

## **Novel PPAR- $\gamma$ Agonists as Potential Neuroprotective Agents Against Alzheimer's Disease: Rational Design, Synthesis, *In Silico* Evaluation, PPAR- $\gamma$ Binding Assay, Transactivation and Expression Studies**

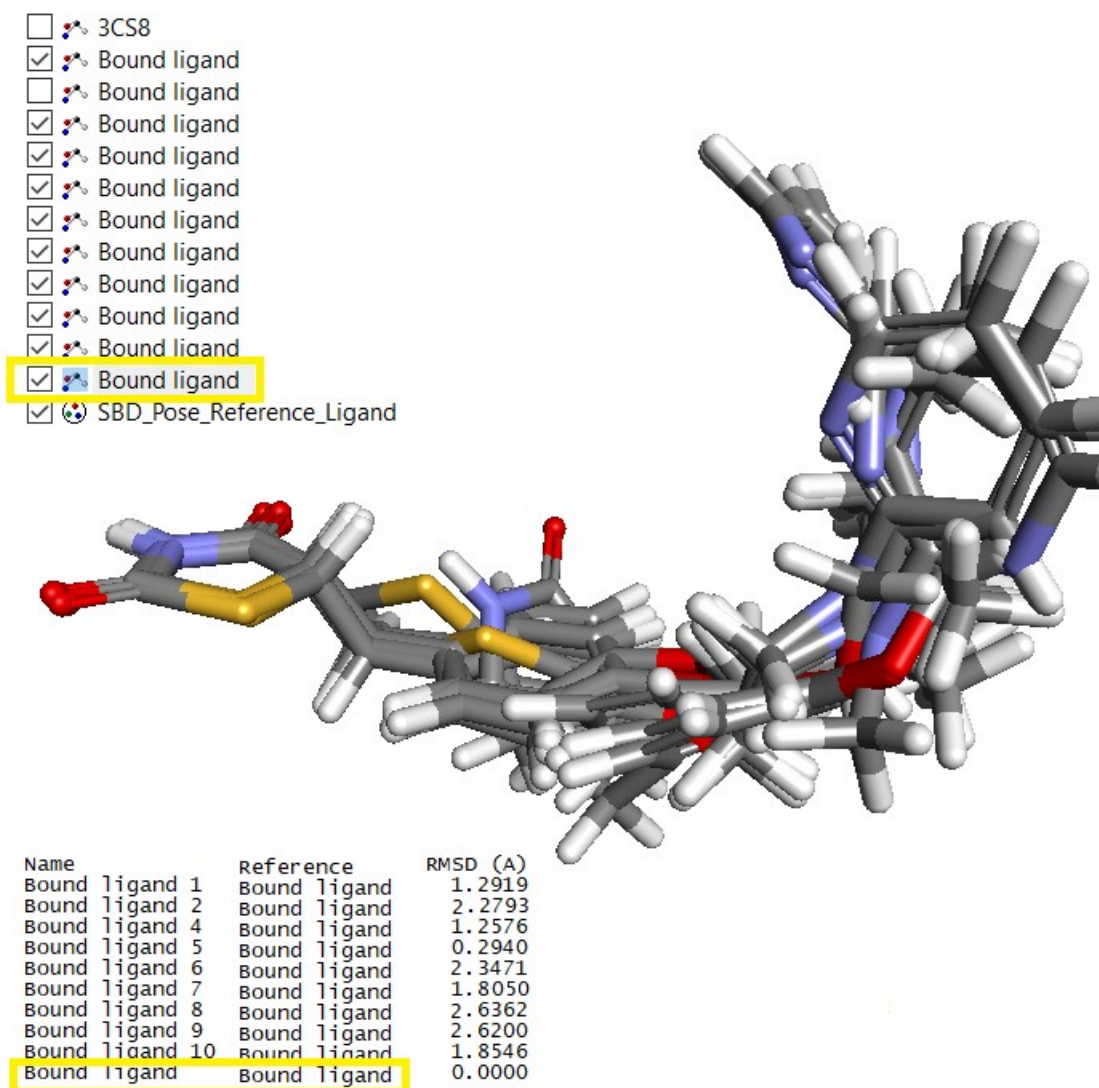
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### **Supplementary Material**

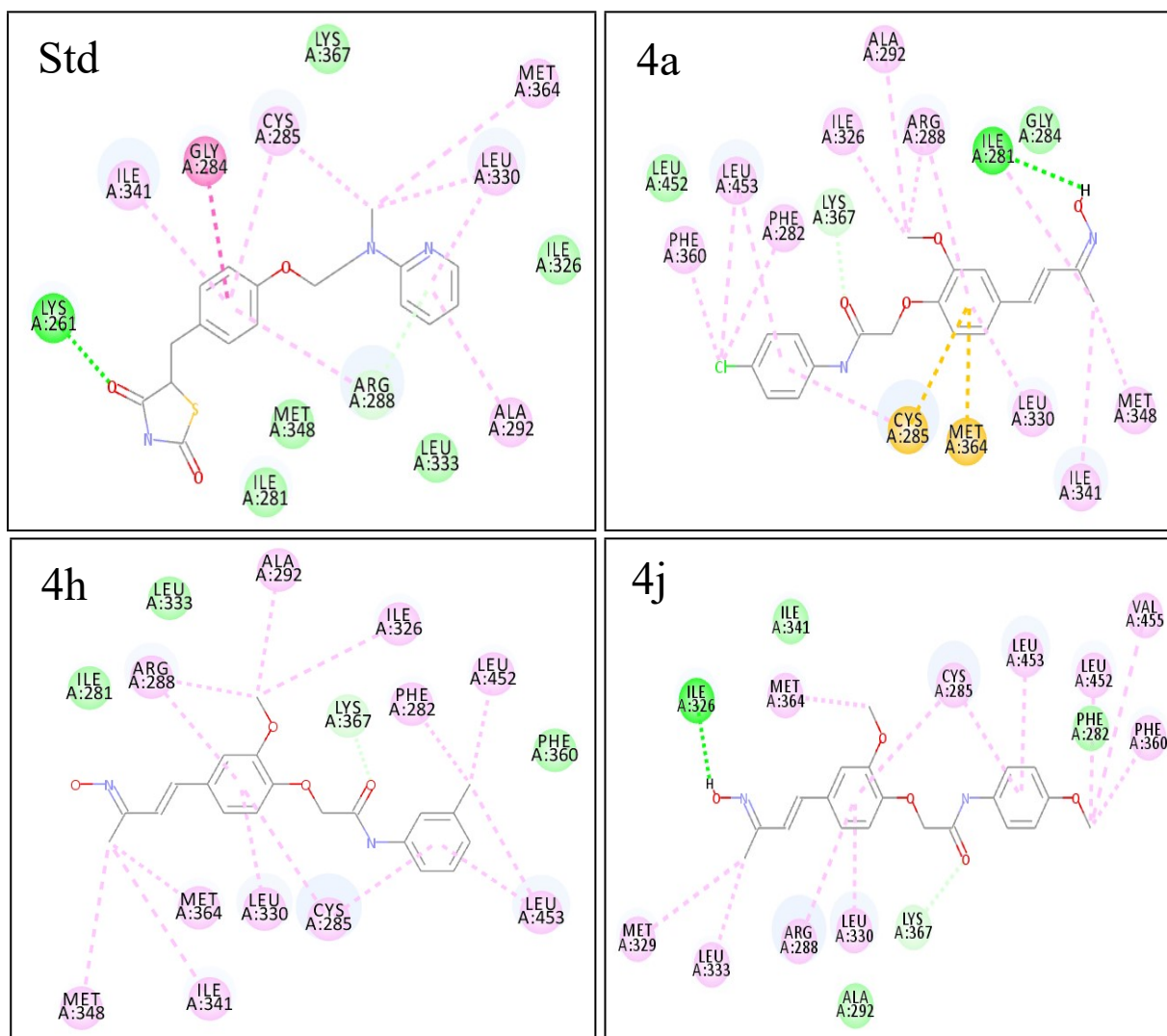
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## DOCKING VALIDATION



**Fig. S1:** Docked poses of reference ligand.

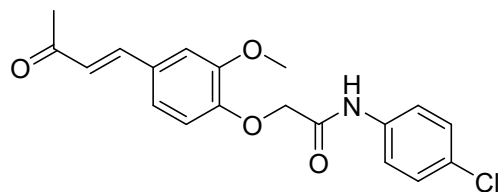
RMSD is the one the best method to validate the docking parameters. The docking RMSD validation is processed by comparing the bound ligand co-ordinates with docked poses. From the above figure and table it was observed that except few poses, other docked poses are less than 2.5 Å.



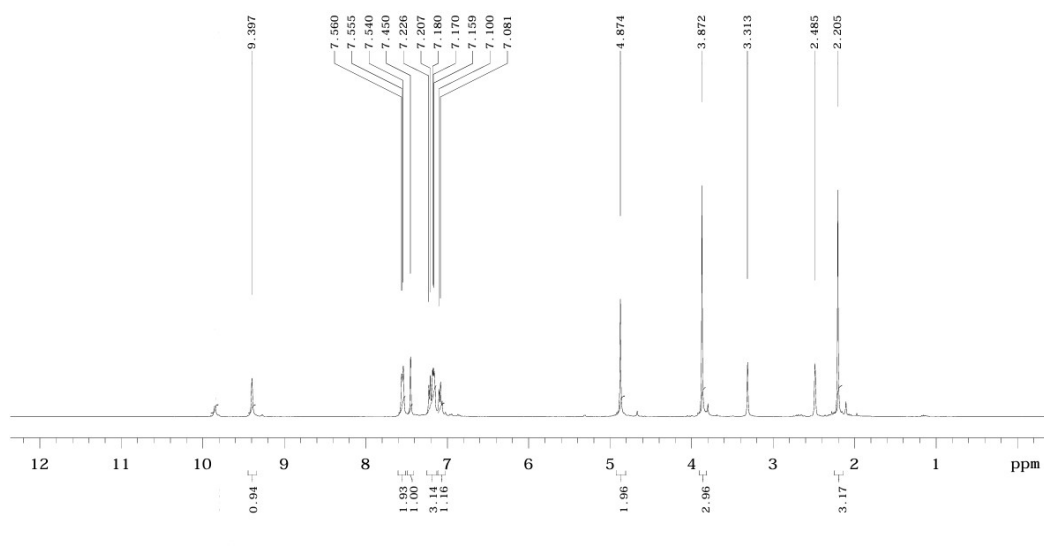
**Fig. S2:** 2D receptor – ligand interactions of the compounds 4a, 4h, 4j and Std (rosiglitazone) in the active binding site of PPAR- $\gamma$ .

# ANALYTICAL SPECTRA

## Compound: 3a



**Fig. S3.** Chemical structure of compound **3a**



**Fig. S4.** <sup>1</sup>H-NMR spectrum of compound **3a**

## Compound: 4a

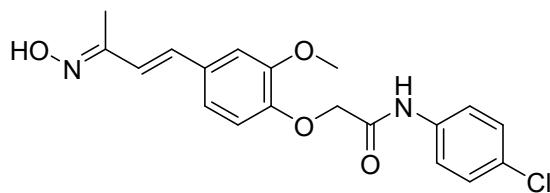


Fig. S5. Chemical structure of compound 4a

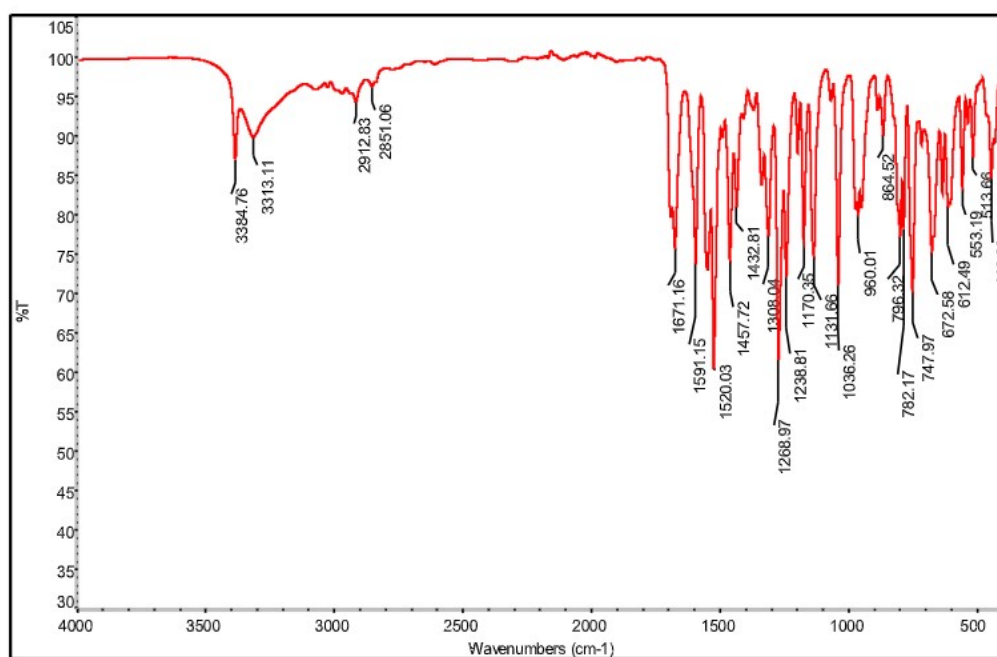


Fig. S6. IR spectrum of compound 4a.

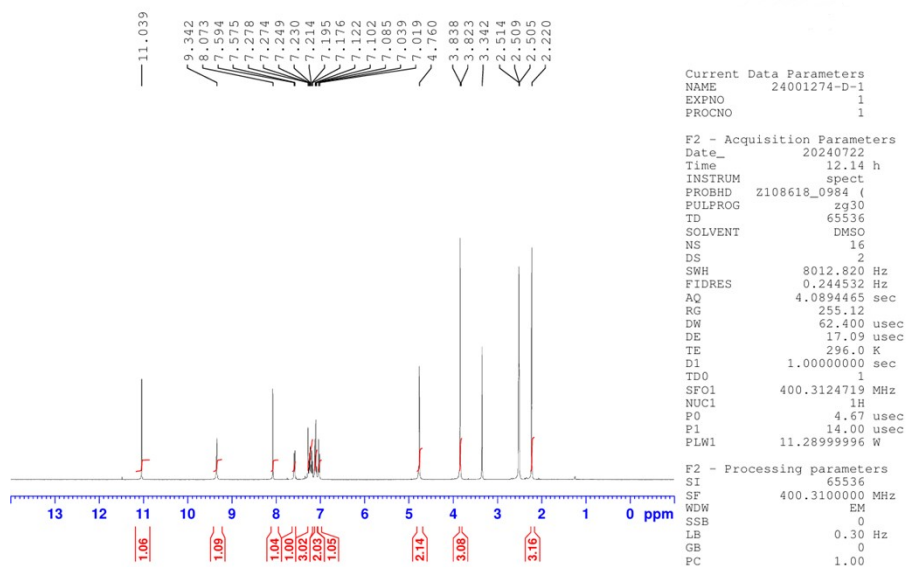


Fig. S7. <sup>1</sup>H-NMR spectrum of compound 4a.

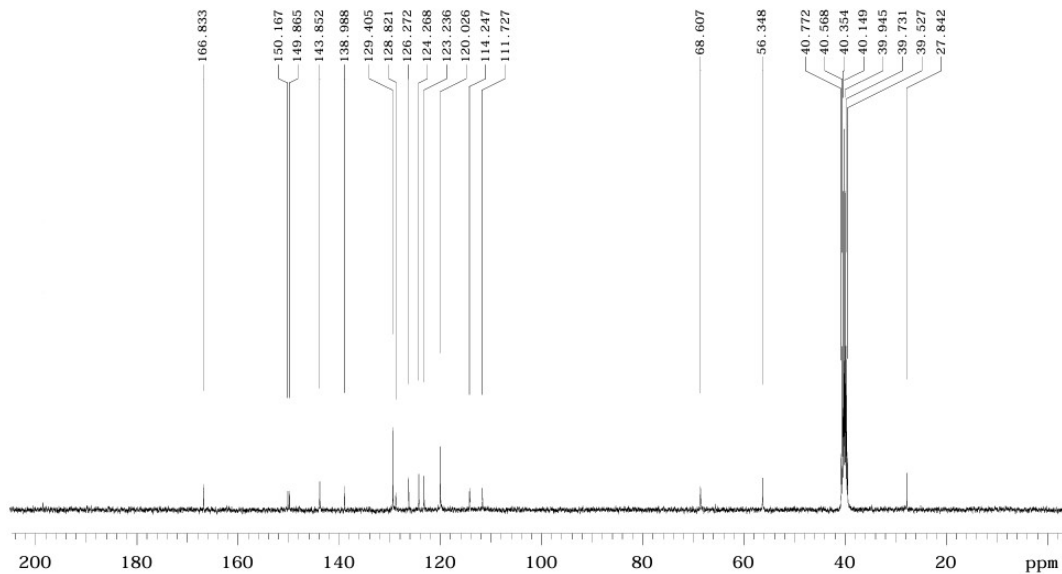


Fig. S8. <sup>13</sup>C-NMR spectrum of compound 4a.

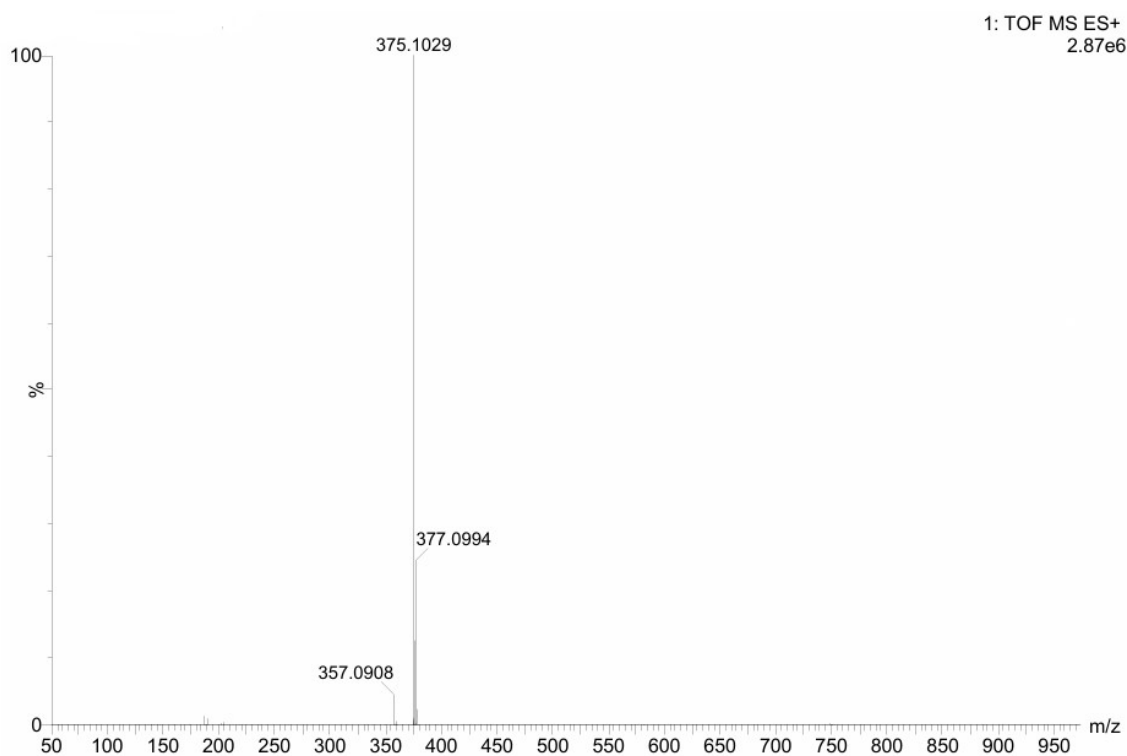
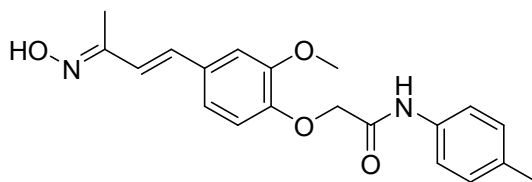
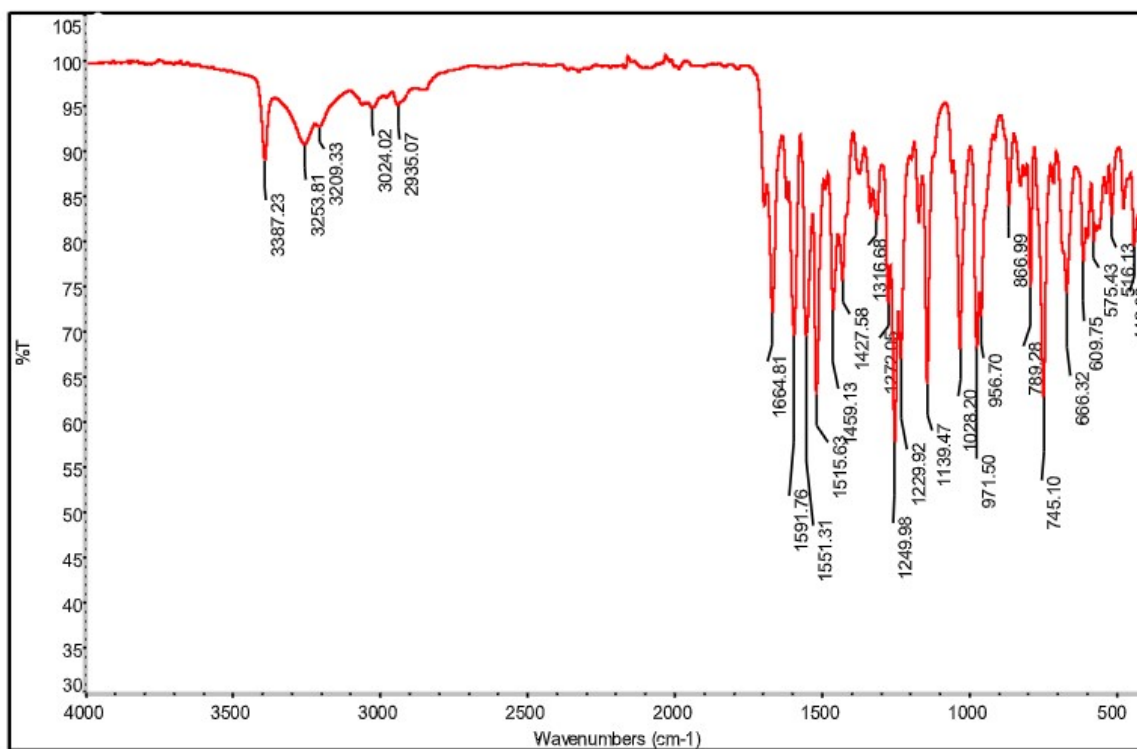


Fig. S9. Mass spectrum of compound 4a.

**Compound:4b**



**Fig. S10.** Chemical structure of compound **4b**.



**Fig. S11.** IR spectrum of compound **4b**.

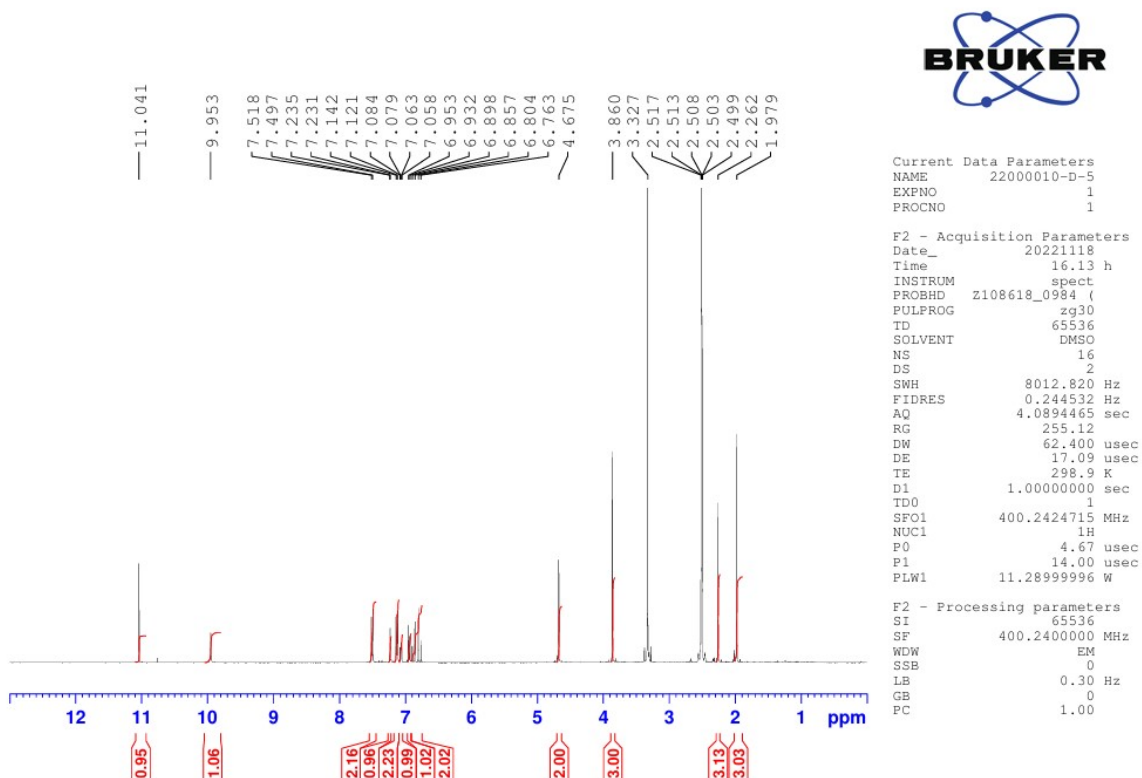


Fig. S12. <sup>1</sup>H-NMR spectrum of compound **4b**.

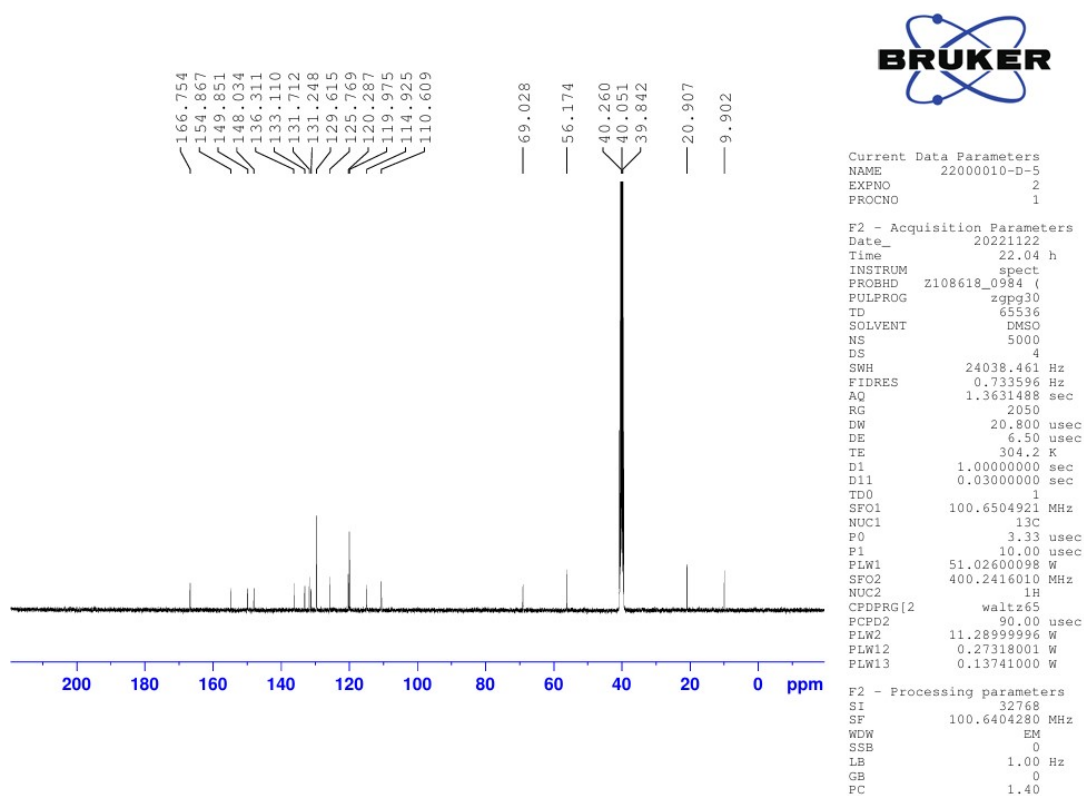
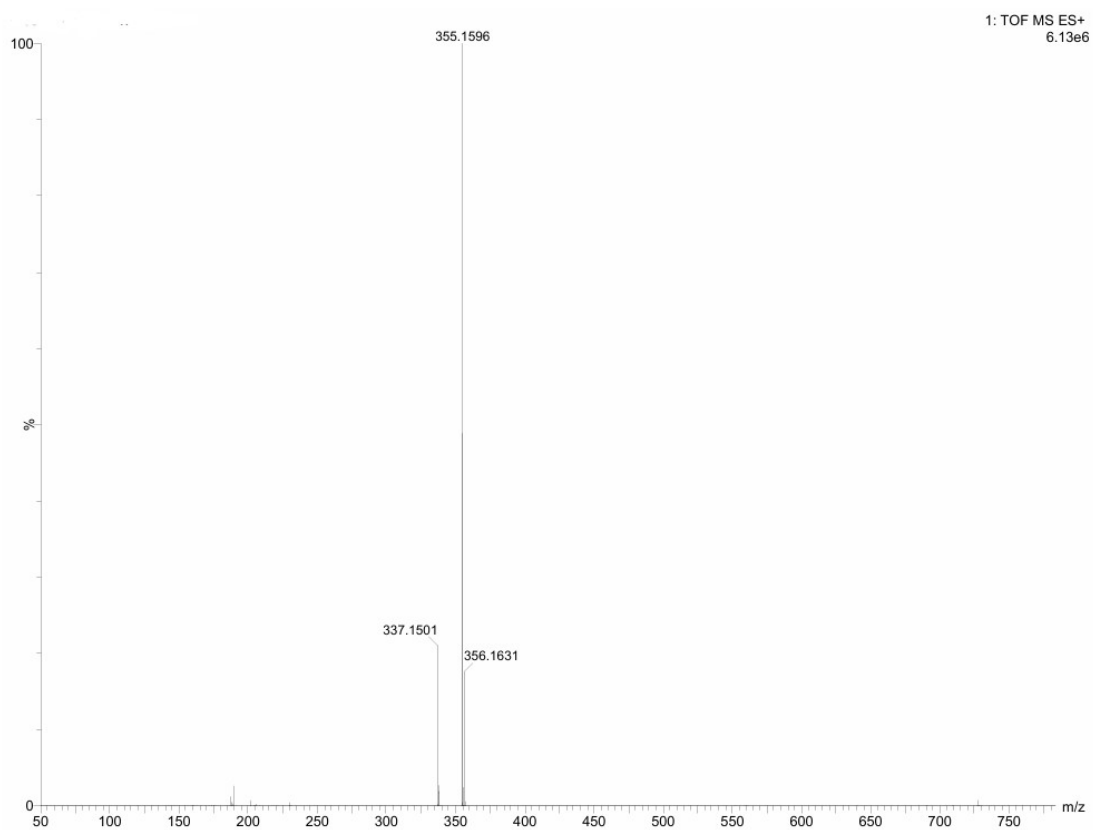


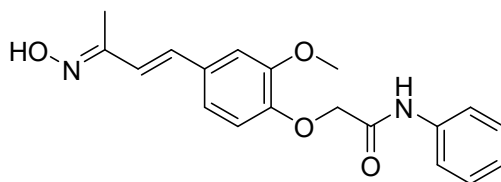
Fig. S13. <sup>13</sup>C-NMR spectrum of compound **4b**.



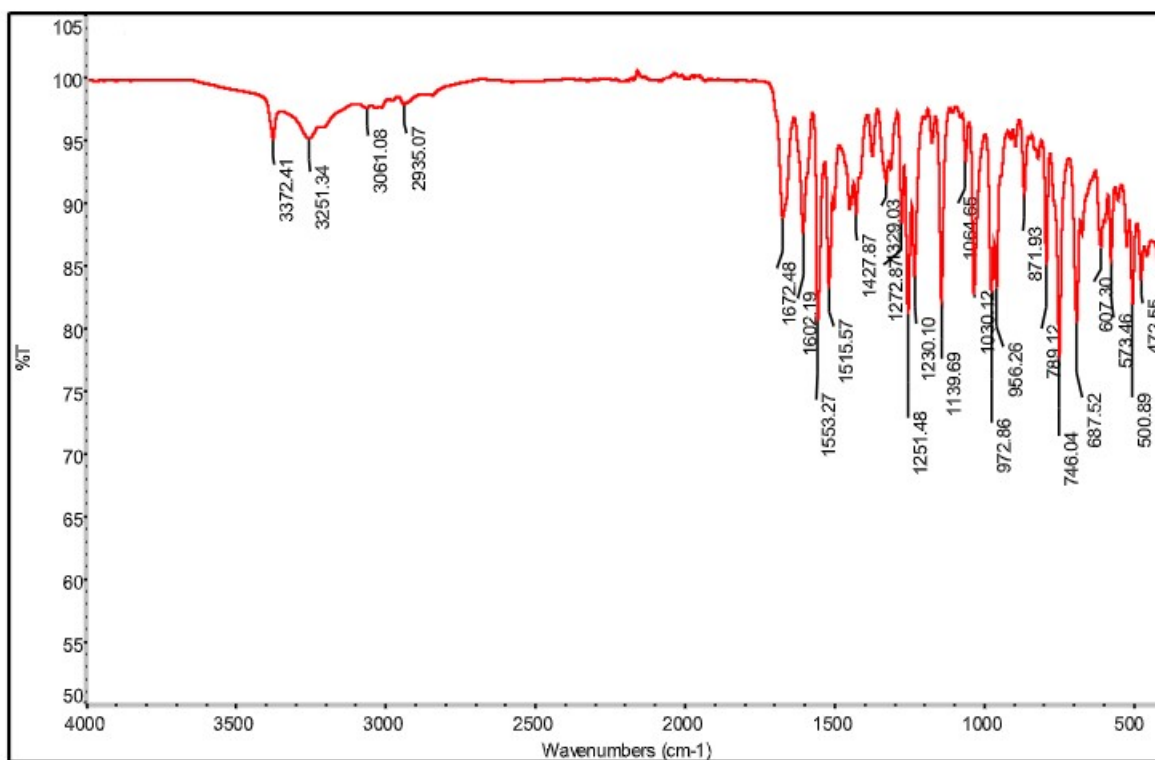


**Fig. S14.** Mass spectrum of compound **4b**.

**Compound:4c**



**Fig. S15.** Chemical structure of compound 4c.



**Fig. S16.** IR spectrum of compound 4c.

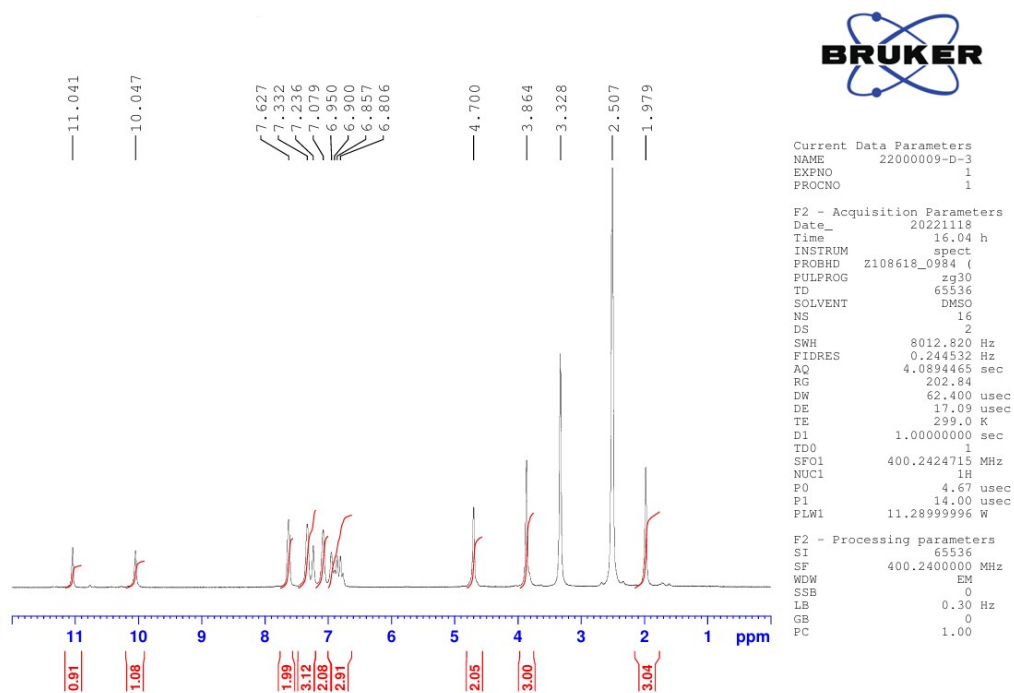


Fig. S17. <sup>1</sup>H-NMR spectrum of compound 4c.

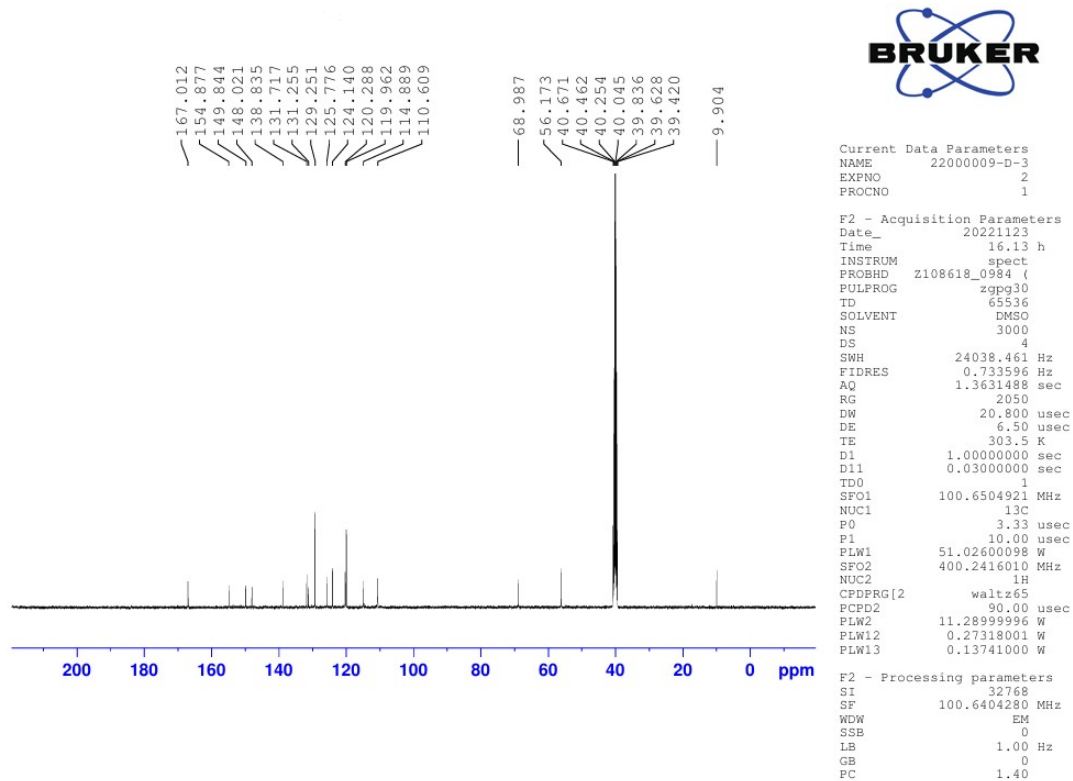
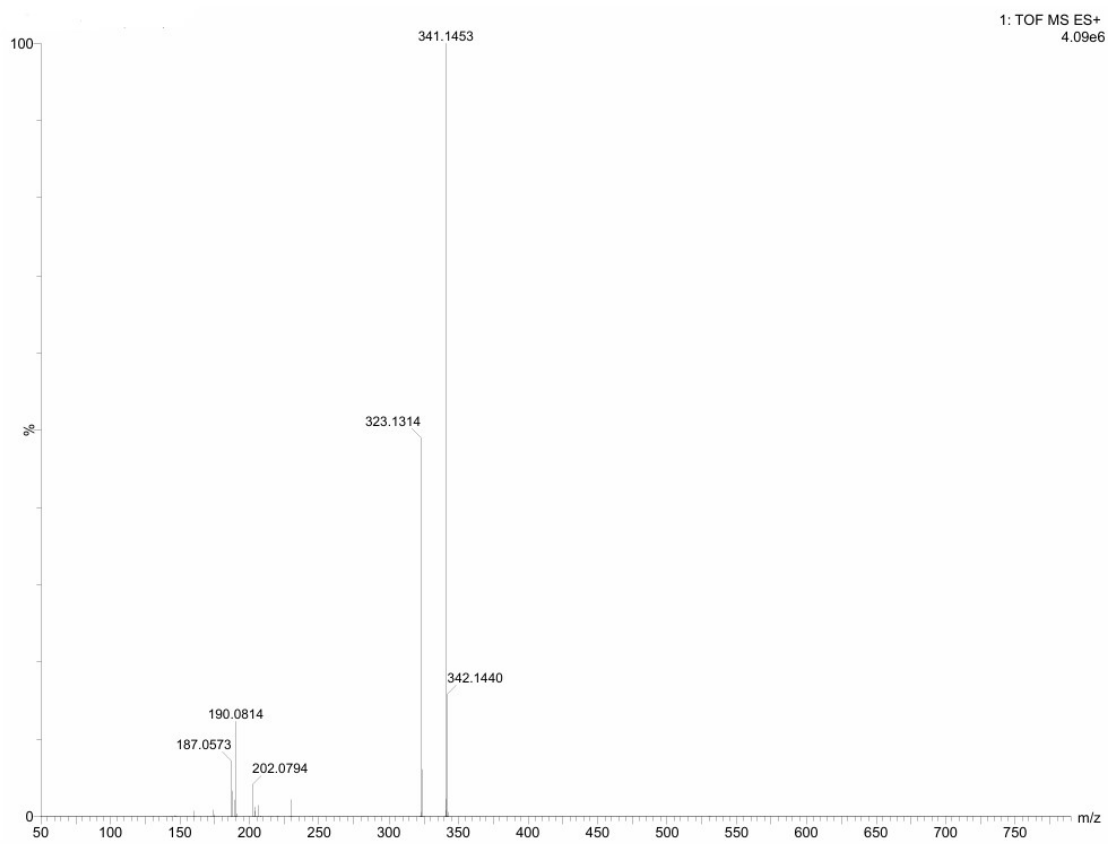
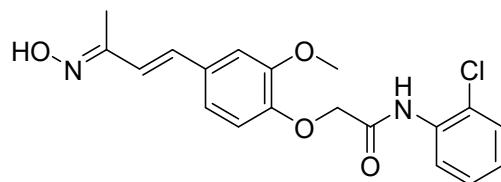


Fig. S18. <sup>13</sup>C-NMR spectrum of compound 4c.

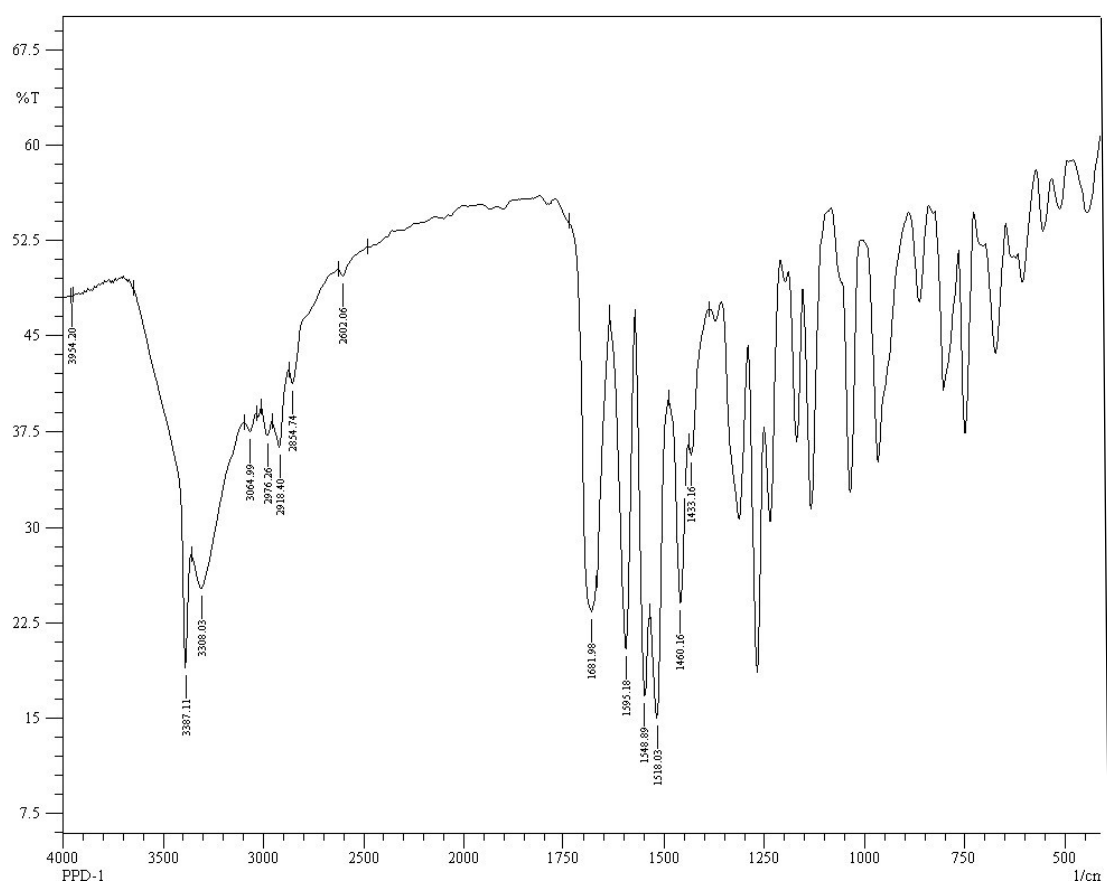


**Fig. S19.** Mass spectrum of compound **4c**.

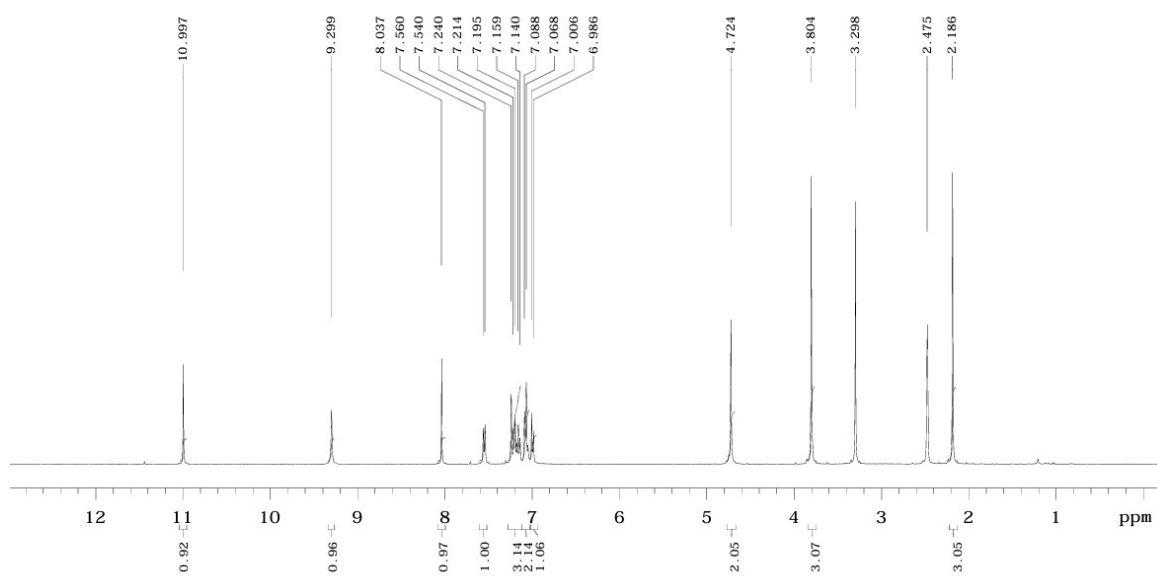
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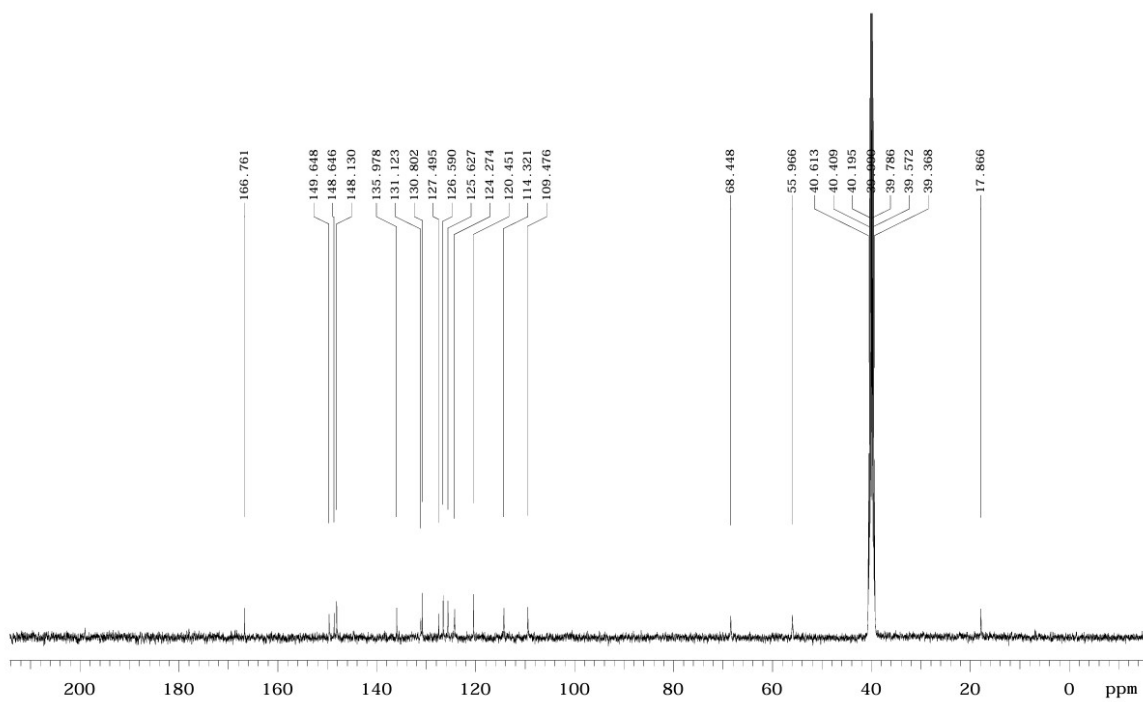
**Fig. S20.** Chemical structure of compound **4d**.



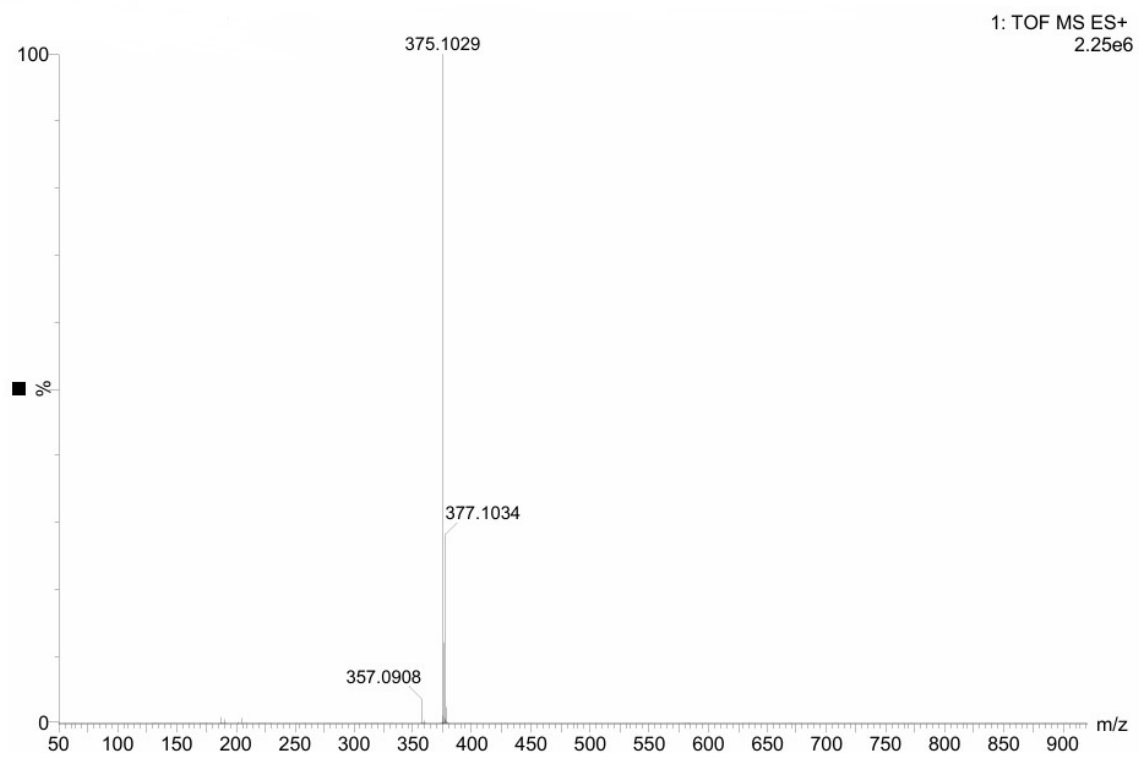
**Fig. S21.** IR spectrum of compound **4d**.



**Fig. S22.**  $^1\text{H}$ -NMR spectrum of compound **4d**.

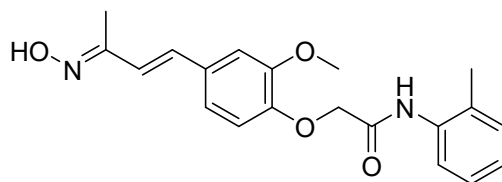


**Fig. S23.**  $^{13}\text{C}$ -NMR spectrum of compound **4d**.

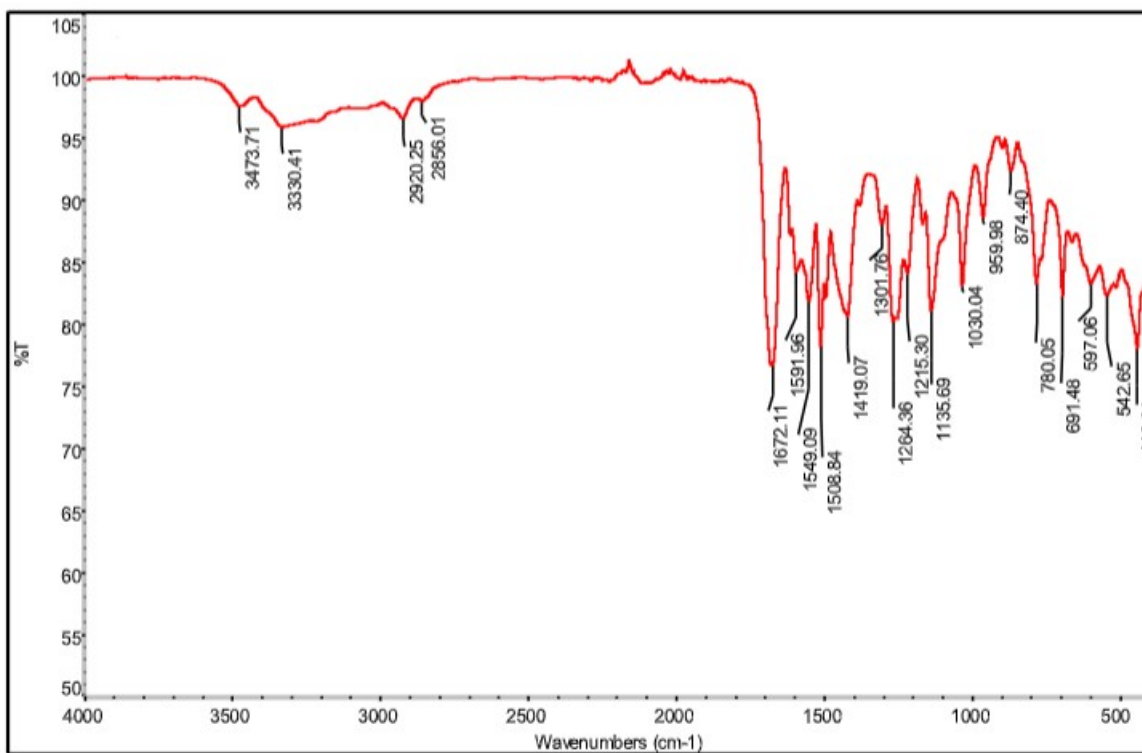


**Fig. S24.** Mass spectrum of compound **4d**.

**Compound:4e**



**Fig. S25.** Chemical structure of compound **4e**.



**Fig. S26.** IR spectrum of compound **4e**.



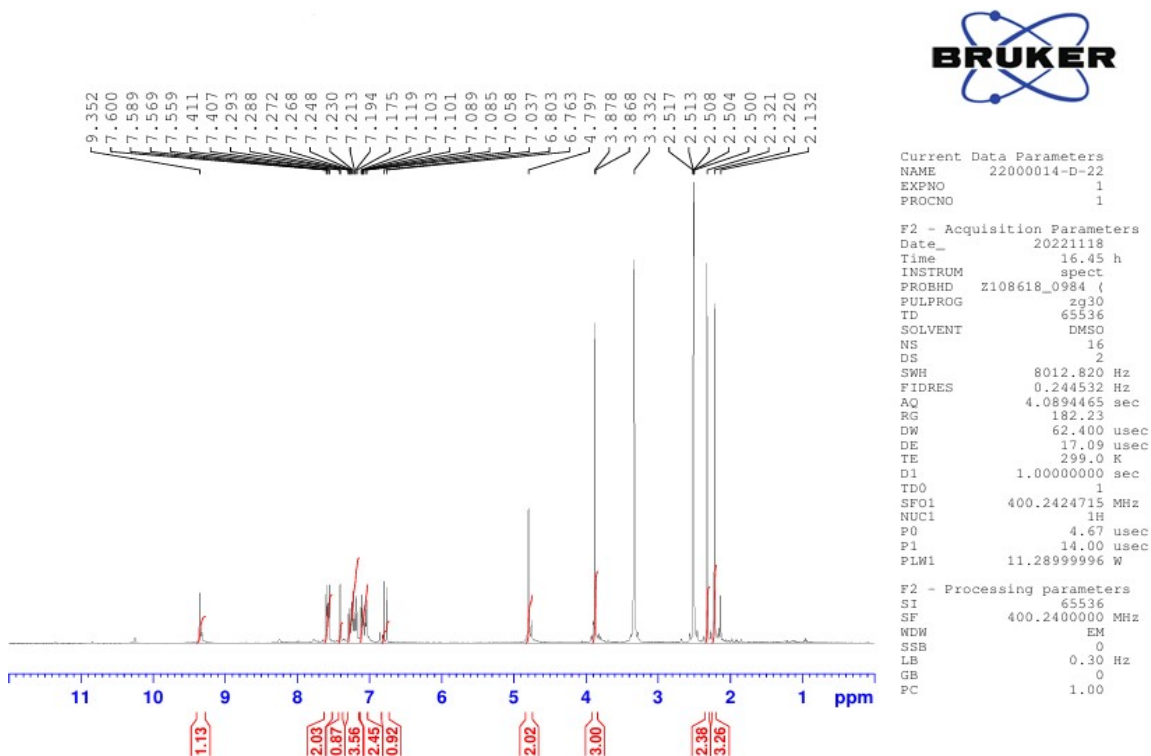


Fig. S27. <sup>1</sup>H-NMR spectrum of compound 4e.

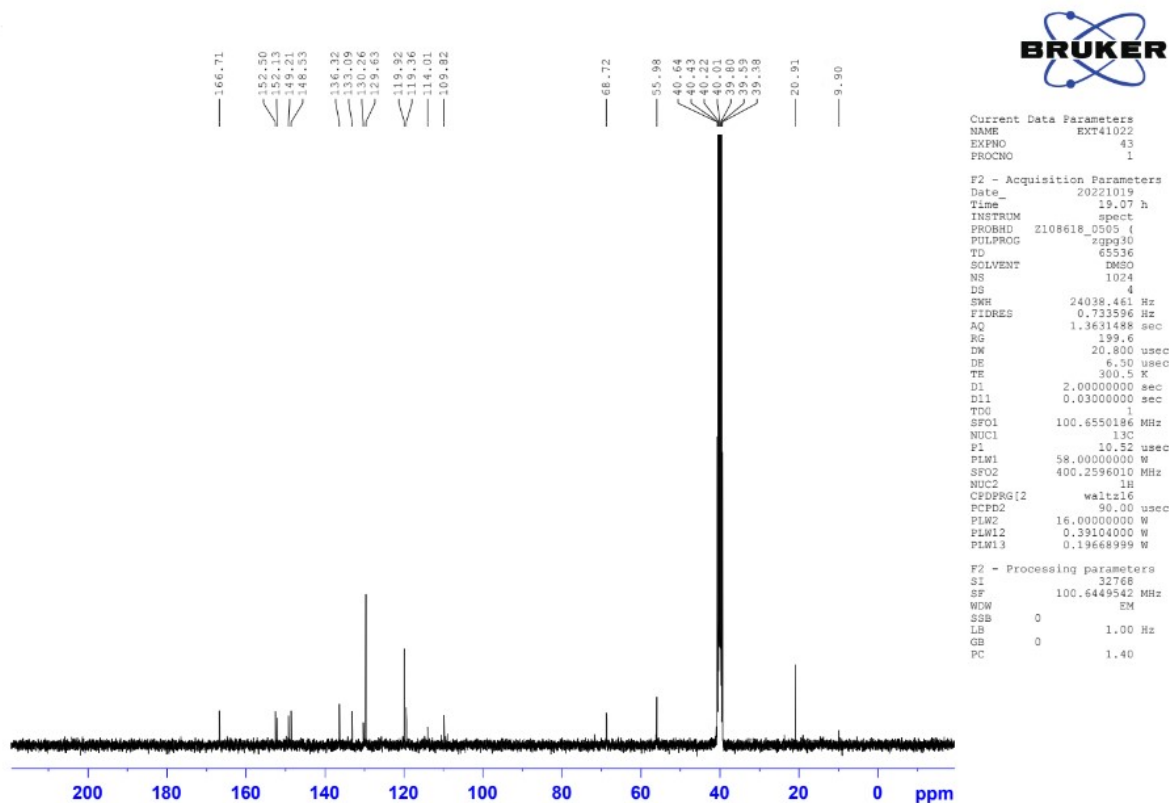
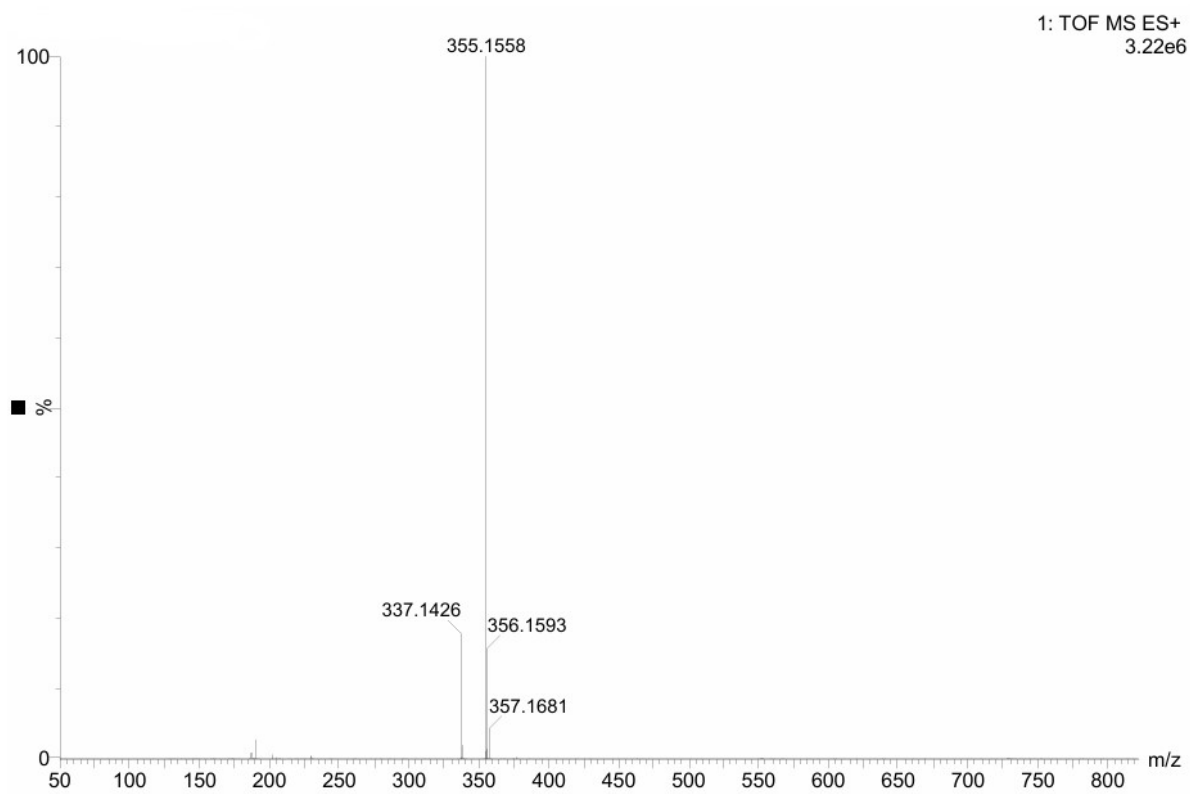


Fig. S28. <sup>13</sup>C-NMR spectrum of compound 4e.



**Fig. S29.** Mass spectrum of compound **4e**.

### Compound:4f

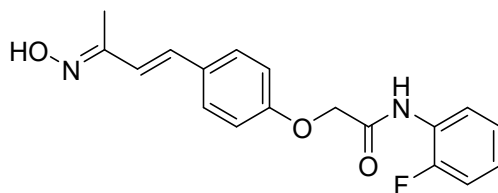


Fig. S30. Chemical structure of compound 4f.

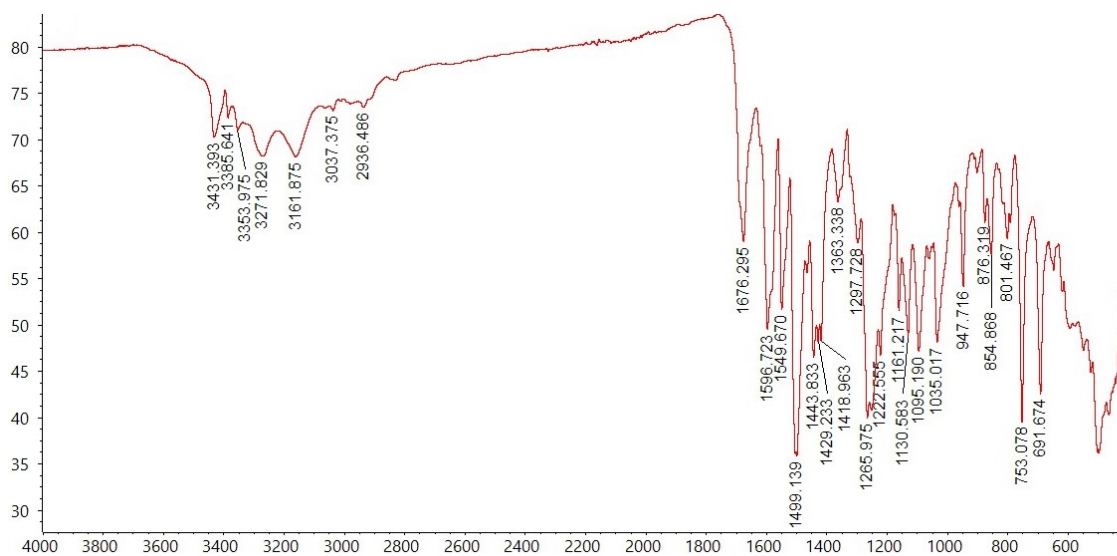


Fig. S31. IR spectrum of compound 4f.

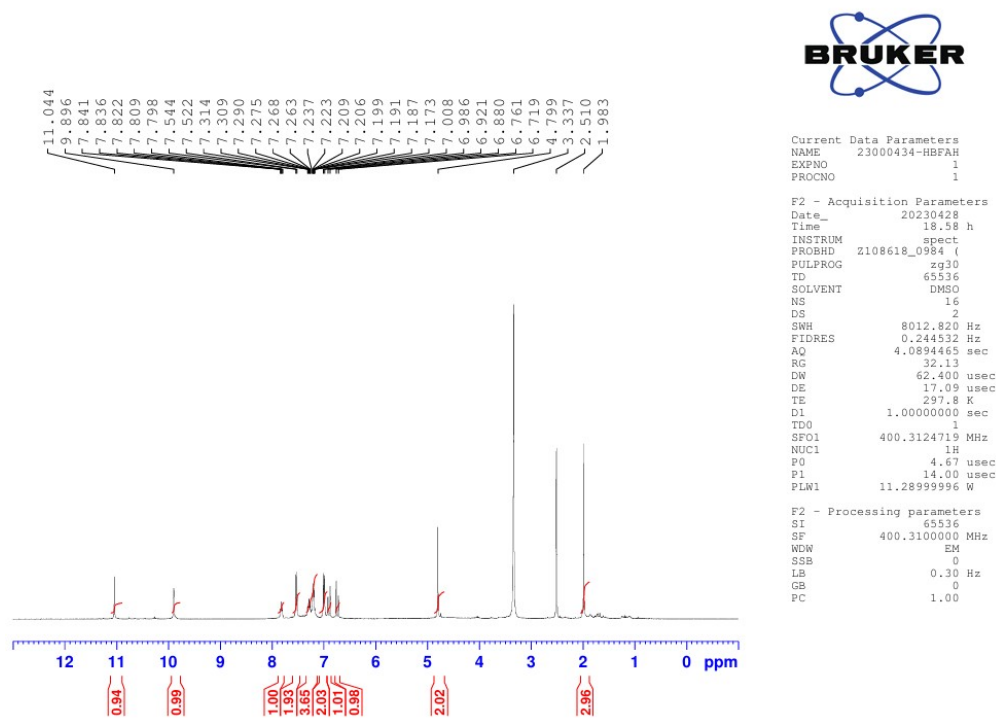


Fig. S32. <sup>1</sup>H-NMR spectrum of compound 4f.

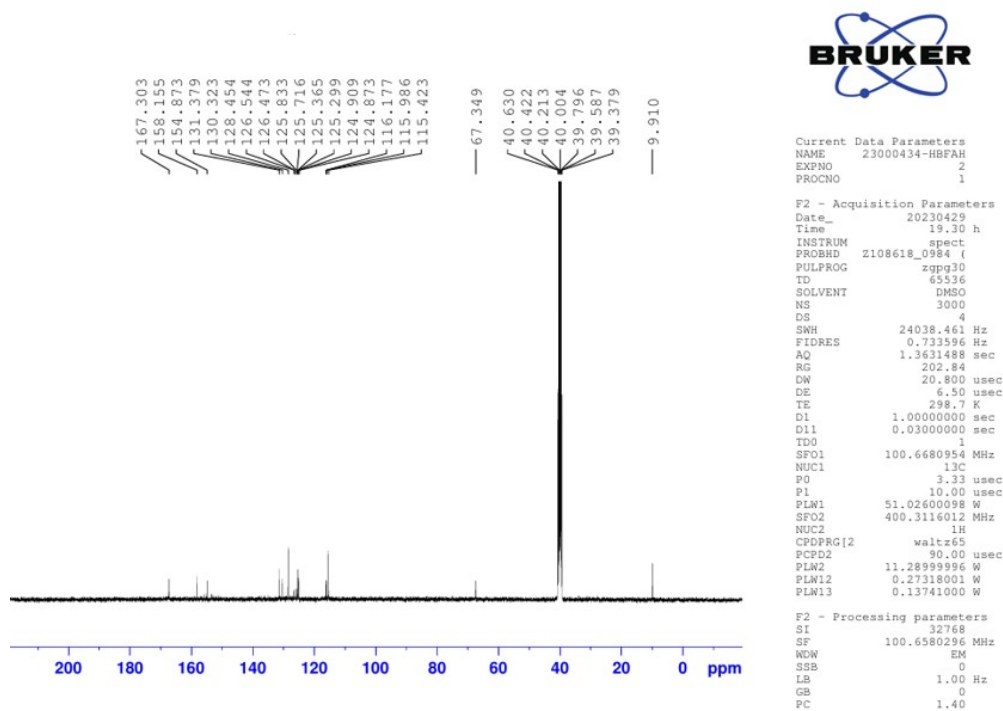


Fig. S33. <sup>13</sup>C-NMR spectrum of compound 4f.

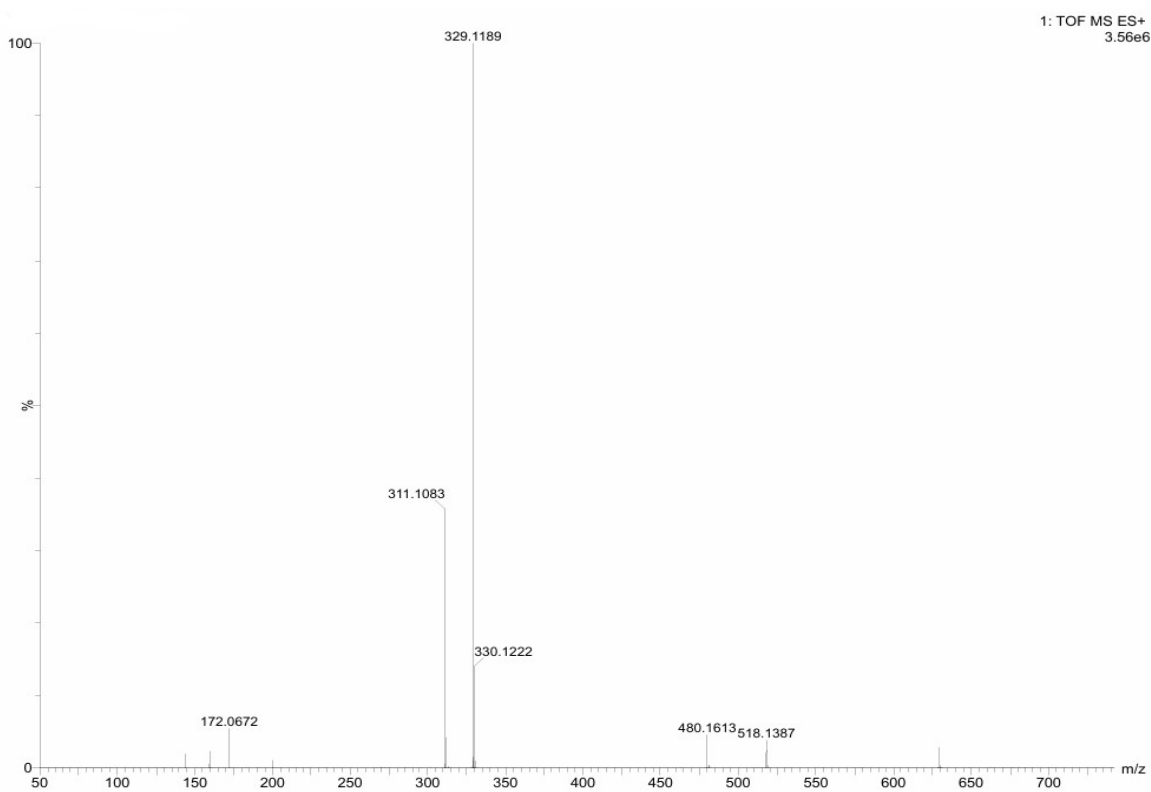
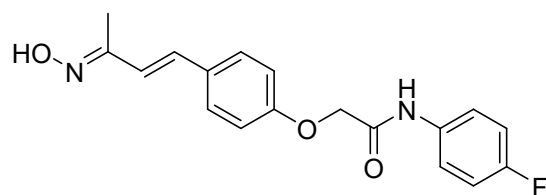
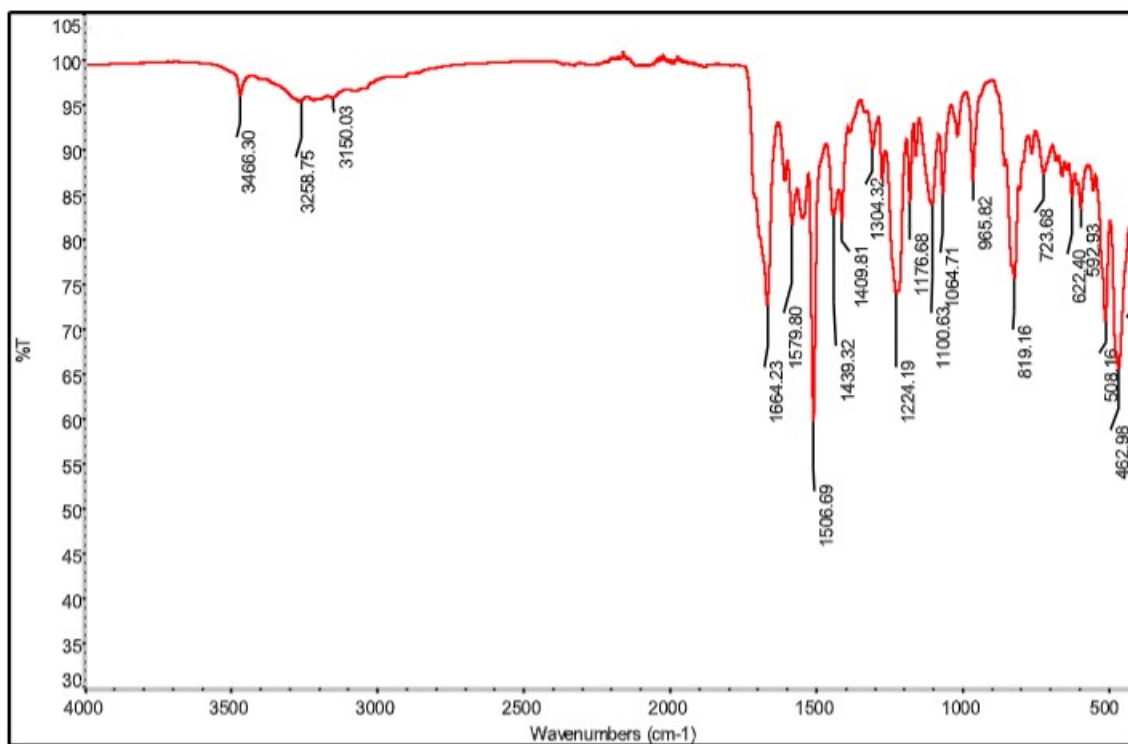


Fig. S34. Mass spectrum of compound 4f.

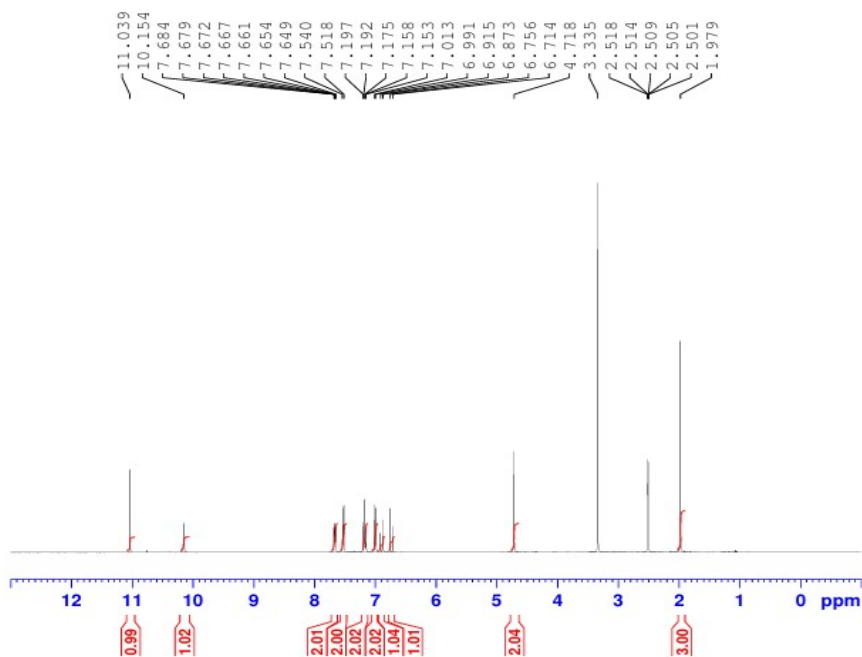
**Compound:4g**



**Fig. S35.** Chemical structure of compound **4g**.



**Fig. S36.** IR spectrum of compound **4g**.

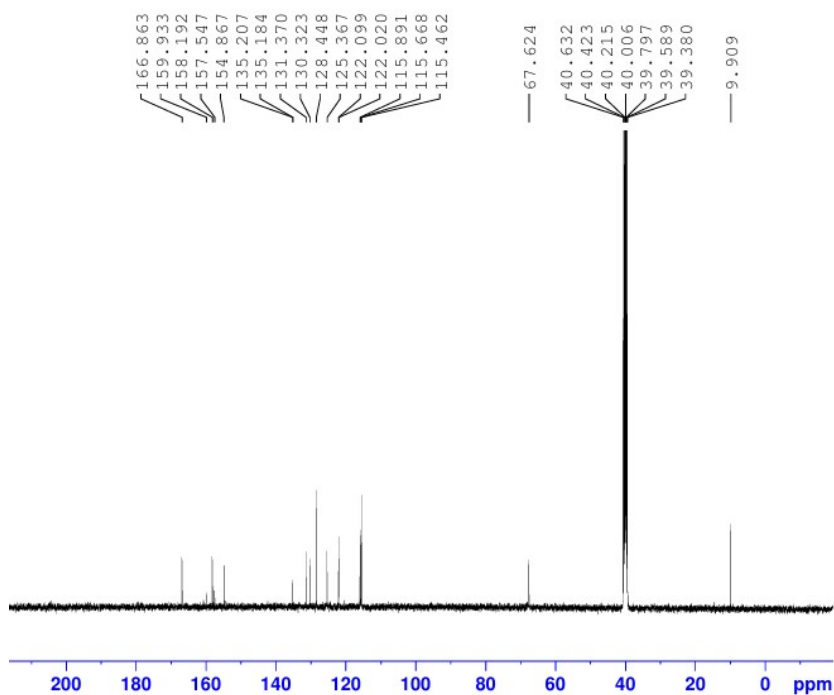


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 DE 17.09 usec  
 TE 297.5 K  
 D1 1.00000000 sec  
 TD0 1  
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F2 - Processing parameters  
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Fig. S37. <sup>1</sup>H-NMR spectrum of compound 4g.

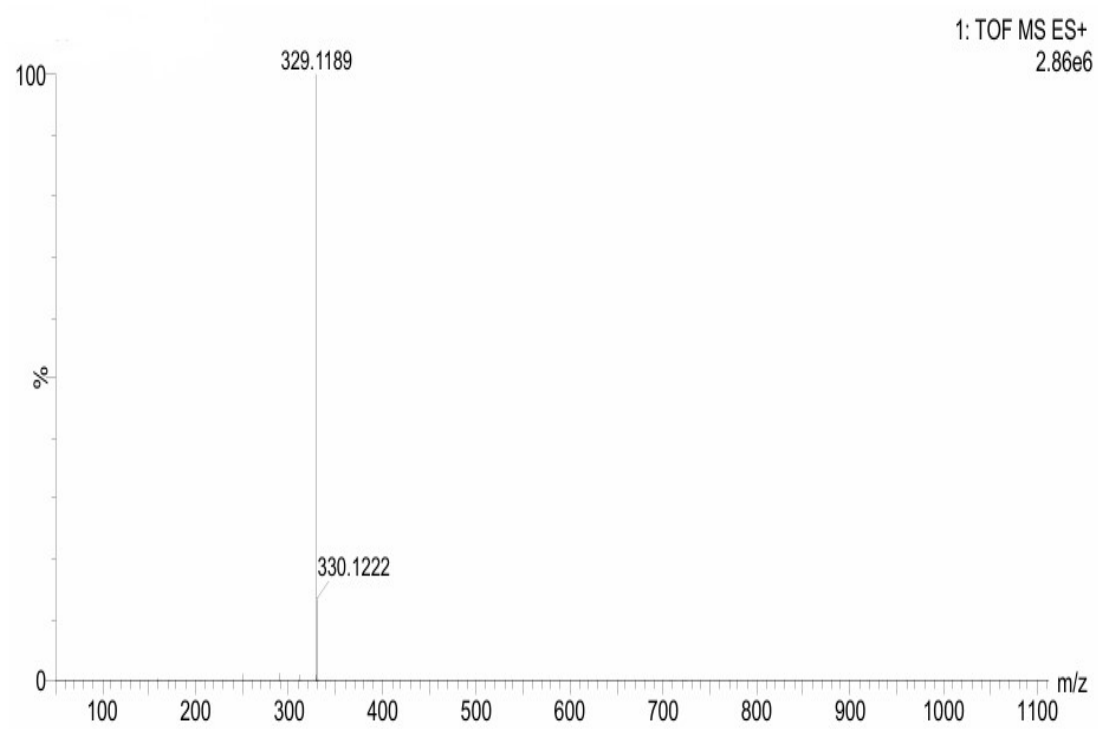


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 FIDRES 0.733596 Hz  
 AQ 1.3631488 sec  
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 DW 20.800 usec  
 DE 6.50 usec  
 TE 298.3 K  
 D1 1.00000000 sec  
 D11 0.03000000 sec  
 TD0 1  
 SFO1 100.6680954 MHz  
 NUC1 13C  
 P0 3.33 usec  
 P1 10.00 usec  
 PLW1 51.02600098 W  
 SFO2 400.3116012 MHz  
 NUC2 1H  
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 PLW12 0.27318001 W  
 PLW13 0.13741000 W

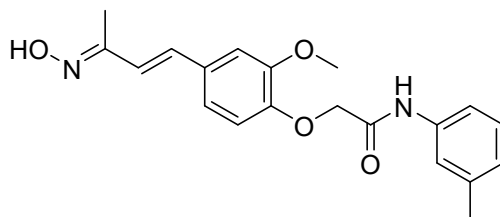
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Fig. S38. <sup>13</sup>C-NMR spectrum of compound 4g.

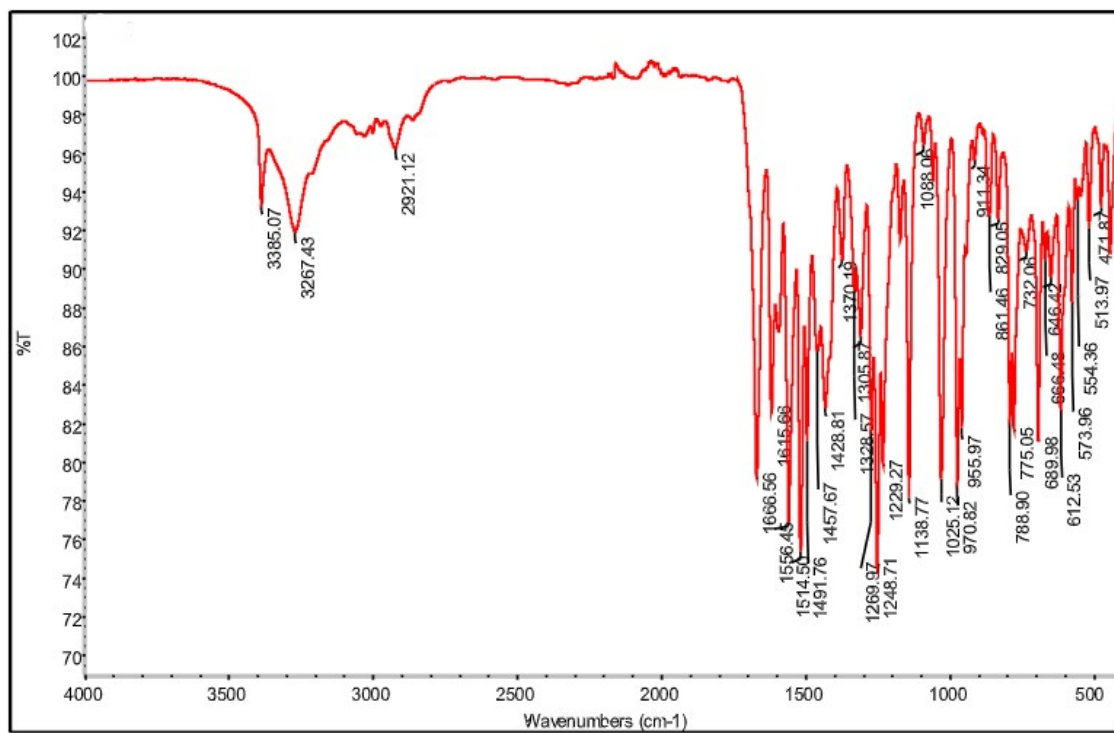


**Fig. S39.** Mass spectrum of compound **4g**.

### Compound:4h

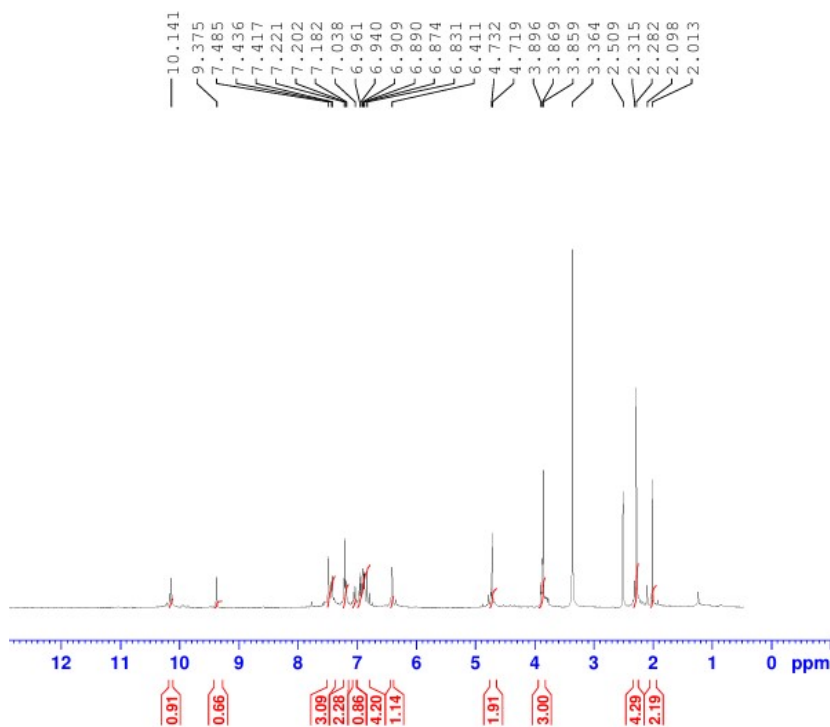


**Fig. S40.** Chemical structure of compound **4h**.



**Fig. S41.** IR spectrum of compound **4h**.



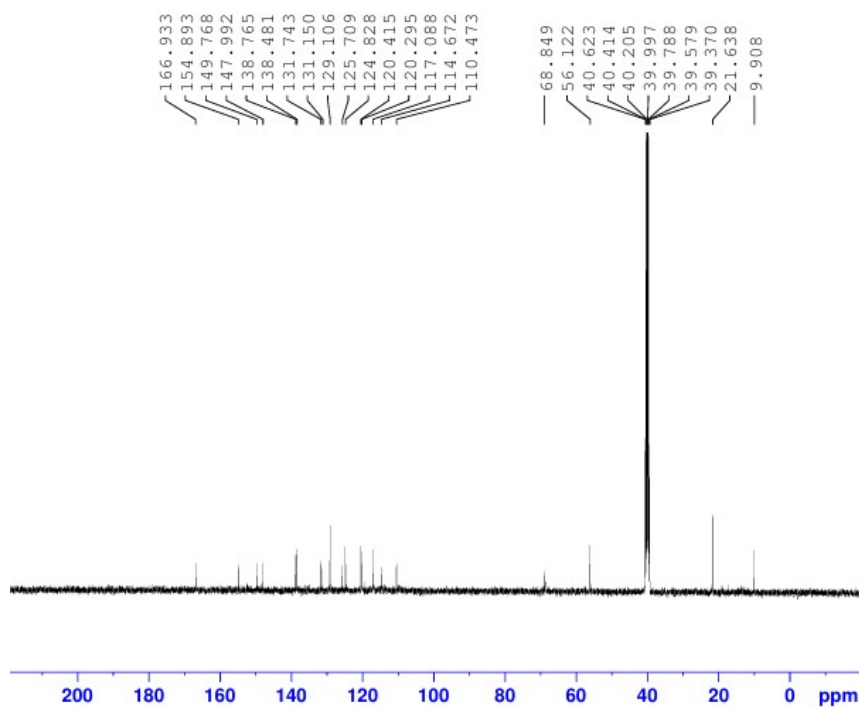


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FIDRES 0.244532 Hz  
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RG 32.13  
DW 62.400 usec  
DE 17.09 usec  
TE 297.1 K  
D1 1.00000000 sec  
TD0 1  
SFO1 400.3124719 MHz  
NUC1 1H  
PO 4.67 usec  
P1 14.00 usec  
PLW1 11.28999996 W

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Fig. S42. <sup>1</sup>H-NMR spectrum of compound 4h.

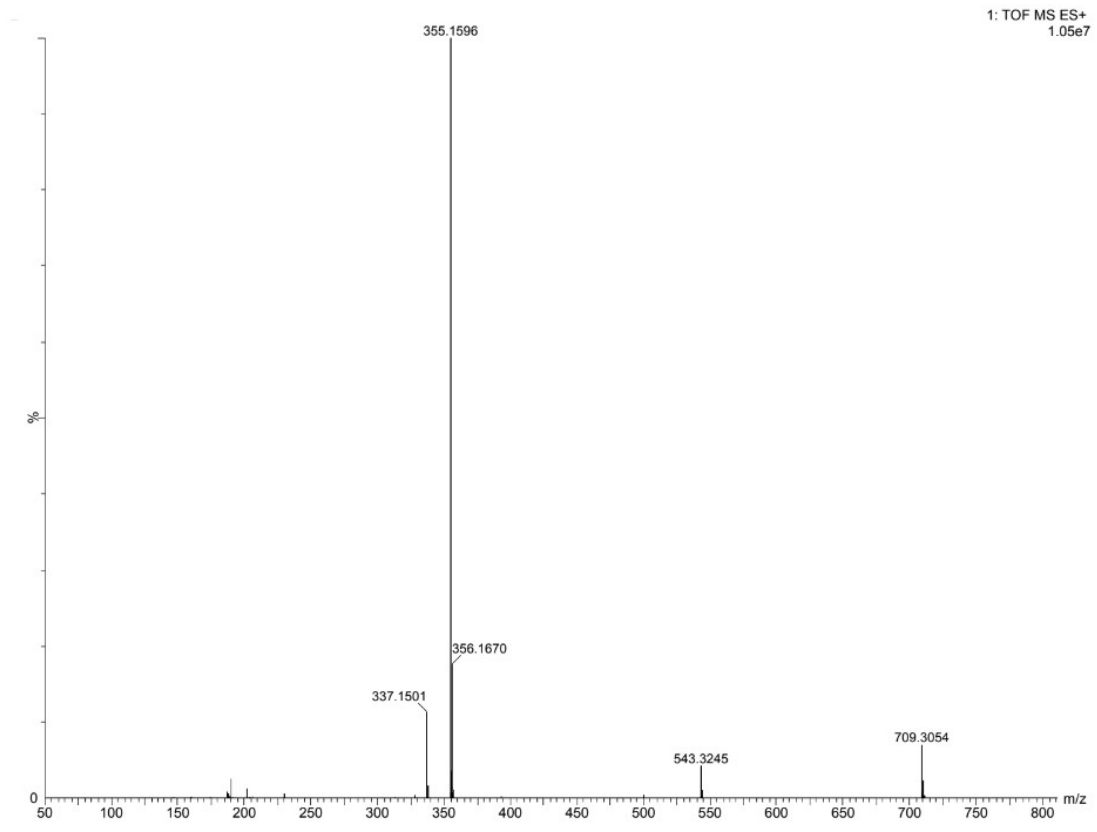


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DE 6.50 usec  
TE 298.1 K  
D1 1.00000000 sec  
D11 0.03000000 sec  
TD0 1  
SFO1 100.6680954 MHz  
NUC1 13C  
PO 3.33 usec  
P1 10.00 usec  
PLW1 51.02600098 W  
SFO2 400.3116012 MHz  
NUC2 1H  
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PLW2 11.28999996 W  
PLW12 0.27318001 W  
PLW13 0.13741000 W

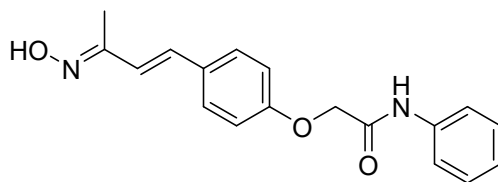
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Fig. S43. <sup>13</sup>C-NMR spectrum of compound 4h.

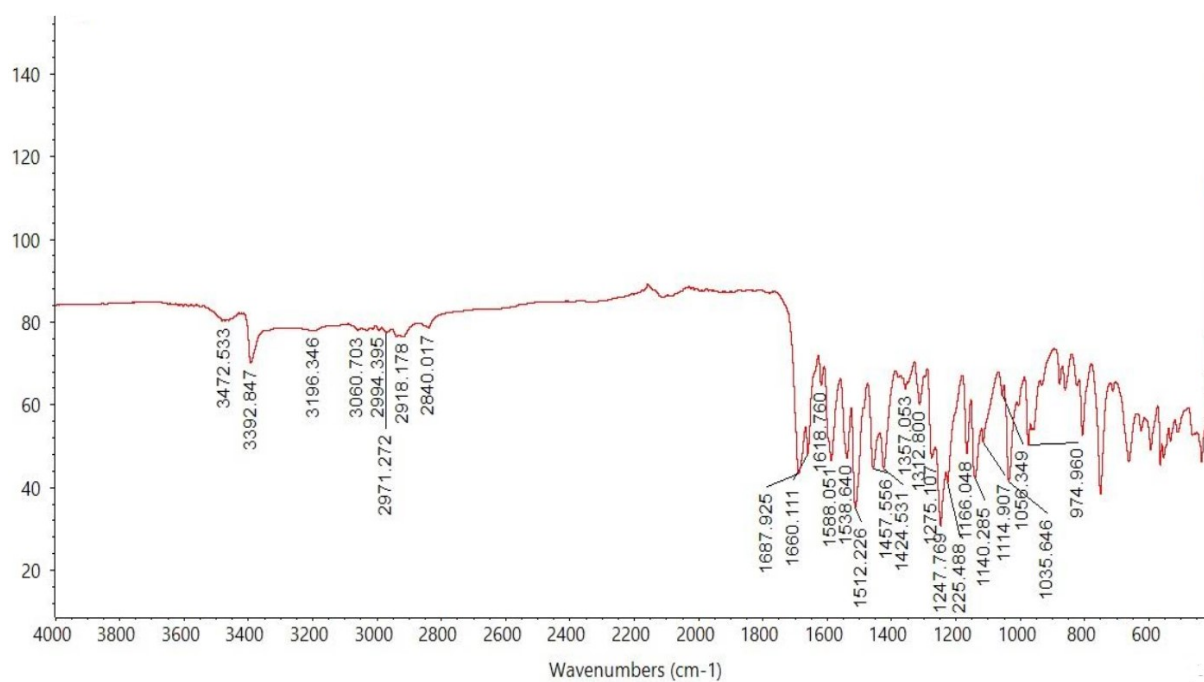


**Fig. S44.** Mass spectrum of compound **4h**.

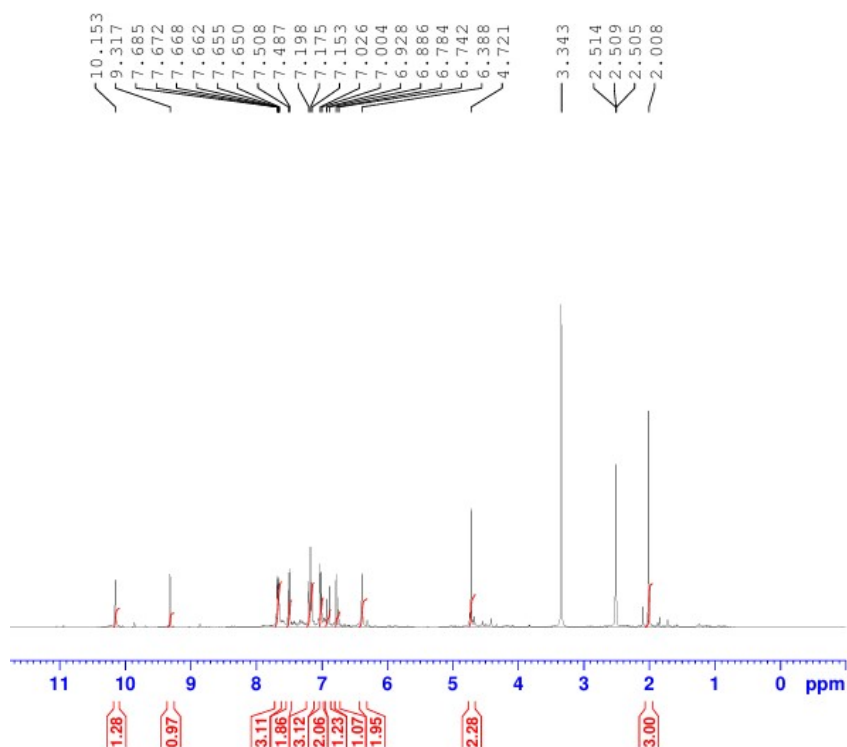
**Compound:4i**



**Fig. S45.** Chemical structure of compound **4i**.



**Fig. S46.** IR spectrum of compound **4i**.

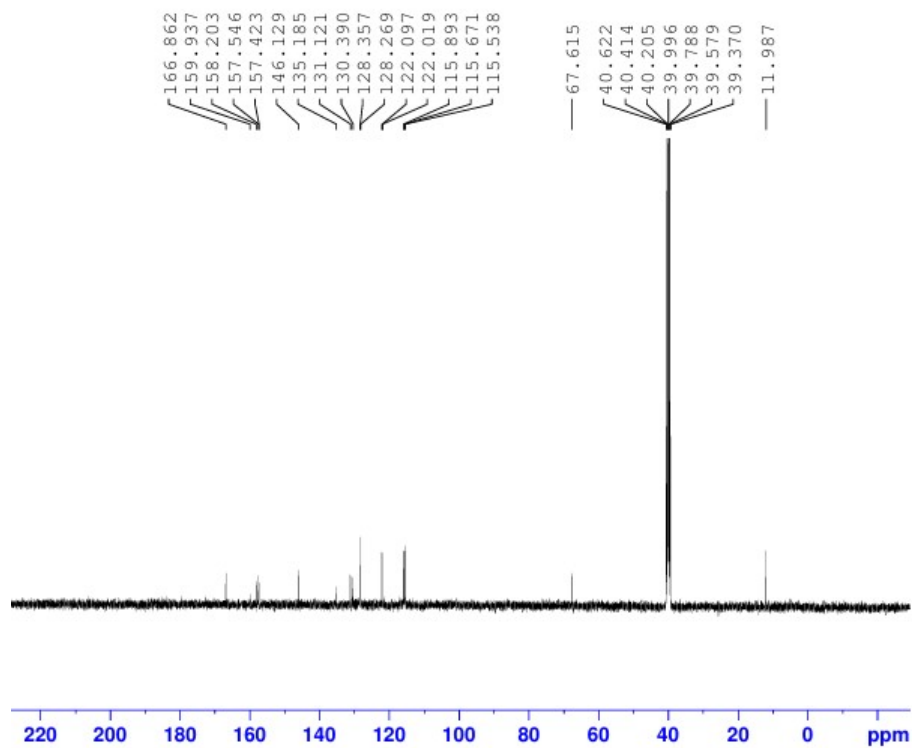


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FIDRES 0.244532 Hz  
AQ 4.0894465 sec  
RG 32.13  
DW 62.400 usec  
DE 17.09 usec  
TE 297.3 K  
D1 1.00000000 sec  
TDO 1  
SFO1 400.3124719 MHz  
NUC1 1H  
PO 4.67 usec  
P1 14.00 usec  
PLW1 11.28999996 W

F2 - Processing parameters  
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GB 0  
PC 1.00

Fig. S47. <sup>1</sup>H-NMR spectrum of compound 4i.

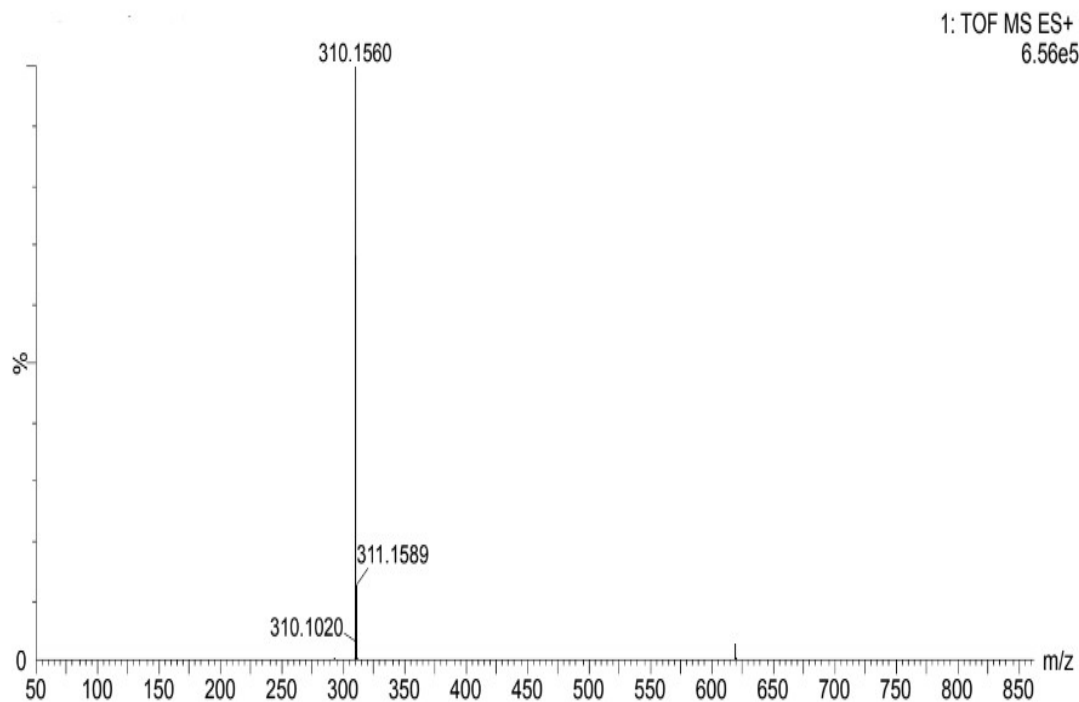


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RG 202.84  
DW 19.200 usec  
DE 6.50 usec  
TE 298.4 K  
D1 1.00000000 sec  
D11 0.03000000 sec  
TD0 1  
SF01 100.6680954 MHz  
NUC1 13C  
PQ 3.33 usec  
P1 10.00 usec  
PLW1 51.02600098 W  
SF02 400.3116012 MHz  
NUC2 1H  
CPDPRG2 waltz65  
PCPD2 90.00 usec  
PLW2 11.289999996 W  
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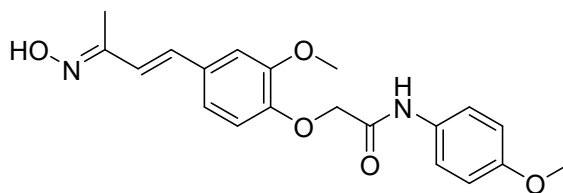
Fig. S48. <sup>13</sup>C-NMR spectrum of compound 4i.



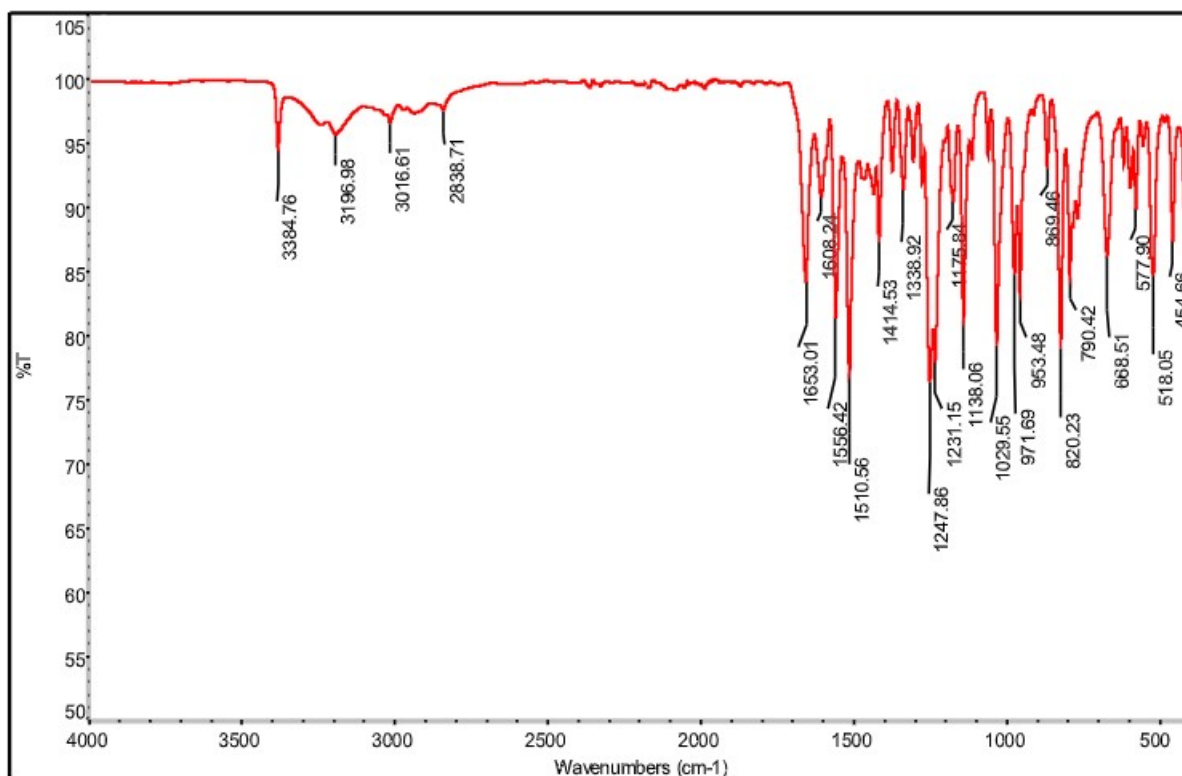
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6.56e5

Fig. S49. Mass spectrum of compound 4i.

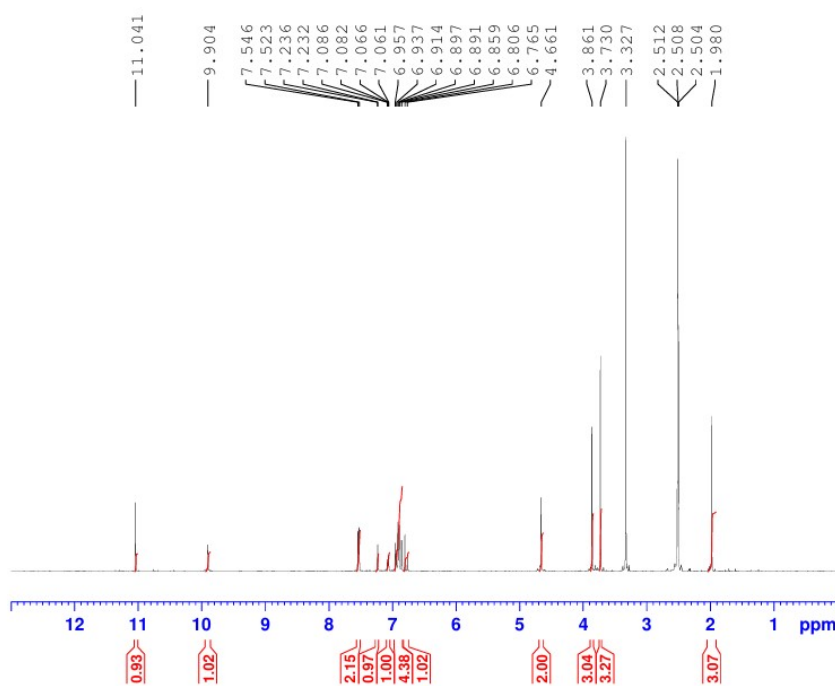
**Compound:4j**



**Fig. S50.** Chemical structure of compound 4j.



**Fig. S51.** IR spectrum of compound 4j.



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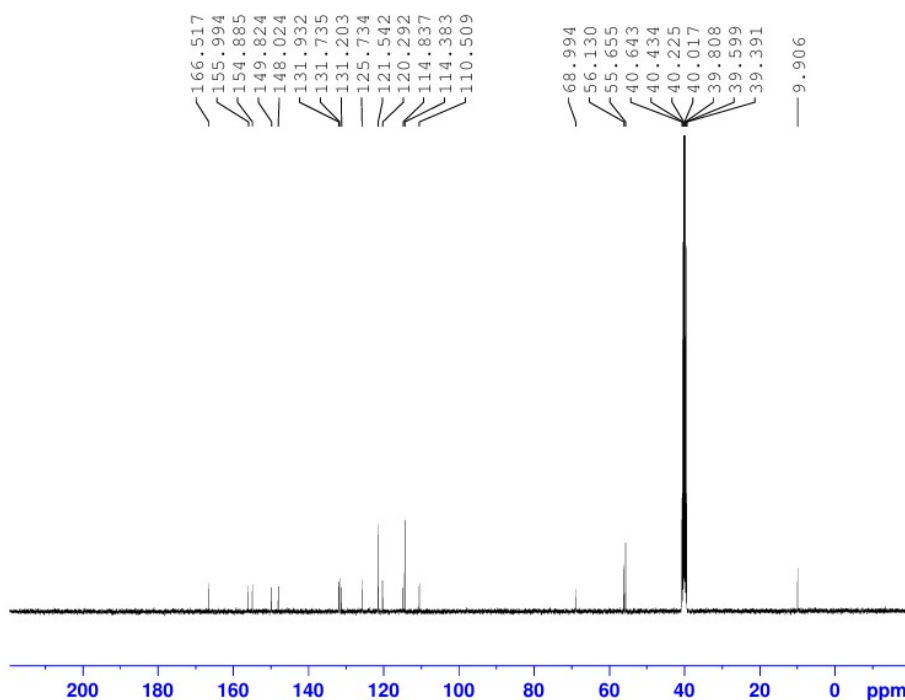
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DS        2
SWH       8012.820 Hz
FIDRES    0.244532 Hz
AQ        4.0894465 sec
RG        2050
DW        62.400 usec
DE        17.09 usec
TE        298.9 K
D1        1.00000000 sec
TD0       1
SFO1     400.2424715 MHz
NUC1     1H
P0       4.67 usec
P1       14.00 usec
PLW1     11.28999996 W

F2 - Processing parameters
SI        65536
SF        400.2400000 MHz
WDW       EM
SSB       0
LB        0.30 Hz
GB        0
PC        1.00

```

Fig. S52. <sup>1</sup>H-NMR spectrum of compound 4j.



```

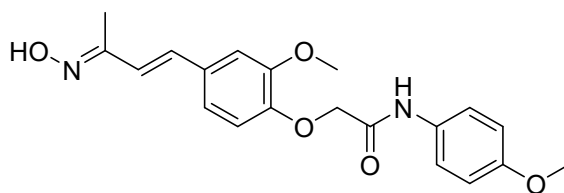
Current Data Parameters
NAME      22000011-D-10
EXPNO    2
PROCNO   1

F2 - Acquisition Parameters
Date_    20221123
Time     13.38 h
INSTRUM spect
PROBHD   Z108618_0984 (
PULPROG zgpg30
TD        65536
SOLVENT  DMSO
NS        874
DS        4
SWH       24038.461 Hz
FIDRES    0.733596 Hz
AQ        1.3631488 sec
RG        2050
DW        20.800 usec
DE        6.50 usec
TE        301.5 K
D1        1.00000000 sec
D11      0.03000000 sec
TD0       1
SFO1     100.6504921 MHz
NUC1     13C
P0       3.33 usec
P1       10.00 usec
PLW1     51.02600098 W
SFO2     400.2416010 MHz
NUC2     1H
CPDPRG[2] waltz65
PCPD2    90.00 usec
PLW2     11.28999996 W
PLW12    0.27318001 W
PLW13    0.13741000 W

F2 - Processing parameters
SI        32768
SF        100.6404280 MHz
WDW       EM
SSB       0
LB        1.00 Hz
GB        0
PC        1.40

```

Fig. S53. <sup>13</sup>C-NMR spectrum of compound 4j.



Chemical structure of compound 4j

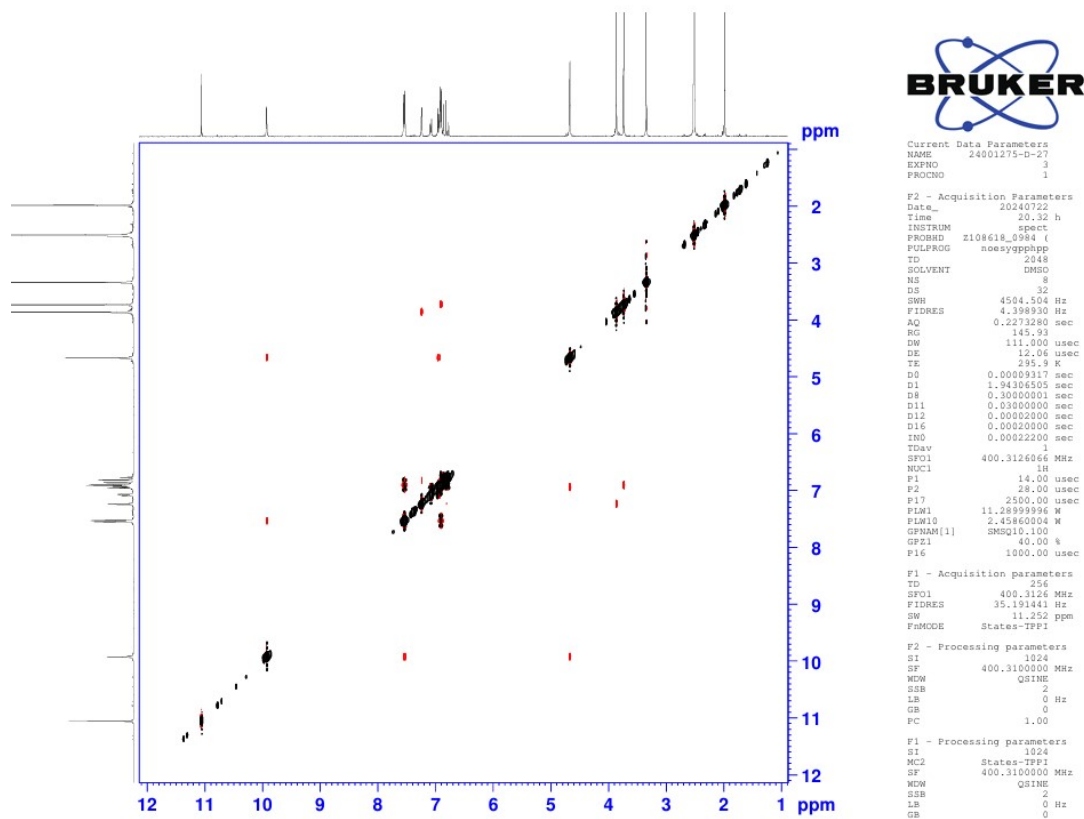
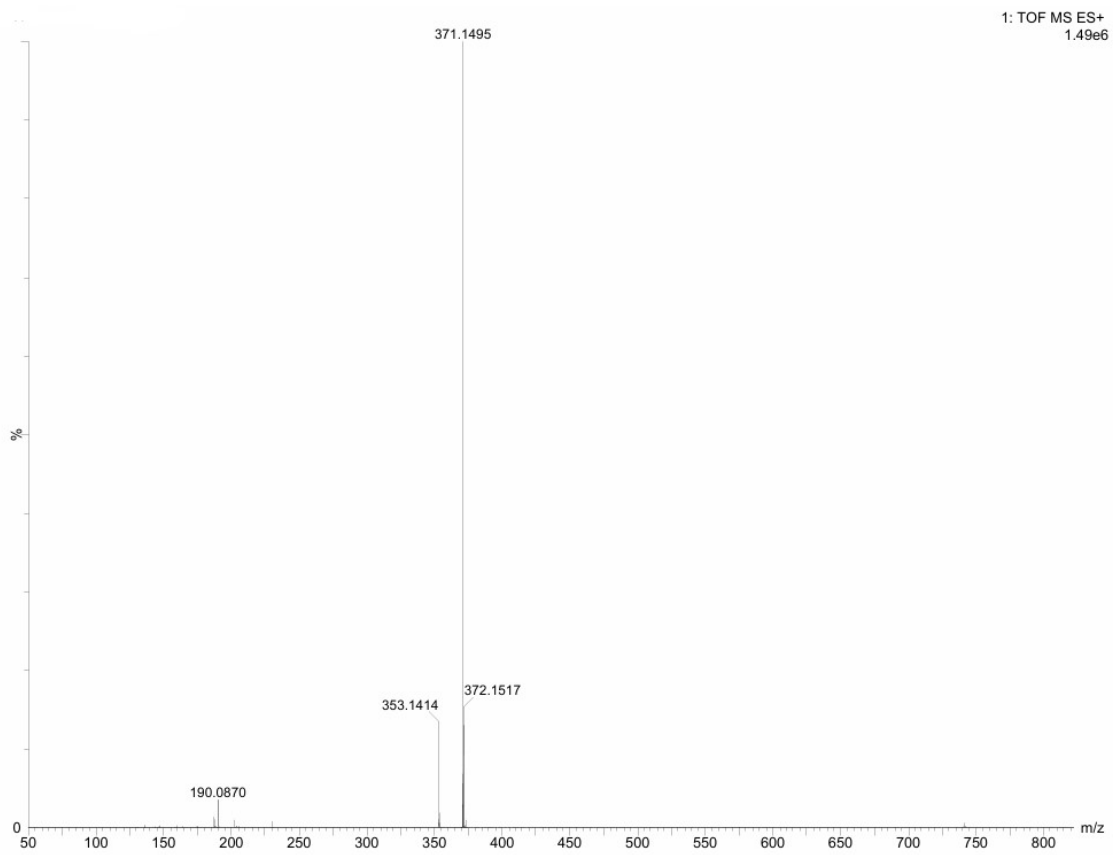


Fig. S54. <sup>1</sup>H-<sup>1</sup>H NOESY spectrum of compound 4j.





**Fig. S55.** Mass spectrum of compound **4j**.

## MTT Assay – IC<sub>50</sub> Curves

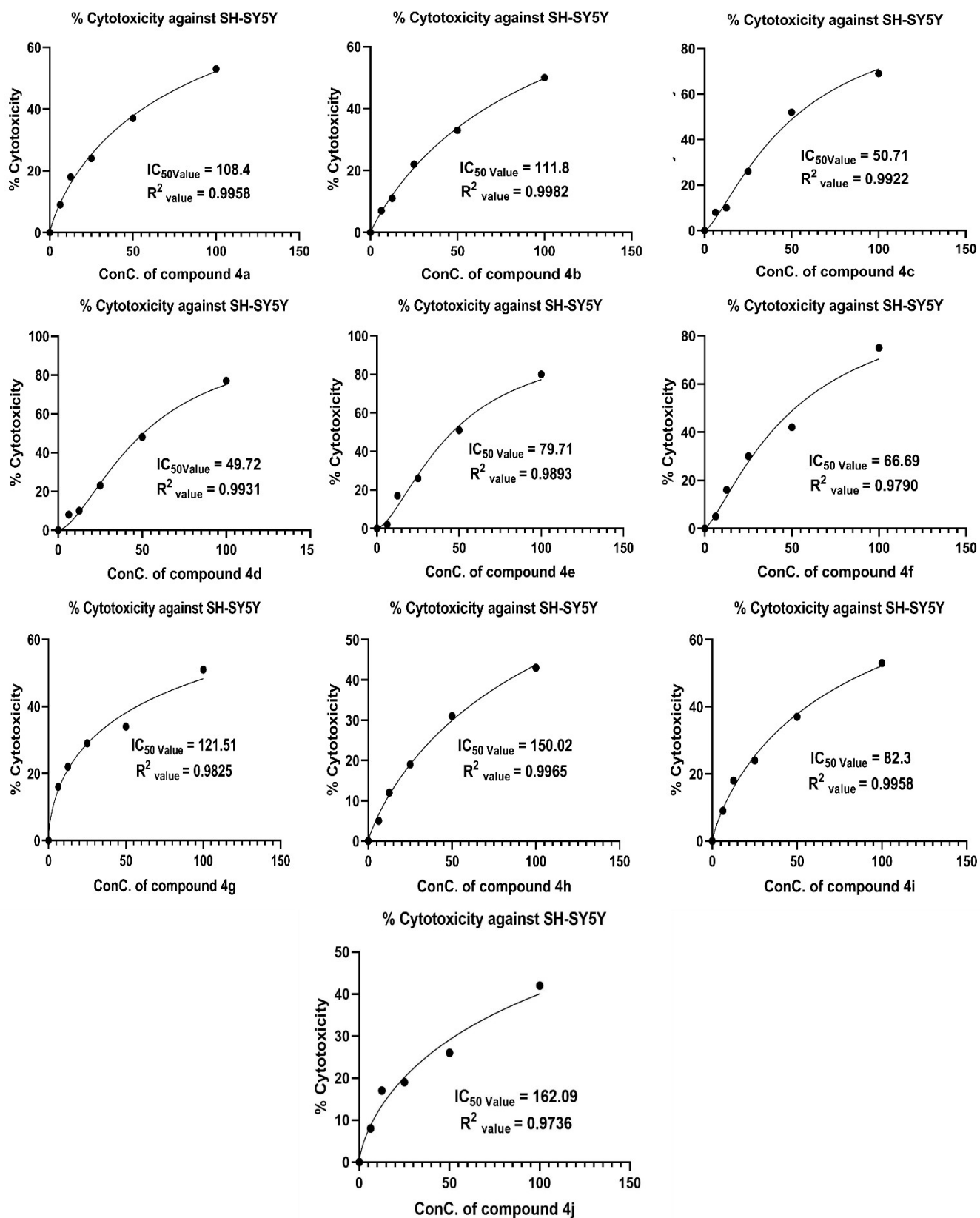
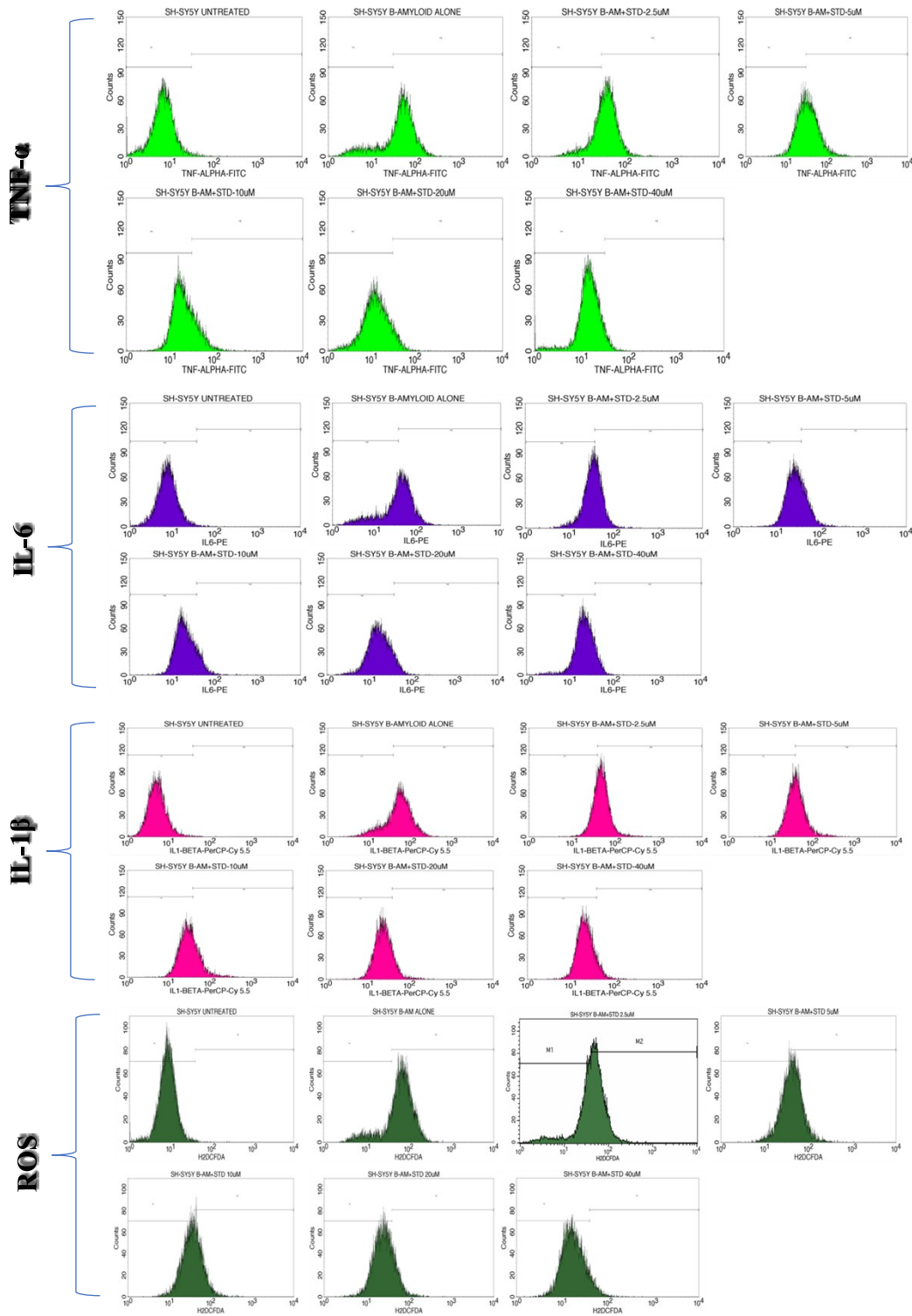
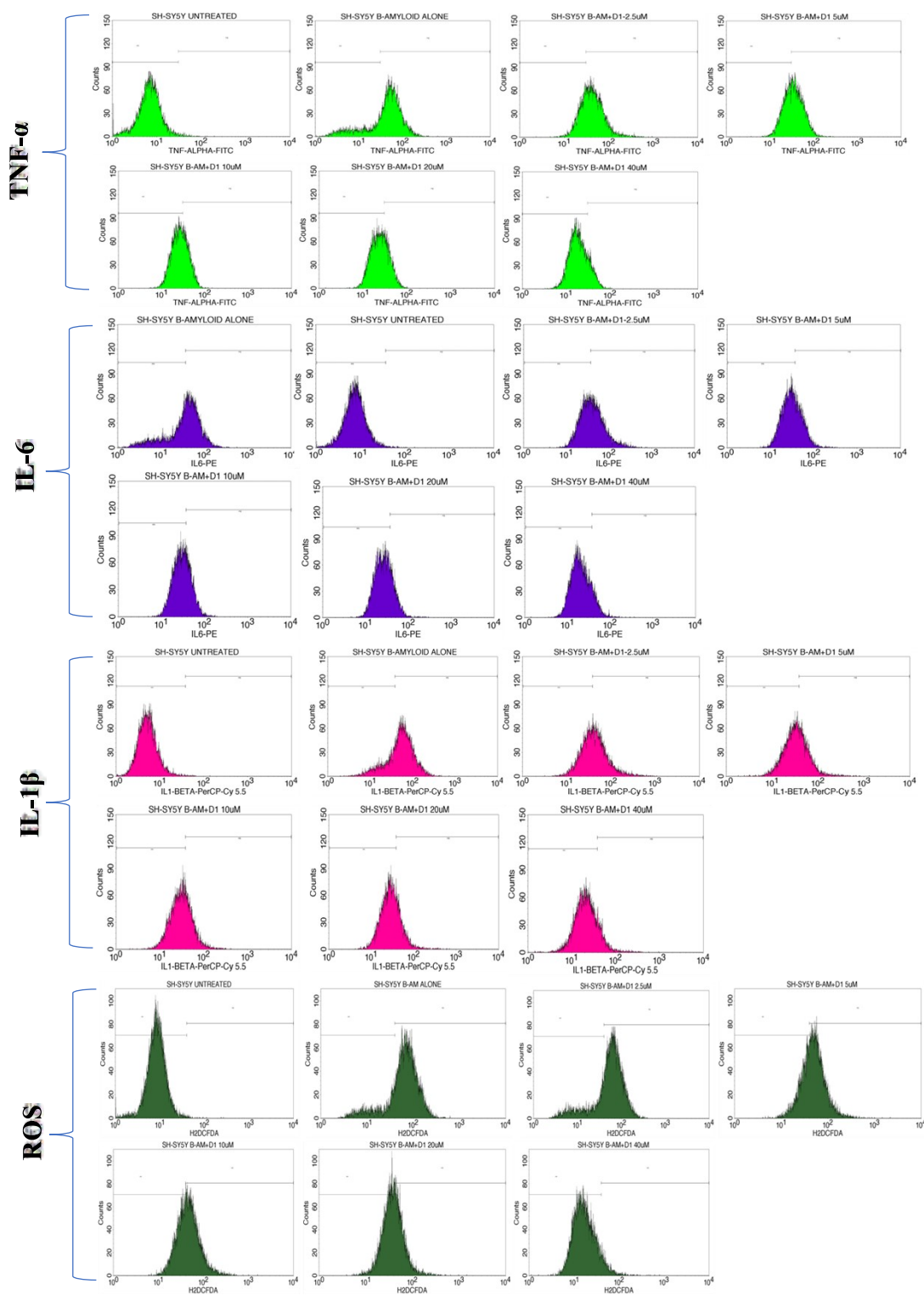


Fig. S56. The IC<sub>50</sub> curves for the MTT assay for the compounds 4(a-j).

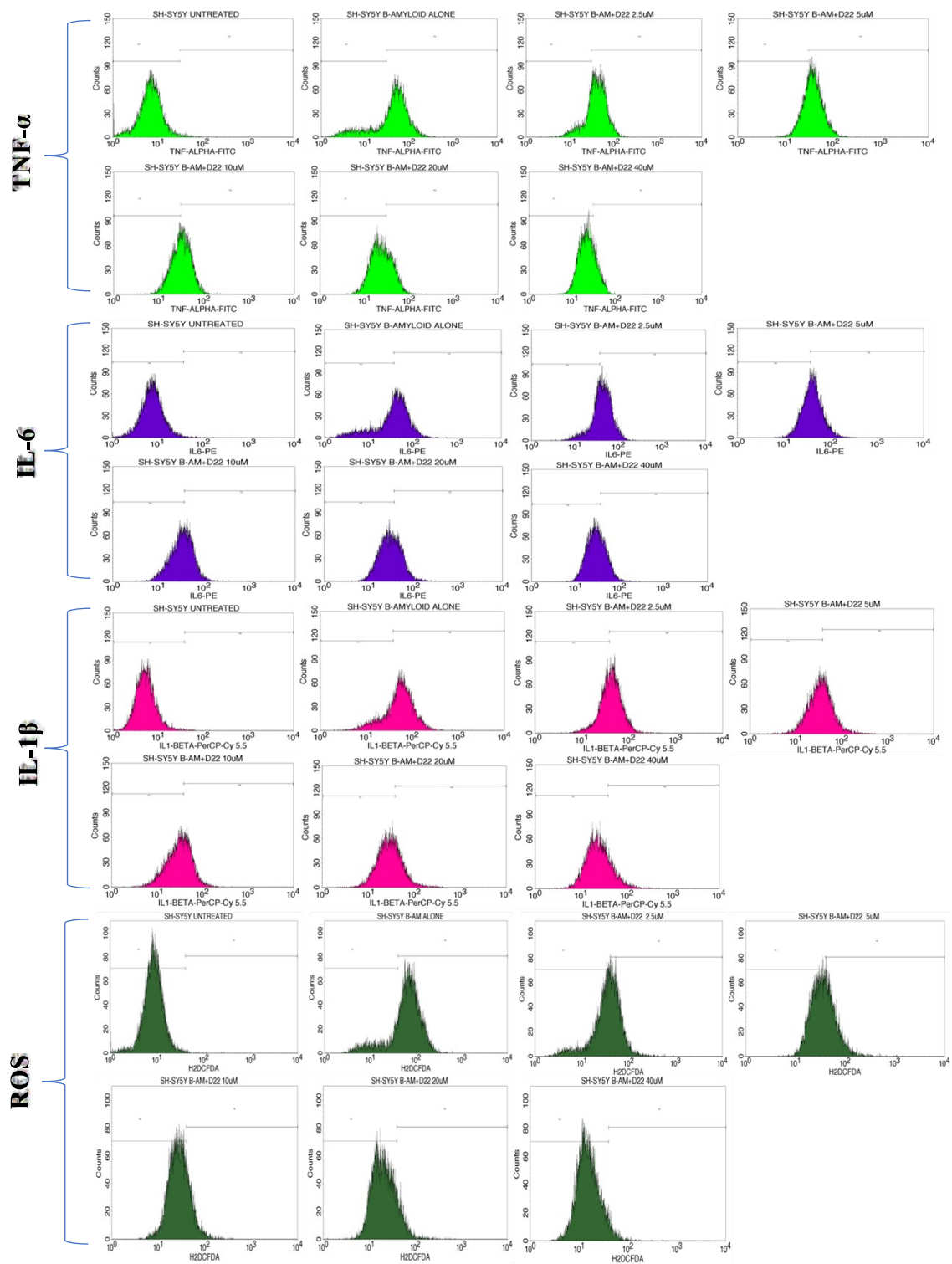
## Flow cytometry histograms



**Fig. S57.** Histogram showing the % cells expressed TNF- $\alpha$ , IL-6 and IL-1 $\beta$  intensity and ROS in Beta amyloid induced SHSY-5Y cell line with the treatment of standard drug.



**Fig. S58.** Histogram showing the % cells expressed TNF- $\alpha$ , IL-6 and IL-1 $\beta$  intensity and ROS in Beta amyloid induced SHSY-5Y cell line with the treatment of compound 4a.



**Fig. S59.** Histogram showing the % cells expressed TNF- $\alpha$ , IL-6 and IL-1 $\beta$  intensity and ROS in Beta amyloid induced SHSY-5Y cell line with the treatment of compound 4h.