SUPPLEMENTARY MATERIAL

Contents

1. General Information

NMR of Prodrugs

All commercially available reagents and solvents were purchased and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian 400 MHz or Varian 600 MHz spectrometers in CD_3OD or $CDCl_3$ as indicated. For spectra recorded in CD_3OD, chemical shifts are reported in ppm with CD_3OD (3.31 ppm) as reference for ^{1}H NMR spectra and CD_3OD (49.0 ppm) for ^{13}C NMR spectra. Alternatively, for spectra recorded in $CDCl_3$, chemical shifts are reported in ppm relative to $CDCl_3$ (7.26 ppm for ^{1}H NMR, 77.23 ppm for ^{13}C NMR). The coupling constants (*J* value) are reported as Hertz (Hz). The splitting patterns of the peaks were described as: singlet (s); doublet (d); triplet (t); quartet (q); multiplet (m) and septet (septet).

Chromatographic Analysis of Prodrugs

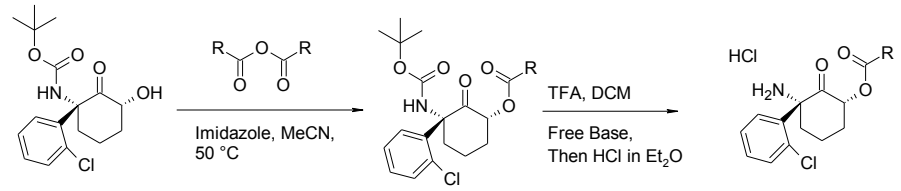
Samples were analyzed for purity on an Agilent 1200 series LC/MS equipped with a Luna C18 (3 mm x 75 mm, 3 µm) reversed-phase column with UV detection at λ=220 nm and λ=254 nm. The mobile phase consisted of water containing 0.05% trifluoroacetic acid as component A and acetonitrile containing 0.025% trifluoroacetic acid as component B. A linear gradient was run as follows: 0 min 4% B; 7 min 100% B; 8 min 100% B; at a flow rate of 0.8 ml/min. High resolution mass spectrometry (HRMS) was recorded on Agilent 6210 Time-of-Flight (TOF) LC/MS system. Optical rotations were measured on a PerkinElmer model 341 polarimeter using a 10 cm cell, at 589 nM and room temperature.

Chiral Analysis of Prodrugs

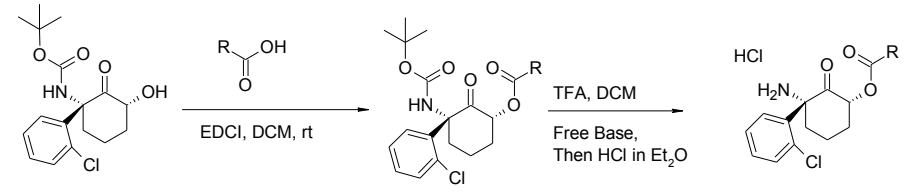
Chiral analysis was carried out with an Agilent 1200 series HPLC using an analytical Chiralpak AD or OJ column (4.6 mm x 250 mm; 5 µm). The mobile phase consisted of ethanol containing 0.1% diethylamine as component A and hexanes containing 0.1% diethylamine as component B. An isocratic elution was run at 0.4 ml/min with 60% A.

2. Synthetic Schemes

Scheme 1:



Scheme 2:



Note, the synthesis of the starting material *tert*-butyl ((*1R,3R*)-1-(2-chlorophenyl)-3-hydroxy-2-oxocyclohexyl)carbamate has been previously described in Zanos *et al*.[1]

3. Synthetic methods and analytical data

(1R,3R)-3-((tert-butoxycarbonyl)amino)-3-(2-chlorophenyl)-2-oxocyclohexyl acetate

Acetic anhydride (406 mg, 3.97 mmol, 0.375 ml) was added to a solution of tert-butyl ((1R,3R)-1-(2-chlorophenyl)-3-hydroxy-2-oxocyclohexyl)carbamate (450 mg, 1.32 mmol) in acetonitrile (4.0 ml). Then imidazole (270 mg, 3.97 mmol) was added as a solid. The reaction was heated to 50 °C and stirred for 16 h under a nitrogen atmosphere. The reaction was then cooled, washed with aqueous saturated sodium bicarbonate and extracted into ethyl acetate. The organic solvent was removed by rotary evaporation to give the crude product. Purification by silica gel chromatography (0% to 60% ethyl acetate in hexanes) gave the desired product in 63.5% yield (321 mg) as a white solid.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.79 – 7.69 (m, 1H), 7.41 – 7.22 (m, 3H), 6.59 (s, 1H), 5.13 (dd, *J* = 11.9, 6.3 Hz, 1H), 3.86 (d, *J* = 14.6 Hz, 1H), 2.36 – 2.20 (m, 1H), 2.11 (d, *J* = 0.7 Hz, 3H), 1.99 – 1.63 (m, 4H), 1.29 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.6, 169.3, 153.2, 134.2, 133.7, 131.4, 131.1, 129.7, 126.2, 79.3, 73.5, 67.2, 38.5, 35.7, 28.2, 20.7, 19.8. HRMS: *m/z* (M+Na) = 404.1253 Calculated for $C_{19}H_{24}ClNNaO_5$ = 404.1241. $[\alpha]_D^{20}$: -34.3 ° (*c* 1.0, $CHCl_3$).

2a *((1R,3R)-3-amino-3-(2-chlorophenyl)-2-oxocyclohexyl acetate hydrochloride)*

Trifluoroacetic acid (1.48 g, 13.0 mmol, 1.00 ml) was added to a solution of (*1R,3R*)-3-((tert-butoxycarbonyl)amino)-3-(2-chlorophenyl)-2-oxocyclohexyl acetate (255 mg, 0.668 mmol) in dichloromethane (2.0 ml). The reaction was stirred for 1 h at room temperature under ambient atmosphere. The solvent and excess trifluoroacetic acid were then removed by rotary evaporation to give the crude trifluoroacetic acid salt. The crude material was dissolved in a mixture of water and ethyl acetate, transferred to a separatory funnel, washed with saturated aqueous sodium bicarbonate, and extracted into ethyl acetate. The organic phase was collected, and the solvent removed by rotary evaporation. The resulting material was dissolved in diethyl ether (10 ml) and hydrochloric acid (HCl) in diethyl ether (2.0 M, 1.0 mmol, 0.5 ml) was added. A white solid immediately precipitated from solution. The organic solvent was removed by rotary evaporation, and the resulting white solid (156 mg, 73.4% yield) was collected and utilized without further purification.

^{1}H NMR (400 MHz, CD3OD) δ 7.90 – 7.84 (m, 1H), 7.64 – 7.51 (m, 3H), 5.31 (dd, J = 11.8, 6.7 Hz, 1H), 3.40 – 3.31 (m, 1H), 2.37 – 2.27 (m, 1H), 2.11 (s, 3H), 2.06 – 1.95 (m, 2H), 1.95 – 1.73 (m, 2H). ^{13}C NMR (101 MHz, CD3OD) δ 202.4, 170.9, 135.6, 133.6, 133.4, 132.0, 131.1, 129.6, 75.4, 69.0, 38.0, 35.9, 20.4, 20.1. HRMS: m/z (M+H) 282.0903. Calculated for C14H17ClNO3 = 282.0897. [α]D20: -50.1° (c 1.0, H20).

(1R,3R)-3-((tert-butoxycarbonyl)amino)-3-(2-chlorophenyl)-2-oxocyclohexyl propionate

Proprionic anhydride (508 mg, 3.90 mmol, 0.500 ml) was added to a solution of tert-butyl ((1R,3R)-1-(2-chlorophenyl)-3-hydroxy-2-oxocyclohexyl)carbamate (300 mg, 0.883 mmol) in acetonitrile (4.0 ml). Then imidazole (500 mg, 7.34 mmol) was added as a solid. The reaction was heated to 50 °C and stirred for 16 h under a nitrogen atmosphere. The reaction was then cooled, washed with aqueous saturated sodium bicarbonate and extracted into ethyl acetate. The organic solvent was removed by rotary evaporation to give the crude product. Purification by

silica gel chromatography (0% to 60% ethyl acetate in hexanes) gave the desired product in 87.0% yield (303 mg) as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.71 (m, 1H), 7.43 – 7.21 (m, 3H), 6.59 (s, 1H), 5.14 (dd, *J* = 12.0, 6.4 Hz, 1H), 3.85 (d, *J* = 14.5 Hz, 1H), 2.50 – 2.30 (m, 2H), 2.30 – 2.22 (m, 1H), 1.94 – 1.63 (m, 4H), 1.16 (s, 9H), 1.13 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.7, 172.8, 153.2, 134.2, 133.7, 131.4, 131.1, 129.6, 126.2, 79.3, 73.3, 67.1, 38.5, 35.7, 28.2, 27.3, 19.8, 9.0. HRMS: *m/z* (M+Na) 418.1405. Calculated for $C_{20}H_{26}ClNNaO_5$ = 418.1397. $[\alpha]_D^{20}$: -27.5 ° (*c* 1.0, $CHCl_3$)

2b *((1R,3R)-3-amino-3-(2-chlorophenyl)-2-oxocyclohexyl propionate hydrochloride)*

Trifluoroacetic acid (1.48 g, 13.0 mmol, 1.00 ml) was added to a solution of (*1R,3R*)-3-((tert-butoxycarbonyl)amino)-3-(2-chlorophenyl)-2-oxocyclohexyl propionate (230 mg, 0.581 mmol) in dichloromethane (3.0 ml). The reaction was stirred for 1 h at room temperature under ambient atmosphere. The solvent and excess trifluoroacetic acid were then removed by rotary evaporation to give the crude trifluoroacetic acid salt. The crude material was dissolved in a mixture of water and ethyl acetate, transferred to a separatory funnel, washed with saturated aqueous sodium bicarbonate, and extracted into ethyl acetate. The organic phase was collected, and the solvent removed by rotary evaporation. The resulting material was dissolved in diethyl ether (10 ml) and HCl in diethyl ether (2.0 M, 1.0 mmol, 0.5 ml) was added. A white solid immediately precipitated from solution. The organic solvent was removed by rotary evaporation, and the resulting white solid (150 mg, 78.0% yield) was collected and utilized without further purification.
^{1}H NMR (400 MHz, CD3OD) δ 7.91 – 7.83 (m, 1H), 7.66 – 7.49 (m, 3H), 5.32 (dd, J = 11.8, 6.7 Hz, 1H), 3.41 – 3.31 (m, 1H), 2.51 – 2.37 (m, 2H), 2.37 – 2.29 (m, 1H), 2.05 – 1.94 (m, 2H), 1.94 – 1.77 (m, 2H), 1.13 (t, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, CD3OD) δ 202.4, 174.3, 135.6, 133.6, 133.4, 132.1, 131.0, 129.6, 75.2, 69.0, 38.0, 35.9, 27.9, 20.1, 9.3. HRMS: m/z (M+Na) 318.0859. Calculated for C15H18ClNNaO3 = 318.0873. [α]D20 : -52.0° (c 1.0, H20).

(1R,3R)-3-((tert-butoxycarbonyl)amino)-3-(2-chlorophenyl)-2-oxocyclohexyl pentanoate

Pentanoic acid (117 mg, 1.15 mmol) was added to a solution of tert-butyl ((*1R,3R*)-1-(2-chlorophenyl)-3-hydroxy-2-oxocyclohexyl)carbamate (300 mg, 0.883 mmol) in dichloromethane (5.0 ml). Then 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) (178 mg, 1.15 mmol), followed by 4-dimethylaminopyridine (21.5, 0.177 mmol) were added to the reaction as solids. The reaction stirred for 16 h at room temperature under a nitrogen atmosphere. The temperature was then raised to 30 °C, and the reaction was stirred for an additional 2 h. The reaction was then washed with aqueous saturated sodium bicarbonate and extracted with dichloromethane. The organic solvent was removed by rotary evaporation to give the crude product. Purification by silica gel chromatography (0% to 50% ethyl acetate in hexanes) gave the desired product in 42.5% yield (159 mg) as a viscous liquid.
^{1}H NMR (400 MHz, CDCl3) δ 7.80 – 7.71 (m, 1H), 7.45 – 7.23 (m, 3H), 6.61 (s, 1H), 5.15 (dd, J = 12.0, 6.4 Hz, 1H), 3.91 – 3.80 (m, 1H), 2.52 – 2.30 (m, 2H), 2.29 – 2.22 (m, 1H), 2.01 – 1.67 (m, 4H), 1.66 – 1.56 (m, 2H), 1.39 – 1.30 (m, 2H), 1.29 (bs, 9H), 0.90 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 202.8, 172.2, 153.3, 134.2, 133.7, 131.4, 131.1, 129.7, 126.2, 79.3, 73.2, 67.1, 38.5, 35.7, 33.7, 28.2, 26.9, 22.1, 19.8, 13.6. HRMS m/z (M+Na) 446.1693. Calculated for C22H30ClNNaO5 = 446.1710. [α]D20: - 26.8° (c 1.0, CHCl3)

2c *((1R,3R)-3-amino-3-(2-chlorophenyl)-2-oxocyclohexyl pentanoate hydrochloride)*

Trifluoroacetic acid (1.48 g, 13.0 mmol, 1.00 ml) was added to a solution of (*1R,3R*)-3-((tert-butoxycarbonyl)amino)-3-(2-chlorophenyl)-2-oxocyclohexyl pentanoate (127 mg, 0.300 mmol) in dichloromethane (4.0 ml). The reaction was stirred for 1 h at room temperature under ambient atmosphere. The solvent and excess trifluoroacetic acid were then removed by rotary evaporation to give the crude trifluoroacetic acid salt. The crude material was dissolved in a mixture of water and ethyl acetate, transferred to a separatory funnel, washed with saturated aqueous sodium bicarbonate, and extracted into ethyl acetate. The organic phase was collected, and the solvent removed by rotary evaporation. The resulting material was dissolved in diethyl ether (10 ml) and HCl in diethyl ether (2.0 M, 1.0 mmol, 0.5 ml) was added. A white solid immediately precipitated from solution. The organic solvent was removed by rotary evaporation, and the resulting white solid (84.8 mg, 79.0% yield) was collected and utilized without further purification.

^{1}H NMR (400 MHz, CD3OD) δ 7.89 – 7.81 (m, 1H), 7.64 – 7.48 (m, 3H), 5.32 (dd, J = 11.9, 6.8 Hz, 1H), 3.35 (dd, J = 13.4, 2.5 Hz, 1H), 2.47 – 2.35 (m, 2H), 2.35 – 2.27 (m, 1H), 2.09 – 1.96 (m, 2H), 1.96 – 1.78 (m, 2H), 1.69 – 1.54 (m, 2H), 1.47 – 1.32 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, CD3OD) δ 202.4, 173.6, 135.6, 133.6, 133.4, 132.1, 131.0, 129.6, 75.1, 69.0, 37.9, 35.9, 34.4, 28.1, 23.1, 20.1, 14.0. HRMS m/z (M+H) 324.1355. Calculated for C17H23ClNO5 = 324.1366. [α]D20: -44.7° (c 1.0, EtOH).

(1R,3R)-3-((tert-butoxycarbonyl)amino)-3-(2-chlorophenyl)-2-oxocyclohexyl octanoate

Octanoic acid (121 mg, 0.842 mmol) was added to a solution of tert-butyl ((*1R,3R*)-1-(2-chlorophenyl)-3-hydroxy-2-oxocyclohexyl)carbamate (300 mg, 0.883 mmol) in dichloromethane (5.0 ml). Then 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) (131 mg, 0.842 mmol), followed by 4-dimethylaminopyridine (15.8, 0.129 mmol) were added to the reaction as solids. The reaction stirred for 16 h at room temperature under a nitrogen atmosphere. The temperature was then raised to 30 °C, and the reaction was stirred for an additional 2 h. The reaction was then washed with aqueous saturated sodium bicarbonate and extracted with dichloromethane. The organic solvent was removed by rotary evaporation to give the crude product. Purification by silica gel chromatography (0% to 50% ethyl acetate in hexanes) gave the desired product in 47.7% yield (144 mg) as a viscous liquid.

^{1}H NMR (400 MHz, CDCl3) δ 7.79 – 7.71 (m, 1H), 7.41 – 7.25 (m, 3H), 6.60 (s, 1H), 5.16 (dd, J = 12.5, 6.3 Hz, 1H), 3.90 – 3.80 (m, 1H), 2.45 – 2.30 (m, 2H), 2.30 – 2.22 (m, 1H), 1.97 – 1.68 (m, 4H), 1.66 – 1.56 (m, 2H), 1.37 – 1.12 (m, 17H), 0.86 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 202.8, 172.2, 153.3, 134.2, 133.7, 131.4, 131.1, 129.6, 126.2, 79.3, 73.2, 67.1, 38.5, 35.7, 34.0, 31.6, 28.9, 28.8, 28.2, 24.9, 22.5, 19.8, 14.0. HRMS m/z (M+Na) 488.2177. Calculated for C25H36ClNNaO5 = 488.2179. [α]D20: - 30.0°, (c 1.0, CHCl3).

2d *((1R,3R)-3-amino-3-(2-chlorophenyl)-2-oxocyclohexyl octanoate hydrochloride)*

Trifluoroacetic acid (1.48 g, 13.0 mmol, 1.00 ml) was added to a solution of (*1R,3R*)-3-((tert-butoxycarbonyl)amino)-3-(2-chlorophenyl)-2-oxocyclohexyl octanoate (115 mg, 0.247 mmol) in dichloromethane (4.0 ml). The reaction was stirred for 1 h at room temperature under ambient atmosphere. The solvent and excess trifluoroacetic acid were then removed by rotary evaporation to give the crude trifluoroacetic acid salt. The crude material was dissolved in a

mixture of water and ethyl acetate, transferred to a separatory funnel, washed with saturated aqueous sodium bicarbonate, and extracted into ethyl acetate. The organic phase was collected, and the solvent removed by rotary evaporation. The resulting material was dissolved in diethyl ether (10 ml) and HCl in diethyl ether (2.0 M, 1.0 mmol, 0.5 ml) was added. The organic solvent was removed by rotary evaporation, and the resulting off-white solid (70.3 mg, 70.8% yield) was collected and utilized without further purification.
^{1}H NMR (400 MHz, CD3OD) δ 7.92 – 7.82 (m, 1H), 7.66 – 7.49 (m, 3H), 5.32 (dd, J = 12.0, 7.2 Hz, 1H), 3.36 (dq, J = 14.0, 2.7 Hz, 1H), 2.50 – 2.36 (m, 2H), 2.34 – 2.29 (m, 1H), 2.11 – 1.98 (m, 2H), 1.98 – 1.79 (m, 2H), 1.73 – 1.55 (m, 2H), 1.44 – 1.20 (m, 8H), 0.89 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, CD3OD) δ 202.3, 173.6, 135.6, 133.6, 133.4, 132.1, 130.9, 129.6, 75.1, 69.0, 37.9, 35.9, 34.6, 32.8, 30.0, 30.0, 26.0, 23.6, 20.1, 14.4. HRMS m/z (M+H): 366.1824. Calculated for C20H29ClNO3 = 366.1836. [α]D20 :-53.7° (c 1.0, EtOH).

(1R,3R)-3-((tert-butoxycarbonyl)amino)-3-(2-chlorophenyl)-2-oxocyclohexyl benzoate

Benzoic anhydride (700 mg, 3.09 mmol) was added to a solution of tert-butyl ((*1R,3R*)-1-(2-chlorophenyl)-3-hydroxy-2-oxocyclohexyl)carbamate (350 mg, 1.03 mmol) in acetonitrile (4.0 ml). Then imidazole (500 mg, 7.34 mmol) was added as a solid. The reaction was heated to 50°C and stirred for 16 h under a nitrogen atmosphere. The reaction was then cooled, washed with aqueous saturated sodium bicarbonate and extracted into ethyl acetate. The organic solvent was removed by rotary evaporation to give the crude product. Purification by silica gel chromatography (0% to 60% ethyl acetate in hexanes) gave the desired product in 92.0% yield (420 mg) as a white solid.
^{1}H NMR (400 MHz, CDCl3) δ 8.09 (dt, J = 8.5, 1.4 Hz, 2H), 7.84 – 7.77 (1H), 7.60 – 7.50 (m, 1H), 7.50 – 7.24 (m, 5H), 6.64 (s, 1H), 5.45 – 5.35 (m, 3.91 (d, J = 14.5 Hz, 1H), 2.45 – 2.38 (m, 1H), 2.10 – 1.85 (m, 3H), 1.80 – 1.70 (m, 1H), 1.30 (s, 9H). ^{13}C NMR (101 MHz, CDCl3) δ 202.5, 164.9, 153.3, 134.2, 133.8, 133.5, 133.3, 131.4, 131.2, 130.1, 129.9, 129.7, 129.5, 128.3, 126.2, 79.4, 73.9, 67.2, 38.5, 35.9, 28.2, 19.9. HRMS m/z (M+Na) 466.1394. Calculated for C24H26ClNaNO5 = 466.1397. [α]D20 : -78.5 ° (c 1.0, CHCl3)

2e *((1R,3R)-3-amino-3-(2-chlorophenyl)-2-oxocyclohexyl benzoate hydrochloride)*

Trifluoroacetic acid (1.48 g, 13.0 mmol, 1.00 ml) was added to a solution of (*1R,3R*)-3-((tert-butoxycarbonyl)amino)-3-(2-chlorophenyl)-2-oxocyclohexyl benzoate (370 mg, 0.833 mmol) in dichloromethane (3.0 ml). The reaction was stirred for 1 h at room temperature under ambient atmosphere. The solvent and excess trifluoroacetic acid were then removed by rotary evaporation to give the crude trifluoroacetic acid salt. The crude material was dissolved in a mixture of water and ethyl acetate, transferred to a separatory funnel, washed with saturated aqueous sodium bicarbonate, and extracted into ethyl acetate. The organic phase was collected, and the solvent removed by rotary evaporation. The resulting material was dissolved in diethyl ether (10 ml) and HCl in diethyl ether (2.0 M, 1.0 mmol, 0.5 ml) was added. A white solid immediately precipitated from solution. The organic solvent was removed by rotary evaporation, and the resulting white solid (220 mg, 69.4% yield) was collected and utilized without further purification.
^{1}H NMR (400 MHz, CD3OD) δ 8.10 – 8.03 (m, 2H), 7.96 – 7.91 (m, 1H), 7.68 – 7.55 (m, 4H), 7.55 – 7.48 (m, 2H), 5.62 – 5.52 (m, 1H), 3.39 (d, J = 12.9 Hz, 1H), 2.53 – 2.45 (m, 1H), 2.14 – 1.92 (m, 4H). ^{13}C NMR (101 MHz, CD3OD) δ 202.3, 166.2, 135.7, 134.8, 133.7, 133.5, 132.1,

131.1, 130.8, 130.5, 129.7, 129.7, 75.9, 69.1, 38.0, 36.0, 20.1. HRMS m/z (M+Na): 366.0883. Calculated for C19H18ClNO5 = 366.0873. [α]D20: -77.2 ° (c 1.0, MeOH).

4. NMR Spectra

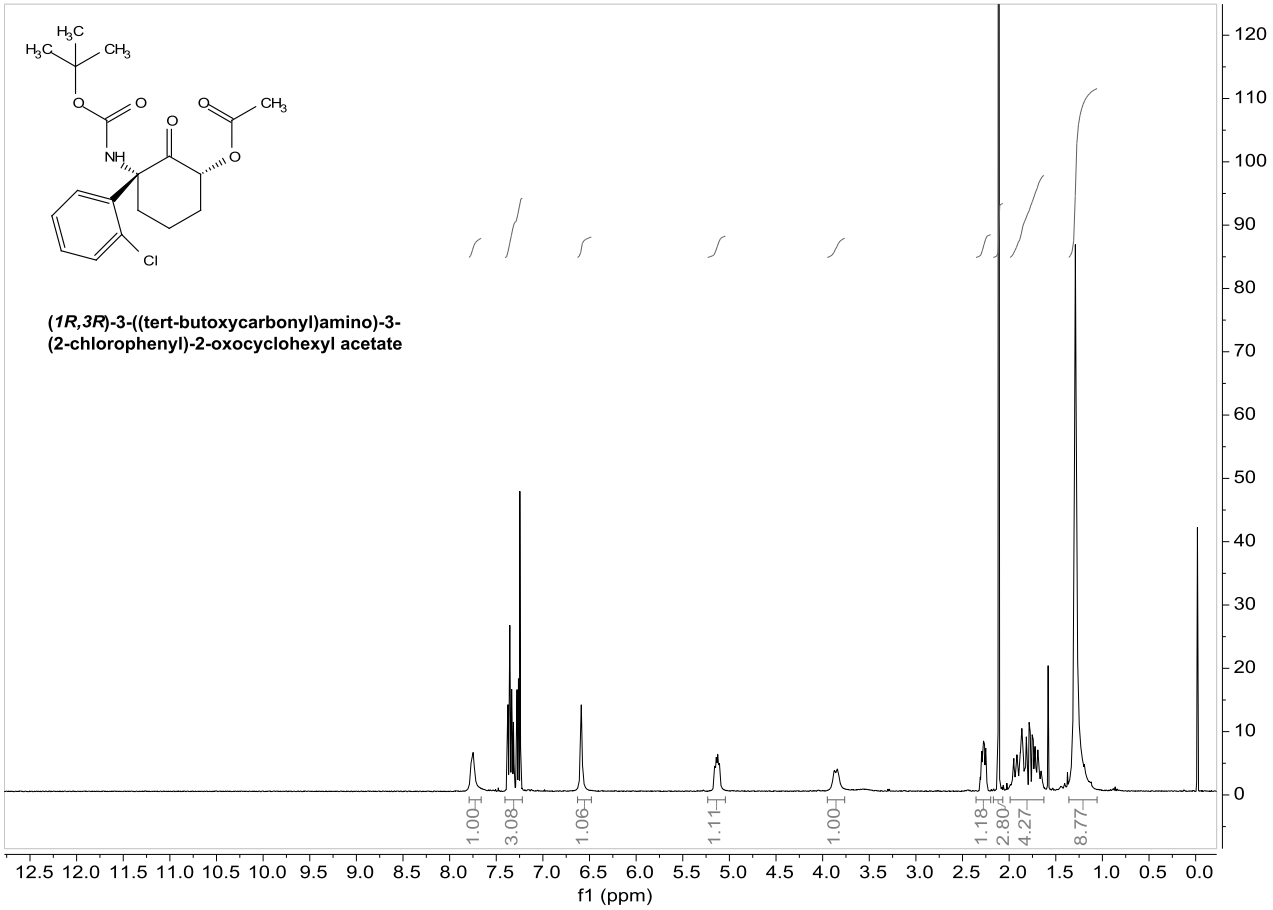


Figure S1. ^{1}H NMR spectrum of (*1R,3R*)-3-((tert-butoxycarbonyl)amino)-3-(2-chlorophenyl)-2-oxocyclohexyl acetate.

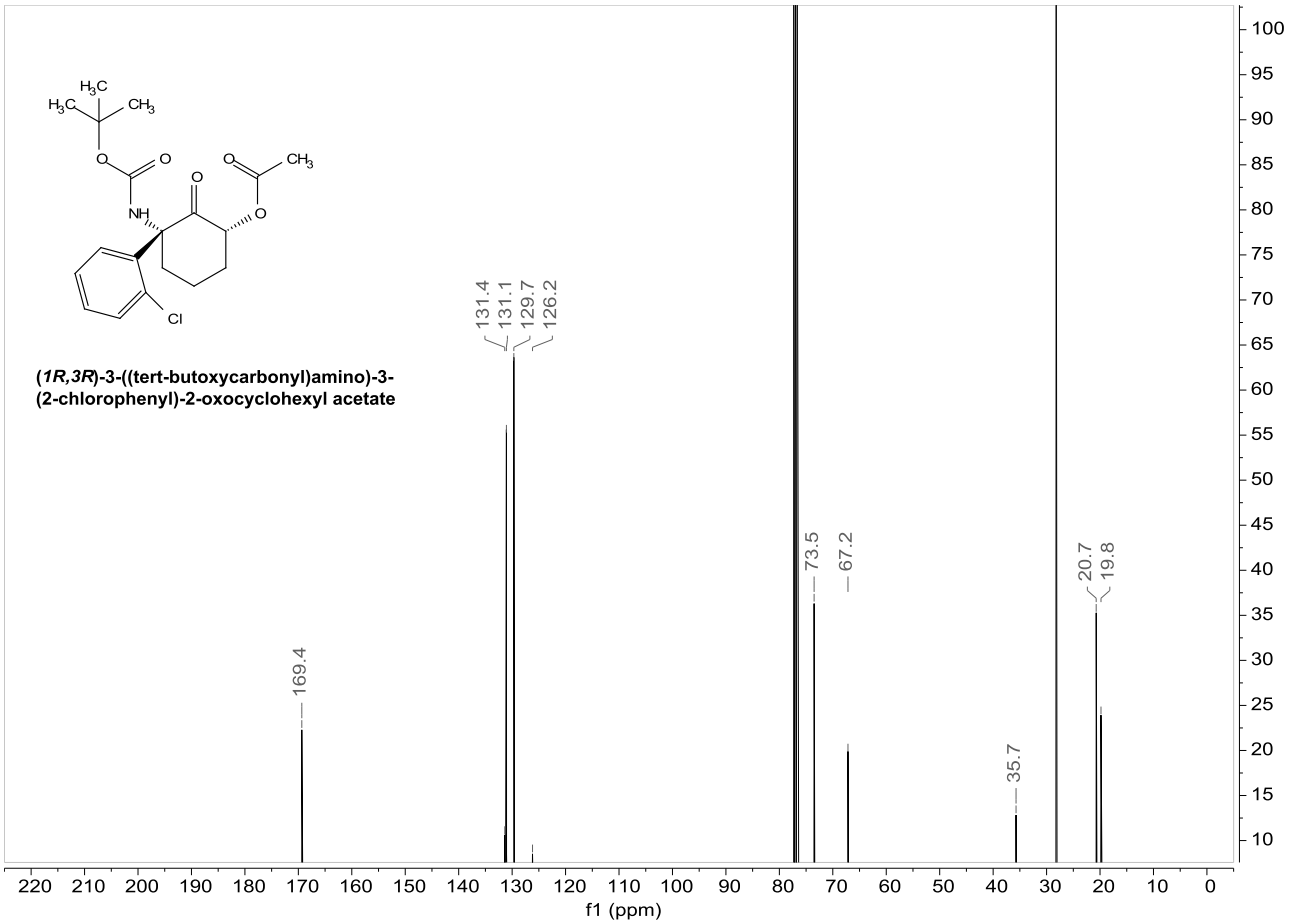


Figure S2. ^{13}C NMR spectrum of (*1R,3R*)-3-((tert-butoxycarbonyl)amino)-3-(2-chlorophenyl)-2-oxocyclohexyl acetate.

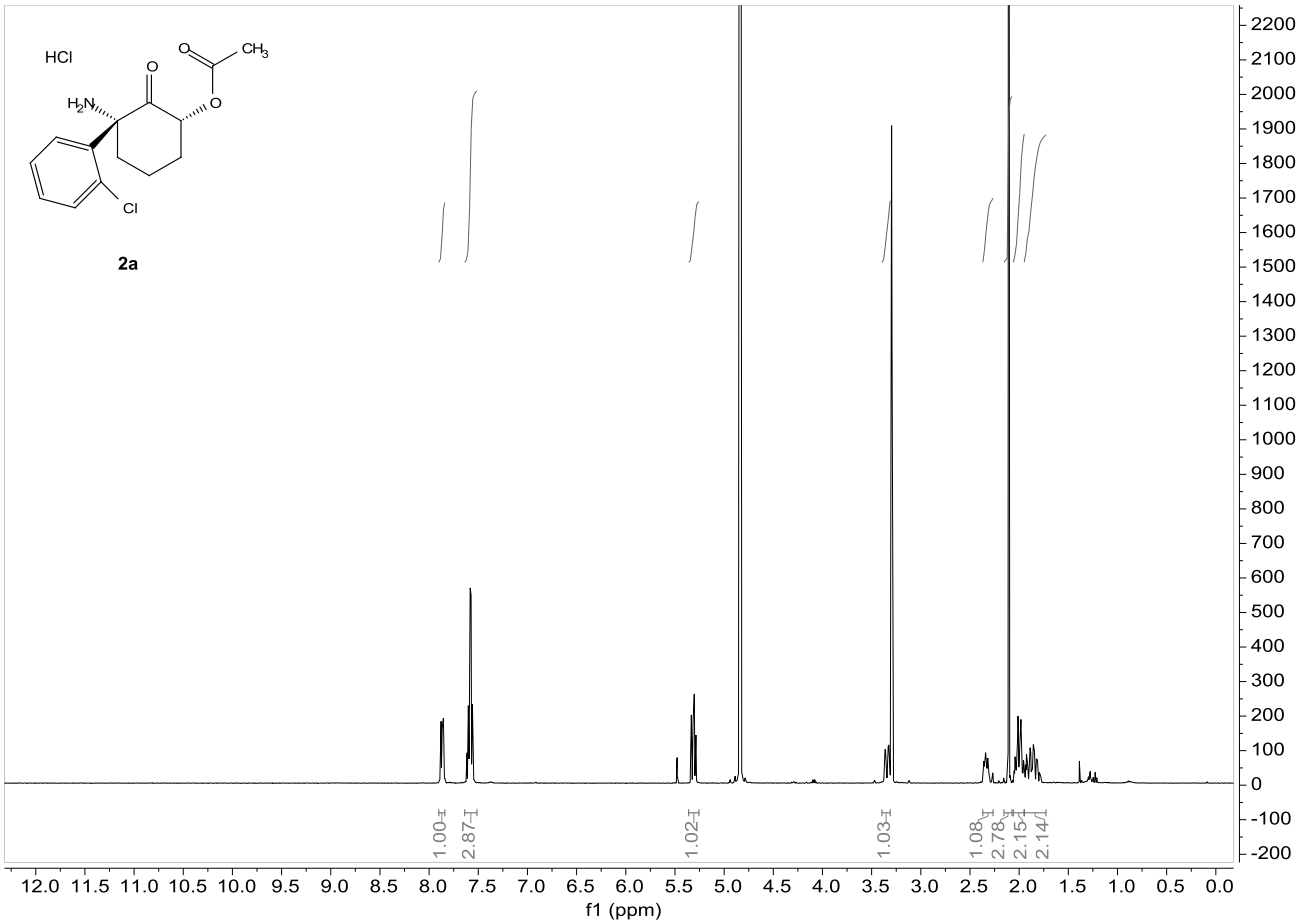


Figure S3. ^{1}H NMR spectrum of 2a.

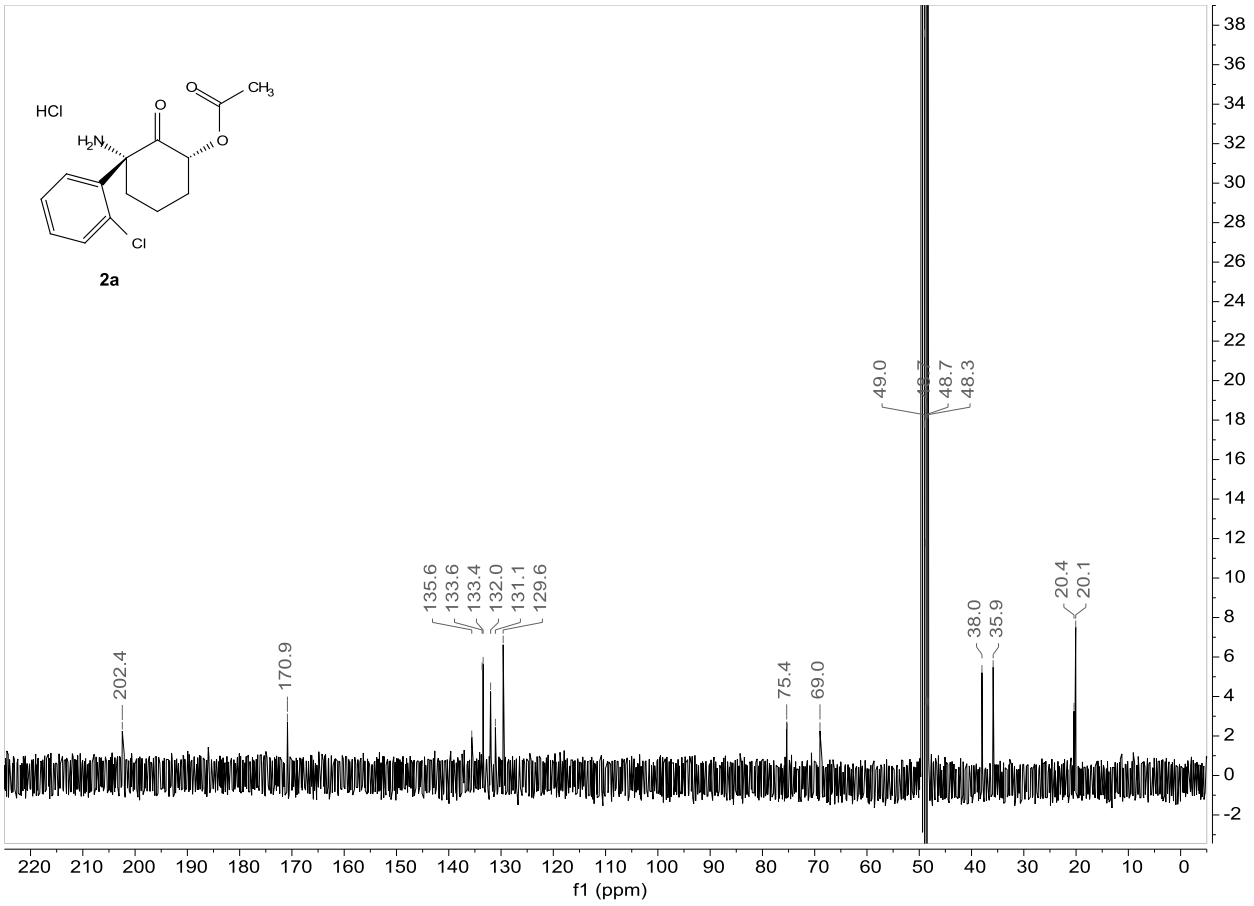


Figure S4. ^{13}C NMR spectrum of 2a.

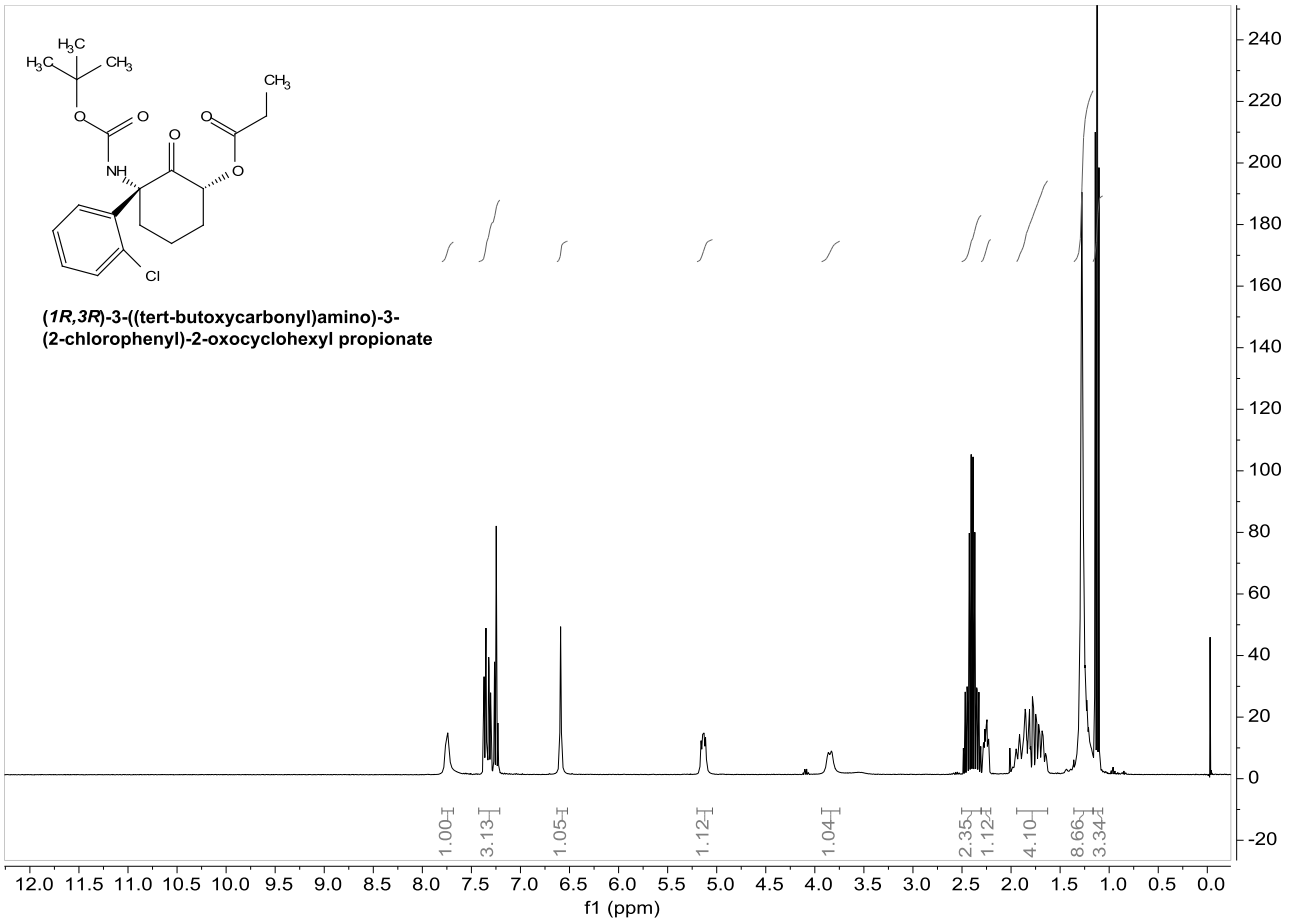


Fig S5. ^{1}H NMR spectrum of (*1R,3R*)-3-((tert-butoxycarbonyl)amino)-3-(2-chlorophenyl)-2-oxocyclohexyl propionate.

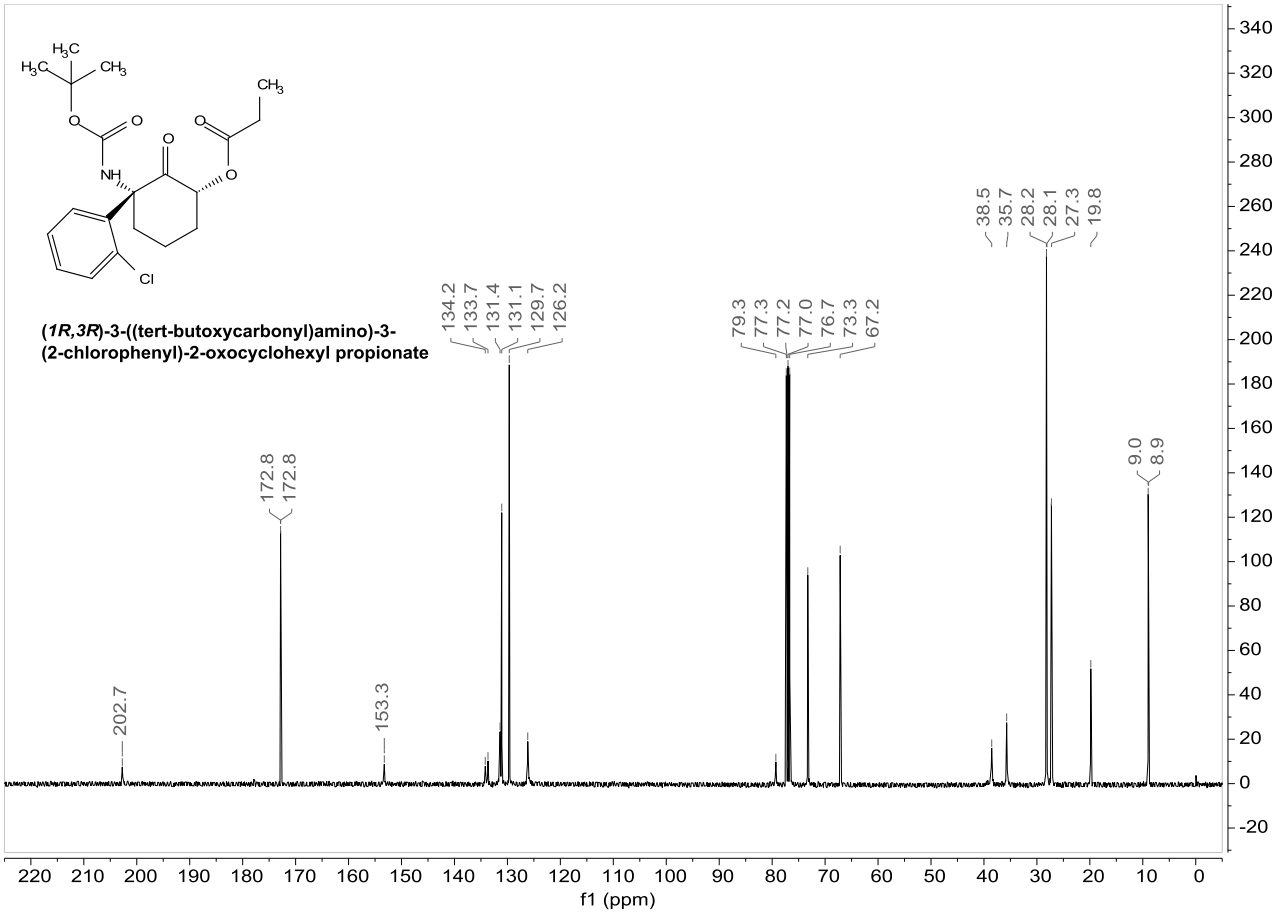


Fig S6. ^{13}C NMR spectrum of (*1R,3R*)-3-((tert-butoxycarbonyl)amino)-3-(2-chlorophenyl)-2-oxocyclohexyl propionate.

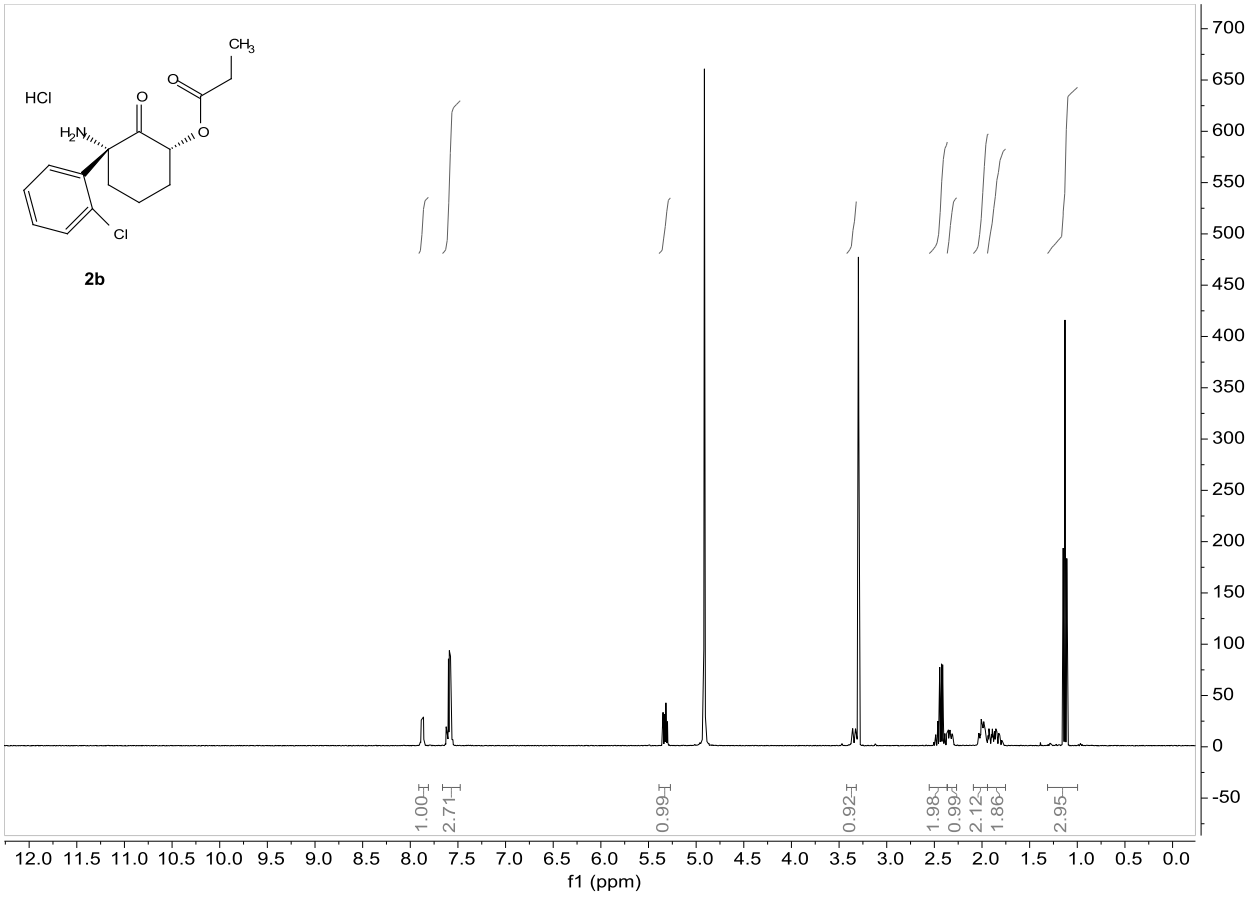


Fig S7. ^{1}H NMR spectrum of 2b.

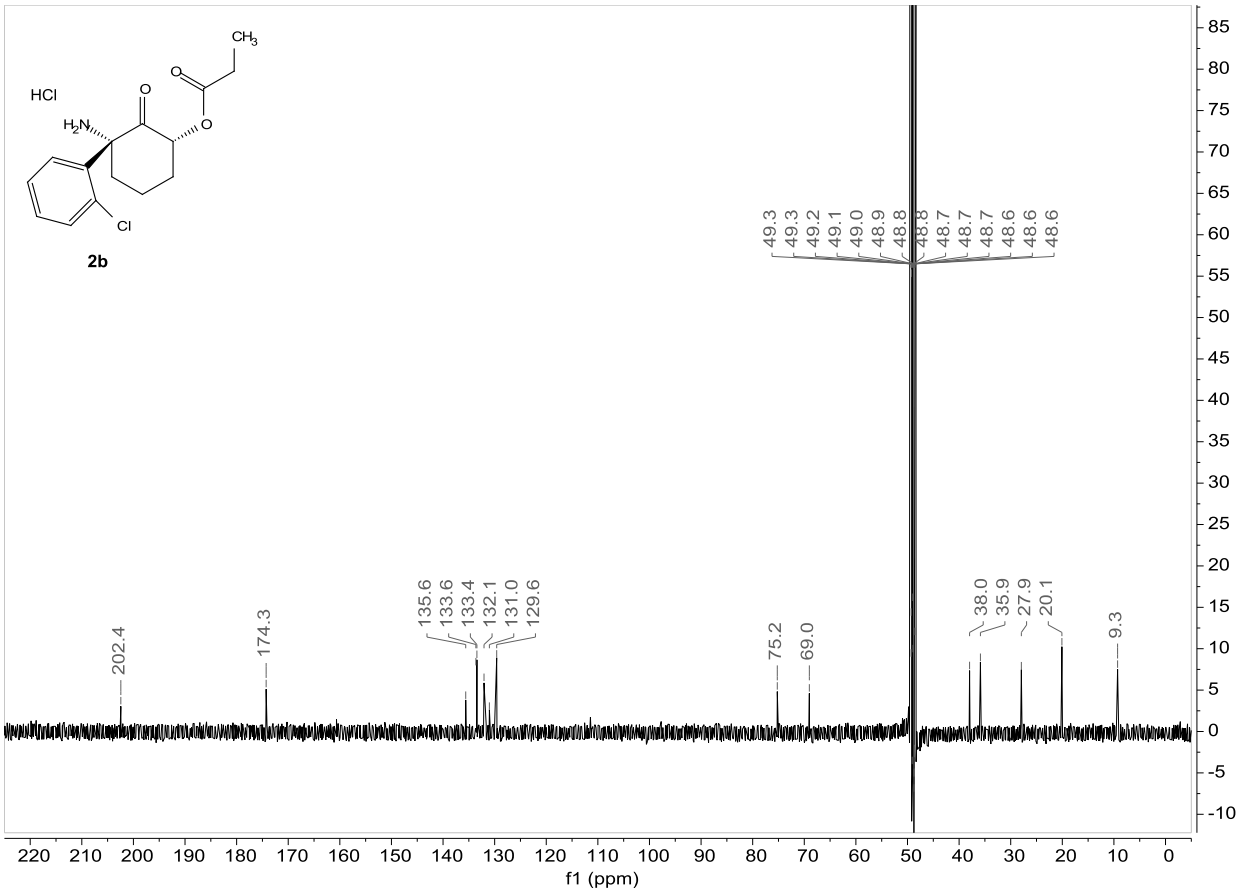


Fig S8. ^{13}C NMR spectrum of 2b.

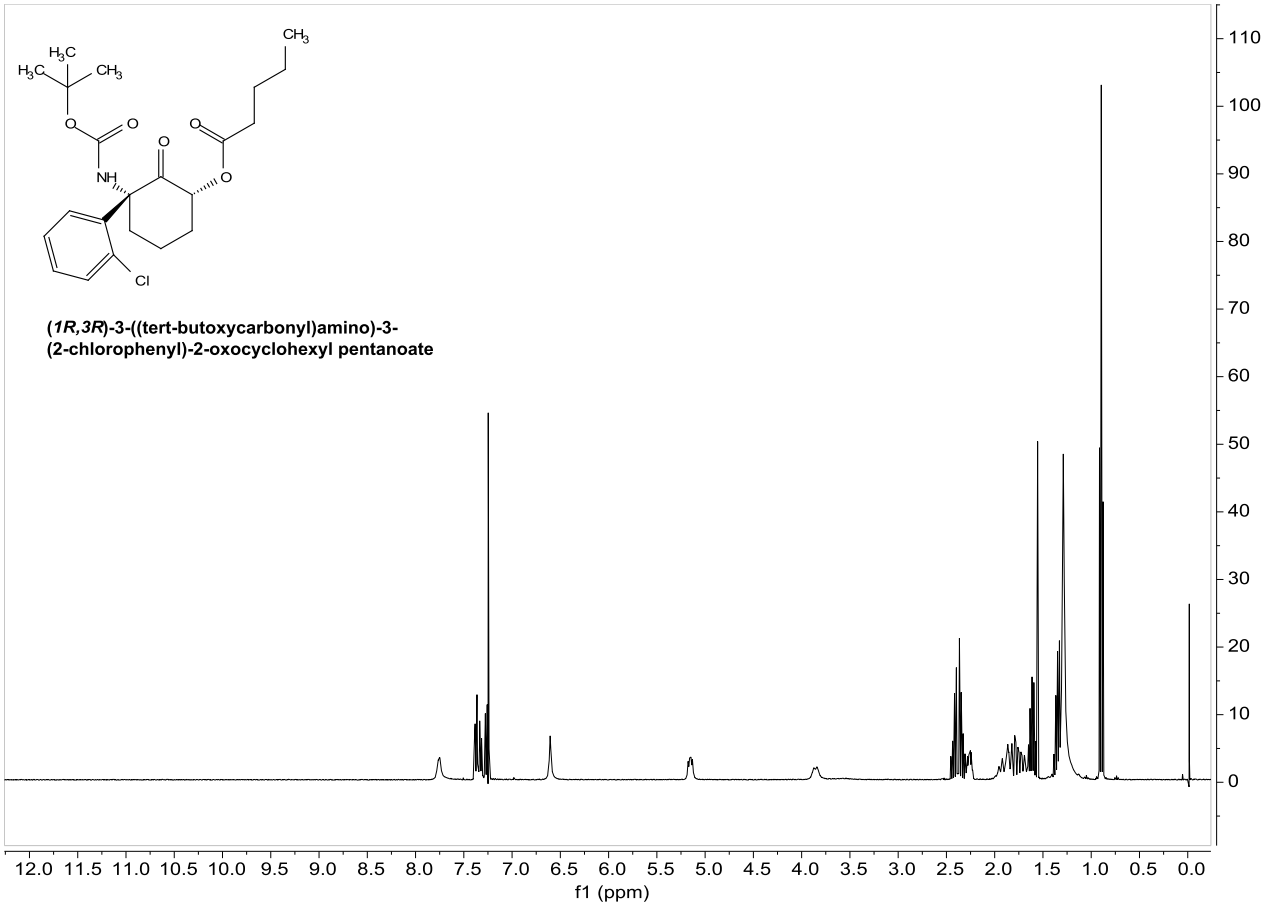


Fig S9. ^{1}H NMR spectrum of (*1R,3R*)-3-((tert-butoxycarbonyl)amino)-3-(2-chlorophenyl)-2-oxocyclohexyl pentanoate.

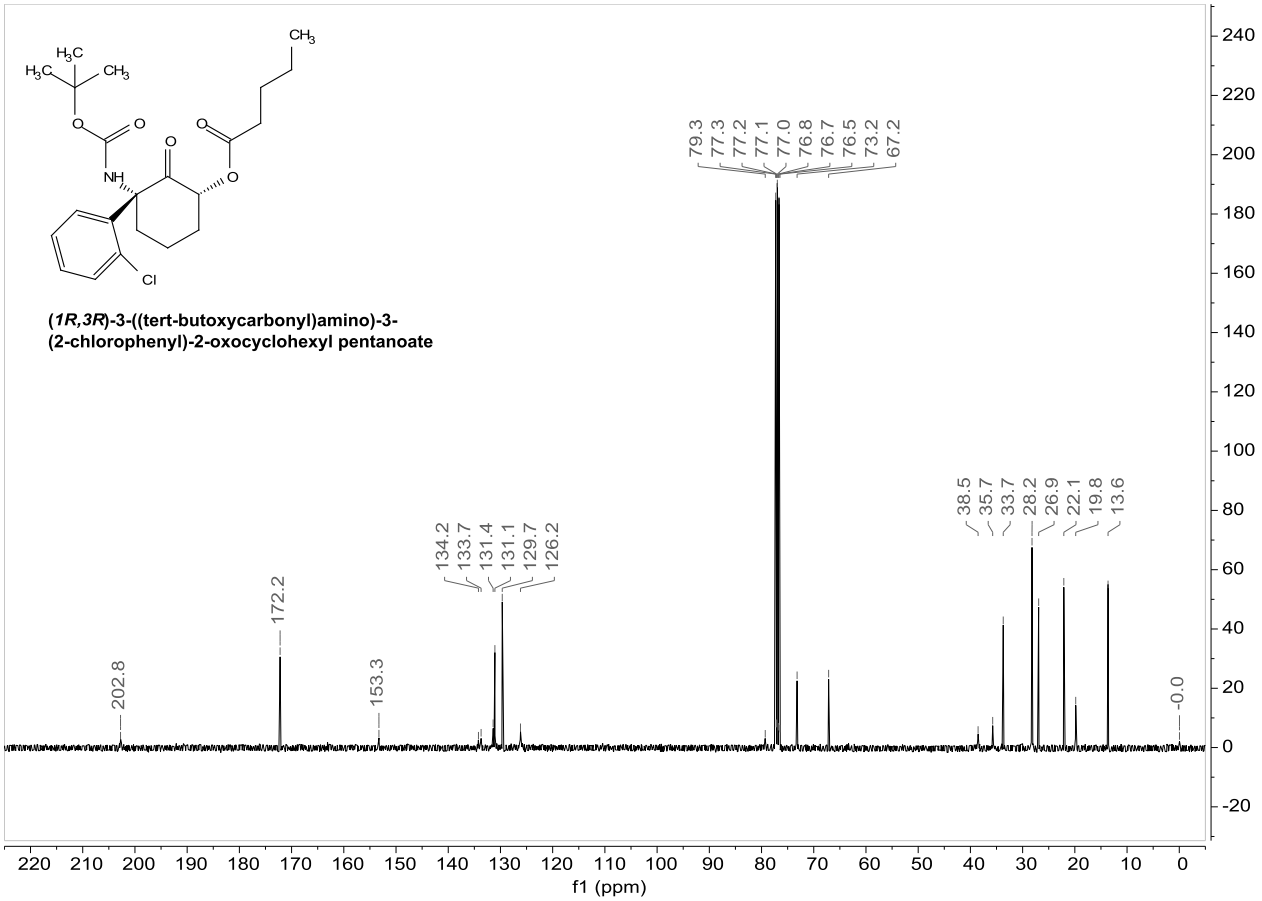


Fig S10. ^{13}C NMR spectrum of (*1R,3R*)-3-((tert-butoxycarbonyl)amino)-3-(2-chlorophenyl)-2-oxocyclohexyl pentanoate.

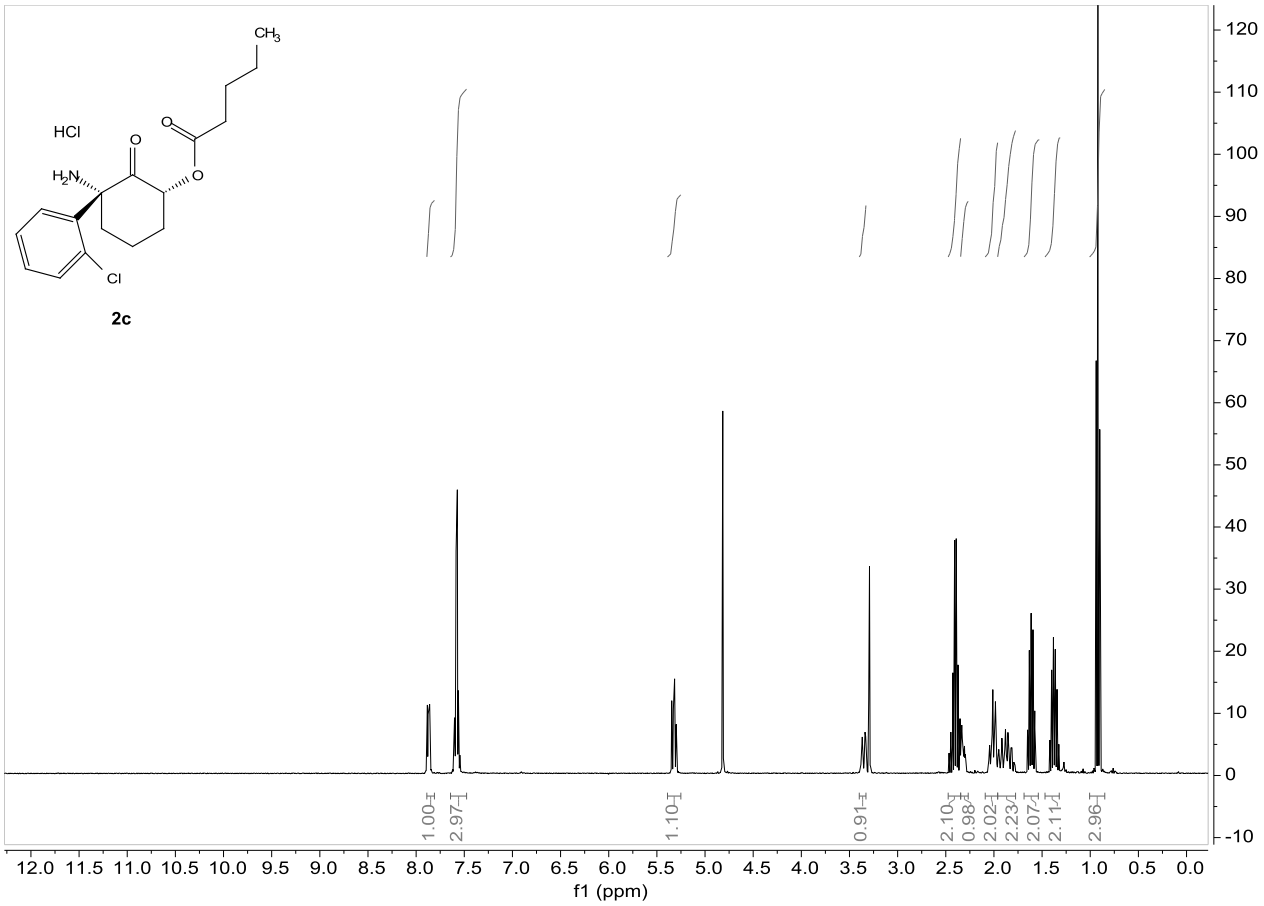


Fig S11. ^{1}H NMR spectrum of 2c.

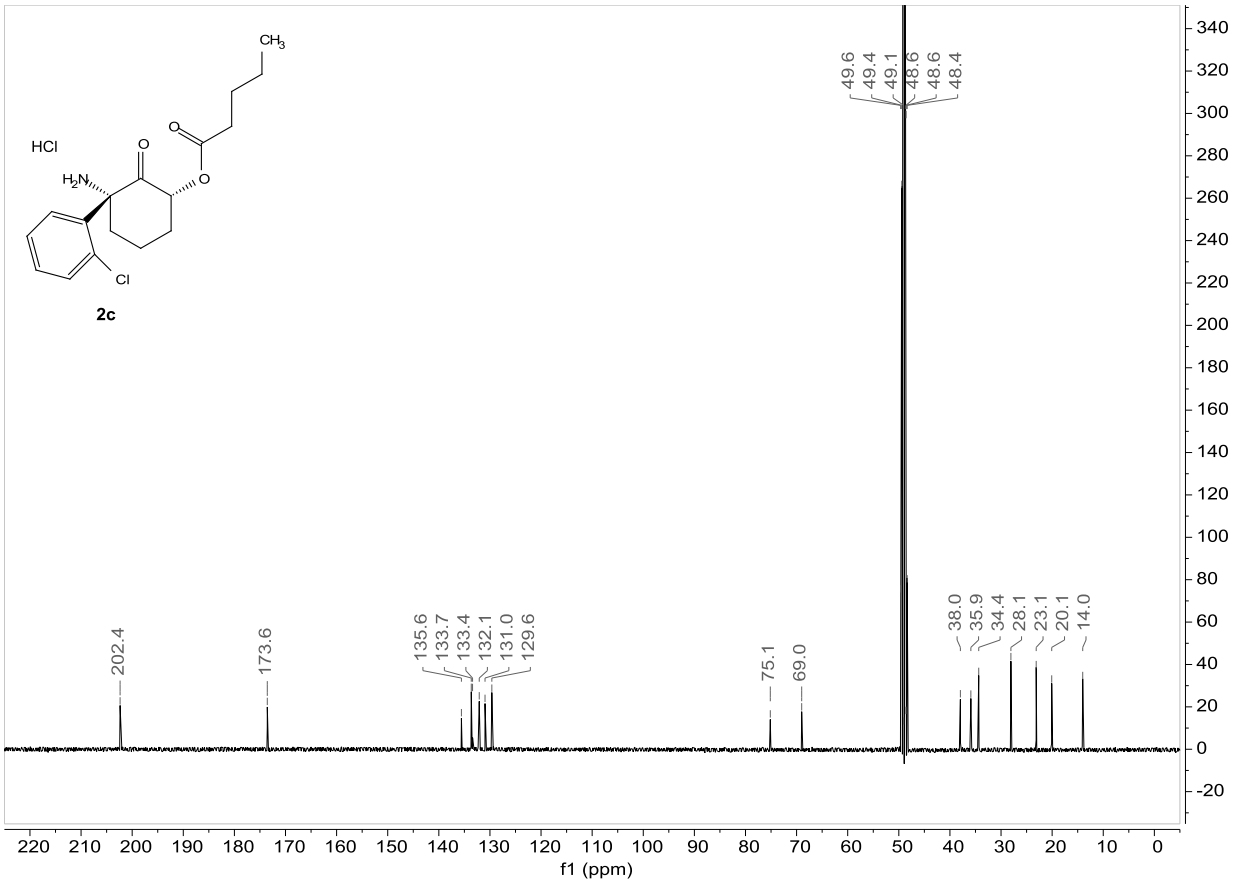


Fig S12. ^{13}C NMR spectrum of 2c.

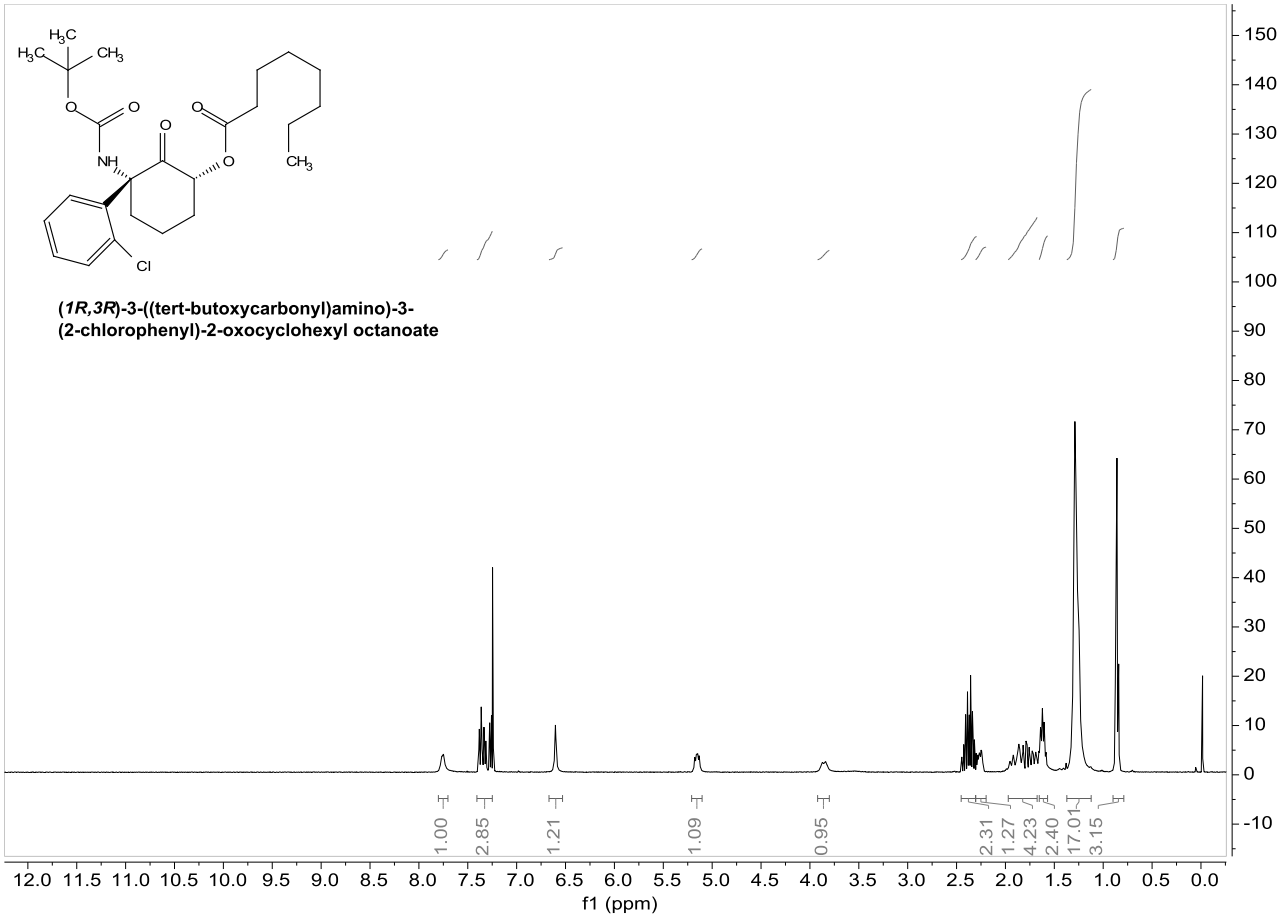
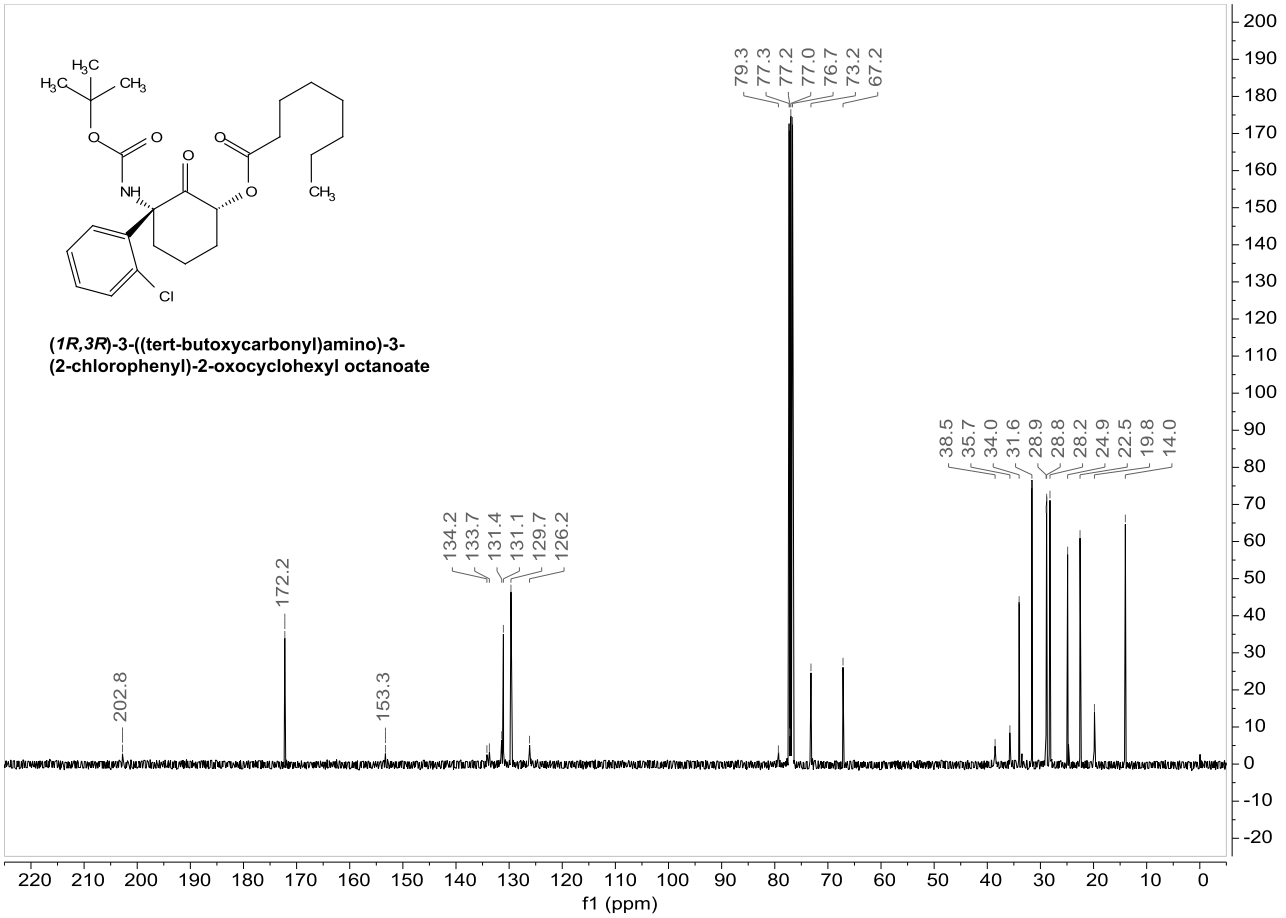


Fig S13. ^{1}H NMR spectrum of (*1R,3R*)-3-((tert-butoxycarbonyl)amino)-3-(2-chlorophenyl)-2-oxocyclohexyl octanoate.



S14. ^{13}C NMR spectrum of (*1R,3R*)-3-((tert-butoxycarbonyl)amino)-3-(2-chlorophenyl)-2-oxocyclohexyl octanoate.

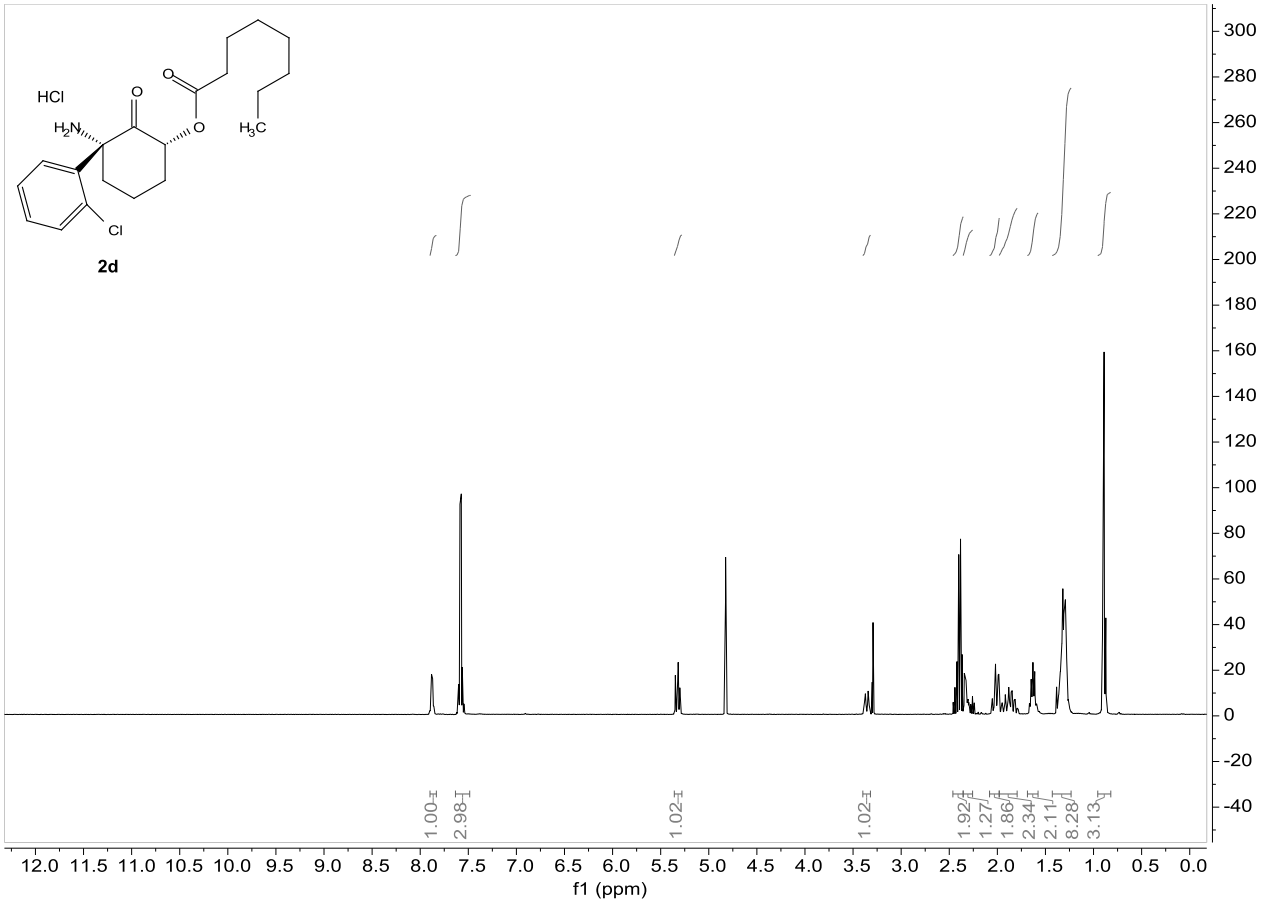


Fig S15. ^{1}H NMR spectrum of 2d.

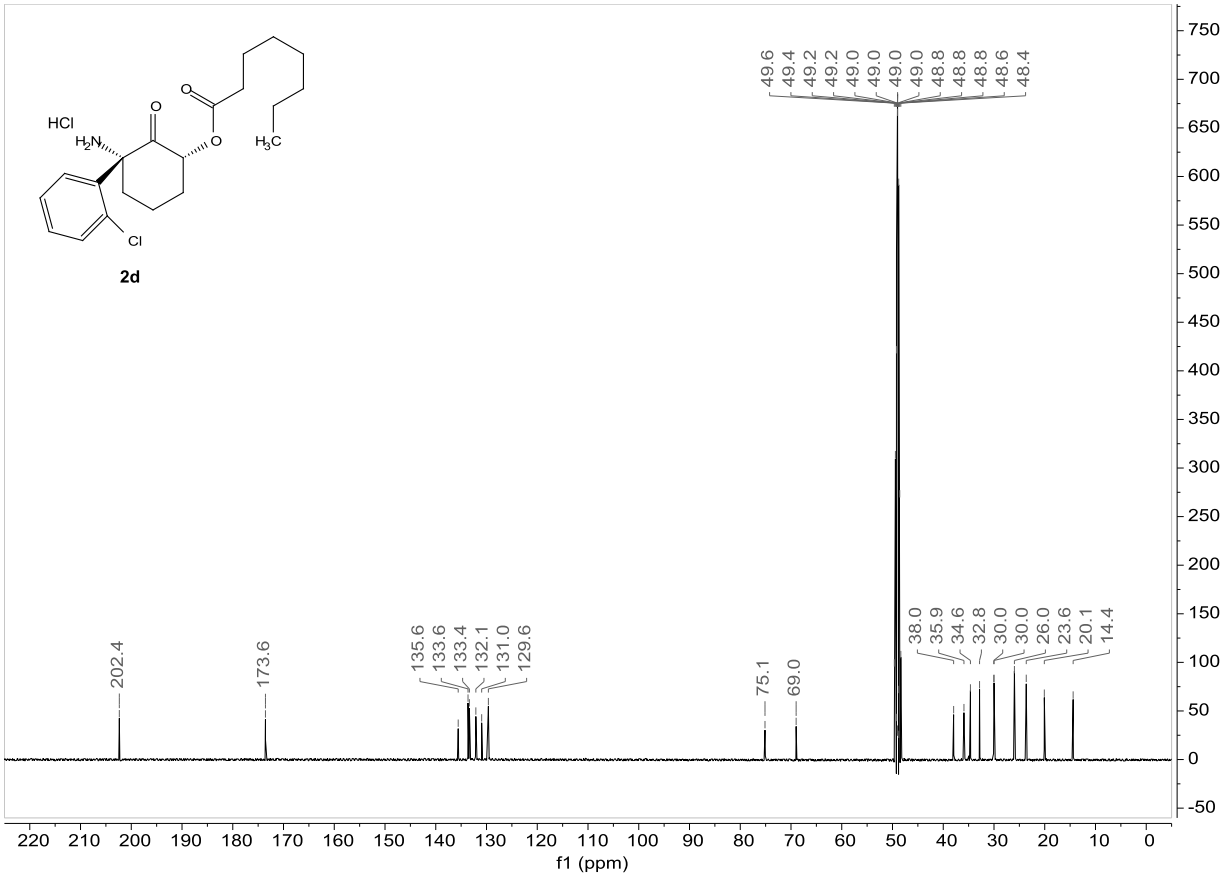


Fig S16. ^{13}C NMR spectrum of 2d.

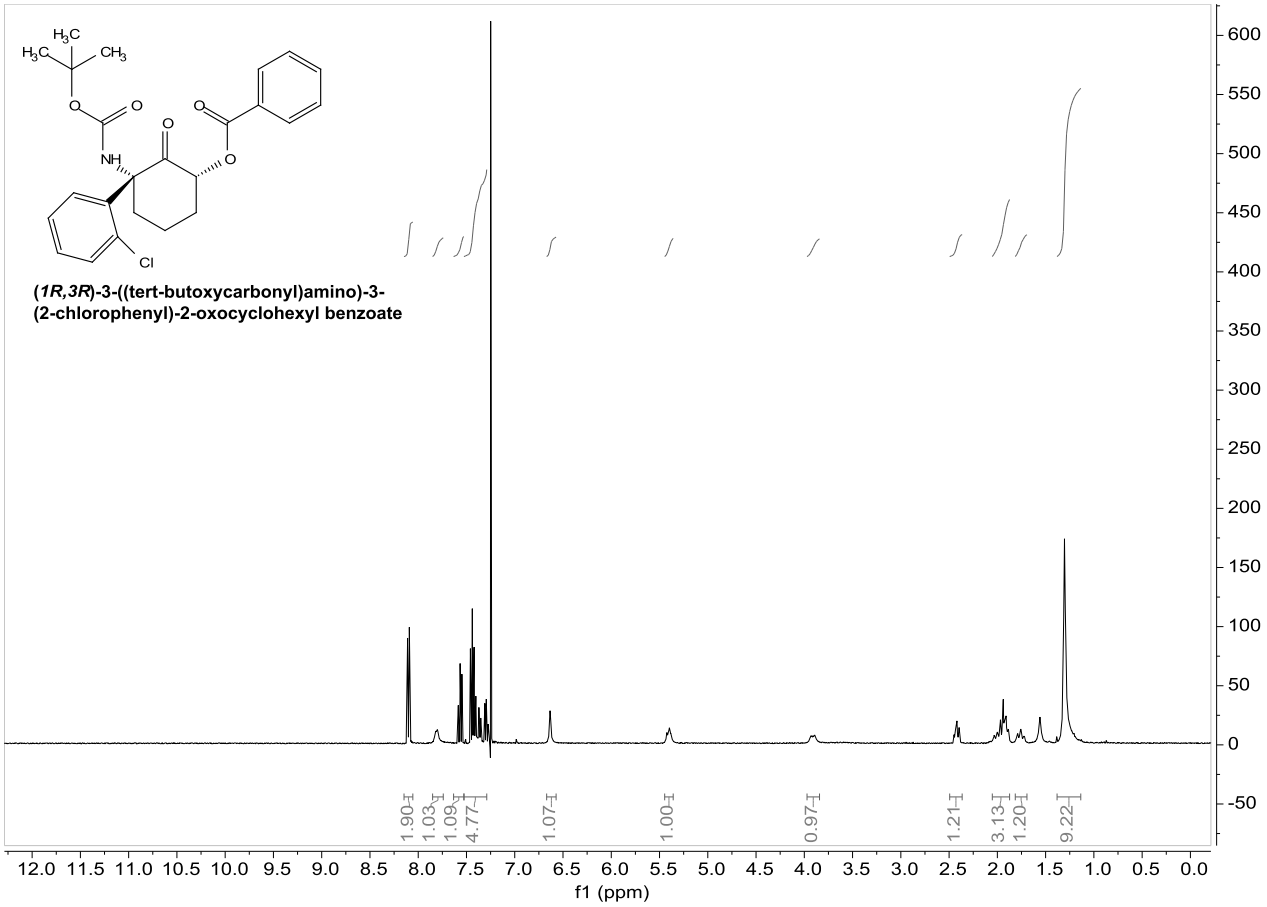


Fig S17. ^{1}H NMR spectrum of (*1R,3R*)-3-((tert-butoxycarbonyl)amino)-3-(2-chlorophenyl)-2-oxocyclohexyl benzoate.

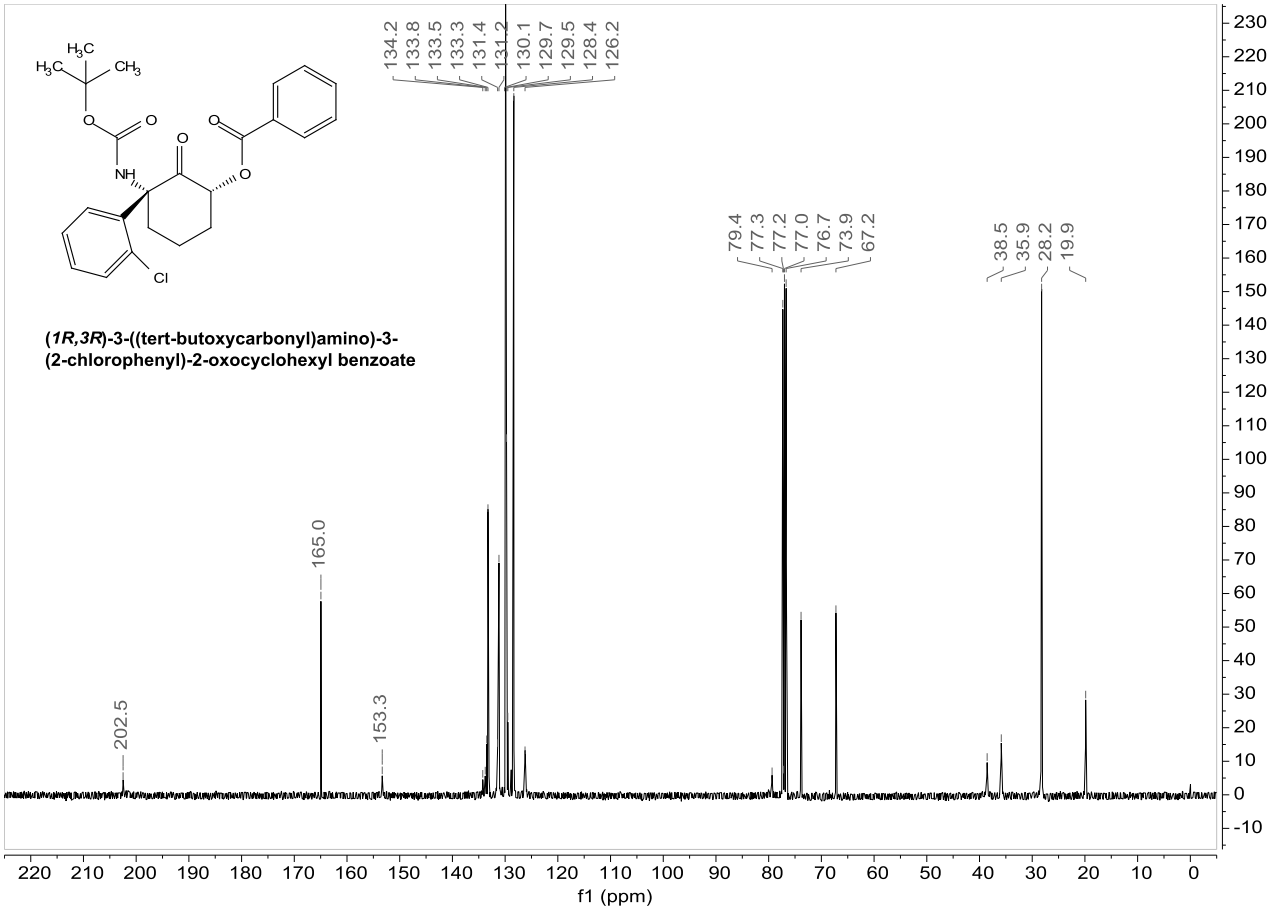


Fig S18. ^{13}C NMR spectrum of (*1R,3R*)-3-((tert-butoxycarbonyl)amino)-3-(2-chlorophenyl)-2-oxocyclohexyl benzoate.

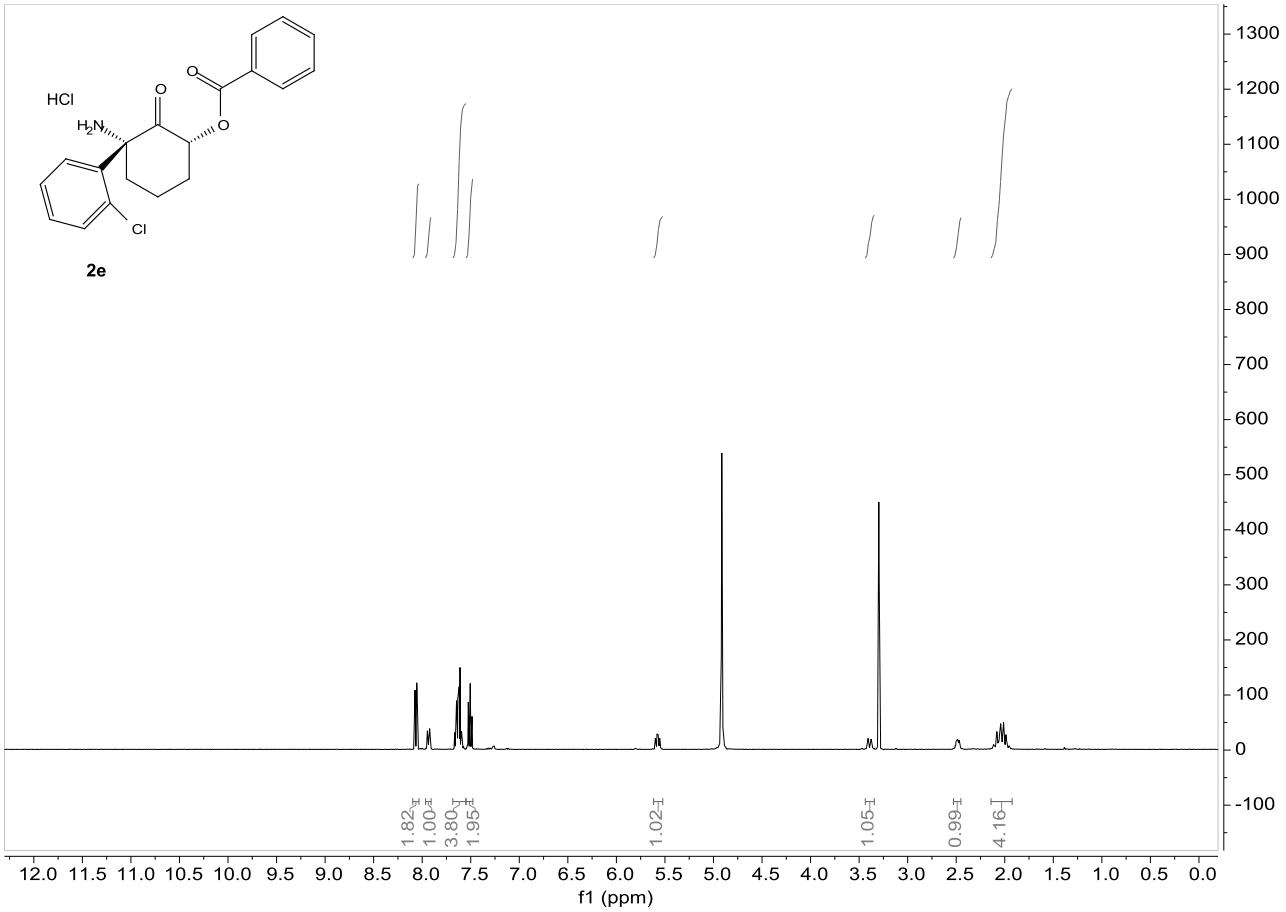


Fig S19. ^{1}H NMR spectrum of 2e.

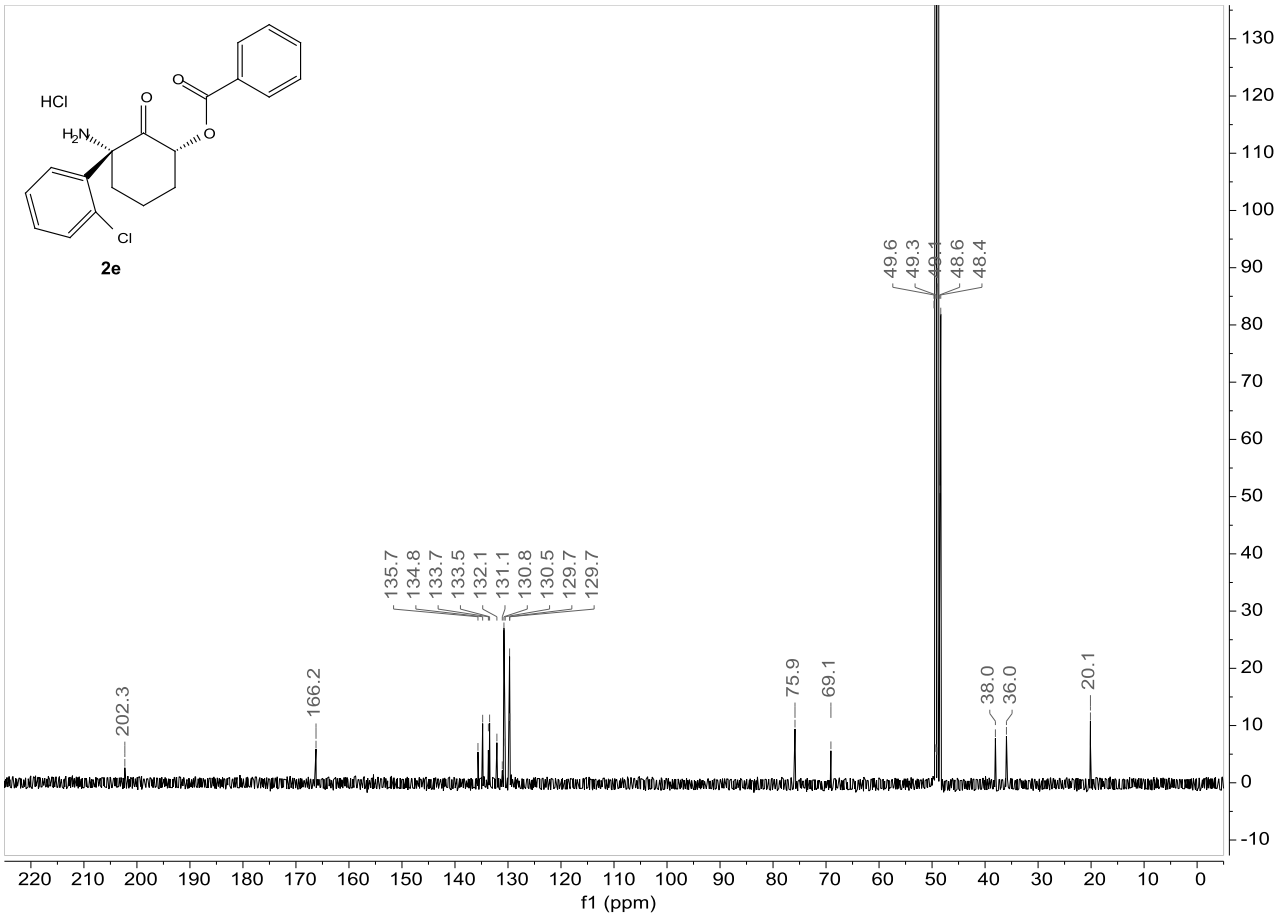


Fig S20. ^{13}C NMR spectrum of 2e.

5. MRM transitions and parameters

Table S1. MRM transitions for mouse plasma and brain samples.

Compound	Q1 (Da)	Q3 (Da)	DP (V)	CE (eV)	CXP (V)
(*2R*,*6R*)-HNK (**1**)	240.0	125.1	70	30	12
d4-ketamine	242.0	129.0	70	30	12
2a	282.2	125.2	70	37	15
2b	295.8	125.2	70	35	12
2c	324.2	177.3	65	40	12
2d	366.3	125.2	100	45	12
2e	344.2	177.5	60	40	12

Note: DP, declustering potential; CE, collision energy; CXP, collision cell exit potential; Q1 and Q3, quadrupole 1 and 3 masses, respectively.

Table S2. MRM transitions for rat plasma and brain samples.

Compound	Q1 (Da)	Q3 (Da)	DP (V)	CE (eV)	CXP (V)
(*2R*,*6R*)-HNK	240.12	116.00	46	47	14
dexamethasone	393.30	373.10	46	47	14

Note: DP, declustering potential; CE, collision energy; CXP, collision cell exit potential; Q1 and Q3, quadrupole 1 and 3 masses, respectively.

Table S3. MRM transitions for dog plasma samples.

Compound	Q1 (Da)	Q3 (Da)	DP (V)	CE (eV)	CXP (V)
(*2R*,*6R*)-HNK	240.5	124.9	60	40	20
d4-ketamine	242.5	183.1	100	15	20

Note: DP, declustering potential; CE, collision energy; CXP, collision cell exit potential; Q1 and Q3, quadrupole 1 and 3 masses, respectively.