SUPPORTING INFORMATION

Design, Synthesis, Biological Evaluation, and In Silico Studies of Novel 1,3-Thiazole Derivatives

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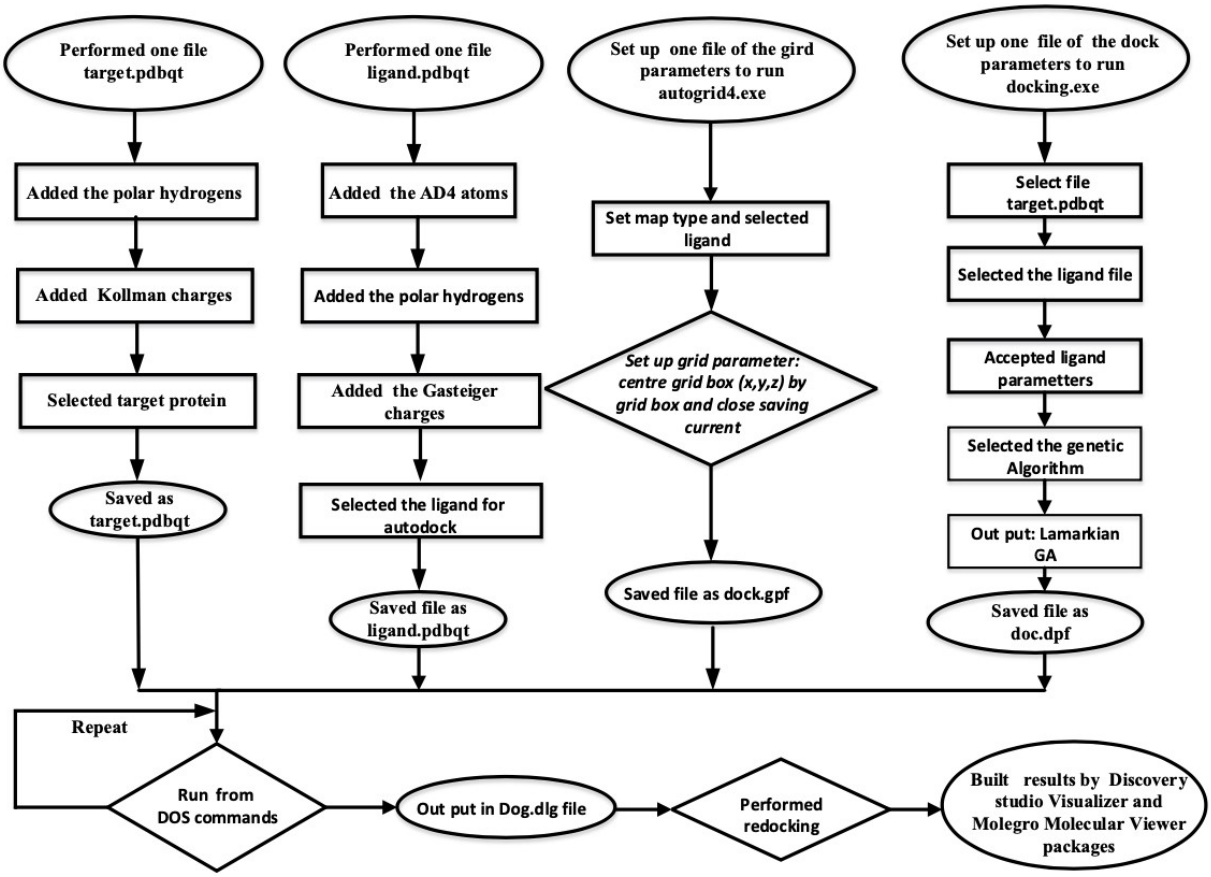
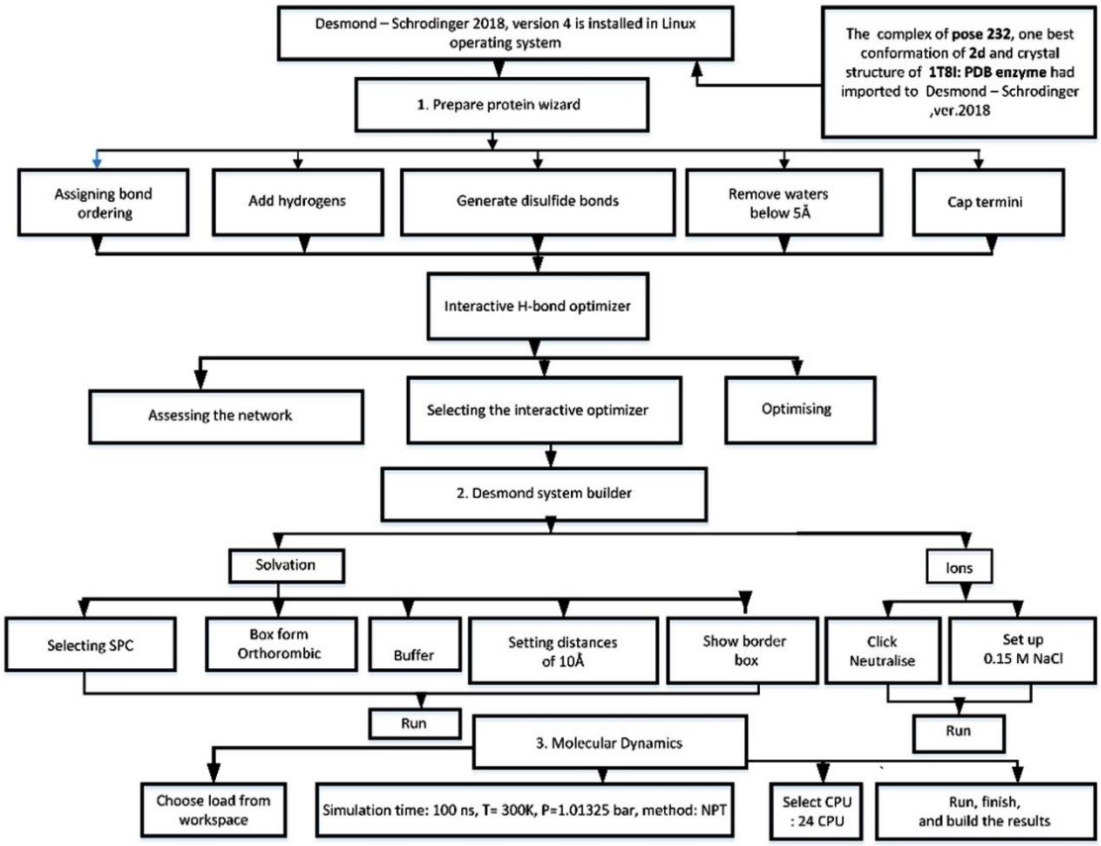
The Supporting Information file contains spectral characteristics, drug-likeness assessments, and molecular dynamics (MD) simulations, which reinforce the results and interpretations discussed in the main text. Schemes S1–S2 illustrate the docking interactions between the ligands and the receptor, as well as the MD simulation process of compound **4l** (pose 612) with the 4J5T enzyme. Figs. S1 to S82 provide the FT-IR, ^{1}H NMR, ^{13}C NMR, and HR-MS spectral data of compounds 1, 2, 3, and **4a** to **4q,** confirming their structures. Tables S1-S8 present the ADMET (absorption, distribution, metabolism, excretion, and toxicity) profiles, demonstrating the drug-likeness and potential safety of the compounds. Figs S83–S96 provide the *in vitro* antibacterial and antifungal profiles of the synthesised compounds and reference drugs, comprising agar plate assays and minimum inhibitory concentration (MIC) measurements. Figs S97–S102 present the molecular dynamics (MD) simulation results for the 4l–4J5T complex, illustrating its conformational stability, hydrogen-bonding interactions, and binding behaviour throughout the 100 ns trajectory.

- **Scheme S1**. Framework of docking between ligand and receptor.
- **Scheme S2.** MD simulation of **4l** (pose 612) with 4J5T enzyme.
- **Figs.S1-S82.** FT-IR, ^{1}H-NMR, ^{13}C-NMR, HR-MS spectra of compounds **(1, 2 , 3, 4a–4q)**.
- **Table S1.** Physicochemical properties of compound **4l**.
- **Table S2.** Medicinal chemistry descriptors of compound **4l**.
- **Table S3.** Absorption properties of compound **4l**.
- **Table S4.** Distribution properties of compound **4l**.
- **Table S5**. Metabolism properties of compound **4l**.
- **Table S6.** Excretion properties of compound **4l**.
- **Table S7.** Toxicity profiles of compound **4l**.
- **Table S8.** Toxicophoric alerts of compound **4l**.
- **Figs. S83-S96.** Supplements on the inhibitory potential *in vitro* bioactivity of compounds and positive controls
- **Figs. S97-S102.** Result MD of **4l-4J5T** complex



Scheme S1. The overarching framework of docking between a ligand and a receptor/compound is illustrated by an enzyme or the crystalline structure of an enzyme, such as 1T8I, 4WCU, and 4J5T.



Scheme S2. Procedure to simulate complex pose 612 or compound 4l and the crystal structure of 4J5T enzyme by NPT method via Desmond software, version 2018, in Linux OS.

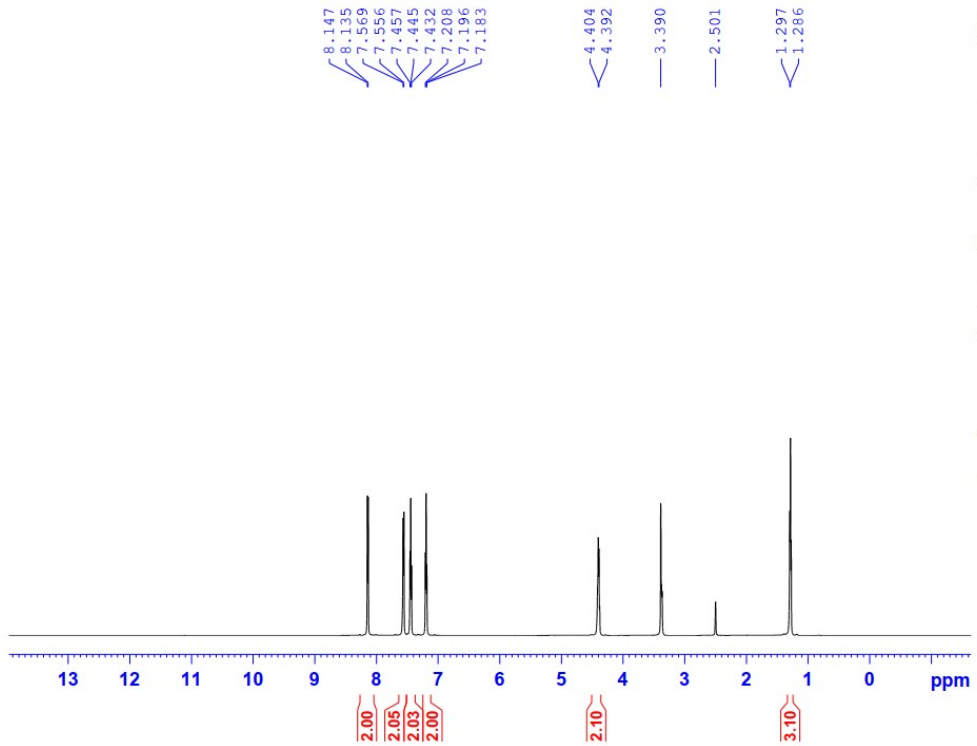



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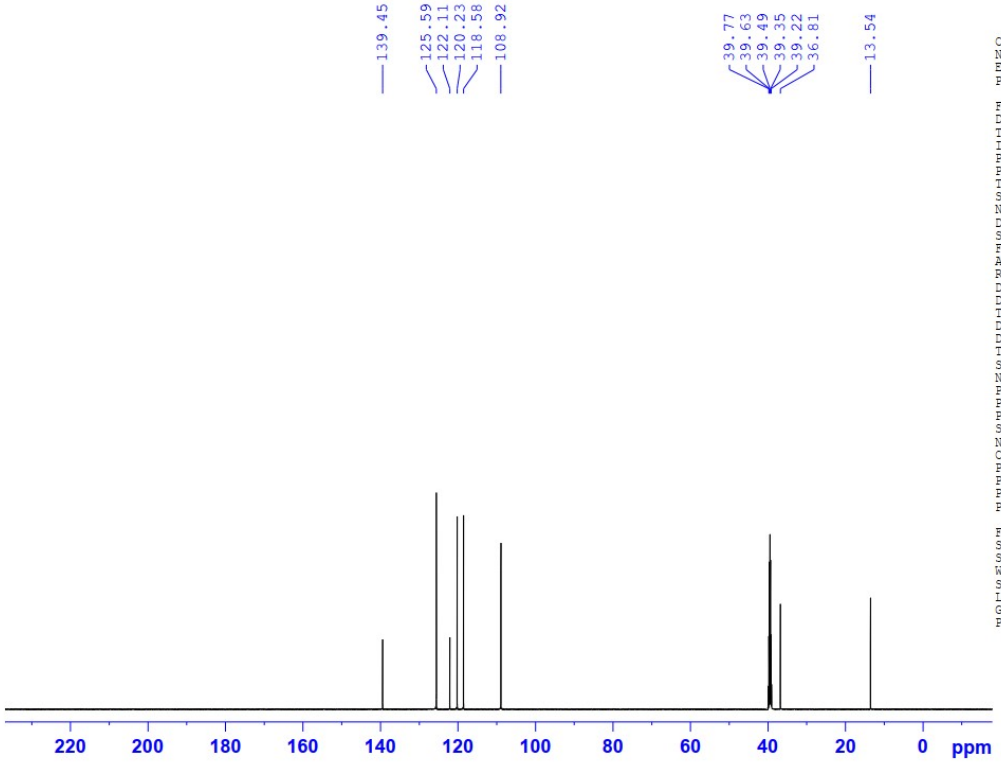
Fig. S 1. ^{1}H-NMR spectrum of compound **1.**

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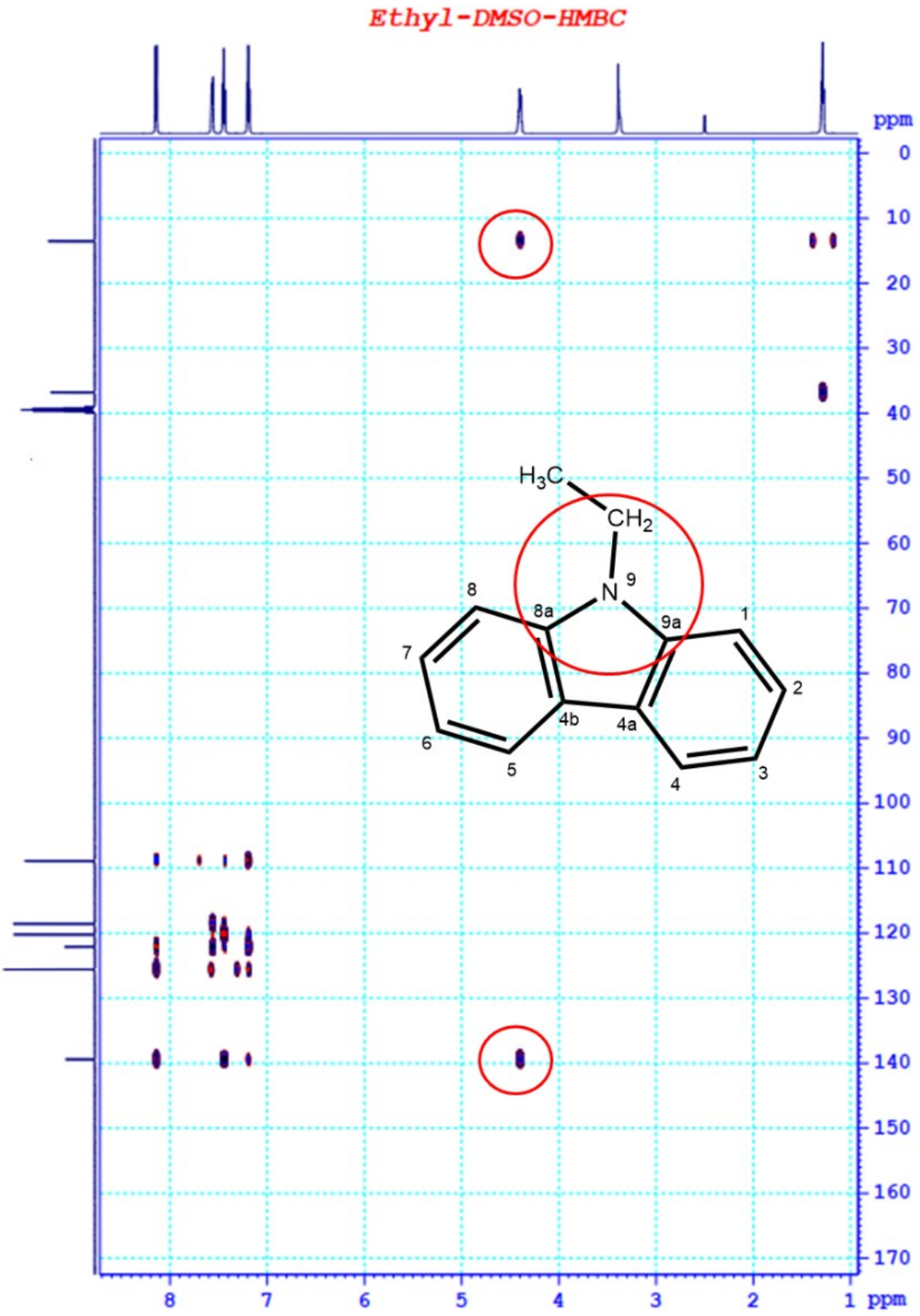

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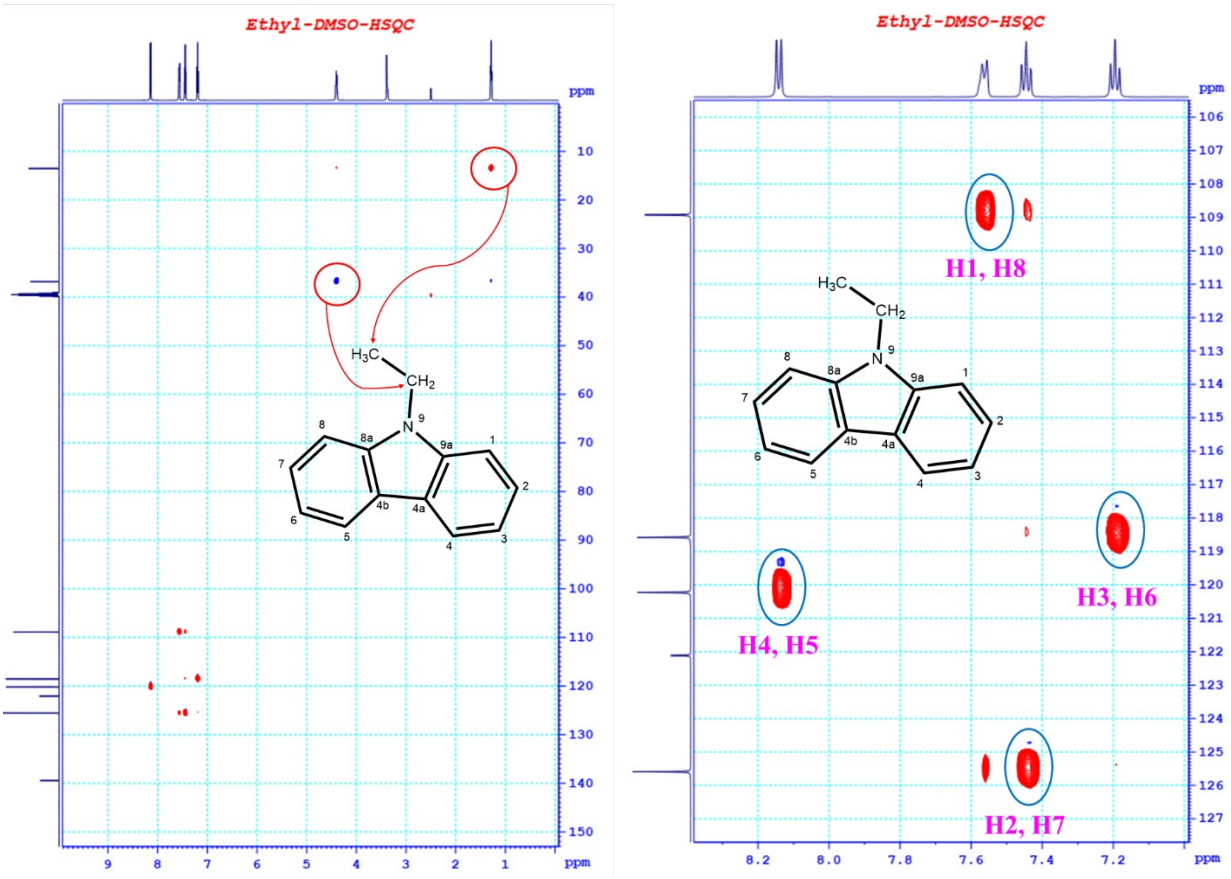


Fig. S 4. HSQC spectrum of compound **1.**

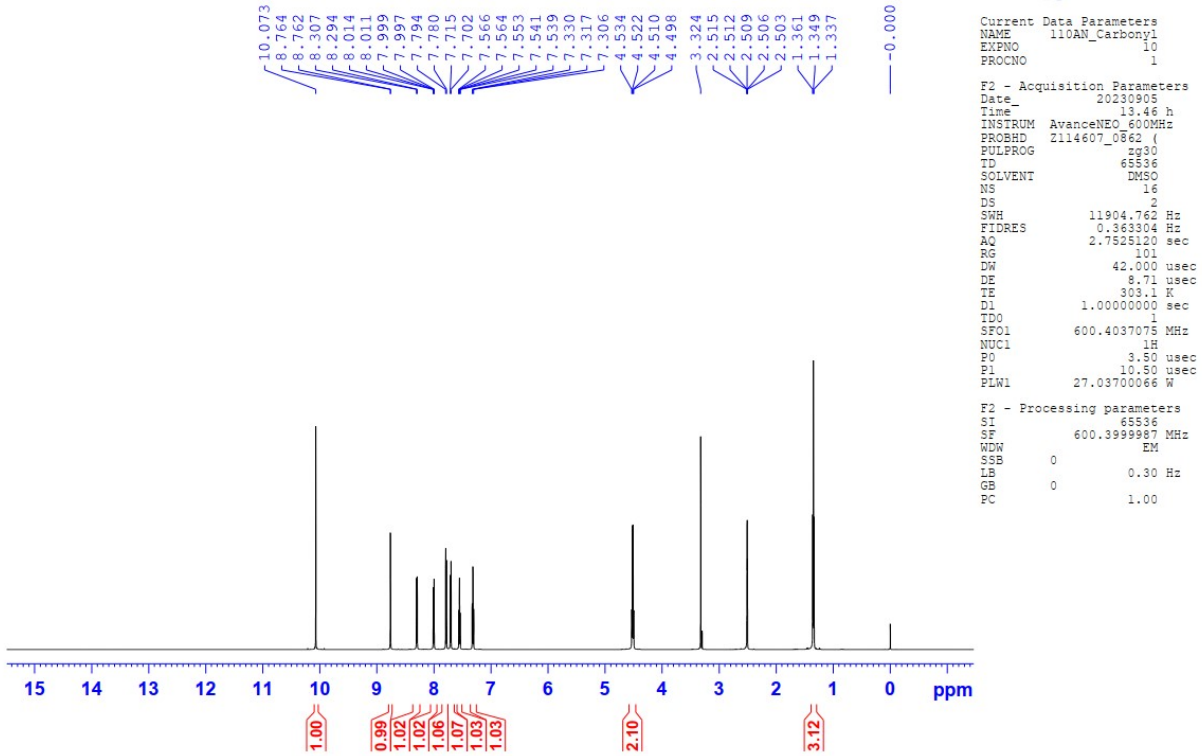


Fig. S 5. [1]H-NMR spectrum of compound **2.**

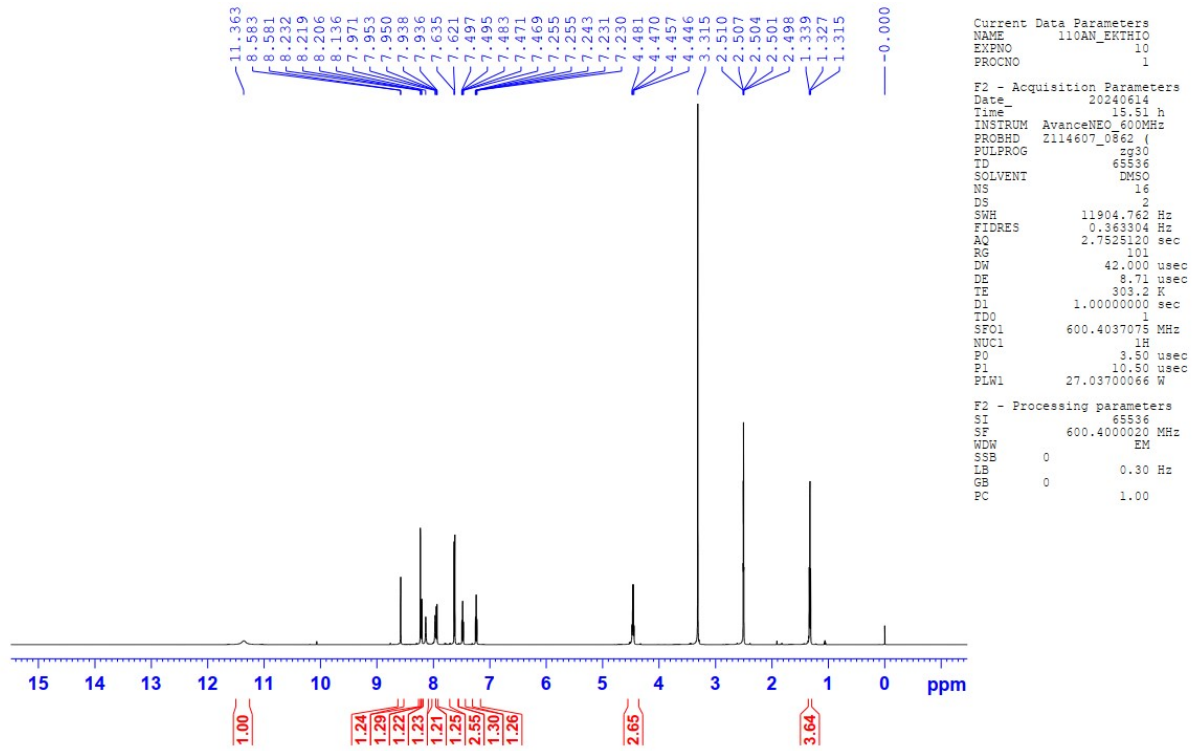


Fig. S 6. [1]H-NMR spectrum of compound **3.**

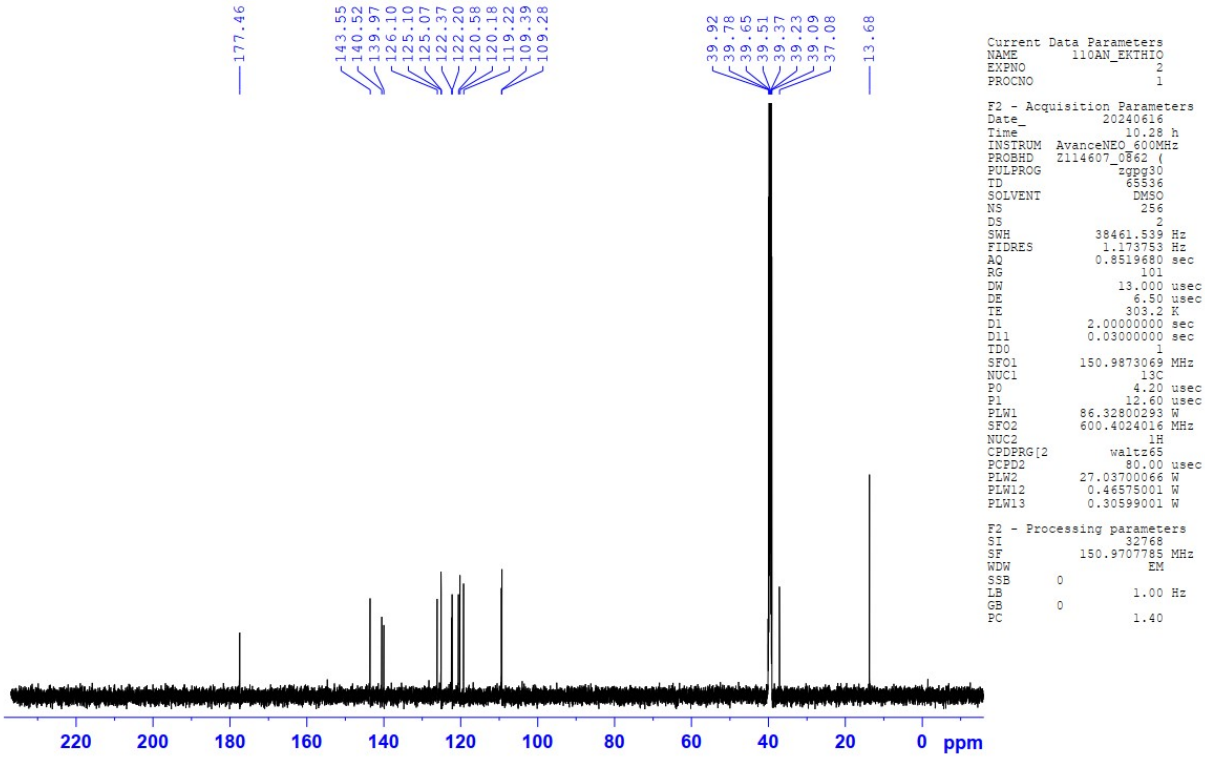


Fig. S 7. [13]C-NMR spectrum of compound **3.**

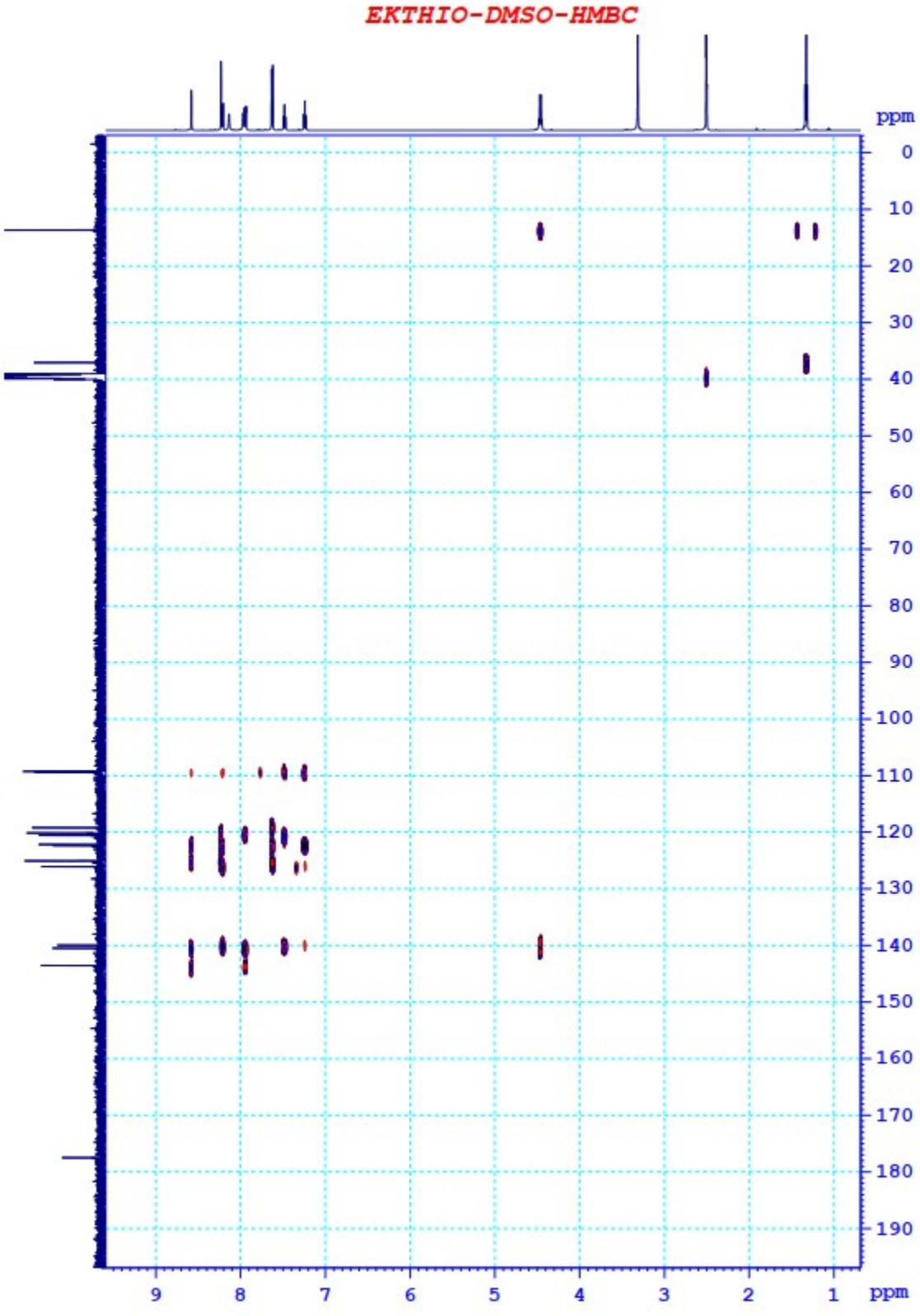


Fig. S 8. HMBC spectrum of compound **3.**

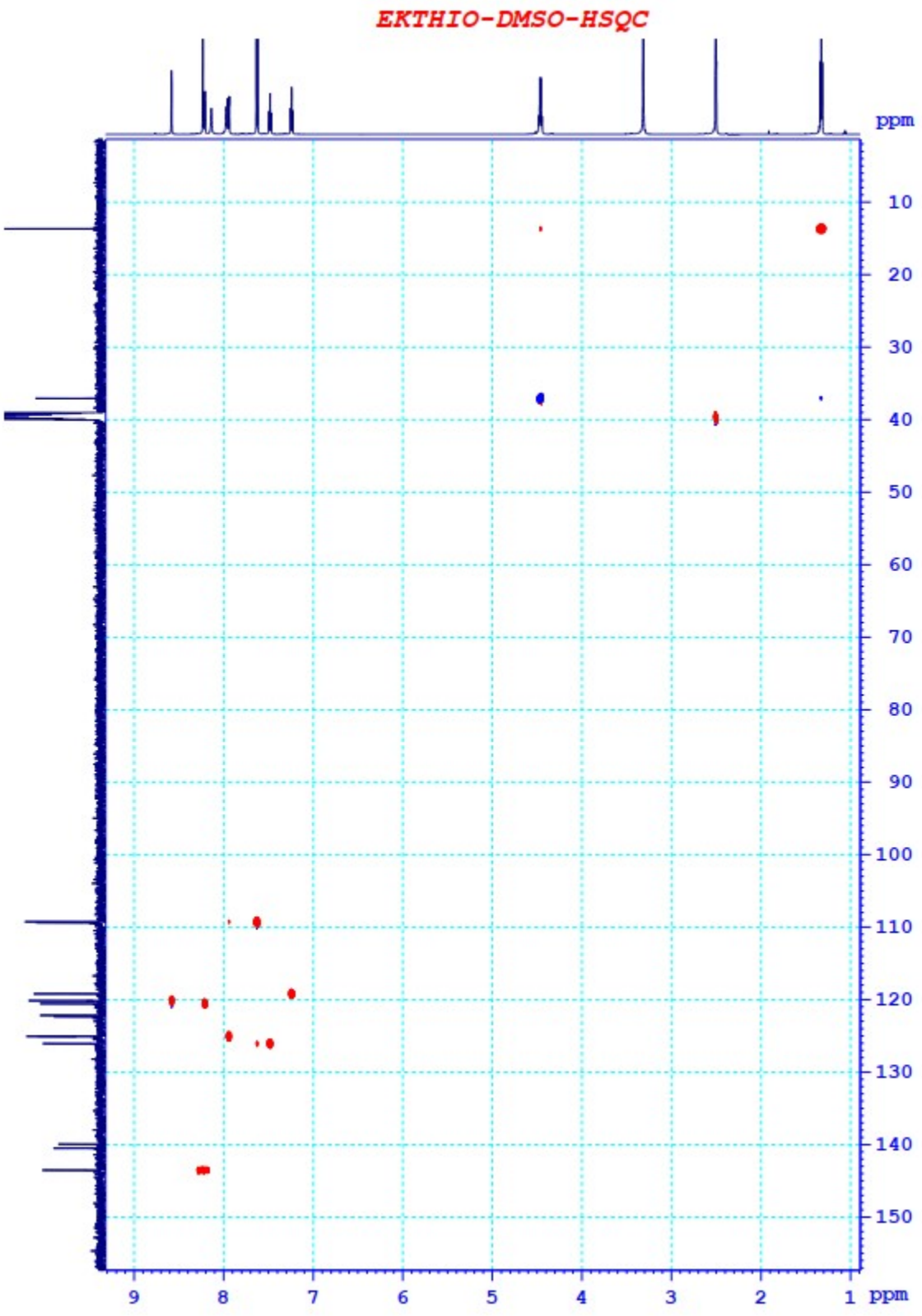


Fig. S 9. HSQC spectrum of compound **3.**

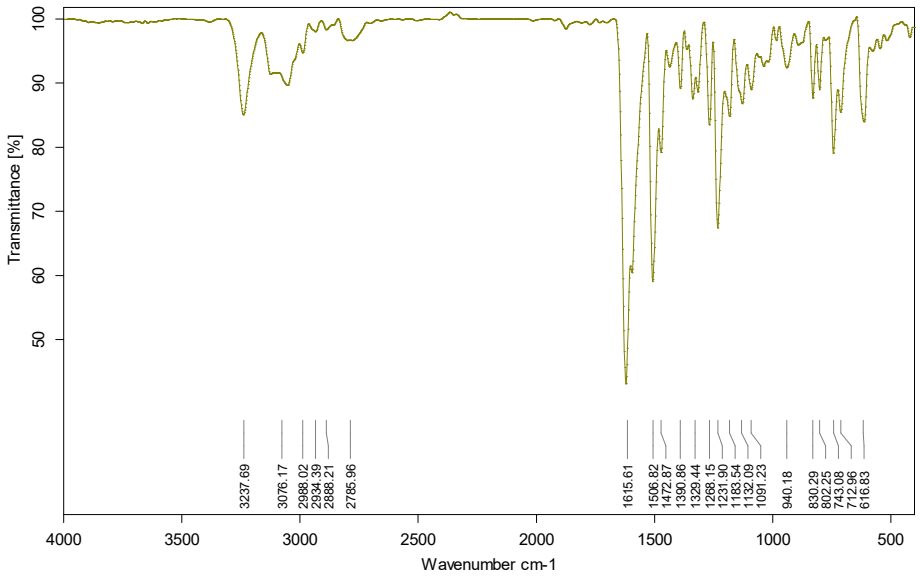


Fig. S 10. FT-IR spectrum of compound **4a**.

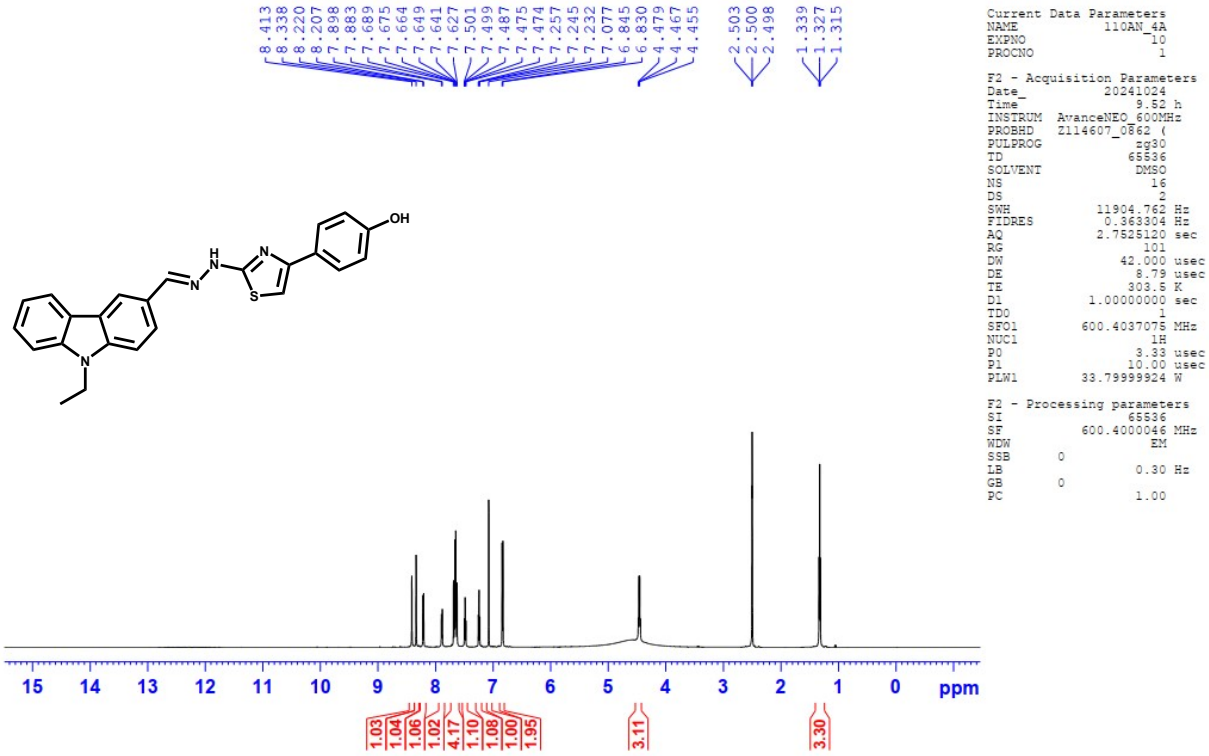


Fig. S 11. [1]H-NMR spectrum of compound **4a.**

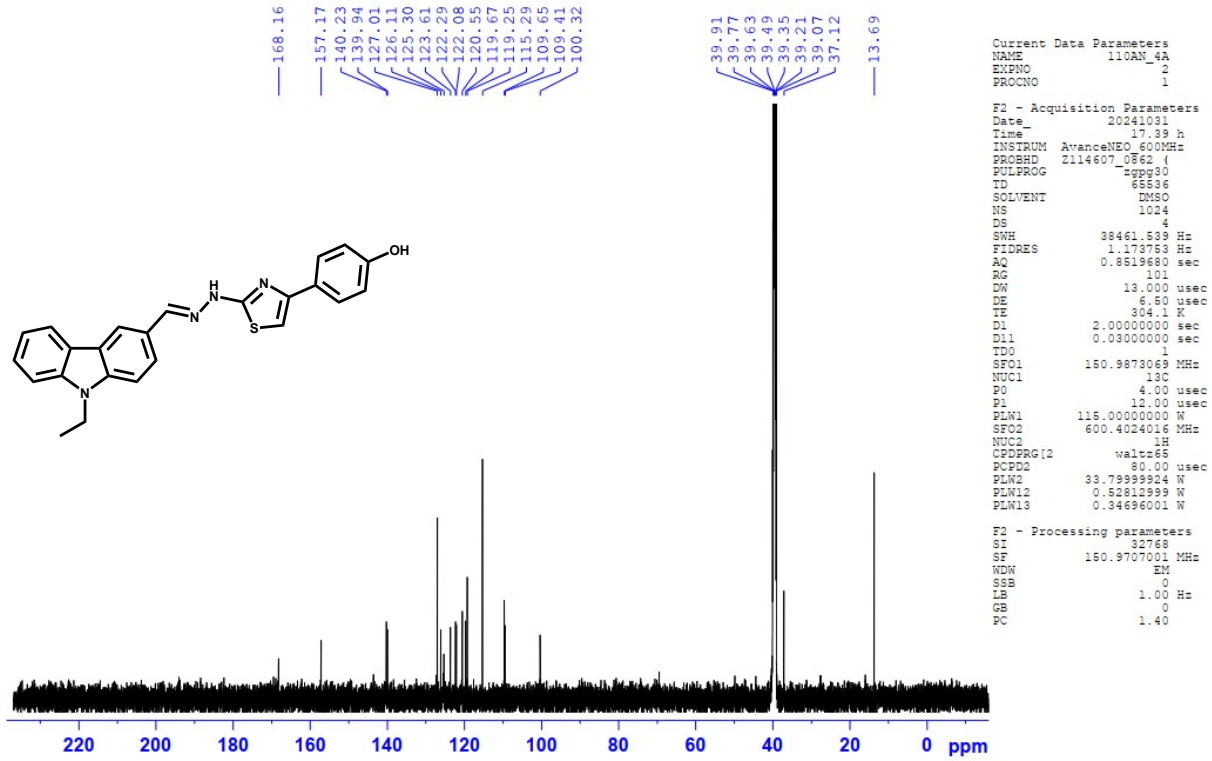


Fig. S 12. ^{13}C-NMR spectrum of compound **4a**.

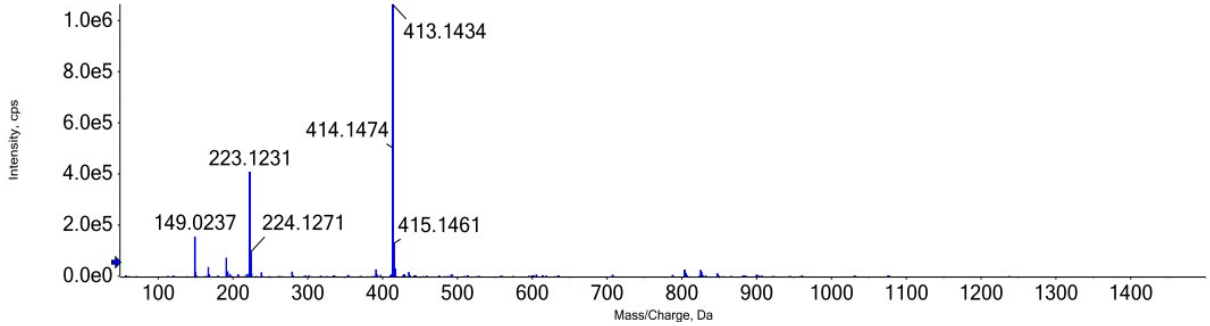


Fig. S 13. HR-MS spectrum of compound **4a**.

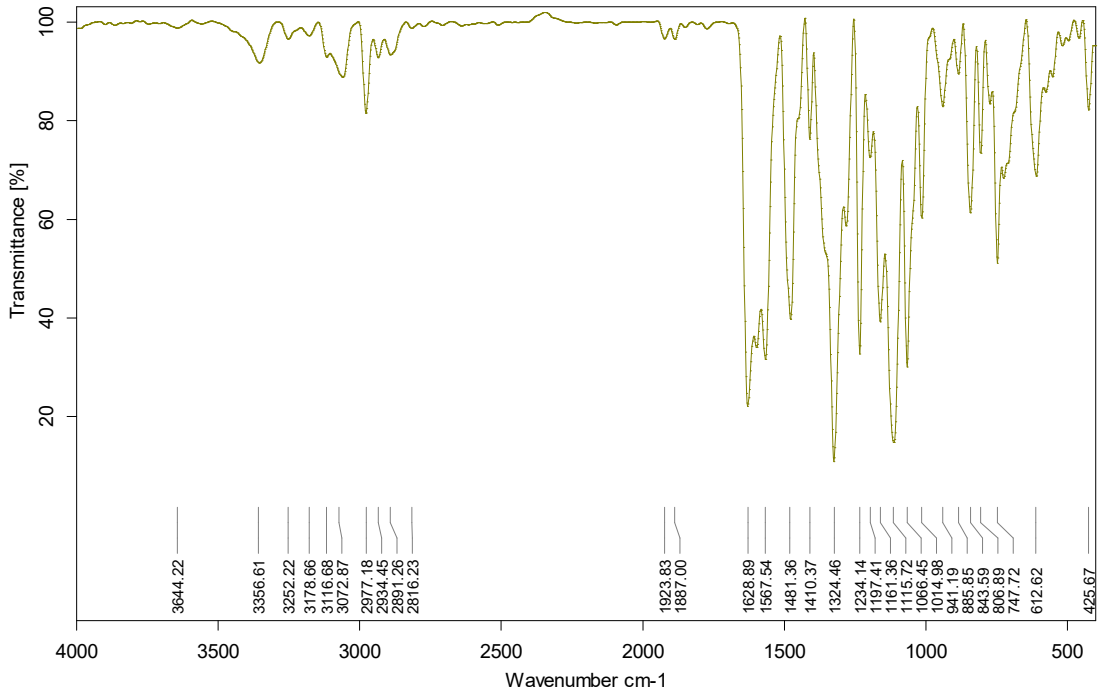


Fig. S 14. FT-IR spectrum of compound **4b**.

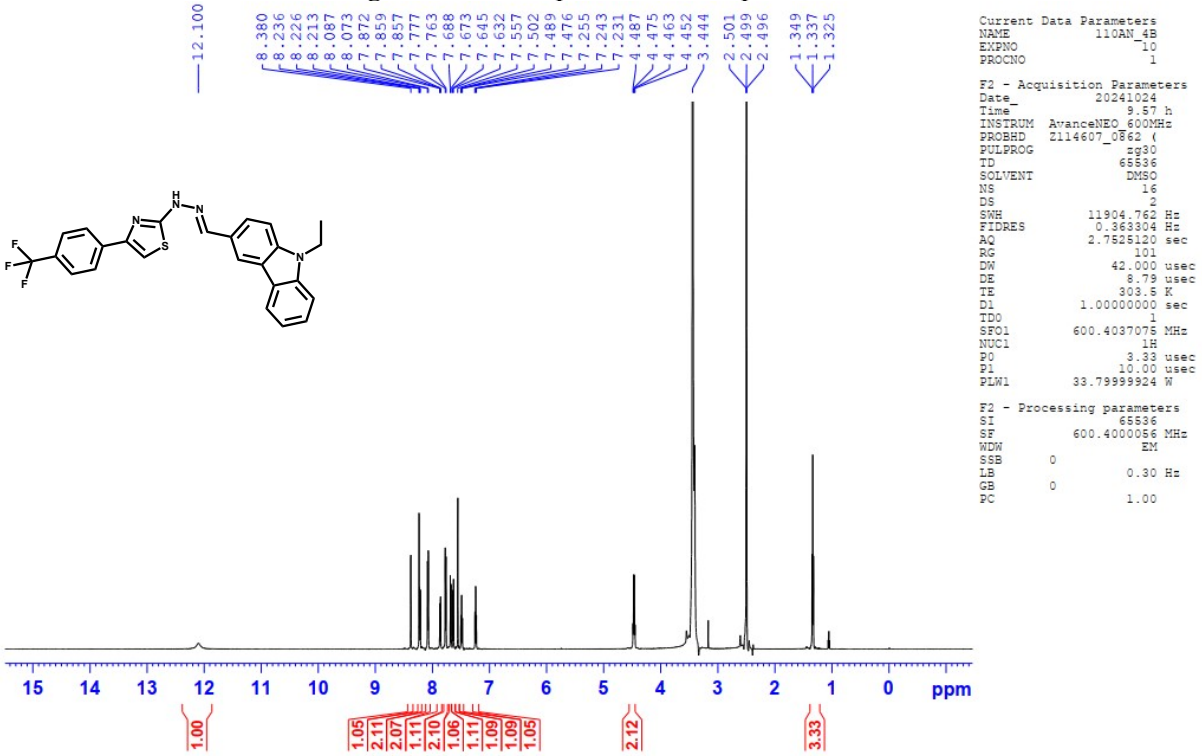
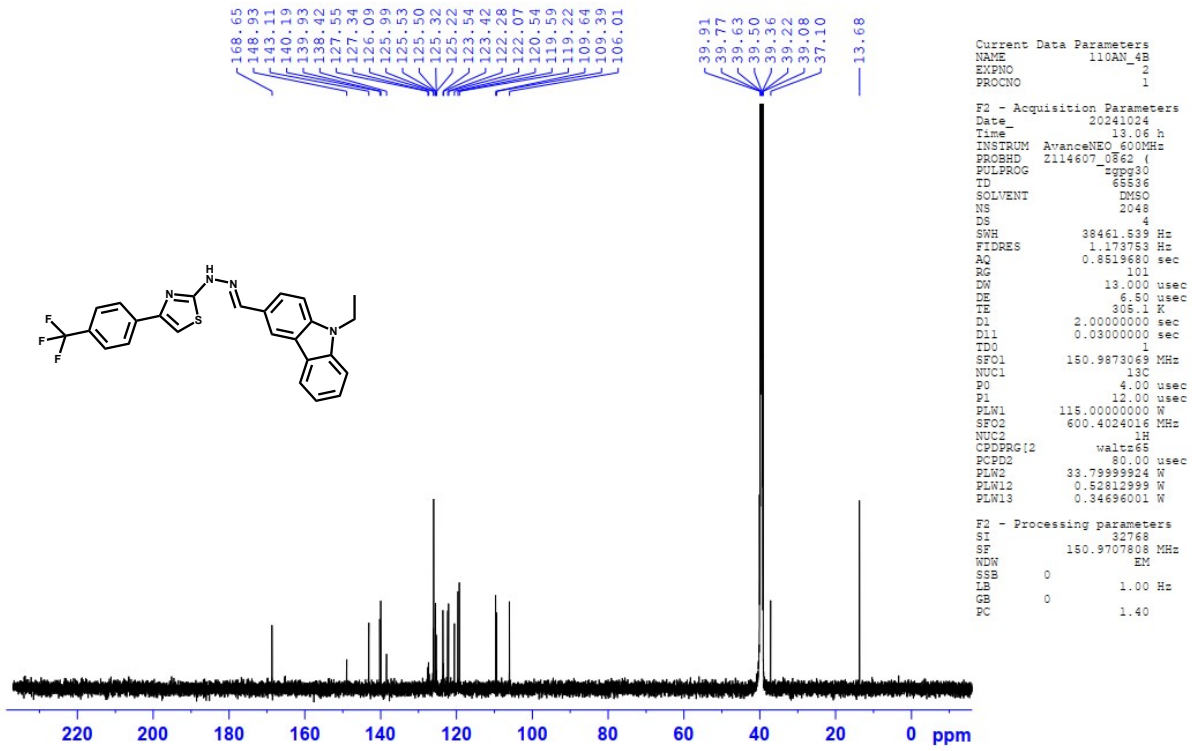


Fig. S 15. ^{1}H-NMR spectrum of compound **4b**.

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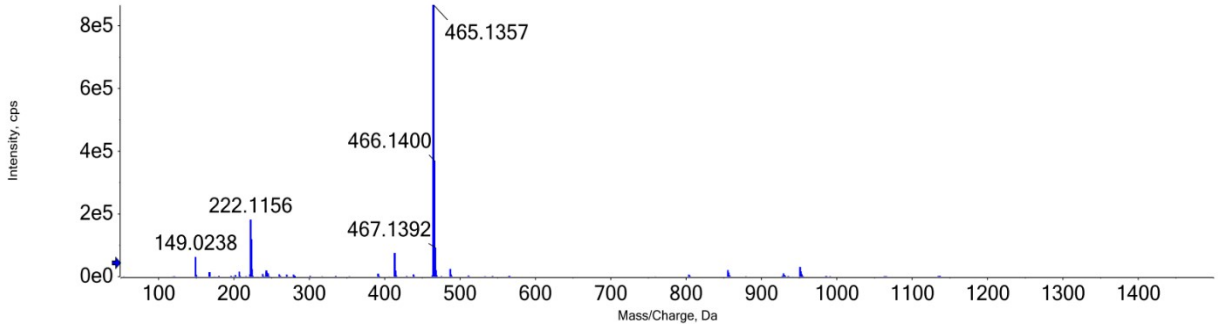


Fig. S 17. HR-MS spectrum of compound **4b**.

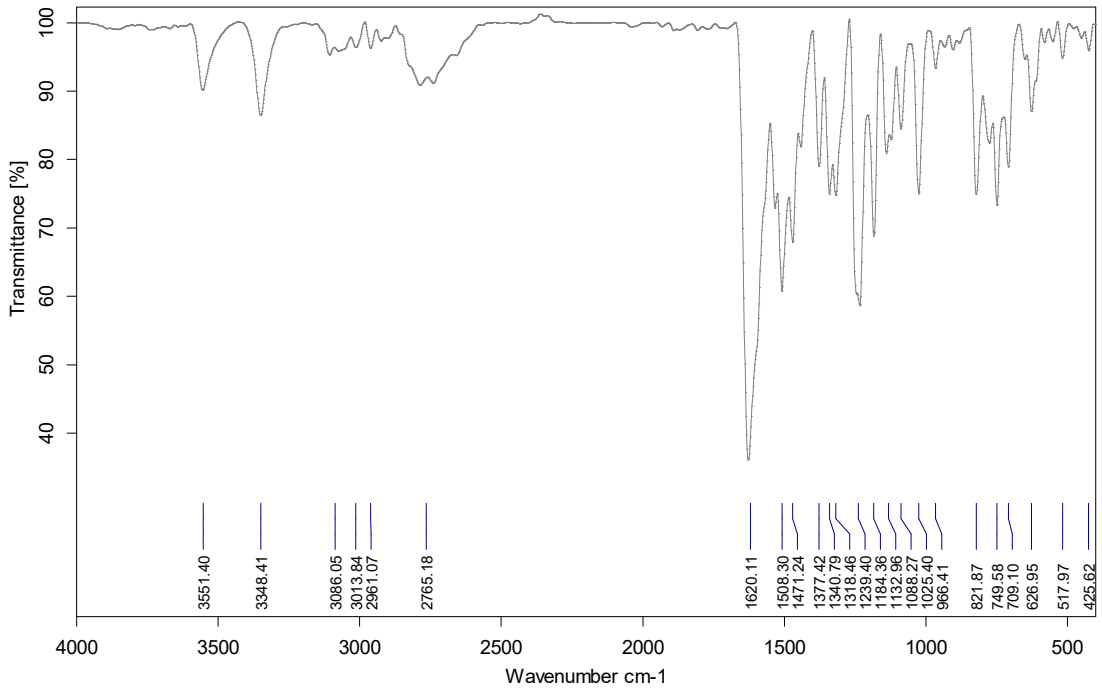


Fig. S 18. FT-IR spectrum of compound **4c**.

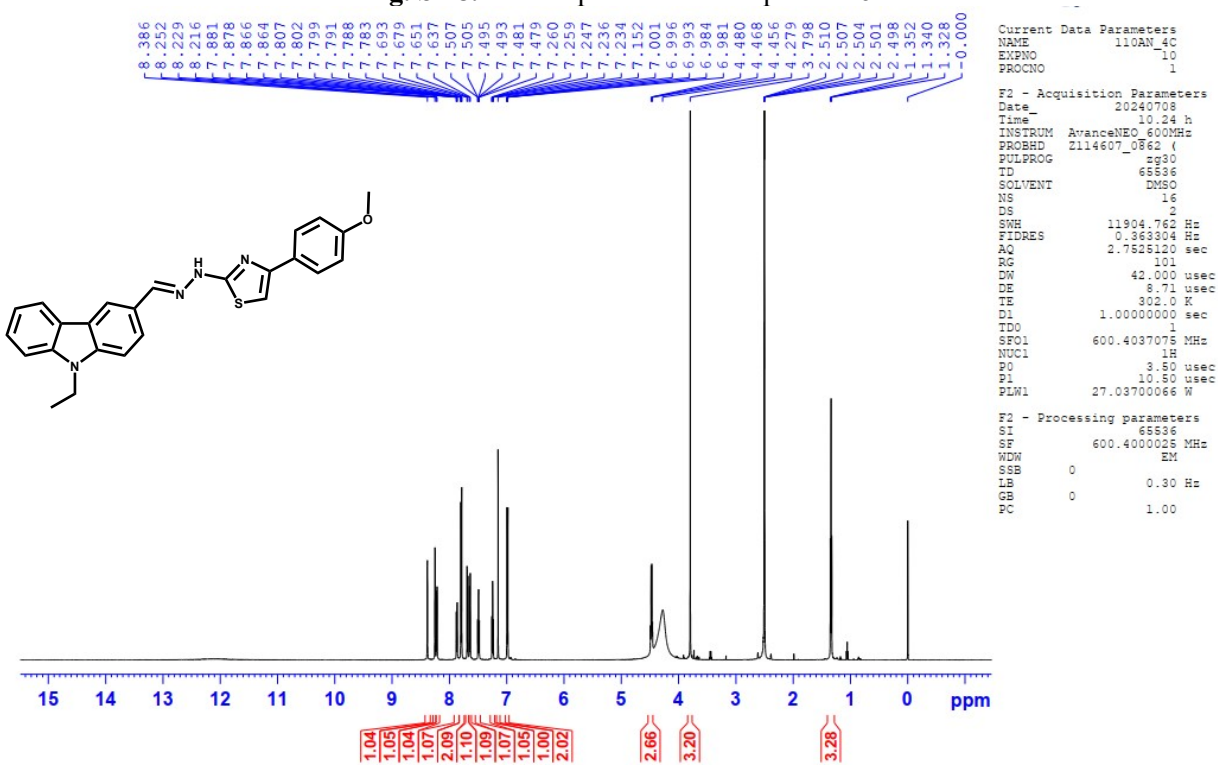
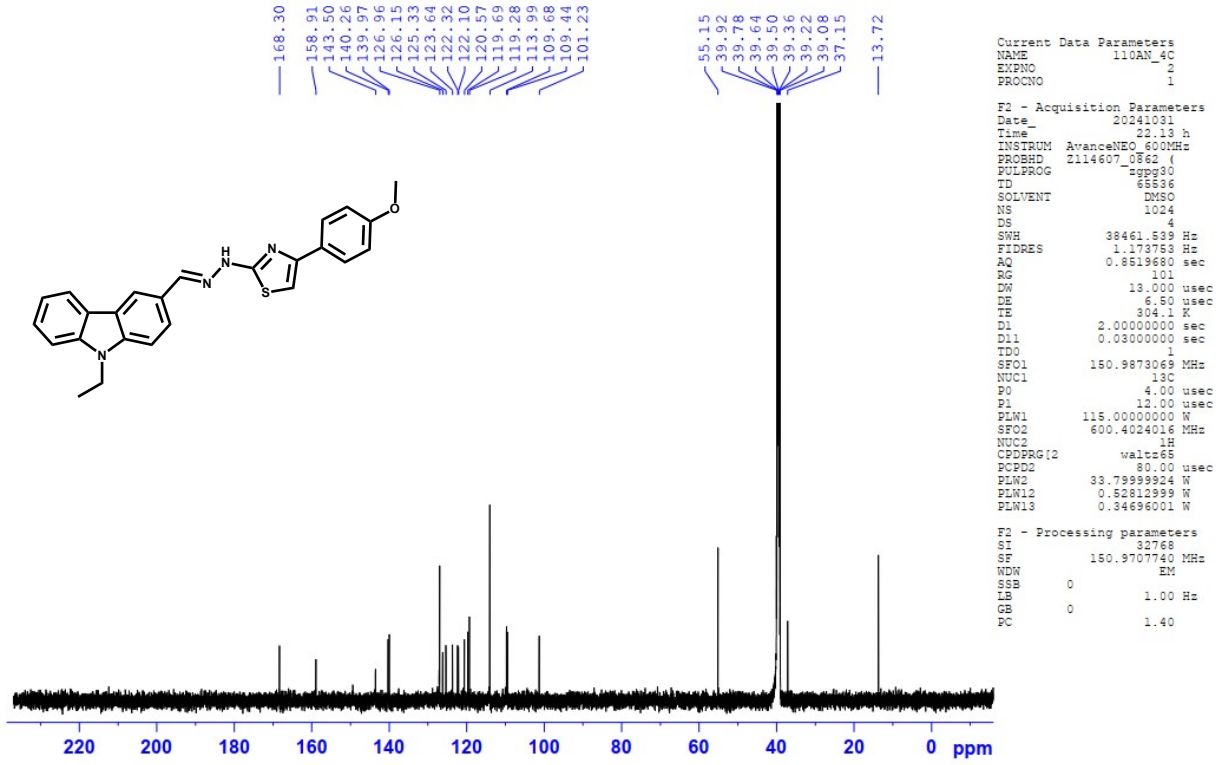


Fig. S 19. ^{1}H-NMR spectrum of compound **4c**.



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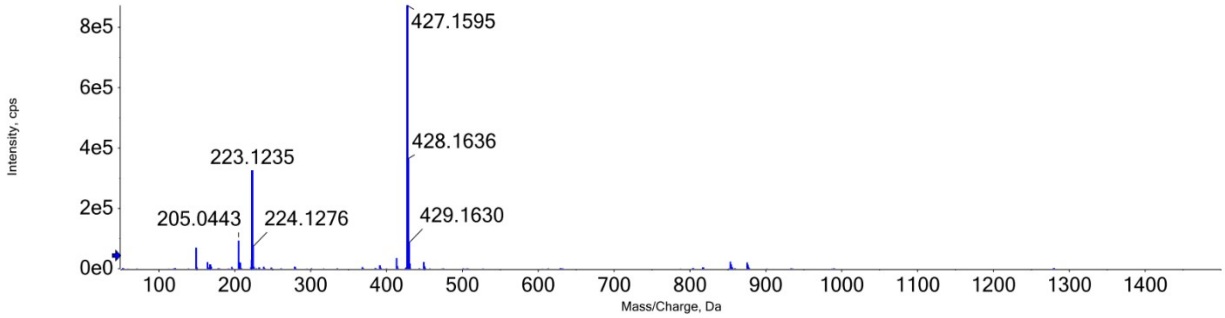


Fig. S 21. HR-MS spectrum of compound **4c**.

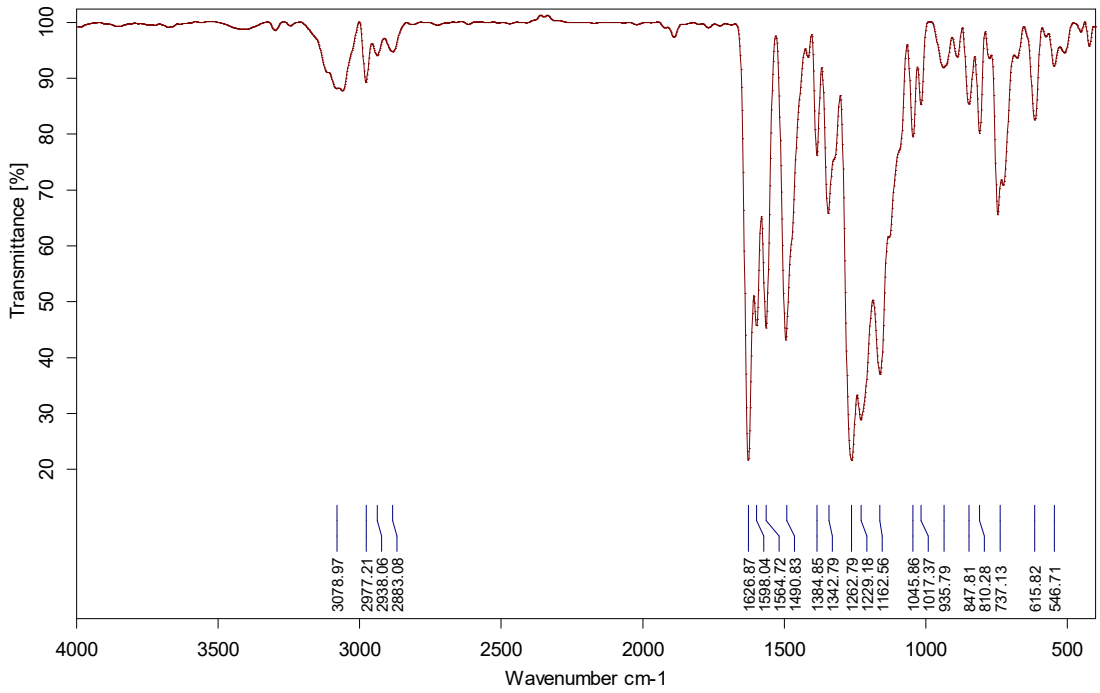


Fig. S 22. FT-IR spectrum of compound **4d**.

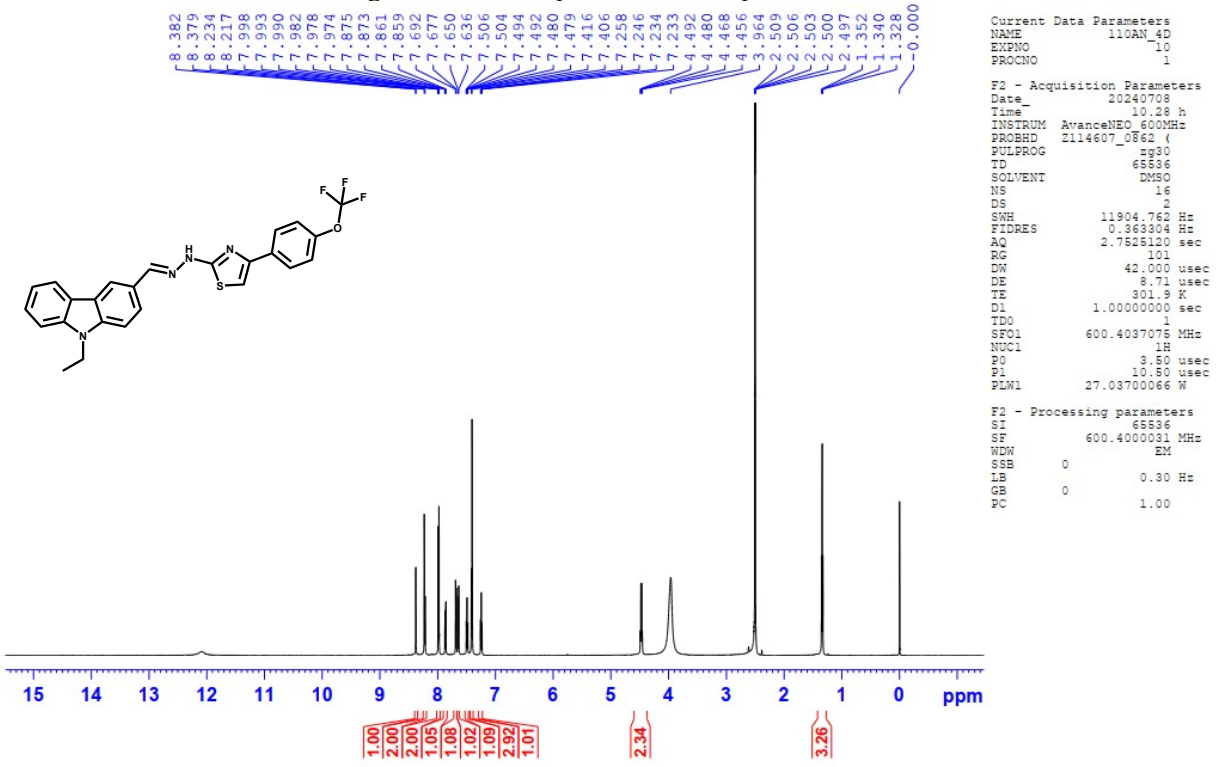


Fig. S 23. ^{1}H-NMR spectrum of compound **4d**.

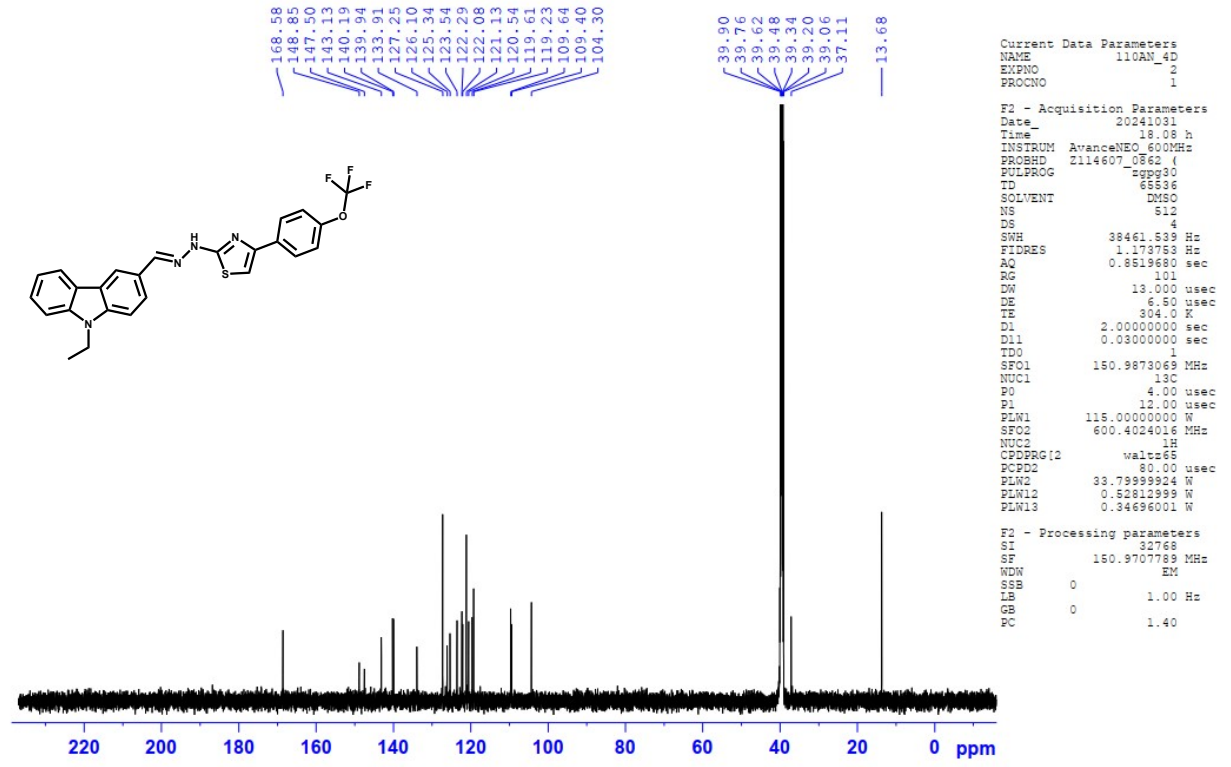


Fig. S 24. ^{13}C-NMR spectrum of compound **4d**.

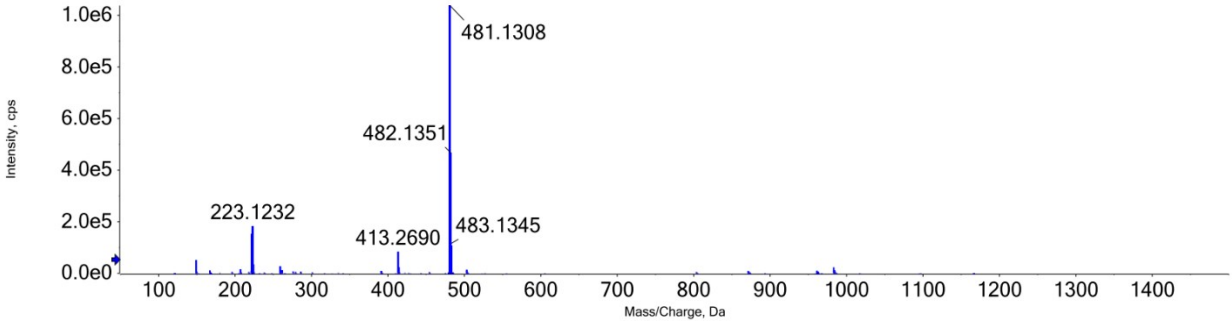


Fig. S 25. HR-MS spectrum of compound **4d**.

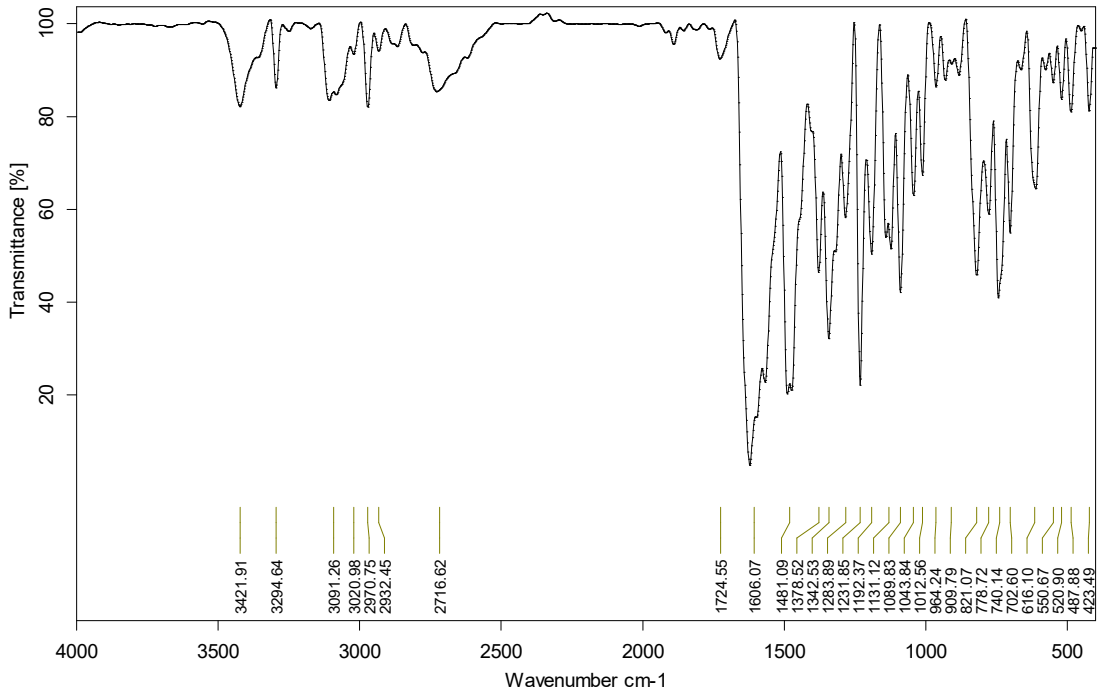
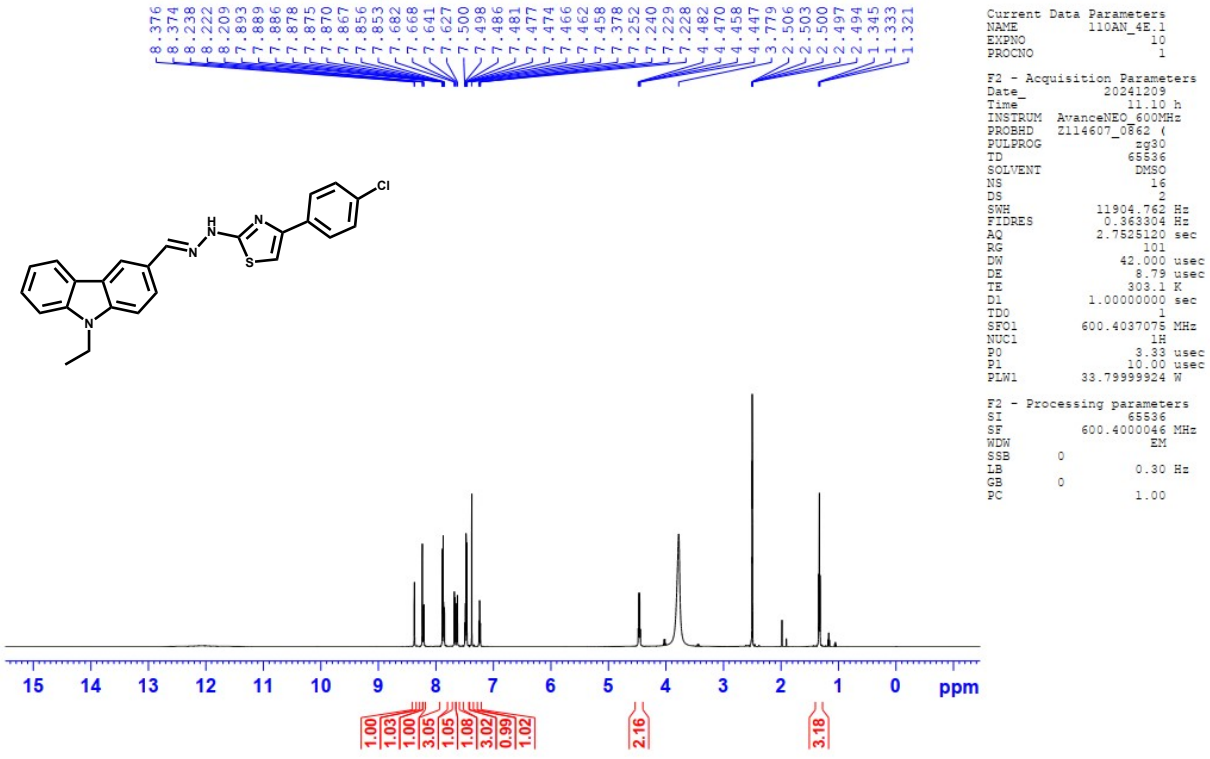


Fig. S 26. FT-IR spectrum of compound **4e**.



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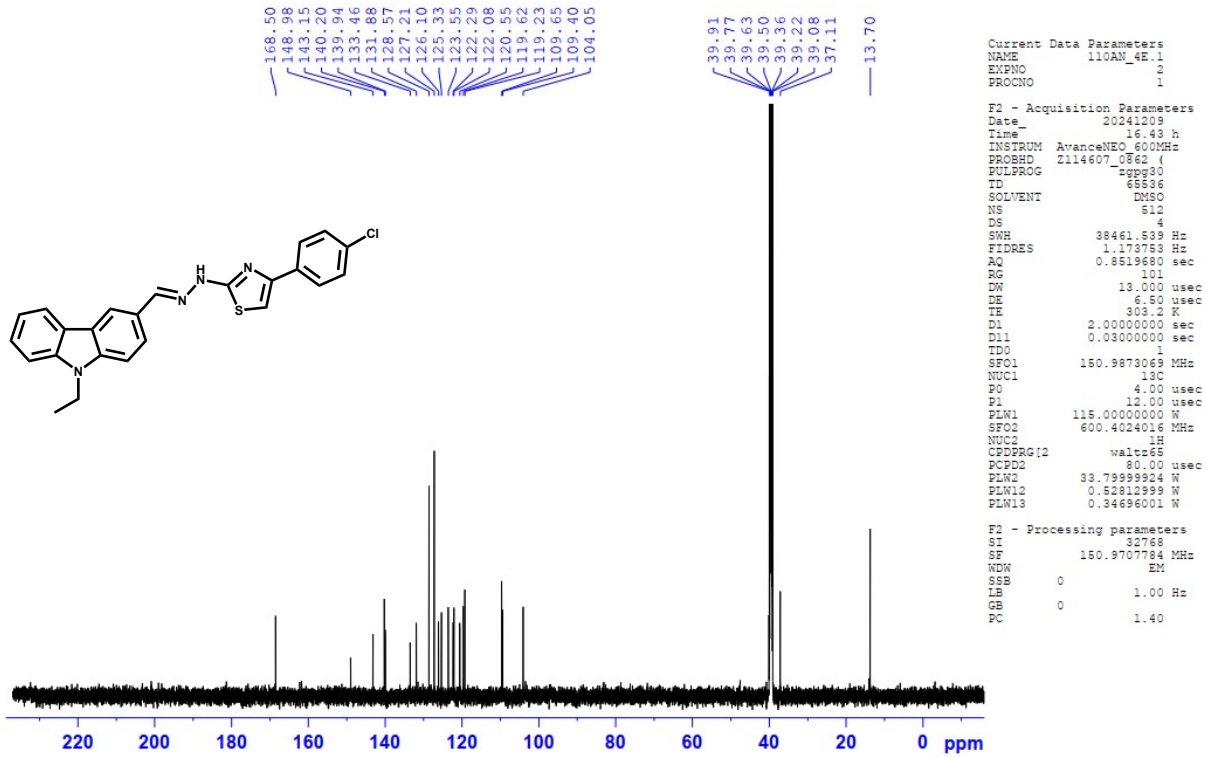


Fig. S 28. ^{13}C-NMR spectrum of compound **4e**.

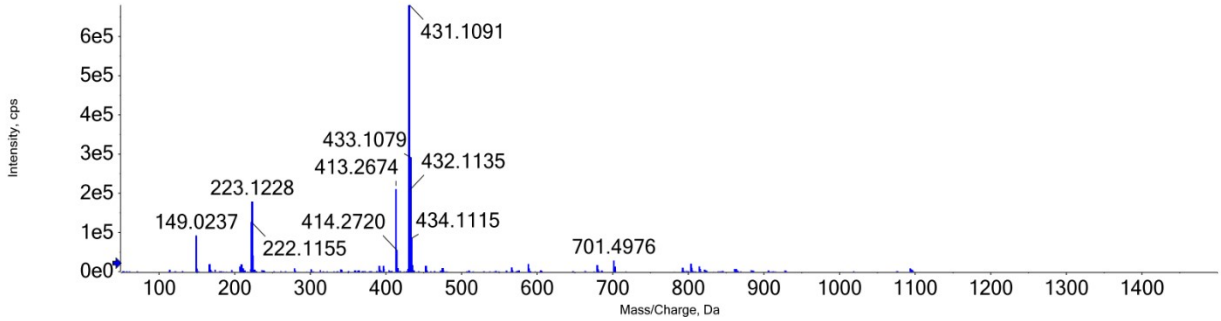


Fig. S 29. HR-MS spectrum of compound **4e**.

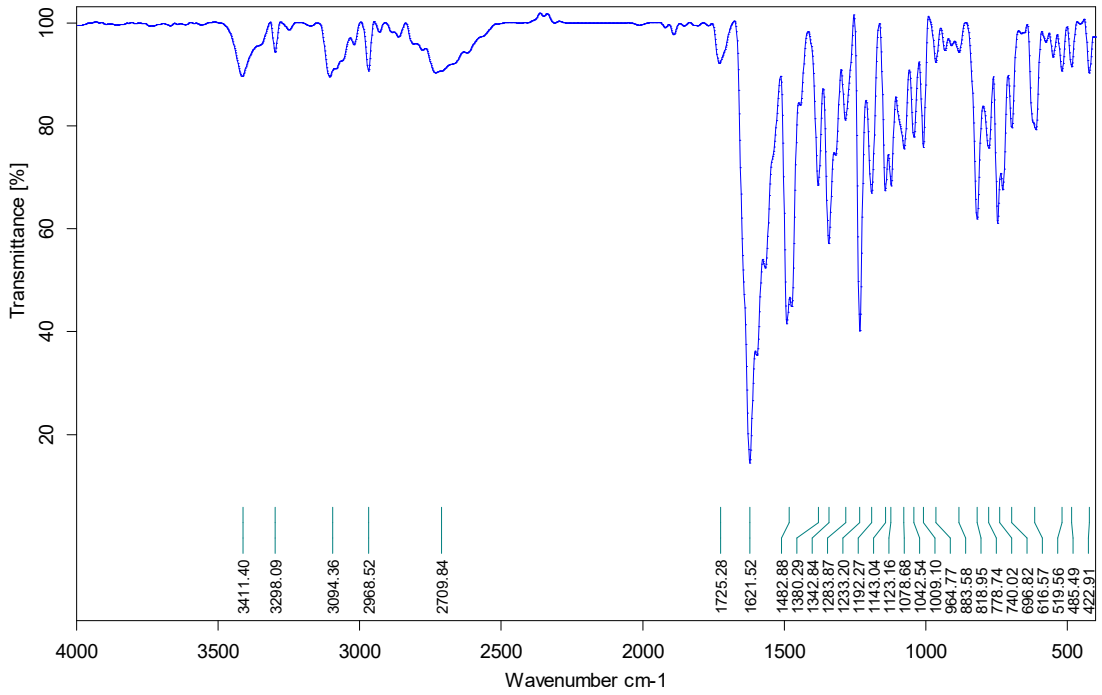


Fig. S 30. FT-IR spectrum of compound **4f**.

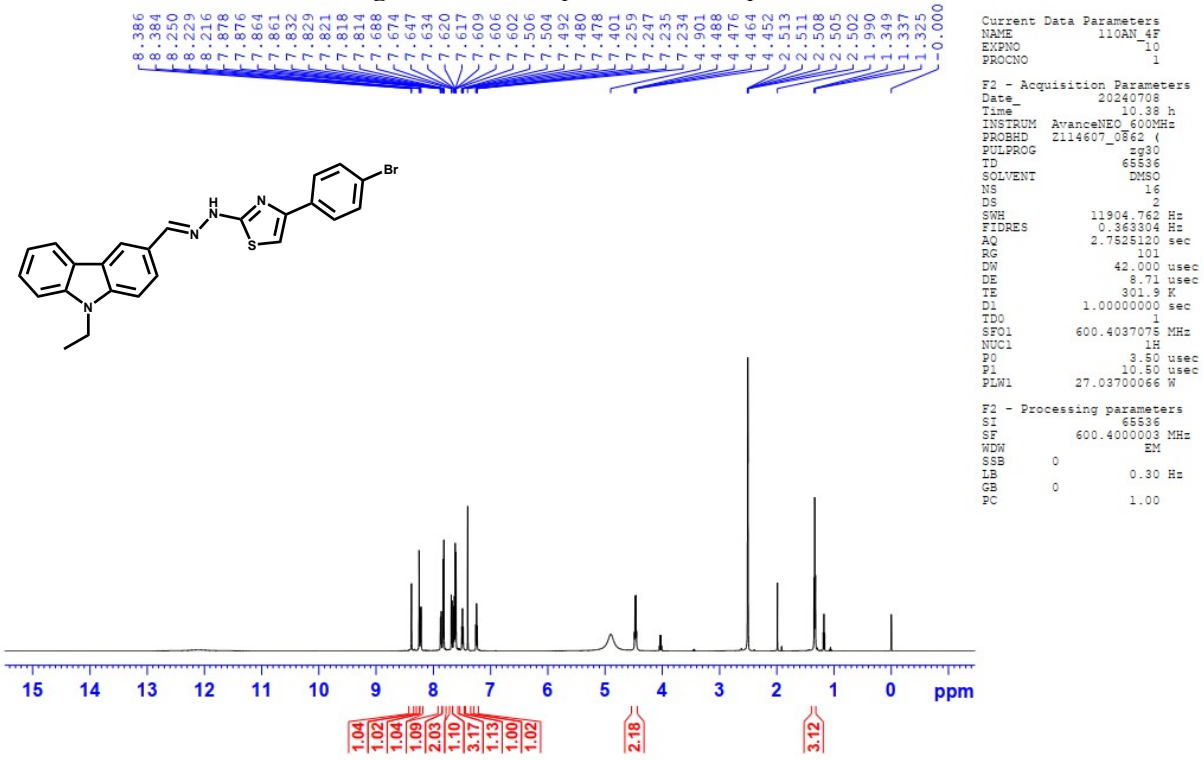


Fig. S 31. ^{1}H-NMR spectrum of compound **4f**.

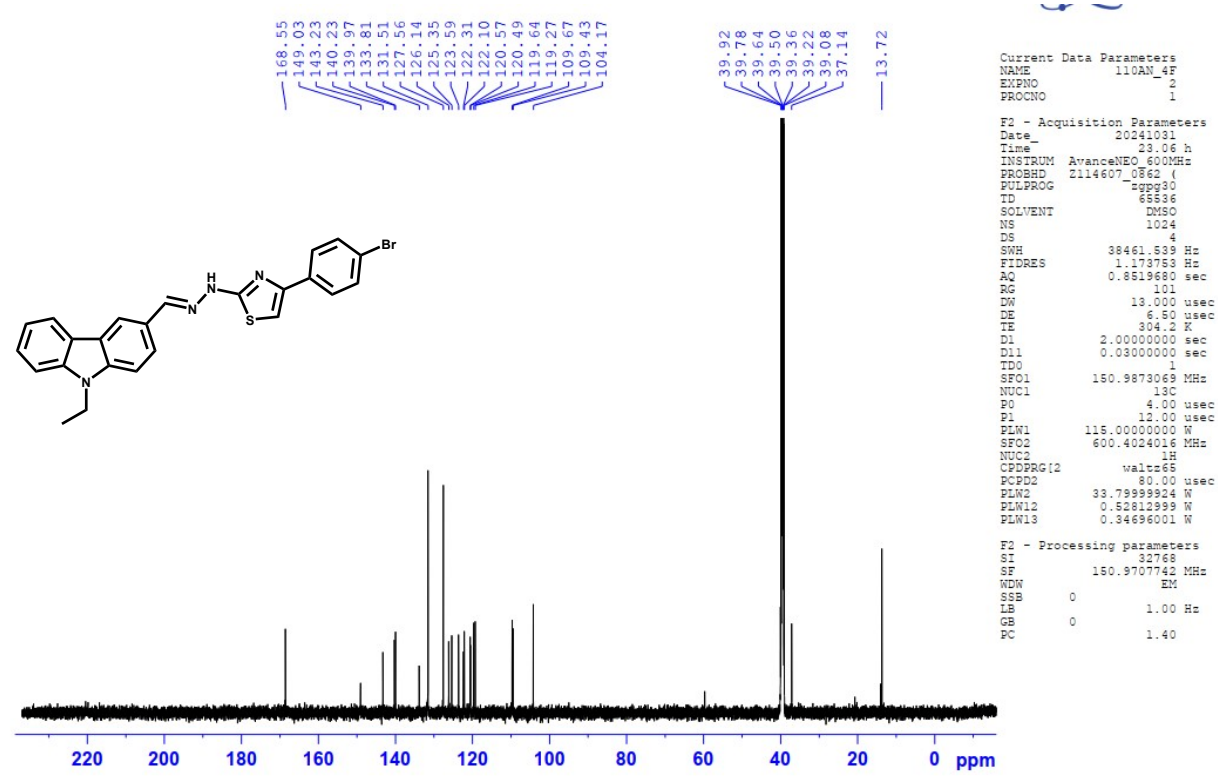


Fig. S 32. ^{13}C-NMR spectrum of compound **4f**.

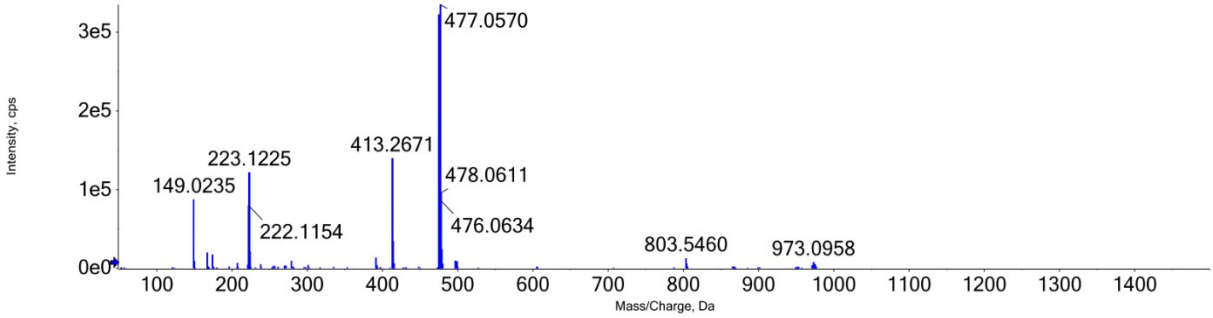


Fig. S 33. HR-MS spectrum of compound **4f**.

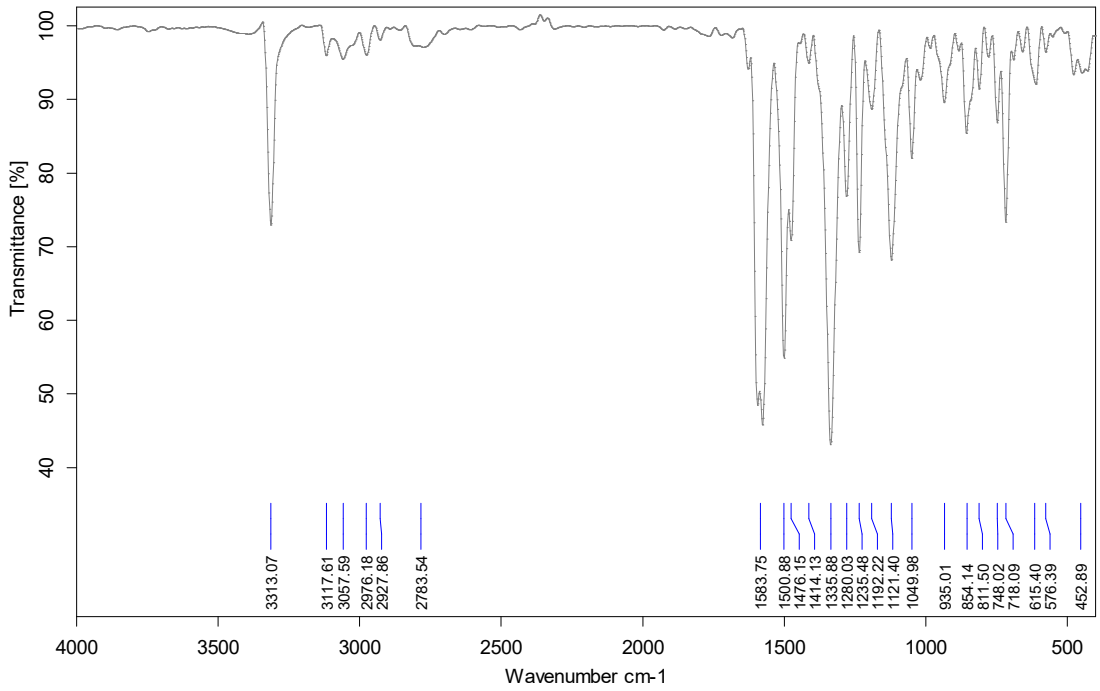


Fig. S 34. FT-IR spectrum of compound **4g**.

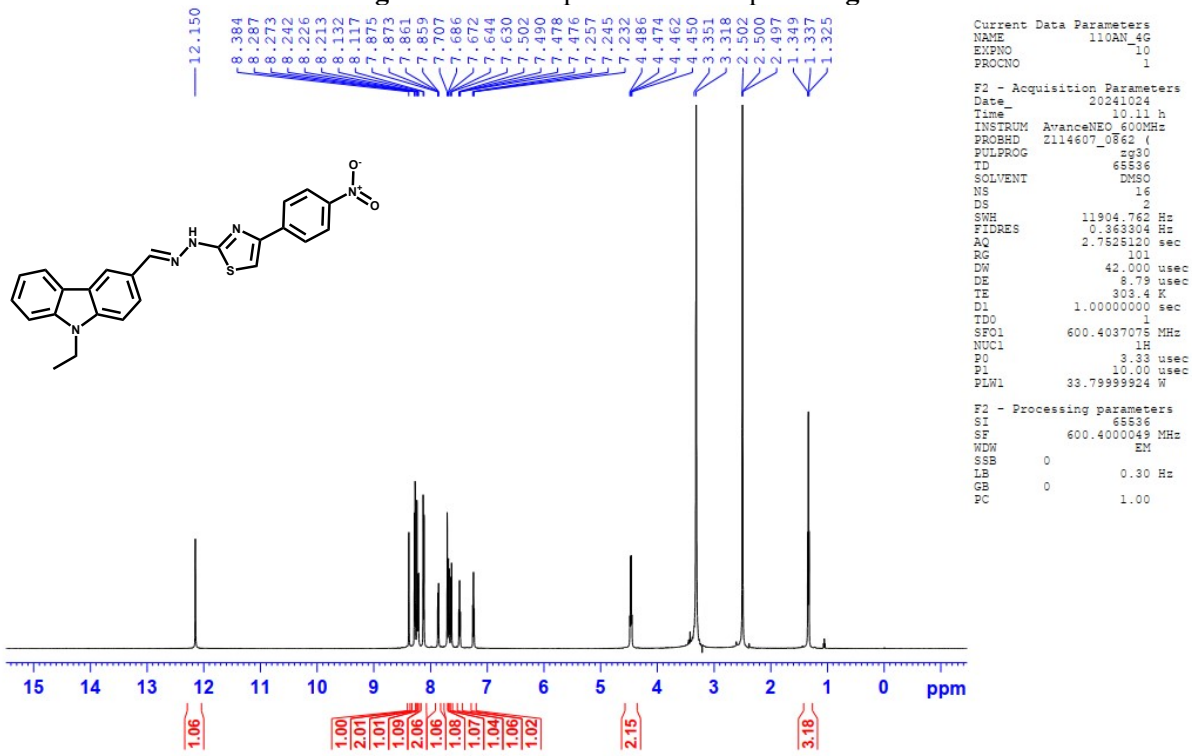
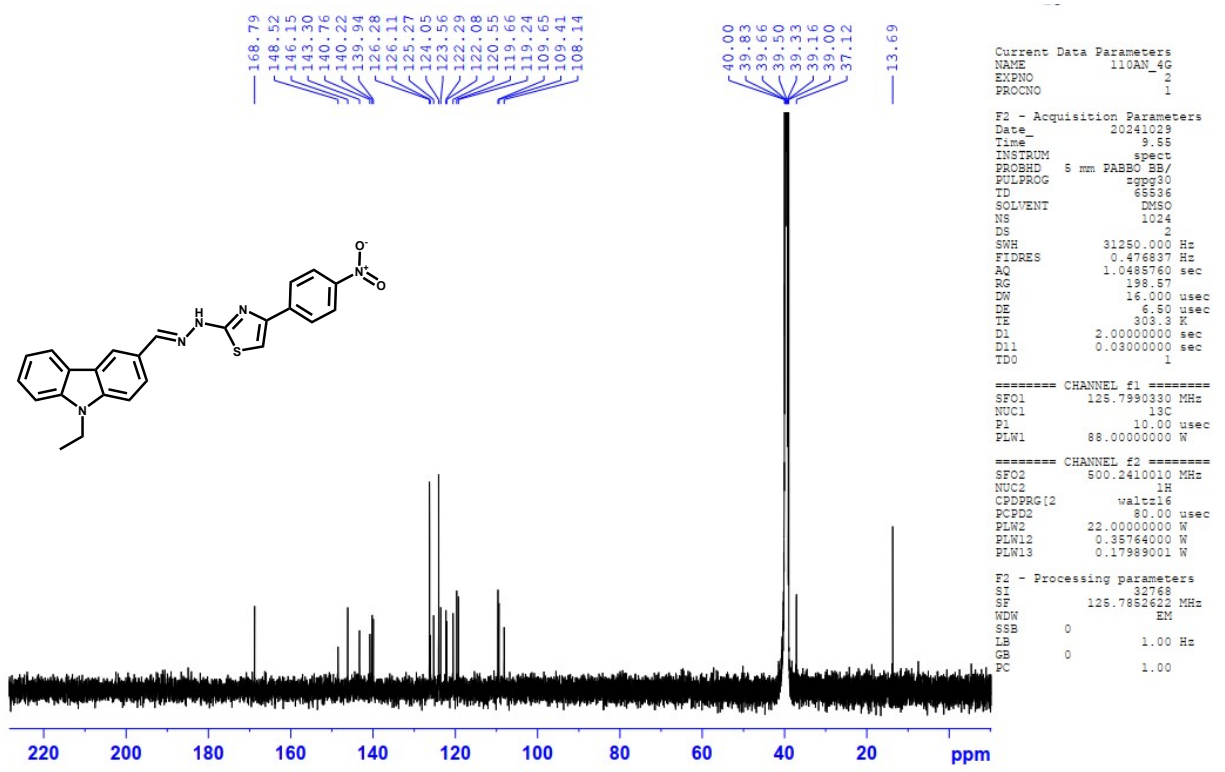


Fig. S 35. ^{1}H-NMR spectrum of compound **4g**.

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D11                0.03000000 sec
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Fig. S 36. ^{13}C-NMR spectrum of compound **4g**.

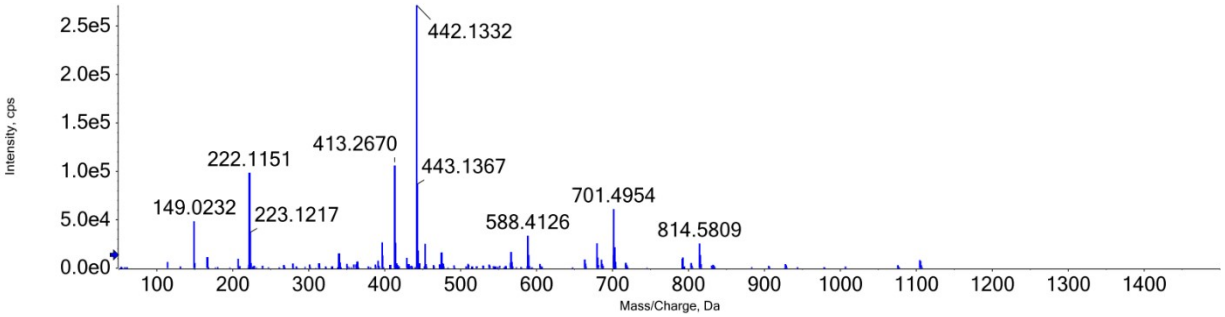


Fig. S 37. HR-MS spectrum of compound **4g**.

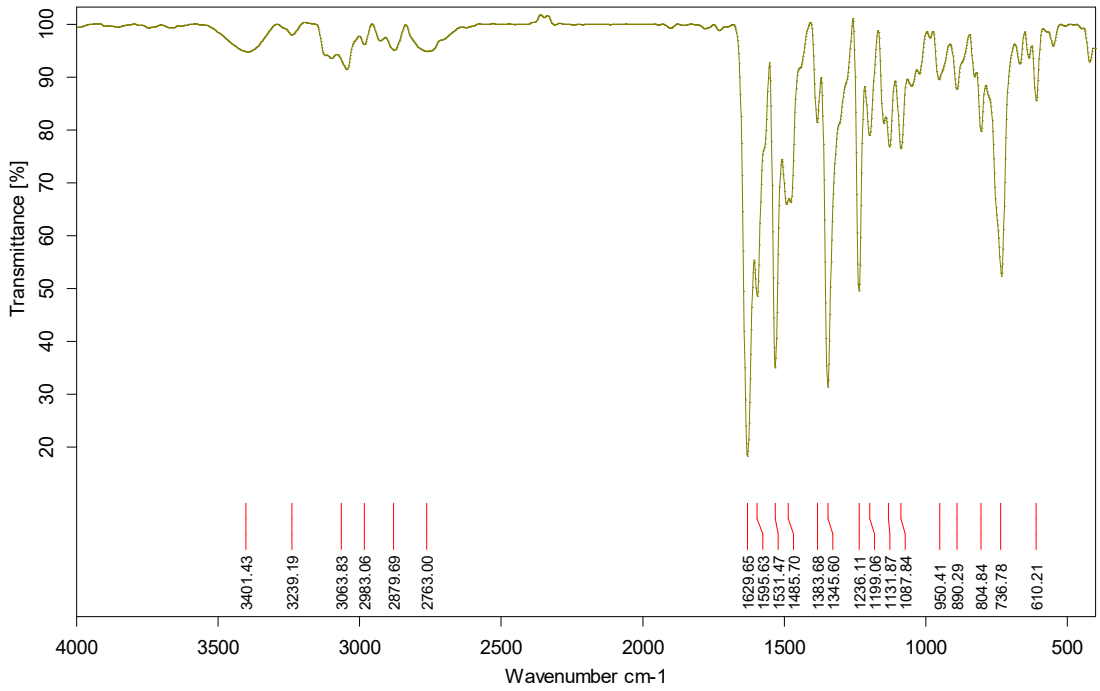


Fig. S 38. FT-IR spectrum of compound **4h**.

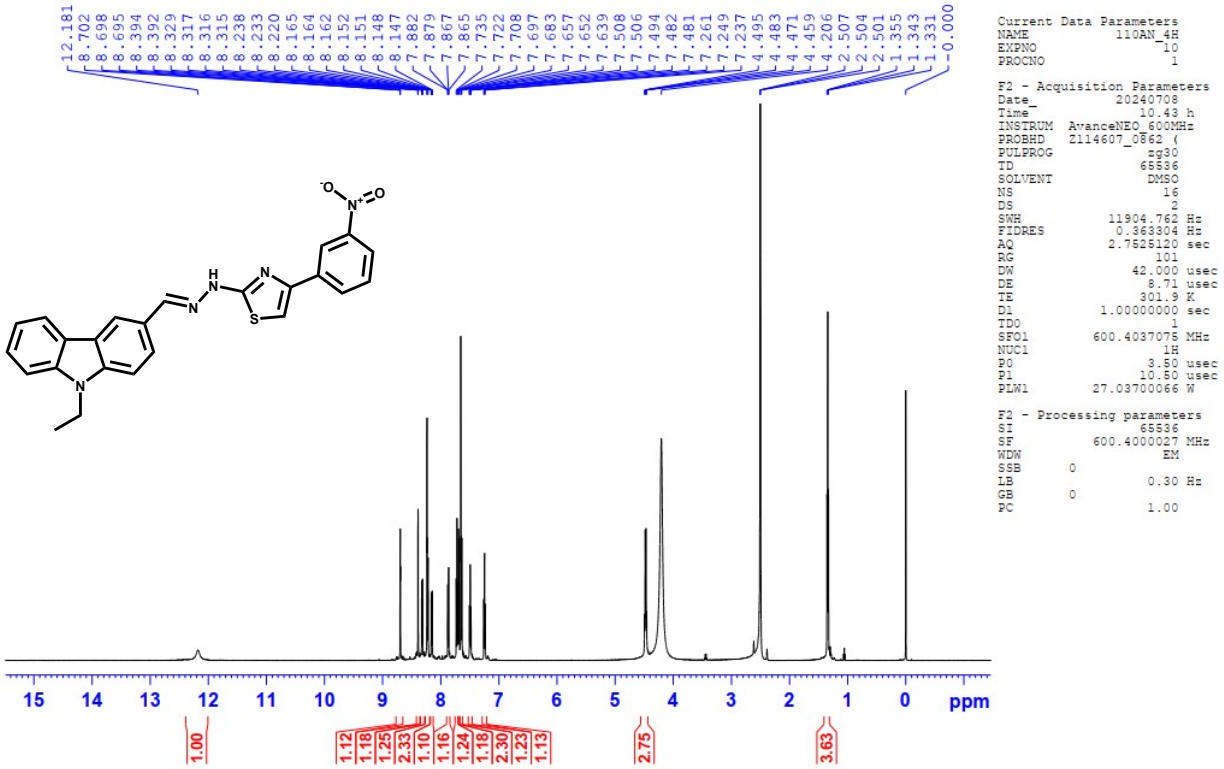
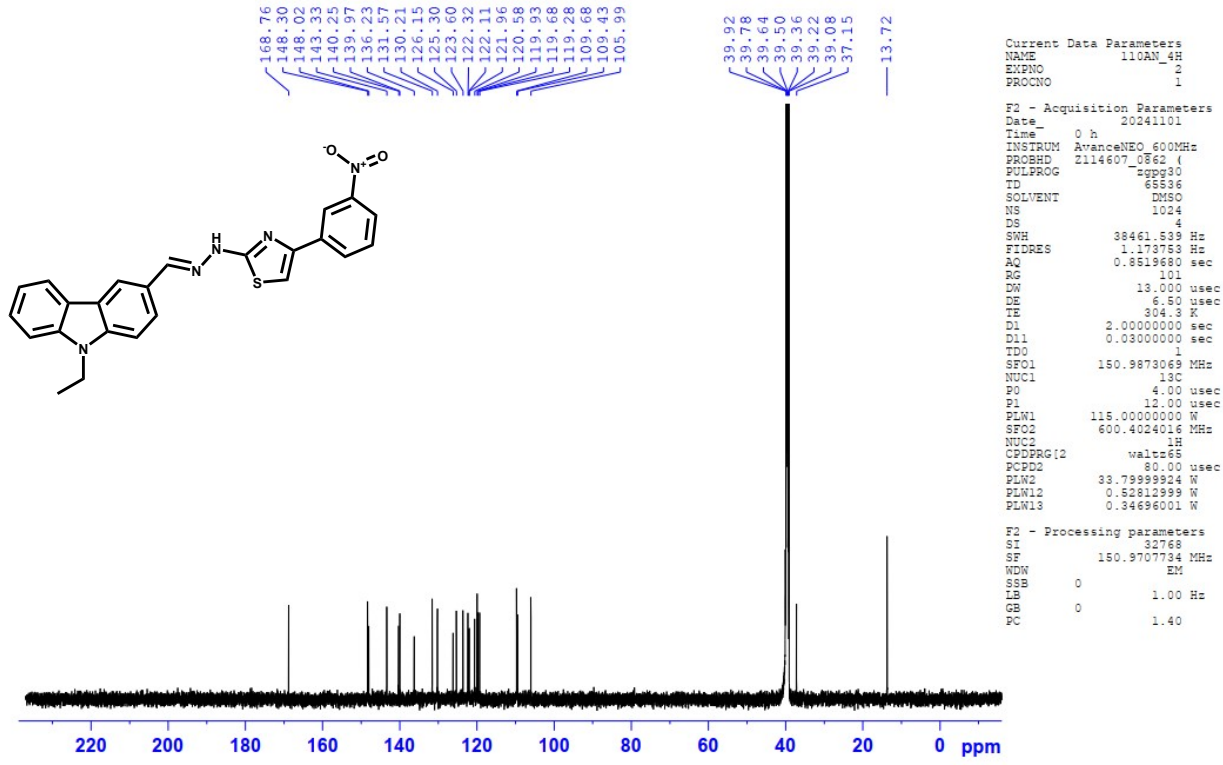


Fig. S 39. ^{1}H-NMR spectrum of compound **4h**.

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Current Data Parameters
NAME            110AN_4H
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_          20241101
Time       0 h
INSTRUM  AvanceNEO_600MHz
PROBHD   Z114607_0862 (
PULPROG          zgpg30
TD                65536
SOLVENT            DMSO
NS                 1024
DS                    4
SWH           38461.539 Hz
FIDRES         1.173753 Hz
AQ             0.8519680 sec
RG                  101
DW                13.000 usec
DE                 6.50 usec
TE                304.3 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                   1
SFO1         150.9873069 MHz
NUC1                13C
P0                 4.00 usec
P1                12.00 usec
PLW1        115.00000000 W
SFO2         600.4024016 MHz
NUC2                1H
CPDPRG[2         waltz65
PCPD2             80.00 usec
PLW2         33.79999924 W
PLW12         0.52812999 W
PLW13         0.34696001 W

F2 - Processing parameters
SI                 32768
SF           150.9707734 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```

Fig. S 40. ^{13}C-NMR spectrum of compound **4h**.

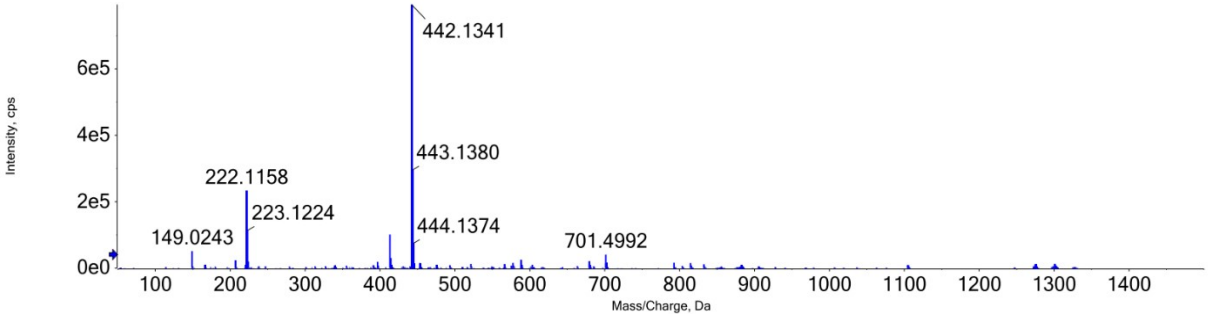


Fig. S 41. HR-MS spectrum of compound **4h**.

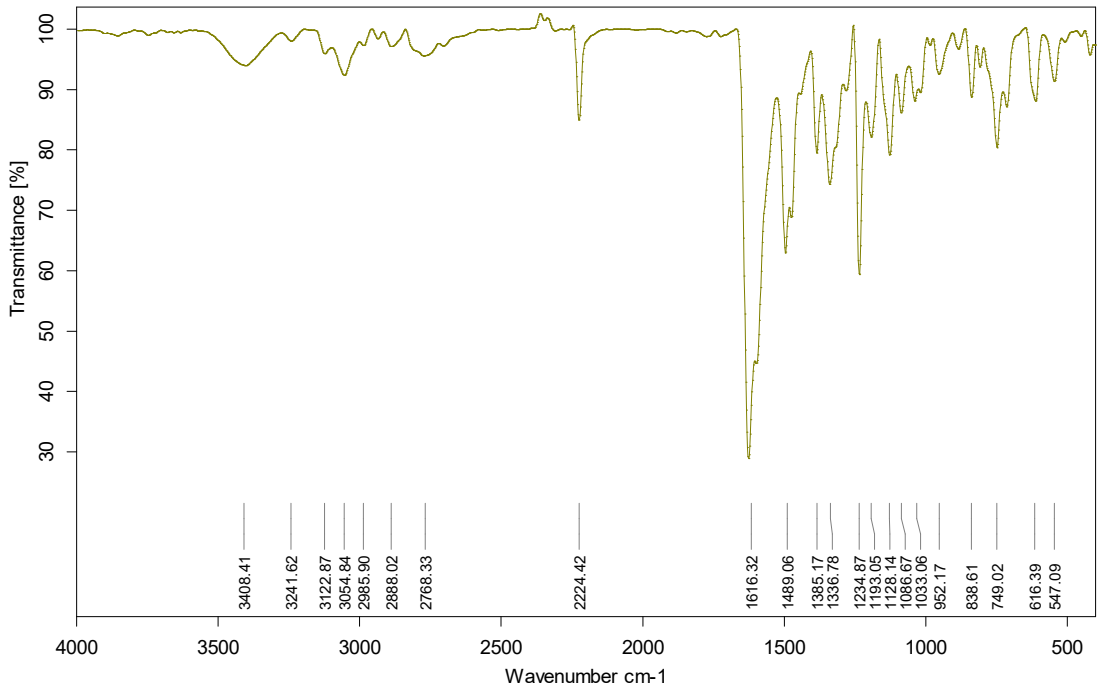


Fig. S 42. FT-IR spectrum of compound **4i**.

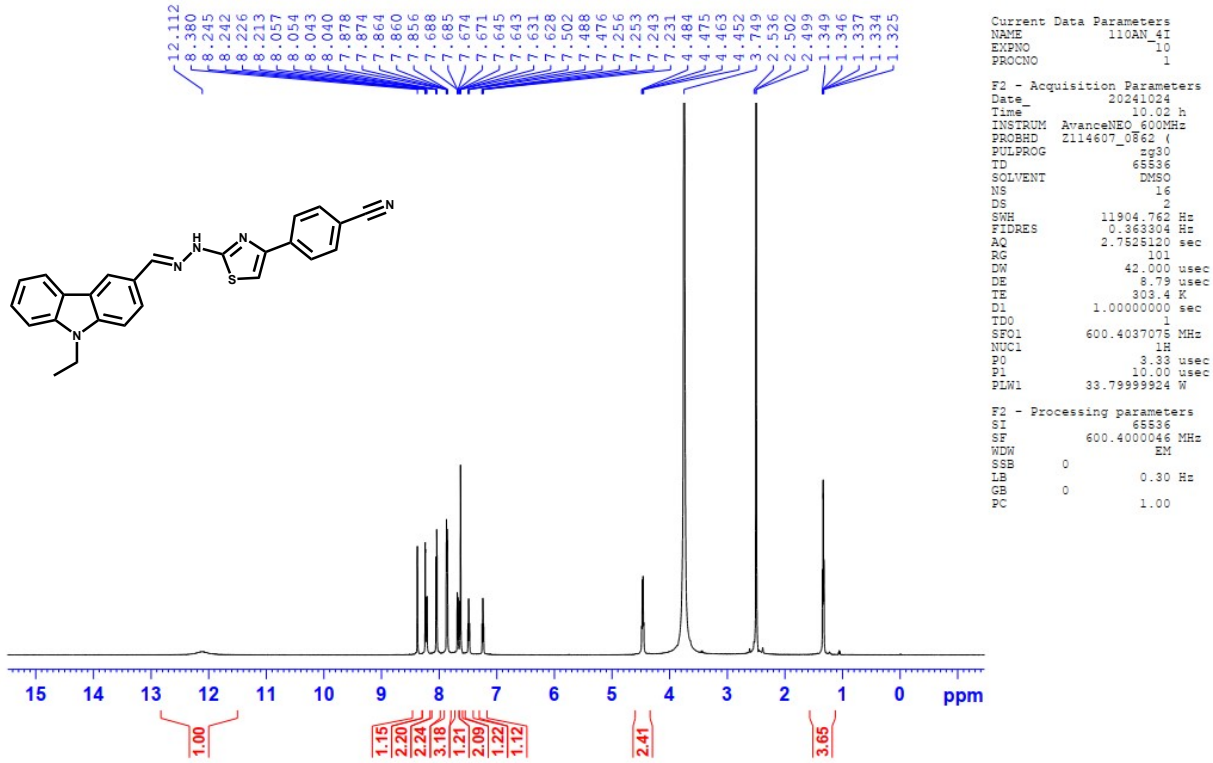


Fig. S 43. [1]H-NMR spectrum of compound **4i**.

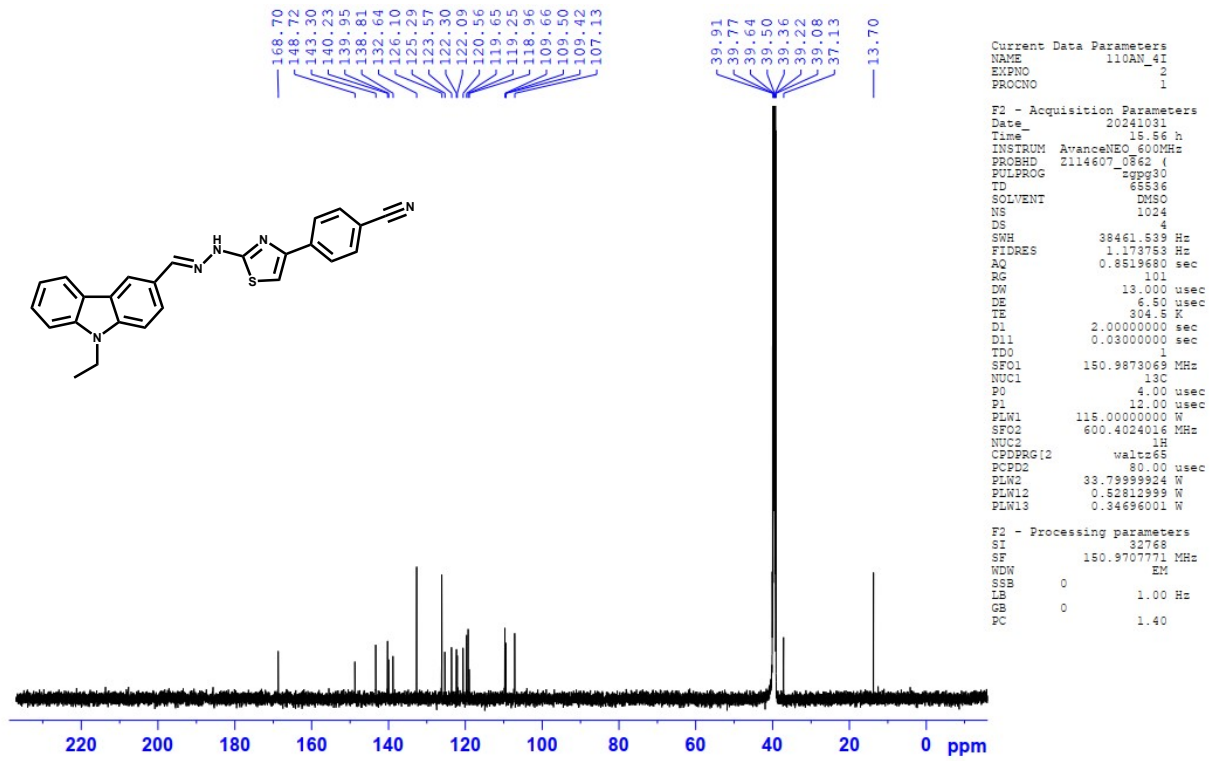


Fig. S 44. ^{13}C-NMR spectrum of compound **4i**.

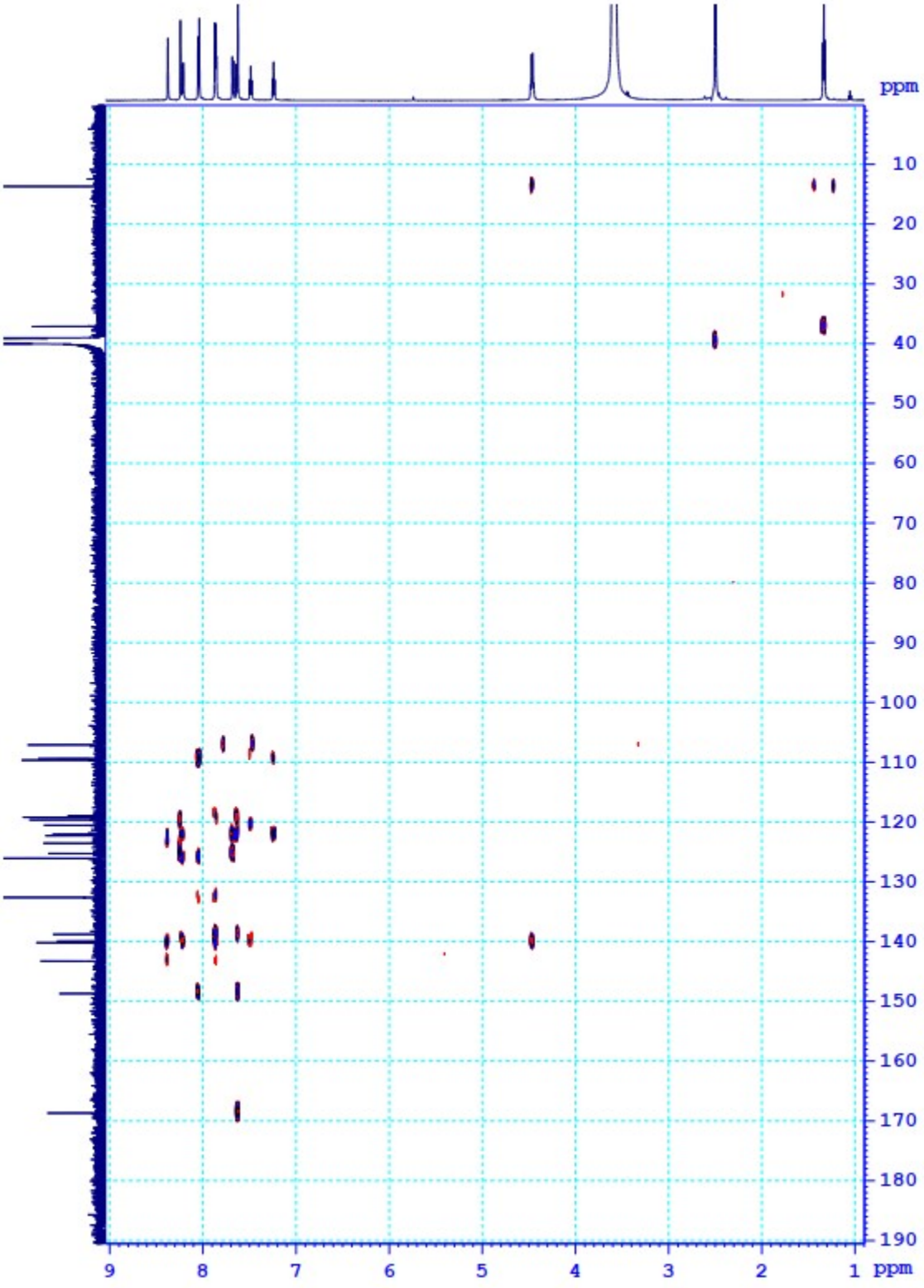


Fig. S 45. HMBC spectrum of compound **4i**.

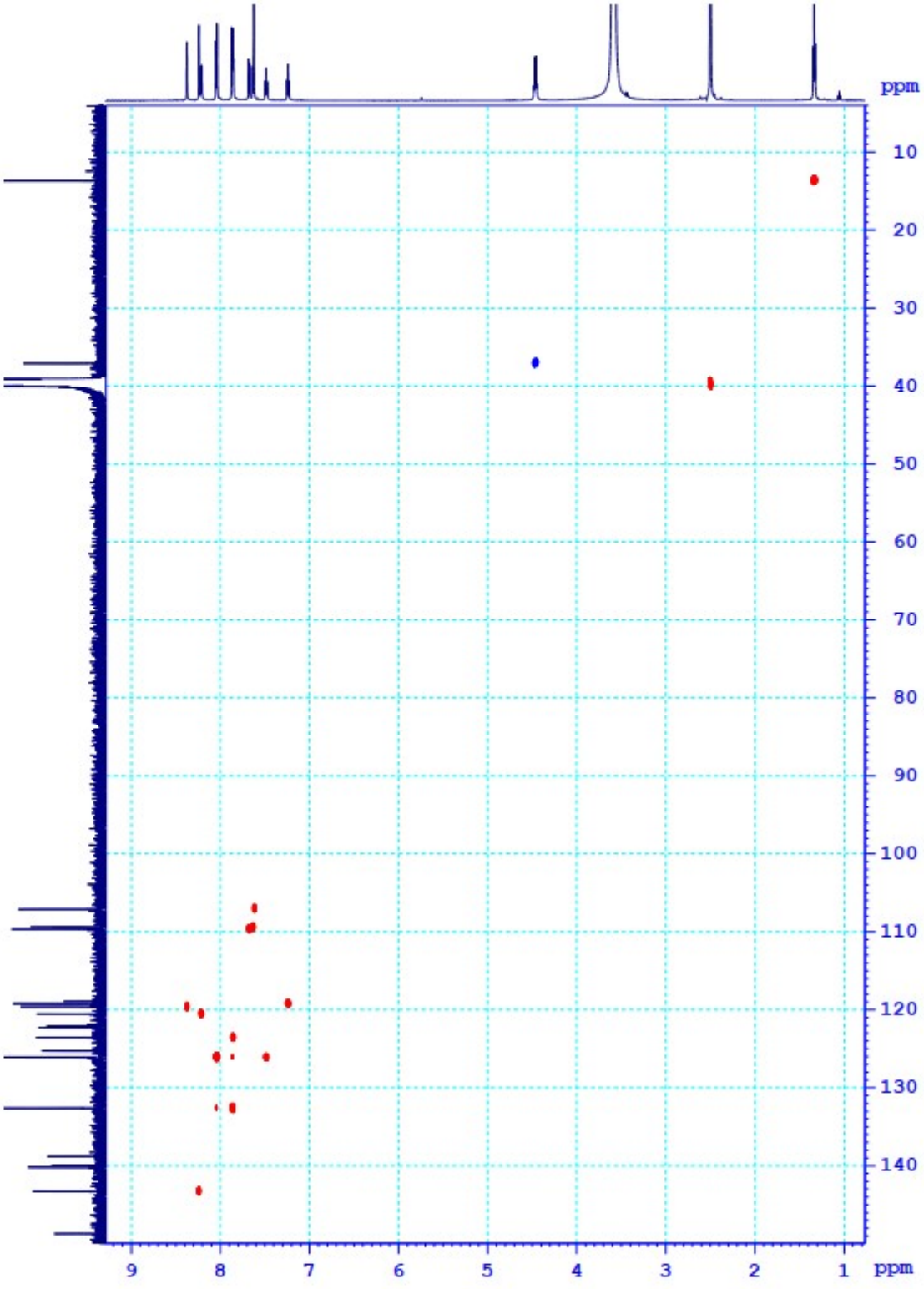


Fig. S 46. HSQC spectrum of compound **4i**.

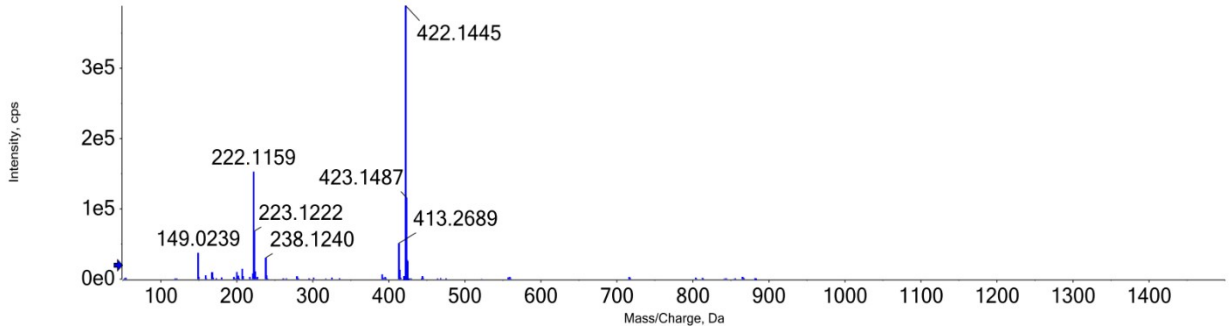


Fig. S 47. HR-MS spectrum of compound **4i**.

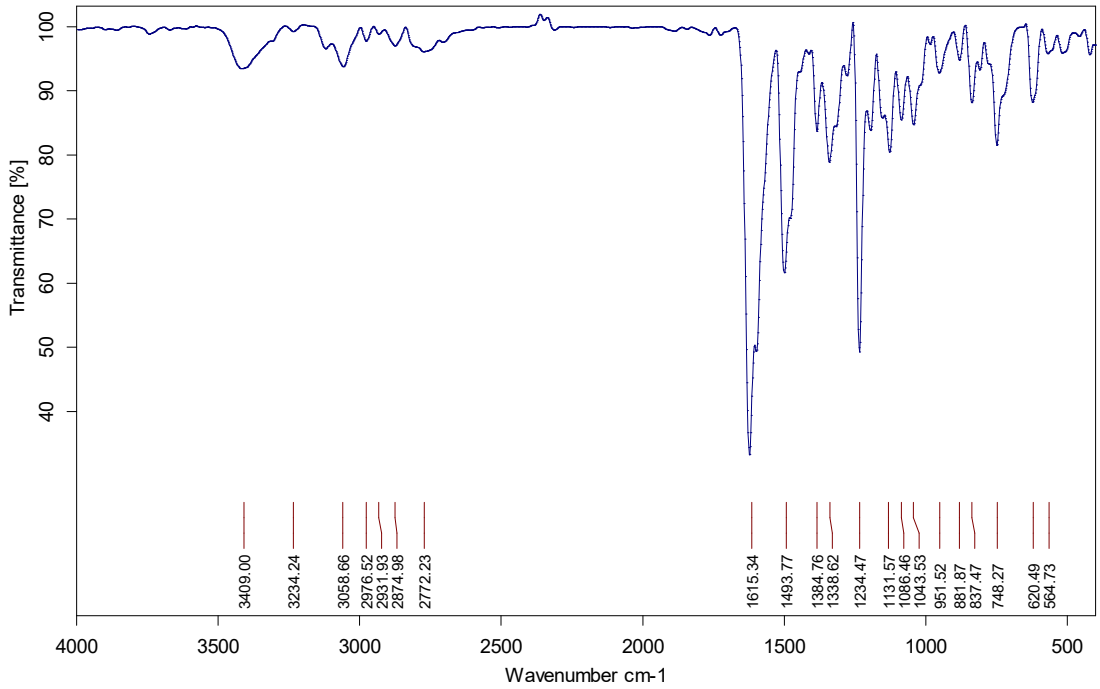


Fig. S 48. FT-IR spectrum of compound **4j**.

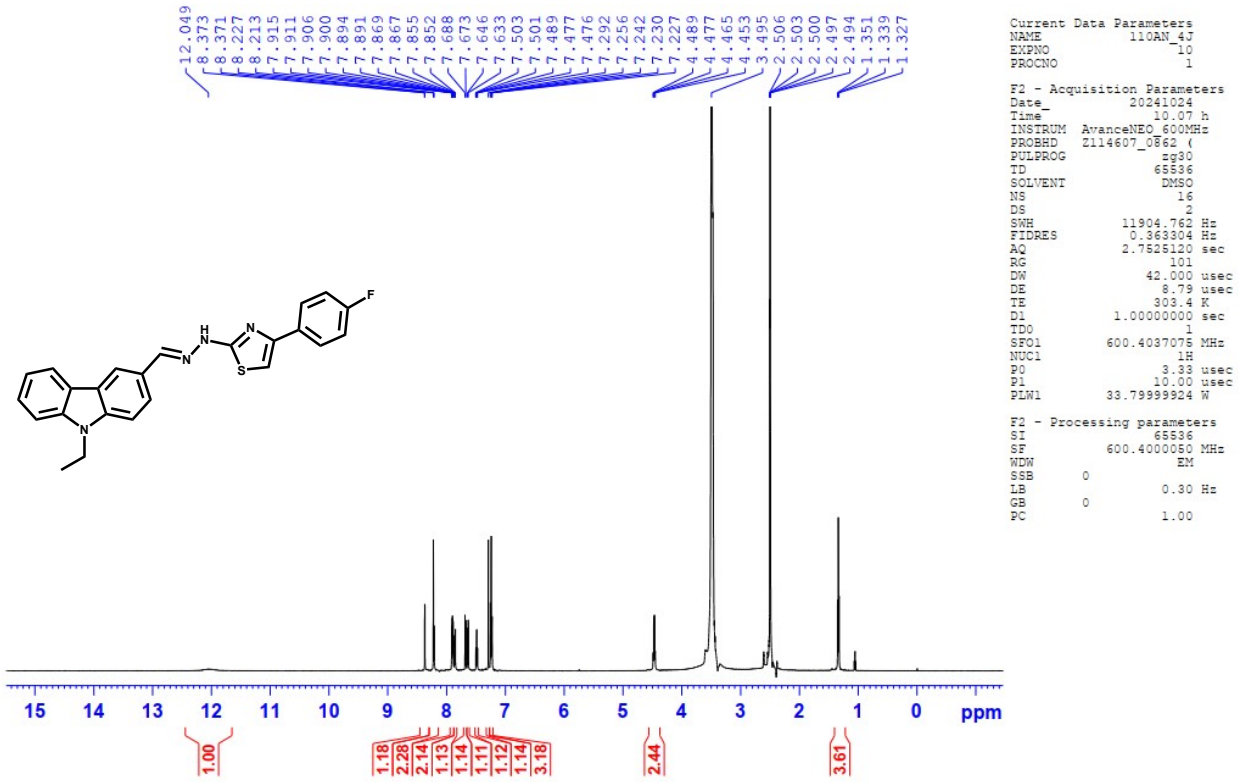


Fig. S 49. [1]H-NMR spectrum of compound **4j**.

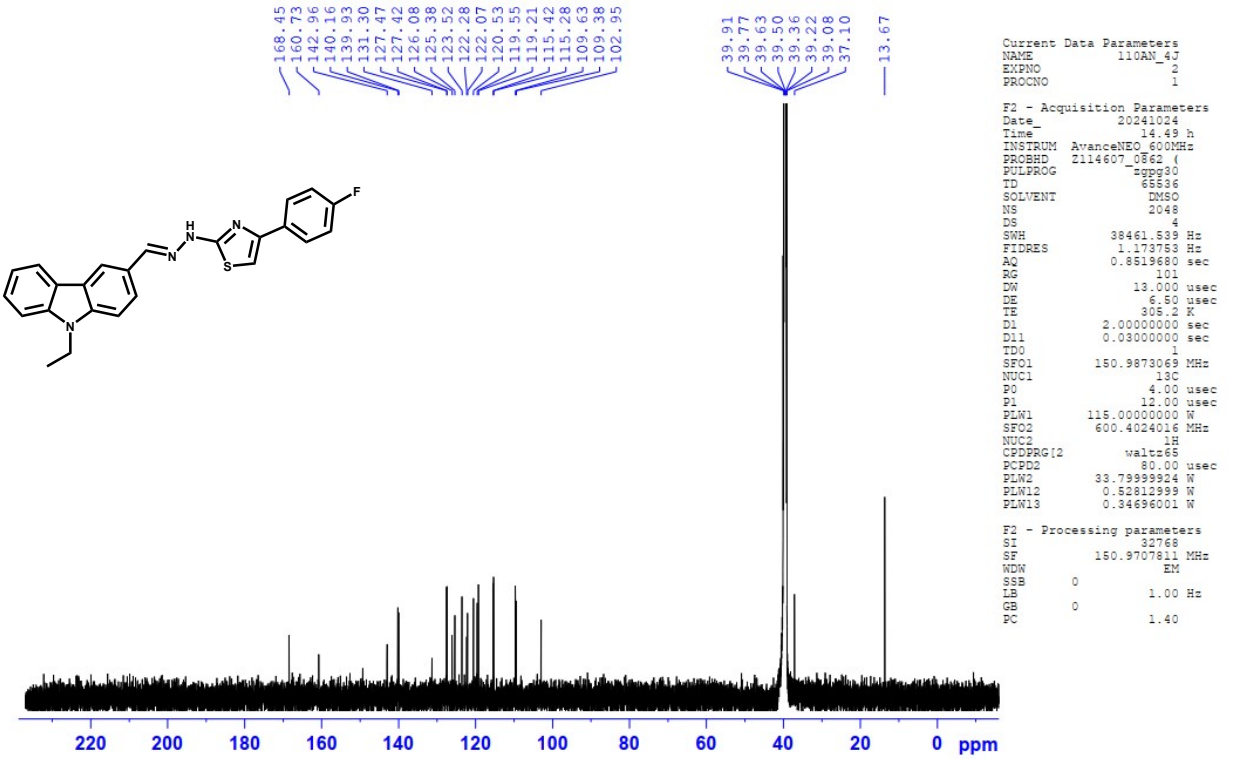


Fig. S 50. [13]C-NMR spectrum of compound **4j**.

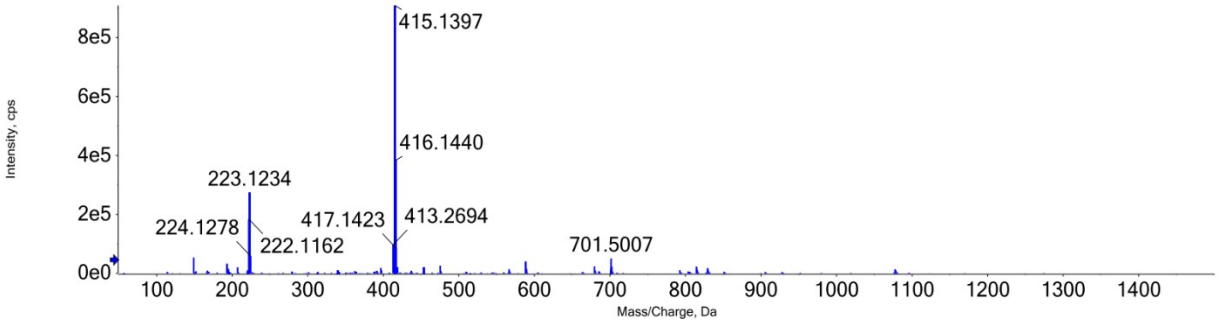


Fig. S 51. HR-MS spectrum of compound **4j**.

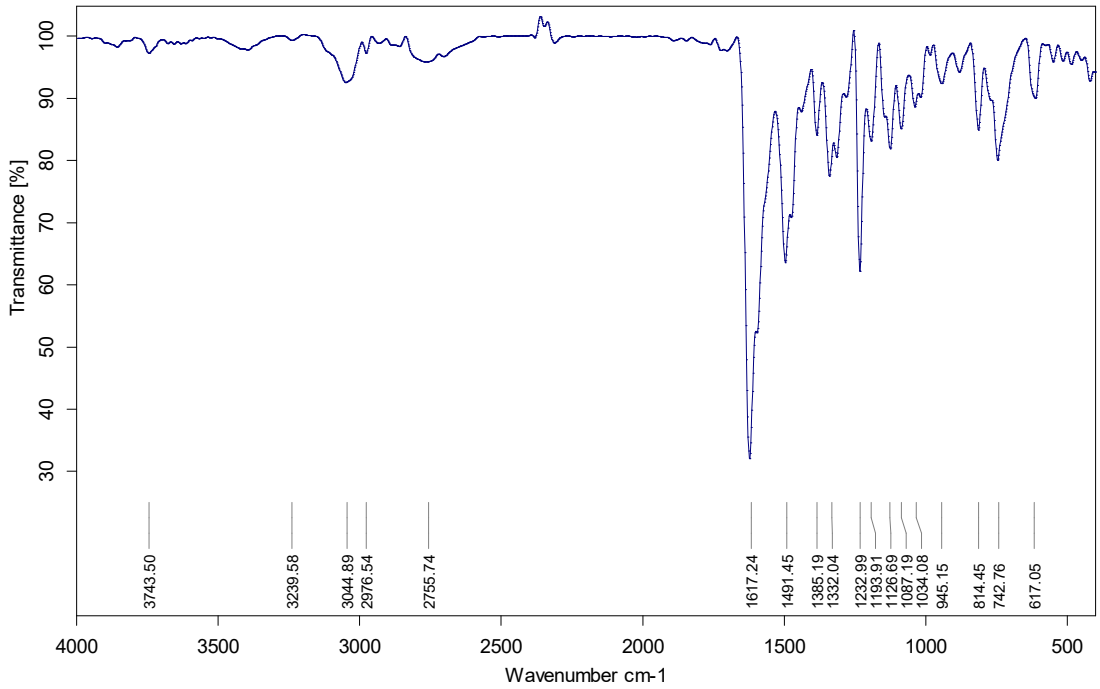


Fig. S 52. FT-IR spectrum of compound **4k**.

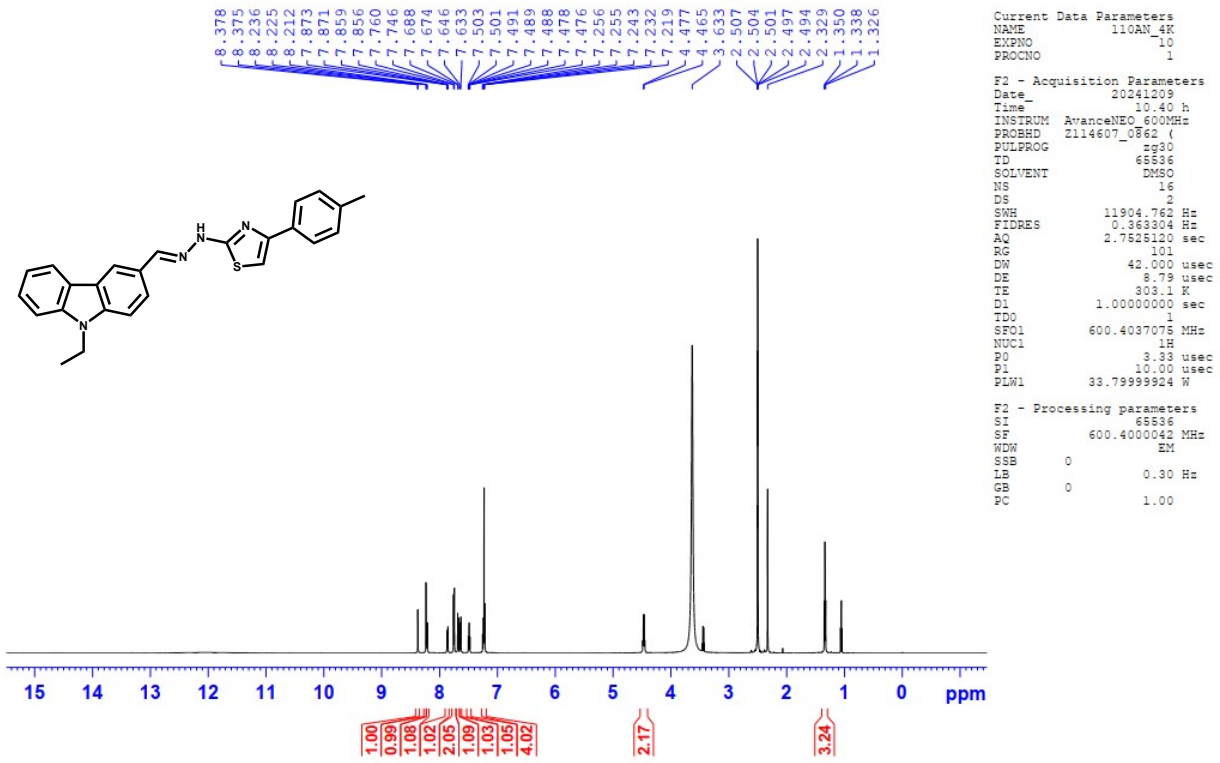


Fig. S 53. ^{1}H-NMR spectrum of compound **4k**.

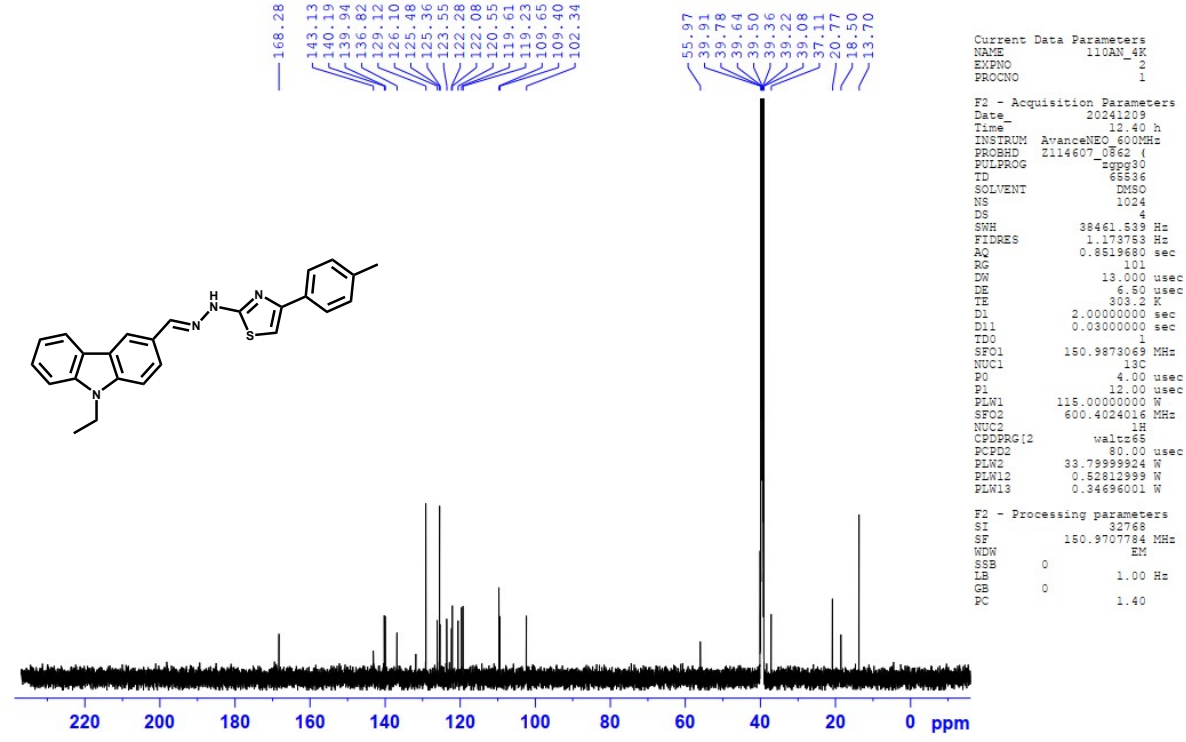


Fig. S 54. ^{13}C-NMR spectrum of compound **4k**.

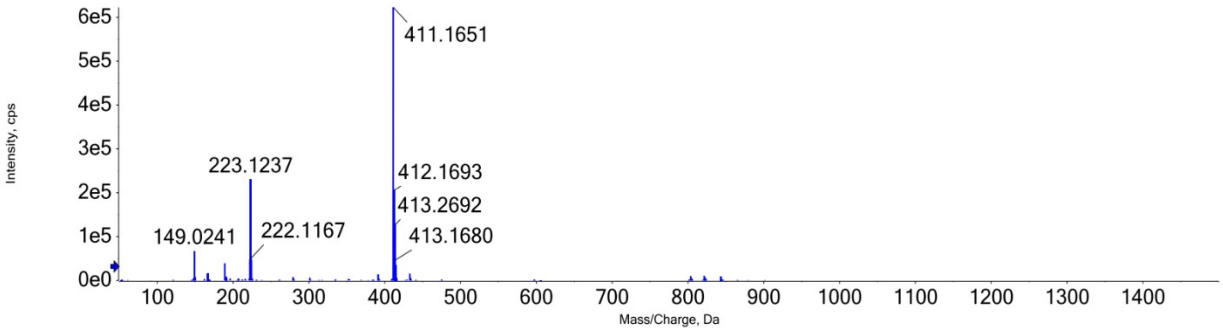


Fig. S 55. HR-MS spectrum of compound **4k**.

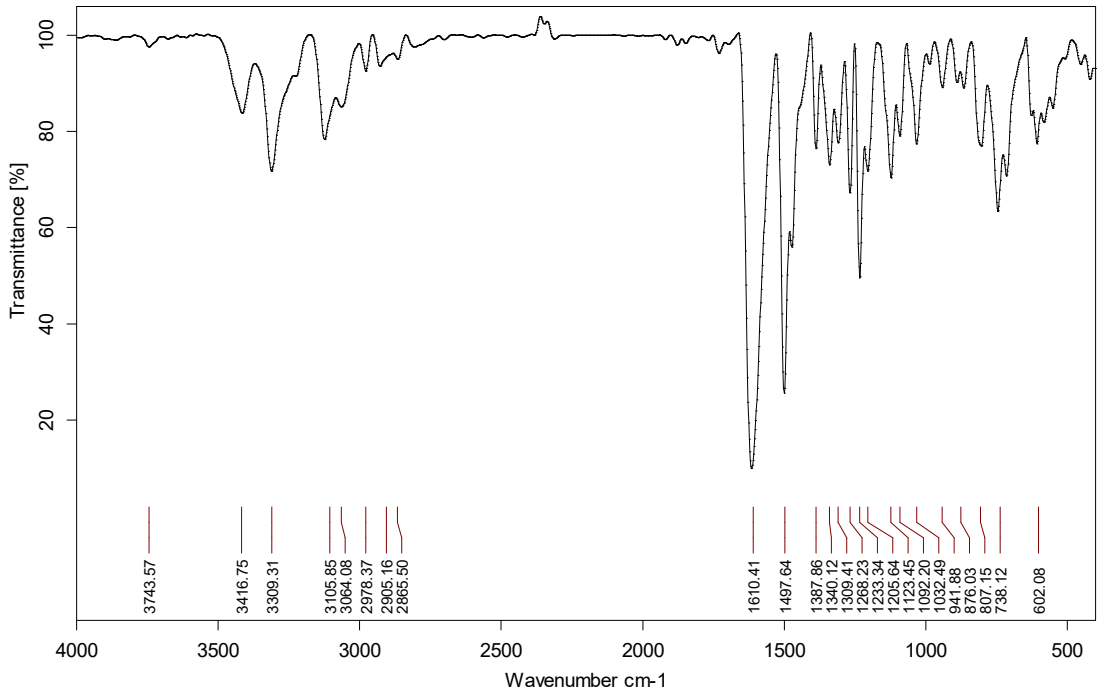
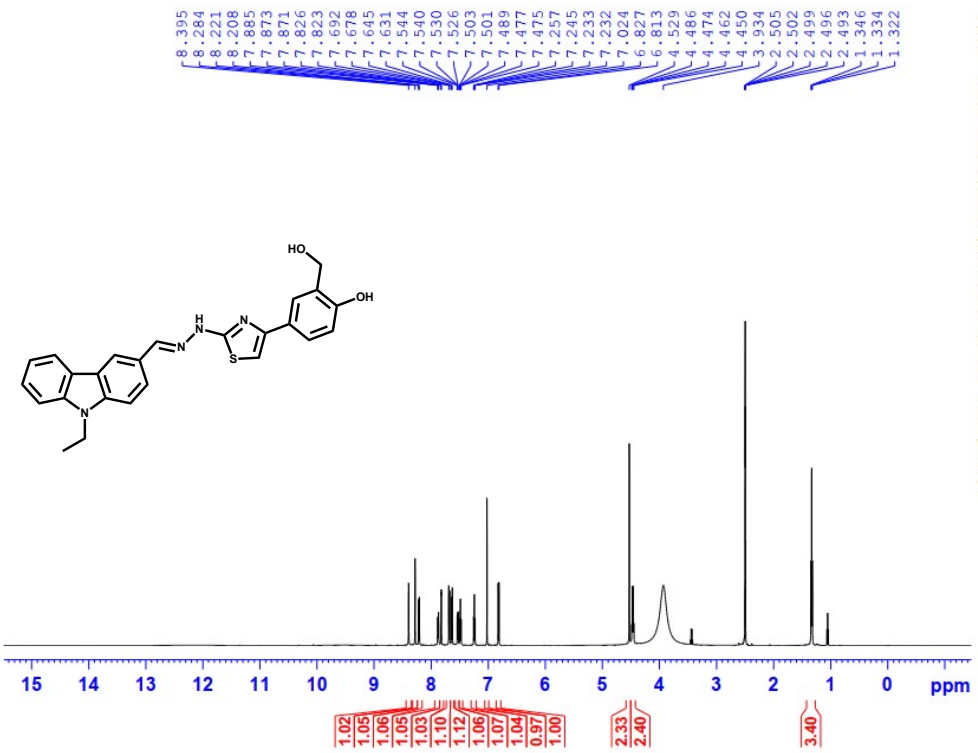


Fig. S 56. FT-IR spectrum of compound **4l**.

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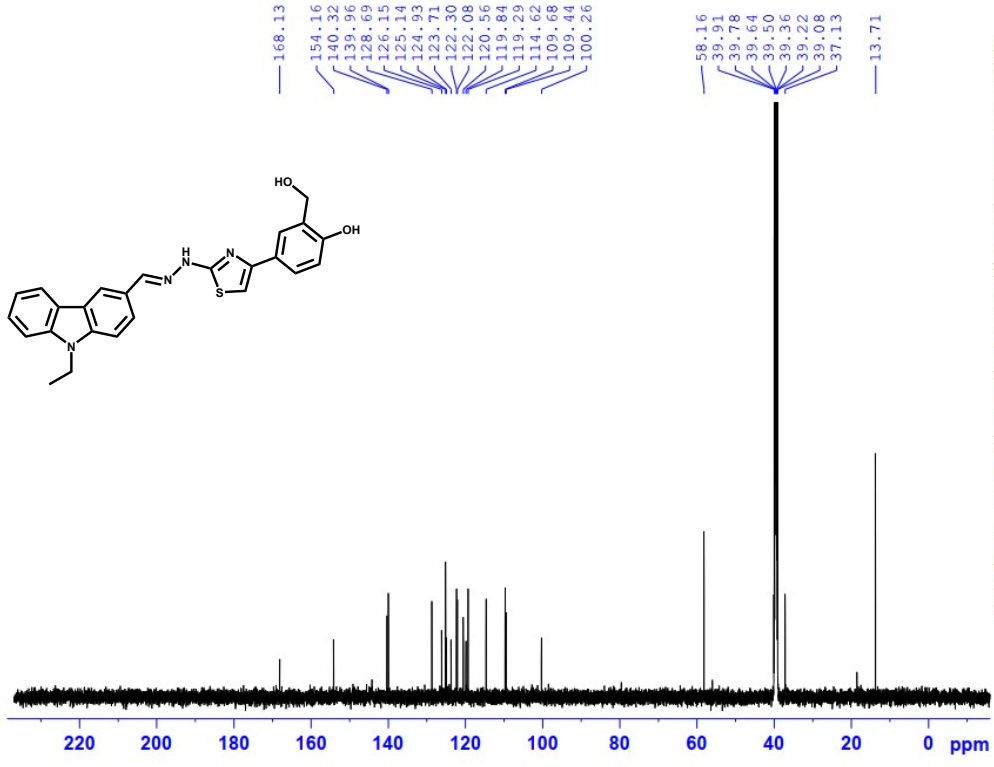
Current Data Parameters
NAME                  110AN_4L
EXPNO                       10
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20241209
Time                     10.44 h
INSTRUM  AvanceNEO_600MHz
PROBHD   Z114607_0862 (
PULPROG                   zg30
TD                       65536
SOLVENT                   DMSO
NS                          16
DS                           2
SWH                  11904.762 Hz
FIDRES                0.363304 Hz
AQ                   2.7525120 sec
RG                         101
DW                      42.000 usec
DE                       8.79 usec
TE                      303.2 K
D1                   1.00000000 sec
TD0                          1
SFO1                600.4037075 MHz
NUC1                        1H
P0                       3.33 usec
P1                      10.00 usec
PLW1                33.79999924 W

F2 - Processing parameters
SI                       65536
SF                  600.4000053 MHz
WDW                         EM
SSB                  0
LB                       0.30 Hz
GB                   0
PC                       1.00
```

Fig. S 57. ^{1}H-NMR spectrum of compound **4l**.




```
Current Data Parameters
NAME                  110AN_4L
EXPNO                       2
PROCNO                      1

F2 - Acquisition Parameters
Date_                 20241209
Time                     13.33 h
INSTRUM  AvanceNEO_600MHz
PROBHD   Z114607_0862 (
PULPROG                zgpg30
TD                       65536
SOLVENT                   DMSO
NS                         1024
DS                            4
SWH                  38461.539 Hz
FIDRES                1.173753 Hz
AQ                   0.8519680 sec
RG                         101
DW                      13.000 usec
DE                       6.50 usec
TE                      303.2 K
D1                   2.00000000 sec
D11                  0.03000000 sec
TD0                          1
SFO1                150.9873069 MHz
NUC1                        13C
P0                       4.00 usec
P1                      12.00 usec
PLW1                115.00000000 W
SFO2                600.4024016 MHz
NUC2                        1H
CPDPRG[2                waltz65
PCPD2                   80.00 usec
PLW2                33.79999924 W
PLW12                0.52812999 W
PLW13                0.34696001 W

F2 - Processing parameters
SI                       32768
SF                  150.9707771 MHz
WDW                         EM
SSB                  0
LB                       1.00 Hz
GB                   0
PC                       1.40
```

Fig. S 58. ^{13}C-NMR spectrum of compound **4l**.

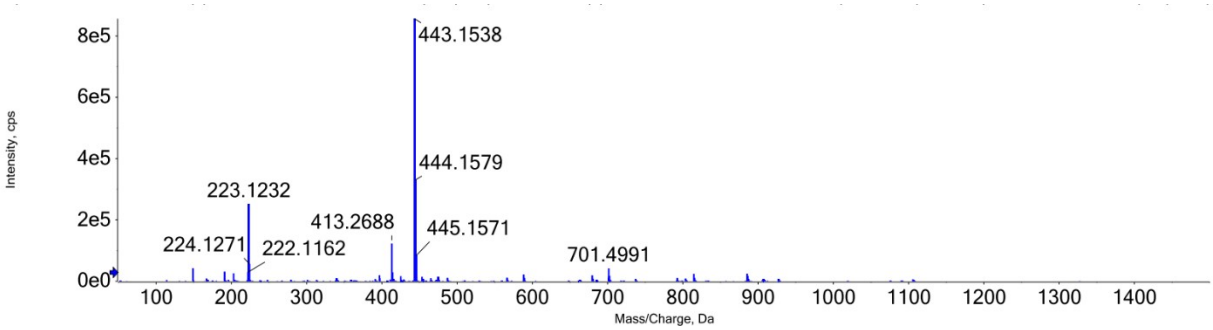


Fig. S 59. HR-MS spectrum of compound **4l**.

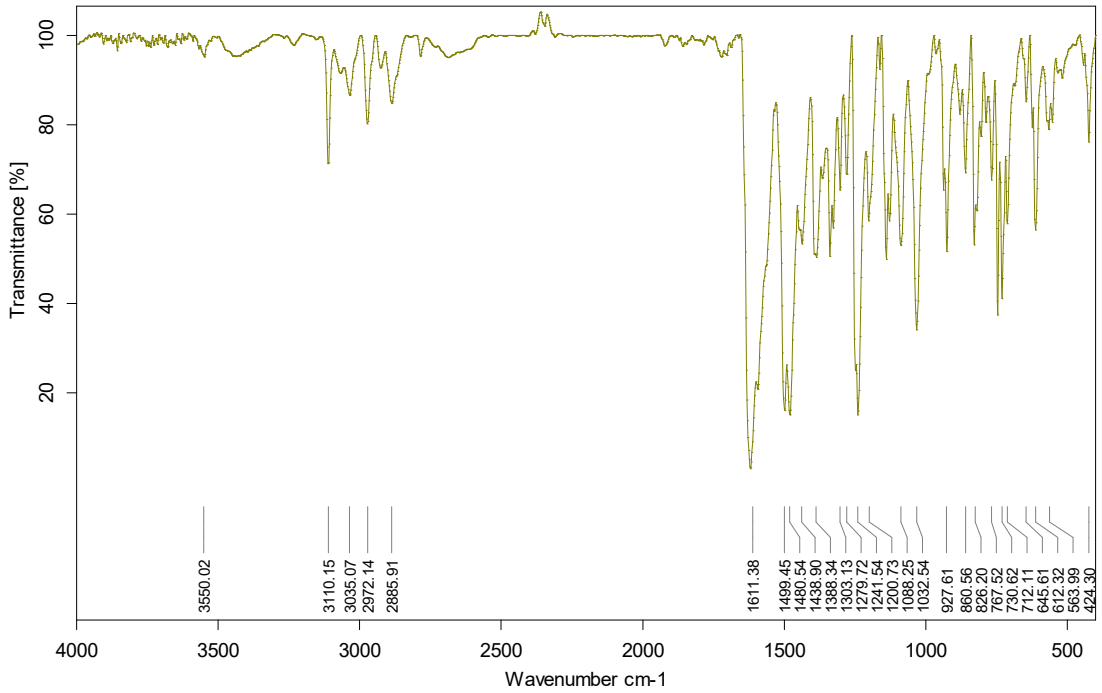
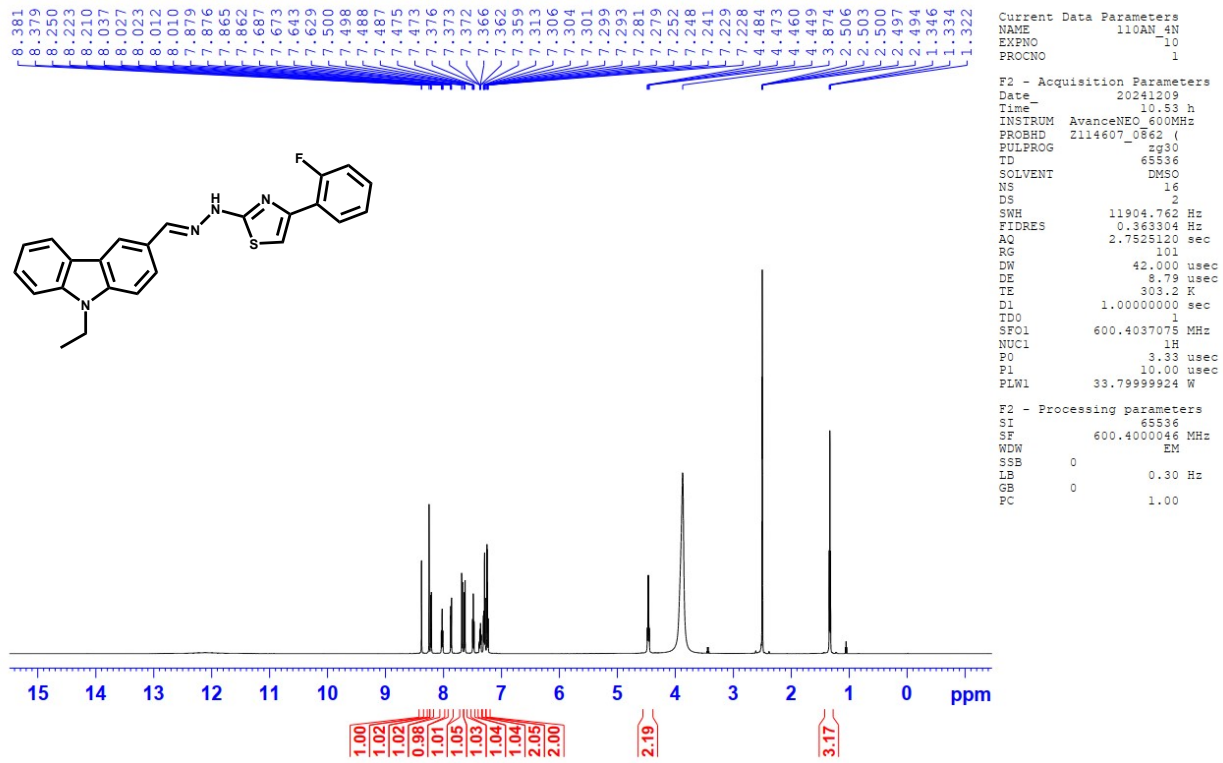


Fig. S 60. FT-IR spectrum of compound **4m**.

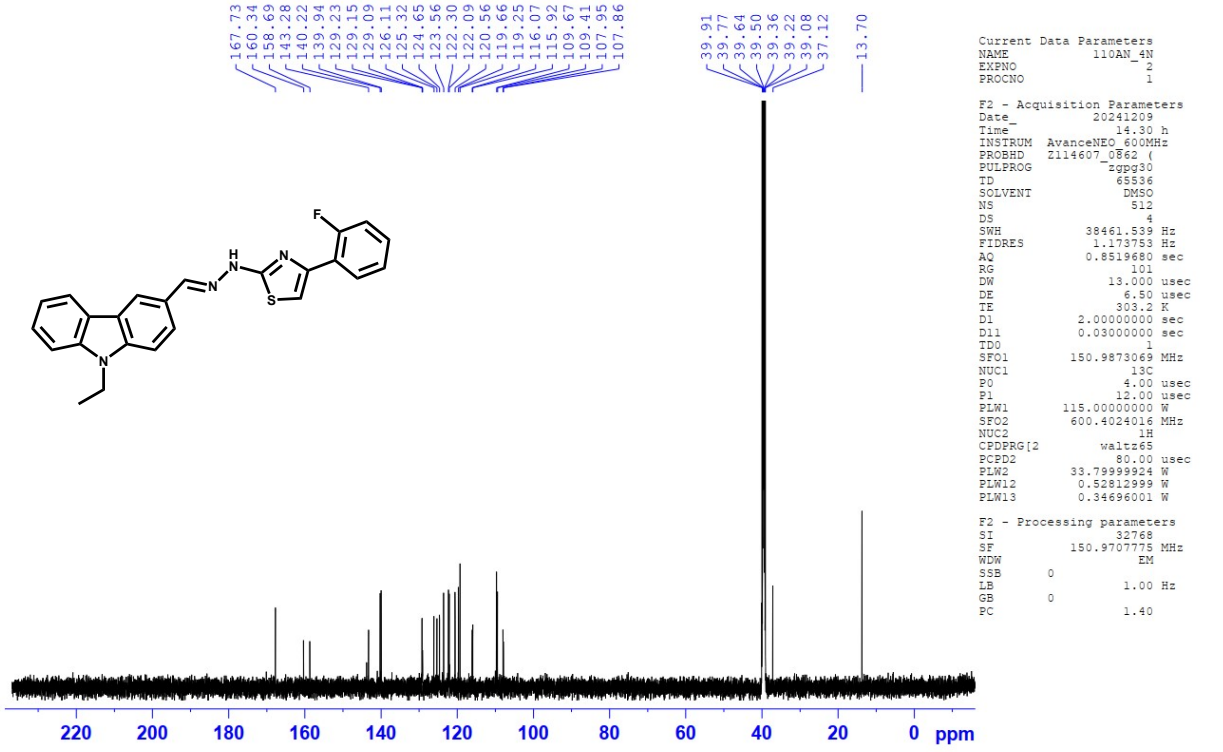



```
Current Data Parameters
NAME                  110AN_4N
EXPNO                       10
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20241209
Time                     10.53 h
INSTRUM  AvanceNEO 600MHz
PROBHD   Z114607_0862 (
PULPROG                  zg30
TD                      65536
SOLVENT                  DMSO
NS                         16
DS                          2
SWH                 11904.762 Hz
FIDRES                0.363304 Hz
AQ                  2.7525120 sec
RG                        101
DW                     42.000 usec
DE                      8.79 usec
TE                     303.2 K
D1                  1.00000000 sec
TD0                         1
SFO1               600.4037075 MHz
NUC1                       1H
P0                      3.33 usec
P1                     10.00 usec
PLW1               33.79999924 W

F2 - Processing parameters
SI                      65536
SF                 600.4000046 MHz
WDW                        EM
SSB          0
LB                      0.30 Hz
GB           0
PC                      1.00
```

Fig. S 61. ^{1}H-NMR spectrum of compound **4m**.




```
Current Data Parameters
NAME                  110AN_4N
EXPNO                       2
PROCNO                      1

F2 - Acquisition Parameters
Date_                 20241209
Time                     14.30 h
INSTRUM  AvanceNEO 600MHz
PROBHD   Z114607_0862 (
PULPROG                zgpg30
TD                      65536
SOLVENT                  DMSO
NS                         512
DS                           4
SWH                 38461.539 Hz
FIDRES                1.173753 Hz
AQ                  0.8519680 sec
RG                        101
DW                     13.000 usec
DE                      6.50 usec
TE                     303.2 K
D1                  2.00000000 sec
D11                 0.03000000 sec
TD0                         1
SFO1               150.9873069 MHz
NUC1                       13C
P0                      4.00 usec
P1                     12.00 usec
PLW1               115.00000000 W
SFO2               600.4024016 MHz
NUC2                       1H
CPDPRG[2                waltz65
PCPD2                   80.00 usec
PLW2               33.79999924 W
PLW12               0.52812999 W
PLW13               0.34696001 W

F2 - Processing parameters
SI                      32768
SF                 150.9707775 MHz
WDW                        EM
SSB          0
LB                      1.00 Hz
GB           0
PC                      1.40
```

Fig. S 62. ^{13}C-NMR spectrum of compound **4m**.

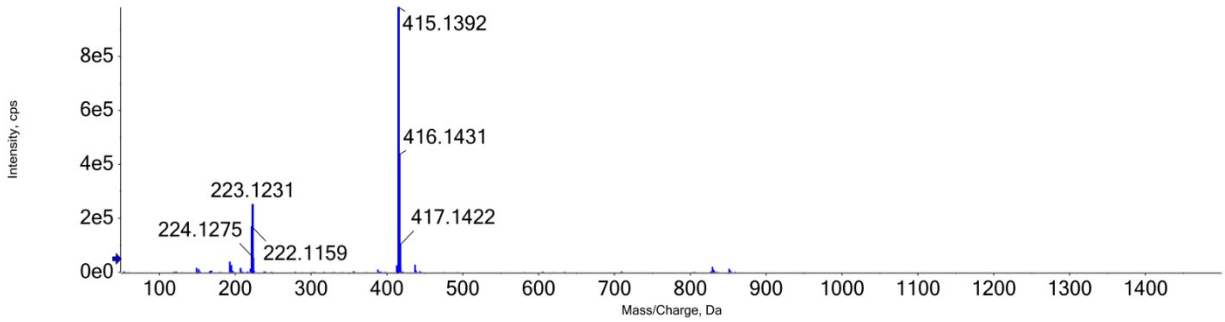


Fig. S 63. HR-MS spectrum of compound **4m**.

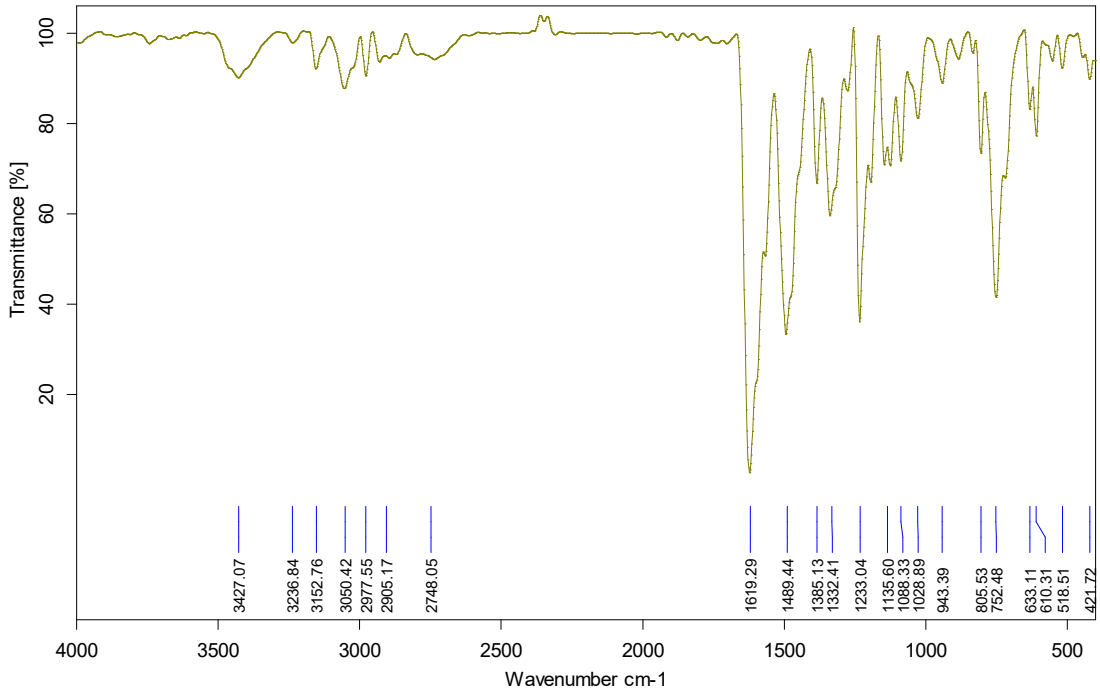
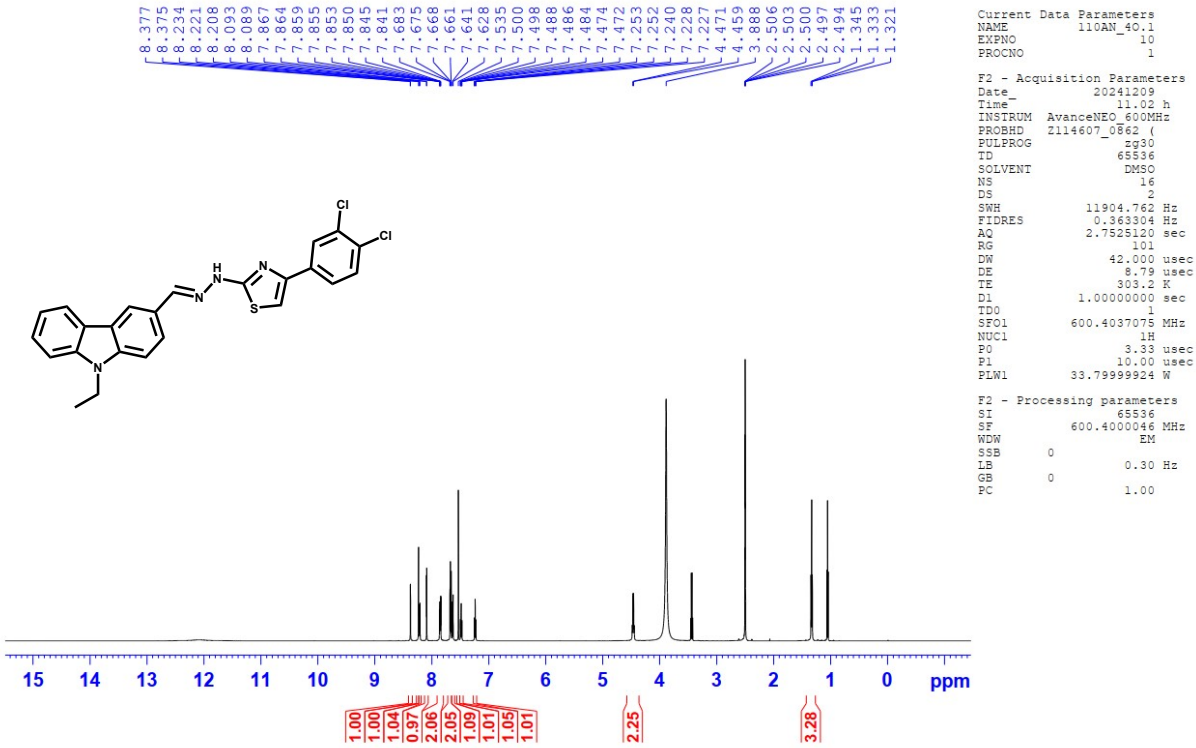


Fig. S 64. FT-IR spectrum of compound **4n**.

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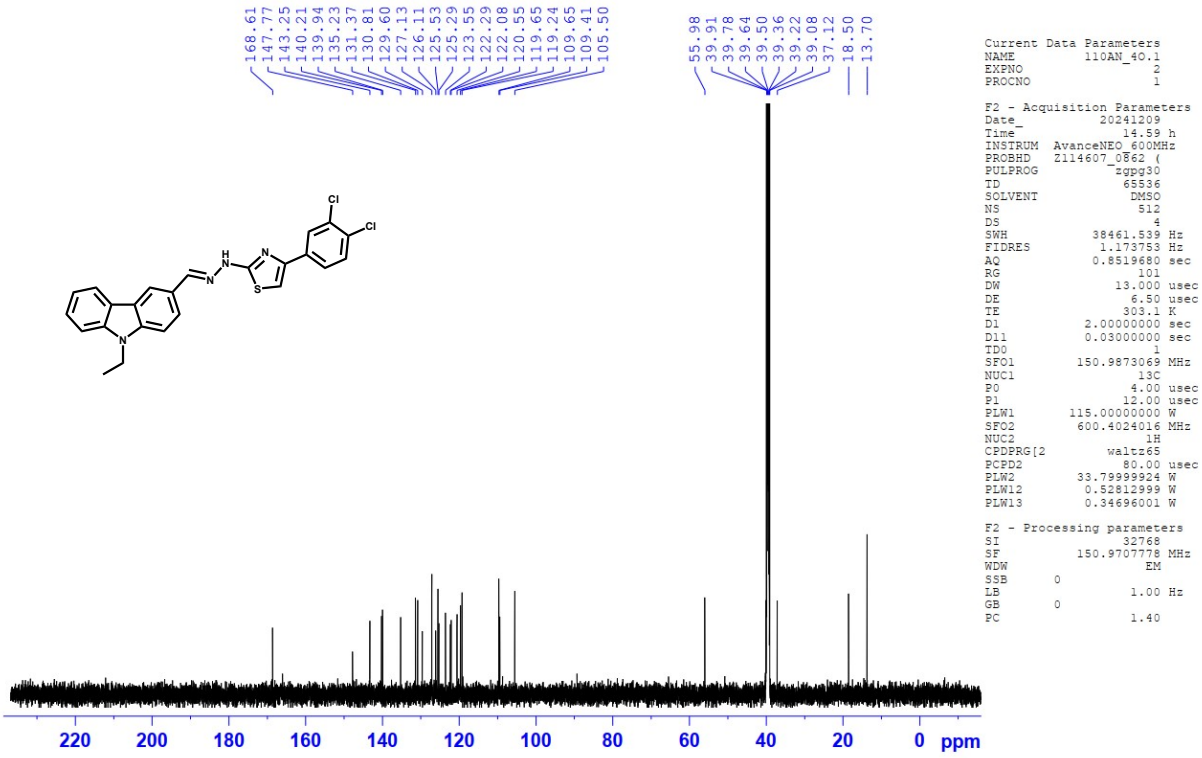
Current Data Parameters
NAME          110AN_4O.1
EXPNO                 10
PROCNO                 1

F2 - Acquisition Parameters
Date_           20241209
Time              11.02 h
INSTRUM  AvanceNEO 600MHz
PROBHD   Z114607_0862 (
PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                    16
DS                     2
SWH           11904.762 Hz
FIDRES         0.363304 Hz
AQ            2.7525120 sec
RG                   101
DW                42.000 usec
DE                 8.79 usec
TE                303.2 K
D1            1.00000000 sec
TD0                    1
SFO1         600.4037075 MHz
NUC1                  1H
P0                 3.33 usec
P1                10.00 usec
PLW1         33.79999924 W

F2 - Processing parameters
SI                 65536
SF          600.4000046 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

Fig. S 65. ^{1}H-NMR spectrum of compound **4n**.




```
Current Data Parameters
NAME          110AN_4O.1
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20241209
Time              14.59 h
INSTRUM  AvanceNEO 600MHz
PROBHD   Z114607_0862 (
PULPROG          zgpg30
TD                 65536
SOLVENT             DMSO
NS                   512
DS                     4
SWH           38461.539 Hz
FIDRES         1.173753 Hz
AQ            0.8519680 sec
RG                   101
DW                13.000 usec
DE                 6.50 usec
TE                303.1 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                    1
SFO1         150.9873069 MHz
NUC1                  13C
P0                 4.00 usec
P1                12.00 usec
PLW1        115.00000000 W
SFO2         600.4024016 MHz
NUC2                  1H
CPDPRG[2         waltz65
PCPD2              80.00 usec
PLW2         33.79999924 W
PLW12         0.52812999 W
PLW13         0.34696001 W

F2 - Processing parameters
SI                 32768
SF          150.9707778 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```

Fig. S 66. ^{13}C-NMR spectrum of compound **4n**.

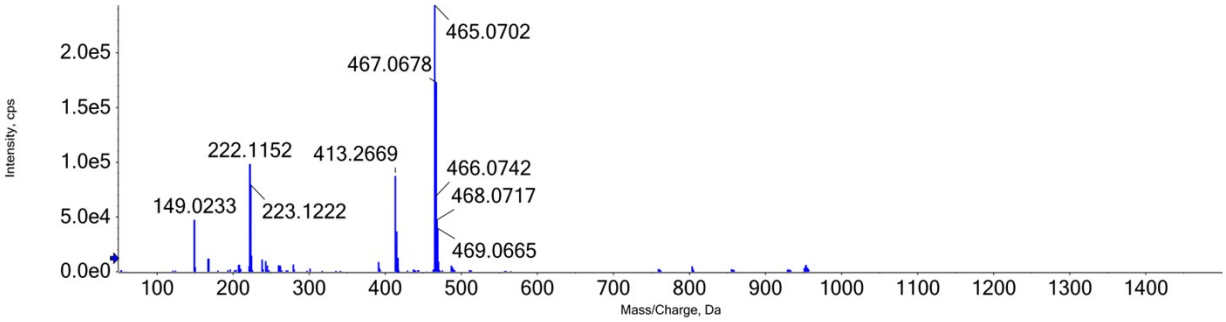


Fig. S 67. HR-MS spectrum of compound **4n**.

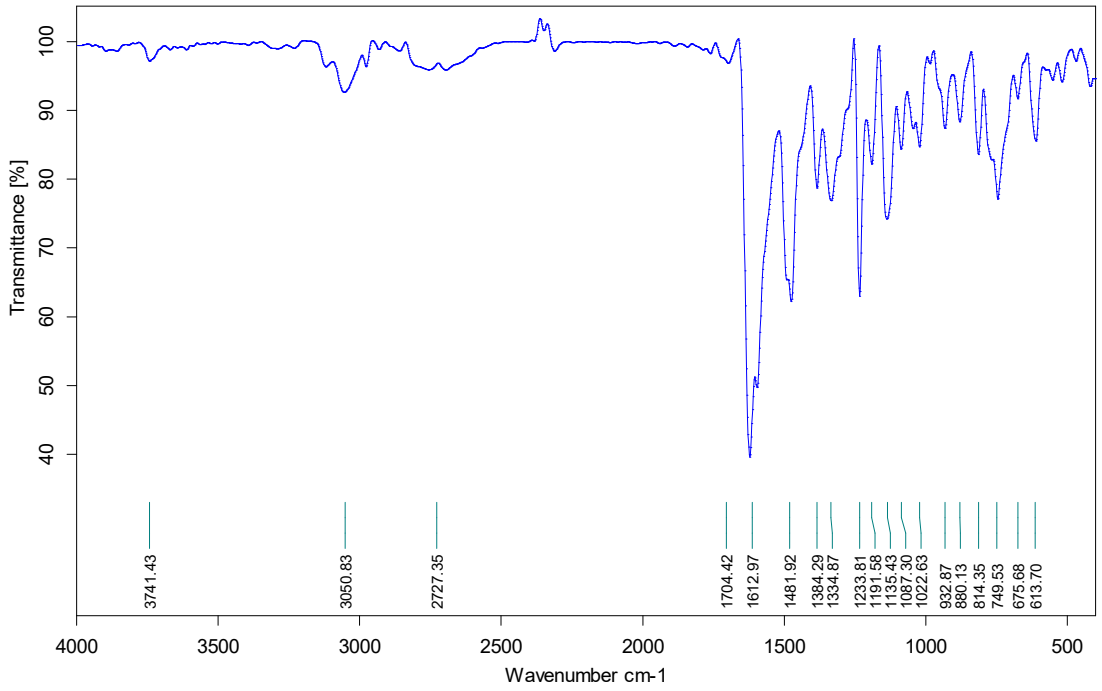


Fig. S 68. FT-IR spectrum of compound **4o**.

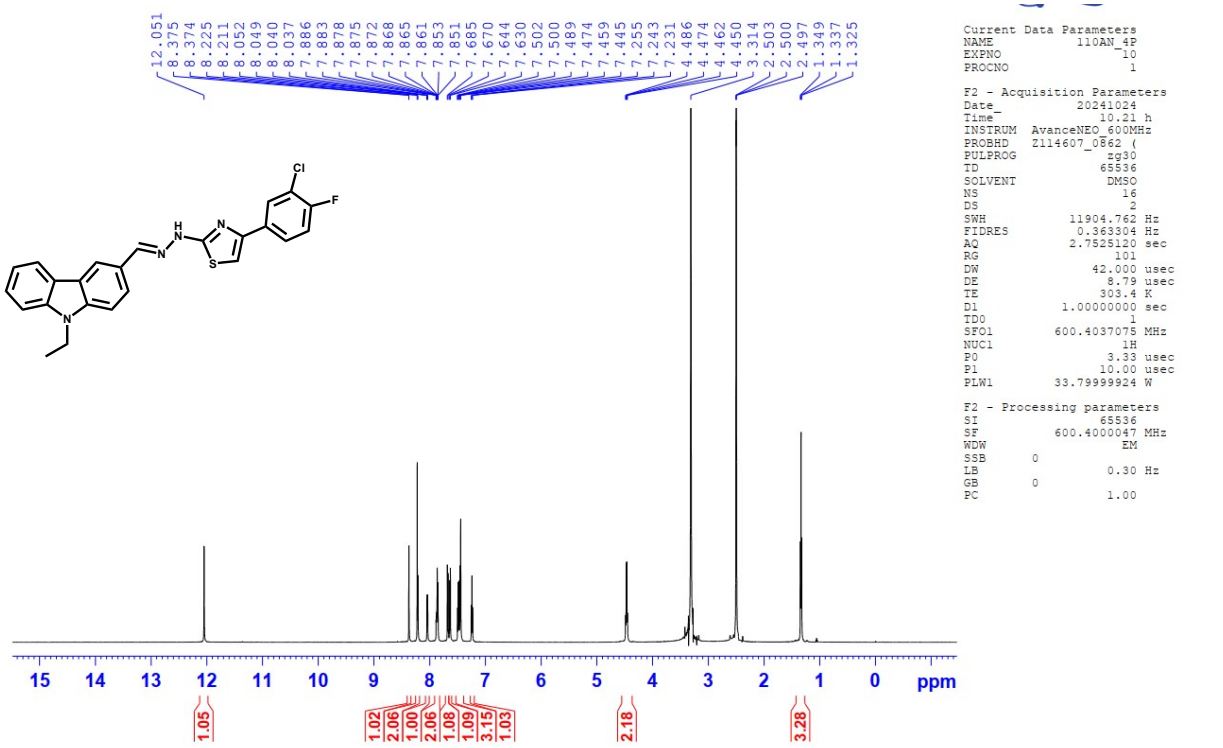


Fig. S 69. ^{1}H-NMR spectrum of compound **4o**.

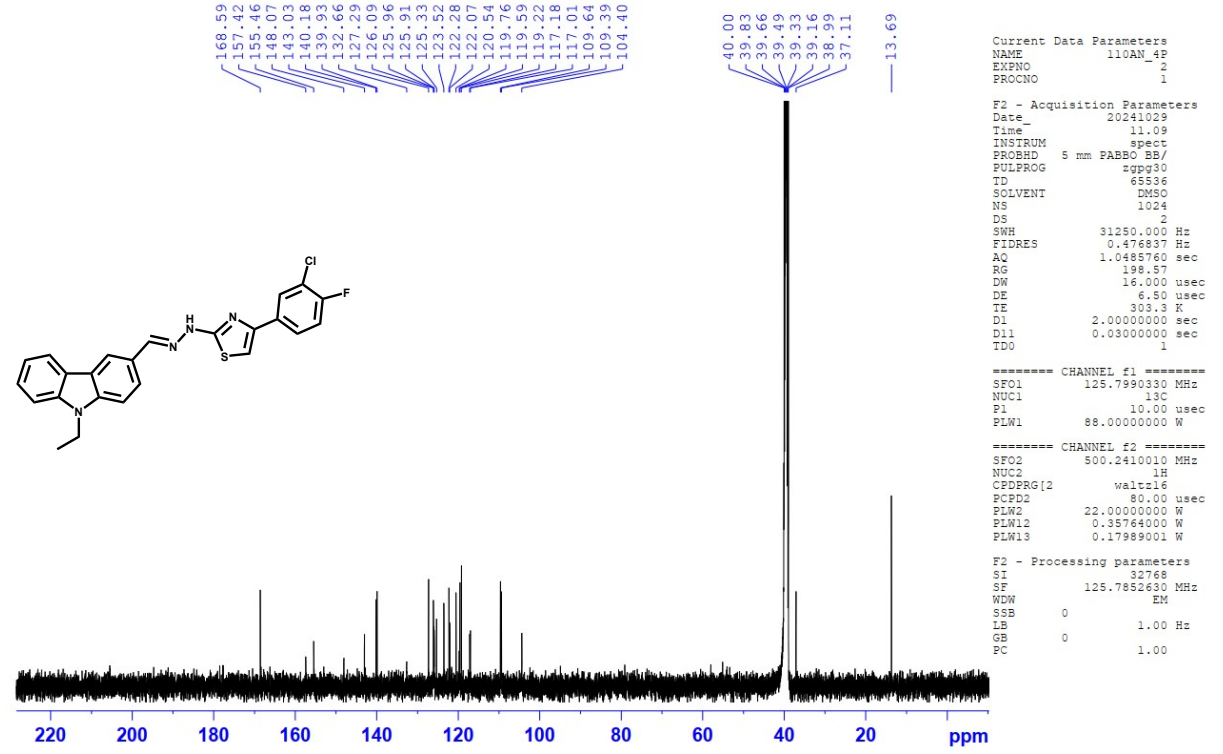


Fig. S 70. ^{13}C-NMR spectrum of compound **4o**.

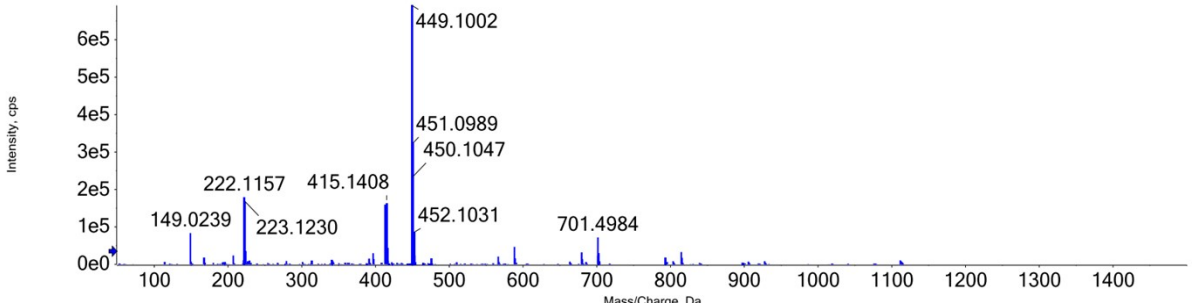


Fig. S 71. HR-MS spectrum of compound **4o**.

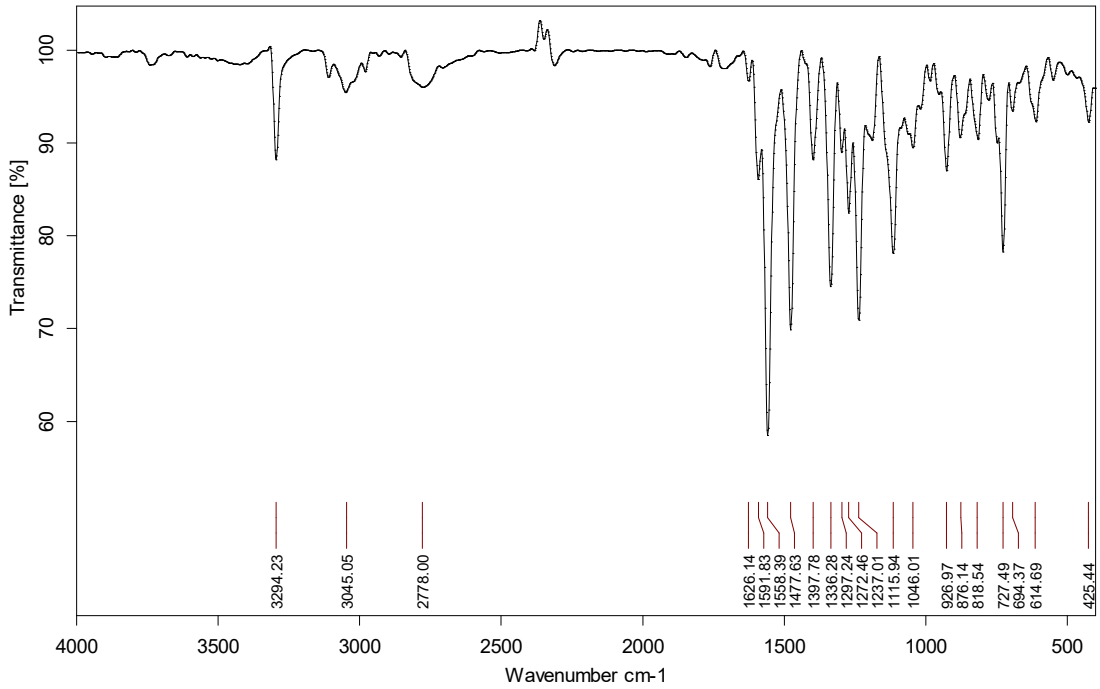
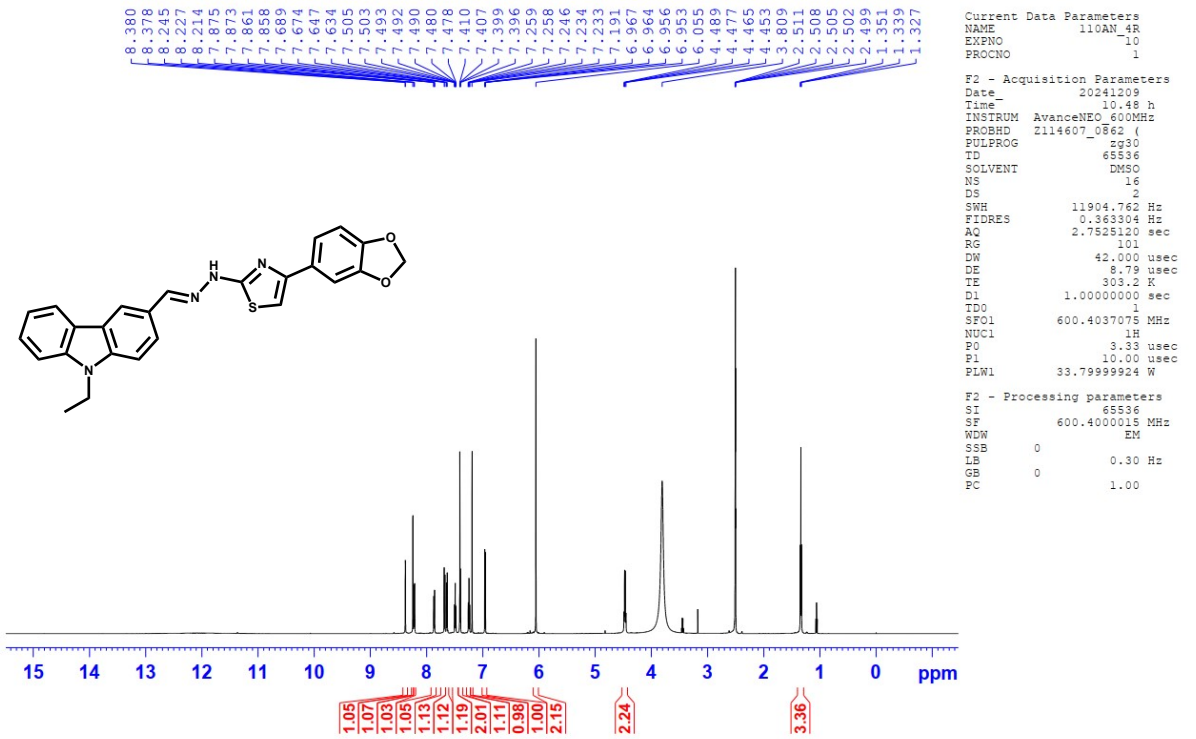


Fig. S 72. FT-IR spectrum of compound **4p**.

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Current Data Parameters
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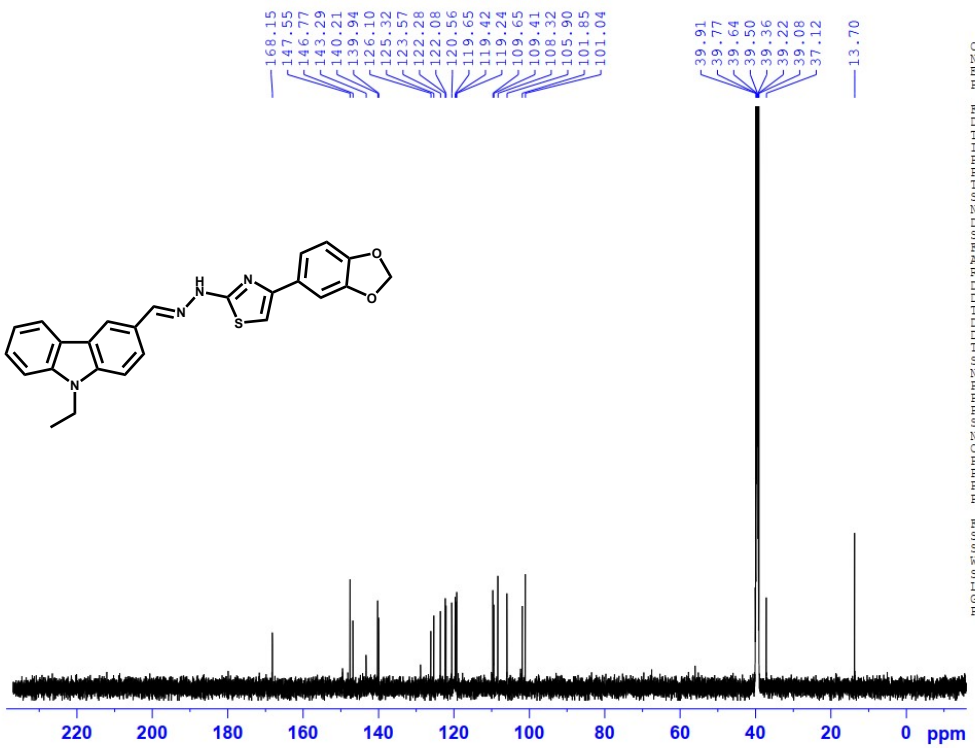
EXPNO                 10
PROCNO                 1

F2 - Acquisition Parameters
Date_           20241209
Time                10.48 h
INSTRUM  AvanceNEO_600MHz
PROBHD   Z114607_0862 (
PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                    16
DS                     2
SWH           11904.762 Hz
FIDRES         0.363304 Hz
AQ            2.7525120 sec
RG                   101
DW                42.000 usec
DE                 8.79 usec
TE                303.2 K
D1           1.00000000 sec
TD0                    1
SFO1        600.4037075 MHz
NUC1                  1H
P0                 3.33 usec
P1                10.00 usec
PLW1        33.79999924 W

F2 - Processing parameters
SI                 65536
SF          600.4000015 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

Fig. S 73. [1]H-NMR spectrum of compound **4p**.

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Current Data Parameters
NAME            110AN_4R
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
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Time                14.02 h
INSTRUM  AvanceNEO_600MHz
PROBHD   Z114607_0862 (
PULPROG          zgpg30
TD                 65536
SOLVENT             DMSO
NS                   512
DS                     4
SWH           38461.539 Hz
FIDRES         1.173753 Hz
AQ            0.8519680 sec
RG                   101
DW                13.000 usec
DE                 6.50 usec
TE                303.2 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                    1
SFO1        150.9873069 MHz
NUC1                  13C
P0                 4.00 usec
P1                12.00 usec
PLW1       115.00000000 W
SFO2        600.4024016 MHz
NUC2                  1H
CPDPRG[2          waltz65
PCPD2             80.00 usec
PLW2        33.79999924 W
PLW12        0.52812999 W
PLW13        0.34696001 W

F2 - Processing parameters
SI                 32768
SF          150.9707781 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```

Fig. S 74. [13]C-NMR spectrum of compound **4p**.

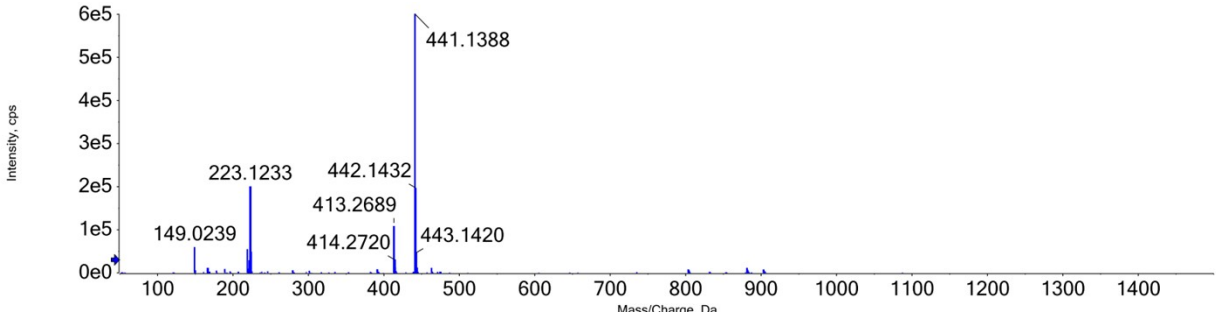


Fig. S 75. HR-MS spectrum of compound **4p**.

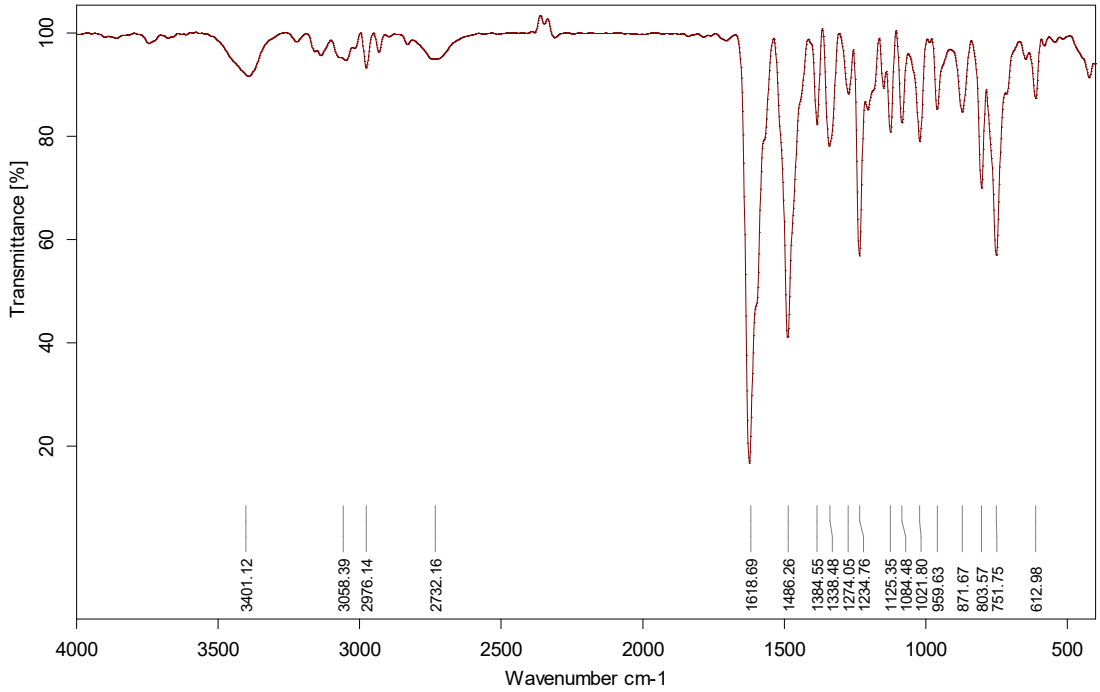


Fig. S 76. FT-IR spectrum of compound **4q**.

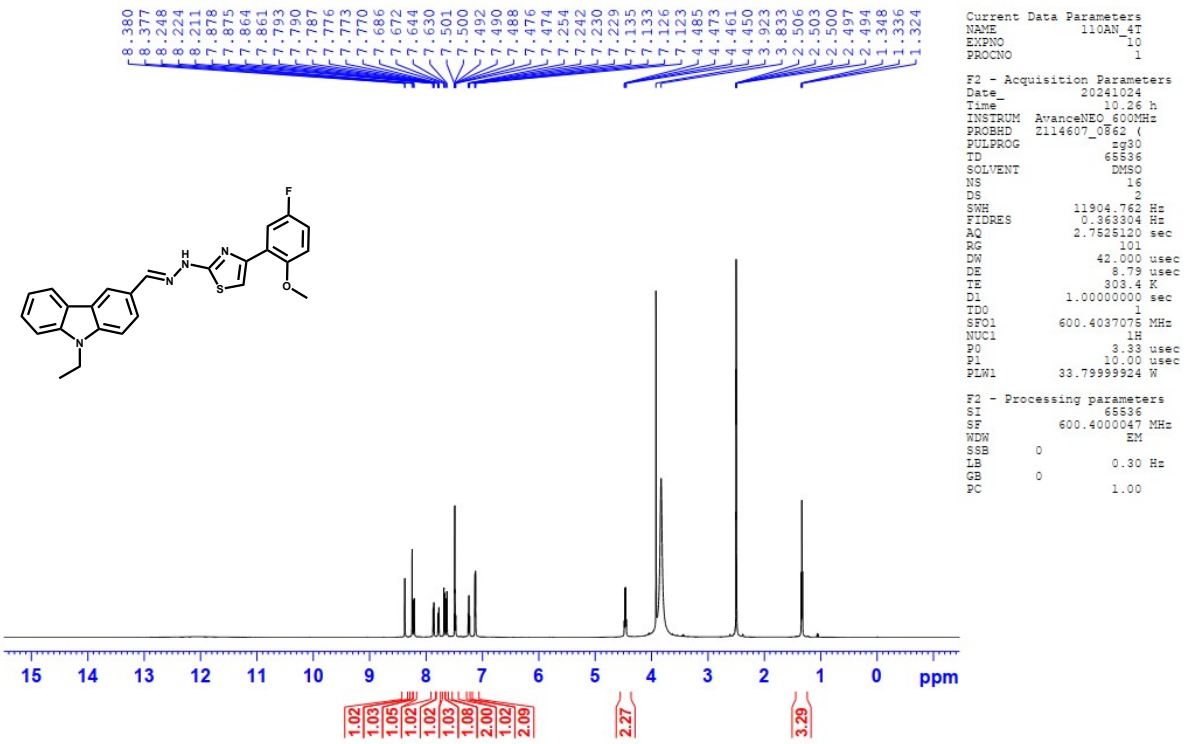


Fig. S 77. ^{1}H-NMR spectrum of compound **4q**.

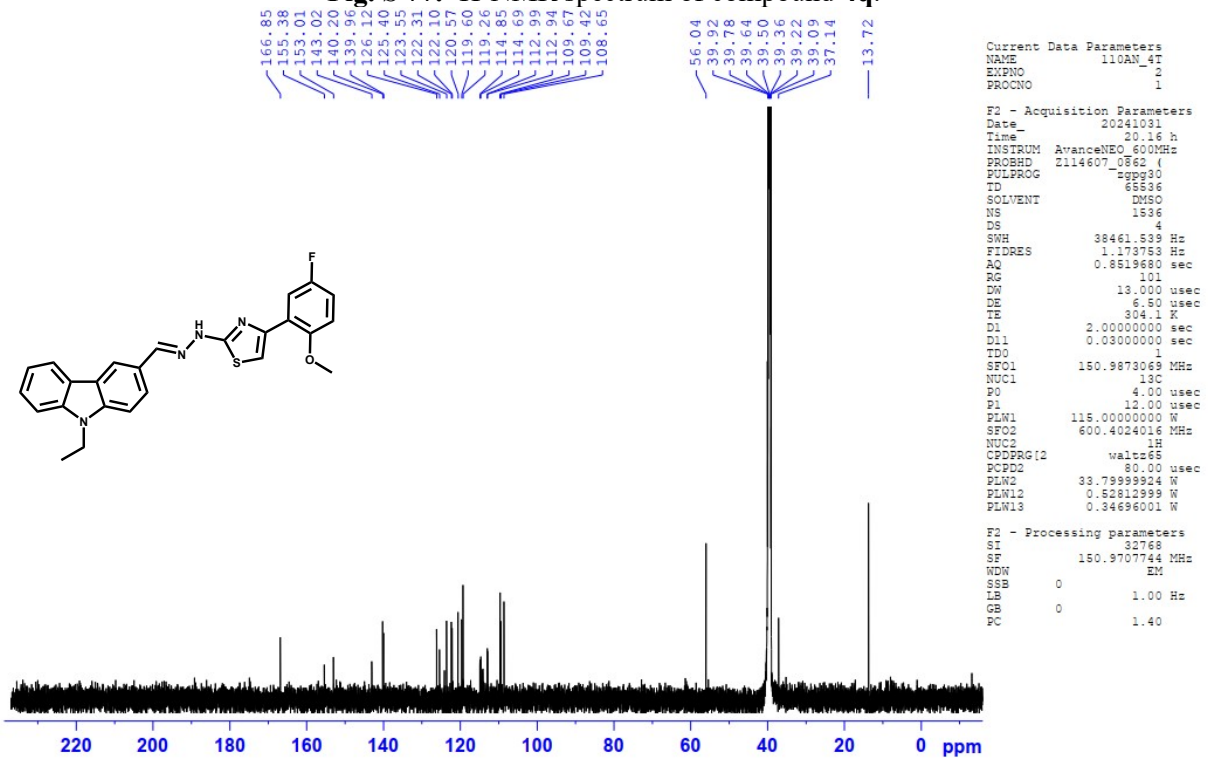


Fig. S 78. ^{13}C-NMR spectrum of compound **4q**.

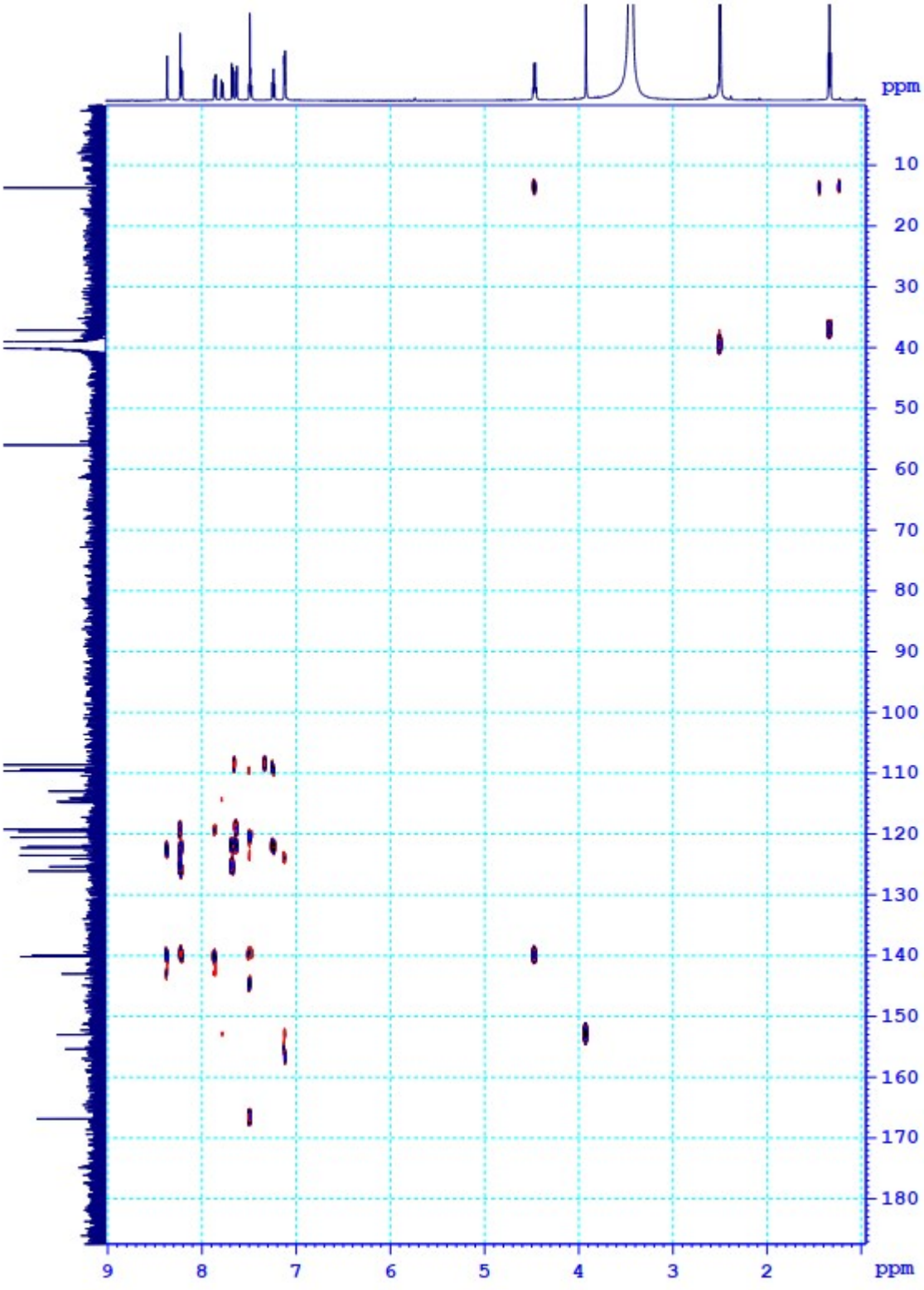


Fig. S 79. HMBC spectrum of compound **4q**.

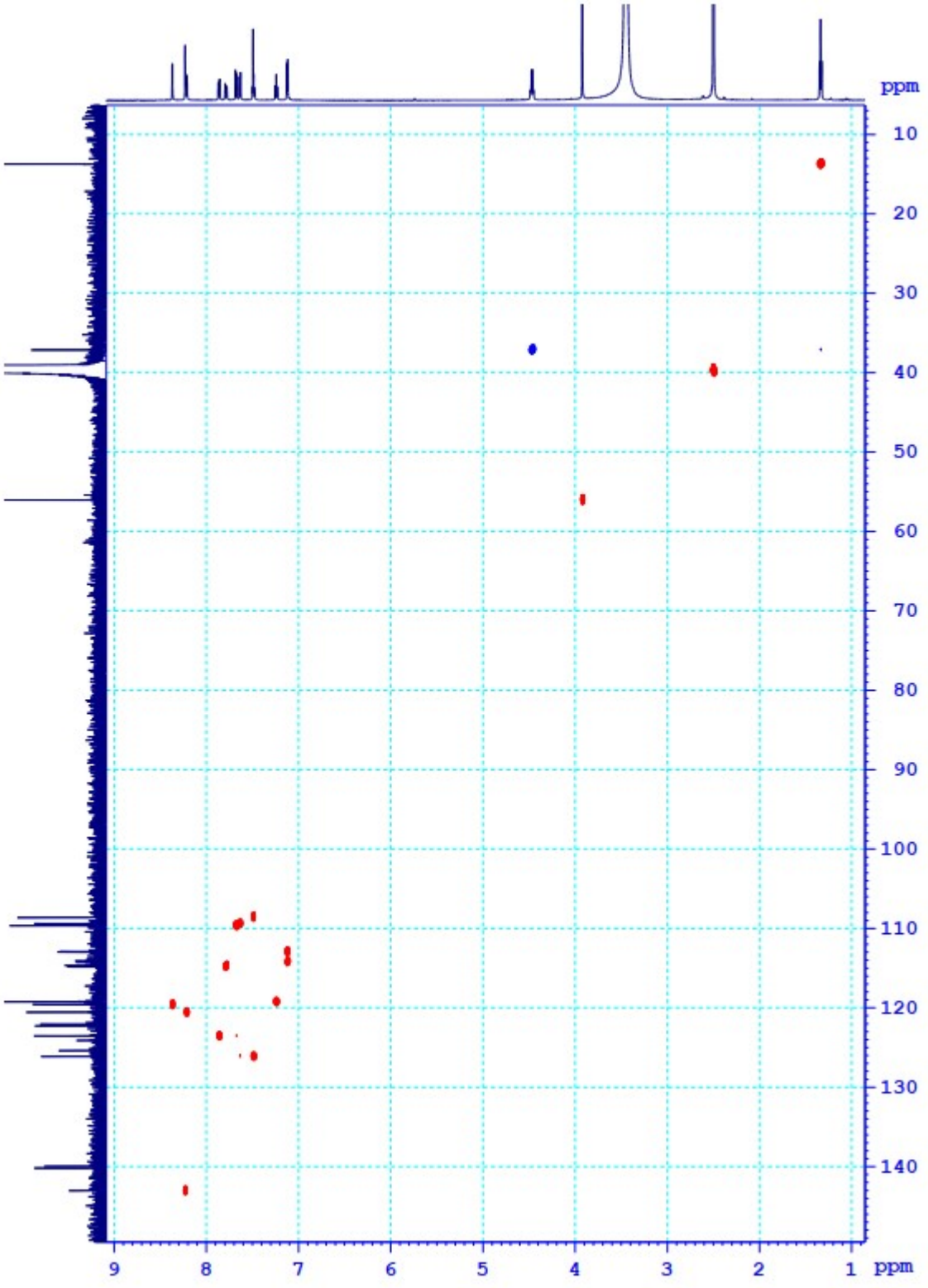


Fig. S 80. HSQC spectrum of compound **4q**.

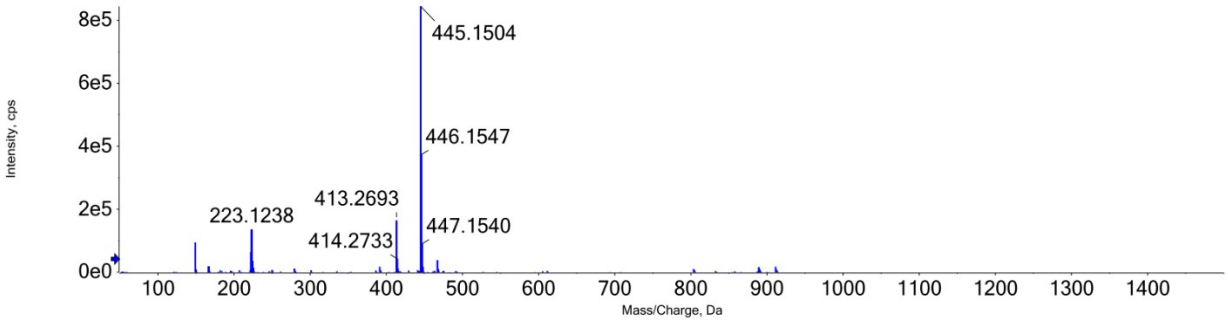


Fig. S 81. HR-MS spectrum of compound **4q**.

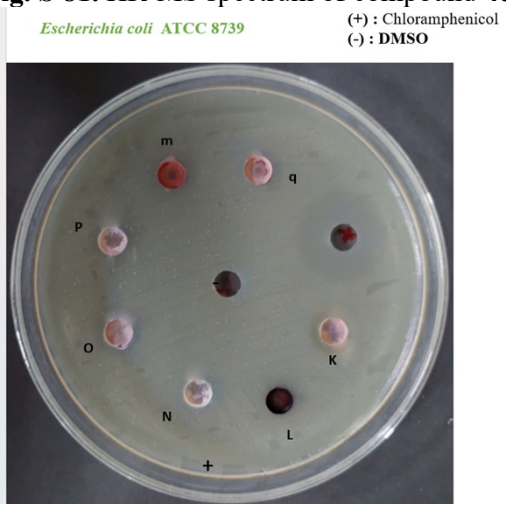


Fig. S 82. Antibacterial activity of compounds against *E.Coli* on agar plates

Fig. S 83. Antibacterial activity of compounds against *S.Aureus* on agar plates

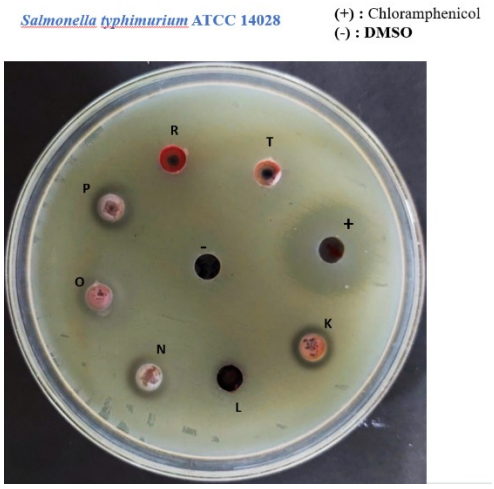


Fig. S 84. Antibacterial activity of compounds against *S.typhimurium* on agar plates

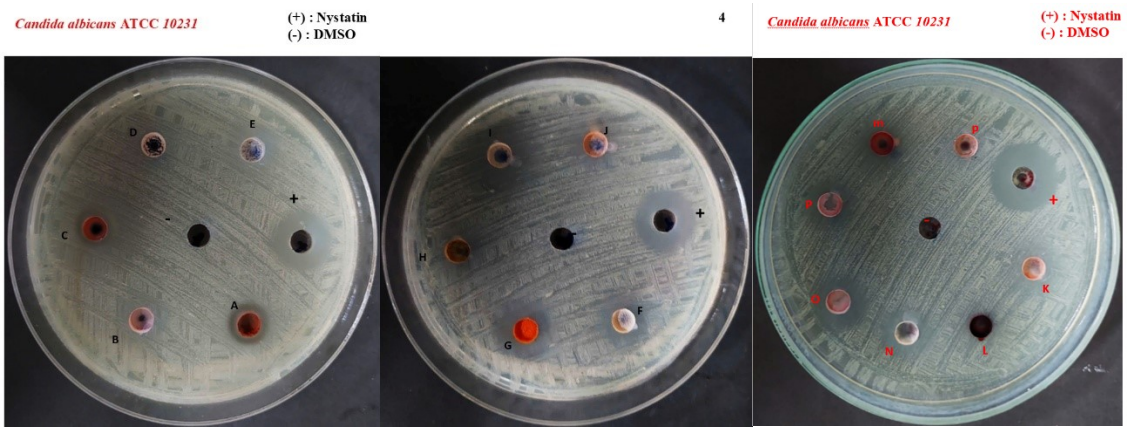


Fig. S 85. Antibacterial activity of compounds against *C.albicans* on agar plates

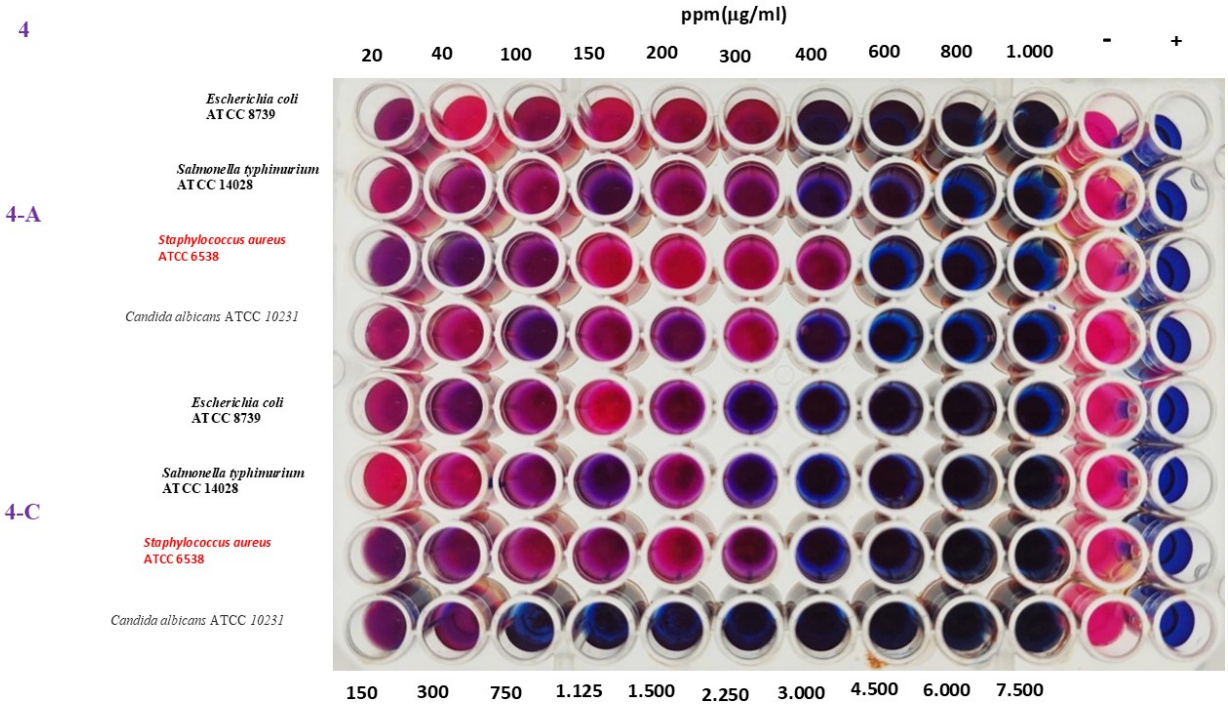


Fig. S 86. Antibacterial MIC measurement test of compounds **4a** and **4c**

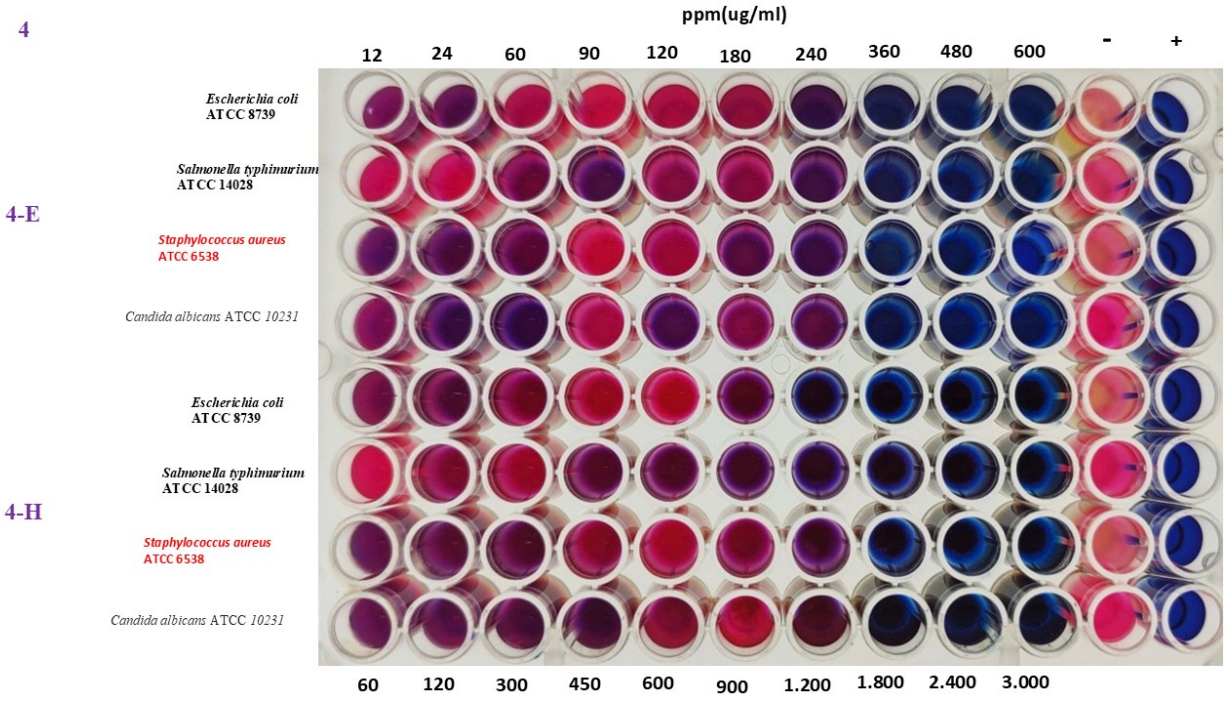


Fig. S 87. Antibacterial MIC measurement test of compounds **4e** and **4h**

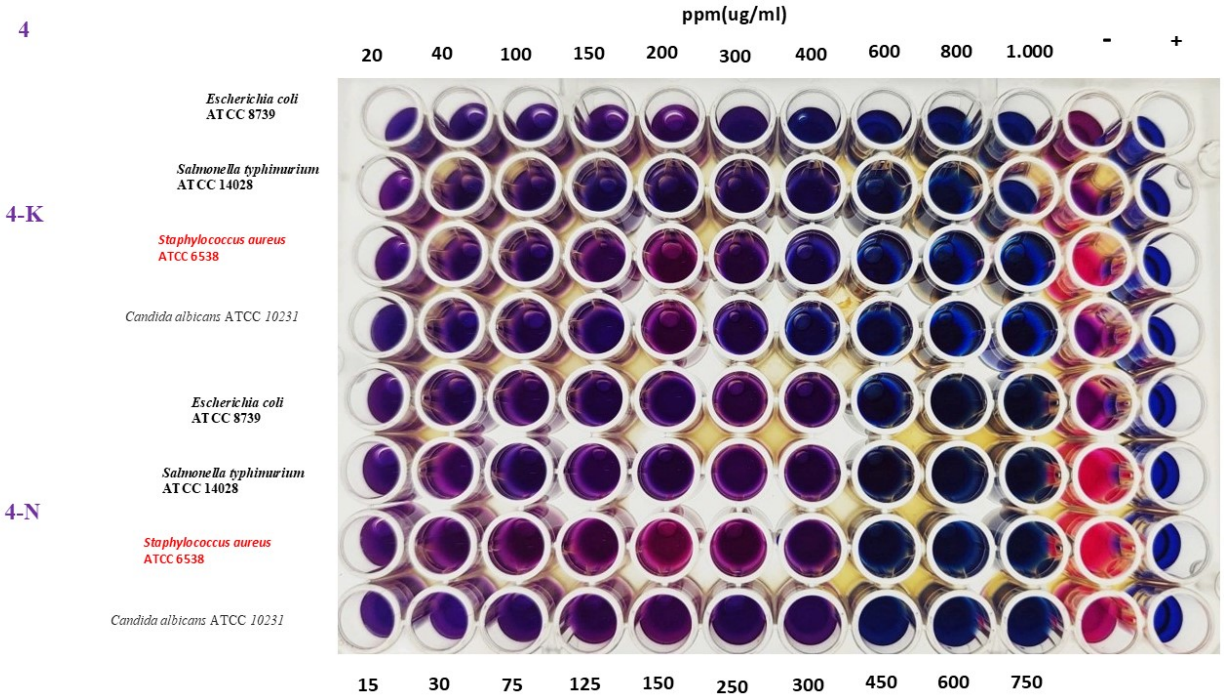


Fig. S 88. Antibacterial MIC measurement test of compounds **4k** and **4n**

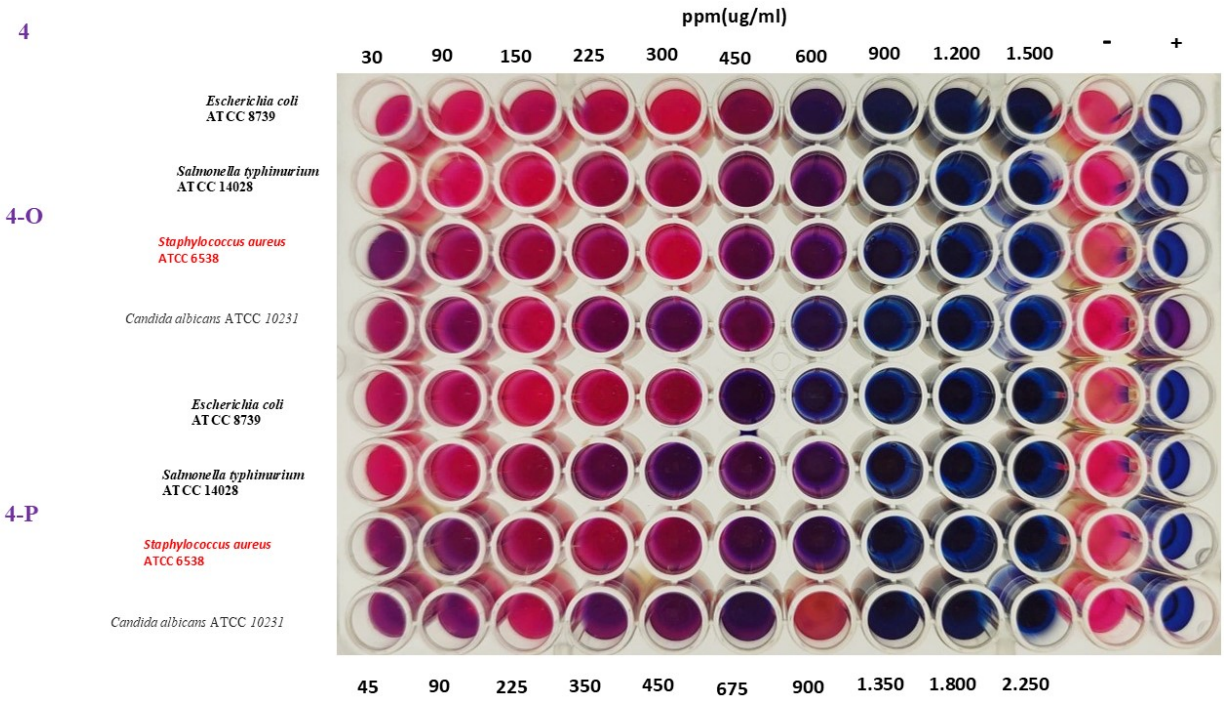


Fig. S 89. Antibacterial MIC measurement test of compounds **4o** and **4p**

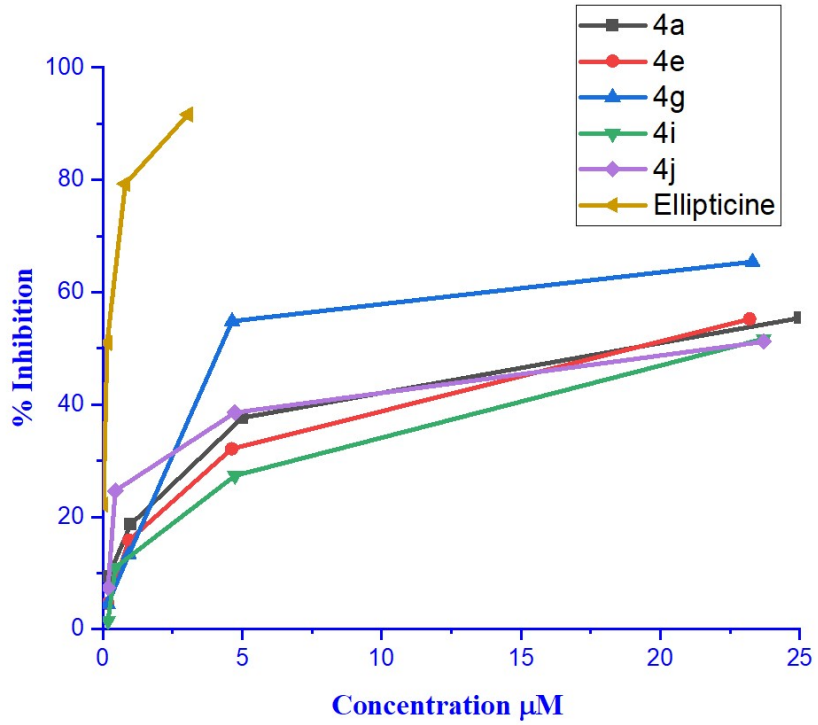


Fig. S 90. Inhibitory effects of active compounds and Ellipticine on cancer cells with MCF-7

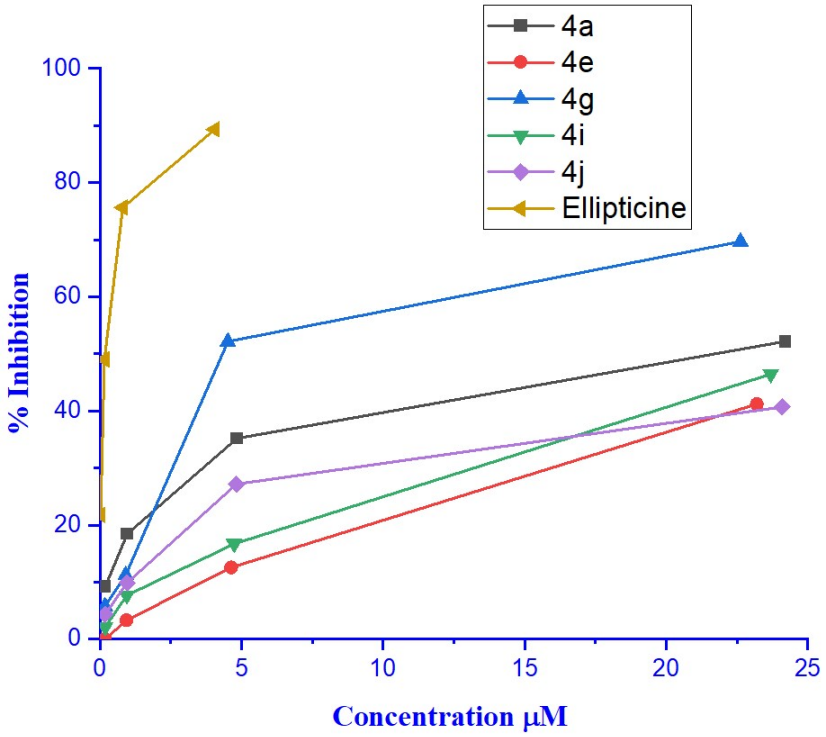


Fig. S 91. Inhibitory effects of active compounds and Ellipticine on cancer cells with A549

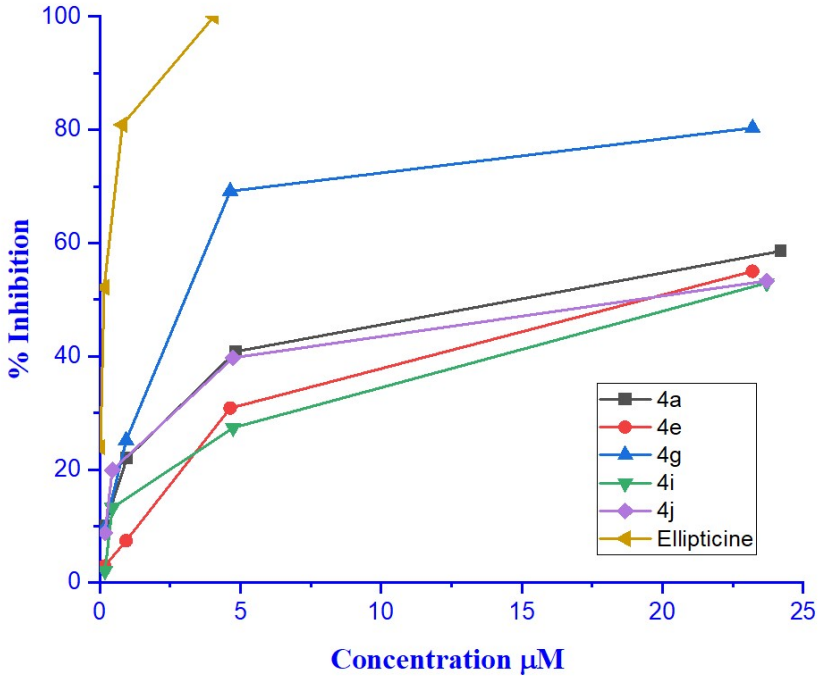


Fig. S 92. Inhibitory effects of active compounds and Ellipticine on cancer cells with HepG2

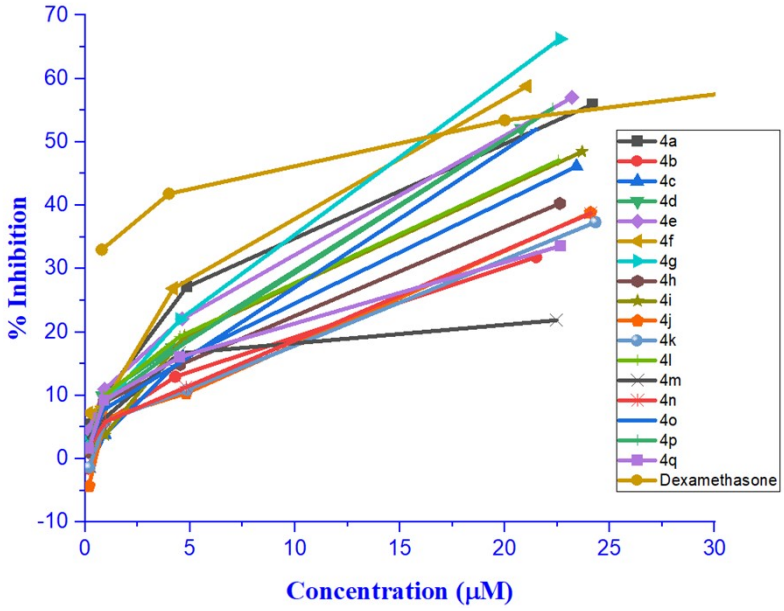


Fig. S 93. Anti-inflammatory inhibitory ability of active compounds and Dexamethasone.

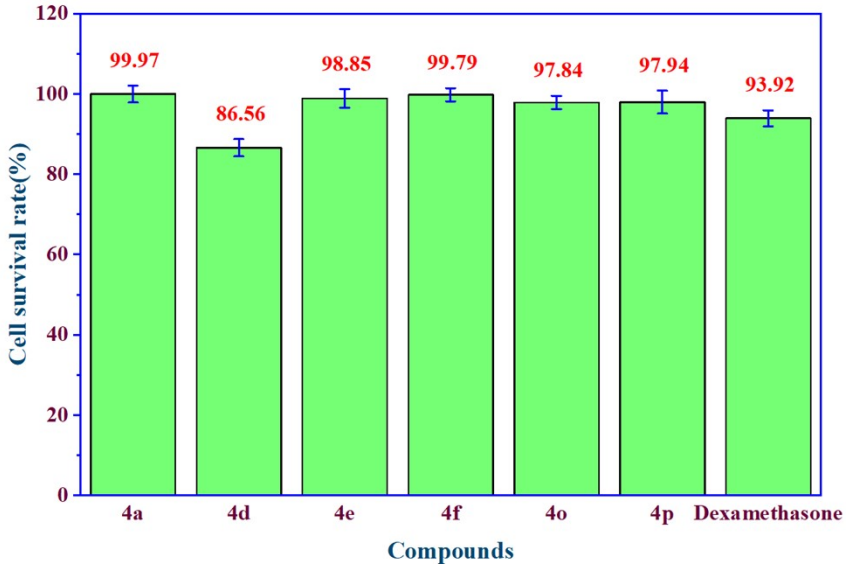


Fig. S 94. The cell viability rate at the maximum concentration in the anti-inflammatory chemical analysis of compounds attained the IC_{50}.

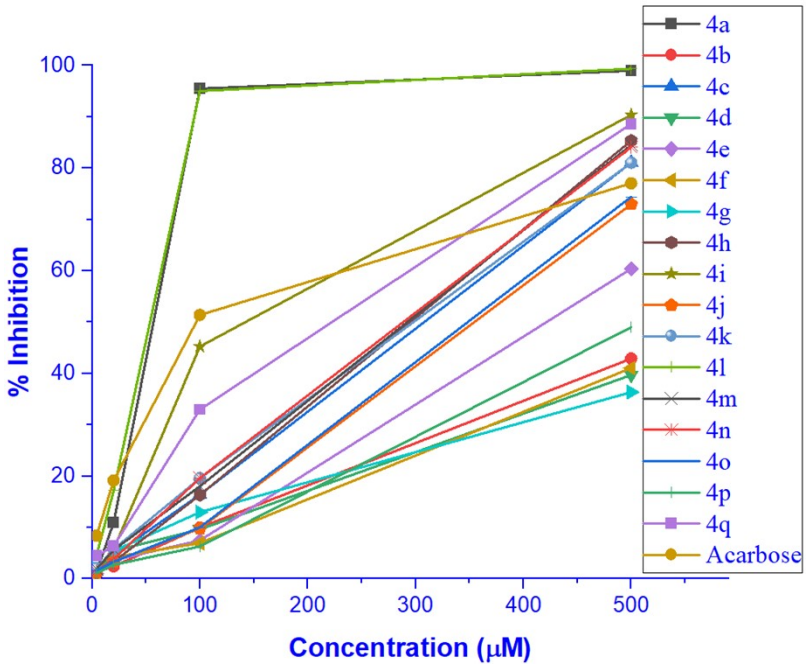


Fig. S 95. Inhibitory ability of the glucosidase enzymes of active compounds and Arcarbose

Table S1. Physicochemical Chemistry of the compound **4l**

Property	***Value***	***Comment***
LogS	-7.57	Log of aqueous solubility (log mol/L); Optimal: -4 to 0.5
LogD	4.43	LogP at physiological pH 7.4; Optimal: 1–3
LogP	5.89	Octanol/water partition coefficient; Optimal ≤ 5
TPSA	98.34	Topological Polar Surface Area; Optimal: 0–140 Å²
MW	474.53	Molecular weight: Optimal: 100–600 Da

Property	*Value*	*Comment*
nHA	7	Number of hydrogen bond acceptors; Optimal: 0–12
nHD	2	Number of hydrogen bond donors; Optimal: 0–7
nRot	5	Number of rotatable bonds; Optimal: 0–11
nRing	4	Number of rings: Optimal: 0–6
Density	1.12	Density = MW/Volume

Table S2. Medical Chemistry of compound **4l**

Property	*Value*	*Comment*
QED	0.661	Quantitative Estimate of Drug-likeness; Attractive: >0.67
SAscore	3.15	Synthetic accessibility score; SAscore <6 = easy to synthesize
Fsp^3	0.22	Fraction of sp^3 hybridized carbons; $Fsp^3 \geq 0.42$ considered suitable
MCE-18	26.0	Medicinal chemistry evolution index; MCE-18 ≥ 45 considered suitable
NP-likeness	-1.10	Natural product-likeness score; Range: -5 to +5
Lipinski rule	Accepted	MW ≤ 500; logP ≤ 5; H-acc ≤ 10; H-don ≤ 5
Pfizer rule	Accepted	logP > 3; TPSA < 75; Compounds exceeding limits are likely toxic
GSK rule	Rejected	MW ≤ 400; logP ≤ 4; Compound does not satisfy GSK criteria
Golden Triangle	Accepted	200 ≤ MW ≤ 500; -2 ≤ logD ≤ 5; Favorable ADMET profile expected

Table S3. Absorption properties of compound **4l**

Property	*Value*	*Comment*
Caco-2-permeanbility	-4.97	Optimal: > -5.15 log unit
Pgp-inhibitor	0.137	Category 1: inhibitor; Category 0: non-inhibitor; Probability of being an inhibitor
Pgp-substrate	0.001	Category 1: substrate; Category 0: non-substrate; Very low probability
HIA	0.013	Human intestinal absorption; Optimal: > 0.3
F(20%)	0.968	Fraction absorbed ≥ 20%; high absorption probability
F(30%)	1.000	Fraction absorbed ≥ 30%; excellent absorption

Table S4. Distribution properties of compound **4l**

Property	*Value*	*Comment*
PPB	98.7%	Plasma protein binding; Optimal < 90%; high binding may

Property	*Value*	*Comment*
		reduce free drug level
VD	0.38	Volume of distribution (L/kg); Optimal range: 0.04–20
BBB penetration	0.152	Probability of crossing the blood–brain barrier
Fu	1.4%	Fraction unbound in plasma; Low: <5%; indicates strong plasma binding

Table S5. Metabolism properties of compound **4l**

Property	*Value*	*Comment*
CYP1A2 inhibitor	0.824	Category 1: inhibitor; compound may inhibit CYP1A2
CYP2C19 inhibitor	0.334	Category 1: inhibitor; moderate probability
CYP2C9 inhibitor	0.476	Category 1: inhibitor; possible CYP2C9 inhibition
CYP2D6 inhibitor	0.201	Category 0: non-inhibitor; unlikely to inhibit CYP2D6
CYP3A4 inhibitor	0.547	Category 1: inhibitor; potential CYP3A4 inhibition
CYP1A2 substrate	0.198	Category 0: non-substrate; unlikely to be metabolized by CYP1A2
CYP2C9 substrate	0.741	Category 1: substrate; likely to be metabolized by CYP2C9
CYP2D6 substrate	0.835	Category 1: substrate; likely to be metabolized by CYP2D6
CYP3A4 substrate	0.118	Category 0: non-substrate; not a substrate for CYP3A4

Table S6. Excretion properties of compound **4l**

Property	*Value*	*Comment*
CL	4.86	Clearance rate (mL/min/kg); Low: <5
$T_{1/2}$	0.69	Probability of long half-life; 0.5–1 indicates moderate half-life potential

Table S7. Toxicity properties of compound **4l**

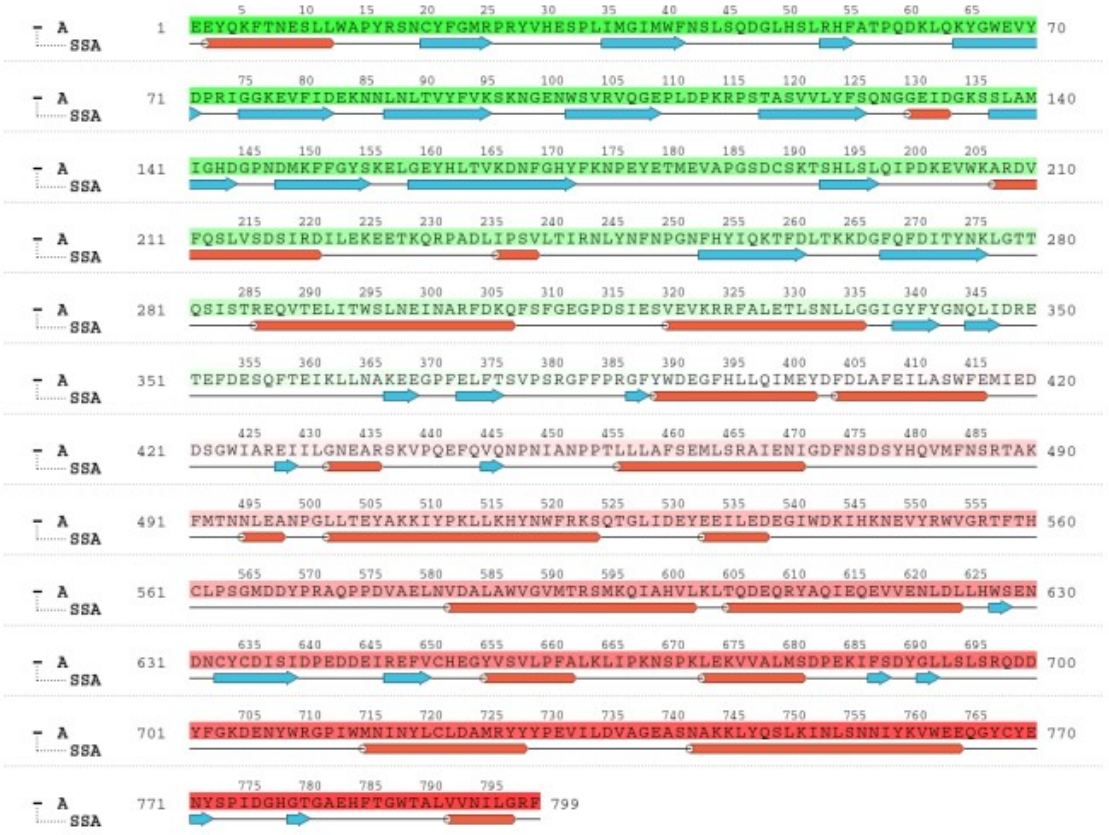
Property	*Value*	*Comment*
hERG blocker	0.062	Probability of cardiotoxicity; <0.3 = safe
H-HT	0.926	Human hepatotoxicity: high probability of liver toxicity
DILI	0.811	Drug-induced liver injury; compound at risk of liver toxicity
AMES toxicity	0.045	Ames mutagenicity test; non-mutagenic
FDAMDD	0.054	Maximum recommended daily dose (FDA); safe
Skin sensitization	0.489	Probability of skin sensitization: moderate
Carcinogenicity	0.567	Probability of carcinogenicity: moderate
Eye irritation	0.031	Probability of eye irritation: low
Respiratory	0.098	Probability of respiratory toxicity: low

Property	*Value*	*Comment*
Table S8. Toxicophoric alerts of compound **4l**		
Property	***Value***	***Comment***
Acute toxicity rule	0 alerts	No structural alerts for acute oral toxicity
Genotoxic carcinogenicity rule	2 alerts	Two substructures associated with genotoxic carcinogenicity
Skin sensitization rule	1 alerts	One structural alert for potential skin irritation
Aquatic toxicity rule	0 alerts	No alerts for aquatic toxicity
Non-biodegradable rule	0 alerts	Biodegradable; no non-biodegradability alerts detected

CPU #	Job Type	Ensemble	Temp. [K]	Sim. Time [ns]	# Atoms	# Waters	Charge
1	mdsim	NPT	300.0	100.102	63649	16882	0

Protein Information

Tot. Residues	Prot. Chain(s)	Res. in Chain(s)	# Atoms	# Heavy Atoms	Charge
799	'A'	ict_values([799]	12813	6547	-42



Ligand Information

SMILES	c1cccc(c1c23)n(CC)c2ccc(c3)/C=N/N=c(\[nH]4)scc4-c(c5)ccc(O)c5CO

Fig. S 96. Information protein 4J5T and ligand (pose 612 of compound **4l**)

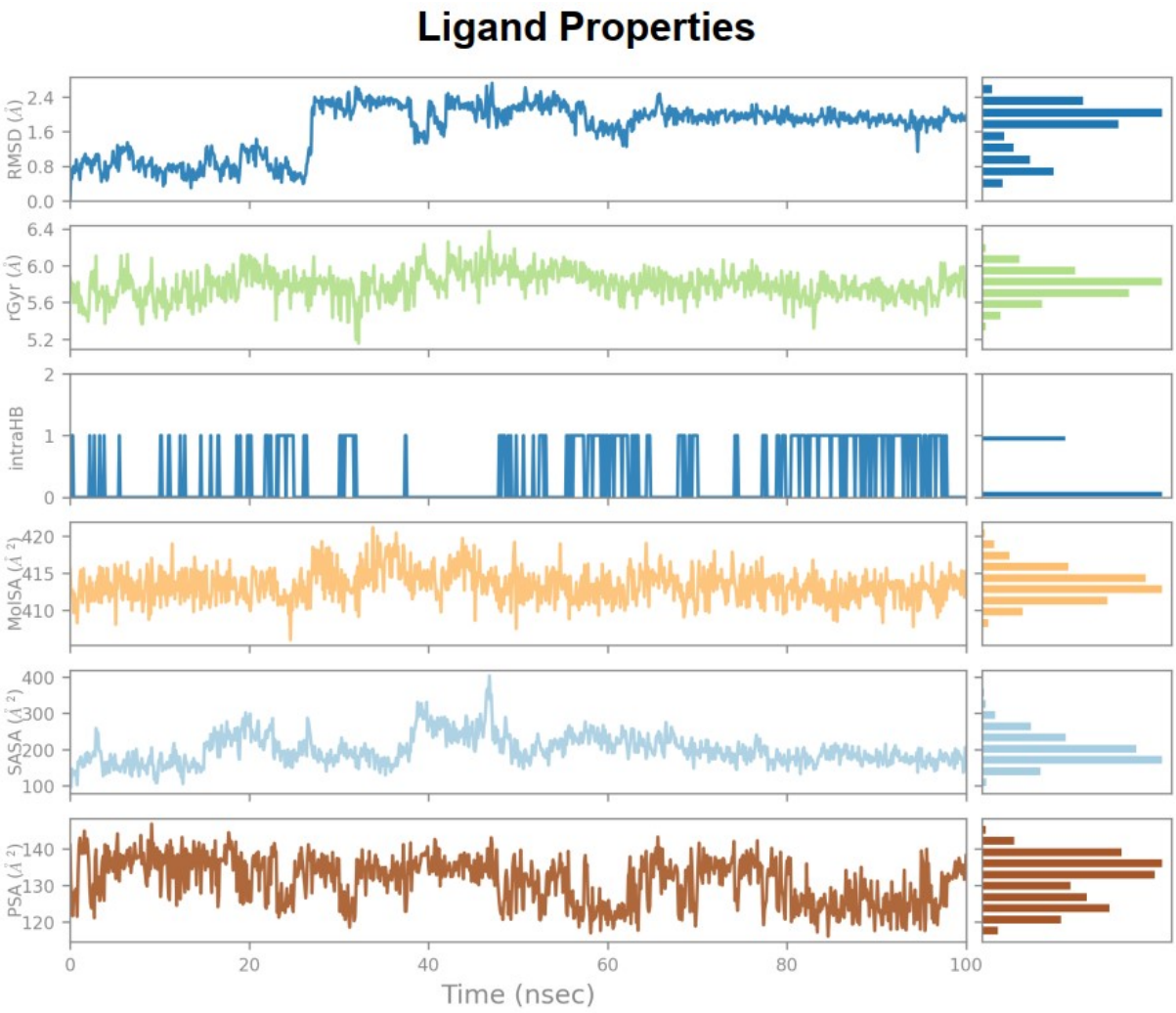


Fig. S 97. Ligand (pose 612 of compound **4l**) properties

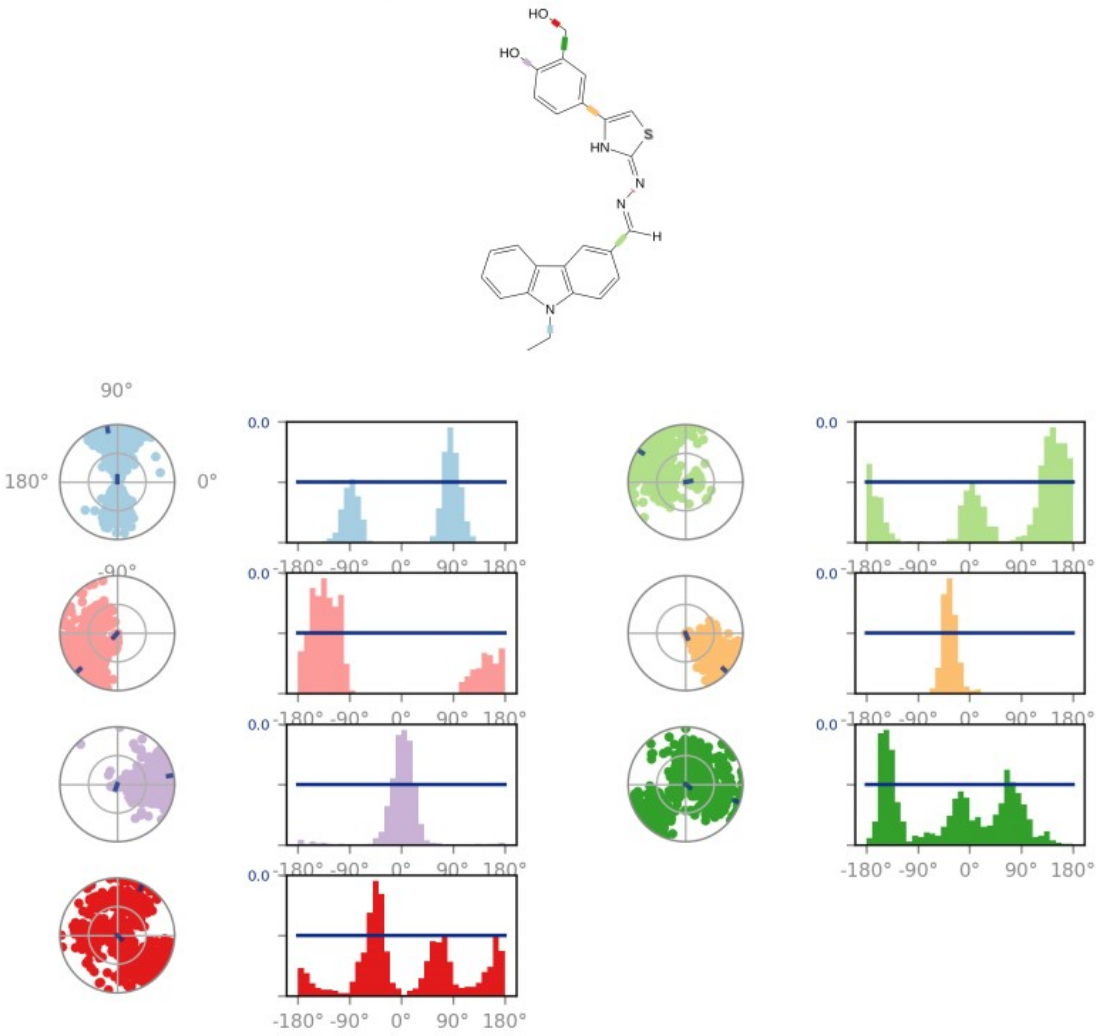


Fig. S 98. Ligand (pose 612 of compound **4l**) Torsion Profile

Fig. S 99. Protein (4J5T) Secondary Structure

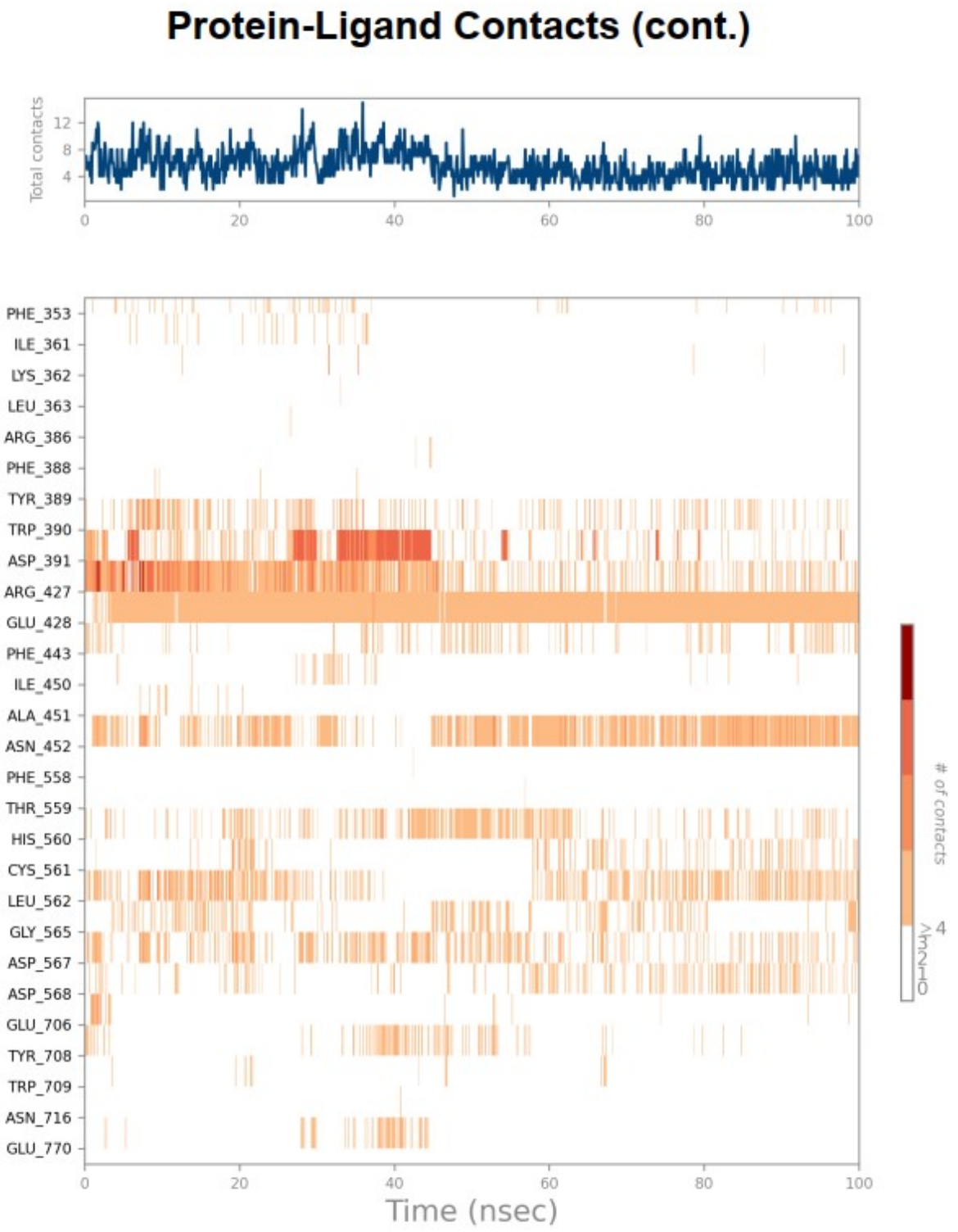


Fig. S 100. Protein – Ligand contact

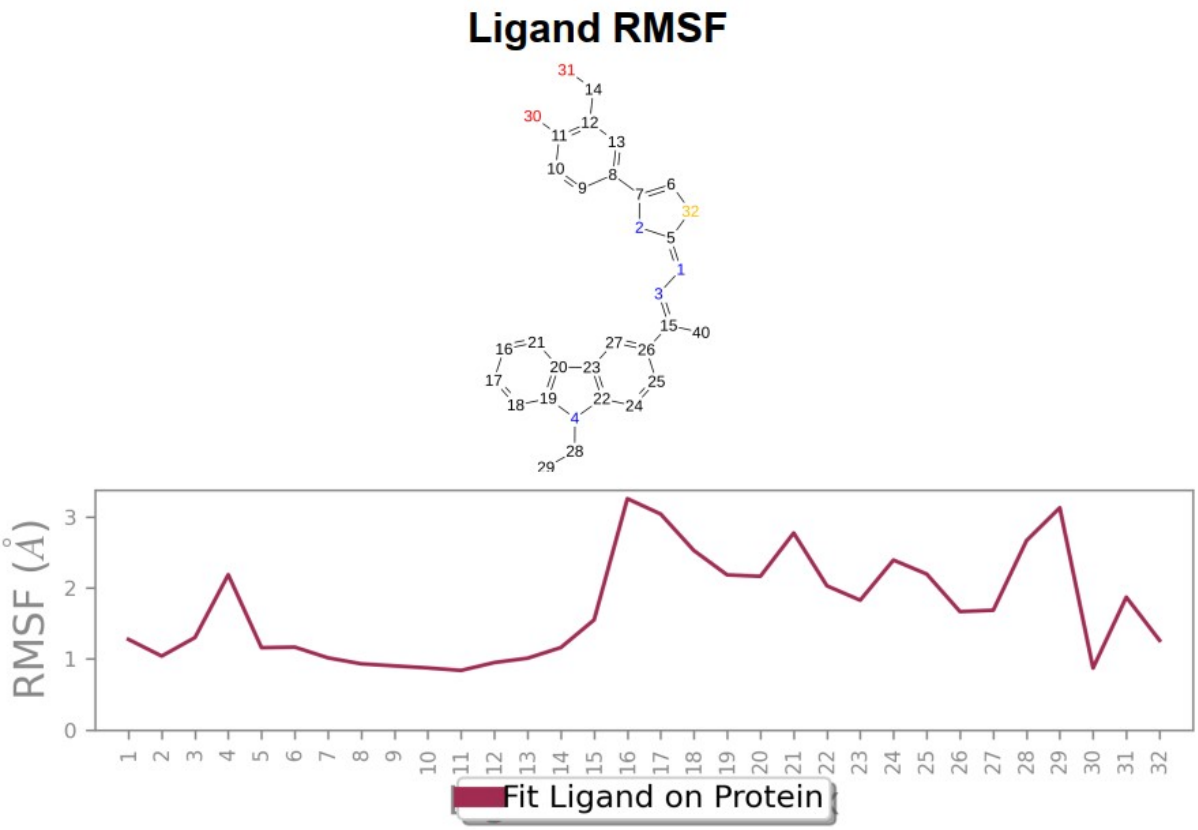
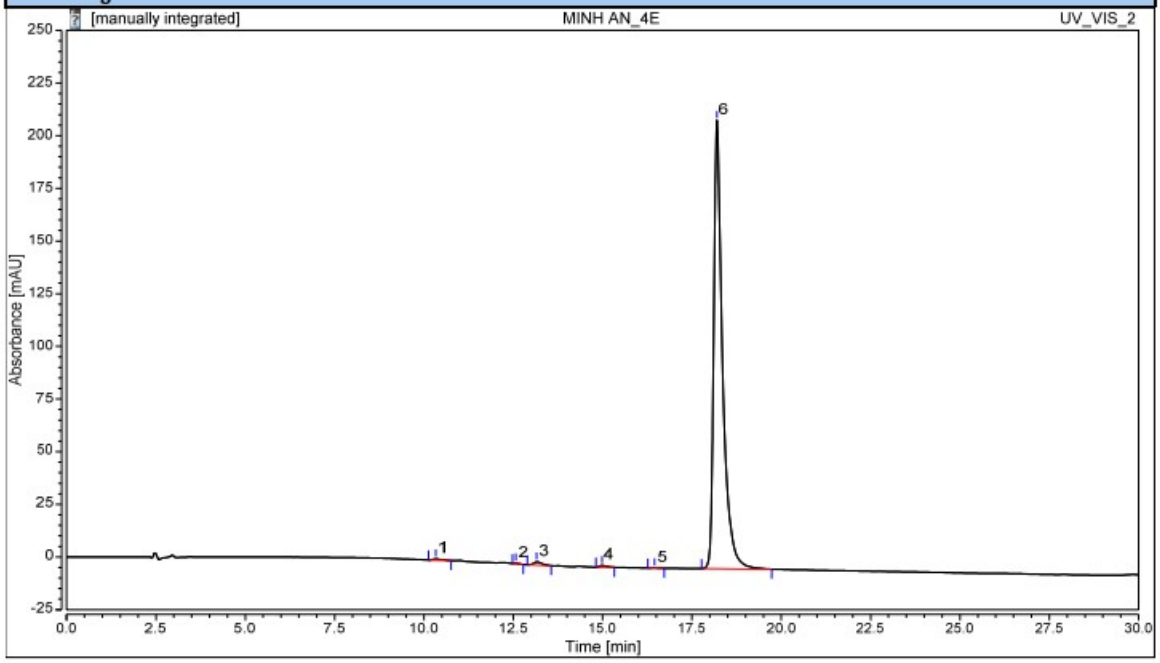


Fig. S 101. RMSF Ligand (pose 612 of compound **4l**)

Injection Details

Injection Name:	**MINH AN_4E**	*Run Time (min):*	**30**
Vial Number:	**GE4**	*Injection Volume:*	**2.00**
Injection Type:	**Unknown**	*Channel:*	**UV_VIS_2**
Calibration Level:		*Wavelength:*	**254**
Instrument Method:	**TEST**	*Bandwidth:*	**4**
Processing Method:	**NATPRO**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**25/Dec/25 13:06**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

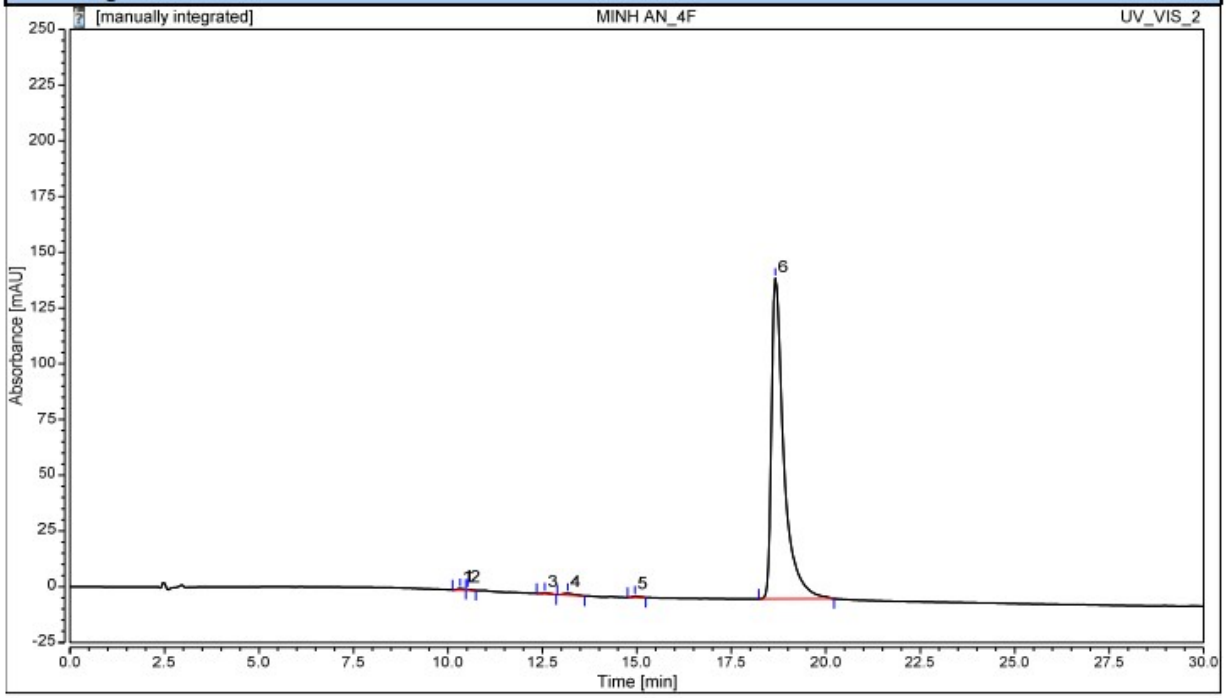
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		10.333	0.178	0.614	0.29	0.28	n.a.
2		12.573	0.044	0.358	0.07	0.17	n.a.
3		13.150	0.400	1.488	0.65	0.69	n.a.
4		14.983	0.183	0.831	0.30	0.38	n.a.
5		16.453	0.032	0.155	0.05	0.07	n.a.
6		18.197	60.619	212.812	98.64	98.41	n.a.
Total:			**61.457**	**216.257**	**100.00**	**100.00**	

Fig. S102. HPLC of compound **4e**.

Injection Details

Injection Name:	**MINH AN_4F**	*Run Time (min):*	**30**
Vial Number:	**GE3**	*Injection Volume:*	**2.00**
Injection Type:	**Unknown**	*Channel:*	**UV_VIS_2**
Calibration Level:		*Wavelength:*	**254**
Instrument Method:	**TEST**	*Bandwidth:*	**4**
Processing Method:	**NATPRO**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**25/Dec/25 12:29**	*Sample Weight:*	**1.0000**

Chromatogram



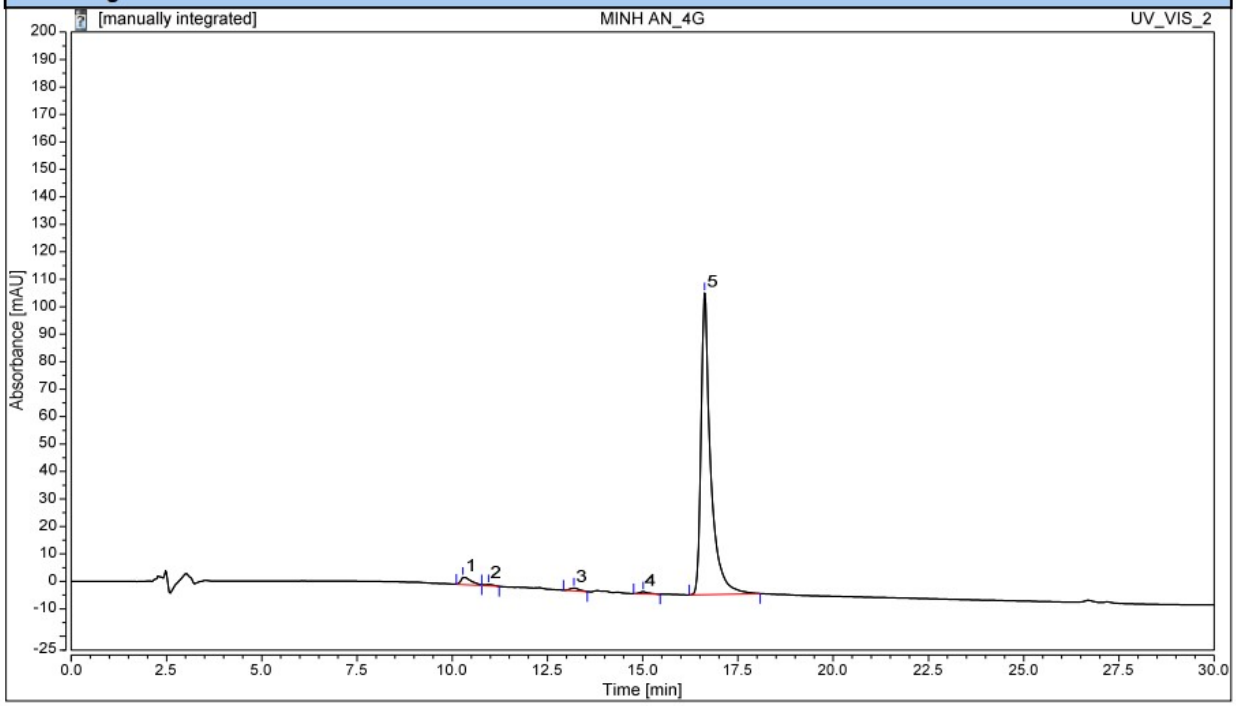
Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		10.320	0.134	0.648	0.24	0.44	n.a.
2		10.523	0.067	0.421	0.12	0.29	n.a.
3		12.563	0.118	0.558	0.21	0.38	n.a.
4		13.170	0.283	0.804	0.51	0.55	n.a.
5		14.947	0.138	0.674	0.25	0.46	n.a.
6		18.667	54.610	143.890	98.66	97.89	n.a.
Total:			**55.350**	**146.993**	**100.00**	**100.00**	

Fig. S103. HPLC of compound **4f**.

Injection Details			
Injection Name:	**MINH AN_4G**	*Run Time (min):*	**30**
Vial Number:	**GE5**	*Injection Volume:*	**2.00**
Injection Type:	**Unknown**	*Channel:*	**UV_VIS_2**
Calibration Level:		*Wavelength:*	**254**
Instrument Method:	**TEST**	*Bandwidth:*	**4**
Processing Method:	**NATPRO**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**25/Dec/25 15:38**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

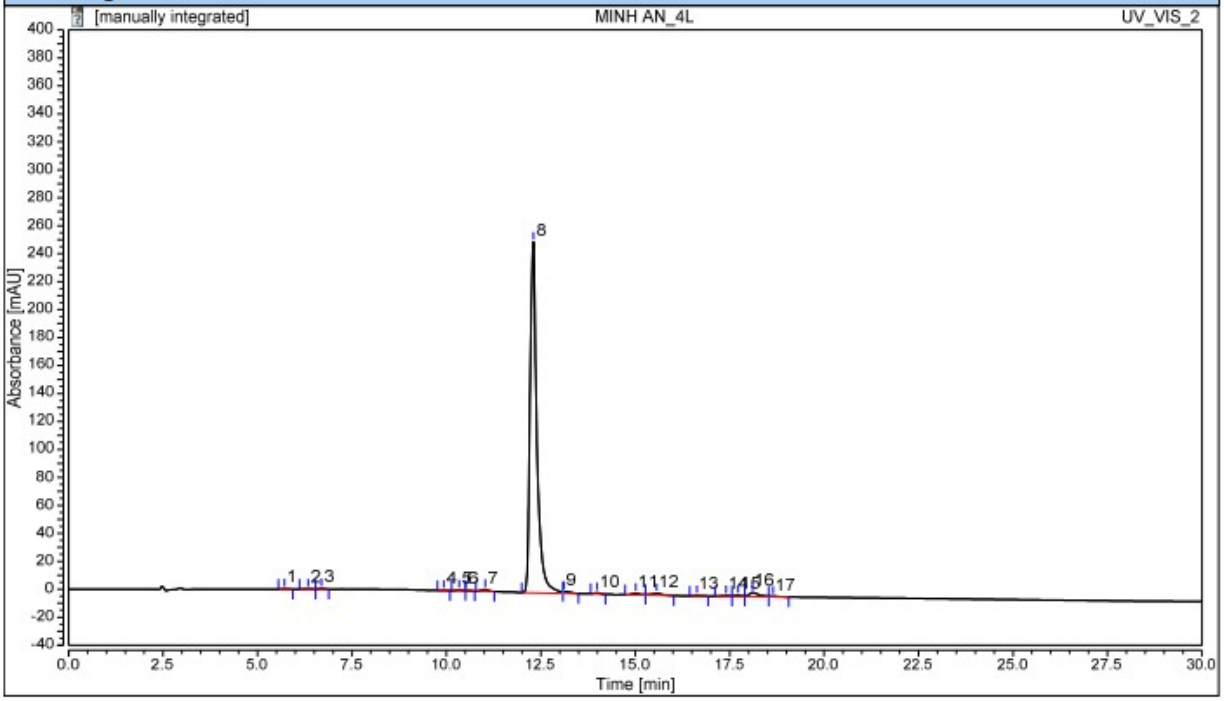
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		10.280	0.856	2.612	2.54	2.28	n.a.
2		10.953	0.130	0.416	0.39	0.36	n.a.
3		13.197	0.278	0.959	0.82	0.84	n.a.
4		15.010	0.205	0.794	0.61	0.69	n.a.
5		16.627	32.266	109.886	95.64	95.83	n.a.
Total:			**33.736**	**114.667**	**100.00**	**100.00**	

Fig. S104. HPLC of compound **4g**.

Injection Details

Injection Name:	**MINH AN_4L**	*Run Time (min):*	**30**
Vial Number:	**GE2**	*Injection Volume:*	**2.00**
Injection Type:	**Unknown**	*Channel:*	**UV_VIS_2**
Calibration Level:		*Wavelength:*	**254**
Instrument Method:	**TEST**	*Bandwidth:*	**4**
Processing Method:	**NATPRO**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**25/Dec/25 14:22**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		5.713	0.027	0.184	0.05	0.07	n.a.
2		6.340	0.029	0.124	0.05	0.05	n.a.
3		6.690	0.059	0.409	0.11	0.16	n.a.
4		9.930	0.037	0.232	0.07	0.09	n.a.
5		10.340	0.117	0.562	0.21	0.21	n.a.
6		10.510	0.044	0.235	0.08	0.09	n.a.
7		11.030	0.269	1.320	0.49	0.50	n.a.
8		12.300	52.316	250.875	94.37	95.15	n.a.
9		13.113	0.306	1.310	0.55	0.50	n.a.
10		13.990	0.150	0.879	0.27	0.33	n.a.
11		15.010	0.289	1.158	0.52	0.44	n.a.
12		15.563	0.454	1.327	0.82	0.50	n.a.
13		16.630	0.070	0.357	0.13	0.14	n.a.
14		17.403	0.104	0.476	0.19	0.18	n.a.
15		17.723	0.181	0.843	0.33	0.32	n.a.
16		18.107	0.868	2.916	1.57	1.11	n.a.
17		18.650	0.116	0.450	0.21	0.17	n.a.
Total:			**55.434**	**263.656**	**100.00**	**100.00**	

Fig. S105. HPLC of compound **4l**.

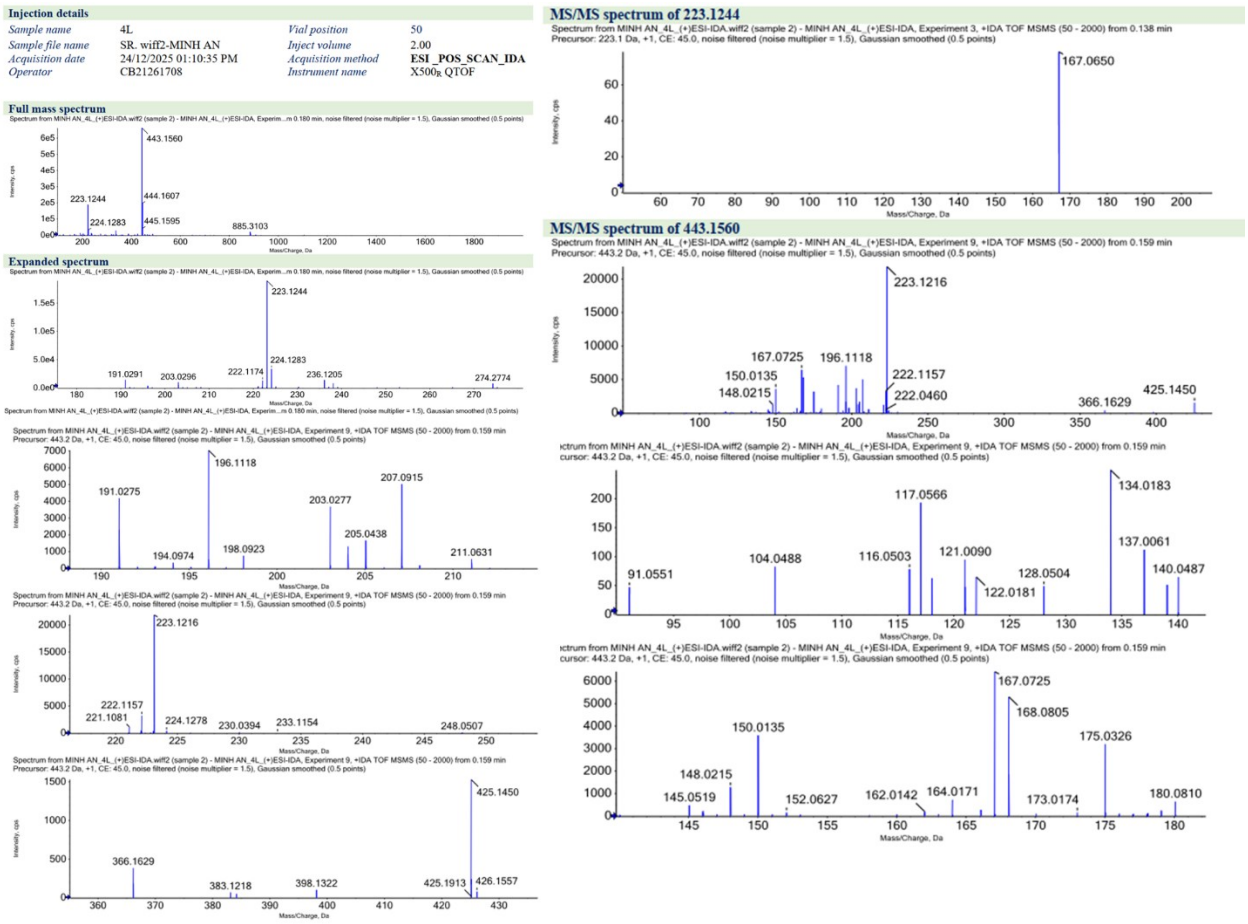


Fig. S106. MS/MS of compound **4l**.