

# **Supplementary Materials**

## ***Bis-Cinnamamide Derivatives as APE/Ref-1 Inhibitors for the Treatment of Human Melanoma***

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## Analytical HPLC profile of representative compounds

The analytical HPC was conducted on Shimadzu RP-HPLC system and C18 column (250 cm × 4.60 mm) using water (0.1% TFA) as eluent A and acetonitrile (0.1 % TFA) as eluent B, over 80 min.

### (2E,2'E)-N,N'-(Dodecane-1,12-diyl)bis(3-phenylacrylamide)(Bis-cinnamoyl-1,12-dodecamethylenediamine) (2)

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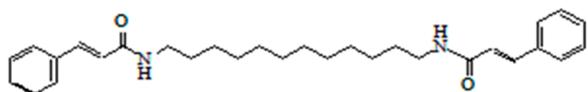
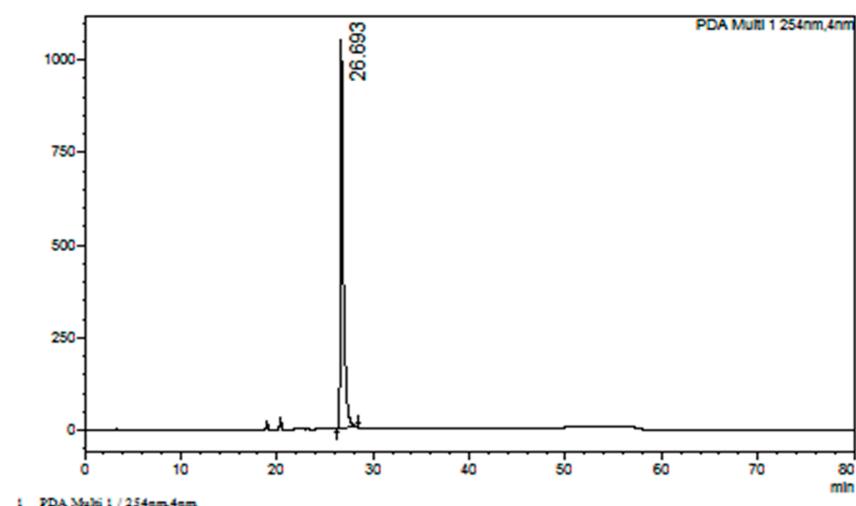
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**(2E,2'E)-N,N'-(Dodecane-1,12-diyl)bis(3-(4-hydroxyphenyl)acrylamide (4)**

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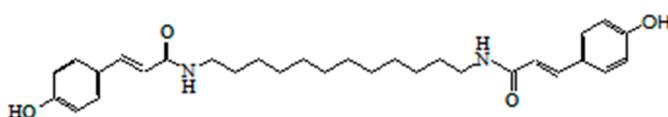
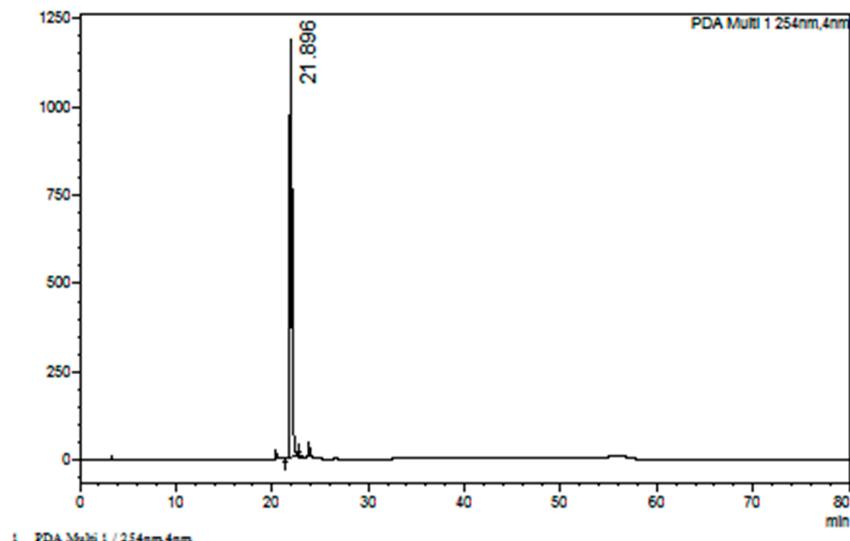
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(2E,2'E)-N,N'-(dodecane-1,12-diyl)bis(3-(3-hydroxyphenyl)acrylamide) (7)

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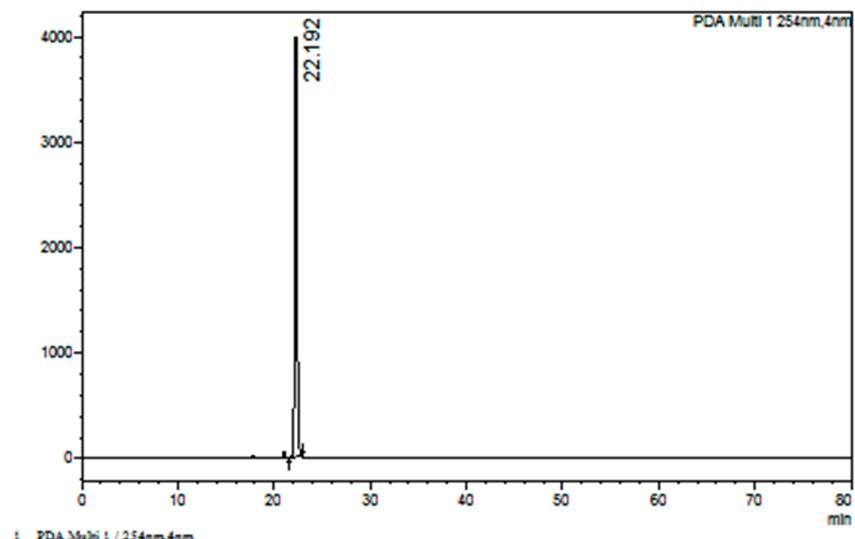
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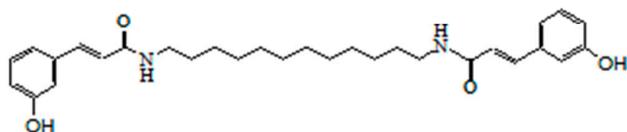
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**(E)-N-(12-Aminododecyl)-3-(3-hydroxyphenyl) acrylamide (8)**

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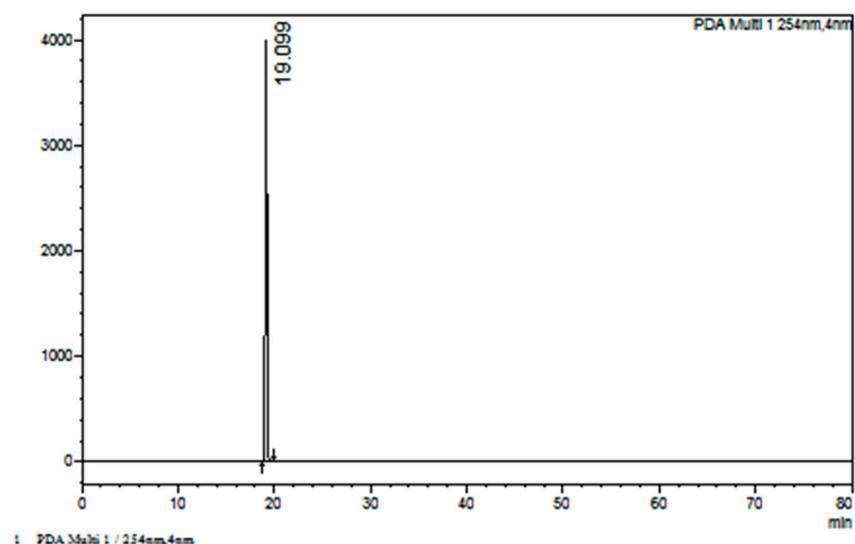
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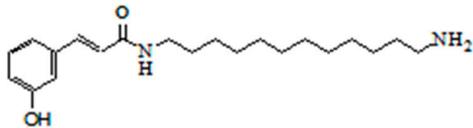
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## (E)-N-(12-Cinnamamidododecyl)-3-(3-hydroxyphenyl) acrylamide (9)

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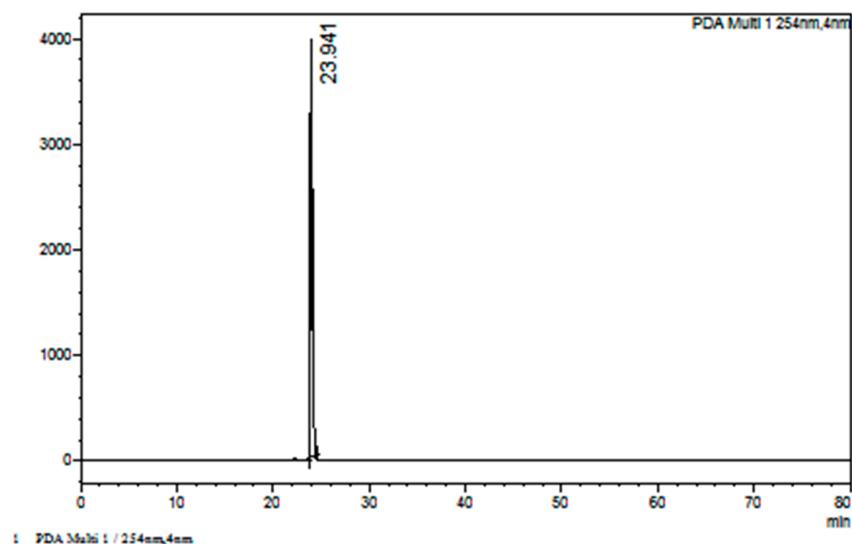
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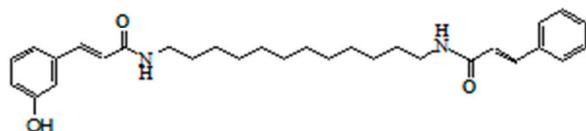
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## N-(12-Aminododecyl)cinnamamide (10)

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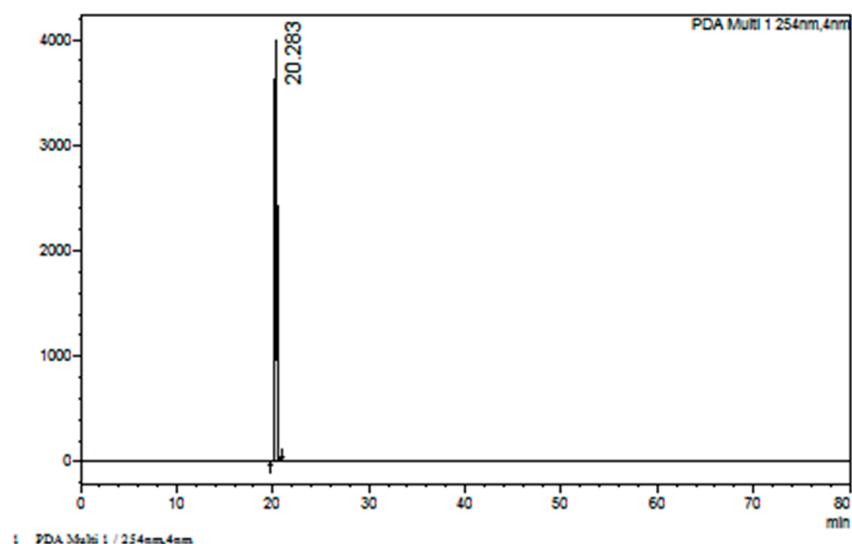
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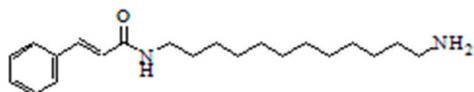
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(E)-N-(12-Cinnamamidododecyl)-3-(4-hydroxyphenyl) acrylamide (11)

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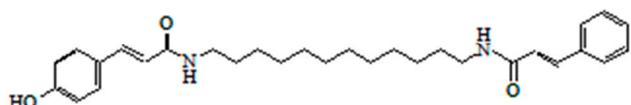
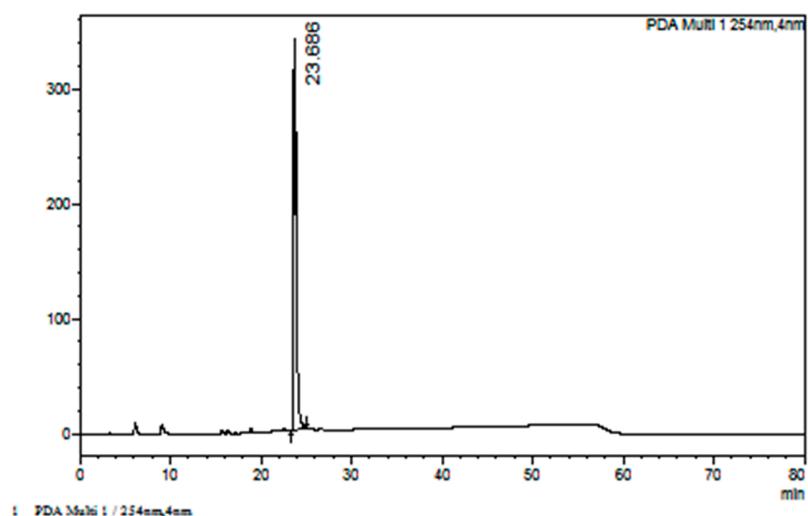
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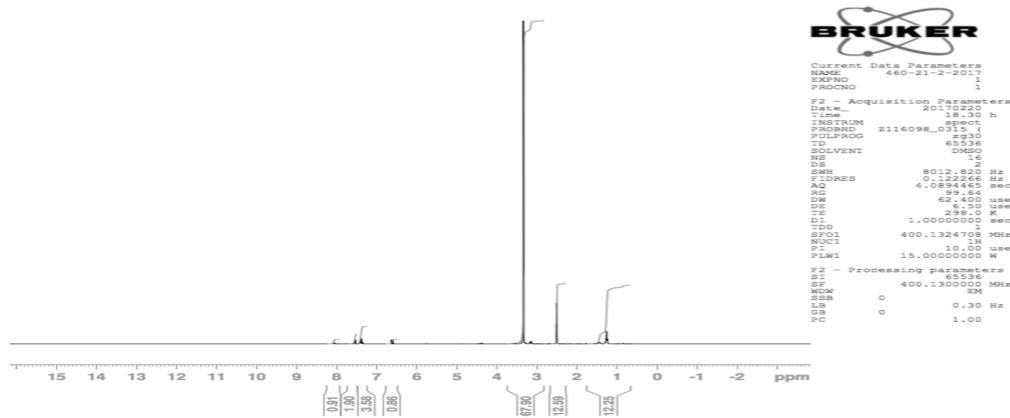
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## <sup>1</sup>H NMR, <sup>13</sup>C NMR, and Mass Spectra of Compounds



**Figure S1.** <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) of (2E,2'E)-bis-cinnamoyl-1,12-dodecamethylenediamine (**2**).

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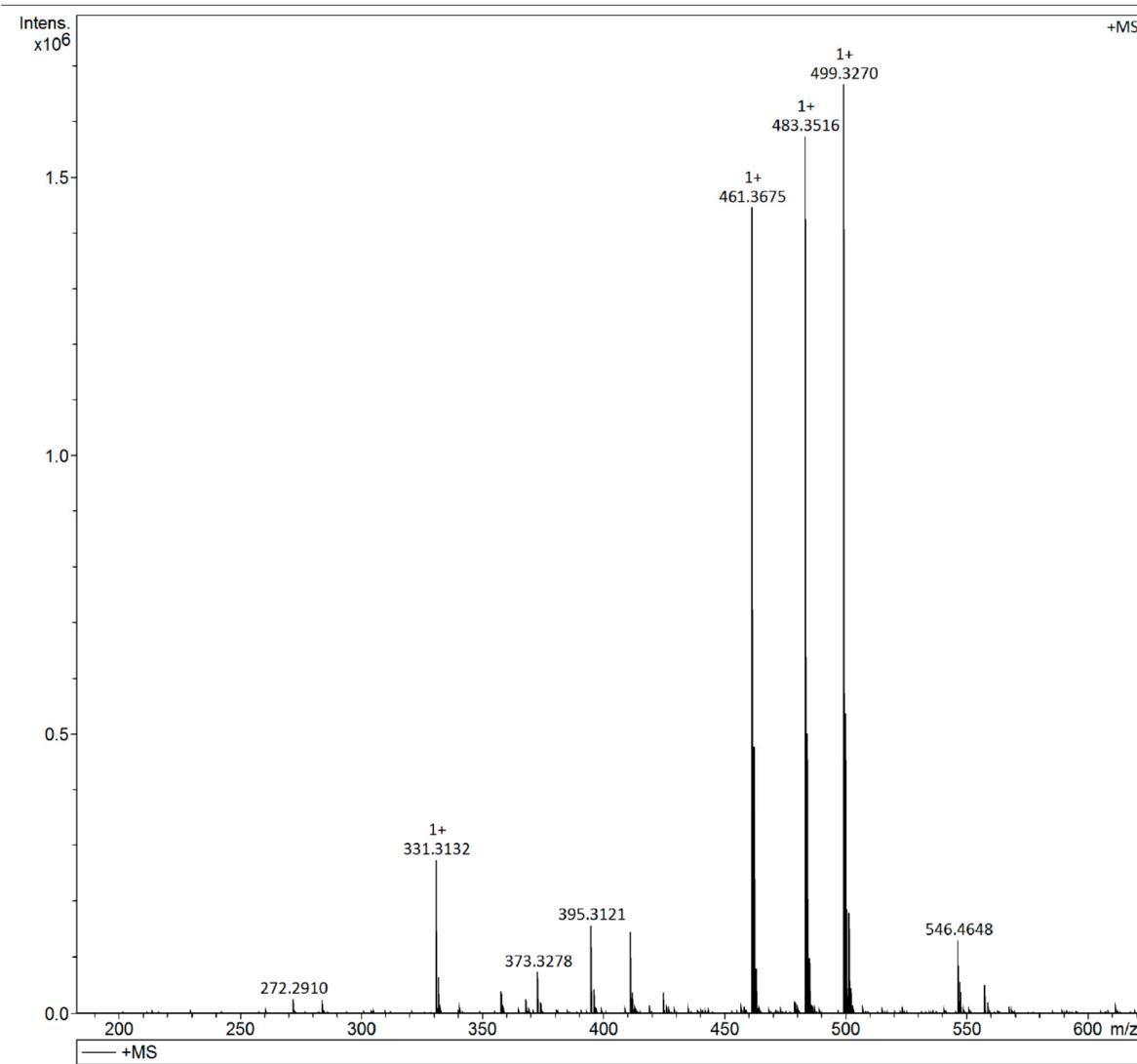
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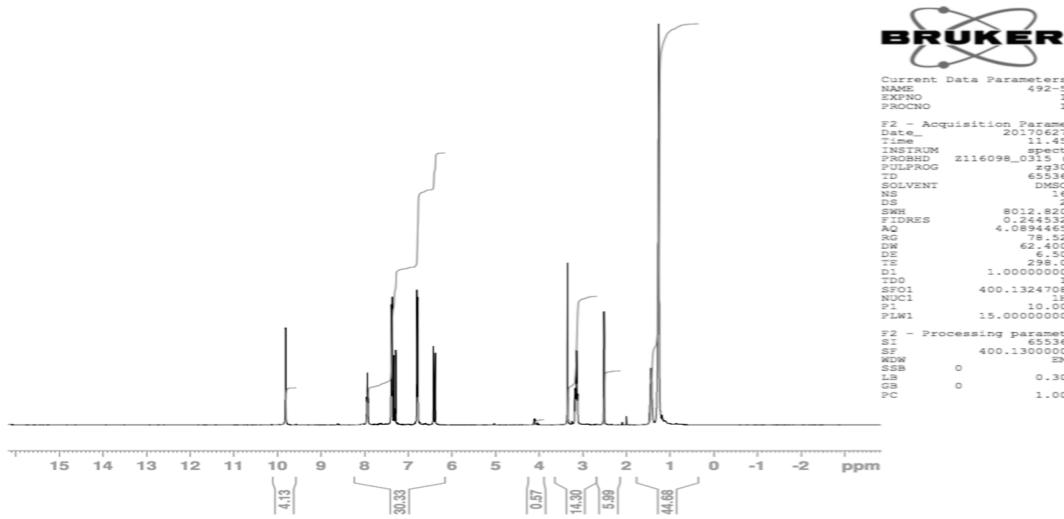
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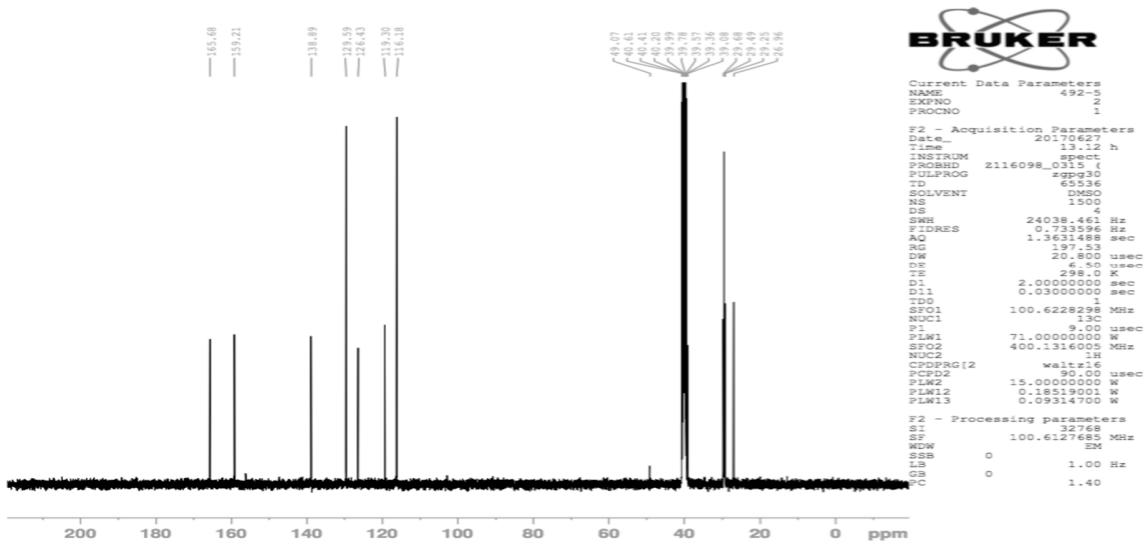
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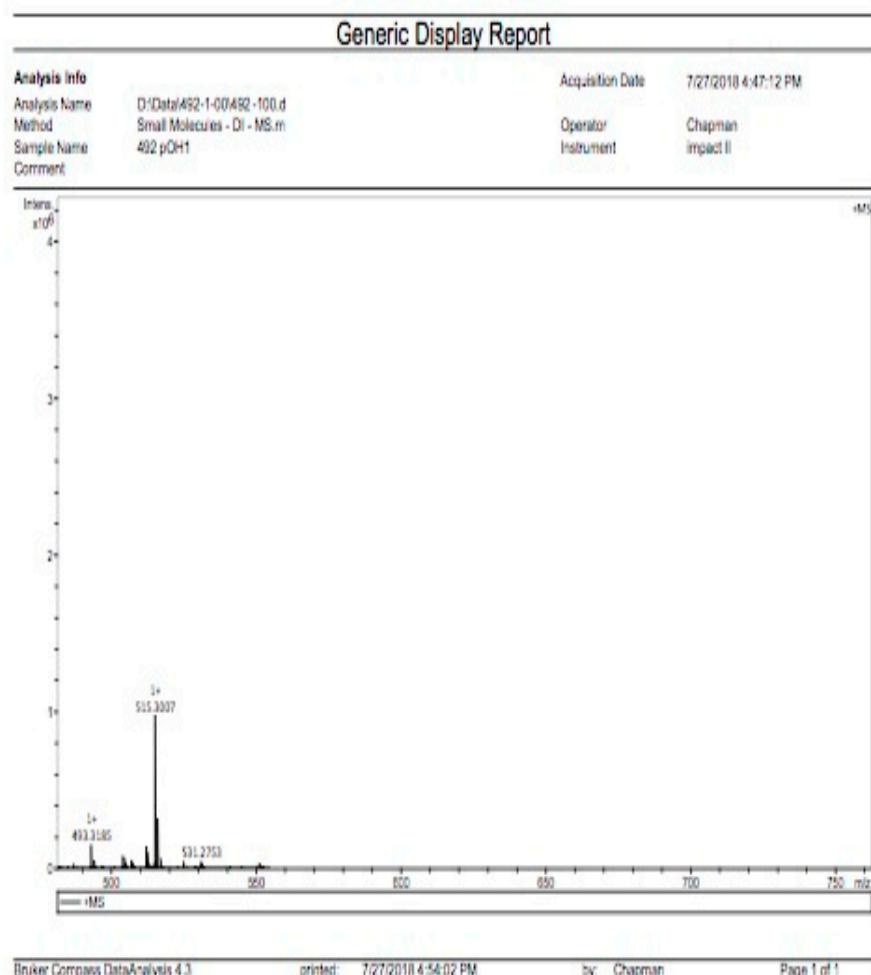
**Figure S3.** Mass spectra of (2E,2'E)-bis-cinnamoyl-1,12-dodecamethylenediamine (**2**).



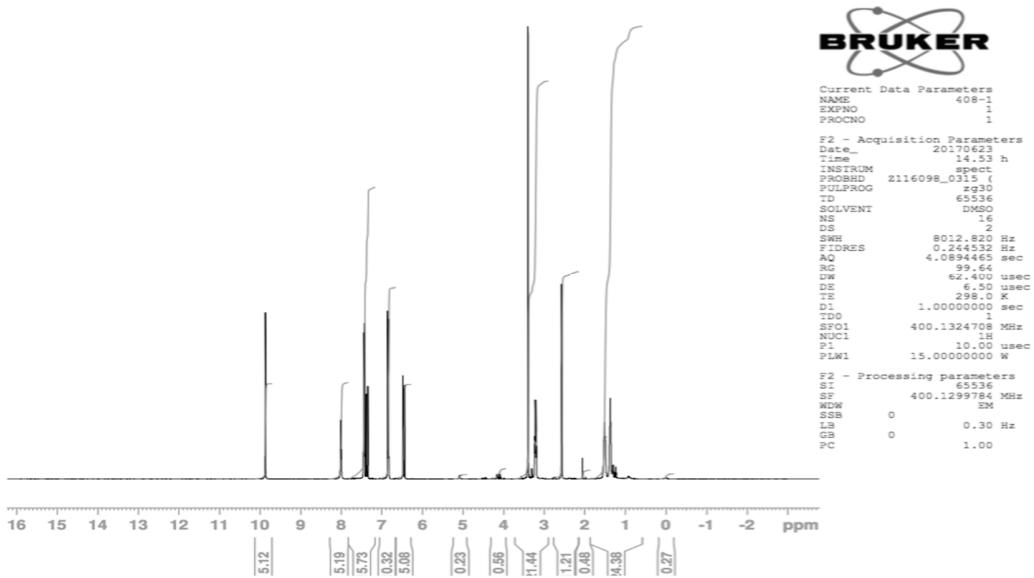
**Figure S4.**  $^1\text{H}$  NMR (400 MHz, DMSO- $\text{d}_6$ ) of (2E,2'E)- $N,N'$ -(dodecane-1,12-diyl)bis(3-(4-hydroxyphenyl)acrylamide (**4**).



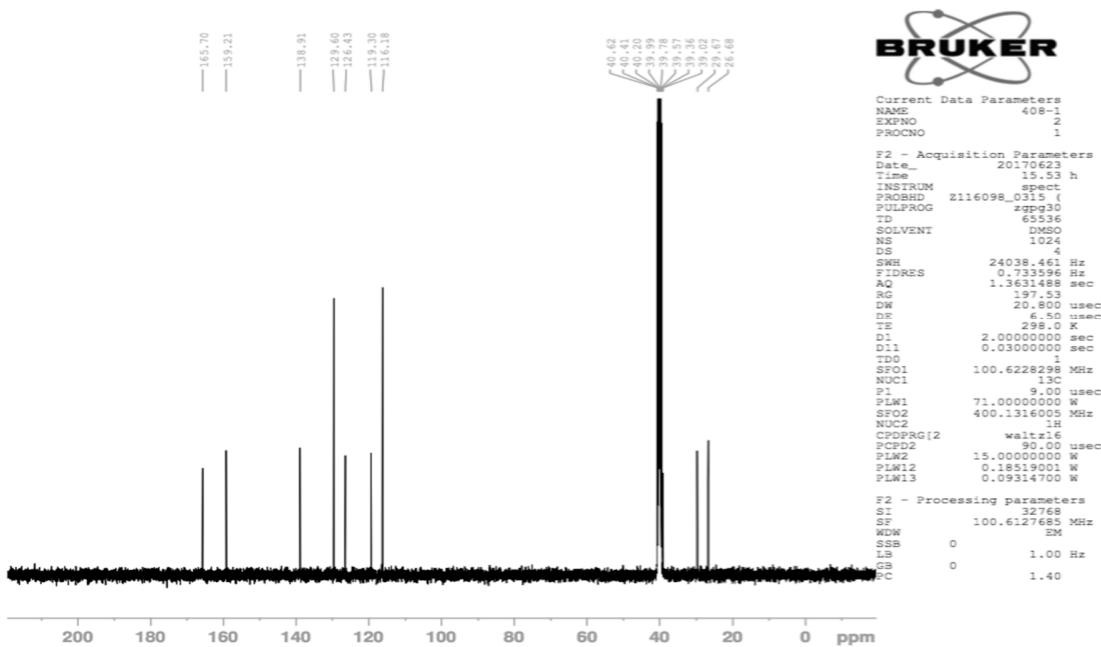
**Figure S5.**  $^{13}\text{C}$  NMR (100 MHz, DMSO- $\text{d}_6$ ) of (2E,2'E)-*N,N'*-(dodecane-1,12-diyl)bis(3-(4-hydroxyphenyl) acrylamide (**4**).



**Figure S6.** Mass spectra of (2E,2'E)-*N,N'*-(dodecane-1,12-diyl)bis(3-(4-hydroxyphenyl)acrylamide (**4**).



**Figure S7.**  $^1\text{H}$  NMR (400 MHz, DMSO- $\text{d}_6$ ) of (2E,2'E)- $N,N'$ -(hexane-1,6-diyl)bis(3-(4-hydroxyphenyl)acrylamide) (**5**).



**Figure S8.**  $^{13}\text{C}$  NMR (100 MHz, DMSO- $\text{d}_6$ ) of (2E,2'E)- $N,N'$ -(hexane-1,6-diyl) bis(3-(4-hydroxyphenyl) acrylamide) (**5**).

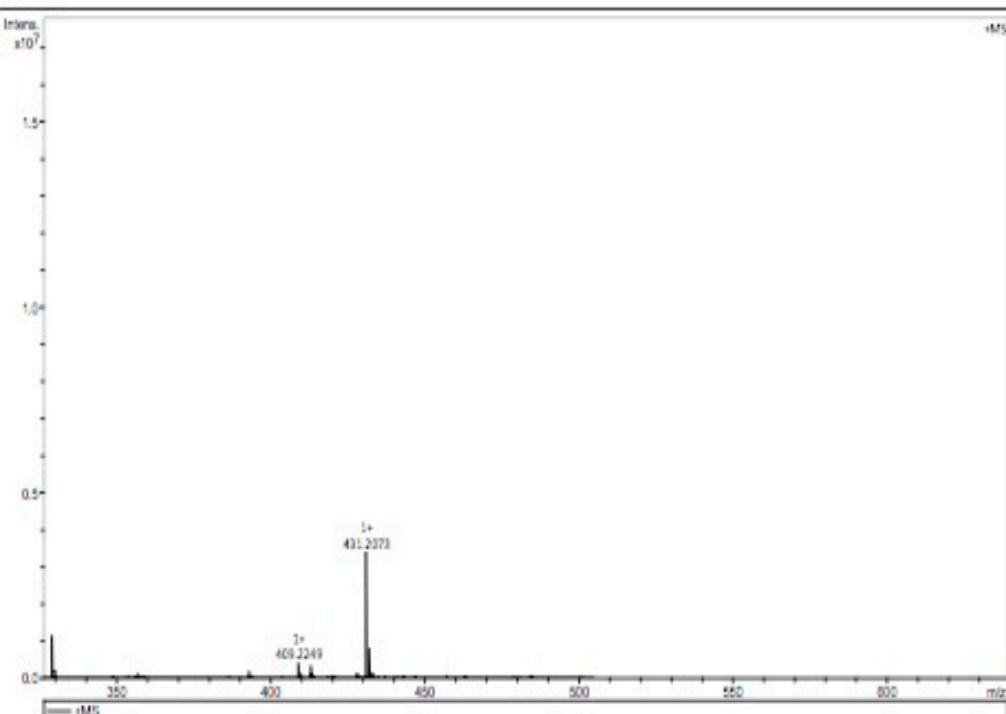
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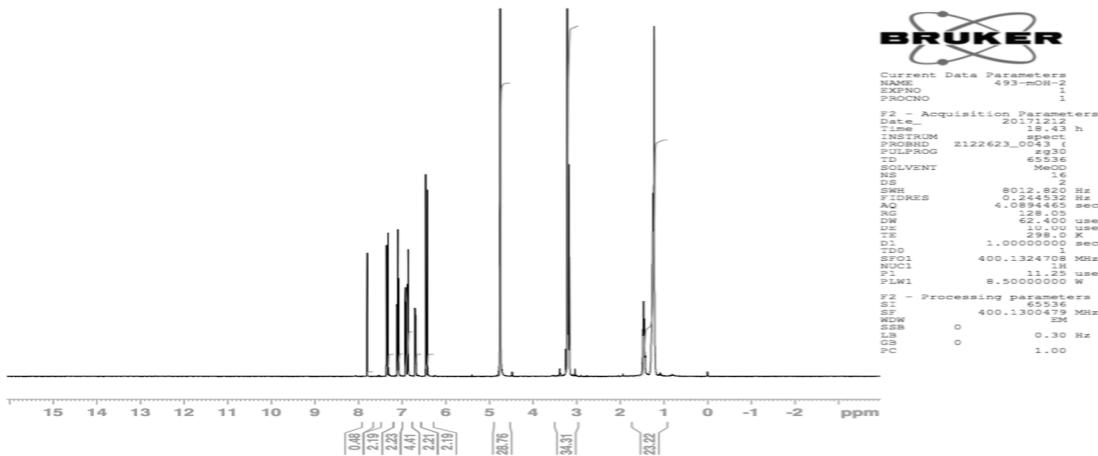
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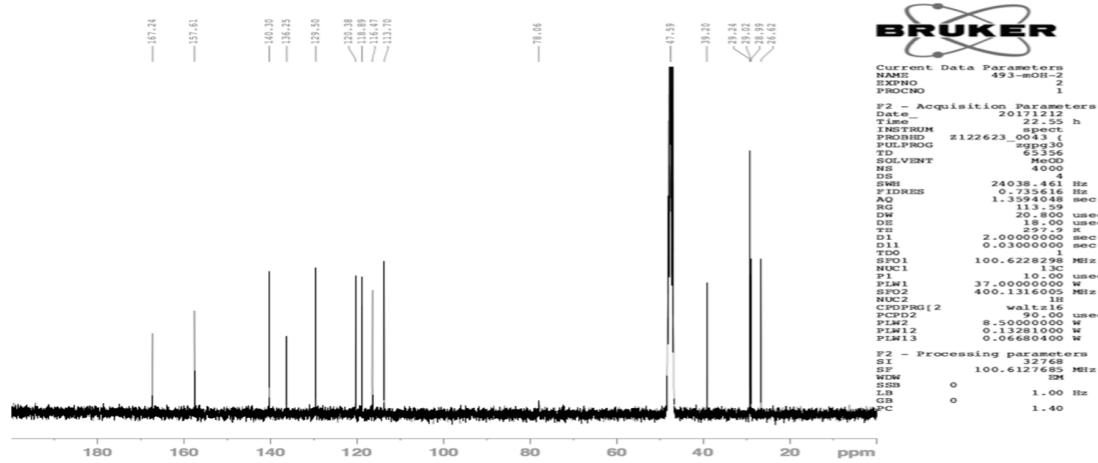
by: Chapman

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**Figure S9.** Mass spectra of (2E,2'E)-N,N'-(hexane-1,6-diyl) bis(3-(4-hydroxyphenyl) acrylamide) (**5**).



**Figure S10.**  $^1\text{H}$  NMR (400 MHz, DMSO-d<sub>6</sub>) of (2E,2'E)-N,N'-(dodecane-1,12-diyl)bis(3-(3-hydroxyphenyl)acrylamide) (7).



**Figure S11.**  $^{13}\text{C}$  NMR (100 MHz, DMSO-d<sub>6</sub>) of (2E,2'E)-N,N'-(dodecane-1,12-diyl) bis(3-(3-hydroxyphenyl) acrylamide) (7).

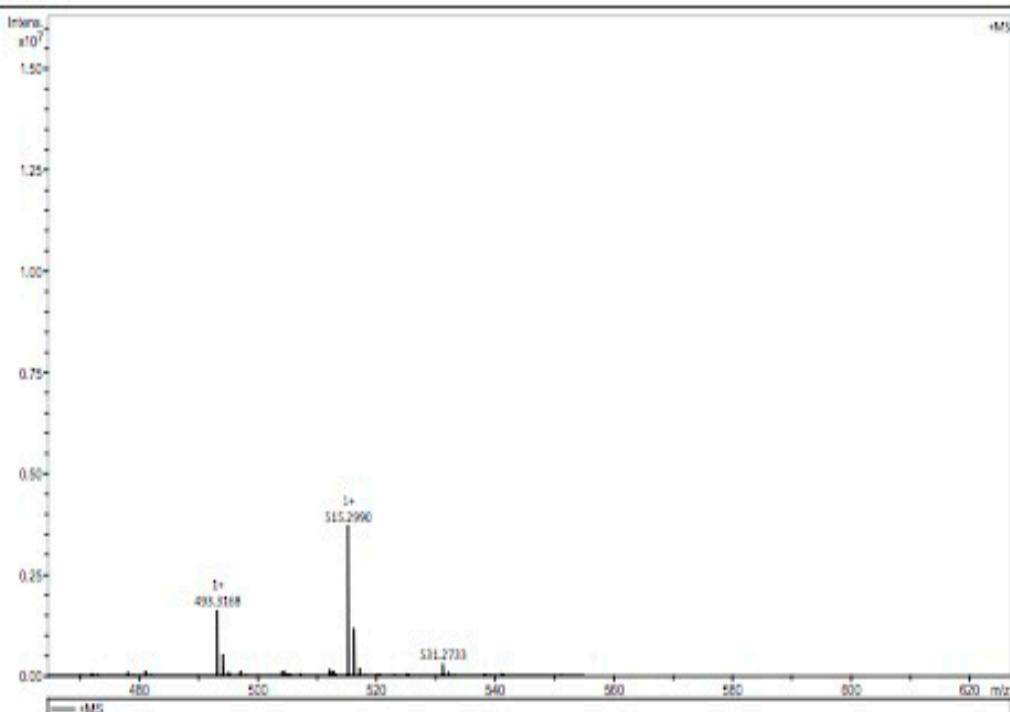
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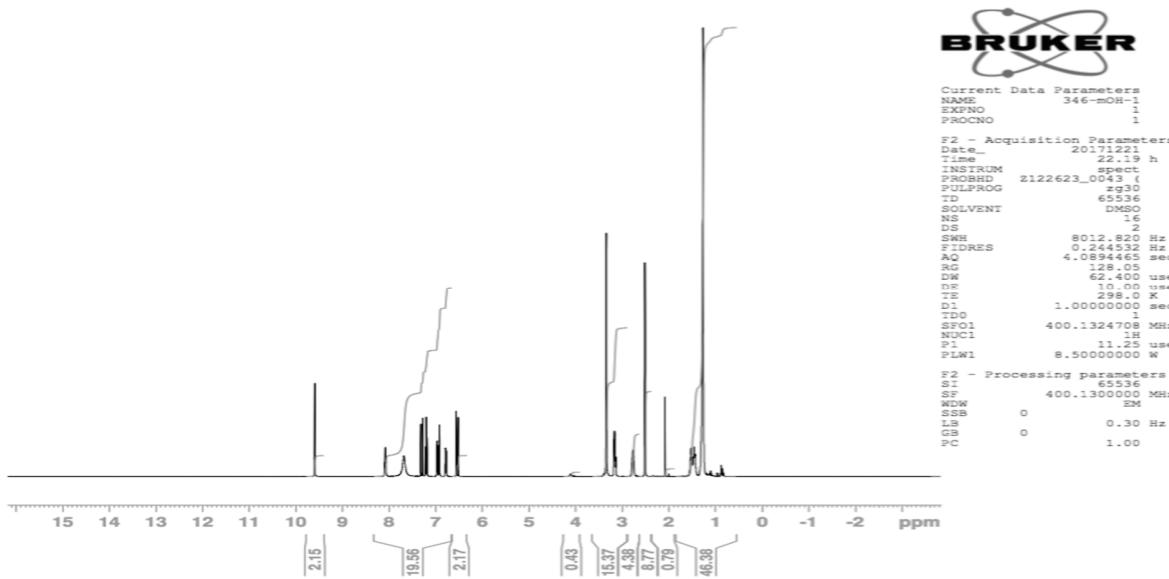
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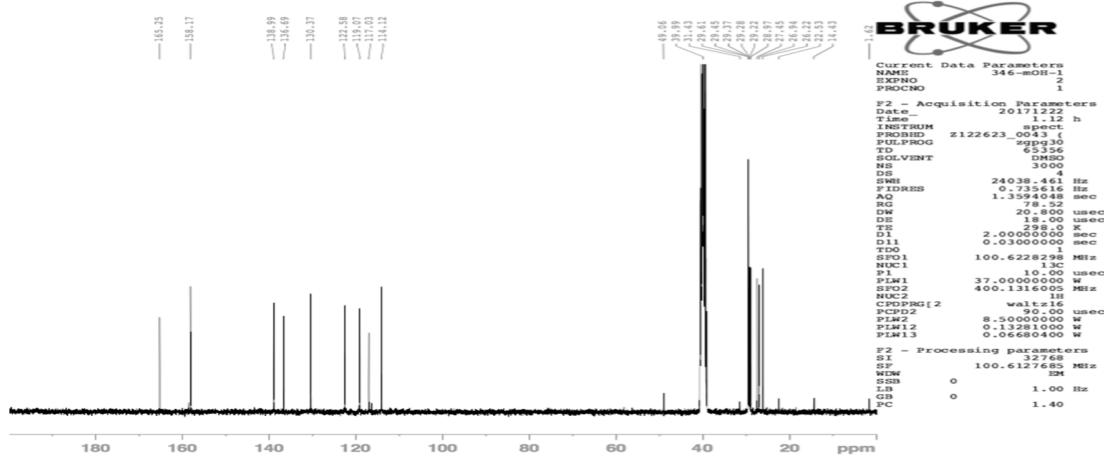
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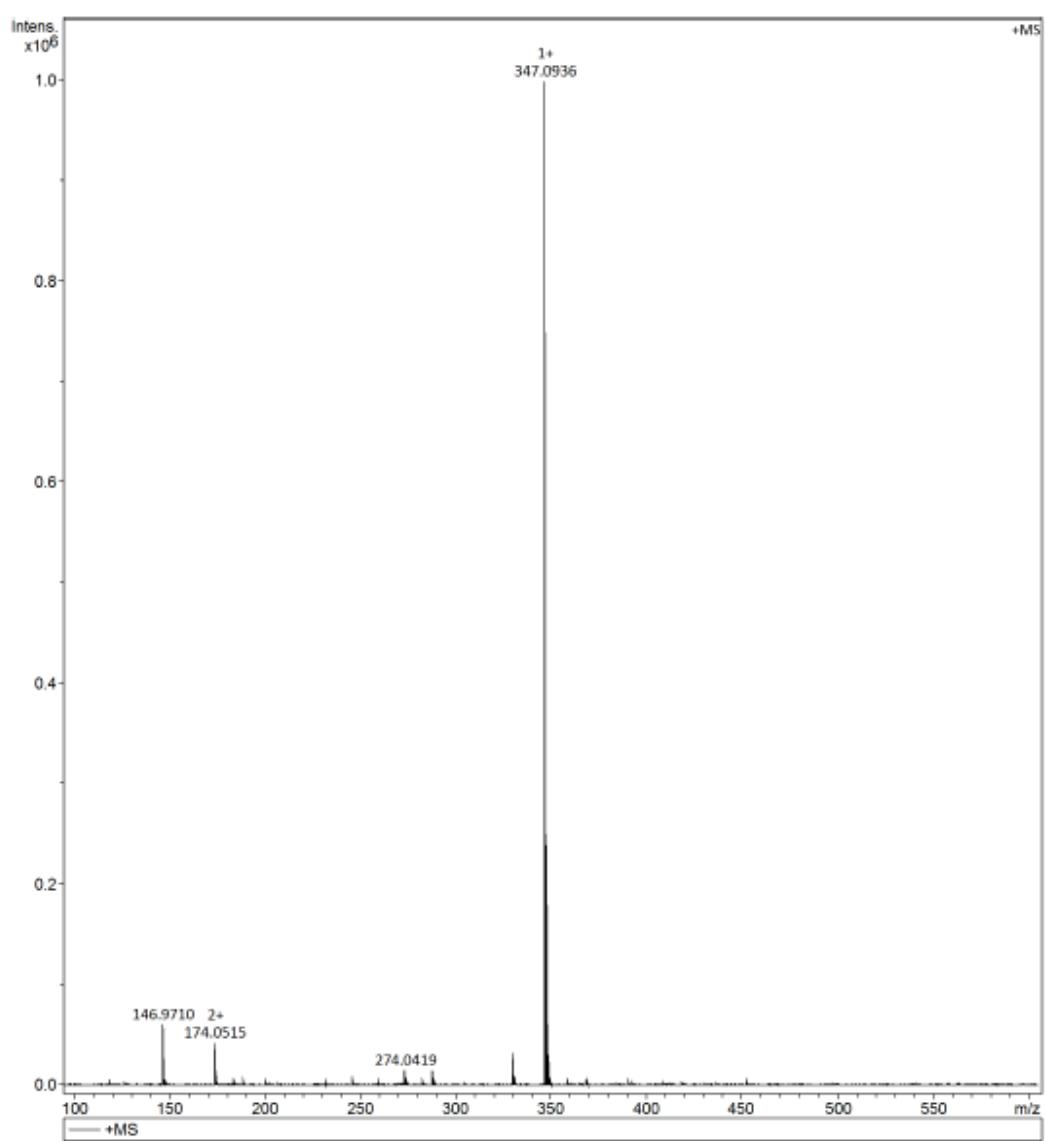
**Figure S12.** Mass spectra of (2E,2'E)-N,N'-(dodecane-1,12-diyl) bis(3-(3-hydroxyphenyl) acrylamide) (7).



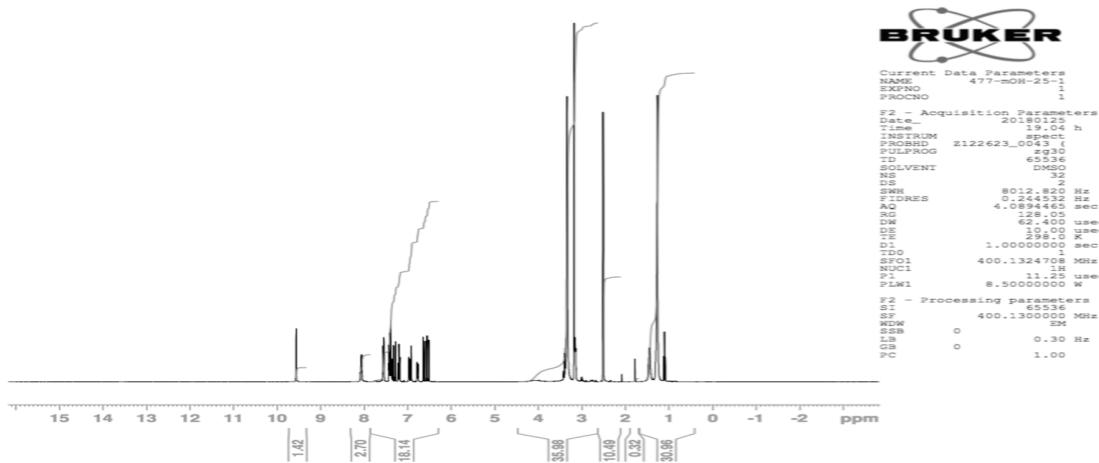
**Figure S13.**  $^1\text{H}$  NMR (400 MHz, DMSO- $\text{d}_6$ ) of (E)-*N*-(12-aminododecyl)-3-(3-hydroxyphenyl) (8).



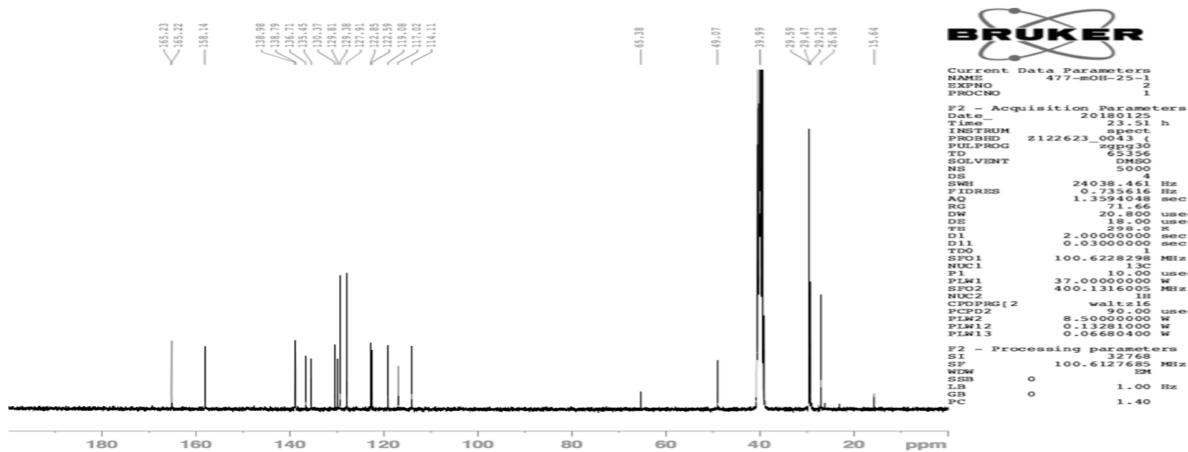
**Figure S14.**  $^{13}\text{C}$  NMR (100 MHz, DMSO- $\text{d}_6$ ) of (E)-*N*-(12-aminododecyl)-3-(3-hydroxyphenyl) (8).



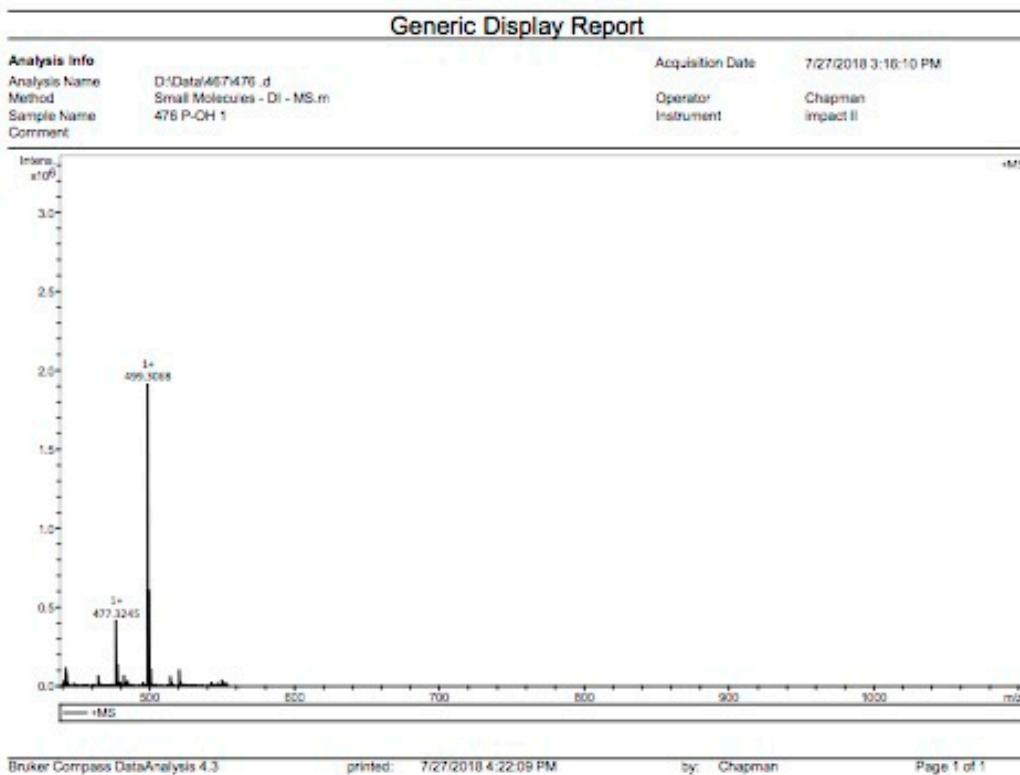
**Figure S15.** Mass spectra of (E)-N-(12-aminododecyl)-3-(3-hydroxyphenyl) (**8**).



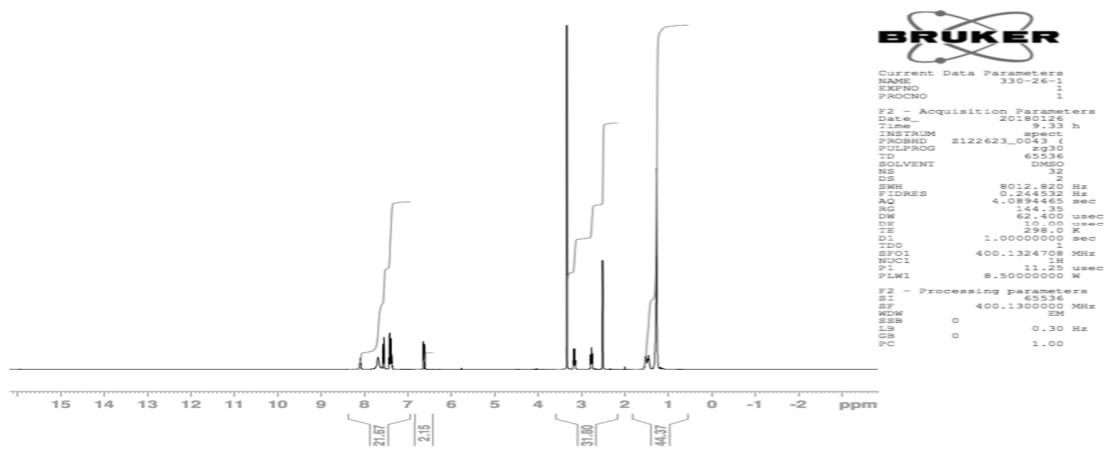
**Figure S16.** <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) of (E)-N-(12-cinnamamidododecyl)-3-(3-hydroxyphenyl) acrylamide (**9**).



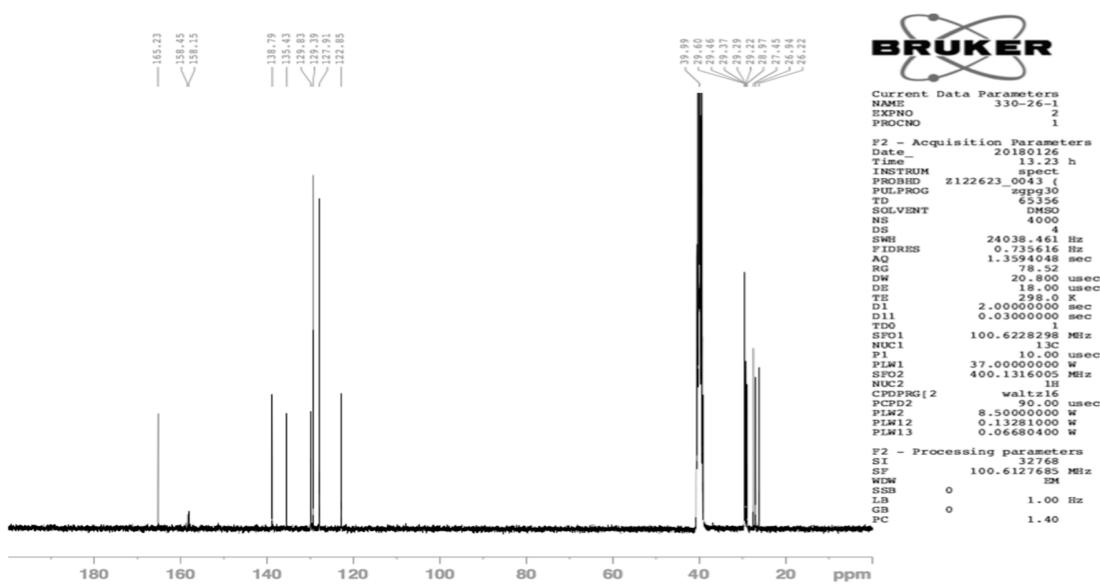
**Figure S17.** <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>) of (E)-N-(12-cinnamamidododecyl)-3-(3-hydroxyphenyl) acrylamide (**9**).



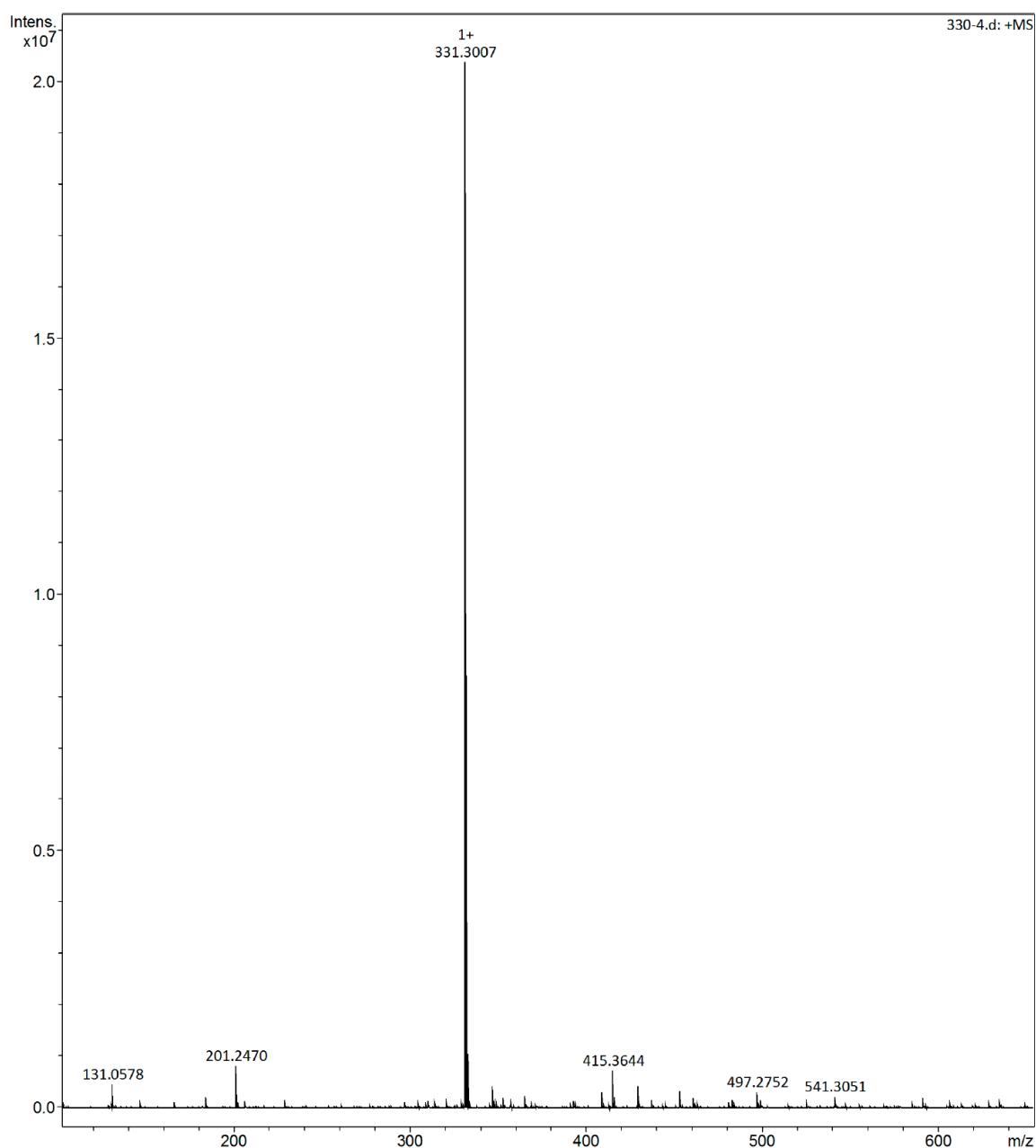
**Figure S18.** Mass spectra of (E)-N-(12-cinnamamidododecyl)-3-(3-hydroxyphenyl) acrylamide (**9**).



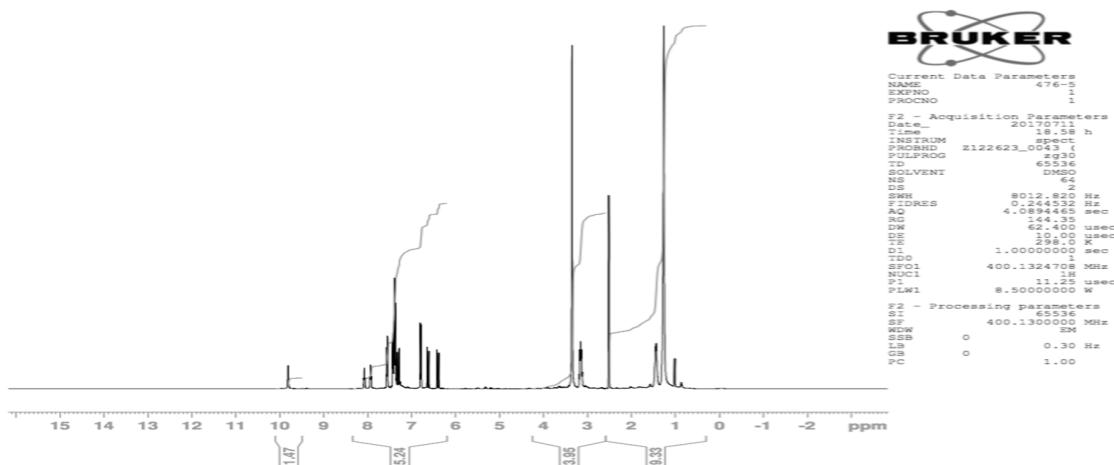
**Figure S19.**  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-d}_6$ ) of *N*-(12-aminododecyl) cinnamamide (**10**).



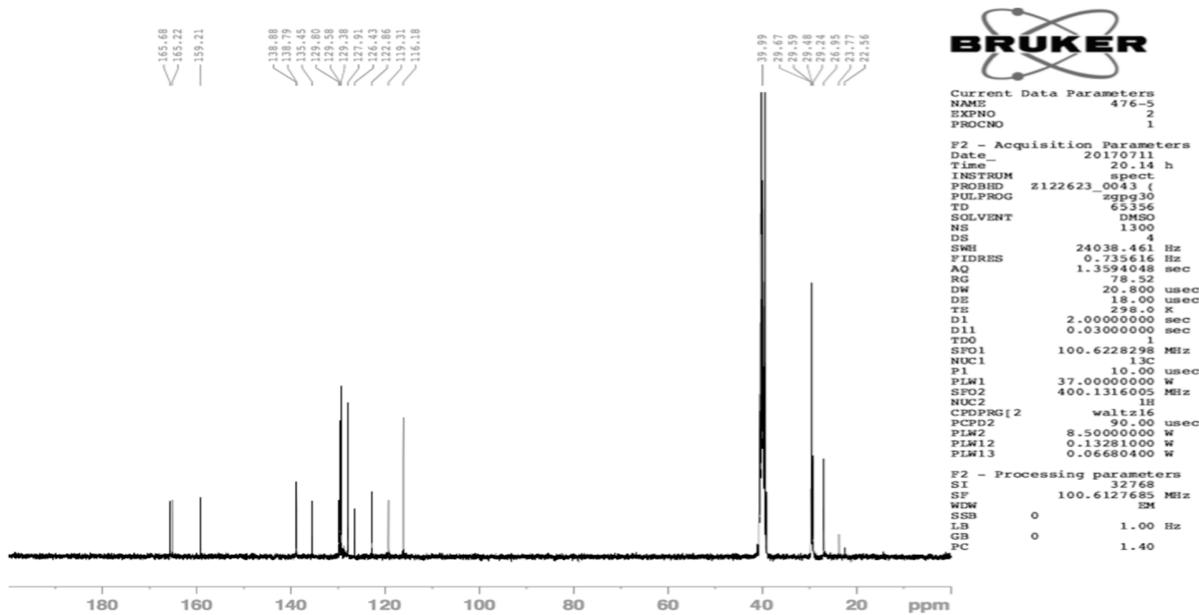
**Figure S20.**  $^{13}\text{C}$  NMR (100 MHz, DMSO-d<sub>6</sub>) of *N*-(12-aminododecyl) cinnamamide (**10**).



**Figure S21.** Mass spectra of N-(12-aminododecyl) cinnamamide (**10**).



**Figure S22.** <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) of (E)-N-(12-cinnamamidododecyl)-3-(4-hydroxyphenyl) (**11**).

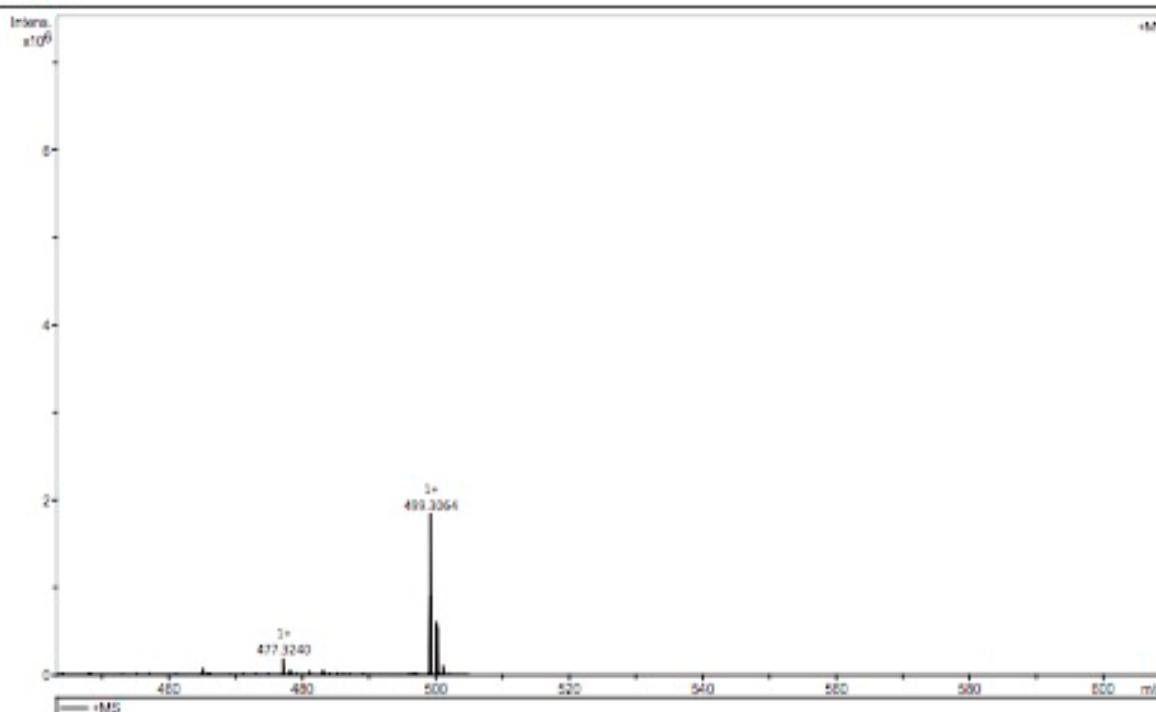


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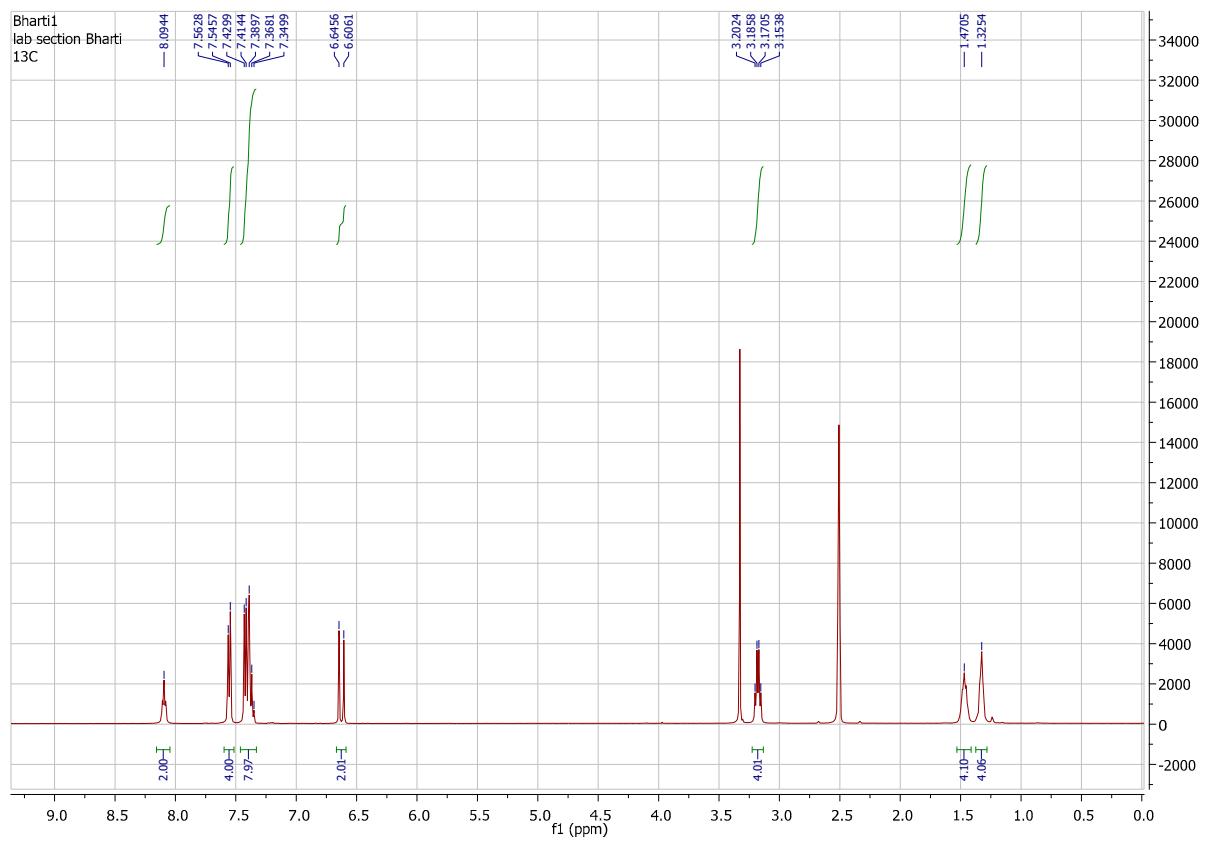
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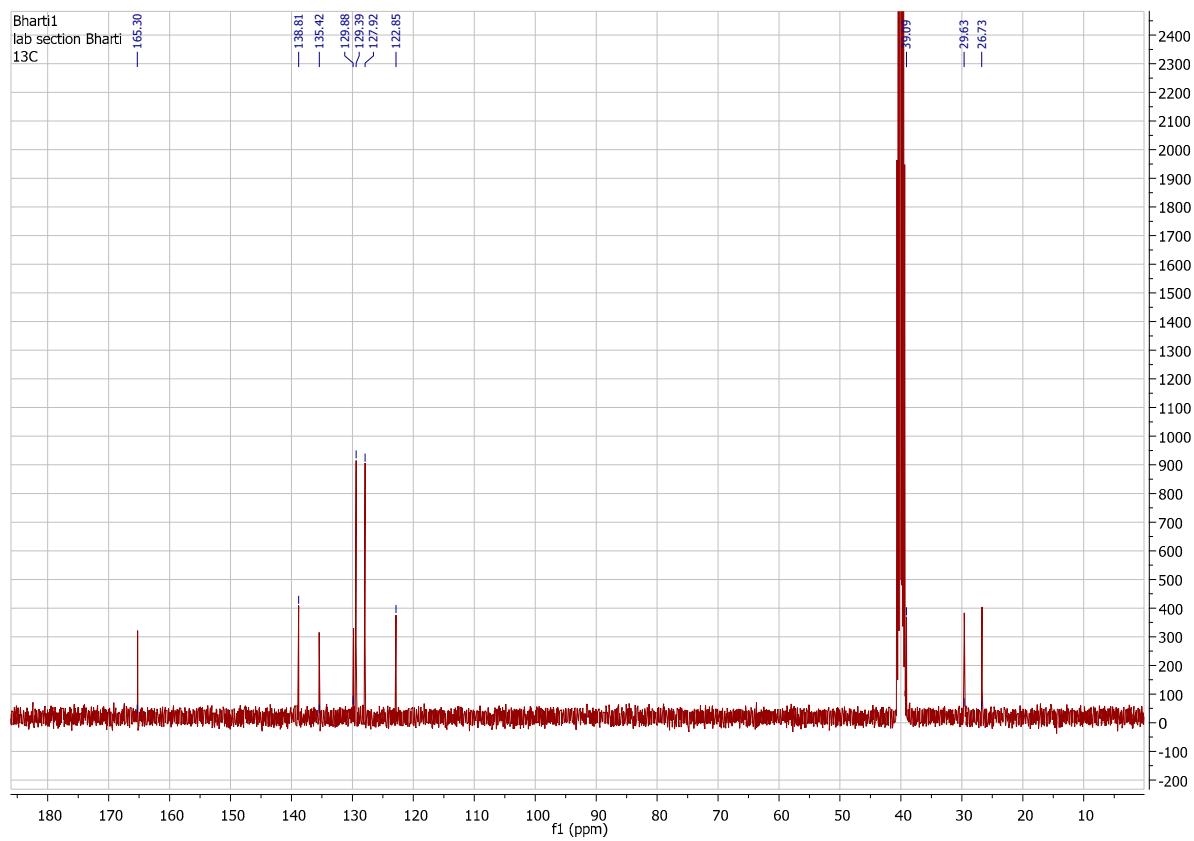
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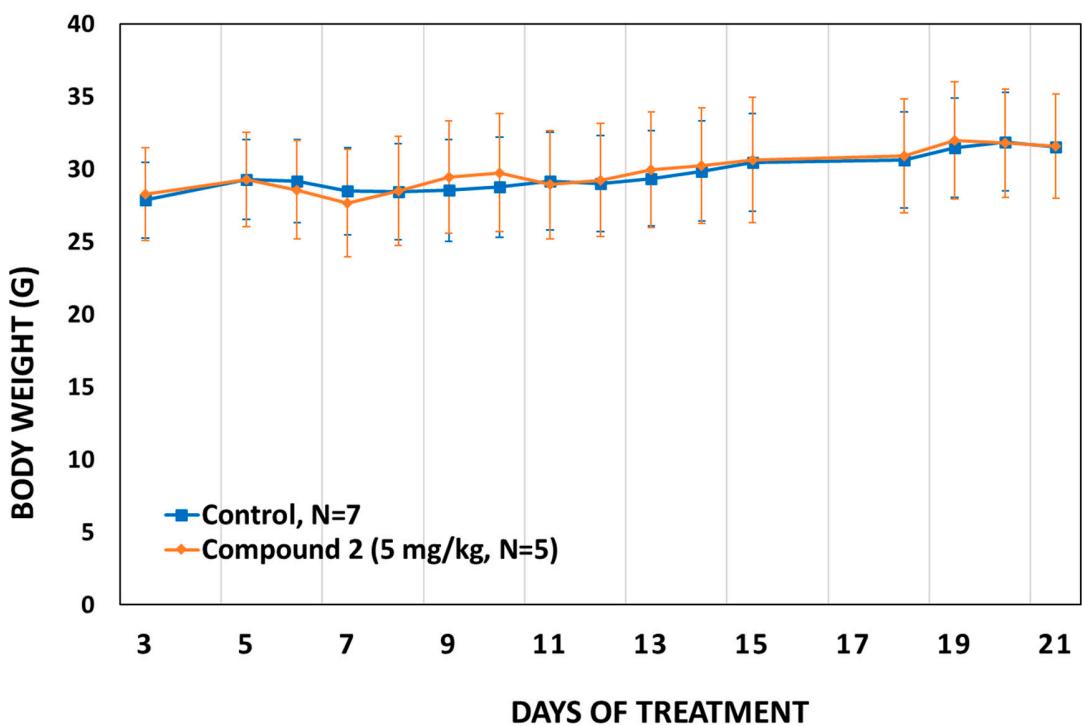
**Figure S24.** Mass spectra of (*E*)-*N*-(12-cinnamamidododecyl)-3-(4-hydroxyphenyl) (**11**).



**Figure S25.**  $^1\text{H}$  NMR (400 MHz, DMSO-d<sub>6</sub>) of (2E,2'E)-N,N'-(hexane-1,6-diyl)bis(3-phenylacrylamide) (**12**).



**Figure S26.**  $^{13}\text{C}$  NMR (100 MHz, DMSO-d<sub>6</sub>) of (2E,2'E)-N,N'-(hexane-1,6-diyl)bis(3-phenylacrylamide) (**12**).



**Figure S27.** No significant bodyweight reduction was evident in mice treated with compound 2 (5 mg/kg, *i.p.*, daily) for 21 days in a melanoma xenograft mouse model.  $P>0.05$  compared to control group.