**Supporting Information**

# Structure-activity relationship study of the neuroprotective effects of Vitamin K derivatives

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**FIGURE S1: Dose-response curves of Vitamin $K_1$, Vitamin $K_2$, and control compounds Necrostatin-1, Idebenone, Coenzyme $Q_{10}$, and Trolox.** Cell viability assay was conducted as described in the Methods sections of the main text.

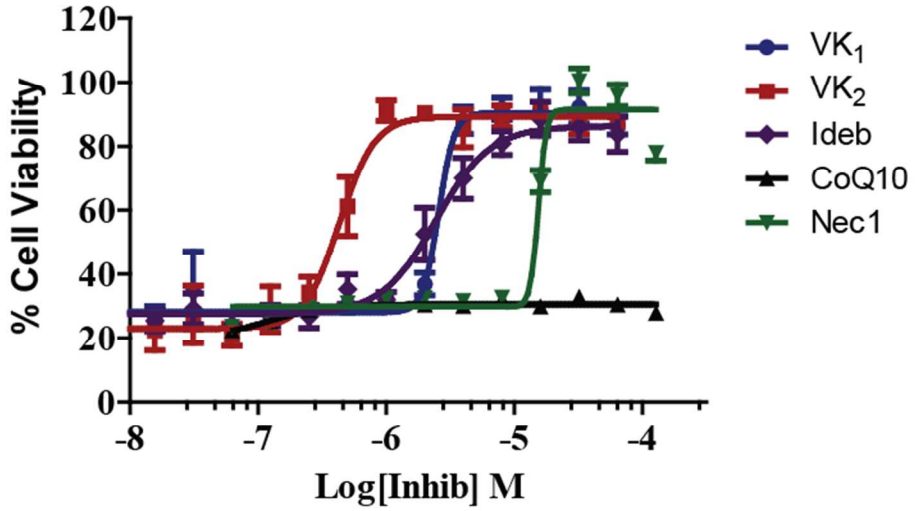
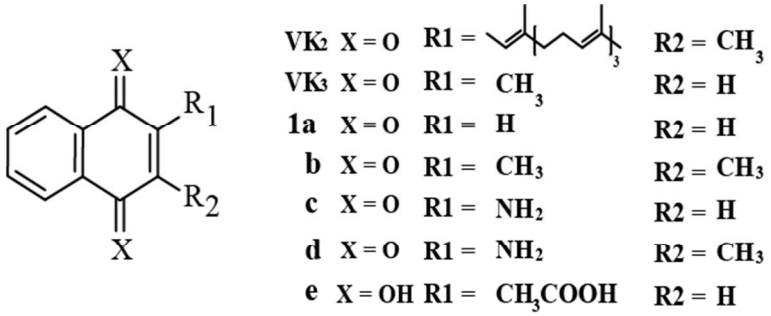



**Figure S2: Scaffold optimization and cell viability assay results.** Cell viability assay was conducted as described in the Methods sections of the main text.



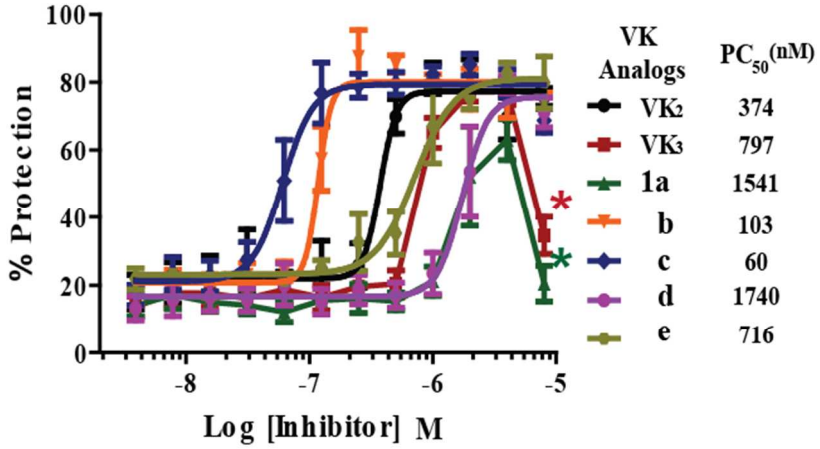



**Figure S3**: **Western blot of HO-1 and NQO-1.** HT22 cells were treated as described for 8 hrs and the cells were harvested and .

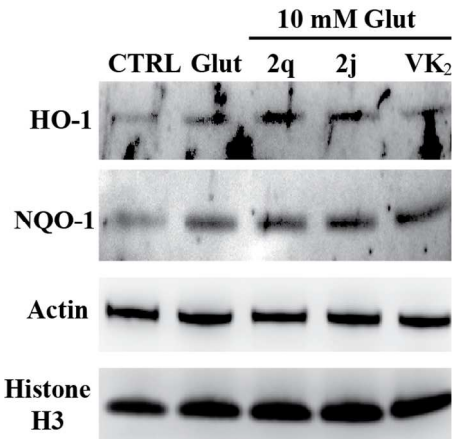


**Figure S4: t-BuOOH protection results.** Cell viability assay was conducted as described in the Methods sections of the main text.

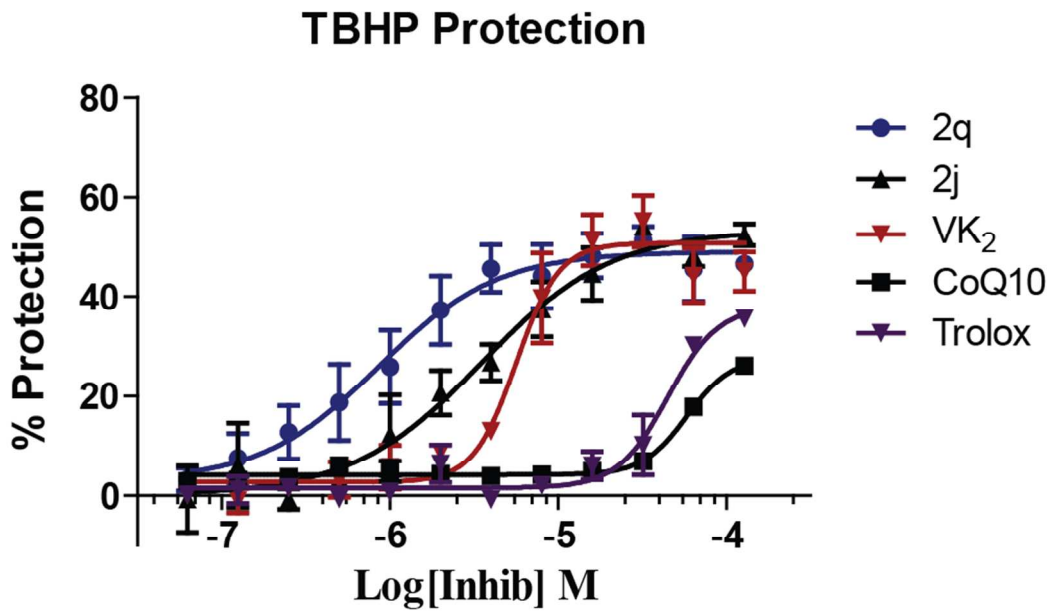
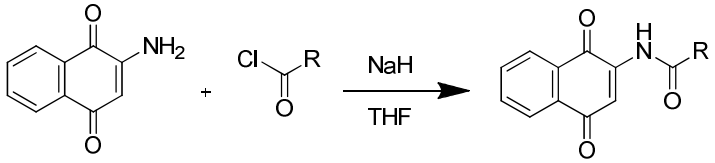
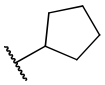
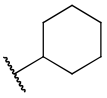
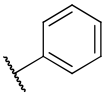
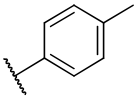
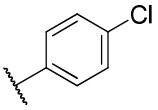
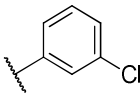
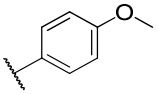
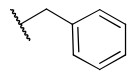
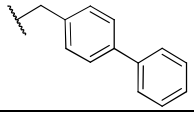


**TABLE S1.** In Vitro Neuroprotective Activity of 2-amido-1,4-naphthoquinones

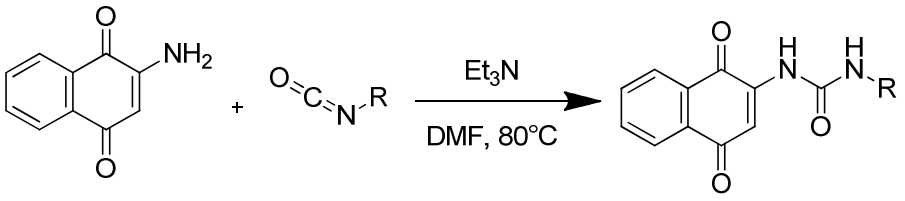



**3**

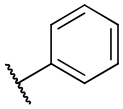
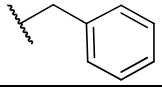
| Compound | R | Protection[a] $PC_{50}$ (nM) | Toxicity[b] $TC_{50}$ (nM) | Safety Index $TC_{50}$ / $PC_{50}$ |
|---|---|---|---|---|
| **3a** | -Me | 616 | >100,000 | 162 |
| **3b** | -Et | 760 | 80,000 | 105 |
| **3c** |  | 69 | 5,000 | 72 |
| **3d** |  | >1000 | 8,000 | 0 |
| **3e** |  | >1000 | 6,000 | 0 |
| **3f** |  | 275 | 14,000 | 51 |
| **3g** |  | 500 | 17,000 | 34 |
| **3h** |  | 382 | 24,000 | 63 |
| **3i** |  | 405 | 27,000 | 67 |
| **3j** |  | 492 | >100,000 | 203 |
| **3k** |  | 658 | 32,000 | 49 |
| **3l** |  | 890 | 42,000 | 47 |
| **3m** |  | 161 | >100,000 | 621 |

In vitro neuroprotective activity and [b]neurotoxicity assessed by treating HT22 cells with various concentrations of compounds with or without 10 mM glutamate for 24 hrs. Cell viability was estimated by treating cells with MTS and measuring absorbance at 490 nM. $PC_{50}$, concentration producing 50% protection, values calculated using GraphPad Prism based on 12 point titrations, $n \geq 4$; $TC_{50}$, concentration producing 50% toxicity, values calculated using GraphPad Prism based on 7 point titrations, $n \geq 3$.

**TABLE S2**. In Vitro Neuroprotective Activity of 2-ureyl-1,4-naphthoquinones.

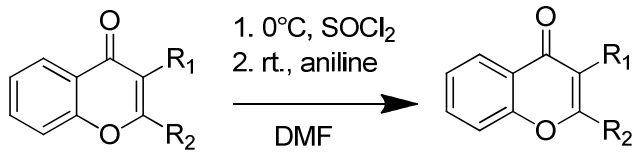



**4**

| Compound | R | Protection[a] PC$_{50}$ (nM) | Toxicity[b] TC$_{50}$ (nM) | Safety Index TC$_{50}$ / PC$_{50}$ |
|---|---|---|---|---|
| **4a** | -Et | 177 | 5,000 | 28 |
| **4b** |  | 64 | 8,000 | 125 |
| **4c** |  | 890 | >100,000 | 112 |
| **4d** |  | 740 | >100,000 | 135 |

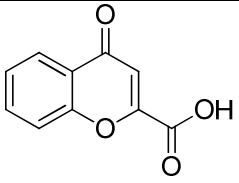
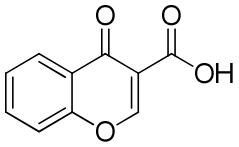
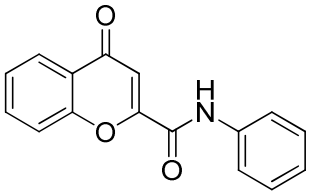
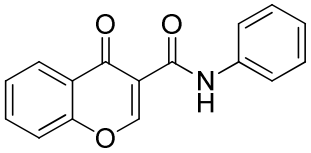
[a]In vitro neuroprotective activity and [b]neurotoxicity assessed by treating HT22 cells with various concentrations of compounds with or without 10 mM glutamate for 24 hrs. Cell viability was estimated by treating cells with MTS and measuring absorbance at 490 nM. PC$_{50}$, concentration producing 50% protection, values calculated using GraphPad Prism based on 12 point titrations, $n \geq 4$; TC$_{50}$, concentration producing 50% toxicity, values calculated using GraphPad Prism based on 7 point titrations, $n \geq 3$.

**TABLE S3**. In Vitro Neuroprotective Activity of chromone derivatives.




a) $R_1$: H; $R_2$: COOH
b) $R_1$: COOH; $R_2$: H

a) $R_1$: H; $R_2$: CONHAr
b) $R_1$:CONHAr; $R_2$: H

| Compound | Protection[a] $PC_{50}$ (nM) | Toxicity[b] $TC_{50}$ (nM) |
|---|---|---|
|  | >1000 | >100,000 |
|  | >1000 | >100,000 |
|  | >1000 | >100,000 |
|  | >1000 | >100,000 |

[a]In vitro neuroprotective activity and [b]neurotoxicity assessed by treating HT22 cells with various concentrations of compounds with or without 10 mM glutamate for 24 hrs. Cell viability was estimated by treating cells with MTS and measuring absorbance at 490 nM. $PC_{50}$, concentration producing 50% protection, values calculated using GraphPad Prism based on 12 point titrations, $n \geq 4$; $TC_{50}$, concentration producing 50% toxicity, values calculated using GraphPad Prism based on 7 point titrations, $n \geq 3$.

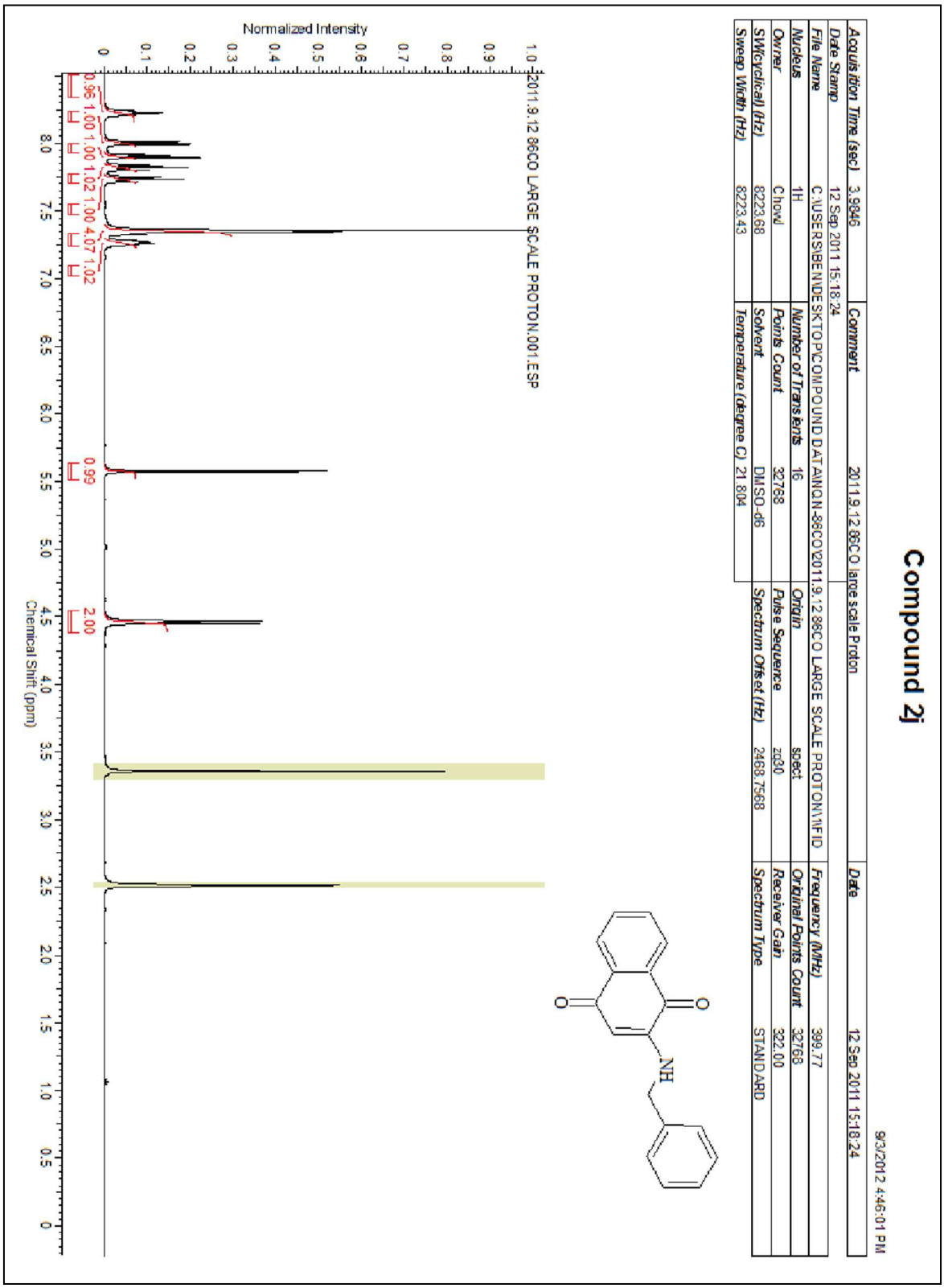
**TABLE S4**. Mouse Blood Chemistry Results.

| | | Vehicle Control | | Compound 2q (50 mg/kg; 3 wks i.p.) | | |
|---|---|---|---|---|---|---|
| **Parameter** | **Units** | **1** | **2** | **1** | **2** | **3** |
| ALP | U/L | 90 | 79 | 72 | 80 | 60 |
| ALT | U/L | 35 | 32 | 34 | 28 | 33 |
| AST | U/L | 60 | 50 | 89 | 71 | 78 |
| Total Bilirubin | mg/dL | 0.20 | 0.20 | 0.20 | 0.20 | 0.20 |
| Total Protein | g/dL | 4.9 | 5.0 | 5.2 | 5.3 | 4.9 |
| Albumin | mg/dL | 2.9 | 2.8 | 3.0 | 3.2 | 2.8 |
| Creatinine | mg/dL | 0.23 | 0.15 | 0.16 | 0.23 | 0.18 |
| BUN | mg/dL | 18 | 17 | 19 | 19 | 20 |
| Glucose | mg/dL | 199 | 219 | 195 | 205 | 195 |

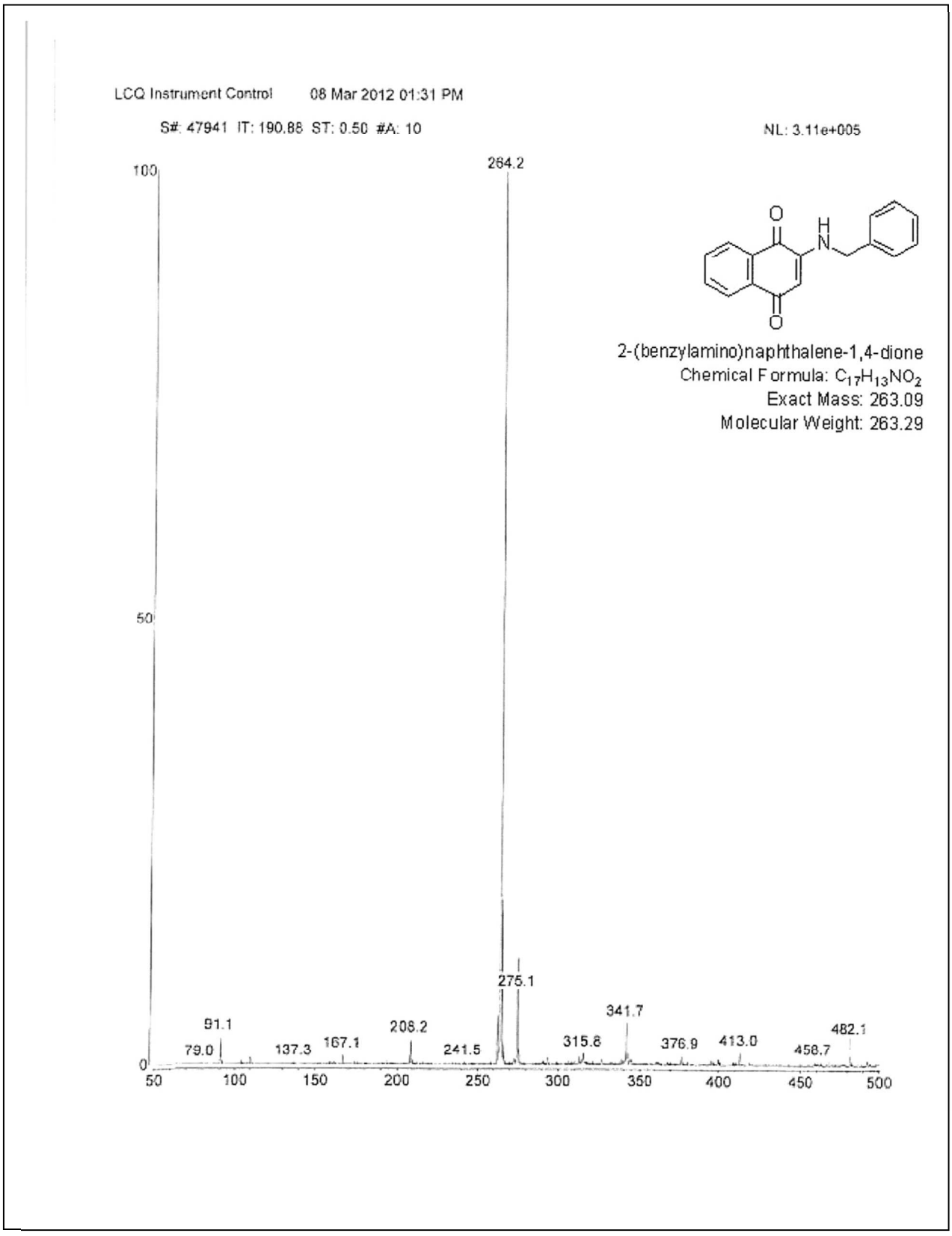
**TABLE S5**. Mouse Complete Blood Count Results.

| | | Vehicle Control | | Compound 2q (50 mg/kg; 3 wks i.p.) | | |
|---|---|---|---|---|---|---|
| **Parameter** | **Units** | **1** | **2** | **1** | **2** | **3** |
| **Leukocytes** | | | | | | |
| WBC | K/uL | 7.00 | 10.58 | 9.28 | 8.82 | 6.62 |
| NE | K/uL | 1.56 | 4.38 | 5.55 | 3.03 | 3.78 |
| LY | K/uL | 4.78 | 4.50 | 3.30 | 5.14 | 2.45 |
| MO | K/uL | 0.64 | 1.51 | 0.32 | 0.43 | 0.35 |
| EO | K/uL | 0.02 | 0.13 | 0.10 | 0.17 | 0.01 |
| BA | K/uL | 0.01 | 0.07 | 0.01 | 0.05 | 0.02 |
| **Erythrocytes** | | | | | | |
| RBC | M/uL | 9.70 | 4.44 | 9.39 | 9.46 | 9.37 |
| Hb | g/dL | 14.8 | 16.0 | 13.9 | 14.5 | 13.9 |
| HCT | % | 54.6 | 24.6 | 51.1 | 53.2 | 51.3 |
| MCV | fl | 56.3 | 55.4 | 54.4 | 56.2 | 54.8 |
| MCH | pg | 15.3 | 36.0 | 14.8 | 15.3 | 14.8 |
| MCHC | g/dL | 27.1 | 65.0 | 27.2 | 27.3 | 27.1 |
| RDW | % | 17.6 | 24.2 | 17.8 | 17.7 | 17.4 |
| **Thrombocytes** | | | | | | |
| PLT | K/uL | 988 | 690 | 1139 | 946 | 1050 |
| MPV | fl | 4.6 | 4.8 | 4.5 | 4.6 | 4.4 |

**Compound 2j $H^1$ NMR spectra**



**Compound 2j Mass Spectra**



**Compound 2j Analytical HPLC**

Purity: >97%

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    Different Inj Volume from Sequence !     Actual Inj Volume : 10 µl
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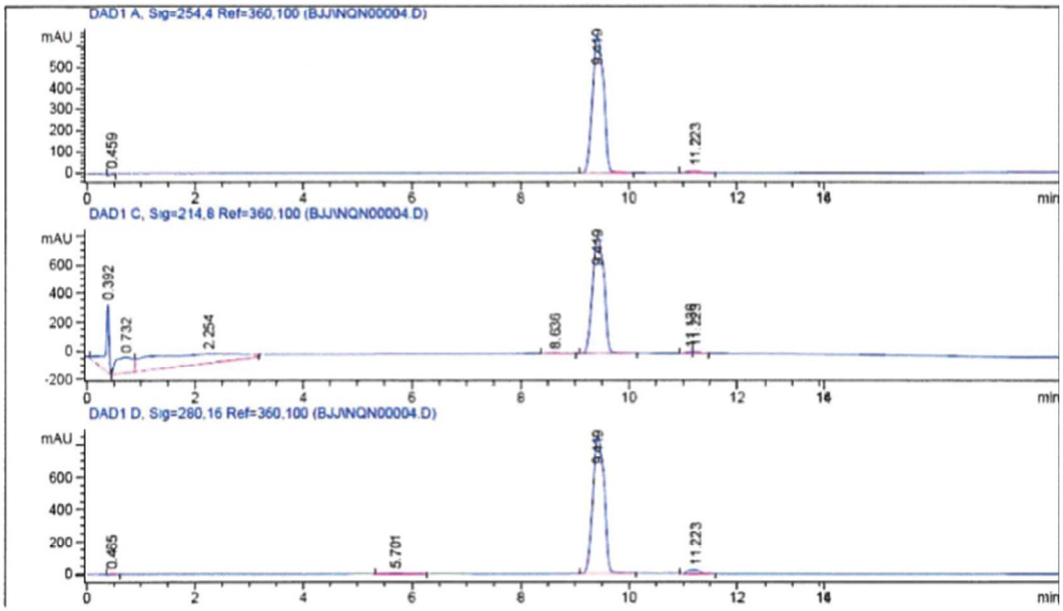
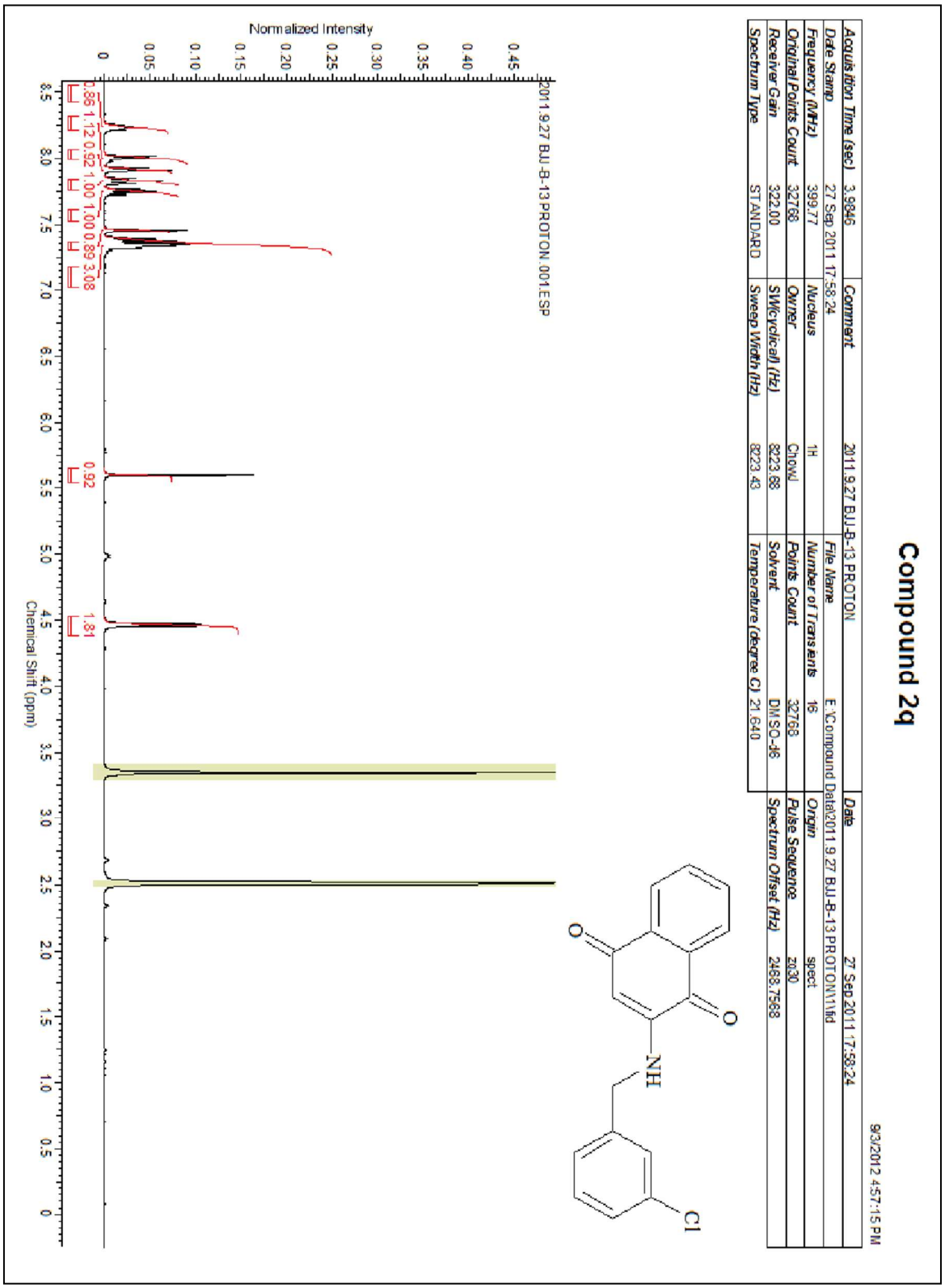
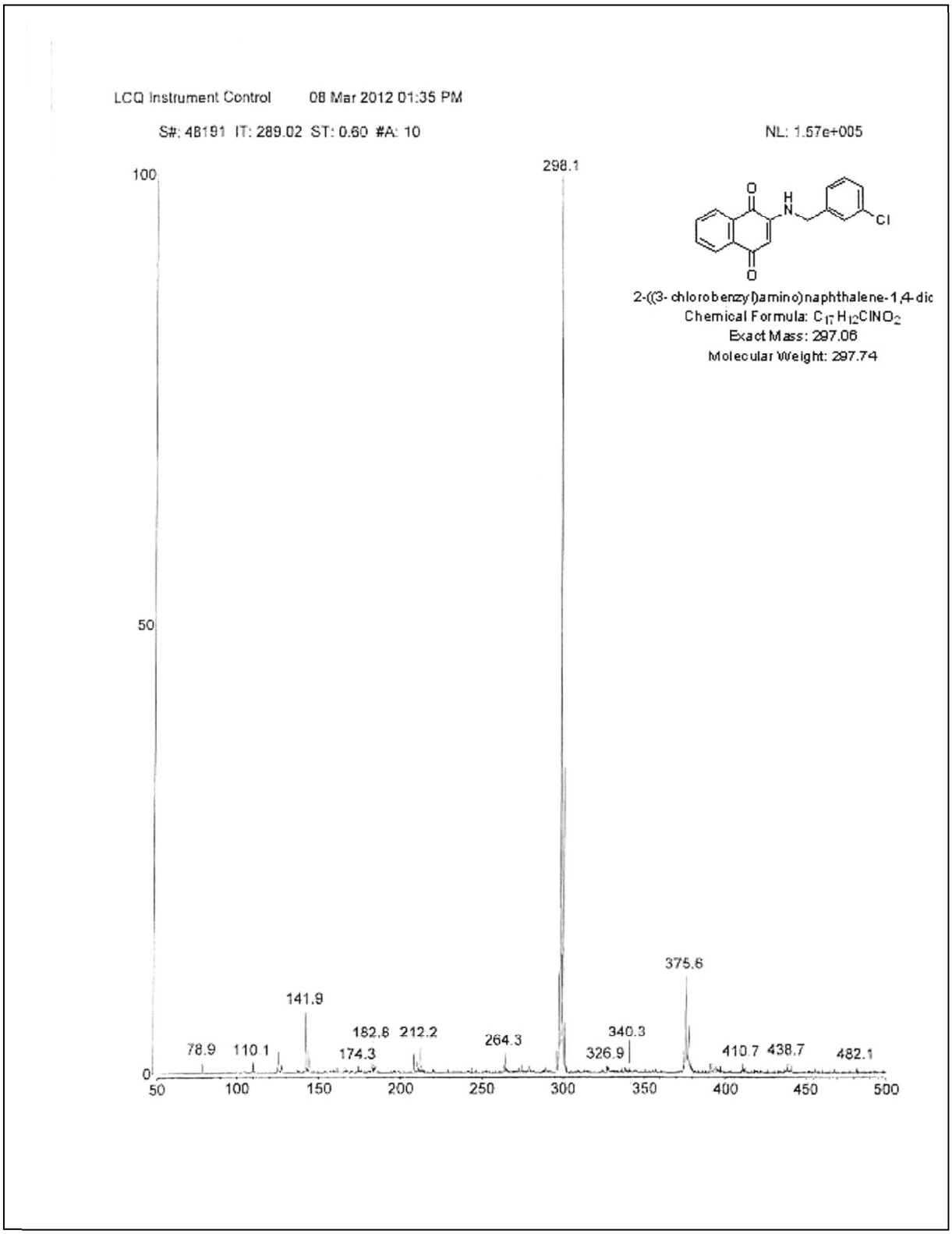


**Compound 2q $H^1$ NMR Spectra**



**Compound 2q Mass Spectra**



**Compound 2q Analytical HPLC**

Purity: >95%

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    Acq. Instrument : Agilent1100                  Inj Volume : 5 µl
    Different Inj Volume from Sequence !     Actual Inj Volume : 10 µl
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