SUPPLEMENTARY INFORMATION

Identification of novel tau positron emission tomography tracers for chronic traumatic encephalopathy by comprehensive in silico screening and molecular dynamics simulation

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Table S1 Parameter ranges for the physicochemical properties of CNS PET MPO

Parameter	Type of Transformation Function	Weight	CNS PET MPO	
			Desirable range	Undesirable range
MW (g/mol)	Monotonic decreasing	1	MW ≤ 305.3	MW > 350.5
ClogP	Monotonic decreasing	1	Clog P ≤ 2.8	Clog P > 4
$ClogD_{7.4}$	Monotonic decreasing	1	$ClogD_{7.4}$ ≤ 1.7	$ClogD_{7.4}$ > 2.8
TPSA ($Å^2$)	Hump function	1	44.8 < TPSA ≤ 63.3	TPSA ≤ 32.3; TPSA > 86.2
HBD	Monotonic decreasing	1	HBD ≤ 1	HBD > 2
p*K*a	Monotonic decreasing	1	pKa ≤ 7.2	pKa > 9.5

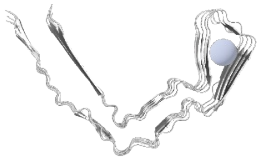
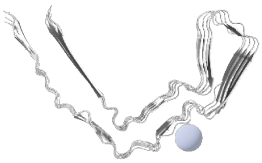
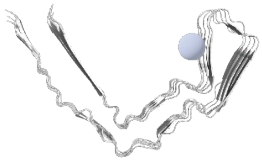
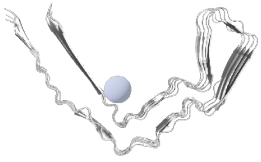
MW: molecular weight, TPSA: topological polar surface area, HBD: hydrogen bond donor, p*K*a: ionization constant of the most basic center.

Table S2 Simulation details for each system

System	Simulation time (ns)	Number of trajectories	Number of atoms
tau+CNS-4	500	4	92057
tau+CNS-12	500	4	92057
tau+CNS-18	500	4	92071

tau+CNS-25	500	4	92062

Table S3 Prediction of possible binding sites for compounds in CTE tau protofibril [a]

Predicted binding sites	Schematic representation	SiteScore	Dscore
Site 1		1.209	1.294
Site 2		0.859	0.924
Site 3		0.809	0.817
Site 4		0.595	0.456

[a] Purple sphere represent possible binding sites of compounds to tau protofibrils.

Table S4 SP docking results of reported CNS PET tracers with CTE tau protofibrils

Compound Number	Compound	Docking score (kcal/mol)	Glide g-score (kcal/mol)	Glide e-model (kcal/mol)
1	18F-PM-PBB3	-8.23	-8.26	-69.24
2	18F-CBD-2115	-8.05	-8.05	-63.98
3	18F-PI-2620	-7.09	-7.27	-49.73
4	18F-RO-948	-7.29	-7.47	-52.98
5	18F-MK-6240	-7.48	-7.66	-50.11
6	18F-Flortaucipir	-7.61	-7.65	-53.66

Table S5 The source, molecular formula, and SMILES details of candidate compounds

Compound Number	CNS BBB Library ID Number	Molecular Formula	SMILE
1	T408-0727	$C_{24}H_{30}N_4O_2S$	O=C(C(CC1)Cc2c1sc(C(N1CCCCC1)=O)c2)N(CC1)CCN1c1ncccc1
2	IB03-8110	$C_{27}H_{30}N_4OS$	N=C1N(CCC2CCN(Cc3ccccc3)CC2)CC(O)=C1c1nc(-c2ccccc2)cs1
3	T160-0467	$C_{25}H_{28}FN_3O_2$	Cc1cnc(CC(CC2)CCN2C(c(cc2)cc(F)c2OC)=O)n1Cc1ccccc1
4	V017-7820	$C_{24}H_{26}F_3N_3O_3$	O=C(c(ccc(F)c1)c1F)N1CC(CN(CCC2)CCN2C(c(cc2)ccc2F)=O)OCC1
5	P801-0566	$C_{26}H_{29}N_5O$	O=C(c(cc1)cnc1N1CC(c2ccccc2)NCC1)N(CC1)CCN1c1ccccc1
6	T160-0582	$C_{25}H_{28}FN_3O$	Cc1cnc(CC(CC2)CCN2C(c2cc(C)ccc2)=O)n1Cc(cc1)ccc1F
7	D454-0334	$C_{23}H_{25}ClN_4O$	O=C(C1CCCCC1)Nc(ccc(N1Cc2nc(cccc3)c3n2CC1)c1)c1Cl
8	P801-0571	$C_{26}H_{28}FN_5O$	O=C(c(cc1)cnc1N1CC(c2ccccc2)NCC1)N(CC1)CCN1c(cc1)ccc1F
9	S993-0623	$C_{22}H_{26}N_4O_3$	CC(C)CN(CC(N(CC1)C2CCN1C(c1nc3ccccc3cc1)=O)=O)C2=O
10	V021-8191	$C_{26}H_{33}FN_4O_4S$	COc(ccc(C(N1CCN(CC(C2)OCCN2C(Nc(cc2)ccc2F)=S)CCC1)=O)c1)c1OC
11	7894-6124	$C_{28}H_{28}F_3N_3O$	O=C(c1ccc(CN(CC2)Cc3c2cccc3)cc1)N(CC1)CCN1c1cccc(C(F)(F)F)c1
12	S776-0061	$C_{24}H_{30}N_4O$	Cc1cnc(C2CC2)n1CCC(CC1)CCN1C(Cc1c[nH]c2c1cccc2)=O
13	V001-3797	$C_{25}H_{25}F_3N_4O$	O=C(c1cn(CC(CC2)c3ccccc3)c2n1)N(CC1)CCN1c1cccc(C(F)(F)F)c1
14	C598-0388	$C_{24}H_{23}ClFN_3O$	O=C(c1ccc2c(Cl)c(CCCC3)c3nc2c1)N(CC1)CCN1c(cccc1)c1F
15	V021-4414	$C_{21}H_{23}ClF_3N_3O$	CC(C(NCc1cc(C(F)(F)F)ccc1)=O)N(CC1)CCN1c(cc1)ccc1Cl
16	C598-0434	$C_{24}H_{23}ClFN_3O$	O=C(c1ccc2c(Cl)c(CCCC3)c3nc2c1)N(CC1)CCN1c(cc1)ccc1F
17	L275-0441	$C_{25}H_{31}N_5O_2$	Cc(cc1)c(C)cc1C(N1CCN(Cc2nc(cc(cc3)C(N(C)C)=O)c3n2C)CC1)=O
18	S567-0465	$C_{26}H_{33}N_3O_2$	Cc(cc1)ncc1C(N1CCC(CC2)(CCC2(CN(CC2)c3c2cccc3)O)CC1)=O
19	T160-0459	$C_{25}H_{29}N_3O$	Cc1cnc(CC(CC2)CCN2C(c2cc(C)ccc2)=O)n1Cc1ccccc1
20	D672-0115	$C_{27}H_{28}FN_3O$	O=C(c1ccc(CN(CC2)Cc3c2cccc3)cc1)N(CC1)CCN1c(cc1)ccc1F
21	G856-8799	$C_{22}H_{20}F_3N_5O$	O=C(c1ccc(C(F)(F)F)cc1)N(CC1)CCN1c(cc1)nnc1Nc1ccccc1
22	S691-0847	$C_{24}H_{26}FN_3O$	Cc1cnc(CC(CC2)CN2C(Cc2cccc(F)c2)=O)n1Cc1ccccc1
23	S691-0905	$C_{27}H_{31}N_3O_2$	Cc1cnc(CC(CC2)CN2C(C2(CC2)c(cc2)ccc2OC)=O)n1Cc1ccccc1
24	C304-0340	$C_{28}H_{29}N_3OS$	CCC1=Nc(cc(cc2)C(N(CC3)CC(C)N3c3cc(C)ccc3)=O)c2Sc2c1cccc2
25	T828-0465	$C_{21}H_{25}FN_4O$	O=C(C(CC1)Cc2c1nc(N1CCCCC1)nc2)NCc(cc1)ccc1F

Table S6 Prediction biological properties of candidate compounds [b]

Compound Number	MW (g/mol)	ClogP	ClogD7.4	TPSA (Å^2)	HBD	pKa	CNS PET MPO	P-gp substrate
1	438.59	3.60	3.56	84.99	0	6.42	2.39	Yes

2	458.62	2.96	1.08	91.69	2	15.0	1.87	no
3	421.52	3.87	3.63	47.36	0	7.33	3.05	yes
4	461.49	2.55	2.18	53.09	0	7.53	4.46	no
5	427.55	3.74	2.89	51.71	1	8.18	2.8	no
6	405.52	4.54	4.30	38.13	0	7.33	2.41	yes
7	408.93	5.17	5.17	50.16	1	4.60	3.00	yes
8	445.54	3.89	3.04	51.71	1	8.18	2.67	no
9	394.48	1.22	1.22	73.82	0	1.98	4.45	yes
10	516.63	2.89	2.52	66.51	1	7.54	3.95	yes
11	479.55	5.59	4.84	26.79	0	8.07	1.62	yes
12	390.53	3.19	2.98	53.92	1	7.27	3.64	no
13	454.50	4.67	4.67	41.37	0	3.74	2.73	yes
14	423.92	5.24	5.24	36.44	0	3.34	2.33	no
15	425.88	4.60	4.38	35.58	1	7.23	2.25	no
16	423.92	5.24	5.24	36.44	0	3.37	2.33	no
17	433.56	2.75	2.74	61.68	0	5.66	4.13	yes
18	419.57	2.98	2.98	56.67	1	5.19	3.85	no
19	387.53	4.40	4.16	38.13	0	7.33	2.41	yes
20	429.54	4.86	4.10	26.79	0	8.07	1.62	yes
21	427.43	4.32	4.32	61.36	1	8.81	2.30	yes
22	391.49	3.64	3.58	38.13	0	6.60	2.77	yes
23	429.56	3.97	3.91	47.36	0	6.60	3.03	yes
24	455.62	6.57	6.57	35.91	0	4.49	2.29	no
25	368.46	3.52	3.52	58.12	1	2.77	3.40	no

[b] MW: molecular weight, TPSA: topological polar surface area, HBD: hydrogen bond donor, p*K*a: ionization constant of the most basic center. ChemAxon (Marvin Sketch version 21.16) was used to estimate six fundamental physicochemical properties of the candidate compounds, including ClogP, ClogD7.4, and p*K*a.

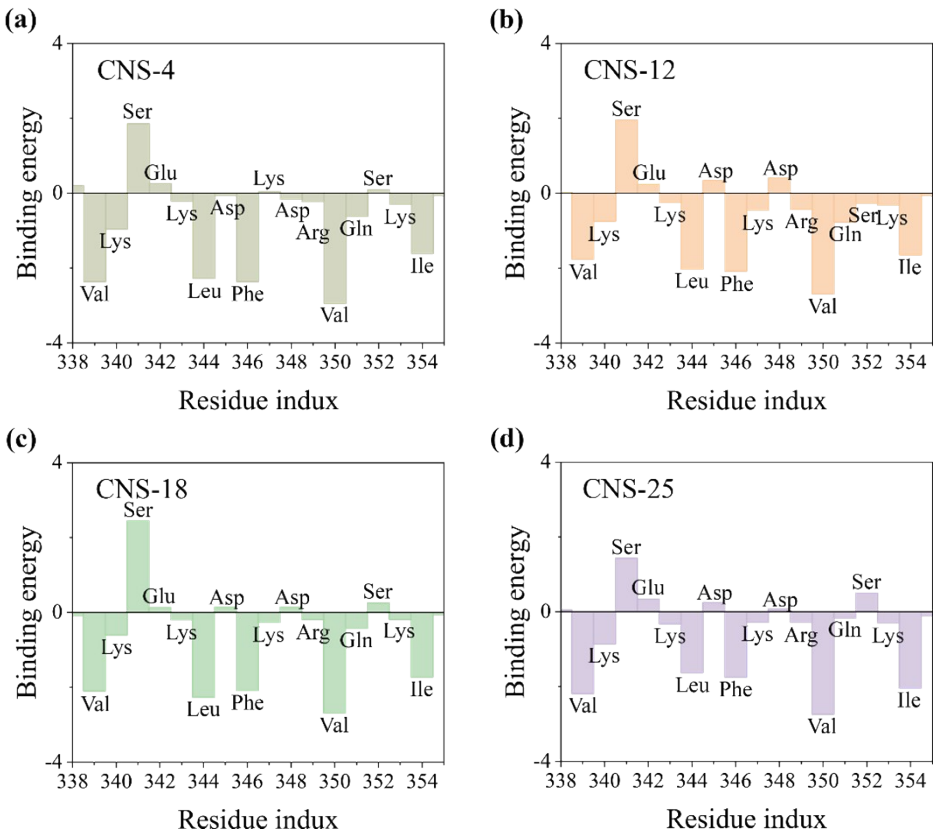


Fig. S1 The binding energy (kcal/mol) contribution of CNS-4 (a), CNS-12 (b), CNS-18 (c) or CNS-25 (d) to each residue in Site 1 of tau protofibril.