

Supplementary Data

		Food intake (g per day and mouse)							
		Control diet				TRO diet			
Age (months)		1	2	3	4	1	2	3	4
TRO19622									
high dose		3.6±0.13	3.3±0.14	3.6±0.14	3.8±0.16	3.5±0.12	3.5±0.17	3.7±0.12	4.0±0.22
TRO19622									
low dose		3.7±0.15	3.6±0.15	3.6±0.15	4.2±0.18	3.6±0.14	3.8±0.14	3.8±0.12	4.0±0.17
TRO40303									
high dose		4.1±0.16	3.9±0.25	4.0±0.14	4.4±0.20	4.3±0.17	4.5±0.19	3.8±0.21	4.1±0.25
TRO40303									
low dose		4.4±0.20	4.3±0.17	4.5±0.24	4.3±0.21	4.6±0.17	3.9±0.13	4.3±0.23	4.6±0.25

Table S1: Daily food intake of mice (wildtype and Thy1-aSyn housed together) during treatment with control diet or diet with TRO compounds over 3 months (1-4 months of age). No significant differences in food intake between TRO treated and control diet treated mice (2x4 ANOVA, mean±SEM). N=19-21 per group.

		Age (months)		
		2	3	4
TRO19622 high dose	Plasma	11.17 ± 0.27 (1)	11.64 ± 3.60 (1)	15 ± 2.52 (1) 14.24 ± 2.21 (2)
	Brain	3.74 ± 0.48 (1)	3.29 ± 0.21 (1)	3.37 ± 0.48 (1) 3.73 ± 0.30 (2)
TRO19622 low dose	Plasma	1.89 ± 0.27 (1)	2.34 ± 0.28 (1)	1.41 ± 0.14 (1) 1.42 ± 0.16 (2)
	Brain	0.52 ± 0.05 (1)	0.48 ± 0.13 (1)	0.40 ± 0.06 (1) 0.43 ± 0.06 (2)
TRO40303 high dose	Plasma	4.04 ± 0.33 (1)	5.79 ± 0.08 (1)	4.04 ± 0.55 (1) 4.52 ± 0.43 (2)
	Brain	1.01 ± 0.05 (1)	1.22 ± 0.12 (1)	0.81 ± 0.09 (1) 0.89 ± 0.07 (2)
TRO40303 low dose	Plasma	0.14 ± 0.003 (1)	0.32 ± 0.04 (1)	0.31 ± 0.05 (1) 0.20 ± 0.03 (2)
	Brain	0.14 ± 0.06 (1)	0.19 ± 0.02 (1)	0.11 ± 0.012 (1) 0.08 ± 0.017 (2)

Table S2: Plasma and brain levels in mice fed with food pellets enriched with TRO19622 or TRO40303 high or low dosages. TRO19622 and TRO40303 plasma ($\mu\text{g/ml}$) and brain ($\mu\text{g/g}$) levels at 2, 3, 4 months of age (1, 2, 3 months of drug administration, respectively). Values are means \pm SEM of 3 to 5 mice. (1): wild type mice, (2): Thy1-aSyn mice

		Body Weight (g)							
		Control diet				TRO diet			
Age		1	2	3	4	1	2	3 months	4 months
		month	months	months	months	months	months		
TRO19622 high dose									
WT		17±0.42	28±0.86	33±1.23	36±1.25	17±0.50	28±0.89	33±1.18	37±1.27
Thy1		16±0.41	25±0.61	29±0.82	30±0.98	16±0.49	25±0.61	29±0.76	32±1.04#
TRO19622 low dose									
WT		15±0.57	28±0.79	32±0.96	35±0.95	16±0.36	29±0.73	35±1.01	37±0.99
Thy1		15±0.69	25±0.69	27±1.00	30±1.04	16±0.43	27±0.49#	31±0.83#	33±0.80#
TRO40303 high dose									
WT		16±0.60	29±0.77	35±0.98	38±1.25	16±0.60	29±0.85	33±1.12	35±1.53
Thy1		16±0.45	27±0.68	31±0.85	34±1.01	15±0.97	26±0.99	28±0.99##	30±1.05##
TRO40303 low dose									
WT		17±0.52	26 ±0.92	36±0.82	36 ±1.05	17 ±0.59	28 ±0.70	35 ±0.95	36 ±0.92
Thy1		17±0.42	27 ±0.65	32±0.86	33 ±0.92	17 ±0.46	26±0.44	30±0.73	31±0.61##

Table S3 Effect of TRO19622 and TRO40303 on body weight: Body weight in wildtype (WT) and Thy1-aSyn (Thy1) mice at the beginning of the experiment (1 month of age) and following 3 months of treatment with TRO or control diet (up to 4 months of age). #p<0.05, ## p<0.01 compared to respective control-treated group (mean ± SEM, 2X2X4 ANOVA followed by Fisher's LSD). N=17-22 per group.

Tables S4-S10 (lists of genes and gene ontology), excel files

Genotype	WT				Thy1- α Syn			
	1 months		3 months		1 months		3 months	
Treatment	control	19622 low	control	19622 low	control	19622 low	control	19622 low
Errors per steps	0.11 \pm 0.02	0.10 \pm 0.01	0.09 \pm 0.02	0.08 \pm 0.01	0.38## \pm 0.03	0.46*## \pm 0.02	0.48^^ \pm 0.04	0.6**^^ \pm 0.05
Pole (turn in sec)	3.39 \pm 1.03	2.38 \pm 0.46	8.85^^ \pm 2.11	9.10^^ \pm 1.95	14.8## \pm 2.13	28.3## \pm 4.35	23.6^^ \pm 1.68	47.1^ \pm 3.23
Pole (total in sec)	7.61 \pm 1.99	5.69 \pm 0.77	17.6 \pm 4.16	17.6 \pm 3.63	19.8## \pm 2.26	38.4## \pm 4.47	25.0^^ \pm 1.74	49.7^ \pm 3.53

Genotype	WT				Thy1- α Syn			
	1 months		3 months		1 months		3 months	
Treatment	control	19622 high	control	19622 high	control	19622 high	control	19622 high
Errors per steps	0.06 \pm 0.01	0.07 \pm 0.01	0.11^ \pm 0.02	0.05** \pm 0.01	0.44## \pm 0.03	0.40## \pm 0.03	0.43 \pm 0.03	0.51*^^ \pm 0.03
Pole (turn in sec)	3.11 \pm 0.90	2.24 \pm 0.32	5.06^ \pm 1	3.68 \pm 0.74	15.1## \pm 2.44	14.8## \pm 2.03	21 \pm 1.53	24.9^^ \pm 1.39
Pole (total in sec)	6.65 \pm 1.28	5.52 \pm 0.48	10.22 \pm 1.89	7.44 \pm 1.32	29.2## \pm 5.17	27.8## \pm 5.17	39.9 \pm 3.77	47.1^^ \pm 4.15

Genotype	WT				Thy1- α Syn			
	1 months		3 months		1 months		3 months	
Treatment	control	40303 low	control	40303 low	control	40303 low	control	40303 low
Errors per steps	0.18 \pm 0.04	0.15 \pm 0.01	0.15 \pm 0.01	0.2 \pm 0.03	0.58## \pm 0.02	0.53## \pm 0.04	0.66 \pm 0.03	0.67^^ \pm 0.05
Pole (turn in sec)	5.25 \pm 1.44	4.48 \pm 1.28	7.66 \pm 1.56	5.33 \pm 1.72	21.6## \pm 2.06	20.3## \pm 1.45	26.2^ \pm 1.4	23.5 \pm 1.74
Pole (total in sec)	11.1 \pm 2.82	8.26 \pm 2.51	15.6^ \pm 2.94	11.0 \pm 3.38	41.7## \pm 4.35	39.6## \pm 3.12	51.8^^ \pm 2.90	46.3 \pm 3.62

Genotype	WT				Thy1- α Syn			
	1 months		3 months		1 months		3 months	
Treatment	control	40303 high	control	40303 high	control	40303 high	control	40303 high
Errors per steps	0.14 \pm 0.01	0.19 \pm 0.01	0.17 \pm 0.02	0.16 \pm 0.02	0.61## \pm 0.03	0.65## \pm 0.04	0.63 \pm 0.03	0.87**^^ \pm 0.04
Pole (turn in sec)	4.89 \pm 1.37	2.13 \pm 0.37	7.22^ \pm 1.17	8.16^^ \pm 1.76	16.9## \pm 2.02	18.1## \pm 1.93	23.65^ \pm 1.83	26.9^^ \pm 1.29
Pole (total in sec)	10.1 \pm 2.64	5.03 \pm 0.69	13.3 \pm 2.27	15.9^^ \pm 3.47	32.6## \pm 3.99	34.5## \pm 3.88	47.1^^ \pm 3.72	53.2^^ \pm 2.84

Table S11 Effect of TRO compounds on motor skills. Errors per step were recorded on the challenging beam test. For the pole test, mice were placed snout up on top of a vertical pole and time to turn upside down and total time from beginning of the test to reaching the floor were measured. Mean of five trials, SEM; ##p<0.01 compared to wildtype (WT) (transgene effect, only shown for 1 month treatment, but also present after 3 months treatment), *p<0.05, **p<0.01 compared to control diet (drug effect after 1 or 3 months of treatment), ^p<0.05, ^^p< 0.01 compared to 1 month treatment (progression of transgene effect); 2x2x2 ANOVA followed by Fisher's LSD for errors per step, Mann Whitney U and Wilcoxon signed rank test for pole test, n=16-20 per group.

		Wildtype		Thy1-aSyn	
		Control diet	TRO diet	Control diet	TRO diet
TRO19622 high dose					
Activity	FLSteps	69.45 ± 5.51	63.95 ± 3.51	41.90** ± 3.39	40.8** ± 3.54
	HLSteps	41.90 ± 4.65	44.35 ± 3.67	10.05** ± 2.26	7.8** ± 1.52
TRO19622 low dose					
Activity	FLSteps	54.35 ± 5.29	55.59 ± 4.11	36.80* ± 4.32	37.45** ± 2.86
	HLSteps	50.60 ± 5.24	45.68 ± 4.31	10.70** ± 2.56	8.20** ± 1.67
TRO40303 high dose					
Activity	FLSteps	37.63 ± 2.36	36.05 ± 2.82	37 ± 4.68	40.10 ± 3.62
	HLSteps	25.13 ± 3.50	26.62 ± 2.97	6.83** ± 1.30	12.15** ± 1.95
TRO40303 low dose					
Activity	FLSteps	51.50 ± 3.95	50.63 ± 3.38	43.70 ± 3.41	41.24 ± 2.59
	HLSteps	43 ± 4.68	43.89 ± 4.51	11.85** ± 1.90	9.52** ± 1.54

Table S12 Effect of TRO compounds on spontaneous activity. Effect of 3 months TRO19622 and TRO40303 administration on spontaneous activity in the cylinder test. WT (control diet=18-20, TRO19622=16, TRO40303=19) and Thy1-aSyn (control diet=19-20, TRO19622=18, TRO40303=19) mice treated with TRO19622 or TRO40303 at high or low dose compared to respective control groups treated with control diet. **p<0.01 Thy1-aSyn control diet compared to WT control diet, (transgene effect, 2x2x2 ANOVA, Fisher's LSD, mean ± SEM). FLSteps= forelimb steps, HLSteps=hindlimb steps.

	control diet		TRO diet	
	number (n/ 100 μm^2)	area covered (%)	number (n/ 100 μm^2)	area covered (%)
TRO40303 high dl	0.46 ± 0.020	1.29 ± 0.077	0.48 ± 0.036	1.32 ± 0.142
TRO40303 high dm	0.44 ± 0.019	1.04 ± 0.063	0.38 ± 0.036	0.98 ± 0.061
TRO40303 high vl	0.50 ± 0.022	1.46 ± 0.030	0.52 ± 0.027	1.57 ± 0.161
TRO40303 high vm	0.51 ± 0.032	1.49 ± 0.126	0.54 ± 0.030	1.55 ± 0.124
TRO19622 high dl	0.48 ± 0.047	0.61 ± 0.099	0.61 ± 0.027*	0.96 ± 0.087*
TRO19622 high dm	0.40 ± 0.043	0.46 ± 0.060	0.42 ± 0.044	0.51 ± 0.072
TRO19622 high vl	0.53 ± 0.030	0.81 ± 0.070	0.61 ± 0.034	1.11 ± 0.097*
TRO19622 high vm	0.51 ± 0.031	0.71 ± 0.055	0.59 ± 0.035	0.99 ± 0.008*
TRO19622 low dl	0.61 ± 0.099	0.43 ± 0.060	0.96 ± 0.087	0.44 ± 0.024
TRO19622 low dm	0.46 ± 0.060	0.39 ± 0.053	0.51 ± 0.072	0.38 ± 0.029
TRO19622 low vl	0.81 ± 0.070	0.40 ± 0.056	1.11 ± 0.097	0.48 ± 0.016
TRO19622 low vm	0.51 ± 0.031	0.41 ± 0.043	0.59 ± 0.035	0.46 ± 0.030

Table S13 Effects of TRO compounds on number and percentage area covered by alpha-synuclein positive aggregates in substantia nigra of Thy1-aSyn mice. TRO40303 at the high dose (n=5 per group) had no effects on aggregate number or surface covered by aggregates (%) in the dorsolateral (dl), dorsomedial (dm), ventrolateral (vl) or ventromedial (vm) substantia nigra. TRO19622 at the high dose (n=7 per group) but not low dose (n=5 per group) significantly increased aggregate number in the dorsolateral substantia nigra, as well as the surface covered by aggregates in the dorsolateral, ventrolateral and ventromedial substantia nigra (*p<0.05, 4x2 repeated measures ANOVA, Holm-Sidak), mean+SEM.