Facile synthesis of 1,2,4,5-tetrahydro-1,4-benzodiazepin-3-ones via cyclization of *N*-alkoxy *α*-halogenoacetamides with *N*-(2-chloromethyl)aryl) amides

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1. General information

All reactions were performed in anhydrous solvents under an argon atmosphere and were monitored by thin-layer chromatography carried out on silica gel aluminum sheets (60F-254) and spots were visualized with UV light. All solvents were purchased from commercial suppliers and were purified according to standard procedures. *N*-alkoxy *α*-halogenoacetamides **1**[1] and *N*-(ortho-chloromethyl)aryl amides **2**[2] can be prepared according to known procedures. ^{1}H NMR and ^{13}C NMR spectra were recorded at room temperature on BRUKER Avance 400 spectrometers. Chemical shifts were reported in parts per million (ppm, δ units), and tetramethylsilane (TMS) was used as an internal reference. Coupling constants (J) were expressed in hertz. High-resolution mass spectra (HRMS) were recorded on TOF perimer for ESI^{+}.

2. General procedure for the Cycloadditions of *N*-alkoxy *α*-halogenoacetamides with *N*-(2-chloromethyl)aryl) amides

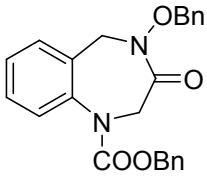
To the solution of *N*-alkoxy *α*-halogenoacetamides **1** (0.2 mmol) and *N*-(ortho-chloromethyl)aryl amides **2** (0.24 mmol) in DMF (2 mL), Cs_2CO_3 (2.5 equiv) was added. The resulting mixture was stirred at room temperature under argon atmosphere for the required period of time. After completion of the reaction as monitored by TLC, the reaction mixture was diluted with 10 mL EA, which was washed with water and brine successively, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (PE/EtOAc, 5:1) to afford the product **3** or **5**.

3. Transformation of 3a

The reaction of Pd/C (5 mol %, palladium on activated carbon, 10% Pd basis) was added to a solution of **3a** (100.0 mg, 0.25 mmol) in MeOH (5 mL). Then the flask was purged with hydrogen using a balloon for three times. The reaction was stirred under hydrogen atmosphere for 2 hour at room temperature. After completion of the reaction as monitored by TLC, the crude reaction mixture was filtered through celite and washed with CH_2Cl_2. The solvent was removed under reduced pressure. Then the residue was purified by silica gel chromatography (PE/EtOAc, 2:1) to afford the desired product **4**[3] (35.9 mg, 88%).

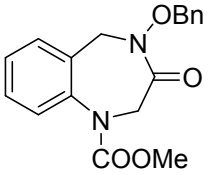
4. Characterization Data

Benzyl 4-(benzyloxy)-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[e][1,4]diazepine-1-carboxylate (3a)



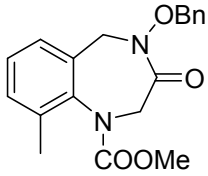
Colorless oil (60 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.42 (m, 2H), 7.42-7.36 (m, 5H), 7.35-7.28 (m, 3H), 7.26-7.22 (m, 3H), 6.95 (d, J = 7.4 Hz, 1H), 5.18 (s, 2H), 5.00 (s, 2H), 4.57 (s, 2H), 4.41 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 154.4, 140.7, 135.8, 135.2, 132.8, 129.8, 128.9, 128.8, 128.6, 128.4, 128.1, 128.1, 127.6, 127.3, 76.6, 67.8, 54.8, 53.0. HRMS calcd for $C_{24}H_{22}N_2O_4Na$ $[M+Na]^+$ 425.4398, found 425.4395. IR (KBr): ν 3032, 1712, 1663, 1498, 1456, 1397, 1315, 1243, 1165, 1046, 699 cm^{-1}.

Methyl 4-(benzyloxy)-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[e][1,4]diazepine-1-carboxylate (3b)



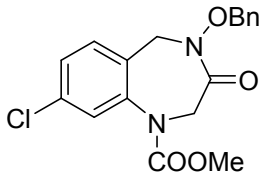
Colorless oil (41 mg, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.43 (m, 2H), 7.41-7.39 (m, 4H), 7.24 (dd, J = 11.7, 4.2 Hz, 2H), 6.95 (d, J = 7.3 Hz, 1H), 5.01 (s, 2H), 4.54 (s, 2H), 4.42 (s, 2H), 3.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 155.1, 135.3, 129.9, 129.0, 128.9, 128.6, 128.1, 127.3, 76.7, 54.9, 53.5, 53.1. HRMS calcd for $C_{18}H_{18}N_2O_4Na$ $[M+Na]^+$ 349.3418, found 349.3422. IR (KBr): ν 2977, 2932, 1716, 1498, 1457, 1397, 1314, 1242, 1046, 905, 765, 698 cm^{-1}.

Methyl 4-(benzyloxy)-9-methyl-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[e][1,4]diazepine-1-carboxylate (3c)



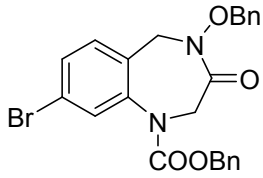
Colorless oil (37 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.2 Hz, 1H), 7.43-7.38 (m, 3H), 7.34-7.32 (m, 2H), 7.16 (dd, J = 8.2, 1.5 Hz, 1H), 7.10 (d, J = 1.6 Hz, 1H), 4.90 (s, 2H), 4.75 (s, 2H), 4.10 (s, 2H), 3.77 (s, 3H), 2.30 s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 155.0, 134.4, 133.4, 131.9, 130.3, 129.5, 129.4, 129.0, 128.8, 128.3, 127.9, 77.8, 52.3, 48.2, 40.6, 20.7. HRMS calcd for $C_{19}H_{20}N_2O_4Na$ $[M+Na]^+$ 363.3688, found 363.3693. IR (KBr): ν 2963, 2927, 1715, 1655, 1498, 1456, 1404, 1229, 1061, 749, 700, 679 cm^{-1}.

Methyl 4-(benzyloxy)-8-chloro-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[e][1,4]diazepine-1-carboxylate (3d)



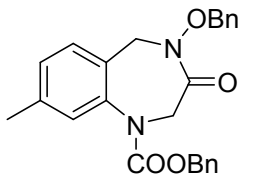
Colorless oil (31 mg, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.43 (m, 1H), 7.40-7.36 (m, 2H), 7.33-7.28 (m, 4H), 7.26 (s, 1H), 5.10 (s, 2H), 5.01 (s, 2H), 4.51 (s, 2H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 150.5, 141.2, 137.5, 135.1, 130.6, 130.2, 128.7, 128.2, 128.0, 127.9, 127.8, 127.1, 76.3, 69.0, 53.6, 49.2. HRMS calcd for $C_{18}H_{17}N_2O_4ClNa$ $[M+Na]^+$ 383.7838, found 383.7833. IR (KBr): ν 2923, 1709, 1658, 1452, 1412, 1315, 1260, 1043, 698 cm^{-1}.

Benzyl 4-(benzyloxy)-8-bromo-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[e][1,4]diazepine-1-carboxylate (3e)



Colorless oil (48 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.29 (m, 12H), 6.69 (d, J = 8.1 Hz, 1H), 5.16 (s, 2H), 4.95 (s, 2H), 4.51 (s, 2H), 4.29 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 141.9, 135.6, 135.2, 131.2, 130.7, 130.1, 129.9, 129.0, 128.7, 128.6, 128.4, 122.7, 76.8, 68.2, 54.4, 52.9. HRMS calcd for $C_{24}H_{21}N_2O_4BrNa$ $[M+Na]^+$ 504.3358, found 504.3363. IR (KBr): ν 2924, 1714, 1662, 1490, 1455, 1394, 1358, 1240, 1044, 749, 698 cm^{-1}.

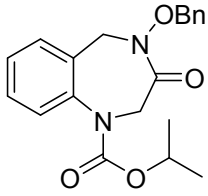
Benzyl 4-(benzyloxy)-8-methyl-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[e][1,4]diazepine-1-carboxylate (3f)



Colorless oil (53 mg, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.26 (m, 9H), 7.25-7.10 (m, 1H), 7.02 (d, J = 7.5 Hz, 2H), 6.80 (d, J = 7.8 Hz, 1H), 5.15 (s, 2H), 4.96 (s, 2H), 4.51 (s, 2H), 4.34 (s, 2H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 154.4, 140.1, 136.0, 135.2, 129.8, 128.8, 128.8, 128.7, 128.6, 128.4, 128.2, 127.7, 76.6, 67.8, 54.5, 53.1, 21.1. HRMS calcd for $C_{25}H_{24}N_2O_4Na$ $[M+Na]^+$ 439.4668, found 439.4664. IR (KBr): ν 3063, 2924, 1712, 1662, 1508, 1455, 1395, 1303, 1245, 1128, 1047, 976, 912, 750, 698 cm^{-1}.

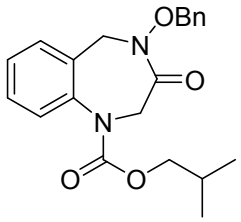
Isopropyl 4-(benzyloxy)-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[e][1,4]diazepine-1-

carboxylate (**3g**)



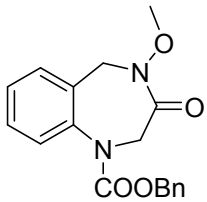
Colorless oil (58 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.46-7.40 (m, 2H), 7.40-7.33 (m, 4H), 7.20 (t, *J* = 7.5 Hz, 2H), 6.92 (d, *J* = 7.4 Hz, 1H), 4.99 (s, 2H), 4.96-4.93 (m, 1H), 4.51 (s, 2H), 4.39 (s, 2H), 1.23-1.00 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 154.2, 141.1, 135.2, 132.7, 129.8, 129.8, 128.8, 128.6, 128.5, 128.3, 127.9, 127.3, 76.6, 70.2, 54.9, 52.8, 21.8. HRMS calcd for $C_{20}H_{22}N_2O_4Na$ $[M+Na]^+$ 377.3958, found 377.3966. IR (KBr): ν 2982, 1713, 1650, 1499, 1458, 1389, 1340, 1245, 1172, 1046, 983, 750, 721 cm^{-1}.

Isobutyl 4-(benzyloxy)-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[e][1,4]diazepine-1-carboxylate (**3h**)



Colorless oil (55 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.27 (m, 7H), 7.24 -7.22(m, 2H), 5.11 (s, 2H), 4.98 (s, 2H), 4.50 (s, 2H), 3.94 (d, *J* = 6.6 Hz, 2H), 1.95-1.85 (m, 1H), 0.90 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 151.0, 140.3, 137.6, 129.5, 129.4, 129.1, 128.9, 128.8, 128.2, 127.9, 127.8, 127.6, 126.8, 76.1, 72.4, 69.8, 49.1, 27.8, 19.0. HRMS calcd for $C_{21}H_{24}N_2O_4Na$ $[M+Na]^+$ 391.4228, found 391.4231. IR (KBr): ν 3266, 2956, 1718, 1656, 1537, 1453, 1405, 1060, 960, 748, 697 cm^{-1}.

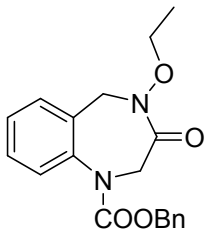
Benzyl 4-methoxy-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[e][1,4]diazepine-1-carboxylate (**3k**)



Colorless oil (59 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.26 (m, 8H), 7.26-7.12 (m, 1H), 5.16 (s, 2H), 4.65 (s, 2H), 4.52 (s, 2H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 154.5, 140.9, 135.9, 133.4, 130.1, 128.8, 128.5, 128.5, 128.3, 128.1, 128.0, 127.7, 68.0, 61.9, 53.2, 53.0. HRMS calcd for $C_{18}H_{18}N_2O_4Na$ $[M+Na]^+$ 349.3418, found 349.3425. IR (KBr): ν 2932, 1711, 1662, 1529, 1498, 1456, 1027, 980, 764, 724, 698 cm^{-1}.

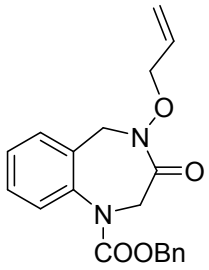
Benzyl 4-ethoxy-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[e][1,4]diazepine-1-

carboxylate (3l)



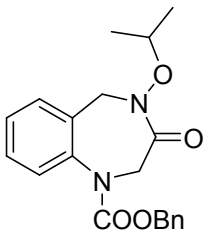
Colorless oil (65 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.08 (m, 9H), 5.14 (s, 2H), 4.63 (s, 2H), 4.50 (s, 2H), 4.00 (q, J = 7.0 Hz, 2H), 1.32-1.17 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 154.2, 140.5, 135.6, 133.0, 129.6, 128.5, 128.2, 128.0, 127.9, 127.4, 127.3, 69.5, 67.6, 53.7, 52.6, 13.3. HRMS calcd for $C_{19}H_{20}N_2O_4Na$ $[M+Na]^+$ 363.3688, found 363.3684. IR (KBr): ν 2958, 2890, 1706, 1660, 1499, 1464, 1413, 1364, 1319, 1156, 1080, 795, 772, 749, 698 cm^{-1}.

Benzyl 4-(allyloxy)-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[e][1,4]diazepine-1-carboxylate (3m)



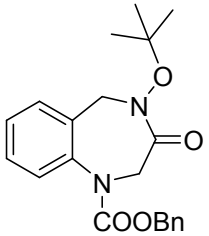
Colorless oil (62 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.39 (m, 1H), 7.36-7.10 (m, 8H), 6.08-5.98 (m, 1H), 5.36-5.26 (m, 2H), 5.18 (s, 1H), 4.66 (s, 2H), 4.54 (s, 1H), 4.47 (d, J = 6.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 154.4, 140.9, 135.9, 133.1, 132.0, 129.9, 128.9, 128.4, 128.2, 128.2, 127.7, 127.5, 121.2, 75.6, 67.9, 54.5, 52.9. HRMS calcd for $C_{20}H_{20}N_2O_4Na$ $[M+Na]^+$ 375.3798, found 375.3803. IR (KBr): ν 2933, 1719, 1663, 1455, 1400, 1362, 1161, 1082, 788, 774, 677 cm^{-1}.

Benzyl 4-isopropoxy-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[e][1,4]diazepine-1-carboxylate (3n)



Colorless oil (64 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.27 (m, 9H), 5.14 (s, 2H), 4.59 (s, 2H), 4.50 (s, 2H), 4.34-4.29 (m, 1H), 1.21 (d, J = 6.1 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 154.1, 140.5, 135.6, 132.8, 129.5, 128.6, 128.1, 127.9, 127.5, 127.2, 76.1, 67.5, 55.0, 52.7, 20.5. HRMS calcd for $C_{20}H_{22}N_2O_4Na$ $[M+Na]^+$ 377.3958, found 377.3961. IR (KBr): ν 2934, 1709, 1659, 1497, 1457, 1400, 1319, 1245, 1045, 990, 748, 724, 699 cm^{-1}.

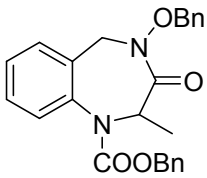
Benzyl 4-(tert-butoxy)-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[e][1,4]diazepine-1-carboxylate (3o)



Colorless oil (63 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-

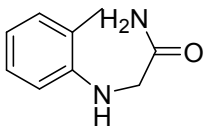
7.31 (m, 8H), 7.23-7.17 (m, 1H), 5.22 (s, 2H), 5.07 (s, 2H), 4.53 (s, 2H), 1.24 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ154.1, 149.0, 140.3, 135.8, 130.9, 129.2, 129.0, 128.3, 128.1, 128.0, 127.7, 127.3, 126.5, 78.5, 69.5, 67.7, 49.3, 27.1. HRMS calcd for $C_{21}H_{24}N_2O_4Na$ $[M+Na]^+$ 391.4228, found 391.4223. IR (KBr): ν 3034, 2976, 1712, 1496, 1397, 1363, 1314, 1213, 1026, 947, 766, 741, 698 cm^{-1}.

Benzyl 4-(benzyloxy)-2-methyl-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[e][1,4]diazepine-1-carboxylate (**3p**)



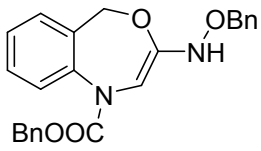
Colorless oil (62 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.37 (m, 2H), 7.37-7.30 (m, 5H), 7.31-7.26 (m, 2H), 7.20-7.06 (m, 4H), 6.86 (d, J = 7.4 Hz, 1H), 5.57-5.35 (m, 1H), 5.25-5.04 (m, 2H), 4.94 (q, J = 10.9 Hz, 2H), 4.71 (d, J = 14.3 Hz, 1H), 3.99 (d, J = 14.4 Hz, 1H), 1.24-1.19 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 154.2, 137.6, 135.8, 135.1, 133.1, 129.8, 129.3, 129.1, 128.7, 128.6, 128.4, 128.3, 128.0, 127.3, 76.1, 67.4, 57.1, 55.0, 18.0. HRMS calcd for $C_{25}H_{24}N_2O_4Na$ $[M+Na]^+$ 439.4668, found 439.4671. IR (KBr): ν 3032, 2938, 1712, 1531, 1455, 1397, 1318, 1124, 1045, 994, 726, 699 cm^{-1}.

2-(o-tolylamino)acetamide (**4**)



Known compound[3], White solid (36 mg, 88%). mp 139−140 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.34 (s, 1H), 7.10 (s, 1H), 6.99 (dd, J = 7.4, 2.9 Hz, 2H), 6.55 (dd, J = 7.3, 0.8 Hz, 1H), 6.34 (d, J = 7.8 Hz, 1H), 5.18 (s, 1H), 3.63 (s, 2H), 2.12 (s, 3H). HRMS calcd for $C_9H_{12}N_2ONa$ $[M+Na]^+$ 187.1978, found 187.1981.

Benzyl 3-((benzyloxy)amino)benzo[e][1,4]oxazepine-1(5*H*)-carboxylate (**5**)



Colorless oil (68 mg, 85%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.14 (s, 1H), 7.50-7.38 (m, 10H), 7.37-7.27 (m, 3H), 7.17 (t, J = 7.5 Hz, 1H), 6.90 (s, 1H), 5.17 (s, 2H), 5.01 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 154.2, 136.8, 136.4, 132.7, 131.3, 129.9, 129.8, 129.5, 129.1, 128.5, 128.1, 128.0, 124.1, 122.7, 78.0, 66.8, 62.7, 48.5. HRMS calcd for $C_{24}H_{22}N_2O_4Na$ $[M+Na]^+$ 425.4398, found 425.4405. IR (KBr): ν 3276, 3036, 3021, 2967, 1717, 1657, 1592, 1453, 1297, 1227, 1099, 1052, 989, 755, 620 cm^{-1}.

5. References

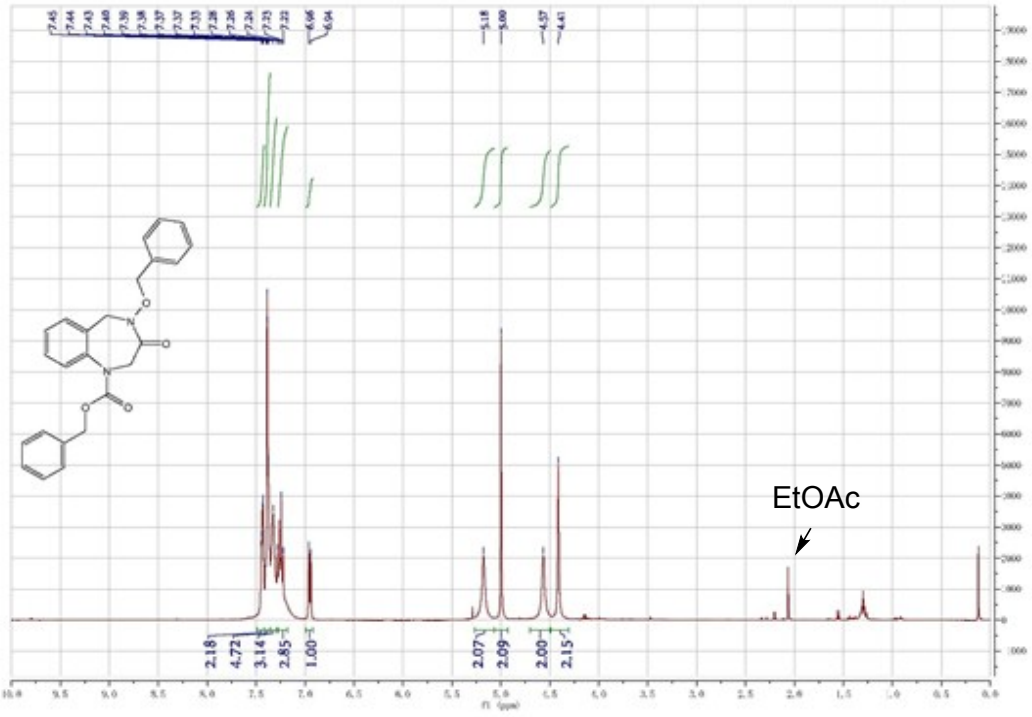
(1) C. S. Jeffrey, K. L. Barnes, J. A. Eickhoff and C. R. Carson, *J. Am. Chem. Soc.* 2011, **133**, 7688.

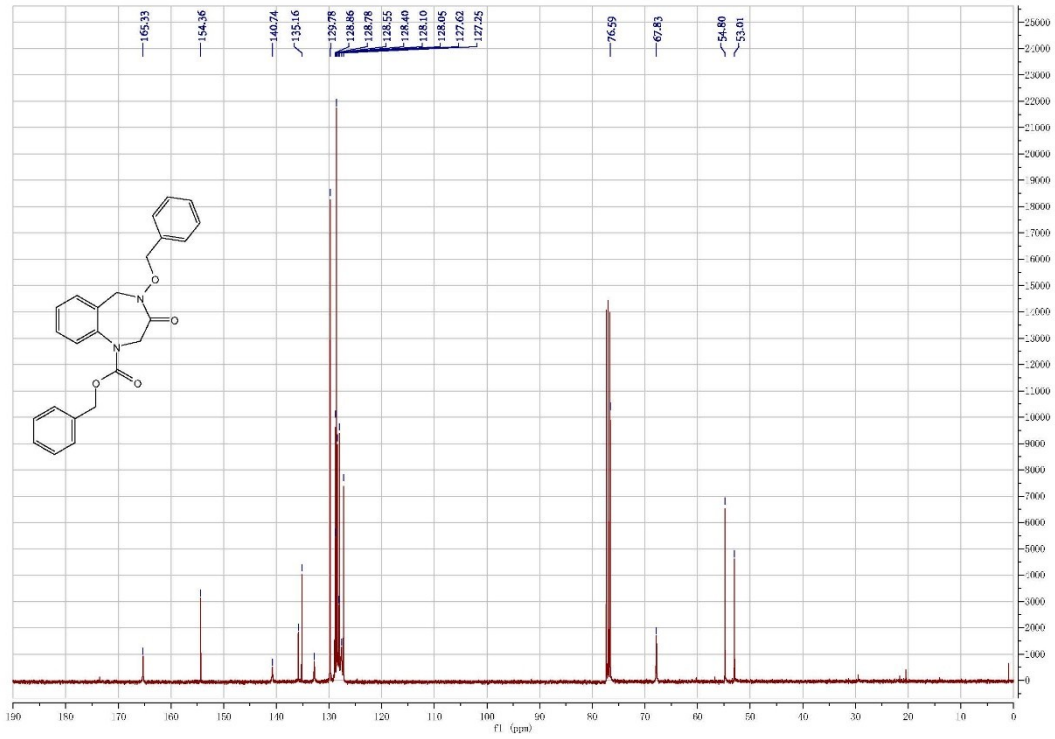
(2) A. Lee, A. Younai, C. K. Price, J. Izquierdo, R. K. Mishra and K. A. Scheidt, *J. Am. Chem. Soc.* 2014, **136**, 10589.

(3) (a) V. A. Chornous, M. K. Bratenko, and M. V. Vovk, *Russ. J. Org. Chem.,* 2009, **45**, 1210; (b) L. N. He and R. Y. Chen, *Phosphorus, Sulfur Silicon Relat. Elem.,* 1997, **129**, 111; (c) A. J. Hill, E. B. Keisoy, *J. Am. Chem. Soc.,* 1922, **44**, 2357.

6. Copies of NMR spectra for products 3

3a





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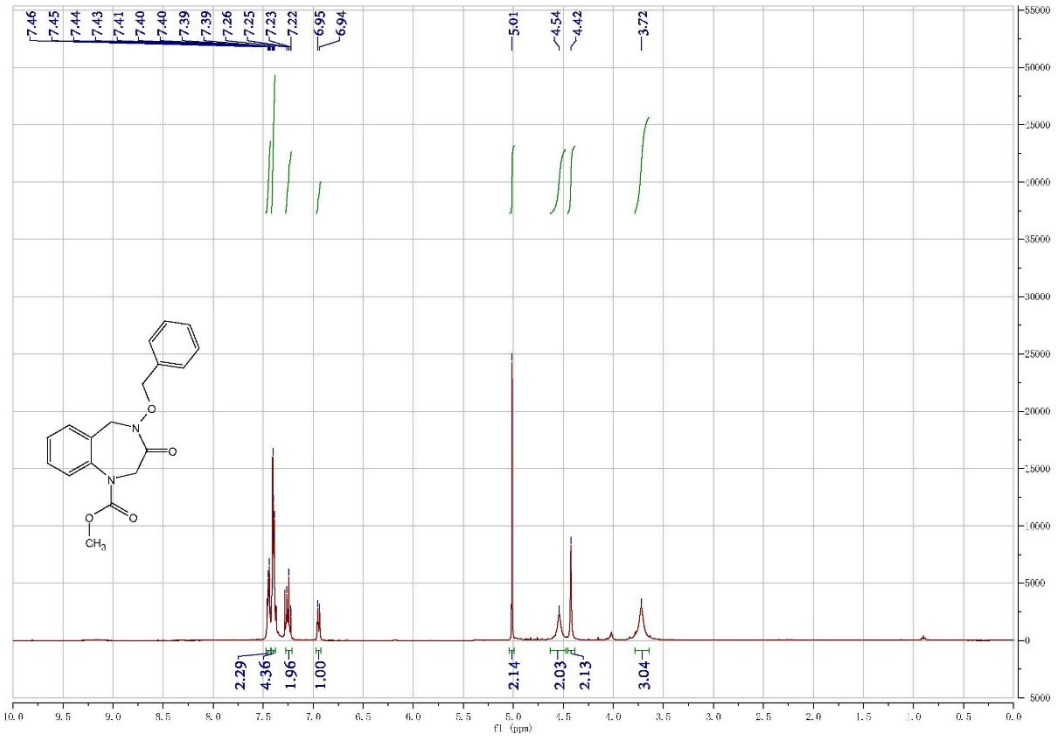
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6.94
5.01
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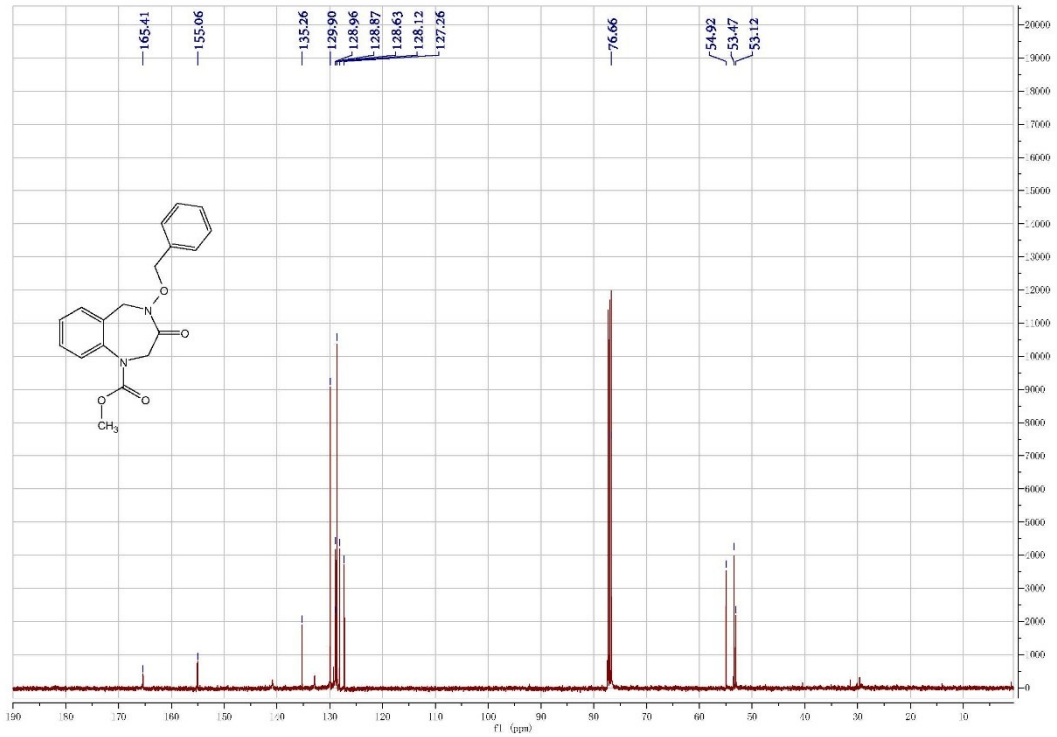
f1 (ppm)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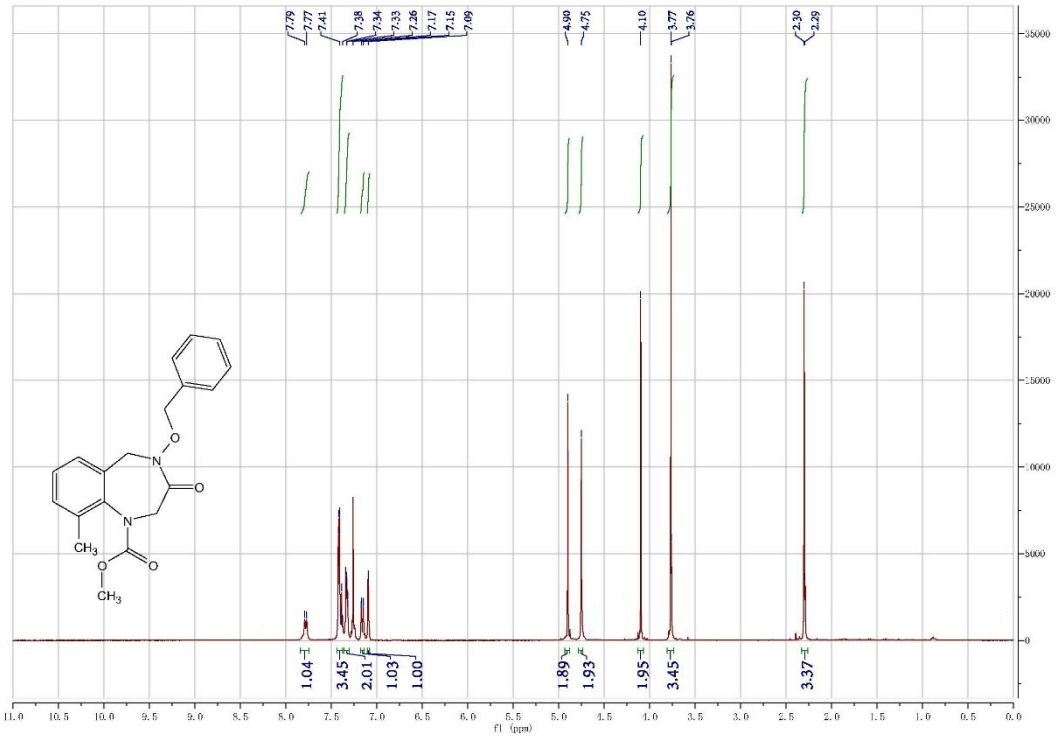
3c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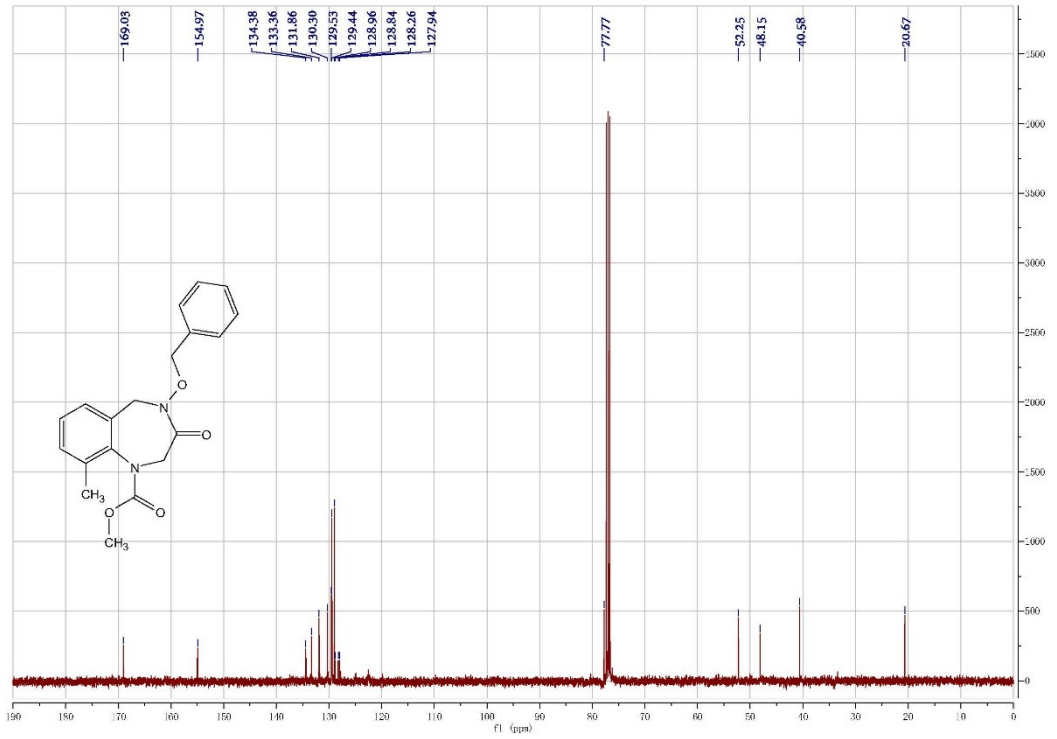
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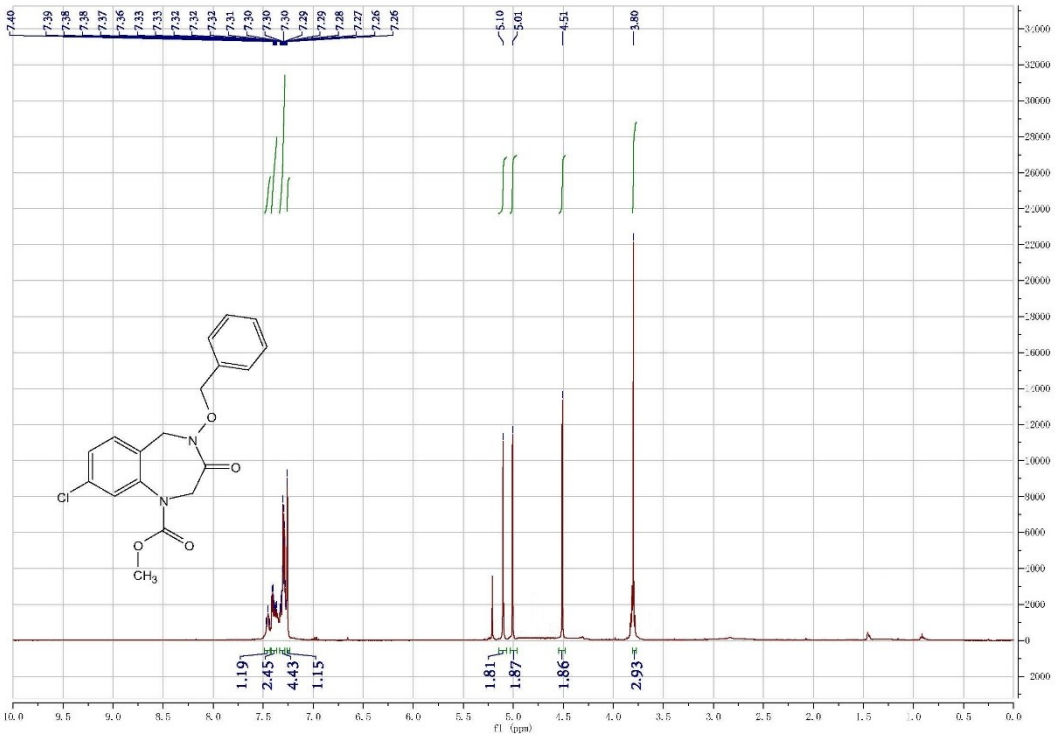
3d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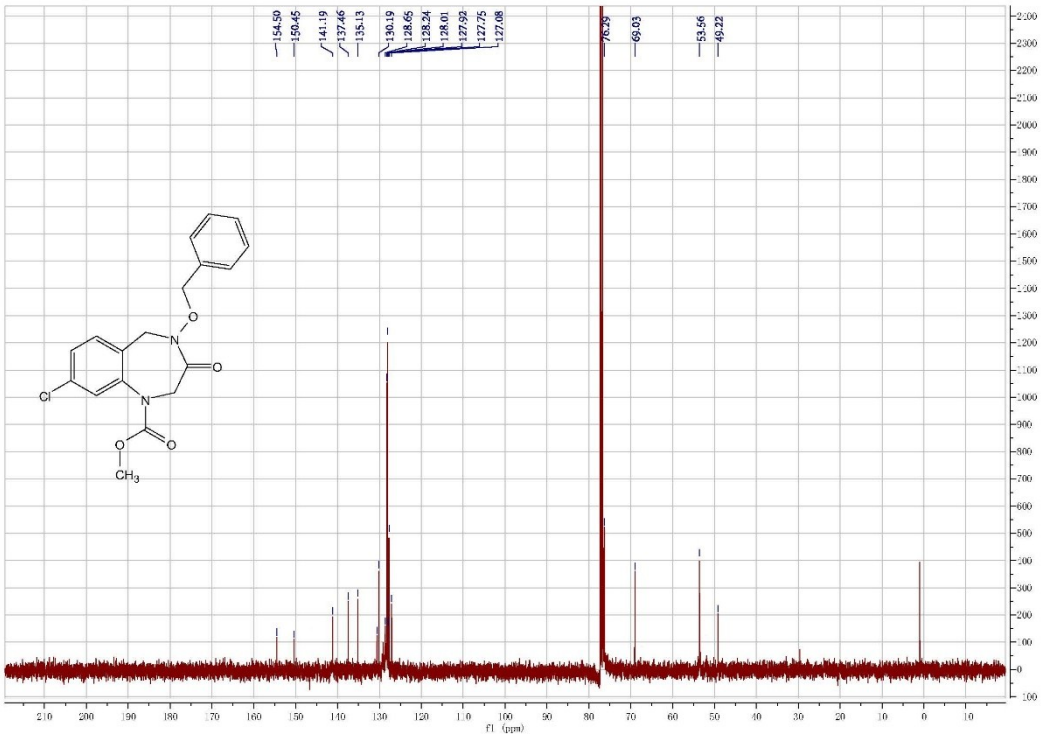
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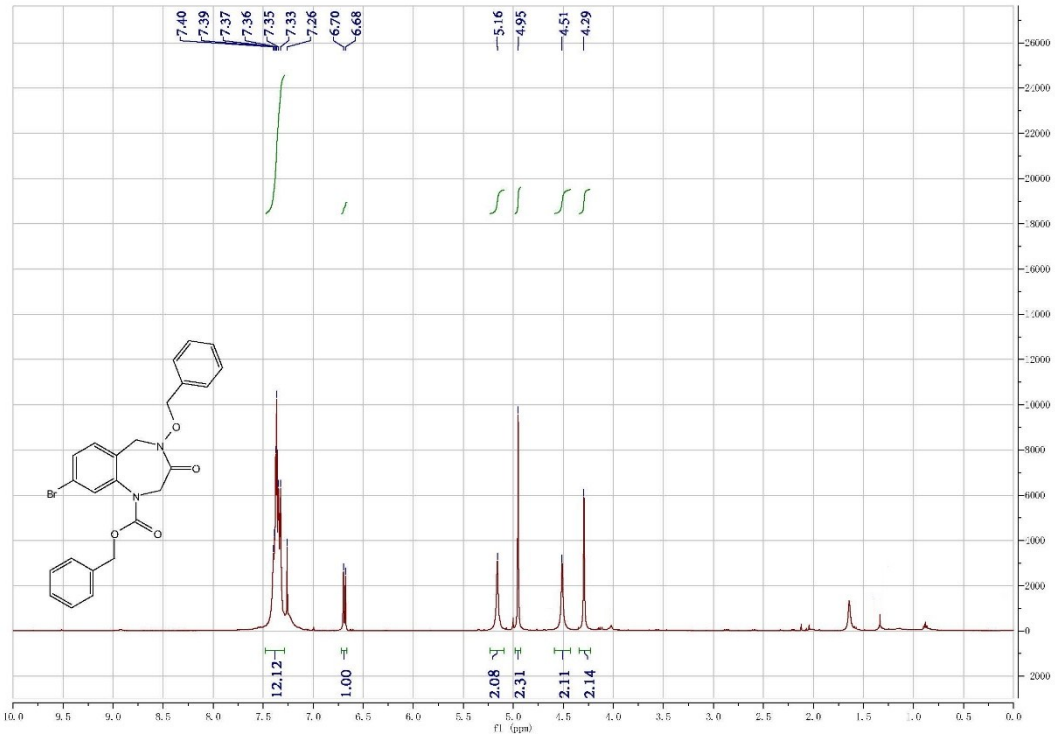
3e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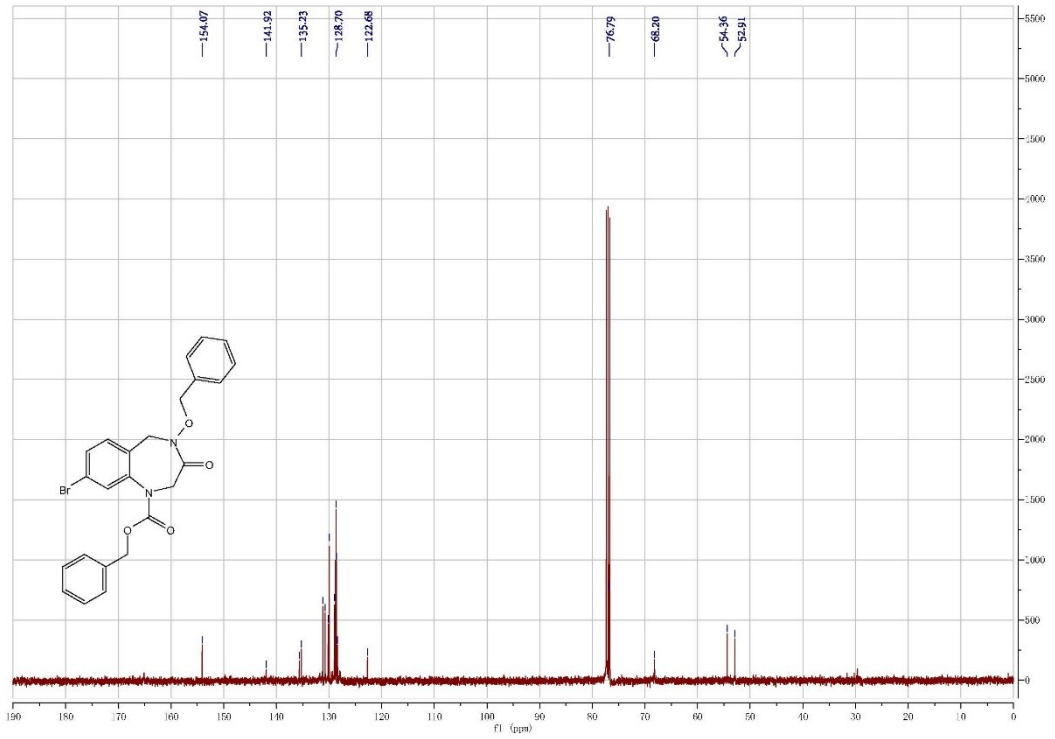
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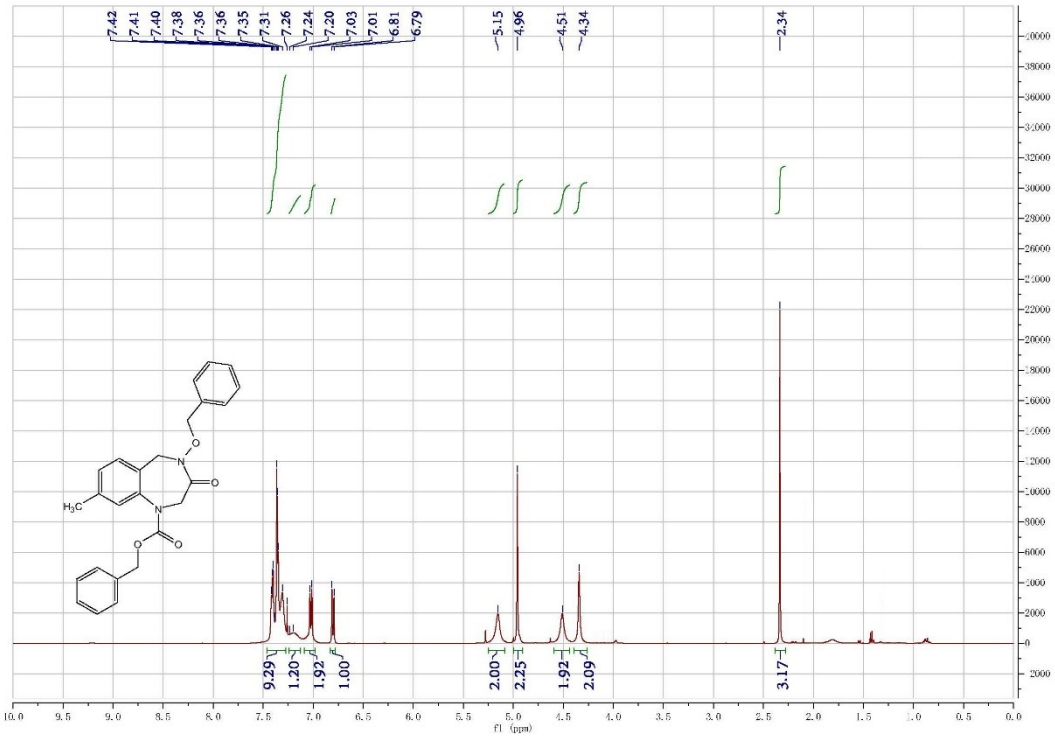
3f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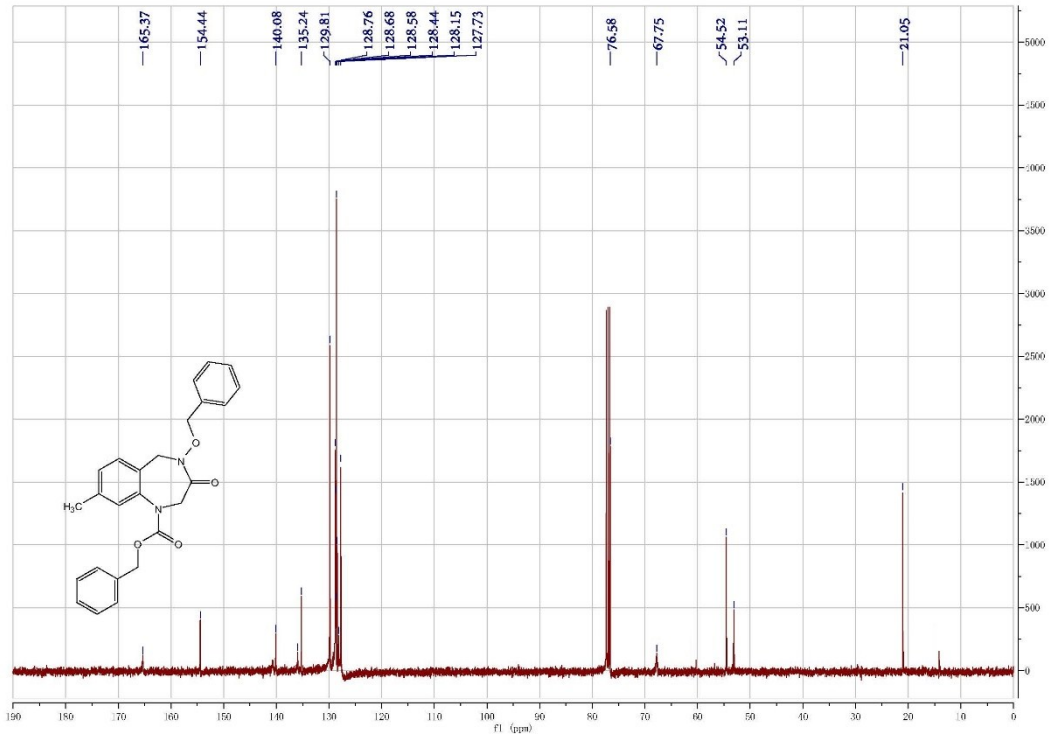
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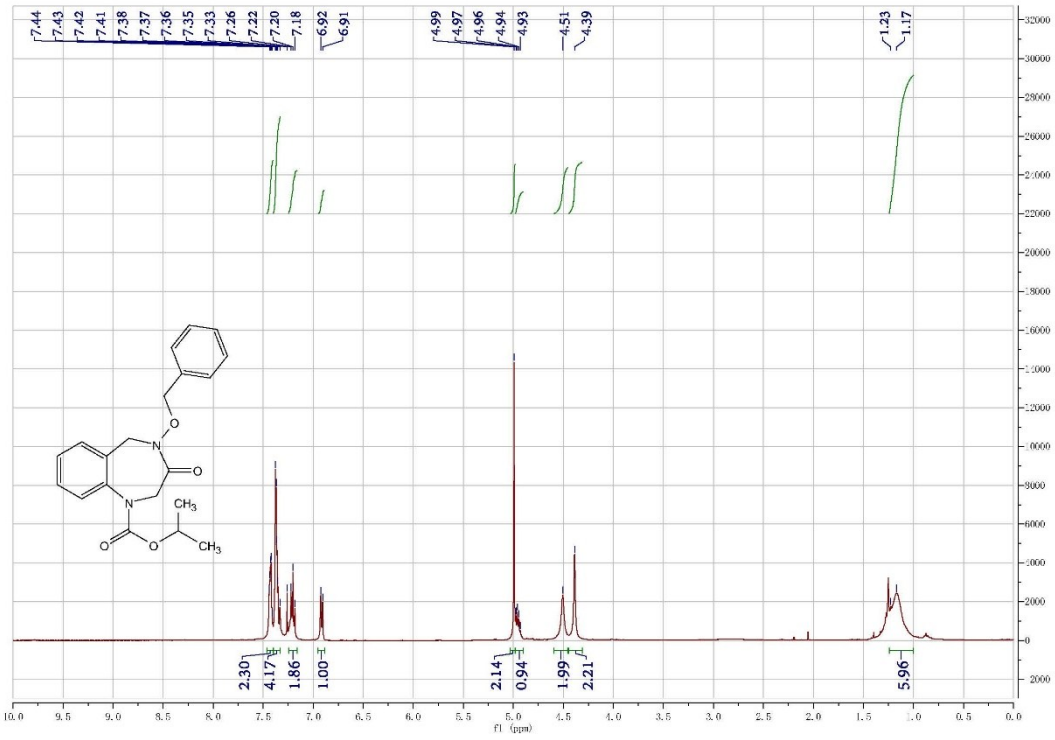
3g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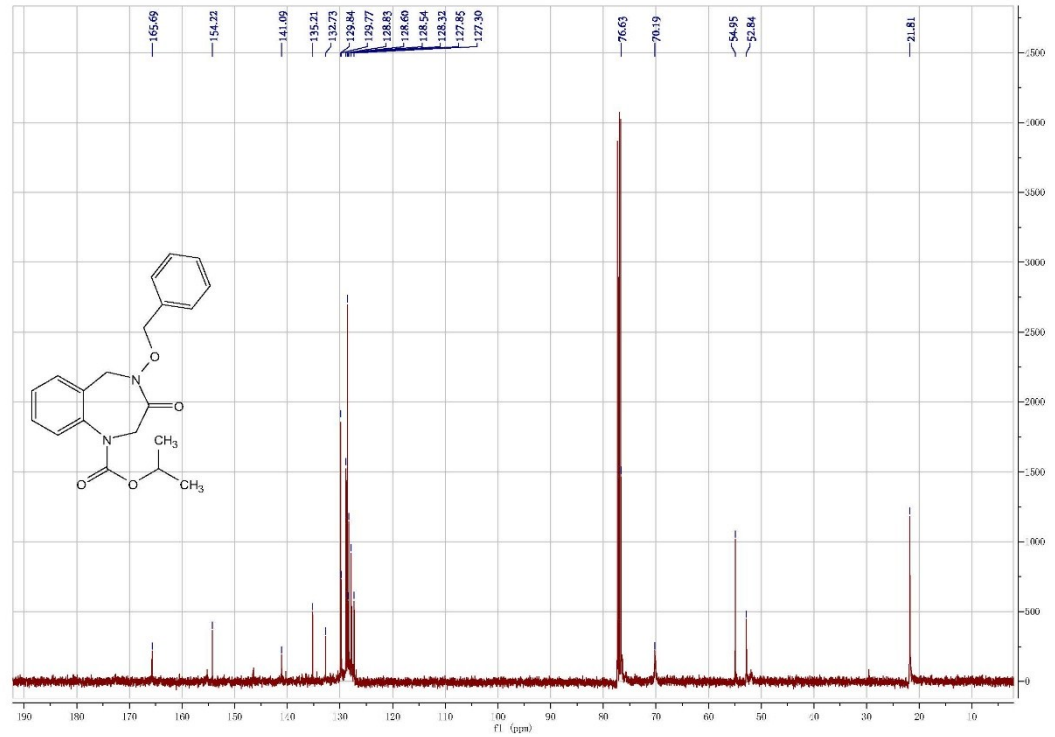
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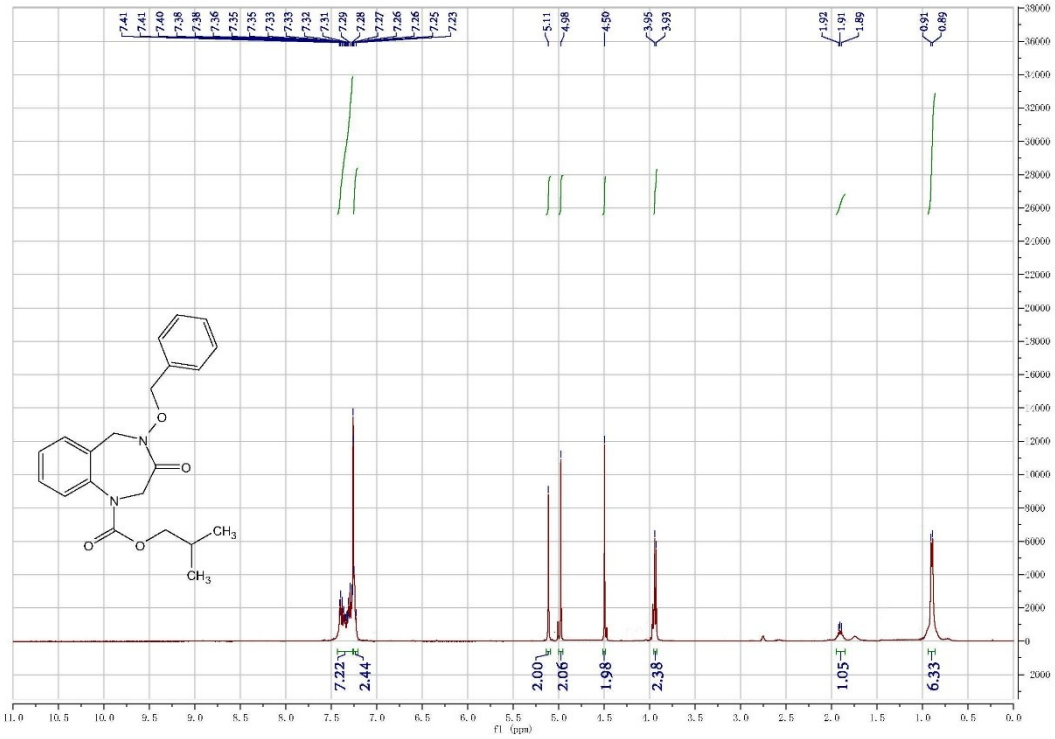
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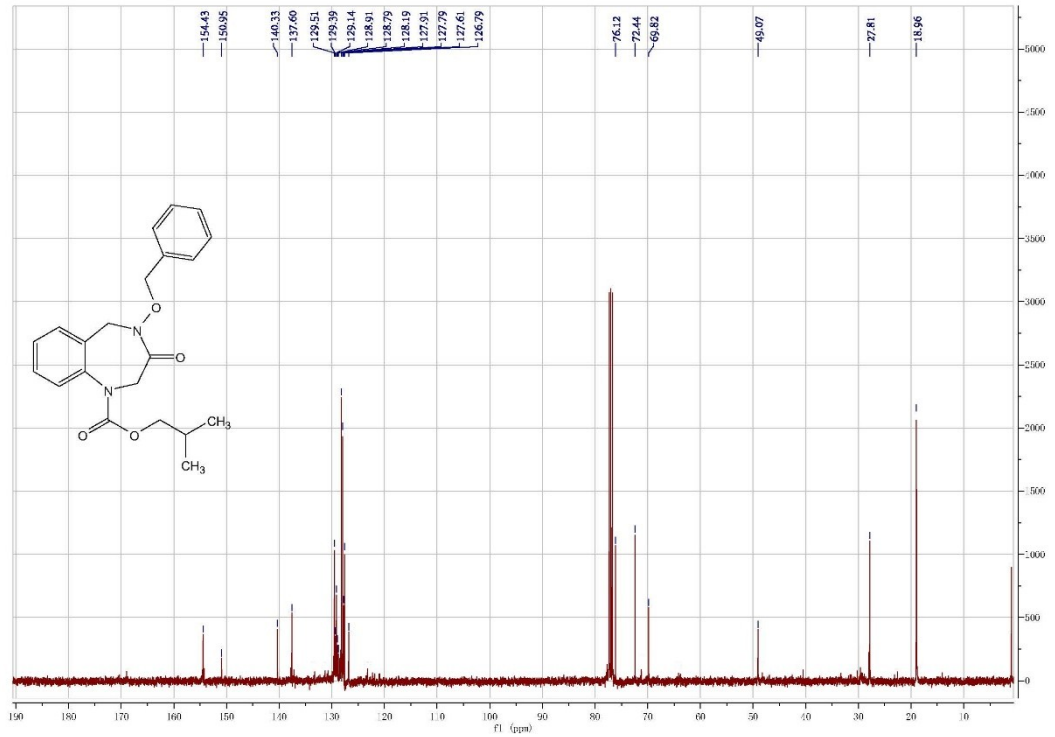
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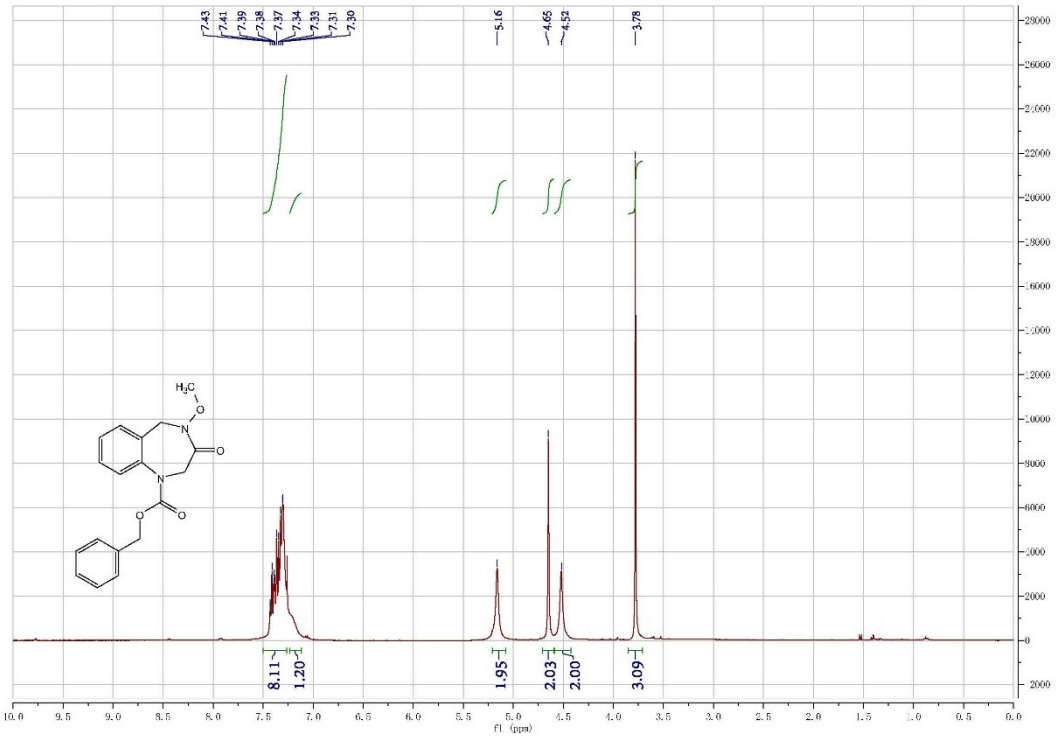
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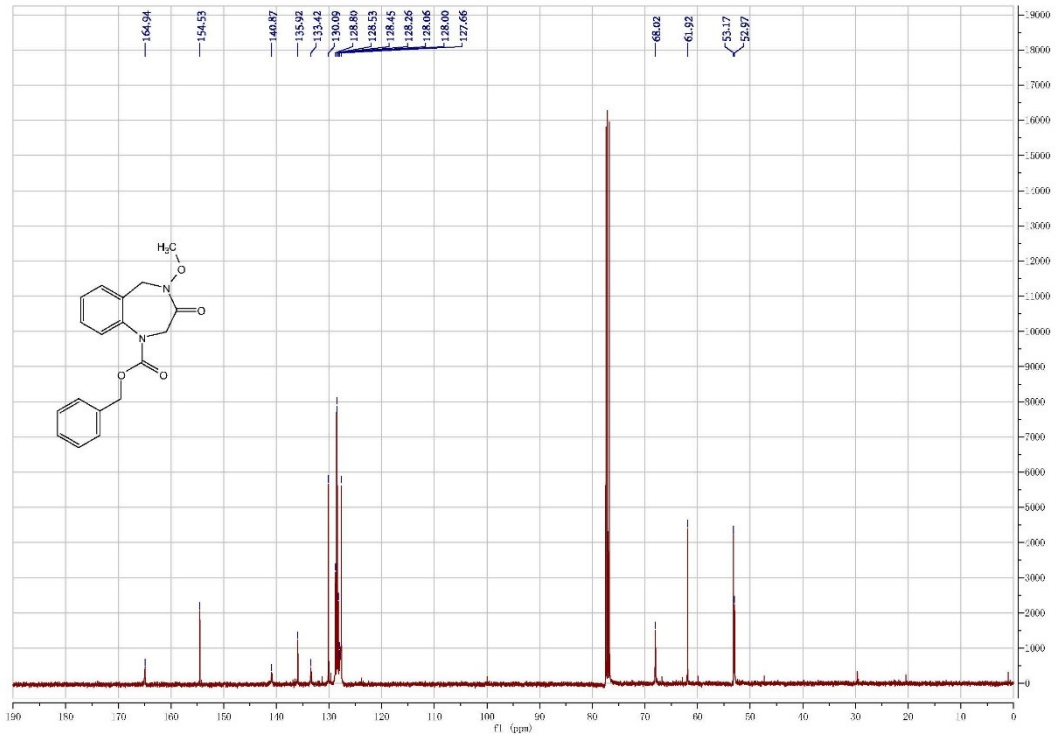
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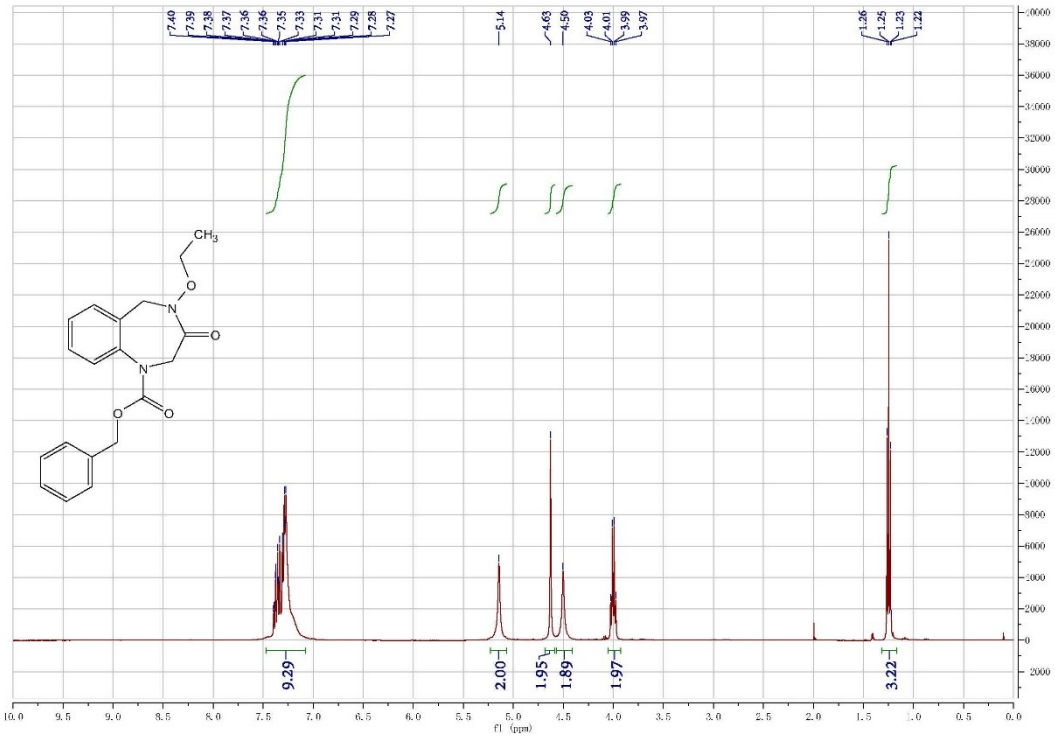
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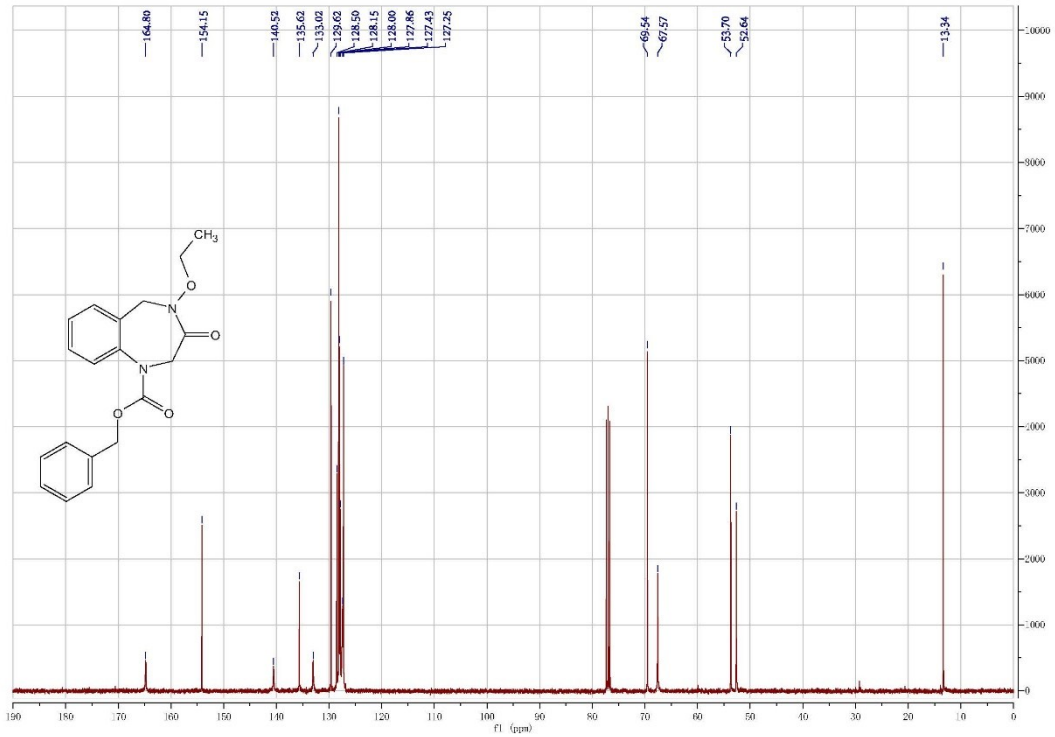
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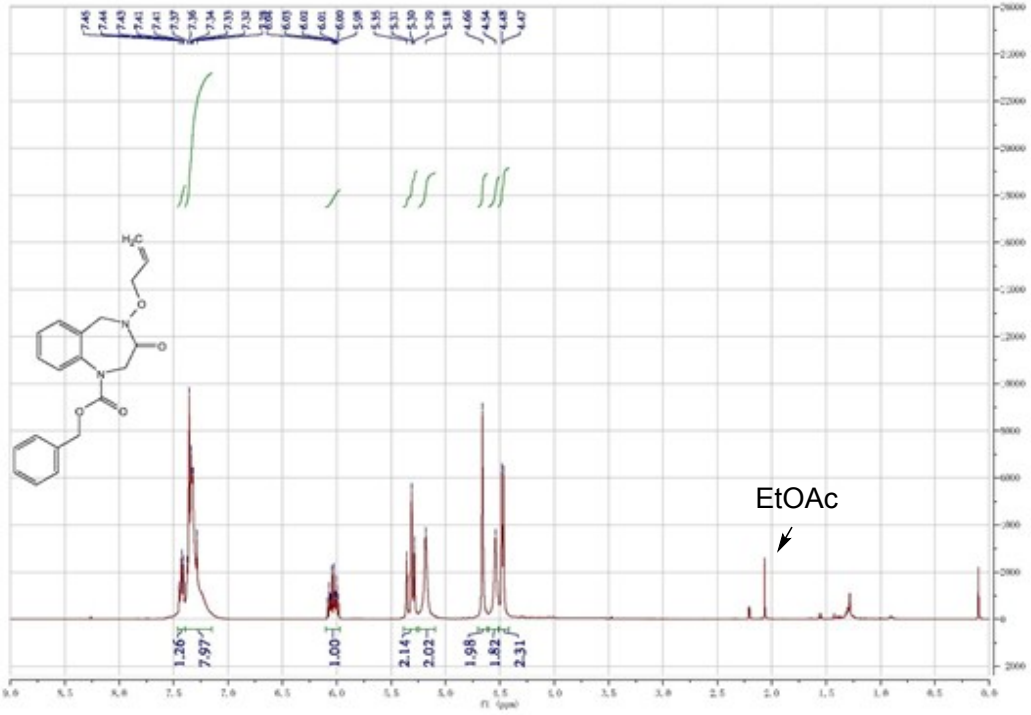
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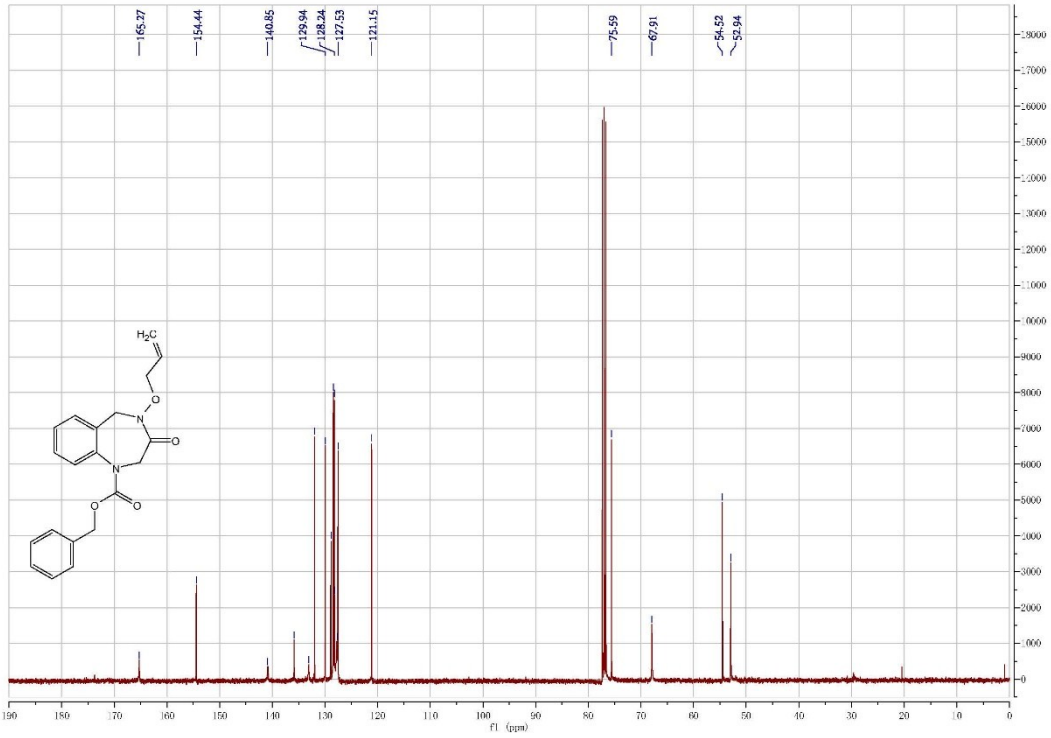
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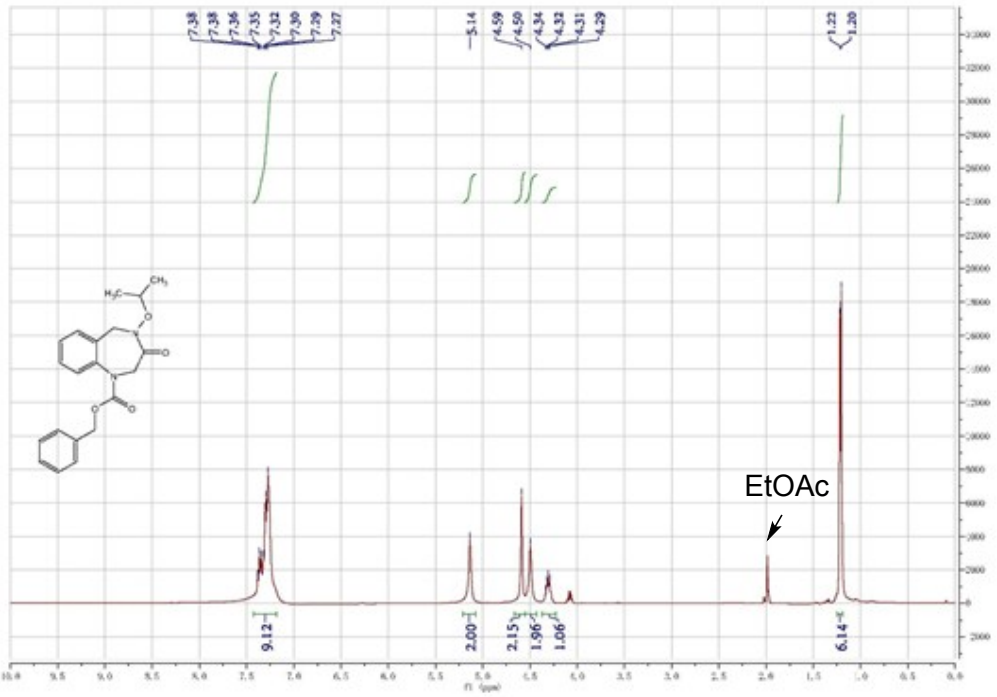

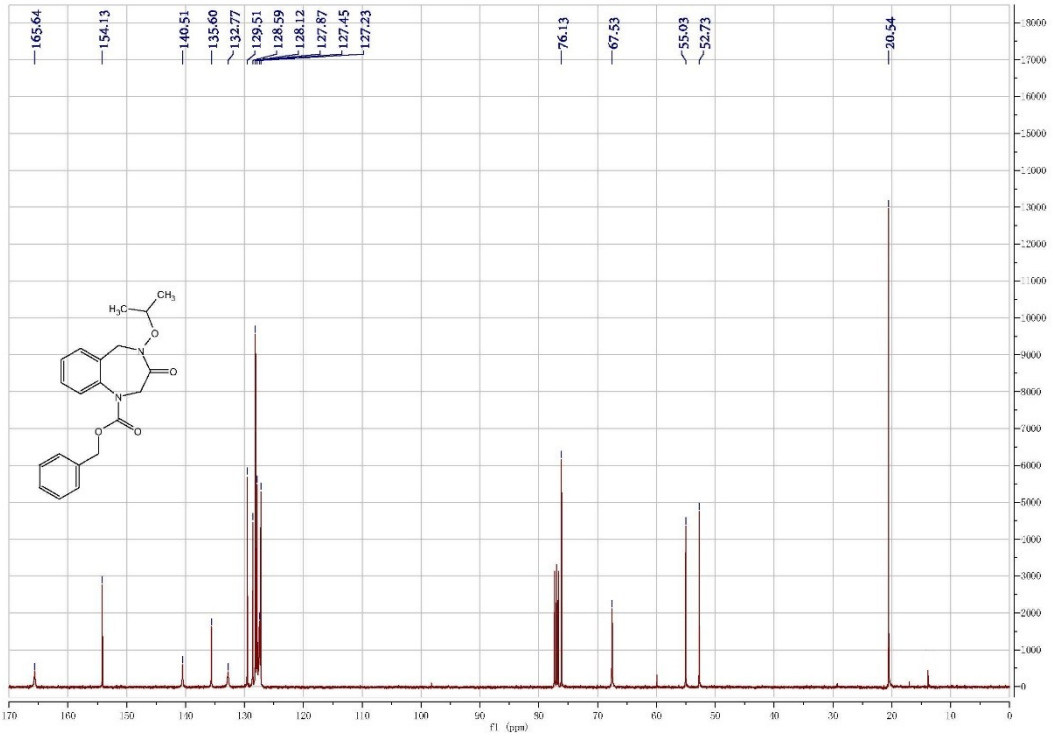

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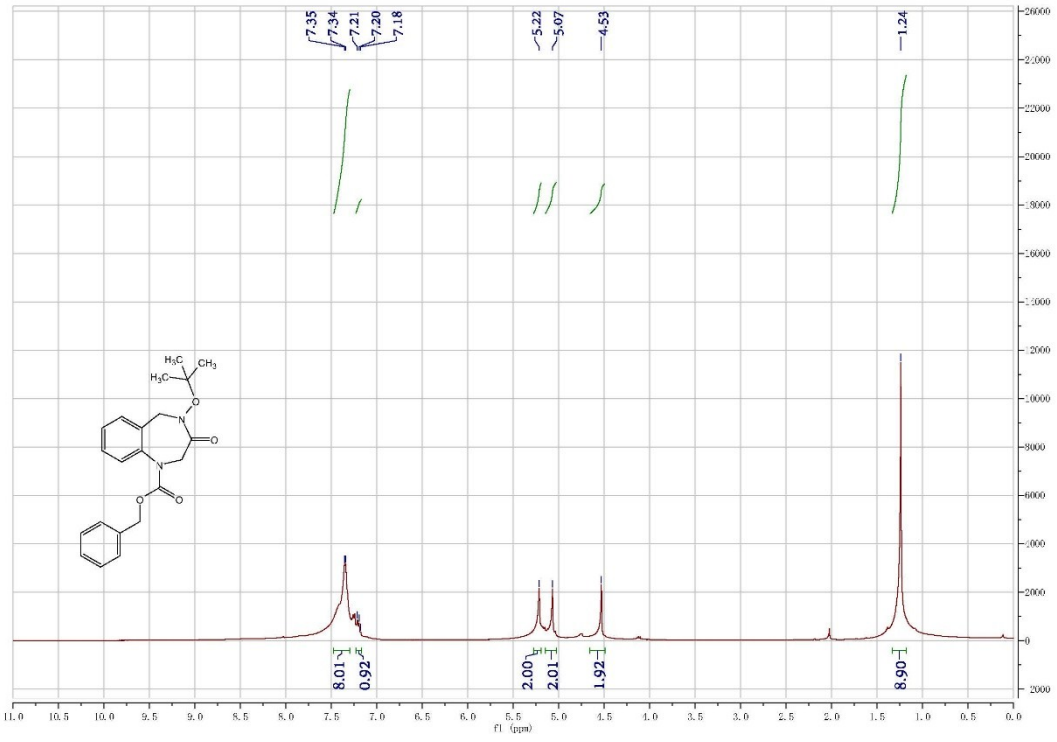
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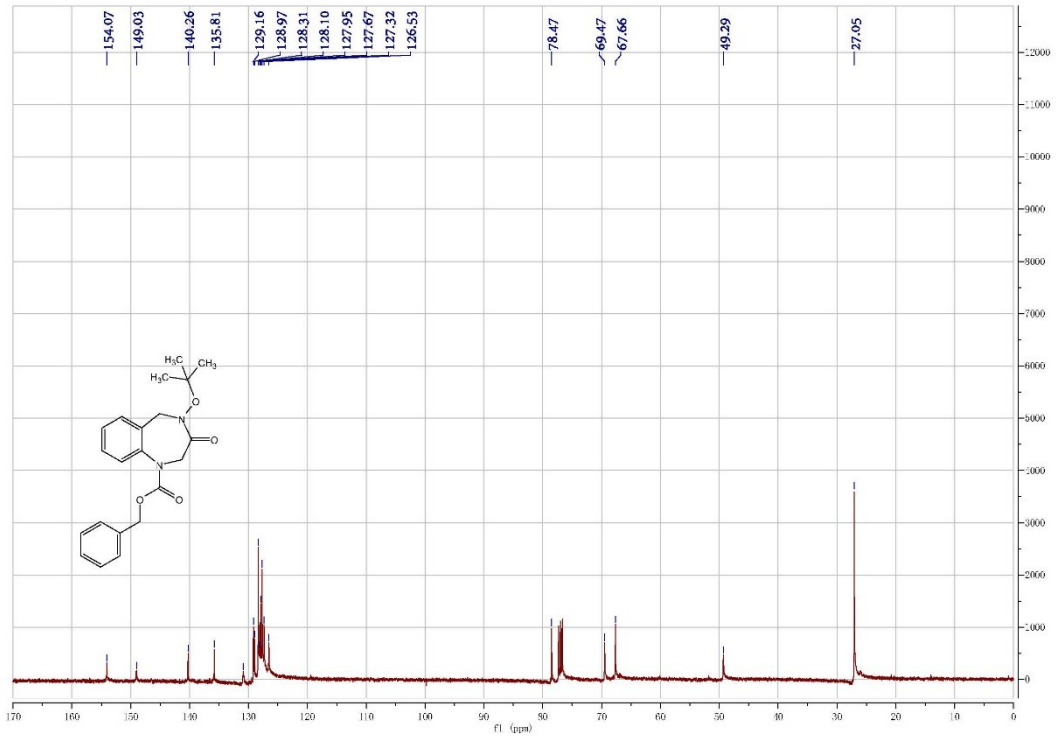
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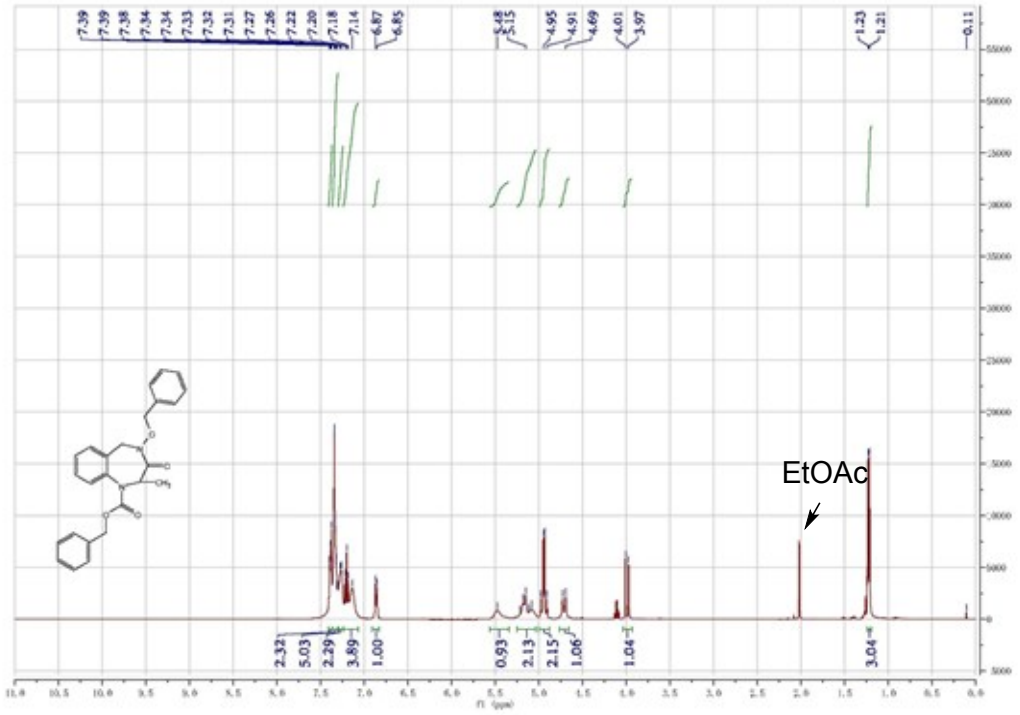
3p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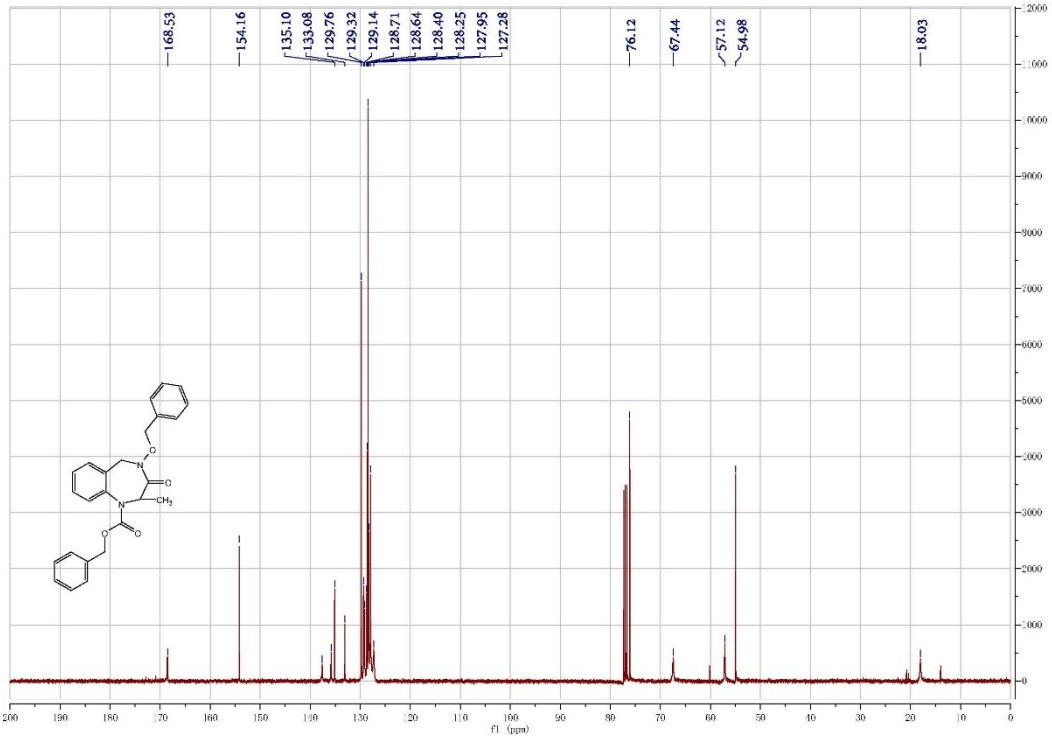
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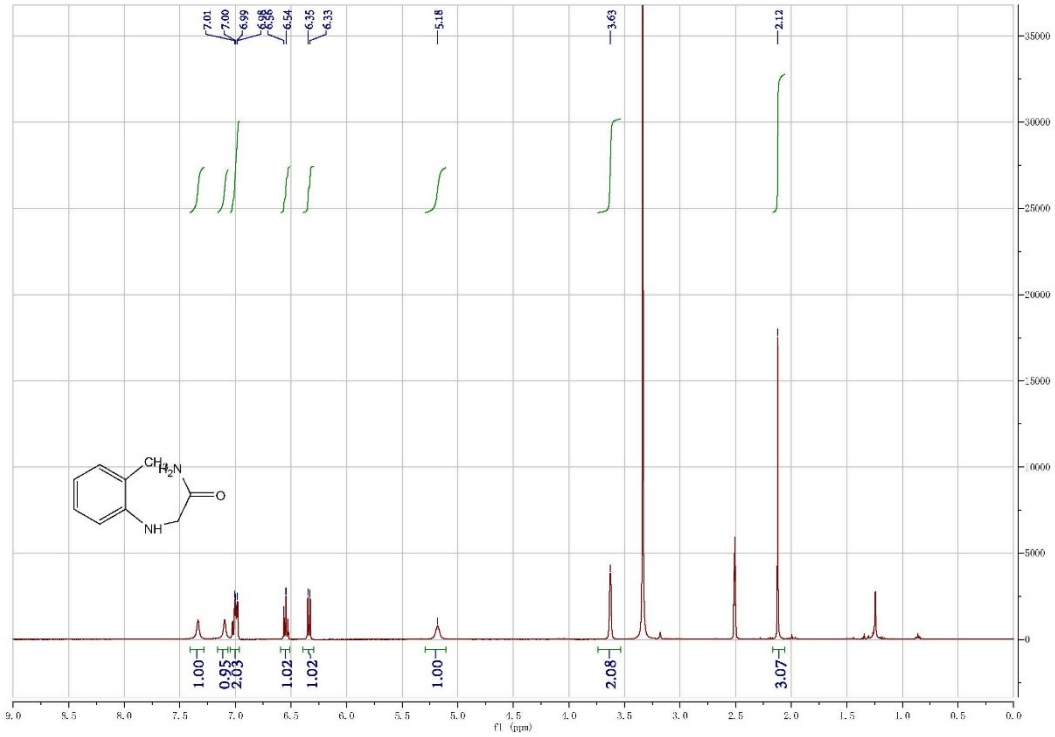
4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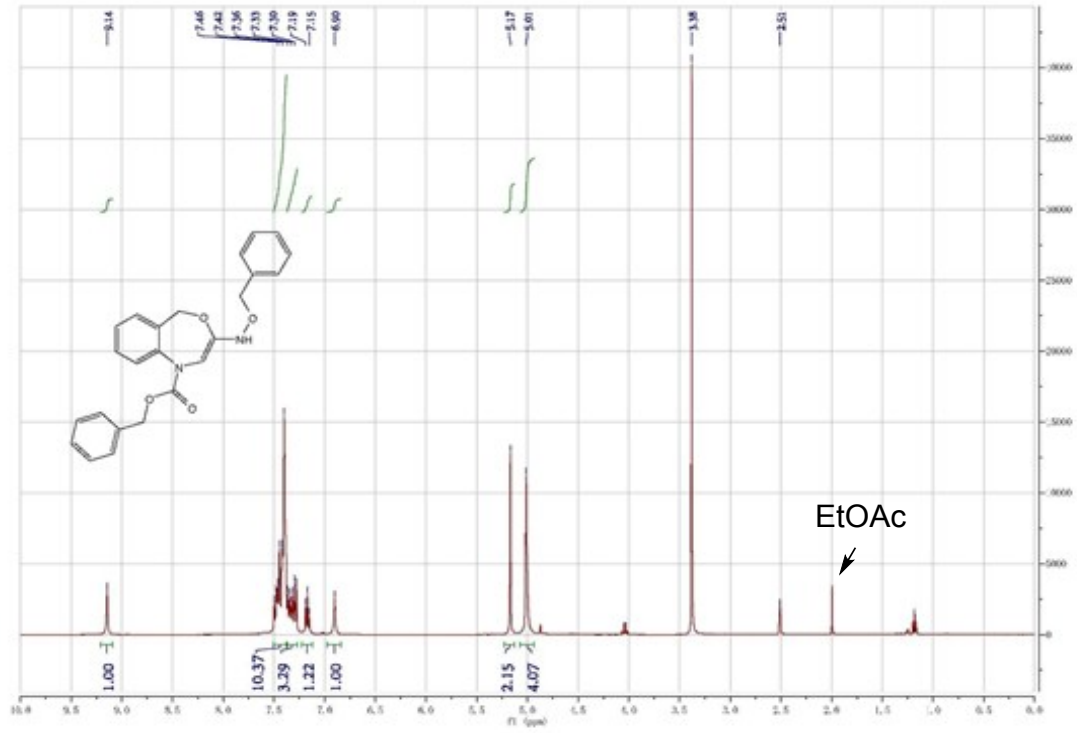
5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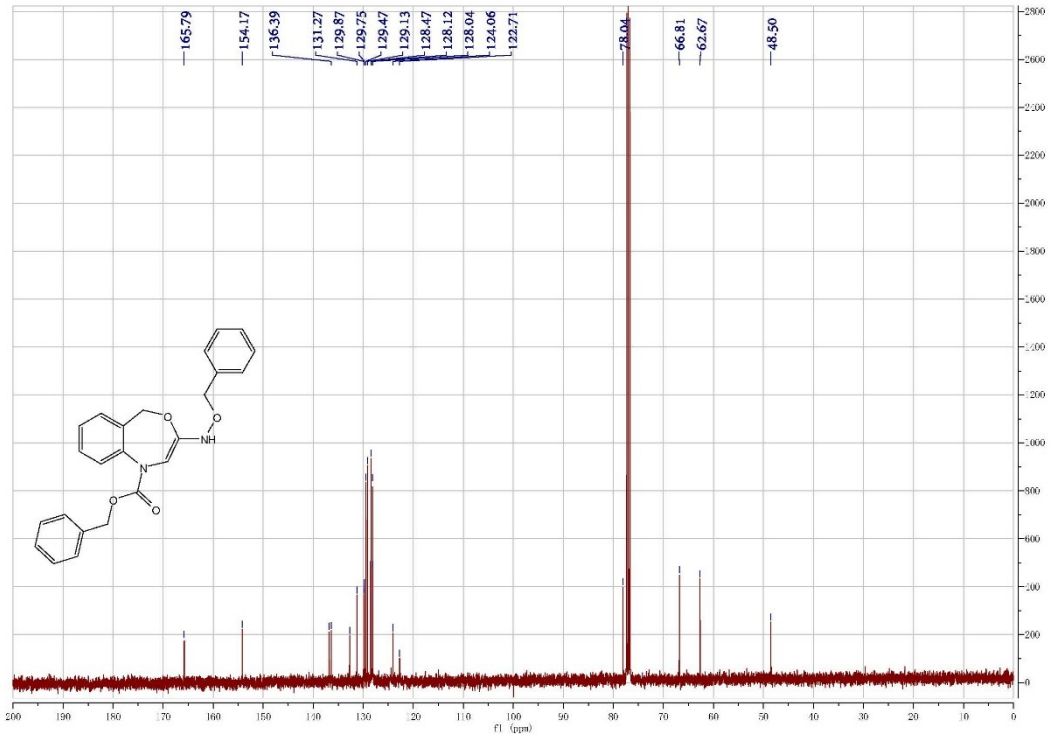
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66.81
62.67
48.50
NH
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N
O
O
f1 (ppm)