Synthesis and NMDA receptor activity of ketamine metabolites

Patrick J. Morris, Ruin Moaddel, Panos Zanos, Curtis E. Moore, Todd Gould, Carlos A. Zarate Jr. and Craig J. Thomas*

Supporting information

Table of contents

General Synthetic Methods: All commercially available reagents and solvents were purchased and used without further purification. All microwave reactions were carried out in a sealed microwave vial equipped with a magnetic stir bar and heated in a Biotage Initiator Microwave Synthesizer. The ThalesNano H-cube utilized for hydrogenations was manufactured by ThalesNano Nanotechnology Inc., Graphisoft Park, Záhony u.7. H-1031 Budapest, Hungary. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian 400 MHz or Varian 600 MHz spectrometers in CD_3OD, CD_3CN, $CDCl_3$, or D_6-DMSO 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. For spectra recorded in $CDCl_3$, chemical shifts are reported in ppm relative to dueterochloroform (7.26 ppm for ^{1}H NMR, 77.23 ppm for ^{13}C NMR). For spectra recorded in CD_3CN, chemical shifts are reported in ppm relative to CD_3CN (1.93 ppm for ^{1}H NMR, 1.3 ppm for ^{13}C NMR). For spectra in D_6-DMSO chemical shifts are reported in ppm relative to D_6-DMSO (2.50 ppm for ^{1}H NMR, 39.5 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). 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. Optical rotations were measured on the free base, unless otherwise noted. Selected hydroxynorketamine metabolites ((*2R,4R*)-HNK, (*2R,4S*)-HNK and enantiomers thereof) were converted into the HCl salt for enhanced water solubility, and are noted and reported in the experimental as the HCl salt.

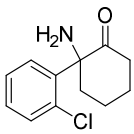
Chiral analysis was carried out with an Agilent 1200 series HPLC using an analytical Chiralpak AD or OJ column (4.6 mm X 250 mm; 5 μm). The mobile phase consisted of ethanol containing 0.1% diethylamine as component A and hexanes containing 0.1% diethylamine as component B. An isocratic gradient was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

General biological methods: Radioligand displacement assays for NMDA receptor inhibition constants were performed by Eurofins Panlabs, (Taipei, Taiwan), using standardized conditions adopted from the literature.[1,2] IC_{50} values were determined by a non-linear, least squares regression analysis using $MathIQ_{TM}$. Ki values were calculated using the equation of Cheng and Prusoff,[3] using the observed IC_{50} of the tested compound, the concentration of the radioligand employed in the [^{3}H]-MK-801 radioligand displacement assays for the NMDAR (5 nM), and the historical values for the K_D of the ligand (12 nM). An N=3 for each compound was assessed.

Previously synthesized compounds: (1-Bromocyclopentyl)(2-chlorophenyl)methanone (**13**)[4] and 1-((2-chlorophenyl)(imino)methyl)cyclopentan-1-ol (**14**)[5] were synthesized via literature methods. (*2R,6R*)-HNK (**7a**)**,** its enantiomer (*2S,6S*)-HNK (**7b**) and the precursors *tert*-butyl (R)-(1-(2-chlorophenyl)-2-oxocyclohexyl)carbamate **15a**, *tert*-butyl (*S*)-(1-(2-chlorophenyl)-2-oxocyclohexyl)carbamate (**15b**), *tert*-butyl ((*1R,3R*)-1-(2-chlorophenyl)-3-hydroxy-2-oxocyclohexyl)carbamate (**17a**) and ((*1S,3S*)-1-(2-chlorophenyl)-3-hydroxy-2-oxocyclohexyl)carbamate (**17b**) are previously reported by Zanos, *et. al*.[6]

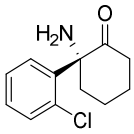
.

Compound Synthesis and Characterization



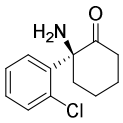
(*R,S*)-Norketamine (**2**)

Crude 1-((2-chlorophenyl)(imino)methyl)cyclopentan-1-ol (32 grams, 140 mmol)[5] was dissolved in isopropanol (120 ml). The solution was split into eight 20 ml vials each containing a stirbar. The vials were then sealed and heated *via* microwave irradiation to 170 °C for 1 hour. The batches were cooled, combined, and the solvent removed by rotary evaporation. The crude mixture was then dissolved in 300 ml of 0.50 N aqueous hydrochloric acid. The aqueous phase was washed with ethyl acetate (300 mL). Then, aqueous sodium hydroxide (1.0 M, 160 mL) was added. The pH was measured and observed to be pH = 12. The aqueous phase was then extracted with ethyl acetate (2X, 400 ml), the organic layers were combined and the solvent was removed by rotary evaporation to give norketamine as a yellow liquid, which solidified to an off white solid upon standing (19 grams, 45% yield from 1-bromocyclobenzyl(2-chlorophenyl)ketone). ^{1}H NMR spectra matched literature spectra[7] and is reported below. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69 (dd, J = 7.8, 1.7 Hz, 1H), 7.41 – 7.31 (m, 2H), 7.36 – 7.21 (m, 1H), 2.83 – 2.72 (m, 1H), 2.64 – 2.53 (m, 1H), 2.55 – 2.41 (m, 1H), 1.92 – 1.74 (m, 4H), 1.78 – 1.61 (m, 1H).



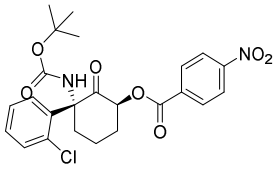
(*R*)-norketamine (**2a**). **NCGC00421876**

Racemic norketamine (54.0 g, 1.00 eq., 241 mmol, free base) was dissolved in 1.10 L ethanol. Then (L)-(S)-pyroglutamic acid (15.8 g, 0.500 eq., 121 mmol) was added as a solid. The reaction was stirred and heated to reflux for 5 minutes. While heating, a white suspension formed. Once the suspension reached reflux, it was allowed to cool to room temperature while stirring for 16 hours. The reaction was filtered and the white solid was collected. The resulting white solid was then suspended in 0.9 L of ethanol and the suspension was heated to reflux for 5 minutes. The suspension was allowed to cool to room temperature over 2 hours while stirring. The solid was collected by filtration, then suspended a third time in ethanol (0.8 L), heated to reflux for 5 minutes, then allowed to cool to room temperature while stirring. The solid was filtered, collected and dried under vacuum to give (R)-(-)-norketamine L-pyroglutamate (38.4 g, 45.1% yield). The enantiomeric excess measured by chiral HPLC to give an enantiomeric excess of 98.3%. The (R)-(-)-norketamine L-pyroglutamate salt was converted to the free base by treatment with 1 N aqueous sodium hydroxide, extraction into ethyl acetate, and removal of the organic solvent by rotary evaporation to provide (R)-(-)-norketamine as the free base, as a white solid. (24.4 g, 91.8% yield from the pyroglutamate salt). ^{1}H NMR spectra matched literature values.[7] **Chiral HPLC**: 98% ee. (Chiralpak AD, 60% ethanol in hexanes with 0.01% diethyl amine, 1 mL/min, rt: 6.8 min. (S)-enantiomer observed 5.2 min). **$[\alpha]_D^{20}$**: -75° (*c* 1.0, H_2O, L-pyroglutamate salt)



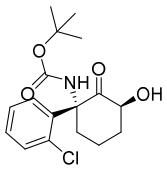
(*S*)-norketamine (**2b**). **NCGC00479288**

Compound was synthesized in an analogous fashion to (R)-norketamine, by use of (D)-(R)-pyroglutamic acid as a chiral resolution agent. $[\alpha]_D^{20}$: +81° (*c* 1.0, H_2O, L-pyroglutamate salt)



(*1S,3R*)-3-((*tert*-Butoxycarbonyl)amino)-3-(2-chlorophenyl)-2-oxocyclohexyl 4-nitrobenzoate (**19a**). **NCGC00483942**

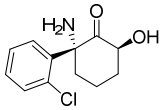
tert-Butyl ((*1R,3R*)-1-(2-chlorophenyl)-3-hydroxy-2-oxocyclohexyl)carbamate[7] (2.80 grams, 8.30 mmol) was placed in a round bottom flask with a stirbar. Dichloromethane (20 ml) was added, followed by pyridine (1.30 grams, 16.6 mmol). The reaction was then placed under a nitrogen atmosphere, stirred until all reagents dissolved, and cooled to 0 °C. Then trifluoromethanesulfonic anhydride (1.00 M in dichloromethane, 9.43 mL, 9.43 mmol) was added via syringe. The reaction was stirred for 45 minutes at 0 °C, then quenched by being poured into a solution of saturated aqueous sodium bicarbonate. The mixture was extracted with dichloromethane, and the solvent was removed by rotary evaporation to give the crude triflate, which was used without further purification. The triflate required either immediate use or storage at – 80 °C to avoid decomposition. The crude triflate (3.92 grams, 8.30 mmol, based on 100% yield) was dissolved in dimethylformamide (50.0 ml). Then 4-nitrobenzoic acid (5.55 grams, 33.2 mmol), followed by potassium carbonate (1.15 grams, 8.30 mmol) was added. The suspension was stirred vigorously at room temperature for 16 hours. The reaction was then poured into a separatory funnel containing diethyl ether (200 ml) and water (100 ml). The organic phase was washed twice with water (100 ml) and once with saturated aqueous sodium chloride (100 ml). The organic phase was taken, and the solvent removed by rotary evaporation. Purification by silica gel chromatography (0% to 100% ethyl acetate in hexanes) provided the title compound as a slightly yellow solid (2.90 grams, 71.5% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.23 – 8.11 (m, 2H), 7.95 – 7.85 (m, 2H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.36 – 7.27 (m, 1H), 7.27 – 7.20 (m, 1H), 7.20 – 7.14 (m, 1H), 5.99 (s, 1H), 5.93 (dd, *J* = 8.7, 4.9 Hz, 1H), 3.19 – 3.09 (m, 1H), 2.43 – 2.31 (m, 2H), 2.27 – 2.00 (m, 3H), 1.32 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 199.4, 163.3, 154.0, 150.5, 136.2, 134.8, 133.6, 131.3, 130.9, 129.7, 128.6, 126.4, 123.3, 80.5, 76.2, 68.5, 37.9, 33.8, 28.0, 18.9. **HRMS** (ESI+): Expected 511.1242 [M+Na^+] ($C_{24}H_{25}ClN_2NaO_7^+$). Observed 511.1248. $[\alpha]_D^{20}$: +9.5° (*c* 1.0, $CHCl_3$)



tert-Butyl ((1*R,3S*)-1-(2-chlorophenyl)-3-hydroxy-2-oxocyclohexyl)carbamate (**20a**). **NCGC00489076**

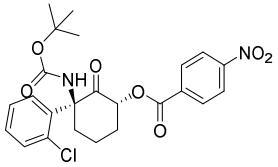
(*1S,3R*)-3-((*tert*-butoxycarbonyl)amino)-3-(2-chlorophenyl)-2-oxocyclohexyl 4-nitrobenzoate (2.00 grams, 4.09 mmol) was dissolved in methanol (50.0 ml). The reaction was cooled to 0 °C, and potassium carbonate (0.565 mg, 4.09 mmol) was added. The reaction was stirred for 30 minutes at 0 °C. The reaction was then quenched by being poured into an aqueous solution of saturated sodium bicarbonate. The mixture was extracted with ethyl acetate, the organic layer was taken, and the solvent removed by rotary evaporation. Purification by silica gel chromatography (0% to 100% ethyl acetate in hexanes) gave the desired product as a white solid (901 mg, 65.0% yield).**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 –

7.40 (m, 1H), 7.40 – 7.33 (m, 1H), 7.33 – 7.23 (m, 2H), 5.28 (s, 1H), 4.65 (dd, *J* = 12.1, 6.5 Hz, 1H), 3.02 – 2.88 (m, 1H), 2.50 – 2.40 (m, 1H), 2.19 – 2.00 (m, 2H), 1.85 – 1.75 (m, 9H), 1.75 – 1.64 (m, 1H), 1.38 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 203.4, 154.3, 136.6, 133.4, 131.8, 129.1, 127.7, 126.7, 81.2, 72.7, 67.8, 38.3, 36.7, 28.1, 19.1. **HRMS** (ESI+): Expected 362.1130 [M+Na^+] ($C_{17}H_{22}ClNaNO_4^+$). Observed 362.1139. **$[\alpha]_D^{20}$**: -2.3° (*c* 1.0, $CHCl_3$).



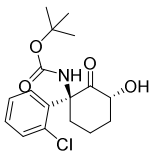
(*2R,6S*)-2-Amino-2-(2-chlorophenyl)-6-hydroxycyclohexan-1-one (**4a**). **NCGC00483973**

tert-Butyl ((*1R,3S*)-1-(2-chlorophenyl)-3-hydroxy-2-oxocyclohexyl)carbamate (860 mg, 2.5 mmol) was dissolved in dichloromethane (8.0 ml) and cooled to 0 °C. Then trifluoroacetic acid (4.0 ml, 52 mmol) was added. The reaction was stirred at 0 °C for 45 minutes. The solvent and trifluoroacetic acid were then removed by rotary evaporation. Ethyl acetate and a pH 7 saturated potassium phosphate buffer was added to the crude material, and the material was transferred to a separatory funnel, where it was extracted with ethyl acetate twice, while keeping the pH between 6 and 7. The organic phase was taken and the solvent removed by rotary evaporation to give a crude white solid. The solid was purified by reverse phase high pressure liquid chromatography (5% to 80% MeCN in H_2O, with 0.1% TFA). The desired fractions were neutralized with pH 7 buffer, extracted with ethyl acetate twice, and the organic phase was taken and the solvent removed by rotary evaporation to give a white solid. The solid was dissolved in ethanol and the ethanol removed by rotary evaporation to give the desired product as a white solid (260 mg, 44% yield). Absolute and relative stereochemistry were proven by x-ray crystallography. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 – 7.58 (m, 1H), 7.43 – 7.36 (m, 1H), 7.36 – 7.23 (m, 2H), 4.89 (dd, *J* = 11.8, 6.5 Hz, 1H), 2.59 – 2.52 (m, 1H), 2.46 – 2.42 (m, 1H), 2.22 – 2.08 (m, 1H), 1.98 (ddt, *J* = 14.1, 3.9, 2.5 Hz, 1H), 1.93 – 1.80 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.3, 141.0, 133.0, 131.1, 129.1, 127.1 (2C), 72.3, 64.9, 39.4, 35.3, 19.4. **HRMS** (ESI+): Expected 240.0786 [M+H^+] ($C_{12}H_{15}ClNO_2^+$). Observed 240.0794. **$[\alpha]_D^{20}$**: +75.4° (*c* 1.0, $CHCl_3$).



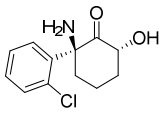
(*1R,3S*)-3-((*tert*-Butoxycarbonyl)amino)-3-(2-chlorophenyl)-2-oxocyclohexyl 4-nitrobenzoate (**19b**). **NCGC00492460**

Compound was synthesized in an analogous fashion to its enantiomer, by using the *tert*-butyl ((1S,3S)-1-(2-chlorophenyl)-3-hydroxy-2-oxocyclohexyl)carbamate[7] as a starting material. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.27 – 8.10 (m, 2H), 7.92 (s, 2H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.32 (td, *J* = 7.6, 1.6 Hz, 1H), 7.27 – 7.12 (m, 2H), 6.03 (s, 1H), 5.94 (dd, *J* = 8.8, 4.9 Hz, 1H), 3.23 – 2.99 (m, 1H), 2.37 (dq, *J* = 12.5, 6.2 Hz, 2H), 2.28 – 1.92 (m, 3H), 1.33 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 200.2, 163.4, 154.0, 150.7, 136.2, 134.8, 133.8, 131.4, 131.0, 129.2, 128.9, 126.5, 123.4, 80.8, 76.5, 68.6, 38.1, 34.2 28.2, 18.9. **HRMS** (ESI+): Expected 511.1242 [M+Na^+] ($C_{24}H_{25}ClNaN_2O_7^+$). Observed 511.1236. **$[\alpha]_D^{20}$** : -11.0° (*c* 1.0, $CHCl_3$)



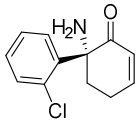
tert-Butyl ((*1S,3R*)-1-(2-chlorophenyl)-3-hydroxy-2-oxocyclohexyl)carbamate (**20b**). **NCGC00481339**

Compound was synthesized in an analogous fashion to its enantiomer, by using the (*1R,3S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2-chlorophenyl)-2-oxocyclohexyl 4-nitrobenzoate as a starting material. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 – 7.21 (m, 4H), 5.15 (s, 1H), 4.71 – 4.55 (m, 1H), 3.63 (d, *J* = 4.6 Hz, 1H), 3.04 – 2.90 (m, 1H), 2.47 (ddq, *J* = 12.9, 6.4, 3.2 Hz, 1H), 2.23 – 2.00 (m, 2H), 1.95 – 1.68 (m, 2H), 1.39 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 203.5, 154.4, 136.8, 133.6, 132.0, 129.3, 127.9, 126.9, 72.9, 68.0, 38.5, 36.9, 28.3, 19.3, 0.2. **HRMS** (ESI+): Expected 362.1130 [M+Na^+] ($C_{17}H_{22}ClNaNO_4^+$). Observed 362.1135. **$[\alpha]_D^{20}$**: + 1.2° (*c* 1.0, $CHCl_3$)



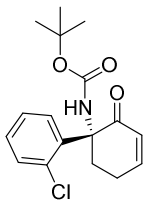
(*2S,6R*)-2-Amino-2-(2-chlorophenyl)-6-hydroxycyclohexan-1-one (**4b**). **NCGC00481329**

Compound was synthesized in an analogous fashion to its enantiomer, by using the *tert*-butyl ((*1S,3R*)-1-(2-chlorophenyl)-3-hydroxy-2-oxocyclohexyl)carbamate. Absolute and relative stereochemistry were proven by x-ray crystallography. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.38 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.30 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.24 (dt, *J* = 7.7, 1.9 Hz, 1H), 4.89 (dd, *J* = 7.0, 12 Hz, 1H), 3.52 (bs, 1H), 2.51 (dt, *J* = 13.6, 4.4 Hz, 1H), 2.48 – 2.40 (m, 1H), 2.22-2.07 (m, 1H), 1.99-1.82 (m, 1H), 1.91-1.78 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.3, 141.3, 132.9, 130.9, 128.8, 126.9 (2C), 72.0, 64.6, 39.4, 35.2, 19.4. **HRMS** (ESI+): Expected 240.0786 [M+H^+] ($C_{12}H_{14}ClNNaO_2^+$). Observed 240.0786. **$[\alpha]_D^{20}$**: -73.6° (*c* 1.0, $CHCl_3$).



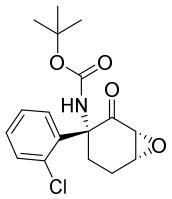
(*R*)-1-Amino-2'-chloro-5,6-dihydro-[1,1'-biphenyl]-2(1H)-one (**3a**). **NCGC00389094**

Following a modified procedure by Parcell and Sanchez,[5] (*R*)-norketamine (4.6 g, 21 mmol) was placed in acetic acid (30 ml). Then pyridinium tribromide (6.6 g, 21 mmol) was added. The reaction was sealed and heated to 125 °C for 1 hour via microwave irradiation while stirring. The solution was then cooled, and the acetic acid removed by rotary evaporation. The crude material was then washed with aqueous sodium bicarbonate and extracted into ethyl acetate, ensuring the pH remained at pH 10. The organic phase was taken, and the solvent removed by rotary evaporation to give crude 6-bromo-(*R*)-norketamine. This crude product was immediately dissolved in acetonitrile (30 ml). 1,8-Diazabicyclo(5.4.0)undec-7-ene (3.1 ml, 21 mmol) was added and the reaction was sealed and heated to 120 °C for 30 minutes via microwave irradiation. The reaction was cooled, then partitioned between ethyl acetate and saturated sodium bicarbonate. The organic phase was taken, and the solvent removed by rotary evaporation. Purification by silica gel chromatography (0% to 100% ethyl acetate in hexanes) gave the title product as an off white solid (2.5 g, 55% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69 – 7.58 (m, 1H), 7.37 – 7.28 (m, 1H), 7.28 – 7.17 (m, 2H), 6.93 (dddd, *J* = 10.2, 5.1, 3.1, 1.0 Hz, 1H), 6.18 (ddd, *J* = 10.2, 2.4, 1.7 Hz, 1H), 2.95 (ddd, *J* = 14.0, 9.5, 5.4 Hz, 1H), 2.59 – 2.42 (m, 1H), 2.30 (dtdd, *J* = 19.5, 5.4, 4.1, 1.7 Hz, 1H), 1.86 (dddd, *J* = 14.0, 5.2, 4.1, 1.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 198.8, 148.4, 141.6, 132.3, 131.2, 128.9, 128.6, 128.2, 126.9, 62.6, 34.0, 23.3. **HRMS** (ESI+): Expected 222.0680 [M+H^+] ($C_{12}H13ClNO^+$). Observed 222.0679. **$[\alpha]_D^{20}$**: -61.2° (*c* 1.0, $CHCl_3$)



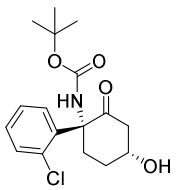
tert-Butyl-(*R*)-(2'-chloro-6-oxo-3,6-dihydro-[1,1'-biphenyl]-1(2H)-yl)carbamate (**21a**). **NCGC00486996**

(*R*)-1-amino-2'-chloro-5,6-dihydro-[1,1'-biphenyl]-2(1H)-one (2.5 grams, 11 mmol) was placed in a round bottom flask with a stir bar. Toluene (80 ml), was added, followed by BOC-anhydride (3.2 grams, 15 mmol) and potassium carbonate (1.6 grams, 11 mmol). The reaction was heated to 80 °C for 16 hours. It was then cooled, washed with aqueous sodium bicarbonate, extracted into ethyl acetate, the organic phase taken, and the solvent removed by rotary evaporation. Purification by silica gel chromatography (0% to 60% ethyl acetate in hexanes) gave the title product as an off white solid (2.2 g, 59% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.26 (m, 2H), 7.26 – 7.11 (m, 2H), 6.84 – 6.71 (m, 1H), 6.18 (ddd, *J* = 10.1, 2.5, 1.5 Hz, 1H), 5.60 (s, 1H), 3.29 (dtd, *J* = 14.3, 4.6, 1.1 Hz, 1H), 2.80 – 2.60 (m, 1H), 2.39 (dqd, *J* = 19.7, 4.7, 1.5 Hz, 1H), 2.17 (dddt, *J* = 19.8, 9.1, 4.8, 2.9 Hz, 1H), 1.37 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 196.7, 154.6, 149.2, 135.6, 135.6, 132.9, 131.8, 130.0, 129.4, 129.4, 128.6, 126.5, 79.8, 77.5, 77.2, 76.8, 65.1, 30.9, 28.4, 24.7. **HRMS** (ESI+): Expected 344.1024 [M+Na^+] ($C_{17}H_{20}ClNaNO_3^+$). Observed 344.1021. **$[\alpha]_D^{20}$**: -104.6° (*c* 1.0, $CHCl_3$).



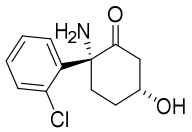
tert-Butyl ((*1R,3R,6R*)-3-(2-chlorophenyl)-2-oxo-7-oxabicyclo[4.1.0]heptan-3-yl)carbamate (**22a**). **NCGC00487046**

Sodium hydroxide (10 mg, 0.25 mmol) was added to a solution of *tert*-butyl-(*R*)-(2'-chloro-6-oxo-3,6-dihydro-[1,1'-biphenyl]-1(2H)-yl)carbamate (250 mg, 0.77 mmol) in methanol (6.0 ml) at 0 °C. Then a solution of hydrogen peroxide (30% in water, 0.6 ml, 5.3 mmol) was added. The reaction was vigorously stirred for 1 hour, and was then quenched by being poured into aqueous sodium bicarbonate. The reaction was extracted with ethyl acetate, the organic phase taken, and the solvent removed by rotary evaporation. Purification by silica gel chromatography (0% to 100% ethyl acetate in hexanes) gave the title product as a white solid (110 mg, 40% yield). Relative stereochemistry was determined by derivatizing the compound to the final desired product (*2R,5R*-HNK, **5a**) and the x-ray crystallography at that stage. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.31 (m, 1H), 7.31 – 7.22 (m, 3H), 5.61 (s, 1H), 3.53 (dd, *J* = 3.5, 0.6 Hz, 1H), 3.41 (dt, *J* = 3.6, 2.0 Hz, 1H), 2.81 (d, *J* = 14.5 Hz, 1H), 2.39 (ddd, *J* = 14.1, 12.8, 4.5 Hz, 1H), 2.29 – 2.12 (m, 1H), 1.71 (dddd, *J* = 15.6, 12.8, 5.0, 1.7 Hz, 1H), 1.37 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 201.9, 154.3, 135.3, 132.6, 132.1, 130.7, 129.8, 126.9, 80.2, 65.7, 54.3, 53.7, 28.4, 25.7, 21.9. **HRMS** (ESI+): Expected 360.0973 [M+Na^+] ($C_{17}H_{20}ClNaNO_4^+$). Observed 360.0981. **$[\alpha]_D^{20}$**: -37.6° (*c* 1.0, $CHCl_3$).



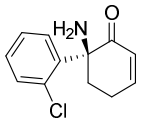
tert-Butyl ((*1R,4R*)-1-(2-chlorophenyl)-4-hydroxy-2-oxocyclohexyl)carbamate (**23a**). **NCGC00487087**-

Samarium diiodide (3.0 ml, 0.10 M in THF, 0.30 mmol) was placed in a sealed vial, under an argon balloon, and was cooled to – 78 °C. *Tert*-butyl ((*1R,3R,6R*)-3-(2-chlorophenyl)-2-oxo-7-oxabicyclo[4.1.0]heptan-3-yl)carbamate was dissolved in THF (2.0 ml) and added to the vial via syringe. The reaction was stirred for 5 minutes, then quenched by the addition of aqueous sodium bicarbonate. The reaction was then poured into aqueous sodium bicarbonate, extracted with ethyl acetate, the organic phase taken, and the solvent removed by rotary evaporation. Purification by silica gel chromatography (0% to 100% ethyl acetate in hexanes) gave the desired product as a white solid (41 mg, 41% yield).**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.8 Hz, 1H), 7.35 (td, *J* = 7.7, 1.3 Hz, 2H), 7.31 – 7.19 (m, 1H), 6.61 (s, 1H), 4.42 (td, *J* = 3.1, 1.9 Hz, 1H), 3.67 (d, *J* = 14.6 Hz, 1H), 2.67 – 2.48 (m, 2H), 2.14 (td, *J* = 14.1, 4.1 Hz, 1H), 2.00 – 1.77 (m, 3H), 1.30 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 205.8, 153.7, 134.6, 134.0, 131.3 (2C), 129.6, 126.4, 79.4, 71.7, 67.1, 45.9, 33.2, 30.00, 28.4. **HRMS** (ESI+): Expected 362.1130 [M+Na^+] ($C_{17}H_{22}ClNaNO_4^+$). Observed 362.1131. **$[\alpha]_D^{20}$:** -53.8° (c 1.0, $CHCl_3$).



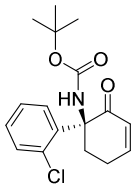
(*2R,5R*)-2-Amino-2-(2-chlorophenyl)-5-hydroxycyclohexan-1-one (**5a**). **NCGC00488764**

Tert-butyl ((*1R,4R*)-1-(2-chlorophenyl)-4-hydroxy-2-oxocyclohexyl)carbamate (46 mg, 0.13 mmol) was placed in a vial with a stirbar. The vial was cooled to 0 °C. Dichloromethane (2.0 ml) was added followed by trifluoroacetic acid (2.0 ml). The reaction was stirred for 15 minutes at 0 °C. The solvent and acid were then removed by rotary evaporation. The crude TFA salt was treated with aqueous sodium bicarbonate, and extracted into ethyl acetate. The organic phase was taken, the the solvent removed by rotary evaporation. Purification by silica gel chromatography (0% to 100% ethyl acetate in hexanes, then 0% to 15% methanol in dichloromethane) gave the title product as a white solid (8.0 mg, 25% yield). Absolute and relative stereochemistry were proven by x-ray crystallography. **^{1}H NMR** (400 MHz, CD_3CN) δ 7.89 – 7.75 (m, 1H), 7.41 – 7.24 (m, 3H), 4.18 (dt, *J* = 8.7, 4.3 Hz, 1H), 3.26 – 3.12 (m, 1H), 2.79 – 2.56 (m, 2H), 2.49 – 2.32 (m, 1H), 2.02 – 1.96 (m, 1H), 1.86 (dddd, *J* = 12.9, 10.7, 8.8, 4.2 Hz, 1H), 1.80 – 1.72 (m, 1H). **^{13}C NMR** (101 MHz, CD_3CN) δ 209.3, 143.7, 133.1, 131.4, 129.7, 129.4, 128.0, 68.9, 64.8, 47.5, 35.1, 31.1. **HRMS** (ESI+): Expected 240.0786 [M+H^+] ($C_{12}H_{15}ClNO2^+$). Observed 240.0793. **$[\alpha]_D^{20}$** :+17.4° (*c* 1.0, EtOH)



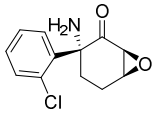
(*S*)-1-Amino-2'-chloro-5,6-dihydro-[1,1'-biphenyl]-2(1H)-one (**3b**). **NCGC00488956**

Compound was synthesized in an analogous fashion to (*R*)-dehydronorketamine (**3a**), by using (*S*)-norketamine instead of (*R*)-norketamine. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 – 7.59 (m, 1H), 7.41 – 7.30 (m, 1H), 7.30 – 7.13 (m, 2H), 6.93 (dddd, *J* = 10.2, 5.1, 3.1, 1.0 Hz, 1H), 6.18 (ddd, *J* = 10.2, 2.4, 1.6 Hz, 1H), 2.94 (ddd, *J* = 14.1, 9.6, 5.4 Hz, 1H), 2.64 – 2.42 (m, 1H), 2.39 – 2.21 (m, 1H), 1.86 (dddd, *J* = 14.0, 5.2, 4.0, 1.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 198.8, 148.4, 141.5, 132.3, 131.1, 128.9, 128.6, 128.2, 126.9, 62.5, 34.0, 23.2. **HRMS** (ESI+): Expected 222.0680 [M+H^+] ($C_{12}H_{14}ClNO^+$). Observed 222.0689. **$[\alpha]_D^{20}$**: +57.0° (*c* 1.0, $CHCl_3$)



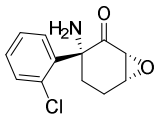
tert-Butyl (*S*)-(2'-chloro-6-oxo-3,6-dihydro-[1,1'-biphenyl]-1(2H)-yl)carbamate (**21b**). **NCGC00489141**

Compound was synthesized in an analogous manner to its enantiomer, by use of (*S*)-1-amino-2'-chloro-5,6-dihydro-[1,1'-biphenyl]-2(1H)-one as a starting material. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 – 7.33 (m, 2H), 7.30 – 7.20 (m, 2H), 6.87 – 6.79 (m, 1H), 6.22 (d, *J* = 10.1 Hz, 1H), 5.63 (s, 1H), 3.32 (dt, *J* = 14.2, 4.6 Hz, 1H), 2.81 – 2.68 (m, 1H), 2.47 – 2.38 (m, 1H), 2.25 – 2.13 (m, 1H), 1.41 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 196.7, 154.6, 149.2, 135.6, 132.9, 131.9, 130.0, 129.5, 128.6, 126.5, 79.8, 65.1, 30.9, 28.4, 24.8. **HRMS** (ESI+): Expected 344.1024 [M+Na$^+$] ($C_{17}H_{20}ClNNaO_3^+$). Observed 344.1021. **$[\alpha]_D^{20}$** : + 91.2°(*c* 1.0, $CHCl_3$)



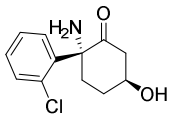
(*1S,3R,6S*)-3-Amino-3-(2-chlorophenyl)-7-oxabicyclo[4.1.0]heptan-2-one (**24a**). **NCGC00490644**

A solution of (*R*)-1-amino-2'-chloro-5,6-dihydro-[1,1'-biphenyl]-2(1H)-one (1.7 g, 7.7 mmol) in methanol (20 ml) was placed in a round bottom flask containing a stirbar. The flask was cooled to 0 °C and sodium hydroxide (0.060 g, 1.5 mmol) was added as a solid, followed by hydrogen peroxide (30% in water, 0.78 ml, 7.7 mmol). The reaction was stirred vigorously for 45 minutes at 0 °C. It was then quenched by being poured into a 50:50 aqueous solution of sodium thiosulfate and sodium bicarbonate. The reaction was extracted with ethyl acetate, the organic phase taken, and the solvent removed by rotary evaporation. Purification by silica gel chromatography (0% to 70% acetone in hexanes) separated the two diastereomeric epoxide products as white solids. The title product was the second eluting diastereomer and the relative stereochemistry was determined by derivatization to (*2R,5S*)-hydroxynorketamine and x-ray crystallography on that product The title product was obtained in 58% yield (1.1 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (dd, J = 7.6, 1.6 Hz, 1H), 7.41 – 7.11 (m, 3H), 3.66-3.63 (m, 1H), 3.46 (d, *J* = 3.8 Hz, 1H), 2.58 (ddd, *J* = 14.2, 12.2, 5.1 Hz, 1H), 2.29 (ddt, *J* = 15.4, 5.2, 2.6 Hz, 1H), 2.25 – 2.07 (m, 1H), 1.43 (dddt, *J* = 14.2, 5.0, 2.8, 0.7 Hz, 1H). **^{13}C NMR** (101 MHz, DMSO) δ 204.8, 141.7, 131.9, 130.7, 129.0, 127.6, 127.0, 62.0, 55.1, 54.2, 28.8, 20.2. **HRMS** (ESI+): Expected 238.0633 [M+H$^+$] ($C_{12}H_{14}ClNO_2^+$). Observed 238.0629. **$[\alpha]_D^{20}$** -45.4° (*c* 1.0, $CHCl_3$)



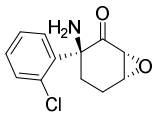
(*1R,3R,6R*)-3-Amino-3-(2-chlorophenyl)-7-oxabicyclo[4.1.0]heptan-2-one (**25a**). **NCGC00488940**

A solution of (*R*)-1-amino-2'-chloro-5,6-dihydro-[1,1'-biphenyl]-2(1H)-one (1.7 g, 7.7 mmol) in methanol (20 ml) was placed in a round bottom flask containing a stirbar. The flask was cooled to 0 °C and sodium hydroxide (0.060 g, 1.5 mmol) was added as a solid, followed by hydrogen peroxide (30% in water, 0.78 ml, 7.7 mmol). The reaction was stirred vigorously for 45 minutes at 0 °C. It was then quenched by being poured into a 50:50 solution of saturated aqueous sodium thiosulfate and saturated aqueous sodium bicarbonate. The reaction was extracted with ethyl acetate, the organic phase taken, and the solvent removed by rotary evaporation. Purification by silica gel chromatography (0% to 70% acetone in hexanes) separated the two diastereomeric epoxide products as white solids. The above product was the first eluting diastereomer, and the relative stereochemistry was determined by derivatization to (*2R,5R*)-hydroxynorketamine and x-ray crystallography on that product. The title product was obtained in 20% yield (370 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 (dd, *J*= 2.0, 8,0 Hz, 1H), 7.38 – 7.30 (dd, J = 2.4, 8.0 Hz, 1H), 7.30 – 7.17 (m, 2H), 3.69 – 3.59 (m, 1H), 3.54 (dd, *J* = 3.8, 0.5 Hz, 1H), 2.34 (dddd, *J* = 14.1, 5.6, 3.9, 0.7 Hz, 1H), 2.28 – 2.18 (m, 1H), 2.11 (dddd, *J* = 15.3, 11.1, 5.6, 1.6 Hz, 1H), 1.99 – 1.91 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 205.6, 141.6, 131.6, 130.9, 128.9, 128.5, 127.1, 62.3, 56.1, 54.4, 32.0, 21.4. **HRMS** (ESI+): Expected 260.0449 [M+Na$^+$] ($C_{12}H_{12}ClNNaO_2^+$). Observed 260.0459. **$[\alpha]_D^{20}$** : +45.4° (*c* 1.0, $CHCl_3$).



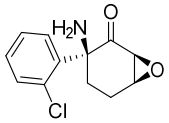
(*2R,5S*)-2-Amino-2-(2-chlorophenyl)-5-hydroxycyclohexan-1-one (**9a**). **NCGC00488759**

A solution of samarium diiodide (0.10 M, 0.30 mmol) in THF (3.0 ml) was added via syringe to a sealed vial containing a stirbar under an argon balloon. The resulting dark blue solution in the vial was cooled to – 78 °C. Then, a solution of (1S,3R,6S)-3-amino-3-(2-chlorophenyl)-7-oxabicyclo[4.1.0]heptan-2-one (46 mg, 0.19 mmol) was dissolved in a 1:1 solution of THF: methanol (2.0 ml total). This solution was added via syringe to the solution of samarium diiodide at – 78 °C over ~ 10 seconds. After about 50% of the material was added, the dark blue solution turned a light yellow color. The reaction was stirred at – 78 °C for 10 minutes before being quenched by the addition of aqueous saturated sodium bicarbonate (0.5 ml). The reaction mixture was extracted into ethyl acetate and washed with a solution of saturated sodium bicarbonate. Aqueous saturated potassium carbonate was added to the aqueous wash, and the aqueous layer was extracted a second time with ethyl acetate. The organic layers were combined, and the solvent removed by rotary evaporation. The crude product was then purified by silica gel chromatography (0% to 100% ethyl acetate in hexanes) to obtain the title product as a white solid (14 mg, 30% yield). Absolute and relative stereochemistry were proven by x-ray crystallography. **^{1}H NMR** (400 MHz, CD_3CN) δ 7.75 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.43 – 7.25 (m, 3H), 4.06 (tt, *J* = 7.7, 4.1 Hz, 1H), 2.96 – 2.85 (m, 1H), 2.80 (ddd, *J* = 14.5, 8.0, 4.0 Hz, 1H), 2.42 – 2.32 (m, 1H), 2.17 – 2.04 (m, 1H), 1.68 (dddd, *J* = 13.8, 8.8, 7.7, 4.0 Hz, 1H), 1.49 (ddd, *J* = 14.5, 8.9, 3.9 Hz, 1H).**^{13}C NMR** (101 MHz, CD_3CN) δ 209.1, 142.3, 134.0, 131.8, 129.9, 129.6, 128.1, 70.9, 66.6, 47.9, 35.0, 30.6. **HRMS** (ESI+): Expected 240.0786 [M+H$^+$] ($C_{12}H_{15}ClNO2^+$). Observed 240.0791. **$[\alpha]_D^{20}$**: -63° (*c* 1.0, EtOH).



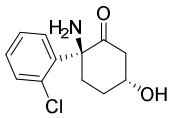
(*1R,3S,6R*)-3-Amino-3-(2-chlorophenyl)-7-oxabicyclo[4.1.0]heptan-2-one (**24b**). **NCGC00489862**

Compound was synthesized in an analogous fashion to its enantiomer by using (*S*)-1-amino-2'-chloro-5,6-dihydro-[1,1'-biphenyl]-2(1H)-one as a starting material. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 7.9, 1.8, 1H), 7.35 – 7.19 (m, 3H), 3.69 – 3.60 (m, 1H), 3.46 (dt, *J* = 3.8, 0.5 Hz, 1H), 2.64 – 2.50 (m, 1H), 2.36 – 2.25 (m, 1H), 2.25 – 2.09 (m, 1H), 1.43 (dddt, *J* = 14.2, 4.9, 2.7, 0.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.9, 141.8, 131.9, 130.7, 129.1, 127.6, 127.0, 62.0, 55.1, 54.2, 28.9, 20.2. **HRMS** (ESI+): Expected 238.0629 [M+H$^+$] ($C_{12}H_{13}ClNO_2^+$). Observed 238.0631. **$[\alpha]_D^{20}$**: +44.9° (*c* 1.0, $CHCl_3$).



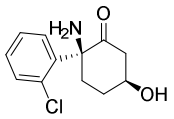
(*1S,3S,6S*)-3-Amino-3-(2-chlorophenyl)-7-oxabicyclo[4.1.0]heptan-2-one (**25b**). **NCGC00490643**

Compound was synthesized in an analogous fashion to its enantiomer by using (*S*)-1-amino-2'-chloro-5,6-dihydro-[1,1'-biphenyl]-2(1H)-one as a starting material. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.31 (dd, *J* = 7.8, 3.1 Hz, 1H), 7.28 – 7.14 (m, 2H), 3.64 – 3.58 (m, 1H), 3.52 (dd, *J* = 3.7, 0.6 Hz, 1H), 2.32 (dddd, *J* = 14.1, 5.6, 3.9, 0.7 Hz, 1H), 2.26 – 2.15 (m, 1H), 2.13 – 2.04 (m, 1H), 1.93 (ddd, *J* = 14.1, 11.1, 5.5 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 205.8, 141.8, 131.7, 131.0, 129.0, 128.6, 127.2, 62.4, 56.2, 54.5, 32.1, 21.5. **HRMS** (ESI+): Expected 238.0629 [M+H$^+$] ($C_{12}H_{14}ClNO_2^+$). Observed 238.0636. **$[\alpha]_D^{20}$**: -44.9° (*c* 1.0, $CHCl_3$).



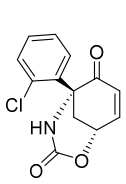
(*2S,5R*)-2-Amino-2-(2-chlorophenyl)-5-hydroxycyclohexan-1-one (**9b**). **NCGC00489857**

A solution of samarium diiodide (12 ml, 0.10 M in THF, 1.2 mmol) was added to a sealed vial with a stirbar, under an argon balloon. The vial was cooled to -78 °C. Then a solution of (*1R,3S,6R*)-3-amino-3-(2-chlorophenyl)-7-oxabicyclo[4.1.0]heptan-2-one (200 mg, 1.2 mmol) in THF (2.0 ml) and methanol (2.0 ml) was added via syringe. The reaction was stirred for 5 minutes at -78 °C and was then quenched by being poured into saturated aqueous sodium bicarbonate. The reaction was extracted with ethyl acetate twice. The organic layers were combined, and the solvent removed by rotary evaporation. Purification by silica gel chromatography (0% to 15% methanol in dichloromethane) gave the title product as a white solid (50 mg, 25% yield). Absolute and relative stereochemistry were proven by x-ray crystallography. **^{1}H NMR** (400 MHz, CD_3CN) δ 7.74 (ddd, *J* = 7.1, 2.2, 1.0 Hz, 1H), 7.44 – 7.33 (m, 2H), 7.30 (tdd, *J* = 7.6, 1.8, 0.8 Hz, 1H), 4.05 (tt, *J* = 7.8, 4.3 Hz, 1H), 2.89 (ddt, *J* = 13.1, 4.6, 1.1 Hz, 1H), 2.78 (ddd, *J* = 14.5, 8.0, 4.0 Hz, 1H), 2.35 (ddt, *J* = 13.2, 7.4, 0.9 Hz, 1H), 2.07 (dddd, *J* = 9.0, 3.9, 2.8, 1.4 Hz, 1H), 1.74 – 1.59 (m, 1H), 1.54 – 1.41 (m, 1H). **^{13}C NMR** (101 MHz, CD_3CN) δ 209.1, 142.3, 134.0, 131.8, 129.9, 129.6, 128.1, 118.3, 70.9, 66.6, 47.8, 35.0, 30.6. **HRMS** (ESI+): Expected 240.0786 [$M+H^+$] ($C_{12}H_{16}ClNO_2^+$). Observed 240.0794. **$[\alpha]_D^{20}$**: +63.8° (*c* 1.0, MeOH).



(*2S,5S*)-2-Amino-2-(2-chlorophenyl)-5-hydroxycyclohexan-1-one (**8b**). **NCGC00389131**

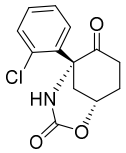
Samarium diiodide (12 mL, 0.10 M in THF, 1.1 mmol) was added to a sealed vial with a stirbar, under an argon balloon. The solution was cooled to -78 °C. A solution of (*1S,3S,6S*)-3-amino-3-(2-chlorophenyl)-7-oxabicyclo[4.1.0]heptan-2-one (91 mg, 0.38 mmol) in tetrahydrofuran (2.0 mL) and methanol (1.0 mL) was added via syringe. The reaction was stirred for 15 minutes, then quenched by being poured into aqueous sodium bicarbonate. The mixture was extracted twice with ethyl acetate, the organic phase taken, and the solvent removed by rotary evaporation. Purification by silica gel chromatography (0% to 100% ethyl acetate in hexanes, then 0% to 15% methanol in dichloromethane) gave the title product as a white solid (12 mg, 13% yield). Absolute and relative stereochemistry were proven by x-ray crystallography. **^{1}H NMR** (400 MHz, CD_3CN) δ 7.89 – 7.76 (m, 1H), 7.46 – 7.24 (m, 3H), 4.25 – 4.07 (m, 1H), 2.78 – 2.57 (m, 2H), 2.42 (ddd, *J* = 14.4, 11.1, 4.4 Hz, 1H), 2.04 – 1.96 (m, 1H), 1.86 (dddd, *J* = 13.1, 11.0, 8.8, 4.2 Hz, 1H), 1.76 (ddd, *J* = 14.4, 5.4, 4.2 Hz, 1H). **^{13}C NMR** (101 MHz, CD_3CN) δ 209.3, 143.7, 133.1, 131.4, 129.7, 129.4, 128.0, 68.8, 64.8, 47.5, 35.0, 31.0. **HRMS** (ESI+): Expected 240.0786 [$M+H^+$] ($C_{12}H_{16}ClNO_2^+$). Observed 240.0779. **$[\alpha]_D^{20}$**: -2.2° (c 0.5, MeOH).



(*1R,5R*)-5-(2-Chlorophenyl)-2-oxa-4-azabicyclo[3.3.1]non-7-ene-3,6-dione (**27a**). **NCGC00486896**

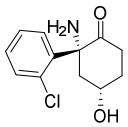
*tert-B*utyl (*R*)-(2'-chloro-6-oxo-3,6-dihydro-[1,1'-biphenyl]-1(2H)-yl)carbamate (2.5 g, 7.8 mmol) was added to a round bottom flask with a stirbar. Carbon tetrachloride (50 mL) was added, followed by *N*-bromosuccinimide (1.4 grams, 7.8 mmol) and azobisisobutyronitrile (0.25 g, 1.6 mmol). The reaction was stirred and heated to reflux for 2 hours. The reaction was then cooled, the solid was filtered off, and the organic solvent was removed by rotary evaporation to give the crude material. The filtered solid was washed with ethyl acetate, and the organic phase taken, the solvent removed and the material was combined with the other crude material. Purification by silica gel chromatography (0% to 100% ethyl acetate

in hexanes), yielded two desired products, the semicrude *tert*-butyl ((*1R*)-3-bromo-2'-chloro-6-oxo-3,6-dihydro-[1,1'-biphenyl]-1(2H)-yl)carbamate and the desired (*1R,5R*)-5-(2-chlorophenyl)-2-oxa-4-azabicyclo[3.3.1]non-7-ene-3,6-dione. The semi-crude (*1R,5R*)-5-(2-chlorophenyl)-2-oxa-4-azabicyclo[3.3.1]non-7-ene-3,6-dione was dissolved in methanol (50 mL) and potassium iodide (100 mg, 0.60 mmol) was added. The reaction was heated to reflux and stirred for 5 hours. The reaction was then cooled, and aqueous sodium thiosulfate (10 ml) was then added. The solvent was removed by rotary evaporation and the material was purified by silica gel chromatography (0% to 100% ethyl acetate in hexanes) to yield an additional 350 mg of (*1R,5R*)-5-(2-chlorophenyl)-2-oxa-4-azabicyclo[3.3.1]non-7-ene-3,6-dione. This material was combined with the purified material from the previous column to give the desired product as a white solid (1.1 g, 55% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.49 – 7.31 (m, 3H), 7.18 (ddd, *J* = 10.0, 6.1, 1.8 Hz, 1H), 6.45 (d, *J* = 10.0 Hz, 1H), 5.80 (s, 1H), 5.07 (ddd, *J* = 5.9, 3.3, 2.4 Hz, 1H), 3.32 (dt, *J* = 14.1, 2.4 Hz, 1H), 2.24 (ddd, *J* = 14.1, 3.4, 1.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 190.7, 151.4, 142.0, 135.2, 132.0, 131.4, 130.9, 130.3, 127.9, 126.9, 67.5, 63.2, 32.9. **HRMS** (ESI+): Expected 264.0422 [M+H$^+$] ($C_{13}H_{11}ClNO_3^+$). Observed 264.0429. **$[\alpha]_D^{20}$** :+146° (*c* 1.0, EtOH)



(*1S,5R*)-5-(2-Chlorophenyl)-2-oxa-4-azabicyclo[3.3.1]nonane-3,6-dione (**28a**). **NCGC00486899**

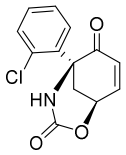
(*1R,5R*)-5-(2-Chlorophenyl)-2-oxa-4-azabicyclo[3.3.1]non-7-ene-3,6-dione (1.1 g, 4.2 mmol) was dissolved in ethyl acetate (40 ml). This material was hydrogenated via the use of a Thales-Nano H-Cube, with the use of a 10% Pd/c 70 mm cartridge, 1 atmosphere of hydrogen, and a flow rate of 2 ml/min at 23 °C. The resulting crude product in ethyl acetate was concentrated down by rotary evaporation, then purified by silica gel chromatography (0% to 100% ethyl acetate in hexanes) to give the desired product as a white solid (940 mg, 85% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 – 7.27 (m, 4H), 6.05 (s, 1H), 4.94 (s, 1H), 3.34 – 3.17 (m, 1H), 2.71 – 2.59 (m, 3H), 2.13 (td, *J* = 14.8, 14.0, 6.0 Hz, 1H), 1.56 – 1.51 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 204.9, 152.7, 134.9, 132.7, 131.4, 130.4, 127.7, 127.2, 77.5, 77.2, 76.8, 71.8, 65.2, 35.0, 33.0, 32.8. **HRMS** (ESI+): Expected 266.0578 [M+H$^+$] ($C_{13}H_{13}ClNO3^+$). Observed 266.0591. **$[\alpha]_D^{20}$** : +155.2° (*c* 1.0, $CHCl_3$).



(*2R,4S*)-2-Amino-2-(2-chlorophenyl)-4-hydroxycyclohexan-1-one hydrochloride (**10a**). **NCGC00389998**

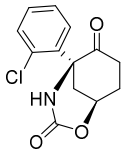
Lithium hydroxide (170 mg, 7.1 mmol) was added to a vial containing a solution of (*1S,5R*)-5-(2-chlorophenyl)-2-oxa-4-azabicyclo[3.3.1]nonane-3,6-dione (650 mg, 2.4 mmol) in a 2:1 mixture of tetrahydrofuran and 1.0 M aqueous sodium hydroxide (15 ml). The reaction was heated to 100 °C via microwave irradiation for 90 minutes. The reaction was then cooled, extracted with ethyl acetate, washed with aqueous sodium bicarbonate, the organic phase taken, and the solvent removed by rotary evaporation. The crude product was purified by reverse phase medium pressure liquid chromatography (5% to 50% acetonitrile in water, with 0.1% trifluoroacetic acid modifier) to give the purified product. The material was washed with sodium bicarbonate , extracted into ethyl acetate, and the solvent removed by rotary evaporation to give the purified free base. The free base was dissolved in ethyl acetate (~0.5 ml) and hydrogen chloride in diethyl ether (1 ml, 2.0M) was added to form the HCl salt. The solvent was removed by rotary evaporation to give the HCl salt as a white solid (90 mg, 13% yield). Absolute and relative stereochemistry were proven by x-ray crystallography. **^{1}H NMR** (400 MHz, CD_3OD) δ 8.01 – 7.87 (m, 1H), 7.70 – 7.45 (m, 3H), 4.20 – 4.07 (m, 1H), 3.33 – 3.26 (m, 1H), 2.72 – 2.47 (m, 2H), 2.34 – 2.23 (m, 1H) 2.02 (ddd, *J* = 13.6, 11.0, 1.0 Hz, 1H), 1.76 (qd, *J* = 12.8, 5.3 Hz, 1H). **^{13}C NMR** (101 MHz,

CD_3OD) δ 207.1, 134.8, 133.6, 133.2, 132.3, 131.1, 129.7, 66.4, 65.1, 45.5, 37.5, 36.1. **HRMS** (ESI+): Expected 262.0605 [M+H$^+$] ($C_{12}H_{14}ClNNaO_2^+$). Observed 262.0618. **[α]$_D^{20}$** -39.0° (*c* 1.0, MeOH, HCl salt).



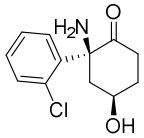
(*1S,5S*)-5-(2-Chlorophenyl)-2-oxa-4-azabicyclo[3.3.1]non-7-ene-3,6-dione (**27b**). **NCGC00489093**

Compound was prepared in an analogous fashion to its enantiomer by the use of *tert*-butyl (*S*)-(2'-chloro-6-oxo-3,6-dihydro-[1,1'-biphenyl]-1(2H)-yl)carbamate as a starting material, as opposed to the (*R*)-enantiomer. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.50 – 7.31 (m, 3H), 7.16 (ddd, *J* = 10.0, 6.1, 1.8 Hz, 1H), 6.58 (s, 1H), 6.43 (dd, *J* = 10.0, 0.7 Hz, 1H), 5.05 (ddd, *J* = 5.9, 3.3, 2.4 Hz, 1H), 3.30 (dt, *J* = 14.1, 2.3 Hz, 1H), 2.20 (ddd, *J* = 14.1, 3.4, 1.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 190.7, 151.5, 142.0, 135.2, 131.9, 131.4, 130.9, 130.3, 127.9, 127.0, 67.5, 63.2, 32.9. **HRMS** (ESI+): Expected 264.0422 [M+H$^+$] ($C_{13}H_{11}ClNO_2^+$). Observed 264.0431. **[α]$_D^{20}$**: -135.0° (*c* 1.0, $CHCl_3$)



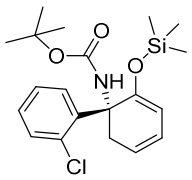
(*1R,5S*)-5-(2-Chlorophenyl)-2-oxa-4-azabicyclo[3.3.1]nonane-3,6-dione (**28b**). **NCGC00481482-01**

Compound was synthesized in an analogous form to its enantiomer, by use of (*1S,5S*)-5-(2-chlorophenyl)-2-oxa-4-azabicyclo[3.3.1]non-7-ene-3,6-dione as a starting material, as opposed to (*1R,5R*)-5-(2-chlorophenyl)-2-oxa-4-azabicyclo[3.3.1]non-7-ene-3,6-dione. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.51 – 7.30 (m, 3H), 7.16 (ddd, *J* = 10.0, 6.1, 1.8 Hz, 1H), 6.62 (s, 1H), 6.43 (dd, *J* = 10.0, 0.7 Hz, 1H), 5.05 (ddd, *J* = 5.9, 3.3, 2.4 Hz, 1H), 3.30 (dt, *J* = 14.1, 2.3 Hz, 1H), 2.20 (ddd, *J* = 14.1, 3.4, 1.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.9, 152.6, 134.6, 132.5, 131.3, 130.3, 127.6, 127.1, 71.7, 65.1, 34.8, 32.8, 32.7. **HRMS** (ESI+): Expected 266.0578 [M+H$^+$] ($C_{13}H_{14}ClNO_3^+$). Observed 266.0588**. [α]$_D^{20}$** : -189.9° (*c* 1.0, $CHCl_3$).



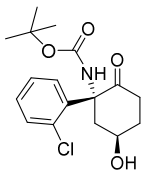
(*2S,4R*)-2-Amino-2-(2-chlorophenyl)-4-hydroxycyclohexan-1-one hydrochloride (**10b**). **NCGC00481516**

Compound was synthesized in an analogous fashion to its enantiomer by using (*1R,5S*)-5-(2-chlorophenyl)-2-oxa-4-azabicyclo[3.3.1]nonane-3,6-dione as a starting material instead of the (*1S,5R*) enantiomer. **^{1}H NMR** (400 MHz, CD_3OD) δ 8.00 – 7.88 (m, 1H), 7.73 – 7.46 (m, 3H), 4.13 (tdd, *J* = 10.9, 4.7, 3.7 Hz, 1H), 3.34 – 3.27 (m, 1H), 2.68 – 2.44 (m, 2H), 2.29 (dddt, *J* = 12.5, 5.7, 4.6, 3.3 Hz, 1H), 2.02 (dd, *J* = 13.6, 11.0 Hz, 1H), 1.84 – 1.67 (m, 1H). **^{13}C NMR** (101 MHz, CD_3OD) δ 207.2, 134.8, 133.6, 133.2, 132.3, 131.2, 129.7, 66.3, 65.1, 45.5, 37.5, 36.1. **HRMS** (ESI+): Expected 240.0786 [M+H$^+$] ($C_{12}H_{15}ClNO_2^+$). Observed 240.0790. **[α]$_D^{20}$**: + 51.4° (*c* 1.0, EtOH, HCl salt)



tert-Butyl (*R*)-(2'-chloro-6-((trimethylsilyl)oxy)-[1,1'-biphenyl]-1(2H)-yl)carbamate (**29a**). **NCGC00488915**

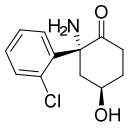
tert-Butyl (R)-(2'-chloro-6-oxo-3,6-dihydro-[1,1'-biphenyl]-1(2H)-yl)carbamate (2.1 grams, 6.9 mmol) was placed in a round bottom flask with a stirbar. The flask was sealed and put under nitrogen. Tetrahydrofuran (100 ml) was added. The reaction was then cooled to – 78 °C. Lithium diisopropylamide (8.0 mL, 16 mmol, 2.0M in THF/heptane/ethyl benzene) was then added via syringe. The reaction was stirred for 1 hour at – 78 °C. Then chlorotrimethylsilane (1.8 grams, 17 mmol, 2.1 ml) was added via syringe. The reaction was stirred for 0.5 hours at – 78 °C, then allowed to warm to room temperature over 0.5 hours. The reaction was then quenched by addition to saturated aqueous sodium bicarbonate. The reaction was extracted into ethyl acetate and the solvent was removed by rotary evaporation. Purification by silica gel chromatography (0% to 100% ethyl acetate in hexanes) gave the desired product as a viscous oil in ~90% purity (1.2 g, 46% yield). The compound was found to be unstable to further attempts to increase the purity by silica gel chromatography. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 – 7.43 (m, 1H), 7.41 – 7.31 (m, 1H), 7.22 – 7.09 (m, 2H), 5.82 (ddt, *J* = 9.6, 6.0, 1.8 Hz, 1H), 5.46 (dtd, *J* = 9.4, 4.3, 0.8 Hz, 1H), 5.38 – 5.22 (m, 1H), 5.11 (s, 1H), 3.45 – 3.20 (m, 2H), 1.43 (s, 9H), 0.18 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.6, 138.5, 132.7, 131.8, 129.5, 128.7, 126.4, 123.0, 119.3, 103.1, 79.2, 62.3, 34.7, 28.6, 0.4, 0.1**. HRMS** (ESI+): Expected 416.1419 [M+Na$^+$] ($C_{20}H_{28}ClNNaO_3Si^+$). Observed 360.0793 ($C_{16}H_{20}ClNNaO_3Si^+$). The observed mass matches the replacement of the *tert*-butyl group from the *tert*-butyl carbamate with a hydrogen atom under the HRMS conditions. **$[\alpha]_D^{20}$**: - 12.6° (*c* 1.0, $CHCl_3$)



tert-Butyl ((*1R,5R*)-1-(2-chlorophenyl)-5-hydroxy-2-oxocyclohexyl)carbamate (**32a**). **NCGC00499295**

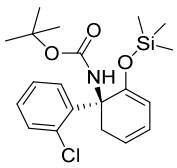
Sodium bicarbonate (260 mg, 3.1 mmol) was added to a solution of *tert*-butyl (*R*)-(2'-chloro-6-((trimethylsilyl)oxy)-[1,1'-biphenyl]-1(2H)-yl)carbamate (1.2 g, 3.1 mmol) in toluene (50 ml). The reaction was cooled to 0 °C and 3-chloroperbenzoic acid (770 mg, 75% by weight, 3.1 mmol) was added as a solid. The reaction was stirred for 1 hour at 0 °C and was then quenched by being poured into a 1:1 solution of aqueous sodium bicarbonate and aqueous sodium thiosulfate. The mixture was extracted with ethyl acetate, and the solvent was removed by rotary evaporation. The resulting crude product was dissolved in tetrahydrofuran (50 mL) and a stir bar was added. The solution was cooled to 0 °C, and acetic acid (0.15 mL, 0.16 g, 2.60 mmol) was added, followed by tetrabutylammonium fluoride (3.1 mL, 1.0 M in tetrahydrofuran, 3.1 mmol). The reaction was stirred for 2 minutes at 0 °C, and was then quenched by being poured into aqueous sodium bicarbonate. The mixture was extracted with ethyl acetate, and the organic solvent was removed by rotary evaporation to give the crude product. Purification by silica gel chromatography (0% to 100% ethyl acetate in hexanes) gave the desired diastereomer (first eluting) in 7.5% yield (77 mg) at ~90% purity, and the undesired diastereomer (second eluting) in 47% yield (480 mg). The desired diastereomer proved to be too unstable for further purification, and required being taken on to the next synthetic step without further purification. The semi-crude ^{1}H NMR spectrum is reported here.. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.26 (m, 4H), 7.05 (d, *J* = 10.5 Hz, 1H), 6.21 – 6.05 (dd, *J* =1.6, 10.5 Hz, 1H), 4.84 (s, 1H), 4.79 – 4.73 (m, 1H), 3.57 – 3.48 (m, 1H), 2.97 (dd, *J* = 13.5, 9.5 Hz, 1H), 1.49 (s, 9H). In the second step, 10% palladium on carbon (3.5 mg) was added to a vial with a stirbar. The vial was sealed, evacuated, and backfilled with nitrogen. Water (0.05 ml), followed by methanol (2.0 ml) was added via syringe. Then semi-crude *tert*-butyl ((*1R,3S*)-2'-chloro-3-hydroxy-6-oxo-3,6-dihydro-[1,1'-biphenyl]-1(2H)-yl)carbamate (77 mg, 0.23 mmol) in methanol (1.0 ml) was added. The vial was placed under vacuum briefly, then a balloon of hydrogen gas was added. The reaction was stirred for 30 minutes. Then the hydrogen gas was removed and the reaction was filtered through a nylon 0.45 μM syringe filter. The resulting solution had the solvent removed by rotary evaporation. Purification by silica gel chromatography (0% to 100% ethyl acetate in hexanes) gave the title product as a white solid (25 mg, 2.4% yield from the starting material). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.37 – 7.13 (m, 3H), 5.86 (s, 1H), 4.31 (tq, *J* = 6.6, 4.4 Hz, 1H), 3.43

(dd, J = 15.2, 6.3 Hz, 1H), 2.75 – 2.55 (m, 2H), 2.31 (d, J = 14.6 Hz, 1H), 2.26 – 2.12 (m, 1H), 2.09 – 2.02 (m, 1H), 1.34 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 205.9 (via ^{1}H-^{13}C HMBC) 154.0, 136.8, 133.0, 131.2, 130.5, 129.5, 126.3, 80.4, 66.9, 65.6, 36.2, 34.9, 28.4. **HRMS** (ESI+): Expected 362.1130 [M+Na^+] ($C_{17}H_{22}ClNNaO_4^+$). Observed 362.1144. **$[\alpha]_D^{20}$**: -22.0° (*c* 1.0, $CHCl_3$)



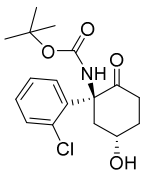
(*2R,4R*)-2-Amino-2-(2-chlorophenyl)-4-hydroxycyclohexan-1-one hydrochloride (**11a**). **NCGC00488918**

Trifluoroacetic acid (1.0 mL, 13 mmol) was added to a solution of *tert*-butyl ((*1R,5R*)-1-(2-chlorophenyl)-5-hydroxy-2-oxocyclohexyl)carbamate (20 mg, 0.059 mmol) in dichloromethane (1.0 mL) at 0 °C. The reaction was stirred for 30 minutes at 0 °C. The solvent and trifluoroacetic acid were then removed by rotary evaporation. The crude material was treated with aqueous sodium bicarbonate and extracted into ethyl acetate. The solvent was removed by rotary evaporation to give the free base. The compound was dissolved in ethyl acetate (0.5 ml). Hydrogen chloride in diethyl ether (2.0 M, 0.50 ml) was then added. The solvent was then removed by rotary evaporation to give the hydrochloride salt as a white solid (10 mg, 61% yield). **^{1}H NMR** (400 MHz, CD_3OD) δ 7.98 – 7.86 (m, 1H), 7.54 – 7.35 (m, 3H), 4.26 (p, J = 3.9 Hz, 1H), 3.40 (d, J = 14.6 Hz, 1H), 3.04 (ddd, J = 13.2, 11.6, 5.6 Hz, 1H), 2.62 (dt, J = 13.2, 4.9 Hz, 1H), 2.27 – 1.95 (m, 3H). **^{13}C NMR** (101 MHz, CD_3OD) δ 208.9, 135.5, 133.6, 132.3 (2C), 132.3, 128.3, 67.4, 65.3, 37.1, 36.1. **HRMS** (ESI+): Expected 240.0786 [M+H^+] ($C_{12}H_{16}ClNO_2^+$). Observed 240.0788. **$[\alpha]_D^{20}$:** - 10.2° (*c* 0.5, MeOH, HCl salt).



tert-Butyl (*S*)-(2'-chloro-6-((trimethylsilyl)oxy)-[1,1'-biphenyl]-1(2H)-yl)carbamate (**29b**). **NCGC00505098**

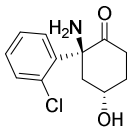
Compound was synthesized in an analogous form to its enantiomer, by use of *tert*-butyl (S)-(2'-chloro-6-oxo-3,6-dihydro-[1,1'-biphenyl]-1(2H)-yl)carbamate. Compound was isolated in ~70% purity. Further purification resulted in degradation of the compound. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 – 7.44 (m, 1H), 7.39 – 7.32 (m, 1H), 7.24 – 7.14 (m, 2H), 5.82 (ddt, J = 9.5, 6.0, 1.7 Hz, 1H), 5.49 – 5.39 (m, 1H), 5.35 – 5.26 (m, 1H), 5.11 (s, 1H), 3.49 – 3.18 (m, 2H), 1.43 (s, 9H) 0.35 – -0.03 (m, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.6, 138.6, 132.7, 131.81, 129.6, 128.6, 126.4, 123.0, 119.3, 103.1, 79.2, 62.3, 34.8, 28.6 0.30, 0.10. **HRMS** (ESI+): Expected 416.1419 ($C_{20}H_{28}ClNNaO_3Si^+$). Observed 416.1402 **$[\alpha]_D^{20}$:** +6.2° (*c* 1.0, $CHCl_3$)



tert-Butyl ((*1S,5S*)-1-(2-chlorophenyl)-5-hydroxy-2-oxocyclohexyl)carbamate (**32b**). **NCGC00499627**

Compound was synthesized in an analogous form to its enantiomer by use of *tert*-butyl (*S*)-(2'-chloro-6-((trimethylsilyl)oxy)-[1,1'-biphenyl]-1(2H)-yl)carbamate. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (dd, J = 7.9, 1.8 Hz, 1H), 7.39 – 7.26 (m, 2H), 5.87 (s, 1H), 4.38 – 4.30 (m, 1H), 3.54 – 3.46 (m, 1H), 2.77 – 2.56 (m, 2H), 2.38 – 2.29 (m, 1H),

2.24 – 2.15 (m, 1H), 2.07 (dtd, J = 13.6, 6.8, 1.6 Hz, 1H), 1.36 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 206.0, 154.1, 136.8, 133.0, 131.2, 130.4, 129.4, 126.3, 80.4, 66.9, 65.6, 44.3, 36.1, 34.9, 28.4. **HRMS** (ESI+): Expected 362.1130 [M+Na$^+$] ($C_{12}H_{16}ClNO_2^+$). Observed 362.1140. **$[\alpha]_D^{20}$**: +22°(c 1.0, $CHCl_3$)



(*2S,4S*)-2-amino-2-(2-chlorophenyl)-4-hydroxycyclohexan-1-one hydrochloride (**11b**). **NCGC00492317**

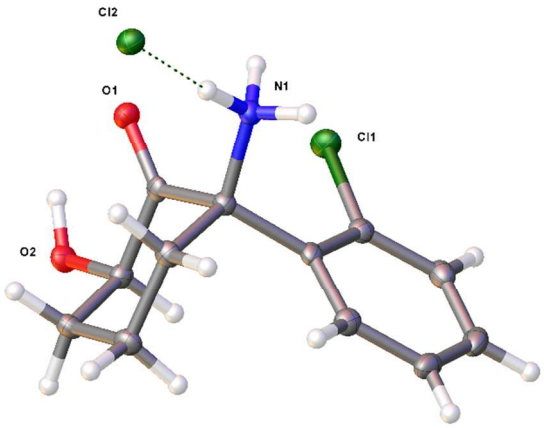
Compound was synthesized in an analogous form to its enantiomer by use of *tert*-butyl ((*1S,5S*)-1-(2-chlorophenyl)-5-hydroxy-2-oxocyclohexyl)carbamate. **^{1}H NMR** (400 MHz, CD_3OD, hydrochloride salt) δ 7.98 – 7.81 (m, 1H), 7.54 – 7.42 (m, 3H), 4.26 – 4.22 (m, 1H), 3.50 – 3.42 (m, 1H), 3.08 (dt, J = 12.7, 6.4 Hz, 1H), 2.58 (dt, J = 12.9, 4.4 Hz, 1H), 2.20 – 1.94 (m, 3H). **^{13}C NMR** (101 MHz, CD_3OD) δ 208.6, 134.2, 133.7, 132.7, 132.6, 132.4, 128.4, 67.7, 65.2, 44.2, 37.5, 36.1. **HRMS** (ESI+): Expected 240.0786 [M+H$^+$] ($C_{12}H_{16}ClNO_2^+$). Observed 240.0798. **$[\alpha]_D^{20}$** + 38° (c 1.0, MeOH, HCl salt).

X-ray crystallography structural data

Introduction and General Experimental: The absolute and relative stereochemistry for all hydroxynorketamines was established unambiguously by single crystal x-ray crystallography. All crystal structures are also available as a crystallographic information file and have been uploaded to the Cambridge Crystallographic Data Center (CCDC). The single crystal X-ray diffraction studies were carried out on a Bruker Kappa APEX-II CCD diffractometer equipped with Mo K_α radiation (λ = 0.71073 Å). Data were collected in a nitrogen gas stream at 100(2) K using ϕ and ϖ scans. The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. All other hydrogen atoms (H-bonding) were located in the difference map. Their relative positions were restrained using DFIX commands and their thermals freely refined. Detailed experimentals, structural representations, and data are provided below.

(*2R,6R*)-2-amino-2-(2-chlorophenyl)-6-hydroxycyclohexan-1-one. NCGC00378227. CCDC 1560522

Crystals of the subject compound were grown by dissolving approximately 1mg of sample in 350µL of methanol and then allowing the resultant solution to slowly evaporate over two days. A 0.107 x 0.051 x 0.026 mm piece of a colorless block was mounted on a Cryoloop with Paratone oil. Crystal-to-detector distance was 35 mm and exposure time was 5 seconds per frame using a scan width of 2.0°. Data collection was 100% complete to 25.00° in θ. A total of 14291 reflections were collected covering the indices, -9<=h<=9, -9<=k<=9, -14<=l<=14. 2510 reflections were found to be symmetry independent, with a R_{int} of 0.0438. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be $P2_1$. The absolute stereochemistry of the molecule was established by anomalous dispersion using the Parson's method with a Flack parameter of 0.037(26).



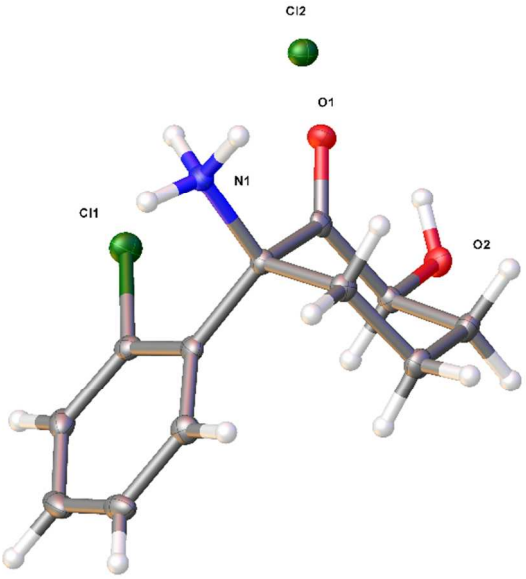
Crystal data and structure refinement for NCGC00378227.

Report date	2016-07-03
Identification code	NCGC00378227-17
Empirical formula	C12 H15 Cl2 N O2
Molecular formula	C12 H15 Cl N O2, Cl

Formula weight	276.15	
Temperature	100.0 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 7.3539(8) Å	α= 90°.
	b = 7.4949(7) Å	β= 96.835(3)°.
	c = 11.3571(13) Å	γ = 90°.
Volume	621.52(11) $Å^3$	
Z	2	
Density (calculated)	1.476 Mg/m^3	
Absorption coefficient	0.511 mm^{-1}	
F(000)	288	
Crystal size	0.107 x 0.051 x 0.026 mm^3	
Crystal color, habit	Colorless Block	
Theta range for data collection	1.806 to 26.351°.	
Index ranges	-9<=h<=9, -9<=k<=9, -14<=l<=14	
Reflections collected	14291	
Independent reflections	2510 [R(int) = 0.0438]	
Completeness to theta = 25.000°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.0932 and 0.0694	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2510 / 5 / 170	
Goodness-of-fit on F^2	1.036	
Final R indices [I>2sigma(I)]	R1 = 0.0213, wR2 = 0.0525	
R indices (all data)	R1 = 0.0223, wR2 = 0.0532	
Absolute structure parameter	0.04(3)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.193 and -0.159 $e.Å^{-3}$	

(*2S,6S*)-2-amino-2-(2-chlorophenyl)-6-hydroxycyclohexan-1-one NCGC00373033. CCDC 1560521

Crystals of the subject compound were grown by dissolving approximately 1mg of sample in 350µL of a 50/50 dichloroethane/methanol solution, which was then vapor diffused with diethyl ether over two days. A 0.467 x 0.323 x 0.215 mm piece of a colorless rod was mounted on a Cryoloop with Paratone oil. Crystal-to-detector distance was 40 mm and exposure time was 5 seconds per frame using a scan width of 2.0°. Data collection was 100% complete to 25.00° in *θ*. A total of 10243 reflections were collected covering the indices, -9<=h<=8, -9<=k<=9, -14<=l<=11. 2513 reflections were found to be symmetry independent, with a R_{int} of 0.0267. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be $P2_1$. The absolute stereochemistry of the molecule was established by anomalous dispersion using the Parson's method with a Flack parameter of 0.008(18).



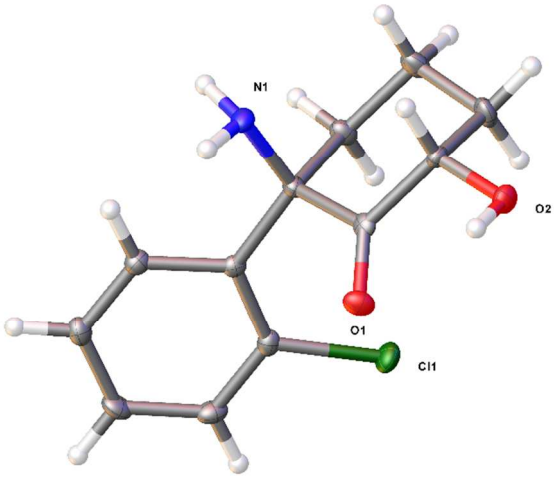
Crystal data and structure refinement for NCGC00373033

Report date	2016-08-04	
Identification code	NIH17	
Empirical formula	C12 H15 Cl2 N O2	
Molecular formula	C12 H15 Cl N O2, Cl	
Formula weight	276.15	
Temperature	100 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 7.3612(9) Å	α= 90°.
	b = 7.4951(9) Å	β= 96.832(3)°.
	c = 11.3569(13) Å	λ = 90°.
Volume	622.14(13) $Å^3$	
Z	2	
Density (calculated)	1.474 Mg/m^3	
Absorption coefficient	0.510 mm^{-1}	
F(000)	288	
Crystal size	0.467 x 0.323 x 0.215 mm^3	
Crystal color, habit	Colorless Rod	
Theta range for data collection	1.806 to 26.386°.	
Index ranges	-9<=h<=8, -9<=k<=9, -14<=l<=11	
Reflections collected	10243	
Independent reflections	2513 [R(int) = 0.0267, R(sigma) = 0.0229]	
Completeness to theta = 25.000°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.0932 and 0.0664	

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2513 / 5 / 170
Goodness-of-fit on F^2	1.046
Final R indices [I>2sigma(I)]	R1 = 0.0200, wR2 = 0.0509
R indices (all data)	R1 = 0.0209, wR2 = 0.0515
Absolute structure parameter	0.008(18)
Extinction coefficient	n/a
Largest diff. peak and hole	0.235 and -0.152 e.Å^{-3}

(*2R,6S*)-2-amino-2-(2-chlorophenyl)-6-hydroxycyclohexan-1-one NCGC00483973. CCDC 1560520

Crystals of the subject compound were grown by dissolving approximately 1mg of sample in 350µL of dichloroethane, which was then vapor diffused with pentane over two days. A 0.417 x 0.405 x 0.386 mm piece of a colorless block was mounted on a Cryoloop with Paratone oil. Crystal-to-detector distance was 40 mm and exposure time was 2 seconds per frame using a scan width of 1.0°. Data collection was 99.7% complete to 25.00° in θ. A total of 14877 reflections were collected covering the indices, -9<=h<=8, -10<=k<=10, -22<=l<=23. 2330 reflections were found to be symmetry independent, with a R_{int} of 0.0355. Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be $P2_12_12_1$. The absolute stereochemistry of the molecule was established by anomalous dispersion using the Parson's method with a Flack parameter of -0.002(20).



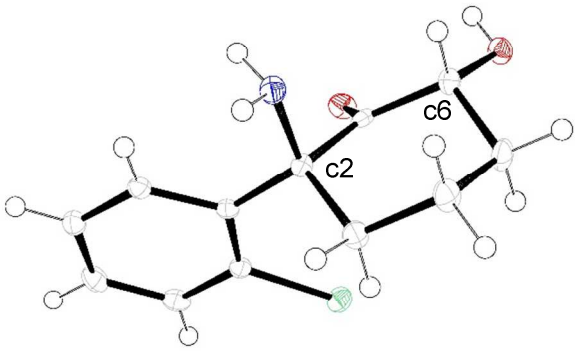
Crystal data and structure refinement for NCGC00483973

Report date	2016-08-04	
Identification code	NCGC00483973-01	
Empirical formula	C12 H14 Cl N O2	
Molecular formula	C12 H14 Cl N O2	
Formula weight	239.69	
Temperature	100 K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 7.2604(2) Å	α= 90°.
	b = 8.2772(2) Å	β= 90°.
	c = 18.9206(4) Å	λ = 90°.

Volume	1137.05(5) $Å^3$
Z	4
Density (calculated)	1.400 Mg/m^3
Absorption coefficient	0.320 mm^{-1}
F(000)	504
Crystal size	0.417 x 0.405 x 0.386 mm^3
Crystal color, habit	Colorless Block
Theta range for data collection	2.686 to 26.374°.
Index ranges	-9<=h<=8, -10<=k<=10, -22<=l<=23
Reflections collected	14877
Independent reflections	2330 [R(int) = 0.0355, R(sigma) = 0.0232]
Completeness to theta = 25.000°	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.2602 and 0.2236
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2330 / 3 / 157
Goodness-of-fit on F^2	1.057
Final R indices [I>2sigma(I)]	R1 = 0.0234, wR2 = 0.0570
R indices (all data)	R1 = 0.0249, wR2 = 0.0577
Absolute structure parameter	0.00(2)
Extinction coefficient	n/a
Largest diff. peak and hole	0.213 and -0.180 $e.Å^{-3}$

(*2S,6R*)-2-amino-2-(2-chlorophenyl)-6-hydroxycyclohexan-1-one. NCGC00481329. CCDC 1560517

X-ray quality crystals were grown from a saturated 1,2-dichloroethane/ethanol/methanol solution followed by the slow vapor diffusion of heptane to deposit the crystal diffracted. A colorless prism 0.070 x 0.060 x 0.050 mm in size was mounted on a Cryoloop with Paratone oil. Crystal-to-detector distance was 60 mm and exposure time was 1 seconds per frame using a scan width of 2.0°. Data collection was 99.6% complete to 67.000° in θ. A total of 13849 reflections were collected covering the indices, -8<=*h*<=6, -9<=*k*<=9, -22<=*l*<=22. 2066 reflections were found to be symmetry independent, with an R_{int} of 0.0255. Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be P 21 21 21 (No. 19). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT-2014) produced a complete heavy-atom phasing model consistent with the proposed structure. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2016. Absolute stereochemistry was unambiguously determined to be *R* at C6 and *S* at C2, respectively.



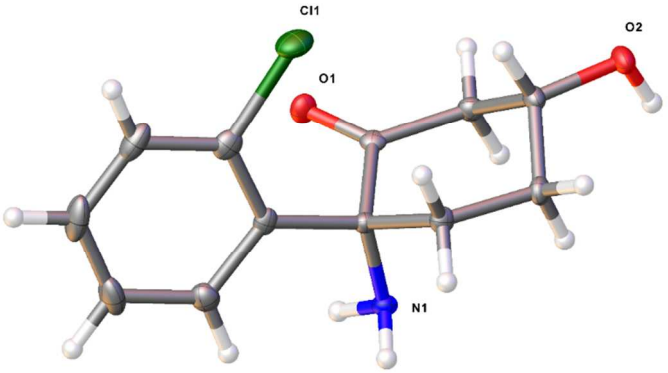
Crystal data and structure refinement for NCGC00481329

X-ray ID	ncats02	
Sample/notebook ID	NCGC00481329	
Empirical formula	C12 H14 Cl N O2	
Formula weight	239.69	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 7.2478(4) Å	α = 90°.
	b = 8.2707(4) Å	β = 90°.
	c = 18.9058(10) Å	λ = 90°.
Volume	1133.30(10) $Å^3$	
Z	4	
Density (calculated)	1.405 Mg/m^3	
Absorption coefficient	2.862 mm^{-1}	
F(000)	504	
Crystal size	0.070 x 0.060 x 0.050 mm^3	
Theta range for data collection	4.678 to 68.479°.	
Index ranges	-8<=h<=6, -9<=k<=9, -22<=l<=22	
Reflections collected	13849	
Independent reflections	2066 [R(int) = 0.0255]	
Completeness to theta = 67.000°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.753 and 0.623	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2066 / 0 / 146	
Goodness-of-fit on F^2	1.099	
Final R indices [I>2sigma(I)]	R1 = 0.0229, wR2 = 0.0597	
R indices (all data)	R1 = 0.0229, wR2 = 0.0598	
Absolute structure parameter	0.008(4)	
Extinction coefficient	n/a	

Largest diff. peak and hole	0.220 and -0.183 e.Å^{-3}

(*2R,5R*)-2-amino-2-(2-chlorophenyl)-5-hydroxycyclohexan-1-one. NCGC00488764. CCDC 1558893

Crystals of the subject compound were grown by dissolving approximately 1mg of sample in 350µL of ethanol, which was then vapor diffused with Pentane over several. Crystal-to-detector distance was 40 mm and exposure time was 5 seconds per frame using a scan width of 1.0°. Data collection was 99.9% complete to 25.00° in θ. A total of 15998 reflections were collected covering the indices, -9<=h<=9, -9<=k<=8, -24<=l<=25. 2262 reflections were found to be symmetry independent, with a R_{int} of 0.0455. Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be $P2_12_12_1$. The absolute stereochemistry of the molecule was established by anomalous dispersion using the Parson's method with a Flack parameter of 0.068(34).



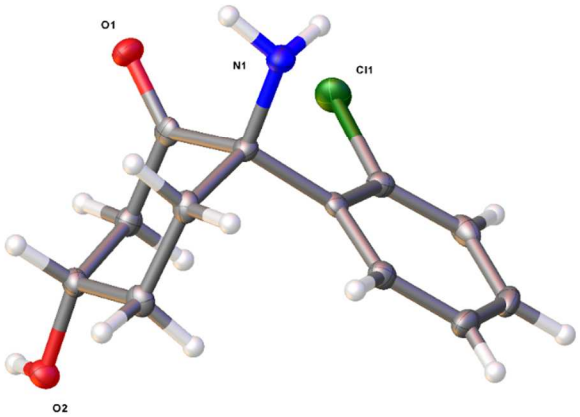
Crystal data and structure refinement for NCGC00488764

Report date	2017-01-25	
Identification code	NCGC00488764-02	
Empirical formula	C12 H14 Cl N O2	
Molecular formula	C12 H14 Cl N O2	
Formula weight	239.69	
Temperature	100.0 K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 7.4095(7) Å	α= 90°.
	b = 7.4183(7) Å	β= 90°.
	c = 20.1227(18) Å	λ = 90°.
Volume	1106.06(18) Å^3	
Z	4	
Density (calculated)	1.439 Mg/m^3	
Absorption coefficient	0.329 mm^{-1}	

F(000)	504
Crystal size	0.279 x 0.253 x 0.216 mm^3
Crystal color, habit	Colorless Block
Theta range for data collection	2.927 to 26.365°.
Index ranges	-9<=h<=9, -9<=k<=8, -24<=l<=25
Reflections collected	15998
Independent reflections	2262 [R(int) = 0.0455, R(sigma) = 0.0333]
Completeness to theta = 25.000°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.2602 and 0.2259
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2262 / 3 / 157
Goodness-of-fit on F^2	1.060
Final R indices [I>2sigma(I)]	R1 = 0.0301, wR2 = 0.0629
R indices (all data)	R1 = 0.0360, wR2 = 0.0656
Absolute structure parameter	0.07(3)
Extinction coefficient	n/a
Largest diff. peak and hole	0.204 and -0.186 e.$Å^{-3}$

(*2R,5S*)-2-amino-2-(2-chlorophenyl)-5-hydroxycyclohexan-1-one NCGC00488759. CCDC 1558891

Crystals of the subject compound were grown by dissolving approximately 1mg of sample in 350µL of dichloromethane, which was then vapor diffused with Pentane over several days. A 0.218 x 0.207 x 0.134 mm piece of a colorless block was mounted on a Cryoloop with Paratone oil. Crystal-to-detector distance was 45 mm and exposure time was 3 seconds per frame using a scan width of 1.5°. Data collection was 99.9% complete to 25.00° in θ. A total of 13443 reflections were collected covering the indices, -8<=h<=8, -8<=k<=8, -17<=l<=25. 2091 reflections were found to be symmetry independent, with a R_{int} of 0.0393. Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be $P2_12_12_1$. The absolute stereochemistry of the molecule was established by anomalous dispersion using the Parson's method with a Flack parameter of 0.012(28).

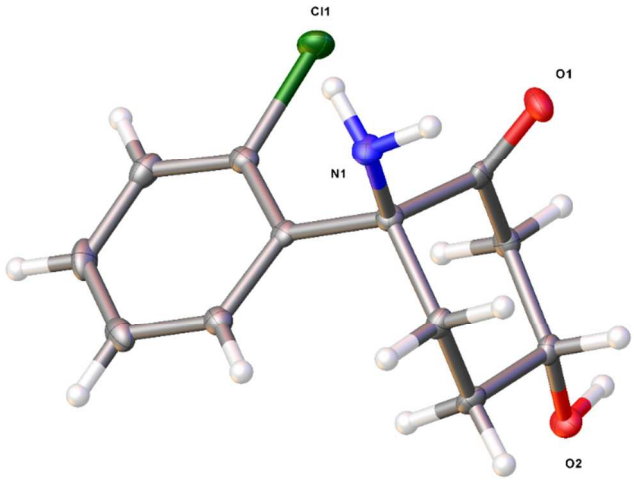


Crystal data and structure refinement for NCGC00488759

Report date	2017-01-25	
Identification code	NCGC00488759-02	
Empirical formula	C12 H14 Cl N O2	
Molecular formula	C12 H14 Cl N O2	
Formula weight	239.69	
Temperature	100.0 K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 7.2205(6) Å	α= 90°.
	b = 7.3718(5) Å	β= 90°.
	c = 21.3401(15) Å	λ = 90°.
Volume	1135.89(15) $Å^3$	
Z	4	
Density (calculated)	1.402 Mg/m^3	
Absorption coefficient	0.320 mm^{-1}	
F(000)	504	
Crystal size	0.218 x 0.207 x 0.134 mm^3	
Crystal color, habit	Colorless Block	
Theta range for data collection	2.923 to 25.390°.	
Index ranges	-8<=h<=8, -8<=k<=8, -17<=l<=25	
Reflections collected	13443	
Independent reflections	2091 [R(int) = 0.0393, R(sigma) = 0.0282]	
Completeness to theta = 25.000°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.2590 and 0.2265	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2091 / 3 / 157	
Goodness-of-fit on F^2	1.066	
Final R indices [I>2sigma(I)]	R1 = 0.0265, wR2 = 0.0604	
R indices (all data)	R1 = 0.0296, wR2 = 0.0620	
Absolute structure parameter	0.01(3)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.221 and -0.165 e.$Å^{-3}$	

(*2S,5R*)-2-amino-2-(2-chlorophenyl)-5-hydroxycyclohexan-1-one. NCGC00489857. CCDC 1560519

Crystals of the subject compound were grown by dissolving approximately 1mg of sample in 350µL of dichloroethane, which was then vapor diffused with Pentane over several days. A 0.209 x 0.095 x 0.087 mm piece of a colorless block was mounted on a Cryoloop with Paratone oil. Crystal-to-detector distance was 40 mm and exposure time was 2 seconds per frame using a scan width of 2.0°. Data collection was 100% complete to 25.00° in θ. A total of 12041 reflections were collected covering the indices, -8<=h<=8, -8<=k<=8, -25<=l<=21. 2083 reflections were found to be symmetry independent, with a R_{int} of 0.0615. Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be $P2_12_12_1$. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. All other hydrogen atoms (H-bonding) were located in the difference map. The absolute stereochemistry of the molecule was established by anomalous dispersion using the Parson's method with a Flack parameter of 0.007(41).



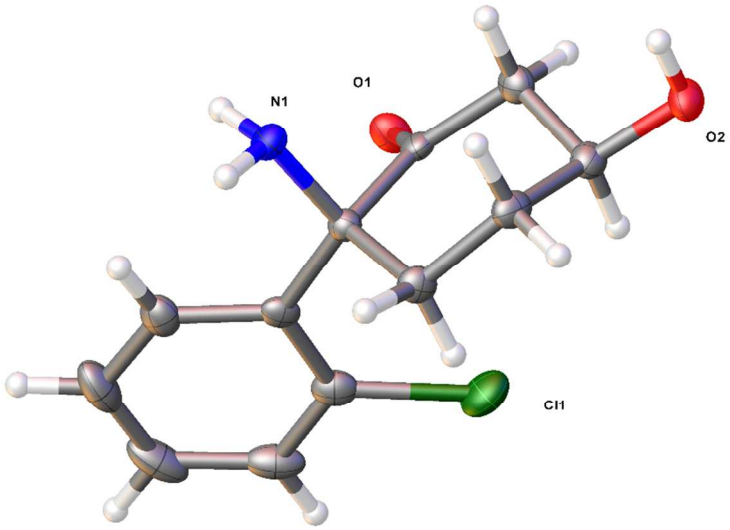
Crystal data and structure refinement for NCGC0048957

Report date	2016-10-20	
Identification code	NCGC0048957-01	
Empirical formula	C12 H14 Cl N O2	
Molecular formula	C12 H14 Cl N O2	
Formula weight	239.69	
Temperature	100.0 K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 7.2277(3) Å	α= 90°.
	b = 7.3744(3) Å	β= 90°.
	c = 21.3606(8) Å	λ= 90°.
Volume	1138.52(8) $Å^3$	
Z	4	
Density (calculated)	1.398 Mg/m^3	
Absorption coefficient	0.319 mm^{-1}	
F(000)	504	

Crystal size	0.209 x 0.095 x 0.087 mm^3
Crystal color, habit	Colorless Rod
Theta range for data collection	1.907 to 25.331°.
Index ranges	-8<=h<=8, -8<=k<=8, -25<=l<=21
Reflections collected	12041
Independent reflections	2083 [R(int) = 0.0615, R(sigma) = 0.0425]
Completeness to theta = 25.000°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.2417 and 0.2061
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2083 / 3 / 157
Goodness-of-fit on F^2	1.050
Final R indices [I>2sigma(I)]	R1 = 0.0297, wR2 = 0.0751
R indices (all data)	R1 = 0.0312, wR2 = 0.0761
Absolute structure parameter	0.007(41)
Extinction coefficient	n/a
Largest diff. peak and hole	0.242 and -0.211 $e.Å^{-3}$

(*2S,5S*)-2-amino-2-(2-chlorophenyl)-5-hydroxycyclohexan-1-one. NCGC00389131. CCDC 1558890

Crystals of the subject compound were grown by dissolving approximately 1mg of sample in 350µL of dichloromethane, which was then vapor diffused with MTBE over several days. A 0.167 x 0.133 x 0.054 mm piece of a colorless block was mounted on a Cryoloop with Paratone oil. Crystal-to-detector distance was 35 mm and exposure time was 4 seconds per frame using a scan width of 2.0°. Data collection was 99.9% complete to 25.00° in θ.. A total of 13037 reflections were collected covering the indices, -9<=h<=7, -9<=k<=9, -25<=l<=25. 2250 reflections were found to be symmetry independent, with a R_{int} of 0.0361. Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be $P2_12_12_1$. The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.. All other hydrogen atoms (H-bonding) were located in the difference map. Their relative positions were restrained using DFIX commands and their thermals freely refined. The absolute stereochemistry of the molecule was established by anomalous dispersion using the Parson's method with a Flack parameter of -0.025(30).

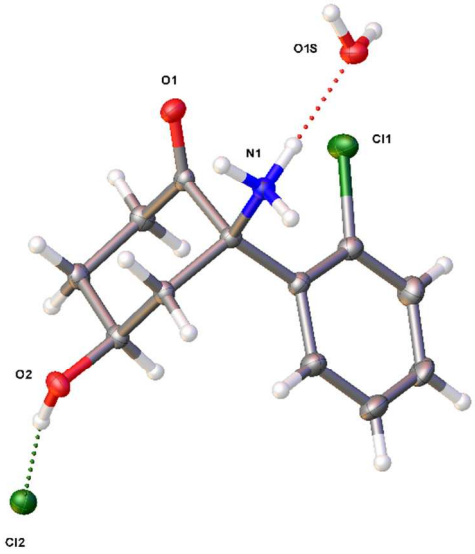


Crystal data and structure refinement for NCGC00389131

Report date	2017-05-05	
Identification code	NCGC00389131	
Empirical formula	C12 H14 Cl N O2	
Molecular formula	C12 H14 Cl N O2	
Formula weight	239.69	
Temperature	100 K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 7.3777(5) Å	α= 90°.
	b = 7.4315(5) Å	β= 90°.
	c = 20.1273(14) Å	γ = 90°.
Volume	1103.53(13) $Å^3$	
Z	4	
Density (calculated)	1.443 Mg/m^3	
Absorption coefficient	0.330 mm^{-1}	
F(000)	504	
Crystal size	0.167 x 0.133 x 0.054 mm^3	
Crystal color, habit	Colorless Block	
Theta range for data collection	2.922 to 26.371°.	
Index ranges	-9<=h<=7, -9<=k<=9, -25<=l<=25	
Reflections collected	13037	
Independent reflections	2250 [R(int) = 0.0361, R(sigma) = 0.0298]	
Completeness to theta = 25.000°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.0932 and 0.0697	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2250 / 3 / 157	
Goodness-of-fit on F^2	1.095	
Final R indices [I>2sigma(I)]	R1 = 0.0345, wR2 = 0.0733	
R indices (all data)	R1 = 0.0401, wR2 = 0.0753	
Absolute structure parameter	-0.03(3)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.252 and -0.200 $e.Å^{-3}$	

(*2R,4S*)-2-amino-2-(2-chlorophenyl)-4-hydroxycyclohexan-1-one. NCGC00389998. CCDC 1560518

Crystals of the subject compound were grown by dissolving approximately 1mg of sample in 350 µL of dichloroethane, which was then vapor diffused with pentane over several days. A 0.213 x 0.207 x 0.128 mm piece of a colorless block was mounted on a Cryoloop with Paratone oil. Crystal-to-detector distance was 35 mm and exposure time was 2 seconds per frame using a scan width of 2.0°. Data collection was 100% complete to 25.00° in θ. A total of 25445 reflections were collected covering the indices, -9<=h<=9, -11<=k<=11, -12<=l<=15. 3572 reflections were found to be symmetry independent, with a R_{int} of 0.0475. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be $P2_1$. All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. All other hydrogen atoms (H-bonding) were located in the difference map. Their relative positions were restrained using DFIX commands and their thermals freely refined. The absolute stereochemistry of the molecule was established by anomalous dispersion using the Parson's method with a Flack parameter of 0.018(22).



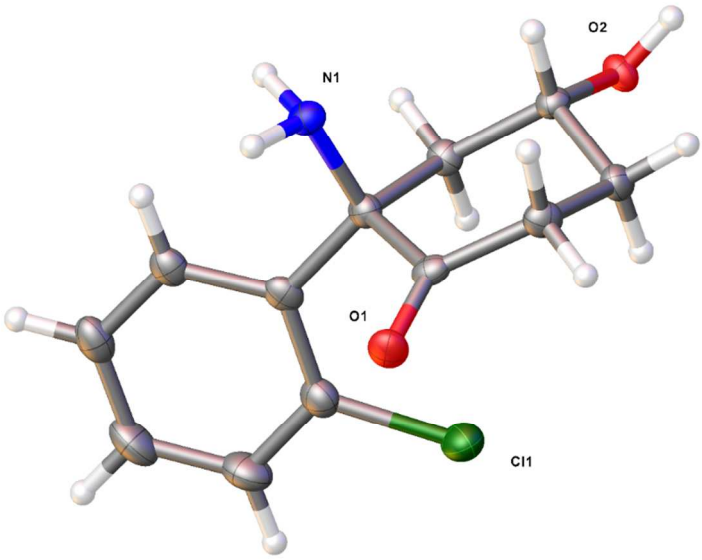
Crystal data and structure refinement for NCGC00389998

Report date	2017-03-22	
Identification code	NCGC00389998-02	
Empirical formula	C12 H17 Cl2 N O3	
Molecular formula	C12 H15 Cl N O2, Cl, H2 O	
Formula weight	294.16	
Temperature	100.0 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 7.4047(4) Å	α= 90°.
	b = 8.7079(5) Å	β= 107.542(2)°.
	c = 11.7729(6) Å	λ = 90°.
Volume	723.81(7) $Å^3$	
Z	2	

Density (calculated)	1.350 Mg/m^3
Absorption coefficient	0.448 mm^{-1}
F(000)	308
Crystal size	0.213 x 0.207 x 0.128 mm^3
Crystal color, habit	Colorless Block
Theta range for data collection	1.814 to 28.300°.
Index ranges	-9<=h<=9, -11<=k<=11, -12<=l<=15
Reflections collected	25445
Independent reflections	3572 [R(int) = 0.0475, R(sigma) = 0.0302]
Completeness to theta = 25.000°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.0891 and 0.0635
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3572 / 7 / 187
Goodness-of-fit on F^2	1.063
Final R indices [I>2sigma(I)]	R1 = 0.0260, wR2 = 0.0652
R indices (all data)	R1 = 0.0264, wR2 = 0.0655
Absolute structure parameter	0.02(2)
Extinction coefficient	n/a
Largest diff. peak and hole	0.239 and -0.193 $e.Å^{-3}$

(*2R,4R*)-2-amino-2-(2-chlorophenyl)-4-hydroxycyclohexan-1-one. NCGC00488918. CCDC 1558889

Crystals of the subject compound were grown by dissolving approximately 1mg of sample in 350µL of Dichloroethane, which was then vapor diffused with MTBE over several days, followed by slow evaporation of the resultant solution for 3 days. Crystal-to-detector distance was 40 mm using variable exposure time (2s-10s) depending on θ with a scan width of 1.0°. Data collection was 100% complete to 68.00° in *θ*. A total of 13135 reflections were collected covering the indices, -9<=h<=9, -10<=k<=10, -39<=l<=39. 4251 reflections were found to be symmetry independent, with a R_{int} of 0.0502. Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be $P2_12_12_1$. All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. All other hydrogen atoms (H-bonding) were located in the difference map. Their relative positions were restrained using DFIX commands and their thermals freely refined. The absolute stereochemistry of the molecule was established by anomalous dispersion using the Parson's method with a Flack parameter of -0.005(12).



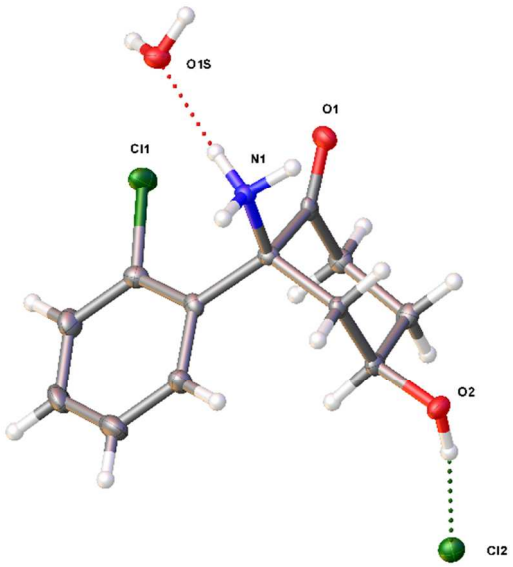
Crystal data and structure refinement for NCGC00488918.

Report date	2017-05-05	
Identification code	NCGC00488918	
Empirical formula	C12 H14 Cl N O2	
Molecular formula	C12 H14 Cl N O2	
Formula weight	239.69	
Temperature	100.0 K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 8.1094(2) Å	α= 90°.
	b = 8.6923(2) Å	β= 90°.
	c = 33.1247(7) Å	γ = 90°.
Volume	2334.94(9) $Å^3$	
Z	8	
Density (calculated)	1.364 Mg/m^3	
Absorption coefficient	2.778 mm^{-1}	
F(000)	1008	
Crystal size	0.113 x 0.057 x 0.016 mm^3	
Crystal color, habit	Colorless Plate	
Theta range for data collection	2.668 to 68.306°.	
Index ranges	-9<=h<=9, -10<=k<=10, -39<=l<=39	
Reflections collected	13135	
Independent reflections	4251 [R(int) = 0.0502, R(sigma) = 0.0496]	
Completeness to theta = 68.000°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.5210 and 0.4136	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4251 / 6 / 313	
Goodness-of-fit on F^2	1.015	
Final R indices [I>2sigma(I)]	R1 = 0.0408, wR2 = 0.0944	

R indices (all data)	R1 = 0.0501, wR2 = 0.0988
Absolute structure parameter	-0.005(12)
Extinction coefficient	n/a
Largest diff. peak and hole	0.355 and -0.335 e.Å^{-3}

(*2S,4R*)-2-amino-2-(2-chlorophenyl)-4-hydroxycyclohexan-1-one. NCGC00481516. CCDC 1558894

Crystals of the subject compound were grown by dissolving approximately 1mg of sample in 350µL of a 50/50 dichloroethane/methanol solution, which was then vapor diffused with diethyl ether over two days, followed by slow evaporation of the resultant solution for 2 days. A 0.273 x 0.106 x 0.052 mm piece of a colorless plank was mounted on a Cryoloop with Paratone oil. Crystal-to-detector distance was 40 mm and exposure time was 2 seconds per frame using a scan width of 2.0°. Data collection was 100% complete to 25.00° in θ. A total of 12479 reflections were collected covering the indices, -6<=h<=9, -10<=k<=10, -14<=l<=14. 2945 reflections were found to be symmetry independent, with a R_{int} of 0.0462. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be $P2_1$. All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. All other hydrogen atoms (H-bonding) were located in the difference map. Their relative positions were restrained using DFIX commands and their thermals freely refined. The absolute stereochemistry of the molecule was established by anomalous dispersion using the Parson's method with a Flack parameter of -0.013(28).



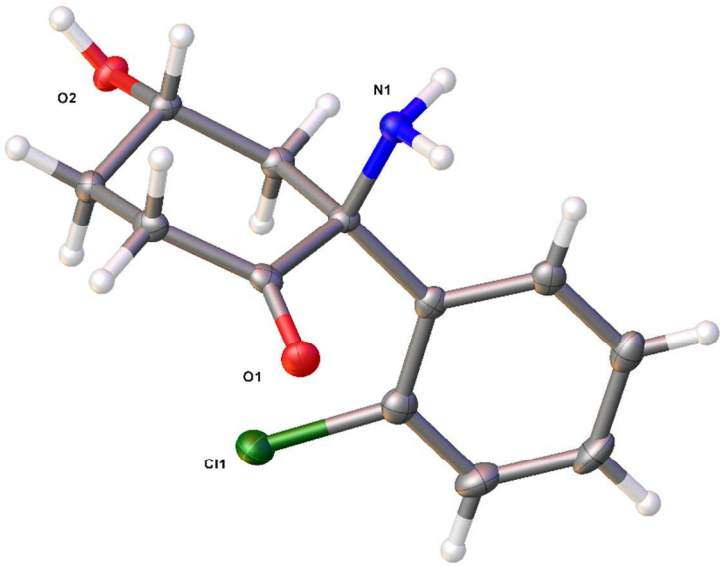
Crystal data and structure refinement for NCGC00481516.

Report date	2016-10-20
Identification code	NCGC00481516-02
Empirical formula	C12 H17 Cl2 N O3
Molecular formula	C12 H15 Cl N O2, Cl, H2 O
Formula weight	294.16
Temperature	100.0 K
Wavelength	0.71073 Å
Crystal system	Monoclinic

Space group	P 1 21 1	
Unit cell dimensions	a = 7.4051(6) Å	α= 90°.
	b = 8.6895(8) Å	β= 107.588(2)°.
	c = 11.7644(11) Å	λ = 90°.
Volume	721.61(11) $Å^3$	
Z	2	
Density (calculated)	1.354 Mg/m^3	
Absorption coefficient	0.449 mm^{-1}	
F(000)	308	
Crystal size	0.273 x 0.106 x 0.052 mm^3	
Crystal color, habit	Colorless Plank	
Theta range for data collection	1.816 to 26.410°.	
Index ranges	-6<=h<=9, -10<=k<=10, -14<=l<=14	
Reflections collected	12479	
Independent reflections	2945 [R(int) = 0.0462, R(sigma) = 0.0379]	
Completeness to theta = 25.000°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.2602 and 0.2275	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2945 / 7 / 187	
Goodness-of-fit on F^2	1.049	
Final R indices [I>2sigma(I)]	R1 = 0.0252, wR2 = 0.0587	
R indices (all data)	R1 = 0.0270, wR2 = 0.0599	
Absolute structure parameter	-0.01(3)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.218 and -0.184 e.$Å^{-3}$	

(*2S,4S*)-2-amino-2-(2-chlorophenyl)-4-hydroxycyclohexan-1-one. NCGC00492317. CCDC 1558888

Crystals of the subject compound were grown by dissolving approximately 1mg of sample in 350µL of Dichloromethane, which was then vapor diffused with Pentane over several days. A 0.239 x 0.156 x 0.117 mm piece of a colorless block was mounted on a Cryoloop with Paratone oil. Crystal-to-detector distance was 60 mm and exposure time was 10 seconds per frame using a scan width of 0.75°. Data collection was 99.8% complete to 25.00° in θ. A total of 26165 reflections were collected covering the indices, -9<=h<=9, -10<=k<=10, -33<=l<=39. 4296 reflections were found to be symmetry independent, with a R_{int} of 0.452. Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be $P2_12_12_1$. All other hydrogen atoms (H-bonding) were located in the difference map. Their relative positions were restrained using DFIX commands and their thermals freely refined. The absolute stereochemistry of the molecule was established by anomalous dispersion using the Parson's method with a Flack parameter of 0.006(25).



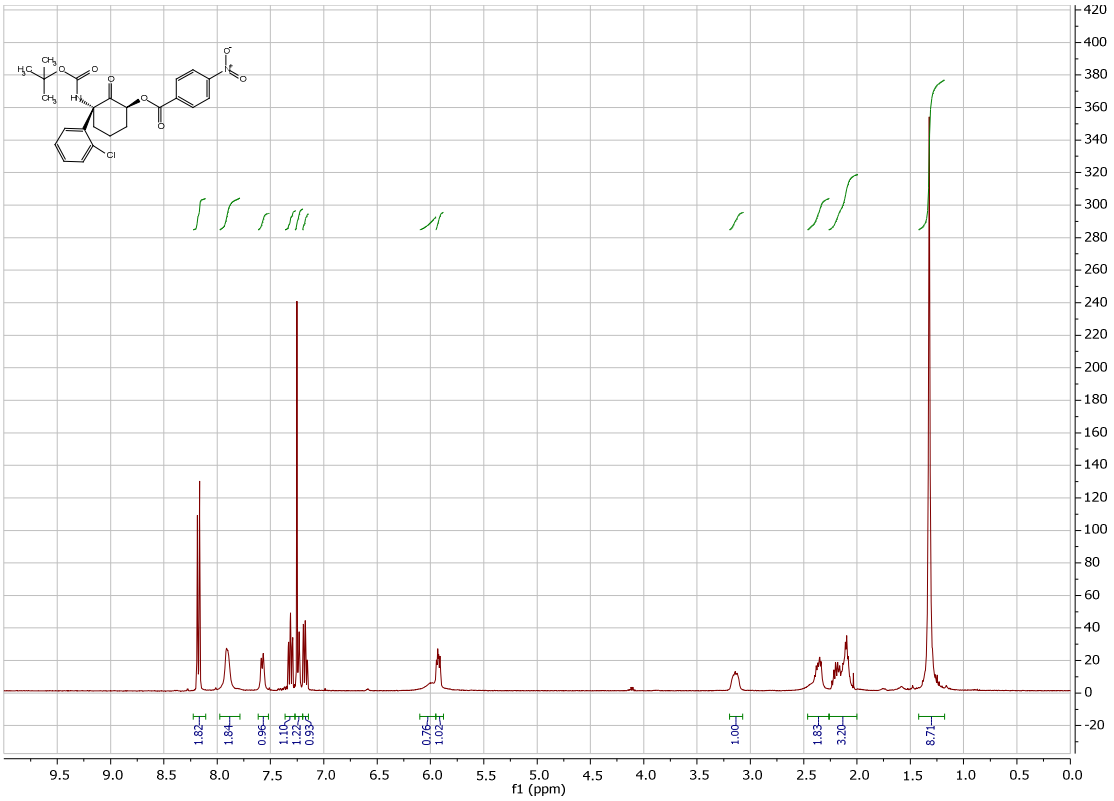
Crystal data and structure refinement for NCGC00492317.

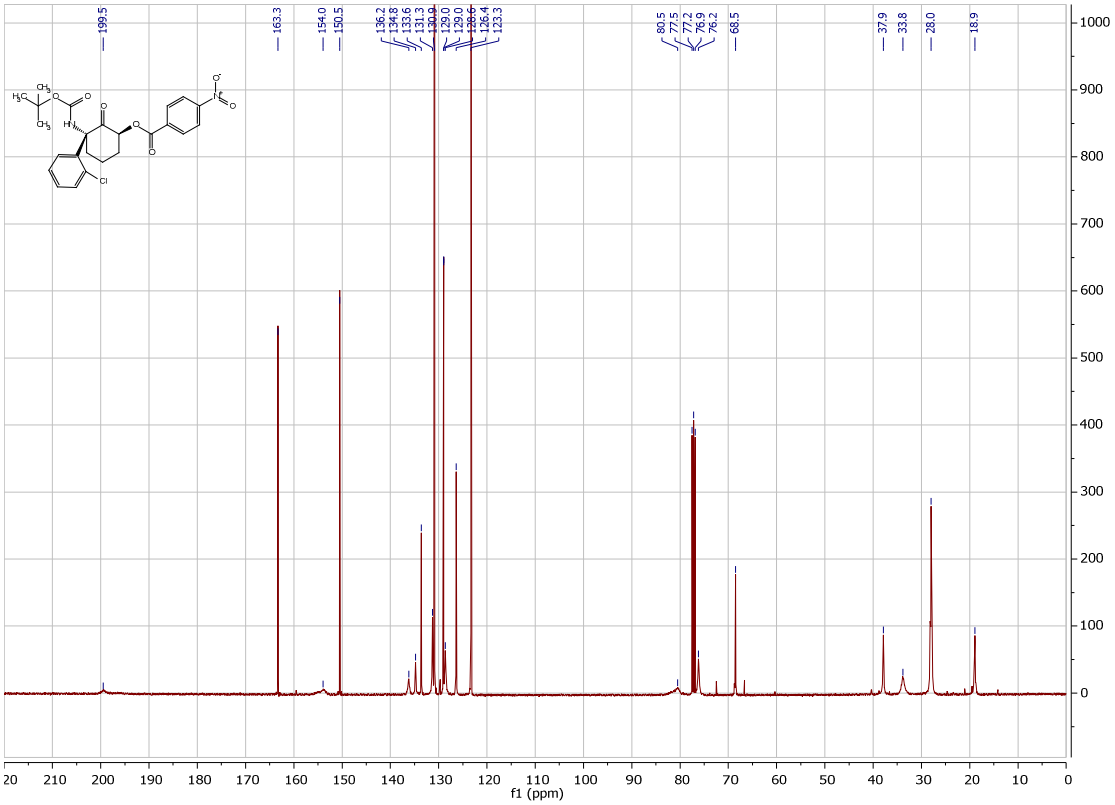
Report date	2017-06-05	
Identification code	NCGC00492317	
Empirical formula	C12 H14 Cl N O2	
Molecular formula	C12 H14 Cl N O2	
Formula weight	239.69	
Temperature	100 K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 8.1621(2) Å	α= 90°.
	b = 8.6928(3) Å	β= 90°.
	c = 33.1313(10) Å	γ = 90°.
Volume	2350.72(12) $Å^3$	
Z	8	
Density (calculated)	1.355 Mg/m^3	
Absorption coefficient	0.309 mm^{-1}	
F(000)	1008	
Crystal size	0.239 x 0.156 x 0.117 mm^3	
Crystal color, habit	Colorless Block	
Theta range for data collection	2.422 to 25.386°.	
Index ranges	-9<=h<=9, -10<=k<=10, -33<=l<=39	
Reflections collected	26165	
Independent reflections	4296 [R(int) = 0.0452, R(sigma) = 0.0303]	
Completeness to theta = 25.000°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.1480 and 0.1237	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	4296 / 6 / 313
Goodness-of-fit on F^2	1.019
Final R indices [I>2sigma(I)]	R1 = 0.0284, wR2 = 0.0625
R indices (all data)	R1 = 0.0324, wR2 = 0.0645
Absolute structure parameter	0.01(3)
Extinction coefficient	n/a
Largest diff. peak and hole	0.192 and -0.184 e.$Å^{-3}$

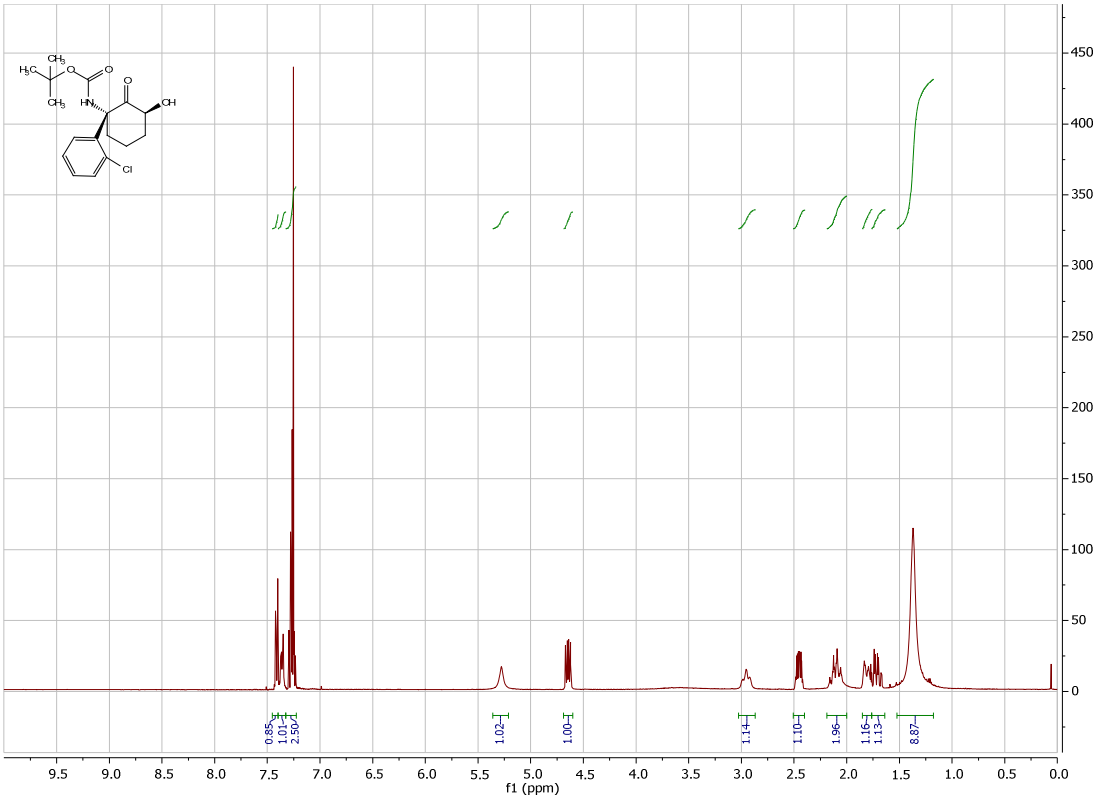
Supplementary Spectra

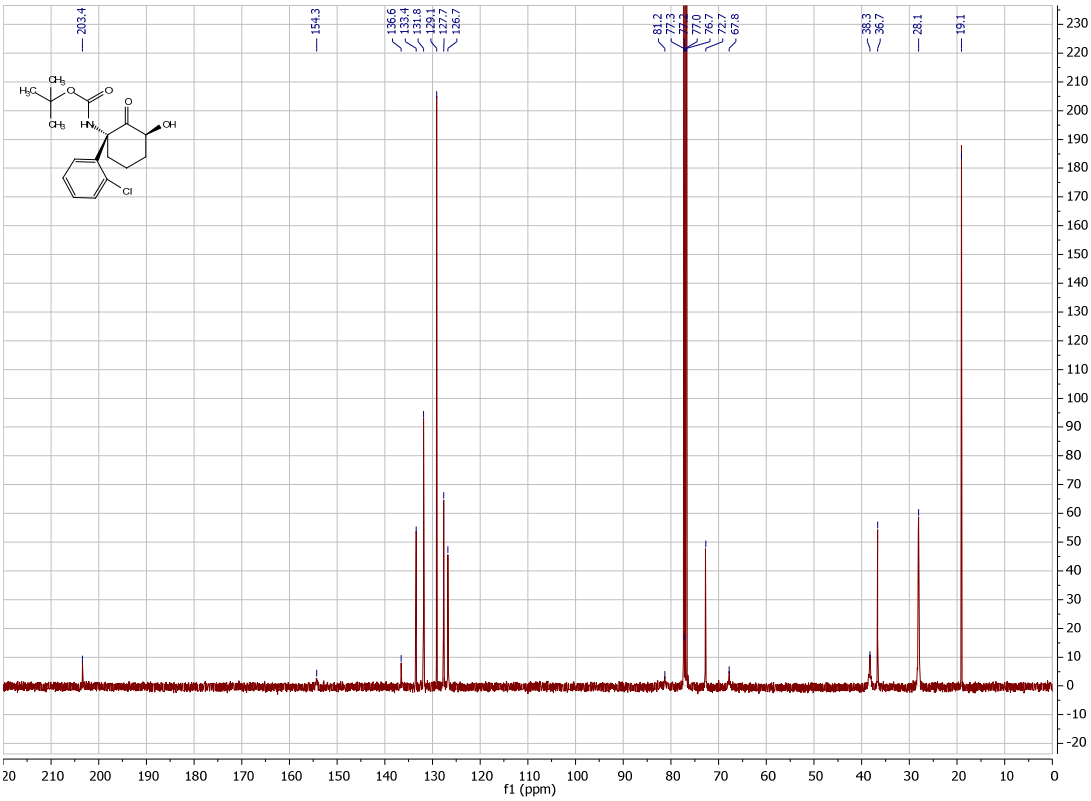
(*1S,3R*)-3-((tert-butoxycarbonyl)amino)-3-(2-chlorophenyl)-2-oxocyclohexyl 4-nitrobenzoate (**19a**). **NCGC00483942**



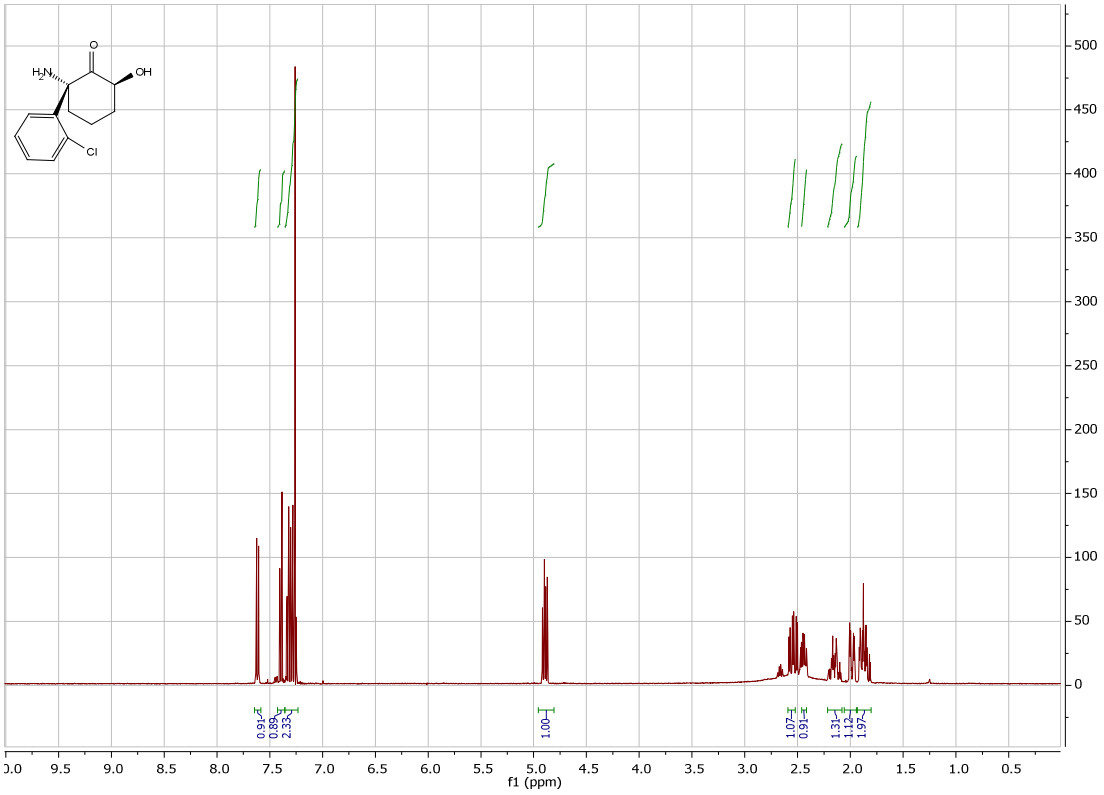


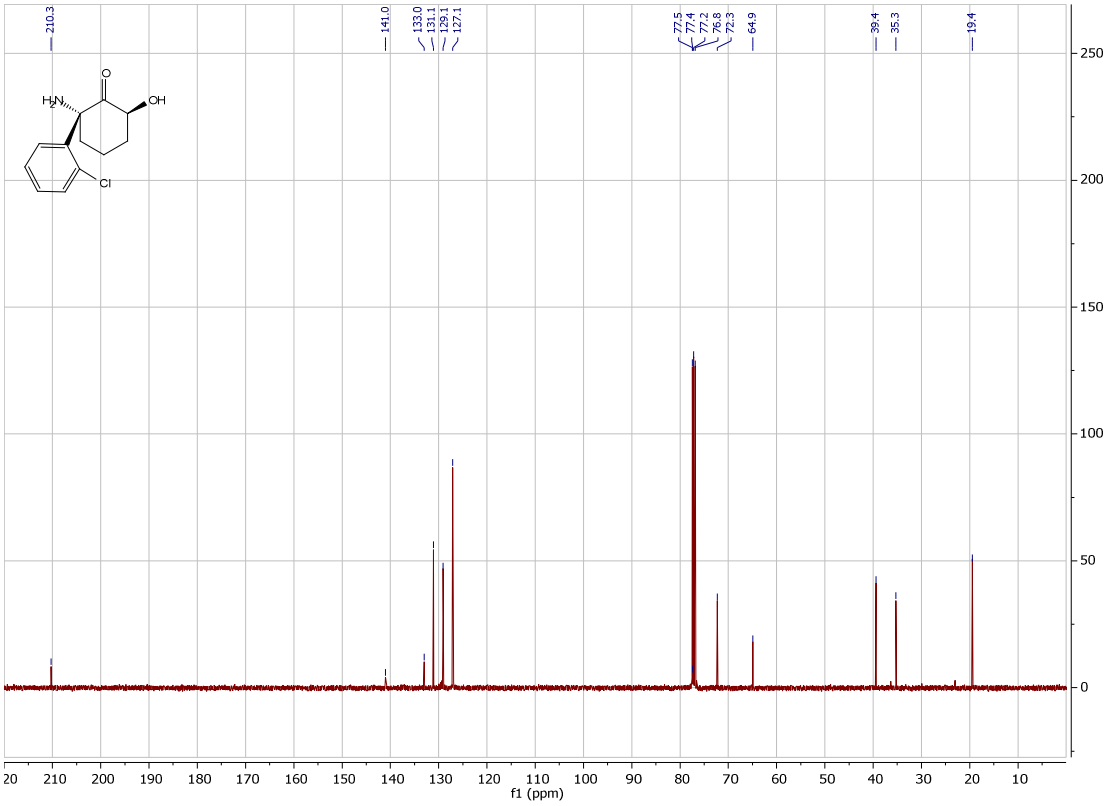
tert-Butyl ((1*R,3S*)-1-(2-chlorophenyl)-3-hydroxy-2-oxocyclohexyl)carbamate (**20a**). **NCGC00489076**

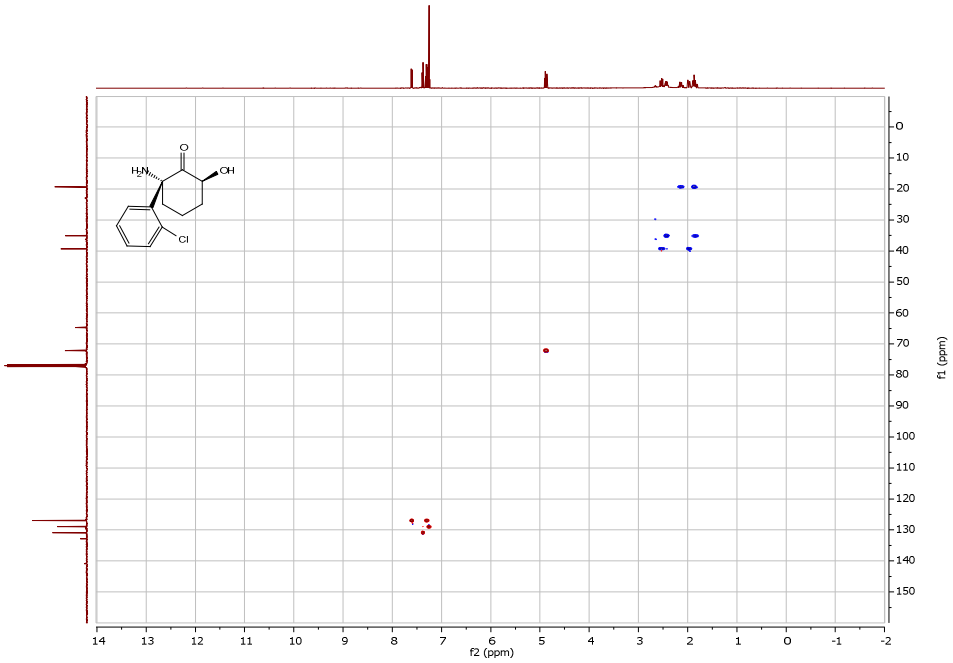


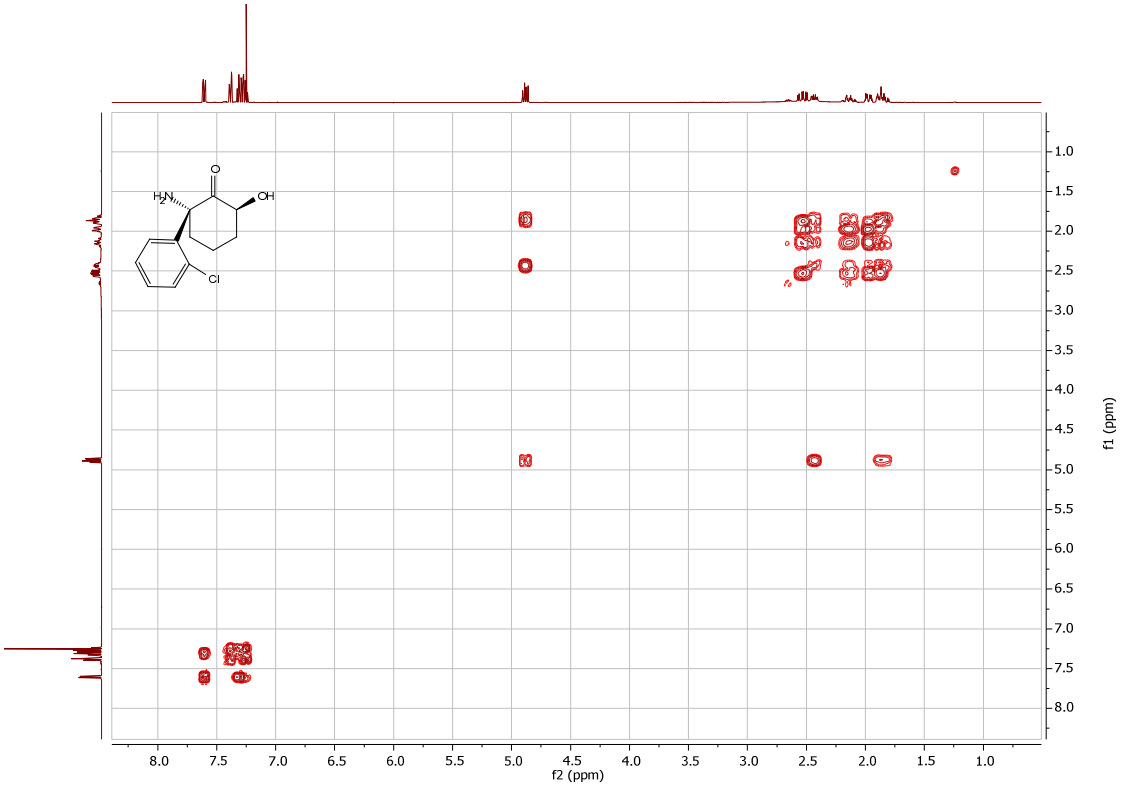


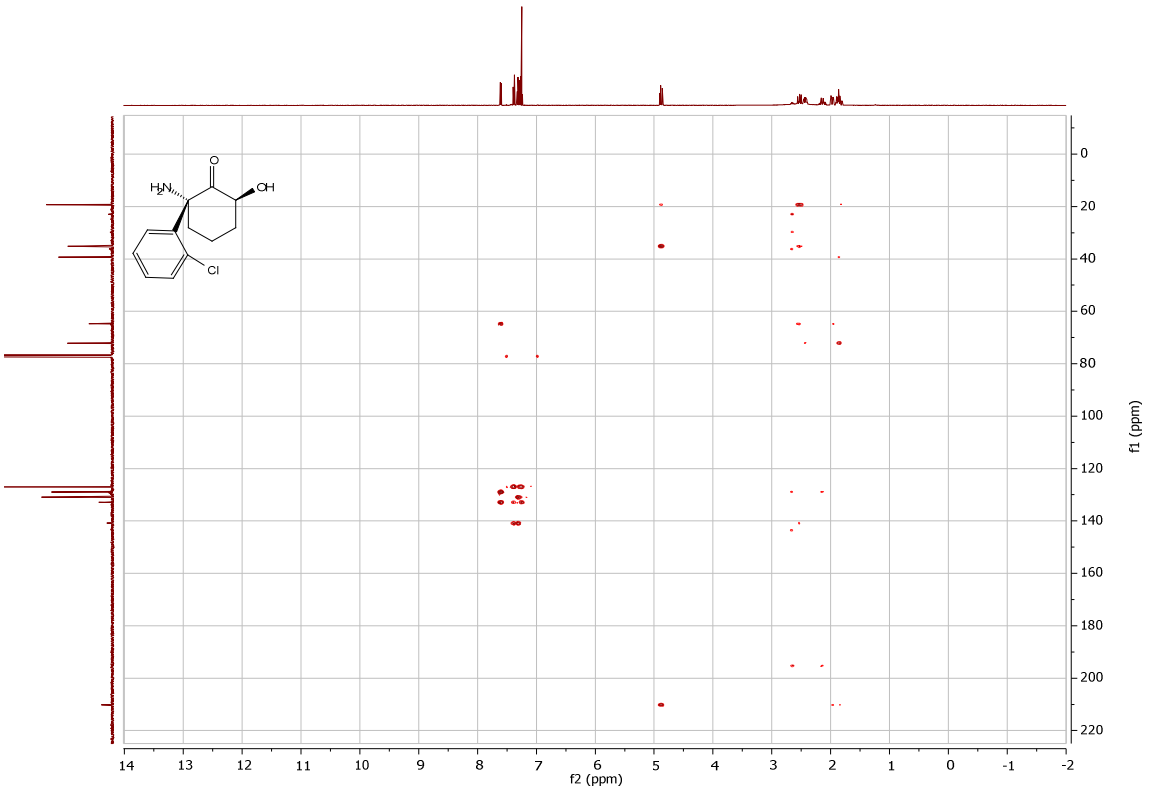
(*2R,6S*)-2-amino-2-(2-chlorophenyl)-6-hydroxycyclohexan-1-one (**4a**). **NCGC00483973**



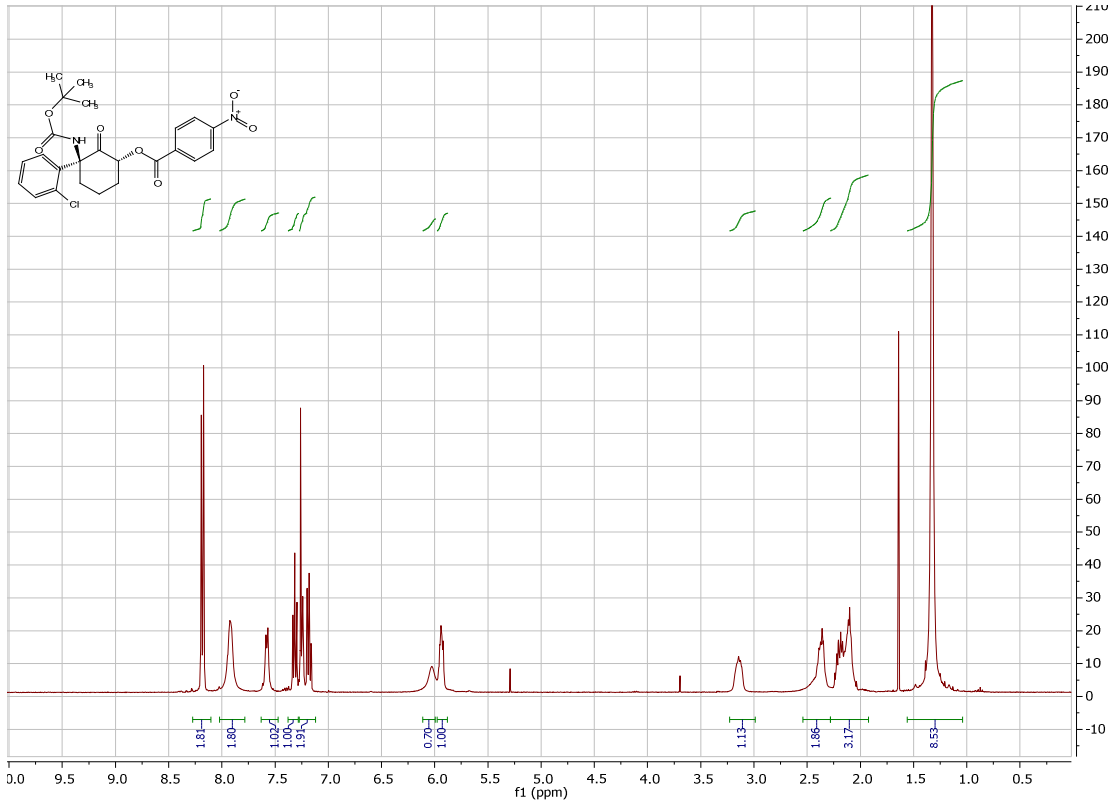


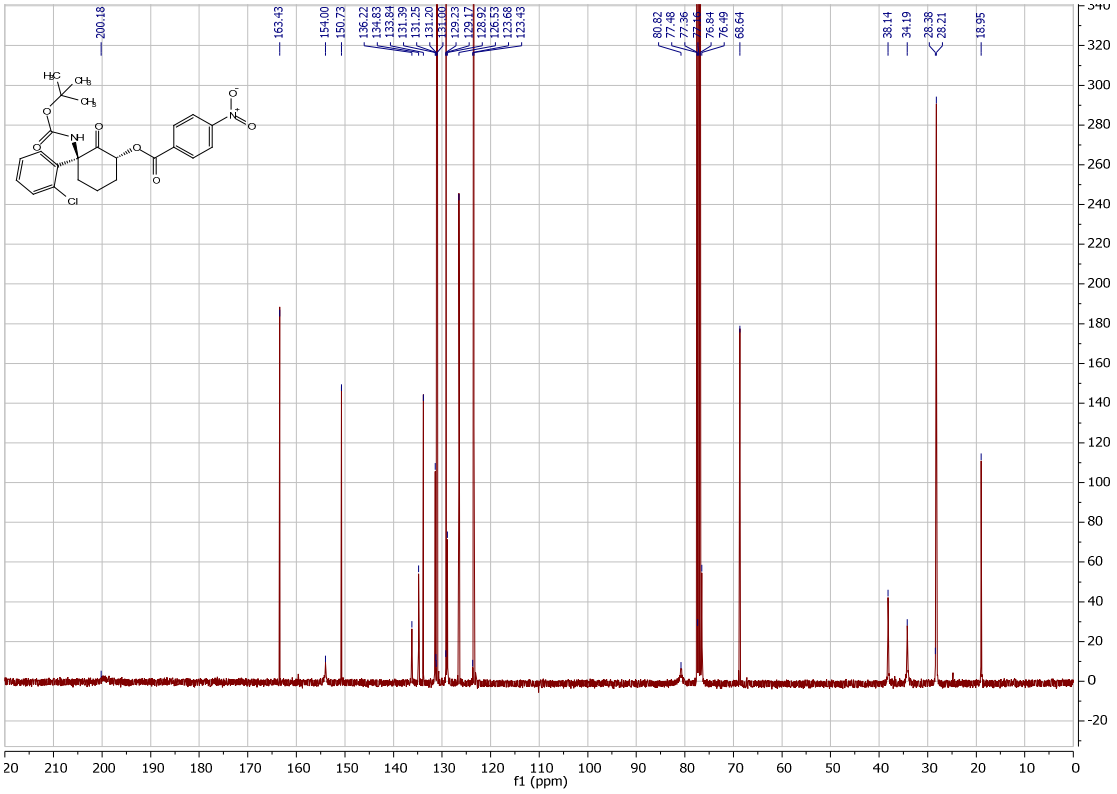

O
H2N
OH
Cl
f2 (ppm)
f1 (ppm)


O
H2N
OH
Cl
f2 (ppm)
f1 (ppm)

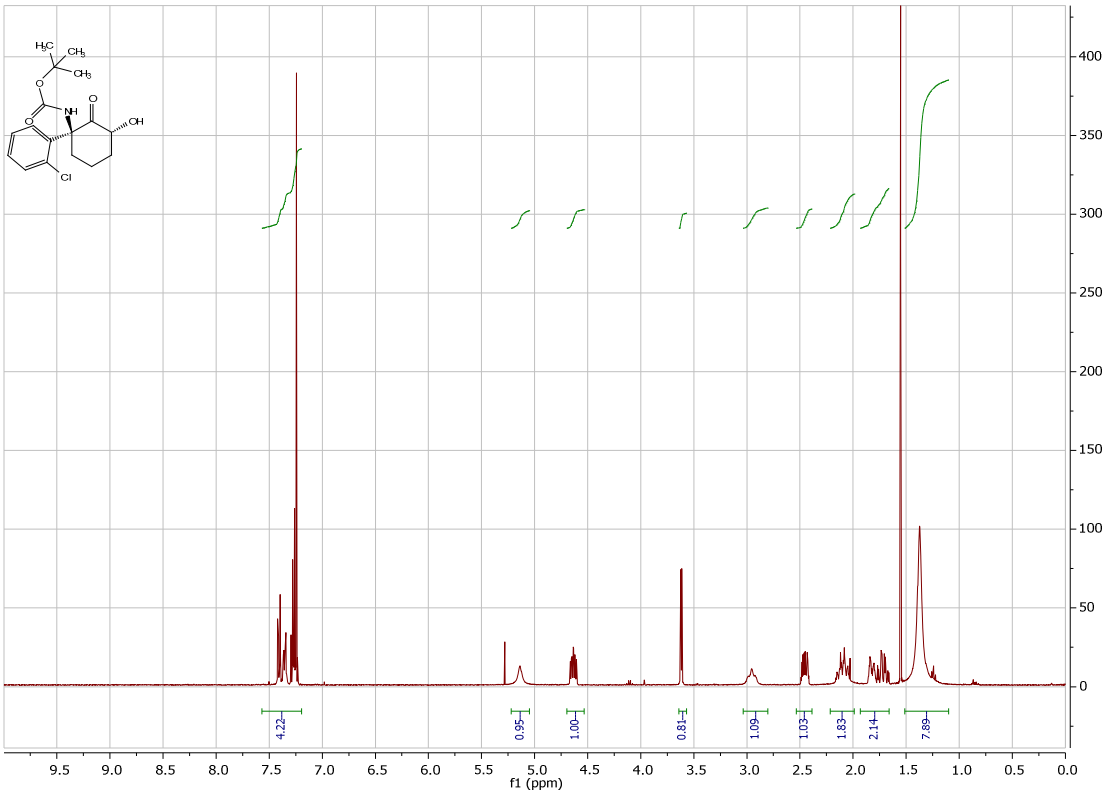

O
H2N
OH
Cl
f1 (ppm)
f2 (ppm)

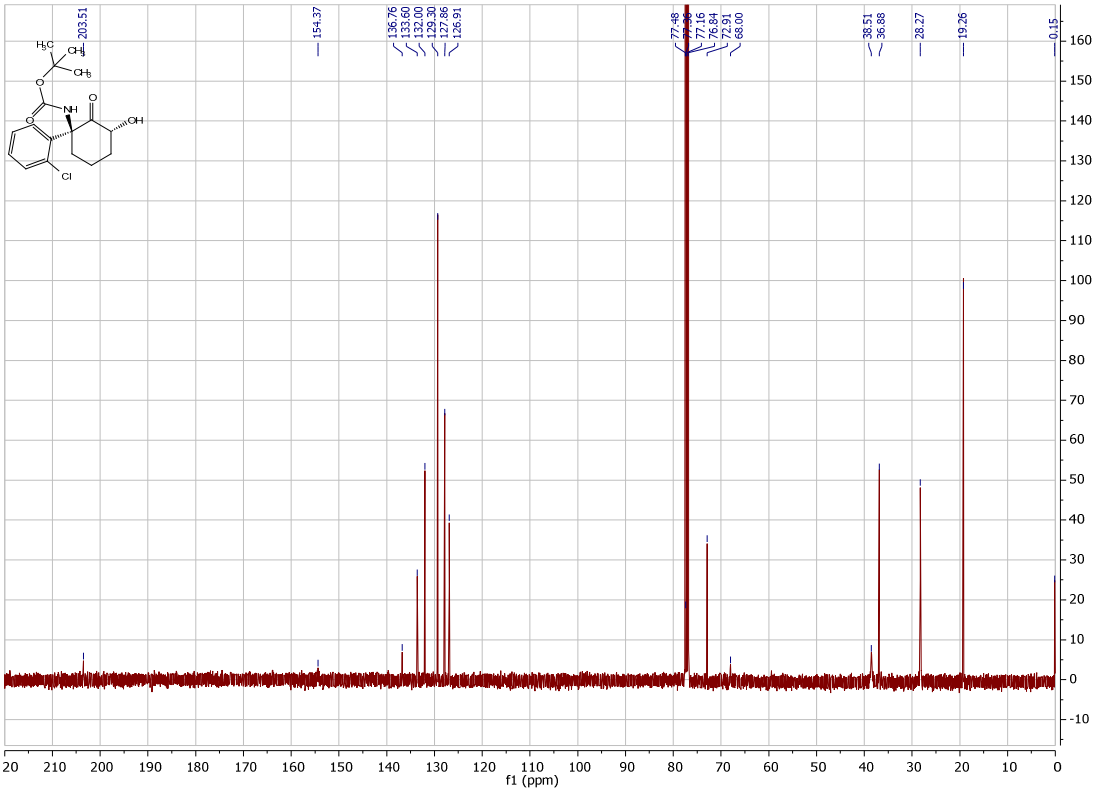
(*1R,3S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2-chlorophenyl)-2-oxocyclohexyl 4-nitrobenzoate (**19b**). **NCGC00492460**



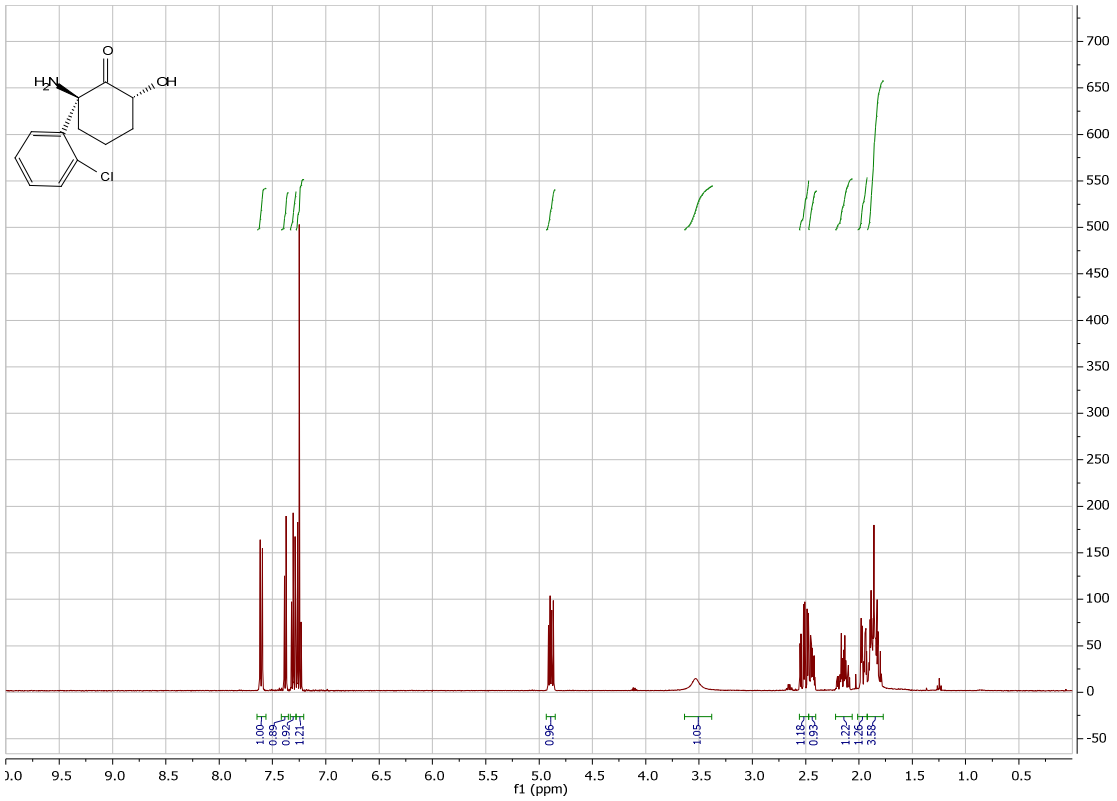


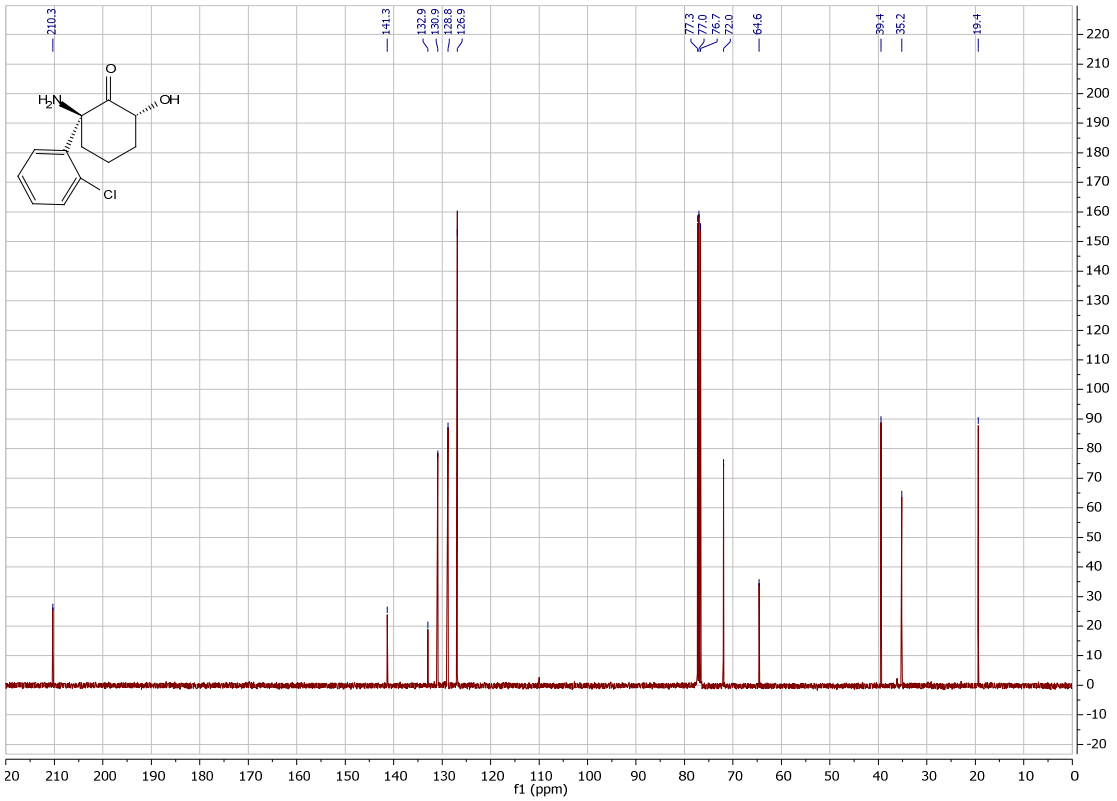
tert-butyl ((*1S,3R*)-1-(2-chlorophenyl)-3-hydroxy-2-oxocyclohexyl)carbamate (**20b**). **NCGC00481339**

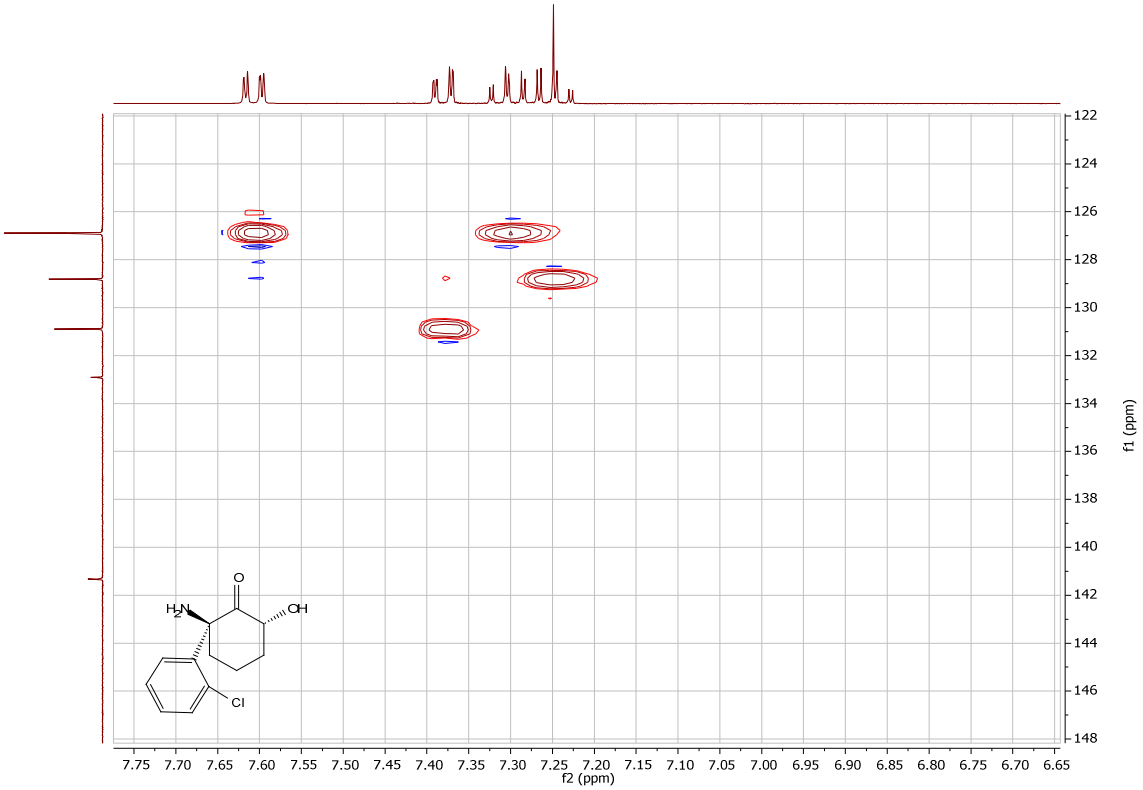




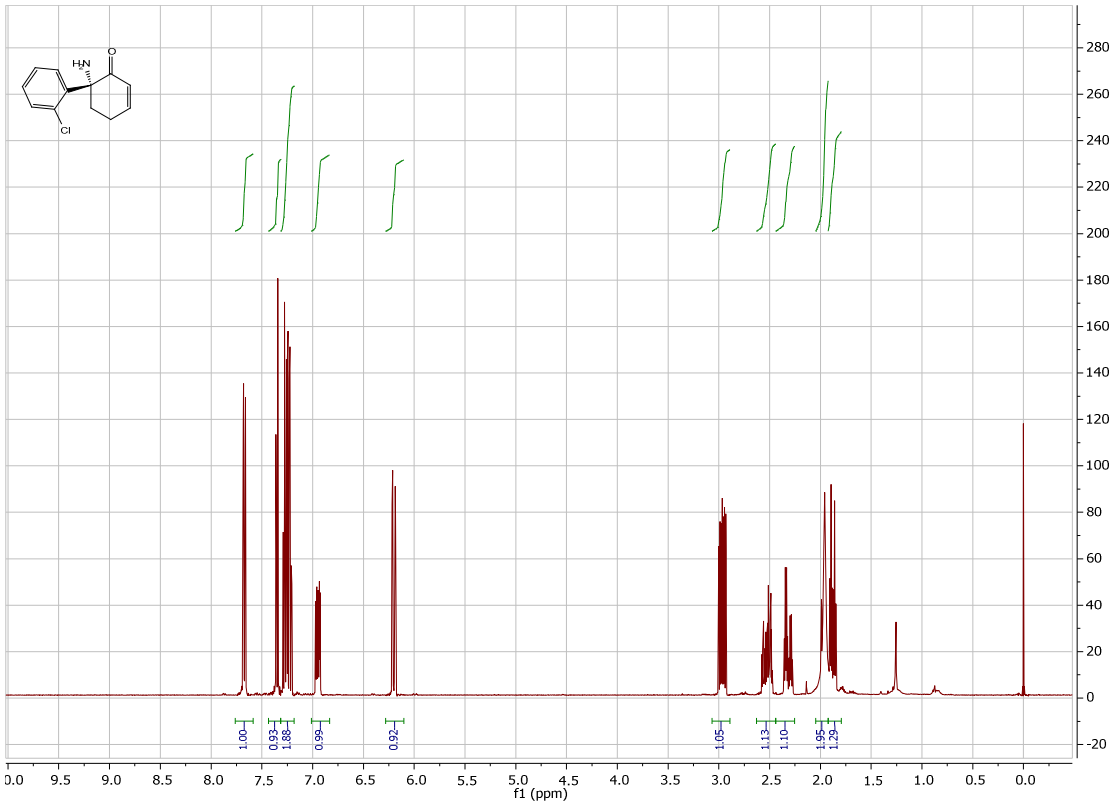
(*2S,6R*)-2-amino-2-(2-chlorophenyl)-6-hydroxycyclohexan-1-one (**4b**). **NCGC00481329**

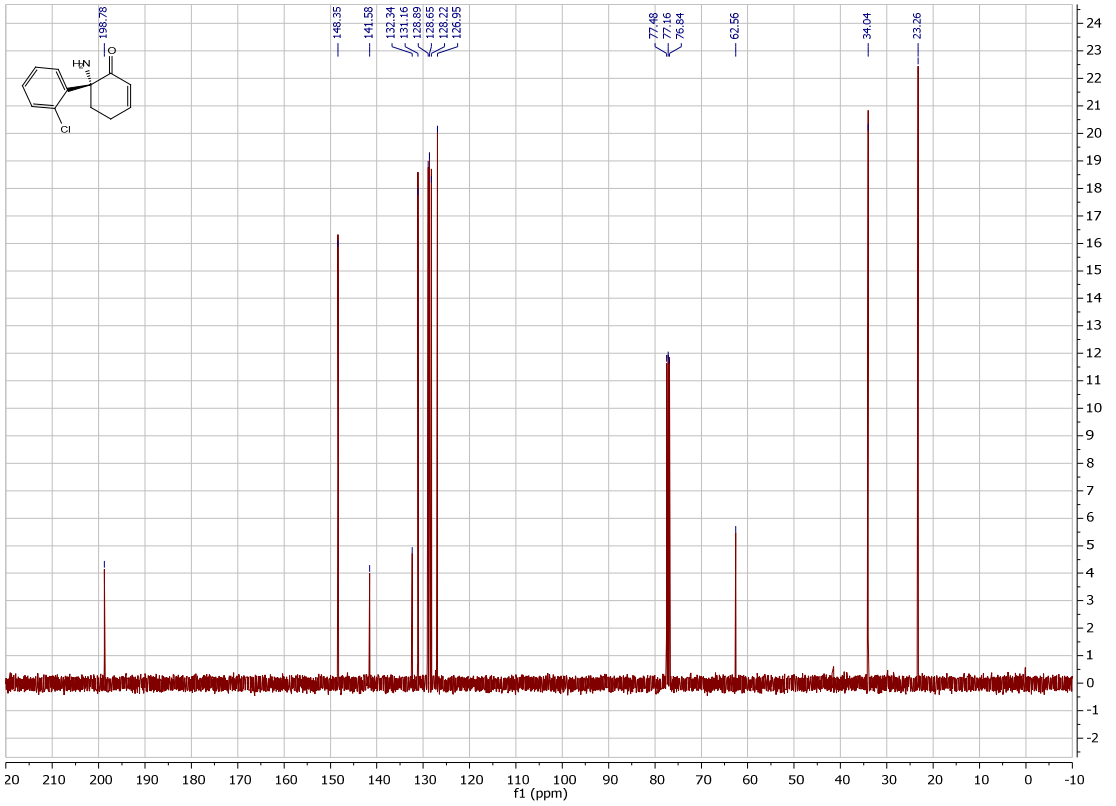




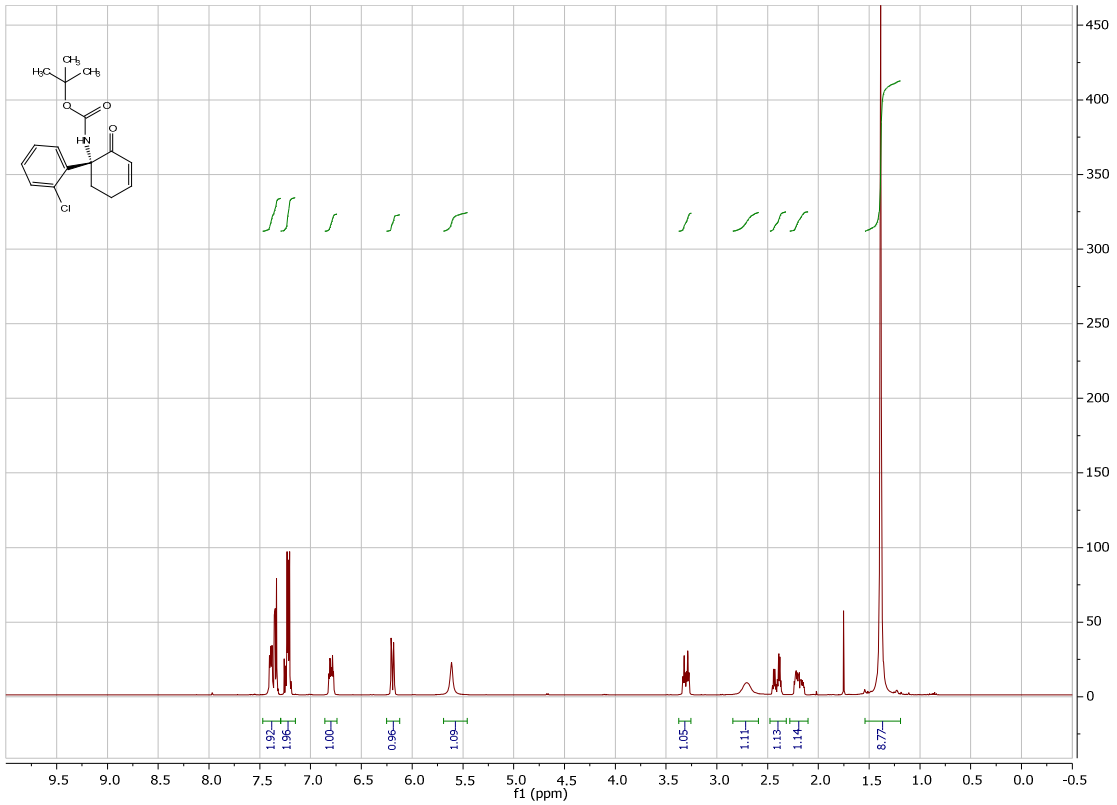

O
H2N
OH
Cl
122
124
126
128
130
132
134
136
138
140
142
144
146
148
f1 (ppm)
7.75 7.70 7.65 7.60 7.55 7.50 7.45 7.40 7.35 7.30 7.25 7.20 7.15 7.10 7.05 7.00 6.95 6.90 6.85 6.80 6.75 6.70 6.65
f2 (ppm)

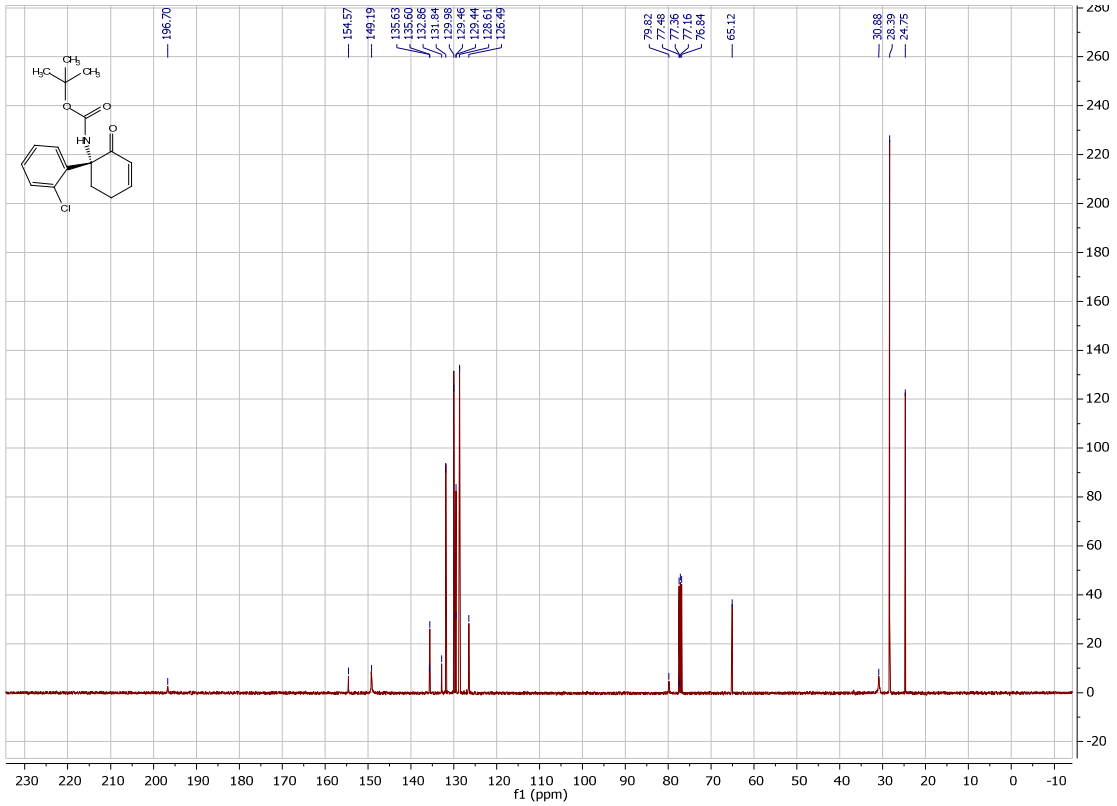
(*R*)-1-amino-2'-chloro-5,6-dihydro-[1,1'-biphenyl]-2(1H)-one (**3a**). **NCGC00389094**



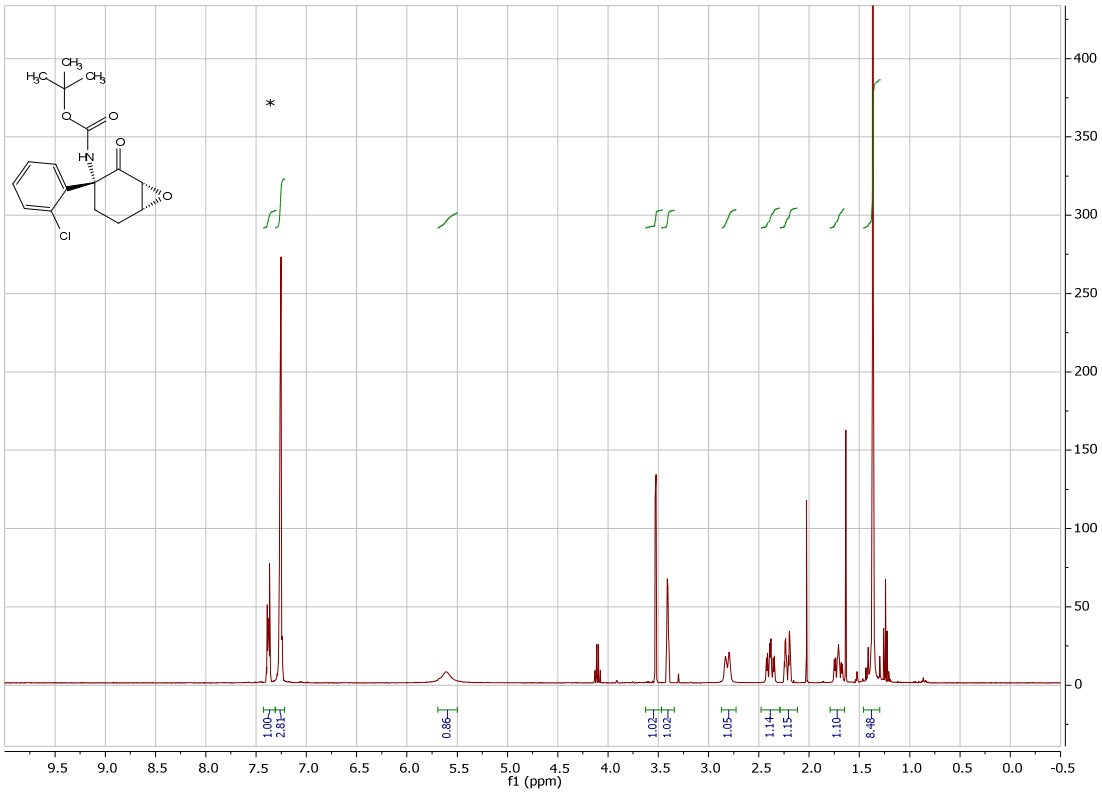


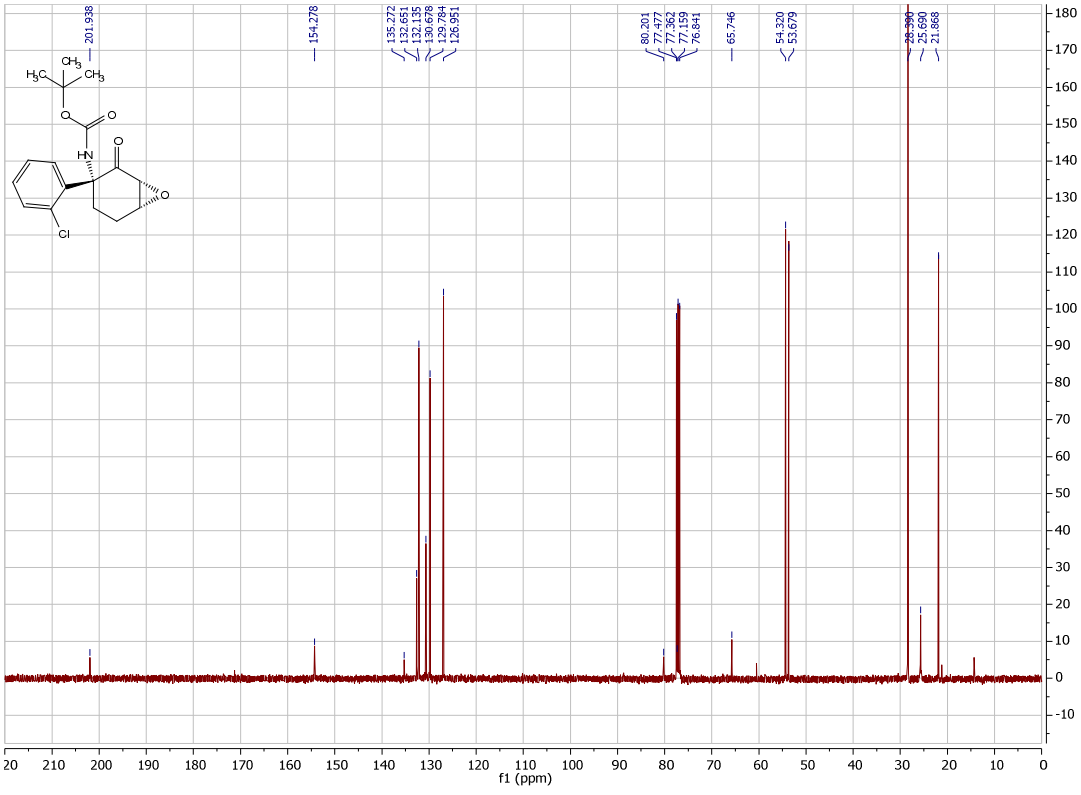
tert-Butyl-(*R*)-(2'-chloro-6-oxo-3,6-dihydro-[1,1'-biphenyl]-1(2H)-yl)carbamate (**21a**). **NCGC00486996**



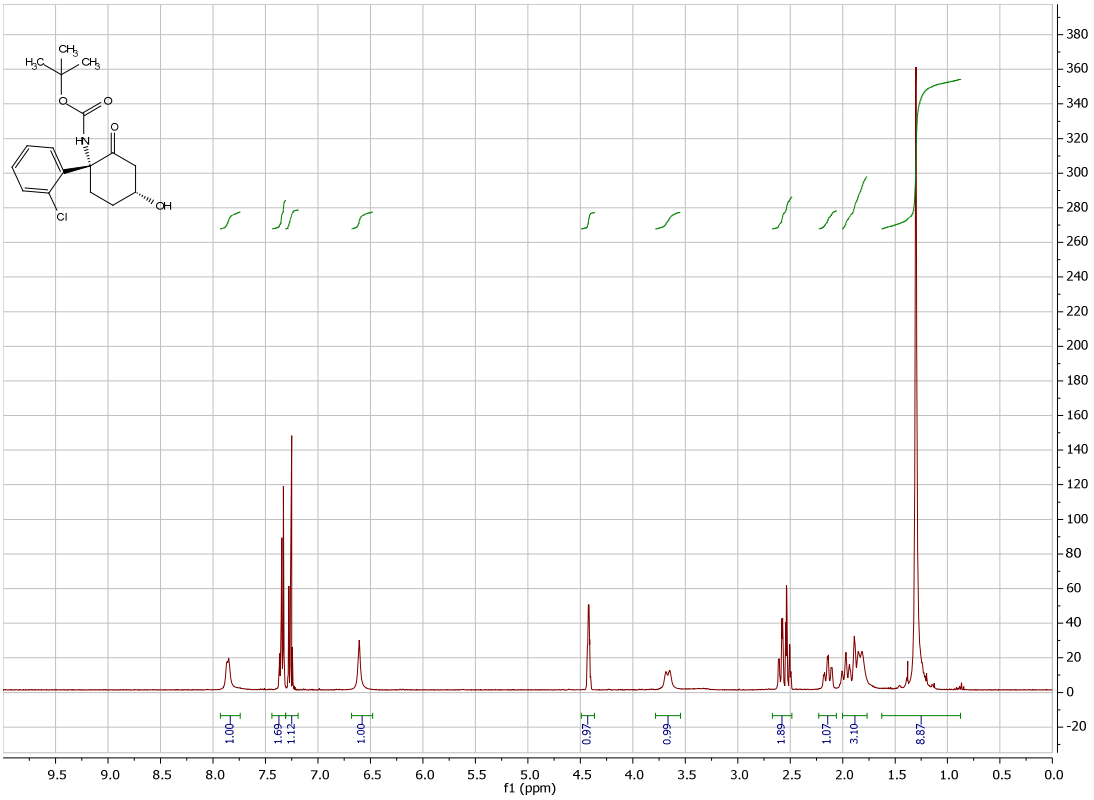


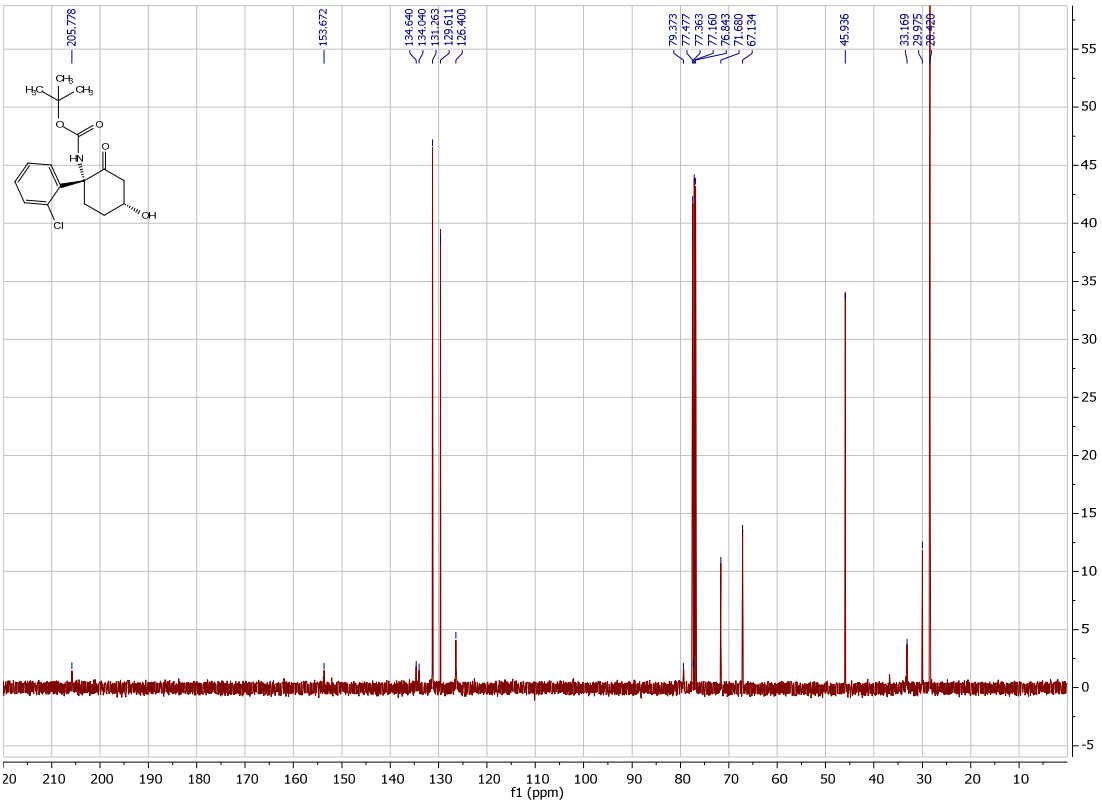
tert-Butyl ((*1R,3R,6R*)-3-(2-chlorophenyl)-2-oxo-7-oxabicyclo[4.1.0]heptan-3-yl)carbamate (**22a**). **NCGC00487046**



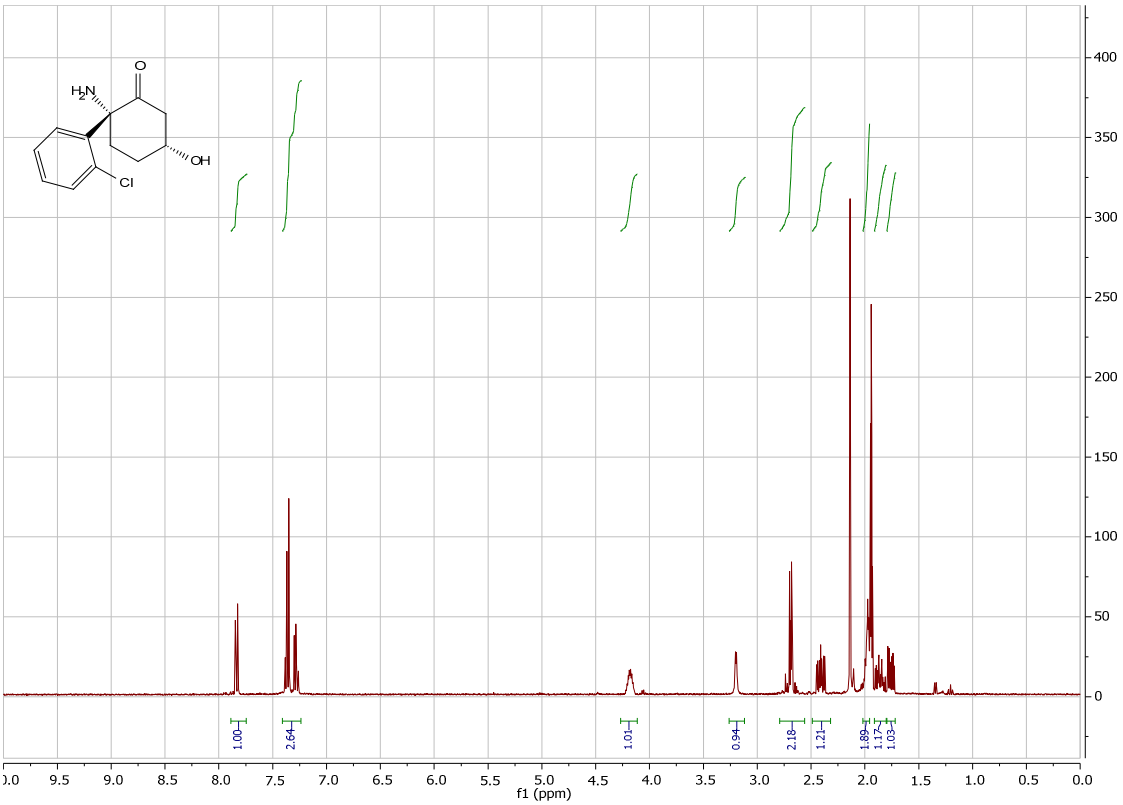


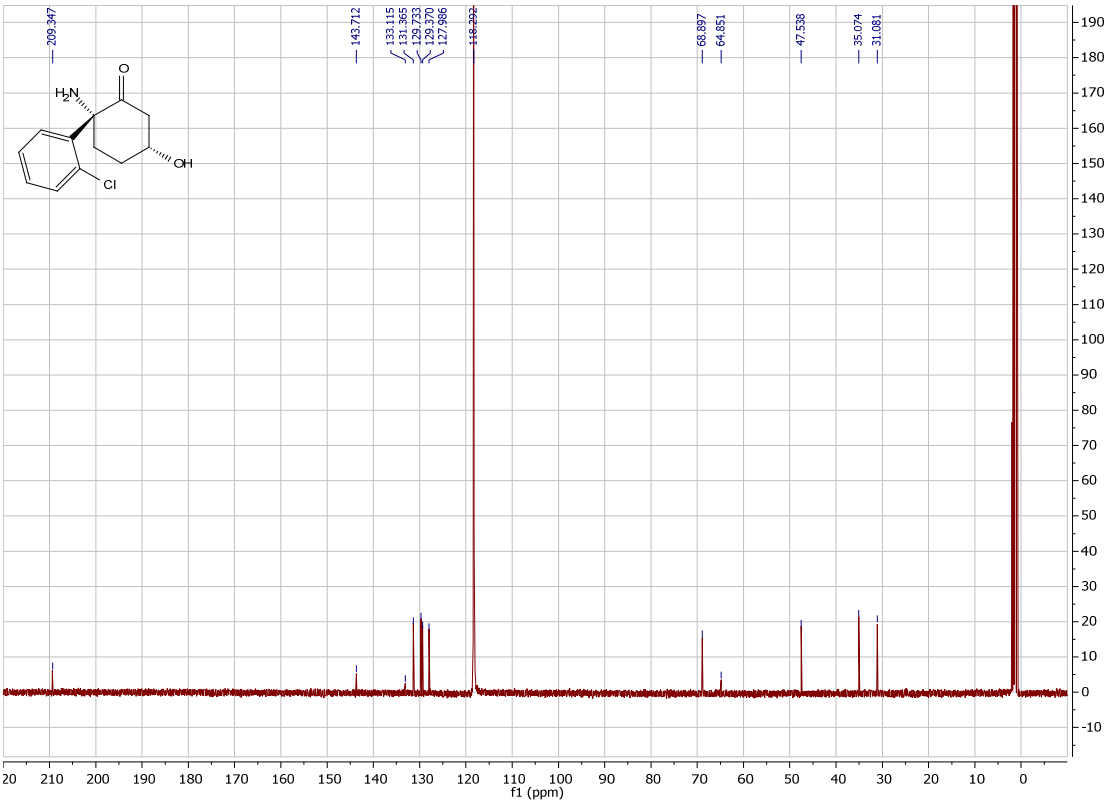
tert-Butyl ((*1R,4R*)-1-(2-chlorophenyl)-4-hydroxy-2-oxocyclohexyl)carbamate (**23a**). **NCGC00487087**



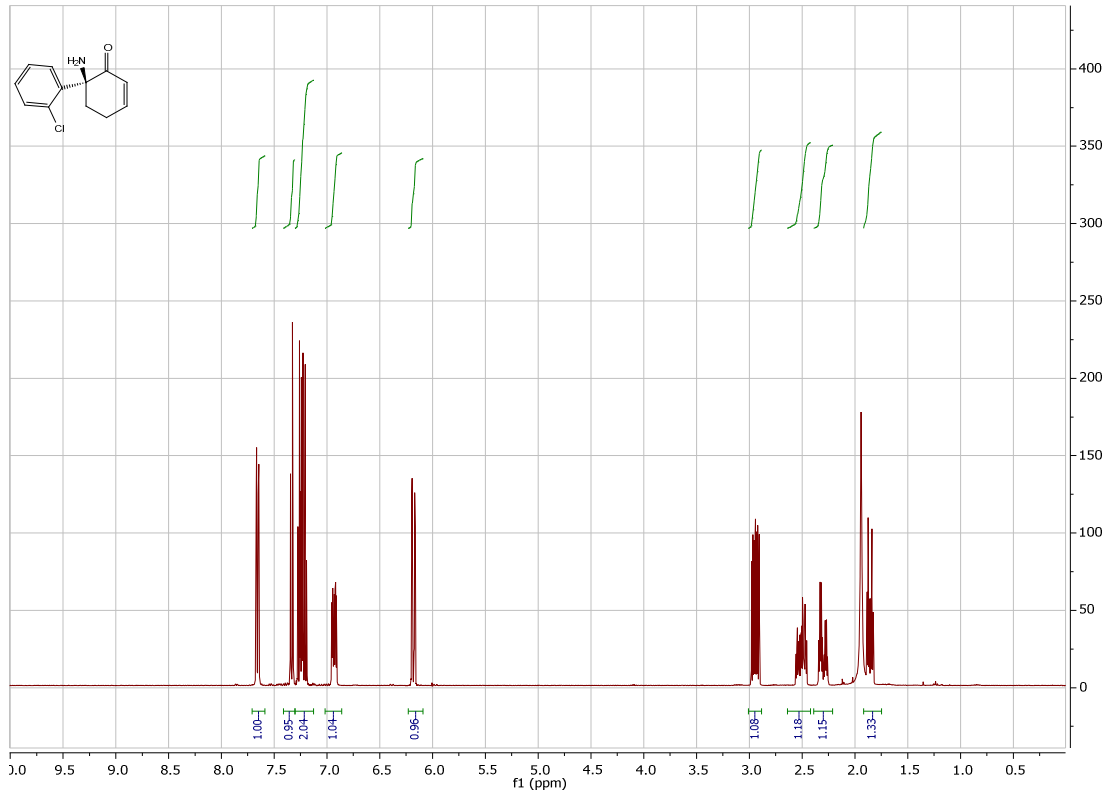


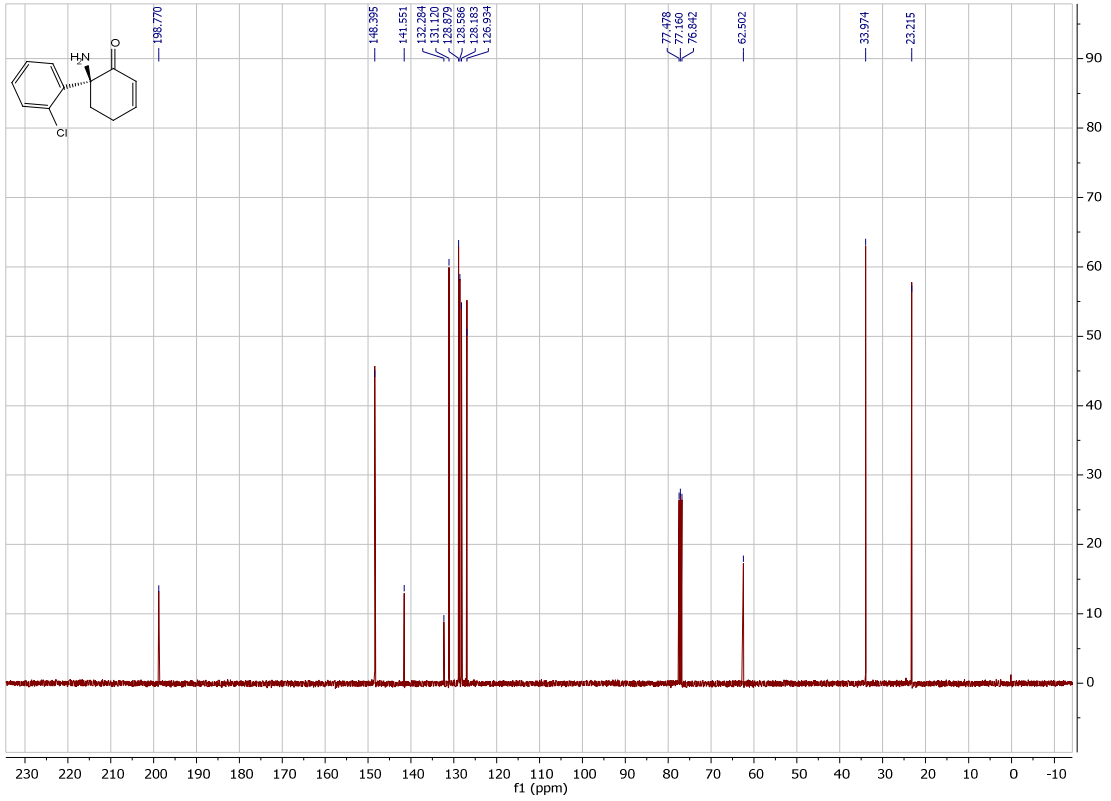
(*2R,5R*)-2-Amino-2-(2-chlorophenyl)-5-hydroxycyclohexan-1-one (**5a**). **NCGC00488764**



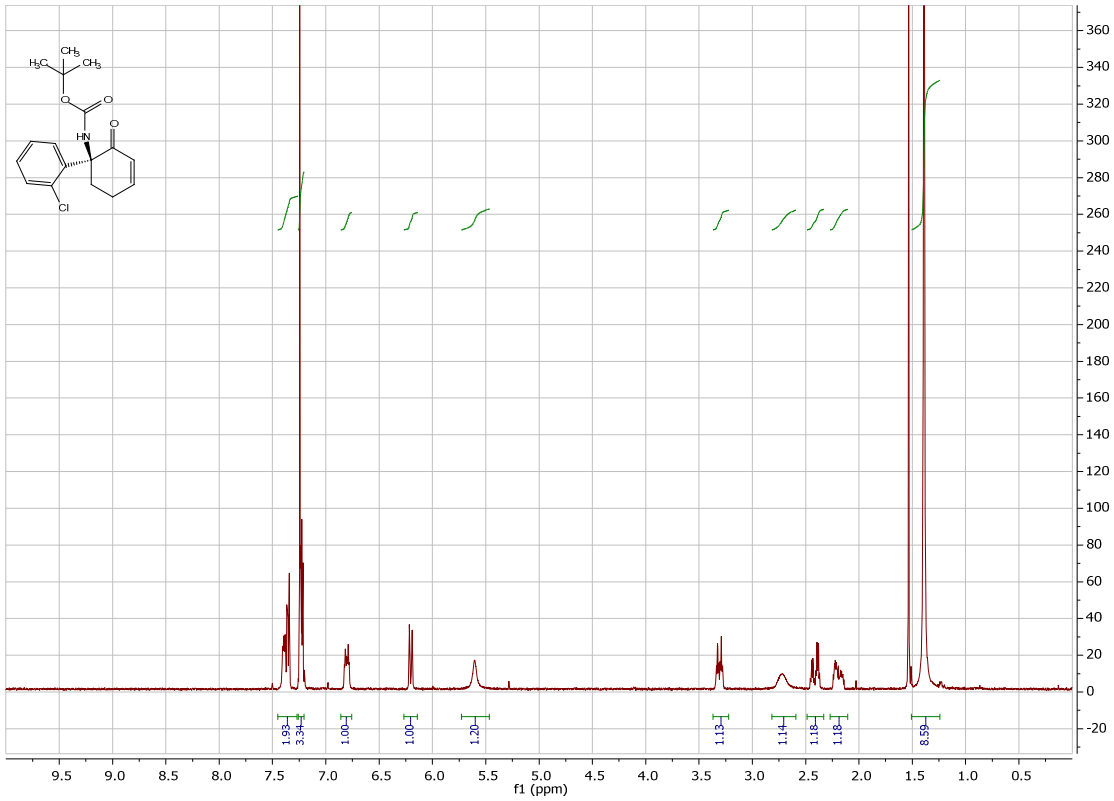


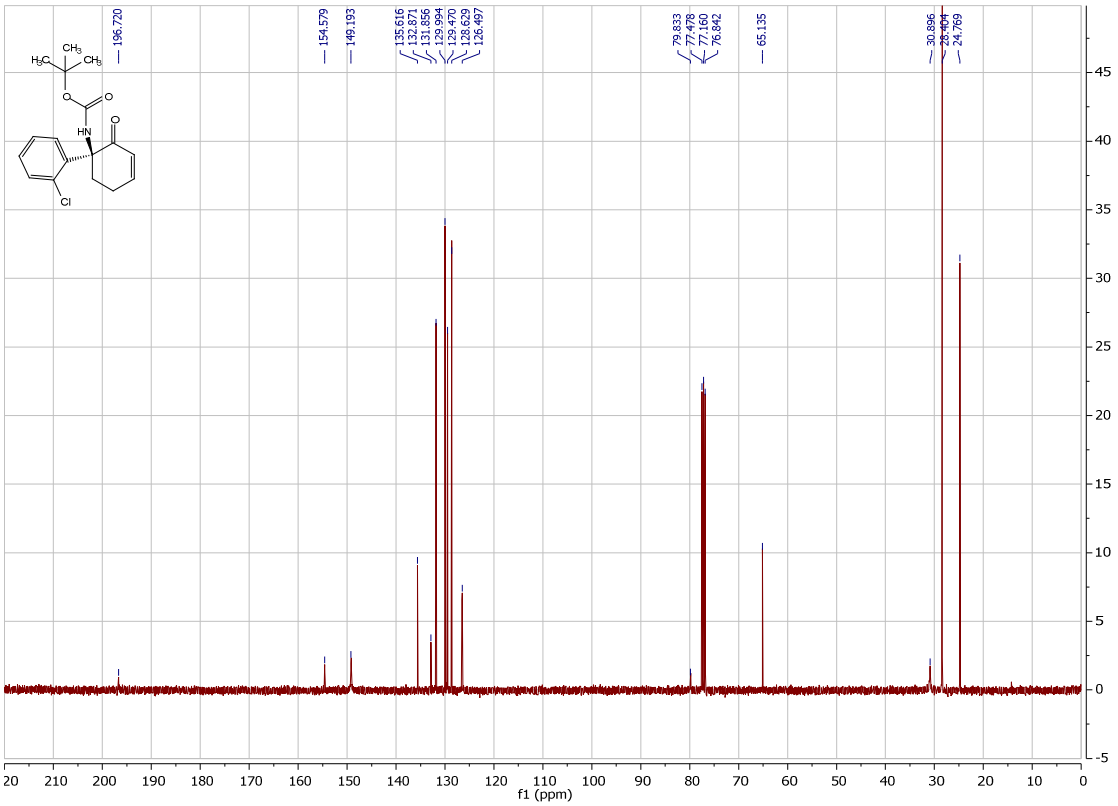
(*S*)-1-Amino-2'-chloro-5,6-dihydro-[1,1'-biphenyl]-2(1H)-one (**3b**). **NCGC00488956**



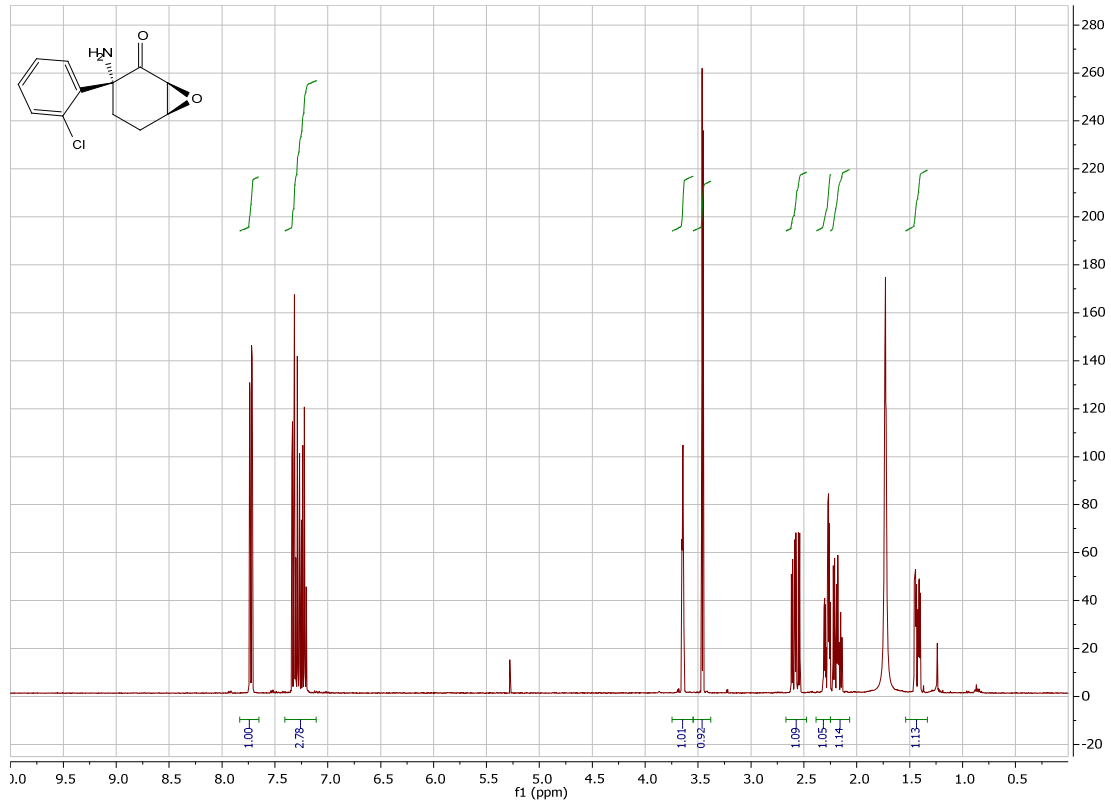


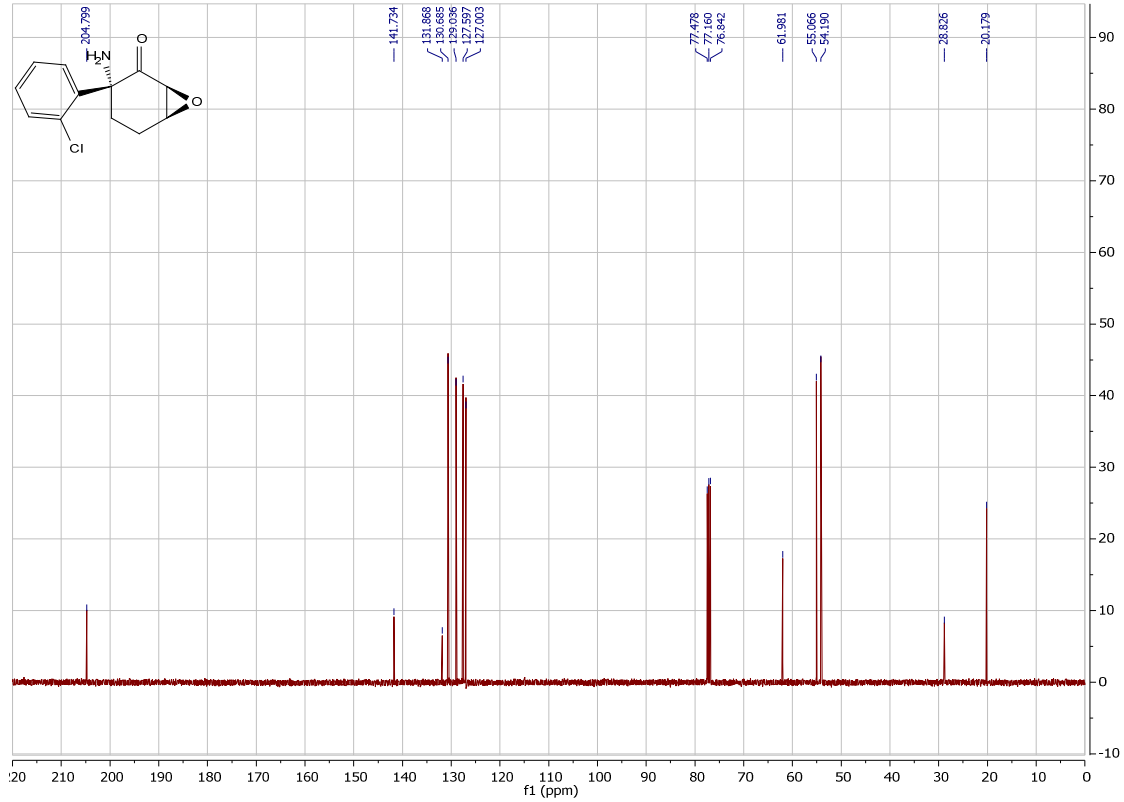
tert-Butyl (*S*)-(2'-chloro-6-oxo-3,6-dihydro-[1,1'-biphenyl]-1(2H)-yl)carbamate (**21b**). **NCGC00489141**



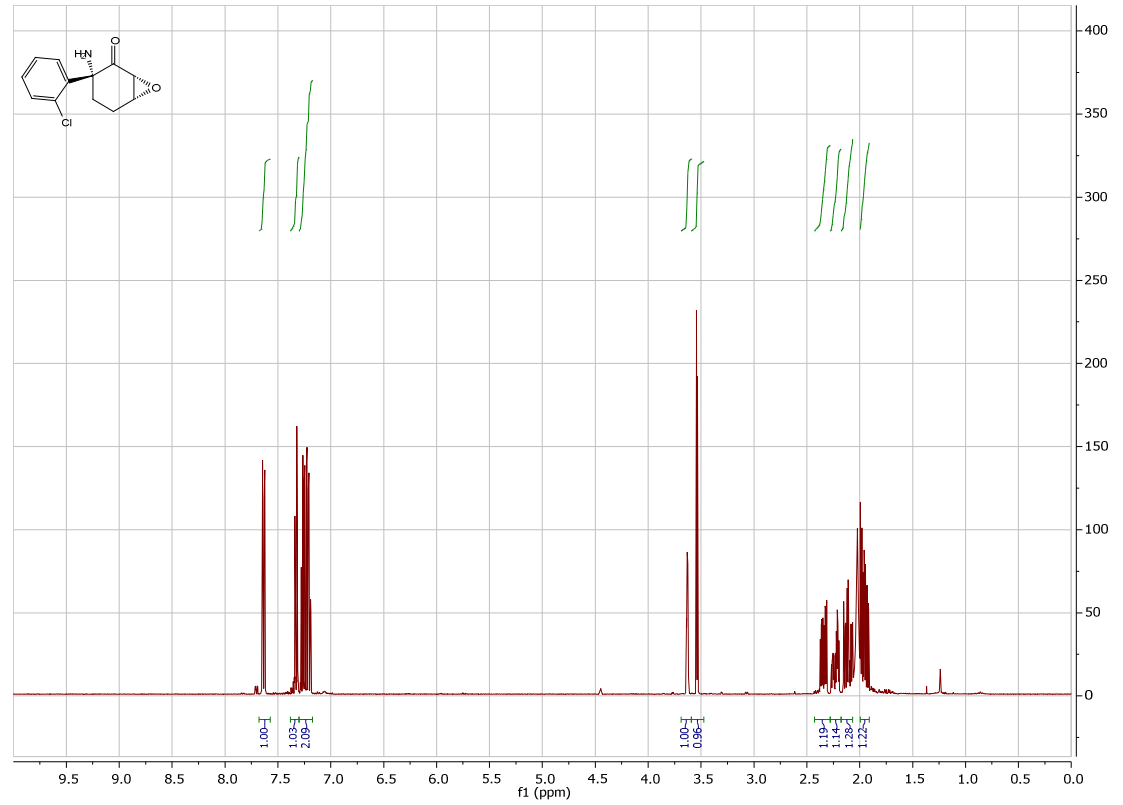


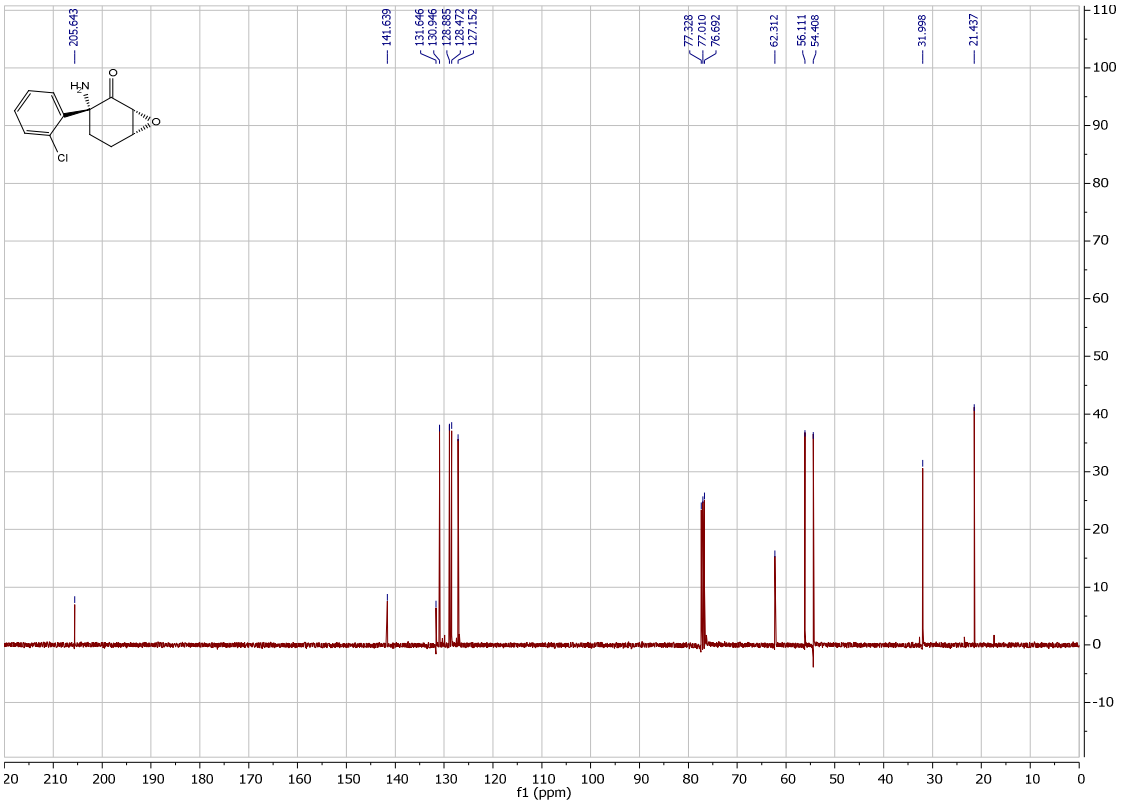
(*1R,3R,6R*)-3-Amino-3-(2-chlorophenyl)-7-oxabicyclo[4.1.0]heptan-2-one (**25a**). **NCGC00488940**



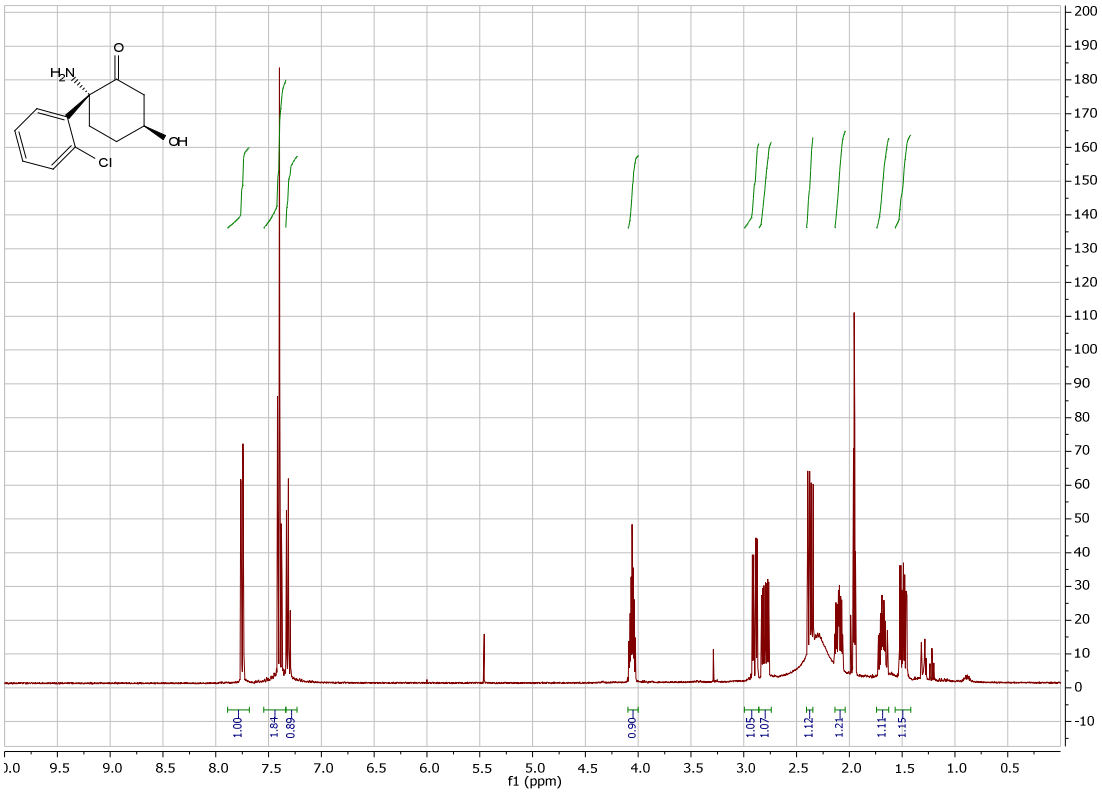


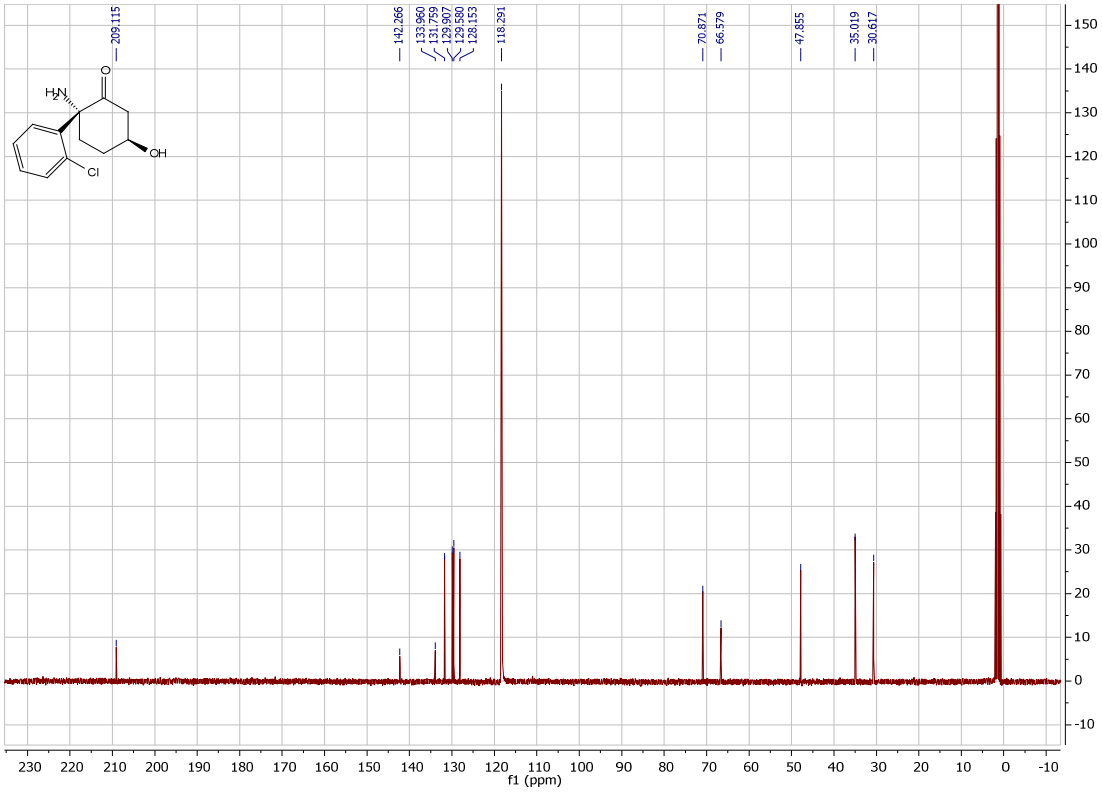
(*1R,3R,6R*)-3-Amino-3-(2-chlorophenyl)-7-oxabicyclo[4.1.0]heptan-2-one (**25a**). **NCGC00488940**



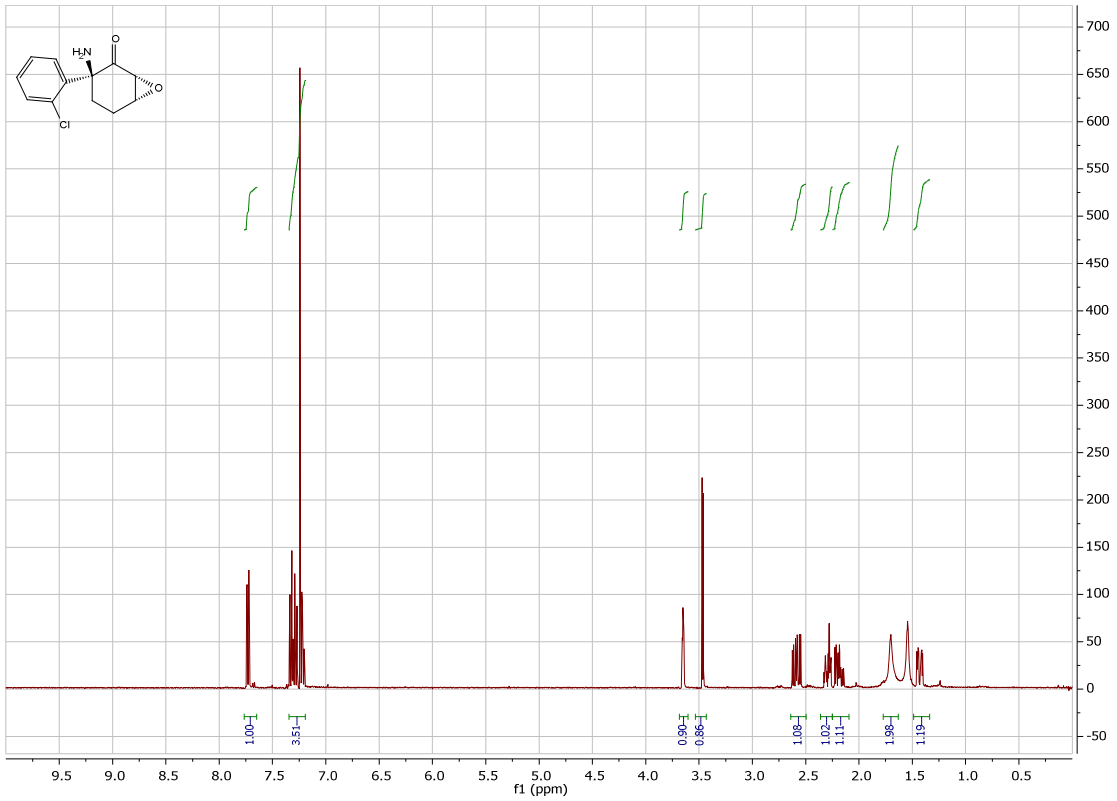


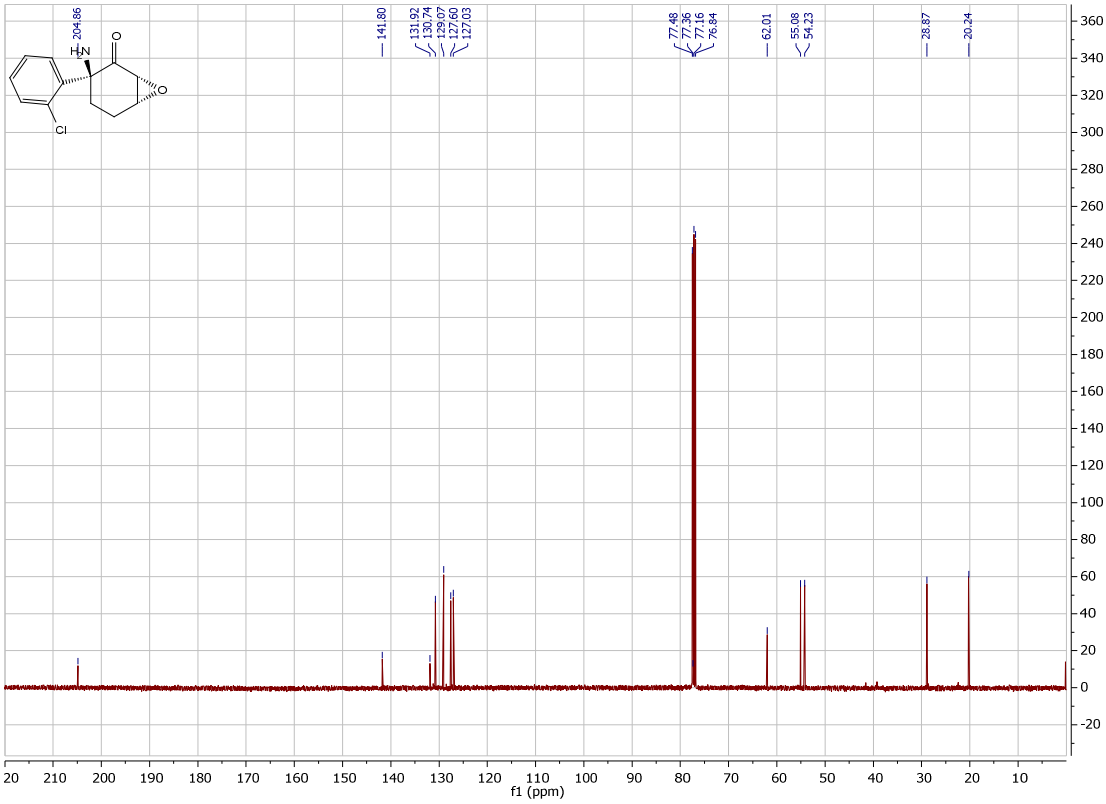
(*2R,5S*)-2-Amino-2-(2-chlorophenyl)-5-hydroxycyclohexan-1-one (**9a**). **NCGC00488759**



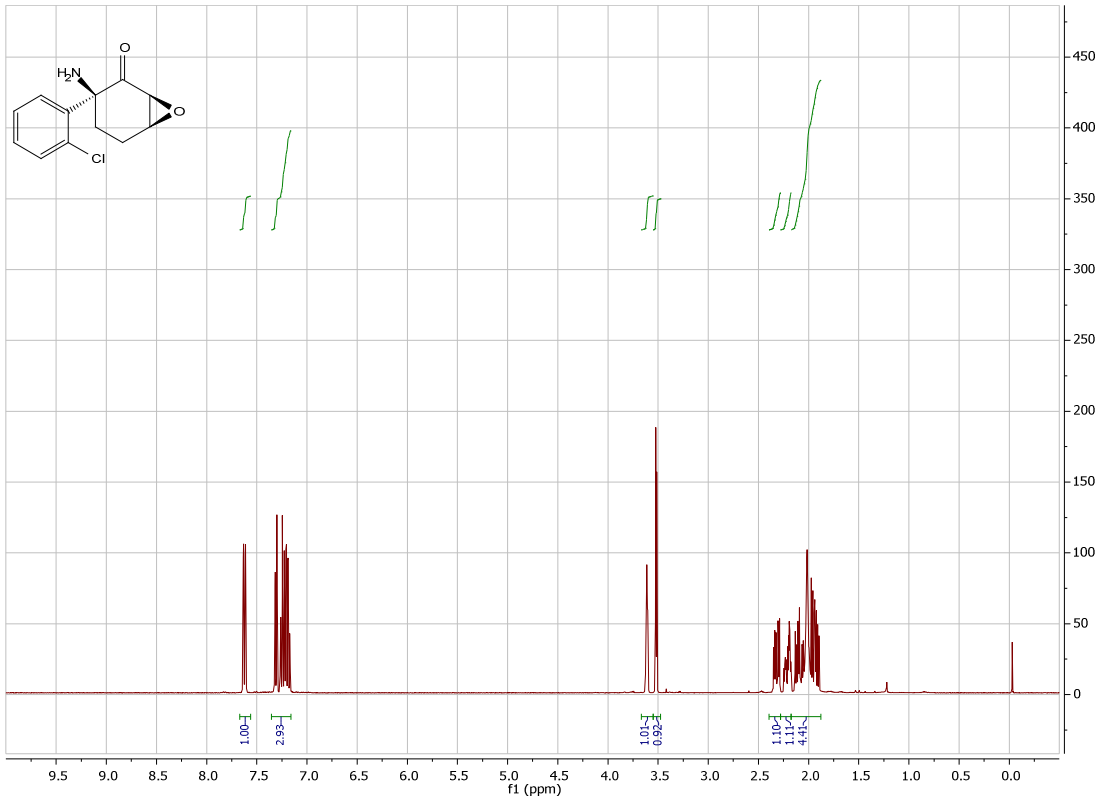


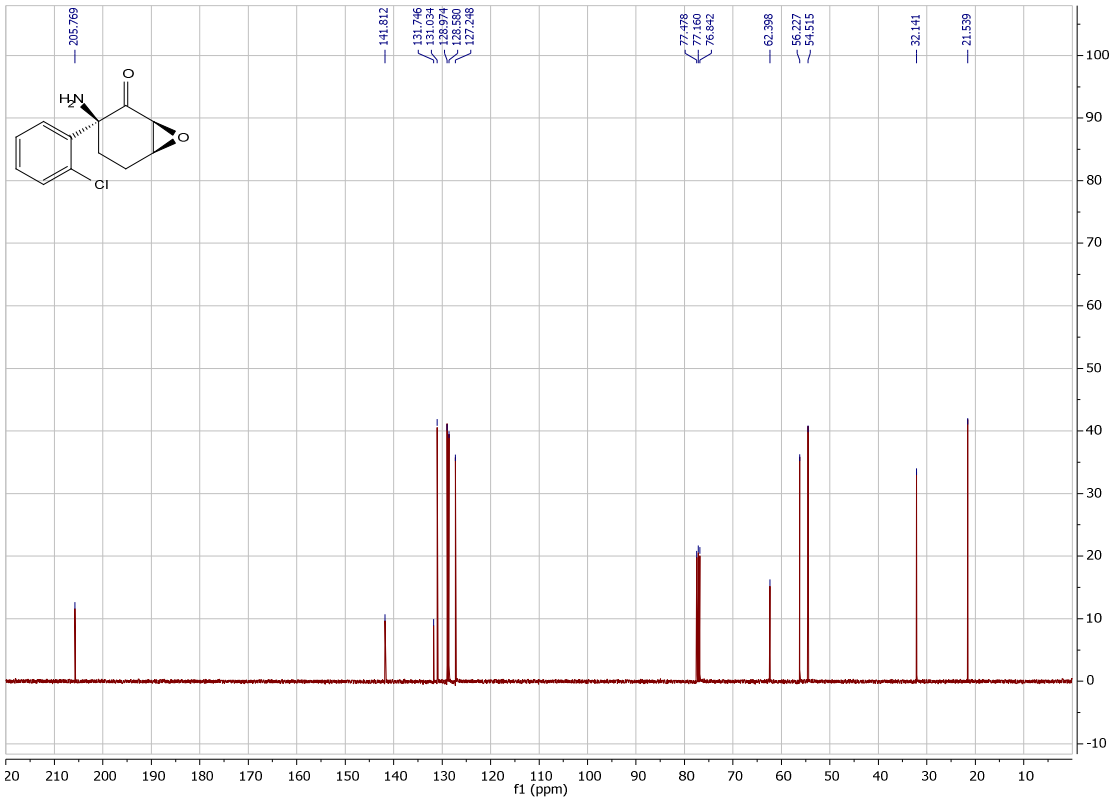
(*1R,3S,6R*)-3-amino-3-(2-chlorophenyl)-7-oxabicyclo[4.1.0]heptan-2-one (**24b**). **NCGC00489862**



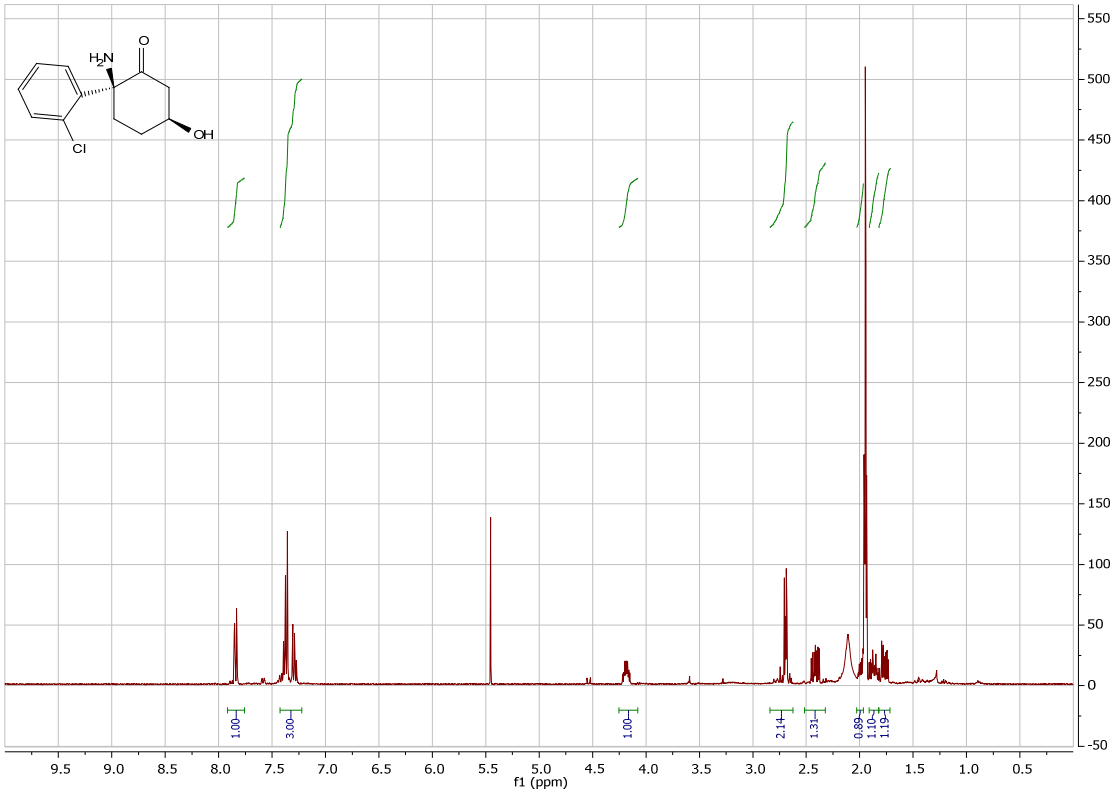


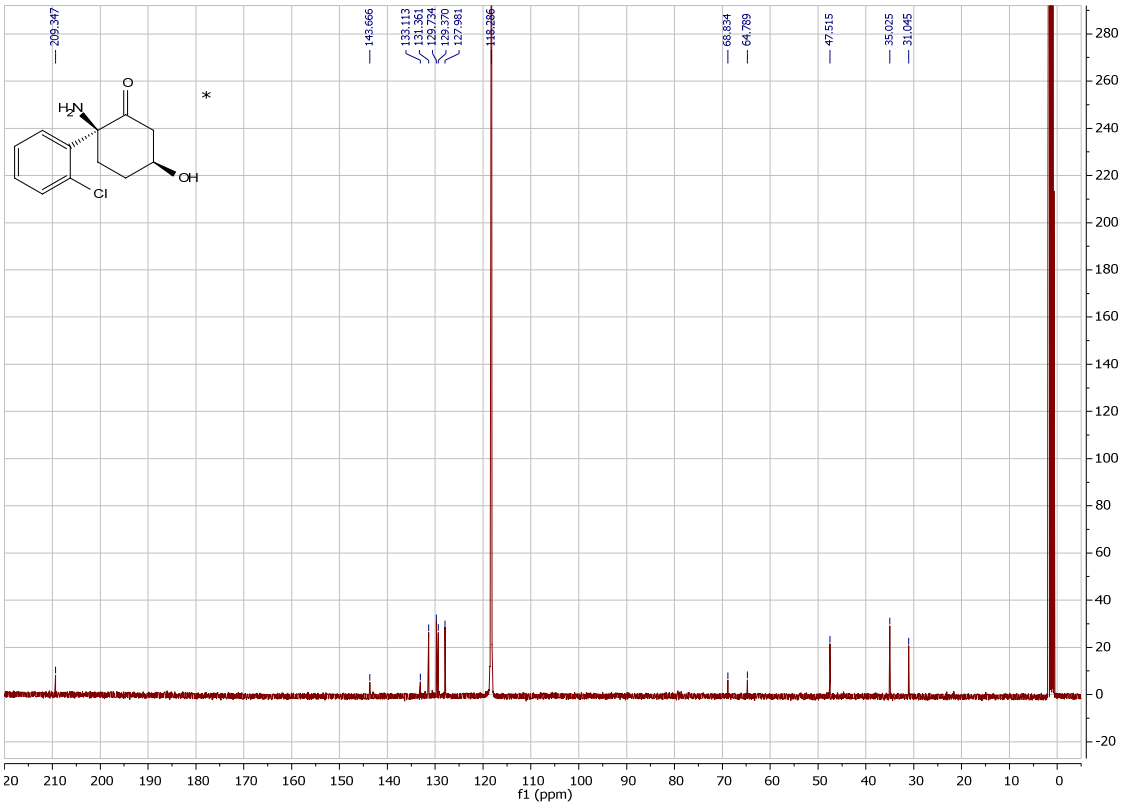
(*1S,3S,6S*)-3-amino-3-(2-chlorophenyl)-7-oxabicyclo[4.1.0]heptan-2-one (**25b**). **NCGC00490643**



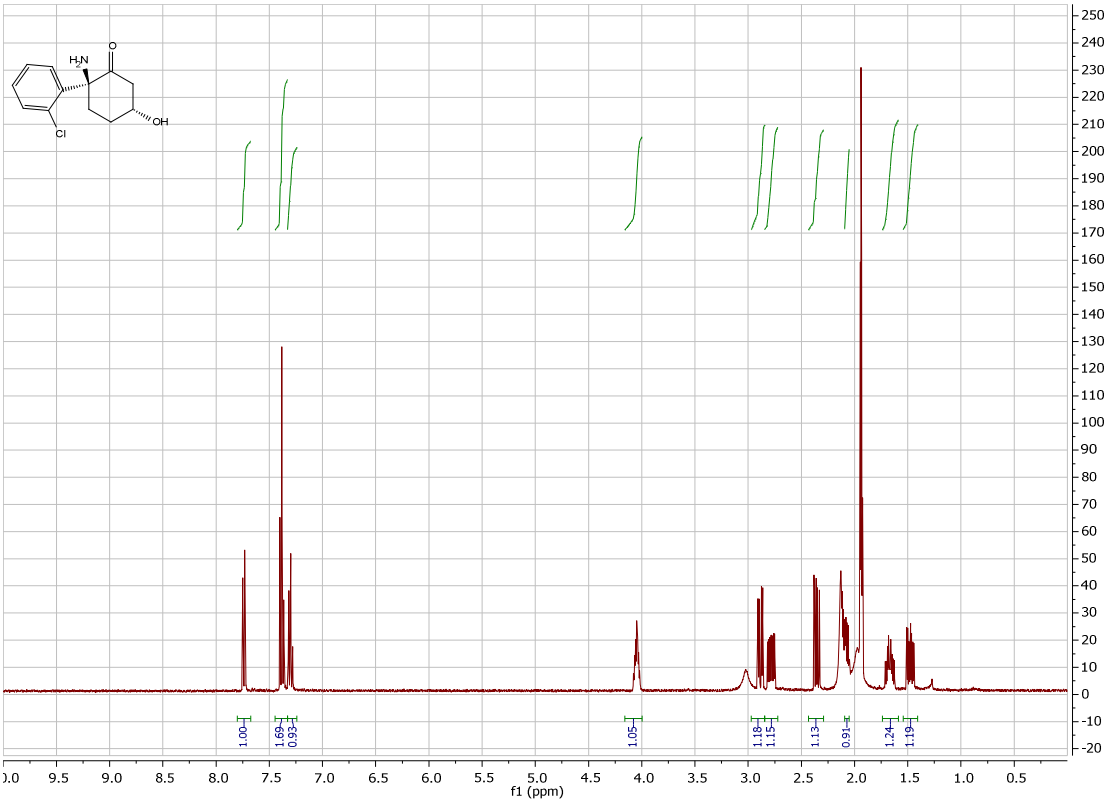


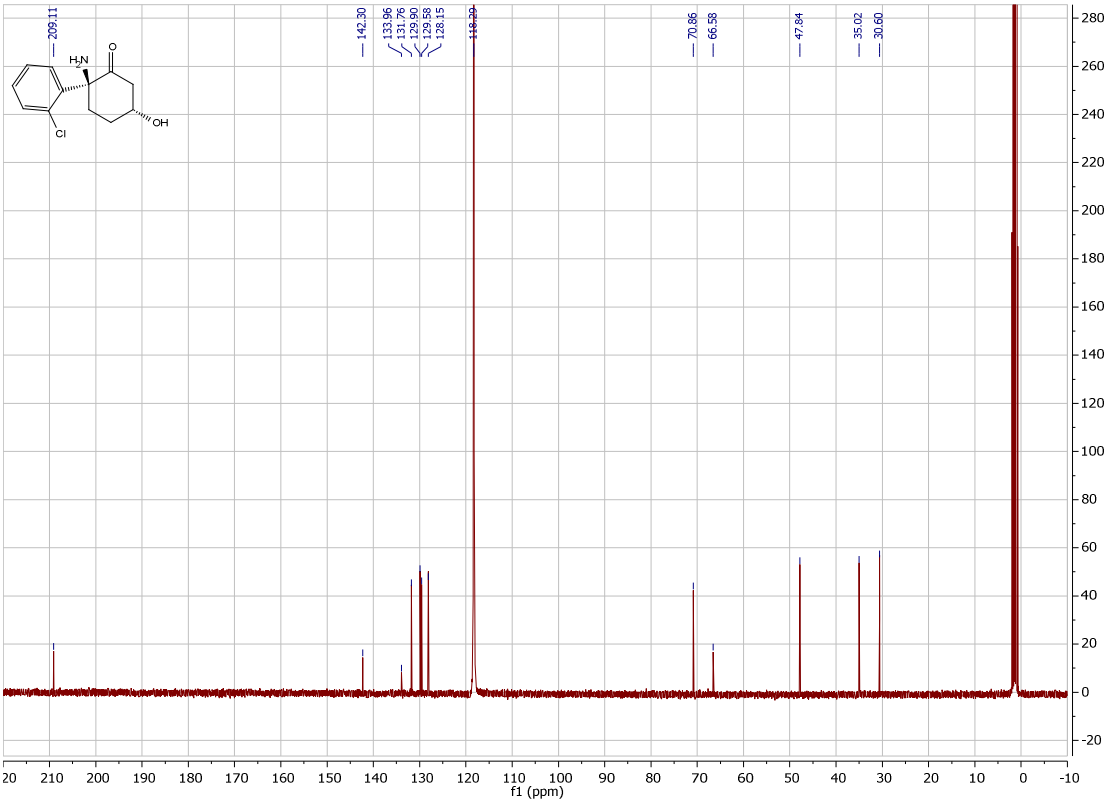
(*2S,5S*)-2-Amino-2-(2-chlorophenyl)-5-hydroxycyclohexan-1-one (**8b**). **NCGC00389131**



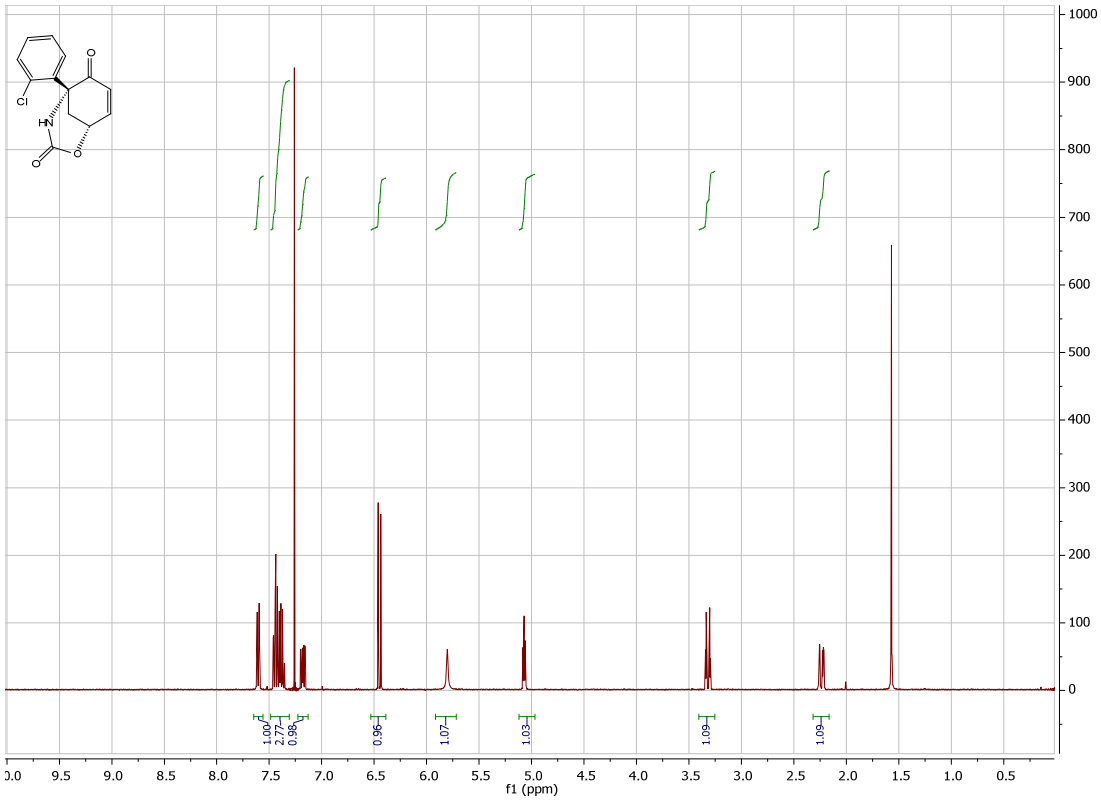


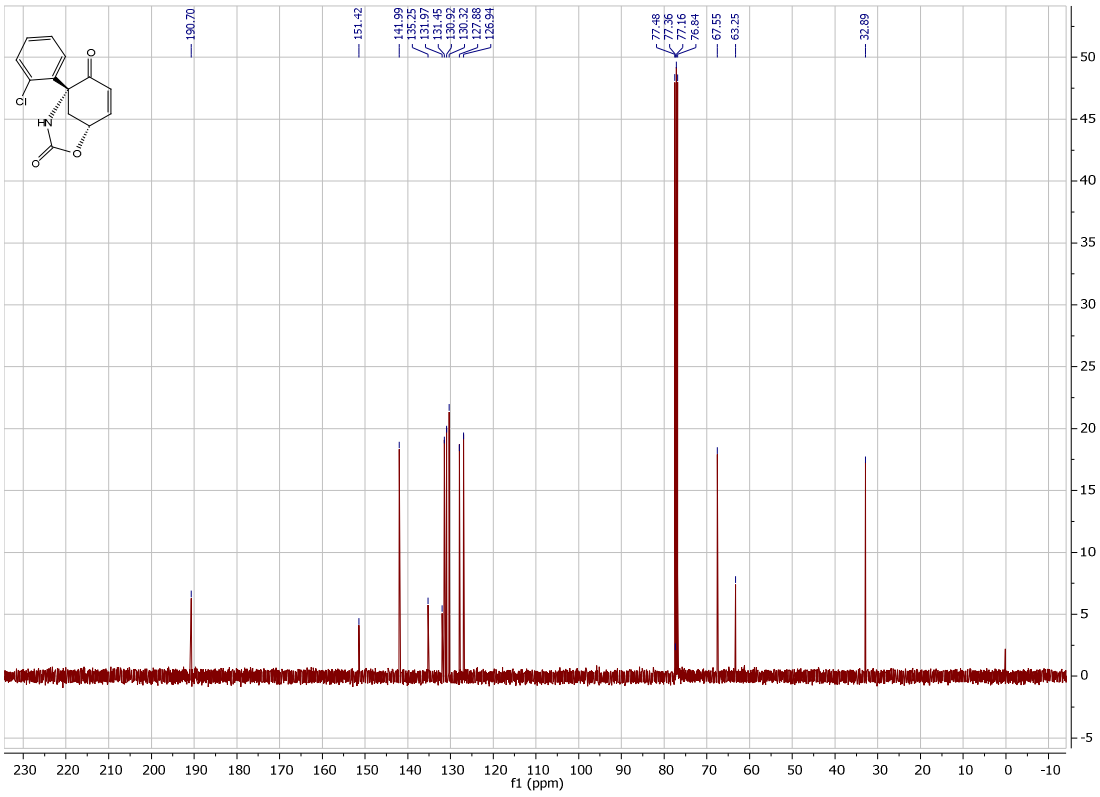
(*2S,5R*)-2-amino-2-(2-chlorophenyl)-5-hydroxycyclohexan-1-one (**9b**). **NCGC00489857**



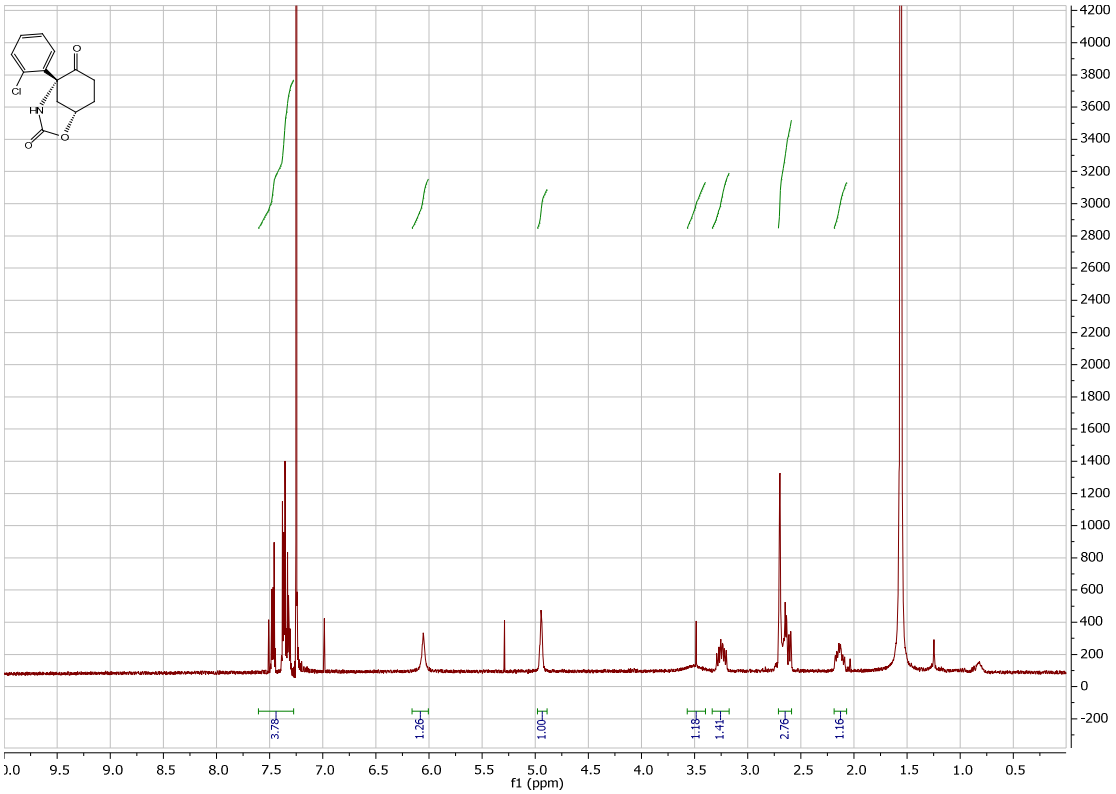


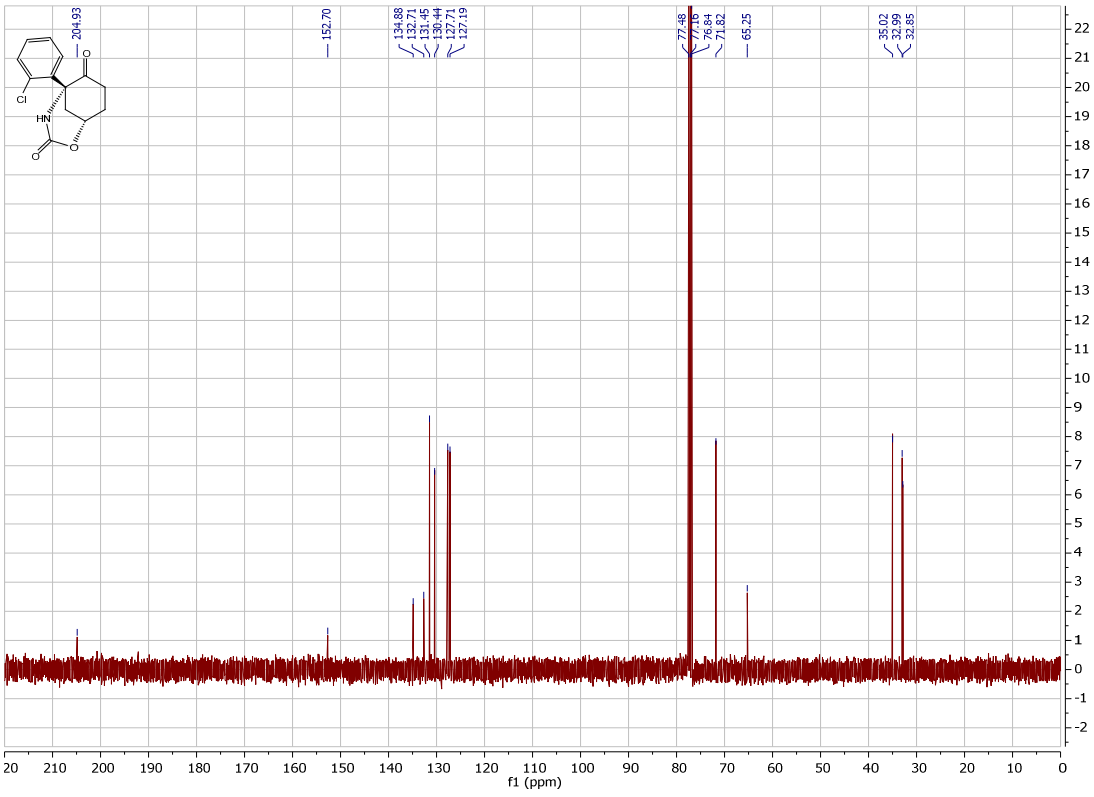
(*1R,5R*)-5-(2-Chlorophenyl)-2-oxa-4-azabicyclo[3.3.1]non-7-ene-3,6-dione (**27a**). **NCGC00486896**



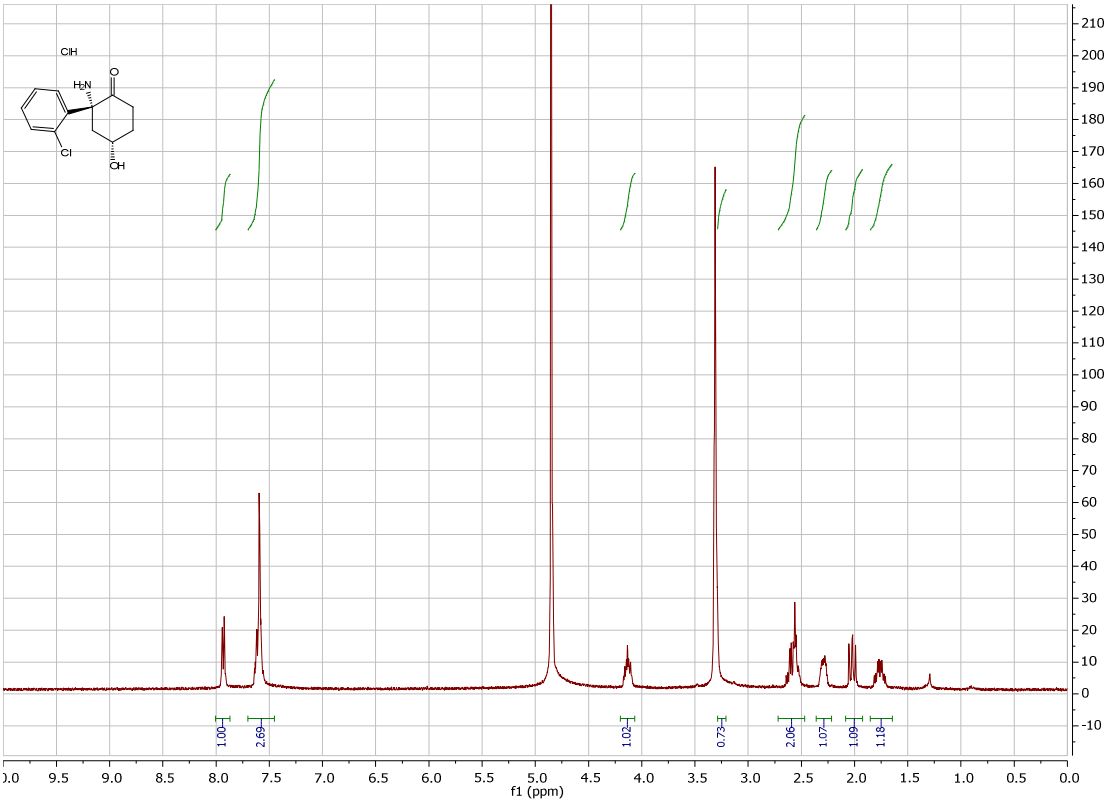


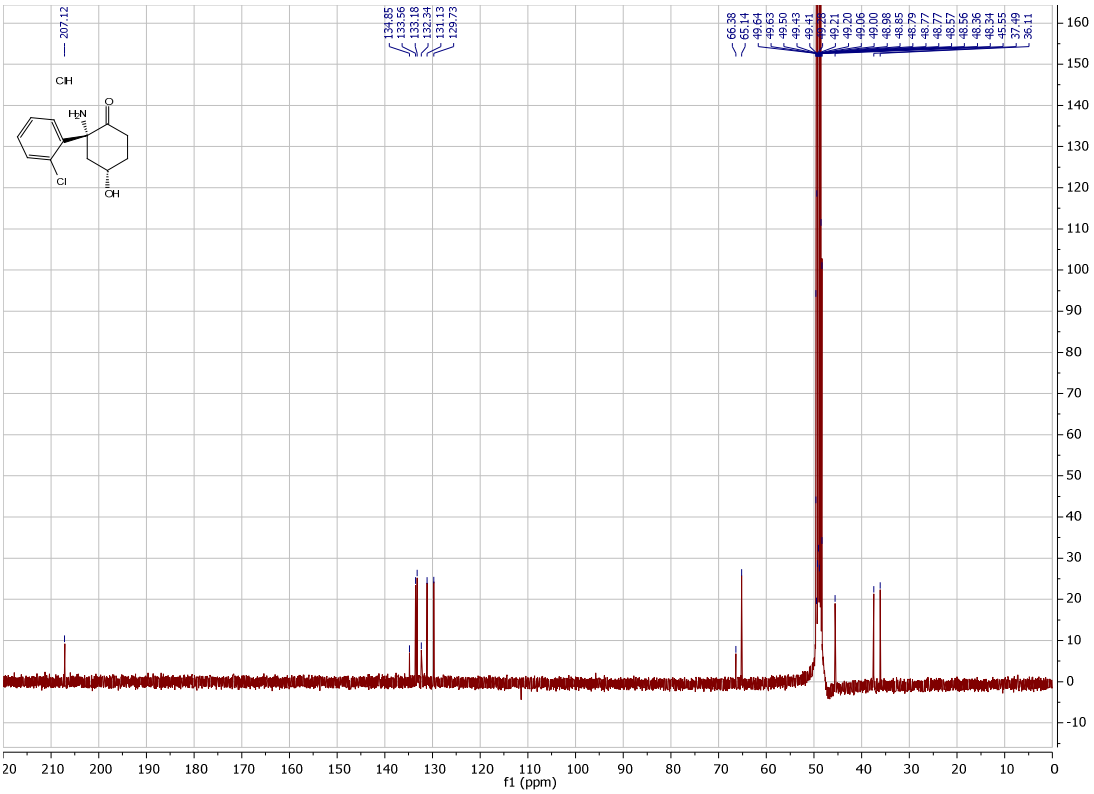
(*1S,5R*)-5-(2-Chlorophenyl)-2-oxa-4-azabicyclo[3.3.1]nonane-3,6-dione (**28a**). **NCGC00486899**



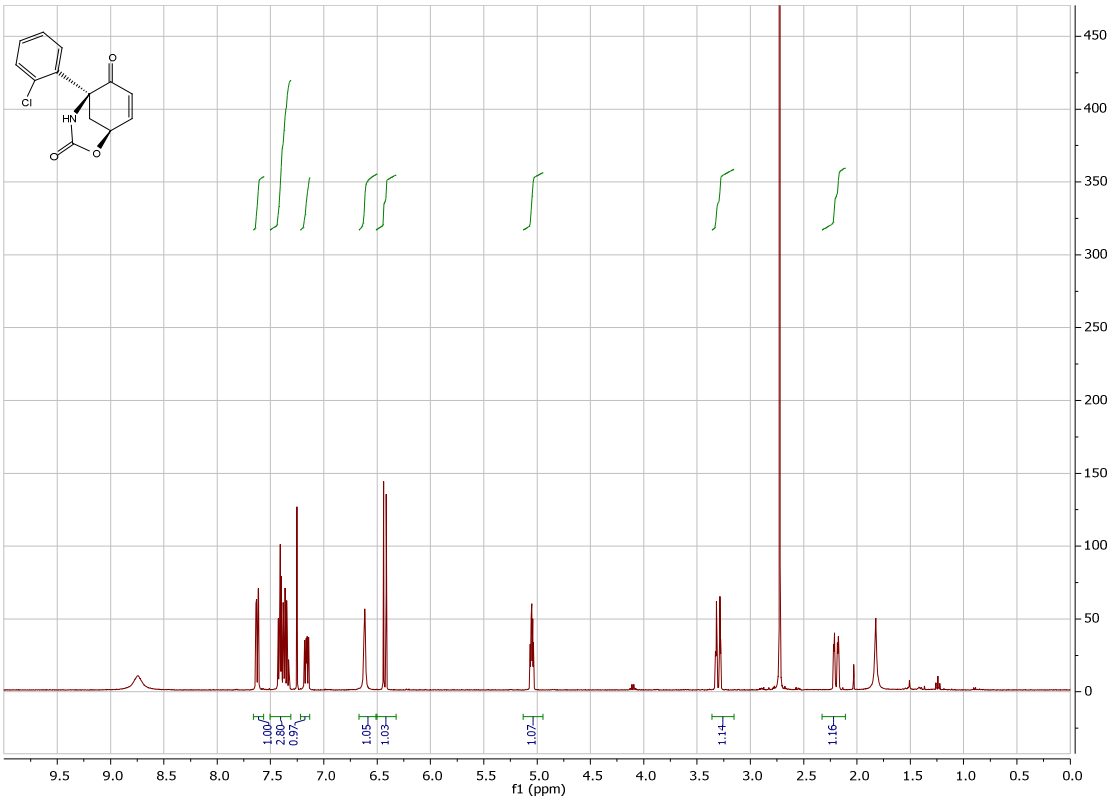


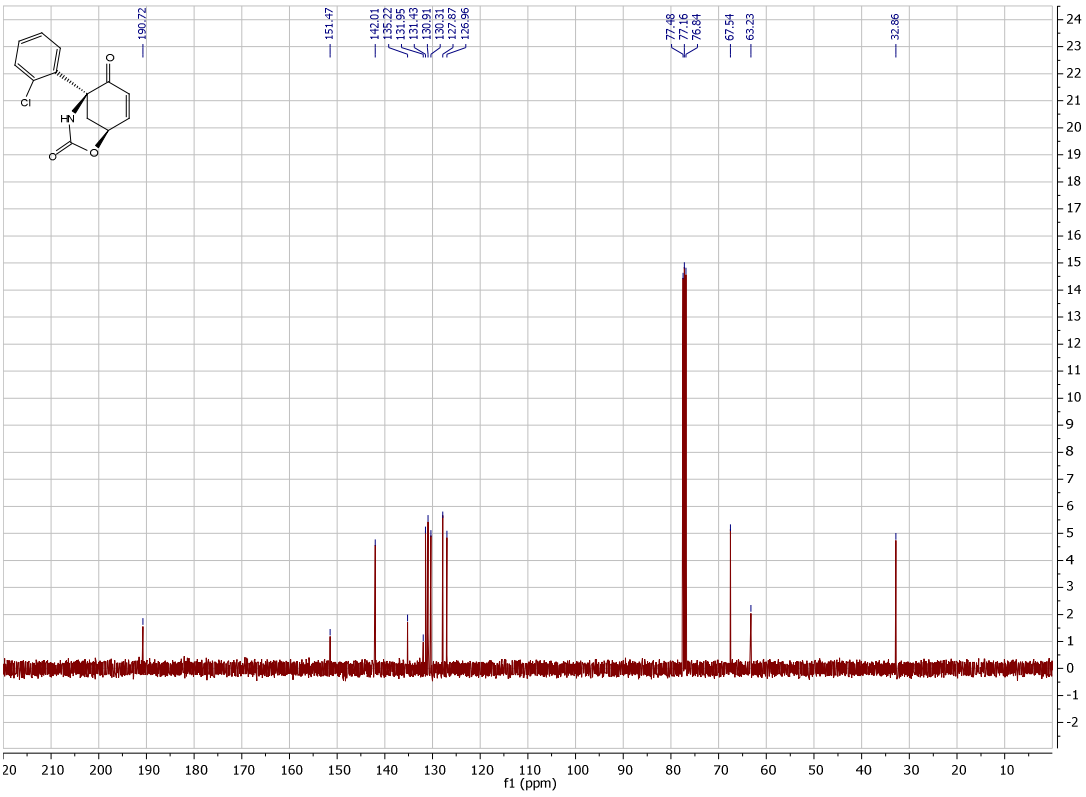
(*2R,4S*)-2-Amino-2-(2-chlorophenyl)-4-hydroxycyclohexan-1-one (**10a**). **NCGC00389998**



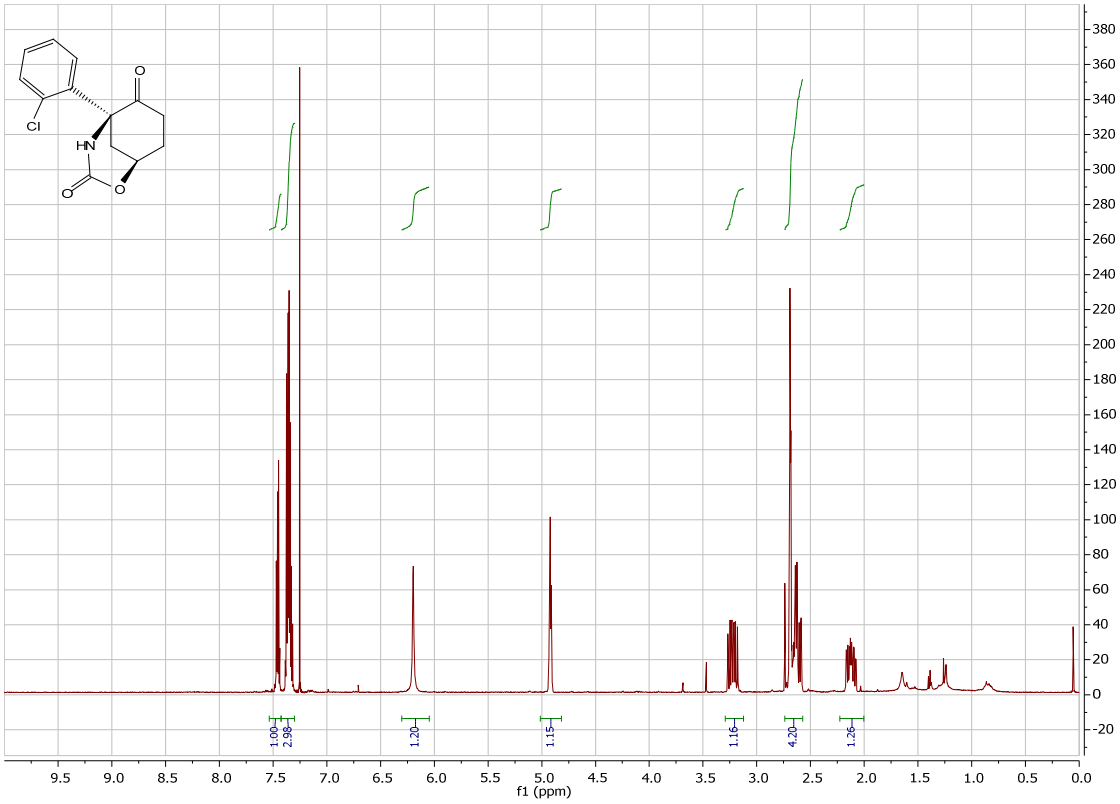


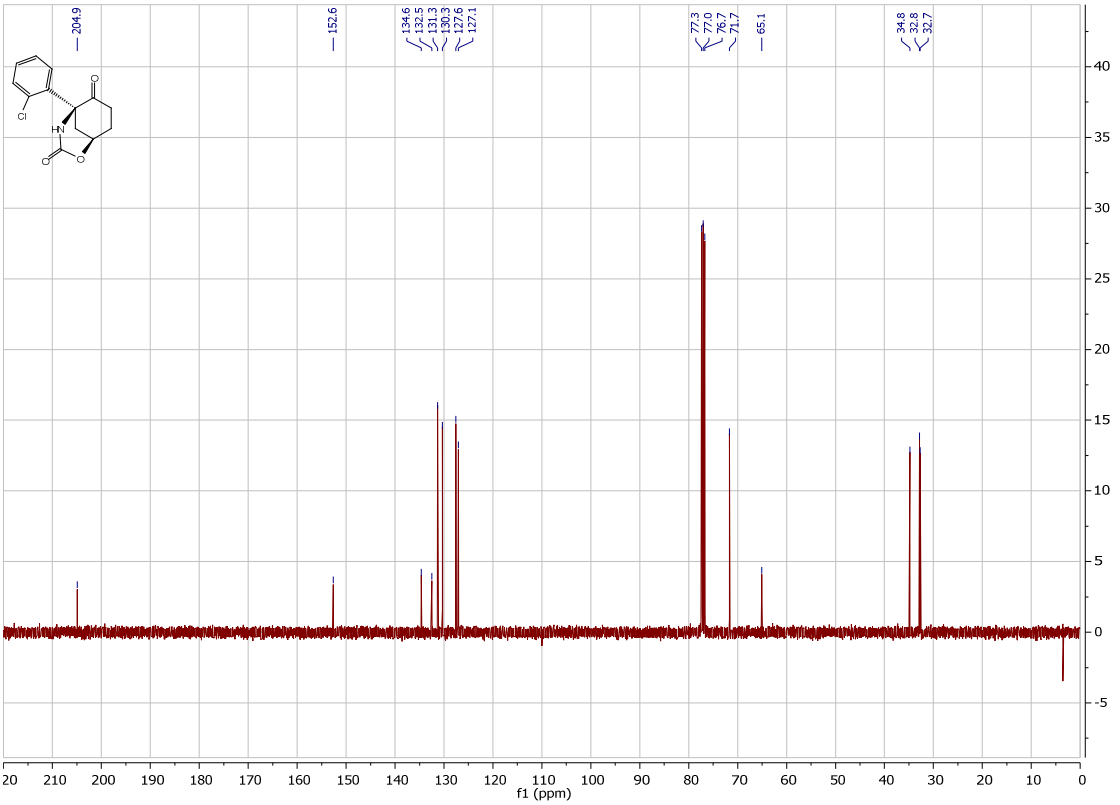
(*1S,5S*)-5-(2-Chlorophenyl)-2-oxa-4-azabicyclo[3.3.1]non-7-ene-3,6-dione (**27b**). **NCGC00489093**



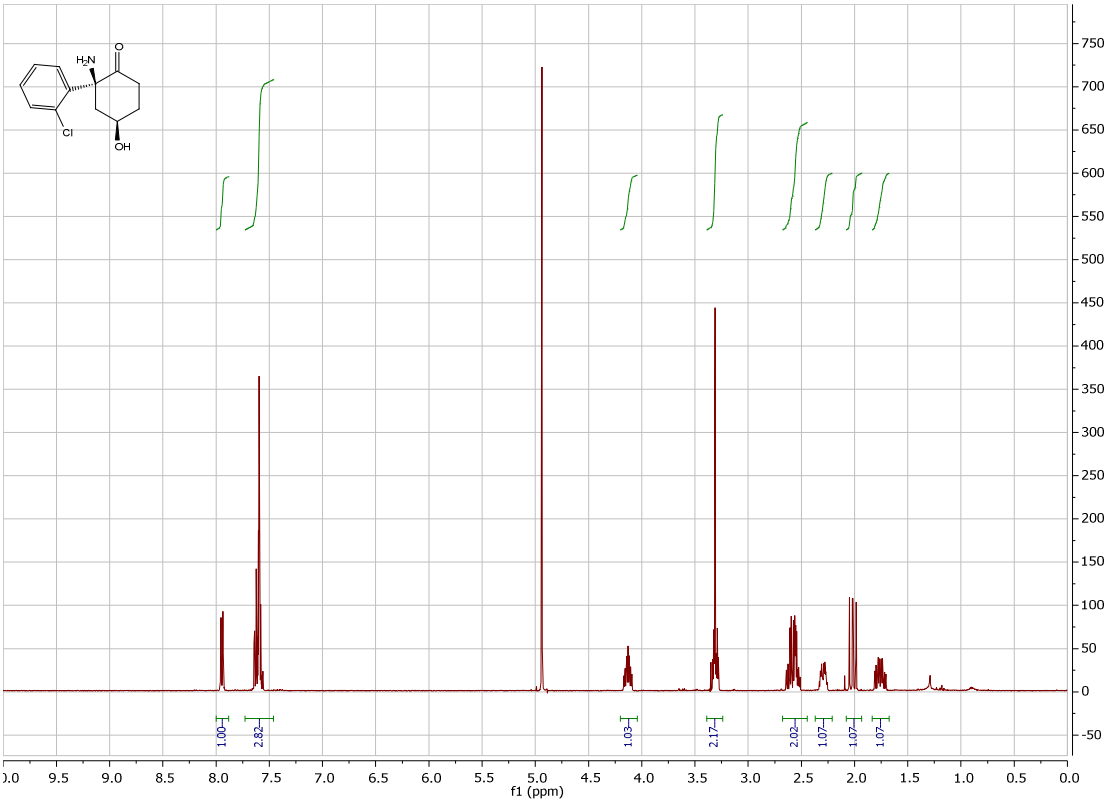


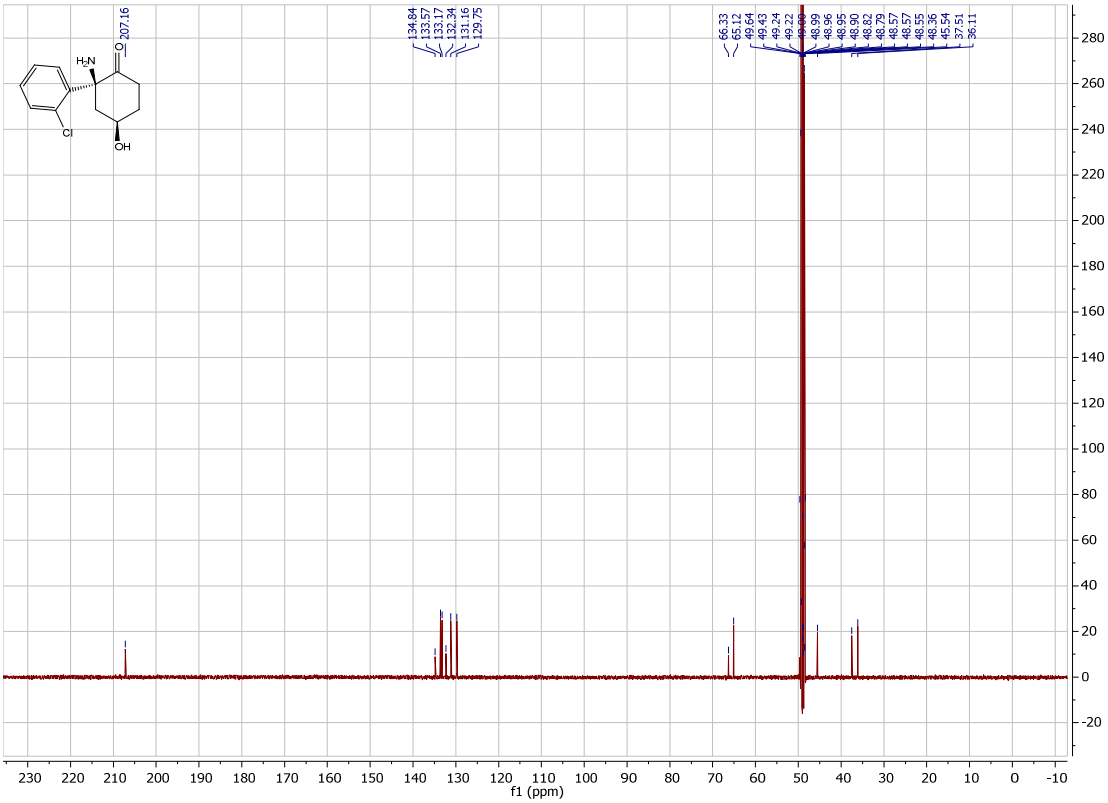
(*1R,5S*)-5-(2-Chlorophenyl)-2-oxa-4-azabicyclo[3.3.1]nonane-3,6-dione (**28b**). **NCGC00481482**



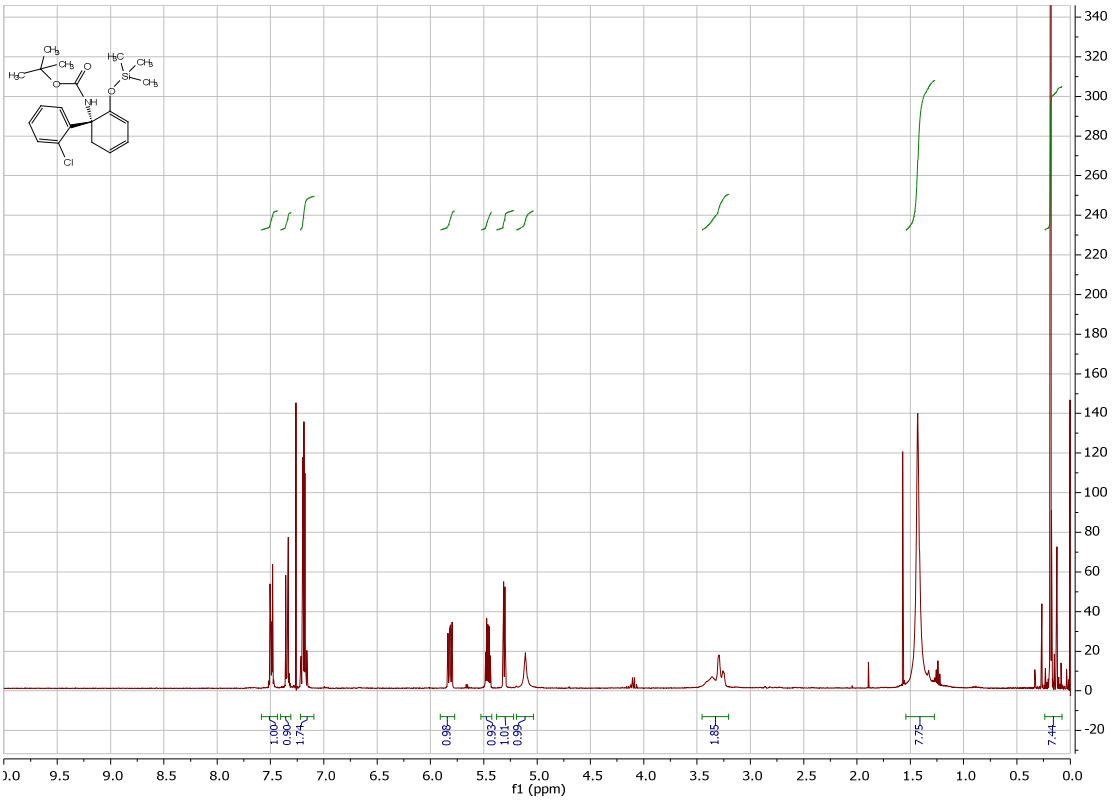


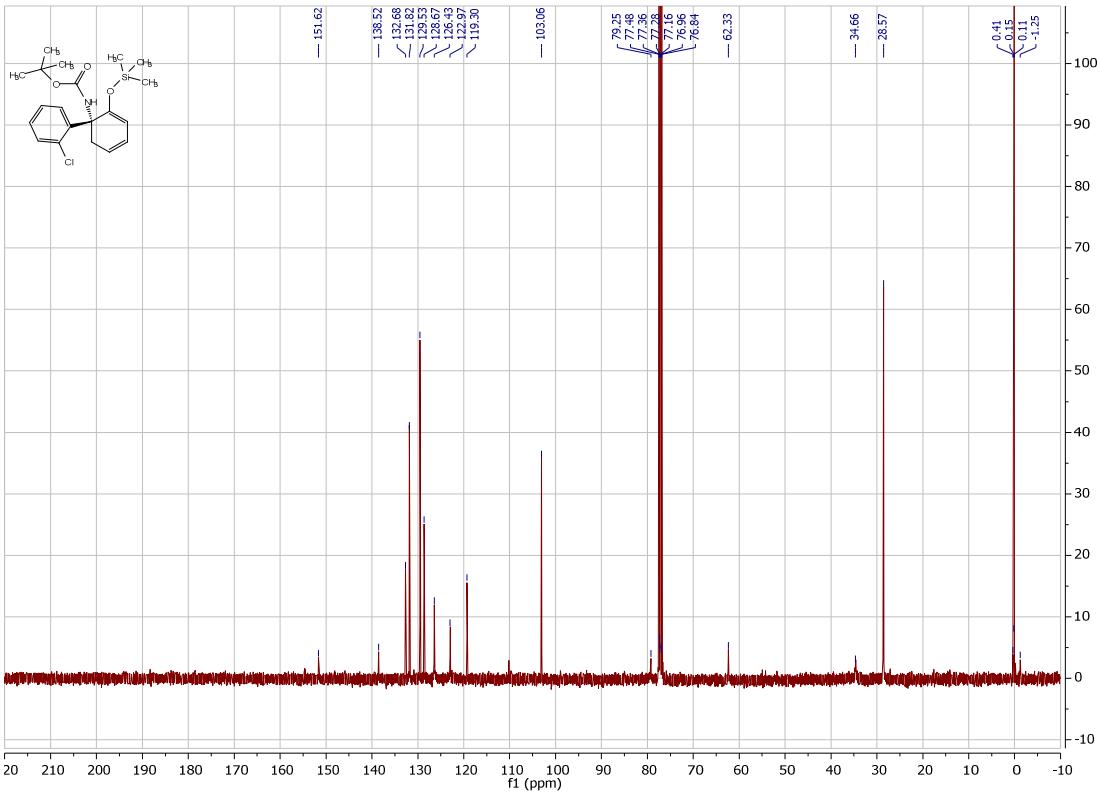
(*2S,4R*)-2-Amino-2-(2-chlorophenyl)-4-hydroxycyclohexan-1-one (**10b**). **NCGC00481516**



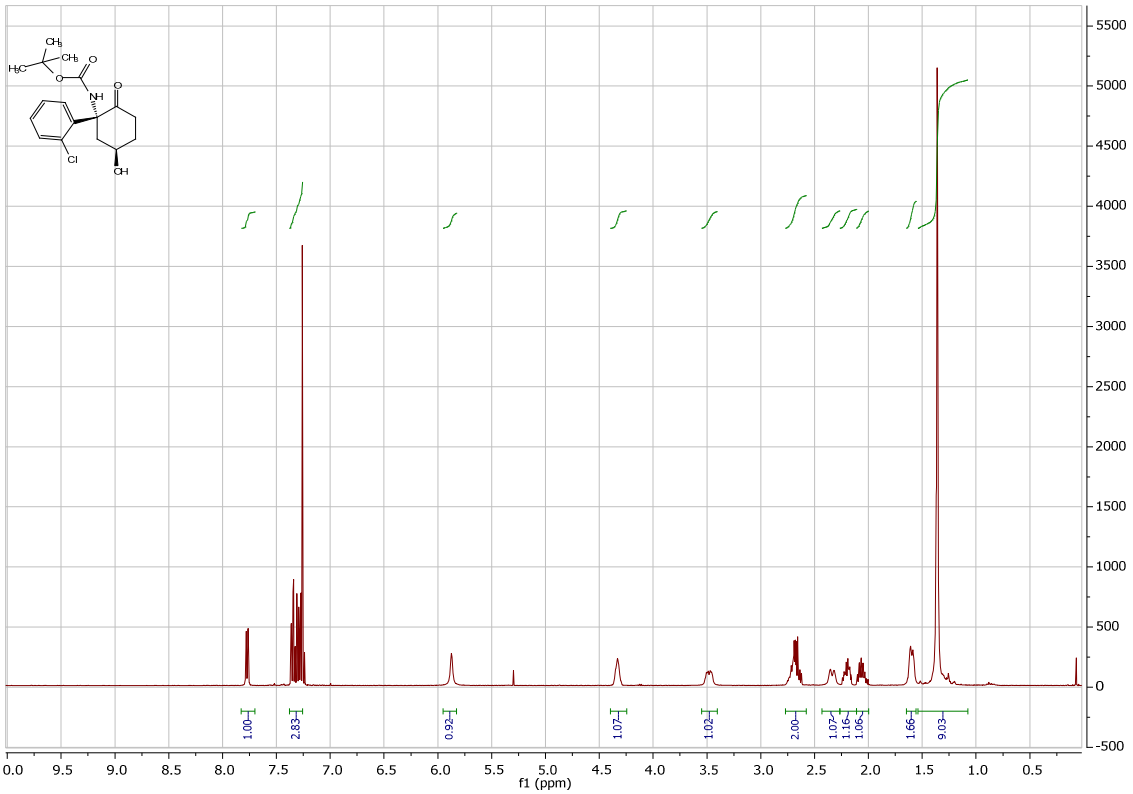


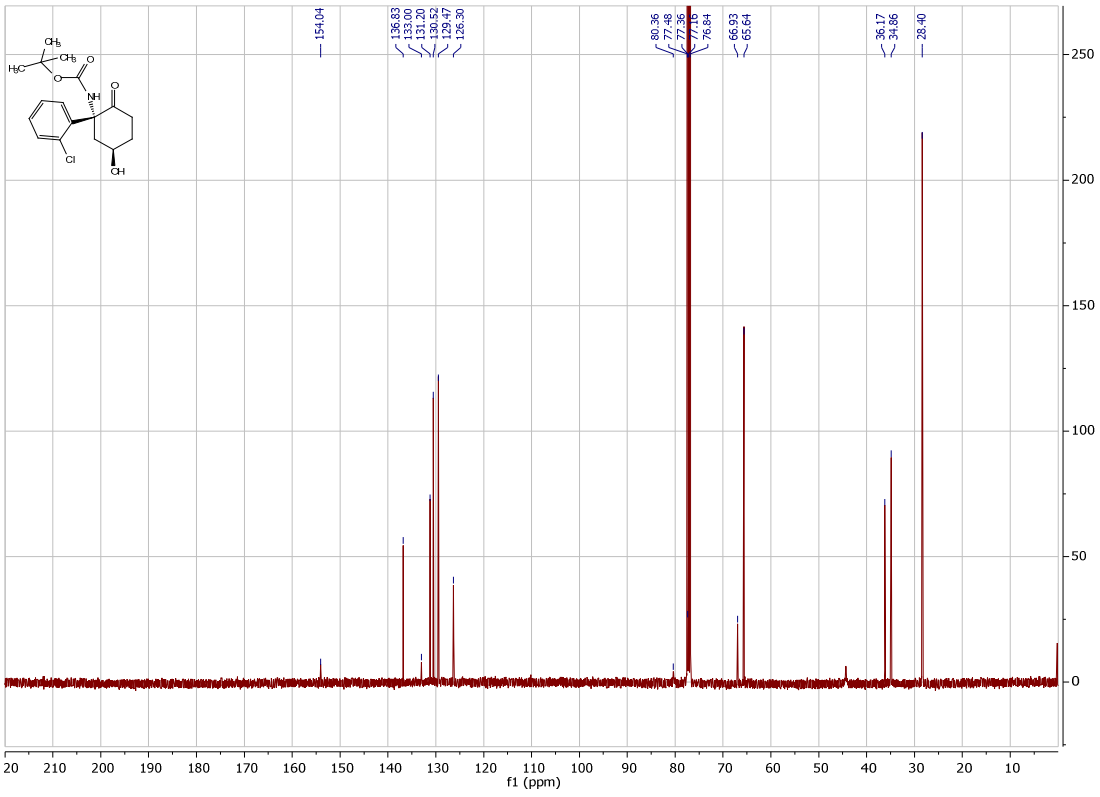
tert-Butyl (*R*)-(2'-chloro-6-((trimethylsilyl)oxy)-[1,1'-biphenyl]-1(2H)-yl)carbamate (**29a**). **NCGC00488915**

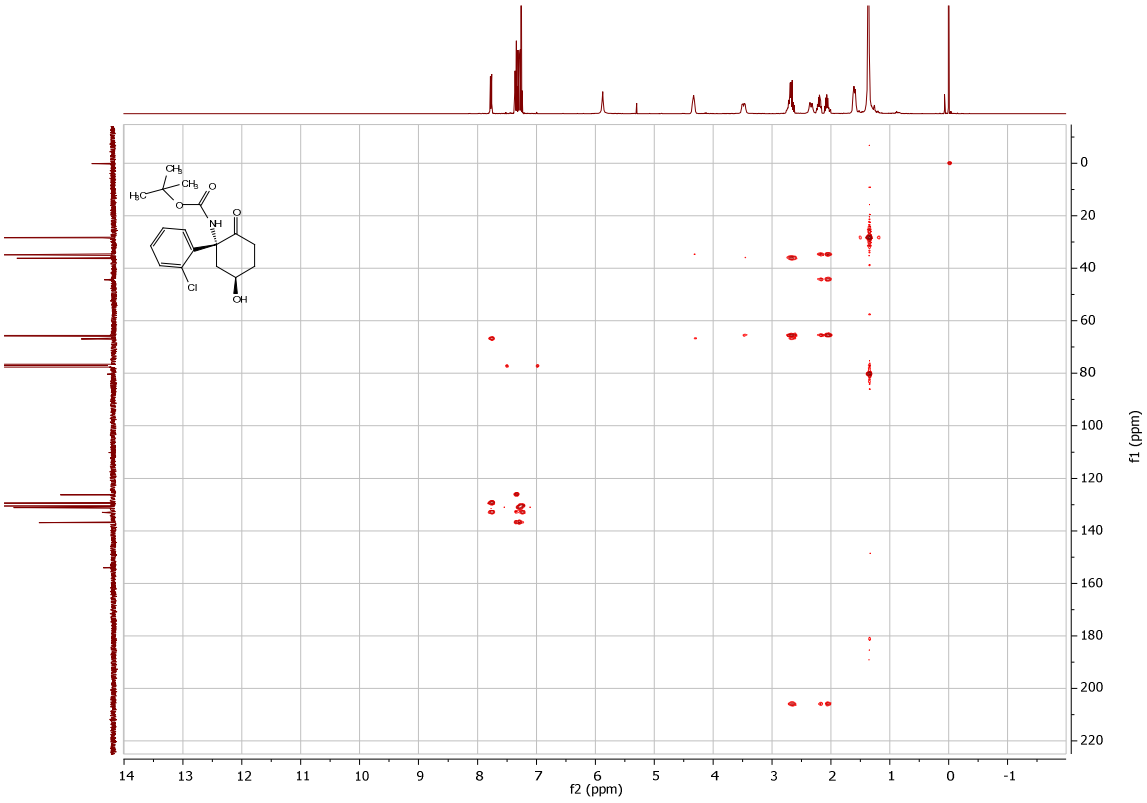




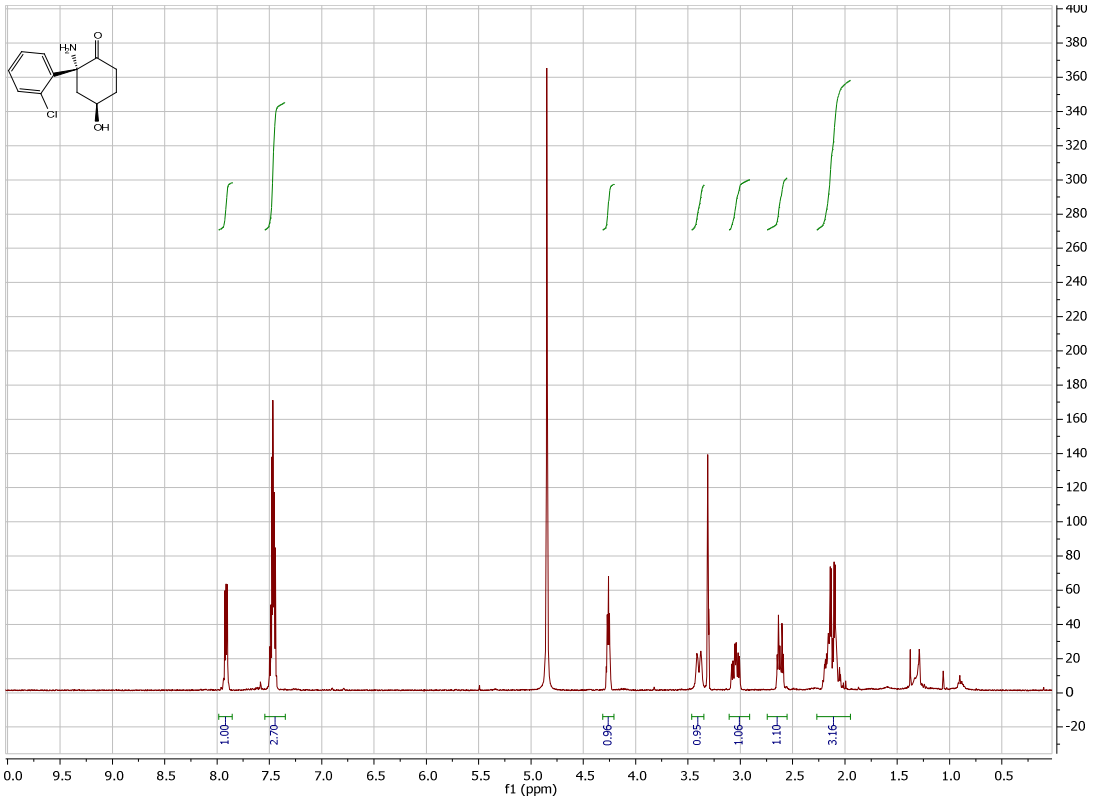
tert-Butyl ((*1R,5R*)-1-(2-chlorophenyl)-5-hydroxy-2-oxocyclohexyl)carbamate (**32a**). **NCGC00499295**

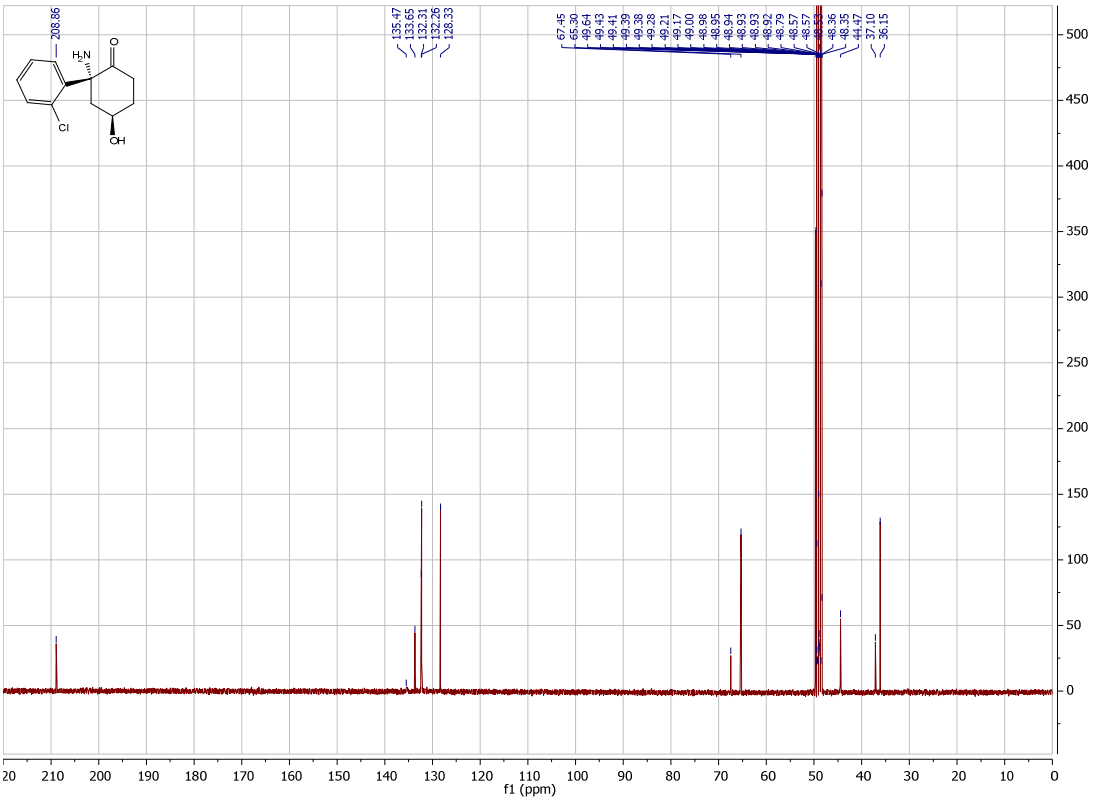


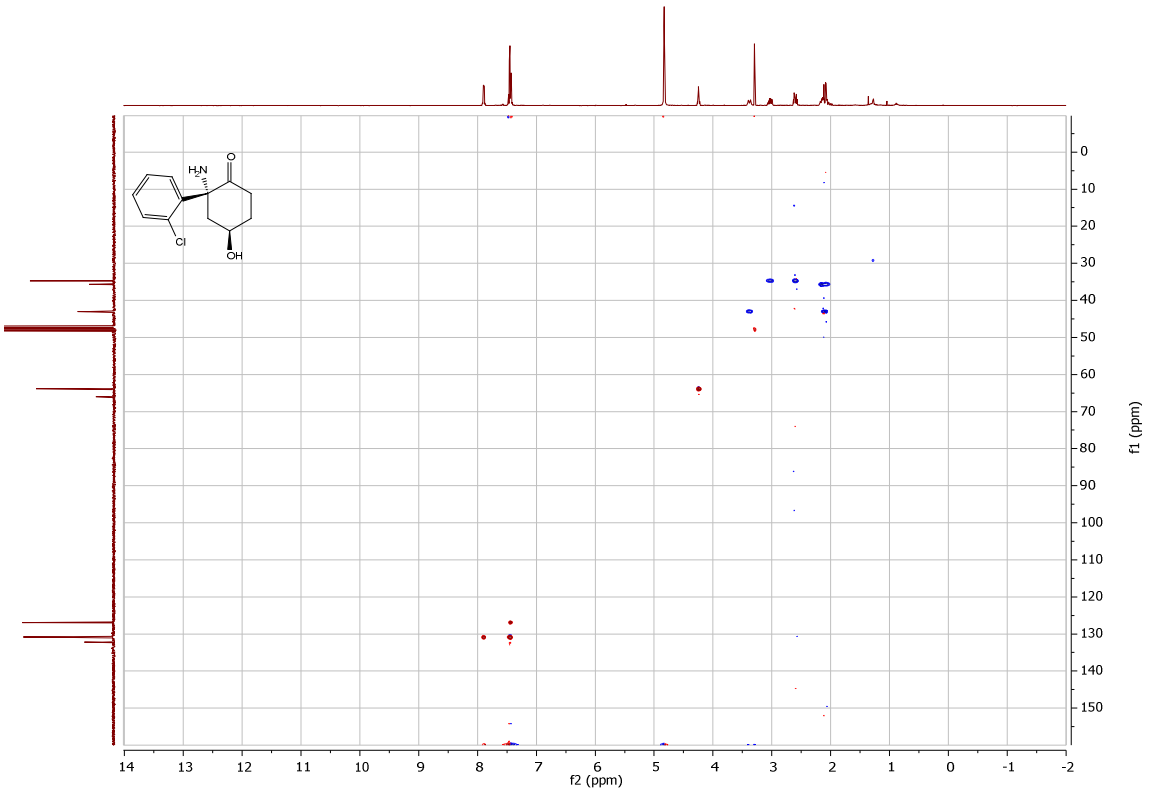



f2 (ppm)
f1 (ppm)

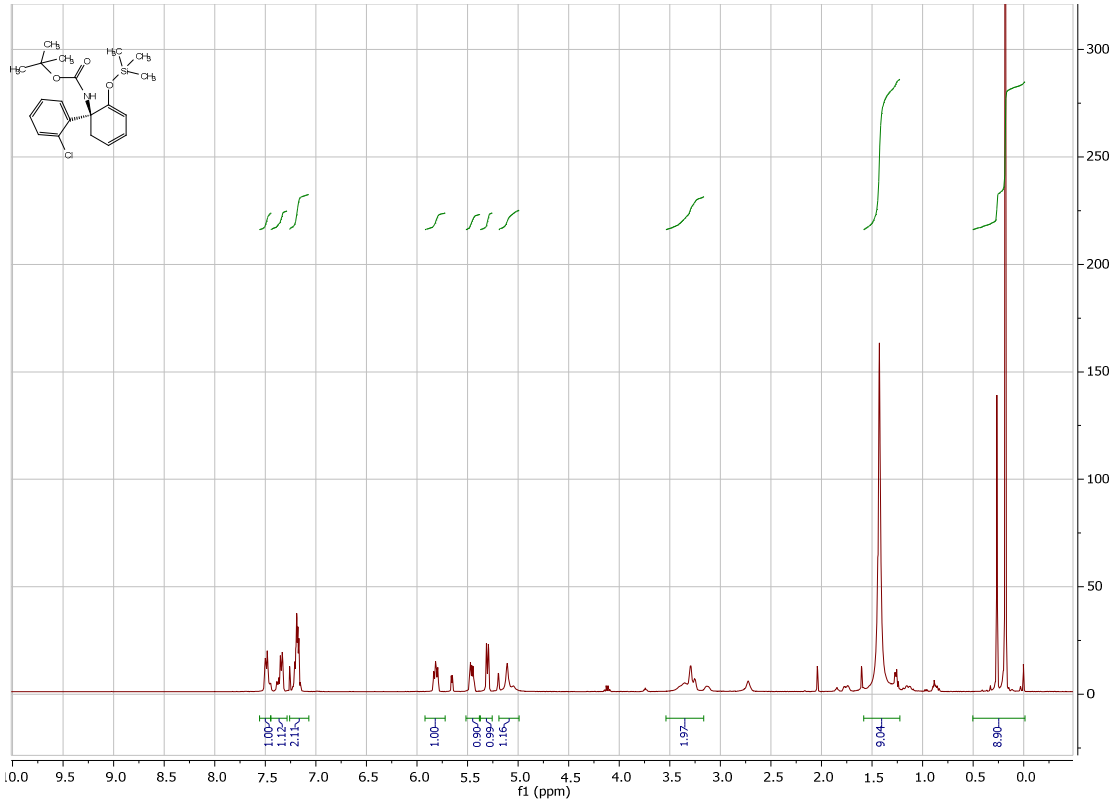
(*2R,4R*)-2-Amino-2-(2-chlorophenyl)-4-hydroxycyclohexan-1-one (**11a**). **NCGC00488918**

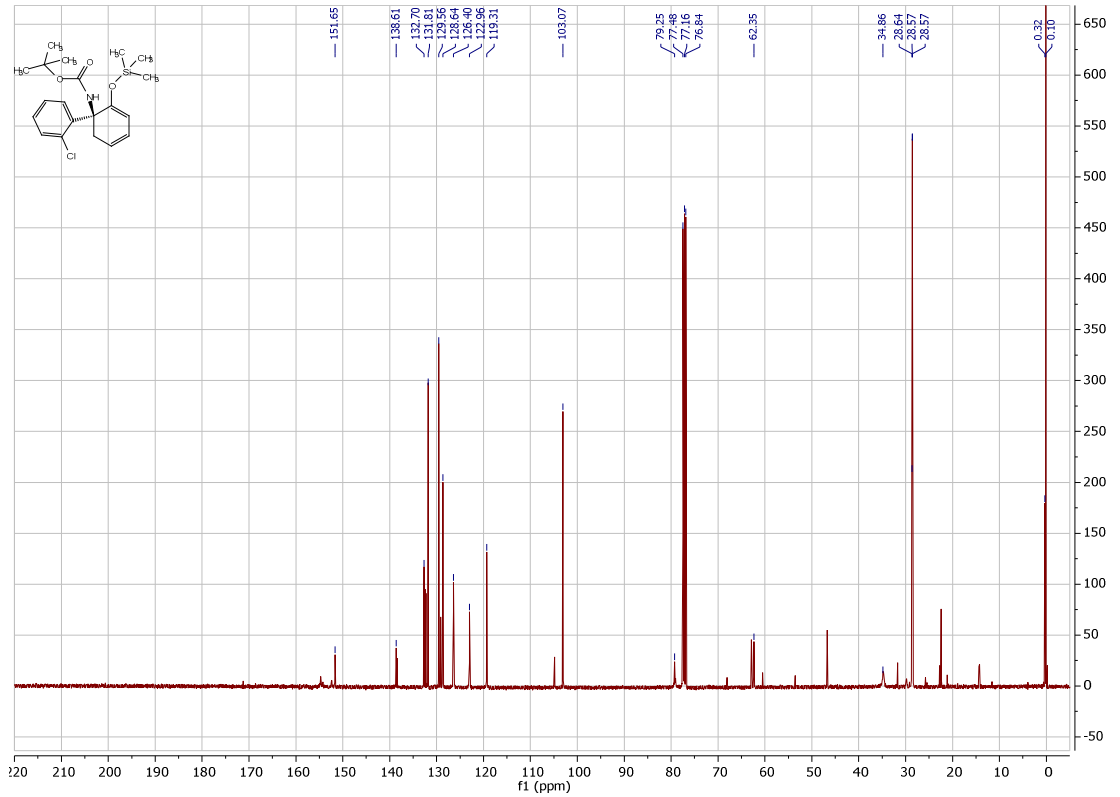




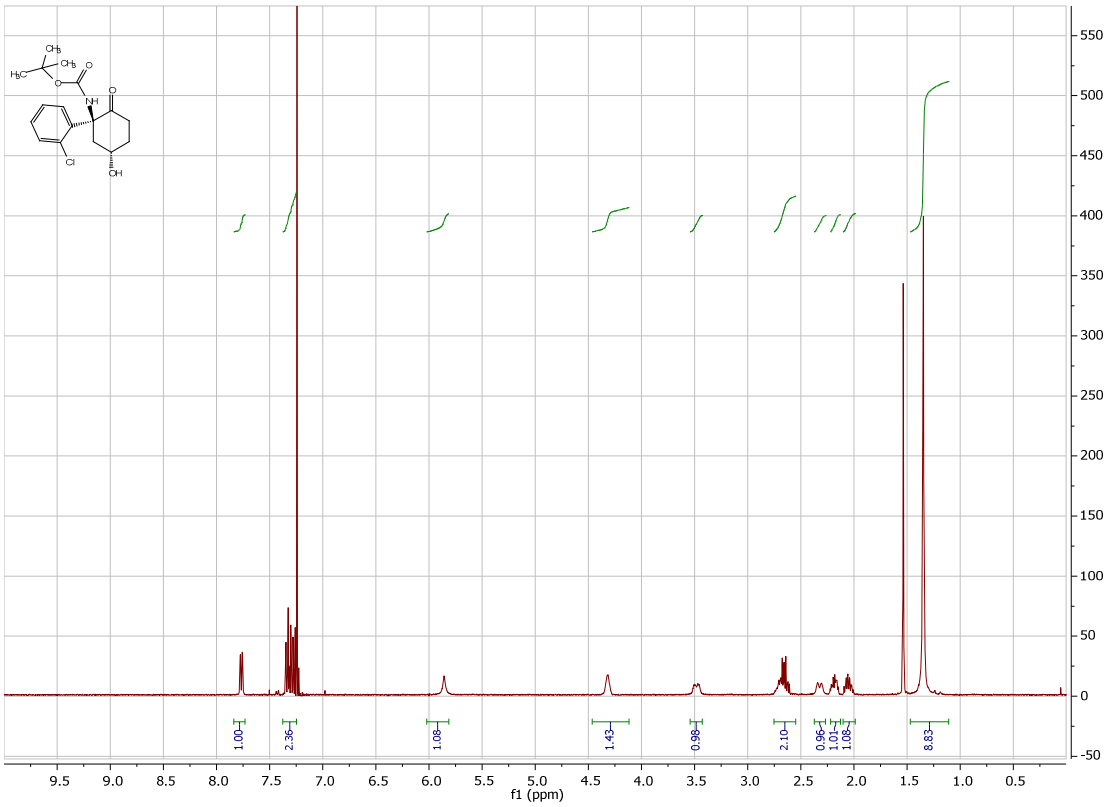

H2N
O
Cl
OH
f2 (ppm)
f1 (ppm)

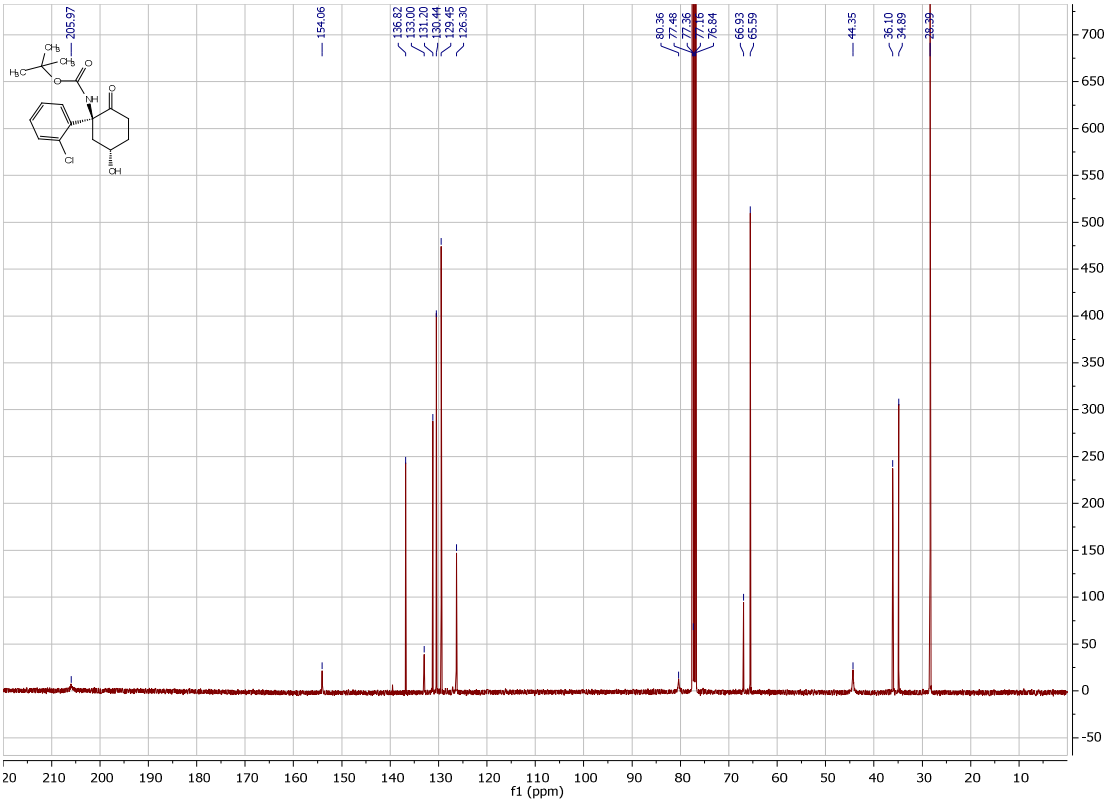
tert-Butyl (*S*)-(2'-chloro-6-((trimethylsilyl)oxy)-[1,1'-biphenyl]-1(2H)-yl)carbamate (**29b**). **NCGC00505098** (~70% purity)



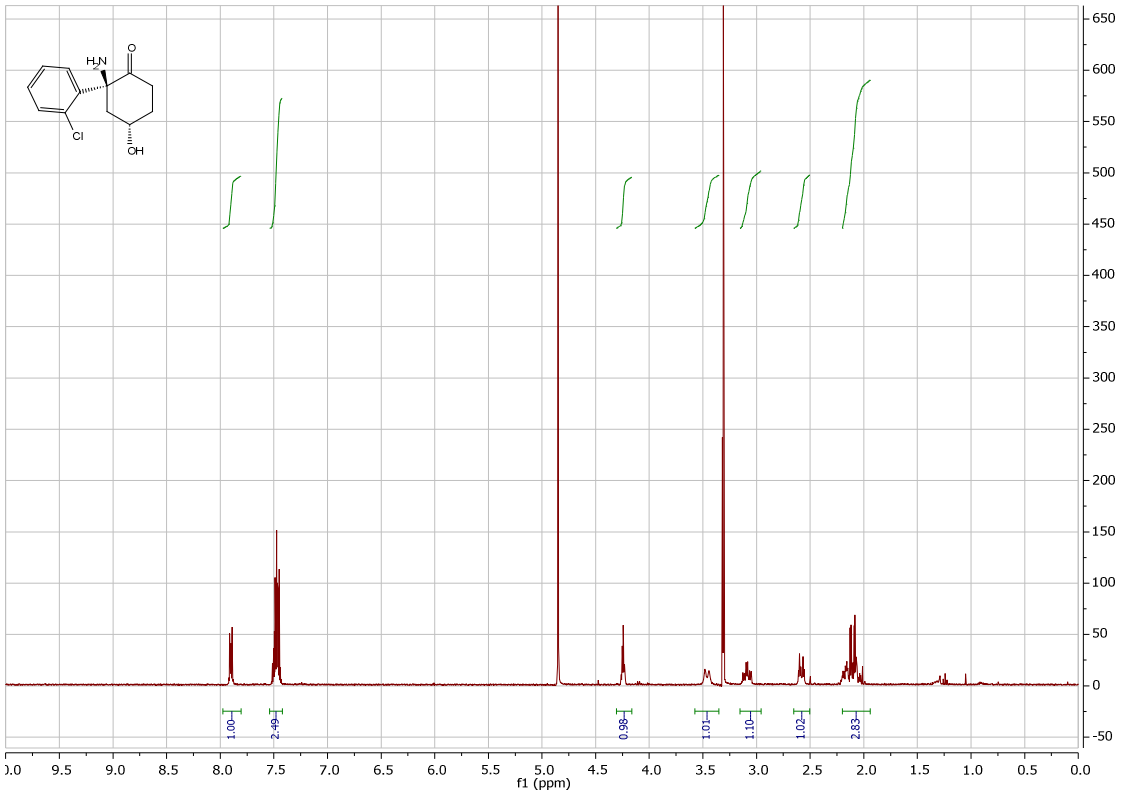


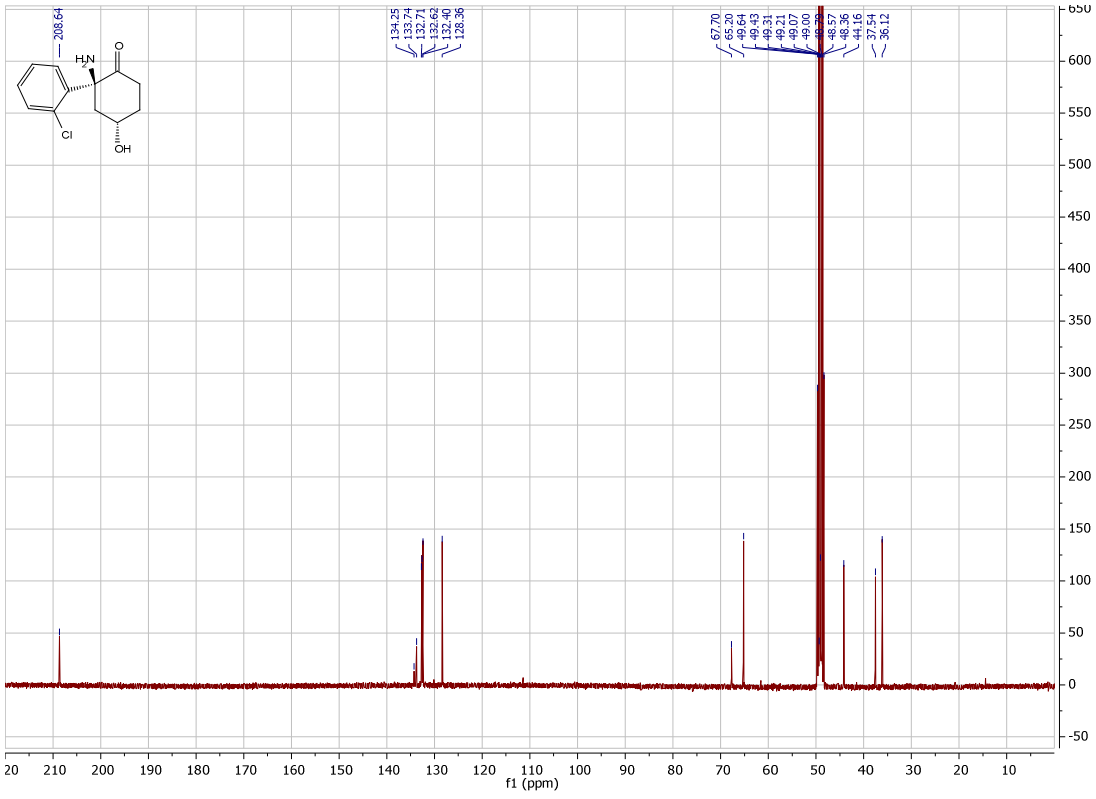
tert-Butyl ((*1S,5S*)-1-(2-chlorophenyl)-5-hydroxy-2-oxocyclohexyl)carbamate (**32b**). **NCGC00499627**





(*2S,4S*)-2-amino-2-(2-chlorophenyl)-4-hydroxycyclohexan-1-one hydrochloride (**11b**). **NCGC00492317**





References:

1) Javitt, D. C. and Zukin, S.R.; *Proc. Natl. Acad. Sci*. **1989,** *86*, 740.
2) Reynolds, I. J.,; Murphy, S. N.; Miller, R. J.; *Proc. Natl. Acad. Sci.* **1987**, *84*, 7744.
3) Cheng, Y.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099.
4) Parcell, R.F.; Sanchez, J. P. *J. Org. Chem*. **1981**, *46*, 5055.
5) Hong, S. C.; Davisson, J. N. *J. Pharm. Sci.* **1982**, *71*, 912.
6) Zanos, P. Moaddel, R.; Morris, P. J.; Georgiou, P. Fischell, J.; Elmer, G. I.; Alkondon, M.; Yuan, P. Pribut, H. J.; Singh, N. S.; Dossou, K. S. S.; Fang, Y.; Huang, X-P.; Mayo, C. L.; Wainer, I. W.; Alburquerque, E. X.; Thompson, S. M.; Thomas, C. J.; Zarate Jr. C. A.; Gould, T. D.. *Nature*, **2016**, *533*, 481.
7) Jose, J.; Gamage, S. A.; Harvey, M. G.; Voss, L. J.; Sleigh, J. W.; Denny, W. A. *Bioorg. Med. Chem*. **2013**, *21*, 5098.