Novel Multifunctional Ascorbic Triazole Derivatives for Amyloidogenic Pathway Inhibition, Anti-inflammation, and Neuroprotection

1. Synthesis

The percent yields of synthesized compounds were report in **table S1**. The ^{1}H-NMR and ^{1}C-NMR spectrums of final synthesized compounds were shown in figures **S1**-**S12**.

Table S1. The percent yields and structures of synthesized compounds.

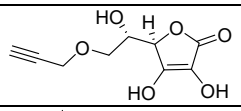
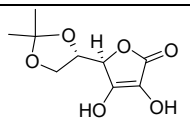
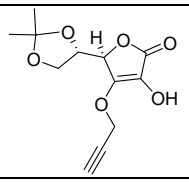
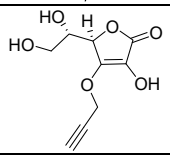
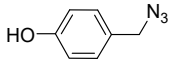
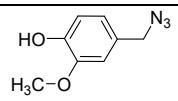
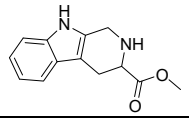
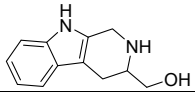
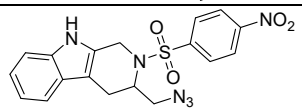
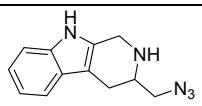
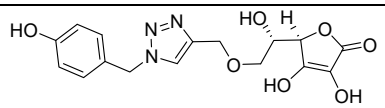
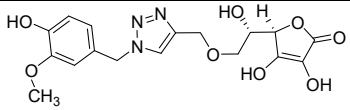
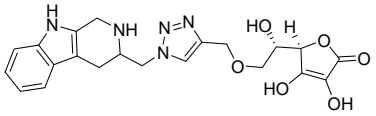
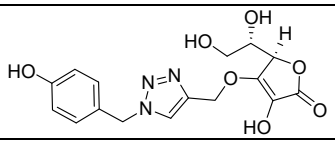
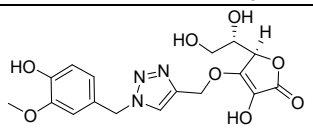
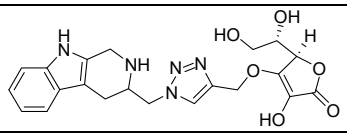
Compound	Structure	% yield
2		29.00
3		65.88
4		51.13
5		86.14
a		16.15
b		13.51
In-c1		99.64
In-c2		58.32
In-c4		78.28
c		41.19
2a		8.58
2b		12.30
2c		24.52

Table S1. The percent yields and structures of synthesized compounds (cont.).

Compound	Structure	% yield
5a		13.70
5b		24.61
5c		13.32

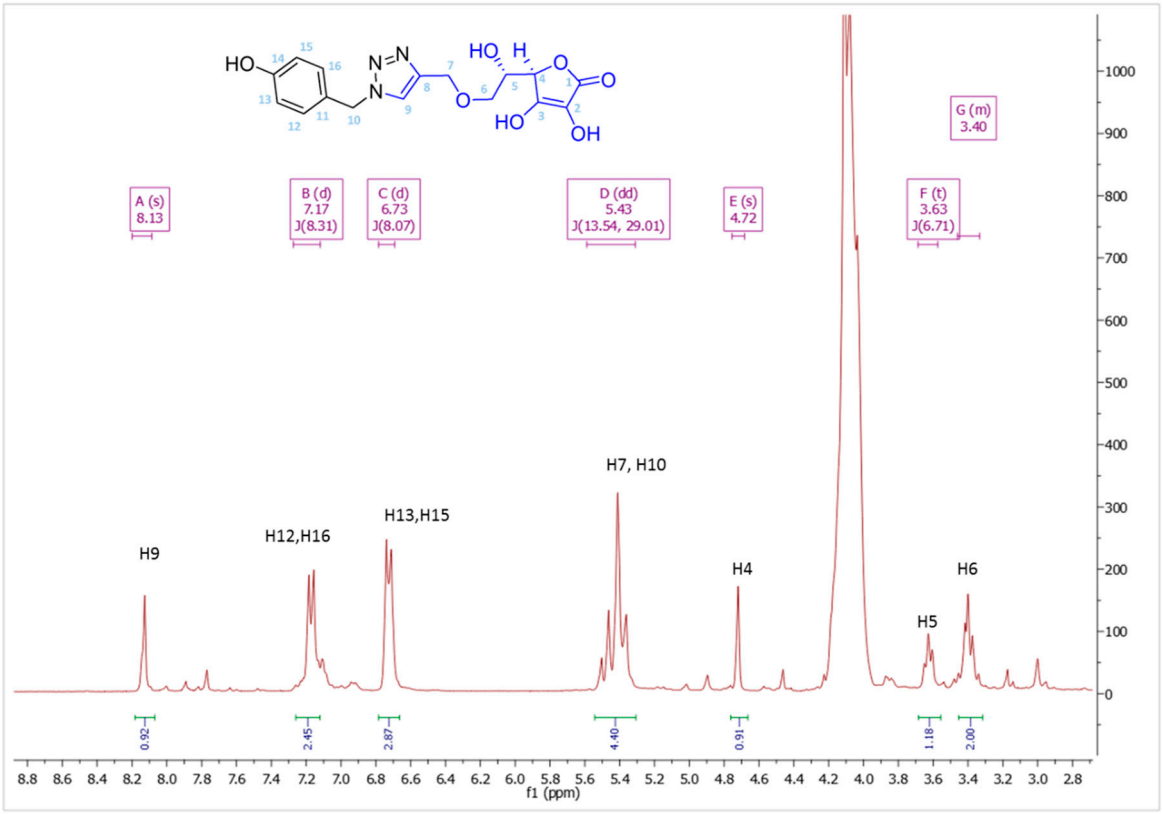


Figure S1. [1]HNMR spectrum (300 MHz) of compound **[2a]** in DMSO-d_6.

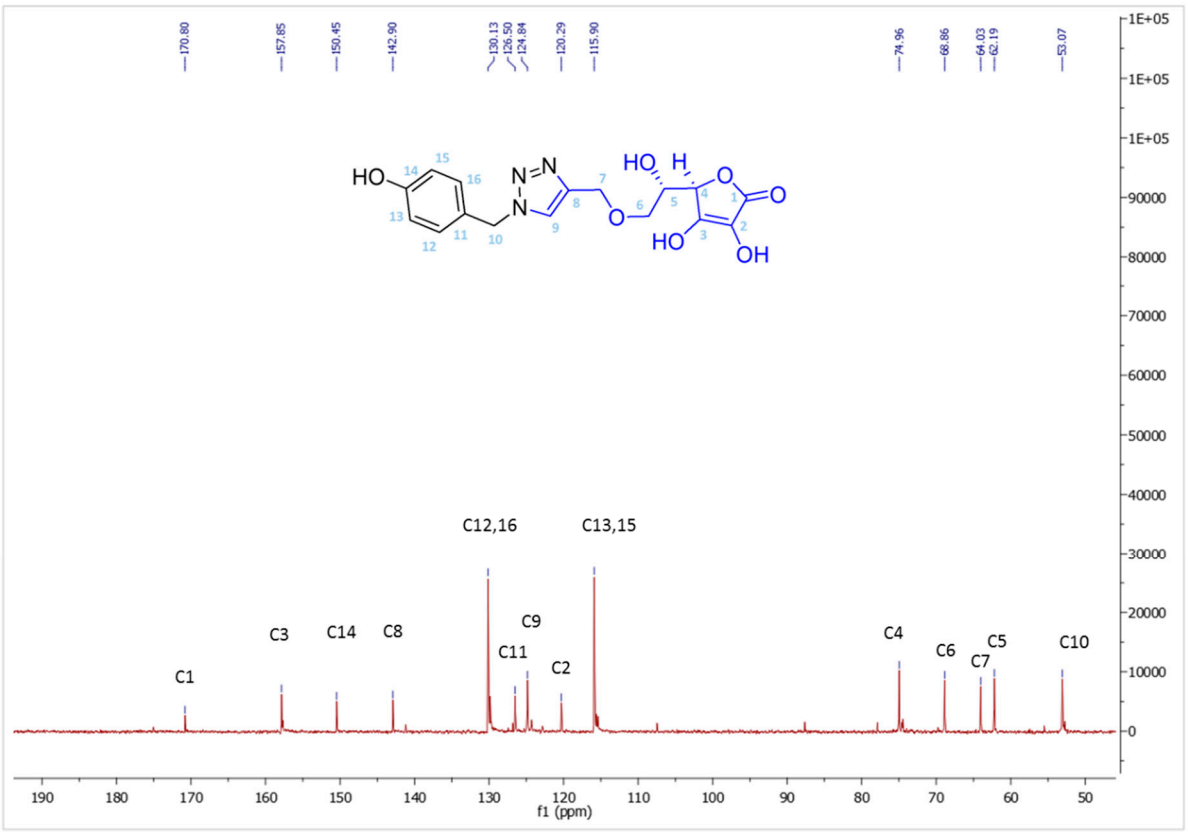


Figure S2. ^{13}CNMR spectrum (300 MHz) of compound **[2a]** in DMSO-d$_6$.

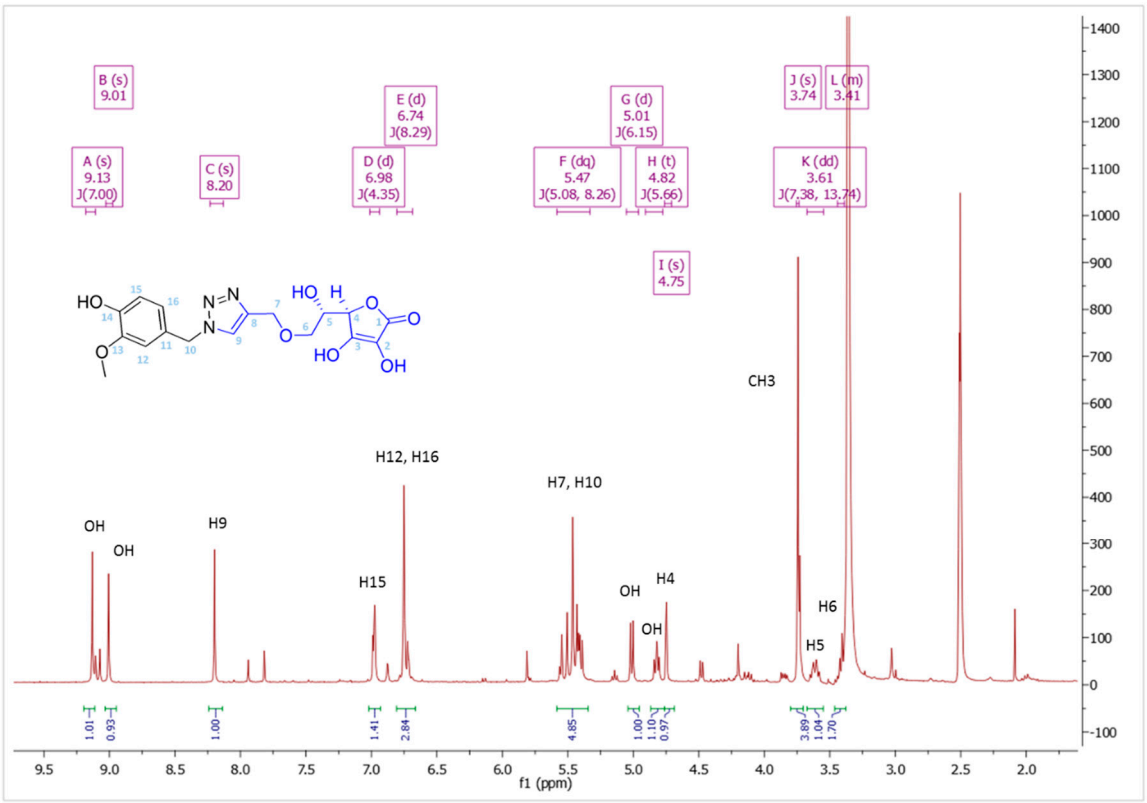


Figure S3. ^{1}HNMR spectrum (300 MHz) of compound **[2b]** in DMSO-d$_6$.

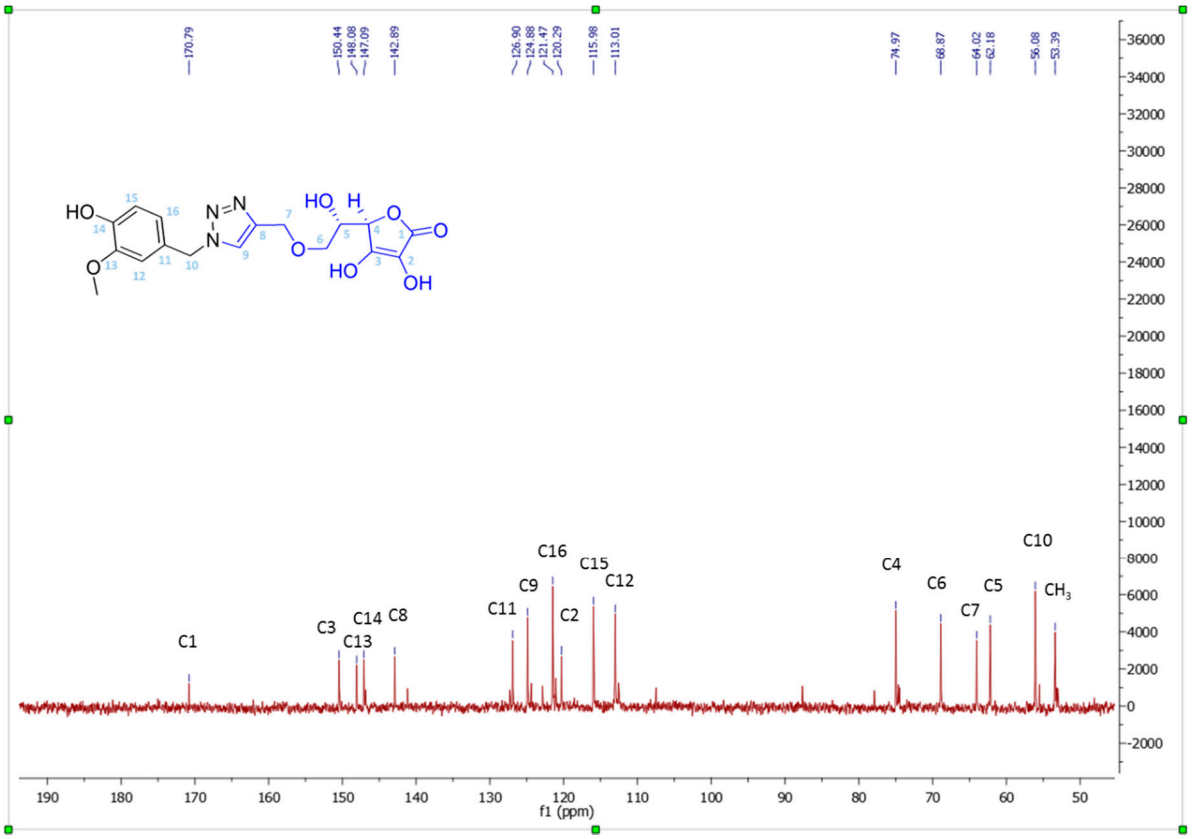


Figure S4. ^{13}CNMR spectrum (300 MHz) of compound **[2b]** in DMSO-d$_6$.

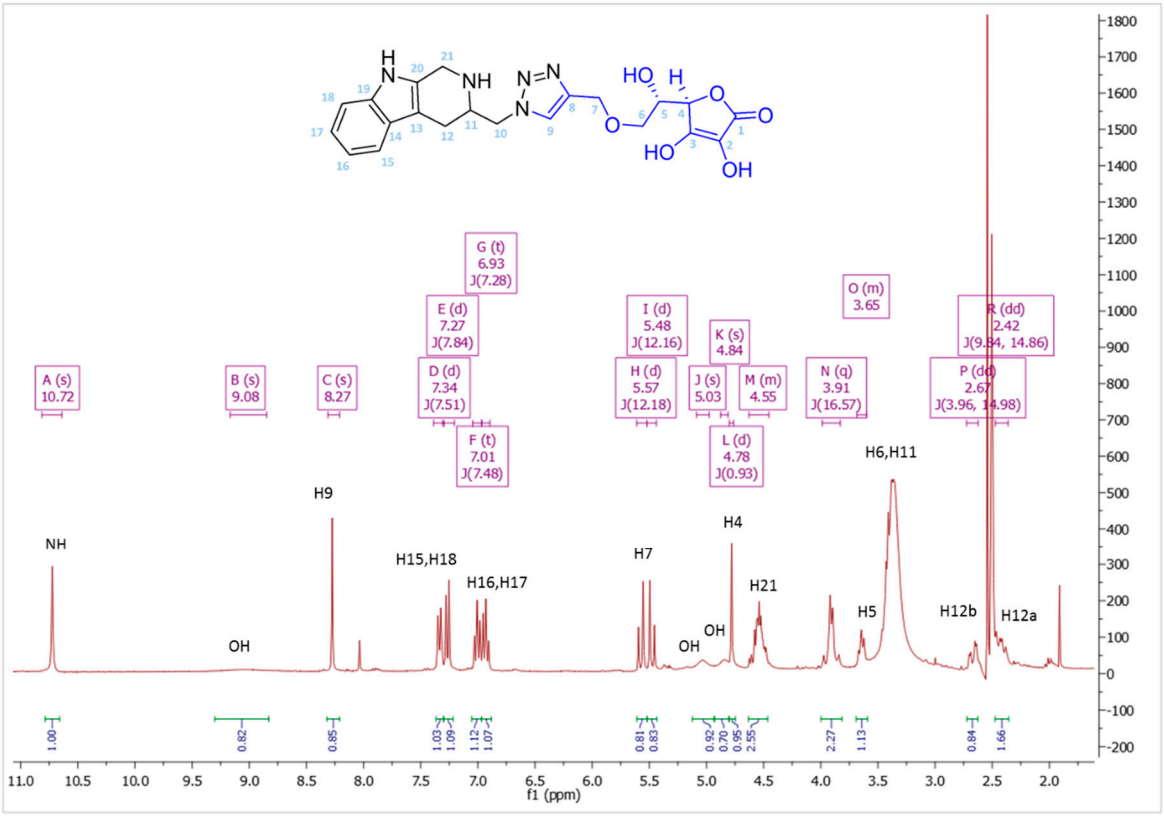


Figure S5. ^{1}HNMR spectrum (300 MHz) of compound **[2c]** in DMSO-d$_6$.

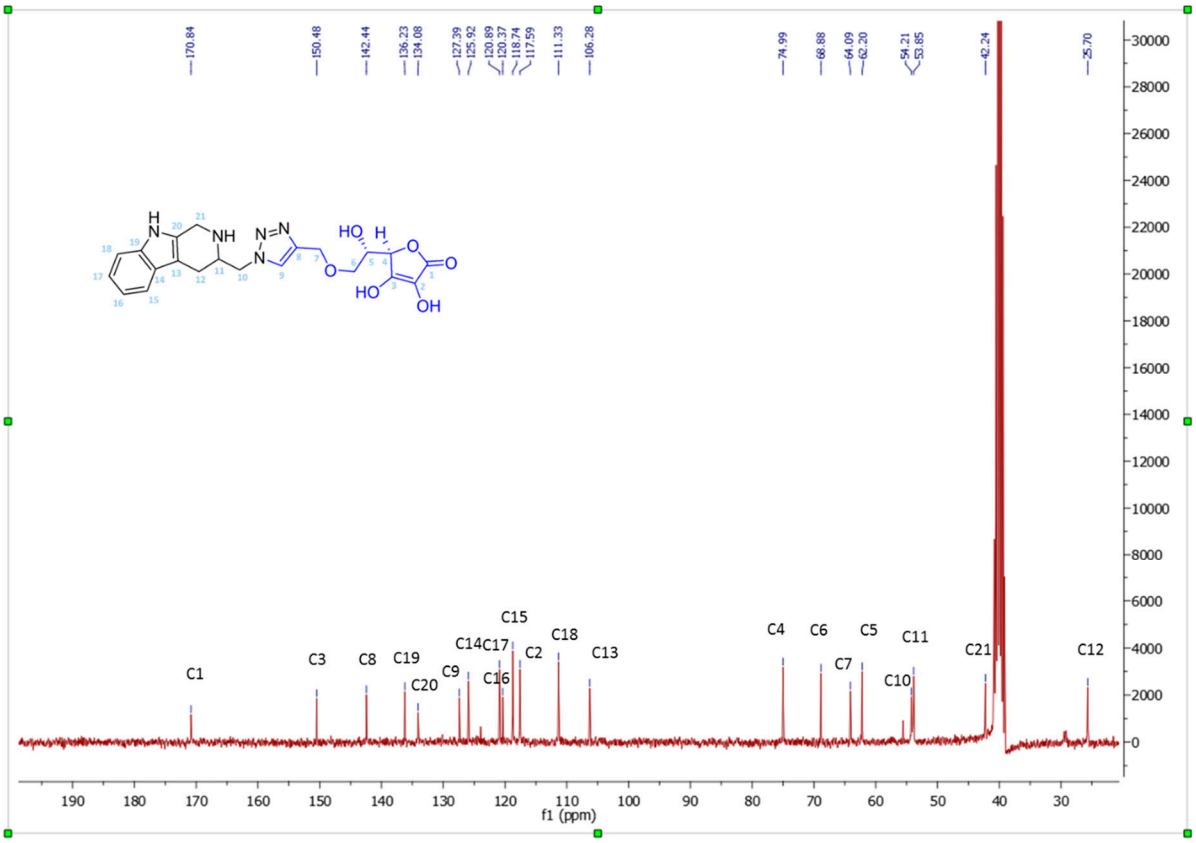


Figure S6. ^{13}CNMR spectrum (300 MHz) of compound **[2c]** in DMSO-d$_6$.

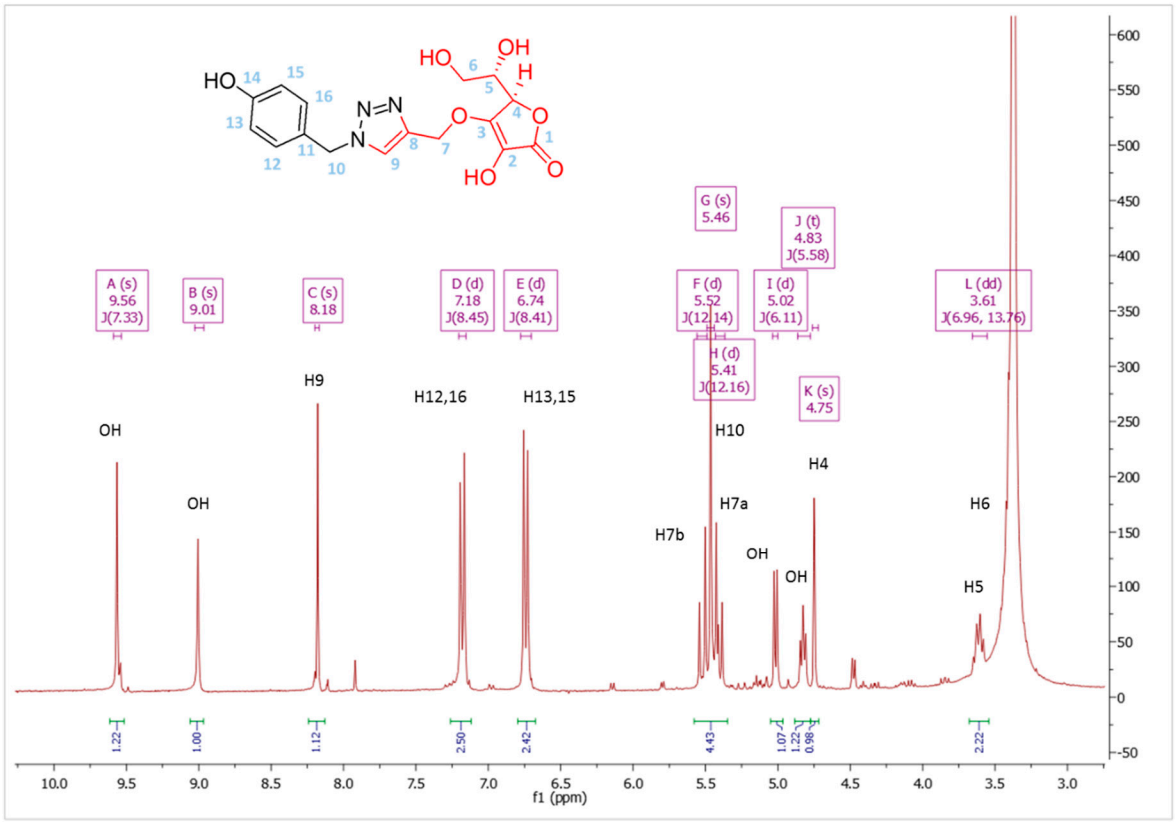


Figure S7. [1]HNMR spectrum (300 MHz) of compound **[5a]** in DMSO-d6.

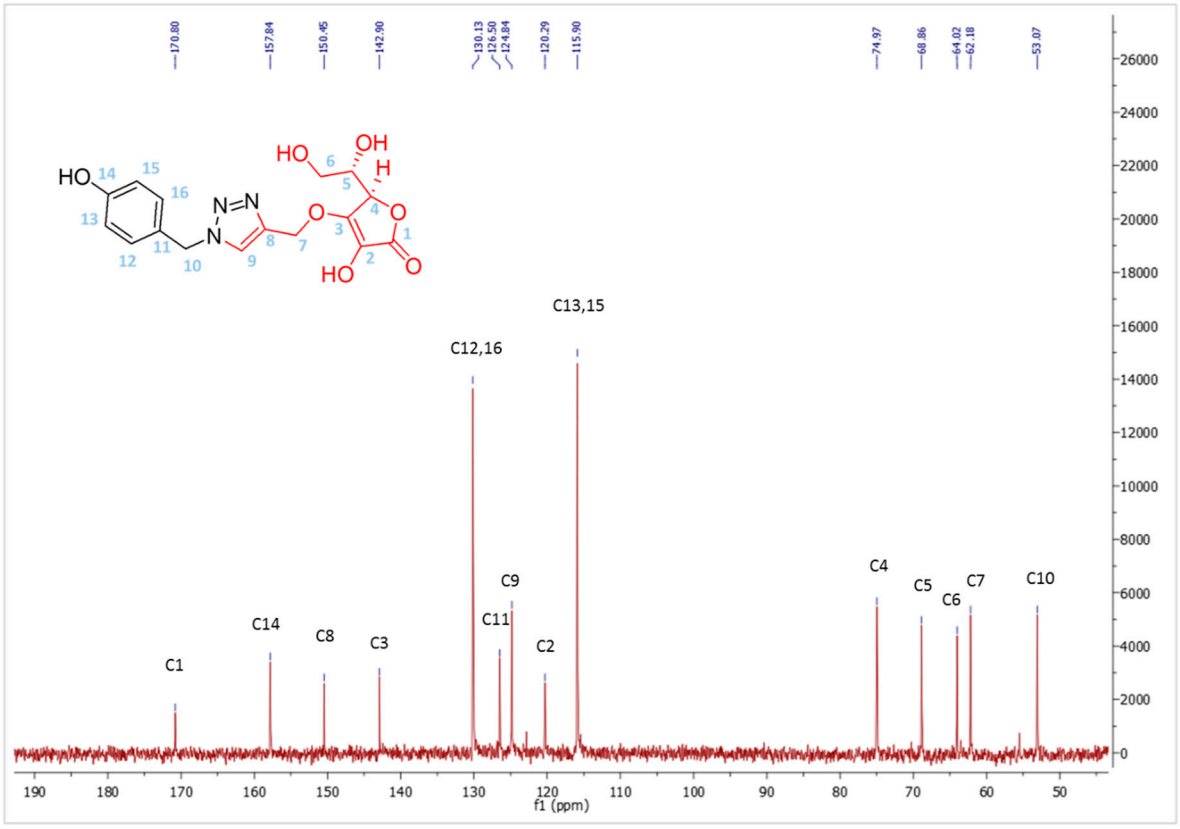


Figure S8. [13]CNMR spectrum (300 MHz) of compound **[5a]** in DMSO-d6.

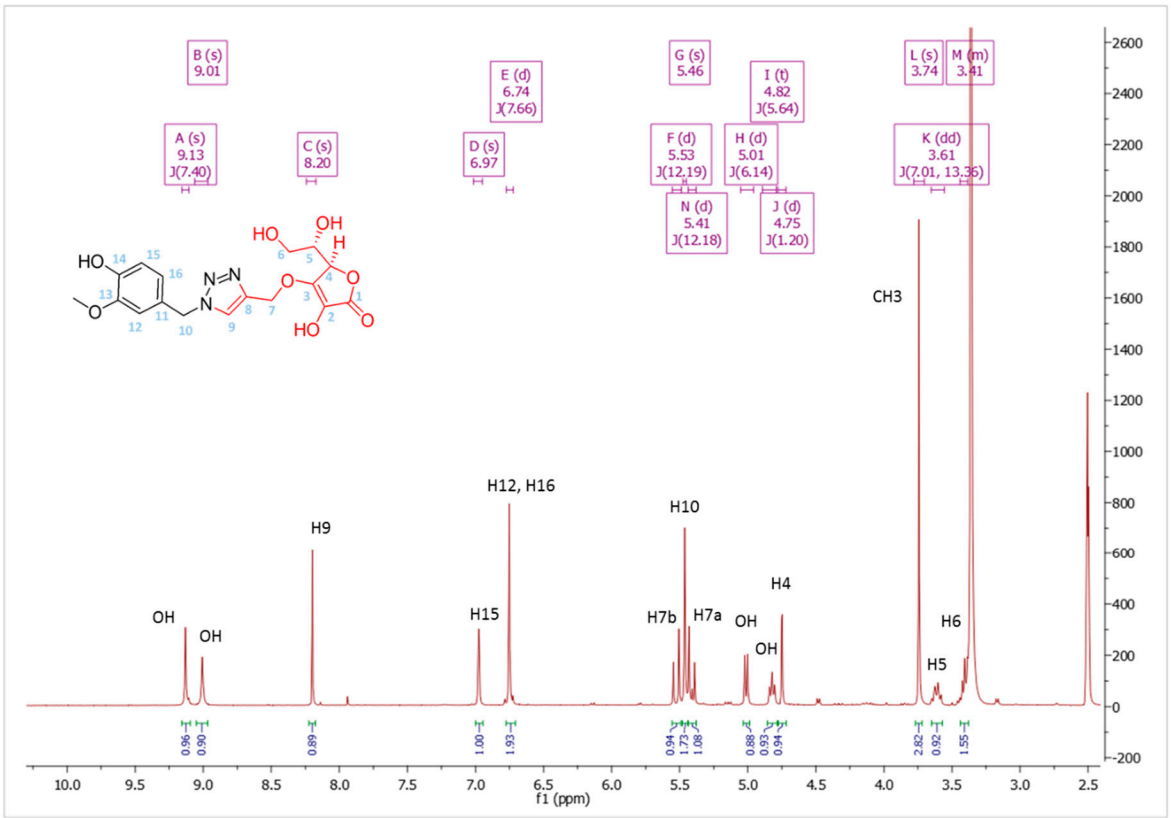


Figure S9. [1]HNMR spectrum (300 MHz) of compound **[5b]** in DMSO-d6.

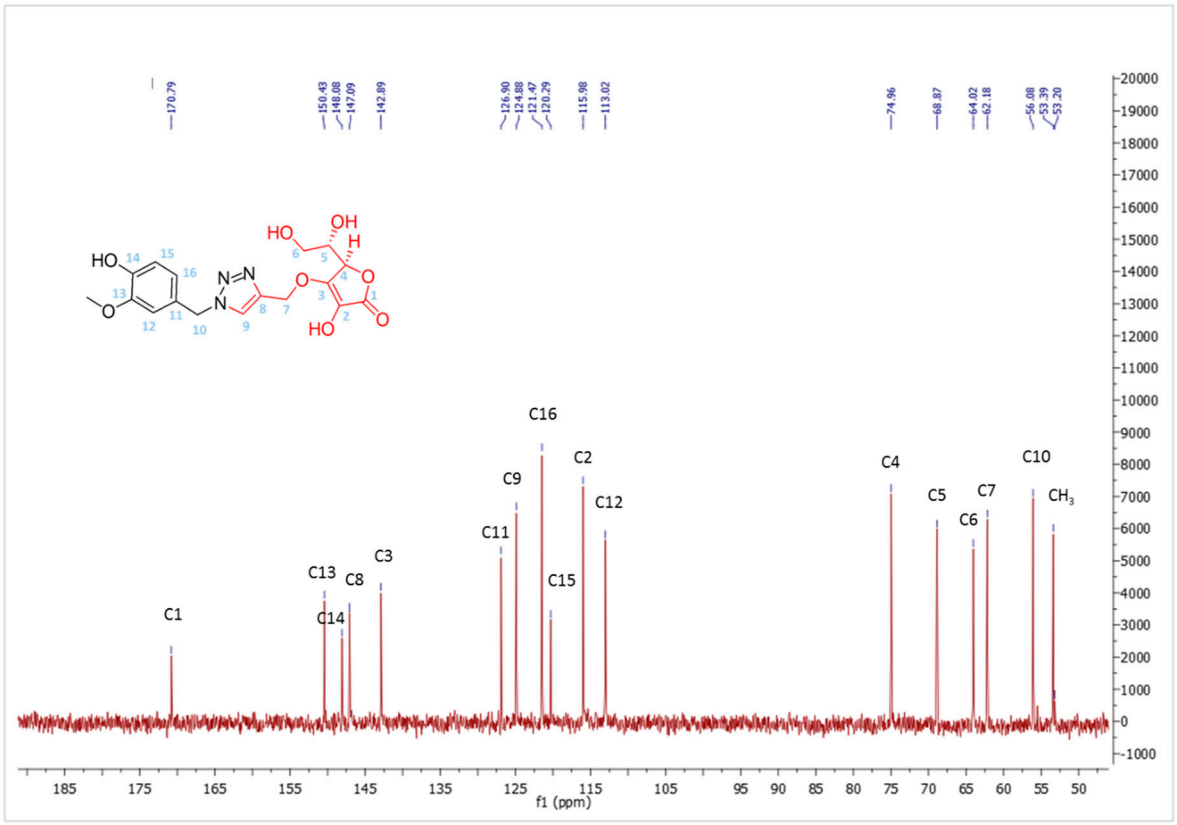


Figure S10. ^{13}CNMR spectrum (300 MHz) of compound **[5b]** in DMSO-d$_6$.

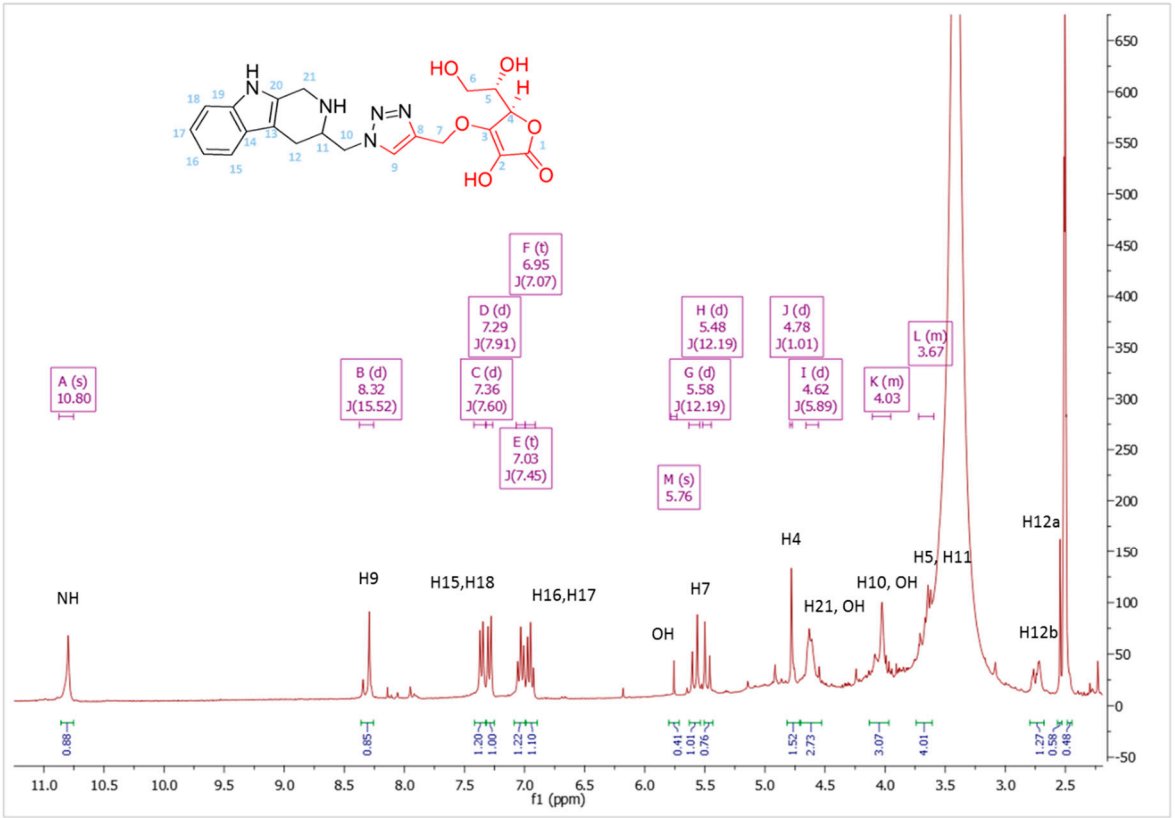


Figure S11. ^{1}HNMR spectrum (300 MHz) of compound **[5c]** in DMSO-d$_6$.

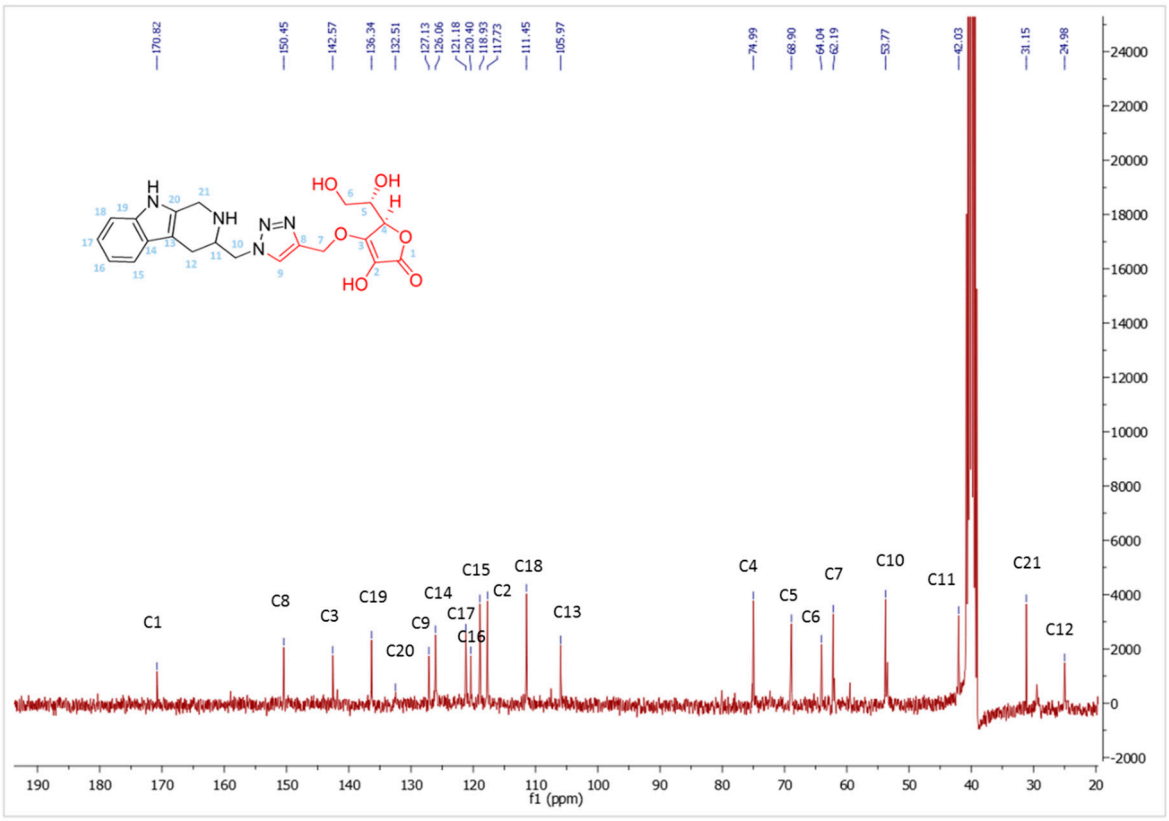


Figure S12. ^{13}CNMR spectrum (300 MHz) of compound **[5c]** in DMSO-d_6.

2. Biological activity assays

Cell viability assays for neurotoxicity assessments of ascorbic acid and derivatives (**2a-2c** and **5a-5c**) were conducted at various concentrations of 1 to 10^4 nM on P19-derived neurons and measured by XTT method. All compounds except ascorbic acid had cell viabilities higher than 100% at 1 nM (Figure S13).

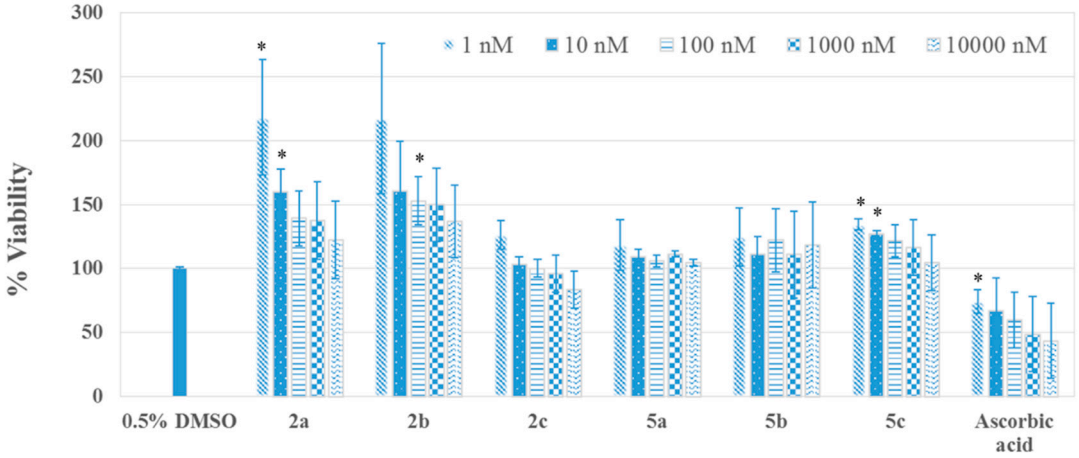


Figure S13. Effects of ascorbic acid and derivatives (**2a-2c** and **5a-5c**) at concentrations of 1 to 10^4 nM on the viability of P19-derived neurons. The cytotoxicity was evaluated by XTT assay. Each bar is presented as mean ± SD (n = 3). * indicates significant differences with 0.5% DMSO (p-value < 0.05) based on t-test by using Microsoft Excel version 2013.

Cell viability assays for anti-inflammatory assessments of ascorbic acid, **2c**, and **5c** were performed at various concentrations of 0.001 to 100 nM on RAW 264.7 and measured by MTT method. The ascorbic acid, **2c**, and **5c** did not exhibit cytotoxicity after 24-hour exposure (Figure S14).

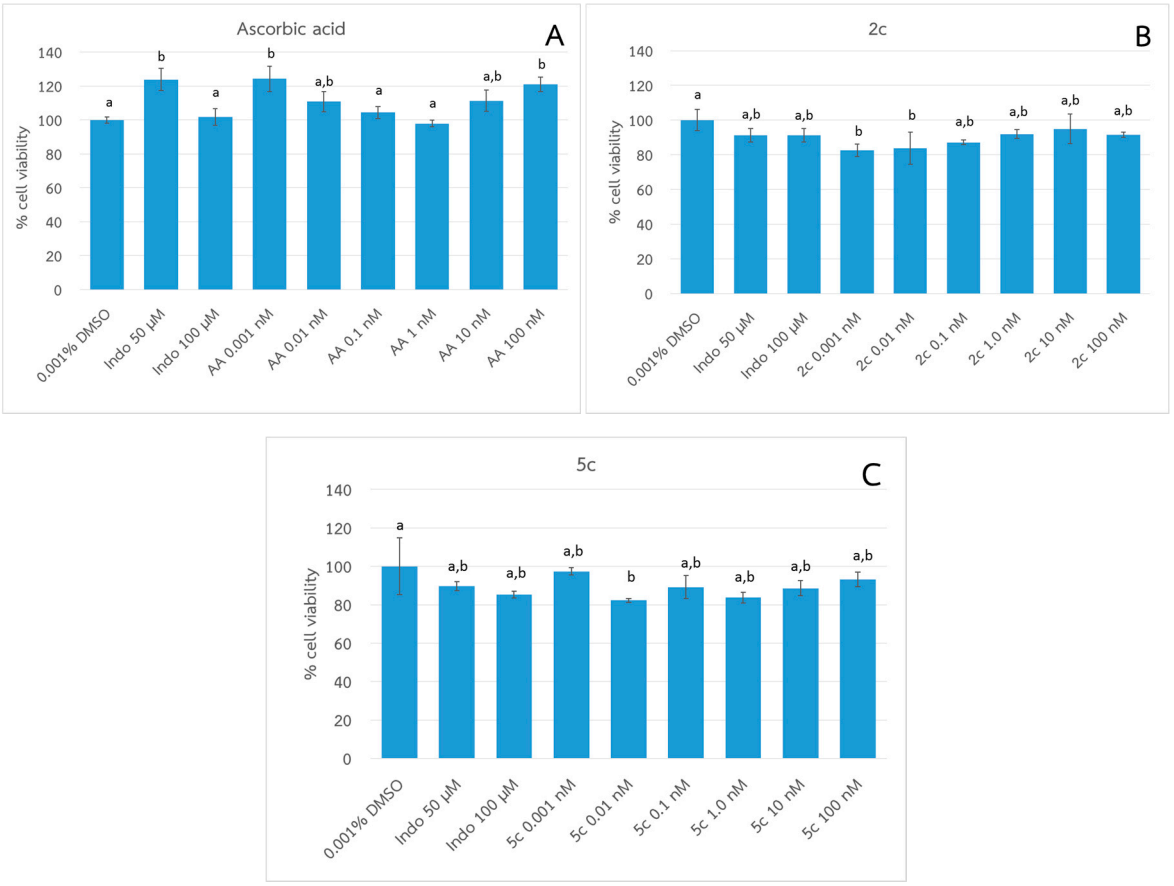


Figure S14. Effects of ascorbic acid (A), **2c** (B) and **5c** (C) on the viability of RAW 264.7. The cytotoxicity was evaluated by MTT assay. Each bar is presented as mean ± SD (n = 3). Letters (a and b) indicate significant differences (p-value < 0.05) based on Tukey's HSD one-way ANOVA by using PAST version 3.14.