

Synthesis and Biological Evaluation of 2,2-Dimethylbenzopyran Derivatives as Potent Neuroprotection Agents

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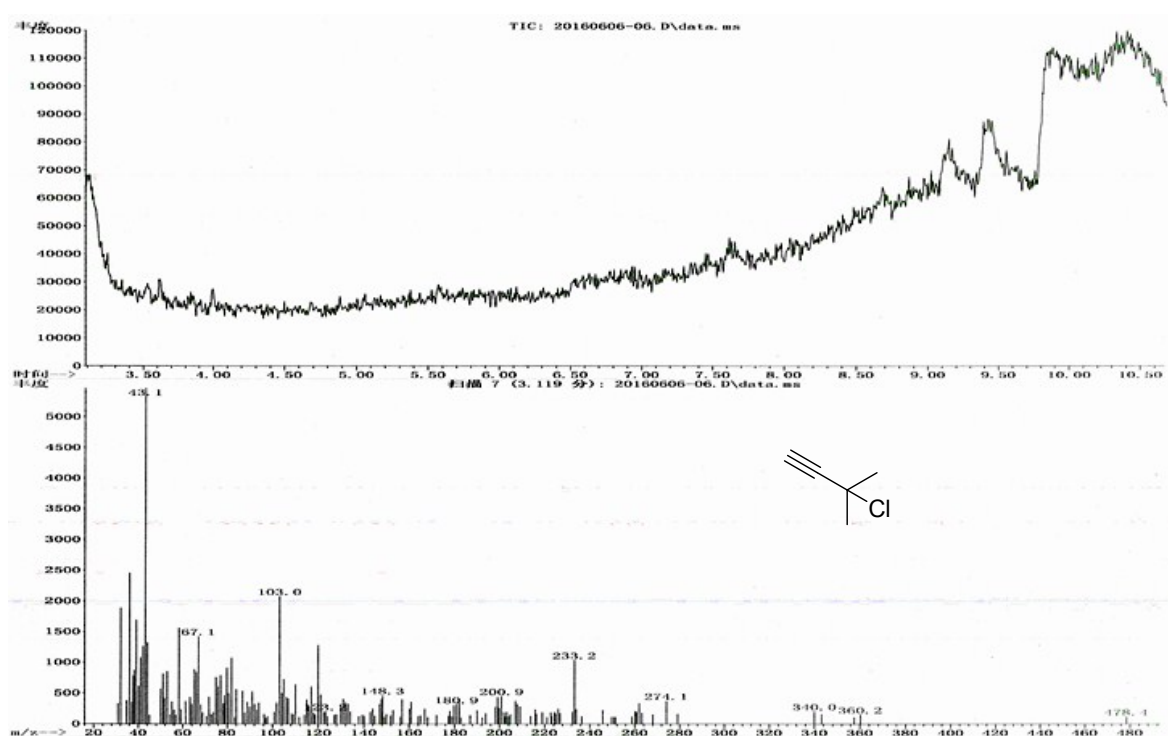
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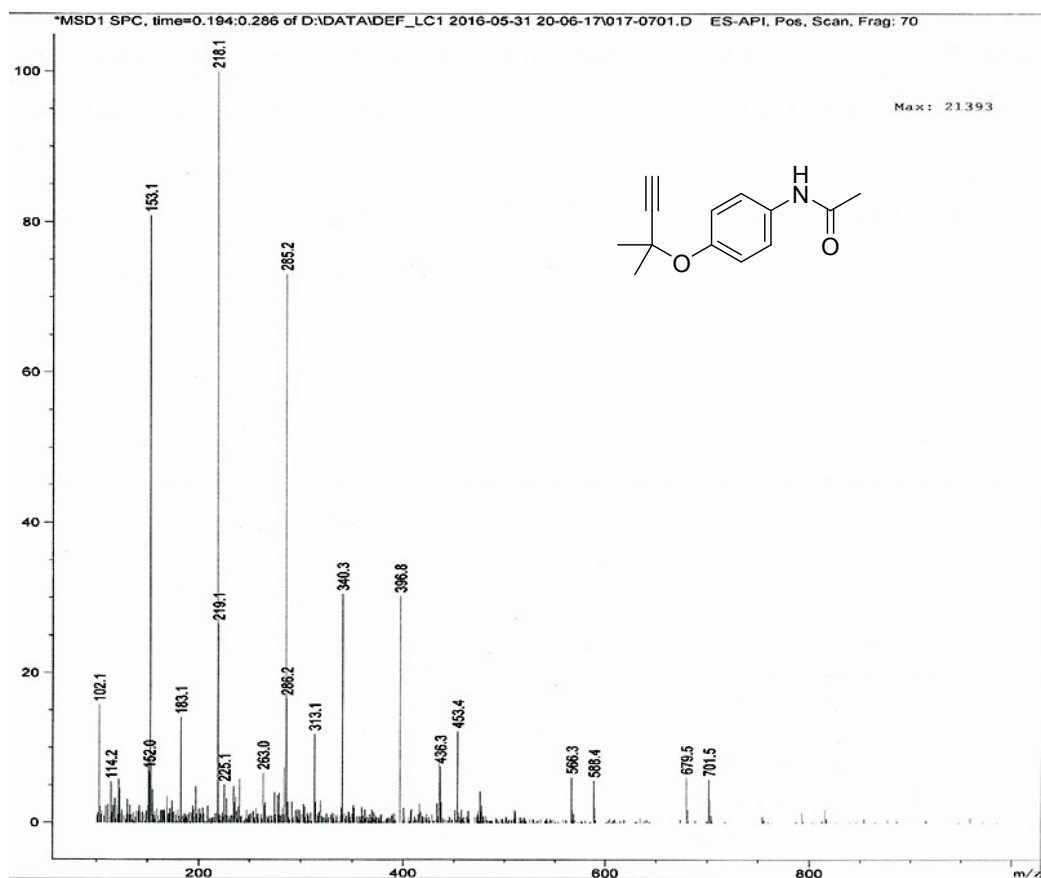
1. General procedures

All reagents used were commercially available. All the ^1H -NMR and ^{13}C -NMR spectra were recorded on a Bruker 400 MHz and 600 MHz spectrometer in $\text{DMSO}-d_6$. Chemical shifts (δ) were expressed in parts per million using tetramethylsilane as an internal reference. ESI-MS data were obtained using an Agilent 1100 instrument. LC-MS-ESI was recorded by Agilent 1100 Series MSD Trap (SL). GC-MS-ESI was recorded by Agilent 6890-5975 GC-MS. Melting points were measured on X-4 digital melting point instrument. The purity was determined by Shimadzu LC-2010AHT high performance liquid chromatography. Reactions were monitored by thin-layer chromatography (TLC) and visualized by UV-light. Column chromatography was performed on silica gel (160-200 mesh).

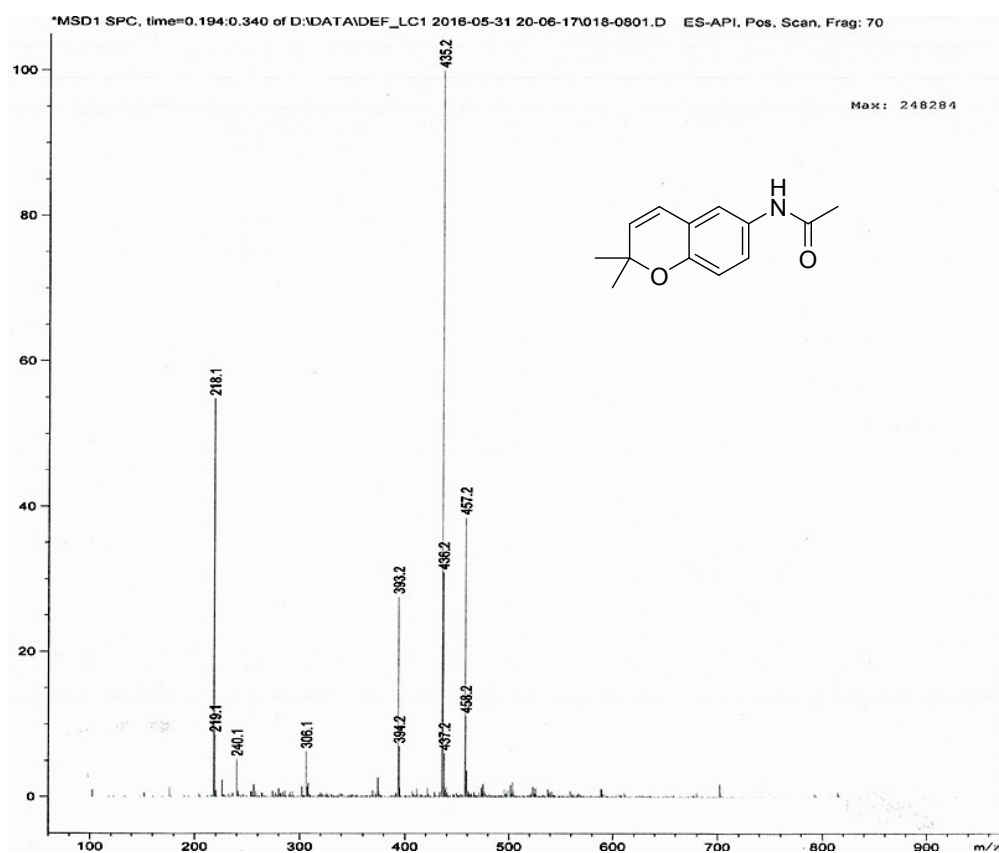
2. GC-MS spectrum of 3-Chloro-3-methylbut-1-yne (3)



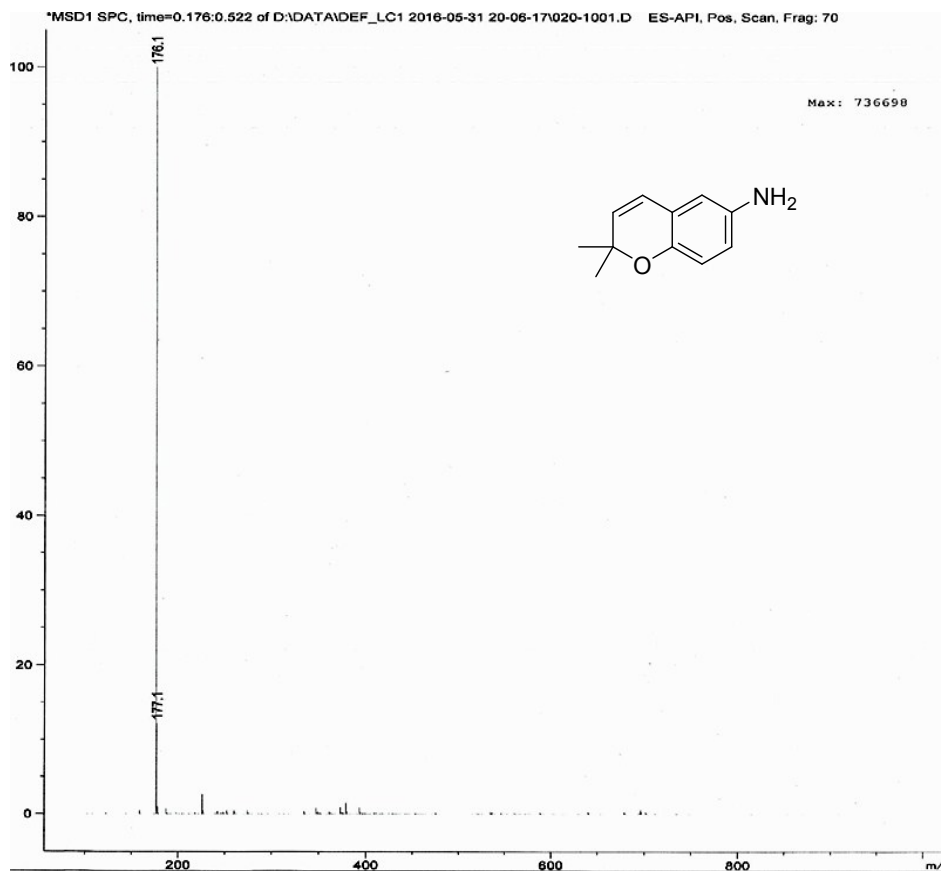
3. LC-MS spectrum of *N*-(4-((2-methylbut-3-yn-2-yl)oxy)phenyl)acetamide (7)



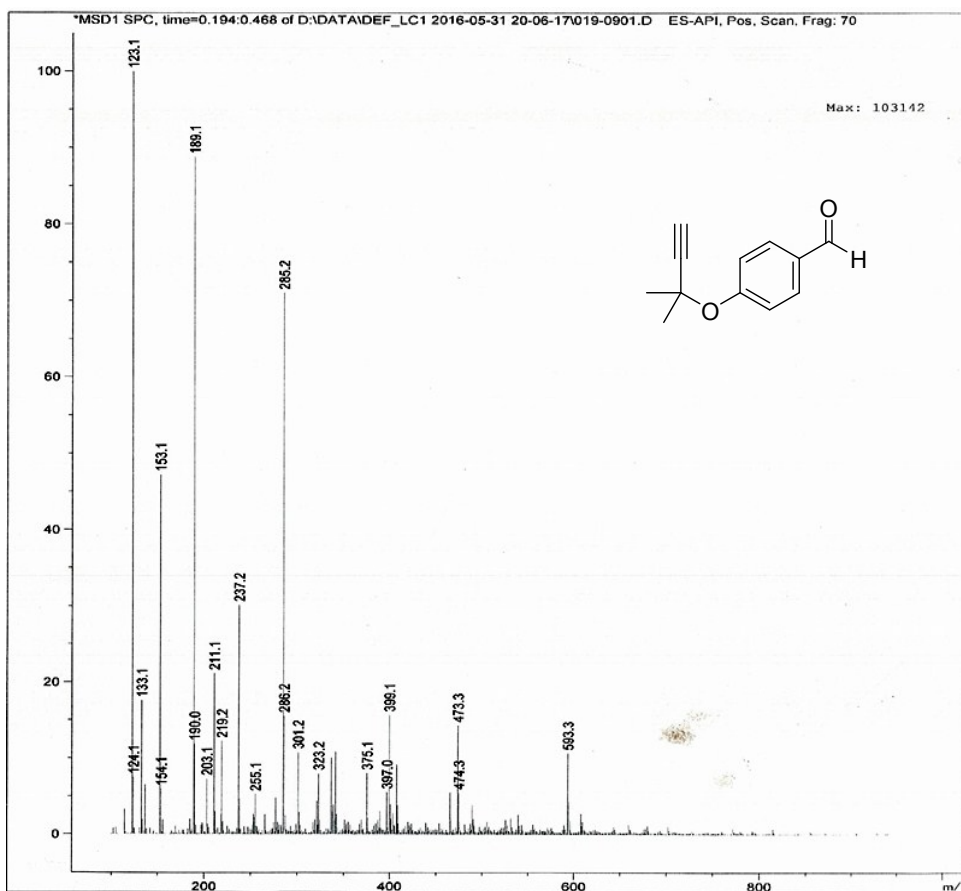
4. LC-MS spectrum of *N*-(2,2-dimethyl-2H-chromen-6-yl)acetamide (8)



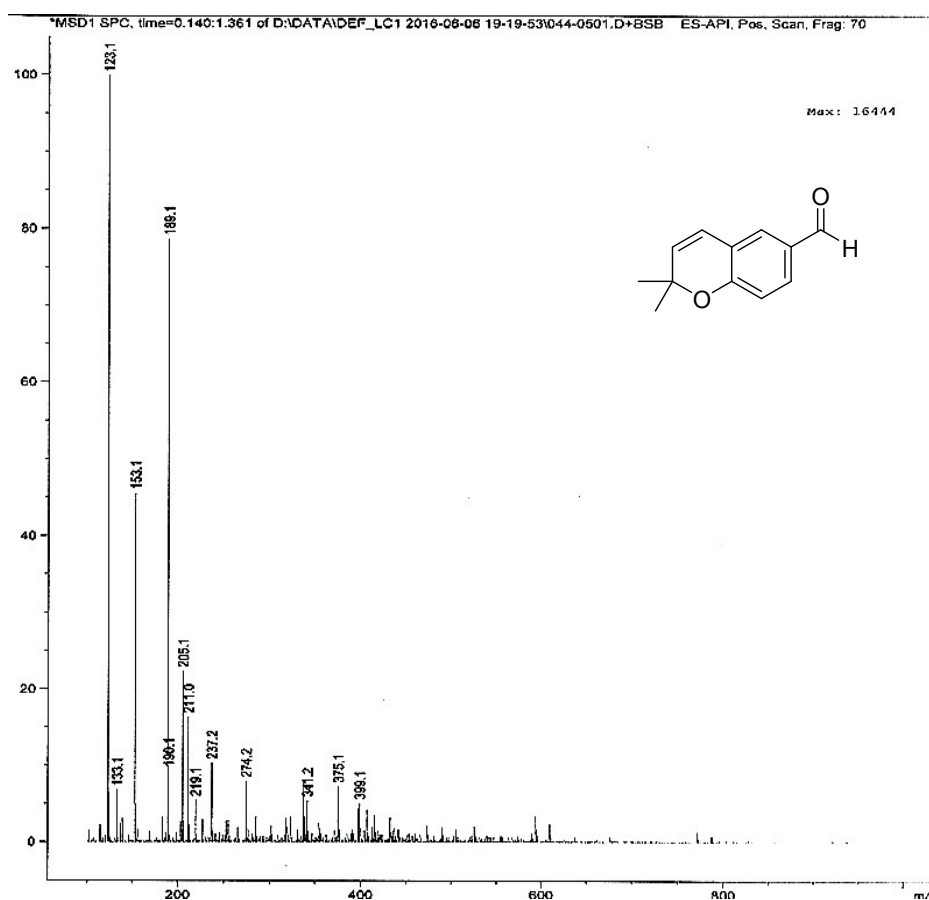
5. LC-MS spectrum of 2,2-dimethyl-2*H*-chromen-6-amine (9)



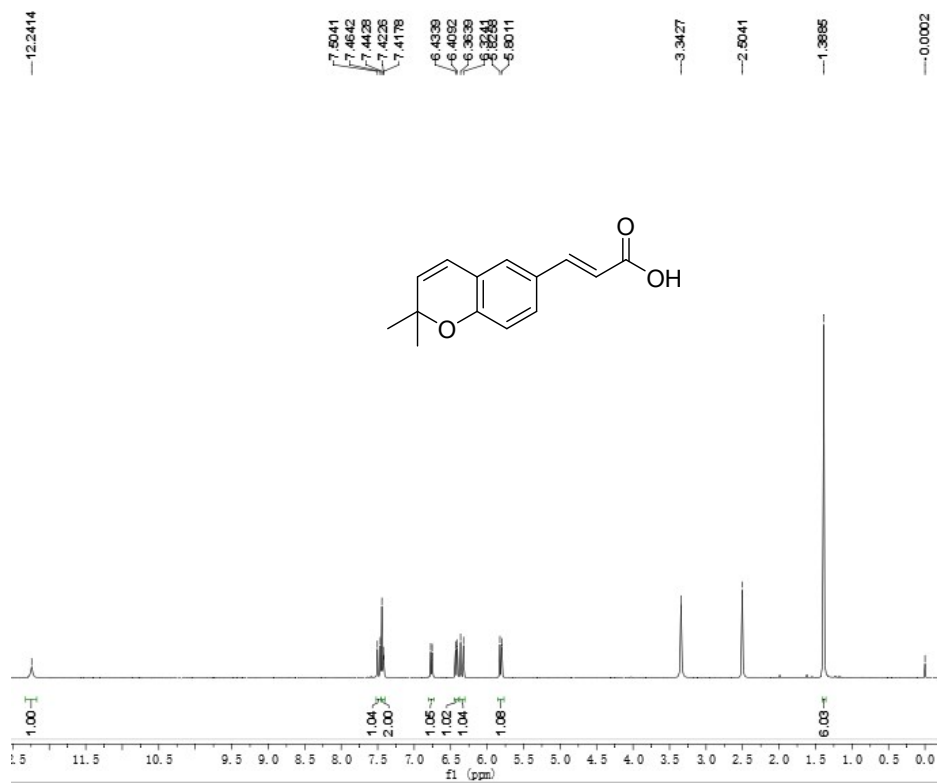
6. LC-MS spectrum of 4-((2-methylbut-3-yn-2-yl)oxy)benzaldehyde (11)



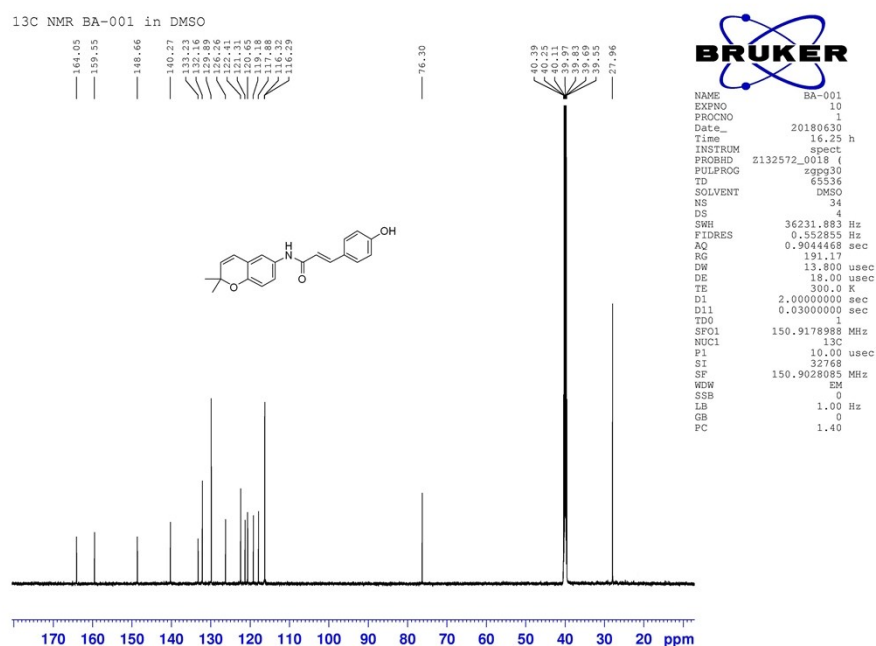
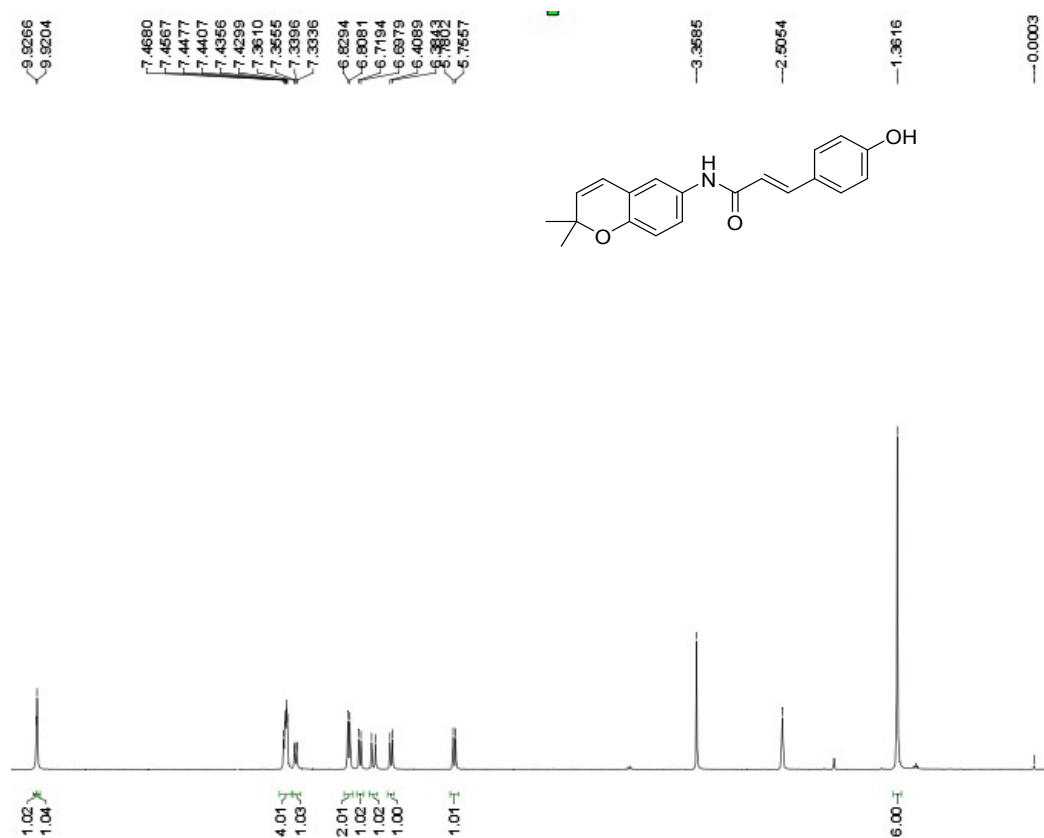
7. LC-MS spectrum 2,2-dimethyl-2*H*-chromene-6-carbaldehyde (12)



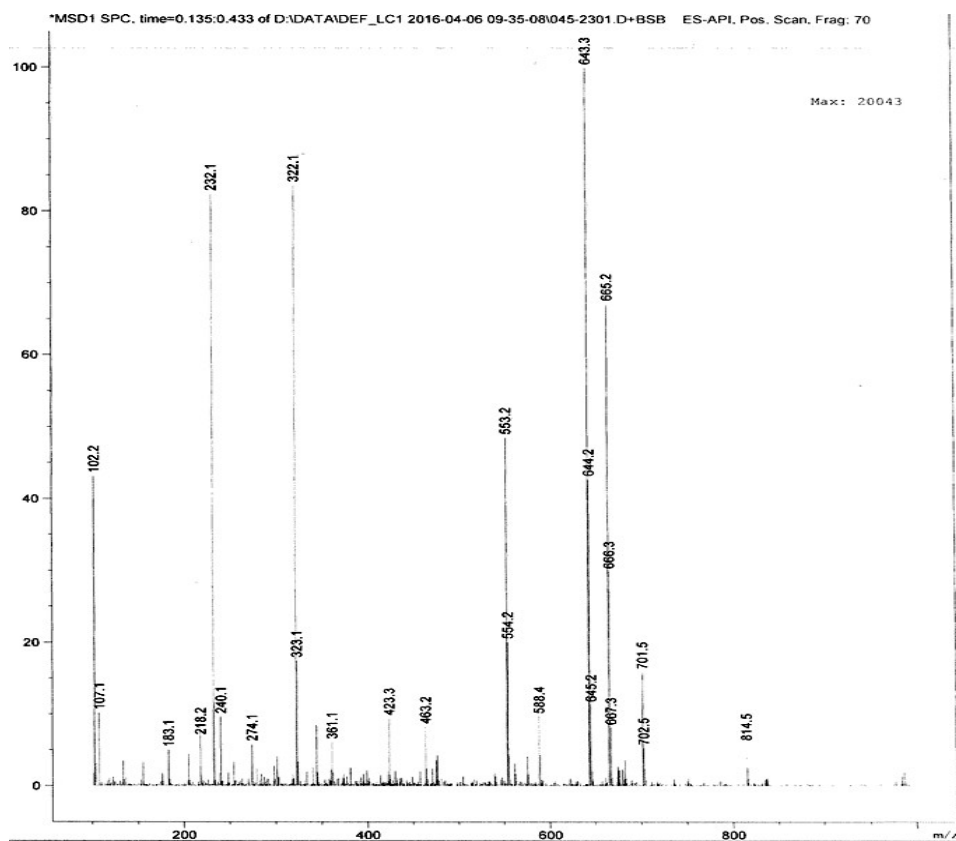
8. ^1H -NMR spectrum of compound 13 in CDCl_3



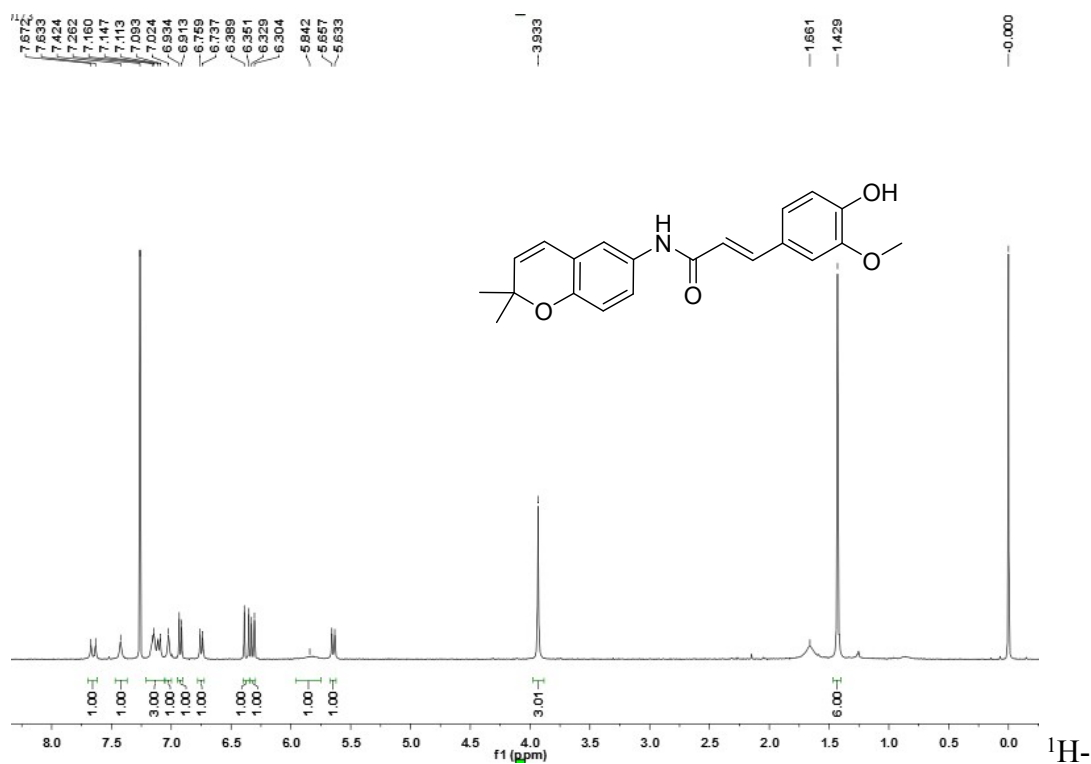
9. ^1H , ^{13}C NMR spectra and MS spectra of BA-01~BA-11



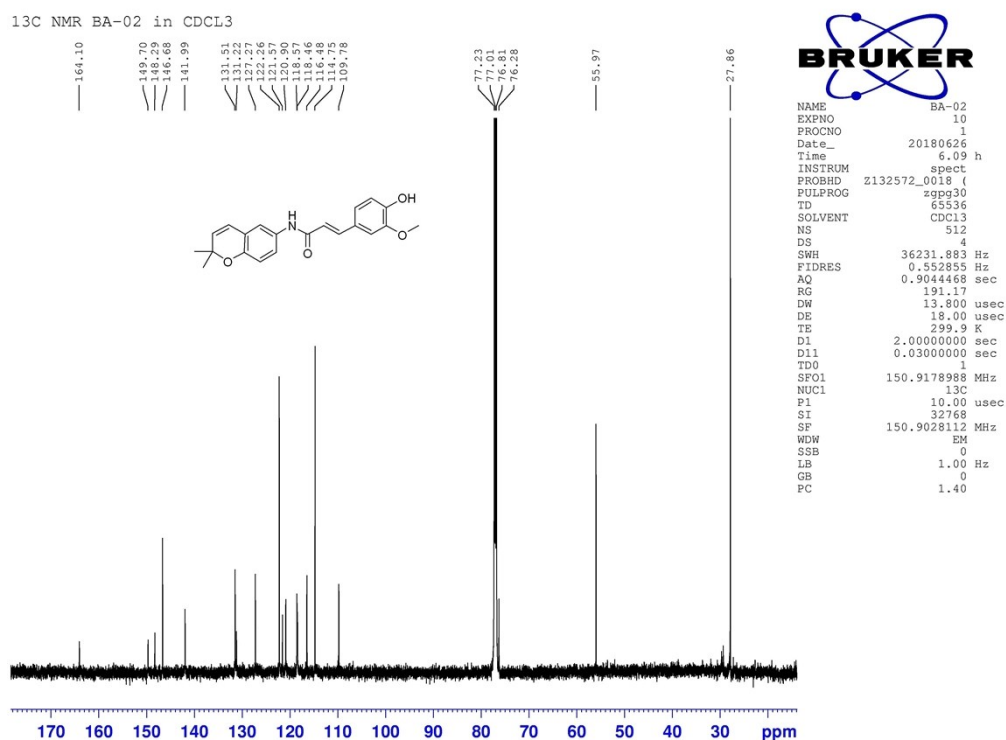
^{13}C -NMR spectrum of compound **BA-01** in $\text{DMSO}-d_6$



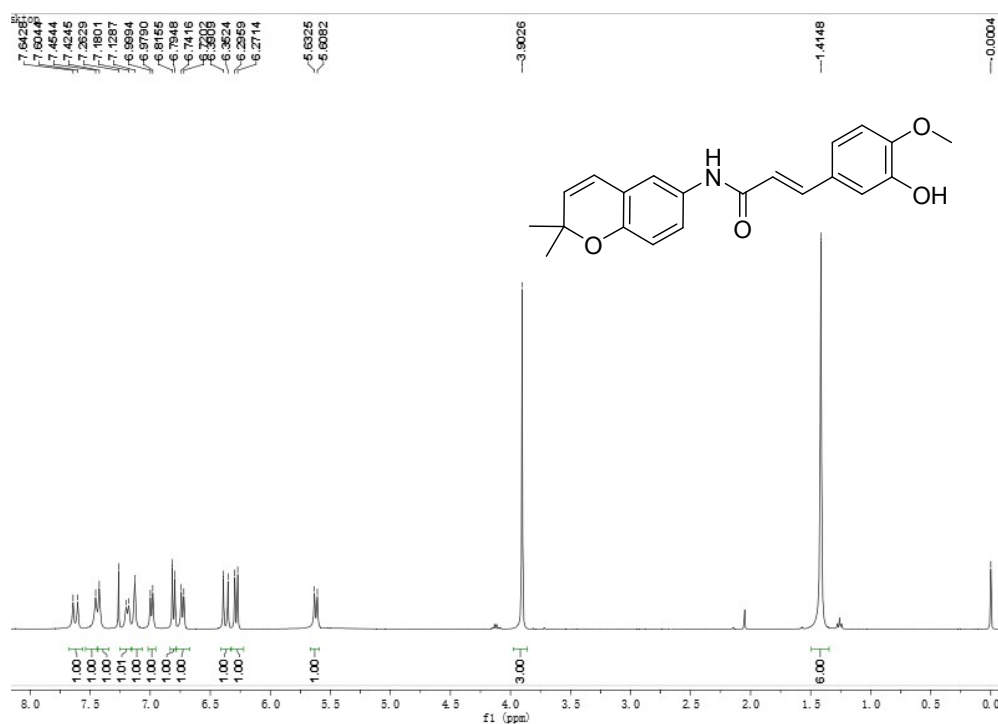
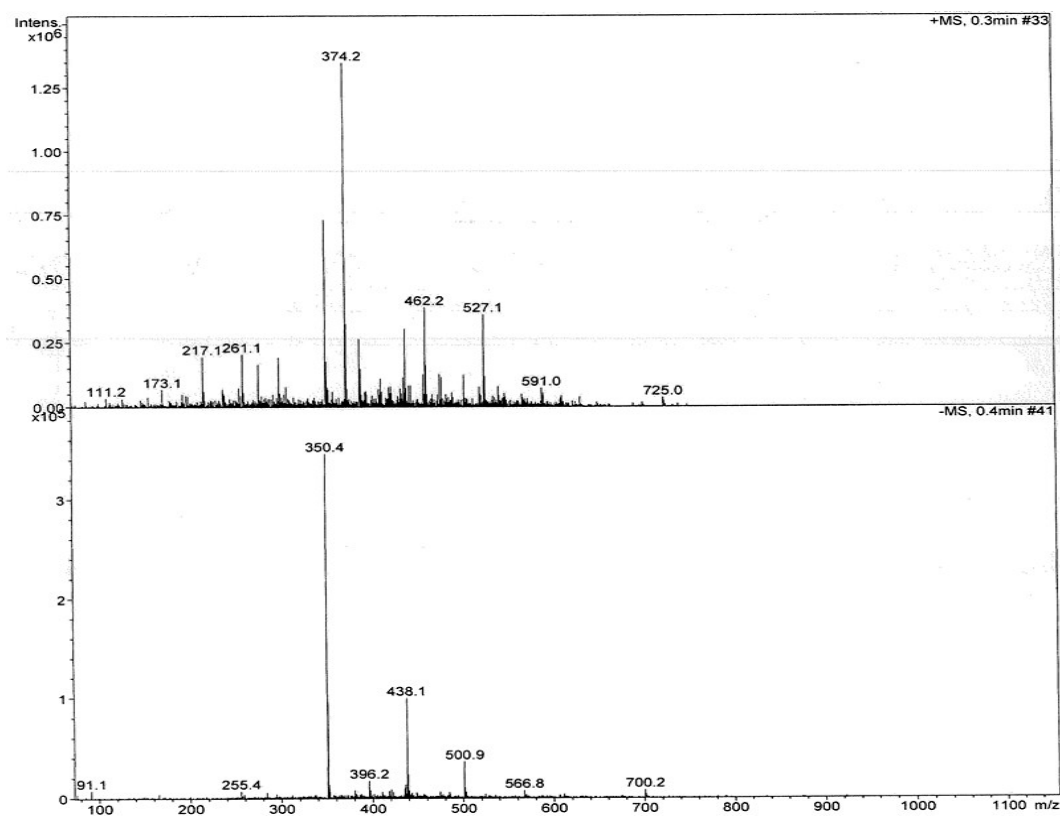
LC-MS spectrum of compound **BA-01**



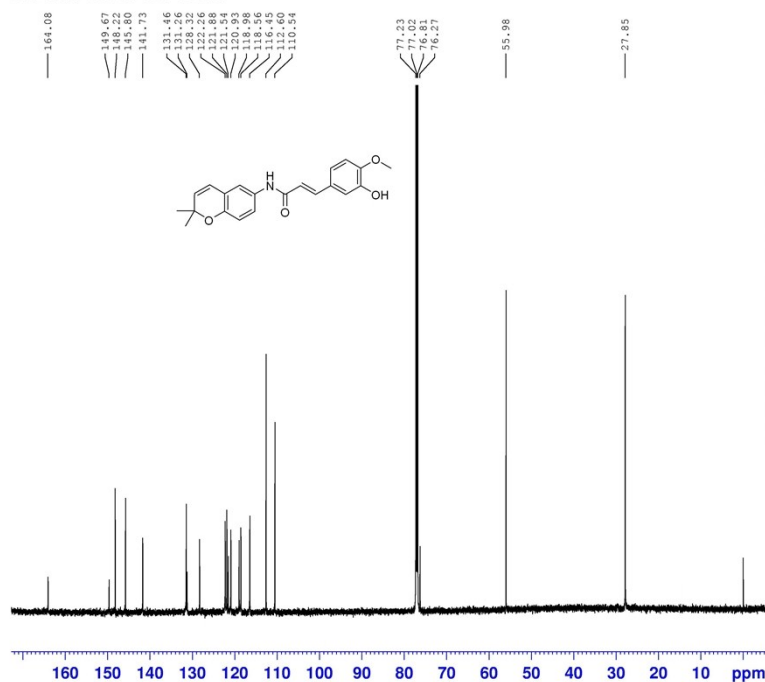
NMR spectrum of compound **BA-02** in CDCl₃



¹³C-NMR spectrum of compound **BA-02** in CDCl₃

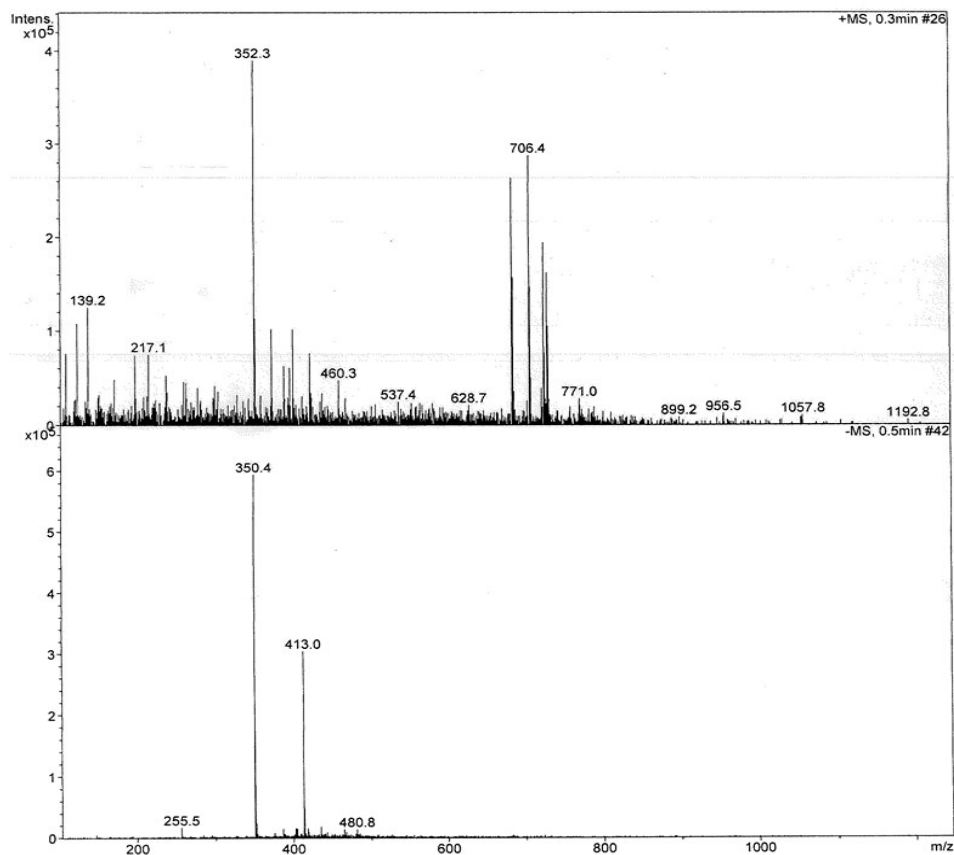


¹³C NMR BA-03 in CDCl₃

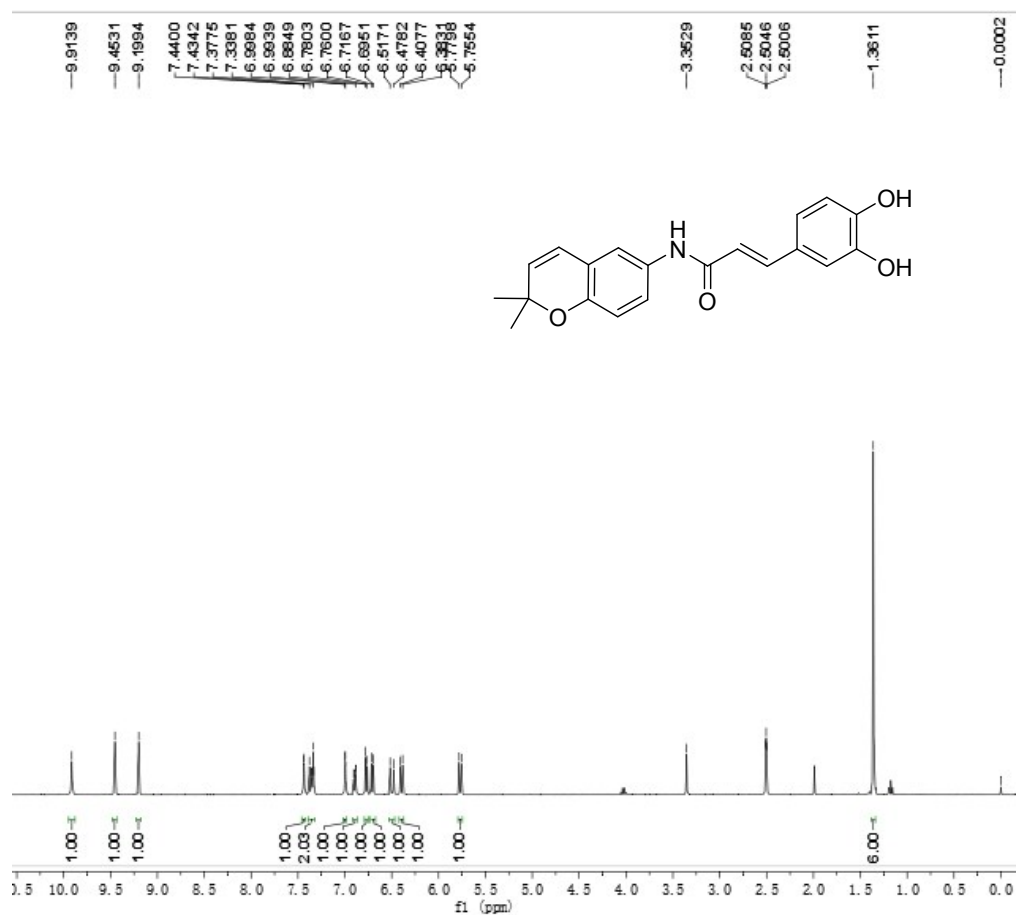


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PROCNO	1
Date_	20180625
Time	17.05 h
INSTRUM	spect
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PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	125
DS	4
SWH	36231.883 Hz
FIDRES	0.552855 Hz
AQ	0.9044468 sec
RG	191.17
DW	13.800 usec
DE	18.00 usec
TE	300.1 K
D1	2.0000000 sec
D11	0.0300000 sec
TD0	1
SFO1	150.9178988 MHz
NUC1	13C
P1	10.00 usec
SI	32768
SF	150.9028113 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

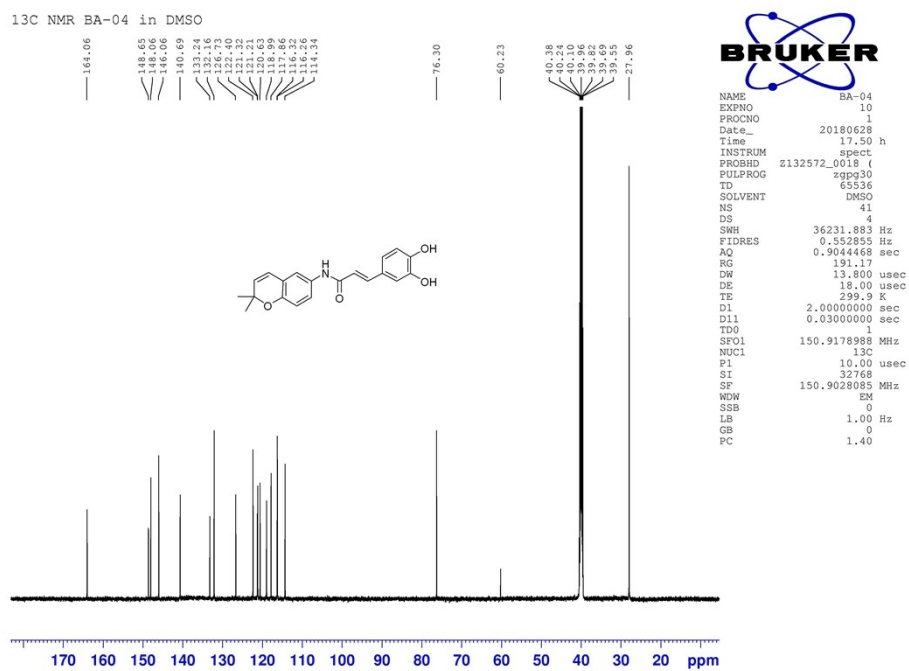
¹³C-NMR spectrum of compound **BA-03** in CDCl₃



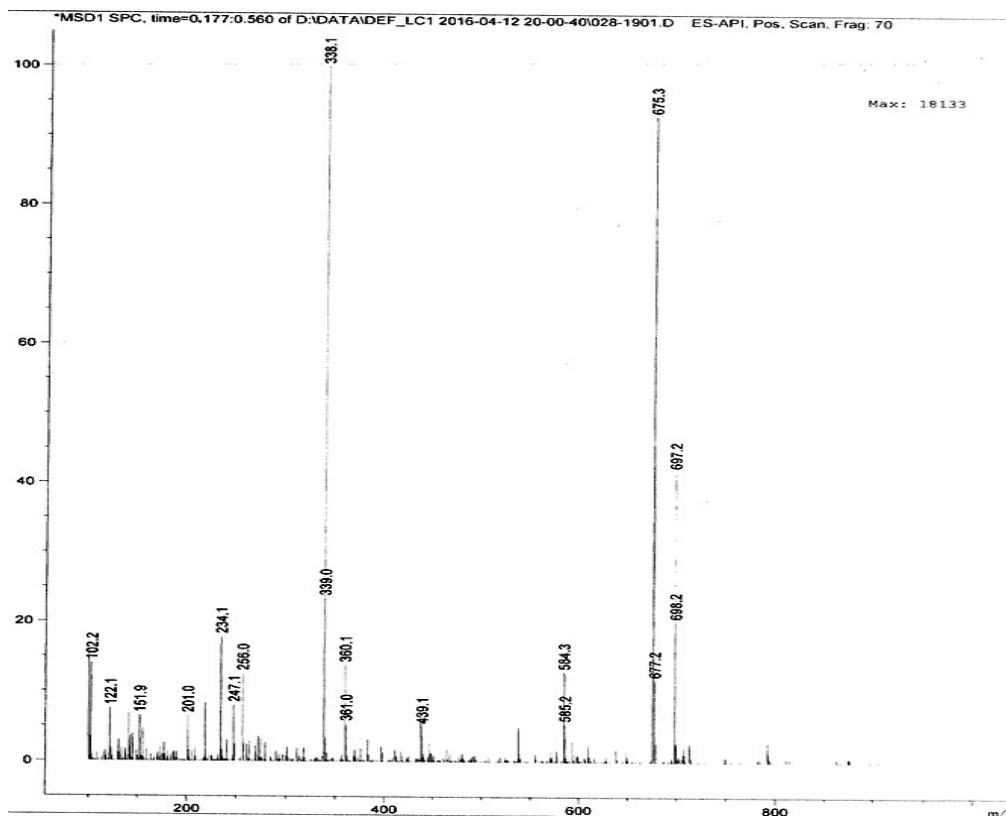
LC-MS spectrum of compound **BA-03**



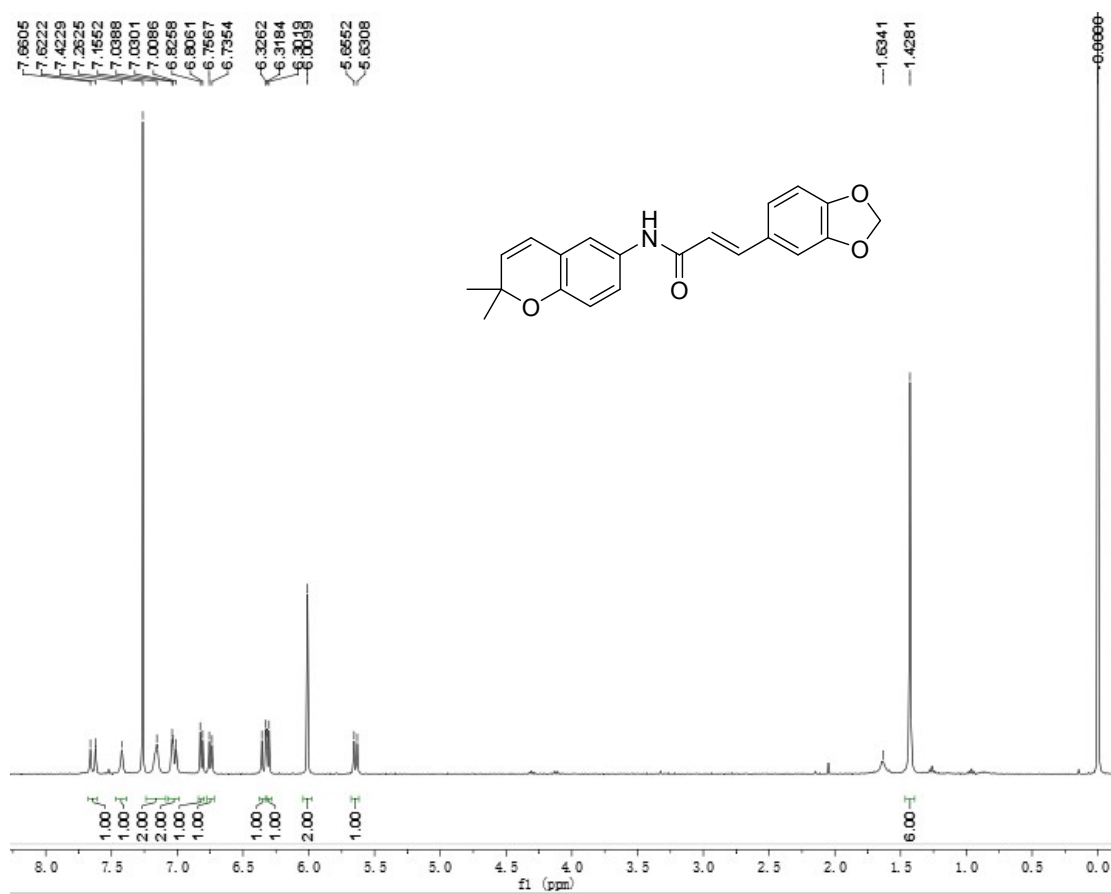
¹H-NMR spectrum of compound BA-04 in DMSO-*d*₆



¹³C-NMR spectrum of compound BA-04 in DMSO-*d*₆

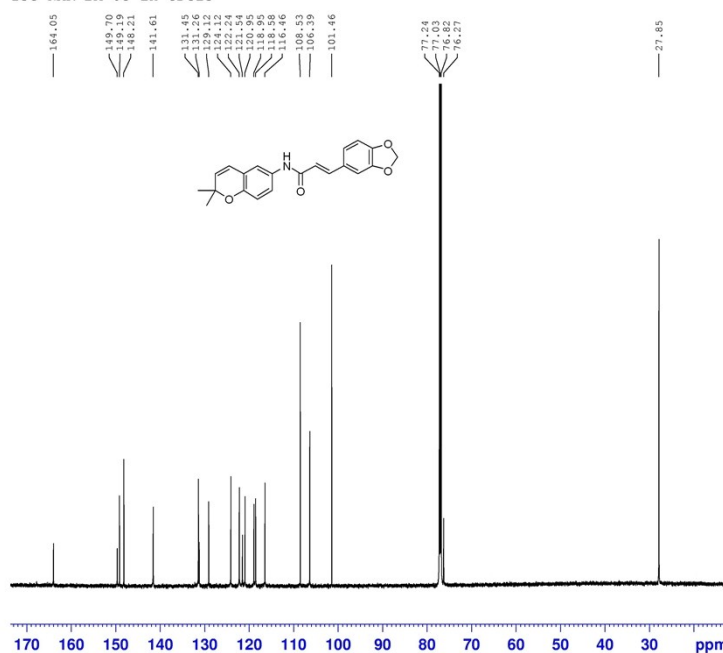


LC-MS spectrum of compound **BA-04**



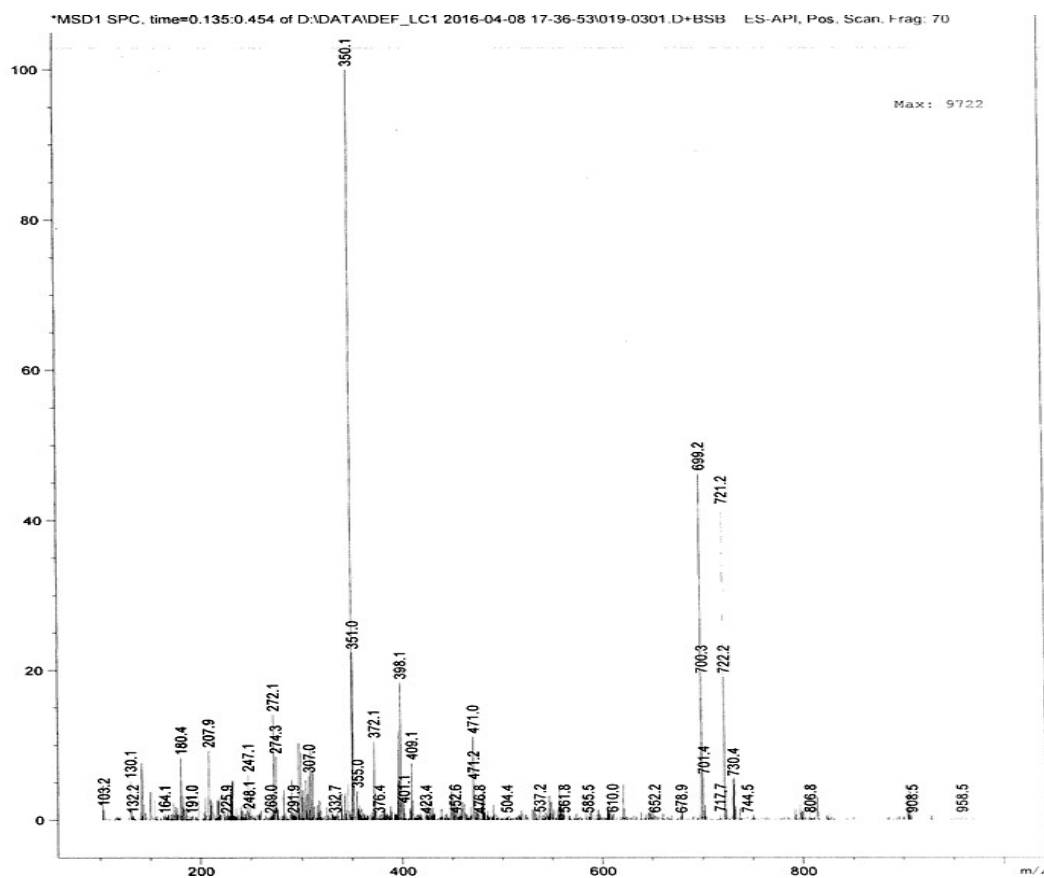
^1H -NMR spectrum of compound **BA-05** in CDCl_3

¹³C NMR BA-05 in CDCl₃

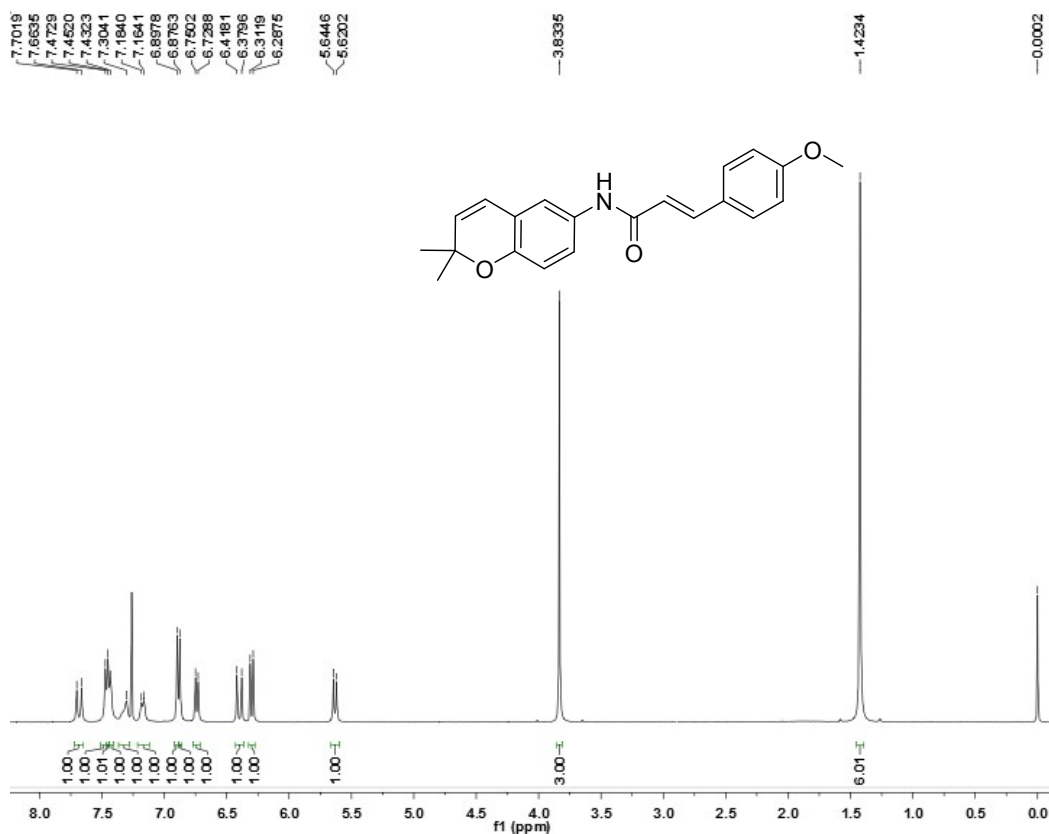


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EXPNO 10
PROCNO 1
Date_ 20180625
Time 16.23 h
INSTRUM spect
PROBHD z132572_0018 (4
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 133
DS 4
SWH 36231.883 Hz
FIDRES 0.552855 Hz
AQ 0.9044468 sec
RG 191.17
DW 13.800 usec
DE 18.00 usec
TE 299.9 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.9178988 MHz
NUC1 13C
P1 10.00 usec
SI 32768
SF 150.9028115 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

¹³C-NMR spectrum of compound **BA-05** in CDCl₃

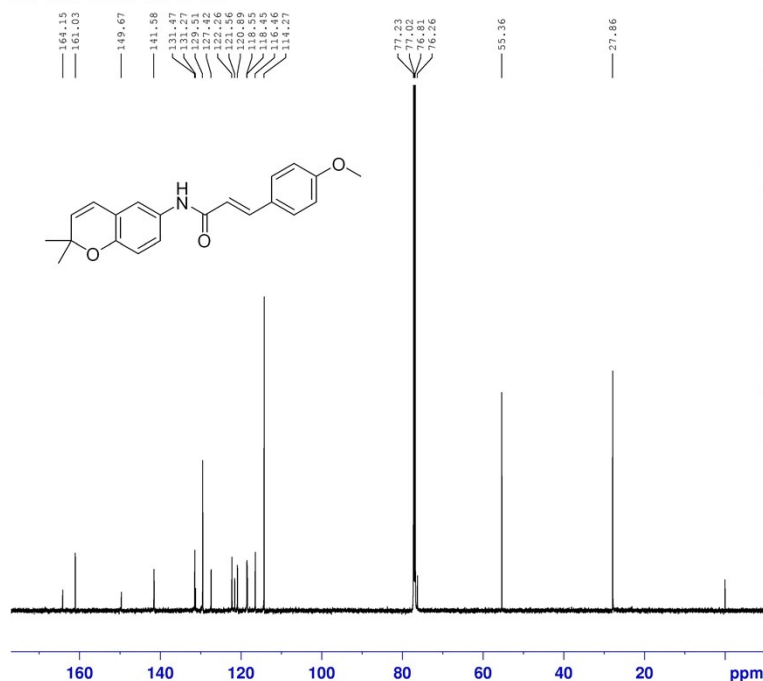


LC-MS spectrum of compound **BA-05**



¹H-NMR spectrum of compound **BA-06** in CDCl₃

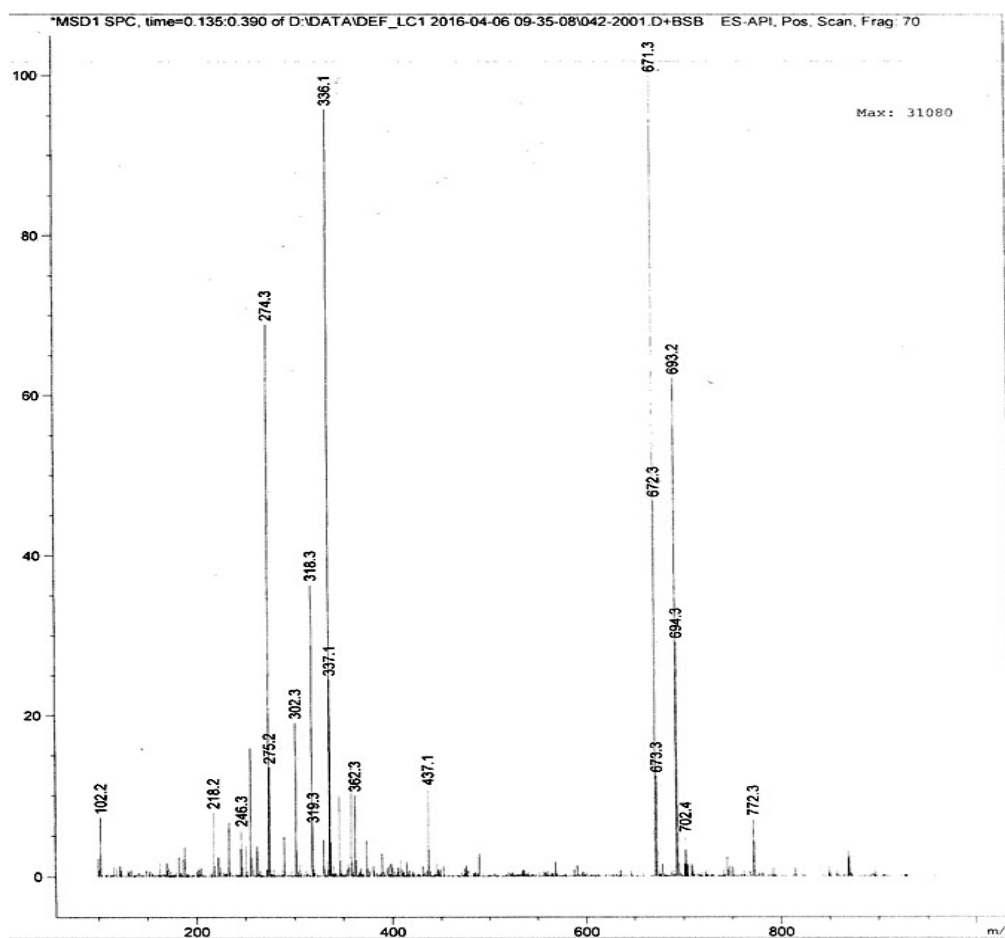
¹³C NMR BA-06 in CDCl₃



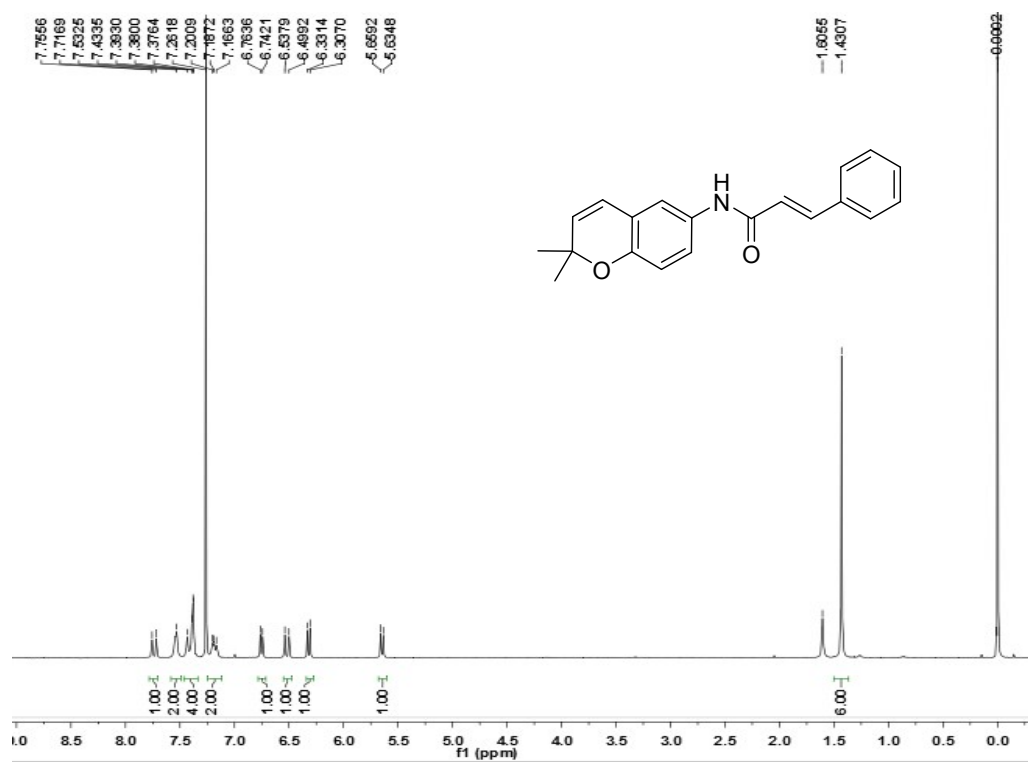
¹³C-NMR spectrum of compound **BA-06** in CDCl₃



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EXPNO 10
PROCNO 1
Date_ 20180625
Time 16.50 h
INSTRUM spect
PROBHD Z132572_0018 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl₃
NS 114
DS 4
SWH 36231.883 Hz
FIDRES 0.552855 Hz
AQ 0.9044468 sec
RG 191.17
DW 13.800 usec
DE 18.00 usec
TE 299.9 K
D1 2.0000000 sec
D11 0.0300000 sec
TD0 1
SF01 150.9178988 MHz
NUC1 13C
P1 10.00 usec
SI 32768
SF 150.9028113 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

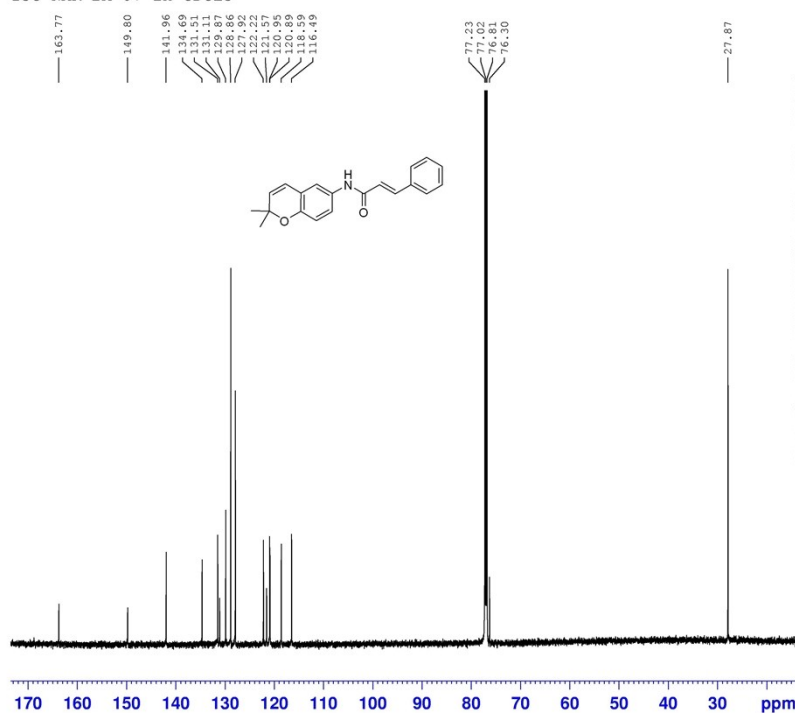


LC-MS spectrum of compound **BA-06**



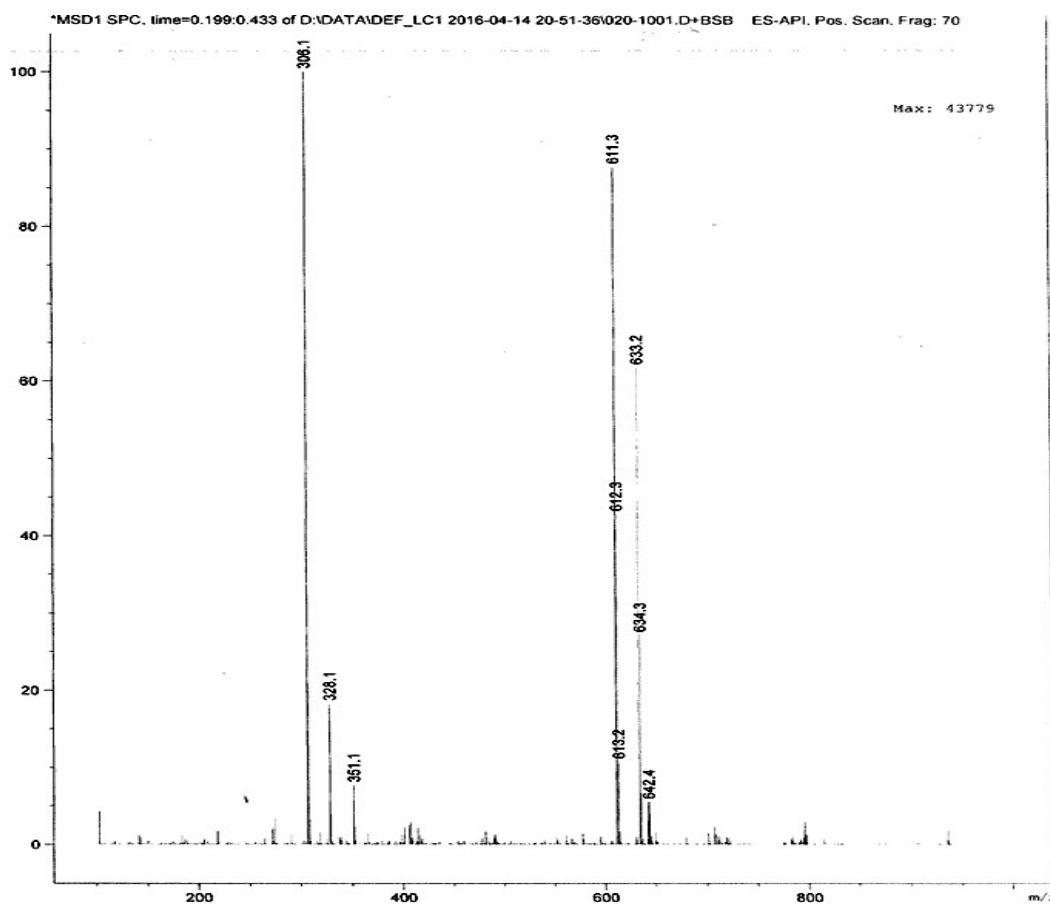
¹H-NMR spectrum of compound **BA-07** in CDCl₃

¹³C NMR BA-07 in CDCl₃

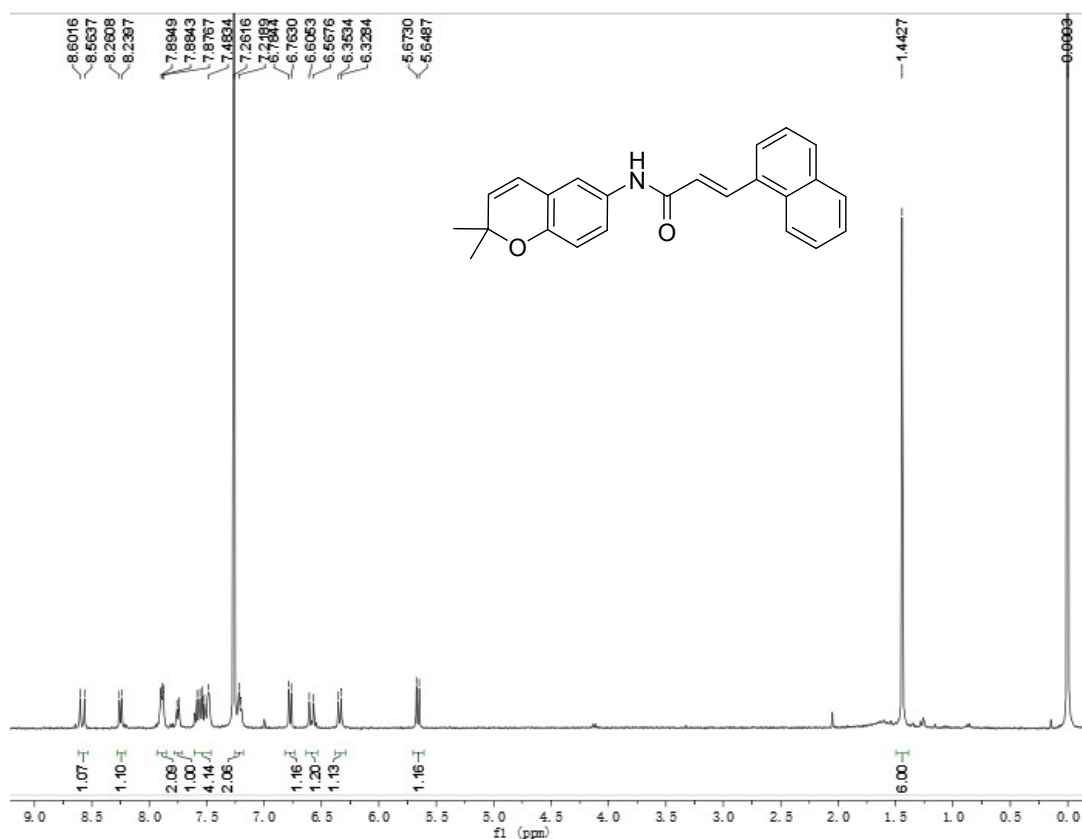


NAME BA-07
EXPNO 10
PROCNO 1
Date_ 20180625
Time 16.38 h
INSTRUM spect
PROBHD z132572_0018 (zpgpg30)
PULPROG zpgpg30
TD 65536
SOLVENT CDCl₃
NS 107
DS 4
SWH 36231.883 Hz
FIDRES 0.552855 Hz
AQ 0.9044468 sec
RG 191.17
DW 13.800 usec
DE 18.00 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.9178988 MHz
NUC1 13C
P1 10.00 usec
SI 32768
SF 150.9028114 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

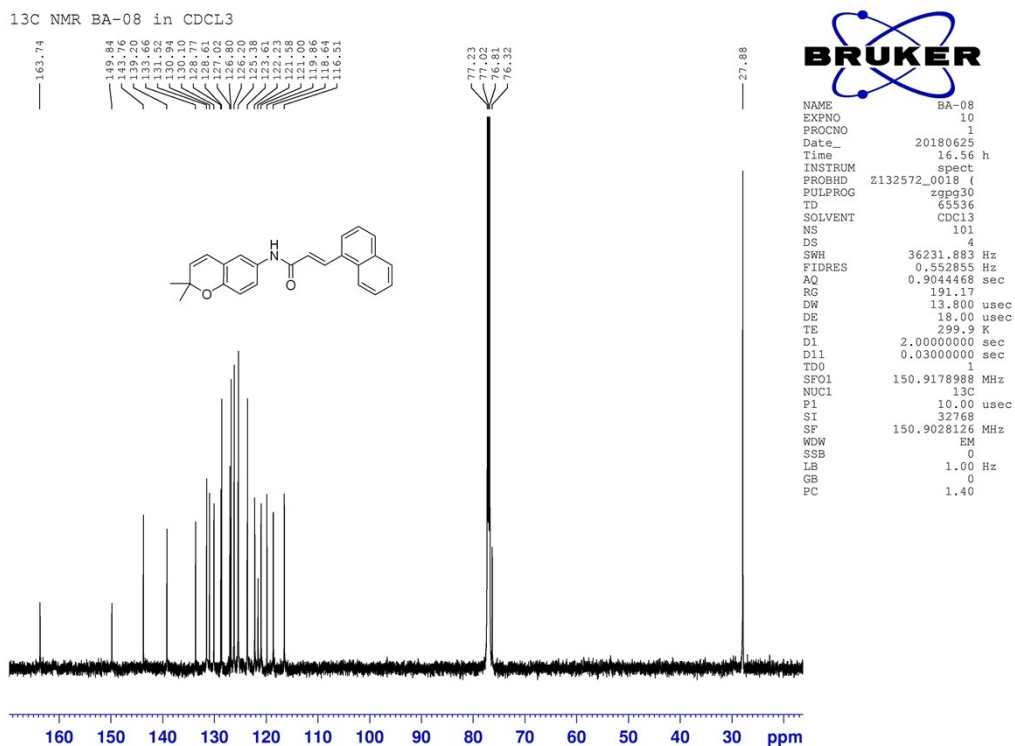
¹³C-NMR spectrum of compound BA-07 in CDCl₃



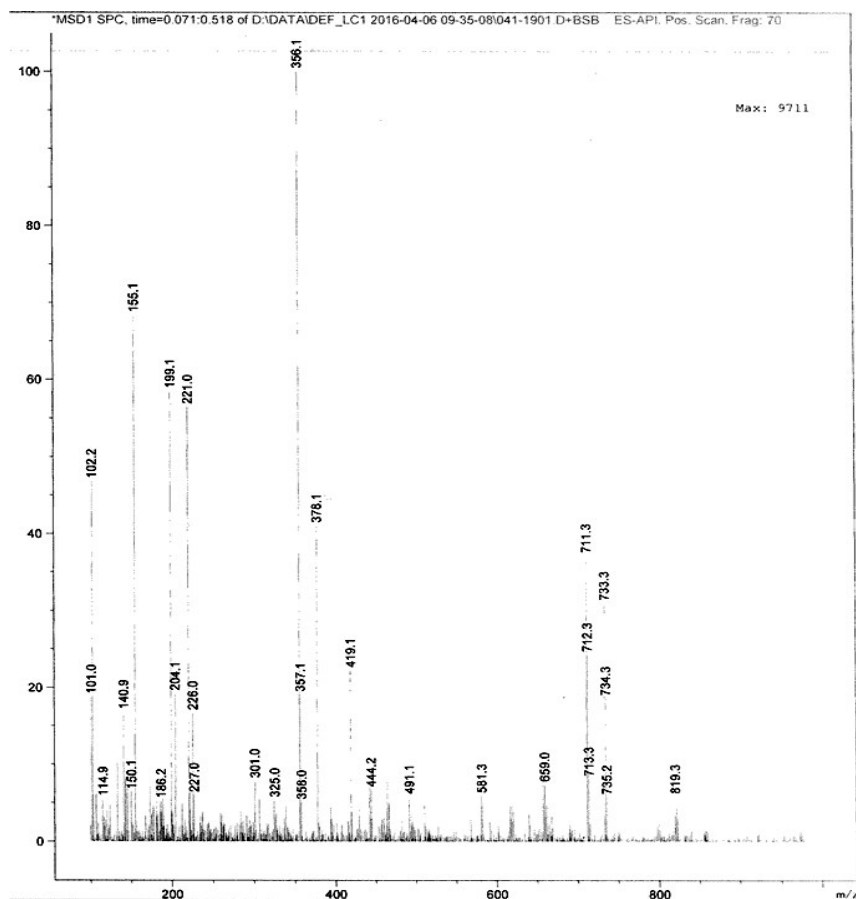
LC-MS spectrum of compound BA-07



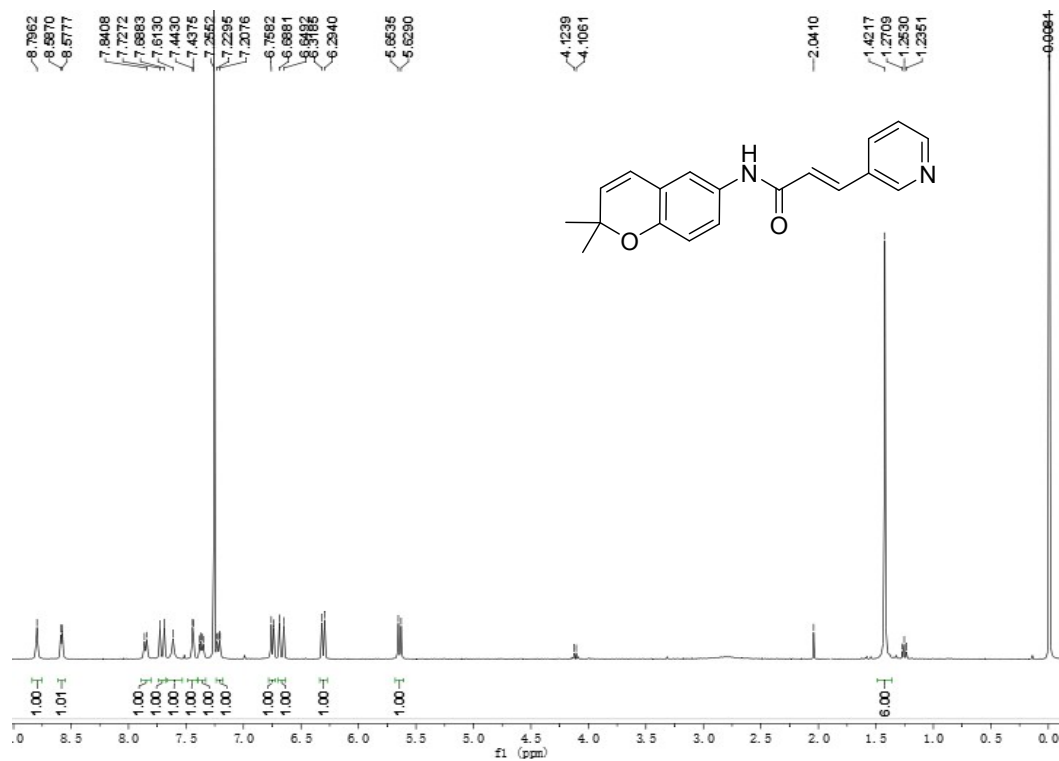
^1H -NMR spectrum of compound **BA-08** in CDCl_3



^{13}C -NMR spectrum of compound **BA-08** in CDCl_3

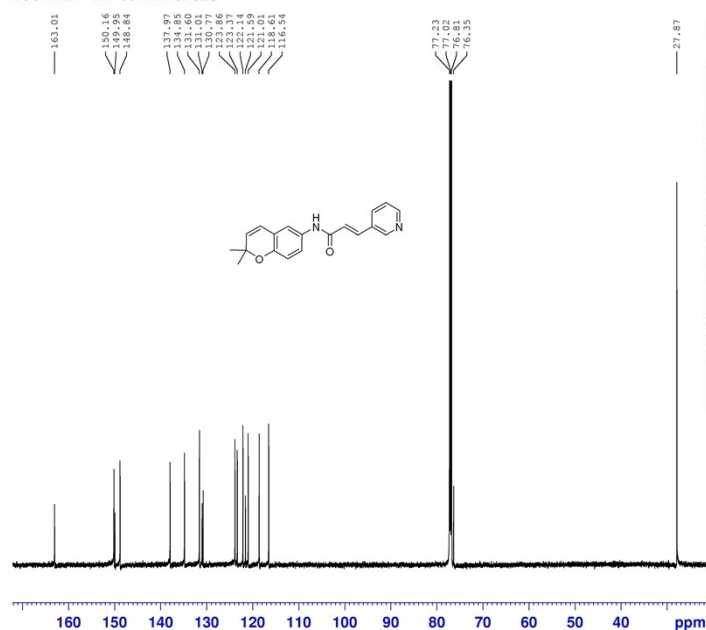


LC-MS spectrum of compound **BA-08**



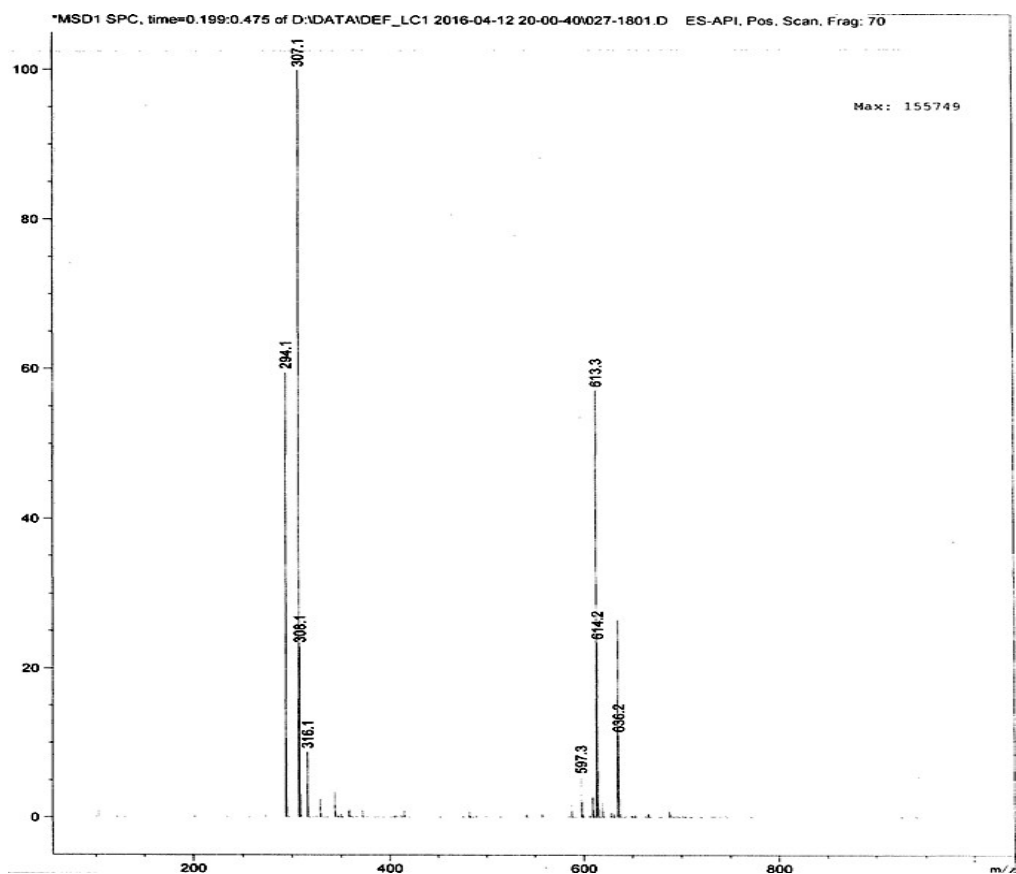
¹H-NMR spectrum of compound **BA-09** in CDCl₃

¹³C NMR BA-09 in CDCl₃

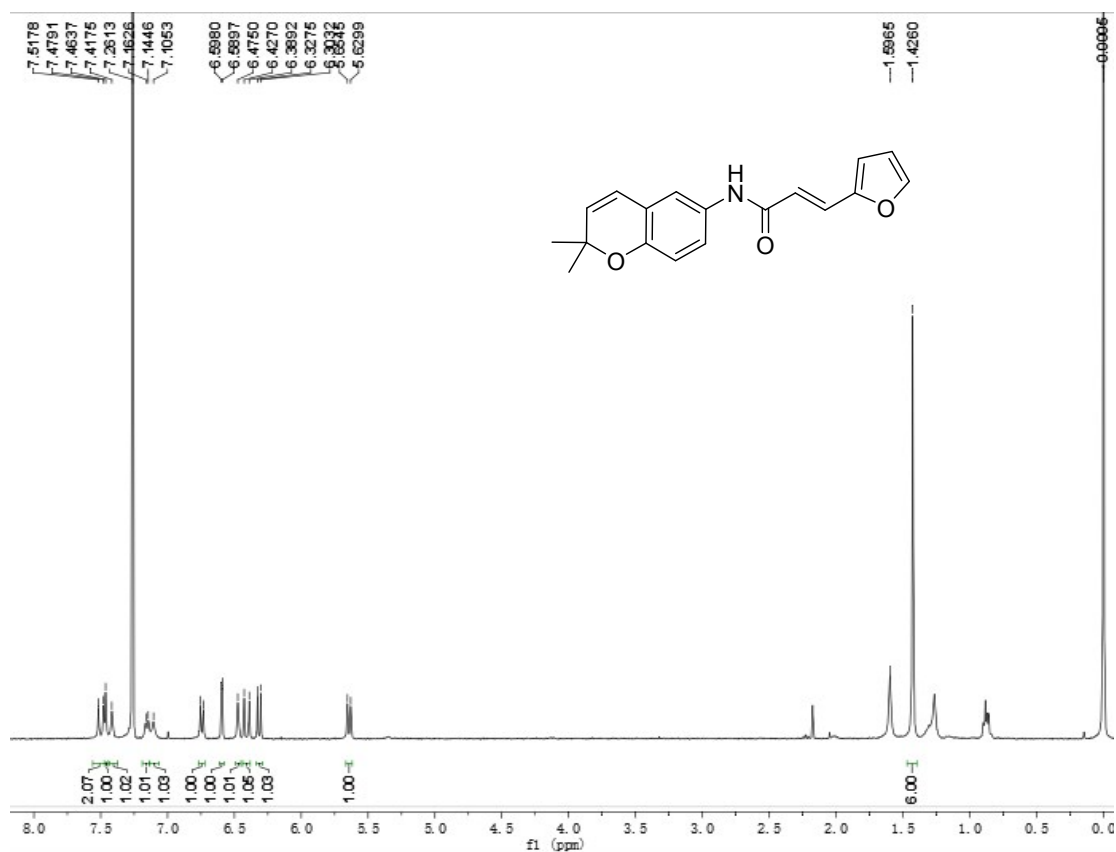


NAME BA-09
EXPNO 10
PROCNO 1
Date_ 20180625
Time 16.14 h
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PROBHD Z132572_0018 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 144
DS 4
SWH 36231.883 Hz
FIDRES 0.552855 Hz
AQ 0.9044468 sec
RG 191.17
DW 13.800 usec
DE 18.00 usec
TE 299.9 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.9178988 MHz
NUC1 13C
P1 10.00 usec
SI 32768
SF 150.9028111 MHz
SP EM
WDW 0
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

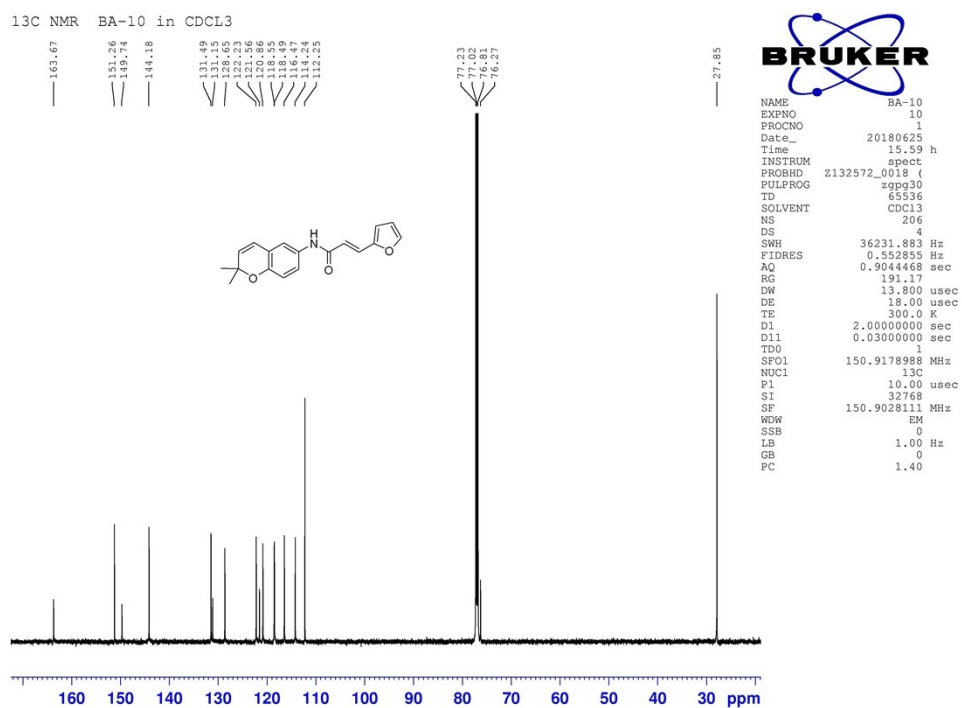
¹³C-NMR spectrum of compound **BA-09** in CDCl₃



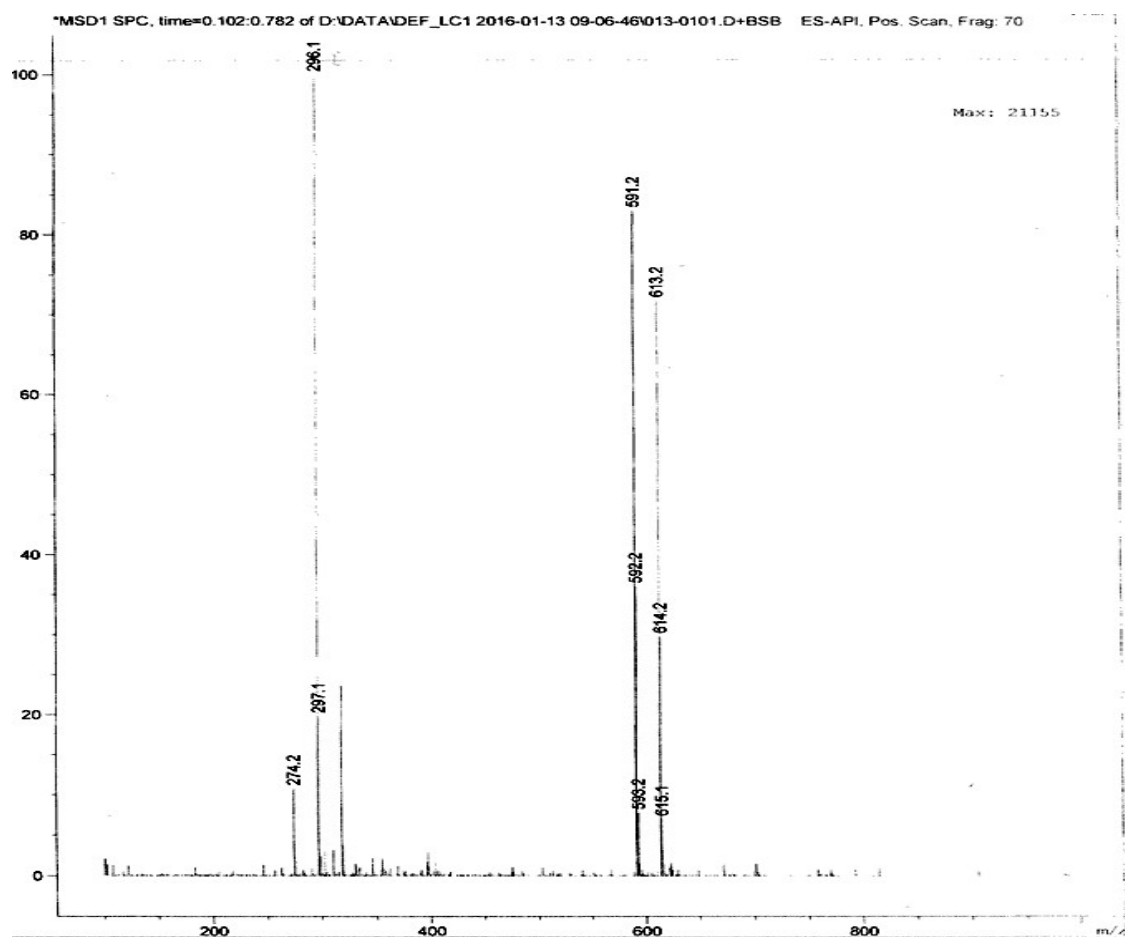
LC-MS spectrum of compound **BA-09**



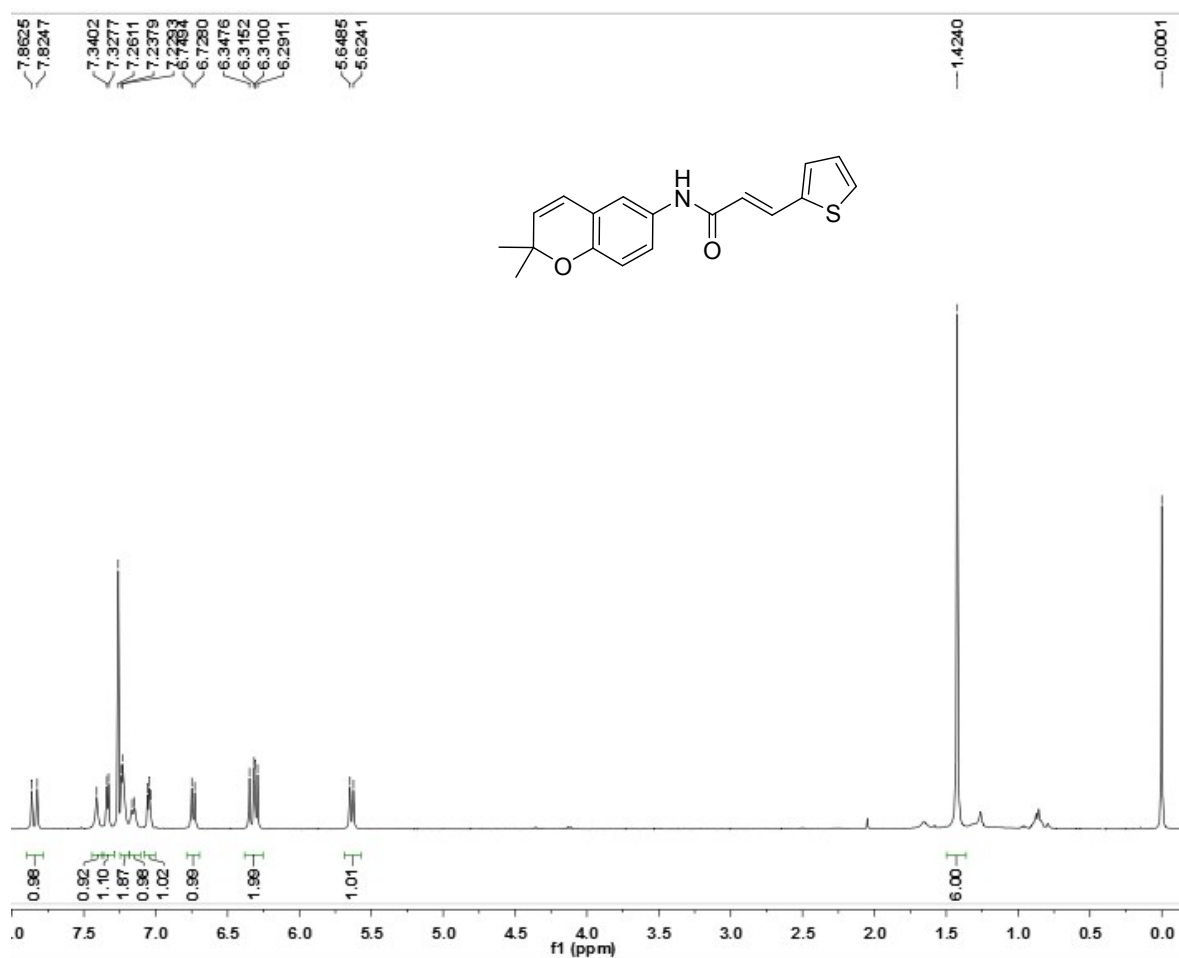
¹H-NMR spectrum of compound **BA-10** in CDCl₃



¹³C-NMR spectrum of compound **BA-10** in CDCl₃

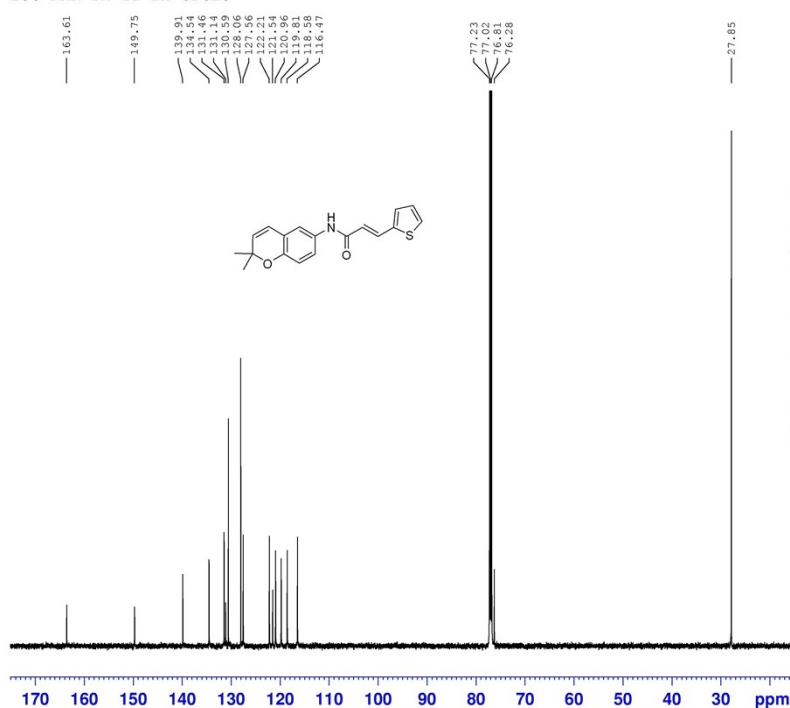


LC-MS spectrum of compound **BA-10**



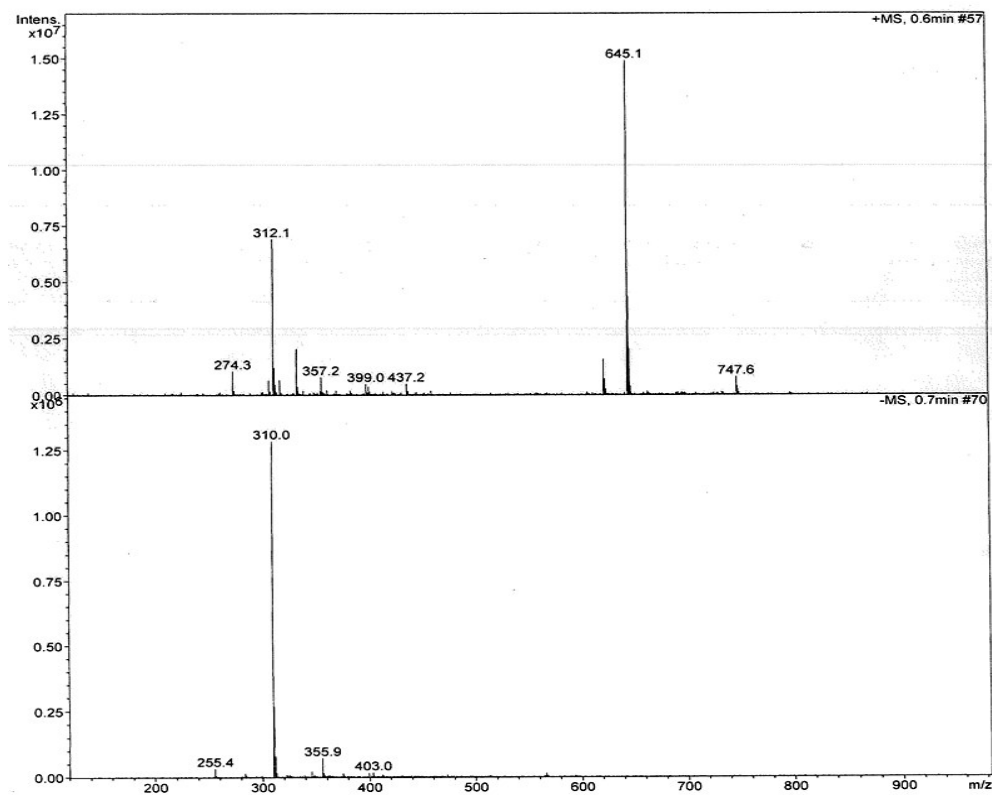
¹H-NMR spectrum of compound **BA-11** in CDCl₃

¹³C NMR BA-11 in CDCl₃



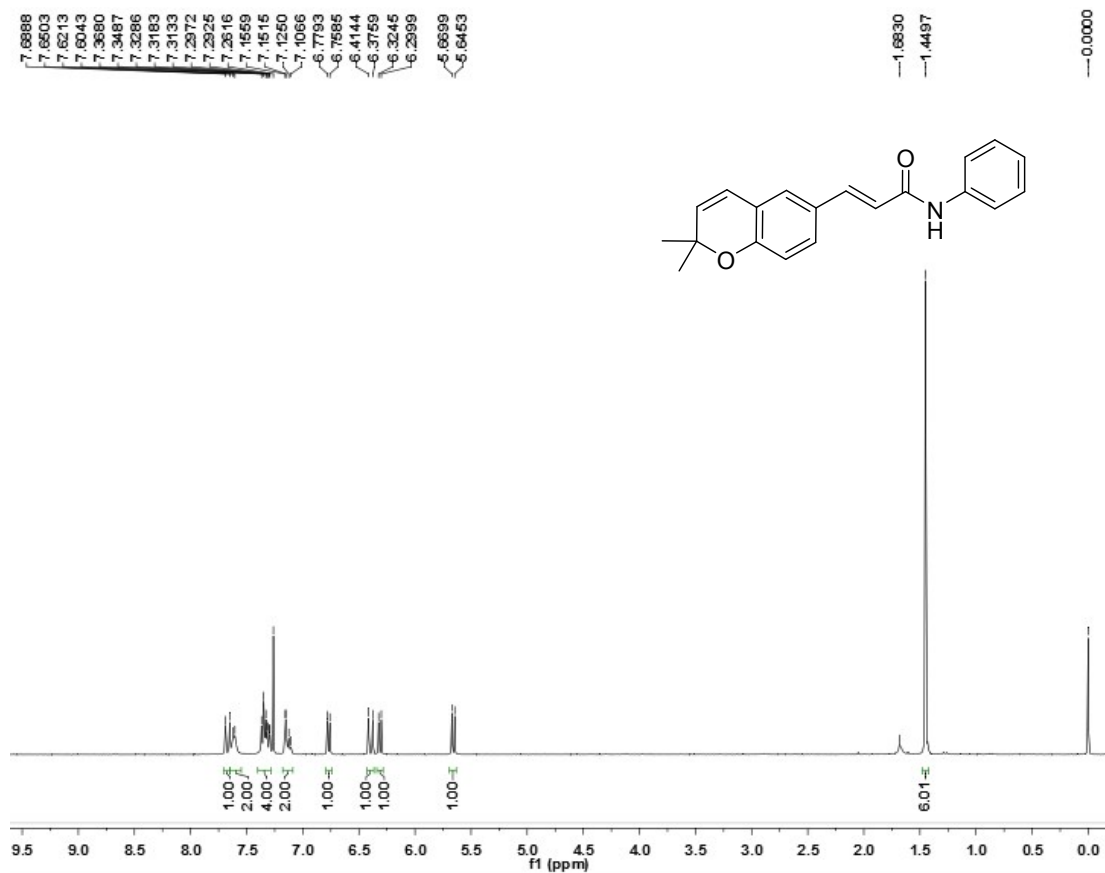
NAME BA-11
EXPNO 10
PROCNO 1
Date_ 20180628
Time 17.57 h
INSTRUM spect
PROBHD Z132572_0018 (zpgpg30)
PULPROG 65536
TD 80
SOLVENT CDCl₃
NS 4
DS 36231.883 Hz
SWH 0.552855 Hz
FIDRES 0.9044468 sec
AQ 191.17
RG 13.800 usec
DE 18.00 usec
TE 299.9 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.9178988 MHz
NUC1 13C
P1 10.00 usec
SI 32768
SF 150.9028125 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

¹³C-NMR spectrum of compound BA-11 in CDCl₃



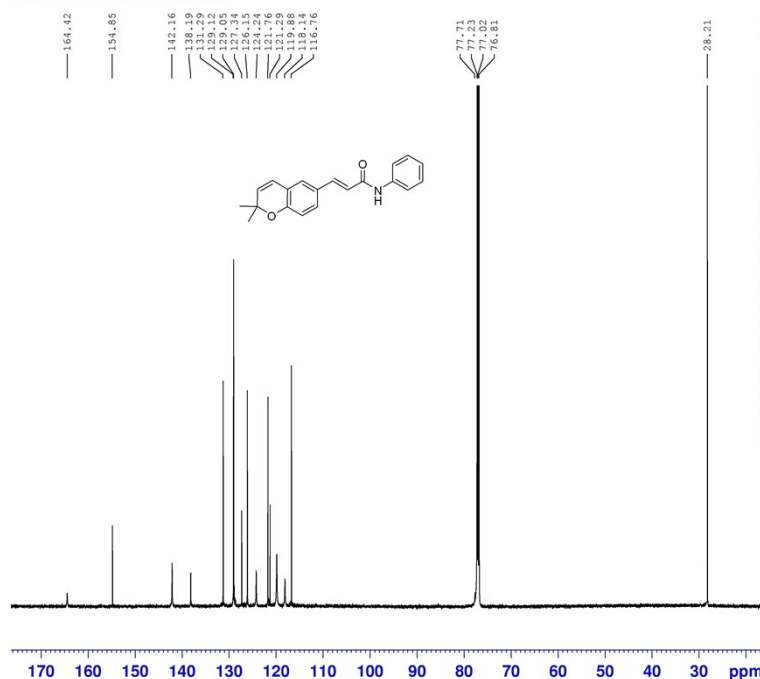
LC-MS spectrum of compound BA-11

10. ^1H , ^{13}C NMR spectra and MS spectra of BA-01~BN-10



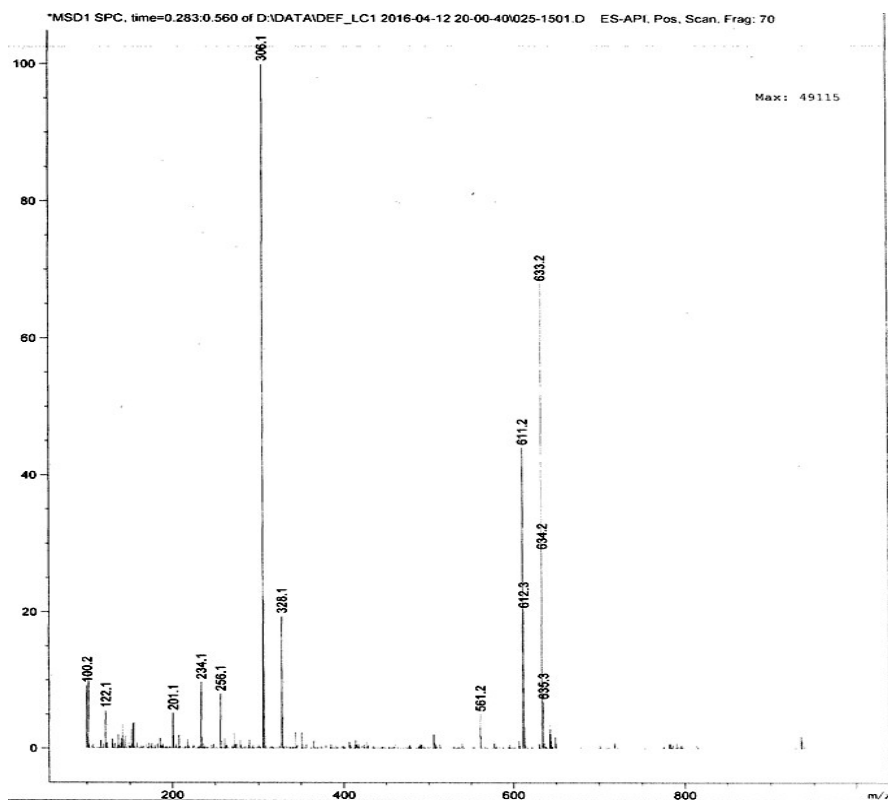
^1H -NMR spectrum of compound BN-01 in CDCl_3

¹³C NMR BN-01 in CDCl₃

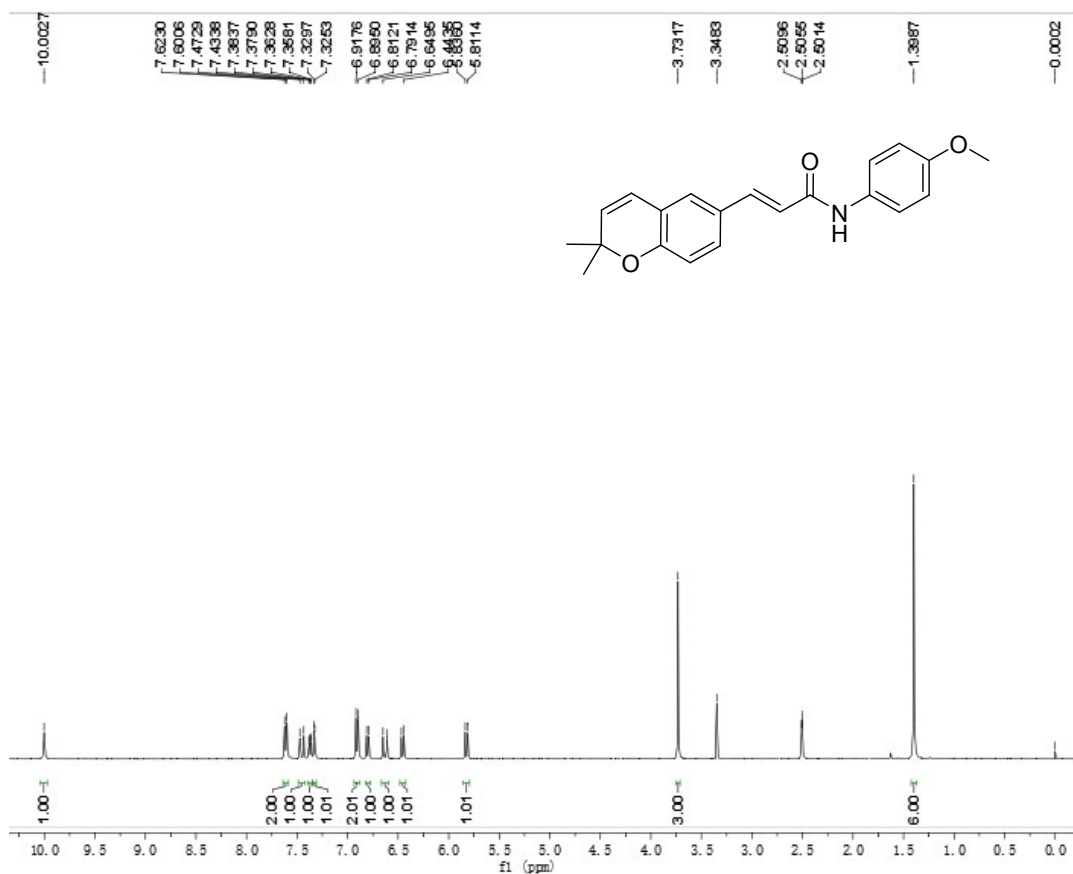


NAME BN-01
EXPNO 11
PROCNO 1
Date 20180630
Time 8.23 h
INSTRUM spect
PROBHD Z132572_0018 (4
PULPROG zgpg30
TD 65536
SOLVENT CDCl₃
NS 300
DS 4
SWH 36231.883 Hz
FIDRES 0.552855 Hz
AQ 0.9044468 sec
RG 191.17
DW 13.800 usec
DE 19.00 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.9178988 MHz
NUC1 13C
P1 10.00 usec
SI 32768
SF 150.9028117 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

¹³C-NMR spectrum of compound **BN-01** in CDCl₃

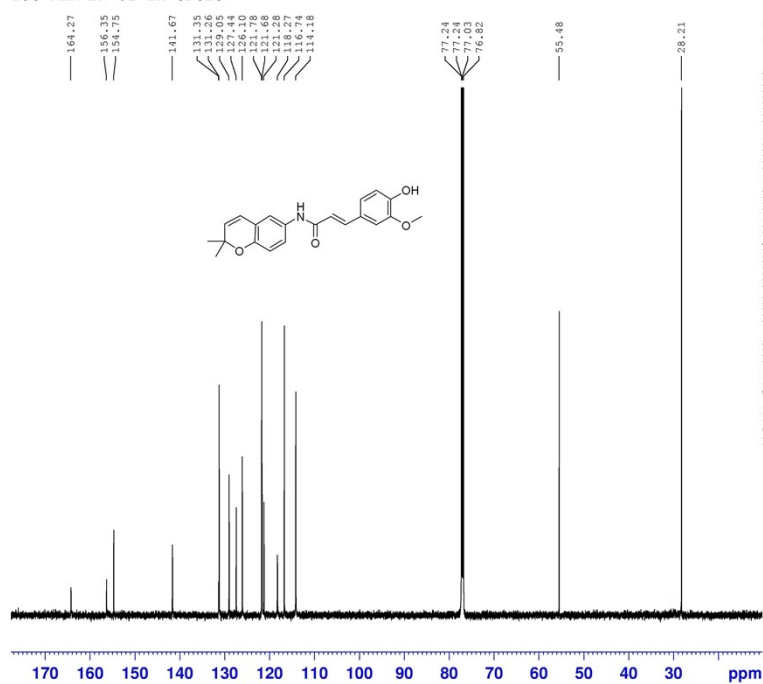


LC-MS spectrum of compound **BN-01**



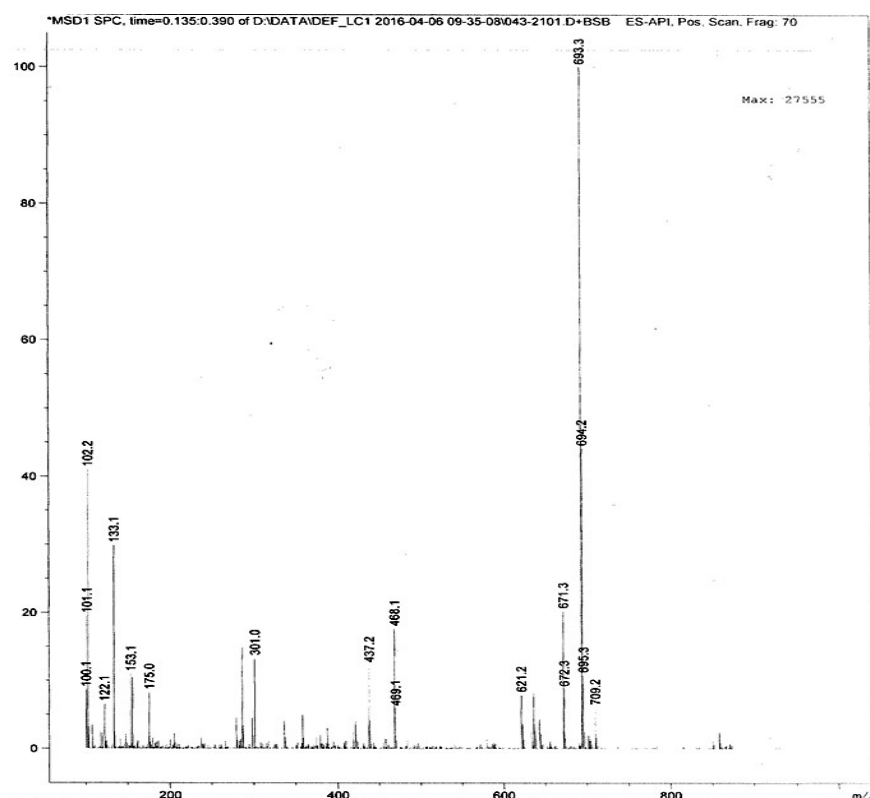
¹H-NMR spectrum of compound **BN-02** in DMSO-*d*₆

¹³C NMR BN-02 in CDCl₃

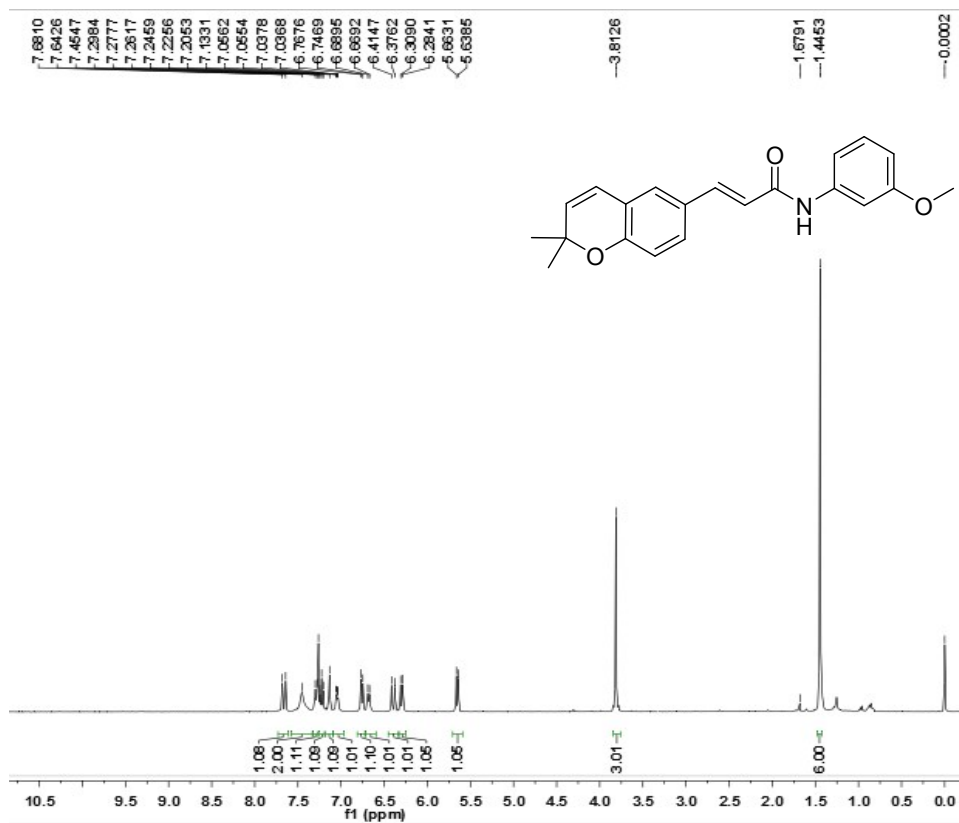


NAME BN-02
EXPNO 10
PROCNO 1
Date_ 20180628
Time 17.28 h
INSTRUM spect
PROBHD Z132572_0018 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl₃
NS 61
DS 4
SWH 36231.883 Hz
FIDRES 0.552855 Hz
AQ 0.9044468 sec
RG 191.17
DW 13.800 usec
DE 18.00 usec
TE 299.9 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SF01 150.9178988 MHz
NUC1 13C
P1 10.00 usec
SI 32768
SF 150.9028113 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

¹³C-NMR spectrum of compound **BN-02** in CDCl₃

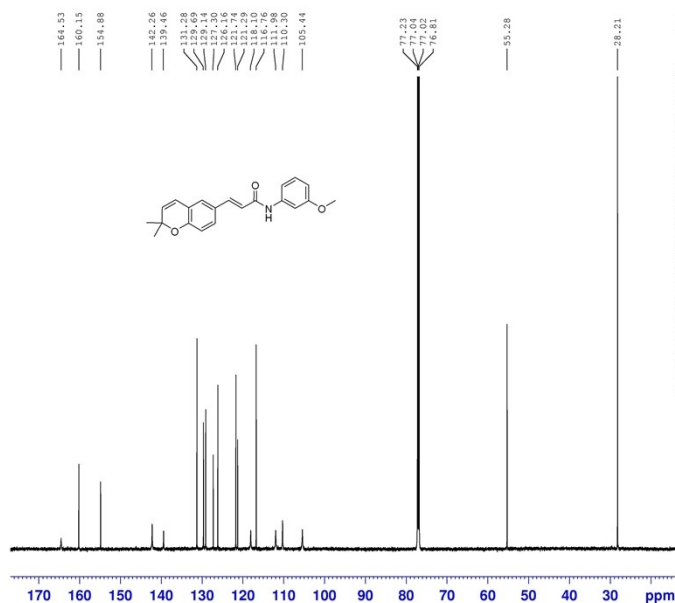


LC-MS spectrum of compound **BN-02**



¹H-NMR spectrum of compound **BN-03** in CDCl₃

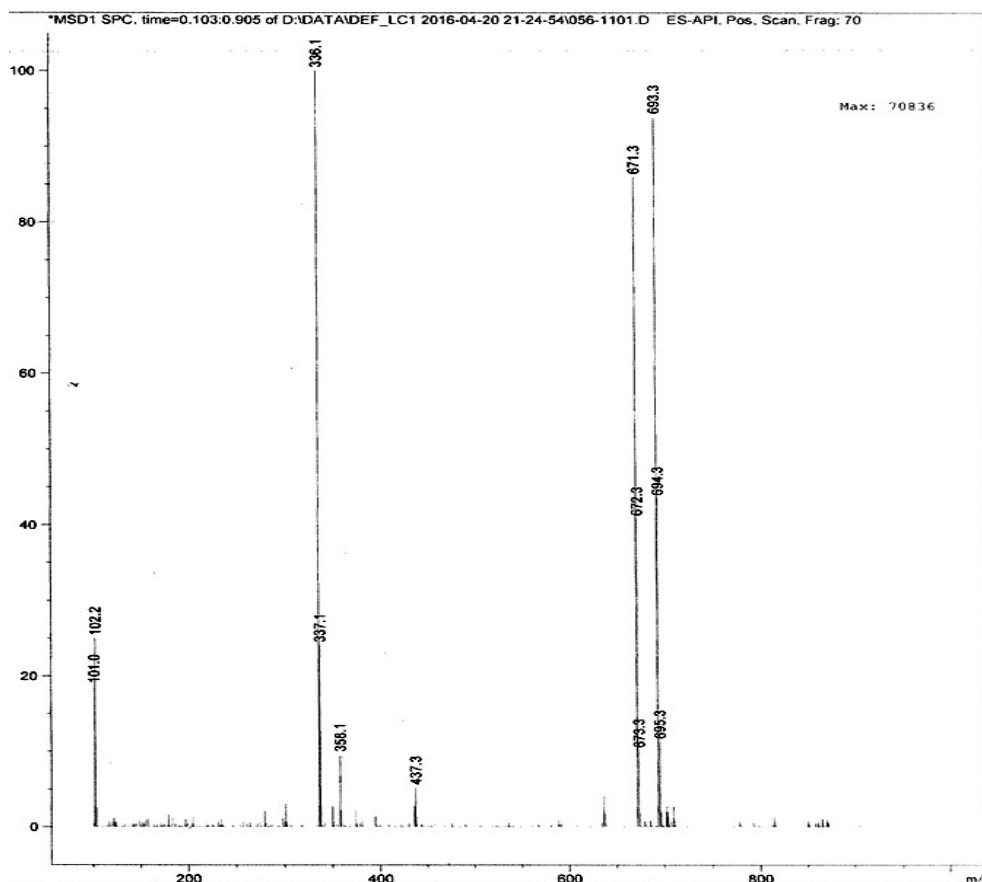
¹³C NMR BN-03 in CDCl₃



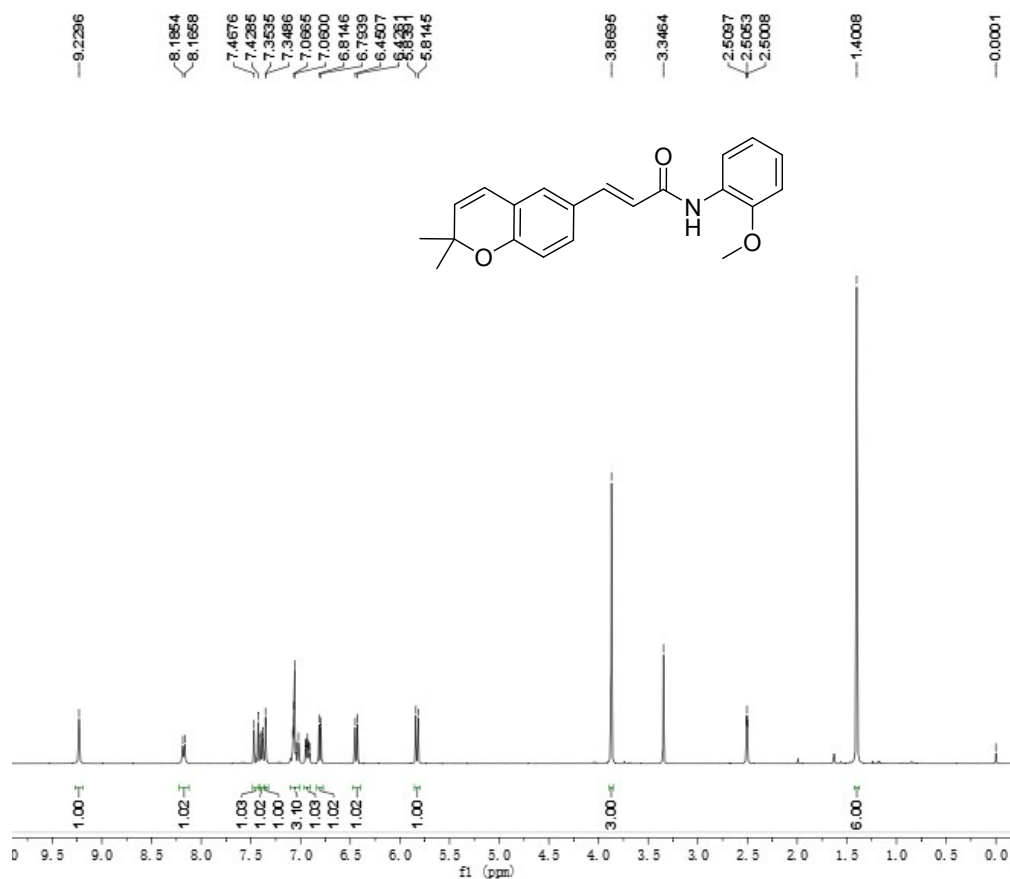
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EXPNO 10
PROCNO 1
Date_ 20180628
Time 17.41 h
INSTRUM spect
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PULPROG zgpg30
TD 65536
SOLVENT CDCl₃
NS 105
DS 4
SWH 36231.883 Hz
FIDRES 0.552855 Hz
AQ 0.9044468 sec
RG 191.17
DM 13.800 usec
DE 18.00 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.9178988 MHz
NUC1 13C
P1 10.00 usec
SI 32768
SF 150.9028123 MHz
WOW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

¹³C-

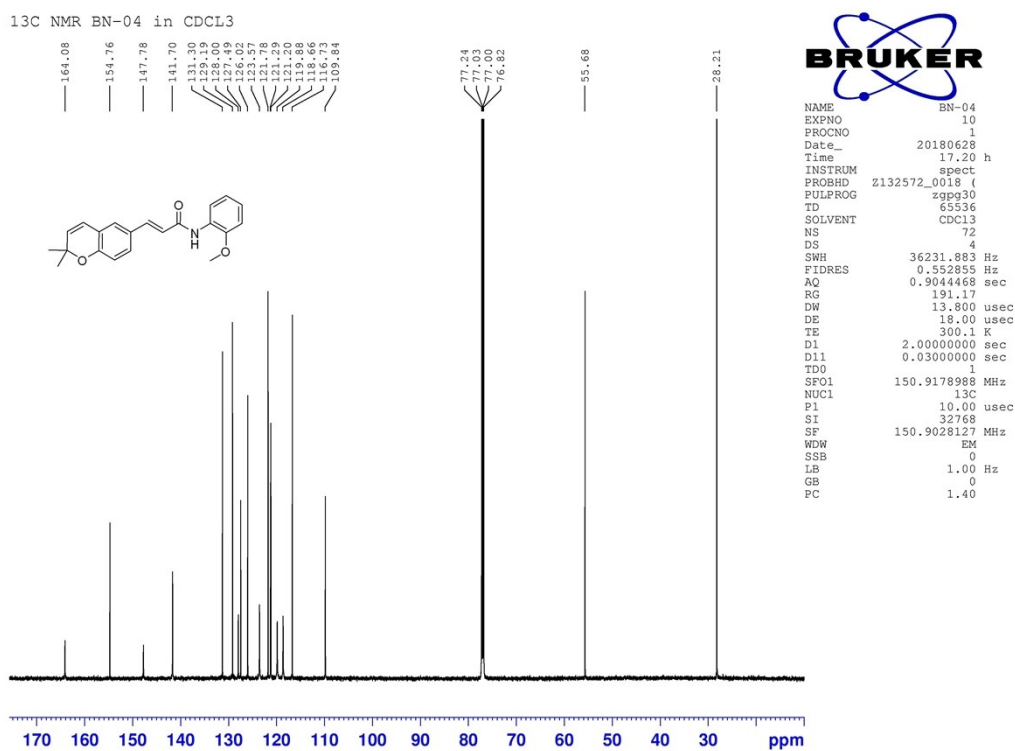
NMR spectrum of compound **BN-03** in CDCl₃



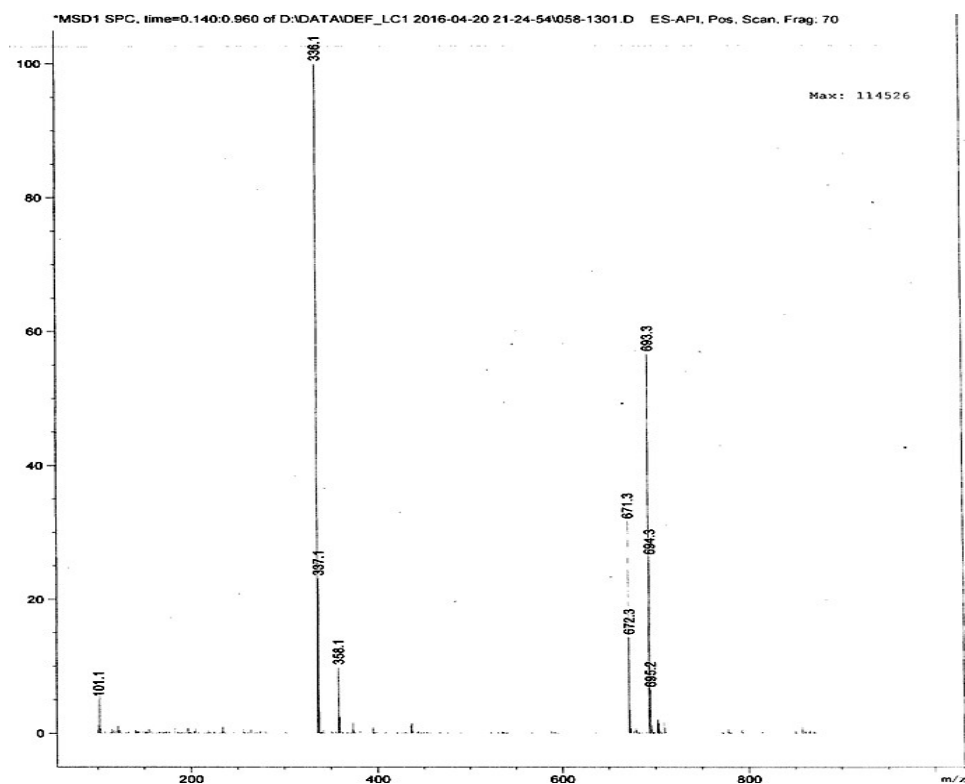
LC-MS spectrum of compound **BN-03**



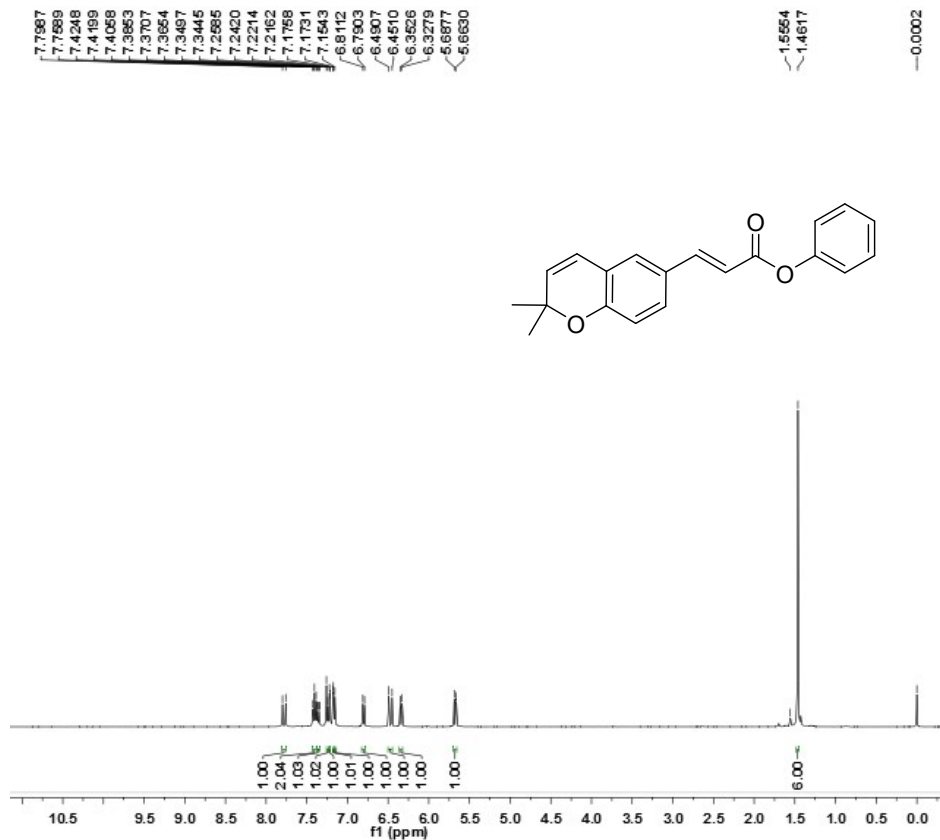
¹H-NMR spectrum of compound **BN-04** in DMSO-*d*₆



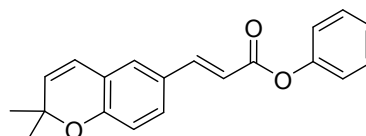
¹³C-NMR spectrum of compound **BN-04** in CDCl₃



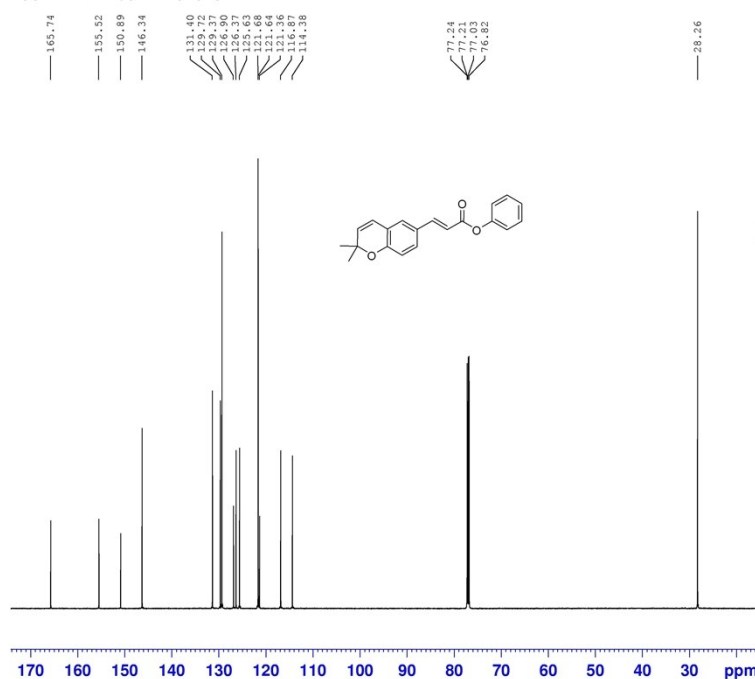
LC-MS spectrum of compound **BN-04**



¹H-NMR spectrum of compound **BN-05** in CDCl₃

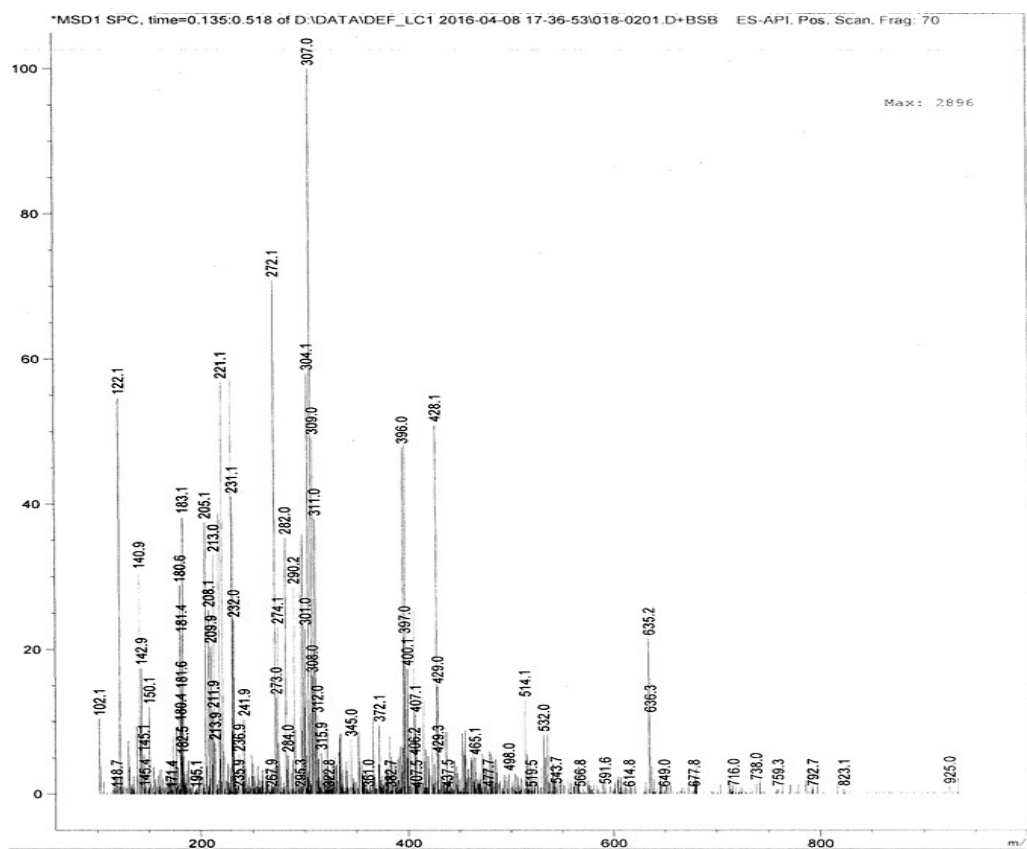


¹³C NMR BN-05 in CDCl₃

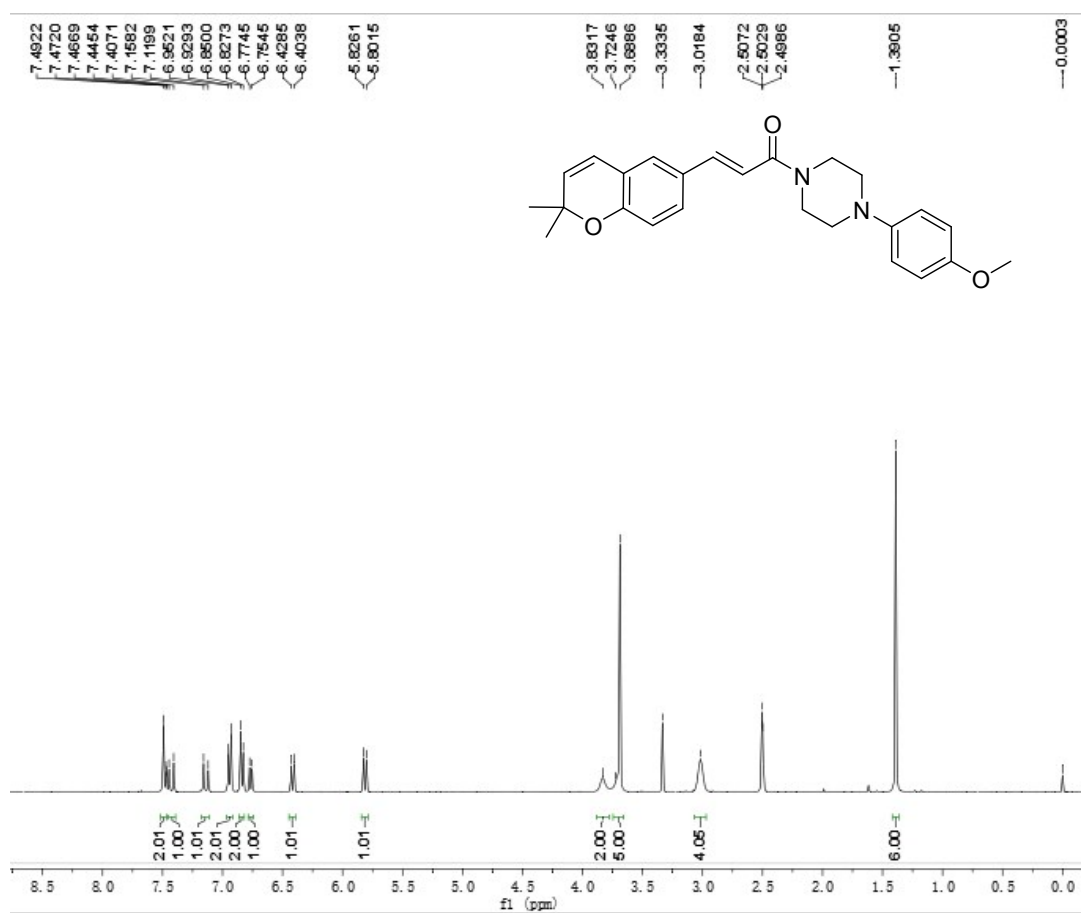


NAME BN-05
EXPNO 10
PROCNO 1
Date_ 20180628
Time 17.37 h
INSTRUM spect
PROBHD Z132572.0018 (6
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 89
DS 4
SWH 36231.883 Hz
FIDRES 0.552855 Hz
AQ 0.9044468 sec
RG 191.17
DW 13.800 usec
DE 18.00 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.9178988 MHz
NUC1 13C
P1 10.00 usec
SI 32768
SF 150.9028170 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

¹³C-NMR spectrum of compound **BN-05** in CDCl₃

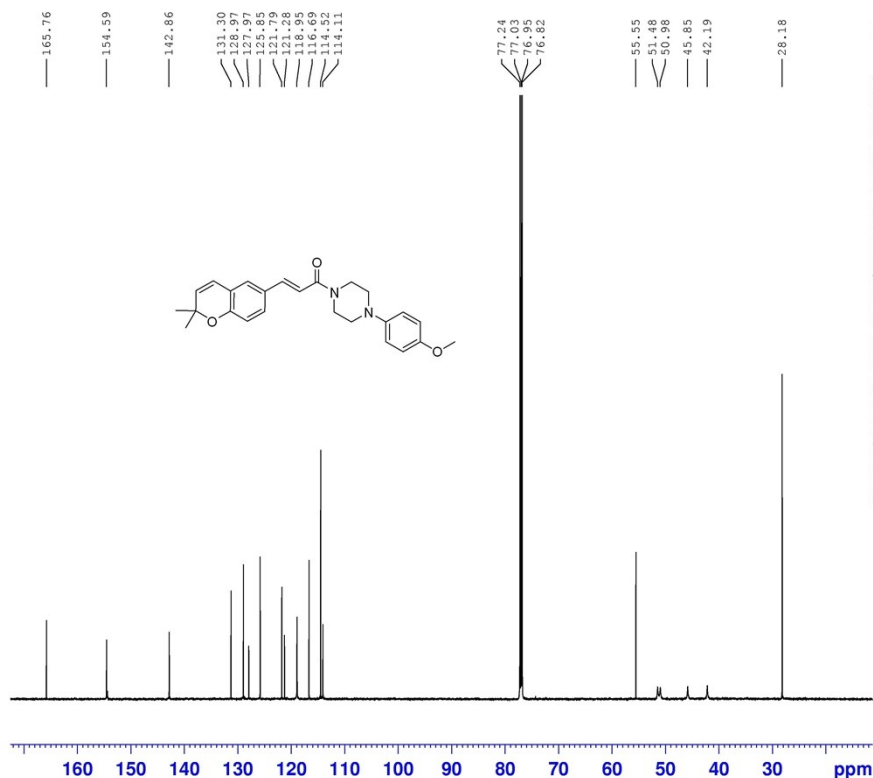


LC-MS spectrum of compound **BN-05**



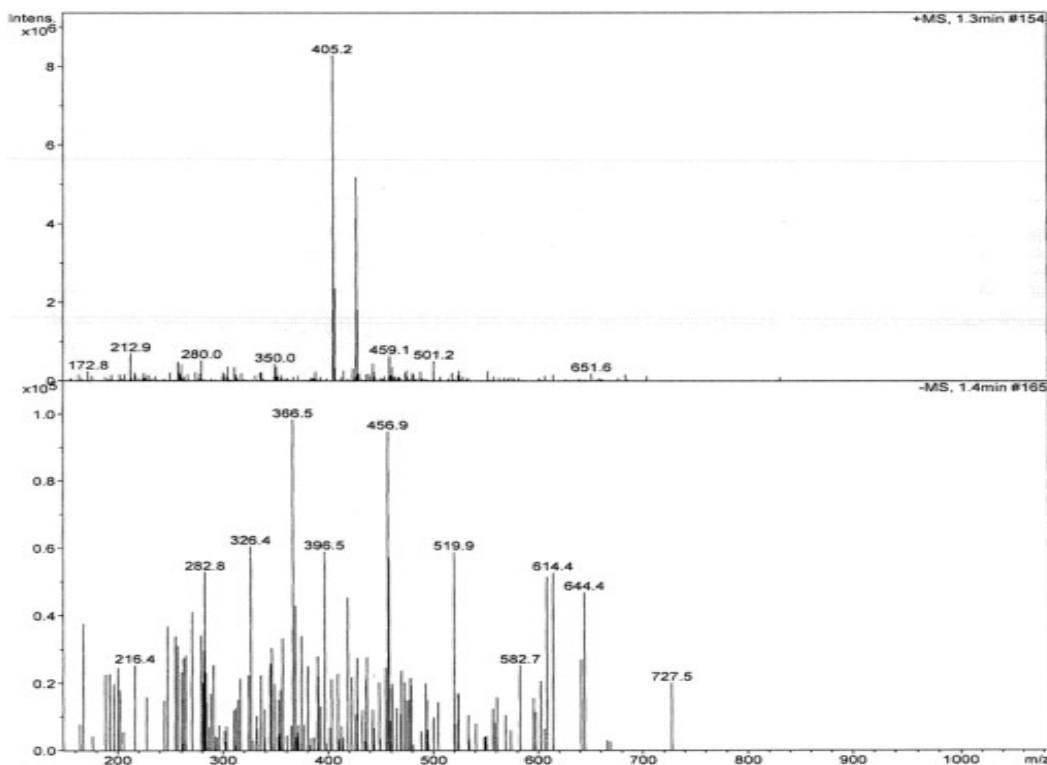
¹H-NMR spectrum of compound **BN-06** in DMSO-*d*₆

¹³C NMR BN-06 in CDCl₃

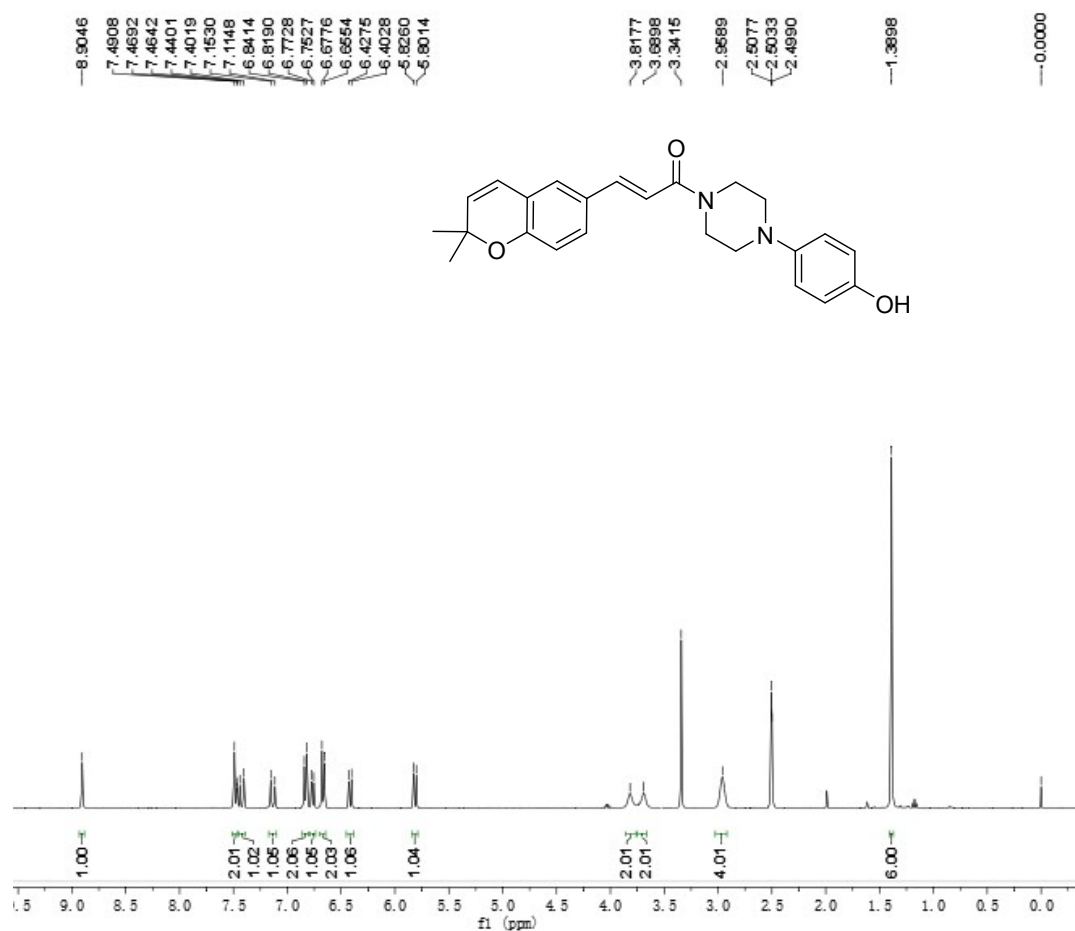


NAME BN-06
EXPNO 10
PROCNO 1
Date_ 20180628
Time 17.08 h
INSTRUM spect
PROBHD Z132572_0018 (Z132572_0018)
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 101
DS 4
SWH 36231.883 Hz
FIDRES 0.552855 Hz
AQ 0.9044468 sec
RG 191.17
DW 13.800 usec
DE 18.00 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SF01 150.9178988 MHz
NUC1 13C
P1 10.00 usec
SI 32768
SF 150.9028124 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

¹³C-NMR spectrum of compound **BN-06** in CDCl₃

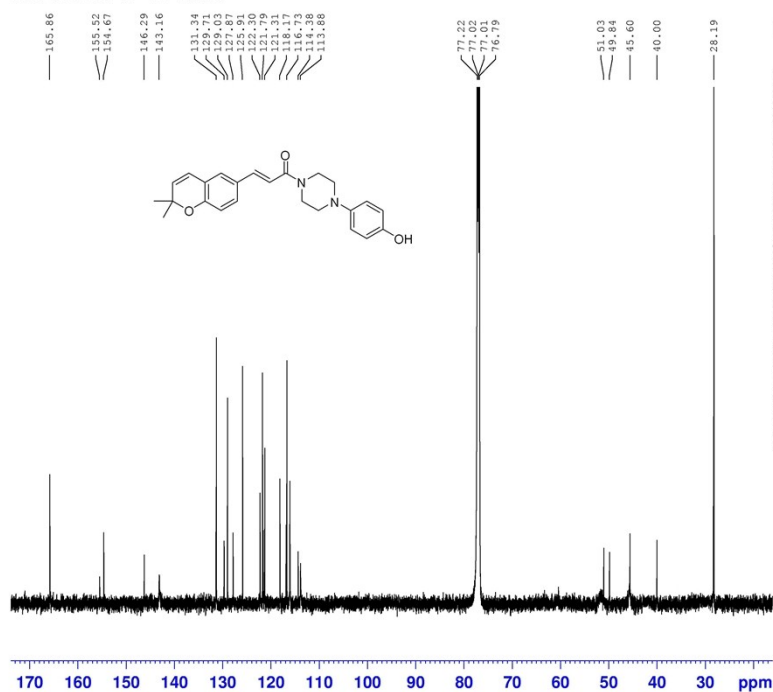


LC-MS spectrum of compound **BN-06**



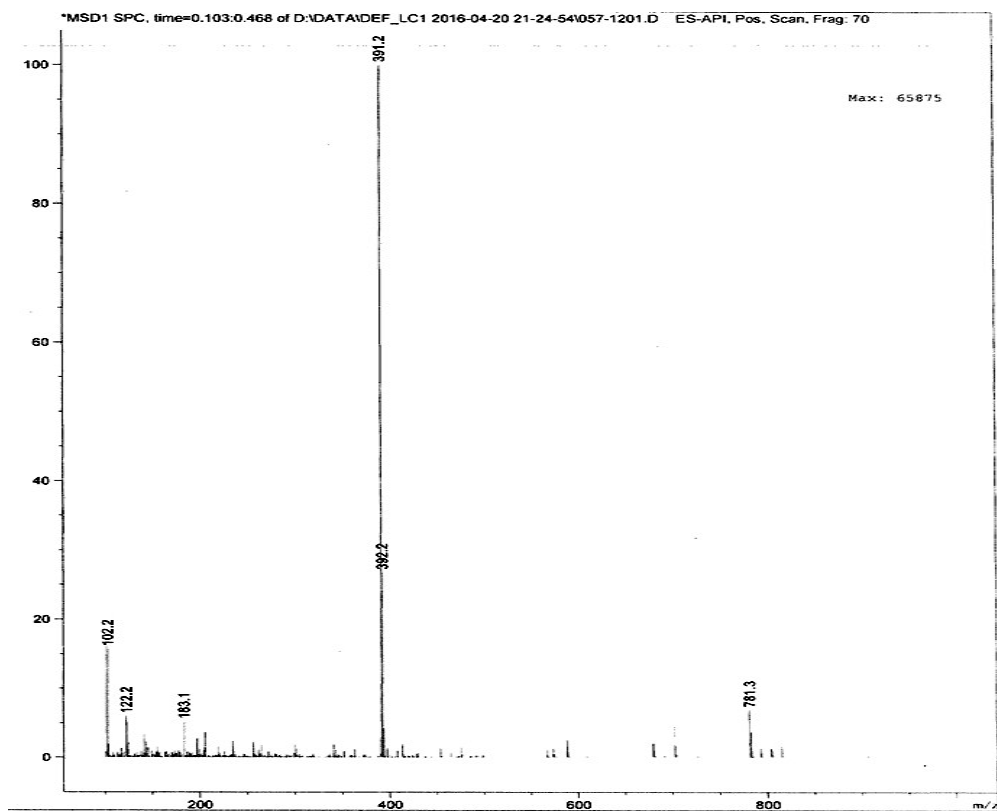
^1H -NMR spectrum of compound **BN-07** in $\text{DMSO}-d_6$

¹³C NMR BN-07 in CDCl₃

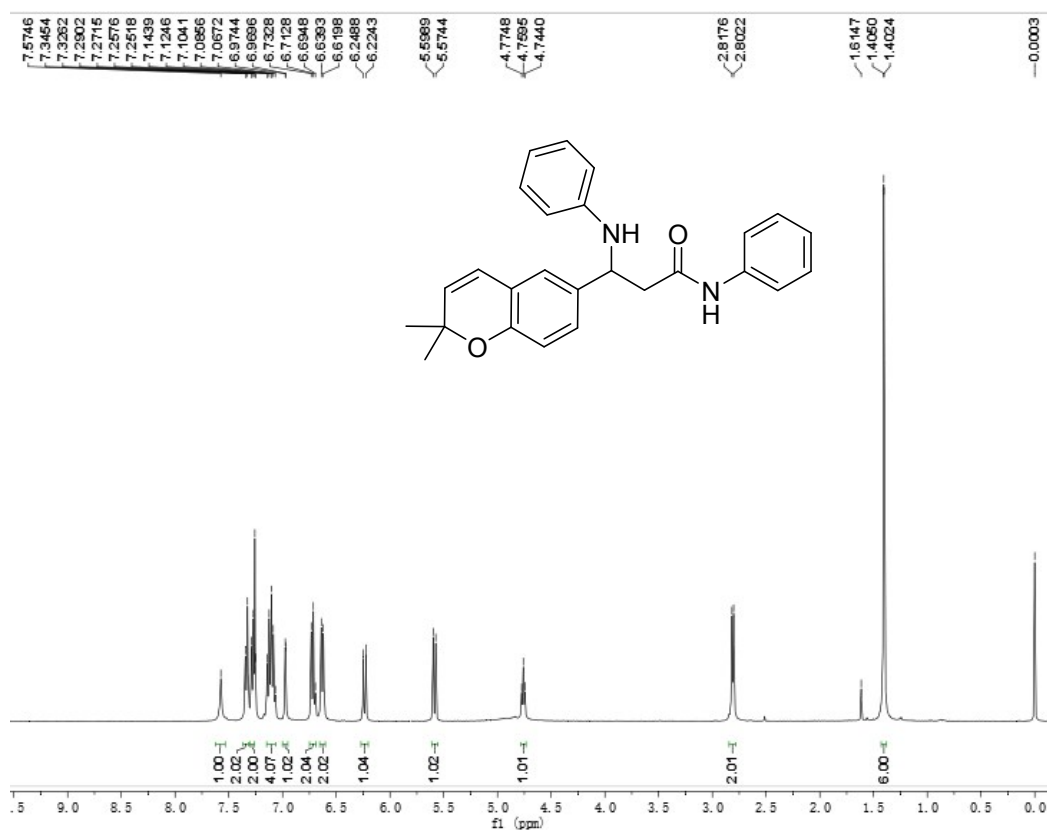


NAME BN-07
EXPNO 10
PROCNO 1
Date_ 20180630
Time 6.22 h
INSTRUM spect
PROBHD Z132572_0018 (1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1024
DS 4
SWH 36231.883 Hz
FIDRES 0.552855 Hz
AQ 0.9044468 sec
RG 191.17
DW 13.800 usec
DE 18.00 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TDO
SF01 150.9178988 MHz
NUC1 13C
P1 10.00 usec
SI 32768
SF 150.9028114 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

¹³C-NMR spectrum of compound **BN-07** in CDCl₃

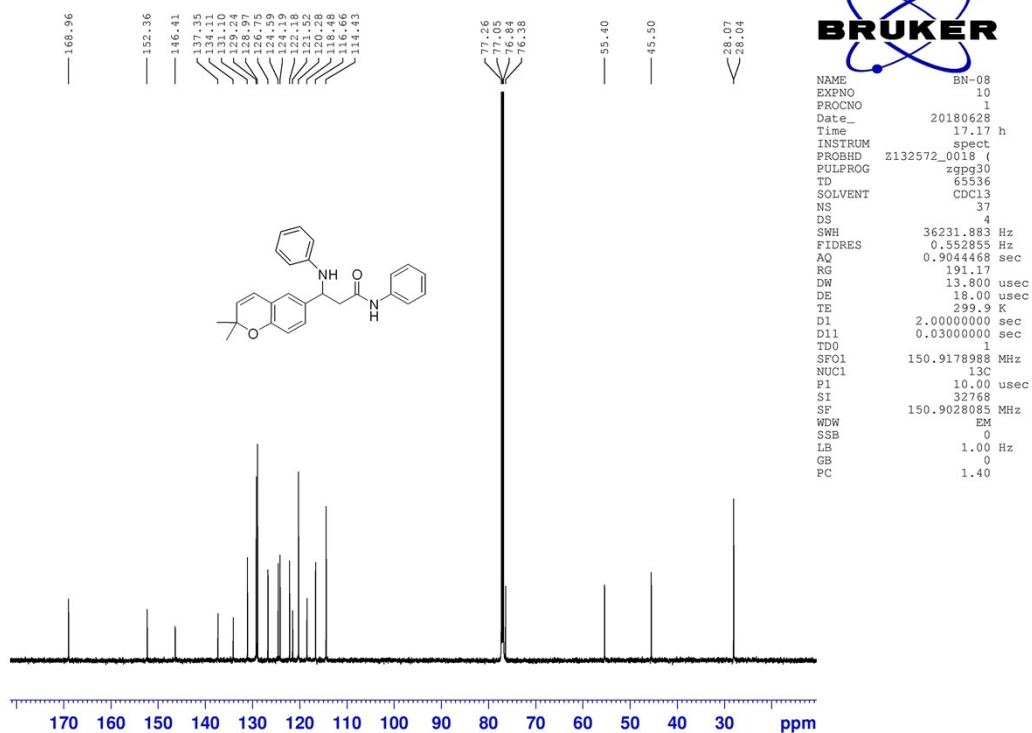


LC-MS spectrum of compound **BN-07**

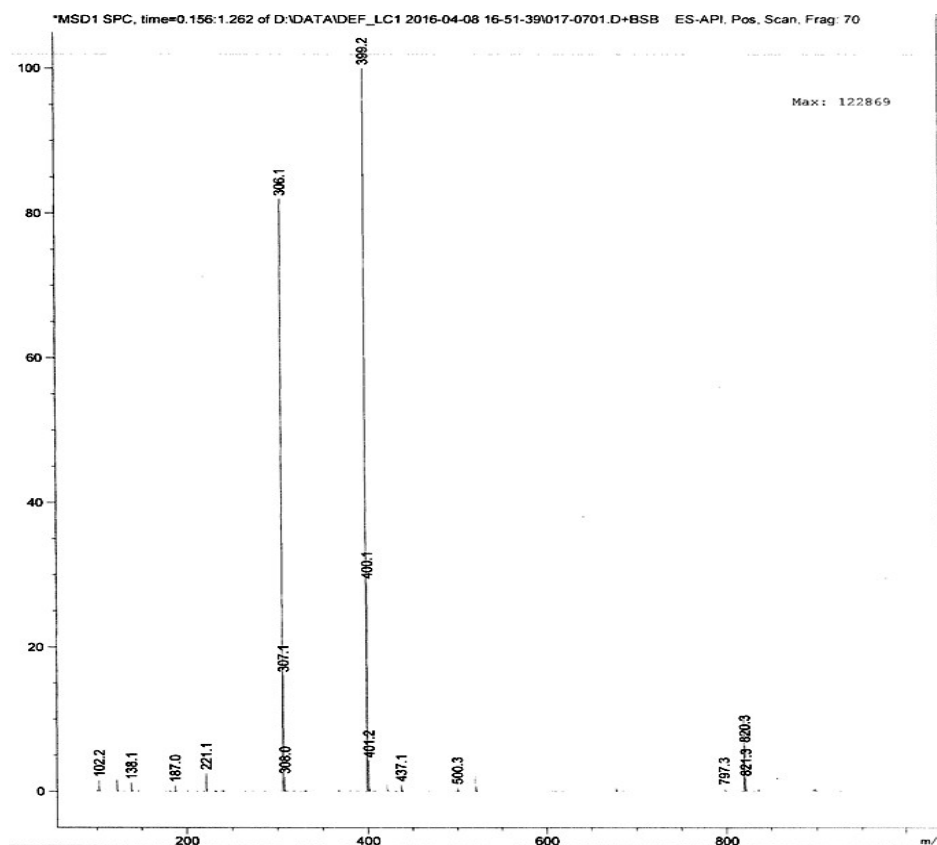


¹H-NMR spectrum of compound BN-08 in CDCl₃

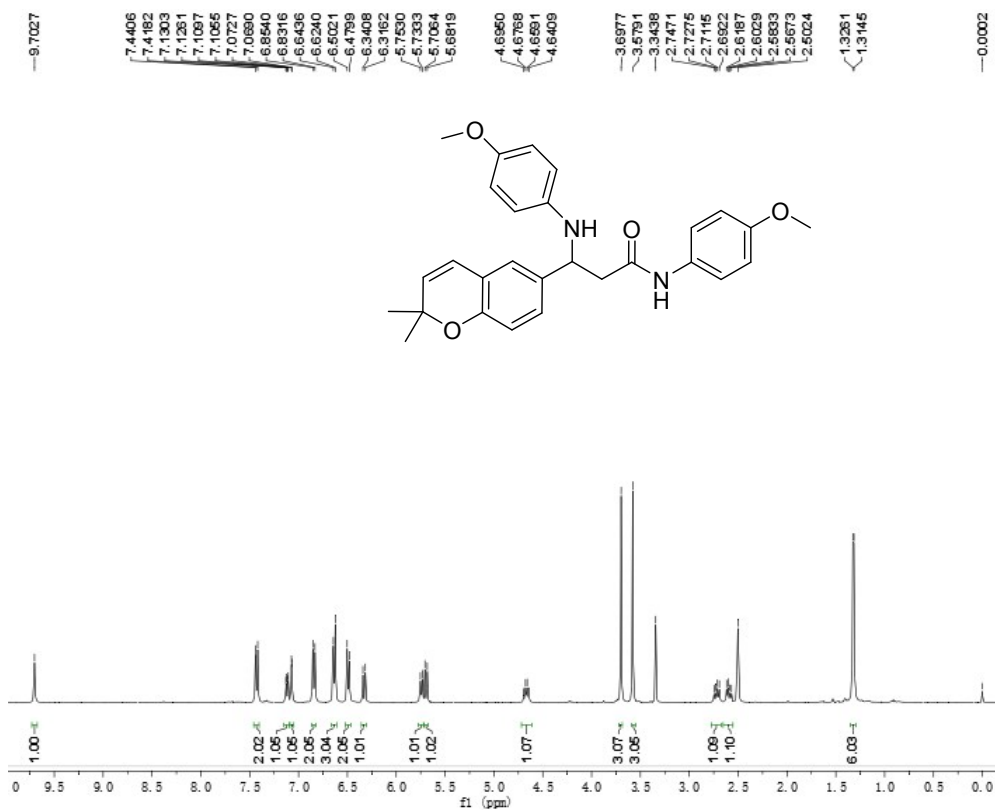
¹³C NMR BN-08 in CDCl₃



¹³C-NMR spectrum of compound BN-08 in CDCl₃

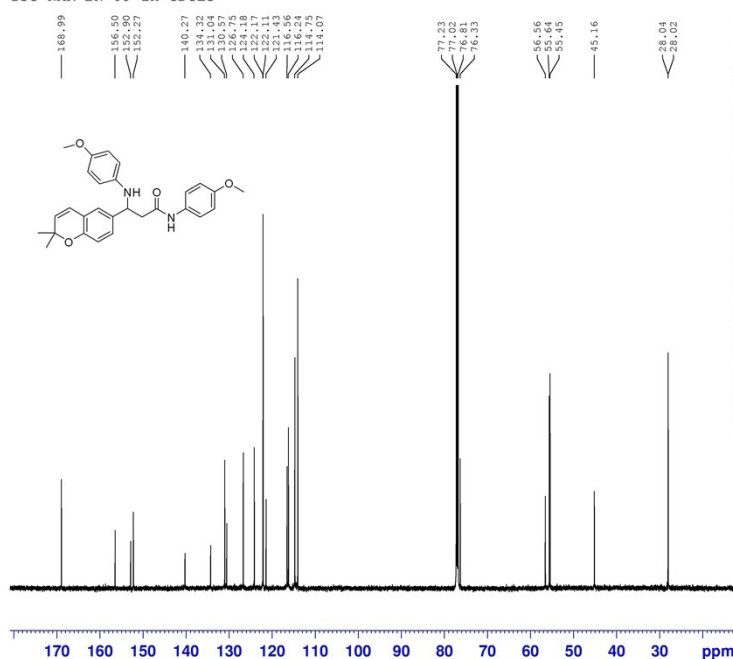


LC-MS spectrum of compound **BN-08**



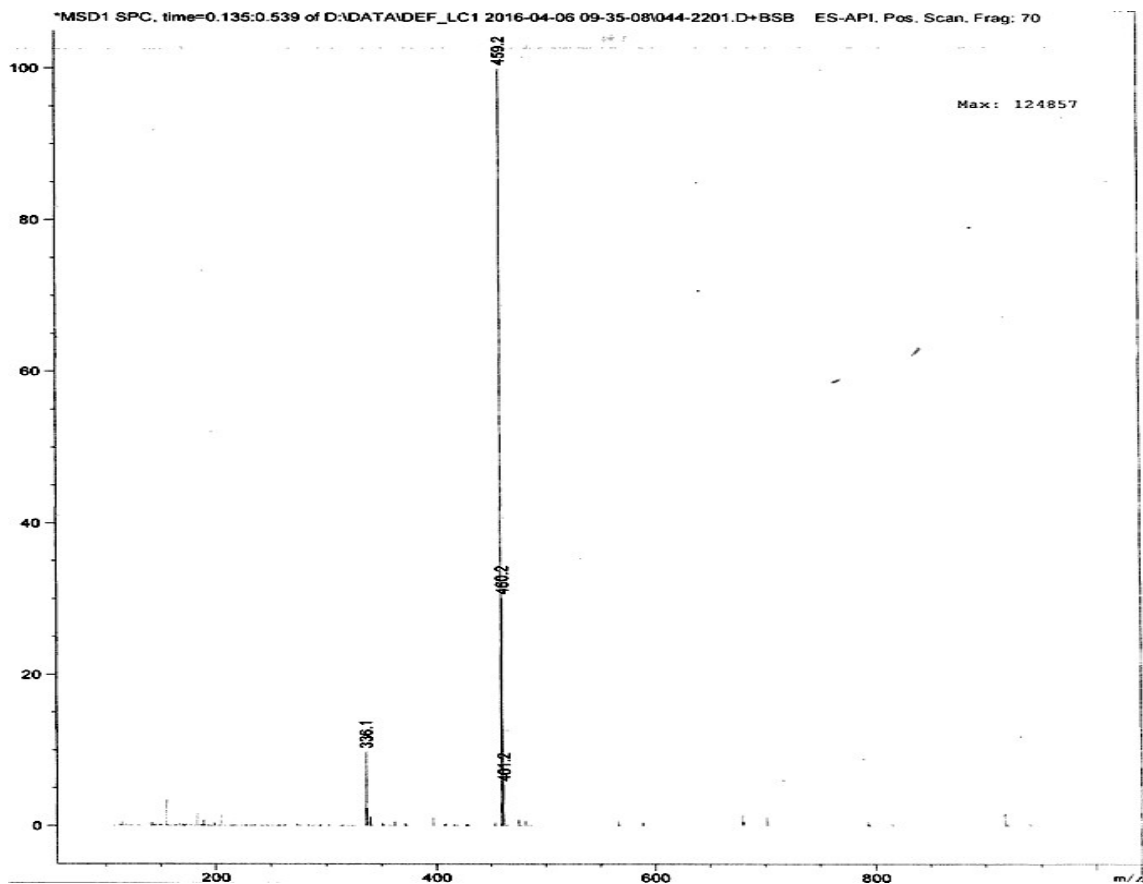
^1H -NMR spectrum of compound **BN-09** in $\text{DMSO}-d_6$

¹³C NMR BN-09 in CDCl₃

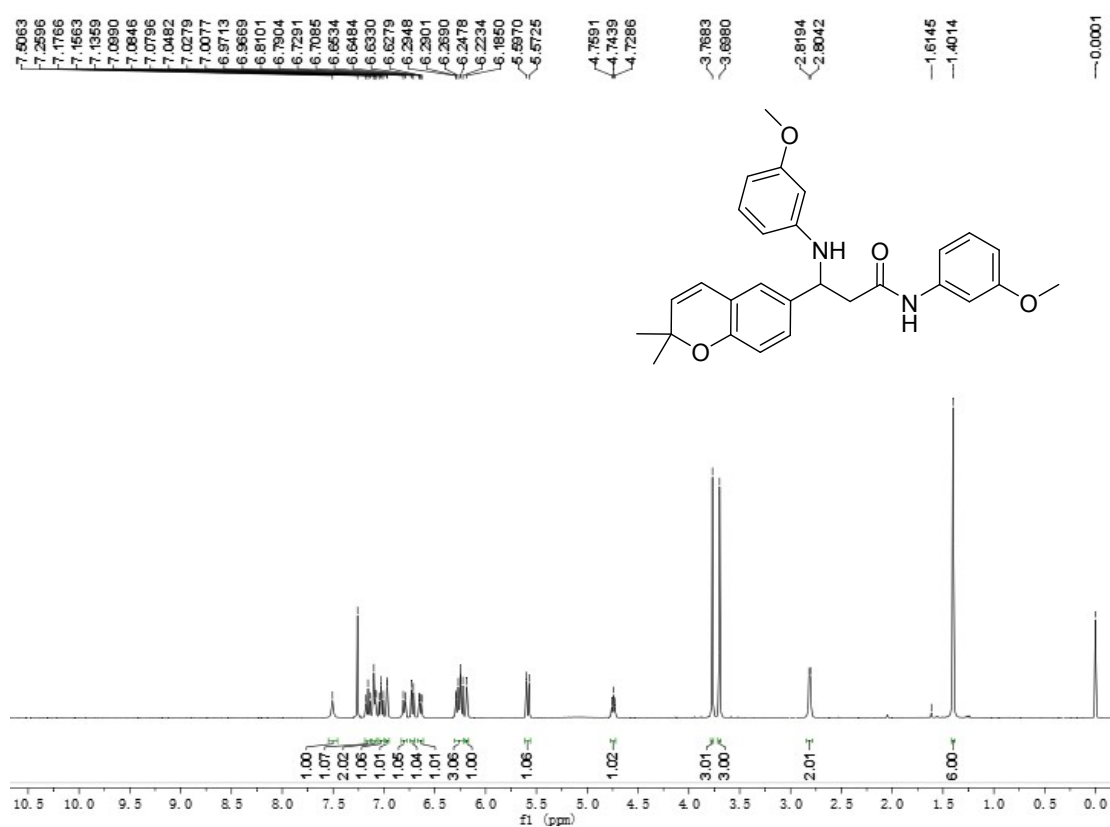


NAME BN-09
EXPNO 10
PROCNO 1
Date_ 20180628
Time 17.02 h
INSTRUM spect
PROBHD Z132572_0018 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 51
DS 4
SWH 36231.883 Hz
FIDRES 0.552855 Hz
AQ 0.9044468 sec
RG 191.17
DW 13.800 usec
DE 18.00 usec
TE 300.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TDO 1
SFO1 150.9178988 MHz
NUC1 13C
FI 10.00 usec
SI 32768
SF 150.9028124 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

¹³C-NMR spectrum of compound BN-09 in CDCl₃

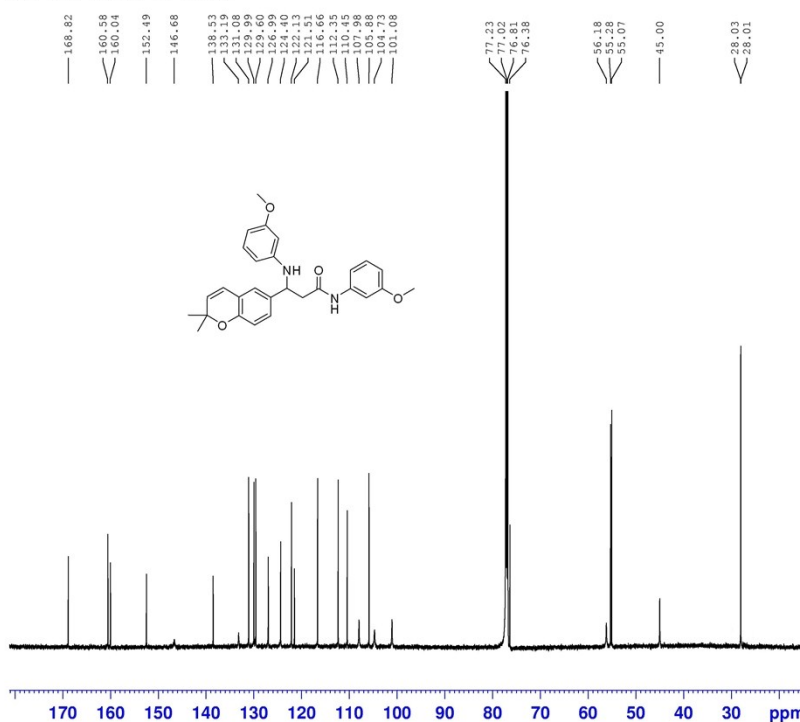


LC-MS spectrum of compound BN-09



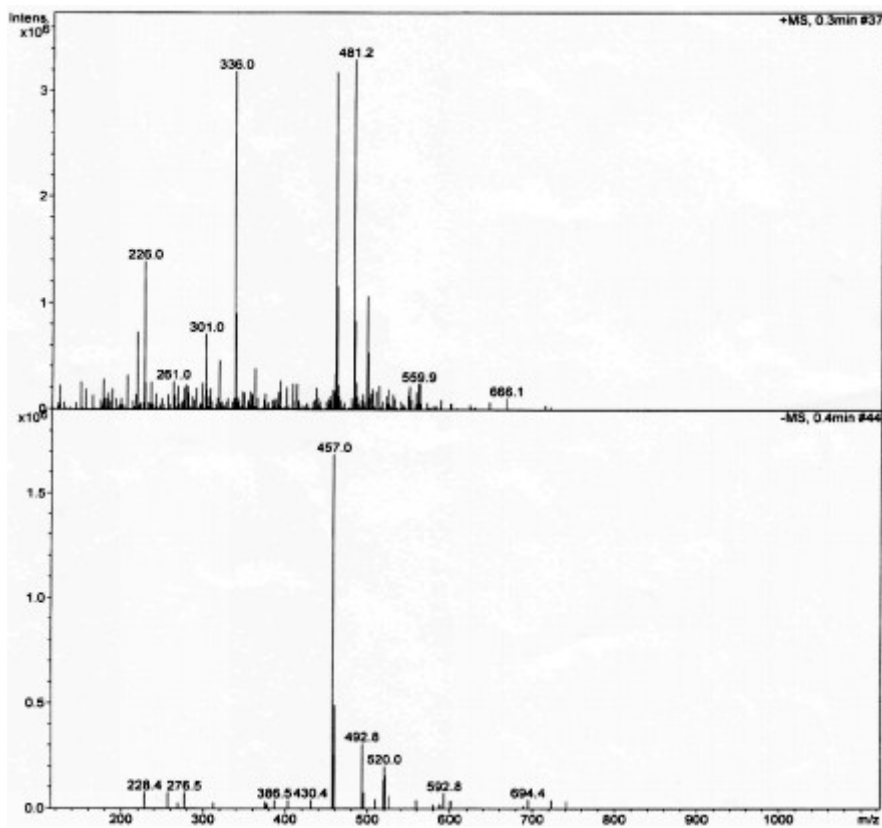
The ¹H-NMR spectrum of compound **BN-10** in CDCl₃

¹³C NMR BN-10 in CDCl₃



NAME BN-10
EXPNO 11
PROCNO 1
Date_ 20180630
Time 8.04 h
INSTRUM spect
PROBHD Z132572_0018 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 512
DS 4
SWH 36231.883 Hz
FIDRES 0.552855 Hz
AQ 0.9044468 sec
RG 191.17
DW 13.800 usec
DE 18.00 usec
TE 299.9 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.9178988 MHz
NUC1 13C
P1 10.00 usec
SI 32768
SF 150.9028114 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

¹³C-NMR spectrum of compound **BN-10** in CDCl₃



The LC-MS spectrum of compound **BN-10**

11. Morphology of primary cortical neurons of the rats

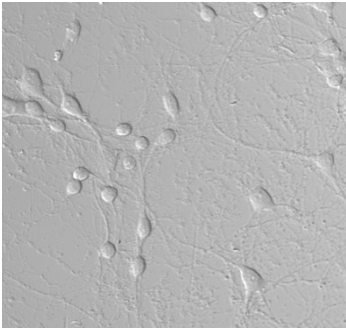


Fig. S1. Primary cortical neurons

12. Cell survival rate of primary neurons after administration in BA compounds

(%)

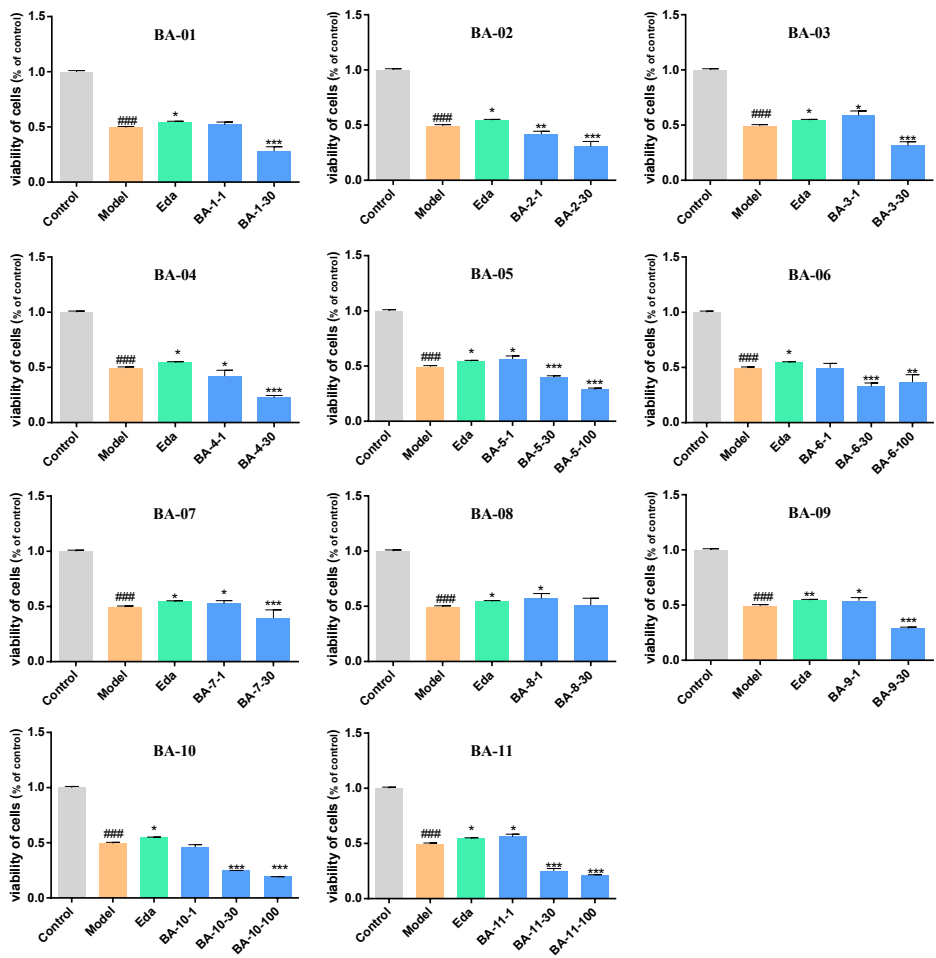


Fig. S2. Cell survival rate of primary neurons after administration in BA compounds (%)

13. Cell survival rate of primary neurons after administration in BN compounds

(%)

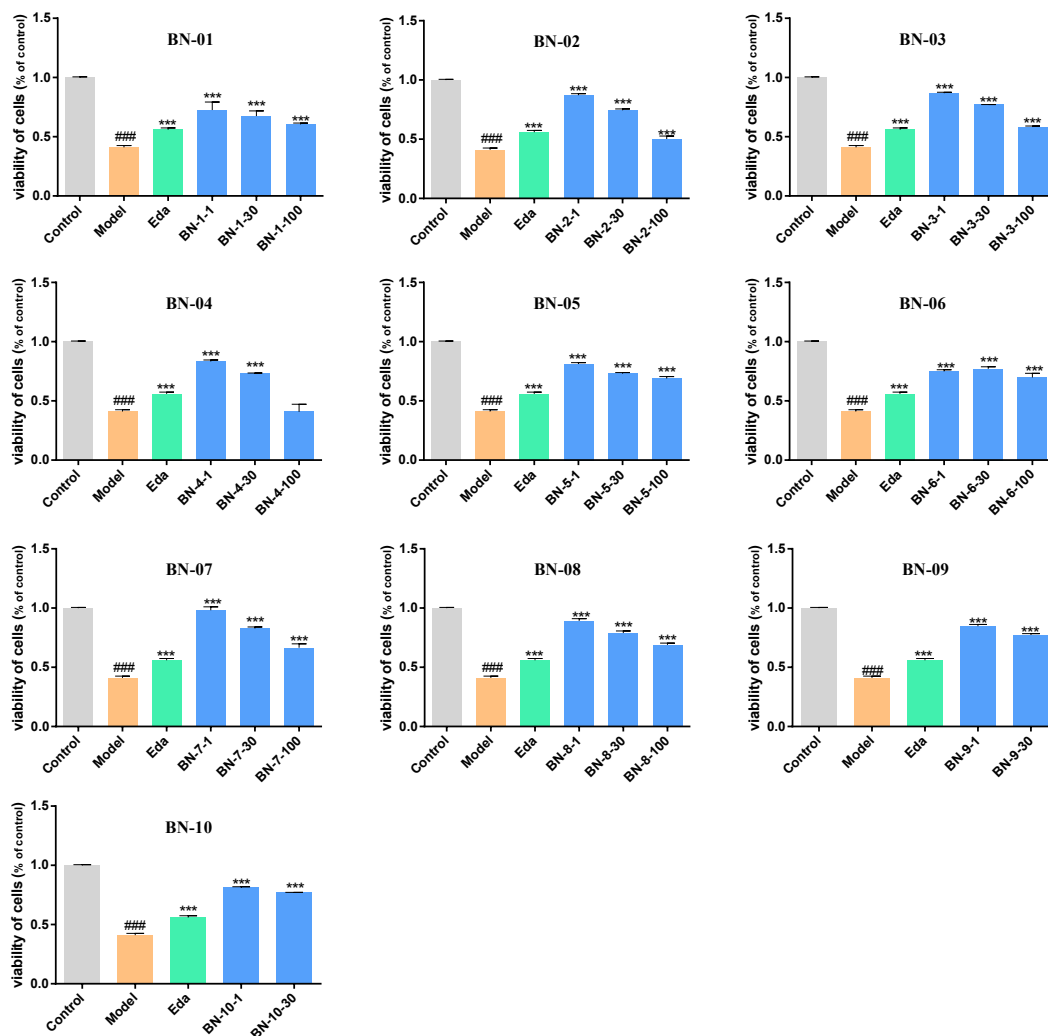


Fig. S3. Cell survival rate of primary neurons after administration in BN compounds (%)

14. The morphological changes of neurons after administration in BN compounds



Fig. S4. The morphological changes of neurons after administration in BN compounds

15. ADMET plot

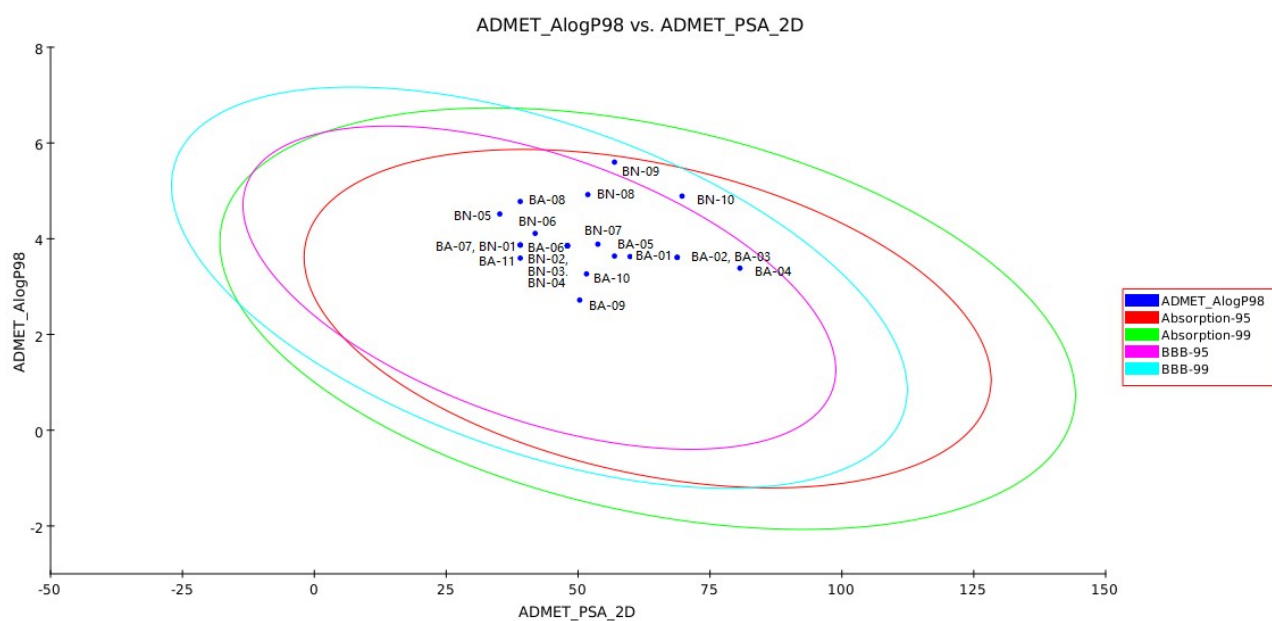


Fig. S5. ADMET plot