Supplementary Information

Synthesis, *in vitro* biological evaluation and molecular docking study of coumarin-1,4-dihydropyridine derivatives as potent anti-inflammatory agents

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Chemical shift in δ ppm	**Structural information**
2.45 (s, 3H)	: C_6-CH_3 of coumarin
3.41 (s, 3H)	: OCH_3 of ester
3.51 (s, 3H)	: OCH_3 of ester
5.18 (s, 1H)	: C_4-CH of DHP
5.87 (s, 2H)	: -NH_2 of DHP
6.13 (s, 1H)	: C_3-H of coumarin
7.32 (m, 5H)	: -CH of Phenyl ring
7.46 (s, 1H)	: C_5-H of coumarin
7.55 (d, 1H, *J*=8Hz)	: C_7-H of coumarin
8.07 (d, 1H, *J*=8Hz)	: C_8-H of coumarin

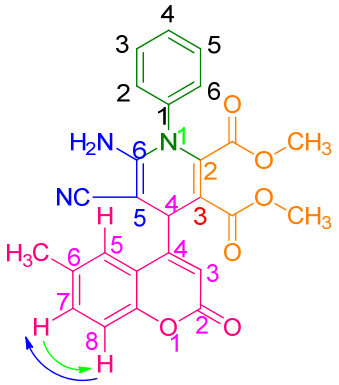


Figure S1. Assignment of chemical shift and coupling constant of compound **6a**

Chemical shift in δ ppm	**Structural information**
21.55	: C_6-CH_3 of coumarin
52.71	: OCH_3 of ester
53.14	: OCH_3 of ester
33.73	: C_4-CH of DHP
117.47	: CN
161.10	: CO of coumarin
163.13	: CO of ester
164.90	: CO of ester

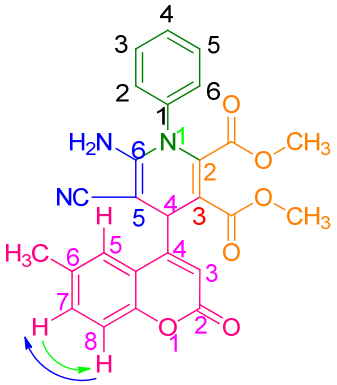


Figure S2. Assignment of ^{13}C-NMR chemical shift of compound **6a**

3.3. Data

3.3.1. Dimethy 6-amino-5-cyano-4-(6-methyl-2-oxo-2H-chromen-4-yl)-1-phenyl-1,4-dihydropyridine-2,3-dicarboxylate (6a)

The compound **6a** obtained from 6-methyl-2-oxo-2H-chromene-4-carbaldehyde (1.0mmol), DMAD (1.0mmol), malononitrile (1.0mmol), aniline (1.0mmol). Yellow solid; Yield: 85%; mp: 268-270 °C; IR (KBr): 3423, 2180, 1753 and 1712 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.41(s, 3H, C_6-CH_3 of coumarin), 3.35(s, 3H, -OCH_3 of ester), 3.45(s, 3H, -OCH_3 of ester), 5.12(s, 1H, CH of dihydropyridine), 5.84(s, 2H, NH_2), 6.18(s, 1H, C_3-H of coumarin), 7.26(dd, 1H, *J*=9.2 Hz, *J*=2 Hz, C_7-H of coumarin), 7.25-7.27 (m, 3H, CH of phenyl ring), 7.49(s, 1H, C_5-H of coumarin), 7.49-7.50(m, 2H, CH of phenyl ring), 8.02 (d, 1H, *J*=8.4 Hz, C_8-H of coumarin); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 21.55 (C_6-CH_3), 33.73 (C_4-CH of DHP), 52.75 (OCH_3 of ester), 53.14 (OCH_3 of ester), 57.46, 102.71, 111.80, 114.62, 115.65, 117.47 (CN), 120.88, 125.66, 126.05, 130.33, 130.75, 135.04, 135.49, 144.02, 144.17, 152.54, 154.24, 159.11, 159.49, 161.10 (CO of coumarin), 163.13 (CO of ester), 164.90 (CO of ester); GC-MS (*m/z*): 471 (M^+).

3.3.2. Dimethyl 6-amino-5-cyano-1-(3,4-dimethylphenyl)-4-(6-methyl-2-oxo-2H-chromen-4-yl)-1,4-dihydropyridine-2,3-dicarboxylate (6b)

The compound **6b** obtained from 6-methyl-2-oxo-2H-chromene-4-carbaldehyde (1.0mmol), DMAD (1.0mmol), malononitrile (1.0mmol), 3,4-dimethylamine (1.0mmol). Gray solid; Yield: 87%; mp: 268-270 °C; IR (KBr): 3413, 2185, 1750 and 1711 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.28 (s, 6H, C_3& C_4-CH_3 of phenyl ring), 2.45 (s, 3H, C_6-CH_3 of coumarin), 3.47(s, 3H, -OCH_3 of ester), 3.55(s, 3H, -OCH_3 of ester), 4.24(s, 2H, NH_2), 5.12(s, 1H, CH of dihydropyridine), 6.36(s, 1H, C_3-H of coumarin), 7.04(dd, 1H, *J*=8 Hz, *J*=2 Hz, C_7-H of coumarin), 7.07(s, 1H, C_5-H of coumarin), 7.19(m, 3H, CH of phenyl ring), 7.91(d, 1H, *J*=8 Hz, C_8-H of coumarin); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 19.74(C_3- CH_3 of phenyl), 19.86 ((C_4- CH_3 of phenyl)), 21.73(C_6-CH_3), 32.87(C_4-CH of DHP), 52.50(OCH_3 of ester), 52.88(OCH_3 of ester), 59.15, 99.99, 102.43, 112.81, 115.52, 117.55(CN), 120.13, 124.50, 125.77, 127.45, 130.74, 131.15, 140.12, 143.66, 143.88, 151.36, 153.11, 154.28, 158.61, 162.25(CO of coumarin), 162.94(CO of ester), 164.83(CO of ester); Anal. Calc. for $C_{28}H_{25}N_3O_6$: C, 67.33; H, 5.04; N, 8.41. Found: C, 67.36; H, 5.02; N, 8.44. GC-MS (*m/z*): 499 (M^+).

3.3.3. **Dimethyl-6-amino-1-(4-chlorophenyl)-5-cyano-4-(6-methyl-2-oxo-2H-chromen-4-yl)-1,4-dihydropyridine-2,3-dicarboxylate (6c)**

The compound **6c** obtained from 6-methyl-2-oxo-2H-chromene-4-carbaldehyde (1.0mmol), DMAD (1.0mmol), malononitrile (1.0mmol), 4-chlorobenzenamine (1.0mmol). Gray solid; Yield: 83%; mp: 252-254 °C; IR (KBr): 3346, 2185, 1750 and 1700 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.42 (s, 3H, C_6-CH_3 of coumarin), 3.43(s, 3H, -OCH_3 of ester), 3.62(s, 3H, -OCH_3 of ester), 4.21(s, 2H, NH_2), 5.21(s, 1H, CH of dihydropyridine), 6.23(s, 1H, C_3-H of coumarin), 7.15(dd, 1H, *J*=8 Hz, *J*=2 Hz, C_7-H of coumarin), 7.22(d, 1H, *J*=7.2 Hz, C_5-H of coumarin), 7.27(d, 4H, *J*=8 Hz, CH of phenyl ring), 7.87(d, 1H, *J*=8 Hz, C_8-H of coumarin); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 22.54(C_6-CH_3), 33.27(C_4-CH of DHP), 51.91(OCH_3 of ester), 52.31(OCH_3 of ester), 58.25, 100.19, 105.23, 115.57, 117.02, 117.85(CN), 119.34, 123.21, 125.37, 130.64, 132.27, 139.45, 141.27, 144.67, 151.36, 155.04, 157.11, 161.24(CO of coumarin), 163.17(CO of ester), 165.23(CO of ester); Anal. Calc. for $C_{26}H_{20}ClN_3O_6$: C, 61.73; H, 3.98; N, 8.31. Found: C, 61.78; H, 3.96; N, 8.36. GC-MS (*m/z*): 505 (M^+).

3.3.4. **Dimethyl 6-amino-5-cyano-4-(7-methyl-2-oxo-2H-chromen-4-yl)-1-phenyl-1,4-dihydropyridine-2,3-dicarboxylate (6d)**

The compound **6d** obtained from 7-methyl-2-oxo-2H-chromene-4-carbaldehyde (1.0mmol), DMAD (1.0mmol), malononitrile (1.0mmol), aniline (1.0mmol). Cream solid; Yield: 86%; mp: 238-232 °C; IR (KBr): 3432, 2178, 1749 and 1710 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.35 (s, 3H, C_7-CH_3 of coumarin), 3.42(s, 3H, -OCH_3 of ester), 3.48(s, 3H, -OCH_3 of ester), 5.18(s, 1H, CH of dihydropyridine), 5.64(s, 2H, NH_2), 6.24(s, 1H, C_3-H of coumarin), 7.21(dd, 1H, *J*=8 Hz, *J*=2 Hz, C_6-H of coumarin), 7.23-7.29(m, 3H, CH of phenyl ring), 7.51(s, 1H, C_8-H of coumarin), 7.52-7.55(m, 2H, CH of phenyl ring), 7.89(d, 1H, *J*=8.4 Hz, C_5-H of coumarin); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 23.13(C_7-CH_3), 35.02(C_4-CH of DHP), 53.17(OCH_3 of ester), 54.35(OCH_3 of ester), 56.08, 101.11, 113.20, 113.87, 115.67, 116.46(CN), 119.14, 121.76, 128.15, 131.47, 133.27, 135.19, 137.49, 142.49, 143.07, 151.62, 155.17, 157.22, 158.45, 162.87(CO of coumarin), 163.72(CO of ester), 165.49(CO of ester); Anal. Calc. for $C_{26}H_{21}N_3O_6$: C, 66.24; H, 4.49; N, 8.91. Found: C, 66.26; H, 4.48; N, 8.94. GC-MS (*m/z*):471 (M^+).

3.3.5. **Dimethyl 6-amino-5-cyano-1-(3,4-dimethylphenyl)-4-(7-methyl-2-oxo-2H-chromen-4-yl)-1,4-dihydropyridine-2,3-dicarboxylate (6e)**

The compound **6e** obtained from 7-methyl-2-oxo-2H-chromene-4-carbaldehyde (1.0mmol), DMAD (1.0mmol), malononitrile (1.0mmol), 3,4-dimethylamine (1.0mmol). Gray solid; Yield: 89%; mp: 222-224 °C; IR (KBr): 3432, 2175, 1754 and 1718 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.28 (s, 6H, C_3& C_4-CH_3 of phenyl ring), 2.45(s, 3H, C_7-CH_3 of coumarin), 3.48(s, 3H, -OCH_3 of ester), 3.57(s, 3H, -OCH_3 of ester), 4.25(s, 2H, NH_2), 5.12(s, 1H, CH of dihydropyridine), 6.40(s, 1H, C_3-H of coumarin), 7.05(d, 2H, *J*=8.4 Hz, CH of phenyl ring), 7.22(d, 1H, *J*=8 Hz, C_5-H of coumarin), 7.26(s, 1H, CH of phenyl ring), 7.37(d, 1H, *J*=8 Hz, C_6-H of coumarin), 7.82 (s, 1H, C_8-H of coumarin); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm:19.74(C_3- CH3 of phenyl), 19.86(C_4- CH3 of phenyl), 21.27, 32.89(C_4-CH of DHP), 52.52(OCH_3 of ester), 52.89(OCH_3 of ester), 59.03, 102.44, 113.79, 117.05(CN), 117.60, 120.10, 124.81, 127.23, 130.75, 131.16, 131.83, 133.30, 134.18, 139.20, 140.12, 143.90, 151.48, 152.31, 158.21, 162.13(CO of coumarin), 162.94(CO of ester), 164.83(CO of ester). Anal. Calc. for $C_{28}H_{25}N_3O_6$: C, 67.33; H, 5.04; N, 8.41. Found: C, 67.35; H, 5.06; N, 8.46. GC-MS (*m/z*): 499 (M^+).

3.3.6. **Dimethyl 6-amino-1-(4-chlorophenyl)-5-cyano-4-(7-methyl-2-oxo-2H-chromen-4-yl)-1,4-dihydropyridine-2,3-dicarboxylate (6f)**

The compound **6f** obtained from 7-methyl-2-oxo-2H-chromene-4-carbaldehyde (1.0mmol), DMAD (1.0mmol), malononitrile (1.0mmol), 4-chlorobenzamine (1.0mmol). White solid; Yield: 78%; mp: 232-234 °C; IR (KBr): 3438,3337, 2277, 1748 and 1726 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.53 (s, 3H, C_7-CH_3 of coumarin), 3.58(s, 3H, -OCH_3 of ester), 3.62(s, 3H, -OCH_3 of ester), 4.19(s, 2H, NH_2), 5.60(s,1H, CH of dihydropyridine), 6.26(s, 1H, C_3-H of coumarin), 7.35(d, 2H, *J*=7.8 Hz, C_6-H of coumarin), 7.47(dd, 3H, *J*=8.4 Hz, C_5-H of coumarin), 7.82(d, 4H, *J*=8 Hz, CH of phenyl ring), 8.23(s, 1H, C_8-H of coumarin); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 20.83, 45.64(C_4-CH of DHP), 53.53(OCH_3 of ester), 54.65(OCH_3 of ester), 61.30, 102.30, 105.23, 108.21, 116.87, 118.10 (CN), 118.94, 120.07, 122.19, 125.43, 129.63, 131.37, 134.03, 140.96, 143.27, 147.38, 153.74, 156.34, 159.70, 160.29(CO of coumarin), 163.06(CO of ester), 167.58(CO of ester); Anal. Calc. for $C_{26}H_{20}ClN_3O_6$: C, 61.73; H, 3.98; N, 8.31. Found: C, 61.75; H, 3.96; N, 8.35. GC-MS (*m/z*):505 (M^+).

3.3.7. **Dimethyl-6-amino-5-cyano-4-(6-methoxy-2-oxo-2H-chromen-4-yl)-1-(4-methoxyphenyl)-1,4-dihydropyridine-2,3-dicarboxylate (6g)**

The compound **6g** obtained from 6-methoxy-2-oxo-2H-chromene-4-carbaldehyde (1.0mmol), DMAD (1.0mmol), malononitrile (1.0mmol), 4-methoxybenzenamine (1.0mmol). Light yellow solid; Yield: 78%; mp: 218-220 °C; IR (KBr): 3401, 3334, 2220, 1745 and 1725 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 3.49 (s, 3H, -OCH_3 of ester), 3.59 (s, 3H, -OCH_3 of ester), 3.80 (s, 6H, C_6-OCH_3), 5.03 (s, 1H, CH of dihydropyridine), 5.76(s, 2H, NH_2), 6.23(s, 1H, C_3-H of coumarin), 7.01-7.03(m, 2H, Ar-H), 7.24-7.32(m, 3H, Ar-H), 7.85 (t, 2H Ar-H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 23.13, 35.02(C_4-CH of DHP), 53.17(OCH_3 of ester), 54.35(OCH_3 of ester), 56.08, 101.11, 113.87, 115.67, 116.46(CN), 119.14, 121.76, 124.43, 128.15, 131.47, 133.27, 135.19, 137.49, 142.49, 143.07, 151.62, 155.17, 157.22, 158.45, 160.37(CO of coumarin), 163.72(CO of ester), 165.49(CO of ester). Anal. Calc. for $C_{27}H_{23}N_3O_8$: C, 62.67; H, 4.48; N, 8.12. Found: C, 62.69; H, 4.45; N, 8.16. LC-MS (*m/z*):517 (M^+).

3.3.8. **Dimethyl-6-amino-5-cyano-1-(3,4-dimethylphenyl)-4-(6-methoxy-2-oxo-2H-chromen-4-yl)-1,4-dihydropyridine-2,3-dicarboxylate (6h)**

The compound **6h** obtained from 6-methoxy-2-oxo-2H-chromene-4-carbaldehyde (1.0mmol), DMAD (1.0mmol), malononitrile (1.0mmol), 3,4-dimethylamine (1.0mmol). Gray solid; Yield: 84%; mp: 232-234 °C; IR (KBr): 3431, 2179, 1748 and 1707 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.29(s, 6H, C_3& C_4-CH_3 of phenyl ring), 3.94(s, 3H, C_6-OCH_3 of coumarin), 3.49(s, 3H, -OCH_3 of ester), 3.59(s, 3H, -OCH_3 of ester), 4.26(s, 2H, NH_2), 5.08(s, 1H, CH of dihydropyridine), 6.42 (s, 1H, C_3-H of coumarin), 7.06(d, 2H, *J*=8 Hz, CH of phenyl ring), 7.21(s, 1H, CH of phenyl ring), 7.15(dd, 1H, *J*=8.8 Hz, *J*=2.8 Hz, C_7-H of coumarin), 7.30(d, 1H, *J*=8.8 Hz, C_8-H of coumarin), 7.47(d, 1H, *J*=2.8 Hz, C_5-H of coumarin); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 19.74(C_3- CH3 of phenyl), 19.86(C_4- CH3 of phenyl), 21.27, 32.89(C_4-CH of DHP), 52.52(OCH_3 of ester), 52.89(OCH_3 of ester), 59.03, 102.44, 113.79, 117.05, 117.60(CN), 120.10, 124.81, 127.23, 130.75, 131.16, 131.83, 133.30, 134.18, 139.20, 140.12, 143.90, 151.48, 152.31, 158.21, 162.13(CO of coumarin), 162.94(CO of ester), 164.83(CO of ester); Anal. Calc. for $C_{28}H_{25}N_3O_7$: C, 65.24; H, 4.89; N, 8.15. Found: C, 65.28; H, 4.85; N, 8.19. GC-MS (*m/z*):515 (M^+).

3.3.9. **Dimethyl 6-amino-1-(4-chlorophenyl)-5-cyano-4-(6-methoxy-2-oxo-2H-chromen-4-yl)-1,4-dihydropyridine-2,3-dicarboxylate (6i)**

The compound **6i** obtained from 6-methoxy-2-oxo-2H-chromene-4-carbaldehyde (1.0mmol), DMAD (1.0mmol), malononitrile (1.0mmol), 4-chlorobenzamine (1.0mmol). Gray solid; Yield: 82%; mp: 230-232 °C; IR (KBr): 3414,3334, 2219, 1748 and 1726 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 3.71(s, 3H, -OCH_3 of ester), 3.73(s, 3H, -OCH_3 of ester), 3.88(s, 3H, C_6-OCH_3 of coumarin), 4.27(s, 2H, NH_2), 5.21(s, 1H, CH of dihydropyridine), 6.14(s, 1H, C_3-H of coumarin), 7.10(t, 2H, *J*=8.7 and Hz, *J*= 8.5 Hz, Ar-H), 7.19(m, 3H,Ar-H), 7.29(d, 2H, *J*=4.2 Hz, Ar-H), 7.80(d, 1H, J= 8.6Hz, Ar-H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 22.19, 47.06(C_4-CH of DHP), 52.37(OCH_3 of ester), 55.73(OCH_3 of ester), 60.01,100.30, 105.77, 110.16, 117.34, 117.90(CN), 119.46, 121.03, 123.00, 127.88, 130.63, 132.07, 136.47, 142.23, 145.82, 150.18, 155.04, 157.38, 159.64, 162.86(CO of coumarin), 165.67(CO of ester), 169.78(CO of ester); Anal. Calc. for $C_{26}H_{20}ClN_3O_7$: C, 59.83; H, 3.86; N, 8.05. Found: C, 59.86; H, 3.85; N, 8.09. GC-MS (*m/z*):521 (M^+).

3.4. **Dimethyl-6-amino-5-cyano-4-(3-oxo-3H-benzo[f]chromen-1-yl)-1-phenyl-1,4-dihydropyridine-2,3-dicarboxylate (6j)**

The compound **6j** obtained from 3-oxo-3H-benzo[f]chromene-1-carbaldehyde1.0mmol), DMAD (1.0mmol), malononitrile (1.0mmol), aniline (1.0mmol). Pink solid; Yield: 74%; mp: 247-249 °C; IR (KBr): 3393, 2219, 1732 and 1695 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 3.67(s, 3H, -OCH_3 of ester), 3.93(s, 3H, -OCH_3 of ester), 4.32(s, 1H, CH of dihydropyridine), 5.18(s, 2H, NH_2), 6.00(s, 1H, C_3-H of coumarin), 7.60-6.70(m, 5H, of phenyl ring), 7.80(dd, 2H, *J*=8.4 Hz, *J*=1.2 Hz, C_6 & C_7-H of coumarin), 8.11(d, 2H, *J*=7.2 Hz, C_9& C_{10}-H of coumarin), 8.29(d, 1H, *J*=8.8Hz, C_5-H of coumarin), 8.65(d, 1H, *J*=8.4 Hz, C_8-H of coumarin); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 37.14(C_4-CH of DHP), 53.66(OCH_3 of ester), 56.09(OCH_3 of ester), 57.34, 113., 115.33, 117.94(CN), 120.54, 121.39, 123.77, 124.84, 125.76, 126.29, 126.73, 129.23, 130.62, 131.49, 134.68, 139.67, 141.77, 144.00, 153.16, 155.23, 157.01, 159.42, 160.72(CO of coumarin), 161.97, 162.04(CO of ester), 163.88(CO of ester); Anal. Calc. for $C_{29}H_{21}N_3O_6$: C, 68.63; H, 4.17; N, 8.28. Found: C, 68.68; H, 4.15; N, 8.31. GC-MS (*m/z*):507 (M^+).

3.4.2. **Dimethyl-6-amino-5-cyano-1-(3,4-dimethylphenyl)-4-(3-oxo-3H-benzo[f]chromen-1-yl)-1,4-dihydropyridine-2,3-dicarboxylate (6k)**

The compound **6k** obtained from 3-oxo-3H-benzo[f]chromene-1-carbaldehyde1.0mmol), DMAD (1.0mmol), malononitrile (1.0mmol), 3,4-dimethylamine (1.0mmol). Pink solid; Yield: 76%; mp: 248-250 °C; IR (KBr): 3426, 3337, 2225, 1746 and 1726 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.38 & 2.43 (s, 6H, C_3& C_4-CH_3 of phenyl ring), 3.53(s, 3H, -OCH_3 of ester), 3.65(s, 3H, -OCH_3 of ester), 4.78(s, 2H, NH_2), 5.19(s,1H, 1H, CH of dihydropyridine), 6.21(s, 1H, C_3-H of coumarin), 7.31(d, 1H, Ar-H , *J*=8.0 Hz), 7.43(t, 2H, Ar-H), 7.67(m, 4H, Ar-H), 7.64(t, 1H,Ar-H), 7.72(d, 2H, *J*=6.4 Hz, Ar-H), 7.91(s, 1H, Ar-H), 8.04(d, 1H, *J*=4 Hz, Ar-H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 22.76(C_3- CH3 of phenyl), 23.17(C_4- CH3 of phenyl), 36.12(C_4-CH of DHP), 54.03(OCH_3 of ester), 55.43(OCH_3 of ester), 57.18, 100.26, 111.45, 112.19, 114.34, 117.44(CN), 118.69, 122.31, 123.08, 124.77, 126.25, 129.11, 130.37, 134.18, 137.02, 137.46, 140.76, 142.83, 152.81, 155.27, 155.92, 157.94, 159.42, 161.53(CO of coumarin), 162.89(CO of ester), 165.75(CO of ester). Anal. Calc. for $C_{31}H_{25}N_3O_6$: C, 69.52; H, 4.71; N, 7.85. Found: C, 69.58; H, 4.65; N, 7.87. GC-MS (*m/z*):535 (M^+).

3.4.3. **Dimethyl-6-amino-1-(4-chlorophenyl)-5-cyano-4-(3-oxo-3H-benzo[f]chromen-1-yl)-1,4-dihydropyridine-2,3-dicarboxylate (6l)**

The compound **6l** obtained from 3-oxo-3H-benzo[f]chromene-1-carbaldehyde10.0mmol), DMAD (1.0mmol), malononitrile (1.0mmol), 4-chloroaniline (1.0mmol). Pink solid; Yield: 75%; mp: 246-248 °C; IR (KBr): 3398, 2198, 1742 and 1724 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 3.59(s, 3H, -OCH_3 of ester), 3.91(s, 3H, -OCH_3 of ester), 4.23(s, 1H, CH of dihydropyridine), 5.18(s, 2H, NH_2), 5.67(s, 1H, C_3-H of coumarin), 6.63 (d, 2H, *J*=7.2 Hz, CH of phenyl ring), 6.96 (d, 2H, *J*=7.2 Hz, CH of phenyl ring), 7.53-7.74(m, 4H, of coumarin), 8.09 (d, 1H, *J*=8.4 Hz, C_5-H of coumarin), 8.28(d, 1H, *J*=9.2 Hz, C_9-H of coumarin); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 32.93(C_4-CH of DHP), 54.17(OCH_3 of ester), 54.66(OCH_3 of ester), 56.23, 112.11, 112.87, 113.22, 114.37, 117.29(CN), 118.33, 122.41, 122.89, 123.54, 125.02, 127.45, 130.00, 131.24, 133.49, 135.62, 139.88, 142.17, 152.84, 154.31, 155.03, 158.15, 159.28, 161.94(CO of coumarin), 164.68(CO of ester), 165.49(CO of ester). Anal. Calc. for

$C_{29}H_{20}ClN_3O_6$: C, 64.27; H, 3.72; N, 7.75. Found: C, 64.30; H, 3.70; N, 7.79. GC-MS (*m/z*):541.94 (M^+).

3.4.4. **Dimethyl-6-amino-5-cyano-4-(2-oxo-2H-benzo[h]chromen-4-yl)-1-phenyl-1,4-dihydropyridine-2,3-dicarboxylate (6m)**

The compound **6m** obtained from 2-oxo-2H-benzo[h]chromene-4-carbaldehyde (1.0mmol), DMAD (1.0mmol), malononitrile (1.0mmol), aniline (1.0mmol). Gray solid; Yield: 74%; mp: 247-249 °C; IR (KBr): 3464, 2182, 1751 and 1708 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 3.36(s, 3H, -OCH_3 of ester), 3.43(s, 3H, -OCH_3 of ester), 4.31(s, 1H, CH of dihydropyridine), 5.30(s, 2H, NH_2), 6.35(s, 1H, C_3-H of coumarin), 7.49-6.54 (m, 5H, of phenyl ring), 7.26-7.30 (m, 2H, of coumarin), 7.71-7.74 (m, 2H, of coumarin), 7.95(d, 1H, *J*=8.8 Hz, C_9-H of coumarin), 8.65 (d, 1H, *J*=9.2 Hz, C_5-H of coumarin); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 35.14(C_4-CH of DHP), 52.74, 53.15(OCH_3 of ester), 56.54(OCH_3 of ester), 100.39, 102.84, 113.38, 114.63, 117.45(CN), 120.87, 121.61, 122.34, 122.92, 127.11, 129.28, 130.72, 133.77, 135.22, 138.45, 140.78, 141.21, 151.09, 152.51, 154.77, 158.45, 160.37, 162.87(CO of coumarin), 163.62(CO of ester), 164.94(CO of ester); Anal. Calc. for $C_{29}H_{21}N_3O_6$: C, 68.63; H, 4.17; N, 8.28. Found: C, 68.69; H, 4.15; N, 8.30. GC-MS (*m/z*):507 (M^+).

3.4.5. **Dimethyl 6-amino-5-cyano-1-(3,4-dimethylphenyl)-4-(2-oxo-2H-benzo[h]chromen-4-yl)-1,4-dihydropyridine-2,3-dicarboxylate (6n)**

The compound **6n** obtained from 2-oxo-2H-benzo[h]chromene-4-carbaldehyde (1.0mmol), DMAD (1.0mmol), malononitrile (1.0mmol), 3,4-dimethylamine (1.0mmol). Gray solid; Yield: 74%; mp: 247-249 °C; IR (KBr): 3428, 3338, 2260, 1755 and 1728 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.38(s, 3H, C_3-CH_3 of phenyl ring), 2.49(s, 3H, C_4-CH_3 of phenyl ring), 3.53(s, 3H, -OCH_3 of ester), 3.54(s, 3H, -OCH_3 of ester), 5.28(s, 1H, CH of dihydropyridine), 5.49 (s, 2H, NH_2), 6.36(s, 1H, C_3-H of coumarin), 6.65(d, 1H, *J*=8Hz,Ar-H), 6.97(d, 1H, *J* = 8Hz, Ar-H), 7.12(t, 2H, Ar-H), 7.72-7.30(m, 3H, Ar-H), 7.38(s, 1H,Ar-H), 7.96(d. 1H, *J*=8 Hz, Ar-H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 19.12(C_3- CH3 of phenyl), 19.84(C_4- CH3 of phenyl), 35.17(C_4-CH of DHP), 53.3(OCH_3 of ester), 54.17(OCH_3 of ester), 57.22, 100.42, 111.01, 113.44, 115.00, 117.26(CN), 120.54, 122.67, 123.49, 124.93, 128.11, 128.75, 130.57, 131.84, 136.27, 139.19, 141.97, 144.58, 150.39, 154.69, 156.12, 159.01, 161.21, 161.94(CO of

coumarin), 162.17(CO of ester), 164.94(CO of ester); Anal. Calc. for $C_{31}H_{25}N_3O_6$: C, 69.52; H, 4.71; N, 7.85. Found: C, 69.56; H, 4.67; N, 7.87. GC-MS (*m/z*):535 (M^+).

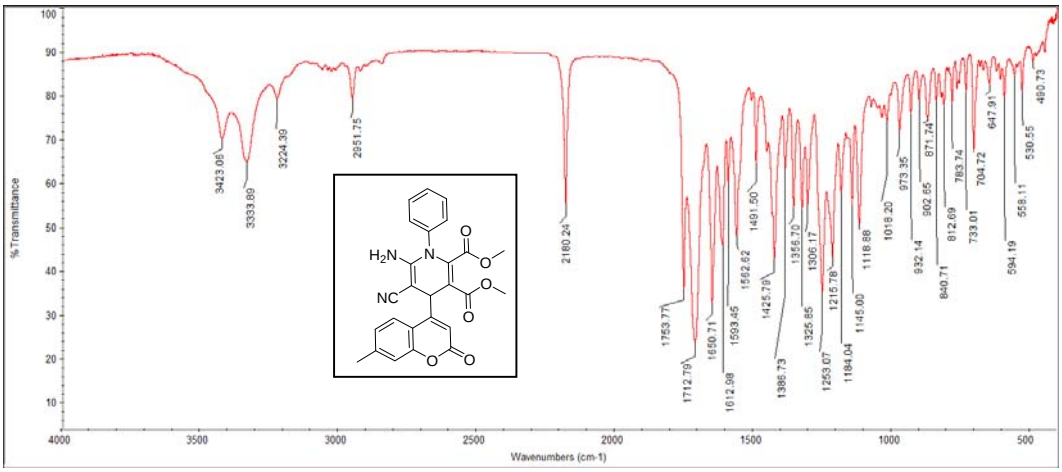
3.4.6. **Dimethyl 6-amino-1-(4-chlorophenyl)-5-cyano-4-(2-oxo-2H-benzo[h]chromen-4-yl)-1,4-dihydropyridine-2,3-dicarboxylate (6o)**

The compound **6o** obtained from 2-oxo-2H-benzo[h]chromene-4-carbaldehyde (1.0 mmol), DMAD (1.0 mmol), malononitrile (1.0 mmol), 4-chloroaniline (1.0 mmol). Gray solid; Yield: 75%; mp: 247-249 °C; IR (KBr): 3439, 3320, 2232, 1743 and 1722cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 3.37(s, 3H, -OCH_3 of ester), 3.45(s, 3H, -OCH_3 of ester), 5.18(s, 1H, CH of dihydropyridine), 5.42(s, 2H, NH_2), 6.37(s, 1H, C_3-H of coumarin), 6.91(d, 1H, *J*=8.0 Hz,Ar-H), 7.32(d, 1H,*J* = 8.0 Hz, Ar-H), 7.41(d, 1H, *J*=4.0 Hz,Ar-H), 7.48(d, 1H, *J*=8 Hz, Ar-H), 7.56(d, 3H,*J* = 12Hz, Ar-H), 7.78 (m, 2H, Ar-H) 8.29(d,1H, *J*=8.0 Hz, Ar-H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 35.07(C_4-CH of DHP), 53.38(OCH_3 of ester), 54.12(OCH_3 of ester), 56.47, 101.01, 111.80, 113.25, 116.00, 116.76(CN), 119.37, 122.16, 125.17, 125.84, 126.46, 127.35, 130.49, 133.17, 135.27, 139.23, 141.78, 142.48, 152.07, 155.89, 157.45, 159.46, 160.11, 161.83(CO of coumarin), 162.54(CO of ester), 164.92(CO of ester); Anal. Calc. for $C_{29}H_{20}ClN_3O_6$: C, 64.27; H, 3.72; N, 7.75. Found: C, 64.31; H, 3.70; N, 7.76. GC-MS (*m/*z):541 (M+).

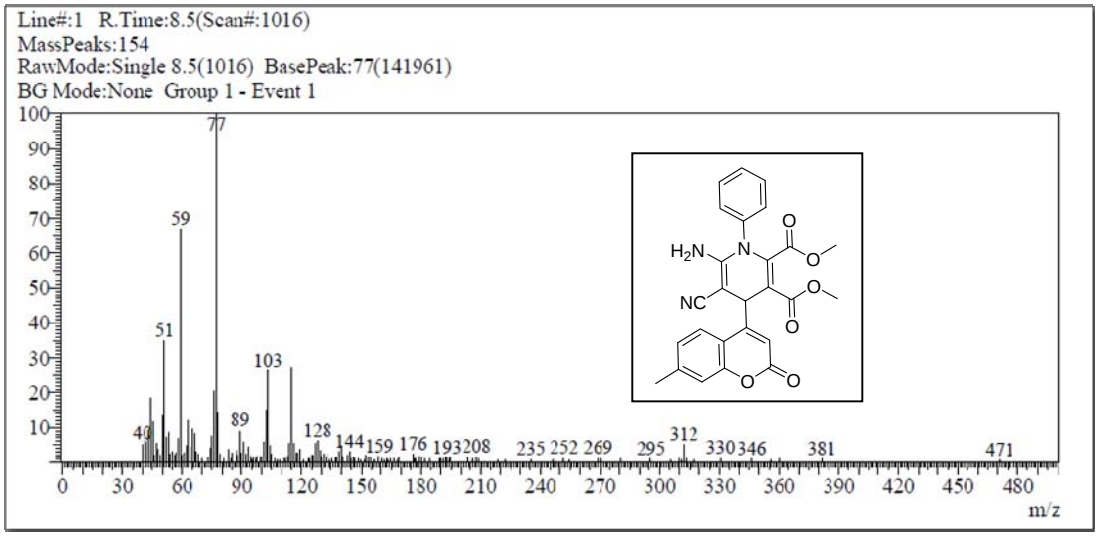
TRUSPEC

Name	Mass	Method	Analysis Date	Carbon %	Hydrogen %	Nitrogen %
6a	0.0404	ASTM	27/ 09 / 2019 10:48:53 AM	66.27	4.47	8.91
6b	0.0421	ASTM	27 / 09 / 2019 11:10:21 AM	67.36	5.02	8.44
6c	0.0342	ASTM	27 / 09 / 2019 11:20:49 AM	61.78	3.96	8.36
6d	0.0413	ASTM	27 / 09 / 2019 11:25:55 AM	66.26	4.48	8.96
6e	0.0452	ASTM	27 / 09 / 2019 12:30:23 PM	67.35	5.06	8.46
6f	0.0435	ASTM	30 / 09 / 2019 11:27:39 AM	61.75	3.96	8.35
6g	0.0324	ASTM	30 / 09 / 2019 11:35:42 AM	62.69	4.45	8.16
6h	0.0391	ASTM	30 / 09 / 2019 11:52:48 AM	65.28	4.85	8.19
6i	0.0418	ASTM	01 / 10 / 2019 12:06:32 PM	59.86	3.85	8.09
6j	0.0428	ASTM	01 / 10 / 2019 12:17:55 PM	68.68	4.15	8.31
6k	0.0426	ASTM	03 / 10 / 2019 11:24:48 AM	69.58	4.65	7.87
6l	0.0431	ASTM	03 / 10 / 2019 12:08:35 PM	64.30	3.70	7.79
6m	0.0425	ASTM	04 / 10 / 2019 12:15:54 PM	68.69	4.15	8.30
6n	0.0409	ASTM	04 / 10 / 2019 12:18:41 PM	69.56	4.67	7.87
6o	0.0422	ASTM	04 / 10 / 2019 12:24:47 PM	64.31	3.70	7.76

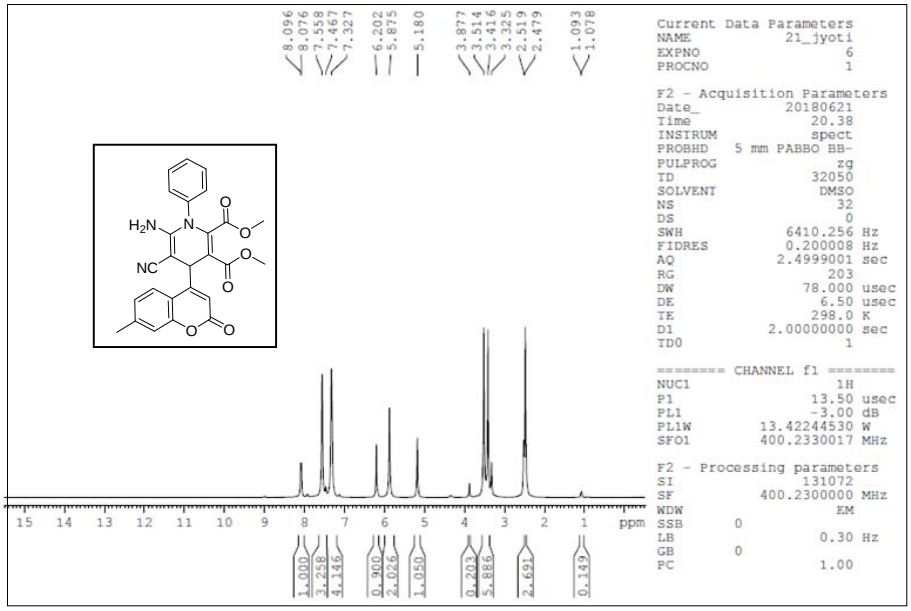
Figure –S3: CHN Analysis of compounds **6a-6o**



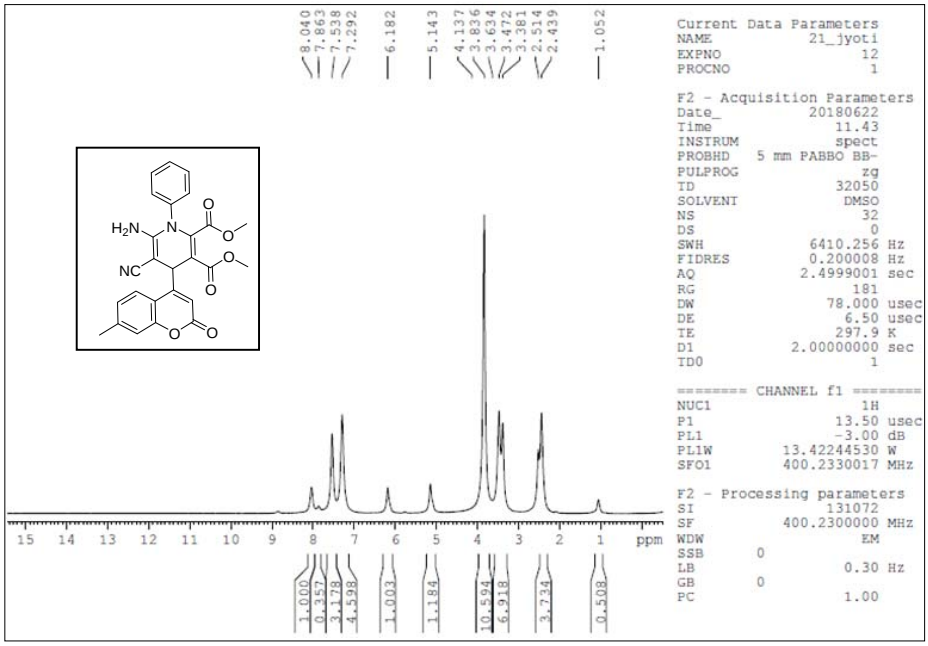
Spectrum No. 1: IR of compound **6a**



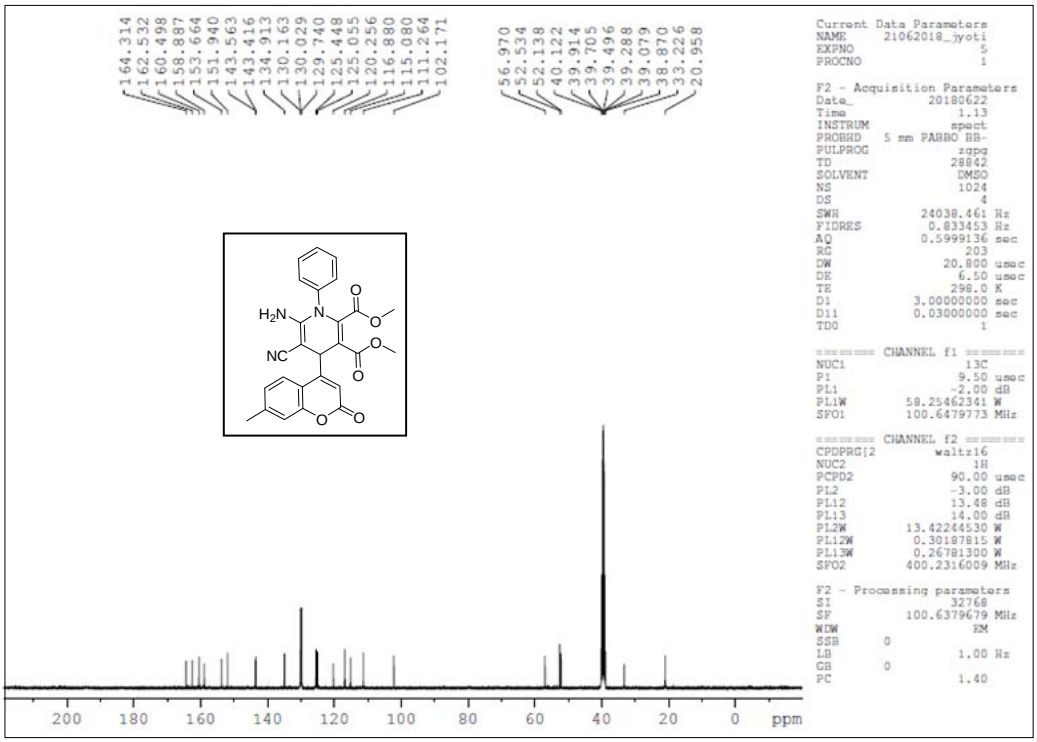
Spectrum No. 2: GCMS of compound **6a**



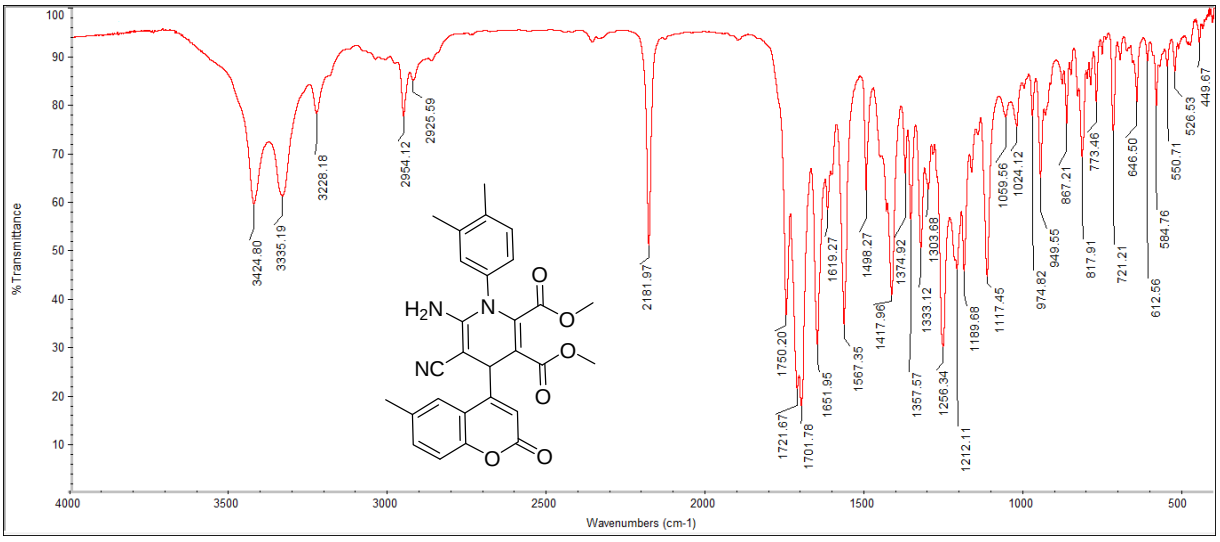
Spectrum No. 3: ^{1}H-NMR of compound **6a**



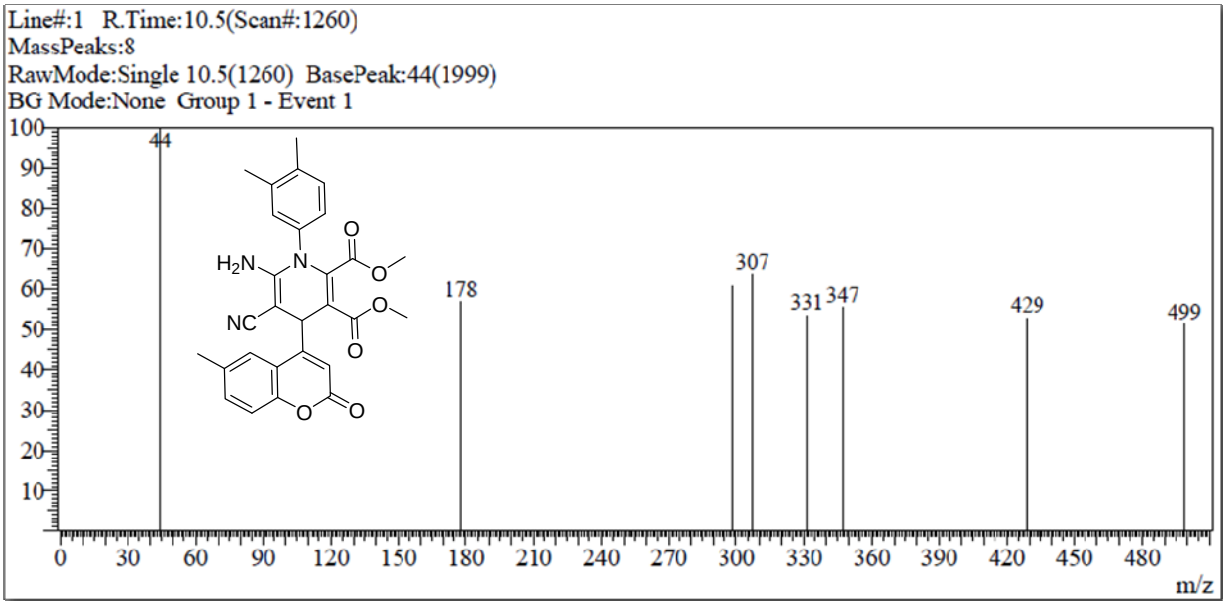
Spectrum No. 4: D_2O spectrum exchange of compound **6a** in DMSO-d_6



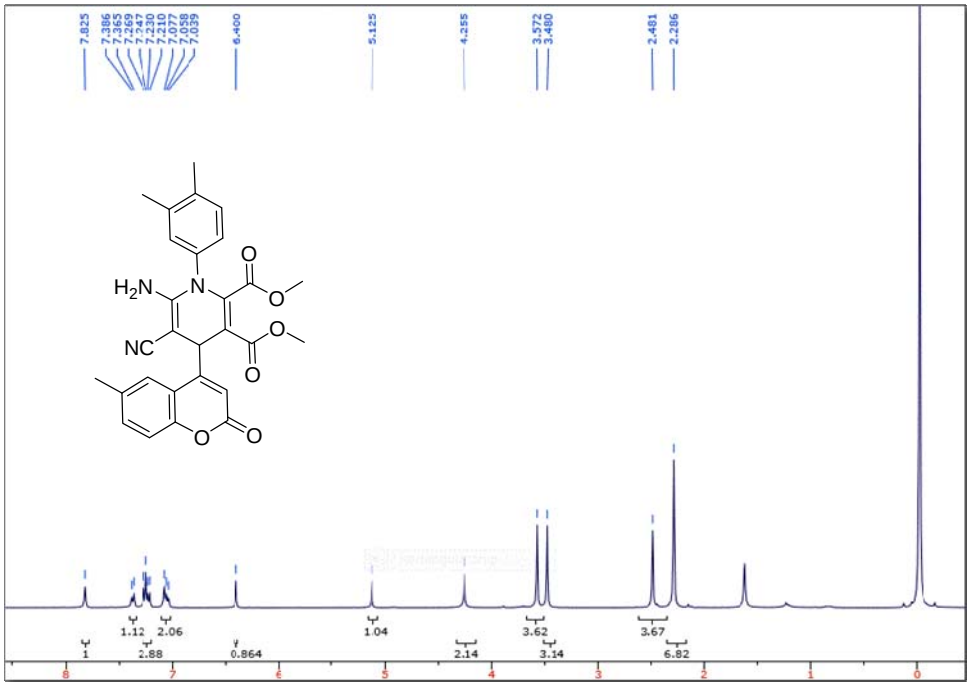
Spectrum No. 5: ^{13}C-NMR of compound **6a**



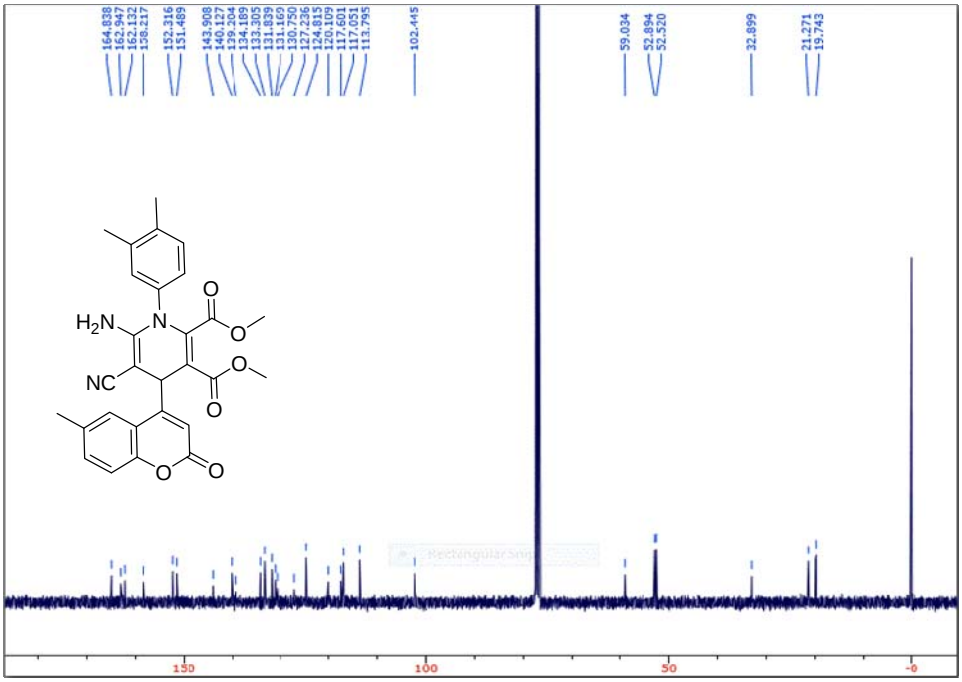
Spectrum No. 6: IR of compound **6b**



Spectrum No. 7: GCMS of compound **6b**

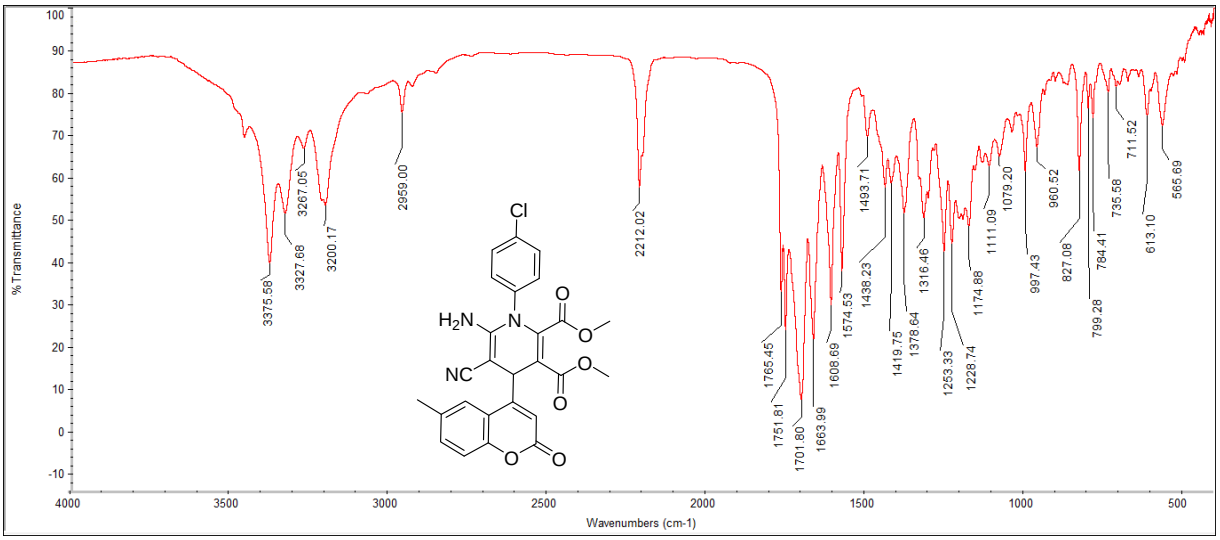


Spectrum No. 8: ^{1}H-NMR of compound **6b**

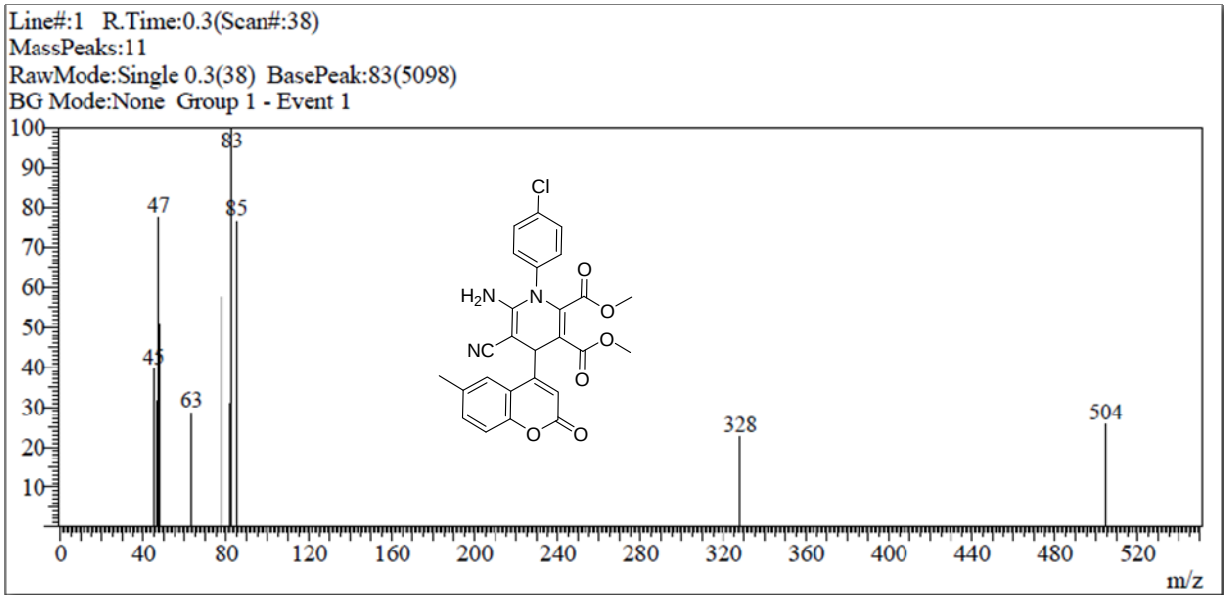


Spectrum No. 9: ^{13}C-NMR of compound **6b**

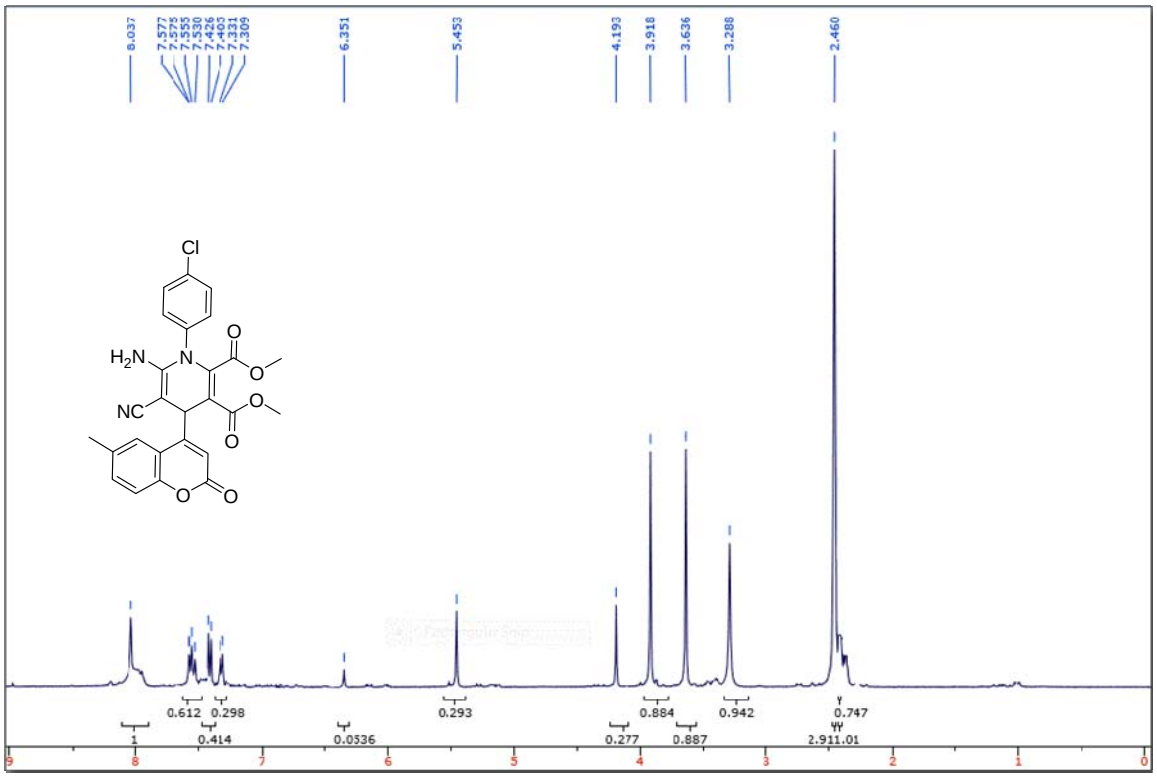
Dimethyl 6-amino-1-(4-chlorophenyl)-5-cyano-4-(6-methyl-2-oxo-2H-chromen-4-yl)-1,4-dihydropyridine-2,3-dicarboxylate (6c)



Spectrum No. 10: IR of compound **6c**

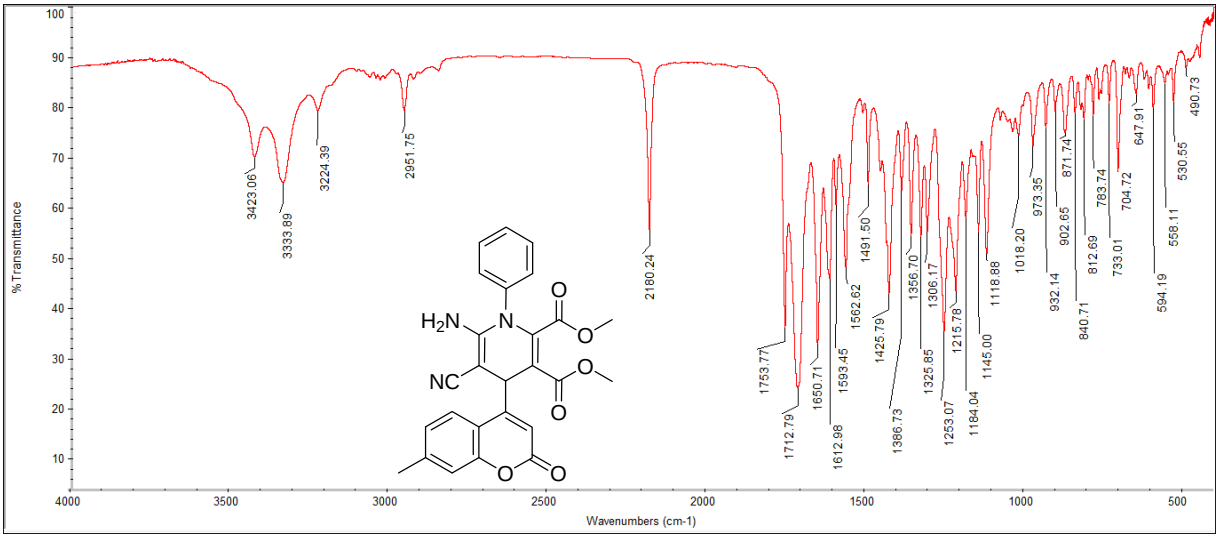


Spectrum No. 11: GCMS of compound **6c**

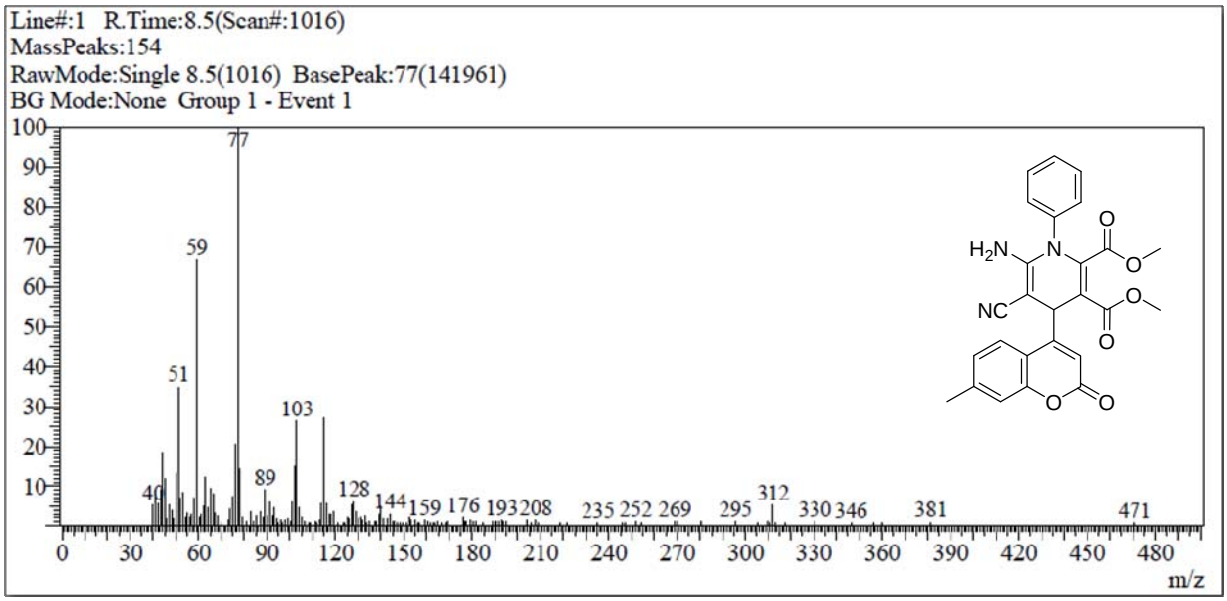


Spectrum No. 12: ^{1}H-NMR of compound **6c**

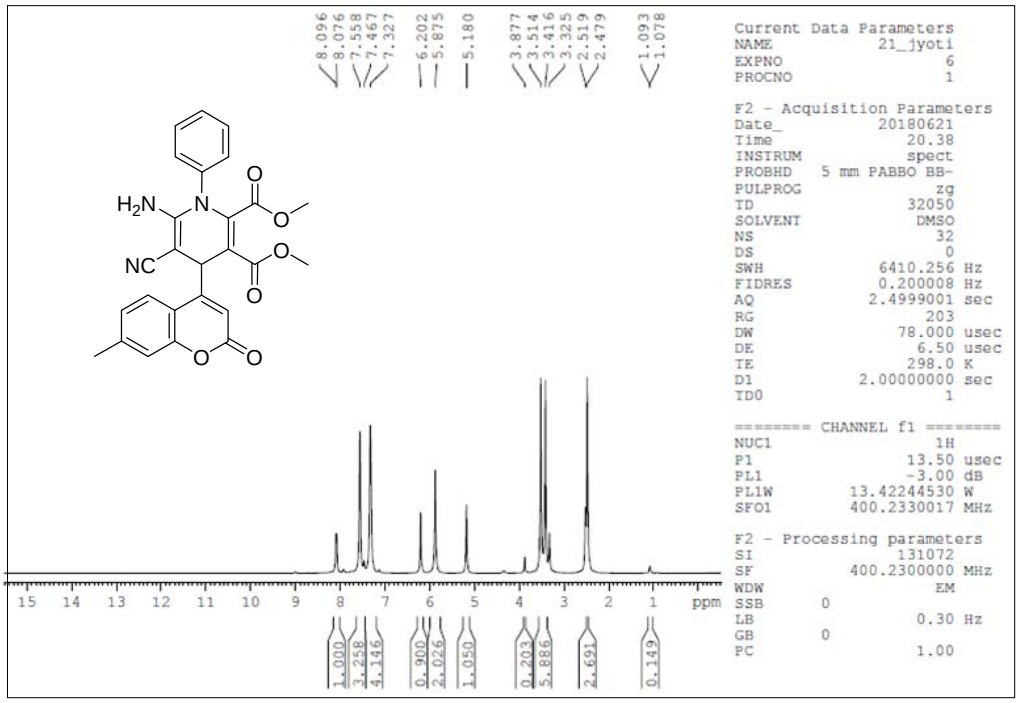
Dimethyl 6-amino-5-cyano-4-(7-methyl-2-oxo-2H-chromen-4-yl)-1-phenyl-1,4-dihydropyridine-2,3-dicarboxylate (6d)



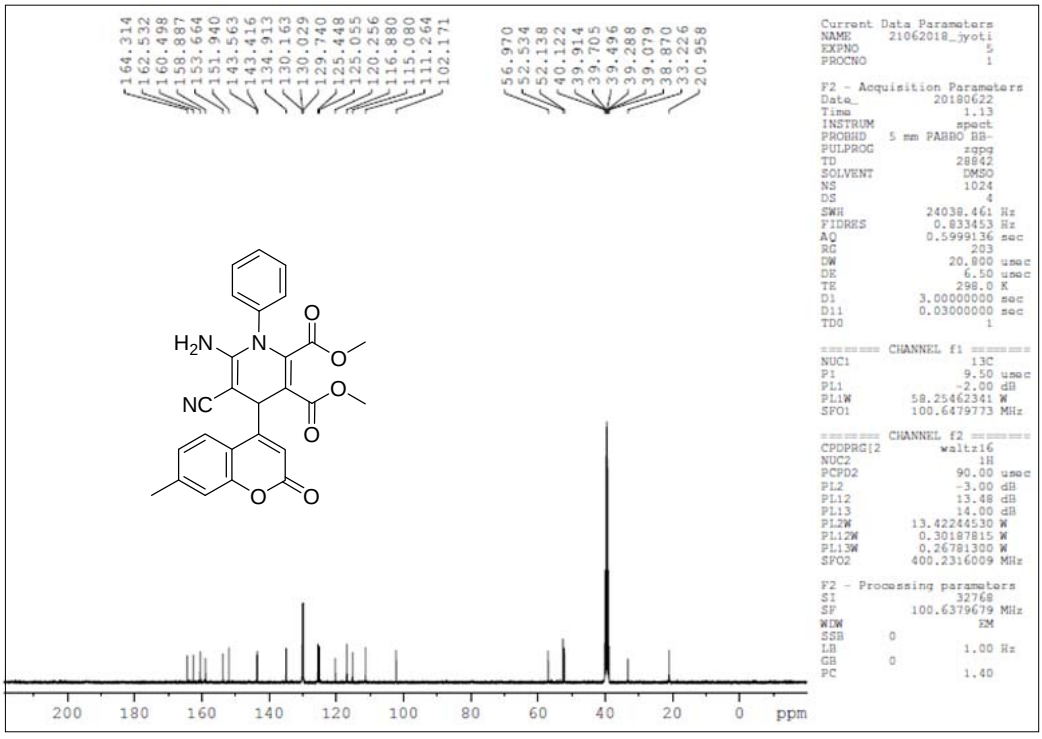
Spectrum No. 13: IR of compound **6d**



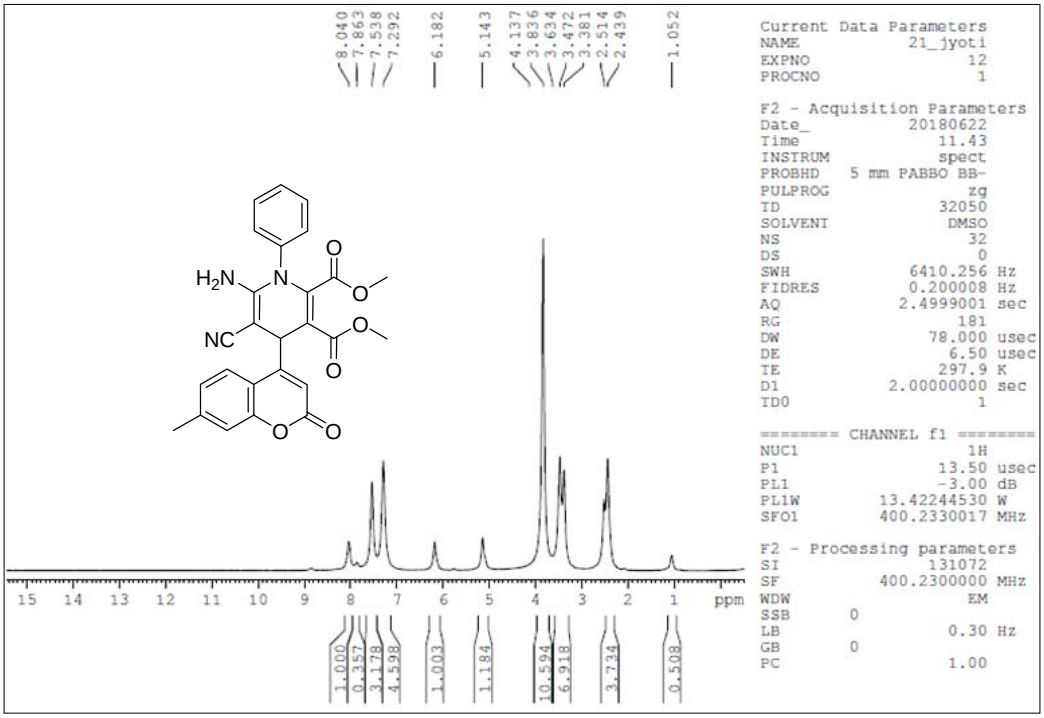
Spectrum No. 14: GCMS of compound **6d**



Spectrum No. 15: ^{1}H-NMR of compound **6d**

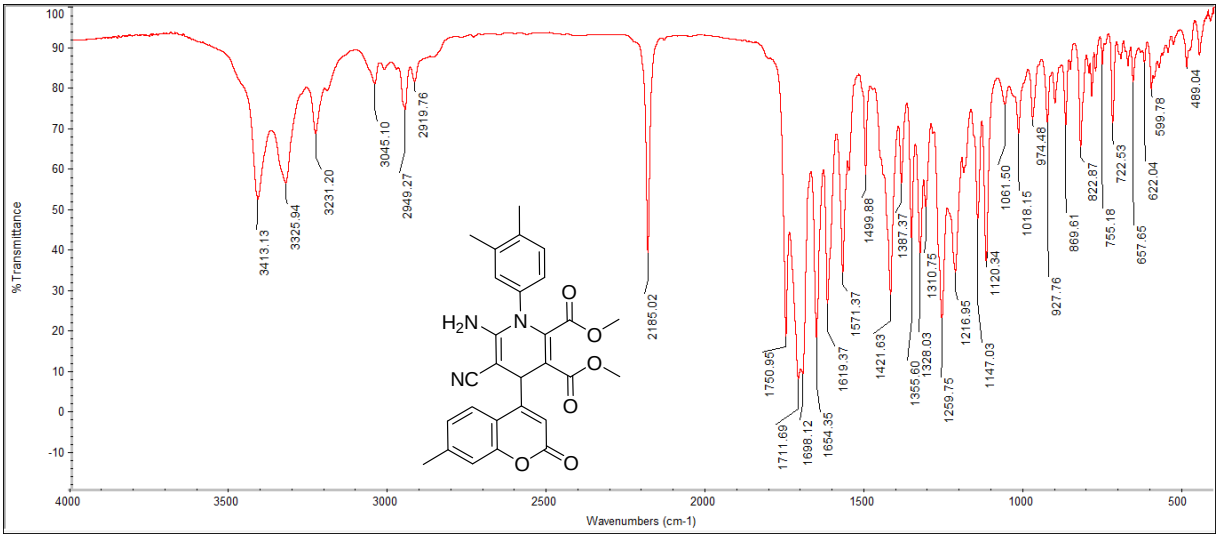


Spectrum No. 16: ^{13}C-NMR of compound **6d**

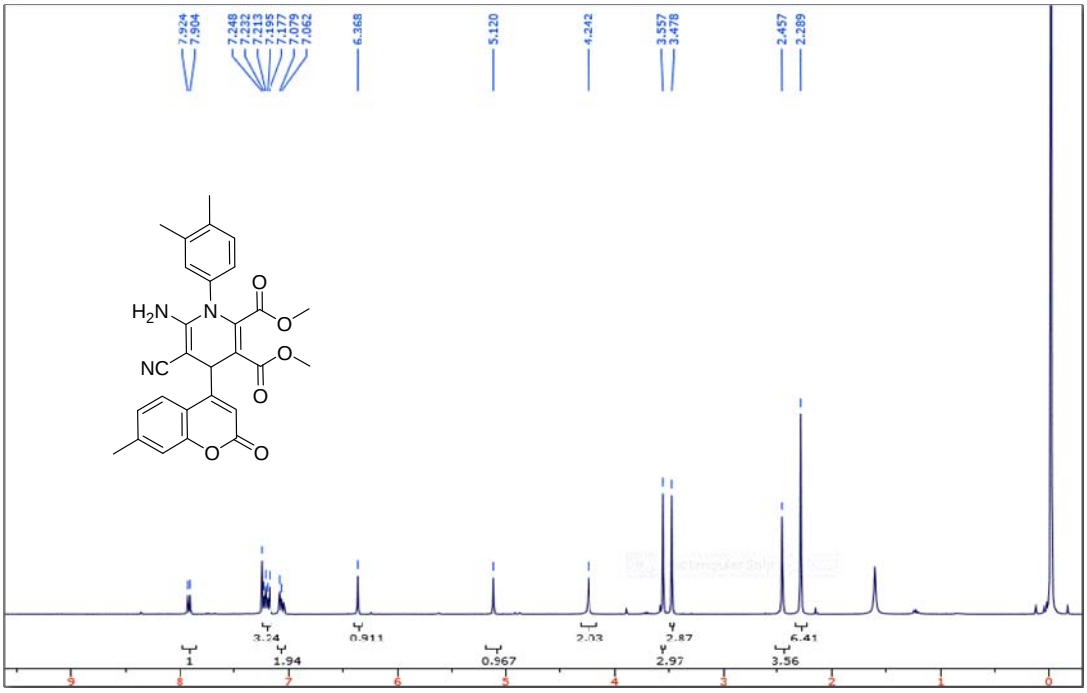


Spectrum No. 17: D_2O exchange of compound **6d**

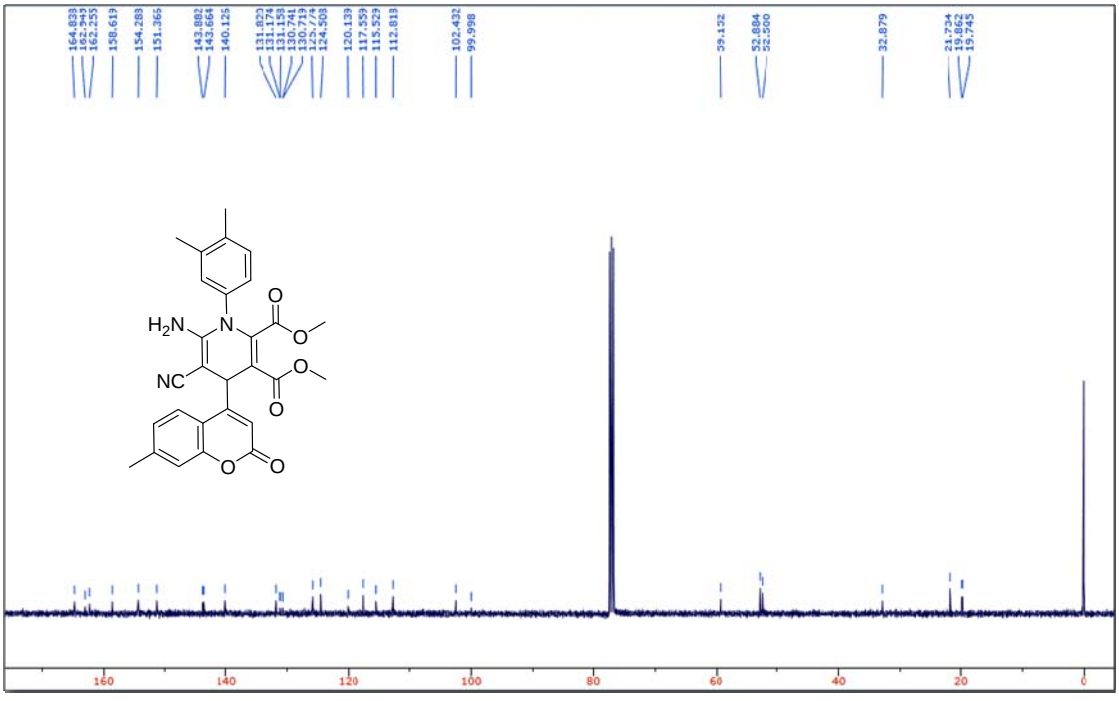
Dimethyl 6-amino-5-cyano-1-(3,4-dimethylphenyl)-4-(7-methyl-2-oxo-2H-chromen-4-yl)-1,4-dihydropyridine-2,3-dicarboxylate (6e)



Spectrum No. 18: IR of compound **6e**

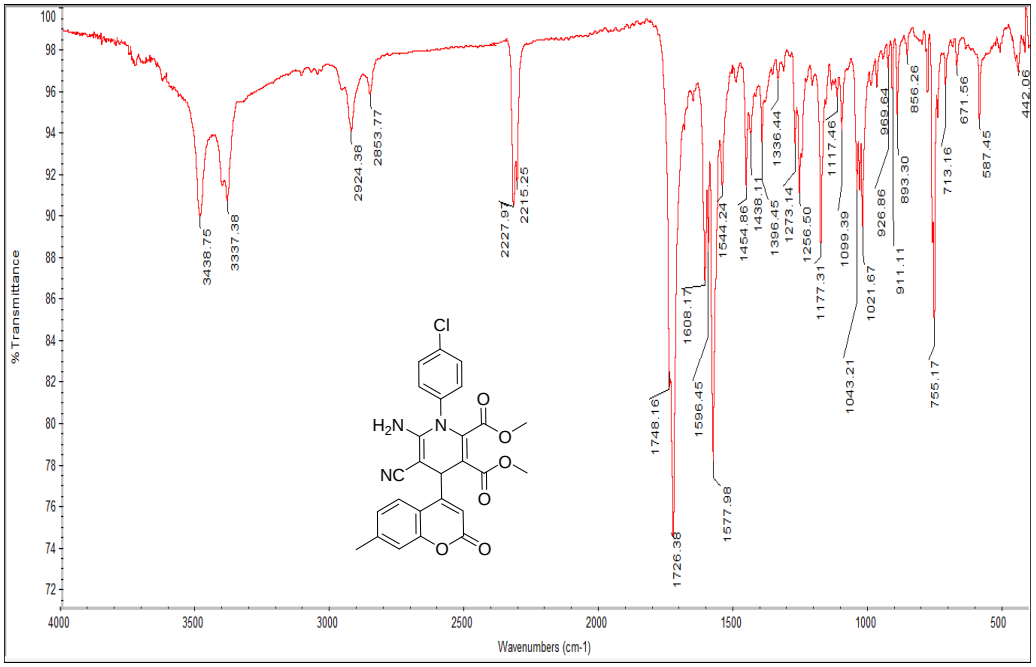


Spectrum No. 19: ^{1}H-NMR of compound **6e**

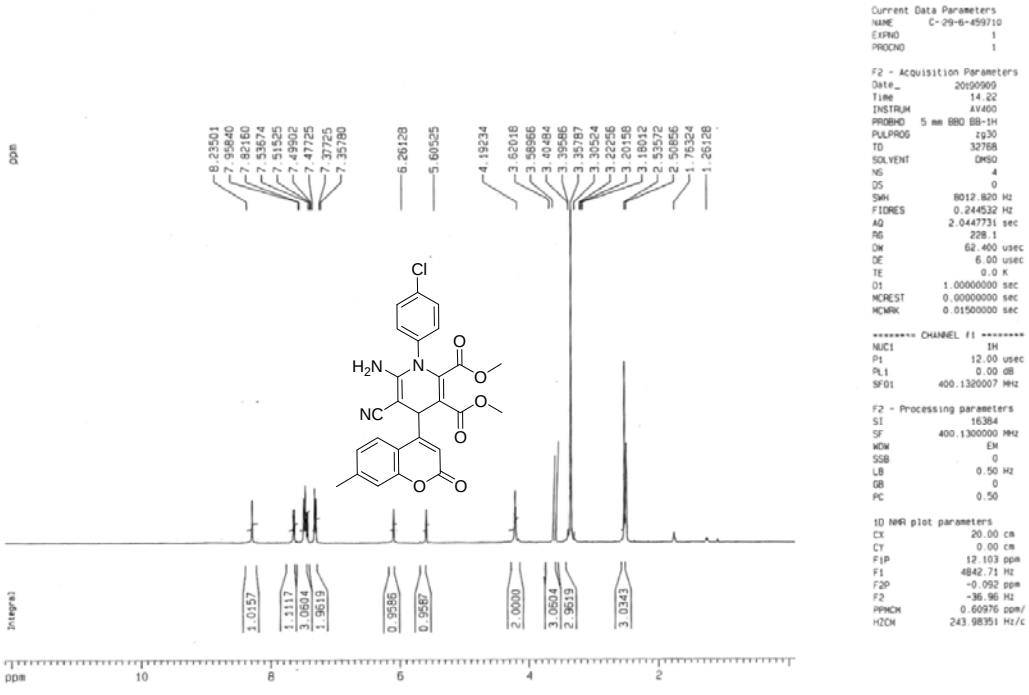


Spectrum No. 20: ^{13}C-NMR of compound **6e**

Dimethyl-6-amino-1-(4-chlorophenyl)-5-cyano-4-(7-methyl-2-oxo-2H-chromen-4-yl)-1,4-dihydropyridine-2,3-dicarboxylate (6f)



Spectrum No. 21: IR of compound **6f**

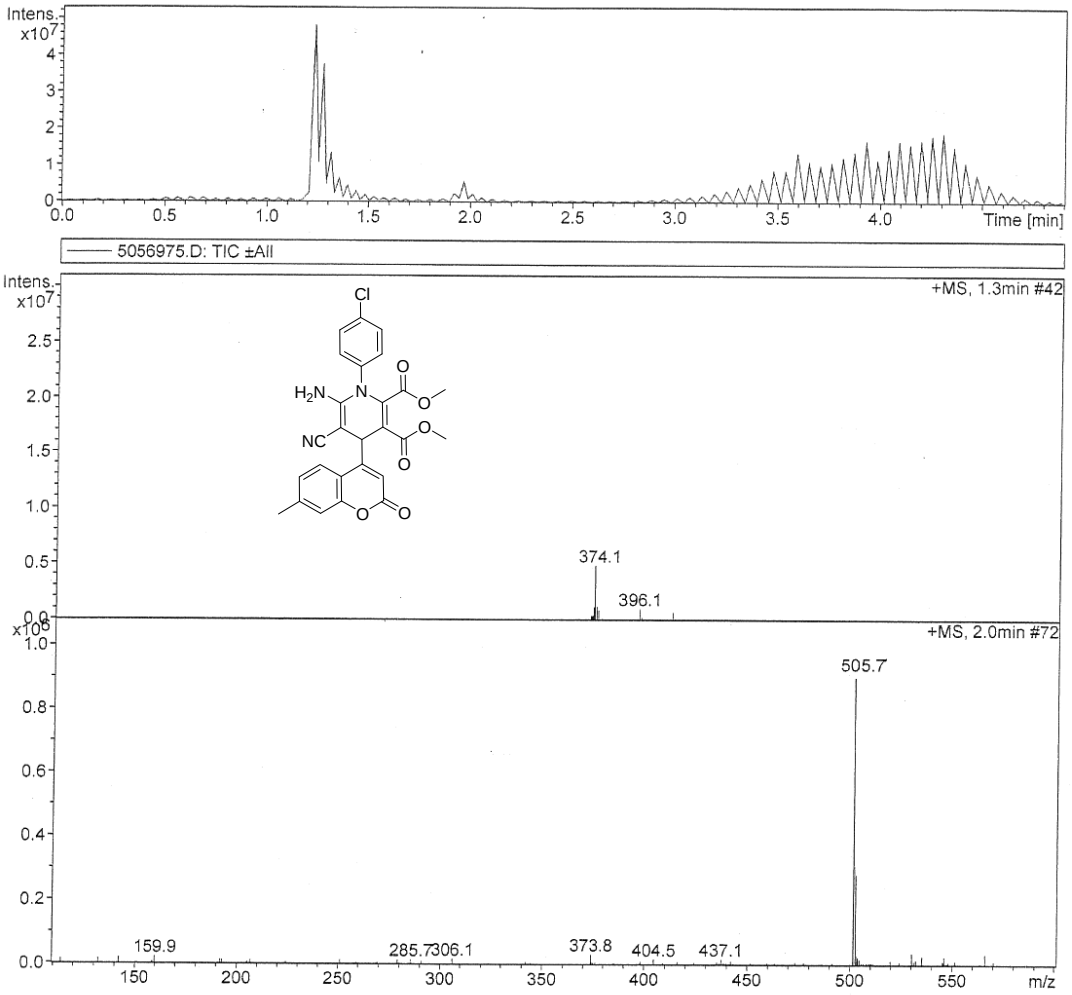


Spectrum No. 22: ^{1}H-NMR of compound **6f**

MASS REPORT

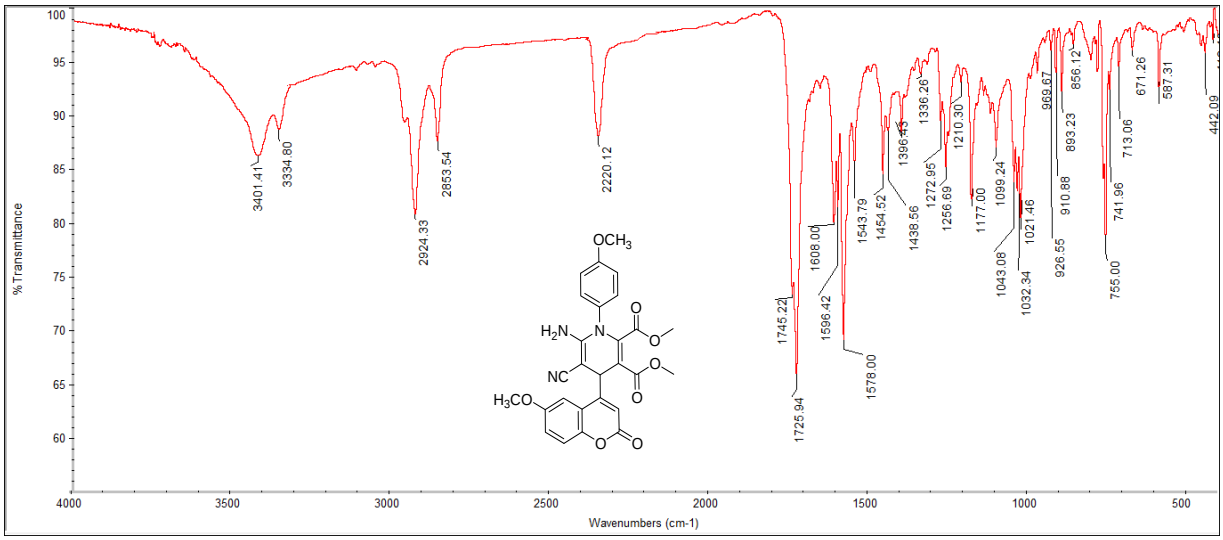
Data File : 5056975.D **Instrume** LC-MSD-Trap-XCT

Method: VYDACPOL.M **Sample Name:** C-12

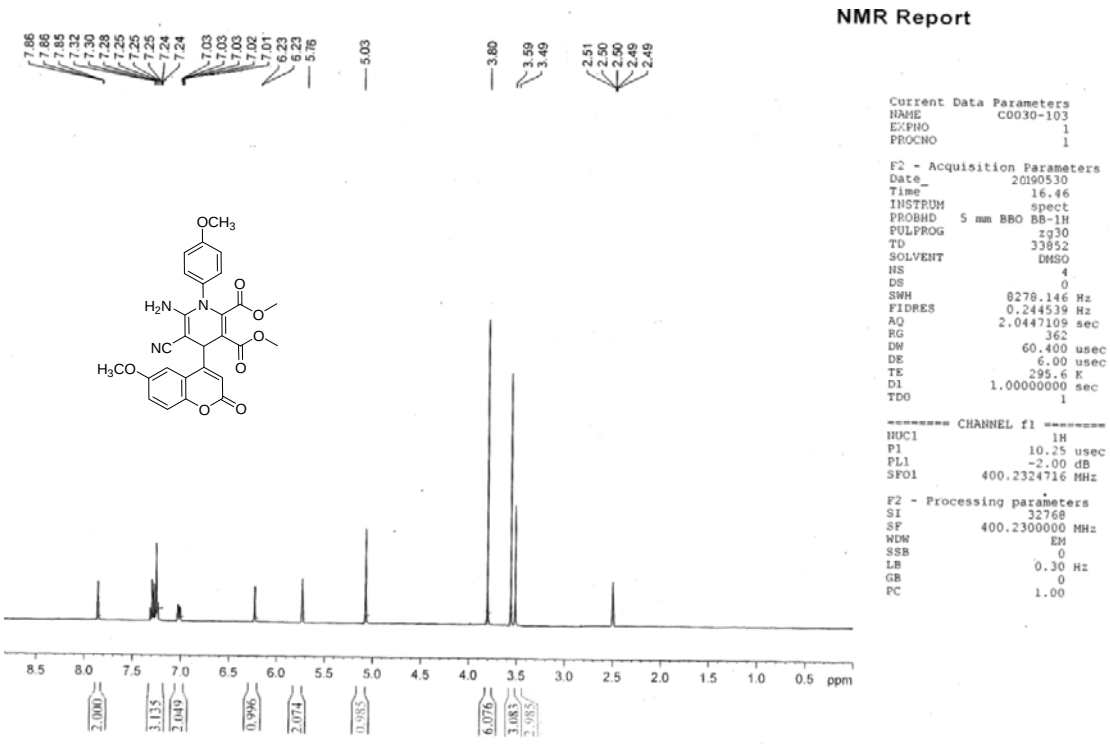


Spectrum No. 23: LCMS of compound **6f**

Dimethyl-6-amino-5-cyano-4-(6-methoxy-2-oxo-2H-chromen-4-yl)-1-(4-methoxyphenyl)-1,4-dihydropyridine-2,3-dicarboxylate (6g)



Spectrum No. 24: IR of compound **6g**

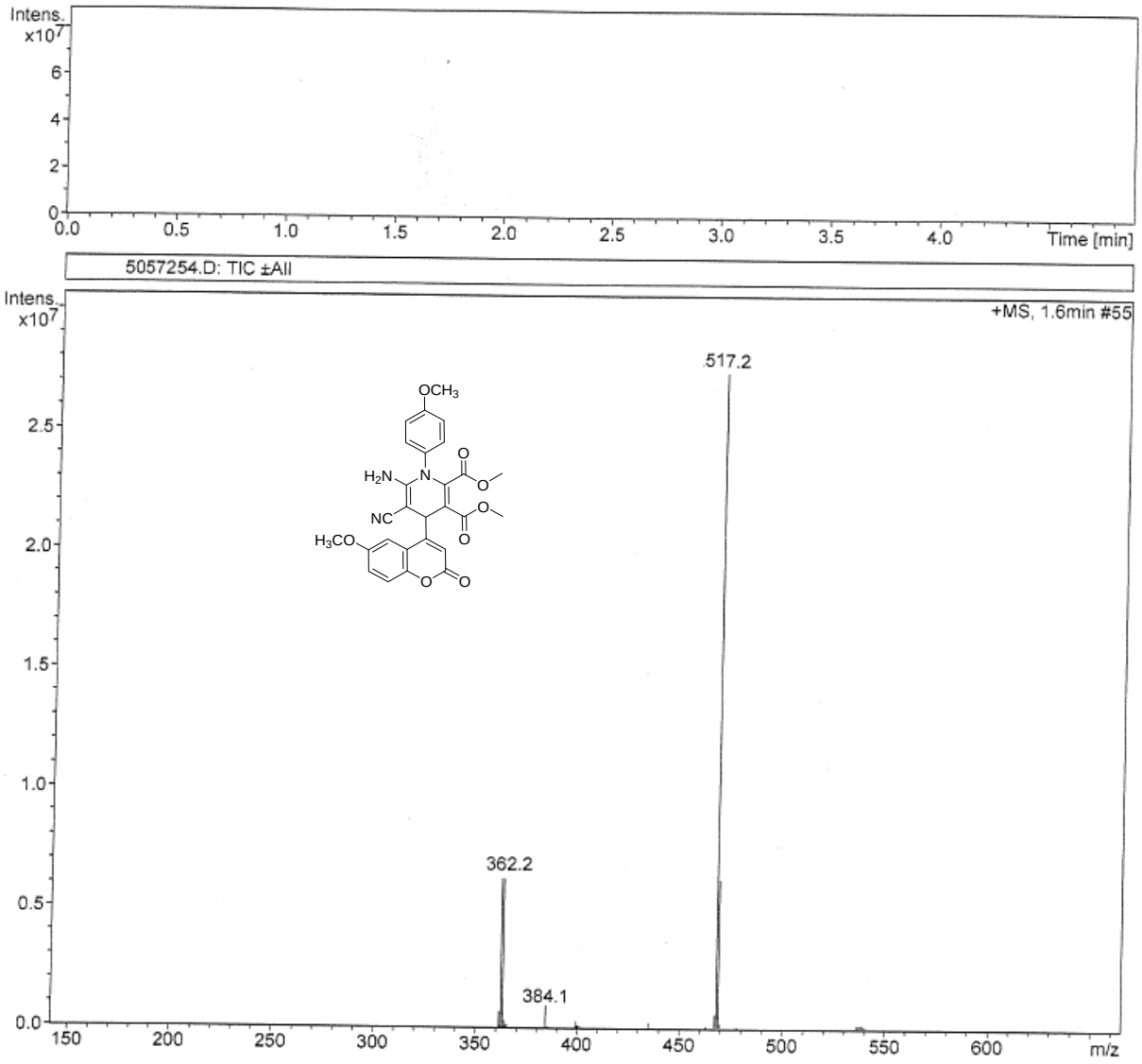


Spectrum No. 25: ^{1}H-NMR of compound **6g**

MASS REPORT

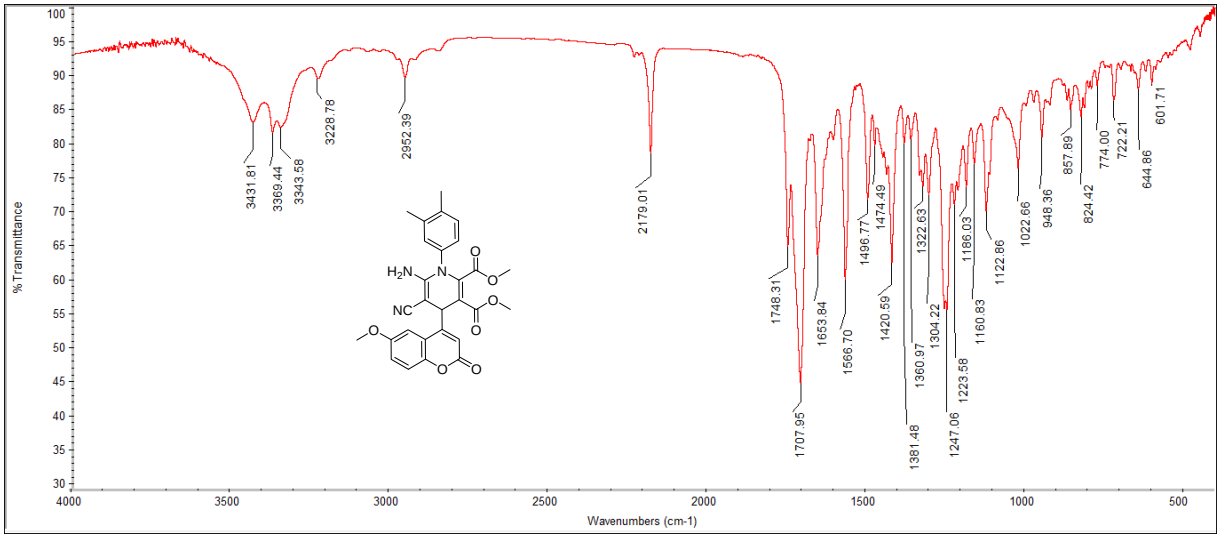
Data File : 5057254.D **Instrume** LC-MSD-Trap-XCT

Method: VYDACPOL.M **Sample Name:** C -15

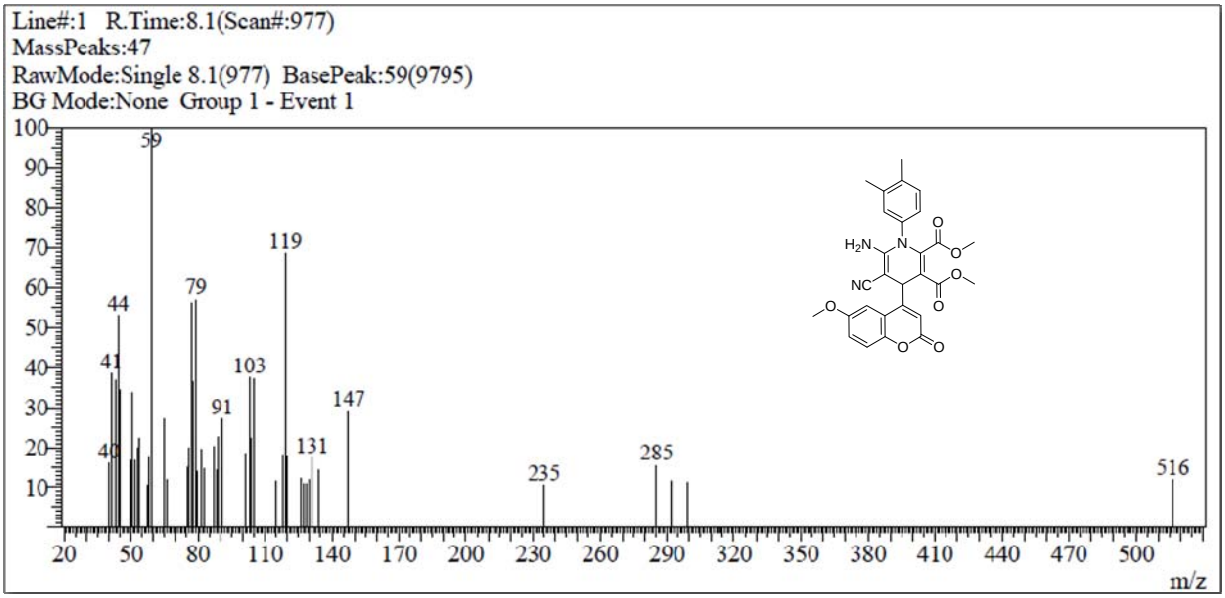


Spectrum No. 26: LCMS of compound **6g**

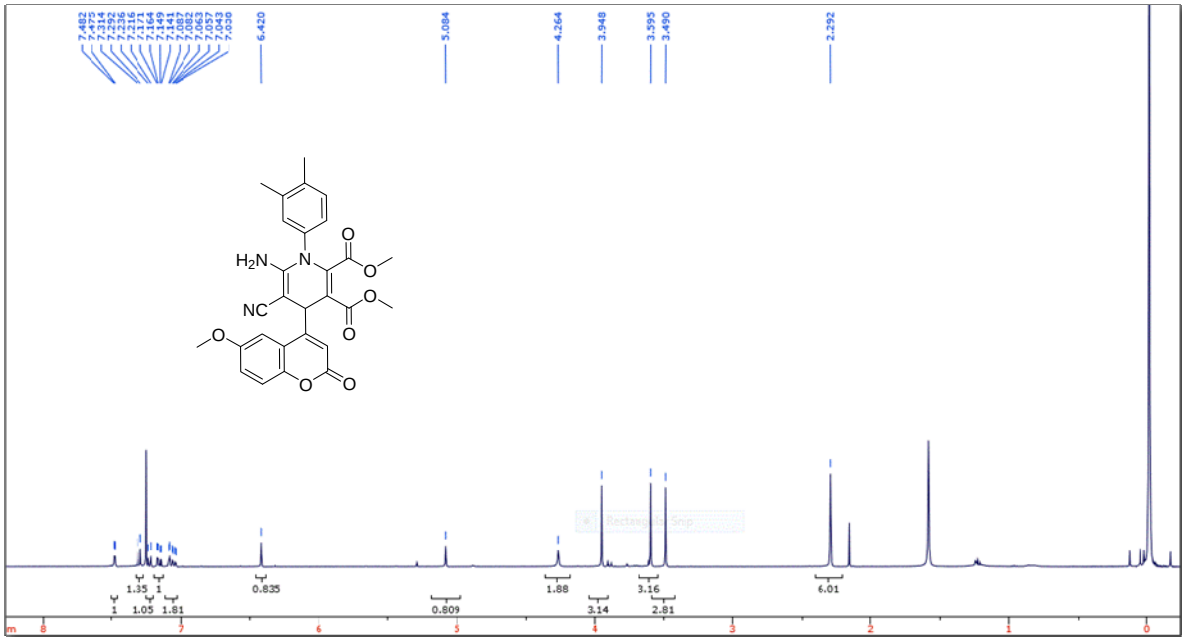
Dimethyl 6-amino-5-cyano-1-(3,4-dimethylphenyl)-4-(6-methoxy-2-oxo-2H-chromen-4-yl)-1,4-dihydropyridine-2,3-dicarboxylate (6h)



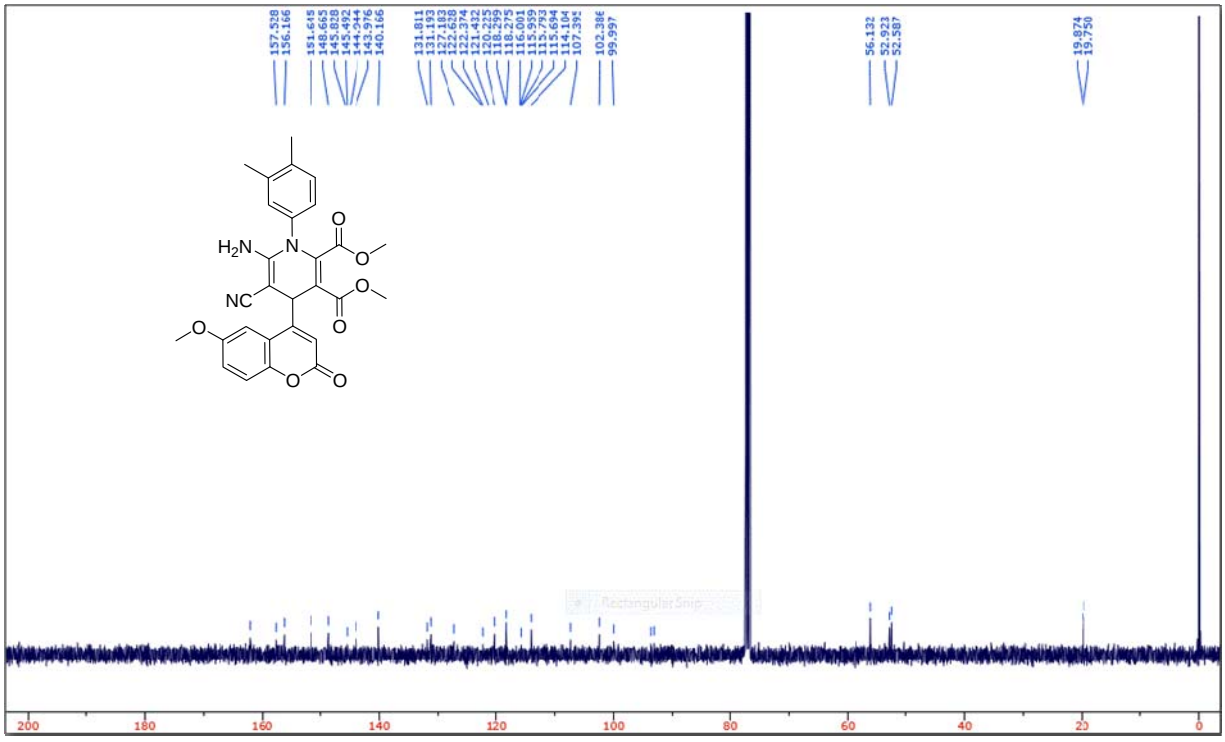
Spectrum No. 27: IR of compound **6h**



Spectrum No. 28: GCMS of compound **6h**

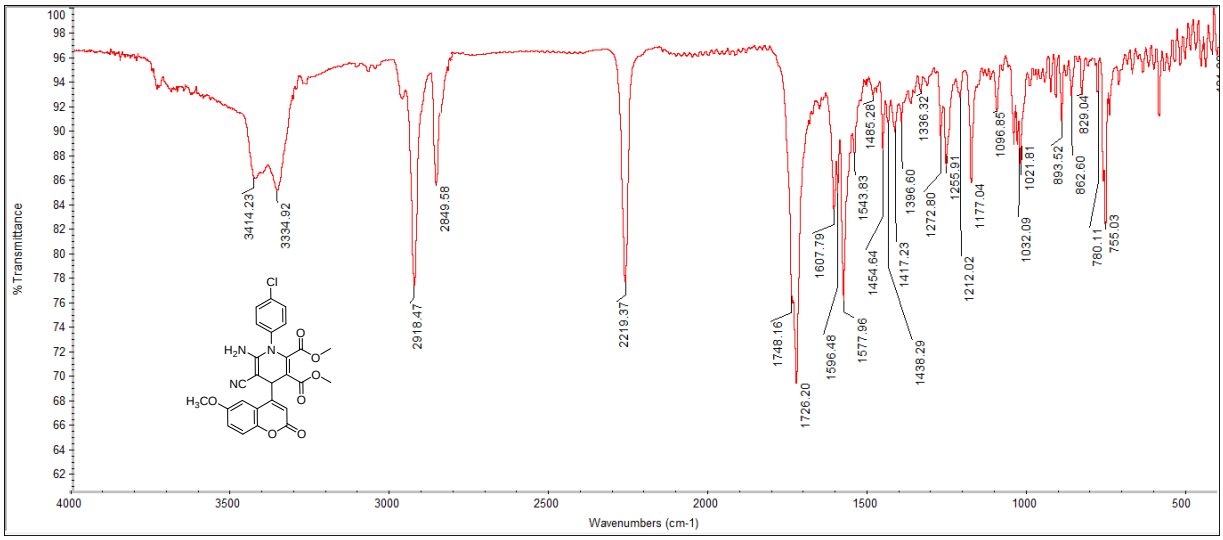


Spectrum No. 29: ^{1}H-NMR of compound **6h**

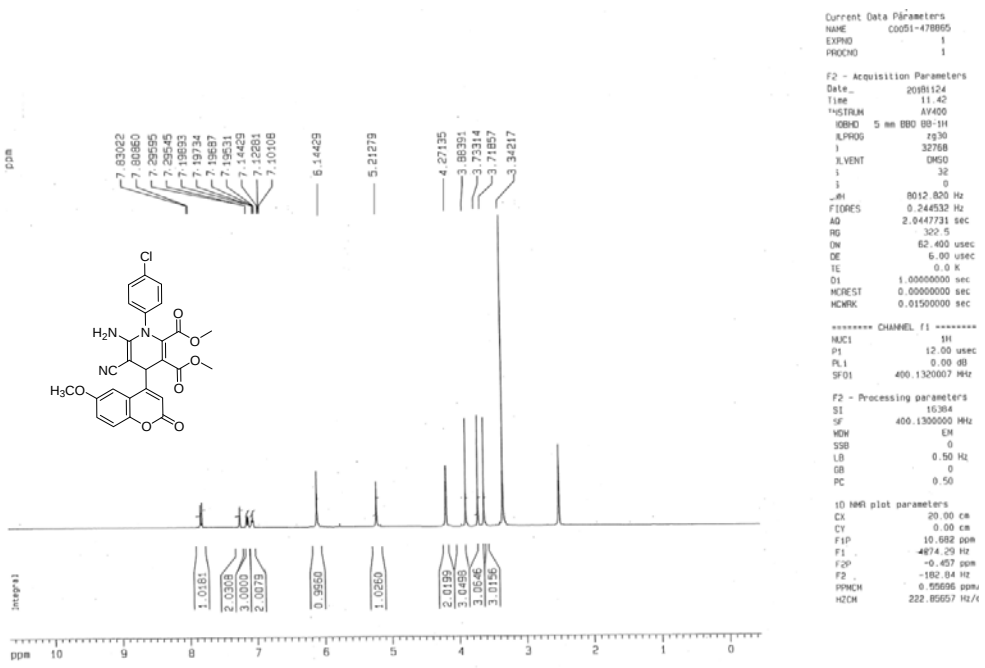


Spectrum No. 30: ^{13}C-NMR of compound **6h**

Dimethyl 6-amino-1-(4-chlorophenyl)-5-cyano-4-(6-methoxy-2-oxo-2H-chromen-4-yl)-1,4-dihydropyridine-2,3-dicarboxylate (6i)



Spectrum No. 31: IR of compound **6i**

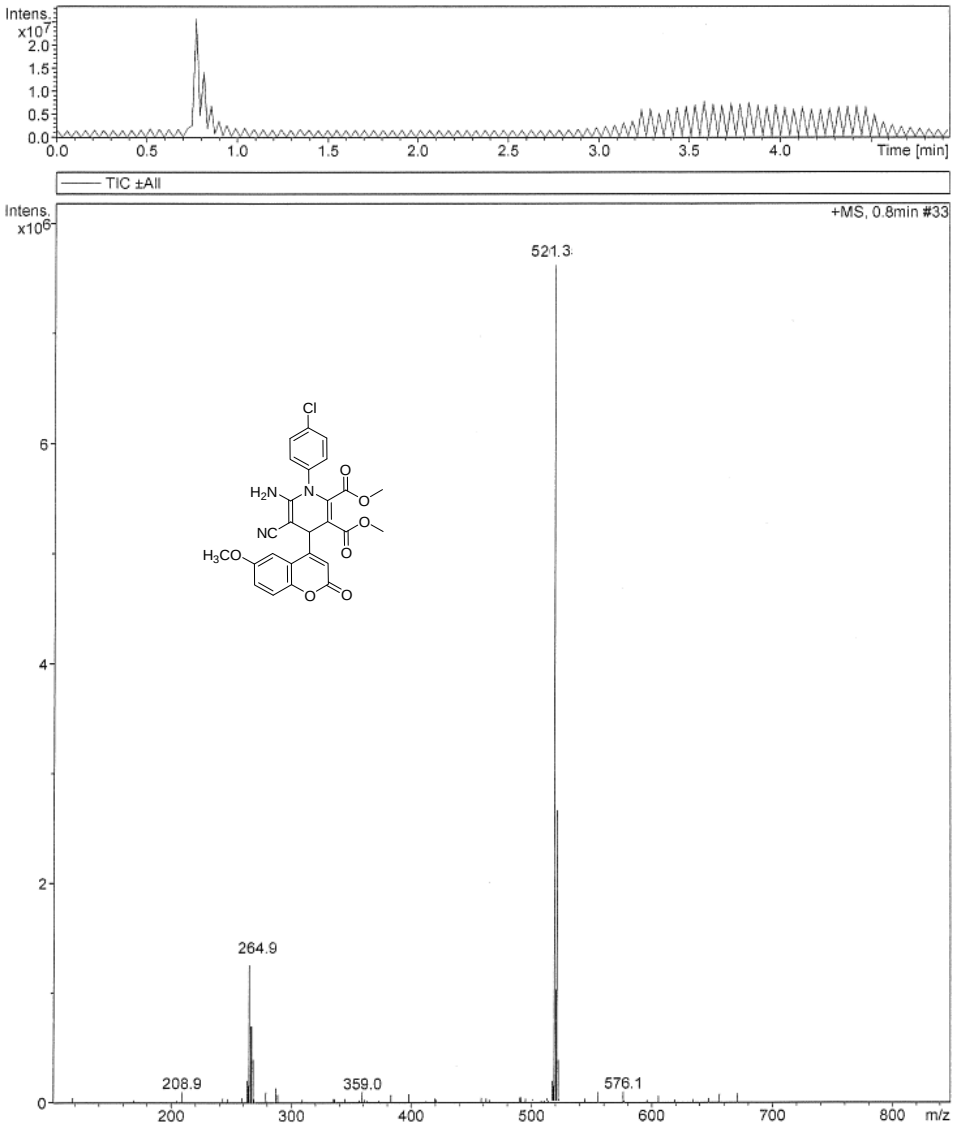


Spectrum No. 32: ^{1}H-NMR of compound **6i**

MASS REPORT

Data File: 5087192.D **Method:** VYDACPOL.M

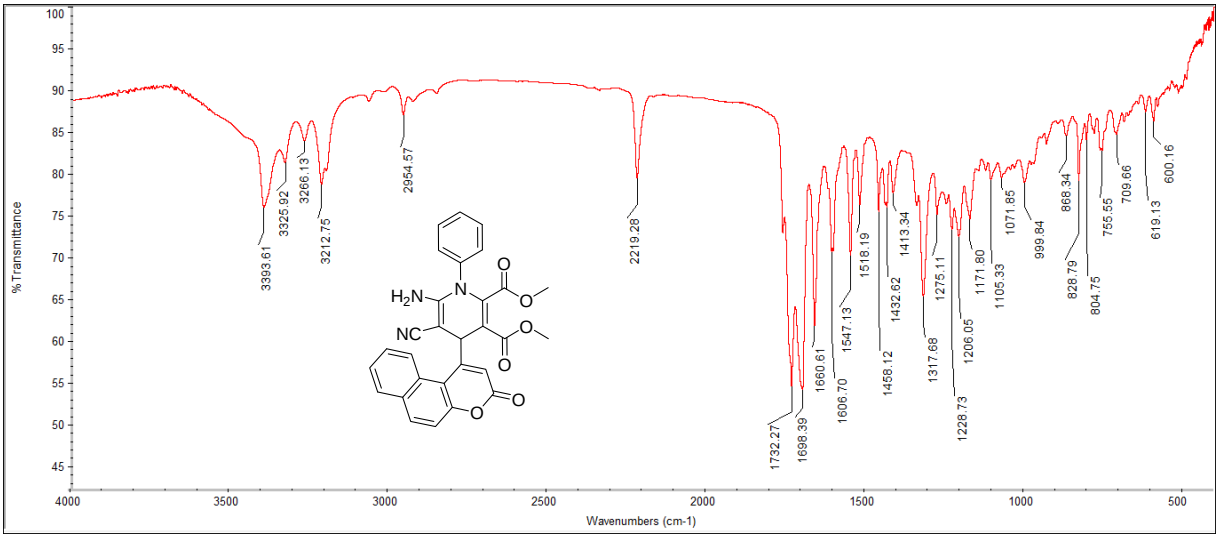
Sample Name: C -56 **Instrument :** LC-MSD-Trap-XCT



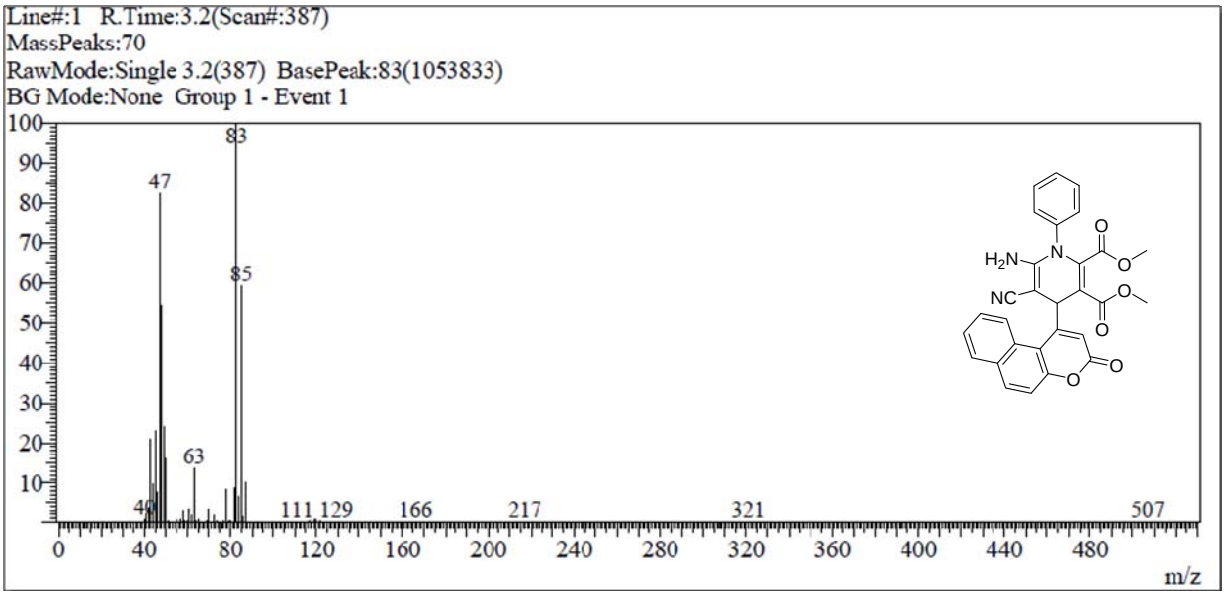
Analysed By Instrument Code : SC/AD/10-002

Spectrum No. 33: LCMS of compound **6i**

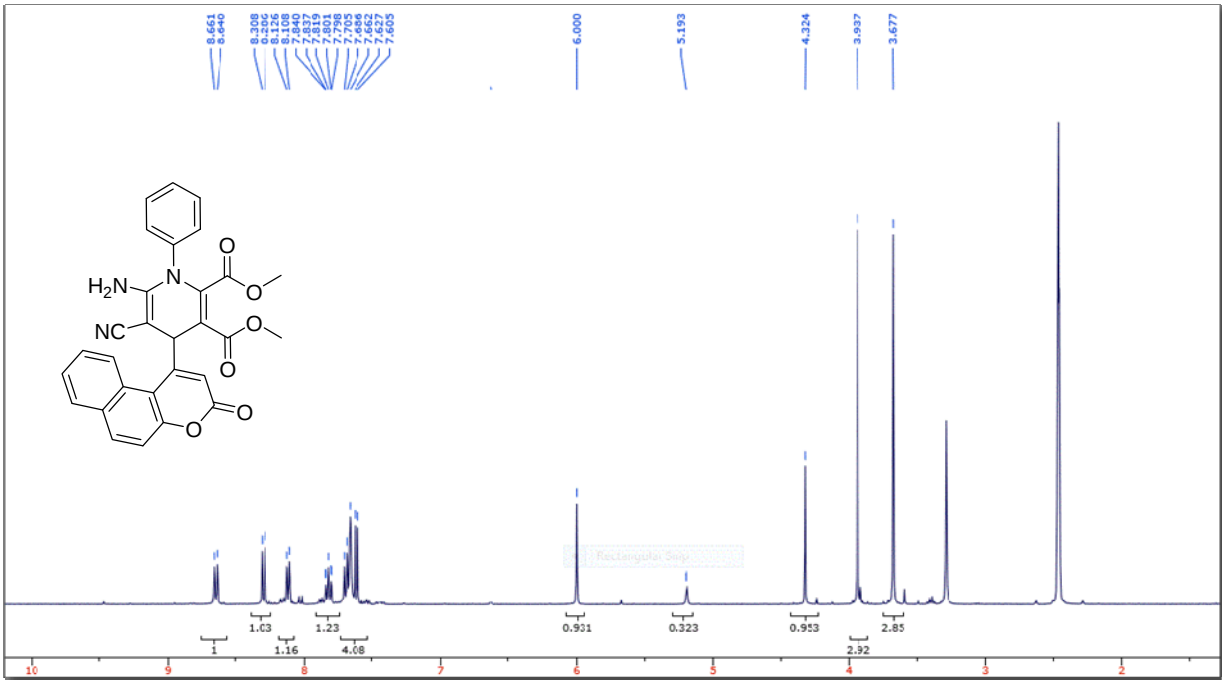
Dimethyl 6-amino-5-cyano-4-(3-oxo-3H-benzo[f]chromen-1-yl)-1-phenyl-1,4-dihydropyridine-2,3-dicarboxylate (6j)



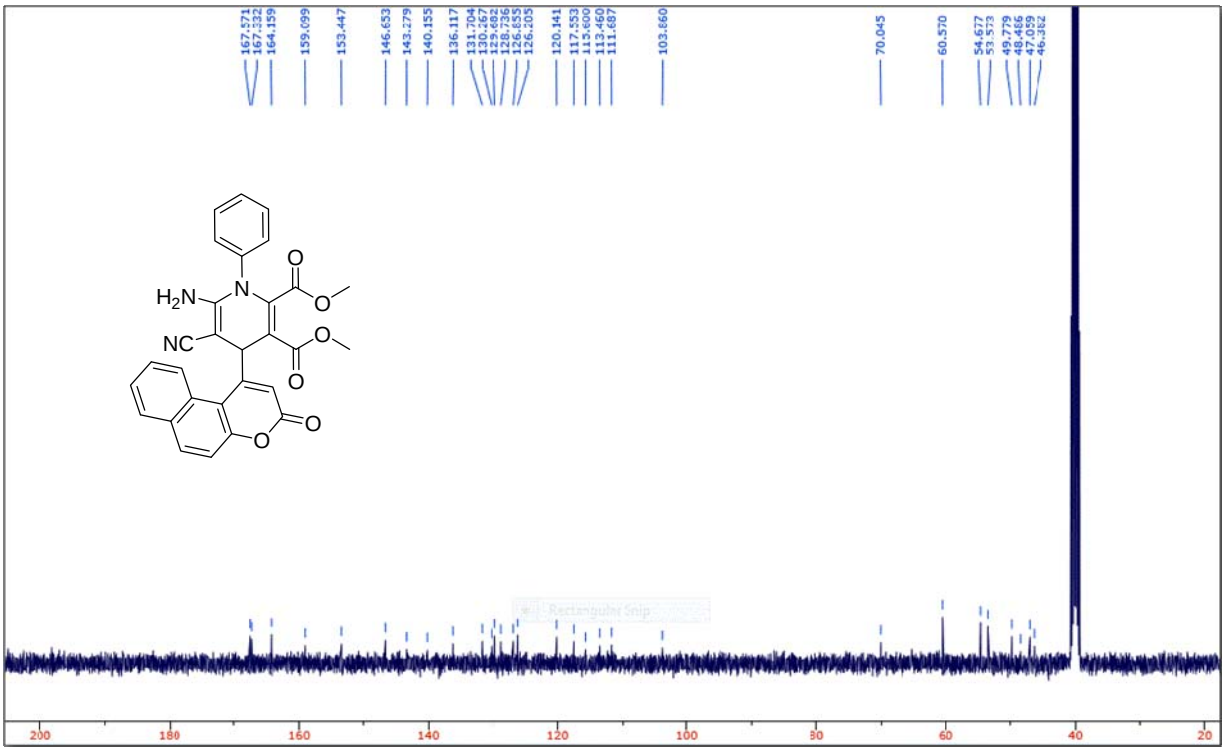
Spectrum No. 34: IR of compound **6j**



Spectrum No. 35: GCMS of compound **6j**

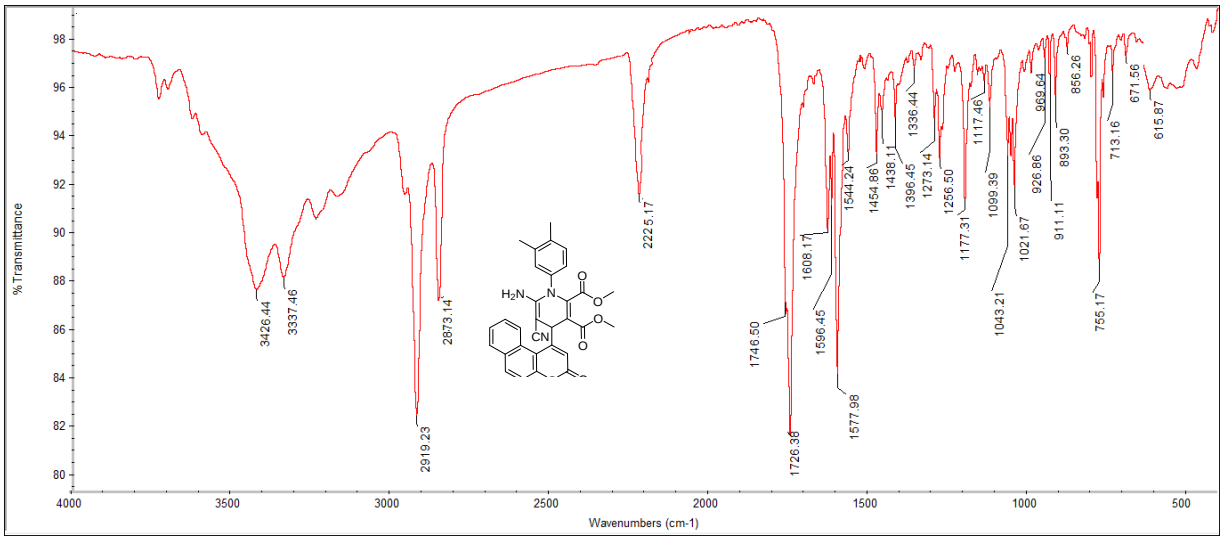


Spectrum No. 36: ^{1}H-NMR of compound **6j**

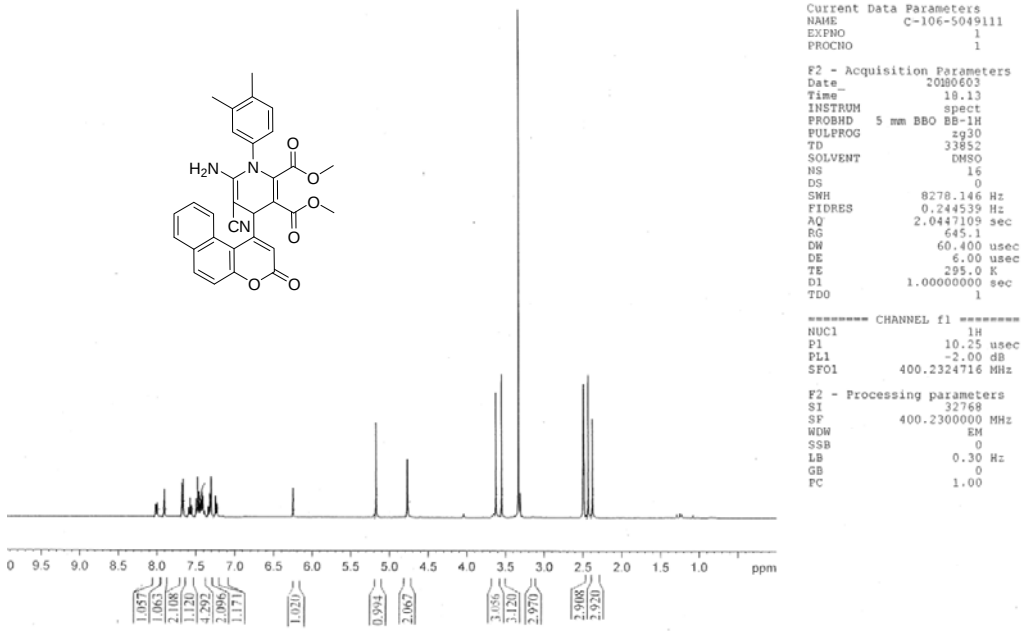


Spectrum No. 37: ^{13}C-NMR of compound **6j**

Dimethyl-6-amino-5-cyano-1-(3,4-dimethylphenyl)-4-(3-oxo-3H-benzo[f]chromen-1-yl)-1,4-dihydropyridine-2,3-dicarboxylate (6k)



Spectrum No. 38: IR of compound **6k**

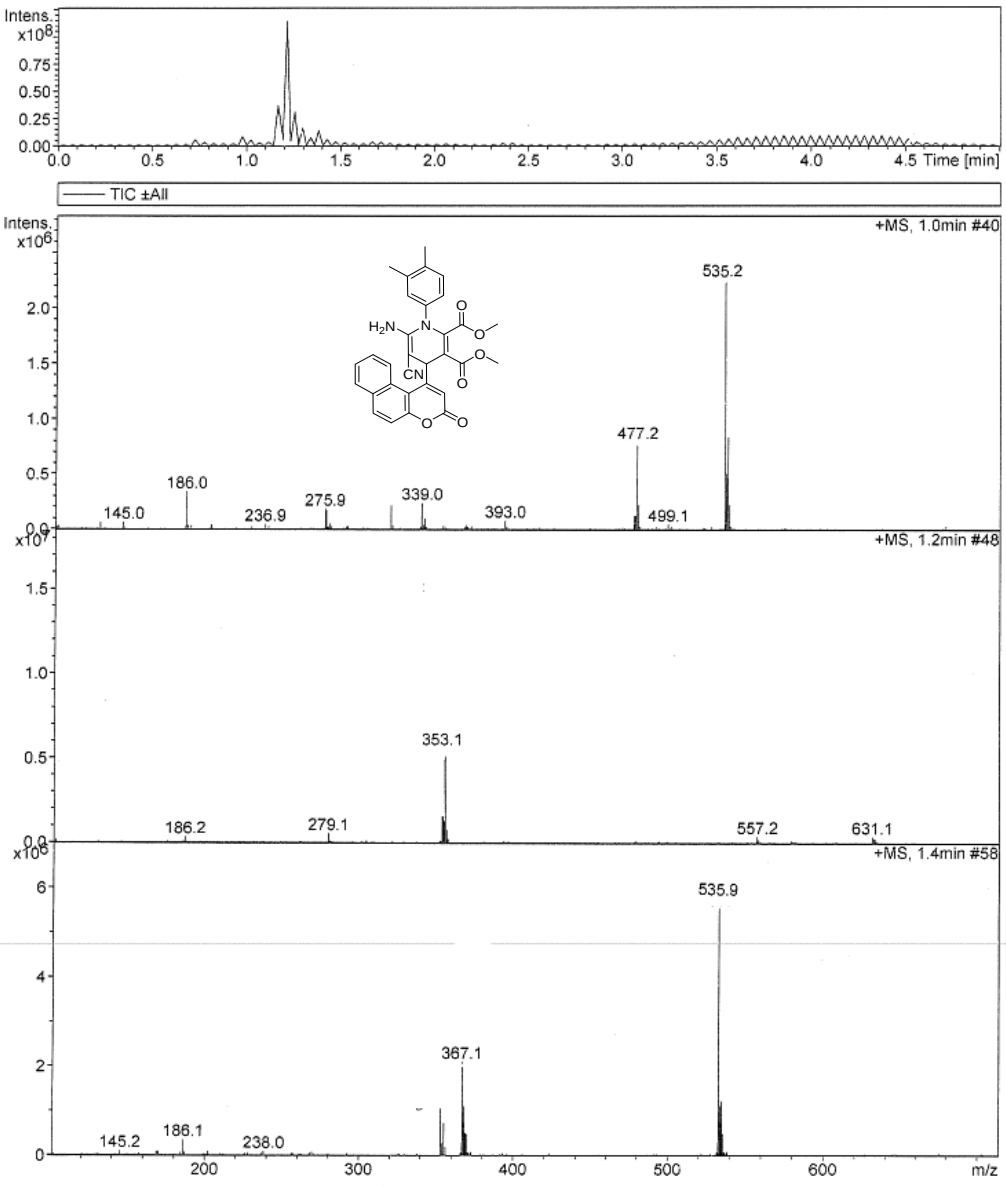


Spectrum No. 39: ^{1}H-NMR of compound **6k**

MASS REPORT

Data File: 5067355.D **Method:** VYDACPOL.M

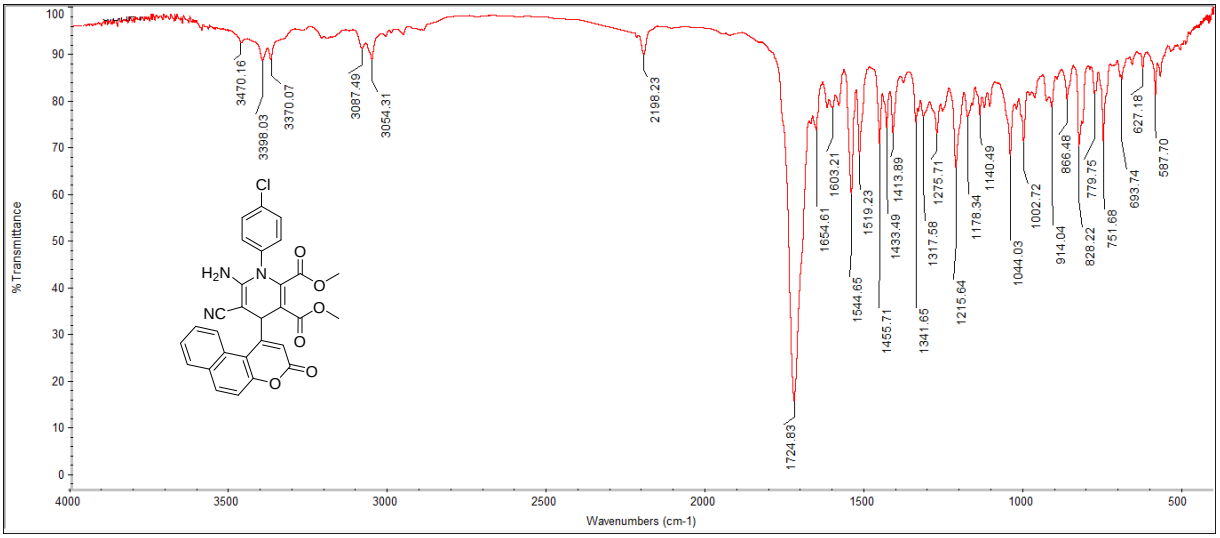
Sample Name: C -35 **Instrument :** LC-MSD-Trap-XCT



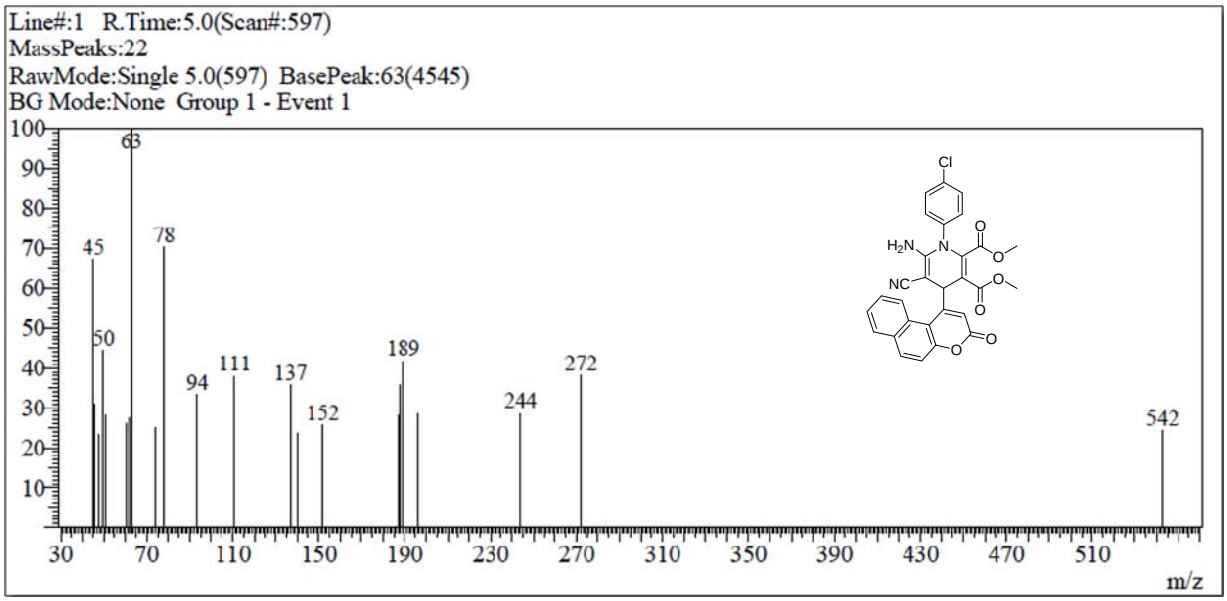
Analysed By Instrument Code : SC/AD/10-002

Spectrum No. 40: GCMS of compound **6k**

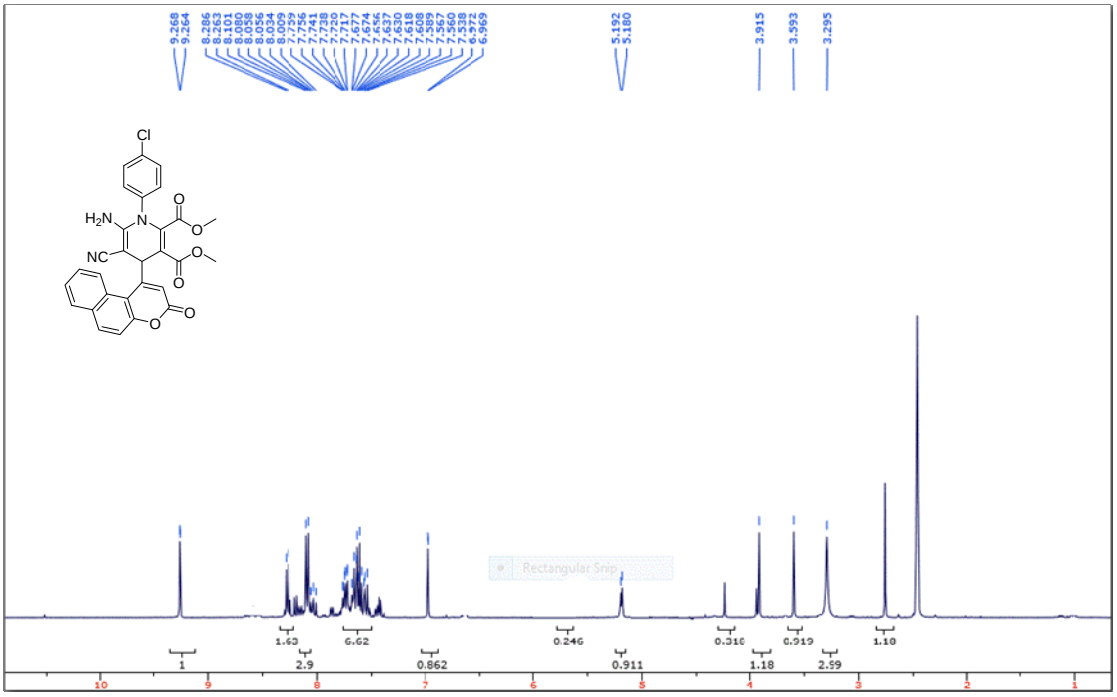
Dimethyl 6-amino-1-(4-chlorophenyl)-5-cyano-4-(3-oxo-3H-benzo[f]chromen-1-yl)-1,4-dihydropyridine-2,3-dicarboxylate (6l)



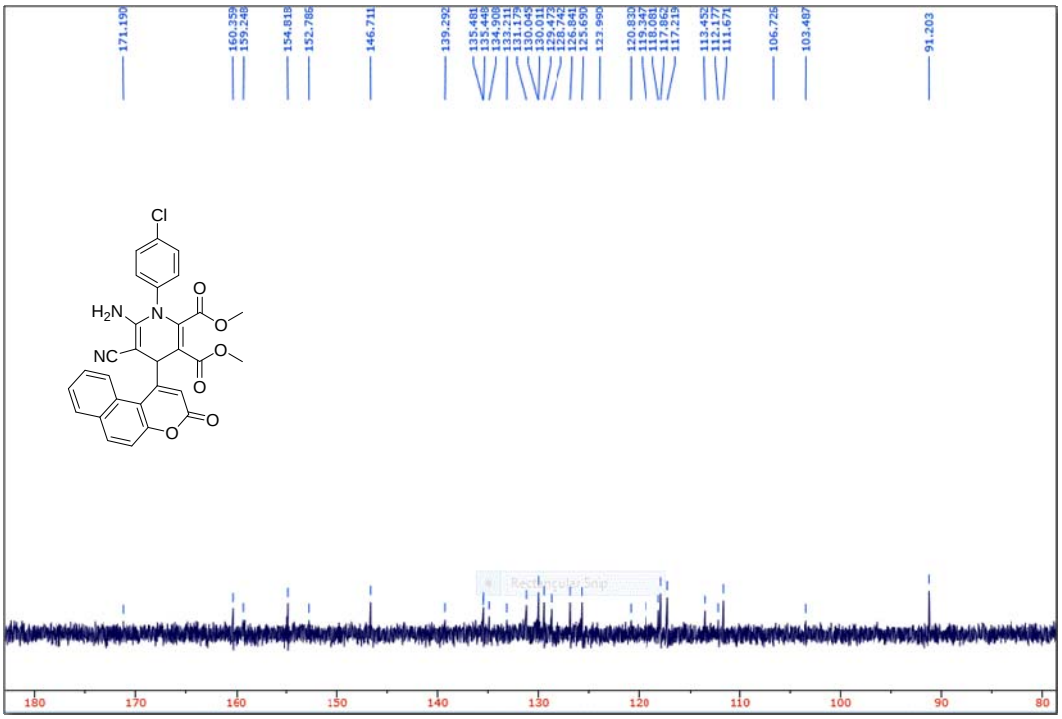
Spectrum No. 41: IR of compound **6l**



Spectrum No. 42: GCMS of compound **6l**

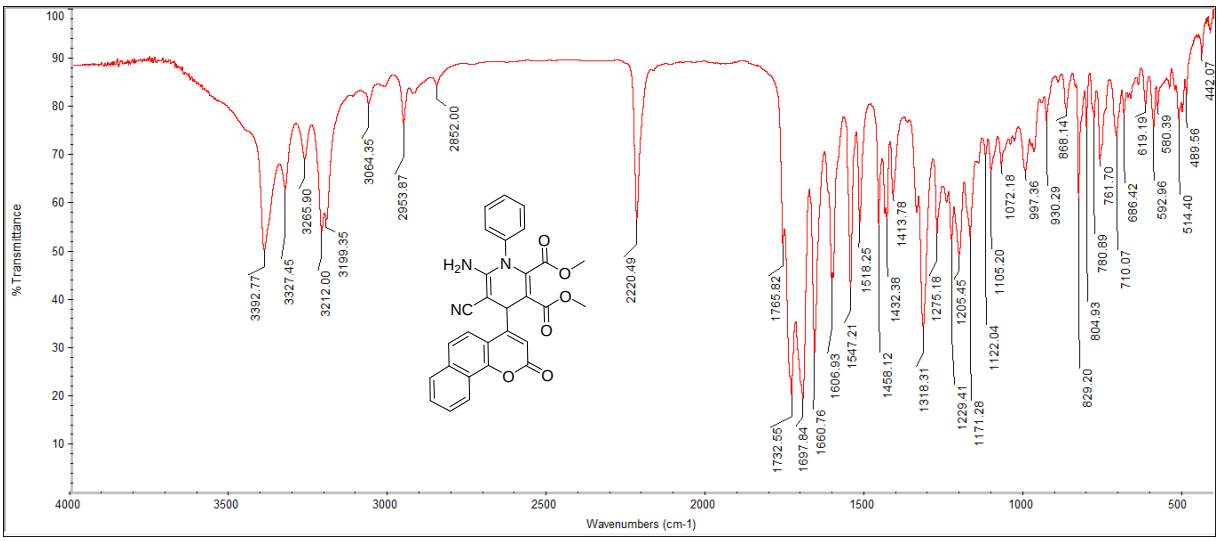


Spectrum No. 43: ^{1}H-NMR of compound **6l**

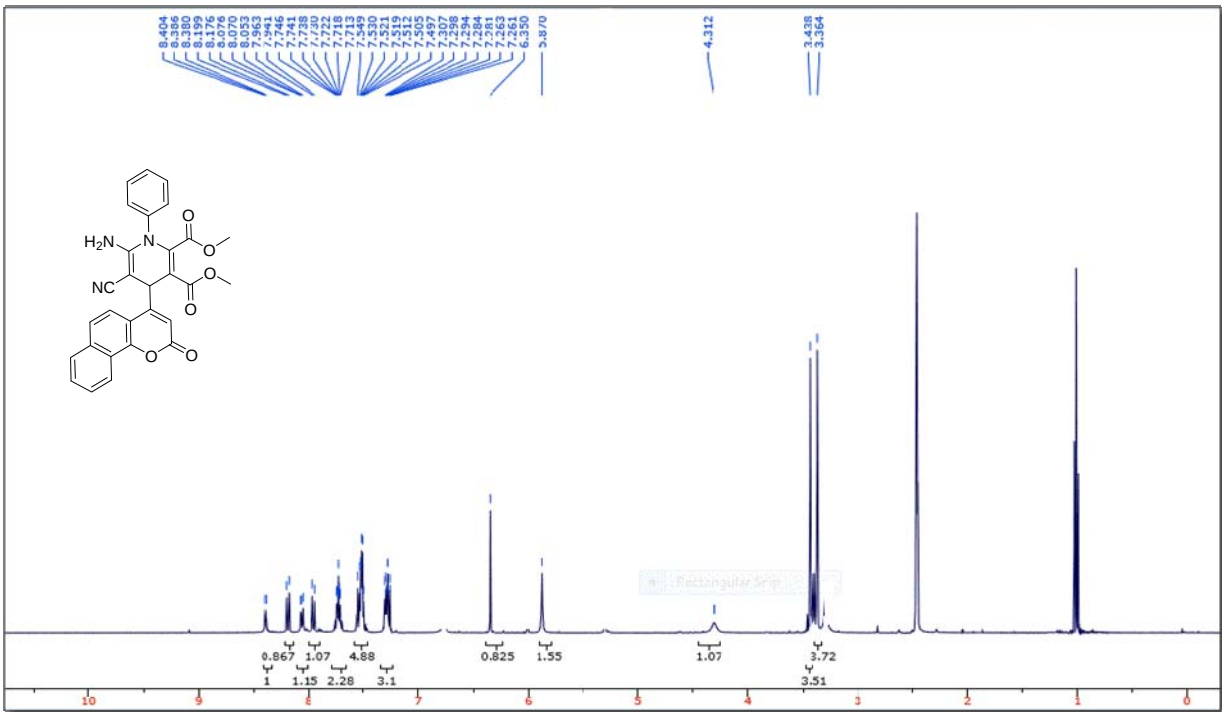


Spectrum No. 44: ^{13}C-NMR of compound **6l**

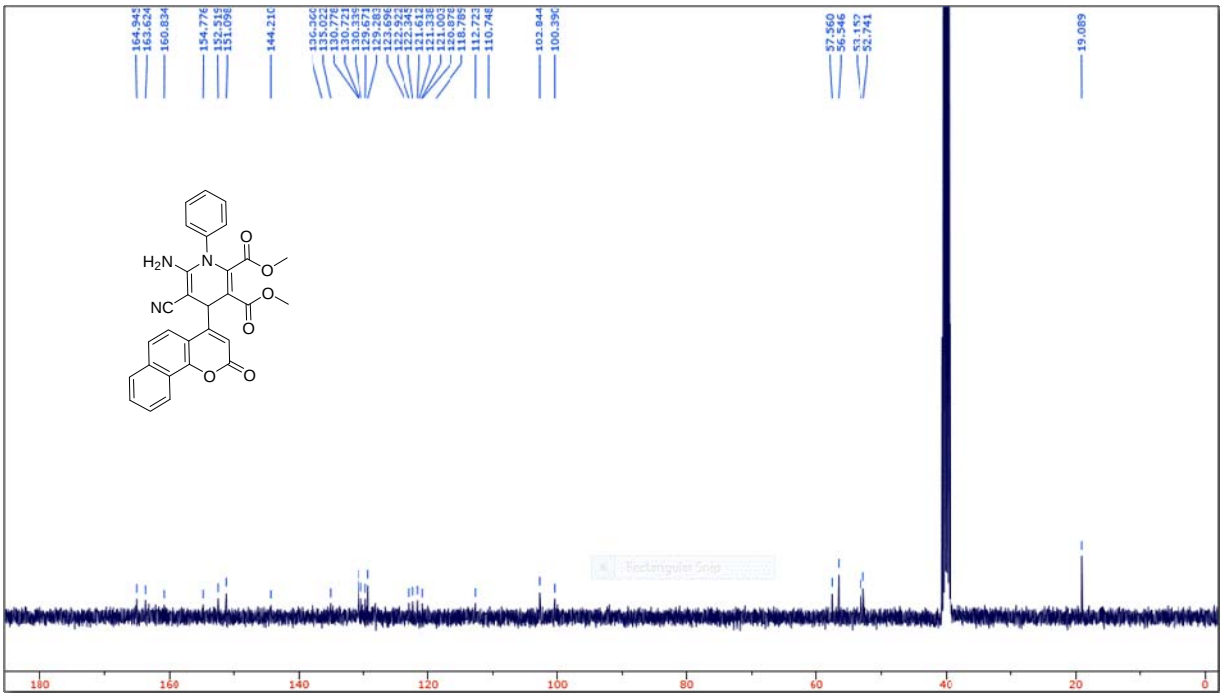
Dimethyl 6-amino-5-cyano-4-(2-oxo-2H-benzo[h]chromen-4-yl)-1-phenyl-1,4-dihydropyridine-2,3-dicarboxylate (6m)



Spectrum No. 45: IR of compound **6m**

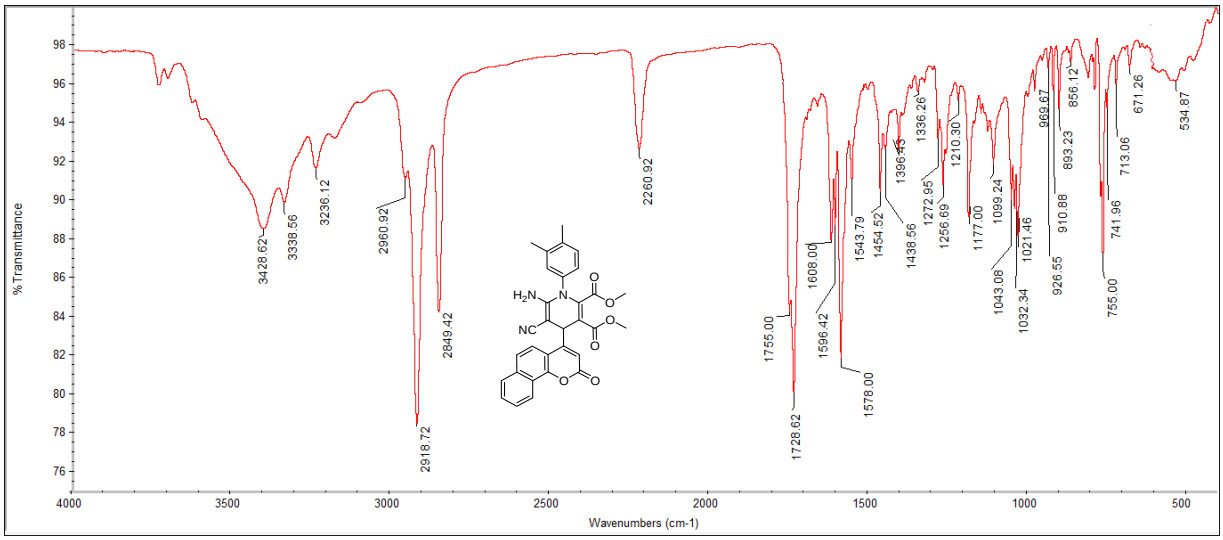


Spectrum No. 46: ^{1}H-NMR of compound **6m**

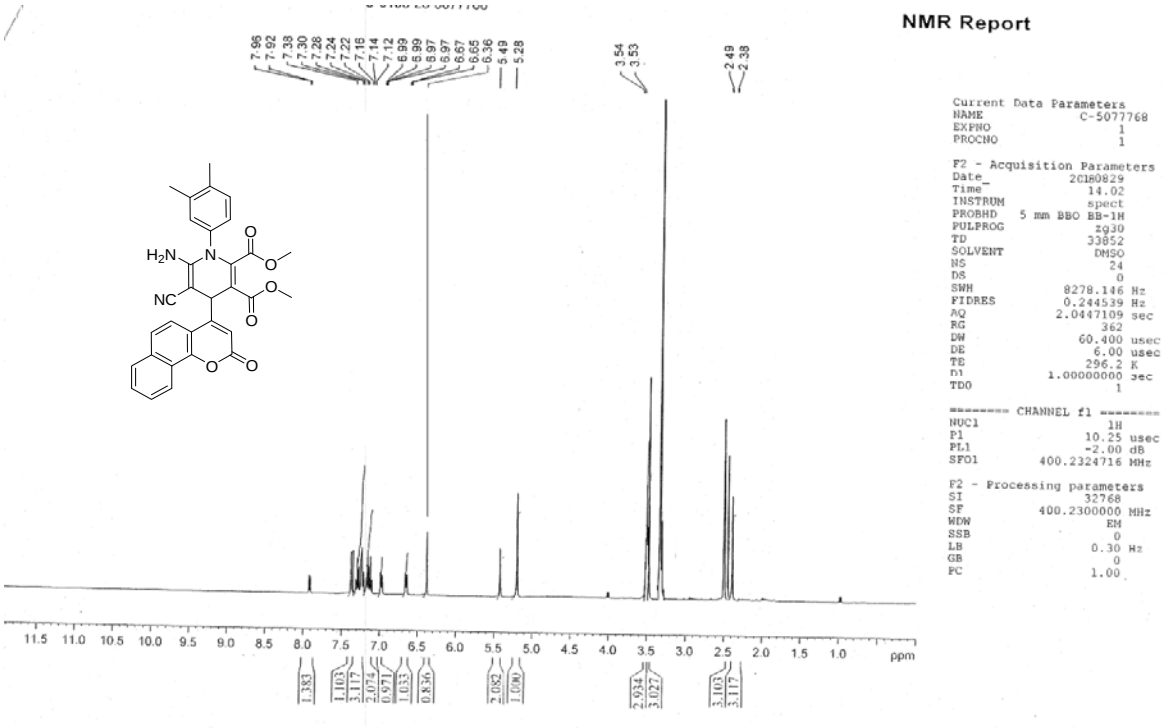


Spectrum No. 47: ^{13}C-NMR of compound **6m**

Dimethyl 6-amino-5-cyano-1-(3,4-dimethylphenyl)-4-(2-oxo-2H-benzo[h]chromen-4-yl)-1,4-dihydropyridine-2,3-dicarboxylate (6n)



Spectrum No. 48: IR of compound **6n**

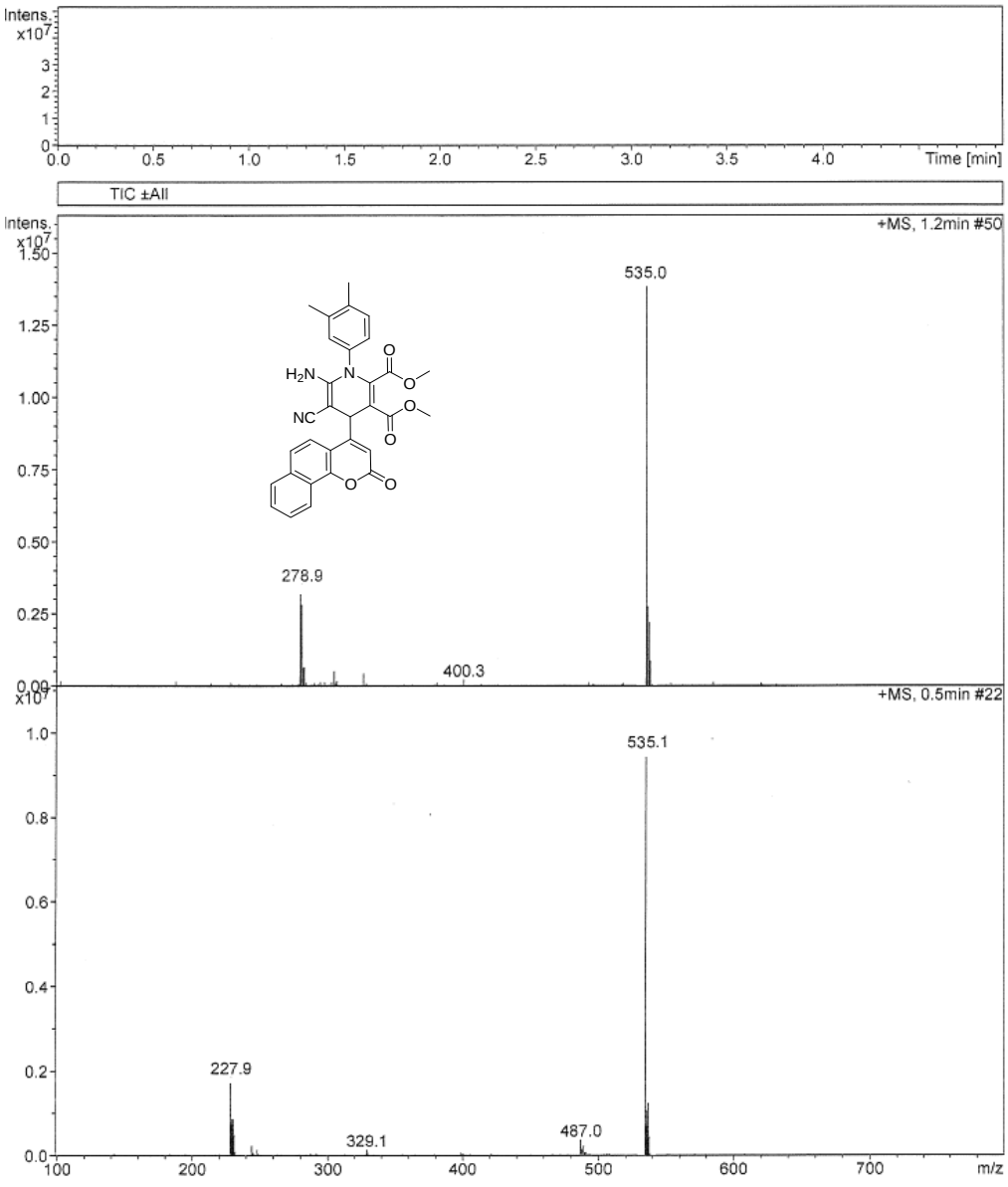


Spectrum No. 49: ^{1}H-NMR of compound **6n**

MASS REPORT

Data File: 5086394.D **Method:** VYDACPOL.M

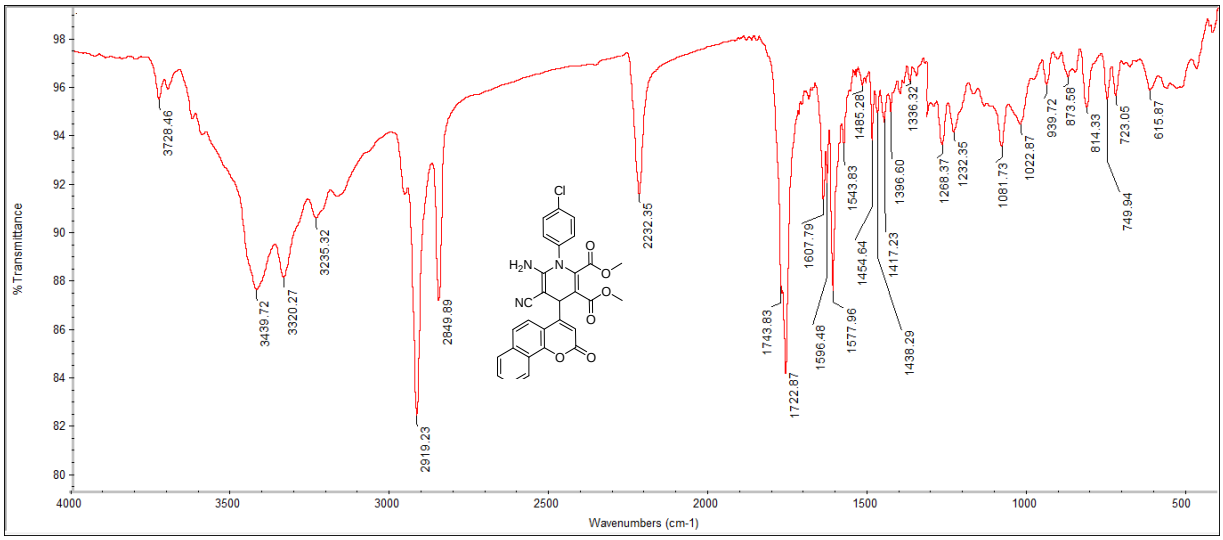
Sample Name: C 8-55 **Instrument :** LC-MSD-Trap-XCT



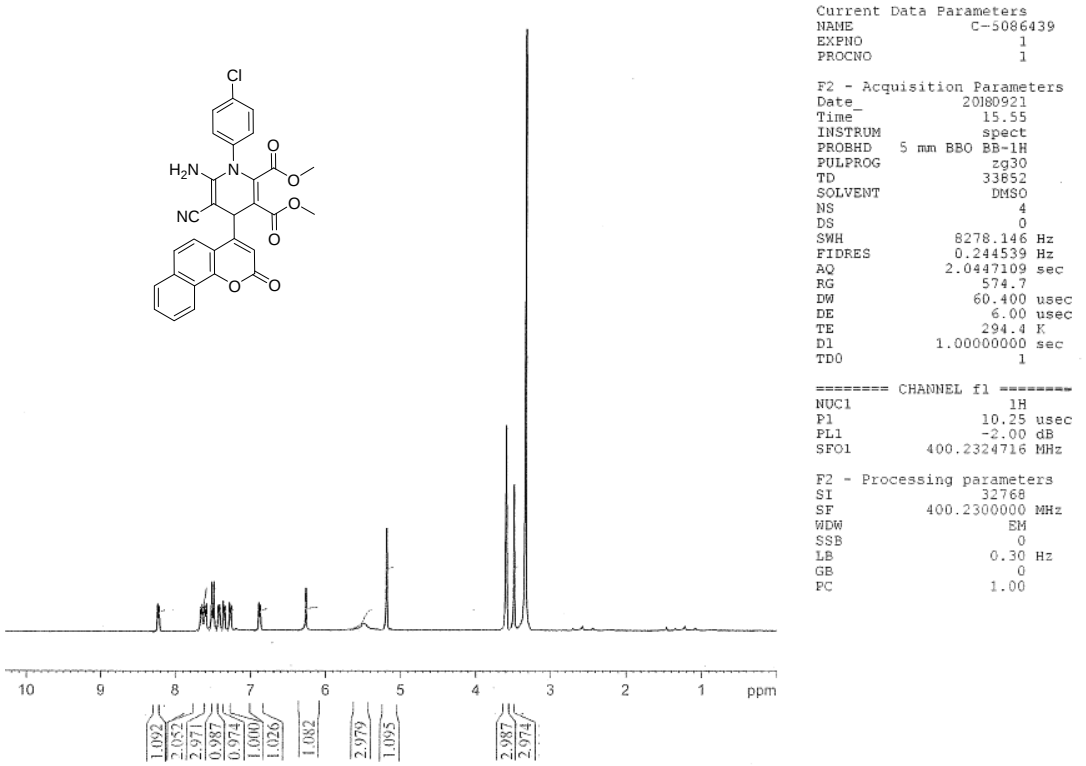
Analysed By : Instrument Code : SC/AD/10-002

Spectrum No. 50: LCMS of compound **6n**

Dimethyl 6-amino-1-(4-chlorophenyl)-5-cyano-4-(2-oxo-2H-benzo[h]chromen-4-yl)-1,4-dihydropyridine-2,3-dicarboxylate (6o)



Spectrum No. 51: IR of compound **6o**

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DE                    6.00 usec
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D1            1.00000000 sec
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PL1                  -2.00 dB
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LB                    0.30 Hz
GB                        0
PC                    1.00
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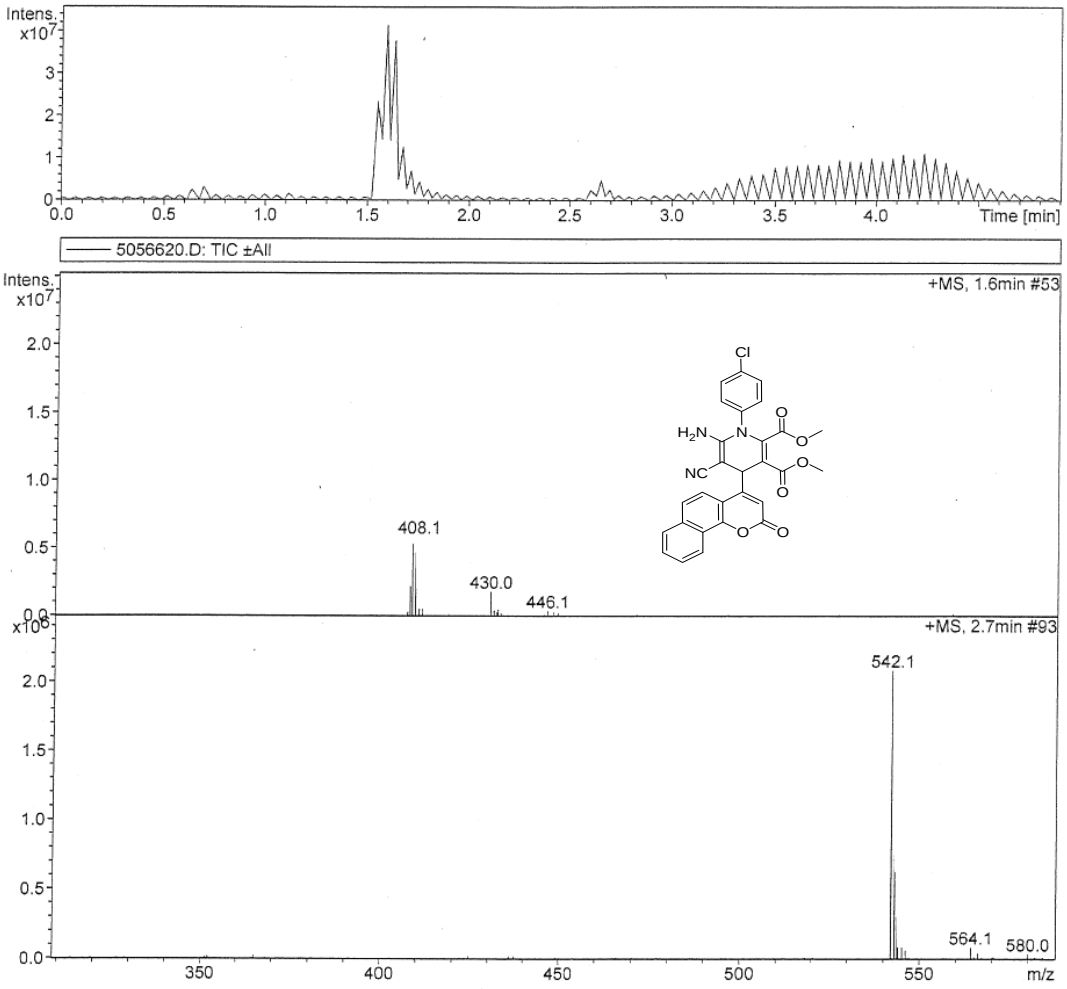
Spectrum No. 52: ^{1}H-NMR of compound **6o**

MASS REPORT

Data File : 5056620.D **Instrume** LC-MSD-Trap-XCT

Method: VYDACPOL.M **Sample Name:** C-17



Spectrum No. 53: GCMS of compound **6o**

Biological protocol

***In vitro* antimicrobial activity**

Minimum Inhibitory Concentration Determination

The MIC values were measured by the broth dilution method. A stock solution (10.24 µg/mL) of each tested compound in dimethyl sulfoxide (DMSO) were prepared and then diluted with Mueller-Hinton broth to 1024 µg/mL. The strains were grown briefly at 37 ºC in Mueller-Hinton media. After 5 h of bacterial growth, the bacterial culture was diluted to obtain a concentration of 5 $X10^5$ cells/mL. Then, 150 µL bacterial and fungal suspensions were added to each well of the flat-bottomed 96-well tissue culture plate. Two-fold serial dilutions were carried out from the fist well to the tenth well; the final concentrations of the compounds ranged from 1-512 µg/mL; and excess media (150 µL) were discarded from the last well. The plates were incubated at 37 ºC for 24 h. The MIC of the sample showing no turbidity was recorded as the lowest concentration of compound that inhibited bacterial growth completely. The test organisms are then added to the dilutions of the products, incubated, and scored for growth. Ampicillin, Gentamycin and Amphotericin-B were used as positive controls in the assay.

***In vitro* anti-inflammatory activity**

Anti-inflammatory activity of newly synthesized compounds **6(a-o**) was evaluated by protein denaturation method. Diclofenac sodium is a powerful non steroidal anti-inflammatory drug which was used as a standard drug. The reaction mixture consisting of 2mL of known concentration of compound **6(a-o)**(100 µg/mL) or standard Diclofenac sodium (100 and 200 µg/mL) and 2.8 mL of phosphate buffered saline (pH 6.4) was mixed with 2 mL of egg albumin (from fresh hen's egg) and incubated at (27±1) °C for 15 min. Denaturation was induced by keeping the reaction mixture at 70 °C in a water bath for 10 min. After cooling, the absorbance was measured at 660 nm by using double distilled water as blank. Each experiment was done in triplicate and the average was taken. The percentage inhibition of protein denaturation was calculated by using the following formula.

$$\% \text{ inhibition} = \frac{At - Ac}{Ac} \times 100$$

Where, A_t =absorbance of test sample; A_c=absorbance of control.

Molecular Docking study

Molecular docking was used to clarify the binding mode of the compounds to provide straightforward information for further structural optimization. The crystal structure of the twinned 3.35A structure of *S. aureus* Gyrase complex with ciprofloxacin and DNA (PDB ID: 2XCT) was extracted from the Brookhaven Protein Database (PDB http://www.rcsb.org/pdb). The proteins were prepared for docking by adding polar hydrogen atom with Gasteiger-Huckel charges and water molecules were removed. The 3D structure of the ligands was generated by the SKETCH module implemented in the SYBYL program (Tripos Inc., St. Louis, USA) and its energy-minimized conformation was obtained with the help of the Tripos force field using Gasteiger-Huckel charges and molecular docking was performed with Surflex-Dock program that is interfaced with Sybyl-X 2.0. and other miscellaneous parameters were assigned with the default values given by the software.

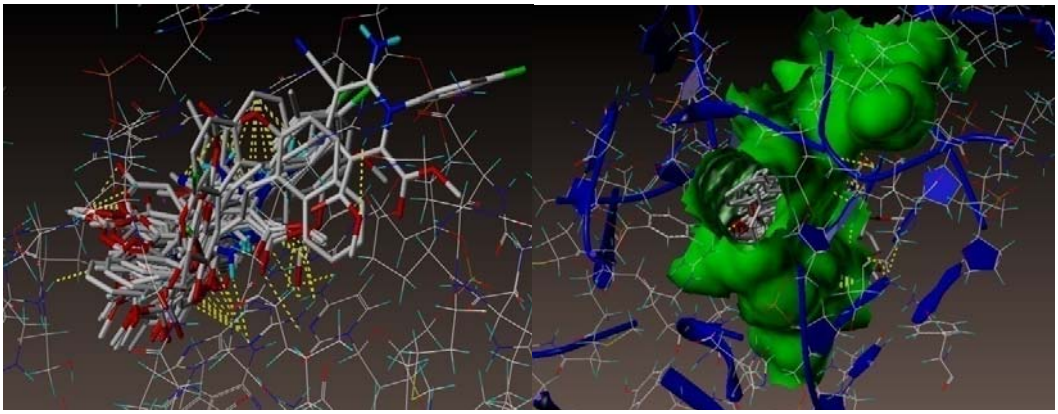


Figure S4. Docked view of all the compounds at the active site of the enzyme (PDB ID: 2XCT)

As depicted in the **Figure S5,** thecompound **6d** showed three bonding interactions at the active site of the enzyme (PDB ID: 2XCT). The carboxylate group of oxygen atom present at the 3rd position of dihydropyridine ring makes one hydrogen bonding interaction with U/SER1084 (C=O···H-U/SER1084, 1.91 Å) amino acid residue. Coumarin ring oxygen atom raises one hydrogen bonding interaction with U/DA7 (O···H-U/DA7, 2.11 Å) amino acid residue. Whereas, another hydrogen bonding interaction raised from the hydrogen atom of

amino group present on the 6th position of dihydropyridine ring with nitrogen of X/DC13 (NH···N-X/DC13, 2.88 Å) amino acid residue.

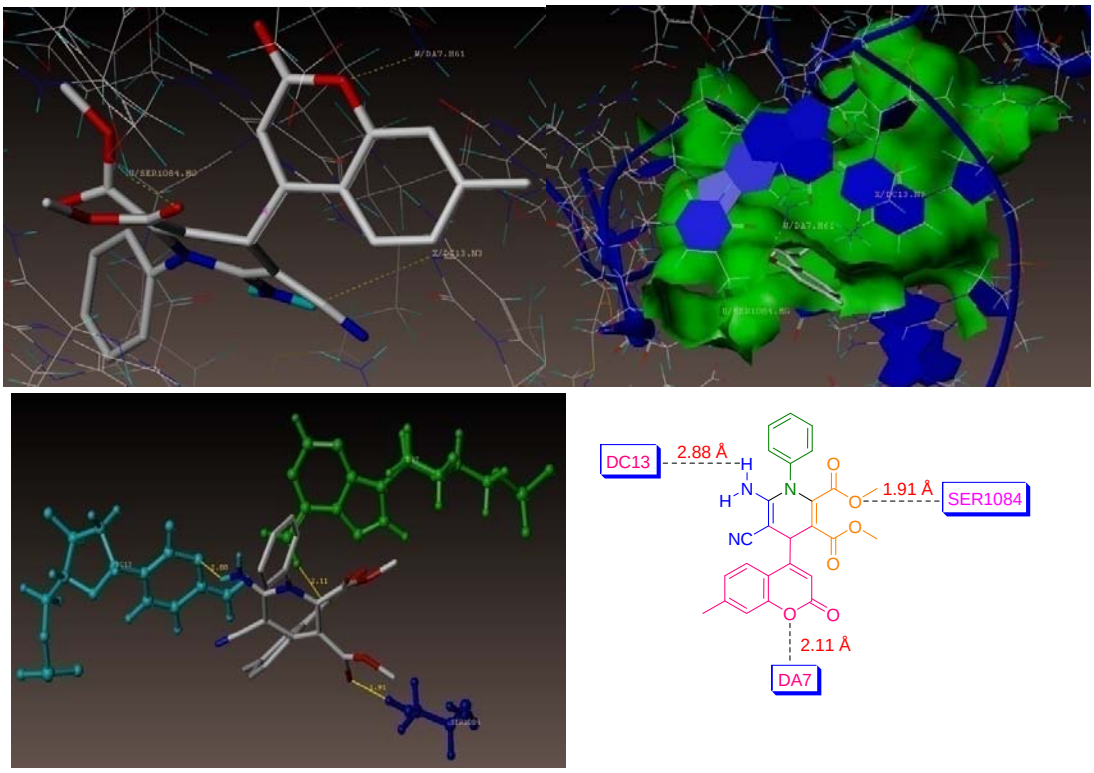


Figure S5. Docked view of compound **6d** at the active site of the enzyme (PDB ID: 2XCT)

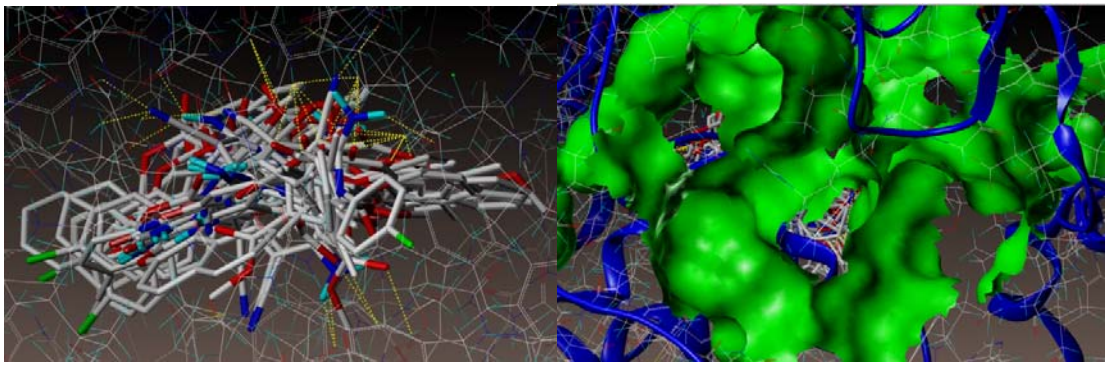


Figure S6. Docked view of all the compounds at the active site of the enzyme PDB ID: 4PH9

From **Figure S7(A-C)** we noticed that three hydrogen bonding interactions compound **6e** with at the active site of the enzyme (PDB ID: 4PH9). The 3rd position oxygen atom of carboxylate group of dihydropyridine ring makes a hydrogen bonding interaction with hydrogen

of ARG121 (C-O---H-AR121, 2.63 Å). Similarly, oxygen atom of carboxylate group present at the 2nd position of dihydropyridine ring makes a hydrogen bonding interaction with hydrogen of SER354 (C=O----H-SER354, 2.61 Å) amino acid and remaining one hydrogen bonding interaction raised from the nitrogen atom of cyano group present on the 5th position of dihydropyridine ring with oxygen of SER531 (CN----H-SER531, 2.73 Å) amino acid residue.

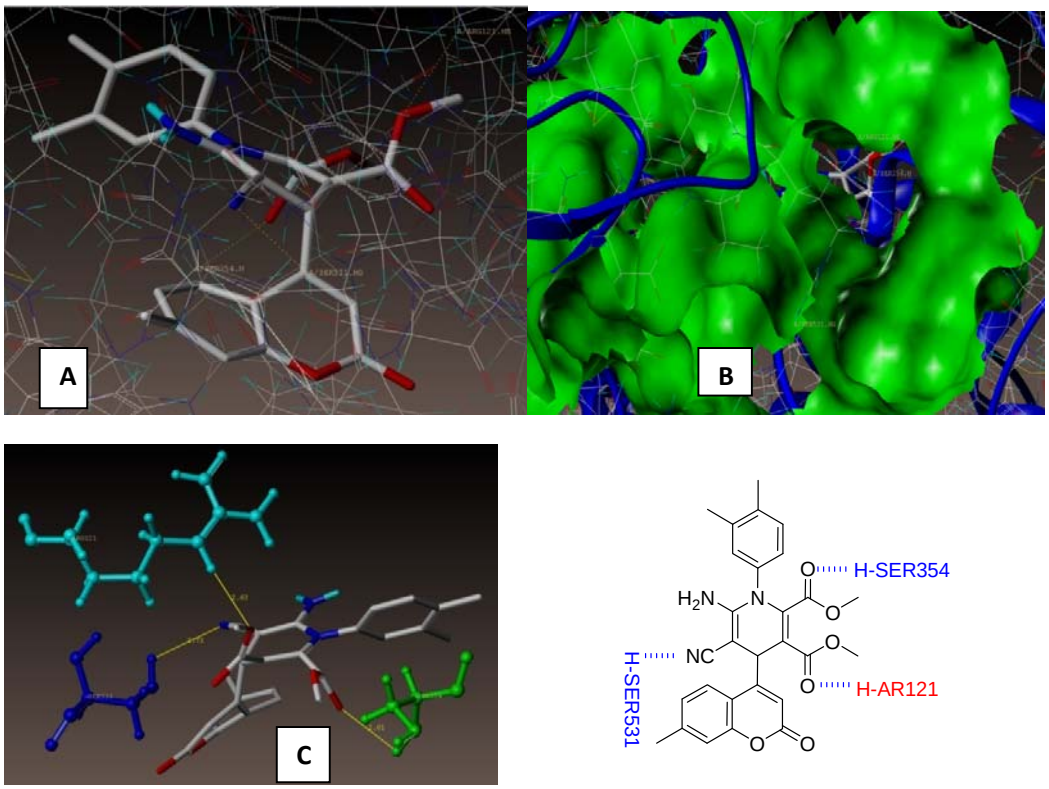


Figure S7. Docked view of compound **6e** at the active site of the enzyme PDB: 4PH9

Table S1. Surflex Docking score (kcal/mol) of the coumarin derivatives

Compd	C Score[a]	Crash Score[b]	Polar Score[c]	D Score[d]	PMF Score[e]	G Score[f]	Chem Score[g]
6a	8.31	-4.20	3.34	-165.868	-158.030	-270.196	-24.632
6b	4.81	-6.13	2.42	-124.200	-85.819	-279.366	-16.769
6c	7.25	-4.40	3.57	-173.634	-176.010	-335.546	-25.217
6d	8.75	-3.62	3.73	-166.662	-168.050	-331.586	-26.724
6e	4.93	-8.05	3.14	-188.133	-160.957	-346.224	-35.964
6f	8.56	-4.12	3.59	-172.527	-163.355	-347.889	-27.511
6g	4.82	-6.64	5.44	-141.575	-135.090	-175.568	-35.160
6h	7.60	-5.29	3.48	-197.618	-196.541	-310.450	-27.625
6i	5.84	-5.91	3.66	-198.023	-187.498	-313.446	-28.512
6j	7.30	-4.83	2.28	-199.093	-172.946	-307.852	-24.117
6k	6.11	-5.09	0.72	-212.041	-165.519	-383.404	-22.908
6l	5.34	-8.28	3.18	-214.539	-169.672	-350.267	-32.677
6m	5.59	-6.36	5.00	-169.452	-154.595	-285.944	-25.352
6n	5.06	-6.19	4.69	-166.515	-146.057	-278.263	-23.561
6o	7.12	-3.48	0.02	-190.946	-105.612	-328.526	-18.046
Ciprofloxacin	10.32	-1.82	5.96	-105.008	-99.252	-199.166	-25.901

[a] C Score (Consensus Score) integrates a number of popular scoring functions for ranking the affinity of ligands bound to the active site of a receptor and reports the output of total score.
[b] Crash-score revealing the inappropriate penetration into the binding site. Crash scores close to 0 are favorable. Negative numbers indicate penetration.
[c] Polar indicating the contribution of the polar interactions to the total score. The polar score may be useful for excluding docking results that make no hydrogen bonds.
[d] D-score for charge and van der Waals interactions between the protein and the ligand.
[e] PMF-score indicating the Helmholtz free energies of interactions for protein-ligand atom pairs (Potential of Mean Force, PMF).
[f] G-score showing hydrogen bonding, complex (ligand-protein), and internal (ligand-ligand) energies.
[g] Chem-score points for H-bonding, lipophilic contact, and rotational entropy, along with an intercept term.

Table S2. Surflex Docking score (kcal/mol) of the derivatives

Compd	C Score[a]	Crash Score[b]	Polar Score[c]	D Score[d]	PMF Score[e]	G Score[f]	Chem Score[g]
Ibuprofen	10.80	-0.73	4.42	-120.694	-30.190	-233.808	-34.764
6a	8.60	-21.18	0.01	-223.576	-87.876	-387.312	-46.830
6b	7.56	-33.21	0.91	-265.444	-11.734	-462.850	-52.426
6c	8.12	-26.79	0.01	-240.979	-88.320	-404.211	-50.108
6d	9.01	-18.35	1.46	-219.762	-57.502	-349.507	-47.656
6e	9.02	-19.06	0.02	-237.647	-21.375	-432.821	-45.403
6f	8.80	-21.76	0.87	-245.654	-71.905	-409.981	-52.967
6g	6.98	-36.38	1.06	-251.753	10.780	-402.935	-44.211
6h	8.02	-28.15	0.03	-252.555	-57.106	-449.275	-53.388
6i	8.52	-25.45	1.12	-241.264	-87.191	-403.294	-49.873
6j	6.54	-58.28	0.54	-246.834	64.110	-357.959	-55.631
6k	7.12	-35.00	0.24	-252.075	-51.147	-444.399	-58.909
6l	6.82	-44.78	0.02	-255.006	-6.749	-350.270	-55.667
6m	9.01	-19.14	0.00	-238.648	-114.499	-437.796	-52.914
6n	6.90	-43.81	0.00	-261.734	-78.808	-433.449	-59.705
6o	7.24	-30.18	0.01	-257.653	-34.100	-415.336	-52.087

[a] C Score (Consensus Score) integrates a number of popular scoring functions for ranking the affinity of ligands bound to the active site of a receptor and reports the output of total score.
[b] Crash-score revealing the inappropriate penetration into the binding site. Crash scores close to 0 are favorable. Negative numbers indicate penetration.
[c] Polar indicating the contribution of the polar interactions to the total score. The polar score may be useful for excluding docking results that make no hydrogen bonds.
[d] D-score for charge and van der Waals interactions between the protein and the ligand.
[e] PMF-score indicating the Helmholtz free energies of interactions for protein-ligand atom pairs (Potential of Mean Force, PMF).
[f] G-score showing hydrogen bonding, complex (ligand-protein), and internal (ligand-ligand) energies.
[g] Chem-score points for H-bonding, lipophilic contact, and rotational entropy, along with an intercept term.