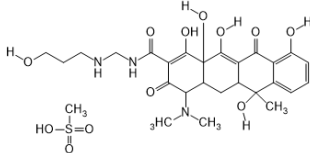
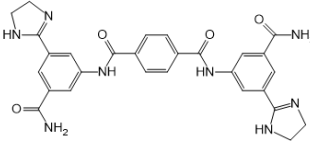
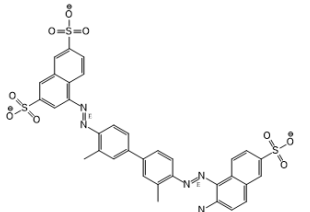
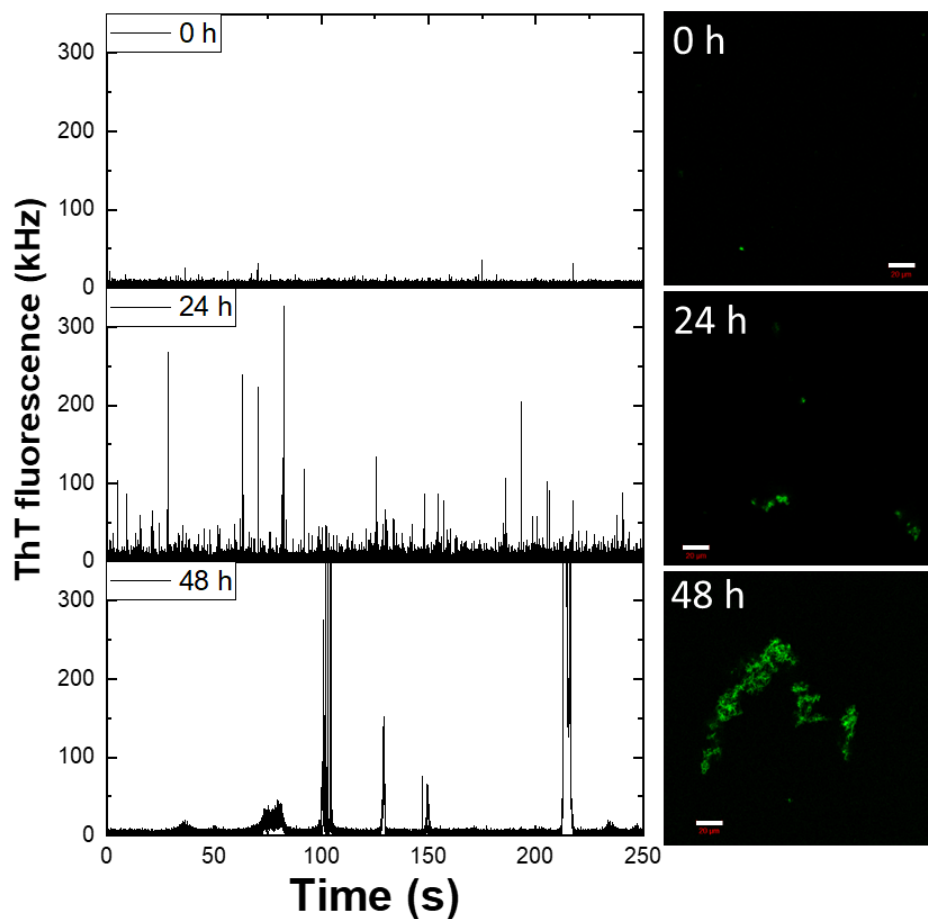


Supplementary Material

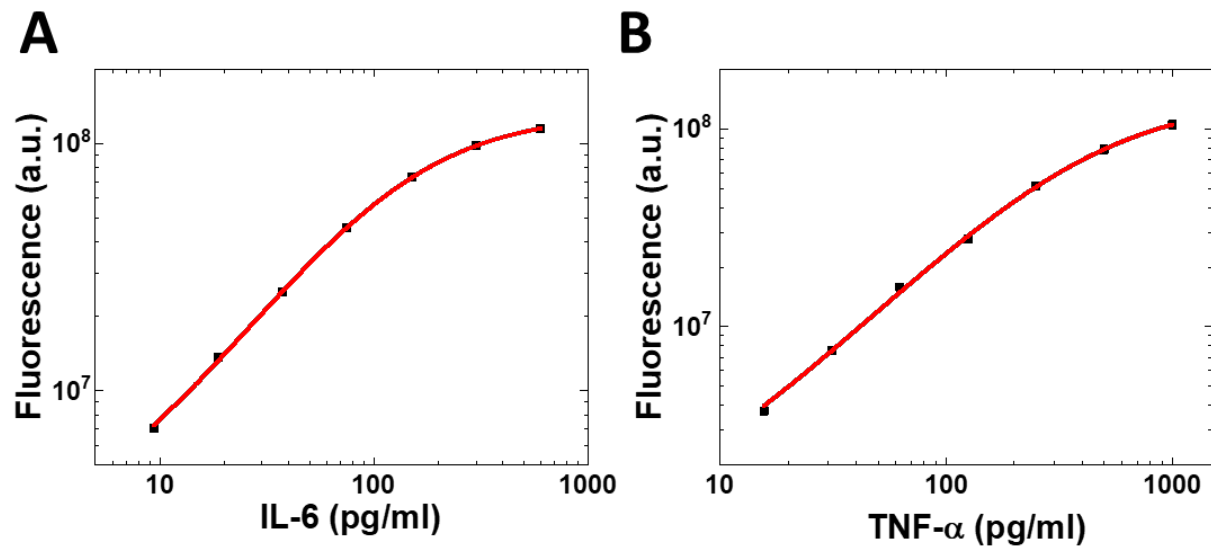
Small Molecule Decoy of Amyloid- β Aggregation Blocks Activation of Microglia-Like Cells

Compound name	Structure
NSC 69318	 <p>The structure of NSC 69318 is a complex polycyclic molecule. It features a central core with multiple fused rings, including a benzene ring and a pyridine ring. The structure is substituted with a hydroxyl group, a methoxy group, a methyl group, and a dimethylamino group. A side chain consists of a propyl chain terminated with a hydroxyl group, connected via a secondary amine to a primary amine, which is further connected to the polycyclic core.</p>
NSC 100873	 <p>The structure of NSC 100873 is a linear molecule consisting of two 2-aminobenzamide units connected to a central benzene ring. Each 2-aminobenzamide unit is further substituted with a pyrrolidine ring at the 6-position and an amide group at the 1-position.</p>
NSC 16224	 <p>The structure of NSC 16224 is a complex molecule featuring a central benzene ring substituted with two methyl groups and two amide groups. Each amide group is connected to a benzene ring, which is further substituted with a methyl group and a sulfonamide group. The sulfonamide groups are connected to a central benzene ring, which is also substituted with a methyl group and a sulfonamide group.</p>

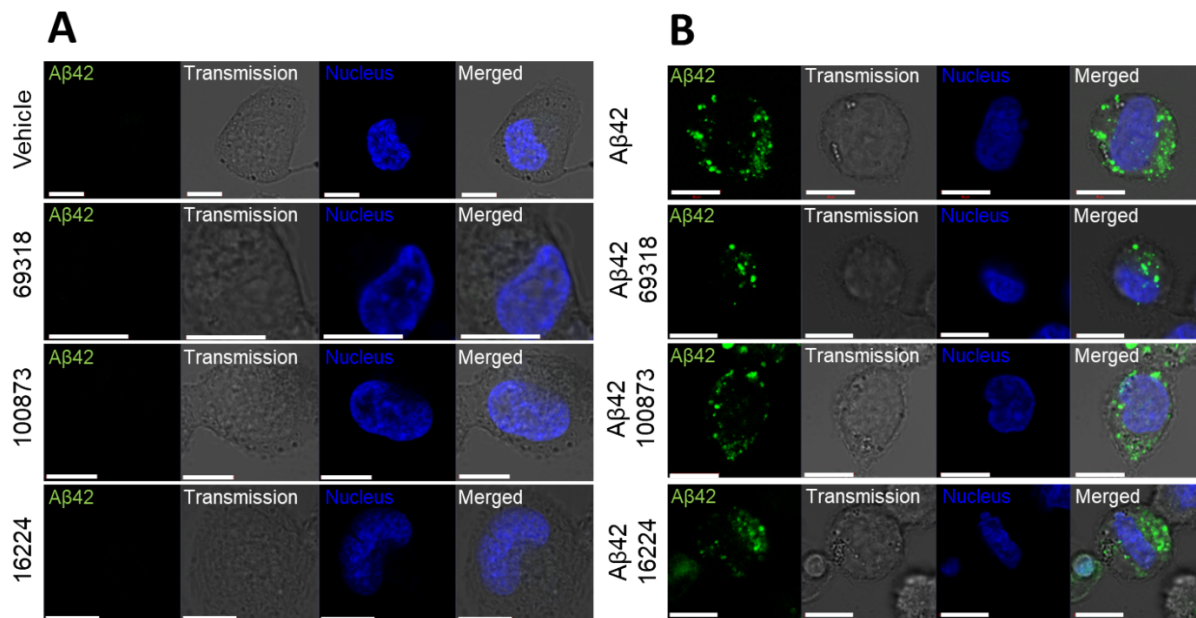
Supplementary Figure 1. Small molecule decoy structures.



Supplementary Figure 2. Recombinant amyloid-β 42 (Aβ₄₂) aggregation state in treatment medium. Recombinant Aβ₄₂ peptide in PBS was diluted with phenol-red free RPMI medium to 10 μM concentration and mixed with 20 μM Thioflavin T (ThT). Fluorescence signals over time were recorded in the solution in the confocal microscope without scanning. Each fluorescent burst corresponds to the event passing ThT-positive oligomers through the confocal observation area (Left). Fluorescence images are taken of the cover glass to show the precipitated ThT-positive large aggregates. Scale bar: 20 μm (Right).



Supplementary Figure 3A-B. Standard curve in ELISA. Standard curves were generated for interleukin 6 (IL-6) (A) and tumor necrosis factor (TNF)- α (B). Black: experimental data points, Red: four-parameter logistic curve fitting. A.U., arbitrary units



Supplementary Figure 4A-B. A β ₄₂ phagocytosis in live dTHP-1 cells. Confocal Laser Scanning Microscopy (CLSM) imaging of live dTHP-1 cells treated with vehicle and small-molecule decoys (NSC 69318, NSC 100873 and NSC 16224) as negative controls (A) or incubated with 200 nM fluorescently labelled A β ₄₂ and the same molar concentration of decoys (B). Scale bars: 10 μ m.

A					B				
Data 1	Data 2	MeanDiff	Prob	Alpha	Data 1	Data 2	MeanDiff	Prob	Alpha
Vehicle	NSC 69318	0	1	0.05	Vehicle	NSC 69318	-1.46152	1	0.05
Vehicle	NSC 100873	0	1	0.05	Vehicle	NSC 100873	-3.53079	1	0.05
Vehicle	NSC 16224	0	1	0.05	Vehicle	NSC 16224	-0.54165	1	0.05
Vehicle	A β 42	101.87592	4.29E-07	0.05	Vehicle	A β 42	986.58181	1.81E-08	0.05
Vehicle	A β 42 + NSC 69318	65.4925	9.76E-04	0.05	Vehicle	A β 42 + NSC 69318	935.89848	4.69E-08	0.05
Vehicle	A β 42 + NSC 100873	92.36025	2.60E-06	0.05	Vehicle	A β 42 + NSC 100873	940.76014	4.64E-08	0.05
Vehicle	A β 42 + NSC 16224	0	1	0.05	Vehicle	A β 42 + NSC 16224	2.73864	1	0.05
NSC 69318	NSC 100873	0	1	0.05	NSC 69318	NSC 100873	-2.06927	1	0.05
NSC 69318	NSC 16224	0	1	0.05	NSC 69318	NSC 16224	0.91987	1	0.05
NSC 69318	A β 42	101.87592	4.29E-07	0.05	NSC 69318	A β 42	988.04333	1.80E-08	0.05
NSC 69318	A β 42 + NSC 69318	65.4925	9.76E-04	0.05	NSC 69318	A β 42 + NSC 69318	937.36	4.68E-08	0.05
NSC 69318	A β 42 + NSC 100873	92.36025	2.60E-06	0.05	NSC 69318	A β 42 + NSC 100873	942.22167	4.62E-08	0.05
NSC 69318	A β 42 + NSC 16224	0	1	0.05	NSC 69318	A β 42 + NSC 16224	4.20016	1	0.05
NSC 100873	NSC 16224	0	1	0.05	NSC 100873	NSC 16224	2.98914	1	0.05
NSC 100873	A β 42	101.87592	4.29E-07	0.05	NSC 100873	A β 42	990.1126	1.79E-08	0.05
NSC 100873	A β 42 + NSC 69318	65.4925	9.76E-04	0.05	NSC 100873	A β 42 + NSC 69318	939.42927	4.65E-08	0.05
NSC 100873	A β 42 + NSC 100873	92.36025	2.60E-06	0.05	NSC 100873	A β 42 + NSC 100873	944.29093	4.60E-08	0.05
NSC 100873	A β 42 + NSC 16224	0	1	0.05	NSC 100873	A β 42 + NSC 16224	6.26943	1	0.05
NSC 16224	A β 42	101.87592	4.29E-07	0.05	NSC 16224	A β 42	987.12346	1.80E-08	0.05
NSC 16224	A β 42 + NSC 69318	65.4925	9.76E-04	0.05	NSC 16224	A β 42 + NSC 69318	936.44012	4.69E-08	0.05
NSC 16224	A β 42 + NSC 100873	92.36025	2.60E-06	0.05	NSC 16224	A β 42 + NSC 100873	941.30179	4.63E-08	0.05
NSC 16224	A β 42 + NSC 16224	0	1	0.05	NSC 16224	A β 42 + NSC 16224	3.28028	1	0.05
A β 42	A β 42 + NSC 69318	-36.38342	0.20043	0.05	A β 42	A β 42 + NSC 69318	-50.68333	0.99963	0.05
A β 42	A β 42 + NSC 100873	-9.51567	0.99736	0.05	A β 42	A β 42 + NSC 100873	-45.82167	0.99981	0.05
A β 42	A β 42 + NSC 16224	-101.87592	4.29E-07	0.05	A β 42	A β 42 + NSC 16224	-983.84318	1.82E-08	0.05
A β 42 + NSC 69318	A β 42 + NSC 100873	26.86775	0.56452	0.05	A β 42 + NSC 69318	A β 42 + NSC 100873	4.86167	1	0.05
A β 42 + NSC 69318	A β 42 + NSC 16224	-65.4925	9.76E-04	0.05	A β 42 + NSC 69318	A β 42 + NSC 16224	-933.15984	4.73E-08	0.05
A β 42 + NSC 100873	A β 42 + NSC 16224	-92.36025	2.60E-06	0.05	A β 42 + NSC 100873	A β 42 + NSC 16224	-938.02151	4.67E-08	0.05

Supplementary Table 1A-B. Analysis of interleukin-6 (IL-6) (A) and tumor necrosis factor (TNF)- α (B) by ELISA after incubation of dTHP-1 cells with A β ₄₂ and the small molecule compounds as shown in Fig. 1. MeanDiff: mean difference between data 1 and data 2, Prob: probability value for significant difference, Alpha: criterion of significance. Significant differences are highlighted in yellow.

A

Data 1	Data 2	MeanDiff	Prob	Alpha
Vehicle	NSC 69318	-0.04767	0.99965	0.05
Vehicle	NSC 100873	-0.11825	0.92275	0.05
Vehicle	NSC 16224	-0.12292	0.90705	0.05
Vehicle	A β 40	0.60483	6.97E-06	0.05
Vehicle	A β 40 + NSC 69318	0.65917	1.37E-06	0.05
Vehicle	A β 40 + NSC 100873	0.46747	0.00112	0.05
Vehicle	A β 40 + NSC 16224	0.02792	0.99999	0.05
NSC 69318	NSC 100873	-0.07058	0.99568	0.05
NSC 69318	NSC 16224	-0.07525	0.99362	0.05
NSC 69318	A β 40	0.6525	1.66E-06	0.05
NSC 69318	A β 40 + NSC 69318	0.70683	2.90E-07	0.05
NSC 69318	A β 40 + NSC 100873	0.51513	2.71E-04	0.05
NSC 69318	A β 40 + NSC 16224	0.07558	0.99344	0.05
NSC 100873	NSC 16224	-0.00467	1	0.05
NSC 100873	A β 40	0.72308	1.86E-07	0.05
NSC 100873	A β 40 + NSC 69318	0.77742	5.68E-08	0.05
NSC 100873	A β 40 + NSC 100873	0.58572	3.12E-05	0.05
NSC 100873	A β 40 + NSC 16224	0.14617	0.80225	0.05
NSC 16224	A β 40	0.72775	1.64E-07	0.05
NSC 16224	A β 40 + NSC 69318	0.78208	5.27E-08	0.05
NSC 16224	A β 40 + NSC 100873	0.59038	2.71E-05	0.05
NSC 16224	A β 40 + NSC 100873	0.15083	0.77641	0.05
A β 40	A β 40 + NSC 69318	0.05433	0.99918	0.05
A β 40	A β 40 + NSC 100873	-0.13737	0.87562	0.05
A β 40	A β 40 + NSC 16224	-0.57692	1.72E-05	0.05
A β 40 + NSC 69318	A β 40 + NSC 100873	-0.1917	0.57406	0.05
A β 40 + NSC 69318	A β 40 + NSC 16224	-0.63125	2.99E-06	0.05
A β 40 + NSC 100873	A β 40 + NSC 16224	-0.43955	0.00253	0.05

B

Data 1	Data 2	MeanDiff	Prob	Alpha
Vehicle	NSC 69318	0.02692	1	0.05
Vehicle	NSC 100873	-0.06142	1	0.05
Vehicle	NSC 16224	0.07333	1	0.05
Vehicle	A β 40	19.51483	3.85E-08	0.05
Vehicle	A β 40 + NSC 69318	18.62058	5.37E-07	0.05
Vehicle	A β 40 + NSC 100873	18.56985	1.60E-07	0.05
Vehicle	A β 40 + NSC 16224	0.25875	0.99999	0.05
NSC 69318	NSC 100873	-0.08833	1	0.05
NSC 69318	NSC 16224	0.04642	1	0.05
NSC 69318	A β 40	19.48792	2.78E-06	0.05
NSC 69318	A β 40 + NSC 69318	18.59367	5.36E-07	0.05
NSC 69318	A β 40 + NSC 100873	18.54293	1.59E-07	0.05
NSC 69318	A β 40 + NSC 16224	0.23183	1	0.05
NSC 100873	NSC 16224	0.13475	1	0.05
NSC 100873	A β 40	19.57625	3.85E-08	0.05
NSC 100873	A β 40 + NSC 69318	18.682	5.40E-07	0.05
NSC 100873	A β 40 + NSC 100873	18.63127	1.60E-07	0.05
NSC 100873	A β 40 + NSC 16224	0.32017	0.99997	0.05
NSC 16224	A β 40	19.4415	2.77E-06	0.05
NSC 16224	A β 40 + NSC 69318	18.54725	5.34E-07	0.05
NSC 16224	A β 40 + NSC 100873	18.49652	1.59E-07	0.05
NSC 16224	A β 40 + NSC 100873	0.18542	1	0.05
A β 40	A β 40 + NSC 69318	-0.89425	0.97967	0.05
A β 40	A β 40 + NSC 100873	-0.94498	0.9788	0.05
A β 40	A β 40 + NSC 16224	-19.25608	1.79E-07	0.05
A β 40 + NSC 69318	A β 40 + NSC 100873	-0.05073	1	0.05
A β 40 + NSC 69318	A β 40 + NSC 16224	-18.36183	5.26E-07	0.05
A β 40 + NSC 100873	A β 40 + NSC 16224	-18.3111	1.56E-07	0.05

Supplementary Table 2A-B. Analysis of interleukin-6 (IL-6) (A) and tumor necrosis factor (TNF)- α (B) by ELISA after incubation of dTHP-1 cells with A β ₄₀ and the small molecule compounds as shown in Fig. 2. MeanDiff: mean difference between data 1 and data 2, Prob: probability value for significant difference, Alpha: criterion of significance. Significant differences are highlighted in yellow.

A

Data 1	Data 2	MeanDiff	Prob	Alpha
Vehicle	NSC 69318	454	0.99952	0.05
Vehicle	NSC 100873	217.33333	1	0.05
Vehicle	NSC 16224	322.33333	0.99995	0.05
Vehicle	A β 42	12402	1.46E-07	0.05
Vehicle	A β 42 + NSC 69318	11534.66667	1.12E-07	0.05
Vehicle	A β 42 + NSC 100873	12067	1.44E-07	0.05
Vehicle	A β 42 + NSC 16224	10893.33333	1.31E-07	0.05
NSC 69318	NSC 100873	-236.66667	0.99999	0.05
NSC 69318	NSC 16224	-131.66667	1	0.05
NSC 69318	A β 42	11948	1.44E-07	0.05
NSC 69318	A β 42 + NSC 69318	11080.66667	1.22E-07	0.05
NSC 69318	A β 42 + NSC 100873	11613	1.11E-07	0.05
NSC 69318	A β 42 + NSC 16224	10439.33333	1.56E-07	0.05
NSC 100873	NSC 16224	105	1	0.05
NSC 100873	A β 42	12184.66667	1.45E-07	0.05
NSC 100873	A β 42 + NSC 69318	11317.33333	1.16E-07	0.05
NSC 100873	A β 42 + NSC 100873	11849.66667	1.44E-07	0.05
NSC 100873	A β 42 + NSC 16224	10676	1.42E-07	0.05
NSC 16224	A β 42	12079.66667	1.44E-07	0.05
NSC 16224	A β 42 + NSC 69318	11212.33333	1.18E-07	0.05
NSC 16224	A β 42 + NSC 100873	11744.66667	1.09E-07	0.05
NSC 16224	A β 42 + NSC 16224	10571	1.47E-07	0.05
A β 42	A β 42 + NSC 69318	-867.33333	0.97575	0.05
A β 42	A β 42 + NSC 100873	-335	0.99994	0.05
A β 42	A β 42 + NSC 16224	-1508.66667	0.71661	0.05
A β 42 + NSC 69318	A β 42 + NSC 100873	532.33333	0.99866	0.05
A β 42 + NSC 69318	A β 42 + NSC 16224	-641.33333	0.99573	0.05
A β 42 + NSC 100873	A β 42 + NSC 16224	-1173.66667	0.89247	0.05

B

Data 1	Data 2	MeanDiff	Prob	Alpha
Vehicle	NSC 69318	-0.22667	1	0.05
Vehicle	NSC 100873	-0.20667	1	0.05
Vehicle	NSC 16224	-0.19	1	0.05
Vehicle	A β 42	37.69667	0	0.05
Vehicle	A β 42 + NSC 69318	35.54667	3.61E-08	0.05
Vehicle	A β 42 + NSC 100873	36.46	3.65E-08	0.05
Vehicle	A β 42 + NSC 16224	32.27667	5.17E-07	0.05
NSC 69318	NSC 100873	0.02	1	0.05
NSC 69318	NSC 16224	0.03667	1	0.05
NSC 69318	A β 42	37.92333	0	0.05
NSC 69318	A β 42 + NSC 69318	35.77333	3.62E-08	0.05
NSC 69318	A β 42 + NSC 100873	36.68667	3.66E-08	0.05
NSC 69318	A β 42 + NSC 16224	32.50333	1.35E-06	0.05
NSC 100873	NSC 16224	0.01667	1	0.05
NSC 100873	A β 42	37.90333	0	0.05
NSC 100873	A β 42 + NSC 69318	35.75333	3.62E-08	0.05
NSC 100873	A β 42 + NSC 100873	36.66667	3.66E-08	0.05
NSC 100873	A β 42 + NSC 16224	32.48333	5.22E-07	0.05
NSC 16224	A β 42	37.88667	0	0.05
NSC 16224	A β 42 + NSC 69318	35.73667	3.62E-08	0.05
NSC 16224	A β 42 + NSC 100873	36.65	3.66E-08	0.05
NSC 16224	A β 42 + NSC 16224	32.46667	5.21E-07	0.05
A β 42	A β 42 + NSC 69318	-2.15	0.94687	0.05
A β 42	A β 42 + NSC 100873	-1.23667	0.99768	0.05
A β 42	A β 42 + NSC 16224	-5.42	0.1679	0.05
A β 42 + NSC 69318	A β 42 + NSC 100873	0.91333	0.99967	0.05
A β 42 + NSC 69318	A β 42 + NSC 16224	-3.27	0.70016	0.05
A β 42 + NSC 100873	A β 42 + NSC 16224	-4.18333	0.42846	0.05

Supplementary Table 3A-B. Analysis of phagocytosis after incubation of dTHP-1 cells with A β ₄₂ and the small molecule compounds as shown in Fig. 3. (A) Average fluorescence intensity and (B) percentage of dTHP-1 cells that had taken up A β ₄₂-488. MeanDiff: mean difference between data 1 and data 2, Prob: probability value for significant difference, Alpha: criterion of significance. Significant differences are highlighted in yellow.