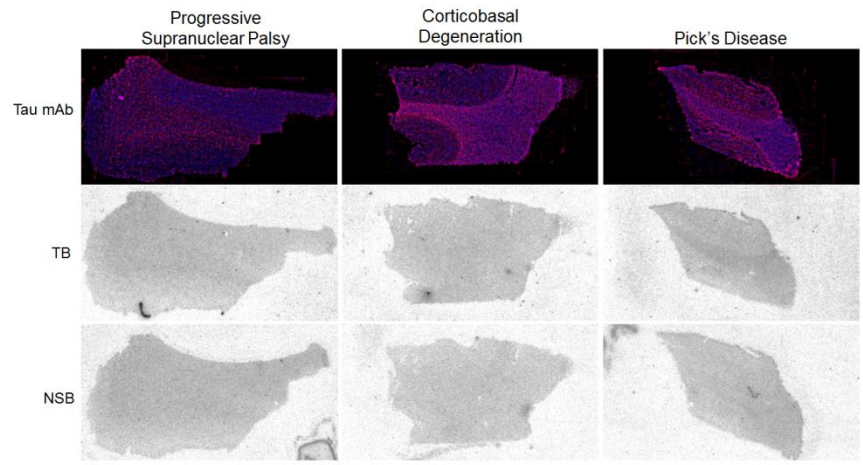
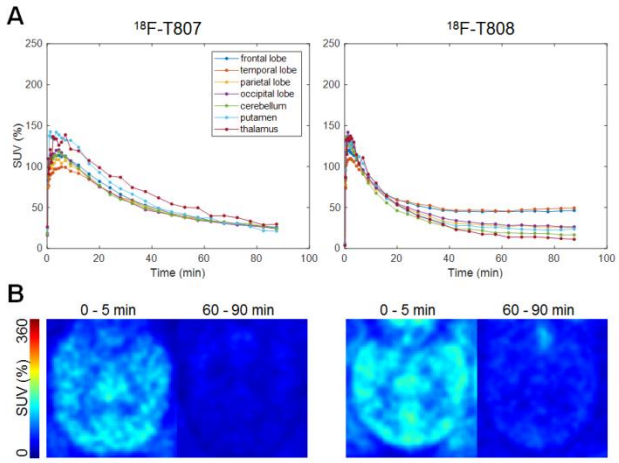
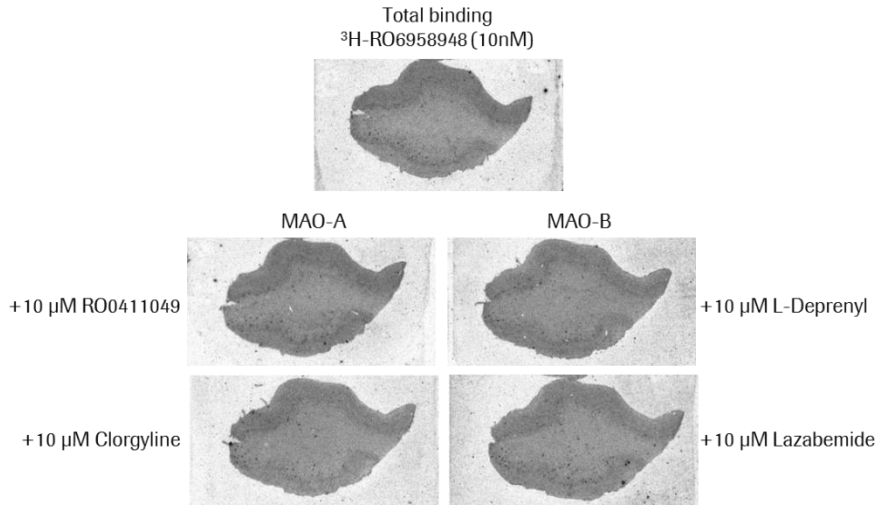


SUPPLEMENTAL FIGURE 1: Tau mAb staining of cortical tissue sections from a progressive supranuclear palsy, corticobasal degeneration and Pick's disease patient and corresponding autoradiographies of ^{3}H-RO6958948 (3 nM) on adjacent sections in absence and presence of 10 µM T808.



SUPPLEMENTAL FIGURE 2: (A) Regional time-activity curves of ^{18}F-T807 and ^{18}F-T808 in baboon PET. (B) Averaged trans-axial images of individual radioligands for earlier and later time points.



SUPPLEMENTAL FIGURE 3: In vitro autoradiography of ^{3}H-RO6958948 in absence and presence of various MAO-A and MAO-B ligands using native tissue sections of inferior temporal cortex from a Braak V AD tissue donor.

Supplemental Table 1: Selectivity screens

Selectivity screens were performed at Cerep, France, according to their standard operating procedures (see www.cerep.com; for details) using a small panel of representative, frequently hit targets which were identified and selected in a collaborative effort (for details see Peters, JU, Hert, J, Bissantz, C, et al. Can we discover pharmacological promiscuity early in the drug discovery process? *Drug Discov. Today.* 2012;17:325−335)

Results for RO6958948

Target/binding site	Species	Concentration (µM)	% Inhibition of control
5HT2A	HUMAN	10	16
5HT2B	HUMAN	10	20
5HT3	HUMAN	10	0
ACETYLCHOLINESTERASE	HUMAN	10	59
ADENOSINE A3 RECEPTOR	HUMAN	0.0001	7
ADENOSINE A3 RECEPTOR	HUMAN	0.001	6
ADENOSINE A3 RECEPTOR	HUMAN	0.003	6
ADENOSINE A3 RECEPTOR	HUMAN	0.01	25
ADENOSINE A3 RECEPTOR	HUMAN	0.03	44
ADENOSINE A3 RECEPTOR	HUMAN	0.1	69
ADENOSINE A3 RECEPTOR	HUMAN	0.3	82
ADENOSINE A3 RECEPTOR	HUMAN	3	96
ADENOSINE A3 RECEPTOR	HUMAN	10	97
ANGIOTENSIN II RECEPTOR 1	HUMAN	10	2
CA2+ CHANNEL (DILTIAZEM SITE)	RAT	10	-4
CDK2	HUMAN	10	-5
CYCLO OXYGENASE 2	HUMAN	10	-9
ESTROGEN RECEPTOR alpha	HUMAN	10	-15
GLYCINE RECEPTOR, STRYCHNINE INSENSITIVE	RAT	10	1

GSK-3A	HUMAN	10	-13
GSK-3B	HUMAN	10	-109
HISTAMINE H2 RECEPTOR	HUMAN	10	9
HIV-1 PROTEASE	HUMAN	10	21
ML3R	HAMSTER	10	74
MONOAMINE OXIDASE-A	HUMAN	0.001	5
MONOAMINE OXIDASE-A	HUMAN	0.01	1
MONOAMINE OXIDASE-A	HUMAN	0.1	3
MONOAMINE OXIDASE-B	HUMAN	0.001	-29
MONOAMINE OXIDASE-B	HUMAN	0.01	-23
MONOAMINE OXIDASE-B	HUMAN	0.1	-16
MONOAMINE OXIDASE-B	HUMAN	10	10
mu OPIOID RECEPTOR	HUMAN	10	48
NICOTINIC RECEPTOR, MUSCLE	HUMAN	10	2
PCP RECEPTOR	RAT	10	3
PHOSPHODIESTERASE 5	HUMAN	10	22
PPARgamma	HUMAN	10	2
PROSTAGLANDIN F RECEPTOR	HUMAN	10	0
SIGMA	HUMAN	10	11
XANTHINE OXIDASE	BOVINE	10	2
ZAP70	HUMAN	10	8

Results for RO6924963

Target/binding site	Species	Concentration (μM)	% Inhibition of control
5HT1A	HUMAN	1	3
5HT2A	HUMAN	1	-2

5HT2B	HUMAN	1	32
5HT3	HUMAN	1	6
ACETYLCHOLINESTERASE	HUMAN	1	5
ADENOSINE A1 RECEPTOR	HUMAN	1	-5
ADENOSINE A3 RECEPTOR	HUMAN	1	2
alpha1A-ADRENOCEPTOR	HUMAN	1	6
alpha2A-ADRENOCEPTOR	HUMAN	1	14
ANDROGEN RECEPTOR	HUMAN	1	-6
ANGIOTENSIN CONVERTING ENZYME	HUMAN	1	-5
ANGIOTENSIN II RECEPTOR 1	HUMAN	1	-29
beta1-ADRENOCEPTOR	HUMAN	1	-1
CA2+ CHANNEL (DILTIAZEM SITE)	RAT	1	2
CDK2	HUMAN	1	-1
CYCLO OXYGENASE 2	HUMAN	1	17
DOPAMINE D1 RECEPTOR	HUMAN	1	-3
DOPAMINE D2 RECEPTOR (short)	HUMAN	1	-3
ESTROGEN RECEPTOR alpha	HUMAN	1	-9
GABA-A (BENZODIAZAPINE BINDING SITE)	RAT	1	-4
GLUCOCORTICOID RECEPTOR	HUMAN	1	-4
GLYCINE RECEPTOR, STRYCHNINE INSENSITIVE	RAT	1	-8
GSK-3A	HUMAN	1	2
GSK-3B	HUMAN	1	-1
HISTAMINE H1 RECEPTOR	HUMAN	1	-6
HISTAMINE H2 RECEPTOR	HUMAN	1	-11
HISTAMINE H3 RECEPTOR	HUMAN	1	1
HIV-1 PROTEASE	HUMAN	1	21

kappa OPIOID RECEPTOR	RAT	1	5
ML3R	HAMSTER	0.00003	-7
ML3R	HAMSTER	0.0003	-11
ML3R	HAMSTER	0.001	16
ML3R	HAMSTER	0.003	10
ML3R	HAMSTER	0.01	18
ML3R	HAMSTER	0.03	52
ML3R	HAMSTER	0.1	66
ML3R	HAMSTER	1	96.5
MONOAMINE OXIDASE-A	HUMAN	1	16
MONOAMINE OXIDASE-B	HUMAN	1	-15
mu OPIOID RECEPTOR	HUMAN	1	28
MUSCARINIC RECEPTOR M2	HUMAN	1	-16
MUSCARINIC RECEPTOR M4	HUMAN	1	2
NICOTINIC RECEPTOR, MUSCLE	HUMAN	1	4
NOREPINEPHRINE TRANSPORTER	HUMAN	1	5
PCP RECEPTOR	RAT	1	-2
PHOSPHODIESTERASE 5	HUMAN	1	-1
PPARgamma	HUMAN	1	-3
PROSTAGLANDIN F RECEPTOR	HUMAN	1	8
SEROTONIN TRANSPORTER	HUMAN	1	1
SIGMA	HUMAN	1	2
SODIUM CHANNEL (Site 2)	RAT	1	13
SOMATOSTATIN RECEPTOR 4	HUMAN	1	20
XANTHINE OXIDASE	BOVINE	1	8
ZAP70	HUMAN	1	10

Results for RO6931643

Target/binding site	Species	Concentration (μM)	% Inhibition of control
5HT1A	HUMAN	1	18
5HT2A	HUMAN	1	-18
5HT2B	HUMAN	1	18
5HT3	HUMAN	1	12
ACETYLCHOLINESTERASE	HUMAN	1	-3
ADENOSINE A1 RECEPTOR	HUMAN	1	1
ADENOSINE A3 RECEPTOR	HUMAN	1	25
alpha1A-ADRENOCEPTOR	HUMAN	1	5
alpha2A-ADRENOCEPTOR	HUMAN	1	-6
ANDROGEN RECEPTOR	HUMAN	1	0
ANGIOTENSIN CONVERTING ENZYME	HUMAN	1	-6
ANGIOTENSIN II RECEPTOR 1	HUMAN	1	-17
beta1-ADRENOCEPTOR	HUMAN	1	6
CA2+ CHANNEL (DILTIAZEM SITE)	RAT	1	0
CDK2	HUMAN	1	-5
CYCLO OXYGENASE 2	HUMAN	1	18
DOPAMINE D1 RECEPTOR	HUMAN	1	0
DOPAMINE D2 RECEPTOR (short)	HUMAN	1	-3
ESTROGEN RECEPTOR alpha	HUMAN	1	4
GABA-A (BENZODIAZAPINE BINDING SITE)	RAT	1	-9
GLUCOCORTICOID RECEPTOR	HUMAN	1	2
GLYCINE RECEPTOR, STRYCHNINE INSENSITIVE	RAT	1	1
GSK-3A	HUMAN	1	-2

GSK-3B	HUMAN	1	2
HISTAMINE H1 RECEPTOR	HUMAN	1	2
HISTAMINE H2 RECEPTOR	HUMAN	1	-4
HISTAMINE H3 RECEPTOR	HUMAN	1	-16
HIV-1 PROTEASE	HUMAN	1	15
kappa OPIOID RECEPTOR	RAT	1	0
ML3R	HAMSTER	0.001	-19
ML3R	HAMSTER	0.01	7
ML3R	HAMSTER	0.03	18
ML3R	HAMSTER	0.1	51
ML3R	HAMSTER	0.3	87
ML3R	HAMSTER	1	86
ML3R	HAMSTER	3	91
ML3R	HAMSTER	30	100
MONOAMINE OXIDASE-A	HUMAN	1	12
MONOAMINE OXIDASE-B	HUMAN	1	-16
mu OPIOID RECEPTOR	HUMAN	1	10
MUSCARINIC RECEPTOR M2	HUMAN	1	5
MUSCARINIC RECEPTOR M4	HUMAN	1	-1
NICOTINIC RECEPTOR, MUSCLE	HUMAN	1	-2
NOREPINEPHRINE TRANSPORTER	HUMAN	1	7
PCP RECEPTOR	RAT	1	-3
PHOSPHODIESTERASE 5	HUMAN	1	-10
PPARgamma	HUMAN	1	-7
PROSTAGLANDIN F RECEPTOR	HUMAN	1	-8
SEROTONIN TRANSPORTER	HUMAN	1	-9
SIGMA	HUMAN	1	0

SODIUM CHANNEL (Site 2)	RAT	1	35
SOMATOSTATIN RECEPTOR 4	HUMAN	1	-25
XANTHINE OXIDASE	BOVINE	1	4
ZAP70	HUMAN	1	-2

Supplemental Table 2: Metabolite data of ^{3}H-RO6958948, ^{11}C-RO6931643 and ^{11}C-RO6924963

	^{18}F-RO6958948		^{11}C-RO6931643		^{11}C-RO6924963	
TIME POST INJECTION	RETENTION TIME	% DECAY CORRECTED	RETENTION TIME	% DECAY CORRECTED	RETENTION TIME	% DECAY CORRECTED
0 min						
Parent			11.8	90.0	11.9	94.2
Metabolite 1			3.7	2.8	1.3	1.9
Metabolite 2			6.4	3.3	7.3	3
Metabolite 3			9.4	3.9	9.1	0.9
5 min						
Parent	11.4	29.4	11.8	30.0	11.6	11.9
Metabolite 1	0.6	15.4	1.2	41.1	1.3	67.1
Metabolite 2	6.7	18.2	6.3	21.9	7.3	15.7
Metabolite 3	7.7	37	8.7	7.0	8.8	5.3
10 min						
Parent	11.5	19.9	12.1	18.7	11.7	6.3
Metabolite 1	0.7	17	1.1	50.2	1	76.1
Metabolite 2	6.6	31.6	6.4	27.7	7.2	17.2
Metabolite 3	7.7	31.5	9.5	3.4	9.8	0.4
20 min						
Parent	11.4	10.6	12.0	8.8	11.7	3.1
Metabolite 1	0.8	23.4	1.7	59.4	1.2	78.4
Metabolite 2	6.7	37.5	6.5	30.7	7.3	14.6
Metabolite 3	7.7	28.5	8.9	1.2	8.6	3.9
30 min						
Parent	11.5	6.3	12.0	8.6	11.5	2.3
Metabolite 1	0.7	28.1	2.2	59.4	1.3	79.7
Metabolite 2	6.7	41.7	6.4	28.5	7.2	18
Metabolite 3	7.8	23.9	8.8	3.5	10.5	<0.01

60 min						
Parent	11.4	2.3	11.9	3.8	11.6	0.8
Metabolite 1	0.9	28.3	1.9	72.1	0.8	86.8
Metabolite 2	6.4	49.7	6.4	24.9	7.2	10.2
Metabolite 3	7.8	19.8	9.3	<0.01	8.3	2.2
90 min						
Parent	11.5	0.8	11.7	2.2		
Metabolite 1	0.8	38.2	2.3	77.5		
Metabolite 2	6.4	43.2	6.5	19.4		
Metabolite 3	7.8	17.8	8.7	0.9		