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Supplemental information

Activation of mitochondrial TRAP1 stimulates mitochondria-lysosome crosstalk and correction of lysosomal dysfunction

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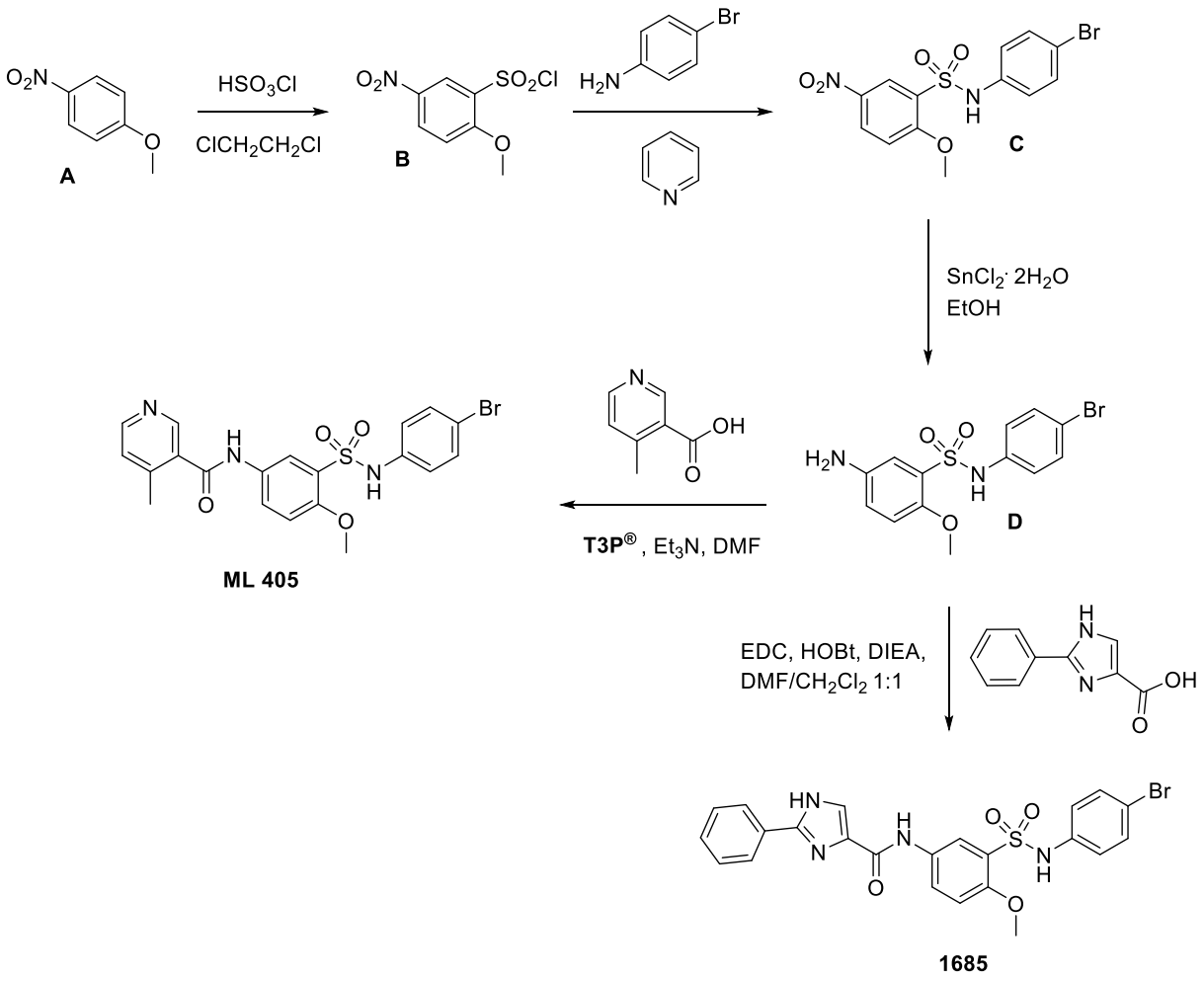
Supplemental Information



T3P® = 2,4,6-tripropyl-l,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide

Figure S1. Scheme for synthesis of lead compounds, related to STAR Methods.

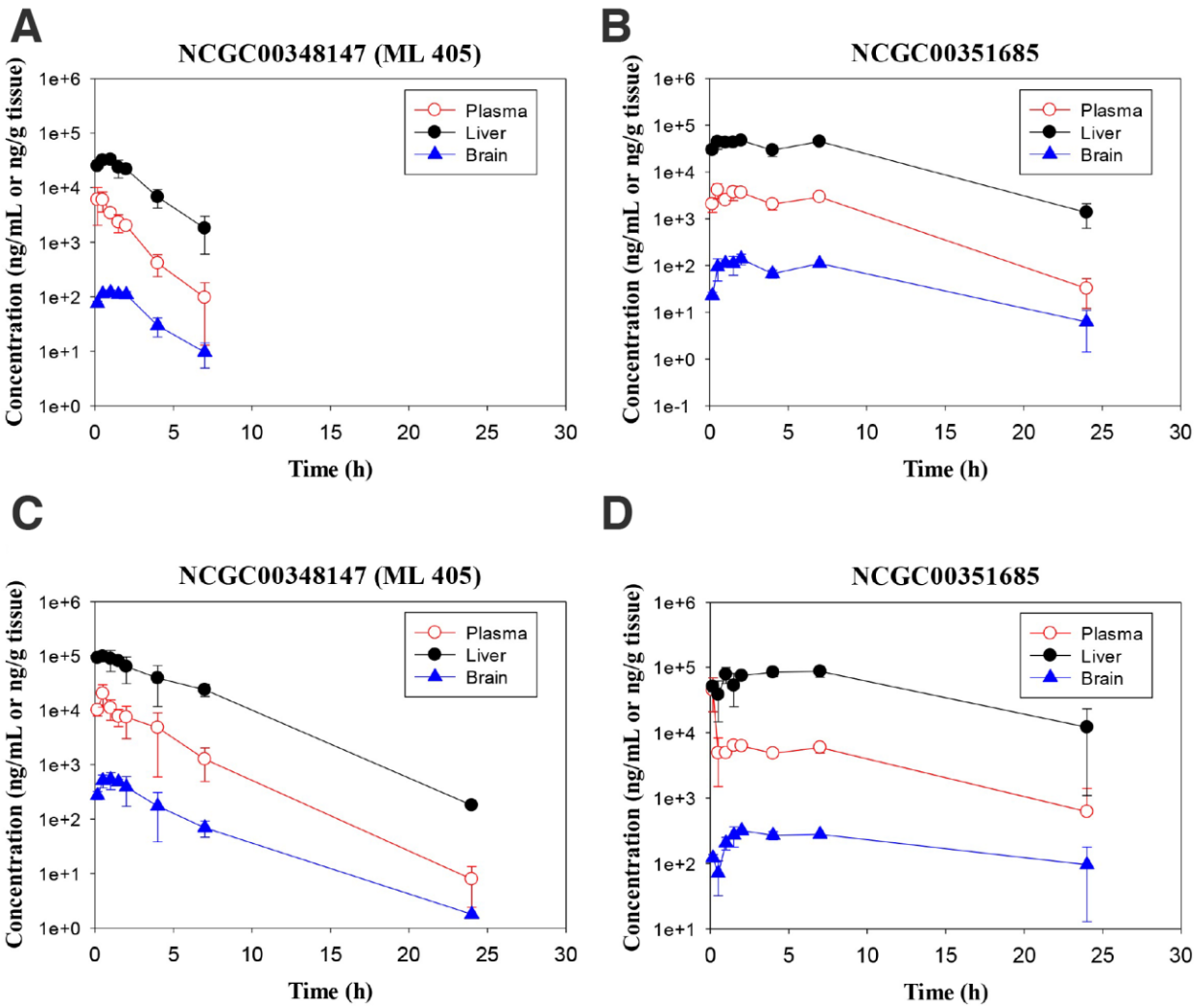


Figure S2. Pharmacokinetic profiles of NCGC00348147 (ML 405) and NCGC00351685 (1685) in C57BL/6 mice, related to Figure 1A. (A-B) Following single IP injection at 10 mg/kg, systemic exposures measured by C_{max} and $AUC_{0-\infty}$ were 6050 ng/mL and 9980 ng*h/mL for ML405, and 4100 ng/mL and 44500 ng.h/mL for 1685, respectively. The higher AUC observed for 1685 may be due to slower elimination, as the $t_{1/2}$ of 1685 was ca. 2.5-fold longer (i.e., 3.2 hr for 1685 vs 1.3 hr for ML405). **(C-D)** As the dose increased to 30 mg/kg, in vivo exposures increased with the dose with a longer $t_{1/2}$ for both compounds (see also Table S1). Values are expressed as mean ± SEM (n=3 for each sampling time point).

Test Article	NCGC00348147 (ML405)					
Sample	Plasma	Brain	Liver	Plasma	Brain	Liver
Dose (mg/kg)	10	10	10	30	30	30
AUC_{0-t} (ng*h/mL)	9790	368	87000	54000	2410	559000
$AUC_{0-\infty.}$ (ng*h/mL)	9980	391	91100	54000	2420	560000
$t_{1/2}$ (h)	1.3	1.7	1.6	2.2	3.1	2.5
T_{max} (h)	0.167	1	1	0.5	1	0.5
C_{max} (ng/mL)	6050	119	32800	20200	531	97200
AUC ratio (tissue/plasma)		0.04	7.4		0.03	6.8

Test Article	NCGC00351685 (1685)					
Sample	Plasma	Brain	Liver	Plasma	Brain	Liver
Dose (mg/kg)	10	10	10	30	30	30
AUC_{0-t} (h*ng/mL)	44400	1650	659000	103000	4960	1360000
$AUC_{0-\infty.}$ (h*ng/mL)	44500	1700	667000	109000	ND	ND
$t_{1/2}$ (h)	3.2	5.1	4.1	5	ND	ND
T_{max} (h)	0.5	2	2	0.167	2	7
C_{max} (ng/mL)	4100	138	46800	44700	317	86000
AUC ratio (tissue/plasma)		0.04	15		0.05	13

ND = Not determined because the elimination phase was not fully captured in the tissue

Table S1. Pharmacokinetics of ML405 and 1685 in plasma, brain and liver of Male C57Bl6 Mice after Single IP Administration, related to Figure 1A. The liver to plasma AUC ratios were about 7 and 14 for ML405 and 1685, respectively. The brain AUC of ML405 and 1685 was ~ 4% of plasma AUC values, which indicated that both compounds had low brain penetration.