Supplementary Information

The synthesis of pharmacologically important oxindoles via the asymmetric aldol reaction of isatin, and the investigation of the organocatalytic activity of new alicyclic β-amino acid derivatives

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Experimental procedures and analytical data

General methods

All reactions were conducted using magnetic stirring in oven-dried glassware. To purify the products using column chromatography, Merck KGaA Darmstadt, Germany's Kieselgel 60 (0.063–0.200 mm 70–230 mesh ASTM) was employed. Thin layer chromatography was carried out on silica-coated aluminium backing plates 60A F254. Spots were visualized using an UV lamp (254 nm). Sulphuric acid and vanillin were utilized for detection.

In a microwave (CEM, Discover, SP) chamber, sealed reaction vials (10 mL) were used to conduct microwave-promoted reactions (CEM Corporation, Matthwes, NC, USA).

All high-speed ball milling measurements were carried out with Retsch 400 Mixer Mill with 10 mL agate jars and 5 mm agate balls (Retsch Gmbh Germany).

Ethyl acetate (EtOAc), *n*-hexane, chloroform, acetone, ethanol and diethyl ether (Et_2O) were used as solvents of the highest analytical grade that were purchased from Molar Chemicals Kft (Halásztelek, Hungary).

HPLC-grade *i*-PrOH, *n*-hexane and tetrahydrofuran (THF) were purchased from VWR Chemicals (Fontenary-sous-Bois, France). *N*,*N*'-Diisopropylcarbodiimide (DIC) was bought from Alfa Aesar (Thermo Fischer, Kandel, Germany), Boc_2O was from Reanal Zrt. (Budapest, Hungary). 1-Hydroxybenzotriazole hydrate (HOBt), (+)-*O*,*O*'-dibenzoiltartaric acid (DBTA), *O*,*O*'-di-*p*-toluoyltartaric acid (DPTTA), (*S*)-(+)-1-(2-naphthyl)ethylamine and (*S*)-(–)-1-(1-naphthyl)ethylamine were obtained from Sigma Aldrich (St. Louis, USA). 2-Methyl-2-butanol (98%), (*R*)-(+)-1-(2-naphthyl)ethylamine and (*R*)-(+)-1-(1-naphthyl)ethylamine were bought from TCI (Tokyo Chemical Industry Co., Zwijndrecht, Belgium). (*S*)-(–)-α-Methylbenzyl isocyanate was purchased from Acros Organics (Geel, Belgium), isatin and LiOH were bought from Fluka Chemie Gmbh (Sigma Aldrich Chemie Gmbh Steinheim Germany). Anhydrous sodium sulfate (Na_2SO_4) used as drying agent, was purchased from Sigma Aldrich (Merck KGaA Darmstadt, Germany).

The samples were prepared for HPLC analysis by removing the solvent under vacuum, adding 1 mL of the HPLC eluent (*n*-hexane/*i*-PrOH 80:20), and sonicating the mixture for 5 minutes in an ultrasonic bath (Elma Elmasonic S 30/H ultrasonic device, Elma Schmidbauen GmbH Gottlieb-Daimler Straße 17, 78224 Singen).

After homogenisation, the samples were filtered with PTFE 0.45 µm filter and injected to the HPLC. HPLC measurements were carried out with JASCO HPLC (PU-4086 Binary Semi Preparative Pump, MD-4015 Photo Diode Array Detector, JASCO 2967-5 Ishikawa-machi Hachioji-shi Tokyo Japan 192-8537). The *ee* values for **3a–h** were determined by HPLC using Chiralpak IA column (Particle size: 5 µm, dimensions: 4.6 mm × 15 mm) (eluent: a mixture of *n*-hexane and IPA (80:20), flow rate: 0.5 mL/min.

FT-IR spectra of the compounds were obtained by Fourier-transform infrared spectroscopy (Thermo Nicolet AVATAR 330, USA) equipped with the GRAMS/AI ver. 7 program. With 150 mg dry KBr, samples were crushed and made into pastilles. The pastilles were scanned 128 times in the wavenumber range 4000–400 cm^{-1} at a resolution of 4 cm^{-1}.

^1H NMR spectra were recorded at 500.20 MHz, while the ^{13}C NMR spectra were measured at 125.62 MHz in $CDCl_3$ or in DMSO-d_6 at ambient temperature, with a Bruker AV NEO Ascend 500 spectrometer (Bruker Biospin, Karlsruhe, Germany) with Double Resonance Broad Band Probe (BBO). Chemical shifts are given, relative to tetramethylsilane (Me_4Si) as internal standard, in δ (ppm).

The HRMS flow injection analysis was performed with Thermo Scientific Q Exactive Plus hybrid quadrupole-Orbitrap (Thermo Fisher Scientific, Waltham, MA, USA) mass spectrometer coupled to a Waters Acquity I-Class UPLC™ (Waters, Manchester, UK).

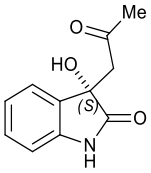
Optical rotations were measured with JASCO P-2000 Polarimeter. Melting points were determined with a Hinotex-X4 micro melting point apparatus (Hinotek, Ningbo, China) and are uncorrected.

General procedure for the aldol reaction in solvent using organocatalyst 6–21, synthesis of 3a–h

Organocatalysts **6–21** (corresponding catalyst loading 20 mol %) were directly added to a stirred solution of isatin **1a–h** (0.28 mmol, 1 equiv), acetone (5 mL, 325 equiv) and additive (LiOH 1 mmol) at 25 °C and stirred for the corresponding time. The resulting mixture was stirred at that temperature for specified time. After completion of the reaction (monitored by TLC) the crude mixture was purified by column chromatography on silica gel (using EtOAc). Further purification was carried out if required by crystallizing the product in Et_2O to obtain the aldol adducts **3a–h**.

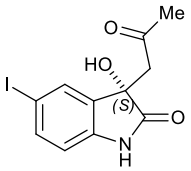
In case of solvent screening: The organocatalysts **6–21** (corresponding catalyst loading 20 mol %) were directly added to a stirred solution of isatin **1a–h** (0.28 mmol, 1 equiv) acetone (2.5 mL, 162.5 equiv) and different tested solvents (2.5 mL) and additive (LiOH 1 mmol) at 25 °C and stirred for the corresponding time. The resulting mixture was stirred at that temperature for specified time. After completion of the reaction (monitored by TLC) the crude mixture was purified by column chromatography on silica gel (using EtOAc). Further purification was carried out if required by crystallizing the product in Et_2O to obtain the aldol adducts **3a–h**.

(*S*)-3-Hydroxy-3-(2-oxopropyl)indolin-2-one (3a)



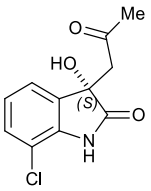
Yield (40 mg, 70%), white solid, mp 178–183 °C, mp (lit., 1 166–168°C, $[\alpha]_D^{25}$ -23.3 (c 0.5 in MeOH, 57 % *ee* % **Table 4** entry 1), (lit. 1 $[\alpha]_D^{25}$ -18.4 (c 0.82 in MeOH, 67% *ee*%)). The *ee* % was determined by HPLC method using Chiralpak IA column *n*-hexane/*i*-PrOH 80:20, flow rate 0.5mL/min; tR = 14.0 min (*S*)-enantiomer); tR = 17.0 min (*R*)-enantiomer). ^{1}H-NMR δH (500.20 MHz, DMSO-d_6, 30 °C, Me_4Si) 2.00 (3H, s, CH_3), 2.99 (1 H, d, *J* = 16.6 Hz, CH^1CO), 3.25 (1 H, d, *J* = 16.6 Hz, CH^2CO), 5.95 (1 H, s, OH), 6.77 (1 H, d, *J* = 7.7 Hz, Ar), 6.90 (1H, t, *J* = 7.4 Hz, Ar), 7.16 (1 H, t, *J* = 7.5 Hz, Ar), 7.23 (1H, d, *J* = 7.3 Hz, Ar) 10.19 (1 H, brs, NH), ^{13}C-NMR δC (125.62 MHz, DMSO-d_6, 30 °C, Me_4Si) 31.04,50.74, 73.13, 109.87, 121.67, 124.15, 129.42, 131.99, 142.98, 178.59, 205.58. HRMS (ESI) [M+H]+ m/z calcd for $C_{11}H_{11}NO_3$: 206.07389, found: 206.08101

(*S*)-3-Hydroxy-5-iodo-3-(2-oxopropyl)indolin-2-one (3b)



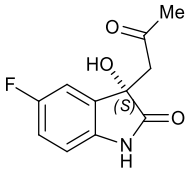
Yield (40 mg, 40%), white solid, mp 222–225 °C, $[\alpha]_D^{25}$ -5.8 (c 0.5 in MeOH, 65 % *ee* % **Table 7** entry 8) The *ee* % was determined by HPLC method using Chiralpak IA column *n*-hexane/*i*-PrOH 80:20, flow rate 0.5mL/min; tR = 13.5 min (*S*)-enantiomer); tR = 19.5 min (*R*)-enantiomer). ^{1}H-NMR δH (500.20 MHz, DMSO-d_6, 30 °C, Me_4Si) 2.00 (3H, s, CH_3), 3.04 (1 H, d, *J* = 17.3 Hz, CH^1CO), 3.34 (1 H, d, *J* = 17.3 Hz, CH^2CO), 6.06 (1 H, s, OH), 6.63 (1 H, t, *J* = 8.1 Hz, Ar), 7.50 (1H, d, *J* = 8.1 Hz Ar), 7.55 (1H, d, *J* = 1.7 Hz, Ph), 10.17 (1 H, s, NH). ^{13}C-NMR δC (125.62 MHz, DMSO-d_6, 30 °C, Me_4Si) 30.8, 50.5, 72.9, 84.4, 112.4, 132.5, 134.9, 137.8, 143.0, 178.0, 205,8. HRMS (ESI) [M+Na]+ m/z calcd for $C_{11}H_{10}INO_3Na$: 353.96031, found: 353.95972

(*S*)-7-Chloro-3-hydroxy-3-(2-oxopropyl)indolin-2-one (3c)



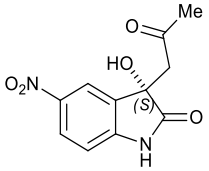
Yield (31 mg, 42 %), white solid, mp 188–189 °C, mp (lit.2 175–177 °C) , $[\alpha]_D^{25}$ -33.4 (c 0.4 in MeOH, 98% *ee*% **Table 7** entry 12), (lit 2.$[\alpha]_D^{20}$ -14.5 (c 0.4 in MeOH, 66% *ee*%)). The *ee* was determined by HPLC method using Chiralpak IA column *n*-hexane/*i*-PrOH 80:20, flow rate 0.5mL/min; tR = 12.6 min (*S*)-enantiomer); tR = 17.2 min (*R*)-enantiomer). ^{1}H-NMR δH (500.20 MHz, DMSO-d_6, 30 °C, Me_4Si) 2.00 (3H, s, CH_3), 3.08 (1 H, d, *J* = 17.2 Hz, *CH*^{1}CO), 3.34 (1 H, d, *J* = 17.3 Hz, *CH*^{2}CO), 6.11 (1 H, s, OH), 6.93 (1 H, t, *J* = 7.6 Hz, Ar), 7.21 (1H, d, *J* = 7.5 Hz Ar), 7.23 (1H, d, *J* = 7.9 Hz, Ph), 10.62 (1 H, s, NH).^{13}C-NMR δC (125.62 MHz, DMSO-d_6, 30 °C, Me_4Si) 30.8, 50.6, 73.6, 114.1, 122.7, 123.1, 129.8, 134,1, 140,8, 178.6, 205.7. HRMS (ESI) [M+Na]+ m/z calcd for $C_{11}H_{10}ClNO_3Na$: 262.02469, found: 262.02413

(*S*)-5-fluoro-3-hydroxy-3-(2-oxopropyl)indolin-2-one (3d)



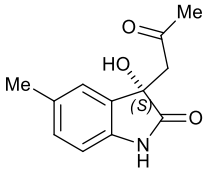
Yield: (50 mg, 50%), white solid, mp 158–161 °C, mp (lit. 6 183–185 °C); $[\alpha]_D^{25}$ -2.9 (c 0.1 in MeOH, 37% *ee*% **Table 7** entry 15), (lit. 6$[\alpha]_D^{25}$ -17.0 (c 1.0 in MeOH, 77% *ee*%)). The *ee* was determined by HPLC method using Chiralpak IA column *n*-hexane/*i*-PrOH 80:20, flow rate 0.5mL/min; tR = 14.1 min (*S*)-enantiomer); tR = 19.4 min (*R*)-enantiomer). ^{1}H-NMR δH (500.20 MHz, DMSO-d_6, 30 °C, Me_4Si) 2.01 (3H, s, CH_3), 3.04 (1 H, d, *J* = 17.2 Hz, *CH*^{1}CO), 3.34 (1 H, s, *CH*^{2}CO), 6.07–6.78 (1 H, m, Ar), 6.96–7.02 (1 H, m, Ar), 7.12–7.17 (1 H, m, Ar), 10.22 (1H, s, NH). ^{13}C-NMR δC (125.62 MHz, DMSO-d_6, 30 °C, Me_4Si) 30.4, 49.0, 74.5, 113.2, 123.3, 128.5, 128.8, 129.6, 129,8, 130.9, 143.0, 177.8, 205.8. HRMS (ESI) [M+H]+ m/z calcd for $C_{11}H_{11}O_3NF$: 224.07137, found: 224.07175

(*S*)-3-hydroxy-5-nitro-3-(2-oxopropyl)indolin-2-one (3e)



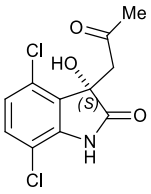
Yield: (30 mg, 30%), white solid, mp 226–230 °C, mp (lit. 9 222–224 °C); $[\alpha]_D^{25}$ -4.0 (c 0.2 in MeOH, 41% *ee*% **Table 7** entry 15), (lit. 9 $[\alpha]_D^{20}$ -17.3 (c 1.82 in MeOH, 45% *ee*%)). The *ee* was determined by HPLC method using Chiralpak IA column *n*-hexane/*i*-PrOH 80:20, flow rate 0.5mL/min; tR = 15.0 min (*S*)-enantiomer); tR = 20.0 min (*R*)-enantiomer). ^{1}H-NMR δH (500.20 MHz, DMSO-d_6, 30 °C, Me_4Si) 2.02 (3H, s, CH_3), 3.17 (1 H, d, *J* = 17.85 Hz, *CH*^{1}CO), 3.60 (1 H, d, *J* = 17.84 Hz, *CH*^{2}CO), 6.27 (1 H, s, OH), 6.96–7.00 (1 H, m, Ar), 8.15–8.18 (2 H, m, Ar), 10.94 (1H, s, NH).^{13}C-NMR δC (125.62 MHz, DMSO-d_6, 30 °C, Me_4Si) 0.58, 30.5, 50.3, 72.6, 110.0, 120.0, 126.9, 133.2, 149.9, 179.0, 206.0. HRMS (ESI) [M+H]+ m/z calcd for $C_{11}H_{11}O_5N$: 251.06579, found: 251.06625

(*S*)-3-hydroxy-5-methyl-3-(2-oxopropyl)indolin-2-one (3f)



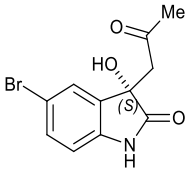
Yield: (24 mg, 27%), white solid, mp 170–173 °C, mp (lit.6 158–160 °C); $[\alpha]_D^{25}$ -4.5 (c 0.1 in MeOH, 39% *ee*% **Table 7** entry 18), (lit. 6 $[\alpha]_D^{25}$ -13.0 (c 1.0 in MeOH, 66% *ee*%)). The *ee* was determined by HPLC method using Chiralpak IA column *n*-hexane/*i*-PrOH 80:20, flow rate 0.5mL/min; tR = 12.9 min (*S*)-enantiomer); tR = 16.9 min (*R*)-enantiomer). ^{1}H-NMR δH (500.20 MHz, DMSO-d_6, 30 °C, Me_4Si) 2.00 (3H, s, CH_3), 2.22 (3 H, s, CH_3Ar), 2.97 (1 H, d, *J* = 16.51 Hz, *CH*^{1}CO), 3.22 (1 H, d, *J* = 16.47 Hz, *C1*^{2}CO), 5.90 (1 H, s, OH), 6.65 (1 H, d, *J* = 7.78 Hz Ar), 6.96 (1 H, d, *J* = 7.8 Hz, Ar), 7.1 (1 H, s, Ar), 10.09 (1H, s, NH).^{13}C-NMR δC (125.62 MHz, DMSO-d_6, 30 °C, Me_4Si) 21.1, 29.5, 31.0, 50.8, 73.2, 109.6, 124.8, 130.4, 132.1, 140.5, 178.6, 205.6. HRMS (ESI) [M+Na]+ m/z calcd for $C_{12}H_{13}O_5NNa$: 242.07825, found: 242.07876

(*S*)-4,7-dichloro-3-hydroxy-3-(2-oxopropyl)indolin-2-one (3g)



Yield: (99 mg, 96%), white solid, mp 204–208 °C, mp (lit. 10 235–237 °C); $[\alpha]_D^{25}$ -21.1 (c 0.4 in MeOH, *97%* **Table 7** entry 21). The *ee* was determined by HPLC method using Chiralpak IA column *n*-hexane/*i*-PrOH 80:20, flow rate 0.5mL/min; tR = 13.0 min (*S*)-enantiomer); tR = 26.6 min (*R*)-enantiomer). ^{1}H-NMR δH (500.20 MHz, DMSO-d_6, 30 °C, Me_4Si) 2.03 (3H, s, CH_3), 3.21 (1 H, d, *J* = 17.72 Hz, *CH*^{1}CO), 3.69 (1 H, d, *J* = 17.72 Hz, *CH*^{2}CO), 6.30 (1 H, s, OH), 6.92 (1 H, d, *J* = 8.71 Hz Ar), 7.29 (1 H, d, *J* = 8.71 Hz, Ar), 10.16 (1H, s, NH).^{13}C-NMR δC (125.62 MHz, DMSO-d_6, 30 °C, Me_4Si) 30.4, 49.0,74.5, 113.3, 123.7, 128.5, 128.8, 129.6, 129.8, 130.9, 143.0, 177.8, 205.8. HRMS (ESI) [M+Na]+ m/z calcd for $C_{11}H_9O_3NCl_2Na$: 295.98459, found: 295.98517

(*S*)-5-bromo-3-hydroxy-3-(2-oxopropyl)indolin-2-one (3h)



Yield: (30 mg, 34%), white solid, mp 211–214 °C, mp (lit.1 145–147 °C); $[\alpha]_D^{25}$ -6.2(c 0.1 in MeOH, 49% **Table 7** entry 24), (lit.1 $[\alpha]_D^{25}$ -17.6 (c 0.7 in MeOH, 75% *ee*%)). The *ee* was determined by HPLC method using Chiralpak IA column *n*-hexane/*i*-PrOH 80:20, flow rate 0.5mL/min; tR = 13.9 min (*S*)-enantiomer); tR = 20.0 min (*R*)-enantiomer). ^{1}H-NMR δH (500.20 MHz, DMSO-d_6, 30 °C, Me_4Si) 2.01 (3H, s, CH_3), 3.06 (1 H, d, *J* = 17.25 Hz, *CH*^{1}CO), 3.38 (1 H, d, *J* = 17.25 Hz, *CH*^{2}CO), 6.07 (1 H, s, OH), 6.74 (1 H, d, *J* = 8.21 Hz Ar), 7.33–7.36 (1 H, m, Ar), 7.42 (1 H, d, J = 2.00 Hz), 10.33 (1H, s, NH).^{13}C-NMR δC (125.62 MHz, DMSO-d_6, 30 °C, Me_4Si) 30.8, 50.4, 73.1, 111.8, 113.4, 127.1, 132.0, 134.6, 142.5, 178.2, 205.7. HRMS (ESI) [M+Na]+ m/z calcd for $C_{11}H_{10}O_3NBrNa$: 305.97325, found: 305.97363

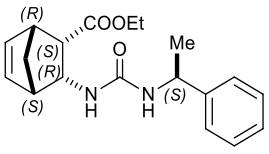
General procedure for the aldol reaction in High Speed Ball Milling (HSBM)

All High Speed Ball Milling measurements were carried out with Retsch 400 Mixer Mill with 10 mL agate jars and 5 mm agate balls (Retsch Gmbh Germany). In case of examining the effect of ball size under already optimized catalyst loading conditions: the measurements were done with 25 mL stainless steel jars and 10 mm balls. By all studies regarding the sampling, 10 minutes long pauses were taken. The applied frequencies and the reaction times were changed by every attempts. Then the gained samples from jars were solved in EtOAc, were sonicated completely, and purificated by column chromatography and after that were samples measured by HPLC.

General procedure for synthesis of urea type of organocatalysts (–)-6 and (–)-8

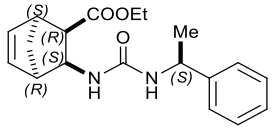
The enantiomeric *diendo* ethyl 3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylate (–)-**4** and (+)-**4** were prepared from racemic *diendo* norbornene β–amino ester (±)-**4** by diastereomeric salt formation with (+)-DBTA (0.5 equiv) or (–)-DBTA (0.5 equiv) according to the literature.[3] Amino ester base (–)-**4** or (+)-**4** (100 mg, 0.55 mmol) was dissolved in anhydrous Et_2O (20 mL) and a 10 % excess of (S)-(–)-α-methylbenzyl isocyanate (100 mg, 0.55 mmol) was added The reaction mixture was allowed to stand for 24 h at room temperature. After evaporation, the resulting white crystalline urea adduct was recrystallized from *i*Pr_2O.

(1*R*,2*S*,3*R*,4*S*)-Ethyl 3-(3-((*S*)-1-phenylethyl)ureido)bicyclo[2.2.1]hept-5-ene-2-carboxylate (–)-6



Yield (139 mg, 77 %), white solid, mp 108–111 °C, $[\alpha]_D^{25}$ –12.3 (c 0.4 in EtOH). ^{1}H-NMR δH (500.20 MHz, $CDCl_3$, 30 °C, Me_4Si) 1.19 (3 H, t, *J* = 7.1 Hz, CH_2CH_3), 1.29 (1 H, d, *J* = 8.9 Hz, 7-H), 1.36–1.42 (4 H, m, $CHCH_3$, 7-H), 2.94 (1 H, s, 2-H), 3.03 (1 H, s, 4-H), 3.11 (1 H, dd, J_1 = 9.2 Hz, *J* = 3.3 Hz, 1-H), 3.94–4.08 (2 H, m, OCH_2CH_3), 4.53–4.63 (2 H, m, 3-H, *NH*CO), 4.65-4.71 (1 H, m, NH*CH*CH_3), 4.97 (1 H, d, *J* = 9.2 Hz, *NH*), 5.63 (1 H, s, 5-H), 6.16–6.21 (1 H, m, 6-H), 7.21–7.35 (5 H, m, Ar), ^{13}C-NMR δC (125.62 MHz, $CDCl_3$, 30 °C, Me_4Si) 14.2, 23.7, 46.9, 47.5, 48.0, 50.6, 53.1, 60.3, 63.4 65.2, 125.9, 127.3, 128.6, 133.5, 137.3, 144.1, 156.7. HRMS (ESI) [M+H]+ m/z calcd for $C_{19}H_{24}N_2O_3$: 329.17869, found: 329.18597

(1*S*,2*R*,3*S*,4*R*)-Ethyl 3-(3-((S)-1-phenylethyl)ureido)bicyclo[2.2.1]hept-5-ene-2-carboxylate (–)-8

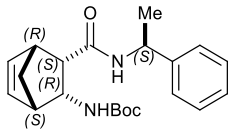


Yield (120 mg, 66 %), white solid crystals, (lit. 3 mp^{lit} 187–189 °C), mp 179–182 °C, (lit 3 $[\alpha]_D^{20}$ –14.5 (c 0.5 in EtOH), $[\alpha]_D^{25}$ –19.6 (c 0.4 in EtOH).^{1}H-NMR δH (500.20 MHz, $CDCl_3$, 30 °C, Me_4Si) 1.21 (3 H, t, *J* = 7.2 Hz, OCH_3CH_2), 1.35 (1 H, d, *J* = 8.9 Hz, 7-H), 1.40–1.47 (4 H, m, *J* = 6.8 Hz, $CHCH_3$, 7-H), 3.07 (2 H, m, 2-H, 4-H), 3.11–3.18 (1 H, m, 1-H), 3.91–4.06 (2 H, m, CH_3 CH_2), 4.41 (1 H, d, *J* = 7.14 Hz, NH), 4.65-4.71 (1 H, m, NH$CHCH_3$), 4.73–4.81 (1 H, m, 3-H), 5.05 (1 H, d, *J* = 8.8 Hz, NH), 6.10–6.16 (1 H, m, 6-H), 6.26–6.32 (1 H, m, 5-H), 7.21–7.24 (1 H, m, Ar), 7.28–7.35 (4 H, m, Ar). ^{13}C-NMR δC (125.62 MHz, $CDCl_3$, 30 °C, Me_4Si) 14.2, 23.2, 47.0, 47.6, 47.60, 47.8, 50.1, 53.4, 60.3, 118.3, 126.0, 127.2, 128.6, 133.8, 137.5, 144.1, 156.8, 173.4. HRMS (ESI) [M+H]+ m/z calcd for $C_{19}H_{24}N_2O_3$: 329.17869, found: 329.18540

General procedure for synthesis of amide type of organocatalysts (–)-7 and 9–16

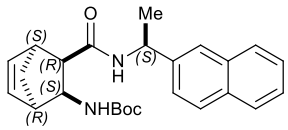
The synthesis of enantiomeric Boc-protected amino acid (+)-**5** and (–)-**5** were performed according to the literature.[4] They were then dissolved (140 mg, 0.55 mmol, 1 equiv) in THF using the corresponding amine (0.55 mmol, 1 equiv) in the presence of DIC (0.72 mmol, 1.3 equiv) and HOBt (0.66 mmol, 1.2 equiv) stirring for a day at room temperature. Different chiral amine, were used for the synthesis of organocatalysts: (*S*)-(–)-1-(2-naphthyl)-ethylamine (for (–)-**9**), (*S*)-(–)-1-(1-naphthyl)-ethylamine (for (–)-**10**), (*R*)-(+)-1-(2-naphthyl)-ethylamine (for (+)-**11** or (+)-**12**), (*R*)-(+)-1-(1-naphthyl)-ethylamine (for (+)-**13** or (+)-**14**) and propargylamine (for (–)-**15**). After completion of the reaction (checked by TLC), the solvent was evaporated. In order to remove the HOBt and DIC, the residue was dissolved in EtOAc/H_2O mixture (15 mL), the aqueous layer extracted with EtOAc (3 × 5 mL). The combined extracts were dried, filtered and evaporated. The product was purified by column chromatography using EtOAc or *n*-hexane/EtOAc 1:1 eluent. The appropriate Boc-protected amides (+)-**11** and (+)-**13** (0.20 mmol) was deprotected by a 20 % ethanolic HCl solution (10 mL) at r.t. for 6 h. After evaporation HCl salts of (+)-**12** and (+)-**14** were used without purification.

***tert*-Butyl ((1*S*,2*R*,3*S*,4*R*)-3-(((*S*)-1-phenylethyl)carbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate (–)-7**



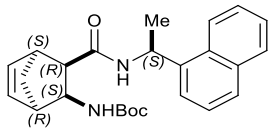
Yield (104 mg, 53 %), white solid, mp 140–145 °C, $[\alpha]_D^{25}$ –7.6 (c 0.5 in EtOH). ^{1}H-NMR δH (500.20 MHz, $CDCl_3$, 30 °C, Me_4Si) 1.17 (1H, d J= 6.4Hz, 7-H), 1.35 (9 H, brs, Boc), 1.44–1.52 (3 H, t, *J* = 6.9 Hz, CH_3), 1.63 (1H, s, 7-H), 2.99 (1H, dd, *J* = 2.3 Hz, *J* = 9.6 Hz, 2-H), 3.07 (2 H, s, 4-H, 1-H), 4.52-4.58 (1 H, m, NH*CH*CH_3), 5.03-5.08 (1 H, m, 3-H), 5.13 (1 H, d, *J* = 9.1 Hz, *NH*), 5.89 (1 H, d, *J* = 5.4 Hz, *NH*), 6.11–6.21 (1 H, m, 5-H), 6.51 (1 H, s, 6-H), 7.22-7.36 (5 H, m, Ar). ^{13}C-NMR δC (125.62 MHz, $CDCl_3$, 30 °C, Me_4Si) 21.9, 28.3, 47.1, 47.5, 47.6, 49.1, 50.5, 54.1, 79.2, 126.1, 127.2, 128.6, 132.1, 138.8, 143.0, 156.0, 171.0. HRMS (ESI) [M+H]+ m/z calcd for $C_{21}H_{28}N_2O_3$: 357.21000, found: 357.21727.

***tert*-Butyl ((1*R*,2*S*,3*R*,4*S*)-3-(((*S*)-1-(naphthalen-2-yl)ethyl)carbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate (–)-9**



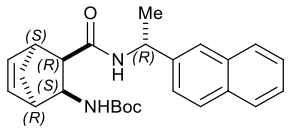
Yield (156 mg, 70 %), light yellow oil, $[\alpha]_D^{25}$ -67.1 (c 0.2 in EtOH). ^{1}H-NMR δH (500.20 MHz, $CDCl_3$, 30 °C, Me_4Si) 1.31 (2 H, d, *J* = 8.6 Hz, 7-H), 1.43 (9 H, s, Boc), 1.51 (3 H, d, *J* = 6.9 Hz, CH_3), 2.96-3.05 (3H, m, 2-H, 4-H, 1-H), 4.59 (1 H, m, NH*CH*CH_3), 4.97 (1 H, d, *J* = 9.7 Hz, NH), 5.13–5.21 (1 H, m, 3-H), 5.95 (1 H, d, *J* = 7.0 Hz, *NH*), 6.08–6.13 (1 H, m, 5-H), 6.51-6.57 (1 H, m, 6-H), 6.98 (1 H, s, Ar), 7.38–7.50 (3 H, m, Ar), 7.73 (1 H, s, Ar), 7.79–7.84 (3 H, m, Ar). ^{13}C-NMR δC (125.62 MHz, $CDCl_3$, 30 °C, Me_4Si) 21.2, 22.0, 28.5, 30.3, 34.2, 46.6, 47.5, 47.6, 49.1, 51.4, 54.2, 79.4, 124.5, 124.6, 125.5, 125.8, 126.2, 127.6, 127.9, 128.5, 131.2, 132.8, 133.4, 139.9, 170.9. HRMS (ESI) [M+H]+ m/z calcd for $C_{25}H_{30}N_2O_3$: 407.22564, found: 407.23291

tert-Butyl ((1*R*,2*S*,3*R*,4*S*)-3-(((*S*)-1-(naphthalen-1-yl)ethyl)carbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate (–)-10



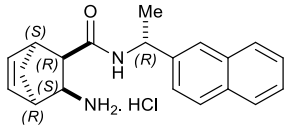
Yield (159 mg, 71 %), light oil, $[\alpha]_D^{25}$ -25.3 (c 0.4 in EtOH).^{1}H-NMR δH (500.20 MHz, $CDCl_3$, 30 °C, Me_4Si) 1.25-1.27 (2 H, m, 7-H), 1.43 (9 H, s, Boc), 1.57–1.63 (4 H, m, CH_3, 7-H), 2.91 (1H, d, 2-H), 2.96 (1H,s, 4-H), 3.03 (1 H, s, 1-H), 3.43–3.52 (1 H, m, 3-H), 4.51–4.60 (1 H, m, CH_3*CH*NH), 5.11 (1 H, d, *J* = 9.5 Hz, *NH*), 5.76-5.80 (1 H, brs, *NH*), 6.11 (1 H, m, 5-H), 6.53-6.60 (1 H, m, 6-H), 7.41–7.48 (5 H, m, Ar), 7.78 (1 H, d, *J* = 7.9 Hz, Ar), 7.86 (1 H, d, *J* = 8.1 Hz, Ar), 8.06 (1 H, d, *J* = 8.4 Hz, Ar).^{13}C-NMR δC (125.62 MHz, $CDCl_3$, 30 °C, Me_4Si) 20.8, 28.5, 30.3, 44.6, 46.8, 47.6, 51.0, 54.1, 79.3, 122.5, 123.3, 125.3, 125.5, 125.8, 126.5, 128.3, 128.8, 131.0, 131.5, 134.0, 138.4, 139.6, 156.0, 170.6. HRMS (ESI) [M+Na]+ m/z calcd for $C_{25}H_{30}N_2O_3Na$: 429.21541, found: 429.21539

tert-Butyl ((1*R*,2*S*,3*R*,4*S*)-3-(((*R*)-1-(naphthalen-2-yl) ethyl)carbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate (+)-11



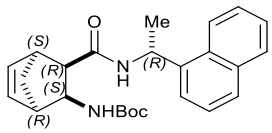
Yield (179 mg, 80 %), light yellow solid crystals, mp 137–141 °C, $[\alpha]_D^{25}$ +93.4 (c 0.3 in EtOH).^{1}H-NMR δH (500.20 MHz, $CDCl_3$, 30 °C, Me_4Si) 1.22 (9 H, m, Boc), 1.30-1.37 (2 H, s, 7-H), 1.56 (3 H, d, *J* = 6.87 Hz, CH_3), 2.98 (1 H, dd, *J* = 2.7 Hz, *J* = 9.4 Hz, 2-H), 3.06 (2 H, d, *J* = 12.9 Hz, 4-H, 1-H), 4.45-4.55 (1 H, m, 3-H), 5.11 (1 H, d, *J* = 7.9 Hz, *NH*), 5.14–5.21 (1 H, m, CH_3*CH*NH), 5.92 (1 H, brs, *NH*), 6.09–6.16 (1 H, m, 5-H), 6.46–6.51 (1 H, m, 6-H), 7.33–7.50 (3 H, m, Ar), 7.70 (1H, s, Ar), 7.74–7.86 (3 H, m, Ar).^{13}C-NMR δC (125.62 MHz, $CDCl_3$, 30 °C, Me_4Si) 21.8, 28.2, 47.1, 47.6, 49.2, 50.5, 54.2, 79.3, 111.0, 117.5, 124.6, 124.7, 125.8, 126.1, 127.5, 128.0, 128.5, 132.1, 132.7, 133.3, 138.9, 140.3, 156.1, 171.2. HRMS (ESI) [M+H]+ m/z calcd for $C_{25}H_{30}N_2O_3$: 407.22564, found: 407.23292

(1*S*,2*R*,3*S*,4*R*)-3-Amino-N-((*R*)-1-(naphthalen-2-yl)ethyl)bicyclo[2.2.1]hept-5-ene-2-carboxamide hydrochloride (+)-12



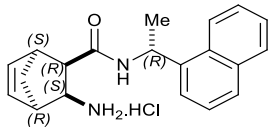
Yield (118 mg, 70 %, light yellow oil, $[\alpha]_D^{25}$ +18.9 (c 0.1 in EtOH).^{1}H-NMR δH (500.20 MHz, DMSO-d6, 30 °C, Me_4Si) 1.09 (1 H, t, *J*= 7.0 Hz, 7-H), 1.21 (3 H, t, *J*= 7.1 Hz,CH_3), 1.41 (2 H, d, *J*= 8.9 Hz, 2-H, 4-H), 1.44 (1 H, s, 7-H), 2.36 (1 H, s, 1-H), 2.64 (1 H, s, 3-H), 5.00-5.05 (1 H, m, CH_3*CH*NH), 6.15-6.20 (1 H, m,NH_2), 6.29-6.32 (1 H, m, 5-H), 6.33-6.36 (1 H, m, 6-H), 7.46–7.53 (3 H, m, Ar), 7.81 (1 H, s, Ar), 7.86-7.90 (3 H, m, Ar), 8.58 (1 H, d, *J*= 8.1 Hz, NH) ^{13}C-NMR δC (125.62 MHz, DMSO-d6, 30 °C, Me_4Si) 22.6, 43.9, 47.3, 47.4, 48.5, 48.6, 52.9, 66.8, 124.7, 125.6, 126.1, 126.6, 127.9, 128.1, 128,3, 132.7, 133.3, 138.6, 142.0, 171.6. HRMS (ESI) [M+H]+ m/z calcd for $C_{20}H_{23}ClN_2O$: 307.17321, found: 307.18049

***tert*-Butyl ((1*R*,2*S*,3*R*,4*S*)-3-(((*R*)-1-(naphthalen-1-yl)ethyl)carbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate (+)-13**



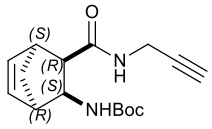
Yield (201 mg, 90 %), light yellow solid crystals, mp 139–143 °C, $[\alpha]_D^{25}$ +34.9 (c 0.3 in EtOH). ^{1}H-NMR δH (500.20 MHz, $CDCl_3$, 30 °C, Me_4Si) 1.27 (9 H, brs, Boc), 1.43 (2 H, s, 7-H),1.63 (3 H, d, *J* = 6.7 Hz, CH_3), 2.94 (1 H, d, *J* = 8.9 Hz, 4-H), 3.07 (2 H, s, 2-H, 1-H), 4.38–4.50 (1 H, m, *3*-H), 5.29 (1 H, d, *J* = 8.8 Hz, NH), 5.78–5.87 (2 H, m, CH_3*CH*NH, NH), 6.10–6.19 (1 H, m, H-5), 6.46 (1 H, s, 6-H), 7.40–7.54 (5 H, m, Ar), 7.76 (1 H, d, *J* = 7.9 Hz, Ar), 7.84 (1 H, d, *J* = 7.9 Hz, Ar), 8.04 (1 H, d, *J* = 8.4 Hz, Ar).^{13}C-NMR δC (125.62 MHz, $CDCl_3$, 30 °C, Me_4Si) 21.3, 28.3, 30.3, 45.0, 47.4, 47.5, 47.6, 49.9, 54.2, 79.1, 122.4, 123.3, 125.2, 125.5, 125.8, 126.5, 128.8, 130.9, 132.7, 134.0, 138.3, 156.0, 171.0.HRMS (ESI) [M+H]+ m/z calcd for $C_{25}H_{30}N_2O_3$: 407.22564, found: 407.23292

((1*S*,2*R*,3*S*,4*R*)-3-Amino-N-((*R*)-1-(naphthalen-1-yl)ethyl)bicyclo[2.2.1]hept-5-ene-2-carboxamide hydrochloride (+)-14



Yield (160 mg, 72 %), white solid, mp 255–260 °C, $[\alpha]_D^{25}$ +14,5 (c 0.1 in EtOH).^{1}H-NMR δH (500.20 MHz, DMSO-d_6, 30 °C, Me_4Si 1.37-1.47 (2 H, m, 7-H), 1.51 (3 H, d, J = 6.76 Hz, CH_3), 3.11 (1 H, d, J = 8.1 Hz, 2-H), 3.15 (1H, s, 4-H), 3. 27 (1H, s, 1-H), 3.84 (1H, s, 3-H), 5.62–5.71 (1H, m, CH_3*CH*NH), 6.15-6.22 (1 H, m, 5-H), 6.26-6.350 (1 H, s, 6-H), 7.47–7.66 (4 H, m, Ar), 7.61 (1 H, d, *J* = 7.0 Hz, Ar), 7.74 (3H, brs, NH_2.HCl)7.83 (1 H, d, *J*= 7.9 Hz, Ar), 7.94 (1 H, d, *J* = 7.7 Hz, Ar), 8.11 (1 H, d, *J* = 8.2 Hz, Ar), 9.00 (1 H, d, *J* = 7.22 Hz, Ar).^{13}C-NMR δC (125.62 MHz, DMSO-d_6, 30 °C, Me_4Si) 22.2, 23.8, 42.9, 44.7, 47.1, 47.4, 48.8, 52.6, 123.49, 123.5, 126.0, 126.1, 126.8, 127.8, 129.1, 130.7, 133.0, 133.8, 140.2, 171.6. HRMS (ESI) [M+H]+ m/z calcd for $C_{20}H_{23}ClN_2O$: 407.22564, found: 407.23292

***tert*-Butyl ((1R,2S,3R,4S)-3-(prop-2-yn-1-ylcarbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate (–)-15**



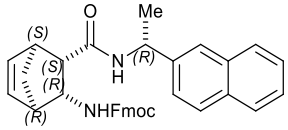
Yield (128 mg, 80 %), white solid, mp 163–164 °C, (mp lit. 4 161–163. $[\alpha]_D^{25}$ -5.1 (c 0.5 in EtOH)) (lit 4 $[\alpha]_D^{25}$ -3.7 (c 0.5 in EtOH) .^{1}H-NMR δH (500.20 MHz, $CDCl_3$, 30 °C, Me_4Si). The ^{1}H NMR and ^{13}C NMR spectroscopic data for the compound **15** are similar to those for the literature compounds.: ^{1}H-NMR δH (500.20 MHz, $CDCl_3$, 30 °C, Me_4Si) = 1.29–1.50 (m, 11H, CH_3, H-7, H-7) 2.19 (t, J = 2.3 Hz, 1H, C≡CH) 2.98–3.10 (m, 3H, H-1, H-2, H-4),3.75–3.83 (m, H, H-3), 4.03–4.13 (m, 1H, NCH_2), 4.78–4.86 (m, 1H, NCH_2) 5.99 (s, 1H, NH) 6.06–6.11 (m, 1H, H-6) 6.59–6.61 (m, 1H, H-5), 13C NMR (125 MHz, $CDCl_3$= 28.4, 29.4, 46.3, 47.1, 47.7, 53.0, 71.7, 79.3, 79.5, 137.5, 138.8, 155.9, 172.8 ppm. HRMS (ESI) [M+H]+ m/z calcd for $C_{16}H_{23}N_2O_3$: 291.17032, found: 291.17053, [M+Na]+ m/z calcd for $C_{16}H_{22}N_2O_3Na$: 313.15226, found: 313.15261, [2M+Na]+ m/z calcd for $C_{32}H_{44}N_4O_6Na$: 603.31531, found: 603.31740.

General procedure for synthesis of organocatalysts 18–20

Enantiomeric *diexo* 2-aminonorbornene ester (+)-**16** was prepared from racemic *diexo* 2-aminonorbornene ester (±)-**16** by diastereomeric salt formation with *O,O'*-di-*p*-toluoyltartaric acid ((+)-DPTTA, 0.5 equiv) according to the literature.[3] Ester (+)-**16** was transformed into amino acid via hydrolysis in microwave reactor. The enantiomeric *diexo* norbornene β-amino acid (135 mg, 0.55 mmol, 1 equiv) was dissolved in a mixture of acetone/water 2:1 (60 ml) and reacted with Fmoc-OSu (92 mg, 0.5 equiv). Crude product was evaporated, treated with aqueous Na_2CO_3 solution, than it was extracted with the mixture of CH_2Cl_2/H_2O, dried with anhydrous Na_2SO_4 and it was evaporated to get (+)-**17**.

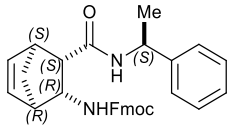
Acid-amine coupling reactions were done with (+)-**17** in order to get **18**–**20** as demonstrated in **Scheme 4**. Chiral amines (0.55 mmol, 1 equiv) were added to N-Fmoc-protected *diexo* norbornene β-amino acid in presence of *N*,*N*'-diisopropylcarbodiimide (DIC) (0.72 mmol, 1.3 equivalent) and hydroxybenzotriazole (HOBt) (0.66 mmol, 1.2 equivalent). The reaction mixture was stirred for a day at room temperature according to the literature.[5] The following chiral amines were used to create a catalyst: (*R*)-(+)-1-(2-naphthyl)-ethylamine (+)-**18**), (*S*)-(–)-1-phenylethylamine (–)-**19**), (*R*)-(+)-1-phenylethylamine (+)-**20**).

(9*H*-Fluoren-9-yl)methyl ((1*R*,2*R*,3*S*,4*S*)-3-(((*R*)-1-(naphthalen-2-yl)ethyl)carbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate (+)-18



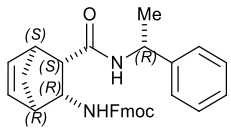
Yield (189 mg, 65 %), white solid, mp 190–194 °C, $[\alpha]_D^{25}$ +15.7 (c 0.2 in EtOH)
^{1}H-NMR δH (500.20 MHz, DMSO-d_6, 30 °C, Me_4Si) 1.29 (3 H, d, *J* = 6.8 Hz, CH_3), 1.34 (1 H, d, *J* = 8.5 Hz, 7-H), 2.17 (1 H, d, *J* = 8.5 Hz 7-H), 2.59 (1 H, s, 2-H), 2.70 (1 H, s, 4-H), 3.76 (1 H, t , *J* = 8.4 Hz, 1-H) 4.30-4.39 (1 H, m, CH-Fmoc) 5.00–5.09 (1 H, m, CH_3*CH*NH), 5.47(2 H, d, *J* = 7.2 Hz, CH_2-FmOc), 6.22 (2 H, d, *J* = 10.8 Hz, 5-H, 6-H), 6.96 (1 H, d, *J* = 8.8 Hz, NH), 7.32–7.96 (16 H, m, Ar), 8.43 (1 H, d, *J* = 7.7 Hz, NH). ^{13}C-NMR δC (125.62 MHz, DMSO-d_6, 30 °C, Me_4Si) 22.7, 45.1, 45.6, 46.4, 47.2, 47.9, 48.6, 53.6, 66.2, 120.6, 124.4, 125.4, 125.6, 125.7, 126.1, 126.6, 127.6, 127.9, 128.1, 128.2, 128.4, 132.5, 133.3, 137.3, 139.8, 141.2, 142.6, 144.3, 156.1, 171.9, HRMS (ESI) [M+H]+ m/z calcd for $C_{35}H_{32}N_2O_3$: 529.24129, found: 529.24910.

(9*H*-Fluoren-9-yl)methyl ((1*R*,2*R*,3*S*,4*S*)-3-(((*S*)-1-phenylethyl)carbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate (–)-19



Yield (113 mg, 43 %), white solid, mp 153–157 °C, $[\alpha]_D^{25}$ –24.3 (c 0.3 in EtOH). ^{1}H-NMR δH-NMR (500.20 MHz, $CDCl_3$, 30 °C, Me_4Si) 1.5 (1 H, d, *J* = 6.8 Hz, CH_3), 1.60 (1 H, d, *J* = 8.9 Hz, 7-H), 2.23 (1 H, d, *J* = 8.9 Hz, 7-H), 2.34 (1 H, d, *J* = 8.0 Hz, 2-H) 2.74 (1 H, s, 4-H), 2.99 (1 H, s, 1-H), 3.94 (1 H, t, *J* = 8.8 Hz, 3-H), 3.97–4.02 (1 H, m, CH_2Fmoc), 4.10 (1 H, t, J = 7,2 Hz CH-Fmoc), 4.21-4.30 (1 H, m, CH_2Fmoc), 5.06–5.16 (1 H, m, CH_3*CH*NH), 5.83 (1H, d, J= 9.1 Hz, NH), 5.89 (1 H, d, J = 7.7 Hz, NH), 6.19-6.27 (2 H, m, 5-H, 6-H), 7.10-7.82 (13 H, m, Ar). ^{13}C-NMR δC (125.62 MHz, $CDCl_3$, 30 °C, Me_4Si) 22.0, 44.6, 46.5, 47.2, 47.7, 48.5, 49.1, 53.2, 67.0, 119.9, 125.3, 126.1, 127.1, 127.4, 127.7, 128.7, 137.6, 138.8, 141.2, 141.3, 142.7, 144.0, 144.1, 156.1, 172.3. HRMS (ESI) [M+H]+ m/z calcd for $C_{31}H_{30}N_2O_3$: 479.22564, found: 479.23292

(9*H*-Fluoren-9-yl)methyl ((1*R*,2*R*,3*S*,4*SR*)-3-(((*R*)-1-phenylethyl)carbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate (+)-20

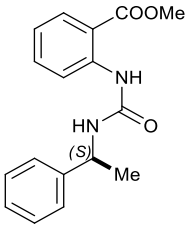


Yield (168 mg, 64 %), white solid, mp 167–172 °C, $[\alpha]_D^{25}$ +20.7 (c 0.2 in EtOH). ^{1}H-NMR δH-NMR (500.20 MHz, $CDCl_3$, 30 °C, Me_4Si) 1.38 (1 H, d, *J* = 6.7 Hz, CH_3), 1.59 (1 H, d, *J* = 9.0 Hz, 7-H), 2.18 (1 H, d, *J* = 8.9 Hz, 7-H), 2.29-2.36 (1 H, m, 2-H) 2.75 (1 H, s, 4-H), 2.93 (1 H, s, 1-H), 3.97 (1 H, t, *J* = 9.0 Hz, 3-H), 4.21 (1 H, t, J = 7,2 Hz CH-Fmoc) 4.26–4.32 (1 H, m, CH_2-Fmoc), 4.39-4.45 (1 H, m, CH_2-Fmoc), 5.04–5.12 (1 H, m, CH_3*CH*NH), 5.73 (1H, d, J= 9.5 Hz, NH), 5.82 (1 H, d, J = 7.2 Hz, NH), 6.15-6.25 (2 H, m, 5-H, 6-H), 7.15-7.79 (13 H, m, Ar). ^{13}C-NMR δC (125.62 MHz, $CDCl_3$, 30 °C, Me_4Si) 21.7, 44.8, 45.9, 47.2, 47.9, 48.3, 49.1, 53.3, 67.1, 120.0, 120.0, 125.1, 125.3, 126.2, 127.1, 127.1, 127.4, 127.7, 127.7, 127.8, 128.8, 137.4, 139.0, 141.3, 141.3, 143.0, 143.9, 144.0, 156.3, 172.0. HRMS (ESI) [M+H]+ m/z calcd for $C_{31}H_{30}N_2O_3$: 479.22564, found: 479.23292

(S)–Phenyalanine lithium salt (–)-21

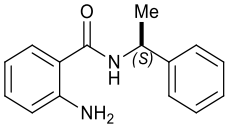
Synthesis of **21** was done according to literature procedure.[6] White solid, mp 213-215 °C, $[\alpha]_D^{25}$ –12.0 (c 0.5 in H_2O).

(*S*)-Methyl 2-(3-(1-phenylethyl)ureido)benzoate (+)-22



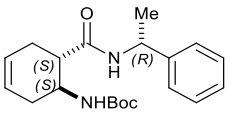
Anthranilic acid methyl ester base (151 mg,1 mmol) was dissolved in anhydrous Et_2O (20 mL) and a 10 % excess of (S)-(–)-α-methylbenzyl isocyanate (161 mg, 1.1 mmol) was added. The reaction mixture was allowed to stand for 24 h at room temperature. After evaporation, the resulting white crystalline urea adduct was recrystallized from iPr_2O. Yield (138 mg, 49 %), light solid, mp 122–124 °C, $[\alpha]_D^{25}$ +17.8 (c 0.5 in EtOH). ^{1}H-NMR δH-NMR (500.20 MHz, DMSO-d_6, 30 °C, Me_4Si) 1.39 (1 H, d, *J* = 7.0 Hz, CH_3,), 3.86 (3 H, s, COO*CH*$_3$), 4.80–4.88 (1 H, m, CH_3*CH*NH), 6.93-7.00 (1 H, m Ar), 7.20-7.50 (5 H, m, Ar), 7.42–7.51 (1 H, m, Ar), 7.88 (1H, dd, J_1=8.2 Hz, J_2 = 1.5 Hz, Ar) 7.99 (1H, d, *J* = 7.5 Hz, Ar) 8.33 (1H, d, *J* = 8.5 Hz, NH) 9.79 (1H, brs, NH) ^{13}C-NMR δC (125.62 MHz, DMSO-d_6, 30 °C, Me_4Si) 23.3, 49.3, 52.7, 114.5, 120.0, 120.8, 126.4, 127.0, 128.7, 130.90, 134.40, 143.1, 145.8, 154.3, 168.2. HRMS (ESI) [M+H]+ m/z calcd for $C_{17}H_{18}N_2O_3$: 283.13488, found: 283.18059

(S)-2-Amino-N-(1-phenylethyl)benzamide (+)-23



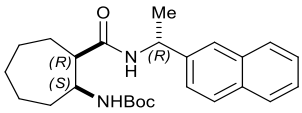
1.1 Equiv of the (S)-α-methylbenzylamine (133 mg, 1.1 mmol) was added to a suspension of isatoic anhydride (1 equiv, 163 mg, 1 mmol) in THF (50 mL). The reaction mixture was refluxed for a day. The solution was then concentrated under reduced pressure. The crude product was purified by column chromatography (hexane–ethyl acetate, 1:1) to afford (+)-**23**, as a white solid: Yield (97 mg, 40% yield), mp 140–144 °C, (lit. 7, 136–138°C) $[\alpha]_D^{25}$ +114.1 (c 0.5 in EtOH) (lit. 7 +110.9 (c 1.0 in $CDCl_3$)). ^{1}H-NMR δH-NMR (500.20 MHz, $CDCl_3$, 30 °C, Me_4Si) 1.58 (3 H, d, *J* = 6.9 Hz, CH_3,), 5.23–5.32 (1 H, m, *CH*$_3$*CH*NH), 5.50 (2H, brs, NH_2) 6.24 (1 H, brs, NH), 6.59–6.70 (2 H, m, Ar), 7.14–7.46 (7 H, m, Ar). ^{13}C-NMR δC (125.62 MHz, $CDCl_3$, 30 °C, Me_4Si) 22.0, 48.9, 116.0, 116.6, 117.4, 126.1, 127.1, 127.4, 128.8, 132.3, 143.4, 148.9, 168.4. HRMS (ESI) [M+H]+ m/z calcd for $C_{15}H_{16}N_2O$: 241.13354, found: 241.13344

***tert*-Butyl ((1*S*,6*S*)-6-(((*R*)-1-phenylethyl)carbamoyl)cyclohex-3-en-1-yl)carbamate (+)-24**



The synthesis of (1*S*,6*S*)-6-(*tert*-butoxycarbonylamino)cyclohex-3-enecarboxylic acid were performed according to the literature.[8] The Boc protected amino acid were then dissolved (140 mg, 0.55 mmol, 1 equiv) in THF using the (S)-α-methylbenzylamine (73 mg, 0.6 mmol, 1.1 equiv) in the presence of DIC (0.72 mmol, 1.3 equiv) and HOBt (0.66 mmol, 1.2 equiv) stirring for a day at room temperature. The general method's instructions for processing the reaction were followed. Yield (113 mg, 60 %), light beige solid, mp 155–162 °C, $[\alpha]_D^{25}$ +62.9 (c 0.4 in EtOH) ^{1}H-NMR δH-NMR (500.20 MHz, DMSO-d_6, 30 °C, Me_4Si) 1.34 (3 H, d, *J* = 6.9 Hz, CH_3,), 1.37 (9 H, s, Boc), 1.87.–1.96 (1 H, m, CH_2), 2.06–2.15 (1 H, m, CH_2), 2.18–2.30 (2 H, m,CH_2), 2.36 (1 H, m, 1-H), 3.53-3.65 (1H, m, 6-H), 4.86–4.94 (1 H, m, CH_3*CH*NH), 5.51-5.65 (2H, m, 3-H, 4-H), 6.53 (1 H, d, *J* = 8.4 Hz, NH), 7.19–7.25 (1 H, m, Ph), 7.38–7.43 (4 H, m, Ph), 7.85 (1 H, d, *J* = 7.8 Hz, NH). ^{13}C-NMR δC (125.62 MHz, DMSO-d_6, 30 °C, Me_4Si) 22.9, 28.7, 29.0, 32.8, 45.2, 48.1, 48.3, 77.9, 125.1, 126.0, 126.4, 127.1, 128.7, 144.9, 155.1, 172.5. HRMS (ESI) [M+H]+ m/z calcd for $C_{20}H_{28}N_2O_3$, Exact Mass: 344,20999,Molecular Weight: 344,44792

***tert*-Butyl ((1*S*,2*R*)-2-(((*R*)-1-(naphthalen-2-yl)ethyl)carbamoyl)cycloheptyl)carbamate (+)-25**



The synthesis of (+)-**25** were performed similar of (+)-**11**, using (1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)-cycloheptane carboxylic acid (141 mg, 0.55 mmol) as starting material. Yield (108 mg, 48 %), light beige solid, mp 119–124 °C, $[\alpha]_D^{25}$ +61.8 (c 0.3 in EtOH) ^{1}H-NMR δH-NMR (500.20 MHz, DMSO-d_6, 30 °C, Me_4Si) 1.25 (9 H, s, Boc), 1.32–1.39 (3H, m, CH_2) 1.42 (3 H, d, *J* = 6.9 Hz CH_3), 1.62-1.92 (7 H, m, CH_2), 2.67–2.75 (1 H, m, 1–H), 3.80-3.91 (1 H, m, 2-H), 4.99–5.10 (1 H, m, CH_3*CH*NH), 5.93 (1 H, brs, NH), 7.43–7.50 (3 H, m, Ar), 7.77 (1 H, s, Ar), 7.81–7.90 (3 H, m, Ar), 8.20 (1 H, d, *J* = 7.7 Hz, NH).^{13}C-NMR δC (125.62 MHz, DMSO-d_6, 30 °C, Me_4Si) 22.5, 23.8, 24.3, 25.9, 26.7, 28.6, 28.7, 33.0, 48.1, 48.4, 52.5, 78.0, 124.4, 125.5, 126.0, 126.4, 127.8, 128.1, 128.2, 132.5, 133.3, 142.5, 155.2, 173.5. HRMS (ESI) [M+H]+ m/z calcd for $C_{25}H_{34}N_2O_3$, Exact Mass: 410,25694,Molecular Weight: 410,54906

1. Notes and references

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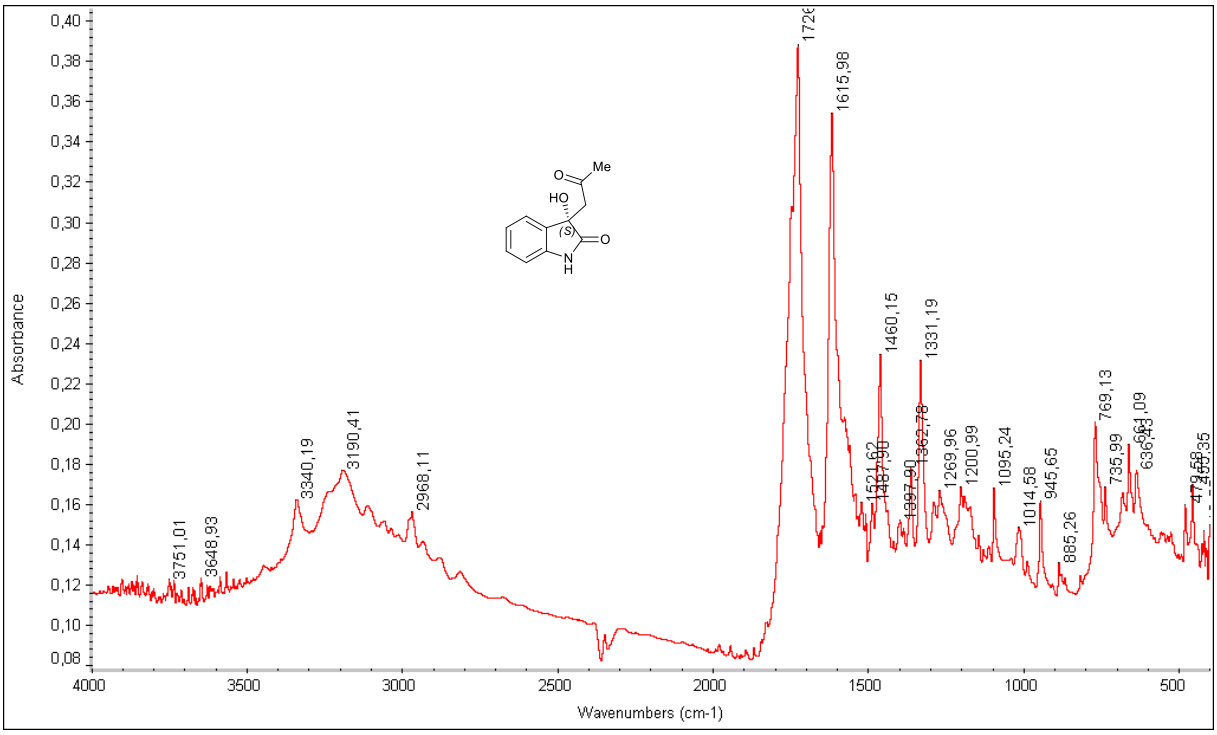
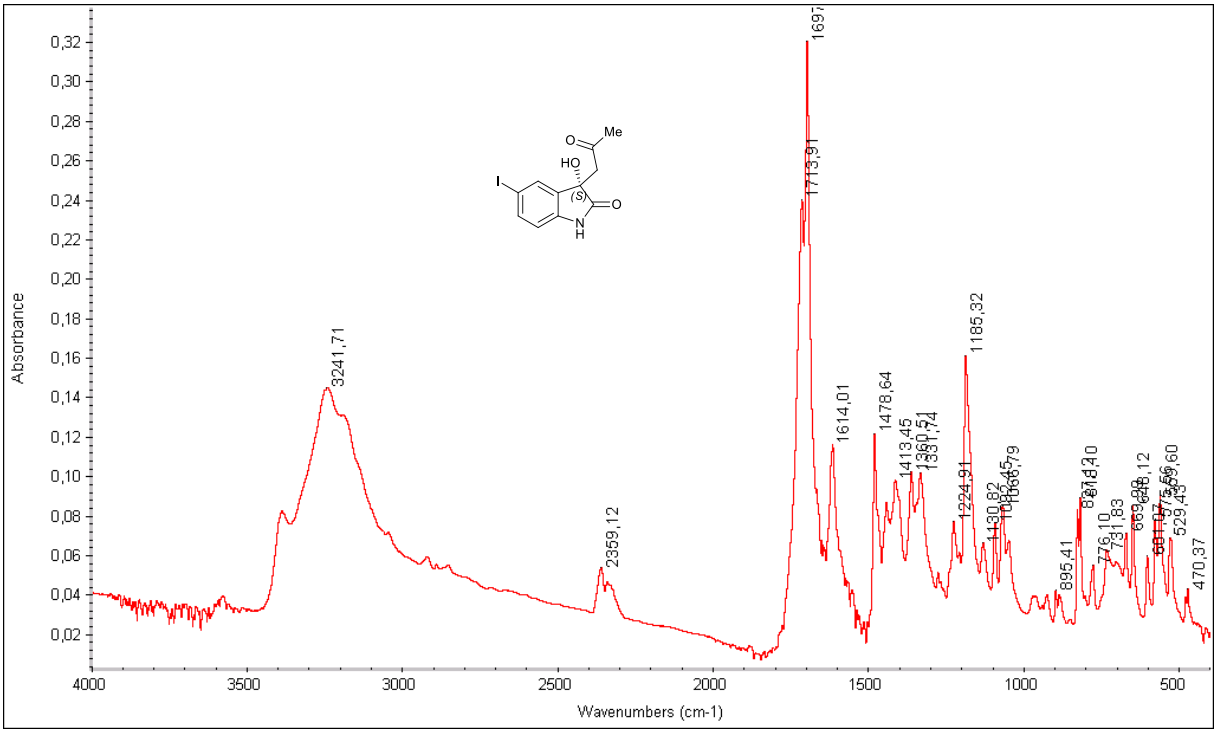
10. Popp, F. D.; Parson, R.; Donigan, B. E., *J. Pharm. Sci.* **1980**, 10, 1235–1237.

2. FT-IR spectra of the synthesized compounds 3a-25

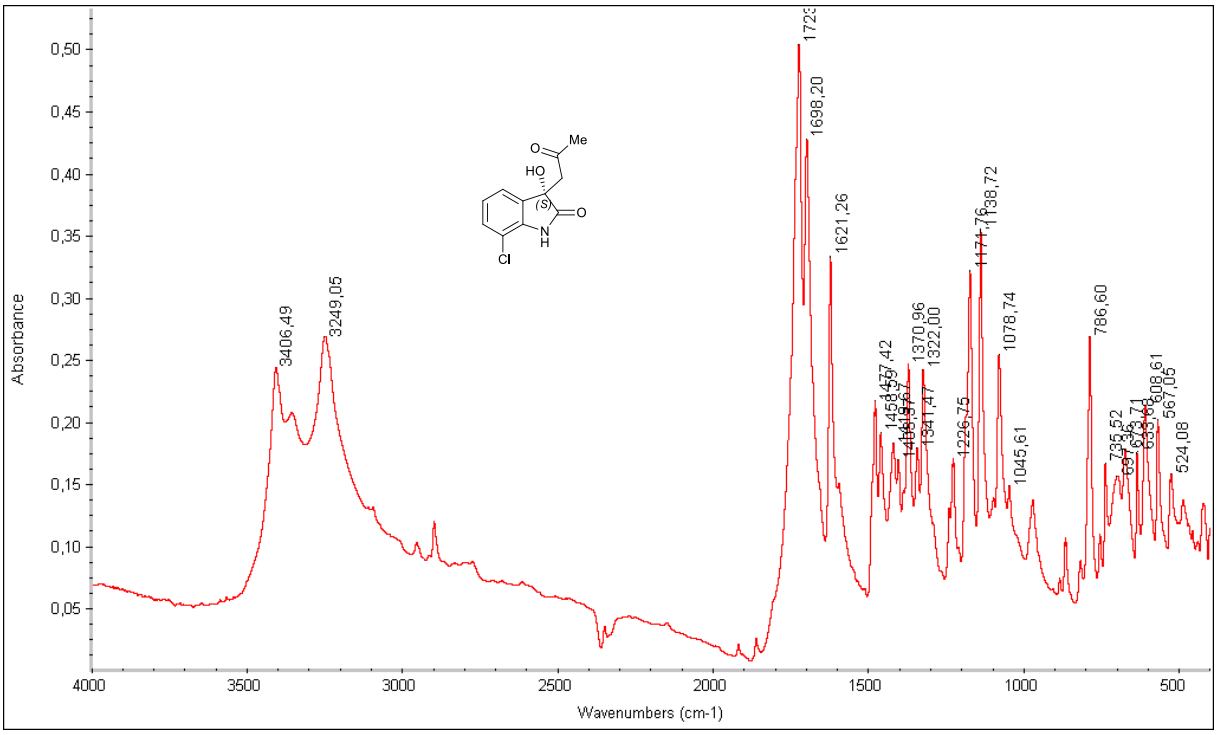
(*S*)-3-Hydroxy-3-(2-oxopropyl) indolin-2-one **3a**



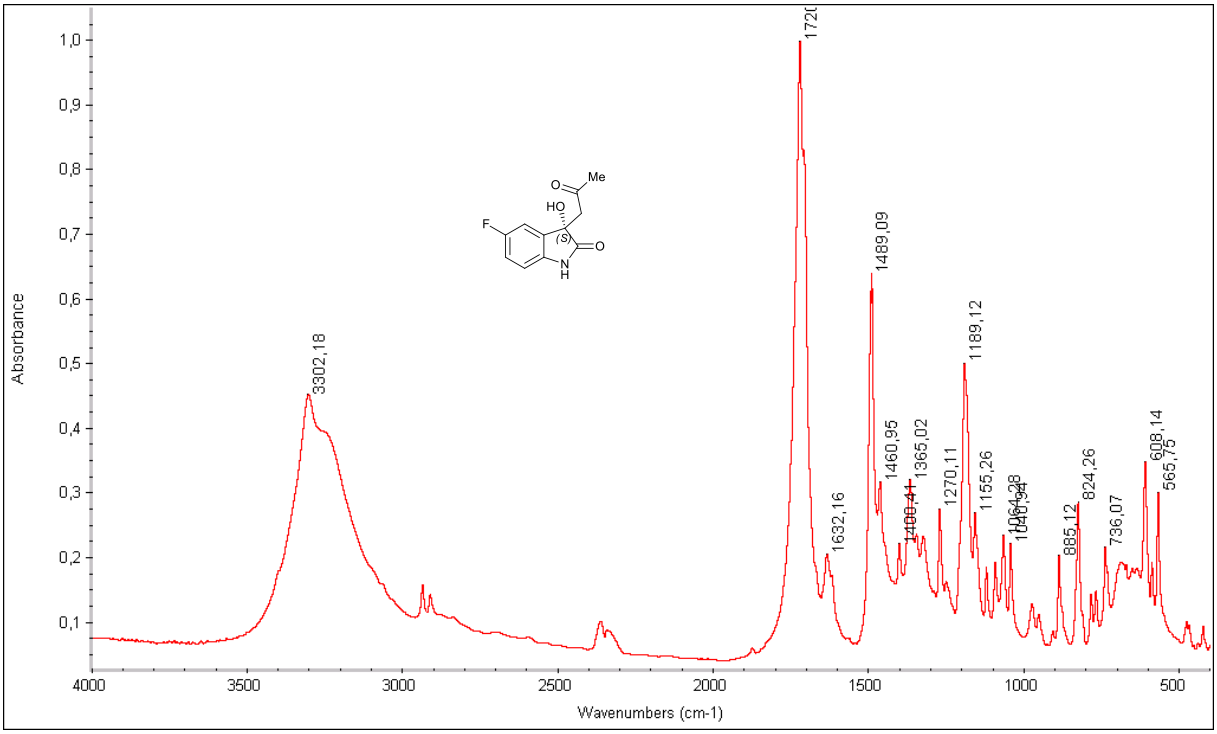
(*S*)-3-Hydroxy-5-iodo-3-(2-oxopropyl) indolin-2-one **3b**



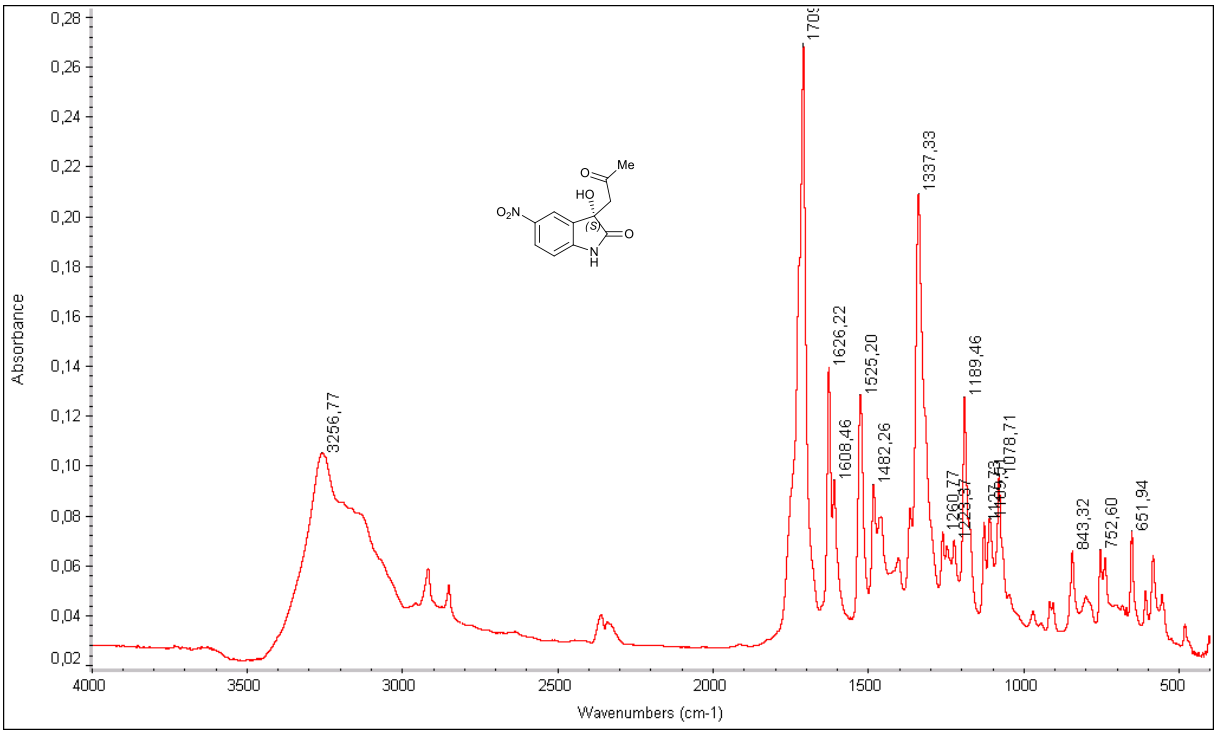
(*S*)-7-Chloro-3-hydroxy-3-(2-oxopropyl) indolin-2-one **3c**



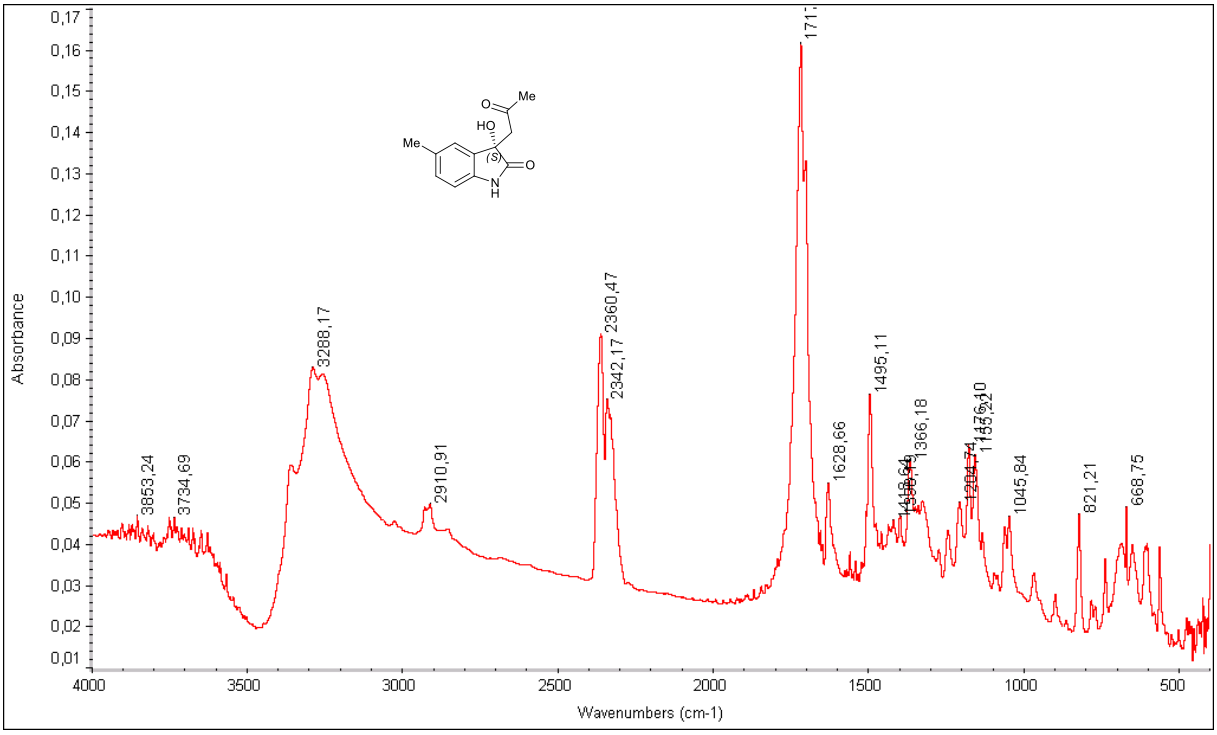
(*S*)-5-fluoro-3-hydroxy-3-(2-oxopropyl)indolin-2-one **3d**



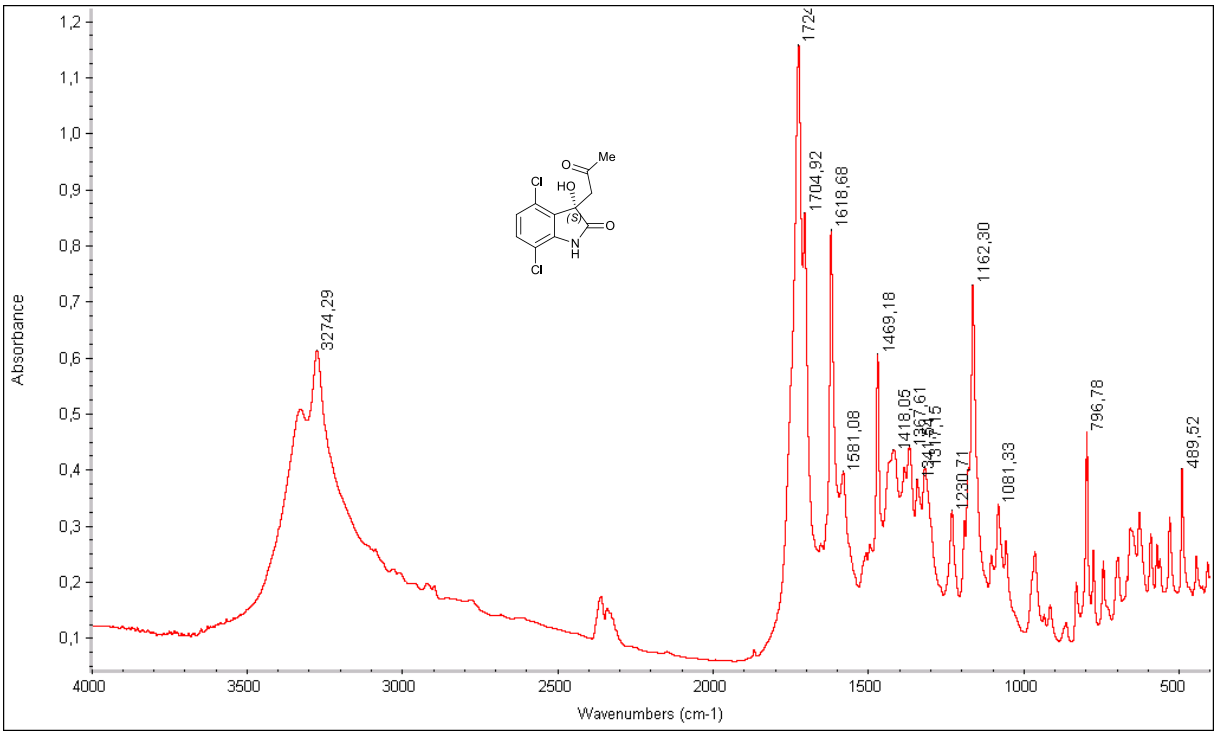
(*S*)-3-hydroxy-5-nitro-3-(2-oxopropyl)indolin-2-one **3e**



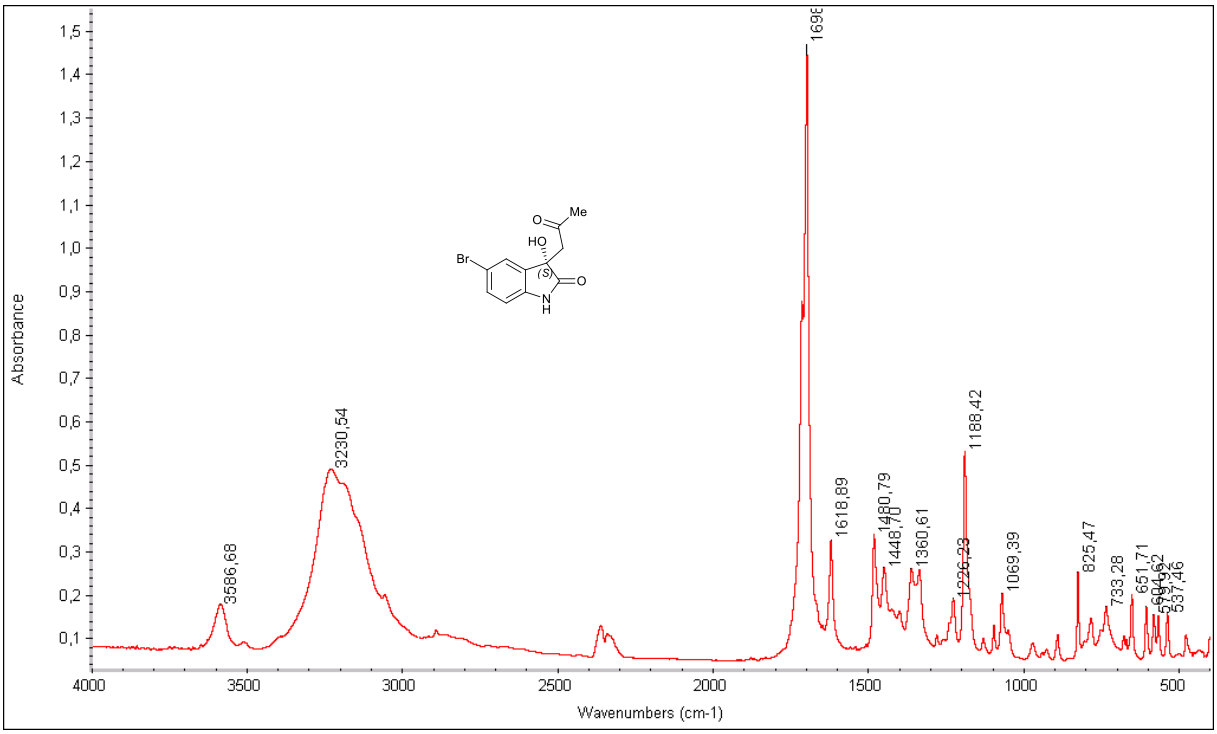
(*S*)-3-hydroxy-5-methyl-3-(2-oxopropyl)indolin-2-one **3f**



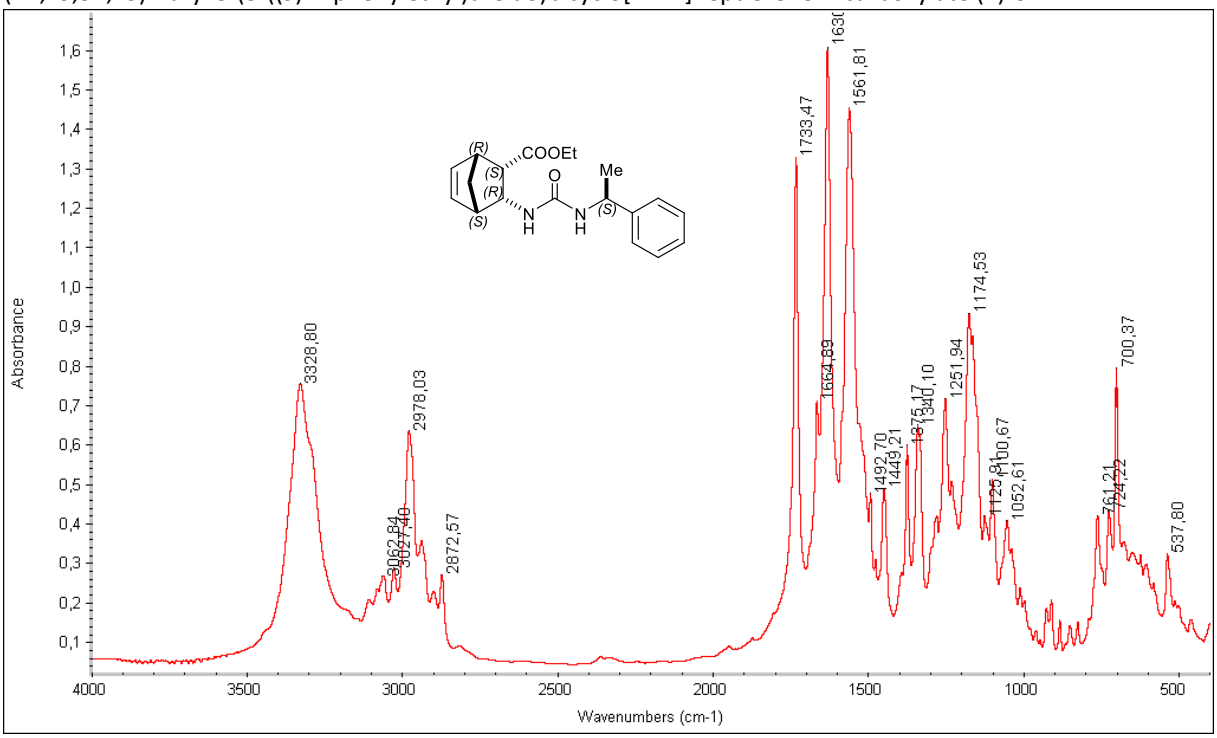
(*S*)-4,7-dichloro-3-hydroxy-3-(2-oxopropyl)indolin-2-one **3g**



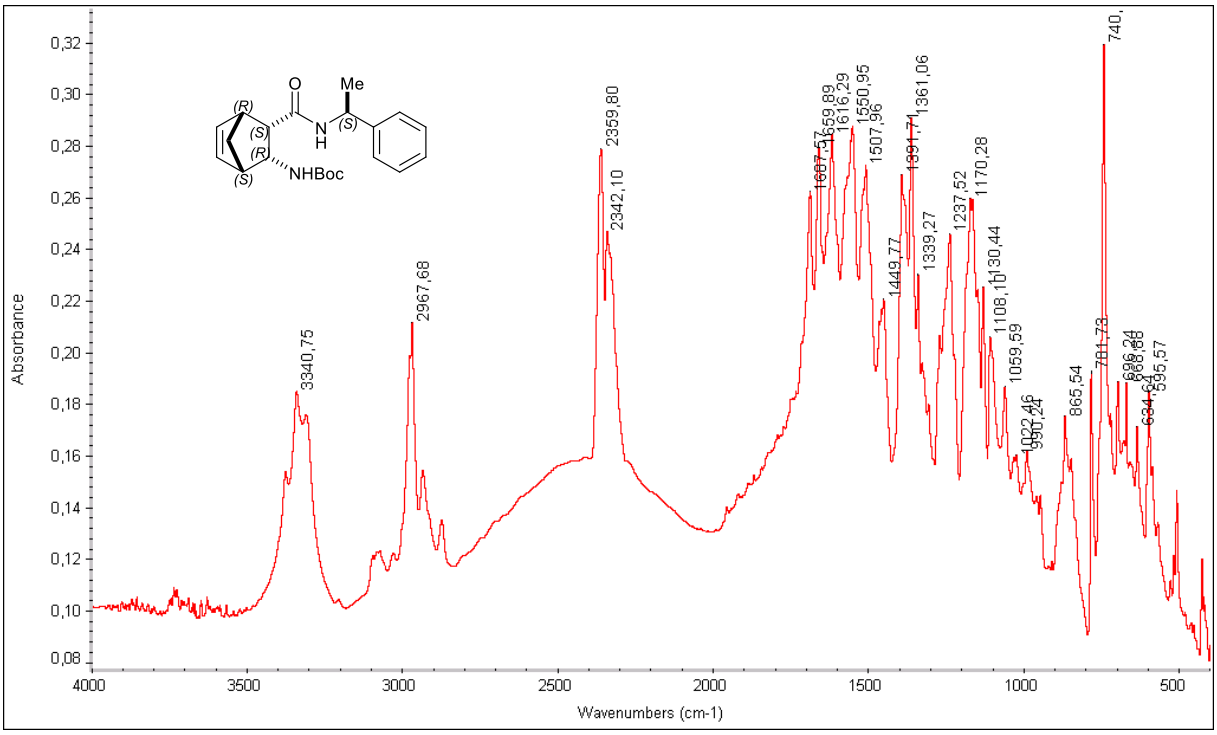
(*S*)-5-bromo-3-hydroxy-3-(2-oxopropyl)indolin-2-one **3h**



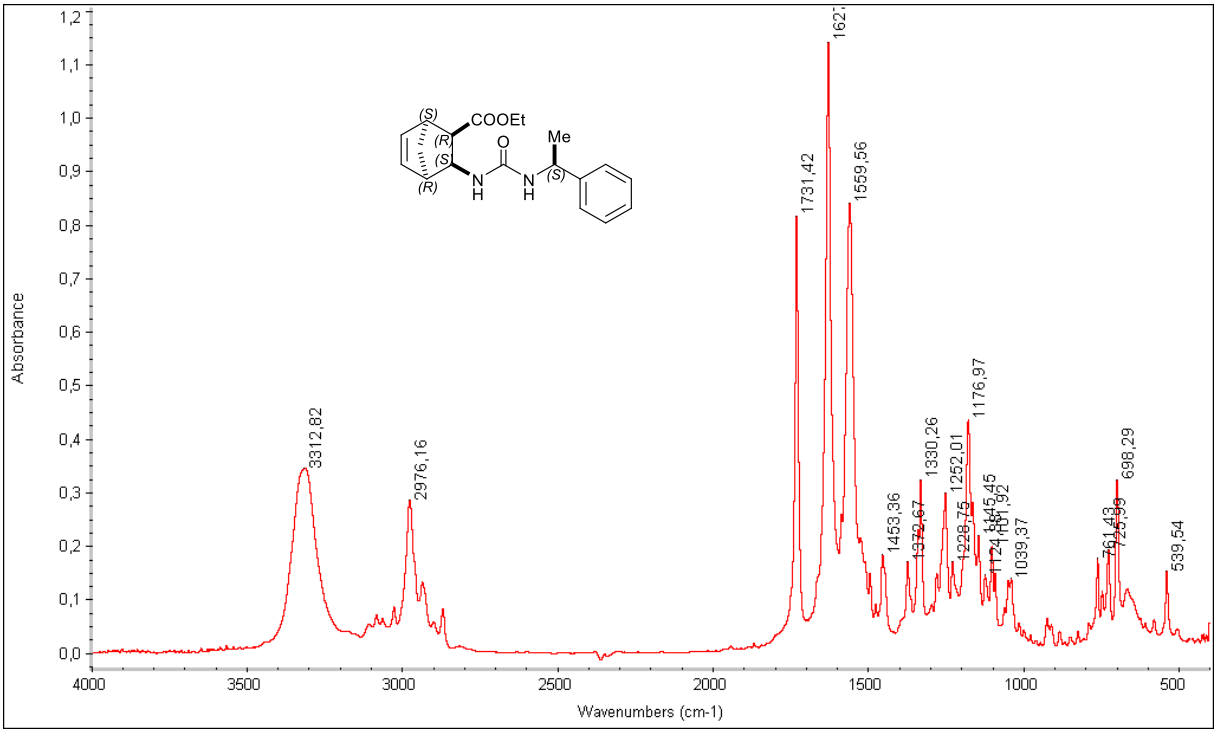
(1*R*,2*S*,3*R*,4*S*)-Ethyl 3-(3-((*S*)-1-phenylethyl)ureido)bicyclo[2.2.1]hept-5-ene-2-carboxylate (–)-**6**



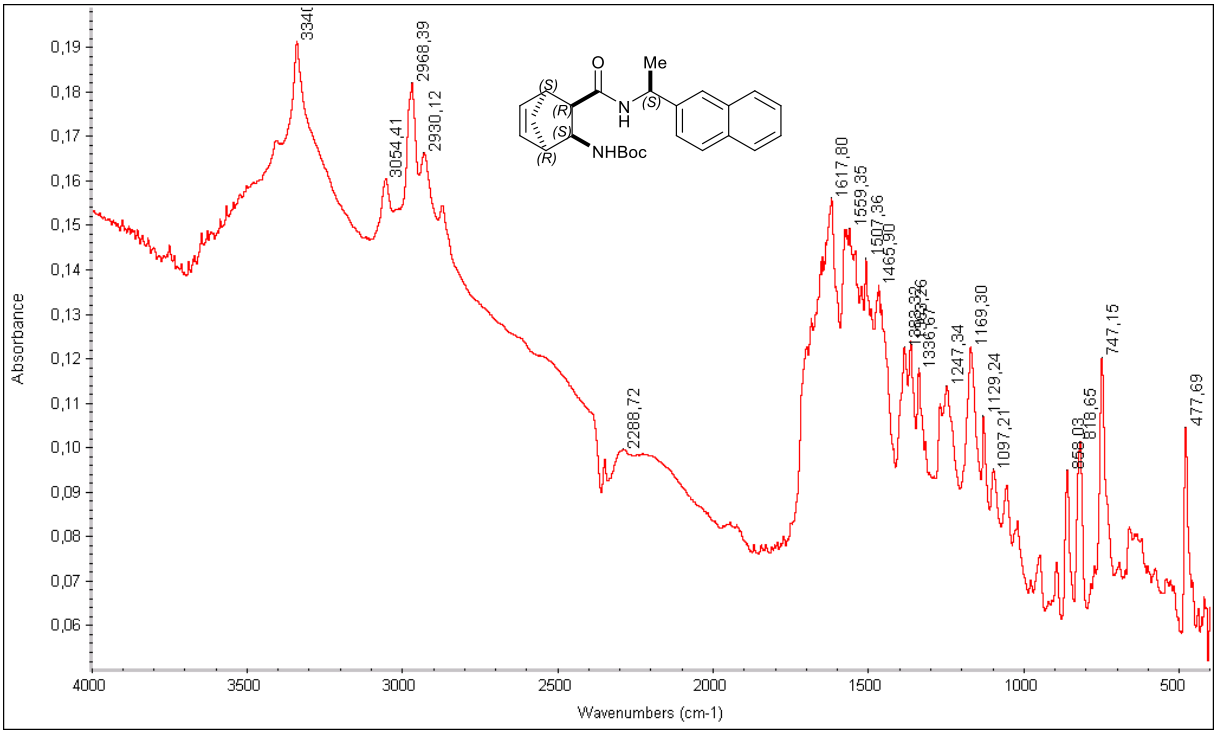
tert-Butyl ((1*S*,2*R*,3*S*,4*R*)-3-(((*S*)-1-phenylethyl)carbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate (–)-**7**



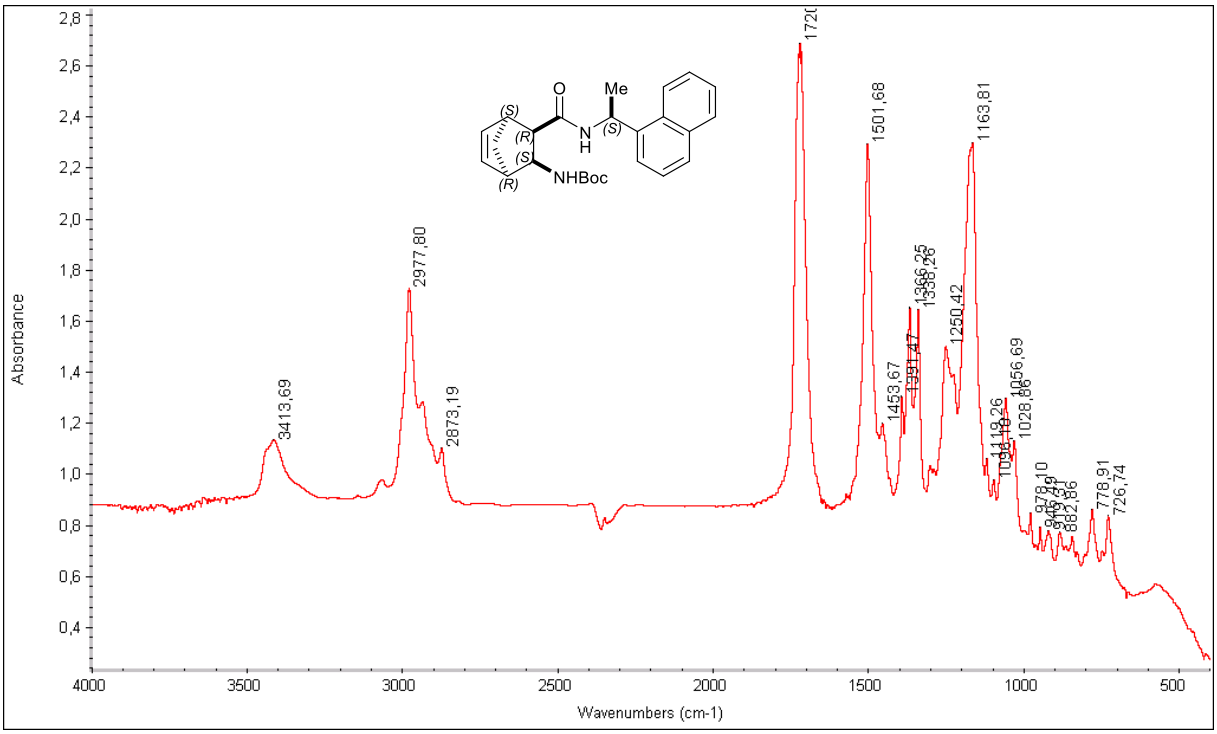
(1*S*,2*R*,3*S*,4*R*)-Ethyl 3-(3-((S)-1-phenylethyl)ureido)bicyclo[2.2.1]hept-5-ene-2-carboxylate (–)-**8**



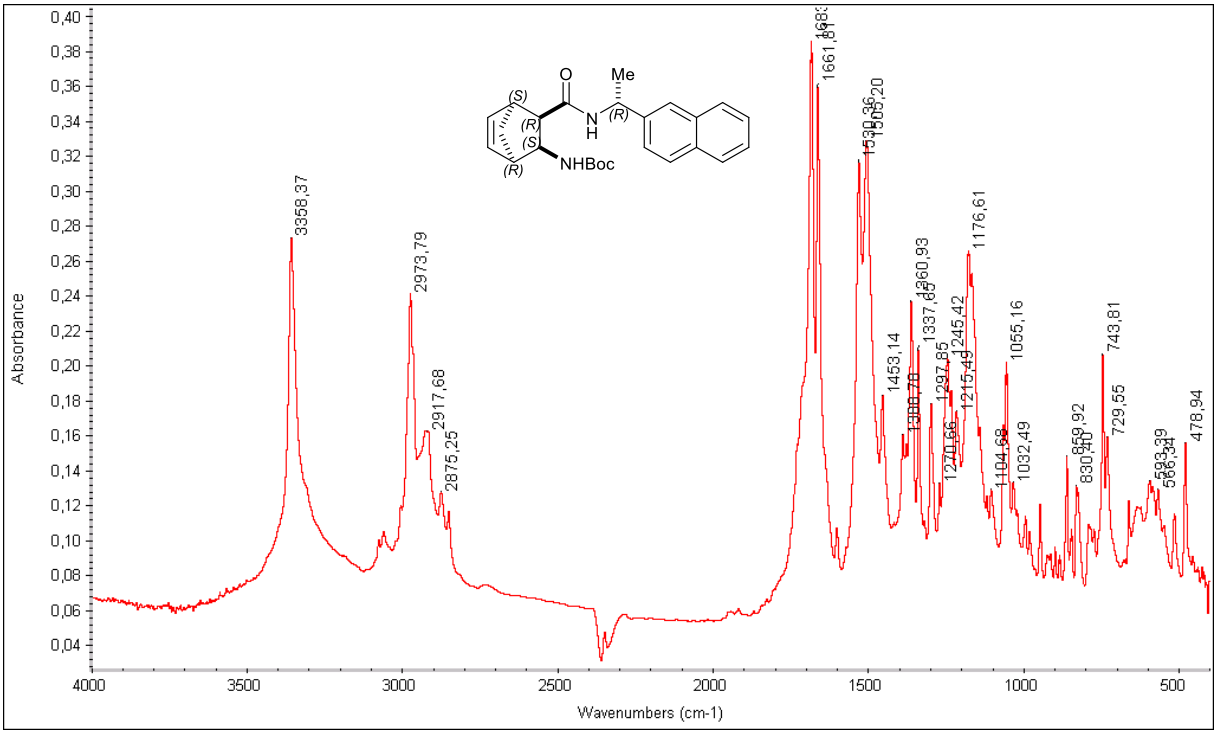
tert-Butyl ((1*R*,2*S*,3*R*,4*S*)-3-(((*S*)-1-(naphthalen-2-yl)ethyl)carbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate (–)-**9**



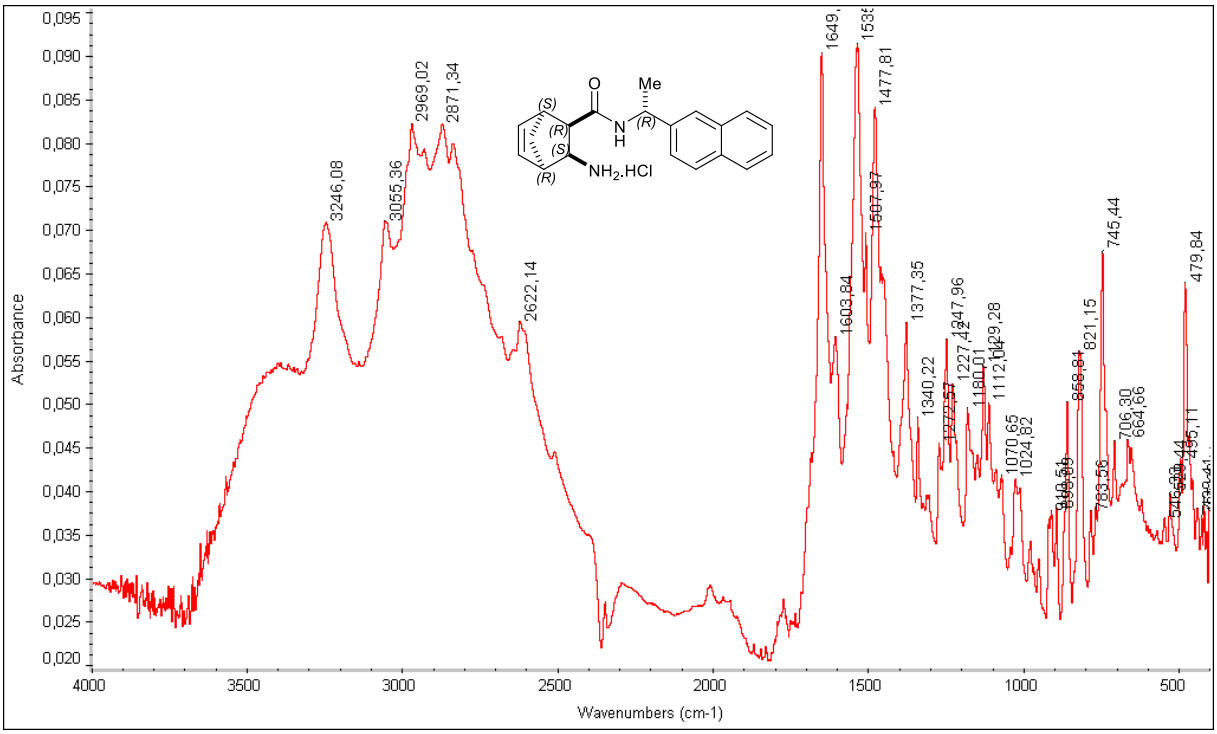
tert-Butyl ((1*R*,2*S*,3*R*,4*S*)-3-(((*S*)-1-(naphthalen-1-yl)ethyl)carbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate (–)-**10**



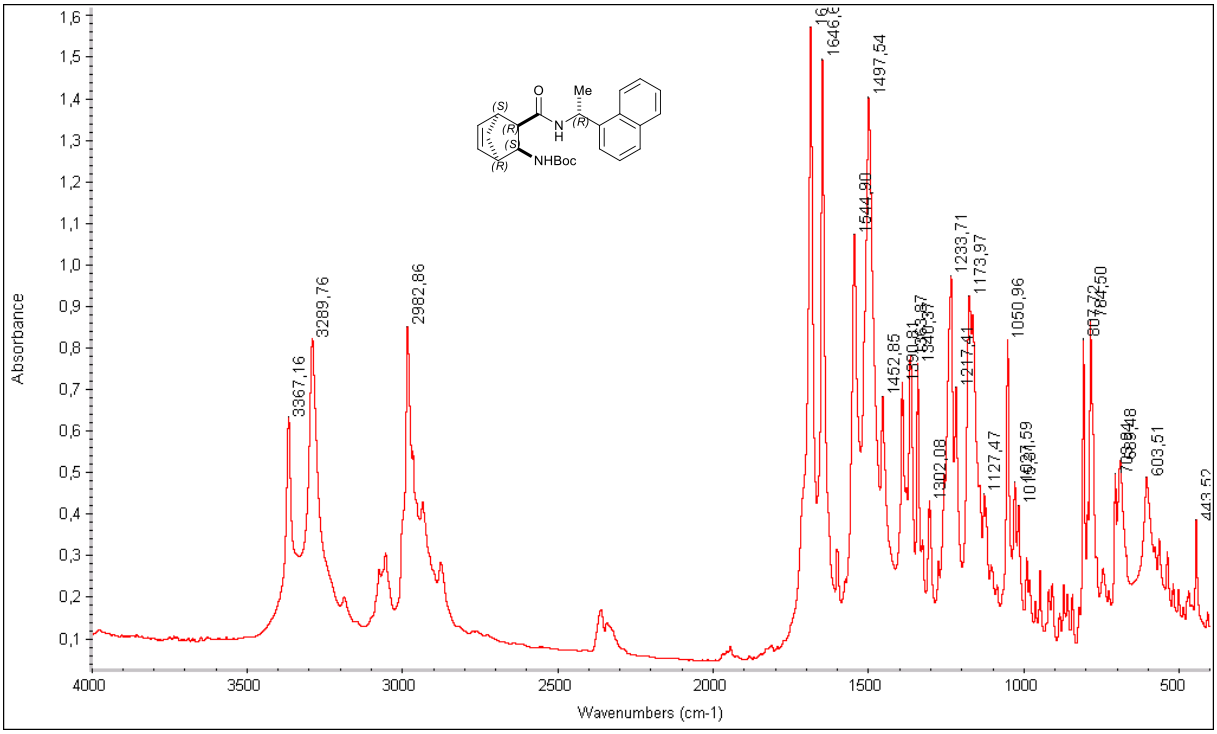
tert-Butyl ((1*R*,2*S*,3*R*,4*S*)-3-(((*R*)-1-(naphthalen-2-yl)ethyl)carbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate (+)-**11**



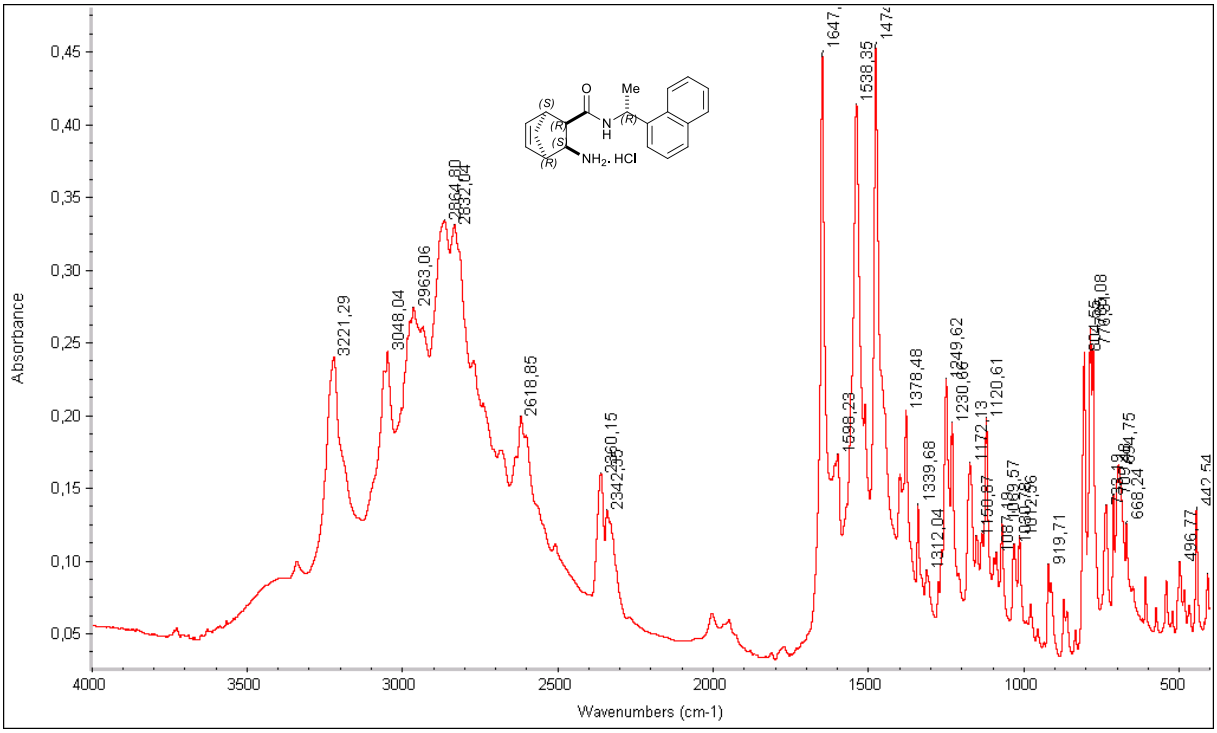
(1*S*,2*R*,3*S*,4*R*)-3-Amino-N-((*R*)-1-(naphthalen-2-yl)ethyl)bicyclo[2.2.1]hept-5-ene-2-carboxamide hydrochloride (+)-**12**



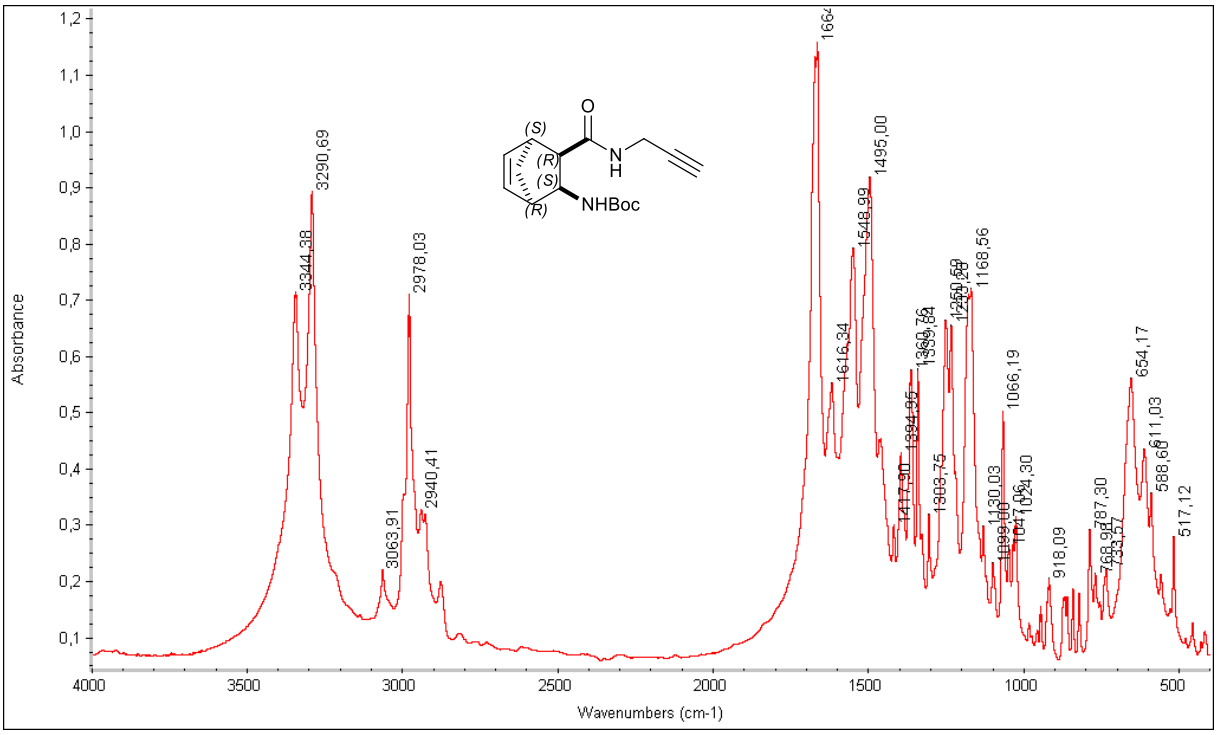
tert-Butyl ((1*R*,2*S*,3*R*,4*S*)-3-(((*R*)-1-(naphthalen-1-yl)ethyl)carbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate (+)-**13**



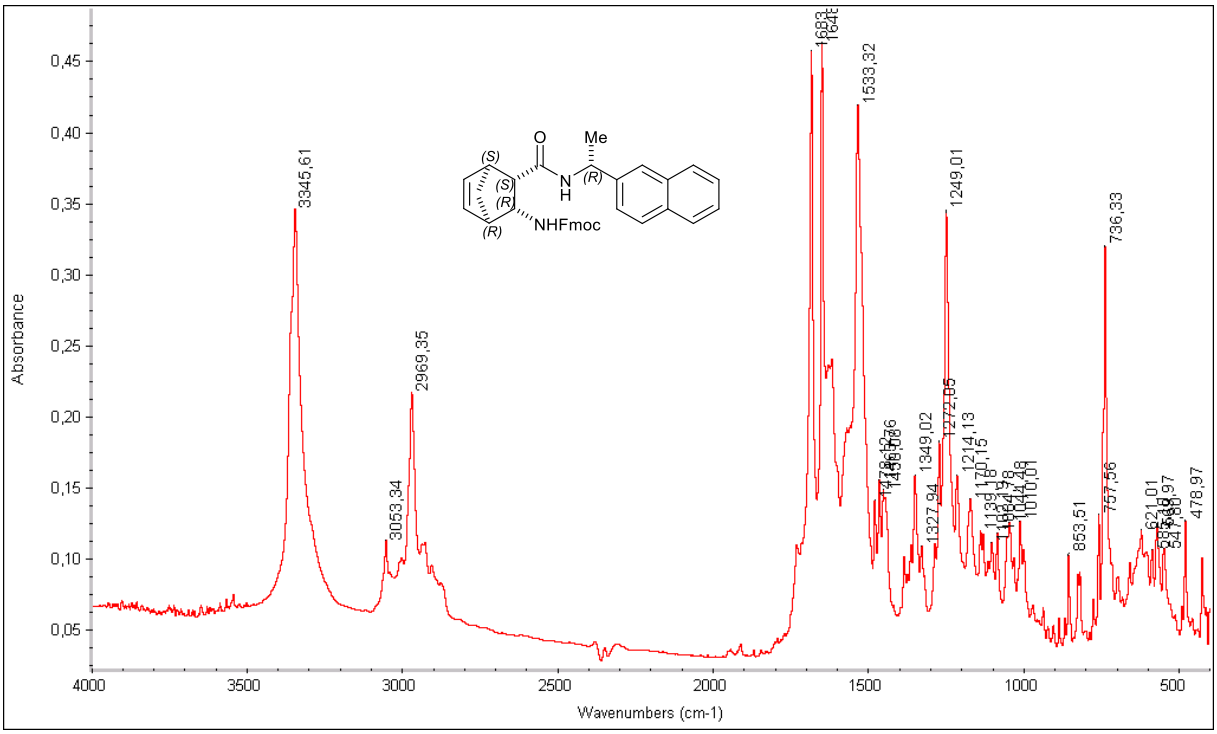
((1*S*,2*R*,3*S*,4*R*)-3-Amino-N-((*R*)-1-(naphthalen-1-yl)ethyl)bicyclo[2.2.1]hept-5-ene-2-carboxamide hydrochloride (+)-**14**



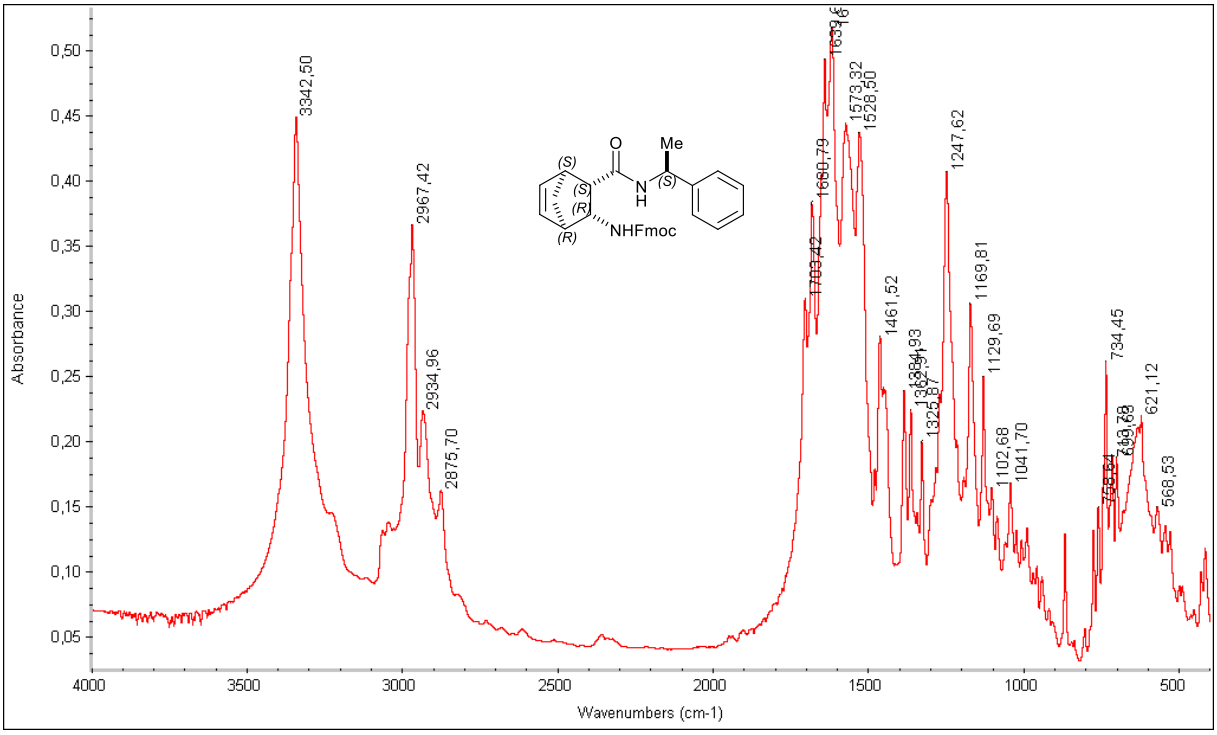
tert-Butyl ((1*R*,2*S*,3*R*,4*S*)-3-(prop-2-yn-1-ylcarbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate (–)-**15**



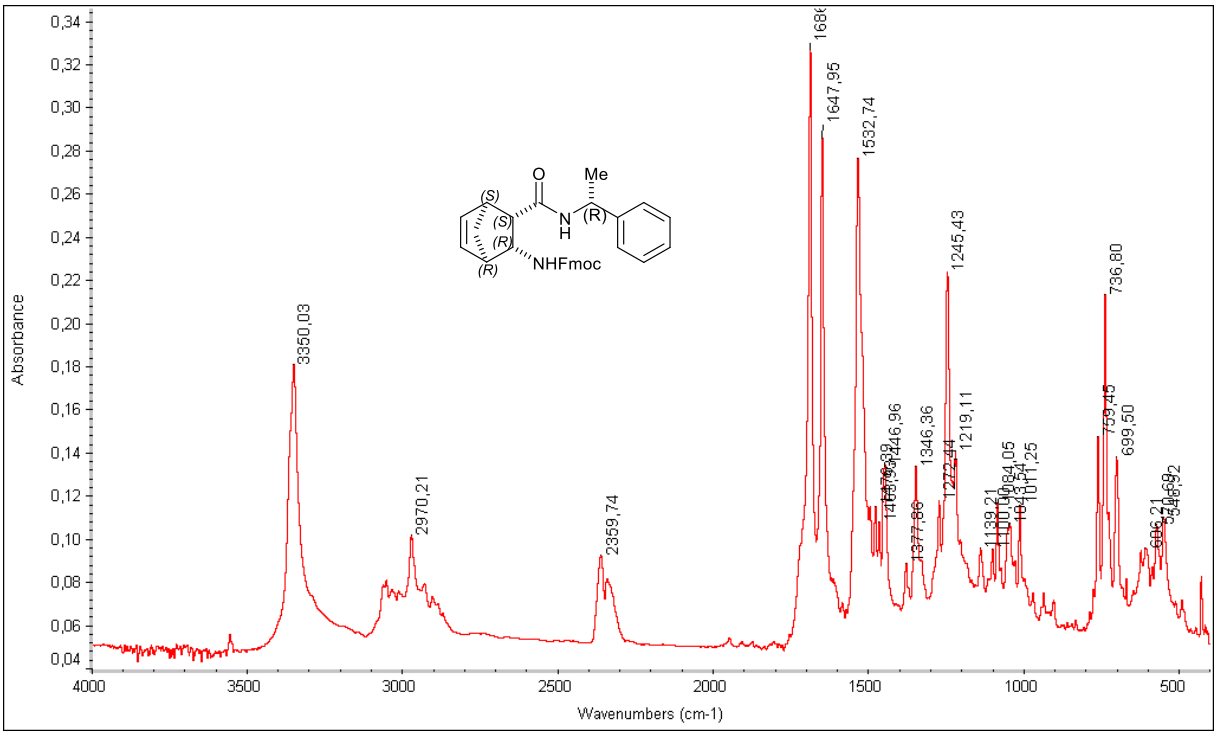
(9*H*-Fluoren-9-yl)methyl ((1*R*,2*R*,3*S*,4*S*)-3-(((*R*)-1-(naphthalen-2-yl)ethyl)carbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate (+)-**18**



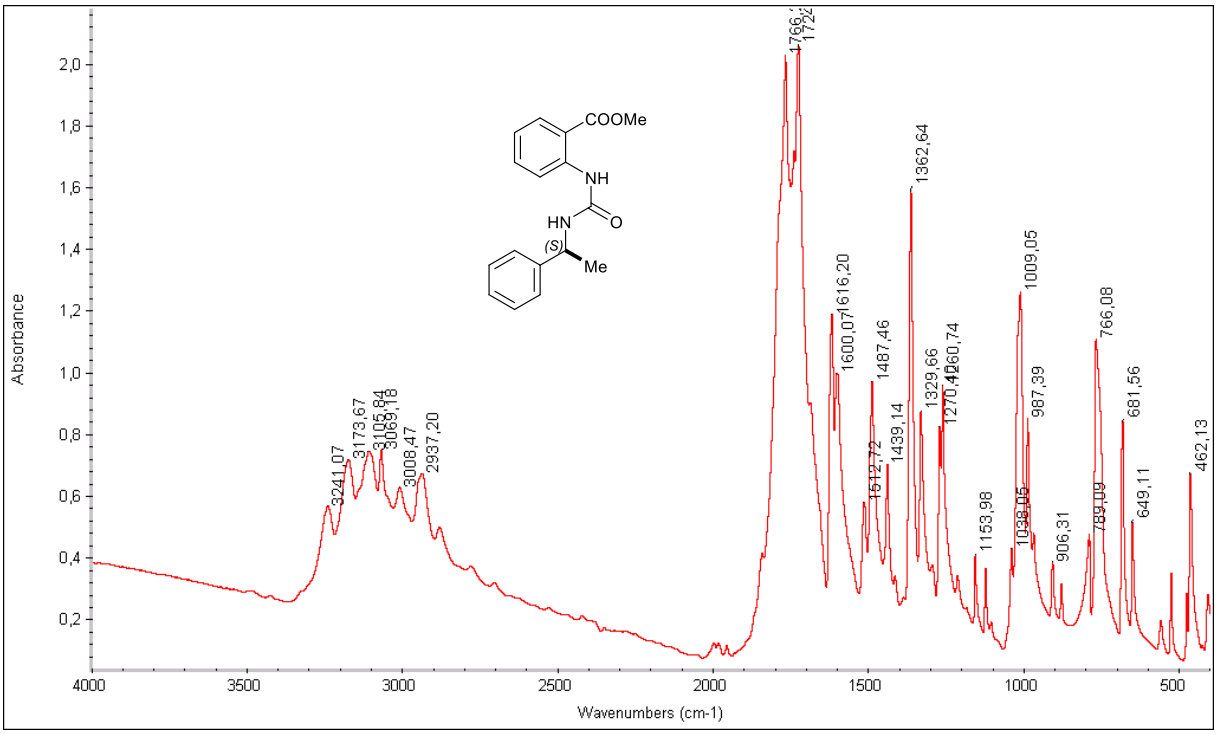
(9*H*-Fluoren-9-yl)methyl ((1*R*,2*R*,3*S*,4*S*)-3-(((*S*)-1-phenylethyl)carbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate (–)-**19**



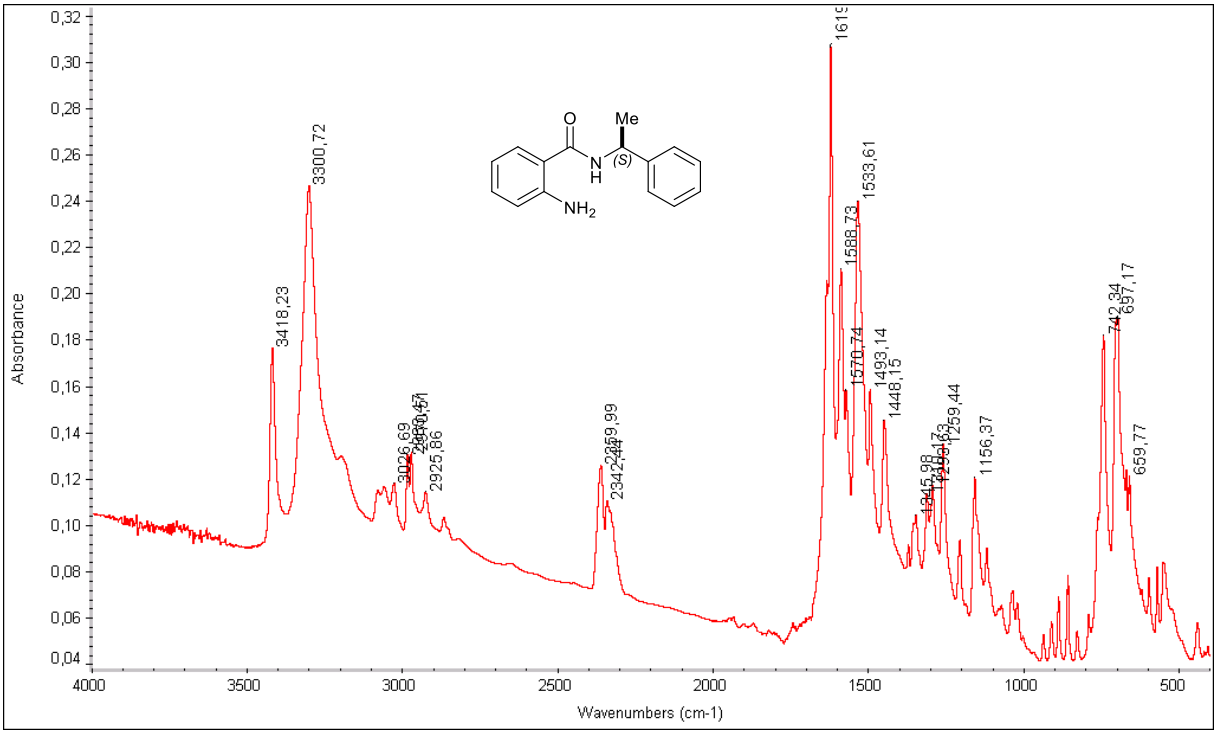
(9*H*-Fluoren-9-yl)methyl ((1*R*,2*R*,3*S*,4*SR*)-3-(((*R*)-1-phenylethyl)carbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate (+)-**20**



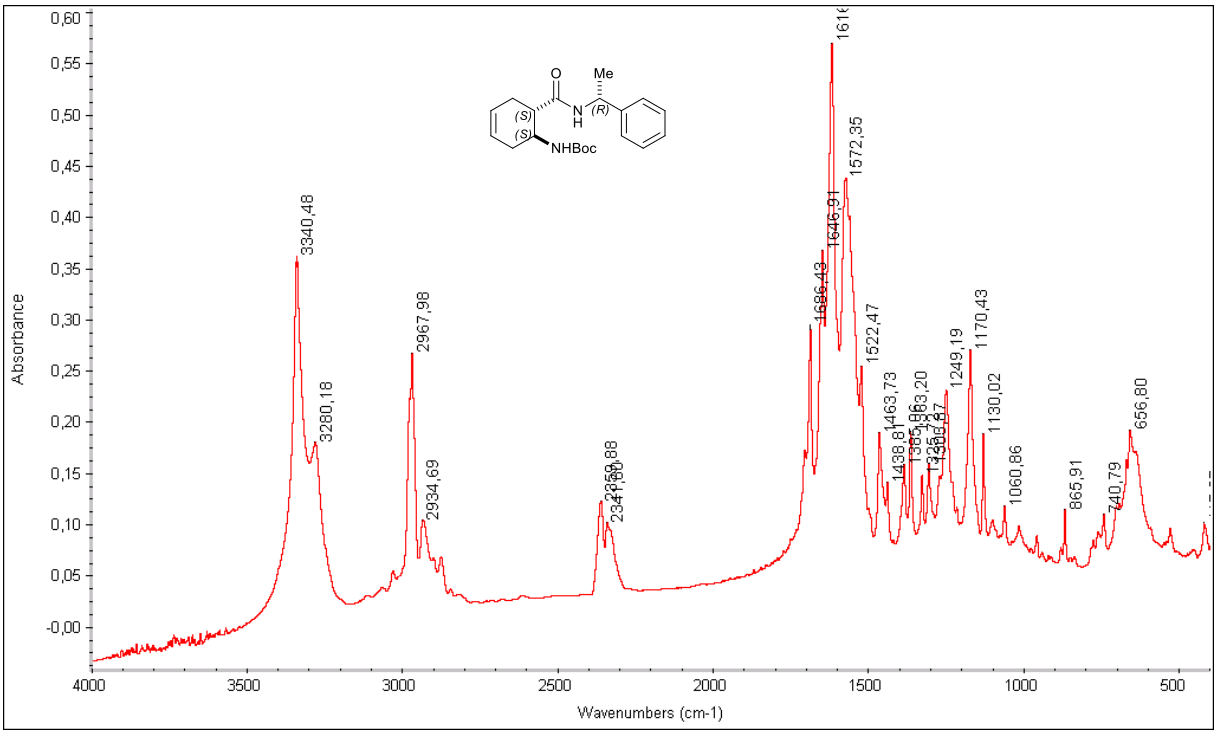
(S)-Methyl 2-(3-(1-phenylethyl)ureido)benzoate (+)-**22**



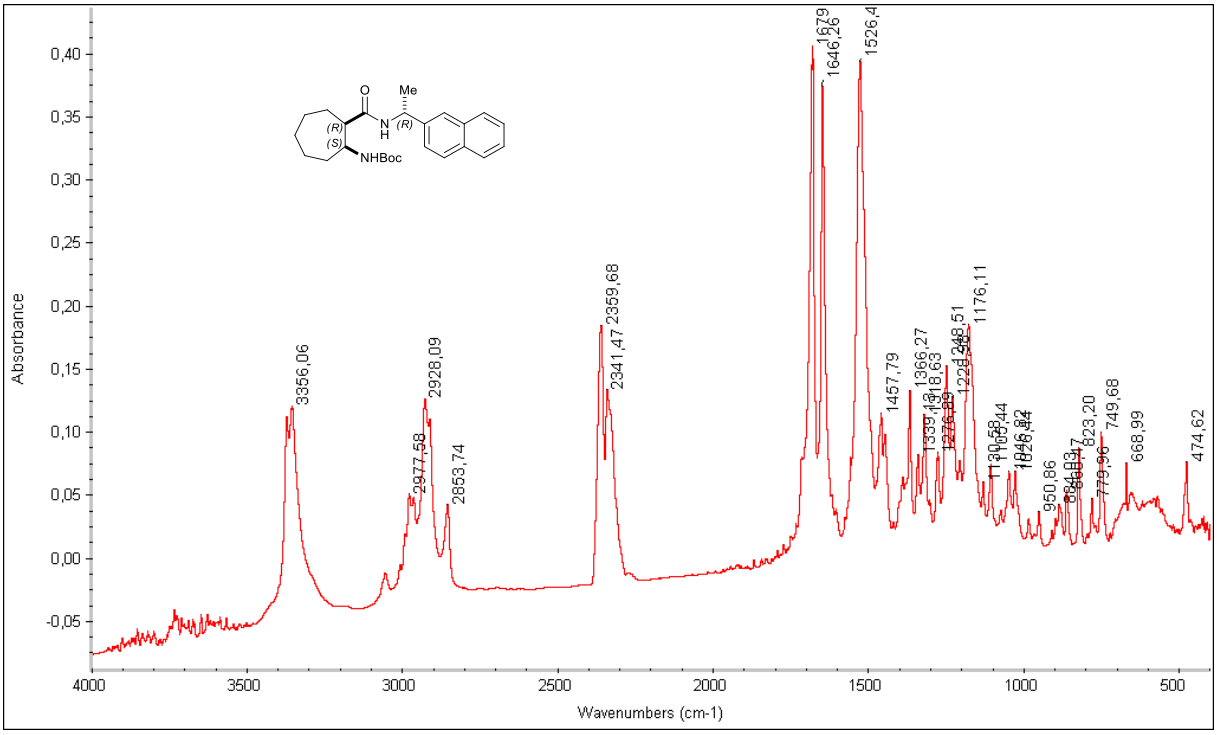
(S)-2-Amino-N-(1-phenylethyl)benzamide (+)-**23**



tert-Butyl ((1*S*,6*S*)-6-(((*R*)-1-phenylethyl)carbamoyl)cyclohex-3-en-1-yl)carbamate (+)-**24**

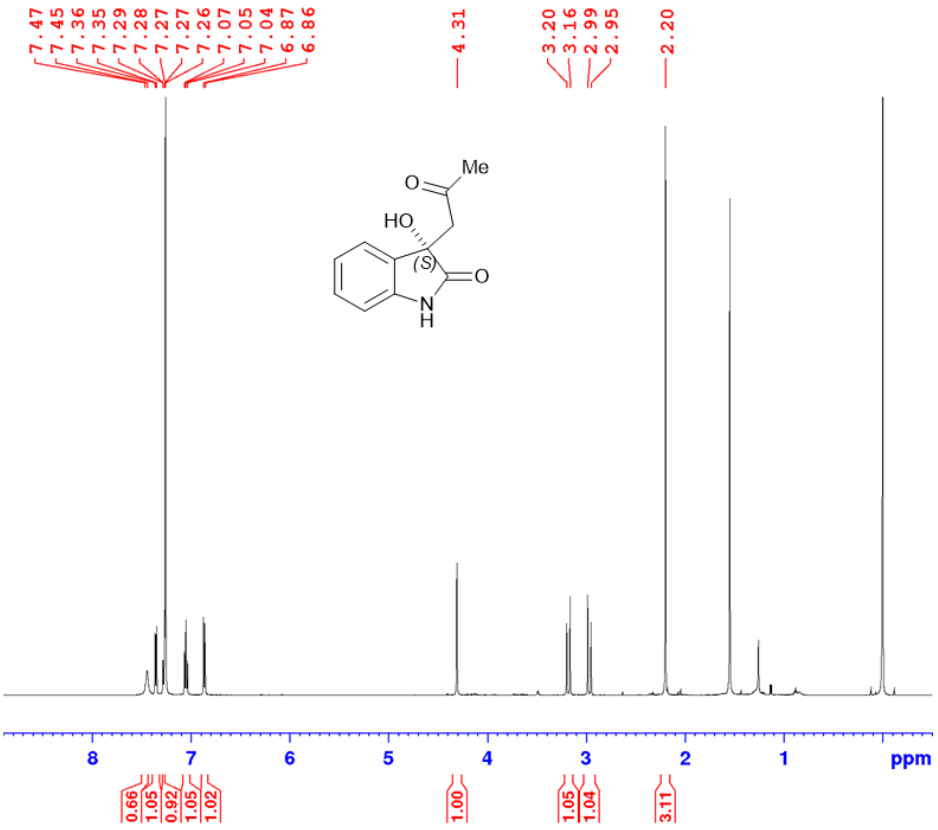


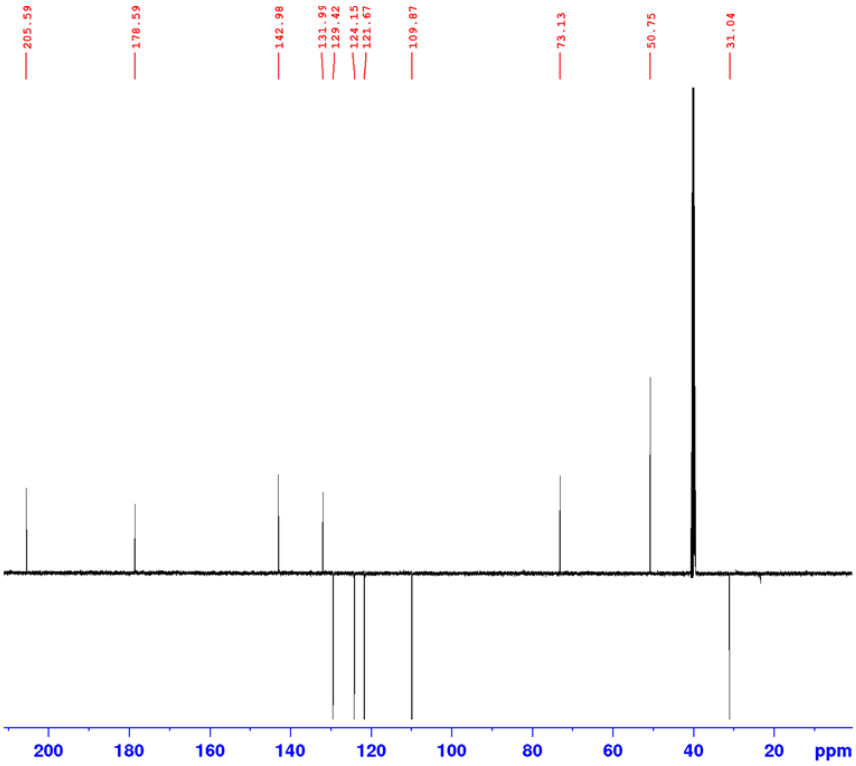
tert-Butyl ((1*S*,2*R*)-2-(((*R*)-1-(naphthalen-2-yl)ethyl)carbamoyl)cycloheptyl)carbamate (+)-**25**



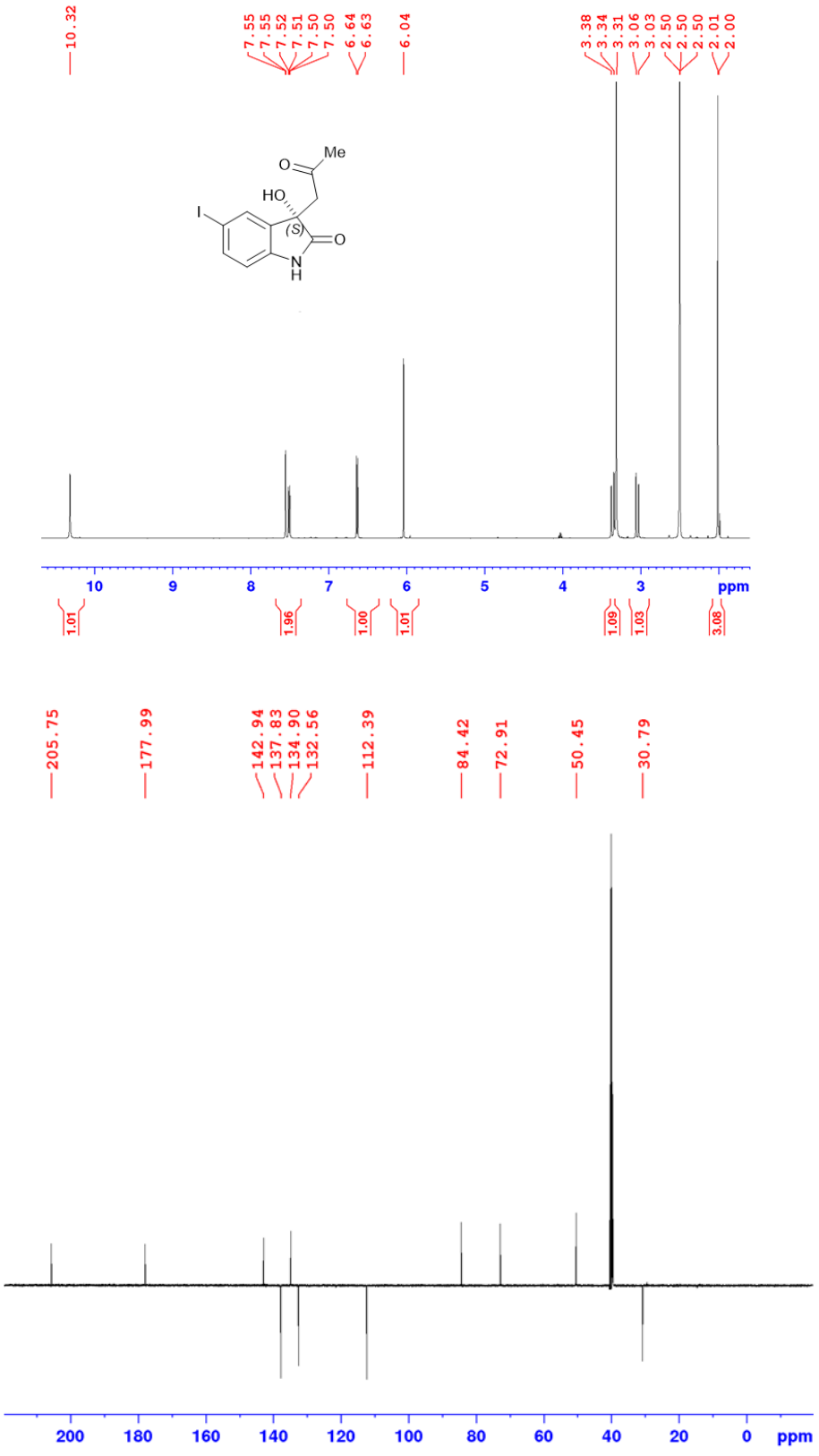
3. ^{1}H and ^{13}C NMR spectra of the compounds 3a-25

(*S*)-3-Hydroxy-3-(2-oxopropyl)indolin-2-one **3a**

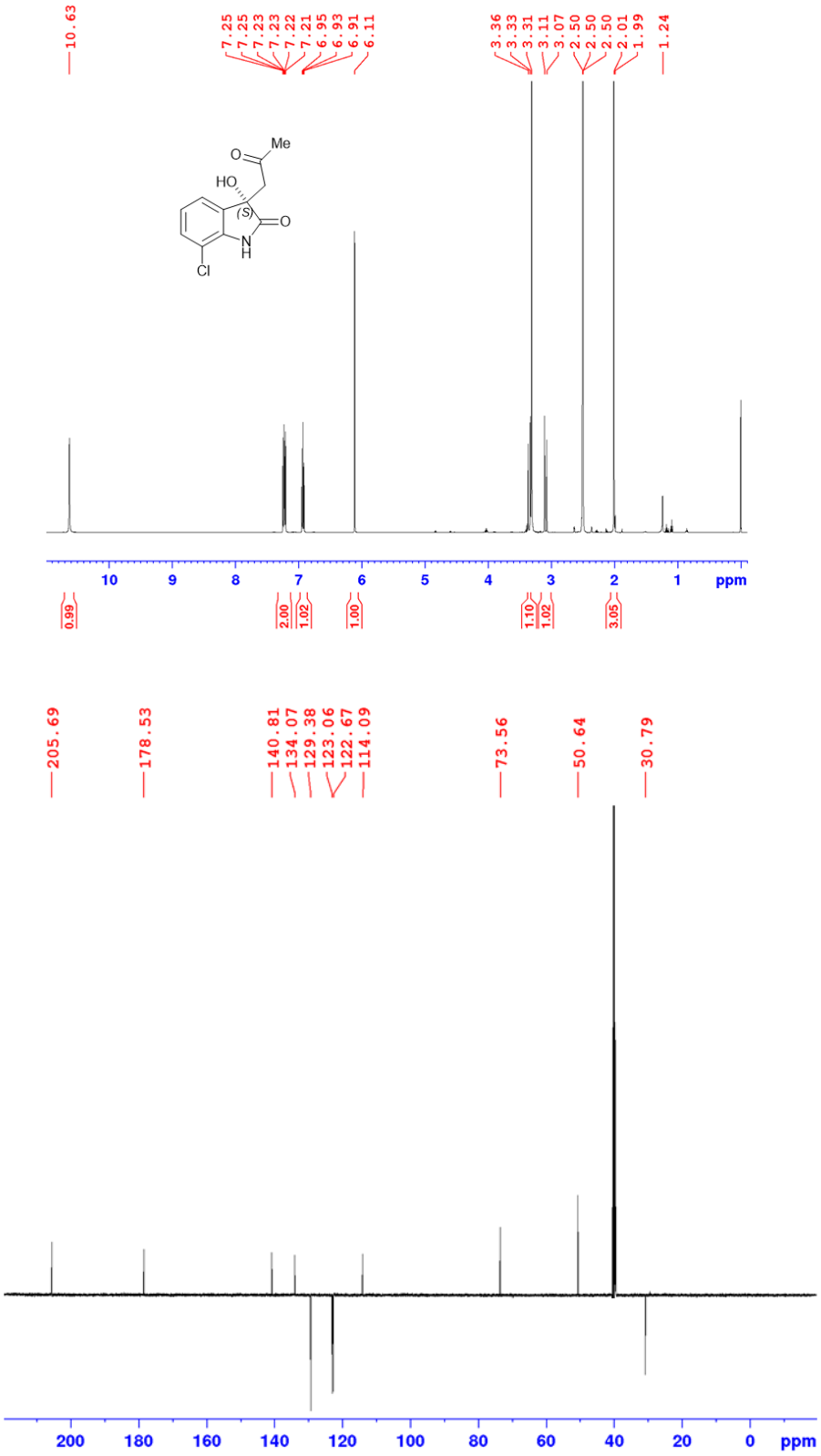




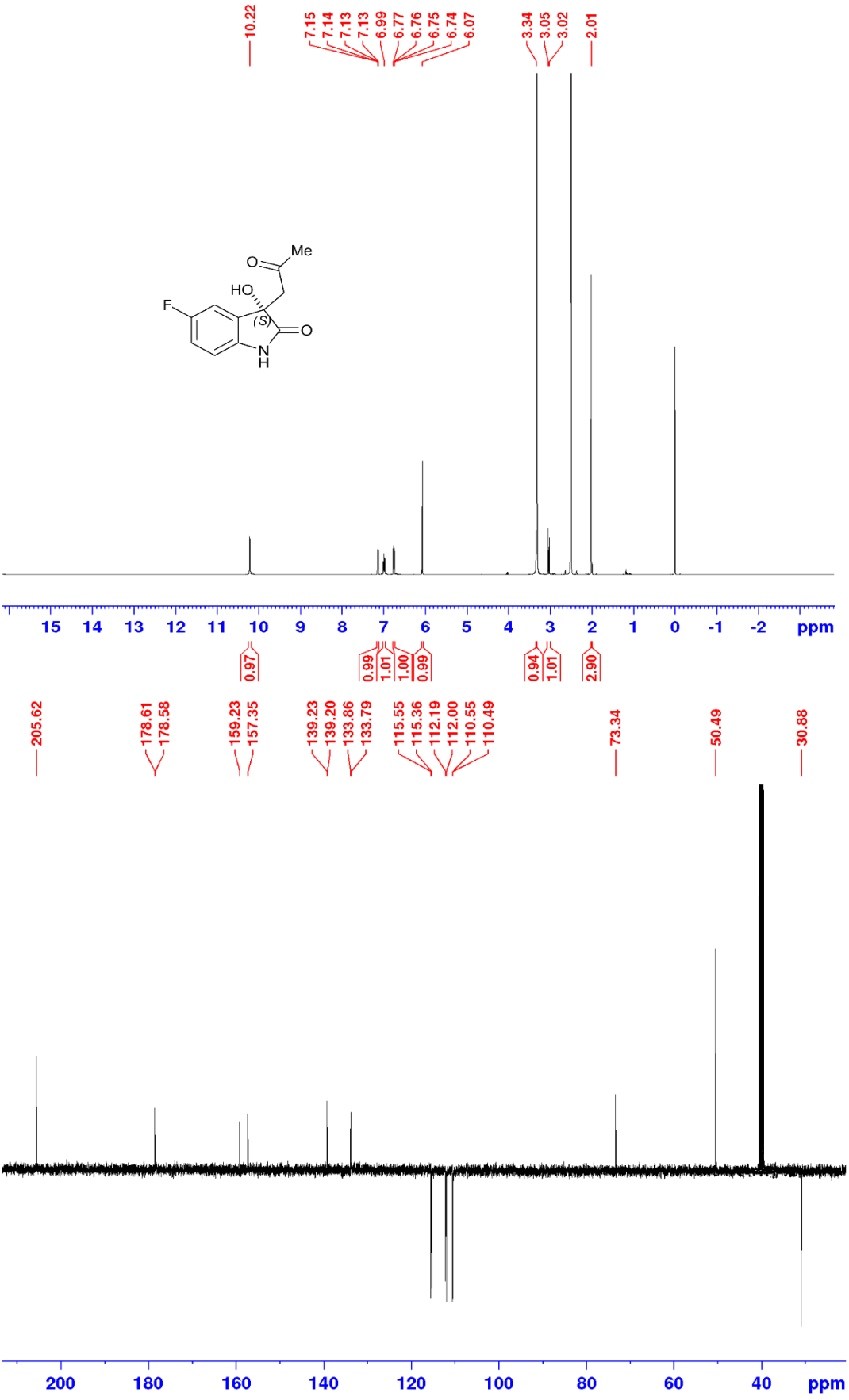
(*S*)-3-Hydroxy-5-iodo-3-(2-oxopropyl)indolin-2-one **3b**



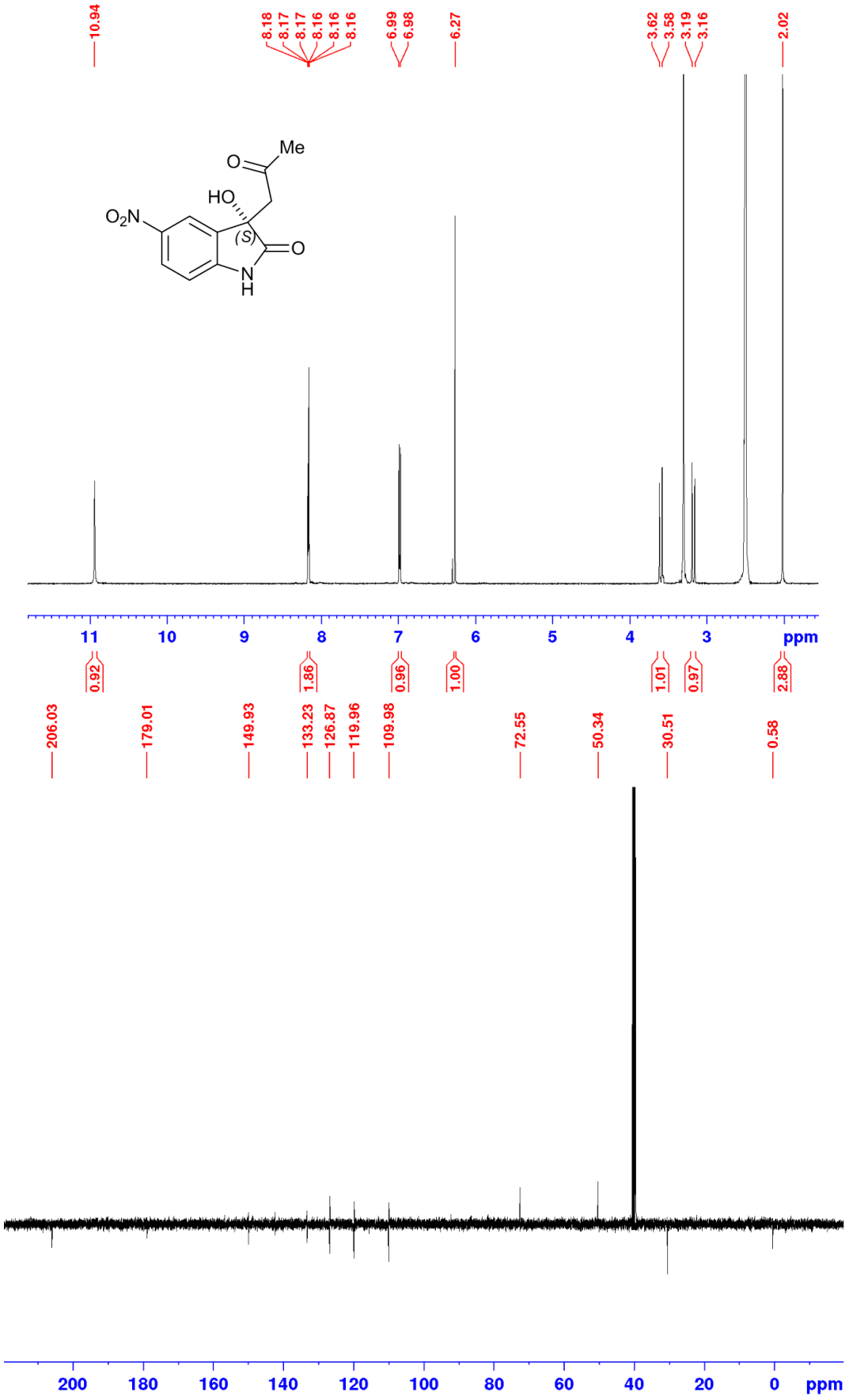
(*S*)-7-Chloro-3-hydroxy-3-(2-oxopropyl)indolin-2-one **3c**



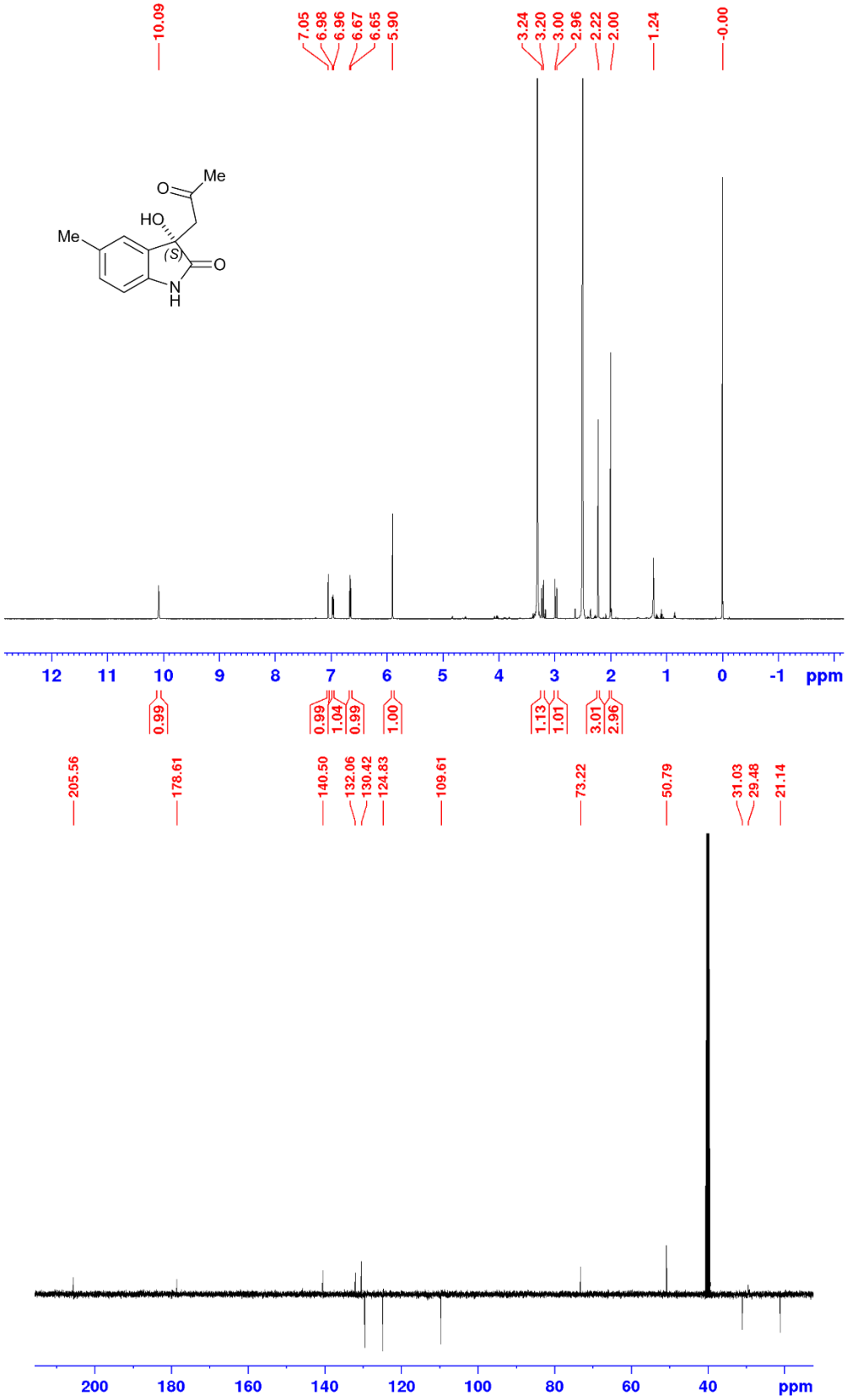
(*S*)-5-fluoro-3-hydroxy-3-(2-oxopropyl)indolin-2-one **3d**



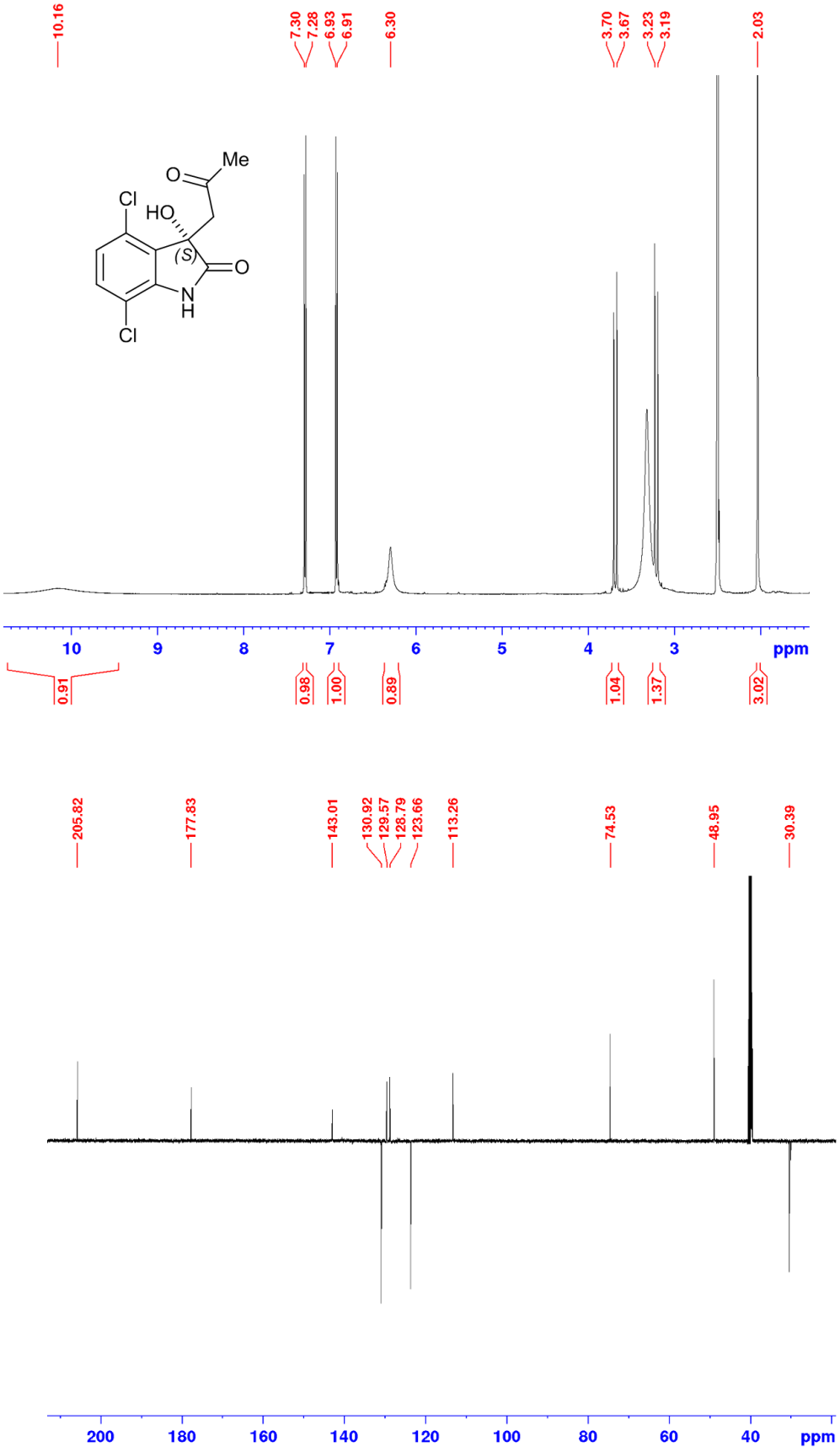
(*S*)-3-hydroxy-5-nitro-3-(2-oxopropyl)indolin-2-one **3e**



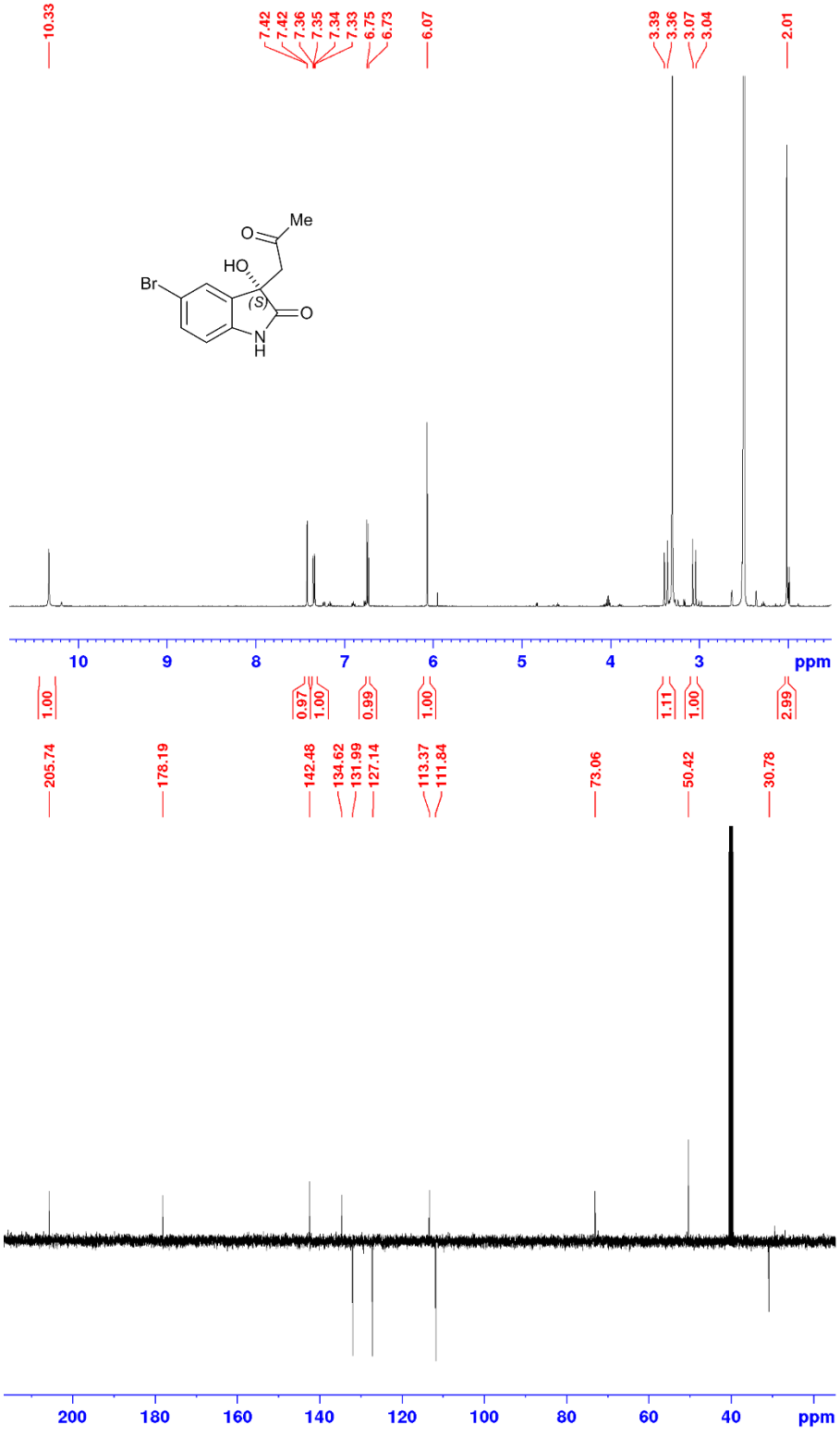
(*S*)-3-hydroxy-5-methyl-3-(2-oxopropyl)indolin-2-one **3f**



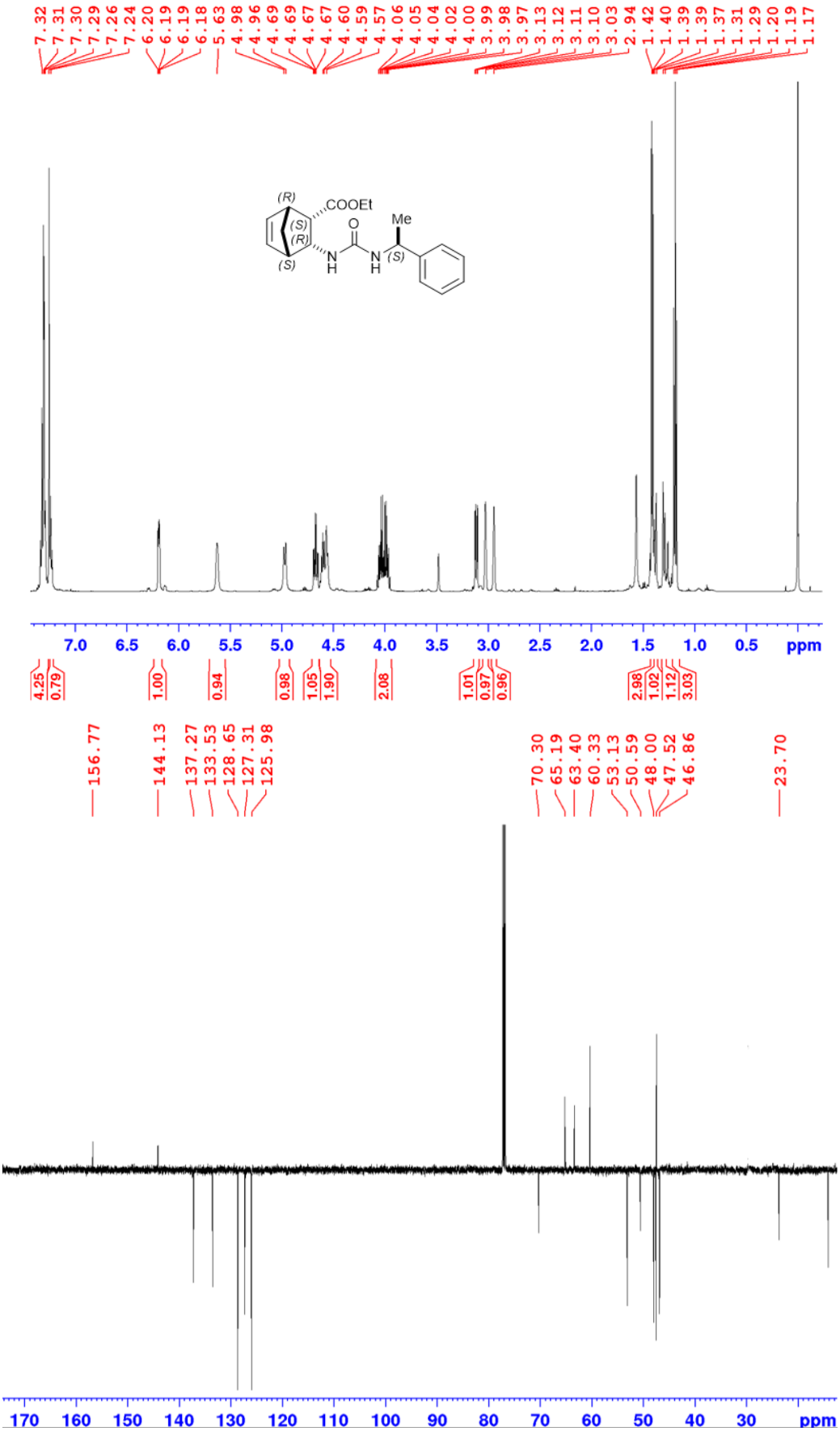
(*S*)-4,7-dichloro-3-hydroxy-3-(2-oxopropyl)indolin-2-one **3g**



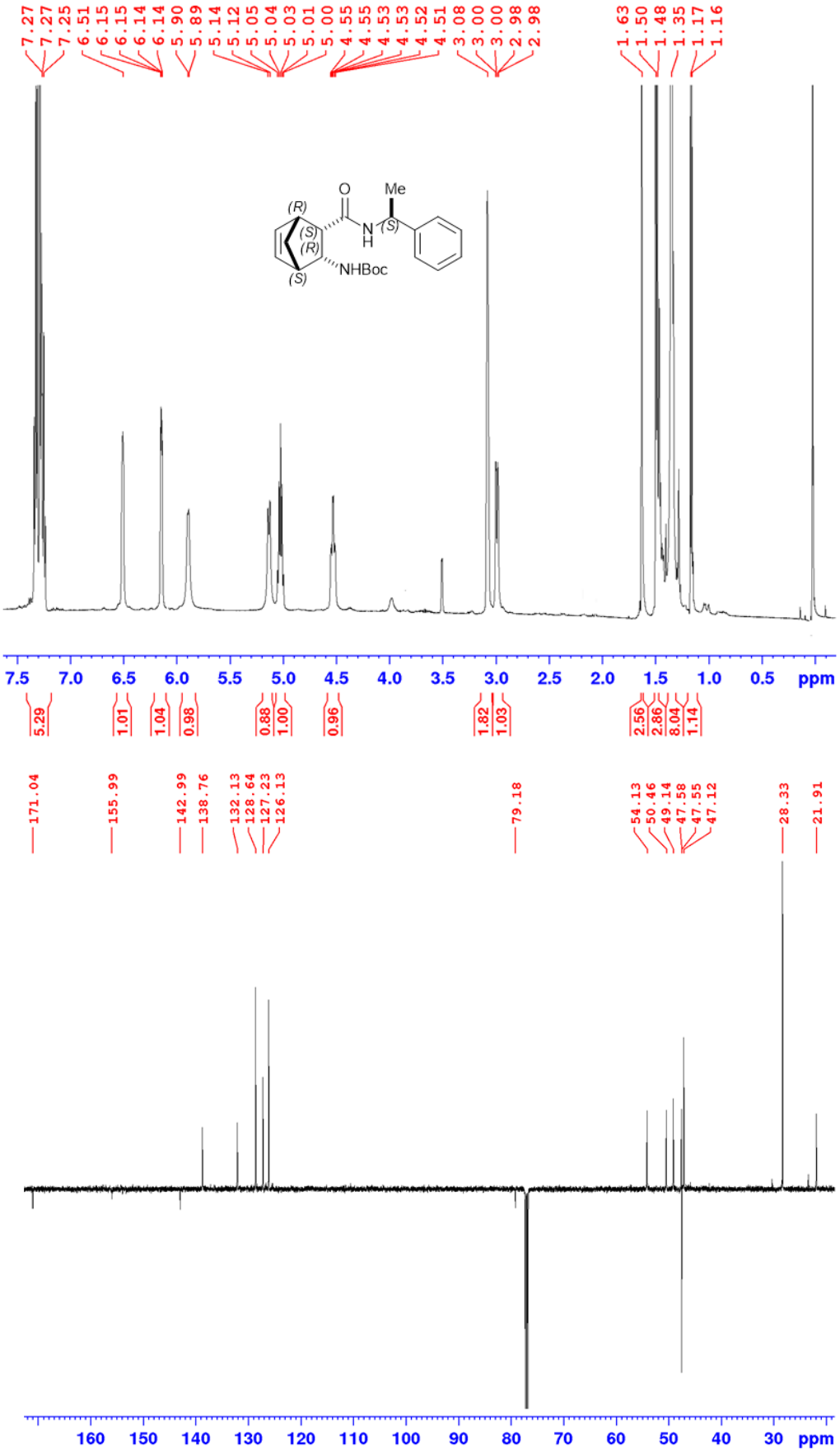
(*S*)-5-bromo-3-hydroxy-3-(2-oxopropyl)indolin-2-one **3h**



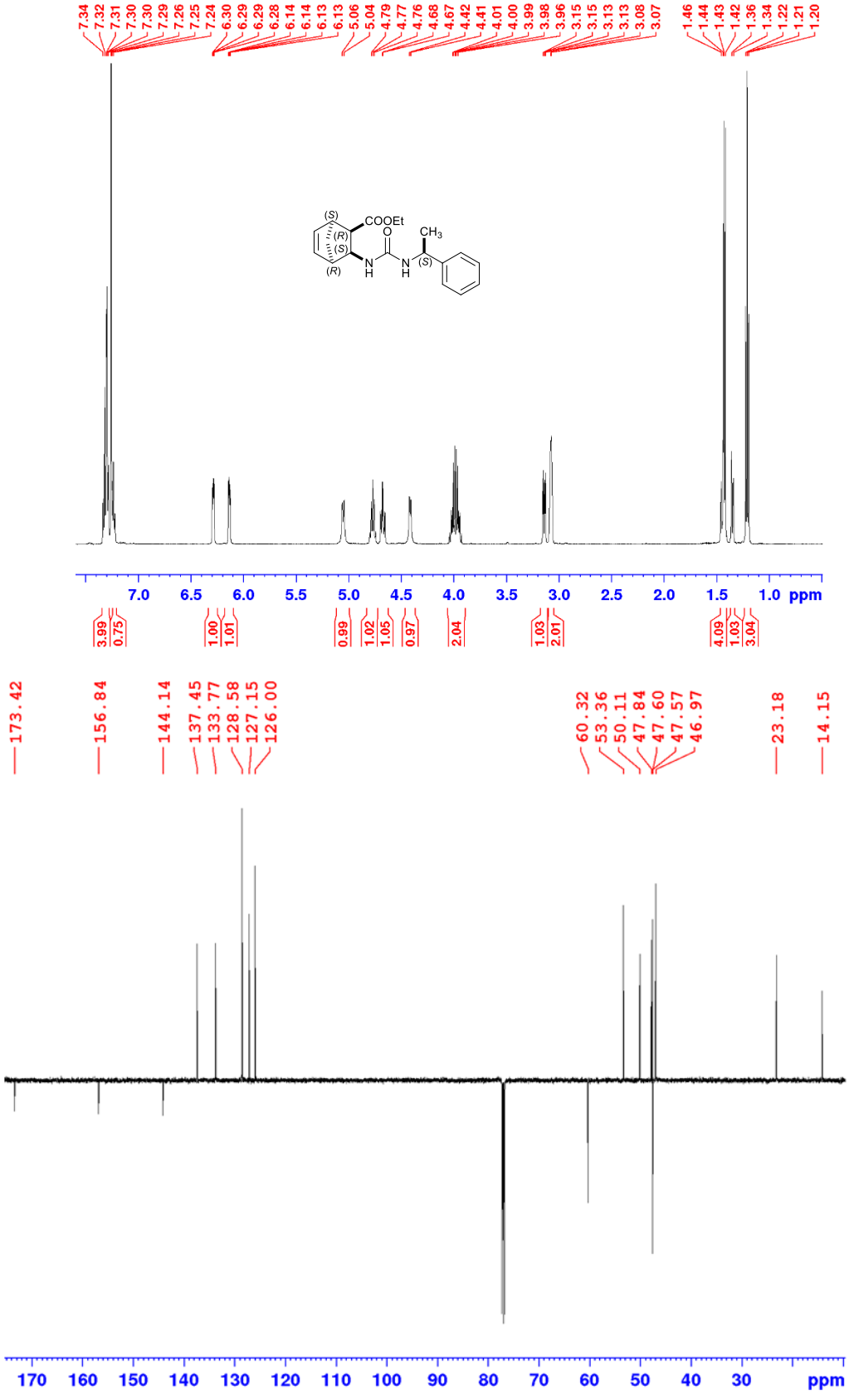
(1*R*,2*S*,3*R*,4*S*)-Ethyl 3-(3-((*S*)-1-phenylethyl)ureido)bicyclo[2.2.1]hept-5-ene-2-carboxylate (–)-**6**



tert-Butyl ((1*S*,2*R*,3*S*,4*R*)-3-(((*S*)-1-phenylethyl)carbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate (–)-**7**

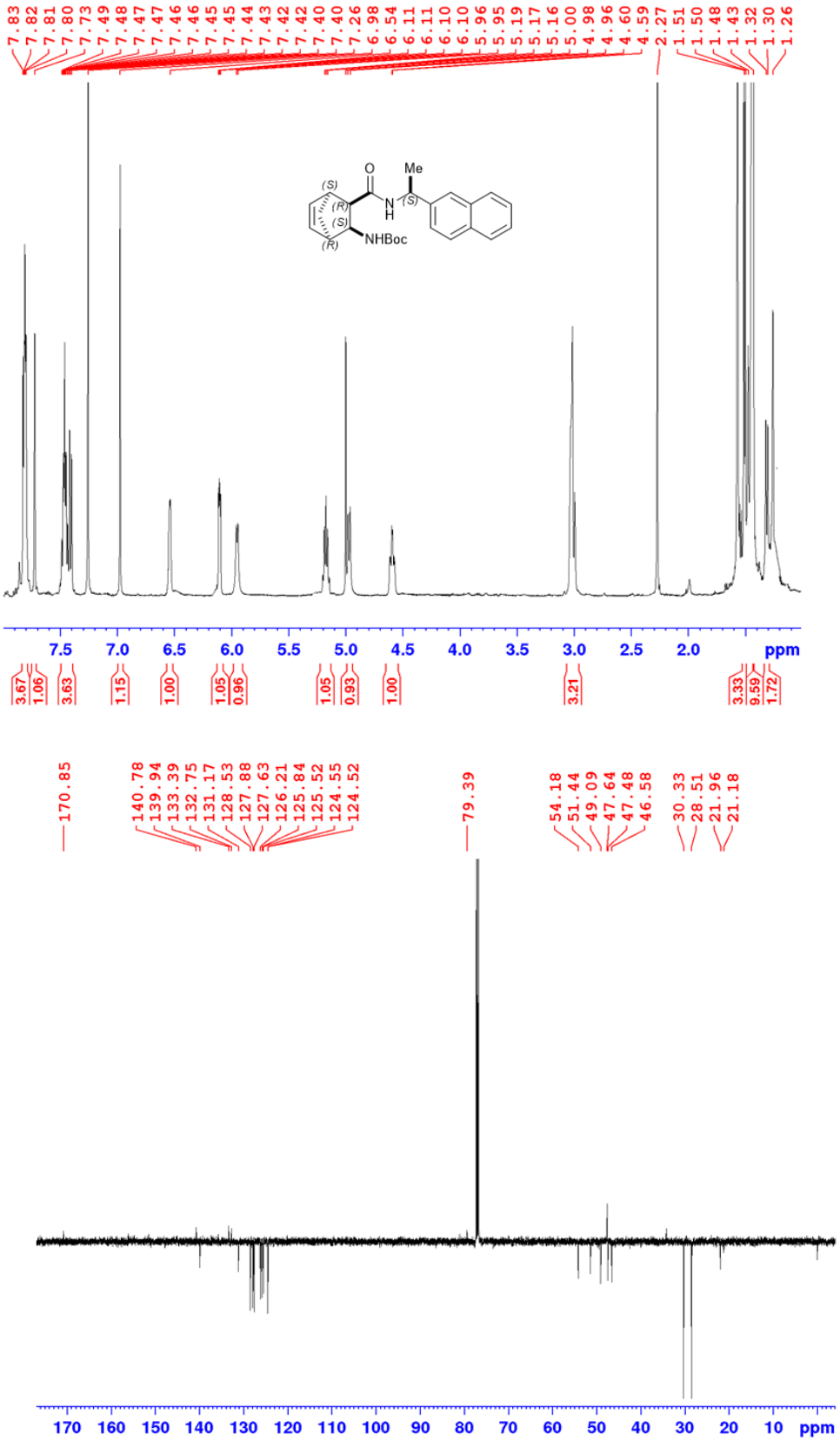


(1*S*,2*R*,3*S*,4*R*)-Ethyl 3-(3-((S)-1-phenylethyl)ureido)bicyclo[2.2.1]hept-5-ene-2-carboxylate (–)-**8**

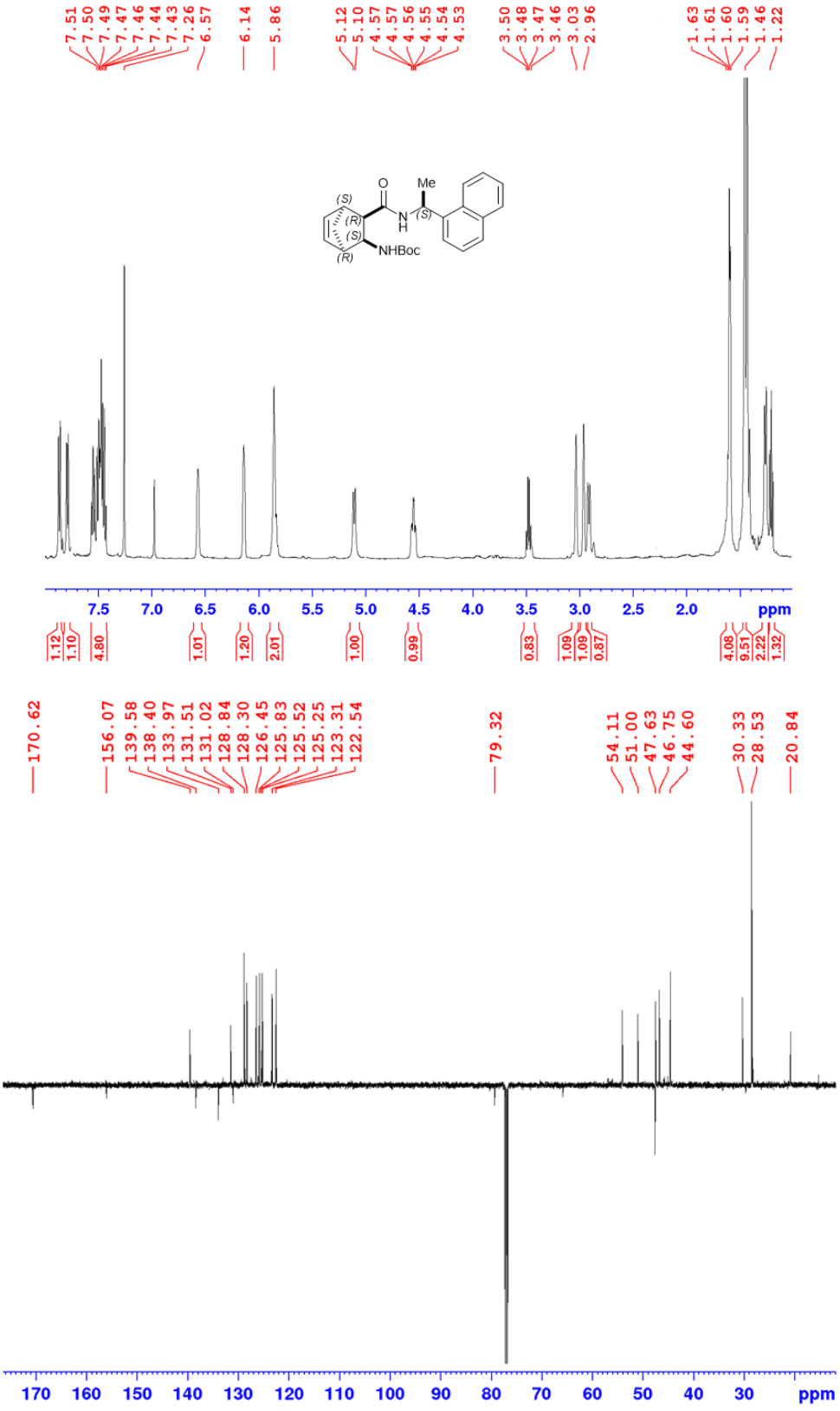


tert-Butyl ((1*R*,2*S*,3*R*,4*S*)-3-(((*S*)-1-(naphthalen-2-yl)ethyl)carbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate

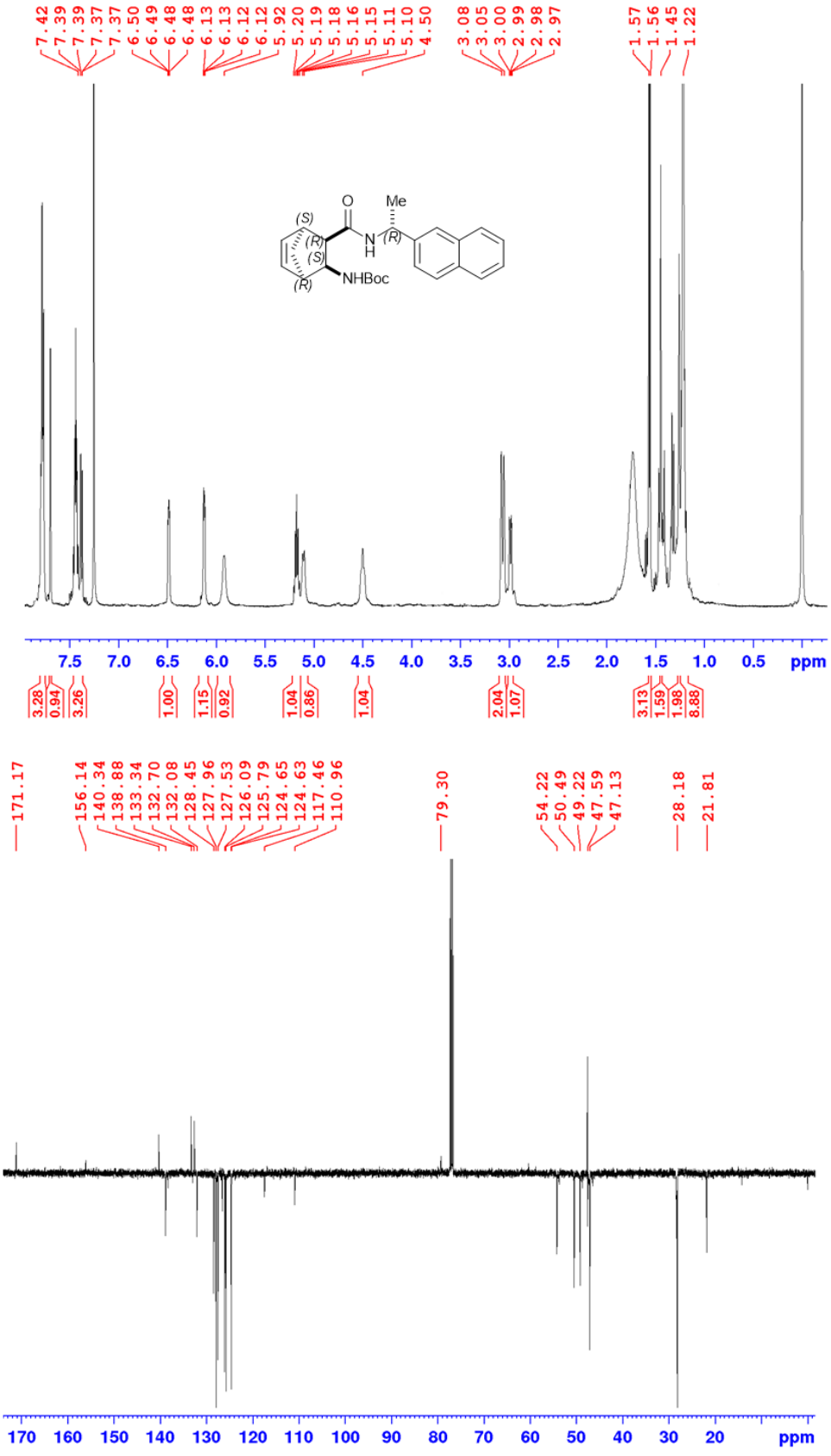
(–)-**9**



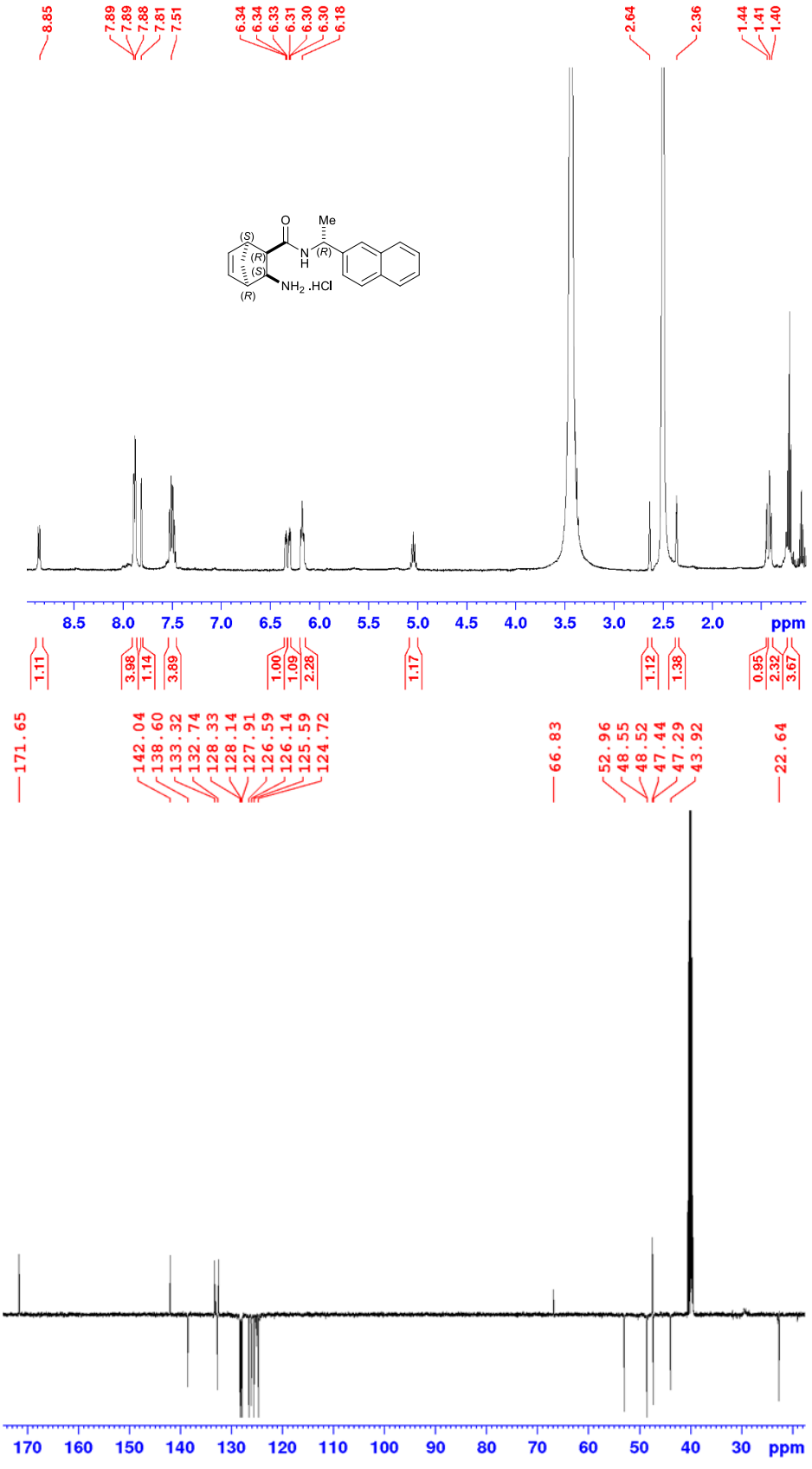
tert-Butyl ((1*R*,2*S*,3*R*,4*S*)-3-(((*S*)-1-(naphthalen-1-yl)ethyl)carbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate (–)-**10**



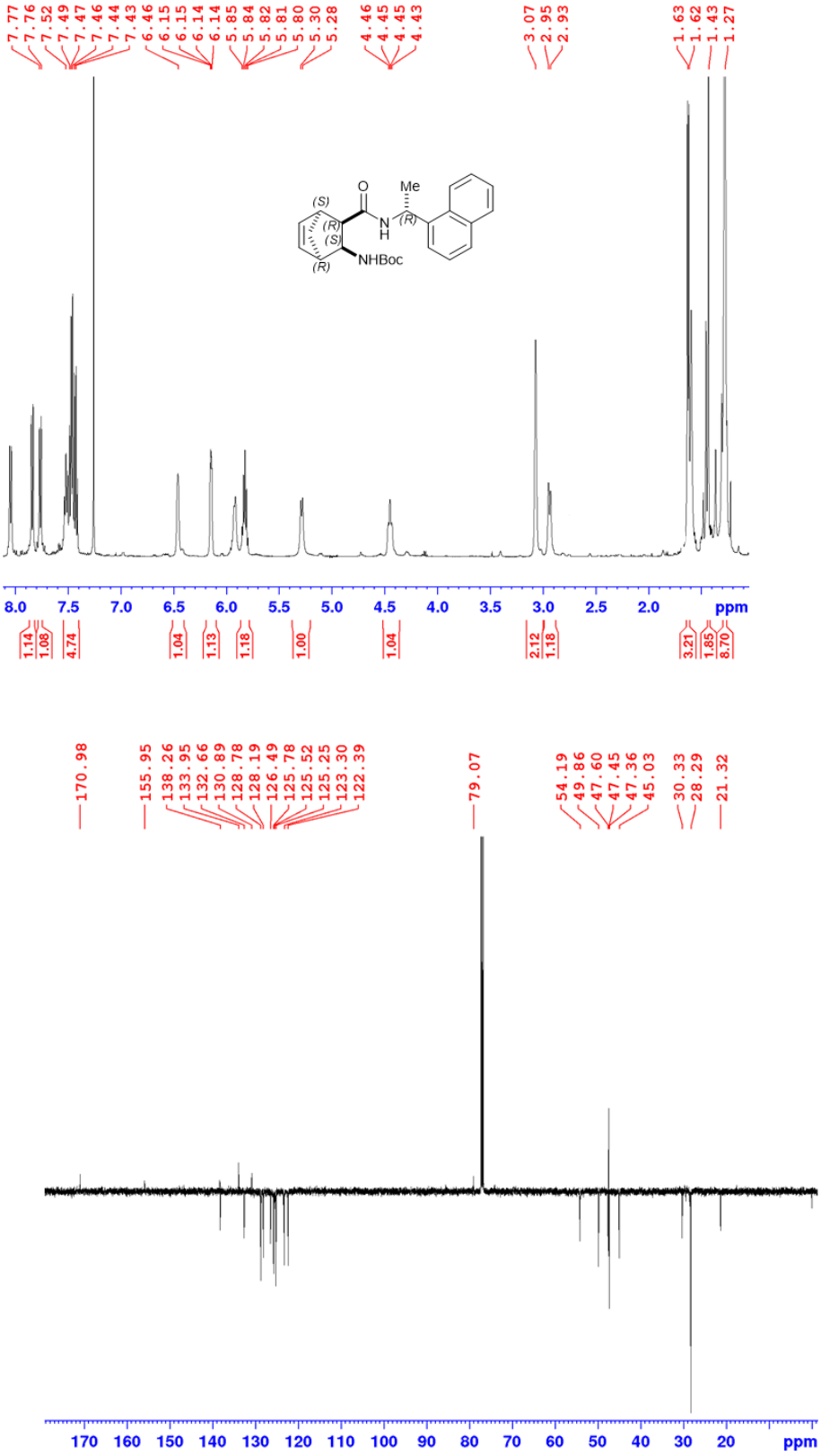
tert-Butyl ((1*R*,2*S*,3*R*,4*S*)-3-(((*R*)-1-(naphthalen-2-yl) ethyl) carbamoyl) bicyclo[2.2.1]hept-5-en-2-yl)carbamate (+)-**11**



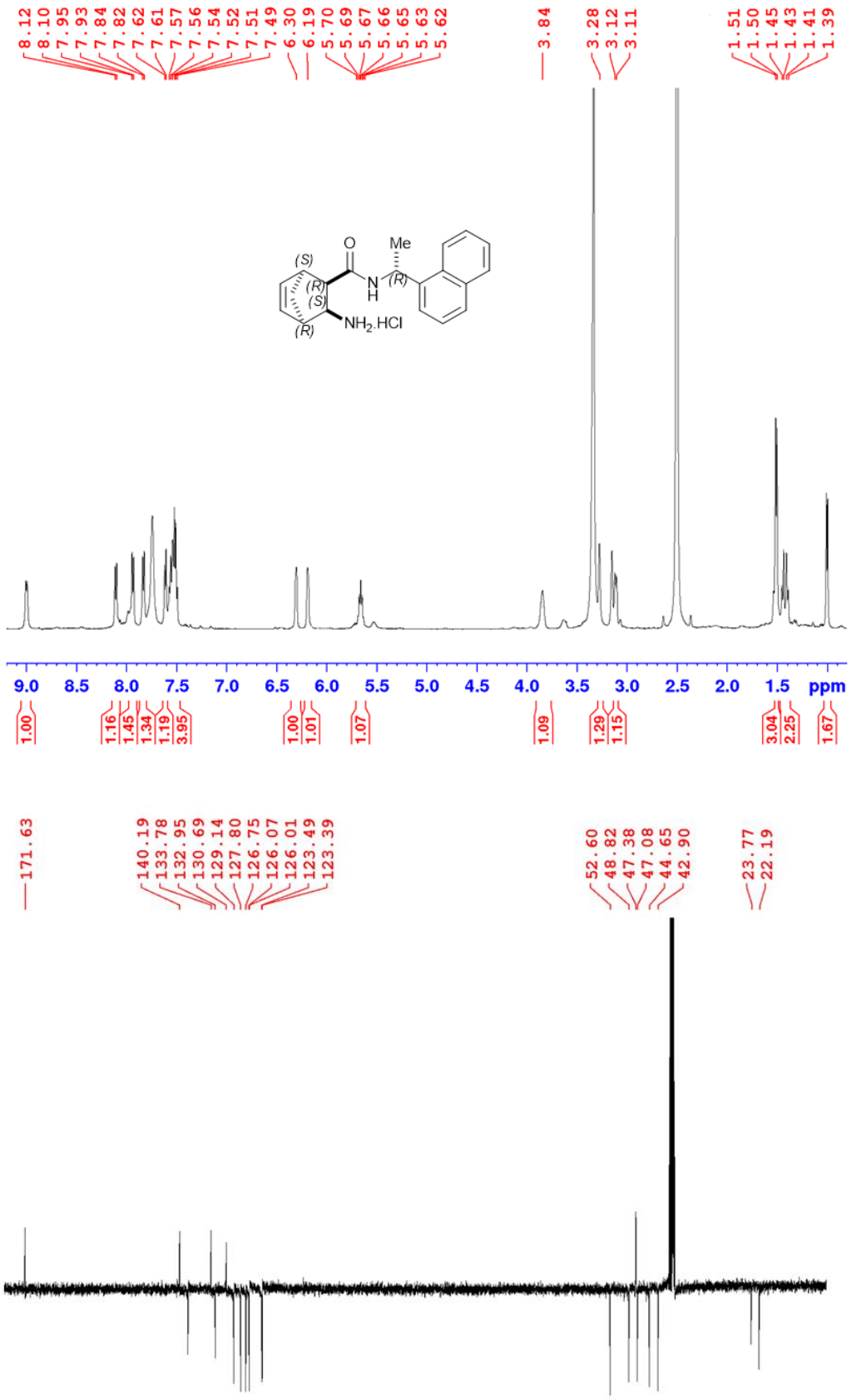
(1*S*,2*R*,3*S*,4*R*)-3-Amino-*N*-((*R*)-1-(naphthalen-2-yl)ethyl)bicyclo[2.2.1]hept-5-ene-2-carboxamide hydrochloride (+)-**12**



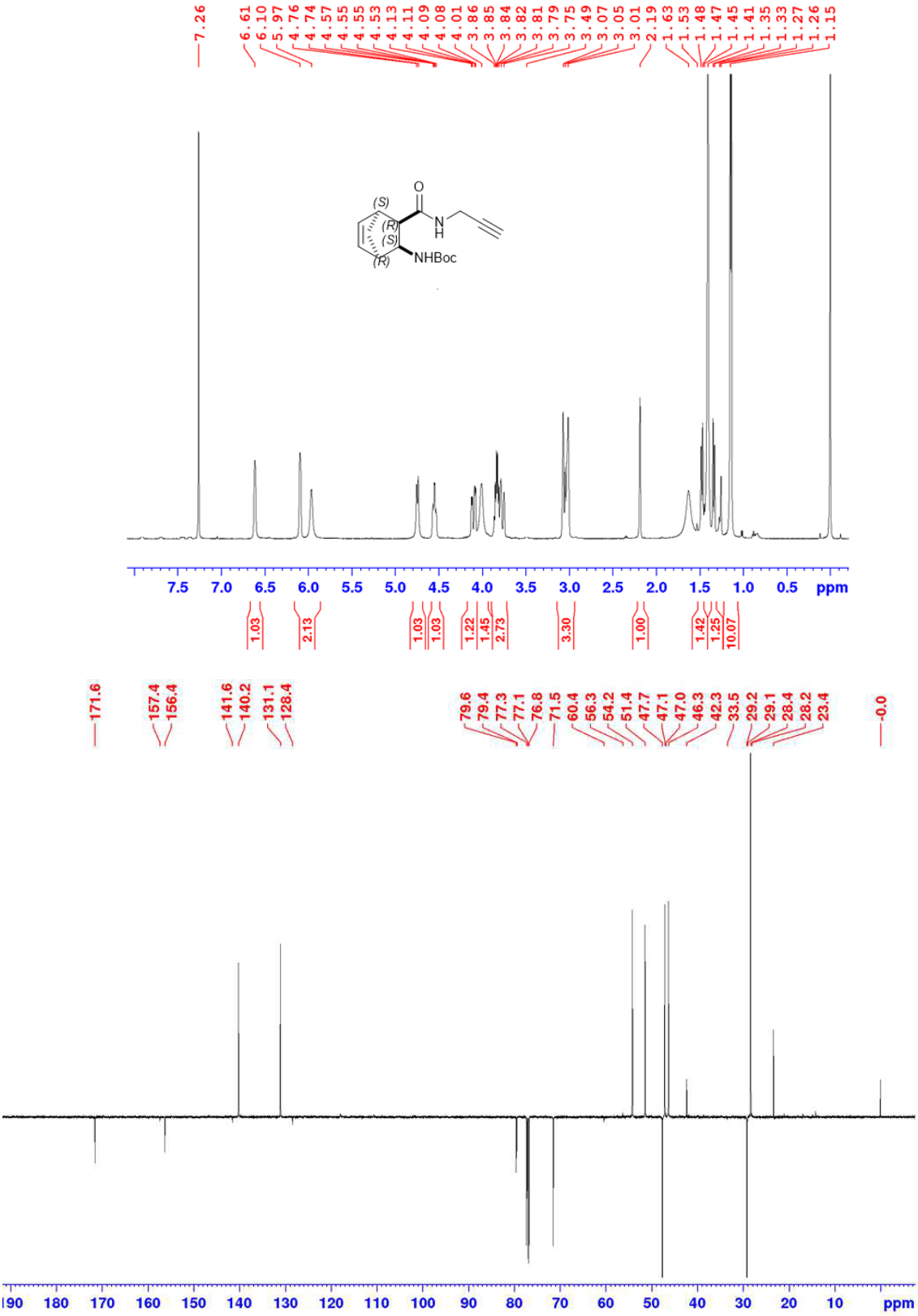
tert-Butyl ((1*R*,2*S*,3*R*,4*S*)-3-(((*R*)-1-(naphthalen-1-yl)ethyl)carbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate (+)-**13**



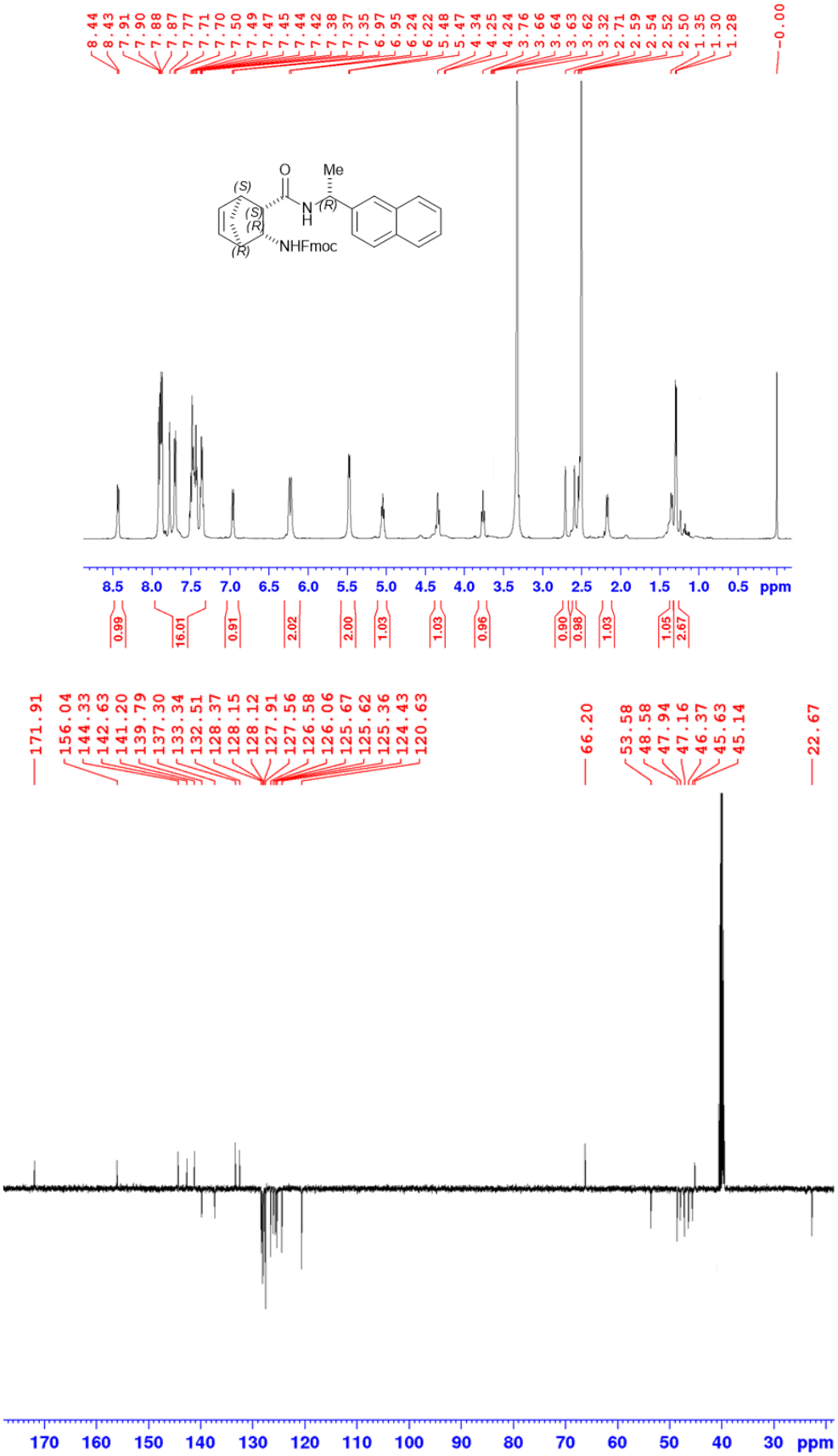
((1*S*,2*R*,3*S*,4*R*)-3-Amino-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)bicyclo[2.2.1]hept-5-ene-2-carboxamide hydrochloride (+)-**14**



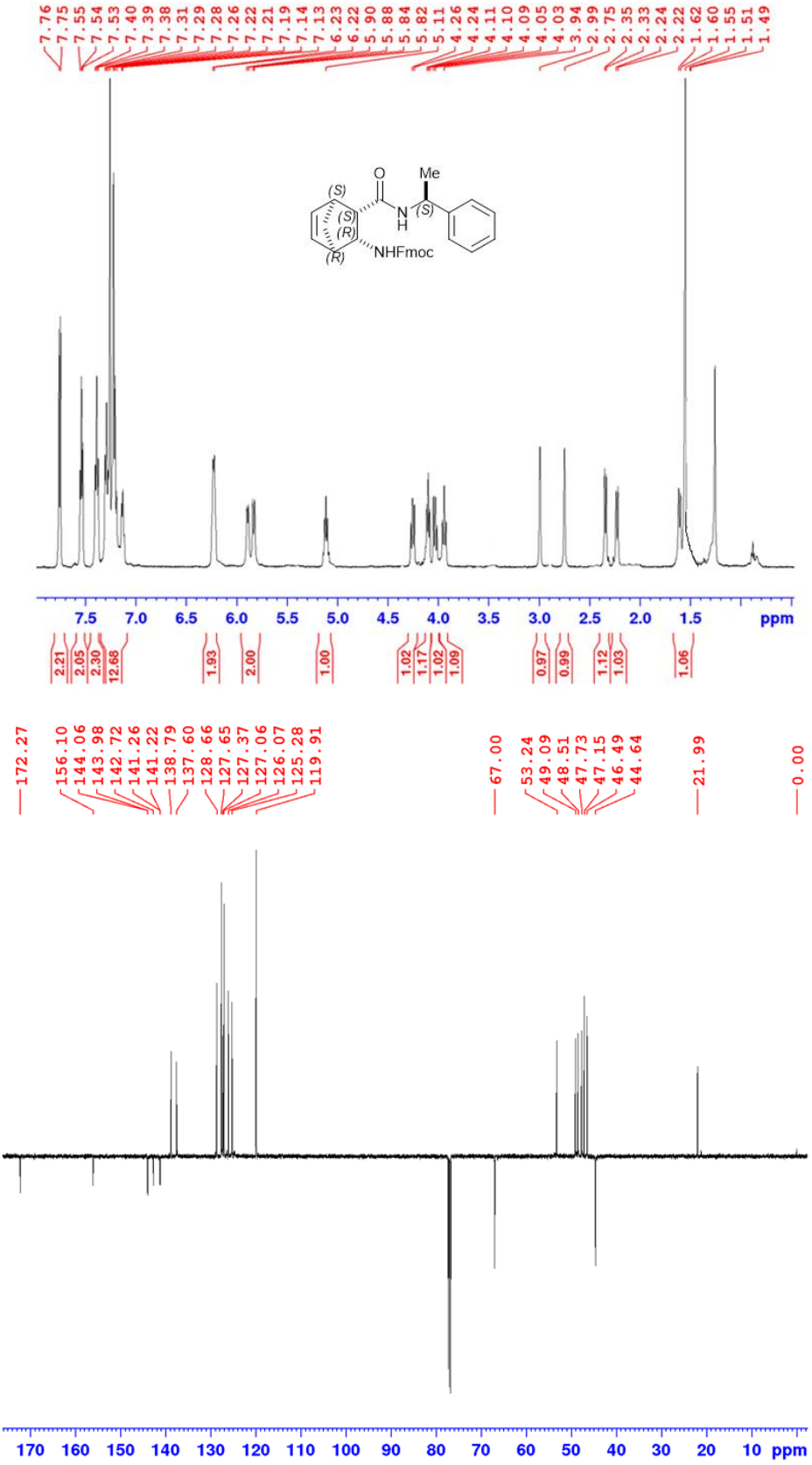
tert-Butyl ((1R,2S,3R,4S)-3-(prop-2-yn-1-ylcarbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate (–)-**15**



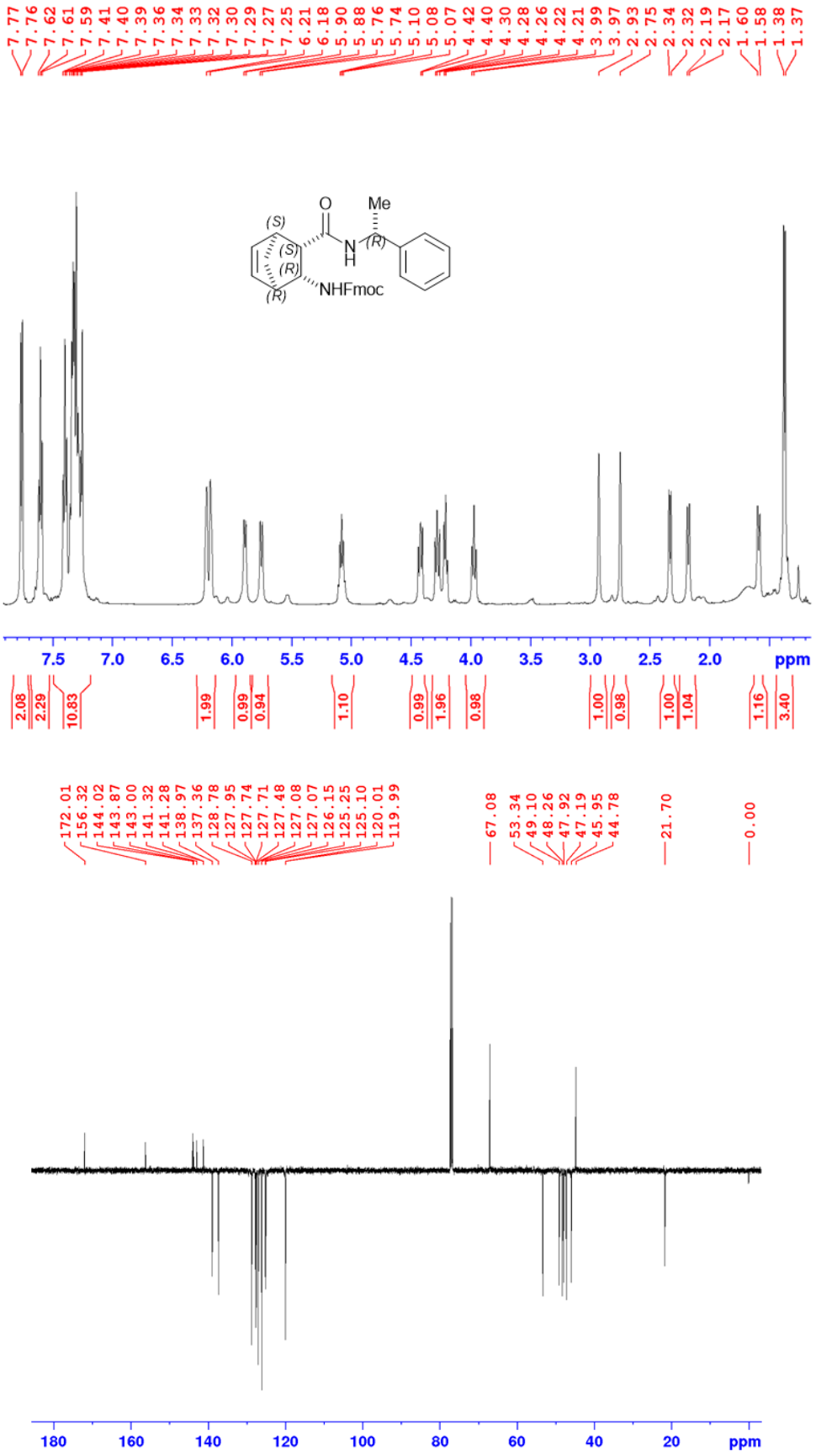
(9*H*-Fluoren-9-yl)methyl ((1*R*,2*R*,3*S*,4*S*)-3-(((*R*)-1-(naphthalen-2-yl)ethyl)carbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate (+)-**18**



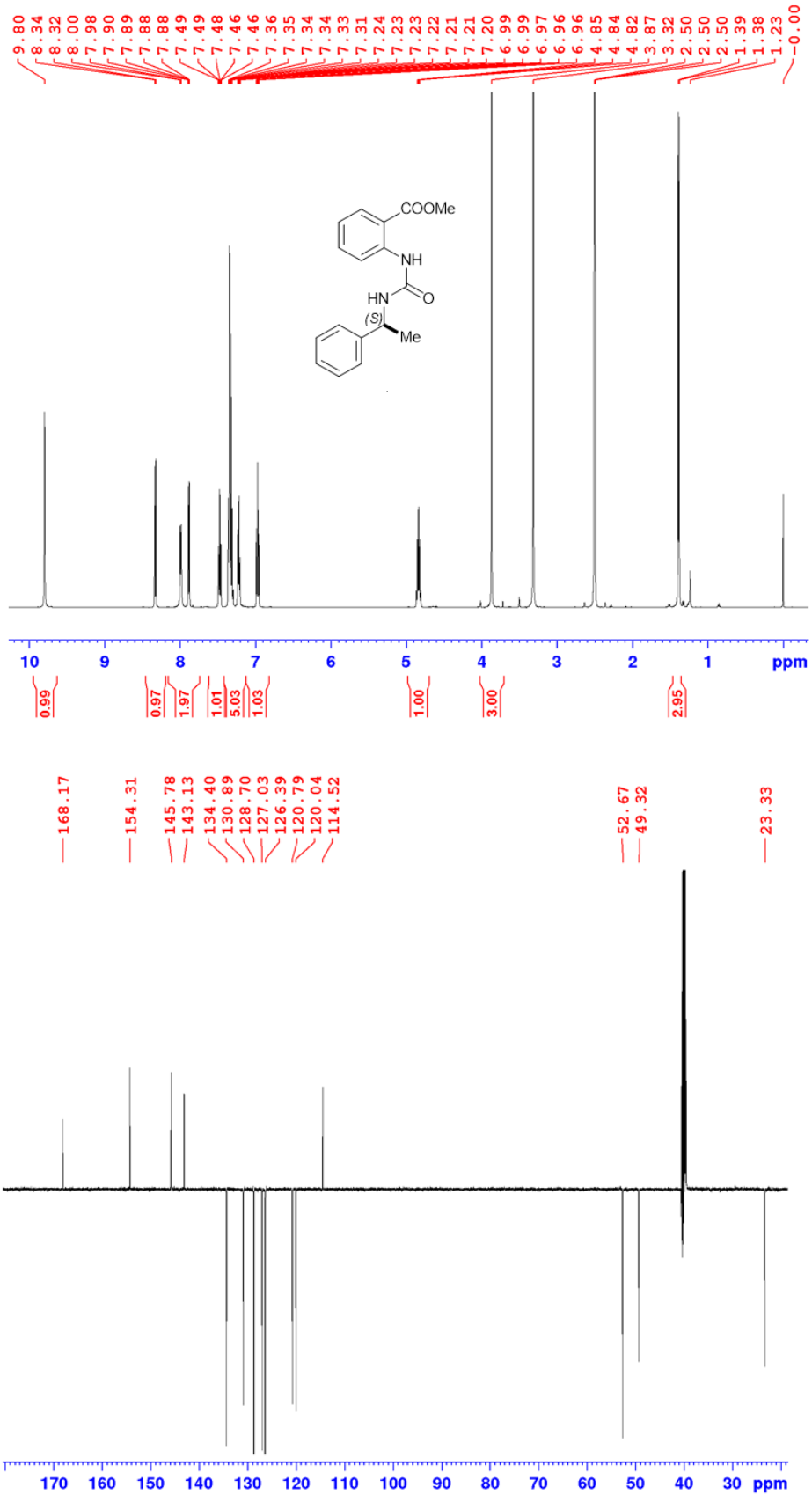
(9*H*-Fluoren-9-yl)methyl ((1*R*,2*R*,3*S*,4*S*)-3-(((*S*)-1-phenylethyl)carbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate (–)-**19**



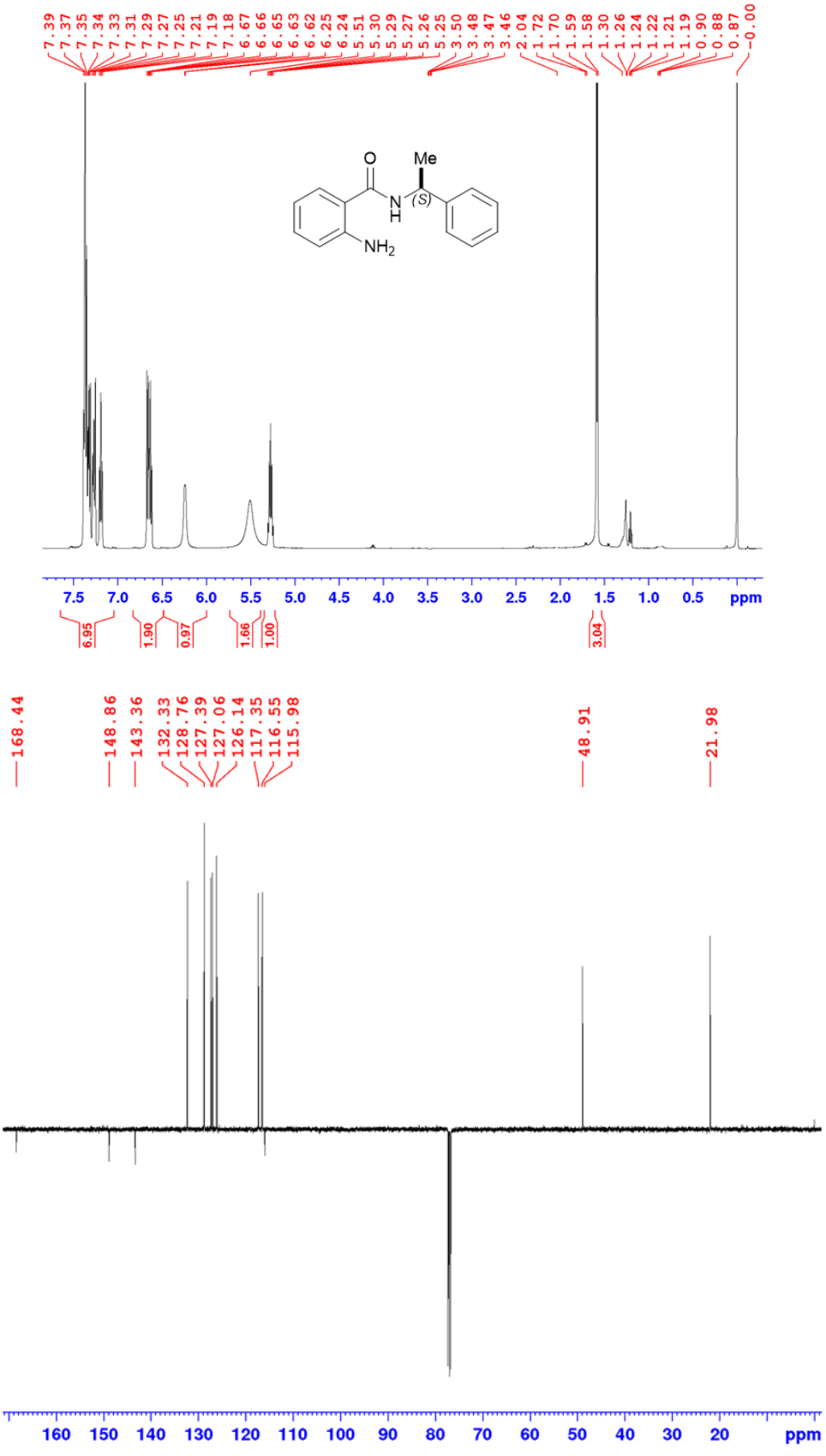
(9*H*-Fluoren-9-yl)methyl ((1*R*,2*R*,3*S*,4*SR*)-3-(((*R*)-1-phenylethyl)carbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate (+)-**20**



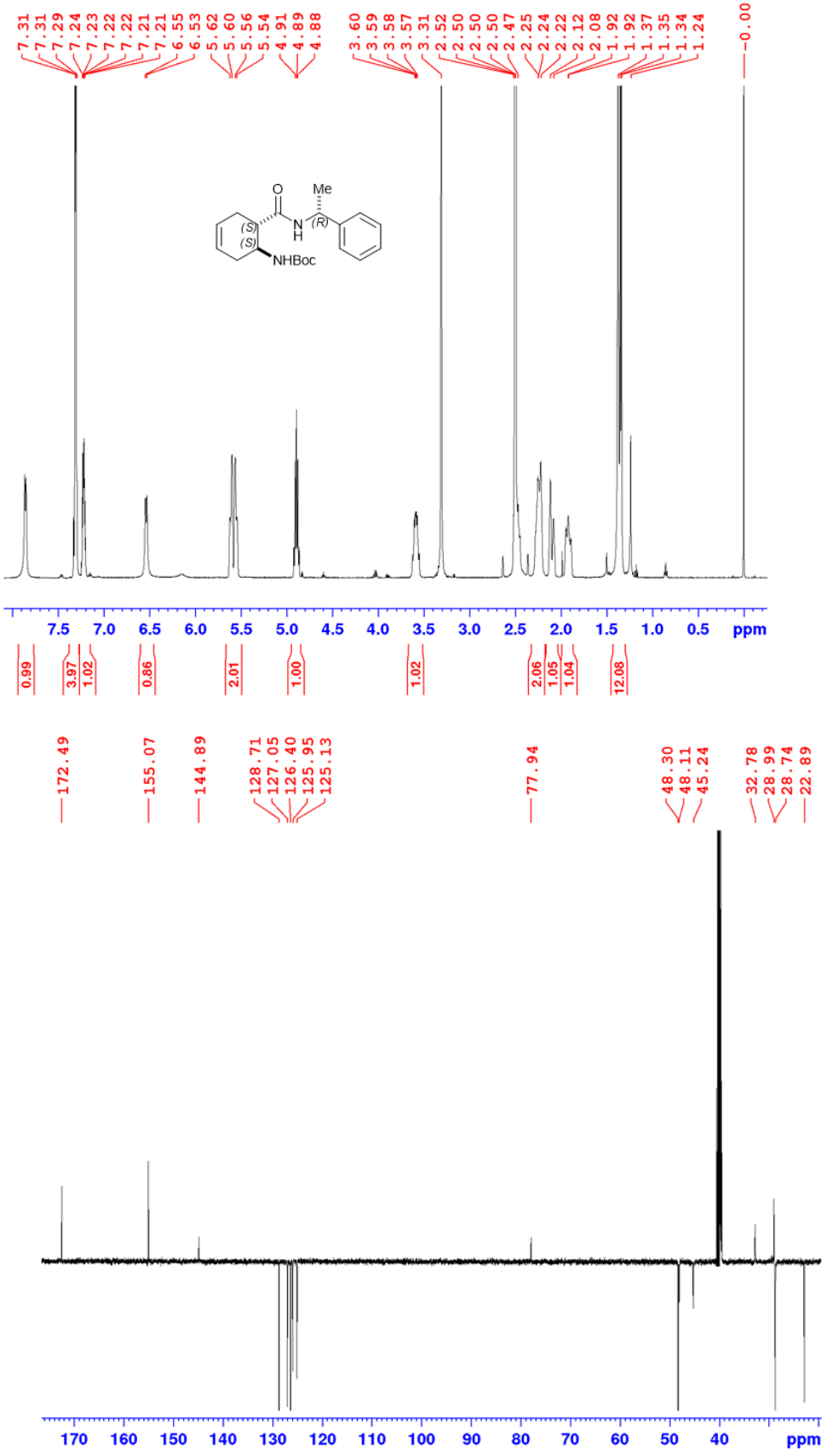
((S)-Methyl 2-(3-(1-phenylethyl)ureido)benzoate) (+)-**22**



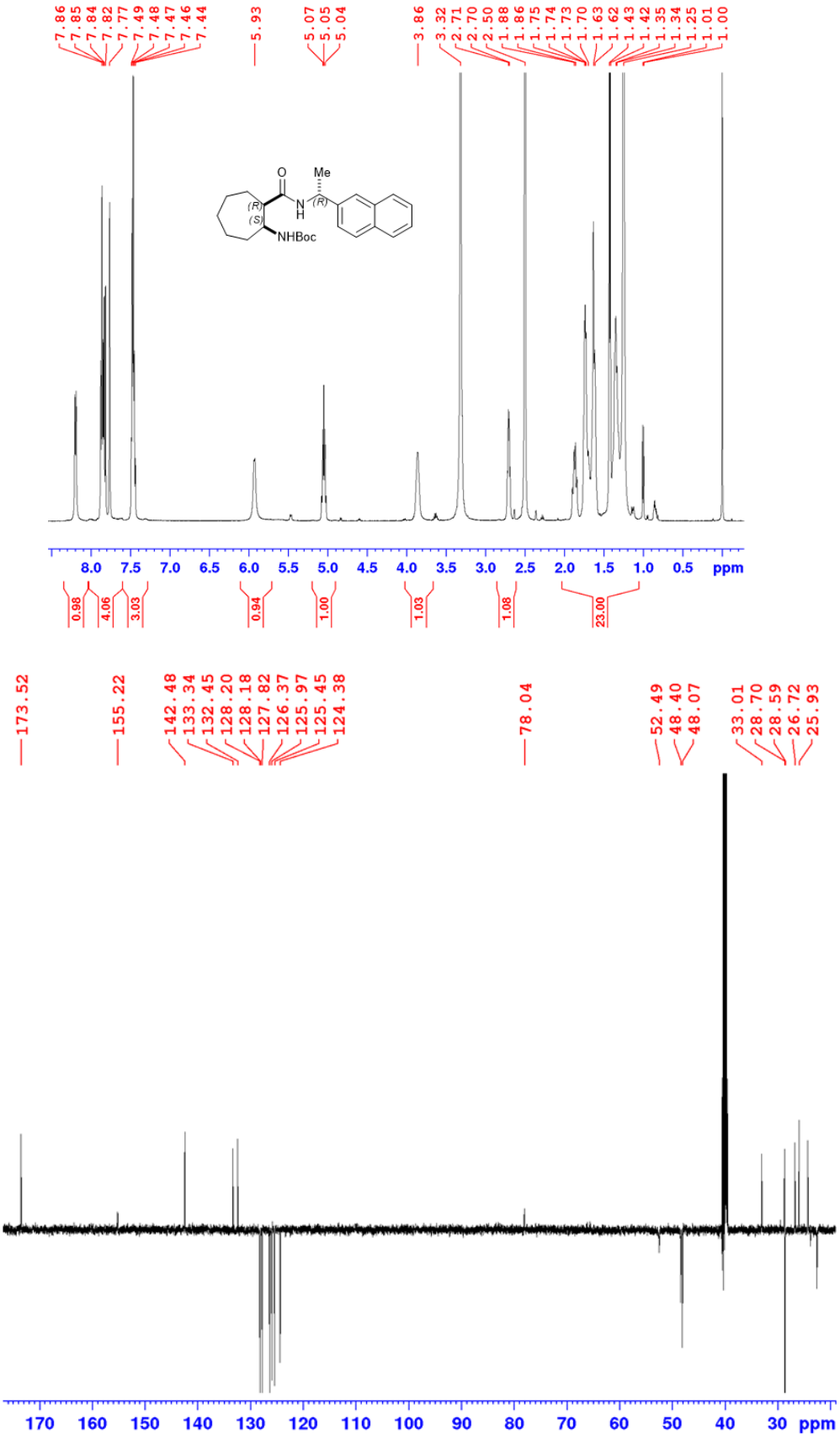
(S)-2-Amino-N-(1-phenylethyl)benzamide (+)-**23**



tert-Butyl ((1*S*,6*S*)-6-(((*R*)-1-phenylethyl)carbamoyl)cyclohex-3-en-1-yl)carbamate (+)-**24**

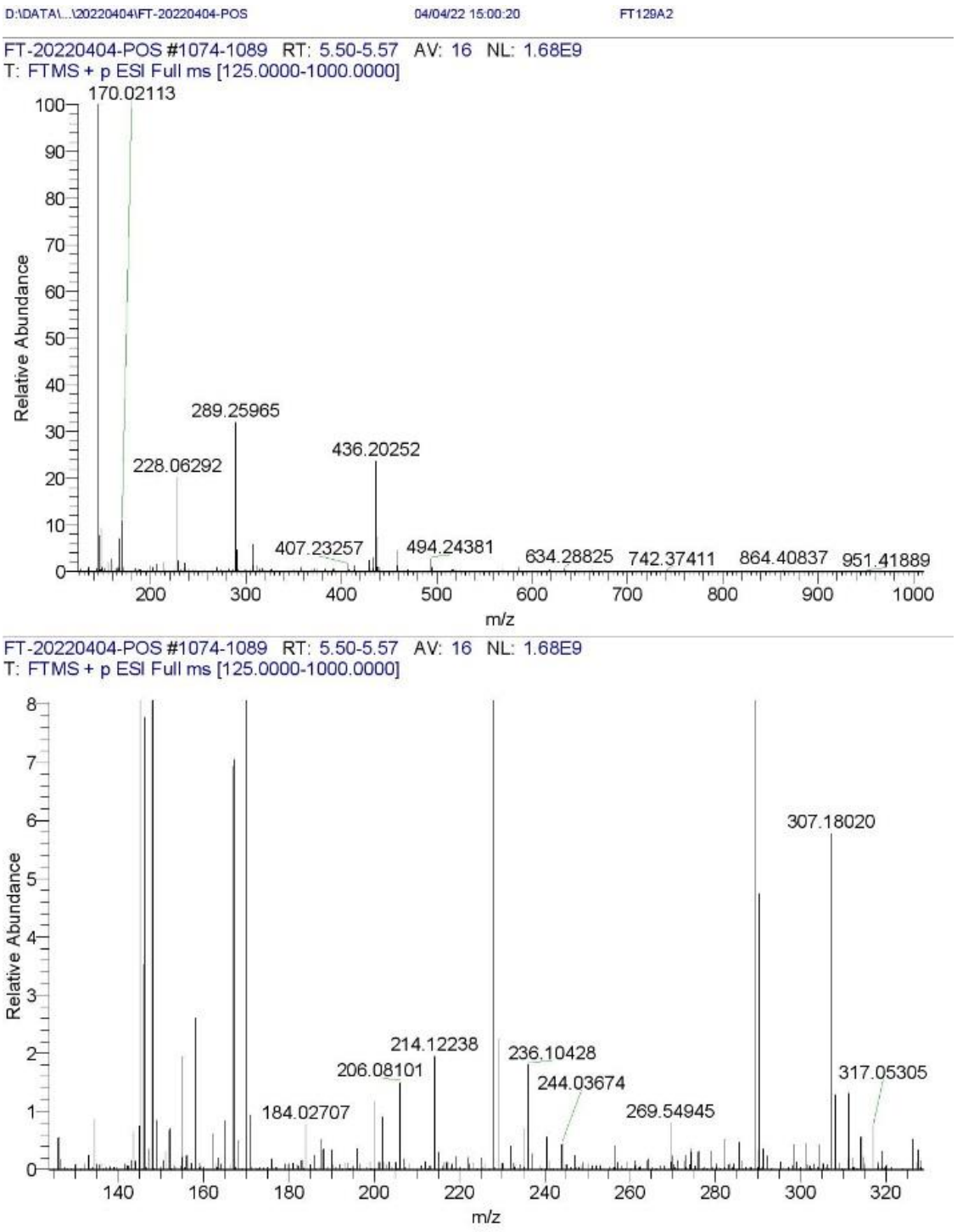


tert-Butyl ((1*S*,2*R*)-2-(((*R*)-1-(naphthalen-2-yl)ethyl)carbamoyl)cycloheptyl)carbamate (+)-**25**

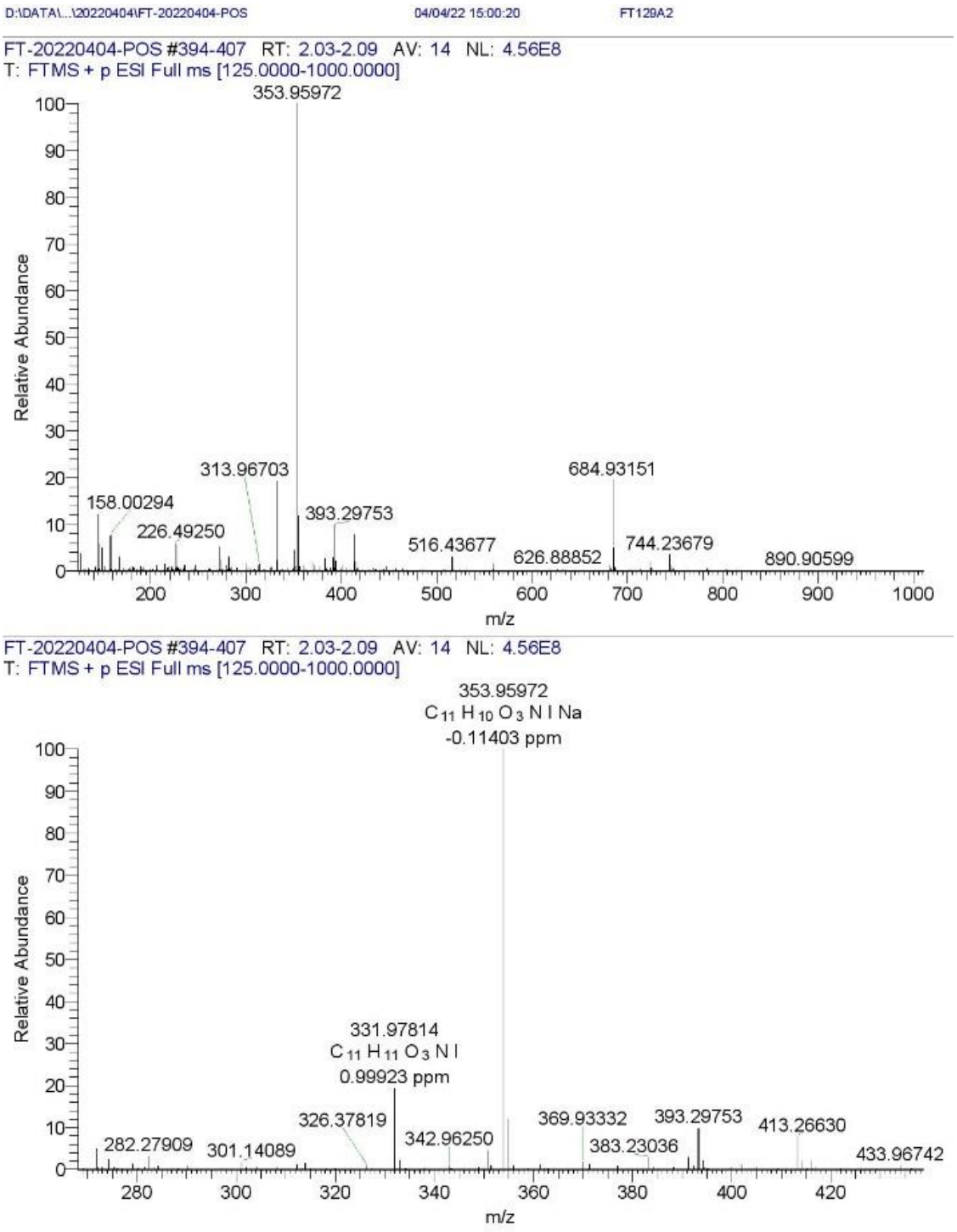


4. Copies of HRMS-ESI Spectra of 3a-25

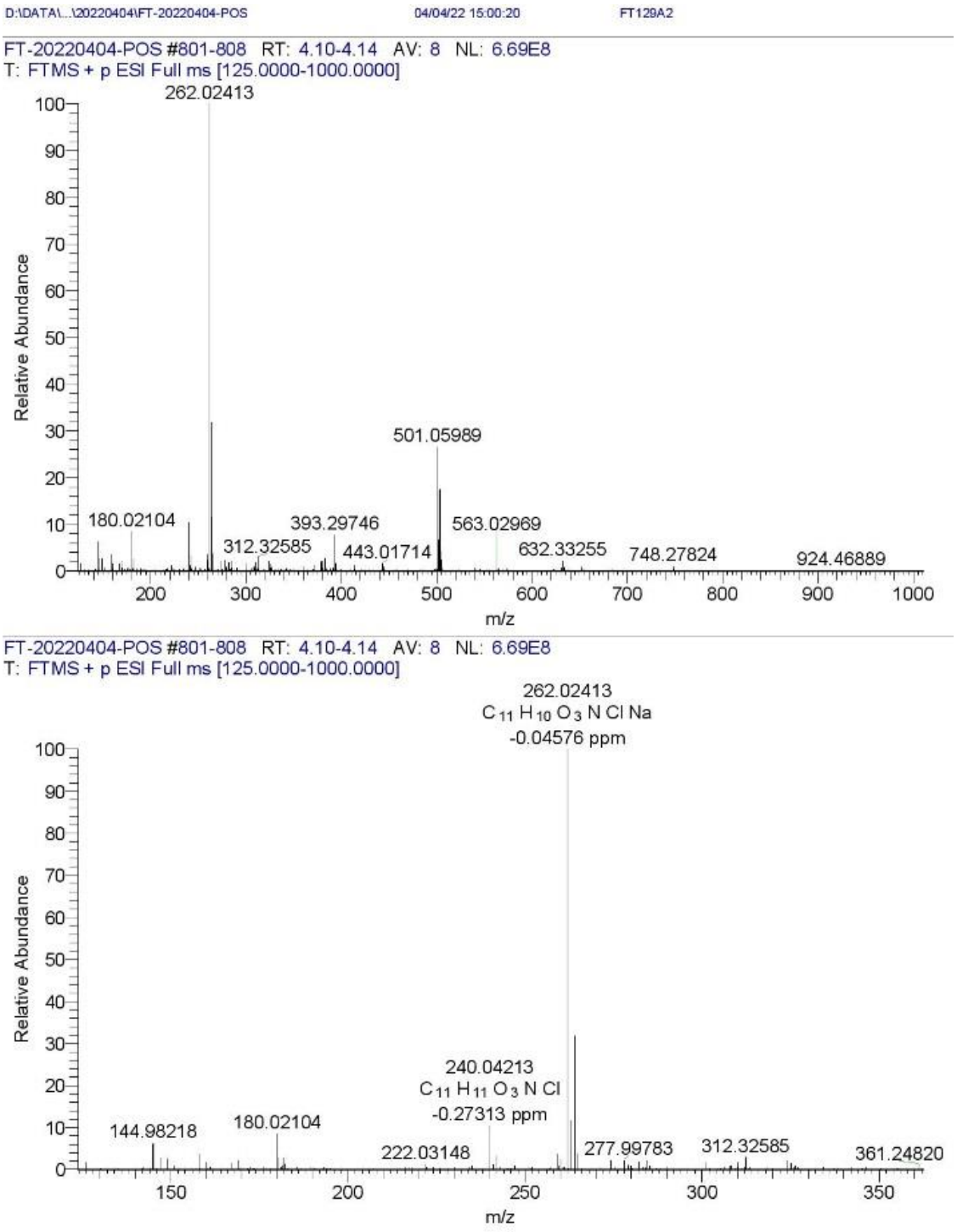
(*S*)-3-Hydroxy-3-(2-oxopropyl)indolin-2-one **3a**



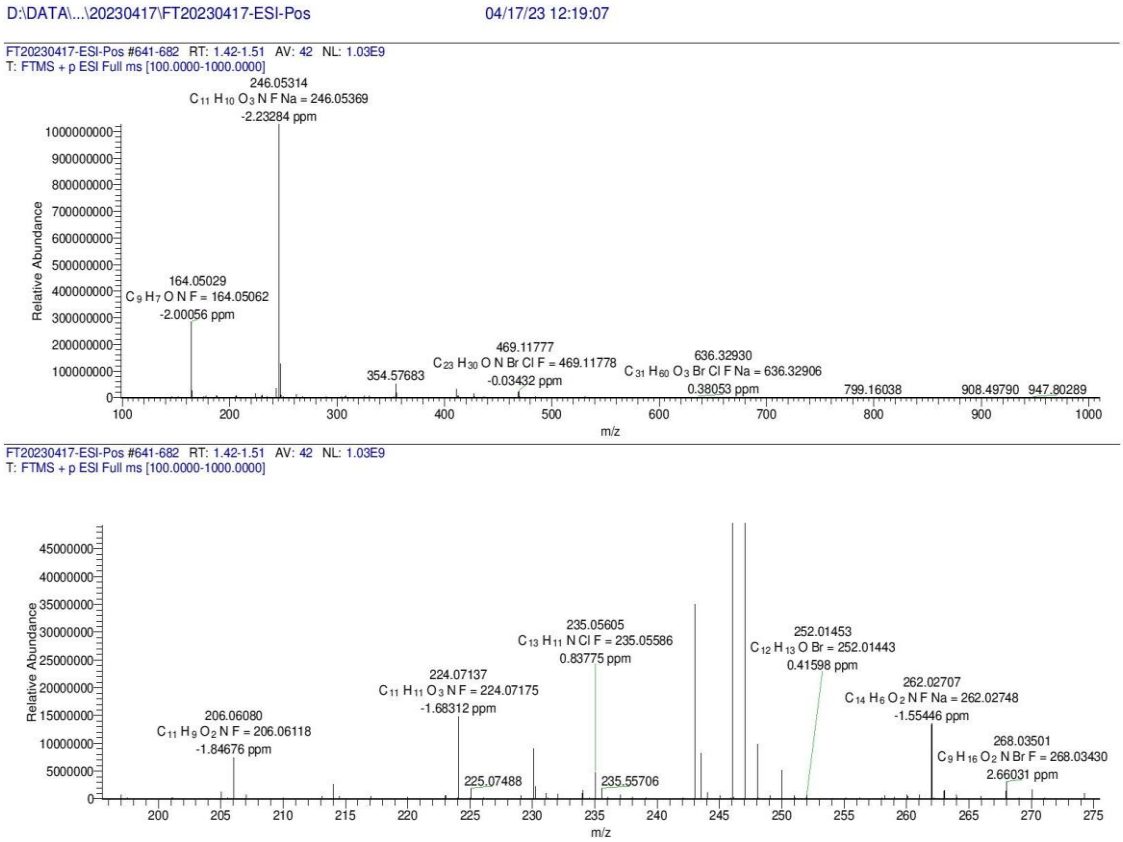
(*S*)-3-Hydroxy-5-iodo-3-(2-oxopropyl)indolin-2-one **3b**



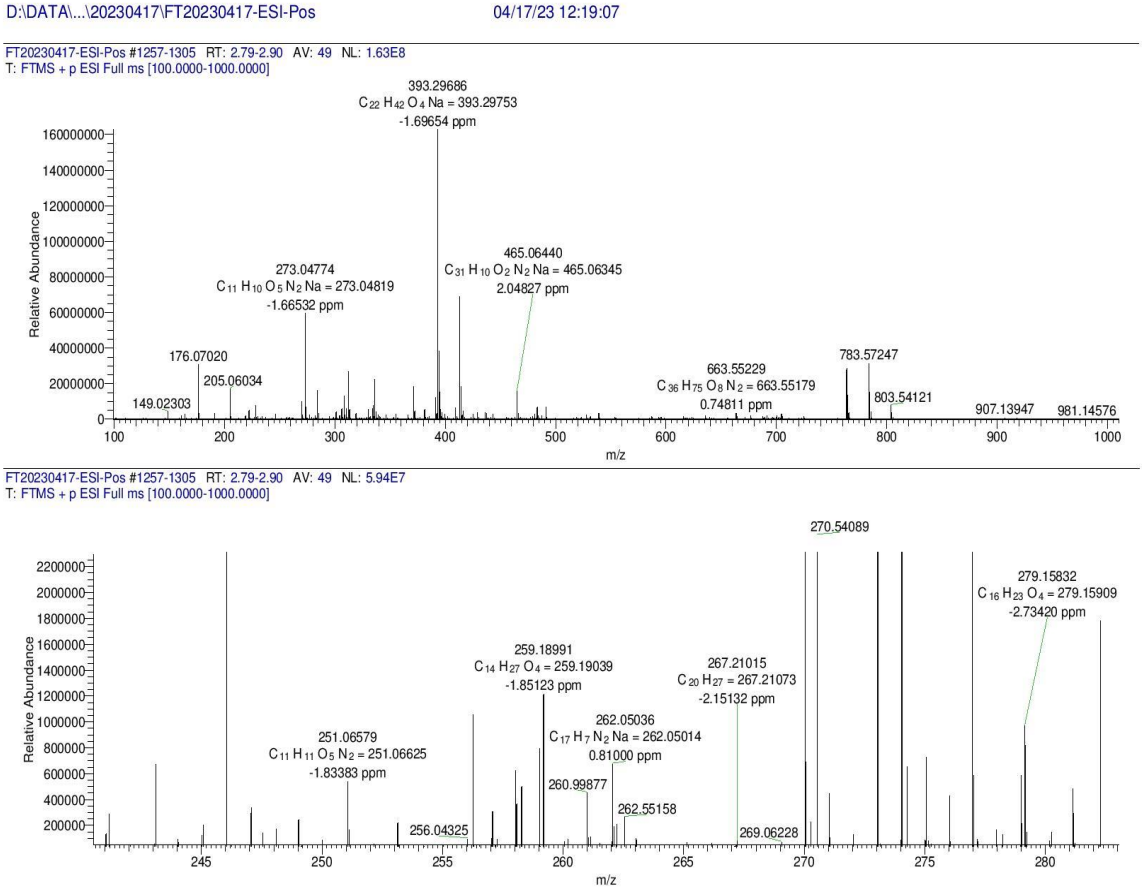
(*S*)-7-Chloro-3-hydroxy-3-(2-oxopropyl)indolin-2-one **3c**



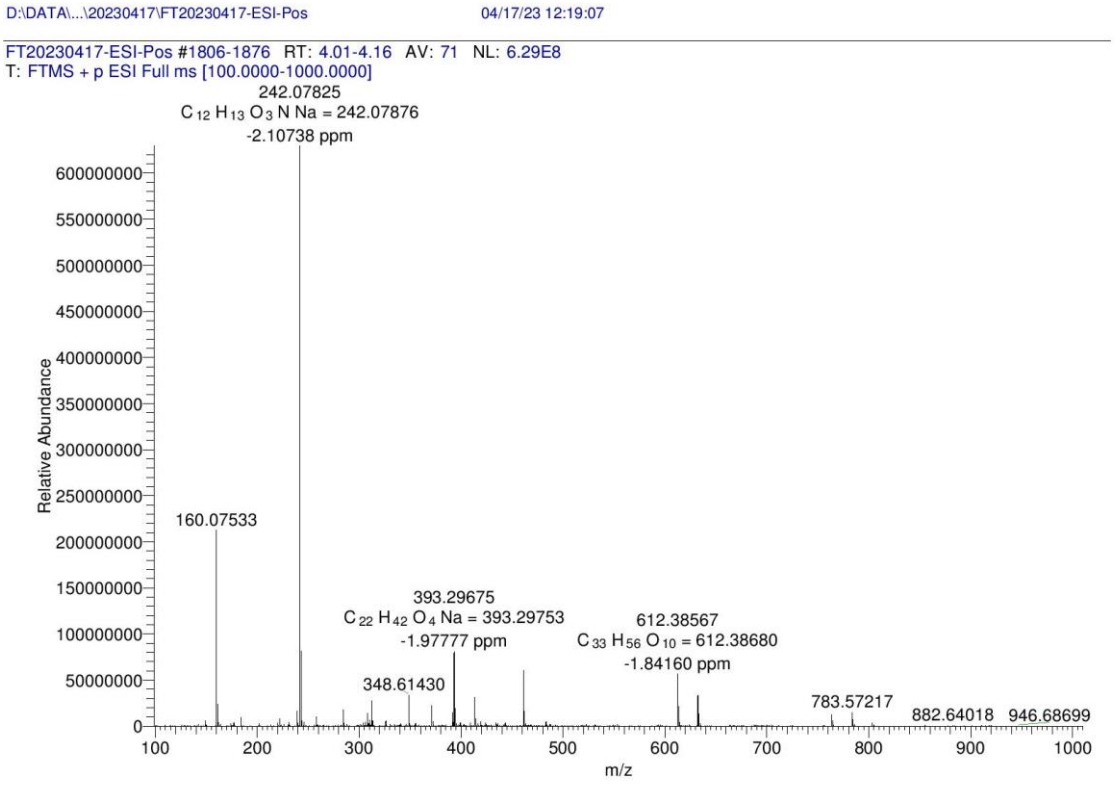
(*S*)-5-fluoro-3-hydroxy-3-(2-oxopropyl)indolin-2-one **3d**



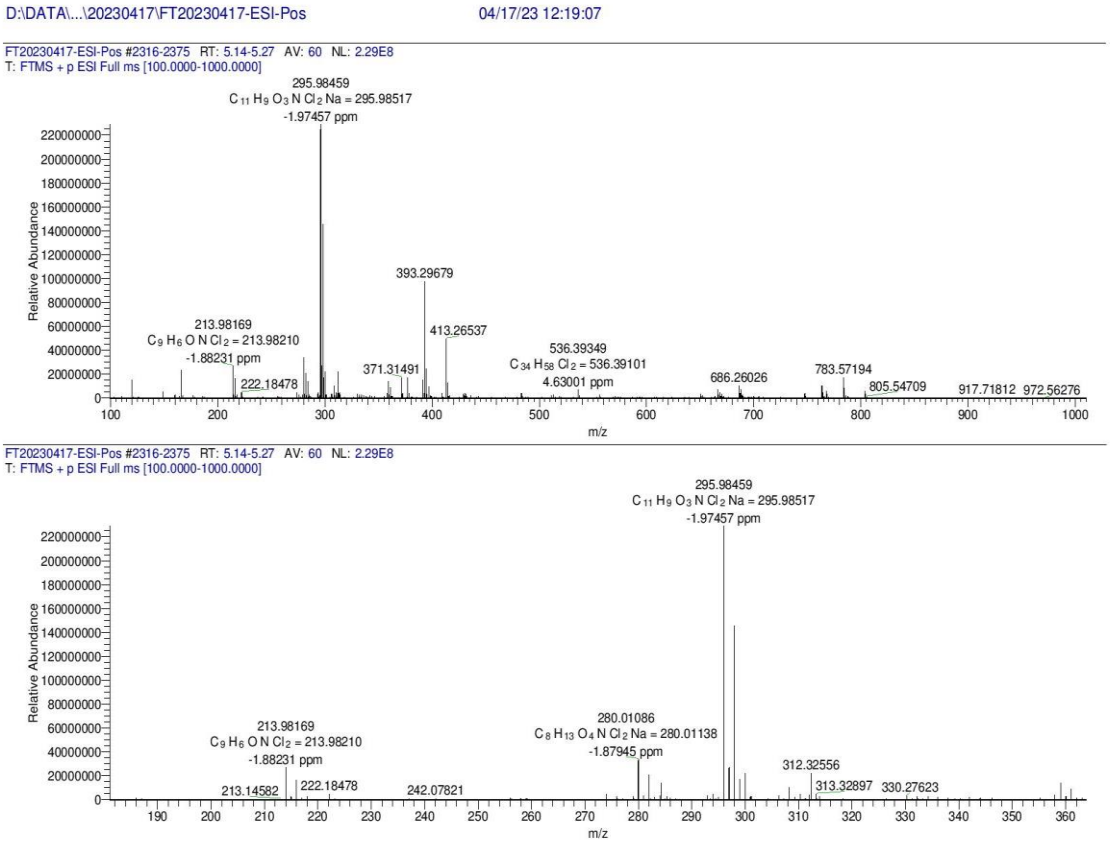
(*S*)-3-hydroxy-5-nitro-3-(2-oxopropyl)indolin-2-one **3e**



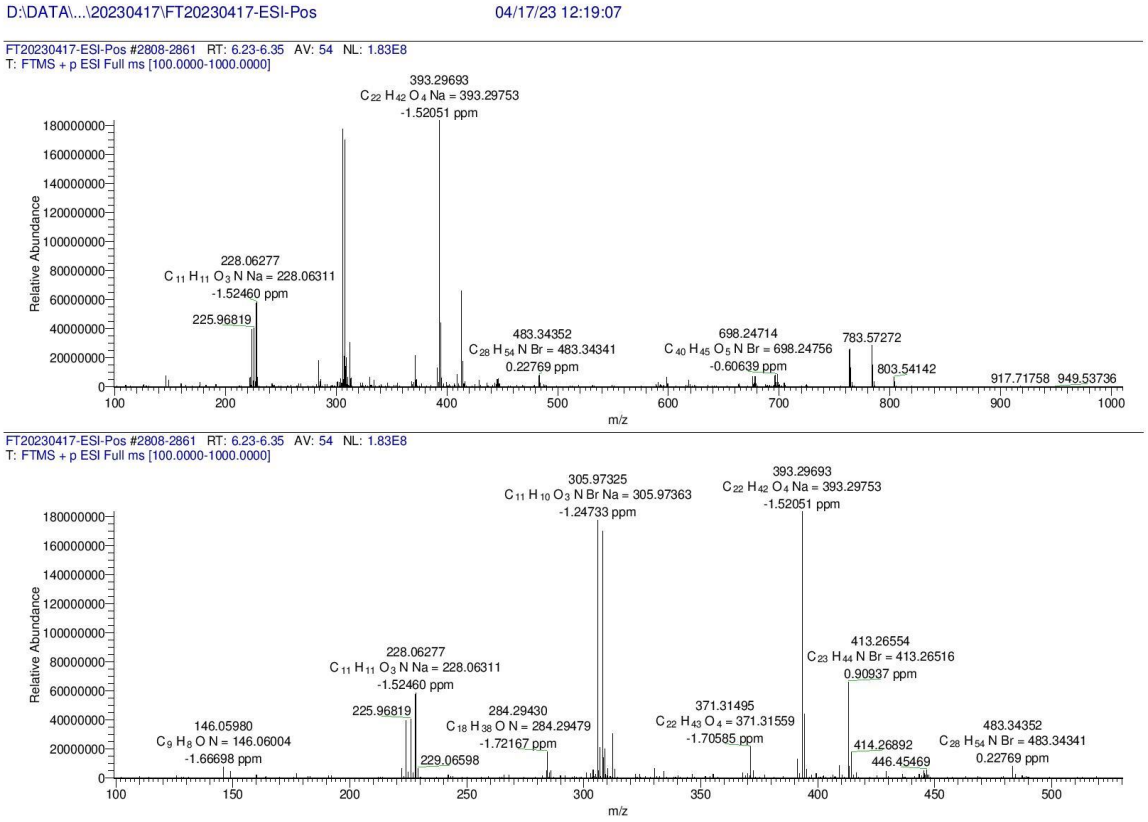
(*S*)-3-hydroxy-5-methyl-3-(2-oxopropyl)indolin-2-one **3f**



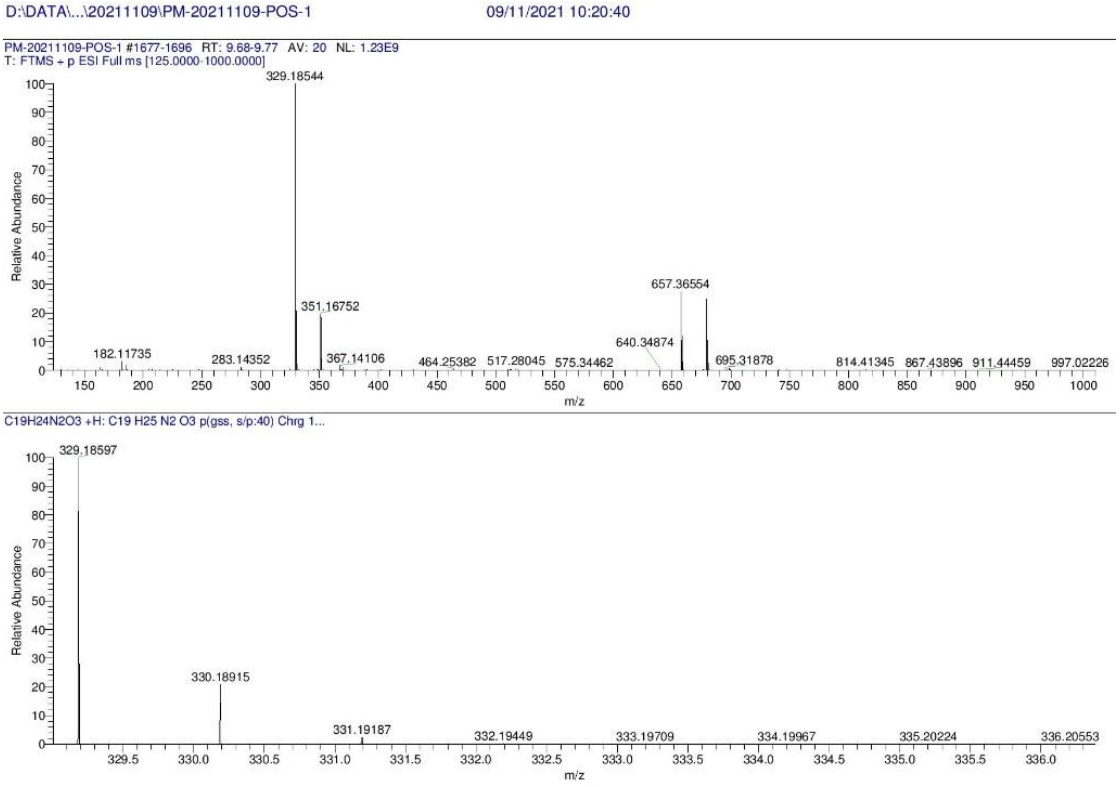
(*S*)-4,7-dichloro-3-hydroxy-3-(2-oxopropyl)indolin-2-one **3g**



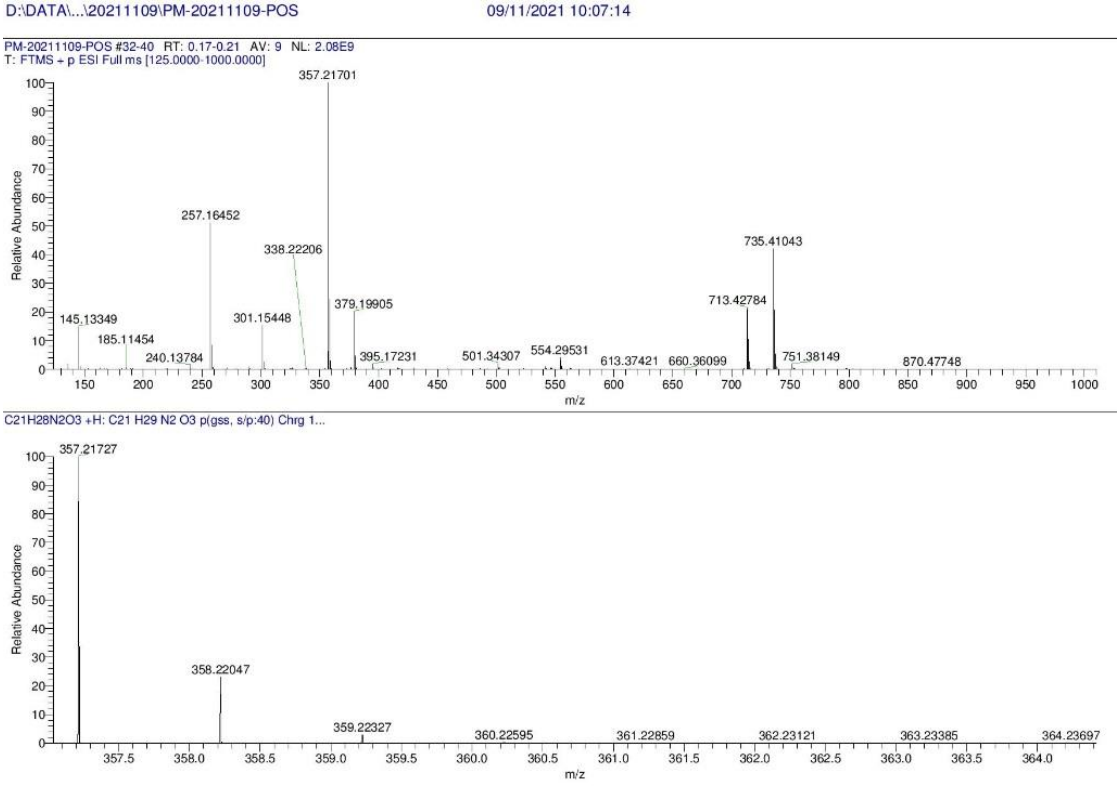
(*S*)-5-bromo-3-hydroxy-3-(2-oxopropyl)indolin-2-one **3h**



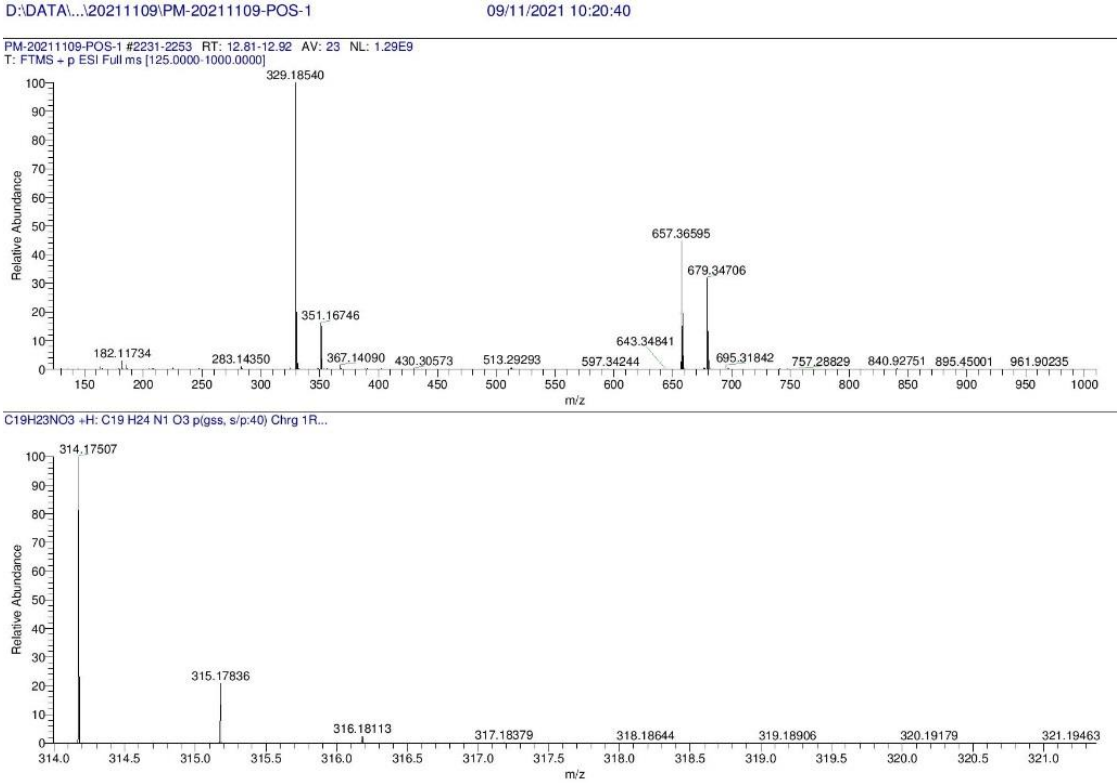
(1*R*,2*S*,3*R*,4*S*)-Ethyl 3-(3-((*S*)-1-phenylethyl)ureido)bicyclo[2.2.1]hept-5-ene-2-carboxylate (–)-**6**



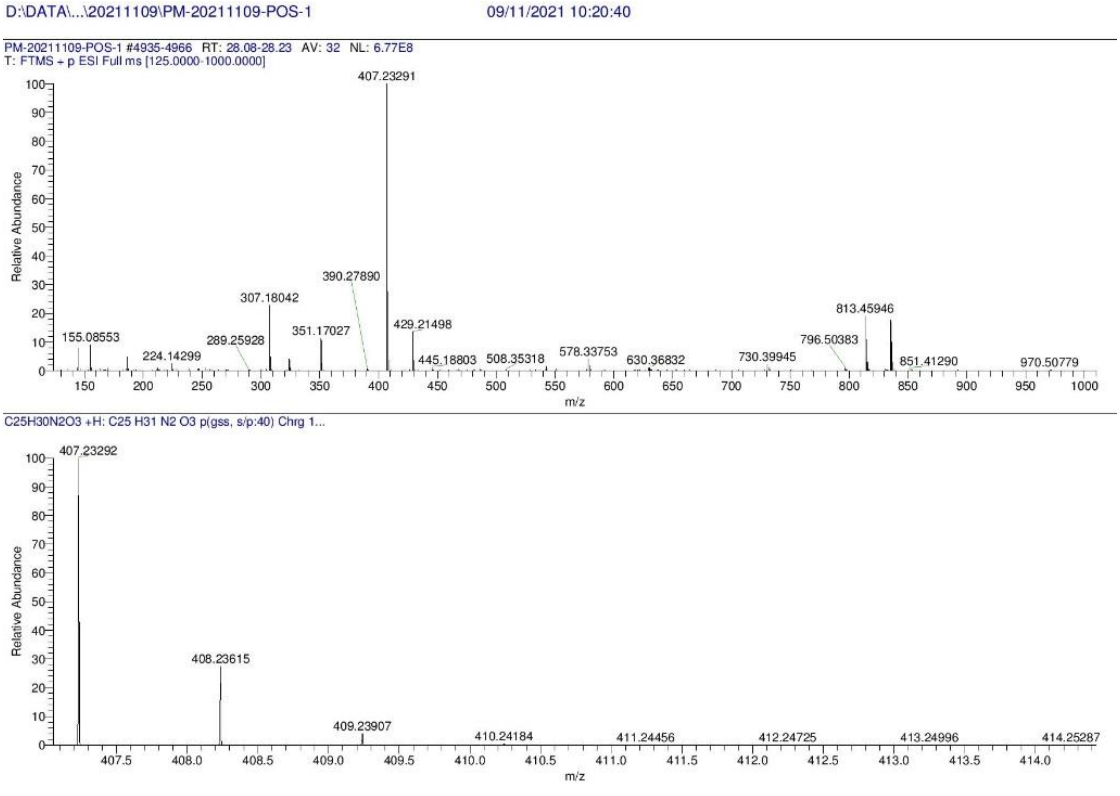
tert-Butyl ((1*S*,2*R*,3*S*,4*R*)-3-(((*S*)-1-phenylethyl) carbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate (–)-**7**



(1*S*,2*R*,3*S*,4*R*)-Ethyl 3-(3-((S)-1-phenylethyl)ureido)bicyclo[2.2.1]hept-5-ene-2-carboxylate (–)-**8**

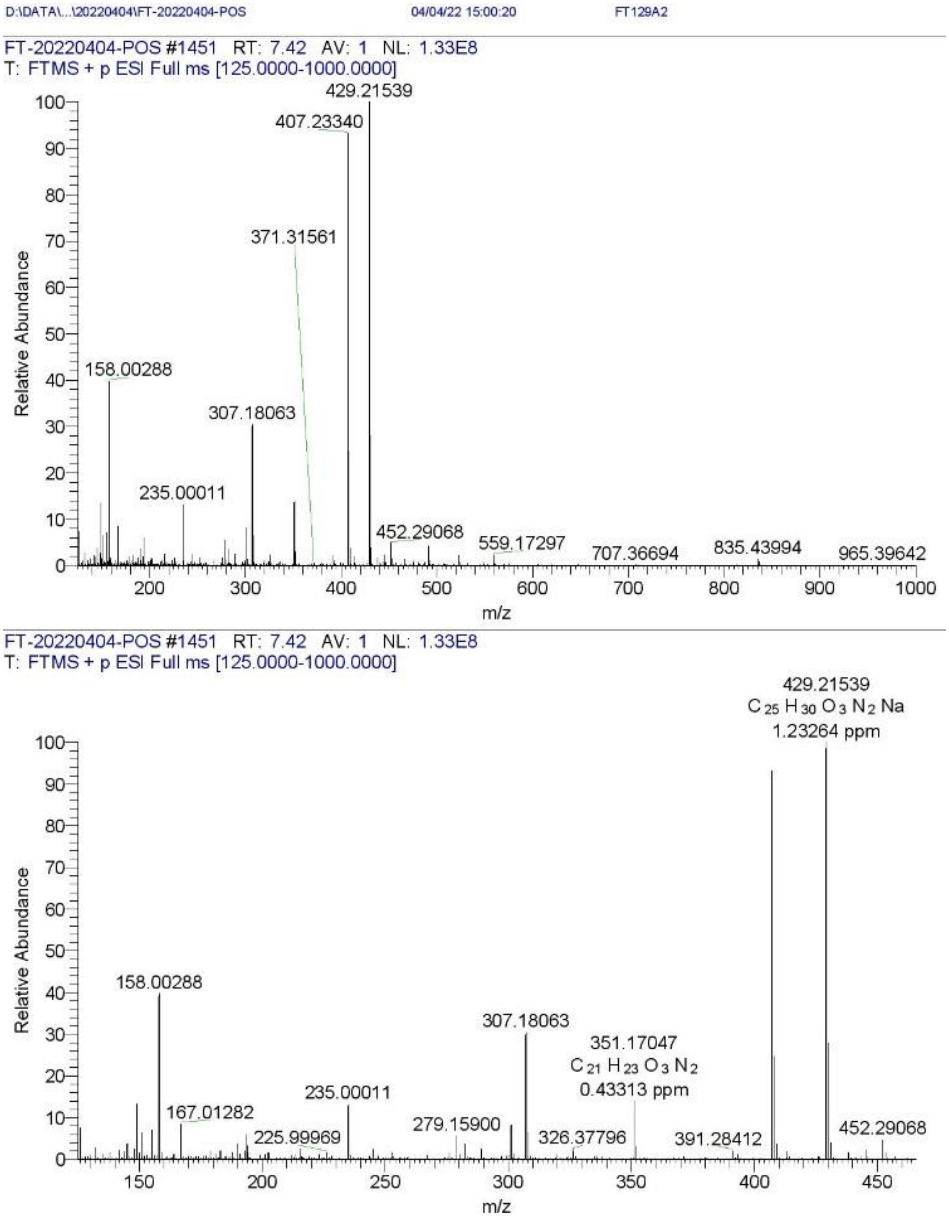


tert-Butyl ((1*R*,2*S*,3*R*,4*S*)-3-(((*S*)-1-(naphthalen-2-yl)ethyl)carbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate (–)-**9**



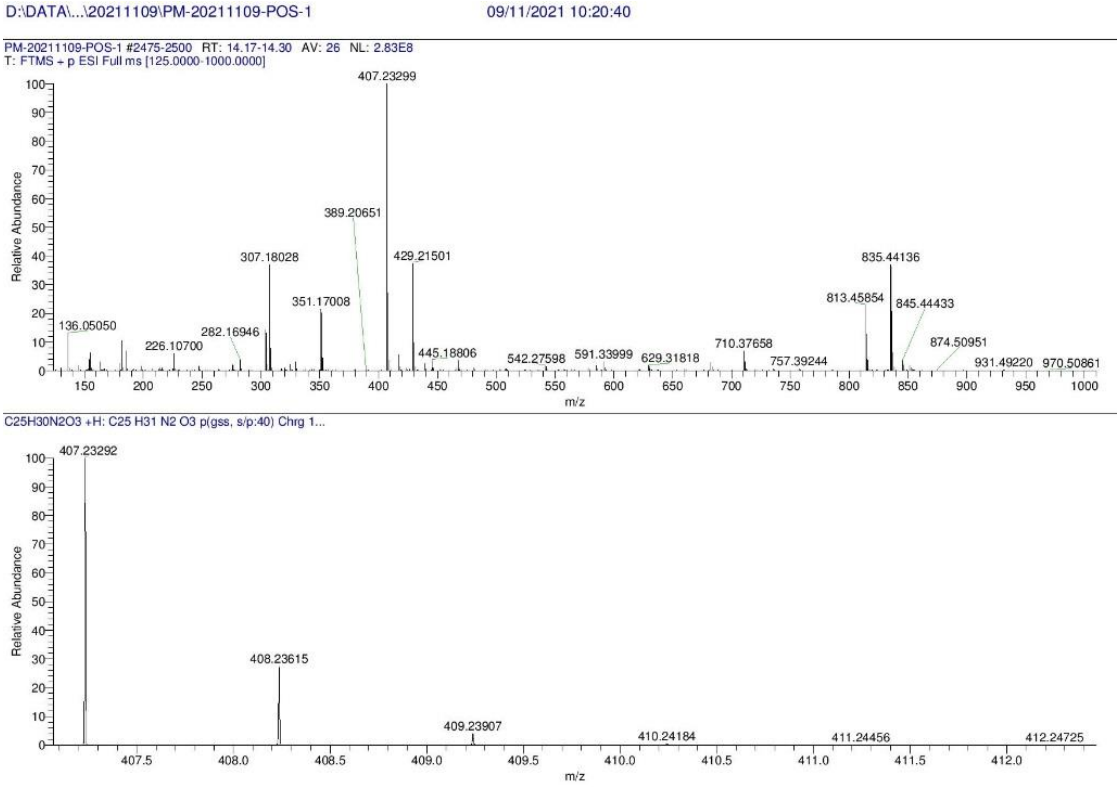
tert-Butyl ((1*R*,2*S*,3*R*,4*S*)-3-(((*S*)-1-(naphthalen-1-yl)ethyl)carbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate

(–)-**10**

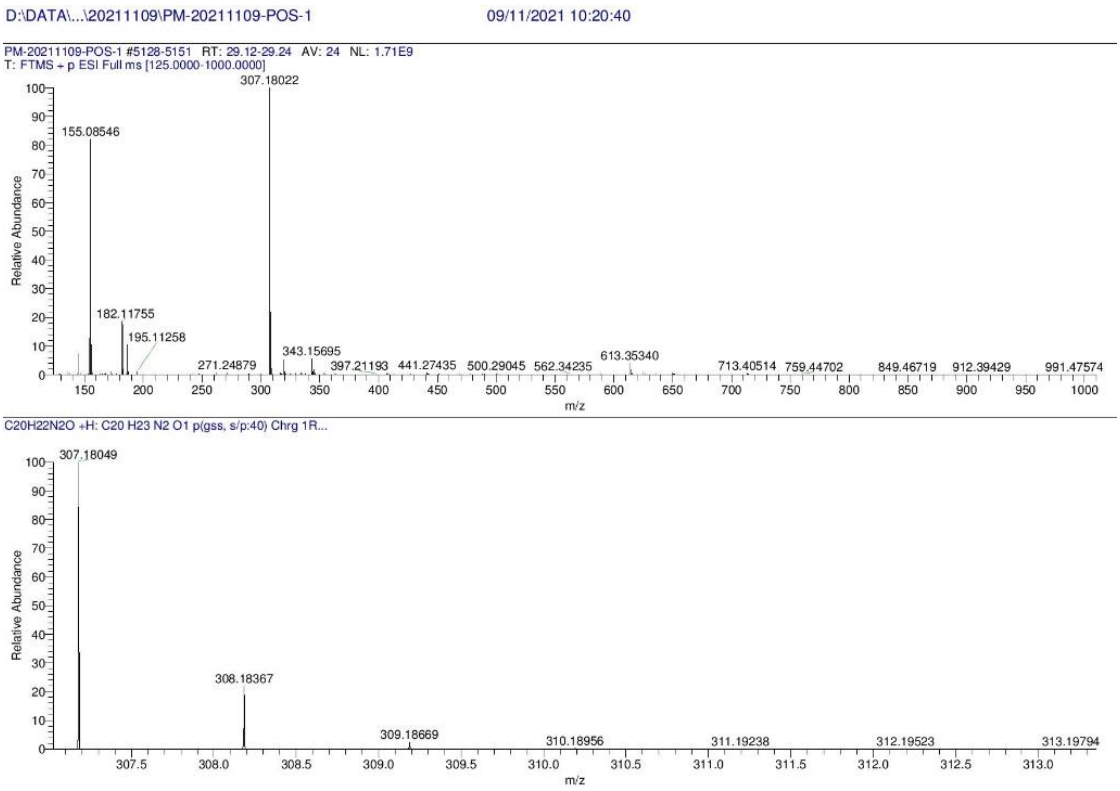


tert-Butyl ((1*R*,2*S*,3*R*,4*S*)-3-(((*R*)-1-(naphthalen-2-yl)ethyl)carbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate

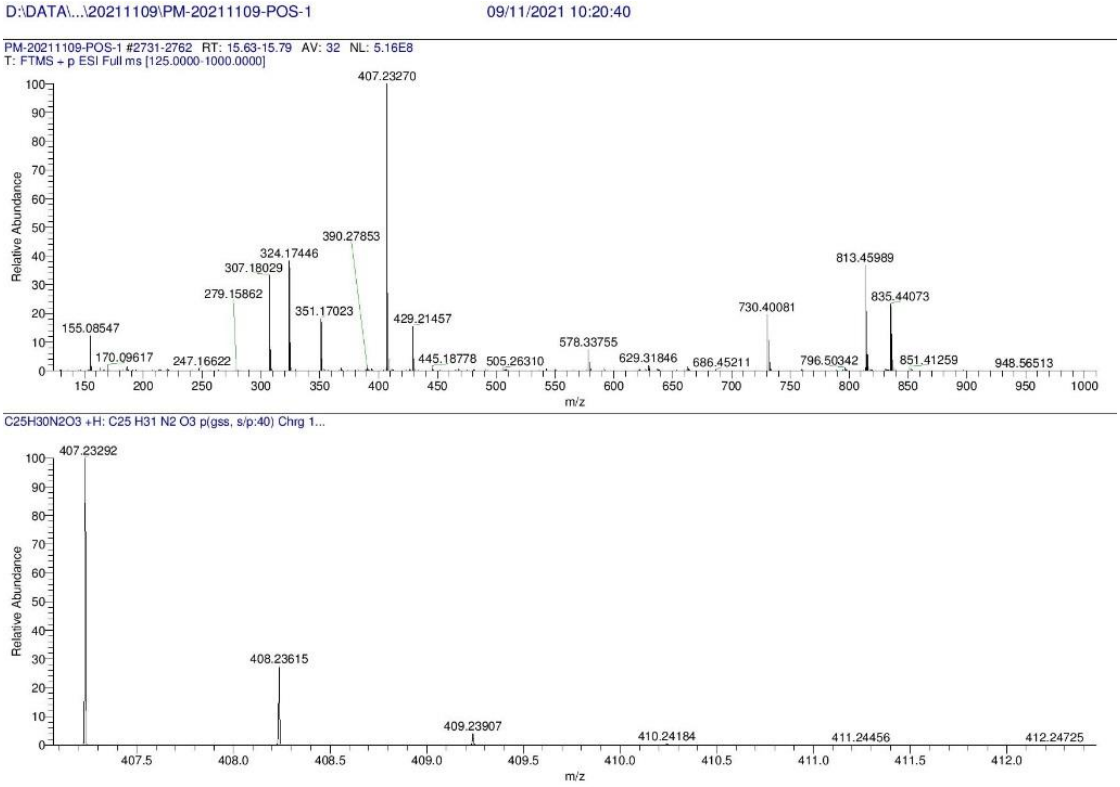
(+)-11



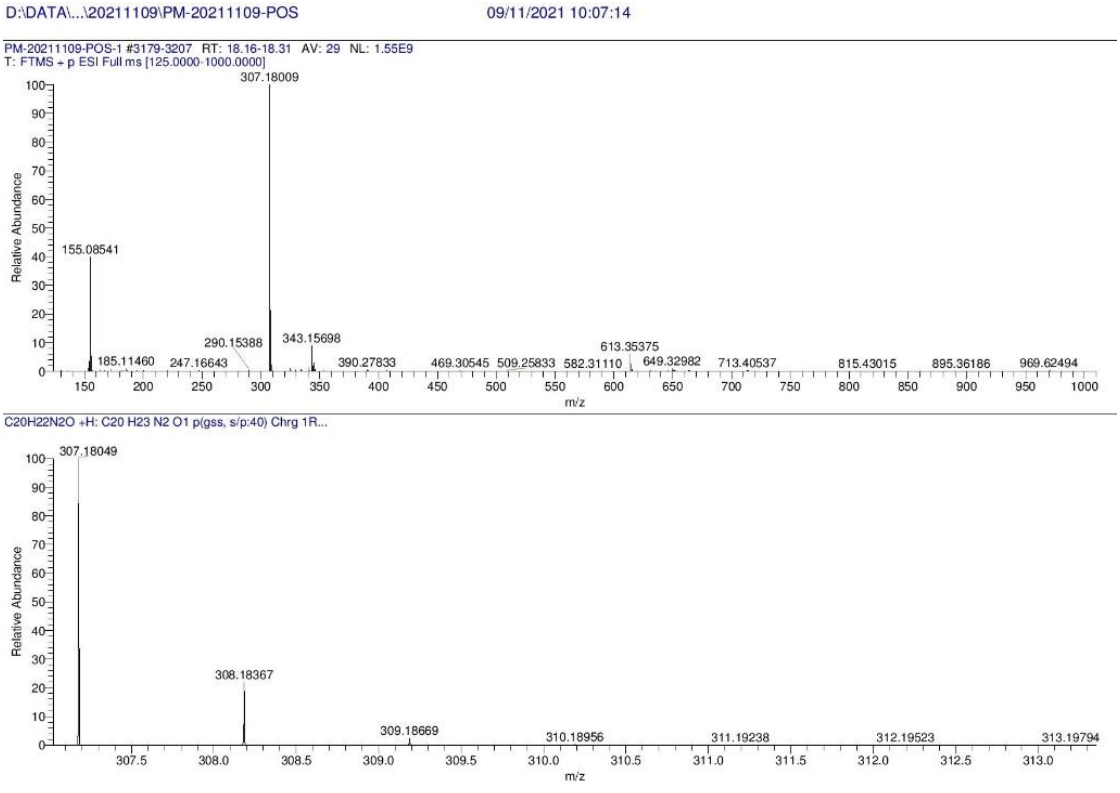
(1*S*,2*R*,3*S*,4*R*)-3-Amino-N-((*R*)-1-(naphthalen-2-yl)ethyl)bicyclo[2.2.1]hept-5-ene-2-carboxamide hydrochloride (+)-**12**



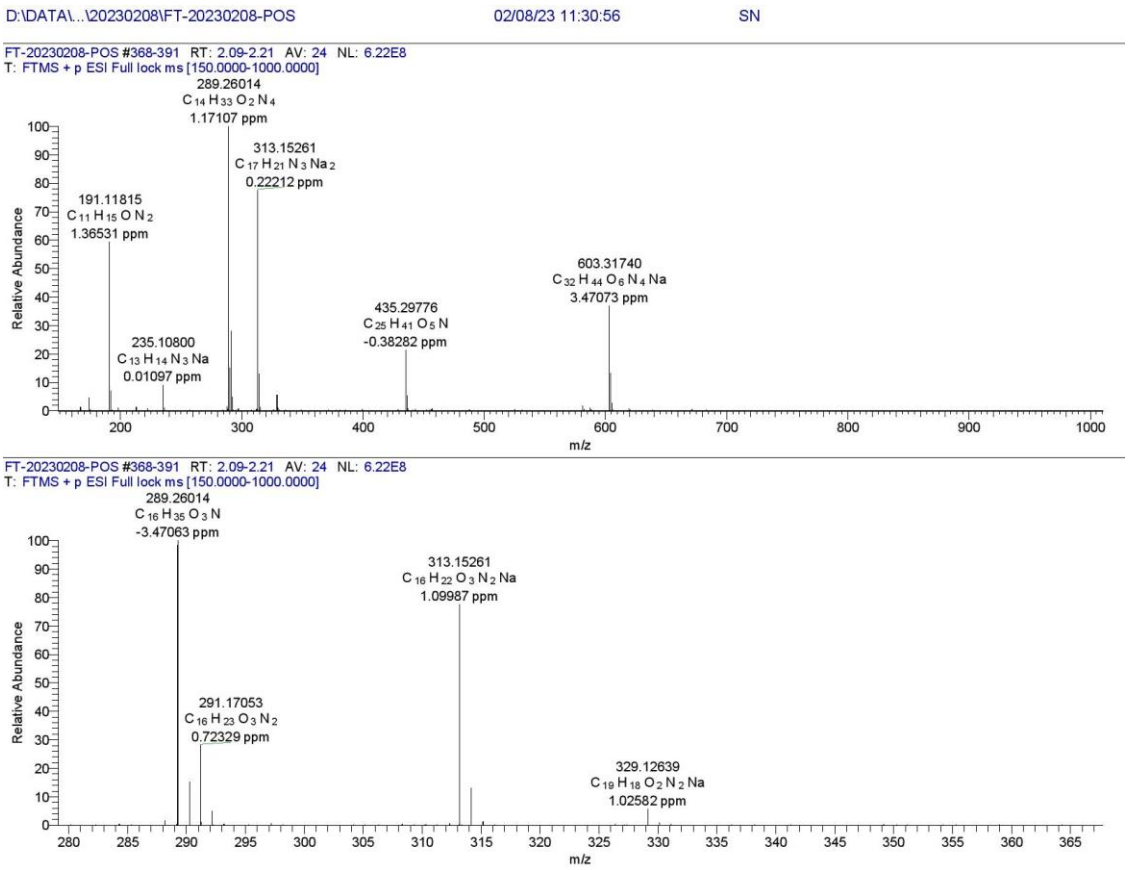
tert-Butyl ((1*R*,2*S*,3*R*,4*S*)-3-(((*R*)-1-(naphthalen-1-yl)ethyl)carbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate (+)-**13**



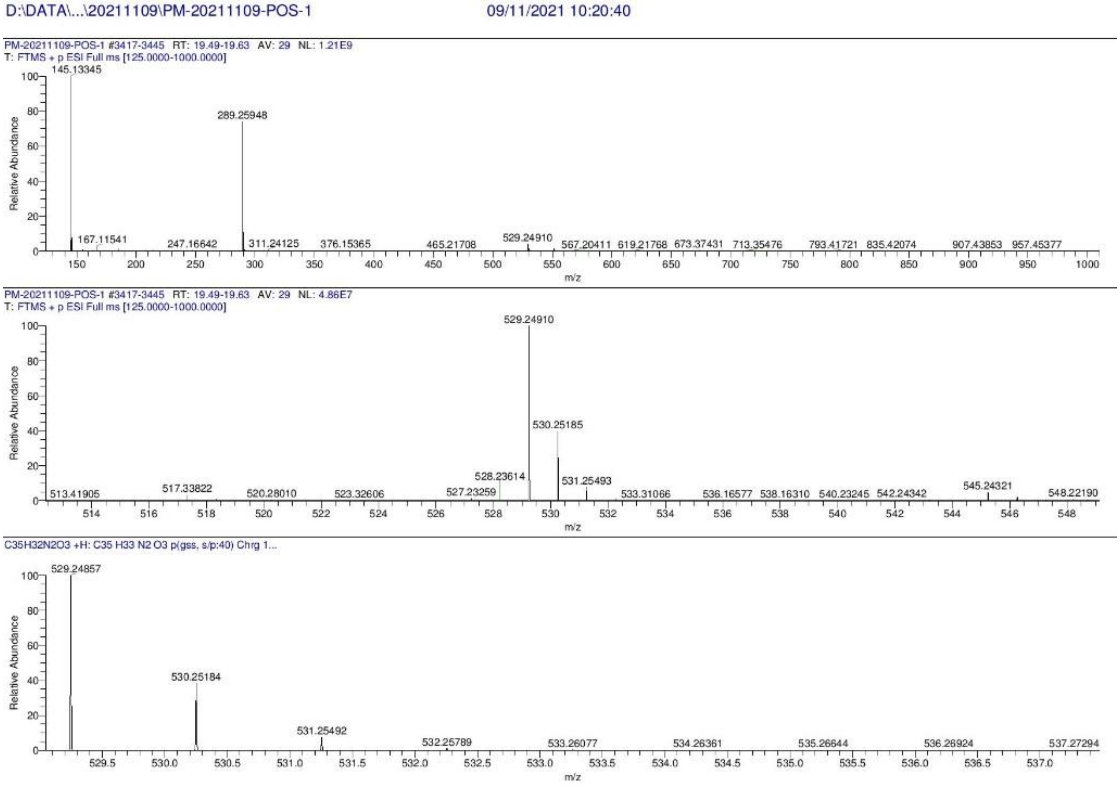
((1*S*,2*R*,3*S*,4*R*)-3-Amino-N-((*R*)-1-(naphthalen-1-yl)ethyl)bicyclo[2.2.1]hept-5-ene-2-carboxamide hydrochloride (+)-**14**



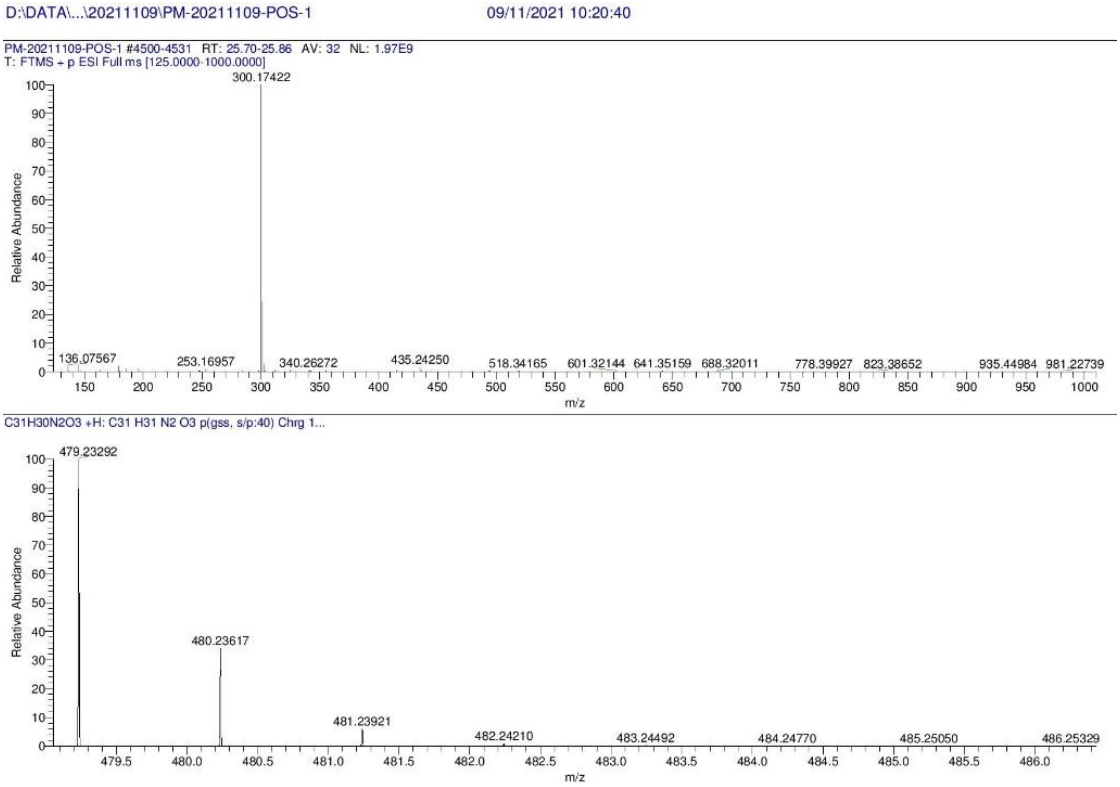
tert-Butyl ((1*R*,2*S*,3*R*,4*S*)-3-(prop-2-yn-1-ylcarbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate (–)-**15**



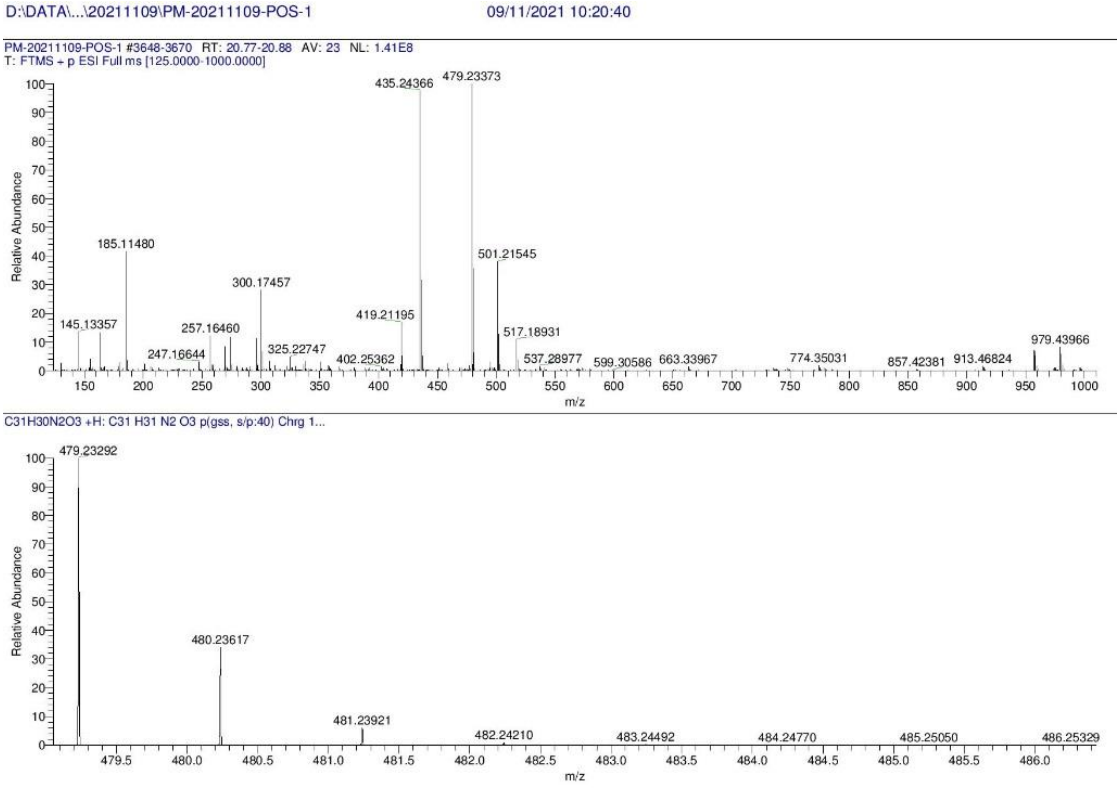
(9*H*-Fluoren-9-yl)methyl ((1*R*,2*R*,3*S*,4*S*)-3-(((*R*)-1-(naphthalen-2-yl)ethyl)carbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate (+)-**18**



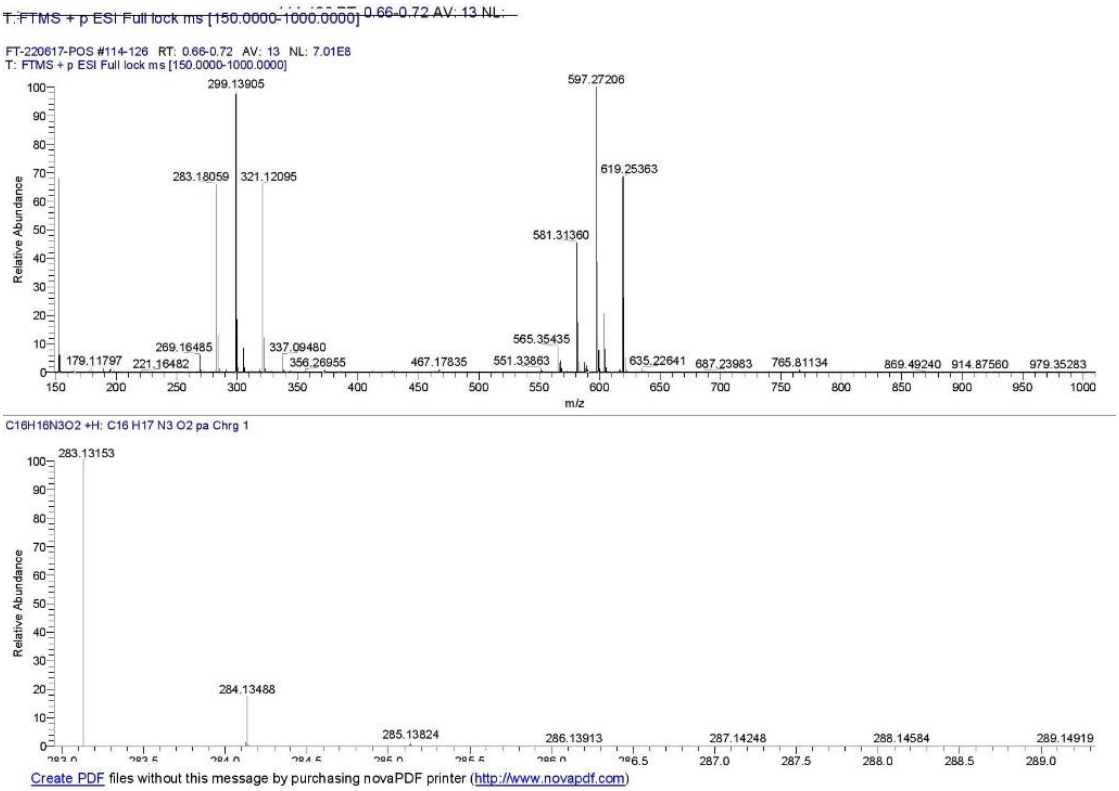
(9*H*-Fluoren-9-yl)methyl ((1*R*,2*R*,3*S*,4*S*)-3-(((*S*)-1-phenylethyl)carbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate (–)-**19**



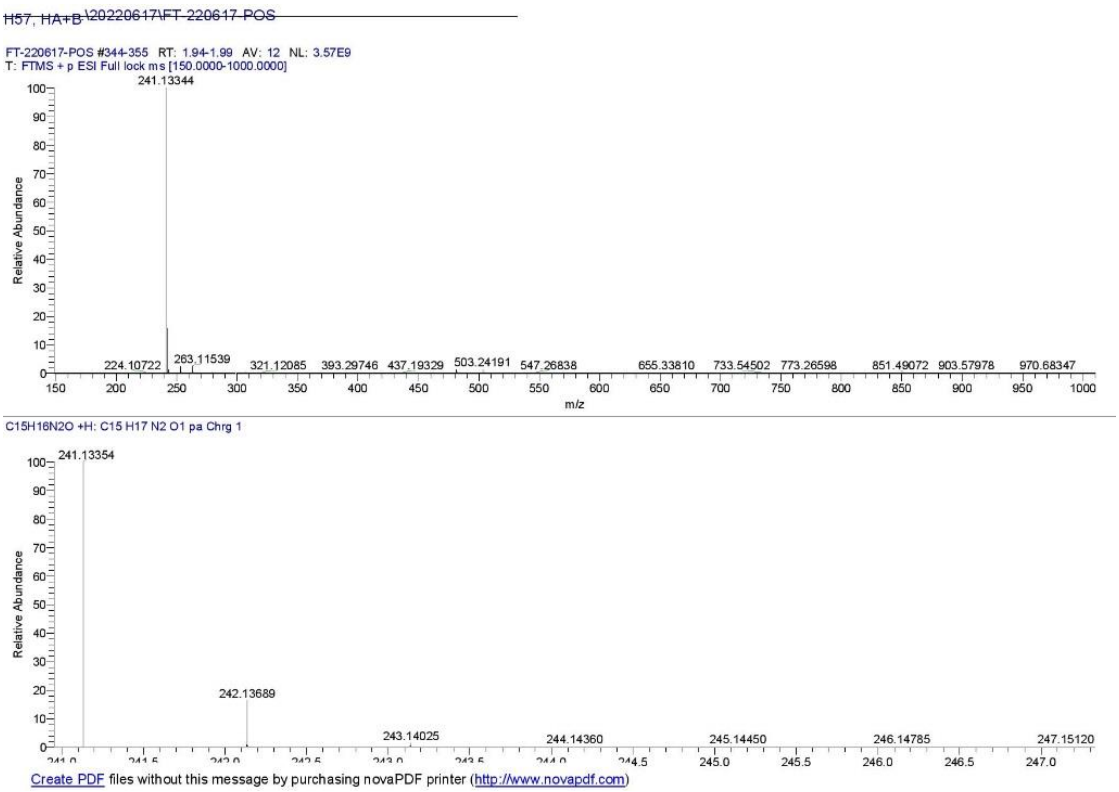
(9*H*-Fluoren-9-yl)methyl ((1*R*,2*R*,3*S*,4*S*R)-3-(((*R*)-1-phenylethyl)carbamoyl)bicyclo[2.2.1]hept-5-en-2-yl)carbamate (+)-**20**



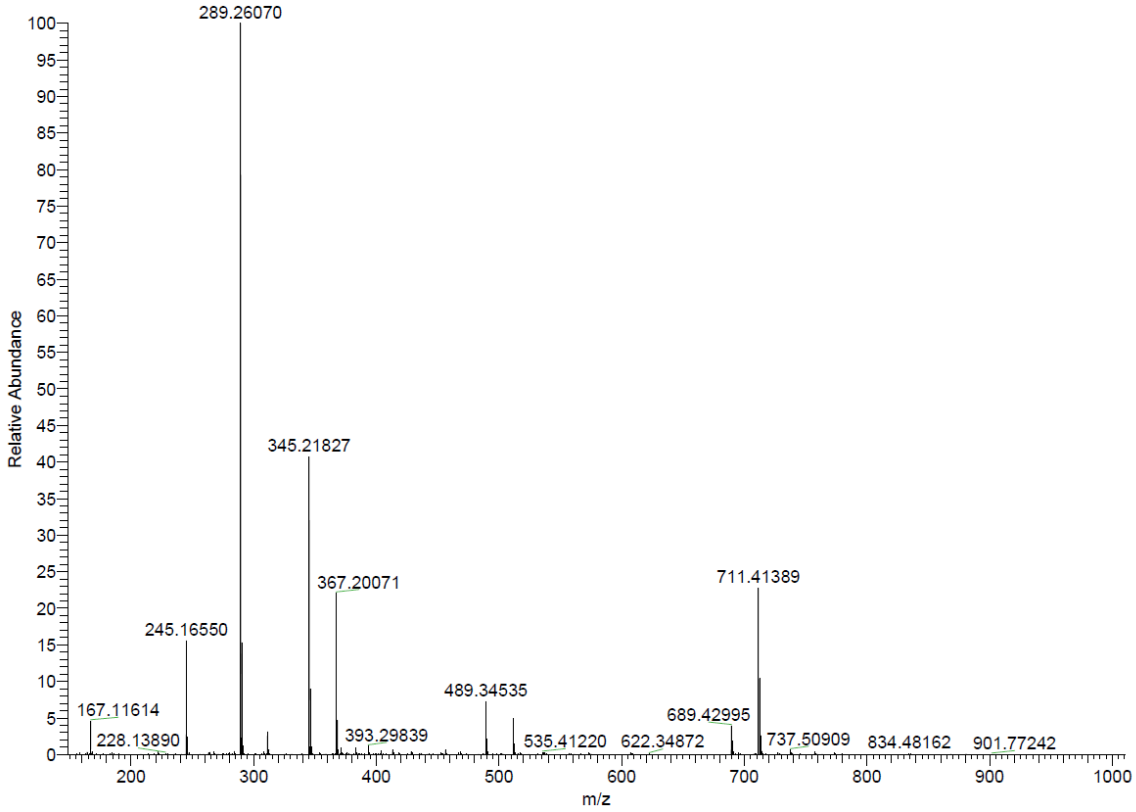
(S)-Methyl 2-(3-(1-phenylethyl)ureido)benzoate (+)-**22**



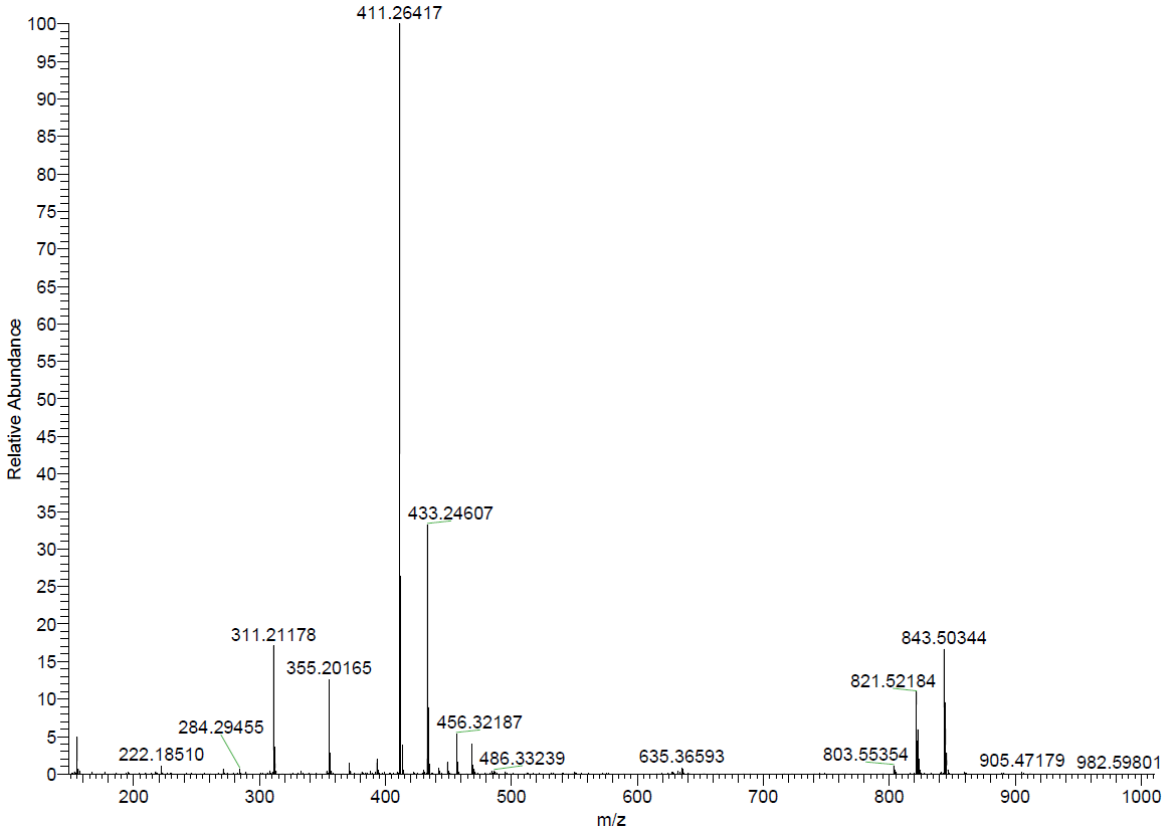
(S)-2-Amino-N-(1-phenylethyl)benzamide (+)-**23**



tert-Butyl ((1*S*,6*S*)-6-(((*R*)-1-phenylethyl)carbamoyl)cyclohex-3-en-1-yl)carbamate (+)-**24**



tert-Butyl ((1*S*,2*R*)-2-(((*R*)-1-(naphthalen-2-yl)ethyl)carbamoyl)cycloheptyl)carbamate **(+)-25**



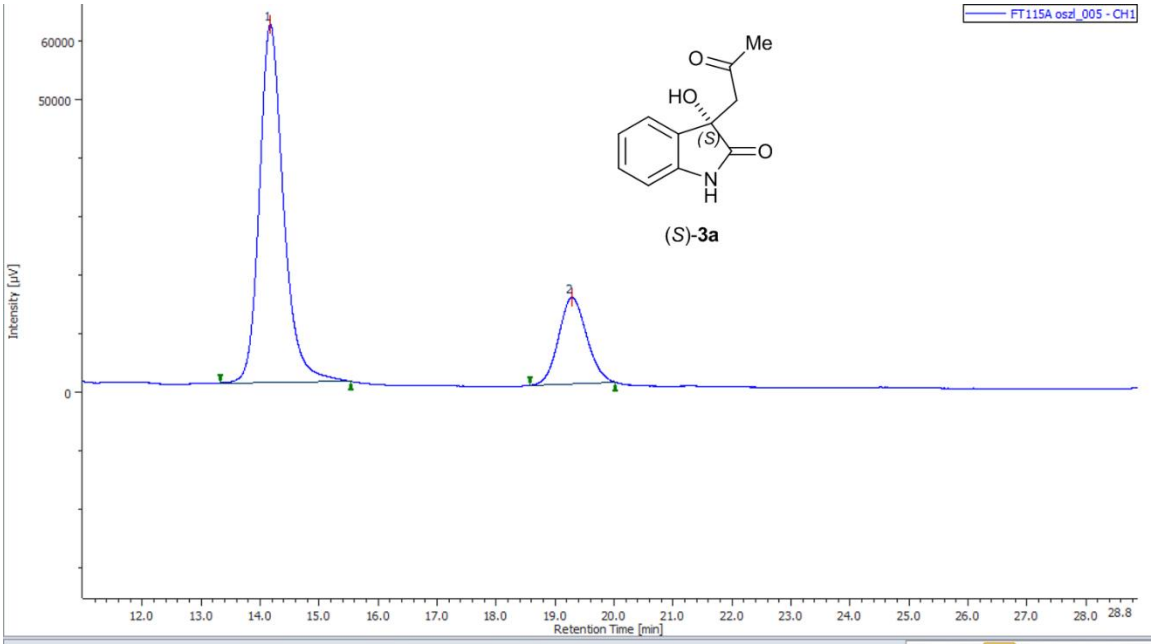
5. HPLC Chromatograms of 3a-h

Sample 1

Catalyst **7** applied in the isatin and acetone reaction using the optimum conditions

(*S*)-3-hydroxy-3-(2-oxopropyl) indolin-2-one (3a)

Method: ChiralPak® IA column Particle size: 5 µm, dimensions: 4.6 mm x 15 mm, mobile phase: hexane:i-PrOH = 80:20; flow rate: 0.5 mL/min, at range 200–600nm.



Peak Info. Table: FT115A oszl_005

#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	1	14.172	1731133	61071	78.136	80.593	N/A	6449	6.503	1.230	
2	Unknown	1	19.278	484409	14706	21.864	19.407	N/A	7876	N/A	1.093	

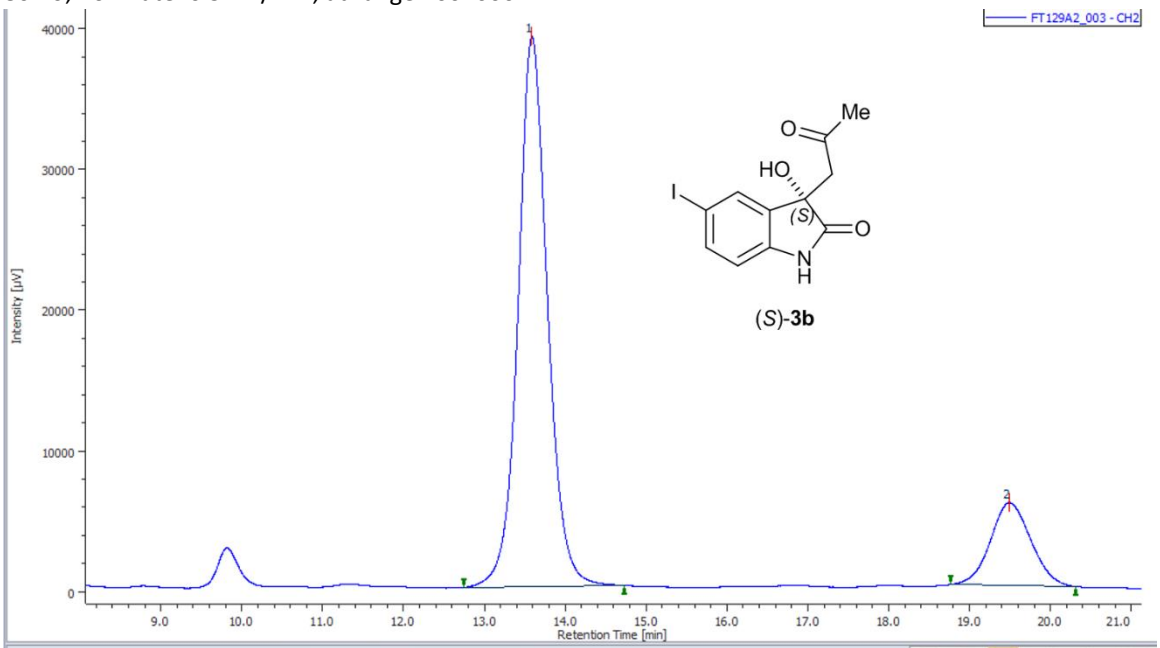
Chiral HPLC using catalyst **7** (5 mol %) in the aldol reaction of isatin **1a** (0.28 mmol) and acetone (5 mL) in the presence of LiOH (5 mol %), giving the (*S*)-enantiomer as a major product 3a in 57 % *ee* % and 96 % yield after 0.5 h (as in the paper **Table 4**, entry 1)

Sample 2

Catalyst **21** applied in the isatin/acetone reaction using the optimum conditions

(*S*)-3-hydroxy-5-iodo-3-(2-oxopropyl)indolin-2-one (3b)

Method: ChiralPak® IA column Particle size: 5 µm, dimensions: 4.6 mm x 15 mm mobile phase: hexane:i-PrOH = 80:20; flow rate: 0.5 mL/min, at range 200–600nm.



Peak Info. Table: FT129A2_003

#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	2	13.582	983921	39015	82.806	86.914	N/A	7382	7.664	1.077	
2	Unknown	2	19.483	204310	5874	17.194	13.086	N/A	7303	N/A	1.061	

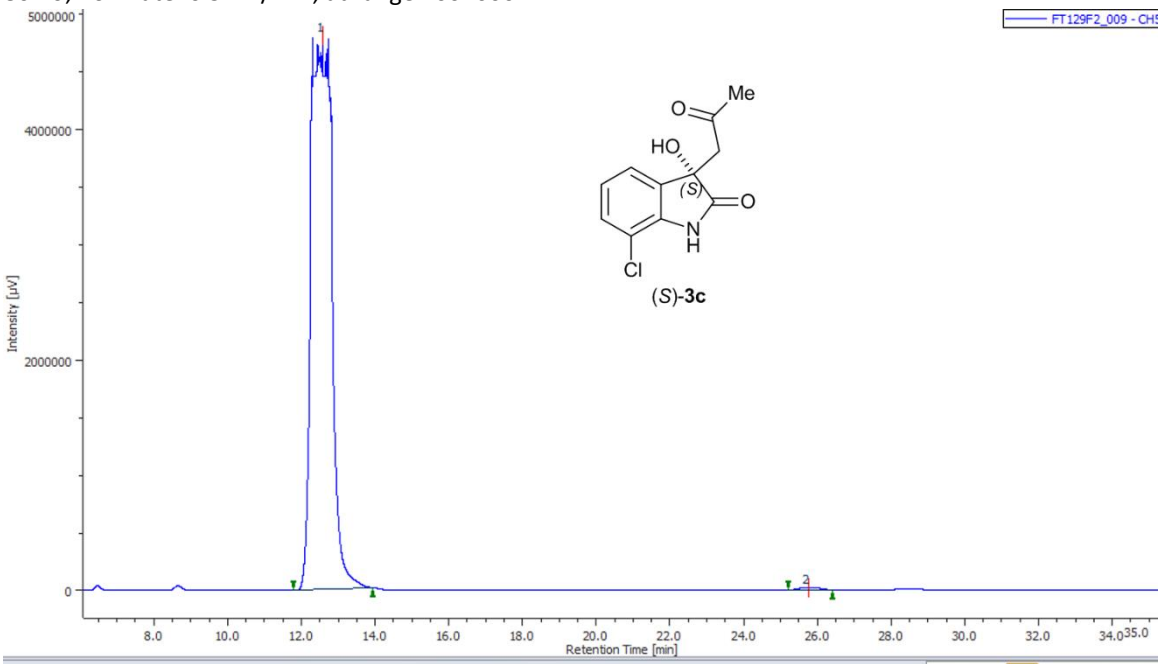
Chiral HPLC using catalyst **21** (20 mol %) in the aldol reaction of 5-Iodoisatin **1b** (0.28 mmol) and acetone (5 mL), giving the (*S*)-enantiomer as a major product **3b** in 65 % *ee*% and 78% yield after 48 h (as in the paper **Table 7**, entry 5)

Sample 3

Catalyst **21** applied in the isatin/acetone reaction using the optimum conditions

(*S*)-7-chloro-3-hydroxy-3-(2-oxopropyl)indolin-2-one (3c)

Method: ChiralPak® IA column Particle size: 5 µm, dimensions: 4.6 mm x 15 mm mobile phase: hexane:i-PrOH = 80:20; flow rate: 0.5 mL/min, at range 200–600nm.



Peak Info. Table: FT129F2_009

#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	12.577	186761176	4793525	99.509	99.525	N/A	2349	12.026	1.050	
2	Unknown	5	25.758	921204	22874	0.491	0.475	N/A	7889	N/A	1.055	

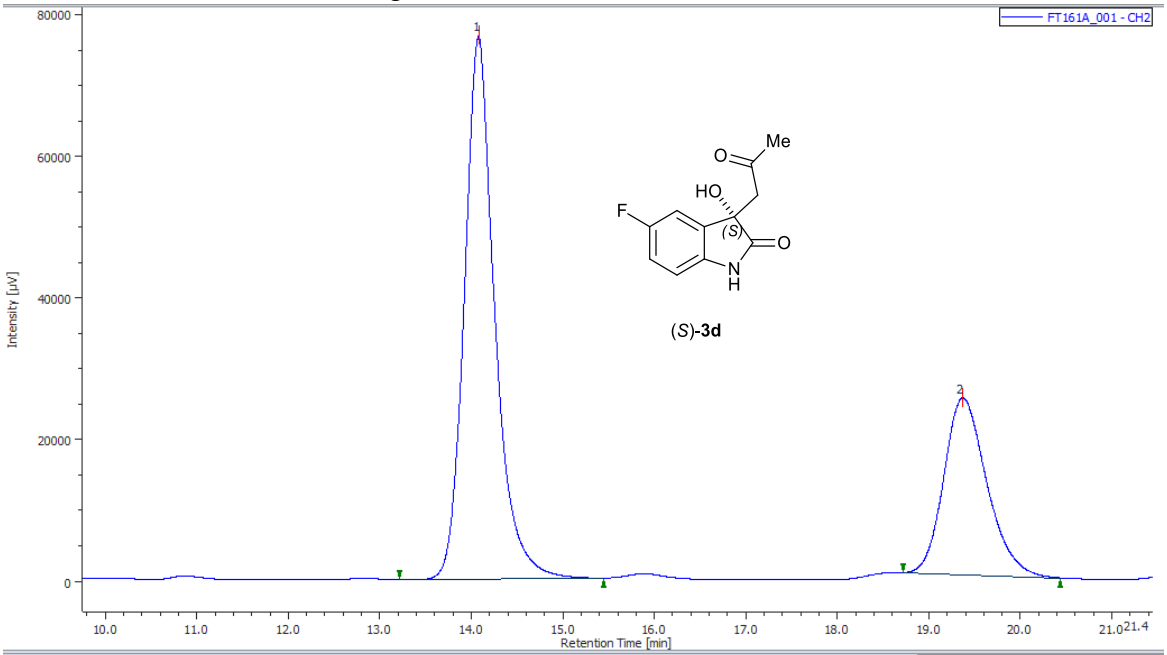
Chiral HPLC using catalyst **21** (20 mol %) in the aldol reaction of 7-Chloroisatin **1c** (0.28 mmol) and acetone (5 mL), giving the (*S*)-enantiomer as a major product **3c** in 98 % *ee*% and 81 % yield after 48 h (as in the paper **Table 7**, entry 9)

Sample 4

Catalyst **21** applied in the isatin/acetone reaction using the optimum conditions

(*S*)-5-fluoro-3-hydroxy-3-(2-oxopropyl)indolin-2-one (3d)

Method: ChiralPak® IA column Particle size: 5 µm, dimensions: 4.6 mm x 15 mm mobile phase: hexane:i-PrOH = 80:20; flow rate: 0.5 mL/min, at range 200–600nm.



Peak Info. Table: FT161A_001

#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	2	14.077	1757979	76645	68.391	75.452	N/A	9774	7.516	1.218	
2	Unknown	2	19.358	812515	24936	31.609	24.548	N/A	8506	N/A	1.233	

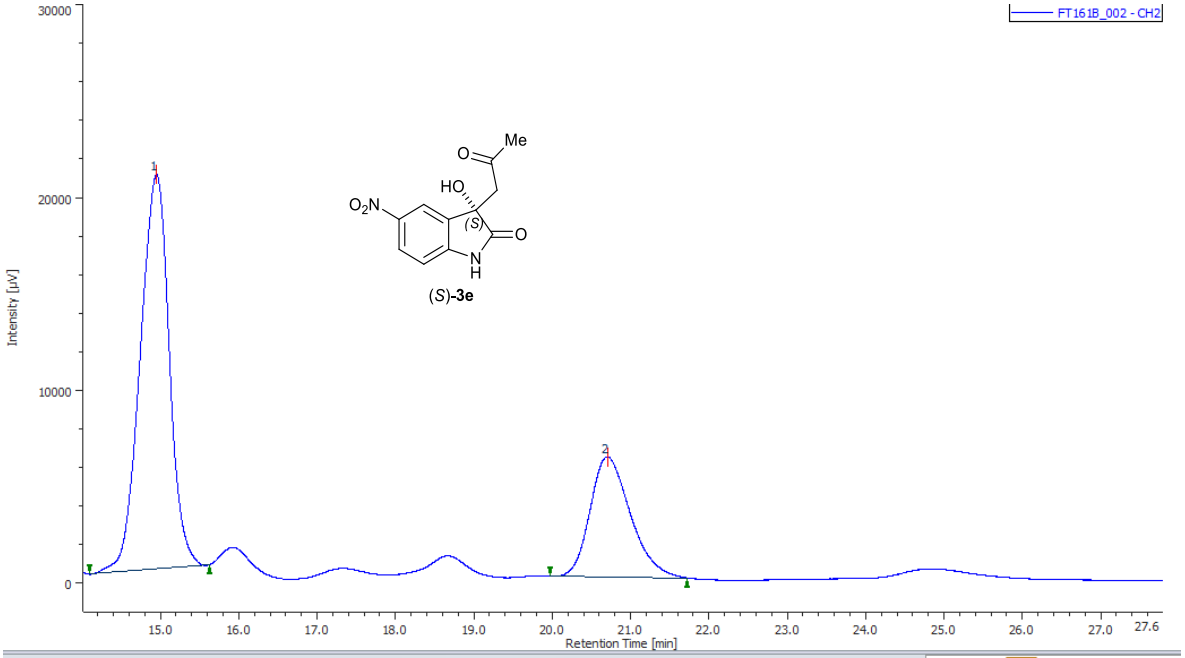
Chiral HPLC using catalyst **21** (20 mol %) in the aldol reaction of 5-Fluoroisatin **1d** (0.28 mmol) and acetone (5 mL), giving the (*S*)-enantiomer as a major product **3d** in 37 % *ee*% and 72% yield after 72 h (as in the paper **Table 7**, entry 12)

Sample 5

Catalyst **21** applied in the isatin/acetone reaction using the optimum conditions

(*S*)-3-hydroxy-5-nitro-3-(2-oxopropyl)indolin-2-one (3e)

Method: ChiralPak® IA column Particle size: 5 µm, dimensions: 4.6 mm x 15 mm mobile phase: hexane:i-PrOH = 80:20; flow rate: 0.5 mL/min, at range 200–600nm.



Peak Info. Table: FT161B_002

#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	2	14.952	525927	20413	70.335	76.626	N/A	7850	7.204	0.942	
2	Unknown	2	20.697	221816	6227	29.665	23.374	N/A	8024	N/A	1.286	

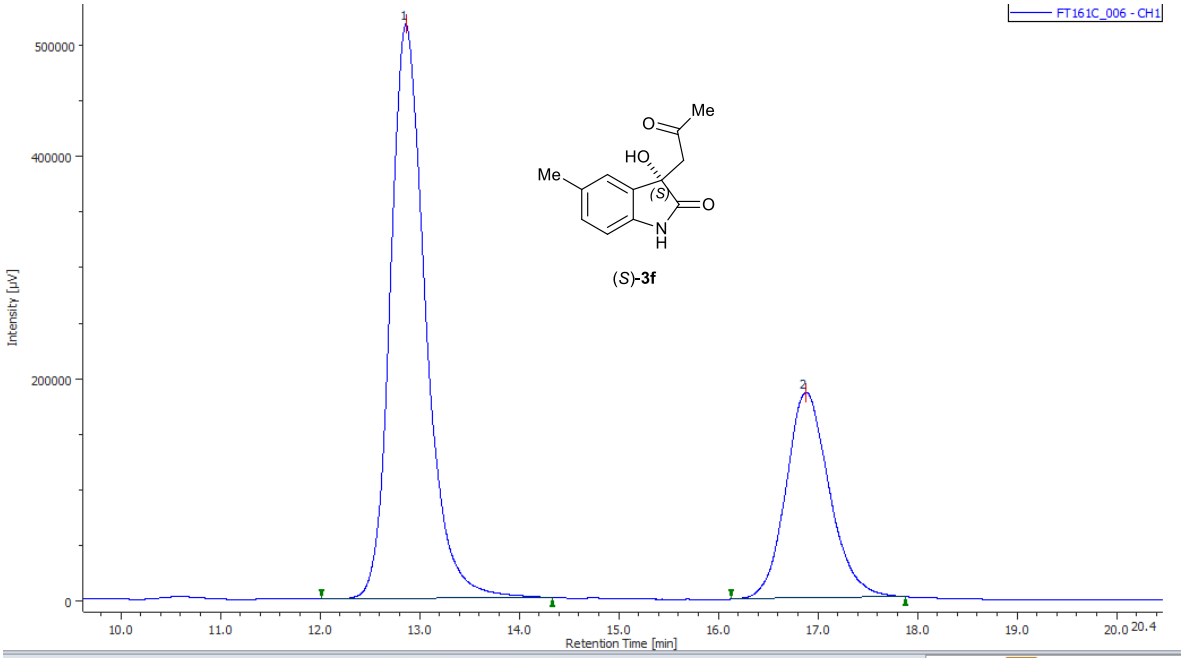
Chiral HPLC using catalyst **21** (20 mol %) in the aldol reaction of 5-Nitroisatin **1e** (0.28 mmol) and acetone (5 mL), giving the (*S*)-enantiomer as a major product **3e** in 41 % *ee*% and 73 % yield after 72 h (as in the paper **Table 7**, entry 15)

Sample 6

Catalyst **21** applied in the isatin/acetone reaction using the optimum conditions

(*S*)-3-hydroxy-5-methyl-3-(2-oxopropyl)indolin-2-one (3f)

Method: ChiralPak® IA column Particle size: 5 µm, dimensions: 4.6 mm x 15 mm mobile phase: hexane:i-PrOH = 80:20; flow rate: 0.5 mL/min, at range 200–600nm.



Peak Info. Table: FT161C_006

#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	1	12.860	12655158	515505	69.314	73.615	N/A	6912	5.774	1.257	
2	Unknown	1	16.877	5602516	184765	30.686	26.385	N/A	7563	N/A	1.146	

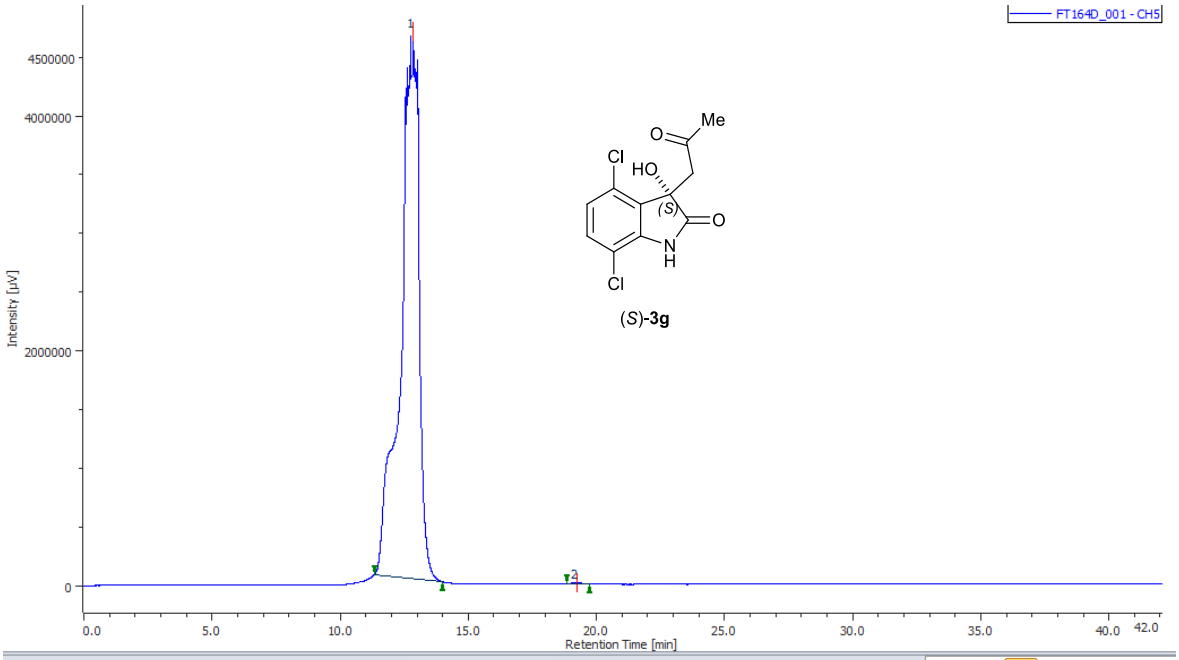
Chiral HPLC using catalyst **21** (20 mol %) in the aldol reaction of 5-Methylisatin **1f** (0.28 mmol) and acetone (5 mL), giving the (*S*)-enantiomer as a major product **3f** in 39 % *ee*% and 65 % yield after 72 h (as in the paper **Table 7**, entry 18)

Sample 7

Catalyst **7** applied in the isatin/acetone reaction using the optimum conditions

(*S*)-4,7-dichloro-3-hydroxy-3-(2-oxopropyl)indolin-2-one (3g)

Method: ChiralPak® IA column Particle size: 5 µm, dimensions: 4.6 mm x 15 mm mobile phase: hexane:i-PrOH = 80:20; flow rate: 0.5 mL/min, at range 200–600nm.



Peak Info. Table: FT164D_001

#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	12.817	229290050	4645054	99.853	99.737	N/A	2317	7.077	0.731	
2	Unknown	5	19.208	338503	12229	0.147	0.263	N/A	10607	N/A	1.134	

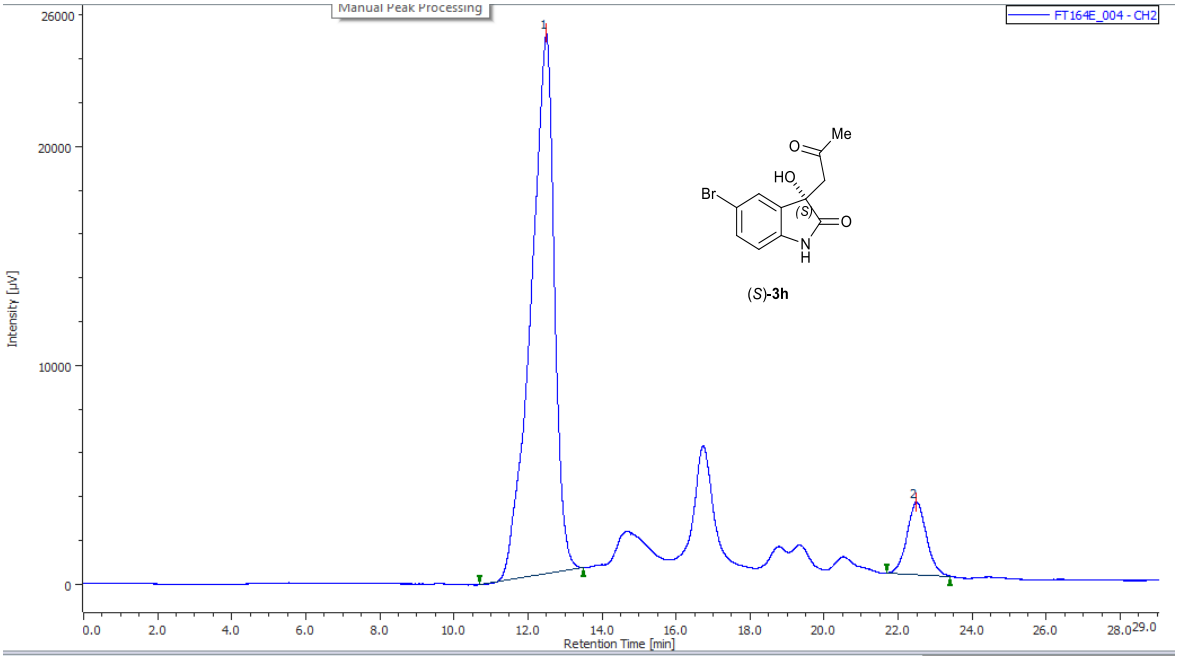
Chiral HPLC using catalyst **7** (5 mol %) in the aldol reaction of 4,7-Dichloroisatin **1g** (0.28 mmol) and acetone (5 mL), giving the (*S*)-enantiomer as a major product **3g** in 99 % *ee*% and 70 % yield after 72 h (as in the paper **Table 7**, entry 19)

Sample 8

Catalyst **7** applied in the isatin/acetone reaction using the optimum conditions

(*S*)-5-bromo-3-hydroxy-3-(2-oxopropyl)indolin-2-one (3h)

Method: ChiralPak® IA column Particle size: 5 µm, dimensions: 4.6 mm x 15 mm mobile phase: hexane:i-PrOH = 80:20; flow rate: 0.5 mL/min, at range 200–600nm.



Peak Info. Table: FT164E_004

#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	2	12.488	1083797	24647	89.970	88.164	N/A	2046	9.739	0.771	
2	Unknown	2	22.462	120825	3309	10.030	11.836	N/A	8961	N/A	1.074	

Chiral HPLC using catalyst **7** (5 mol %) in the aldol reaction of 5-Bromoisatin **1h** (0.28 mmol) and acetone (5 mL), giving the (*S*)-enantiomer as a major product **3h** in 79 % *ee*% and 64 % yield after 72 h (as in the paper **Table 7**, entry 22)