues. Tissue samples were obtained from the frontal lobe of clinically and neuropathologically well-characterized cases. The neuropathological diagnosis of AD was based on the criteria of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (Mirra, S., et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. Neurology 41, 479-486 (1991)) or the National Institute of Aging-Reagan Institute (NIA-RI) (Hyman, B. & Trojanowski, J. Consensus recommendations for the postmortem diagnosis of Alzheimer disease from the National Institute on Aging and the Reagan Institute Working Group on diagnostic criteria for the neuropathological assessment of Alzheimer disease. J Neuropathol Exp Neurol 56, 1095-1097. (1997)). For experiments, highly specific Aβ-targeted antibody (10D5, Eli Lilly, a positive control, used in histopathological core of the ADRC post-mortem cases) confirmed the presence of Aβ plaques. Aβ-targeted F-AI-182 showed abundant staining of Aβ plaques

in the hippocampus of a 90 year-old female with AD (FIG. 5). Additionally, F-AI-182 demonstrated labeling of both the fibrillar and the diffuse plaques. The ability of the F-AI-182 agent to detect diffuse plaques represents an advancement to enable PET imaging of mildly demented individuals (an earlier manifestation of AD) prior to clinical expression (Price, J.L., et al. Neuropathology of nondemented aging: presumptive evidence for preclinical Alzheimer disease. Neurobiology of aging 30, 1026-1036 (2009); Morris, J.C., et al. Cerebral amyloid deposition and diffuse plaques in "normal" aging: Evidence for presymptomatic and very mild Alzheimer's disease. Neurology 46, 707-719 (1996); Price, J.L. & Morris, J.C. Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. Annals of neurology 45, 358-368 (1999); Schmitt, F.A., et al. "Preclinical" AD revisited: neuropathology of cognitively normal older adults. Neurology 55, 370-376 (2000)), thereby offering a window of opportunity for therapeutic interventions for better management of disease.

To demonstrate ability of the agent to label plaques *in vivo*, multiphoton imaging was conducted in live APP/PS1 12 month old mice, post intravenous injection of F-AI-182. Prior to imaging, dextran-Texas Red was injected for mapping the blood vessels. Following labeling of blood vessels, F- AI-182 (2mg/kg, dissolved in DMSO/PEG; 20:80) was intravenously injected. A zstack image series was acquired from cortex surface to a depth of approx. 100µm using microscope LSM 510META NLO (Carl-Zeiss Inc). Multi-photon imaging in live APP/PS1 mice (15 months old) demonstrated that F-AI-182 labeled plaques in blood vessels (CAA) and brain parenchyma. The labeling of brain parenchymal plaques was visible within 10 min, indicating facile clearance from non-targeted regions and remained labeled for 30 min (FIG. 6). Multi-photon imaging can be done using ^{18}F-AI-182, other agents, or second generation agents (Bacskai, B., et al. Four-dimensional multiphoton imaging of brain entry, amyloid binding and clearance of an amyloid-β ligand in transgenic mice. Proc Natl Acad Sci USA 100, 12462-12467 (2003)).

Example 6

This example illustrates methods of assessment of binding sites.

There is an NMR-deduced structure in the protein data bank for $A\beta_{1-42}$ (PDB ID: 2BEG). To assess binding sites of PIB, AV-45, and AI-182, using procedures described earlier in our laboratories (Sundaram, G.S.M, Harpstrite, S.E., Kao, J.L., Collins, S.D. & Sharma, V. A New Nucleoside Analogue with Potent Activity against Mutant sr39 Herpes

Simplex Virus-1 (HSV-1) Thymidine Kinase (TK). Organic letters (2012)), we used sitemap to determine binding sites on $A\beta_{1-42}$, generated a grid, then docked PIB, AV-45, and AI-182 to determine rank order (AV-45 > F-AI-182> PIB) based upon the Glide score (FIG. 7). Ligand interaction diagram indicated that PIB 6-hydroxy substituent of the benzothazole ring forms a hydrogen bond with Leu 17 and smallest surface of hydrophobic interactions with amino acid residues of Aβ-42. While pyridine ring of AV-45 participated in π–π interactions with Phe 19 as well as highest surface of hydrophobic interactions, F-AI-182 retained π–π interactions but also shows intermediate hydrophobic interaction surface thus supporting the rank order of the glide score. Building on the principles that: a) π electrons play a role in biochemical interactions (Kumpf, R.A. & Dougherty, D.A. A mechanism for ion selectivity in potassium channels: computational studies of cation-pi interactions. Science 261, 1708-1710 (1993)); b) Aβ recognizes planner molecules; and c) extended conjugation systems are more likely to offer more flexibility for interaction with other sites, we can explore a focused SAR around two scaffolds : a) slight variations in position of the heteroatoms in the six membered pyridine ring or 5-membered ring of benzothioazole in addition to variation in number of ethylene glycol moieties on the 6-position of benzothiazole ring and b) modification of dialkyl amino group with other functional groups.

Example 7

This example illustrates labeling of Aβ plaques in APPsw+/- (24 months old) mice using F-AI-183.

Examples of brain tissue section staining of APPsw+/- (24 months old) mice using F-AI-183 are shown in FIG. 8. Arrows indicate labeling of Aβ plaques (arrows, fibrillar plaques). The slides were analyzed using a Nikon Ti-E PFS inverted microscope equipped with a Nikon 10x 0.3 NA Plan APO objective, Prior H117 ProScan flat top linear encoded stage, and Prior Lumen 200PRO illumination system with standard DAPI and FITC filter sets. The images were acquired using a Photometries CoolSNAP HQ2 digital camera and MetaMorph microscopy automaton, and imaging software. Images were processed and analyzed using the Image J software package (NIH).

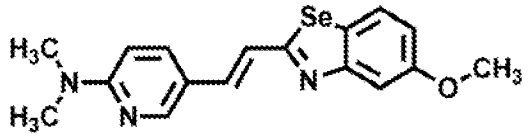
Example 8

This example illustrates detection of compact Aβ plaques in brain cross-sections of frontal lobe by F-AI-183.

F-AI-183 detected compact Aβ plaques in the brain cross-sections of frontal lobe of an 88-year-old female with neuropathologically confirmed Alzheimer's disease as shown in FIG 9. The fluorescent probe (F-AI-183) labels fibrillar amyloid (arrow). The slides were analyzed on a using a Nikon Ti-E PFS inverted microscope equipped with a Nikon 10x 0.3 NA Plan APO objective, Prior H117 ProScan flat top linear encoded stage, and Prior Lumen 200PRO illumination system with standard DAPI and FITC filter sets. The images were acquired using a Photometrics CoolSNAP HQ2 digital camera, and MetaMorph microscopy automaton, and imaging software. Images were processed and analyzed using the Image J software package (NIH).

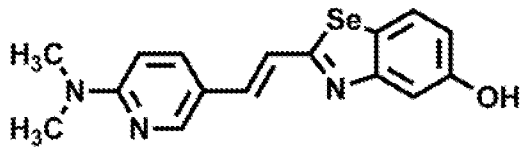
Example 9

This example illustrates NMR data for some compounds of the present teachings.



25

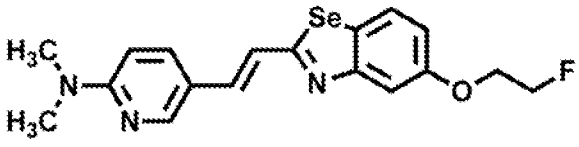
^{1}H NMR (400 MHz, $CDCl_3$): 3.17 (s, 6H), 3.83 (s, 3H), 6.59 (d, J = 8.4 Hz, 1H), 7.02 (d, J = 9.2 Hz, 1H), 7.16 (d, J = 16.0 Hz, 1H), 7.25 (t, J = 14.0 Hz, 2H), 7.74 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 8.45 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 37.14, 55.77, 104.13, 106.05, 115.31, 118.33, 119.21, 123.02, 134.05, 134.22, 148.93, 159.15, 171.33



26

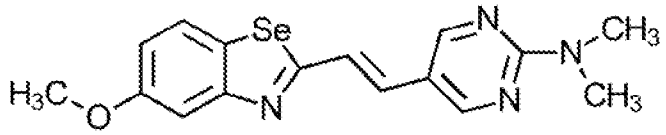
^{1}H NMR (400 MHz, $CDCl_3$): 3.10 (s, 6H), 6.75 (d, J = 8.8 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 16.4 Hz, 1H), 7.43 (d, J = 16.4 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 8.18 (d, J = 8.4 Hz, 1H), 8.37 (s, 1H), 9.62 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 38.21, 107.08,

108.21, 109.62, 115.05, 116.25, 119.69, 121.37, 125.88, 126.44, 135.49, 136.17, 136.54, 157.05, 172.69.

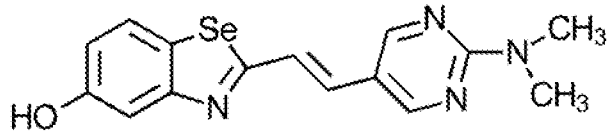


24 (F-AI-183)

^{1}H NMR (400 MHz, $CDCl_3$): 3.15 (s, 6H), 4.28 (d, J = 27.8 Hz, 2H), 4.77 (d, J = 47.2 Hz, 2H), 6.56 (dd, J = 8.8, 3.2 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 7.14 (d, J = 16.4 Hz, 1H), 7.27 (d, J = 6.0 Hz, 1H), 7.52 (d, J = 16.8 Hz, 1H), 7.72(dd, J = 8.6, 3.0 Hz, 2H), 8.31 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 38.12, 67.29, 67.50, 81.00, 82.70, 106.08, 107.81, 115.05, 119.31, 120.78, 124.98, 134.41, 134.80, 136.36, 149.22, 157.85; ^{19}F NMR (282 MHz, $CFCl_3$): -224 ppm; HRMS (FAB) m/z calc. for $C_{18}H_{18}FN_3OSe$: $[M]^+$ 391.0599; found: 391.0602.

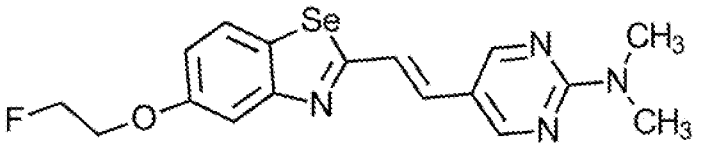


^{1}H NMR (400 MHz, $CDCl_3$): 3.24 (s, 6H), 3.87 (s, 3H), 6.93 (d, J = 7.2 Hz, 1H), 7.16 (s, 2H), 7.50 (s, 1H), 7.70 (d, J = 7.4 Hz, 1H), 8.50 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 37.27, 55.52, 107.18, 114.85, 117.07, 121.54, 124.81, 128.10, 132.81, 156.54, 159.16, 161.64, 172.49



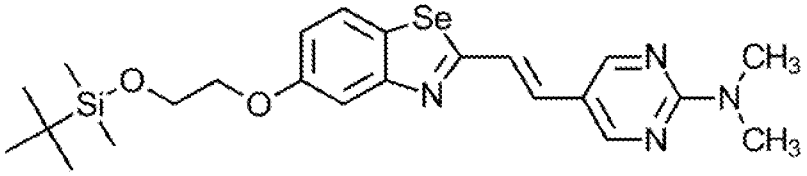
^{1}H NMR (400 MHz, $CDCl_3$): 3.17 (s, 6H), 6.83 (dd, J = 8.0, 1.6 Hz, 1H), 7.30 (s, 1H) 7.40 (d, J = 8.8 Hz, 2H), 7.82 (d, J = 8.8 Hz, 1H), 8.75 (s, 2H), 9.63 (s, 1H); ^{13}C NMR (100

MHz, $CDCl_3$): 39.28, 109.72, 115.23, 117.66, 121.91, 125.92, 126.55, 133.49, 156.95, 157.07, 157.49, 161.59, 172.49

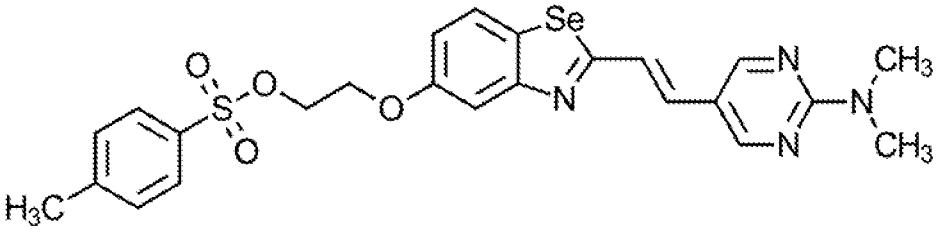


(F-AI-187)

^{1}H NMR (400 MHz, $CDCl_3$): 3.24 (s, 6H), 4.28 (d, J = 27.6 Hz, 2H), 4.80 (d, J = 47.2 Hz, 2H), 6.97 (d, J = 7.2 Hz, 1H), 7.17 (bs, 1H), 7.50 (s, 1H), 7.72 (d, J = 7.2 Hz, 1H), 8.52 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 37.28, 67.31, 67.51, 80.97, 82.67, 107.95, 110.00, 115.36, 117.04, 121.46, 125.01, 128.78, 133.01, 156.47, 156.57, 157.93, 158.57, 161.66, 172.72 ; ^{19}F NMR (282 MHz, $CFCl_3$): -224 ppm; HRMS (FAB) m/z calc. for $C_{17}H_{18}FN_3OSe$: $[M]^+$ 392.0594; found: 392.0603.

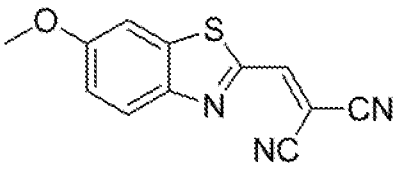


^{1}H NMR (400 MHz, $CDCl_3$): 0.12 (s, 6H), 0.92 (s, 9H), 3.24 (s, 6H), 4.01-4.03 (m, 2H), 4.09-4.12 (m, 2H), 6.94 (dd, J = 8.8, 2.4 Hz, 1H), 7.17 (d, J = 1.2 Hz, 1H), 7.50 (d, J = 2.4 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 8.53 (s, 2H) ; ^{13}C NMR (100 MHz, $CDCl_3$): 31.04, 42.24, 68.44, 76.22, 110.76, 112.22, 121.21, 124.34, 129.86, 140.02, 142.74, 149.96, 152.44, 162.68, 172.86.

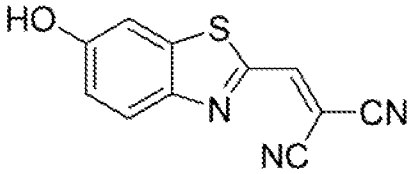


^{1}H NMR (400 MHz, $CDCl_3$): 2.43 (s, 3H), 3.24 (s, 6H), 4.20 (bs, 2H), 4.41 (bs, 2H), 6.71 (d, J = 9.0 Hz, 1H), 6.81 (d, J = 9.0 Hz, 1H), 7.17-7.41 (m, 4H), 7.65-7.69 (m, 1H), 7.82 (d, J = 7.6 Hz, 2H),8.52 (s, 1H), 8.66 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$): 21.64, 37.23,

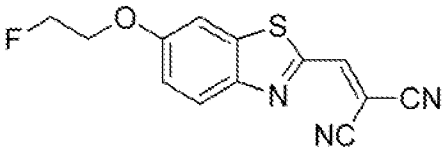
65.72, 68.06, 108.04, 108.25, 115.08, 115.50, 116.88, 121.41, 124.78, 124.96, 125.25, 128.00, 129.85, 131.04, 133.12, 144.95, 156.60, 157.35, 158.59, 162.68, 171.84



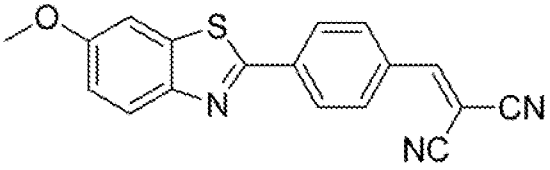
^{1}H NMR (300 MHz, CD_3CN): 8.25 (s, 1H), 8.08 (d, 1H), 7.63 (d, 1H), 7.27 (dd, 1H), 3.92 (s, 3H)



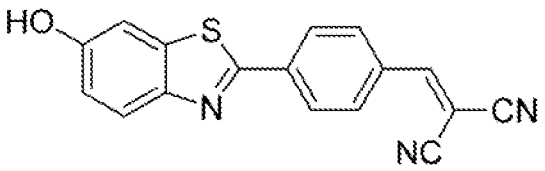
^{1}H NMR (300 MHz, acetone-d_6): 10.00 – 9.00 (br, s, 1H), 8.51 (s, 1H), 8.09 (d, 1H), 7.63 (d, 1H), 7.28 (dd, 1H)



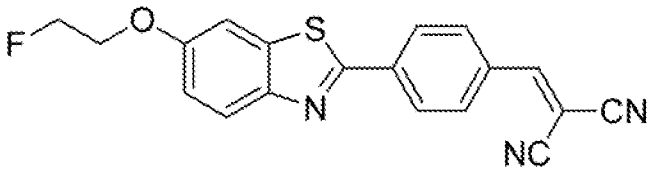
^{1}H NMR (300 MHz, acetone-d_6): 8.55 (s, 1H), 8.16 (d, 1H), 7.85 (d, 1H), 7.39 (d, 1H), 4.93 – 4.29 (m, 4H).



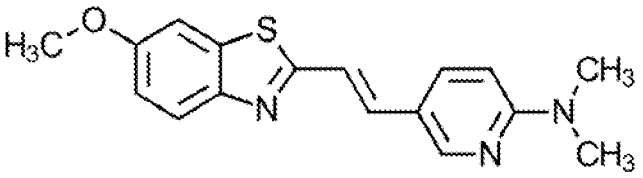
^{1}H NMR (300 MHz, dmso-d_6): 8.59 (s, 1H), 8.25 (d, 2H), 8.08 (d, 2H), 8.00 (d, 1H), 7.77 (d, 1H), 7.18 (dd, 1H), 3.87 (s, 3H)



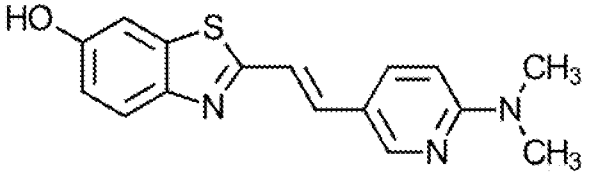
^{1}H NMR (300 MHz, acetone-d_6): 9.00 (br, s, 1H), 8.39 (s, 1H), 8.30 (d, 2H), 8.18 (d, 2H), 7.94 (d, 1H), 7.52 (d, 1H), 7.14 (dd, 1H). MS(LRESI) *m/z* = 304.0547 ($M+H^+$).



^{1}H NMR (300 MHz, acetone-d_6): 8.39 (s, 1H), 8.31 (d, 2H), 8.18 (d, 2H), 8.02 (d, 1H), 7.73 (d, 1H), 7.25 (dd, 1H), 4.94 – 4.36 (m, 4H). MS(LRESI) m/z = 350.2 ($M+H^+$).

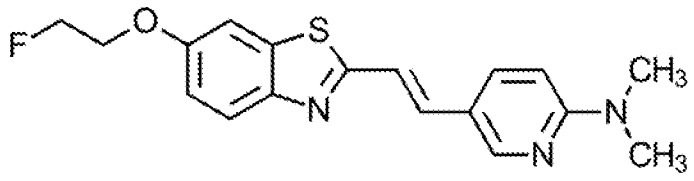


^{1}H NMR (400 MHz, $CDCl_3$): 3.15 (s, 6H), 3.88 (s, 3H), 6.55 (d, J = 8.4 Hz, 1H), 7.04 (d, J = 9.2 Hz, 1H), 7.14 (d, J = 16.0 Hz, 1H), 7.29 (t, J = 14.0 Hz, 2H), 7.71 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 8.29 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 38.14, 55.79, 104.13, 106.05, 115.31, 118.0, 119.41, 123.02, 134.08, 134.22, 148.93, 159.15, 165.33



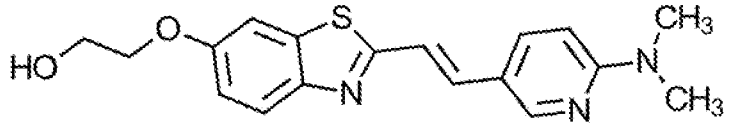
^{1}H NMR (400 MHz, $CDCl_3$): 3.03 (s, 6H), 6.65 (d, *J* = 8.4 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 7.24-7.32 (m, 2H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.90 (d, *J* = 7.6 Hz, 1H), 8.29 (s, 1H),

9.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 38.04, 106.51, 107.08, 116.11, 118.03, 119.58, 123.17, 134.13, 134.96, 135.60, 147.47, 149.36, 155.90, 159.25, 163.97.

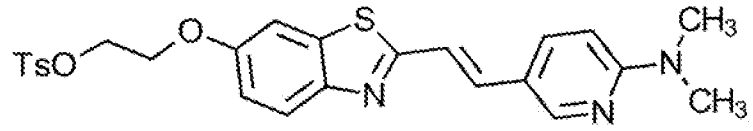


AI-182

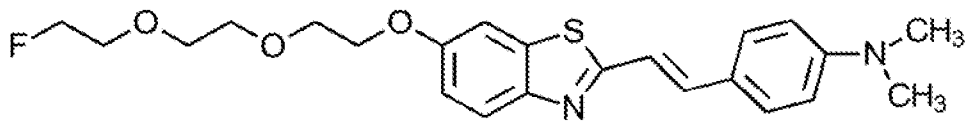
^{1}H NMR (400 MHz, $CDCl_3$): 3.14 (s, 6H), 4.28 (d, J = 26.0 Hz, 2H), 6.65 (d, J = 8.4 Hz, 1H), 4.77 (d, J = 49.6 Hz, 2H), 6.55 (d, J = 8.8 Hz, 1H), 7.08 (d, J = 9.2 Hz, 1H), 7.13 (d, J = 16.4 Hz, 1H), 7.26-7.33 (m,2H), 7.70 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 9.2 Hz, 1H), 8.29 (s, 1H), 9.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 38.10, 38.13, 67.63, 67.84, 81.01, 82.70, 105.32, 106.05, 115.67, 117.86, 119.34, 123.12, 134.23, 134.33, 148.98, 156.36, 159.17, 165.74; ^{19}F NMR (282 MHz, $CFCl_3$): -224 ppm; HRMS (FAB) m/z calc. for $C_{18}H_{18}FN_3OS$: $[M]^+$ 343.1155; found: 343.1152.



^{1}H NMR (400 MHz, $CDCl_3$): 3.17 (s, 6H), 3.96 (s, 2H), 4.20 (s, 2H), 6.56 (d, J = 8.8 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 7.14(d, J = 16.4 Hz, 1H), 7.24-7.32 (m, 2H), 7.72 (d, J = 8.8 Hz, 2H), 7.82 (d, J = 8.8 Hz, 1H), 8.29 (s, 1H).



^{1}H NMR (400 MHz, $CDCl_3$): 2.42 (s, 3H), 3.16 (s, 6H), 4.22 (s, 2H), 4.41 (s, 2H), 6.56 (d, J = 8.8 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 7.14(d, J = 16.4 Hz, 1H), 7.24-7.32 (m, 2H), 7.72 (d, J = 8.8 Hz, 2H), 7.82 (d, J = 8.8 Hz, 1H), 8.22-8.43 (m, 3H), 8.51-8.92 (m, 2H).

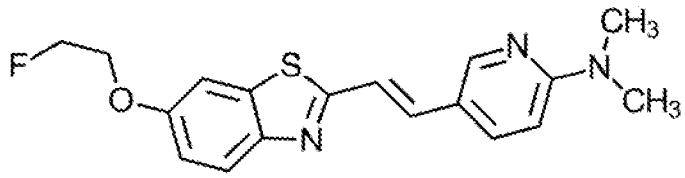


^{1}H NMR (400 MHz, $CDCl_3$): 3.14 (s, 6H), 3.61-3.80 (m, 6H), 3.82 (s, 2H), 4.22 (s, 2H), 4.44 (d, J = 49.4 Hz, 2H), 6.55 (d, J = 8.8 Hz, 1H), 7.08 (d, J = 9.2 Hz, 1H), 7.13 (d, J = 16.4 Hz, 1H), 7.26-7.33 (m,2H), 7.70 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 9.2 Hz, 1H), 8.29 (d, J = 9.2 Hz, 2H); ^{19}F NMR (282 MHz, $CFCl_3$): -224 ppm; HRMS (FAB) m/z calc. for $C_{23}H_{18}FN_3O_3S$: $[M]^+$ 430.1726; found: 430.1780.

Example 10

This example illustrates imaging of cancer cells using AI-182 as a fluorescent probe.

In these experiments, human carcinoma cells were incubated with AI-182



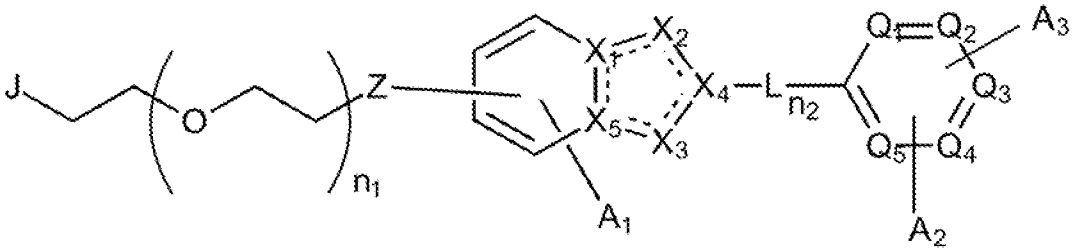
(5μM) at 37°C in the presence of 5% CO2 for 30 min, and examined using a Nikon Ti-E PFS inverted high resolution microscope equipped with a Nikon (Magnification: 20x) Plan APO objective, Prior H117 ProScan flat top linear encoded stage, and Prior Lumen 200PRO illumination system with standard DAPI and FITC filter sets. Results are shown in FIG. 10. Top row: Live Cell Imaging of Human Glioblastoma (U87) Cells Using AI-182. Middle row: Live Cell Imaging of Human Pancreatic Cancer Cells (PANC1) Using AI-182. Bottom row: Live Cell Imaging of Human Pancreatic Cancer Cells (Mia PaCa-2) Using AI-182. Note accumulation of the probe within cells.

All references cited herein are incorporated by reference, each in its entirety. Applicant reserves the right to challenge any conclusions presented by any of the authors of any reference.

Claims

What is claimed is:

1. A compound or a pharmaceutically acceptable salt thereof of structure



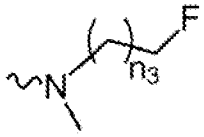
wherein:

J is selected from the group consisting of a halogen, hydroxy, cyano, $COOR^1$, carboxy, amide, immino, nitro, NR^2R^3 and OR^4;

n_1 is an integer from 0-4;

Z is selected from the group consisting of CH_2, O, NR^5, S and Se;

each of A_1, A_2 and A_3 is independently selected from the group consisting of H, F, Cl, Br, I, CN, OH, NO_2, NHR^6, NR^7R^8,OR^9, SR^{10}, $COOR^{11}$, COR^{12}, sulfonic acid,



wherein ~ is a bond , 2-ethylidenemalononitrile, (*E*)-2-(but-2-en-1-ylidene)malononitrile, 2-((2E,4E)-hexa-2,4-dien-1-ylidene)malononitrile, acetyl, -$(OCH_2CH_2)_{n_4}$- and R^{13};

n_3 is an integer from 0-4;

n_4 is an integer from 0-4;

--- is a single or double bond;

X_1 is selected from the group consisting of C and N;

X_2 is selected from the group consisting of CH_2, CH, O, NR^{14}, S, Se and N;

X_3 is selected from the group consisting of CH_2, CH, O, NR^{15}, S, Se and N;

X_4 is C or CH;

X_5 is C, CH or N;

wherein X_4 is CH, X_2 and X_4 are linked by a single bond and X_3 and X_4 are linked by a single bond, or X_4 is C, X_2 and X_4 are linked by a single bond and X_3 and X_4 are linked by a double bond, or X_4 is C, X_2 and X_4 are linked by a double bond and X_3 and X_4 are linked by a single bond;

wherein when X_1 is C then X_1 and X_5 are linked by a double bond;

wherein when X_1 is N, then X_1 and X_5 are linked by a single bond;

wherein when X_2 is NR^{14}, S, O or Se, then X_2 and X_4 are linked by a single bond;

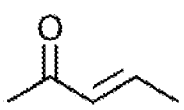
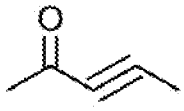
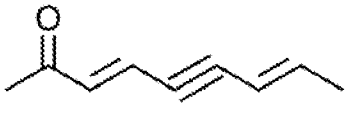
wherein when X_2 is N, then X_2 and X_4 are linked by a double bond;

wherein when X_3 is NR^{15}, S, O or Se, then X_3 and X_5 are linked by a single bond;

wherein when X_3 is N, then X_3 and X_4 are linked by a double bond;

wherein when both the X_2 and X_5 are N, then X_1 and X_2 are linked by a double bond, X_2 and X_4 are linked by a single bond, X_3 and X_4 are linked by a double bond, and X_3 and X_5 are linked by a single bond;

wherein when both the X_1 and X_2 are N, then X_2 and X_4 are linked by a double bond, X_3 and X_4 are linked by a single bond, X_3 and X_5 are linked by a double bond, and X_1 and X_5 are linked by a single bond;

L is selected from the group consisting of (C_1-C_4) alkyl, (C_3-C_6) cycloalkyl, (C_2-C_8) linear alkene, (C_3-C_8) branched alkene, (C_2-C_8) alkyne,  ,  and  ;

n_2 is an integer from 0-4;

each of Q_1, Q_2, Q_3, Q_4 and Q_5 is independently selected from the group consisting of C and N, with provisos that at least two of Q_1, Q_2, Q_3, Q_4 and Q_5 are C and at least one of Q_1, Q_2, Q_3, Q_4 and Q_5 is N; and

each of R^1-R^{15} is independently selected from the group consisting of H, C_{1-12} linear alkyl, C_{2-12} linear alkene, C_{2-12} linear alkyne, C_{3-12} branched chain alkyl, C_{3-12} branched chain alkene, C_{3-12} branched chain alkyne and C_{3-7} cycloalkyl aryl and a combination thereof.

2. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 1, wherein the halogen is selected from the group consisting of Cl, F, Br and I.

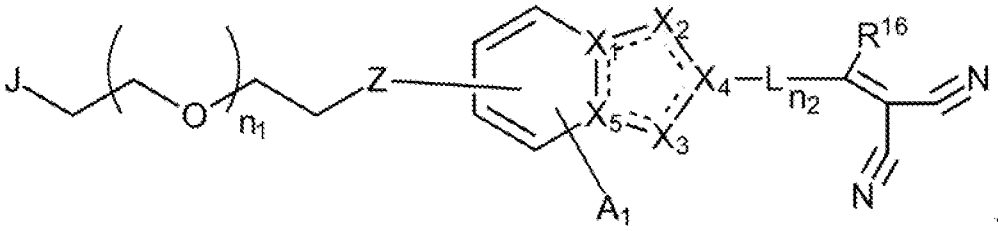
3. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 1, wherein the halogen is selected from the group consisting of F-18, Br-75, Br-76, Br-77, I-123, I-124, I-125 and I-131.

4. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 1, wherein R^4 comprises a radionuclide.

5. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 1, wherein R^4 comprises a C-11.

6. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 1, wherein R^{13} comprises a radionuclide.

7. A compound or a pharmaceutically acceptable salt thereof, of structure



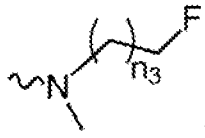
wherein:

J is selected from the group consisting of a halogen, hydroxy, cyano, $COOR^1$, carboxy, amide, immino, nitro, NR^2R^3 and OR^4;

n_1 is an integer from 0-4;

Z is selected from the group consisting of CH_2, O, NR^5, S and Se;

A_1 is selected from the group consisting of H, F, Cl, Br, I, CN, OH, NO_2, NHR^6,



NR^7R^8,OR^9, SR^{10}, $COOR^{11}$, COR^{12}, sulfonic acid, wherein ~ is a bond , 2-ethylidenemalononitrile, (*E*)-2-(but-2-en-1-ylidene)malononitrile, 2-((2E,4E)-hexa-2,4-dien-1-ylidene)malononitrile, acetyl, $(OCH_2\text{-}CH_2)_{n_4}\text{-}(CH_2)_2$ and R^{13};

n_3 is an integer from 0-4;

n_4 is an integer from 0-4;

---- is a single or double bond;

X_1 is selected from the group consisting of C and N;

X_2 is selected from the group consisting of CH_2, CH, O, NR^{14}, S, Se and N;

X_3 is selected from the group consisting of CH_2, CH, O, NR^{15}, S, Se and N;

X_4 is selected from the group consisting of C and CH;

X_5 is selected from the group consisting of N, C and CH;

wherein when X_2 is NR^{14}, S, O or Se, then X_2 and X_4 are linked by a single bond;

wherein when X_2 is N, then X_2 and X_4 are linked by a double bond;

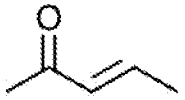
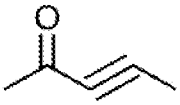
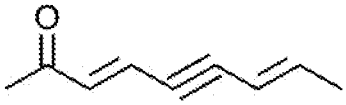
wherein when X_3 is NR^{15},S, O or Se, then X_3 and X_4 are linked by a single bond;

wherein when X_3 is N, then X_3 and X_4 are linked by a double bond;

wherein when both the X_2 and X_5 are N, then X_1 and X_2 are linked by a double bond, X_2 and X_4 are linked by a single bond, X_3 and X_4 are linked by a double bond, and X_3 and X_5

are linked by a single bond;

wherein when both the X_1 and X_2 are N, then X_2 and X_4 are linked by a double bond, X_3 and X_4 are linked by a single bond, X_3 and X_5 are linked by a double bond, and X_1 and X_5 are linked by a single bond;

L is selected from the group consisting of aryl, (C_1-C_4) alkyl, (C_3-C_6) cycloalkyl, (C_2-C_8) straight alkene, (C_3-C_8) branched alkene, (C_2-C_8) alkyne,  ,  and  ;

n_2 is an integer from 0-4; and

each of R^1-R^{16} is independently selected from the group consisting of H, C_{1-12} linear alkyl, C_{2-12} linear alkene, C_{2-12} linear alkyne, C_{3-12} branched chain alkyl, C_{3-12} branched chain alkene, C_{3-12} branched chain alkyne and C_{3-7} cycloalkyl aryl, or a combination thereof.

8. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 7, wherein the halogen is selected from the group consisting of Cl, F, Br and I.

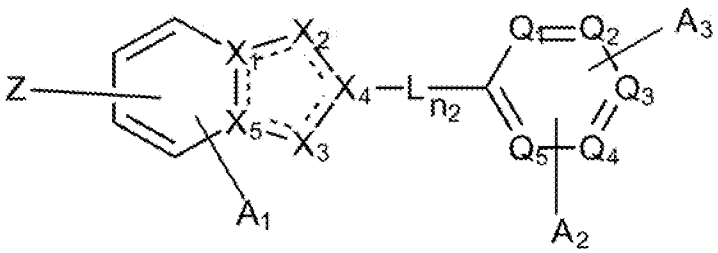
9. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 7, wherein the halogen is selected from the group consisting of F-18, Br-75, Br-76, Br-77, I-123, I-124, I-125 and I-131.

10. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 7, wherein R^4 comprises a radionuclide.

11. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 7, wherein R^4 comprises a C-11.

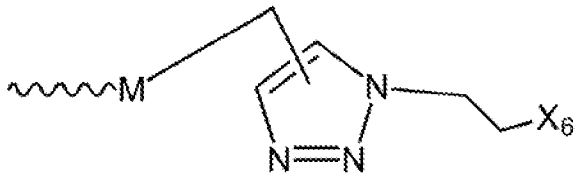
12. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 7, wherein R^{13} comprises a radionuclide.

13. A compound or a pharmaceutically acceptable salt thereof, of structure



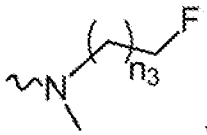
wherein:

Z is selected from the group consisting of CH_2, O, NR^1, S, Se and



wherein ~~~ is a bond;

each of A_1, A_2 and A_3 is independently selected from the group consisting of H, F, Cl, Br, I, CN, OH, NO_2, NHR^2, NR^3R^4,OR^5, SR^6, $COOR^7$, COR^8, sulfonic acid,



wherein ~~~ is a bond, 2-ethylidenemalononitrile, (*E*)-2-(but-2-en-1-ylidene)malononitrile, 2-((2E,4E)-hexa-2,4-dien-1-ylidene)malononitrile, acetyl,-$(OCH_2-CH_2)_{n4}$ and R^9;

n_3 is an integer from 0-4;

n_4 is an integer from 0-4;

X_1 is selected from the group consisting of C and N^+;

X_2 is selected from the group consisting of CH_2,CH, O, NR^{10}, S, Se and N;

X_3 is selected from the group consisting of CH_2,CH, O, NR^{11}, S, Se and N;

X_4 is selected from the group consisting of C and CH;

X_5 is selected from the group consisting of N, C and CH;

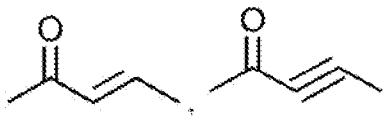
wherein when X_2 is NR^{14} ,S, O or Se, then X_2 and X_4 are linked by a single bond;

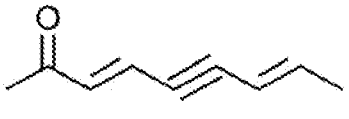
wherein when X_2 is N, then X_2 and X_4 are linked by a double bond;

wherein when X_3 is NR^{15} ,S, O or Se, then X_3 and X_4 are linked by a single bond;

wherein when X_3 is N, then X_3 and X_4 are linked by a double bond;

wherein when both the X_2 and X_5 are N, then X_1 and X_2 are linked by a double bond, X_2 and X_4 are linked by a single bond, X_3 and X_4 are linked by a double bond, and X_3 and X_5 are linked by a single bond; wherein when both the X_1 and X_2 are N, then X_2 and X_4 are linked by a double bond, X_3 and X_4 are linked by a single bond, X_3 and X_5 are linked by a double bond, and X_1 and X_5 are linked by a single bond;

L is selected from the group consisting of (C_1-C_4) alkyl, (C_3-C_6) cycloalkyl, (C_2-C_8) straight alkene, (C_3-C_8) branched alkene, (C_2-C_8) alkyne, 

and  ;

n_2 is an integer from 1-4;

each of Q_1, Q_2, Q_3, Q_4 and Q_5 is independently selected from the group consisting of C and N, with provisos that at least two of Q_1, Q_2, Q_3, Q_4 and Q_5 are C and at least one of Q_1, Q_2, Q_3, Q_4 and Q_5 is N;

M is selected from the group consisting of O, S, Se, NR^{12}, amide, maleimide, urea, haloalkane, haloalkene and haloalkyne;

X_6 is a halogen, NH_2, NHR^{13} OR^{14}, $COOR^{15}$, COR^{16}, OH, NHQ wherein Q is a chelator core;

each of R^1-R^{12} and R^{14}-R^{16} is independently selected from the group consisting of H, C_{1-12} linear alkyl, C_{2-12} linear alkene, C_{2-12} linear alkyne, C_{3-12} branched chain alkyl, C_{3-12} branched chain alkene, C_{3-12} branched chain alkyne and C_{3-7} cycloalkyl aryl.

14. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 13, wherein the halogen is selected from the group consisting of Cl, F, Br and I.

15. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 13, wherein the halogen is selected from the group consisting of F-18, Br-75, Br-76, Br-77, I-123, I-124, I-125 and I-131.

16. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 13, wherein R^4 comprises a radionuclide.

17. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 13, wherein R^4 comprises a C-11.

18. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 13, wherein R^{13} comprises a radionuclide.

19. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 13, wherein the chelator core is selected from the group consisting of NOTA, DOTA, DTPA and triglycine.

20. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 19, wherein the chelator core chelates a metal radionuclide.

21. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 20, wherein the metal radionuclide is an ion selected from the group consisting of an ion of gallium-67 and an ion of gallium-68.

22. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 20, wherein the compound or pharmaceutically acceptable salt comprises an ion selected from the group consisting of an ion of gallium-67, an ion of gallium-68, an ion of an unlabeled gallium, an ion of indium-111 , an ion of iron-52, an ion of iron-59, an ion of copper-62, an ion of copper-64, an ion of thallium-201, an ion of technetium-99m, an ion of technetium-94m, an ion of rhenium-188, an ion of rubidium-82, an ion of strontium-92, an ion of yttrium-86, an ion of yttrium-90, an ion of zirconium-86, an ion of zirconium-89.

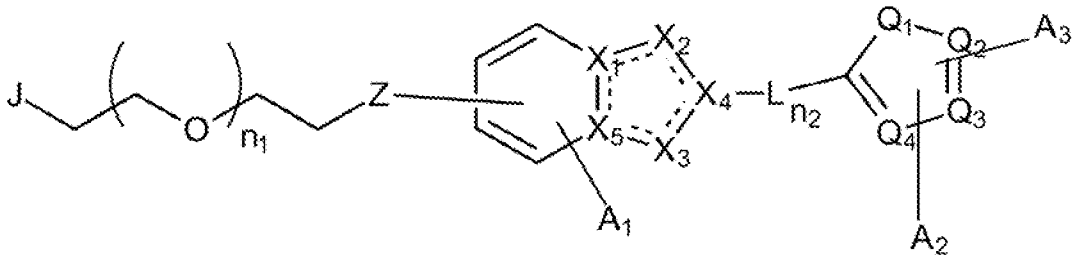
23. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 20, wherein the ion is a paramagnetic metal ion.

24. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 20, wherein the compound or pharmaceutically acceptable salt comprises an ion selected from the group consisting of an ion of iron, an ion of manganese and an ion of cobalt.

25. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 20, wherein the compound or pharmaceutically acceptable salt comprises an ion is a lanthanide metal ion.

26. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 20, wherein the compound or pharmaceutically acceptable salt comprises a gadolinium ion.

27. A compound or a pharmaceutically acceptable salt thereof, of structure



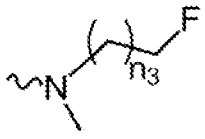
wherein:

J is selected from the group consisting of a halogen, hydroxy, cyano, $COOR^1$, carboxy, amide, immino, nitro, NR^2R^3 and OR^4;

n_1 is an integer from 0-4;

Z is selected from the group consisting of CH_2, O, NR^5, S and Se;

each of A_1, A_2 and A_3 is independently selected from the group consisting of H, F, Cl, Br, I,



CN, OH, NO_2, NHR^6, NR^7R^8,OR^9, SR^{10}, $COOR^{11}$, COR^{12}, sulfonic acid,

wherein ~ is a bond , 2-ethylidenemalononitrile, (*E*)-2-(but-2-en-1-ylidene)malononitrile, 2-((2E,4E)-hexa-2,4-dien-1-ylidene)malononitrile, acetyl, -$(OCH_2-CH_2)_{n_3}$- and R^{13};

n_3 is an integer from 0-4;

n_4 is an integer from 0-4;

~~~ is a single or double bond;

X_1 is selected from the group consisting of C and N;

X_2 is selected from the group consisting of CH_2,CH, O, NR^{14}, S, Se and N;

X_3 is selected from the group consisting of CH_2,CH, O, NR^{15}, S, Se and N;

X_4 is selected from the group consisting of C and CH;

X_5 is selected from the group consisting of N, C and CH;

wherein when X_1 is C then X_1 and X_5 are linked by a double bond;

wherein when X_1 is N, then X_1 and X_5 are linked by a single bond;

wherein when X_2 is NR^{14}, S, O or Se, then X_2 and X_4 are linked by a single bond;

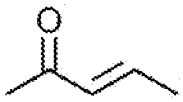
wherein when X_2 is N, then X_2 and X_4 are linked by a double bond;

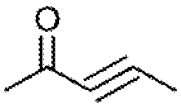
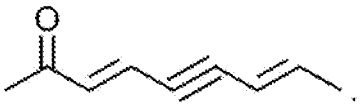
wherein when X_3 is NR^{15}, S, O or Se, then X_3 and X_4 are linked by a single bond;

wherein when X_3 is N, then X_3 and X_4 are linked by a double bond;

wherein when both the X_2 and X_5 are N, then X_1 and X_2 are linked by a double bond, X_2 and X_4 are linked by a single bond, X_3 and X_4 are linked by a double bond, and X_3 and X_5 are linked by a single bond;

wherein when both the X_1 and X_2 are N, then X_2 and X_4 are linked by a double bond, X_3 and X_4 are linked by a single bond, X_3 and X_5 are linked by a double bond, and X_1 and X_5 are linked by a single bond;

L is selected from the group consisting of (C_1-C_4) alkyl, (C_3-C_6) cycloalkyl, (C_2-C_8) linear alkene, (C_2-C_8) linear alkene, (C_3-C_8) branched alkyne,  ,

 and  ;

n_2 is an integer from 0-4;

each of Q_1, Q_2, Q_3 and Q_4 is independently selected from the group consisting of C and N, with provisos that at least two of Q_1, Q_2, Q_3 and Q_4 are C and at least one of Q_1, Q_2, Q_3, and Q_4 is N;

each of R^1-R^{15} is independently selected from the group consisting of H, C_{1-12} linear
~~~

alkyl, C_{2-12} linear alkene, C_{2-12} linear alkyne, C_{3-12} branched chain alkyl, C_{3-12} branched chain alkene, C_{3-12} branched chain alkyne, C_{3-7} cycloalkyl aryl, and a combination thereof.

28. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 27, wherein the halogen is selected from the group consisting of Cl, F, Br and I.

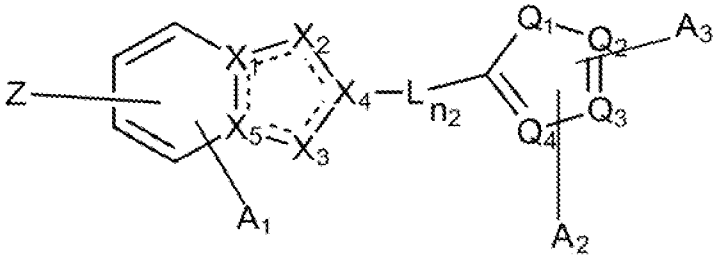
29. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 27, wherein the halogen is selected from the group consisting of F-18, Br-75, Br-76, Br-77, I-123, I-124, I-125 and I-131.

30. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 27, wherein R^4 comprises a radionuclide.

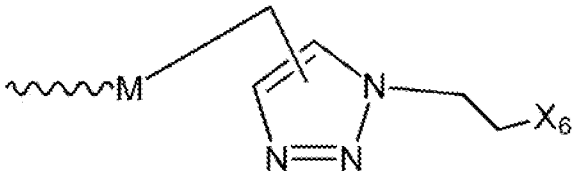
31. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 27, wherein R^4 comprises a C-11.

32. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 27, wherein R^{13} comprises a radionuclide.

33. A compound or a pharmaceutically acceptable salt thereof, of structure

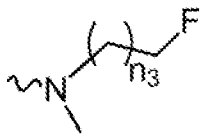


, wherein: Z is selected from the group consisting of CH_2, O, NR^1, S, Se and



wherein ~~~ is a bond;

each of A_1, A_2 and A_3 is independently selected from the group consisting of H, a halogen, CN, OH, NO_2, NHR^2, NR^3R^4,OR^5, SR^6, $COOR^7$, COR^8, sulfonic acid,



wherein ~ is a bond , 2-ethylidenemalononitrile, (*E*)-2-(but-2-en-1-ylidene)malononitrile, 2-((2E,4E)-hexa-2,4-dien-1-ylidene)malononitrile, acetyl-$(OCH_2-CH_2)_{n_4}$-$(CH_2)_2$- and R^9;

n_3 is an integer from 0-4;

n_4 is an integer from 0-4;

X_1 is selected from the group consisting of C and N;

X_2 is selected from the group consisting of CH_2,CH, O, NR^{10}, S, Se and N;

X_3 is selected from the group consisting of CH_2,CH, O, NR^{11}, S, Se and N;

X_4 is selected from the group consisting of C and CH;

X_5 is selected from the group consisting of N, C and CH;

wherein when X_2 is NR^{14}, S, O or Se, then X_2 and X_4 are linked by a single bond;

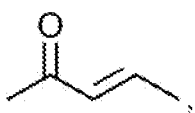
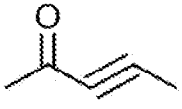
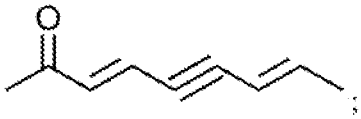
wherein when X_2 is N, then X_2 and X_4 are linked by a double bond;

wherein when X_3 is NR^{15}, S, O or Se, then X_3 and X_4 are linked by a single bond;

wherein when X_3 is N, then X_3 and X_4 are linked by a double bond;

wherein when both the X_2 and X_5 are N, then X_1 and X_2 are linked by a double bond, X_2 and X_4 are linked by a single bond, X_3 and X_4 are linked by a double bond, and X_3 and X_5 are linked by a single bond;

wherein when both the X_1 and X_2 are N, then X_2 and X_4 are linked by a double bond, X_3 and X_4 are linked by a single bond, X_3 and X_5 are linked by a double bond, and X_1 and X_5 are linked by a single bond;

L is selected from the group consisting of (C_1-C_5) alkyl, (C_3-C_6) cycloalkyl, (C_2-C_8) linear alkene, (C_3-C_8) branched alkene, (C_2-C_8) alkyne,  ,  and  ;

n_2 is an integer from 1-4;

each of Q_1, Q_2, Q_3, Q_4 and Q_5 is independently selected from the group consisting of C and N, with provisos that at least two of Q_1, Q_2, Q_3 and Q_4 are C and at least one of Q_1, Q_2, Q_3 and Q_4 is N;

M is selected from the group consisting of O, S, Se, NR^{12}, amide, maleimide, urea, haloalkane, haloalkene and haloalkyne;

X_6 is selected from the group consisting of a halogen, NH_2; NHR^{13}; OR^{14}, $COOR^{15}$, COR^{16}, OH, NHQ wherein Q is a chelator core;

each of R^1-R^{16} is independently selected from the group consisting of H, C_{1-12} linear alkyl, C_{2-12} linear alkene, C_{2-12} linear alkyne, C_{3-12} branched chain alkyl, C_{3-12} branched chain alkene, C_{3-12} branched chain alkyne and C_{3-7} cycloalkyl aryl; and

R^{13} optionally comprises a radionuclide.

34. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 33, wherein the halogen is selected from the group consisting of Cl, F, Br and I.

35. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 33, wherein the halogen is selected from the group consisting of F-18, Br-75, Br-76, Br-77, I-123, I-124, I-125 and I-131.

36. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 33, wherein R^4 comprises a radionuclide.

37. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 33, wherein R^4 comprises a C-11.

38. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 33, wherein R^{13} comprises a radionuclide.

39. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 33, wherein the chelator core is selected from the group consisting of NOTA, DOTA, DTPA and triglycine.

40. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 39, wherein the chelator core chelates a metal radionuclide.

41. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 40, wherein the metal radionuclide is an ion selected from the group consisting of an ion of gallium-67and an ion of gallium-68.

42. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 40, wherein the compound or pharmaceutically acceptable salt comprises an ion selected from the group consisting of an ion of gallium-67, an ion of gallium-68, an ion of an unlabeled gallium, an ion of indium-111 , an ion of iron-52, an ion of iron-59, an ion of copper-62, an ion of copper-64, an ion of thallium-201, an ion of technetium-99m, an ion of technetium-94m, an ion of rhenium-188, an ion of rubidium-82, an ion of strontium-92, an ion of yttrium-86, an ion of yttrium-90, an ion of zirconium-86, an ion of zirconium-89.

43. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 40, wherein the compound or pharmaceutically acceptable salt comprises a paramagnetic metal ion.

44. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 40, wherein the compound or pharmaceutically acceptable salt comprises an ion is selected from the group consisting of an ion of iron, an ion of manganese and an ion of cobalt.

45. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 40, wherein the compound or pharmaceutically acceptable salt comprises a lanthanide metal ion.

46. A compound or a pharmaceutically acceptable salt thereof in accordance with claim 40, wherein the compound or pharmaceutically acceptable salt comprises a gadolinium ion.

47. A gold nanoparticle comprising gold conjugated to a compound of any one of claims 1-46.

48. A complex comprising:

a compound or a pharmaceutically acceptable salt thereof of any one of claims 1-46; and

a gold nanoparticle.

49. A gold nanoparticle conjugated to a compound of any one of claims 1-46.

50. A gold nanoparticle of any one of claims 47, 48 or 49, further comprising a linker.

51. A gold nanoparticle of claim 50, wherein the linker is an aminothiol.

52. A gold nanoparticle of claim 51, wherein the aminothiol is an aminothiophenol.

53. A gold nanoparticle of claim 52, wherein the aminothiophenol is a p-aminothiophenol.

54. A gold nanoparticle of any one of claims 47-53, wherein the gold is Au-199.

55. A gold nanoparticle of any one of claims 47-53, wherein the gold is Au-198.

56. A method of imaging distribution of amyloid beta in a sample or a subject, comprising:

administering a compound or a pharmaceutically acceptable salt thereof of any one of claims 1-55 to the sample or subject wherein the compound or pharmaceutically acceptable salt thereof comprises a radionuclide;

subjecting the subject to PET or SPECT scanning.

57. A method of imaging distribution of amyloid beta in a sample or a subject, comprising:

administering a compound, a pharmaceutically acceptable salt thereof or a gold nanoparticle of any one of claims 1-55 to the sample or subject;

applying electromagnetic radiation to the subject or sample of a wavelength excitatory for fluorescence of the compound or salt thereof.

58. A method of imaging cardiac systemic amyloidosis in a subject, comprising administering an imaging effective amount of a compound, a pharmaceutically acceptable salt thereof or a

gold nanoparticle of any one of claims 1-55 to the subject, and subjecting the subject to PET or SPECT scanning.

59. A method of inhibiting amyloid beta aggregation, comprising administering a compound, a pharmaceutically acceptable salt thereof or a gold nanoparticle of any one of claims 1-55, wherein at least one of Z, X_2 and X_3 is Se.

60. A method of diagnosing or monitoring progression of Alzheimers disease, comprising administering to a subject a compound, a pharmaceutically acceptable salt thereof or a gold nanoparticle of any one of claims 1-55, and subjecting the subject to PET or SPECT scanning.

61. A method of diagnosing or monitoring progression of a neurodegenerative disease, comprising administering to a subject a compound, a pharmaceutically acceptable salt thereof or a gold nanoparticle of any one of claims 1-55, and subjecting the subject to PET or SPECT scanning.

62. A method of diagnosing or monitoring progression of cardiac systemic amyloidosis, comprising administering to a subject a compound, a pharmaceutically acceptable salt thereof or a gold nanoparticle of any one of claims 1-55, and subjecting the subject to PET or SPECT scanning.

63. A method for detecting or ruling out a meningioma in a subject comprising administering to a subject a compound, a pharmaceutically acceptable salt thereof or a gold nanoparticle of any one of claims 1-55.

64. A method for detecting or ruling out a meningioma in a subject in accordance with claim 63, wherein the detecting comprises PET or SPECT scanning with concurrent computed tomography (CT) imaging, magnetic resonance imaging (MRI), or a combination thereof.

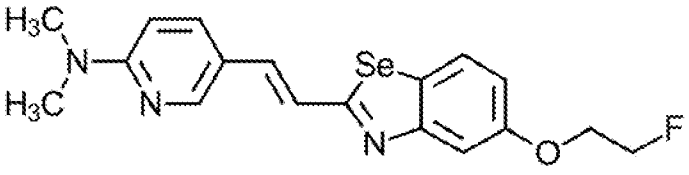
65. A method for differentiating the presence of a meningioma from other tumors types in a subject, comprising:

administering to a subject a diagnostically acceptable amount of a compound, a pharmaceutically acceptable salt thereof or a gold nanoparticle of any one of claims 1-55;

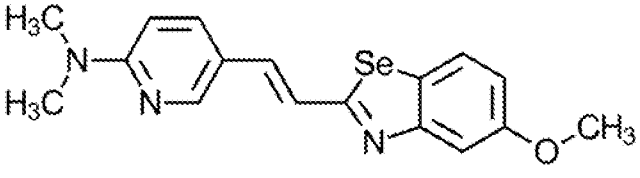
detecting retention of the compound,

wherein greater activity of the compound compared to a control is diagnostic for meningioma.

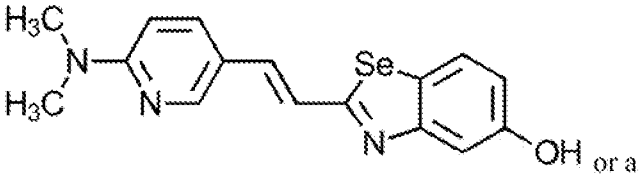
66. A compound of any one of claims 1-55 for use in the differential diagnosis of meningioma compared to other tumors



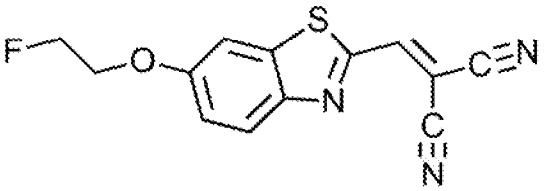
67. A compound of structure or a pharmaceutically acceptable salt thereof.



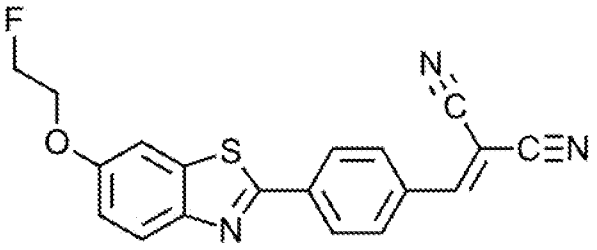
68. A compound of structure or a pharmaceutically acceptable salt thereof.



69. A compound of structure or a pharmaceutically acceptable salt thereof.

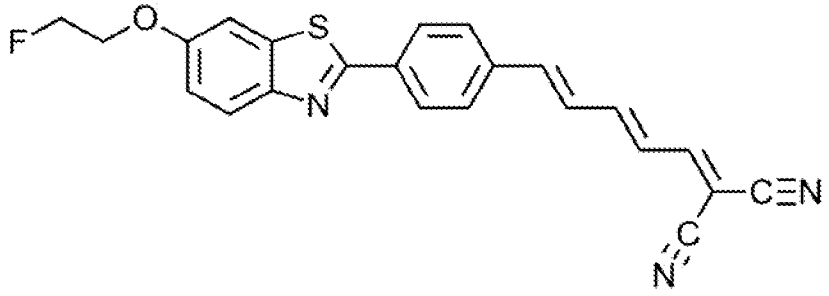


70. A compound of structure or a pharmaceutically acceptable salt thereof.

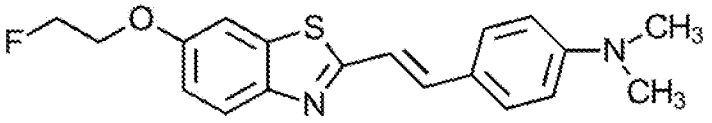


71. A compound of structure or a pharmaceutically acceptable salt thereof.

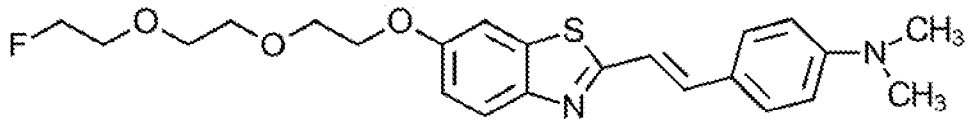
72. A compound of structure



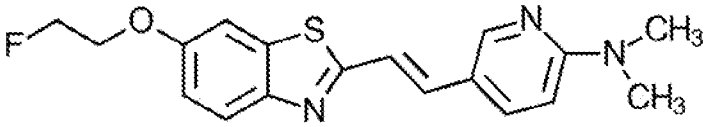
or a pharmaceutically acceptable salt thereof.

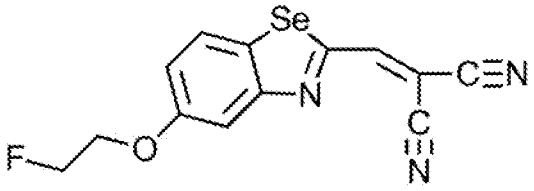
73. A compound of structure  or a pharmaceutically acceptable salt thereof.

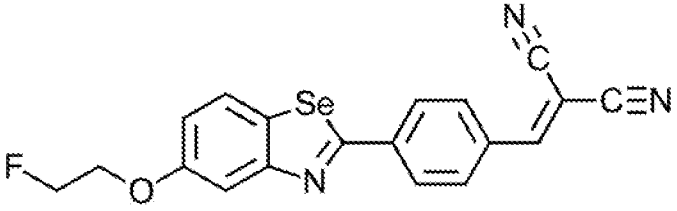
74. A compound of structure



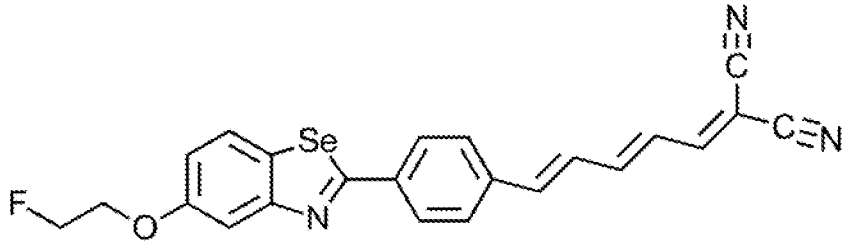
or a pharmaceutically acceptable salt thereof.

75. A compound of structure  or a pharmaceutically acceptable salt thereof.

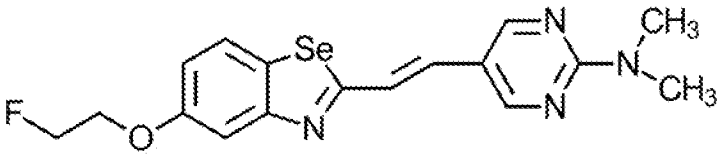
76. A compound of structure  or a pharmaceutically acceptable salt thereof.

77. A compound of structure  or a pharmaceutically acceptable salt thereof.

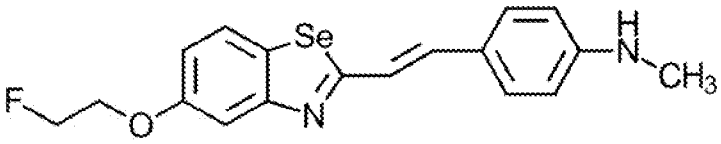
78. A compound of structure



or a pharmaceutically acceptable salt thereof.

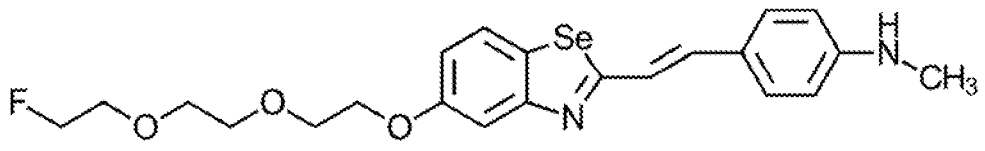
79. A compound of structure 

or a pharmaceutically acceptable salt thereof.

80. A compound of structure 

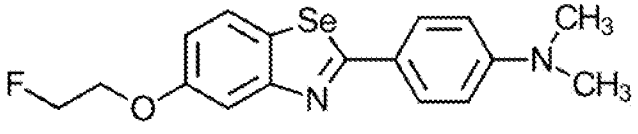
or a pharmaceutically acceptable salt thereof.

81. A compound of structure

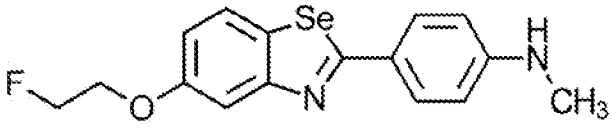


or a pharmaceutically acceptable salt thereof.

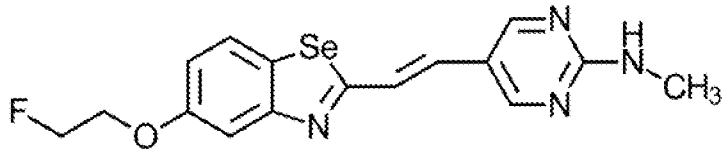
82. A compound of structure



or a pharmaceutically acceptable salt thereof.

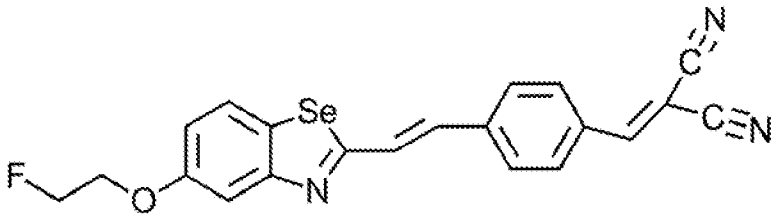
83. A compound of structure  or a pharmaceutically acceptable salt thereof.

84. A compound of structure

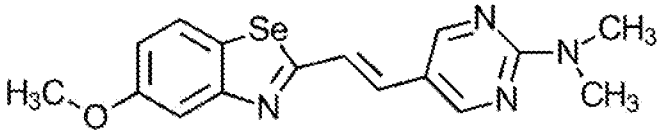


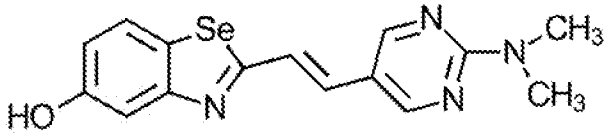
or a pharmaceutically acceptable salt thereof.

85. A compound of structure

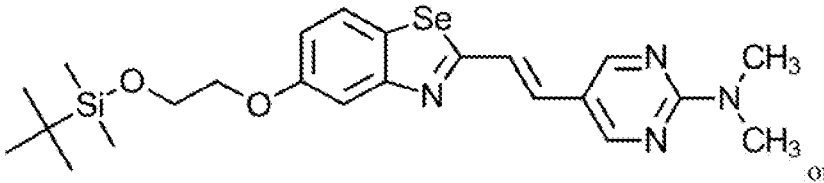


or a pharmaceutically acceptable salt thereof.

86. A compound of structure  or a pharmaceutically acceptable salt thereof.

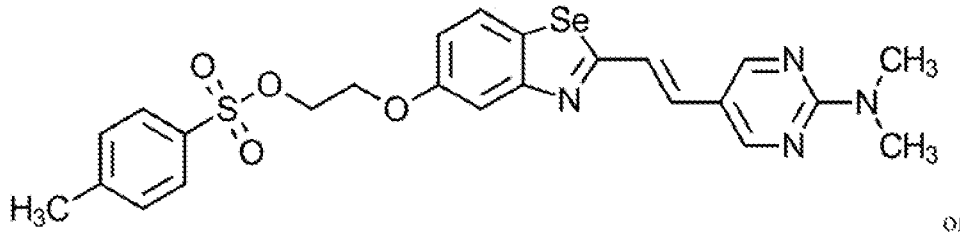
87. A compound of structure  or a pharmaceutically acceptable salt thereof.

88. A compound of structure

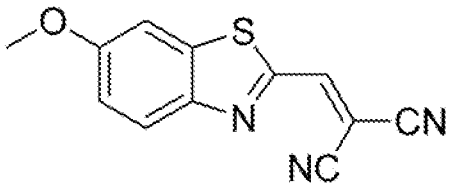


or a pharmaceutically acceptable salt thereof.

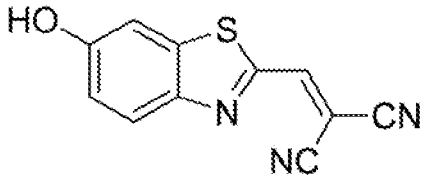
89. A compound of structure



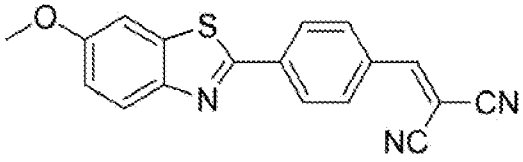
or a pharmaceutically acceptable salt thereof.



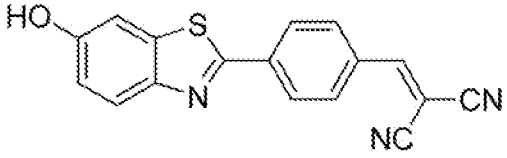
90. A compound of structure or a pharmaceutically acceptable salt thereof.



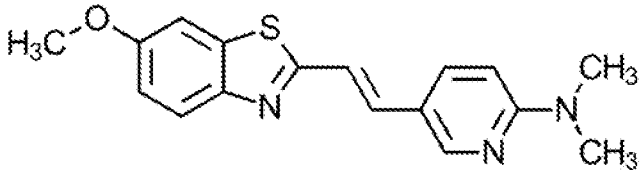
91. A compound of structure or a pharmaceutically acceptable salt thereof.



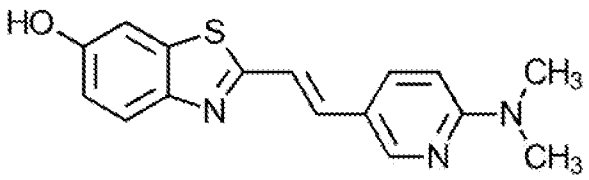
92. A compound of structure or a pharmaceutically acceptable salt thereof.

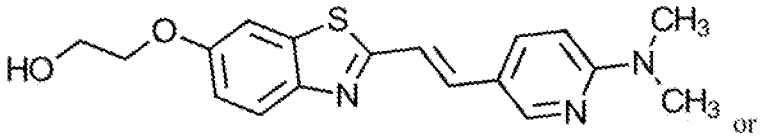


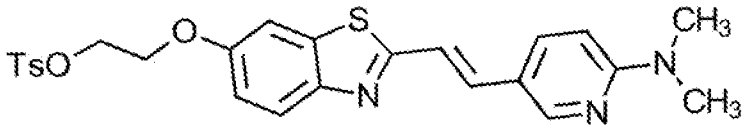
93. A compound of structure or a pharmaceutically acceptable salt thereof.

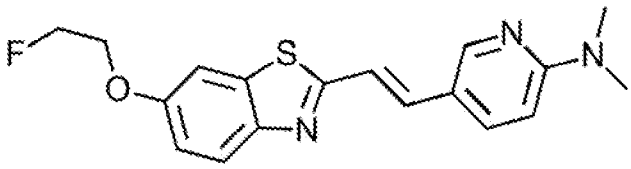


94. A compound of structure or a pharmaceutically acceptable salt thereof.

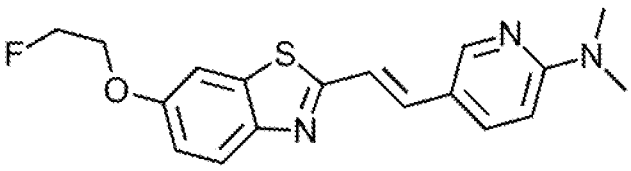
95. A compound of structure  or a pharmaceutically acceptable salt thereof.

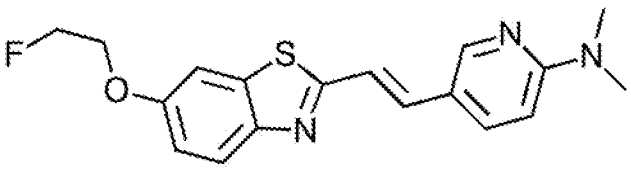
96. A compound of structure  or a pharmaceutically acceptable salt thereof.

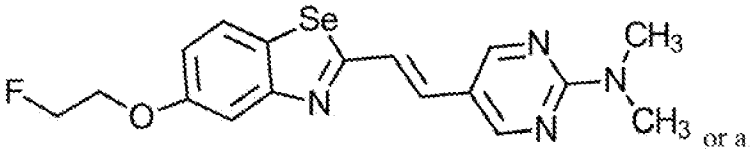
97. A compound of structure  or a pharmaceutically acceptable salt thereof.

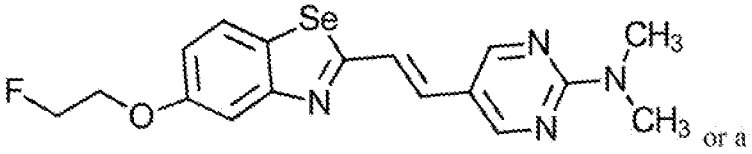
98. Compound  or a pharmaceutically acceptable salt thereof, for use in the detection or diagnosis of amyloid in a subject.

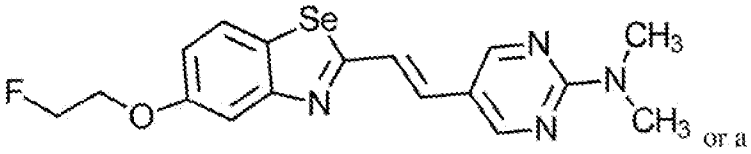
99. The compound of pharmaceutically acceptable salt thereof of claim 98, where in F is an F-18.

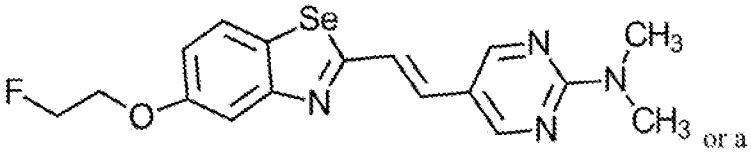
100. Compound  or a pharmaceutically acceptable salt thereof, for use in the diagnosis of Alzheimers Disease in a subject.

101. Compound  or a pharmaceutically acceptable salt thereof, for use in the diagnosis of cardiac systemic amyloidosis in a subject.

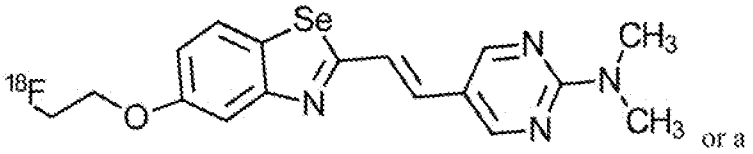
102. Compound  or a pharmaceutically acceptable salt thereof, for use in the diagnosis of Alzheimers Disease in a subject.

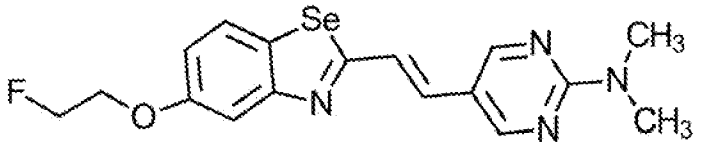
103. Compound  or a pharmaceutically acceptable salt thereof, wherein the F is an F-18.

104. Compound  or a pharmaceutically acceptable salt thereof, for use in the detection of amyloid-β.

105. Compound  or a pharmaceutically acceptable salt thereof, for use in the detection or diagnosis of amyloid- β plaque in the retina.

106. The compound or pharmaceutically acceptable salt of claim 105, wherein the detection comprises fluorescence detection.

107. Compound  or a pharmaceutically acceptable salt thereof, for use in the detection or diagnosis of amyloid- β plaque in the retina, wherein the detection comprises PET imaging.

108. Compound  or a pharmaceutically acceptable salt thereof, for use in the detection or diagnosis of amyloid- β by SPECT.

109. A compound or a pharmaceutically acceptable salt thereof of any one of claims 1-55 for use in the detection or diagnosis of amyloid in a subject.

110. A compound or a pharmaceutically acceptable salt thereof of any one of claims 1-55 for use in the detection or diagnosis of a cancer selected from the group consisting of a prolactinoma, a chroid plexus papilloma, a low grade lymphoma, and a pituitary tumor.

111. A compound or a pharmaceutically acceptable salt thereof of any one of claims 1-55 for use in the detection or diagnosis of a cancer selected from the group consisting of glioblastoma, brain cancer, breast cancer and pancreatic cancer.

112. A compound or a pharmaceutically acceptable salt thereof of any one of claims 1-55 for use in the detection of amyloid precursor protein.

FIG. 1

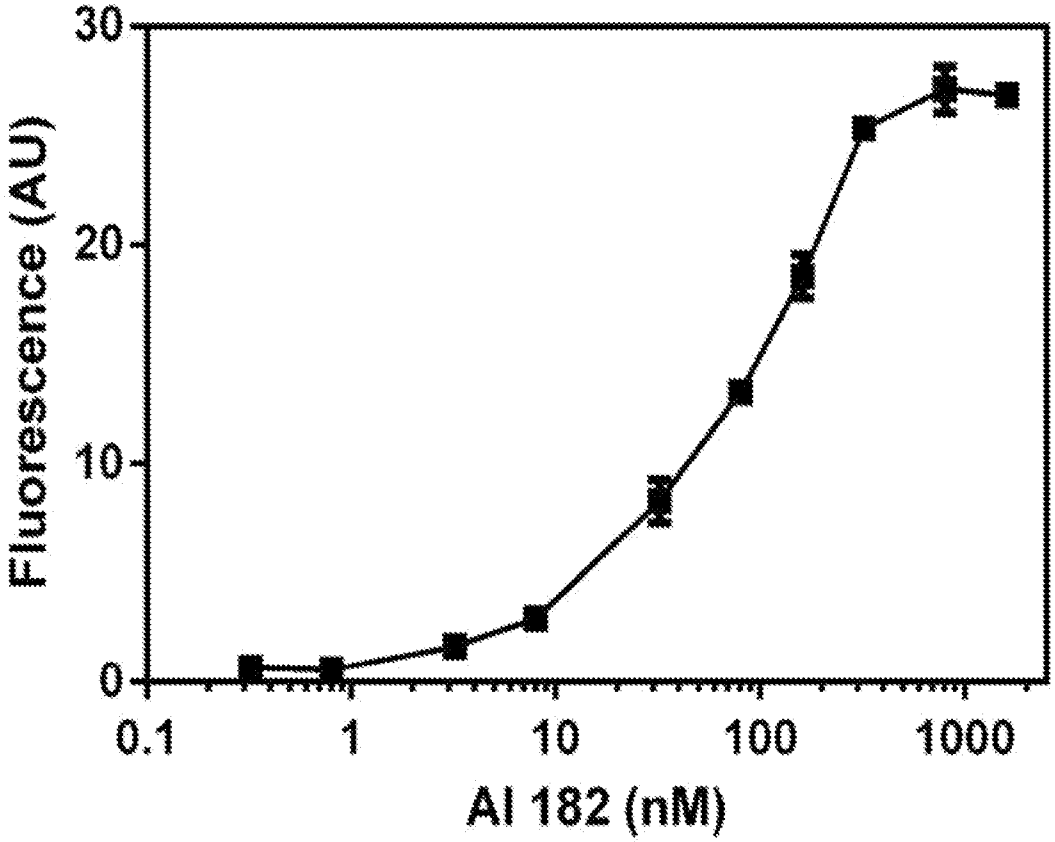


FIG. 2

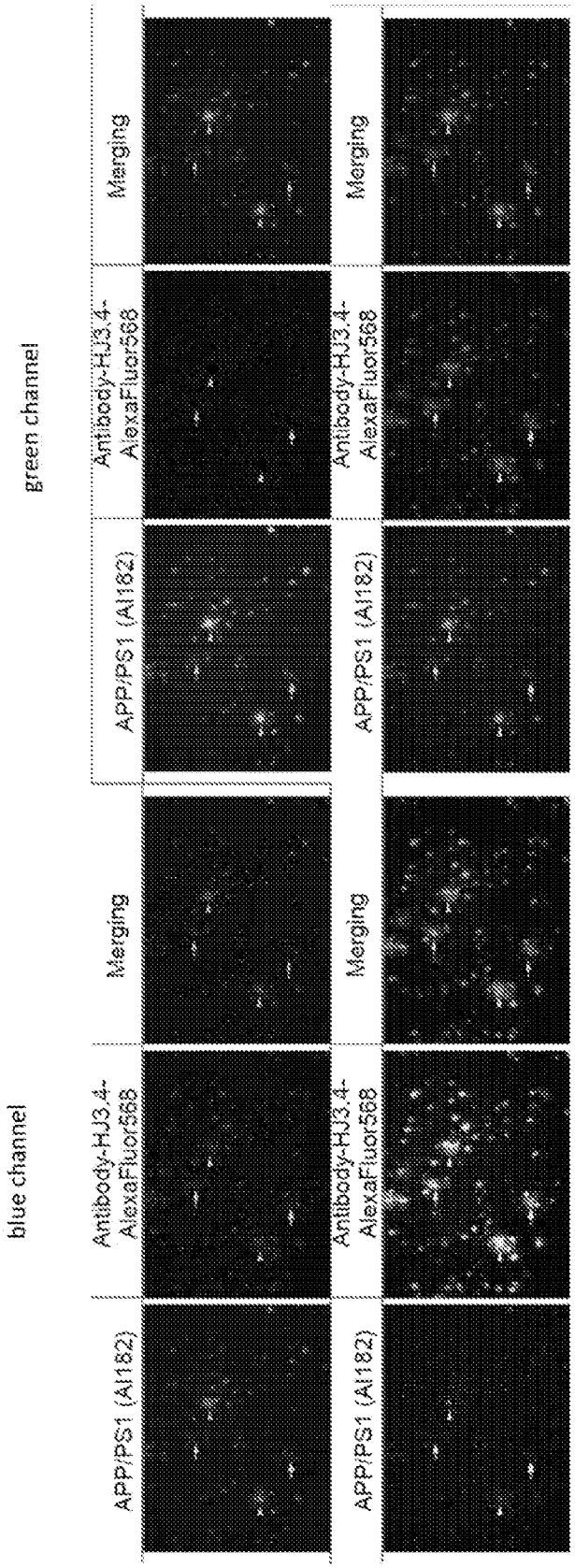

blue channel
green channel
red channel
composite
APP/PS1 (AI182)
Antibody-HJ3.4-AlexaFluor568
Merging
APP/PS1 (AI182)
Antibody-HJ3.4-AlexaFluor568
Merging
APP/PS1 (AI182)
Antibody-HJ3.4-AlexaFluor568
Merging
APP/PS1 (AI182)
Antibody-HJ3.4-AlexaFluor568
Merging

FIG. 3

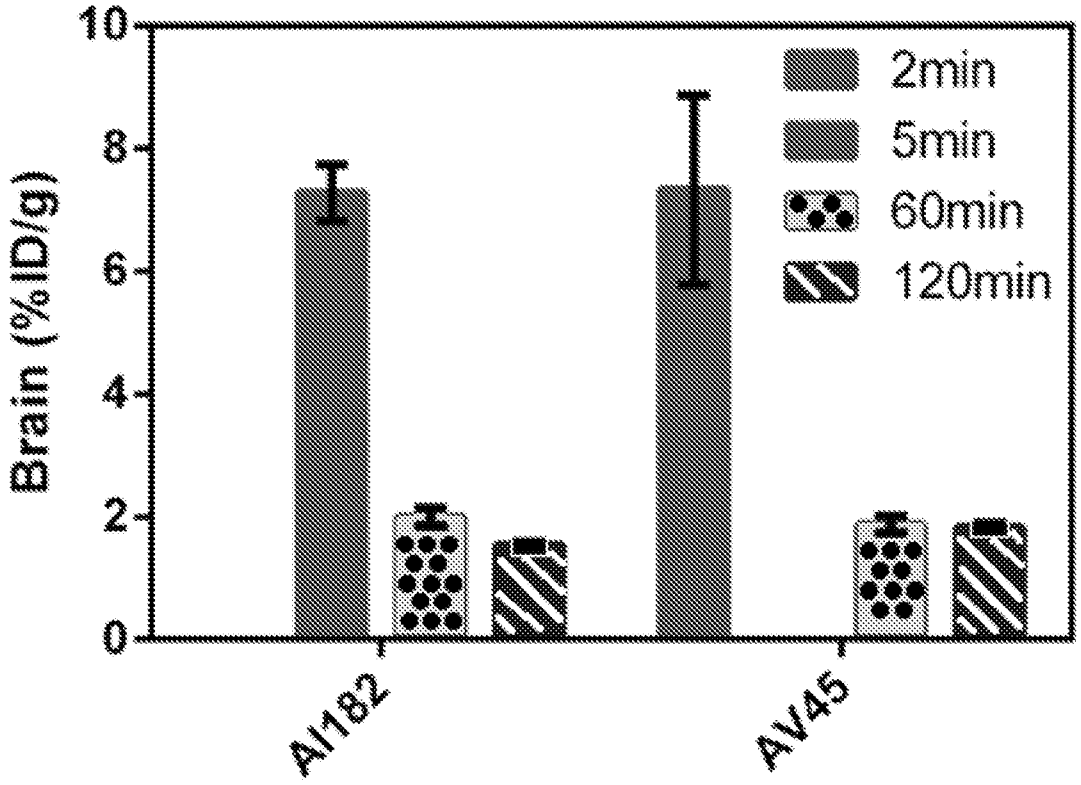


FIG. 4

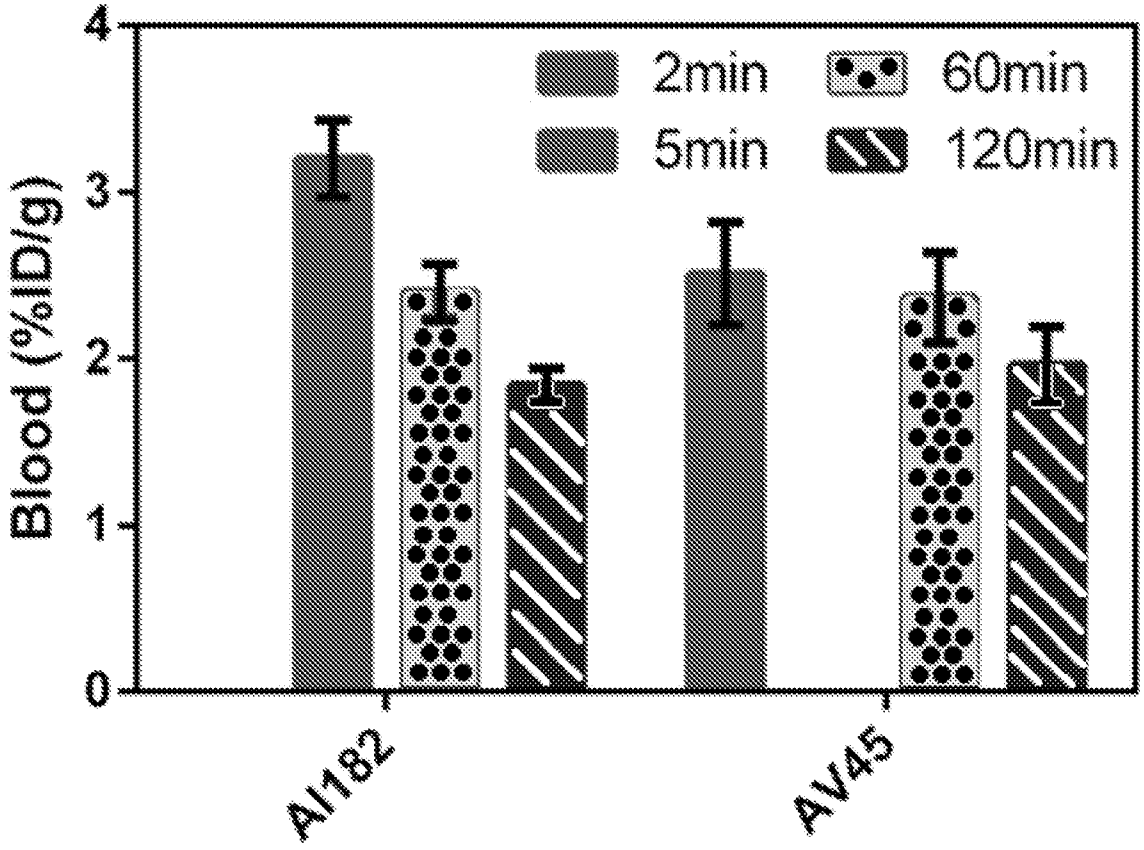


FIG. 5

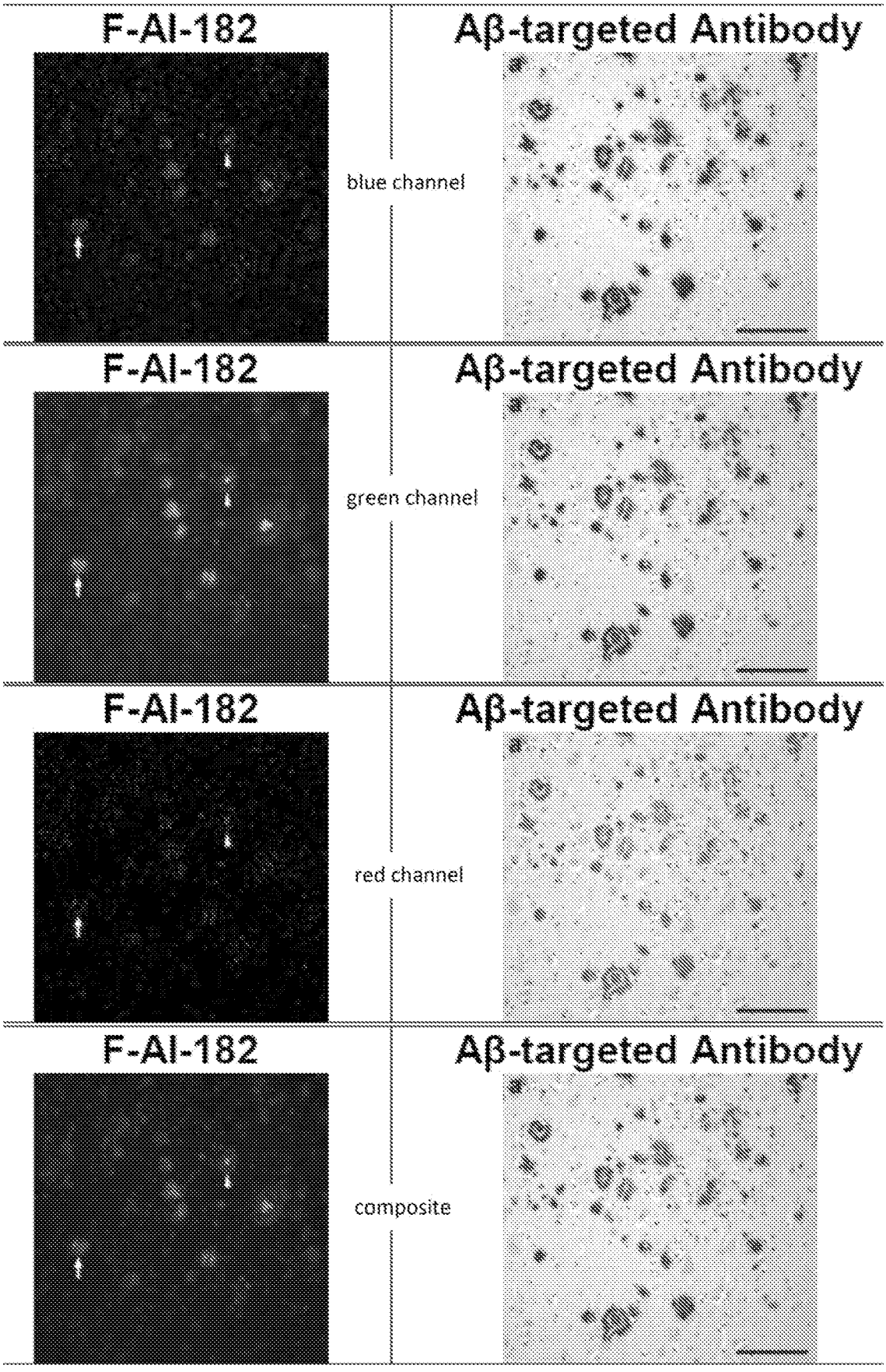

F-AI-182
Aβ-targeted Antibody
blue channel
F-AI-182
Aβ-targeted Antibody
green channel
F-AI-182
Aβ-targeted Antibody
red channel
F-AI-182
Aβ-targeted Antibody
composite

FIG. 6

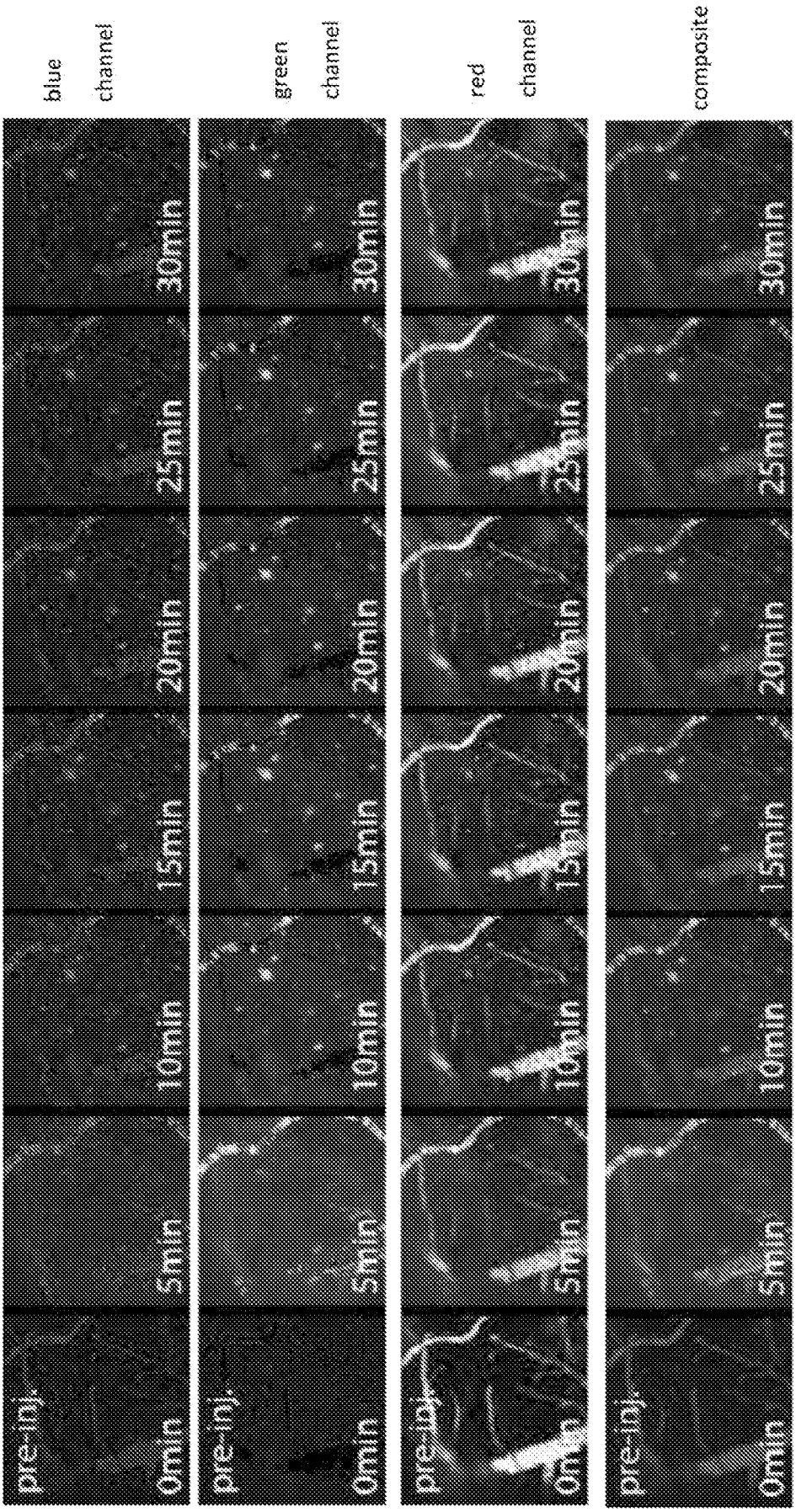

blue channel
green channel
red channel
composite
pre-inj.
0min
5min
10min
15min
20min
25min
30min

FIG. 7

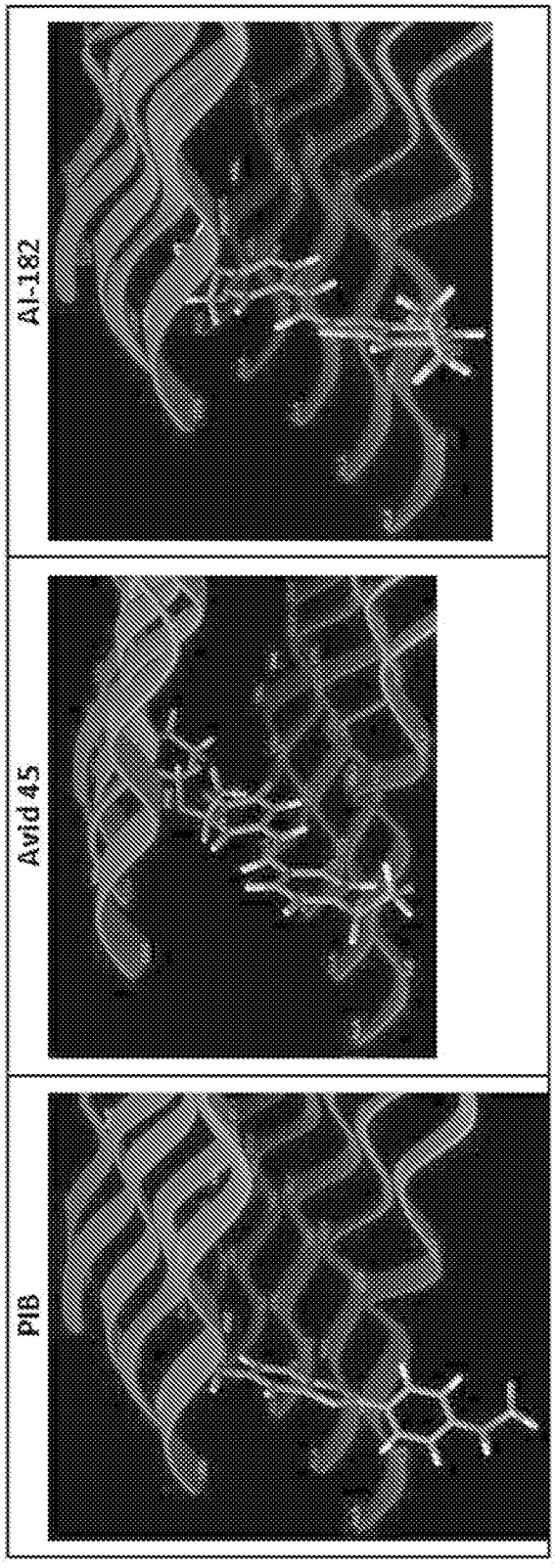


FIG. 8

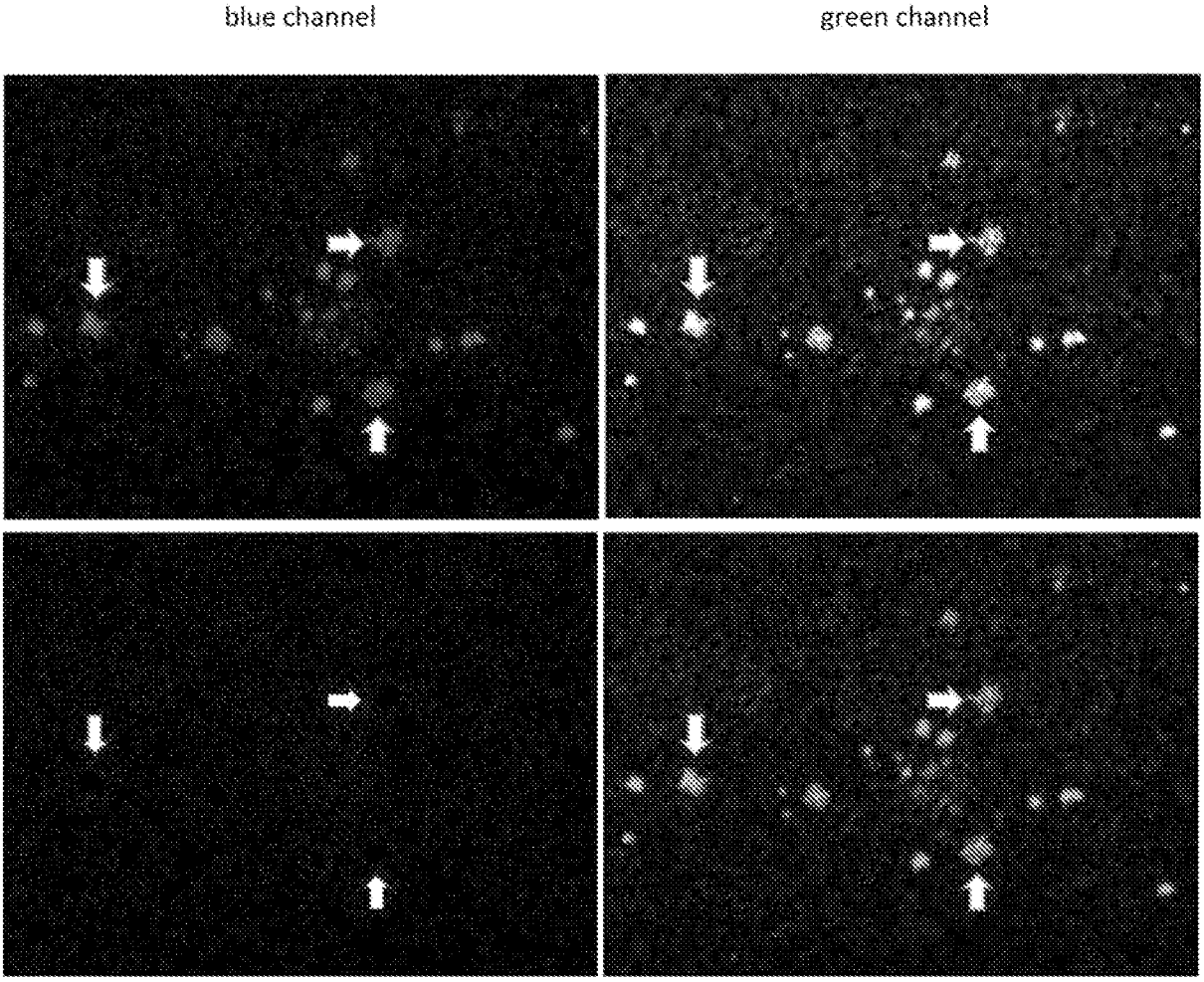


FIG. 9

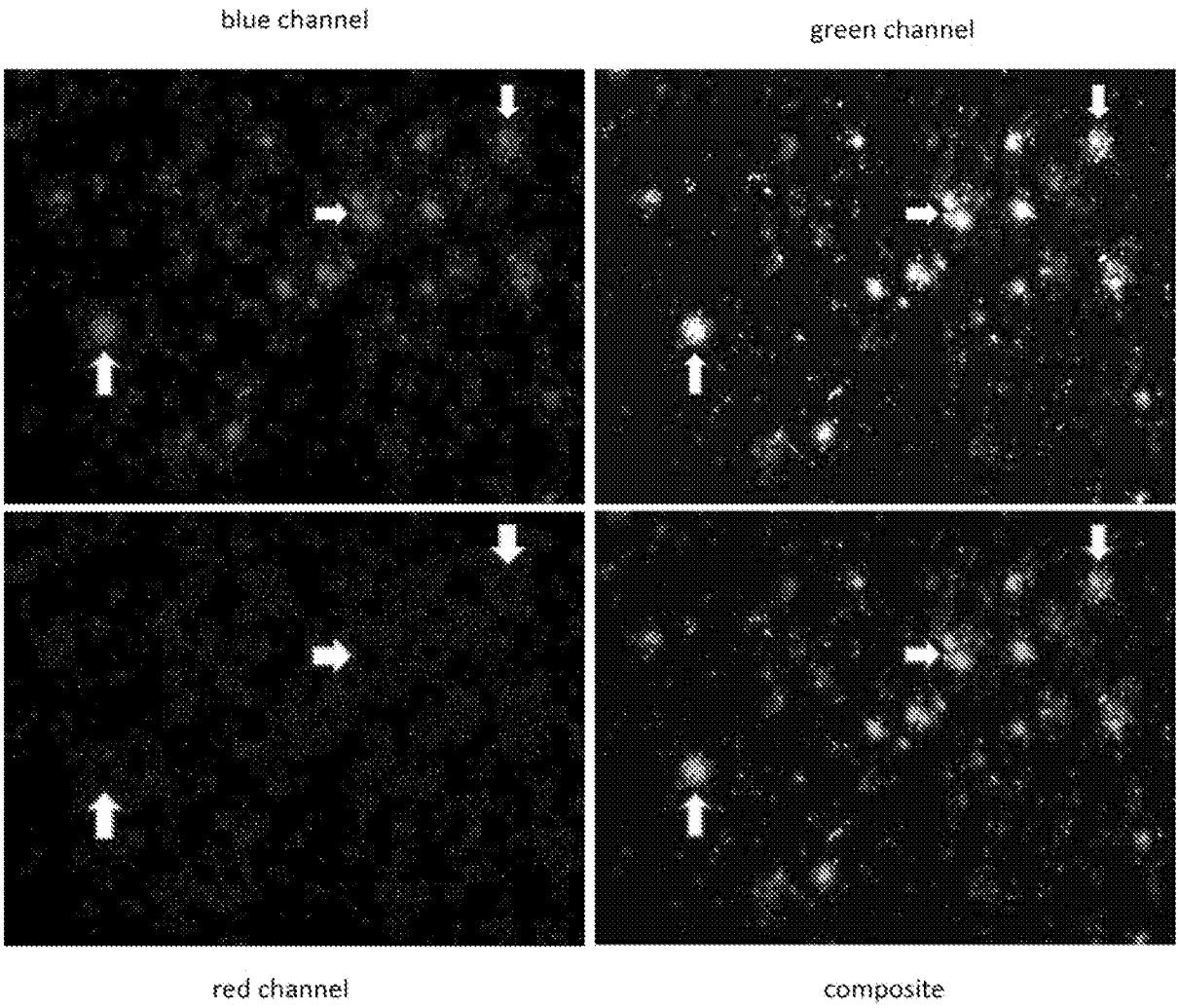
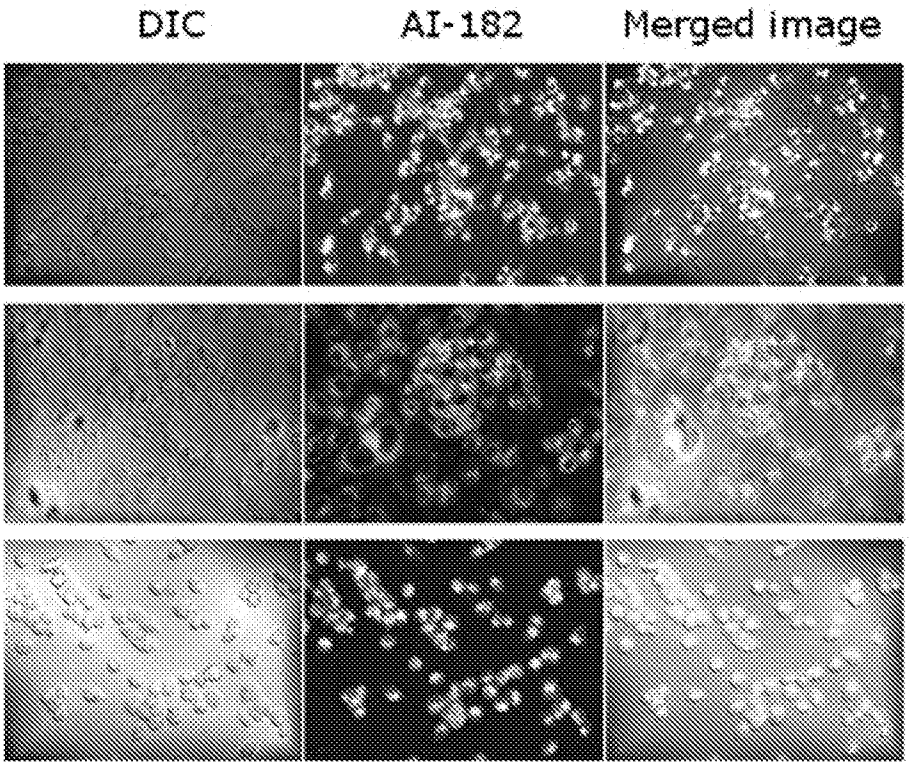


FIG.10



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 2014/058919

A. CLASSIFICATION OF SUBJECT MATTER
(see extra sheet)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
C07D 277/64, 277/66, 293/12, 417/06, 421/06, A61K 31/428, 31/4439, 31/506, 51/04, 101/02, 103/00, 103/10, 103/30, 103/32, A61P 25/28, 35/00, C07B 59/00, G01N 33/53, 33/60
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Espacenet, STN, PatSearch (RUPTO internal)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 2002/016333 A2 (UNIVERSITY OF PITTSBURGH et al.) 28.02.2002, pp. 1-7, 13-16, 18-19, 26-27, examples, claims	1-46, 56, 66-112 47-55, 57-65
X	WO 2007/086800 A1 (ASTRAZENECA AB et al.) 02.08.2007, pp. 1-3, examples, claims	1-112
X	WO 2004/083195 A1 (UNIVERSITY OF PITTSBURGH et al.) 30.09.2004, p. 1-8, 44-46, examples, claims	1-112
Y	WO 2009/062138 A1 (VIRGINIA TECH INTELLECTUAL PROPERTIES, INC. et al.) 14.05.2009, abstract, pp. 1-2, claims 67-77	47-55

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
09 December 2014 (09.12.2014)	18 December 2014 (18.12.2014)
Name and mailing address of the ISA/RU: Federal Institute of Industrial Property, Berezhkovskaya nab., 30-1, Moscow, G-59, GSP-3, Russia, 125993 Facsimile No: (8-495) 531-63-18, (8-499) 243-33-37	Authorized officer A. Semkina Telephone No. 8(495)531-64-81

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 2014/058919

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2007/047204 A1 (UNIVERSITY OF PITTSBURG et al.) 26.04.2007, abstract, claims	57-65
A	LUGOVKIN, B.P. Condensation of 2-pyridinecarboxaldehyde with heterocyclic bases. Synthesis of 1-pyridyl-2-quinolyl-, 1-benzothiazolyl-2-pyridyl-, and 1-benzoselenazolyl-2-pyridylethylenes and their methiodides. Khimia Geterotsiklicheskikh Soedineniy, 1966, 4, pp. 571-574 (abstract) [online] CAS (STN), 66:18685, RN 13206-44-5, 14622-53-8, 13386-32-8	67-68, 76-89, 101-108
A	[online] REGISTRY via STN, 03.12.2009, RN 1195521-46-0	68, 86, 94
A	[online] REGISTRY via STN, 21.03.2005, RN 846055-73-0	89
P, X	SUNDARAM, G.S.M. et al. Characterization of a Brain Permeant Fluorescent Molecule and Visualization of Aβ Parenchymal Plaques, Using Real-Time Multiphoton Imaging in Transgenic Mice. Organic Letters, 08.07.2014, vol. 16, no. 14, pp. 3640-3643 (abstract) [online] CAS (STN), 161:211403	1-112

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 2014/058919

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-66, 109-112 (all partially)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty of compounds defined in independent claims 1, 7, 13, 27, 33. Besides, these claims refer to an extreme large number of possible compounds due to the huge breadth of radical definitions, and a meaningful search over the whole breadth of the claims is impossible. Moreover, support and disclosure in the sense of Articles 6 and 5 PCT is to be found for a very small proportion of the compounds claimed. Consequently, the search was restricted to those claimed compounds, which appear to be supported, i.e. compounds specified in claims 67-108.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Classification of subject matter

International application No.
PCT/US 2014/058919

C07D 277/64 *(2006.01)*
C07D 277/66 *(2006.01)*
C07D 293/12 *(2006.01)*
C07D 417/06 *(2006.01)*
C07D 421/06 *(2006.01)*
A61K 31/428 *(2006.01)*
A61K 31/4439 *(2006.01)*
A61K 31/506 *(2006.01)*
A61K 51/04 *(2006.01)*
A61P 25/28 *(2006.01)*
A61P 35/00 *(2006.01)*
C07B 59/00 *(2006.01)*
G01N 33/53 *(2006.01)*
G01N 33/60 *(2006.01)*
A61K 101/02 (2006.01)
A61K 103/00 (2006.01)
A61K 103/10 (2006.01)
A61K 103/30 (2006.01)
A61K 103/32 (2006.01)