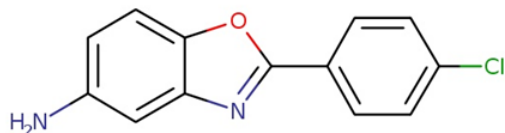
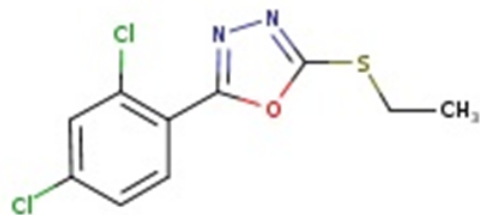


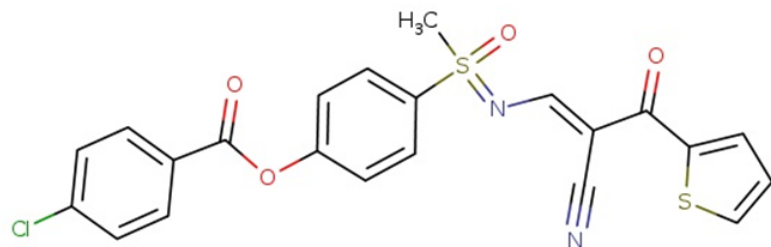
**PS30**



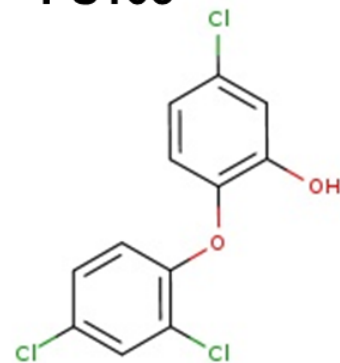
**PS34**



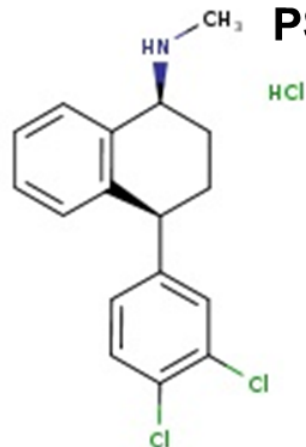
**PS83**



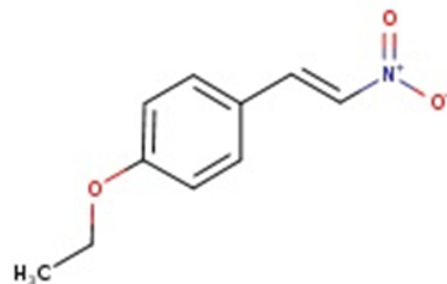
**PS103**



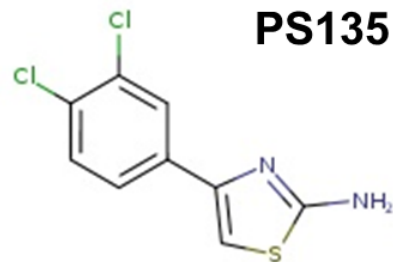
**PS106**



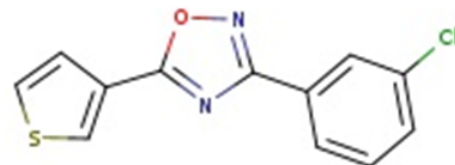
**PS127**



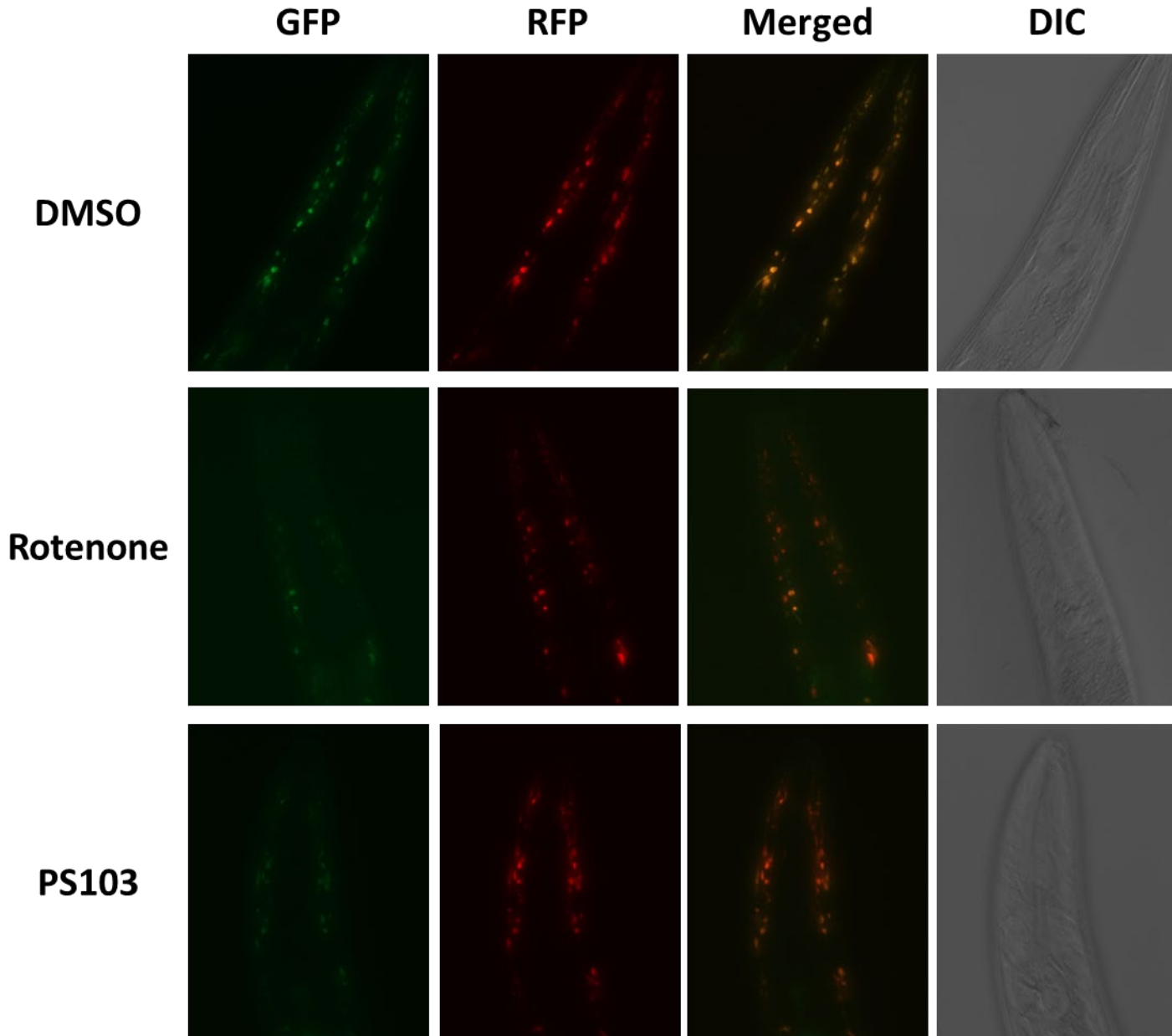
**PS135**



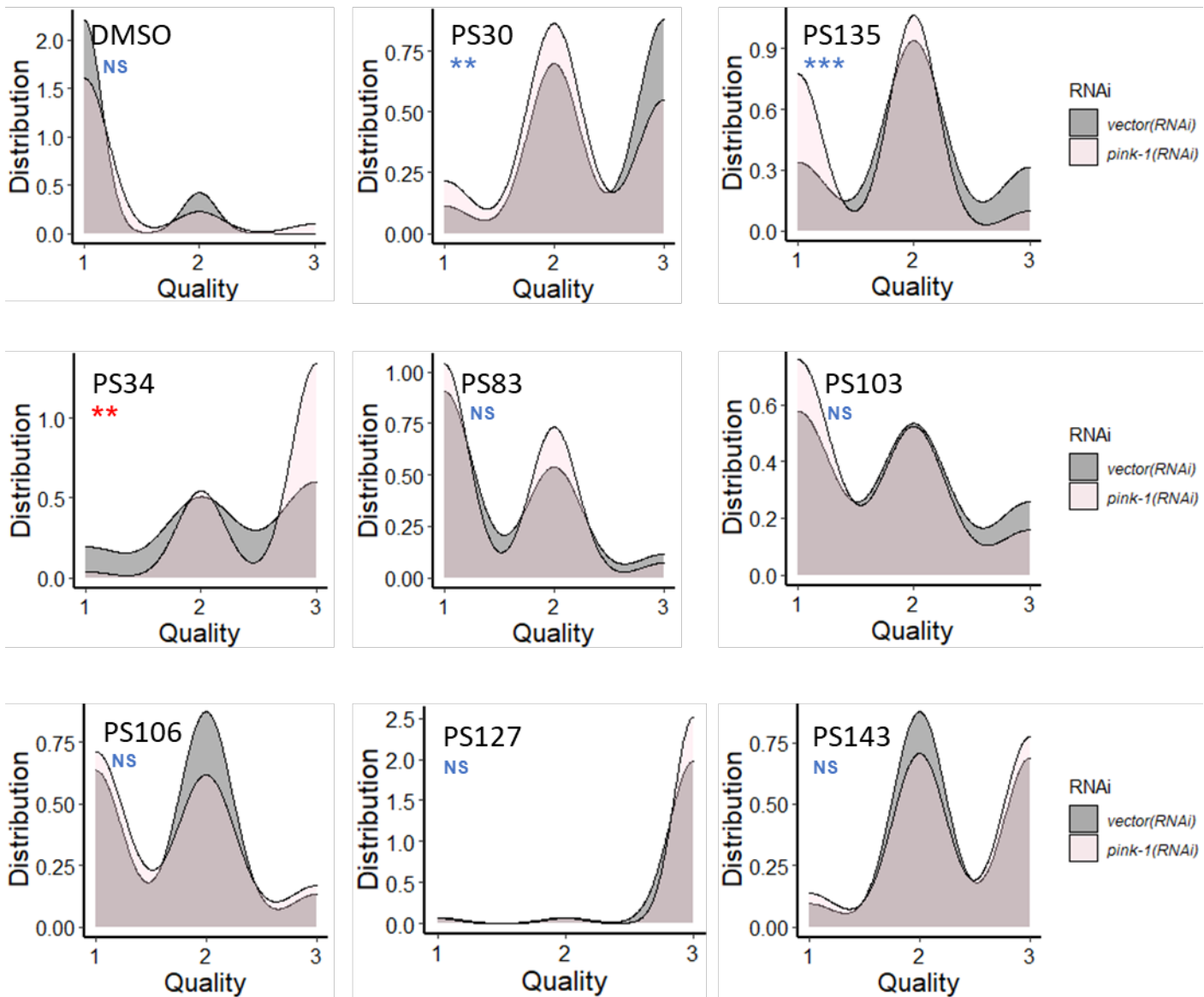
**PS143**



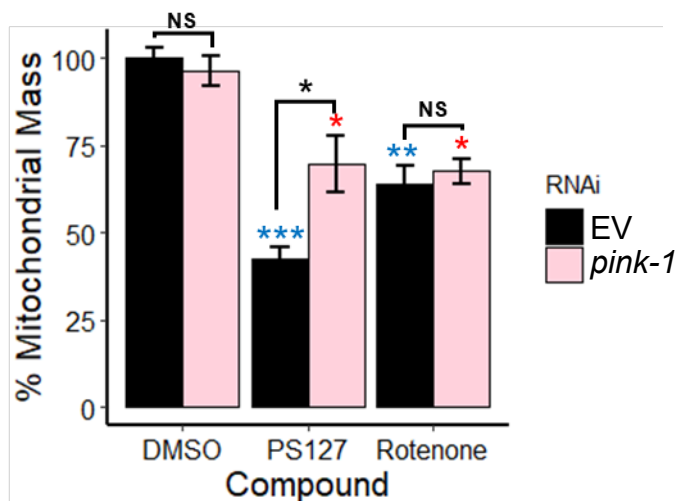
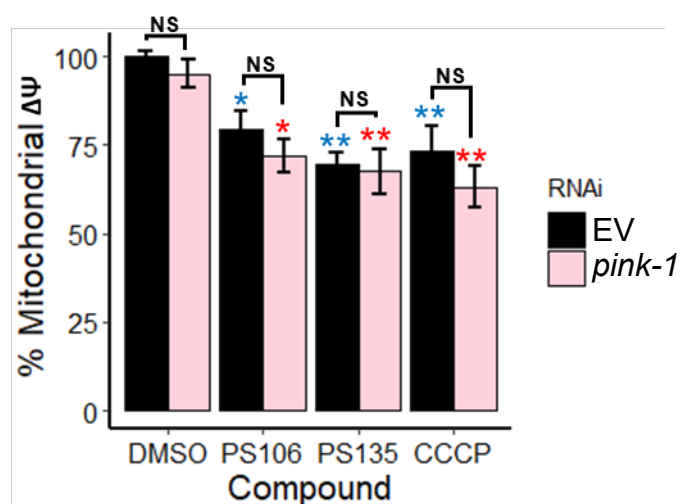
**Figure S1. Chemical structures of the eight PS compounds.**



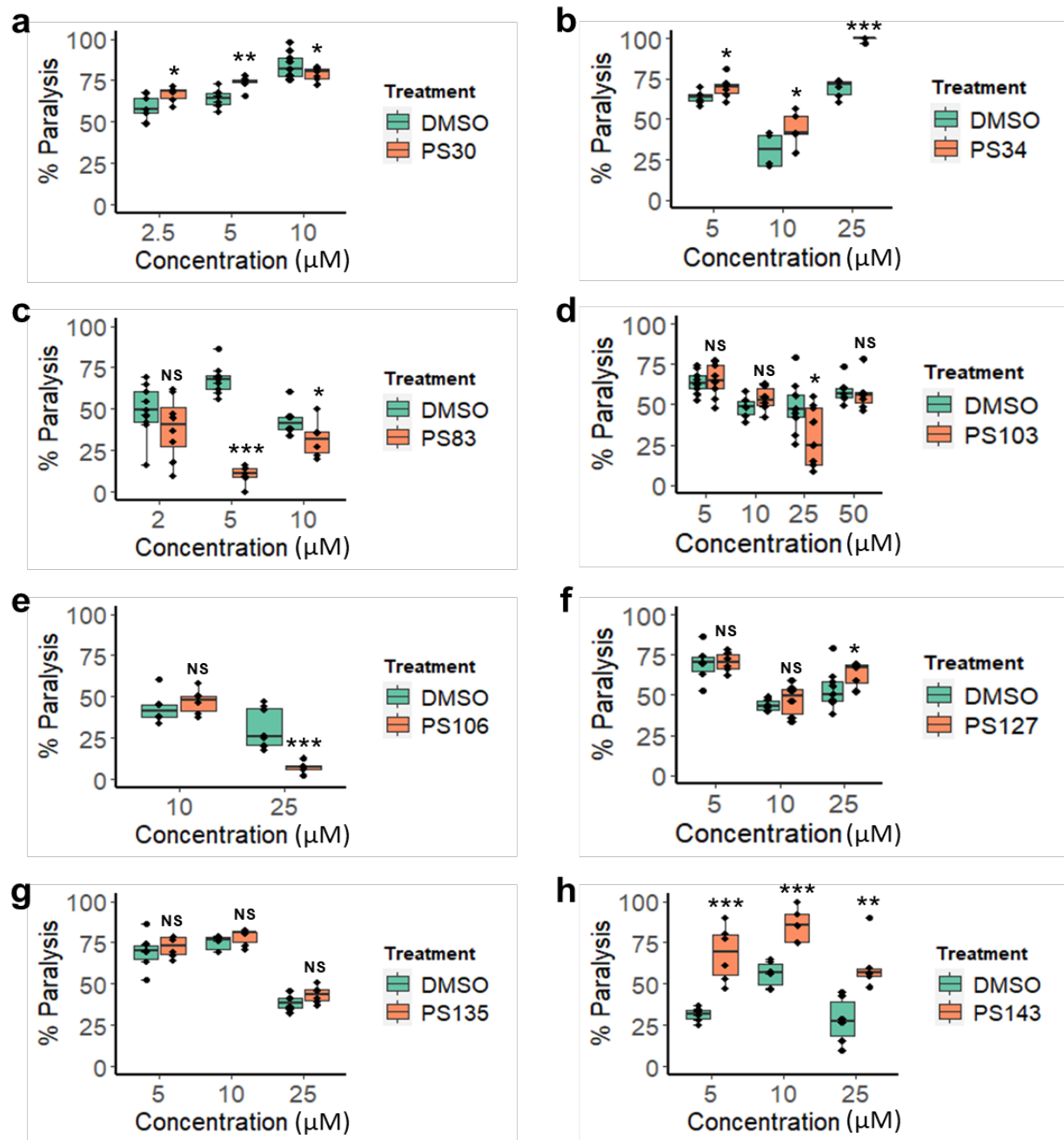
**Figure S2. PS compounds induced mitophagy as observed by utilizing the Rosella<sup>mt</sup> reporter.** Fluorescent (GFP, RFP, and merged) and DIC images of *C. elegans* strains expressing mitochondria-localized Rosella biosensor upon treatment with DMSO, 50  $\mu$ M rotenone, or 50  $\mu$ M PS103.



**Figure S3. Two PS compounds, PS30 and PS135, were partially dependent on PINK-1/PINK1 in inducing mitochondrial fragmentation.** Distribution plot of mitochondrial quality upon 18 h of exposure to PS compounds or DMSO control in *C. elegans* carrying *Pmyo-3::GFP<sup>mt</sup>* reared on empty vector or *pink-1(RNAi)*. Chi-square statistic tests were performed, and *p*-values were indicated on graphs. Three biological replicates of ~20 worms/replicate were analyzed.

**a****b**

**Figure S4. PS compounds' act via multiple mechanisms.** (a, b) Fluorescent quantification of (a) MitoTracker Green (mitochondrial mass) or (b) MitoTracker Red (mitochondrial membrane potential) of wild-type worms reared on vector (EV) or *pink-1*(RNAi) upon 15 h of treatment with (a) 50  $\mu$ M PS127 or 50  $\mu$ M rotenone or (b) 50  $\mu$ M PS106, 50  $\mu$ M PS135, or 10  $\mu$ M CCCP. At least three biological replicates with ~400 worms/replicate were analyzed. *p* values were determined from two-way ANOVA, followed by Dunnett's test. All fold changes were normalized to EV-DMSO control (at 100%). NS not significant, \**p* < 0.05, \*\* *p* < 0.01, \*\*\* *p* < 0.001. Blue stars indicate significance of change compared to EV-DMSO, red stars indicate significance of change compared to *pink-1*(RNAi)-DMSO, and black stars indicate significance of change between EV and *pink-1*(RNAi) for each compound.



**Figure S5. Three PS compounds reduced the rate of paralysis in *C. elegans* Alzheimer's model.** Percent paralysis of *C. elegans* GMC101 that expresses full-length human beta-amyloid upon treatment with (a-h) DMSO control compared to (a) PS30, (b) PS34, (c) PS83, (d) PS103, (e) PS106, (f) PS127, (g) PS135, and (h) PS143. Concentrations of PS compounds were indicated on the graphs. At least three biological replicates with ~180 worms/replicate were analyzed.  $p$  values were determined from Student's  $t$ -test. NS not significant, \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ .

**Table S1. Chemical information of the eight PS compounds.**

| Compound | Library Source | MW (Da) | LogP | Polar area | Donor | Acceptor | Bonds |
|----------|----------------|---------|------|------------|-------|----------|-------|
| PS30     | ChemBridge     | 244.67  | 3.4  | 52.0       | 1     | 3        | 1     |
| PS34     | ChemBridge     | 275.15  | 3.9  | 64.2       | 0     | 4        | 3     |
| PS83     | Maybridge      | 471.00  | 5.5  | 133.0      | 0     | 7        | 7     |
| PS103    | NIHCC          | 289.50  | 5.0  | 29.5       | 1     | 2        | 2     |
| PS106    | UT_Kinase      | 342.70  | 5.1  | 12.0       | 2     | 1        | 2     |
| PS127    | ChemBridge     | 193.20  | 2.6  | 55.0       | 0     | 3        | 3     |
| PS135    | ChemBridge     | 245.13  | 3.5  | 67.2       | 1     | 3        | 1     |
| PS143    | Maybridge      | 262.72  | 3.8  | 67.2       | 0     | 4        | 2     |

| Table S2. Tanimoto coefficient of the eight PS compounds as compared to each other. |       |       |       |       |       |       |       |       |
|-------------------------------------------------------------------------------------|-------|-------|-------|-------|-------|-------|-------|-------|
|                                                                                     | PS30  | PS34  | PS83  | PS103 | PS106 | PS127 | PS135 | PS143 |
| PS30                                                                                | 1     |       |       |       |       |       |       |       |
| PS34                                                                                | 0.291 | 1     |       |       |       |       |       |       |
| PS83                                                                                | 0.134 | 0.158 | 1     |       |       |       |       |       |
| PS103                                                                               | 0.104 | 0.139 | 0.144 | 1     |       |       |       |       |
| PS106                                                                               | 0.192 | 0.167 | 0.157 | 0.135 | 1     |       |       |       |
| PS127                                                                               | 0.119 | 0.126 | 0.183 | 0.218 | 0.110 | 1     |       |       |
| PS135                                                                               | 0.218 | 0.241 | 0.175 | 0.128 | 0.195 | 0.115 | 1     |       |
| PS143                                                                               | 0.192 | 0.184 | 0.191 | 0.096 | 0.178 | 0.102 | 0.267 | 1     |