



(51) International Patent Classification:

A61K 31/395 (2006.01) A61K 31/415 (2006.01)
A61K 31/505 (2006.01) A61K 31/33 (2006.01)

(21) International Application Number:

PCT/US2024/051310

(22) International Filing Date:

15 October 2024 (15.10.2024)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

63/544,317 16 October 2023 (16.10.2023) US

(71) Applicant: **UNIVERSITY OF PITTSBURGH - OF THE COMMONWEALTH SYSTEM OF HIGHER EDUCATION** [US/US]; University of Pittsburgh Innovation Institute, 1st Floor Gardner Steel Conference Center (GSCC), 130 Thackeray Avenue, Pittsburgh, Pennsylvania 15260 (US).

(72) Inventors: **MATHIS, Chester A., Jr.**; c/o University Of Pittsburgh - Of The Commonwealth System Of Higher Education, University of Pittsburgh Innovation Institute, 1st Floor Gardner Steel Conference Center (GSCC), 130 Thackeray Avenue, Pittsburgh, Pennsylvania 15260 (US). **STEHOUWER, Jeffrey S.**; c/o University Of Pittsburgh - Of The Commonwealth System Of Higher Education, University of Pittsburgh Innovation Institute, 1st Floor Gardner

Steel Conference Center (GSCC), 130 Thackeray Avenue, Pittsburgh, Pennsylvania 15260 (US).

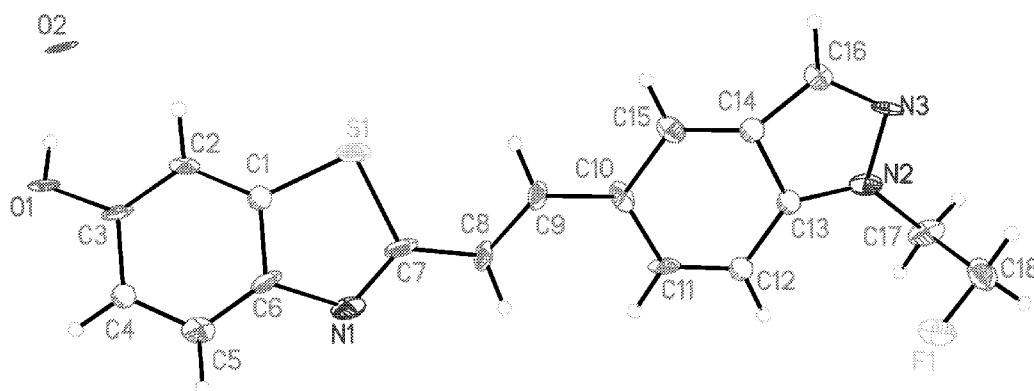
(74) Agent: **SIMKIN, Michele M.** et al.; Foley & Lardner LLP, 3000 K Street NW, Suite 600, Washington, District of Columbia 20007-5109 (US).

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(54) Title: SUBSTITUTED-ALKENYL-INDAZOLES FOR IMAGING AGGREGATED TAU IN TAUOPATHIES

Figure 1



(57) Abstract: Provided are compounds of Formula I or Formula II or their pharmaceutically acceptable salt, solvate, hydrate, formulation, tautomer, stereoisomer, or isotopologue for imaging tau aggregates. Compounds of Formula I or Formula II may be used for the detection of tau aggregates in the diagnosis or monitoring of the progression of a disease or disorder such as Alzheimer's disease, corticobasal degeneration and progressive supranuclear palsy.

Declarations under Rule 4.17:

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

- *with international search report (Art. 21(3))*

SUBSTITUTED-ALKENYL-INDAZOLES FOR IMAGING AGGREGATED TAU IN TAUOPATHIES

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to U.S. Provisional Patent Application No. 63/544,317, filed on October 16, 2023. The contents of this application are incorporated herein by reference in its entirety.

STATEMENT REGARDING FEDERALLY FUNDED RESEARCH

[0002] This invention was made with support from the United States Government under U19 NS110456 awarded by the National Institutes of Health. The government has certain rights in this invention.

BACKGROUND

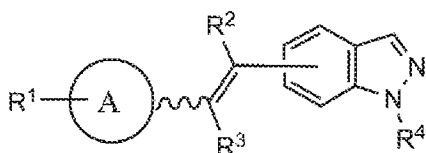
[0003] The development of biomarkers to assess the accumulation of tau protein in the living human brain is crucial to better understand the pathophysiology of non-Alzheimer's Disease (non-AD) tauopathies such as progressive supranuclear palsy (PSP)¹ and corticobasal degeneration (CBD).² 4R-Tau biomarkers could aid clinicians in making more definitive disease diagnoses as well as confirm target engagement and help determine dosing regimens of new anti-tau therapies currently under development. Over the past 20 years, much progress has been made in developing positron emission tomography (PET) imaging biomarkers for AD. While three FDA-approved amyloid- β plaque PET radiopharmaceuticals have become available over the past decade for widespread imaging of amyloid-beta plaques in AD,³⁻⁵ first and second generation AD tau-PET tracers are still emerging.⁶ AD aggregates are comprised of a mixture of both 3R- and 4R-tau, while PSP and CBD tau aggregates are comprised primarily of 4R-tau,⁷ and some PET imaging agents developed for imaging tau deposits in AD (AV-1451, PI-2620, MK-6240, PM-PBB3) may not bind with high affinity to the tau deposits in PSP and CBD patients. Hence, the development of high affinity 4R-tau selective PET imaging agents is among the biggest challenges in PSP and CBD research.⁸ PET imaging studies have been carried out in PSP and CBD patients with [¹⁸F]PI-2620⁹⁻¹¹ and [¹⁸F]APN-1607.^{12,13} However, the in vivo specific signals from the existing 4R-tau

tracers are quite low, and improvement in the binding affinity of 4R-tau PET tracers likely is needed to improve the 4R-tau biomarker imaging signals in PSP and CBD patients.

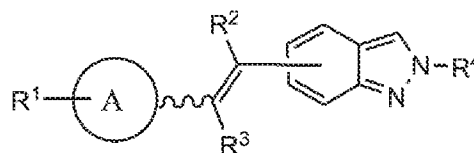
[0004] There is a need in the art for tau binding agents, and the present disclosure satisfies this need.

SUMMARY

[0005] According to one aspect of the present disclosure, described is a compound having a structure of Formula I or Formula II, or a pharmaceutically acceptable salt, solvate, hydrate, formulation, tautomer, stereoisomer, or isotopologue thereof:



Formula I



Formula II

where:

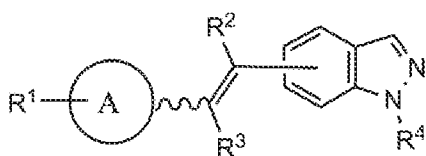
A is aryl or heteroaryl comprising benzothiazolyl, benzisothiazolyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, azaindolyl, benzimidazolyl, indazolyl, azaindazolyl, benzoxazolyl, benzisoxazolyl, benzothiophenyl, benzofuranyl, purinyl, cinnolinyl, phthalazinyl, quinazolinyl, or quinoxalinyl;

R¹ is H, OH, O-alkyl, O-haloalkyl, O-alkylether, O-haloalkylether, O-alkenyl, O-haloalkenyl, 4-fluoro-2-butenyl ether, O-silyl alkyl, glycidyl, glycidyl ether, 3-fluoro-2-hydroxypropyl, 3-fluoro-2-hydroxypropyl ether, amino-3-fluoro-2-hydroxypropyl, halogen, CN, acyl, alkyl, haloalkyl, alkenyl, haloalkenyl, 4-fluoro-2-butenyl, amino-4-fluoro-2-butenyl, cycloalkyl, halocycloalkyl, cycloalkylether, aryl, heteroaryl, NO₂, NH₂, substituted-nitrogen, ammonium salt, OMs, OTs, OTf, O-nosylate, O-brosylate, or other suitable sulfonate species, SnMe₃, SnEt₃, SnPr₃, SnBu₃, or other suitable trialkyltin species, I(O-acyl)₂, ArI⁺X⁻, IR⁵, S(O)Ar, SO₂Ar, BF₃K, B(OH)₂, B(OMe)₂, B(OEt)₂, B(Opr)₂, B(OiPr)₂, B(OiPr)₃Li, B-pinacol, B-neopentyl glycol, or other suitable boron species; wherein X⁻ is a suitable counterion; wherein ArI⁺X⁻ is a suitable iodonium species known in the art; wherein IR⁵ is a suitable iodonium ylide known in the art;

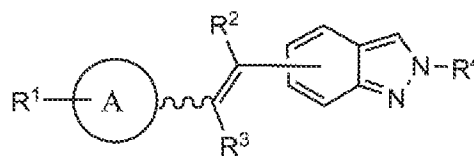
R^2 and R^3 are each independently H, halogen, alkyl, haloalkyl, alkylether, haloalkylether, cycloalkyl, halocycloalkyl, cycloalkylether, halocycloalkylether, aryl, heteroaryl; and

R^4 is H, alkyl, haloalkyl, alkylether, haloalkylether, glycidyl, 3-fluoro-2-hydroxypropyl, 4-fluoro-2-butenyl, cycloalkyl, halocycloalkyl, cycloalkylether, halocycloalkylether, aryl, heteroaryl, *tert*-butoxycarbonyl, tosyl, or other appropriate nitrogen protecting group.

In another aspect, a method for diagnosing a subject with a disease or disorder, and/or monitoring disease or disorder progression in a subject, and/or assessing the accumulation of tau protein in the brain of the subject is provided, the method comprising: (a) administering to the subject a detectable quantity of a labeled compound of Formula I or Formula II, or a pharmaceutically acceptable salt, solvate, hydrate, formulation, tautomer, stereoisomer, or isotopologue thereof:



Formula I



Formula II

where:

A is aryl or heteroaryl comprising benzothiazolyl, benzisothiazolyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, azaindolyl, benzimidazolyl, indazolyl, azaindazolyl, benzoxazolyl, benzisoxazolyl, benzothiophenyl, benzofuranyl, purinyl, cinnolinyl, phthalazinyl, quinazolinyl, or quinoxalinyl;

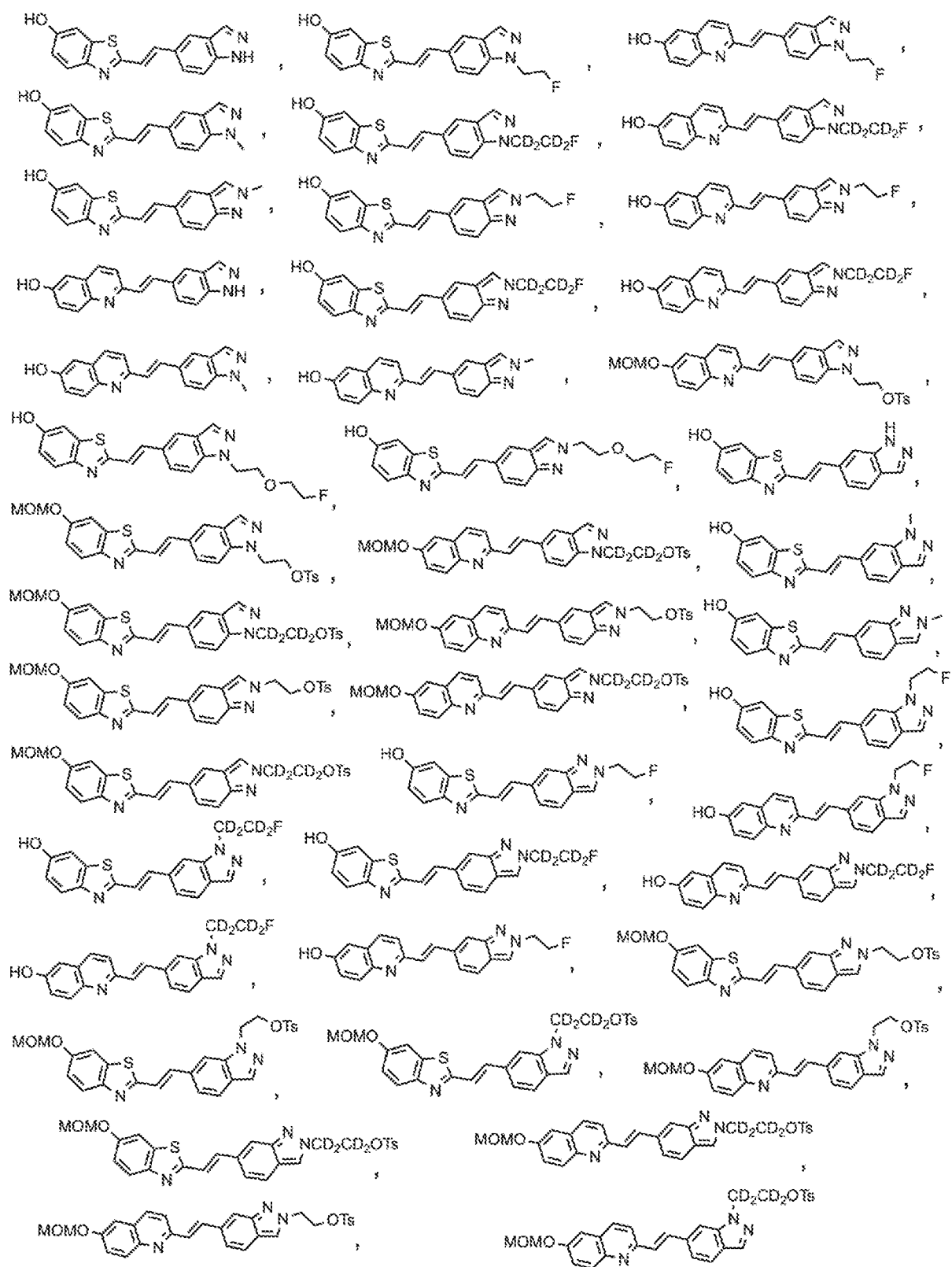
R^1 is H, OH, O-alkyl, O-haloalkyl, O-alkylether, O-haloalkylether, O-alkenyl, O-haloalkenyl, 4-fluoro-2-butenyl ether, O-silyl alkyl, glycidyl, glycidyl ether, 3-fluoro-2-hydroxypropyl, 3-fluoro-2-hydroxypropyl ether, amino-3-fluoro-2-hydroxypropyl, halogen, CN, acyl, alkyl, haloalkyl, alkenyl, haloalkenyl, 4-fluoro-2-butenyl, amino-4-fluoro-2-butenyl, cycloalkyl, halocycloalkyl, cycloalkylether, aryl, heteroaryl, NO_2 , NH_2 , substituted-nitrogen, ammonium salt, OMs, OTs, OTf, O-nosylate, O-brosylate, or other suitable sulfonate species, SnMe_3 , SnEt_3 , SnPr_3 , SnBu_3 , or other suitable trialkyltin species, $\text{I}(\text{O-acyl})_2$, ArI^+X^- , IR^5 , $\text{S}(\text{O})\text{Ar}$, SO_2Ar , BF_3K , $\text{B}(\text{OH})_2$, $\text{B}(\text{OMe})_2$, $\text{B}(\text{OEt})_2$, $\text{B}(\text{Opr})_2$, $\text{B}(\text{O}i\text{Pr})_2$, $\text{B}(\text{O}i\text{Pr})_3\text{Li}$, B-pinacol, B-neopentyl glycol, or other suitable boron species; wherein X^- is a

suitable counterion; wherein ArI^+X^- is a suitable iodonium species known in the art; wherein IR^5 is a suitable iodonium ylide known in the art;

R^2 and R^3 are each independently H, halogen, alkyl, haloalkyl, alkylether, haloalkylether, cycloalkyl, halocycloalkyl, cycloalkylether, halocycloalkylether, aryl, heteroaryl; and

R^4 is H, alkyl, haloalkyl, alkylether, haloalkylether, glycidyl, 3-fluoro-2-hydroxypropyl, 4-fluoro-2-butenyl, cycloalkyl, halocycloalkyl, cycloalkylether, halocycloalkylether, aryl, heteroaryl, *tert*-butoxycarbonyl, tosyl, or other appropriate nitrogen protecting group; and (b) detecting binding of the compound to tau aggregates in the subject.

[0006] In some embodiments, the compound has a structure a structure selected from the following group:



[0007] In some embodiments, the compound binds to any form of aggregated tau. In some embodiments, the compound binds to 3R tau. In some embodiments, the compound binds to 4R tau. In some embodiments, the compound binds to mixed 3R/4R tau.

[0008] In some embodiments, the compound comprises one or more detection labels, and in some embodiments, the detection label is selected from the group consisting of a radionuclide, a positron emitter, an alpha emitter, a gamma emitter, and a fluorescent label.

[0009] In some embodiments, the compound is isotopically labeled with ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{18}F , ^{75}Br , ^{76}Br , ^{77}Br , ^{123}I , ^{124}I , ^{125}I , or ^{131}I . In some embodiments, the detection label is ^{18}F .

[0010] In some embodiments, the compound is used in detection and/or monitoring progression of a disorder or disease, wherein the disease or disorder is a neurodegenerative disease or disorder.

[0011] In some embodiments, the disease or disorder is associated with aberrant protein aggregation. In some embodiments, the disease or disorder is associated with tau protein aggregates.

[0012] In some embodiments, the aberrant protein aggregation is selected from the group consisting of Paired helical filaments in neurofibrillary tangles, Straight filaments and paired helical filaments, Pick bodies, and Straight filaments in neurofibrillary tangles.

[0013] In some embodiments, the disease or disorder is a 3R-tauopathy or a disease or disorder correlated with aggregates of 3R tau. In some embodiments, the disease or disorder is a 4R-tauopathy or a disease or disorder correlated with aggregates of 4R tau. In some embodiments, the disease or disorder is a mixed 3R/4R-tauopathy or a disease or disorder correlated with aggregates of mixed 3R/4R tau.

[0014] In some embodiments, the disorder or disease is selected from the group consisting of a Tauopathy, Alzheimer's Disease (AD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), corticobasal syndrome (CBS), frontal temporal lobar dementias (FTLD's), Parkinson's Disease (PD), frontotemporal dementia, frontotemporal dementia with parkinsonism-17 (FTDP-17), chronic traumatic encephalopathy (CTE), primary age-related tauopathy (PART), Pick's disease, argyrophilic grain disease, glial globular tauopathy, Guam

ALS/parkinsonism, Huntington's disease, Lewy body dementia, and Chronic traumatic encephalopathy.

[0015] In some embodiments, detection is carried out by one or more of positron emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), autoradiography, or fluorescence. In some embodiments, detection is carried out by positron emission tomography (PET) imaging.

[0016] In some embodiments, detecting binding of the compound to tau aggregates in the subject comprises obtaining a biological sample from the subject, followed by evaluating the biological sample for the presence of tau aggregates. In some embodiments, the biological sample is selected from the group consisting of blood, cerebrospinal fluid (CSF) and the fluid surrounding the brain.

[0017] Both the foregoing summary and the following description of the drawings and detailed description are exemplary and explanatory. They are intended to provide further details of the disclosure, but are not to be construed as limiting. Other objects, advantages, and novel features will be readily apparent to those skilled in the art from the following detailed description of the disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] FIG. 1 shows the X-ray crystal structure of Compound 18.

[0019] FIG. 2 shows the X-ray crystal structure of Compound 24.

DETAILED DESCRIPTION

I. Overview

[0020] The present invention is directed to the discovery of new compounds that bind to aggregated tau. The compounds are useful for example in methods of imaging aggregated tau in tauopathies.

[0021] Tau is a protein that helps stabilize the internal skeleton of nerve cells (neurons) in the brain. This internal skeleton has a tube-like shape (microtubules). Tauopathies are age-related neurodegenerative diseases that are characterized by the presence of aggregates of

abnormally phosphorylated tau. In these neurodegenerative diseases, tau detaches from microtubules to form insoluble aggregates leading to tauopathy.

[0022] Six different isoforms of the microtubule-associated protein tau exist in the human adult brain: 0N3R, 0N4R, 1N3R, 1N4R, 2N3R, 2N4R. These isoforms differ in the number of N-terminal inserts (0N, 1N, 2N) and C-terminal repeat domains (3R or 4R) and are differentially expressed depending on the brain region and developmental stage. Human adult tau has approximately equal representation of 3R and 4R tau isoforms, with the 1N3R and 1N4R being the most abundant forms.

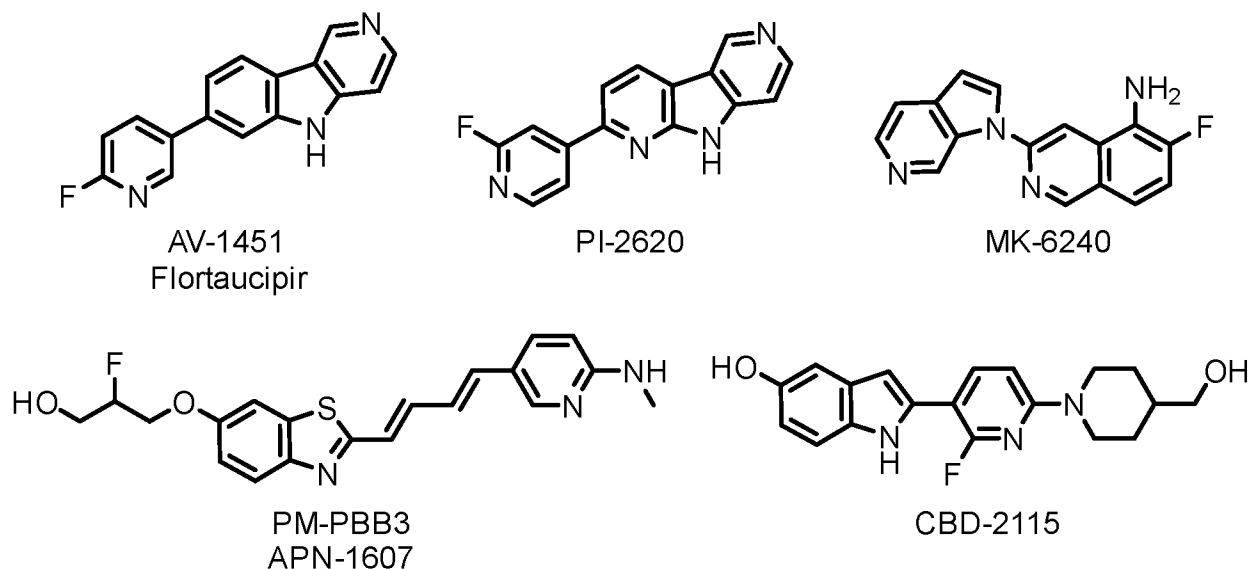
[0023] As used herein, “tau” refers to a highly soluble microtubule binding protein mostly found in neurons and includes the major 6 isoforms, cleaved or truncated forms, and other modified forms such as arising from phosphorylation, glycosylation, glycation, prolyl isomerization, nitration, acetylation, polyamination, ubiquitination, sumoylation and oxidation.

[0024] Although all tau isoforms can aggregate and form neurofibrillary tangles, some tauopathies, such as Pick’s disease and progressive supranuclear palsy, are characterized by the accumulation of specific tau isoforms. AD aggregates are comprised of a mixture of both 3R- and 4R-tau (mixed 3R/4R tau), while PSP and CBD tau aggregates are comprised primarily of 4R-tau.⁷ Expression of the 3R isoform causes more profound axonal transport defects and locomotor impairments, culminating in a shorter lifespan than the 4R isoform. In contrast, the 4R isoform leads to greater neurodegeneration and impairments in learning and memory. Tau isoform expression is directly linked to brain development: during neurogenesis, only the shortest TAU isoform, 0N3R, is expressed, whereas in the adult brain, all six isoforms are present with roughly equal amounts of 3R and 4R isoforms.

[0025] Diagnosis of 4R tau specific neurological diseases has a number of benefits. The development of biomarkers to assess the accumulation of tau protein in the living human brain is crucial to better understand the pathophysiology of AD, as well as non-Alzheimer’s Disease (non-AD) tauopathies, such as progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). 4R-Tau biomarkers can aid clinicians in making more definitive disease diagnoses as well as confirm target engagement and help determine dosing regimens of new anti-tau therapies currently under development.

[0026] Over the past 20 years, much progress has been made in developing positron emission tomography (PET) imaging biomarkers for AD. While several FDA-approved amyloid- β plaque PET radiopharmaceuticals have become available over the past decade for widespread imaging of amyloid-beta plaques in AD (AV-1451, PI-2620, MK-6240, and PM-PBB3), first and second generation AD tau-PET tracers are still emerging. AD aggregates are comprised of a mixture of both 3R- and 4R-tau, while PSP and CBD tau aggregates are comprised primarily of 4R-tau, and PET imaging agents developed for imaging tau deposits in AD (AV-1451, PI-2620, MK-6240, PM-PBB3) may not bind with high affinity to the tau deposits in PSP and CBD patients. Hence, the development of high affinity 4R-tau selective PET imaging agents is among the biggest challenges in PSP and CBD research.⁸ For example, PET imaging studies have been carried out in PSP and CBD patients with [^{18}F]PI-2620 and [^{18}F]APN-1607.¹²⁻¹³

[0027] Previously reported tau ligands include the following:



[0028] ^{18}F -flortaucipir (AV-1451) is a tau PET ligand which binds to paired helical filaments of tau in aging and AD, but its utility in detecting aggregates in frontotemporal dementia is uncertain. PI-2620 and MK-6240 are second generation tau PET tracers, as well as PM-PBB3 and CBD-2115.

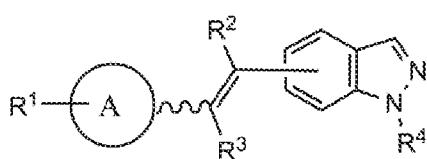
[0029] However, the *in vivo* specific signals from the existing tau tracers are quite low, and improvement in the tau biomarker imaging signals in PSP and CBD patients is needed. The

present invention surprisingly and unexpectedly addresses this problem present in the prior art.

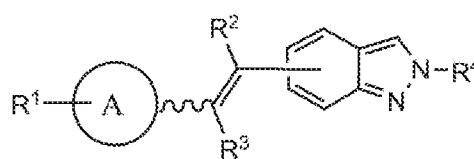
II. Compounds

[0030] Provided herein are compounds for imaging aggregated tau in tauopathies. The compounds described herein bind to aggregated tau at different binding sites compared to some of the other known tau ligands. Additionally, the compounds described herein do not bind to the PM-PBB3 binding site on α -synuclein, nor do the compounds bind to the PiB (Pittsburgh Compound-B) binding site on amyloid-beta. Further, the compounds described herein are photochemically stable, whereas known butadiene-based tau ligands, such as PM-PBB3, PBB3, PBQ3, and related compounds such as those in WO 2014/097474, isomerize and/or decompose under visible light.

[0031] The compounds described herein have a structure of Formula I or Formula II, or a pharmaceutically acceptable salt, solvate, hydrate, formulation, tautomer, stereoisomer, or isotopologue thereof:



Formula I



Formula II

where:

A is aryl or heteroaryl comprising benzothiazolyl, benzisothiazolyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, azaindolyl, benzimidazolyl, indazolyl, azaindazolyl, benzoxazolyl, benzisoxazolyl, benzothiophenyl, benzofuranyl, purinyl, cinnolinyl, phthalazinyl, quinazolinyl, or quinoxalinyl;

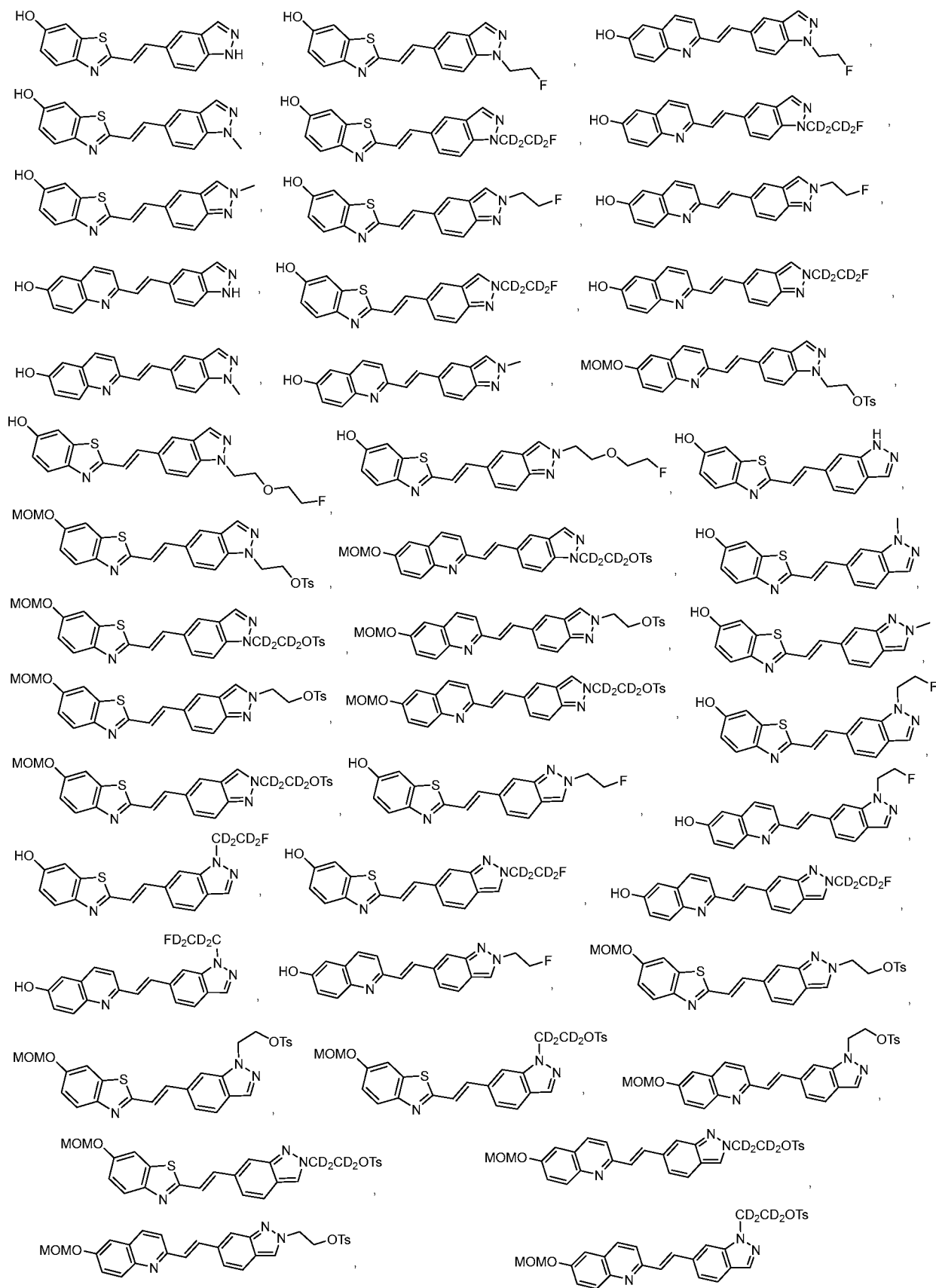
R¹ is H, OH, O-alkyl, O-haloalkyl, O-alkylether, O-haloalkylether, O-alkenyl, O-haloalkenyl, 4-fluoro-2-butenyl ether, O-silyl alkyl, glycidyl, glycidyl ether, 3-fluoro-2-hydroxypropyl, 3-fluoro-2-hydroxypropyl ether, amino-3-fluoro-2-hydroxypropyl, halogen, CN, acyl, alkyl, haloalkyl, alkenyl, haloalkenyl, 4-fluoro-2-butenyl, amino-4-fluoro-2-butenyl, cycloalkyl, halocycloalkyl, cycloalkylether, aryl, heteroaryl, NO₂, NH₂, substituted-nitrogen, ammonium salt, OMs, OTs, OTf, O-nosylate, O-brosylate, or other suitable

sulfonate species, SnMe_3 , SnEt_3 , SnPr_3 , SnBu_3 , or other suitable trialkyltin species, $\text{I}(\text{O-acyl})_2$, ArI^+X^- , IR^5 , $\text{S}(\text{O})\text{Ar}$, SO_2Ar , BF_3K , $\text{B}(\text{OH})_2$, $\text{B}(\text{OMe})_2$, $\text{B}(\text{OEt})_2$, $\text{B}(\text{Opr})_2$, $\text{B}(\text{OiPr})_2$, $\text{B}(\text{OiPr})_3\text{Li}$, B-pinacol, B-neopentyl glycol, or other suitable boron species; wherein X^- is a suitable counterion; wherein ArI^+X^- is a suitable iodonium species known in the art; wherein IR^5 is a suitable iodonium ylide known in the art;

R^2 and R^3 are each independently H, halogen, alkyl, haloalkyl, alkylether, haloalkylether, cycloalkyl, halocycloalkyl, cycloalkylether, halocycloalkylether, aryl, heteroaryl; and

R^4 is H, alkyl, haloalkyl, alkylether, haloalkylether, glycidyl, 3-fluoro-2-hydroxypropyl, 4-fluoro-2-butenyl, cycloalkyl, halocycloalkyl, cycloalkylether, halocycloalkylether, aryl, heteroaryl, *tert*-butoxycarbonyl, tosyl, or other appropriate nitrogen protecting group.

[0032] The compound of Formula I or Formula II may have one of the following structures:



[0033] The salts of the compounds of Formula I or Formula II may be pharmaceutically acceptable salts. Other salts may be useful in the preparation of the compounds according to the disclosure or of their pharmaceutically acceptable salts.

[0034] When the compound of the present disclosure is acidic, suitable "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

[0035] When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pantoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric and tartaric acids.

[0036] A "nitrogen protecting group" is any protecting group which is suitable for protecting a nitrogen group during an envisaged chemical reaction. Examples of suitable protecting groups are well-known to a person skilled in the art. Examples thereof include but are not limited to carbamates, amides, imides, N-alkyl amines, N-aryl amines, imines and enamines.

Suitable protecting groups are discussed, e.g., in the textbook Greene and Wuts, Protecting groups in Organic Synthesis, third edition, page 494-653, which is included herein by reference. Specific preferred examples of the nitrogen-protecting groups include tert-butyloxycarbonyl (Boc), trimethylsilylethoxycarbonyl (Teoc), carbobenzyloxy (Cbz), p-methoxybenzyl carbonyl (Moz or MeOZ), 9-fluorenylmethyloxycarbonyl (Fmoc), acetyl (Ac), or trifluoroacetyl.

[0037] Compounds of Formula I or Formula II may be labelled. A "label" (which may be a radiolabel or other detectable label, or a tag, marker, detectable marker, tracer, radiotracer or equivalent) is any atom or group suitable for imaging and/or assaying (for example, identifying, imaging, diagnosing, evaluating, detecting and/or quantitating) *in vivo* or *in vitro*, and in particular imaging and diagnosing. Suitable labels include, for example, radioisotopes (which may also be referred to as "radiolabeled atoms"), radionuclides, isotopes, positron emitters, alpha emitters, gamma emitters, fluorescent groups, luminescent groups, chromogenic groups, biotin (in conjunction with streptavidin complexation) or photoaffinity groups. The type of label chosen will depend on the desired detection method. The position at which the label is integrated or attached to the compounds of the present invention is not particularly limited. In some embodiments, the compounds of the present disclosure comprise one or more detection labels.

[0038] Examples of isotopes (such as stable isotopes, radioisotopes, radionuclides, positron emitters and gamma emitters) which may be used to label compounds of the invention, include but are not limited to: ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{18}F , ^{75}Br , ^{76}Br , ^{77}Br , ^{123}I , ^{124}I , ^{125}I , and ^{131}I . In some embodiments, the compound is labelled with ^{18}F .

[0039] In some embodiments, the compounds of the present disclosure selectively bind to aggregated tau. The aggregated tau may be 3R-tau, 4R tau, or mixed 3R/4R-tau. In some embodiments, the compounds of the present disclosure can bind tau aggregates both *in vivo* and *in vitro*.

[0040] In an aspect, provided are compositions comprising any one of the compounds of the present disclosure and a pharmaceutically acceptable carrier. In another aspect, provided are pharmaceutical compositions comprising an effective amount of any one of the compounds of the present disclosure and a pharmaceutically acceptable carrier.

[0041] In some embodiments, the compounds of the present disclosure may be for use as a diagnostic agent (for *in vivo* and/or *in vitro* diagnostic use) in the diagnosis of disease or disorder associated with aberrant protein aggregation. In some embodiments, the protein in the aberrant protein aggregation is tau protein. In some embodiments, the compounds of the present disclosure are for use in detection of a disorder or disease associated with tau aggregates.

[0042] In some embodiments, the compounds of the present disclosure are for use in monitoring of a disorder or disease associated with tau aggregates. In some embodiments, the disease or disorder is a 4R-tauopathy or a disease or disorder correlated with aggregates of 4R tau. In some embodiments, the disease or disorder is a 3R-tauopathy or a disease or disorder correlated with aggregates of 3R tau. In some embodiments, the disease or disorder is a mixed 3R/4R-tauopathy or a disease or disorder correlated with aggregates of 3R/4R tau.

[0043] In some embodiments, the disease or disorder is a neurodegenerative disease or disorder. In some embodiments, the disease or disorder is selected from the group consisting of a tauopathy, Alzheimer's Disease (AD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), corticobasal syndrome (CBS), frontal temporal lobar dementias (FTLD's), Parkinson's Disease (PD), frontotemporal dementia, frontotemporal dementia with parkinsonism-17 (FTDP-17), chronic traumatic encephalopathy (CTE), primary age-related tauopathy (PART), Pick's disease, argyrophilic grain disease, glial globular tauopathy, Guam ALS/parkinsonism, Huntington's disease, Lewy body dementia, and Chronic traumatic encephalopathy.

III. Methods

[0044] Also provided herein are methods for diagnosing a subject with a disease or disorder, and/or monitoring disease or disorder progression in a subject, and/or assessing the accumulation of tau protein in the brain of the subject. In one aspect, the disease or disorder is a neurodegenerative disease or disorder associated with aberrant protein aggregation.

[0045] In some embodiments, the aberrant protein aggregation is selected from the group consisting of Paired helical filaments in neurofibrillary tangles, Straight filaments and paired helical filaments, Pick bodies, and Straight filaments in neurofibrillary tangles.

[0001] In one aspect, encompassed is a method of diagnosing a subject with a neurodegenerative disease characterized by the accumulation of 3R tau, 4R tau, or mixed 3R/4R tau aggregates in the subject, followed by administering a treatment for the disease or disorder. The disease or disorder can be, for example, a Tauopathy, Alzheimer's Disease (AD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), corticobasal syndrome (CBS), frontal temporal lobar dementias (FTLD's), Parkinson's Disease (PD), frontotemporal dementia, frontotemporal dementia with parkinsonism-17 (FTDP-17), chronic traumatic encephalopathy (CTE), primary age-related tauopathy (PART), Pick's disease, argyrophilic grain disease, glial globular tauopathy, Guam ALS/parkinsonism, Huntington's disease, Lewy body dementia, and Chronic traumatic encephalopathy.

[0002] The methods of the disclosure can comprise (a) administering to a subject in need a detectable quantity of an isotopically labeled compound of Formula I or Formula II, or a pharmaceutically acceptable salt, solvate, hydrate, formulation, tautomer, stereoisomer, or isotopologue thereof; and (b) detecting binding of the compound to tau aggregates in the patient.

[0046] In some embodiments, detection is carried out by one or more of positron emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), autoradiography, or fluorescence. In some embodiments, detection is carried out by positron emission tomography (PET) imaging.

IV. Definitions

[0047] As used herein, the term "alkyl" refers to both straight and branched chain saturated hydrocarbon groups. Examples of alkyl groups include methyl, ethyl, n-propyl, iso-propyl, n-butyl, t-butyl, i-butyl, sec-butyl, pentyl and hexyl groups. Examples of unbranched alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, n-butyl groups. Examples of branched alkyl groups include, but are not limited to, isopropyl, tertbutyl, isobutyl, 1-ethylpropyl and 1-ethylbutyl groups.

[0048] The term "alkenyl", as used herein, refers to a straight or branched monovalent hydrocarbon radical having at least one carbon-carbon double bond. Examples of alkenyl groups include, but are not limited to, ethenyl, propenyl, isobutenyl, butadienyl and the like.

[0049] The term "halogen," by itself or as part of another substituent, means, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl" and "haloalkoxy" refer to alkyl groups and alkoxy groups, respectively, as defined herein, that are substituted with one or more halogen(s) (e.g., 1-3 halogen(s)). For example, the term "C₁-C₄ haloalkyl" is meant to include trifluoromethyl, difluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like. As another example, the term "C₁-C₃ haloalkoxy" is meant to include trifluoromethoxy, difluoromethoxy, 2,2,2-trifluoroethoxy, 2,2-difluoroethoxy, and the like.

[0050] The term "cycloalkyl" refers to a monocyclic, bicyclic or polycyclic hydrocarbon ring system having, in some embodiments, 3 to 14 carbon atoms (e.g., C₃-C₁₄ cycloalkyl), or 3 to 10 carbon atoms (e.g., C₃-C₁₀ cycloalkyl), or 3 to 8 carbon atoms (e.g., C₃-C₈ cycloalkyl), or 3 to 6 carbon atoms (e.g., C₃-C₆ cycloalkyl) or 3 to 4 carbon atoms (e.g., C₃-C₄ cycloalkyl). Cycloalkyl groups can be saturated or characterized by one or more points of unsaturation (i.e., carbon-carbon double and/or triple bonds), provided that the points of unsaturation do not result in an aromatic system. Examples of monocyclic cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, cycloheptadienyl, cyclooctyl, cyclooctenyl, cyclooctadienyl and the like. The rings of bicyclic and polycyclic cycloalkyl groups can be fused, bridged, or spirocyclic. Non-limiting examples of bicyclic, spirocyclic and polycyclic cycloalkyl groups include bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, adamantyl, indanyl, spiro[5.5]undecane, spiro[2.2]pentane, spiro[2.2]pentadiene, spiro[2.3]hexane, spiro[2.5]octane, spiro[2.2]pentadiene, and the like. In some embodiments, the cycloalkyl groups of the present disclosure are monocyclic C₃-C₆ cycloalkyl moieties (e.g., cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In some embodiments, the cycloalkyl groups of the present disclosure are monocyclic C₃-C₄ cycloalkyl moieties (e.g., cyclopropyl, or cyclobutyl).

[0051] The term "aryl" refers to an aromatic ring system containing one ring, or two or three rings fused together, and having, in some embodiments, six to fourteen (i.e., C₆-C₁₄ aryl), or six to ten (i.e., C₆-C₁₀ aryl), or six (i.e., C₆ aryl) carbon atoms. Non-limiting examples of aryl groups include phenyl, naphthyl and anthracenyl. In some embodiments, aryl groups are phenyl.

[0052] The term "heteroaryl" refers to monocyclic or fused bicyclic aromatic groups (or rings) having, in some embodiments, from 5 to 14 (i.e., 5- to 14-membered heteroaryl), or from 5 to 10 (i.e., 5- to 10-membered heteroaryl), or from 5 to 6 (i.e., 5- to 6-membered heteroaryl) members (i.e., ring vertices), and containing from one to five, one to four, one to three, one to two or one heteroatom independently selected from nitrogen (N), oxygen (O), and sulfur (S). A heteroaryl group can be attached to the remainder of the molecule through a carbon atom or a heteroatom of the heteroaryl group, when chemically permissible. Non-limiting examples of heteroaryl groups include pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, purinyl, thienopyridinyl, thienopyrimidinyl, pyrazolopyrimidinyl, imidazopyridines, isothiazolyl, pyrazolyl, indazolyl, pteridinyl, imidazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiadiazolyl, pyrrolyl, thiazolyl, furyl, thienyl and the like. In some embodiments, the heteroaryl groups of the present disclosure are monocyclic 5- to 6-membered heteroaryl moieties having 1-3 heteroatoms independently selected from N, O, and S (e.g., pyridinyl, pyrimidinyl, pyridazinyl, triazolyl, imidazolyl, pyrazolyl, oxazolyl, oxadiazolyl, or thiazolyl). In some embodiments, the heteroaryl groups of the present disclosure are monocyclic 5- to 6-membered heteroaryl moieties having 1-2 ring nitrogen atoms (e.g., pyridinyl, pyrimidinyl, pyridazinyl, imidazolyl, or pyrazolyl).

[0053] As used herein, "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio.

[0054] "Effective amount" refers to the amount of a compound or composition required to produce a desired effect. One example of an effective amount includes amounts or dosages that yield acceptable levels for detecting a quantity of a labeled compound of Formula I or Formula II.

[0055] The terms "patient" or "subject" are used interchangeably to refer to a human or a non-human animal (e.g., a mammal).

[0056] As used herein, "about" will be understood by persons of ordinary skill in the art and will vary to some extent depending upon the context in which it is used. If there are uses of

the term which are not clear to persons of ordinary skill in the art, given the context in which it is used, “about” will mean up to plus or minus 10% of the particular term.

[0057] The use of the terms “a” and “an” and “the” and similar referents in the context of describing the elements (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (*e.g.*, “such as”) provided herein, is intended merely to better illuminate the embodiments and does not pose a limitation on the scope of the claims unless otherwise stated. No language in the specification should be construed as indicating any non-claimed element as essential.

[0058] Various embodiments are described hereinafter. It should be noted that the specific embodiments are not intended as an exhaustive description or as a limitation to the broader aspects discussed herein. One aspect described in conjunction with a particular embodiment is not necessarily limited to that embodiment and can be practiced with any other embodiment(s).

[0059] The present invention, thus generally described, will be understood more readily by reference to the following examples, which are provided by way of illustration and are not intended to be limiting of the present invention.

EXAMPLES

[0047] **Example 1. Synthesis of tau ligands**

[0048] General reactions schemes to synthesize Compounds 1-44

[0049] 1*H*-Indazole-5-carbaldehyde was *N*-alkylated with various groups (**Scheme 1** shown below) to give *N*¹-substituted compounds **1 – 5** and *N*²-substituted compounds **6 – 9**.

[0050] 2-Methylbenzothiazol-6-ol and 2-Methylquinolin-6-ol (**Scheme 2** shown below) were each *O*-protected with TBDMS-Cl to give compound **10** and compound **11** which were then

each converted to the diethyl phosphonate compound **12** and compound **13**, and compound **14**, respectively. Compound **12** was reacted with compound **1** to give compound **15** which was then deprotected with KHF₂ to give compound **16**. When compound **12** was reacted with compound **2**, compound **17** and the *O*-deprotected compound **18** (X-ray crystal structure shown in FIG. 1) were both obtained, while reaction of compound **12** with compound **3** afforded only the *O*-deprotected compound **19**. Reaction of compound **12** with compound **5** gave compound **20** which was then deprotected with TFA to afford compound **21**.

[0051] In another instance compound **21** was obtained directly from the reaction of compound **12** and compound **5** without obtaining the Boc-protected intermediate compound **20**. Reaction of compound **12** with compound **6** gave compound **22** which was then deprotected with KHF₂ to give compound **23**. Reaction of compound **12** with compound **7** afforded only the *O*-deprotected compound **24** (X-ray crystal structure shown in FIG. 2) while reaction of compound **12** with compound **8** afforded both compound **25** and *O*-deprotected compound **26**.

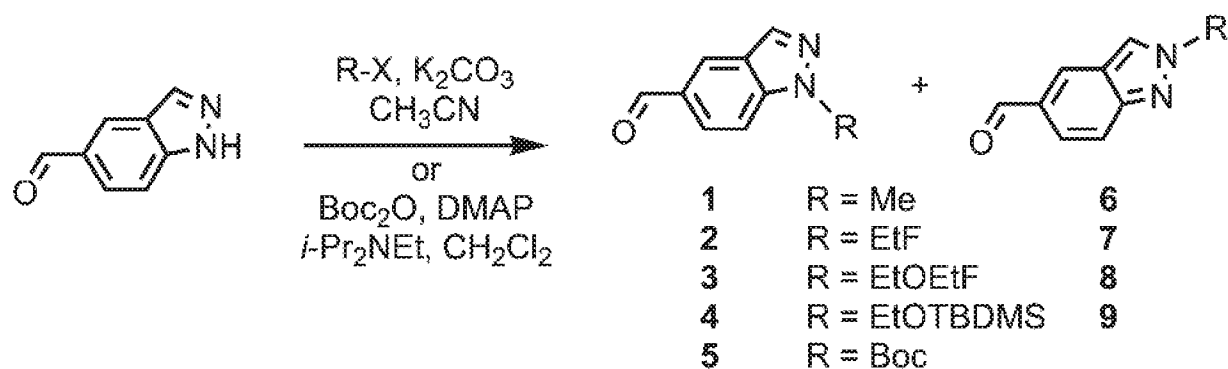
[0052] Compound **14** was reacted with compound **1** or compound **2** to give the *O*-deprotected compound **27** and compound **28**, respectively, while reaction of compound **14** with compound **7** gave compound **29** along with the *O*-deprotected compound **30**. 2-Methylbenzothiazol-6-ol was reacted with MOM-Br (**Scheme 3** shown below) to give the MOM-protected compound **31** which was then converted to the diethyl phosphonate compound **32**.

[0053] Compound **32** was also obtained by reacting compound **13** with MOM-Br. Reaction of compound **32** with compound **4** and compound **9** gave compound **33** and compound **34**, respectively.

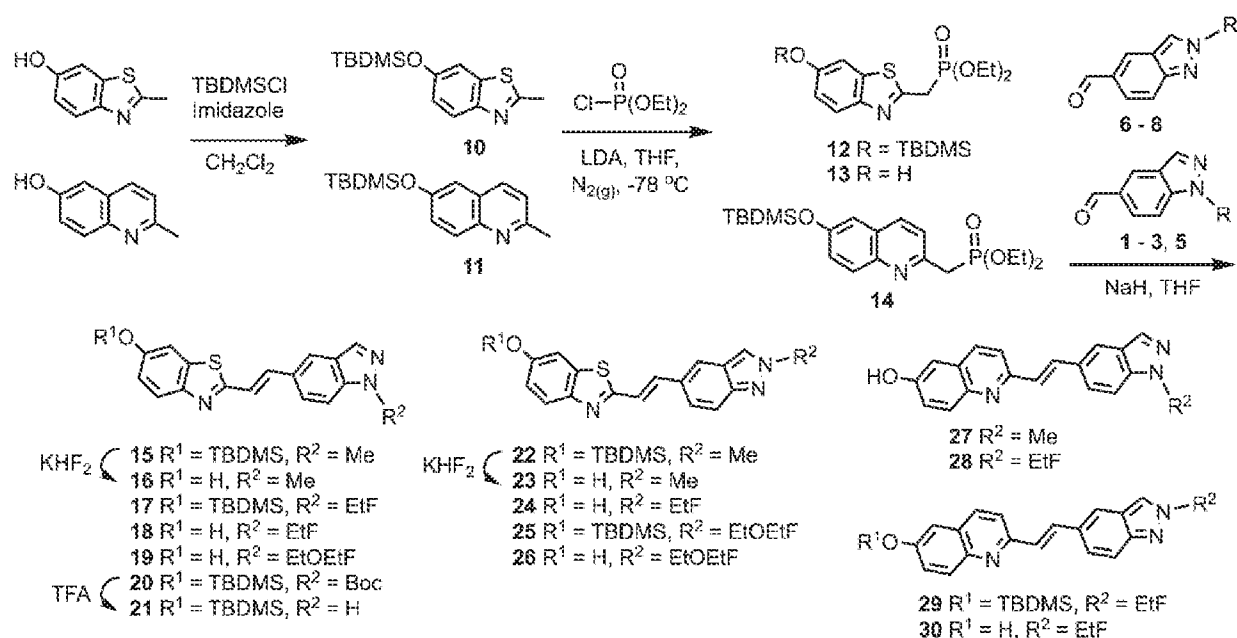
[0054] 1*H*-Indazole-6-carbaldehyde was reacted with methyl tosylate (**Scheme 4** shown below) to give *N*¹-methyl-substituted indazole compound **35** and *N*²-methyl-substituted indazole compound **36**. 1*H*-Indazole-6-carbaldehyde was reacted with fluoroethyltosylate (**Scheme 4** shown below) to give *N*¹-fluoroethyl-substituted indazole compound **37** and *N*²-fluoroethyl-substituted indazole compound **38**. Compound **12** was reacted with compound **35** (**Scheme 5** shown below) to give compound **39**, with compound **37** to give compound **40**, with compound **36** to give compound **41**, and with compound **38** to give compound **42**.

Compound **14** was reacted with compound **37** (**Scheme 5** shown below) to give compound **43**, and with compound **38** to give compound **44**.

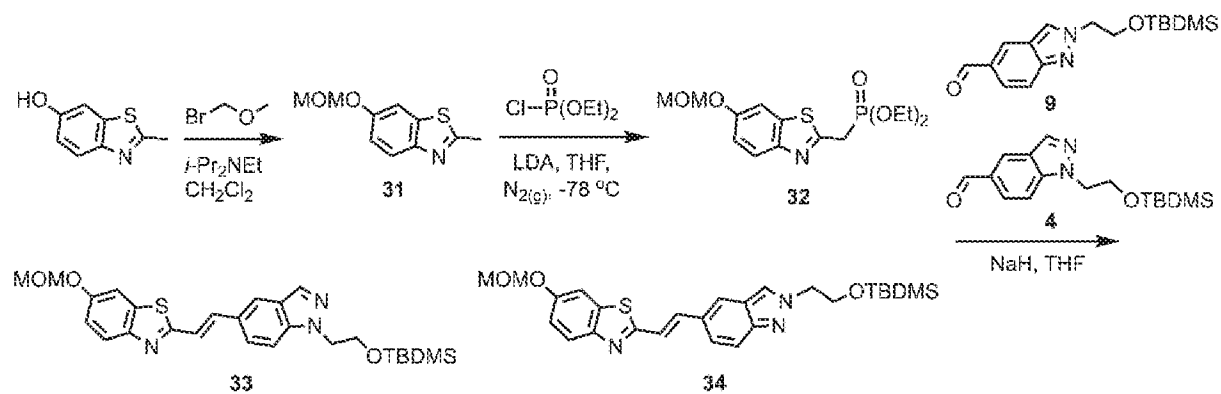
Scheme 1



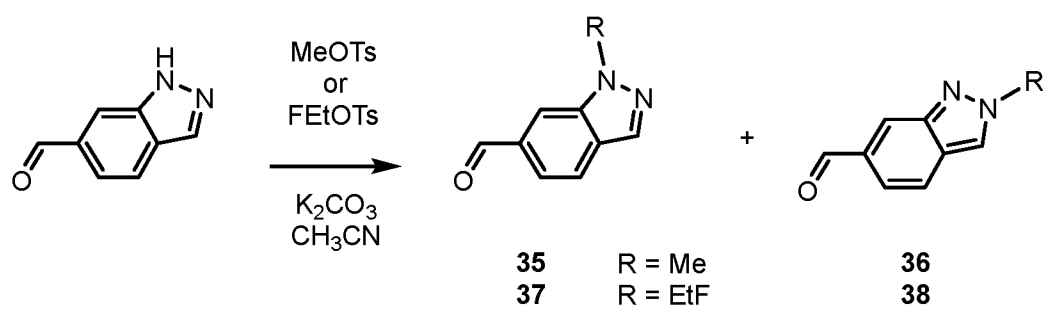
Scheme 2



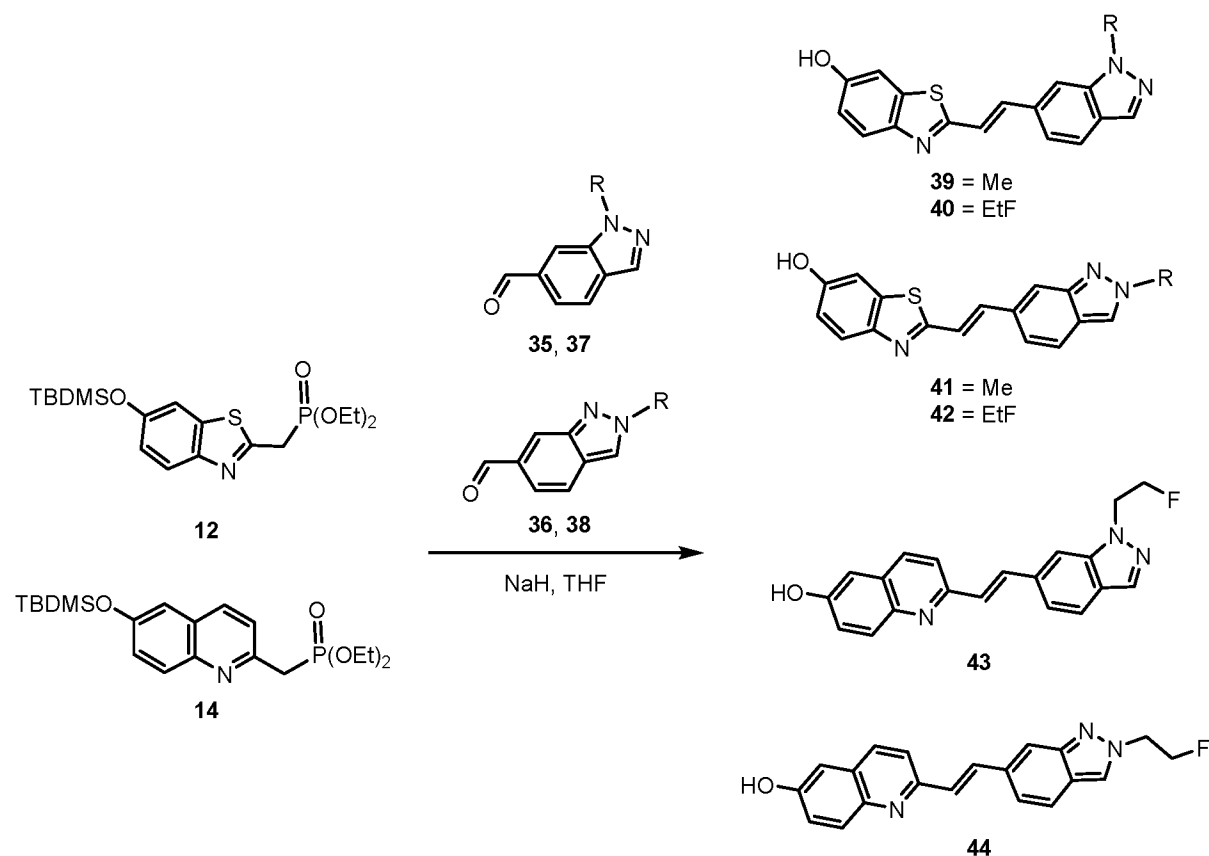
Scheme 3



Scheme 4



Scheme 5



[0055] *Synthesis of Compounds 1-44*

[0056] Solvents and reagents were used as received. NMR spectra were obtained on Bruker Avance III spectrometers at the specified frequencies. Spectra in CDCl₃ are referenced to internal TMS, spectra in other deuterated solvents are referenced to solvent residual protons.

[0057] *N*-Methylation of 1*H*-indazole-5-carbaldehyde to give Compound 1 and Compound 6.

[0058] 1*H*-Indazole-5-carbaldehyde (0.41 g, 2.81 mmol), methyl tosylate (0.64 g, 3.44 mmol, 1.2 equiv.), and K₂CO₃ (0.92 g, 6.66 mmol, 2.4 equiv.) were flushed with N_{2(g)}, then CH₃CN (30 mL) was added. The reaction mixture was stirred at reflux under N_{2(g)} for 15 h, then cooled to ambient temperature, filtered, and the precipitate was rinsed with CH₃CN. The CH₃CN was removed from the filtrate to give an orange syrup, then CH₂Cl₂ and hexane were

added and removed to give an orange residue that was dissolved in CH₂Cl₂, poured onto dry silica (55 mm h x 45 mm i.d.), and eluted under vacuum: CH₂Cl₂ (100 mL), %MeOH/CH₂Cl₂ – 1% (100 mL), 2% (100 mL), 3% (100 mL), 5% (200 mL) to give a yellow/orange residue (0.38 g). Purification by radial chromatography (2 mm silica): CH₂Cl₂ (250 mL), %MeOH/CH₂Cl₂ – 1% (50 mL), 2% (50 mL) gave crude **Compound 1** (yellow solid, 0.25 g) and crude **Compound 6** (light yellow solid, 97 mg) which were further purified as described below.

[0059] 1-methyl-1H-indazole-5-carbaldehyde (Compound 1).

[0060] Crude **Compound 1** (from above) was purified by radial chromatography (2 mm silica): CH₂Cl₂ (150 mL), 1% MeOH/CH₂Cl₂ (100 mL) to afford **Compound 1** (0.23 g, 51%) as an off-white/faint-yellow solid: TLC *R_f* = 0.43 (silica, 3% MeOH/CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 10.05 (s, 1 H), 8.26 (apparent s, 1 H), 8.16 (apparent s, 1 H), 7.96 (dd, 1 H, *J* = 8.8 Hz, *J* = 1.2 Hz), 7.49 (d, 1 H, *J* = 8.8 Hz), 4.13 (s, 3 H); ¹H NMR (300 MHz, CDCl₃) δ 10.05 (s, 1 H), 8.26 (partially resolved apparent q, 1 H, *J* = 0.6 Hz), 8.16 (partially resolved d, 1 H, *J* = 0.6 Hz), 7.96 (dd, 1 H, *J* = 8.7 Hz, *J* = 1.5 Hz), 7.49 (d, 1 H, *J* = 8.7 Hz), 4.13 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 191.61, 142.27, 135.15, 130.50, 127.67, 125.35, 123.85, 109.83, 35.92. X-ray quality crystals were grown by slow evaporation of CDCl₃.

[0061] 2-methyl-2H-indazole-5-carbaldehyde (Compound 6).

[0062] Crude **Compound 6** (from above) was purified by radial chromatography (2 mm silica): %MeOH/CH₂Cl₂ – 1% (50 mL), 2% (35 mL) to afford **Compound 6** (95 mg, 21%) as a light-yellow solid: TLC *R_f* = 0.29 (silica, 3% MeOH/CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 10.00 (s, 1 H), 8.22 (apparent s, 1 H), 8.14 (apparent s, 1 H), 7.82 (dd, 1 H, *J* = 8.8 Hz, *J* = 1.2 Hz), 7.75 (d, 1 H, *J* = 8.8 Hz), 4.27 (s, 3 H); ¹H NMR (300 MHz, CDCl₃) δ 10.01 (s, 1 H), 8.22 (partially resolved apparent t, 1 H), 8.14 (s, 1 H), 7.82 (dd, 1 H, *J* = 9.0 Hz, *J* = 1.2 Hz), 7.75 (partially resolved dd, 1 H, *J* = 9.0 Hz, *J* = 0.6 Hz), 4.27 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 191.87, 151.07, 131.61, 129.05, 126.89, 123.44, 121.59, 118.32, 40.84. X-ray quality crystals were grown by slow evaporation of CDCl₃.

[0063] N-Fluoroethylation of 1H-indazole-5-carbaldehyde to give Compound 2 and Compound 7.

[0064] 1*H*-Indazole-5-carbaldehyde (0.52 g, 3.56 mmol), fluoroethyl tosylate (0.86 g, 3.94 mmol, 1.1 equiv.), K₂CO₃ (2.01 g, 14.54 mmol, 4.1 equiv.), and CH₃CN (50 mL) were stirred at reflux under N_{2(g)} for 2.5 h, then cooled to ambient temperature, filtered, and the precipitate was rinsed with CH₃CN. The CH₃CN was removed from the filtrate to give a cloudy yellow syrup that was dissolved in CH₂Cl₂, poured onto dry silica (55 mm h x 45 mm i.d.), and eluted under vacuum: CH₂Cl₂ (100 mL), %MeOH/CH₂Cl₂ – 1% (100 mL), 2.5% (100 mL), 5% (150 mL) to give a yellow syrup (0.59 g). Purification by radial chromatography (2 mm silica): %MeOH/CH₂Cl₂ – 1% (100 mL), 2% (50 mL) gave crude **Compound 2** (faint yellow syrup, 0.31 g, further purified below), crude **Compound 7** (bright yellow solid, 0.15 g, further purified below), and a mixture of **Compound 2** and **Compound 7** (faint yellow syrup, 0.11 g). The mixture was purified by radial chromatography (2 mm silica): CHCl₃ (200 mL) to give **7** (28 mg, 4%) as a light-yellow solid, and **Compound 2** (80 mg). The sample of **Compound 2** was purified by radial chromatography (1 mm silica) with CHCl₃ (50 mL), and then again purified by radial chromatography (1 mm silica): hexane/EtOAc/NEt₃ v/v/v 90:8:2 (200 mL), 75:20:5 (50 mL) to give **Compound 2** (78 mg, 11%) as a light-tan solid.

[0065] **1-(2-Fluoroethyl)-1*H*-indazole-5-carbaldehyde (Compound 2).**

[0066] Crude **Compound 2** (0.31 g from above) was purified by radial chromatography (2 mm silica): %EtOH/CHCl₃ – 1% (50 mL), 2% (50 mL) to give a faint-yellow syrup (0.29 g) that slowly became a light-tan solid. The solid was purified by radial chromatography (2 mm silica): hexane/EtOAc/NEt₃ v/v/v 90:8:2 (200 mL), 75:20:5 (50 mL), 50:45:5 (50 mL), 20:75:5 (25 mL) to afford **Compound 2** (0.27 g, 40%) as a yellow syrup that slowly became a light-orange solid. Total yield of **Compound 2**: 0.35 g (51%). ¹H NMR (400 MHz, CDCl₃) δ 10.06 (s, 1 H), 8.27 (partially resolved apparent q, 1 H, *J* = 0.8 Hz), 8.22 (partially resolved apparent d, 1 H, *J* = 0.4 Hz), 7.97 (dd, 1 H, *J* = 8.8 Hz, *J* = 1.2 Hz), 7.56 (d, 1 H, *J* = 8.8 Hz), 4.88 (dt, 2 H, ²*J*_{HF} = 46.8 Hz, *J* = 4.8 Hz), 4.72 (dt, 2 H, ³*J*_{HF} = 26.0 Hz, *J* = 4.8 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 191.58, 142.92, 136.20, 130.86, 127.51, 125.83, 124.07, 110.16 (d, *J* = 1.3 Hz), 82.24 (d, ¹*J*_{CF} = 171.4 Hz), 49.77 (d, ²*J*_{CF} = 21.1 Hz); HRMS (ESI) [M+H]⁺ Calcd for C₁₀H₁₀FN₂O: 193.0772, found: 193.0769. X-ray quality crystals were grown by slow evaporation of MeOH.

[0067] **2-(2-Fluoroethyl)-2*H*-indazole-5-carbaldehyde (Compound 7).**

[0068] Crude **Compound 7** (0.15 g from above) was purified by radial chromatography (2 mm silica): %EtOH/CHCl₃ – 1% (50 mL), 2% (50 mL) to give a fraction that was again purified by radial chromatography (2 mm silica): CHCl₃ (200 mL) to give **Compound 7** (29 mg, light yellow solid) and impure **Compound 7** (by TLC). Purification by radial chromatography (2 mm silica): %CH₂Cl₂/hexane – 25% (200 mL), 10% (100 mL), CH₂Cl₂ (250 mL), %MeOH/CH₂Cl₂ – 1% (50 mL), 2% (50 mL) gave **Compound 7** (39 mg, off-white solid) and impure **Compound 7** (by TLC) that was again purified by radial chromatography (2 mm silica): CHCl₃ (150 mL) to afford **Compound 7** (55 mg) as a white solid. Total yield of **Compound 7**: 0.15 g, 22%. ¹H NMR (300 MHz, CDCl₃) δ 10.01 (s, 1 H), 8.26 (apparent s, 1 H), 8.24 (partially resolved apparent q, 1 H, *J* = 0.9 Hz), 7.84 (dd, 1 H, *J* = 9.0 Hz, *J* = 1.5 Hz), 7.76 (dd, 1 H, *J* = 9.3 Hz, *J* = 0.6 Hz), 4.93 (dt, 2 H, ²*J*_{HF} = 46.5 Hz, *J* = 4.5 Hz), 4.75 (dt, 2 H, ³*J*_{HF} = 27.0 Hz, *J* = 4.5 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 191.83, 151.20, 131.88, 129.41, 127.35, 123.75, 121.52, 118.55, 81.56 (d, ¹*J*_{CF} = 171.6 Hz), 54.47 (d, ²*J*_{CF} = 20.4 Hz); HRMS (ESI) [M+H]⁺ Calcd for C₁₀H₁₀FN₂O: 193.0772, found: 193.0763.

[0069] N-2-(2-Fluoroethoxy)ethylation of 1H-indazole-5-carbaldehyde to give Compound 3 and Compound 8.

[0070] 1H-Indazole-5-carbaldehyde (0.15 g, 1.03 mmol), 2-(2-fluoroethoxy)ethyltosylate (0.28 g, 1.07 mmol), K₂CO₃ (0.24 g, 1.77 mmol, 1.7 equiv.), and CH₃CN (20 mL) were stirred at reflux under N_{2(g)} for 2.5 h, then cooled to ambient temperature, filtered, and the precipitate was rinsed with CH₃CN. The filtrate was concentrated, then CH₂Cl₂ and hexane were added and removed to give a residue that was dissolved in CH₂Cl₂, poured onto dry silica (55 mm h x 45 mm i.d.), and eluted under vacuum: CH₂Cl₂ (100 mL), %MeOH/CH₂Cl₂ – 1% (100 mL), 2.5% (100 mL), 5% (150 mL) to give a yellow syrup. Purification by radial chromatography (2 mm silica): CH₂Cl₂ (250 mL), %MeOH/CH₂Cl₂ – 1% (50 mL), 2% (75 mL) gave **Compound 3** (33 mg, 14%) as a colorless syrup that slowly became an off-white solid, crude **Compound 3** (71 mg - further purified below), and crude **Compound 8** (57 mg - further purified below).

[0071] 1-(2-(2-fluoroethoxy)ethyl)-1H-indazole-5-carbaldehyde (Compound 3).

[0072] Crude **Compound 3** (71 mg from above) was purified by radial chromatography (2 mm silica): hexane/EtOAc/NEt₃ v/v/v 90:8:2 (25 mL), 75:20:5 (150 mL) to afford

Compound 3 (62 mg, 25%) as a faint yellow syrup. Total yield of **Compound 3**: 95 mg, 39%. ¹H NMR (400 MHz, CDCl₃) δ 10.05 (s, 1 H), 8.25 (s, 1 H), 8.18 (s, 1 H), 7.95 (d, 1 H, *J* = 8.8 Hz), 7.61 (d, 1 H, *J* = 8.8 Hz), 4.62 (t, 2 H, *J* = 5.2 Hz), 4.42 (dt, 2 H, ²*J*_{FH} = 47.6 Hz, *J* = 4.0 Hz), 3.99 (t, 2 H, *J* = 5.2 Hz), 3.62 (dt, 2 H, ³*J*_{FH} = 29.6 Hz, *J* = 4.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 191.73, 142.93, 135.78, 130.75, 127.54, 125.53, 123.96, 110.73, 83.18 (d, ¹*J*_{FC} = 168.4 Hz), 70.61 (d, ²*J*_{FC} = 19.5 Hz), 70.35, 49.70; HRMS (ESI) [M+H]⁺ Calcd for C₁₂H₁₄FN₂O₂: 237.1034, found: 237.1033.

[0073] 2-(2-(2-fluoroethoxy)ethyl)-2*H*-indazole-5-carbaldehyde (Compound 8).

[0074] Crude **Compound 8** (57 mg from above) was purified by radial chromatography (1 mm silica): CH₂Cl₂ (300 mL), %MeOH/CH₂Cl₂ – 1% (50 mL), 2% (25 mL), 4% (50 mL) to afford **Compound 8** (54 mg, 22%) as a yellow syrup: ¹H NMR (300 MHz, CDCl₃) δ 10.00 (s, 1 H), 8.29 (apparent s, 1 H), 8.24 (partially resolved apparent dd, 1 H, *J* = 1.2 Hz), 7.82 (dd, 1 H, *J* = 9.0 Hz, *J* = 1.2 Hz), 7.74 (dd, 1 H, *J* = 9.0 Hz, *J* = 1.2 Hz), 4.65 (t, 2 H, *J* = 5.1 Hz), 4.50 (doublet of AA'XX', 2 H, ²*J*_{FH} = 47.4 Hz, *J* = 4.2 Hz, *J* = 1.2 Hz), 4.04 (t, 2 H, *J* = 5.1 Hz), 3.67 (doublet of AA'XX', 2 H, ³*J*_{FH} = 29.7 Hz, *J* = 4.2 Hz, *J* = 1.2 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 191.93, 151.02, 131.73, 129.58, 127.52, 123.60, 121.44, 118.51, 83.09 (d, ¹*J*_{FC} = 168.6 Hz), 70.69 (d, ²*J*_{FC} = 19.6 Hz), 69.82, 54.36; HRMS (ESI) [M+H]⁺ Calcd for C₁₂H₁₄FN₂O₂: 237.1034, found: 237.1034.

[0075] *N*-Alkylation of 1*H*-indazole-5-carbaldehyde to give Compound 4 and Compound 9.

[0076] 1*H*-Indazole-5-carbaldehyde (0.67 g, 4.58 mmol) and K₂CO₃ (2.67 g, 19.32 mmol, 4.2 equiv.) were flushed with N_{2(g)} for 10 min, then CH₃CN (70 mL) was added followed by (2-bromoethoxy)(*tert*-butyl)dimethylsilane (1.2 mL, 5.6 mmol, 1.2 equiv.). The reaction mixture was stirred at reflux under N_{2(g)} for 2 h, then cooled to ambient temperature, filtered, and the precipitate was rinsed with CH₃CN. The CH₃CN was removed from the filtrate to give a dark green oil, then CH₂Cl₂ and hexane were added and removed 2x to give a dark yellow oil that was dissolved in CH₂Cl₂, poured onto dry silica (55 mm h x 45 mm i.d.), and eluted under vacuum: CH₂Cl₂ (100 mL), %MeOH/CH₂Cl₂ – 1% (100 mL), 2% (100 mL), 3% (100 mL), 4% (100 mL), 5% (100 mL) to give a yellow oil. Purification by radial

chromatography (4 mm silica) with CHCl₃ (300 mL) afforded **Compound 4** (0.65 g, 47%) as a yellow oil and **Compound 9** (0.37 g, 27%) as a yellow oil.

[0077] 1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1*H*-indazole-5-carbaldehyde (Compound 4).

[0078] ¹H NMR (400 MHz, CDCl₃) δ 10.04 (s, 1 H), 8.24 (s, 1 H), 8.18 (s, 1 H), 7.93 (dd, 1 H, *J* = 8.8 Hz, *J* = 1.2 Hz), 7.59 (d, 1 H, *J* = 8.8 Hz), 4.53 (t, 2 H, *J* = 5.2 Hz), 4.05 (t, 2 H, *J* = 5.2 Hz), 0.70 (s, 9 H), -0.23 (s, 6 H); ¹³C NMR (125 MHz, CDCl₃) δ 191.73, 143.28, 135.66, 130.58, 127.57, 125.17, 123.76, 111.02, 62.64, 51.93, 25.79, 18.19, -5.62; HRMS (ESI) [M+H]⁺ Calcd for C₁₆H₂₅N₂O₂Si: 305.1680, found: 305.1680.

[0079] 2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2*H*-indazole-5-carbaldehyde (Compound 9).

[0080] ¹H NMR (400 MHz, CDCl₃) δ 10.01 (s, 1 H), 8.23 (s - overlapping resonances, 2 H), 7.82 (dd, 1 H, *J* = 9.2 Hz, *J* = 1.2 Hz), 7.75 (d, 1 H, *J* = 9.2 Hz), 4.55 (t, 2 H, *J* = 5.2 Hz), 4.10 (t, 2 H, *J* = 5.2 Hz), 0.81 (s, 9 H), -0.12 (s, 6 H); ¹³C NMR (125 MHz, CDCl₃) δ 191.84, 150.98, 131.54, 129.28, 127.55, 123.42, 121.18, 118.36, 61.99, 56.74, 25.83, 18.24, -5.56; HRMS (ESI) [M+H]⁺ Calcd for C₁₆H₂₅N₂O₂Si: 305.1680, found: 305.1682.

[0081] *tert*-Butyl 5-formyl-1*H*-indazole-1-carboxylate (Compound 5).

[0082] 1*H*-Indazole-5-carbaldehyde (0.70 g, 4.79 mmol), Boc₂O (1.32 g, 6.05 mmol, 1.3 equiv.), DMAP (59 mg, 0.48 mmol, 0.1 equiv.), *i*-Pr₂NEt (1.25 mL, 7.18 mmol, 1.5 equiv.), and CH₂Cl₂ (50 mL) were stirred at ambient temperature under N_{2(g)} for 2 h. The reaction mixture was concentrated, poured onto dry silica (55 mm h x 45 mm i.d.), and eluted under vacuum: CH₂Cl₂ (100 mL), %MeOH/CH₂Cl₂ – 1% (100 mL), 2% (100 mL), 3% (200 mL), 5% (100 mL), to give a faint yellow syrup (0.62 g) and an orange syrup (0.55 g). The faint yellow syrup was purified by radial chromatography (2 mm silica) with CH₂Cl₂ (300 mL) to give a faint yellow syrup (0.62 g) that was again purified by radial chromatography (2 mm silica): hexane/EtOAc/NEt₃ v/v/v 95:4:1 (150 mL), 90:8:2 (75 mL), 75:20:5 (100 mL) to afford **Compound 5** (0.50 g) as a colorless syrup. The orange syrup was purified by radial chromatography (2 mm silica) with CH₂Cl₂ (100 mL) to give a faint yellow syrup (0.51 g) that was again purified by radial chromatography (2 mm silica): hexane/EtOAc/NEt₃ v/v/v

90:8:2 (100 mL), 75:20:5 (50 mL) to afford **Compound 5** (0.43 g) as a colorless syrup (total yield of **Compound 5**: 0.93 g, 79%): ^1H NMR (400 MHz, CDCl_3) δ 10.11 (s, 1 H), 8.34 (d, 1 H, $J = 8.8$ Hz), 8.32 (s, 1 H), 8.28 (partially resolved m, 1 H), 8.09 (dd, 1 H, $J = 8.8$ Hz, $J = 1.6$ Hz), 1.75 (s, 9 H); ^{13}C NMR (125 MHz, CDCl_3) δ 191.25, 148.89, 142.64, 140.38, 132.82, 128.76, 126.08, 125.46, 115.46, 86.02, 28.27; HRMS (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{13}\text{H}_{15}\text{N}_2\text{O}_3$: 247.1077, found: 247.1081.

[0083] 6-((*tert*-butyldimethylsilyl)oxy)-2-methylbenzo[d]thiazole (Compound 10).

[0084] 2-Methylbenzothiazol-6-ol (1.08 g, 6.54 mmol), *t*-butyldimethylsilyl chloride (2.14 g, 14.20 mmol, 2.2 equiv.), imidazole (5.41 g, 79.47 mmol, 12.2 equiv.) and CH_2Cl_2 (225 mL) were stirred at ambient temperature for 6 h. The reaction mixture was concentrated and purified by vacuum flash chromatography on silica (15 cm h x 4 cm i.d.): % CH_2Cl_2 /hexane – 50% (100 mL), 75% (100 mL), CH_2Cl_2 (300 mL), %MeOH/ CH_2Cl_2 – 1% (200 mL), 2.5% (200 mL), 5% (100 mL) to afford **Compound 10** (1.45 g, 79%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 7.77 (d, 1 H, $J = 8.7$ Hz), 7.24 (d, 1 H, $J = 2.4$ Hz), 6.95 (dd, 1 H, $J = 8.7$ Hz, $J = 2.4$ Hz), 2.78 (s, 3 H), 1.00 (s, 9 H), 0.22 (s, 6 H); ^{13}C NMR (125 MHz, CDCl_3) δ 164.75, 153.36, 148.54, 136.84, 122.78, 119.74, 111.74, 25.84, 20.09, 18.38, -4.26.

[0085] 6-((*tert*-Butyldimethylsilyl)oxy)-2-methylquinoline (Compound 11).

[0086] 2-Methylquinolin-6-ol (0.66 g, 4.15 mmol), TBDMS-Cl (1.68 g, 11.15 mmol, 2.7 equiv.), imidazole (3.35 g, 49.21 mmol, 11.9 equiv.) and CH_2Cl_2 (130 mL) were stirred at ambient temperature in a capped flask for 5 h, then concentrated, poured onto dry silica (15 cm h x 4 cm i.d.), and eluted under vacuum: CH_2Cl_2 (100 mL), %MeOH/ CH_2Cl_2 – 1% (100 mL), 2% (100 mL), 3% (100 mL), 4% (100 mL), 5% (300 mL) to give a faint tan oil (1.12 g). Purification by radial chromatography (4 mm silica): CH_2Cl_2 (300 mL), %MeOH/ CH_2Cl_2 – 1% (100 mL), 2% (100 mL), 3% (100 mL) afforded **Compound 11** (1.00 g, 88%) as a colorless oil: ^1H NMR (400 MHz, CDCl_3) δ 7.91 (d, 1 H, $J = 1.6$ Hz), 7.89 (d, 1 H, $J = 2.0$ Hz), 7.26 (m - partially obscured by CHCl_3 resonance, 1 H), 7.22 (d, 1 H, $J = 8.4$ Hz), 7.10 (d, 1 H, $J = 2.8$ Hz), 2.70 (s, 3 H), 1.02 (s, 9 H), 0.25 (s, 6 H); ^{13}C NMR (125 MHz, CDCl_3) δ 156.86, 153.32, 144.20, 135.18, 130.13, 127.58, 125.45, 122.28, 114.47, 25.88, 25.29, 18.44, -4.16; HRMS (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{16}\text{H}_{24}\text{NOSi}$: 274.1622, found: 274.1621.

[0087] Synthesis of Compound 12 and Compound 13.

[0088] Compound **10** (1.24 g, 4.44 mmol) was flushed with N_{2(g)} for 20 min, then dissolved in THF (20 mL) and cooled to -78 °C. LDA solution (2.0 M THF/heptane/ethylbenzene, 5.5 mL, 11 mmol, 2.5 equiv.) was added dropwise over a period of 5 min, then the reaction mixture was stirred at -78 °C under N_{2(g)} for 10 min. Diethyl chlorophosphate (0.90 g, 5.22 mmol, 1.2 equiv.) was dissolved in THF (10 mL), added dropwise to the reaction mixture over a period of 5 min, the reaction mixture was stirred at -78 °C under N_{2(g)} for 5 min, then warmed to ambient temperature and stirred for 2 h. Saturated NH₄Cl_(aq) (1 mL) was added dropwise, the mixture was stirred for 5 min, then filtered, and the precipitate was rinsed with THF. The filtrate was concentrated to an orange oil, then CH₂Cl₂ and hexane were added and removed to give an orange syrup that was dried under vacuum to give a dark orange foam/residue. The foam/residue was dissolved in CH₂Cl₂, poured onto dry silica (55 mm h x 45 mm i.d.), and eluted under vacuum: CH₂Cl₂ (50 mL), %MeOH/CH₂Cl₂ – 1% (100 mL), 2.5% (100 mL), 5% (100 mL), 10% (50 mL) to give a dark yellow/orange syrup (1.66 g). Purification by radial chromatography (4 mm silica): CHCl₃ (25 mL), %EtOH/CHCl₃ – 1% (100 mL), 2% (100 mL), 3% (50 mL) gave crude **Compound 12** as a yellow syrup (1.08 g). The silica plate was then eluted with %MeOH/CH₂Cl₂ – 10% (100 mL), 20% (50 mL) to afford the *O*-deprotected **Compound 13** (0.21 g, 16%) as a yellow/tan solid (see below). Crude **Compound 12** was purified by radial chromatography (4 mm silica): hexane/EtOAc/NEt₃ v/v/v 75:20:5 (200 mL), 50:45:5 (50 mL) to afford **Compound 12** (1.06 g, 57%) as a yellow oil.

[0089] Diethyl ((6-((*tert*-butyldimethylsilyl)oxy)benzo[*d*]thiazol-2-yl)methyl)phosphonate (**Compound 12**).

[0090] ¹H NMR (400 MHz, CDCl₃) δ 7.83 (d, 1 H, *J* = 8.8 Hz), 7.27 (overlap with CHCl₃ resonance, d, 1 H, *J* = 2.4 Hz), 6.97 (dd, 1 H, *J* = 8.8 Hz, *J* = 2.4 Hz), 4.16 (dq, 4 H, ³*J*_{PH} = 7.6 Hz, *J* = 7.2 Hz), 3.68 (d, 2 H, ²*J*_{PH} = 21.2 Hz), 1.32 (t, 6 H, *J* = 7.2 Hz), 1.00 (s, 9 H), 0.22 (s, 6 H); ¹³C NMR (125 MHz, CDCl₃) δ 158.75 (d, ²*J*_{PC} = 9.4 Hz), 153.78, 148.04 (d, *J* = 1.8 Hz), 137.21, 123.33, 120.06, 111.66, 63.00 (d, ²*J*_{PC} = 6.5 Hz), 33.16 (d, ¹*J*_{PC} = 139.0 Hz), 25.82, 18.37, 16.52 (d, ³*J*_{PC} = 5.9 Hz), -4.26; HRMS (ESI) [M+H]⁺ Calcd for C₁₈H₃₁NO₄PSSi: 416.1475, found: 416.1472.

[0091] Diethyl ((6-hydroxybenzo[*d*]thiazol-2-yl)methyl)phosphonate (**Compound 13**).

[0092] ^1H NMR (400 MHz, CDCl_3) δ 8.15 (br s, 1 H), 7.67 (d, 1 H, $J = 8.8$ Hz), 7.25 (d, 1 H, $J = 2.4$ Hz), 6.90 (dd, 1 H, $J = 8.8$ Hz, $J = 2.4$ Hz), 4.19 (dq, 4 H, $^3J_{\text{PH}} = 8.2$ Hz, $J = 7.2$ Hz), 3.69 (d, 2 H, $^2J_{\text{PH}} = 21.2$ Hz), 1.35 (t, 6 H, $J = 7.2$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 156.69 (d, $^2J_{\text{PC}} = 9.3$ Hz), 155.50, 146.76, 136.93, 123.21, 116.32, 107.18, 63.49 (d, $^2J_{\text{PC}} = 6.8$ Hz), 32.90 (d, $^1J_{\text{PC}} = 140.3$ Hz), 16.54 (d, $^3J_{\text{PC}} = 6.0$ Hz); HRMS (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{12}\text{H}_{17}\text{NO}_4\text{PS}$: 302.0610, found: 302.0614.

[0093] **Diethyl ((6-((*tert*-butyldimethylsilyl)oxy)quinolin-2-yl)methyl)phosphonate (Compound 14).**

[0094] **Compound 11** (0.96 g, 3.51 mmol) was flushed with $\text{N}_{2(\text{g})}$ for 1 h, then dissolved in THF (20 mL), and cooled to -78°C . LDA solution (2.0 M THF/heptane/ethylbenzene, 4.4 mL, 8.8 mmol, 2.5 equiv.) was added dropwise over a period of 5 min, the reaction mixture was stirred at -78°C under $\text{N}_{2(\text{g})}$ for 10 min, then a solution of diethyl chlorophosphate (0.76 g, 4.4 mmol, 1.3 equiv.) in THF (10 mL) was added dropwise over a period of 3 min. The reaction mixture was stirred at -78°C for 5 min, then warmed to ambient temperature and stirred for 2 h. Saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (1 mL) was added, the mixture was stirred for 1 h, then the solvent was removed to give an orange syrup. CH_2Cl_2 and hexane were added and removed 2x to give an orange residue that was dissolved in CH_2Cl_2 , poured onto dry silica (55 mm h x 45 mm i.d.), and eluted under vacuum: CH_2Cl_2 (100 mL), %MeOH/ CH_2Cl_2 – 1% (100 mL), 2% (100 mL), 3% (100 mL), 5% (100 mL) to give a yellow/orange syrup (1.52 g). Purification by radial chromatography (4 mm silica): CH_2Cl_2 (100 mL), %MeOH/ CH_2Cl_2 – 1% (100 mL), 2% (100 mL), 3% (100 mL), 4% (100 mL), 5% (100 mL) afforded **Compound 14** (1.25 g) as a yellow oil, and an orange oil (177 mg) that was further purified by radial chromatography (2 mm silica): CHCl_3 (50 mL), %EtOH/ CHCl_3 – 1% (50 mL), 2% (75 mL), 3% (25 mL) to afford **Compound 14** (100 mg) as a yellow oil. Total yield of **Compound 14**: 1.35 g, 94%. ^1H NMR (400 MHz, CDCl_3) δ 7.96 (d, 1 H, $J = 8.4$ Hz), 7.92 (d, 1 H, $J = 8.4$ Hz), 7.46 (dd, 1 H, $J = 8.4$ Hz, $J = 1.6$ Hz), 7.27 (dd - partially obscured by CHCl_3 resonance, 1 H, $J = 2.8$ Hz), 7.12 (d, 1 H, $J = 2.8$ Hz), 4.09 (dq, 4 H, $^3J_{\text{PH}} = 7.4$ Hz, $J = 7.2$ Hz), 3.56 (d, 2 H, $^2J_{\text{PH}} = 22.0$ Hz), 1.26 (t, 6 H, $J = 7.2$ Hz), 1.02 (s, 9 H), 0.26 (s, 6 H); ^{13}C NMR (125 MHz, CDCl_3) δ 153.78, 150.99 (d, $^2J_{\text{PC}} = 8.1$ Hz), 144.28 (d, $^4J_{\text{PC}} = 1.8$ Hz), 135.40, 130.42, 128.06, 125.65, 122.44 (d, $^3J_{\text{PC}} = 3.4$ Hz), 114.32, 62.37 (d, $^2J_{\text{PC}} = 6.5$ Hz),

37.42 (d, $^1J_{\text{PC}} = 133.4$ Hz), 25.79, 18.37, 16.47 (d, $^3J_{\text{PC}} = 5.9$ Hz), -4.22; HRMS (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{20}\text{H}_{33}\text{NO}_4\text{PSi}$: 410.1911, found: 410.1910.

[0095] (E)-6-((tert-Butyldimethylsilyl)oxy)-2-(2-(1-methyl-1H-indazol-5-yl)vinyl)benzo[d]thiazole (Compound 15).

[0096] Compound **12** (0.26 g, 6.26×10^{-4} mol) was flushed with $\text{N}_{2(\text{g})}$ then dissolved in THF (10 mL) and cooled to 0 °C. NaH (60%, 41 mg, 1.03 mmol, 1.6 equiv.) was added, the reaction mixture was stirred at 0 °C under $\text{N}_{2(\text{g})}$ for 10 min, then a solution of **Compound 1** (0.11 g, 6.87×10^{-4} mol, 1.1 equiv.) in THF (1 mL) was added. The reaction mixture was stirred at ambient temperature for 3.5 h, then H_2O (3 drops) was added, the mixture was stirred for 10 min, and the solvent was removed to give a yellow solid that was dissolved in CH_2Cl_2 , poured onto dry silica (55 mm h x 45 mm i.d.), and eluted under vacuum: %MeOH/ CH_2Cl_2 – 1% (100 mL), 2% (100 mL), 3% (100 mL), 4% (50 mL) to give a light yellow solid (0.12 g). Purification by radial chromatography (2 mm silica): %MeOH/ CH_2Cl_2 – 1% (50 mL), 2% (50 mL) afforded **Compound 15** (91 mg, 34%) as a light-yellow solid: ^1H NMR (300 MHz, CDCl_3) δ 8.02 (s, 1 H), 7.86 (s, 1 H), 7.83 (d, 1 H, $J = 8.7$ Hz), 7.68 (dd, 1 H, $J = 8.7$ Hz, $J = 1.2$ Hz), 7.55 (d, 1 H, $J = 16.2$ Hz), 7.42 (d, 1 H, $J = 9.0$ Hz), 7.36 (d, 1 H, $J = 16.2$ Hz), 7.28 (d, 1 H, $J = 2.4$ Hz), 6.98 (dd, 1 H, $J = 9.0$ Hz, $J = 2.4$ Hz), 4.10 (s, 3 H), 1.02 (s, 9 H), 0.25 (s, 6 H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.43, 154.03, 149.14, 140.34, 137.36, 135.65, 133.77, 128.76, 124.97, 124.68, 123.40, 121.62, 121.06, 120.27, 111.86, 109.87, 35.91, 25.89, 18.46, -4.16; HRMS (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{23}\text{H}_{28}\text{N}_3\text{OSSi}$: 422.1717, found: 422.1715.

[0097] (E)-2-(2-(1-Methyl-1H-indazol-5-yl)vinyl)benzo[d]thiazol-6-ol (Compound 16).

[0098] **Compound 15** (86 mg, 2.04×10^{-4} mol), KHF_2 (48 mg, 6.15×10^{-4} mol, 3 equiv.), 18-crown-6 (84 mg, 3.18×10^{-4} mol, 1.6 equiv.), and CHCl_3 (10 mL) were stirred at ambient temperature in a capped vial for 4 h, then the solvent was removed to give a yellow solid. The solid was suspended in 1:1 v/v hexane/ CH_2Cl_2 (5 mL), filtered, rinsed with 1:1 v/v hexane/ CH_2Cl_2 (2.5 mL x 2), H_2O (10 mL), EtOAc (2.5 mL x 2), and dried under vacuum to afford **Compound 16** (54 mg, 86%) as a yellow solid: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 10.00 (br s, 1 H), 8.10 (s, 1 H), 8.06 (s, 1 H), 7.88 (d, 1 H, $J = 8.7$ Hz), 7.75 (d, 1 H, $J = 8.7$ Hz), 7.69 (d, 1 H, $J = 9.0$ Hz), 7.62 (d, 1 H, $J = 16.2$ Hz), 7.51 (d, 1 H, $J = 16.2$ Hz), 7.35 (d,

1 H, $J = 2.1$ Hz), 6.95 (dd, 1 H, $J = 8.7$ Hz, $J = 2.1$ Hz), 4.06 (s, 3 H); ^{13}C NMR (125 MHz, DMSO- d_6) δ 162.97, 155.98, 146.93, 139.74, 136.53, 135.40, 133.19, 128.17, 124.64, 123.82, 122.97, 121.37, 120.38, 115.94, 110.33, 106.66, 35.47; HRMS (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{17}\text{H}_{14}\text{N}_3\text{OS}$: 308.0852, found: 308.0847.

[0099] Synthesis of Compound 17 and Compound 18.

[0100] Compound 12 (0.37 g, 8.90×10^{-4} mol) was flushed with $\text{N}_{2(\text{g})}$, dissolved in THF (14 mL), and cooled to 0 °C. NaH (60%, 55 mg, 1.38 mmol, 1.5 equiv.) was added, the reaction mixture was stirred at 0 °C under $\text{N}_{2(\text{g})}$ for 10 min, then a solution of compound **2** (0.20 g, 1.04 mmol, 1.2 equiv.) in THF (1 mL) was added dropwise over a period of 30 sec. The reaction mixture was stirred at ambient temperature under $\text{N}_{2(\text{g})}$ for 4 h, then H_2O (5 drops) was added, and the mixture was stirred for 10 min. The solvent was removed to give a dark orange oil, then CH_2Cl_2 and hexane were added and removed to give an orange solid. The solid was suspended in CH_2Cl_2 , then MeOH was added until the solid dissolved. The solution was concentrated to an orange oil, the oil was dissolved in CH_2Cl_2 , poured onto dry silica (55 mm h x 45 mm i.d.), and eluted under vacuum: %MeOH/ CH_2Cl_2 – 1% (100 mL), 2.5% (100 mL), 5% (200 mL) to give a yellow solid (0.32 g). The solid was suspended in CH_2Cl_2 (5 mL), filtered, and the precipitate was rinsed with CH_2Cl_2 (2.5 mL x 4) then dried under vacuum to afford **Compound 18** (0.15 g, 50%) as a yellow solid. The filtrate was purified by radial chromatography (2 mm silica): CH_2Cl_2 (150 mL), %MeOH/ CH_2Cl_2 – 1% (50 mL), 2% (50 mL) to give a sticky, light-yellow solid. CH_2Cl_2 and hexane were added and removed to afford **Compound 17** (82 mg, 20%) as an off-white solid.

[0101] (E)-6-((tert-butyldimethylsilyl)oxy)-2-(2-(1-(2-fluoroethyl)-1H-indazol-5-yl)vinyl)benzo[d]thiazole (Compound 17).

[0102] ^1H NMR (300 MHz, CDCl_3) δ 8.07 (d, 1 H, $J = 0.6$ Hz), 7.87 (s, 1 H), 7.83 (d, 1 H, $J = 8.7$ Hz), 7.69 (dd, 1 H, $J = 9.0$ Hz, $J = 1.5$ Hz), 7.55 (d, 1 H, $J = 16.2$ Hz), 7.49 (d, 1 H, $J = 8.7$ Hz), 7.36 (d, 1 H, $J = 16.2$ Hz), 7.29 (d, 1 H, $J = 2.4$ Hz), 6.98 (dd, 1 H, $J = 8.7$ Hz, $J = 2.4$ Hz), 4.87 (dt, 2 H, $^2J_{\text{FH}} = 46.8$ Hz, $J = 4.8$ Hz), 4.68 (dt, 2 H, $^3J_{\text{FH}} = 25.8$ Hz, $J = 4.8$ Hz), 1.02 (s, 9 H), 0.25 (s, 6 H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.33, 154.02, 149.11, 140.77, 137.16, 135.65, 134.82, 129.12, 125.31, 124.80, 123.39, 121.49, 121.20, 120.26, 111.84,

110.07, 82.41 (d, $^1J_{\text{FC}} = 171.5$ Hz), 49.68 (d, $^2J_{\text{FC}} = 21.4$ Hz), 25.87, 18.43, -4.18; HRMS (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{24}\text{H}_{29}\text{FN}_3\text{OSSi}$: 454.1779, found: 454.1783.

[0103] (*E*)-2-(2-(1-(2-fluoroethyl)-1*H*-indazol-5-yl)vinyl)benzo[d]thiazol-6-ol (Compound 18).

[0104] ^1H NMR (300 MHz, acetone- d_6) δ 8.76 (s, 1 H), 8.11 (d, 1 H, $J = 0.9$ Hz), 8.06 (partially resolved apparent t, 1 H, $J = 0.6$ Hz), 7.86 (dd, 1 H, $J = 9.0$ Hz, $J = 1.5$ Hz), 7.78 (d, 1 H, $J = 9.0$ Hz), 7.71 (d, 1 H, $J = 9.0$ Hz), 7.65 (d, 1 H, $J = 16.2$ Hz), 7.45 (d, 1 H, $J = 16.2$ Hz), 7.40 (d, 1 H, $J = 2.4$ Hz), 7.04 (dd, 1 H, $J = 9.0$ Hz, $J = 2.4$ Hz), 4.91 (dt, 2 H, $^2J_{\text{FH}} = 47.1$ Hz, $J = 4.8$ Hz), 4.78 (dt, 2 H, $^3J_{\text{FH}} = 26.4$ Hz, $J = 4.8$ Hz); ^1H NMR (400 MHz, DMSO- d_6) δ 9.86 (s, 1 H), 8.18 (s, 1 H), 8.08 (s, 1 H), 7.89 (d, 1 H, $J = 8.8$ Hz), 7.76 (d, 1 H, $J = 8.4$ Hz), 7.74 (d, 1 H, $J = 8.4$ Hz), 7.62 (d, 1 H, $J = 16.4$ Hz), 7.52 (d, 1 H, $J = 16.4$ Hz), 7.36 (partially resolved apparent d, 1 H, $J = 1.6$ Hz), 6.96 (dd, 1 H, $J = 8.8$ Hz, $J = 2.0$ Hz), 4.85 (dt, 2 H, $^2J_{\text{FH}} = 47.2$ Hz, $J = 4.4$ Hz), 4.77 (dt, 2 H, $^3J_{\text{FH}} = 27.6$ Hz, $J = 4.4$ Hz); ^{13}C NMR (125 MHz, DMSO- d_6) δ 163.09, 155.70, 147.05, 140.13, 136.50, 135.40, 134.10, 128.43, 124.85, 123.96, 123.00, 121.39, 120.48, 115.86, 110.48, 106.68, 82.35 (d, $^1J_{\text{FC}} = 167.5$ Hz), 48.84 (d, $^2J_{\text{FC}} = 20.0$ Hz); HRMS (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{18}\text{H}_{15}\text{FN}_3\text{OS}$: 340.0914, found: 340.0918. X-ray quality crystals were grown by slow evaporation of acetone- d_6 .

[0105] (*E*)-2-(2-(1-(2-(2-fluoroethoxy)ethyl)-1*H*-indazol-5-yl)vinyl)benzo[d]thiazol-6-ol (Compound 19).

[0106] **Compound 12** (0.15 g, 3.61×10^{-4} mol) was flushed with $\text{N}_{2(\text{g})}$, dissolved in THF (8 mL), and cooled to 0 °C. NaH (60%, 34 mg, 8.50×10^{-4} mol, 2.4 equiv.) was added, the reaction mixture was stirred at 0 °C under $\text{N}_{2(\text{g})}$ for 10 min, then a solution of **Compound 3** (89 mg, 3.77×10^{-4} mol) in THF (2 mL) was added dropwise over a period of 30 sec. The reaction mixture was stirred at ambient temperature under $\text{N}_{2(\text{g})}$ for 4 h, then H_2O (5 drops) was added, the mixture was stirred for 20 min, then the solvent was removed to give a dark orange syrup/residue. CH_2Cl_2 was added which produced a precipitate, then MeOH was added until the precipitate dissolved. The solution was poured onto dry silica (45 mm h x 45 mm i.d.) and eluted under vacuum: %MeOH/ CH_2Cl_2 – 1% (100 mL), 2.5% (100 mL), 5% (100 mL) to give a dark orange solid (0.17 g). The solid was placed in a medium-fritted filter funnel, rinsed with CH_2Cl_2 (2 mL x 3), hexane (5 mL), EtOEt (5 mL x 2), and dried under

vacuum to afford **Compound 19** (71 mg, 51%) as a yellow solid. The filtrate was concentrated and purified by radial chromatography (2 mm silica): %MeOH/CH₂Cl₂ – 1% (100 mL), 2% (100 mL), 3% (100 mL) to afford **Compound 19** (25 mg, 18%) as a yellow solid. Total yield of **Compound 19**: 96 mg, 69%. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.86 (s, 1 H), 8.14 (s, 1 H), 8.06 (s, 1 H), 7.86 (d, 1 H, *J* = 8.8 Hz), 7.76 (d, 1 H, *J* = 8.8 Hz), 7.74 (d, 1 H, *J* = 8.8 Hz), 7.62 (d, 1 H, *J* = 16.0 Hz), 7.51 (d, 1 H, *J* = 16.0 Hz), 7.36 (d, 1 H, *J* = 2.4 Hz), 6.96 (dd, 1 H, *J* = 8.8 Hz, *J* = 2.4 Hz), 4.60 (t, 2 H, *J* = 5.6 Hz), 4.42 (dt, 2 H, ²*J*_{FH} = 48.0 Hz, *J* = 4.0 Hz), 3.89 (t, 2 H, *J* = 5.6 Hz), 3.60 (dt, 2 H, ³*J*_{FH} = 31.2 Hz, *J* = 4.0 Hz); ¹H NMR (400 MHz, acetone-*d*₆) δ 8.80 (s, 1 H), 8.07 (s, 1 H), 8.03 (s, 1 H), 7.84 (dd, 1 H, *J* = 8.8 Hz, *J* = 1.2 Hz), 7.78 (d, 1 H, *J* = 8.8 Hz), 7.72 (d, 1 H, *J* = 8.8 Hz), 7.64 (d, 1 H, *J* = 16.4 Hz), 7.45 (d, 1 H, *J* = 16.4 Hz), 7.40 (d, 1 H, *J* = 2.4 Hz), 7.04 (dd, 1 H, *J* = 8.8 Hz, *J* = 2.4 Hz), 4.63 (t, 2 H, *J* = 5.6 Hz), 4.44 (dt, 2 H, ²*J*_{FH} = 48.0 Hz, *J* = 4.0 Hz), 3.98 (t, 2 H, *J* = 5.6 Hz), 3.65 (dt, 2 H, ³*J*_{FH} = 30.4 Hz, *J* = 4.0 Hz); ¹³C NMR (125 MHz, acetone-*d*₆) δ 164.56, 156.79, 149.07, 141.50, 137.74, 136.85, 134.63, 129.62, 125.59, 125.43, 124.26, 122.16, 121.57, 116.72, 111.58, 107.54, 83.90 (d, ¹*J*_{FC} = 166.3 Hz), 71.08 (d, ²*J*_{FC} = 19.4 Hz); HRMS (ESI) [M+H]⁺ Calcd for C₂₀H₁₉FN₃O₂S: 384.1177, found: 384.1175.

[0107] Synthesis of Compound 20 and Compound 21.

[0108] **Compound 5** (0.25 g, 1.02 mmol) was flushed with N_{2(g)} for 15 min then dissolved in THF (5 mL). **Compound 12** (0.47 g, 1.13 mmol) was flushed with N_{2(g)} for 15 min then dissolved in THF (15 mL) and cooled to 0 °C. NaH (60%, 82 mg, 2.05 mmol) was added, the reaction mixture was stirred at 0 °C under N_{2(g)} for 20 min, then the solution of **Compound 5** was added dropwise over a period of 2 min. The reaction mixture was stirred at ambient temperature under N_{2(g)} for 4 h, then the solvent was removed to give an orange residue that was dissolved in CH₂Cl₂ (10 mL) and stirred for 1 h while open to air. The solution was poured onto dry silica (55 mm h x 45 mm i.d.) and eluted under vacuum: CH₂Cl₂ (100 mL), %MeOH/CH₂Cl₂ – 1% (100 mL), 2.5% (100 mL), 5% (200 mL), 10% (100 mL) to give a yellow foam (0.46 g). Purification by radial chromatography (4 mm silica): hexane/EtOAc/NEt₃ v/v/v 90:8:2 (100 mL), 75:20:5 (200 mL), 50:45:5 (100 mL), 20:75:5 (125 mL) gave a yellow foam (crude **Compound 20**, 0.17 g, further purified below) and a light-yellow solid (crude **Compound 21**, 85 mg, further purified below).

[0109] *tert*-Butyl (*E*)-5-(2-(6-((*tert*-butyldimethylsilyl)oxy)benzo[d]thiazol-2-yl)vinyl)-1*H*-indazole-1-carboxylate (Compound 20).

[0110] Crude **Compound 20** (0.17 g from above) was purified by radial chromatography (2 mm silica): CH₂Cl₂ (200 mL), %MeOH/CH₂Cl₂ – 1% (100 mL), 2% (100 mL) to afford **Compound 20** (0.13 g, 25%) as a colorless syrup that became a light-yellow solid after scrapping with a spatula. ¹H NMR (300 MHz, CDCl₃) δ 8.21 (d, 1 H, *J* = 7.8 Hz), 8.20 (s, 1 H), 7.88 (s, 1 H), 7.85 (d, 1 H, *J* = 9.0 Hz), 7.79 (dd, 1 H, *J* = 9.0 Hz, *J* = 1.5 Hz), 7.55 (d, 1 H, *J* = 16.2 Hz), 7.40 (d, 1 H, *J* = 16.2 Hz), 7.29 (d, 1 H, *J* = 2.4 Hz), 6.99 (dd, 1 H, *J* = 8.7 Hz, *J* = 2.4 Hz), 1.75 (s, 9 H), 1.02 (s, 9 H), 0.25 (s, 6 H); HRMS (ESI) [M+H]⁺ Calcd for C₂₇H₃₄N₃O₃SSi: 508.2085, found: 508.2074.

[0111] **Compound 21 (isolated as a side-product).**

[0112] Crude **Compound 21** (85 mg from above) was purified by radial chromatography (1 mm silica): %MeOH/CH₂Cl₂ – 1% (50 mL), 2% (75 mL) to afford **Compound 21** (52 mg, 13%) as a light yellow solid: ¹H NMR (300 MHz, CDCl₃) δ 10.24 (br s, 1 H), 8.13 (d, 1 H, *J* = 0.6 Hz), 7.91 (s, 1 H), 7.83 (d, 1 H, *J* = 9.0 Hz), 7.70 (dd, 1 H, *J* = 9.0 Hz, *J* = 1.2 Hz), 7.56 (d, 1 H, *J* = 16.2 Hz), 7.53 (d, 1 H, *J* = 8.7 Hz), 7.37 (d, 1 H, *J* = 16.2 Hz), 7.29 (d, 1 H, *J* = 2.4 Hz), 6.98 (dd, 1 H, *J* = 8.7 Hz, *J* = 2.4 Hz), 1.02 (s, 9 H), 0.25 (s, 6 H).

[0113] (*E*)-2-(2-(1*H*-indazol-5-yl)vinyl)-6-((*tert*-butyldimethylsilyl)oxy)benzo[d]thiazole (**Compound 21**).

[0114] **Compound 12** (0.19 g, 4.57 × 10⁻⁴ mol) was flushed with N_{2(g)} for 30 min then dissolved in THF (5 mL) and cooled to 0 °C. NaH (60%, 32 mg, 8.00 × 10⁻⁴ mol, 1.7 equiv.) was added, the reaction mixture was stirred at 0 °C under N_{2(g)} for 15 min, then a solution of **Compound 5** (0.11 g, 4.47 × 10⁻⁴ mol) in THF (2 mL) was added dropwise over a period of 30 sec. The reaction mixture was stirred at ambient temperature under N_{2(g)} for 2.5 h, then the solvent was removed to give an orange residue that was dissolved in CH₂Cl₂ (5 mL) and stirred for 1 h while open to air. The solution was then poured onto dry silica (33 mm h x 33 mm i.d.) and eluted under vacuum: CH₂Cl₂ (50 mL), %MeOH/CH₂Cl₂ – 1% (50 mL), 2% (75 mL), 3% (50 mL) to afford **Compound 21** (0.15 g, 80%) as a light yellow solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.22 (s, 1 H), 8.13 (s, 1 H), 8.10 (s, 1 H), 7.83 (dd, 1 H, *J* = 9.0 Hz, *J* = 1.5 Hz), 7.82 (d, 1 H, *J* = 9.0 Hz), 7.68 (d, 1 H, *J* = 16.2 Hz), 7.60 (d, 1 H, *J* = 9.0 Hz),

7.56 (d, 1 H, $J = 2.4$ Hz), 7.51 (d, 1 H, $J = 16.2$ Hz), 7.01 (dd, 1 H, $J = 9.0$ Hz, $J = 2.4$ Hz), 0.98 (s, 9 H), 0.24 (s, 6 H).

[0115] Synthesis of compound 21 by deprotection of Compound 20.

[0116] Compound 20 (55 mg, 1.08×10^{-4} mol) was dissolved in TFA (1 mL, 12.98 mmol, 120 equiv.), stirred at ambient temperature for 20 min, then poured into a mixture of NaHCO_3 (1.28 g, 15.24 mmol, 1.2 equiv. TFA), H_2O (35 mL), and CH_2Cl_2 (35 mL). The mixture was stirred for 20 min, then the layers were separated, and the H_2O layer was extracted with CH_2Cl_2 (5 mL $\times$ 3). The combined CH_2Cl_2 layers were washed with brine (25 mL) and dried over MgSO_4 . The solution was concentrated, poured onto dry silica (33 mm h $\times$ 33 mm i.d.), and eluted under vacuum: %MeOH/ CH_2Cl_2 – 1% (50 mL), 2.5% (50 mL), 5% (75 mL) to give an off-white solid (39 mg) that was purified by radial chromatography (1 mm silica): CHCl_3 (25 mL), %EtOH/ CHCl_3 – 1% (50 mL), 2% (25 mL), 3% (25 mL) to afford **Compound 21** (36 mg, 82%) as an off-white solid: ^1H NMR (300 MHz, CDCl_3) δ 10.23 (br s, 1 H), 8.12 (d, 1 H, $J = 0.6$ Hz), 7.91 (s, 1 H), 7.83 (d, 1 H, $J = 8.7$ Hz), 7.70 (dd, 1 H, $J = 8.7$ Hz, $J = 1.2$ Hz), 7.56 (d, 1 H, $J = 16.2$ Hz), 7.53 (d, 1 H, $J = 8.7$ Hz), 7.37 (d, 1 H, $J = 16.2$ Hz), 7.29 (d, 1 H, $J = 2.4$ Hz), 6.98 (dd, 1 H, $J = 8.7$ Hz, $J = 2.4$ Hz), 1.02 (s, 9 H), 0.25 (s, 6 H); HRMS (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{22}\text{H}_{26}\text{N}_3\text{OSSi}$: 408.1560, found: 408.1564.

[0117] (E)-6-((tert-Butyldimethylsilyl)oxy)-2-(2-(2-methyl-2H-indazol-5-yl)vinyl)benzo[d]thiazole (Compound 22).

[0118] Compound 12 (0.20 g, 4.81×10^{-4} mol) was flushed with $\text{N}_{2(\text{g})}$ then dissolved in THF (10 mL) and cooled to 0 °C. NaH (60%, 26 mg, 6.50×10^{-4} mol, 1.4 equiv.) was added, the reaction mixture was stirred at 0 °C under $\text{N}_{2(\text{g})}$ for 10 min, then a solution of compound 6 (89 mg, 5.56×10^{-4} mol, 1.2 equiv.) in THF (2 mL) was added. The reaction mixture was stirred at ambient temperature for 3.5 h, then H_2O (3 drops) was added, the mixture was stirred for 10 min, and the solvent was removed to give a yellow solid that was dissolved in CH_2Cl_2 , poured onto dry silica (55 mm h $\times$ 45 mm i.d.), and eluted under vacuum: %MeOH/ CH_2Cl_2 – 1% (100 mL), 2.5% (100 mL), 5% (150 mL) to give a yellow solid (90 mg). Purification by radial chromatography (2 mm silica): %MeOH/ CH_2Cl_2 – 1% (100 mL), 5% (50 mL) gave a light-yellow solid (54 mg) that was again purified by radial chromatography (1 mm silica): CHCl_3 (200 mL) to afford **Compound 22** (39 mg, 19%) as an off-white/faint-tan solid: ^1H

NMR (300 MHz, CDCl₃) δ 7.93 (s, 1 H), 7.82 (d, 1 H, J = 8.7 Hz), 7.76 (s, 1 H), 7.71 (d, 1 H, J = 9.3 Hz), 7.59 (dd, 1 H, J = 9.3 Hz, J = 1.5 Hz), 7.52 (d, 1 H, J = 16.2 Hz), 7.34 (d, 1 H, J = 16.2 Hz), 7.28 (d, 1 H, J = 2.4 Hz), 6.97 (dd, 1 H, J = 9.0 Hz, J = 2.4 Hz), 4.23 (s, 3 H), 1.02 (s, 9 H), 0.24 (s, 6 H); ¹³C NMR (125 MHz, CDCl₃) δ 165.57, 153.99, 149.51, 149.18, 137.76, 135.66, 129.72, 124.83, 124.09, 123.37, 122.56, 121.35, 120.94, 120.24, 118.32, 111.85, 40.65, 25.89, 18.46, -4.17; HRMS (ESI) [M+H]⁺ Calcd for C₂₃H₂₈N₃OSSi: 422.1717, found: 422.1715.

[0119] (E)-2-(2-(2-Methyl-2H-indazol-5-yl)vinyl)benzo[d]thiazol-6-ol (Compound 23).

[0120] Compound 22 (34 mg, 8.06 × 10⁻⁵ mol), KHF₂ (21 mg, 2.69 × 10⁻⁴ mol, 3.3 equiv.), 18-crown-6 (36 mg, 1.36 × 10⁻⁴ mol, 1.7 equiv.), and CHCl₃ (5 mL) were stirred at ambient temperature in a capped vial for 130 min. The reaction mixture was poured onto dry silica (33 mm h × 33 mm i.d.) and eluted under vacuum: %MeOH/CH₂Cl₂ – 1% (50 mL), 2% (75%), 3% (100 mL), 5% (50 mL) to afford **Compound 23** (24 mg, 97%) as a light-tan solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.86 (br s, 1 H), 8.41 (s, 1 H), 7.98 (s, 1 H), 7.75 (d, 1 H, J = 9.2 Hz), 7.72 (d, 1 H, J = 9.2 Hz), 7.61 (d, 1 H, J = 9.2 Hz), 7.57 (d, 1 H, J = 16.4 Hz), 7.45 (d, 1 H, J = 16.4 Hz), 7.36 (s, 1 H), 6.95 (d, 1 H, J = 8.8 Hz), 4.17 (s, 3 H); ¹³C NMR (125 MHz, DMSO-*d*₆) δ 163.21, 155.67, 148.23, 147.07, 136.99, 135.37, 128.50, 125.82, 123.41, 122.96, 122.04, 121.78, 120.03, 117.43, 115.84, 106.67, *N*-CH₃ resonance obscured by DMSO-*d*₆ resonance; HRMS (ESI) [M+H]⁺ Calcd for C₁₇H₁₄N₃OS: 308.0852, found: 308.0847.

[0121] (E)-2-(2-(2-(2-fluoroethyl)-2H-indazol-5-yl)vinyl)benzo[d]thiazol-6-ol (Compound 24).

[0122] Compound 12 (0.14 g, 3.37 × 10⁻⁴ mol) was flushed with N_{2(g)}, dissolved in THF (8 mL), and cooled to 0 °C. NaH (60%, 26 mg, 6.50 × 10⁻⁴ mol, 1.9 equiv.) was added, the reaction mixture was stirred at 0 °C under N_{2(g)} for 10 min, then a solution of compound 7 (87 mg, 4.53 × 10⁻⁴ mol, 1.3 equiv.) in THF (1.5 mL) was added dropwise over a period of 30 sec. The reaction mixture was stirred at ambient temperature under N_{2(g)} for 4 h, then H₂O (5 drops) was added, and the mixture was stirred for 10 min. The solvent was removed to give an orange residue that was suspended in CH₂Cl₂, then MeOH was added until the solid dissolved. The solution was concentrated to an orange oil, the oil was dissolved in CH₂Cl₂,

poured onto dry silica (55 mm h x 45 mm i.d.), and eluted under vacuum: %MeOH/CH₂Cl₂ – 1% (100 mL), 2.5% (100 mL), 5% (150 mL) to give a yellow/orange solid (77 mg, purified below) and a yellow solid (65 mg). The yellow solid was suspended in CH₂Cl₂ (5 mL), filtered, and the precipitate was rinsed with CH₂Cl₂ (2.5 mL x 2) then dried under vacuum to afford **Compound 24** (48 mg, 42%) as a yellow solid. The yellow/orange solid was purified by radial chromatography (2 mm silica): CH₂Cl₂ (100 mL), %MeOH/CH₂Cl₂ – 1% (50 mL), 2% (75 mL), 3% (50 mL), 5% (50 mL), 10% (50 mL) to afford **Compound 24** (28 mg, 24%) as a yellow solid. Total yield of **Compound 24**: 76 mg, 66%. ¹H NMR (300 MHz, acetone-*d*₆) δ 8.75 (s, 1 H), 8.38 (s, 1 H), 7.96 (s, 1 H), 7.77 (d, 1 H, *J* = 8.7 Hz), 7.75 (dd, 1 H, *J* = 9.0 Hz, *J* = 1.5 Hz), 7.68 (d, 1 H, *J* = 9.0 Hz), 7.61 (d, 1 H, *J* = 16.5 Hz), 7.41 (d, 1 H, *J* = 16.5 Hz), 7.40 (d, 1 H, *J* = 2.4 Hz), 7.03 (dd, 1 H, *J* = 8.7 Hz, *J* = 2.4 Hz), 4.98 (dt, 2 H, ²*J*_{FH} = 47.1 Hz, *J* = 4.8 Hz), 4.81 (dt, 2 H, ³*J*_{FH} = 27.0 Hz, *J* = 4.8 Hz); ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.85 (br s, 1 H), 8.51 (s, 1 H), 8.01 (s, 1 H), 7.76 (d, 1 H, *J* = 9.0 Hz), 7.65 (d, 1 H, *J* = 9.0 Hz), 7.58 (d, 1 H, *J* = 16.0 Hz), 7.47 (d, 1 H, *J* = 16.0 Hz), 7.36 (d, 1 H, *J* = 2.5 Hz), 6.96 (dd, 1 H, *J* = 9.0 Hz, *J* = 2.5 Hz), 4.93 (dt, 2 H, ²*J*_{FH} = 47.0 Hz, *J* = 2.5 Hz), 4.77 (dt, 2 H, ³*J*_{FH} = 27.5 Hz, *J* = 4.5 Hz); ¹³C NMR (125 MHz, DMSO-*d*₆) δ 163.18, 155.69, 148.35, 147.07, 136.89, 135.39, 128.76, 126.00, 123.74, 122.98, 122.19, 121.60, 120.21, 117.67, 115.85, 106.67, 81.97 (d, ¹*J*_{FC} = 167.5 Hz), 53.27 (d, ²*J*_{FC} = 20.0 Hz); HRMS (ESI) [M+H]⁺ Calcd for C₁₈H₁₅FN₃OS: 340.0914, found: 340.0918. X-ray quality crystals were grown by slow evaporation of acetone-*d*₆.

[0123] Synthesis of Compound 25 and Compound 26.

[0124] **Compound 12** (83 mg, 2.00 x 10⁻⁴ mol) was flushed with N_{2(g)}, dissolved in THF (5 mL), and cooled to 0 °C. NaH (60%, 20 mg, 5.00 x 10⁻⁴ mol, 2.5 equiv.) was added, the reaction mixture was stirred at 0 °C under N_{2(g)} for 10 min, then a solution of **Compound 8** (50 mg, 2.12 x 10⁻⁴ mol) in THF (1.5 mL) was added dropwise over a period of 15 sec. The reaction mixture was stirred at ambient temperature under N_{2(g)} for 4 h, then H₂O (5 drops) was added, the mixture was stirred for 10 min, and the solvent was removed to give a dark orange syrup. The syrup was dissolved in CH₂Cl₂, poured onto dry silica (33 mm h x 33 mm i.d.), and eluted under vacuum: CH₂Cl₂ (50 mL), %MeOH/CH₂Cl₂ – 1% (100 mL), 2% (100 mL), 5% (100 mL) to give a dark orange solid (91 mg). Purification by radial chromatography (1 mm silica): %MeOH/CH₂Cl₂ – 1% (50 mL), 2% (75 mL), 5% (50 mL)

gave crude **Compound 25** (41 mg - further purified below) and crude **Compound 26** (20 mg - further purified below).

[0125] (E)-6-((tert-Butyldimethylsilyl)oxy)-2-(2-(2-(2-(2-fluoroethoxy)ethyl)-2H-indazol-5-yl)vinyl)benzo[d]thiazole (Compound 25).

[0126] Crude **Compound 25** (41 mg from above) was purified by radial chromatography (1 mm silica) with CHCl₃ (125 mL) to afford **Compound 25** (33 mg, 33%) as a yellow syrup: ¹H NMR (300 MHz, CDCl₃) δ 8.08 (s, 1 H), 7.82 (d, 1 H, *J* = 8.7 Hz), 7.78 (s, 1 H), 7.71 (d, 1 H, *J* = 9.0 Hz), 7.60 (dd, 1 H, *J* = 9.0 Hz, *J* = 1.2 Hz), 7.52 (d, 1 H, *J* = 16.2 Hz), 7.33 (d, 1 H, *J* = 16.2 Hz), 7.28 (d, 1 H, *J* = 2.4 Hz), 6.97 (dd, 1 H, *J* = 8.7 Hz, *J* = 2.4 Hz), 4.61 (t, 2 H, *J* = 5.1 Hz), 4.50 (dt, 2 H, ²*J*_{FH} = 47.7 Hz, *J* = 4.2 Hz), 4.02 (t, 2 H, *J* = 5.1 Hz), 3.66 (dt, 2 H, ³*J*_{FH} = 29.7 Hz, *J* = 4.2 Hz), 1.02 (s, 9 H), 0.24 (s, 6 H); ¹³C NMR (125 MHz, CDCl₃) δ 165.56, 153.94, 149.32, 149.13, 137.75, 135.62, 129.60, 125.35, 124.12, 123.33, 122.25, 121.73, 120.84, 120.21, 118.35, 111.83, 83.11 (d, ¹*J*_{FC} = 167.5 Hz), 70.65 (d, ²*J*_{FC} = 18.8 Hz), 70.03, 54.05, 25.86, 18.42, -4.19; HRMS (ESI) [M+H]⁺ Calcd for C₂₆H₃₃FN₃O₂SSi: 498.2047, found: 498.2027.

[0127] (E)-2-(2-(2-(2-(2-Fluoroethoxy)ethyl)-2H-indazol-5-yl)vinyl)benzo[d]thiazol-6-ol (Compound 26).

[0128] Crude **Compound 26** (20 mg from above) was placed in a medium-fritted filter funnel, rinsed with 1:1 v/v CH₂Cl₂/hexane (1 mL x 3), EtOEt (2.5 mL), and dried under vacuum to afford **Compound 26** (15 mg, 20%) as a yellow solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.85 (s, 1 H), 8.45 (s, 1 H), 7.99 (s, 1 H), 7.75 (d, 1 H, *J* = 8.8 Hz), 7.73 (d, 1 H, *J* = 9.2 Hz), 7.63 (d, 1 H, *J* = 9.2 Hz), 7.58 (d, 1 H, *J* = 16.0 Hz), 7.46 (d, 1 H, *J* = 16.0 Hz), 7.36 (d, 1 H, *J* = 2.4 Hz), 6.95 (dd, 1 H, *J* = 8.8 Hz, *J* = 2.4 Hz), 4.60 (t, 2 H, *J* = 5.2 Hz), 4.47 (dt, 2 H, ²*J*_{FH} = 48.0 Hz, *J* = 4.0 Hz), 3.97 (t, 2 H, *J* = 5.2 Hz), 3.65 (dt, 2 H, ³*J*_{FH} = 31.2 Hz, *J* = 4.0 Hz); ¹H NMR (400 MHz, acetone-*d*₆) δ 8.80 (s, 1 H), 8.34 (s, 1 H), 7.95 (s, 1 H), 7.77 (d, 1 H, *J* = 8.8 Hz), 7.73 (dd, 1 H, *J* = 8.8 Hz, *J* = 1.2 Hz), 7.66 (d, 1 H, *J* = 9.2 Hz), 7.60 (d, 1 H, *J* = 16.4 Hz), 7.41 (d, 1 H, *J* = 16.4 Hz), 7.40 (d, 1 H, *J* = 2.4 Hz), 7.04 (dd, 1 H, *J* = 8.8 Hz, *J* = 2.4 Hz), 4.65 (t, 2 H, *J* = 5.2 Hz), 4.50 (dt, 2 H, ²*J*_{FH} = 48.0 Hz, *J* = 4.0 Hz), 4.04 (t, 2 H, *J* = 5.2 Hz), 3.70 (dt, 2 H, ³*J*_{FH} = 30.0 Hz, *J* = 4.0 Hz); ¹³C NMR (125 MHz, acetone-*d*₆) δ 164.66, 156.72, 149.86, 149.12, 138.15, 136.86, 130.08, 126.28, 124.31,

124.24, 123.14, 122.94, 121.29, 119.00, 116.68, 107.53, 83.87 (d, $^1J_{\text{FC}} = 166.4$ Hz), 71.05 (d, $^2J_{\text{FC}} = 19.0$ Hz), 70.43, 54.30; HRMS (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{20}\text{H}_{19}\text{FN}_3\text{O}_2\text{S}$: 384.1182, found: 384.1164.

[0129] (E)-2-(2-(1-Methyl-1H-indazol-5-yl)vinyl)quinolin-6-ol (Compound 27).

[0130] Compound 14 (0.24 g, 5.86×10^{-4} mol) was flushed with $\text{N}_{2(\text{g})}$ for 10 min, then dissolved in THF (9 mL) and cooled to 0 °C. NaH (60%, 40 mg, 1.00 mmol, 1.7 equiv.) was added, the reaction mixture was stirred at 0 °C under $\text{N}_{2(\text{g})}$ for 10 min, then a solution of **Compound 1** (0.10 g, 6.24×10^{-4} mol, 1.1 equiv.) in THF (1 mL) was added. The reaction mixture was stirred at ambient temperature under $\text{N}_{2(\text{g})}$ for 3.5 h, then H_2O (5 drops) was added, and the reaction mixture was stirred open to air for 90 min. The solvent was removed to give a wet yellow solid, then CH_2Cl_2 and hexane were added and removed 2x to give a yellow solid. The solid was dissolved in MeOH, then the MeOH was removed and the solid was dried under vacuum. The solid was suspended in CH_2Cl_2 (~10 mL), then MeOH (~4 mL) was added until the solid dissolved. The solution was poured onto dry silica (55 mm h x 45 mm i.d.), and eluted under vacuum: CH_2Cl_2 (50 mL), %MeOH/ CH_2Cl_2 – 1% (100 mL), 2.5% (100 mL), 5% (100 mL), 10% (100 mL) to give a yellow/tan solid that was dried under vacuum. The solid was placed in a medium-fritted filter funnel and rinsed with CHCl_3 (2.5 mL x 4), hexane (5 mL), and EtOEt (5 mL). The collection flask was changed and the solid was rinsed with MeOH (5 mL x 2), then acetone (5 mL x 2). The solvent was removed from the filtrate to afford **Compound 27** (27 mg, 15%) as a tan solid. The solid that remained on the filter was rinsed with CHCl_3 (5 mL), hexane (5 mL), EtOEt (5 mL) and dried under vacuum to afford **Compound 27** (98 mg, 55%) as a light tan solid: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.00 (s, 1 H), 8.12 (d, 1 H, $J = 8.8$ Hz), 8.08 (s, 1 H), 8.00 (s, 1 H), 7.84 (m - overlapping resonances, 3 H), 7.75 (d, 1 H, $J = 8.4$ Hz), 7.79 (d, 1 H, $J = 8.8$ Hz), 7.40 (d, 1 H, $J = 16.0$ Hz), 7.29 (d, 1 H, $J = 7.6$ Hz), 7.13 (s, 1 H), 4.06 (s, 3 H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 155.28, 152.74, 142.82, 139.52, 134.52, 132.94, 132.91, 130.09, 129.26, 128.23, 127.29, 124.55, 123.91, 122.03, 120.40, 119.79, 110.19, 108.43, 35.44; HRMS (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{19}\text{H}_{16}\text{N}_3\text{O}$: 302.1293, found: 302.1278.

[0131] (E)-2-(2-(1-(2-Fluoroethyl)-1H-indazol-5-yl)vinyl)quinolin-6-ol (Compound 28).

[0132] **Compound 14** (0.15 g, 3.66×10^{-4} mol) was flushed with $N_{2(g)}$ for 10 min, then dissolved in THF (6 mL) and cooled to 0 °C. NaH (60%, 23 mg, 5.75×10^{-4} mol, 1.6 equiv.) was added, the reaction mixture was stirred at 0 °C under $N_{2(g)}$ for 10 min, then a solution of **Compound 2** (75 mg, 3.90×10^{-4} mol, 1.1 equiv.) in THF (1 mL) was added. The reaction mixture was stirred at ambient temperature under $N_{2(g)}$ for 3.5 h, then H_2O (5 drops) was added, and the solution was stirred open to air for 2 h. The solvent was removed to give a wet yellow solid, then CH_2Cl_2 and hexane were added and removed to give a yellow/orange solid that was dried under vacuum. The solid was dissolved in a mixture of CH_2Cl_2 and MeOH, then concentrated to an oil that was dissolved in CH_2Cl_2 , poured onto dry silica (55 mm h x 45 mm i.d.), and eluted under vacuum: CH_2Cl_2 (100 mL), %MeOH/ CH_2Cl_2 – 1% (100 mL), 2.5% (100 mL), 5% (100 mL), 10% (100 mL) to give a yellow/tan solid that was dried under vacuum. The solid was suspended in $CHCl_3$ (2.5 mL), filtered, and the precipitate was rinsed with $CHCl_3$ (2.5 mL x 2), hexane (5 mL), EtOEt (5 mL), then dried under vacuum to afford **Compound 28** (56 mg, 46%) as a yellow solid: 1H NMR (400 MHz, DMSO- d_6) δ 10.00 (s, 1 H), 8.16 (s, 1 H), 8.12 (d, 1 H, $J = 8.4$ Hz), 8.02 (s, 1 H), 7.85 (m – overlapping resonances, 3 H), 7.74 (overlapping resonances – s, 1 H; d, 1 H, $J = 16.4$ Hz), 7.41 (d, 1 H, $J = 16.4$ Hz), 7.29 (dd, 1 H, $J = 9.2$ Hz, $J = 2.4$ Hz), 7.13 (d, 1 H, $J = 2.0$ Hz), 4.84 (dt, 2 H, $^2J_{FH} = 46.4$ Hz, $J = 4.4$ Hz), 4.76 (dt, 2 H, $^3J_{FH} = 27.2$ Hz, $J = 4.4$ Hz); ^{13}C NMR (75 MHz, DMSO- d_6) δ 155.29, 152.71, 142.82, 139.88, 134.53, 133.86, 132.81, 130.10, 129.53, 128.24, 127.42, 124.75, 124.04, 122.04, 120.39, 119.79, 110.33, 108.43, 82.37 (d, $^1J_{FC} = 166.5$ Hz), 48.82 (d, $^2J_{FC} = 19.5$ Hz); HRMS (ESI) $[M+H]^+$ Calcd for $C_{20}H_{17}FN_3O$: 334.1356, found: 334.1340.

[0133] **Synthesis of Compound 29 and Compound 30.**

[0134] **Compound 14** (0.21 g, 5.13×10^{-4} mol) was flushed with $N_{2(g)}$ for 1 h, then dissolved in THF (8 mL) and cooled to 0 °C. NaH (60%, 35 mg, 8.75×10^{-4} mol, 1.7 equiv.) was added, the reaction mixture was stirred at 0 °C under $N_{2(g)}$ for 10 min, then a solution of **7** (0.11 g, 5.72×10^{-4} mol, 1.1 equiv.) in THF (2 mL) was added. The reaction mixture was stirred at ambient temperature under $N_{2(g)}$ for 3 h, then H_2O (10 drops) was added, and the solution was stirred open to air for 1 h. The solvent was removed to give a wet, dark-yellow residue, then CH_2Cl_2 and hexane were added and removed to give an orange solid. The solid was dissolved in MeOH, then concentrated to a dark-yellow syrup that was dissolved in

CH₂Cl₂, poured onto dry silica (55 mm h x 45 mm i.d.), and eluted under vacuum: CH₂Cl₂ (100 mL), %MeOH/CH₂Cl₂ – 1% (100 mL), 2.5% (100 mL), 5% (100 mL), 10% (150 mL) to give a yellow residue (crude **Compound 29**, 134 mg) and a yellow/orange solid (crude **Compound 30**, 79 mg) which were each further purified below.

[0135] (E)-6-((tert-Butyldimethylsilyl)oxy)-2-(2-(2-(2-fluoroethyl)-2H-indazol-5-yl)vinyl)quinoline (Compound 29).

[0136] The yellow residue (crude **Compound 29** from above) was purified by radial chromatography (2 mm silica): %MeOH/CH₂Cl₂ – 1% (100 mL), 2% (100 mL), 3% (100 mL), 4% (100 mL) to afford **Compound 29** (81 mg, 35%) as a yellow solid: ¹H NMR (300 MHz, CDCl₃) δ 8.04 (s, 1 H), 7.99 (d, 1 H, *J* = 4.5 Hz), 7.96 (d, 1 H, *J* = 5.1 Hz), 7.80 (s, 1 H), 7.72 (two sets of resonances – s, 2 H; d, 1 H, *J* = 16.2 Hz), 7.62 (d, 1 H, *J* = 8.7 Hz), 7.35 (d, 1 H, *J* = 16.2 Hz), 7.29 (dd, 1 H, *J* = 9.0 Hz, *J* = 2.7 Hz), 7.12 (d, 1 H, *J* = 2.7 Hz), 4.91 (dt, 2 H, ²*J*_{FH} = 46.8 Hz, *J* = 4.5 Hz), 4.71 (dt, 2 H, ³*J*_{FH} = 26.7 Hz, *J* = 4.5 Hz), 1.03 (s, 9 H), 0.27 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 154.45, 153.77, 149.49, 144.60, 135.20, 134.18, 131.01, 130.70, 128.44, 127.95, 125.79, 127.87, 122.52, 120.68, 119.66, 118.09, 114.51, 81.83 (d, ¹*J*_{FC} = 171.5 Hz), 54.14 (d, ²*J*_{FC} = 20.7 Hz), 25.87, 18.45, -4.13; HRMS (ESI) [M+H]⁺ Calcd for C₂₆H₃₁FN₃OSi: 448.2215, found: 448.2204.

[0137] (E)-2-(2-(2-(2-Fluoroethyl)-2H-indazol-5-yl)vinyl)quinolin-6-ol (Compound 30).

[0138] The yellow/orange solid (crude **Compound 30** from above) was placed in a 2-mL fritted funnel, rinsed with CHCl₃ (1 mL x 3), hexane (5 mL), EtOEt (5 mL) and dried under vacuum to afford **Compound 30** (69 mg, 40%) as a yellow solid: ¹H NMR (300 MHz, acetone-*d*₆) δ 8.90 (s, 1 H), 8.34 (s, 1 H), 8.07 (d, 1 H, *J* = 8.7 Hz), 7.91 (s, 1 H), 7.89 (d, 1 H, *J* = 9.3 Hz), 7.87 (d, 1 H, *J* = 16.5 Hz), 7.77 (dd, 1 H, *J* = 9.3 Hz, *J* = 1.5 Hz), 7.71 (d, 1 H, *J* = 8.7 Hz), 7.67 (d, 1 H, *J* = 9.0 Hz), 7.38 (d, 1 H, *J* = 16.5 Hz), 7.36 (dd, 1 H, *J* = 9.3 Hz, *J* = 2.7 Hz), 7.19 (d, 1 H, *J* = 2.7 Hz), 4.98 (dt, 2 H, ²*J*_{FH} = 47.1 Hz, *J* = 4.8 Hz), 4.80 (dt, 2 H, ³*J*_{FH} = 27.0 Hz, *J* = 4.8 Hz); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 155.28, 152.77, 148.23, 142.84, 134.52, 133.22, 130.10, 129.81, 128.23, 127.13, 125.56, 123.86, 122.03, 121.73, 120.93, 119.84, 117.54, 108.44, 82.01 (d, ¹*J*_{FC} = 167.3 Hz), 53.23 (d, ²*J*_{FC} = 19.7 Hz); HRMS (ESI) [M+H]⁺ Calcd for C₂₀H₁₇FN₃O: 334.1350, found: 334.1352.

[0139] 6-(Methoxymethoxy)-2-methylbenzo[d]thiazole (Compound 31).

[0140] 6-Hydroxy-2-methylbenzothiazole (0.53 g, 3.21 mmol), MOM-Br (0.35 mL, 4.3 mmol, 1.3 equiv.), *i*-Pr₂NEt (0.85 mL, 4.9 mmol, 1.5 equiv.), and CH₂Cl₂ (20 mL) were stirred at ambient temperature under N_{2(g)} for 16 h, then poured onto dry silica (55 mm h x 45 mm i.d.), and eluted under vacuum: CH₂Cl₂ (100 mL), %MeOH/CH₂Cl₂ – 1% (100 mL), 2% (100 mL), 3% (100 mL), 4% (100 mL), 5% (100 mL) to give a dark-orange/red syrup (0.52 g). Purification by radial chromatography (4 mm silica): %MeOH/CH₂Cl₂ – 1% (100 mL), 2% (100 mL), 3% (50 mL) to afford **Compound 31** (0.18 g, 27%) as a yellow oil: ¹H NMR (500 MHz, CDCl₃) δ 7.83 (d, 1 H, *J* = 9.0 Hz), 7.50 (d, 1 H, *J* = 2.5 Hz), 7.14 (dd, 1 H, *J* = 9.0 Hz, *J* = 2.5 Hz), 5.22 (s, 2 H), 3.51 (s, 3 H), 2.79 (s, 3 H).

[0141] Diethyl ((6-(methoxymethoxy)benzo[*d*]thiazol-2-yl)methyl)phosphonate (Compound 32).

[0142] **Compound 31** (0.17 g, 8.12 × 10⁻⁴ mol) was flushed with N_{2(g)} for 15 min, then dissolved in THF (5 mL) and cooled to -78 °C. LDA solution (2.0 M THF/heptane/ethylbenzene, 1 mL, 2 mmol, 2.5 equiv.) was added dropwise over a period of 90 sec, the reaction mixture was stirred at -78 °C under N_{2(g)} for 10 min, then a solution of diethyl chlorophosphate (0.15 mL, 1.0 mmol, 1.3 equiv.) in THF (3 mL) was added dropwise over a period of 1 min. The reaction mixture was stirred at -78 °C under N_{2(g)} for 5 min, then warmed to ambient temperature and stirred for 90 min. Saturated NH₄Cl_(aq) (5 drops) was added, the mixture was stirred open to air for 20 min, then concentrated to an orange oil. CH₂Cl₂ and hexane were added and removed to give a dark-orange residue that was dissolved in CH₂Cl₂, poured onto dry silica (45 mm h x 45 mm i.d.), and eluted under vacuum: %MeOH/CH₂Cl₂ – 1% (100 mL), 2.5% (100 mL), 5% (50 mL) to give a yellow syrup (0.28 g). Purification by radial chromatography (2 mm silica): CHCl₃ (75 mL), %EtOH/CHCl₃ – 1% (50 mL), 2% (75 mL) afforded **Compound 32** (0.28 g, quantitative) as a yellow syrup: ¹H NMR (300 MHz, CDCl₃) δ 7.88 (d, 1 H, *J* = 9.0 Hz), 7.52 (d, 1 H, *J* = 2.4 Hz), 7.16 (dd, 1 H, *J* = 9.0 Hz, *J* = 2.4 Hz), 5.23 (s, 2 H), 4.15 (dq, 4 H, ³*J*_{PH} = 8.1 Hz, *J* = 7.2 Hz), 3.69 (d, 2 H, ²*J*_{PH} = 21.3 Hz), 3.51 (s, 3 H), 1.32 (t, 6 H, *J* = 7.2 Hz).

[0143] Synthesis of compound 32 from Compound 13.

[0144] **Compound 13** (0.19 g, 6.31 × 10⁻⁴ mol), MOM-Br (0.1 mL, 1.2 mmol, 1.9 equiv.), *i*-Pr₂NEt (0.15 mL, 8.6 × 10⁻⁴ mol, 1.4 equiv.), and CH₂Cl₂ (10 mL) were stirred in a septum-

capped vial at ambient temperature for 18 h. The reaction mixture was poured onto dry silica (55 mm h x 45 mm i.d.) and eluted under vacuum: CH₂Cl₂ (50 mL), %MeOH/CH₂Cl₂ – 1% (100 mL), 2.5% (100 mL), 5% (100 mL), 10% (100 mL) to give a faint-yellow/tan syrup (0.28 g). Purification by radial chromatography (2 mm silica): CHCl₃ (25 mL), %EtOH/CHCl₃ – 1% (50 mL), 2% (75 mL) afforded **Compound 32** (101 mg, 46%) as a faint-yellow syrup: ¹H NMR (300 MHz, CDCl₃) δ 7.88 (d, 1 H, *J* = 9.0 Hz), 7.52 (d, 1 H, *J* = 2.7 Hz), 7.16 (dd, 1 H, *J* = 9.0 Hz, *J* = 2.7 Hz), 5.23 (s, 2 H), 4.15 (dq, 4 H, ³*J*_{PH} = 8.1 Hz, *J* = 7.2 Hz), 3.69 (d, 2 H, ²*J*_{PH} = 21.6 Hz), 3.51 (s, 3 H), 1.32 (t, 6 H, *J* = 7.2 Hz); HRMS (ESI) [M+H]⁺ Calcd for C₁₄H₂₁NO₅PS: 346.0873, found: 346.0875.

[0145] (E)-2-(2-(1-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-1*H*-indazol-5-yl)vinyl)-6-(methoxymethoxy)benzo[d]thiazole (Compound 33).

[0146] Compound 32 (0.27 g, 7.82 × 10⁻⁴ mol) was flushed with N_{2(g)} then dissolved in THF (10 mL) and cooled to 0 °C. NaH (60%, 52 mg, 1.30 mmol, 1.7 equiv.) was added, the reaction mixture was stirred at 0 °C under N_{2(g)} for 10 min, then a solution of **Compound 4** (0.26 g, 8.54 × 10⁻⁴ mol, 1.1 equiv.) in THF (2 mL) was added. The reaction mixture was stirred at ambient temperature for 4 h, then H₂O (3 drops) was added, the mixture was stirred briefly, and the solvent was removed to give a dark orange/brown syrup. CH₂Cl₂ and hexane were added and removed to give a brown residue that was dissolved in CH₂Cl₂, poured onto dry silica (55 mm h x 45 mm i.d.), and eluted under vacuum: CH₂Cl₂ (50 mL), %MeOH/CH₂Cl₂ – 1% (100 mL), 2.5% (100 mL), 5% (100 mL), 10% (50 mL) to give a dark orange/brown residue (0.35 g). Purification by radial chromatography (2 mm silica): CH₂Cl₂ (200 mL), %MeOH/CH₂Cl₂ – 1% (100 mL), 2% (75 mL) gave a yellow solid (0.26 g) that was again purified by radial chromatography (2 mm silica) with CHCl₃ (150 mL) to afford **Compound 33** (0.25 g, 65%) as a yellow solid: ¹H NMR (400 MHz, CDCl₃) δ 8.04 (s, 1 H), 7.88 (d, 1 H, *J* = 8.8 Hz), 7.84 (s, 1 H), 7.65 (dd, 1 H, *J* = 8.8 Hz, *J* = 1.2 Hz), 7.56 (d, 1 H, *J* = 16.4 Hz), 7.52 (m - overlapping resonances, 2 H), 7.36 (d, 1 H, *J* = 16.4 Hz), 7.17 (dd, 1 H, *J* = 8.8 Hz, *J* = 2.4 Hz), 5.25 (s, 2 H), 4.50 (t, 2 H, *J* = 5.2 Hz), 4.05 (t, 2 H, *J* = 5.2 Hz), 3.53 (s, 3 H), 0.74 (s, 9 H), -0.21 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 165.77, 155.50, 149.43, 141.05, 137.63, 135.64, 134.18, 128.56, 124.67, 124.43, 123.43, 121.37, 120.71, 117.07, 110.84, 107.76, 95.16, 62.73, 56.25, 51.74, 25.86, 18.24, -5.58; HRMS (ESI) [M+H]⁺ Calcd for C₂₆H₃₄N₃O₃SSi: 496.2085, found: 496.2102.

[0147] **(E)-2-(2-(2-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2*H*-indazol-5-yl)vinyl)-6-(methoxymethoxy)benzo[*d*]thiazole (Compound 34).**

[0148] **Compound 32** (97 mg, 2.81×10^{-4} mol) was flushed with $N_{2(g)}$ then dissolved in THF (4 mL) and cooled to 0 °C. NaH (60%, 19 mg, 4.75×10^{-4} mol, 1.7 equiv.) was added, the reaction mixture was stirred at 0 °C under $N_{2(g)}$ for 10 min, then a solution of **Compound 9** (106 mg, 3.48×10^{-4} mol, 1.2 equiv.) in THF (1 mL) was added. The reaction mixture was stirred at ambient temperature for 4 h, then H_2O (1 drop) was added, the mixture was stirred briefly, and the solvent was removed to give a dark orange syrup. The syrup was dissolved in CH_2Cl_2 , poured onto dry silica (45 mm h x 45 mm i.d.), and eluted under vacuum: CH_2Cl_2 (50 mL), %MeOH/ CH_2Cl_2 – 1% (50 mL), 2% (75 mL), 3% (100 mL) to give an orange syrup (161 mg) that was purified by radial chromatography (2 mm silica) with CH_2Cl_2 (50 mL) to give a yellow syrup that was again purified by radial chromatography (2 mm silica): hexane/EtOAc/ NEt_3 v/v/v 90:8:2 (50 mL), 75:20:5 (50 mL) to give a yellow syrup (111 mg). Purification by radial chromatography (1 mm silica) with $CHCl_3$ (150 mL) afforded **Compound 34** (86 mg, 62%) as a yellow syrup: 1H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1 H), 7.88 (d, 1 H, $J = 8.8$ Hz), 7.78 (s, 1 H), 7.71 (d, 1 H, $J = 8.8$ Hz), 7.60 (dd, 1 H, $J = 9.2$ Hz, $J = 1.2$ Hz), 7.54 (d, 1 H, $J = 16.0$ Hz), 7.53 (d, 1 H, $J = 2.4$ Hz), 7.34 (d, 1 H, $J = 16.0$ Hz), 7.16 (dd, 1 H, $J = 8.8$ Hz, $J = 2.4$ Hz), 5.25 (s, 2 H), 4.51 (t, 2 H, $J = 5.2$ Hz), 4.09 (t, 2 H, $J = 5.2$ Hz), 3.53 (s, 3 H), 0.82 (s, 9 H), -0.11 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.98, 155.52, 149.50, 149.40, 138.06, 135.68, 129.43, 125.51, 123.96, 123.46, 122.08, 121.73, 120.68, 118.33, 117.10, 107.80, 95.21, 62.27, 56.51, 56.29, 25.92, 18.33, -5.49; HRMS (ESI) $[M+H]^+$ Calcd for $C_{26}H_{34}N_3O_3SSi$: 496.2085, found: 496.2102.

[0149] ***N*-Methylation of 1*H*-indazole-6-carbaldehyde to give Compounds 35 and 36.**

[0150] 1*H*-Indazole-6-carbaldehyde (0.41 g, 2.81 mmol), methyl tosylate (0.58 g, 3.11 mmol, 1.1 equiv.), K_2CO_3 (0.98 g, 7.09 mmol, 2.5 equiv.), and CH_3CN (30 mL) were stirred at reflux under $N_{2(g)}$ for 3 h, then cooled to ambient temperature, filtered, and the precipitate was rinsed with CH_3CN . The CH_3CN was removed from the filtrate to give an orange syrup, then CH_2Cl_2 and hexane were added and removed to give an orange/red syrup that was dissolved in CH_2Cl_2 , poured onto dry silica (55 mm h x 45 mm i.d.), and eluted under vacuum: CH_2Cl_2 (100 mL), %MeOH/ CH_2Cl_2 – 1% (100 mL), 2.5% (100 mL), 5% (200 mL)

to give a yellow/brown residue (0.41 g). Purification by radial chromatography (2 mm silica) with CH₂Cl₂ (175 mL) afforded **Compound 36** (0.12 g, 27%) as a yellow solid and crude **Compound 35** (yellow/orange solid, 0.24 g) which were further purified as described below:

[0151] 1-methyl-1*H*-indazole-6-carbaldehyde (Compound 35).

[0152] Crude **Compound 35** was purified by radial chromatography (2 mm silica) with CHCl₃ (50 mL) to give a yellow/orange crystalline solid (0.23 g) that was again purified by radial chromatography (2 mm silica): hexane/EtOAc/NEt₃ v/v/v 90:8:2 (50 mL), 75:20:5 (50 mL) to afford **35** (0.20 g, 45%) as a yellow solid: ¹H NMR (300 MHz, CDCl₃) δ 10.08 (d, 1 H, *J* = 0.6 Hz), 8.21 (partially resolved apparent q, 1 H, *J* = 0.9 Hz), 7.97 (s, 1 H), 7.73 (d, 1 H, *J* = 8.7 Hz), 7.62 (dd, 1 H, *J* = 8.7 Hz, *J* = 1.5 Hz), 4.29 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 192.70, 148.39, 135.21, 125.63, 125.35, 124.46, 121.24, 118.82, 41.05; HRMS (ESI) [M+H]⁺ Calcd for C₉H₉ON₂: 161.0709, found: 161.0712.

[0153] 2-methyl-2*H*-indazole-6-carbaldehyde (Compound 36).

[0154] ¹H NMR (400 MHz, CDCl₃) δ 10.16 (s, 1 H), 8.07 (d, 1 H, *J* = 0.8 Hz), 7.96 (d, 1 H, *J* = 0.8 Hz), 7.86 (d, 1 H, *J* = 8.4 Hz), 7.69 (dd, 1 H, *J* = 8.4 Hz, *J* = 0.8 Hz), 4.18 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 192.48, 139.73, 134.69, 133.27, 127.71, 122.05, 120.52, 112.61, 36.13; HRMS (ESI) [M+H]⁺ Calcd for C₉H₉ON₂: 161.0709, found: 161.0711.

[0155] *N*-Fluoroethylation of 1*H*-indazole-6-carbaldehyde to give Compounds 37 and 38.

[0156] 1*H*-Indazole-6-carbaldehyde (1.21 g, 8.28 mmol), fluoroethyl tosylate (1.94 g, 8.89 mmol, 1.1 equiv.), K₂CO₃ (2.80 g, 20.26 mmol, 2.4 equiv.), and CH₃CN (65 mL) were stirred at reflux under N_{2(g)} for 3 h, then cooled to ambient temperature, filtered, and the precipitate was rinsed with CH₃CN. The filtrate was concentrated to a dark orange syrup that was dissolved in CH₂Cl₂, poured onto dry silica (15 cm h x 4 cm i.d.), and eluted under vacuum: hexane/EtOAc/NEt₃ v/v/v 90:8:2 (100 mL), 75:20:5 (200 mL), 50:45:5 (300 mL), 20:75:5 (250 mL) to give crude **Compound 37** (yellow/orange solid, 0.65 g) and crude **Compound 38** (yellow/orange syrup, 0.44 g) which were each further purified as described below:

[0157] 1-(2-fluoroethyl)-1*H*-indazole-6-carbaldehyde (Compound 37).

[0158] Crude **Compound 37** was purified by radial chromatography (4 mm silica): hexane/EtOAc/NEt₃ v/v/v 95:4:1 (100 mL), 90:8:2 (100 mL), 75:20:5 (150 mL), 50:45:5 (150 mL) to give a yellow/orange solid (0.63 g) that was again purified by radial chromatography (2 mm silica): hexane/EtOAc/NEt₃ v/v/v 95:4:1 (100 mL), 90:8:2 (100 mL), 75:20:5 (200 mL) to give a yellow solid (0.61 g). The solid was purified by radial chromatography (2 mm silica): CH₂Cl₂ (125 mL) to afford **Compound 37** (0.59 g, 37%) as a yellow solid: ¹H NMR (400 MHz, CDCl₃) δ 10.15 (s, 1 H), 8.14 (s, 1 H), 8.02 (s, 1 H), 7.86 (d, 1 H, *J* = 8.4 Hz), 7.71 (dd, 1 H, *J* = 8.4 Hz, *J* = 0.8 Hz), 4.89 (dt, 2 H, ²*J*_{FH} = 46.8 Hz, *J* = 4.8 Hz), 4.77 (dt, 2 H, ³*J*_{FH} = 26.4 Hz, *J* = 4.8 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 192.41, 140.24, 135.01, 134.38, 127.81, 122.06, 120.66, 113.11 (d, *J* = 1.5 Hz), 82.42 (d, ¹*J*_{FC} = 171.5 Hz), 49.96 (d, ²*J*_{FC} = 21.0 Hz); HRMS (ESI) [M+H]⁺ Calcd for C₁₀H₁₀FN₂O: 193.0772, found: 193.0774.

[0159] **2-(2-fluoroethyl)-2*H*-indazole-6-carbaldehyde (Compound 38).**

[0160] Crude **Compound 38** was purified by radial chromatography (2 mm silica): hexane/EtOAc/NEt₃ v/v/v 90:8:2 (100 mL), 75:20:5 (150 mL), 50:45:5 (150 mL) to afford **Compound 38** (0.39 g, 25%) as a yellow/orange solid: ¹H NMR (300 MHz, CDCl₃) δ 10.09 (d, 1 H, *J* = 0.3 Hz), 8.23 (d, 1 H, *J* = 0.9 Hz), 8.10 (s, 1 H), 7.76 (d, 1 H, *J* = 8.7 Hz), 7.63 (dd, 1 H, *J* = 8.7 Hz, *J* = 1.2 Hz), 4.93 (dt, 2 H, ²*J*_{FH} = 46.5 Hz, *J* = 4.5 Hz), 4.77 (dt, 2 H, ³*J*_{FH} = 26.7 Hz, *J* = 4.5); ¹³C NMR (125 MHz, CDCl₃) δ 192.64, 148.60, 135.56, 125.80, 125.18, 124.86, 121.57, 119.02, 81.72 (d, ¹*J*_{FC} = 171.8 Hz), 54.66 (d, ²*J*_{FC} = 20.5 Hz); HRMS (ESI) [M+H]⁺ Calcd for C₁₀H₁₀FN₂O: 193.0772, found: 193.0775.

[0161] **(*E*)-2-(2-(1-methyl-1*H*-indazol-6-yl)vinyl)benzo[*d*]thiazol-6-ol (Compound 39).**

[0162] **Compound 35** (0.19 g, 1.19 mmol, 1.1 equiv) was flushed with N_{2(g)} for 30 min, then dissolved in THF (4 mL). **Compound 12** (0.45 g, 1.08 mmol) was flushed with N_{2(g)} for 15 min, then dissolved in THF (20 mL), and cooled to 0 °C. NaH (75 mg, 60%, 1.88 mmol, 1.7 equiv.) was added, the reaction mixture was stirred at 0 °C under N_{2(g)} for 10 min, then the solution of **Compound 35** was added dropwise over a period of 1 min. The reaction mixture was warmed to ambient temperature, stirred for 4 h, then H₂O (5 drops) was added, and the mixture was stirred open to air for 40 min. The mixture was concentrated to a dark orange/red syrup, then CH₂Cl₂ was added which produced a precipitate, then MeOH was

added to dissolve the precipitate. The solution poured onto dry silica (55 mm h x 45 mm i.d.), and eluted under vacuum: %MeOH/CH₂Cl₂ – 1% (100 ml), 2.5% (100 mL), 5% (100 mL), 10% (150 mL) to give a dark orange solid (0.32 g). The solid was stirred in refluxing CHCl₃ (25 mL) for 5 min, filtered while hot, the precipitate was rinsed with CHCl₃ (5 mL x 2), and dried under vacuum to afford **Compound 39** (0.22 g, 66%) as a yellow/orange solid: ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.90 (s, 1 H), 8.04 (d, 1 H, *J* = 8.0 Hz), 7.78 (d, 1 H, *J* = 9.0 Hz), 7.77 (d, 1 H, *J* = 8.0 Hz), 7.68 (d, 1 H, *J* = 16.0 Hz), 7.63 (d, 1 H, *J* = 16.0 Hz), 7.56 (unresolved dd, 1 H, *J* = 8.5 Hz), 7.38 (d, 1 H, *J* = 2.0 Hz), 6.98 (dd, 1 H, *J* = 9.0 Hz, *J* = 2.5 Hz), 4.08 (s, 3 H); ¹³C NMR (125 MHz, DMSO-*d*₆) δ 162.75, 155.88, 147.06, 140.01, 136.37, 135.54, 133.38, 132.46, 123.69, 123.22, 122.50, 121.12, 119.41, 116.02, 109.33, 106.70, 35.40; HRMS (ESI) [M+H]⁺ Calcd for C₁₇H₁₄N₃OS: 308.0852, found: 308.0850.

[0163] (E)-2-(2-(1-(2-fluoroethyl)-1*H*-indazol-6-yl)vinyl)benzo[*d*]thiazol-6-ol (Compound 40).

[0164] Compound 37 (0.18 g, 9.37 x 10⁻⁴ mol, 1.1 equiv) was flushed with N_{2(g)} for 25 min, then dissolved in THF (2 mL). **Compound 12** (0.35 g, 8.42 x 10⁻⁴ mol) was flushed with N_{2(g)} for 20 min, then dissolved in THF (13 mL), and cooled to 0 °C. NaH (51 mg, 60%, 1.28 mmol, 1.5 equiv.) was added, the reaction mixture was stirred at 0 °C under N_{2(g)} for 10 min, then the solution of **Compound 37** was added dropwise over a period of 1 min. The reaction mixture was warmed to ambient temperature, stirred for 4 h, then H₂O (5 drops) was added, and the mixture was stirred open to air for 30 min. The mixture was concentrated to an orange oil, then CH₂Cl₂ was added which produced a precipitate, then MeOH was added to dissolve the precipitate. The solution poured onto dry silica (55 mm h x 45 mm i.d.) and eluted under vacuum: %MeOH/CH₂Cl₂ – 1% (100 ml), 2.5% (100 mL), 5% (100 mL), 10% (50 mL) to give a yellow solid (0.32 g). The solid was suspended in CHCl₃ (5 mL), filtered, the precipitate was rinsed with CHCl₃ (2.5 mL x 2), hexane (2.5 mL x 2), and dried under vacuum to give a yellow solid (0.17 g). The solid was suspended in CHCl₃ (5 mL), stirred for 5 min, filtered, rinsed with CHCl₃ (1 mL x 5), hexane (5 mL), EtOEt (5 mL x 2), and dried under vacuum to give a yellow solid (0.16 g). The solid was suspended in CHCl₃ (25 mL), heated to reflux, stirred at reflux for 5 min, then filtered while hot, rinsed with CHCl₃ (5 mL), hexane (5 mL x 2), and dried under vacuum to afford **Compound 40** (0.11 g, 38%) as a yellow solid: ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.90 (s, 1 H), 8.13 (s, 1 H), 8.09 (s, 1 H),

7.79 (d, 1 H, $J = 8.5$ Hz), 7.78 (d, 1 H, $J = 9.0$ Hz), 7.68 (d, 1 H, $J = 16.0$ Hz), 7.62 (d, 1 H, $J = 16.0$ Hz), 7.57 (d, 1 H, $J = 8.5$ Hz), 7.38 (d, 1 H, $J = 2.5$ Hz), 6.98 (dd, 1 H, $J = 9.0$ Hz, $J = 2.5$ Hz), 4.87 (dt, 2 H, $^2J_{\text{FH}} = 47.5$ Hz, $J = 4.5$ Hz), 4.78 (dt, 2 H, $^3J_{\text{FH}} = 27.5$ Hz, $J = 4.5$ Hz); ^{13}C NMR (125 MHz, DMSO- d_6) δ 162.71, 155.89, 147.05, 140.31, 136.30, 135.54, 133.59, 133.39, 123.83, 123.23, 122.64, 121.21, 119.74, 116.03, 109.29, 106.70, 82.24 (d, $^1J_{\text{FC}} = 167.3$ Hz), 48.70 (d, $^2J_{\text{FC}} = 20.0$ Hz); HRMS (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{18}\text{H}_{15}\text{FN}_3\text{OS}$: 340.0914, found: 340.0911.

[0165] (E)-2-(2-(2-methyl-2H-indazol-6-yl)vinyl)benzo[d]thiazol-6-ol (Compound 41).

[0166] Compound 36 (98 mg, 6.12×10^{-4} mol, 1.1 equiv) was flushed with $\text{N}_{2(\text{g})}$ for 30 min, then dissolved in THF (2 mL). **Compound 12** (0.23 g, 5.53×10^{-4} mol) was flushed with $\text{N}_{2(\text{g})}$ for 15 min, then dissolved in THF (10 mL), and cooled to 0 °C. NaH (52 mg, 60%, 1.30 mmol, 2.3 equiv.) was added, the reaction mixture was stirred at 0 °C under $\text{N}_{2(\text{g})}$ for 10 min, then the solution of **Compound 36** was added dropwise over a period of 30 sec. The reaction mixture was warmed to ambient temperature, stirred for 4 h, then H_2O (5 drops) was added, and the mixture was stirred open to air for 1 h. The mixture was concentrated to a dark orange/red oil, then CH_2Cl_2 was added which produced a precipitate, then MeOH was added to dissolve the precipitate. The solution poured onto dry silica (45 mm h x 45 mm i.d.) and eluted under vacuum: %MeOH/ CH_2Cl_2 – 1% (100 ml), 2.5% (100 mL) to give a yellow/tan solid (0.18 g). The solid was stirred in refluxing CHCl_3 (10 mL) for 5 min, filtered while hot, the precipitate was rinsed with CHCl_3 (2.5 mL x 2), and dried under vacuum to afford **Compound 41** (85 mg, 50%) as a light tan solid: ^1H NMR (400 MHz, DMSO- d_6) δ 9.88 (s, 1 H), 8.33 (s, 1 H), 7.89 (s, 1 H), 7.77 (d, 1 H, $J = 8.8$ Hz), 7.72 (d, 1 H, $J = 8.8$ Hz), 7.61 (d, 1 H, $J = 16.4$ Hz), 7.53 (d, 1 H, $J = 16.4$ Hz), 7.51 (d, 1 H, $J = 8.8$ Hz), 7.37 (d, 1 H, $J = 2.4$ Hz), 6.96 (dd, 1 H, $J = 8.8$ Hz, $J = 2.4$ Hz), 4.18 (s, 3 H); ^{13}C NMR (125 MHz, DMSO- d_6) δ 163.02, 155.77, 148.33, 147.06, 137.04, 135.50, 132.68, 124.90, 123.09, 121.86, 121.39, 120.98, 118.89, 117.94, 115.93, 106.68, 39.5 (CH_3 resonance obscured by solvent resonance); HRMS (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{17}\text{H}_{14}\text{N}_3\text{OS}$: 308.0852, found: 308.0850.

[0167] (E)-2-(2-(2-(2-fluoroethyl)-2H-indazol-6-yl)vinyl)benzo[d]thiazol-6-ol (Compound 42).

[0168] **Compound 38** (0.12 g, 6.24×10^{-4} mol, 1 equiv) was flushed with $N_{2(g)}$ for 20 min, then dissolved in THF (1.5 mL). **Compound 12** (0.25 g, 6.02×10^{-4} mol) was flushed with $N_{2(g)}$ for 20 min, then dissolved in THF (12 mL), and cooled to 0 °C. NaH (46 mg, 60%, 1.15 mmol, 1.9 equiv.) was added, the reaction mixture was stirred at 0 °C under $N_{2(g)}$ for 10 min, then the solution of **Compound 38** was added dropwise over a period of 1 min. The reaction mixture was warmed to ambient temperature, stirred for 4 h, then H_2O (5 drops) was added, and the mixture was stirred open to air for 30 min. The mixture was concentrated to an orange residue, then CH_2Cl_2 was added which produced a precipitate, then MeOH was added to dissolve the precipitate. The solution poured onto dry silica (55 mm h x 45 mm i.d.) and eluted under vacuum: %MeOH/ CH_2Cl_2 – 1% (100 ml), 2.5% (100 mL), 5% (100 mL), 10% (100 mL) to give a yellow solid (0.22 g). The solid was suspended in $CHCl_3$ (3 mL), filtered, the precipitate was rinsed with $CHCl_3$ (1 mL x 5), hexane (2.5 mL x 2), and dried under vacuum to give a yellow solid (0.16 g). The solid was suspended in $CHCl_3$ (5 mL), stirred for 5 min, filtered, rinsed with $CHCl_3$ (1 mL x 5), hexane (5 mL), EtOEt (5 mL x 2), and dried under vacuum to afford **Compound 42** (0.15 g, 73%) as a yellow solid: 1H NMR (500 MHz, DMSO- d_6) δ 9.87 (s, 1 H), 8.42 (s, 1 H), 7.93 (s, 1 H), 7.77 (d, 1 H, $J = 9.0$ Hz), 7.75 (d, 1 H, $J = 8.5$ Hz), 7.62 (d, 1 H, $J = 16.5$ Hz), 7.55 (d, 1 H, $J = 16.5$ Hz), 7.54 (d, 1 H, $J = 9.0$ Hz), 7.37 (d, 1 H, $J = 2.5$ Hz), 6.97 (dd, 1 H, $J = 9.0$ Hz, $J = 2.5$ Hz), 4.93 (dt, 2 H, $^2J_{FH} = 47.0$ Hz, $J = 4.5$ Hz), 4.77 (dt, 2 H, $^3J_{FH} = 28.0$ Hz, $J = 4.5$ Hz); ^{13}C NMR (125 MHz, DMSO- d_6) δ 162.95, 155.78, 148.34, 147.05, 136.91, 135.53, 133.04, 125.08, 123.11, 121.64, 121.56, 121.19, 119.13, 118.11, 115.95, 106.68, 82.04 (d, $^1J_{FC} = 167.1$ Hz), 53.32 (d, $^2J_{FC} = 19.5$ Hz); HRMS (ESI) $[M+H]^+$ Calcd for $C_{18}H_{15}FN_3OS$: 340.0914, found: 340.0913.

[0169] **(E)-2-(2-(1-(2-fluoroethyl)-1H-indazol-6-yl)vinyl)quinolin-6-ol (Compound 43).**

[0170] **Compound 37** (0.16 g, 8.32×10^{-4} mol, 1.1 equiv) was flushed with $N_{2(g)}$ for 20 min, then dissolved in THF (2 mL). **Compound 14** (0.30 g, 7.33×10^{-4} mol) was flushed with $N_{2(g)}$ for 20 min, then dissolved in THF (13 mL), and cooled to 0 °C. NaH (59 mg, 60%, 1.48 mmol, 2.0 equiv.) was added, the reaction mixture was stirred at 0 °C under $N_{2(g)}$ for 10 min, then the solution of **Compound 37** was added dropwise over a period of 1 min. The reaction mixture was warmed to ambient temperature, stirred for 4 h, then H_2O (5 drops) was added, and the mixture was stirred open to air for 30 min. The mixture was concentrated to a dark orange syrup, then hexane was added and removed to give a dark yellow solid. The solid was

suspended CH_2Cl_2 , dissolved by addition of MeOH, then poured onto dry silica (55 mm h x 45 mm i.d.) and eluted under vacuum: %MeOH/ CH_2Cl_2 – 1% (100 mL), 2.5% (100 mL), 5% (200 mL) to give a light-yellow solid (0.23 g). The solid was suspended in CHCl_3 (12 mL), stirred for 10 min, filtered, rinsed with CHCl_3 (1 mL x 5), hexane (5 mL), EtOEt (5 mL x 2), and dried under vacuum to afford **Compound 43** (0.21 g, 86%) as a faint-yellow/off-white solid: ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.03 (s, 1 H), 8.15 (d, 1 H, $J = 9.0$ Hz), 8.11 (s, 1 H), 8.03 (s, 1 H), 7.86 (d, 1 H, $J = 16.5$ Hz), 7.85 (d, 1 H, $J = 9.0$ Hz), 7.78 (m, 2 H), 7.56 (d, 1 H, $J = 16.5$ Hz), 7.55 (d, 1 H, $J = 9.0$ Hz), 7.31 (dd, 1 H, $J = 9.0$ Hz, $J = 2.5$ Hz), 7.14 (d, 1 H, $J = 2.5$ Hz), 4.87 (dt, 2 H, $^2J_{\text{FH}} = 46.5$ Hz, $J = 4.5$ Hz), 4.79 (dt, 2 H, $^3J_{\text{FH}} = 27.5$ Hz, $J = 4.5$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 155.48, 152.37, 142.85, 140.47, 134.78, 134.66, 133.29, 132.72, 130.21, 129.53, 128.41, 123.47, 122.19, 121.06, 119.91, 119.76, 108.50, 108.42, 82.35 (d, $^1J_{\text{FC}} = 167.1$ Hz), 48.69 (d, $^2J_{\text{FC}} = 20.0$ Hz); HRMS (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{20}\text{H}_{17}\text{FN}_3\text{O}$: 334.1350, found: 334.1349.

[0171] (E)-2-(2-(2-(2-fluoroethyl)-2H-indazol-6-yl)vinyl)quinolin-6-ol (Compound 44).

[0172] Compound 38 (84 mg, 4.37×10^{-4} mol, 1.2 equiv) was flushed with $\text{N}_{2(\text{g})}$ for 20 min, then dissolved in THF (1 mL). **Compound 14** (0.15 g, 3.66×10^{-4} mol) was flushed with $\text{N}_{2(\text{g})}$ for 20 min, then dissolved in THF (7 mL), and cooled to 0 °C. NaH (33 mg, 60%, 8.25×10^{-4} mol, 2.3 equiv.) was added, the reaction mixture was stirred at 0 °C under $\text{N}_{2(\text{g})}$ for 10 min, then the solution of **Compound 38** was added dropwise over a period of 1 min. The reaction mixture was warmed to ambient temperature, stirred for 4 h, then H_2O (5 drops) was added, and the mixture was stirred open to air for 30 min. The mixture was concentrated to a dark orange syrup, then CH_2Cl_2 and hexane were added and removed to give a dark yellow solid. The solid was suspended CH_2Cl_2 , dissolved by addition of MeOH, then poured onto dry silica (55 mm h x 45 mm i.d.) and eluted under vacuum: %MeOH/ CH_2Cl_2 – 1% (100 mL), 2.5% (100 mL), 5% (200 mL) to give a yellow solid (0.11 g). The solid was suspended in CHCl_3 (4 mL), stirred for 5 min, filtered, rinsed with CHCl_3 (1 mL x 5), hexane (5 mL), EtOEt (5 mL x 2), and dried under vacuum to give a yellow solid (95 mg). Purification by radial chromatography (2 mm silica): hexane/EtOAc/ NEt_3 v/v/v 50:45:5 (100 mL), 20:75:5 (100 mL), EtOAc (135 mL), %MeOH/EtOAc – 5% (100 mL), 10% (50 mL) afforded **Compound 44** (45 mg, 37%) as a yellow/tan solid: ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.01 (s, 1 H), 8.41 (s, 1 H), 8.13 (d, 1 H, $J = 8.5$ Hz), 7.85 (d, 1 H, $J = 9.0$ Hz), 7.84 (d, 1 H, $J =$

16.0 Hz), 7.84 (s, 1 H), 7.76 (apparent t, 2 H, $J = 8.5$ Hz), 7.54 (d, 1 H, $J = 9.0$ Hz), 7.44 (d, 1 H, $J = 16.0$ Hz), 7.30 (dd, 1 H, $J = 9.0$ Hz, $J = 2.5$ Hz), 7.13 (d, 1 H, $J = 2.5$ Hz), 4.93 (dt, 2 H, $^2J_{\text{FH}} = 47.0$ Hz, $J = 4.5$ Hz), 4.77 (dt, 2 H, $^3J_{\text{FH}} = 27.5$ Hz, $J = 4.5$ Hz); ^{13}C NMR (125 MHz, DMSO- d_6) δ 155.38, 152.57, 148.67, 142.84, 134.57, 134.12, 133.32, 130.16, 128.47, 128.34, 124.93, 122.10, 121.34, 121.01, 119.97, 119.25, 117.03, 108.42, 81.83 (d, $^1J_{\text{FC}} = 167.3$ Hz), 53.25 (d, $^2J_{\text{FC}} = 19.5$ Hz); HRMS (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{20}\text{H}_{17}\text{FN}_3\text{O}$: 334.1350, found: 334.1349.

[0173] Example 2: Binding Affinity Assays

[0174] Target compounds were screened against $[\text{}^3\text{H}]\text{Z-2340}$ (Graham et al., J. Med. Chem. 2023, 66, 10628-10638), $[\text{}^3\text{H}]\text{PM-PBB3}$, and $[\text{}^3\text{H}]\text{Pittsburgh Compound-B}$ ($[\text{}^3\text{H}]\text{PiB}$) in human post-mortem Alzheimer's Disease (AD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and Parkinson's Disease (PD) brain tissue samples (Table 1). These compounds bind with high affinity to 4R-tau in AD, PSP, and CBD brain tissue samples; but bind with low affinity to the PM-PBB3 binding site on alpha-synuclein in PD brain tissue samples, and low affinity to the PiB binding site on amyloid-beta in AD brain tissue samples.

Table 1. Inhibition constant (K_i) values of selected compounds competed against $[\text{}^3\text{H}]\text{Z-2340}$, $[\text{}^3\text{H}]\text{PM-PBB3}$, and $[\text{}^3\text{H}]\text{PiB}$ in post-mortem human brain tissue samples.^a

compd	$[\text{}^3\text{H}]\text{Z-2340}$			$[\text{}^3\text{H}]\text{PM-PBB3}$				$[\text{}^3\text{H}]\text{PiB}$
	K_i (nM)	K_i (nM)	K_i (nM)	K_i (nM)	K_i (nM)	K_i (nM)	K_i (nM)	K_i (nM)
	AD brain	PSP brain	CBD brain	AD brain	PSP brain	CBD brain	PD brain	AD brain
16	12	15	n.d.	19	23	n.d.	n.d.	n.d.
23	11	15	n.d.	19	18	n.d.	n.d.	n.d.
18	6.8	11	16	8.8	10	12	2000	72
24	8.8	11	18	9.4	11	15	1600	57
19	13	19	n.d.	22	25	26	n.d.	n.d.
26	12	17	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
27	17	20	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
28	9.4	13	23	6.2	7.9	8.1	1300	47
30	22	14	17	19	27	28	n.d.	n.d.
39	16	21	20	n.d.	n.d.	n.d.	n.d.	n.d.
40	17	20	21	n.d.	n.d.	n.d.	n.d.	n.d.
41	13	17	19	n.d.	n.d.	n.d.	n.d.	n.d.
42	20	20	21	n.d.	n.d.	n.d.	n.d.	n.d.
43	21	23	21	n.d.	n.d.	n.d.	n.d.	n.d.
44	26	30	31	n.d.	n.d.	n.d.	n.d.	n.d.

^a) $n = 1$. n.d. = not determined.

[0175] In vitro competition (K_i) assays.

[0176] The equilibrium inhibition constant (K_i) values of the compounds were determined versus tritium-labeled radioligands using published methods (Klunk et al., *J. Neurosci.* 2003, 23, 2086-2092). The assays utilized autopsy-confirmed postmortem AD, PSP, and CBD human brain tissues obtained from the UCSF Neurodegenerative Disease Brain Bank and contained frequent autopsy-confirmed 3R/4R-tau and amyloid-beta aggregates (AD tissue) or only 4R-tau aggregates (PSP and CBD tissues) and no other detectable aggregated amyloid species. Briefly, the tissues were homogenized in ice-cold pH 7.0 phosphate buffered saline (PBS) at 300 mg/mL on ice using a glass homogenizer, diluted 30-fold with PBS to 10 mg/mL and homogenized a second time with a Brinkmann Polytron homogenizer before storage at -80°C . Frozen brain tissue was thawed and diluted 10-fold in PBS to 1 mg/mL. The concentration of unlabeled competitor compound ($\sim 400\text{ }\mu\text{M}$ in the stock solution) was determined by quantitative NMR in DMSO (0.25% DMSO in the final assay vials). The appropriate concentrations (ranging from 0.1-1000 nM) of unlabeled competitor in 400 μL of PBS buffer were combined with 500 μL of the tritium-labeled radioligand in PBS ($\sim 1\text{ nM}$ final concentration of radioligand). The assay was initiated by the addition of 100 μL of 1 mg/mL brain tissue homogenate to achieve a final concentration of 100 μg tissue/mL. After incubation for 60 min at room temperature, the binding mixture was filtered through a Whatman GF/B glass filter via a Brandel M-24R cell harvester (Gaithersburg, MD, USA) and rapidly washed four times with 3 mL PBS buffer. The filters were counted in Cytoscint-ES after thorough vortexing using a liquid scintillation counter. Complete (100%) inhibition of specific binding was defined as the number of counts displaced by 1 μM unlabeled competitor. All assays were performed in triplicate at each concentration. The K_i value was determined by the concentration of inhibitor that resulted in 50% binding inhibition (IC_{50}) of the radioligand: $K_i = IC_{50}/2$.

[0177] Binding affinity (K_d) assays

[0178] Tritium-labeled radioligand binding assays utilized brain AD, PSP, or CBD homogenates to determine equilibrium dissociation constant (K_d) values and were performed with slight modifications of the procedure previously described in detail (Klunk et al., *Life Sciences* 2001, 69, 1471–1484). Briefly, frozen aliquots (-80°C) of homogenized cortex (10 mg/mL in PBS (pH=7.0)) from AD, PSP, or CBD brain were thawed and diluted 10-fold in

PBS to 1 mg/mL. The unlabeled test compound was dissolved in DMSO at 400 μ M and then diluted to 20 μ M with PBS to yield 5% DMSO/PBS. The remaining serial dilutions (typically from 6 μ M to 4 nM) were made with 5% DMSO/PBS to maintain a constant DMSO concentration in the final assay. Fifty μ L of these solutions were combined with 50 μ L of tritiated test compound and 800 μ L of PBS to yield 0.25% DMSO, $\sim$ 1 nM tritiated compound and 0.2 to 1000 nM unlabeled compound in the final assay. The assay began by addition of 100 μ L of the 1 mg/mL brain homogenate to achieve a final concentration of 100 μ g tissue/mL. After incubation for 60 min at room temperature, the binding mixture was filtered through a Whatman GF/B glass filter via a Brandel M-24R cell harvester (Gaithersburg, MD) and rapidly washed three times with 3 mL PBS. The filters were counted in Cytoscint-ES after thorough vortexing and sitting overnight. All assays were performed at least in triplicate. The concentration of bound compound was determined from the radioactivity retained on the filter after correcting for the non-displaceable radioactivity (defined as that remaining with $\sim$ 1 μ M unlabeled compound) and the specific activity of the tritiated compound after dilution with varying concentrations of unlabeled compound. The K_d value was determined by the slope (slope = $-1/K_d$) of a Scatchard plot of the bound/free vs. bound radioligand values at the different ligand concentrations.

[0179] The compounds described herein have $K_i > 1 \mu$ M in Parkinson's Disease brain tissue when competed against [3 H]PM-PBB3, which binds to PD brain tissue with $K_D \sim 5$ nM (Lindberg et al., Nature Communications 2024, 15, 5109), thus indicating that the compounds do not bind to the same site on α -synuclein that [3 H]PM-PBB3 binds to. It is possible that these compounds bind to another site on α -synuclein. Likewise, these compounds have $K_i \geq 47$ nM in Alzheimer's Disease brain tissue when competed against [3 H]PiB. It is possible that there could be other binding sites on amyloid-beta than the PiB binding site.

[0180] The compounds described herein are pan-tau ligands. Besides binding to 4R-tau, they also bind to 3R-tau and mixed 3R/4R-tau. The compounds described herein may work for 3R/4R-tau in AD better than existing tau PET tracers.

[0181] The compounds described herein are an improvement over PM-PBB3, PBB3, PBQ3, and other similar compounds because PM-PBB3, PBB3, PBQ3, and other similar compounds isomerize and/or decompose under visible light. The compounds described herein are more

photochemically stable compared to PM-PBB3, PBB3, PBQ3, and other similar compounds. Additionally, as stated above, the compounds described herein do not bind to the PM-PBB3 binding site on α -synuclein, or the PiB binding site on amyloid-beta.

[0182] Example 3: X-Ray Crystal Structures of Compound 18 and Compound 24

Table 2. Sample and crystal data for **18** (JSS21-024A).

Identification code	JSS21-024A
Chemical formula	C ₁₈ H ₁₄ FN ₃ O _{1.50} S
Formula weight	347.38 g/mol
Temperature	100(2) K
Wavelength	1.54178 Å
Crystal size	0.004 x 0.008 x 0.110 mm
Crystal system	monoclinic
Space group	P 1 2/c 1
Unit cell dimensions	a = 11.736(3) Å $\alpha = 90^\circ$ b = 4.8157(16) Å $\beta = 99.635(17)^\circ$ c = 27.892(7) Å $\gamma = 90^\circ$
Volume	1554.1(8) Å ³
Z	4
Density (calculated)	1.485 g/cm ³
Absorption coefficient	2.077 mm ⁻¹
F(000)	720

Table 3. Sample and crystal data for **24** (JSS21-025A).

Identification code	JSS21-025A		
Chemical formula	C ₁₈ H ₁₄ FN ₃ O ₂ S		
Formula weight	355.38 g/mol		
Temperature	100(2) K		
Wavelength	1.54178 Å		
Crystal size	0.007 x 0.020 x 0.140 mm		
Crystal system	orthorhombic		
Space group	P n a 21		
Unit cell dimensions	a = 22.897(4) Å	α = 90°	
	b = 15.814(2) Å	β = 90°	
	c = 4.4106(9) Å	γ = 90°	
Volume	1597.0(5) Å ³		
Z	4		
Density (calculated)	1.478 g/cm ³		
Absorption coefficient	2.059 mm ⁻¹		
F(000)	736		

[0183] While certain embodiments have been illustrated and described, it should be understood that changes and modifications can be made therein in accordance with ordinary skill in the art without departing from the technology in its broader aspects as defined in the following claims.

[0184] The embodiments, illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein. Thus, for example, the terms “comprising,” “including,” “containing,” etc. shall be read expansively and without limitation. Additionally, the terms and expressions employed herein have been used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the claimed technology. Additionally, the phrase “consisting essentially of” will be understood to include those elements specifically recited and those additional elements that do not materially affect the basic and novel characteristics of the claimed technology. The phrase “consisting of” excludes any element not specified.

[0185] The present disclosure is not to be limited in terms of the particular embodiments described in this application. Many modifications and variations can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. Functionally equivalent methods and compositions within the scope of the disclosure, in addition to those enumerated herein, will be apparent to those skilled in the art from the foregoing descriptions. Such modifications and variations are intended to fall within the scope of the appended claims. The present disclosure is to be limited only by the terms of the appended claims, along with the full scope of equivalents to which such claims are entitled. It is to be understood that this disclosure is not limited to particular methods, reagents, compounds, or compositions, which can of course vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

[0186] In addition, where features or aspects of the disclosure are described in terms of Markush groups, those skilled in the art will recognize that the disclosure is also thereby described in terms of any individual member or subgroup of members of the Markush group.

[0187] As will be understood by one skilled in the art, for any and all purposes, particularly in terms of providing a written description, all ranges disclosed herein also encompass any and all possible subranges and combinations of subranges thereof. Any listed range can be easily recognized as sufficiently describing and enabling the same range being broken down into at least equal halves, thirds, quarters, fifths, tenths, etc. As a non-limiting example, each range discussed herein can be readily broken down into a lower third, middle third and upper third, etc. As will also be understood by one skilled in the art all language such as “up to,” “at least,” “greater than,” “less than,” and the like, include the number recited and refer to ranges which can be subsequently broken down into subranges as discussed above. Finally, as will be understood by one skilled in the art, a range includes each individual member.

[0188] All publications, patent applications, issued patents, and other documents referred to in this specification are herein incorporated by reference as if each individual publication, patent application, issued patent, or other document was specifically and individually indicated to be incorporated by reference in its entirety. Definitions that are contained in text incorporated by reference are excluded to the extent that they contradict definitions in this disclosure.

[0189] Other embodiments are set forth in the following claims.

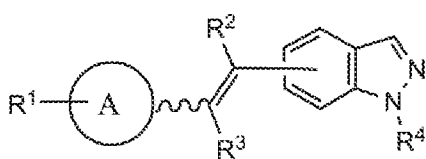
REFERENCES

1. Albert et al., “Subcortical dementia of progressive supranuclear palsy,” *J. of Neurology Neurosurgery and Psychiatry* 1974, 37 (2), 121–130.
2. Armstrong et al., “Criteria for the diagnosis of corticobasal degeneration,” *Neurology* 2013, 80 (5), 496–503.
3. Villemagne et al., “Amyloid Imaging with F-18-Florbetaben in Alzheimer Disease and Other Dementias,” *J. Nucl. Med.* 2011, 52 (8), 1210–1217.
4. Okamura N; Yanai K, Florbetapir, “(F-18), a PET imaging agent that binds to amyloid plaques for the potential detection of Alzheimer’s disease,” *Idrugs* 2010, 13 (12), 890–899.
5. Nelissen et al., “Phase 1 Study of the Pittsburgh Compound B Derivative F-18-Flutemetamol in Healthy Volunteers and Patients with Probable Alzheimer Disease,” *J. Nucl. Med.* 2009, 50 (8), 1251–1259.
6. Leuzy et al., “Tau PET imaging in neurodegenerative tauopathies-still a challenge,” *Molecular Psychiatry* 2019, 24 (8), 1112–1134.
7. Buee L; Delacourte A, “Comparative biochemistry of tau in progressive supranuclear palsy, corticobasal degeneration, FTDP-17 and Pick’s disease,” *Brain Pathology* 1999, 9 (4), 681–693.
8. Betthausen TJ., “In vitro evidence for a nonselective 4R tau PET tracer,” *Mol. Psychiatry*. 2023 Jan 19. doi: 10.1038/s41380-023-01950-2. Epub ahead of print.
9. Messerschmidt et al., “18F-PI-2620 Tau PET Improves the Imaging Diagnosis of Progressive Supranuclear Palsy,” *J. Nucl. Med.* 2022 Nov; 63(11):1754-1760.
10. Song et al., “Feasibility of short imaging protocols for [18F]PI-2620 tau-PET in progressive supranuclear palsy,” *Eur. J. Nucl. Med. Mol. Imaging*. 2021 Nov;48(12):3872-3885.
11. Palleis et al., “Cortical [18F]PI-2620 Binding Differentiates Corticobasal Syndrome Subtypes,” *Mov. Disord.* 2021 Sep;36(9):2104-2115.

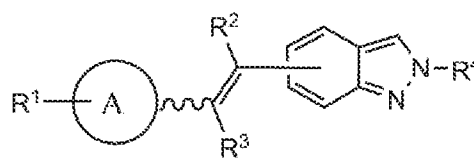
12. Li et al., "Progressive Supranuclear Palsy Neuroimage Initiative (PSPNI). Clinical Utility of ^{18}F -APN-1607 Tau PET Imaging in Patients with Progressive Supranuclear Palsy," *Mov. Disord.* 2021 Oct;36(10):2314-2323.
13. Tagai et al., "An optimized reference tissue method for quantification of tau protein depositions in diverse neurodegenerative disorders by PET with 18F-PM-PBB3 (^{18}F -APN-1607)," *Neuroimage*. 2022 Dec 1;264:119763.

WHAT IS CLAIMED IS:

1. A compound having a structure of Formula I or Formula II, or a pharmaceutically acceptable salt, solvate, hydrate, formulation, tautomer, stereoisomer, or isotopologue thereof:



Formula I



Formula II

wherein:

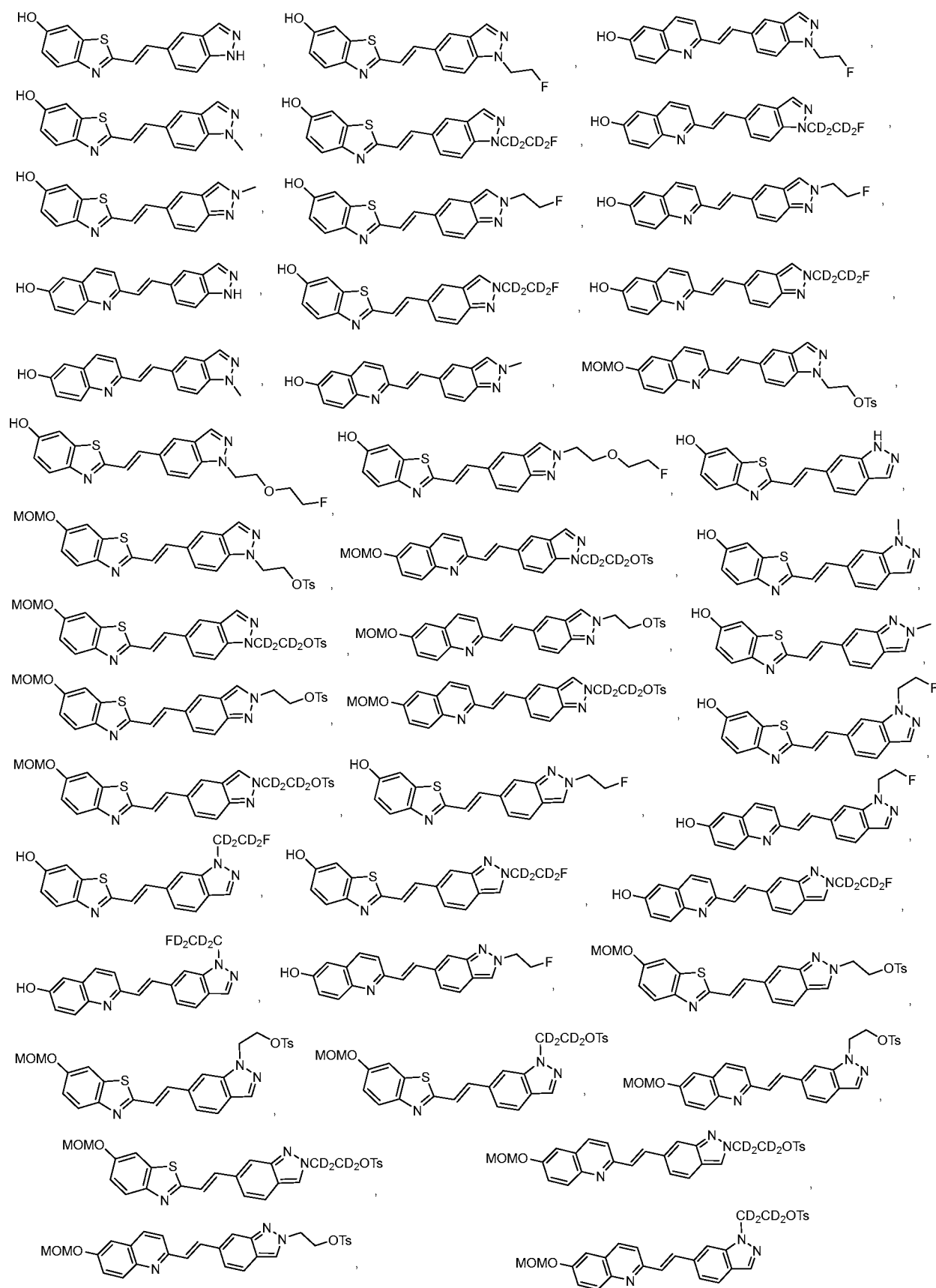
A is aryl or heteroaryl comprising benzothiazolyl, benzisothiazolyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, azaindolyl, benzimidazolyl, indazolyl, azaindazolyl, benzoxazolyl, benzisoxazolyl, benzothiophenyl, benzofuranyl, purinyl, cinnolinyl, phthalazinyl, quinazolinyl, or quinoxalinyl;

R¹ is H, OH, O-alkyl, O-haloalkyl, O-alkylether, O-haloalkylether, O-alkenyl, O-haloalkenyl, 4-fluoro-2-butenyl ether, O-silyl alkyl, glycidyl, glycidyl ether, 3-fluoro-2-hydroxypropyl, 3-fluoro-2-hydroxypropyl ether, amino-3-fluoro-2-hydroxypropyl, halogen, CN, acyl, alkyl, haloalkyl, alkenyl, haloalkenyl, 4-fluoro-2-butenyl, amino-4-fluoro-2-butenyl, cycloalkyl, halocycloalkyl, cycloalkylether, aryl, heteroaryl, NO₂, NH₂, substituted-nitrogen, ammonium salt, OMs, OTs, OTf, O-nosylate, O-brosylate, or other suitable sulfonate species, SnMe₃, SnEt₃, SnPr₃, SnBu₃, or other suitable trialkyltin species, I(O-acyl)₂, ArI⁺X⁻, IR⁵, S(O)Ar, SO₂Ar, BF₃K, B(OH)₂, B(OMe)₂, B(OEt)₂, B(OPr)₂, B(OiPr)₂, B(OiPr)₃Li, B-pinacol, B-neopentyl glycol, or other suitable boron species; wherein X⁻ is a suitable counterion; wherein ArI⁺X⁻ is a suitable iodonium species known in the art; wherein IR⁵ is a suitable iodonium ylide known in the art;

R² and R³ are each independently H, halogen, alkyl, haloalkyl, alkylether, haloalkylether, cycloalkyl, halocycloalkyl, cycloalkylether, halocycloalkylether, aryl, heteroaryl; and

R^4 is H, alkyl, haloalkyl, alkylether, haloalkylether, glycidyl, 3-fluoro-2-hydroxypropyl, 4-fluoro-2-butenyl, cycloalkyl, halocycloalkyl, cycloalkylether, halocycloalkylether, aryl, heteroaryl, *tert*-butoxycarbonyl, tosyl, or other appropriate nitrogen protecting group.

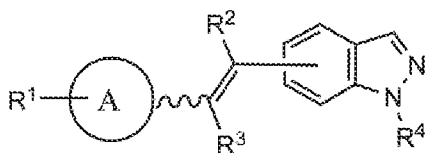
2. The compound of claim 1 having a structure selected from the following group:



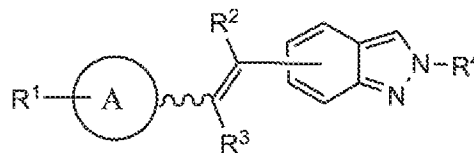
3. The compound of claim 1 or claim 2, wherein the compound binds to 3R-tau, 4R tau, or mixed 3R/4R-tau.
4. The compound of any one of the preceding claims, wherein the compound comprises one or more detection labels.
5. The compound of claim 4, wherein the detection label is selected from the group consisting of a radionuclide, a positron emitter, an alpha emitter, a gamma emitter, and a fluorescent label.
6. The compound of claim 4 or 5, wherein the detection label is selected from the group consisting of ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{18}F , ^{75}Br , ^{76}Br , ^{77}Br , ^{123}I , ^{124}I , ^{125}I , and ^{131}I .
7. The compound of any one of claims 4-6, wherein the detection label is ^{18}F .
8. The compound of any one of the preceding claims for use in detection and/or monitoring progression of a disorder or disease, wherein the disease or disorder is a neurodegenerative disease or disorder.
9. The compound of any one of the preceding claims for use in detection and/or monitoring progression of a disorder or disease associated with aberrant protein aggregation.
10. The compound for use of claim 9, wherein the protein in the aberrant protein aggregation is tau protein.
11. The compound for use of any one of claims 9-10, wherein the aberrant protein aggregation is selected from the group consisting of Paired helical filaments in neurofibrillary tangles, Straight filaments and paired helical filaments, Pick bodies, and Straight filaments in neurofibrillary tangles.
12. The compound for use of any one of claims 8-11 for use in detection and/or monitoring progression of a disorder or disease associated with aggregated tau protein.
13. The compound for use of claim 12, wherein the disease or disorder is a 4R-tauopathy or a disease or disorder correlated with aggregates of 4R tau.

14. The compound for use of claim 12, wherein the disease or disorder is a 3R-tauopathy or a disease or disorder correlated with aggregates of 3R tau.
15. The compound for use of claim 12, wherein the disease or disorder is a mixed 3R/4R-tauopathy or a disease or disorder correlated with aggregates of 3R/4R tau.
16. The compound for use of any one of claims 8-15, wherein the disorder or disease is selected from the group consisting of a tauopathy, Alzheimer's Disease (AD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), corticobasal syndrome (CBS), frontal temporal lobar dementias (FTLD's), Parkinson's Disease (PD), frontotemporal dementia, frontotemporal dementia with parkinsonism-17 (FTDP-17), chronic traumatic encephalopathy (CTE), primary age-related tauopathy (PART), Pick's disease, argyrophilic grain disease, glial globular tauopathy, Guam ALS/parkinsonism, Huntington's disease, Lewy body dementia, and Chronic traumatic encephalopathy.
17. The compound for use of any one of claims 8-16, wherein detection is carried out by one or more of positron emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), autoradiography, or fluorescence.
18. The compound for use of claim 17, wherein detection is carried out by positron emission tomography (PET) imaging.
19. A method for diagnosing a subject with a disease or disorder, and/or monitoring disease or disorder progression in a subject, and/or assessing the accumulation of tau protein in the brain of the subject, the method comprising:

(a) administering to the subject a detectable quantity of a labeled compound of Formula I or Formula II, or a pharmaceutically acceptable salt, solvate, hydrate, formulation, tautomer, stereoisomer, or isotopologue thereof:



Formula I



Formula II

wherein:

A is aryl or heteroaryl comprising benzothiazolyl, benzisothiazolyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, azaindolyl, benzimidazolyl, indazolyl, azaindazolyl, benzoxazolyl, benzisoxazolyl, benzothiophenyl, benzofuranyl, purinyl, cinnolinyl, phthalazinyl, quinazolinyl, or quinoxalinyl;

R^1 is H, OH, O-alkyl, O-haloalkyl, O-alkylether, O-haloalkylether, O-alkenyl, O-haloalkenyl, 4-fluoro-2-butenyl ether, O-silyl alkyl, glycidyl, glycidyl ether, 3-fluoro-2-hydroxypropyl, 3-fluoro-2-hydroxypropyl ether, amino-3-fluoro-2-hydroxypropyl, halogen, CN, acyl, alkyl, haloalkyl, alkenyl, haloalkenyl, 4-fluoro-2-butenyl, amino-4-fluoro-2-butenyl, cycloalkyl, halocycloalkyl, cycloalkylether, aryl, heteroaryl, NO_2 , NH_2 , substituted-nitrogen, ammonium salt, OMs, OTs, OTf, O-nosylate, O-brosylate, or other suitable sulfonate species, SnMe_3 , SnEt_3 , SnPr_3 , SnBu_3 , or other suitable trialkyltin species, $\text{I}(\text{O-acyl})_2$, ArI^+X^- , IR^5 , $\text{S}(\text{O})\text{Ar}$, SO_2Ar , BF_3K , $\text{B}(\text{OH})_2$, $\text{B}(\text{OMe})_2$, $\text{B}(\text{OEt})_2$, $\text{B}(\text{Opr})_2$, $\text{B}(\text{OiPr})_2$, $\text{B}(\text{OiPr})_3\text{Li}$, B-pinacol, B-neopentyl glycol, or other suitable boron species; wherein X^- is a suitable counterion; wherein ArI^+X^- is a suitable iodonium species known in the art; wherein IR^5 is a suitable iodonium ylide known in the art;

R^2 and R^3 are each independently H, halogen, alkyl, haloalkyl, alkylether, haloalkylether, cycloalkyl, halocycloalkyl, cycloalkylether, halocycloalkylether, aryl, heteroaryl; and

R^4 is H, alkyl, haloalkyl, alkylether, haloalkylether, glycidyl, 3-fluoro-2-hydroxypropyl, 4-fluoro-2-butenyl, cycloalkyl, halocycloalkyl, cycloalkylether, halocycloalkylether, aryl, heteroaryl, *tert*-butoxycarbonyl, tosyl, or other appropriate nitrogen protecting group; and

(b) detecting binding of the compound to tau aggregates in the subject.

20. The method of claim 19, wherein the disease or disorder is a neurodegenerative disease or disorder.

21. The method of claim 19 or 20, wherein the disease or disorder is associated with aberrant protein aggregation.

22. The method of any one of claims 19-21, wherein the disease or disorder is associated with tau protein aggregates.
23. The method of claim 19 or 20, wherein the aberrant protein aggregation is selected from the group consisting of Paired helical filaments in neurofibrillary tangles, Straight filaments and paired helical filaments, Pick bodies, and Straight filaments in neurofibrillary tangles.
24. The method of any one of claims 19-23, wherein the disease or disorder is a 4R-tauopathy or a disease or disorder correlated with aggregates of 4R tau.
25. The method of any one of claims 19-23, wherein the disease or disorder is a 3R-tauopathy or a disease or disorder correlated with aggregates of 3R tau.
26. The method of any one of claims 19-23, wherein the disease or disorder is a mixed 3R/4R-tauopathy or a disease or disorder correlated with aggregates of 3R/4R tau.
27. The method of any one of claims 19-26, wherein the disorder or disease is selected from the group consisting of a tauopathy, Alzheimer's Disease (AD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), corticobasal syndrome (CBS), frontal temporal lobar dementias (FTLD's), Parkinson's Disease (PD), frontotemporal dementia, frontotemporal dementia with parkinsonism-17 (FTDP-17), chronic traumatic encephalopathy (CTE), primary age-related tauopathy (PART), Pick's disease, argyrophilic grain disease, glial globular tauopathy, Guam ALS/parkinsonism, Huntington's disease, Lewy body dementia, and Chronic traumatic encephalopathy.
28. The method of any one of claims 19-27, wherein the compound comprises one or more detection labels.
29. The method of claim 28, wherein the detection label is selected from the group consisting of a radionuclide, a positron emitter, an alpha emitter, a gamma emitter, and a fluorescent label.
30. The method of claim 28 or 29, wherein the compound is isotopically labeled with ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{18}F , ^{75}Br , ^{76}Br , ^{77}Br , ^{123}I , ^{124}I , ^{125}I , or ^{131}I .

31. The method of any one of claims 19-30, wherein detection is carried out by one or more of positron emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), autoradiography, or fluorescence.

32. The method of any one of claims 19-31, wherein detecting binding of the compound to tau aggregates in the subject comprises obtaining a biological sample from the subject, followed by evaluating the biological sample for the presence of tau aggregates.

33. The method of claim 32, wherein the biological sample is selected from the group consisting of blood, cerebrospinal fluid (CSF) and the fluid surrounding the brain.

Figure 1

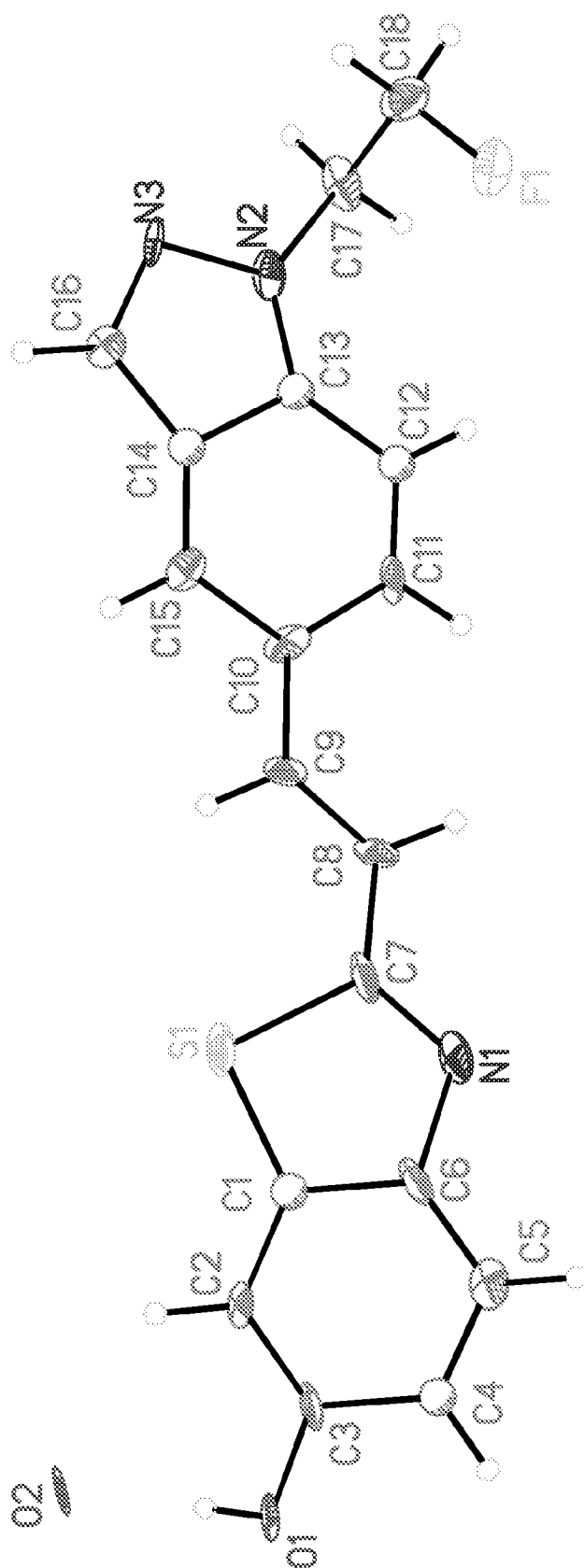
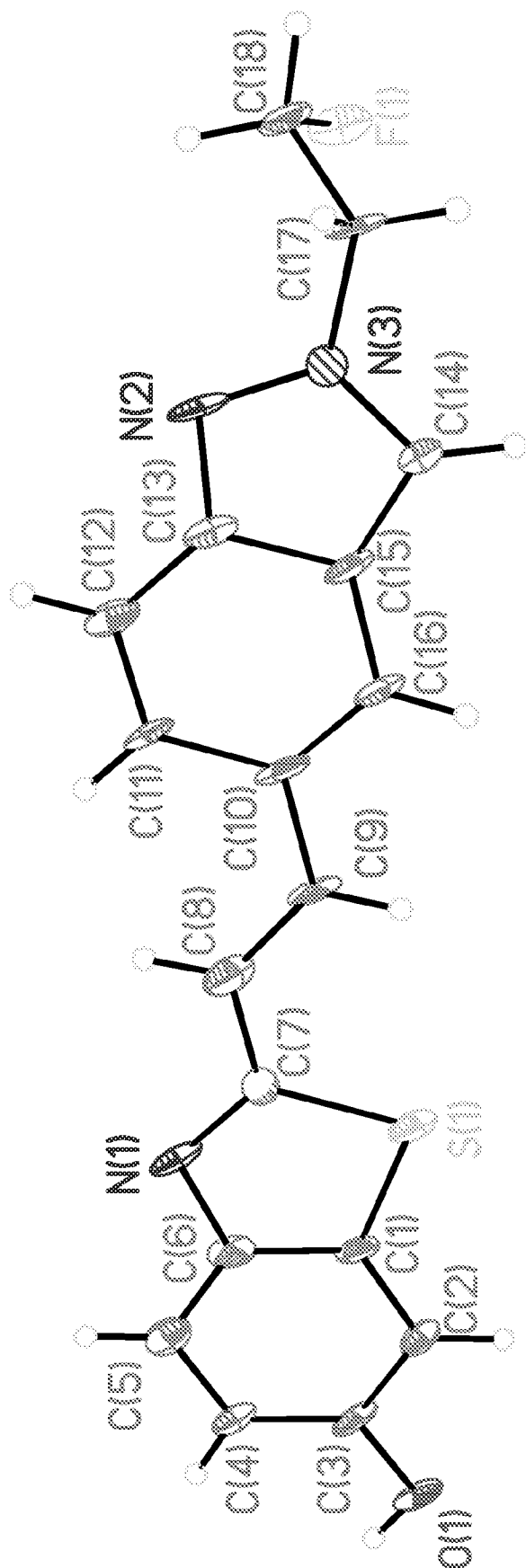


Figure 2



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/051310

A. CLASSIFICATION OF SUBJECT MATTERIPC: **A61K 31/395** (2024.01); **A61K 31/505** (2024.01); **A61K 31/415** (2024.01); **A61K 31/33** (2024.01)CPC: **A61K 31/395**; **A61K 31/505**; **A61K 31/415**; **A61K 31/33**

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)

See Search History Document

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

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2021/011913 A1 (Arvinas Operations, Inc.) 21 January 2021 (21.01.2021) entire document	1;3/1
X	PUBCHEM 479721608 deposited on 25 April 2023 pp. 1-5. pg. 2, structure	1; 3/1
A	MATHIS, et.al. Small Molecule PET Tracers for Imaging Proteinopathies in Semin Nucl Med, 2017, Vol 47(5), pp. 1-50. ENTIRE DOCUMENT	1; 3/1

☐ 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

“D” document cited by the applicant in the international application

“E” earlier application or patent 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

14 November 2024 (14.11.2024)

Date of mailing of the international search report

23 January 2025 (23.01.2025)

Name and mailing address of the ISA/US

COMMISSIONER FOR PATENTS
MAIL STOP PCT, ATTN: ISA/US
P.O. Box 1450
Alexandria, VA 22313-1450
UNITED STATES OF AMERICA

Authorized officer

KARI RODRIQUEZ

Facsimile No. 571-273-8300

Telephone No. PCT Help Desk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/051310

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.:
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:
3. ☒ Claims Nos.: **4-18, 22-33**
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:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Group I+: Claims 1-3 directed to a compound represented by the structure of formula I, including pharmaceutically acceptable salt, solvate, hydrate, formulation, tautomer, stereoisomer, or isotopologue thereof. The compound will be searched to the extent that it encompasses the first species of a compound represented by the structure of formula I, wherein A is an aryl, R1 is H, R2 is H, R3 is H and R4 is H. It is believed that claims 1 and 3/1 read on this first named invention, and thus these claims will be searched without fee. This first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. Applicant is invited to elect additional compounds of claim 1, wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the '+' group(s) will result in only the first claimed invention to be searched. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be the compound represented by the structure of formula I, wherein A is a heteroaryl, R1 is H, R2 is H, R3 is H and R4 is H (Claims 1-3).

Group II: Claims 19-21 directed to a method for diagnosing a subject with a disease or disorder, and/or monitoring the disease or disorder progression in a subject, and /or assessing the accumulation of tau protein in the brain of a subject, the method comprising step (a) and (b) of claim 19.

The group of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I+ includes the technical feature of a unique compound represented by the structure of formula I, which is not required by any other invention of Groups I+ and II.

Group II includes the technical feature of a method for diagnosing a subject with a disease or disorder, and/or monitoring the disease or disorder progression in a subject, and /or assessing the accumulation of tau protein in the brain of a subject, the method comprising step (a) and (b) of claim 19, which is not required by any other invention of Group I+.

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

Common technical features:

The inventions of Group I+ share the technical feature of a compound represented by the structure of formula I which is not required for Groups II.

The inventions of Group II share the technical feature of a method for diagnosing a subject with a disease or disorder, and/or monitoring the disease or disorder progression in a subject, and /or assessing the accumulation of tau protein in the brain of a subject, the method comprising step (a) and (b) of claim 19, which is not required by any other invention of Group I+.

These shared technical features, however, do not provide a contribution over the prior art, as being anticipated PUBCHEM 479721608 (hereinafter "Pubchem"). Pubchem discloses an a compound of formula I, wherein A is an aryl, and each of R2 to R4 is H (pg. 2, structure).

As said compound and compositions were known in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify the inventions of Groups I+ and II. The inventions of Group I+ and II thus lack unity under PCT Rule 13.

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.: **1; 3/1**

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.