Supplementary Tables and Figures

Table S1. The pharmacophore hypothesis for PDE4D ligand.

Hypothesis	Total Cost	Cost difference	Error Cost	RMS	R value	Feature
1	305.64	190.78	287.965	1.601	0.851	AHHHZ
2	308.29	188.13	292.176	1.643	0.842	AHHHH
3	311.09	185.33	295.102	1.671	0.836	AHHHH
4	311.30	185.13	295.178	1.672	0.836	AHHHH
5	312.62	183.81	296.513	1.685	0.833	AHHHH
6	313.01	183.41	294.947	1.669	0.837	AHHH
7	314.82	181.61	297.399	1.693	0.832	AHHHZ
8	316.28	180.15	299.873	1.716	0.826	AHHHH
9	316.54	179.89	298.248	1.701	0.830	AHHH
10	317.67	178.76	301.657	1.733	0.823	AHHHH

Null cost: 496.43. Fixed cost: 224.52. Configuration cost: 14.851. Hydrogen bond acceptors (A), hydrophobic (H), and negative ionizable features (Z) were identified and analyzed for modeling.

Table S2. The pharmacophore hypothesis for ALOX5AP ligand.

Hypothesis	Total Cost	Cost difference	Error Cost	RMS	R value	Feature
1	153.97	41.92	137.94	1.669	0.768	AHHHH
2	158.10	37.80	142.489	1.761	0.737	AHHHZ
3	162.57	33.33	146.511	1.838	0.709	AHHHZ
4	164.18	31.71	148.412	1.873	0.695	AHHHH
5	164.20	31.70	148.211	1.869	0.697	AHHHH
6	164.87	31.03	149.201	1.887	0.689	AHHHH
7	165.76	30.13	147.518	1.856	0.702	AHHHZ
8	166.20	29.70	150.449	1.910	0.680	AHHHH
9	166.72	29.17	149.387	1.891	0.688	AHHHH
10	166.82	29.08	151.152	1.923	0.675	AHHH

Null cost: 195.90. Fixed cost: 113.12. Configuration cost: 14.452. Hydrogen bond acceptors (A), hydrophobic (H), and negative ionizable features (Z) were identified and analyzed for modeling.

Table S3. The interaction energy (kcal/mol) with divalent metal cations for both TCM candidates and L-454560.

Ligand	Zn^{2+}			Mg^{2+}		
	Interaction Energy	Electrostatic Interaction Energy	VDW Interaction Energy	Interaction Energy	Electrostatic Interaction Energy	VDW Interaction Energy
Myristic acid	-290.095	-297.044	6.949	-254.020	-259.442	5.422
Pentadecanoic acid	-257.359	-262.071	4.713	-279.822	-284.465	4.643
L-454560	-80.551	-86.800	6.249	-16.621	-16.473	-0.147

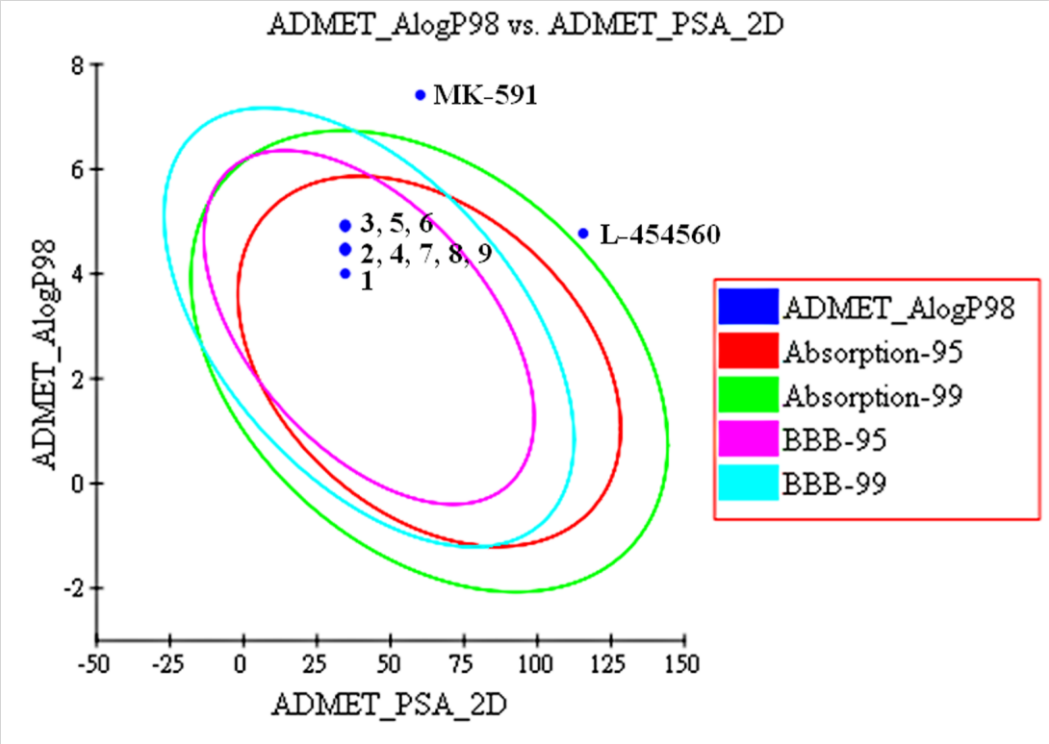

Figure S1. Human intestinal absorption model for (1) Myristic acid, (2) Pentadecanoic acid, (3) 2-pentadecenoic acid, (4) 2-hexadecenoic acid, (5) 9,12-Octadecadienoic acid, (6) Hexadecanoic acid, (7) 11-hexadecenoic acid, (8) Palmitoleic acid, (9) Punicic acid, and controls, L-454560 and MK-591.

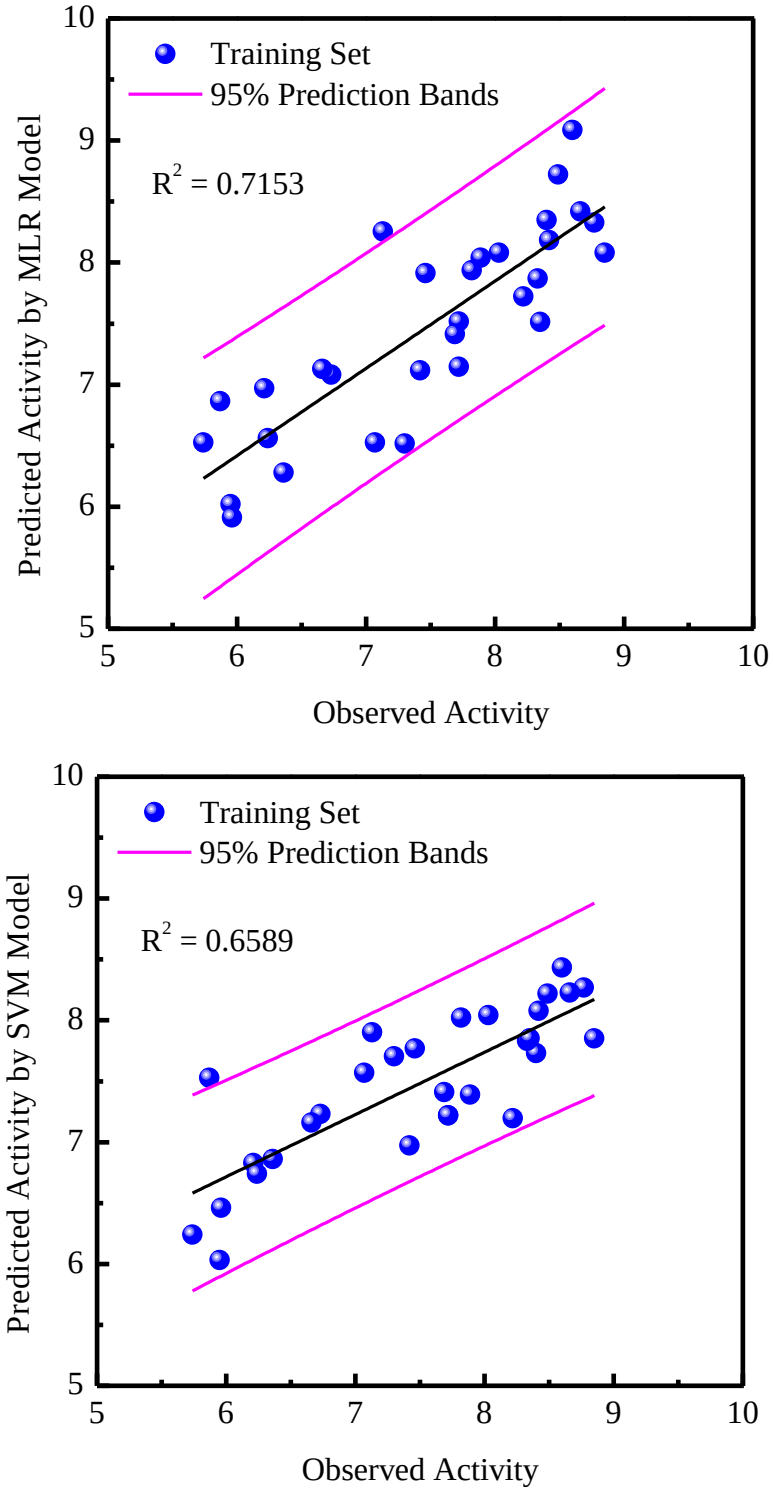

Figure S2. Comparative plots of MLR (top) and SVM (bottom) models for ALOX5AP inhibitors. Correlation trend (black line) and 95% confidence regions (enclosed by magenta lines) were shown. Training set (blue dots) was presented.

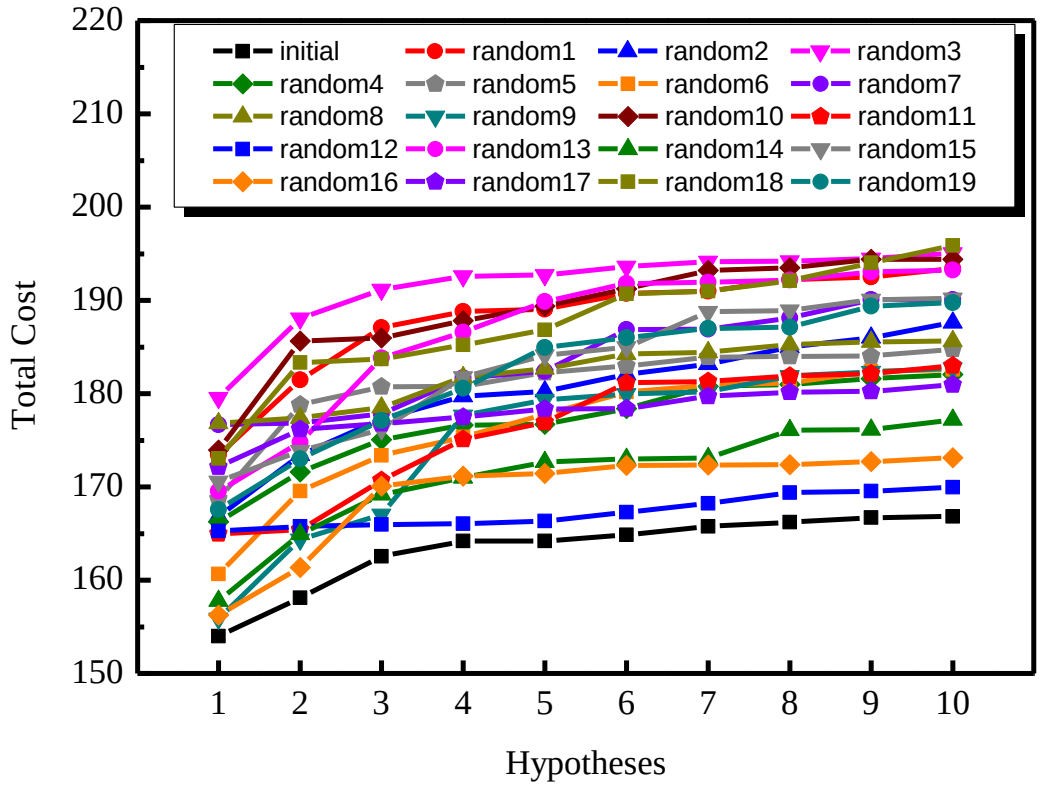

Figure S3. CatScramble validation plot for ALOX5AP that compares Total costs between initial and randomized HypoGen hypothesis.