Supporting Information

Hydrogen-bonding-assisted redox-neutral construction of tetrahydroquinolines via hydride transfer

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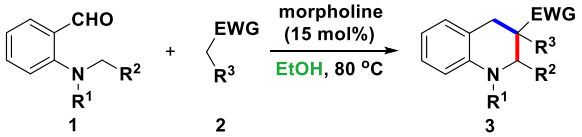
1. General Information

Unless otherwise noted, all reagents and solvents were purchased from the commercial sources and used as received. Thin layer chromatography (TLC) was used to monitor the reaction on Merck 60 F254 precoated silica gel plate (0.2 mm thickness). TLC spots were visualized by UV-light irradiation on Spectroline Model ENF-24061/F 254 nm. The products were purified by flash column chromatography (200-300 mesh silica gel) eluted with the gradient of petroleum ether and ethyl acetate. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker 500 MHz NMR spectrometer ($CDCl_3$ or DMSO-d_6 solvent). The chemical shifts were reported in parts per million (ppm), downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 7.26, singlet) or dimethyl sulfoxide-d_6 (δ 2.54, singlet). Multiplicities were afforded as: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublets of doublet) or m (multiplets). The number of protons for a given resonance is indicated by nH. Coupling constants were reported as a *J* value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) was referenced to the appropriate residual solvent peak. High resolution mass spectral analysis (HRMS) was performed on Waters XEVO G2 Q-TOF. All substituted 2-fluorobenzaldehydes, and all compounds containing active methylene were purchased from adamas-beta. All *o*-aminobenzaldehydes[1] were prepared according to literature.

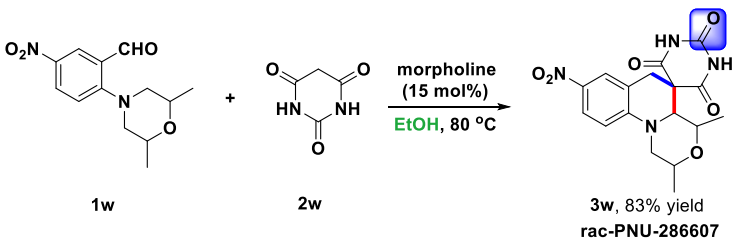
2. General Procedure

2.1 General Procedure for the Synthesis of Tetrahydroquinoline Derivatives



A reaction tube was charged with *o*-aminobenzaldehyde **1** (0.3 mmol), compound containing active methylene **2** (0.36 mmol), morpholine (15 mol%) and EtOH (3.0 mL). The mixture was stirred at 80 °C under an air atmosphere. Upon completion of the reaction as indicated by TLC analysis, the mixture was concentrated in vacuum and the residue was directly purified by flash column chromatography on silica gel (eluent: ethyl acetate/petroleum ether, 1:100) to afford the desired 3,3'-difunctionalized tetrahydroquinoline derivative **3**.

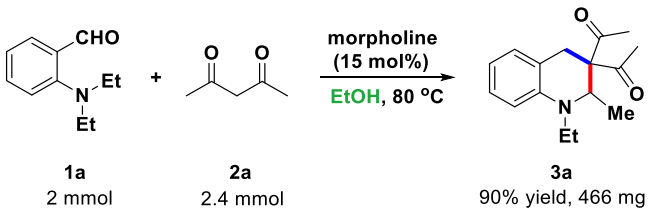
2.2 General Procedure for the Synthesis of PNU-286607



A reaction tube was charged with *o*-aminobenzaldehyde **1w** (0.3 mmol), barbituric acid **2w** (0.36 mmol), morpholine (15 mol%) and EtOH (3.0 mL). The mixture was stirred at 80 °C under an air atmosphere. Upon completion of the reaction as indicated by TLC analysis, the mixture was concentrated in vacuum and the residue was directly purified by flash column chromatography on silica gel (eluent: ethyl acetate/petroleum ether, 1:5) to afford the desired PNU-286607 **3w** in 83%

yield.

2.3 General Procedure for the Large-scale Synthesis of 3a



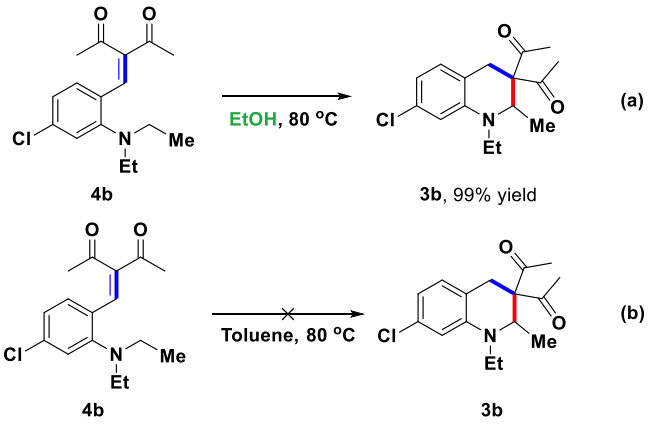
1a
2 mmol

2a
2.4 mmol

3a
90% yield, 466 mg

A round-bottomed flask was charged with *o*-aminobenzaldehyde **1a** (2 mmol), 2,4-pentanedione **2a** (2.4 mmol), morpholine (15 mol%) and EtOH (20 mL). The mixture was stirred at 80 °C under an air atmosphere. Upon completion of the reaction as indicated by TLC analysis, the mixture was concentrated in vacuum and the residue was directly purified by flash column chromatography on silica gel (eluent: ethyl acetate/petroleum ether, 1:100) to afford the desired 3,3'-diacetyl substituted tetrahydroquinoline **3a** in 90% yield (466 mg).

2.4 General Procedure for the Control Experiments



4b

3b, 99% yield

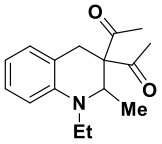
4b

3b

A reaction tube was charged with alkene **4b** (0.1 mmol), and EtOH (1 mL). The mixture was stirred at 80 °C under an air atmosphere. Upon completion of the reaction as indicated by TLC analysis, the alkene **4b** could convert to the cyclic product **3b** absolutely. However, not any reaction occurred at all when alkene **4b** was subjected to toluene at 80 °C.

3. Characterization of Products

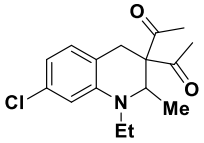
1,1'-(1-ethyl-2-methyl-1,2,3,4-tetrahydroquinoline-3,3-diyl)bis(ethan-1-one) (3a)



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:100) afforded the product (74.6 mg, 96% yield) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 7.5 Hz, 1H), 7.07 (t, *J* = 7.8 Hz, 1H), 6.64 (td, *J* = 7.3, 1.0 Hz, 1H), 6.53 (d, *J* = 8.2 Hz, 1H), 4.37 (qd, *J* = 6.4, 1.8 Hz, 1H), 3.51 (dd, *J* = 16.7, 1.5 Hz, 1H), 3.39 (dt, *J* = 14.1, 7.1 Hz, 1H), 3.30 (dt, *J* = 14.7, 7.3 Hz, 1H), 3.14 (d, *J* = 16.7 Hz, 1H), 2.17 (s, 3H), 2.07 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.98 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 204.5, 203.7, 142.4, 129.5, 127.6, 118.1, 116.3, 111.1, 70.2, 55.9, 45.0, 27.8, 26.4, 25.5, 15.2, 12.9. **HRMS (ESI):** calcd. for $C_{16}H_{22}NO_2$ $[M+H]^+$: 260.1651, found: 260.1654.

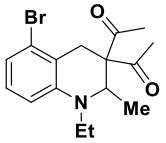
1,1'-(7-chloro-1-ethyl-2-methyl-1,2,3,4-tetrahydroquinoline-3,3-diyl)bis(ethan-1-one) (3b)



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:100) afforded the product (84.3 mg, 96% yield) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (d, *J* = 7.9 Hz, 1H), 6.60 (dd, *J* = 8.0, 1.9 Hz, 1H), 6.48 (d, *J* = 1.8 Hz, 1H), 4.36 (dd, *J* = 6.5, 1.7 Hz, 1H), 3.50 – 3.43 (m, 1H), 3.41 – 3.23 (m, 2H), 3.07 (d, *J* = 16.8 Hz, 1H), 2.16 (d, *J* = 5.6 Hz, 3H), 2.06 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.97 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 204.0, 203.3, 143.5, 133.2, 130.4, 116.5, 116.1, 110.8, 70.0, 55.6, 45.0, 27.2, 26.4, 25.5, 15.4, 12.6. **HRMS (ESI):** calcd. for $C_{16}H_{21}ClNO_2$ $[M+H]^+$: 294.1261, found: 294.1265.

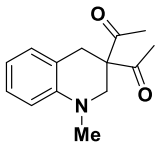
1,1'-(5-bromo-1-ethyl-2-methyl-1,2,3,4-tetrahydroquinoline-3,3-diyl)bis(ethan-1-one) (3c)



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:100) afforded the product (92.0 mg, 91% yield) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.94 – 6.89 (m, 2H), 6.47 (dd, *J* = 6.4, 3.0 Hz, 1H), 4.36 (tt, *J* = 6.5, 3.2 Hz, 1H), 3.77 (dd, *J* = 17.4, 1.6 Hz, 1H), 3.35 (ddt, *J* = 31.0, 14.8, 7.3 Hz, 2H), 2.91 (d, *J* = 17.4 Hz, 1H), 2.20 (s, 3H), 2.06 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 0.97 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 203.9, 203.2, 144.1, 128.3, 125.8, 120.2, 117.6, 110.2, 70.2, 55.8, 45.4, 28.7, 26.5, 25.4, 15.1, 12.7. **HRMS (ESI):** calcd. for $C_{16}H_{21}BrNO_2$ $[M+H]^+$: 338.0756, found: 338.0760.

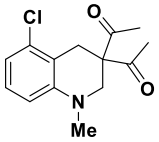
1,1'-(1-methyl-1,2,3,4-tetrahydroquinoline-3,3-diyl)bis(ethan-1-one) (3d)



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:100) afforded the product (52.7 mg, 76% yield) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (t, *J* = 7.7 Hz, 2H), 6.70 (t, *J* = 7.3 Hz, 1H), 6.59 (d, *J* = 8.0 Hz, 1H), 3.61 (s, 2H), 3.28 (s, 2H), 2.91 (s, 3H), 2.17 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 204.1, 145.5, 129.3, 127.5, 119.7, 117.8, 111.5, 66.0, 54.3, 39.2, 32.4, 25.9. **HRMS (ESI):** calcd. for $C_{14}H_{18}NO_2$ $[M+H]^+$: 232.1338, found: 232.1340.

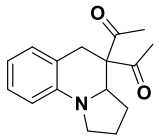
1,1'-(5-chloro-1-methyl-1,2,3,4-tetrahydroquinoline-3,3-diyl)bis(ethan-1-one) (3e)



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:100) afforded the product (60.4 mg, 76% yield) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (t, *J* = 8.1 Hz, 1H), 6.77 (d, *J* = 7.9 Hz, 1H), 6.48 (d, *J* = 8.3 Hz, 1H), 3.59 (s, 2H), 3.28 (s, 2H), 2.91 (s, 3H), 2.17 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 203.6, 147.1, 134.5, 127.7, 118.4, 117.8, 109.9, 65.7, 53.8, 39.6, 30.1, 25.8. **HRMS (ESI):** calcd. for $C_{14}H_{17}ClNO_2$ $[M+H]^+$: 266.0948, found: 266.0955.

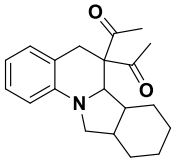
1,1'-(1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinoline-4,4-diyl)bis(ethan-1-one) (3f)



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:100) afforded the product (65.5 mg, 85% yield) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (t, *J* = 7.7 Hz, 1H), 7.07 (d, *J* = 7.4 Hz, 1H), 6.64 (td, *J* = 7.4, 1.0 Hz, 1H), 6.48 (d, *J* = 8.0 Hz, 1H), 3.70 – 3.62 (m, 1H), 3.32 – 3.23 (m, 3H), 3.15 (d, *J* = 16.5 Hz, 1H), 2.21 (tdd, *J* = 6.2, 4.8, 1.7 Hz, 1H), 2.18 (s, 3H), 2.03 – 1.97 (m, 1H), 1.96 (s, 3H), 1.96 – 1.88 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 207.7, 205.7, 144.2, 128.7, 128.0, 118.2, 116.4, 111.4, 63.9, 61.3, 46.9, 34.6, 29.2, 27.7, 27.6, 23.2. **HRMS (ESI):** calcd. for $C_{16}H_{20}NO_2$ $[M+H]^+$: 258.1494, found: 258.1498.

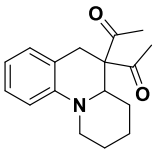
1,1'-5,6,6a,6b,7,8,9,10,10a,11-decahydroisoindolo[2,1-a]quinoline-6,6-diyl)bis(ethan-1-one) (3g)



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:100) afforded the product (74.6 mg, 80% yield) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (t, *J* = 7.7 Hz, 1H), 7.04 (d, *J* = 7.3 Hz, 1H), 6.60 (t, *J* = 7.3 Hz, 1H), 6.45 (d, *J* = 8.1 Hz, 1H), 3.72 (d, *J* = 6.9 Hz, 1H), 3.28 – 3.22 (m, 2H), 3.20 (s, 2H), 2.71 – 2.63 (m, 1H), 2.20 (s, 3H), 2.17 – 2.10 (m, 1H), 1.92 (s, 3H), 1.78 – 1.70 (m, 1H), 1.69 – 1.61 (m, 1H), 1.61 – 1.52 (m, 1H), 1.51 – 1.43 (m, 2H), 1.37 (tdd, *J* = 12.4, 6.2, 3.3 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 207.7, 206.9, 144.2, 128.6, 128.0, 117.3, 115.7, 111.1, 64.7, 62.9, 52.0, 38.7, 36.5, 36.1, 29.0, 28.2, 27.2, 26.9, 23.9, 22.4. **HRMS (ESI):** calcd. for $C_{20}H_{26}NO_2$ $[M+H]^+$: 312.1964, found: 312.1970.

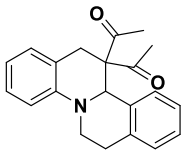
1,1'-(2,3,4,4a,5,6-hexahydro-1H-pyrido[1,2-a]quinoline-5,5-diyl)bis(ethan-1-one) (3h)



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:100) afforded the product (57.7 mg, 71% yield) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 7.4 Hz, 1H), 7.07 (t, *J* = 7.8 Hz, 1H), 6.74 (d, *J* = 8.3 Hz, 1H), 6.68 (t, *J* = 7.3 Hz, 1H), 4.23 (d, *J* = 11.2 Hz, 1H), 4.04 (d, *J* = 14.2 Hz, 1H), 3.59 (d, *J* = 16.2 Hz, 1H), 3.11 – 2.99 (m, 2H), 2.15 (s, 6H), 1.85-1.80 (m, 1H), 1.79-1.73 (m, H), 1.63 – 1.55 (m, 1H), 1.46 – 1.36 (m, 2H), 1.35 – 1.27 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 204.6, 203.7, 143.3, 129.9, 127.7, 120.3, 117.5, 113.0, 69.9, 60.2, 49.3, 28.5, 26.6, 25.7, 24.9, 24.8, 21.7. **HRMS (ESI):** calcd. for $C_{17}H_{22}NO_2$ $[M+H]^+$: 272.1651, found: 272.1654.

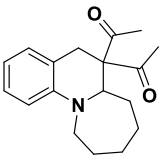
1,1'-(7,11b,12,13-tetrahydro-6H-isoquinolino[2,1-a]quinoline-12,12-diyl)bis(ethan-1-one) (3i)



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:100) afforded the product (91.9 mg, 96% yield) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (t, *J* = 7.4 Hz, 1H), 7.07 – 6.99 (m, 4H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.71 (d, *J* = 8.1 Hz, 1H), 6.68 (t, *J* = 7.2 Hz, 1H), 5.61 (s, 1H), 4.09 (ddd, *J* = 13.8, 6.5, 2.2 Hz, 1H), 3.71 (dd, *J* = 16.1, 1.3 Hz, 1H), 3.59 (ddd, *J* = 13.8, 11.5, 5.4 Hz, 1H), 3.29 – 3.15 (m, 2H), 2.73 (dd, *J* = 16.8, 3.4 Hz, 1H), 2.36 (s, 3H), 2.22 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 205.8, 203.1, 143.6, 136.3, 136.1, 129.6, 129.6, 127.3, 126.9, 125.9, 125.0, 121.4, 118.6, 113.4, 70.9, 60.4, 46.4, 28.9, 27.0, 25.2, 24.9. **HRMS (ESI):** calcd. for $C_{21}H_{22}NO_2$ $[M+H]^+$: 320.1651, found: 320.1655.

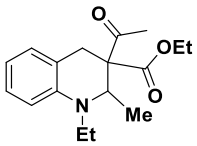
1,1'-(5,6,6a,7,8,9,10,11-octahydroazepino[1,2-a]quinoline-6,6-diyl)bis(ethan-1-one) (3j)



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:100) afforded the product (70.9 mg, 83% yield) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (d, *J* = 7.4 Hz, 1H), 7.05 (t, *J* = 7.7 Hz, 1H), 6.62 (t, *J* = 7.3 Hz, 1H), 6.53 (d, *J* = 8.2 Hz, 1H), 4.31 – 4.22 (m, 1H), 3.88 (ddd, *J* = 15.0, 6.2, 2.8 Hz, 1H), 3.55 (d, *J* = 16.6 Hz, 1H), 3.22 – 3.11 (m, 2H), 2.17 (s, 3H), 2.13 – 2.02 (m, 4H), 1.71-1.65 (m, 2H), 1.58 – 1.51 (m, 3H), 1.41-1.34 (m, 1H), 1.31-1.24 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 204.6, 203.6, 142.9, 129.6, 127.6, 117.4, 116.1, 110.4, 69.7, 61.0, 49.9, 31.3, 28.0, 26.7, 26.5, 26.2, 26.1, 25.4. **HRMS (ESI):** calcd. for $C_{18}H_{24}NO_2$ $[M+H]^+$: 286.1807, found: 286.1804.

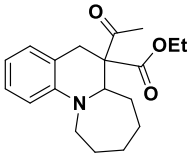
ethyl 3-acetyl-1-ethyl-2-methyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (3k)



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:100) afforded the product (81.5 mg, 94% yield) as a pale yellow oil and the diastereoselectivity was 1.6:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (dd, *J* = 13.3, 6.1 Hz, 2H), 6.60 (dd, *J* = 11.8, 7.0 Hz, 1H), 6.52 (t, *J* = 7.0 Hz, 1H), 4.30 – 4.16 (m, 2H), 4.15 – 3.93 (m, 1H), 3.47 – 3.25 (m, 3H), 3.16 (dd, *J* = 25.7, 16.8 Hz, 1H), 2.25 (s, 1H), 2.15 (s, 2H), 1.28 (t, *J* = 7.1 Hz, 2H), 1.22 (q, *J* = 7.3 Hz, 3H), 1.12 – 1.05 (m, 3H), 0.98 (d, *J* = 6.5 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 203.1, 201.9, 169.7, 169.5, 142.3, 142.2, 129.4, 129.3, 127.5, 127.3, 118.4, 118.0, 116.0, 115.8, 110.9, 110.6, 63.11 (s), 62.2, 61.7, 61.6, 55.8, 55.6, 44.9, 44.8, 28.0, 27.8, 26.4, 25.4, 15.7, 15.3, 14.0, 13.8, 13.0, 12.9. **HRMS (ESI):** calcd. for $C_{17}H_{24}NO_3$ $[M+H]^+$: 290.1756, found: 290.1760.

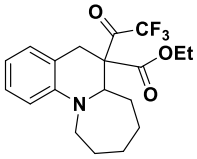
ethyl 6-acetyl-5,6,6a,7,8,9,10,11-octahydroazepino[1,2-a]quinoline-6-carboxylate (3l) (dr = 2:1)



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:100) afforded the product (73.7 mg, 78% yield) as a pale yellow oil and the diastereoselectivity was 2:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 – 7.00 (m, 2H), 6.58 (q, *J* = 6.9 Hz, 1H), 6.52 (dd, *J* = 8.1, 4.8 Hz, 1H), 4.25 – 4.00 (m, 3H), 3.92 – 3.84 (m, 1H), 3.47 – 3.31 (m, 1H), 3.17 (ddd, *J* = 14.7, 10.3, 5.0 Hz, 2H), 2.26 (s, 2H), 2.17 (s, 1H), 2.12 – 1.98 (m, 1H), 1.72 – 1.62 (m, 2H), 1.61 – 1.48 (m, 3H), 1.47 – 1.30 (m, 2H), 1.30 – 1.07 (m, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.9, 202.1, 169.7, 169.4, 142.7, 142.6, 129.4, 129.3, 127.5, 127.4, 117.7, 117.5, 115.9, 115.6, 110.2, 109.9, 62.6, 61.7, 61.6, 61.5, 60.9, 60.6, 50.0, 49.8, 31.6, 30.7, 28.1, 27.9, 27.3, 26.9, 26.4, 26.3, 26.2, 26.0, 25.9, 25.3, 14.0, 13.9. **HRMS (ESI):** calcd. for $C_{19}H_{26}NO_3$ $[M+H]^+$: 316.1913, found: 316.1916.

ethyl 6-(2,2,2-trifluoroacetyl)-5,6,6a,7,8,9,10,11-octahydroazepino[1,2-a]quinoline-6-carboxylate (3m)

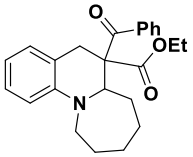


Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:100) afforded the product (90.7 mg, 82% yield) as a pale yellow oil and the diastereoselectivity was 2.3:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09-7.03 (m, 2H), 6.64-6.53 (m, 2H), 4.29 – 4.21 (m, 1H), 4.18 – 4.05 (m, 2H), 3.89 (tdd, *J* = 15.0, 6.3, 3.0 Hz, 1H), 3.51 – 3.28 (m, 2H), 3.26 – 3.11 (m, 1H), 2.08 – 1.97 (m, 1H), 1.78 – 1.71 (m, 1H), 1.70 – 1.60 (m, 2H), 1.60 – 1.42 (m, 4H), 1.27 (t, *J* = 7.1 Hz, 2H), 1.15 – 1.09 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 186.8 (q, *J* = 40.3 Hz), 185.8 (q, *J* = 34.0 Hz), 167.7, 166.9, 142.5, 142.0, 134.2, 130.5, 129.2, 129.1, 128.0, 127.8, 119.6, 118.7, 116.2, 116.2, 115.9 (q, *J* = 294.8 Hz), 115.7 (q, *J* = 294.8 Hz), 115.7, 110.5, 110.4, 62.5, 62.2, 60.0, 59.2, 59.0, 57.9, 50.2, 50.1, 30.9, 30.8,

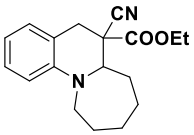
27.9, 27.8, 27.4, 27.1, 26.2, 25.9, 25.9, 25.8, 13.8, 13.8. **HRMS (ESI):** calcd. for $C_{19}H_{23}F_3NO_3$ $[M+H]^+$: 370.1630, found: 370.1636.

ethyl 6-benzoyl-5,6,6a,7,8,9,10,11-octahydroazepino[1,2-a]quinoline-6-carboxylate (3n)



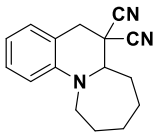
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:100) afforded the product (100.6 mg, 89% yield) as a pale yellow oil and the diastereoselectivity was 1.2:1.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (t, *J* = 6.1 Hz, 2H), 7.61 (d, *J* = 7.4 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.50 – 7.42 (m, 3H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.09 – 6.98 (m, 3H), 6.88 (d, *J* = 7.4 Hz, 1H), 6.58 (t, *J* = 7.2 Hz, 2H), 6.54 – 6.44 (m, 2H), 4.38-4.35 (m, 1H), 4.29 – 4.18 (m, 3H), 4.13 – 3.98 (m, 2H), 3.97-3.92 (m, 1H), 3.65-3.60 (m, 1H), 3.56-3.48 (m, 2H), 3.37-3.40 (m, 1H), 3.28 – 3.18 (m, 2H), 2.74 – 2.65 (m, 1H), 2.08 – 1.98 (m, 1H), 1.97 – 1.88 (m, 1H), 1.81 (dt, *J* = 11.1, 4.9 Hz, 1H), 1.74 – 1.51 (m, 7H), 1.51 – 1.38 (m, 5H), 1.33 – 1.28 (m, 1H), 1.25 (t, *J* = 7.0 Hz, 3H), 1.02 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 196.2, 195.5, 170.9, 170.6, 143.0, 142.6, 137.3, 137.0, 132.7, 131.6, 129.2, 129.2, 128.7, 128.7, 128.5, 128.4, 128.1, 127.6, 127.5, 117.8, 116.9, 115.5, 109.9, 109.9, 61.9, 61.5, 61.4, 60.5, 60.0, 59.3, 50.4, 49.7, 46.0, 31.1, 30.9, 30.7, 30.0, 27.3, 27.2, 26.3, 26.2, 25.9, 14.0, 13.9. **HRMS (ESI):** calcd. for $C_{24}H_{28}NO_3$ $[M+H]^+$: 378.2069, found: 378.2073.

ethyl 6-cyano-5,6,6a,7,8,9,10,11-octahydroazepino[1,2-a]quinoline-6-carboxylate (3o)



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:100) afforded the product (81.3 mg, 91% yield) as a pale yellow oil and the diastereoselectivity was 9:1.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (t, *J* = 7.8 Hz, 1H), 7.03 (d, *J* = 7.4 Hz, 1H), 6.68 (t, *J* = 7.4 Hz, 1H), 6.63 (d, *J* = 8.3 Hz, 1H), 4.31 – 4.15 (m, 2H), 3.90 (dd, *J* = 11.3, 3.9 Hz, 1H), 3.83 (dt, *J* = 15.4, 4.9 Hz, 1H), 3.52 (d, *J* = 16.6 Hz, 1H), 3.23 (d, *J* = 16.6 Hz, 1H), 3.20 – 3.13 (m, 1H), 2.15 – 1.98 (m, 2H), 1.78 – 1.62 (m, 4H), 1.42 (ddd, *J* = 13.2, 9.8, 4.3 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.6, 143.1, 128.9, 127.8, 118.3, 117.2, 116.6, 112.1, 62.8, 62.3, 49.7, 45.0, 31.8, 30.3, 28.2, 26.3, 26.0, 14.0. **HRMS (ESI):** calcd. for $C_{18}H_{23}N_2O_2$ $[M+H]^+$: 299.1760, found: 299.1763.

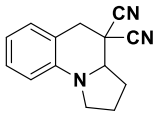
6a,7,8,9,10,11-hexahydroazepino[1,2-a]quinoline-6,6(5H)-dicarbonitrile (3p)



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:100) afforded the product (74.5 mg, 99% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.8 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 6.74 (t, *J* = 7.4 Hz, 2H), 3.96 (dt, *J* = 15.5, 5.0 Hz, 1H), 3.83 (dd, *J* = 11.2, 4.1 Hz, 1H), 3.45 (q, *J* = 16.6 Hz, 2H), 3.34 – 3.23 (m, 1H), 2.21 (dtd, *J* = 10.6, 7.2, 3.5 Hz, 1H), 2.13 – 2.01 (m, 1H), 1.85 – 1.57 (m, 5H), 1.43 (ddd, *J* = 19.6, 11.5, 3.6 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.5, 129.2, 129.0, 117.8, 115.1, 114.9, 113.2, 112.6, 62.7, 49.9, 34.0, 33.6, 30.5, 27.9, 26.3, 25.7. **HRMS (ESI):** calcd. for $C_{16}H_{18}N_3$ $[M+H]^+$: 252.1501, found: 252.1505.

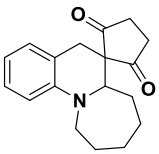
1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoline-4,4(5H)-dicarbonitrile (3q)



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:100) afforded the product (59.5 mg, 89% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (t, *J* = 7.7 Hz, 1H), 7.05 (d, *J* = 7.5 Hz, 1H), 6.73 (t, *J* = 7.4 Hz, 1H), 6.58 (d, *J* = 8.2 Hz, 1H), 3.81 (dd, *J* = 8.6, 6.1 Hz, 1H), 3.59 – 3.50 (m, 2H), 3.49 – 3.37 (m, 2H), 2.53 (ddd, *J* = 14.3, 7.1, 2.0 Hz, 1H), 2.31 – 2.22 (m, 1H), 2.20 – 2.12 (m, 1H), 2.12 – 2.02 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 141.9, 129.3, 129.0, 117.6, 115.1, 113.5, 113.1, 112.2, 62.9, 47.8, 38.2, 33.9, 30.0, 22.8. **HRMS (ESI):** calcd. for $C_{14}H_{14}N_3$ $[M+H]^+$: 224.1188, found: 224.1190.

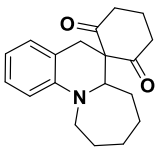
6a,7,8,9,10,11-hexahydro-5H-spiro[azepino[1,2-a]quinoline-6,1'-cyclopentane]-2',5'-dione (3r)



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:100) afforded the product (72.4 mg, 85% yield) as a white solid.

^{1}H NMR (500 MHz, DMSO) δ 7.08 – 6.99 (m, 2H), 6.66 – 6.55 (m, 2H), 3.86 – 3.72 (m, 2H), 3.20 – 2.96 (m, 4H), 2.74 – 2.60 (m, 1H), 2.58 – 2.50 (m, 2H), 1.97 (dd, *J* = 10.1, 4.4 Hz, 1H), 1.68 – 1.55 (m, 2H), 1.49 (dt, *J* = 8.5, 5.6 Hz, 2H), 1.45 – 1.32 (m, 3H); **^{13}C NMR** (126 MHz, DMSO) δ 212.3, 211.7, 143.7, 129.3, 126.9, 118.8, 116.0, 110.9, 58.6, 58.3, 50.1, 35.8, 34.5, 29.7, 28.0, 25.9, 25.7, 25.1. **HRMS (ESI):** calcd. for $C_{18}H_{22}NO_2$ $[M+H]^+$: 284.1651, found: 284.1657.

6a,7,8,9,10,11-hexahydro-5H-spiro[azepino[1,2-a]quinoline-6,1'-cyclohexane]-2',6'-dione (3s)

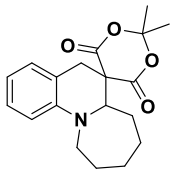


Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:100) afforded the product (79.3 mg, 89% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (d, *J* = 7.4 Hz, 1H), 7.02 (t, *J* = 7.7 Hz, 1H), 6.69 (t, *J* = 7.3 Hz, 1H), 6.55 (d, *J* = 8.2 Hz, 1H), 4.07 (dd, *J* = 9.1, 5.3 Hz, 1H), 4.05 – 3.96 (m, 1H), 3.32 (d, *J* = 17.4 Hz, 1H), 3.12 – 3.00 (m, 2H), 2.94 (d, *J* = 17.3 Hz, 1H), 2.83 (td, *J* = 14.2, 6.7 Hz, 1H), 2.65 (dd, *J* = 14.6, 1.9 Hz, 1H), 2.58 – 2.51 (m, 1H), 2.26 – 2.16 (m, 1H), 2.15 – 2.07 (m, 1H), 1.72 – 1.57 (m, 3H), 1.52 – 1.35 (m, 5H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 205.4, 203.9, 141.5, 129.3, 126.6, 119.8, 117.2, 110.9, 70.1, 64.4,

50.6, 37.9, 36.2, 30.0, 27.2, 25.9, 25.5, 23.6, 18.7. **HRMS (ESI):** calcd. for $C_{19}H_{24}NO_2$ $[M+H]^+$: 298.1807, found: 298.1809.

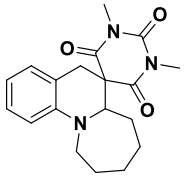
2',2'-dimethyl-6a,7,8,9,10,11-hexahydro-5H-spiro[azepino[1,2-a]quinoline-6,5'-[1,3]dioxane]-4',6'-dione (3t)



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:100) afforded the product (97.7 mg, 99% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (t, *J* = 7.7 Hz, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.77 (t, *J* = 7.4 Hz, 1H), 3.63 (dd, *J* = 12.3, 4.0 Hz, 1H), 3.54 – 3.45 (m, 2H), 3.41 (ddd, *J* = 15.9, 6.2, 2.7 Hz, 1H), 3.20 (d, *J* = 17.0 Hz, 1H), 1.99 – 1.87 (m, 3H), 1.84 – 1.77 (m, 4H), 1.76 – 1.67 (m, 4H), 1.62 (dddd, *J* = 17.1, 12.9, 8.6, 4.5 Hz, 1H), 1.47 (dd, *J* = 22.8, 11.2 Hz, 1H), 1.41 – 1.29 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.4, 166.5, 146.1, 128.6, 126.8, 119.7, 118.3, 115.1, 104.8, 67.6, 50.6, 50.4, 32.8, 30.7, 30.4, 29.5, 28.3, 27.6, 26.7. **HRMS (ESI):** calcd. for $C_{19}H_{24}NO_4$ $[M+H]^+$: 330.1705, found: 330.1708.

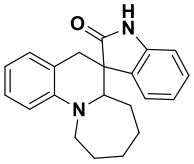
1',3'-dimethyl-6a,7,8,9,10,11-hexahydro-2'H,5H-spiro[azepino[1,2-a]quinoline-6,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione (3u)



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:100) afforded the product (93.1 mg, 91% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (dd, *J* = 13.5, 7.5 Hz, 2H), 6.74 (dd, *J* = 14.9, 7.7 Hz, 2H), 3.60 – 3.49 (m, 2H), 3.34 (s, 2H), 3.30 (s, 6H), 3.20 (ddd, *J* = 15.4, 8.1, 3.5 Hz, 1H), 2.02 – 1.90 (m, 1H), 1.73 – 1.64 (m, 2H), 1.64 – 1.53 (m, 3H), 1.49-1.42 (m, 1H), 1.39-1.31 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.1, 168.7, 151.7, 144.5, 128.6, 126.6, 120.4, 118.0, 113.4, 67.2, 53.3, 50.6, 30.1, 29.6, 29.5, 28.9, 28.8, 27.2, 26.0. **HRMS (ESI):** calcd. for $C_{19}H_{24}N_3O_4$ $[M+H]^+$: 342.1818, found: 342.1820.

6a,7,8,9,10,11-hexahydro-5H-spiro[azepino[1,2-a]quinoline-6,3'-indolin]-2'-one (3v)

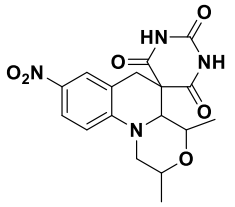


Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:20) afforded the product (66.7 mg, 70% yield) as a pale yellow solid and the diastereoselectivity was 1.7:1.

^{1}H NMR (500 MHz, DMSO) δ 10.60 (s, 1H), 7.16 – 7.09 (m, 2H), 6.93 (d, *J* = 7.3 Hz, 1H), 6.88 (d, *J* = 7.7 Hz, 1H), 6.81 – 6.72 (m, 2H), 6.58 (t, *J* = 7.3 Hz, 1H), 6.52 (d, *J* = 7.5 Hz, 1H), 3.60 – 3.44 (m, 2H),

3.15 (d, *J* = 15.9 Hz, 1H), 2.52 (d, *J* = 15.3 Hz, 2H), 1.71 (d, *J* = 6.0 Hz, 1H), 1.66 – 1.54 (m, 2H), 1.52 – 1.44 (m, 2H), 1.20 (ddd, *J* = 23.7, 18.2, 9.5 Hz, 3H); **^{13}C NMR** (126 MHz, DMSO) δ 180.1, 147.4, 142.4, 130.6, 129.8, 128.2, 127.8, 125.1, 121.6, 119.9, 116.6, 112.7, 109.8, 62.6, 50.1, 49.5, 37.2, 29.8, 29.3, 29.0, 26.0. **HRMS (ESI):** calcd. for $C_{21}H_{23}N_2O$ $[M+H]^+$: 319.1810, found: 319.1811.

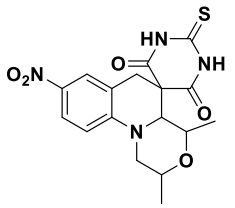
2',4'-dimethyl-8'-nitro-1',2',4',4a'-tetrahydro-2H,6'H-spiro[pyrimidine-5,5'-[1,4]oxazino[4,3-a]quinoline]-2,4,6(1H,3H)-trione (3w)



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:100) afforded the product (93.1 mg, 83% yield) as a yellow solid.

^{1}H NMR (500 MHz, DMSO) δ 11.71 (s, 2H), 7.98 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.84 (d, *J* = 2.1 Hz, 1H), 7.04 (d, *J* = 9.4 Hz, 1H), 4.30 (dd, *J* = 13.6, 1.9 Hz, 1H), 3.92 (d, *J* = 9.0 Hz, 1H), 3.60 (d, *J* = 15.0 Hz, 2H), 3.54 (dd, *J* = 8.9, 6.4 Hz, 1H), 2.99 (dd, *J* = 13.7, 10.7 Hz, 1H), 2.88 (t, *J* = 9.8 Hz, 1H), 1.17 (t, *J* = 5.4 Hz, 3H), 0.95 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (126 MHz, DMSO) δ 171.6, 168.2, 150.9, 149.9, 136.1, 125.1, 124.5, 119.6, 111.2, 72.6, 71.5, 62.9, 53.2, 51.5, 37.4, 18.9, 18.6. **HRMS (ESI):** calcd. for $C_{17}H_{19}N_4O_6$ $[M+H]^+$: 375.1305, found: 375.1309.

2',4'-dimethyl-8'-nitro-2-thioxo-1',2,2',3,4',4a'-hexahydro-4H,6'H-spiro[pyrimidine-5,5'-[1,4]oxazino[4,3-a]quinoline]-4,6(1H)-dione (3x)



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:100) afforded the product (115.8 mg, 99% yield) as a yellow solid.

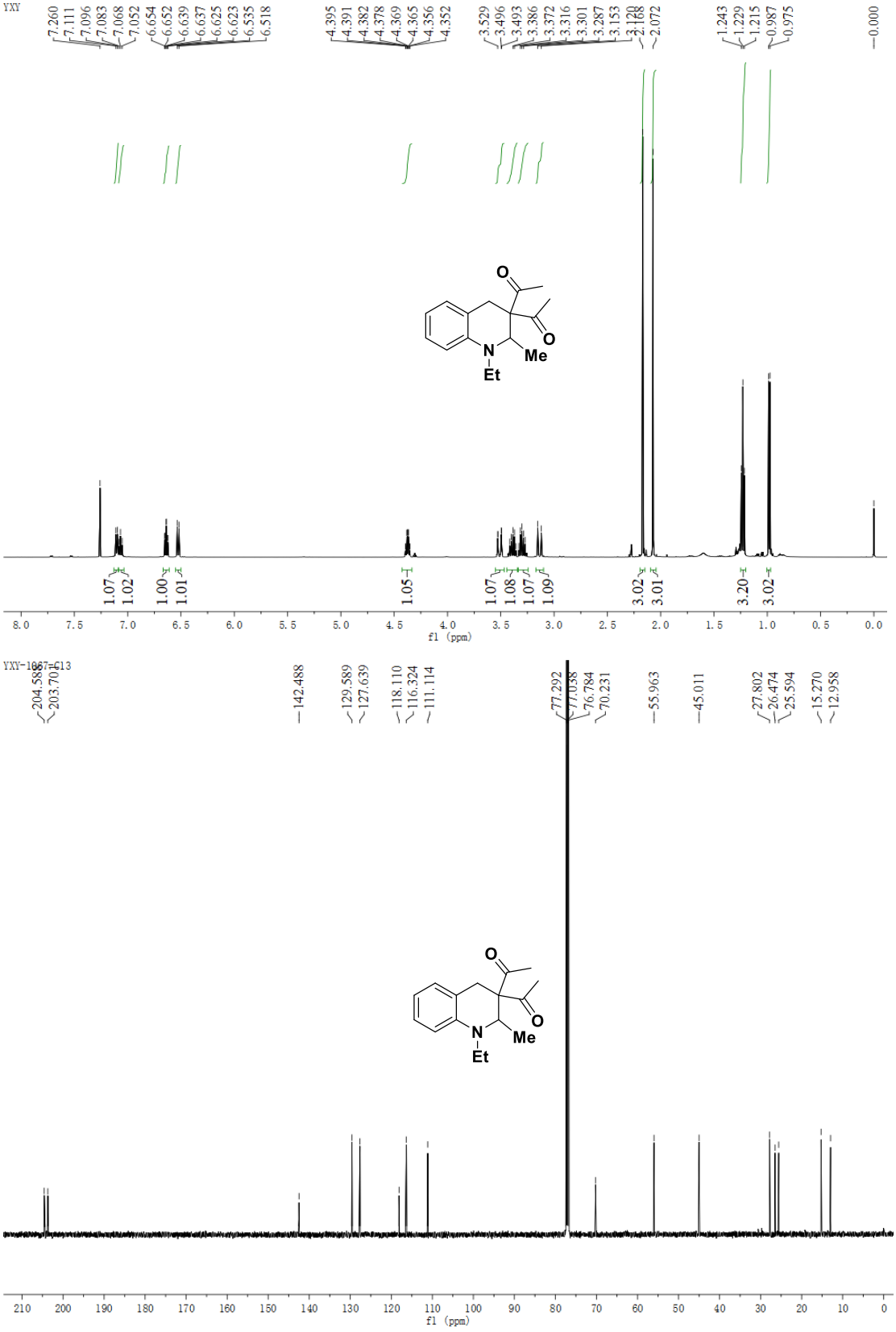
^{1}H NMR (500 MHz, DMSO) δ 12.97 (s, 1H), 12.71 (s, 1H), 7.98 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.87 (d, *J* = 2.2 Hz, 1H), 7.05 (d, *J* = 9.4 Hz, 1H), 4.30 (dd, *J* = 13.5, 1.6 Hz, 1H), 3.90 (d, *J* = 9.0 Hz, 1H), 3.67 – 3.55 (m, 2H), 3.50 (dd, *J* = 8.9, 6.4 Hz, 1H), 3.00 (dd, *J* = 13.7, 10.8 Hz, 1H), 2.90 (d, *J* = 15.0 Hz, 1H), 1.16 (d, *J* = 6.1 Hz, 3H), 0.92 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (126 MHz, DMSO) δ 183.4, 174.3, 170.7, 155.6, 141.0, 129.9, 129.4, 124.0, 116.1, 77.2, 76.3, 67.8, 57.9, 56.7, 41.9, 23.8, 23.3. **HRMS (ESI):** calcd. for $C_{17}H_{19}N_4O_5S$ $[M+H]^+$: 391.1076, found: 391.1079.

Reference

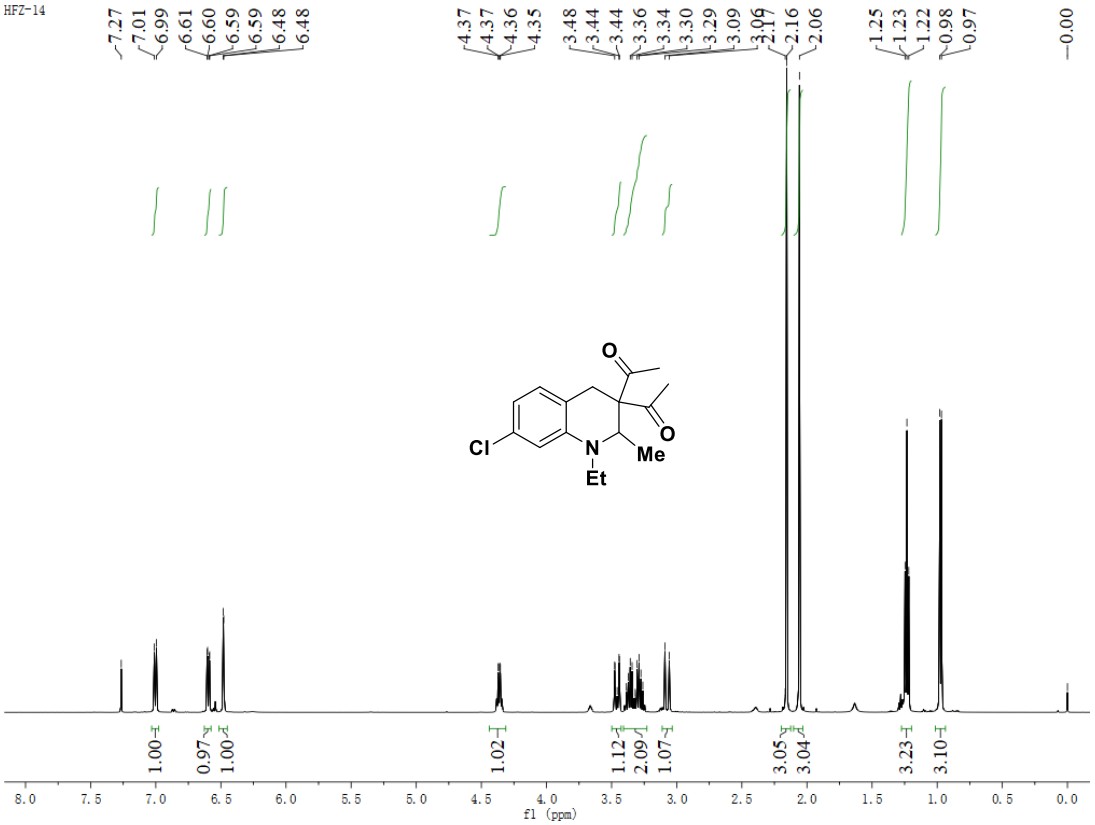
1. Jurberg, I. D.; Peng, B.; W çstefeld, E.; Wasserloos, M.; Maulide, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 1950.

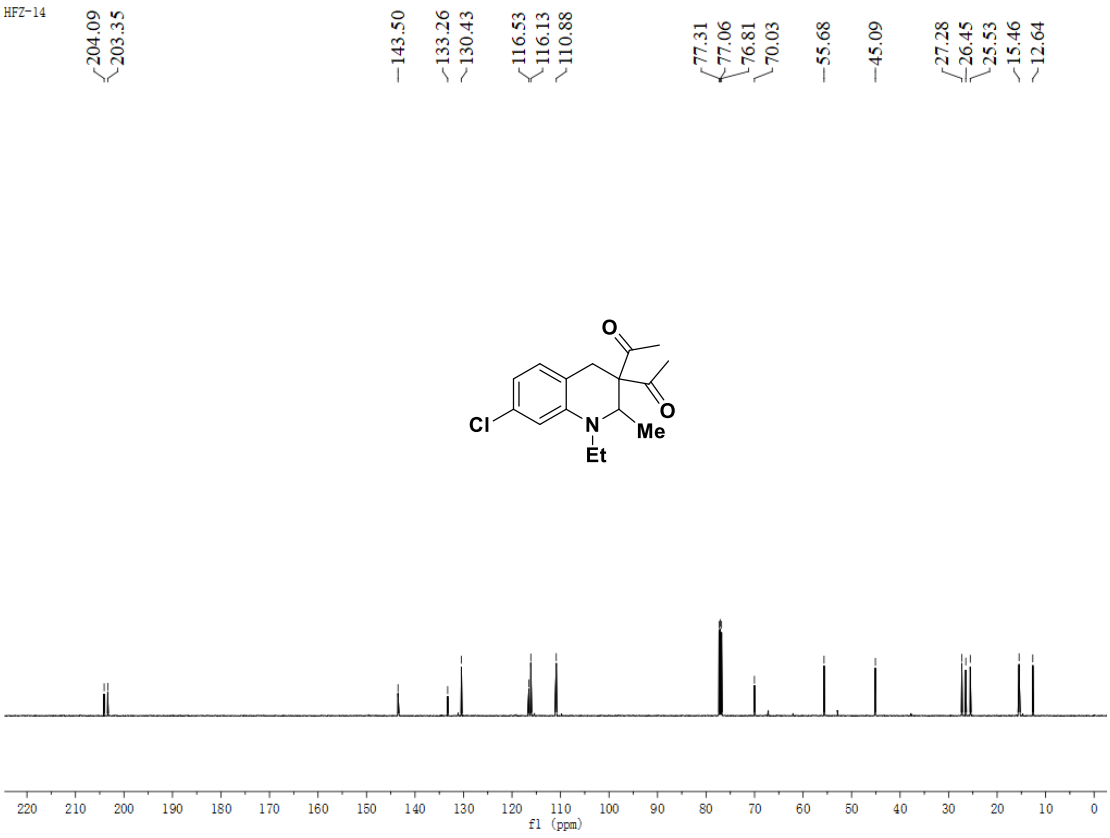
4. ^{1}H and ^{13}C NMR Spectra

1,1'-(1-ethyl-2-methyl-1,2,3,4-tetrahydroquinoline-3,3-diyl)bis(ethan-1-one) (3a)

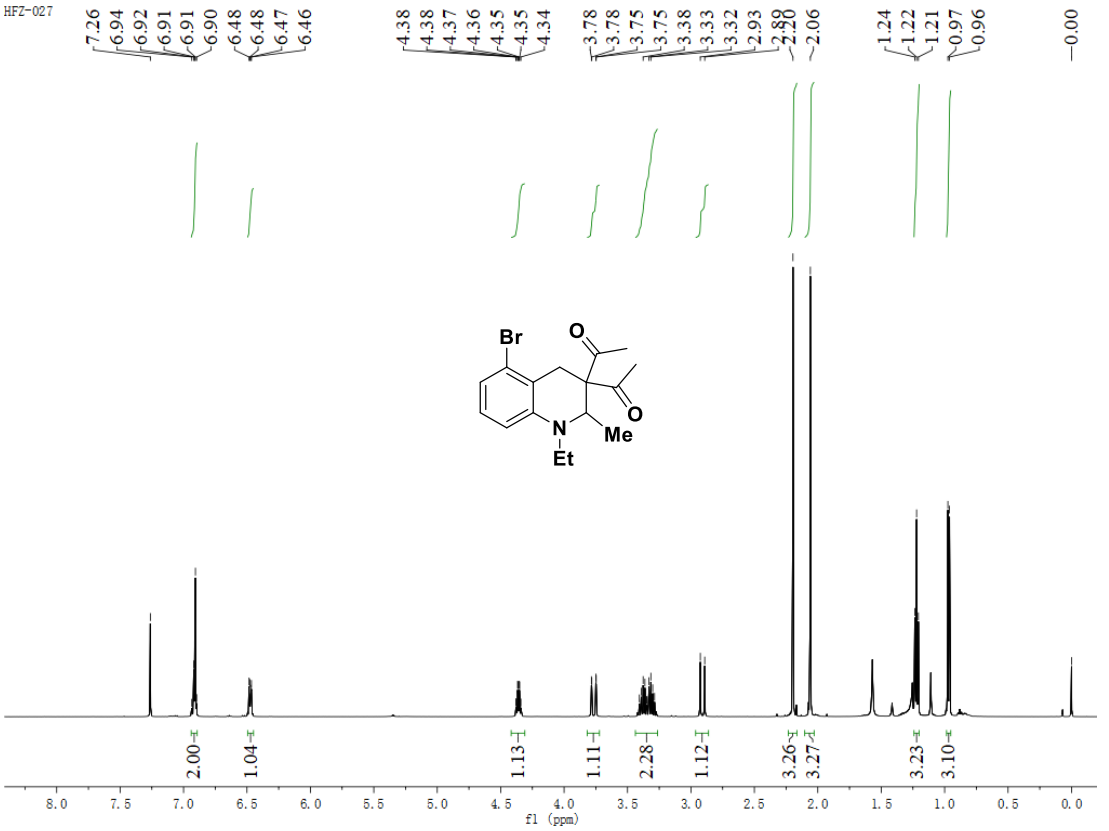


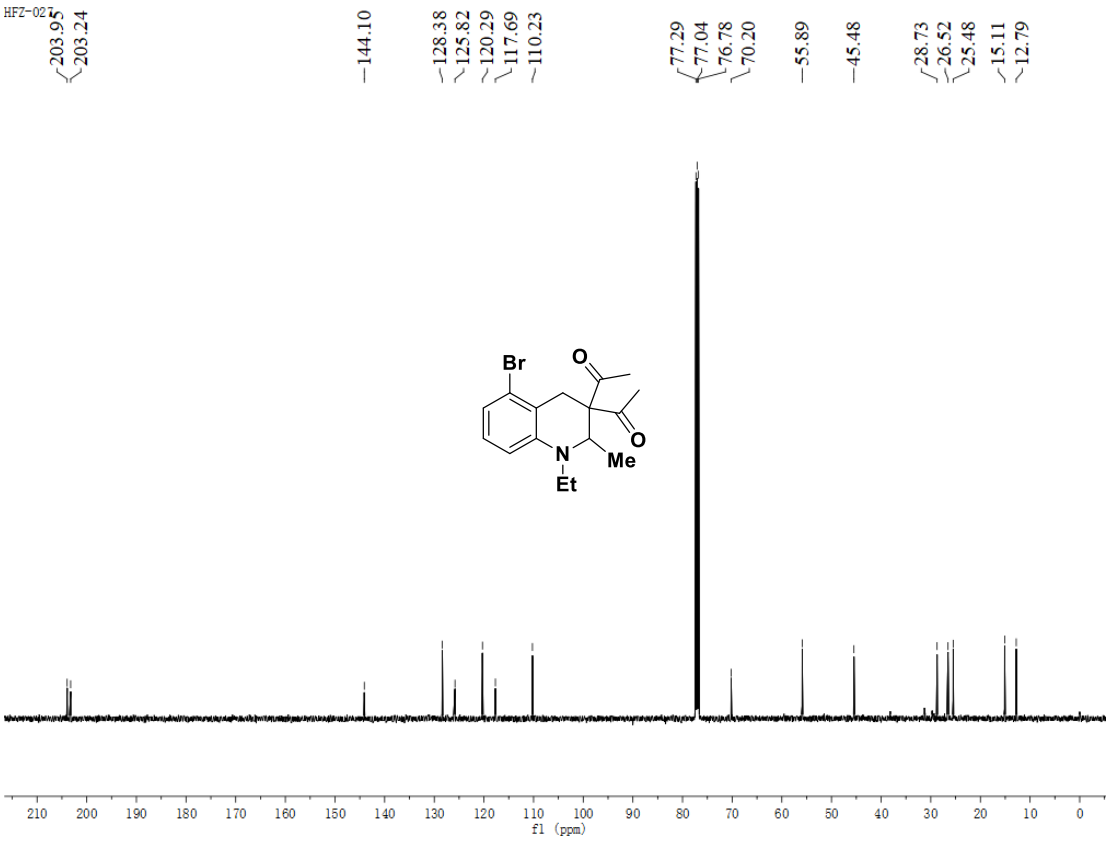
1,1'-(7-chloro-1-ethyl-2-methyl-1,2,3,4-tetrahydroquinoline-3,3-diyl)bis(ethan-1-one) (3b)



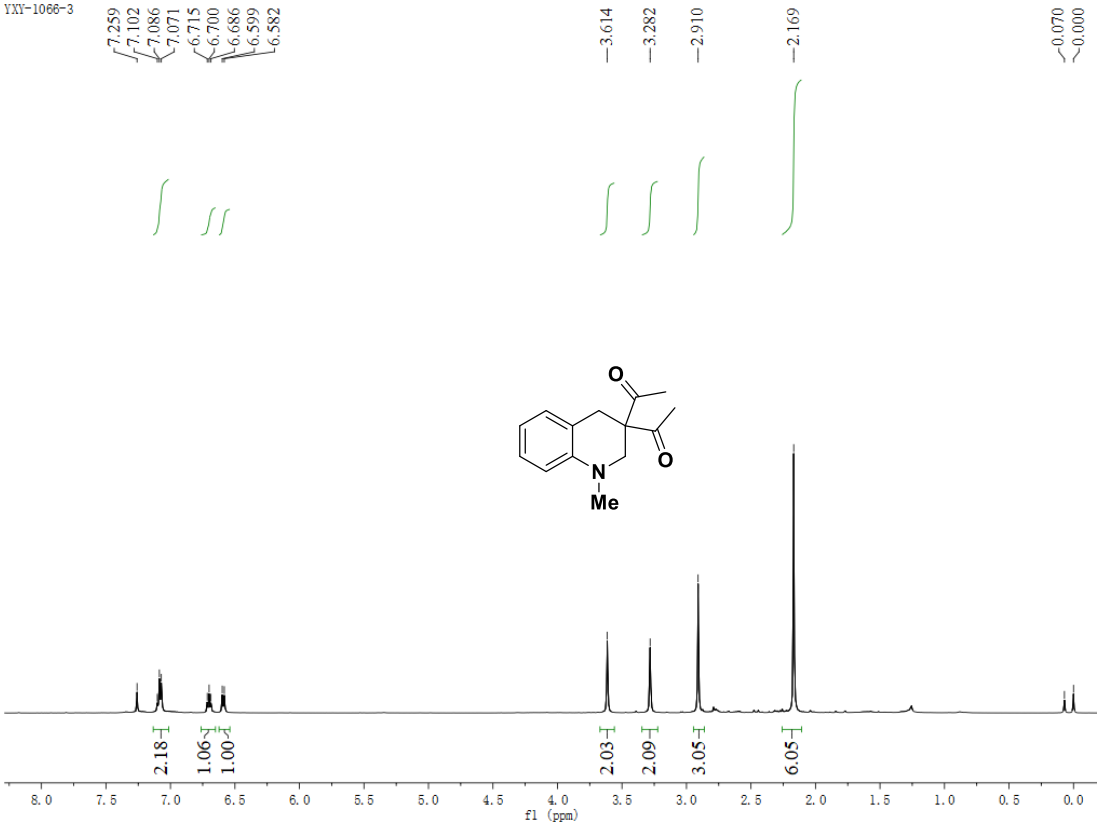


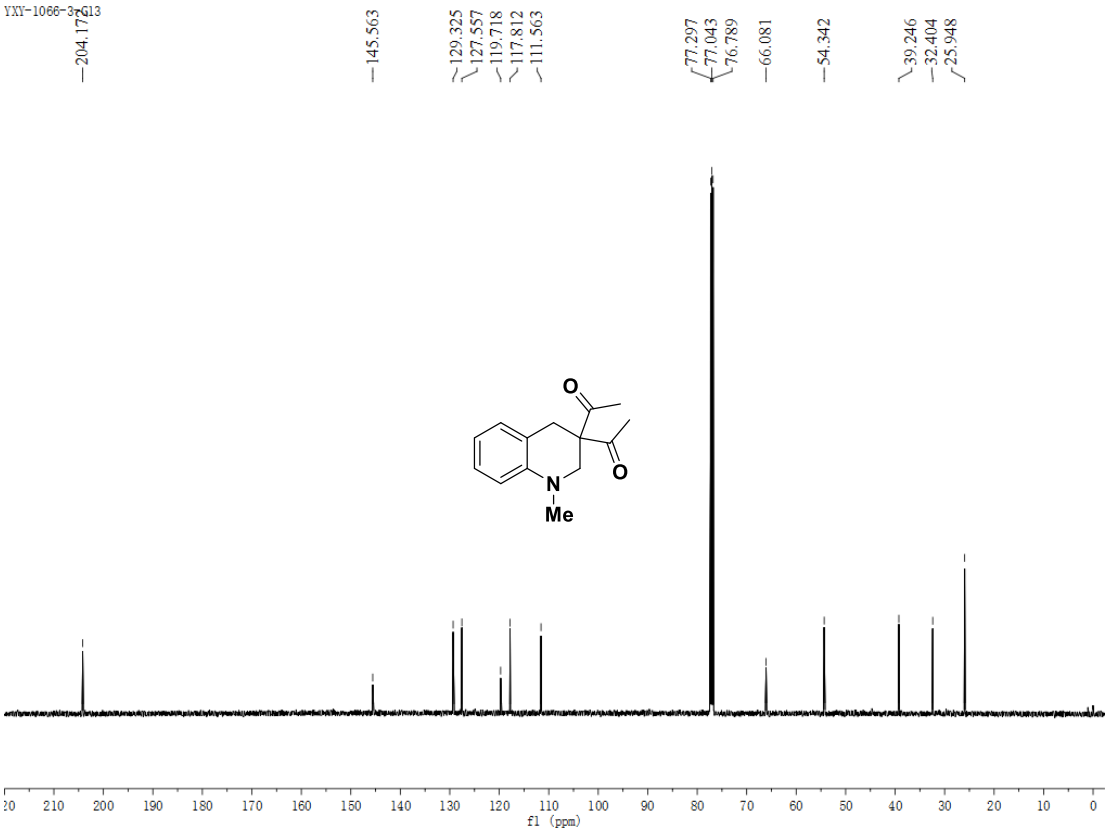
1,1'-(5-bromo-1-ethyl-2-methyl-1,2,3,4-tetrahydroquinoline-3,3-diyl)bis(ethan-1-one) (3c)



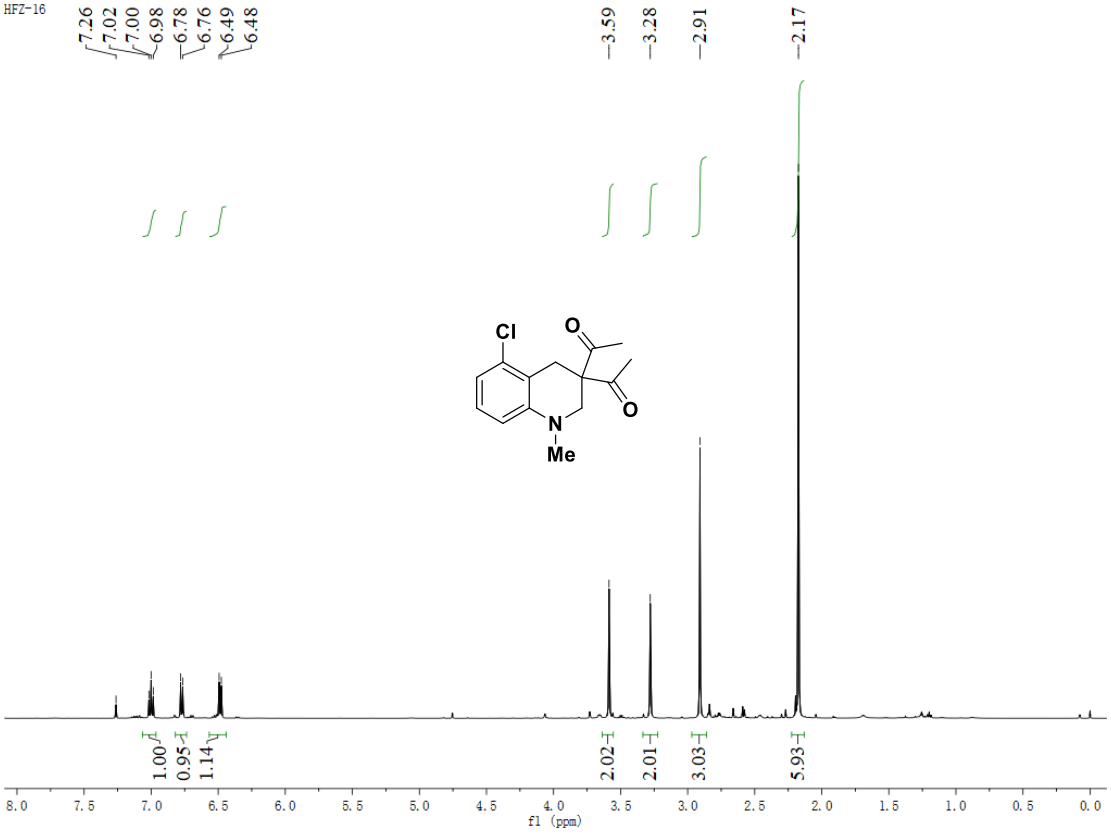


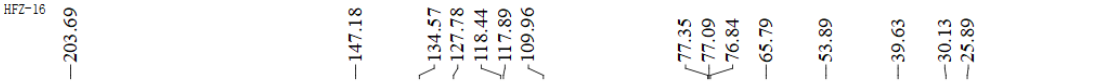
1,1'-(1-methyl-1,2,3,4-tetrahydroquinoline-3,3-diyl)bis(ethan-1-one) (3d)

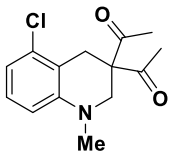


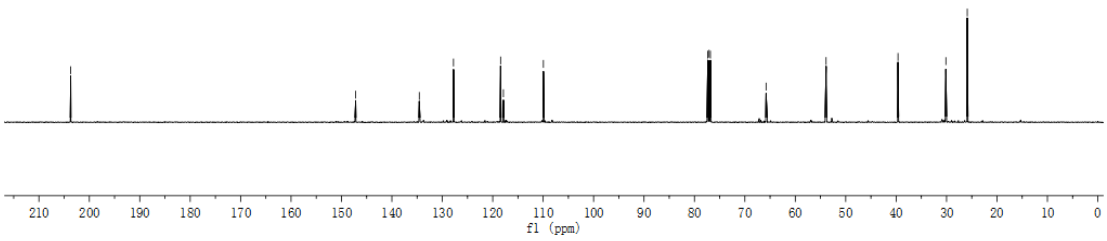


1,1'-(5-chloro-1-methyl-1,2,3,4-tetrahydroquinoline-3,3-diyl)bis(ethan-1-one) (3e)

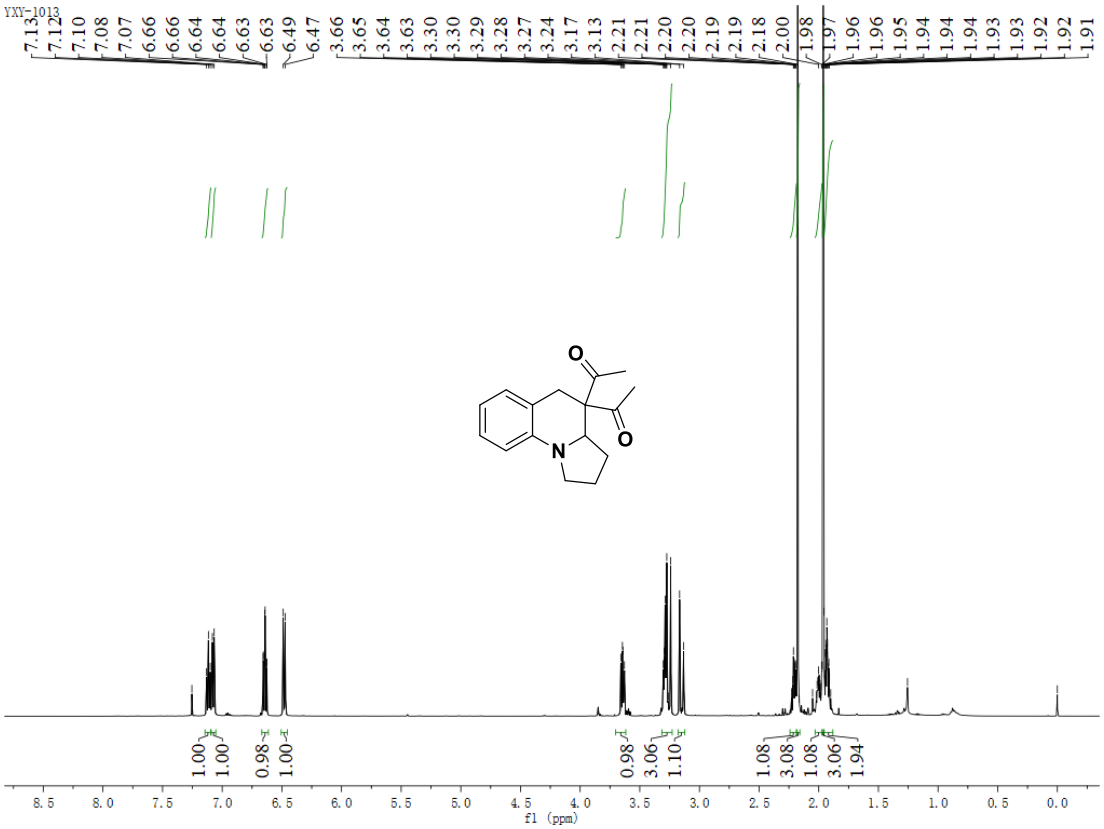


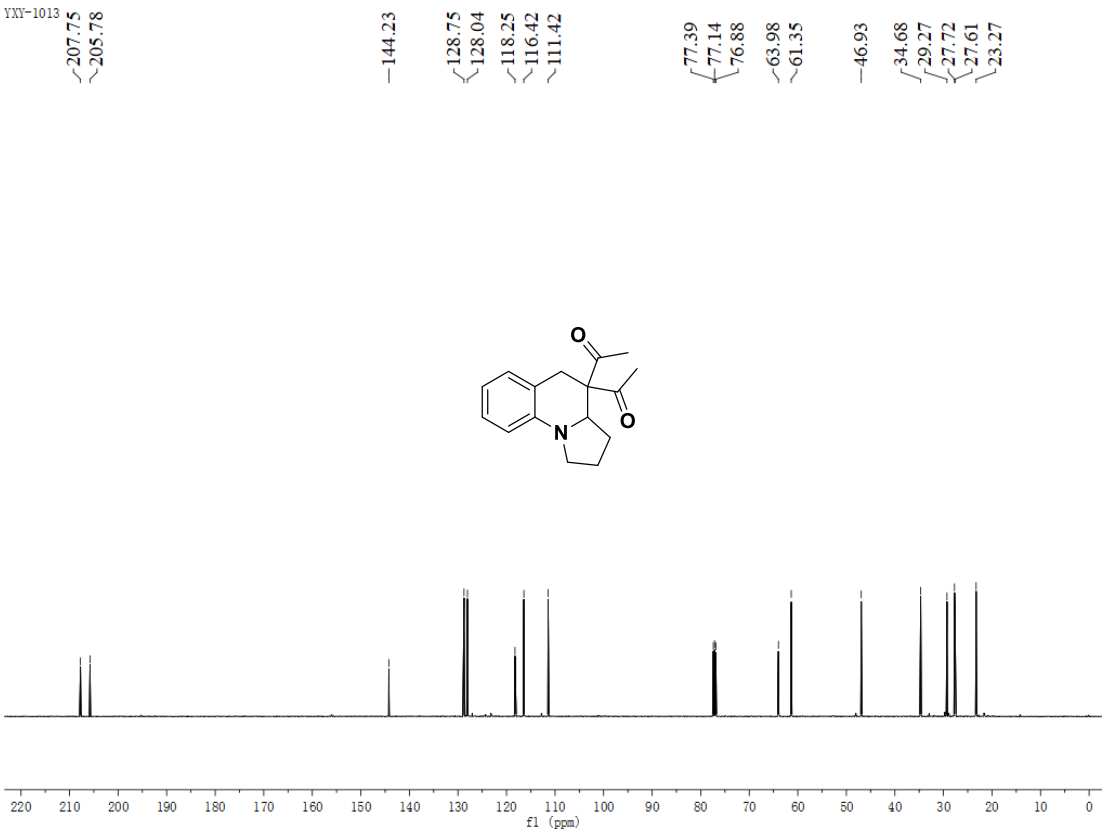




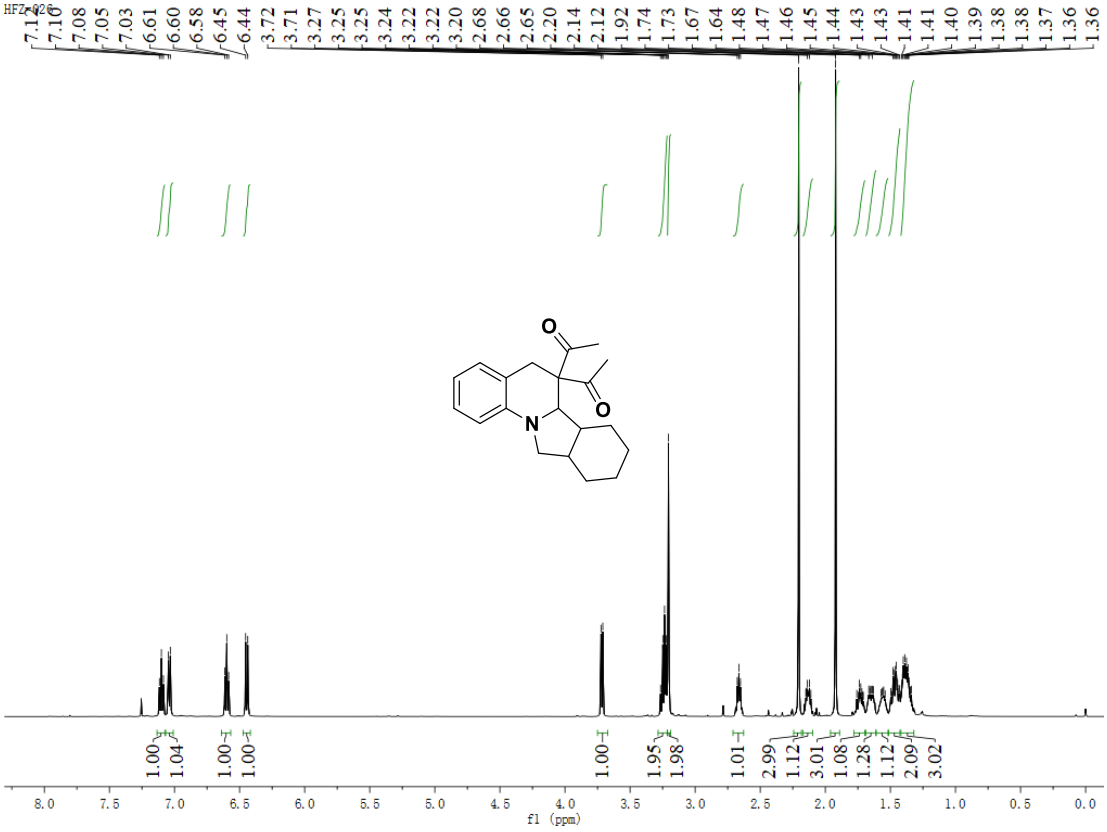


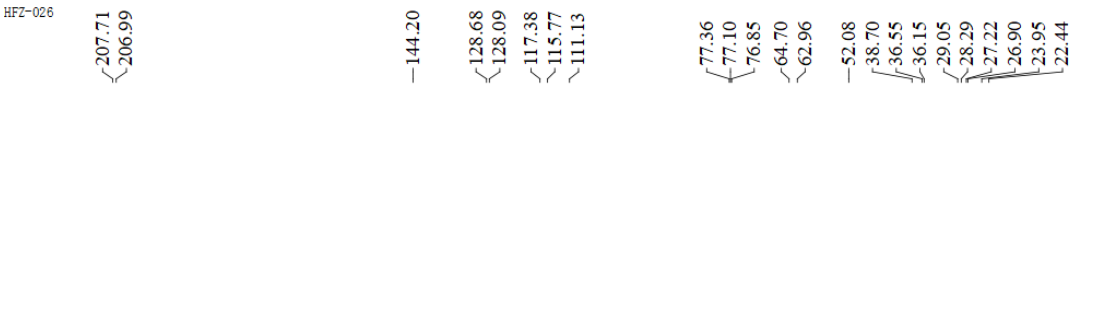
1,1'-(1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinoline-4,4-diyl)bis(ethan-1-one) (3f)

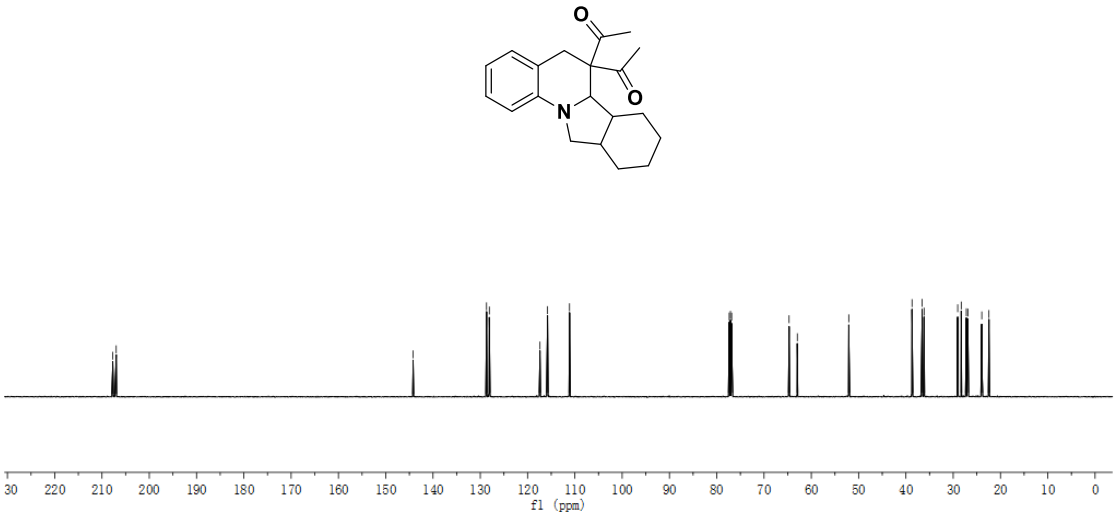




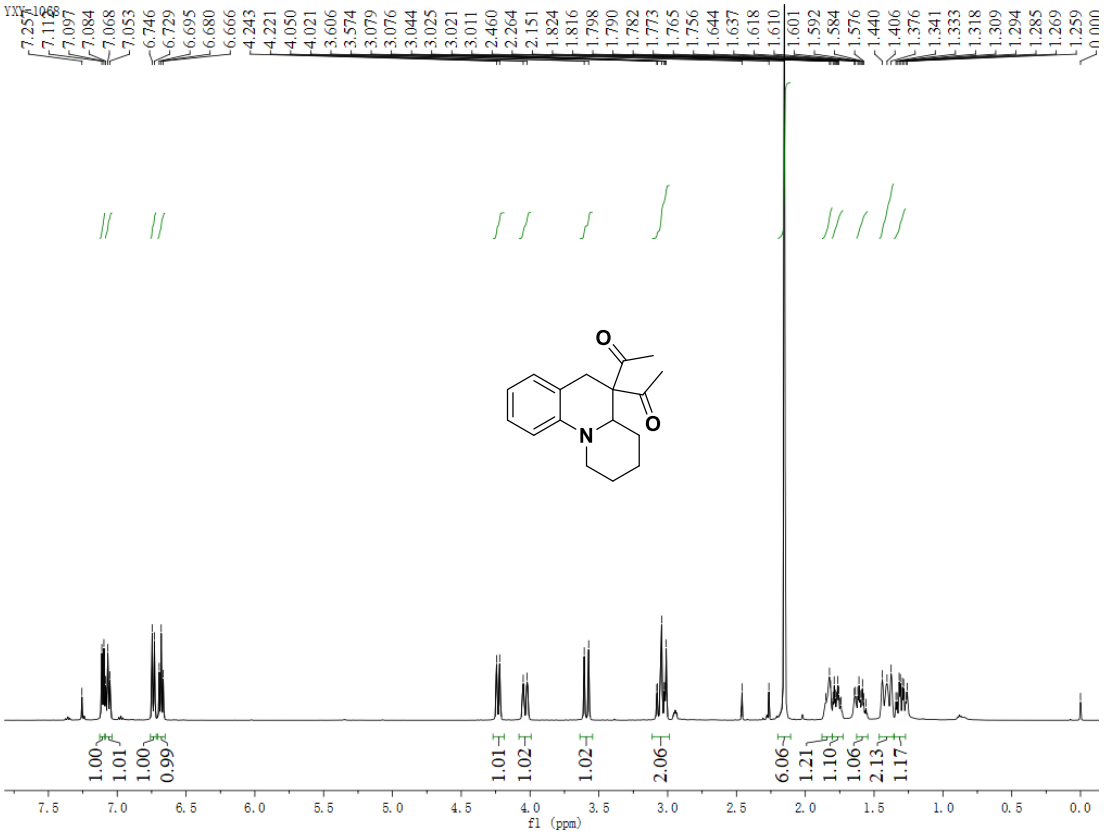
1,1'-5,6,6a,6b,7,8,9,10,10a,11-decahydroisoindolo[2,1-a]quinoline-6,6-diyl)bis(ethan-1-one) (3g)

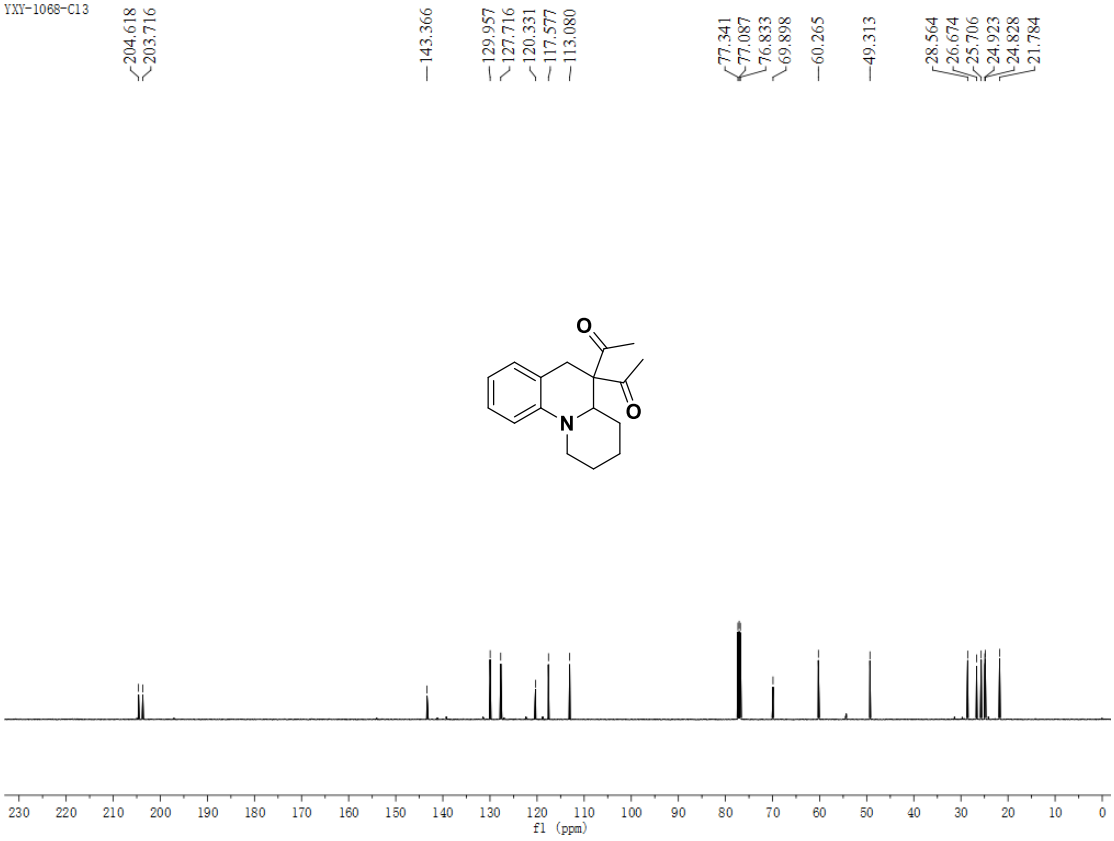




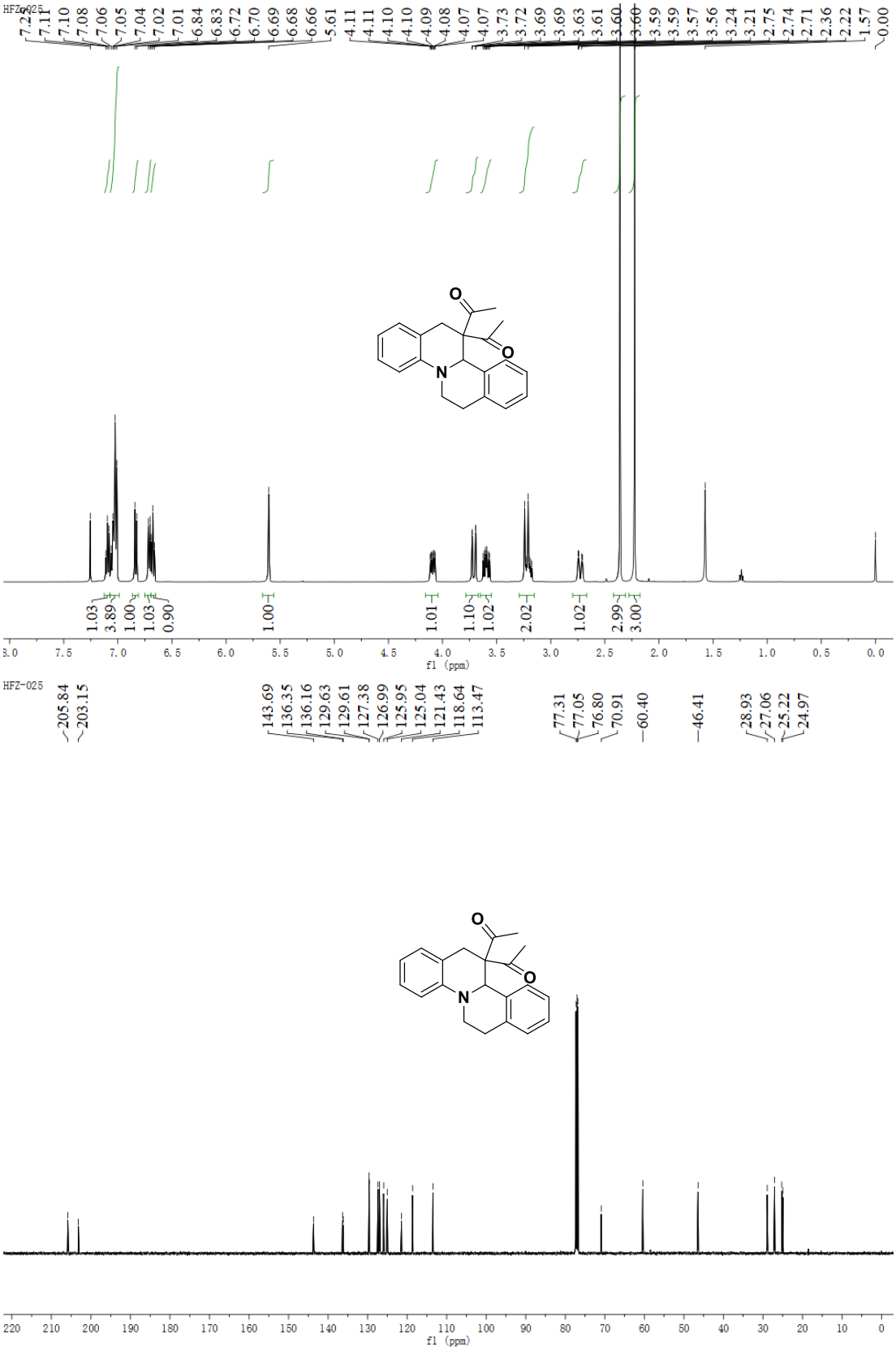


1,1'-(2,3,4,4a,5,6-hexahydro-1H-pyrido[1,2-a]quinoline-5,5-diyl)bis(ethan-1-one) (3h)

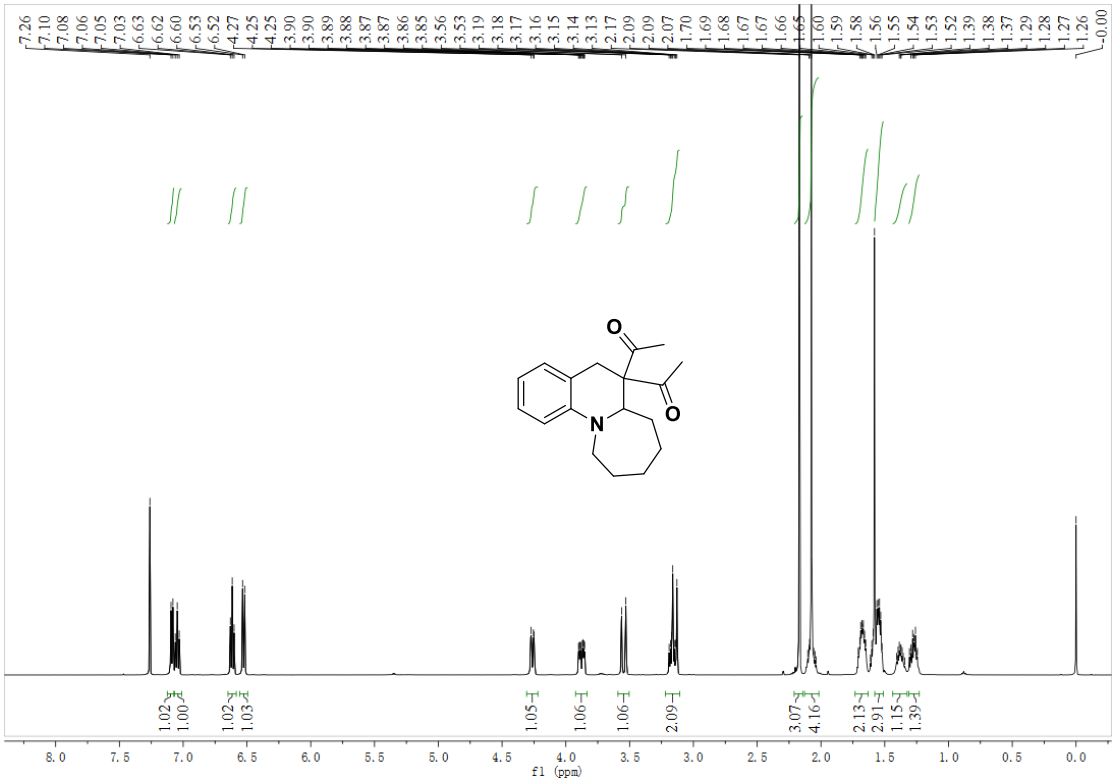


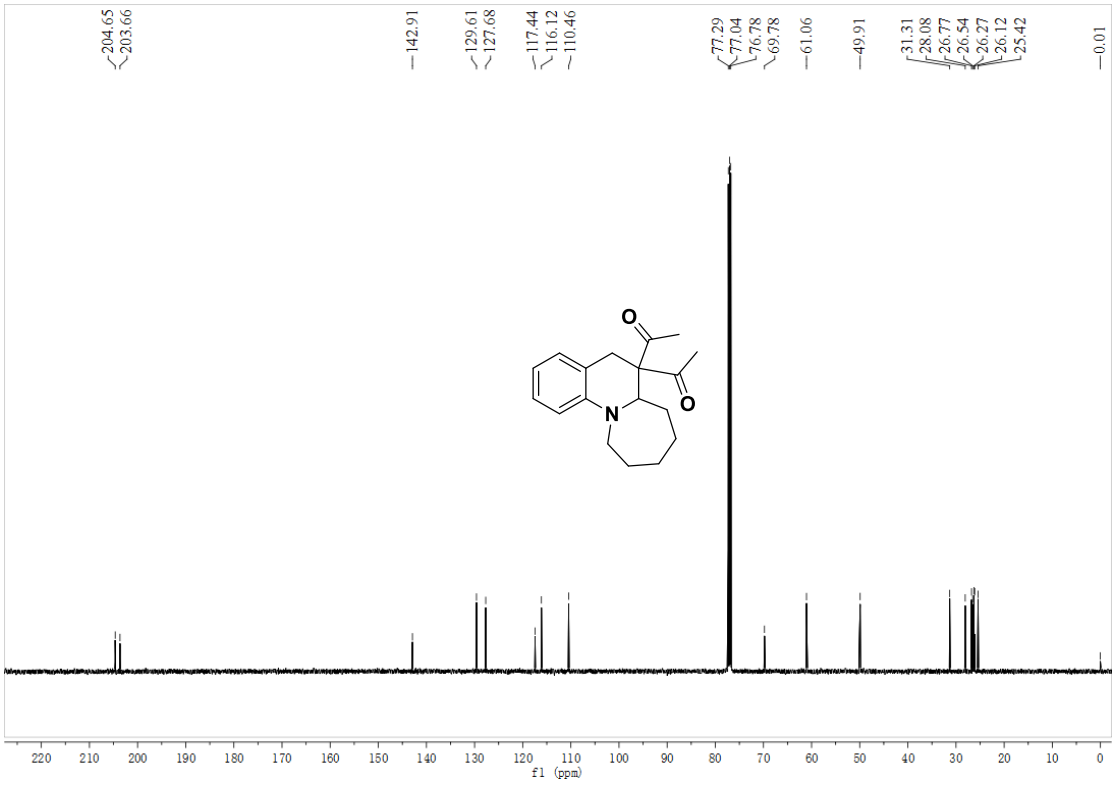


1,1'-(7,11b,12,13-tetrahydro-6H-isoquinolino[2,1-a]quinoline-12,12-diyl)bis(ethan-1-one) (3i)

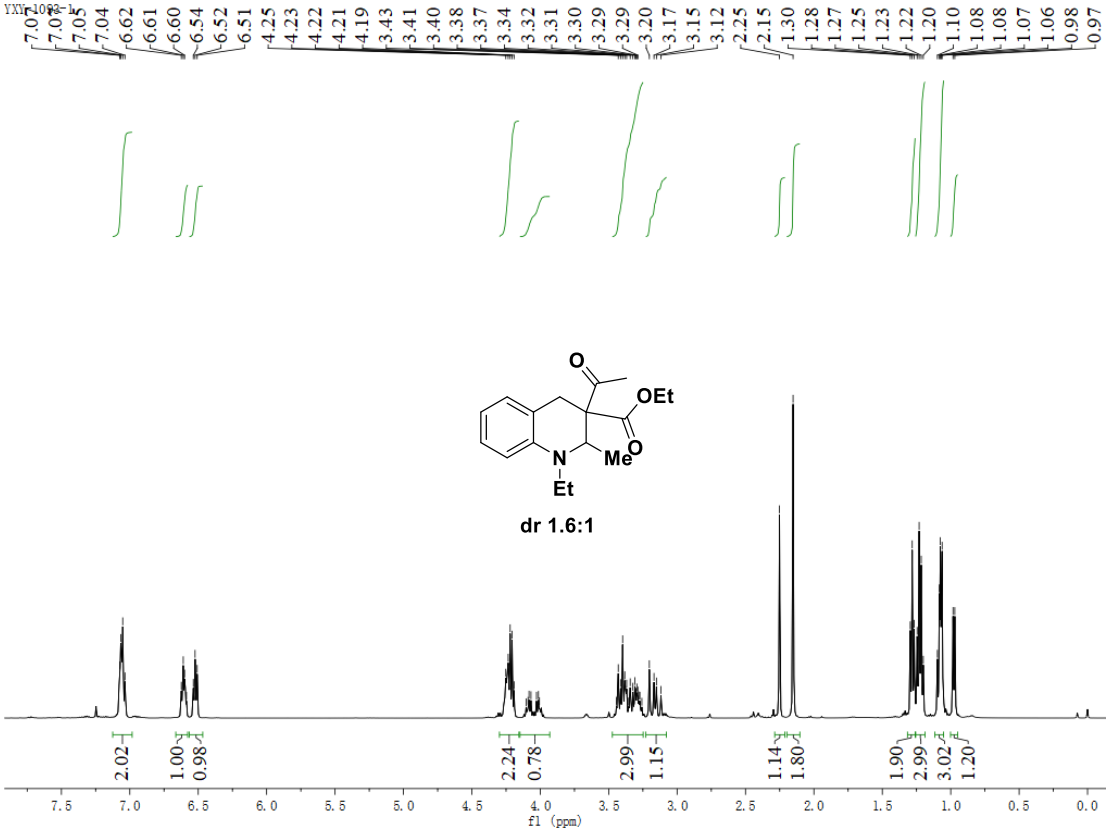


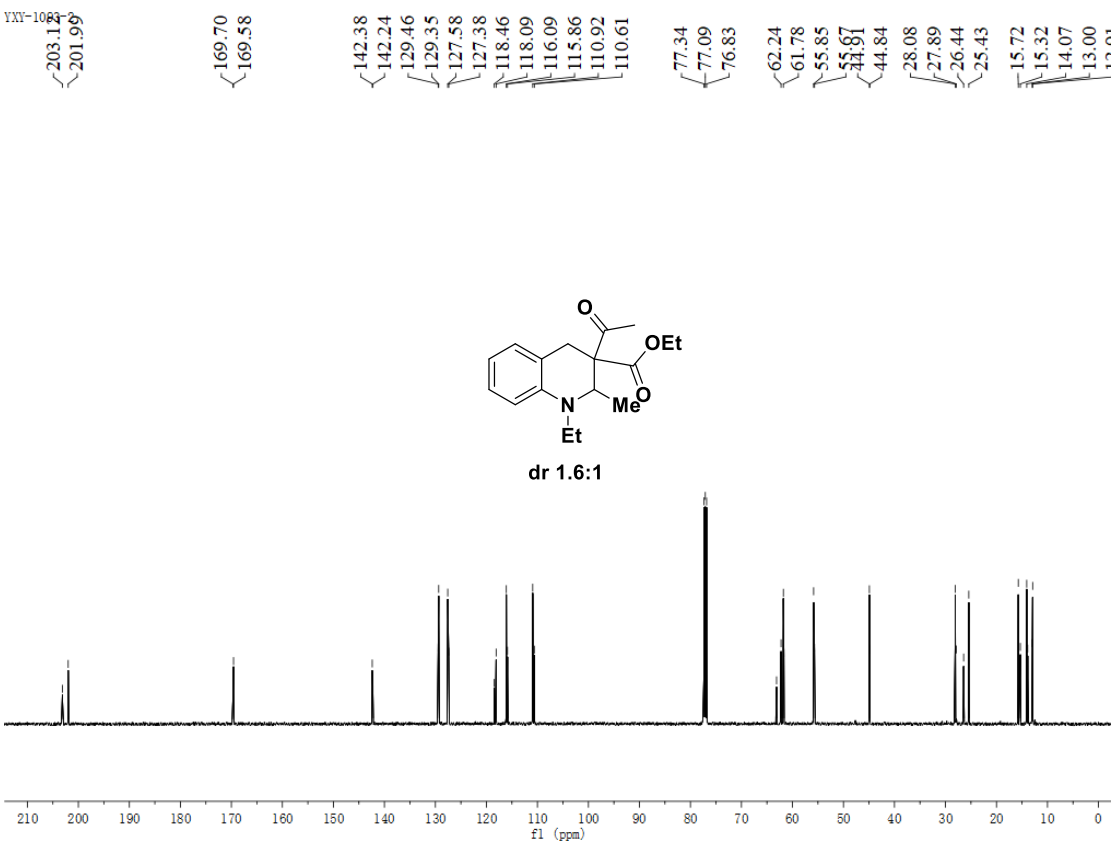
1,1'-(5,6,6a,7,8,9,10,11-octahydroazepino[1,2-a]quinoline-6,6-diyl)bis(ethan-1-one) (3j)



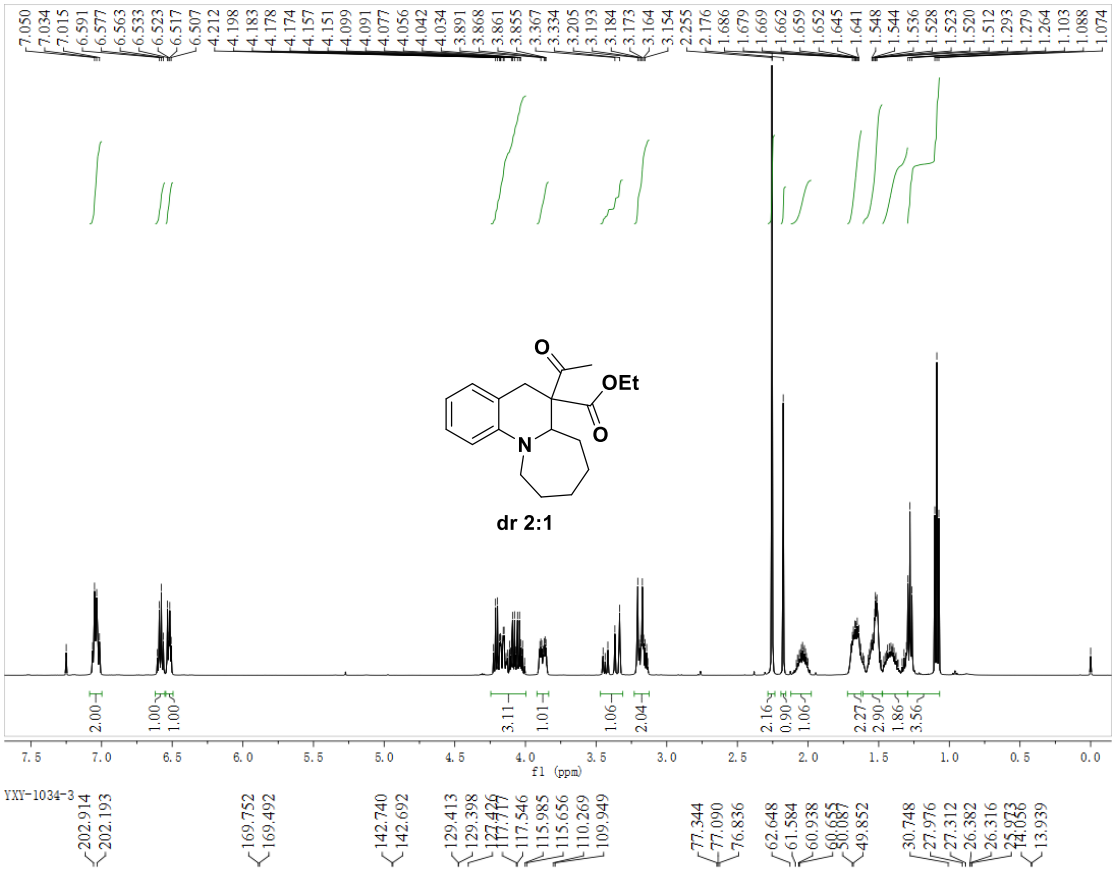


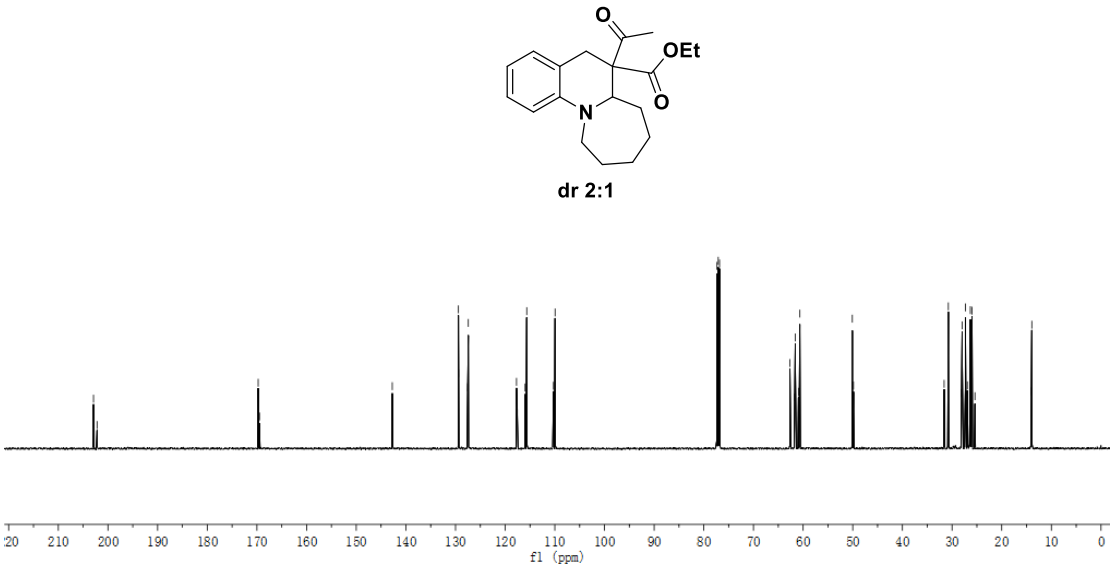
ethyl 3-acetyl-1-ethyl-2-methyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (3k)



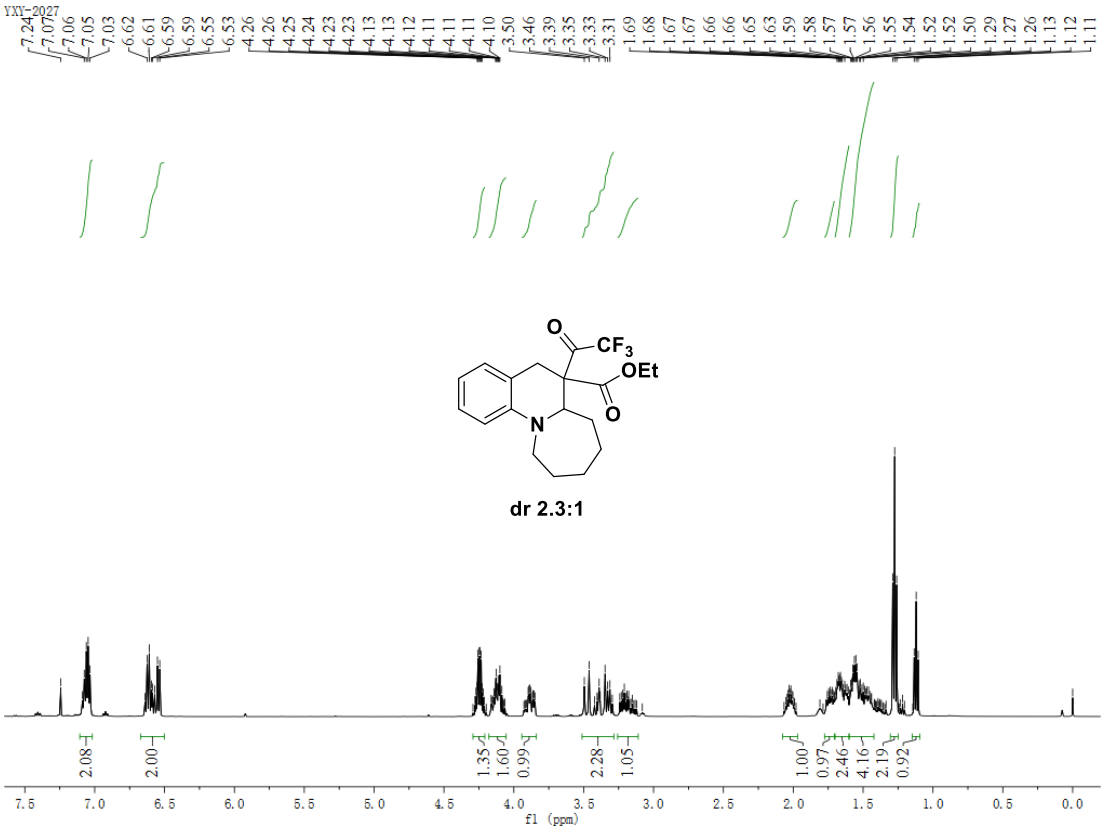


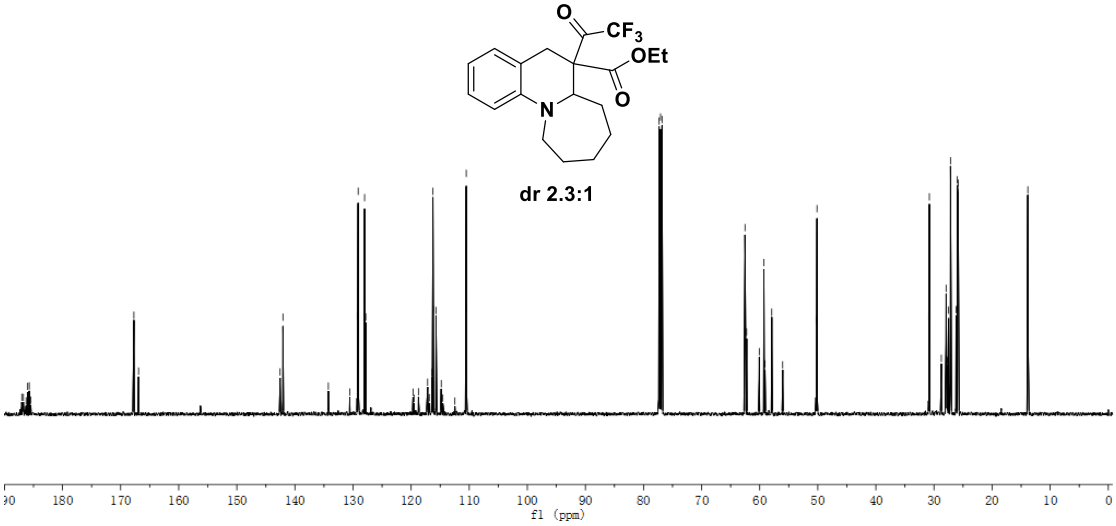
ethyl 6-acetyl-5,6,6a,7,8,9,10,11-octahydroazepino[1,2-a]quinoline-6-carboxylate (3l)



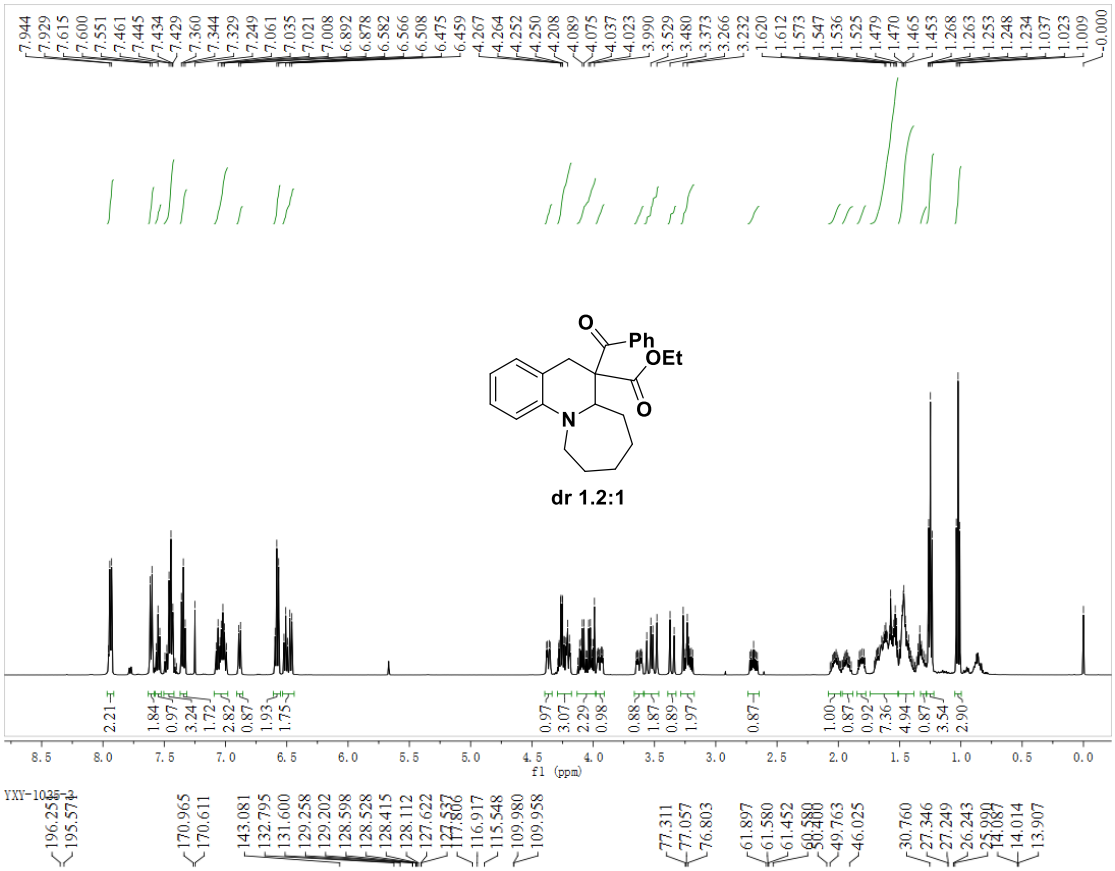


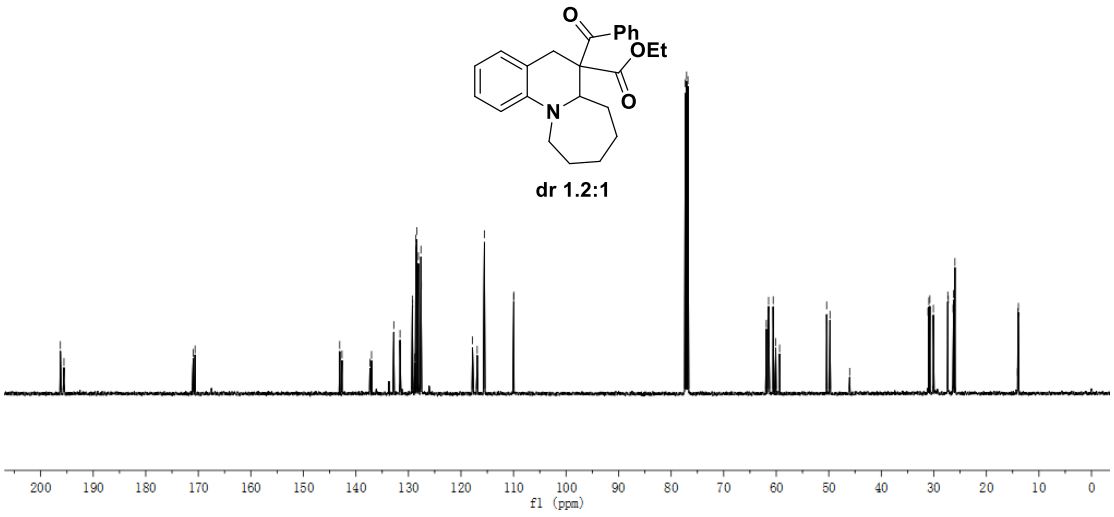
ethyl 6-(2,2,2-trifluoroacetyl)-5,6,6a,7,8,9,10,11-octahydroazepino[1,2-a]quinoline-6-carboxylate (3m)



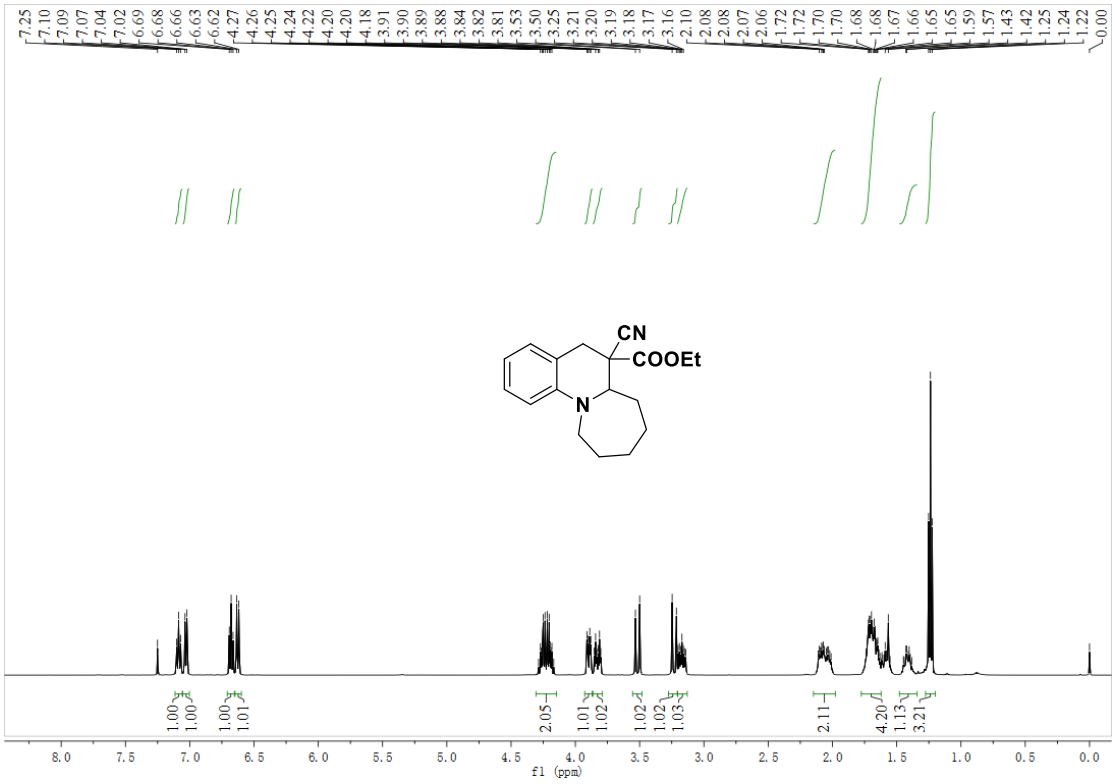


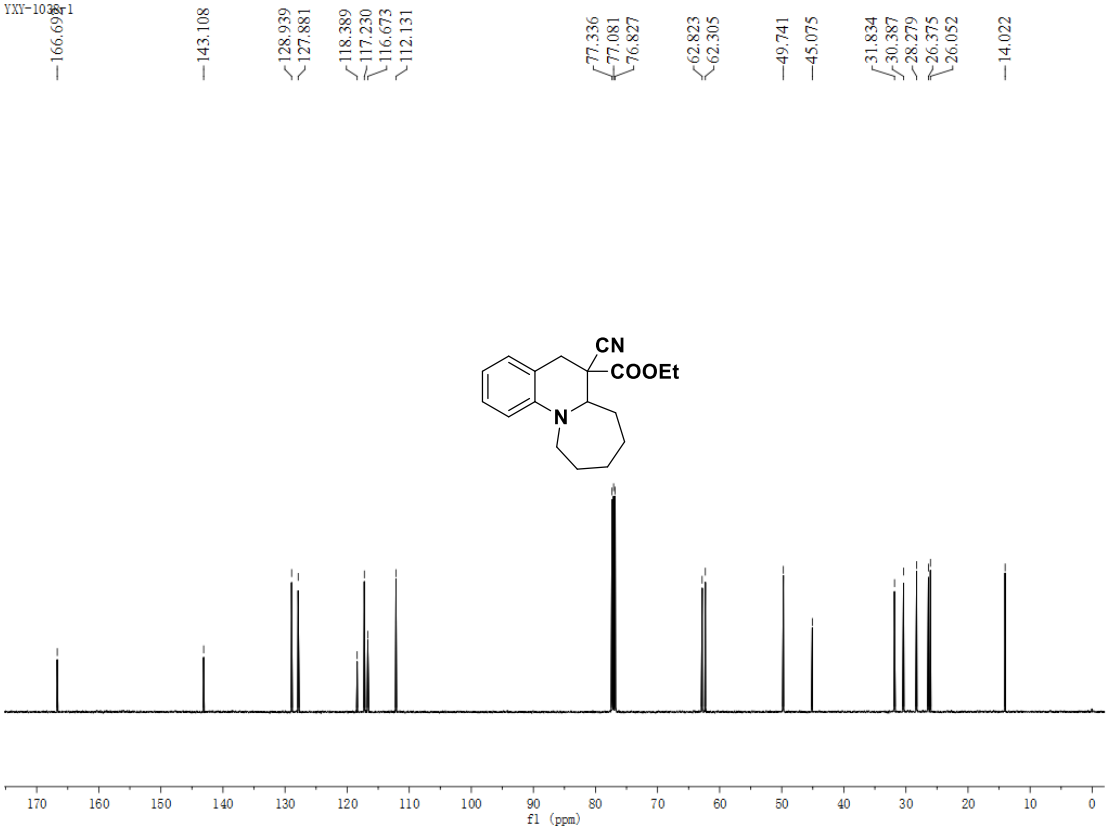
ethyl 6-benzoyl-5,6,6a,7,8,9,10,11-octahydroazepino[1,2-a]quinoline-6-carboxylate (3n)



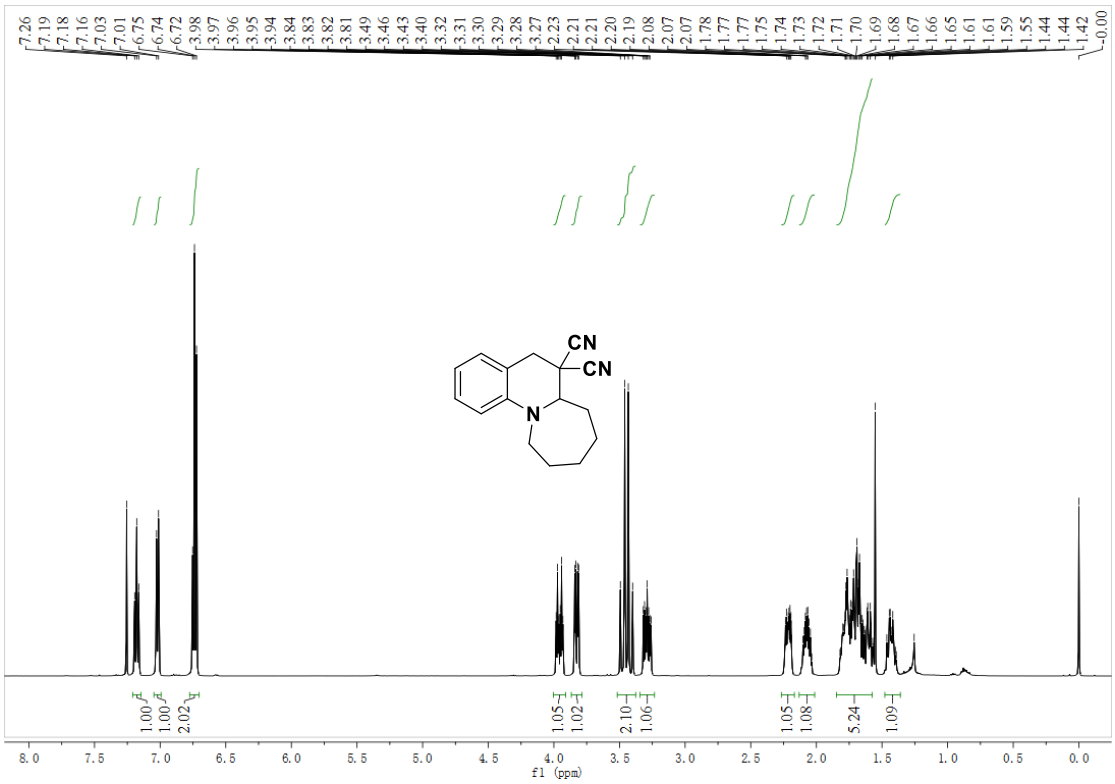


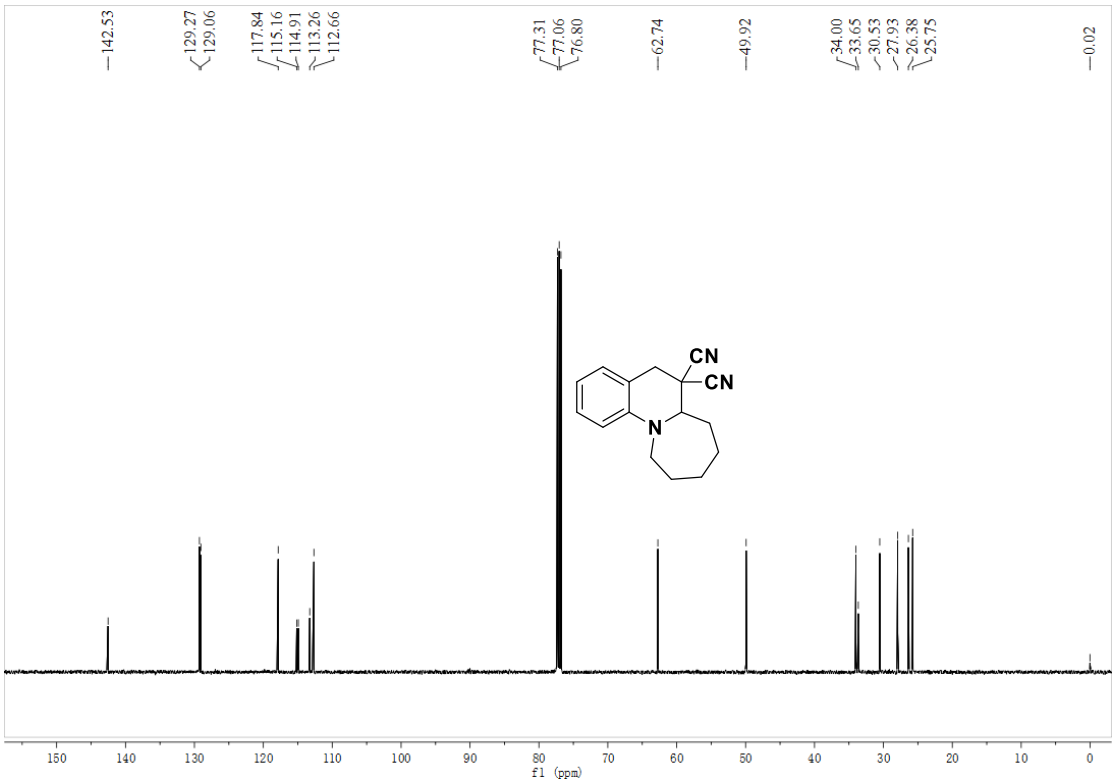
ethyl 6-cyano-5,6,6a,7,8,9,10,11-octahydroazepino[1,2-a]quinoline-6-carboxylate (3o)



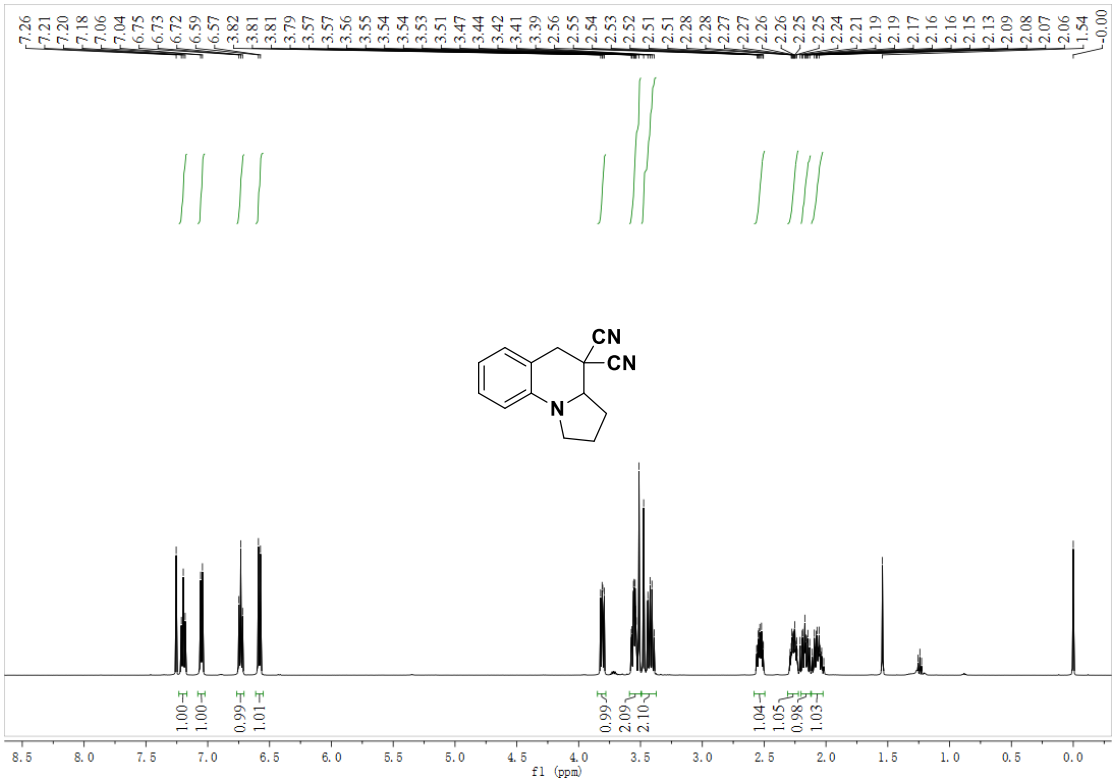


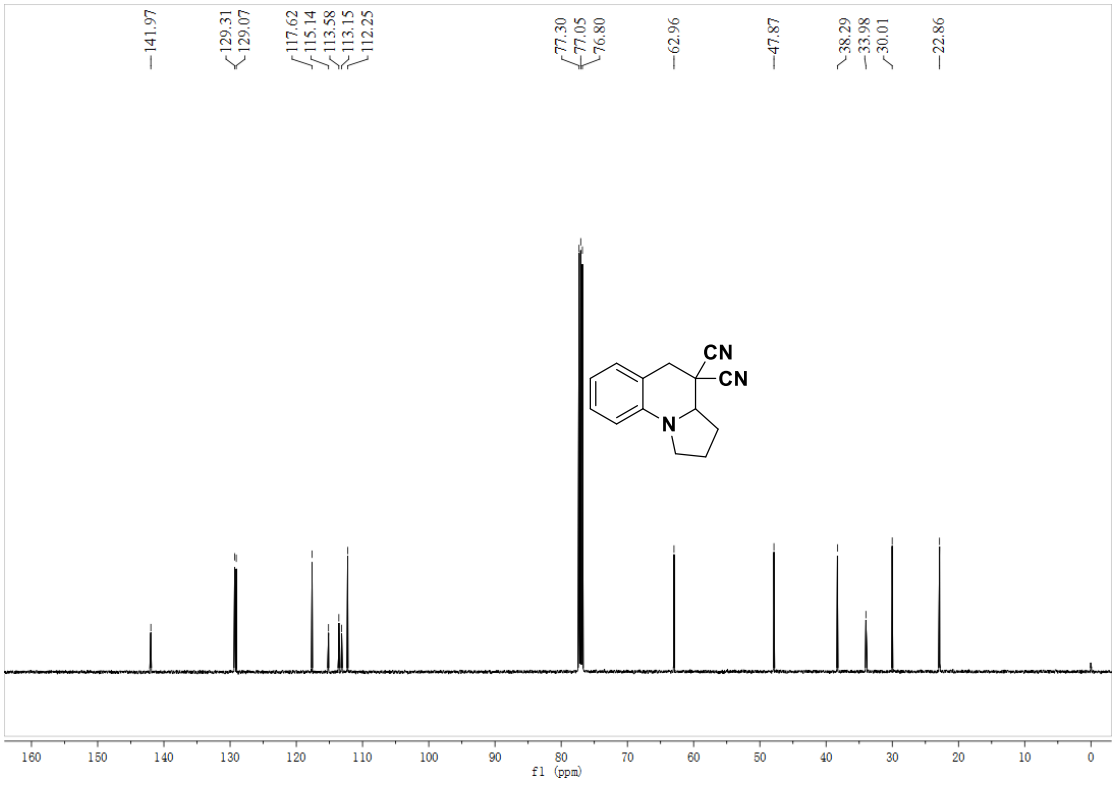
6a,7,8,9,10,11-hexahydroazepino[1,2-a]quinoline-6,6(5H)-dicarbonitrile (3p)



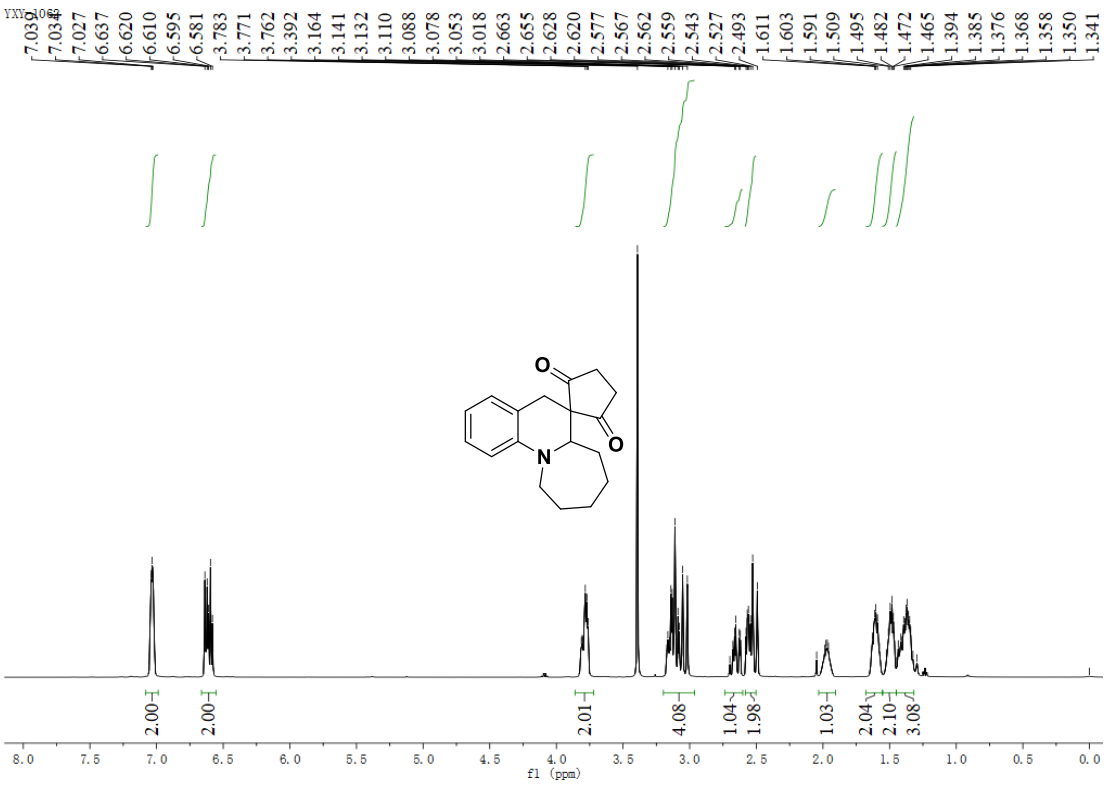


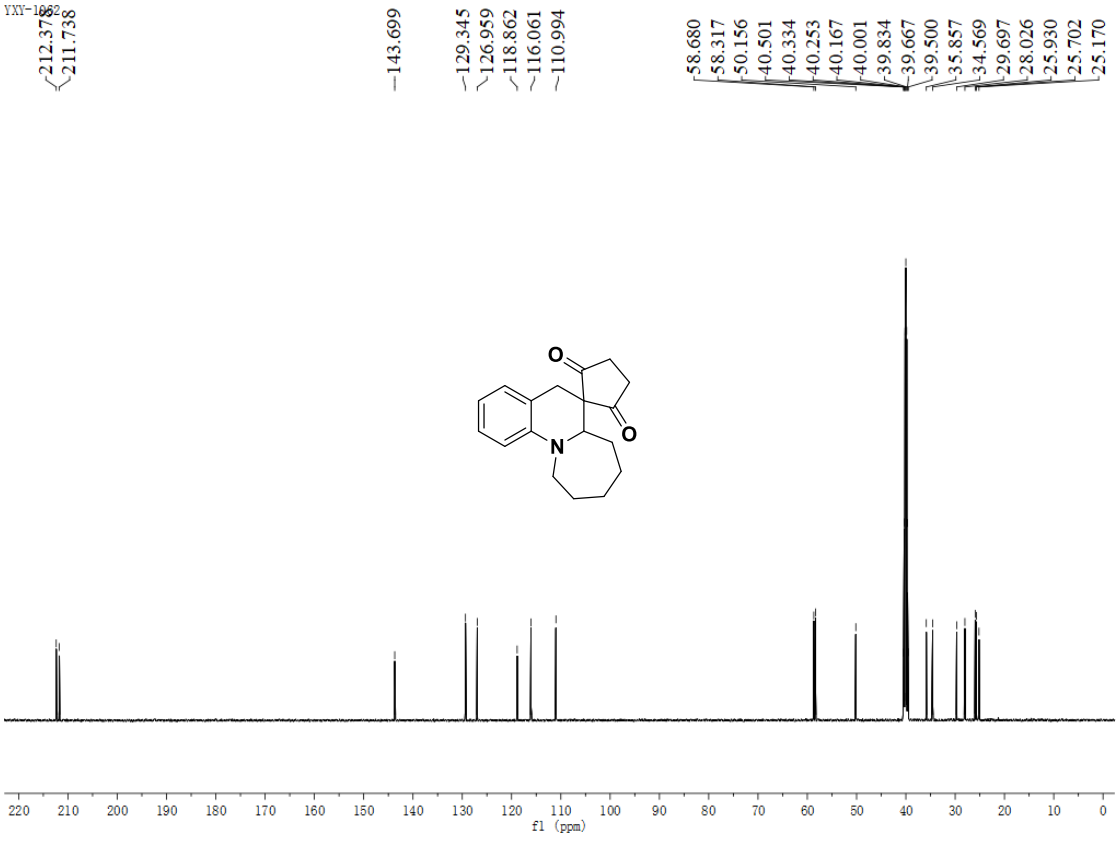
1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoline-4,4(5H)-dicarbonitrile (3q)



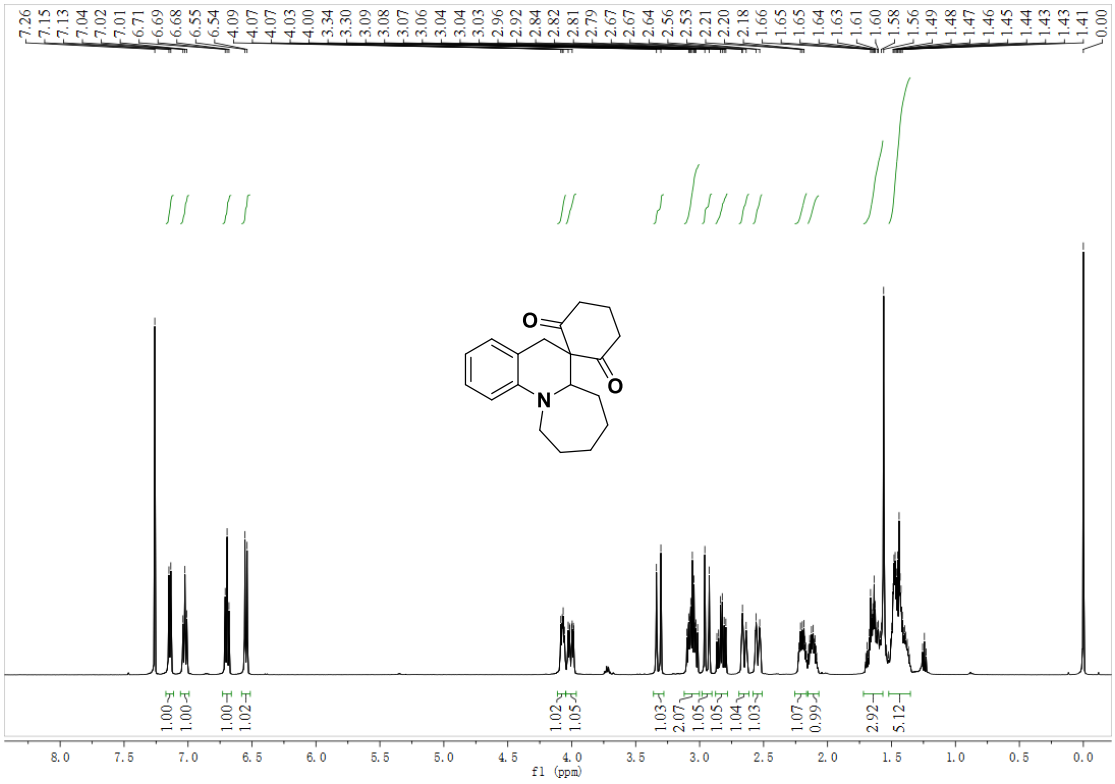


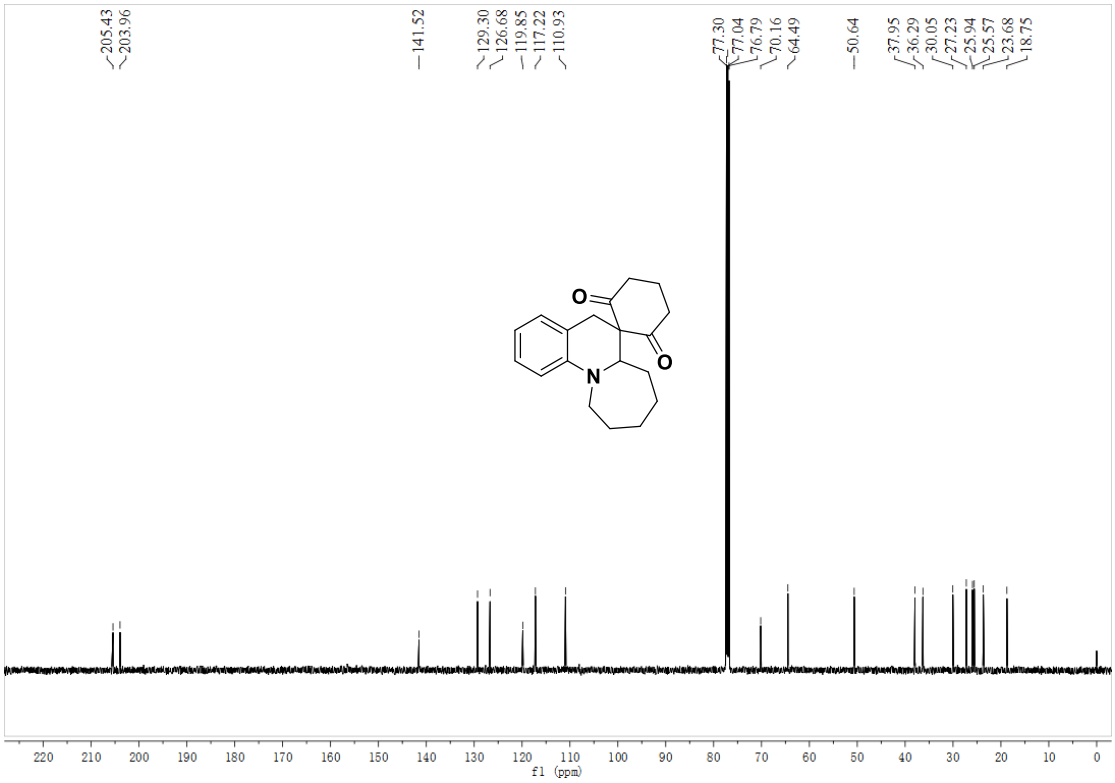
6a,7,8,9,10,11-hexahydro-5H-spiro[azepino[1,2-a]quinoline-6,1'-cyclopentane]-2',5'-dione (3r)



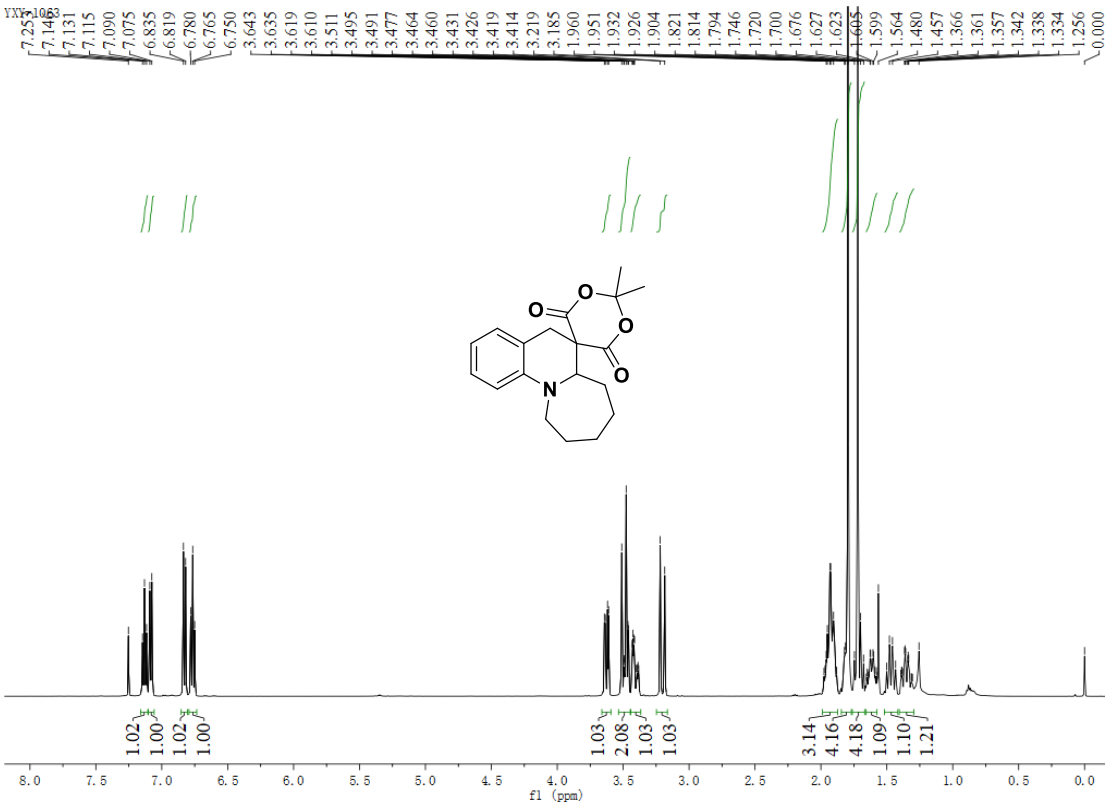


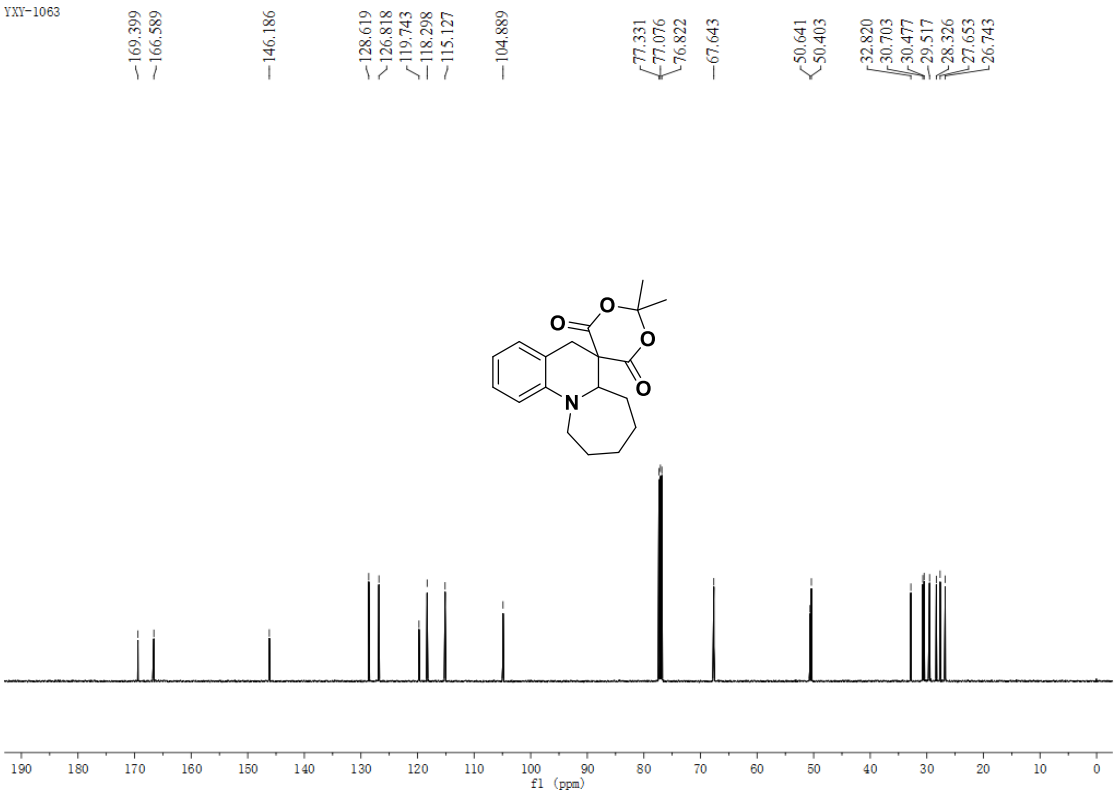
6a,7,8,9,10,11-hexahydro-5H-spiro[azepino[1,2-a]quinoline-6,1'-cyclohexane]-2',6'-dione (3s)



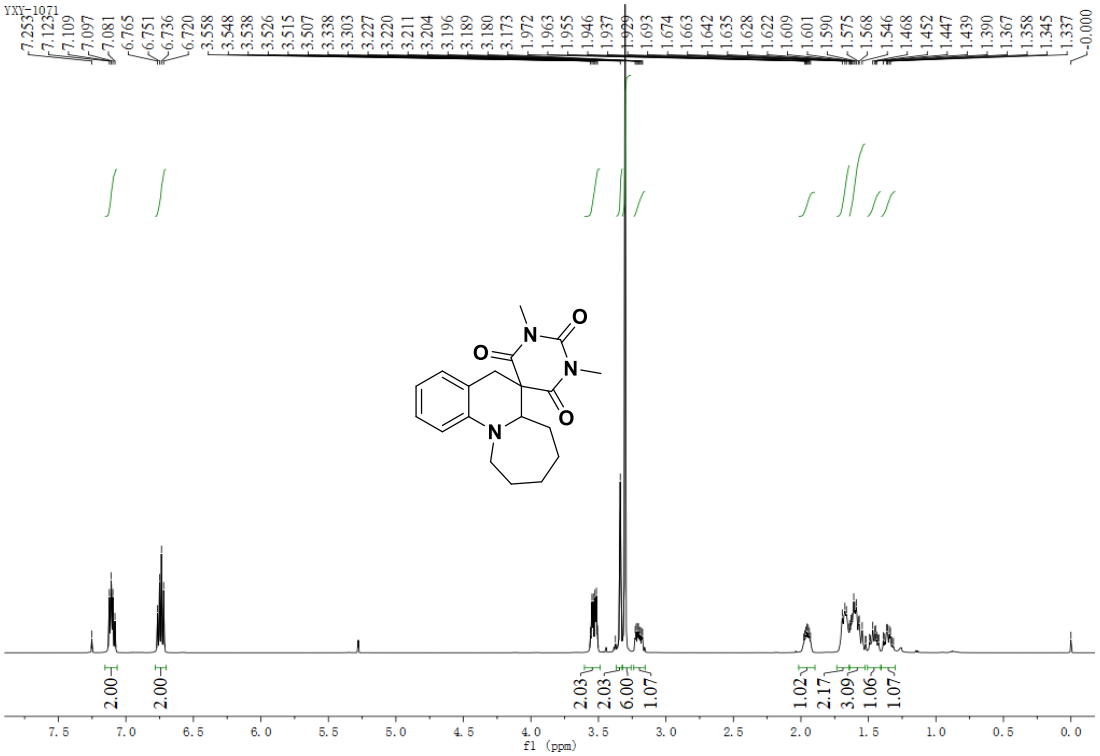


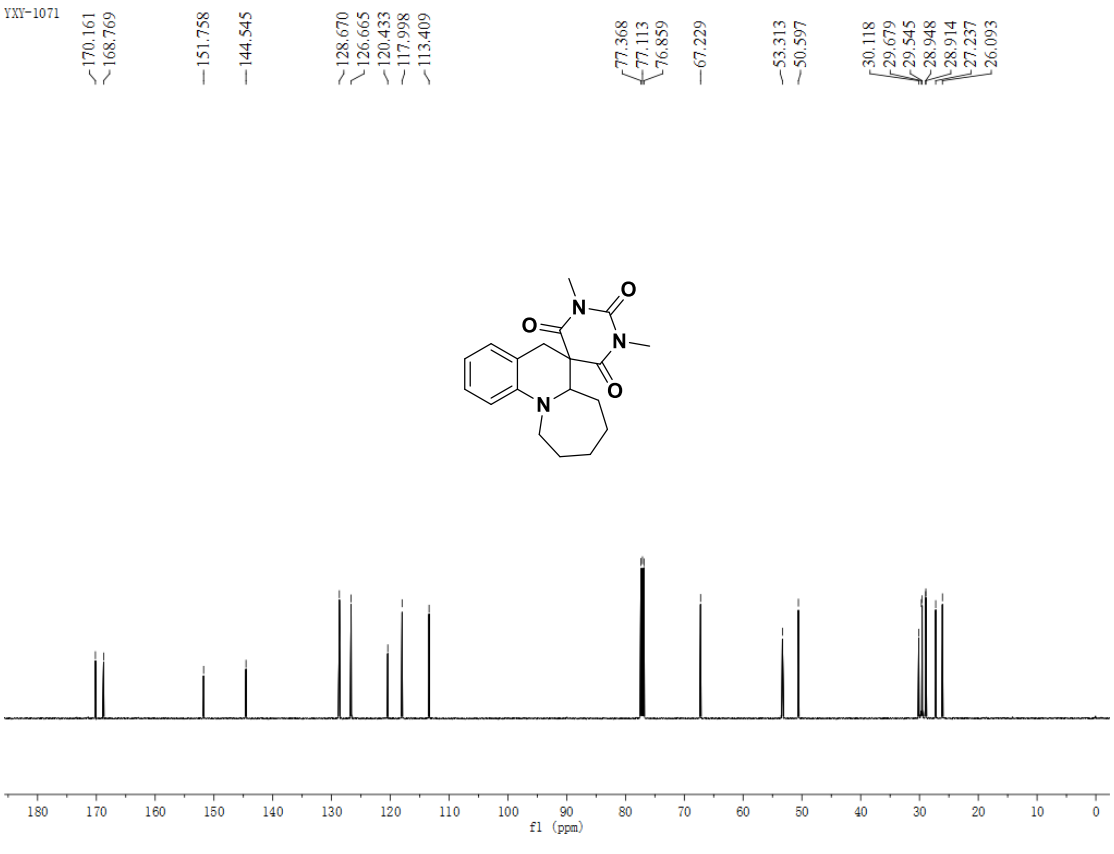
2',2'-dimethyl-6a,7,8,9,10,11-hexahydro-5H-spiro[azepino[1,2-a]quinoline-6,5'-[1,3]dioxane]-4',6'-dione (3t)



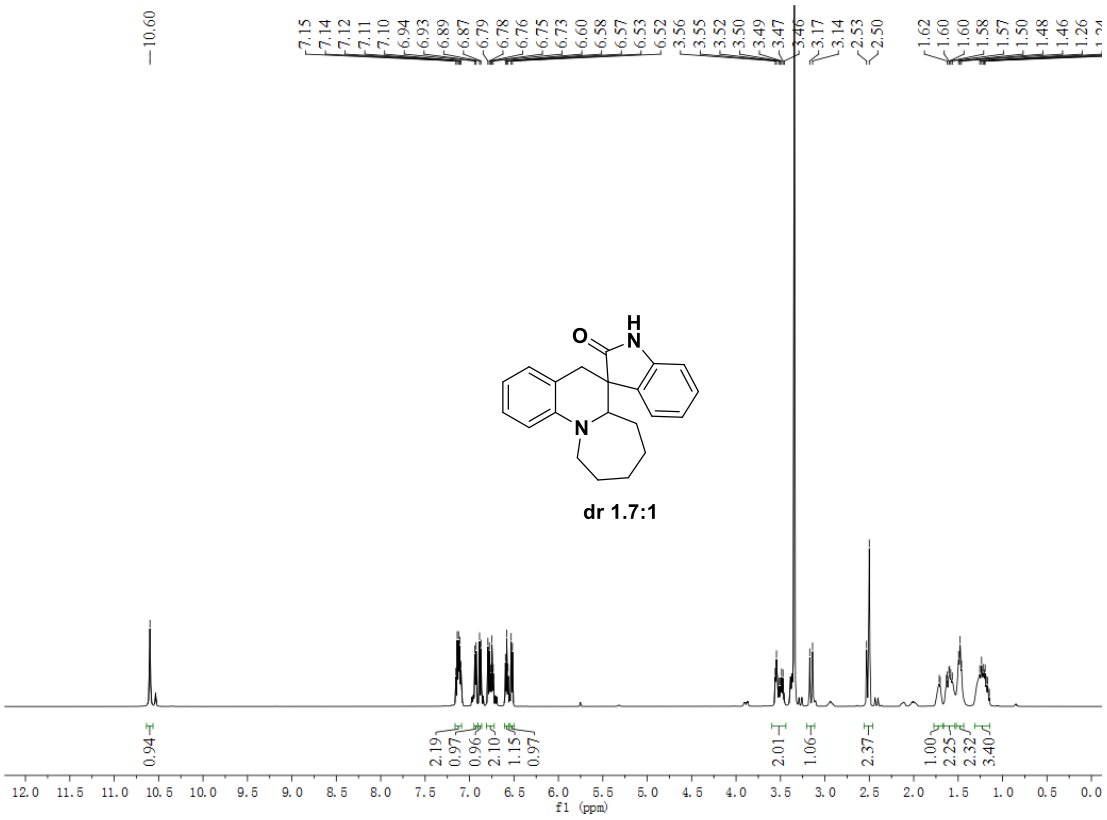


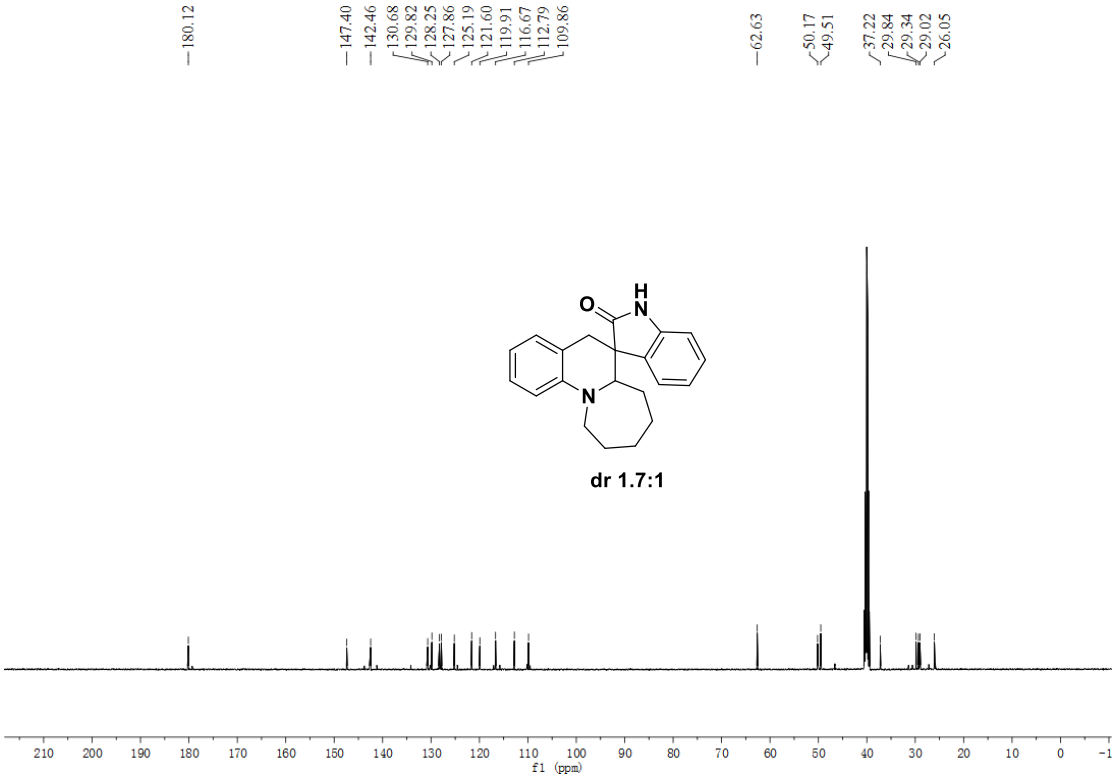
1',3'-dimethyl-6a,7,8,9,10,11-hexahydro-2'H,5H-spiro[azepino[1,2-a]quinoline-6,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione (3u)



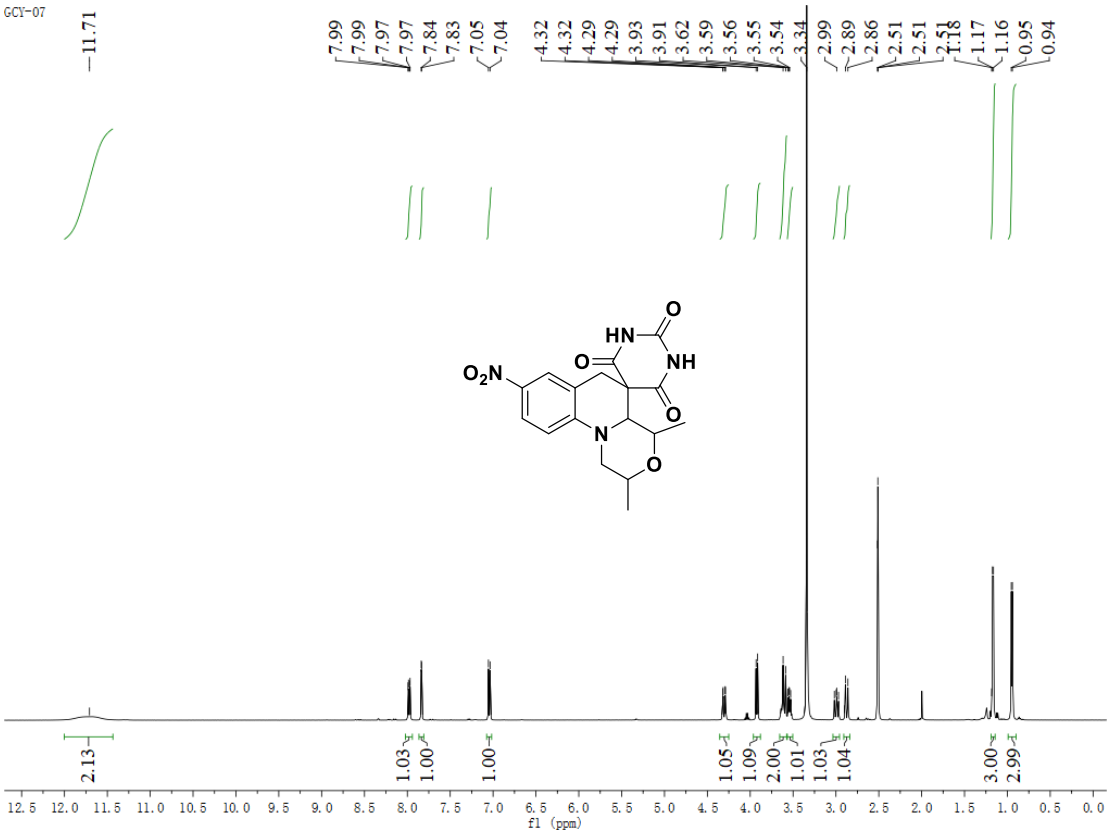


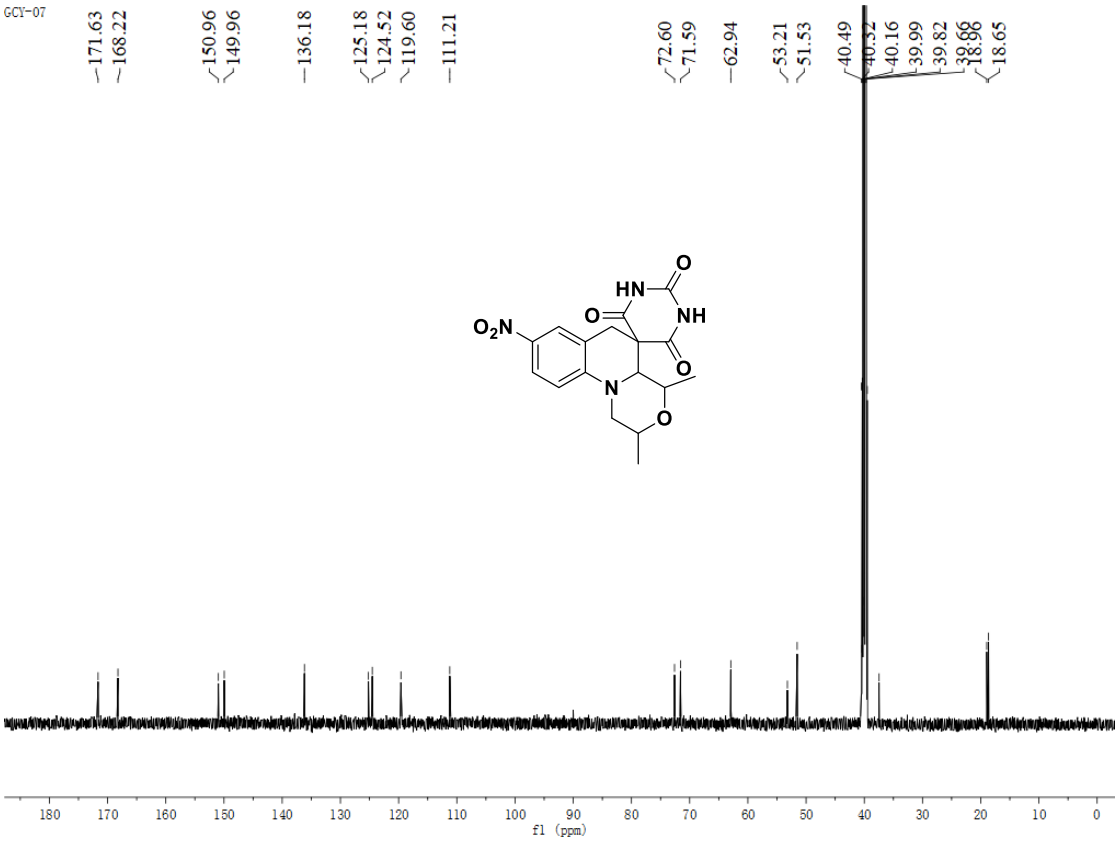
6a,7,8,9,10,11-hexahydro-5H-spiro[azepino[1,2-a]quinoline-6,3'-indolin]-2'-one (3v)





2',4'-dimethyl-8'-nitro-1',2',4',4a'-tetrahydro-2H,6'H-spiro[pyrimidine-5,5'-[1,4]oxazino[4,3-a]quinoline]-2,4,6(1H,3H)-trione (3w)





2',4'-dimethyl-8'-nitro-2-thioxo-1',2,2',3,4',4a'-hexahydro-4H,6'H-spiro[pyrimidine-5,5'-[1,4]oxazino[4,3-a]quinoline]-4,6(1H)-dione (3x)

3-(4-chloro-2-(diethylamino)benzylidene)pentane-2,4-dione (4b)