MECHANO-BIOCATALYTIC RAPID SYNTHESIS OF 2-AMINO-3-CYANO-4*H*-PYRAN DERIVATIVES

Ling Jiang, Qingqing Lu, Jingwen Dong, and Xiaohe Chu *

Collaborative Innovation Center of Yangtze River Delta Region Green

Pharmaceuticals, Zhejiang University of Technology, Hangzhou 310014, PR China

*Corresponding author. E-mail: chuxhe@zjut.edu.cn

1. General information

Bovine serum albumin (BSA) was purchased from Aladdin Chemicals (Shanghai, China). Lipozyme®RM IM (275 U/g) was purchased from Novozyme (Beijing, China). Unless otherwise noted, all reagents were obtained from commercial suppliers and were used without further purification.

All high-speed ball-milling reactions were conducted in a Retsch Mixer Mill MM 400 with 50 mL stainless steel grinding jar and three stainless steel grinding balls (diameter 10 mm). The NMR spectra were recorded on a Bruker AVANCE III 400 spectrometer (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR) or Bruker AVANCE III 500 spectrometer (500 MHz for ^{1}H NMR, 126 MHz for ^{13}C NMR) with DMSO-d_6 as solvent and tetramethylsilane (TMS) as internal standard. The mass spectra were measured by Bruker microTOF-Q II with electrospray ionization (ESI). All melting points were determined on an Optimelt MPA100 melting point apparatus and were uncorrected.

2. Mechano-biocatalytic rapid synthesis of 2-amino-3-cyano-4*H*-pyran derivatives

A mixture of aromatic aldehyde (0.5 mmol), malononitrile (0.5 mmol), dimedone (0.5 mmol) or 3-(dimethylamino)phenol (0.5 mmol), NaCl (300 mg) and BSA (50 mg for reactions with dimedone as substrate **3**, 80 mg for reactions with 3-(dimethylamino)phenol as substrate **3**) was milled for 40 min at 30 Hz in a Retsch MM 400 Mixer Mill (MM 400, Retsch, Germany) using a 50 mL stainless steel grinding jar with three stainless steel grinding balls (diameter 10 mm). After the milling was stopped, the reaction mixture was extracted with ethyl acetate (10 mL). The organic phase was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate, 2~4:1, V/V) to afford the products.

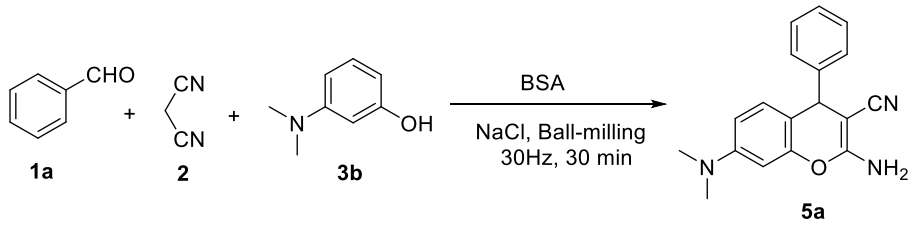
3. Optimization of the reaction conditions for the synthesis of 5a

Initially, the three-component reaction of benzaldehyde (**1a)**, malononitrile (**2**) and 3-(dimethylamino)phenol (**3b**) was used as a model reaction to optimize the reaction conditions including BSA loading, grinding frequency and reaction time.

3.1 Optimization of BSA loading for the synthesis of 5a

As shown in Table S1, the yield of the product was improved greatly by increasing the BSA loading from 0 to 80 mg and reached a plateau after 80 mg (Table S1, entries 1-6). Considering the cost of BSA, 80 mg was chosen as the suitable BSA loading for further investigation.

Table S1 Influence of BSA loading on the model reaction[a]



1a 2 3b 5a

Entry	BSA loading (mg)	Yield (%)[b]
1	0	34
2	40	43
3	50	48
4	60	68
5	80	82
6	100	84

[a] Reaction conditions: benzaldehyde **1a** (0.5 mmol), malononitrile **2** (0.5 mmol), 3-(dimethylamino)phenol **3b** (0.5 mmol), specified amount of BSA and NaCl (300 mg) were placed in a 50 mL stainless steel grinding jar along with three stainless steel grinding balls (diameter 10 mm) and milled for 30 min at 30 Hz.

[b] Isolated yields.

3.2 Optimization of grinding frequency for the synthesis of 5a

The influence of grinding frequency on the model reaction was also investigated and the results are summarized in Table S2. As can be seen from Table S2, When the grinding frequency increased from 15 Hz to 30 Hz, the yields increased from 59% to 82% (Table S2, Entries 1-4). Therefore, 30 Hz was chosen as the optimum grinding frequency for the further reactions.

Table S2 Effect of grinding frequency on the model reaction[a]

Entry	grinding frequency (Hz)	Yield (%)[b]
1	15	59
2	20	75
3	25	81
4	30	82

[a] Reaction conditions: benzaldehyde **1a** (0.5 mmol), malononitrile **2** (0.5 mmol), 3-(dimethylamino)phenol **3b** (0.5 mmol), BSA (80 mg) and NaCl (300 mg) were placed in a 50 mL stainless steel grinding jar along with three stainless steel grinding balls (diameter 10 mm) and milled for 30 min at the specified grinding frequency.

[b] Isolated yields.

3.3 Time course of the model reaction

We then investigated the time course of the model reaction (Figure S1). As shown in Figure S1, the yield increased obviously in the first 20 min. After 40 min of reaction, the yield reached a plateau. Thus, subsequent reactions were carried out for 40 min.

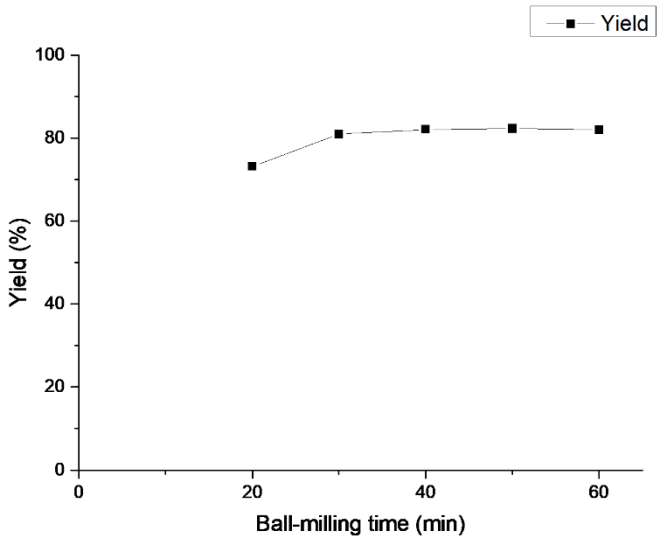
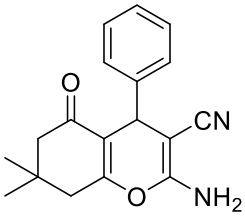


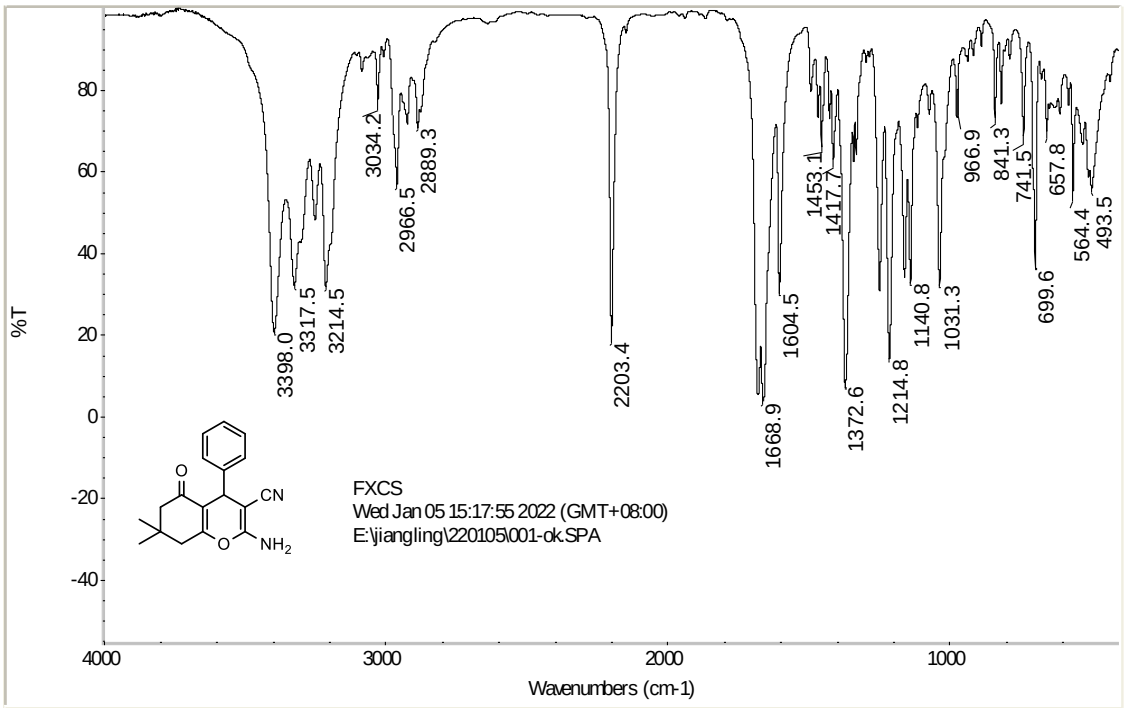
Figure S1 Time course of the model reaction. Reaction conditions: aldehyde (**1a**, 0.5 mmol), malononitrile (**2,** 0.5 mmol), 3-(dimethylamino)phenol (**3b,** 0.5 mmol), BSA (80 mg) and NaCl (300 mg) were placed in a 50 mL stainless steel grinding jar along with three stainless steel grinding balls (diameter 10 mm) and milled at 30 Hz. The yield was calculated based on the weight of purified product.

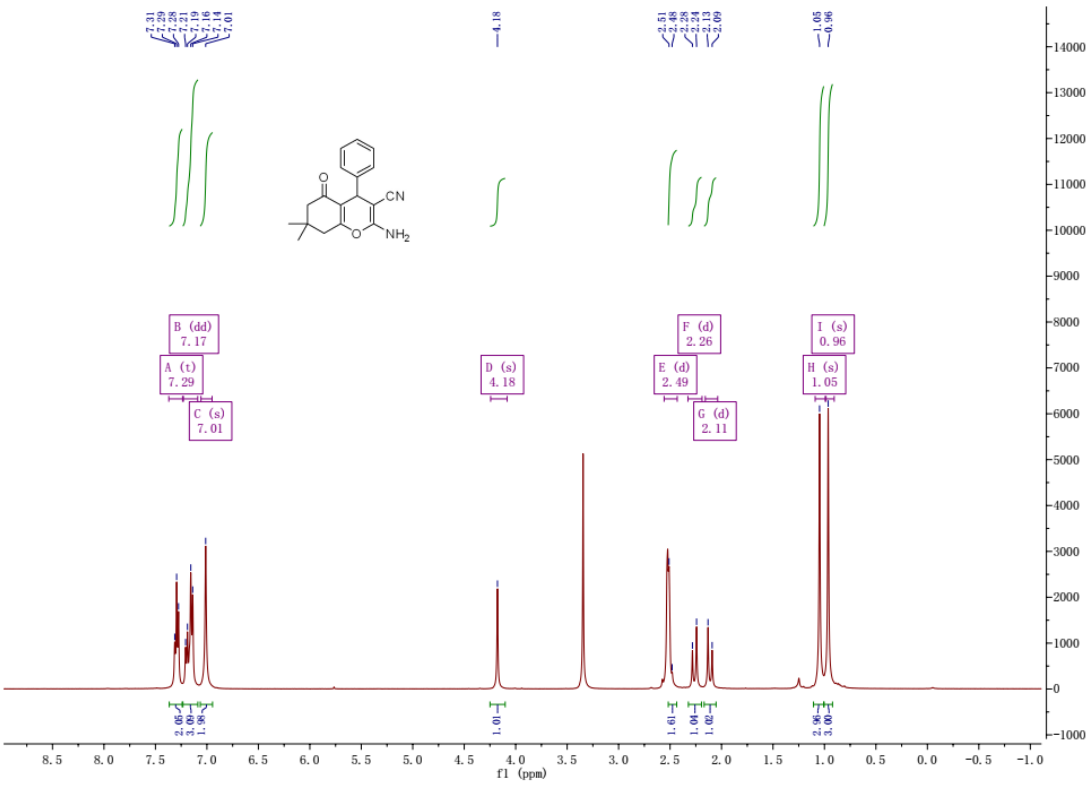
4. Data of the products

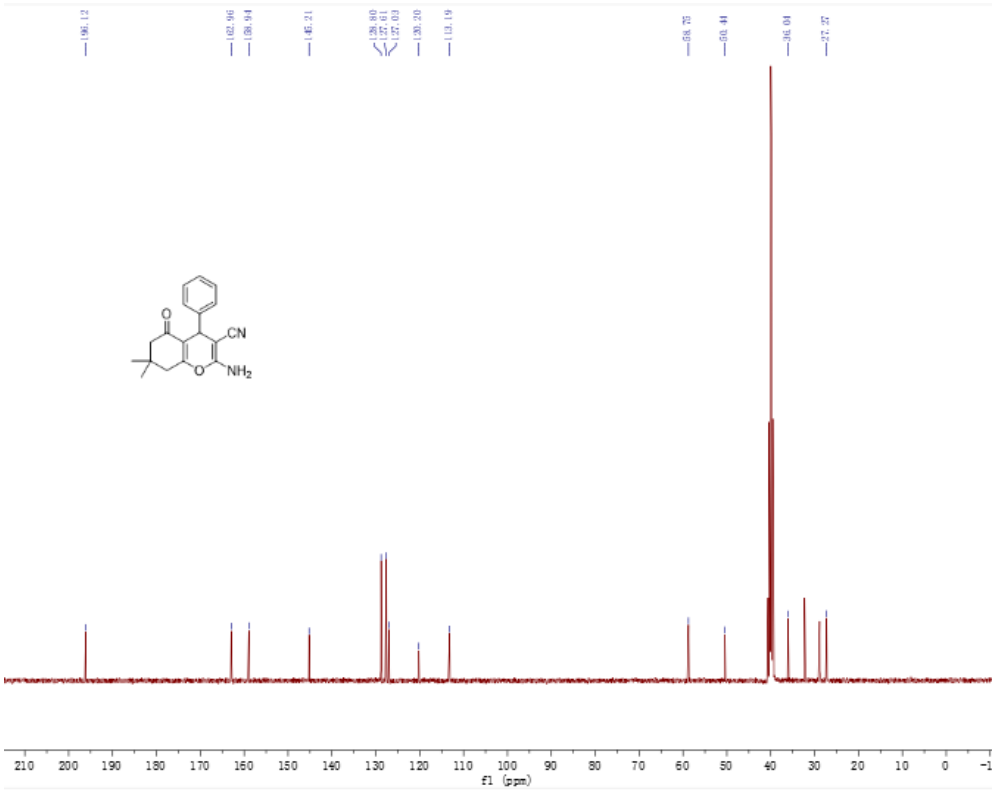


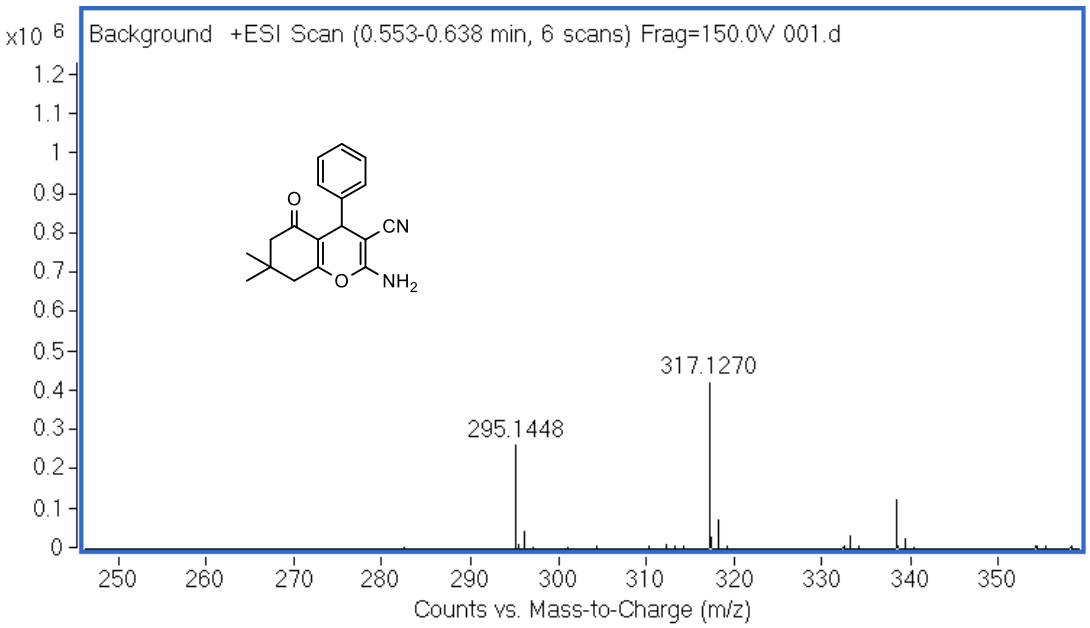
2-Amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4a**, $C_{18}H_{18}N_2O_2$)

White solid; mp 222-223 ℃. IR(KBr): 3398.0, 3317.5, 3214.5, 2966.5, 2203.4, 1668.9, 1604.5, 1372.6, 1214.8, 1140.8, 1031.3, 699.6 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 7.29 (t, J = 7.4 Hz, 2H), 7.17 (dd, J = 20.2, 7.3 Hz, 3H), 7.01 (s, 2H), 4.18 (s, 1H), 2.49 (d, J = 12.1 Hz, 2H), 2.26 (d, J = 16.1 Hz, 1H), 2.11 (d, J = 16.1 Hz, 1H), 1.05 (s, 3H), 0.96 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 196.12, 162.96, 158.94, 145.21, 128.80, 127.61, 127.03, 120.20, 113.19, 58.75, 50.44, 36.04, 27.27. HRMS (ESI) m/z calcd for $C_{18}H_{18}N_2O_2Na$ $[M+Na]^+$: 317.126, found: 317.127.

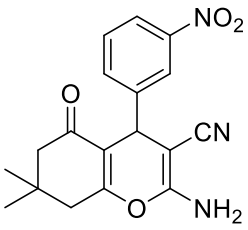



7.31
7.29
7.28
7.21
7.19
7.16
7.14
7.01
4.18
2.51
2.48
2.28
2.24
2.13
2.09
1.05
0.96
O
CN
O
NH2
B (dd)
7.17
A (t)
7.29
C (s)
7.01
D (s)
4.18
F (d)
2.26
E (d)
2.49
G (d)
2.11
I (s)
0.96
H (s)
1.05
2.05
3.09
1.98
1.01
1.61
1.04
1.02
2.96
3.00
f1 (ppm)


196.12
162.96
158.94
145.21
128.80
127.61
127.03
120.20
113.19
58.75
50.44
36.04
27.27
O
CN
O
NH2
f1 (ppm)

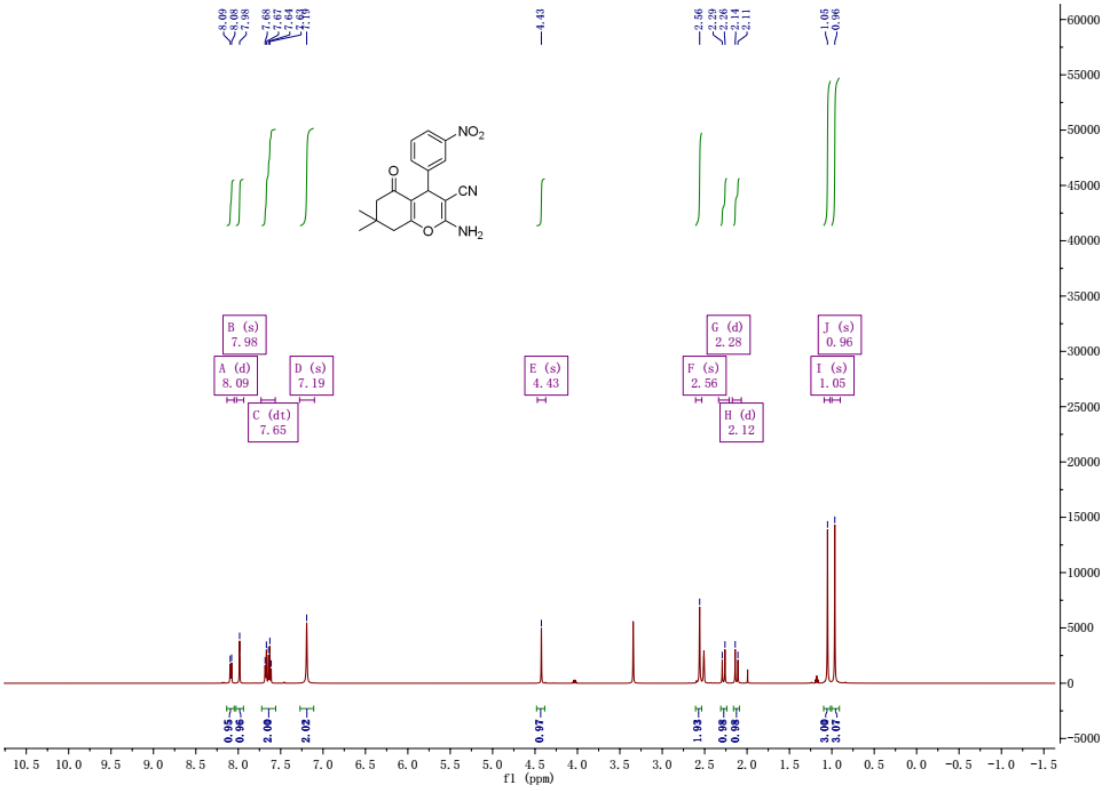


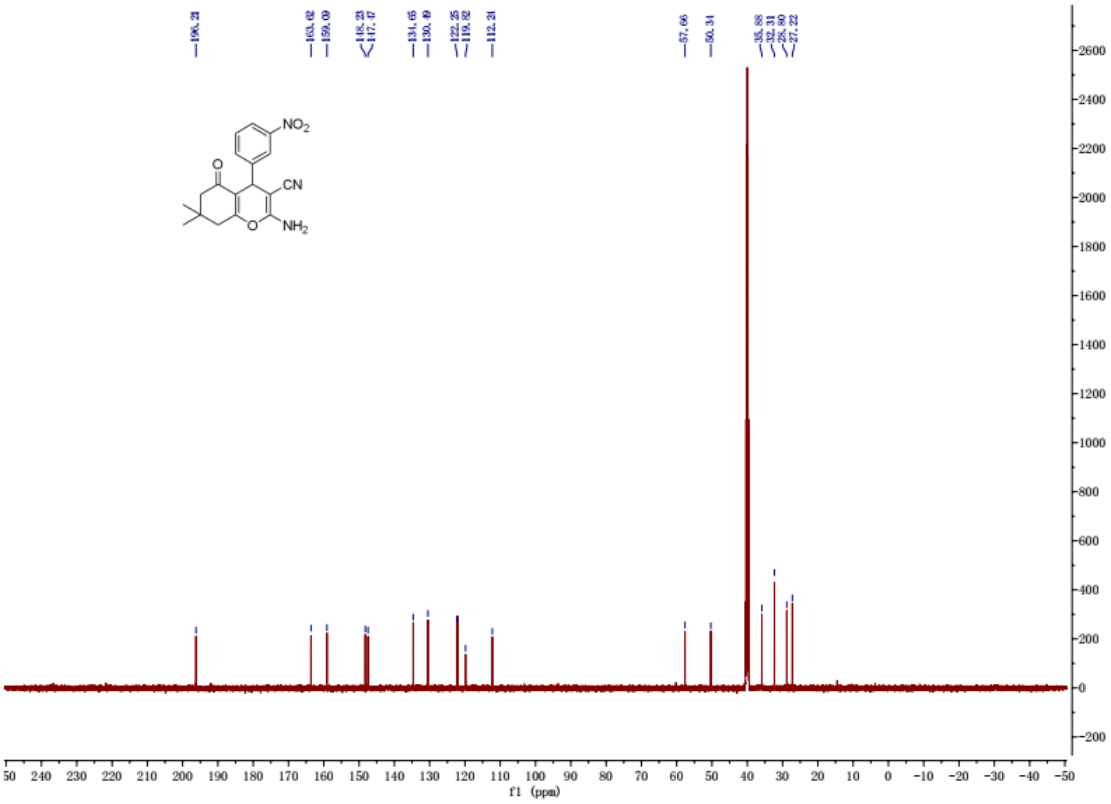
Formula (M)	Ion Formula	m/z	Calc m/z	Diff (ppm)	DBE
C18 H18 N2 O2	C18 H19 N2 O2	295.1448	295.1441	-2.37	11
C18 H18 N2 O2	C18 H18 N2 Na O2	317.127	317.126	-3.23	11

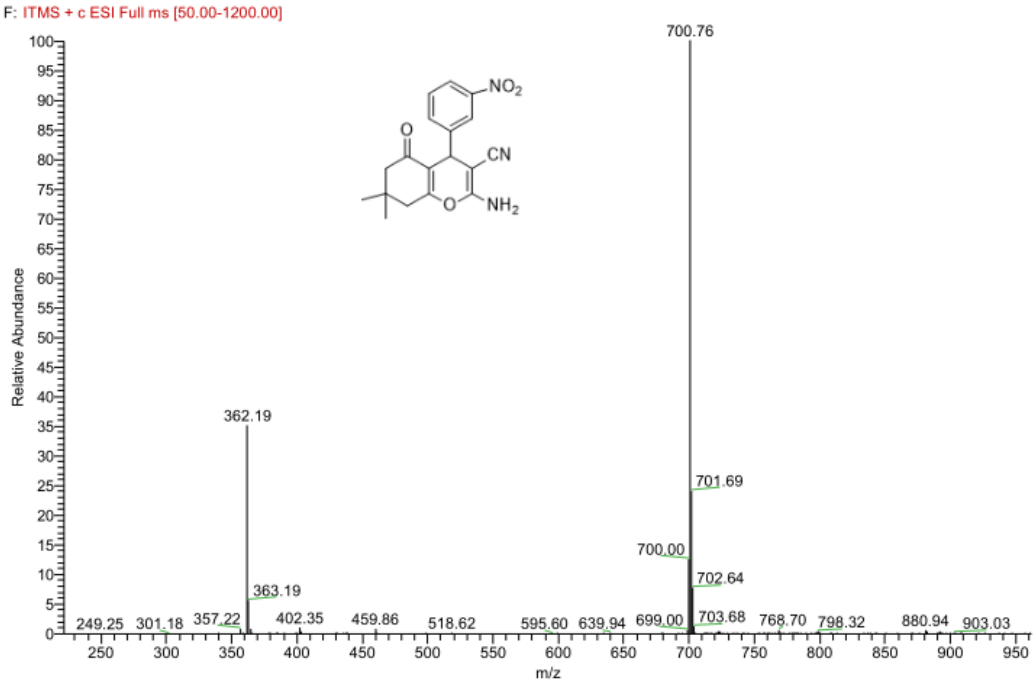


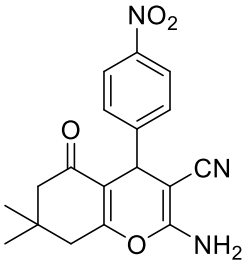
2-Amino-7,7-dimethyl-4-(3-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4b**, $C_{18}H_{17}N_3O_4$)

White solid; mp 213-215 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.09 (d, J = 8.1 Hz, 1H), 7.98 (s, 1H), 7.65 (dt, J = 15.7, 7.7 Hz, 2H), 7.19 (s, 2H), 4.43 (s, 1H), 2.56 (s, 2H), 2.28 (d, J = 16.1 Hz, 1H), 2.12 (d, J = 16.1 Hz, 1H), 1.05 (s, 3H), 0.96 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 196.21, 163.62, 159.09, 148.23, 147.47, 134.65, 130.49, 122.25, 119.82, 112.24, 57.66, 50.34, 35.88, 32.31, 28.80, 27.22. MS (ESI): $[2M+Na]^+$: 701.69.



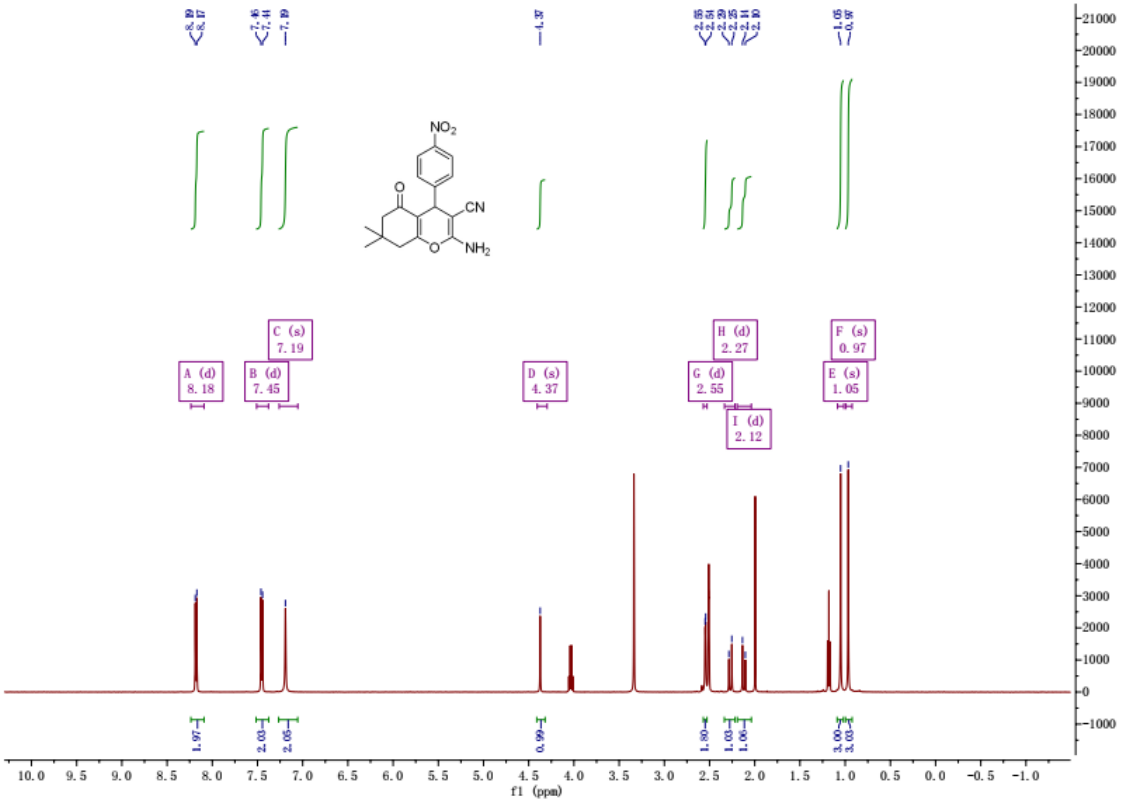

196.28
163.62
159.09
148.23
147.47
134.65
130.49
122.25
119.02
112.21
57.66
50.34
35.88
32.31
28.80
27.22
NO2
CN
NH2
O
f1 (ppm)

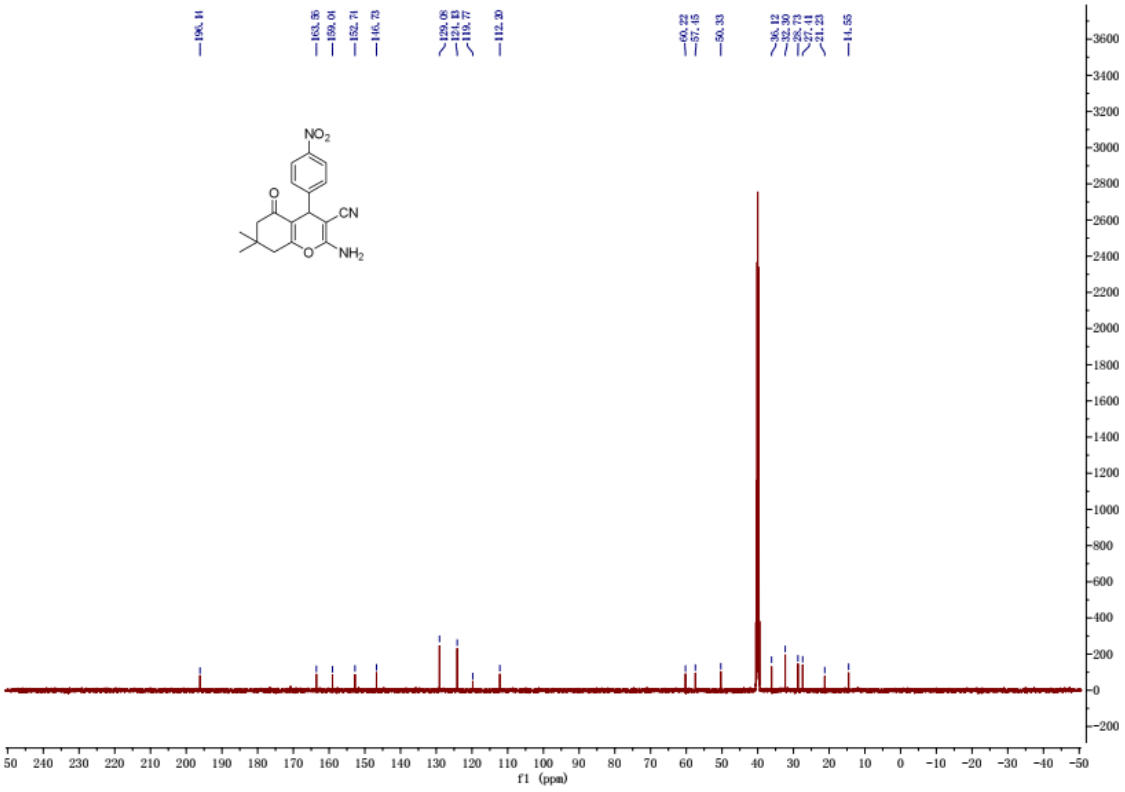

F: ITMS + c ESI Full ms [50.00-1200.00]
700.76
362.19
701.69
700.00
702.64
363.19
249.25
301.18
357.22
402.35
459.86
518.62
595.60
639.94
699.00
703.68
768.70
798.32
880.94
903.03
Relative Abundance
m/z
NO2
CN
NH2
O

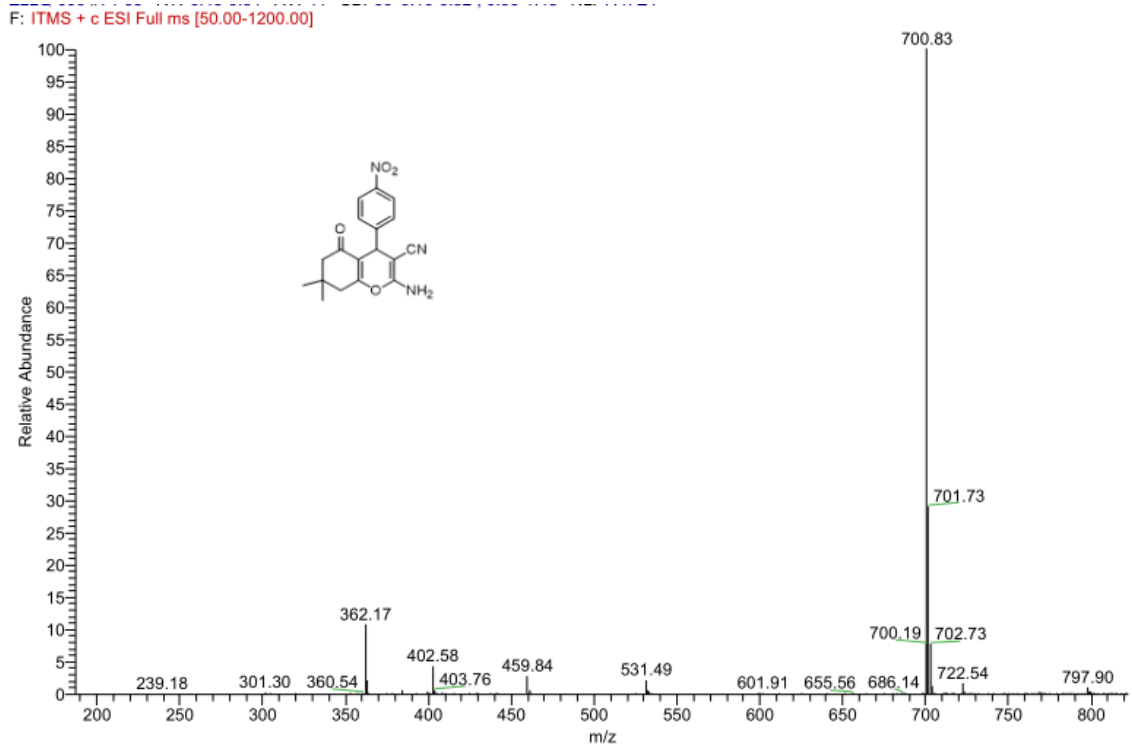


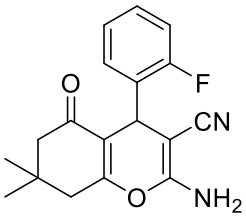
2-Amino-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4c**, $C_{18}H_{17}N_3O_4$)

Faint yellow solid; mp 184-185 ℃. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.18 (d, J = 8.7 Hz, 2H), 7.45 (d, J = 8.7 Hz, 2H), 7.19 (s, 2H), 4.37 (s, 1H), 2.55 (d, J = 3.1 Hz, 2H), 2.27 (d, J = 16.1 Hz, 1H), 2.12 (d, J = 16.1 Hz, 1H), 1.05 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 196.14, 163.56, 159.04, 152.74, 146.73, 129.08, 124.13, 119.77, 112.20, 60.22, 57.45, 50.33, 36.12, 32.30, 28.73, 27.41, 21.23, 14.55. MS (ESI): $[2M+Na]^+$: 701.73.



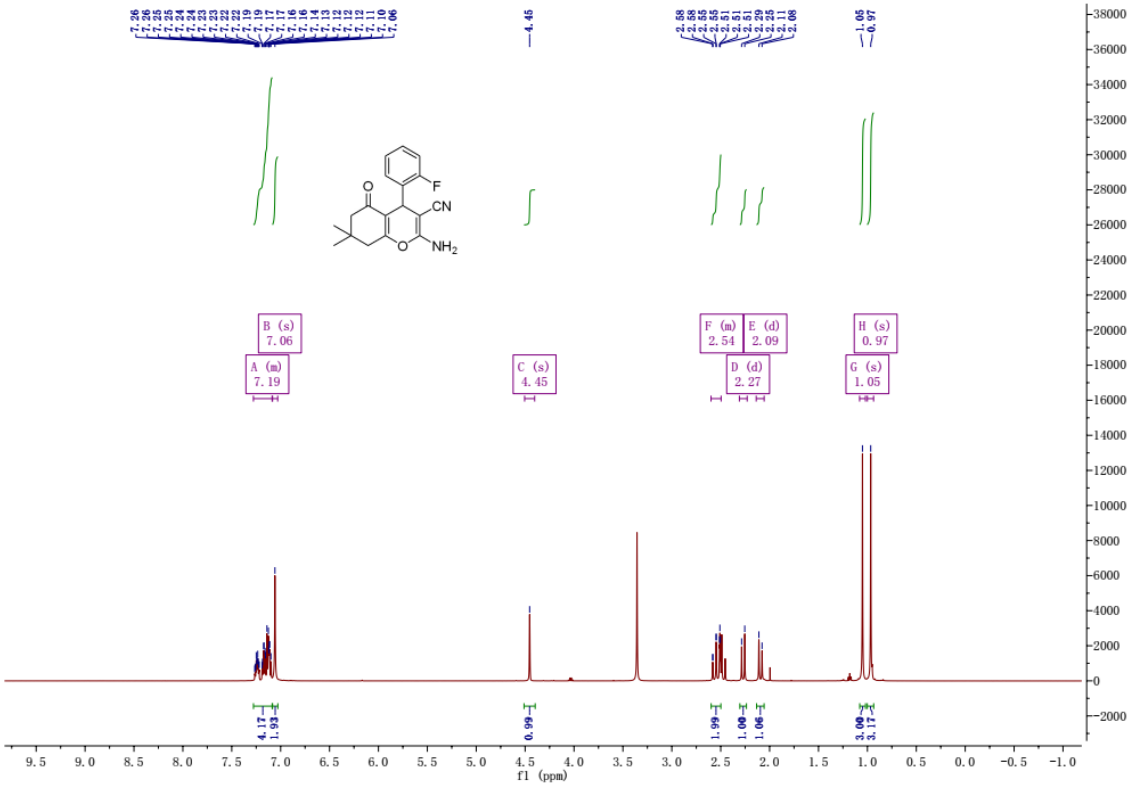

196.11
163.56
159.04
152.71
146.73
129.08
124.13
119.77
112.20
60.22
57.45
50.33
36.12
32.30
28.73
27.41
21.23
14.55
NO2
O
CN
NH2
O
f1 (ppm)

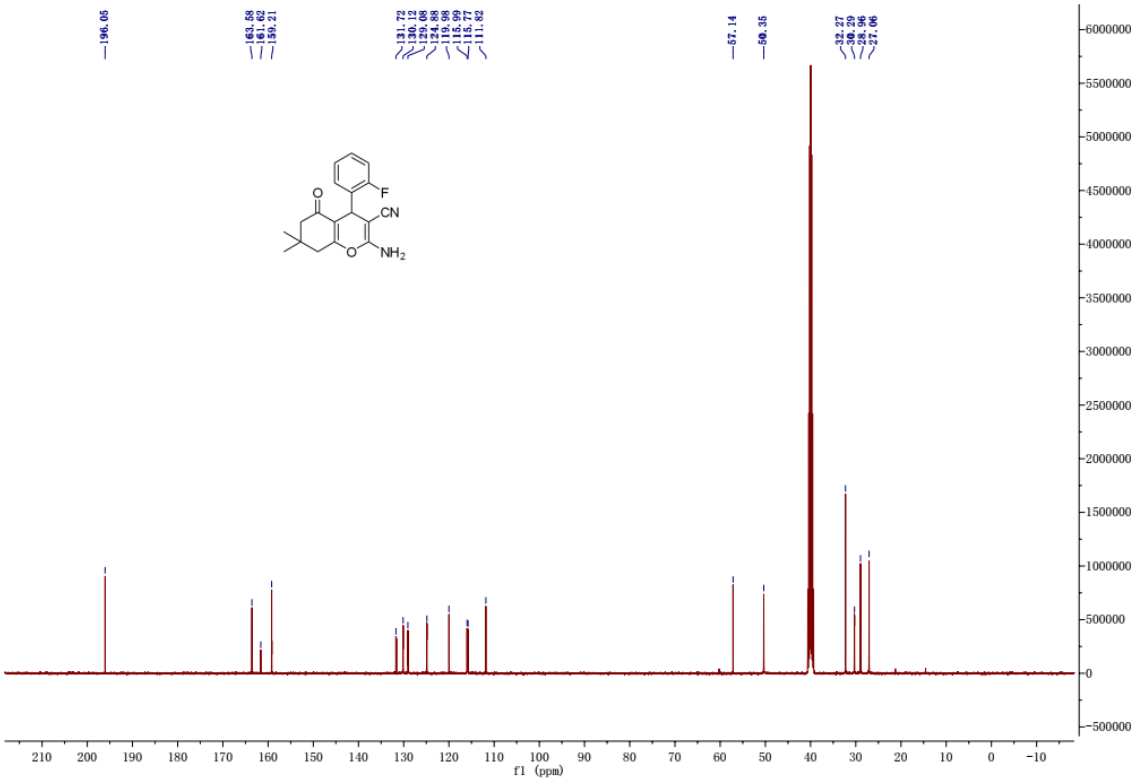

F: ITMS + c ESI Full ms [50.00-1200.00]
Relative Abundance
m/z
700.83
701.73
362.17
700.19
702.73
402.58
459.84
403.76
531.49
722.54
797.90
239.18
301.30
360.54
601.91
655.56
686.14
NO2
O
CN
NH2

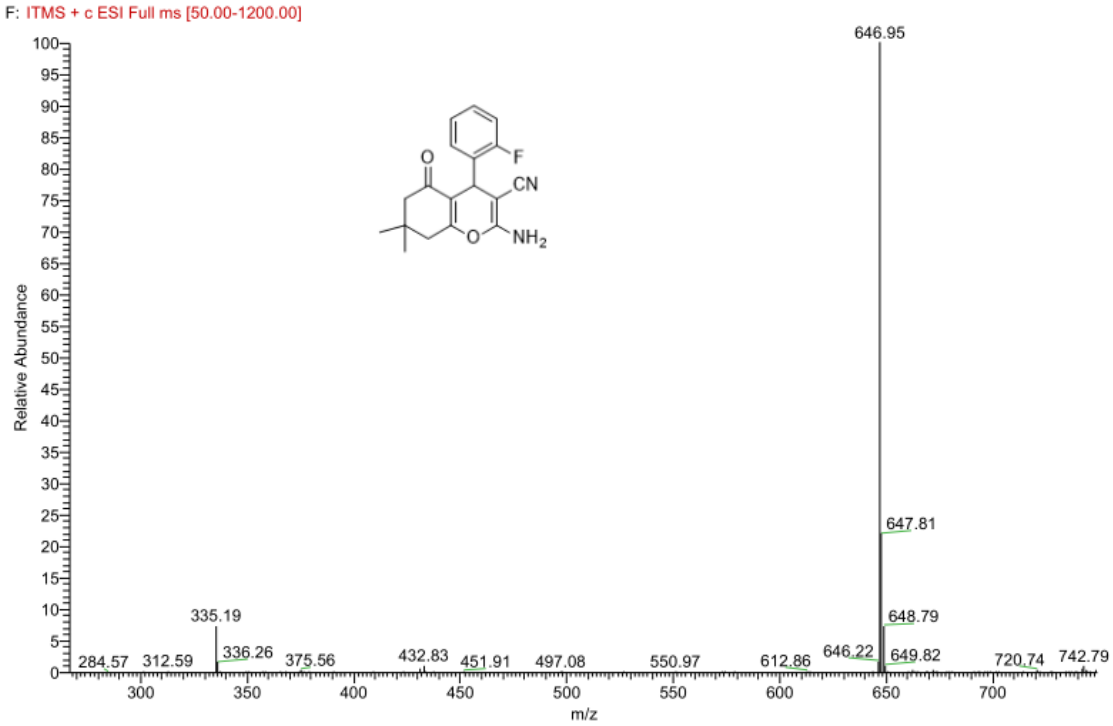


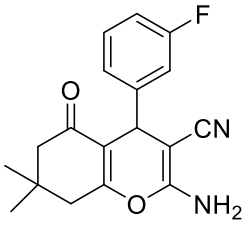
2-Amino-4-(2-fluorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4d**, $C_{18}H_{17}FN_2O_2$)

Yellow solid; mp 237-239 ℃. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.28 – 7.09 (m, 4H), 7.06 (s, 2H), 4.45 (s, 1H), 2.60 – 2.50 (m, 2H), 2.27 (d, J = 16.1 Hz, 1H), 2.09 (d, J = 16.1 Hz, 1H), 1.05 (s, 3H), 0.97 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 196.05, 163.58, 161.62, 159.21, 131.72, 130.12, 129.08, 124.88, 119.98, 115.99, 115.77, 111.82, 57.14, 50.35, 32.27, 30.29, 28.96, 27.06. MS (ESI): $[2M+Na]^+$: 647.81.



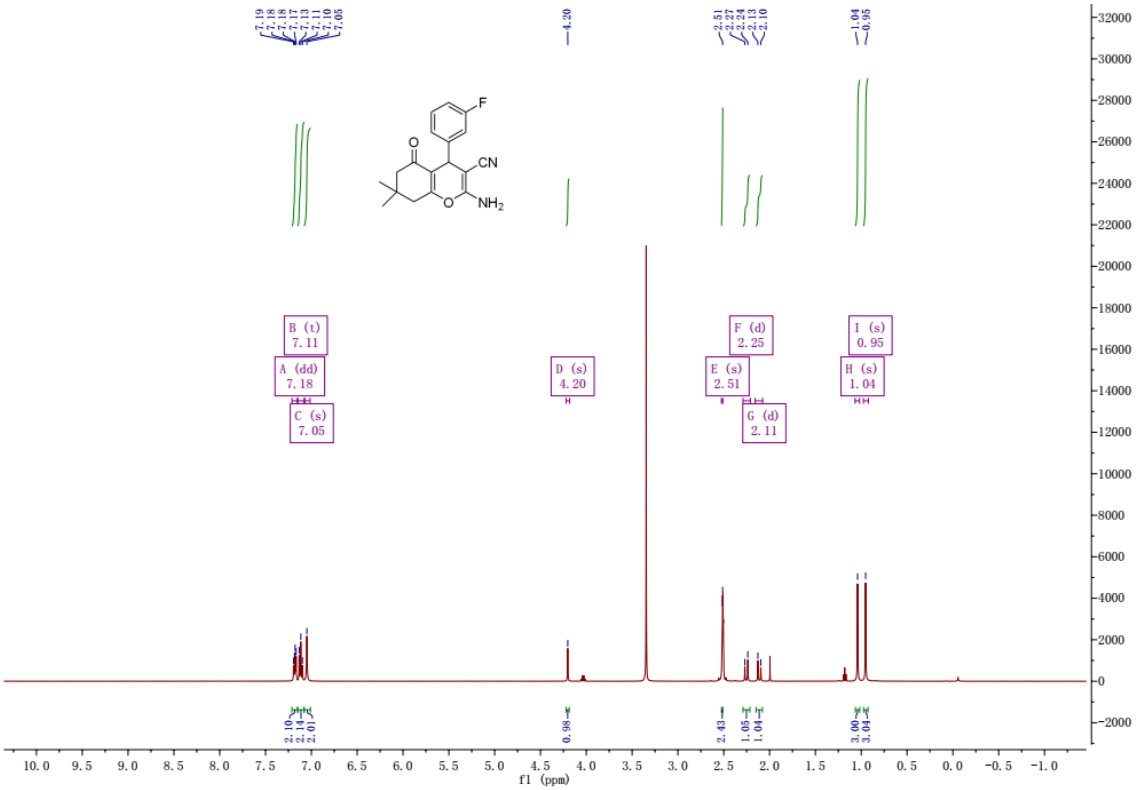

196.05
163.58
161.62
159.21
131.72
130.12
129.08
124.98
119.98
115.99
115.77
111.62
57.14
50.35
32.27
30.29
28.96
27.06
O
F
CN
O
NH2
f1 (ppm)

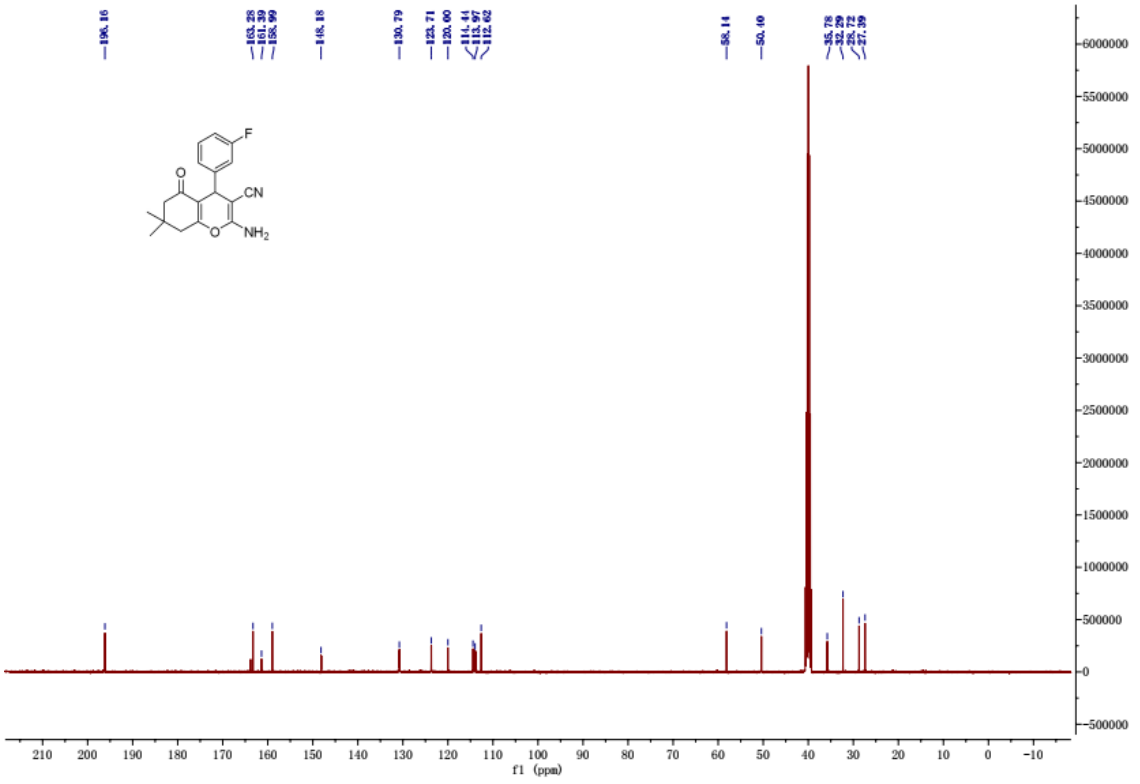

F: ITMS + c ESI Full ms [50.00-1200.00]
646.95
O
F
CN
O
NH2
Relative Abundance
647.81
335.19
648.79
284.57
312.59
336.26
375.56
432.83
451.91
497.08
550.97
612.86
646.22
649.82
720.74
742.79
m/z

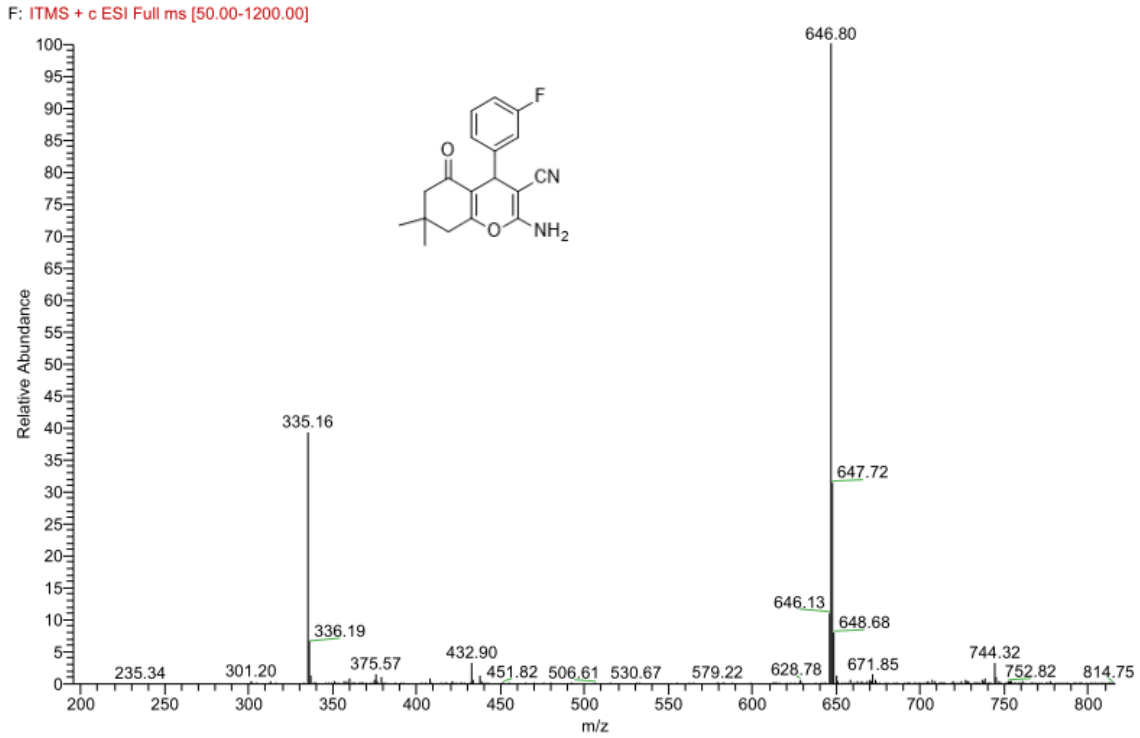


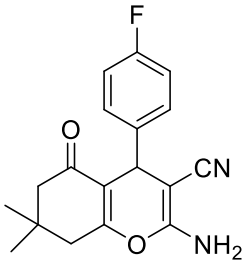
2-Amino-4-(3-fluorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4e**, $C_{18}H_{17}FN_2O_2$)

Yellow solid; mp 211-212 ℃. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.18 (dd, *J* = 8.7, 5.6 Hz, 2H), 7.11 (t, *J* = 8.8 Hz, 2H), 7.05 (s, 2H), 4.20 (s, 1H), 2.51 (s, 2H), 2.25 (d, *J* = 16.1 Hz, 2H), 2.11 (d, *J* = 16.1 Hz, 2H), 1.04 (s, 3H), 0.95 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.16, 163.28, 161.39, 158.99, 148.18, 130.79, 123.71, 120.00, 114.44, 113.97, 112.62, 58.14, 50.40, 35.78, 32.29, 28.72, 27.39. MS (ESI): $[2M+Na]^+$: 647.72.



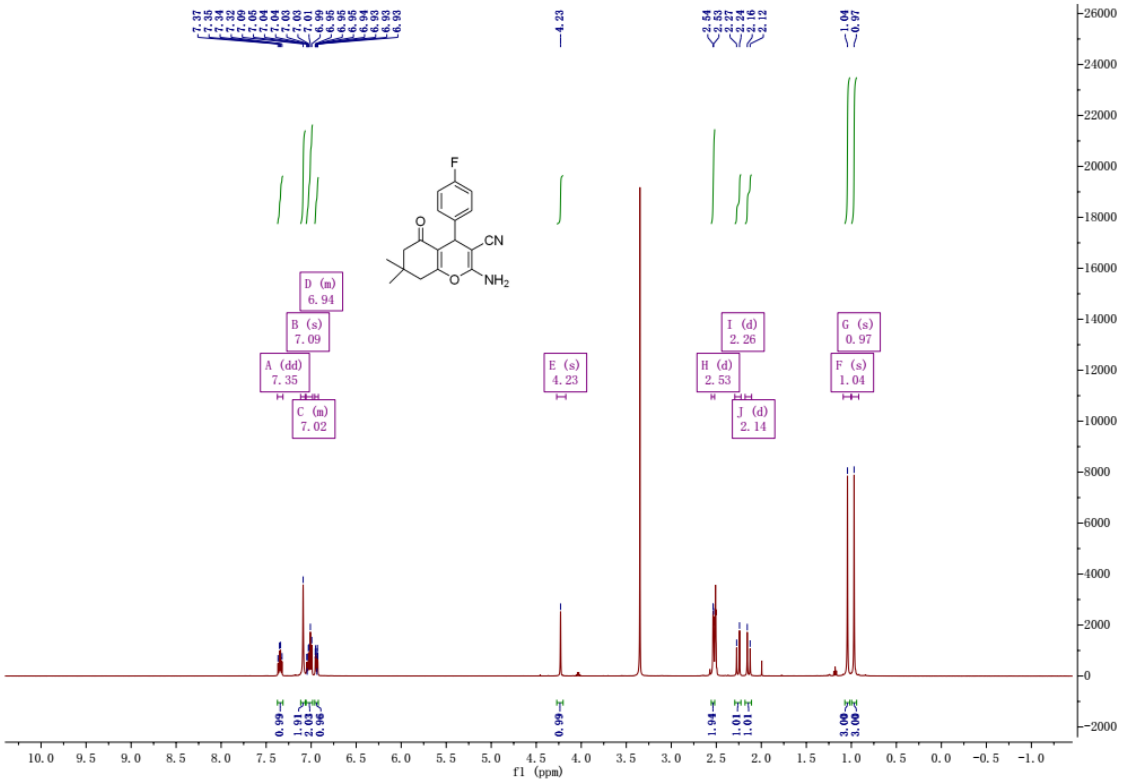

196.16
163.28
161.39
158.99
148.18
130.79
123.71
120.00
111.41
113.97
112.62
58.14
50.40
35.78
32.29
28.72
27.39
F
O
CN
NH2
f1 (ppm)

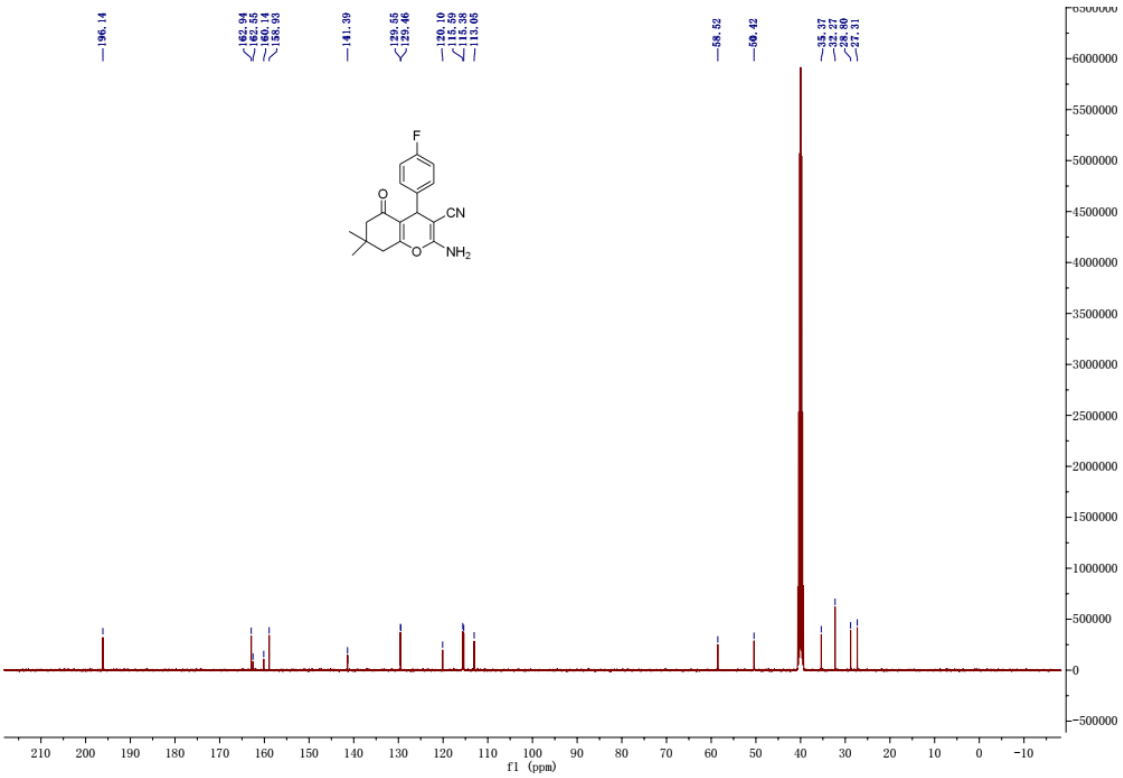

F: ITMS + c ESI Full ms [50.00-1200.00]
646.80
335.16
647.72
646.13
648.68
336.19
432.90
744.32
235.34
301.20
375.57
451.82
506.61
530.67
579.22
628.78
671.85
752.82
814.75
Relative Abundance
m/z
F
O
CN
NH2

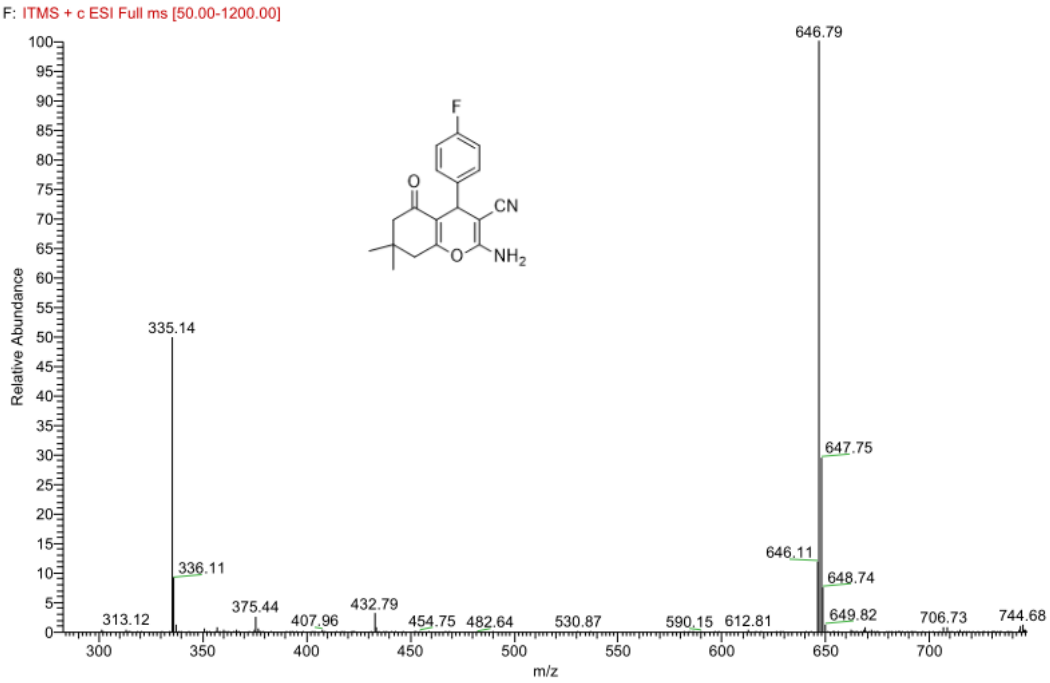


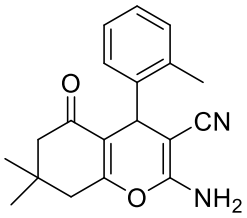
2-Amino-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4f**, $C_{18}H_{17}FN_2O_2$)

White solid; mp 189-191 ℃. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.35 (dd, J = 14.1, 7.9 Hz, 1H), 7.09 (s, 2H), 7.06 – 6.98 (m, 2H), 6.96 – 6.92 (m, 1H), 4.23 (s, 1H), 2.53 (d, J = 2.8 Hz, 2H), 2.26 (d, J = 16.0 Hz, 1H), 2.14 (d, J = 16.0 Hz, 1H), 1.04 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.14, 162.94, 162.55, 160.14, 158.93, 141.39, 129.55, 129.46, 120.10, 115.59, 115.38, 113.05, 58.52, 50.42, 35.37, 32.27, 28.80, 27.31. MS (ESI): $[2M+Na]^+$: 647.75.



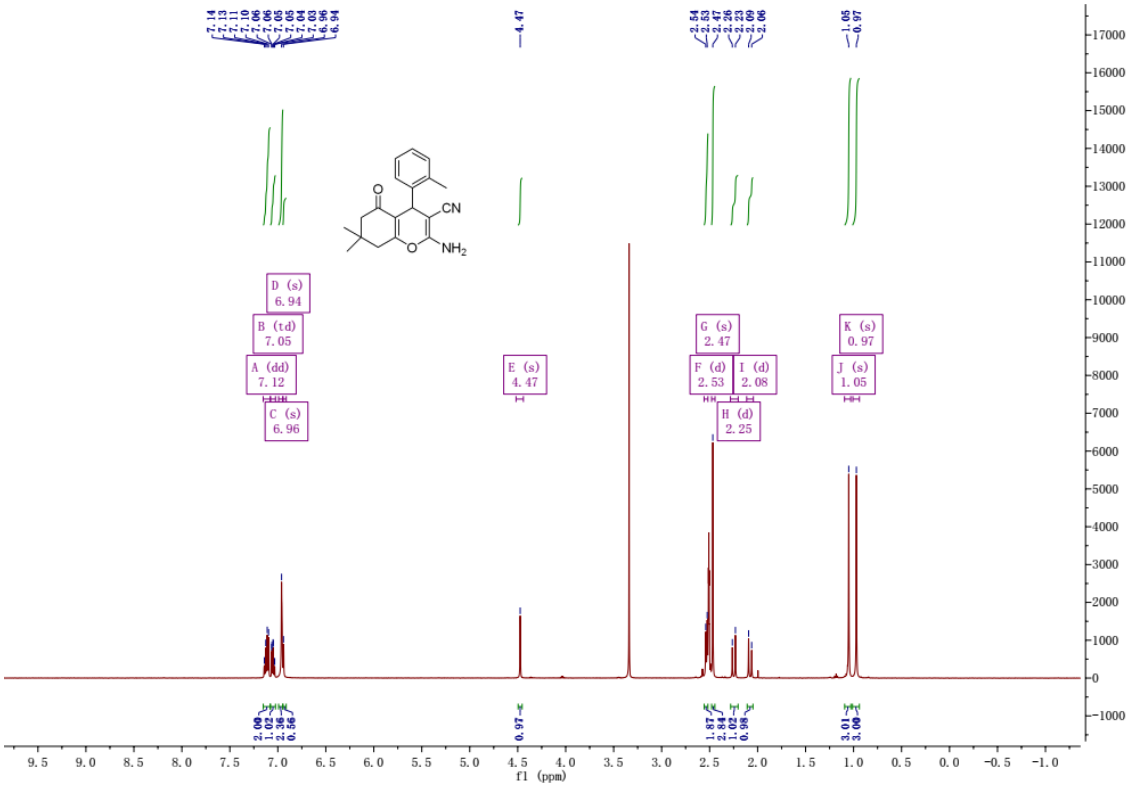

196.14
162.94
162.55
160.14
158.98
141.39
129.55
129.46
120.10
115.99
115.38
113.05
58.52
50.42
35.37
32.27
28.80
27.31
F
O
CN
NH2
O
f1 (ppm)

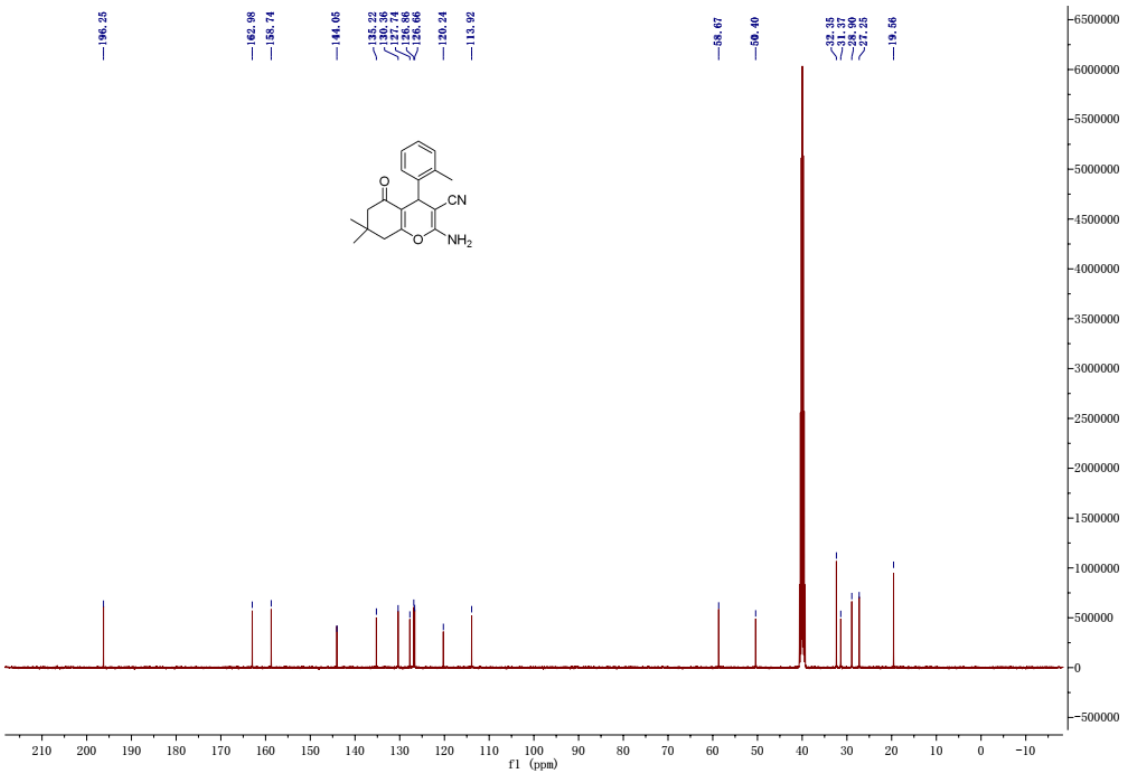

F: ITMS + c ESI Full ms [50.00-1200.00]
Relative Abundance
m/z
646.79
335.14
647.75
646.11
336.11
648.74
649.82
313.12
375.44
407.96
432.79
454.75
482.64
530.87
590.15
612.81
706.73
744.68
F
O
CN
NH2

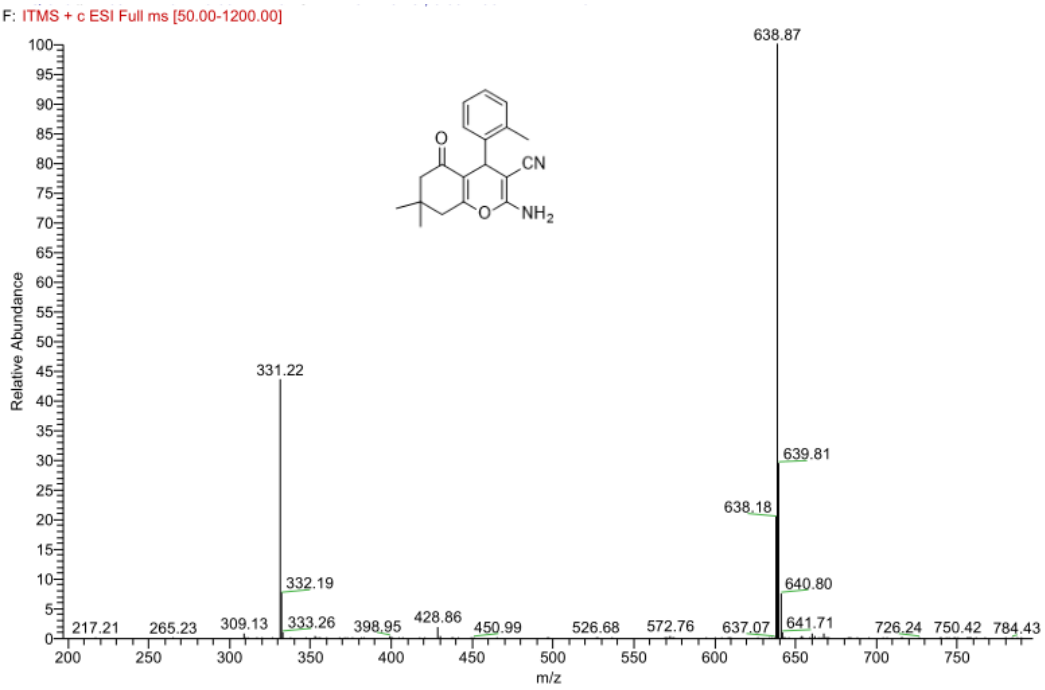


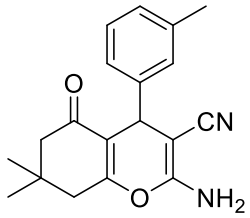
2-Amino-7,7-dimethyl-5-oxo-4-(*o*-tolyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4g**, $C_{19}H_{20}N_2O_2$)

White solid; mp 208-210 ℃. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.12 (dd, J = 14.5, 7.1 Hz, 2H), 7.05 (td, J = 7.4, 1.3 Hz, 1H), 6.96 (s, 2H), 6.94 (s, 1H), 4.47 (s, 1H), 2.53 (d, J = 7.5 Hz, 2H), 2.47 (s, 3H), 2.25 (d, J = 16.1 Hz, 1H), 2.08 (d, J = 16.1 Hz, 1H), 1.05 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.25, 162.98, 158.74, 144.05, 135.22, 130.36, 127.74, 126.86, 126.66, 120.24, 113.92, 58.67, 50.40, 32.35, 31.37, 28.90, 27.25, 19.56. MS (ESI): $[2M+Na]^+$: 639.81.



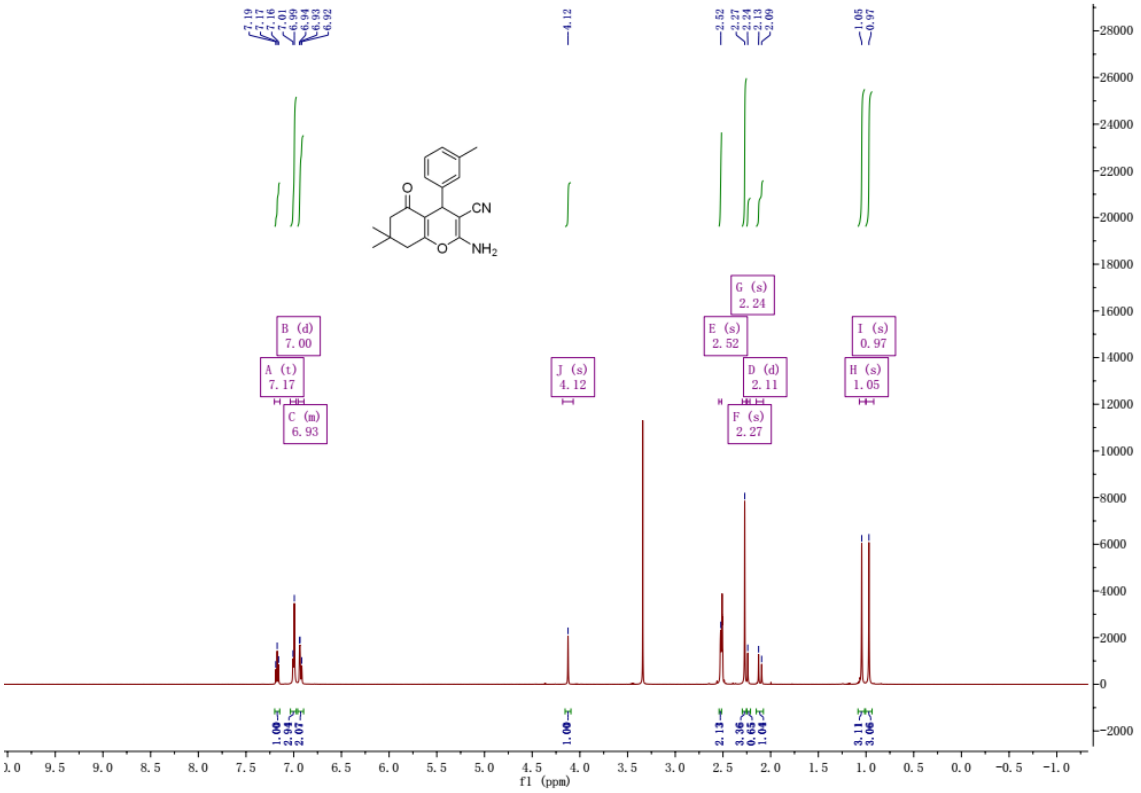

196.25
162.98
158.74
144.05
135.22
130.36
127.74
126.66
126.06
120.24
113.92
58.67
50.40
32.35
31.37
28.90
27.25
19.56
O
CN
NH2
f1 (ppm)

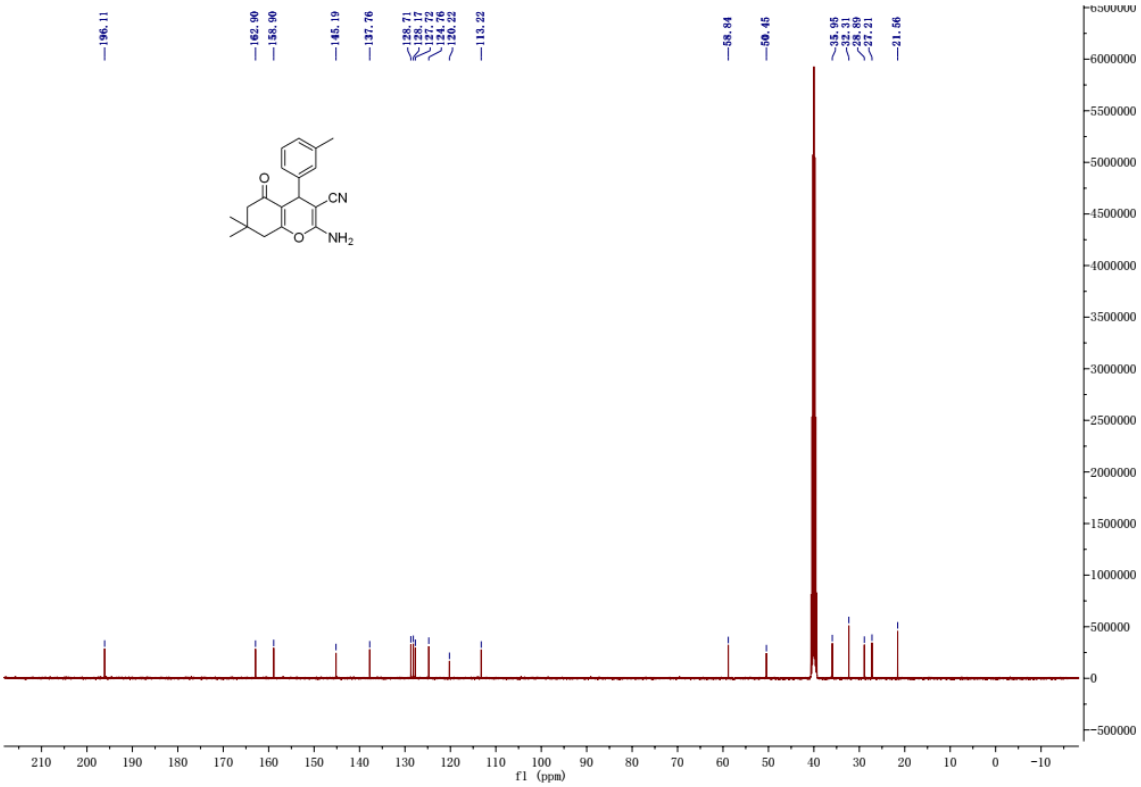

F: ITMS + c ESI Full ms [50.00-1200.00]
638.87
331.22
639.81
638.18
332.19
640.80
641.71
217.21
265.23
309.13
333.26
398.95
428.86
450.99
526.68
572.76
637.07
726.24
750.42
784.43
Relative Abundance
m/z
O
CN
NH2

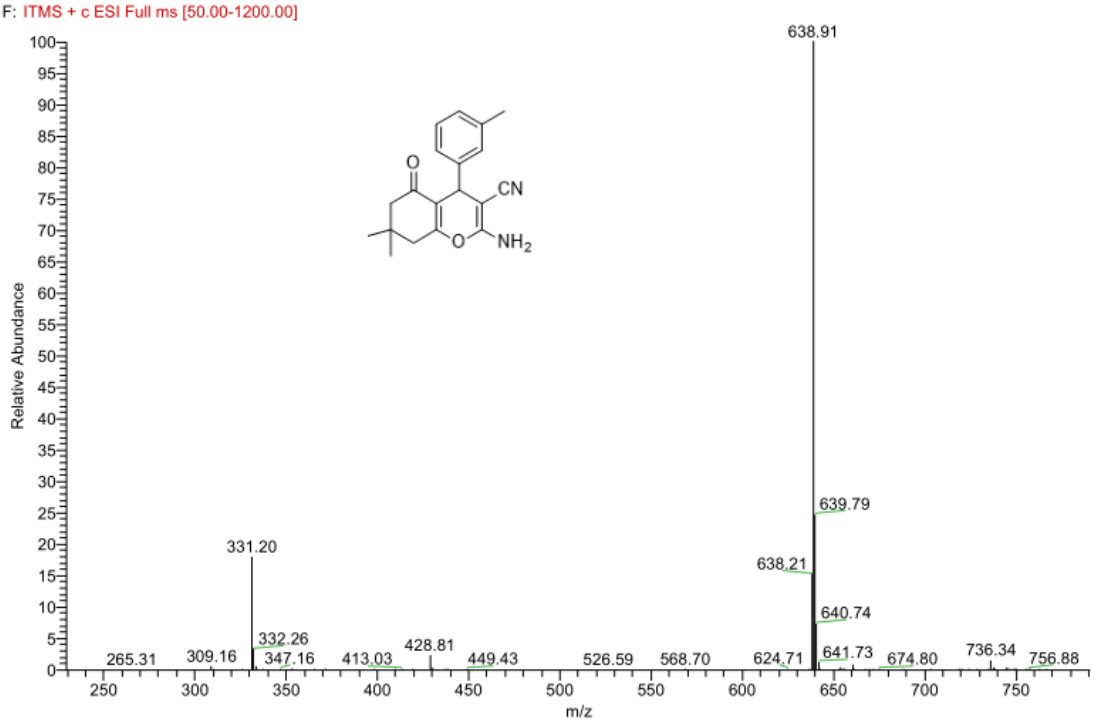


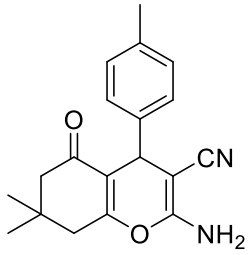
2-Amino-7,7-dimethyl-5-oxo-4-(*m*-tolyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4h**, $C_{19}H_{20}N_2O_2$)

White solid; mp 207-208 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.17 (t, J = 7.5 Hz, 1H), 7.00 (d, J = 7.0 Hz, 3H), 6.95 – 6.89 (m, 2H), 4.12 (s, 1H), 2.52 (s, 2H), 2.27 (s, 3H), 2.24 (s, 1H), 2.11 (d, J = 16.1 Hz, 1H), 1.05 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.11, 162.90, 158.90, 145.19, 137.76, 128.71, 128.17, 127.72, 124.76, 120.22, 113.22, 58.84, 50.45, 35.95, 32.31, 28.89, 27.21, 21.56. MS (ESI): $[2M+Na]^+$: 639.79.



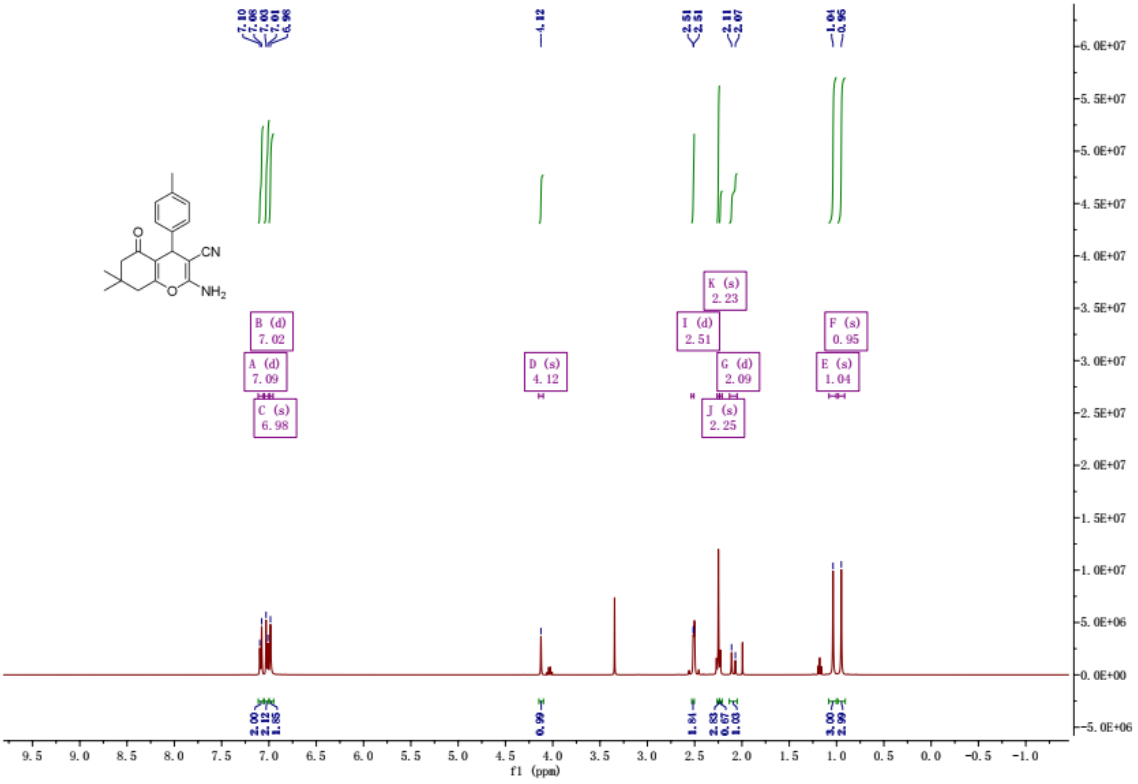

196.11
162.90
158.90
145.19
137.76
128.71
128.17
127.72
124.76
120.22
113.22
58.84
50.45
35.95
32.31
28.89
27.21
21.56
O
CN
O
NH2
f1 (ppm)

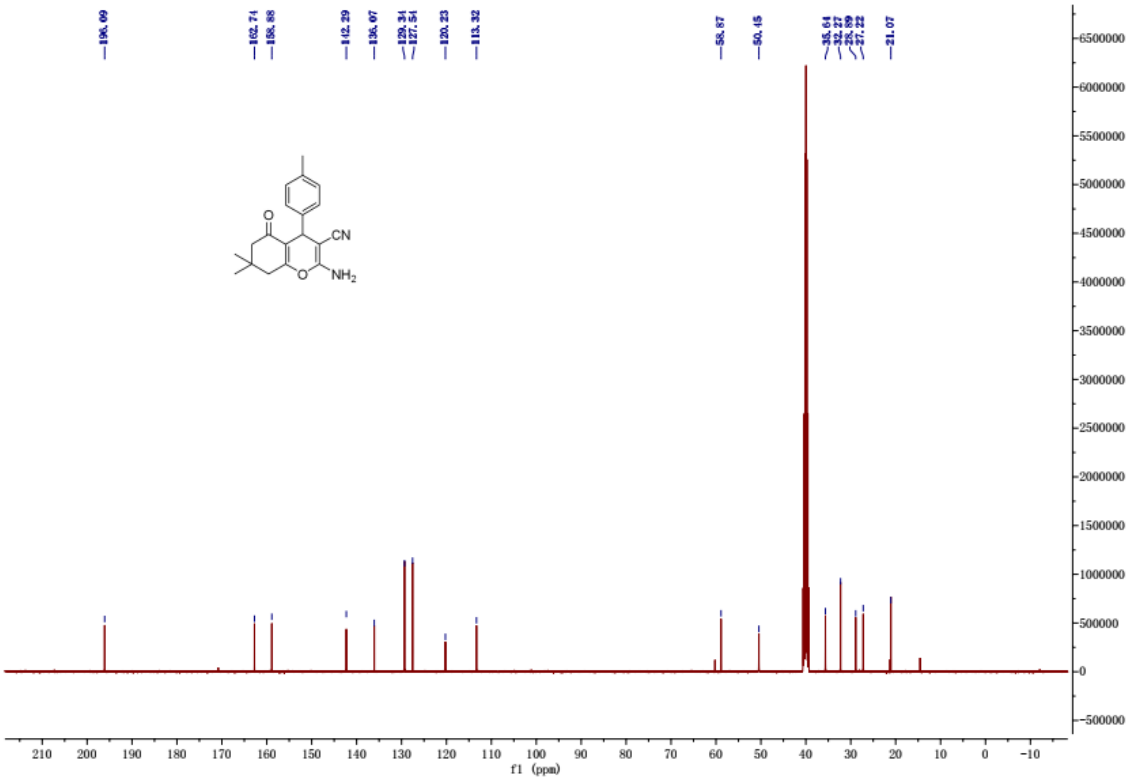

F: ITMS + c ESI Full ms [50.00-1200.00]
638.91
639.79
638.21
640.74
331.20
332.26
641.73
265.31
309.16
347.16
413.03
428.81
449.43
526.59
568.70
624.71
674.80
736.34
756.88
Relative Abundance
m/z
O
CN
O
NH2

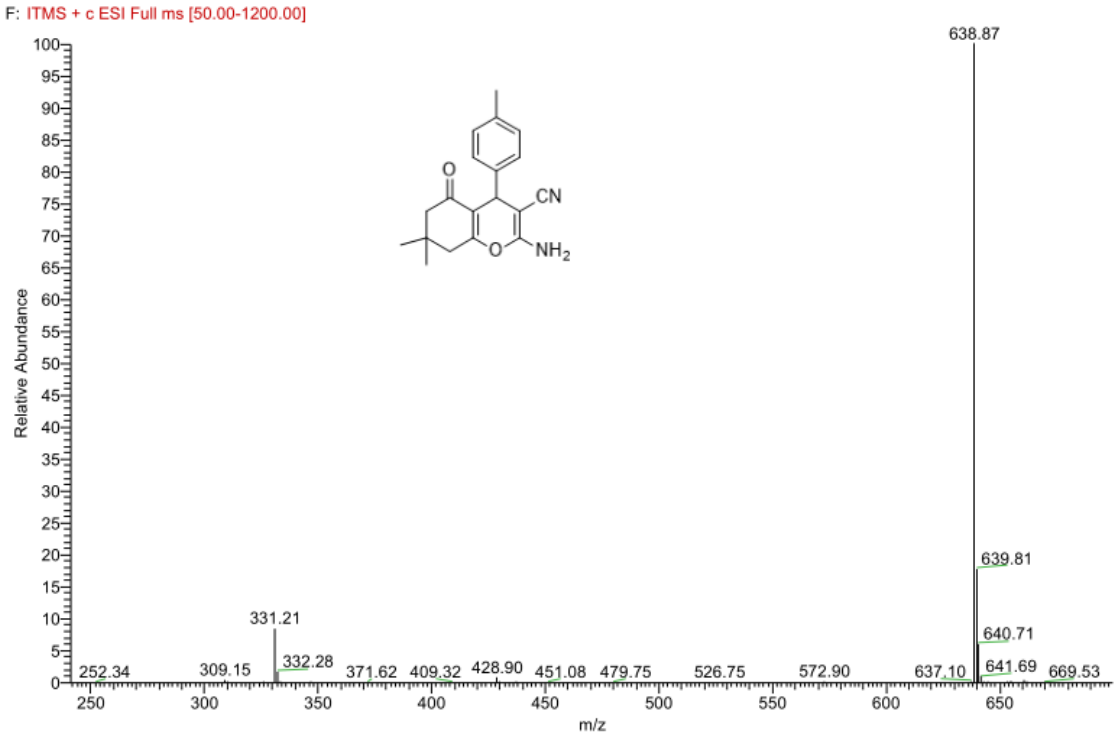


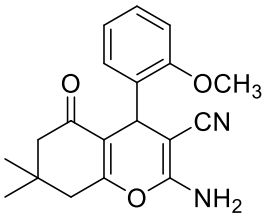
2-Amino-7,7-dimethyl-5-oxo-4-(*p*-tolyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4i**, $C_{19}H_{20}N_2O_2$)

White solid; mp 218-220 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.09 (d, J = 7.9 Hz, 2H), 7.02 (d, J = 8.0 Hz, 2H), 6.98 (s, 2H), 4.12 (s, 1H), 2.51 (d, J = 1.4 Hz, 2H), 2.25 (s, 3H), 2.23 (s, 1H), 2.09 (d, J = 16.1 Hz, 1H), 1.04 (s, 3H), 0.95 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.09, 162.74, 158.88, 142.29, 136.07, 129.34, 127.54, 120.23, 113.32, 58.87, 50.45, 35.64, 32.27, 28.89, 27.22, 21.07. MS (ESI): $[2M+Na]^+$: 639.81.



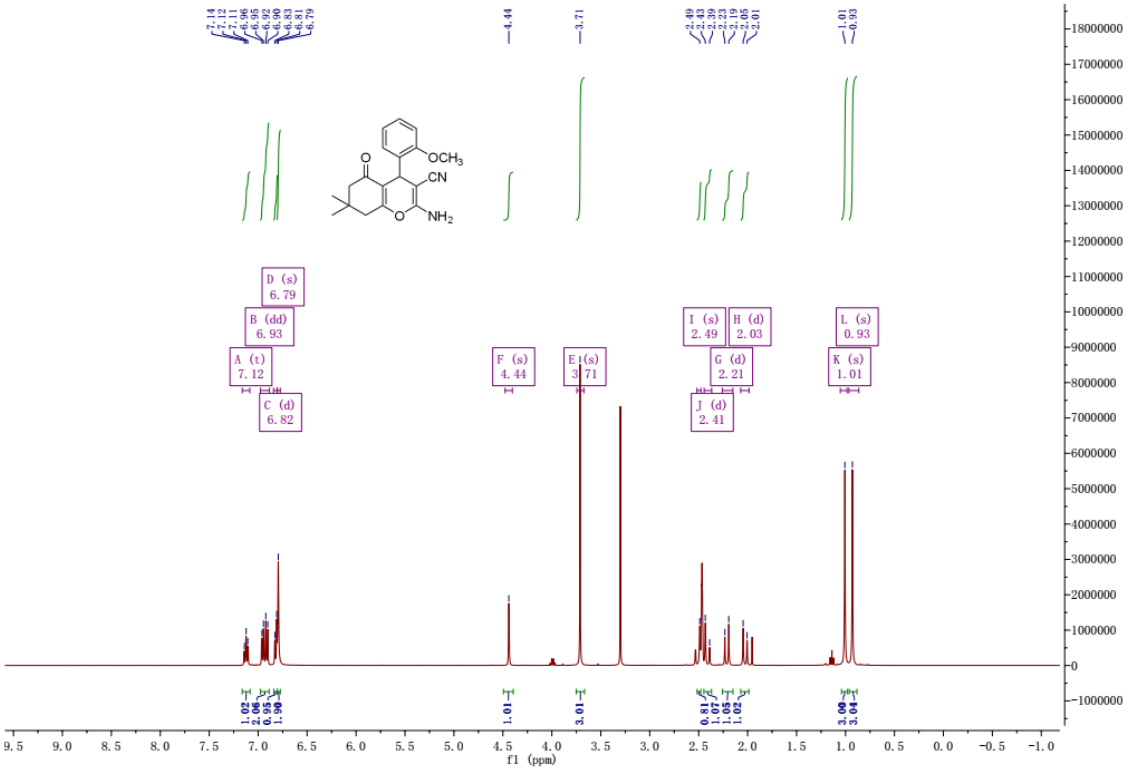

196.69
162.71
158.88
142.29
136.67
129.34
127.54
120.23
113.32
58.87
50.45
35.64
32.27
28.89
27.22
21.07
O
CN
O
NH2
f1 (ppm)

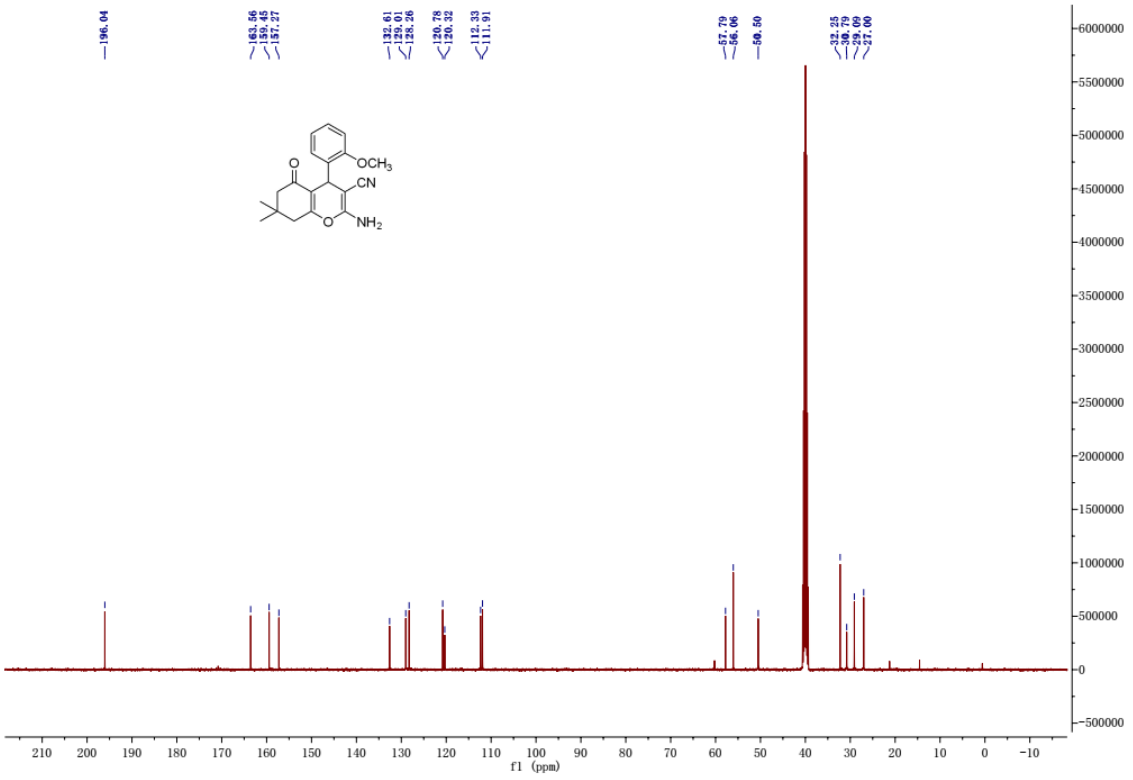

F: ITMS + c ESI Full ms [50.00-1200.00]
Relative Abundance
m/z
638.87
639.81
640.71
641.69
669.53
331.21
332.28
252.34
309.15
371.62
409.32
428.90
451.08
479.75
526.75
572.90
637.10
O
CN
O
NH2

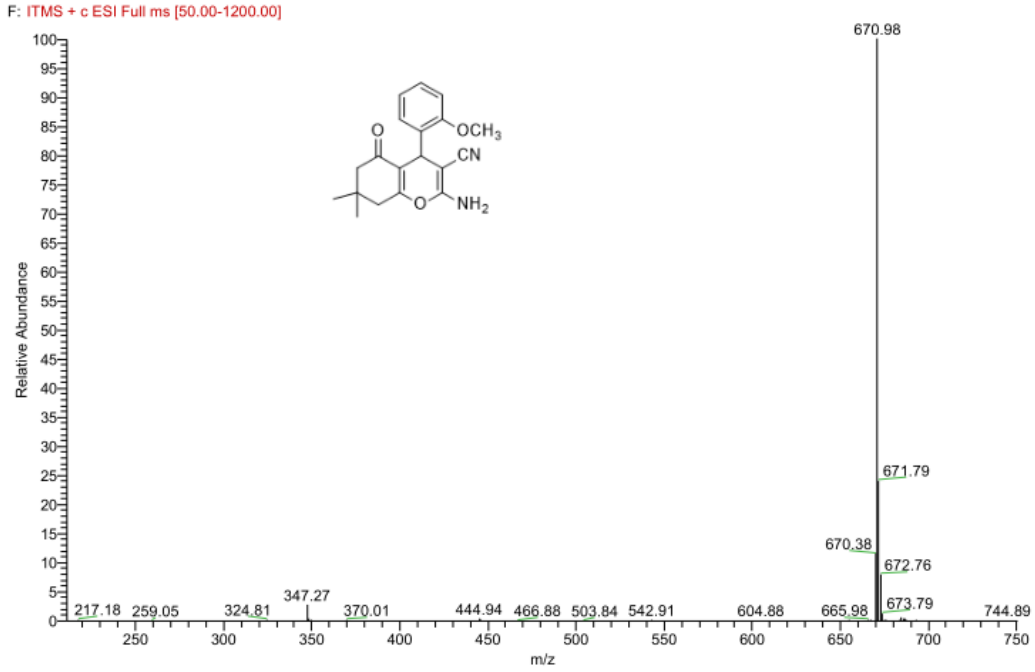


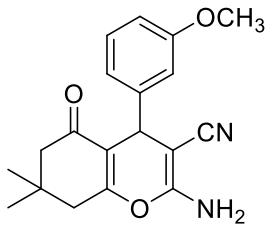
2-Amino-4-(2-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4j**, $C_{19}H_{20}N_2O_3$)

Yellow solid; mp 200-202 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.12 (t, J = 7.0 Hz, 1H), 6.93 (dd, J = 16.7, 7.0 Hz, 2H), 6.82 (d, J = 7.4 Hz, 1H), 6.79 (s, 2H), 4.44 (s, 1H), 3.71 (s, 3H), 2.49 (s, 1H), 2.41 (d, J = 17.6 Hz, 1H), 2.21 (d, J = 16.1 Hz, 1H), 2.03 (d, J = 16.1 Hz, 1H), 1.01 (s, 3H), 0.93 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.04, 163.56, 159.45, 157.27, 132.61, 129.01, 128.26, 120.78, 120.32, 112.33, 111.91, 57.79, 56.06, 50.50, 32.25, 30.79, 29.09, 27.00. MS (ESI): $[2M+Na]^+$: 671.79.



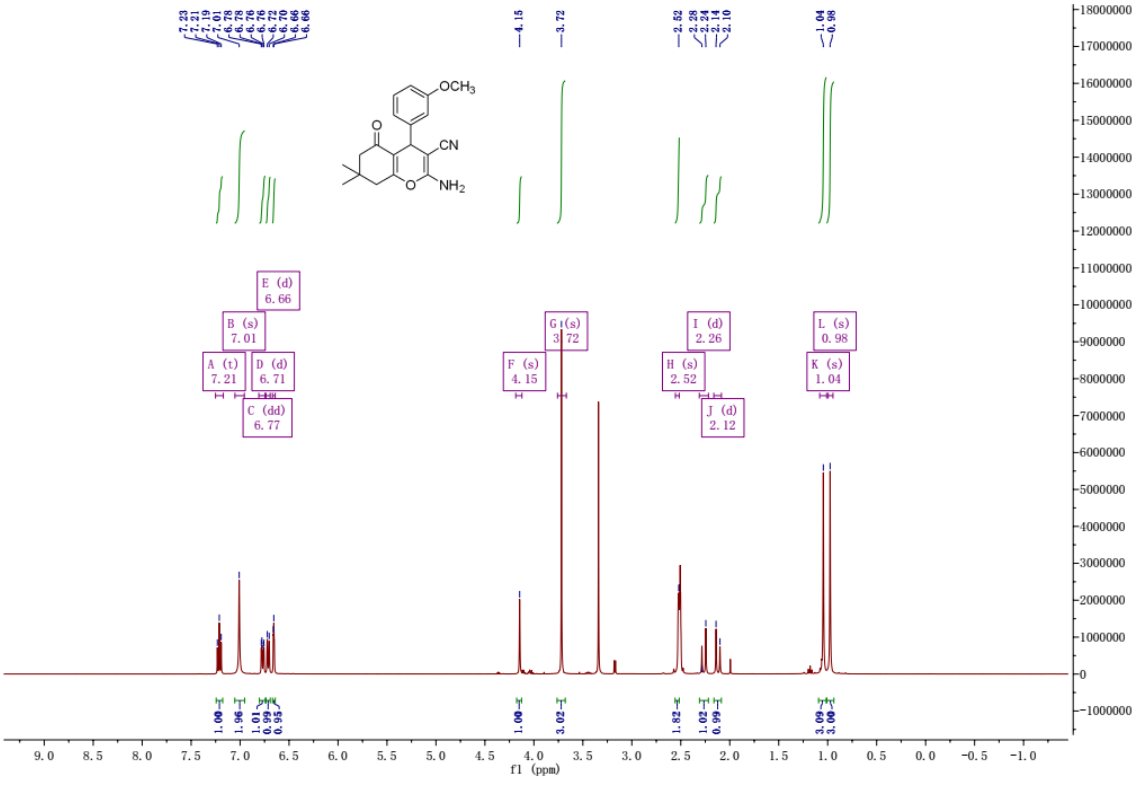

196.04
163.56
158.45
157.27
132.61
129.01
128.26
120.78
120.32
112.33
111.91
67.79
66.06
50.50
32.25
30.79
29.09
27.00
OCH3
CN
NH2
O
f1 (ppm)

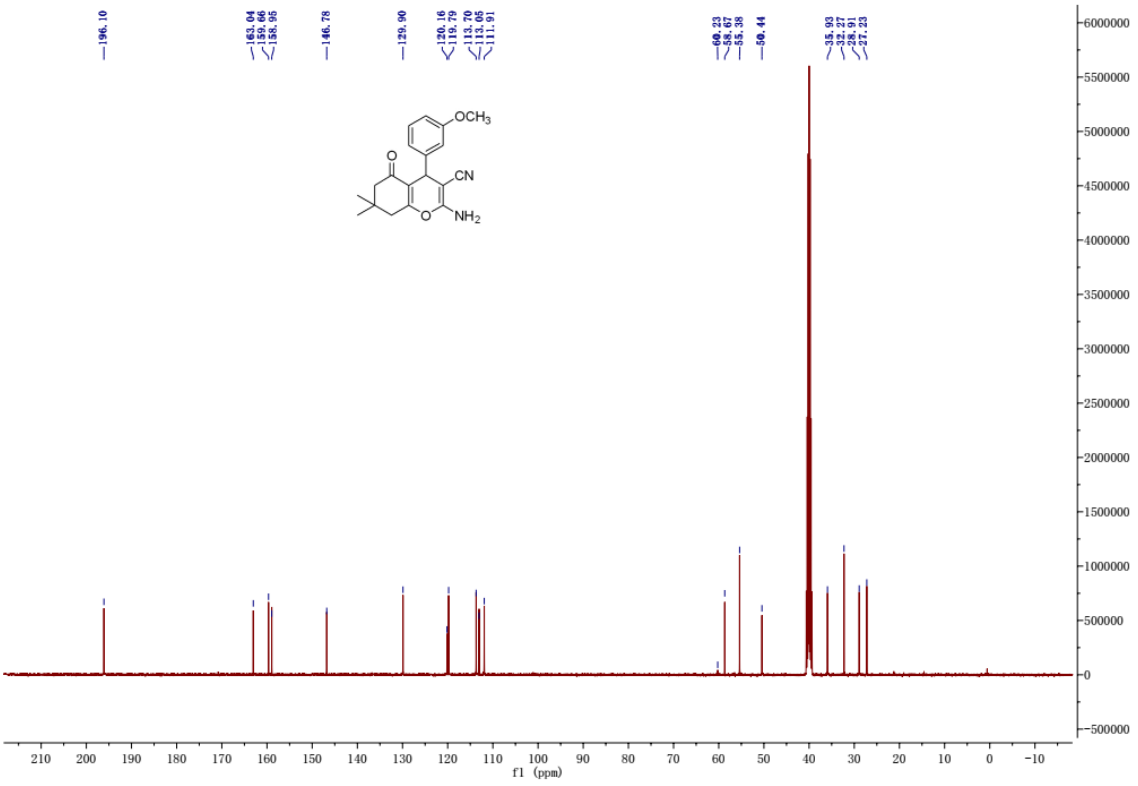

F: ITMS + c ESI Full ms [50.00-1200.00]
670.98
671.79
670.38
672.76
673.79
347.27
217.18
259.05
324.81
370.01
444.94
466.88
503.84
542.91
604.88
665.98
744.89
Relative Abundance
m/z
OCH3
CN
NH2
O

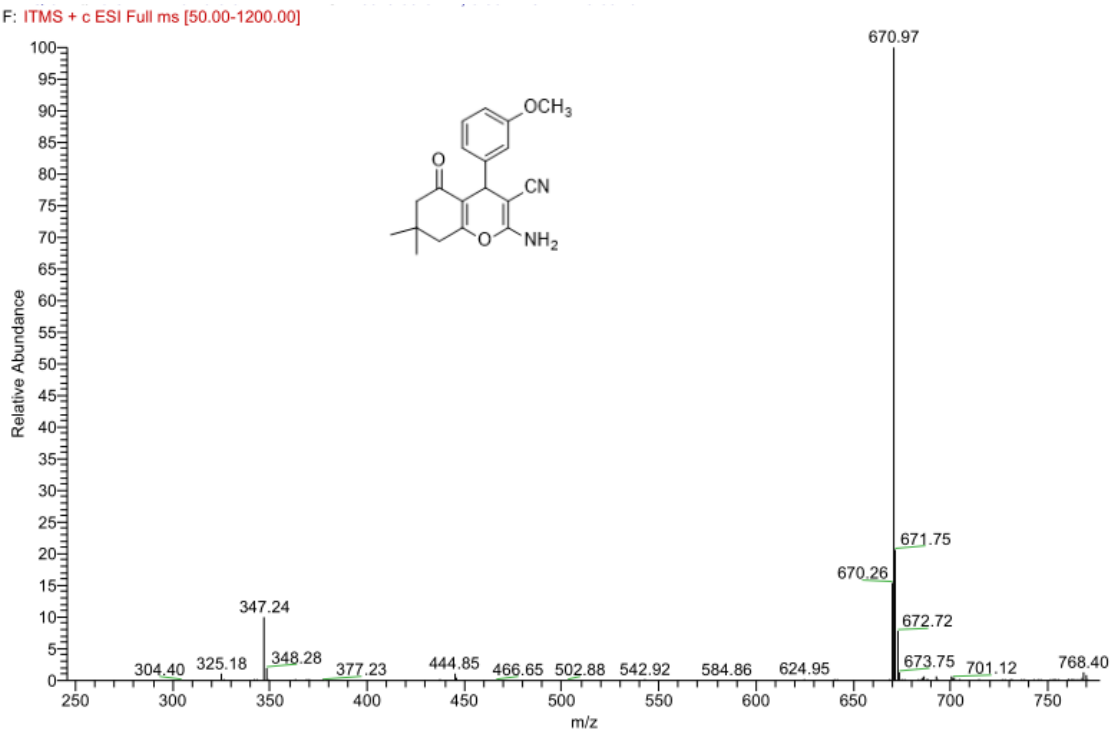


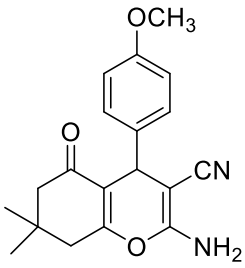
2-Amino-4-(3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4k**, $C_{19}H_{20}N_2O_3$)

White solid; mp 193-195 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.21 (t, *J* = 7.9 Hz, 1H), 7.01 (s, 2H), 6.77 (dd, *J* = 8.1, 2.3 Hz, 1H), 6.71 (d, *J* = 7.7 Hz, 1H), 6.66 (d, *J* = 1.9 Hz, 1H), 4.15 (s, 1H), 3.72 (s, 3H), 2.52 (s, 2H), 2.26 (d, *J* = 15.9 Hz, 1H), 2.12 (d, *J* = 16.1 Hz, 1H), 1.04 (s, 3H), 0.98 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 196.10, 163.04, 159.66, 158.95, 146.78, 129.90, 120.16, 119.79, 113.70, 113.05, 111.91, 60.23, 58.67, 55.38, 50.44, 35.93, 32.27, 28.91, 27.23. MS (ESI): $[2M+Na]^+$: 671.75.



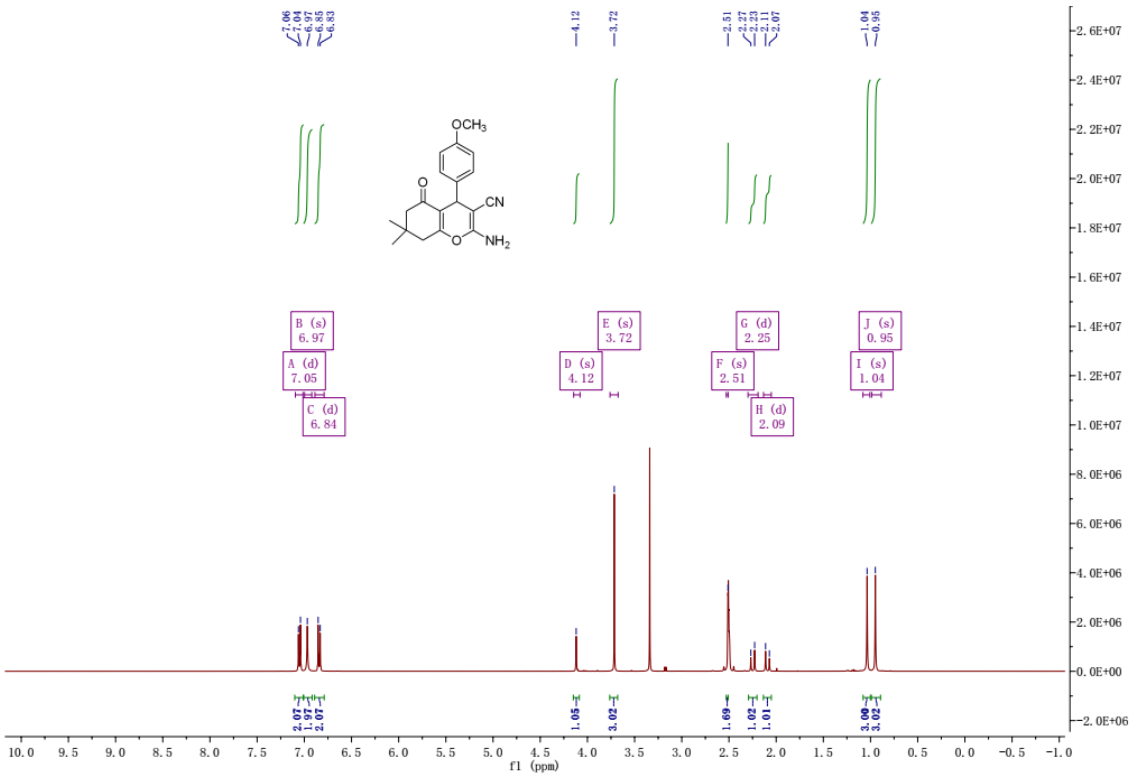

196.10
163.04
159.66
158.95
146.78
129.90
120.16
119.79
113.70
113.05
111.91
60.23
55.67
55.38
50.44
35.93
32.27
28.91
27.23
OCH3
O
CN
NH2
f1 (ppm)

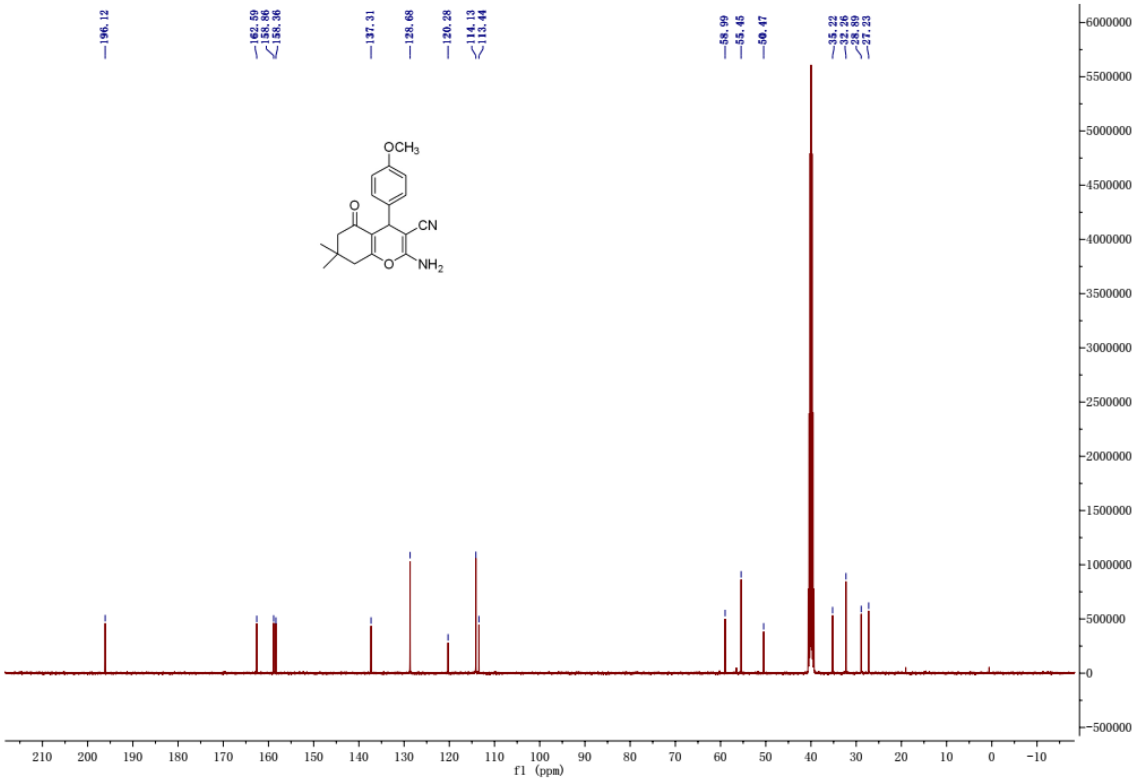

F: ITMS + c ESI Full ms [50.00-1200.00]
Relative Abundance
m/z
670.97
671.75
670.26
672.72
673.75
347.24
348.28
304.40
325.18
377.23
444.85
466.65
502.88
542.92
584.86
624.95
701.12
768.40
OCH3
O
CN
NH2

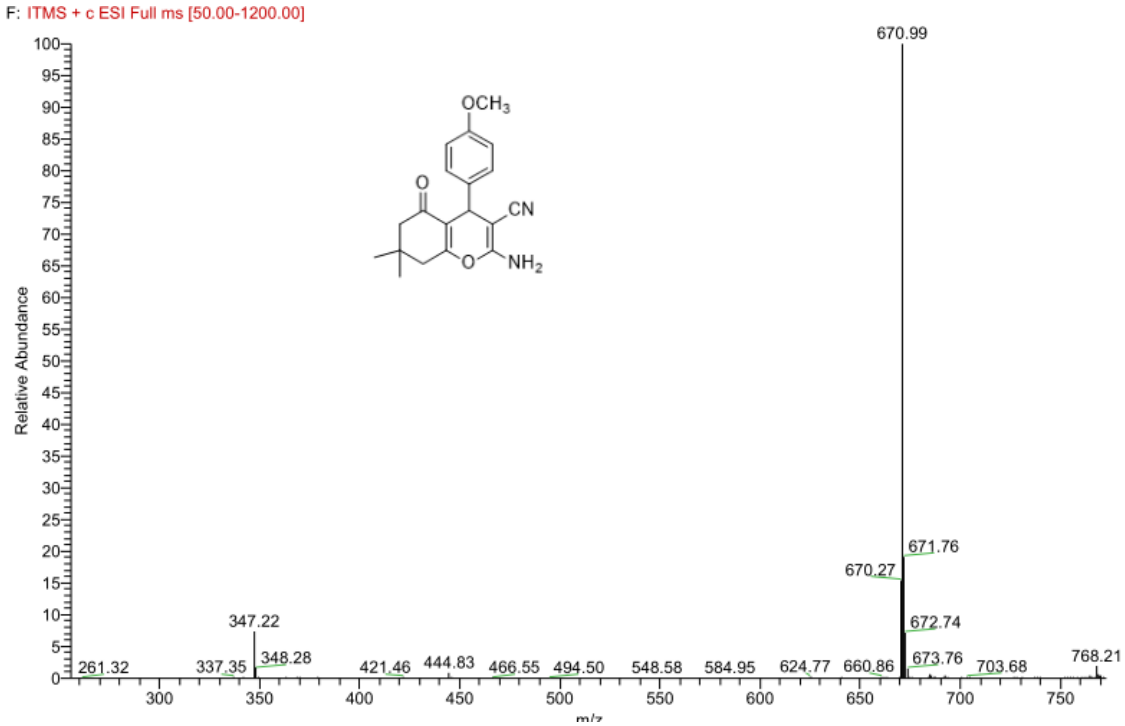


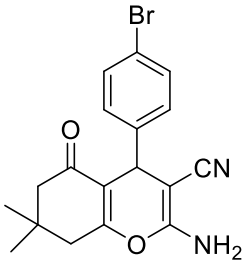
2-Amino-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4l**, $C_{19}H_{20}N_2O_3$)

White solid; mp 202-204 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.05 (d, J = 8.6 Hz, 2H), 6.97 (s, 2H), 6.84 (d, J = 8.6 Hz, 2H), 4.12 (s, 1H), 3.72 (s, 3H), 2.51 (s, 2H), 2.25 (d, J = 16.1 Hz, 1H), 2.09 (d, J = 16.1 Hz, 1H), 1.04 (s, 3H), 0.95 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.12, 162.59, 158.86, 158.36, 137.31, 128.68, 120.28, 114.13, 113.44, 58.99, 55.45, 50.47, 35.22, 32.26, 28.89, 27.23. MS (ESI): $[2M+Na]^+$: 671.76.



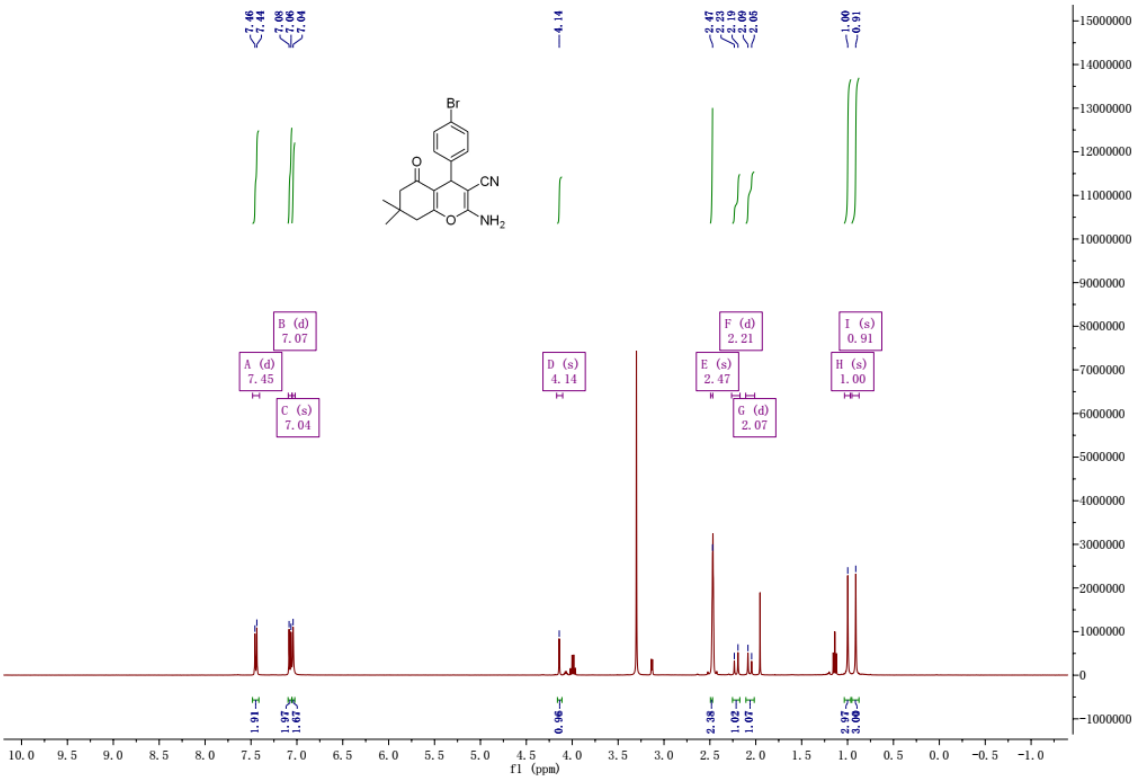

196.12
162.69
158.96
158.36
137.31
128.68
120.28
114.13
113.44
58.99
55.45
50.47
35.22
32.26
28.89
27.23
OCH3
O
CN
NH2
f1 (ppm)

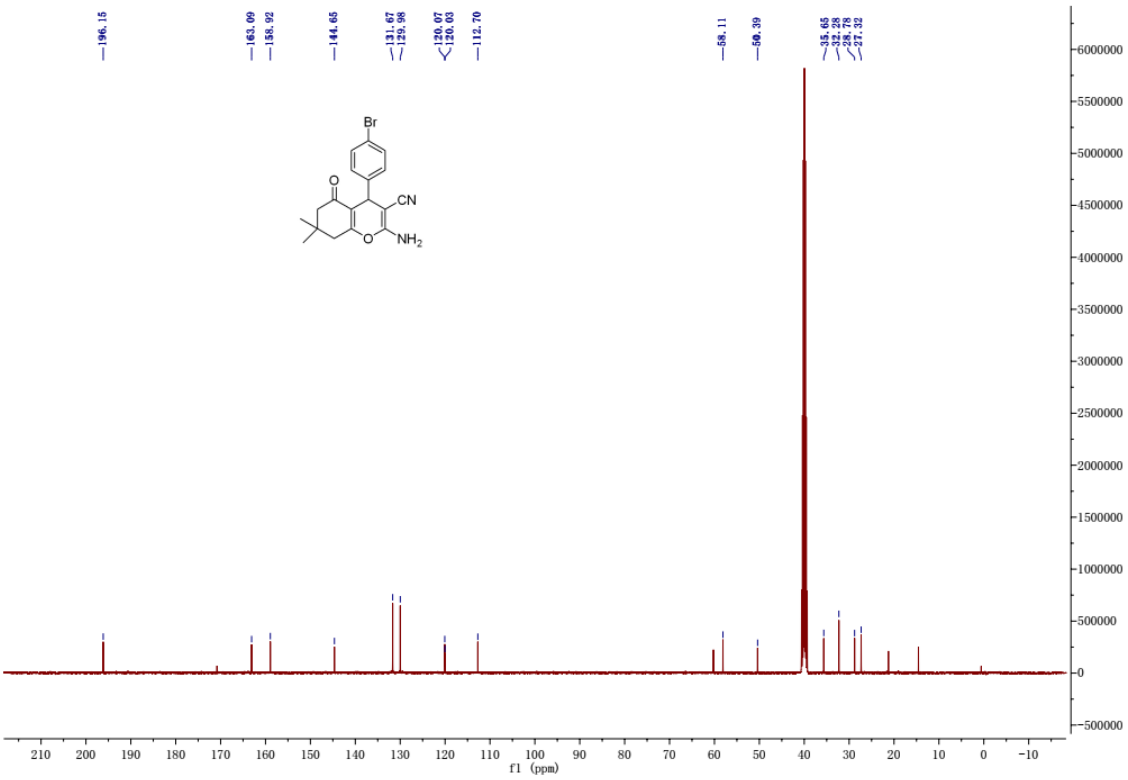

F: ITMS + c ESI Full ms [50.00-1200.00]
Relative Abundance
m/z
670.99
671.76
670.27
672.74
673.76
347.22
348.28
261.32
337.35
421.46
444.83
466.55
494.50
548.58
584.95
624.77
660.86
703.68
768.21
OCH3
O
CN
NH2

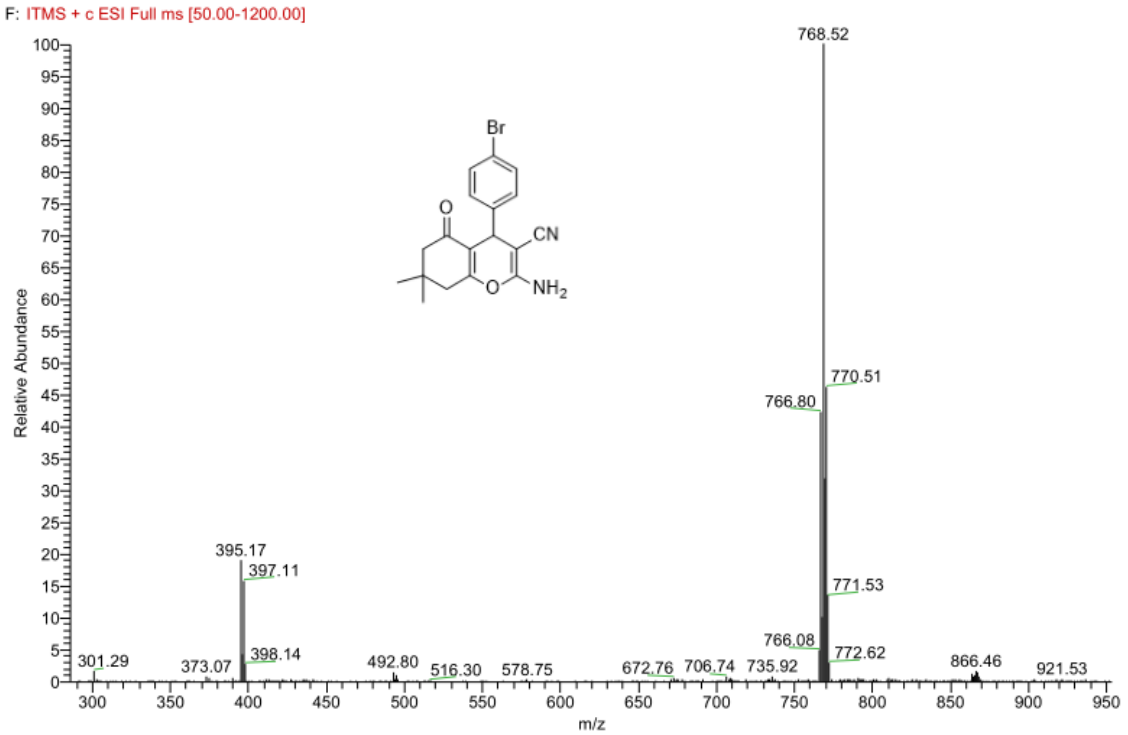


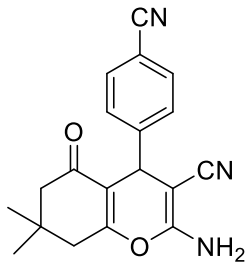
2-Amino-4-(4-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4m**, $C_{18}H_{17}BrN_2O_2$)

Faint yellow solid; mp 201-203 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 (d, J = 8.3 Hz, 2H), 7.07 (d, J = 8.4 Hz, 2H), 7.04 (s, 2H), 4.14 (s, 1H), 2.47 (s, 2H), 2.21 (d, J = 16.1 Hz, 1H), 2.07 (d, J = 16.0 Hz, 1H), 1.00 (s, 3H), 0.91 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.15, 163.09, 158.92, 144.65, 131.67, 129.98, 120.07, 120.03, 112.70, 58.11, 50.39, 35.65, 32.28, 28.78, 27.32. MS (ESI): $[2M+Na]^+$: 768.52.



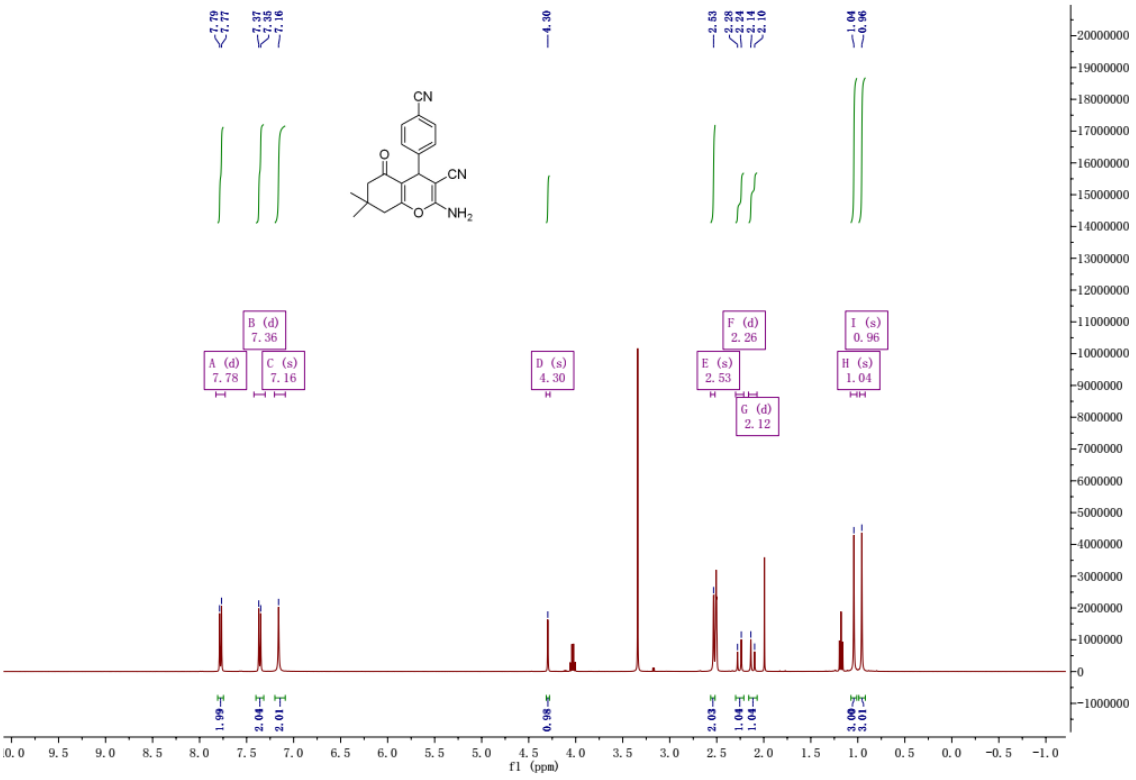

196.15
163.09
158.92
144.65
131.67
129.98
120.07
120.03
112.70
58.11
50.39
35.65
32.28
28.78
27.32
Br
O
CN
NH2
f1 (ppm)

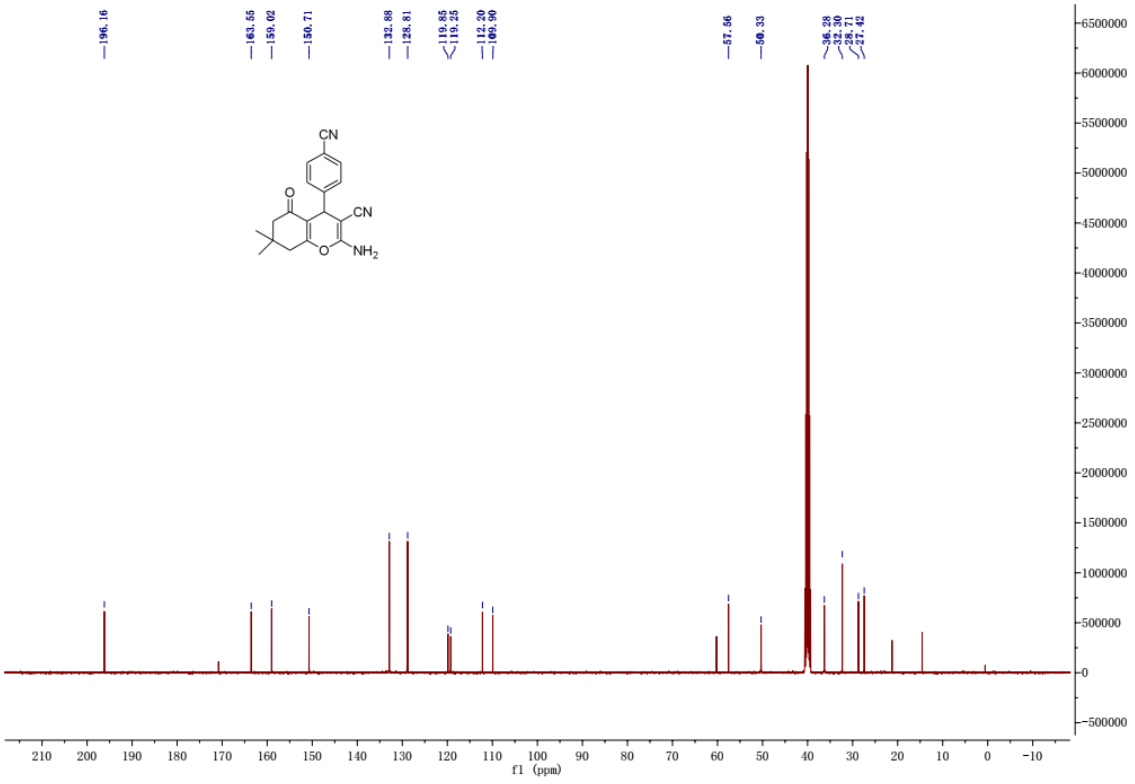

F: ITMS + c ESI Full ms [50.00-1200.00]
Relative Abundance
m/z
768.52
770.51
766.80
771.53
766.08
772.62
395.17
397.11
398.14
301.29
373.07
492.80
516.30
578.75
672.76
706.74
735.92
866.46
921.53
Br
O
CN
NH2

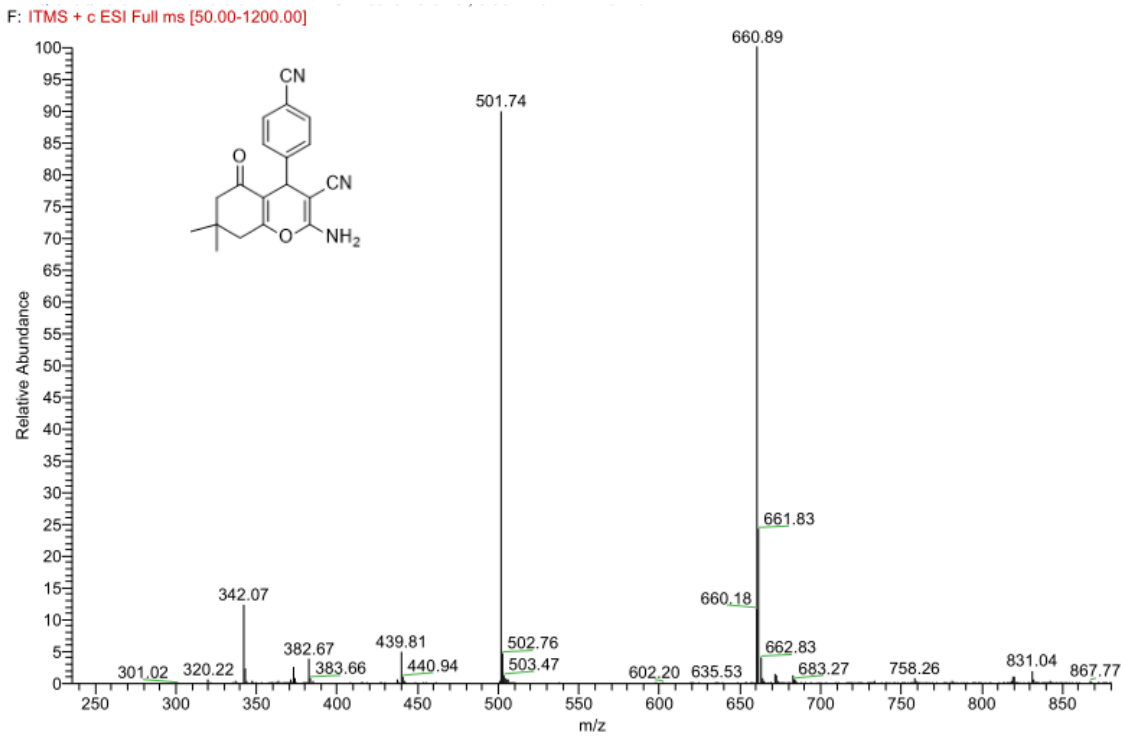


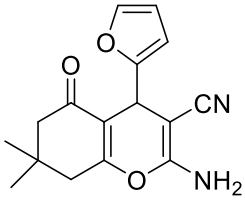
2-Amino-4-(4-cyanophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4n**, $C_{19}H_{17}N_3O_2$)

White solid; mp 225-228 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 7.16 (s, 2H), 4.30 (s, 1H), 2.53 (s, 2H), 2.26 (d, J = 16.0 Hz, 1H), 2.12 (d, J = 16.0 Hz, 1H), 1.04 (s, 3H), 0.96 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.16, 163.55, 159.02, 150.71, 132.88, 128.81, 119.85, 119.25, 112.20, 109.90, 57.56, 50.33, 36.28, 32.30, 28.71, 27.42. MS (ESI): $[2M+Na]^+$: 661.83.



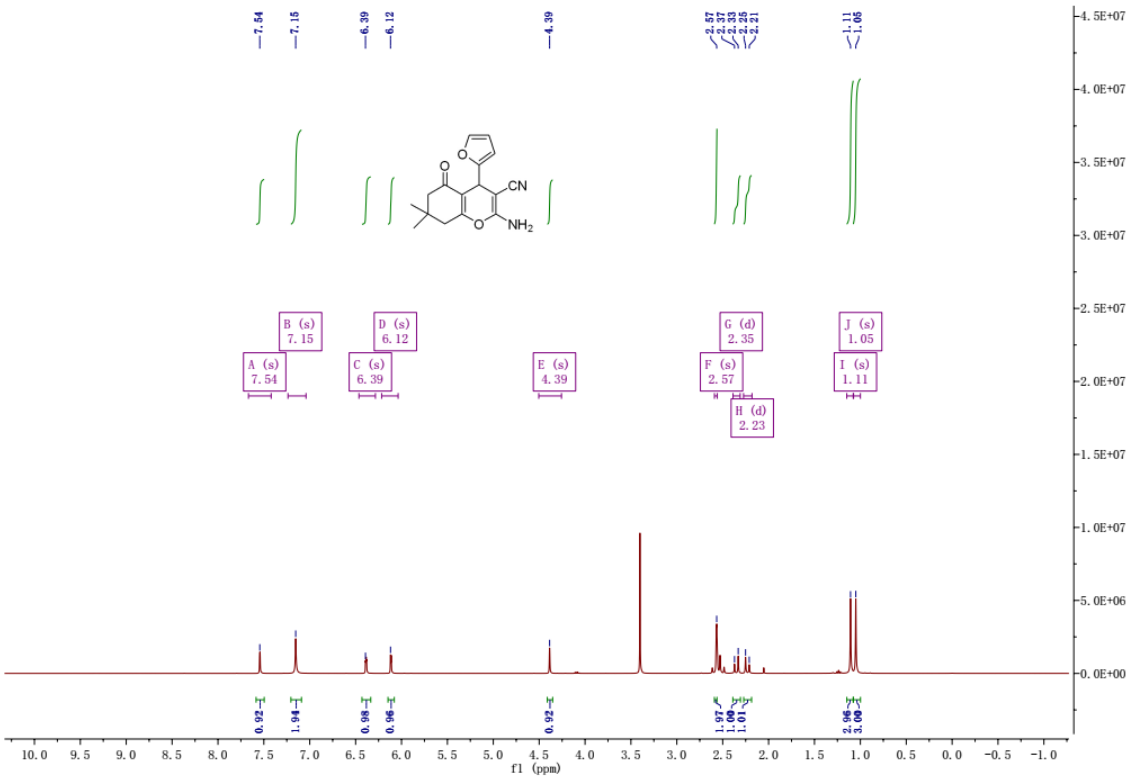

196.16
163.55
159.02
150.71
132.88
128.81
119.85
119.25
112.20
109.90
57.56
50.33
36.28
32.30
28.71
27.42
CN
O
CN
NH2
f1 (ppm)

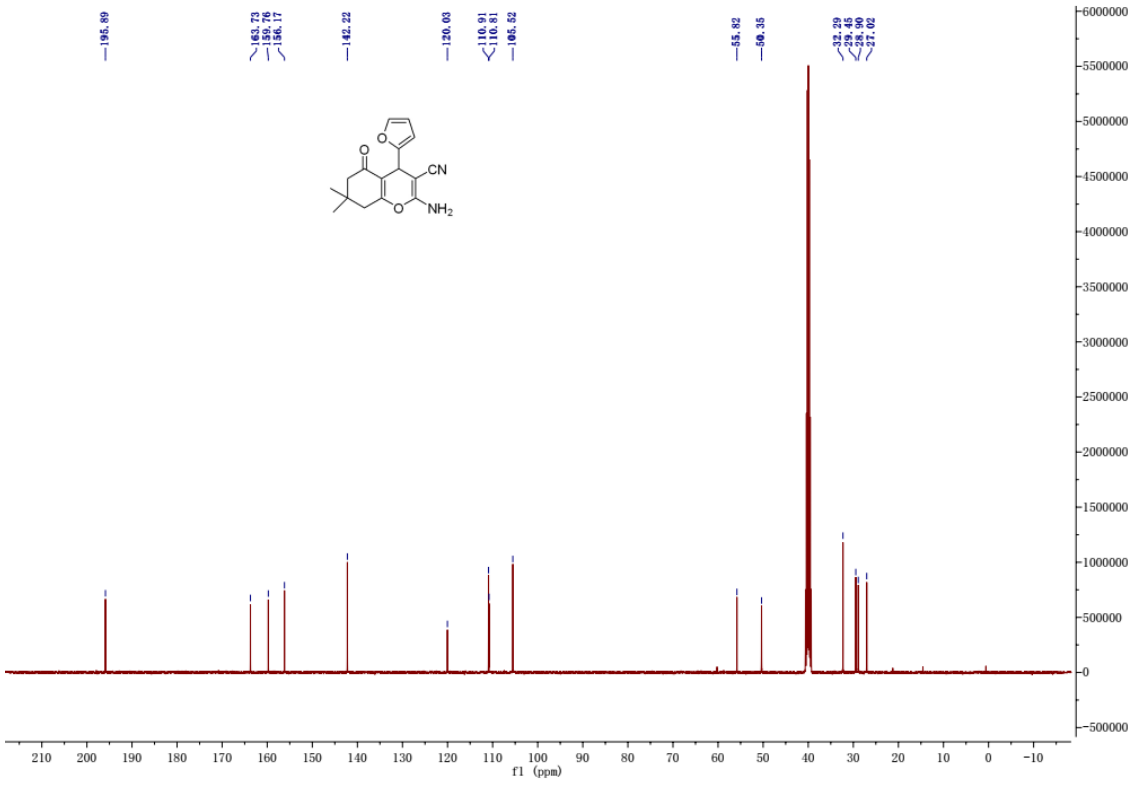

F: ITMS + c ESI Full ms [50.00-1200.00]
CN
O
CN
NH2
660.89
501.74
661.83
660.18
342.07
662.83
439.81
502.76
382.67
503.47
440.94
383.66
301.02
320.22
602.20
635.53
683.27
758.26
831.04
867.77
Relative Abundance
m/z

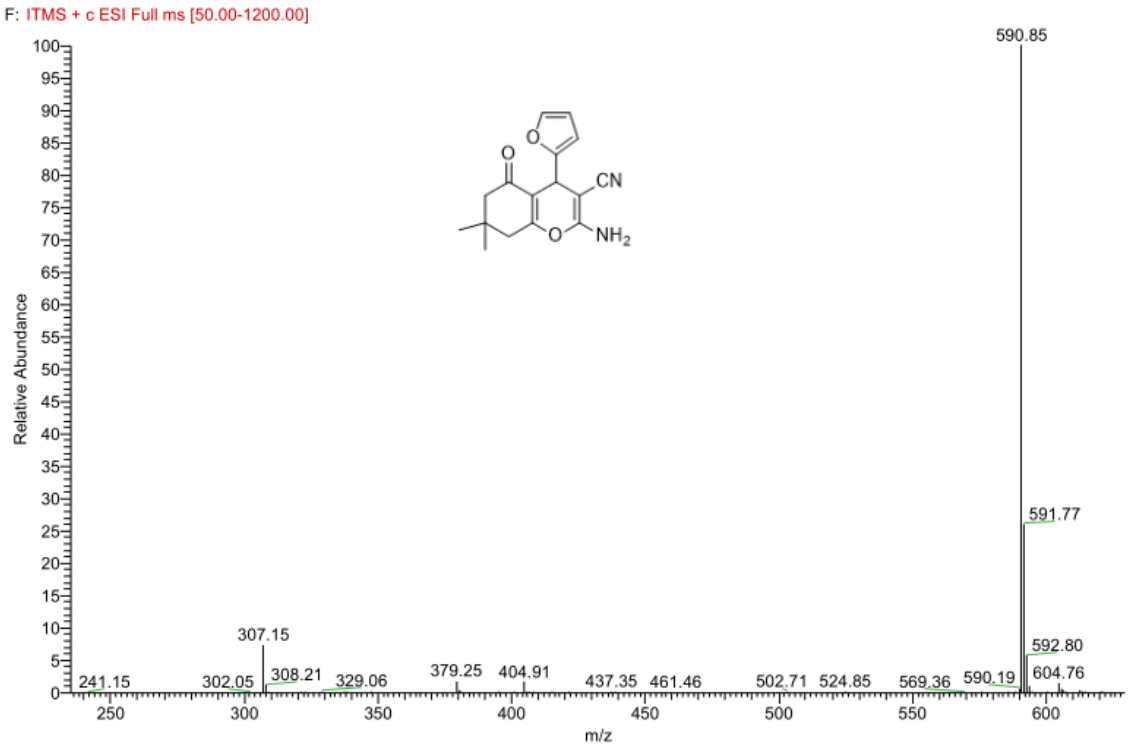


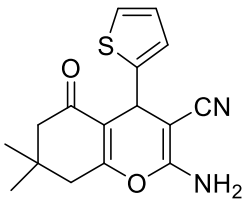
2-Amino-4-(furan-2-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4o**, $C_{16}H_{16}N_2O_3$)

Yellow solid; mp 226-228 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.54 (s, 1H), 7.15 (s, 2H), 6.39 (s, 1H), 6.12 (s, 1H), 4.39 (s, 1H), 2.57 (s, 2H), 2.35 (d, J = 16.1 Hz, 1H), 2.23 (d, J = 16.1 Hz, 1H), 1.11 (s, 3H), 1.05 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 195.89, 163.73, 159.76, 156.17, 142.22, 120.03, 110.91, 110.81, 105.52, 55.82, 50.35, 32.29, 29.45, 28.90, 27.02. MS (ESI): $[2M+Na]^+$: 591.77.



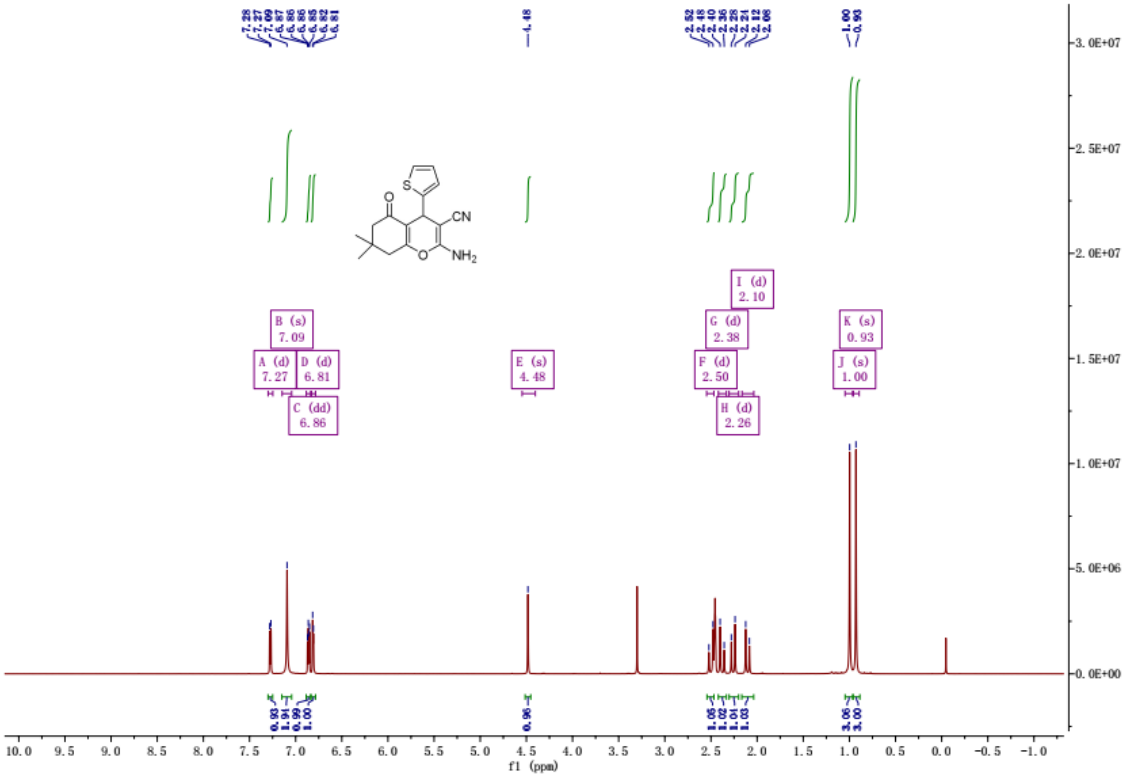

195.89
163.73
158.76
156.17
142.22
120.03
110.91
110.81
105.52
55.82
50.35
32.29
29.45
28.90
27.02
O
CN
O
NH2
f1 (ppm)

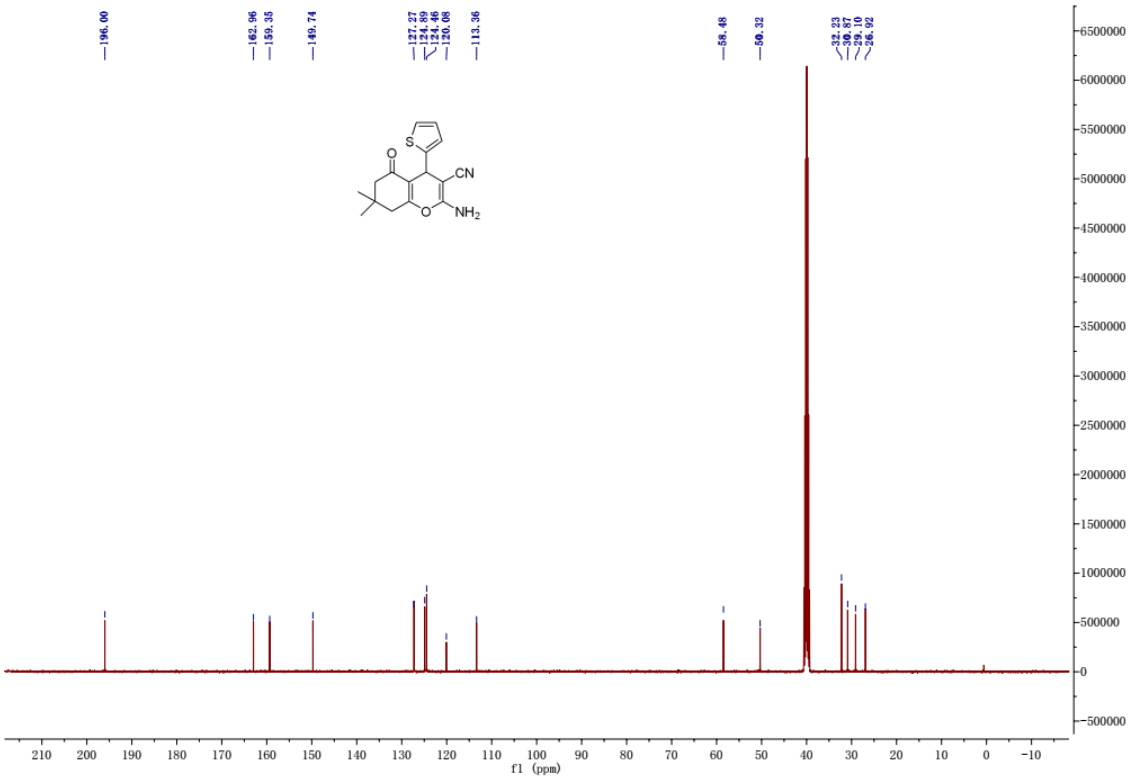

F: ITMS + c ESI Full ms [50.00-1200.00]
590.85
591.77
592.80
604.76
307.15
241.15
302.05
308.21
329.06
379.25
404.91
437.35
461.46
502.71
524.85
569.36
590.19
Relative Abundance
m/z
O
CN
O
NH2

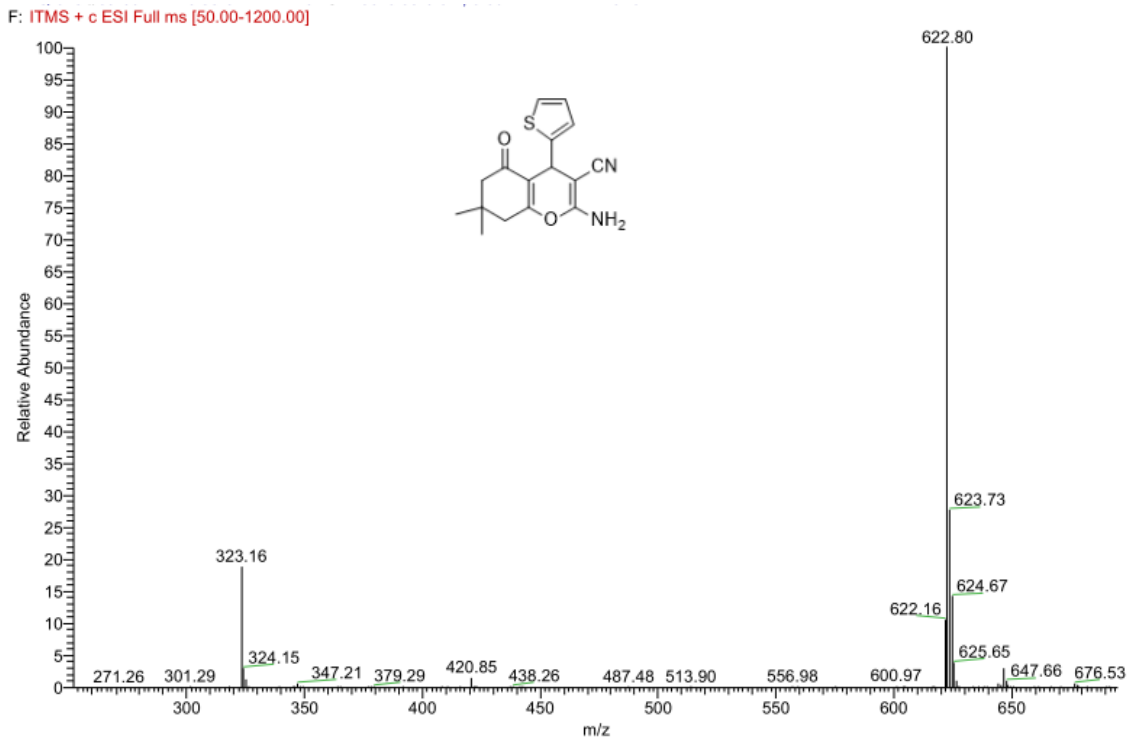


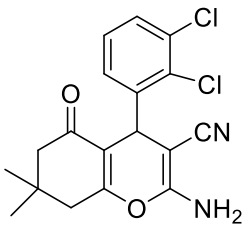
2-Amino-7,7-dimethyl-5-oxo-4-(thiophen-2-yl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4p**, $C_{16}H_{16}N_2O_2S$)

White solid; mp 227-230 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.27 (d, J = 4.9 Hz, 1H), 7.09 (s, 2H), 6.86 (dd, J = 4.9, 3.6 Hz, 1H), 6.81 (d, J = 3.1 Hz, 1H), 4.48 (s, 1H), 2.50 (d, J = 17.7 Hz, 1H), 2.38 (d, J = 17.7 Hz, 1H), 2.26 (d, J = 16.2 Hz, 1H), 2.10 (d, J = 16.2 Hz, 1H), 1.00 (s, 3H), 0.93 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.00, 162.96, 159.35, 149.74, 127.27, 124.89, 124.46, 120.08, 113.36, 58.48, 50.32, 32.23, 30.87, 29.10, 26.92. MS (ESI): $[2M+Na]^+$: 623.73.



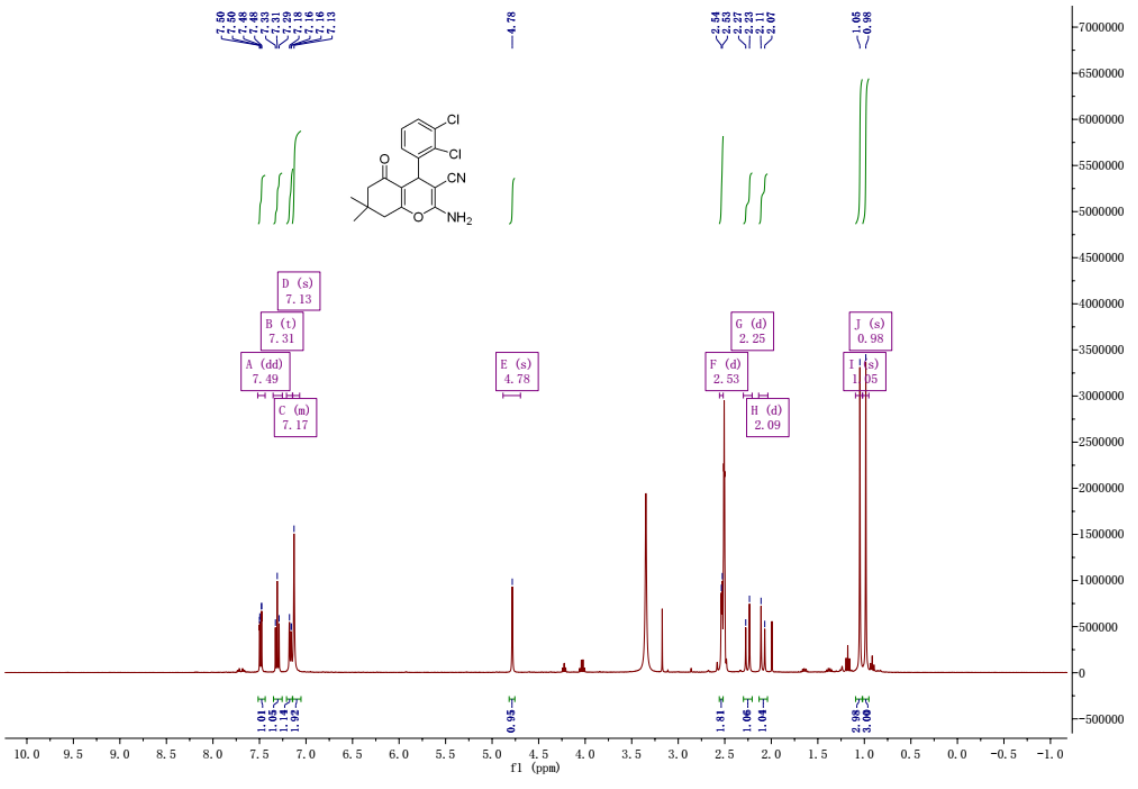

196.00
162.96
159.35
149.74
127.27
124.69
124.46
120.08
113.36
58.48
50.32
32.23
30.87
29.10
26.92
CN
NH2
f1 (ppm)

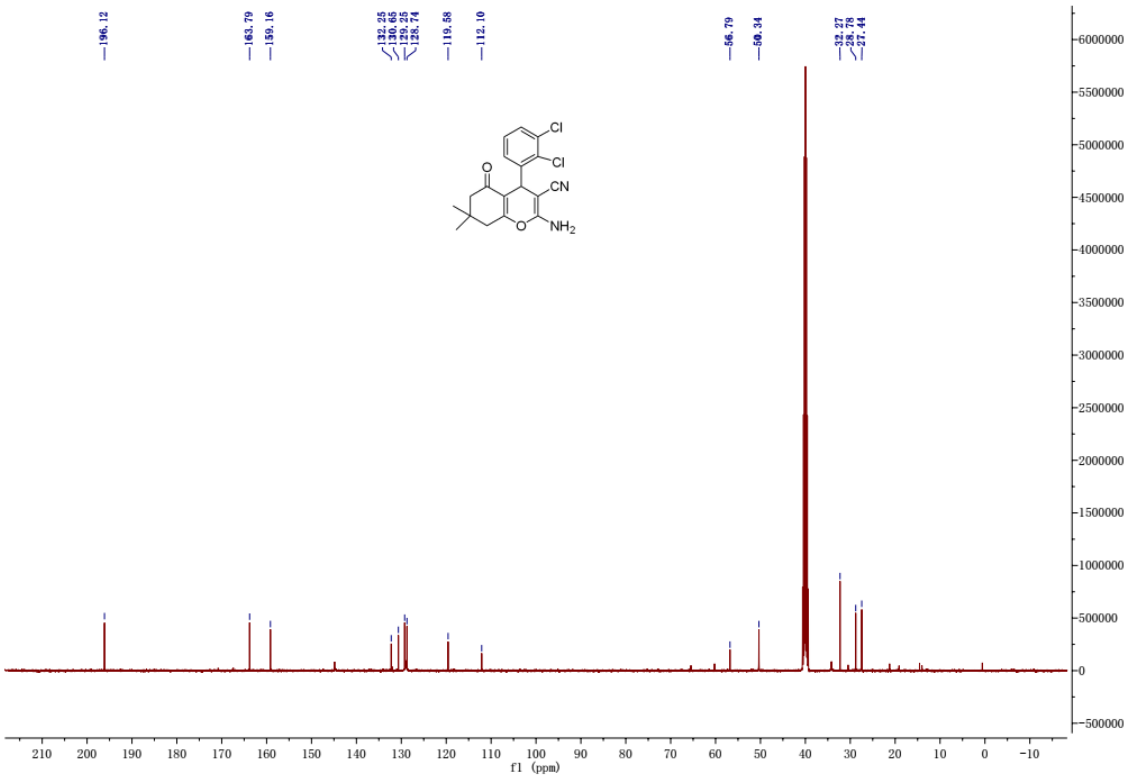

F: ITMS + c ESI Full ms [50.00-1200.00]
Relative Abundance
m/z
622.80
623.73
624.67
622.16
625.65
323.16
324.15
271.26
301.29
347.21
379.29
420.85
438.26
487.48
513.90
556.98
600.97
647.66
676.53
CN
NH2

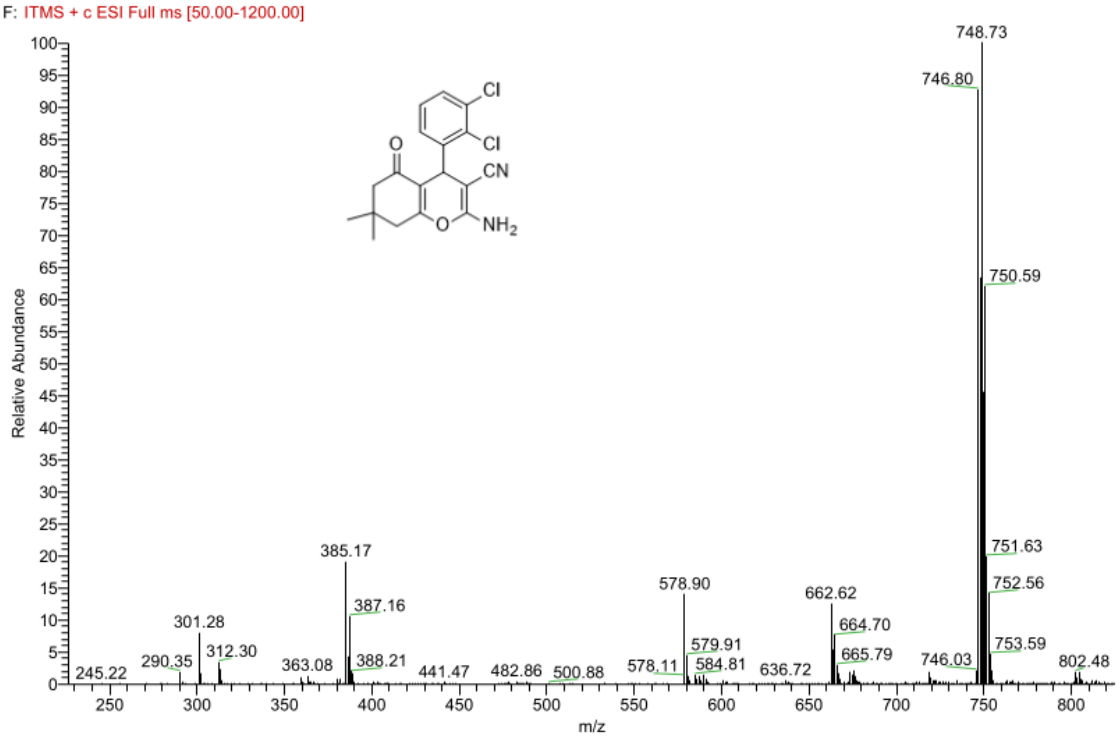


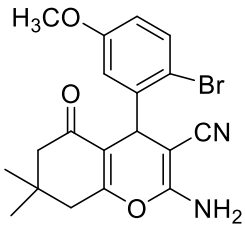
2-Amino-4-(2,3-dichlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4q**, $C_{18}H_{16}Cl_2N_2O_2$)

Yellow solid; mp 231-233 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.49 (dd, J = 7.9, 1.4 Hz, 1H), 7.31 (t, J = 7.9 Hz, 1H), 7.21 – 7.15 (m, 1H), 7.13 (s, 2H), 4.78 (s, 1H), 2.53 (d, J = 4.0 Hz, 2H), 2.25 (d, J = 16.0 Hz, 1H), 2.09 (d, J = 16.0 Hz, 1H), 1.05 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.12, 163.79, 159.16, 132.25, 130.65, 129.25, 128.74, 119.58, 112.10, 56.79, 50.34, 32.27, 28.78, 27.44. MS (ESI): $[2M+Na]^+$: 748.73.



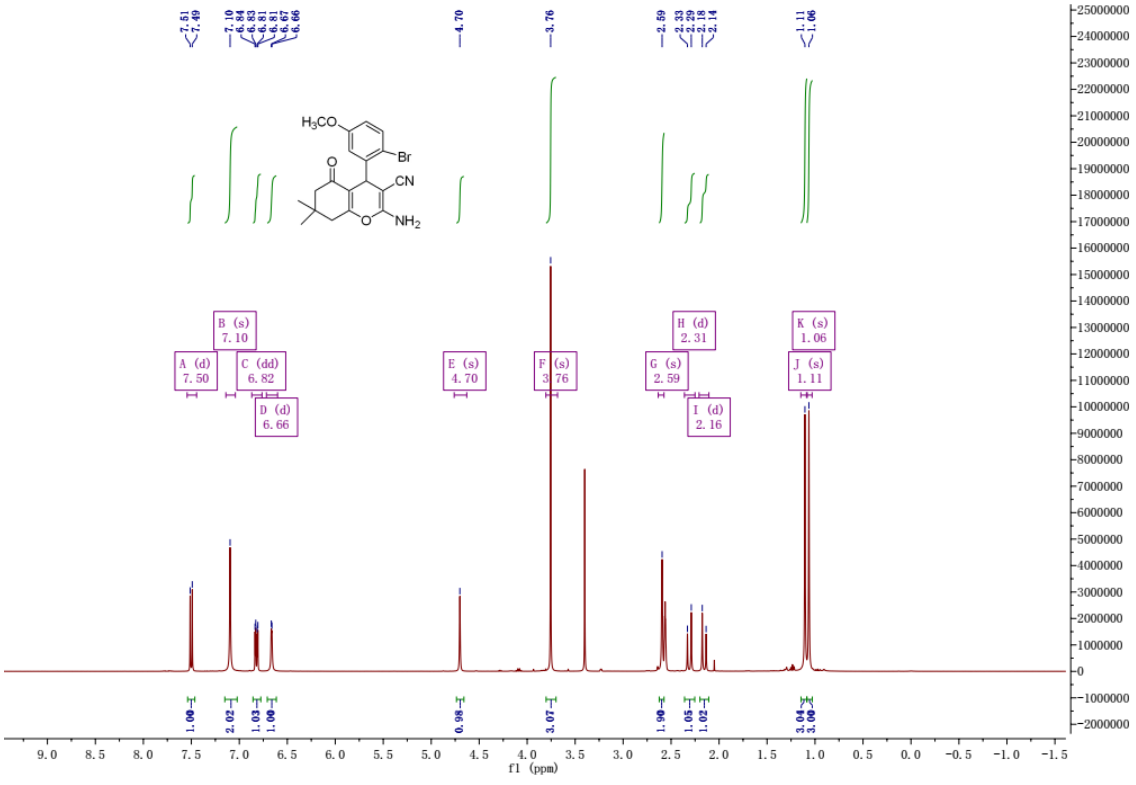

196.12
163.79
159.16
132.25
130.66
130.05
128.74
119.58
112.10
56.79
50.34
32.27
28.75
27.44
Cl
Cl
CN
O
O
NH2
f1 (ppm)

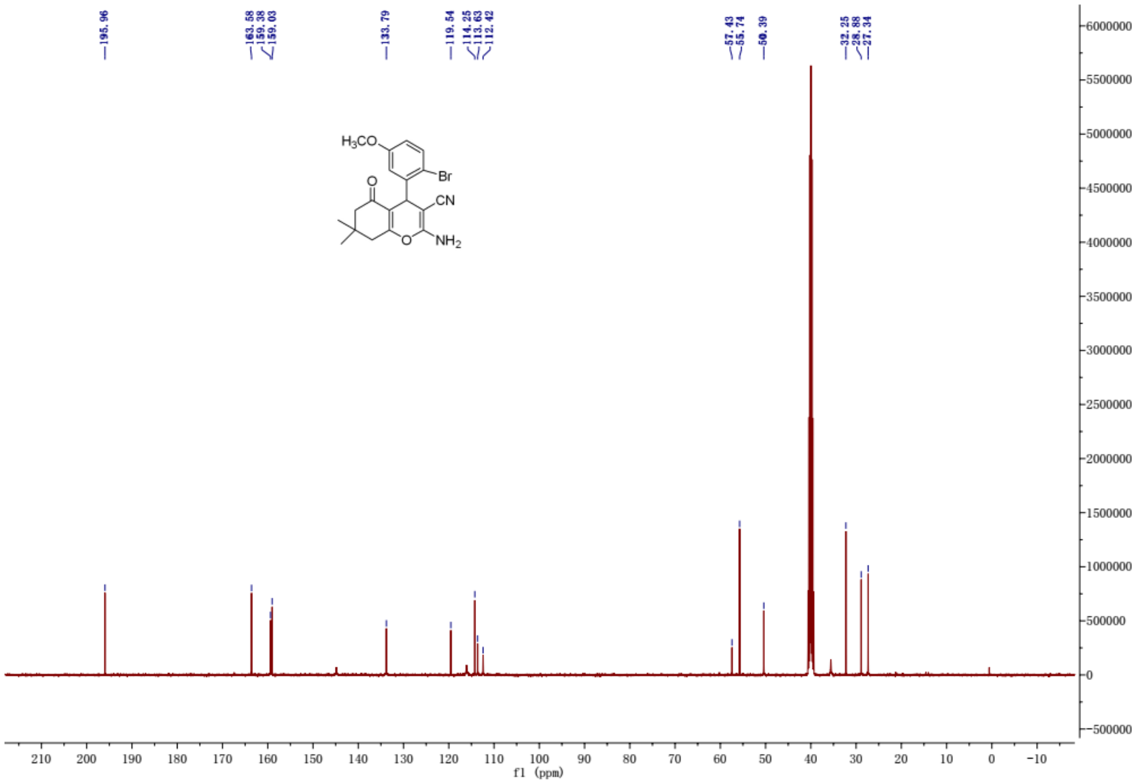

F: ITMS + c ESI Full ms [50.00-1200.00]
Relative Abundance
m/z
748.73
746.80
750.59
751.63
752.56
753.59
802.48
746.03
385.17
387.16
388.21
301.28
312.30
290.35
245.22
363.08
441.47
482.86
500.88
578.90
579.91
584.81
578.11
636.72
662.62
664.70
665.79
Cl
Cl
CN
O
O
NH2



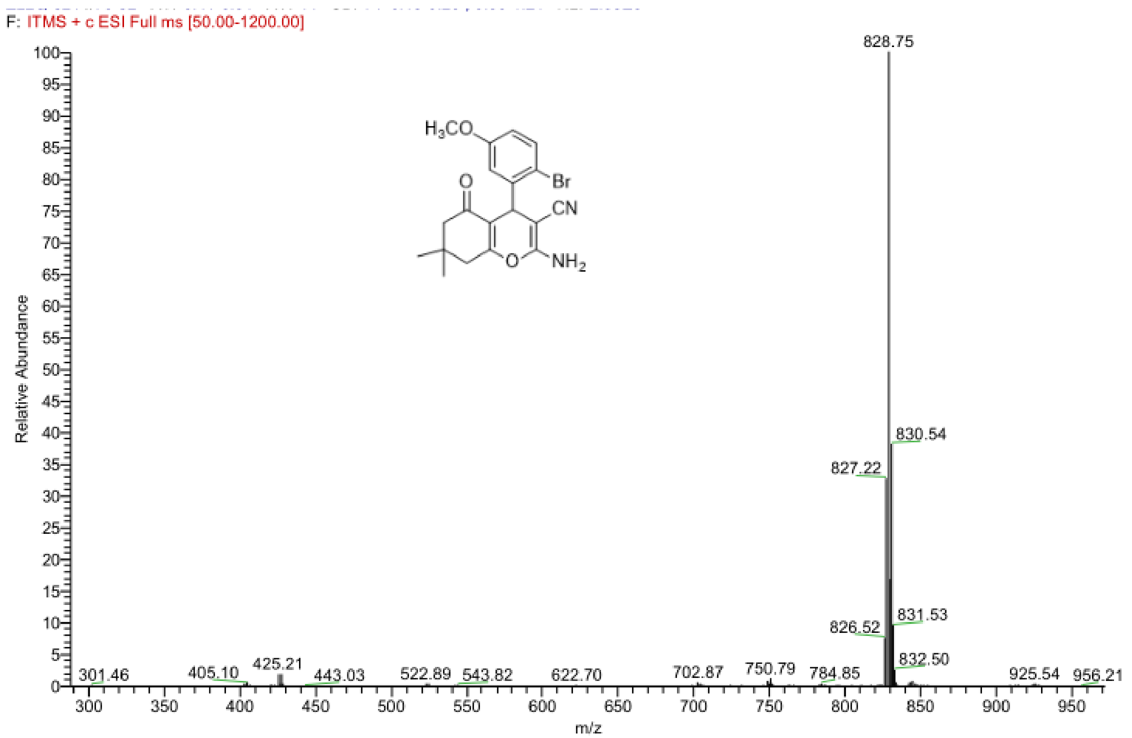
2-Amino-4-(2-bromo-5-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4r**, $C_{19}H_{19}BrN_2O_3$)

Faint yellow solid; mp 184-186 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (d, J = 8.8 Hz, 1H), 7.10 (s, 2H), 6.82 (dd, J = 8.8, 3.0 Hz, 1H), 6.66 (d, J = 2.5 Hz, 1H), 4.70 (s, 1H), 3.76 (s, 3H), 2.59 (s, 2H), 2.31 (d, J = 16.0 Hz, 1H), 2.16 (d, J = 16.0 Hz, 1H), 1.11 (s, 3H), 1.06 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 195.96, 163.58, 159.38, 159.03, 133.79, 119.54, 114.25, 113.63, 112.42, 57.43, 55.74, 50.39, 32.25, 28.88, 27.34. MS (ESI): $[2M+Na]^+$: 828.75.

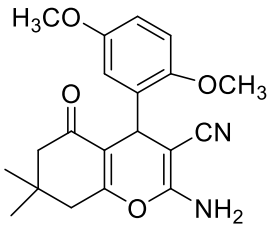




195.96
163.58
159.38
159.03
133.79
119.54
114.25
113.63
112.42
57.43
55.74
50.39
32.25
28.88
27.34
H3CO
Br
CN
O
O
NH2
f1 (ppm)

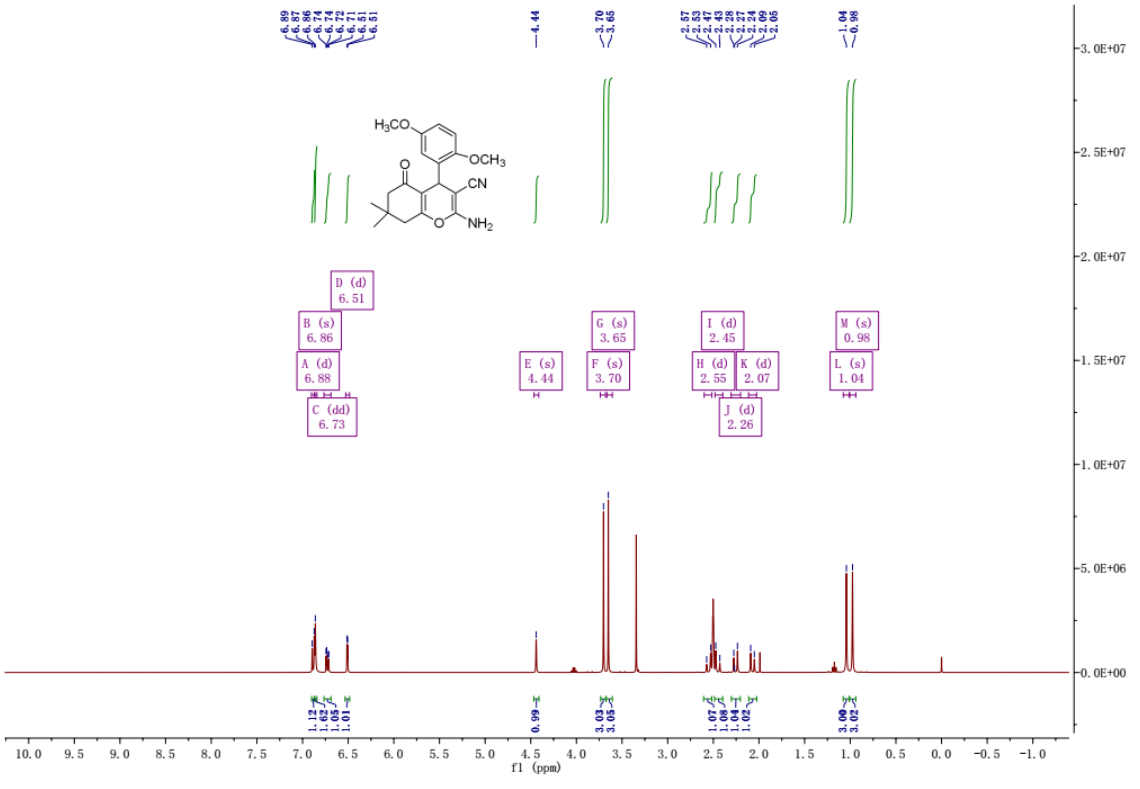


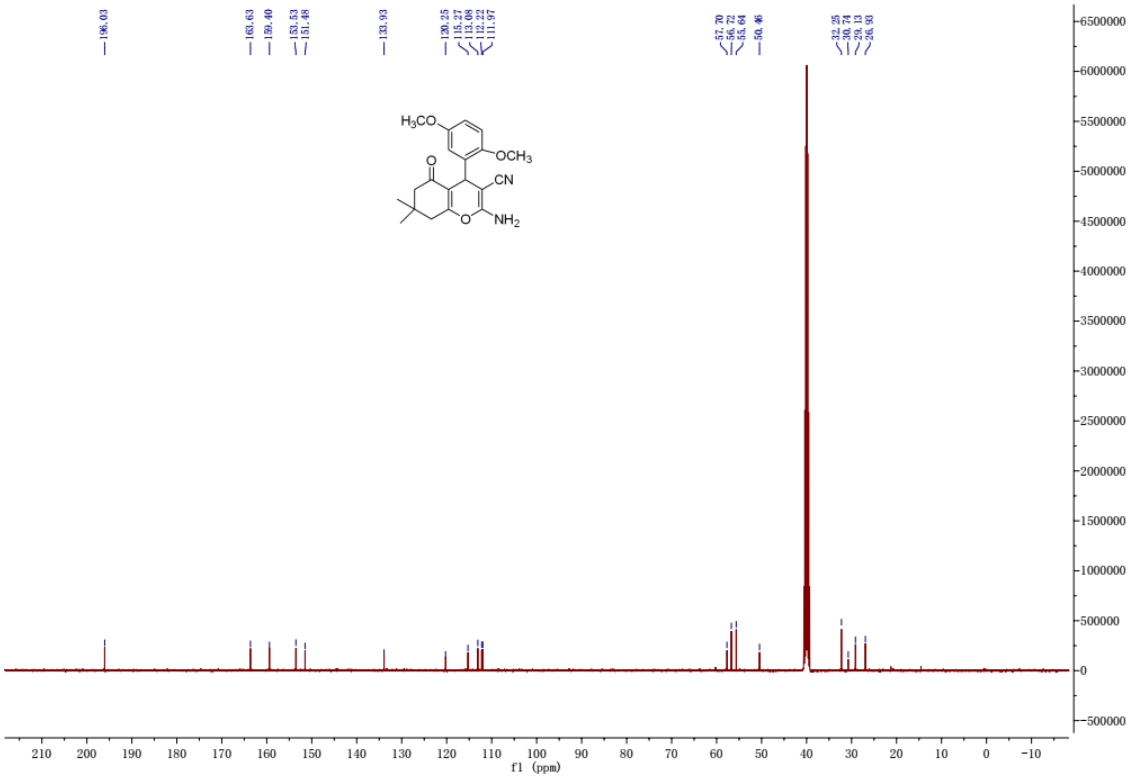
F: ITMS + c ESI Full ms [50.00-1200.00]
828.75
830.54
827.22
826.52
831.53
832.50
301.46
405.10
425.21
443.03
522.89
543.82
622.70
702.87
750.79
784.85
925.54
956.21
Relative Abundance
m/z
H3CO
Br
CN
O
O
NH2

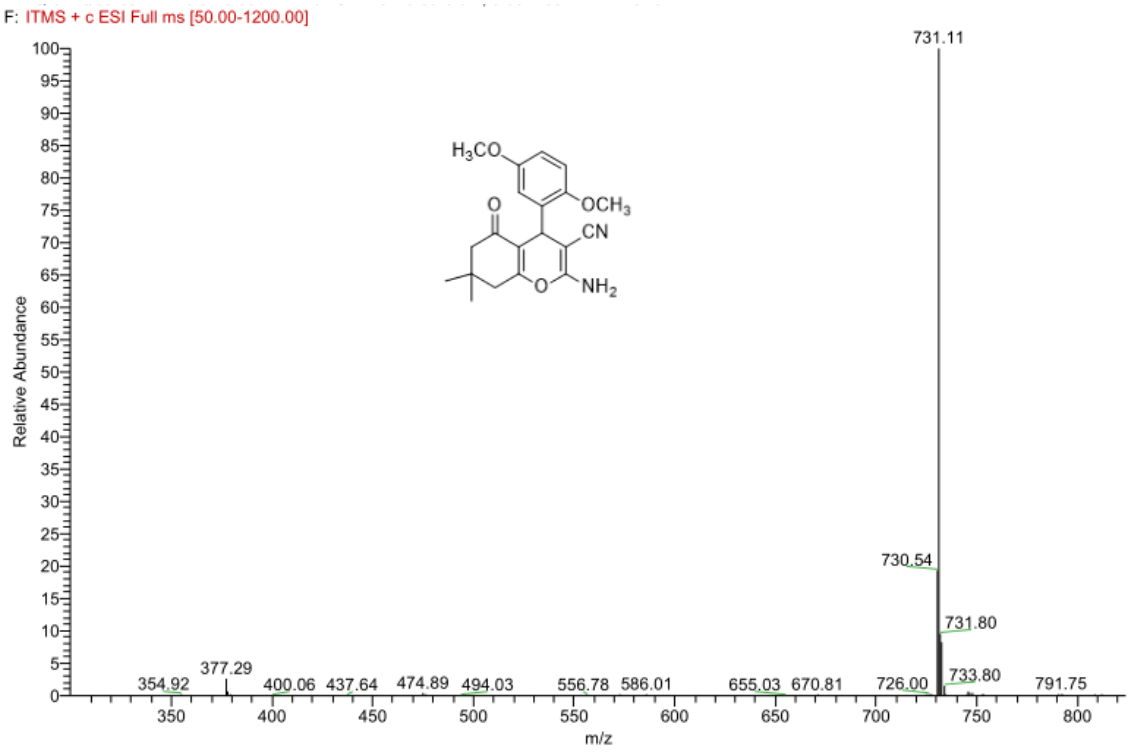


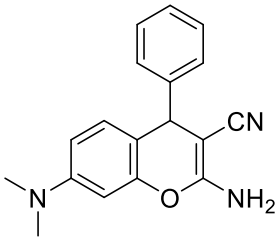
2-Amino-4-(2,5-dimethoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4s**, $C_{20}H_{22}N_2O_4$)

Faint yellow solid; mp 211-213 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.88 (d, J = 8.9 Hz, 1H), 6.86 (s, 2H), 6.73 (dd, J = 8.9, 3.1 Hz, 1H), 6.51 (d, J = 3.0 Hz, 1H), 4.44 (s, 1H), 3.70 (s, 3H), 3.65 (s, 3H), 2.55 (d, J = 17.7 Hz, 1H), 2.45 (d, J = 17.6 Hz, 1H), 2.26 (d, J = 16.1 Hz, 1H), 2.07 (d, J = 16.1 Hz, 1H), 1.04 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.03, 163.63, 159.40, 153.53, 151.48, 133.93, 120.25, 115.27, 113.08, 112.22, 111.97, 57.70, 56.72, 55.64, 50.46, 32.25, 30.74, 29.13, 26.93. MS (ESI): $[2M+Na]^+$: 731.11.



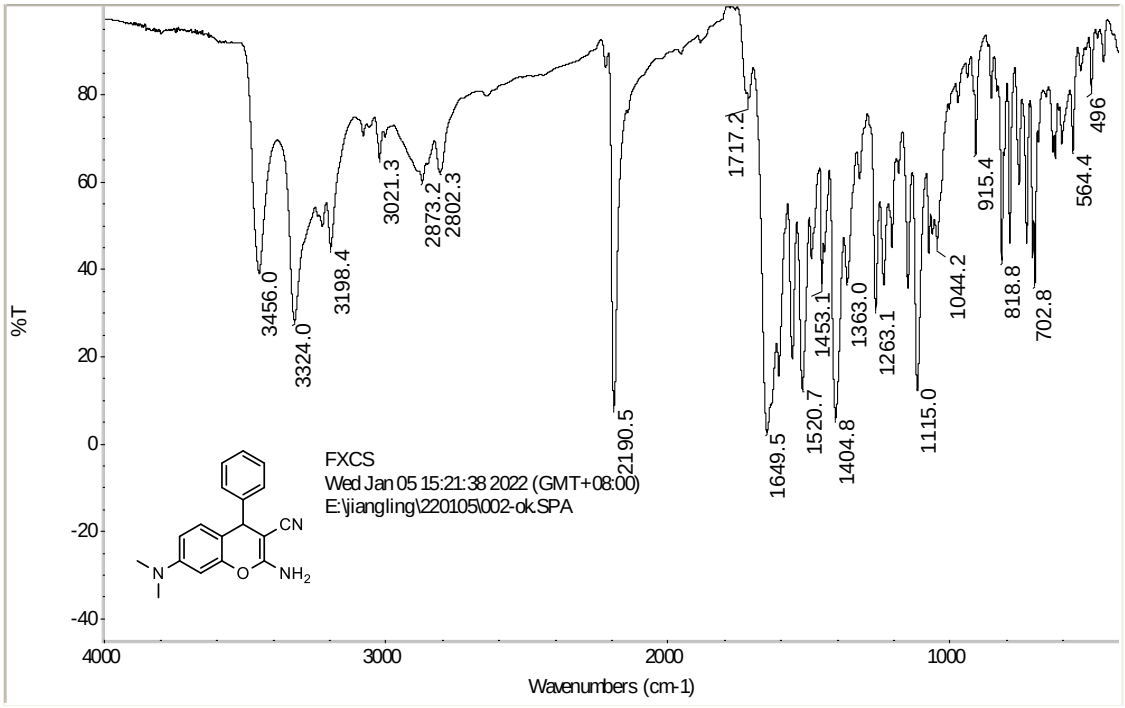

196.03
163.63
159.40
153.53
151.48
133.93
130.25
115.27
113.08
112.22
111.97
57.70
56.72
55.64
50.46
32.25
30.74
28.13
26.93
H3CO
OCH3
CN
O
NH2
f1 (ppm)

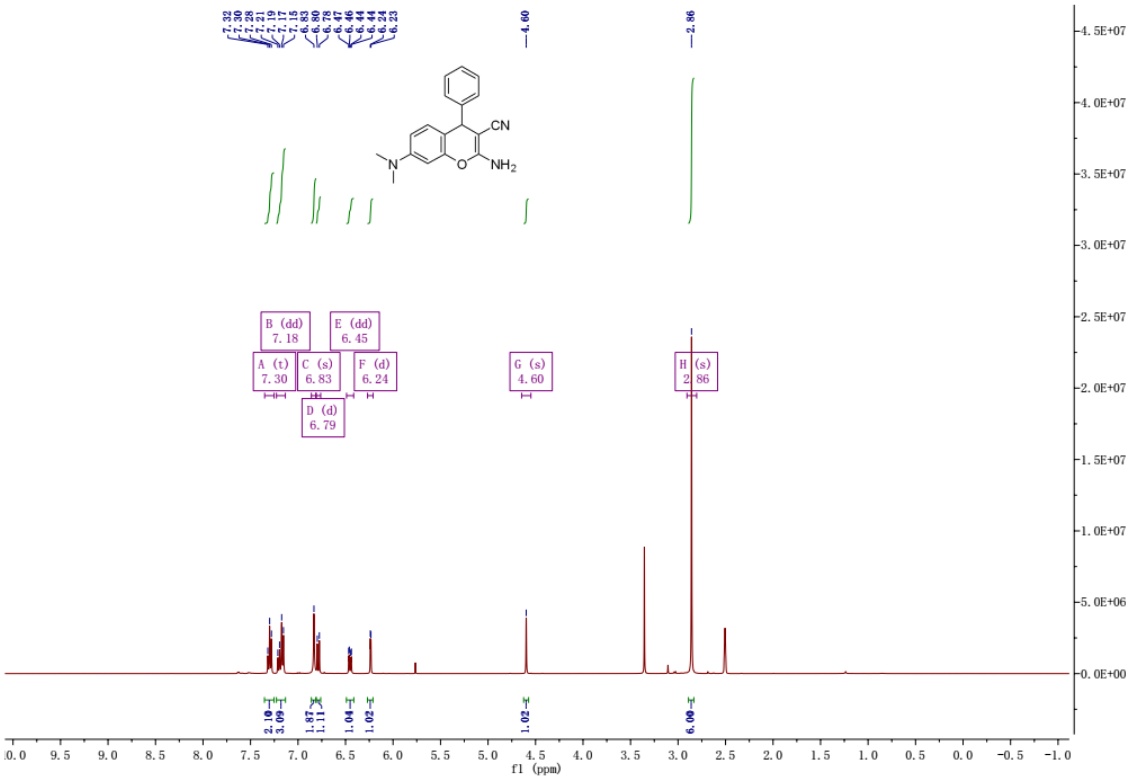

F: ITMS + c ESI Full ms [50.00-1200.00]
Relative Abundance
m/z
731.11
730.54
731.80
733.80
377.29
354.92
400.06
437.64
474.89
494.03
556.78
586.01
655.03
670.81
726.00
791.75
H3CO
OCH3
CN
O
NH2

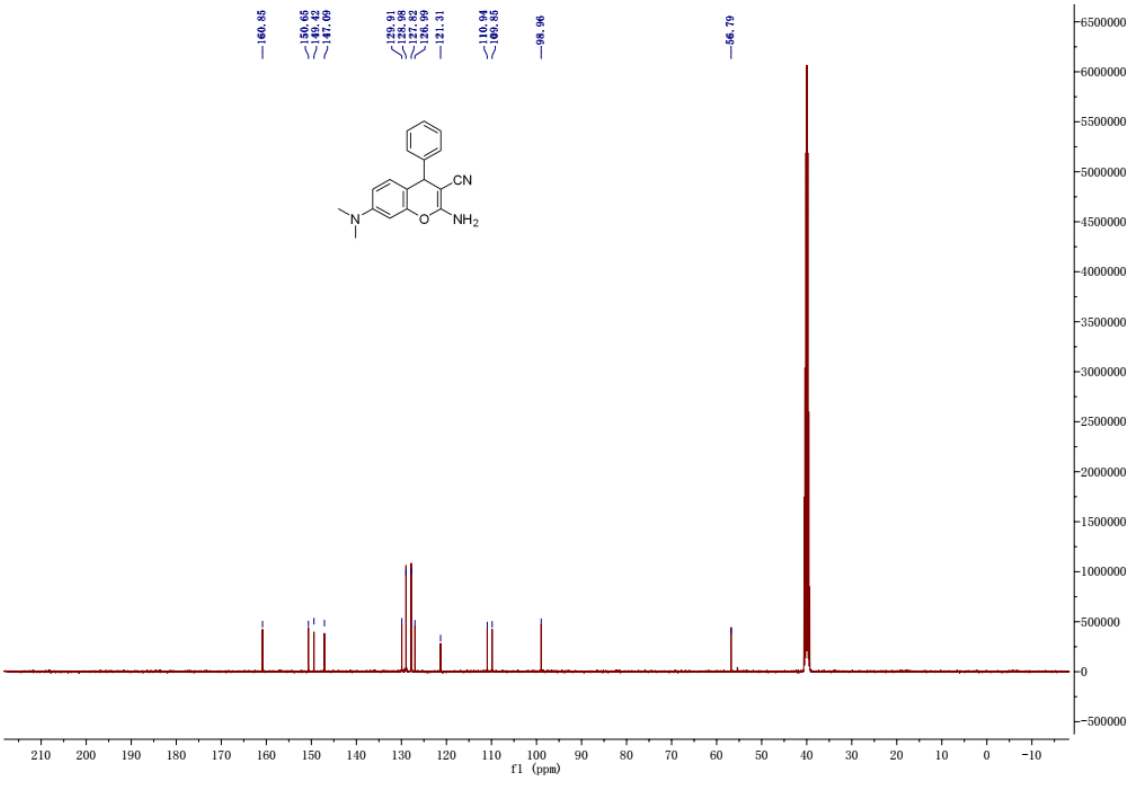


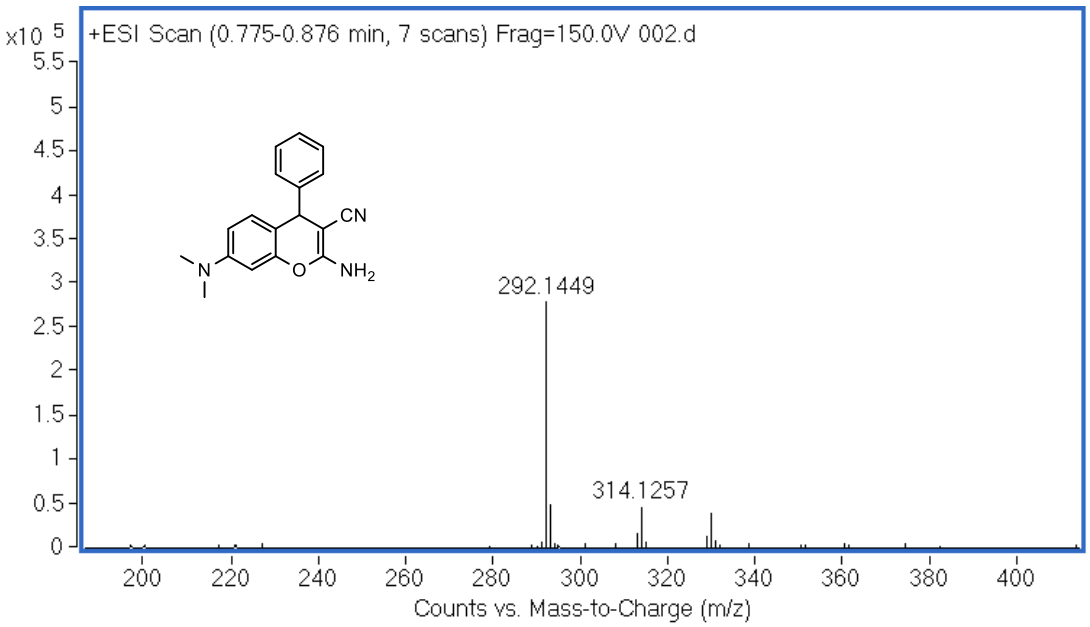
2-Amino-7-(dimethylamino)-4-phenyl-4*H*-chromene-3-carbonitrile (**5a**, $C_{18}H_{17}N_3O$)

Yellow solid; mp 201-203 ℃. IR(KBr): 3456.0, 3324.0, 3198.4, 2190.5, 1649.5, 1520.7, 1404.8, 1263.1, 1115.0, 1044.2, 818.8, 702.8 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 7.30 (t, *J* = 7.5 Hz, 2H), 7.18 (dd, *J* = 16.3, 7.3 Hz, 3H), 6.83 (s, 2H), 6.79 (d, *J* = 8.6 Hz, 1H), 6.45 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.24 (d, *J* = 2.4 Hz, 1H), 4.60 (s, 1H), 2.86 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.85, 150.65, 149.42, 147.09, 129.91, 128.98, 127.82, 126.99, 121.31, 110.94, 109.85, 98.96, 56.79. HRMS (ESI) m/z calcd for $C_{18}H_{17}N_3ONa$ $[M+Na]^+$: 314.1264, found: 314.1257.

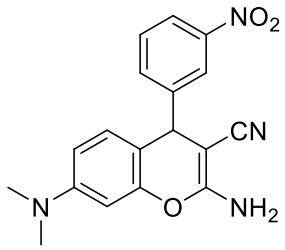



7.32
7.30
7.29
7.21
7.19
7.17
7.15
6.85
6.80
6.78
6.47
6.46
6.44
6.24
6.23
4.60
2.86
CN
NH2
N
O
B (dd) 7.18
E (dd) 6.45
A (t) 7.30
C (s) 6.83
F (d) 6.24
D (d) 6.79
G (s) 4.60
H (s) 2.86
2.10
3.09
1.87
1.11
1.04
1.02
1.02
6.00
f1 (ppm)


160.85
150.65
149.42
147.09
139.91
128.98
127.82
126.99
121.31
110.94
109.85
98.96
56.79
CN
NH2
N
O
f1 (ppm)

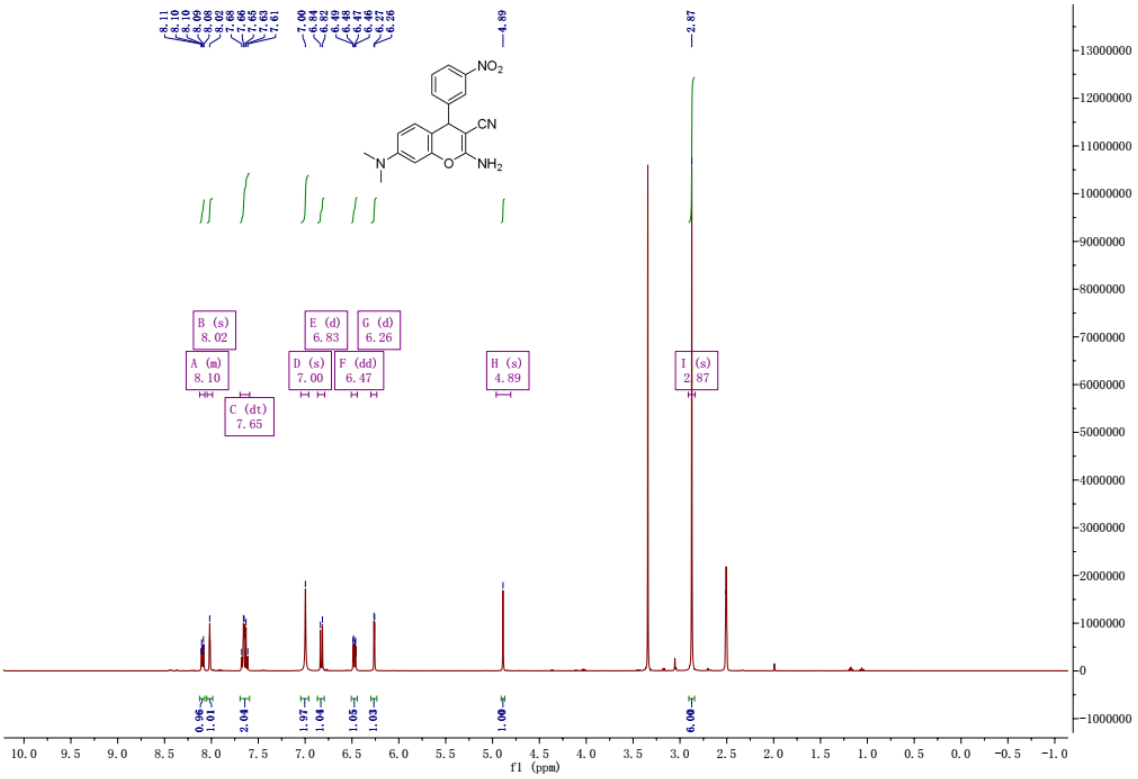


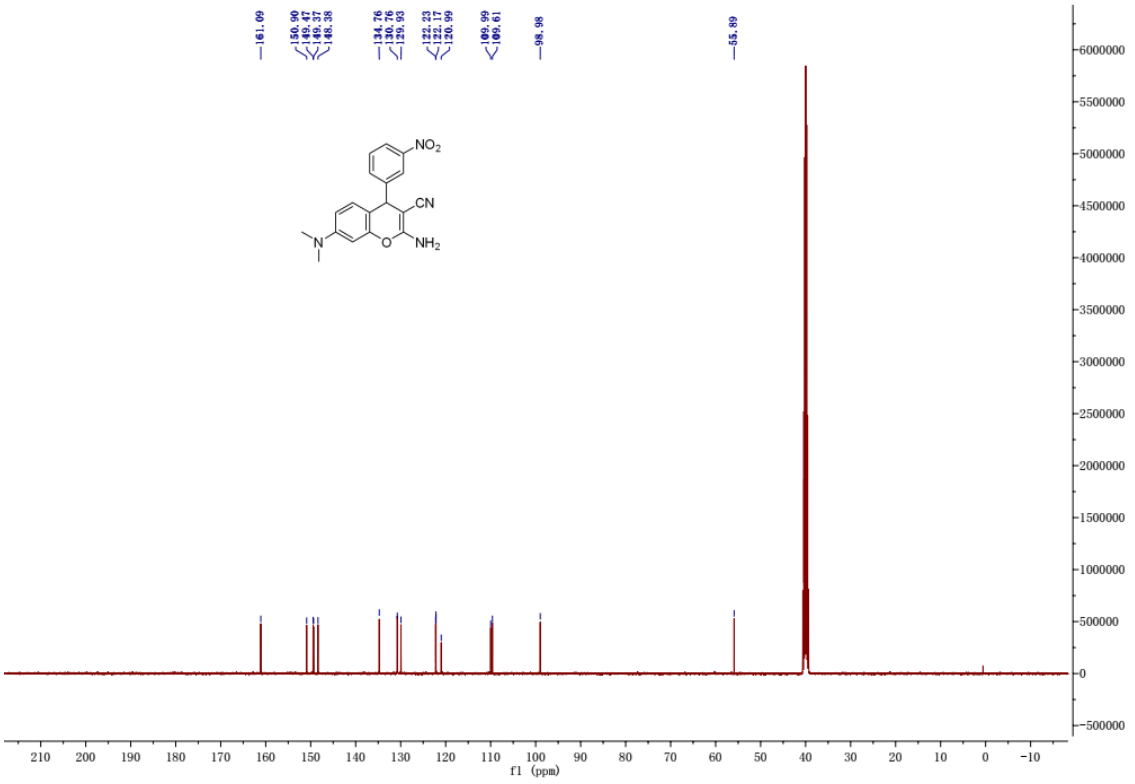
Formula (M)	Ion Formula	m/z	Calc m/z	Diff (ppm)	DBE
C18 H17 N3 O	C18 H18 N3 O	292.1449	292.1444	-1.58	12
C18 H17 N3 O	C18 H17 N3 Na O	314.1257	314.1264	2.35	12

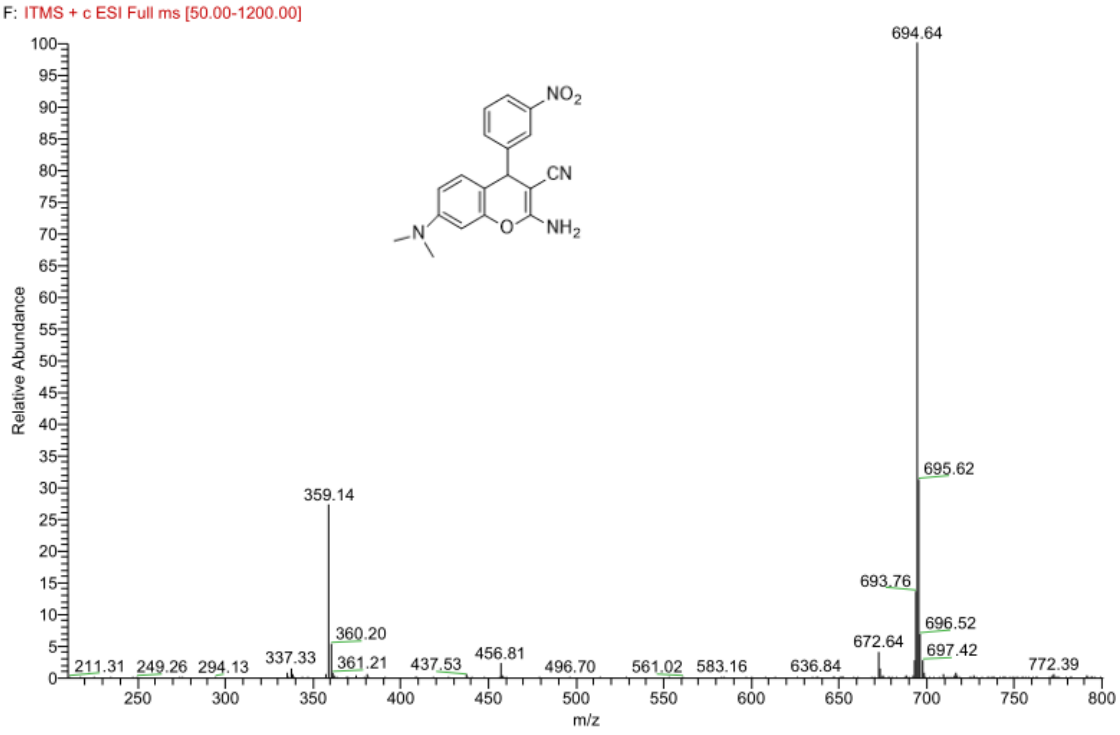


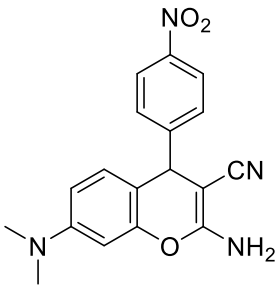
2-Amino-7-(dimethylamino)-4-(3-nitrophenyl)-4*H*-chromene-3-carbonitrile (**5b**, $C_{18}H_{16}N_4O_3$)

Orange solid; mp 196-198 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 – 8.07 (m, 1H), 8.02 (s, 1H), 7.65 (dt, J = 15.4, 7.7 Hz, 2H), 7.00 (s, 2H), 6.83 (d, J = 8.7 Hz, 1H), 6.47 (dd, J = 8.7, 2.5 Hz, 1H), 6.26 (d, J = 2.5 Hz, 1H), 4.89 (s, 1H), 2.87 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.09, 150.90, 149.47, 149.37, 148.38, 134.76, 130.76, 129.93, 122.23, 122.17, 120.99, 109.99, 109.61, 98.98, 55.89. MS (ESI): $[2M+Na]^+$: 695.62.



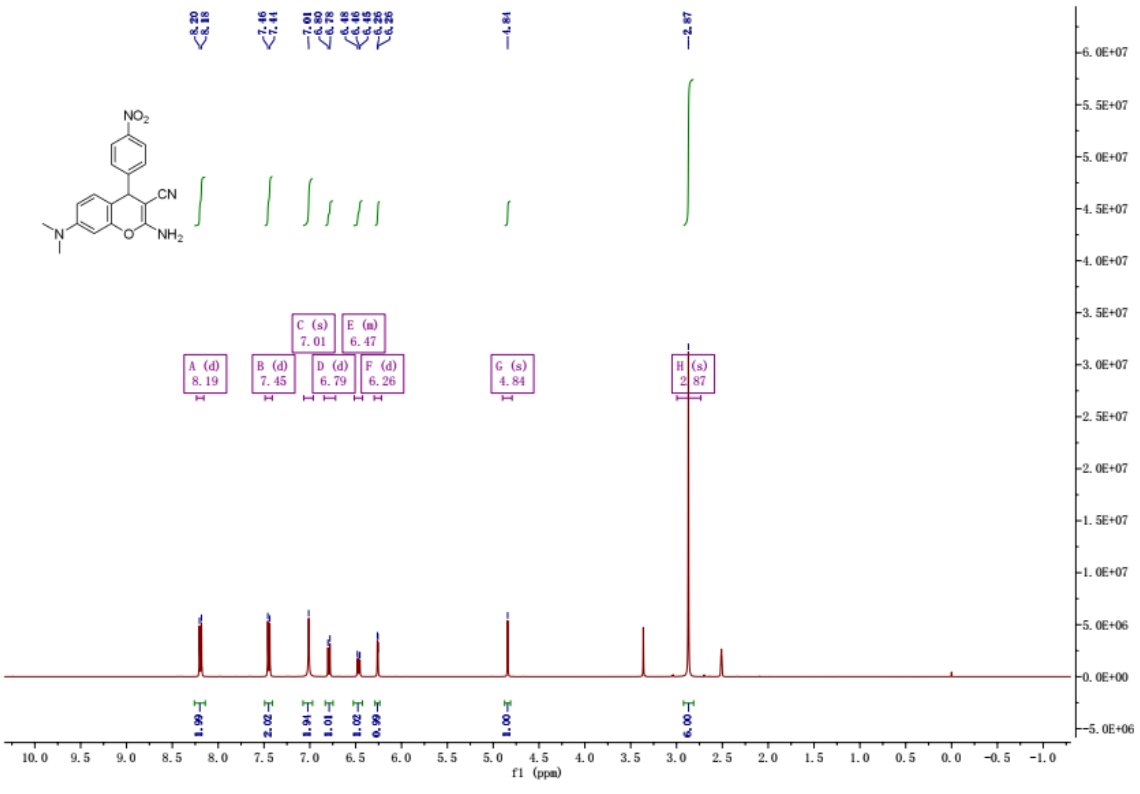

161.09
150.90
149.47
149.37
148.38
134.76
130.76
129.93
122.23
122.17
120.99
109.99
109.61
98.98
55.89
NO2
CN
NH2
N
O
f1 (ppm)

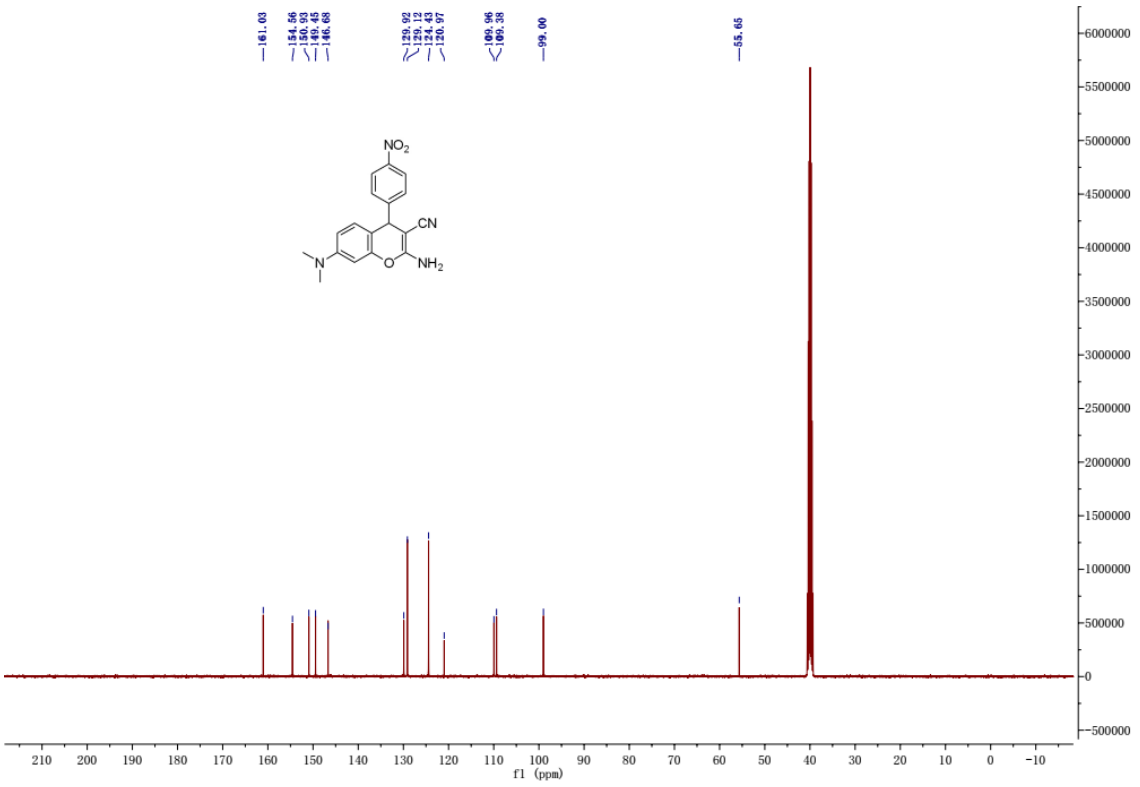

F: ITMS + c ESI Full ms [50.00-1200.00]
Relative Abundance
m/z
694.64
695.62
693.76
696.52
697.42
672.64
359.14
360.20
361.21
211.31
249.26
294.13
337.33
437.53
456.81
496.70
561.02
583.16
636.84
772.39
NO2
CN
NH2
N
O

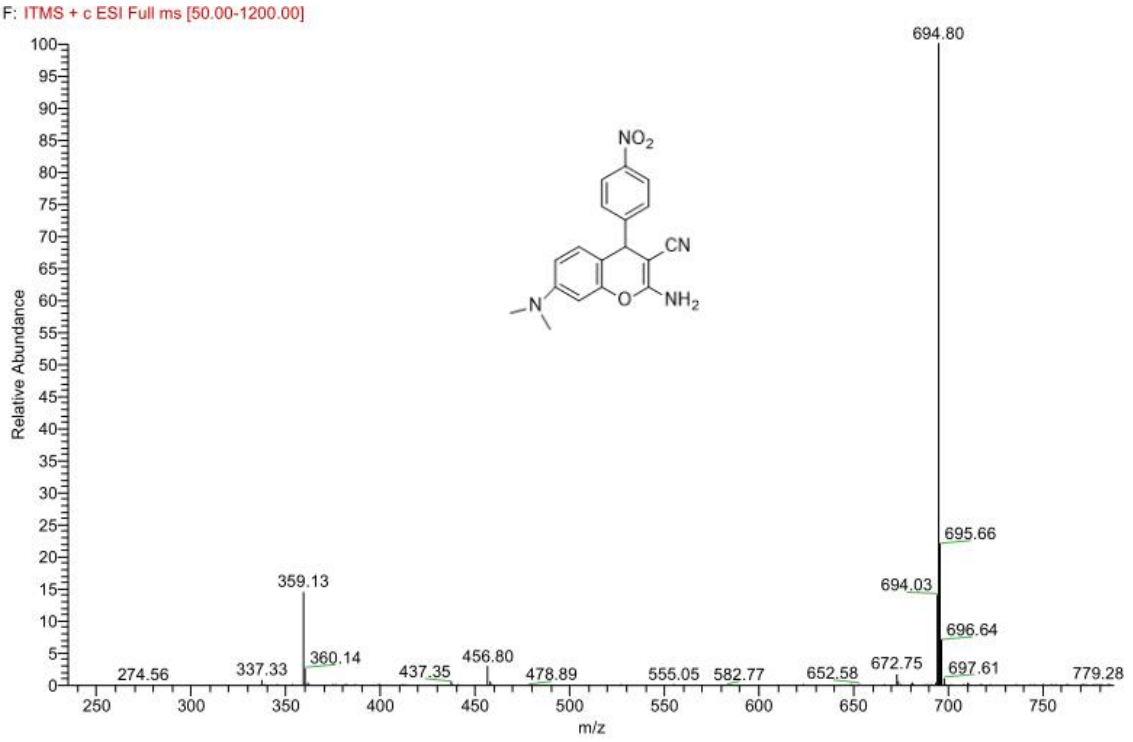


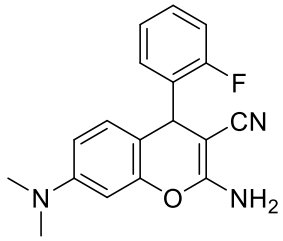
2-Amino-7-(dimethylamino)-4-(4-nitrophenyl)-4*H*-chromene-3-carbonitrile (**5c**, $C_{18}H_{16}N_4O_3$)

Yellow solid; mp 186-188 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (d, J = 8.6 Hz, 2H), 7.45 (d, J = 8.7 Hz, 2H), 7.01 (s, 2H), 6.79 (d, J = 8.7 Hz, 1H), 6.52 – 6.42 (m, 1H), 6.26 (d, J = 2.4 Hz, 1H), 4.84 (s, 1H), 2.87 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.03, 154.56, 150.93, 149.45, 146.68, 129.92, 129.12, 124.43, 120.97, 109.96, 109.38, 99.00, 55.65. MS (ESI): $[2M+Na]^+$: 695.66.



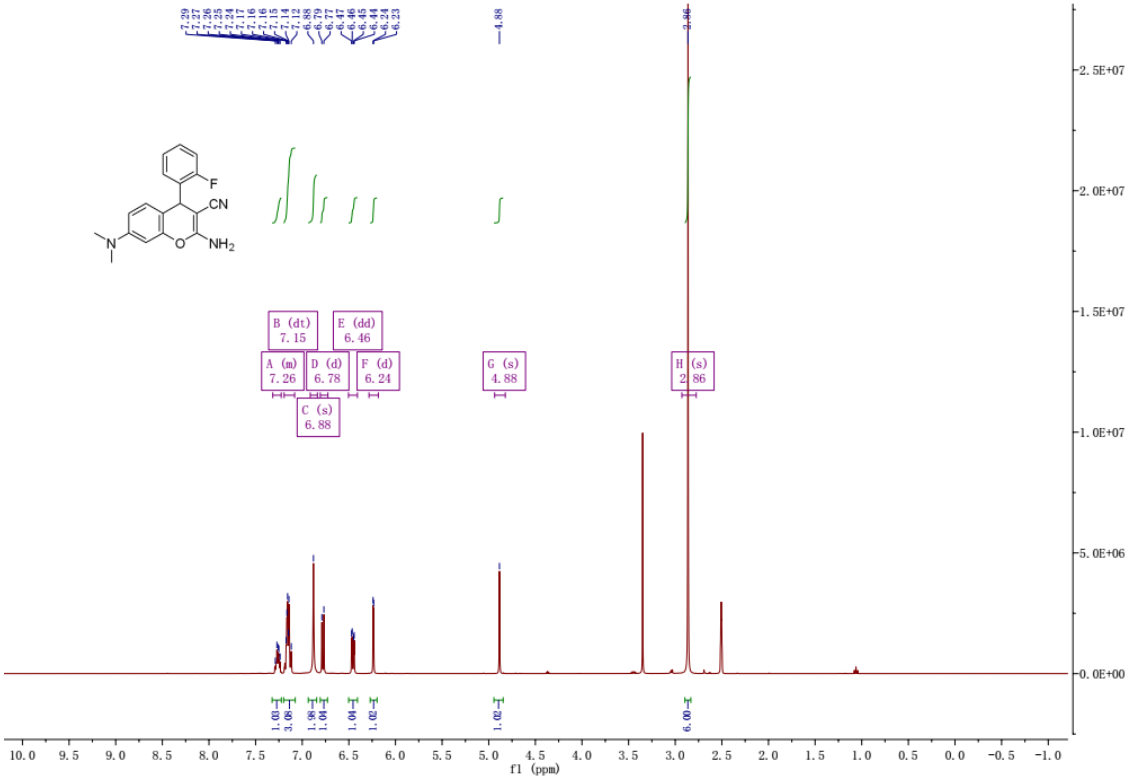

161.03
154.56
150.93
149.45
146.68
129.92
129.12
124.43
120.97
109.96
109.38
99.00
55.65
NO2
CN
NH2
N
O
f1 (ppm)

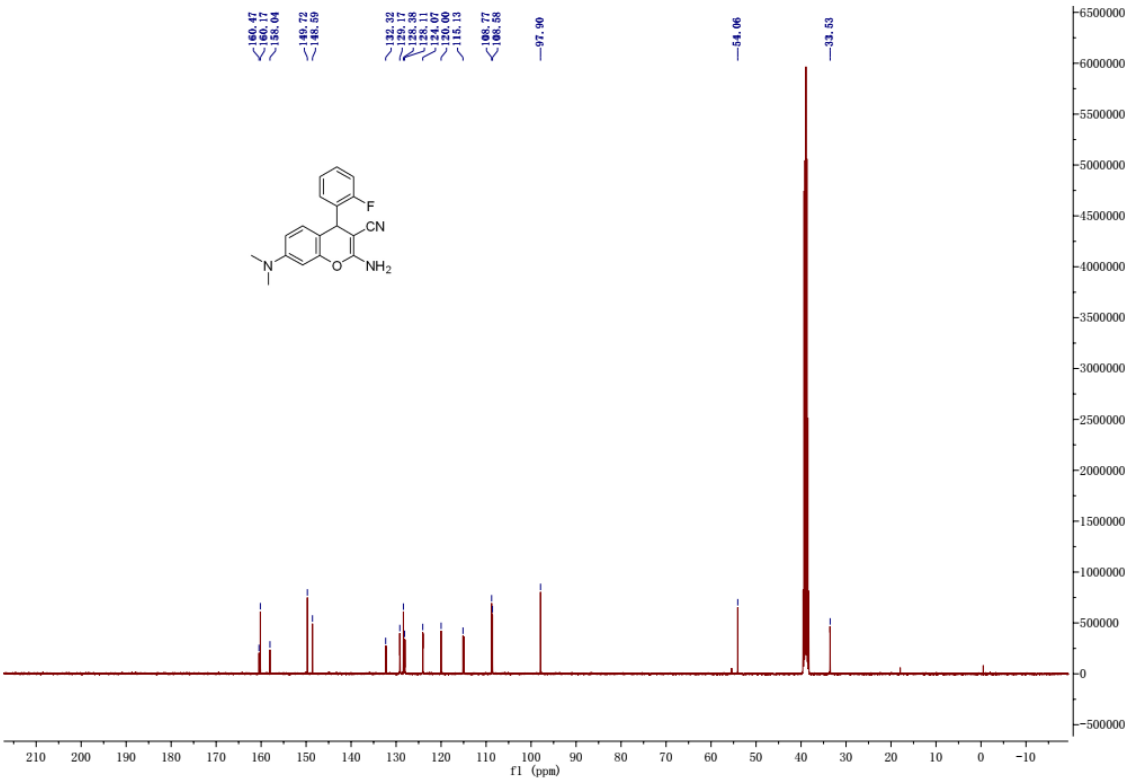

F: ITMS + c ESI Full ms [50.00-1200.00]
Relative Abundance
m/z
694.80
695.66
694.03
696.64
697.61
359.13
360.14
337.33
274.56
437.35
456.80
478.89
555.05
582.77
652.58
672.75
779.28
NO2
CN
NH2
N
O

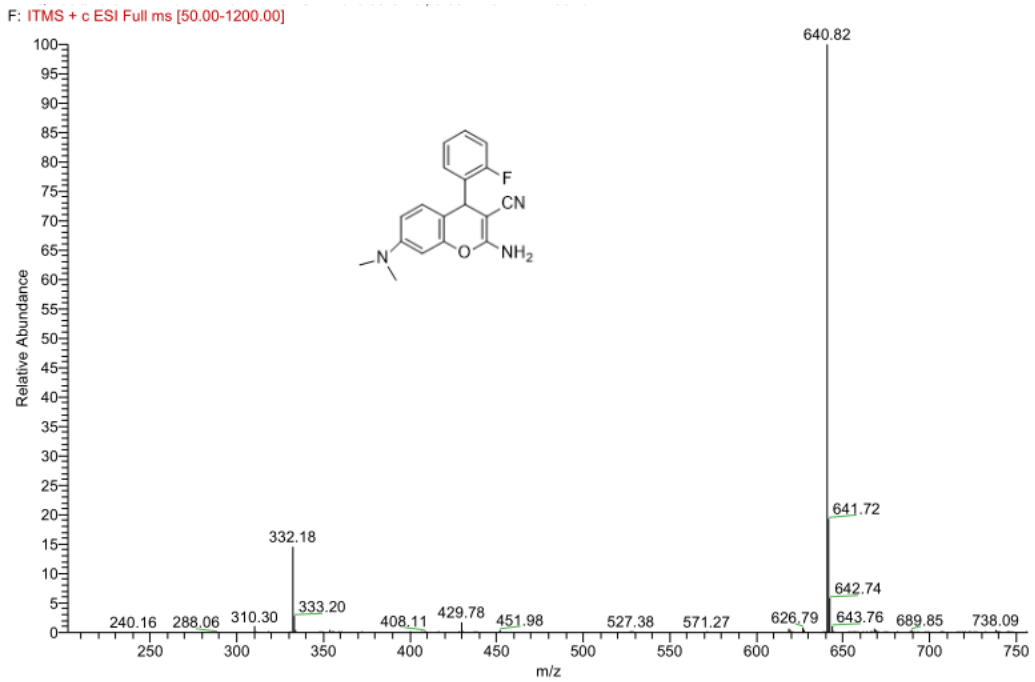


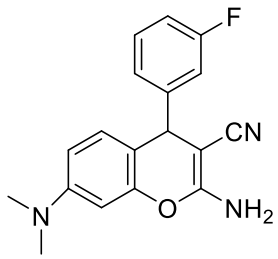
2-Amino-7-(dimethylamino)-4-(2-fluorophenyl)-4*H*-chromene-3-carbonitrile (**5d**, $C_{18}H_{16}FN_3O$)

Purple solid; mp 207-209 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.32 – 7.23 (m, 1H), 7.15 (dt, *J* = 12.5, 6.7 Hz, 3H), 6.88 (s, 2H), 6.78 (d, *J* = 8.6 Hz, 1H), 6.46 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.24 (d, *J* = 2.5 Hz, 1H), 4.88 (s, 1H), 2.86 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.47, 160.17, 158.04, 149.72, 148.59, 132.32, 129.17, 128.38, 128.11, 124.07, 120.00, 115.13, 108.77, 108.58, 97.90, 54.06, 33.53. MS (ESI): $[2M+Na]^+$: 641.72.



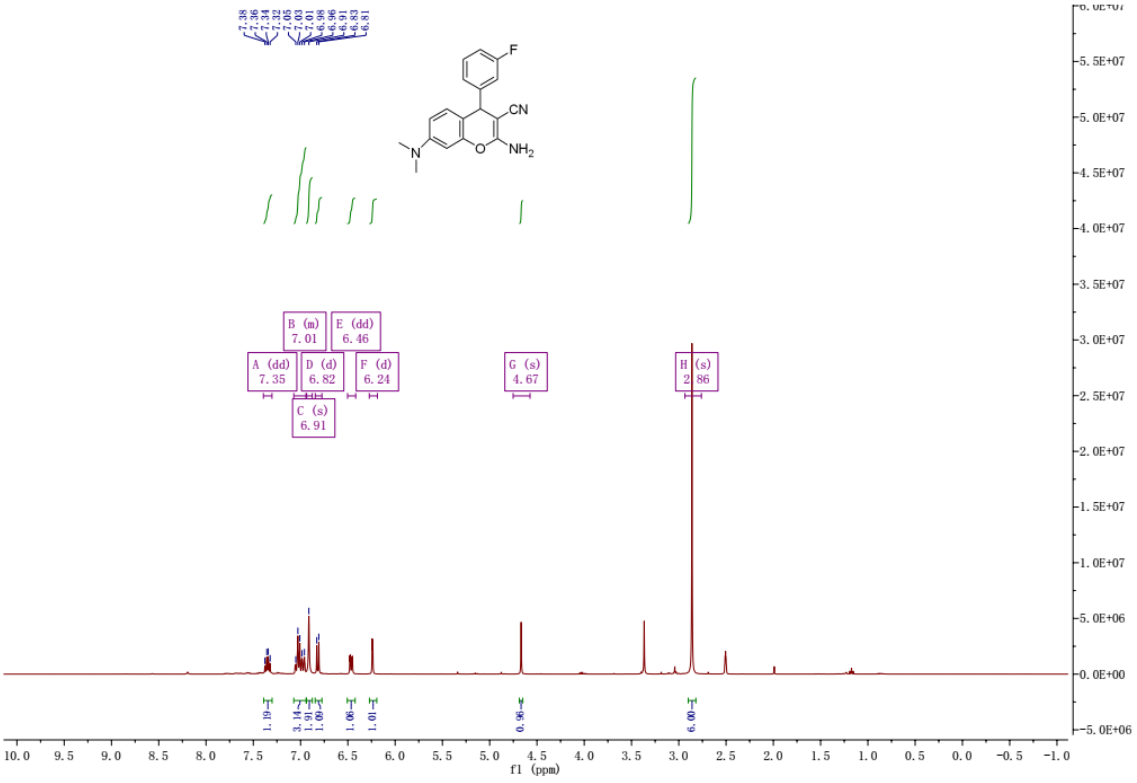

160.47
160.17
158.04
149.72
148.59
132.32
129.17
128.38
128.11
124.07
120.60
115.13
108.77
108.58
97.90
54.06
33.53
F
CN
NH2
N
O
f1 (ppm)

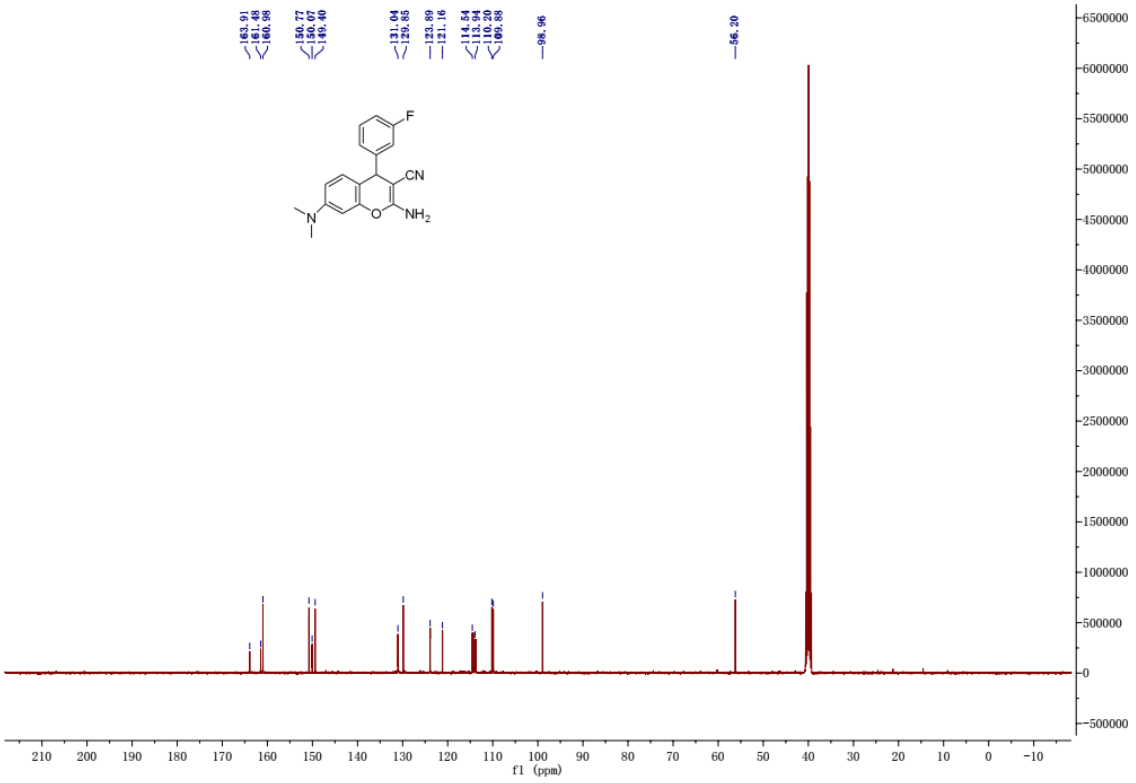

F: ITMS + c ESI Full ms [50.00-1200.00]
Relative Abundance
m/z
640.82
641.72
642.74
643.76
332.18
333.20
240.16
288.06
310.30
408.11
429.78
451.98
527.38
571.27
626.79
689.85
738.09
F
CN
NH2
N
O

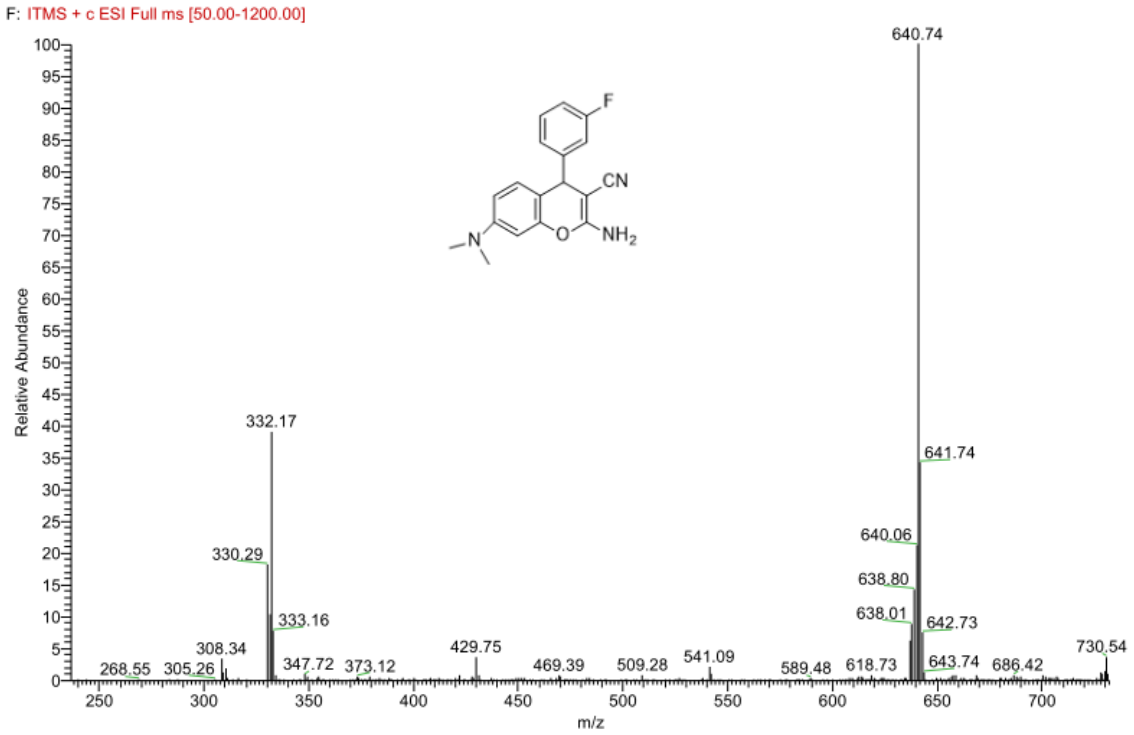


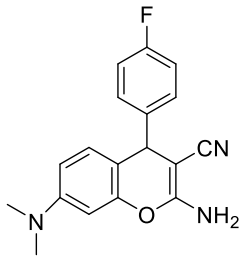
2-Amino-7-(dimethylamino)-4-(3-fluorophenyl)-4*H*-chromene-3-carbonitrile (**5e**, $C_{18}H_{16}FN_3O$)

Orange solid; mp 144-146 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.35 (dd, J = 14.1, 7.9 Hz, 1H), 7.07 – 6.94 (m, 3H), 6.91 (s, 2H), 6.82 (d, J = 8.7 Hz, 1H), 6.46 (dd, J = 8.7, 2.5 Hz, 1H), 6.24 (d, J = 2.5 Hz, 1H), 4.67 (s, 1H), 2.86 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.91, 161.48, 160.98, 150.77, 150.07, 149.40, 131.04, 129.85, 123.89, 121.16, 114.54, 113.94, 110.20, 109.88, 98.96, 56.20. MS (ESI): $[2M+Na]^+$: 641.74.



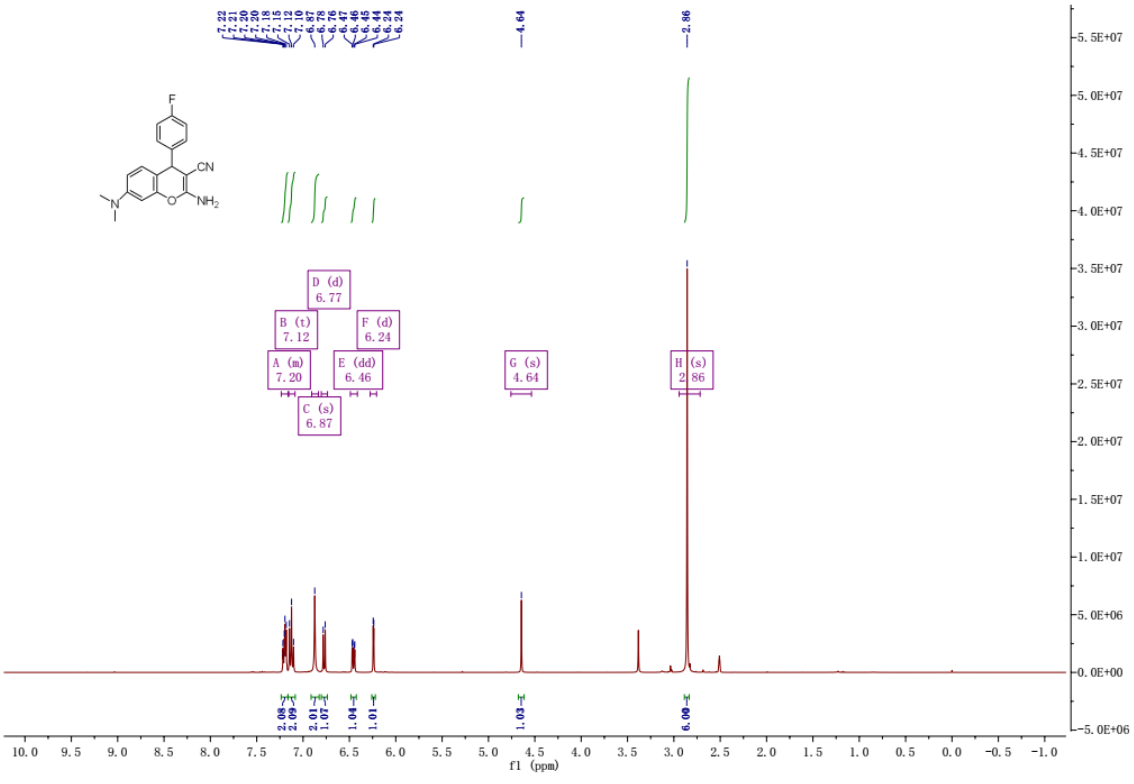

163.91
161.48
160.98
150.77
150.07
149.40
131.04
129.85
123.89
121.16
114.54
113.94
110.20
109.88
98.96
56.20
F
CN
NH2
N
O
f1 (ppm)

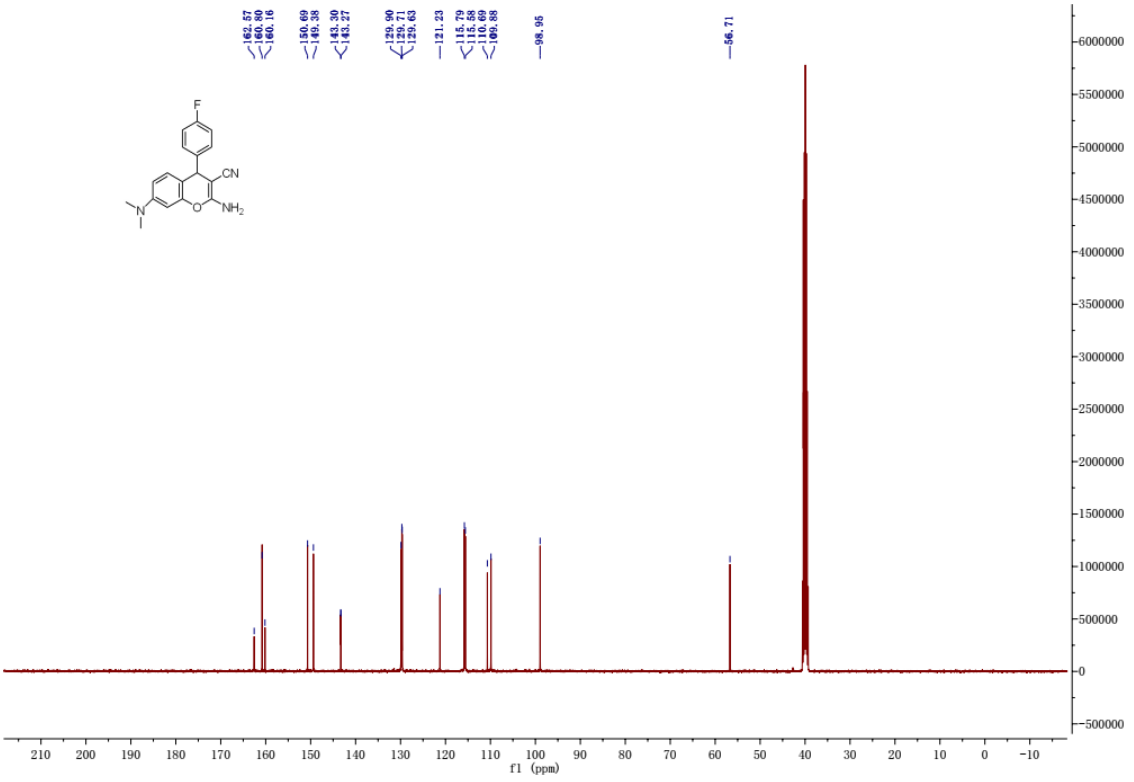

F: ITMS + c ESI Full ms [50.00-1200.00]
Relative Abundance
m/z
640.74
641.74
640.06
638.80
638.01
642.73
643.74
730.54
686.42
618.73
589.48
541.09
509.28
469.39
429.75
373.12
347.72
333.16
332.17
330.29
308.34
305.26
268.55
F
CN
NH2
N
O

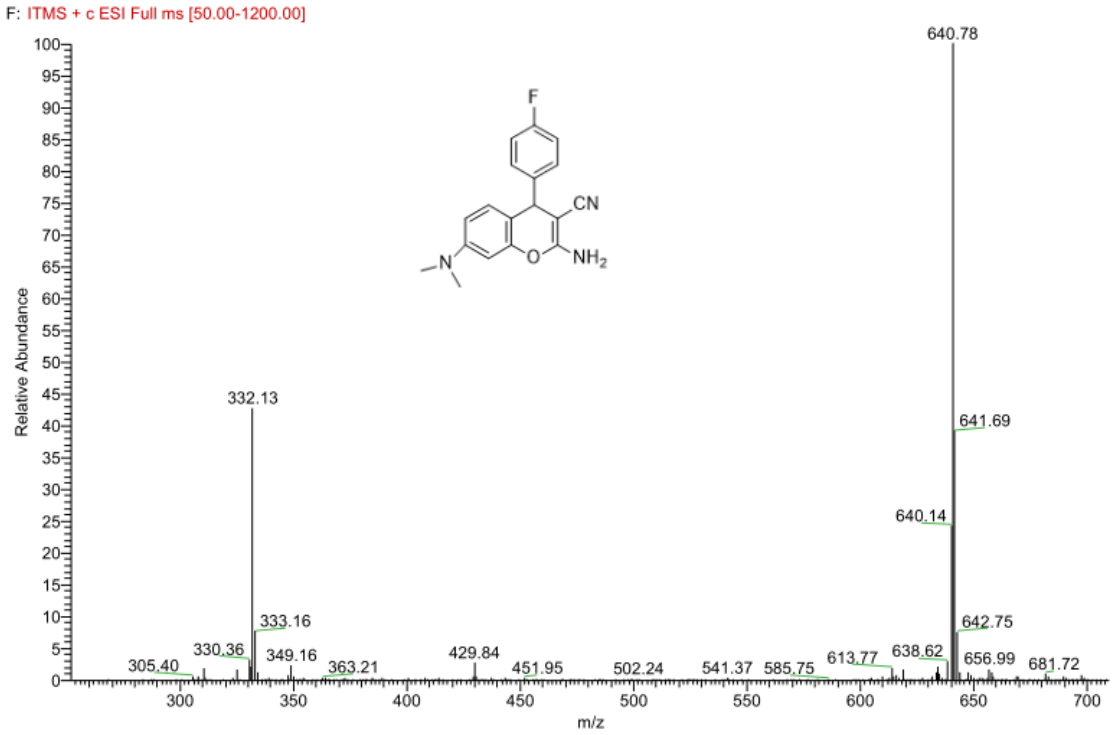


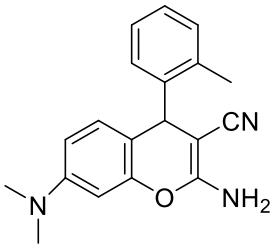
2-Amino-7-(dimethylamino)-4-(4-fluorophenyl)-4*H*-chromene-3-carbonitrile (**5f**, $C_{18}H_{16}FN_3O$)

Yellow solid; mp 141-142 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.24 – 7.16 (m, 2H), 7.12 (t, J = 8.8 Hz, 2H), 6.87 (s, 2H), 6.77 (d, J = 8.7 Hz, 1H), 6.46 (dd, J = 8.7, 2.5 Hz, 1H), 6.24 (d, J = 2.4 Hz, 1H), 4.64 (s, 1H), 2.86 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.57, 160.80, 160.16, 150.69, 149.38, 143.30, 143.27, 129.90, 129.71, 129.63, 121.23, 115.79, 115.58, 110.69, 109.88, 98.95, 56.71. MS (ESI): $[2M+Na]^+$: 641.69.



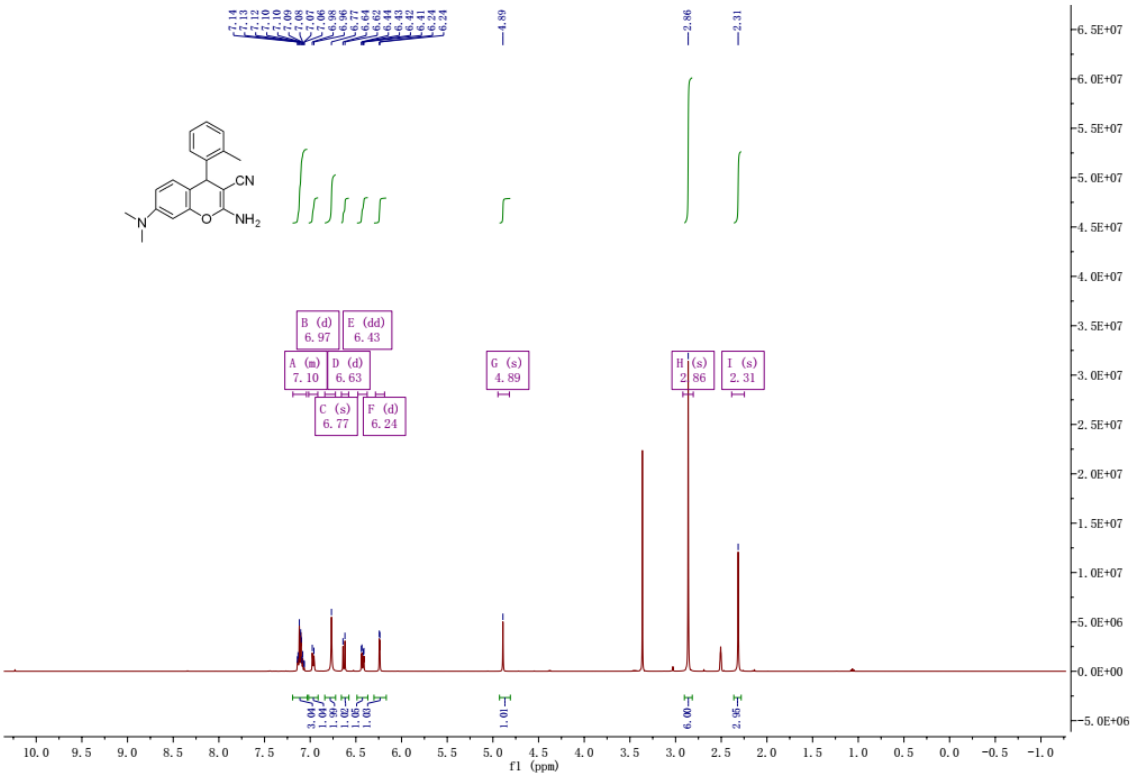

162.57
160.80
160.16
150.69
149.38
143.30
143.27
129.90
129.71
129.63
121.23
115.79
115.58
110.69
109.88
98.95
56.71
F
CN
NH2
N
O
f1 (ppm)

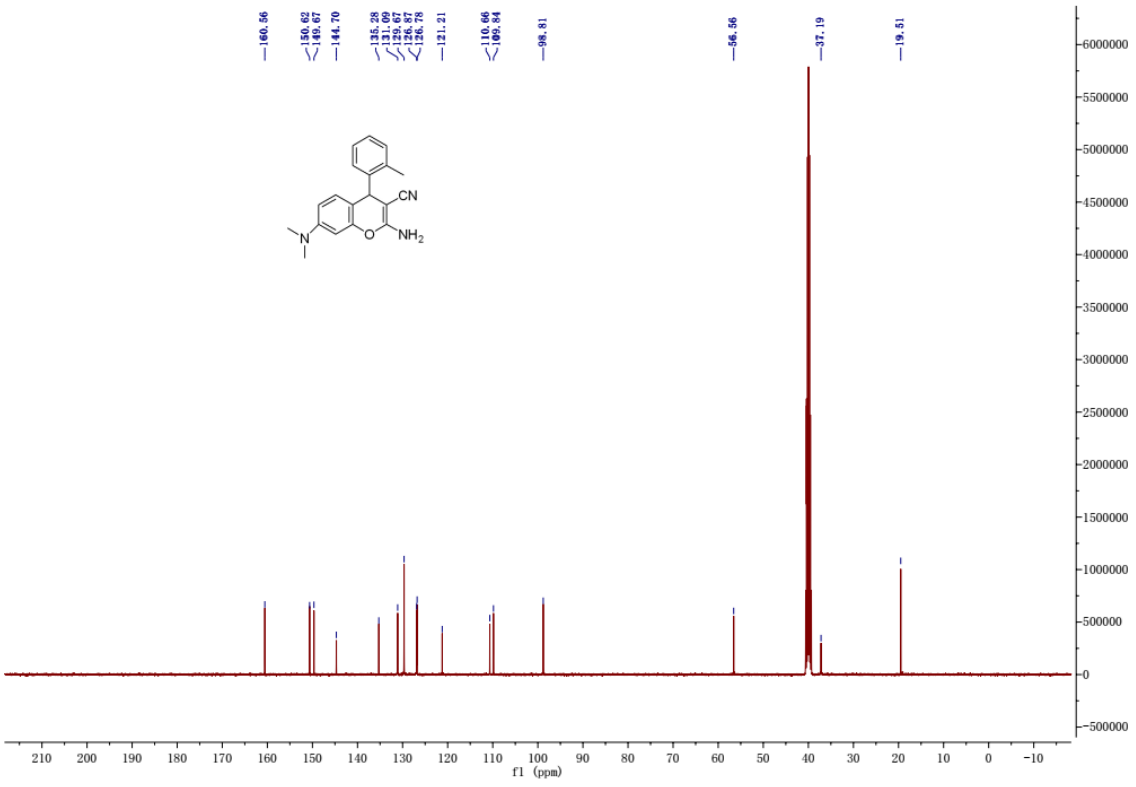

F: ITMS + c ESI Full ms [50.00-1200.00]
Relative Abundance
m/z
640.78
641.69
640.14
642.75
332.13
333.16
330.36
349.16
363.21
305.40
429.84
451.95
502.24
541.37
585.75
613.77
638.62
656.99
681.72
F
CN
NH2
N
O

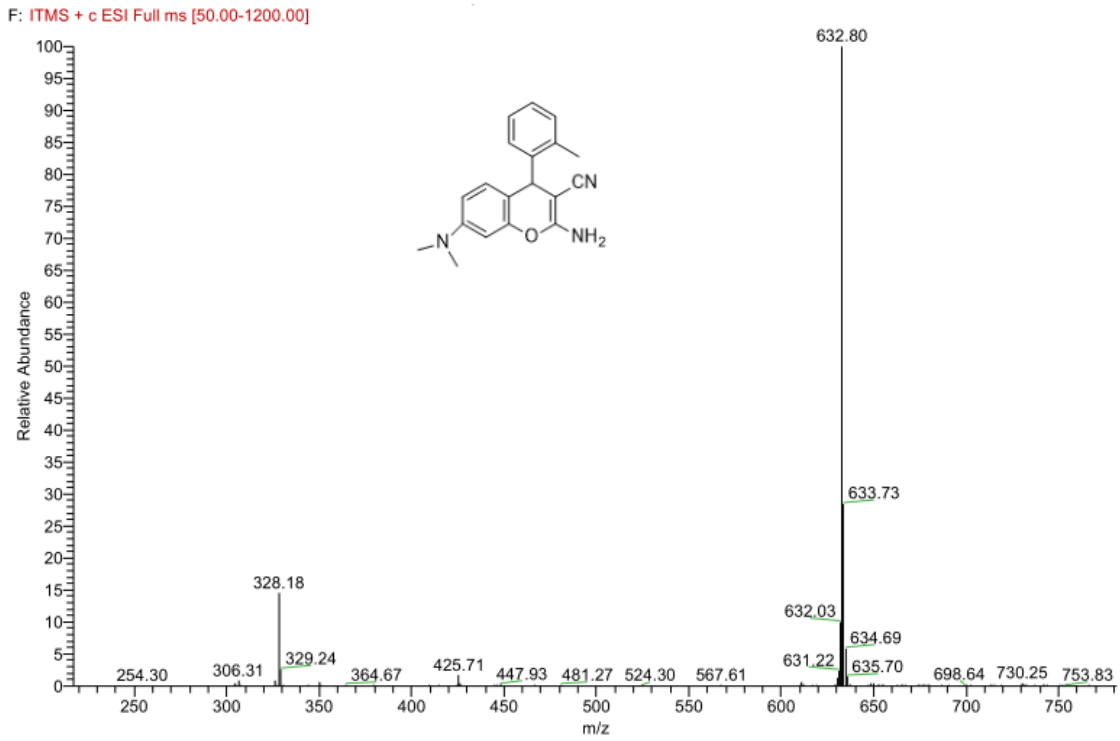


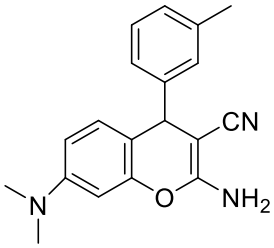
2-Amino-7-(dimethylamino)-4-(*o*-tolyl)-4*H*-chromene-3-carbonitrile (**5g**, $C_{19}H_{19}N_3O$)

Yellow solid; mp 177-179 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.19 – 7.04 (m, 3H), 6.97 (d, J = 7.2 Hz, 1H), 6.77 (s, 2H), 6.63 (d, J = 8.7 Hz, 1H), 6.43 (dd, J = 8.6, 2.5 Hz, 1H), 6.24 (d, J = 2.4 Hz, 1H), 4.89 (s, 1H), 2.86 (s, 6H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.56, 150.62, 149.67, 144.70, 135.28, 131.09, 129.67, 126.87, 126.78, 121.21, 110.66, 109.84, 98.81, 56.56, 37.19, 19.51. MS (ESI): $[2M+Na]^+$: 633.73.

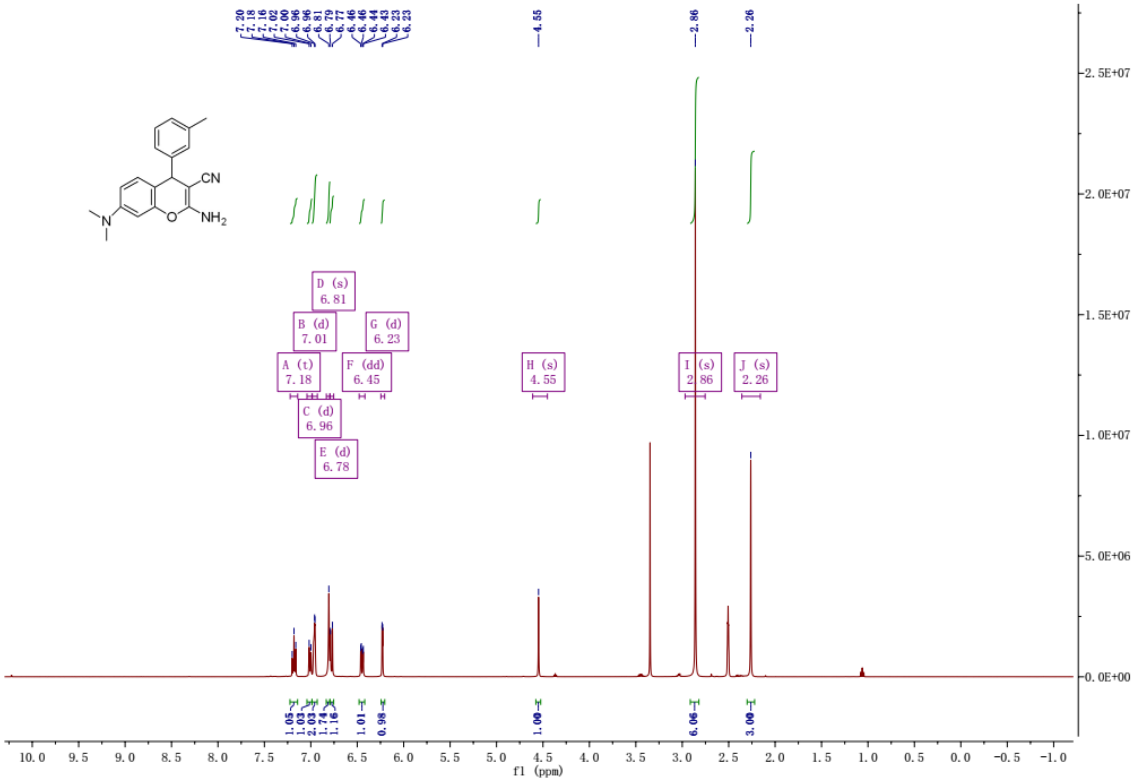


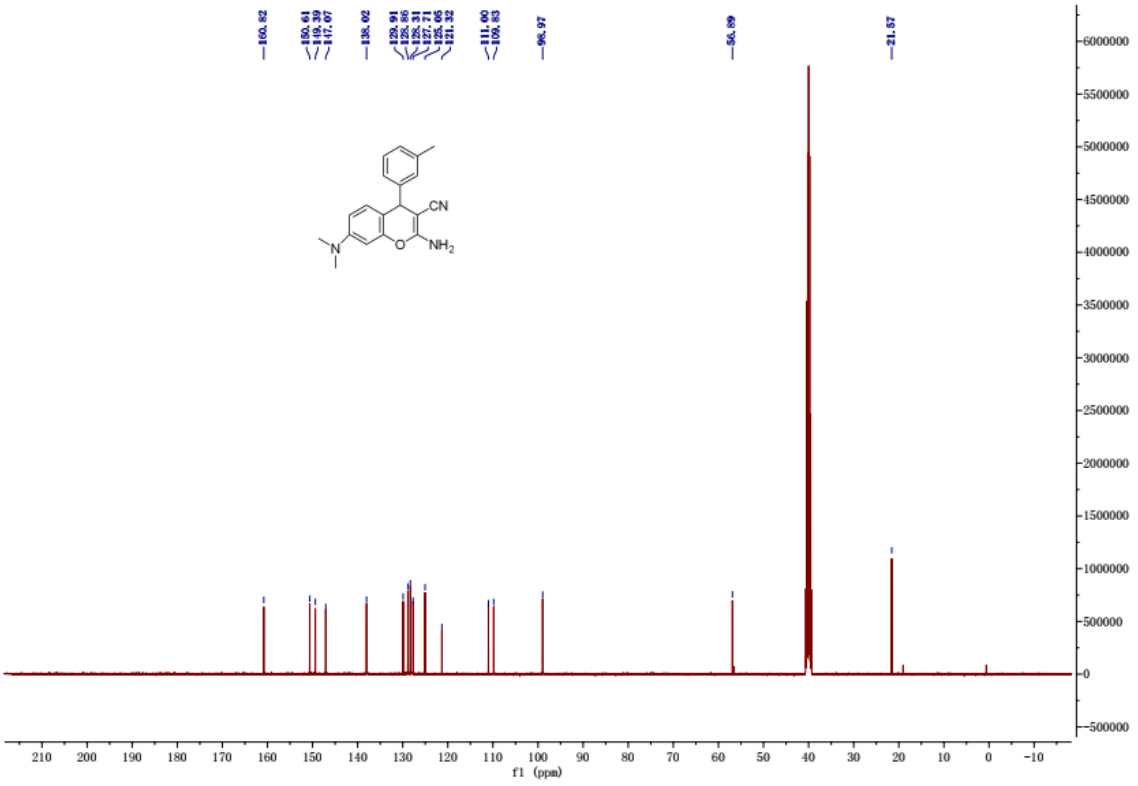

160.56
150.62
149.67
144.70
135.28
131.09
129.67
126.97
126.78
121.21
110.66
109.84
98.81
56.56
37.19
19.51
CN
NH2
N
O
f1 (ppm)

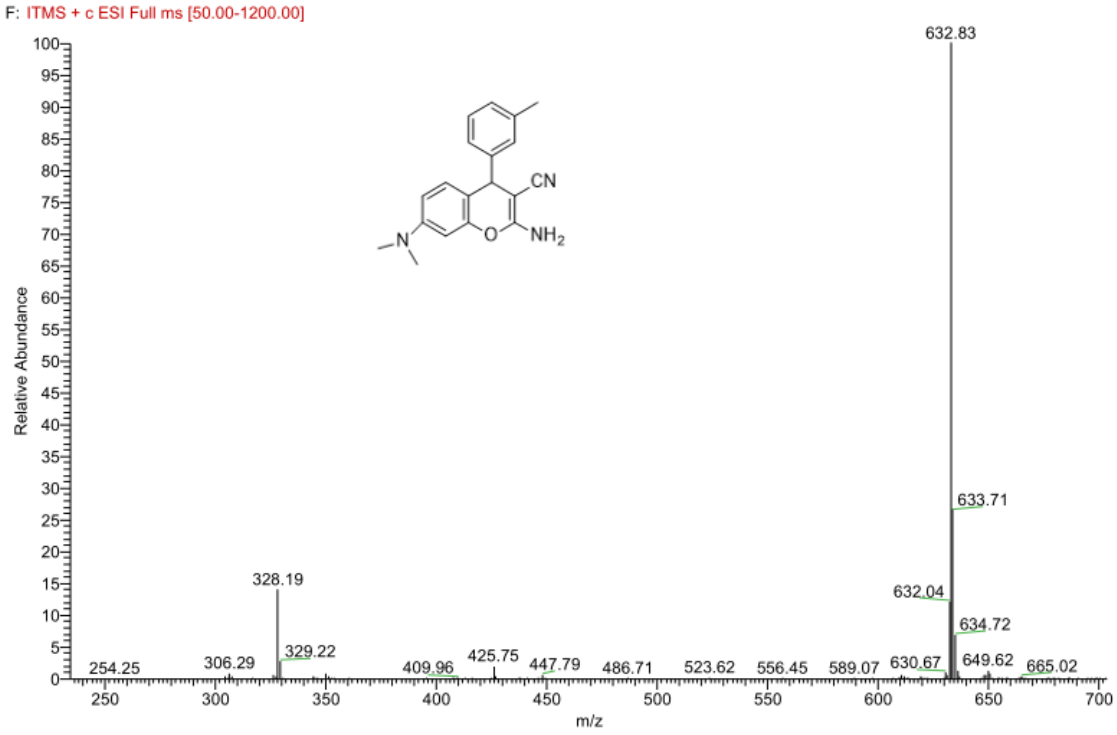

F: ITMS + c ESI Full ms [50.00-1200.00]
632.80
633.73
328.18
632.03
634.69
631.22
635.70
329.24
254.30
306.31
364.67
425.71
447.93
481.27
524.30
567.61
698.64
730.25
753.83
CN
NH2
N
O
Relative Abundance
m/z

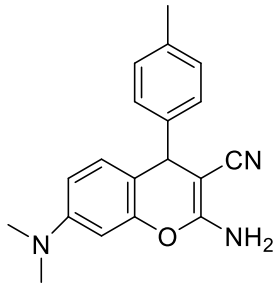


2-Amino-7-(dimethylamino)-4-(*m*-tolyl)-4*H*-chromene-3-carbonitrile (**5h**, $C_{19}H_{19}N_3O$) Yellow solid; mp 174-176 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.18 (t, J = 7.8 Hz, 1H), 7.01 (d, J = 7.6 Hz, 1H), 6.96 (d, J = 1.6 Hz, 2H), 6.81 (s, 2H), 6.78 (d, J = 8.7 Hz, 1H), 6.45 (dd, J = 8.7, 2.6 Hz, 1H), 6.23 (d, J = 2.5 Hz, 1H), 4.55 (s, 1H), 2.86 (s, 6H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.82, 150.61, 149.39, 147.07, 138.02, 129.91, 128.86, 128.31, 127.71, 125.05, 121.32, 111.00, 109.83, 98.97, 56.89, 21.57. MS (ESI): $[2M+Na]^+$: 633.71.



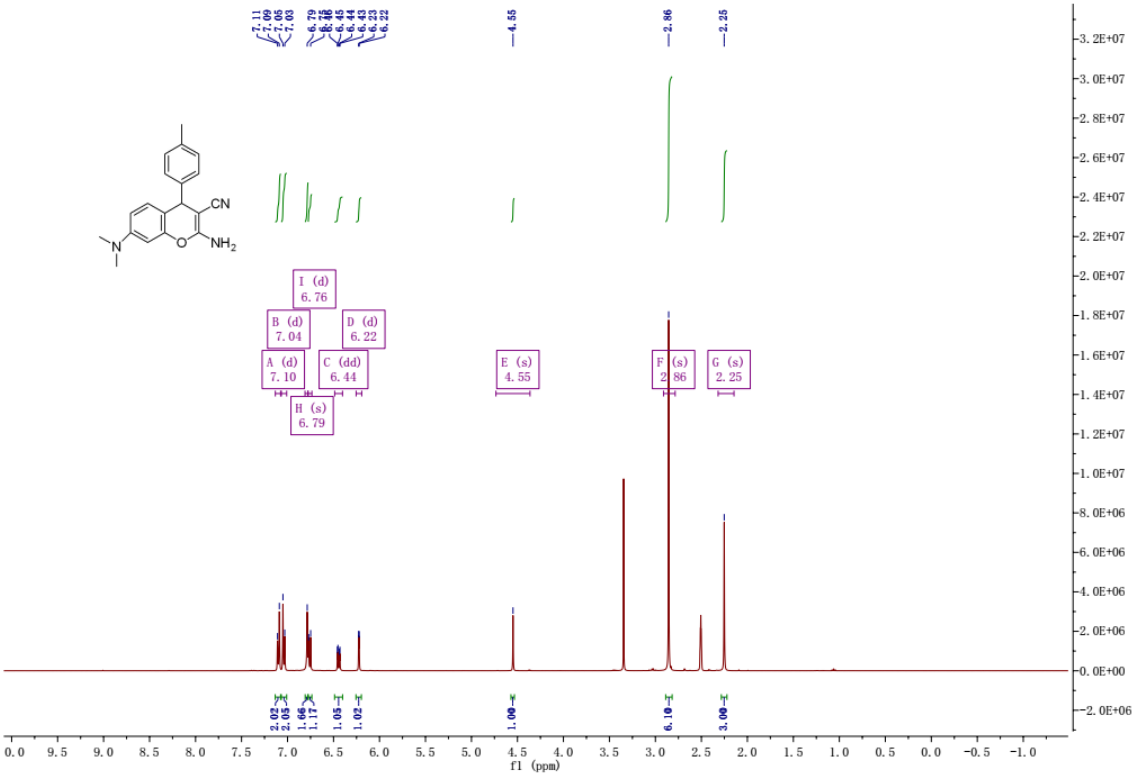

160.82
150.61
149.39
147.07
138.02
129.91
128.55
128.31
127.71
125.05
121.32
111.00
109.83
96.97
56.89
21.57
CN
NH2
N
O
f1 (ppm)

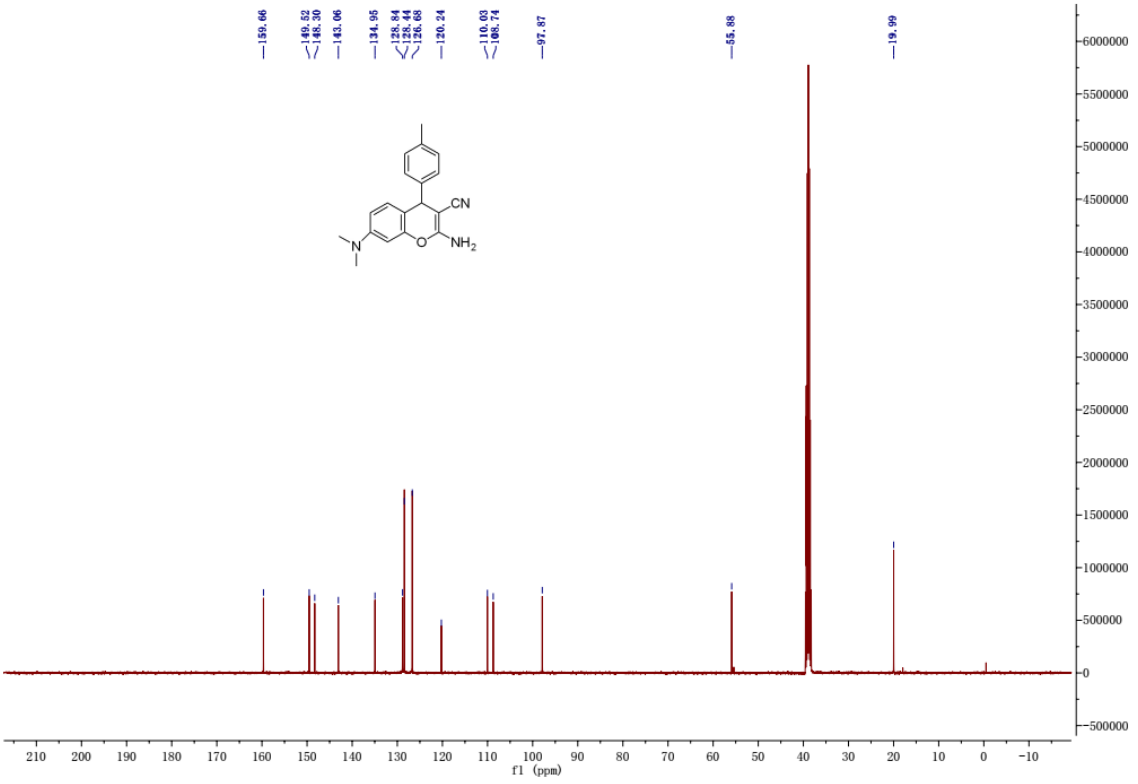

F: ITMS + c ESI Full ms [50.00-1200.00]
632.83
633.71
632.04
634.72
328.19
329.22
649.62
665.02
254.25
306.29
409.96
425.75
447.79
486.71
523.62
556.45
589.07
630.67
CN
NH2
N
O
Relative Abundance
m/z

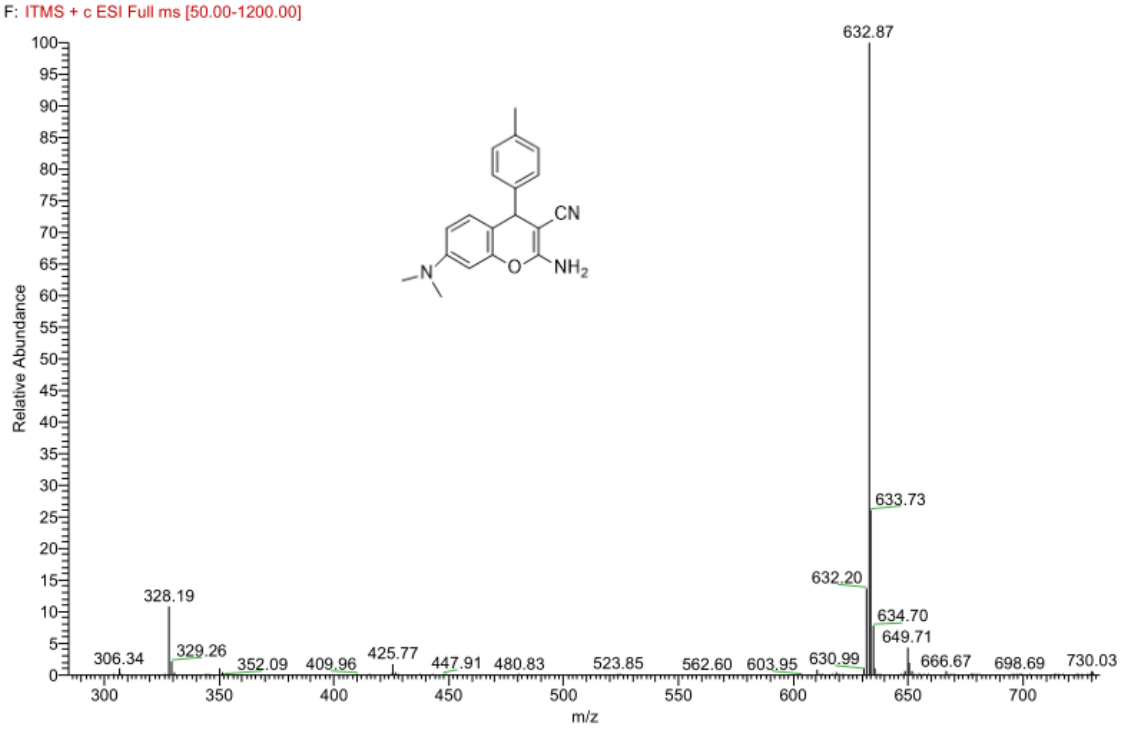


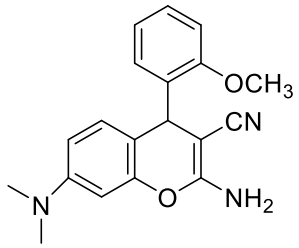
2-Amino-7-(dimethylamino)-4-(*p*-tolyl)-4*H*-chromene-3-carbonitrile (**5i**, $C_{19}H_{19}N_3O$)

Faint yellow solid; mp 164-166 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.10 (d, J = 7.9 Hz, 2H), 7.04 (d, J = 7.9 Hz, 2H), 6.79 (s, 2H), 6.76 (d, J = 8.7 Hz, 1H), 6.44 (dd, J = 8.7, 2.6 Hz, 1H), 6.22 (d, J = 2.5 Hz, 1H), 4.55 (s, 1H), 2.86 (s, 6H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.66, 149.52, 148.30, 143.06, 134.95, 128.84, 128.44, 126.68, 120.24, 110.03, 108.74, 97.87, 55.88, 19.99. MS (ESI): $[2M+Na]^+$: 633.73.



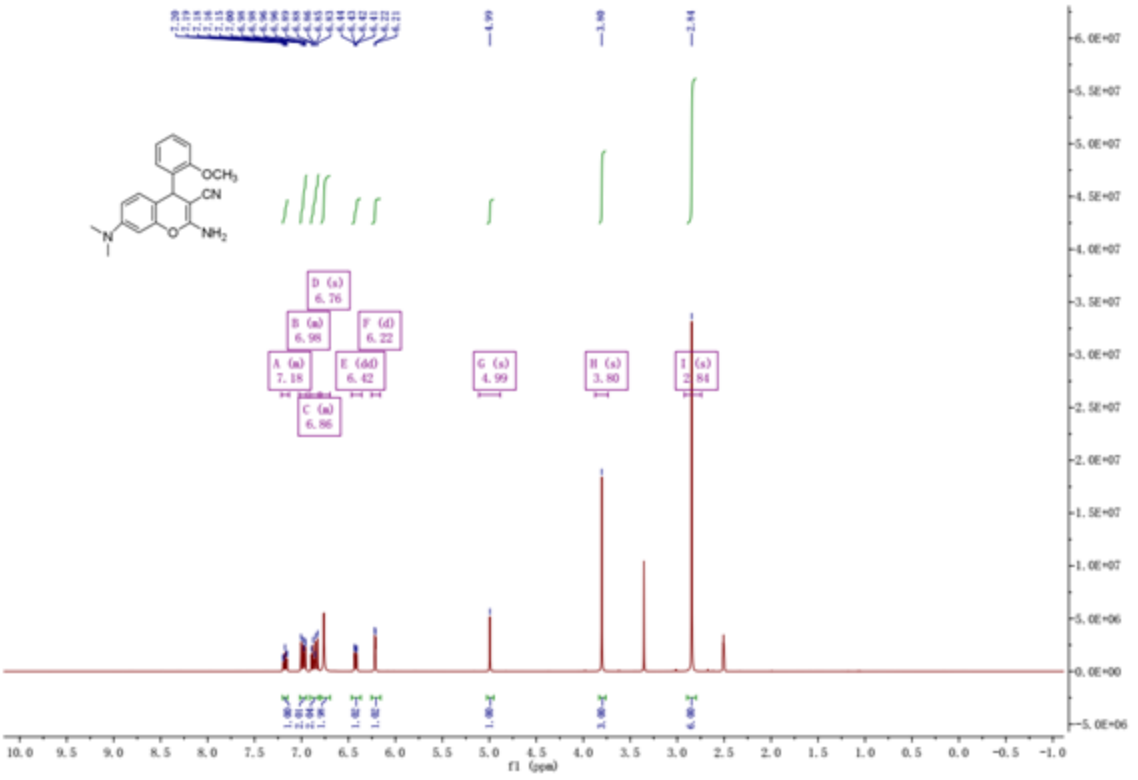

159.66
149.52
148.30
143.06
134.95
128.84
128.44
126.68
120.24
110.03
108.74
97.87
55.88
19.99
CN
NH2
N
O
f1 (ppm)

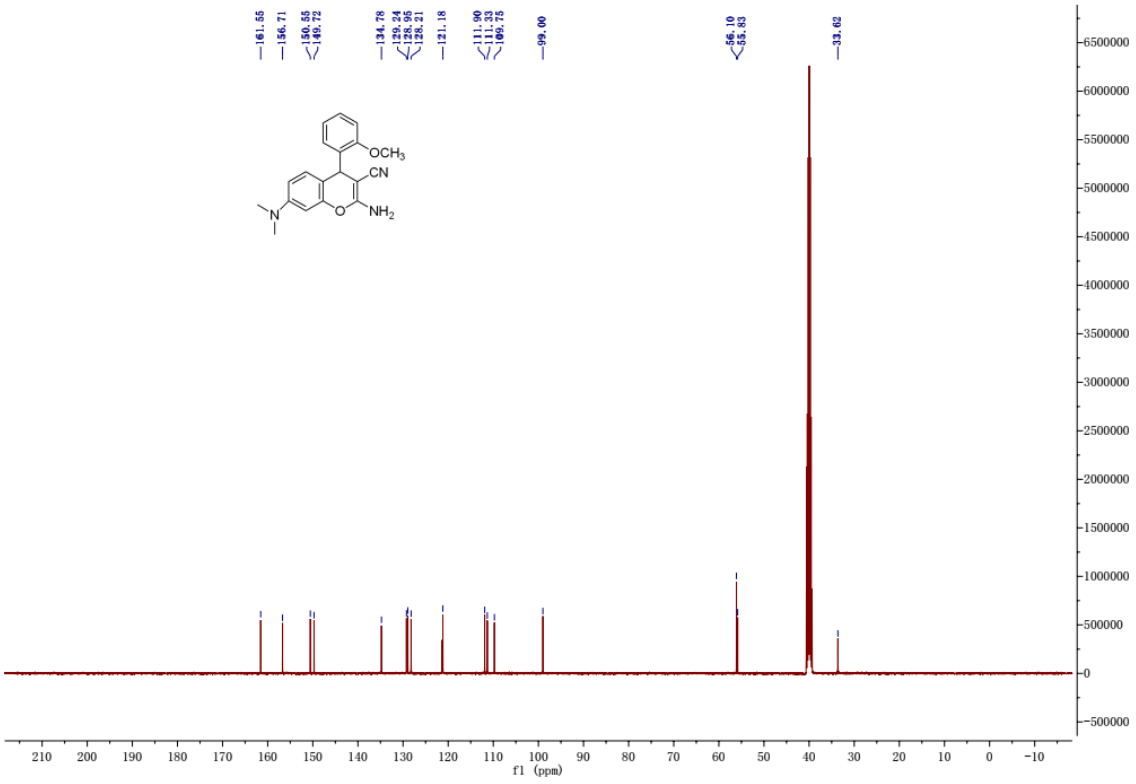

F: ITMS + c ESI Full ms [50.00-1200.00]
Relative Abundance
m/z
632.87
633.73
632.20
634.70
649.71
328.19
329.26
306.34
352.09
409.96
425.77
447.91
480.83
523.85
562.60
603.95
630.99
666.67
698.69
730.03
CN
NH2
N
O

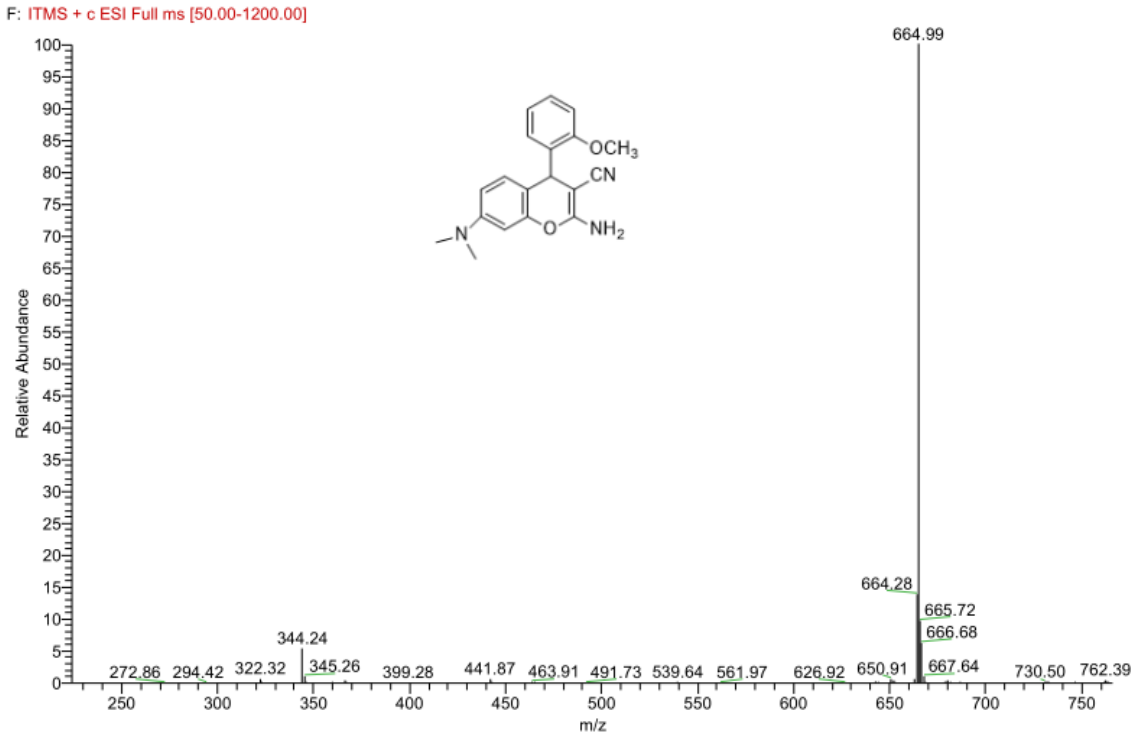


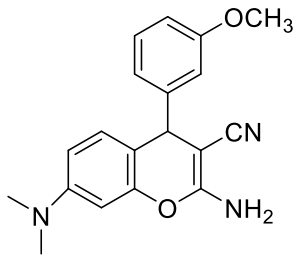
2-Amino-7-(dimethylamino)-4-(2-methoxyphenyl)-4*H*-chromene-3-carbonitrile (**5j**, $C_{19}H_{19}N_3O_2$)

Yellow solid; mp 196-198 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.22 – 7.13 (m, 1H), 7.03 – 6.94 (m, 2H), 6.91 – 6.82 (m, 2H), 6.76 (s, 2H), 6.42 (dd, J = 8.7, 2.5 Hz, 1H), 6.22 (d, J = 2.5 Hz, 1H), 4.99 (s, 1H), 3.80 (s, 3H), 2.84 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.55, 156.71, 150.55, 149.72, 134.78, 129.24, 128.95, 128.21, 121.18, 111.90, 111.33, 109.75, 99.00, 56.10, 55.83, 33.62. MS (ESI): $[2M+Na]^+$: 665.72.



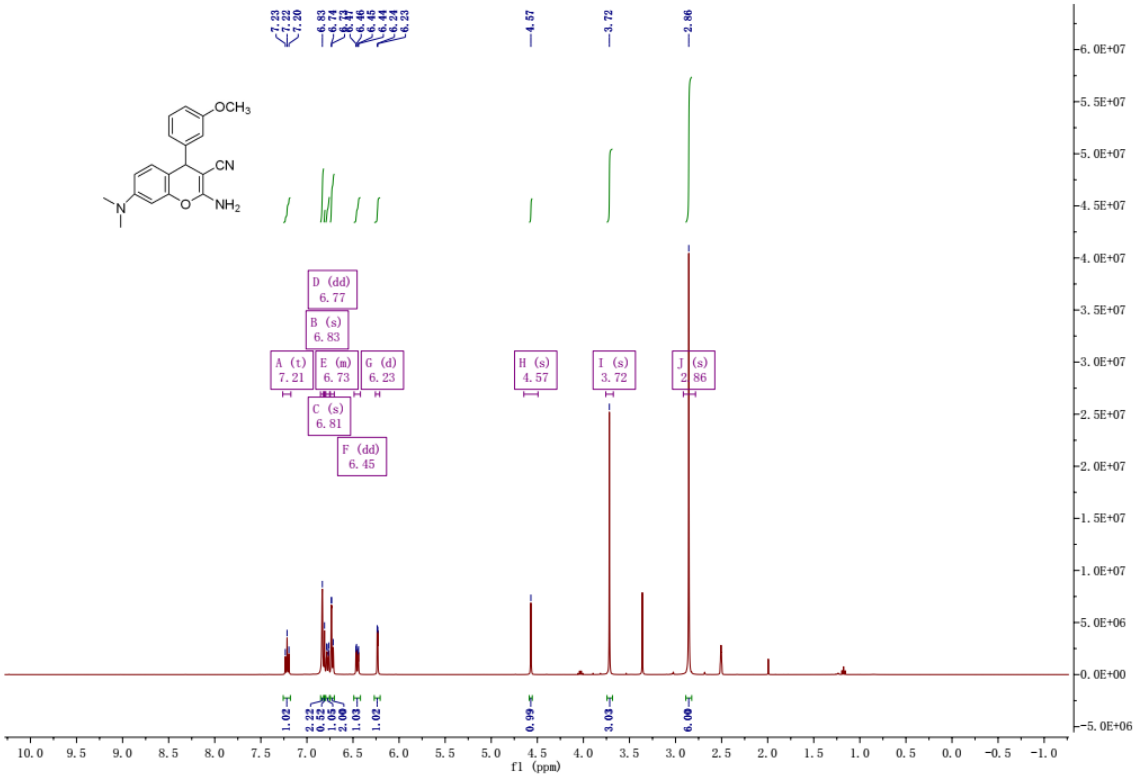

161.55
156.71
150.55
149.72
134.78
129.24
128.96
128.21
121.18
111.90
111.33
109.75
99.00
56.10
56.03
33.62
OCH3
CN
NH2
N
O
f1 (ppm)

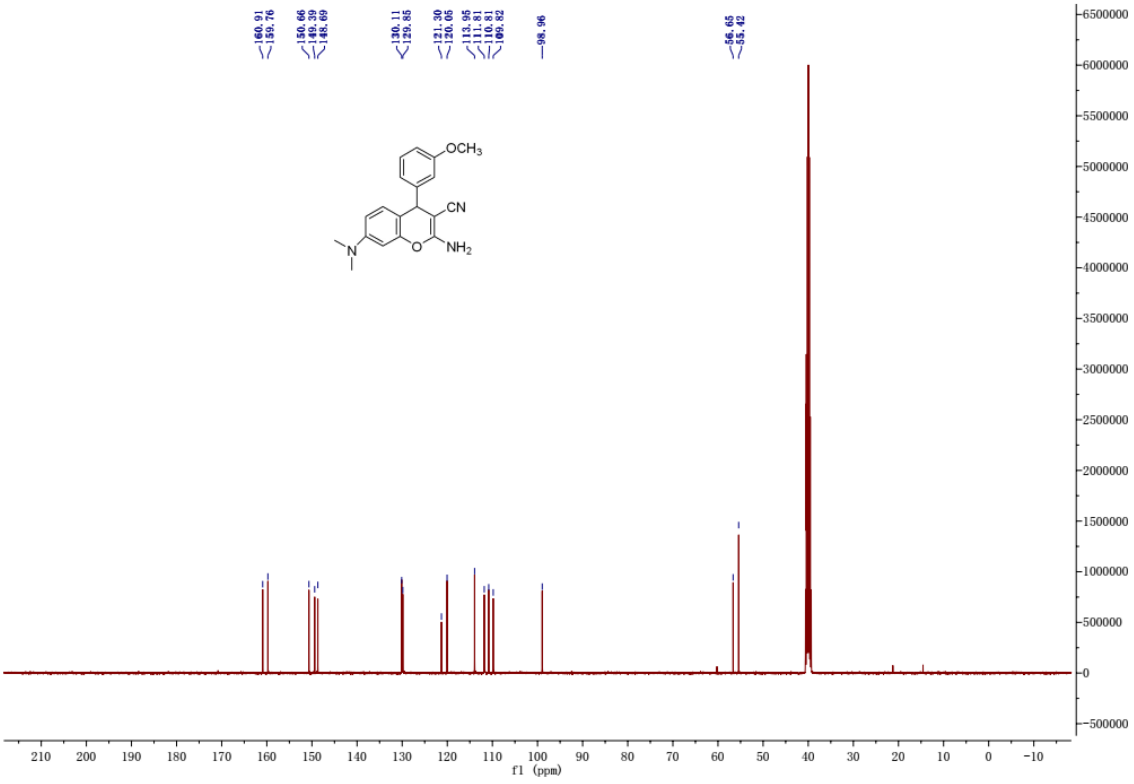

F: ITMS + c ESI Full ms [50.00-1200.00]
Relative Abundance
m/z
664.99
664.28
665.72
666.68
667.64
344.24
345.26
272.86
294.42
322.32
399.28
441.87
463.91
491.73
539.64
561.97
626.92
650.91
730.50
762.39
OCH3
CN
NH2
N
O

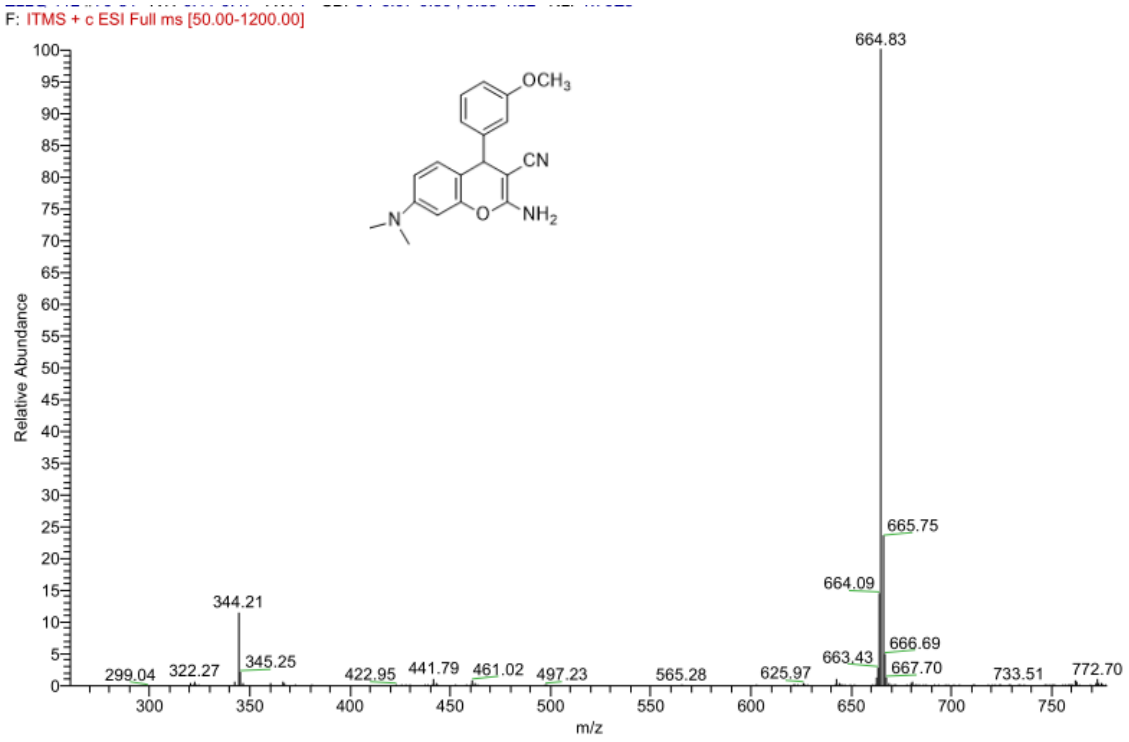


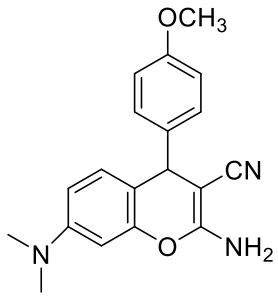
2-Amino-7-(dimethylamino)-4-(3-methoxyphenyl)-4*H*-chromene-3-carbonitrile (**5k**, $C_{19}H_{19}N_3O_2$)

Yellow solid; mp 164-166 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.21 (t, J = 7.9 Hz, 1H), 6.83 (s, 2H), 6.81 (s, 1H), 6.77 (dd, J = 7.4, 2.0 Hz, 1H), 6.75 – 6.70 (m, 2H), 6.45 (dd, J = 8.7, 2.6 Hz, 1H), 6.23 (d, J = 2.5 Hz, 1H), 4.57 (s, 1H), 3.72 (s, 3H), 2.86 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.91, 159.76, 150.66, 149.39, 148.69, 130.11, 129.85, 121.30, 120.05, 113.95, 111.81, 110.81, 109.82, 98.96, 56.65, 55.42. MS (ESI): $[2M+Na]^+$: 665.75.



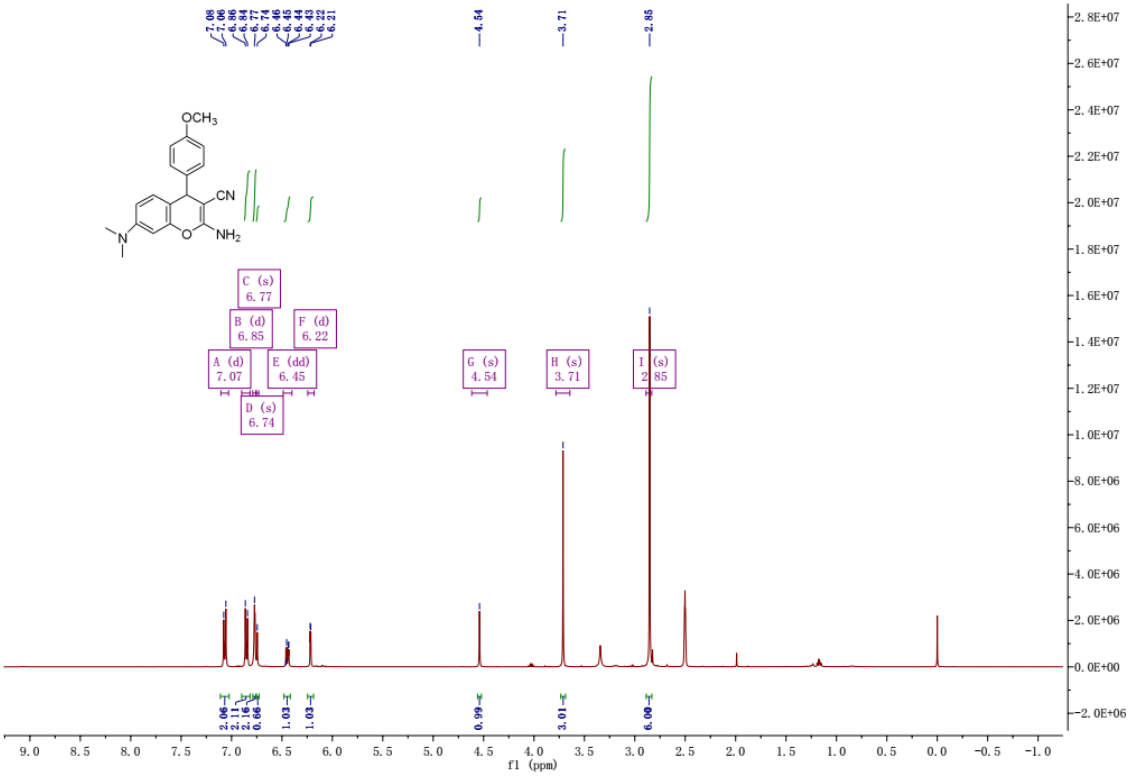

160.91
159.76
150.66
149.39
145.69
130.11
129.85
121.30
120.06
113.96
111.81
110.81
109.82
98.96
56.65
55.42
OCH3
CN
NH2
N
O
f1 (ppm)

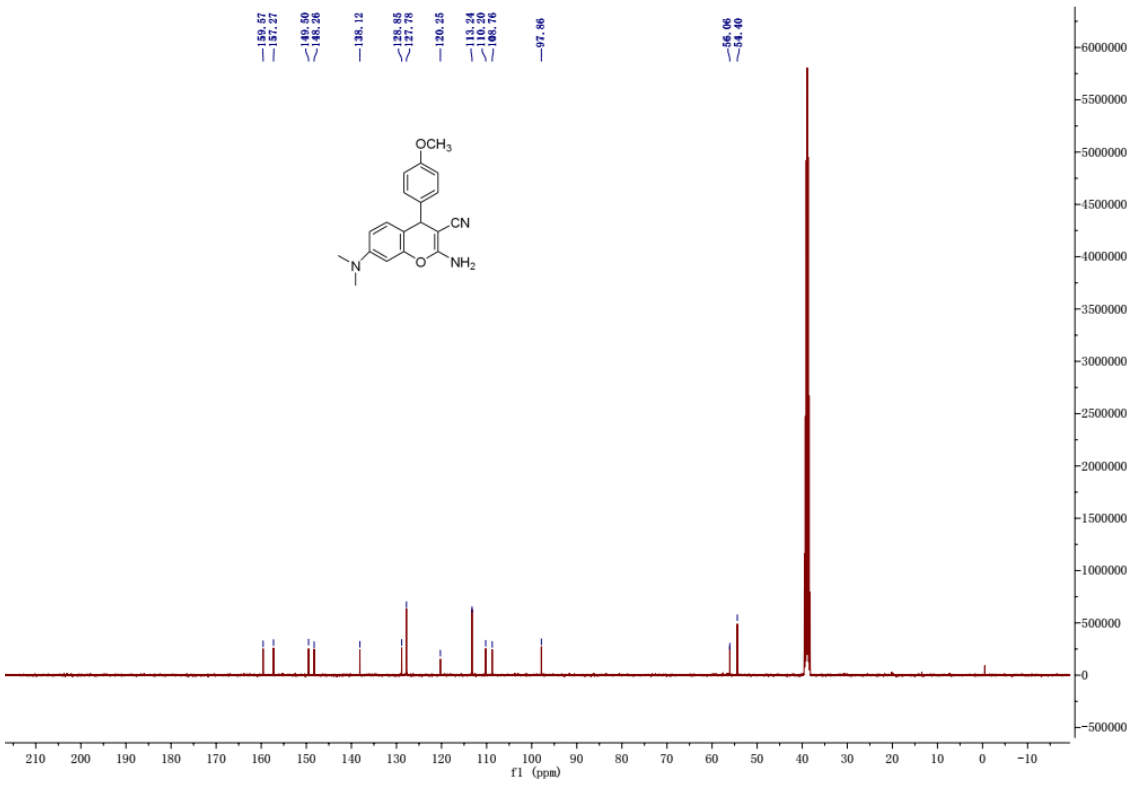

F: ITMS + c ESI Full ms [50.00-1200.00]
Relative Abundance
m/z
664.83
665.75
664.09
666.69
663.43
667.70
344.21
345.25
299.04
322.27
422.95
441.79
461.02
497.23
565.28
625.97
733.51
772.70
OCH3
CN
NH2
N
O

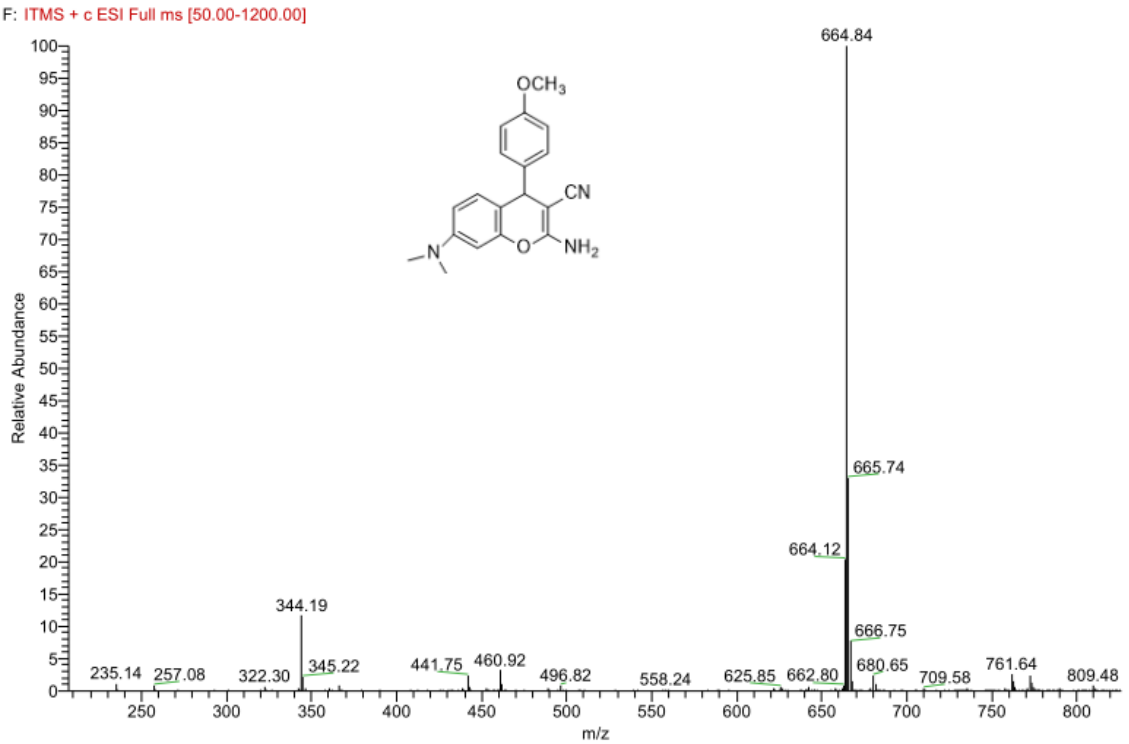


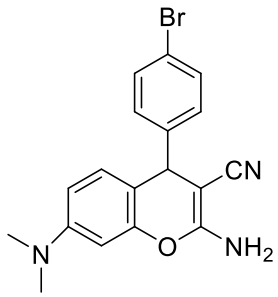
2-Amino-7-(dimethylamino)-4-(4-methoxyphenyl)-4*H*-chromene-3-carbonitrile (**5l**, $C_{19}H_{19}N_3O_2$)

Yellow solid; mp 180-182 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.07 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 6.77 (S, 2H), 6.74 (s, 1H), 6.45 (dd, J = 8.6, 2.4 Hz, 1H), 6.22 (d, J = 2.4 Hz, 1H), 4.54 (s, 1H), 3.71 (s, 3H), 2.85 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.57, 157.27, 149.50, 148.26, 138.12, 128.85, 127.78, 120.25, 113.24, 110.20, 108.76, 97.86, 56.06, 54.40. MS (ESI): $[2M+Na]^+$: 665.74.



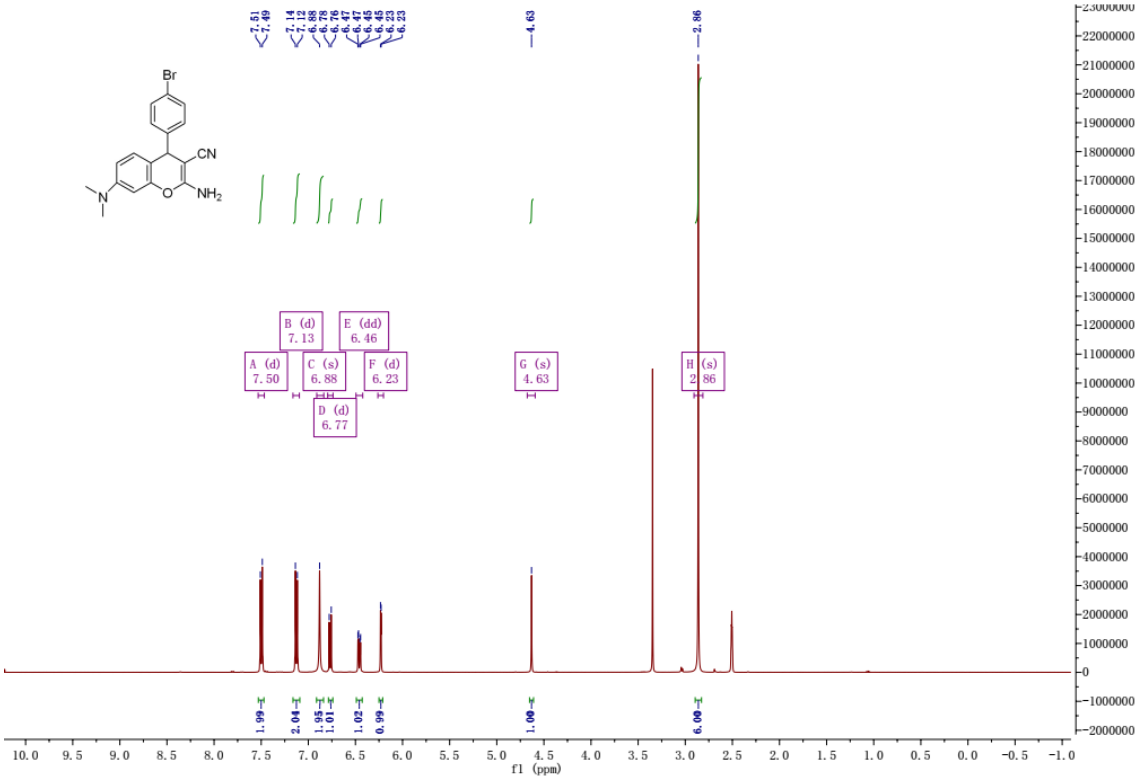

159.57
157.27
149.50
148.26
138.12
128.85
127.78
120.25
113.24
110.20
108.76
97.86
56.06
54.40
OCH3
CN
NH2
N
O
f1 (ppm)

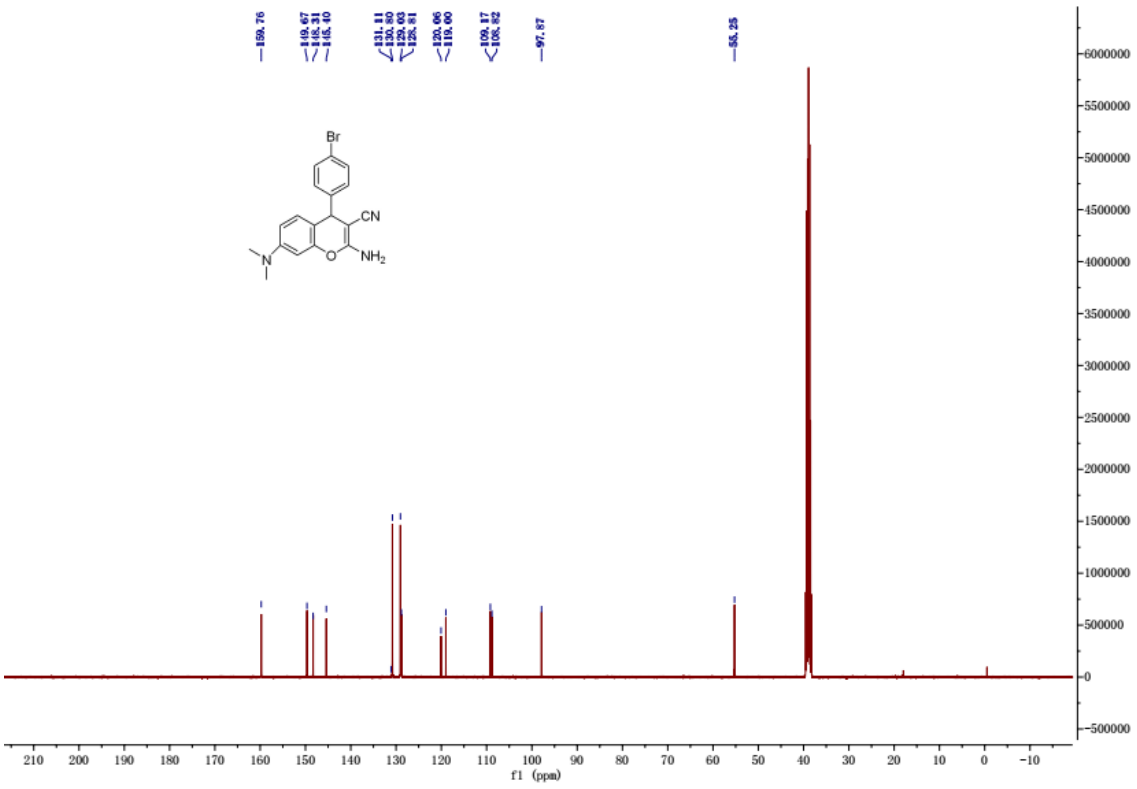

F: ITMS + c ESI Full ms [50.00-1200.00]
Relative Abundance
m/z
664.84
665.74
664.12
666.75
344.19
235.14
257.08
322.30
345.22
441.75
460.92
496.82
558.24
625.85
662.80
680.65
709.58
761.64
809.48
OCH3
CN
NH2
N
O

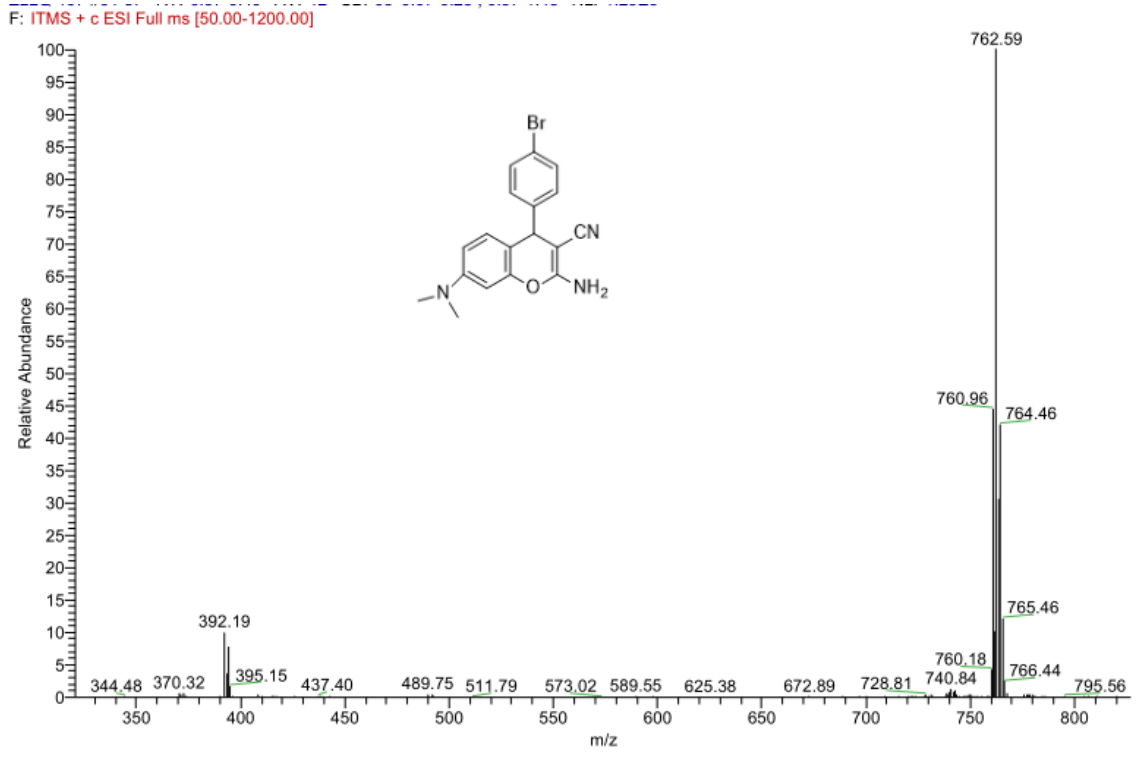


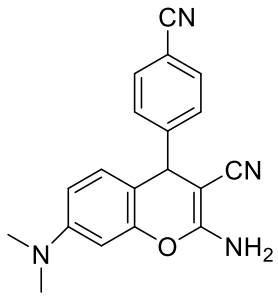
2-Amino-4-(4-bromophenyl)-7-(dimethylamino)-4*H*-chromene-3-carbonitrile (**5m**, $C_{18}H_{16}BrN_3O$)

Yellow solid; mp 211-213 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (d, J = 8.3 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 6.88 (s, 2H), 6.77 (d, J = 8.7 Hz, 1H), 6.46 (dd, J = 8.7, 2.5 Hz, 1H), 6.23 (d, J = 2.5 Hz, 1H), 4.63 (s, 1H), 2.86 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.76, 149.67, 148.31, 145.40, 131.11, 130.80, 129.03, 128.81, 120.06, 119.00, 109.17, 108.82, 97.87, 55.25. MS (ESI): $[2M+Na]^+$: 762.59.



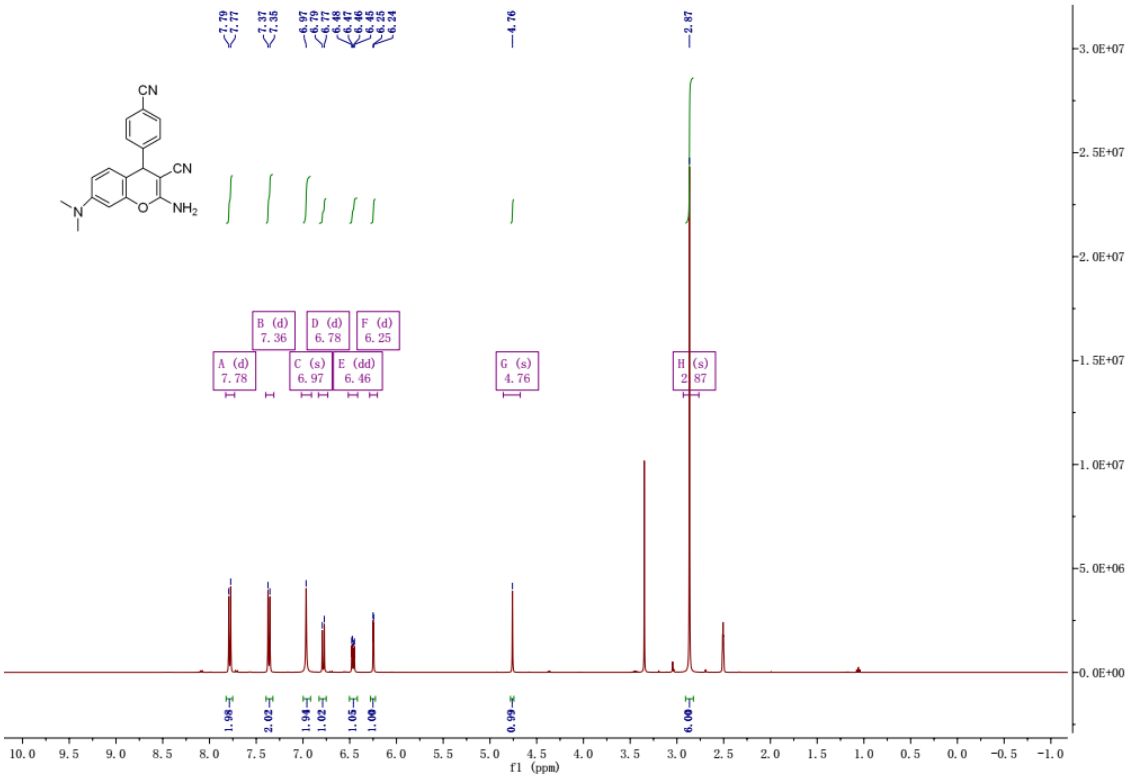

159.76
149.67
148.31
115.10
131.11
130.80
129.03
126.81
120.06
119.00
109.17
106.82
97.87
55.25
Br
CN
NH2
N
O
f1 (ppm)

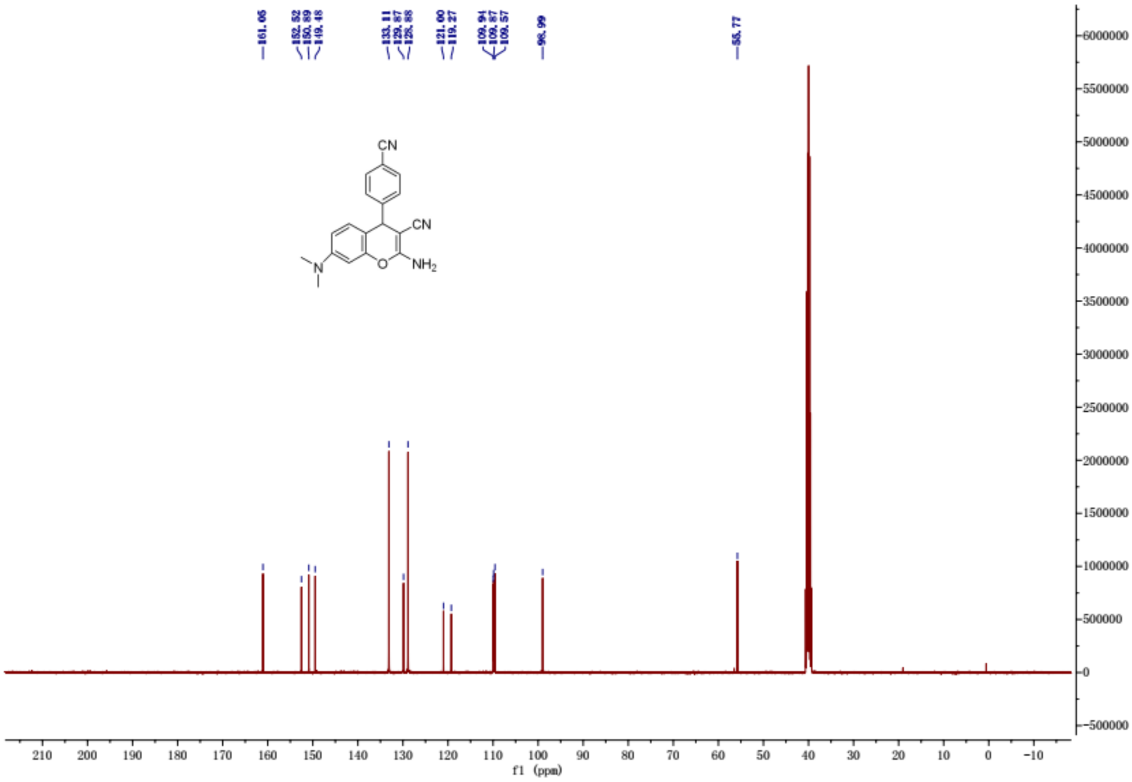

F: ITMS + c ESI Full ms [50.00-1200.00]
762.59
760.96
764.46
765.46
760.18
766.44
740.84
392.19
344.48
370.32
395.15
437.40
489.75
511.79
573.02
589.55
625.38
672.89
728.81
795.56
Br
CN
NH2
N
O
Relative Abundance
m/z

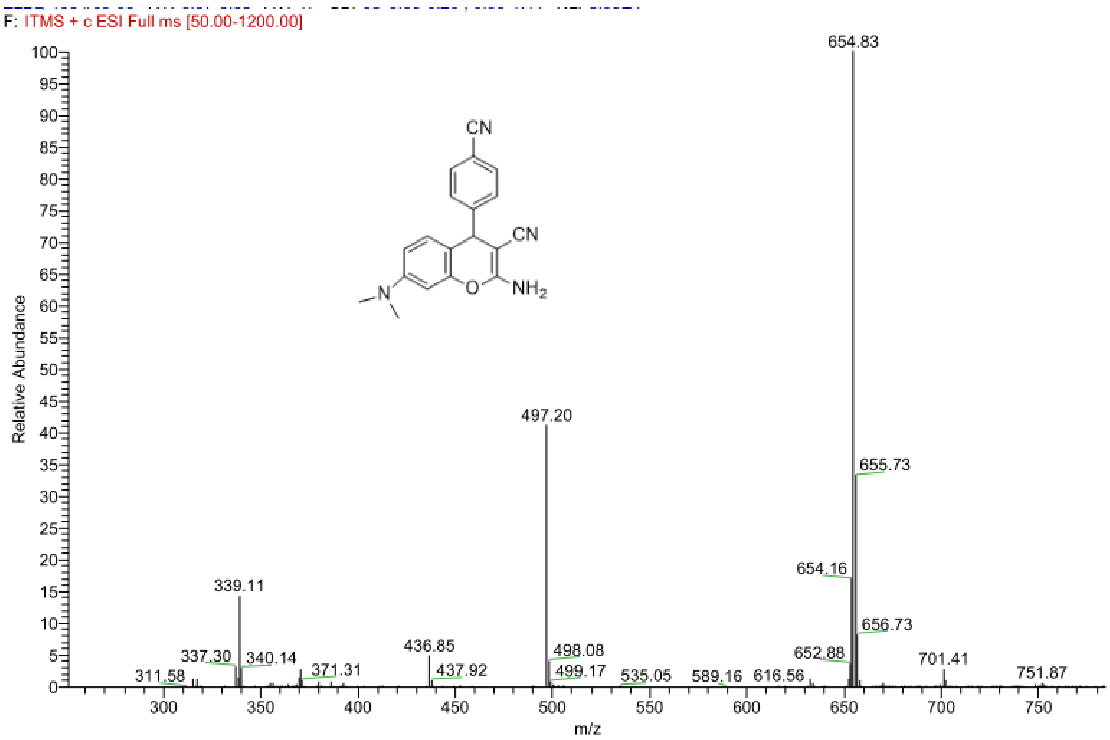


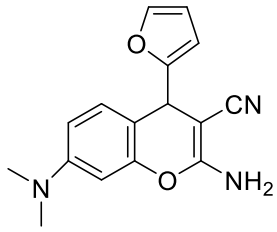
2-Amino-4-(4-cyanophenyl)-7-(dimethylamino)-4*H*-chromene-3-carbonitrile (**5n**, $C_{19}H_{16}N_4O$)

Orange solid; mp 175-177 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 6.97 (s, 2H), 6.78 (d, J = 8.7 Hz, 1H), 6.46 (dd, J = 8.7, 2.5 Hz, 1H), 6.25 (d, J = 2.5 Hz, 1H), 4.76 (s, 1H), 2.87 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.05, 152.52, 150.89, 149.48, 133.11, 129.87, 128.88, 121.00, 119.27, 109.94, 109.87, 109.57, 98.99, 55.77. MS (ESI): $[2M+Na]^+$: 655.73.



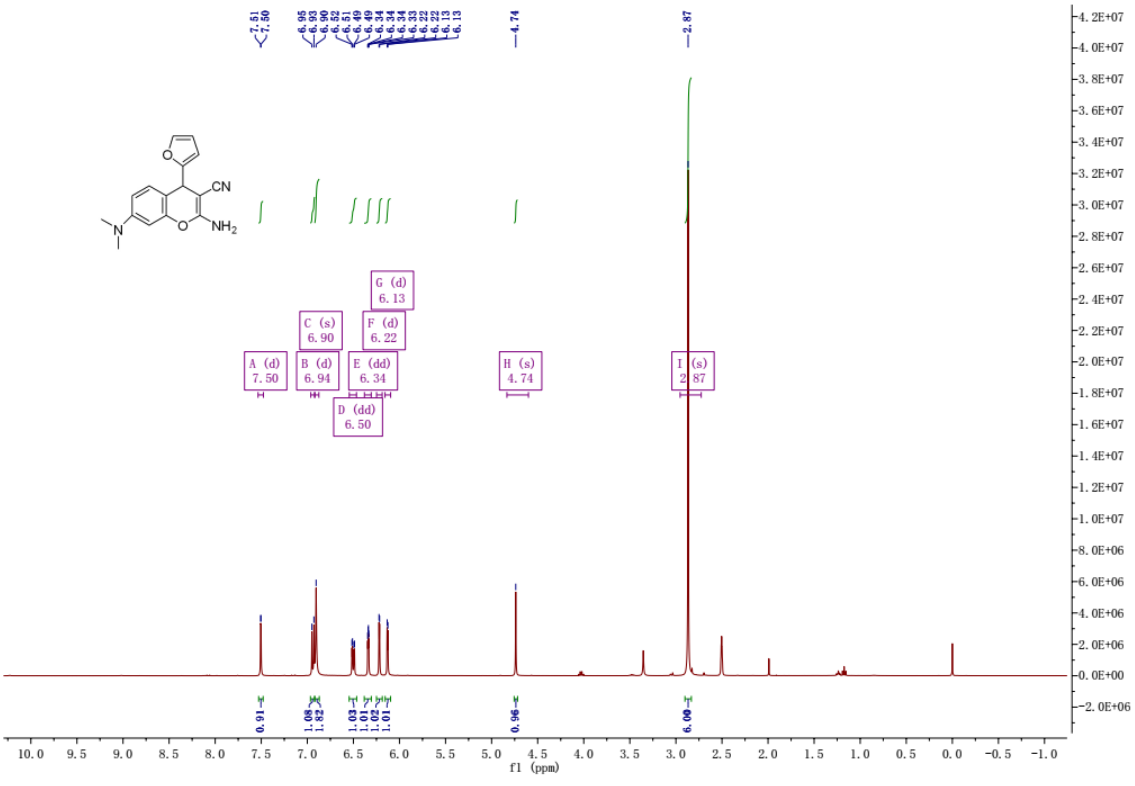

161.05
152.52
150.89
149.48
133.11
129.87
128.88
121.00
119.27
109.94
109.87
109.57
98.99
55.77
CN
CN
N
O
NH2
f1 (ppm)

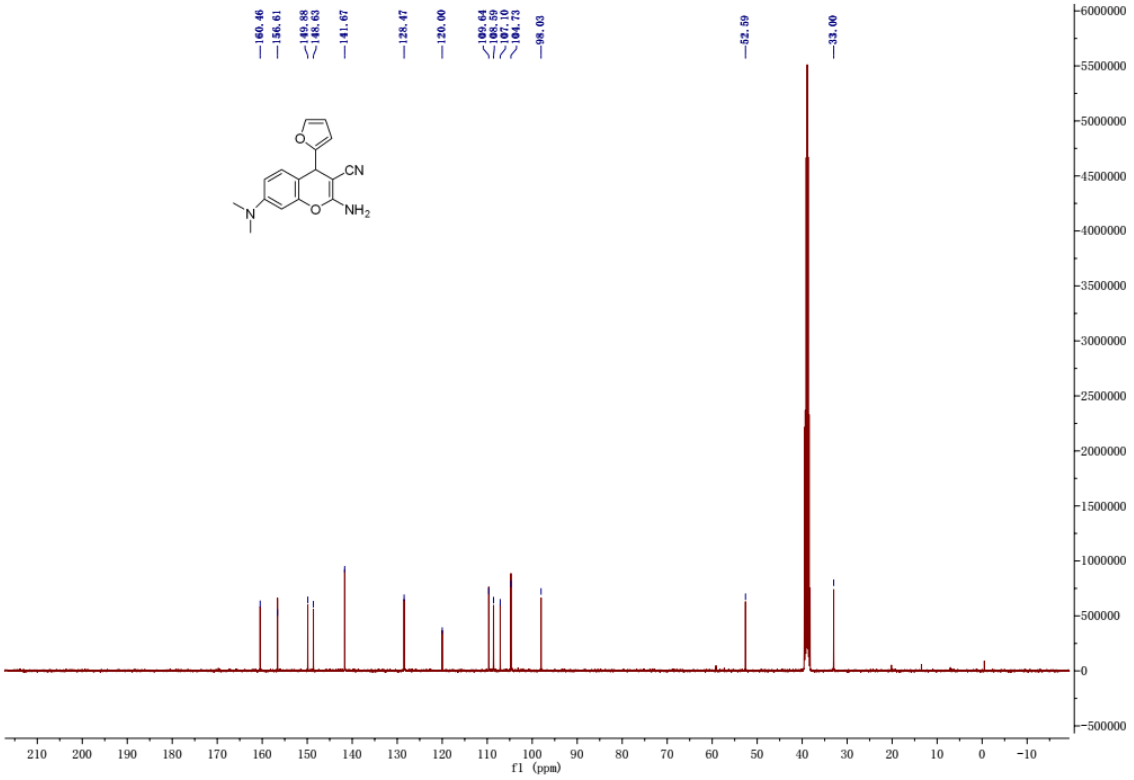

F: ITMS + c ESI Full ms [50.00-1200.00]
Relative Abundance
m/z
654.83
655.73
654.16
656.73
652.88
701.41
751.87
497.20
498.08
499.17
535.05
589.16
616.56
436.85
437.92
339.11
337.30
340.14
371.31
311.58
CN
CN
N
O
NH2

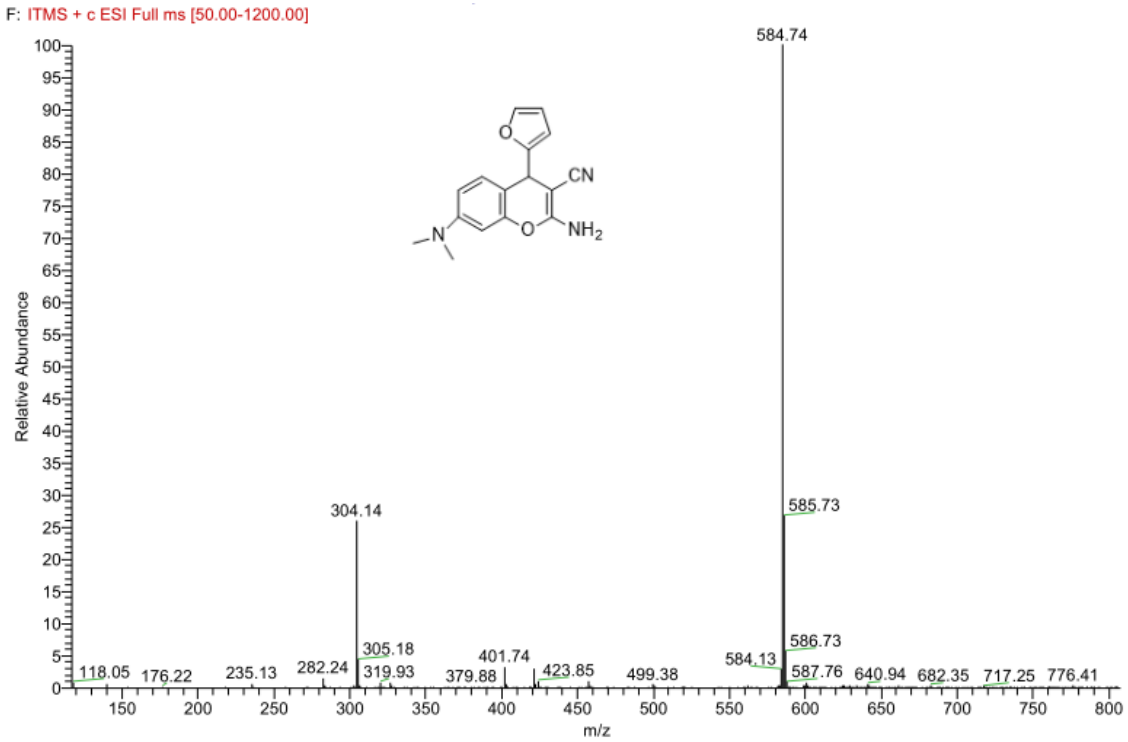


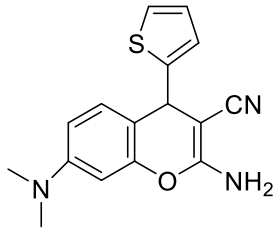
2-Amino-7-(dimethylamino)-4-(furan-2-yl)-4*H*-chromene-3-carbonitrile (**5o**, $C_{16}H_{15}N_3O_2$)

Red solid; mp 178-180 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (d, J = 0.8 Hz, 1H), 6.94 (d, J = 8.7 Hz, 1H), 6.90 (s, 2H), 6.50 (dd, J = 8.6, 2.5 Hz, 1H), 6.34 (dd, J = 3.0, 1.9 Hz, 1H), 6.22 (d, J = 2.4 Hz, 1H), 6.13 (d, J = 3.1 Hz, 1H), 4.74 (s, 1H), 2.87 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.46, 156.61, 149.88, 148.63, 141.67, 128.47, 120.00, 109.64, 108.59, 107.10, 104.73, 98.03, 52.59, 33.00. MS (ESI): $[2M+Na]^+$: 585.73.



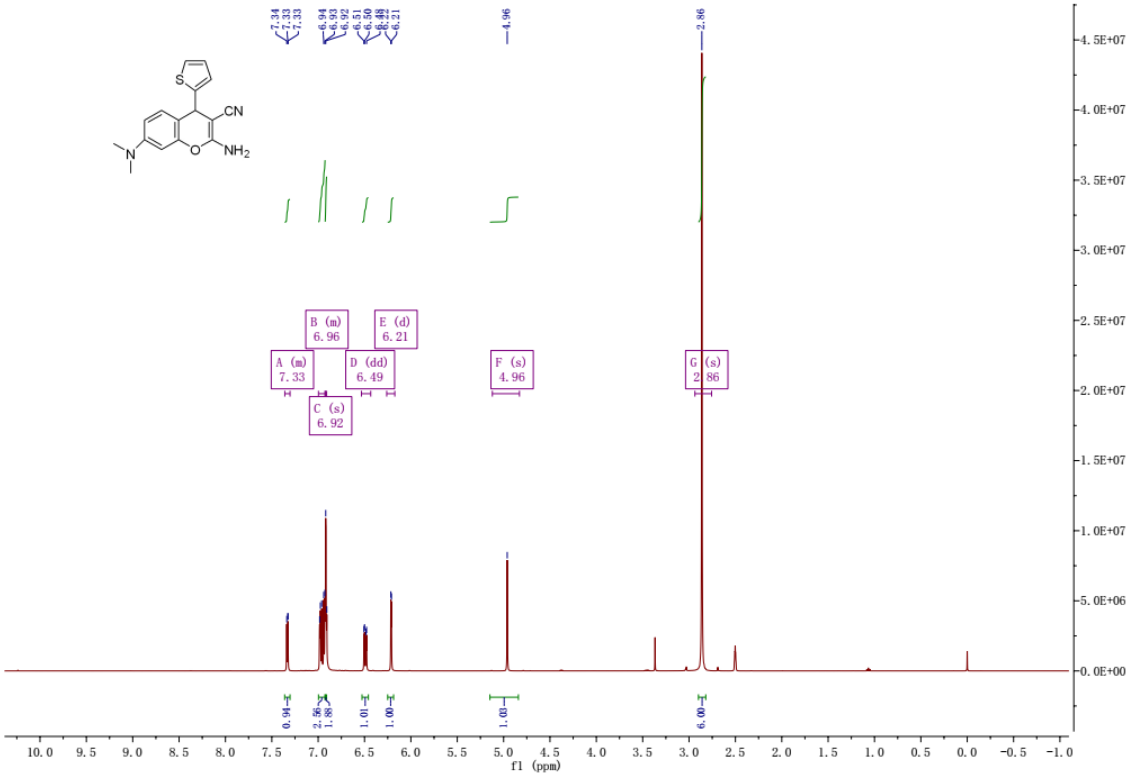

160.46
156.61
149.88
148.63
141.67
128.47
120.00
109.64
108.59
107.10
104.73
98.03
52.89
33.00
CN
NH2
f1 (ppm)

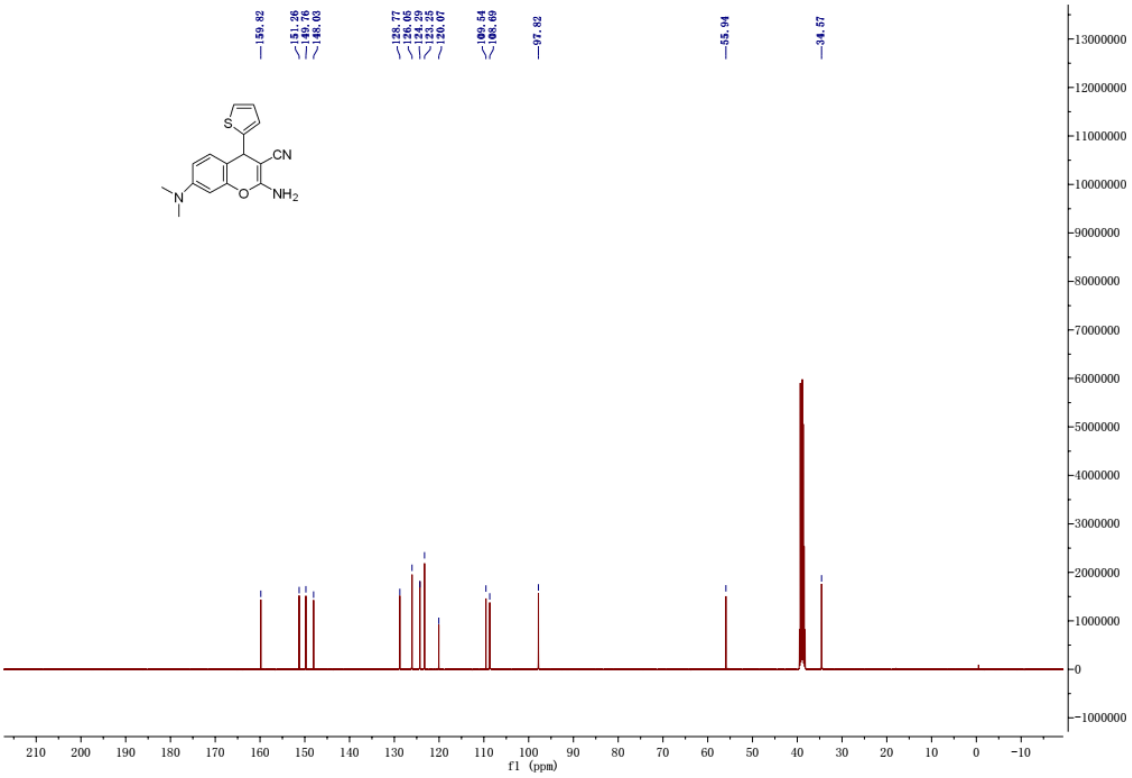

F: ITMS + c ESI Full ms [50.00-1200.00]
584.74
585.73
586.73
304.14
305.18
401.74
CN
NH2
Relative Abundance
m/z

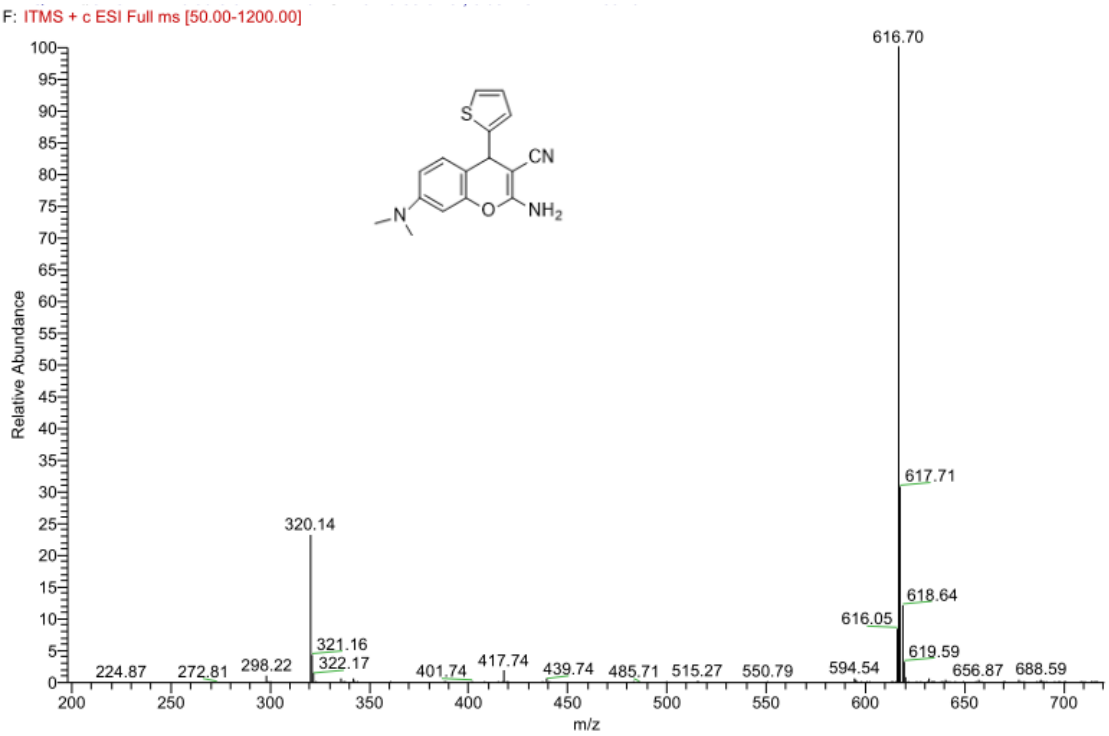


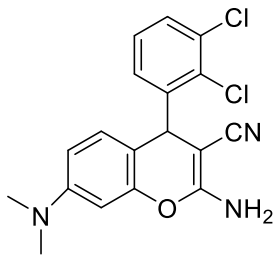
2-Amino-7-(dimethylamino)-4-(thiophen-2-yl)-4*H*-chromene-3-carbonitrile (**5p**, $C_{16}H_{15}N_3OS$)

Purple solid; mp 176-178 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.36 – 7.30 (m, 1H), 7.00 – 6.93 (m, 3H), 6.92 (s, 2H), 6.49 (dd, J = 8.7, 2.5 Hz, 1H), 6.21 (d, J = 2.5 Hz, 1H), 4.96 (s, 1H), 2.86 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.82, 151.26, 149.76, 148.03, 128.77, 126.05, 124.29, 123.25, 120.07, 109.54, 108.69, 97.82, 55.94, 34.57. MS (ESI): $[2M+Na]^+$: 617.71.



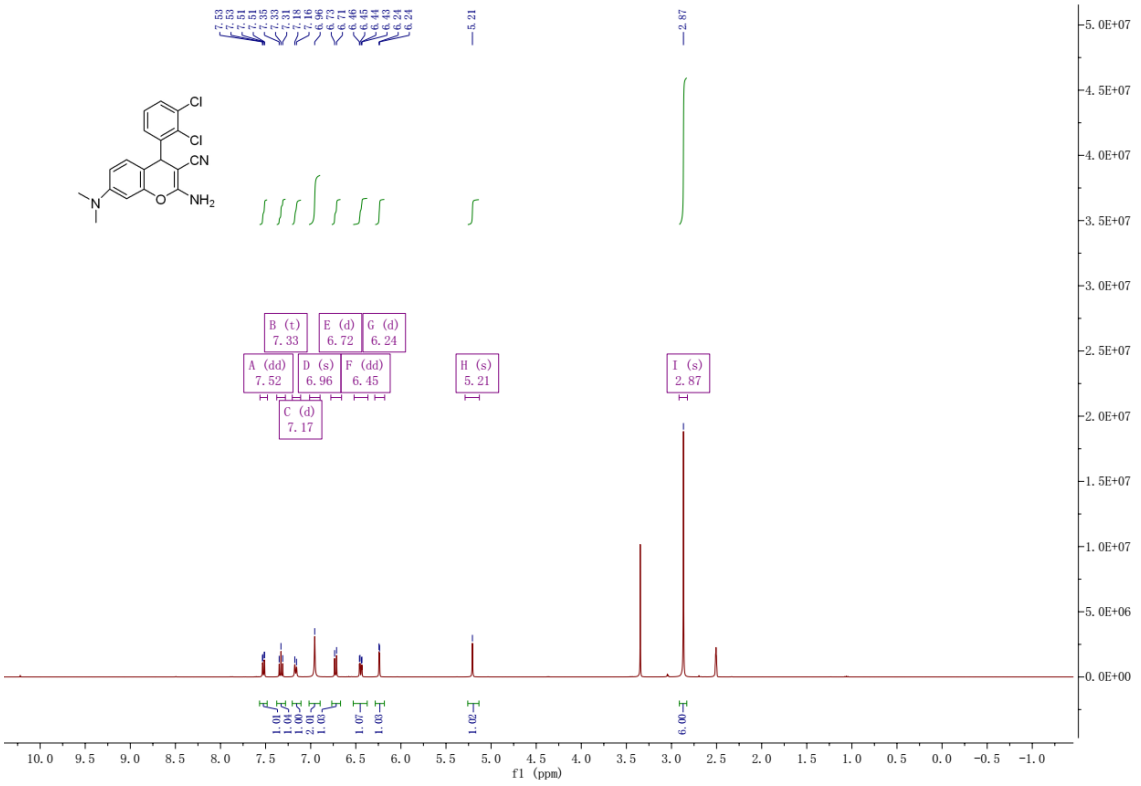

159.82
151.26
149.76
148.03
128.77
126.05
124.29
123.25
120.07
109.54
108.69
97.82
55.94
34.57
S
CN
N
O
NH2
f1 (ppm)

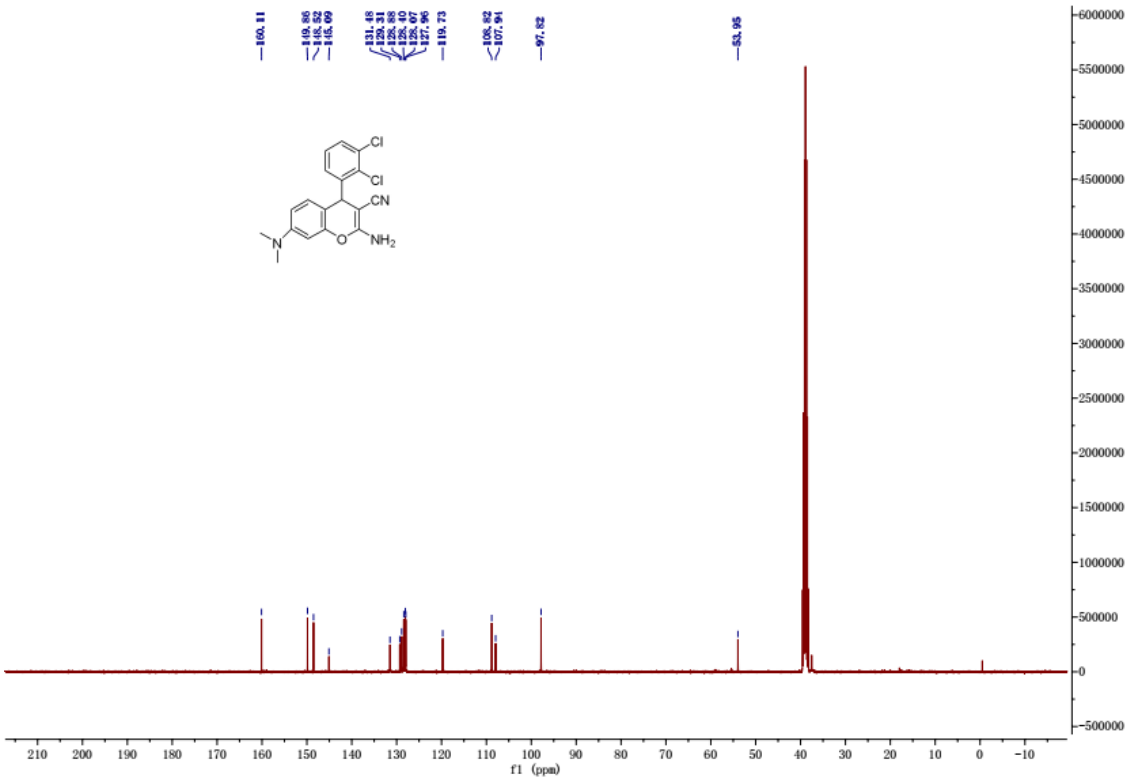

F: ITMS + c ESI Full ms [50.00-1200.00]
Relative Abundance
m/z
616.70
617.71
618.64
619.59
616.05
320.14
321.16
322.17
224.87
272.81
298.22
401.74
417.74
439.74
485.71
515.27
550.79
594.54
656.87
688.59
S
CN
N
O
NH2

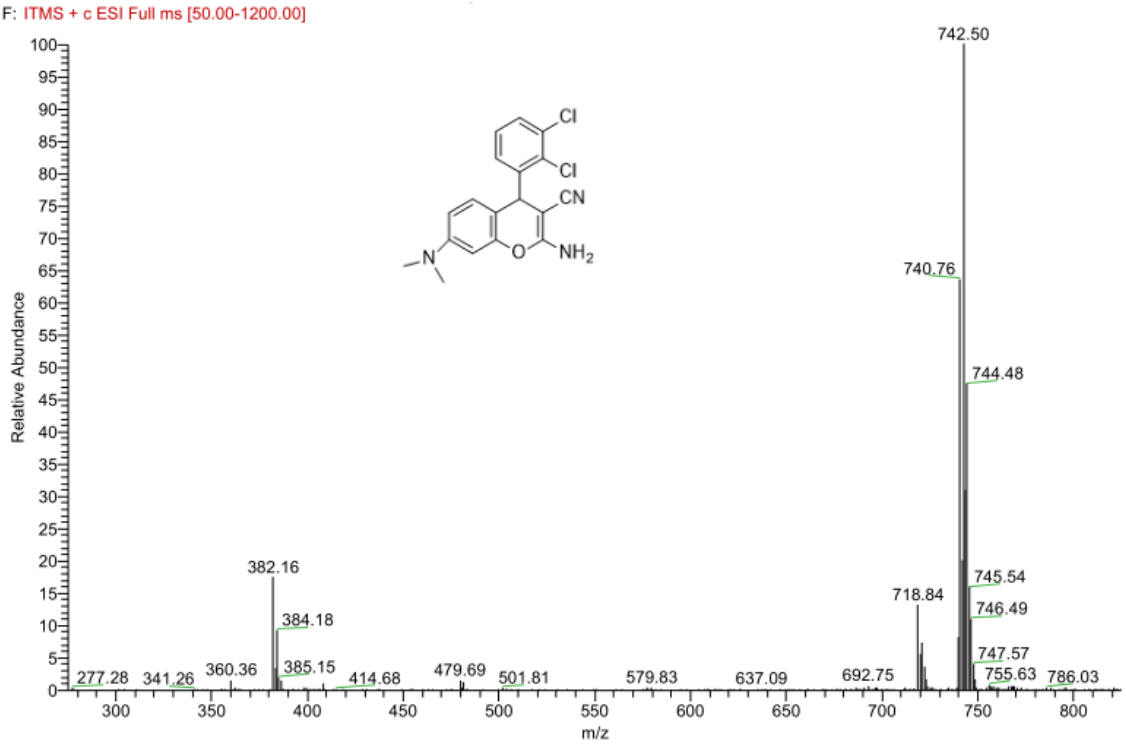


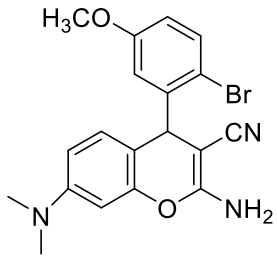
2-Amino-4-(2,3-dichlorophenyl)-7-(dimethylamino)-4*H*-chromene-3-carbonitrile (**5q**, $C_{18}H_{15}Cl_2N_3O$)

White solid; mp 210-211 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.52 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.33 (t, *J* = 7.9 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 6.96 (s, 2H), 6.72 (d, *J* = 8.7 Hz, 1H), 6.45 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.24 (d, *J* = 2.5 Hz, 1H), 5.21 (s, 1H), 2.87 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.11, 149.86, 148.52, 145.09, 131.48, 129.31, 128.88, 128.40, 128.07, 127.96, 119.73, 108.82, 107.94, 97.82, 53.95. MS (ESI): $[2M+Na]^+$: 742.50.



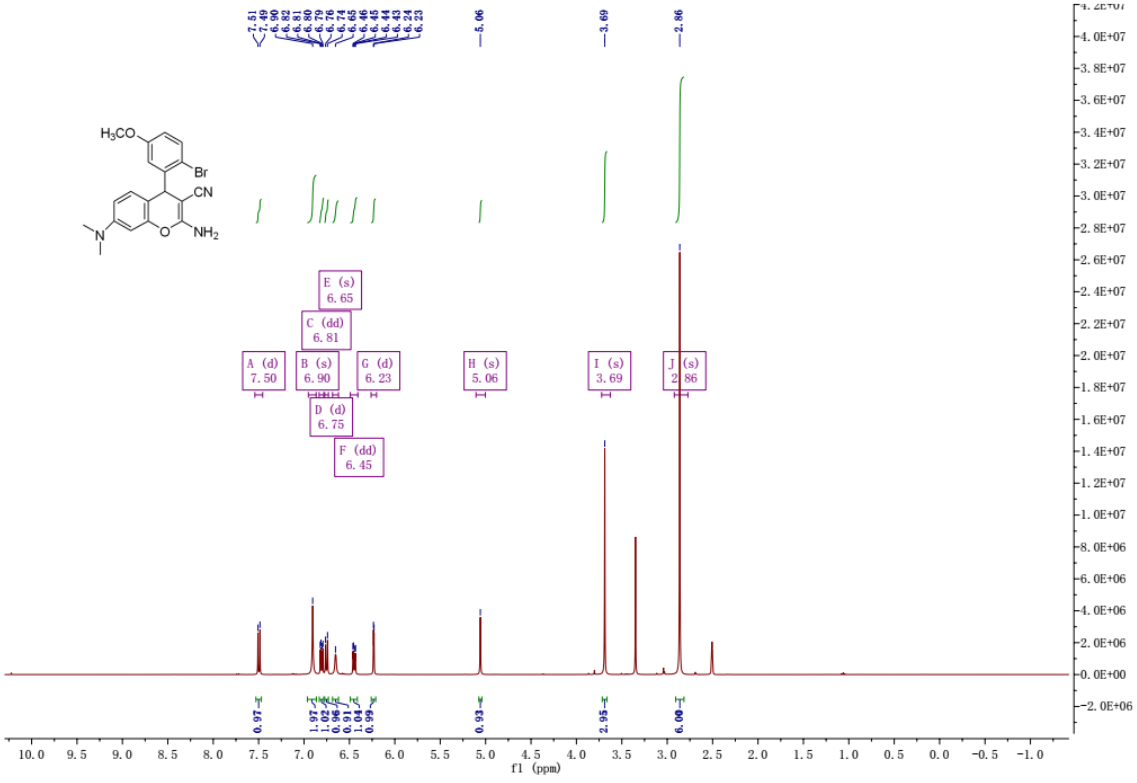

160.11
149.86
148.52
145.09
131.48
129.31
128.85
128.40
128.07
127.96
119.73
108.82
107.94
97.82
53.95
Cl
Cl
CN
NH2
N
O
f1 (ppm)

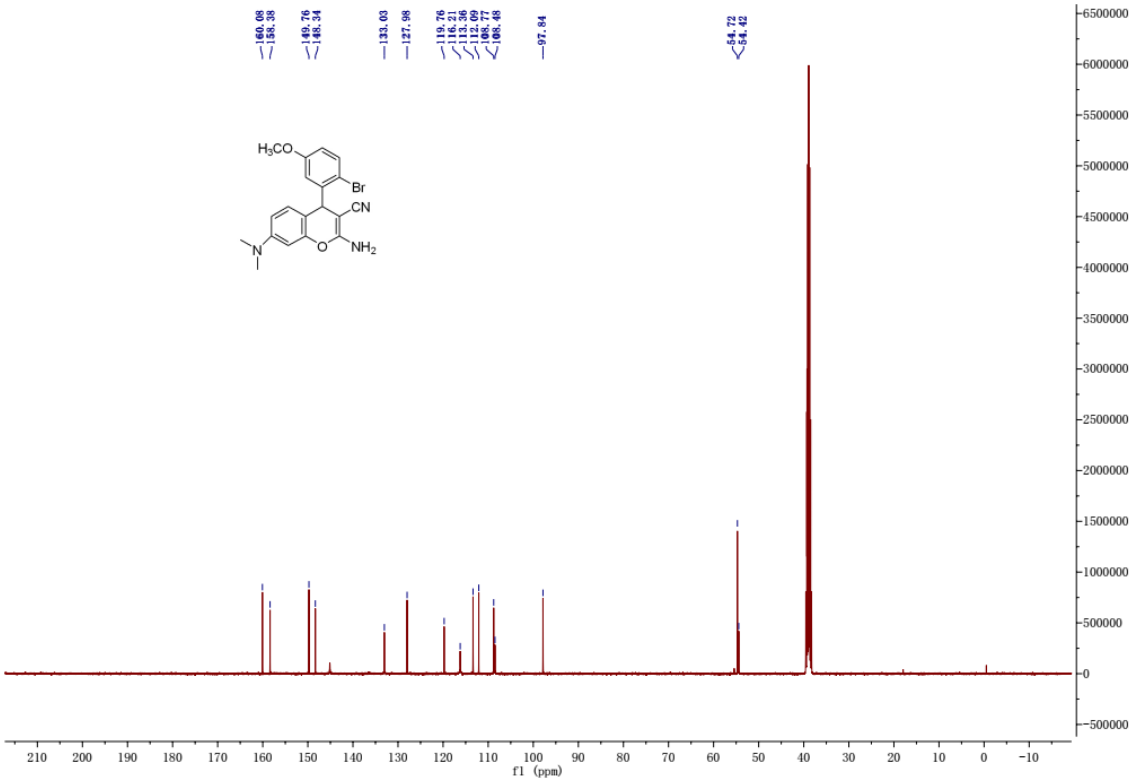

F: ITMS + c ESI Full ms [50.00-1200.00]
Relative Abundance
m/z
742.50
740.76
744.48
745.54
746.49
747.57
755.63
786.03
718.84
382.16
384.18
385.15
277.28
341.26
360.36
414.68
479.69
501.81
579.83
637.09
692.75
Cl
Cl
CN
NH2
N
O

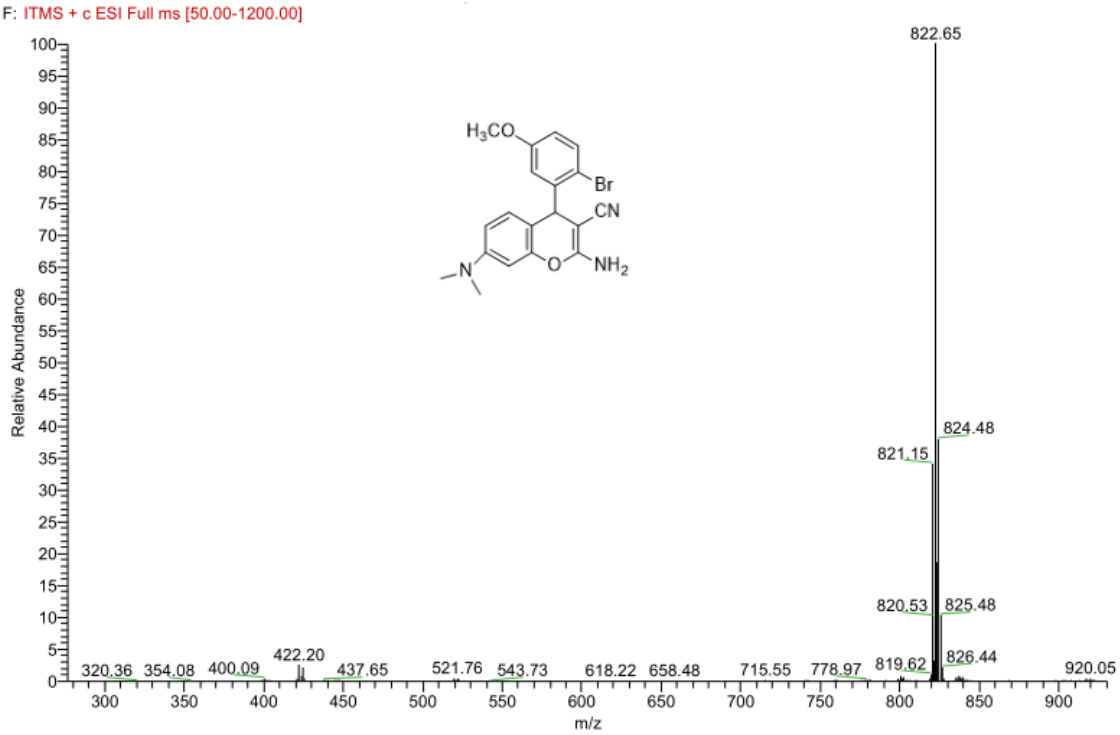


2-Amino-4-(2-bromo-5-methoxyphenyl)-7-(dimethylamino)-4*H*-chromene-3-carbonitrile (**5r**, $C_{19}H_{18}BrN_3O_2$)

Yellow solid; mp 203-205 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (d, J = 8.8 Hz, 1H), 6.90 (s, 2H), 6.81 (dd, J = 8.8, 3.1 Hz, 1H), 6.75 (d, J = 8.7 Hz, 1H), 6.65 (s, 1H), 6.45 (dd, J = 8.7, 2.5 Hz, 1H), 6.23 (d, J = 2.5 Hz, 1H), 5.06 (s, 1H), 3.69 (s, 3H), 2.86 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.08, 158.38, 149.76, 148.34, 133.03, 127.98, 119.76, 116.21, 113.36, 112.09, 108.77, 108.48, 97.84, 54.72, 54.42. MS (ESI): $[2M+Na]^+$: 822.65.




160.08
158.38
149.76
148.34
133.03
127.98
119.76
116.21
113.36
112.00
108.77
108.48
97.84
54.72
54.42
H3CO
Br
CN
NH2
N
O
f1 (ppm)


F: ITMS + c ESI Full ms [50.00-1200.00]
Relative Abundance
m/z
822.65
824.48
821.15
820.53
825.48
826.44
819.62
320.36
354.08
400.09
422.20
437.65
521.76
543.73
618.22
658.48
715.55
778.97
920.05
H3CO
Br
CN
NH2
N
O