A Practical Green Chemistry Approach to Synthesize Fused Bicyclic 4*H*-Pyranes via an Amine Catalysed 1,4-Addition and Cyclization Cascade

Jun-Long Li,[a] Qiang Li,*[a] Kai-Chuan Yang,[a,c] Yi Li,[a] Liang Zhou,[a] Bo Han,[b] Cheng Peng*[a] and Xiao-Jun Gou*[a]

[a.] *Antibiotics Innovation and Advanced Manufacturing Key Laboratory of Sichuan Province, Sichuan Industrial Institute of Antibiotics, Chengdu University, Chengdu 610052, PR China. E-mail: liqiang@cdu.edu.cn; gouxj@163.com*

[b.] *State Key Laboratory Breeding Base of Systematic Research, Development and Utilization of Chinese Medicine Resources, Chengdu University of Traditional Chinese Medicine, Chengdu 611137, China. E-mail: pengcheng@cdutcm.edu.cn*

[c.] *Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041, China.*

Supporting Information

Table of Contents

1. General Information

General Procedures. All reactions were performed in oven-dried or flame-dried reaction vessels, modified Schlenk flasks, or round-bottom flasks. The flasks were fitted with Teflon screw caps and reactions were conducted under an atmosphere of argon if needed. Gas-tight syringes with stainless steel needles were used to transfer air- and moisture-sensitive liquids. All moisture and/or air sensitive solid compounds were manipulated inside normal desiccators. Flash column chromatography was performed using silica gel (40–63 μm, 230–400 mesh).

Analytical thin layer chromatography (TLC) was performed on silica gel 60 F_{254} aluminum plates (Merck) containing a 254 nm fluorescent indicator. TLC plates were visualized by exposure to short wave ultraviolet light (254 nm) and to a solution of $KMnO_4$ (1 g of $KMnO_4$, 6 g of K_2CO_3 and 0.1 g of KOH in 100 mL of H_2O) or vanillin (2 g of vanillin and 4 mL of concentrated H_2SO_4 in 100 mL of EtOH) followed by heating.

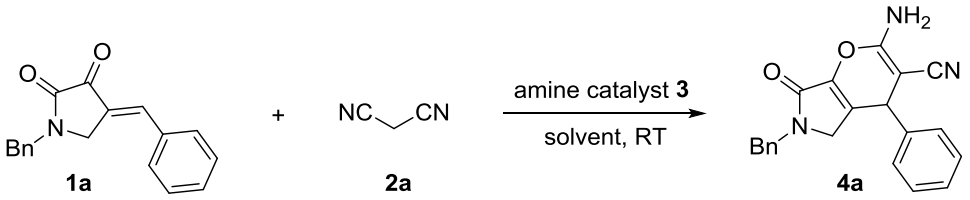
Organic solutions were concentrated at 30-50 ℃ on rotary evaporators at ~10 torr followed by drying on vacuum pump at ~1 torr. Reaction temperatures are reported as the temperature of the bath surrounding the vessel unless otherwise stated.

Materials. Commercial reagents and solvents were were obtained from Adamas-beta, Aldrich Chemical Co., Alfa Aesar, Macklin and Energy Chemical and used as received with the following exceptions: THF, Et_2O and toluene were purified by refluxing over Na-benzophenone under positive argon pressure followed by distillation. [1] The enone substrates were prepared according to literature procedure. [2]

Instrumentation.

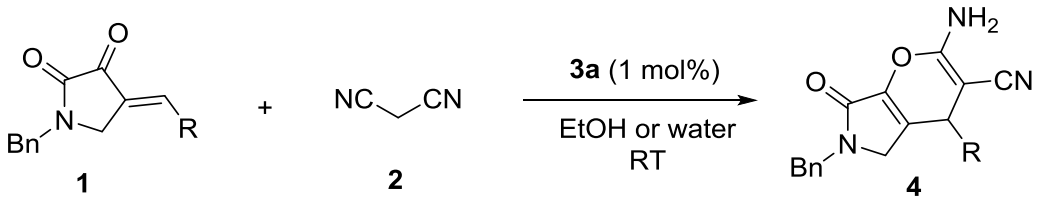
- Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with Bruker AV 400 MHz spectrometers. Proton chemical shifts are reported in parts per million (δ scale), and are referenced using residual protium in the NMR solvent (DMSO-d^6: δ 2.54 (DMSO)). Data are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet), coupling constant(s) (Hz), integration].
- Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with Bruker AV 400 MHz spectrometers. Carbon chemical shifts are reported in parts per million (δ scale), and are referenced using the carbon resonances of the solvent (δ 39.6 (DMSO)). Data are reported as follows: chemical shift [multiplicity (if not singlet), assignment (C_q = fully substituted carbon)].
- High resolution mass spectra (HRMS) were recorded on a Waters SYNAPT G2 using an electrospray (ESI) ionization source.

2. General Procedure for the Optimization of the Reaction Conditions



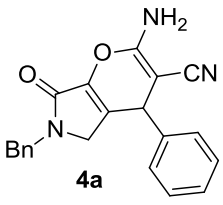
A dried glass tube was charged with 1-benzyl-4-benzylidenepyrrolidine-2,3-dione **1a** (0.1 mmol, 27.7 mg) and malononitrile **2a** (0.11 mmol, 7.3 mg) in an indicated solvent (0.1 M, 1 mL). Amine catalyst **3** (catalyst loading shown in Table 1 in the paper) was added with a syringe, and the reaction was sealed with a Teflon cap and stirred at room temperature for 5 to 30 minutes. When the reaction was complete, the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (methylene dichloride/methanol = 20:1) to afford the corresponding bicyclic 4*H*-pyrane **4a**. Exceptionally, product **4a** could be directly obtained and purified by simple filtration (filtered, washed with the corresponding solvent and dried under vacuum oven) when ethanol or water was used as the reaction medium.

3. General Procedure for the Synthesis of multi-substituted bicyclic 4*H*-pyrane 4



A dried glass tube was charged with pyrrolidine-2,3-dione **1** (0.2 mmol) and malononitrile **2** (0.22 mmol) in EtOH or water (0.1 M, 2 mL). Amine catalyst **3a** (0.02 mmol, 1.4 mg) was added with a syringe, and the reaction was sealed with a Teflon cap and stirred at room temperature for about 15 minutes. When the reaction was complete, the reaction mixture was filtered and washed with the mother liquid and 2 mL fresh ethanol or hot water to afford the corresponding bicyclic 4*H*-pyrane **4a**, which was dried under vacuum oven and further analyzed by ^{1}H-NMR, ^{13}C-HMR, HRMS, *etc.*

2-amino-6-benzyl-7-oxo-4-phenyl-4,5,6,7-tetrahydropyrano[2,3-c]pyrrole-3-carbonitrile 4a



Prepared according to the general procedure using 1-benzyl-4-benzylidenepyrrolidine-2,3-dione **1a** (55.4 mg, 0.2 mmol, 1.0 equiv) and malononitrile **2** (14.5 mg, 0.22 mmol, 1.1 equiv). Purification of the crude product via simple filtration delivered **4a** as a white solid with 96% yield when ethanol as the reaction medium (with 82% yield when water as the reaction medium).

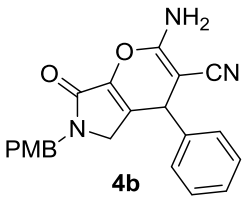
Characterization data for the product **4a***:*

^{1}H NMR (400 MHz, DMSO-d^{6}): δ (ppm): 7.41 – 7.29 (m, 5H), 7.27 – 7.25 (m, 2H), 7.22 – 7.19 (m, 4H), 4.66 (d, *J* = 15.2 Hz, 1H), 4.55 (s, 1H), 4.41 (d, *J* = 15.2 Hz, 1H), 3.85 (d, *J* = 19.2 Hz, 1H), 3.40 (d, *J* = 19.2 Hz, 1H).

^{13}C NMR (100 MHz, DMSO-d^{6}): δ (ppm): 162.4, 161.1, 142.5, 139.4, 137.7, 129.3, 129.1, 128.1, 128.0, 127.9, 127.8, 126.5, 120.5, 56.1, 47.4, 45.8, 39.0

HR-MS (ESI): *m/z* calculated for $C_{21}H_{17}N_3O_2Na^+$: 366.1218, found: 366.1227.

2-amino-6-(4-methoxybenzyl)-7-oxo-4-phenyl-4,5,6,7-tetrahydropyrano[2,3-c]pyrrole-3-carbonitrile 4b



4b

Prepared according to the general procedure using 4-benzylidene-1-(4-methoxybenzyl) pyrrolidine-2,3-dione **1b** (61.4 mg, 0.2 mmol, 1.0 equiv) and malononitrile **2** (14.5 mg, 0.22 mmol, 1.1 equiv). Purification of the crude product via simple filtration delivered **4b** as a white solid with 90% yield when ethanol as the reaction medium.

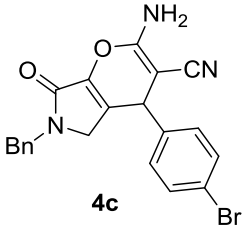
Characterization data for the product **4b***:*

^{1}H NMR (400 MHz, DMSO-d^{6}): δ (ppm): 7.38 – 7.34 (m, 2H), 7.29 – 7.25 (m, 1H), 7.22 – 7.20 (m, 2H), 7.13 – 7.11 (m, 4H), 6.87 (d, *J* = 8.4 Hz, 2H), 4.54 (d, *J* = 14.8 Hz, 1H), 4.29 (d, *J* = 14.8 Hz, 1H), 3.78 (d, *J* = 19.2 Hz, 1H), 3.71 (s, 1H), 3.32 (d, *J* = 19.2 Hz, 1H).

^{13}C NMR (100 MHz, DMSO-d^{6}): δ (ppm): 162.2, 161.1, 159.1, 142.5, 139.4, 129.7, 129.5, 129.3, 128.0, 127.9, 126.4, 120.5, 114.5, 56.1, 55.5, 47.1, 45.2, 39.0

HR-MS (ESI): *m/z* calculated for $C_{22}H_{19}N_3O_3Na^+$: 396.1324, found: 396.1321.

2-amino-6-benzyl-4-(4-bromophenyl)-7-oxo-4,5,6,7-tetrahydropyrano[2,3-c]pyrrole-3-carbonitrile 4c



4c

Prepared according to the general procedure using 1-benzyl-4-(4-bromo-benzylidene) pyrrolidine-2,3-dione **1c** (71.2 mg, 0.2 mmol, 1.0 equiv) and malononitrile **2** (14.5 mg, 0.22 mmol, 1.1 equiv). Purification of the crude product via simple filtration delivered **4c** as a

white solid with 85% yield when ethanol as the reaction medium (with 92% yield when water as the reaction medium).

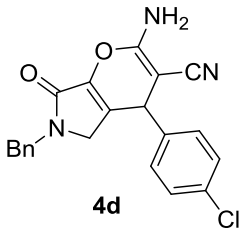
Characterization data for the product **4c***:*

^{1}H NMR (400 MHz, DMSO-d^{6}): δ (ppm): 7.59 (d, *J* = 8.4 Hz, 2H), 7.38 – 7.34 (m, 2H), 7.32 – 7.28 (m, 1H), 7.25 – 7.21 (m, 6H), 4.69 (d, *J* = 15.2 Hz, 1H), 4.57 (s, 1H), 4.38 (d, *J* = 15.2 Hz, 1H), 3.84 (d, *J* = 19.2 Hz, 1H), 3.44 (d, *J* = 19.2 Hz, 1H).

^{13}C NMR (100 MHz, DMSO-d^{6}): δ (ppm): 161.8, 160.7, 141.4, 139.0, 137.1, 131.7, 129.9, 128.6, 127.7, 127.4, 125.4, 120.6, 119.9, 55.2, 46.8, 45.4, 37.9

HR-MS (ESI): *m/z* calculated for $C_{21}H_{16}BrN_3O_2Na^+$: 444.0324, found: 444.0323.

2-amino-6-benzyl-4-(4-chlorophenyl)-7-oxo-4,5,6,7-tetrahydropyrano[2,3-c]pyrrole-3-arbonitrile 4d



4d

Prepared according to the general procedure using 1-benzyl-4-(4-chloro-benzylidene) pyrrolidine-2,3-dione **1d** (62.2 mg, 0.2 mmol, 1.0 equiv) and malononitrile **2** (14.5 mg, 0.22 mmol, 1.1 equiv). Purification of the crude product via simple filtration delivered **4d** as a white solid with 93% yield when ethanol as the reaction medium (with 88% yield when water as the reaction medium).

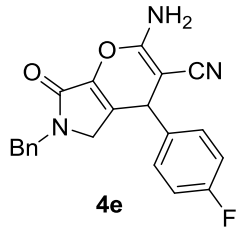
Characterization data for the product **4d***:*

^{1}H NMR (400 MHz, DMSO-d^{6}): δ (ppm): 7.45 (d, *J* = 8.4 Hz, 2H), 7.38 – 7.34 (m, 2H), 7.31 – 7.29 (m, 3H), 7.23 – 7.20 (m, 4H), 4.68 (d, *J* = 15.2 Hz, 1H), 4.58 (s, 1H), 4.38 (d, *J* = 15.2 Hz, 1H), 3.84 (d, *J* = 18.8 Hz, 1H), 3.43 (d, *J* = 18.8 Hz, 1H).

^{13}C NMR (100 MHz, DMSO-d^{6}): δ (ppm): 161.9, 160.8, 141.1, 139.1, 137.2, 132.2, 129.6, 128.9, 128.8, 127.8, 127.5, 125.6, 120.0, 55.4, 46.9, 45.5, 38.0

HR-MS (ESI): *m/z* calculated for $C_{21}H_{16}ClN_3O_2Na^+$: 400.0829, found: 400.0828.

2-amino-6-benzyl-4-(4-fluorophenyl)-7-oxo-4,5,6,7-tetrahydropyrano[2,3-c]pyrrole-3-carbonitrile 4e



4e

Prepared according to the general procedure using 1-benzyl-4-(4-fluorobenzylidene) pyrrolidine-2,3-dione **1e** (71.2 mg, 0.2 mmol, 1.0 equiv) and malononitrile **2** (14.5 mg, 0.22 mmol, 1.1 equiv). Purification of the crude product via simple filtration delivered **4e** as a white solid with 80% yield when ethanol as the reaction medium.

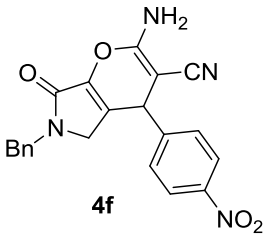
Characterization data for the product **4e***:*

^{1}H NMR (400 MHz, DMSO-d^{6}): δ (ppm): 7.38 – 7.28 (m, 5H), 7.24 – 7.20 (m, 6H), 4.68 (d, *J* = 15.2 Hz, 1H), 4.58 (s, 1H), 4.39 (d, *J* = 15.2 Hz, 1H), 3.85 (d, *J* = 19.2 Hz, 1H), 3.42 (d, *J* = 19.2 Hz, 1H).

^{13}C NMR (100 MHz, DMSO-d^{6}): δ (ppm): 162.7, 161.9, 160.7, 160.3, 139.0, 138.4, 138.3, 137.3, 129.7, 129.6, 128.8, 127.8, 127.5, 125.9, 120.1, 115.8, 115.6, 55.7, 46.9, 45.5, 37.9

HR-MS (ESI): *m/z* calculated for $C_{21}H_{16}FN_3O_2Na^+$: 384.1124, found: 384.1125.

2-amino-6-benzyl-4-(4-nitrophenyl)-7-oxo-4,5,6,7-tetrahydropyrano[2,3-c]pyrrole-3-carbonitrile 4f



4f

Prepared according to the general procedure using 1-benzyl-4-(4-nitrobenzylidene) pyrrolidine-2,3-dione **1f** (64.4 mg, 0.2 mmol, 1.0 equiv) and malononitrile **2** (14.5 mg, 0.22 mmol, 1.1 equiv). Purification of the crude product via simple filtration delivered **4f** as a white solid with 72% yield when ethanol as the reaction medium. (with 77% yield when water as the reaction medium).

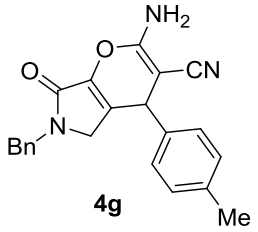
Characterization data for the product **4f***:*

^{1}H NMR (400 MHz, DMSO-d^{6}): δ (ppm): 8.27 (d, *J* = 8.8 Hz, 2H), 7.59 (d, *J* = 8.8 Hz, 2H), 7.38 – 7.28 (m, 5H), 7.23 – 7.21 (m, 2H), 4.78 (s, 1H), 4.70 (d, *J* = 15.2 Hz, 1H), 4.37 (d, *J* = 15.2 Hz, 1H), 3.88 (d, *J* = 19.2 Hz, 1H), 3.45 (d, *J* = 19.2 Hz, 1H).

^{13}C NMR (100 MHz, DMSO-d^{6}): δ (ppm): 161.8, 161.0, 149.5, 147.0, 139.5, 137.2, 129.2, 128.8, 127.8, 127.5, 124.7, 124.2, 119.8, 54.7, 46.9, 45.5, 38.4

HR-MS (ESI): *m/z* calculated for $C_{21}H_{16}N_4O_4Na^+$: 411.1069, found: 411.1068.

2-amino-6-benzyl-7-oxo-4-(p-tolyl)-4,5,6,7-tetrahydropyrano[2,3-c]pyrrole-3-carbonitrile 4g



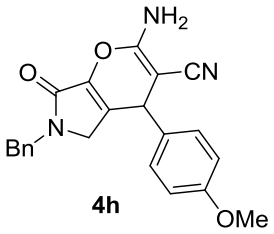
4g

Prepared according to the general procedure using 1-benzyl-4-(4-methylbenzylidene) pyrrolidine-2,3-dione **1g** (58.2 mg, 0.2 mmol, 1.0 equiv) and malononitrile **2** (14.5 mg, 0.22 mmol, 1.1 equiv). Purification of the crude product via simple filtration delivered **4g** as a white solid with 85% yield when ethanol as the reaction medium. (with 82% yield when water as the reaction medium).

Characterization data for the product **4g***:*

^{1}H NMR (400 MHz, DMSO-d^6): δ (ppm): 7.38 – 7.27 (m, 3H), 7.22 – 7.18 (m, 4H), 7.15 – 7.12 (m, 4H), 4.64 (d, *J* = 15.2 Hz, 1H), 4.50 (s, 1H), 4.41 (d, *J* = 15.2 Hz, 1H), 3.83 (d, *J* = 19.2 Hz, 1H), 3.40 (d, *J* = 19.2 Hz, 1H), 2.31 (s, 3H).
^{13}C NMR (100 MHz, DMSO-d^6): δ (ppm): 161.9, 160.6, 139.1, 138.7, 137.2, 136.6, 129.4, 128.6, 127.7, 127.4, 126.2, 120.0, 55.8, 46.8, 45.3, 38.1, 20.6
HR-MS (ESI): *m/z* calculated for $C_{22}H_{19}N_3O_2Na^+$: 380.1375, found: 380.1375.

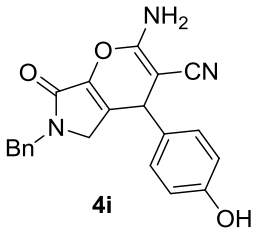
2-amino-6-benzyl-4-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydropyrano[2,3-c]pyrrole-3-carbonitrile 4h



4h

Prepared according to the general procedure using 1-benzyl-4-(4-methoxybenzylidene) pyrrolidine-2,3-dione **1h** (61.4 mg, 0.2 mmol, 1.0 equiv) and malononitrile **2** (14.5 mg, 0.22 mmol, 1.1 equiv). Purification of the crude product via simple filtration delivered **4h** as a white solid with 82% yield when ethanol as the reaction medium.
Characterization data for the product **4h***:*
^{1}H NMR (400 MHz, DMSO-d^6): δ (ppm): 7.38 – 7.27 (m, 3H), 7.23 – 7.14 (m, 6H), 6.94 (d, *J* = 8.4 Hz, 2H), 4.65 (d, *J* = 15.2 Hz, 1H), 4.49 (s, 1H), 4.41 (d, *J* = 15.2 Hz, 1H), 3.83 (d, *J* = 19.2 Hz, 1H), 3.77 (s, 3H), 3.40 (d, *J* = 19.2 Hz, 1H).
^{13}C NMR (100 MHz, DMSO-d^6): δ (ppm): 162.0, 160.6, 158.6, 138.8, 137.3, 134.2, 128.8, 128.7, 127.8, 127.5, 126.5, 120.2, 114.3, 56.1, 55.2, 47.0, 45.5, 37.8
HR-MS (ESI): *m/z* calculated for $C_{22}H_{19}N_3O_3Na^+$: 396.1324, found: 396.1324.

2-amino-6-benzyl-4-(4-hydroxyphenyl)-7-oxo-4,5,6,7-tetrahydropyrano[2,3-c]pyrrole-3-carbonitrile 4i



4i

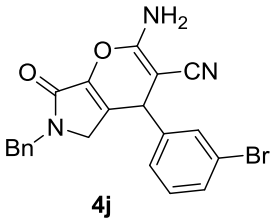
Prepared according to the general procedure using 1-benzyl-4-(4-hydroxybenzylidene) pyrrolidine-2,3-dione **1i** (58.6 mg, 0.2 mmol, 1.0 equiv) and malononitrile **2** (14.5 mg, 0.22 mmol, 1.1 equiv). Purification of the crude product via simple filtration delivered **4i** as a white solid with 88% yield when ethanol as the reaction medium. (with 78% yield when water as the reaction medium).
Characterization data for the product **4i***:*
^{1}H NMR (400 MHz, DMSO-d^6): δ (ppm): 9.43 (s, 1H), 7.37 – 7.26 (m, 3H), 7.21 – 7.19 (m, 2H), 7.08 (br s, 2H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 1H), 4.64 (d, *J* = 15.2 Hz,

1H), 4.41 (s, 1H), 4.40 (d, *J* = 15.2 Hz, 1H), 3.81 (d, *J* = 19.2 Hz, 1H), 3.38 (d, *J* = 19.2 Hz, 1H).

^{13}C NMR (100 MHz, DMSO-d^6): δ (ppm): 162.0, 160.4, 156.6, 138.5, 137.2, 132.4, 128.6, 128.5, 127.6, 127.4, 126.7, 120.1, 115.5, 56.2, 46.8, 45.3, 37.7

HR-MS (ESI): *m/z* calculated for $C_{21}H_{17}N_3O_3Na^+$: 382.1168, found: 382.1164.

2-amino-6-benzyl-4-(3-bromophenyl)-7-oxo-4,5,6,7-tetrahydropyrano[2,3-c]pyrrole-3-carbonitrile 4j



4j

Prepared according to the general procedure using 1-benzyl-4-(3-bromobenzylidene) pyrrolidine-2,3-dione **1j** (71.2 mg, 0.2 mmol, 1.0 equiv) and malononitrile **2** (14.5 mg, 0.22 mmol, 1.1 equiv). Purification of the crude product via simple filtration delivered **4j** as a white solid with 80% yield when ethanol as the reaction medium (with 83% yield when water as the reaction medium).

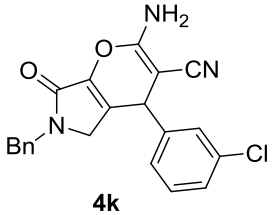
Characterization data for the product **4j***:*

^{1}H NMR (400 MHz, DMSO-d^6): δ (ppm): 7.54 – 7.47 (m, 2H), 7.39 – 7.34 (m, 3H), 7.32 – 7.21 (m, 6H), 4.70 (d, *J* = 15.2 Hz, 1H), 4.59 (s, 1H), 4.38 (d, *J* = 15.2 Hz, 1H), 3.85 (d, *J* = 19.2 Hz, 1H), 3.45 (d, *J* = 19.2 Hz, 1H).

^{13}C NMR (100 MHz, DMSO-d^6): δ (ppm): 161.9, 160.9, 144.9, 139.2, 137.3, 131.2, 130.5, 130.4, 128.8, 127.8, 127.5, 126.9, 125.3, 122.2, 120.0, 55.2, 46.9, 45.5, 38.2

HR-MS (ESI): *m/z* calculated for $C_{21}H_{16}BrN_3O_2Na^+$: 444.0324, found: 444.0326

2-amino-6-benzyl-4-(3-chlorophenyl)-7-oxo-4,5,6,7-tetrahydropyrano[2,3-c]pyrrole-3-carbonitrile 4k



4k

Prepared according to the general procedure using 1-benzyl-4-(3-chlorobenzylidene) pyrrolidine-2,3-dione **1k** (62.2 mg, 0.2 mmol, 1.0 equiv) and malononitrile **2** (14.5 mg, 0.22 mmol, 1.1 equiv). Purification of the crude product via simple filtration delivered **4k** as a white solid with 87% yield when ethanol as the reaction medium (with 90% yield when water as the reaction medium).

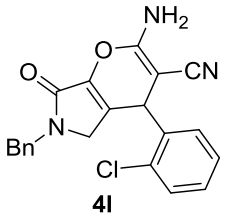
Characterization data for the product **4k***:*

^{1}H NMR (400 MHz, DMSO-d^6): δ (ppm): 7.46 – 7.30 (m, 6H), 7.26 – 7.21 (m, 5H), 4.70 (d, *J* = 15.2 Hz, 1H), 4.60 (s, 1H), 4.38 (d, *J* = 15.2 Hz, 1H), 3.86 (d, *J* = 19.2 Hz, 1H), 3.45 (d, *J* = 19.2 Hz, 1H).

^{13}C NMR (100 MHz, DMSO-d^6): δ (ppm): 161.8, 160.8, 144.5, 139.1, 137.1, 133.4, 130.8, 128.6, 127.6, 127.5, 127.4, 126.4, 125.2, 119.9, 55.0, 46.8, 45.3, 38.1

HR-MS (ESI): *m/z* calculated for $C_{21}H_{16}ClN_3O_2Na^+$: 400.0829, found: 400.0830.

2-amino-6-benzyl-4-(2-chlorophenyl)-7-oxo-4,5,6,7-tetrahydropyrano[2,3-c]pyrrole-3-carbonitrile 4l



4l

Prepared according to the general procedure using 1-benzyl-4-(2-chlorobenzylidene) pyrrolidine-2,3-dione **1l** (62.2 mg, 0.2 mmol, 1.0 equiv) and malononitrile **2** (14.5 mg, 0.22 mmol, 1.1 equiv). Purification of the crude product via simple filtration delivered **4l** as a white solid with 85% yield when ethanol as the reaction medium.

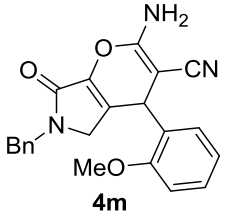
Characterization data for the product **4l***:*

^{1}H NMR (400 MHz, DMSO-d^6): δ (ppm): 7.49 – 7.47 (m, 1H), 7.44 – 7.32 (m, 5H), 7.30 – 7.26 (m, 3H), 7.22 – 7.20 (m, 2H), 5.01 (s, 1H), 4.64 (d, *J* = 15.2 Hz, 1H), 4.43 (d, *J* = 15.2 Hz, 1H), 3.92 (d, *J* = 19.2 Hz, 1H), 3.46 (d, *J* = 19.2 Hz, 1H).

^{13}C NMR (100 MHz, DMSO-d^6): δ (ppm): 161.7, 161.2, 139.4, 138.5, 137.1, 132.2, 130.4, 129.7, 129.3, 128.6, 128.1, 127.6, 127.4, 124.7, 119.7, 56.0, 54.2, 46.9, 45.3

HR-MS (ESI): *m/z* calculated for $C_{21}H_{16}ClN_3O_2Na^+$: 400.0829, found: 400.0829.

2-amino-6-benzyl-4-(2-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydropyrano[2,3-c]pyrrole-3-carbonitrile 4m



4m

Prepared according to the general procedure using 1-benzyl-4-(2-methoxybenzylidene) pyrrolidine-2,3-dione **1m** (61.4 mg, 0.2 mmol, 1.0 equiv) and malononitrile **2** (14.5 mg, 0.22 mmol, 1.1 equiv). Purification of the crude product via simple filtration delivered **4m** as a white solid with 78% yield when ethanol as the reaction medium.

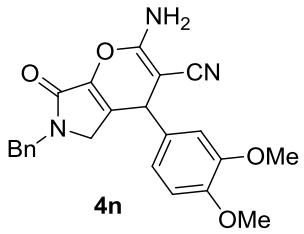
Characterization data for the product **4m***:*

^{1}H NMR (400 MHz, DMSO-d^6): δ (ppm): 7.38 – 7.27 (m, 4H), 7.21 – 7.16 (m, 5H), 7.06 – 6.98 (m, 2H), 4.84 (s, 1H), 4.60 (d, *J* = 15.2 Hz, 1H), 4.46 (d, *J* = 15.2 Hz, 1H), 3.89 (d, *J* = 19.2 Hz, 1H), 3.79 (s, 3H), 3.45 (d, *J* = 19.2 Hz, 1H).

^{13}C NMR (100 MHz, DMSO-d^6): δ (ppm): 162.0, 161.5, 156.6, 139.0, 137.3, 129.3, 128.8, 128.7, 128.5, 127.6, 127.5, 126.3, 121.0, 120.2, 111.4, 55.6, 54.2, 47.4, 45.4, 32.5

HR-MS (ESI): *m/z* calculated for $C_{22}H_{19}N_3O_3Na^+$: 396.1324, found: 396.1325.

2-amino-6-benzyl-4-(3,4-dimethoxyphenyl)-7-oxo-4,5,6,7-tetrahydropyrano[2,3-c]pyrrole-3-carbonitrile 4n



4n

Prepared according to the general procedure using 1-benzyl-4-(3,4-dimethoxybenzylidene) pyrrolidine-2,3-dione **1n** (67.4 mg, 0.2 mmol, 1.0 equiv) and malononitrile **2** (14.5 mg, 0.22 mmol, 1.1 equiv). Purification of the crude product via simple filtration delivered **4n** as a white solid with 70% yield when ethanol as the reaction medium.

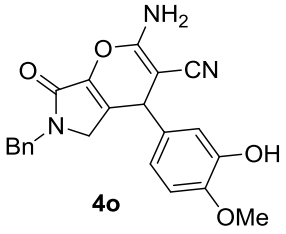
Characterization data for the product **4n***:*

^{1}H NMR (400 MHz, DMSO-d^{6}): δ (ppm): 7.38 – 7.27 (m, 3H), 7.23 – 7.20 (m, 2H), 7.13 (br s, 2H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.81 – 6.76 (m, 2H), 4.64 (d, *J* = 15.2 Hz, 1H), 4.48 (s, 1H), 4.44 (d, *J* = 15.2 Hz, 1H), 3.84 (d, *J* = 19.2 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.44 (d, *J* = 19.2 Hz, 1H).

^{13}C NMR (100 MHz, DMSO-d^{6}): δ (ppm): 162.0, 160.5, 148.8, 148.0, 138.6, 137.2, 134.4, 128.6, 127.6, 127.4, 126.3, 120.1, 119.6, 111.9, 110.9, 55.8, 55.5, 55.4, 46.8, 45.3, 38.1

HR-MS (ESI): *m/z* calculated for $C_{23}H_{21}N_3O_4Na^+$: 426.1423, found: 426.1423.

2-amino-6-benzyl-4-(3-hydroxy-4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydropyrano[2,3-c]pyrrole-3-carbonitrile 4o



4o

Prepared according to the general procedure using 1-benzyl-4-(3-hydroxy-4-methoxy-benzylidene)-pyrrolidine-2,3-dione **1o** (64.6 mg, 0.2 mmol, 1.0 equiv) and malononitrile **2** (14.5 mg, 0.22 mmol, 1.1 equiv). Purification of the crude product via simple filtration delivered **4o** as a white solid with 62% yield when ethanol as the reaction medium.

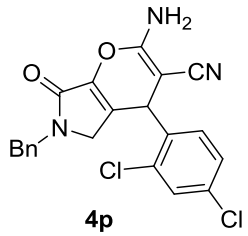
Characterization data for the product **4o***:*

^{1}H NMR (400 MHz, DMSO-d^{6}): δ (ppm): 9.09 (s, 1H), 7.38 – 7.27 (m, 3H), 7.23 – 7.21 (m, 2H), 7.12 (br s, 2H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.66 – 6.62 (m, 2H), 4.65 (d, *J* = 15.2 Hz, 1H), 4.41 (d, *J* = 15.2 Hz, 1H), 4.38 (s, 1H), 3.83 (d, *J* = 19.2 Hz, 1H), 3.77 (s, 3H), 3.42 (d, *J* = 19.2 Hz, 1H).

^{13}C NMR (100 MHz, DMSO-d^{6}): δ (ppm): 162.0, 160.6, 147.1, 146.9, 138.6, 137.3, 134.8, 128.8, 127.8, 127.5, 126.8, 120.2, 118.2, 114.6, 112.3, 56.2, 55.6, 47.0, 45.4, 38.0

HR-MS (ESI): *m/z* calculated for $C_{22}H_{19}N_3O_4Na^+$: 412.1273, found: 412.1269.

2-amino-6-benzyl-4-(2,4-dichlorophenyl)-7-oxo-4,5,6,7-tetrahydropyrano[2,3-c]pyrrole-3-carbonitrile 4p



4p

Prepared according to the general procedure using (E)-1-benzyl-4-(2,4-dichlorobenzylidene) pyrrolidine-2,3-dione **1p** (69.2 mg, 0.2 mmol, 1.0 equiv) and malononitrile **2** (14.5 mg, 0.22 mmol, 1.1 equiv). Purification of the crude product via simple filtration delivered **4p** as a white solid with 81% yield when ethanol as the reaction medium.

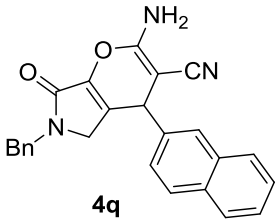
Characterization data for the product **4p***:*

^{1}H NMR (400 MHz, DMSO-d^{6}): δ (ppm): 7.67 (d, *J* = 2.0 Hz, 1H), 4.64 (dd, *J* = 8.4 Hz, *J* = 2.0 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.38 – 7.28 (m, 5H), 7.23 – 7.21 (m, 2H), 5.01 (s, 1H), 4.67 (d, *J* = 15.2 Hz, 1H), 4.41 (d, *J* = 15.2 Hz, 1H), 3.91 (d, *J* = 19.2 Hz, 1H), 3.52 (d, *J* = 19.2 Hz, 1H).

^{13}C NMR (100 MHz, DMSO-d^{6}): δ (ppm): 161.6, 161.2, 139.6, 137.1, 133.1, 132.9, 131.9, 129.1, 128.6, 128.3, 127.6, 127.4, 124.2, 119.6, 56.0, 53.9, 46.9, 45.4

HR-MS (ESI): *m/z* calculated for $C_{21}H_{15}Cl_2N_3O_2Na^+$: 434.0439, found: 434.0434.

2-amino-6-benzyl-4-(naphthalen-2-yl)-7-oxo-4,5,6,7-tetrahydropyrano[2,3-c]pyrrole-3-carbonitrile 4q



4q

Prepared according to the general procedure using 1-benzyl-4-(naphthalen-2-ylmethylene) pyrrolidine-2,3-dione **1q** (65.4 mg, 0.2 mmol, 1.0 equiv) and malononitrile **2** (14.5 mg, 0.22 mmol, 1.1 equiv). Purification of the crude product via simple filtration delivered **4q** as a white solid with 83% yield when ethanol as the reaction medium. (with 75% yield when water as the reaction medium).

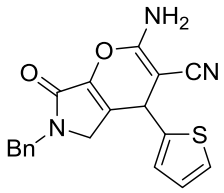
Characterization data for the product **4q***:*

^{1}H NMR (400 MHz, DMSO-d^{6}): δ (ppm): 7.97 – 7.93 (m, 3H), 7.80 (s, 1H), 7.58 – 7.52 (m, 2H), 7.43 – 7.40 (m, 1H), 7.36 – 7.27 (m, 3H), 7.25 (br s, 2H), 7.21 – 7.19 (m, 2H), 4.73 (s, 1H), 4.67 (d, *J* = 15.2 Hz, 1H), 4.37 (d, *J* = 15.2 Hz, 1H), 3.88 (d, *J* = 19.2 Hz, 1H), 3.42 (d, *J* = 19.2 Hz, 1H).

^{13}C NMR (100 MHz, DMSO-d^{6}): δ (ppm): 161.9, 160.7, 139.4, 139.0, 137.1, 132.9, 132.4, 128.7, 128.6, 127.7, 127.6, 127.5, 127.4, 126.4, 126.2, 126.1, 125.9, 125.5, 120.1, 55.6, 46.9, 45.3, 38.7

HR-MS (ESI): *m/z* calculated for $C_{25}H_{19}N_3O_2Na^+$: 416.1375, found: 416.1372.

2-amino-6-benzyl-7-oxo-4-(thiophen-2-yl)-4,5,6,7-tetrahydropyrano[2,3-c]pyrrole-3-carbonitrile 4r



4r

Prepared according to the general procedure using 1-benzyl-4-(thiophen-2-ylmethylene) pyrrolidine-2,3-dione **1r** (56.6 mg, 0.2 mmol, 1.0 equiv) and malononitrile **2** (14.5 mg, 0.22 mmol, 1.1 equiv). Purification of the crude product via simple filtration delivered **4r** as a white solid with 96% yield when ethanol as the reaction medium. (with 84% yield when water as the reaction medium).

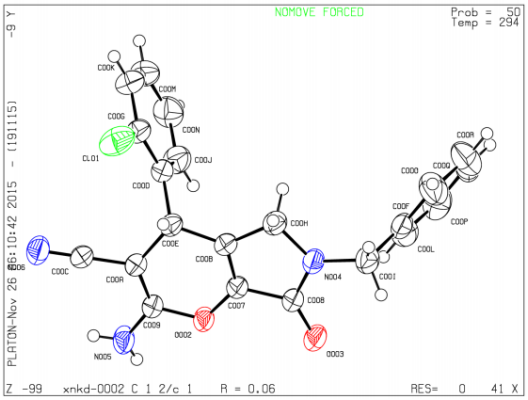
Characterization data for the product **4r***:*

^{1}H NMR (400 MHz, DMSO-d^{6}): δ (ppm): 7.51 – 7.49 (m, 1H), 7.39 – 7.29 (m, 3H), 7.25 – 7.22 (m, 4H), 7.03 – 7.00 (m, 2H), 4.93 (s, 1H), 4.66 (d, *J* = 15.2 Hz, 1H), 4.47 (d, *J* = 15.2 Hz, 1H), 3.91 (d, *J* = 19.2 Hz, 1H), 3.57 (d, *J* = 19.2 Hz, 1H).

^{13}C NMR (100 MHz, DMSO-d^{6}): δ (ppm): 162.2, 160.9, 147.3, 139.1, 137.6, 129.2, 128.1, 127.9, 127.6, 126.5, 126.3, 125.8, 120.3, 56.8, 47.4, 45.9, 34.2

HR-MS (ESI): *m/z* calculated for $C_{19}H_{15}N_3O_2SNa^+$: 372.0783, found: 372.0781.

4. Crystal data and structure refinement for the representative product 4l



Identification code	**4l**
Empirical formula	$C_{21}H_{16}ClN_3O_2$
Formula weight	377.82
Temperature/K	294.39(10)
Crystal system	monoclinic
Space group	C2/c

a/Å	19.0108(8)
b/Å	10.0865(3)
c/Å	20.7318(9)
α/°	90
β/°	116.291(5)
γ/°	90
Volume/$Å^3$	3564.1(3)
Z	8
$\rho_{calc}g/cm^3$	1.408
μ/mm^{-1}	2.080
F(000)	1568.0
Crystal size/mm^3	0.3 × 0.2 × 0.1
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	9.516 to 134.13
Index ranges	$-22 \leq h \leq 19$, $-12 \leq k \leq 9$, $-24 \leq l \leq 23$
Reflections collected	8044
Independent reflections	3175 [R_{int} = 0.0290, R_{sigma} = 0.0315]
Data/restraints/parameters	3175/0/252
Goodness-of-fit on F^2	1.034
Final R indexes [I>=2σ (I)]	R_1 = 0.0567, wR_2 = 0.1556
Final R indexes [all data]	R_1 = 0.0647, wR_2 = 0.1655
Largest diff. peak/hole / e $Å^{-3}$	0.36/-0.29

5. Procedure for in vitro minimum inhibitory concentration assay.

- Motivation of this study: We were inspired by the 4*H*-pyrane core structure of the products, which has already been demonstrated to show antibacterial activity [3]. Moreover, bicyclic frameworks with lactam functionalities are widely existed in the framework of many clinically used antibiotics such as cephalosporins. Therefore, we expected the synthesized novel bicyclic 4*H*-pyranes with γ-lactam functionalities would also have potential antibacterial bioactivity.

- Detailed work procedure: The minimum inhibitory concentration (MIC) of each compound was determined using a standard broth microdilution assay.[4] The procedure is that MIC data was determined by a microdilution method, following the National Committee for Clinical Laboratory Standards (NCCLS) (now called the Clinical Laboratory Standards Institute [CLSI]) The stock solutions of test compounds were diluted to give a serial, 2-fold series, yielding final chemical concentrations that ranged from 128 to 16μg/mL. The MIC was defined as the lowest concentration of the chemical that inhibited the development of visible bacterial growth after an incubation for 16 h at 37^{o}C.

6. References and notes

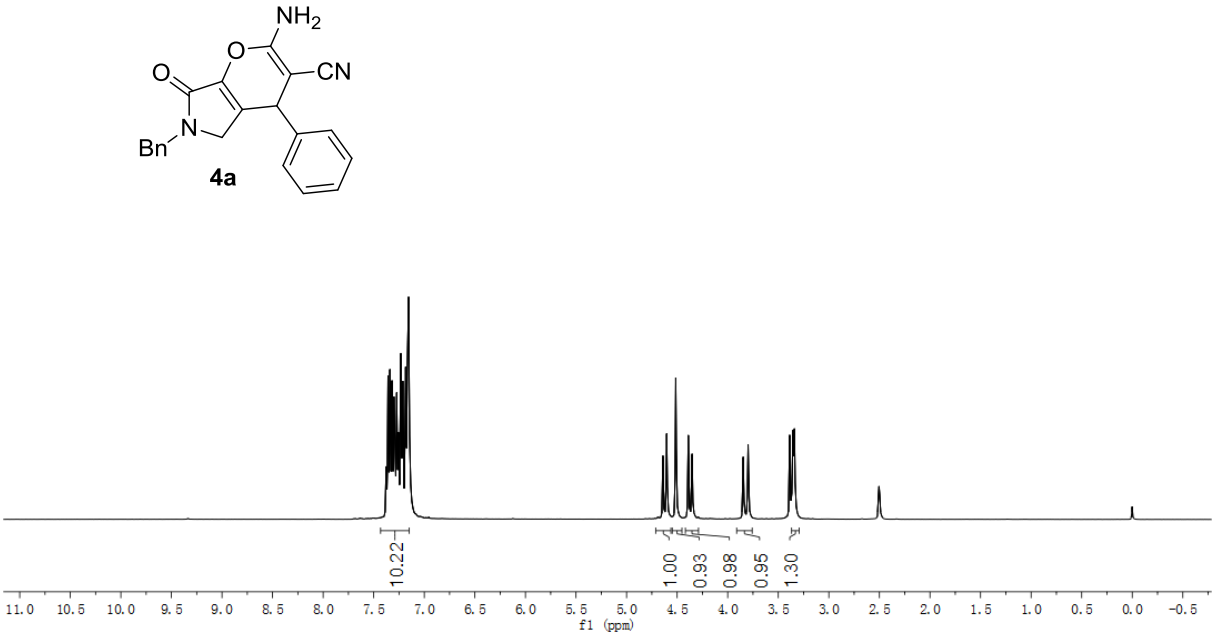
[1] a) E. Krell, *Handbook of Laboratory Distillation*, Elseriver Publishing Company, Amsterdam-London-New York, **1963**; b) M. J. Rosengart, *The Technique of Distillation and Rectification in the Laboratory*, VEB Verlag Technik, Berlin, **1954**; c) H. Stage *Columns for laboratory distillation*, *Angew. Chem.*, **1947**, *B19*, 175.

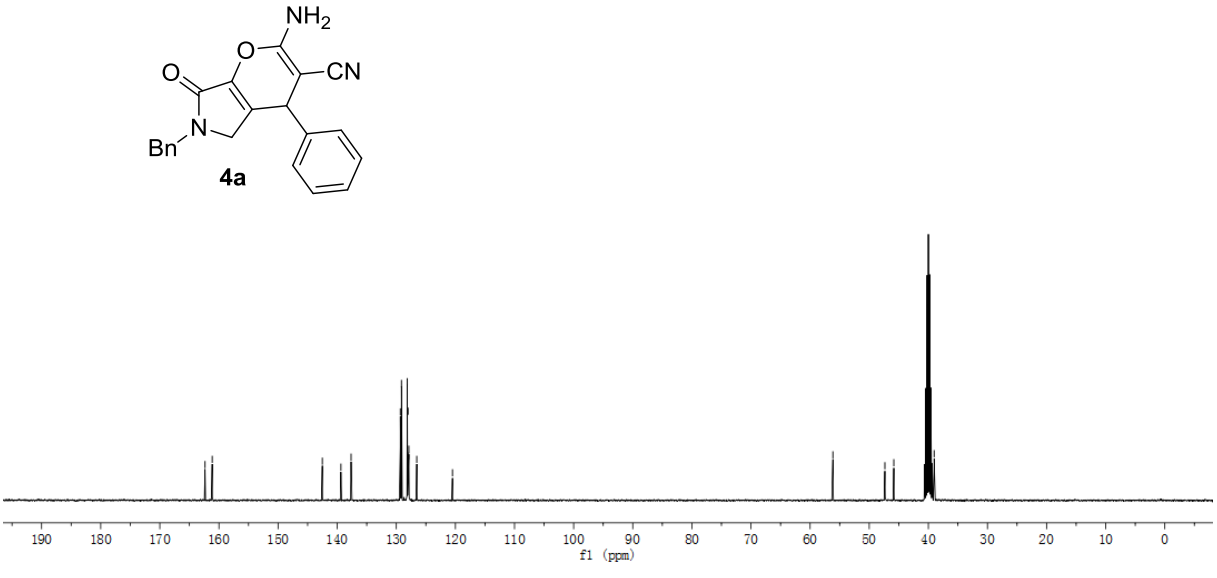
[2] P. L. Southwick, E. F. Barnas, *J. Org. Chem.*, **1962**, *27*, 98.

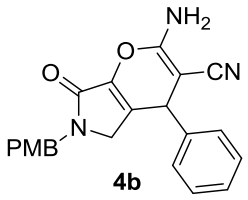
[3] M. Kidwai, S. Saxena, M. K. R. Khan, S. S. Thukral, *Bioorg. Med. Chem. Lett.*, **2005**, *15*, 4295.

[4] L. Ouyang, Y. Huang, Y. Zhao, G. He, Y. Xie, J. Liu, J. He, B. Liu, Y. Wei, *Bioorg. Med.Chem. Lett.*, **2012**, *22*, 3044.

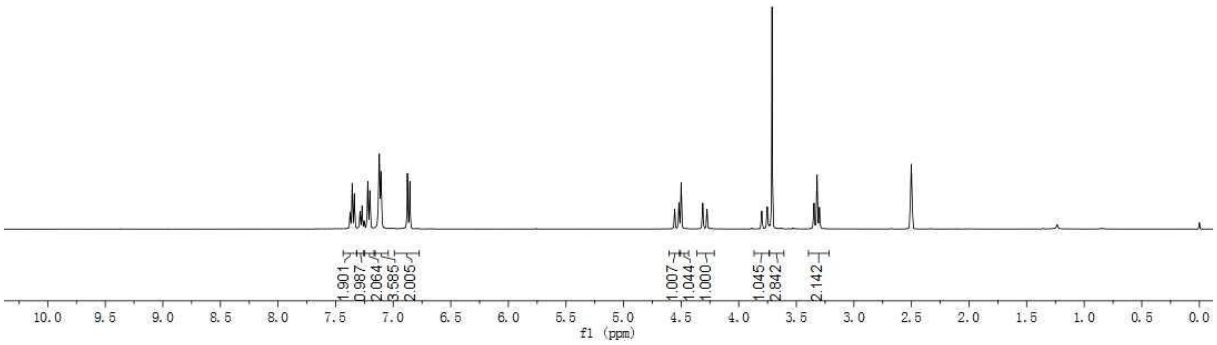
7. NMR Spectra of the multi-substituted bicyclic 4H-pyranes

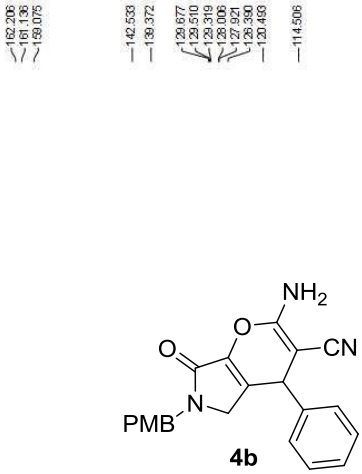





NH2
O
CN
O
N
PMB

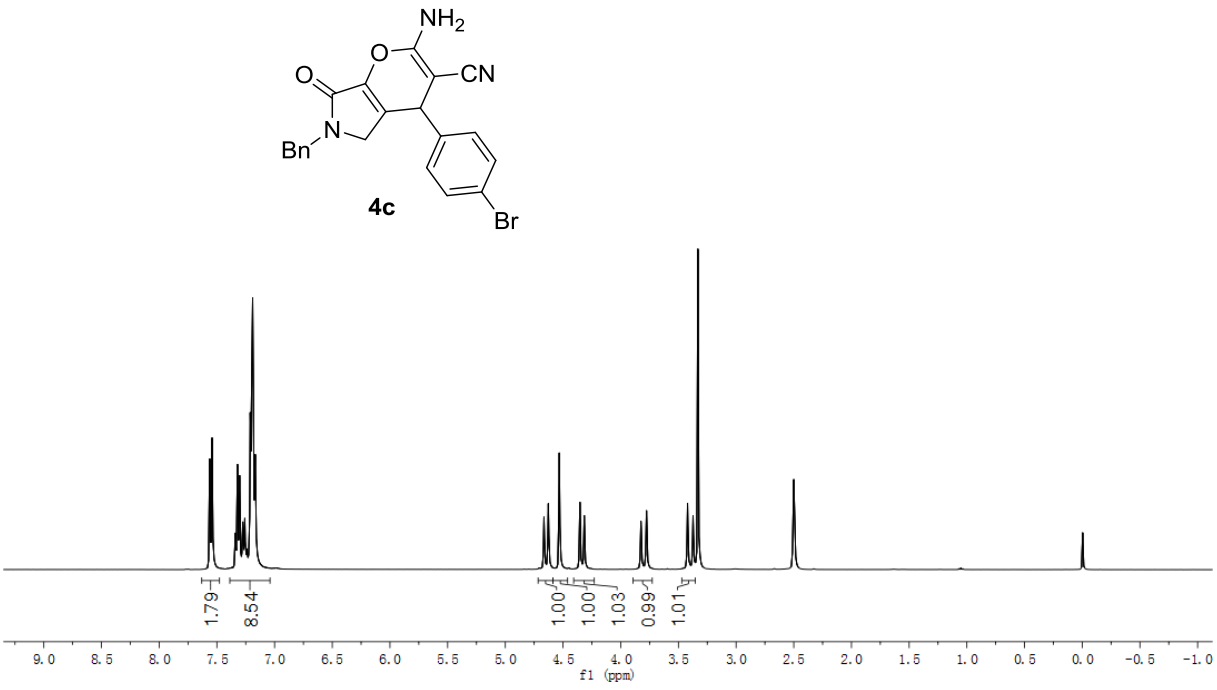
4b

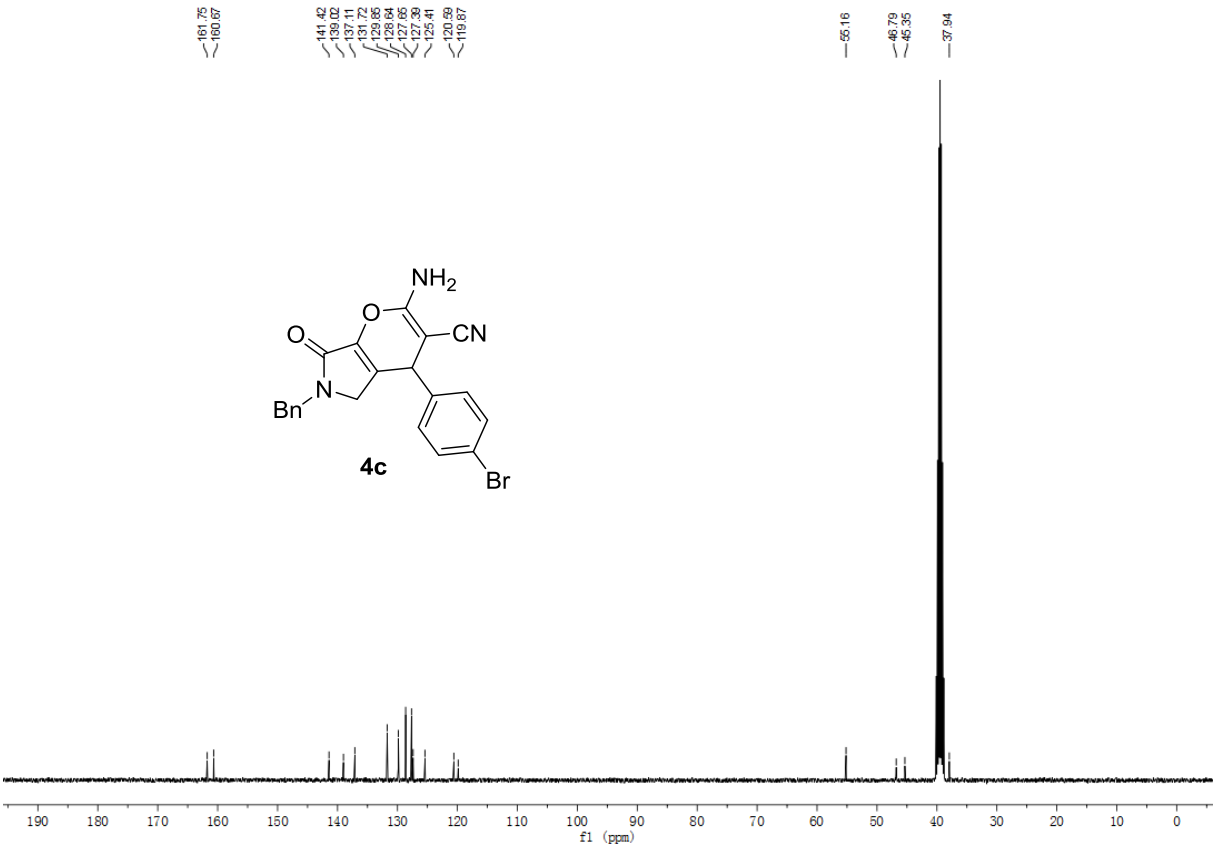

1.901
0.987
2.064
3.585
2.005
1.007
1.044
1.000
1.045
2.842
2.142
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

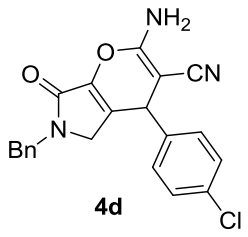

NH2
O
CN
O
N
PMB

4b

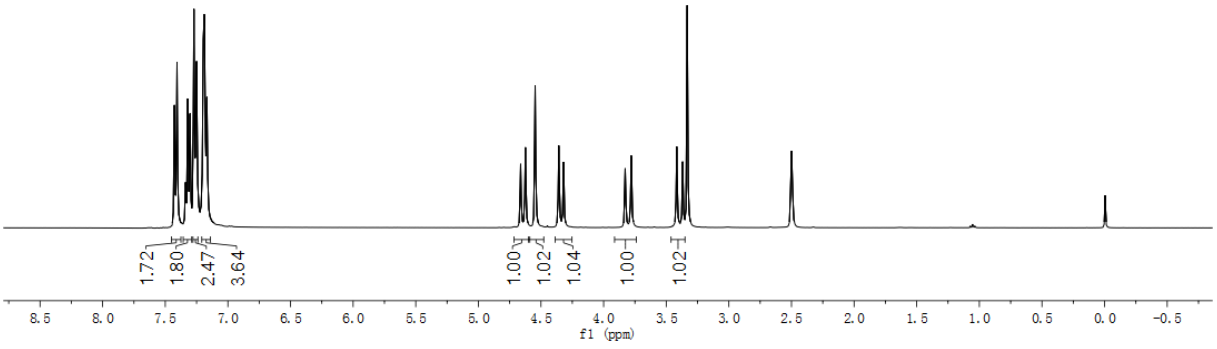
162.206
161.130
159.075
142.533
139.372
129.677
129.510
129.319
128.006
127.921
126.390
120.493
114.506
56.126
55.520
47.107
45.244
38.994
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

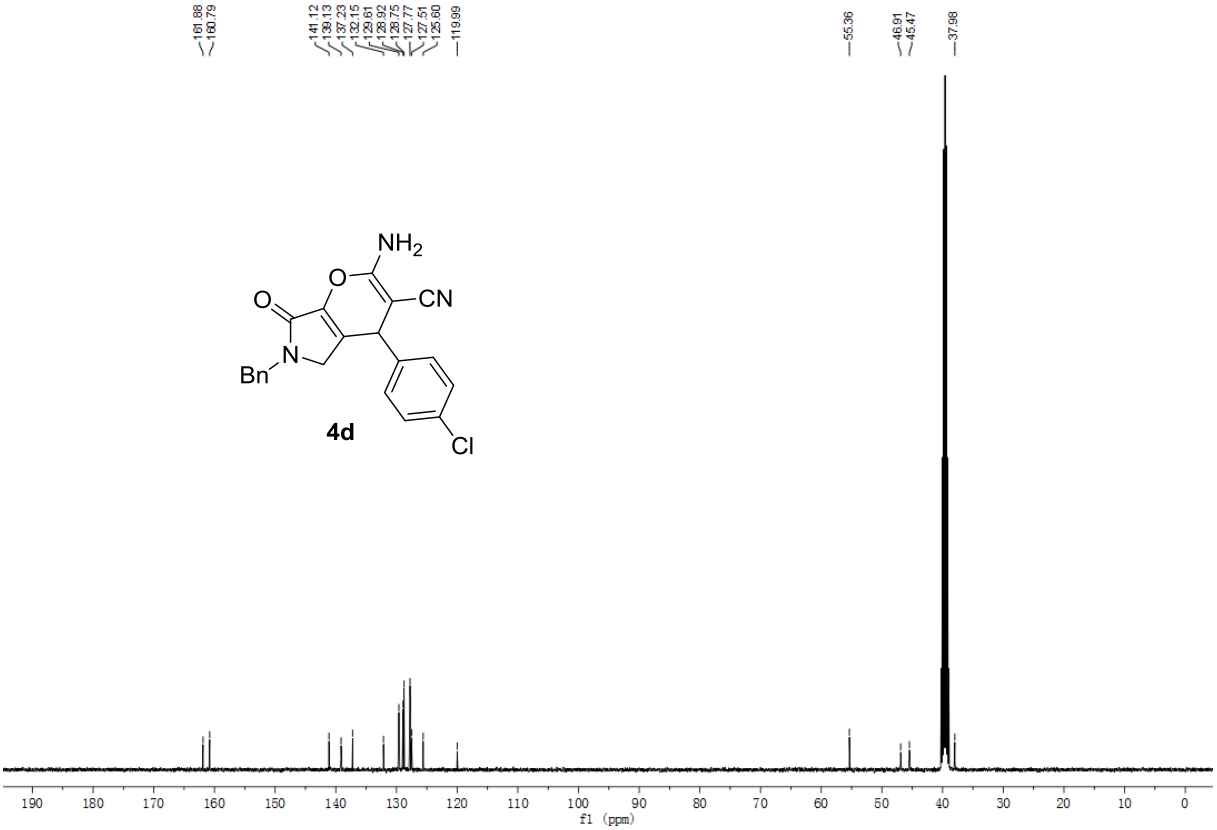

NH2
O
CN
O
N
Bn
Br
4c
1.79
8.54
1.00
1.00
1.03
0.99
1.01
f1 (ppm)


161.75
160.67
141.42
139.02
137.11
131.72
129.85
128.64
128.45
127.39
125.41
120.59
119.87
55.16
46.79
45.35
37.94
NH2
O
CN
O
N
Bn
Br
4c
f1 (ppm)


NH2
O
CN
O
N
Bn
Cl

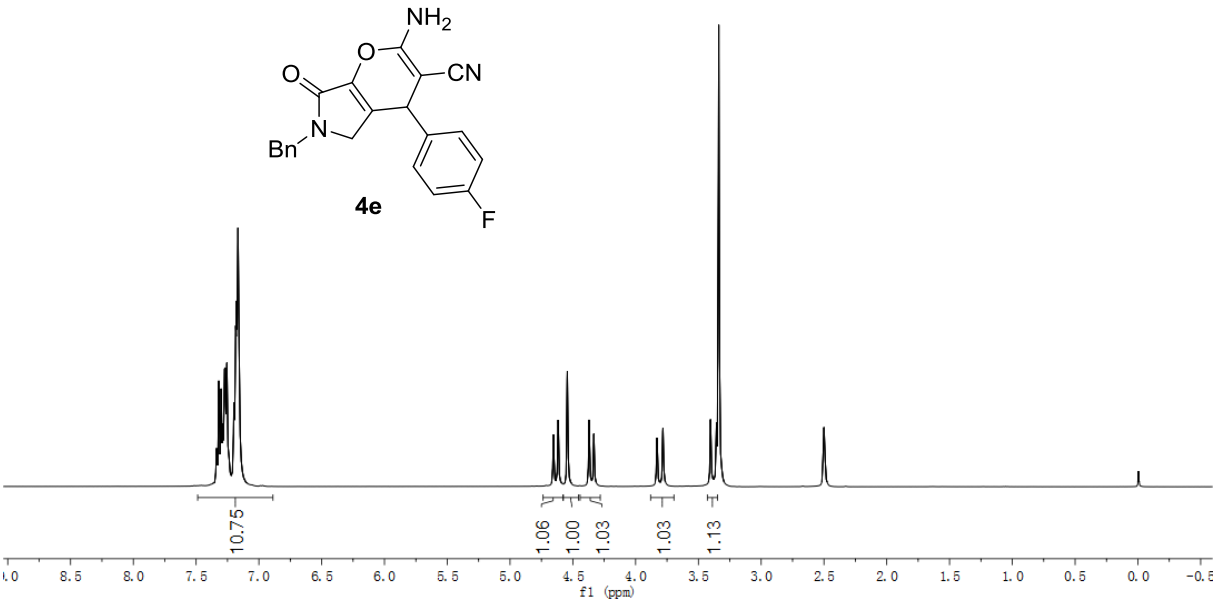
4d

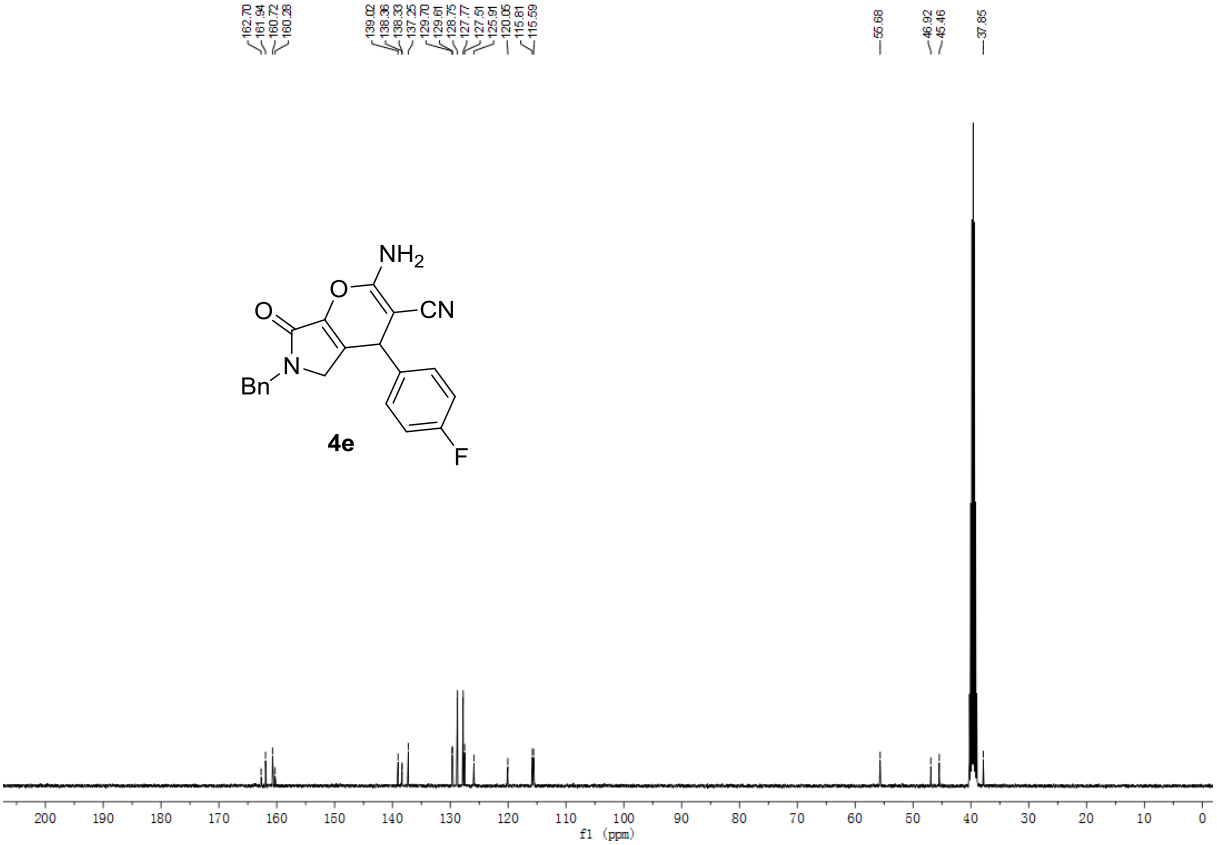

1.72
1.80
2.47
3.64
1.00
1.02
1.04
1.00
1.02
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

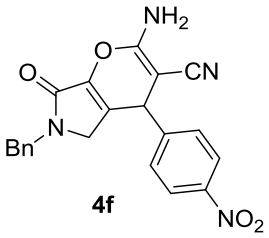

161.88
160.79
141.12
138.13
137.23
132.15
129.61
128.92
128.75
127.77
127.51
125.60
119.99
55.36
46.91
45.47
37.98
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

NH2
O
CN
O
N
Bn
Cl

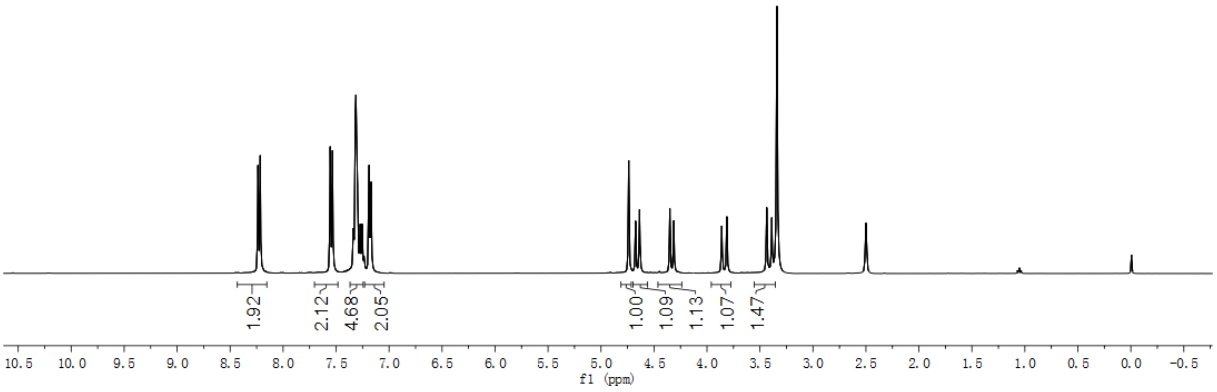
4d

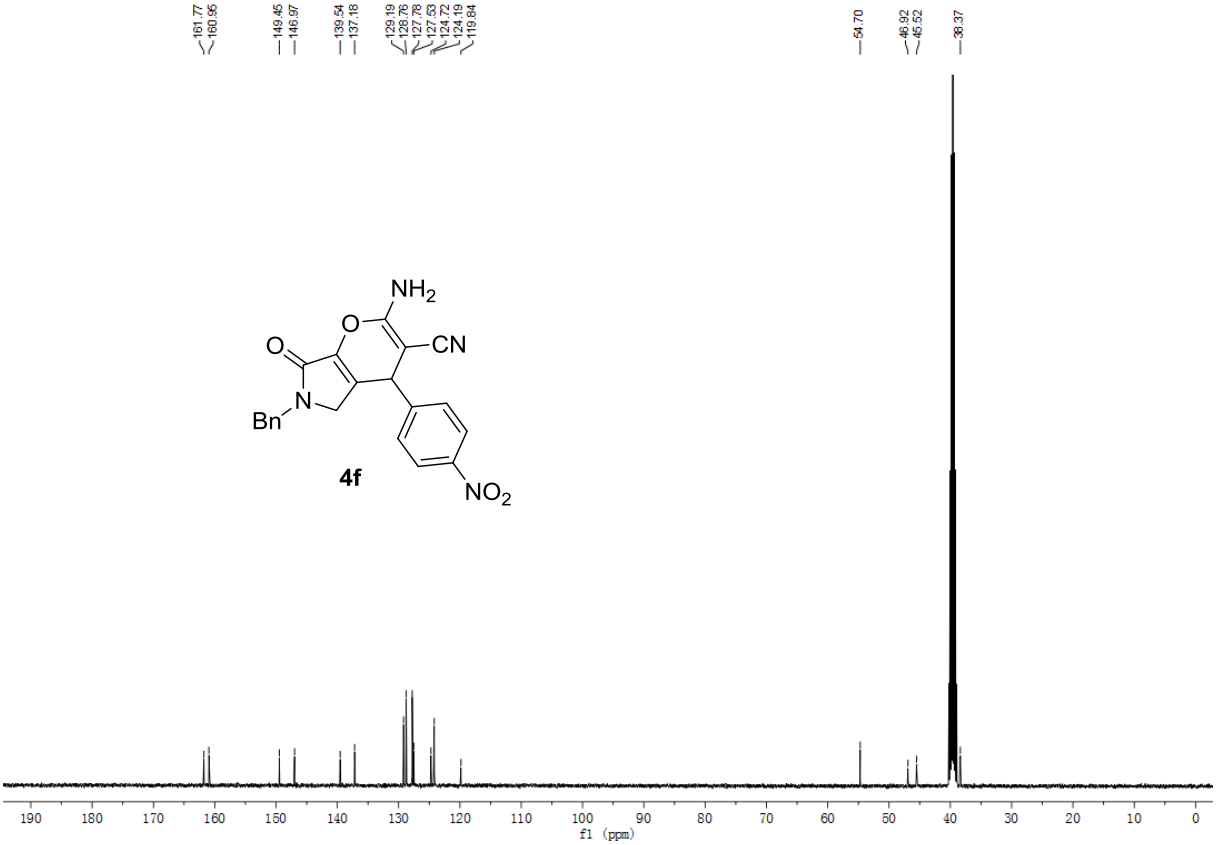

NH2
O
CN
O
N
Bn
F
4e
10.75
1.06
1.00
1.03
1.03
1.13
f1 (ppm)


162.70
161.94
160.72
160.28
139.02
138.36
138.33
137.25
129.70
129.61
128.75
127.77
127.51
125.91
120.05
115.81
115.59
55.68
46.92
45.46
37.85
NH2
O
CN
O
N
Bn
F
4e
f1 (ppm)


NH2
O
CN
O
N
Bn
NO2

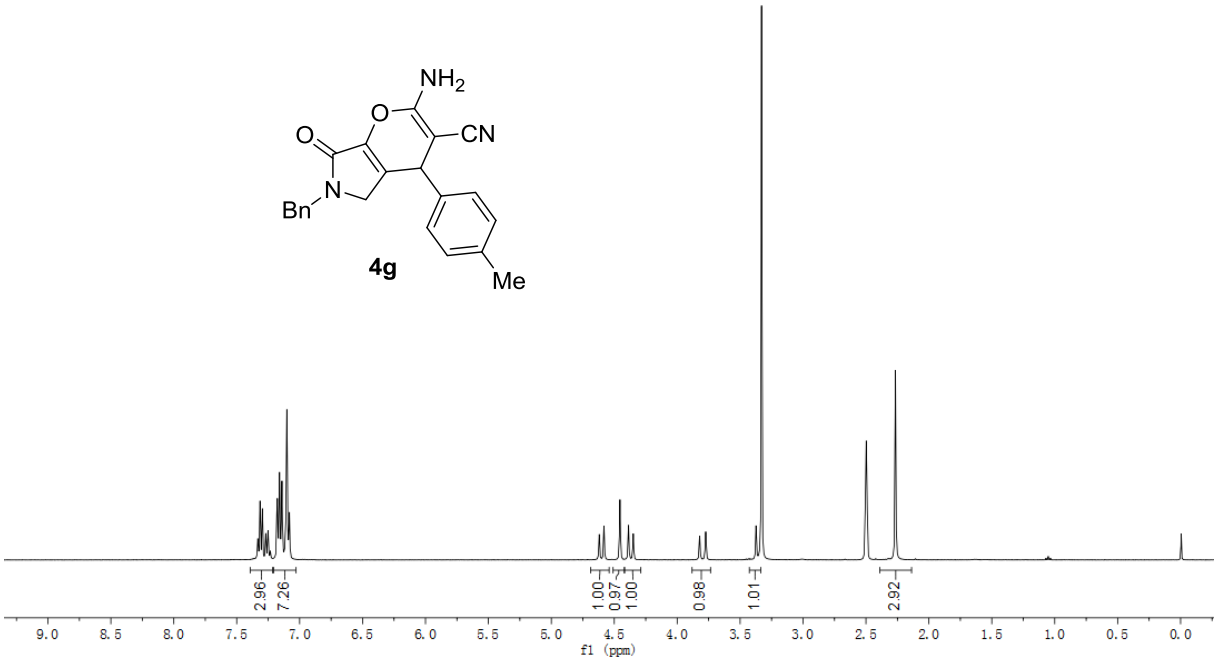
4f

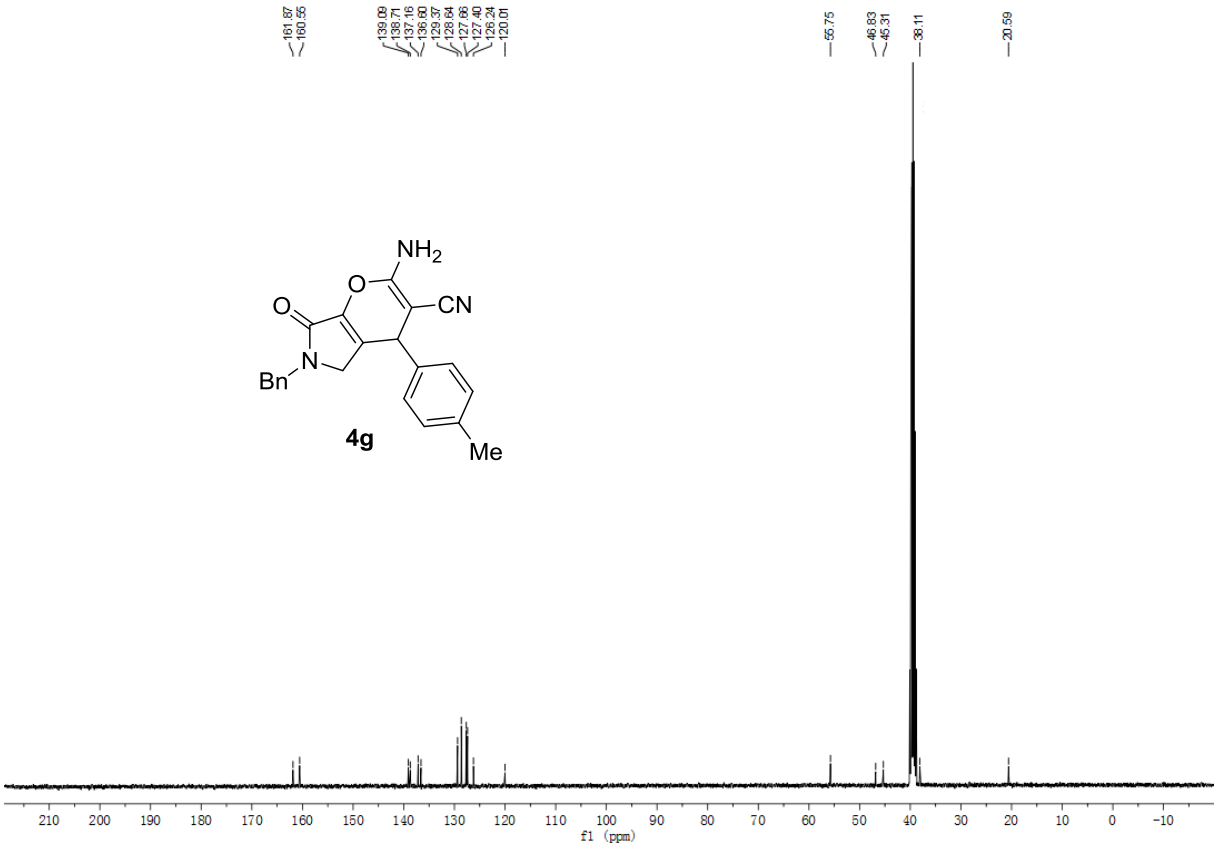

1.92
2.12
4.68
2.05
1.00
1.09
1.13
1.07
1.47
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

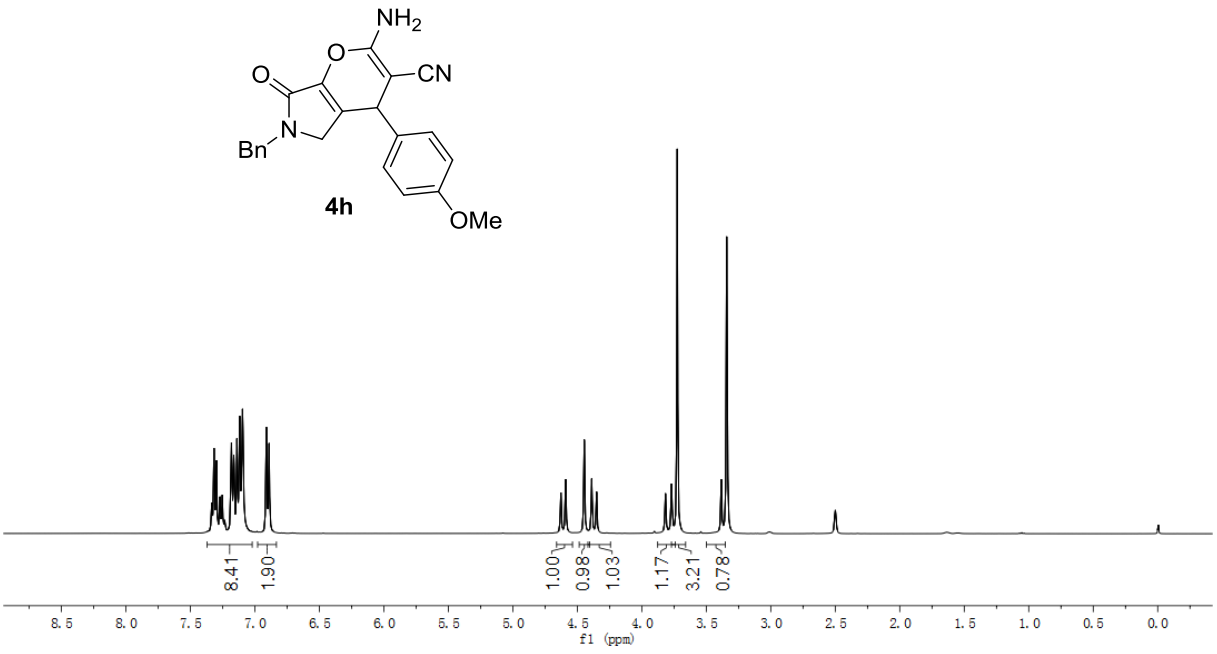

161.77
160.95
149.45
146.97
139.54
137.18
129.19
128.76
127.78
127.53
124.72
124.19
119.84
54.70
46.92
45.52
38.37
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

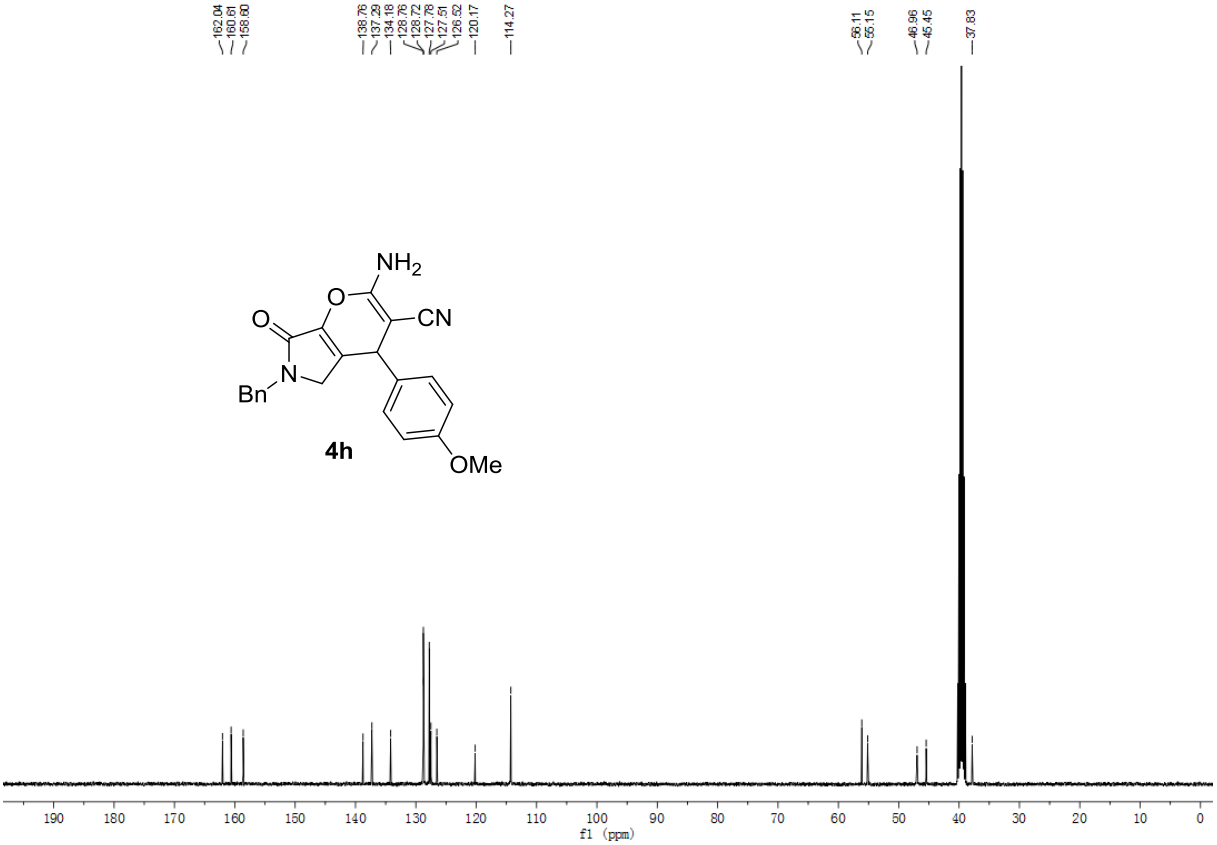
NH2
O
CN
O
N
Bn
NO2

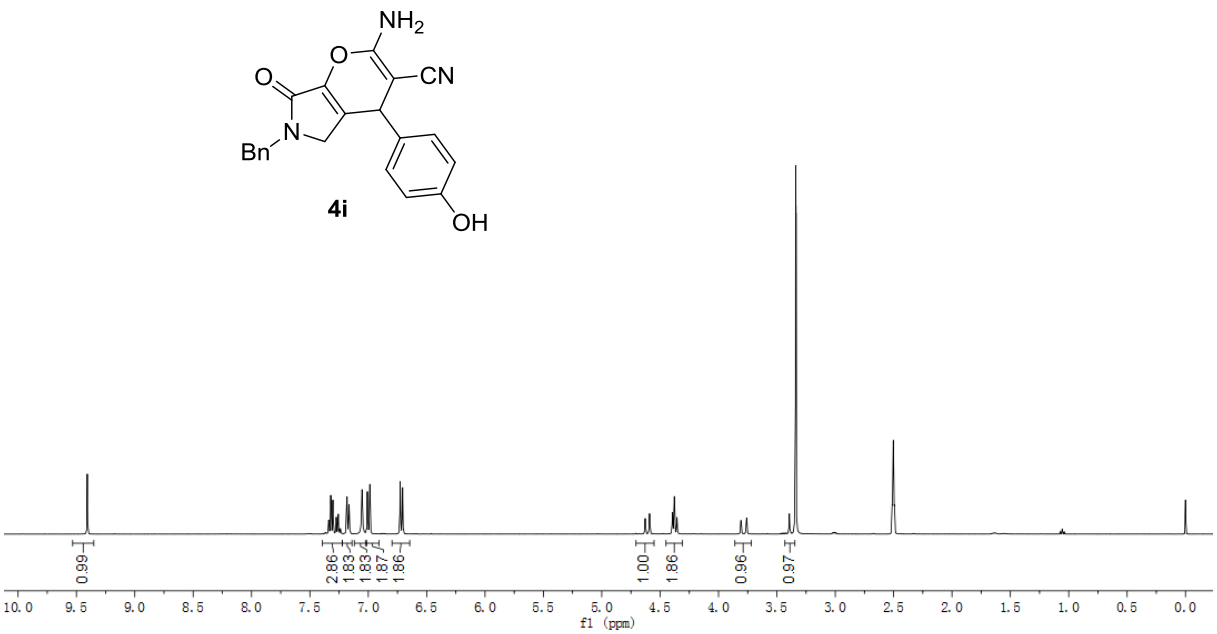
4f

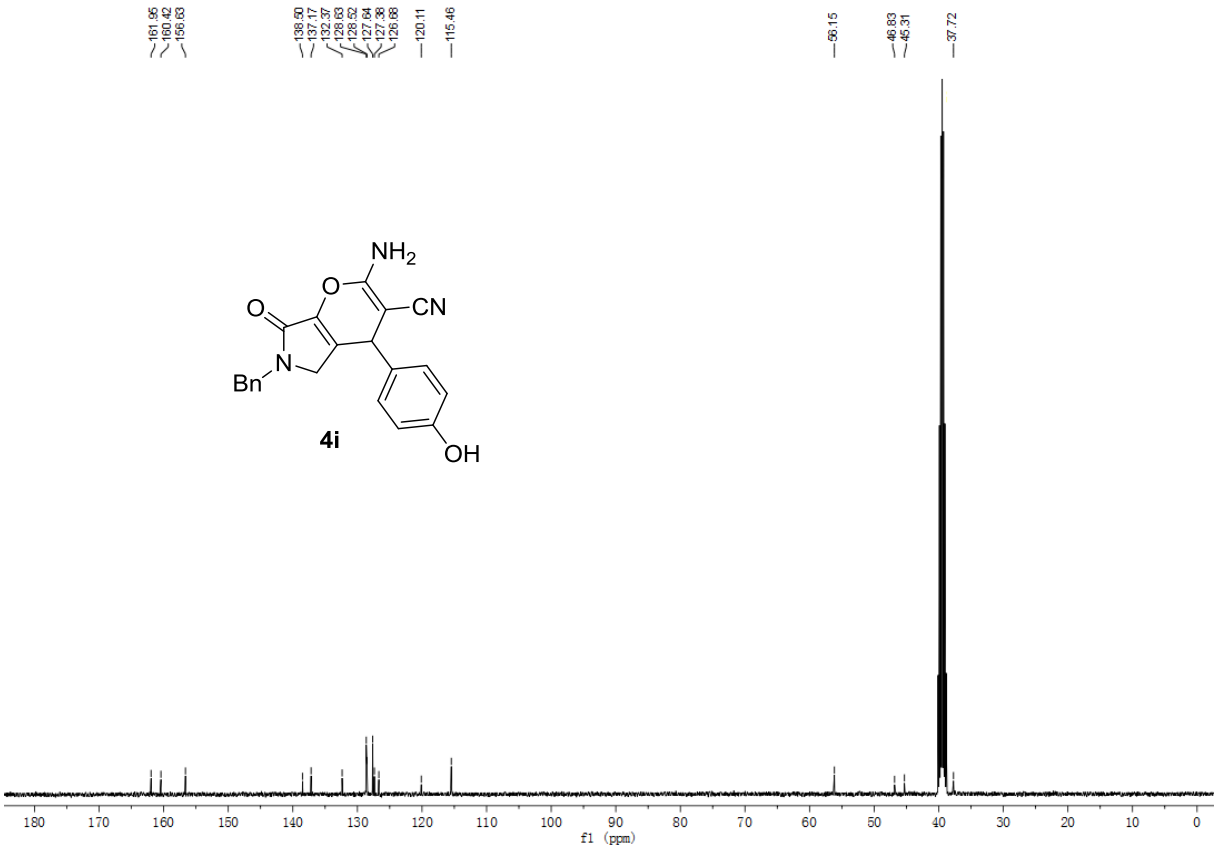

NH2
O
CN
O
N
Bn
Me
4g
2.96
7.26
1.00
0.97
1.00
0.98
1.01
2.92
f1 (ppm)

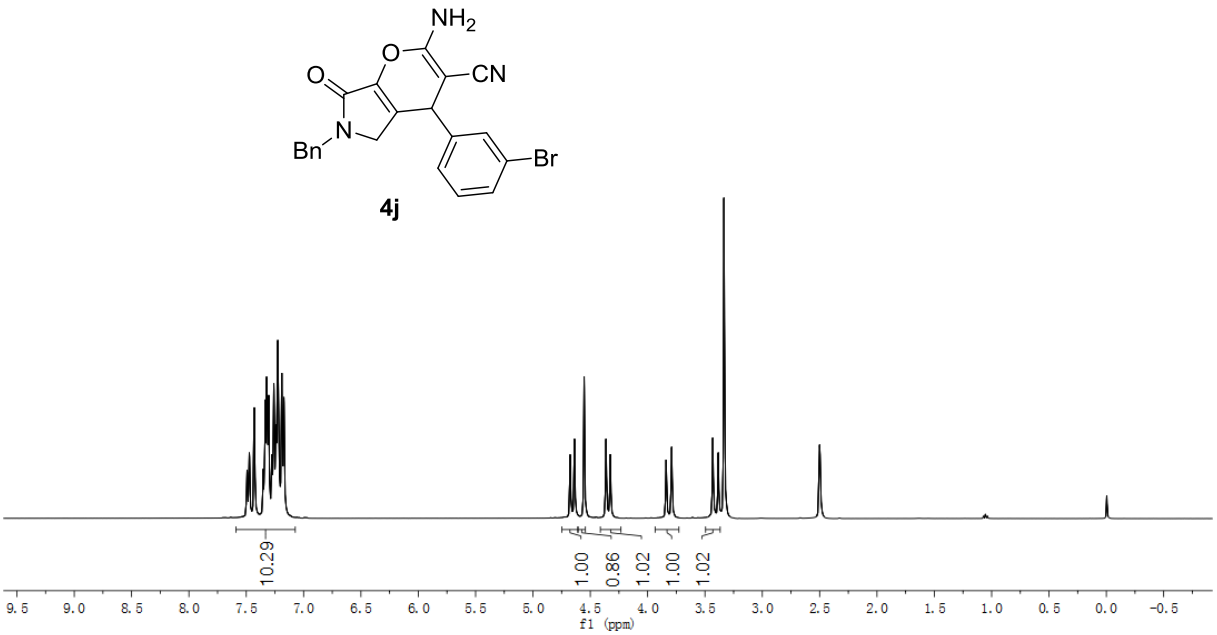

161.87
160.55
139.09
138.71
137.16
136.60
129.37
128.64
127.66
127.40
126.24
120.01
55.75
46.83
45.31
38.11
20.59
NH2
O
CN
O
N
Bn
Me
4g
f1 (ppm)


NH2
O
CN
O
N
Bn
4h
OMe
8.41
1.90
1.00
0.98
1.03
1.17
3.21
0.78
f1 (ppm)

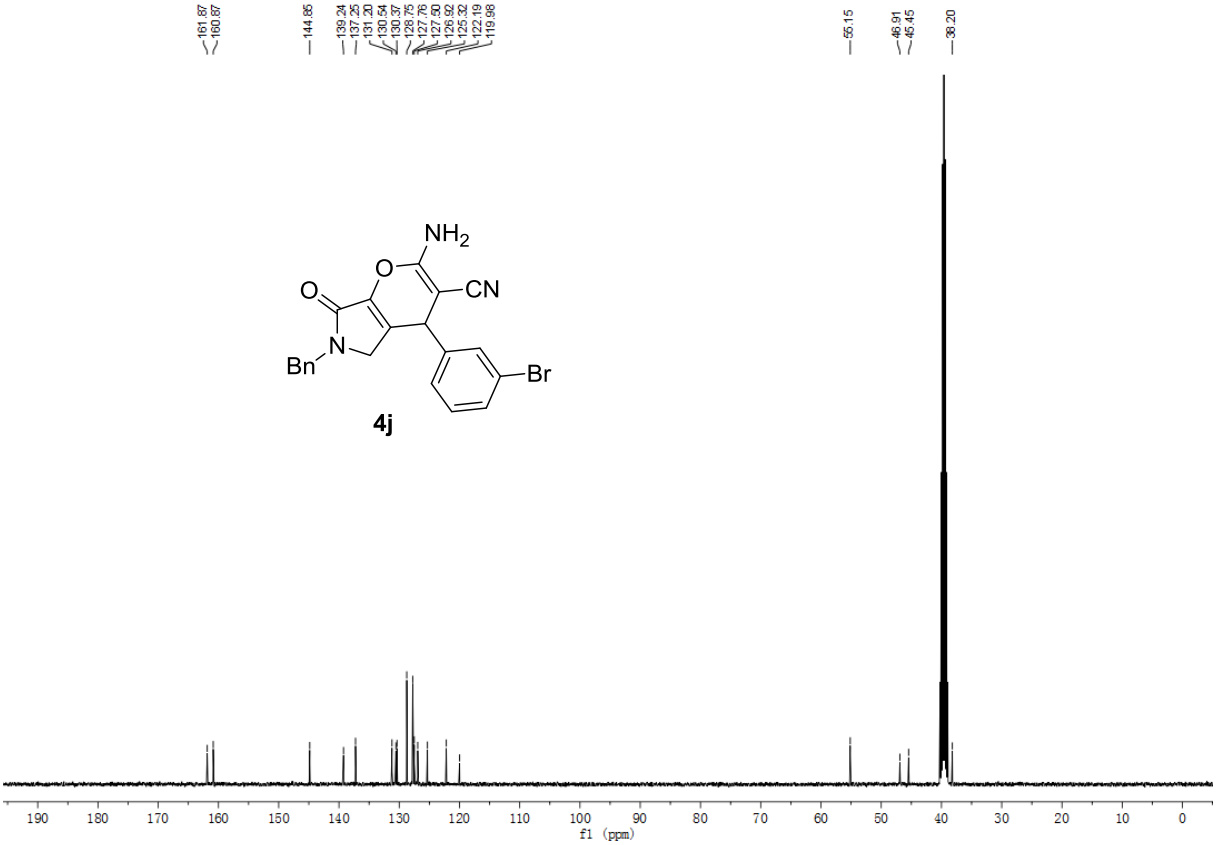

162.04
160.61
158.80
138.76
137.29
134.18
128.76
128.72
127.78
127.51
126.52
120.17
114.27
66.11
55.15
46.96
45.45
37.83
NH2
O
CN
O
N
Bn
4h
OMe
f1 (ppm)


NH2
O
CN
O
N
Bn
OH
4i
0.99
2.86
1.83
1.83
1.87
1.86
1.00
1.86
0.96
0.97
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

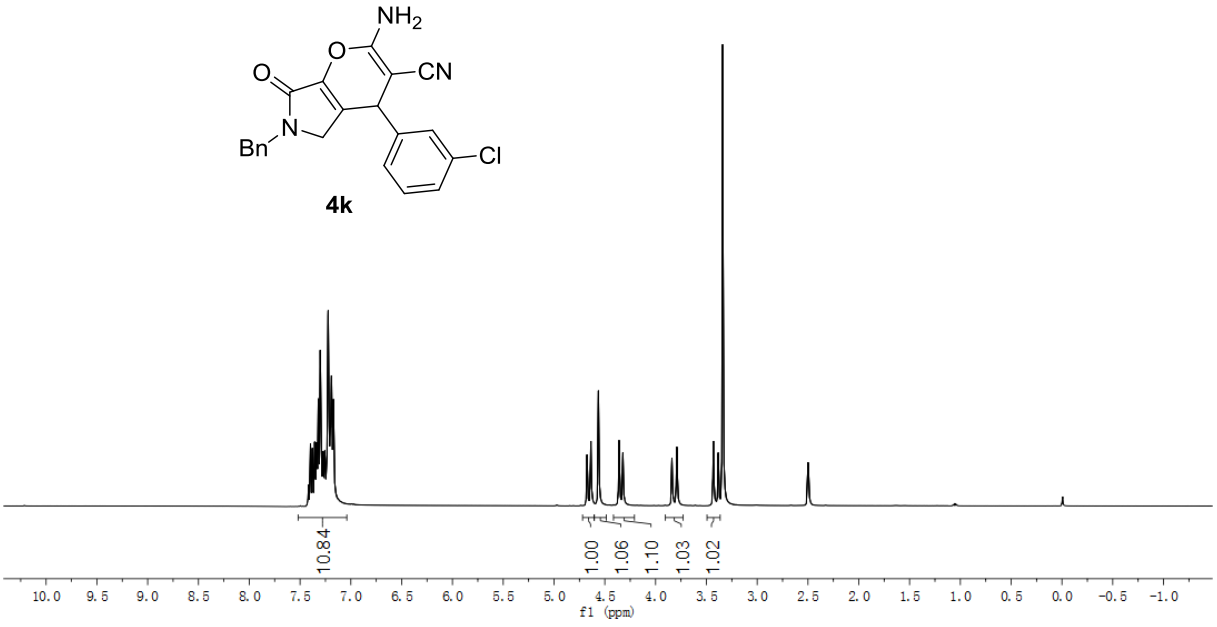

161.95
160.42
156.63
138.50
137.17
132.37
128.63
128.52
127.64
127.38
126.88
120.11
115.46
56.15
46.83
45.31
37.72
NH2
O
CN
O
N
Bn
OH
4i
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


NH2
O
CN
O
N
Bn
Br
10.29
1.00
0.86
1.02
1.00
1.02
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

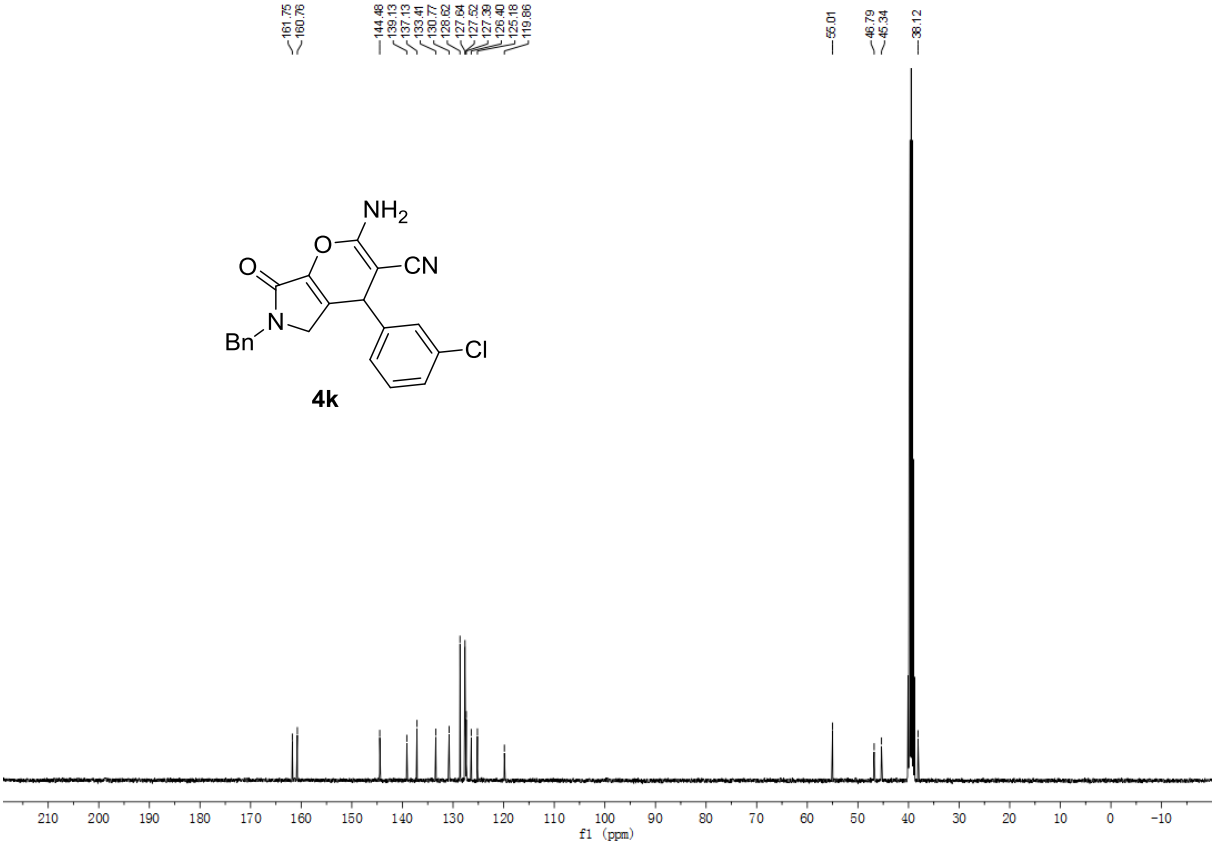
4j


161.87
160.87
144.85
139.24
137.25
131.20
130.54
130.37
128.75
127.76
127.50
126.92
125.32
122.19
119.98
55.15
46.91
45.45
38.20
NH2
O
CN
O
N
Bn
Br
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

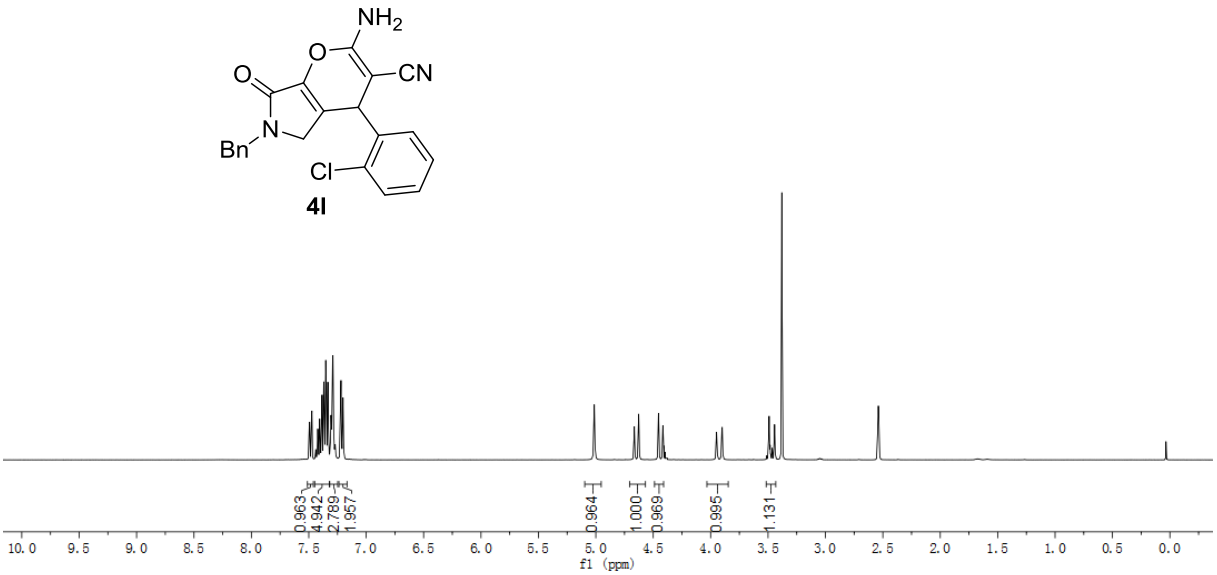
4j

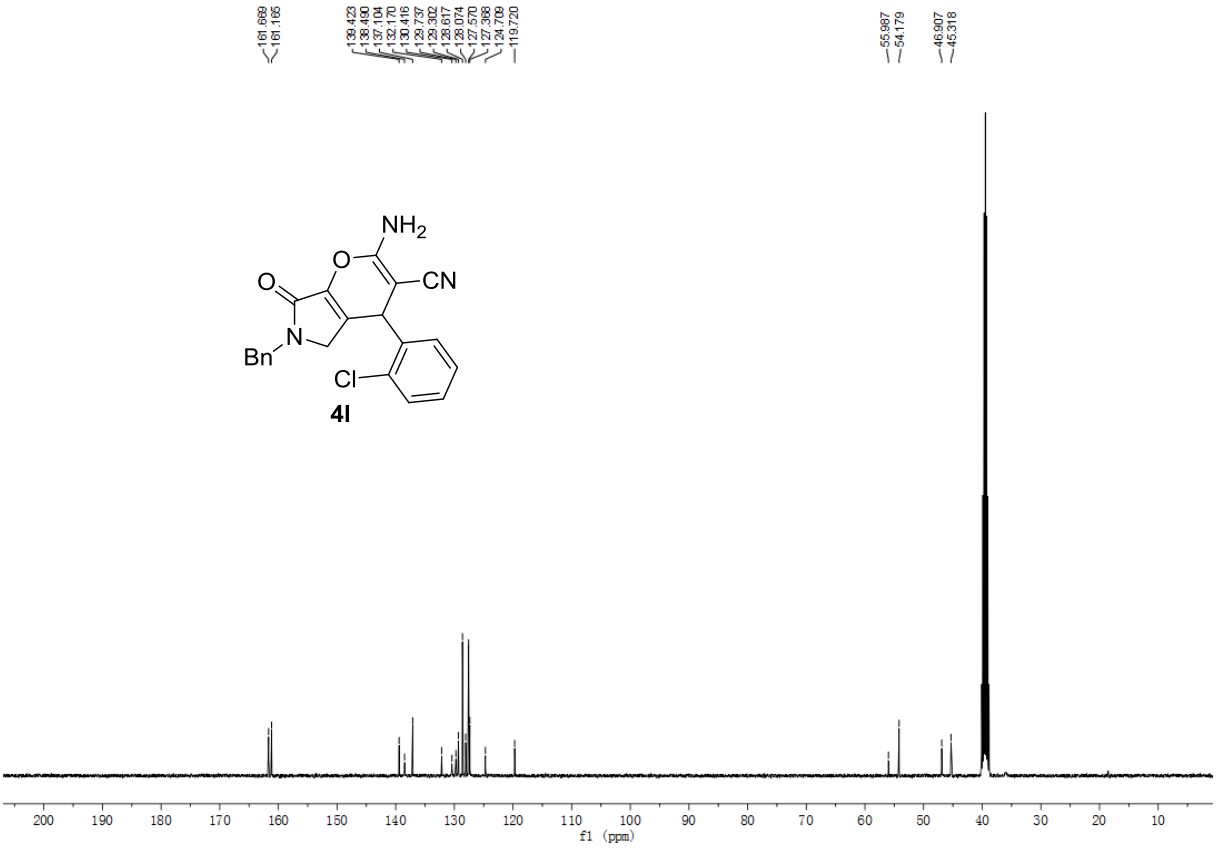

NH2
O
CN
O
N
Bn
Cl
10.84
1.00
1.06
1.10
1.03
1.02
f1 (ppm)

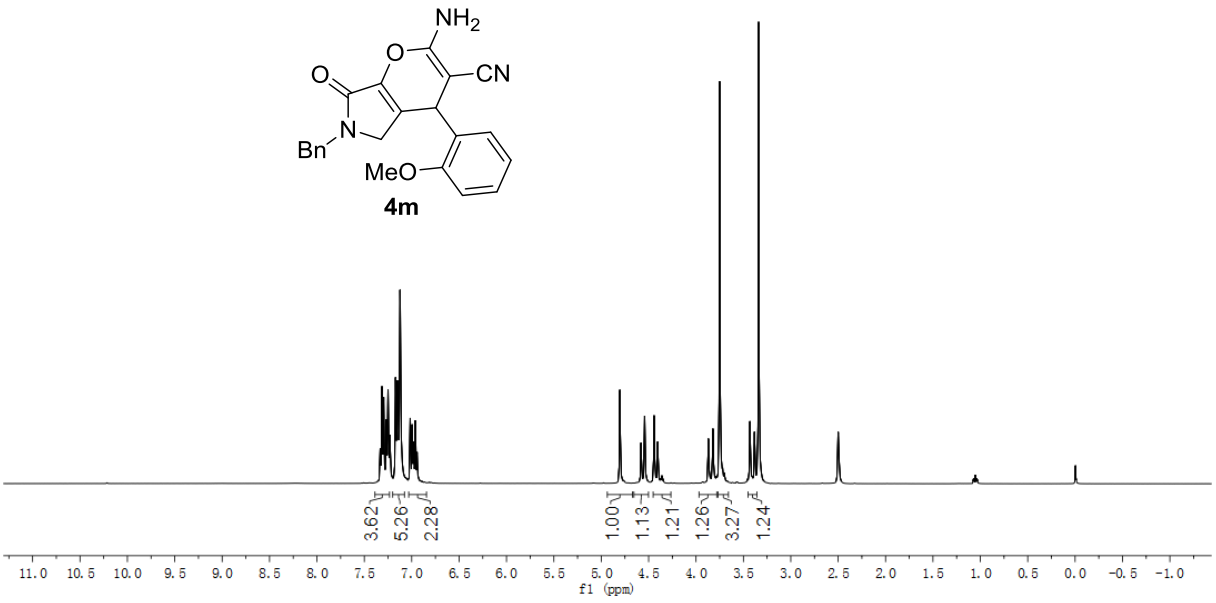
4k

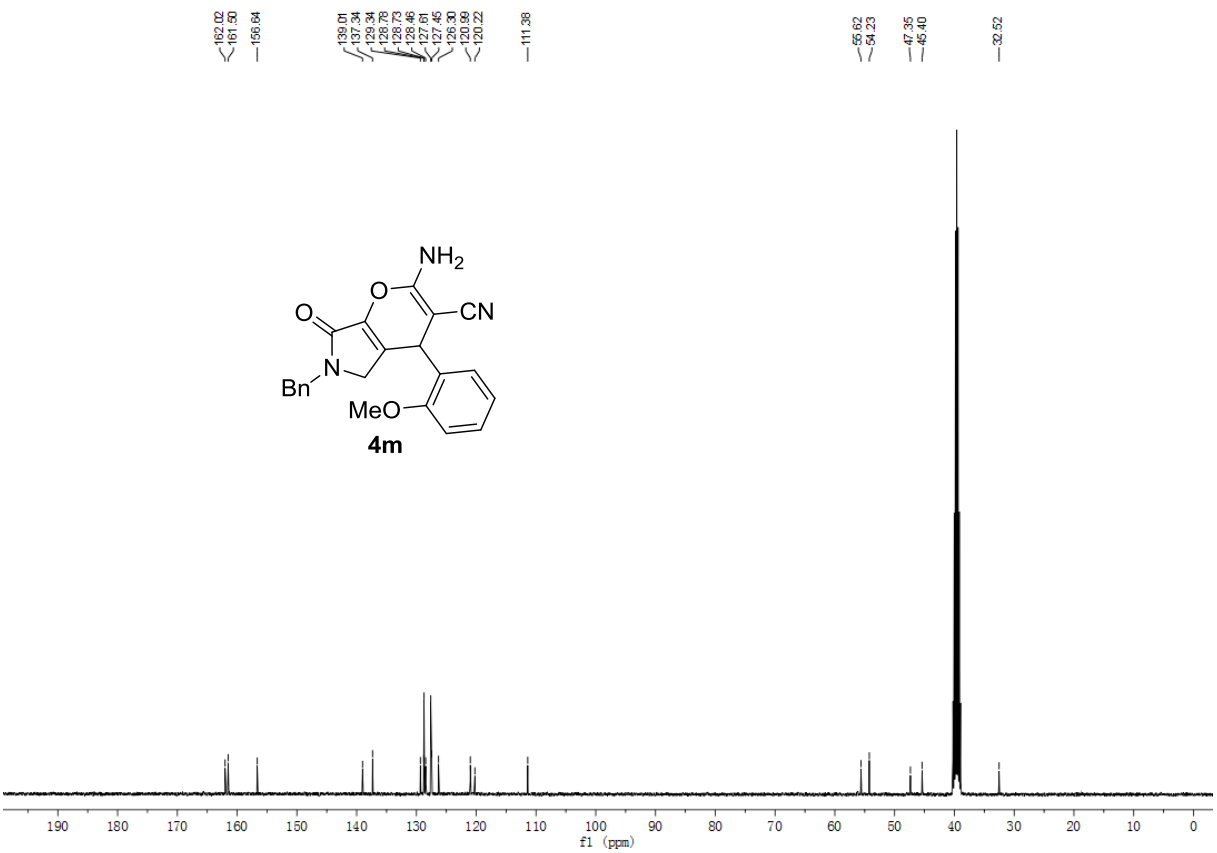

161.75
160.76
144.48
139.13
137.13
133.41
130.77
128.62
127.64
127.52
127.39
126.40
125.18
119.86
55.01
46.79
45.34
38.12
NH2
O
CN
O
N
Bn
Cl
f1 (ppm)

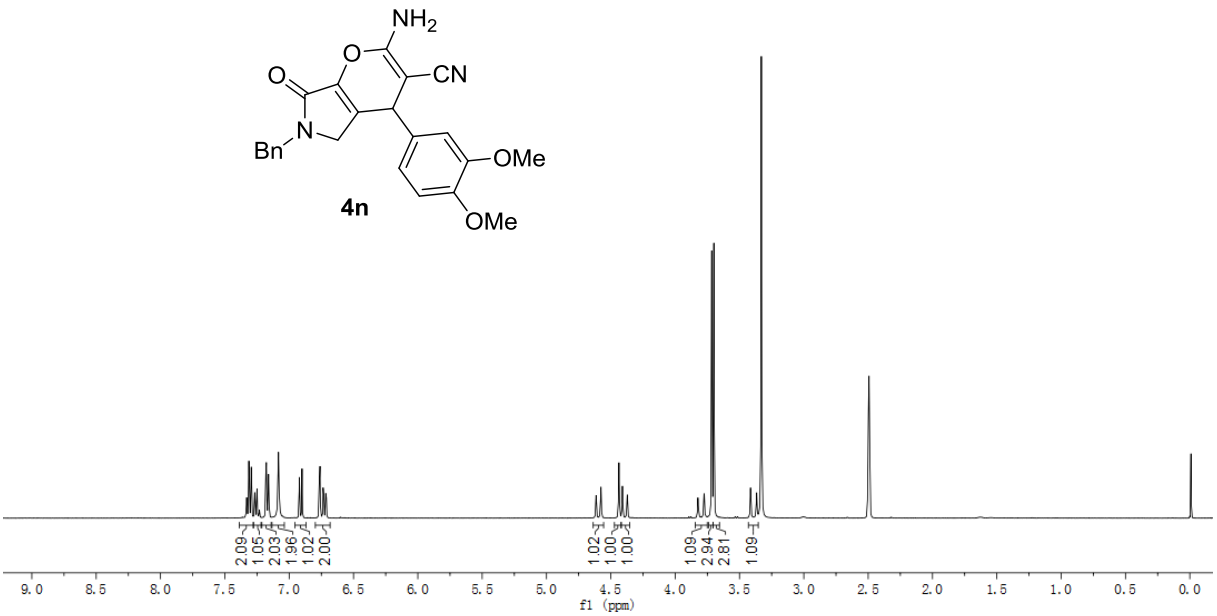
4k

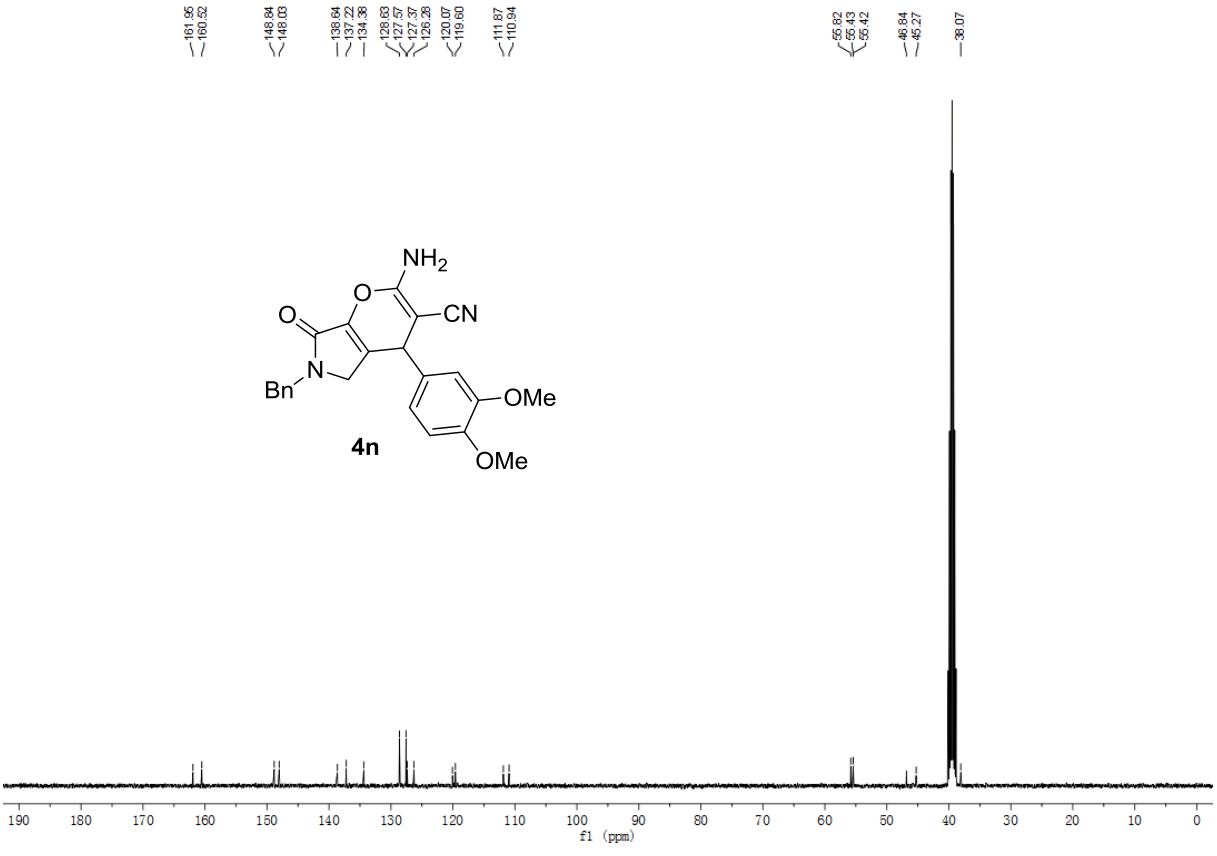

NH2
O
CN
O
N
Bn
Cl
4l
0.963
4.942
2.789
1.957
0.964
1.000
0.969
0.995
1.131
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

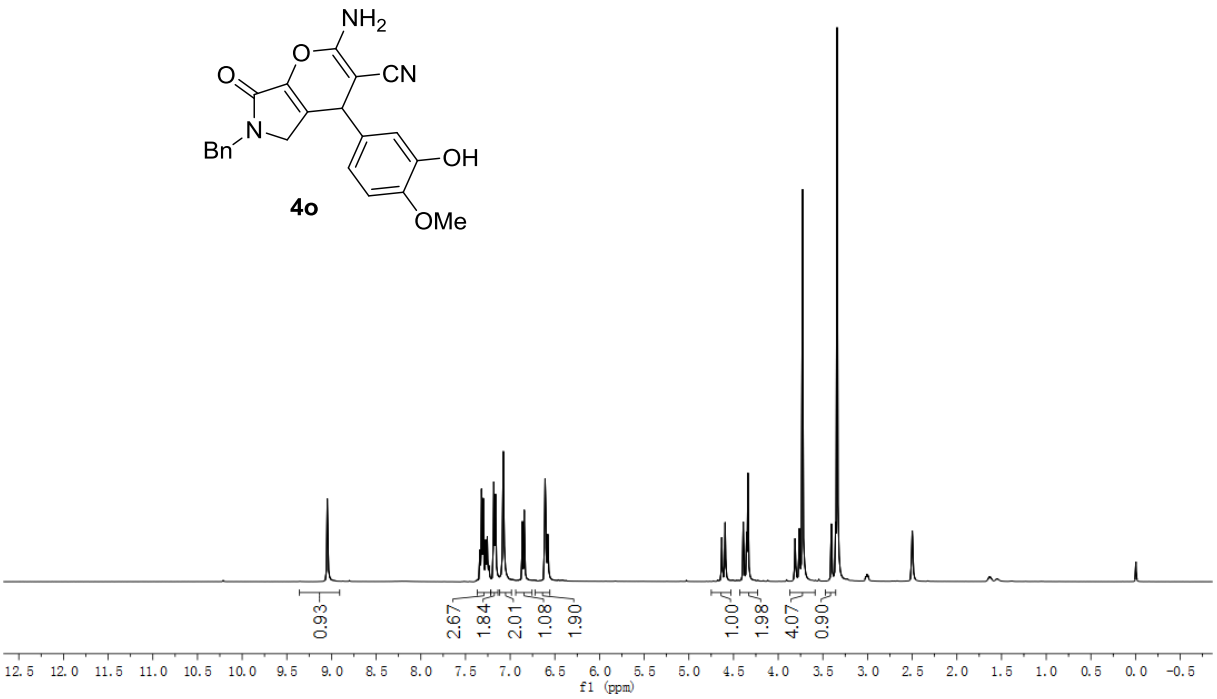

161.689
161.165
139.423
138.490
137.104
132.170
130.416
129.737
129.302
128.617
127.074
127.570
127.398
124.709
119.720
55.987
54.179
46.907
45.318
NH2
O
CN
O
N
Bn
Cl
4l
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

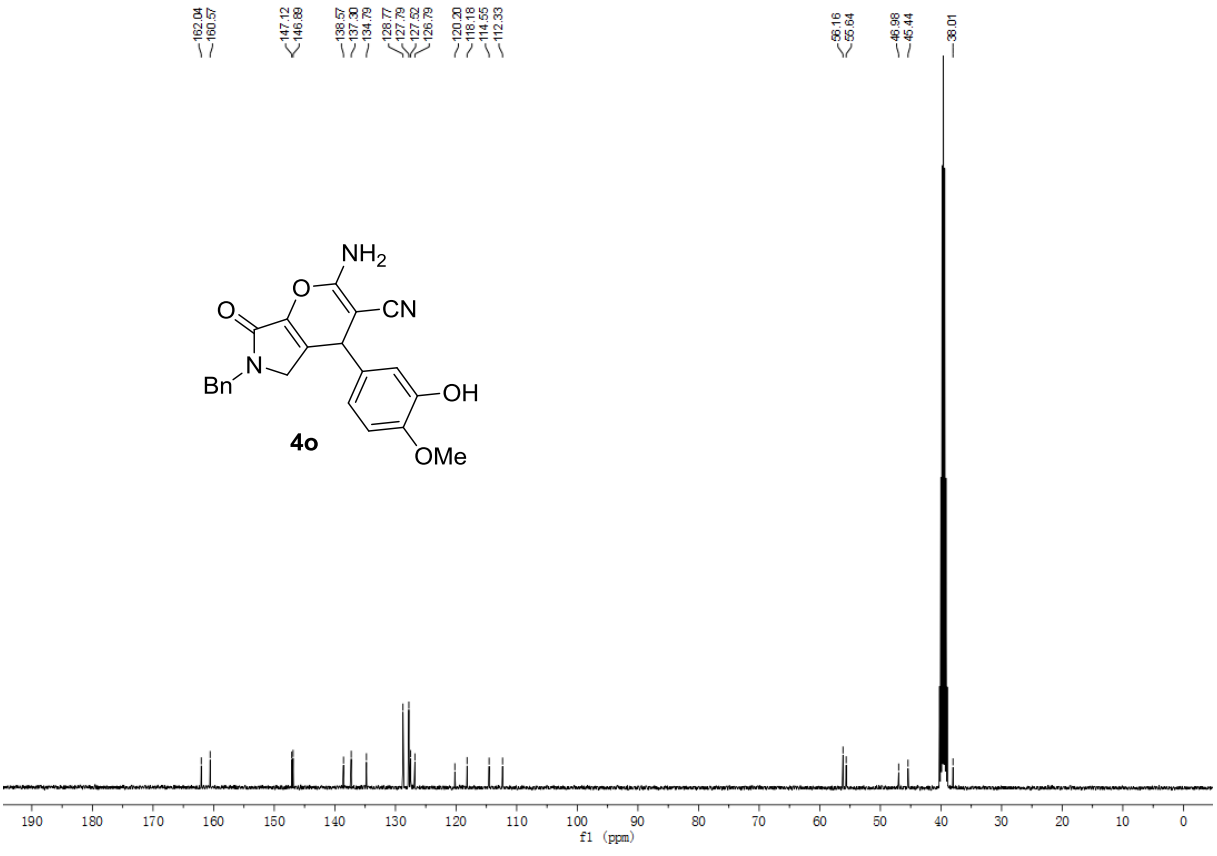

NH2
O
CN
O
N
Bn
MeO
4m
3.62
5.26
2.28
1.00
1.13
1.21
1.26
3.27
1.24
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

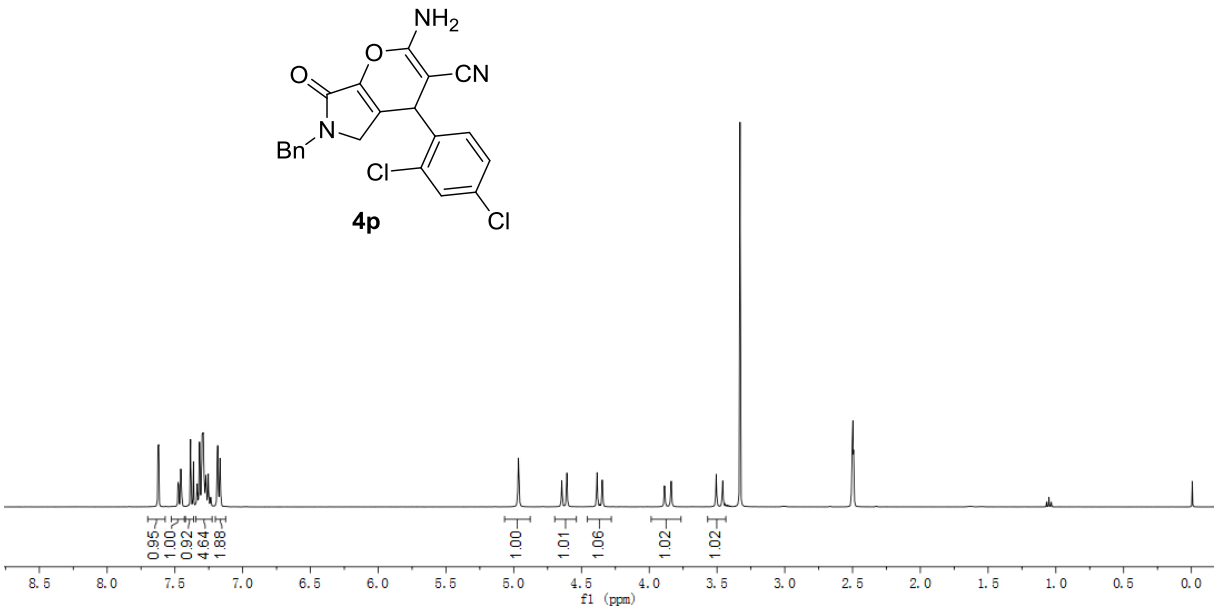

162.02
161.50
156.64
139.01
137.34
129.34
128.78
128.73
128.46
127.61
127.45
126.30
120.99
120.22
111.38
55.62
54.23
47.35
45.40
32.52
NH2
O
CN
O
N
Bn
MeO
4m
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

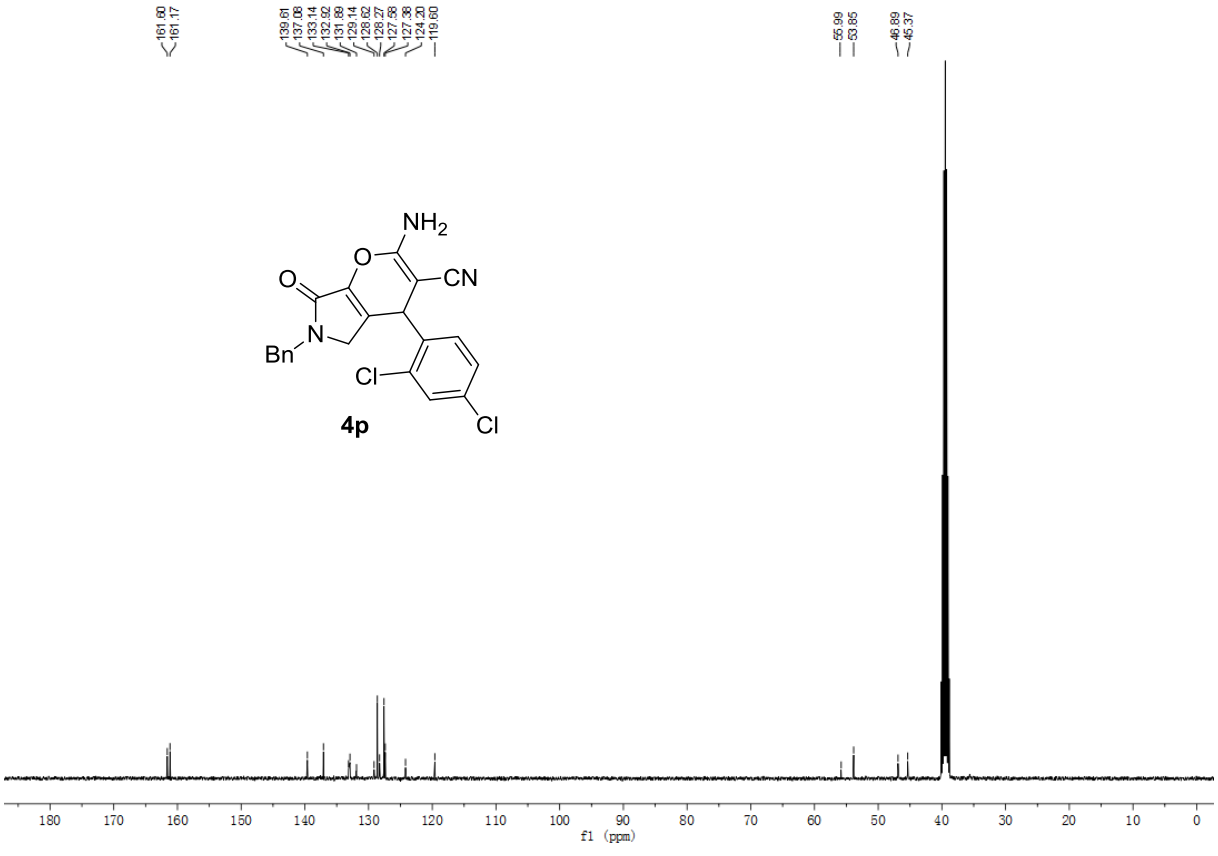

NH2
O
CN
O
N
Bn
OMe
OMe
4n
2.09
1.05
2.03
1.96
1.02
2.00
1.02
1.00
1.00
1.09
2.94
2.81
1.09
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

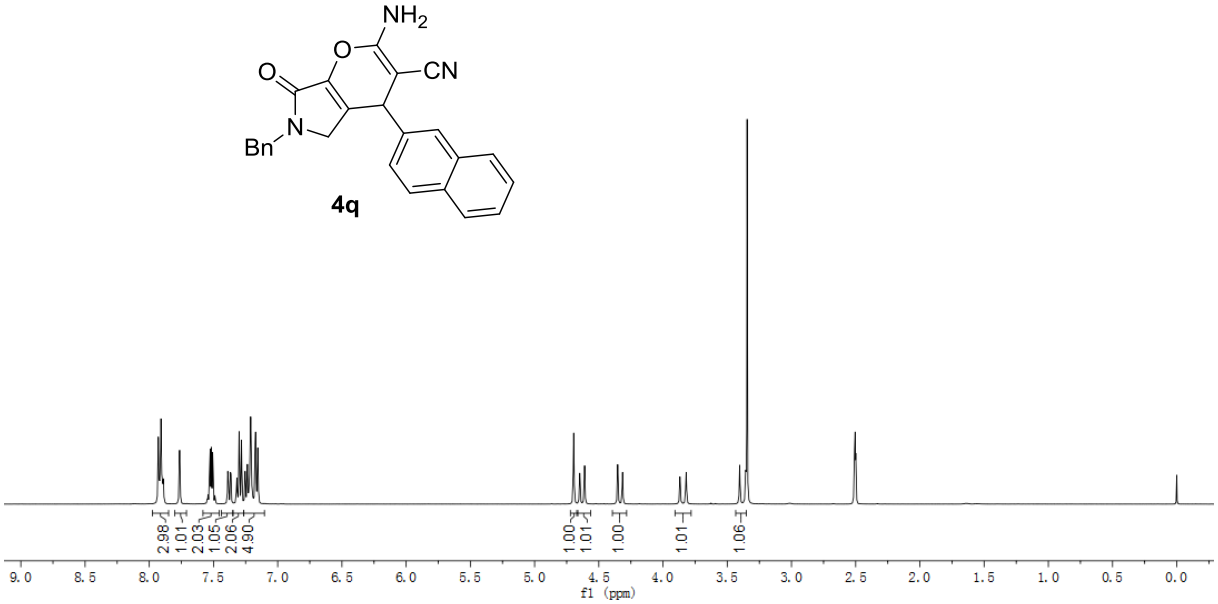

161.95
160.52
148.84
148.03
138.64
137.22
134.38
128.63
127.57
127.37
126.28
120.07
119.60
111.87
110.94
55.82
55.43
55.42
46.84
45.27
38.07
NH2
O
CN
O
N
Bn
OMe
OMe
4n
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

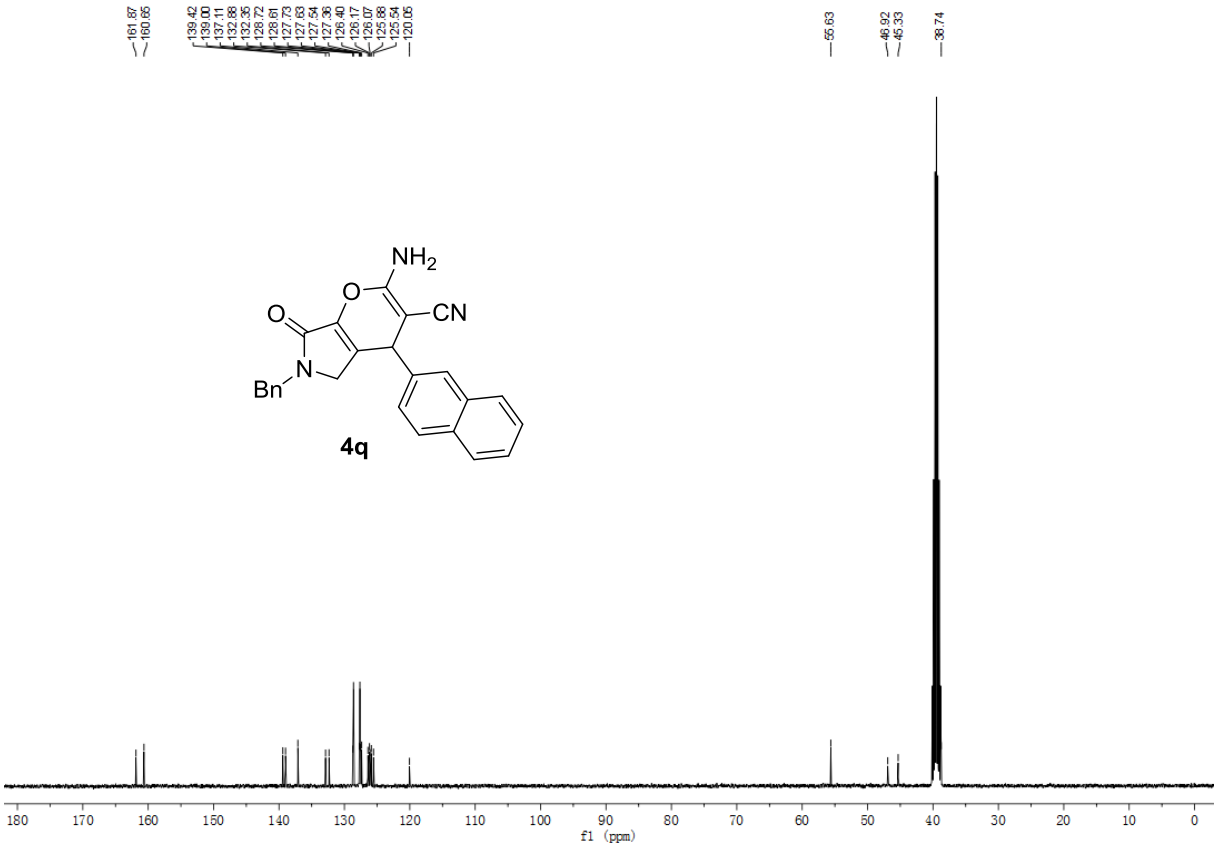

NH2
O
CN
O
N
Bn
OH
OMe
4o
0.93
2.67
1.84
2.01
1.08
1.90
1.00
1.98
4.07
0.90
f1 (ppm)

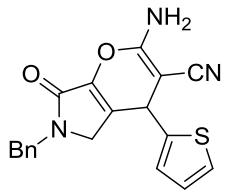

162.04
160.57
147.12
146.89
138.57
137.30
134.79
128.77
127.79
127.62
126.79
120.20
118.18
114.55
112.33
56.16
55.64
45.98
45.44
38.01
NH2
O
CN
O
N
Bn
OH
OMe
4o
f1 (ppm)


NH2
O
CN
O
N
Bn
Cl
Cl
4p
0.95
1.00
0.92
4.64
1.88
1.00
1.01
1.06
1.02
1.02
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

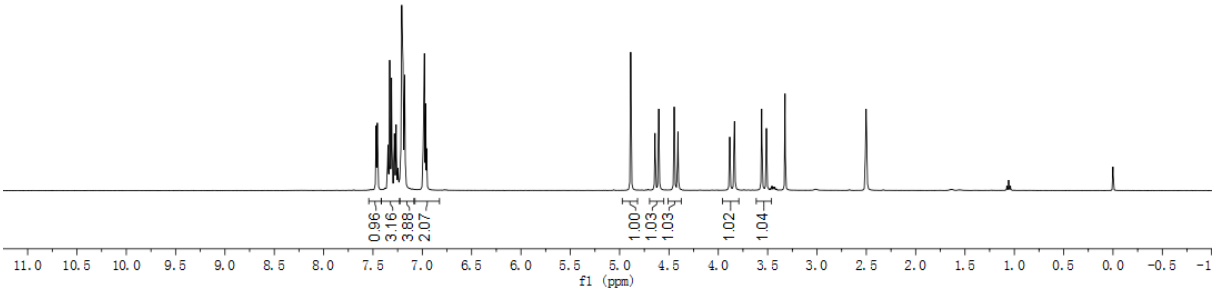

161.90
161.17
139.61
137.08
133.14
132.92
131.89
129.14
128.62
128.27
127.68
127.38
124.20
119.60
55.99
53.85
46.89
45.37
NH2
O
CN
O
N
Bn
Cl
Cl
4p
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

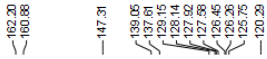

NH2
O
CN
O
N
Bn
4q
2.98
1.01
2.03
1.05
2.06
4.90
1.00
1.01
1.00
1.01
1.06
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

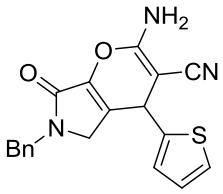

161.87
160.65
139.42
139.00
137.11
132.88
132.35
128.72
128.61
127.73
127.63
127.54
127.36
126.40
126.17
126.07
125.88
125.54
120.05
55.63
46.92
45.33
38.74
NH2
O
CN
O
N
Bn
4q
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


NH2
O
CN
O
N
Bn
S

4r


0.96
3.16
3.88
2.07
1.00
1.03
1.03
1.02
1.04
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)


162.20
160.88
147.31
139.05
137.61
129.15
128.14
127.92
127.68
126.45
126.26
125.75
120.29
66.76
47.35
45.86
34.21


NH2
O
CN
O
N
Bn
S

4r

00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)