Supporting Information

for

A Glycosylated Prodrug to Attenuate Neuroinflammation and Improve Cognitive Deficits in Alzheimer's Disease Transgenic Mice

Mingeun Kim,[†,+] Min Hee Park,[‡,§,∥,+] Geewoo Nam,[†] Misun Lee,[#,†] Juhye Kang,[†,▽] Im-Sook Song,[¥] Min-Koo Choi,[∮] Hee Kyung Jin,[*,‡,⊥] Jae-sung Bae,[*,‡,§,∥] Mi Hee Lim[*,†]

[†]Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 34141, Republic of Korea

[‡]KNU Alzheimer's Disease Research Institute, Kyungpook National University, Daegu 41566, Republic of Korea

[§]Department of Physiology, School of Medicine, Kyungpook National University, Daegu 41944, Republic of Korea

[∥]Department of Biomedical Science, BK21 Plus Kyungpook National University Biomedical Convergence Program, Kyungpook National University, Daegu 41944, Republic of Korea

[#]Department of Chemistry, Ulsan National Institute of Science and Technology (UNIST), Ulsan 44919, Republic of Korea

[▽]Technical Support Center, Office of Research Affairs, Pohang University of Science and Technology, Pohang 37673, Republic of Korea

[¥]College of Pharmacy and Research Institute of Pharmaceutical Sciences, Kyungpook National University, Daegu 41566, Republic of Korea

[∮]College of Pharmacy, Dankook University, Cheon-an 31116, Republic of Korea

[⊥]Department of Laboratory Animal Medicine, College of Veterinary Medicine, Kyungpook National University, Daegu 41566, Republic of Korea

[+]These authors contributed equally to this work.

*To whom correspondence should be addressed: miheelim@kaist.ac.kr, jsbae@knu.ac.kr, and hkjin@knu.ac.kr

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Table S1. Pharmacokinetics (PK) in the plasma and brain of mice administrated with **Glu-DAPPD** [30 mg/kg; per os (p.o.) injections].

		Glu-DAPPD	**MAPPD**	**DAPPD**
Matrix	Time (h)	Concentration (ng/mL)[a]	Concentration (ng/mL)[a]	Concentration (ng/mL)[a]
Plasma	0.25	23259.2 ± 9516.5	36.6 ± 11.9	1173.6 ± 316.9
	0.5	7348.7 ± 2912.2	30.1 ± 8.0	1310.7 ± 237.9
	1	1111.3 ± 684.0	11.1 ± 5.2	468.6 ± 308.7
	2	211.0 ± 142.7	7.5 ± 1.5	477.4 ± 240.6
	4	53.0 ± 26.1	3.1 ± 1.4	264.9 ± 196.6
	8	9.6 ± 4.5	2.8 ± 1.1	346.5 ± 197.0
Brain	0.25	872.1 ± 23.6	12.8 ± 0.8	320.7 ± 201.0
	0.5	206.9 ± 100.8	7.4 ± 1.7	550.2 ± 246.1
	1	69.7 ± 39.5	–	349.1 ± 69.1
	2	31.1 ± 8.6	–	301.2 ± 64.9
	4	9.4 ± 2.0	–	125.5 ± 49.4
	8	–	–	60.9 ± 21.7

Matrix	PK Parameters	**Glu-DAPPD**	**MAPPD**	**DAPPD**
Plasma	C_{max} (ng/mL)[b]	23259.2 ± 9516.5	36.6 ± 11.8	1437.3 ± 132.3
	t_{max} (h)[c]	0.3 ± 0.0	0.3 ± 0.1	0.4 ± 0.1
	AUC_{last} (ng·h/mL)[d]	9898.9 ± 1846.8	54.7 ± 2.5	3340.2 ± 448.5
	AUC_{inf} (ng·h/mL)[d]	9917.5 ± 1856.1	67.6 ± 1.9	5754.1 ± 1699.8
	$t_{1/2}$ (h)[e]	1.3 ± 0.2	3.4 ± 0.9	4.8 ± 0.7
	MRT (h)[f]	0.5 ± 0.01	4.2 ± 0.9	7.9 ± 1.7
Brain	C_{max} (ng/mL)[b]	872.1 ± 23.6	12.8 ± 0.8	559.6 ± 236.6
	t_{max} (h)[c]	0.3 ± 0.0	0.3 ± 0.0	0.7 ± 0.3
	AUC_{last} (ng·h/mL)[d]	422.7 ± 29.2	6.0 ± 0.7	1498.3 ± 77.0
	AUC_{inf} (ng·h/mL)[d]	418.7 ± 28.1	–	1732.6 ± 184.4
	$t_{1/2}$ (h)[e]	1.1 ± 0.2	–	2.6 ± 0.7
	MRT (h)[f]	0.9 ± 0.1	–	3.8 ± 0.7

[a]Mean (n = 3); [b]maximum concentration (C_{max}); [c]time of reach C_{max} (t_{max}); [d]area under the curve (AUC); [e]half-life ($t_{1/2}$); [f]mean residence time (MRT).

Table S2. Pharmacokinetics (PK) in the plasma and brain of mice administrated with **DAPPD** [30 mg/kg; per os (p.o.) injections].

		DAPPD
Matrix	Time (h)	Concentration (ng/mL)[a]
Plasma	0.25	13260.2 ± 7343.5
	0.5	5817.7 ± 500.1
	1	2042.6 ± 378.8
	2	1450.6 ± 376.7
	4	667.2 ± 112.9
	8	424.2 ± 272.8
Brain	0.25	4054.5 ± 1107.5
	0.5	2711.1 ± 28.4
	1	1340.2 ± 319.4
	2	708.4 ± 40.4
	4	233.8 ± 54.9
	8	102.5 ± 47.6

Matrix	PK Parameters	**DAPPD**
Plasma	C_{max} (ng/mL)[b]	13451.9 ± 7046.5
	t_{max} (h)[c]	0.3 ± 0.1
	AUC_{last} (ng·h/mL)[d]	12054.6 ± 1840.7
	AUC_{inf} (ng·h/mL)[d]	16824.1 ± 5580.3
	$t_{1/2}$ (h)[e]	2.3 ± 0.7
	MRT (h)[f]	2.3 ± 0.5
Brain	C_{max} (ng/mL)[b]	4054.5 ± 1107.5
	t_{max} (h)[c]	0.3 ± 0.0
	AUC_{last} (ng·h/mL)[d]	5004.3 ± 325.5
	AUC_{inf} (ng·h/mL)[d]	5316.4 ± 230.9
	$t_{1/2}$ (h)[e]	1.9 ± 0.6
	MRT (h)[f]	2.2 ± 0.7

[a]Mean (n = 3); [b]maximum concentration (C_{max}); [c]time of reach C_{max} (t_{max}); [d]area under the curve (AUC); [e]half-life ($t_{1/2}$); [f]mean residence time (MRT).

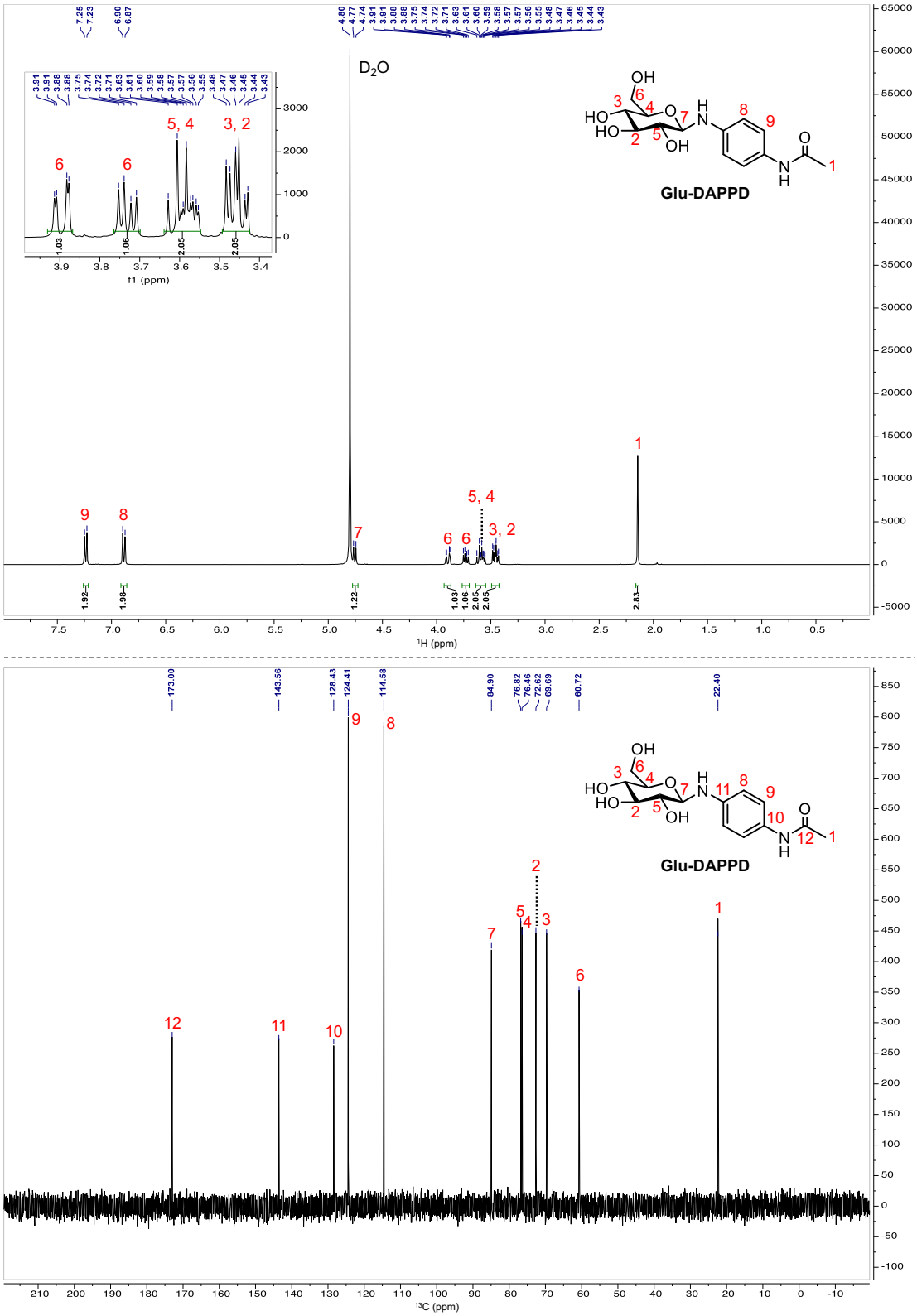


Figure S1. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of **Glu-DAPPD** in D_2O.

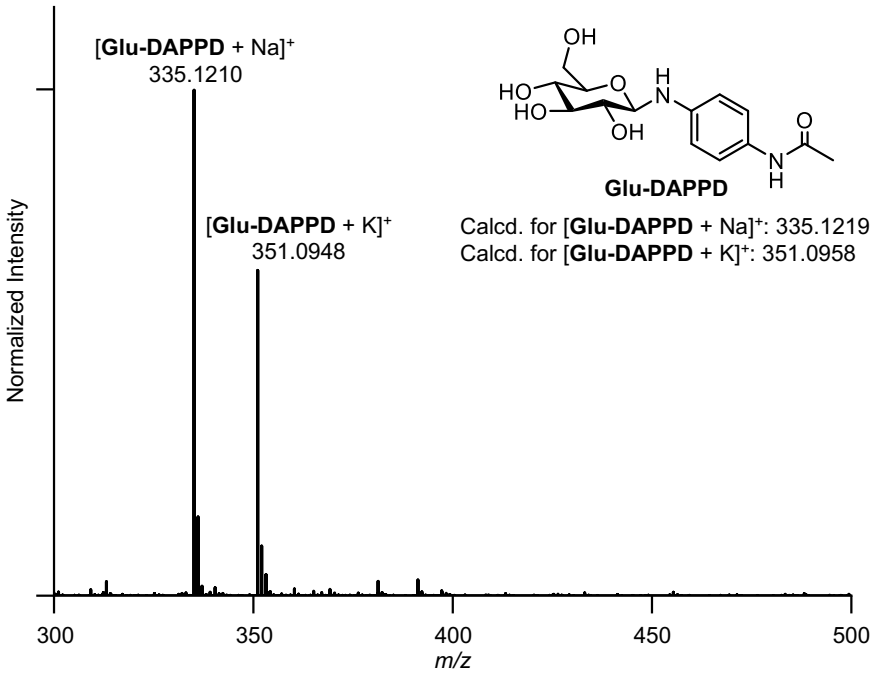
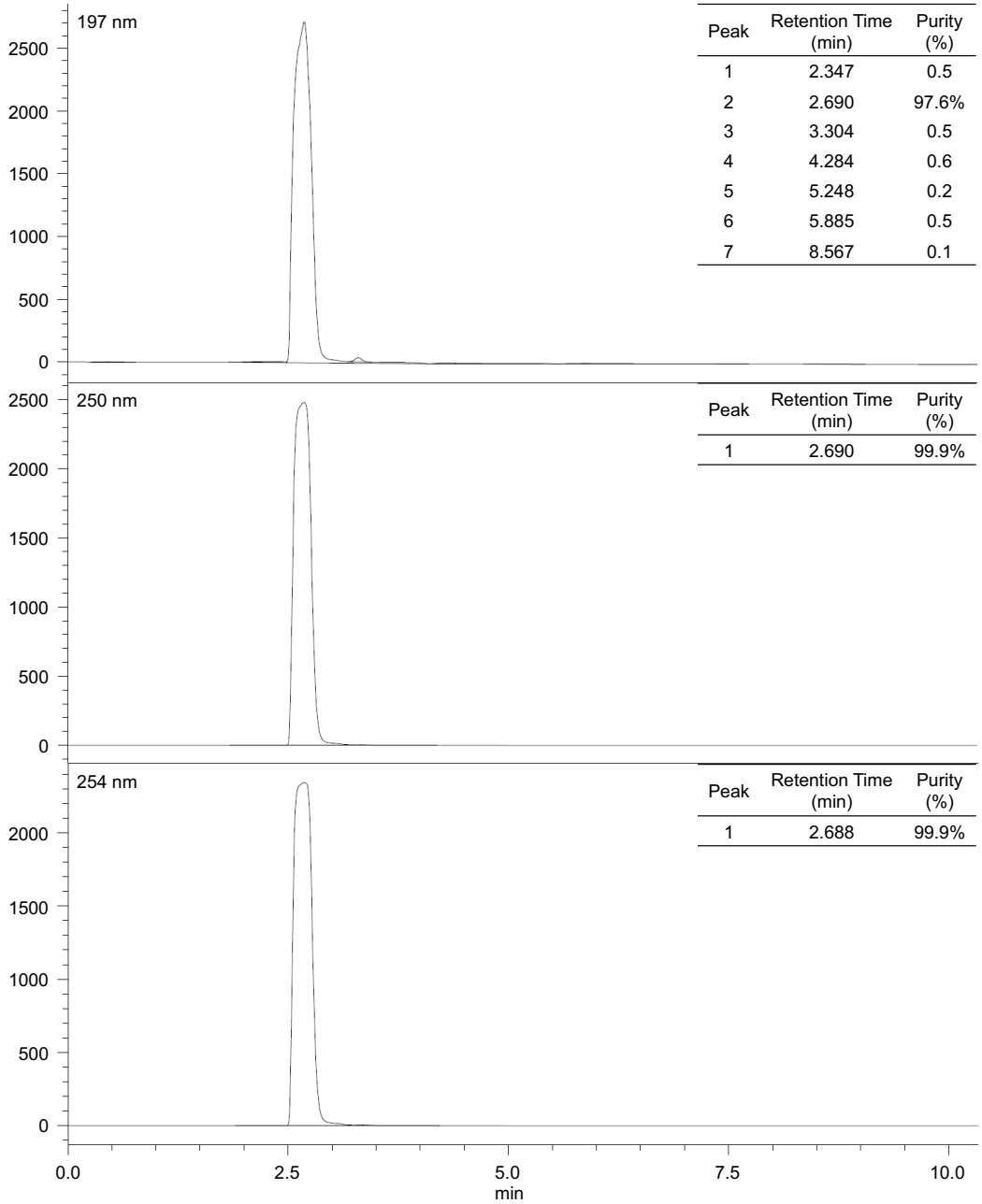


Figure S2. High-resolution mass spectrometric data of **Glu-DAPPD**.



Peak	Retention Time (min)	Purity (%)
1	2.347	0.5
2	2.690	97.6%
3	3.304	0.5
4	4.284	0.6
5	5.248	0.2
6	5.885	0.5
7	8.567	0.1

Peak	Retention Time (min)	Purity (%)
1	2.690	99.9%

Peak	Retention Time (min)	Purity (%)
1	2.688	99.9%

Figure S3. High-performance liquid chromatographic data of **Glu-DAPPD**.

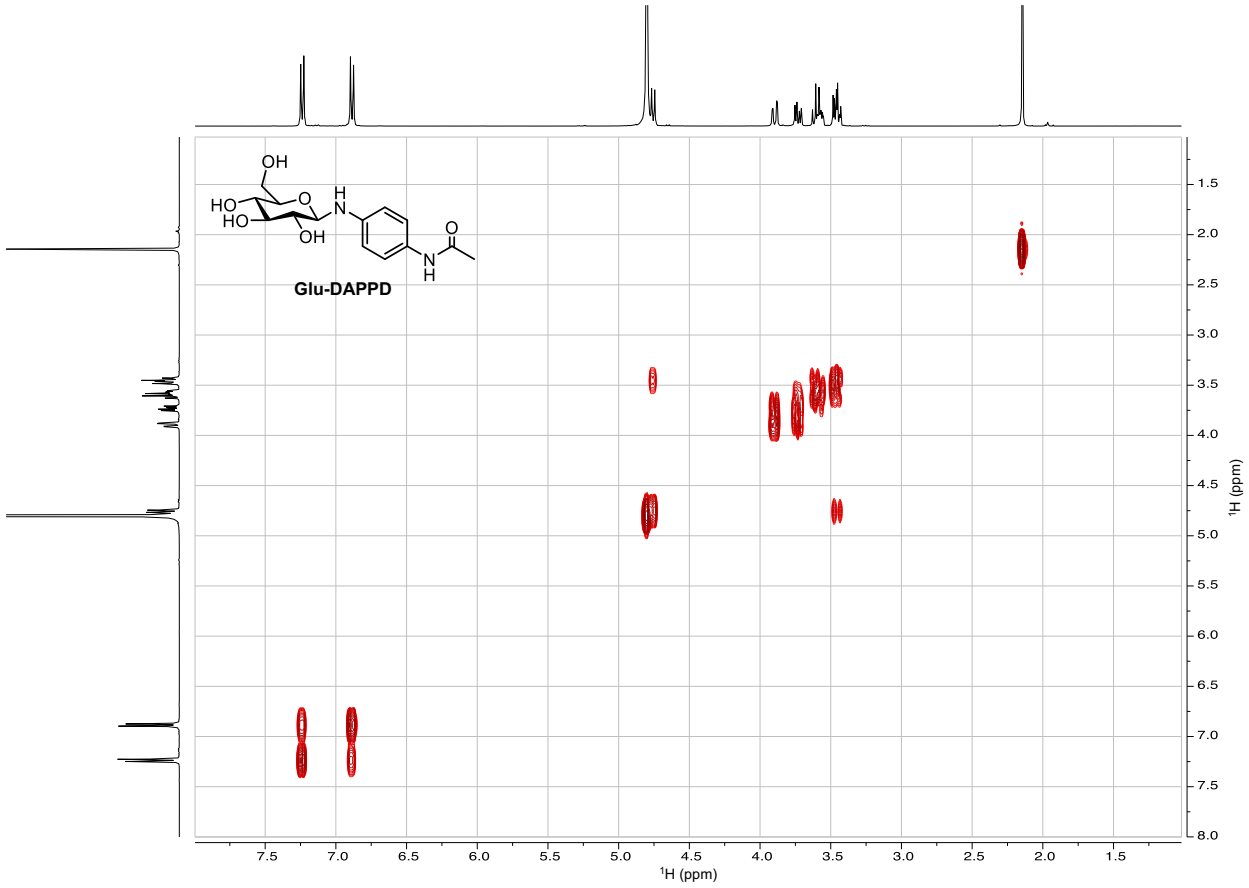


Figure S4. ^{1}H–^{1}H correlation spectroscopy (COSY) (400 MHz) spectra of **Glu-DAPPD** in D_2O.

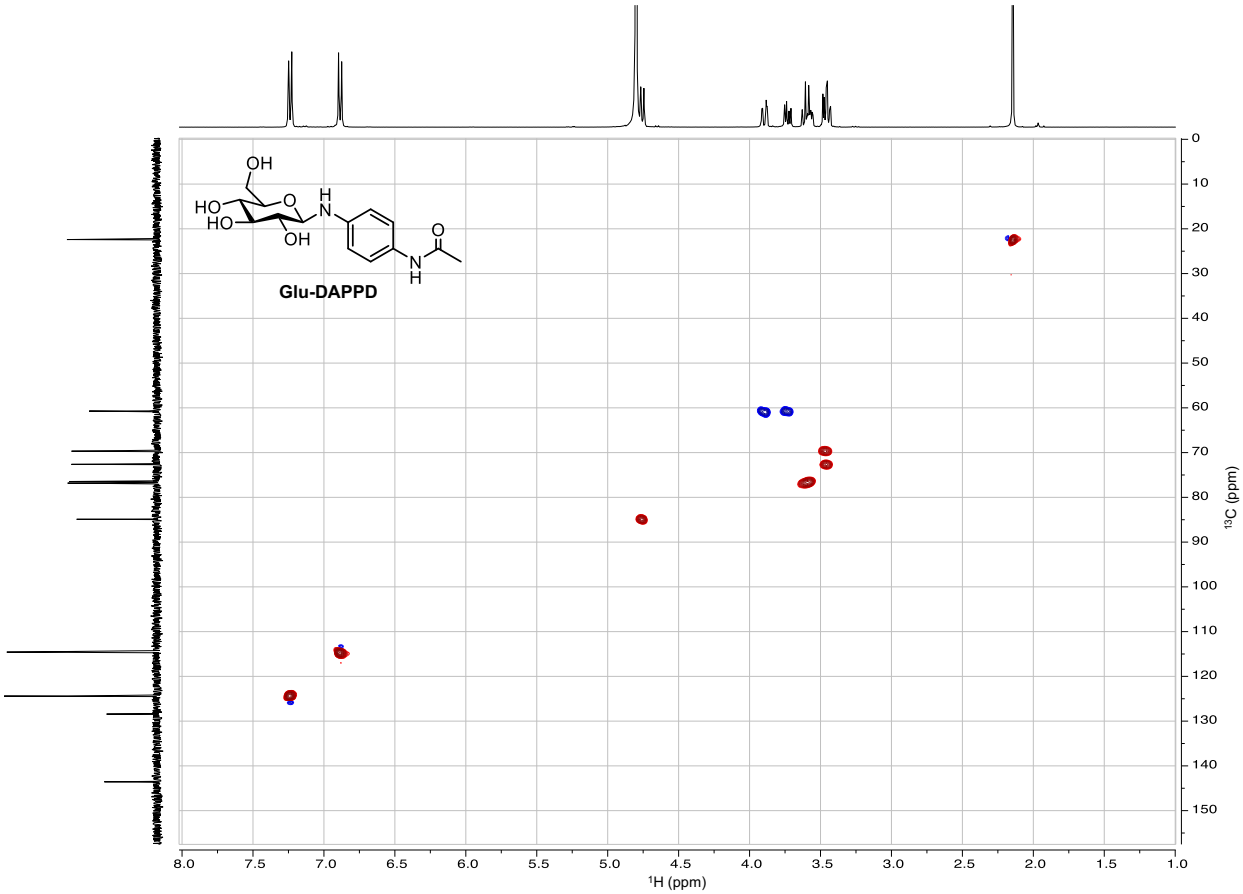


Figure S5. ^{1}H–^{13}C heteronuclear single quantum coherence (HSQC) (400 MHz) spectra of **Glu-DAPPD** in D_2O.

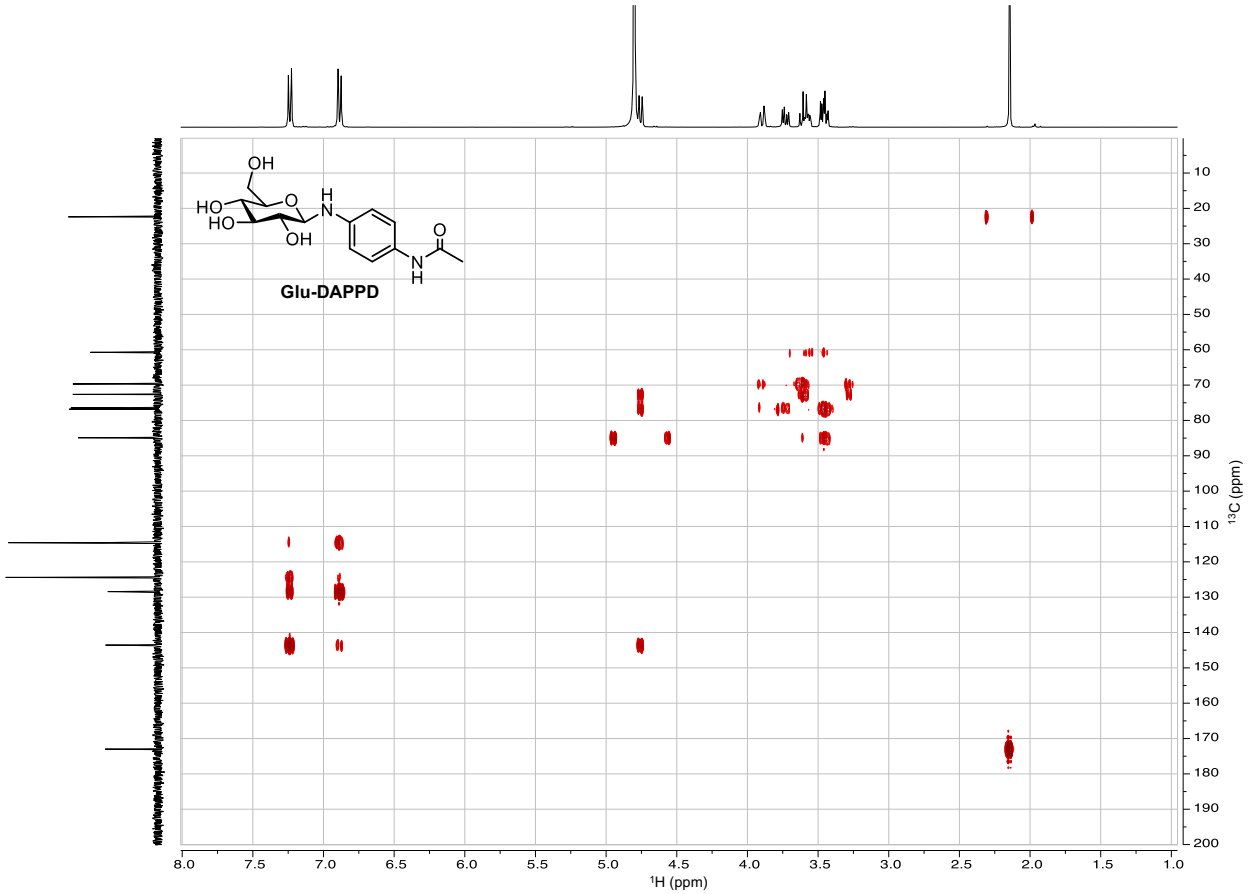


Figure S6. ^{1}H–^{13}C heteronuclear multiple bond correlation (HMBC) (400 MHz) spectra of **Glu-DAPPD** in D_2O.

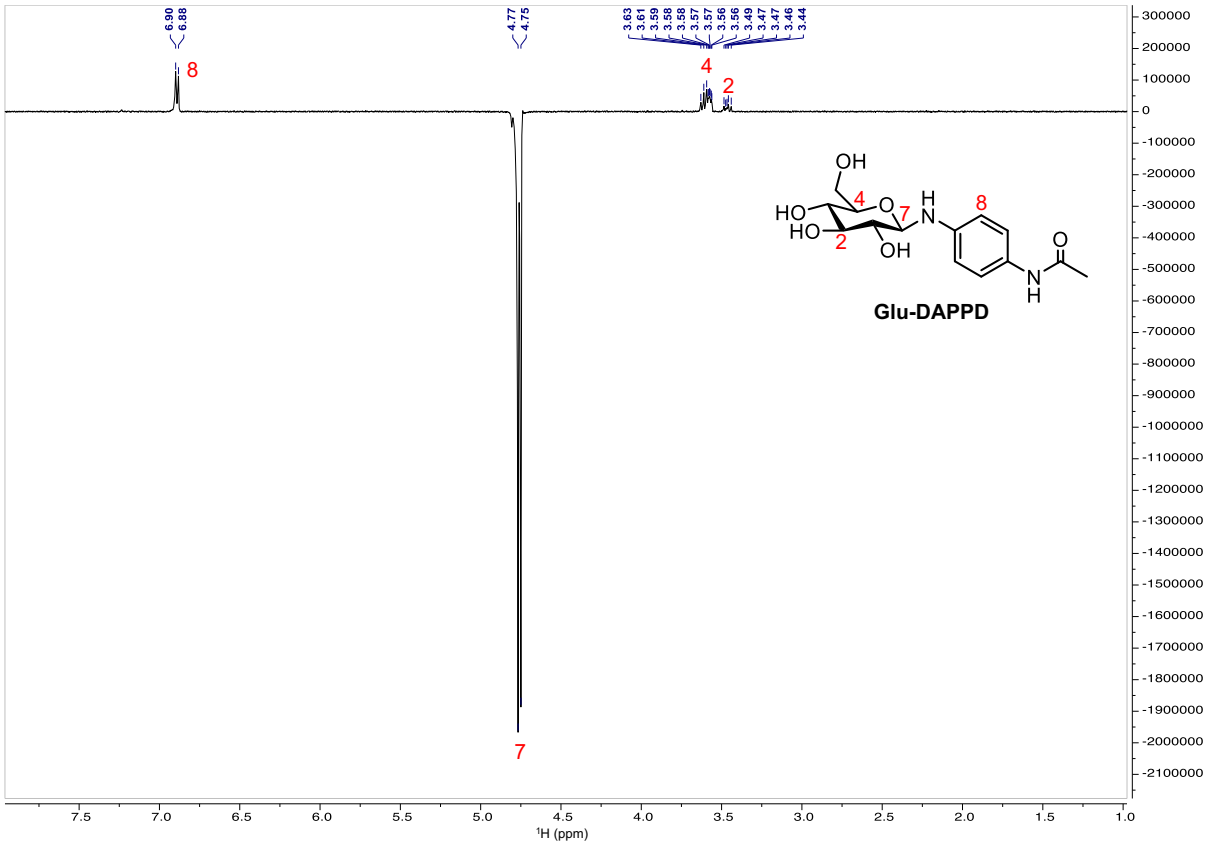


Figure S7. Selective 1D nuclear overhauser effect spectroscopy (NOESY) (500 MHz) spectra of **Glu-DAPPD** in D_2O.

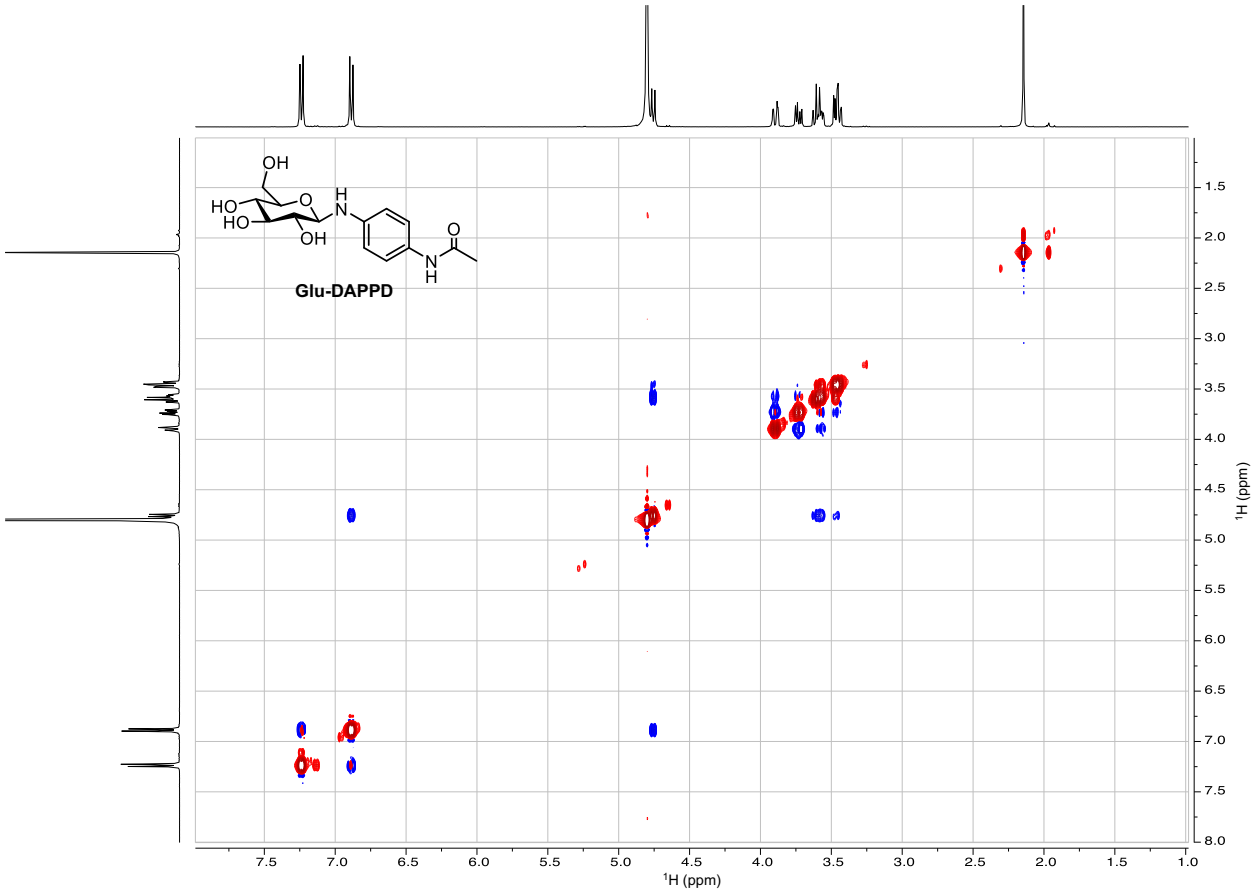


Figure S8. ^{1}H–^{1}H NOESY (400 MHz) spectra of **Glu-DAPPD** in D_2O.

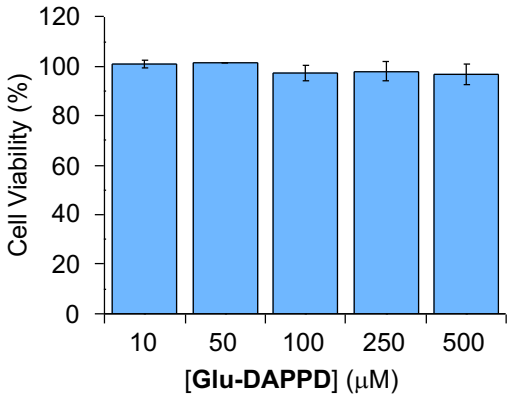


Figure S9. Toxicity of **Glu-DAPPD** in living cells. Cell viability (%) of Neuro-2a (N2a) neuroblastoma cells treated with various concentrations of **Glu-DAPPD**, determined by the MTT assay, was calculated relative to that of cells treated with an equivalent amount of DMSO (1% v/v). Error bars indicate the standard error of the mean (SEM) from three independent experiments. Conditions: [**Glu-DAPPD**] = 10, 50, 100, 250, and 500 μM (1% v/v DMSO); 37 °C; 24 h.

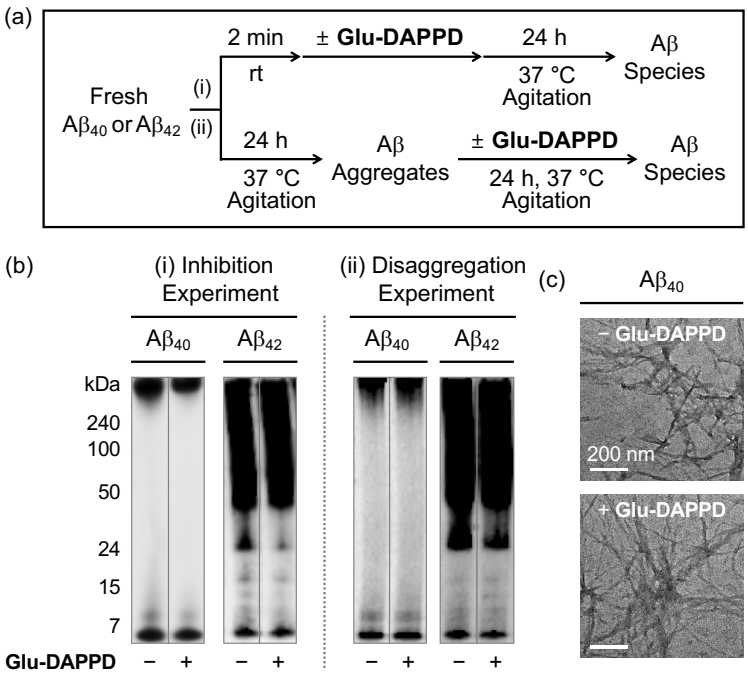


Figure S10. Effect of **Glu-DAPPD** on the aggregation of Aβ. (a) Scheme of the (i) inhibition and (ii) disaggregation experiments. (b) Gel/Western blots of the resultant Aβ species from (i) and (ii) using an anti-Aβ antibody (6E10). Lanes: (−) $A\beta_{40}$ or $A\beta_{42}$ only; (+) $A\beta_{40}$ or $A\beta_{42}$ + **Glu-DAPPD**. (c) TEM images of the samples obtained from (b, i). Scale bar = 200 nm. Conditions: [$A\beta_{40}$ or $A\beta_{42}$] = 25 μM; [**Glu-DAPPD**] = 50 μM; 20 mM HEPES, pH 7.4, 150 mM NaCl; 24 h; 37 °C; constant agitation.