

# New Genetic Bomb Trigger: Design, Synthesis, Molecular Dynamics Simulation, and Biological Evaluation of Novel BIBR1532-Related Analogs Targeting Telomerase against Non-Small Cell Lung Cancer

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## Supplementary Material

Spectral data section .....	S2-S54
Biological section .....	S55-S59

anwar amine Asp hnmr-M

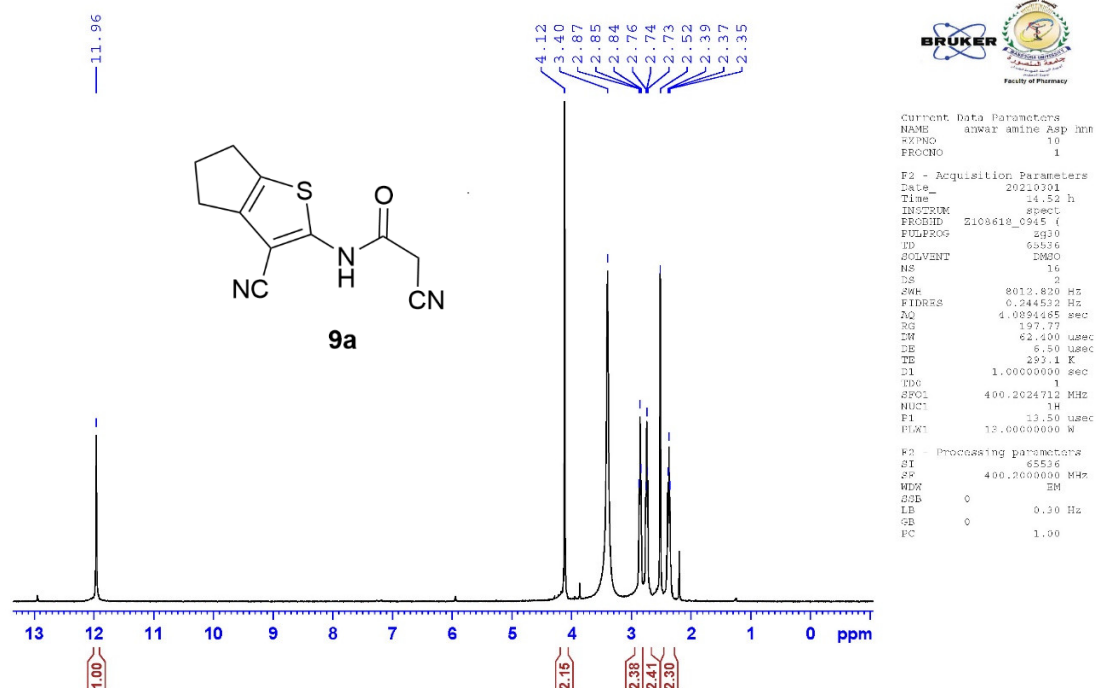


Figure S1. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) spectrum of compound **9a**.

Anwar Amin-AS-AS-proton

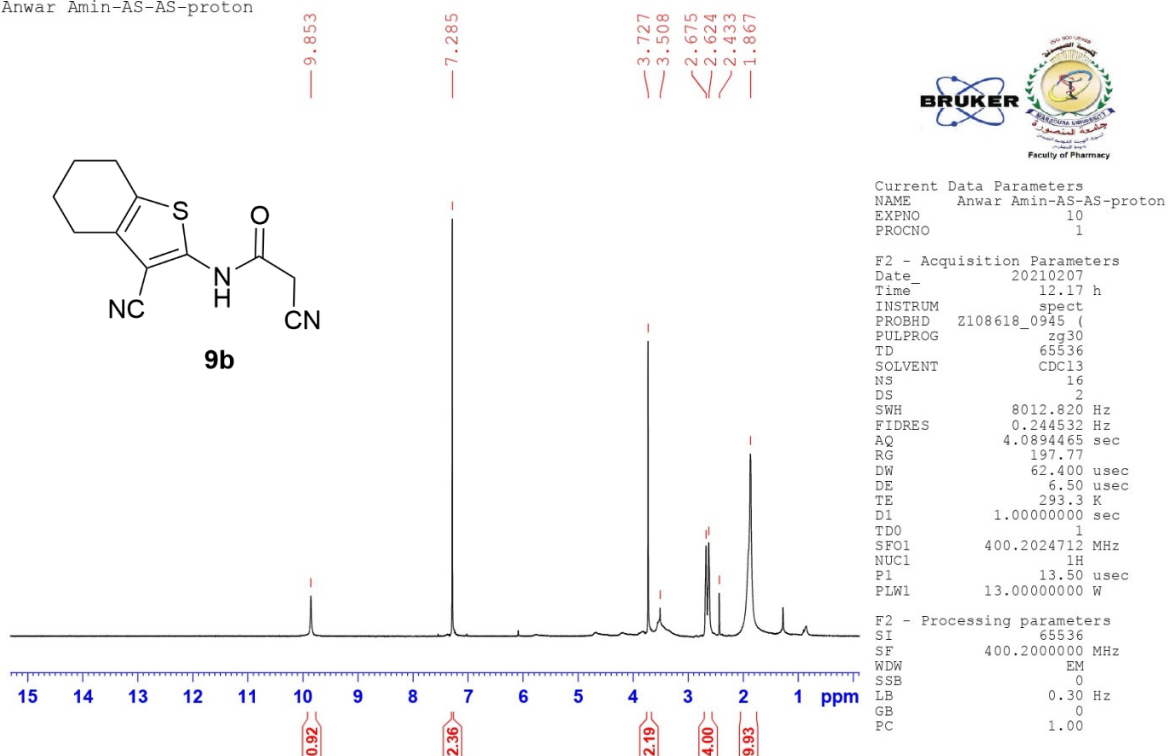


Figure S2. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) spectrum of compound **9b**.

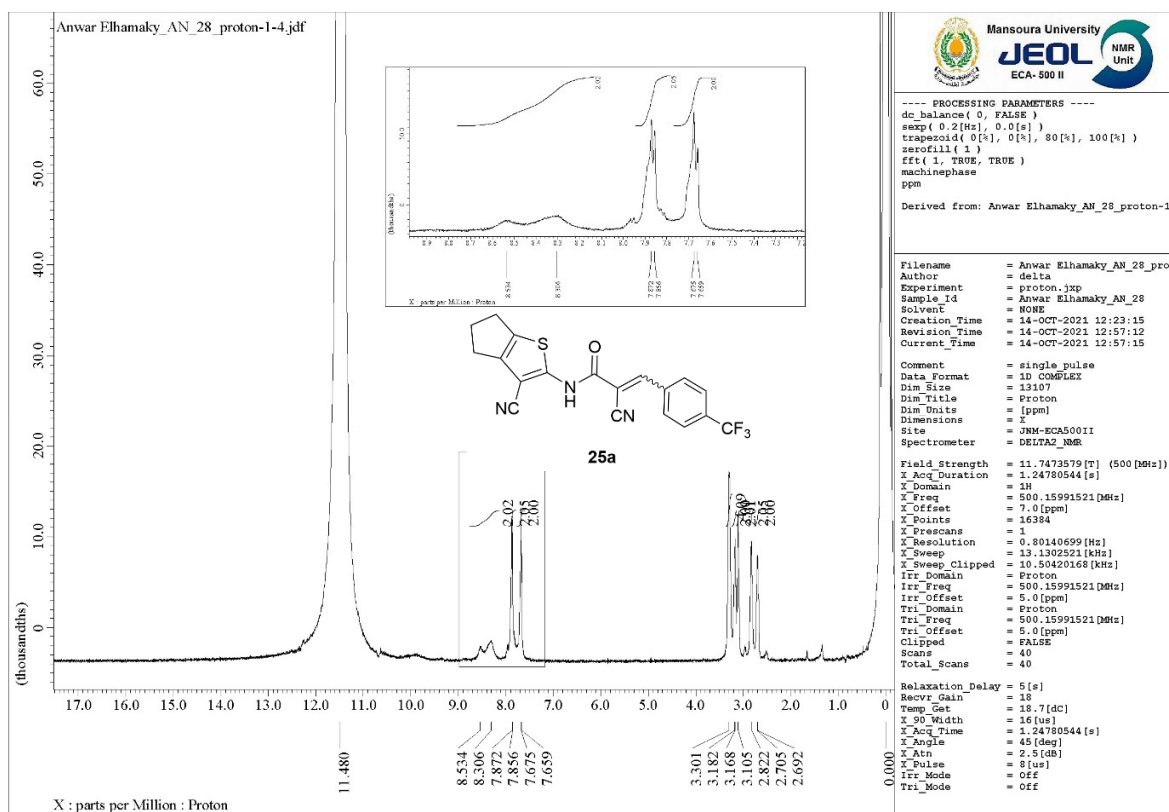


Figure S3.  $^1\text{H}$  NMR (500 MHz,  $\text{CF}_3\text{COOD}$ ) spectrum of compound **25a** as *E/Z* mixture.

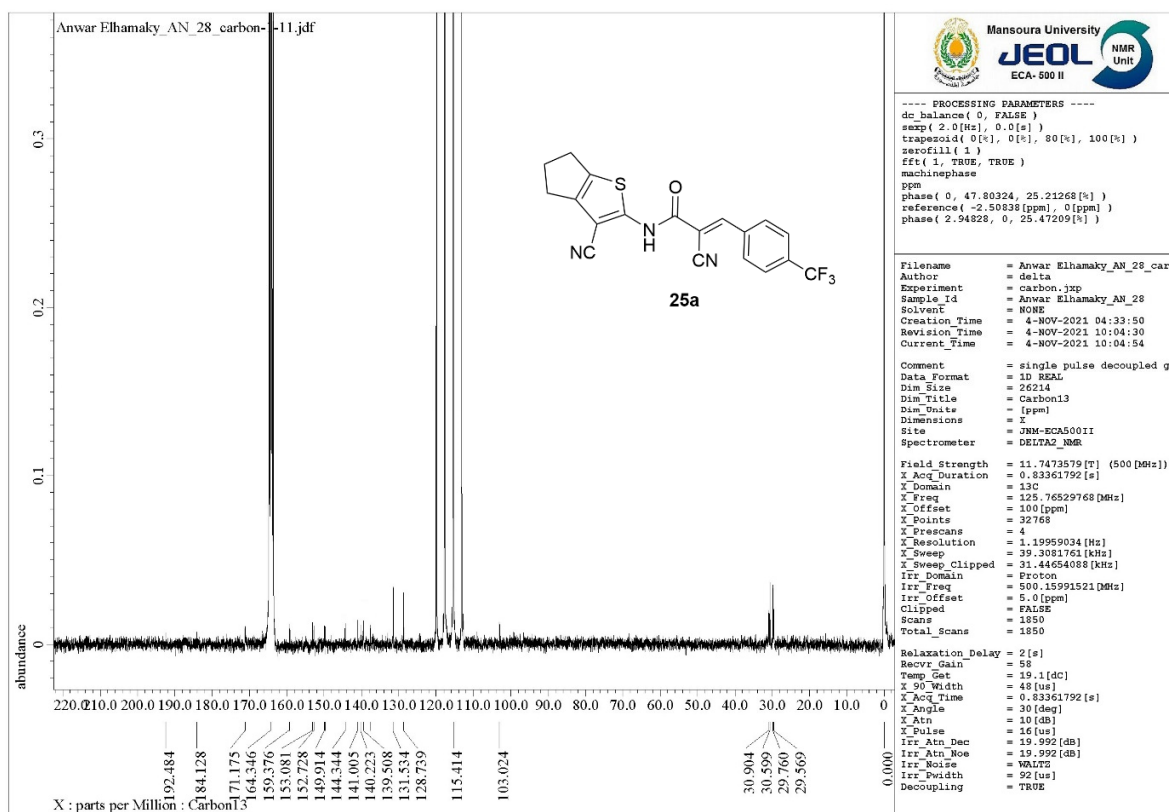


Figure S4.  $^{13}\text{C}$  NMR (125 MHz,  $\text{CF}_3\text{COOD}$ ) spectrum of compound **25a**.

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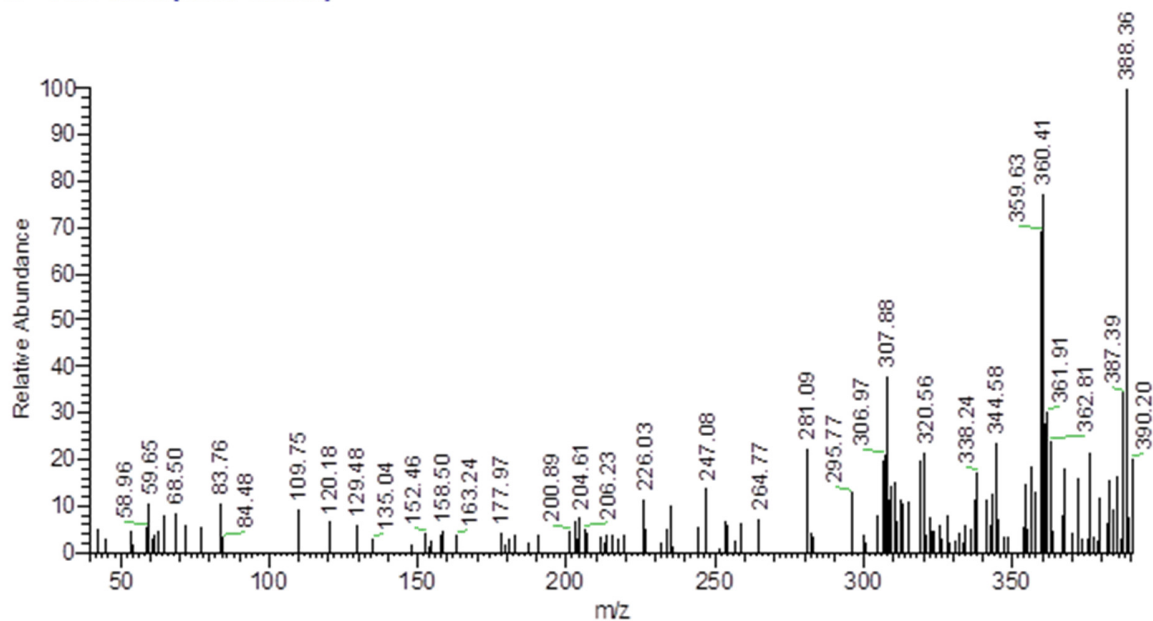


Figure S5. Mass spectrum of compound 25a.

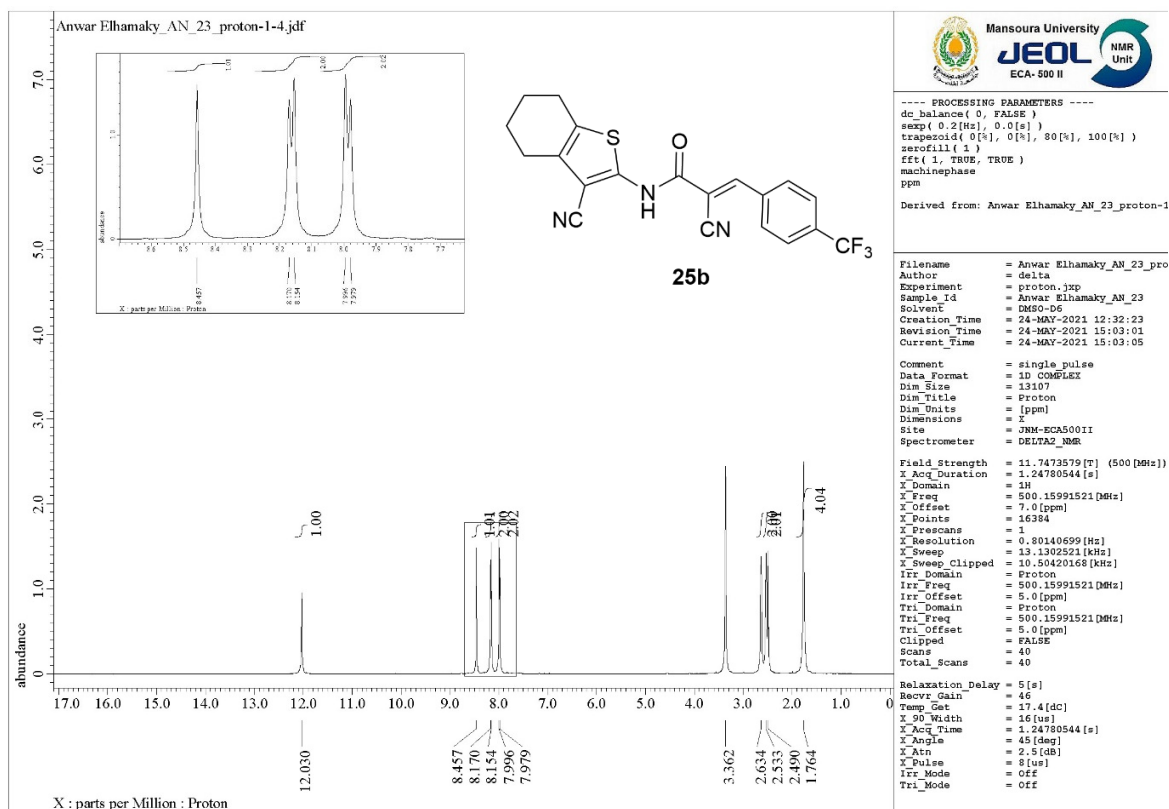


Figure S6.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ ) spectrum of compound 25b in E configuration.





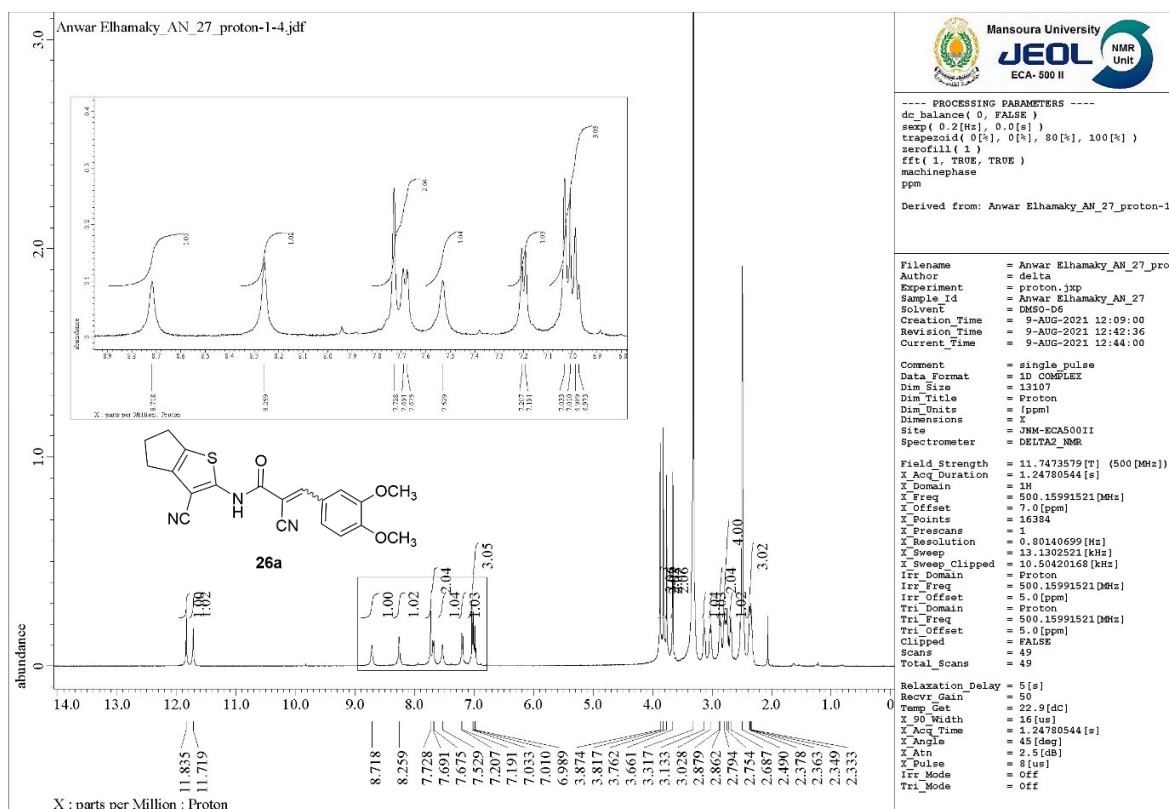


Figure S9.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ ) spectrum of compound **26a** as *E/Z* mixture.

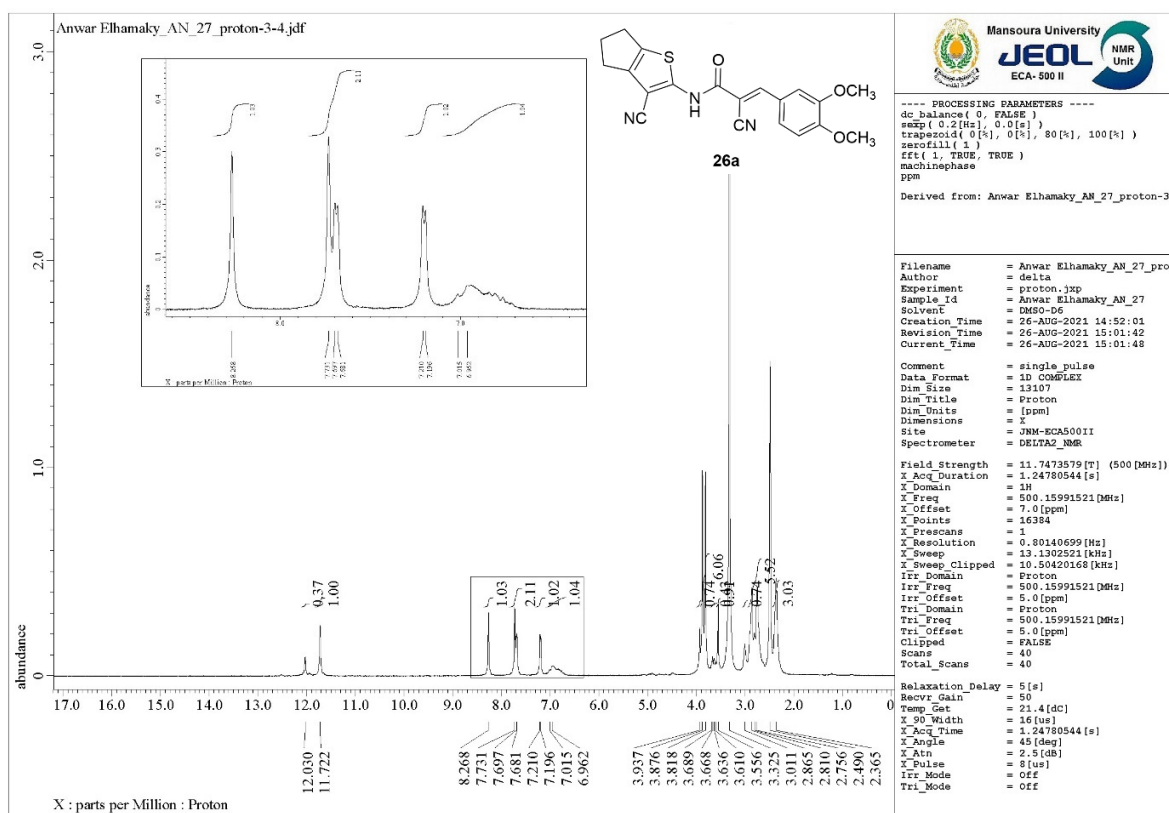


Figure S10.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ ) spectrum of compound **26a** as a pure *E* configuration.

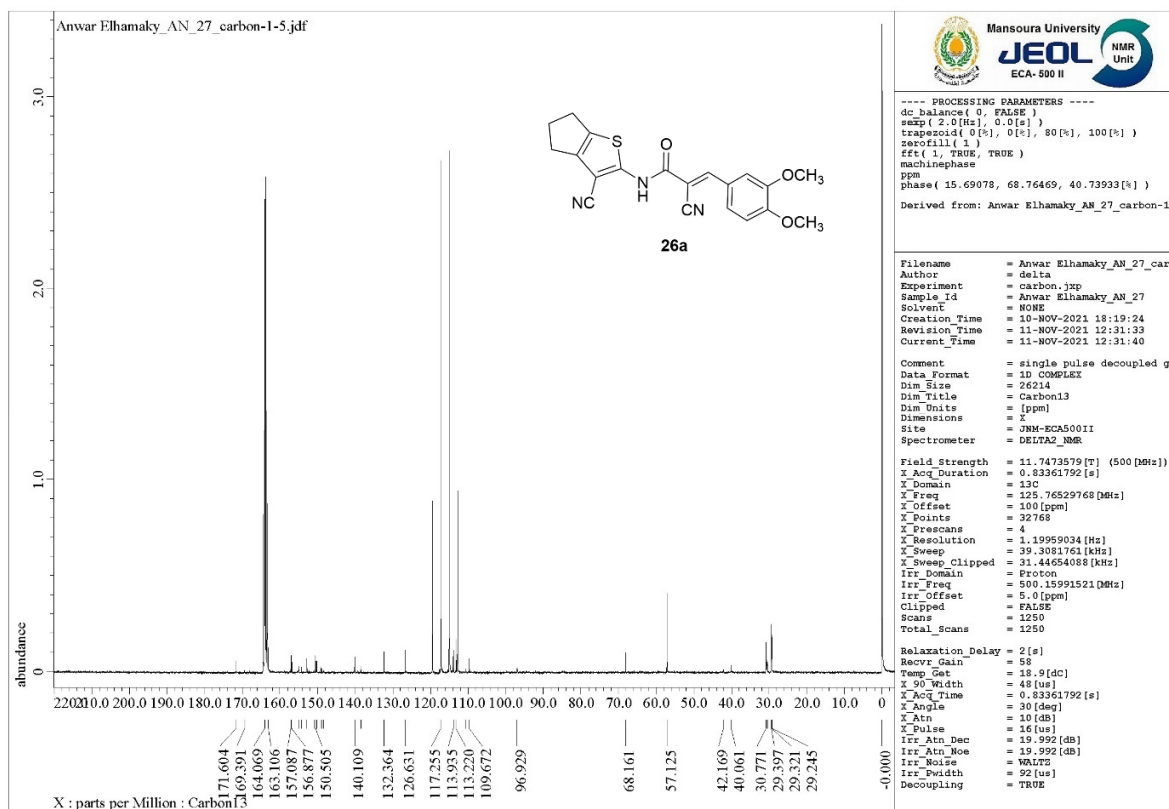
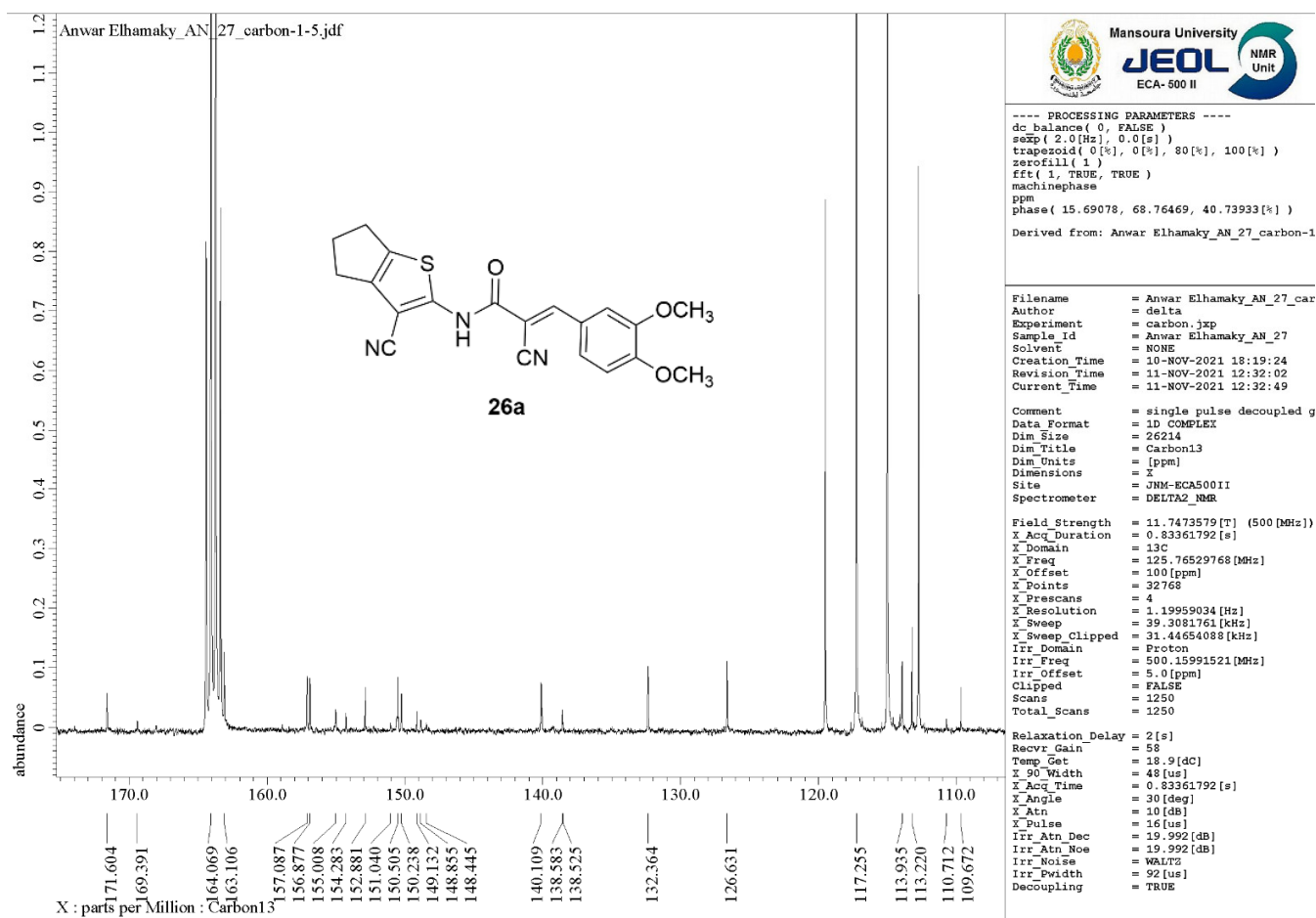
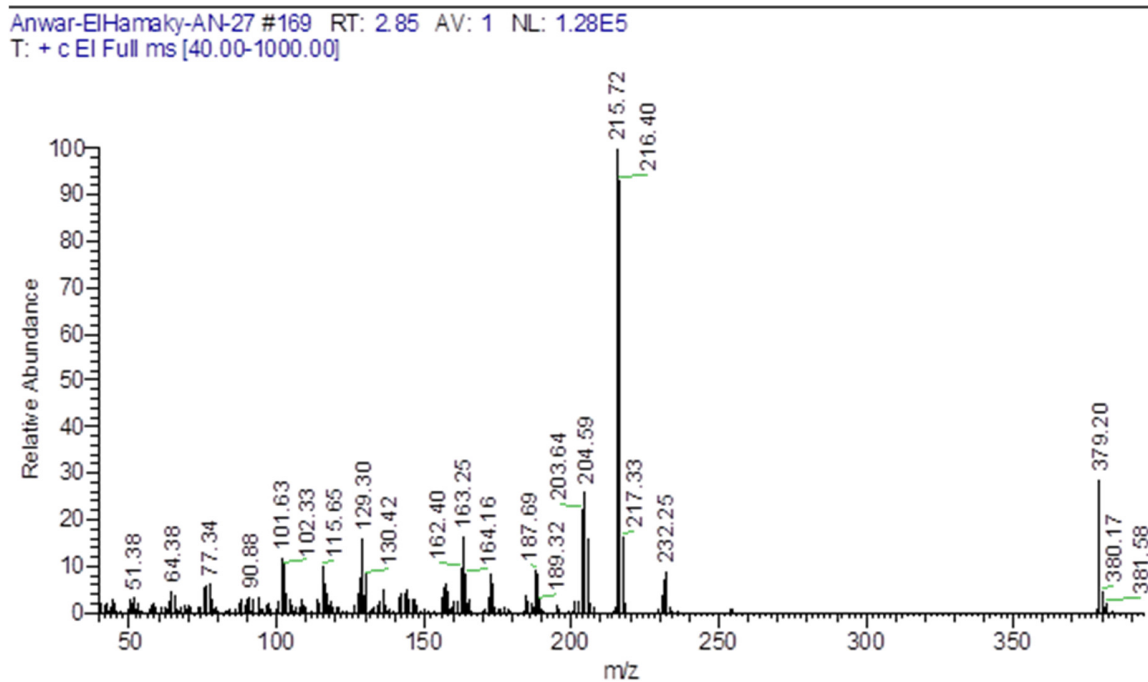


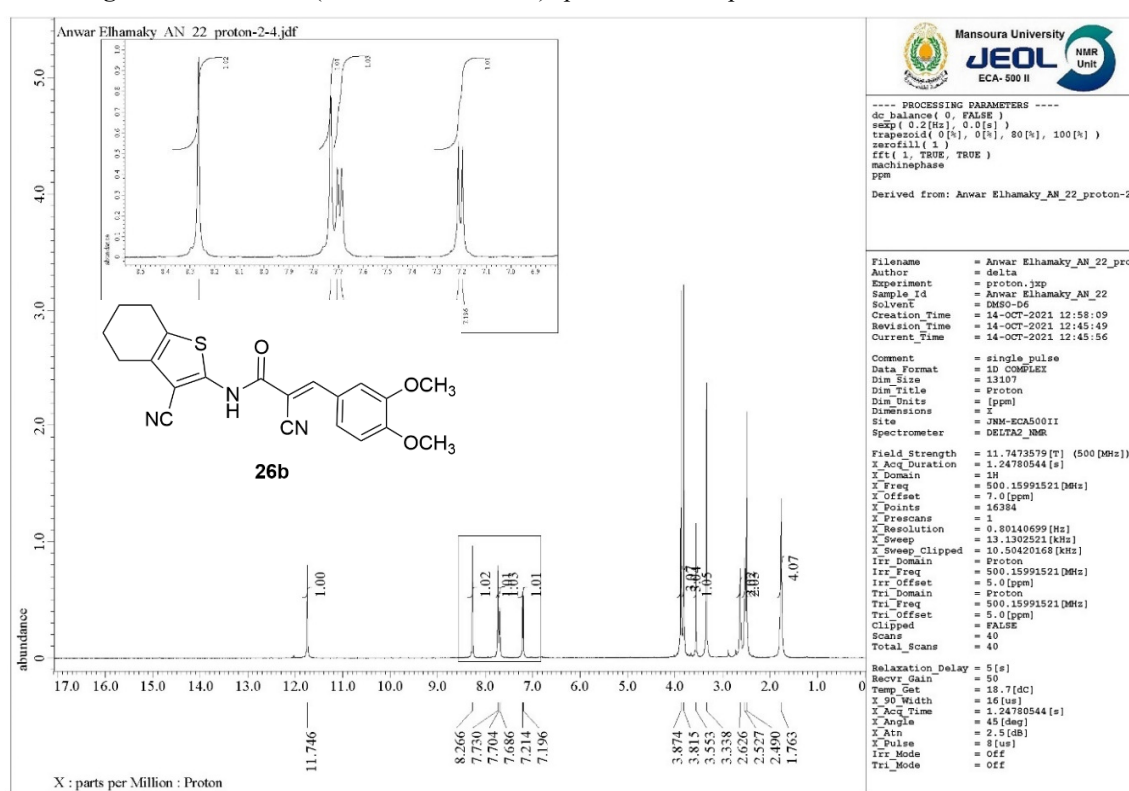
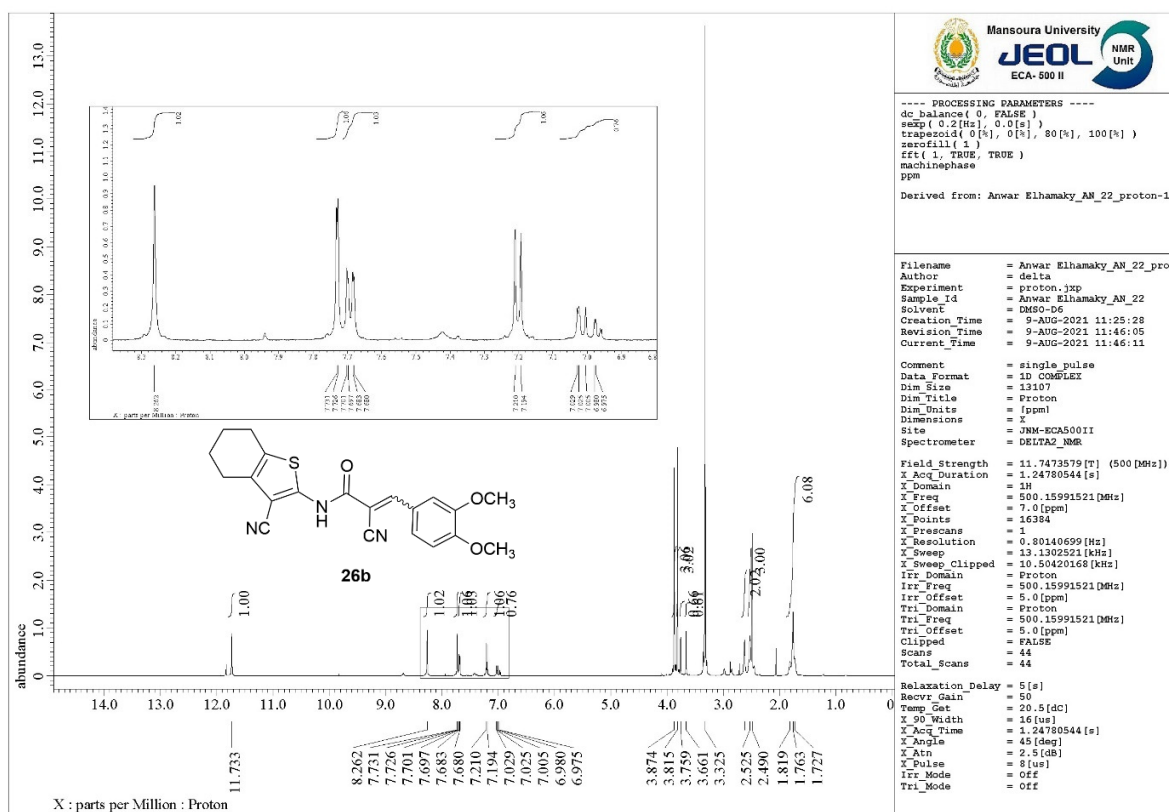
Figure S11 a.  $^{13}\text{C}$  NMR (125 MHz,  $\text{CF}_3\text{COOD}$ ) spectrum of compound 26a.



**Figure S11 b.**  $^{13}\text{C}$  NMR (125 MHz,  $\text{CF}_3\text{COOD}$ ) spectrum of compound **26a** (focusing on 109.0-172.0 ppm).



**Figure S12.** Mass spectrum of compound **26a**.



**Figure S14. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) spectrum of compound **26b** as a pure *E* configuration.**

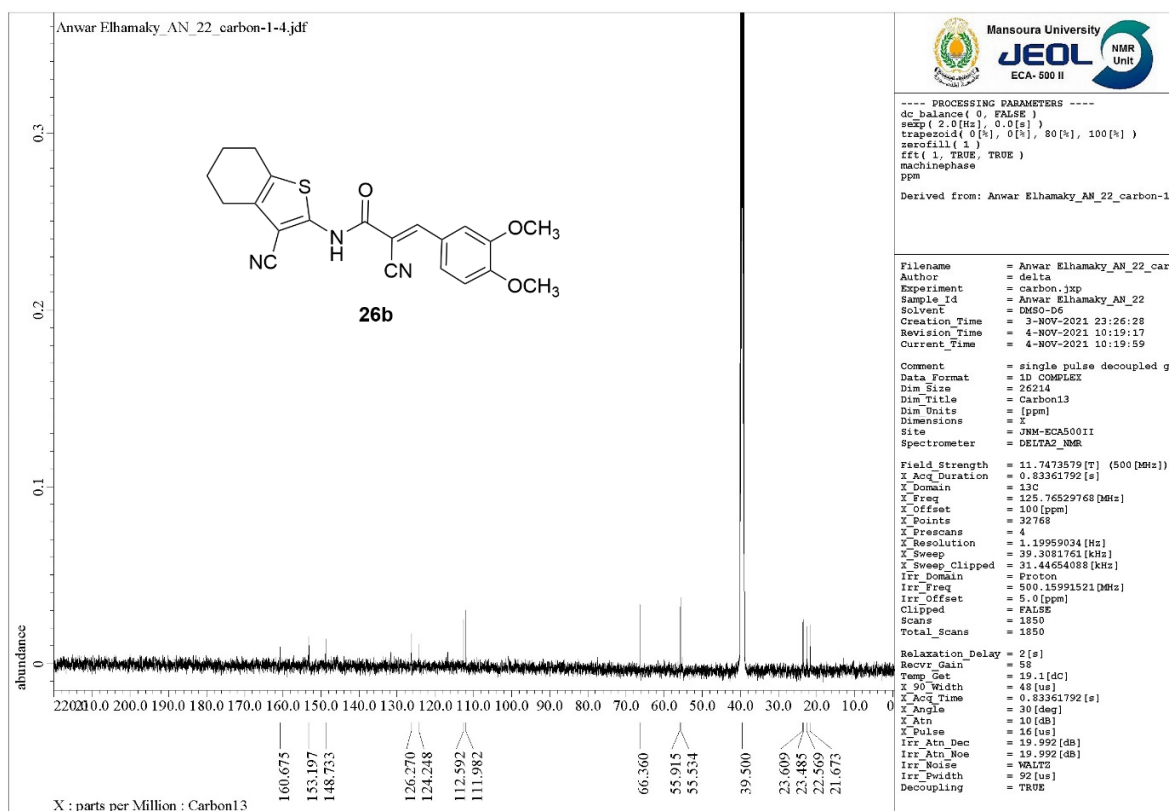


Figure S15.  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO}-d_6$ ) spectrum of compound **26b**.

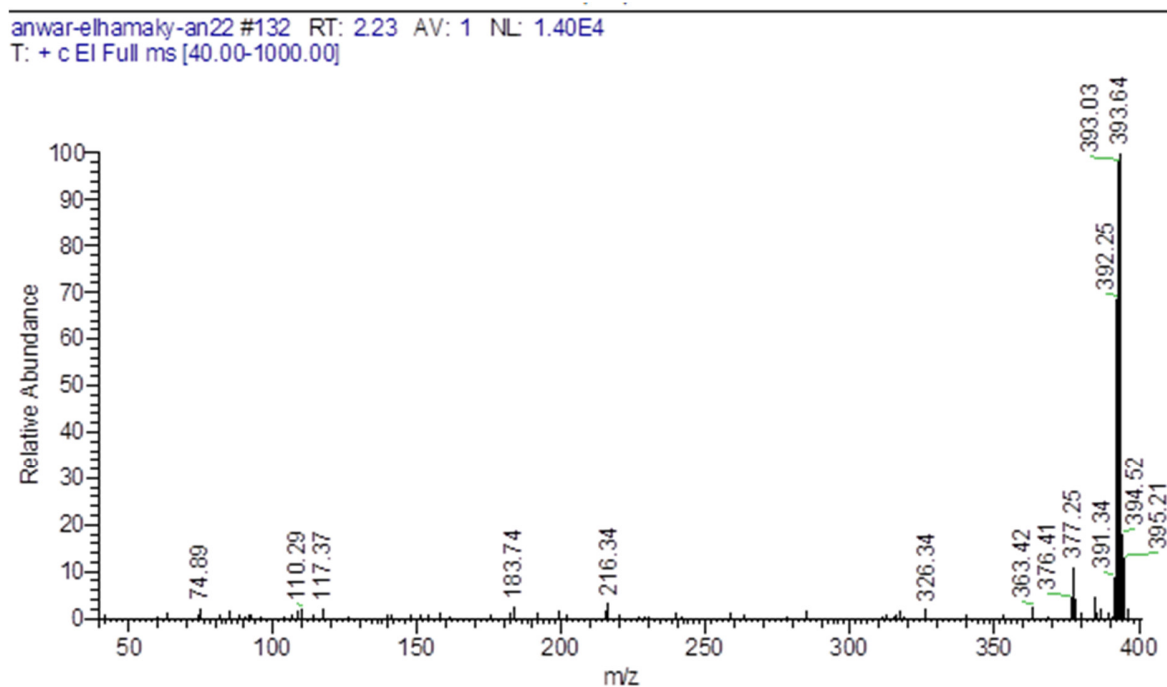
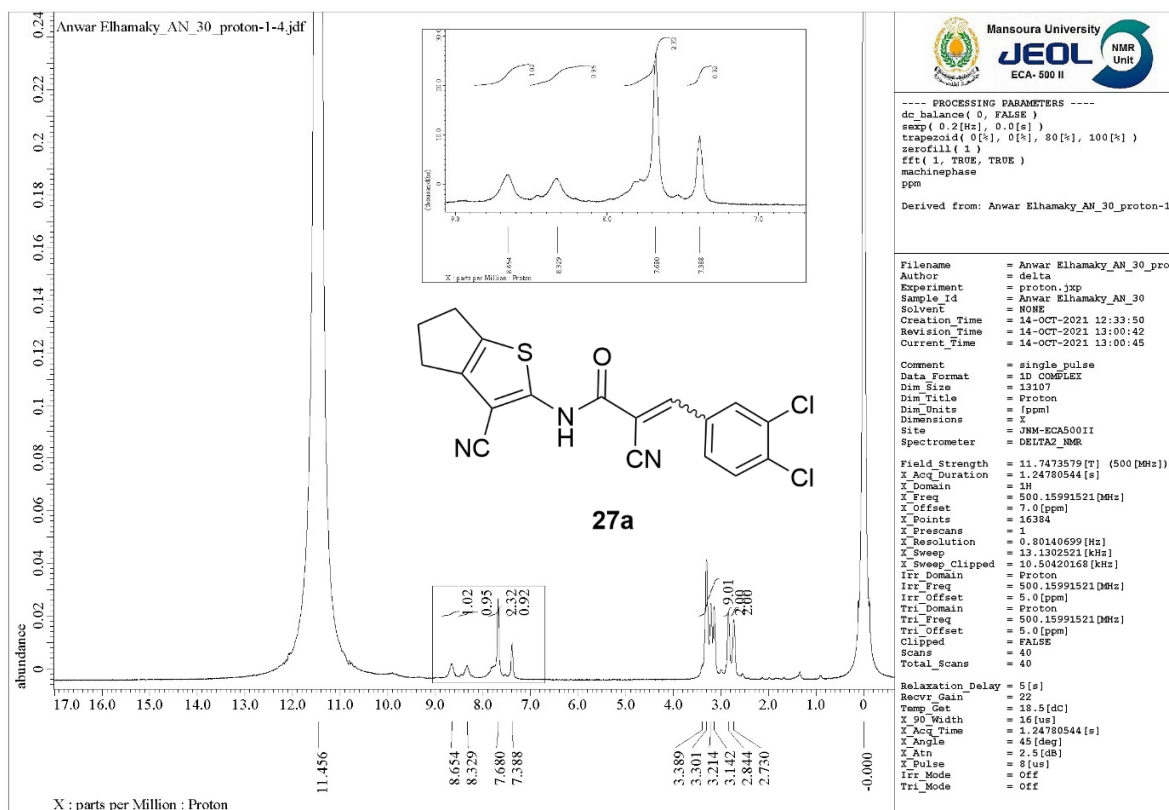
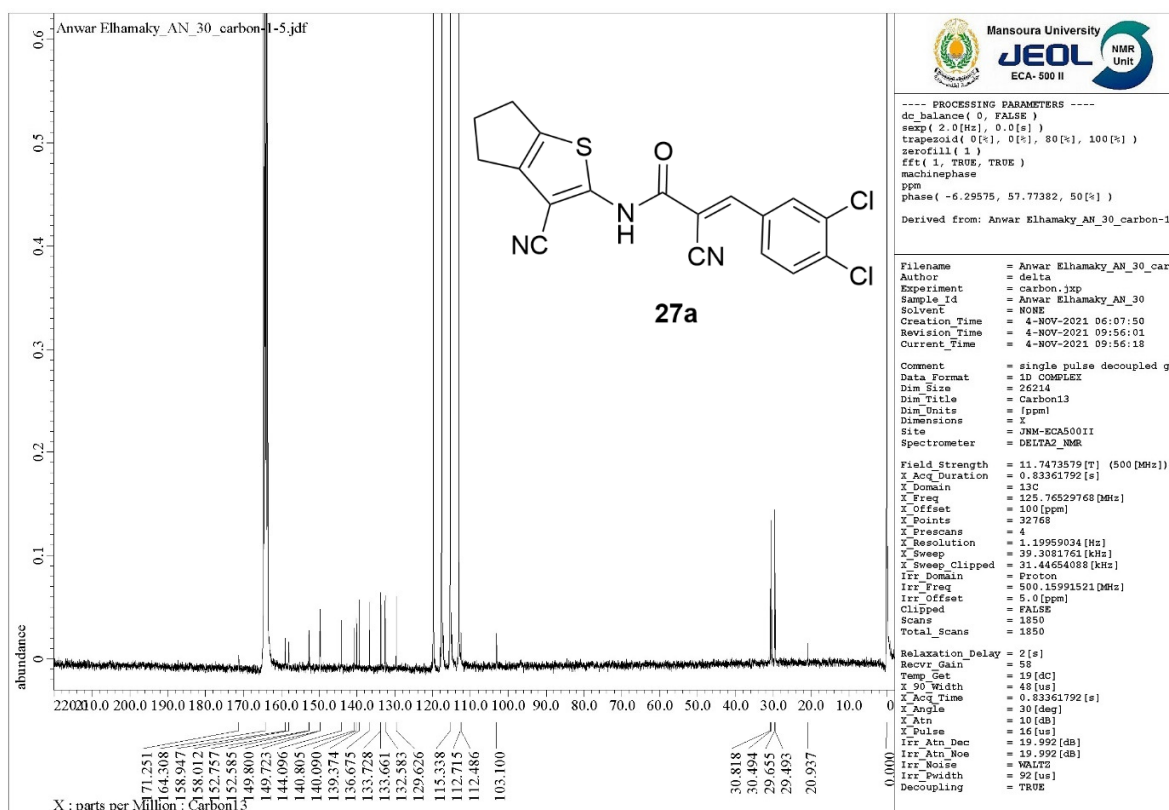


Figure S16. Mass spectrum of compound **26b**.



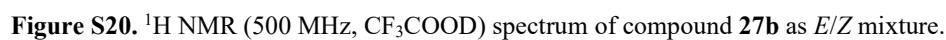
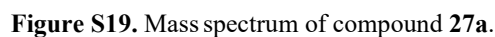


**Figure S17. <sup>1</sup>H NMR (500 MHz, CF<sub>3</sub>COOD) spectrum of compound **27a** as *E/Z* mixture.**



**Figure S18. <sup>13</sup>C NMR (125 MHz, CF<sub>3</sub>COOD) spectrum of compound **27a**.**





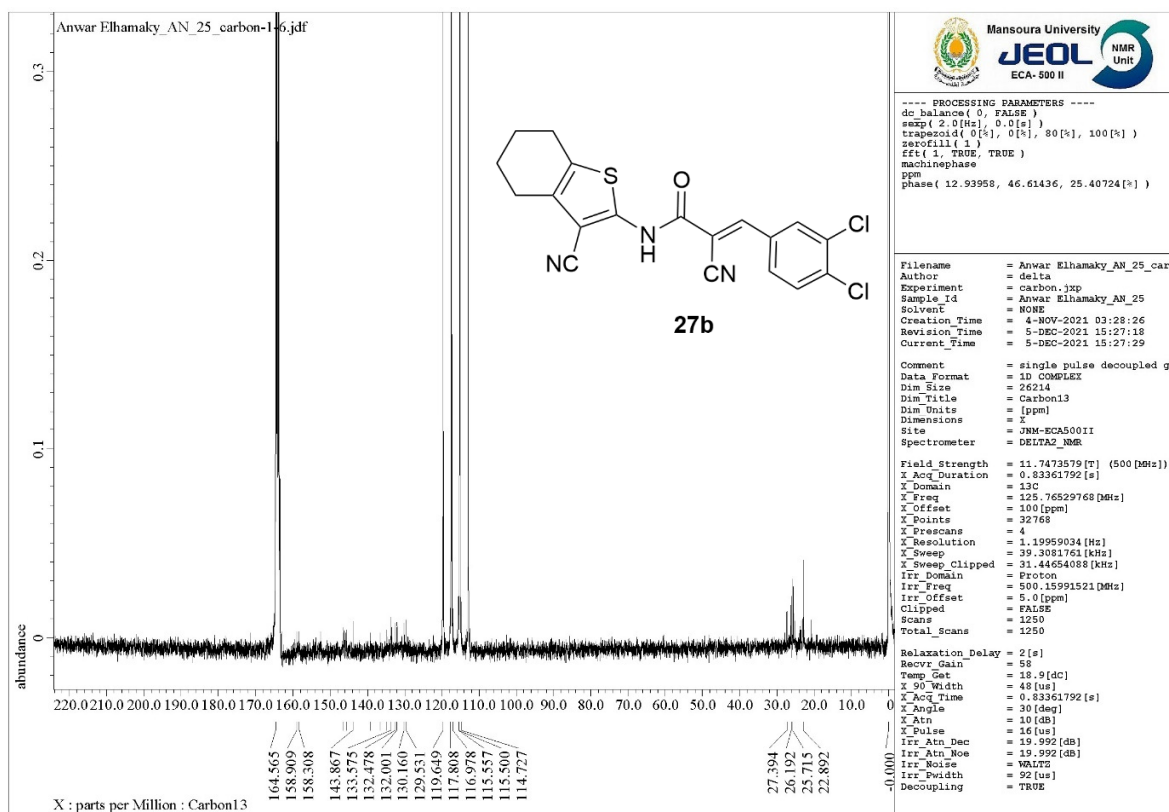


Figure S21 a.  $^{13}\text{C}$  NMR (125 MHz,  $\text{CF}_3\text{COOD}$ ) spectrum of compound 27b.

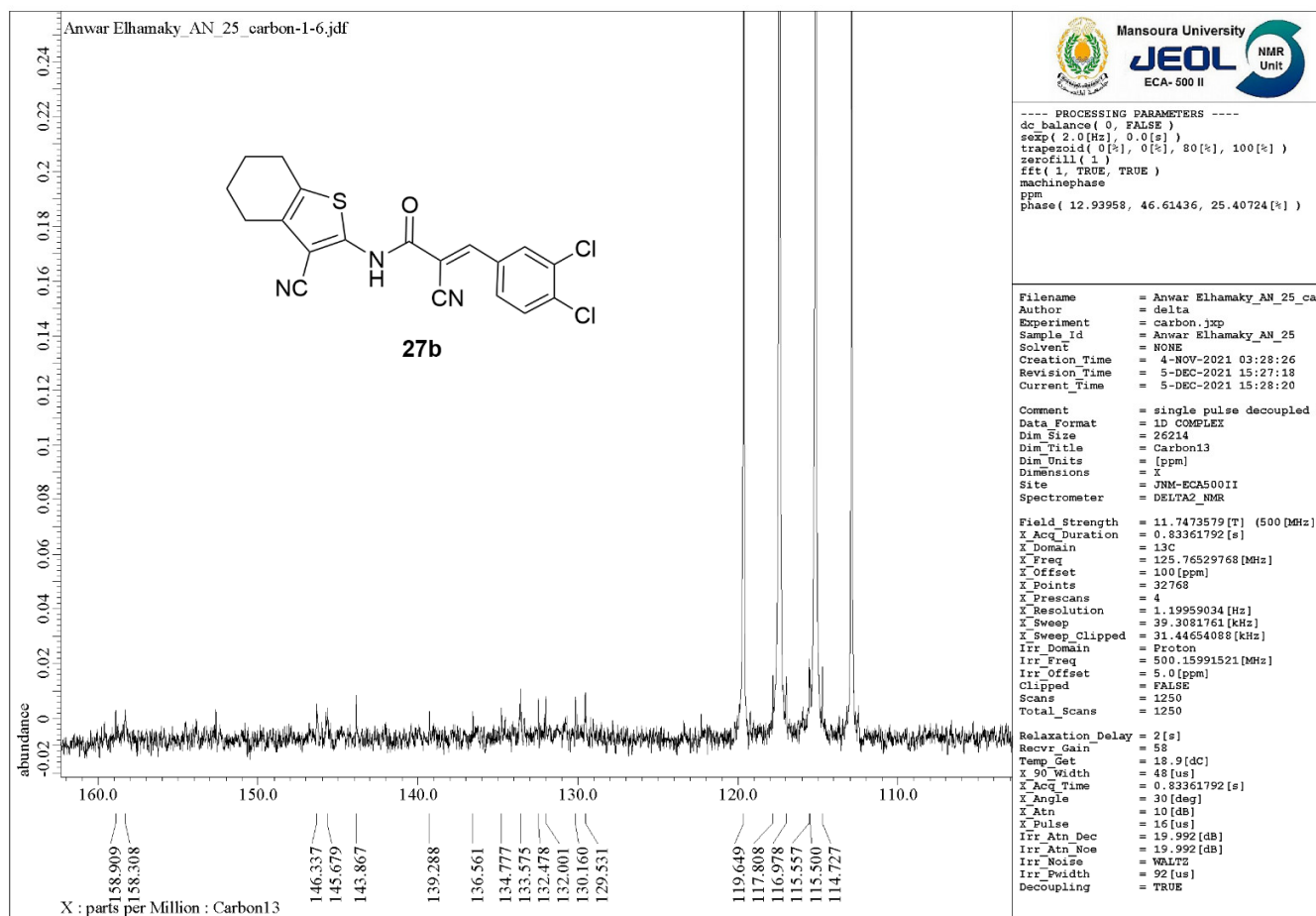


Figure S21 b.  $^{13}\text{C}$  NMR (125 MHz,  $\text{CF}_3\text{COOD}$ ) spectrum of compound **27b** (focusing on 110.0-160.0 ppm).

Anwar-ElHamaky-AN-25 #135-136 RT: 2.28-2.29 AV: 2 NL: 1.17E4  
T: + c EI Full ms [40.00-1000.00]

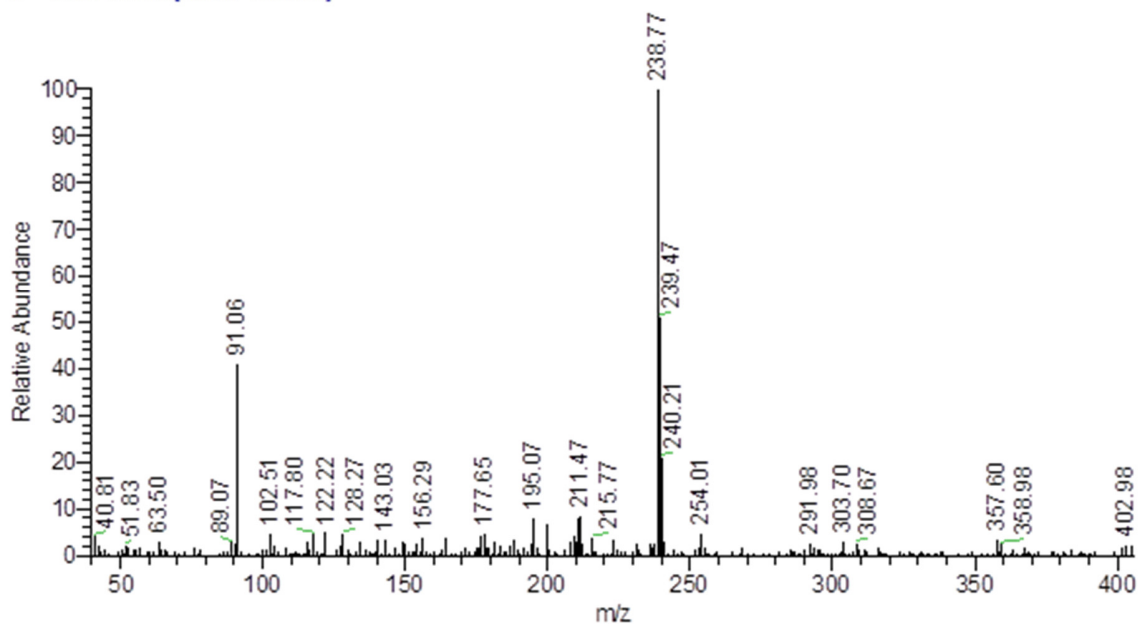


Figure S22. Mass spectrum of compound **27b**.

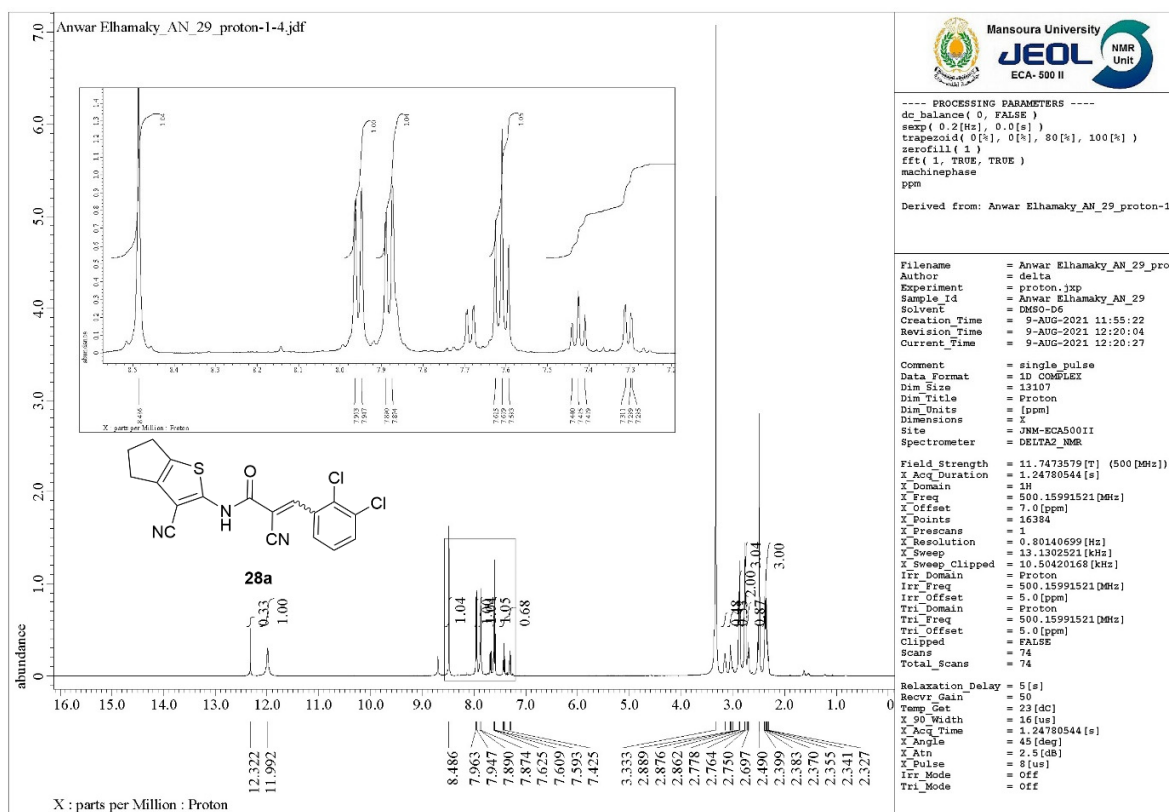


Figure S23.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ ) spectrum of compound **28a** as *E/Z* mixture.

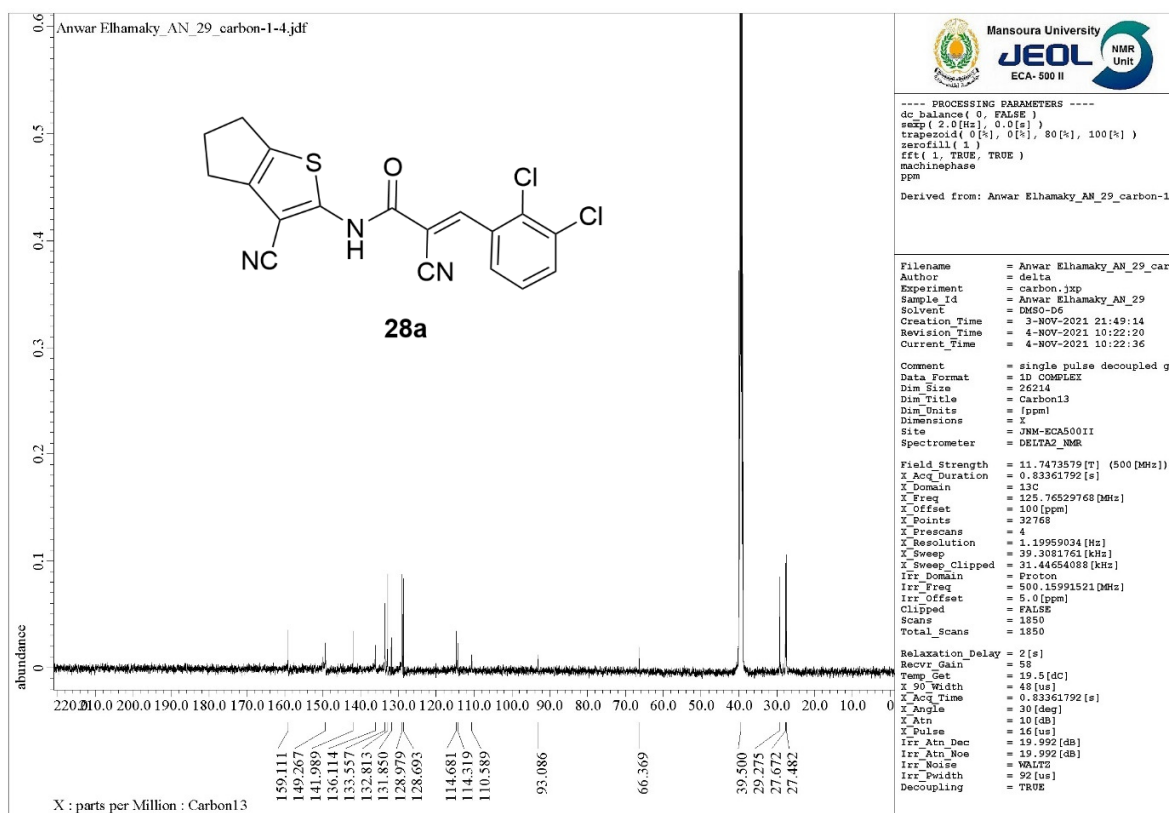


Figure S24.  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO}-d_6$ ) spectrum of compound **28a**.

anwar-elhamaky-an29 #149 RT: 2.51 AV: 1 NL: 6.74E4  
T: + c EI Full ms [40.00-1000.00]

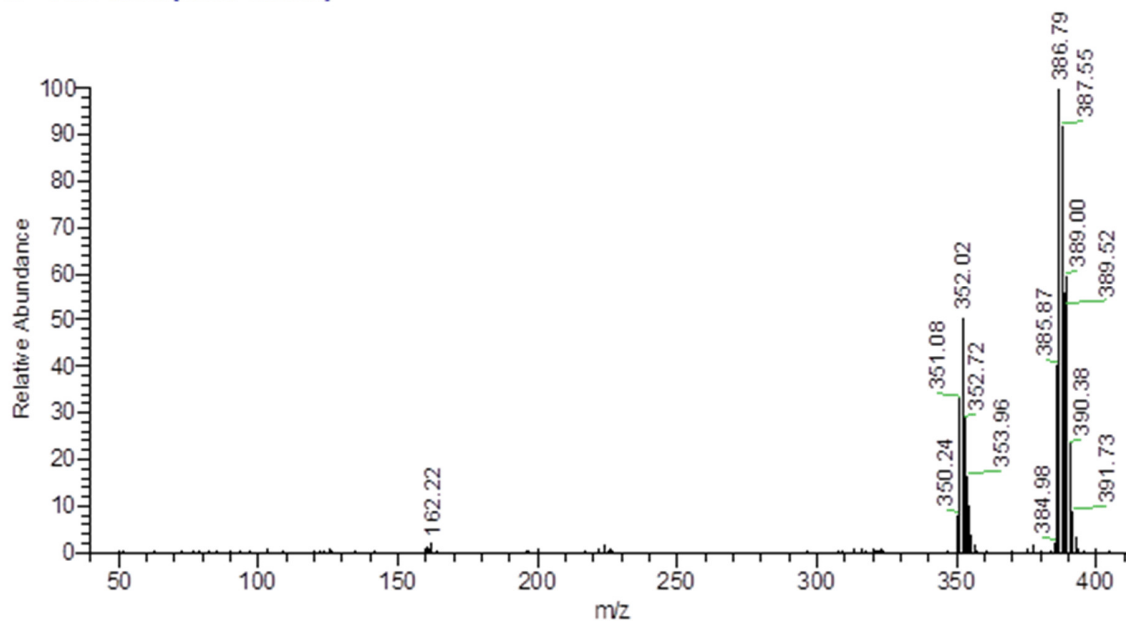


Figure S25. Mass spectrum of compound **28a**.

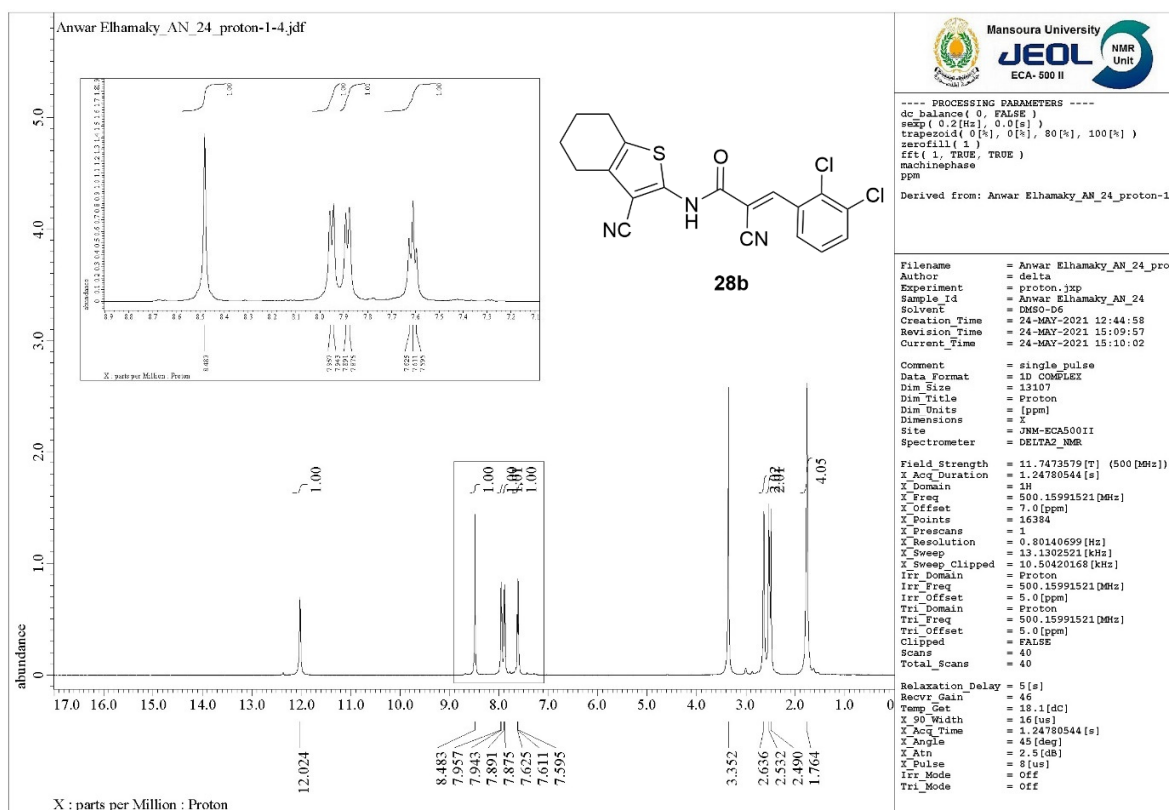


Figure S26. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) spectrum of compound **28b** in *E* configuration.

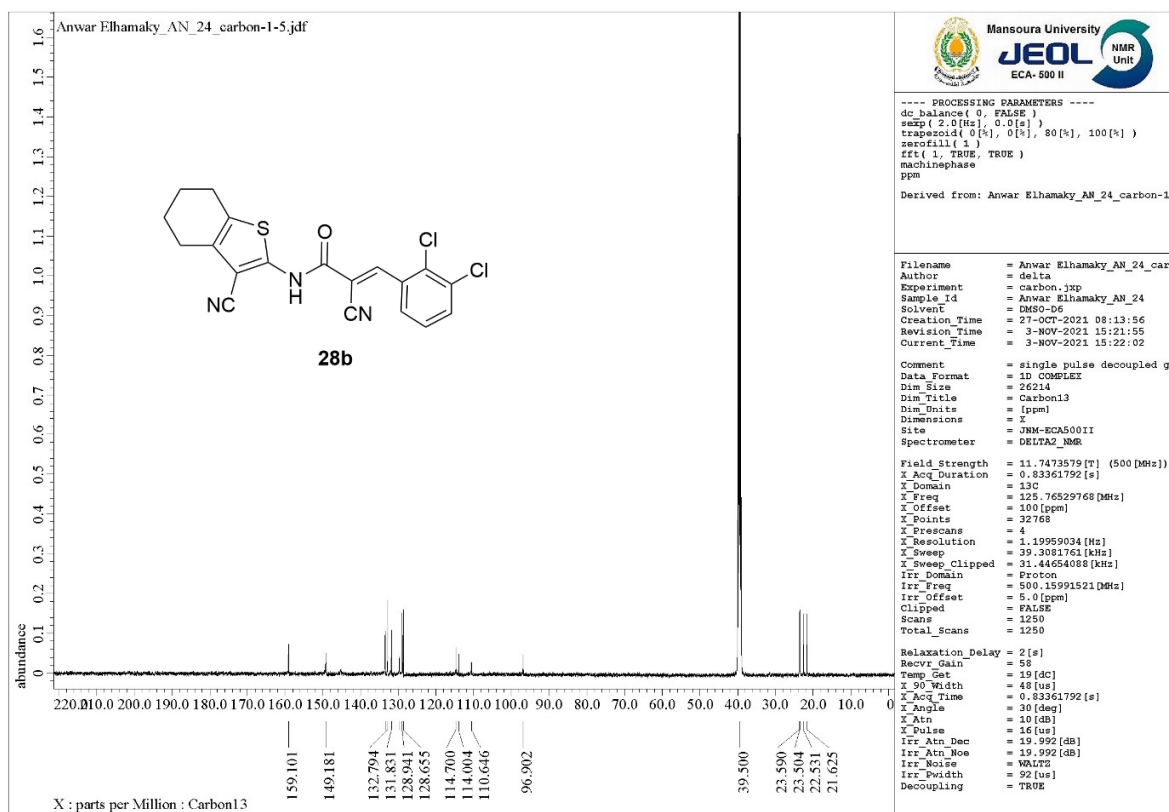


Figure S27.  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO}-d_6$ ) spectrum of compound **28b**.

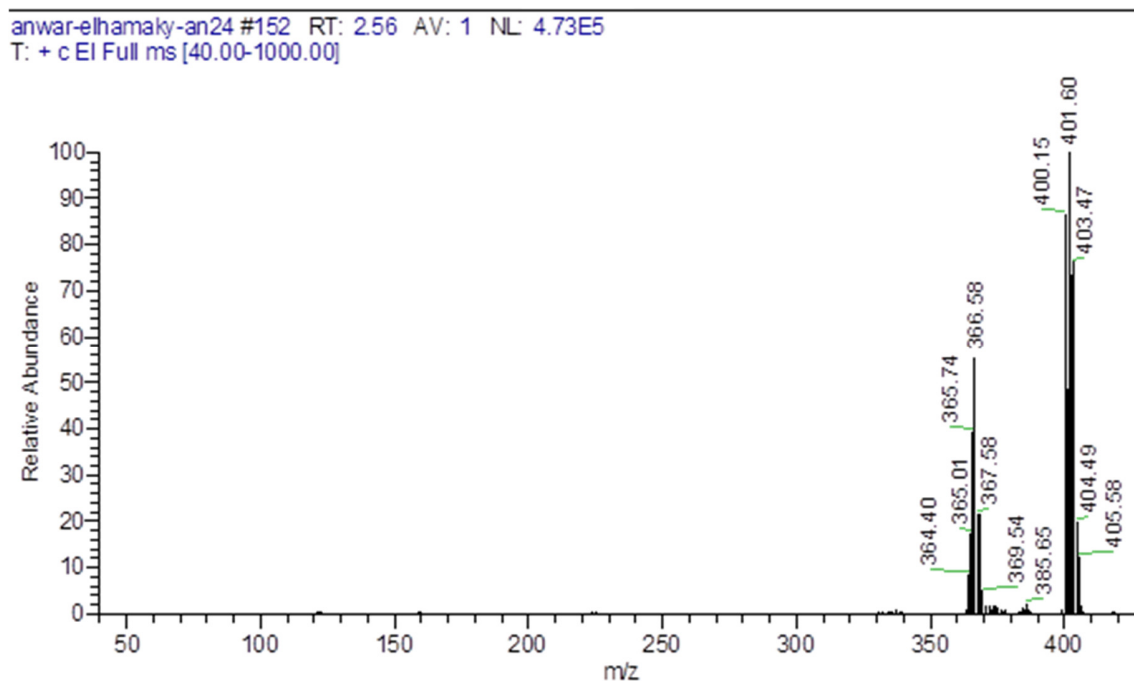


Figure S28. Mass spectrum of compound **28b**.



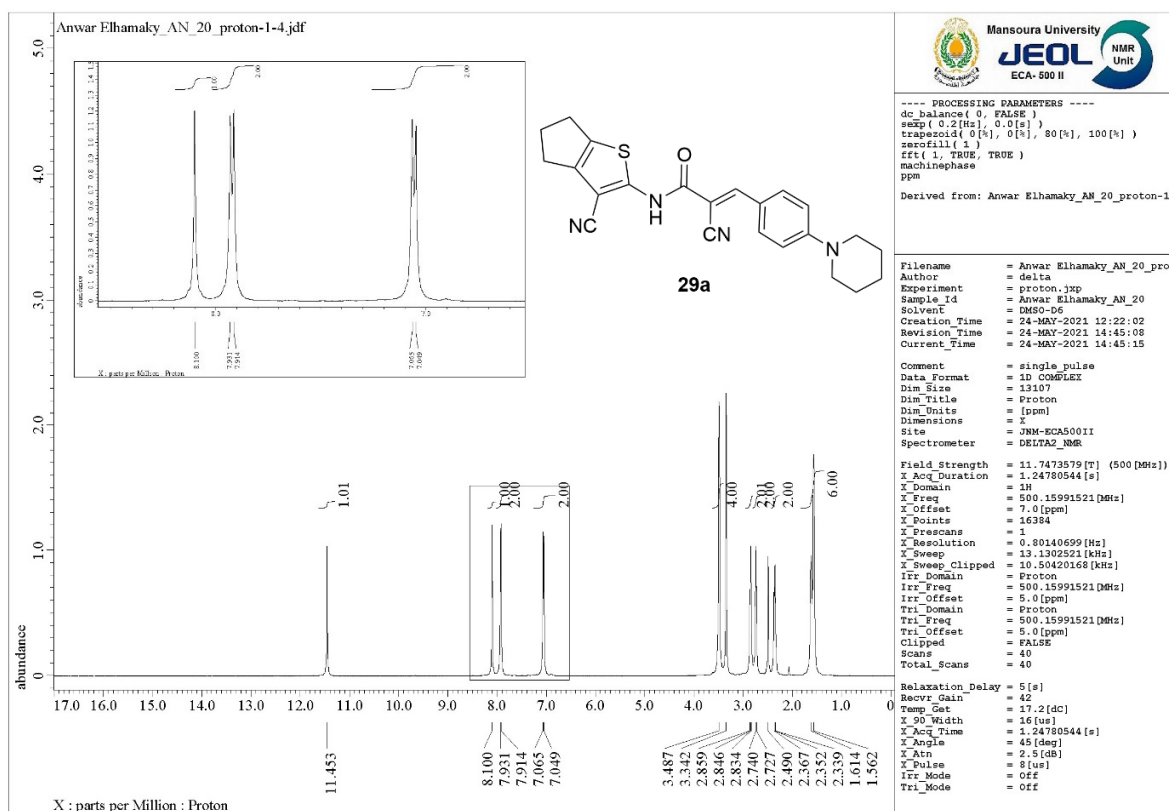


Figure S29.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ ) spectrum of compound **29a** in *E* configuration.

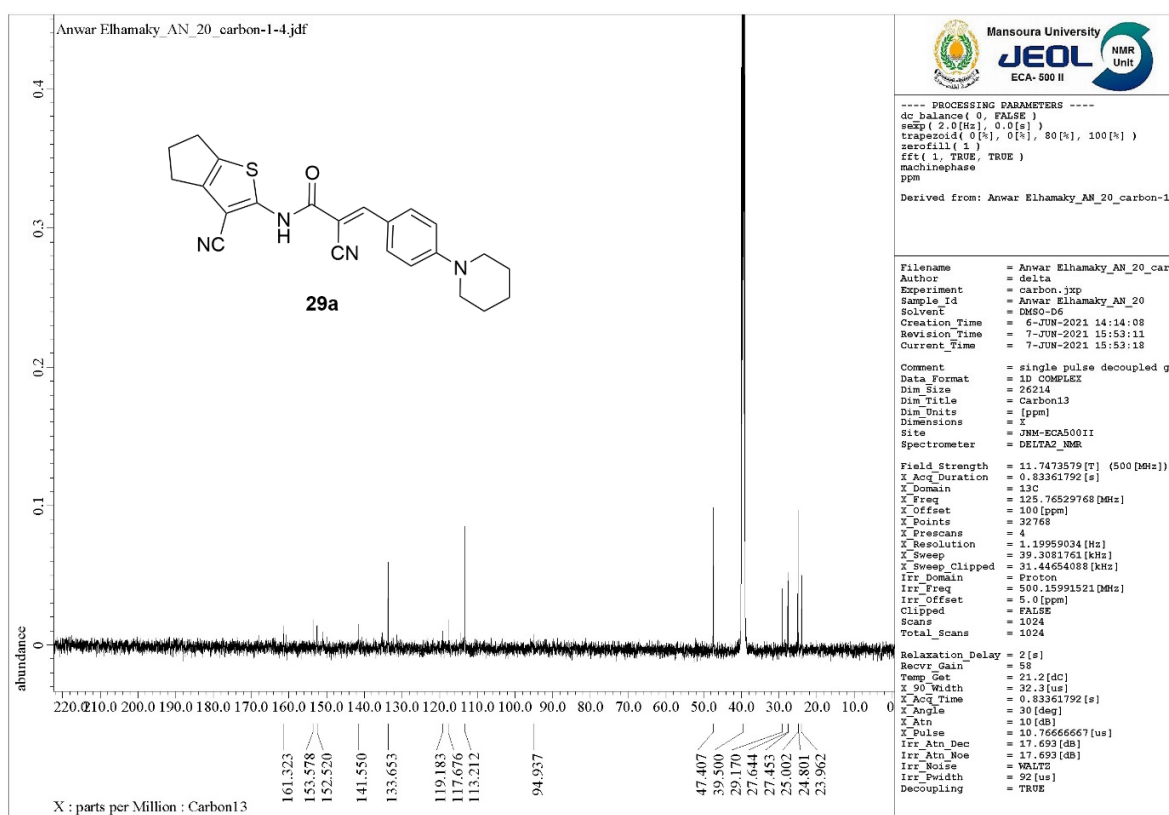


Figure S30.  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO}-d_6$ ) spectrum of compound **29a**.



Anwar-ElHamaky-AN-20 #98 RT: 1.66 AV: 1 NL: 1.32E5  
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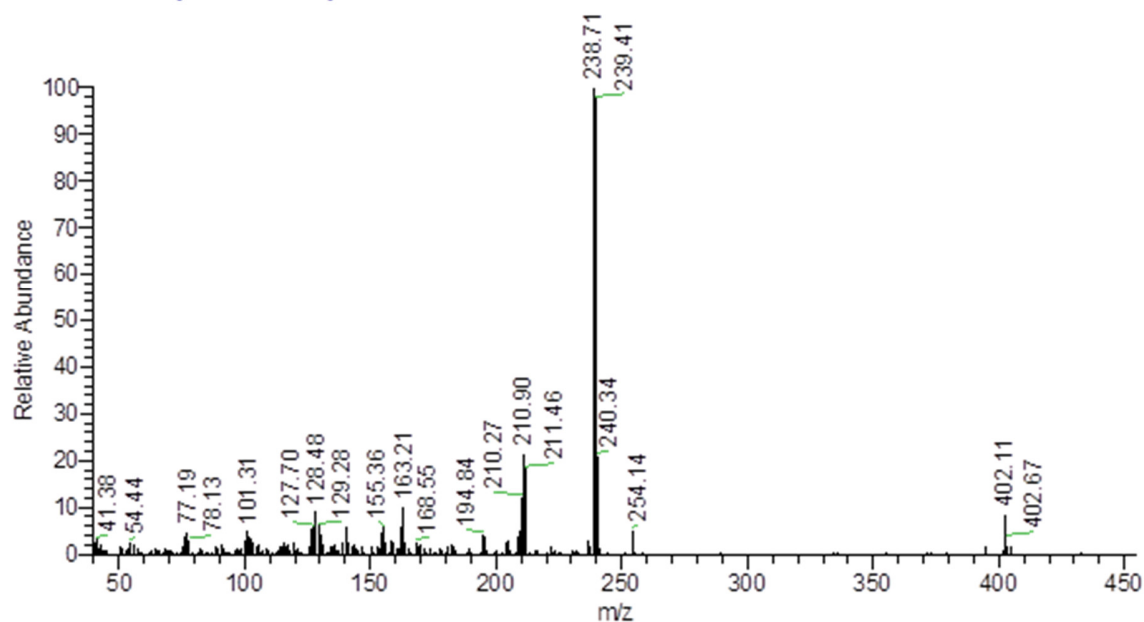


Figure S31. Mass spectrum of compound 29a.

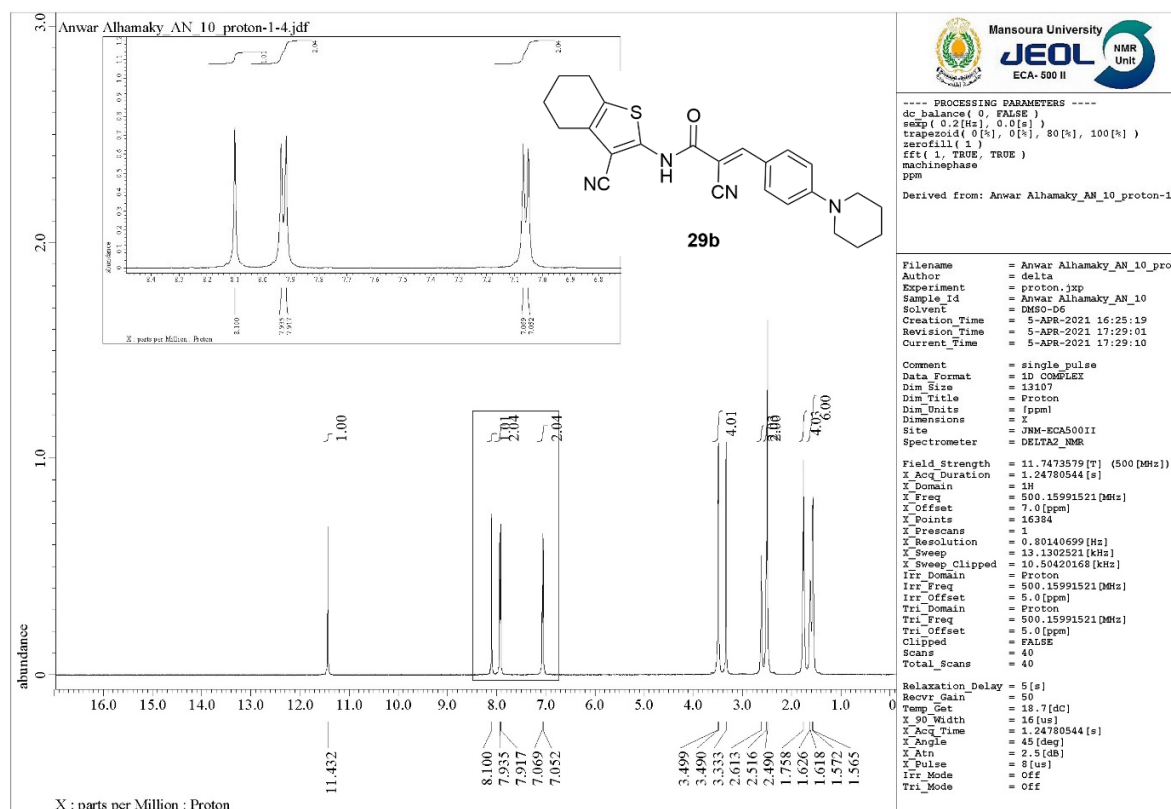


Figure S32. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) spectrum of compound 29b in *E* configuration.

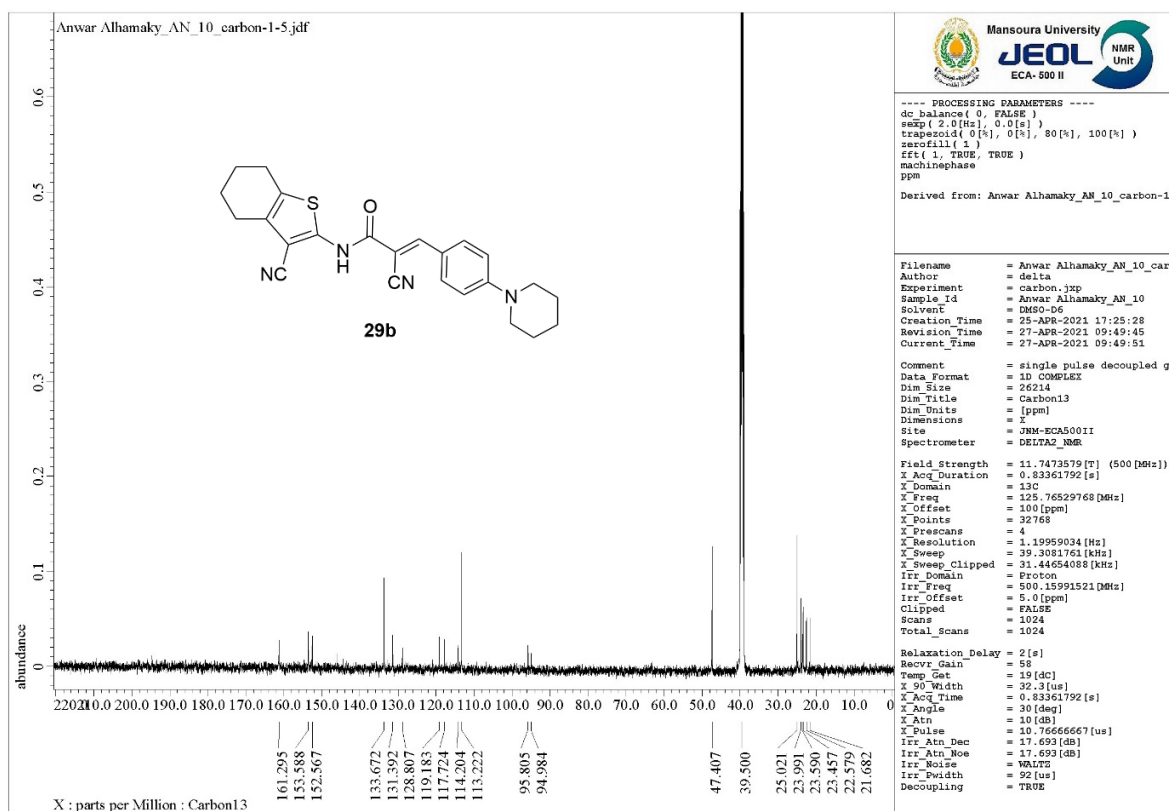


Figure S33.  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO}-d_6$ ) spectrum of compound **29b**.

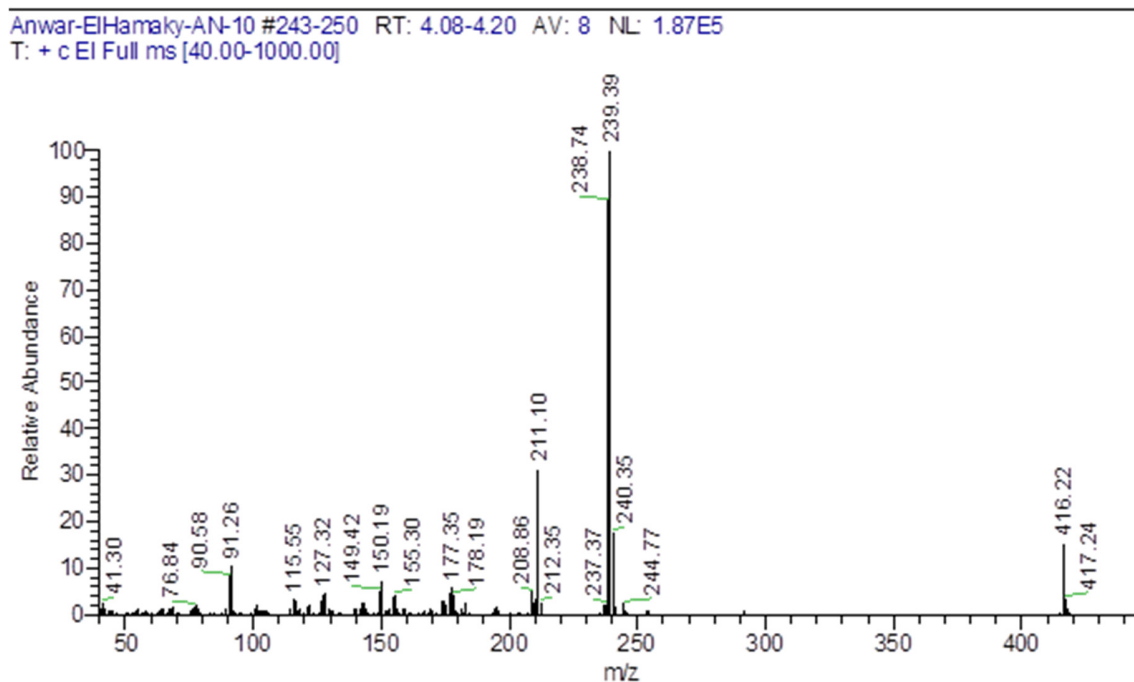


Figure S34. Mass spectrum of compound **29b**.

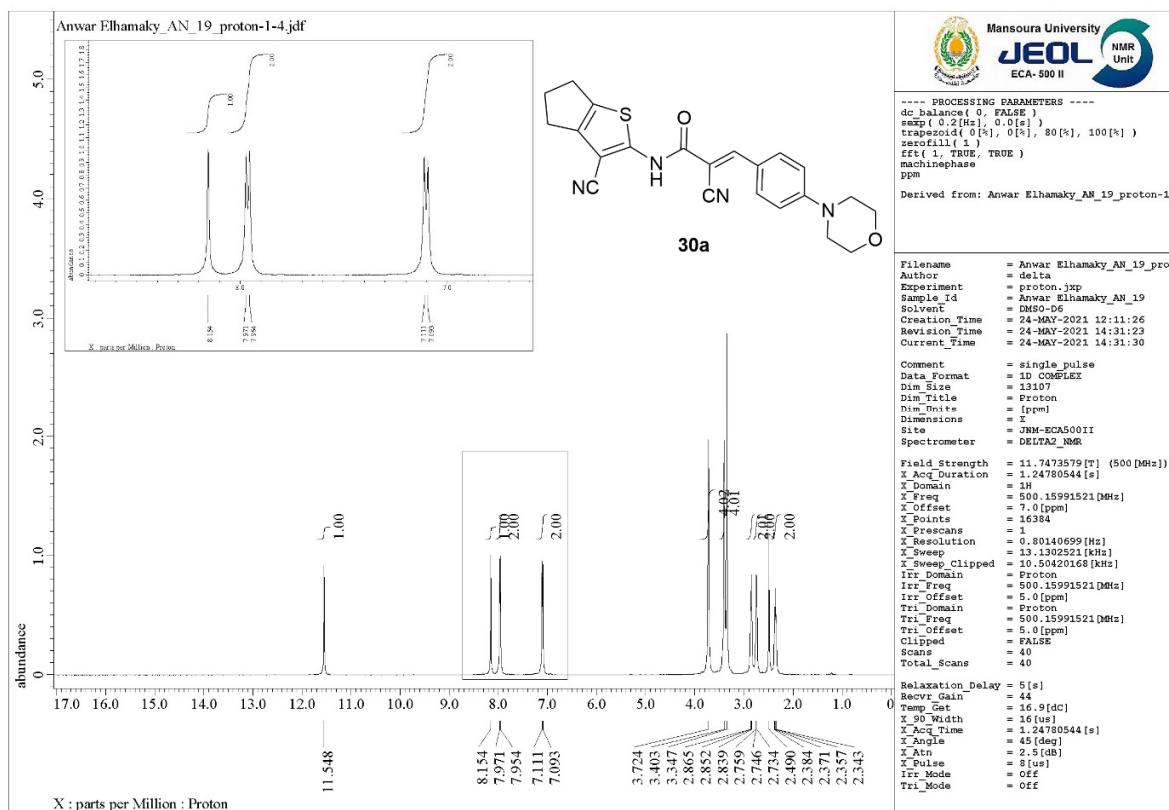


Figure S35.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ ) spectrum of compound **30a** in *E* configuration.

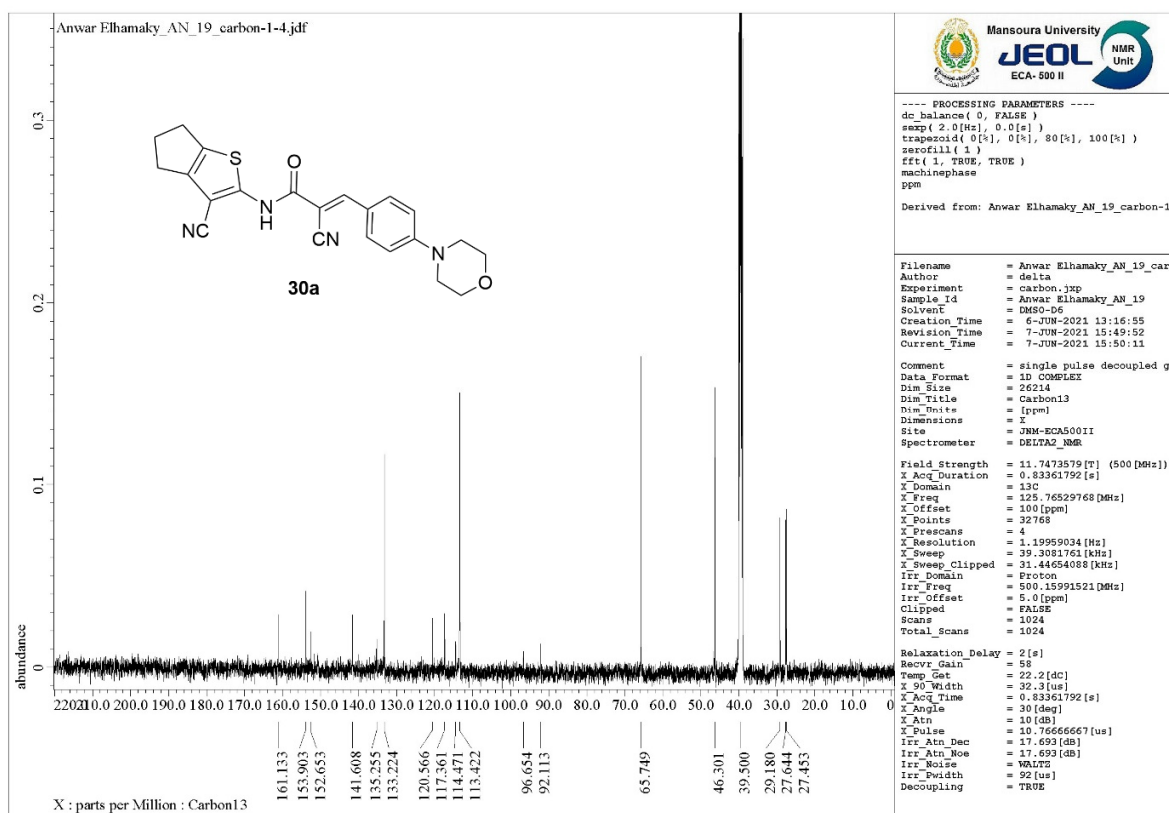


Figure S36.  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO}-d_6$ ) spectrum of compound **30a**.

anwar-elhamaky-an19 #201-230 RT: 3.38-3.87 AV: 30 NL: 3.55E4  
T: + c EI Full ms [40.00-1000.00]

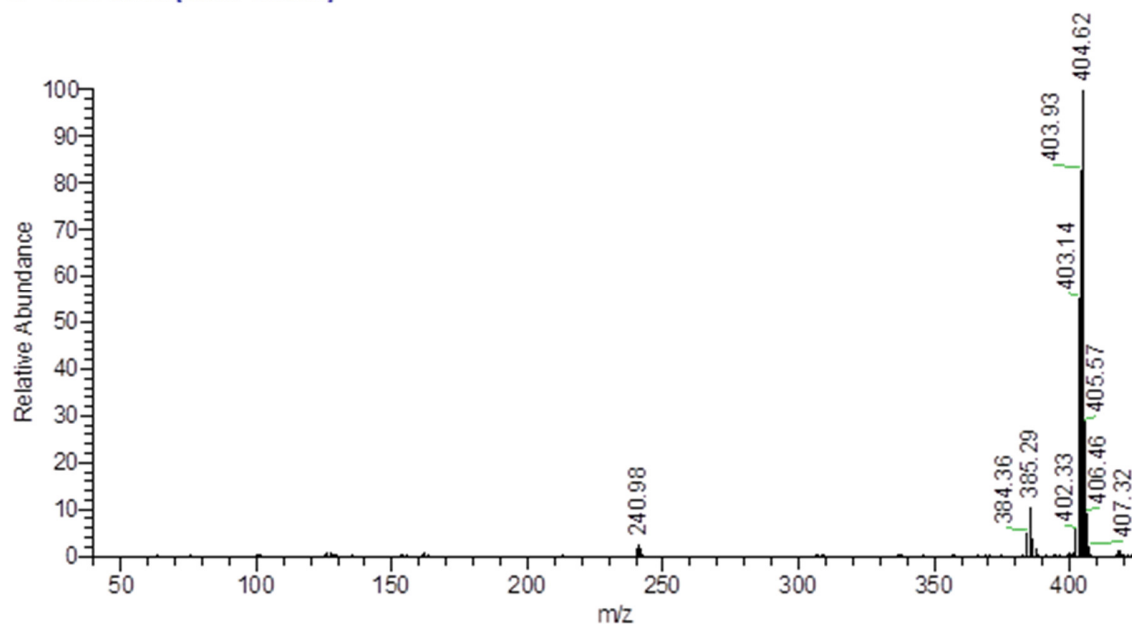


Figure S37. Mass spectrum of compound **30a**.

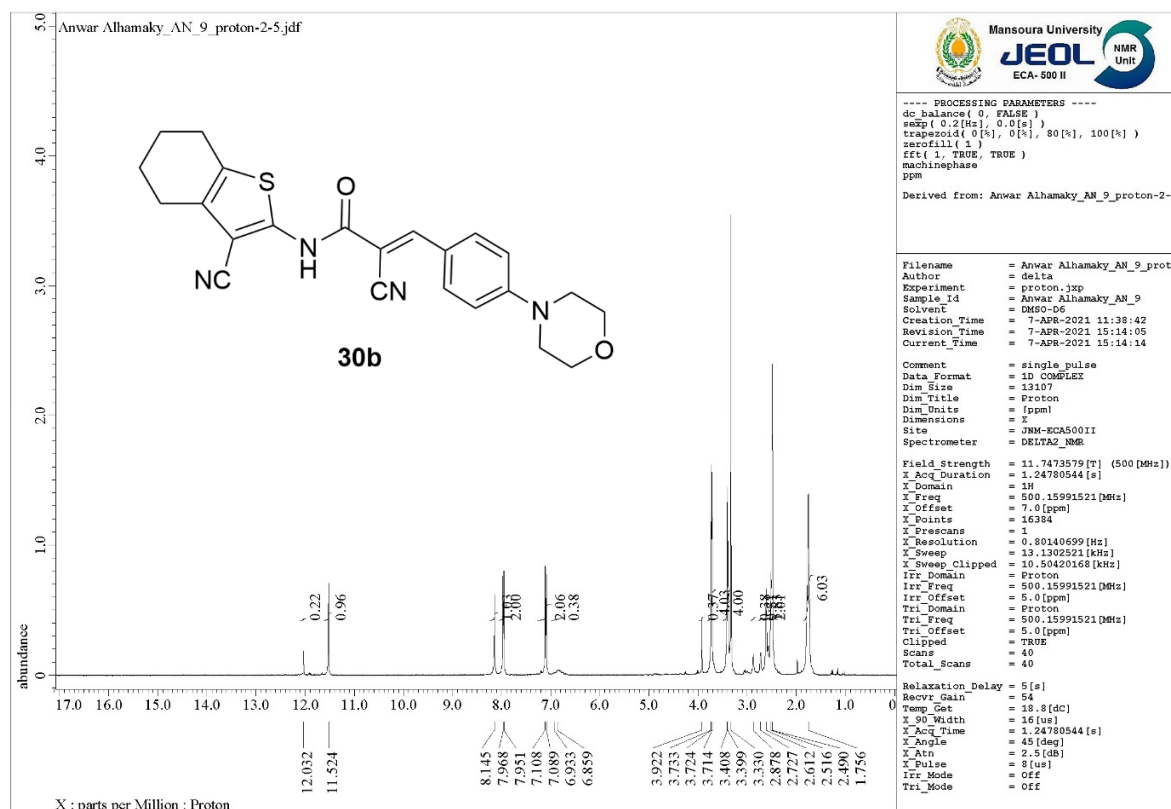


Figure S38. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) spectrum of compound **30b** in *E* configuration.

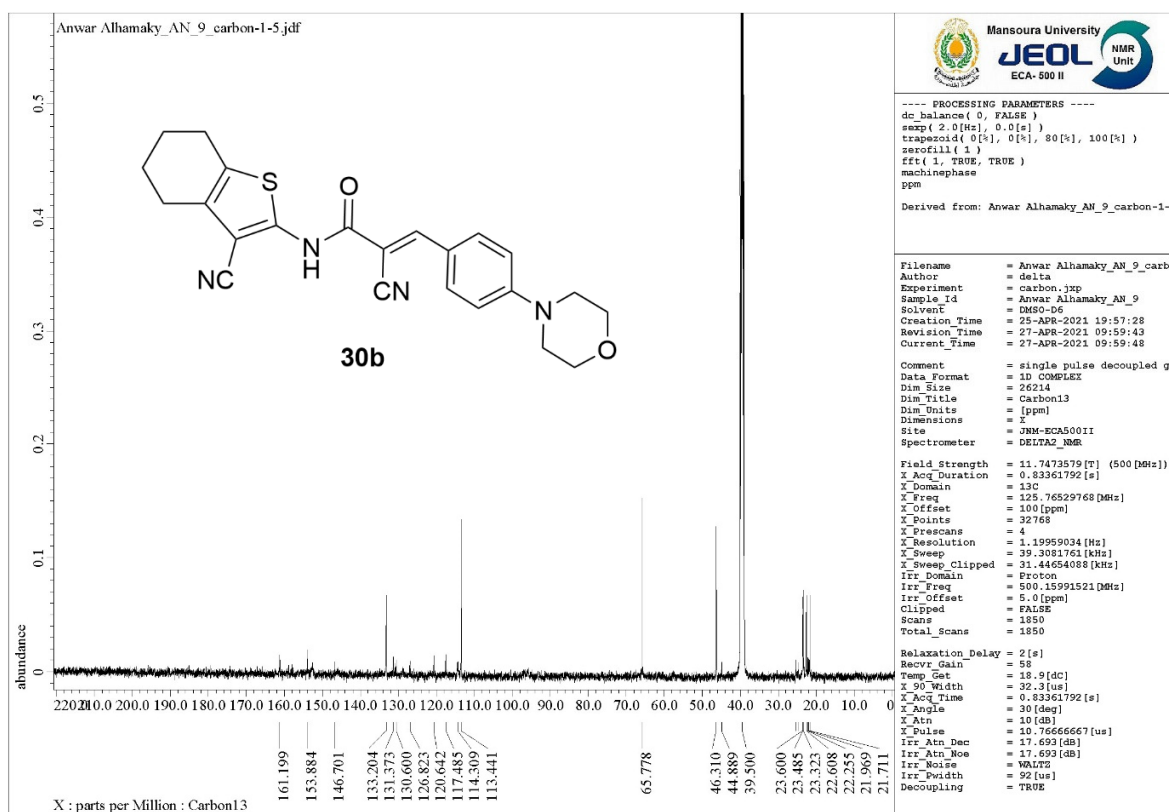


Figure S39.  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO}-d_6$ ) spectrum of compound **30b** in *E* configuration.

anwar-elhamaky-an09 #245 RT: 4.12 AV: 1 NL: 3.87E4  
T: + c EI Full ms [40.00-1000.00]

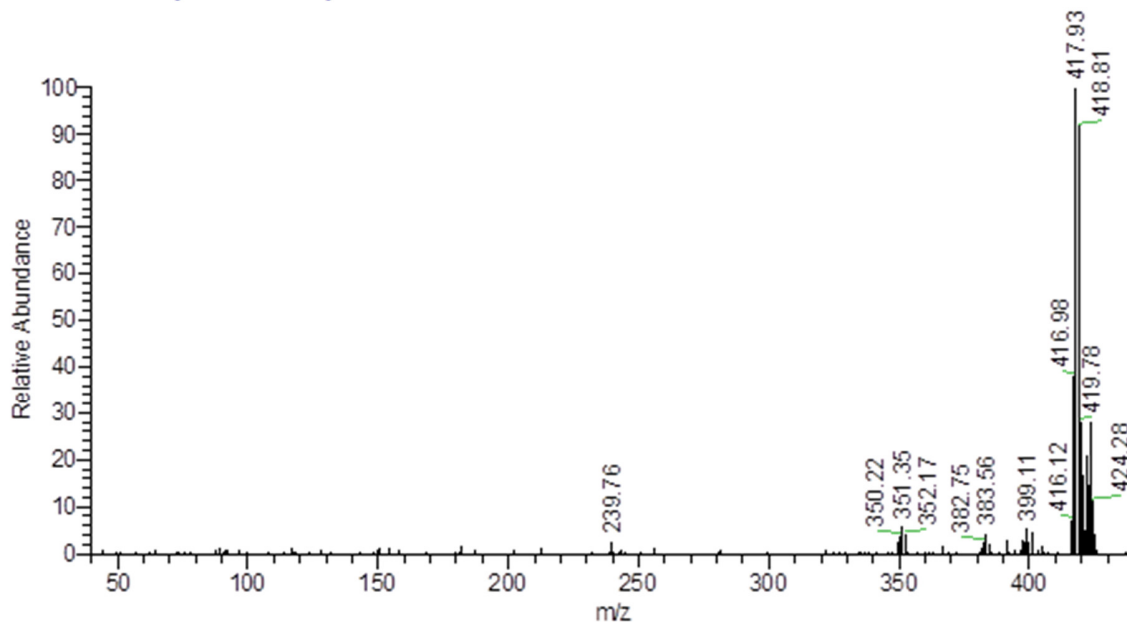


Figure S40. Mass spectrum of compound **30b**.

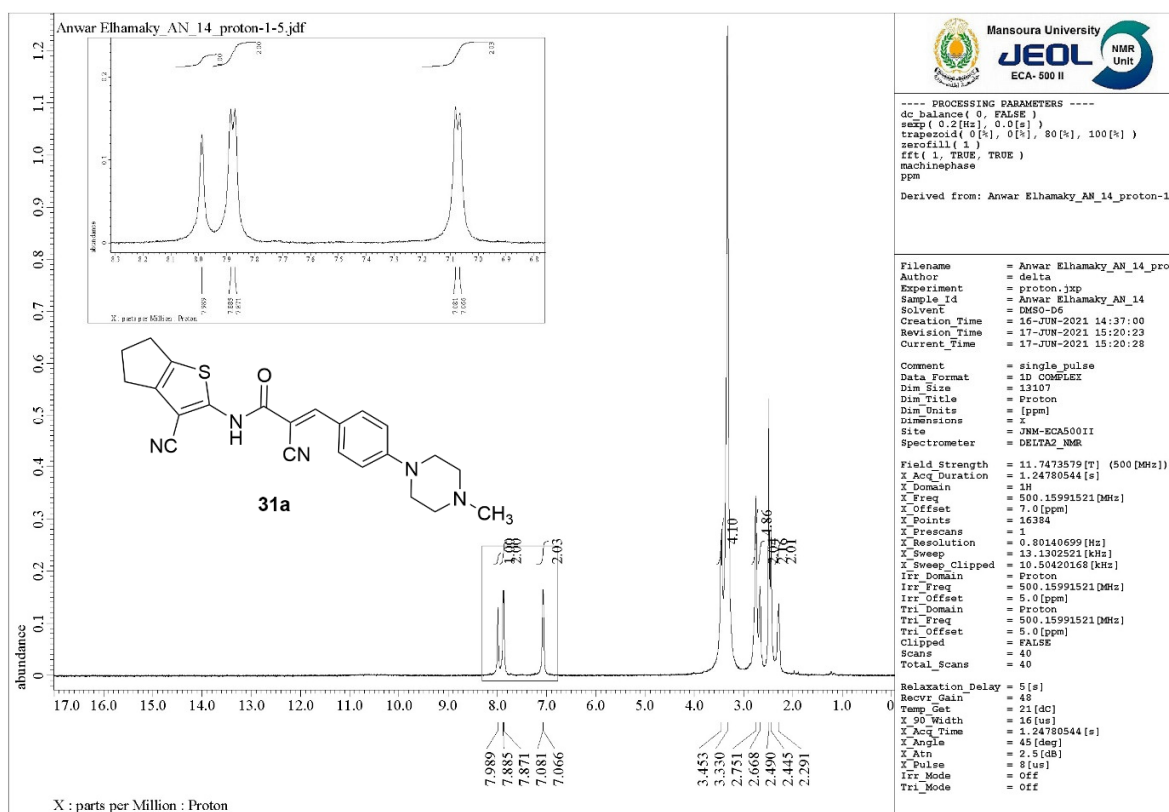


Figure S41.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ ) spectrum of compound **31a** in *E* configuration.

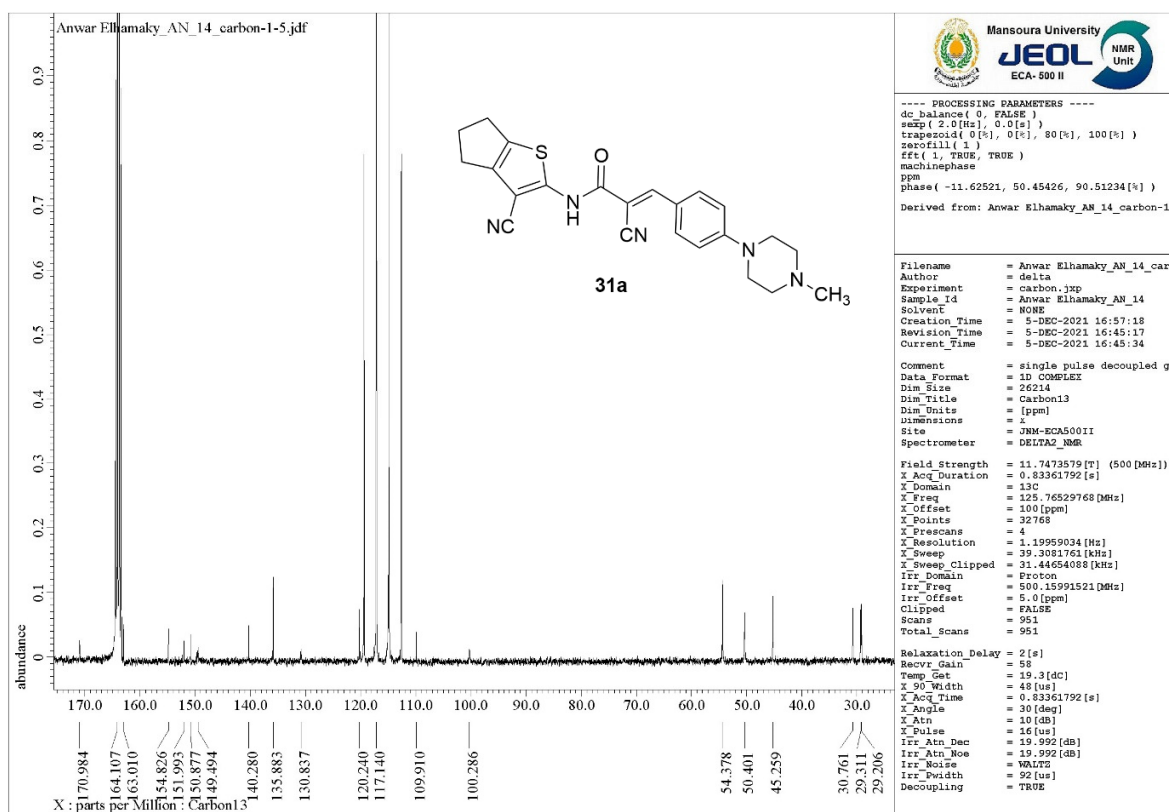


Figure S42.  $^{13}\text{C}$  NMR (125 MHz,  $\text{CF}_3\text{COOD}$ ) spectrum of compound **31a** in *E* configuration.



anwar-elhamaky-an14 #188 RT: 3.16 AV: 1 NL: 1.22E5  
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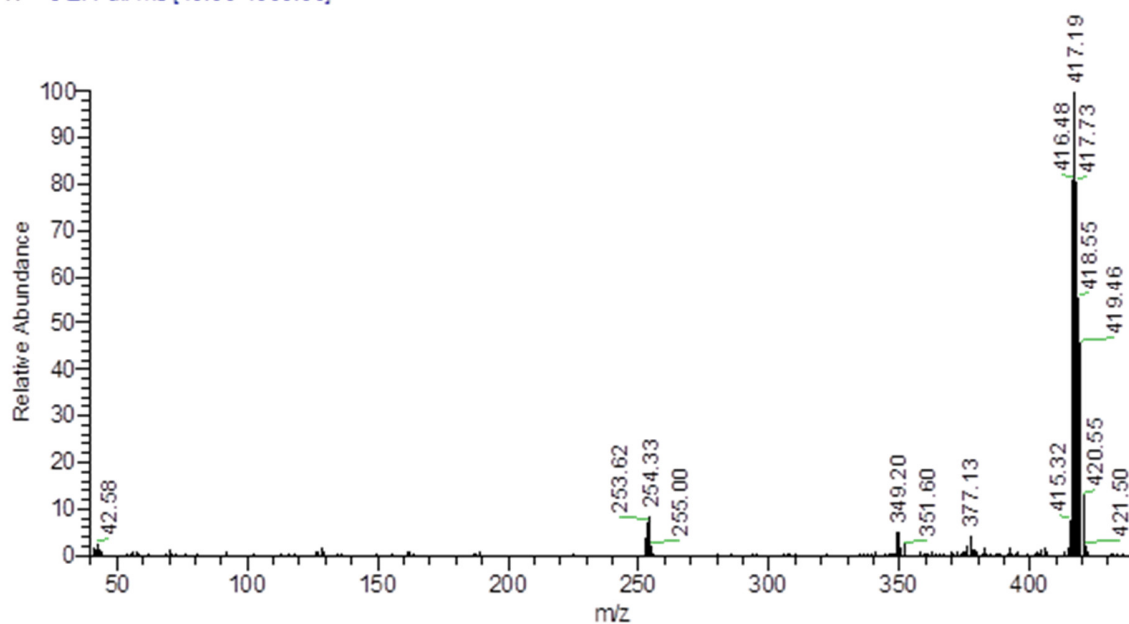


Figure S43. Mass spectrum of compound 31a.

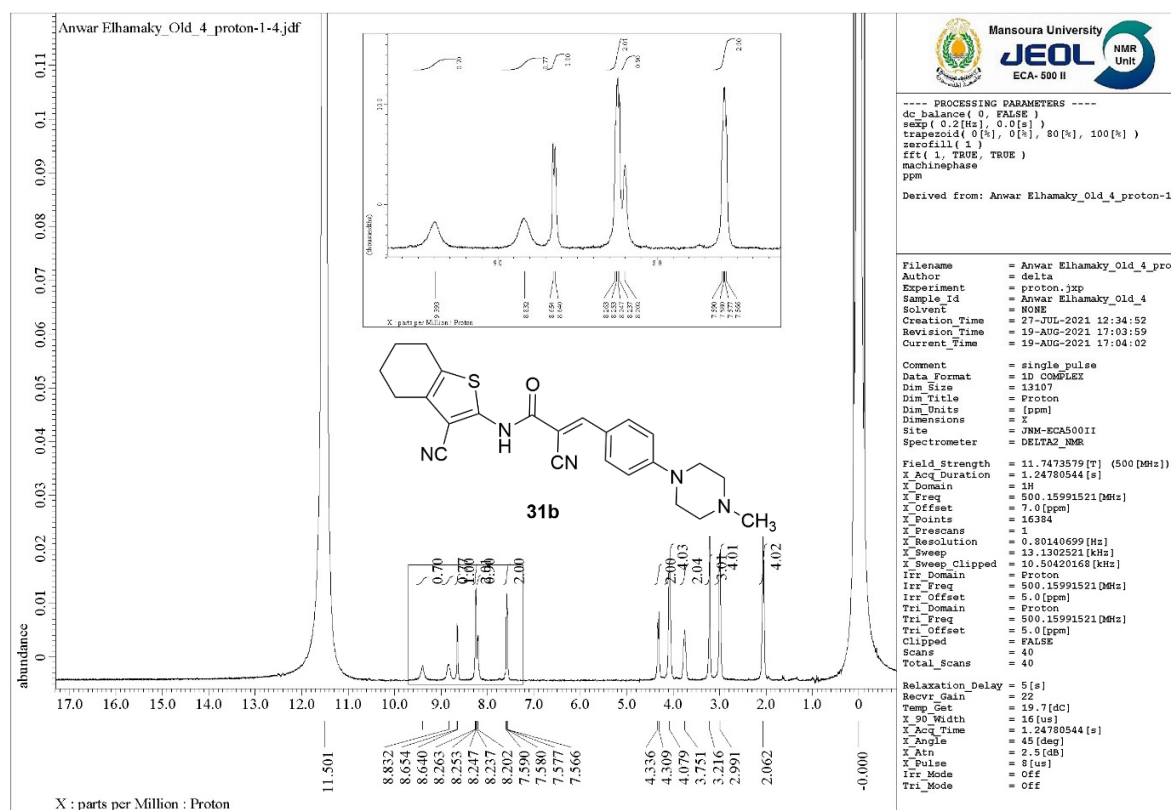


Figure S44. <sup>1</sup>H NMR (500 MHz, CF<sub>3</sub>COOD) spectrum of directly precipitated powder of compound 31b in *E* configuration.



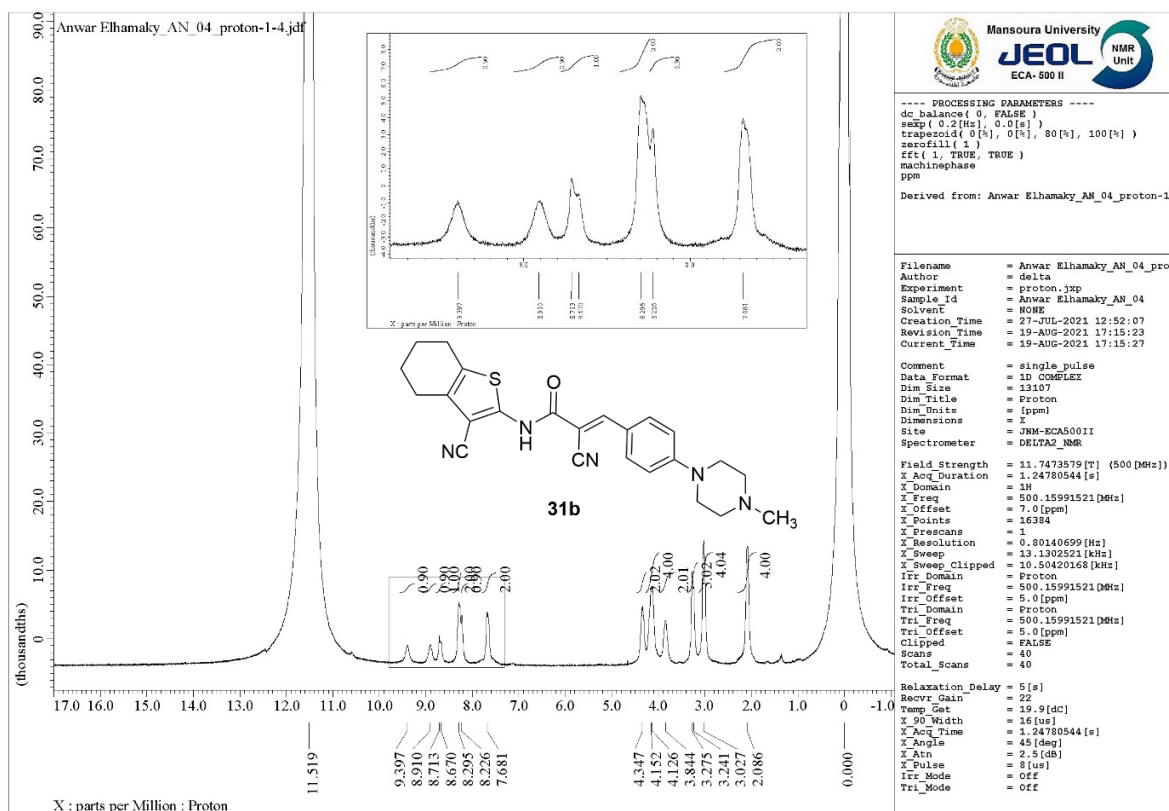


Figure S45.  $^1\text{H}$  NMR (500 MHz,  $\text{CF}_3\text{COOD}$ ) spectrum for the powder obtained by extraction of compound **31b** in *E* configuration.

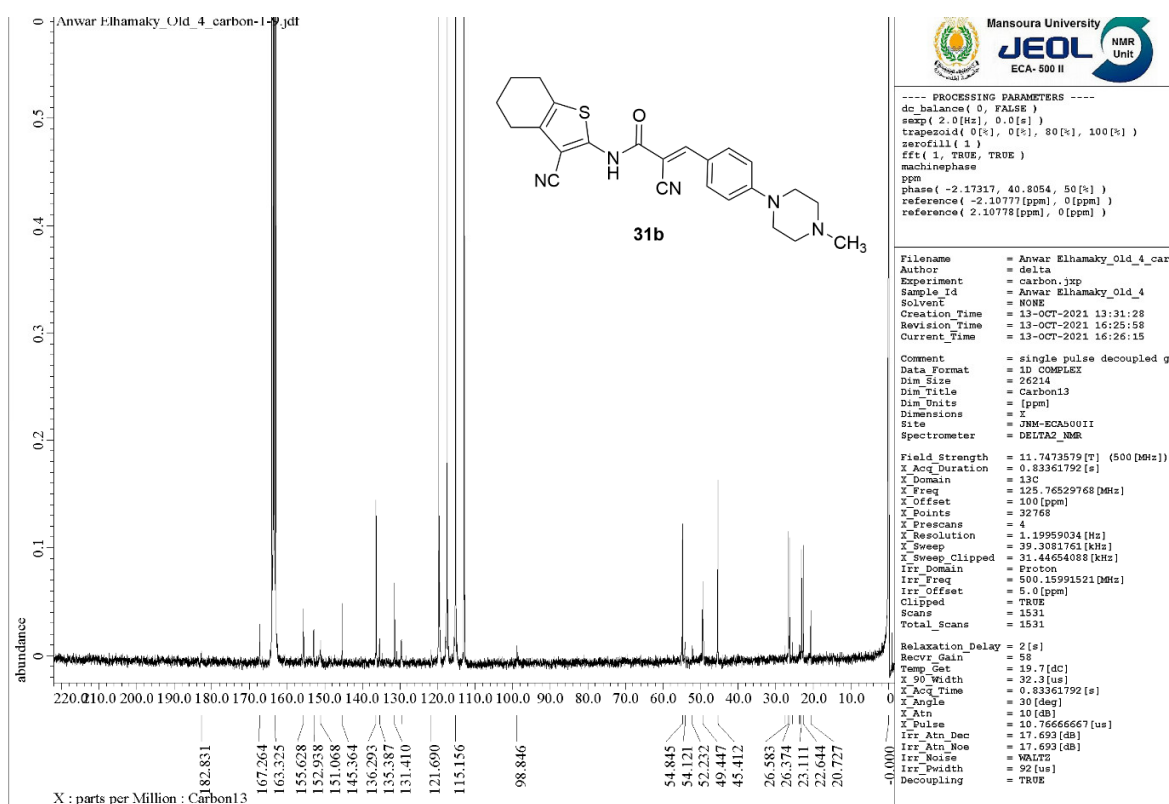


Figure S46.  $^{13}\text{C}$  NMR (125 MHz,  $\text{CF}_3\text{COOD}$ ) spectrum of compound **31b**.

Anwar-ElHamaky-AN-04 #235 RT: 3.95 AV: 1 NL: 9.10E4  
T: + c EI Full ms [40.00-1000.00]

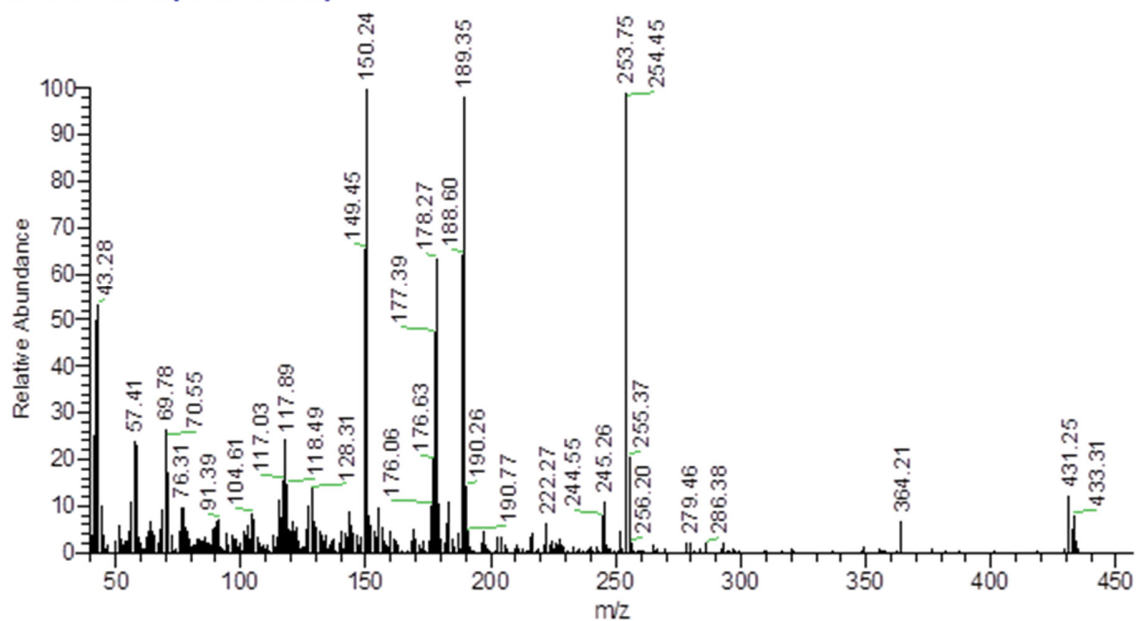


Figure S47. Mass spectrum of compound **31b**.

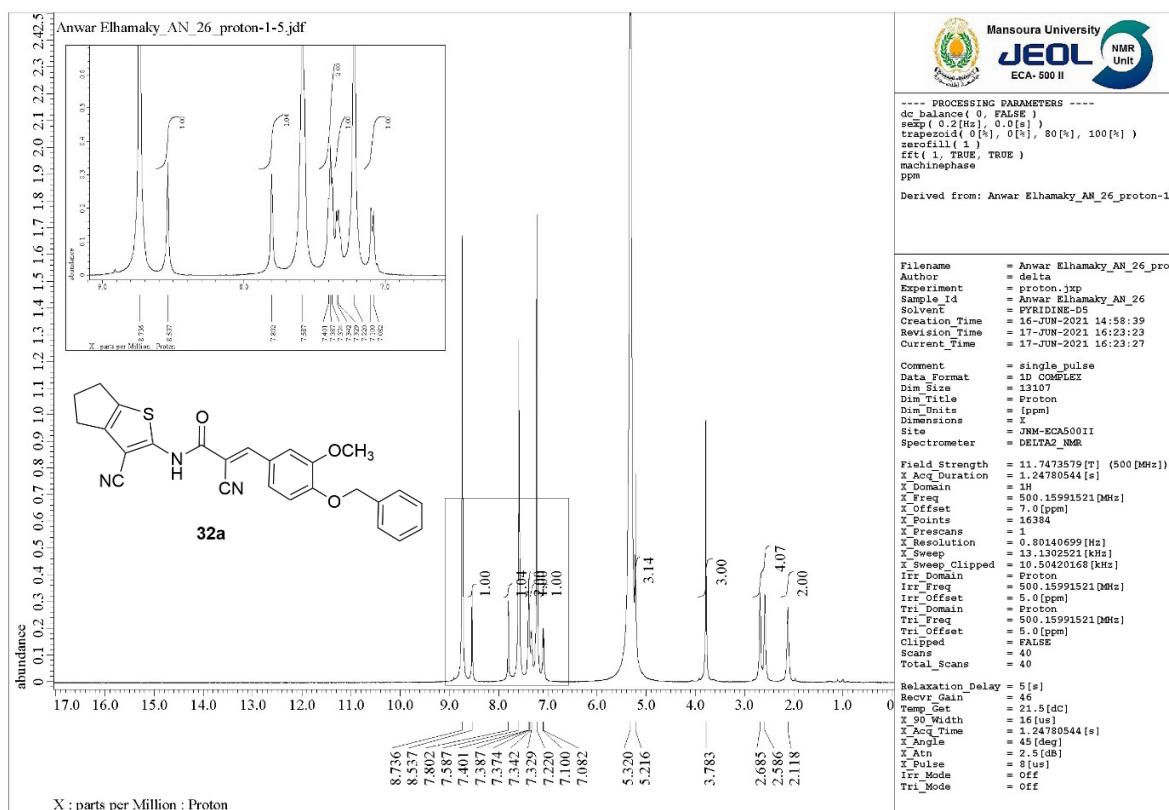


Figure S48. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) spectrum of compound **32a** in *E* configuration.

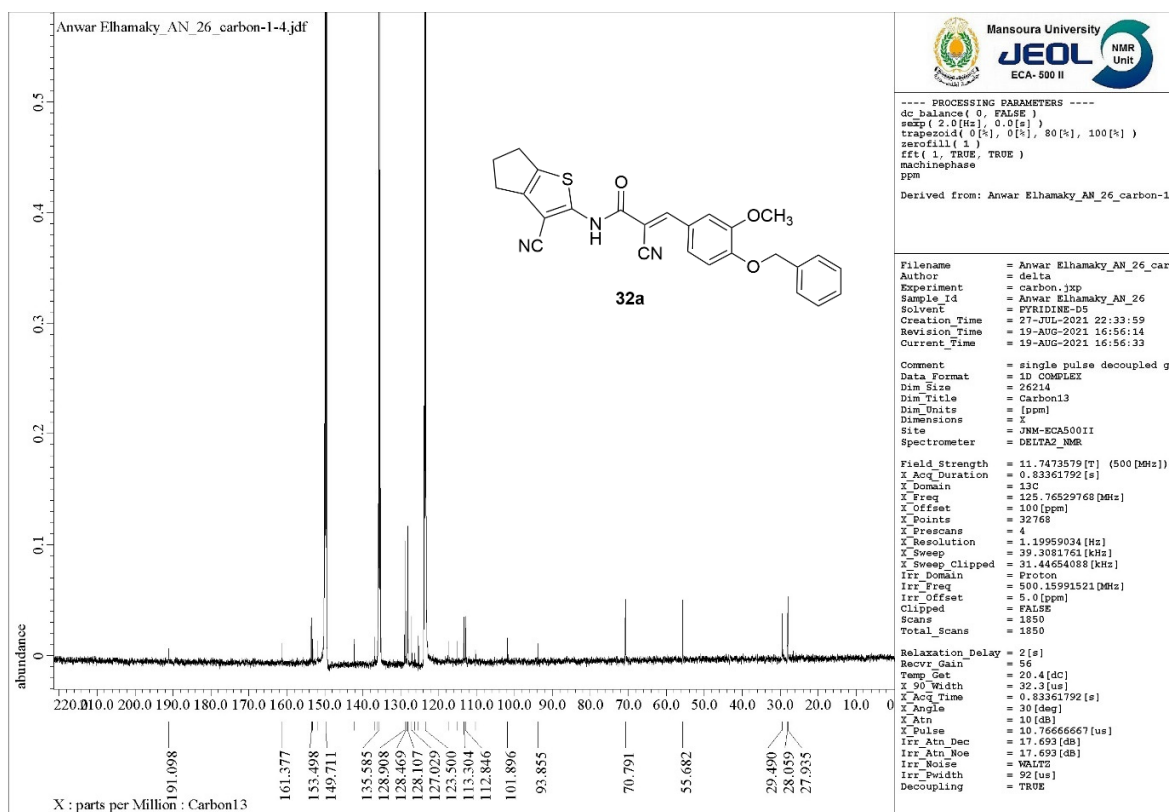


Figure S49.  $^{13}\text{C}$  NMR (125 MHz, pyridine- $d_5$ ) spectrum of compound 32a.

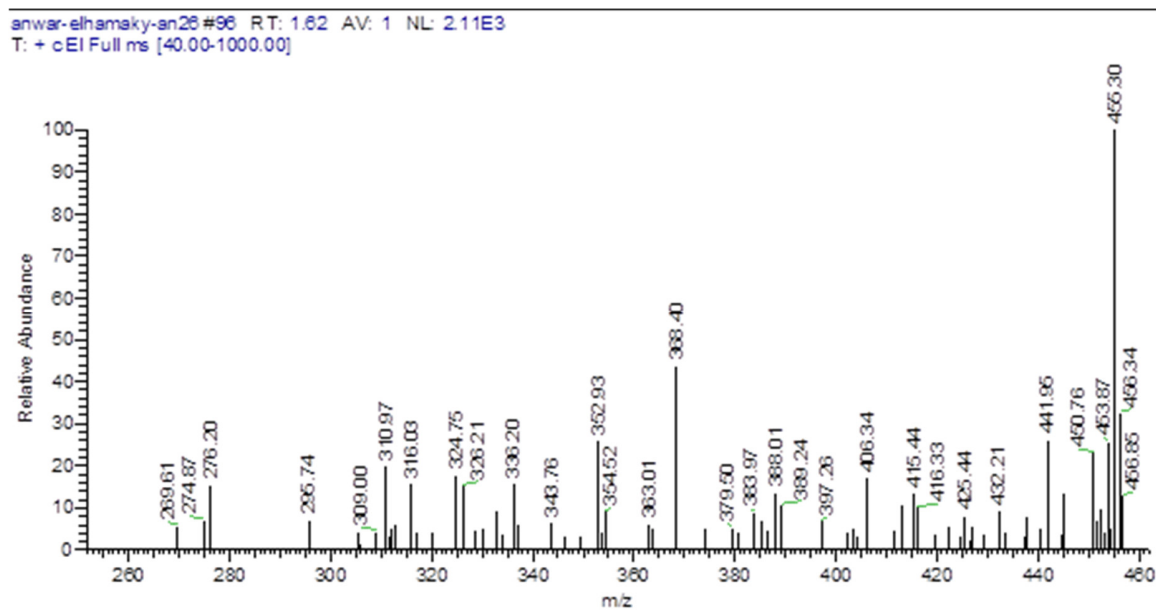


Figure S50. Mass spectrum of compound 32a.



Anwar-ElHamaky-AN-21\_211101142451#235 RT: 3.95 AV: 1 NL: 1.67E5  
T: + c EI Full ms [40.00-1000.00]

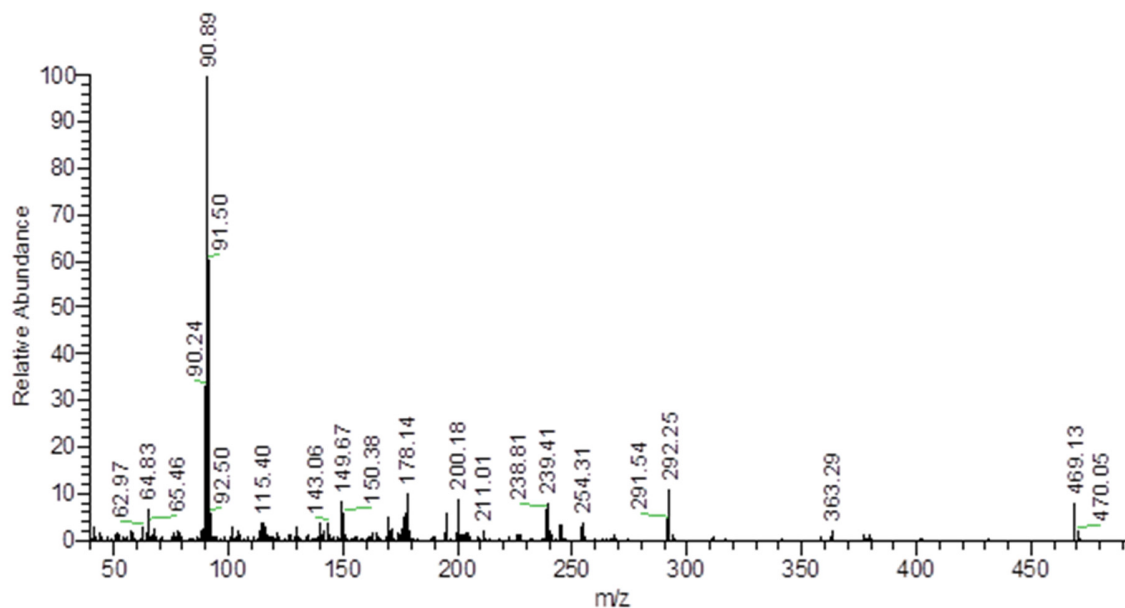


Figure S53. Mass spectrum of compound **32b**.

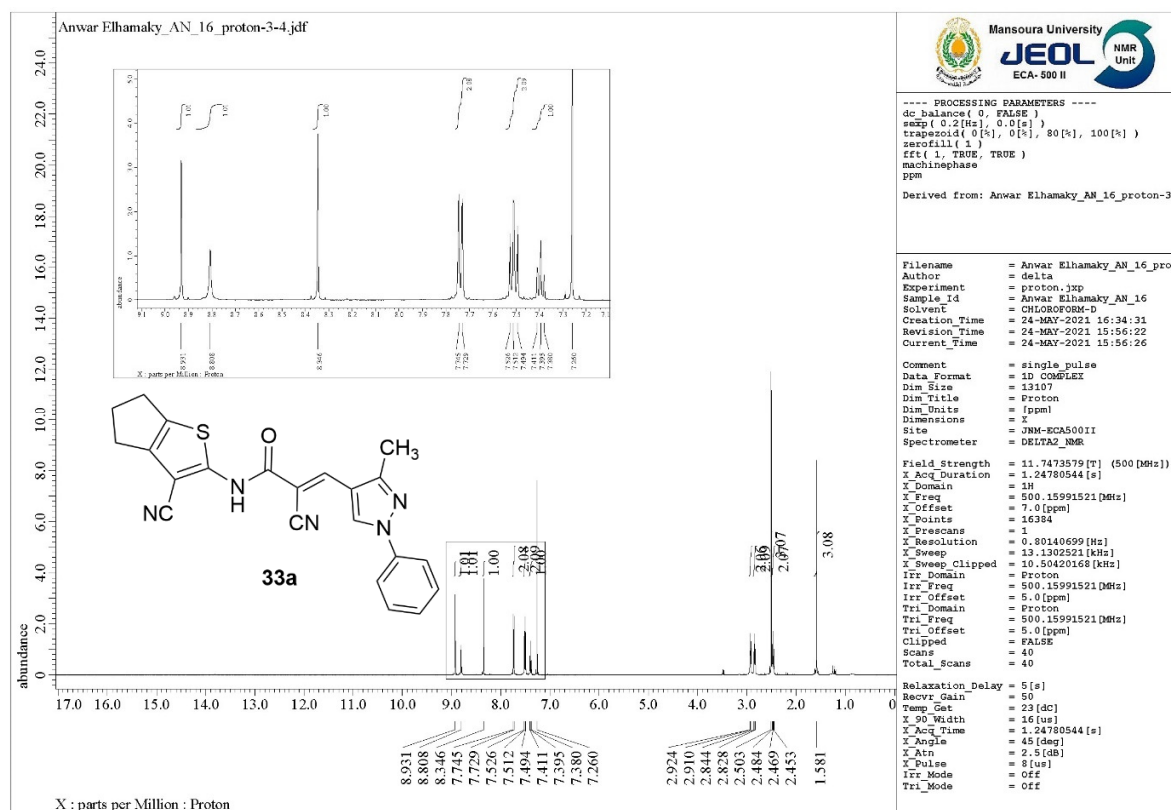


Figure S54. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) spectrum of compound **33a** in *E* configuration.

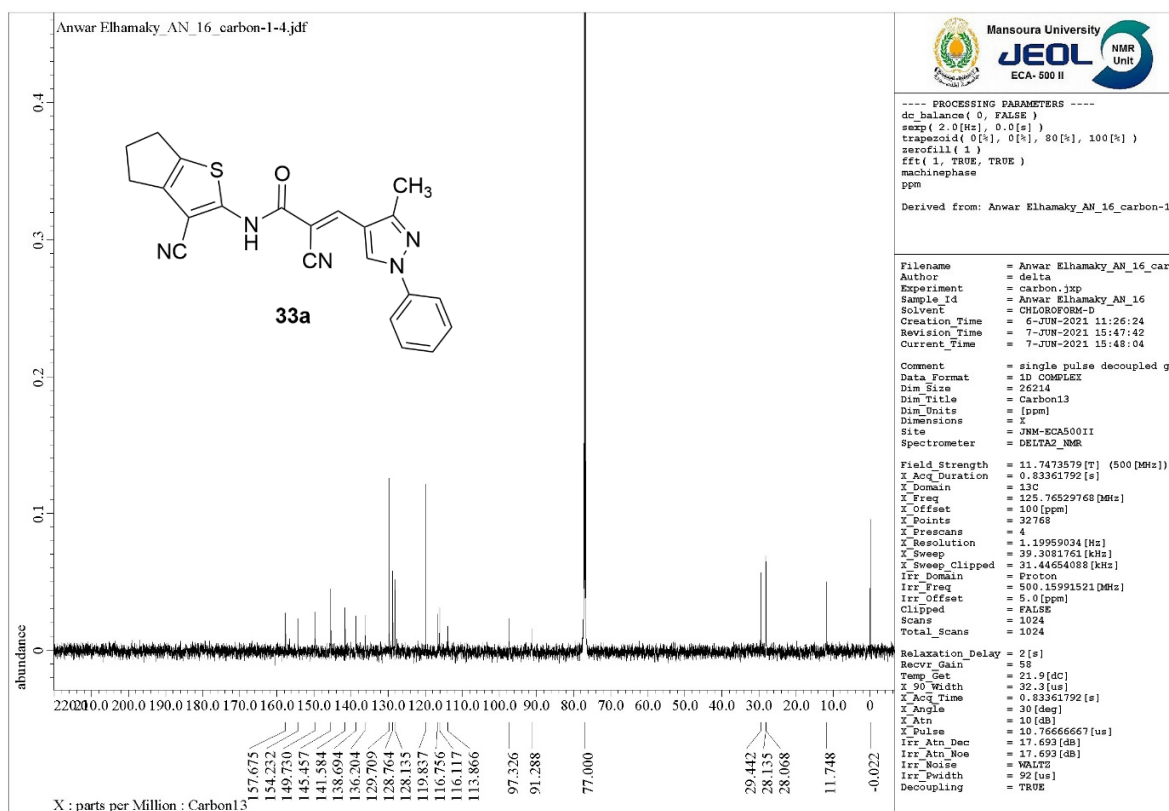


Figure S55.  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ) spectrum of compound 33a.

anwar-elhamaky-an16 #243 RT: 4.08 AV: 1 NL: 1.70E4  
T: + c EI Full ms [40.00-1000.00]

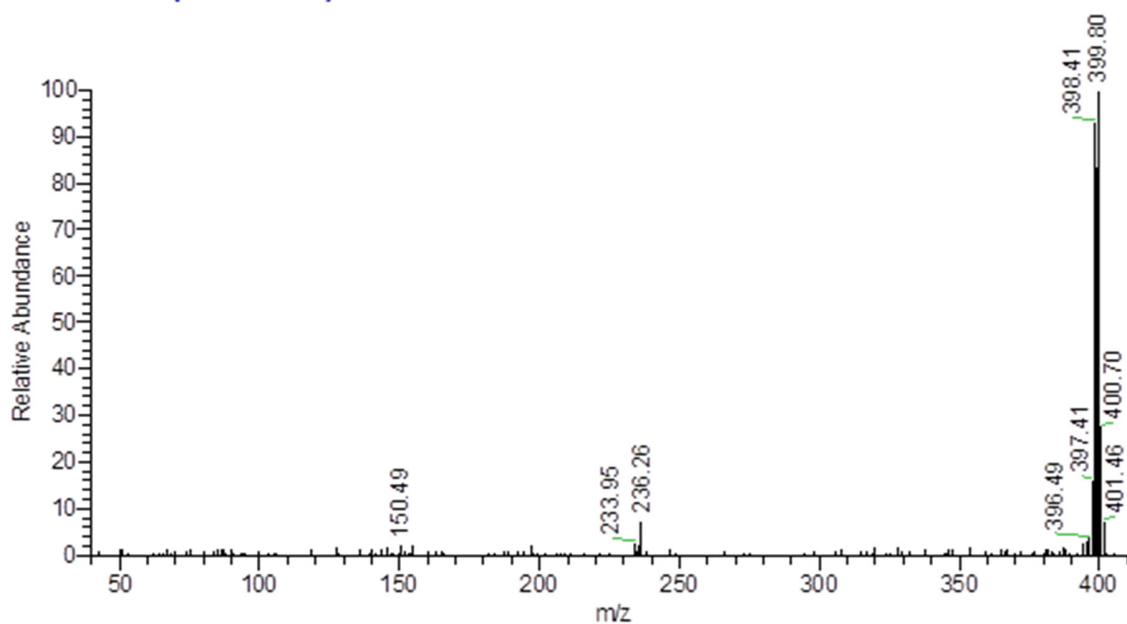


Figure S56. Mass spectrum of compound 33a.



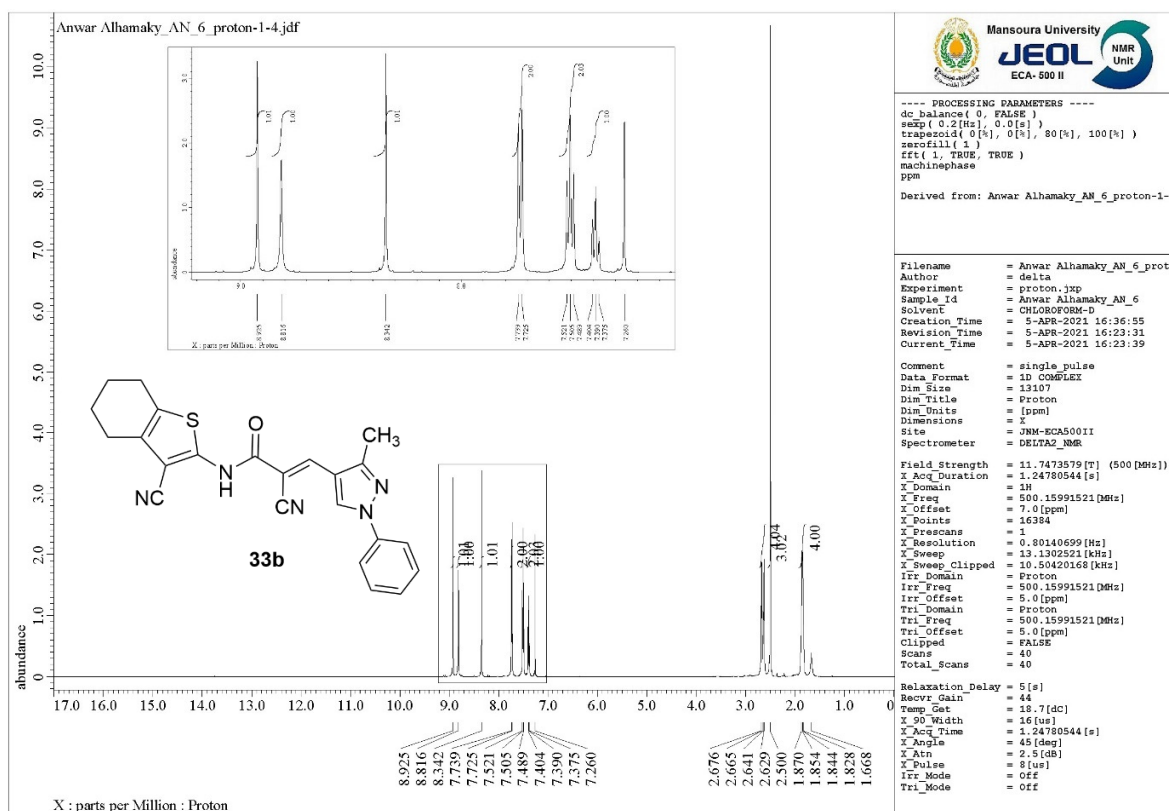


Figure S57.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) spectrum of compound **33b** in *E* configuration.

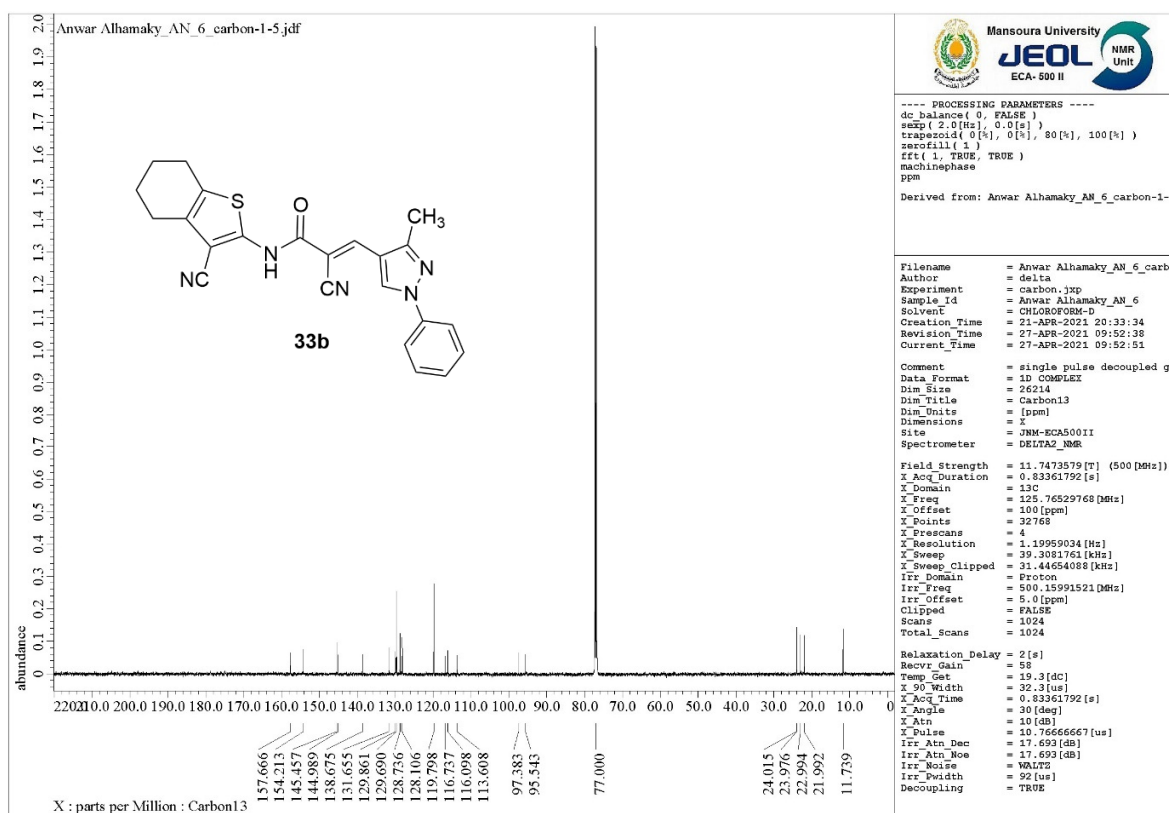


Figure S58.  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ) spectrum of compound **33b**.



Anwar-ElHamaky-AN-06 #172 RT: 2.90 AV: 1 NL: 1.19E5  
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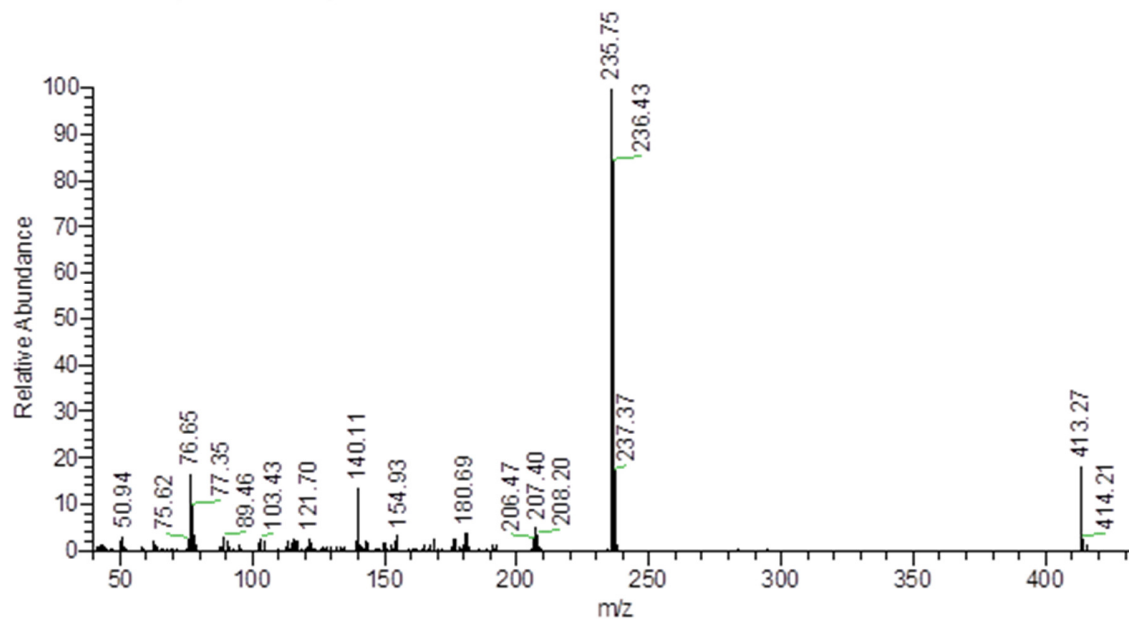
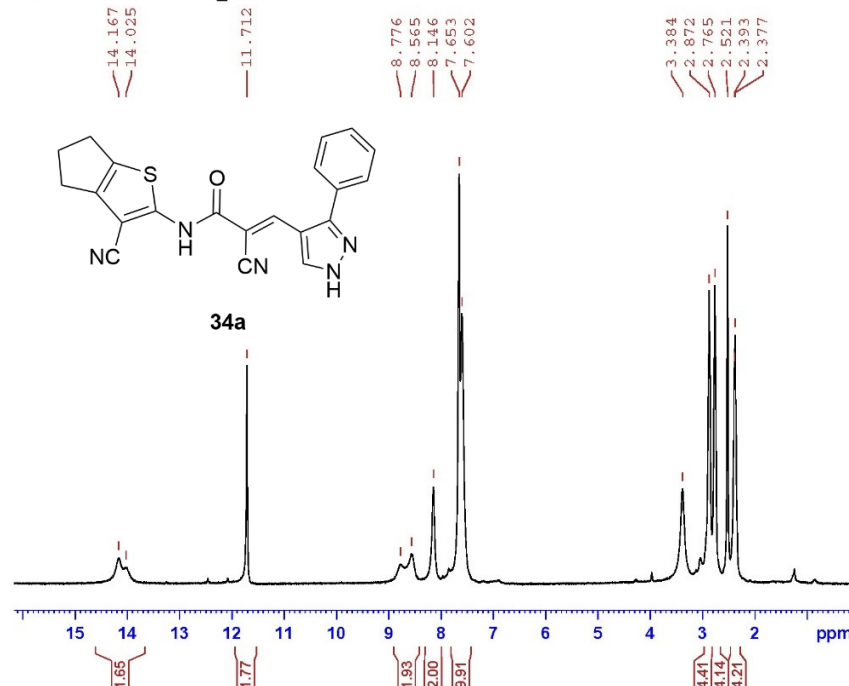


Figure S59. Mass spectrum of compound 33b.

Anwar Amin-AN17-HNMR\_DMSO-AF



Current Data Parameters  
NAME Anwar Amin-AN17-HNMR\_DM  
EXPNO 10  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20210224  
Time\_ 12:46 h  
INSTRUM spect  
PROBHD Z108618\_0945 (1  
PULPROG zgpg30  
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SOLVENT DMSO  
NS 16  
DS 2  
SWH 8012.820 Hz  
FIDRES 0.244532 Hz  
AQ 4.0894465 sec  
RG 176.72  
DW 62.400 usec  
DE 6.50 usec  
TE 292.0 K  
D1 1.00000000 sec  
TD0 1  
SFO1 400.2024712 MHz  
NUC1 1H  
P1 13.50 usec  
PLW1 13.00000000 W

F2 - Processing parameters  
SI 65536  
SF 400.2000000 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00

Figure S60. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) spectrum of compound 34a in *E* configuration.



anwar amine A 8 hnmr-M

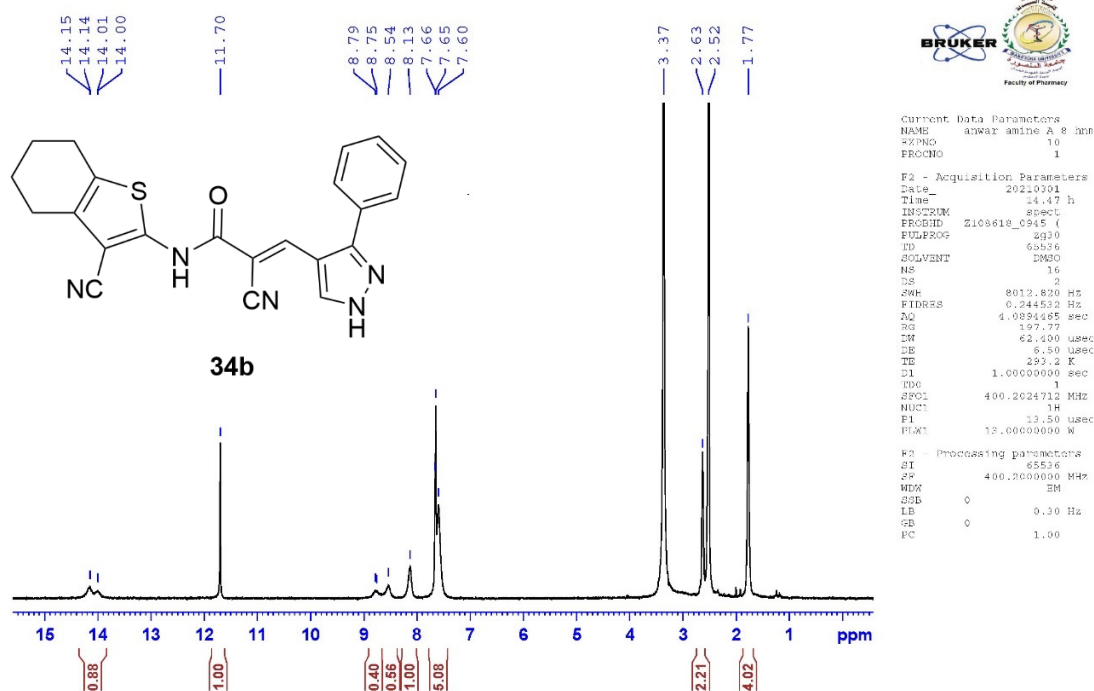


Figure S63. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) spectrum of compound **34b** in *E* configuration.

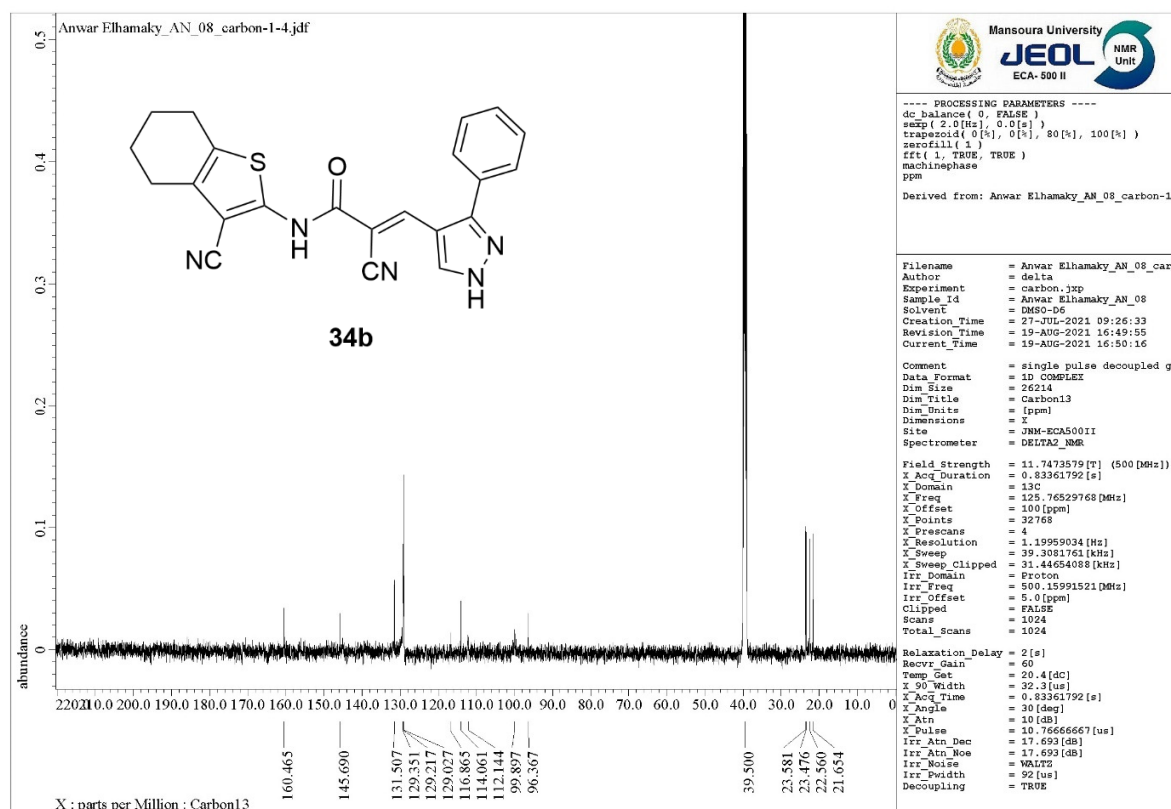


Figure S64. <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) spectrum of compound **34b**.

Anwar-ElHamaky-AN-08 #221 RT: 3.72 AV: 1 NL: 4.43E4  
T: + c EI Full ms [40.00-1000.00]

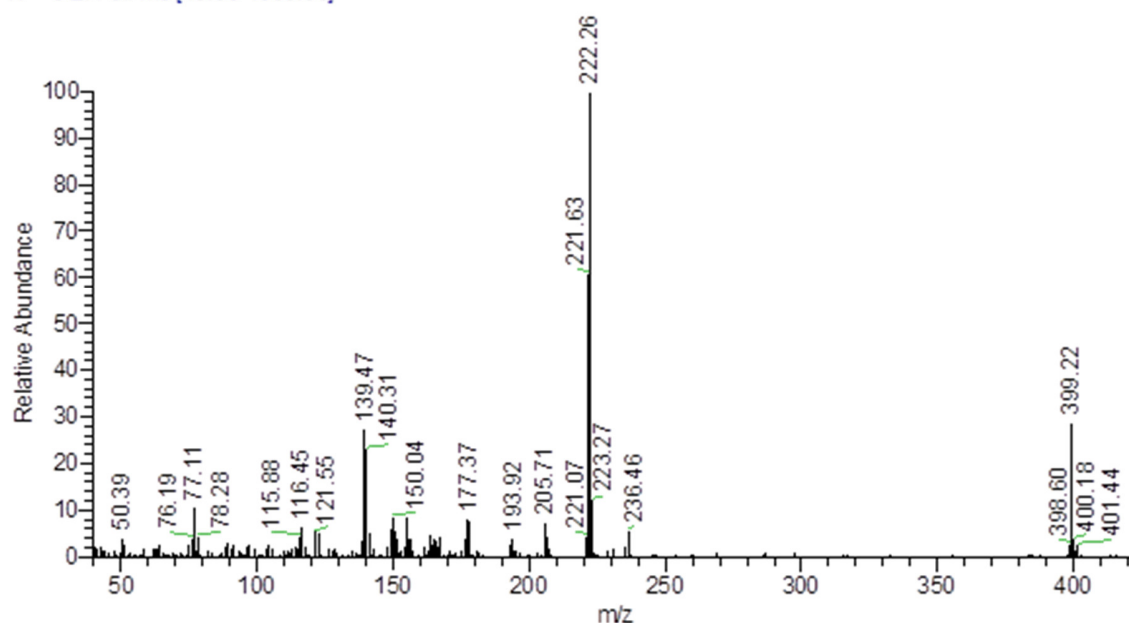


Figure S65. Mass spectrum of compound 34b.

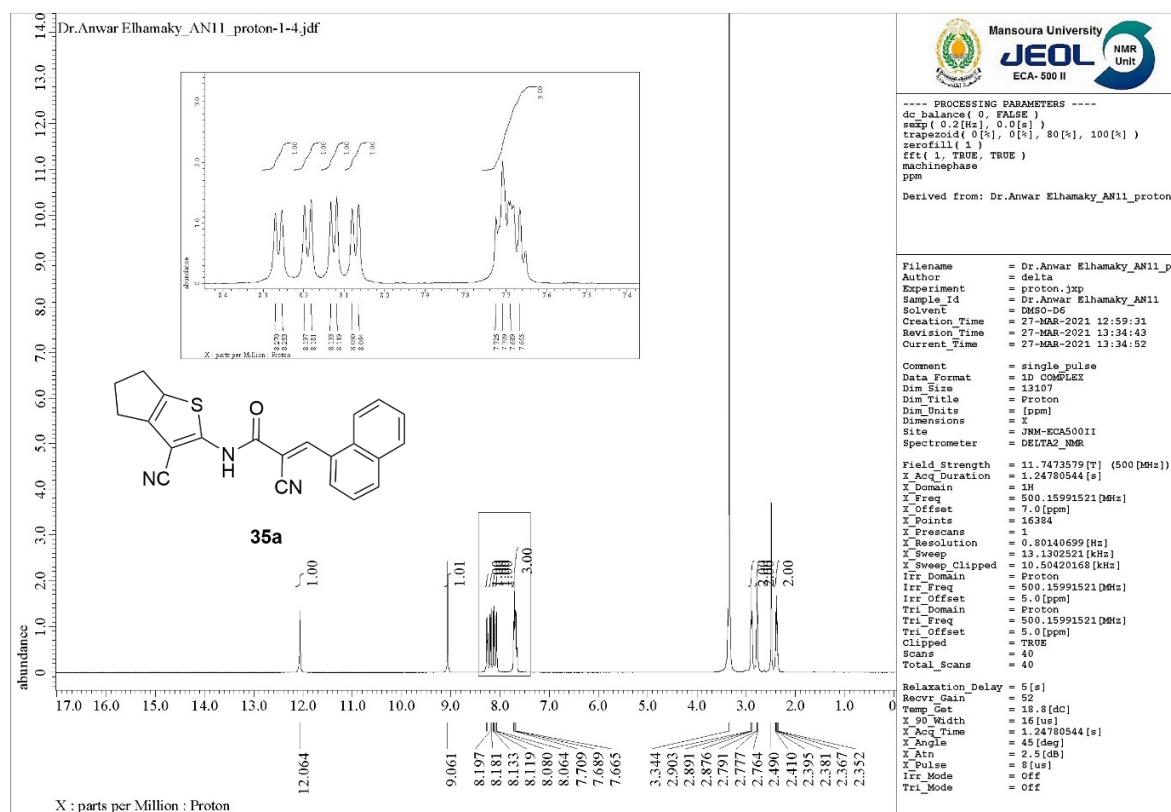


Figure S66. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) spectrum of compound 35a in *E* configuration.

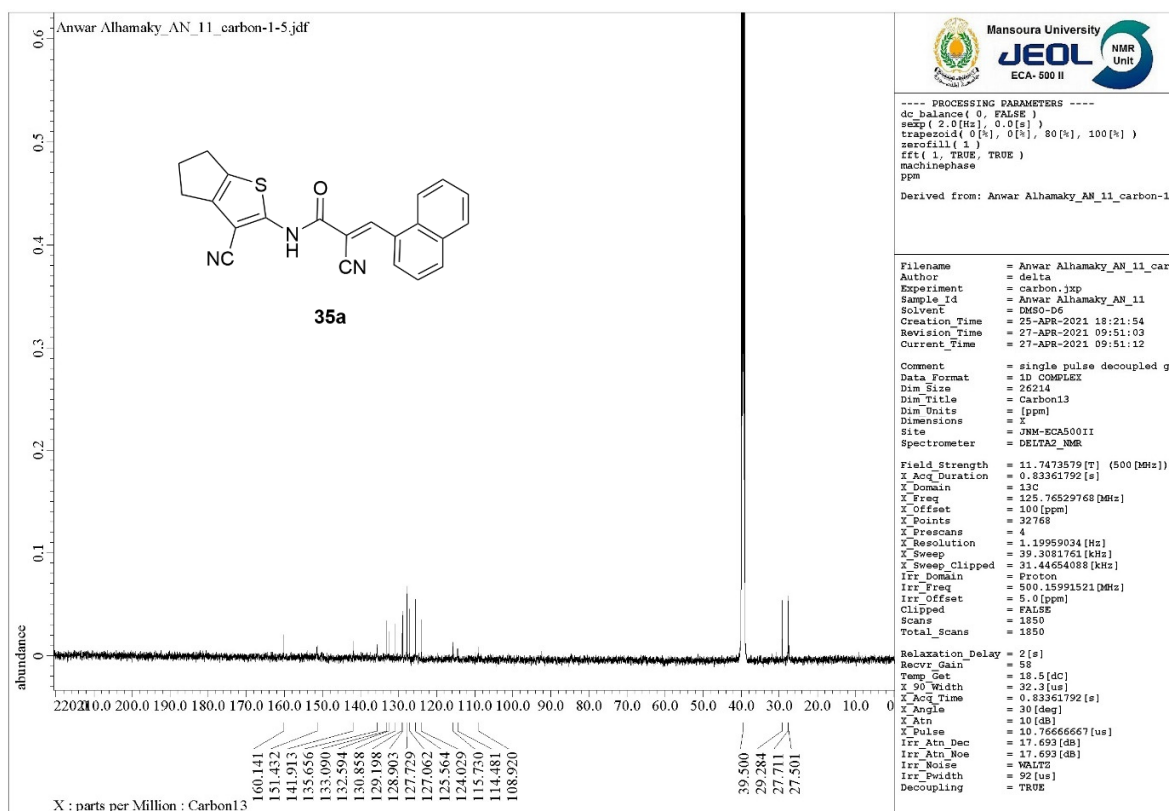


Figure S67.  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO}-d_6$ ) spectrum of compound **35a**.

anwar-elhamaky-an11 #151 RT: 2.54 AV: 1 NL: 4.65E4  
T: + c EI Full ms [40.00-1000.00]

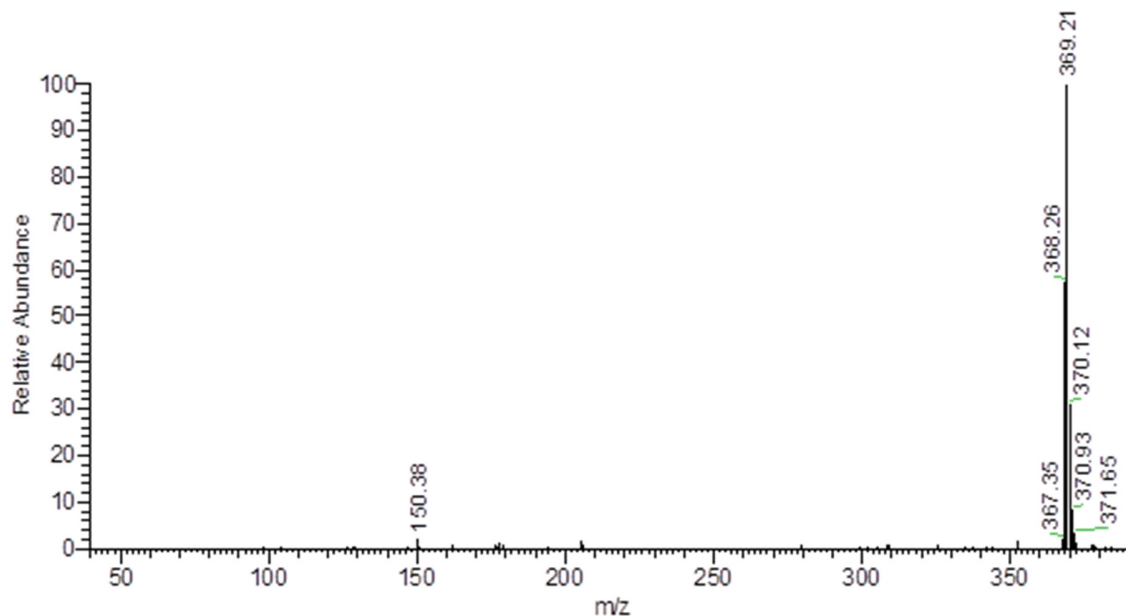


Figure S68. Mass spectrum of compound **35a**.

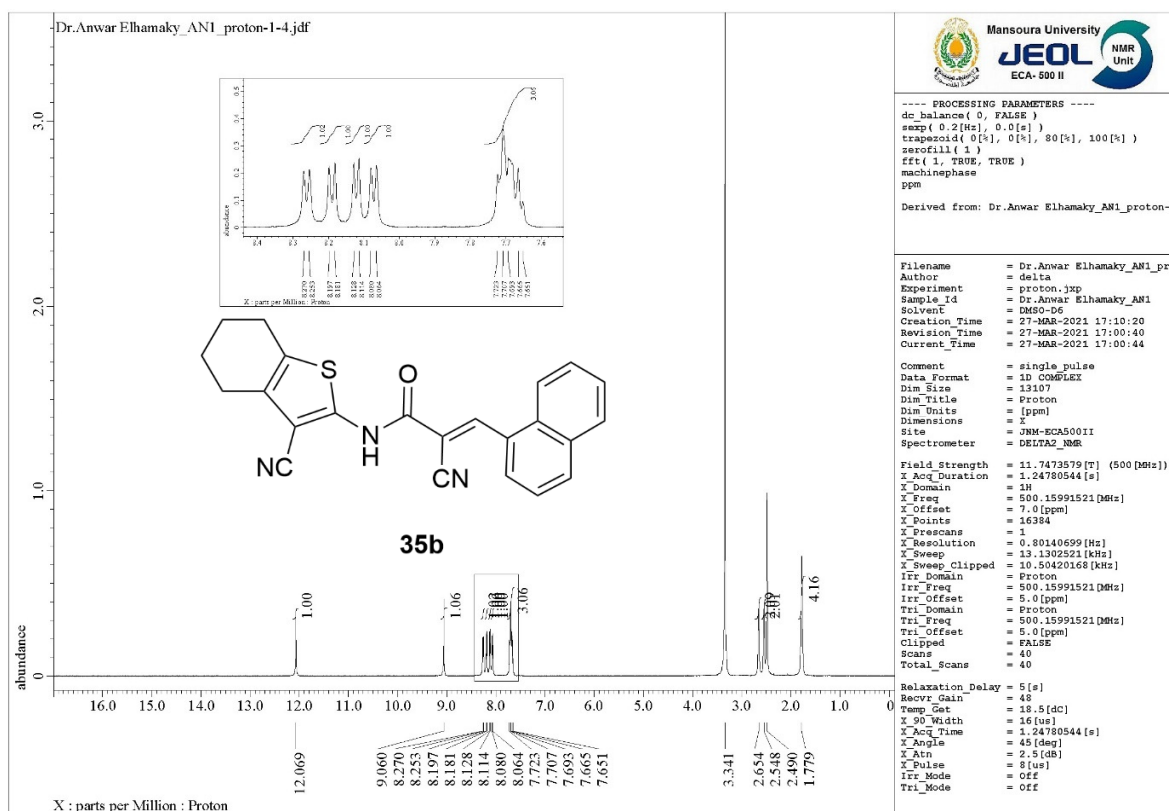


Figure S69.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ ) spectrum of compound **35b** in *E* configuration.

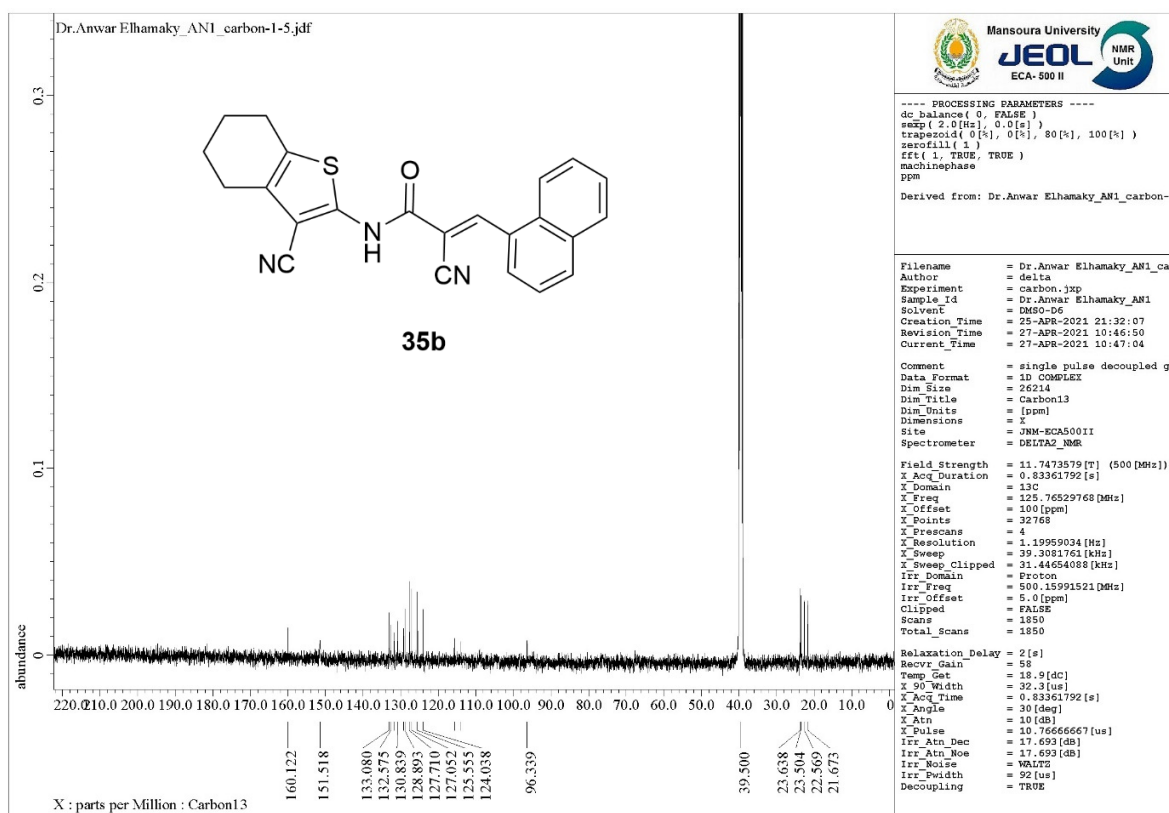


Figure S70.  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO}-d_6$ ) spectrum of compound **35b**.



Anwar-ElHamaky-AN-01 #198 RT: 3.33 AV: 1 NL: 2.32E4  
T: + c EI Full ms [40.00-1000.00]

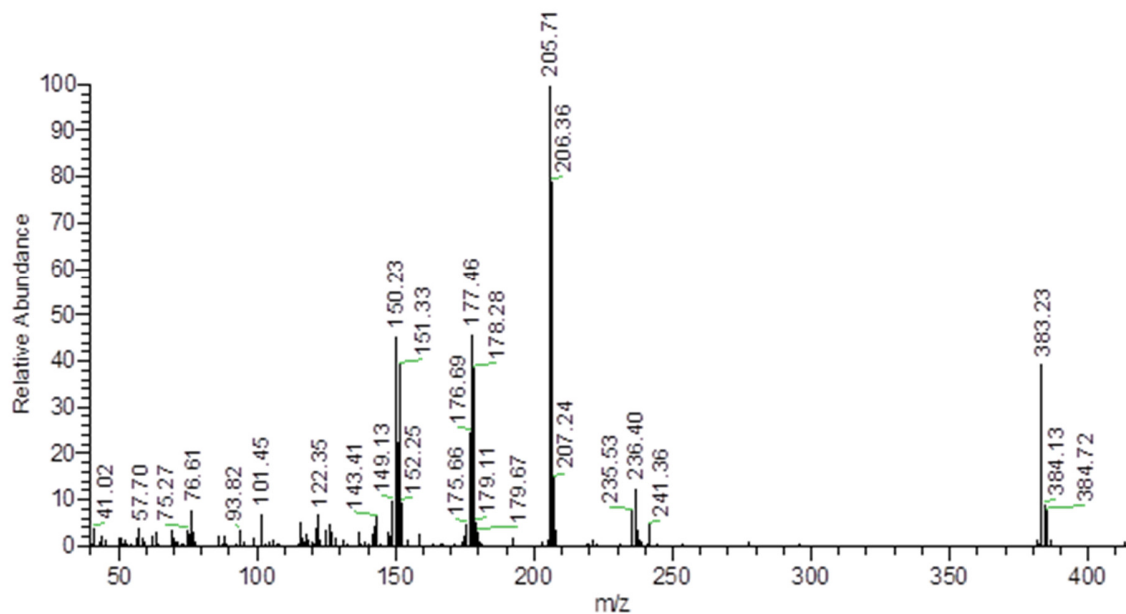


Figure S71. Mass spectrum of compound **35b**.

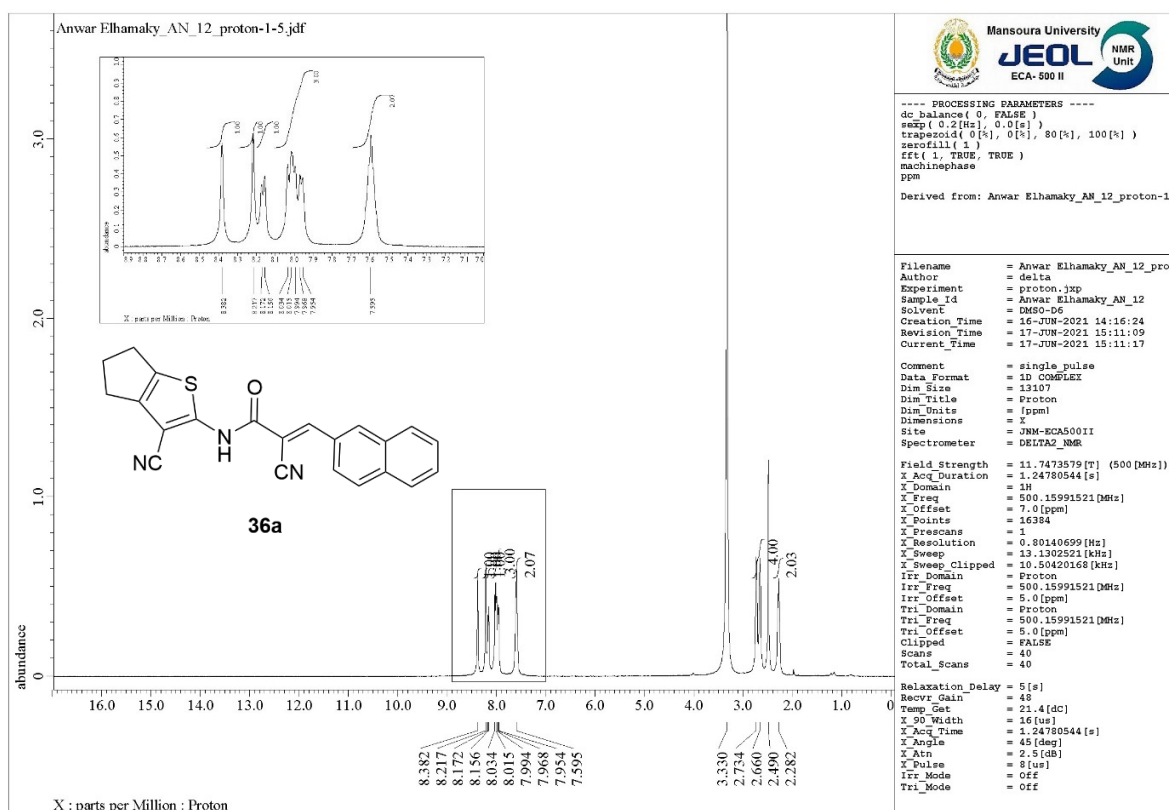


Figure S72.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ ) spectrum of compound **36a** in *E* configuration.

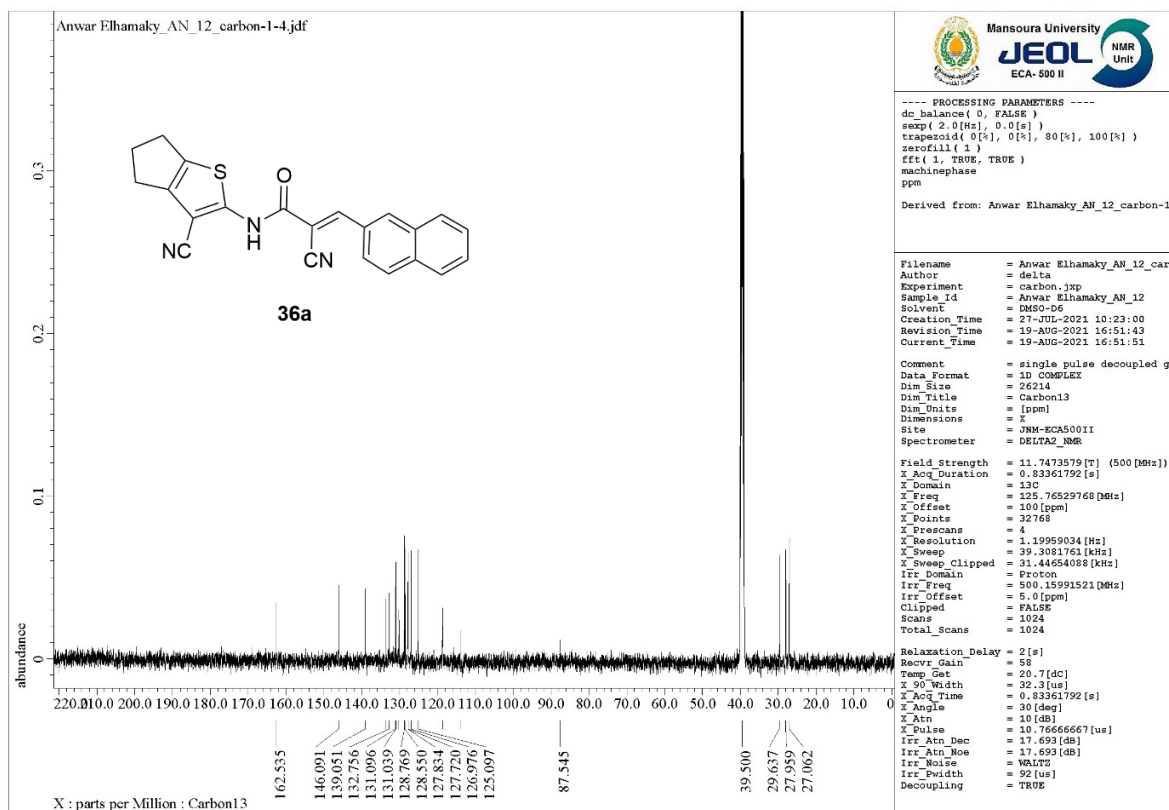


Figure S73.  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO}-d_6$ ) spectrum of compound **36a**.

anwar-elhamaky-an12 #251 RT: 4.22 AV: 1 NL: 7.54E3  
 T: + c EI Full ms [40.00-1000.00]

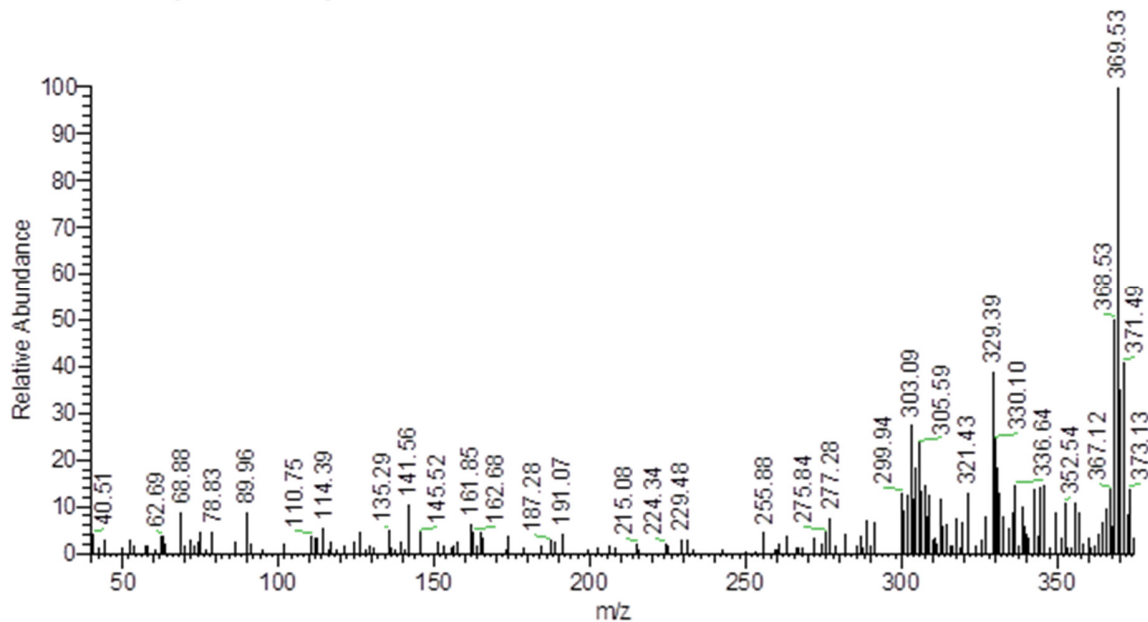


Figure S74. Mass spectrum of compound **36a**.

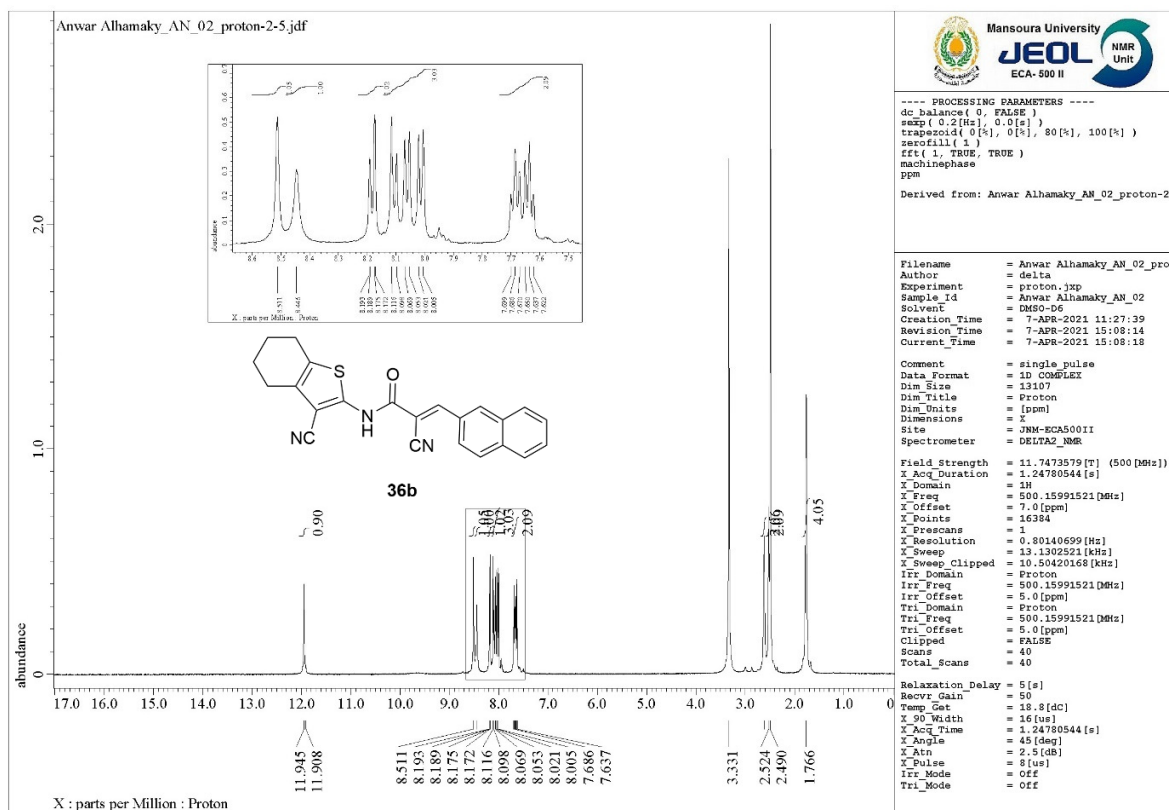


Figure S75.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ ) spectrum of compound 36b in *E* configuration.

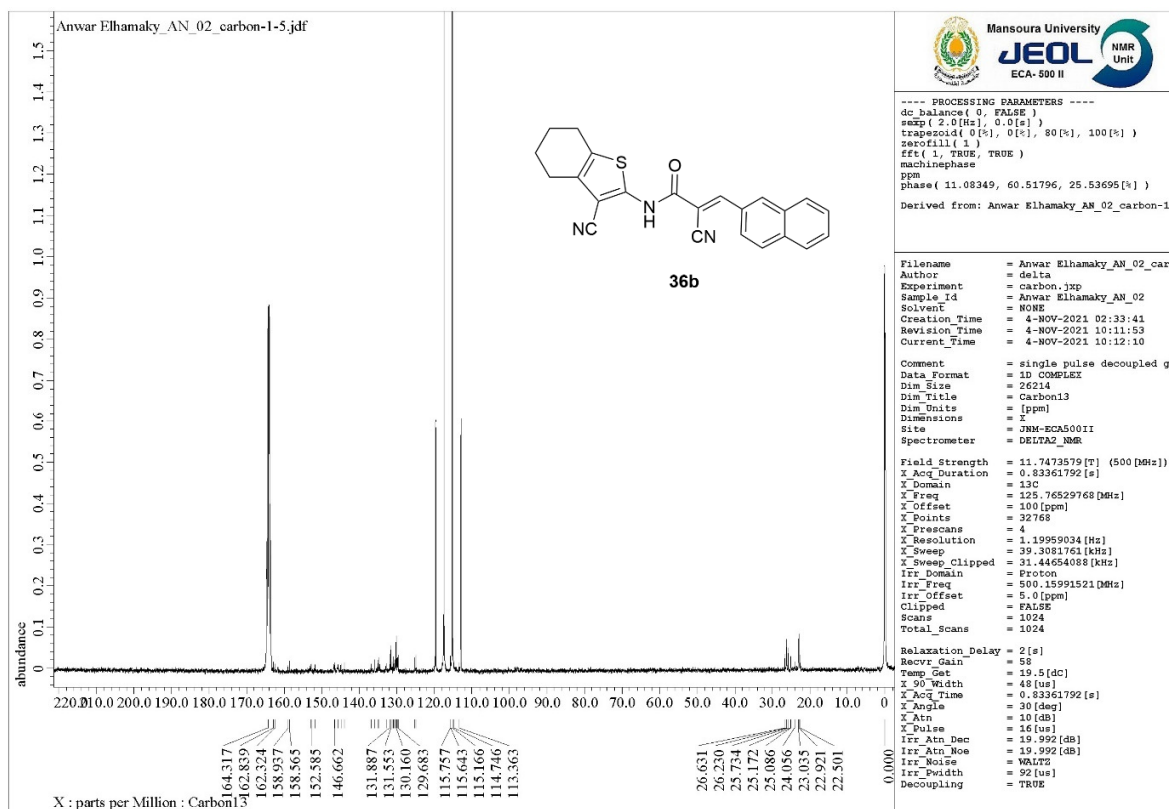


Figure S76 a.  $^{13}\text{C}$  NMR (125 MHz,  $\text{CF}_3\text{COOD}$ ) spectrum of compound 36b.

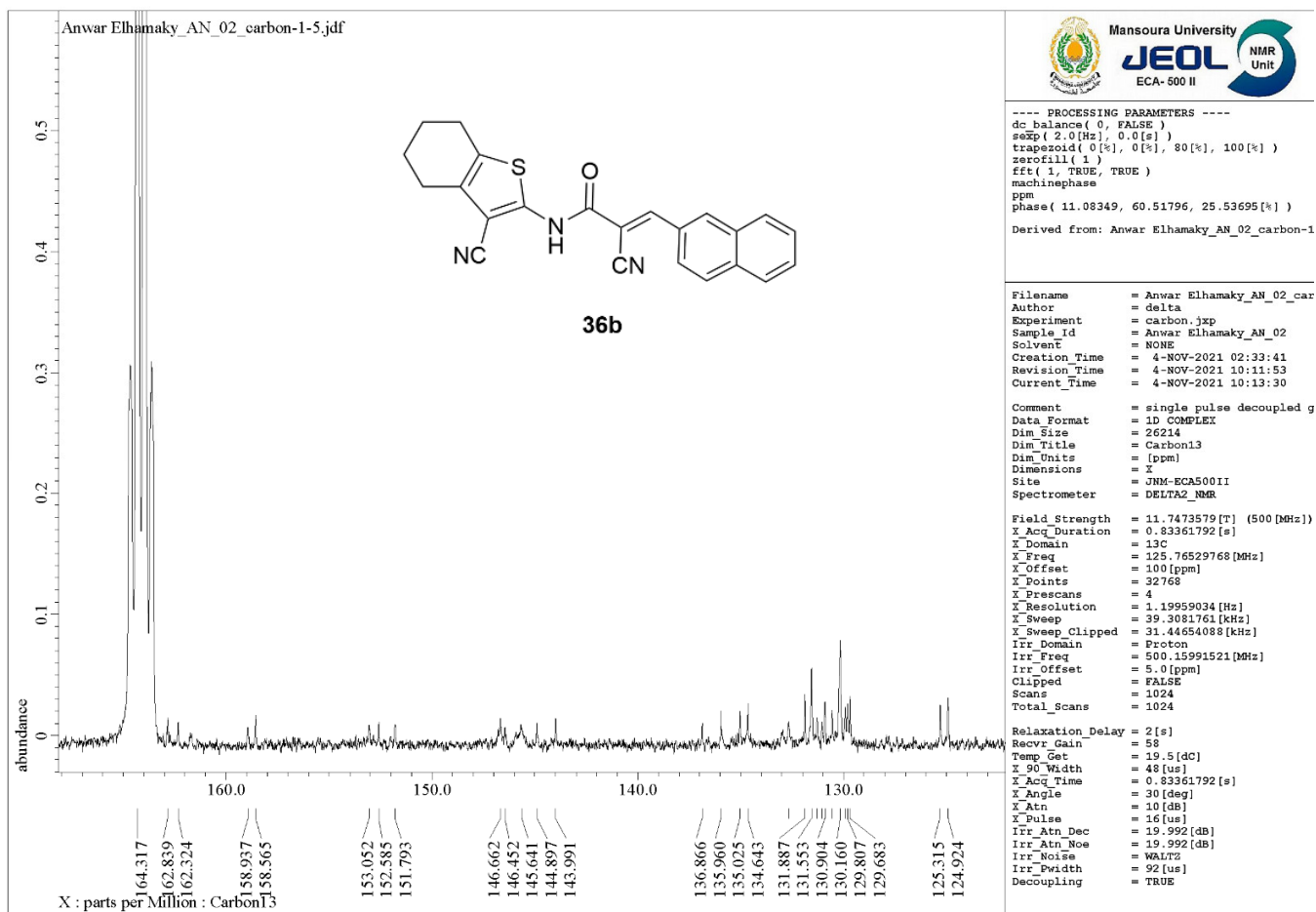


Figure S76 b.  $^{13}\text{C}$  NMR (125 MHz,  $\text{CF}_3\text{COOD}$ ) spectrum of compound **36b** (focusing on 124.0-165.0 ppm).

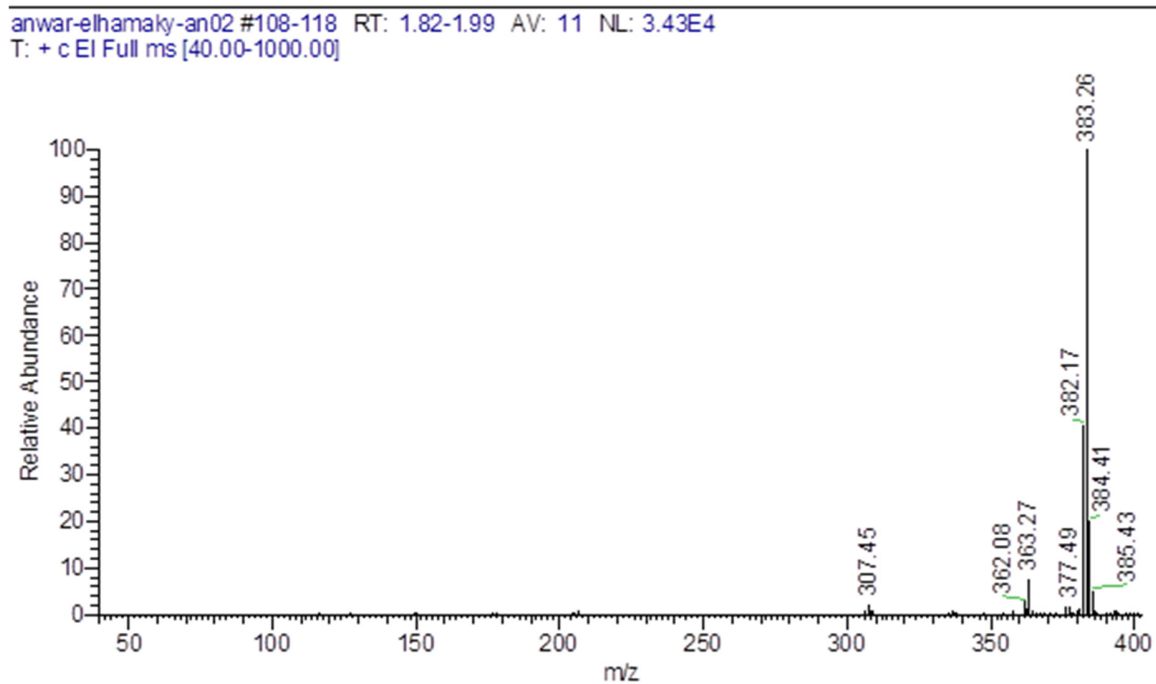


Figure S77. Mass spectrum of compound **36b**.

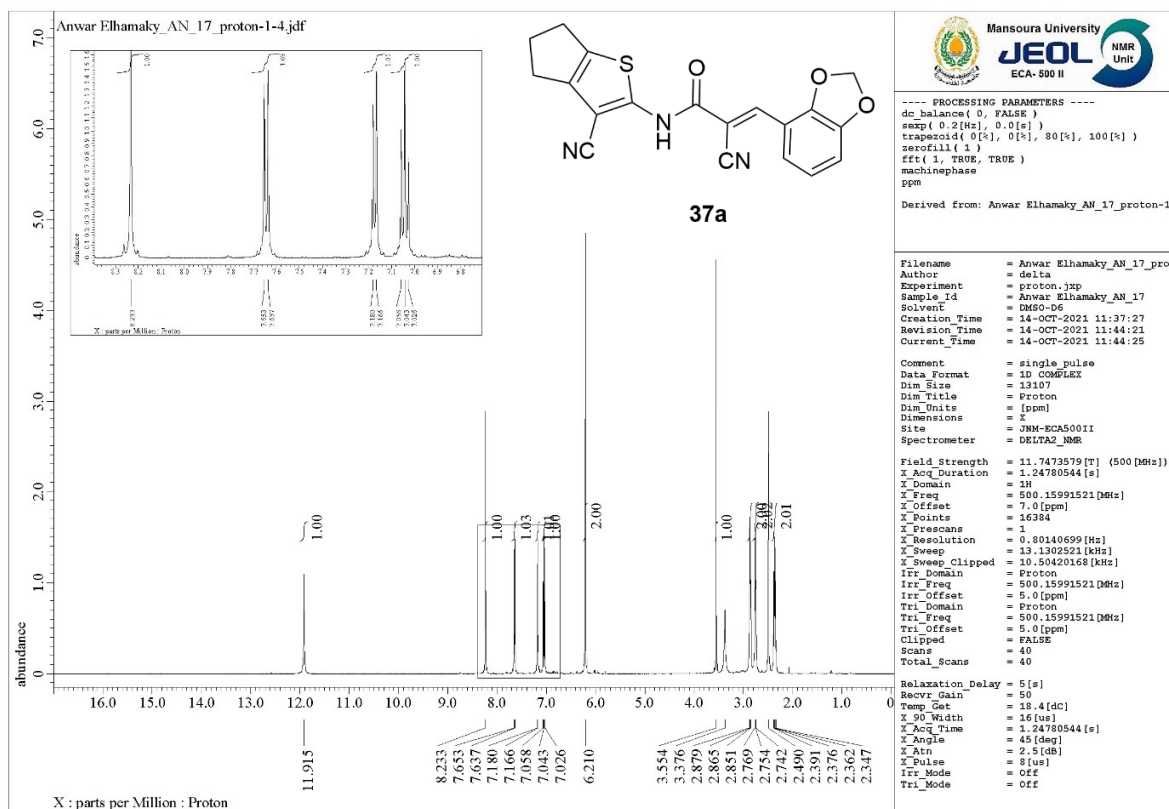


Figure S78. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) spectrum of compound 37a in *E* configuration.

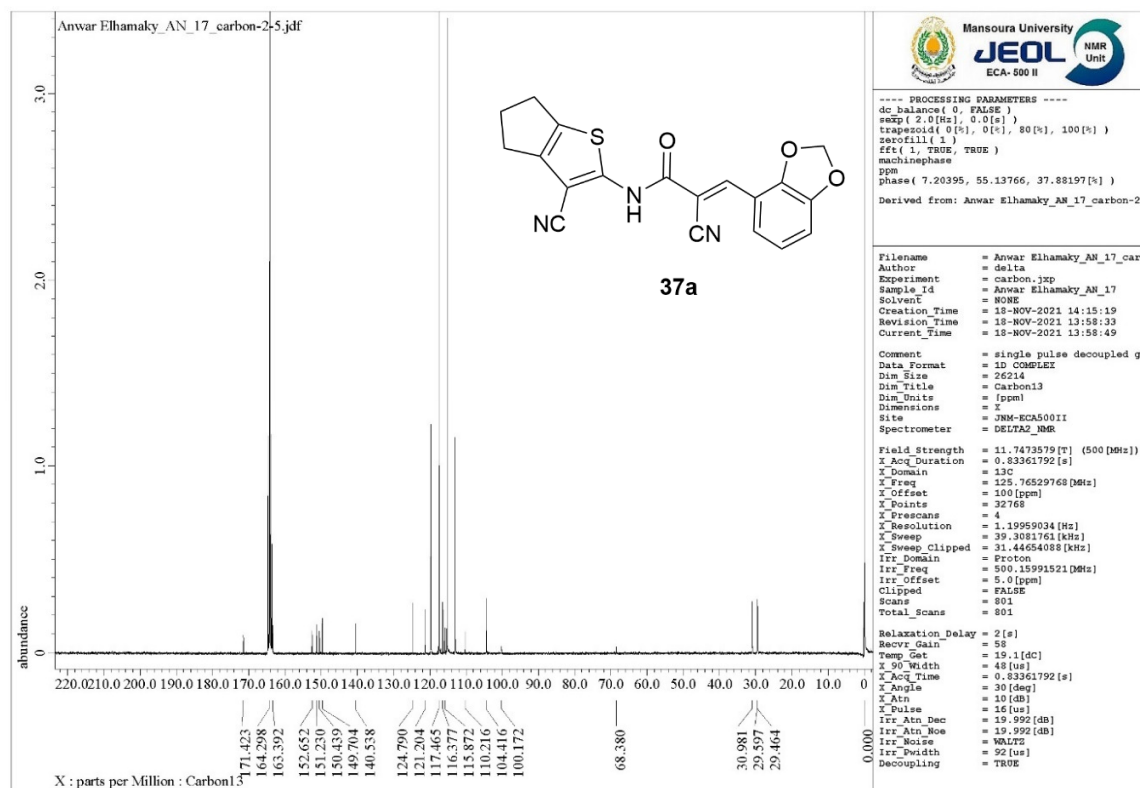


Figure S79 a. <sup>13</sup>C NMR (125 MHz, CF<sub>3</sub>COOD) spectrum of compound 37a.

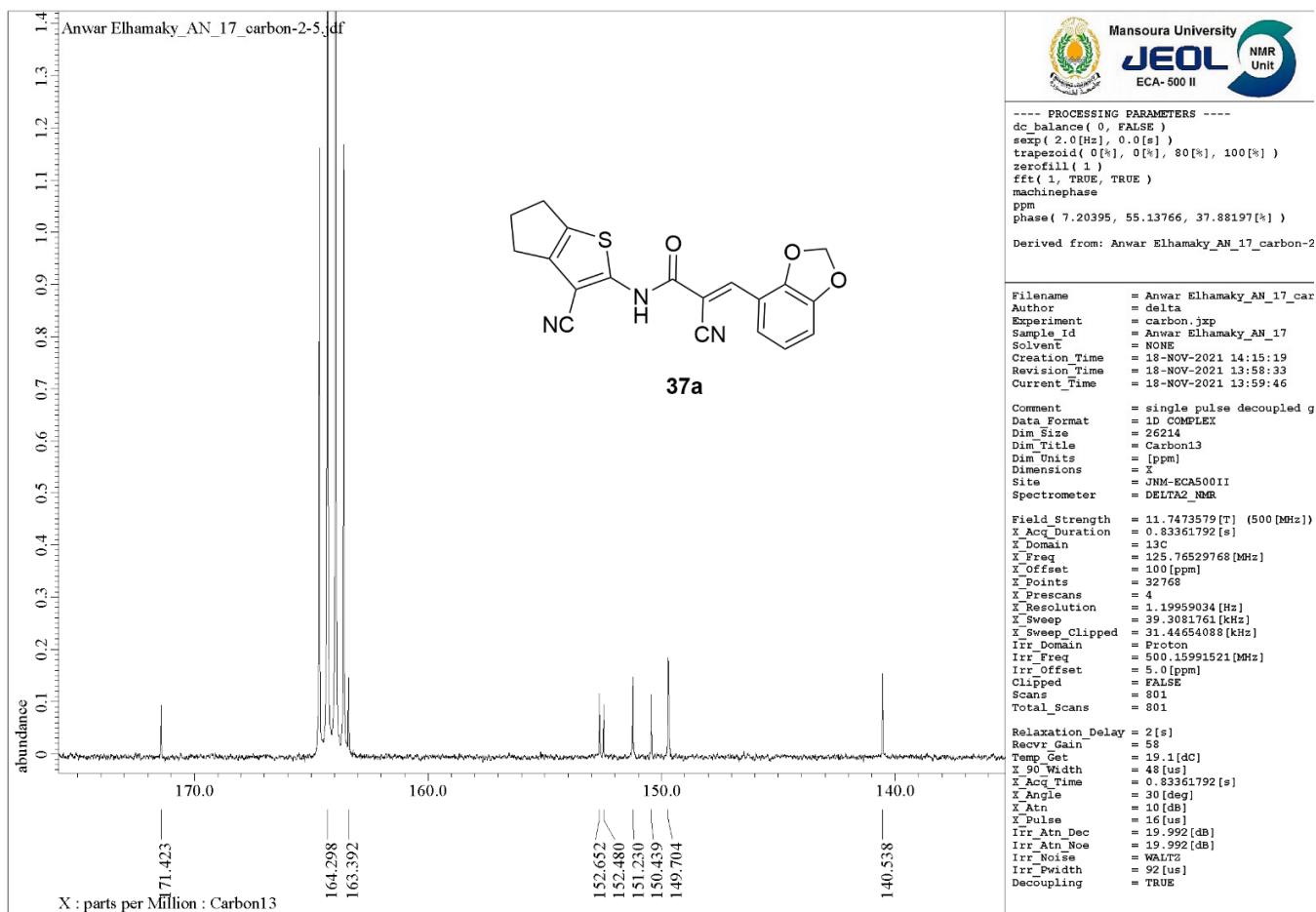


Figure S79 b.  $^{13}\text{C}$  NMR (125 MHz,  $\text{CF}_3\text{COOD}$ ) spectrum of compound **37a** (focusing on 140.0-172.0 ppm).

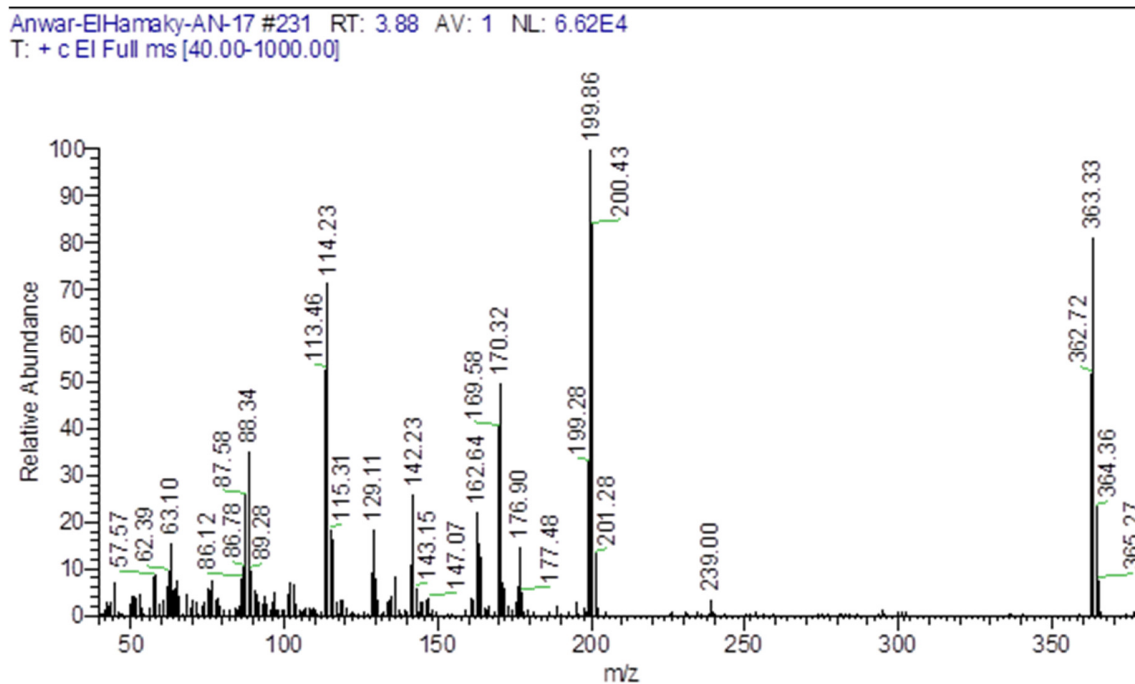


Figure S80. Mass spectrum of compound **37a**.



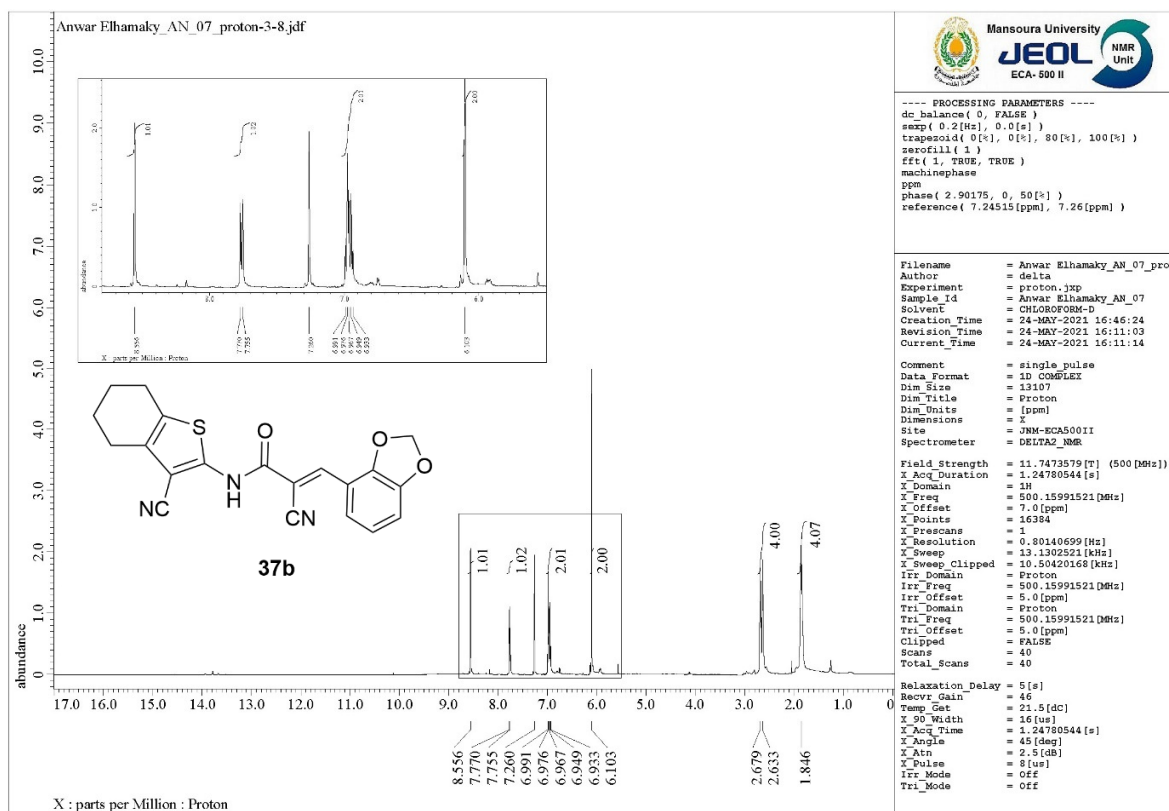


Figure S81.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) spectrum of compound **37b** in *E* configuration.

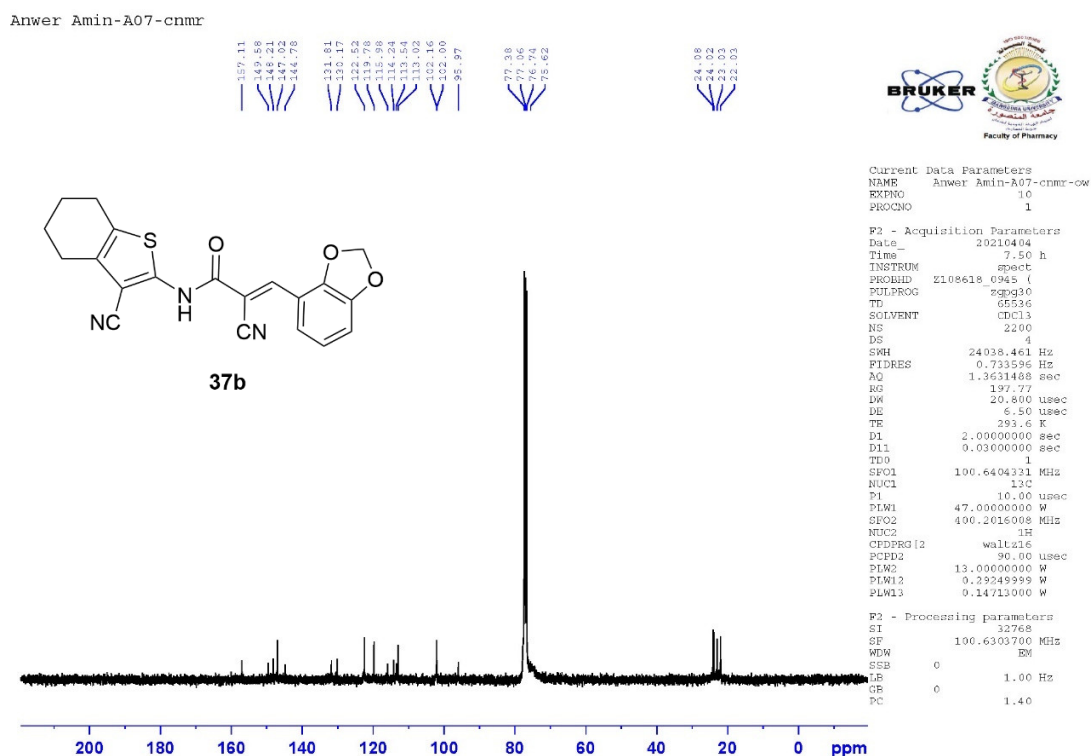


Figure S82.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) spectrum of compound **37b**.

Anwar-ElHamaky-AN-07 #179 RT: 3.01 AV: 1 NL: 2.72E5  
T: + c EI Full ms [40.00-1000.00]

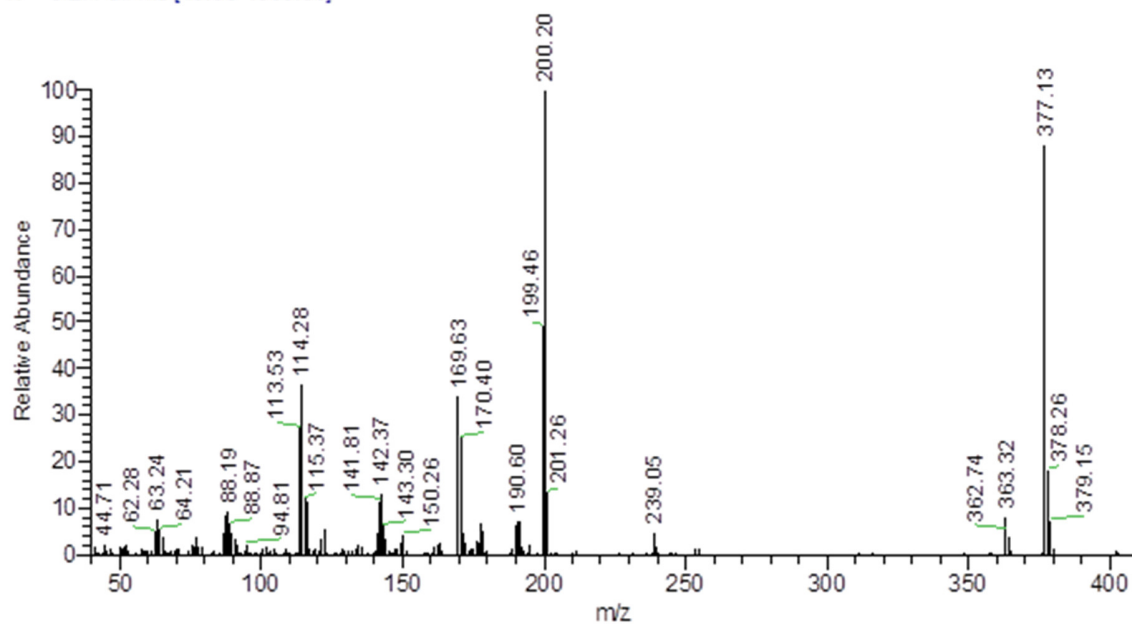


Figure S83. Mass spectrum of compound **37b**.

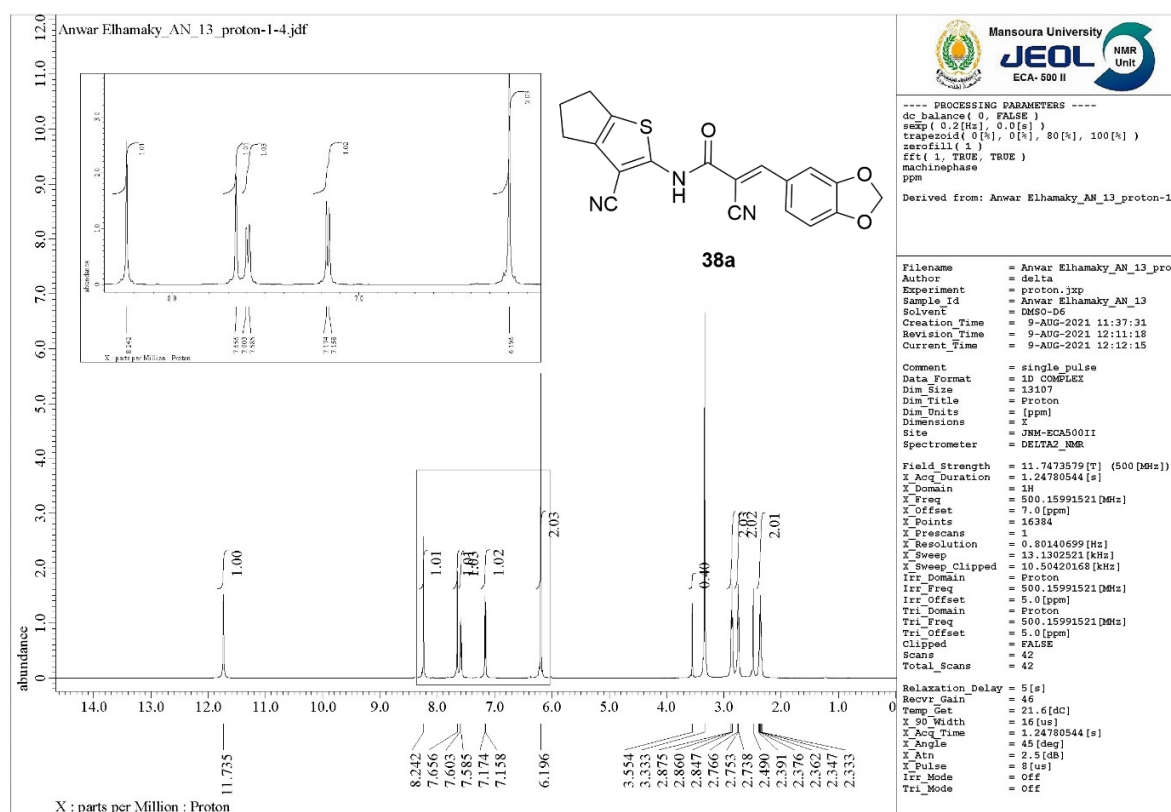


Figure S84. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) spectrum of compound **38a** in *E* configuration.

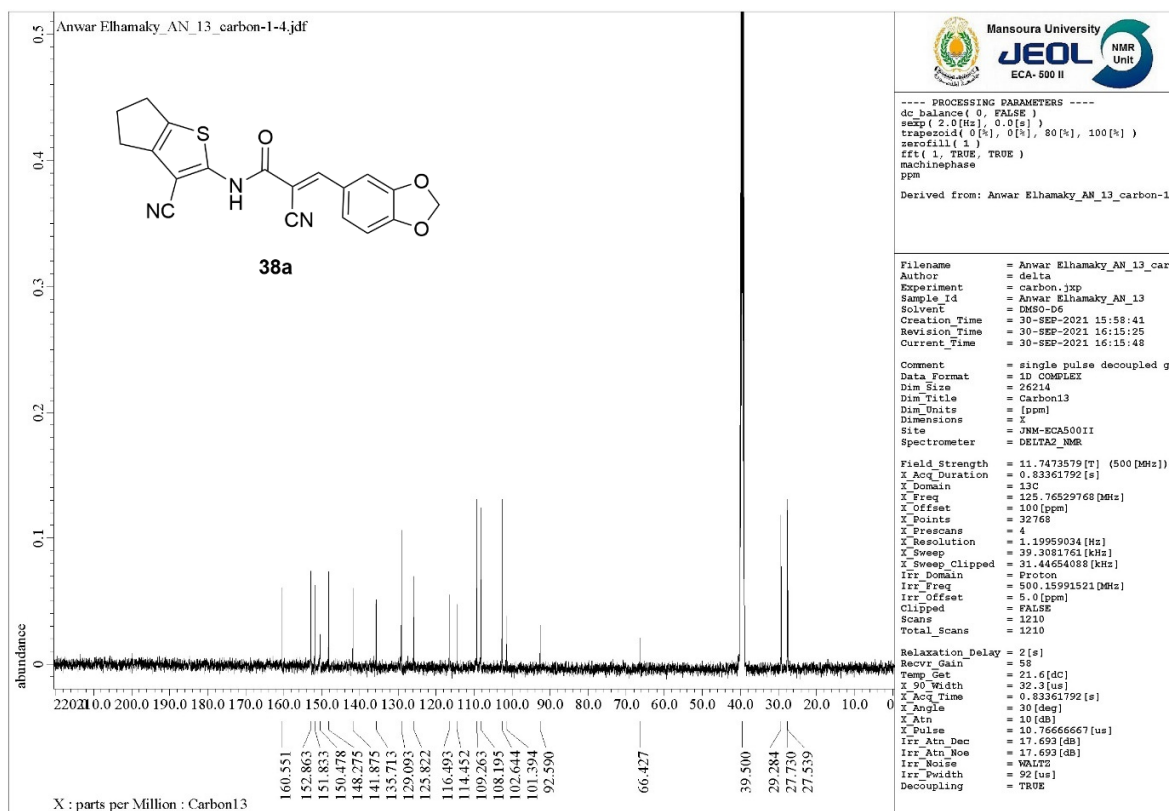


Figure S85.  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO}-d_6$ ) spectrum of compound **38a**.

Anwar-ElHamaky-AN-13 #166 RT: 2.80 AV: 1 NL: 2.15E3  
 T: + c EI Full ms [40.00-1000.00]

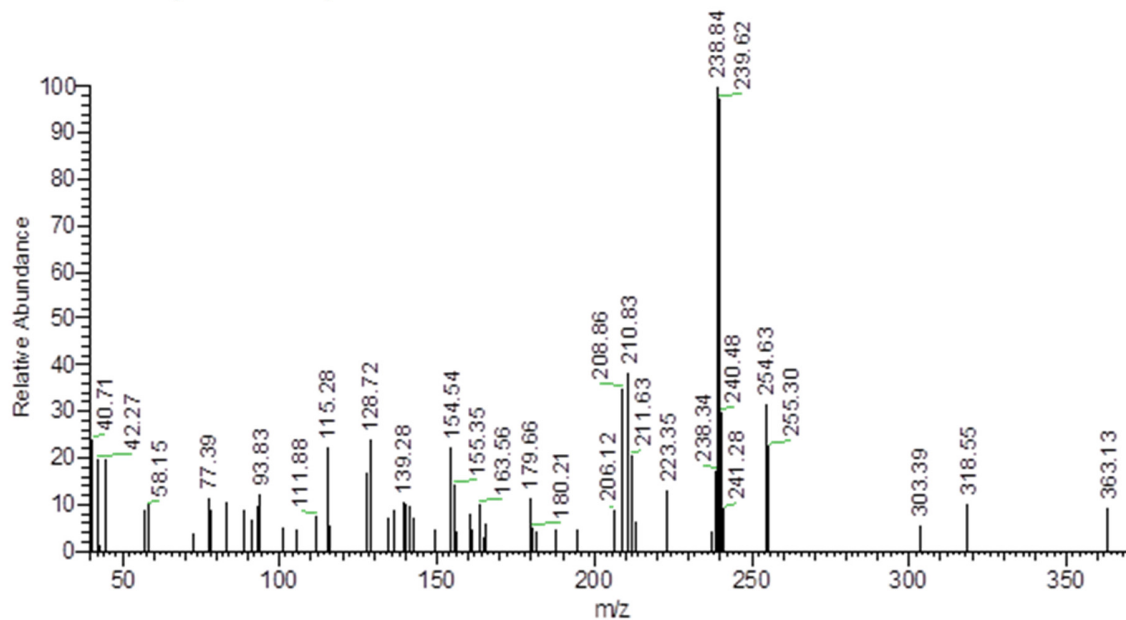
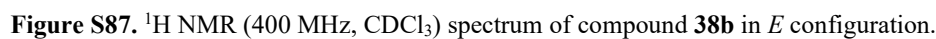
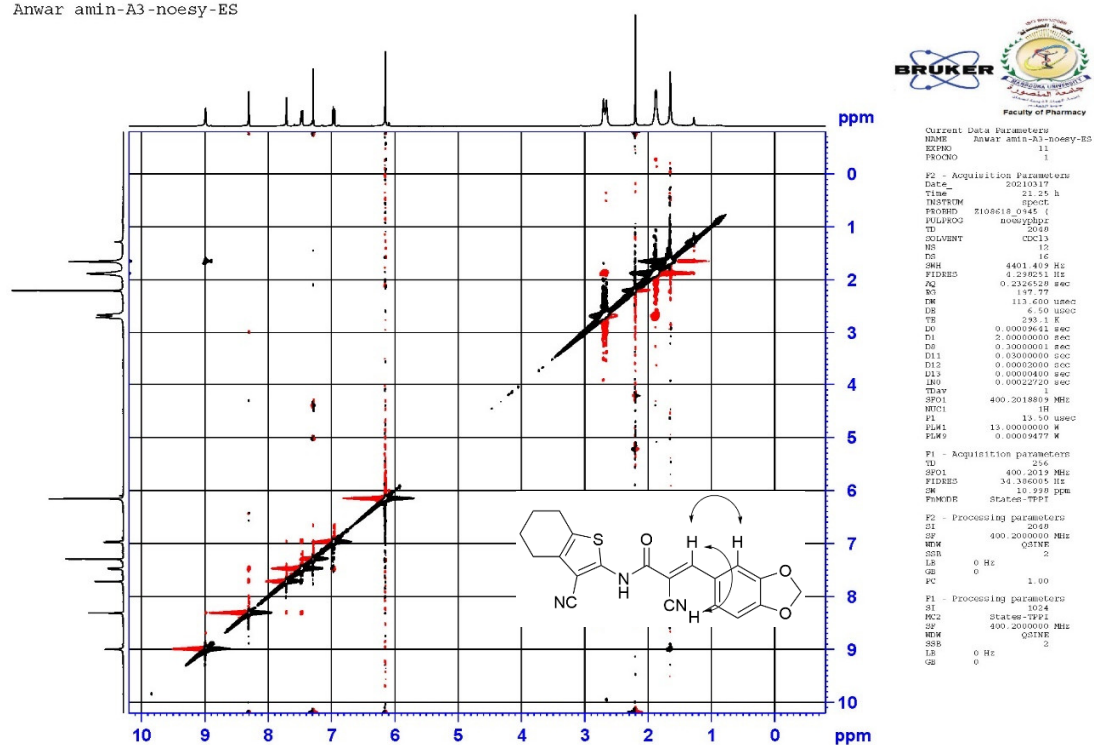


Figure S86. Mass spectrum of compound **38a**.





Chemical structure of 38b is shown in the center of the plot.

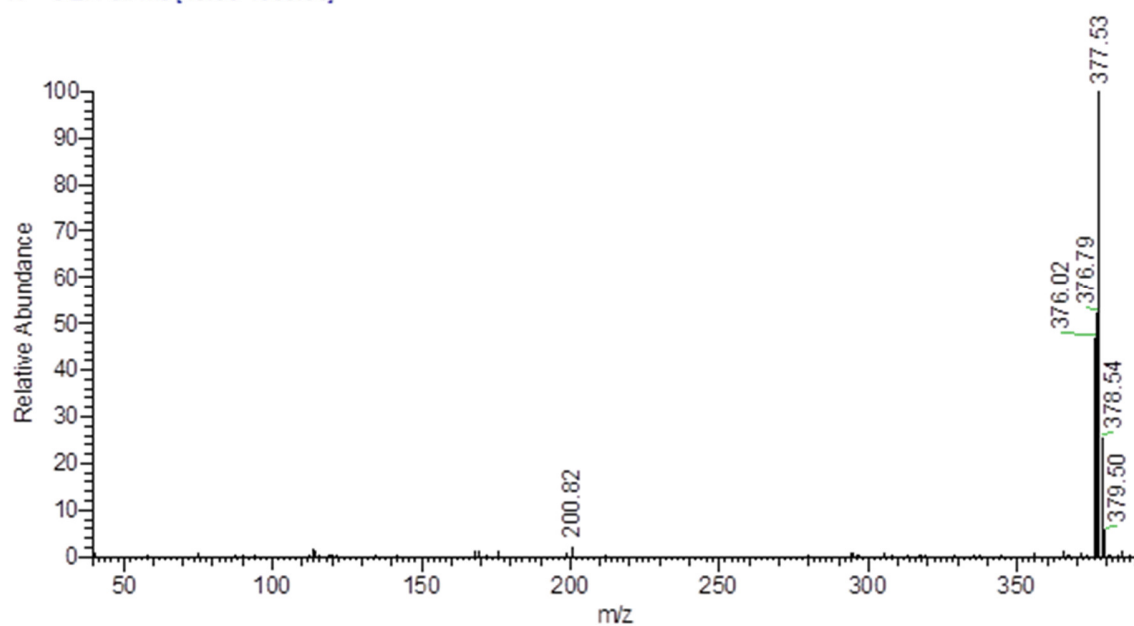
IR Spectrum (Wavenumber  $\text{cm}^{-1}$  vs. Transmittance [%]):

Key peaks (Wavenumber  $\text{cm}^{-1}$ ):

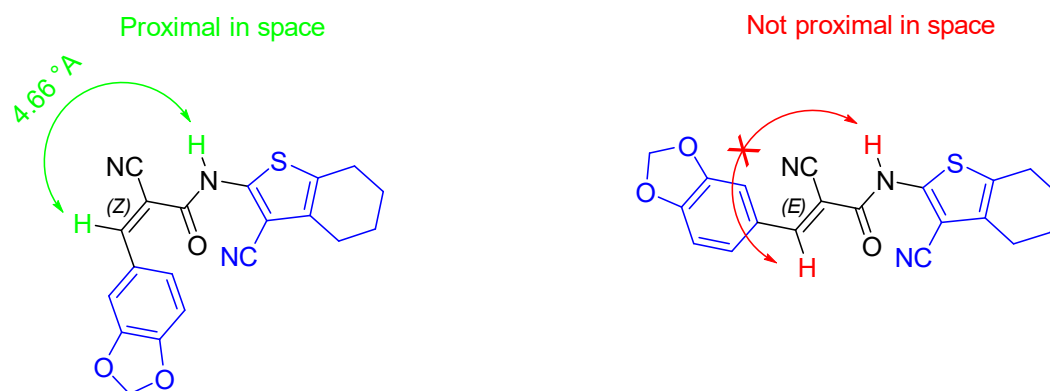
- 3433.83
- 3259.42
- 3002.25
- 2931.53
- 2849.77
- 2720.96
- 2257.98
- 2223.38
- 2092.48
- 1673.84
- 1648.26
- 1556.74
- 1515.76
- 1446.16
- 1412.50
- 1338.84
- 1279.83
- 1211.66
- 1159.66
- 1032.49
- 965.63
- 907.16
- 861.89
- 790.52
- 705.17
- 628.21
- 542.62

**Figure S90.** IR spectrum for compound **38b**.

anwar-elhamaky-an03 #151 RT: 2.54 AV: 1 NL: 4.64E4  
T: + c EI Full ms [40.00-1000.00]

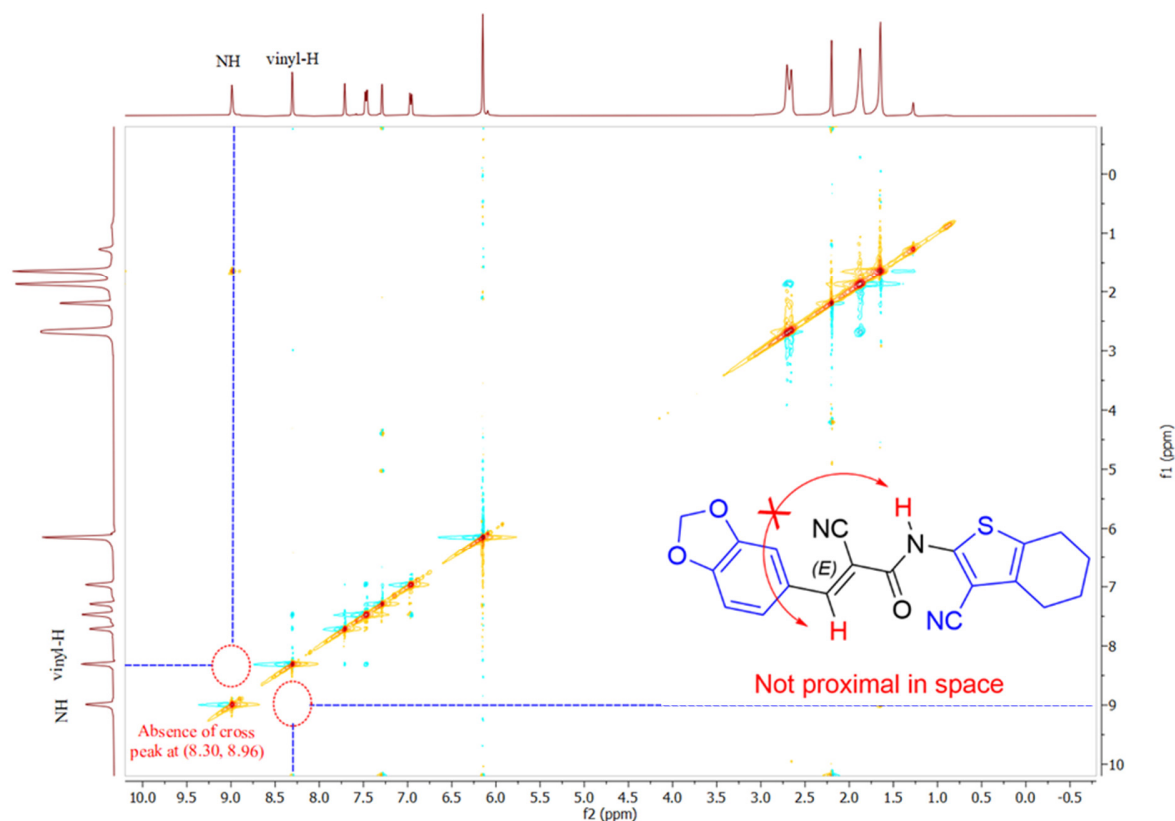


**Figure S91.** Mass spectrum of compound **38b**.

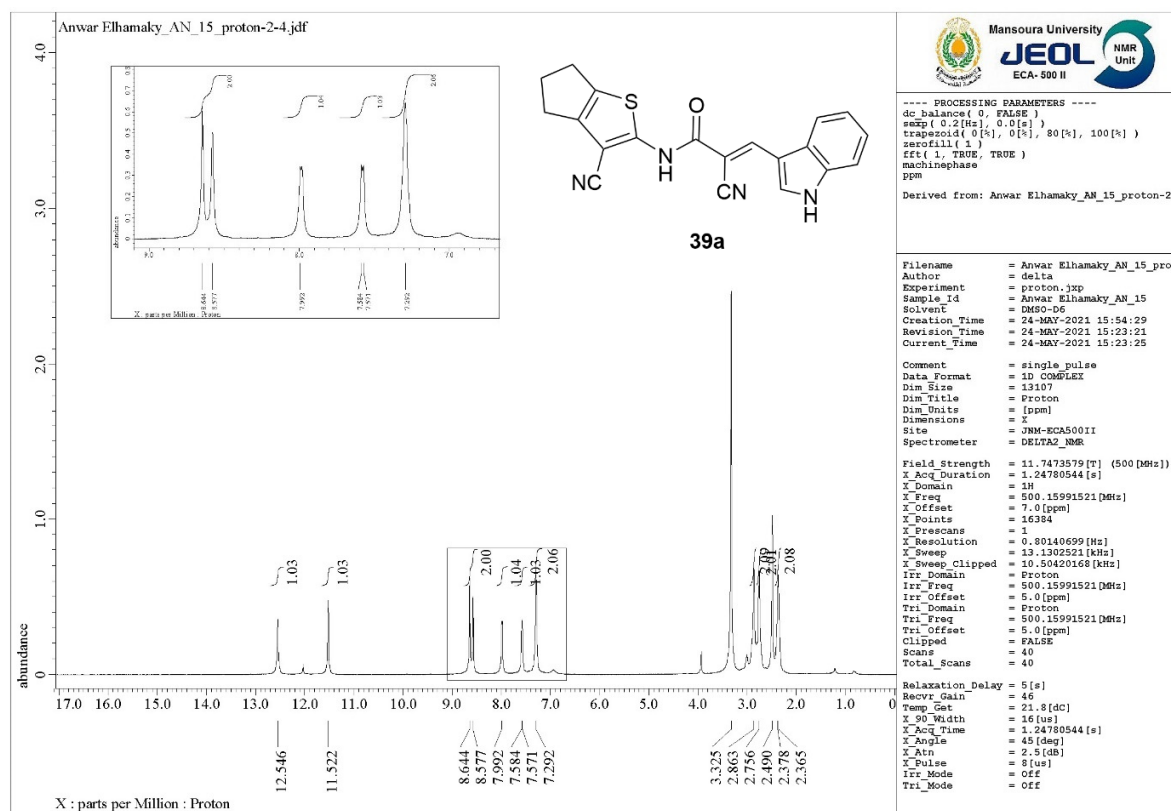


**Figure S92.** Spatial difference between vinyl and nitrogen protons in *Z* and *E* configurations of **38b**.





**Figure S93.** 2D NOESY NMR for compound **38b** in *E* configuration showing the absence of cross peak between vinyl and nitrogen protons.



**Figure S94.**  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ ) spectrum of compound **39a** in *E* configuration.

Anwer Amin-A15-cnmr

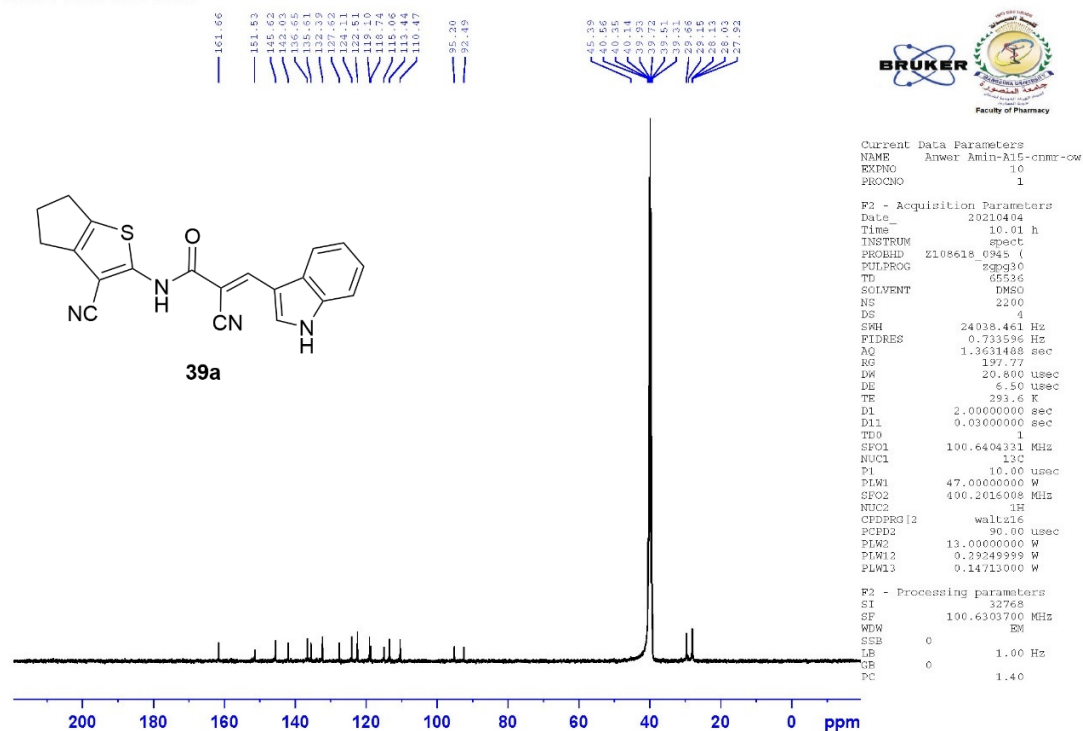


Figure S95. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) spectrum of compound 39a.

Anwar-ElHamaky-AN-15 #221 RT: 3.72 AV: 1 NL: 1.05E4  
T: + c EI Full ms [40.00-1000.00]

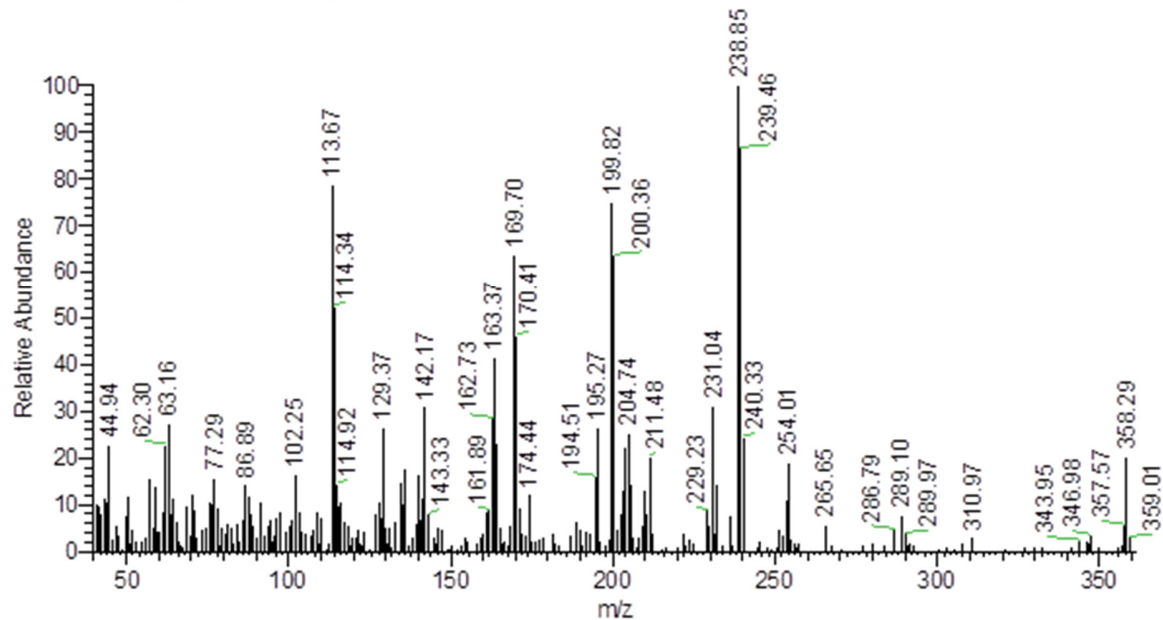


Figure S96. Mass spectrum of compound 39a.

Chemical structure of **39b** is shown above the spectrum. The structure is a 1-cyano-2-(1H-indol-3-yl)-1H-thiophene-3-carboxamide derivative.

<sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>) of **39b** shows the following peaks (ppm) and integrations:

- 12.58 (NH, 0.92H)
- 11.57 (NH, 0.97H)
- 8.67 (H, 2.00H)
- 8.61 (H, 1.08H)
- 8.02 (H, 1.14H)
- 7.61 (H, 2.16H)
- 7.32 (H, 4.56H)
- 3.37 (CH<sub>2</sub>, 2.58H)
- 3.17 (CH<sub>2</sub>, 5.52H)
- 2.65 (CH<sub>2</sub>, 2.58H)
- 1.80 (CH<sub>2</sub>, 4.56H)

Anwar Ameen-A5-carbon-WH

161.69  
146.61  
146.70  
136.67  
136.70  
131.91  
129.23  
129.33  
127.91  
127.94  
122.41  
119.15  
118.76  
118.76  
113.46  
110.46  
95.28

43.50  
43.39  
42.18  
39.97  
39.97  
39.56  
39.35  
31.19  
31.19  
23.95  
23.07  
22.17

N#Cc1c2ccccc2sc1C(=O)/C=C/C#Nc1ccccc1

**39b**

BRUKER

Current Data Parameters  
NAME Anwar Ameen-A5-carbon-WH  
EXFO 10  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20210306  
Time 17.15 h  
INSTRUM spect  
PROBHD Z108618-0945 (4  
PULPROG zgpg30  
TD 65536  
SOLVENT DMSO  
NS 2200  
DS 4  
SWH 24038.461 Hz  
FIDRES 0.721596 Hz  
AQ 1.3631488 sec  
RG 197.77  
DW 20.800 usec  
DK 6.50 usec  
TE 300 K  
D1 2.00000000 sec  
D11 0.03000000 sec  
TWO 1  
SP01 100.6240331 MHz  
NUC1 13C  
F1 10.00 usec  
PLK1 47.00000000 W  
SP02 400.2016008 MHz  
NUC2 1H  
CPDPRG2 waltz16  
PCPD2 90.00 usec  
PLK2 13.00000000 W  
PLK12 0.25249999 W  
PLK13 0.14713000 W

F2 - Processing parameters  
SI 32768  
SF 100.6263700 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40

200 180 160 140 120 100 80 60 40 20 0 ppm

53

Anwar-ElHamaky-AN-05 #240 RT: 4.03 AV: 1 NL: 1.76E4  
T: + c EI Full ms [40.00-1000.00]

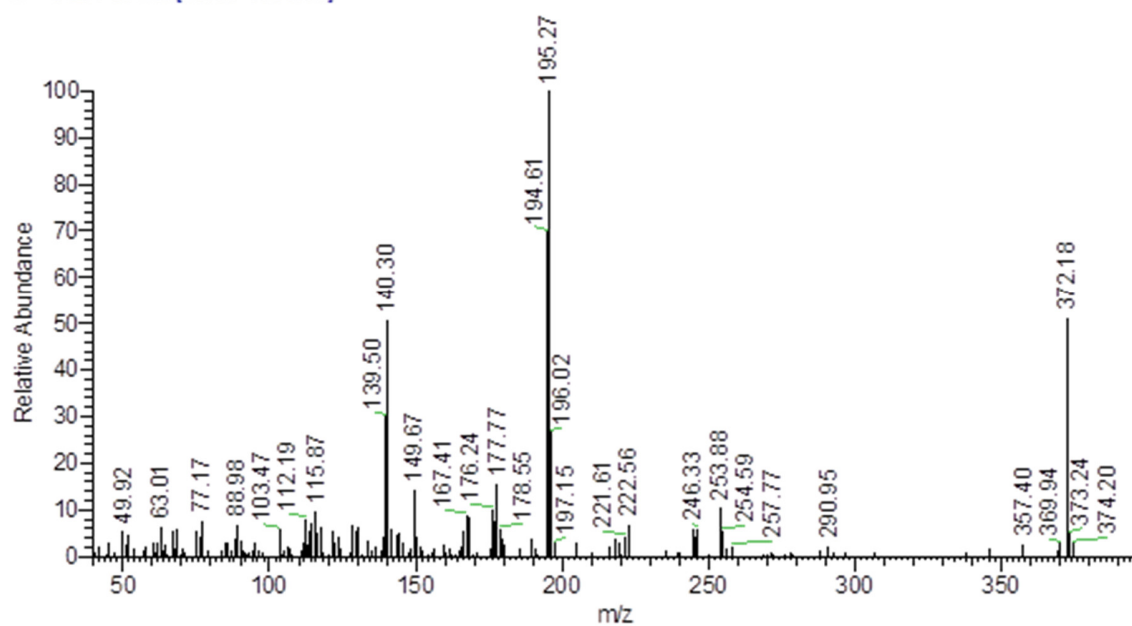
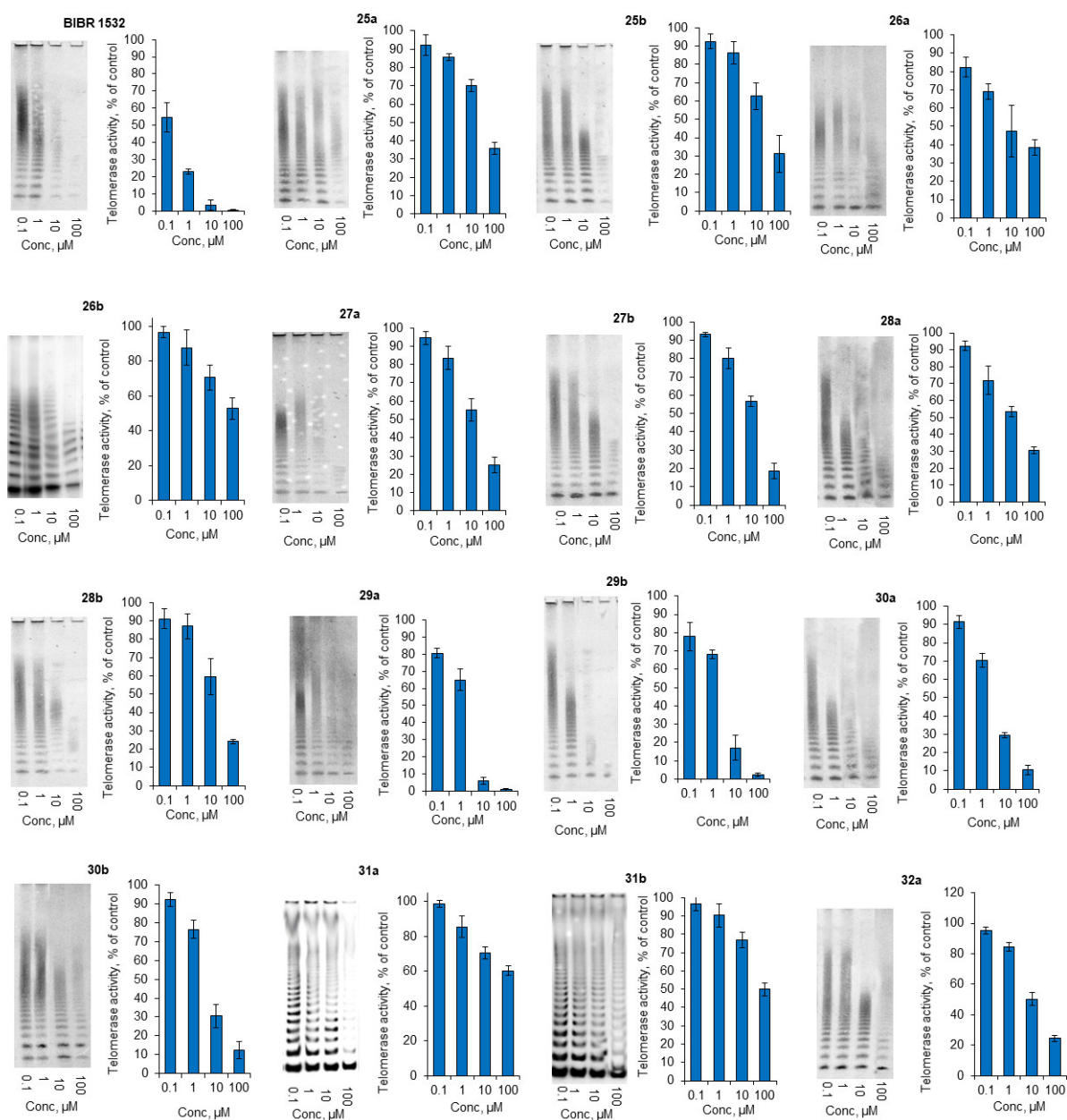
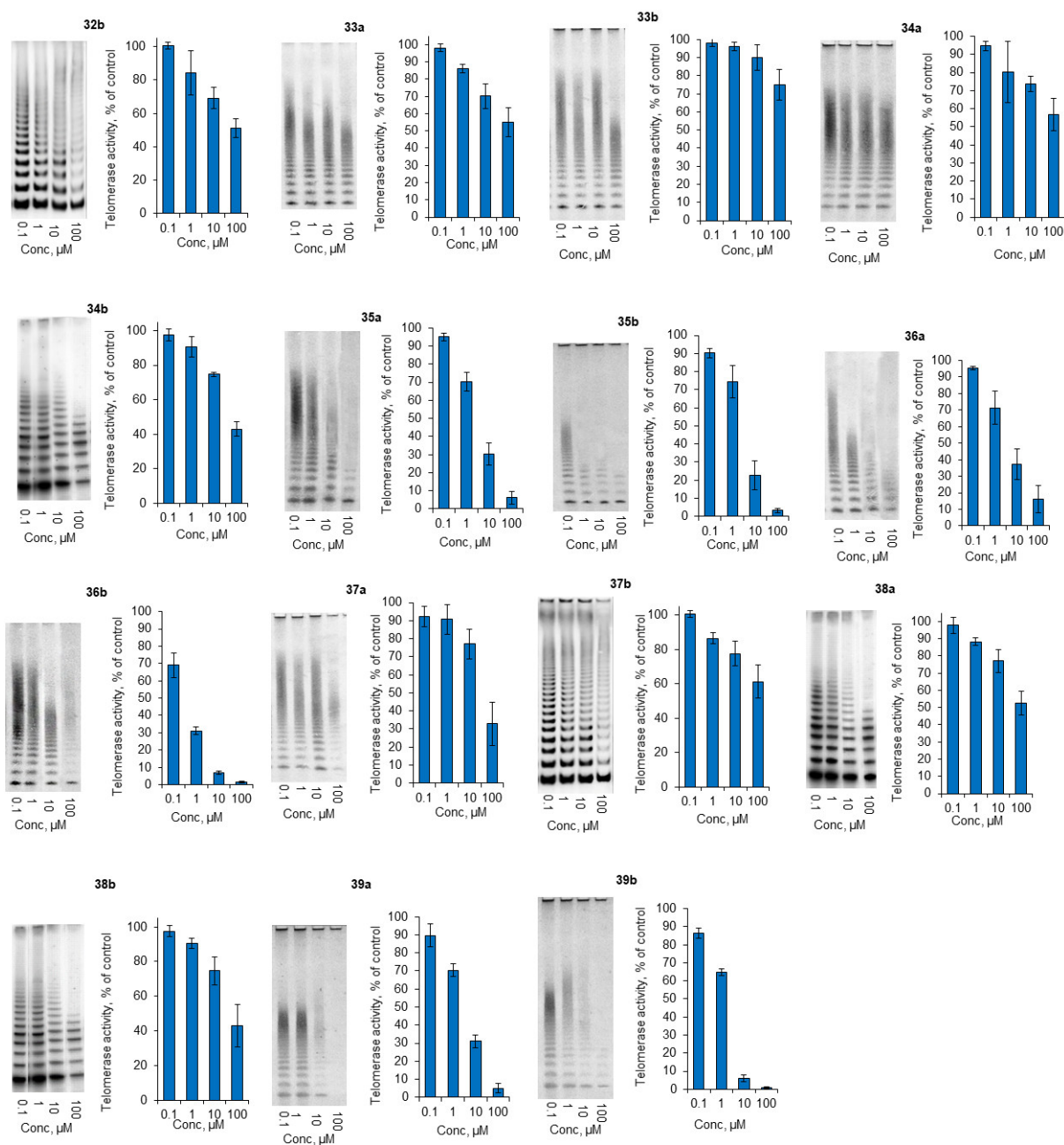


Figure S99. Mass spectrum of compound 39b.

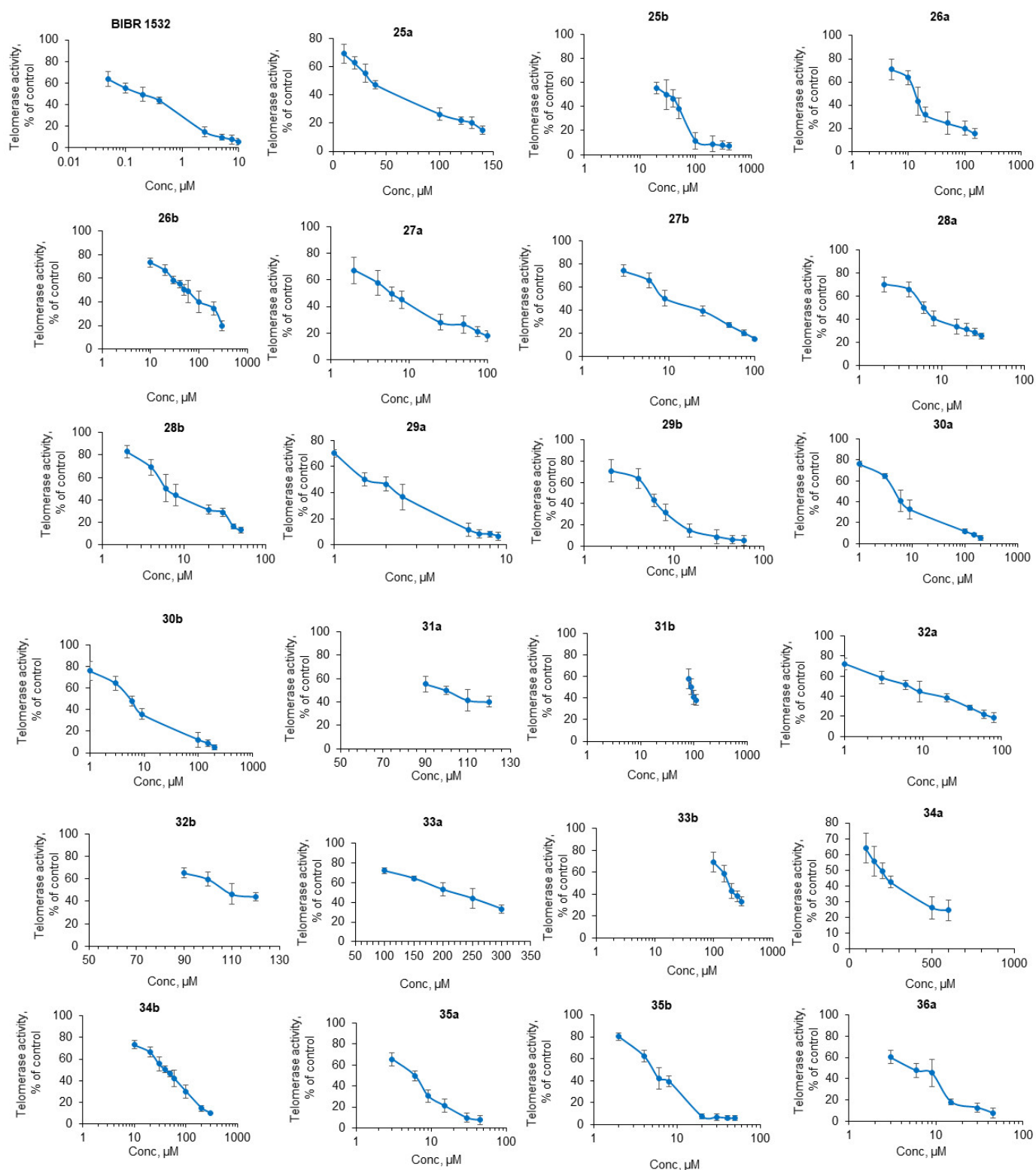


**Figure S100.** Suppression of telomerase activity in A549 cell-free lysates treated with different concentrations of inhibitors. Representative telomeric repeat amplification protocol (TRAP) gel electrophoresis for treated lysates and quantification of TRAP. One representative TRAP gel of a total of four for each of the experiments is shown. The results are presented as the mean  $\pm$  standard error of the mean.

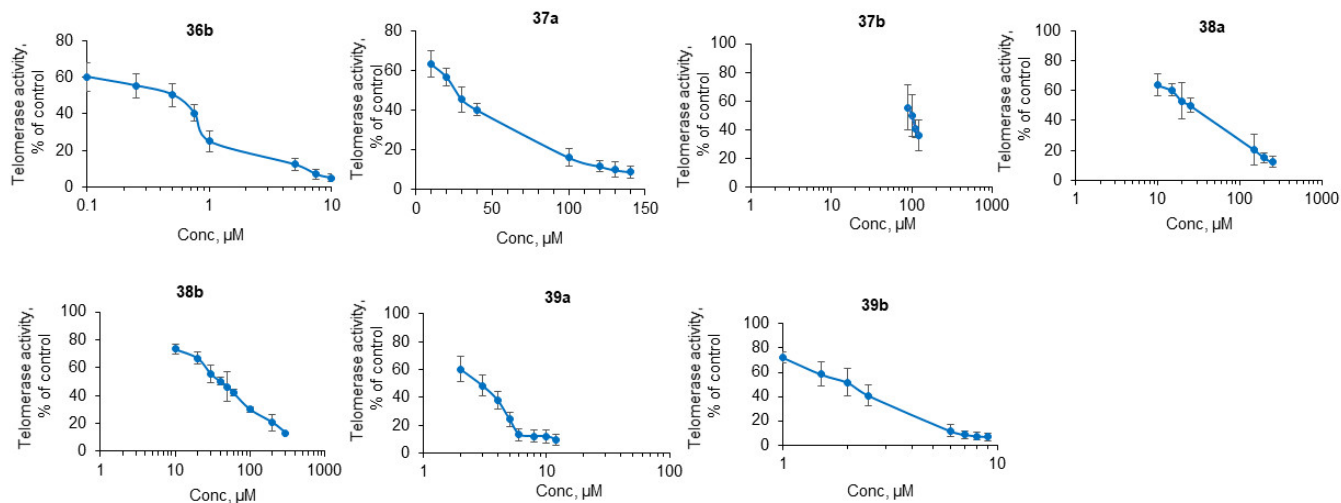


**Figure S100.** Suppression of telomerase activity in A549 cell-free lysates treated with different concentrations of inhibitors. Representative telomeric repeat amplification protocol (TRAP) gel electrophoresis for treated lysates and quantification of TRAP. One representative TRAP gel of a total of four for each of the experiments is shown. The results are presented as the mean  $\pm$  standard error of the mean. (Continued).

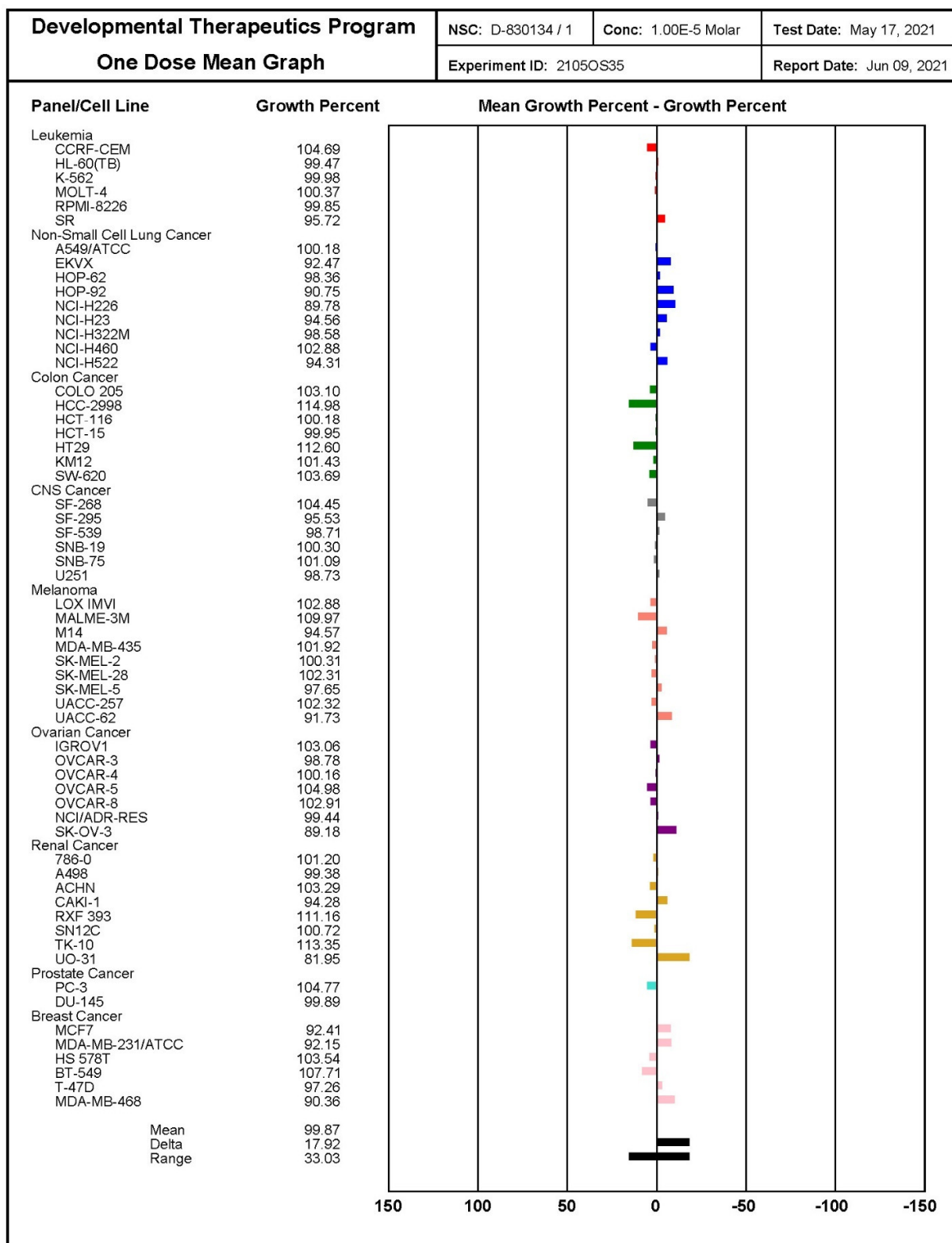




**Figure S101.** Dose-dependent curves which were used for calculation of  $\text{IC}_{50}$  and  $\text{IC}_{90}$  values. N = 4. These data were obtained by RTQ-TRAP.



**Figure S101.** Dose-dependent curves which were used for calculation of  $\text{IC}_{50}$  and  $\text{IC}_{90}$  values.  $N = 4$ . These data were obtained by RTQ-TRAP (Continued).



**Figure S102.** One dose mean graph for compound **36b** (NSC 830134) at 10  $\mu$ M.