

Supporting Information for

Ring-Opening of Epoxides with Amines for Synthesis of β -Amino Alcohols in a Continuous-Flow Biocatalysis System

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Experimental setup.



Figure 1. Syringe pump and reactant injector.



Figure 2. Photograph of the continuous flow system.

Reaction conditions and results of blank trial

Reaction conditions: continuous-flow microreactor, feed 1, 5.0 mmol aniline (**1a**) was dissolved in 10 mL solvent, feed 2, 5.0 mmol epichlorohydrin (**2a**) was dissolved in 10 mL solvent, Lipozyme TL IM 870 mg, flow rate: 104.7 $\mu\text{L min}^{-1}$, 30 min, 40 °C.

Reaction result: no detection about β -amino alcohols in this experiment. Recovery of reactants: amine: 94.2%; epichlorohydrin: 96.4%.

Proposed mechanism of enzymatic synthesis of β -amino alcohols.

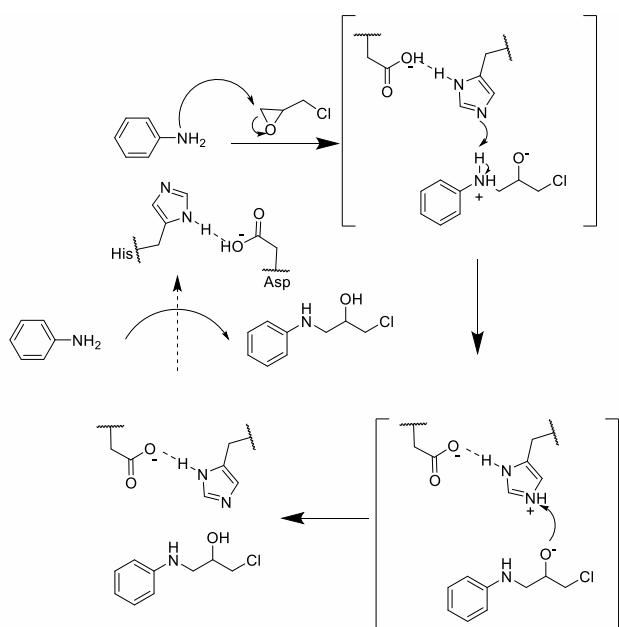
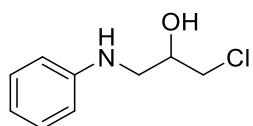
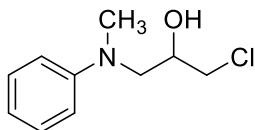


Figure 3. Proposed mechanism of lipase catalyzed ring-opening reaction of epoxide.

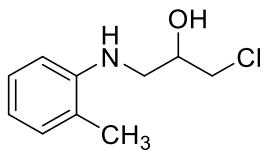
Characterization data for products



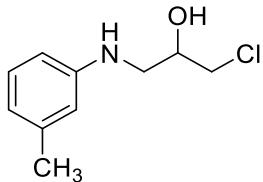
1-chloro-3-(phenylamino)propan-2-ol (3a).^[1] Yellow oil. 0.845g. **¹H NMR** (500 MHz, DMSO-*d*₆): δ 7.16 – 7.06 (m, 2H), 6.71 – 6.62 (m, 2H), 6.58 (tt, *J* = 7.3, 1.1 Hz, 1H), 5.42 (s, 2H), 3.97 – 3.87 (m, 1H), 3.73 (dd, *J* = 11.1, 4.5 Hz, 1H), 3.64 (dd, *J* = 11.1, 5.7 Hz, 1H), 3.24 (dd, *J* = 13.2, 5.6 Hz, 1H), 3.10 (dd, *J* = 13.1, 6.3 Hz, 1H); **¹³C NMR** (126 MHz, CDCl₃): δ 147.33, 129.42, 118.65, 113.66, 69.71, 47.55, 47.41.



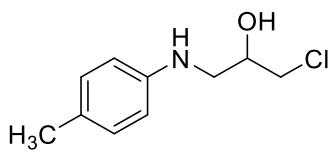
1-chloro-3-(methyl(phenyl)amino)propan-2-ol (3b).^[2] Yellow oil. 0.728g. ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.23 – 7.16 (m, 2H), 6.80 – 6.71 (m, 2H), 6.65 (tt, *J* = 7.2, 1.0 Hz, 1H), 5.37 (d, *J* = 4.0 Hz, 1H), 3.99 (s, 1H), 3.67 (dd, *J* = 11.1, 4.5 Hz, 1H), 3.61 (dd, *J* = 11.1, 5.5 Hz, 1H), 3.52 (dd, *J* = 14.9, 5.3 Hz, 1H), 3.32 (dd, *J* = 14.9, 7.0 Hz, 1H), 2.97 (s, 3H); ¹³C NMR (126 MHz, DMSO-*d*₆): δ 129.35, 117.88, 113.18, 68.98, 56.77, 47.71, 39.76.



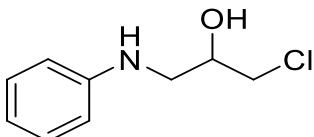
1-chloro-3-(o-tolylamino)propan-2-ol (3c).^[2] Yellow oil. 0.821g. ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.20-7.07 (m, 2H), 6.78-6.68 (m, 2H), 5.39 (d, *J* = 6.3 Hz, 2H), 4.20-4.13 (m, 1H), 3.77-3.64 (m, 2H), 3.46 (dd, *J* = 4.4, 13.1 Hz, 1H), 3.30 (dd, *J* = 7.3, 13.1 Hz, 1H), 2.20 (s, 3H); ¹³C NMR (126 MHz, DMSO-*d*₆): δ 145.3, 130.4, 127.2, 123.0, 118.3, 110.6, 69.7, 47.8, 47.4, 17.5.



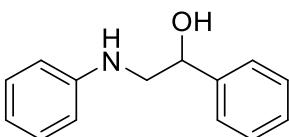
1-chloro-3-(m-tolylamino)propan-2-ol (3d).^[4] Yellow oil. 0.882g. ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.14 (1H, s), 6.39-6.60 (3H, m), 5.35 (d, *J* = 6.1 Hz, 2H), 3.79 (d, *J* = 7.1 Hz, 1H), 3.69 (dd, *J* = 12.2, 4.4 Hz, 1H), 3.59 (dd, *J* = 12.2, 5.8 Hz, 1H), 3.08 (dd, *J* = 12.9, 5.8 Hz, 1H), 3.00 (dd, *J* = 12.9, 5.8 Hz, 1H), 2.15 (s, 3H); ¹³C NMR (126 MHz, DMSO-*d*₆): δ 147.5, 139.2, 129.4, 117.4, 113.2, 110.5, 76.2, 50.8, 48.9, 21.3.



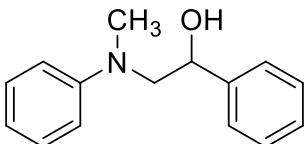
1-chloro-3-(p-tolylamino)propan-2-ol (3e).^[2] White powder, 0.922g, 81–82°C. **1H NMR** (500 MHz, DMSO-*d*₆): δ 6.99 – 6.82 (m, 2H), 6.59 – 6.44 (m, 2H), 5.31 (d, *J* = 5.5 Hz, 2H), 3.82 (d, *J* = 7.1 Hz, 1H), 3.69 (dd, *J* = 11.1, 4.4 Hz, 1H), 3.59 (dd, *J* = 11.1, 5.7 Hz, 1H), 3.14 (dd, *J* = 13.1, 5.8 Hz, 1H), 3.00 (dd, *J* = 13.1, 6.2 Hz, 1H), 2.15 (s, 3H); **13C NMR** (126 MHz, CDCl₃): δ 144.87, 129.92, 128.23, 114.00, 69.73, 48.01, 47.65, 20.41.



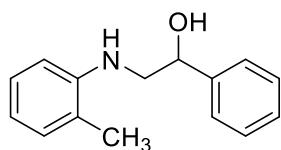
1-chloro-3-((4-chlorophenyl)amino)propan-2-ol (3f).^[3] Yellow oil. 0.772g. **1H NMR** (500 MHz, DMSO-*d*₆) δ 7.09 (d, *J* = 8.9 Hz, 2H), 6.62 (d, *J* = 8.9 Hz, 2H), 5.77 (s, 1H), 5.38 (s, 1H), 3.90 – 3.80 (m, 1H), 3.69 (dd, *J* = 11.1, 4.5 Hz, 1H), 3.60 (dd, *J* = 11.1, 5.6 Hz, 1H), 3.18 (dd, *J* = 13.3, 5.5 Hz, 1H), 3.04 (dd, *J* = 13.3, 6.3 Hz, 1H); **13C NMR** (126 MHz, CDCl₃): δ 146.32, 129.18, 122.84, 114.44, 69.80, 47.56, 47.22.



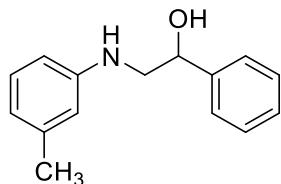
1-phenyl-2-(phenylamino)ethan-1-ol (3g).^[1] Yellow oil. 0.932g. **1H NMR** (500 MHz, DMSO-*d*₆): δ 7.49 – 7.43 (m, 2H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.04 (dd, *J* = 8.5, 7.2 Hz, 2H), 6.60 (d, *J* = 7.4 Hz, 2H), 6.54 (t, *J* = 7.2 Hz, 1H), 5.99 (d, *J* = 5.9 Hz, 1H), 5.07 (t, *J* = 5.8 Hz, 1H), 4.48 – 4.42 (m, 1H), 3.77 – 3.63 (m, 2H); **13C NMR** (126 MHz, CDCl₃): δ 143.56, 137.60, 129.25, 128.86, 128.17, 127.42, 120.92, 116.69, 66.14, 62.97.



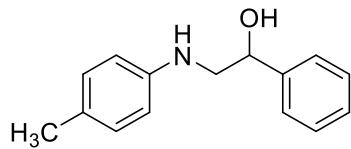
2-(methyl(phenyl)amino)-1-phenylethan-1-ol (3h).^[2] Yellow oil. 0.810g. **1H NMR** (500 MHz, DMSO-*d*₆): δ 7.32 (t, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 7.3 Hz, 2H), 7.26 – 7.21 (m, 1H), 7.15 (dd, *J* = 8.8, 7.2 Hz, 2H), 6.78 (d, *J* = 8.2 Hz, 2H), 6.61 (t, *J* = 7.2 Hz, 1H), 4.98 – 4.92 (m, 1H), 4.89 (s, 1H), 3.91 (qd, *J* = 11.4, 6.9 Hz, 2H), 2.82 (s, 3H); **13C NMR** (126 MHz, DMSO-*d*₆): δ 150.14, 139.99, 128.84, 128.26, 127.19, 126.81, 115.76, 112.31, 62.92, 61.81, 32.20.



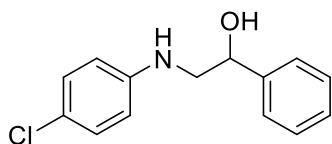
1-phenyl-2-(o-tolylamino)ethan-1-ol (3i).^[2] Yellow oil. 0.925g. ^1H NMR (500 MHz, DMSO- d_6): δ 7.76–7.38 (m, 4H), 7.36–7.31 (m, 1H), 7.17–7.12 (m, 1H), 7.10–7.06 (m, 1H), 6.74–6.68 (m, 2H), 5.63 (d, $J = 5.9$ Hz, 1H), 4.98 (t, $J = 6.2$ Hz, 1H), 3.48 (dd, $J = 5.9, 4.0$ Hz, 2H), 3.36 (dt, $J = 6.2, 4.0$ Hz, 1H), 2.15 (s, 3H); ^{13}C NMR (126 MHz, DMSO- d_6): δ 145.9, 142.2, 130.4, 128.8, 128.2, 127.3, 126.0, 122.9, 117.8, 110.5, 72.6, 51.8, 17.6.



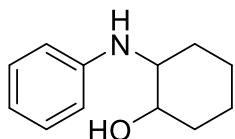
1-phenyl-2-(m-tolylamino)ethan-1-ol (3j).^[5] Yellow oil. 1.019g. ^1H NMR (500 MHz, DMSO- d_6): δ 7.45–7.39 (m, 2H), 7.36 (dd, $J = 8.3, 6.9$ Hz, 2H), 7.25 – 7.16 (m, 1H), 6.95 (dd, $J = 8.5, 7.2$ Hz, 1H), 6.43 (s, 1H), 6.35–6.39 (m, 2H), 6.01 (d, $J = 6.1$ Hz, 1H), 5.09 (t, $J = 6.01$ Hz, 1H), 4.48 – 4.42 (m, 1H), 3.77 – 3.63 (m, 2H), 2.11 (s, 3H); ^{13}C NMR (126 MHz, DMSO- d_6): δ 145.8, 140.2, 138.9, 129.8, 129.5, 127.6, 127.0, 121.5, 116.9, 110.9, 66.3, 61.5, 22.2.



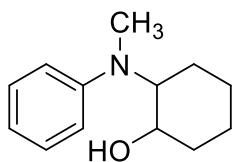
1-phenyl-2-(p-tolylamino)ethan-1-ol (3k).^[2] Yellow oil. 1.065g. ^1H NMR (500 MHz, DMSO- d_6): δ 7.43 – 7.38 (m, 2H), 7.30 (dd, $J = 8.3, 6.9$ Hz, 2H), 7.25 – 7.16 (m, 1H), 6.82 (d, $J = 8.3$ Hz, 2H), 6.47 (d, $J = 8.4$ Hz, 2H), 5.73 (d, $J = 5.8$ Hz, 1H), 4.99 (t, $J = 5.8$ Hz, 1H), 4.36 (dt, $J = 7.2, 5.0$ Hz, 1H), 3.71 – 3.55 (m, 2H), 2.11 (s, 3H); ^{13}C NMR (126 MHz, DMSO- d_6): δ 145.87, 142.25, 129.13, 128.12, 126.95, 126.68, 124.25, 113.09, 66.24, 59.92, 20.04.



2-((4-chlorophenyl)amino)-1-phenylethan-1-ol (3l).^[16] Clear oil. 0.945g. **¹H NMR** (500 MHz, DMSO-*d*₆): δ 7.40 – 7.33 (m, 2H), 7.30 (dd, *J* = 8.4, 6.8 Hz, 2H), 7.25 – 7.18 (m, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.52 (d, *J* = 8.9 Hz, 2H), 6.22 (d, *J* = 6.5 Hz, 1H), 4.96 (s, 1H), 4.34 (td, *J* = 6.9, 5.1 Hz, 1H), 3.59 (dd, *J* = 12.3, 6.2 Hz, 2H); **¹³C NMR** (126 MHz, DMSO-*d*₆): δ 147.02, 141.60, 128.32, 128.17, 126.88, 126.80, 118.98, 114.10, 65.96, 59.56.



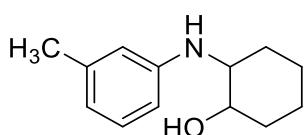
2-(phenylamino)cyclohexan-1-ol (3m).^[1] White powder, 0.743g, 57–58°C. **¹H NMR** (500 MHz, DMSO-*d*₆): δ 7.07 – 7.00 (m, 2H), 6.59 (d, *J* = 7.6 Hz, 2H), 6.47 (t, *J* = 7.2 Hz, 1H), 5.22 (d, *J* = 6.9 Hz, 1H), 4.55 (d, *J* = 4.7 Hz, 1H), 2.98 (s, 1H), 1.98 (dd, *J* = 12.3, 3.6 Hz, 1H), 1.90 – 1.84 (m, 1H), 1.68 – 1.55 (m, 2H), 1.36 – 1.19 (m, 4H), 1.12 – 1.03 (m, 1H); **¹³C NMR** (126 MHz, CDCl₃): δ 147.01, 129.34, 118.94, 114.93, 74.23, 60.63, 33.21, 31.30, 24.94, 24.23.



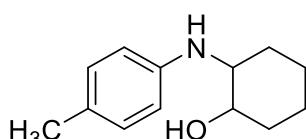
2-(methyl(phenyl)amino)cyclohexan-1-ol (3n).^[2] Yellow oil. 0.666g. **¹H NMR** (500 MHz, DMSO-*d*₆): δ 7.20 – 7.07 (m, 2H), 6.77 (dd, *J* = 8.6, 2.3 Hz, 2H), 6.58 (dt, *J* = 6.4, 5.8, 3.4 Hz, 1H), 4.49 – 4.41 (m, 1H), 3.61 – 3.50 (m, 1H), 3.44 – 3.36 (m, 1H), 2.79 – 2.69 (m, 3H), 2.00 – 1.93 (m, 1H), 1.70 – 1.58 (m, 3H), 1.41 (qd, *J* = 12.2, 3.2 Hz, 1H), 1.34 – 1.21 (m, 3H); **¹³C NMR** (126 MHz, DMSO-*d*₆): δ 150.78, 128.66, 115.24, 112.62, 69.21, 63.74, 35.15, 30.46, 27.45, 24.94, 24.28.



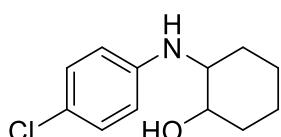
2-(o-tolylamino)cyclohexan-1-ol (3o).^[2] Colorless oil. 0.702g. **¹H NMR** (500 MHz, DMSO-*d*₆): δ 7.26-7.06 (m, 2H), 6.80-6.68 (m, 2H), 5.32 (d, *J* = 7.1 Hz, 1H), 4.27 (d, *J* = 4.7 Hz, 1H), 3.24-3.18 (m, 1H), 2.74 (ddt, *J* = 12.3, 7.6, 4.2 Hz, 1H), 2.16 (s, 3H), 2.13 (s, 2H), 1.79-1.72 (m, 2H), 1.45-1.29 (m, 3H), 1.09-1.02 (m, 1H); **¹³C NMR** (126 MHz, DMSO-*d*₆) δ 145.90, 130.66, 127.39, 123.35, 118.14, 111.85, 74.96, 60.12, 33.43, 32.09, 25.27, 24.51, 17.90.



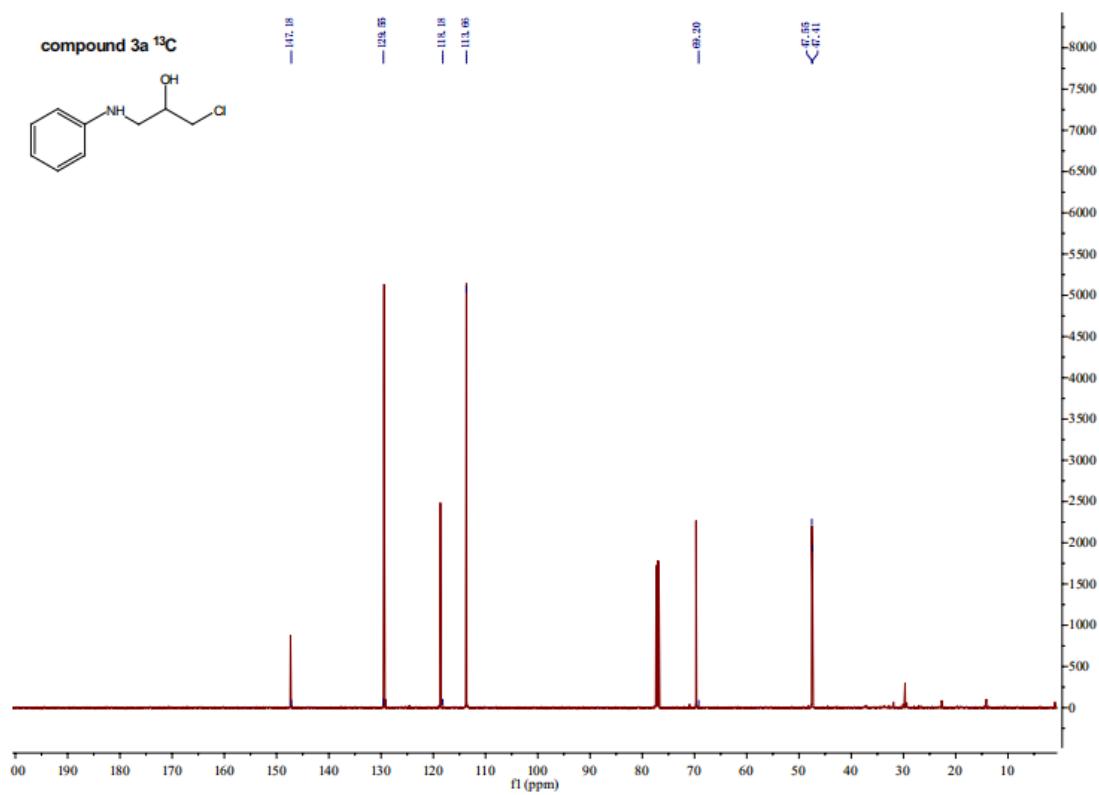
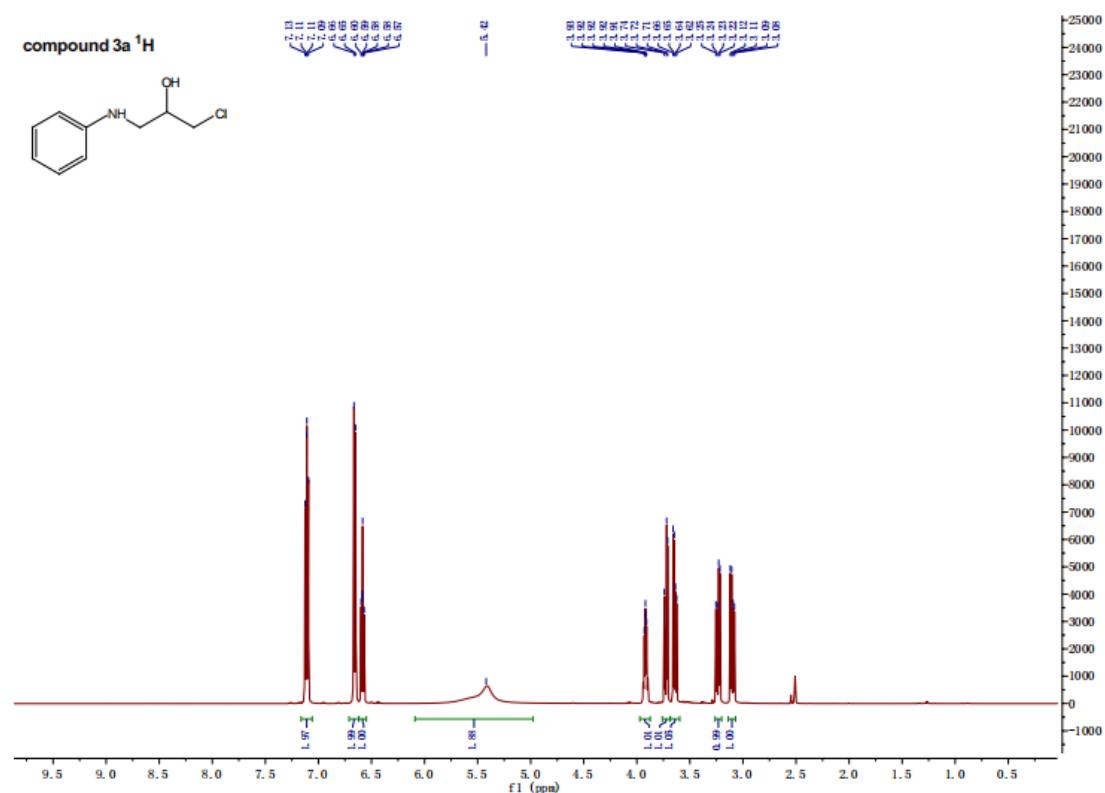
2-(m-tolylamino)cyclohexan-1-ol (3p).^[7] Colorless oil. 0.733g. **¹H NMR** (500 MHz, DMSO-*d*₆): δ 7.02 (s, 1H), 6.39-6.60 (m, 3H), 4.59 (t, *J* = 3.6 Hz, 1H), 3.43 – 3.33 (m, 1H), 3.19-3.27 (m, 1H), 3.02-3.08 (m, 1H) 2.21 (s, 3H), 2.00-2.05 (m, 2H), 1.61-1.69 (m, 2H), 1.17-1.35 ppm (m, 4H); **¹³C NMR** (126 MHz, DMSO-*d*₆): δ 21.5, 23.7, 25.0, 31.0, 33.4, 59.9, 75.6, 111.5, 115.6, 118.5, 128.7, 139.0, 148.0.

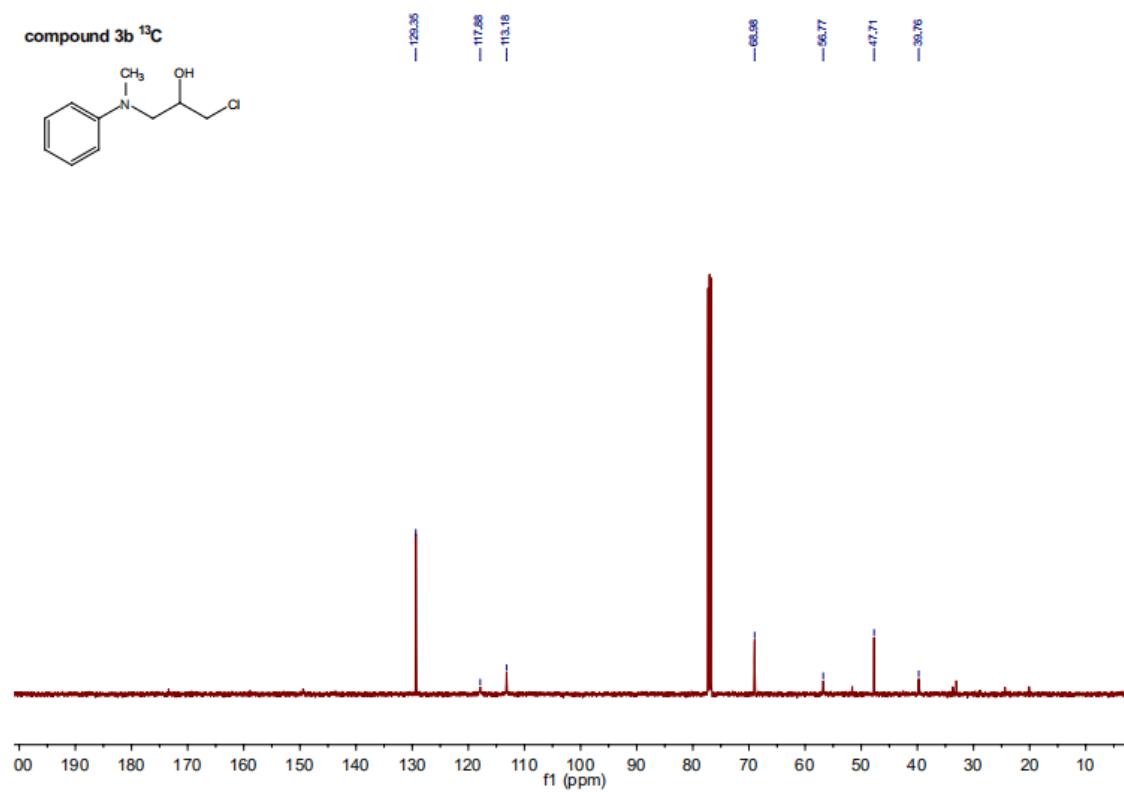
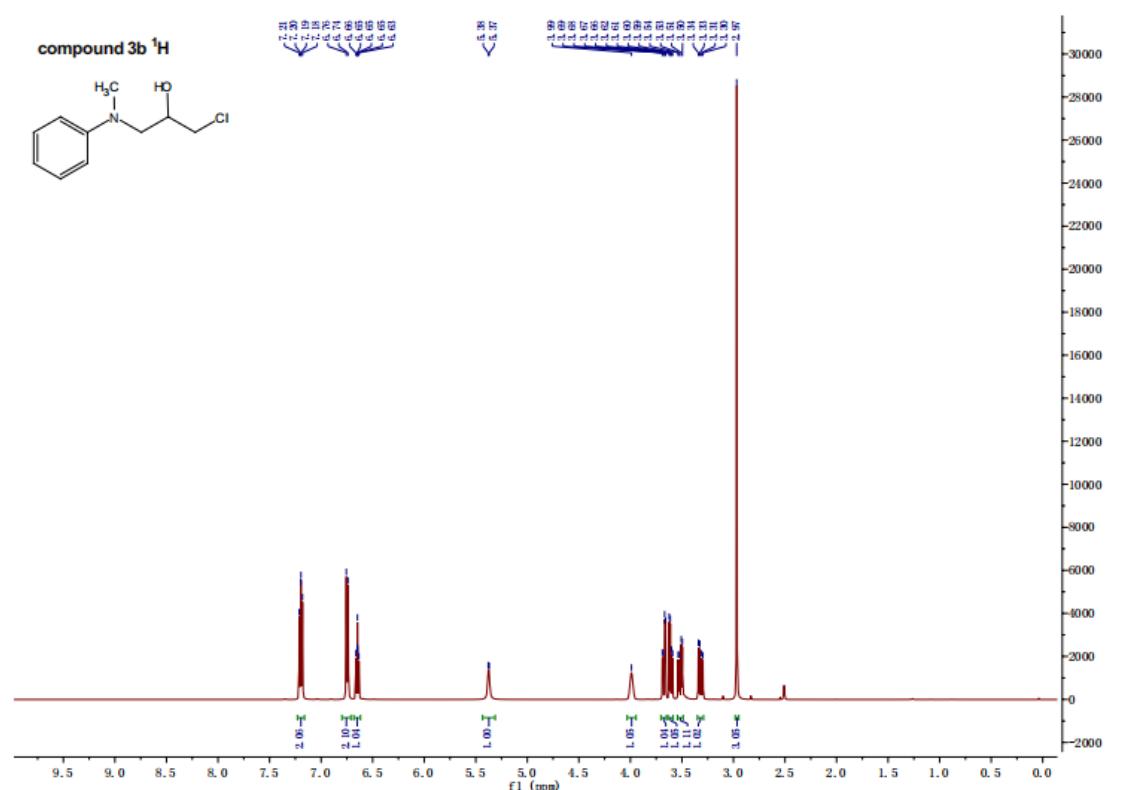


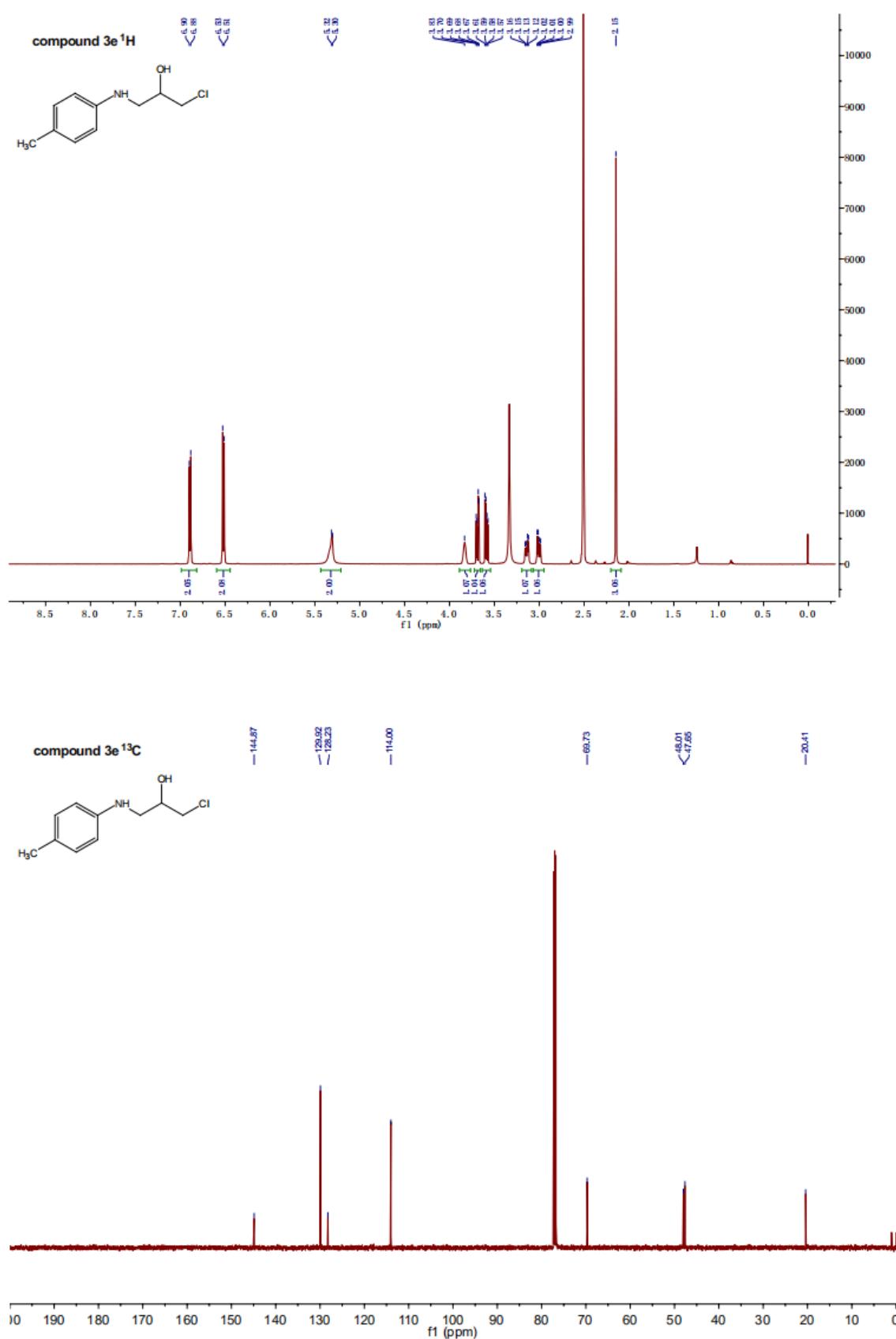
2-(p-tolylamino)cyclohexan-1-ol (3q).^[3] Yellow oil. 0.775g. **¹H NMR** (500 MHz, DMSO-*d*₆): δ 6.90 (d, *J* = 8.2 Hz, 2H), 6.57 (d, *J* = 8.4 Hz, 2H), 4.97 (s, 1H), 4.59 (t, *J* = 3.6 Hz, 1H), 3.43 – 3.33 (m, 1H), 3.00 (s, 1H), 2.19 (s, 3H), 2.11 – 2.00 (m, 1H), 1.99 – 1.90 (m, 1H), 1.66 (ddd, *J* = 32.4, 8.3, 3.8 Hz, 2H), 1.39 – 1.25 (m, 3H), 1.14 – 1.03 (m, 1H); **¹³C NMR** (126 MHz, DMSO-*d*₆): δ 146.52 , 129.22 , 123.70 , 112.75 , 71.81 , 58.28 , 33.64 , 30.58 , 23.88 , 23.87 , 20.09.

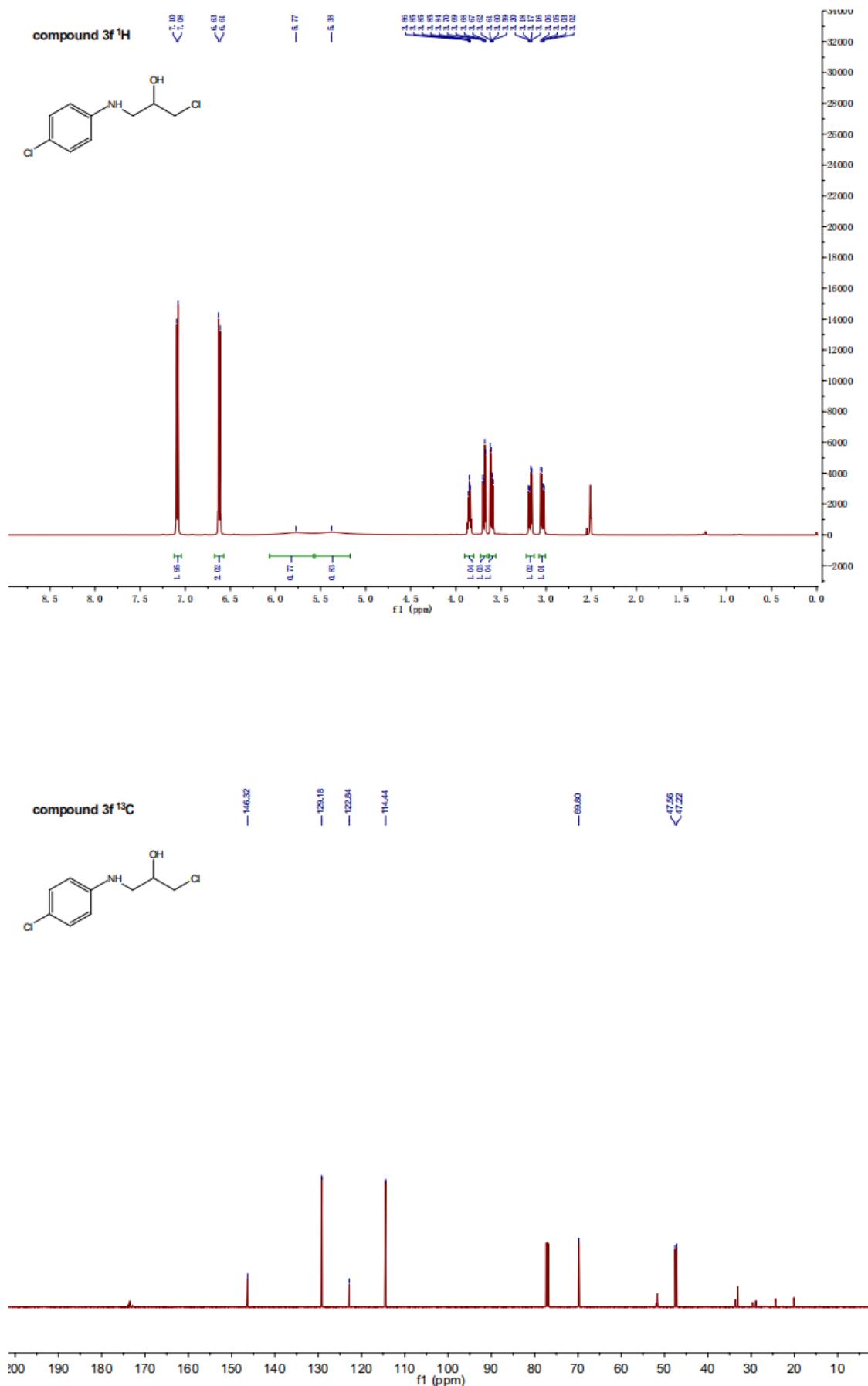


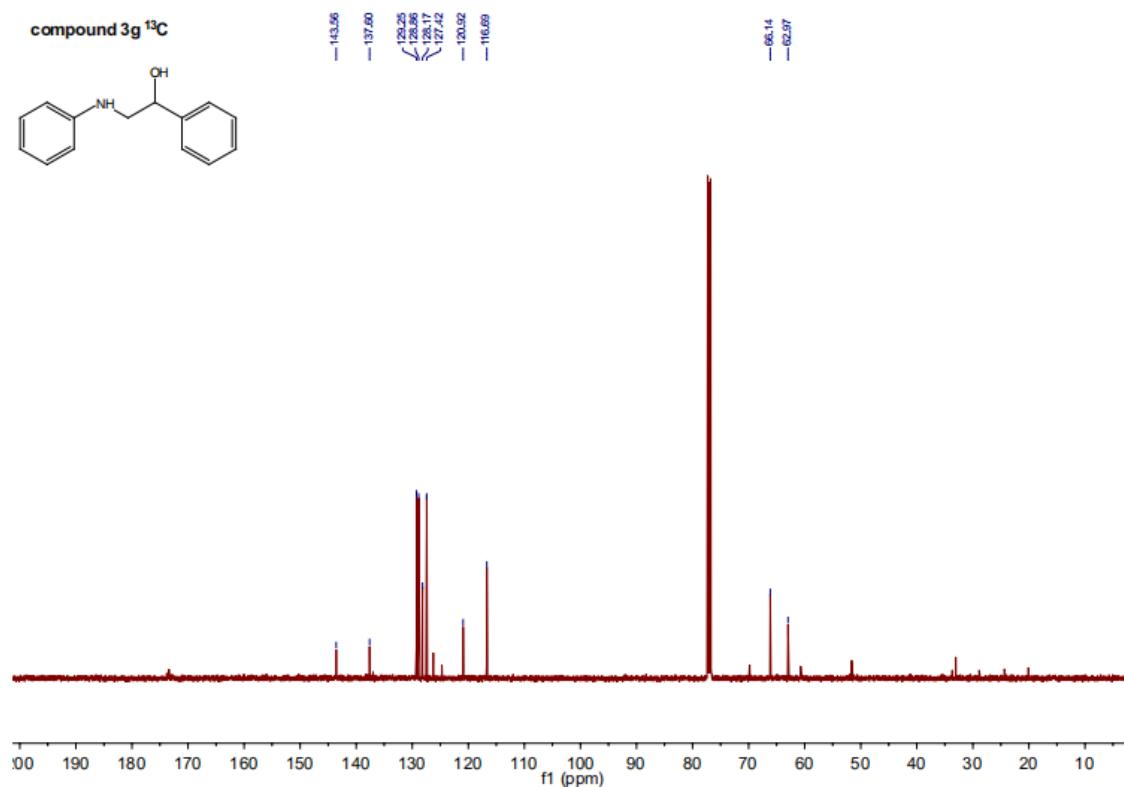
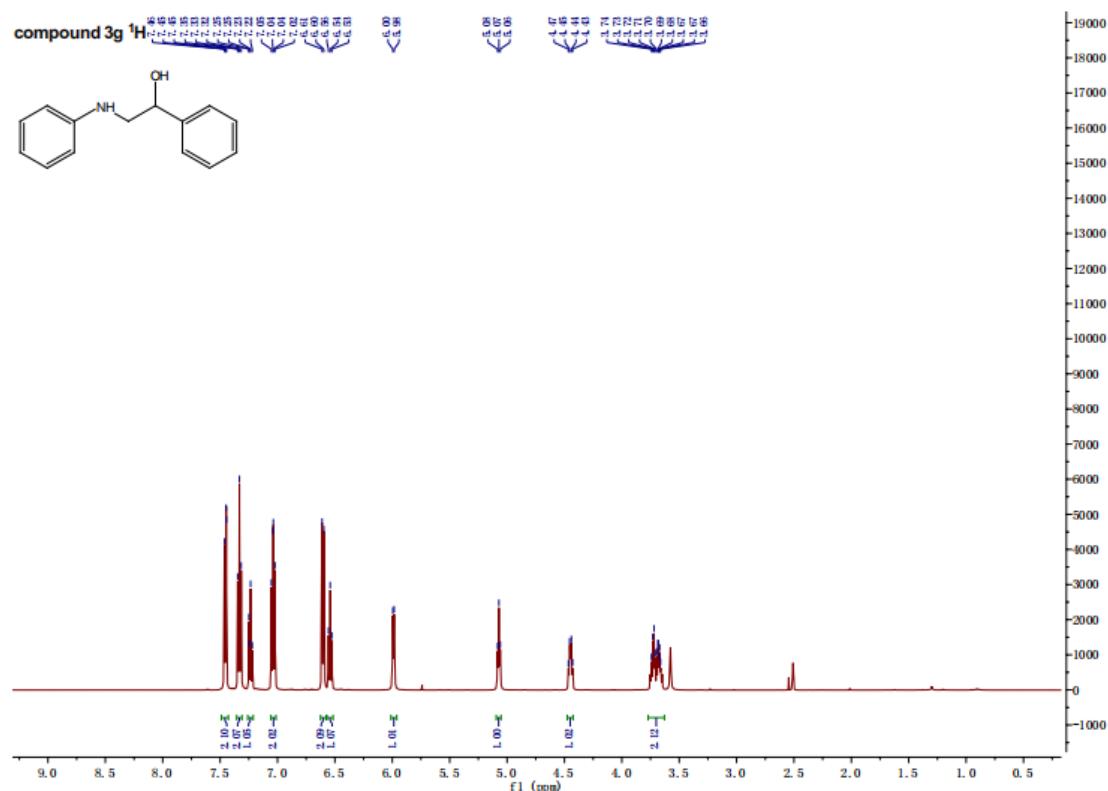
2-((4-chlorophenyl)amino)cyclohexan-1-ol (3r).^[3] White solid, 0.746g, 61–62°C. **¹H NMR** (500 MHz, DMSO-*d*₆): δ 7.04 (d, *J* = 8.9 Hz, 2H), 6.59 (d, *J* = 8.9 Hz, 2H), 5.49 (d, *J* = 7.1 Hz, 1H), 4.57 (d, *J* = 4.7 Hz, 1H), 2.96 (ddt, *J* = 11.6, 7.8, 3.9 Hz, 1H), 1.94 (dd, *J* = 13.3, 4.0 Hz, 1H), 1.86 (dd, *J* = 9.6, 5.3 Hz, 1H), 1.68 – 1.55 (m, 2H), 1.32 – 1.21 (m, 4H), 1.07 (t, *J* = 11.0 Hz, 1H); **¹³C NMR** (126 MHz, DMSO-*d*₆): δ 147.76, 128.35, 118.03, 113.58, 71.80, 57.67, 33.66, 30.32, 23.74, 23.65.

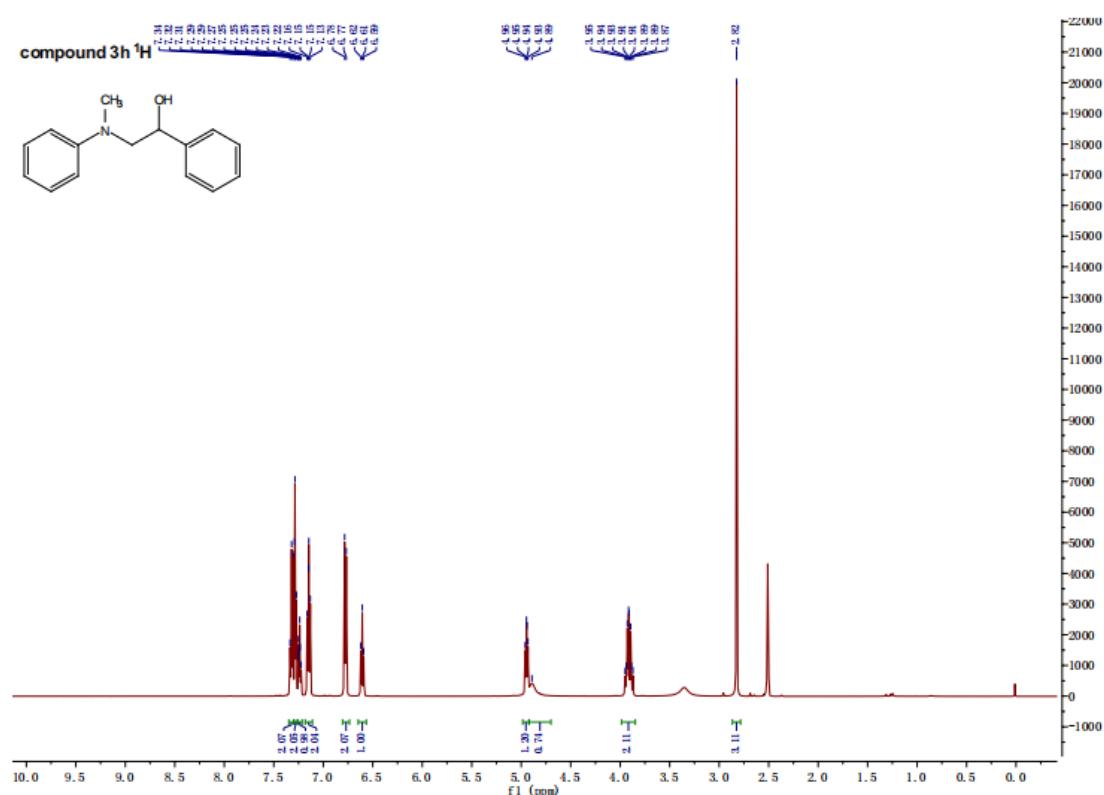


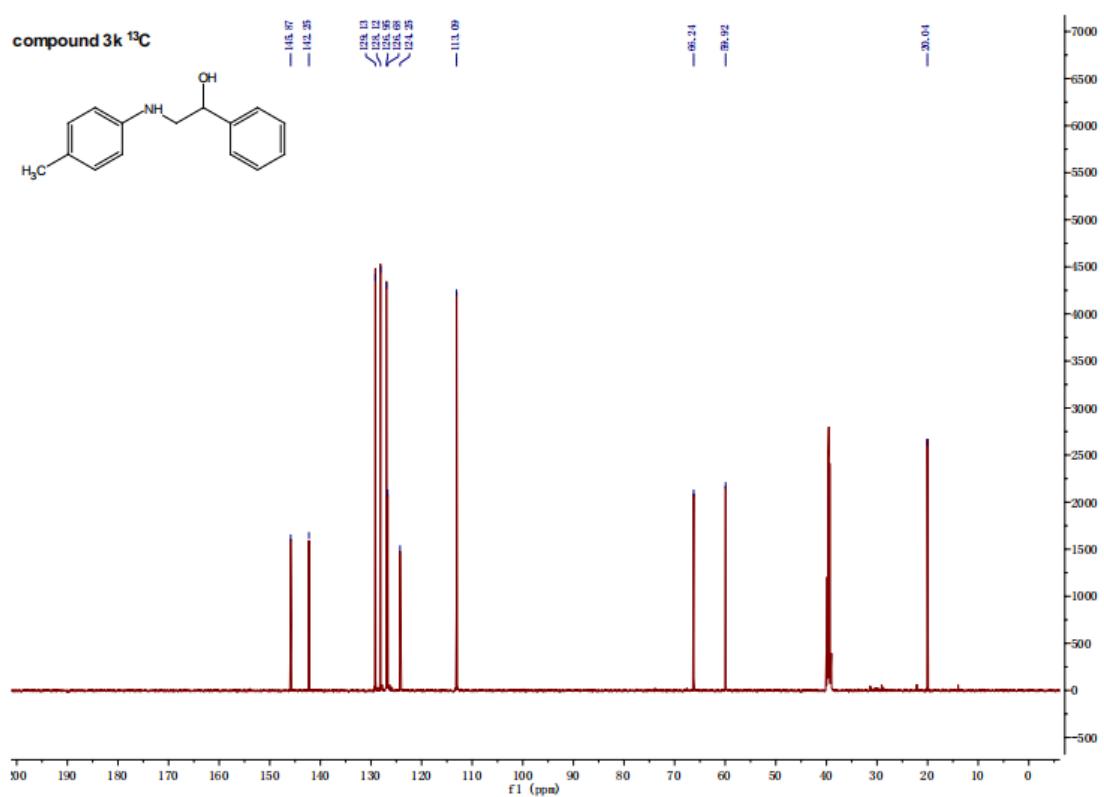
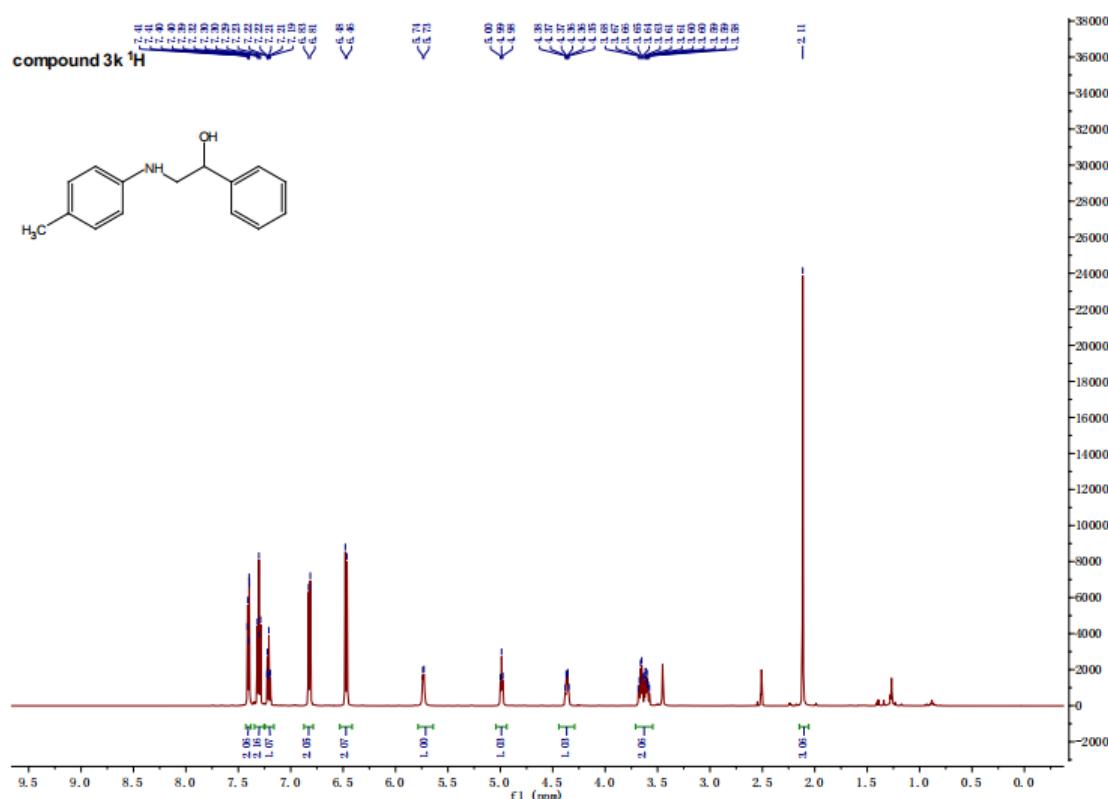


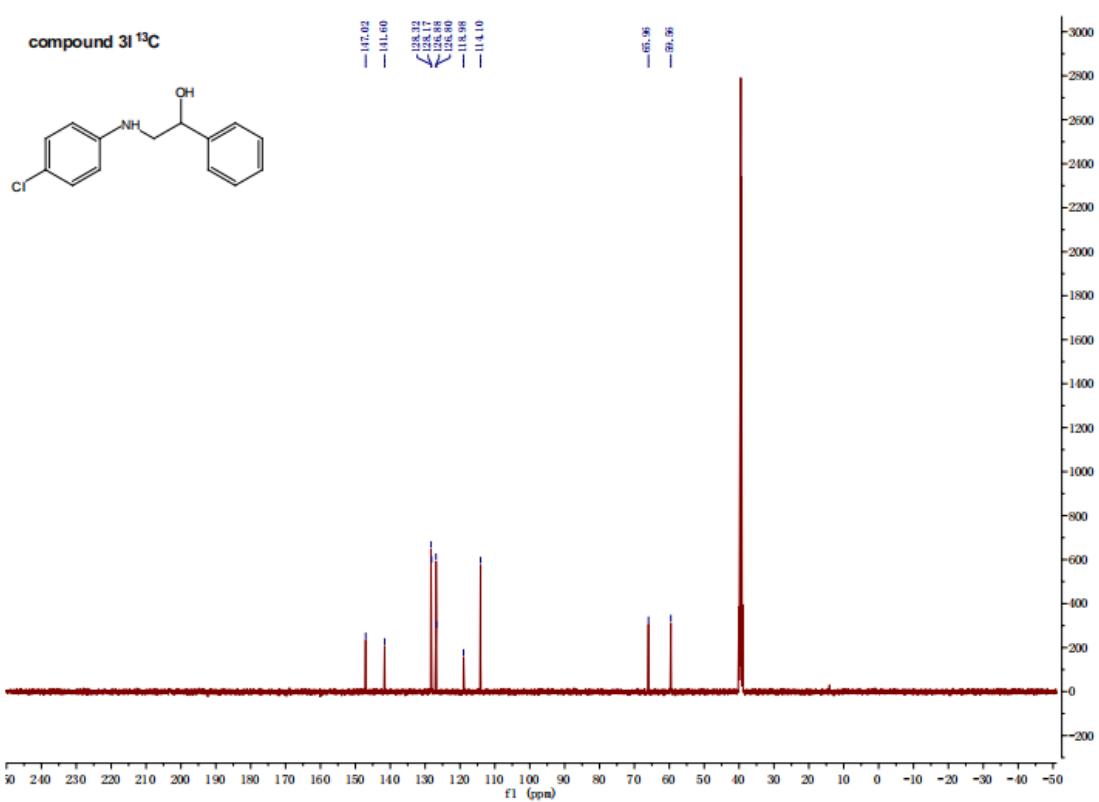
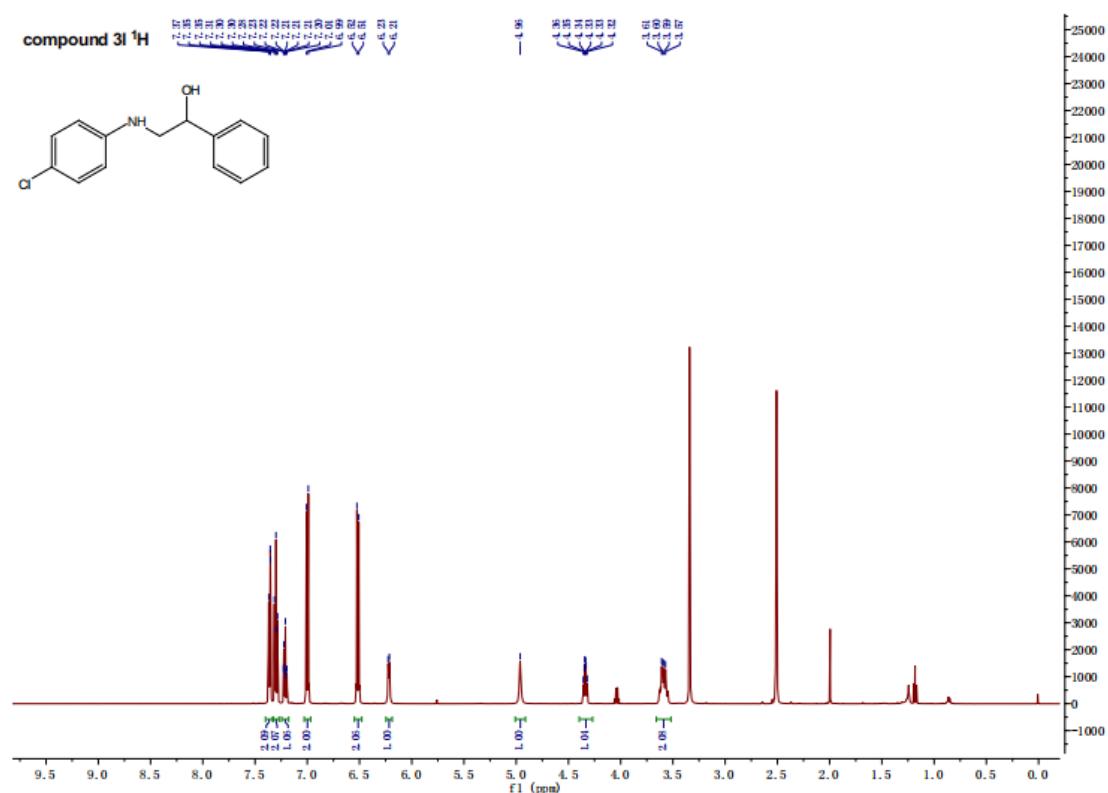


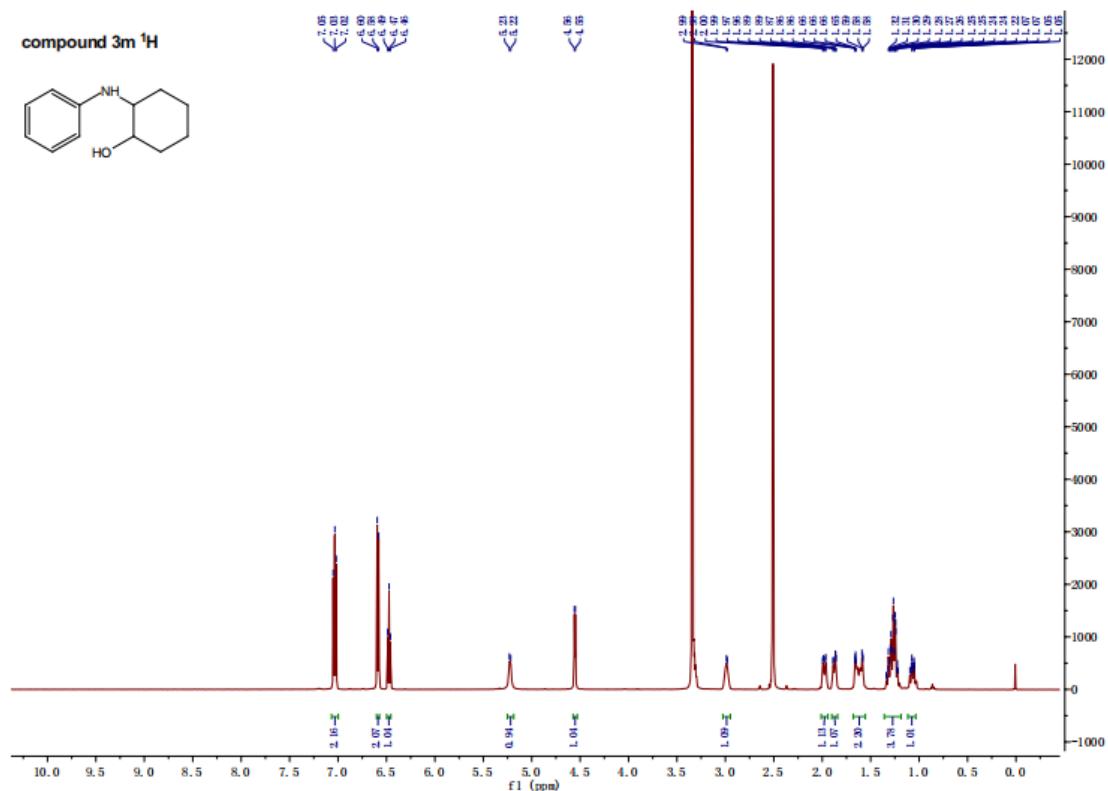


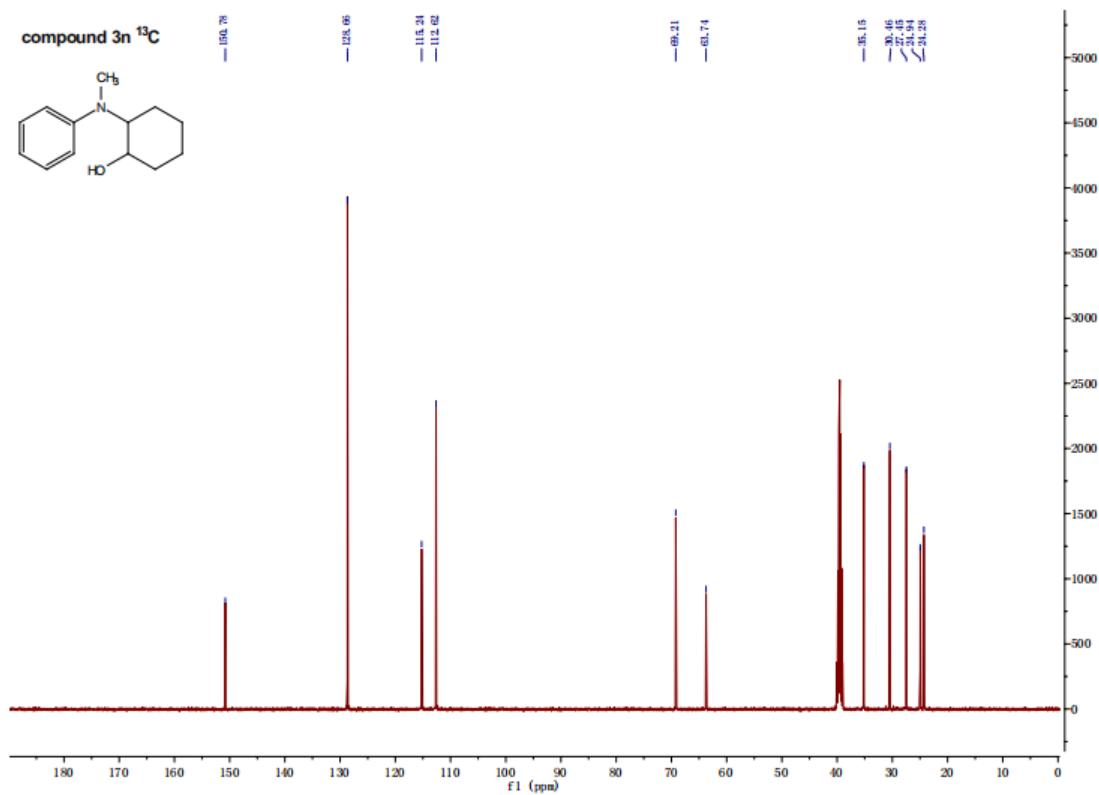
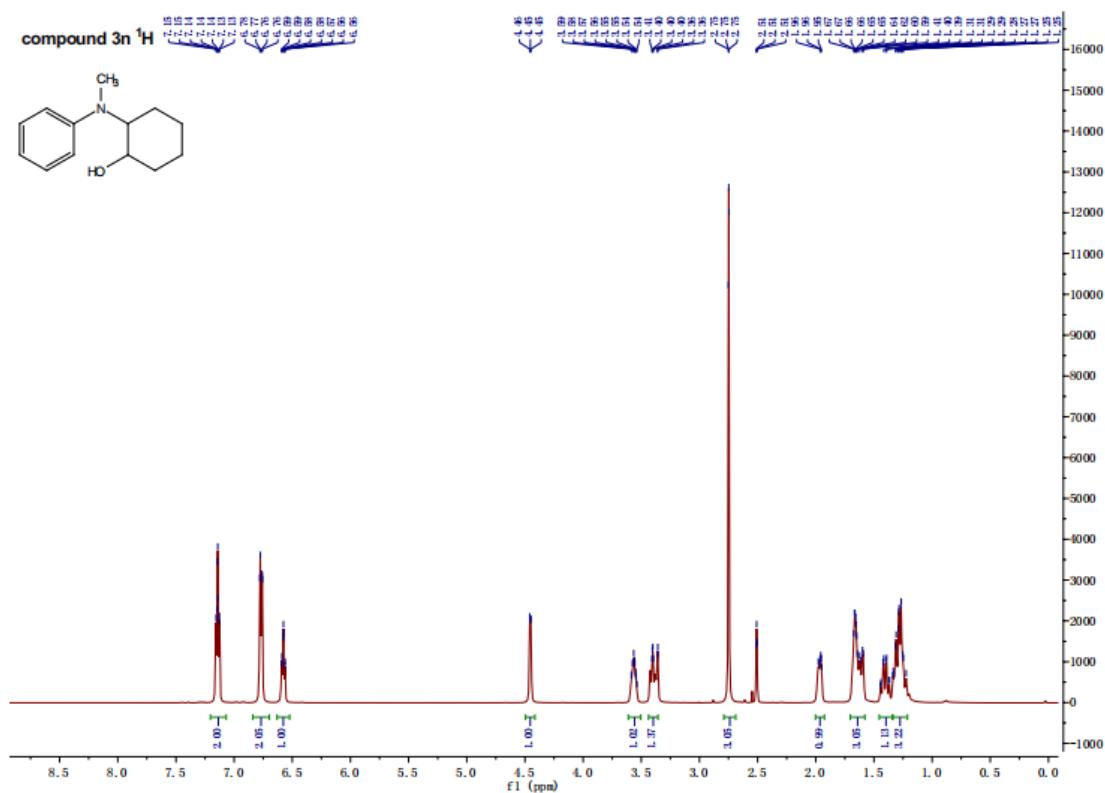


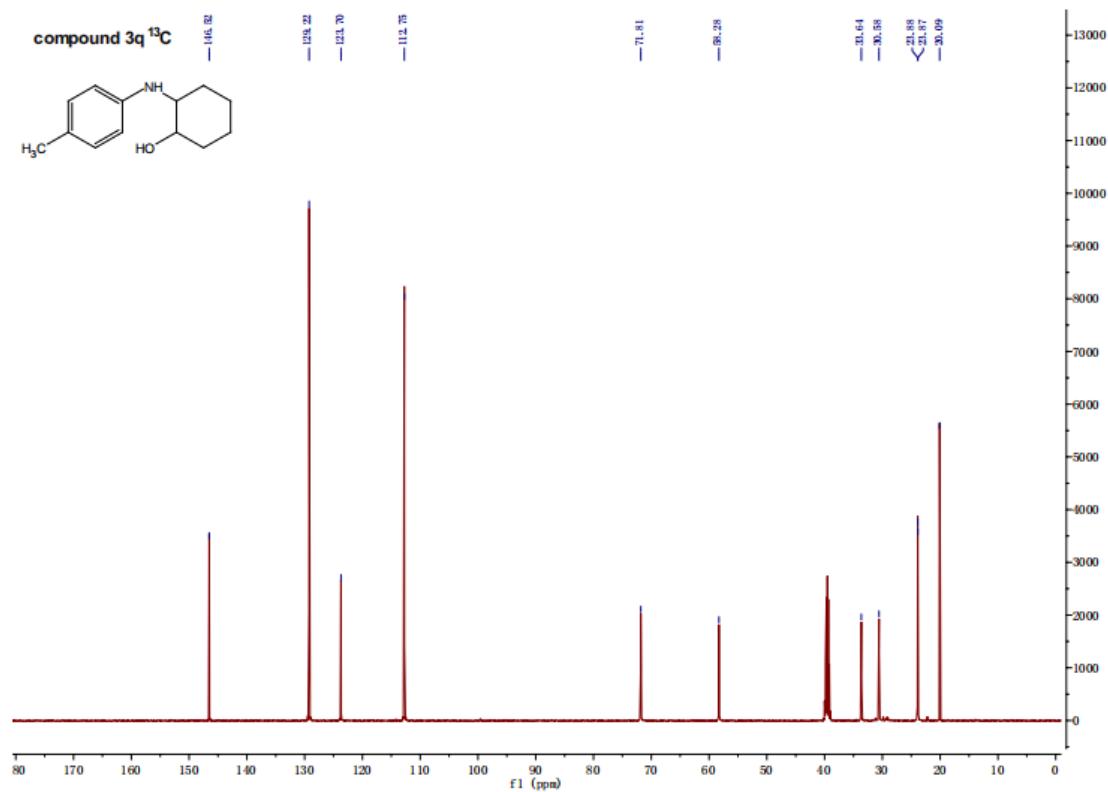
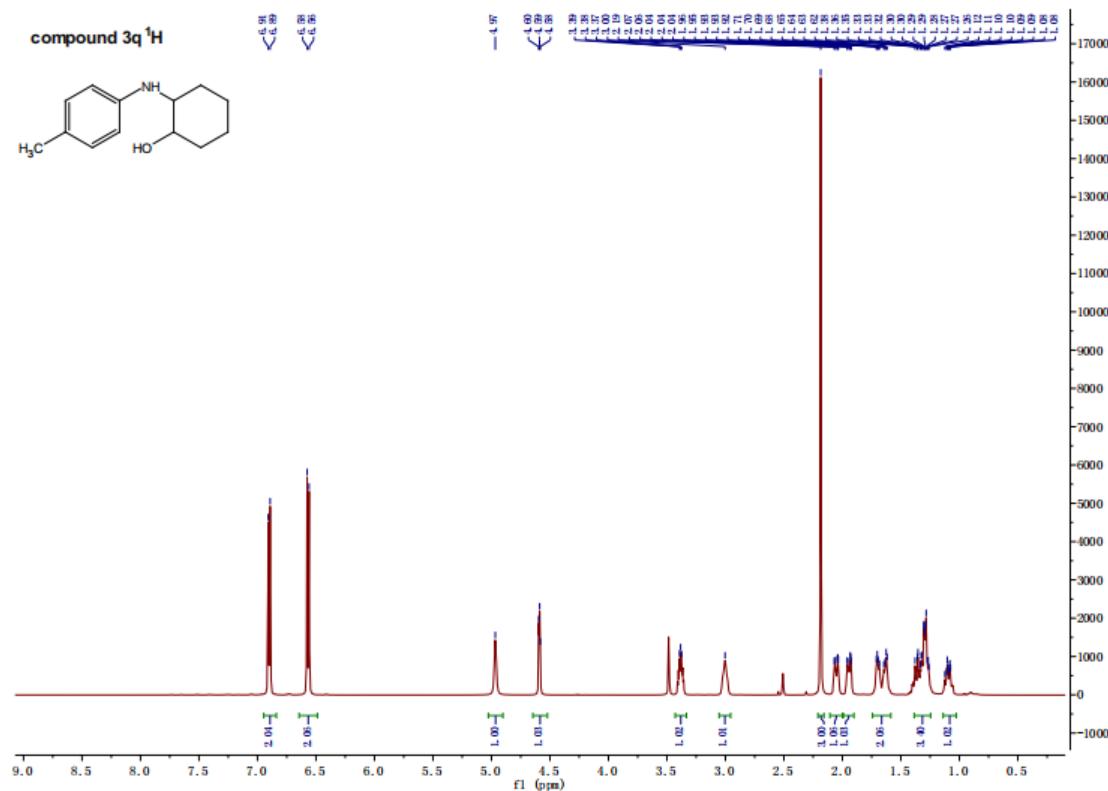


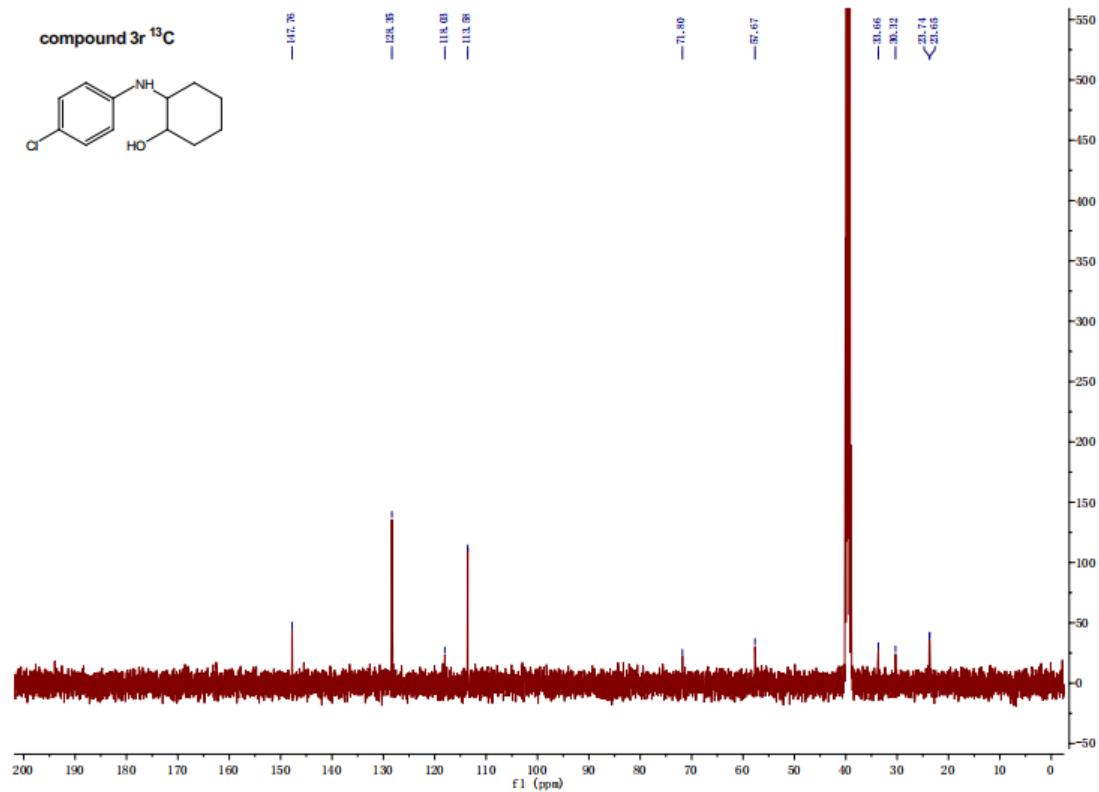
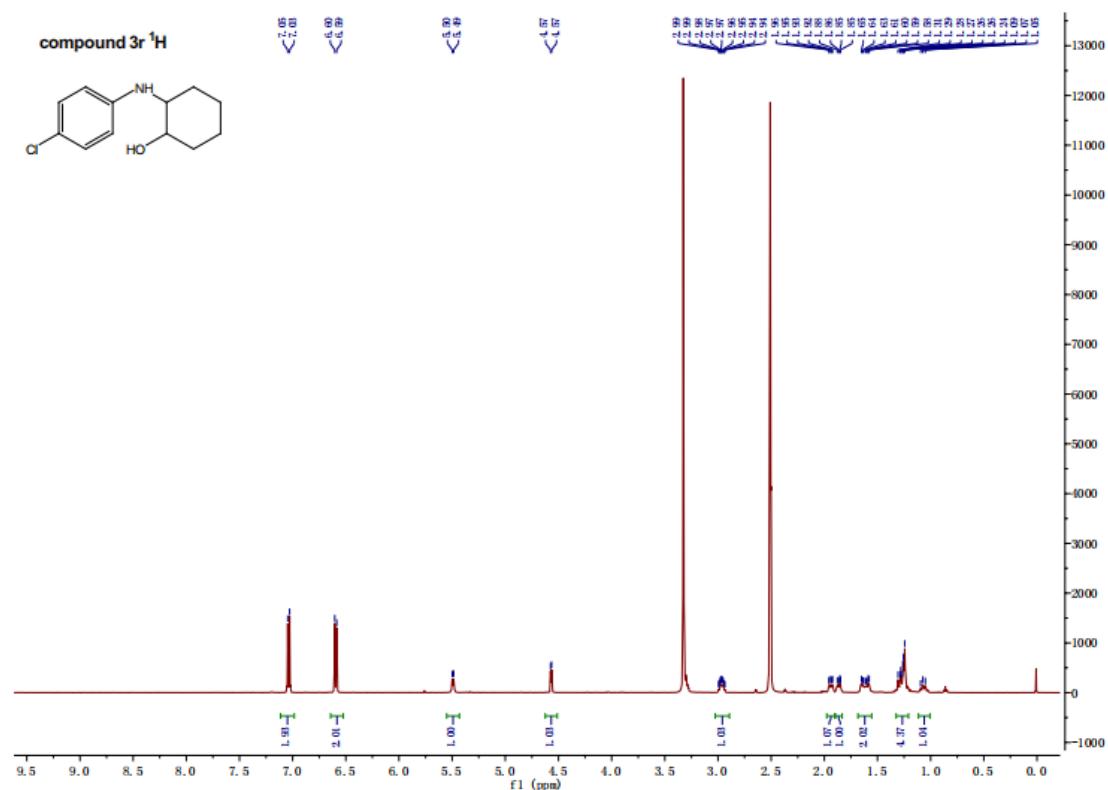




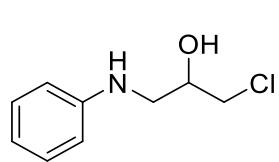




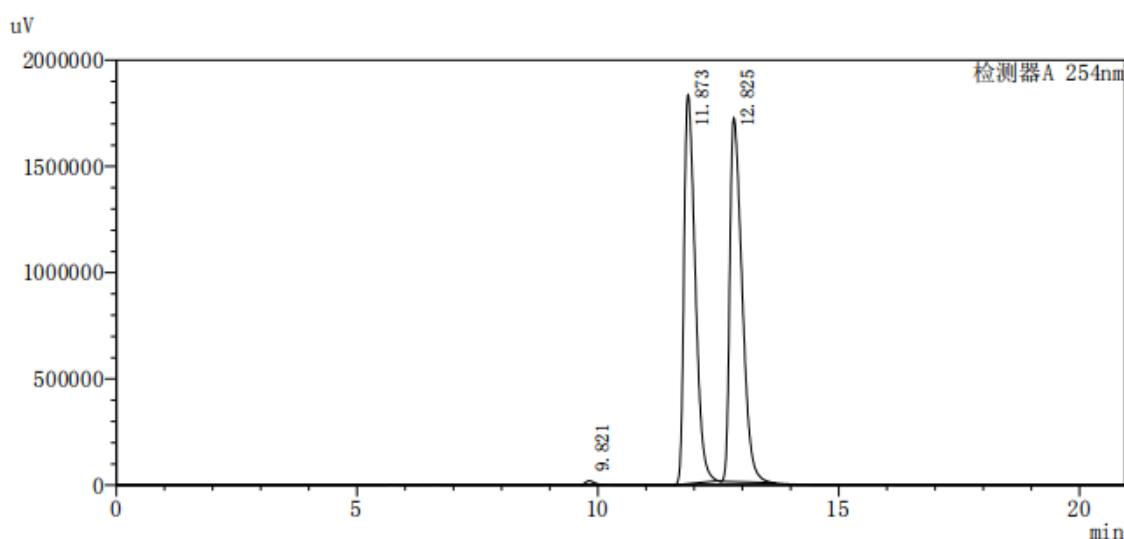




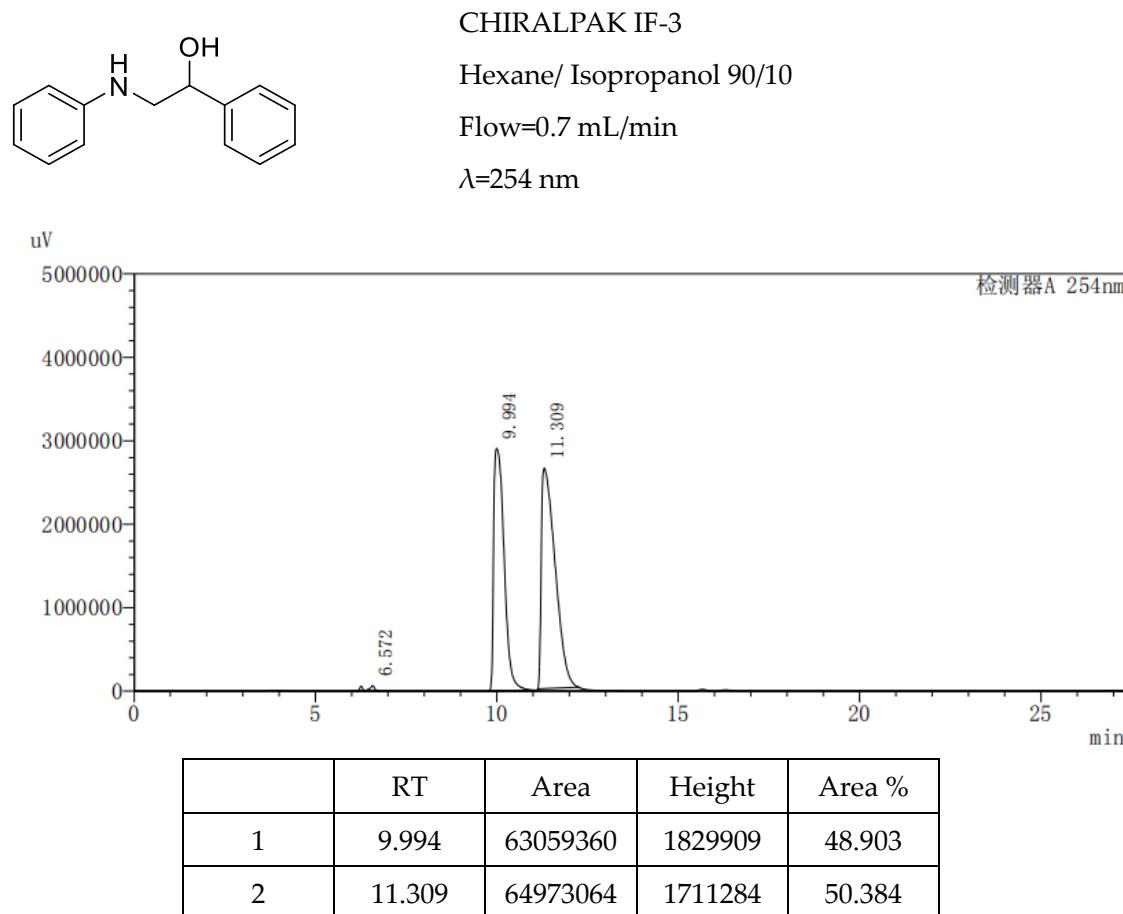
HPLC information

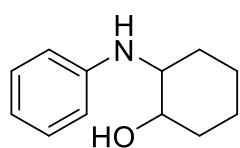


CHIRALPAK IF-3
Hexane/ Isopropanol 90/10
Flow=0.7 mL/min
 $\lambda=254\text{ nm}$



	RT	Area	Height	Area %
1	11.873	29569938	1829909	49.170
2	12.825	30345817	1711284	50.460

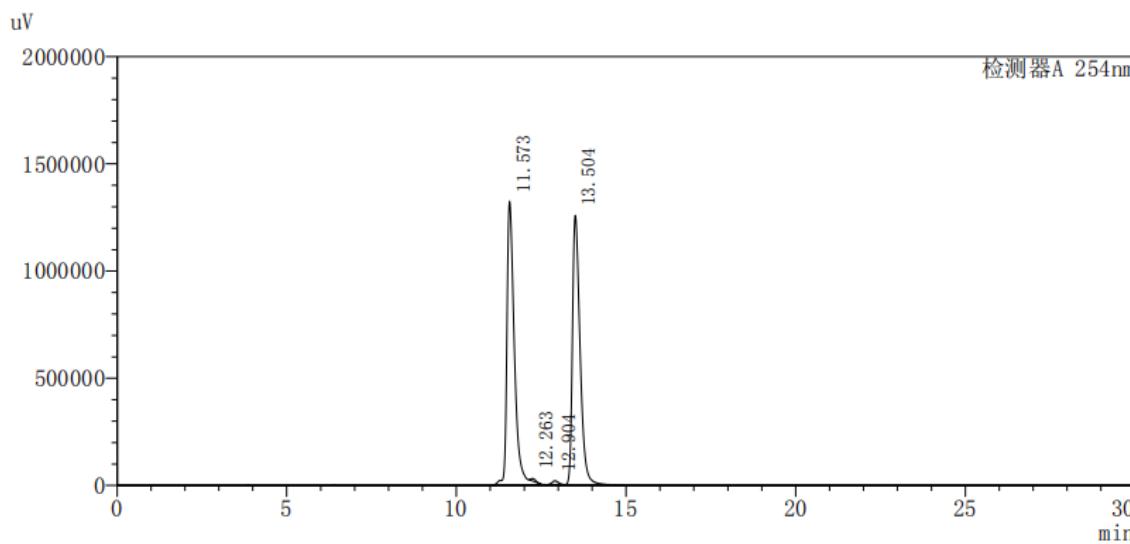




CHIRALPAK IF-3

Hexane/ Isopropanol 90/10

Flow=0.7 mL/min

 $\lambda=254\text{ nm}$ 

	RT	Area	Height	Area %
1	11.573	20136289	1320926	48.903
2	13.504	19613239	1256418	50.384

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