

Supporting Information:

1. Search Strategy

Table S1. Summary of search strategy based on PRISM guidelines.

Section/topic	#	Checklist item	Location(s) Reported	Timing
INFORMATION SOURCES AND METHODS				
Database name	1	PubChem	https://pubchem.ncbi.nlm.nih.gov	May 2019 – November 2020
		ChEMBL	https://www.ebi.ac.uk/chembl/	May 2019 – November 2019
		Reaxys	https://www.reaxys.com	May 2019 – November 2019
		World Intellectual Property Organization (WIPO)	https://www.wipo.int/portal/en/index.html	May – July 2019
		PubMed	https://pubmed.ncbi.nlm.nih.gov/	May 2019 – November 2020
Online resources and browsing	2	International Society of Radiopharmaceutical Sciences conference 2019		May 2019 – November 2019
		Annual Congress of the European Association of Nuclear Medicine		May 2019 – November 2019
SEARCH STRATEGIES				
Full search strategies	1	PubChem search profile	SNCA gene (human) – sort by activity	-

	2	ChEMBL search profile	Target SNCA – division based on standard units and sort by nM activities	-
	3	Reaxys search profile	Target search (α -syn, human-wild)	-
	4	World Intellectual Property Organization (WIPO) search profile	Search profile: compounds and alpha and synuclein	-
	5	PubMed search profile	Manual search about alpha synuclein and PET imaging	-

2. Summary table of Radiolabeled compounds

Table S2. Summary table of all radiolabeled compounds with reported results from *in vitro* assays and preclinical studies. *Note to the table:* *n.d.* = not determined;

[#]	<i>In vitro</i> assays			Preclinical evaluation				Advantages	Limitations
	Affinity [< 1 nM]	Selectivity [30-50 fold]	Tested on LB-, LN-, GCI-enriched brain fraction	RCY [%]	A _M [GBq/ μ mol]	BBB permeability with early peak uptake of SUV > 1.5	$\geq 0.4\%$ ID/g (rat brain) or $\geq 4.0\%$ ID/g (mouse brain)		
[¹⁸ F]SIL26	No.	No.	Yes	55 – 65 (decay-corrected to EOB)	>200	Passing BBB. No <i>in vivo</i> PET imaging.	No.	- moderate affinity on human PD brain homogenates	- low brain uptake and slow clearance
[¹¹ C]SIL5	No.	No.	Yes.	35 – 45 (decay-corrected to EOB)	>363	Yes.	No.	- high brain uptake	- low affinity on human PD brain homogenates - low selectivity profile

[¹¹C]BF-227	No.	No.	Yes.	>50% (based on [¹¹ C]CH ₃ OTf)	119-138	Yes.	N.d.	- confirmed binding to GCl rich brain regions confirmed by PET study on patients	- contradictory results among different research groups concerning binding towards α-syn aggregates
[¹⁸F]BF-227	No.	No.	Yes.	N.d.	40-840	N.d.	N.d.	-	- no binding towards α-syn aggregates.
[¹⁸F]2FBox	No.	Yes.	Yes.	10 – 19	68-543	Passing BBB, SUV < 1.5	N.d.	-	-no binding to α-syn aggregates confirmed by postmortem tissue investigation.
[¹⁸F]15a	No.	Yes.	No.	N.d.	29.6-185	N.d.	N.d.	- high binding affinity and selectivity.	- too lipophilic, slow clearance - lack of information about binding in human derived brain tissue
[¹⁸F]S3-1	No.	Yes.	N.d.	N.d.	N.d.	No.	No.	- high affinity and selectivity	- lack of information about bidding in human derived brain tissue - lack of more detailed scientific literature - rapid clearance with marginally increase in the later timepoints
[¹¹C]PBB3	No.	No.	Yes.	N.d.	133	-	-	-moderate affinity tested on human derived brain tissue (DLB)	- low selectivity
[³H]C05-01	No.	No.	Yes.	N.d.	0.81	N.d.	N.d.	-high affinity tested on human derived DLB brain tissue	-low selectivity
[¹²⁵I]BI-2	No.	No.	Yes.	N.d.	81.4	Yes.	No.	- moderate selectivity	- low affinity - high lipophilicity and low brain uptake
[¹¹C]anle253b	N.d.	N.d.	No.	47	15.1±3.4	-	Yes.	-IC ₅₀ value of 1.6 nM	-lack of information about affinity using human derived brain tissue -moderate brain uptake

[¹¹C]MODAG-001	Yes.	Yes.	Yes.	3.6 ± 1.1 and 11.4 ± 3.7	31.3 ± 6.4 and 98.6 ± 24.7	Yes.	Yes.	- high affinity - no binding to aggregated tau was detected in PSP and AD brain tissues	-fast metabolism and detection of radiometabolites in the mouse brain - lack of strong binding and high nonspecific binding in human LBD brain tissue
[¹²⁵I]IDP-4	No.	No.	Yes.	19-60	81.4	Passing BBB.	Yes.	-high binding affinity and moderate selectivity	- low brain uptake
[¹⁸F]42	No.	No.	No.	32 ± 3	128	Passing BBB.	N.d.	-high affinity -moderate affinity only over Aβ	-low selectivity over tau -lack of information about binding using human derived brain tissue - lack of detailed scientific literature
[¹¹C]52	No.	No.	No.	50±10	>148 (d.c. to EOB)	N.d.	N.d.	-	-lack of selectivity
[¹⁸F]53	No.	No.	No.	21 ± 7	>27 (d.c. to EOS)	N.d.	N.d.	- moderate affinity towards α-syn fibrils	-lack of selectivity
[¹⁸F]54	No.	No.	No.	30 ± 4	>37 (d.c. to EOS)	N.d.	N.d.	- moderate affinity towards α-syn fibrils	-lack of selectivity
[¹²⁵I]TZ6184	Yes.	N.d.	N.d.	50-60	N.d.	N.d.	N.d.	-excellent binding affinity on α-syn fibrils	-lack of information about selectivity profile -limited detailed scientific literature available
[¹²⁵I]83	No.	No.	No.	57	81	N.d.	N.d.	-high binding affinity -moderate selectivity	-lack of binding affinity tested on human derived tissue -high non-specific binding
[³H]55	N.d.	N.d.	Yes.	N.d.	77 Ci/mmol	-	-	-	-lack of detailed scientific literature

[¹¹C]84	N.d.	N.d.	No.	N.d	>37	Passing BBB. Evaluated in NHP.	-	-	-lack of binding and selectivity profile tested on human derived brain tissue
[¹¹C]85	N.d.	N.d.	No.	N.d.	>37	Passing BBB. Evaluated in NHP.	-	-	
[¹⁸F]BQ2	No.	No.	Yes.	1.2	8.9	N.d.	No.	-moderate brain uptake and binding affinity	-lack of selectivity -high non-specific binding-