Electronic Supplementary Material (ESI) for ChemComm.

Supporting Information

An Efficient, Stereocontrolled and Versatile Synthetic Route to Bicyclic Partially Saturated Privileged Scaffolds

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Contents

1. Experimental Details

1.1. General Experimental Details

All non-aqueous reactions were performed in dry glassware under a stream of nitrogen using anhydrous solvents. Tetrahydrofuran was dried over sodium wire and distilled from a mixture of lithium aluminium hydride and calcium hydride with triphenylmethane as the indicator. Dichloromethane, toluene and methanol were all distilled from calcium hydride. Petroleum ether was distilled before use and refers to the fraction between 40-60 ^{o}C.

Chemicals were purchased from Sigma Aldrich and used as received unless otherwise stated.

Reactions were carried out at ambient temperature unless otherwise stated. All temperatures below 0 ^{o}C are achieved with an external bath: those of 0 ^{o}C were maintained using an ice/water bath, those of lower temperatures using a dry ice/ DMF bath.

Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. Analytical thin layer chromatography (TLC) was performed on commercially available glass pre-coated Merck Kiesel gel 60 F254 plates. Visualisation was achieved by quenching of UV fluorescence (λ_{max} = 254 nm) or by staining with potassium permanganate. R_f values are quoted to the nearest 0.01. Where possible, reactions were monitored using TLC. Flash column chromatography was performed using slurry-packed SiO_2 (Merck Grade 9385, 230-400 mesh) under a positive pressure of N_2.

Infrared spectra were recorded neat (unless otherwise stated) on a Perkin Elmer Spectrum One FT-IR spectrometer with internal referencing. Selected absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}) and are assigned as: weak (w), medium (m), strong (s) or broad (br).

Melting points were obtained on a Buchi B-545 melting point apparatus and are uncorrected.

Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded using an internal deuterium lock at ambient probe temperatures (unless otherwise stated) on the following instruments: Bruker DPX-400 (400 MHz), Bruker Avance 400 QNP (400 MHz), Bruker BB 500 (500 MHz) and Bruker Avance 500 Cryo Ultrashield (500 MHz). Chemical shifts (δ_H) are referenced to the residual non-deuterated solvent peak and quoted in parts per million (ppm) to the nearest 0.01 ppm. Coupling constants are quoted in Hertz to the nearest 0.1 Hz. Data are reported in the format: chemical shift, integration, multiplicity [app = apparent; br = broad; s =s singlet; d = doublet; t = triplet; q = quartet; quin = quintet; m = multiplet; or as a combination of these, e.g. dd], coupling constant(s), assignment. Proton assignments were determined either on the basis of unambiguous chemical shift, coupling patterns, by patterns

observed in the two-dimensional experiments (^{1}H-^{1}H COSY, HMBC and HMQC) or by analogy to fully interpreted spectra for related compounds.

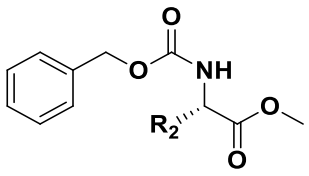
Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded by broadband proton spin decoupling at ambient probe temperatures (unless otherwise stated) using an internal deuterium lock on the following instruments: Bruker DPX-400 (100 MHz), Bruker Avance 400 QNP (100 MHz), Bruker BB 500 (125 MHz) and Bruker Avance 500 Cryo Ultrashield (125 MHz). Chemical shifts (δ_C) are referenced to the residual non-deuterated solvent peak and quoted in parts per million (ppm) to the nearest 0.1 ppm. Assignments are supported by either chemical shift, APT/DEPT, two dimensional experiments (HMBC and HMQC) or by analogy to fully interpreted spectra for related compounds.

The numbering of molecules for the assignment of ^{13}C and ^{1}H spectra does not follow the IUPAC naming system.

High resolution mass spectrometry (HRMS), measurements were carried out on a Micromass LCT Premier spectrometer using electron spray ionisation (ESI) techniques. Masses are quoted within the error limits of ±5ppm mass units.

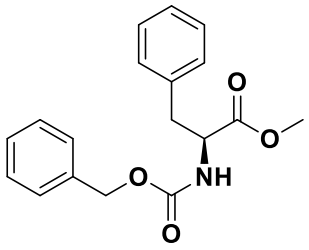
1.2. Efficient Synthesis of 1,2,4-Triazole heterocycles: *cis*-diastereomer

1.2.1. Methyl ((benzyloxy)carbonyl) amino esters (2a-h)



General Procedure 2: Thionyl chloride (1.4 eq.) was added dropwise over 10 minutes to a stirred solution of the N-(benzyloxycarbonyl)amino acid in methanol (0.2 M) at 0 °C. The mixture was stirred for 2 hours until the acid had been consumed. The methanol was removed under reduced pressure. The crude compound was purified by flash column chromatography on silica to yield the title compound.

1.2.1.1. Methyl ((benzyloxy)carbonyl)-L-phenylalaninate (2a)



Following General Procedure 2: (benzyloxycarbonyl)-L-phenylalanine **1b** (12.0 g, 40.1 mmol), thionyl chloride (4.09 mL, 56.1 mmol) and methanol (200 mL) were used. The crude product was purified by flash column chromatography eluting with ethyl acetate (100%) to yield the title compound **2b** as a cloudy oil (12.53 g, 39.9 mmol, 99%).

R_f = 0.70 (EtOAc)

$[\alpha]_D^{20}$ = -13.2 (c = 1.0 in MeOH) - [Literature Value = -14.4 (c = 1.3 in MeOH)][2]

IR ν_{max} = 3344 (w, N-H), 2988 (s, C-H), 2901 (s, C-H), 1704 (s, br, C=O), 1497 (m, C=C), 1454 (m, C=C), 1406 (m, C=C)

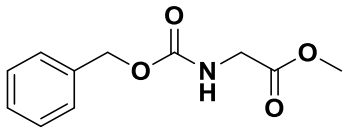
^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.38-7.31 (5H, m), 7.30-7.23 (3H, m), 7.12 (2H, dd, J = 7.9, 1.5 Hz), 5.23 (1H, d, J = 5.8 Hz), 5.12 (1H, d, J = 12.2 Hz) 5.09 (1H, d, J = 12.2 Hz), 4.68 (1H, dt, J = 6.1, 5.8 Hz), 3.74 (3H, s), 3. 16 (1H, dd, J = 13.7, 5.8 Hz), 3.11 (1H, dd, J = 13.8, 6.1 Hz)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 171.9, 155.6, 136.2, 135.6, 129.2, 128.6, 128.5, 128.2, 128.1, 127.1, 67.0, 54.8, 52.3, 38.2

HRMS (ESI+): found $[M + H]^+$ 314.1382, $C_{18}H_{20}NO_4^+$ required 314.1392

This data is in accordance with that previously reported.[2]

1.2.1.2. Methyl ((benzyloxy)carbonyl)glycinate (2b)



Following General Procedure 2: Z-L-glycine **1a** (15.0 g, 71.7 mmol), thionyl chloride (7.30 mL, 100 mmol) and methanol (350 mL) were used. The crude product was purified by flash column chromatography eluting with 50% ethyl acetate in 40-60 petroleum ether to yield the title compound **2a** as a cloudy white oil (15.4 g, 68.9 mmol, 96%).

R_f = 0.17 (50% EtOAc in 40-60 petroleum ether)

IR: ν_{max} = 3351 (m, C-N), 2954 (m, C-H), 1704 (s, C=O), 1520 (s, N-H)

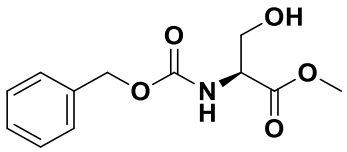
^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.28 - 7.40 (5H, m), 5.31 (1H, br s), 5.13 (2H, s), 3.99 (2H, d, *J* = 5.5 Hz), 3.75 (3H, s)

^{13}C NMR (500 MHz, $CDCl_3$): δ_c = 170.4, 156.2, 136.2, 128.5, 128.2, 128.1, 67.1, 52.3, 42.6

HRMS (ESI+): found $[M + Na]^+$ 246.0741, $C_{11}H_{13}NO_4Na^+$ required 246.0737

This data is in accordance with that previsouly recorded.[1]

1.2.1.3. Methyl ((benzyloxy)carbonyl)-L-serinate (2c)



Following General Procedure 2: methyl-(benzyloxycarbonyl)-L-serine **1c** (9.9 g, 41.4 mmol), thionyl chloride (4.23 mL, 57.9 mmol) and methanol (165 mL) were used. The crude product was purified by flash column chromatography eluting with 40% ethyl acetate in 40-60 petroleum ether to yield the title compound **2c** as a pale-yellow oil (10.5 g, 41.3 mmol, 100%).

R_f = 0.29 (40% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = -12.6 (c = 1.2 in MeOH) - [Literature Value = -13.2 (c = 10.0 in MeOH)][3]

IR ν_{max} = 3359 (w, N-H), 3250 (w, br, O-H), 2987 (s, C-H), 2901 (s, C-H), 1695 (s, br, C=O), 1515 (m, C=C), 1453 (m, C=C), 1438 (m, C=C), 1406 (m, C=C)

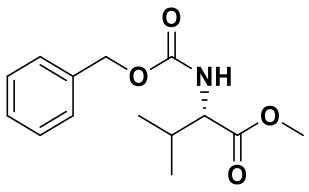
^{1}H NMR (400 MHz, d_6-DMSO): δ_H = 7.54 (1H, d, *J* = 8.2 Hz), 7.35 - 7.40 (4H, m), 7.29 - 7.34 (1 H, m) 5.04 (2H, s), 4.97 (1 H, t, *J* = 6.0 Hz) 4.15 (1H, dt, *J* = 8.2, 5.2 Hz), 3.66 (2H, t, *J*=5.2 Hz), 3.63 (3H, s),

^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 171.4, 156.1, 137.0, 128.5, 128.0, 127.9, 65.7, 61.3, 56.8, 52.0

HRMS (ESI+): found $[M + H]^+$ 254.1032, $C_{12}H_{16}NO_5^+$ required 254.1028

This data is in accordance with that previously reported.[3]

1.2.1.4. Methyl ((benzyloxy)carbonyl)-L-valinate (2d)



Following General Procedure 2: methyl-(benzyloxycarbonyl)-L-valine **1d** (9.90 g, 39.4 mmol), thionyl chloride (4.03 mL, 55.2 mmol) and methanol (165 mL) were used. The crude product was purified by flash column chromatography eluting with EtOAc (100%) to yield the title compound **2d** as a cloudy oil (10.5 g, 39.4 mmol, 100%).

R_f = 0.68 (EtOAc)

$[\alpha]_D^{20}$ = -19.7 (c = 1.0 in MeOH) - [Literature Value = -19.4 (c = 1.0 in MeOH)][4]

IR ν_{max} = 3364 (w, N-H), 2972 (s, C-H), 2901 (s, C-H), 1705 (s, br, C=O), 1512 (m, C=C), 1454 (m, C=C), 1436 (m, C=C), 1406 (m, C=C)

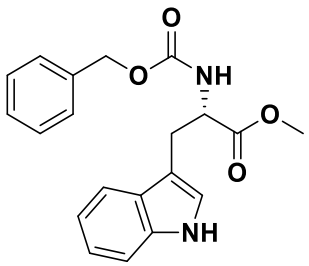
^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 7.63 - 7.74 (1H, d, *J* = 8.1 Hz), 7.33 - 7.40 (4H, m), 7.29 - 7.33 (1H, m), 5.03 (2H, s), 3.92 (1H, dd, *J* = 8.1, 6.5 Hz), 3.63 (3H, s), 2.02 (1H, qd, *J* = 6.8, 6.5 Hz), 0.87 (3H, d, *J* = 6.8 Hz), 0.86 (3H, d, *J* = 6.8 Hz)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 127.8, 156.8, 137.4, 128.8, 128.3, 128.2, 66.0, 60.2, 52.1, 30.1, 19.4, 18.7

HRMS (ESI+): found $[M + Na]^+$ 266.1386, $C_{14}H_{20}NO_4^+$ required 266.1387

This data is in accordance with that previously reported.[4]

1.2.1.5. Methyl ((benzyloxy)carbonyl)-L-tryptophanate (2e)



Following General Procedure 2: methyl-(benzyloxycarbonyl)-L-tryptophan **1e** (2.00 g, 5.91 mmol), thionyl chloride (0.60 mL, 8.27 mmol) and methanol (30 mL) were used. The crude product was purified by flash column chromatography eluting with 40% EtOAc in 40-60 petroleum ether to yield the title compound **2e** as a brown oil (2.05 g, 5.82 mmol, 98%).

R_f = 0.63 (40% EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -10.1 (c = 0.7 in MeOH) - [Literature Value = -11.0 (c = 0.4 in MeOH)][5]

IR ν_{max} = 3407 (w, br, N-H), 2988 (s, C-H), 2901 (s, C-H), 1697 (s, br, C=O), 1507 (m, C=C), 1455 (m, C=C), 1435 (m, C=C), 1407 (m, C=C)

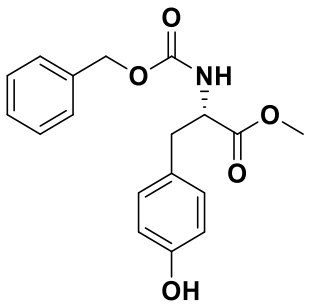
^{1}H NMR (400 MHz, d_6-DMSO): δ_H = ppm 10.88 (1H, br. s), 7.79 (1H, d, *J* = 7.8 Hz), 7.51 (1H, d, *J* = 7.5 Hz), 7.25 - 7.38 (4H, m), 7.17 (1H, d, *J* = 1.4 Hz), 7.07 (1H, t, *J* = 7.2 Hz), 6.95 - 7.02 (1H, m), 4.92 - 5.06 (2H, m), 4.21 - 4.41 (1H, m), 3.61 (3H, s), 3.19 (1H, dd, *J* = 14.8, 5.2 Hz), 3.03 (1H, dd, *J* = 14.8, 9.2 Hz)

^{13}C NMR (101 MHz, d_6-DMSO): δ_C = 172.8, 156.1, 136.9, 136.2, 128.4, 127.9, 127.7, 127.1 (C11) 123.9, 121.1, 118.5, 118.1, 111.6, 109.7, 65.2, 55.1, 52.0, 27.0

HRMS (ESI+): found $[M + H]^+$ 353.1500, $C_{20}H_{21}N_2O_4^+$ required 353.1501

This data is in accordance with that previously reported.[5]

1.2.1.6. Methyl ((benzyloxy)carbonyl)-L-tyrosinate (2f)



Following General Procedure 2: methyl-(benzyloxycarbonyl)-L-tyrosine **1f** (2.00 g, 6.34 mmol), thionyl chloride (0.65 mL, 8.88 mmol) and methanol (35 mL) were used. The crude product was purified by flash column chromatography eluting with 40% EtOAc in 40-60 petroleum ether to yield the title compound **2f** as a yellow-orange oil (2.09 g, 6.34 mmol, 100%).

R_f = 0.54 (40% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = -7.2 (c = 0.9 in MeOH) - [Literature Value = -7.9 (c = 0.5 in MeOH)][6]

IR ν_{max} = 3362 (w, br, O-H), 3360 (w, N-H), 2988 (s, C-H), 2901 (s, C-H), 1694 (s, br, C=O), 1513 (s, C=C), 1437 (s, C=C), 1407 (s, C=C)

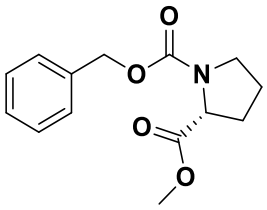
^{1}H NMR (400 MHz, d_6-DMSO): δ_H = 9.27 (1H, s), 7.77 (1H, d, *J* = 8.2 Hz), 7.19 - 7.49 (5H, m), 7.02 (2H, d, *J* = 7.5 Hz), 6.68 (2H, d, *J* = 7.5 Hz), 4.98 (2H, s), 4.04 - 4.31 (1H, m), 3.61 (3H, s), 2.91 (1H, dd, *J* = 13.6, 4.4 Hz), 2.67 - 2.81 (1H, m)

^{13}C NMR (101 MHz, d_6-DMSO): δ_C = 172.6, 156.1, 137.0, 130.1, 128.4, 127.8, 127.6, 127.4, 115.1, 65.4, 56.0, 52.0, 35.9

HRMS (ESI+): found $[M + H]^+$ 352.1152, $C_{18}H_{19}NO_5S^+$ required 352.1155

This data is in accordance with that previously reported.[6]

1.2.1.7. Methyl ((benzyloxy)carbonyl)-L-prolinate (2g)



Following General Procedure 2: methyl-(benzyloxycarbonyl)-L-proline **1g** (2.00 g, 8.02 mmol), thionyl chloride (0.82 mL, 11.2 mmol) and methanol (40 mL) were used. The crude product was purified by flash column chromatography eluting with 40% EtOAc in 40-60 petroleum ether to yield the title compound **2g** as a yellow oil (2.02 g, 7.67 mmol, 96%).

R_f = 0.45 (40%EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -52.8 (c = 1.0 in MeOH) - [Literature Value = -57.0 (c = 1.0 in MeOH)][7]

IR ν_{max} = 2988 (s, C-H), 2901 (s, C-H), 1744 (s, C=O), 1699 (s, C=O), 1409 (s, C=C)

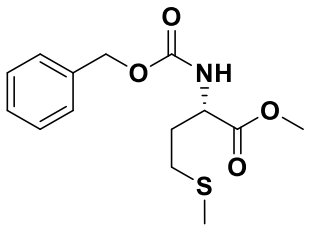
^{1}H NMR (400 MHz, d_6-DMSO): δ_H = 7.22 - 7.42 (5H, m), 4.92 - 5.14 (2H, m), 4.22 - 4.36 (1H, m), 3.52 - 3.68 (3H, m), 3.30 - 3.50 (2H, m), 2.12 - 2.33 (1H, m), 1.74 - 1.96 (3H, m) – Mixture of rotamers

^{13}C NMR (101 MHz, d_6-DMSO): δ_C = 173.1, 172.8, 154.1, 153.5, 137.0, 136.9, 128.5, 128.4, 127.9, 127.8, 127.6, 127.3, 66.1, 66.1, 58.9, 58.4, 52.0, 46.9, 46.3, 30.5, 29.5, 24.1, 23.2

HRMS (ESI+): found $[M + Na]^+$ 286.1046, $C_{14}H_{17}NO_4Na^+$ required 286.1055

This data is in accordance with that previously reported.[7]

1.2.1.8. Methyl ((benzyloxy)carbonyl)-L-methioninate (2h)



Following General Procedure 2: methyl-(benzyloxycarbonyl)-L-methionine **1h** (2.00 g, 7.06 mmol), thionyl chloride (0.72 mL, 9.88 mmol) and methanol (35 mL) were used. The crude product was purified by flash column chromatography eluting with 40% EtOAc in 40-60 petroleum ether to yield the title compound **2h** as a yellow oil (2.10 g, 7.06 mmol, 100%).

R_f = 0.88 (40% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = -32.5 (c = 1.1 in MeOH) - [Literature Value = -34.1 (c = 1.1 in MeOH)][8]

IR ν_{max} = 3339 (m, N-H), 2988 (s, C-H), 2901 (s, C-H), 1746 (s, C=O), 1685 (s, C=O), 1526 (s, C=C), 1443 (m, C=C), 1406 (m, C=C)

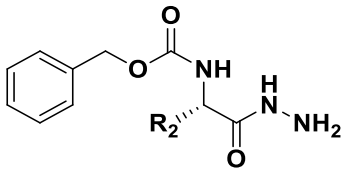
^{1}H NMR (400 MHz, d_6-DMSO): δ_H = 7.79 (1H, d, *J* = 7.8 Hz), 7.24 - 7.44 (5H, m), 5.04 (2H, s), 4.15 - 4.27 (1H, m), 3.64 (3H, s), 2.52 - 2.48 (2H, m), 2.02 (3H, s), 1.80 - 1.98 (2H, m)

^{13}C NMR (101 MHz, d_6-DMSO): δ_C = 172.7, 156.2, 137.0, 128.5, 128.0, 127.8, 65.6, 52.8, 52.1, 30.3, 29.6, 14.6

HRMS (ESI+): found $[M + Na]^+$ 320.0920, $C_{14}H_{19}NO_4SNa^+$ required 320.0927

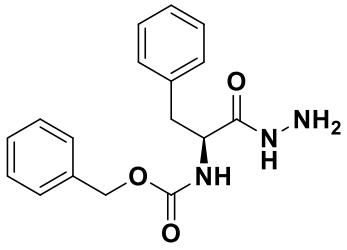
This data is in accordance with that previously reported.[8]

1.2.2. Methyl ((benzyloxy)carbonyl) amino hydrazides (3a-h)



General Procedure 3: A solution of the methyl ((benzyloxy)carbonyl) amino ester and hydrazine monohydrate (5 eq.) in methanol (0.5 M) was stirred overnight at room temperature. Water (0.25 M) was added and the product collected by vacuum filtration. The title compound was carried forward without further purification.

1.2.2.1. Benzyl (S)-(1-hydrazinyl-1-oxo-3-phenylpropan-2-yl)carbamate (3a)



Following General Procedure 3: methyl ((benzyloxy)carbonyl)phenylalaninate **2b** (12.92 g, 41.2 mmol) and hydrazine monohydrate (10 mL, 206 mmol) in methanol (85 mL) were used to yield the title compound **3b** as a white solid (12.24 g, 39.1 mmol, 95%).

R_f = 0.23 (EtOAc)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -4.2 (c = 1.1 in MeOH) - [Literature Value = +10.3 (c = 1.0 in MeOH)][9]

IR ν_{max} = 3298 (m, N-H), 2988 (s, C-H), 2901 (s, C-H), 1688 (m, C=O), 1651 (m, C=O), 1626 (m, C=C), 1606 (m, C=C), 1535 (s, C=C), 1493 (w, C=C), 1454 (w, C=C)

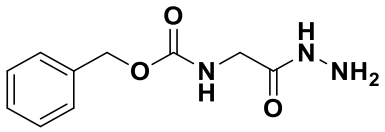
^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 9.22 (1H, br. s), 7.52 (1H, d, *J* = 8.5 Hz), 7.03 - 7.41 (10H, m), 4.91 (2H, s), 4.23 - 4.40 (2H, br.), 4.18 (1H, ddd, *J* = 10.2, 8.5, 4.4 Hz), 2.90 (1H, dd, *J* = 13.7, 4.4 Hz), 2.76 (1H, dd, *J* = 13.7, 10.2 Hz)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 170.8, 155.8, 138.2, 137.1, 129.3, 128.4, 128.1, 127.8, 127.6, 126.3, 65.2, 55.0, 37.8

HRMS (ESI+): found $[M + H]^+$ 314.1505, $C_{17}H_{20}N_3O_3^+$ required 314.1505

This data is in accordance with that previously reported.[9]

1.2.2.2. Benzyl (2-hydrazinyl-2-oxoethyl)carbamate (3b)



Following General Procedure 3: methyl ((benzyloxy)carbonyl)glycinate **2a** (15.0 g, 67.2 mmol) and hydrazine monohydrate (16.0 mL, 336 mmol) in methanol (130 mL) were used to yield the title compound **3b** as a white solid (14.8 g, 66.3 mmol, 98%).

R_f = 0.42 (EtOAc)

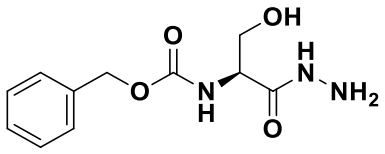
IR: ν_{max} = 3302 (s, N-H), 3034 (m, C-H), 1726 (s, C=O), 1651 (s, C=O), 1604 (m, C=C0, 1528 (s, N-H)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.29 - 7.43 (5H, m), 5.41 (1H, br s), 5.14 (2H, s), 3.87 (3H, app. d, *J* = 6.1 Hz), 1.63 (2H, br s)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 169.7, 156.6, 135.9, 128.6, 128.4, 128.2, 67.4, 43.4

HRMS (ESI+): found $[M + H]^+$ 224.1030, $C_{10}H_{14}N_3O_3^+$ required 224.1030

1.2.2.3. Benzyl (S)-(1-hydrazinyl-3-hydroxy-1-oxopropan-2-yl)carbamate (3c)



Following General Procedure 3: methyl ((benzyloxy)carbonyl)serinate **2c** (9.00 g, 35.5 mmol) and hydrazine monohydrate (8.62 mL, 178 mmol) in methanol (65 mL) were used to yield the title compound **3c** as a white solid (7.74 g, 30.5 mmol, 86%).

R_f = 0.48 (EtOAc)

$[\alpha]_D^{20}$ = -18.0 (c = 1.0 in MeOH)

IR ν_{max} = 3282 (s, br, O-H, N-H), 2988 (s, C-H), 2901 (s, C-H), 1690 (s, C=O), 1651 (s, C=O), 1615 (m, C=C), 1536 (s, C=C), 1463 (m, C=C), 1451 (m, C=C)

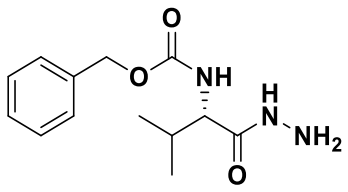
^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 9.10 (1H, br s), 7.35 - 7.40 (4H, m), 7.27 - 7.34 (1H, m) 7.15 (1H, d, *J* = 8.5 Hz), 5.02 (2H, s), 4.84 (1H, t, *J* = 5.8 Hz), 4.21 (2H, br s), 4.02 (1H, dt, *J* = 8.5, 6.0 Hz), 3.47 - 3.58 (2H, m)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 169.8, 156.2, 137.5, 128.8, 128.2, 128.2, 65.9, 62.2, 56.5

HRMS (ESI+): found $[M + H]^+$ 254.1135, $C_{11}H_{16}N_3O_4^+$ required 254.1141

This data is in accordance with that previously reported.[10]

1.2.2.4. Benzyl (S)-(1-hydrazinyl-3-methyl-1-oxobutan-2-yl)carbamate (3d)



Following General Procedure 3: methyl ((benzyloxy)carbonyl)valinate **2d** (9.00 g, 33.92 mmol) and hydrazine monohydrate (8.23 mL, 169 mmol) in methanol (65 mL) were used to yield the title compound **3d** as a white solid (8.85 g, 33.4 mmol, 98%).

R_f = 0.78 (EtOAc)

$[\alpha]_D^{20}$ = +6.6 (c = 1.0 in DMF) - [Literature Value = -12.6 (c = 1.0 in MeOH)][9]

IR ν_{max} = 3313 (m, N-H), 3246 (m, N-H), 2971 (s, C-H), 2901 (s, C-H), 1683 (m, C=O), 1656 (s, C=O), 1527 (s, C=C), 1469 (m, C=C), 1454 (m, C=C)

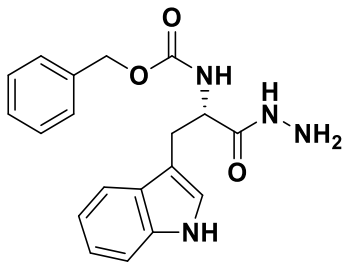
^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 9.09 (1H, br s), 7.28 - 7.37 (5H, m), 7.25 (1H, d, *J* = 8.4 Hz), 4.98 (2H, s), 4.21 (2H, d, *J* = 4.0 Hz), 3.73 (1H, t, *J* = 8.4 Hz), 1.88 (1H, dq, *J* = 8.4, 6.7 Hz), 0.83 (3H, d, *J* = 6.7 Hz), 0.81 (3H, d, *J* = 6.7 Hz)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 170.9, 156.4, 137.6, 128.8, 128.2, 128.1, 65.8, 59.5, 30.7, 19.6, 19.0

HRMS (ESI+): found $[M + H]^+$ 266.1494, $C_{13}H_{20}N_3O_3^+$ required 266.1505

This data is in accordance with that previously reported.[9]

1.2.2.5. Benzyl (S)-(1-hydrazinyl-3-(1H-indol-3-yl)-1-oxopropan-2-yl)carbamate (3e)



Following General Procedure 3: methyl ((benzyloxy)carbonyl)tryptophanate **2e** (2.00 g, 4.26 mmol) and hydrazine monohydrate (1.38 mL, 28.4 mmol) in methanol (10 mL) were used to yield the title compound **3e** as a beige solid (1.24 g, 3.51 mmol, 82%).

R_f = 0.80 (EtOAc)

$[\alpha]_D^{20}$ = -20.6 (c = 1.0 in DMF)

IR ν_{max} = 3431 (w, N-H), 3296 (m, N-H), 3248 (w, N-H), 2988 (s, C-H), 2901 (s, C-H), 1682 (s, C=O), 1648 (s, C=O). 1619 (m, C=C), 1538 (m, C=C), 1461 (m, C=C), 1490 (m, C=C)

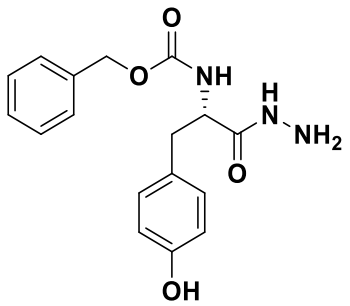
^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 10.79 (1H, br. s.), 9.24 (1H, s), 7.61 (1H, d, *J* = 7.5 Hz), 7.40 (1H, d, *J* = 8.2 Hz), 7.20 - 7.35 (6H, m), 7.13 (1H, s), 7.05 (1H, t, *J* = 7.5 Hz), 6.96 (1H, t, *J* = 7.5 Hz), 4.94 (1H, d, *J* = 12.5 Hz), 4.90 (1H, d, *J* = 12.5 Hz), 4.11 - 4.39 (2H, m), 3.03 (1H, dd, *J* = 14.5, 5.0 Hz), 2.90 (1H, dd, *J* = 14.5, 9.6 Hz)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 171.2, 155.8, 137.1, 136.1, 128.4, 127.8, 127.6, 127.3, 123.9, 120.9, 118.6, 118.3, 111.4, 110.2, 65.3, 54.2, 28.1

HRMS (ESI+): found $[M + H]^+$ 353.1622, $C_{19}H_{21}N_4O_3^+$ required 353.1614

This data is in accordance with that previously reported.[11]

1.2.2.6. Benzyl (S)-(1-hydrazinyl-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)carbamate (3f)



Following General Procedure 3: methyl ((benzyloxy)carbonyl)tyrosinate **2f** (1.50 g, 4.55 mmol) and hydrazine monohydrate (1.10 mL, 22.8 mmol) in methanol (10 mL) were used to yield the title compound **3f** as a white solid (1.27 g, 3.86 mmol, 85%).

R_f = 0.78 (EtOAc)

$[\alpha]_D^{20}$ = -11.9 (c = 0.6 in DMF) - [Literature Value = -11.2 (c = 1.0 in DMF)][12]

IR ν_{max} = 3295 (m, N-H), 3267 (m, O-H), 2988 (s, C-H), 2901 (s, C-H), 1689 (s, C=O), 1665 (s, C=O), 1625 (m, C=C), 1532 (m, C=C), 1513 (m, C=C0, 1453 (m, C=C)

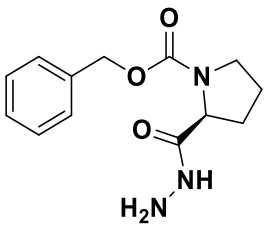
^{1}H NMR (400 MHz, d_6-DMSO): δ_H = 9.17 (1H, s), 9.16 (1H, s), 7.44 (1H, d, *J* = 8.9 Hz), 7.20 - 7.36 (5H, m), 7.03 (2H, d, *J* = 8.7 Hz), 6.63 (1H, , d, *J* = 8.7 Hz), 4.92 (2H, s), 4.21 (2H, br. s), 4.09 (1H, ddd, *J* = 10.2, 8.9, 4.8 Hz), 2.77 (1H, dd, *J* = 13.6, 4.8 Hz), 2.62 (1H, dd, *J* = 13.6, 10.2 Hz)

^{13}C NMR (101 MHz, d_6-DMSO): δ_C = 171.0, 155.8, 155.7, 137.2, 130.2, 128.4, 128.2, 127.7, 127.5, 114.9, 65.2, 55.4, 37.1

HRMS (ESI+): found $[M + H]^+$ 330.1467, $C_{17}H_{20}N_3O_4^+$ required 330.1454

This data is in accordance with that previously reported.[12]

1.2.2.7. Benzyl (S)-2-(hydrazinecarbonyl)pyrrolidine-1-carboxylate (3g)



Following General Procedure 3: methyl ((benzyloxy)carbonyl)pyrrolinate **2g** (1.50 g, 5.70 mmol) and hydrazine monohydrate (1.38 mL, 28.5 mmol) in methanol (12 mL) were used to yield the title compound **3g** as a brown solid (1.44 g, 5.47 mmol, 96%).

R_f = 0.68 (EtOAc)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -48.5 (c = 1.0 in MeOH)

IR ν_{max} = 3315 (w, br, N-H), 3248 (w, br, N-H), 2987 (s, C-H), 2901 (s, C-H), 1659 (s, br, C=O), 1520 (m, C=C), 1411 (s, C=C)

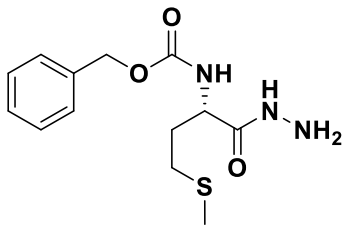
^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 9.15 (2H, d, *J* = 11.9 Hz), 7.25 - 7.44 (10H, m), 5.00 - 5.10 (4H, m), 4.21 (2H, br. s.), 4.16 (1H, dd, *J* = 8.2, 3.4 Hz), 4.12 (1H, dd, *J* = 8.4, 3.2 Hz), 3.37 - 3.52 (4H, m), 2.01 - 2.17 (2H, m), 1.73 - 1.91 (6H, m) – mixture of rotamers

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 171.9, 171.6, 154.4, 154.2, 137.5, 128.8, 128.8, 128.2, 128.0, 127.9, 127.5, 66.3, 66.2, 59.3, 58.7, 47.5, 46.9, 31.6, 30.5, 24.4, 23.5

HRMS (ESI+): found $[M + H]^+$ 264.1336, $C_{13}H_{18}N_3O_3^+$ required 264.1348

This data is in accordance with that previously reported.[13]

1.2.2.8. Benzyl (S)-(1-hydrazinyl-4-(methylthio)-1-oxobutan-2-yl)carbamate (3h)



Following General Procedure 3: methyl ((benzyloxy)carbonyl)methionate **2h** (1.05 g, 3.53 mmol) and hydrazine monohydrate (0.86 mL, 17.6 mmol) in methanol (10 mL) were used to yield the title compound **3h** as a grey solid (849 mg, 2.86 mmol, 81%).

R_f = 0.80 (EtOAc)

$[\alpha]_D^{20}$ = -17.9 (c = 1.0 in MeOH) - [Literature Value = -14.1 (c = 1.0 in MeOH)][14]

IR ν_{max} = 3289 (s, N-H), 2988 (s, C-H), 2901 (s, C-H), 1691 (s, C=O), 1649 (s, C=O), 1534 (s, C=C), 1443 (m, C=C)

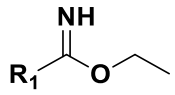
^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 9.11 (1H, br. s.), 7.44 (1H, d, *J* = 8.2 Hz), 7.32 - 7.38 (3H, m), 7.26 - 7.32 (2H, m), 4.99 (2H, S), 4.20 (2H, br. s.), 4.02 (1H, td, *J* = 8.2, 5.8 Hz), 2.35 - 2.48 (2H, m), 2.01 (3H, s), 1.73 - 1.88 (2H, m)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 170.8, 155.9, 137.1, 128.4, 127.9, 127.8, 65.5, 52.6, 31.8, 29.7, 14.6

HRMS (ESI+): found $[M + H]^+$ 298.1219, $C_{17}H_{20}N_3O_3S^+$ required 298.1225

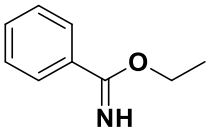
This data is in accordance with that previously reported.[14]

1.2.3. General procedure for the formation of Imidates (5a-f)



General Procedure 1: Acetyl chloride (8 eq.) was added dropwise over 15 minutes to a stirred solution of the required nitrile in ethanol (12 eq.). The mixture was stirred at room temperature overnight. The solution was cooled to 0 °C before the addition of saturated aqueous sodium hydrogen carbonate until the evolution of gas ceased. The solution was then warmed to room temperature and extracted with diethyl ether (3 x 150 mL). The combined organic fractions were washed with brine (50 mL) and dried ($MgSO_4$) before the solvent was removed under reduced pressure to yield the crude compound. The title compound was reacted on without further purification.

1.2.3.1. Ethylphenylcarbimidate (5a)



Following General Procedure 1: benzonitrile **4a** (5.00 mL, 48.5 mmol), acetyl chloride (27.6 mL, 388 mmol) and ethanol (34 mL, 582 mmol) were used to yield the title compound **5a** as a yellow liquid (7.11 g, 47.7 mmol, 98%).

R_f = 0.66 (EtOAc)

IR ν_{max} = 3301 (w, N-H), 2980 (w, C-H), 1631 (s, C=N), 1578 (m, C=C)

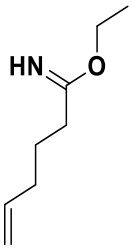
^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.74 (2H, d, *J* = 5.5 Hz), 7.46-7.38 (3H, m), 4.33 (2H, q, *J* = 6.8 Hz), 1.42 (3H, t, *J* = 6.8 Hz)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 167.9, 132.9, 130.7, 128.5, 126.6, 61.8, 14.2

HRMS (ESI+): found $[M + H]^+$ 150.0915, $C_9H_{12}NO^+$ required 150.0919

This data is in accordance with that previously reported.[15]

1.2.3.2. Ethyl hex-5-enimidate (5b)



Following General Procedure 1: 5-hexenenitrile **4b** (0.910 mL, 8.00 mmol), acetyl chloride (4.55 mL, 64.0 mmol) and ethanol (5.60 mL, 96.0 mmol) were used the yield the title compound **5b** as an orange liquid (1.13 g, 8.00 mmol, 100%).

R_f = 0.21 (20% EtOAc in hexane)

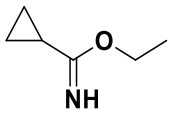
IR ν_{max} = 2936 (m, C-H), 1642 (s, C=N), 1537 (s, C=C)

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 11.45 (1H, s), 5.75 (1H, ddt, *J* = 17.1, 10.3, 7.1 Hz), 4.98 - 5.09 (2H, m), 4.62 (2H, q, *J* = 6.9 Hz), 2.73 (2H, t, *J* = 7.1 Hz), 2.13 (2H, q, *J* = 7.1 Hz), 1.83 (2H, quin, *J* = 7.1 Hz), 1.47 (3H, t, *J* = 6.9 Hz)

^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 179.1, 136.3, 116.3, 70.6, 32.6, 32.4, 24.8, 13.5

This data is in accordance with that previously reported.

1.2.3.3. Ethyl cyclopropanecarbimidate (5c)



Following General Procedure 1: cyclopropanebenzonitrile **4c** (2.80 mL, 38.1 mmol), acetyl chloride (12.2 mL, 171 mmol) and ethanol (27 mL) was used the yield the title compound as a white solid **5c** (2.97 g, 26.2 mmol, 69%).

R_f = 0.14 (20 %EtOAc in hexane)

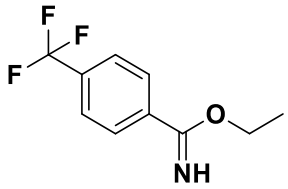
IR: ν_{max} = 2924 (m, C-H), 1636 (s, C=N),

^{1}H NMR (400 MHz, d_6DMSO): δ_H = 4.38 (2H, q, *J* = 7.0 Hz), 2.19 (1H, tt, *J* = 7.8, 4.6 Hz), 2.13 (2H, q, *J* = 7.1 Hz), 1.29 (3H, q, *J* = 7.1 Hz,), 1.10 - 1.23 (4H, m)

^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 178.9, 68.6, 13.2, 12.3, 10.0

This data is in accordance with that previously reported.[16]

1.2.3.4. Ethyl 4-(trifluoromethyl)benzimidate (5d)



Following General Procedure 1: 4-(triflluoromethyl)benzonitrile **4d** (123 mg, 0.73 mmol), acetyl chloride (0.40 mL, 5.70 mmol) and ethanol (0.5 mL) were used the yield the title compound **5d** as a yellow liquid (127 mg, 0.58 mmol, 80%).

R_f = 0.27 (20% EtOAc in hexane)

IR ν_{max} = 3366 (m, N-H), 3048 (m, C-H), 1653 (s, C=N), 1624 (s, C=C), 1577 (m, C=C)

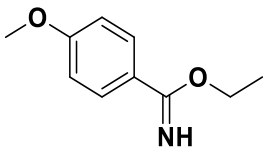
^{1}H NMR (400 MHz, d_6-DMSO): δ_H = 8.31 (2H, d, *J* = 8.2 Hz), 8.02 (2H, d, *J* = 8.2 Hz), 4.65 (2H, q, *J* = 7.0 Hz), 1.49 (3H, t, *J* = 7.0 Hz)

^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 169.8, 131.3, 130.4, 128.8, 126.4, 115.6, 69.9, 13.9

HRMS (ESI+): found $[M + H]^+$ 218.0798, $C_{10}H_{11}F_3NO^+$ required 218.0793

This data is in accordance with that previously reported.[17]

1.2.3.5. Ethyl 4-methoxybenzimidate (5e)



Following General Procedure 1: 4-methoxybenzonitrile **4e** (1.06 g, 8.00 mmol), acetyl chloride (4.55 mL, 64.0 mmol) and ethanol (5.6 mL, 96.0 mmol) were used the yield the title compound **5e** as an orange liquid (1.28 g, 7.14 mmol, 89%).

R_f = 0.84 (EtOAc)

IR ν_{max} = 2980 (m, C-H), 1630 (s, C=N), 1607 (s, C=C), 1512 (m, C=C)

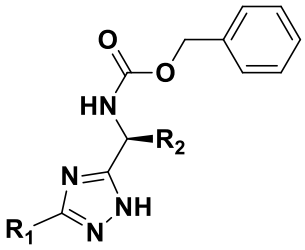
^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 8.39 - 8.81 (1H, br s), 7.80 (2H, d, *J* = 9.0 Hz), 6.97 (2H, d, *J* = 9.0 Hz), 4.20 (2H, q, *J* = 6.8 Hz), 3.79 (3H, s), 1.31 (2H, t, *J* = 6.8 Hz)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 161.2, 131.3, 128.6, 114.1, 113.7, 60.6, 55.4, 14.3

HRMS (ESI+): found $[M + H]^+$180.1020, $C_{10}H_{14}NO_2^+$ required 180.1025

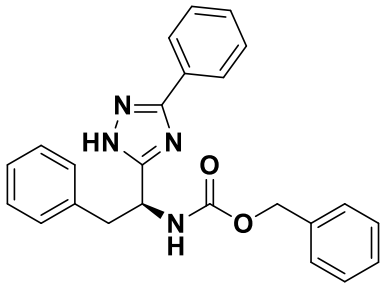
This data is in accordance with that previously reported.[18]

1.2.4. General Procedure for the Formation of Benzyl –(S)-(2-R_2-((3-R_1-1H-1,2,4-triazol-5-yl)methyl)carbamates (6a-l)



General Procedure 4: A stirred solution of the required imidate (1.2 eq.) and methyl ((benzyloxy)carbonyl) amino hydrazide (1.0 eq.) in ethanol (0.5 M) was heated at reflux for 2 hours. Acetic acid (1 M) was added and the solution was refluxed for 2 hours. The solvent was removed under reduced pressure. The resultant crude product was purified by flash column chromatography to yield the title compound

1.2.4.1. Benzyl (S)-(2-phenyl-1-(3-phenyl-1H-1,2,4-triazol-5-yl)ethyl)carbamate (6a)



Following General Procedure 4: ethyl benzimidate **5a** (4.00 g, 12.8 mmol) and benzyl (*S*)-(1-hydrazinyl-1-oxo-3-phenylpropan-2-yl)carbamate **3b** (2.28 g, 15.3 mmol) in ethanol (25 mL), followed by acetic acid (13 mL) were used. The crude product was purified by flash column chromatography eluting with 50% EtOAc in hexane to yield the title compound **6a** as a white solid (4.35 g, 10.9 mmol, 85%).

$\mathbf{R_f}$ = 0.56 (50% EtOAc in hexane)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -6.1 (c = 0.4 in MeOH)

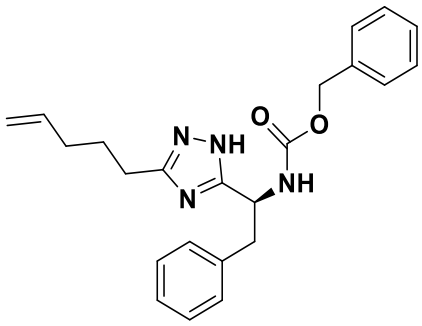
IR ν_{max} = 3250 (w, br, N-H), 2988 (s, C-H), 2901 (s, C-H), 1691 (s, C=O), 1495 (m, C=C), 1454 (m, C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 8.01 (2H, d, *J* = 7.0 Hz), 7.50 (3H, br. s.), 7.33 (2H, d, *J* = 7.3 Hz), 7.30 (1H, d, *J* = 7.3 Hz), 7.25 - 7.29 (6H, m), 7.22 (1H, dt, *J* = 8.2, 4.1 Hz), 5.00 (1H, d, *J* = 12.8 Hz), 4.96 (2H, d, *J* = 12.8 Hz), 3.29 (1H, dd, *J* = 13.6, 4.4 Hz), 3.10 (1H, t, *J* = 13.6 Hz)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 161.0, 158.1, 155.8, 138.0, 137.2, 131.5, 129.3, 128.9, 128.3, 128.2, 128.1, 127.7, 127.5, 126.4, 125.9, 65.3, 49.8, 39.5

HRMS (ESI+): found $[M + H]^+$ 399.1814, $C_{24}H_{23}N_4O_2^+$ required 399.1816

1.2.4.2. Benzyl (S)-(1-(3-(pent-4-en-1-yl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (6b)



Following General Procedure 4: ethyl hex-5-enimidate **5b** (0.65 g, 4.62 mmol) and benzyl (S)-(1-hydrazinyl-1-oxo-3-phenylpropan-2-yl)carbamate **3b** (1.21 g, 3.85 mmol) in ethanol (8 mL), followed by acetic acid (4 mL) were used. The crude product was purified by flash column chromatography eluting with 40% EtOAc in 40-60 petroleum ether to yield the title compound **6b** as a yellow liquid (1.29 g, 3.30 mmol, 86%).

R_f = 0.32 (40% EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -15.9 (c = 0.4 in MeOH)

IR ν_{max} = 3237 (w, N-H), 2988 (s, C-H), 2902 (s, C-H), 1694 (s, C=O), 1522 (m, C=C), 1495 (m, C=C), 1454 (m, C=C)

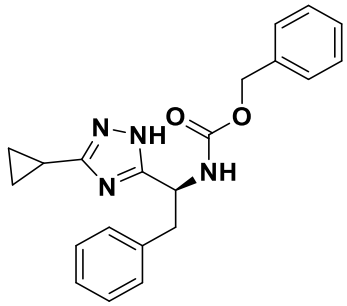
^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 13.34 - 13.43 (1H, m), 7.68 (1H, d, *J* = 9.2 Hz), 7.27 - 7.36 (3H, m), 7.15 - 7.26 (7H, m), 5.83 (1H, ddd, *J* = 17.1, 10.4, 7.5 Hz), 4.91 - 5.08 (4H, m), 4.83 (1H, td, *J* = 9.6, 5.5

Hz), 3.15 (1H, dd, *J* = 13.7, 5.5 Hz), 2.98 (1H, dd, *J* = 13.7, 9.6 Hz), 2.68 (2H, t, *J* = 7.5 Hz), 2.06 (2H, q, *J* = 7.5 Hz), 1.75 (2H, quin, *J* = 7.5 Hz)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 164.0, 157.0, 156.1, 139.0, 138.4, 137.7, 129.7, 128.7, 128.4, 128.0, 127.8, 126.5, 115.8, 65.4, 51.5, 39.5, 33.0, 27.0, 25.6

HRMS (ESI+): found $[M + H]^+$ 391.2122, $C_{23}H_{26}N_4O_2^+$ required 391.2134

1.2.4.3. Benzyl (S)-(1-(3-cyclopropyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (6c)



Following General Procedure 4: ethyl cyclopropanecarbimidate **5c** (0.95 g, 8.42 mmol) and benzyl (*S*)-(1-hydrazinyl-1-oxo-3-phenylpropan-2-yl)carbamate **3b** (2.10 g, 7.02 mmol) in ethanol (14 mL), followed by acetic acid (7 mL) were used. The crude product was purified by flash column chromatography eluting with 50% EtOAc in 40-60 petroleum ether to yield the title compound **6c** as a white solid (2.07 g, 5.71 mmol, 81%).

R_f = 0.30 (50% EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -16.0 (c = 0.2 in CH_3Cl)

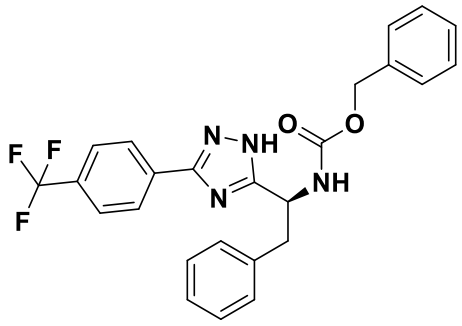
IR ν_{max} = 3315 (m, N-H), 2988 (s, C-H), 2901 (s, C-H), 1682 (s, C=O), 1511 (m, C=C), 1452 (w, C=C), 1393 (m, C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 13.87 (1H, d, *J* = 7.9 Hz), 7.64 (1H, d, *J* = 8.9 Hz), 7.26 - 7.36 (3H, m), 7.13 - 7.25 (7H, m), 4.88 - 5.00 (2H, m), 4.77 (1H, dd, *J* = 10.4, 5.8 Hz), 3.11 (1H, dd, *J* = 13.5, 5.8 Hz), 2.95 (1H, dd, *J* = 13.5, 10.4 Hz), 1.88 - 2.02 (1H, m), 0.99 (2H, d, *J* = 6.1 Hz), 0.86 (2H, br. s.)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 163.4, 158.6, 155.6, 138.5, 137.3, 129.2, 128.2, 128.0 (C9 & 17), 127.6, 127.3, 126.1, 64.9, 51.0, 8.0, 7.0 – sp^3 peak obscured by DMSO peak

HRMS (ESI+): found $[M + H]^+$ 363.1819, $C_{21}H_{23}N_4O_2^+$ required 363.1821

1.2.4.4. Benzyl (S)-(2-phenyl-1-(3-(4-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-5-yl)ethyl)carbamate (6d)



Following General Procedure 4: ethyl 4-(trifluoromethyl)benzimidate **5d** (0.84 g, 3.86 mmol) and benzyl (S)-(1-hydrazinyl-1-oxo-3-phenylpropan-2-yl)carbamate **3b** (1.01 g, 3.22 mmol) in ethanol (7 mL), followed by acetic acid (3.5 mL) were used. The crude product was purified by flash column chromatography eluting with 40% EtOAc in 40-60 petroleum ether to yield the title compound **6d** as a white solid(1.27 g, 2.73 mmol, 85%).

R_f = 0.70 (40% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = -2.3 (c = 0.4 in MeOH)

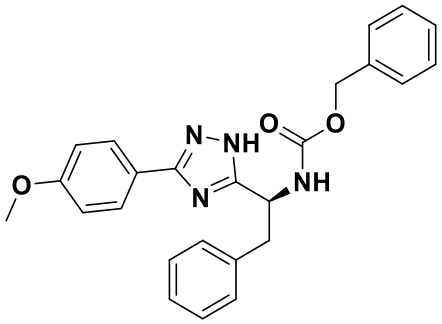
IR ν_{max} = 3250 (w, N-H), 2988 (s, C-H), 2901 (s, C-H), 1698 (s, C=O), 1529 (m, C=C), 1439 (m, C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 14.03 - 14.43 (1H, m), 8.21 (2H, d, *J* = 8.0 Hz), 8.03 (1H, br. s.), 7.86 (2H, d, *J* = 8.0 Hz), 7.23 - 7.36 (9H, m), 7.18 - 7.23 (1H, m), 5.02 (1H, m), 5.02 (1H, d, *J* = 16.0 Hz), 4.95 (1H, d, *J* = 16.0 Hz), 3.30 (1H, dd, *J* = 13.7, 5.4 Hz), 3.11 (1H, dd, *J* = 13.7, 9.7 Hz)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 159.7, 158.6, 155.8, 137.1, 136.1, 135.3, 129.3, 128.4, 128.3, 127.8, 127.5, 126.8, 126.5, 125.9, 125.4, 123.2, 65.4, 49.7, 38.9

HRMS (ESI+): found $[M + H]^+$ 467.1690, $C_{25}H_{22}F_3N_4O_2^+$ required 467.1695

1.2.4.5. Benzyl (S)-(1-(3-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (6e)



Following General Procedure 4: ethyl 4-methoxybenzimidate **5e** (0.75 g, 4.20 mmol) and benzyl (S)-(1-hydrazinyl-1-oxo-3-phenylpropan-2-yl)carbamate **3b** (1.10 g, 3.50 mmol) in ethanol (9 mL), followed by acetic acid (4.5 mL) were used. The crude product was purified by flash column chromatography eluting with 50% EtOAc in 40-60 petroleum ether to yield the title compound **6e** as a white solid (1.31 g, 3.05 mmol, 87%).

R_f = 0.52 (50% EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = +4.7 (c = 0.5 in MeOH)

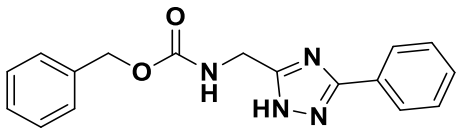
IR ν_{max} = 3220 (w, br, N-H), 2988 (s, C-H), 2901 (s, C-H), 1692 (s, C=O), 1614 (m, C=C), 1583 (w, C=C), 1496 (m, C=C)

^{1}H NMR (400 MHz, d_6-DMSO): δ_H = 7.89 (2H, d, *J* = 8.5 Hz), 7.29 (3H, dd, *J* = 5.2, 1.8 Hz), 7.20 - 7.25 (2H, m), 7.15 - 7.19 (3H, m), 7.09 (2H, d, *J* = 5.2 Hz), 6.90 (2H, d, *J* = 8.5 Hz), 6.31 (1H, d, *J* = 7.4 Hz), 5.29 (1H, q, *J* = 7.4 Hz), 5.09 (1H, d, *J* = 12.5 Hz), 4.96 (1H, d, *J* = 12.2 Hz), 3.83 (3H, s), 3.30 (1H, dd, *J* = 13.7, 6.7 Hz), 3.24 (1H, dd, *J* = 13.7, 7.9 Hz)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 160.9, 158.9, 156.3, 136.5, 136.1, 129.3, 128.4, 128.4, 128.0, 127.8, 126.7, 121.4, 114.2, 66.9, 55.3, 50.2, 40.5

HRMS (ESI+): found $[M + H]^+$ 429.1921, $C_{25}H_{25}N_4O_3^+$ required 429.1927

1.2.4.6. Benzyl ((3-phenyl-1H-1,2,4-triazol-5-yl)methyl)carbamate (6f)



Following General Procedure 4: ethyl benzimidate **5a** (4.01 g, 26.9 mmol) and benzyl (2-hydrazinyl-2-oxoethyl)carbamate **3a** (5.00 g, 22.4 mmol) in ethanol (45 mL), followed by acetic acid (22.5 mL) were used. The crude product was purified by flash column chromatography eluting with ethyl acetate (0-100%) in 40-60 petroleum ether to yield the title compound **6f** as a white solid (4.32 g, 14.0 mmol, 63%).

R_f = 0.33 (50% EtOAc in 40-60 petroleum ether)

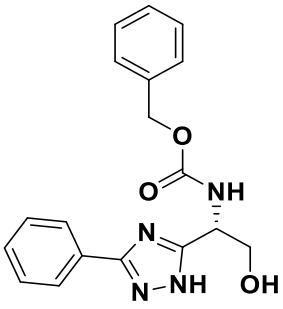
IR: ν_{max} = 3318 (m, N-H), 3126 (m, N-H), 2917 (m, C-H), 1682 (s, C=O), 1537 (s, N-H)

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.02 (2H, d, *J* = 7.2 Hz), 7.45 - 7.58 (3H, m), 7.30 - 7.42 (5H, m), 5.81 (1H, br s), 5.18 (2H, s), 4.71 (2H, d, *J* = 5.8 Hz)

^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 165.3, 163.5, 156.1, 135.9, 131.8, 129.0, 128.5, 128.2, 128.1, 126.9, 123.4, 67.3, 36.2

HRMS (ESI+): found $[M + H]^+$ 309.1356, $C_{17}H_{17}N_4O_2^+$ required 309.1352

1.2.4.7. Benzyl (S)-(2-hydroxy-1-(3-phenyl-1H-1,2,4-triazol-5-yl)ethyl)carbamate (6g)



Following General Procedure 4: ethyl benzimidate **5a** (1.62 g, 10.9 mmol) and benzyl (S)-(1-hydrazinyl-3-methyl-1-oxobutan-2-yl)carbamate **3c** (2.30 g, 9.08 mmol) in ethanol (7 mL), followed by acetic acid (3.5 mL) were used. The crude product was purified by flash column chromatography eluting with 50% EtOAc in heptane to yield the title compound **6g** as a white solid (2.03 g, 6.00 mmol, 66%).

R_f = 0.57 (50% EtOAc in heptane)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -44.8 (c = 0.2 in MeOH)

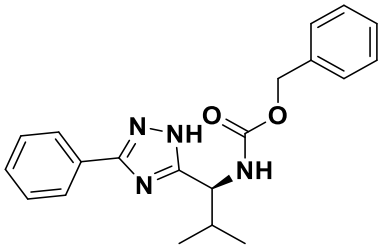
IR ν_{max} = 3397 (w, O-H), 3254 (w, N-H), 2988 (s, C-H), 2901 (s, C-H), 1678 (s, C=O), 1519 (s, C=C), 1470 (m, C=C), 1444 (m, C=C)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 14.00 (1H, br. s.), 7.96 (2H, d, *J*=7.0 Hz), 7.63 (1H, br. s.), 7.44 - 7.51 (2H, m), 7.42 (1H, d, *J* = 7.0 Hz), 7.32 - 7.39 (4H, m), 7.27 - 7.32 (1H, m), 5.06 (1H, d, *J* = 12.3 Hz), 5.02 (1H, d, *J* = 12.3 Hz), 4.79 (1H, q, *J* = 6.7 Hz), 3.80 (1H, dd, *J* = 10.5, 5.6 Hz), 3.69 (1H, dd, *J* = 10.5, 7.2 Hz)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 164.2, 164.1, 156.4, 137.5, 137.5, 129.3, 129.2, 128.8, 128.3, 128.2, 126.3, 66.0, 63.0, 53.1

HRMS (ESI+): found $[M + H]^+$ 339.1457, $C_{18}H_{19}N_4O_3^+$ required 339.1457

1.2.4.8. Benzyl (S)-(2-methyl-1-(3-phenyl-1H-1,2,4-triazol-5-yl)propyl)carbamate (6h)



Following General Procedure 4: ethyl benzimidate **5a** (1.55 g, 10.4 mmol) and benzyl (S)-(1-hydrazinyl-3-methyl-1-oxobutan-2-yl)carbamate **3d** (2.30 g, 8.67 mmol) in ethanol (7 mL), followed by acetic acid (3.5 mL) were used. The crude product was purified by flash column chromatography eluting with 40% EtOAc in 40-60 petroleum ether to yield the title compound **6h** as a white solid (2.48 g, 7.08 mmol, 82%).

R_f = 0.52 (40% EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -62.2 (c = 0.4 in MeOH)

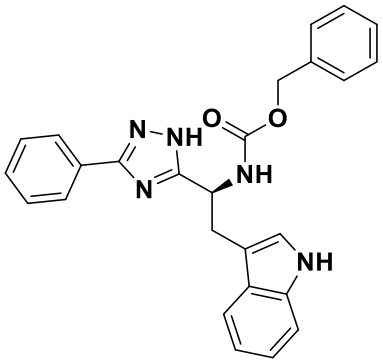
IR ν_{max} = 3250 (w, N-H), 2988 (s, C-H), 2901 (s, C-H), 1679 (s, C=O), 1552 (m, C=C), 1496 (m, C=C), 1452 (m, C=C)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.99 (2H, br. s.), 7.38 - 7.48 (3H, m), 7.27 - 7.35 (5H, m), 6.13 (1H, d, *J* = 8.2 Hz), 5.16 (1H, d, *J* = 12.5 Hz), 5.07 (1H, d, *J* = 12.5 Hz), 4.81 (1H, t, *J* = 8.2 Hz), 2.34 (1H, dd, *J* = 8.2, 6.7 Hz), 0.99 (3H, d, *J* = 6.7 Hz), 0.91 (3H, d, *J* = 6.7 Hz)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 160.1, 159.8, 156.7, 136.1, 129.8, 129.4, 128.8, 128.5, 128.2, 128.0, 126.5, 67.2, 54.5, 32.3, 19.2, 18.4

HRMS (ESI+): found $[M + H]^+$ 351.1813, $C_{20}H_{23}N_4O_2^+$ required 351.1816

1.2.4.9. Benzyl (S)-(2-(1H-indol-3-yl)-1-(3-phenyl-1H-1,2,4-triazol-5-yl)ethyl)carbamate (6i)



Following General Procedure 4: ethyl benzimidate **5a** (0.51 g, 3.41 mmol) and benzyl (S)-(1-hydrazinyl-3-(1H-indol-3-yl)-1-oxopropan-2-yl)carbamate **3e** (1.00 g, 2.84 mmol) in ethanol (5 mL), followed by acetic acid (3 mL) were used. The crude product was purified by flash column chromatography eluting with 50% EtOAc in heptane to yield the title compound **6i** as a yellow solid (0.91 g, 2.09 mmol, 74%).

R_f = 0.48 (50% EtOAc in heptane)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = +9.4 (c = 0.4 in MeOH)

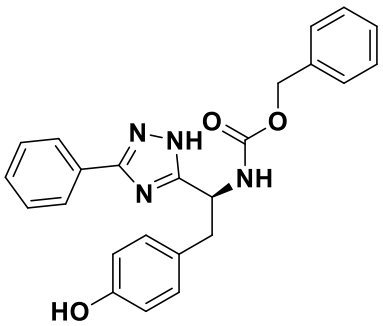
IR ν_{max} = 3258 (w, N-H), 2988 (s, C-H), 2901 (s, C-H), 1669 (s, C=O), 1614 (m, C=C), 1515 (s, C=C), 1475 (m, C=C), 1444 (m, C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 13.90 (1H, br. s.), 10.79 (1H, br. s.), 8.00 (2H, d, *J* = 7.3 Hz), 7.58 (1H, d, *J* = 7.5 Hz), 7.40 - 7.53 (3H, m), 7.30 - 7.34 (3H, m), 7.25 - 7.29 (3H, m), 7.08 (1H, d, *J* = 1.8 Hz), 7.05 (1H, , t, *J* = 7.5 Hz), 6.96 (1H, t, *J* = 7.5 Hz), 5.03 (1H, d, *J* = 6.4 Hz), 4.93 (2H, s), 3.35 - 3.45 (1H, m), 3.18 - 3.28 (1H, m)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 161.8, 161.3, 156.2, 137.5, 136.5, 132.0, 129.2, 128.8, 128.1, 127.9, 127.7, 127.2, 126.3, 124.2, 121.3, 118.8, 118.7, 111.8, 110.3, 79.4, 65.7, sp^3 peak obscured by DMSO peak.

HRMS (ESI+): found $[M + H]^+$ 438.1911, $C_{26}H_{24}N_5O_2^+$ required 438.1930

1.2.4.10. Benzyl (S)-(2-(4-hydroxyphenyl)-1-(3-phenyl-1H-1,2,4-triazol-5-yl)ethyl)carbamate (6j)



Following General Procedure 4: ethyl benzimidate **5a** (0.65 g, 4.34 mmol) and benzyl (S)-(1-hydrazinyl-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)carbamate **3f** (1.19 g, 3.62 mmol) in ethanol (8 mL), followed by acetic acid (3.6 mL) were used. The crude product was purified by flash column chromatography eluting with 50% EtOAc in 40-60 petroleum ether to yield the title compound **6j** as a yellow solid (1.25 g, 3.01 mmol, 83%).

R_f = 0.73 (50% EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = +9.5 (c = 0.4 in MeOH)

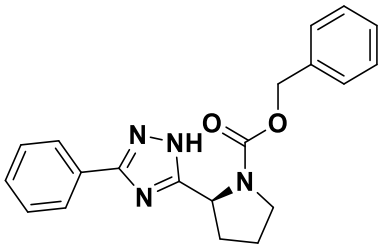
IRν_{max} = 3411 (m, O-H), 3322 (w, N-H), 3254 (m, N-H), 2971 (s, C-H), 2901 (s, C-H), 1699 (s, C=O), 1615 (w, C=C), 1533 (s, C=C), 1469 (m, C=C), 1454 (m, C=C), 1443 (m,C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 9.30 (1 H, br, s.), 7.96 (2H, d, , *J* = 7.5 Hz), 7.82 (1H, br., s.), 7.42 - 7.47 (3H, m), 7.25 - 7.32 (3H, m), 7.22 (1H, d, *J* = 7.0 Hz), 7.01 (2H, d, *J* = 8.5 Hz), 6.62 (2H, d, *J* = 8.5 Hz), 4.98 (1H, d, *J* = 13.0 Hz), 4.92 (1H, d, *J* = 13.0 Hz), 4.86 (1H, dd, *J* = 9.9, 6.0 Hz), 3.12 (1H, dd, *J* = 13.6, 6.0 Hz), 2.93 (1H, dd, *J* = 13.6, 9.9 Hz)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 172.5, 170.8, 156.3, 156.2, 137.6, 130.6, 129.3, 128.7, 128.1, 127.8, 127.0, 126.3, 115.4, 65.6, 60.2, sp^3 peak obscured by DMSO peak.

HRMS (ESI+): found $[M + H]^+$ 415.1758, $C_{24}H_{23}N_4O_3^+$ required 415.1770

1.2.4.11. Benzyl (S)-2-(3-phenyl-1H-1,2,4-triazol-5-yl)pyrrolidine-1-carboxylate (6k)



Following General Procedure 4: ethyl benzimidate **5a** (0.61 g, 4.10 mmol) and benzyl (S)-2-(hydrazinecarbonyl)pyrrolidine-1-carboxylate **3g** (0.90 g, 3.42 mmol) in ethanol (8 mL), followed by acetic acid (4 mL) were used. The crude product was purified by flash column chromatography eluting with 50% EtOAc in 40-60 petroleum ether to yield the title compound **6k** as a white solid (0.83 g, 2.39 mmol, 70%).

R_f = 0.36 (50% EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -73.5 (c = 0.4 in MeOH)

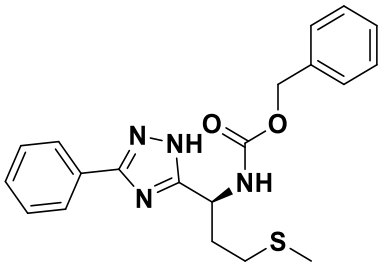
IR ν_{max} = 3062 (m, C-H), 1670 (s, br, C=O), 1555 (w, C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 13.75 - 14.32 (1H, m), 7.99 (2H, br. s.), 7.28 - 7.59 (5H, m), 6.99 - 7.19 (2H, m), 4.85 - 5.15 (3H, m), 3.55 - 3.70 (1H, m), 3.48 (1H, t, *J* = 7.9 Hz), 2.19 - 2.40 (1H, m), 1.83 - 2.11 (3H, m)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 161.4, 159.6, 159.3, 154.6, 154.2, 137.6, 137.3, 132.0, 131.7, 130.5, 129.5 129.3, 129.1, 128.8, 128.7, 128.5, 127.9, 127.1, 126.4, 126.2, 66.5, 66.2, 54.5, 54.1, 47.4, 46.8, 33.3, 32.3, 24.2, 23.4 - mixture of rotamers.

HRMS (ESI+): found $[M + H]^+$ 349.1659, $C_{20}H_{21}N_4O_2^+$ required 349.1665

1.2.4.12. Benzyl (S)-(3-(methylthio)-1-(3-phenyl-1H-1,2,4-triazol-5-yl)propyl)carbamate (6l)



Following General Procedure 4: ethyl benzimidate **5a** (181 mg, 1.21 mmol) and benzyl (S)-(1-hydrazinyl-4-(methylthio)-1-oxobutan-2-yl)carbamate **3h** (300 mg, 1.01 mmol) in ethanol (2 mL), followed by acetic acid (1 mL) were used. The crude product was purified by flash column chromatography eluting with 50% EtOAc in 40-60 petroleum ether to yield the title compound **6l** as a white solid (370 mg, 0.97 mmol, 98%).

R_f = 0.71 (50% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = -40.2 (c = 0.6 in MeOH)

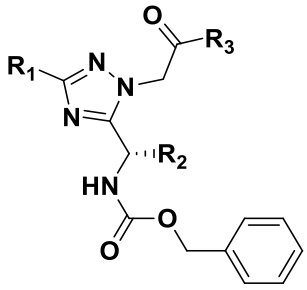
IR ν_{max} = 3269 (w, N-H), 2988 (s, C-H), 2901 (s, C-H), 1691 (m, C=O), 1532 (m, C=C)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 8.00 (1H, d, *J* = 7.0 Hz), 7.39 - 7.48 (3H, m), 7.28 - 7.38 (5H, m), 5.08 - 5.17 (3H, m), 2.51 - 2.64 (2H, m), 2.33 (1H, dt, *J* = 14.3 6.4 Hz), 2.24 (1H, dt, *J* = 14.3, 7.5 Hz), 2.10 (3H, s)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 160.6, 160.0, 156.2, 136.2, 129.8, 128.7, 128.6, 128.8, 128.2, 128.2, 126.4, 67.1, 48.2, 33.8, 30.1, 15.4

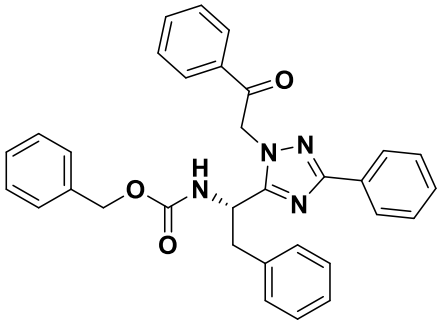
HRMS (ESI+): found $[M + H]^+$ 383.1542, $C_{20}H_{23}N_4O_2S^+$ required 383.1542

1.2.5. General Procedure for the Alkylation of the Heterocycle (7a-p)



General Procedure 5: A solution of the required triazole carbamate (1.0 eq.), the required α-bromoketone (1.2 eq.) and potassium carbonate (1.0 eq.) in DMF (0.2 M) was stirred at room temperature until complete. The reaction was quenched with water and extracted with ethyl acetate (3 x 20 mL). The combined organic fractions were washed brine (10 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure. The resultant crude compound was purified by flash column chromatography on silica to yield the title compound.

1.2.5.1. Benzyl ((1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)methyl)carbamate (7a)



Following General Procedure 5: benzyl ((3-phenyl-1H-1,2,4-triazol-5-yl)methyl)carbamate **6a** (500 mg, 1.26 mmol), 2-bromoacetophenone (300 mg, 1.51 mmol) and potassium carbonate (174 mg, 1.26 mmol) in DMF (3 mL) were used. The crude product was purified by flash column chromatography eluting with 50% EtOAc in heptane to yield the title compound **7a** as a yellow white solid (521 mg, 1.01 mmol, 80%).

R_f = 0.65 (50% EtOAc in heptane)

$[\alpha]_D^{20}$ = +8.5 (c = 0.4 in $CHCl_3$)

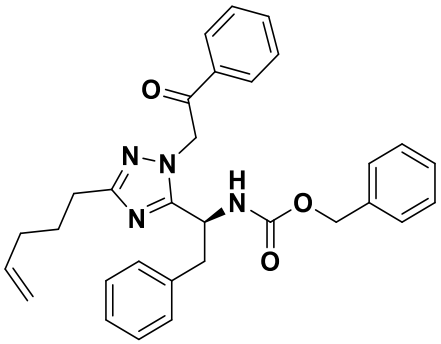
IR ν_{max} = 3209 (w, N-H), 2936 (w, C-H), 1771 (w, C=O), 1711 (s, C=O), 1539 (m, C=N)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 8.10 (2H, dd, *J* = 8.1, 1.4 Hz), 7.92 (2H, d, *J* = 7.5 Hz), 7.65 (1H, tt, *J* = 7.5, 1.2 Hz), 7.52 (2H, t, *J* = 7.5 Hz), 7.38 - 7.47 (3H, m), 7.25 - 7.34 (6H, m), 7.18 - 7.24 (4H, m, H11 & 18), 5.73 (1H, d, *J* = 8.2 Hz), 5.66 (1H, d, *J* = 18.0 Hz), 5.37 (1H, d, *J* = 18.0 Hz), 5.01 (1H, d, *J* = 12.5 Hz), 4.96 (1H, d, *J* = 8.2 Hz), 4.92 (1H, d, *J* = 12.5 Hz), 3.41 (2H, d, *J* = 7.3 Hz)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 191.1, 161.4, 157.3, 156.0, 136.7, 136.0, 134.3, 134.1, 130.8, 129.4, 129.3, 129.0, 128.7, 128.6, 128.5, 128.3, 128.2, 127.8, 127.0, 126.5, 67.0, 54.5, 48.7, 40.5

HRMS (ESI+): found $[M + H]^+$ 517.2232, $C_{32}H_{29}N_4O_3^+$ required 517.2234

1.2.5.2. Benzyl (S)-(1-(1-(2-oxo-2-phenylethyl)-3-(pent-4-en-1-yl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (7b)



Following General Procedure 5: benzyl (S)-(1-(3-(pent-4-en-1-yl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate **6b** (146 mg, 0.370 mmol), 2-bromoacetophenone (92.0 mg, 0.460 mmol) and potassium carbonate (52.0 mg, 0.370 mmol) in DMF (1 mL) were used. The crude product was purified by flash column chromatography eluting with ethyl acetate (0-60%) in 40-60 petroleum ether to yield the title compound **7b** as a yellow liquid (123 mg, 0.240 mmol, 65%).

R_f = 0.42 (40% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = -15.7 (c = 0.1 in $CHCl_3$)

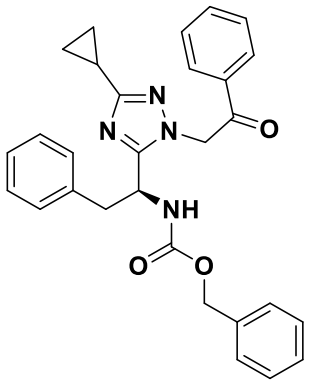
IR: ν_{max} = 3367 (w, N-H), 2988 (s, C-H), 2901 (s, C-H), 1699 (s, C=O), 1597 (w, C=C), 1496 (m, C=C), 1450 (m, C=C)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.97 (2H, d, *J* = 7.9 Hz), 7.63 - 7.72 (1H, m), 7.49 - 7.58 (2H, m), 7.28 - 7.40 (5H, m), 7.14 - 7.23 (3H, m), 6.98 - 7.08 (2H, m), 5.71 - 5.84 (1H, m), 5.51 (1H, d, *J* = 7.9 Hz), 5.46 (2H, s), 5.17 - 5.26 (1H, m), 4.92 - 5.15 (3H, m), 3.25 - 3.32 (1H, m), 3.17 - 3.24 (1H, m), 2.60 (2H, t, *J* = 7.4 Hz), 2.12 (2H, q, *J* = 7.4 Hz), 1.87 (2H, quin, *J*=7.4 Hz)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 190.5, 162.3, 157.9, 155.6, 137.6, 136.6, 136.6, 134.4, 134.1, 129.7, 129.1, 128.5, 128.4, 128.4, 128.1, 128.0, 126.5, 115.6, 66.6, 54.1, 50.8, 41.0, 33.0, 26.5, 25.1

HRMS (ESI+): found $[M + H]^+$ 509.2547, $C_{31}H_{33}N_4O_3^+$ required 509.2553

1.2.5.3. Benzyl (S)-(1-(3-cyclopropyl-1-(2-oxo-2-phenylethyl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (7c)



Following General Procedure 5: benzyl (S)-(1-(3-cyclopropyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate **6c** (763 mg, 2.11 mmol), 2-bromoacetophenone (503 mg, 2.53 mmol) and potassium carbonate (291 mg, 2.11 mmol) in acetone (2 mL) were used. The crude product was purified by flash column chromatography eluting with 30% EtOAc in 40-60 petroleum ether to yield the title compound **7c** as a yellow white solid (540 mg, 1.12 mmol, 53%).

R_f = 0.26 (30% EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = +10.6 (c = 0.3 in $CHCl_3$)

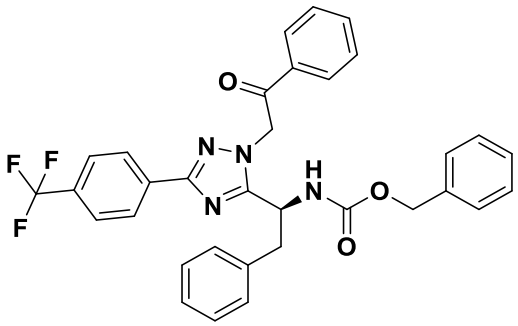
IR ν_{max} = 2902 (s, C-H), 2851 (m, C-H), 1711 (s, C=O), 1604 (w, C=C), 1496 (m, C=C), 1453 (m, C=C)

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.91 (2H, d, *J* = 7.6 Hz), 7.66 (1H, t, *J* = 7.6 Hz), 7.52 (2H, t, *J* = 7.6 Hz), 7.30 - 7.37 (4H, m), 7.21 - 7.28 (4H, m), 7.15 (2H, d, *J* = 5.6 Hz), 5.46 - 5.58 (2H, m), 5.25 (1H, d, *J* = 17.9 Hz), 5.00 (1H, d, *J* = 12.2 Hz), 4.93 (1H, d, *J* = 12.2 Hz), 4.86 (1H, q, *J* = 7.6 Hz), 3.29 (2H, d, *J* = 7.6 Hz), 1.99 - 2.08 (1H, m), 0.95 - 1.01 (4H, m)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 191.2, 165.2, 156.4, 155.8, 136.6, 136.0, 134.2, 134.1, 129.3, 128.9, 128.7, 128.6, 128.4, 128.1, 127.7, 126.9, 66.9, 54.0, 48.4, 40.4, 8.9, 7.8

HRMS (ESI+): found $[M + H]^+$ 481.2237, $C_{29}H_{29}N_4O_3^+$ required 481.2240

1.2.5.4. Benzyl (S)-(1-(1-(2-oxo-2-phenylethyl)-3-(4-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (7d)



Following General Procedure 5: benzyl (S)-(2-phenyl-1-(3-(4-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-5-yl)ethyl)carbamate **6d** (185 mg, 0.400 mmol), 2-bromoacetophenone (95.0 mg, 0.480 mmol) and potassium carbonate (55.0 mg, 0.400 mmol) in acetone (4 mL) were used. The crude product was purified by flash column chromatography eluting with ethyl acetate (0-40%) in 40-60 petroleum ether to yield the title compound **7d** as a white solid (169 mg, 0.290 mmol, 73%).

R_f = 0.45 (20% EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = +4.9 (c = 0.4 in $CHCl_3$)

IR: ν_{max} = 3314 (w, N-H), 2988 (s, C-H), 2901 (s, C-H), 1697 (s, C=O), 1614 (w, C=C), 1533 (m, C=C), 1478 (m, C=C), 1435 (m, C=C), 1406 (m, C=C)

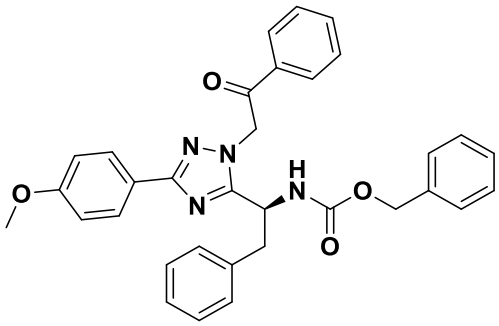
^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 8.21 (2H, d, *J* = 8.0 Hz), 8.11 (1H, d, *J* = 8.9 Hz), 8.01 - 8.06 (2H, m), 7.85 (2H, d, *J* = 8.0 Hz), 7.69 - 7.75 (1H, m), 7.55 - 7.62 (2H, m), 7.16 - 7.32 (8H, m), 7.07 (2H, dd, *J* =

7.3, 2.1 Hz), 6.20 (1H, d, *J* = 18.3 Hz), 6.03 (1H, d, *J* = 18.3 Hz), 5.05 (1H, ddd, *J* = 10.1, 8.9, 4.9 Hz), 4.77 (1H, d, *J* = 12.8 Hz), 4.67 (1H, d, *J* = 12.8 Hz), 3.28 (1H, dd, *J* = 14.0, 10.1 Hz), 3.24 (1H, dd, *J* = 14.0, 4.9 Hz)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 192.7, 159.2, 159.0, 156.3, 138.0, 137.2, 135.1, 134.7, 134.6, 129.8, 129.5, 128.7, 128.5, 128.1, 127.8, 126.9, 126.8, 126.4, 126.3, 123.6, 121.4, 65.8, 55.7, 48.1, 38.5

HRMS (ESI+): found $[M + H]^+$ 585.2124, $C_{33}H_{28}F_3N_4O_3^+$ required 585.2114

1.2.5.5. Benzyl (S)-(1-(3-(4-methoxyphenyl)-1-(2-oxo-2-phenylethyl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (7e)



Following General Procedure 5: benzyl (S)-(1-(3-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate **6e** (500 mg, 1.17 mmol), 2-bromoacetophenone (279 mg, 1.40 mmol) and potassium carbonate (162 mg, 1.17 mmol) in DMF (7 mL) were used. The crude product was purified by flash column chromatography eluting with ethyl acetate (0-40%) in 40-60 petroleum ether to yield the title compound **7e** as a pale yellow solid (494 mg, 0.900 mmol, 77%).

R_f = 0.68 (40% EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = +2.5 (c = 0.4 in $CHCl_3$)

IR: ν_{max} = 3321 (w, N-H), 2988 (s, C-H), 2901 (s, C-H), 1697 (s, C=O), 1613 (w, C=C), 1534 (m, C=C), 1477 (m, C=C), 1451 (m, C=C), 1434 (m, C=C), 1421 (m, C=C)

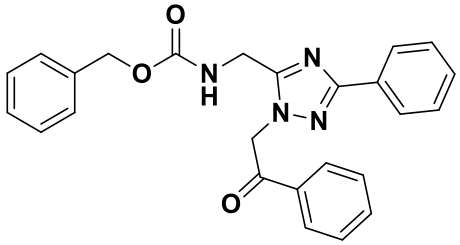
^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 8.08 (1H, d, *J* = 8.5 Hz), 8.04 (2H, dd, *J* = 7.8, 1.2 Hz), 7.90 - 7.95 (2H, m), 7.71 (1H, t, *J* = 7.8 Hz), 7.58 (2H, t, *J* = 7.8 Hz), 7.16 - 7.32 (8H, m), 7.08 (2H, dd, *J* = 7.5, 2.0 Hz), 7.02 (2H, dd, *J* = 8.5, 2.0Hz), 6.13 (1H, d, *J* = 18.3 Hz), 5.95 (1H, d, *J* = 18.3 Hz), 4.98 (1H, ddd, *J* = 10.1,

8.5, 4.9 Hz), 4.77 (1H, d, *J* = 12.5 Hz), 4.68 (1H, d, *J* = 12.5 Hz), 3.80 (1H, s), 3.27 (1H, dd, *J* = 14.0, 10.1 Hz), 3.22 (1H, dd, *J* = 14.0, 4.9 Hz)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 192.9, 160.4, 160.1, 158.4, 156.3, 138.2, 137.2, 134.6, 134.5, 129.8, 129.4, 128.7, 128.7, 128.5, 128.1, 127.7, 127.6, 126.8, 124.0, 114.6, 65.7, 55.7, 55.4, 48.2, 38.6

HRMS (ESI+): found $[M + H]^+$ 547.2345, $C_{33}H_{31}N_4O_4^+$ required 547.2345

1.2.5.6. Benzyl ((1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)methyl)carbamate (7f)



Following General Procedure 5: benzyl ((3-phenyl-1H-1,2,4-triazol-5-yl)methyl)carbamate **6f** (4.00 mg, 13.0 mmol), 2-bromoacetophenone (3.10 mg, 15.6 mmol) and potassium carbonate (1.79 mg, 13.0 mmol) in acetone (10 mL) were used. The crude product was purified by flash column chromatography eluting with ethyl acetate (0-60%) in 40-60 petroleum ether to yield the title compound **7f** as a pale yellow solid (3.99 mg, 9.33 mmol, 72%).

R_f = 0.47 (40% EtOAc in 40-60 petroleum ether)

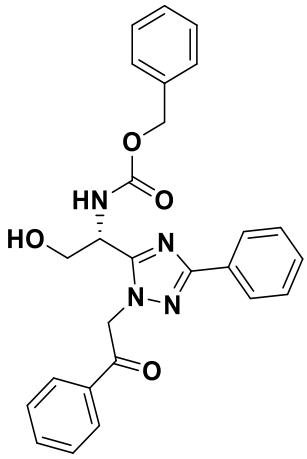
IR: ν_{max} = 3209 (m, N-H0, 2936 (m, C-H), 1771 (m, C=O), 1711 (s, C=O), 1539 (m, N-H)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 8.08 (2H, dd, *J* = 8.1, 1.4 Hz), 8.03 (2H, d, *J* = 7.6 Hz), 7.70 (1H, t, *J* = 7.6 Hz), 7.57 (2H, t, *J* = 7.9 Hz), 7.39 - 7.48 (3H, m), 7.31 - 7.37 (3H, m), 7.30 (2H, m), 5.92 (2H, s), 5.71 (1H, br s), 5.00 (2H, s), 4.54 (2H, d, *J* = 6.1 Hz)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 191.1, 161.1, 156.5, 154.6, 135.9, 134.4, 134.0, 130.3, 129.4, 129.1, 128.6, 128.6, 128.5, 128.2, 128.0, 126.3, 67.2, 55.1, 36.2

HRMS (ESI+): found $[M + H]^+$ 427.1752, $C_{25}H_{23}N_4O_3^+$ required 427.1770

1.2.5.7. (S)-benzyl 2-hydroxy-1-(1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)ethylcarbamate (7g)



Following General Procedure 5: benzyl (S)-(2-hydroxy-1-(3-phenyl-1H-1,2,4-triazol-5-yl)ethyl)carbamate **6g** (300 mg, 0.890 mmol), 2-bromoacetophenone (212 mg, 1.07 mmol) and potassium carbonate (123 mg, 0.890 mmol) in acetone (4 mL) were used. The crude product was purified by flash column chromatography eluting with ethyl acetate (0-40%) in 40-60 petroleum ether to yield the title compound **7g** as a white solid (220 mg, 0.480 mmol, 55%).

R_f = 0.58 (50% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = -23.8 (c = 0.4 in $CHCl_3$)

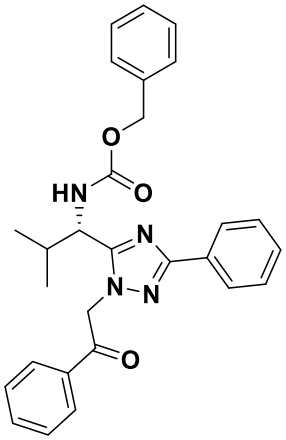
IR: ν_{max} = 3297 (w, br, O-H), 3254 (w, N-H), 2987 (s, C-H), 2901 (s, C-H), 1690 (s, C=O), 1532 (m, C=C), 1446 (m, C=C), 1407 (m, C=C)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 8.06 (2H, dd, *J* = 8.1, 1.7 Hz), 8.01 (2H, d, *J* = 7.8 Hz), 7.67 (1H, t, *J* = 7.8 Hz), 7.55 (2H, t, *J* = 7.8 Hz), 7.38 - 7.45 (3H, m), 7.30 - 7.36 (3H, m), 7.27 (2H, dd, *J* = 8.0, 1.8 Hz), 6.07 (1H, d, *J* = 8.0 Hz), 6.07 (1H, d, *J* = 8.9 Hz), 5.94 (1H, d, *J* = 8.9 Hz), 5.04 (1H, d, *J* = 12.2 Hz), 4.91 (1H, d, *J* = 12.2 Hz), 4.80 (1H, ddd, *J* = 8.0, 3.7, 2.1 Hz), 4.31 (1H, dd, *J* = 11.4, 2.1 Hz), 3.94 (1H, dd, *J* = 11.4, 3.7 Hz)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 191.6, 161.0, 156.9, 156.3, 135.8, 134.4, 134.1, 130.2, 129.5, 129.4, 129.1, 128.6, 128.5, 128.2, 127.9, 126.4, 67.2, 64.0, 55.1, 46.6

HRMS (ESI+): found $[M + H]^+$ 457.1876, $C_{26}H_{25}N_4O_4^+$ required 457.1876

1.2.5.8. Benzyl (S)-(2-methyl-1-(1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)propyl)carbamate (7h)



Following General Procedure 5: benzyl (S)-(2-methyl-1-(3-phenyl-1H-1,2,4-triazol-5-yl)propyl)carbamate **6h** (509 mg, 1.45 mmol), 2-bromoacetophenone (347 mg, 1.74 mmol) and potassium carbonate (201 mg, 1.45 mmol) in DMF (3 mL) were used. The crude product was purified by flash column chromatography eluting with ethyl acetate (0-40%) in 40-60 petroleum ether to yield the title compound **7h** as a white solid (520 mg, 1.14 mmol, 79%).

R_f = 0.50 (30% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$= -62.1 (c = 0.5 in $CHCl_3$)

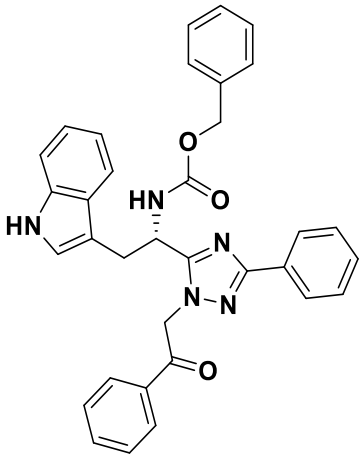
IR: ν_{max} = 3291 (w, N-H), 2988 (s, C-H), 2901 (s, C-H), 1694 (s, C=O), 1597 (w, C=C), 1540 (m, C=C), 1503 (m, C=C), 1470 (m, C=C), 1445 (m, C=C), 1406 (m, C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 8.06 (2H, dd, *J* = 7.5, 1.5 Hz), 7.99 (3H, dt, *J* = 8.2, 1.2 Hz), 7.74 (1H, tt, *J* = 7.5, 1.2 Hz), 7.61 (2H, t, *J* = 7.5 Hz), 7.45 - 7.50 (2H, m), 7.42 (1H, t, *J*=7.0 Hz), 7.27 - 7.36 (5H, m), 6.17 (1H, d, *J* = 18.5 Hz), 6.08 (1H, d, *J* = 18.5 Hz), 4.95 (1H, d, *J* = 12.5 Hz), 4.89 (1H, d, *J* = 12.5 Hz), 4.53 (1H, t, *J* = 9.2 Hz), 2.33 (1H, dt, *J* = 9.2, 6.7 Hz), 1.00 (3H, d, *J* = 6.7 Hz), 0.84 (3H, d, *J* = 6.7 Hz)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 192.7, 160.2, 158.5, 156.6, 137.3, 134.7, 134.5, 131.4, 129.6, 129.4, 129.2, 128.8, 128.7), 128.3, 128.1, 126.1, 66.0, 55.4, 52.8, 31.3, 20.0, 19.4

HRMS (ESI+): found $[M + H]^+$ 469.2240, $C_{28}H_{29}N_4O_3^+$ required 469.2240

1.2.5.9. Benzyl (S)-(2-(1H-indol-3-yl)-1-(1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)ethyl)carbamate (7i)



Following General Procedure 5: benzyl (S)-(2-(1H-indol-3-yl)-1-(3-phenyl-1H-1,2,4-triazol-5-yl)ethyl)carbamate **6i** (100 mg, 0.230 mmol), 2-bromoacetophenone (55.0 mg, 0.270 mmol) and potassium carbonate (32.0 mg, 0.230 mmol) in DMF (1 mL) were used. The crude product was purified by flash column chromatography eluting with ethyl acetate (0-70%) in 40-60 petroleum ether to yield the title compound **7i** as a white solid (103 mg, 0.190 mmol, 81%).

R_f = 0.56 (50% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = +39.3 (c = 0.4 in $CHCl_3$)

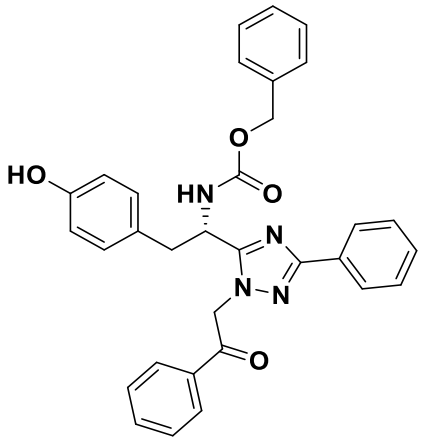
IR: ν_{max} = 3316 (w, N-H), 2988 (s, C-H), 2901 (s, C-H), 1698 (s, C=O), 1533 (m, C=C), 1445 (m, C=C), 1408 (m, C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 10.84 (1H, d, *J* = 2.1 Hz), 8.16 (1H, d, *J* = 8.2 Hz), 8.07 (2H, d, *J* = 7.3 Hz), 8.04 (2H, dt, *J* = 7.3, 1.5 Hz), 7.74 (1H, tt, *J* = 7.3, 1.3 Hz), 7.62 (2H, t, *J* = 7.3 Hz), 7.48 - 7.53 (3H, m,), 7.45 (1H, tt, *J* = 7.3, 1.8 Hz), 7.33 (1H, d, *J* = 7.0 Hz), 7.24 - 7.31 (3H, m), 7.22 (1H, d, *J* = 2.1 Hz), 7.15 (2H, dd, *J* = 7.6, 1.8 Hz), 7.04 (1H, t, *J* = 7.0 Hz), 6.88 (1H, t, *J* = 7.0 Hz), 6.16 (1H, d, *J* = 18.3 Hz), 6.00 (1H, d, *J* = 18.3 Hz), 4.91 (1H, ddd, *J* = 10.1, 8.2, 5.0 Hz), 4.83 (1H, d, *J* = 12.5 Hz), 4.78 (1H, d, *J* = 12.5 Hz), 3.43 (1H, dd, *J* = 14.9, 10.1 Hz), 3.34 (1H, dd, *J* = 14.9, 5.0 Hz)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C =193.0, 160.2, 159.0, 156.4, 137.1, 136.5, 134.8, 134.4, 131.4, 129.6, 129.4, 129.2, 128.7, 128.7, 128.2, 127.9, 127.5, 126.2, 124.7, 121.3, 118.8, 118.5, 111.9, 110.3, 65.9, 55.6, 47.7, 28.9

HRMS (ESI+): found $[M + H]^+$ 556.2332, $C_{34}H_{30}N_5O_3^+$ required 556.2349

1.2.5.10. Benzyl (S)-(1-(1-(2-(4-hydroxyphenyl)-2-oxoethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (7j)



Following General Procedure 5: benzyl (S)-(2-(4-hydroxyphenyl)-1-(3-phenyl-1H-1,2,4-triazol-5-yl)ethyl)carbamate **6j** (131 mg, 0.320 mmol), 2-bromoacetophenone (75.0 mg, 0.380 mmol) and potassium carbonate (47.0 mg, 0.320 mmol) in acetone (1 mL) were used. The crude product was purified by flash column chromatography eluting with ethyl acetate (0-60%) in 40-60 petroleum ether to yield the title compound **7j** as a white solid (57.0 mg, 0.110 mmol, 33%).

R_f = 0.47 (40% EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = +43.5 (c = 0.2 in MeOH)

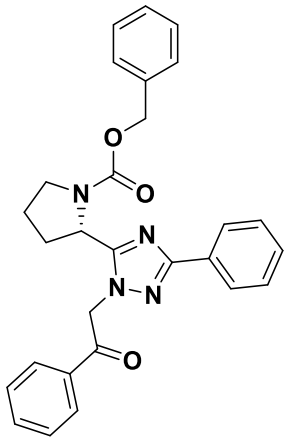
IR: ν_{max} = 3318 (w, N-H), 3290 (w, br, O-H), 2988 (s, C-H), 2901 (s, C-H), 1689 (s, C=O), 1598 (w, C=C), 1515 (m, C=C), 1474 (m, C=C), 1448 (m, C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 9.18 (1H, s), 8.04 (2H, d, *J* = 7.8 Hz), 7.95 - 8.05 (3H,m , H3 & 14), 7.72 (1H, t, *J* = 7.8 Hz), 7.59 (2H, t, *J* = 7.8 Hz), 7.47 (2H, t, *J* = 7.6 Hz), 7.39 - 7.44 (1H, m), 7.23 - 7.28 (3H, m), 7.08 (3H, t, *J* = 8.5 Hz), 6.62 (2H, d, *J* = 8.5 Hz), 6.13 (1H, d, *J* = 18.6 Hz), 5.97 (1H, d, *J* = 18.6 Hz), 4.90 (1H, td, *J* = 10.0, 5.3 Hz), 4.79 (1H, d, *J* = 13.0 Hz), 4.69 (1H, d, *J* = 13.0 Hz), 3.15 (1H, dd, *J* = 14.0, 10.0 Hz), 3.09 (1H, dd, *J* = 14.0, 5.3 Hz)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 192.8, 160.2, 158.7, 156.3, 156.3, 137.2, 124.8, 134.7, 134.5, 131.2, 130.7, 129.4, 129.3, 128.7, 128.6, 128.2, 128.1, 127.6, 126.1, 115.4, 65.7, 55.4, 48.5, 37.8

HRMS (ESI+): found $[M + H]^+$ 533.2178, $C_{32}H_{29}N_4O_4^+$ required 533.2162

1.2.5.11. Benzyl (S)-2-(1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)pyrrolidine-1-carboxylate (7k)



Following General Procedure 5: benzyl (S)-2-(3-phenyl-1H-1,2,4-triazol-5-yl)pyrrolidine-1-carboxylate **6k** (300 mg, 0.860 mmol), 2-bromoacetophenone (180 mg, 0.900 mmol) and potassium carbonate (119 mg, 0.860 mmol) in DMF (2 mL) were used. The crude product was purified by flash column chromatography eluting with ethyl acetate (0-50%) in 40-60 petroleum ether to yield the title compound **7k** as a pale yellow solid (322 mg, 0.690 mmol, 80%).

R_f = 0.41 (30% EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = +3.9 (c = 0.4 in $CHCl_3$)

IR: ν_{max} = 2987 (s, C-H), 2901 (s, C-H), 1694 (s, C=O), 1597 (w, C=C), 1581 (w, C=C), 1479 (w, C=C), 1446 (m, C=C), 1410 (m, C=C)

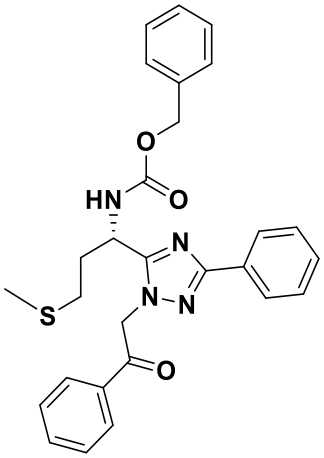
^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 8.12 (2H, d, *J* = 7.3 Hz), 7.94 - 8.01 (5H, m), 7.71 - 7.79 (2H, m), 7.57 - 7.66 (4H, m), 7.39 - 7.51 (6H, m), 7.26 - 7.36 (5H, m), 7.15 - 7.25 (2H, m), 7.09 (2H, d, *J* = 7.3 Hz), 6.24 (1H, d, *J* = 18.6 Hz), 6.13 (1H, d, *J* = 18.6 Hz), 5.90 (1H, d, *J* = 18.6 Hz), 5.79 (1H, d, *J* = 18.6 Hz), 5.11 (1H, dd, *J* = 7.2, 4.1 Hz), 5.06 (1H, dd, *J* = 7.2, 4.1 Hz), 5.00 - 5.05 (2H, m), 4.93 - 5.00 (2H, m), 3.56 - 3.65

(2H, m), 3.48 - 3.55 (2H, m), 2.28 - 2.42 (2H, m), 2.16 - 2.28 (2H, m), 2.08 - 2.01 (2H, m), 1.85 - 2.00 (2H, m) – mixture of rotamers.

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 193.1, 192.8, 160.4, 160.2, 159.6, 159.1, 154.6, 153.8, 137.3, 137.2, 134.7, 134.6, 134.5, 131.3, 129.6, 129.4, 129.4, 129.2, 128.8, 128.7, 128.6, 128.2, 128.1, 127.8, 127.8, 126.2, 126.1, 66.5, 55.4, 55.0, 52.3, 51.7, 47.4, 46.8, 33.0, 31.8, 24.6, 23.6

HRMS (ESI+): found $[M + H]^+$ 467.2071, $C_{28}H_{27}N_4O_3^+$ required 467.2083

1.2.5.12. Benzyl (S)-(3-(methylthio)-1-(1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)propyl)carbamate (7l)



Following General Procedure 5: benzyl (S)-(3-(methylthio)-1-(3-phenyl-1H-1,2,4-triazol-5-yl)propyl)carbamate **6l** (500 mg, 1.00 mmol), 2-bromoacetophenone (239 mg, 1.20 mmol) and potassium carbonate (138 mg, 1.00 mmol) in DMF (2 mL)were used. The crude product was purified by flash column chromatography eluting with ethyl acetate (0-60%) in 40-60 petroleum ether to yield the title compound **7l** as a white solid (468 mg, 0.930 mmol, 93%).

R_f = 0.90 (50% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = -23.1 (c = 0.2 in $CHCl_3$)

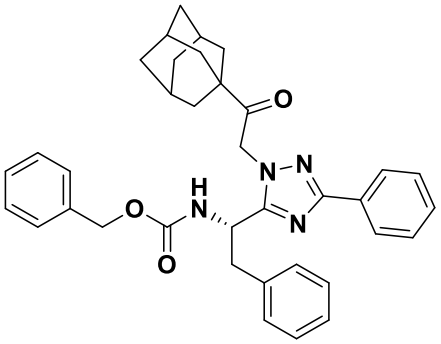
IR: ν_{max} = 3280 (w, N-H), 2987 (s, C-H), 2901 (s, C-H), 1691 (s, C=O), 1596 (w, C=C), 1526 (m, C=C), 1512 (m, C=C), 1475 (m, C=C), 1445 (m, C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 8.08 (1H, d, *J* = 8.2 Hz), 8.05 (2H, d, *J* = 7.8 Hz), 7.97 (2H, dd, *J* = 8.4, 1.4 Hz), 7.69 - 7.78 (1H, m), 7.60 (2H, t, *J* = 7.8 Hz), 7.44 - 7.48 (2H, m), 7.41 (1H, m, *J* = 1.4 Hz), 7.29 - 7.32 (5H, m), 6.17 (1H, d, *J* = 18.5 Hz), 6.04 (1H, d, *J* = 18.5 Hz), 4.92 (1H, d, *J* = 12.5 Hz), 4.85 - 4.90 (1H, m), 4.83 (1H, d, *J* = 12.5 Hz), 2.42 - 2.52 (1H, m), 2.41 - 2.47 (1H, m), 2.17 (2H, m), 1.99 (3H, s)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 192.9, 160.3, 158.6, 156.5, 137.1, 134.7, 134.6, 131.3, 129.6, 129.4, 129.2, 128.8, 128.7, 128.3, 128.1, 126.1, 66.1, 55.5, 45.7, 32.5, 30.0, 14.9

HRMS (ESI+): found $[M + H]^+$ 501.1946, $C_{28}H_{29}N_4O_3S^+$ required 501.1960

1.2.5.13. (S)-benzyl 1-(1-(2-oxo-2-((1R,3R)-adamantan-1-yl)ethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethylcarbamate (7m)



Following General Procedure 5: benzyl (S)-(2-phenyl-1-(3-phenyl-1H-1,2,4-triazol-5-yl)ethyl)carbamate **6a** (300 mg, 0.750 mmol), 1-((3*R*, 5*R*, 7*R*)-adamantam-1-yl)-2-bromo-ethan-1-one (232 mg, 0.900 mmol) and potassium carbonate (104 mg, 0.750 mmol) in DMF (2 mL), was used to yield the title compound **7m** as a white solid (374 mg, 0.650 mmol, 87%).

R_f = 0.67 (30% EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -20.7 (c = 0.4 in $CHCl_3$)

IR: ν_{max} = 3313 (w, N-H), 2971 (s, C-H), 2902 (w, C-H), 1698 (s, C=O), 1536 (m, C=C), 1475 (m, C=C), 1445 (m, C=C), 1404 (m, C=C)

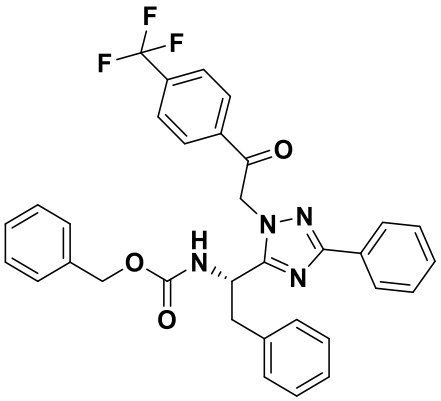
^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 8.12 (1H, d, *J* = 8.9 Hz), 7.97 (2H, dt, *J* = 7.4, 1.4 Hz), 7.46 (2H, t, *J* = 7.4 Hz), 7.41 (1H, tt, *J* = 7.4, 1.4 Hz), 7.24 - 7.31 (7H, m), 7.21 (1H, tt, *J* = 6.6, 2.5 Hz), 7.16 (2H, d, *J* = 6.1

Hz), 5.53 (1H, d, *J* = 18.5 Hz), 5.46 (1H, d, *J* = 18.5 Hz), 4.93 (1H, d, *J* = 12.5 Hz), 4.87 (1H, d, *J* = 12.5 Hz), 4.78 (1H, ddd, *J* = 10.1, 8.9, 4.6 Hz), 3.26 (1H, dd, *J* = 13.7, 10.1 Hz), 3.15 (1H, dd, *J* = 13.7, 4.6 Hz), 2.01 (3H, br. s.), 1.87 (6H, q, *J* = 12.2 Hz), 1.69 (6H, br. s.)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 207.7, 160.1, 158.4, 156.4, 138.2, 137.2, 131.3, 129.8, 129.6, 129.2, 128.7, 128.6, 128.2, 127.8, 126.9, 126.1, 65.9, 53.9, 48.2, 45.4, 38.6, 37.6, 36.3, 27.7

HRMS (ESI+): found $[M + H]^+$ 575.3016, $C_{36}H_{39}N_4O_3^+$ required 575.3022

1.2.5.14. (S)-benzyl 1-(1-(2-oxo-2-(4-(trifluoromethyl)phenyl)ethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethylcarbamate (7n)



Following General Procedure 5: benzyl (S)-(2-phenyl-1-(3-phenyl-1H-1,2,4-triazol-5-yl)ethyl)carbamate **6a** (300 mg, 0.750 mmol), 2-bromo-1-(4-(trifluoromethyl)phenyl)ethan-1-one (240 mg, 0.900 mmol) and potassium carbonate (104 mg, 0.750 mmol) in acetone (1.5 mL) were used. The crude product was purified by flash column chromatography eluting with ethyl acetate (0-40%) in 40-60 petroleum ether to yield the title compound **7n** as a white solid (290 mg, 0.500 mmol, 66%).

R_f = 0.67 (50% EtOAc in heptane)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = +3.8 (c = 0.4 in $CHCl_3$)

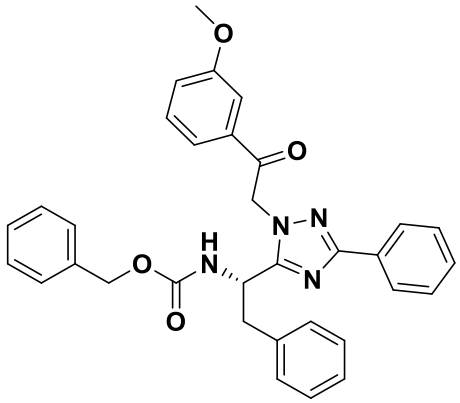
IR: ν_{max} = 3310 (w, N-H), 2974 (s, C-H), 2901 (s, C-H), 1698 (s, C=O), `535 (m, C=C), 1475 (m, C=C), 1445 (m, C=C), 1408 (m, C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 8.21 (2H, d, *J* = 8.2 Hz), 8.09 (1H, d, *J* = 9.4 Hz), 7.99 - 8.03 (2H, m), 7.96 (2H, d, *J* = 8.2 Hz), 7.45 - 7.51 (2H, m), 7.42 (1H, tt, *J* = 7.3, 1.8 Hz), 7.31 (2H, d, *J* = 7.0 Hz), 7.16 - 7.28 (6H, m), 7.06 (2H, dd, *J* = 7.2, 2.3 Hz), 6.23 (1H, d, *J* = 18.6 Hz), 6.06 (1H, d, *J* = 18.6 Hz), 5.06 (1H, td, *J* = 9.4, 5.0 Hz), 4.76 (1H, d, *J* = 12.5 Hz), 4.67 (1H, d, *J* = 12.5 Hz), 3.26 - 3.30 (1H, m), 3.22 (1H, dd, *J* = 14.0, 5.0 Hz)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 192.5, 160.3, 158.6, 156.2, 138.1, 137.8, 137.2, 133.7,131.3, 129.9, 129.6, 129.3, 129.1, 128.7, 128.5, 128.1, 127.7, 126.9, 126.3, 126.2, 123.1, 65.7, 55.8, 48.0, 38.5

HRMS (ESI+): found $[M + H]^+$ 585.2093, $C_{33}H_{28}F_3N_4O_3^+$ required 585.2114

1.2.5.15. Benzyl (S)-(1-(1-(2-(3-methoxyphenyl)-2-oxoethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (7o)



Following General Procedure 5: benzyl (S)-(2-phenyl-1-(3-phenyl-1H-1,2,4-triazol-5-yl)ethyl)carbamate **6a** (200 mg, 0.500 mmol), 2-bromo-3'-methoxyacetophenone (137 mg, 0.600 mmol) and potassium carbonate (69.0 mg, 0.500 mmol) in acetone (1 mL), was used to yield the title compound **7o** as a white solid (137 mg, 0.250 mmol, 50%).

R_f = 0.74 (50% EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = +10.0 (c = 0.3 in $CHCl_3$)

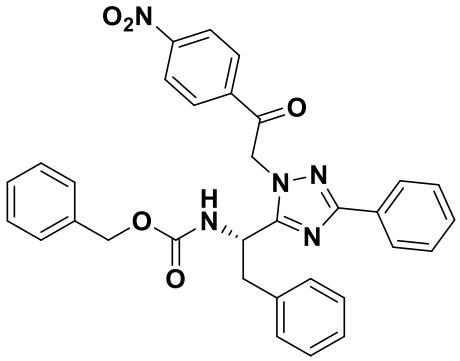
IR: ν_{max} = 3300 (w, N-H), 2972 (s, C-H), 2901 (s, C-H), 1698 (s, C=O), 1536 (m, C=C), 1475 (m, C=C), 1445 (m, C=C), 1408 (m, C=C)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 8.11 (2H, d, *J* = 7.0 Hz), 7.40 - 7.52 (7H, m), 7.29 - 7.36 (5H, m), 7.23 - 7.27 (2H, m), 7.22 (1H, dd, *J* = 2.6, 1.1 Hz), 7.21 (2H, dt, *J* = 4.0, 1.5 Hz), 5.58 - 5.70 (2H, m), 5.32 (1H, d, *J* = 18.0 Hz), 5.03 (1H, d, *J* = 12.2 Hz), 4.92 - 4.99 (2H, m), 3.88 (3H, s), 3.43 (1H, dd, *J*=14.0, 7.9 Hz), 3.39 (1H, dd, *J* = 14.0, 6.4 Hz)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 191.0, 161.4, 160.0, 157.3, 155.9, 136.6, 136.0, 135.4, 130.8, 130.0, 129.4, 129.2, 128.7, 128.5, 128.5, 128.1, 127.8, 127.0, 126.4, 120.9, 120.6, 112.3, 67.0, 55.5, 54.5, 48.7, 40.6

HRMS (ESI+): found $[M + H]^+$ 547.2343, $C_{33}H_{31}N_4O_4^+$ required 547.2345

1.2.5.16. Benzyl (S)-(1-(1-(2-(4-nitrophenyl)-2-oxoethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (7p)



Following General Procedure 5: benzyl (S)-(2-phenyl-1-(3-phenyl-1H-1,2,4-triazol-5-yl)ethyl)carbamate **6a** (185 mg, 0.460 mmol), 2-bromo-4'-nitroacetophenone (136 mg, 0.560 mmol) and potassium carbonate (64.0 mg, 0.460 mmol) in DMF (5 mL) were used. The crude product was purified by flash column chromatography eluting with ethyl acetate (0-40%) in 40-60 petroleum ether to yield the title compound **7p** as a yellow solid (131 mg, 0.230 mmol, 50%).

R_f = 0.24 (30% EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = +18.3 (c = 0.1 in $CHCl_3$)

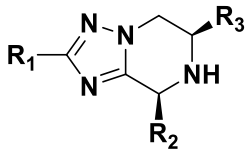
IR: ν_{max} = 3299 (w, N-H), 2971 (s, C-H), 2901 (s, C-H), 1698 (s, C=O), 1536 (s, N-O), 1475 (m, C=C), 1445 (m, C=C), 1407 (m, C=C), 1324 (m, N-O)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 8.38 (2H, d, *J* = 8.9 Hz), 8.24 (2H, d, *J* = 8.9 Hz), 8.10 (1H, d, *J* = 9.4 Hz), 8.00 (2H, d, *J* = 7.3 Hz), 7.48 (2H, t, *J* = 7.3 Hz), 7.43 (1H, t, *J* = 7.3 Hz), 7.31 (2H, d, *J* = 7.3 Hz), 7.15 - 7.26 (6H, m), 7.04 - 7.10 (2H, m), 6.26 (1H, d, *J* = 18.6 Hz), 6.07 (1H, d, *J* = 18.6 Hz), 5.08 (1H, td, *J* = 9.4, 5.0 Hz), 4.77 (1H, d, *J* = 12.5 Hz), 4.68 (1H, d, *J* = 12.5 Hz), 3.26 - 3.30 (1H, m), 3.23 (1H, dd, *J* = 14.0, 5.0 Hz)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 192.3, 160.3, 158.7, 156.3, 150.8, 139.3, 138.0, 137.2, 131.3, 130.1, 129.9, 129.7, 129.3, 128.7, 128.5, 128.1, 127.7, 126.9, 126.2, 124.4, 65.7, 55.9, 47.9, 38.5

HRMS (ESI+): found $[M + H]^+$ 562.2106, $C_{32}H_{28}N_5O_5^+$ required 562.2090

1.2.6. General Procedure for Cyclisation to the Amine (8a-p)

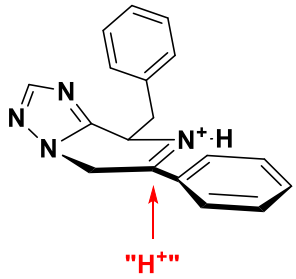


General Procedure 6: To a stirred solution of benzyl –(*S*)-(2-R_2-((3-R_1-1H-1,2,4-triazol-5-yl)methyl)carbamate (1.0 eq.) in minimal ethyl acetate, and a mixture of methanol and water (0.15 M, 3:1 v:v) was added ammonium formate (30 eq.) and palladium dihydroxide (20 mol %). The mixture was stirred overnight until complete conversion to the amine was observed. The catalyst was removed by filtration through celite and the filter pad washed with methanol (3 x 30 mL). The solvent was removed under reduced pressure. The crude compound was purified by flash column chromatography on silica to yield the title compound.

For the purpose of stability, to a stirred solution of the title compound in minimal dichloromethane was added hydrochloride solution (10 eq., 2M in diethyl ether), and the desired salt collected by filtration.

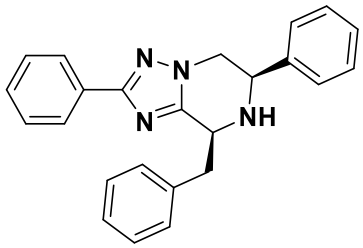
Explanation for stereochemical outcome

The favoured conformation of the imine intermediate will place the benzyl substituent in a pseudo-equatorial orientation, thus hydride attack will be favoured from the convex face of the imine.



Attack from the convex face

1.2.6.1. (6R,8S)-8-benzyl-2,6-diphenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (8a)



Following General Procedure 6: benzyl (S)-(1-(1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate **7a** (188 mg, 364 µmol), ammonium formate (688 mg, 10.9 mmol) and palladium dihydroxide (51.0 mg, 72.8 µmol) in ethyl acetate (1 mL), methanol and water (2 mL, 3:1 v:v,) wereused eluting with 30% ethyl acetate in 40-60 petroleum ether to yield the title compound **8a** as a yellow solid (121 mg, 330 µmol, 91%).

R_f = 0.53 (30% EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -94.3 (c = 0.3 in MeOH)

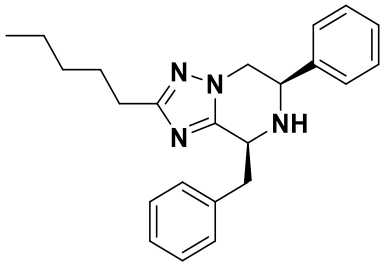
IR ν_{max} = 3028 (m, C-H), 1697 (m, C=N), 1602 (m, C=C)

^{1}H NMR (500 MHz, CD_3OD): δ_H = 8.07 - 8.14 (2H, m), 7.65 - 7.70 (2H, m), 7.55 - 7.60 (3H, m), 7.54 (2H, d, *J* = 7.3 Hz), 7.49 (3H, d, *J* = 6.4 Hz), 7.42 (2H, t, *J* = 7.3 Hz), 7.36 (1H, t, *J* = 7.3 Hz), 5.31 (1H, dd, *J* = 8.9, 5.2 Hz), 5.18 (1H, dd, *J* = 11.0, 5.8 Hz), 4.84 (1H, dd, *J* = 14.0, 5.8 Hz), 4.81 (1H, dd, *J* = 14.0, 11.0 Hz), 3.96 (1H, dd, *J* = 14.8, 5.2 Hz), 3.42 (1H, dd, *J* = 14.8, 8.9 Hz)

^{13}C NMR (126 MHz, CD_3OD): δ_C = 164.0, 151.2, 135.9, 133.4, 131.9, 131.7, 131.1, 131.0, 130.9, 130.3, 129.9, 129.4, 129.1, 127.6, 59.8, 58.2, 50.6, 38.1

HRMS (ESI+): found $[M + H]^+$ 367.1931, $C_{24}H_{23}N_4^+$ required 367.1923

1.2.6.2. (6R,8S)-8-benzyl-2-pentyl-6-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (8b)



Following General Procedure 6: Benzyl (S)-(1-(1-(2-oxo-2-phenylethyl)-3-(pent-4-en-1-yl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate **7b** (102 mg, 201 µmol), ammonium formate (379 mg, 6.02 mmol) and palladium dihydroxide (28.0 mg, 40.1 µmol) in ethyl acetate (1 mL), methanol and water (1 mL, 3:1 v:v,) were used. The crude product was purified by flash column chromatography eluting with 50% ethyl acetate in hexane to yield the title compound **8b** as a white solid (44.0 mg, 125 µmol, 60%).

R_f = 0.14 (20% EtOAc in hexane)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -16.4 (c = 0.1 in MeOH)

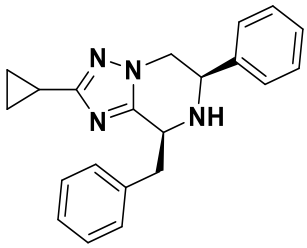
IR ν_{max} = 2929 (m, C-H), 1508 (m, C=C)

^{1}H NMR (500 MHz, CD_3OD): δ_H = 7.64 (2H, dd, *J* = 7.6, 4.0 Hz), 7.51 - 7.55 (3H, m, H18 & 19), 7.47 (2H, d, *J* = 7.3 Hz), 7.39 (2H, t, *J* = 7.3 Hz), 7.32 (1H, t, *J* = 7.3 Hz), 5.20 (1H, dd, *J* = 8.5, 3.7 Hz), 5.04 (1H, dd, *J* = 7.9, 6.7 Hz), 4.61 - 4.74 (2H, m), 3.84 (1H, dd, *J* = 14.8, 3.7 Hz, H9a), 3.37 (1H, dd, *J* = 14.8, 8.5 Hz, H9b), 2.78 (2H, t, *J* = 7.3 Hz), 1.79 (2H, quin, *J* = 7.3 Hz), 1.37 - 1.43 (4H, m, H2 & 3), 0.95 (3H, t, *J* = 6.7 Hz)

^{13}C NMR (126 MHz, CD_3OD): δ_C = 165.9, 150.7, 135.8, 133.9, 131.7, 130.9, 130.7, 130.3, 129.3, 129.1, 59.6, 57.8, 50.7, 38.0, 32.6, 29.0, 28.9, 23.6, 14.5

HRMS (ESI+): found $[M + H]^+$ 361.2401, $C_{23}H_{29}N_4^+$ required 361.2392

1.2.6.3. (6R,8S)-8-benzyl-2-cyclopropyl-6-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (8c)



Following General Procedure 6: benzyl (S)-(1-(3-cyclopropyl-1-(2-oxo-2-phenylethyl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate **7c** (100 mg, 208 µmol), ammonium formate (394 mg, 6.24 mmol) and palladium dihydroxide (29.0 mg, 41.6 µmol) in ethyl acetate (1 mL), methanol and water (1 mL, 3:1 v:v,) were used. The crude product was purified by flash column chromatography eluting with 30% ethyl acetate in hexane to yield the title compound **8c** as a white solid (51.0 mg, 154 µmol, 74%).

R_f = 0.32 (30% EtOAc in hexane)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -40.5 (c = 0.2 in MeOH)

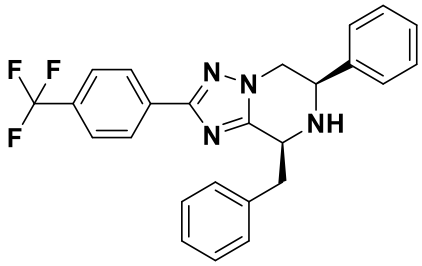
IR: ν_{max} = 2862 (m, C-H)1575 (m,C=C)

^{1}H NMR (500 MHz, CD_3OD): δ_H = 7.60 (2H, dd, *J* = 3.7, 2.1 Hz), 7.51 - 7.56 (3H, m), 7.45 (2H, d, *J* = 7.0 Hz), 7.39 (2H, ddt, *J* = 7.6, 7.0, 1.5 Hz), 7.33 (1H, tt, *J* = 7.6, 1.5 Hz), 5.17 (1H, dd, *J* = 8.9, 4.6 Hz), 5.05 (1H, dd, *J* = 11.3, 5.2 Hz), 4.64 - 4.70 (1H, m), 4.61 (1H, dd, *J* = 12.2, 5.2 Hz), 3.82 (1H, dd, *J* = 15.0, 4.6 Hz), 3.27 (1H, dd, *J* = 15.0, 8.9 Hz), 2.09 (1H, tt, *J* = 8.2, 5.0 Hz), 1.03 - 1.07 (2H, m), 0.93 - 1.03 (2H, m)

^{13}C NMR (126 MHz, CD_3OD): δ_C = 159.6, 150.4, 135.8, 133.6, 131.8, 130.9, 130.8, 130.3, 129.3, 129.1, 59.6, 57.9, 50.4, 38.1, 9.6, 8.7

HRMS (ESI+): found $[M + H]^+$ 331.1923, $C_{21}H_{23}N_4^+$ required 331.1923

1.2.6.4. (6R,8S)-8-benzyl-6-phenyl-2-(4-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (8d)



Following General Procedure 6: benzyl (S)-(1-(1-(2-oxo-2-phenylethyl)-3-(4-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate **7d** (100 mg, 171 µmol), ammonium formate (323 mg, 5.13 mmol) and palladium dihydroxide (24.0 mg, 34.2 µmol) in ethyl acetate (1 mL), methanol and water (1 mL, 3:1 v:v,) were used. The crude product was purified by flash column chromatography eluting with 30% ethyl acetate in hexane to yield the title compound **8d** as a white solid (44.0 mg, 101 µmol, 59%).

R_f = 0.82 (30% EtOAc in hexane)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -98.2 (c = 0.3 in MeOH)

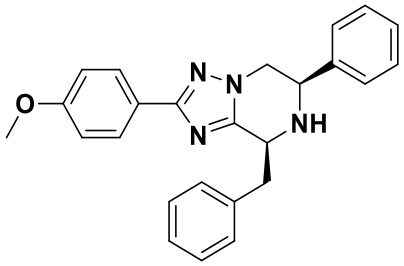
IR ν_{max} = 2972 (m, C-H), 1625 (m, C=N), 1529 (m, C=C)

^{1}H NMR (500 MHz, CD_3OD): δ_H = 8.27 (2H, d, *J* = 8.1 Hz), 7.78 (2H, d, *J* = 8.1 Hz), 7.67 - 7.71 (2H, m), 7.50 - 7.57 (5H, m), 7.40 (2H, t, *J* = 7.3 Hz), 7.33 (1H, tt, *J* = 7.3, 1.2 Hz), 5.30 (1H, dd, *J* = 8.7, 5.3 Hz), 5.16 (1H, dd, *J* = 9.8, 6.7 Hz), 4.80 - 4.85 (2H, m) 3.93 (1H, dd, *J* = 14.8, 5.33 Hz), 3.45 (1H, dd, *J* = 14.8, 8.7 Hz)

^{13}C NMR (126 MHz, CD_3OD): δ_C = 162.7, 151.8, 136.0, 135.5, 133.5, 132.7, 131.9, 131.0, 130.9, 130.3, 129.5, 129.0, 128.0, 126.9, 124.6, 59.8, 58.1, 50.8, 38.0

HRMS (ESI+): found $[M + H]^+$ 435.1790, $C_{25}H_{22}N_4F_3^+$ required 435.1797

1.2.6.5. (6R,8S)-8-benzyl-2-(4-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (8e)



Following General Procedure 6: benzyl (S)-(1-(3-(4-methoxyphenyl)-1-(2-oxo-2-phenylethyl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate **7e** (137 mg, 251 µmol), ammonium formate (474 mg, 7.52 mmol) and palladium dihydroxide (35.0 mg, 50.1 µmol) in methanol and water (1 mL, 3:1 v:v,) were used. The crude product was purified by flash column chromatography eluting with 30% ethyl acetate in hexane to yield the title compound **8e** as a white solid (78.1 mg, 197 µmol, 77%).

R_f = 0.39 (30% EtOAc in hexane)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -48.6 (c = 0.3 in MeOH)

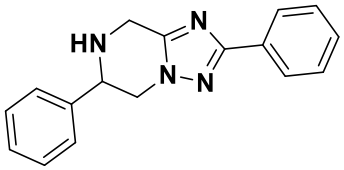
IR ν_{max} = 2969 (m, C-H), 1611 (m, C=N), 1539 (m, C=C)

^{1}H NMR (500 MHz, CD_3OD): δ_H = 8.01 (2H, dt, *J* = 9.1, 2.1 Hz), 7.65 - 7.69 (2H, m), 7.51 - 7.56 (4H, m), 7.50 (1H, s), 7.39 (2H, t, *J* = 7.5 Hz), 7.32 (1H, t, *J* = 7.5 Hz), 7.01 (2H, dt, *J* = 9.1, 2.7 Hz), 5.26 (1H, dd, *J* = 8.7, 4.7 Hz), 5.14 (1H, dd, *J* = 10.1, 6.4 Hz), 4.74 - 4.81 (2H, m), 3.93 (1H, dd, *J* = 14.8, 4.7 Hz), 3.85 (3H, s), 3.42 (1H, dd, *J* = 14.8, 8.7 Hz)

^{13}C NMR (126 MHz, CD_3OD): δ_C = 163.9, 162.8, 151.0, 136.0, 133.4, 131.9, 131.0, 130.8, 130.3, 129.5, 129.1, 129.1, 124.1, 115.3, 59.3, 58.2, 56.0, 50.5, 38.0

HRMS (ESI+): found $[M + H]^+$ 397.2029, $C_{25}H_{24}N_4O^+$ required 397.2028

1.2.6.6. 2,6-diphenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (8f)



Following General Procedure 6: benzyl ((1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)methyl)carbamate **7f** (50.0 mg, 117 µmol), ammonium formate (15.0 mg, 234 mmol) and palladium dihydroxide (16.0 mg, 23.4 µmol) in methanol and water (1 mL, 3:1 v:v,) were used. The crude product was purified by flash column chromatography eluting with ethyl acetate (0-100%) in 40-60 petroleum ether to yield the title compound **8f** as a white solid (23.0 mg, 95.9 µmol, 82%).

R_f = 0.50 (60% EtOAc in 40-60 petroleum ether)

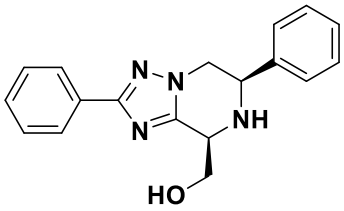
IR: ν_{max} = 2962 (m, C-H), 2938 (m, C-H), 1709 (s, C=N), 1701 (s, C=N)

^{1}H NMR (400 MHz, CD_3OD): δ_H = 8.00 - 8.17 (2H, m), 7.67 - 7.73 (2H, m), 7.58 - 7.64 (3H, m), 7.46 - 7.52 (3H, m), 5.25 (1H, dd, *J* = 11.2, 4.8 Hz), 4.74 - 4.89 (4H, m)

^{13}C NMR (101 MHz, CD_3OD): δ_C = 163.6, 147.5, 133.1, 131.8, 131.2, 131.0, 130.9, 129.8, 128.9, 127.3, 58.5, 58.5, 42.5

HRMS (ESI+): found $[M + H]^+$ 277.1439, $C_{17}H_{17}N_4^+$ required 277.1448

1.2.6.7. ((6R,8R)-2,6-diphenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazin-8-yl)methanol (8g)



Following General Procedure 6: benzyl (S)-(2-hydroxy-1-(1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)ethyl)carbamate **7g** (56.0 mg, 123 µmol), ammonium formate (232 mg, 3.68 mmol) and palladium dihydroxide (17.0 mg, 24.5 µmol) in ethyl acetate (1 mL), methanol and water (1 mL, 3:1

v:v,) were used. The crude product was purified by flash column chromatography eluting with 80% ethyl acetate in hexane to yield the title compound **8g** as a brown solid (31.0 mg, 101 µmol, 82%).

R_f = 0.44 (80% EtOAc in hexane)

$[\alpha]_D^{20}$ = -108.6 (c = 0.3 in MeOH)

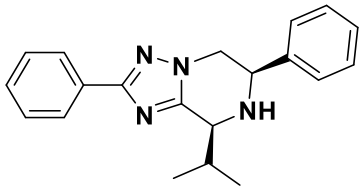
IR ν_{max} = 2927 (m, C-H), 1686 (m, C=N), 1611 (m, C=C), 1556 (m, C=C)

^{1}H NMR (500 MHz, CD_3OD): δ_H = 8.07 - 8.11 (2H, m), 7.72 - 7.77 (2H, m), 7.59 - 7.64 (3H, m), 7.46 - 7.51 (3H, m), 5.28 (1H, dd, *J* = 11.3, 4.9 Hz), 5.14 (1H, dd, *J* = 7.3, 3.7 Hz), 4.85 (1H, ddd, *J* = 13.7, 4.9, 0.6 Hz), 4.79 (1H, ddd, *J* = 13.7, 11.3, 1.2 Hz), 4.48 (1H, dd, *J* = 12.2, 3.7 Hz), 4.28 (1H, dd, *J* = 12.2, 7.3 Hz)

^{13}C NMR (126 MHz, CD_3OD): δ_C = 164.1, 149.2, 133.3, 131.9, 131.6, 131.1, 130.9, 129.9, 129.4, 127.6, 60.6, 59.1, 58.6, 50.5

HRMS (ESI+): found $[M + H]^+$ 307.1539, $C_{18}H_{19}N_4O$ required 307.1553

1.2.6.8. (6R,8S)-8-isopropyl-2,6-diphenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (8h)



Following General Procedure 6: benzyl (S)-(2-methyl-1-(1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)propyl)carbamate **7h** (173 mg, 369 µmol), ammonium formate (693 mg, 11.1 mmol) and palladium dihydroxide (52.0 mg, 73.8 µmol) in ethyl acetate (1 mL), methanol and water (3 mL, 3:1 v:v,) were used. The crude product was purified by flash column chromatography eluting with 30% ethyl acetate in hexane to yield the title compound **8h** as a white solid (99.0 mg, 311 µmol, 84%).

R_f = 0.66 (30% EtOAc in hexane)

$[\alpha]_D^{20}$ = -64.8 (c = 0.2 in MeOH)

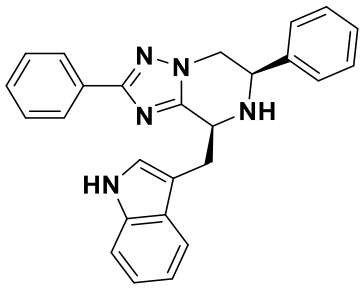
IR ν_{max} = 2974 (m, C-H), 2905 (m, C-H), 1537 (m, C=N), 1520 (m, C=C0, 1488 (m, C=C)

^{1}H NMR (500 MHz, CD_3OD): δ_H = 8.08 (2H, dd, *J* = 7.9, 1.8 Hz), 7.74 - 7.79 (2H, m), 7.56 - 7.61 (3H, m), 7.43 - 7.48 (3H, m), 5.22 (1H, dd, *J* = 11.4, 5.2 Hz), 4.92 (1H, d, *J* = 4.9 Hz), 4.82 (1H, dd, *J* = 13.7, 11.4 Hz), 4.78 (1H, dd, *J* = 13.7, 5.2 Hz), 2.65 (1H, dsep, *J* = 4.9, 7.0 Hz), 1.38 (3H, d, *J* = 7.0 Hz), 1.38 (3H, d, *J* = 7.0 Hz)

^{13}C NMR (400 MHz, CD_3OD): δ_C = 163.9, 150.7, 133.3, 132.0, 131.8, 131.0, 130.9, 129.9, 129.7, 127.5, 62.5, 60.2, 50.4, 31.9, 19.7, 18.9

HRMS (ESI+): found $[M + H]^+$ 319.1912, $C_{20}H_{23}N_4^+$ required 319.1923

1.2.6.9. (6R,8S)-8-((1H-indol-3-yl)methyl)-2,6-diphenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (8i)



Following General Procedure 6: benzyl (S)-(2-(1H-indol-3-yl)-1-(1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)ethyl)carbamate **7i** (100 mg, 180 µmol), ammonium formate (340 mg, 5.40 mmol) and palladium dihydroxide (25.0 mg, 36.0 µmol) in ethyl acetate (1 mL), methanol and water (1 mL, 3:1 v:v) were used. The crude product was purified by flash column chromatography eluting with 30% ethyl acetate in hexane to yield the title compound **8i** as an orange solid (68.0 mg, 168 µmol, 93%).

R_f = 0.41 (30% EtOAc in hexane)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -57.9 (c = 0.2 in MeOH)

IR: ν_{max} = 2969 (m, C-H), 2920 (m, C-H), 1697 (m, C=N), 1618 (m, C=C), 1521 (m, C=C)

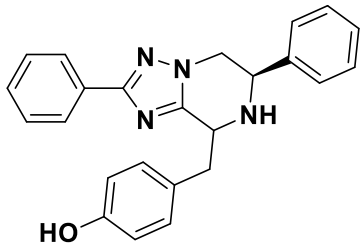
^{1}H NMR (400 MHz, CD_3OD): δ_H = 8.15 (2H, d, *J* = 7.8 Hz), 7.80 (1H, d, *J* = 7.8 Hz), 7.65 (2H, d, *J* = 3.7 Hz), 7.47 - 7.57 (6H, m), 7.41 (1H, d, *J* = 8.2 Hz), 7.39 (1H, s), 7.14 - 7.20 (1H, m), 7.08 - 7.14 (1H, m), 5.32

(1H, dd, *J* = 8.9, 3.1 Hz), 5.14 (1H, dd, *J* = 9.4, 5.6 Hz), 4.76 - 4.85 (2H, m), 4.16 (1H, dd, *J* = 15.3, 3.1 Hz), 3.68 (1H, dd, *J* = 15.3, 8.9 Hz)

^{13}C NMR (101 MHz, CD_3OD): δ_H = 163.7, 151.3, 138.4, 133.3, 131.6, 131.4, 131.1, 130.7, 129.9, 129.7, 128.6, 127.6, 126.5, 123.0, 120.4, 119.3, 112.8, 107.9, 59.8, 57.6, 50.8, 28.1

HRMS (ESI+): found $[M + H]^+$ 406.2027, $C_{26}H_{24}N_5^+$ required 406.2032

1.2.6.10. 4-(((6R,8S)-2,6-diphenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazin-8-yl)methyl)phenol (8j)



Following General Procedure 6: benzyl (S)-(1-(1-(2-(4-hydroxyphenyl)-2-oxoethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate **7j** (54.0 mg, 101 µmol), ammonium formate (192 mg, 3.04 mmol) and palladium dihydroxide (14.0 mg, 20.3 µmol) in ethyl acetate (1 mL), methanol and water (1 mL, 3:1 v:v) were used. The crude product was purified by flash column chromatography eluting with 50% ethyl acetate in hexane to yield the title compound **8j** as a white solid (32.0 mg, 83.7 µmol, 83%).

R_f = 0.55 (55% EtOAc in hexane)

$[\alpha]_D^{20}$ = -87.6 (c = 0.2 in MeOH)

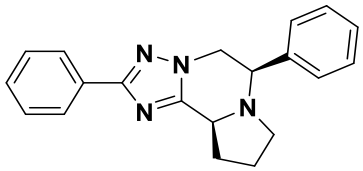
IR: ν_{max} = 3209 (m, br, O-H), 2929 (m, C-H), 1701 (m, C=N), 1612 (m, C=C), 1514 (m, C=C)

^{1}H NMR (500 MHz, CD_3OD): δ_H = 8.10 (2H, dd, *J* = 7.3, 1.5 Hz), 7.68 (2H, d, *J* = 3.4 Hz), 7.55 (3H, d, *J* = 3.4 Hz), 7.43 - 7.52 (3H, m), 7.33 (2H, d, *J* = 8.2 Hz), 6.82 (2H, d, *J* = 8.2 Hz), 5.09 - 5.25 (2H, m), 4.80 (2H, d, *J* = 6.1 Hz), 3.87 (1H, d, *J* = 13.7 Hz), 3.36 (1H, dd, *J* = 13.7, 8.2 Hz)

^{13}C NMR (126 MHz, CD_3OD): δ_C = 164.0, 158.5, 151.3, 133.4, 132.1, 131.8, 131.7, 131.1, 130.8, 129.9, 129.5, 127.6, 126.2, 117.0, 59.8, 58.5, 50.6, 37.3

HRMS (ESI+): found $[M + H]^+$ 383.1874, $C_{24}H_{22}N_4O^+$ required 383.1872

1.2.6.11. (6R,10aS)-2,6-diphenyl-5,6,8,9,10,10a-hexahydropyrrolo[1,2-a][1,2,4]triazolo[5,1-c]pyrazine (8k)



Following General Procedure 6: benzyl (S)-2-(1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)pyrrolidine-1-carboxylate **7k** (65.6 mg, 141 µmol), ammonium formate (267 mg, 4.24 mmol) and palladium dihydroxide (19.8 mg, 28.2 µmol) in ethyl acetate (1 mL), methanol and water (1 mL, 3:1 v:v) were used. The crude product was purified by flash column chromatography eluting with 30% ethyl acetate in hexane to yield the title compound **8k** as a yellow solid (26.8 mg, 84.7 µmol, 60%).

R_f = 0.27 (30% EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -29.3 (c = 0.1 in MeOH)

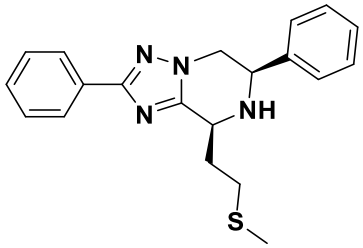
IR: ν_{max} = 2918 (m, C-H), 1703 (m, C=N), 1675 (m, C=C)

^{1}H NMR (500 MHz, CD_3OD): δ_H = 8.01 - 8.10 (2H, m), 7.75 (2H, dd, *J* = 3.4, 2.1 Hz), 7.57 - 7.63 (3H, m), 7.43 - 7.50 (3H, m), 5.57 (1H, dd, *J* = 11.7, 3.8 Hz), 5.44 - 5.46 (1H, m), 5.18 (1H, dd, *J* = 13.1, 11.7 Hz), 3.56 - 3.67 (1H, m), 2.72 (2H, t, *J* = 6.7 Hz), 2.19 (1H, td, *J* = 14.3, 6.7 Hz), 2.10 (1H, td, *J* = 14.3, 6.7 Hz) – 2H obscured by solvent

^{13}C NMR (126 MHz, CD_3OD): δ_C = 164.2, 150.1, 132.5, 131.6, 131.4, 131.2, 131.1, 130.5, 130.0, 127.6, 62.9, 60.7, 52.5, 37.5, 22.7 – 1C obscured by solvent

HRMS (ESI+): found $[M + H]^+$ 317.1780, $C_{20}H_{21}N_4^+$ required 317.1766

1.2.6.12. (6R,8S)-8-(2-(methylthio)ethyl)-2,6-diphenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (8l)



Following General Procedure 6: benzyl (S)-(3-(methylthio)-1-(1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)propyl)carbamate **7l** (123 mg, 245 µmol), ammonium formate (463 mg, 7.34mmol) and palladium dihydroxide (68.7 mg, 489 µmol) in ethyl acetate (1 mL), methanol and water (1 mL, 3:1 v:v) were used. The crude product was purified by flash column chromatography eluting with 50% ethyl acetate in hexane to yield the title compound **8l** as a white solid (43.7 mg, 125 µmol, 51%).

R_f = 0.50 (30% EtOAc in hexane)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -31.0 (c = 0.2 in MeOH)

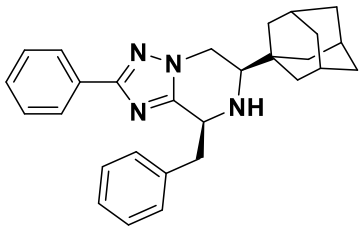
IR: ν_{max} = 2916 (m, C-H), 1705 (m, C=N), 1687 (m, C=C)

^{1}H NMR (500 MHz, CD_3OD): δ_H = 8.08 (2H, dd, *J* = 7.5, 2.1 Hz), 7.66 - 7.71 (2H, m), 7.57 - 7.62 (3H, m), 7.42 - 7.48 (3H, m), 5.25 (1H, dd, *J* = 11.7, 4.9 Hz), 5.20 (1H, t, *J* = 6.6 Hz), 4.82 (1H, dd, *J* = 13.7, 4.9 Hz), 4.73 (1H, dd, *J* = 13.7, 11.7 Hz), 3.05 - 3.17 (2H, m), 2.70 (1H, td, *J* = 14.1, 7.4 Hz), 2.34 (1H, td, *J* = 14.1, 7.3 Hz), 2.21 (3H, s)

^{13}C NMR (126 MHz, CD_3OD): δ_C = 164.1, 151.4, 133.4, 132.1, 131.7, 131.1, 131.0, 129.9, 129.3, 127.5, 59.5, 55.2, 50.5, 31.7, 31.0, 15.2

HRMS (ESI+): found $[M + H]^+$ 351.1646, $C_{20}H_{23}N_4{}^{32}S^+$ required 351.1643

1.2.6.13. (6R,8S)-6-((1r,3R)-adamantan-1-yl)-8-benzyl-2-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (8m)



Following General Procedure 6: benzyl ((1*S*)-1-(1-(2-((1*S*,3*R*)-adamantan-1-yl)-2-oxoethyl)-3-phenyl-1*H*-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate **7m** (117 mg, 204 µmol), ammonium formate (385 mg, 6.11 mmol) and palladium dihydroxide (29.0 mg, 40.7 µmol) in ethyl acetate (1 mL), methanol and water (1 mL, 3:1 v:v) were used. The crude product was purified by flash column chromatography eluting with 10% ethyl acetate in hexane to yield the title compound **8m** as a white solid (79.0 mg, 186 µmol, 91%).

R_f = 0.16 (10% EtOAc in hexane)

$[\alpha]_D^{20}$ = -81.1 (c = 0.3 in MeOH)

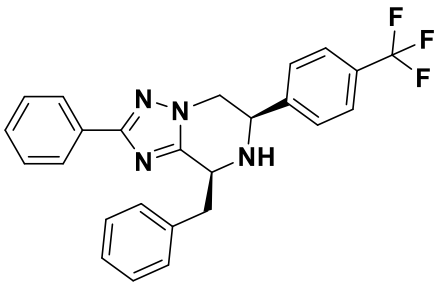
IR: ν_{max} = 2920 (m, C-H), 1703 (m, C=N), 1632 (m, C=C)

^{1}H NMR (400 MHz, d_6-DMSO): δ_H = 8.01 (2H, m, *J* = 4.4 Hz), 7.63 (2H, d, *J* = 7.2 Hz), 7.41 - 7.49 (5H, m), 7.35 (1H, t, *J* = 7.2 Hz), 5.18 (1H, dd, *J* = 8.7, 3.6 Hz), 4.67 (1H, dd, *J* = 13.6, 4.4Hz), 4.47 - 4.56 (1H, m), 3.81 (1H, dd, *J* = 12.1, 4.4 Hz), 3.64 (1H, dd, *J* = 14.3, 3.6 Hz), 3.54 (1H, dd, *J* = 14.3, 8.7 Hz), 2.12 - 2.20 (3H, m), 2.00 (3H, d, *J* = 11.9 Hz), 1.80 - 1.93 (6H, m), 1.77 (3H, d, *J* = 11.9 Hz)

^{13}C NMR (101 MHz, d_6-DMSO): δ_C = 163.6, 151.6, 137.1, 131.5, 131.0, 130.9, 129.7, 129.6, 128.4, 127.3, 65.2, 58.0, 45.7, 38.7, 37.6, 37.3, 35.9, 29.5

HRMS (ESI+): found $[M + H]^+$ 425.2684, $C_{28}H_{32}N_4^+$ required 425.2705

1.2.6.14. (6R,8S)-8-benzyl-2-phenyl-6-(4-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (8n)



Following General Procedure 6: benzyl (S)-(1-(1-(2-oxo-2-(4-(trifluoromethyl)phenyl)ethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate **7n** (66.3 mg, 113 µmol), ammonium formate (215 mg, 3.40 mmol) and palladium dihydroxide (15.9 mg, 22.7 µmol) in ethyl acetate (1 mL), methanol and water (1 mL, 3:1 v:v) were used. The crude product was purified by flash column chromatography eluting with 50% ethyl acetate in hexane to yield the title compound **8n** as a white solid (35.0 mg, 80.6 µmol, 71%).

R_f = 0.75 (30% EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -45.7 (c = 0.4 in MeOH)

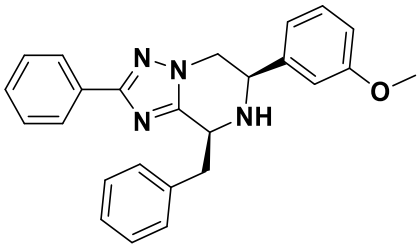
IR: ν_{max} = 2919 (m, C-H), 1702 (m, C=N), 1595 (m, C=C)

^{1}H NMR (500 MHz, CD_3OD): δ_H = 8.10 (2H, d, *J* = 7.9 Hz), 7.89 (2H, d, *J* = 8.2 Hz), 7.85 (2H, d, *J* = 8.2 Hz), 7.53 (2H, d, *J* = 7.3 Hz), 7.48 (3H, dd, *J* = 7.9, 1.2 Hz), 7.41 (2H, t, *J* = 7.3 Hz), 7.34 (1H, t, *J* = 7.3 Hz), 5.25 (1H, dd, *J* = 8.9, 4.3 Hz), 5.20 (1H, dd, *J* = 11.3, 4.3 Hz), 4.81 (1H, dd, *J* = 13.4, 4.3 Hz), 4.76 (1H, d, *J* = 13.4, 11.3 Hz), 3.96 (1H, dd, *J* = 14.8, 4.3 Hz), 3.44 (1H, dd, *J* = 14.8, 8.9 Hz)

^{13}C NMR (126 MHz, CD_3OD): δ_C = 163.8, 151.7, 136.2, 133.5, 133.3, 131.6, 131.1, 131.0, 130.3, 130.2, 129.9, 129.0, 127.6, 127.5, 124.3, 59.0, 58.1, 50.9, 38.3

HRMS (ESI+): found $[M + H]^+$ 435.1779, $C_{25}H_{22}F_3N_4^+$ required 435.1791

1.2.6.15. (6R,8S)-8-benzyl-6-(3-methoxyphenyl)-2-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (8o)



Following General Procedure 6: benzyl (S)-(1-(1-(2-(4-methoxyphenyl)-2-oxoethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate **7o** (100 mg, 183 µmol), ammonium formate (346 mg, 5.49 mmol) and palladium dihydroxide (26.0 mg, 36.9 µmol) in ethyl acetate (1 mL), methanol and water (1 mL, 3:1 v:v) were used. The crude product was purified by flash column chromatography eluting with 20% ethyl acetate in hexane to yield the title compound **8o** as a white solid (56.0 mg, 141 µmol, 77%).

R_f = 0.32 (20% EtOAc in hexane)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -18.2 (c = 0.2 in MeOH)

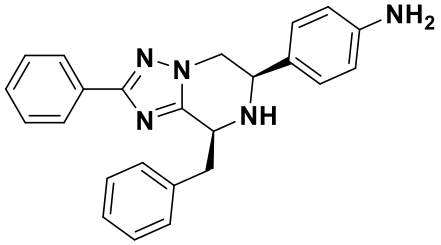
IR: ν_{max} = 2930 (m, C-H), 1678 (m, C=N), 1607 (m, C=C)

^{1}H NMR (400 MHz, CD_3OD): δ_H = 8.03 - 8.14 (2H, m), 7.55 (2H, d, *J* = 7.5 Hz), 7.44 - 7.50 (3H, m7.37 - 7.43 (4H, m), 7.32 (1H, t, *J* = 7.2 Hz), 7.28 (1H, d, *J* = 7.2 Hz), 7.06 (1H, d, *J* = 8.2 Hz), 5.27 - 5.29 (1H, m), 5.14 (1H, d, *J* = 8.2 Hz), 4.76 (1H, d, *J* = 13.6 Hz), 3.95 (1H, d, *J* = 14.6 Hz), 3.86 (3H, s), 3.56 (1H, dd, *J* = 14.6, 7.5 Hz) – 1H obscured by methanol peak

^{13}C NMR (101 MHz, CD_3OD): δ_C = 163.9, 162.0, 151.2, 136.0, 134.7, 131.9, 131.7, 131.1, 131.0, 130.2, 129.9, 129.0, 127.5, 121.4, 117.3, 115.1, 59.8, 58.3, 56.3, 50.7, 37.9

HRMS (ESI+): found $[M + H]^+$ 397.2018, $C_{25}H_{25}N_4O^+$ required 397.2028

1.2.6.16. 4-((6R,8S)-8-benzyl-2-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazin-6-yl)aniline (8p)



Following General Procedure 6: benzyl (S)-(1-(1-(2-(4-nitrophenyl)-2-oxoethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate **7p** (68.0 mg, 121 µmol), ammonium formate (229 mg, 3.63 mmol) and palladium dihydroxide (17.0 mg, 24.2 µmol) in ethyl acetate (1 mL), methanol and water (1 mL, 3:1 v:v) were used. The crude product was purified by flash column chromatography eluting with 30% ethyl acetate in 40-60 petroleum ether to yield the title compound **8p** as a white solid (32.6 mg, 85.4 µmol, 71%).

R_f = 0.25 (60% EtOAc in hexane)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -119.0 (c = 0.2 in MeOH)

IR: ν_{max} = 3319 (w, N-H), 2729 (m, C-H), 1518 (C=N), 1491 (m, C=C)

^{1}H NMR (500 MHz, CD_3OD): δ_H = 8.04 - 8.12 (2H, m), 7.86 (2H, d, *J* = 8.5 Hz), 7.53 (2H, d, *J* = 7.5 Hz), 7.49 (2H, d, *J* = 8.5 Hz), 7.43 - 7.48 (3H, m), 7.39 (2H, t, *J* = 7.5 Hz), 7.32 (1H, t, *J* = 7.5 Hz), 5.23 (1H, dd, *J* = 9.2, 4.8 Hz), 5.16 (1H, dd, *J* = 10.4, 6.0 Hz), 4.73 - 4.83 (2H, m), 3.94 (1H, dd, *J* = 14.7, 4.8 Hz), 3.48 (1H, dd, *J* = 14.7, 9.2 Hz)

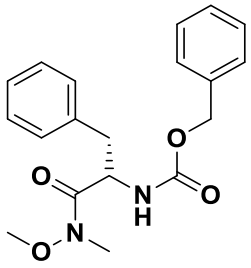
^{13}C NMR (126 MHz, CD_3OD): δ_C = 163.8, 151.5, 144.7, 136.2, 131.6, 131.6, 131.1, 131.1, 130.3, 129.9, 129.4, 129.0, 127.6, 124.6, 58.9, 58.1, 50.7, 38.2

HRMS (ESI+): found $[M + H]^+$ 382.2050, $C_{24}H_{24}N_5^+$ required 382.2032

1.3. Efficient Synthesis of Other Heterocycles

1.3.1. Pyrazole Heterocycle

1.3.1.1. Benzyl (S)-(1-(methoxy(methyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (9a)



To a stirred solution of Z-L-phenylalanine **1b** (1.0 g, 3.34 mmol, 1.0 eq.) and N,O-dimethylhydroxylamine hydrochloride (489 mg, 5.01 mmol, 1.5 eq.) in dichloromethane (15 mL, 0.2 M) was added HOBt (496 mg, 3.67 mmol, 1.1 eq.), HBTU (1.39 g, 3.37 mmol, 1.1 eq.) and diisopropylethylamine (1.51 mL, 8.69 mmol, 2.6 eq.). The solution was stirred at room temperature until the starting material had been consumed. The reaction was quenched with saturated aqueous sodium hydrogen carbonate solution (15 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic fractions were washed with brine (15 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude compound was purified by flash column chromatography on silica eluting with dichloromethane to yield the title compound **9a** as a cloudy liquid (975 mg, 3.34 mmol, 100%).

R_f = 0.53 (Dichloromethane)

$[\alpha]_D^{20}$ = +22.5 (c = 0.2 in $CHCl_3$) - [Literature Value = +20.0 (c = 0.1 in DCM)][19]

IR: ν_{max} = 3305 (m, N-H), 2943 (m, C-H), 1714 (s, C=O), 1650 (s, C=O), 1522 (m, C=C), 1496 (m, C=C)

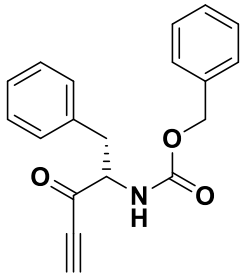
^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.31 - 7.40 (5H, m), 7.21 - 7.30 (3H, m), 7.17 (2H, d, *J* = 6.7 Hz), 5.44 (1H, d, *J* = 8.5 Hz), 5.11 (1H, d, *J* = 12.2 Hz), 4.97 - 5.08 (2H, m), 3.70 (3H, s), 3.20 (3H, s), 3.10 (1H, dd, *J* = 13.6, 6.0 Hz), 2.93 (1H, dd, *J* = 13.6, 7.3 Hz)

^{13}C NMR (101 MHz, d_6-DMSO): δ_C = 171.9, 156.7, 155.8, 136.3, 129.4, 128.5, 128.4, 128.1, 128.0, 126.9, 66.8, 61.5, 52.1, 38.7, 32.0

HRMS (ESI+): found $[M + H]^+$ 343.1644, $C_{19}H_{22}N_2O_4^+$ required 343.1658

This data is in accordance with that previously recorded.[19]

1.3.1.2. Benzyl (S)-(3-oxo-1-phenylpent-4-yn-2-yl)carbamate (9b)



Ethynyl magnesium bromide (9.30 mL, 0.5 M solution in THF, 4.67 mmol, 4.5 eq.) was added dropwise to a stirred solution of benzyl (*S*)-(1-(methoxy(methyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate **9a** (350 mg, 1.02 mmol, 1.0 eq.) in THF (7.0 mL, 0.15M) at -78 °C. The resulting mixture was stirred at room temperature overnight. After cooling to 0 °C, the reaction was quenched with a saturated aqueous solution of ammonium chloride (10 mL). After stirring for 1 h at room temperature, the reaction was extracted with ethyl acetate (3 x 10 mL); the combined organic fractions were washed with brine (15 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude compound was purified by flash column chromatography on silica eluting with 30% ethyl acetate in 40-60 petroleum ether to yield the title compound **9b** as a yellow solid (228 mg, 0.741 mmol, 73%).

R_f = 0.58 (25% EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = +30.8 (c = 0.1 in $CHCl_3$) - [Literature Value = +1.27 (c = 1.1 in $CHCl_3$)][20]

IR: ν_{max} = 3343 (s, N-H), 3032 (m, C-H), 2095 (s, C≡C-H), 1683 (s, C=O), 1670 (s, C=O), 1531 (s, N-H)

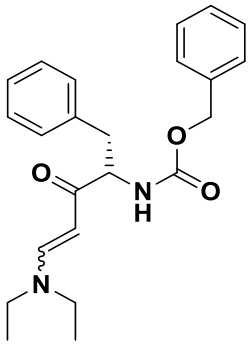
^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.28 - 7.22 (8H, m), 7.13 (2H, dd, *J* = 7.5, 1.7 Hz), 5.23 (1H, d, *J* = 7.5 Hz), 5.11 (2H, s), 4.74 - 4.84 (1H, m), 3.41 (1H, s), 3.27 - 3.34 (1H, m), 3.20 - 3.27 (1H, m)

^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 184.9, 155.6, 136.1, 134.9, 129.4, 128.7, 128.5, 128.3, 128.1, 127.3, 82.6, 79.7, 67.1, 62.3, 36.8

HRMS (ESI+): found $[M + H]^+$ 308.1298, $C_{19}H_{18}NO_3^+$ required 308.1287

This data is in accordance with that previously recorded.[20]

1.3.1.3. Benzyl (S)-(5-(diethylamino)-3-oxo-1-phenylpent-4-en-2-yl)carbamate (9c)



Diethylamine (0.07 mL, 0.70 mmol, 1.1 eq.) was added dropwise to a stirred solution of benzyl (*S*)-(3-oxo-1-phenylpent-4-yn-2-yl)carbamate **9b** (196 mg, 0.642 mmol, 1.0 eq.) in dichloromethane (5.0 mL, 0.15 M) at 0 °C. The mixture was stirred at room temperature for 18 hours, before dilution with water (15 mL). The reaction was extracted with dichloromethane (3 x 20 mL) and the combined organic fractions were washed with brine (15 mL), dried (Mg SO_4) and concentrated under reduced pressure. The crude compound was purified by flash column chromatography on silica eluting with 50% ethyl acetate in 40-60 petroleum ether to yield the title compound **9c** as a yellow oil (232 mg, 0.611 mmol, 95%).

R_f = 0.40 (50% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = +37.0 (c = 0.1 in $CHCl_3$) - [Literature Value = +34.4 (c = 1.1 in $CHCl_3$)][20]

IR: ν_{max} = 2973 (m, C-H), 2934 (m, C-H), 1715 (s, C=O), 1647 (s, C=O), 1555 (s, N-H), 1495 (m, C=C)

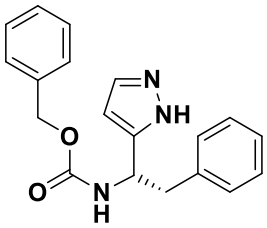
^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.29 - 7.39 (6H, m), 7.23 - 7.27 (2H, m), 7.13 - 7.23 (3H, m), 5.84 (1H, d, *J* = 7.2 Hz), 5.11 (2H, s), 4.87 (1H, d, *J* = 12.6 Hz), 4.58 (1H, m), 3.25 (2H, br, s), 2.95 - 3.12 (4H, m), 1.20 (3H, t, *J* = 6.5 Hz), 1.06 (3H, t, *J* = 6.6 Hz)

^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 193.1, 155.7, 137.5, 136.8, 129.6, 128.4, 128.2, 128.1, 128.0, 127.9, 126.4, 66.4, 50.5, 42.6, 39.6, 14.6, 11.4 – 2C obscured by chloroform peak

HRMS (ESI+): found $[M + Na]^+$ 403.2014, $C_{23}H_{28}N_2O_3Na^+$ required 403.1998

This data is in accordance with that previously recorded.[20]

1.3.1.4. Benzyl (S)-(2-phenyl-1-(1H-pyrazol-5-yl)ethyl)carbamate (9)



A solution of benzyl (*S*)-(5-(diethylamino)-3-oxo-1-phenylpent-4-en-2-yl)carbamate **9c** (200 mg, 0.530 mmol, 1.0 eq.), hydrazine monohydrate (30.0 µL, 0.551 mmol, 1.1 eq.), and concentrated aqueous hydrochloric acid (37% w/w, 50.0 µL, 0.551 mmol, 1.1 eq.) in ethanol (3 mL, 0.16 M) was refluxed for 3 h. The reaction was cooled to room temperature and the solvent removed under reduced pressure. The resulting residue was diluted with water (10 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic fractions were washed with saturated aqueous sodium hydrogen carbonate (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude compound was purified by flash column chromatography on silica eluting with 50% ethyl acetate in 40-60 petroleum ether to yield the title compound **9** as a white solid (151 mg, 0.470 mmol, 89%).

R_f = 0.38 (50% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = +37.0 (c = 0.1 in $CHCl_3$)

IR: ν_{max} = 3351 (m, N-H), 2920 (m, C-H), 1689 (s, C=O), 1533 (s, N-H)

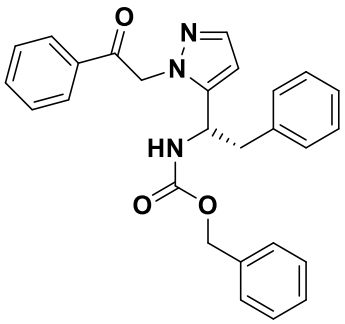
^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.44 (1H, s), 7.27 - 7.38 (6H, m), 7.14 - 7.24 (3H, m), 7.08 (2H, d, *J* = 6.6 Hz), 6.06 (1H, s), 5.48 (1H, br. s.), 5.12 (1H, m, *J* = 6.8 Hz), 5.08 (2H, s), 3.18 (2H, d, *J* = 6.8 Hz)

^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 155.9, 148.9, 137.1, 136.4, 129.5, 128.5, 128.3, 128.1, 127.9, 126.6, 124.7, 103.4, 66.8, 50.3, 41.4

HRMS (ESI+): found $[M + H]^+$ 322.1564, $C_{19}H_{20}N_3O_2^+$ required 322.1556

This data is in accordance with that previously recorded.[20]

1.3.1.5. Benzyl (S)-(1-(1-(2-oxo-2-phenylethyl)-1H-pyrazol-5-yl)-2-phenylethyl)carbamate (10a)



Following General Procedure 5: benzyl (*S*)-(2-phenyl-1-(1H-pyrazol-5-yl)ethyl)carbamatete **9** (200 mg, 0.620 mmol), 2-bromoacetophenone (136 mg, 0.681 mmol) and potassium carbonate (86.0 mg, 0.620 mmol) in acetone (2 mL) were used eluting with 30% ethyl acetate in 40-60 petroleum ether to yield the title compound **10a** as a white solid (174 mg, 0.390 mmol, 64%).

R_f = 0.30 (30% EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -13.3 (c = 0.1 in MeOH)

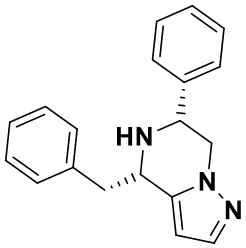
IR: ν_{max} = 2928 (m, C-H), 1702 (s, C=O), 1496 (m, C=C)

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.00 (2H, d, *J* = 7.5 Hz), 7.66 (1H, t, *J* = 7.5 Hz), 7.54 (2H, d, *J* = 7.8 Hz), 7.40 (1H, d, *J* = 2.4 Hz), 7.30 - 7.38 (5H, m), 7.18 - 7.27 (4H, m), 7.09 (2H, d, *J* = 6.8 Hz), 6.06 (1H, d, *J*=2.4 Hz), 5.44 (2H, d, *J* = 8.2 Hz), 5.04 - 5.19 (3H, m), 3.13 - 3.28 (2H, m)

^{13}C NMR (101MHz, $CDCl_3$): δ_C = 191.9, 155.4, 152.3, 137.0, 136.3, 134.2, 133.8, 131.3, 129.8, 129.4, 129.2, 128.7, 128.1, 127.8, 127.7, 126.0, 104.7, 66.3, 57.4, 50.8, 41.6

HRMS (ESI+): found $[M + H]^+$ 440.1969, $C_{27}H_{26}N_3O_3^+$ required 440.1974

1.3.1.6. (4S,6R)-4-benzyl-6-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine (10)



Following General Procedure 6: benzyl (S)-(1-(1-(2-oxo-2-phenylethyl)-1H-pyrazol-5-yl)-2-phenylethyl)carbamate **10a** (14.0 mg, 31.9 µmol), ammonium formate (8.60 mg, 1.37 mmol) and palladium dihydroxide (6.00 mg, 6.37 µmol) in ethyl acetate (1 mL) and methanol and water (1 mL, 3:1 v:v,) was used eluting with 10% methanol in ethyl acetate to yield the title compound **10** as a white solid (7.00 mg, 26.3 µmol, 82%).

R_f = 0.24 (30% MeOH in EtOAc)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = +53.9 (c = 0.2 in MeOH)

IR: ν_{max} = 2921 (m, C-H), 1597 (m, N-H)

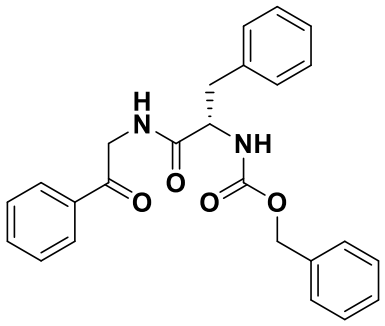
^{1}H NMR (500 MHz, CD_3OD): δ_H = 7.39 - 7.43 (1H, m), 7.21 - 7.35 (8H, m), 7.17 (2H, d, *J* = 7.9 Hz), 6.12 - 6.16 (1H, m), 5.00 (1H, t, *J* = 5.8 Hz), 4.54 (1H, td, *J* = 7.5, 3.1 Hz), 4.25 - 4.31 (2H, m), 3.20 - 3.24 (2H, m)

^{13}C NMR (126 MHz, CD_3OD): δ_C = 150.4, 143.2, 137.5, 133.7, 130.7, 129.9, 129.6, 129.1, 128.4, 127.3, 104.8, 74.2, 60.3, 52.4, 41.8

HRMS (ESI+): found $[M + H]^+$ 291.1530, $C_{19}H_{19}N_3^+$ required 289.1957

1.3.2. Imidazole Heterocycle

1.3.2.1. Benzyl (S)-(1-oxo-1-((2-oxo-2-phenylethyl)amino)-3-phenylpropan-2-yl)carbamate (11a)



To a stirred solution of 2-aminoacetophenone hydrochloride (2.00 g, 11.7 mmol, 1.0 eq.) and Z-L-phenylalanine **1b** (3.49 g, 11.7 mmol, 1.0 eq.) in dichloromethane (100 mL, 0.1 M) was added 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (2.35 g, 12.2 mmol, 1.05 eq.), *N*-methylmorpholine (1.35 mL, 12.2 mmol, 1.05 eq.) and 1-hydroxy-7-azabenzotriazole (1.66 g, 12.2 mmol, 1.05 eq.) at 0 °C. The reaction mixture was then stirred at room temperature for 3 hours. Upon completion the reaction mixture was quenched with aqueous saturated sodium hydrogen carbonate solution and extracted with dichloromethane (3 x 150 mL). The combined organic fractions were washed with brine (50 mL) and dried ($MgSO_4$) before the solvent was removed under reduced pressure to yield the crude compound. The resultant crude product was purified by flash column chromatography on silica eluting with ethyl acetate (0-100%) in 40-60 petroleum ether to yield the title compound **11a** as a yellow solid (4.44 g, 11.7 mmol, 100%).

R_f = 0.20 (30% EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -15.8 (c = 1.0 in MeOH)

IR: ν_{max} = 3675 (m, N-H), 3298 (m, N-H), 2988 (s, C-H), 2901 (s, C-H), 1694 (s, C=O), 1644 (s, C=O), 1597 (m, C=C), 1531 (m, C=C), 1494 (m, C=C), 1448 (m, C=C)

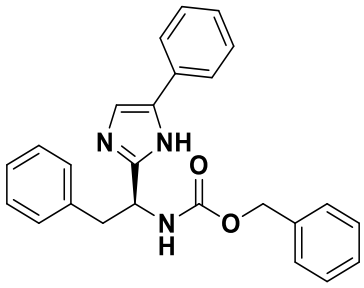
^{1}H NMR (400 MHz, d_6-DMSO): δ_H = 8.43 (1H, t, *J* = 5.4 Hz), 8.01 (1H, d, *J* = 7.4 Hz), 7.68 (1H, t, *J* = 7.4 Hz), 7.57 (2H, q, *J* = 7.4 Hz), 7.12 - 7.38 (10H, m), 4.94 (2H, s), 4.71 (1H, dd, *J* = 18.5, 5.4 Hz), 4.71 (1H, dd, *J* = 18.5, 5.4 Hz), 4.37 (1H, ddd, *J* = 11.2, 8.8, 3.5 Hz), 3.09 (1H, dd, *J* = 13.7, 3.5 Hz), 2.77 (1H, dd, *J* = 13.7, 11.2 Hz)

^{13}C NMR (101 MHz, d_6-DMSO): δ_C = 195.2, 172.2, 156.0, 138.4, 137.1, 135.0, 133.7, 128.9, 129.3, 128.4, 128.2, 127.7, 127.9, 127.5, 126.3, 65.3, 56.3, 46.1, 46.1

HRMS (ESI+): found $[M + H]^+$ 417.1796, $C_{25}H_{25}N_2O_4^+$ required 417.1814

This data is in accordance with that previously reported.[21]

1.3.2.2. Benzyl (S)-(2-phenyl-1-(5-phenyl-1H-imidazol-2-yl)ethyl)carbamate (11)



A solution of benzyl (S)-(1-oxo-1-((2-oxo-2-phenylethyl)amino)-3-phenylpropan-2-yl)carbamate **11a** (1.00 g, 2.40 mmol, 1.0 eq.) and ammonium acetate (1.85 g, 24.0 mmol, 10.0 eq.) in xylene (8 mL, 0.3 M) was refluxed using Dean-Stark apparatus. After complete consumption of the starting material, the reaction mixture was concentrated. The residue was re-dissolved in dichloromethane, washed with brine (10 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure. The resultant crude compound was purified by flash column chromatography on silica eluting with ethyl acetate (0-100%) in 40-60 petroleum ether to yield the title compound **11** as an orange solid (768 mg, 1.93 mmol, 81%).

R_f = 0.41 (40% EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -0.1 (c = 0.7 in MeOH)

IR: ν_{max} = 3675 (m, N-H), 2988 (s, C-H), 2901 (s, C-H), 1690 (m, br, C=O), 1494 (m, C=C), 1453 (m, C=C), 1406 (m, C=C)

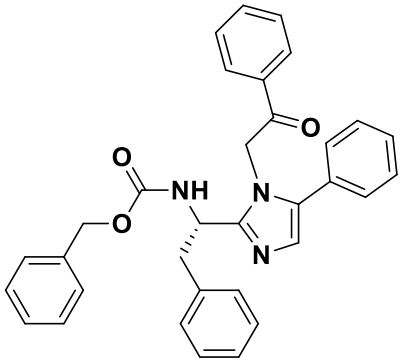
^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 11.96 (1H, br. s.), 7.81 (1H, d, *J* = 8.9 Hz), 7.78 (2H, d, *J* = 7.3 Hz), 7.63 (1H, d, *J* = 7.3 Hz), 7.51 (1H, d, *J* = 1.5 Hz), 7.39 (1H, t, *J* = 7.8 Hz), 7.29 - 7.37 (4H, m), 7.15 - 7.28 (7H, m), 5.02 (1H, d, *J* = 12.8 Hz), 4.96 (1H, d, *J* = 12.8 Hz), 4.93 (1H, ddd, *J* = 9.3, 8.9, 5.8 Hz), 3.31 (1H, dd, *J* = 13.6, 5.8 Hz), 3.06 (1H, dd, *J* = 13.6, 9.3 Hz)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 156.2, 149.0, 140.0, 138.8, 137.6, 135.4, 129.7, 129.3, 128.8, 128.7, 128.5, 127.8, 126.7, 126.3, 124.7, 113.0, 65.6, 51.5, 39.5

HRMS (ESI+): found $[M + H]^+$ 398.1865, $C_{25}H_{24}N_3O_2^+$ required 398.1869

This data is in accordance with that previously reported.[21]

1.3.2.3. Benzyl (S)-(1-(1-(2-oxo-2-phenylethyl)-5-phenyl-1H-imidazol-2-yl)-2-phenylethyl)carbamate (12a)



Following General Procedure 5: benzyl (S)-(2-phenyl-1-(5-phenyl-1H-imidazol-2-yl)ethyl)carbamate **11** (200 mg, 0.501 mmol), 2-bromoacetophenone (105 mg, 0.531 mmol) and potassium carbonate (70.0 mg, 0.501 mmol) in DMF (2 mL) were used. The crude product was purified by flash column chromatography on silica eluting with 50% ethyl acetate in 40-60 petroleum ether to yield the title compound **12a** as a pale yellow solid (202 mg, 0.391 mmol, 78%).

R_f = 0.44 (30% EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -18.8 (c = 0.4 in MeOH)

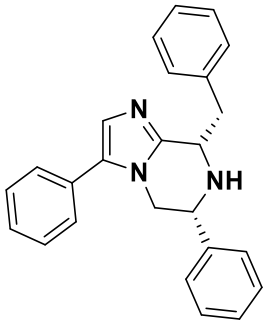
IR: ν_{max} = 2927 (m, C-H), 1689 (S, C=O), 1684 (s, C=O), 1521 (m, C=C), 1496 (m, C=C)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.87 (2H, d, *J* = 7.3 Hz), 7.79 (2H, dd, *J* = 8.2, 1.2 Hz), 7.65 (1H, tt, *J* = 7.3, 1.2 Hz), 7.51 (2H, t, *J* = 7.3 Hz), 7.37 - 7.41 (3H, m), 7.28 - 7.33 (3H, m), 7.20 - 7.26 (5H, m), 7.16 (2H, t, *J* = 5.8 Hz), 7.05 (1H, s), 5.84 (1H, d, *J* = 7.3 Hz), 5.17 (1H, d, *J* = 18.3 Hz), 5.03 - 4.96 (2H, m),4.85 - 4.92 (2H, m), 3.34 - 3.45 (2H, m)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 191.6, 155.8, 148.0, 140.7, 137.4, 136.3, 134.2, 134.1, 134.0, 129.6, 129.0, 128.5, 128.5, 128.5, 128.2, 128.0, 127.8, 126.8, 126.7, 125.0, 116.7, 66.7, 51.4, 49.2, 41.3

HRMS (ESI+): found $[M + H]^+$ 516.2271, $C_{33}H_{30}N_3O_3^+$ required 516.2287

1.3.2.4. (6S,8R)-8-benzyl-3,6-diphenyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine (12)



Following the protocol for the ring closure, benzyl (S)-(1-(1-(2-oxo-2-phenylethyl)-5-phenyl-1H-imidazol-2-yl)-2-phenylethyl)carbamate **12a** (93.0 mg, 0.181 mmol), ammonium formate (341 mg, 5.42 mmol) and palladium dihydroxide (25.0 mg, 36.0 µmol) in ethyl acetate (1 mL) and methanol and water (1 mL, 3:1 v:v,) were used. The crude product was purified by flash column chromatography eluting with 30% ethyl acetate in 40-60 petroleum ether to yield the title compound **12** as a yellow solid (46.0 mg, 130 µmol, 74%).

R_f = 0.44 (50% EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = +82.9 (c = 0.1 in MeOH)

IR: ν_{max} = 2974 (m, C-H), 1713 (s, C=N), 1521 (m, C=C), 1485 (m, C=C)

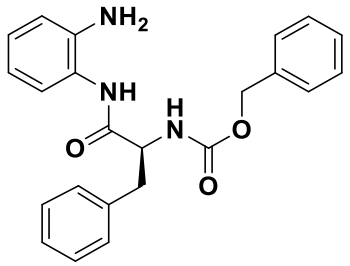
^{1}H NMR (500 MHz, CD_3OD): δ_H = 7.98 (1H, s), 7.83 (2H, d, *J* = 7.3 Hz), 7.71 (2H, d, *J* = 6.4 Hz), 7.56 - 7.62 (2H, m), 7.52 - 7.56 (3H, m), 7.45 - 7.52 (3H, m), 7.40 (2H, t, *J* = 7.5 Hz), 7.33 (1H, t, *J* = 7.6 Hz), 5.33 (1H, d, *J* = 8.3 Hz), 4.62 - 4.76 (2H, m), 3.97 (1H, d, *J* = 13.6 Hz), 3.65 (1H, dd, *J* = 13.6, 8.3 Hz)

^{13}C NMR (126 MHz, CD_3OD): δ_C = 143.2, 136.5, 135.5, 135.4, 131.4, 131.2, 131.1, 130.7, 130.5, 130.3, 129.3, 129.1, 127.9, 127.4, 118.9, 58.7, 56.3, 50.8, 38.2

HRMS (ESI+): found $[M + H]^+$ 366.1953, $C_{25}H_{24}N_3^+$ required 366.1965

1.3.3. Benzimidazole Heterocycles

1.3.3.1. Benzyl (1-((2-aminophenyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (13a)



A solution of Z-L-phenylalanine **1b** (1.00 g, 3.34 mmol, 1.0 eq.), HATU (1.40 g, 3.67 mmol, 1.1 eq.) and diisopropylethylamine (3.00 mL, 16.7 mmol, 5.0 eq.) was stirred at room temperature for 5 minutes, before the addition of *o*-phenylenediamine (542 mg, 5.01 mmol, 1.5 eq.). The reaction was then stirred at room temperature overnight. The reaction was diluted with water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic fractions were washed with brine (15 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude compound was purified by flash column chromatography on silica eluting with ethyl acetate (0-100%) in 40-60 petroleum ether to yield the title compound **13a** as a yellow solid (1.19 g, 3.05 mmol, 91%).

R_f = 0.58 (50% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = +6.3 (c = 0.4 in $CHCl_3$)

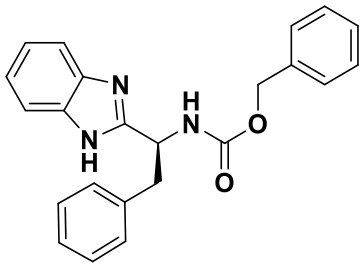
IR: ν_{max} = 3344 (m, N-H), 3304 (m, N-H), 1690 (s, C=O), 1648 (m, C=O), 1526 (s, N-H), 1453 (m, C=C)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.47 (2H, br s), 7.32 - 7.40 (7H, m), 7.23 - 7.31 (3H, m), 7.16 (1H, s), 7.07 (1H, d, *J* = 7.6 Hz), 7.03 (1H, td, *J* = 7.6, 1.1 Hz), 6.75 (1H, td, *J* = 7.6, 1.1 Hz), 6.72 (1H, dd, *J* = 7.6, 1.1 Hz), 5.57 (1H, br s), 5.11 (2H, s), 4.57 (1H, q, *J* = 7.4 Hz), 3.20 (1H, dd, *J* = 13.7, 7.4 Hz), 3.16 (1H, dd, *J* = 13.7, 7.4 Hz)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C =169.7, 156.2, 140.3, 136.3, 136.0, 129.4, 129.0, 128.6, 128.3, 128.1, 127.4, 126.4, 125.5, 123.1, 119.3, 117.5, 67.3, 57.1, 38.5

HRMS (ESI+): found $[M + H]^+$ 390.1819, $C_{23}H_{24}N_3O_3^+$ required 390.1818

1.3.3.2. Benzyl (1-(1H-benzo[d]imidazol-2-yl)-2-phenylethyl)carbamate (13)



A solution of benzyl (1-((2-aminophenyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate **13a** (652 mg, 1.67 mmol, 1.0 eq.) was stirred in acetic acid (2 mL, 0.6 M) at 40 °C for 2 h. The reaction was neutralised with saturated aqueous sodium carbonate and extracted with ethyl acetate (3 x 50 mL). The combined organic fractions were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude compound was purified by flash column chromatography on silica eluting with ethyl acetate (0-30%) in 40-60 petroleum ether to yield the title compound **13** as an orange liquid (706 mg, 1.67 mmol, 100%).

R_f = 0.87 (30% EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -15.0 (c = 0.2 in $CHCl_3$)

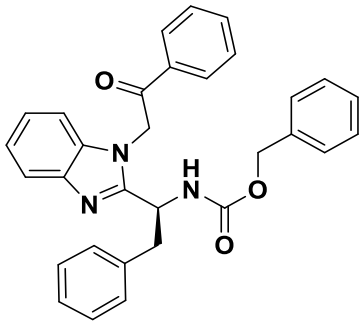
IR: ν_{max} = 3032 (m, N-H), 1694 (s, C=O), 1520 (s, N-H), 1496 (m, C=C), 1454 (m, C=C)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.43 (2H, dd, *J* = 5.3, 2.9 Hz), 7.29 - 7.36 (4H, m), 7.21 - 7.26 (4H, m), 7.15 - 7.20 (3H, m), 7.07 - 7.13 (2H, m), 5.30 (1H, q, *J* = 7.6 Hz), 5.03 (1H, d, *J* = 12.5 Hz), 4.96 (1H, d, *J* = 12.5 Hz), 3.38 (2H, d, *J* = 7.6 Hz)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 157.1, 154.0, 136.6, 136.4, 136.3, 136.1, 129.2, 128.6, 128.5, 128.1, 127.6, 126.9, 123.3, 123.2, 114.9, 67.0, 51.6, 40.2

HRMS (ESI+): found $[M + H]^+$ 372.1718, $C_{23}H_{22}N_3O_2^+$ required 372.1712

1.3.3.3. Benzyl (1-(1-(2-oxo-2-phenylethyl)-1H-benzo[d]imidazol-2-yl)-2-phenylethyl)carbamate (14a)



Following general procedure 5: benzyl (1-(1H-benzo[d]imidazol-2-yl)-2-phenylethyl)carbamate **13** (400 mg, 1.07 mmol), 2-bromoacetophenone (257 mg, 1.29 mmol) and potassium carbonate (149 mg, 1.07 mmol) in acetone (4 mL) were used. The crude product was purified by flash column chromatography eluting with ethyl acetate (0-50%) in 40-60 petroleum ether to yield the title compound **14a** as a white solid (321 mg, 0.650 mmol, 61%).

R_f = 0.34 (30% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = +23.8 (c = 0.2 in $CHCl_3$)

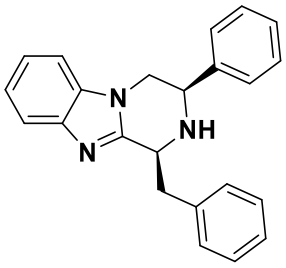
IR: ν_{max} = 3300 (m, N-H), 2928 (m, C-H), 1689 (s, C=O), 1523 (m, N-H), 1460 (m, C=C)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.99 (2H, d, *J* = 7.6 Hz), 7.82 (1H, d, *J* = 7.9 Hz), 7.70 (1H, t, *J* = 7.6 Hz), 7.56 (2H, t, *J* = 7.6 Hz), 7.29 - 7.34 (4H, m), 7.27 (1H, d, *J* = 7.9 Hz), 7.25 - 7.26 (1H, m), 7.24 (2H, d, *J* = 2.4 Hz), 7.18 (4H, d, *J* = 4.0 Hz), 7.14 (1H, d, *J* = 7.9 Hz), 5.76 (1H, d, *J* = 7.0 Hz), 5.59 (1H, d, *J* = 18.3 Hz), 5.41 (1H, d, *J* = 18.3 Hz), 5.11 (1H, q, *J* = 7.0 Hz), 4.95 (1H, d, *J* = 12.5 Hz), 4.81 (1H, d, *J* = 12.5 Hz), 3.50 (1H, dd, *J* = 13.7, 7.0 Hz), 3.46 (1H, dd, *J* = 13.7, 7.0 Hz)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 191.5, 155.9, 154.4, 142.2, 136.9, 136.1, 135.2, 134.3, 134.2, 129.4, 129.2, 129.0, 128.4, 128.1, 128.0, 127.6, 126.8, 123.1, 122.5, 119.8, 109.3, 66.8, 49.3, 49.2, 40.8

HRMS (ESI+): found $[M + H]^+$ 490.2138, $C_{31}H_{28}N_3O_3^+$ required 490.2131

1.3.3.4. (1S,3R)-1-benzyl-3-phenyl-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazine (14)



Following general procedure 6: benzyl (1-(1-(2-oxo-2-phenylethyl)-1H-benzo[d]imidazol-2-yl)-2-phenylethyl)carbamate **14a** (90.0 mg, 0.180 mmol), ammonium formate (348 mg, 5.51 mmol) and palladium dihydroxide (26.0 mg, 36.7 µmol) in methanol and water (1 mL, 3:1 v:v,) were used. The crude product was purified by flash column chromatography eluting with ethyl acetate (0-40%) in 40-60 petroleum ether to yield the title compound **14** as a yellow solid (55.0 mg, 0.160 mmol, 89%).

R_f = 0.23 (20% EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = +3.0 (c = 0.1 in MeOH)

IR: ν_{max} = 2905 (m, C-H), 1694 (m, C=C), 1617 (m, C=C), 1536 (m, C=C)

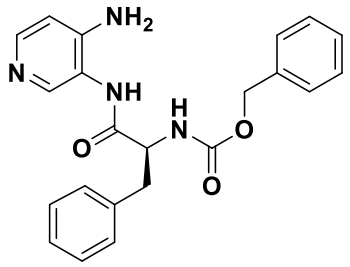
^{1}H NMR (500 MHz, CD_3OD): δ_H = 7.83 - 7.90 (2H, m), 7.63 - 7.71 (4H, m), 7.43 - 7.51 (5H, m), 7.34 - 7.39 (2H, m), 7.27 - 7.32 (1H, m), 5.28 (1H, dd, *J* = 9.8, 3.7 Hz), 4.83 (1H, dd, *J* = 11.7, 4.1 Hz), 4.75 (1H, dd, *J* = 11.7, 4.1 Hz), 4.48 (1H, t, *J* = 11.7 Hz), 3.83 (1H, dd, *J* = 14.3, 3.7 Hz), 3.50 (1H, dd, *J* = 14.3, 9.8 Hz)

^{13}C NMR (126 MHz, CD_3OD): δ_C = 149.9, 137.3, 136.1, 133.3, 133.2, 131.0, 130.7, 130.4, 130.2, 129.0, 128.9, 128.5, 127.6, 115.8, 113.7, 58.1, 56.3, 49.8, 38.7

HRMS (ESI+): found $[M + H]^+$ 340.1817, $C_{23}H_{22}N_3^+$ required 340.1814

1.3.4. Benzimidazole Heterocycle

1.3.4.1. Benzyl (1-((4-aminopyridin-3-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (15a)



A solution of Z-L-phenylalanine **1b** (1.00 g, 3.34 mmol, 1.0 eq.), HATU (1.40 g, 3.67 mmol, 1.1. eq.) and diisopropylethylamine (3 mL, 16.7 mmol, 5.0 eq.) was stirred at room temperature for 5 minutes, before the addition of 3,4-diaminopyridine (550 mg, 5.01 mmol, 1.5 eq.). The reaction was then stirred at room temperature overnight. The reaction was diluted with water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic fractions were washed with brine (15 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude compound was purified by flash column chromatography on silica eluting with methanol (0-30%) in diethyl ether to yield the title compound **15a** as a yellow solid (931 mg, 2.39 mmol, 71%).

R_f = 0.41 (EtOAc)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = +128.0 (c = 0.1 in $CHCl_3$)

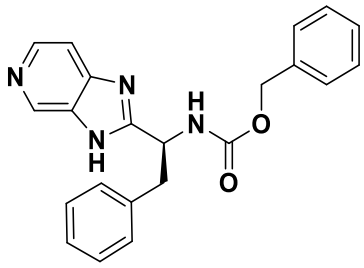
IR: ν_{max} = 3348 (m, N-H), 3175 (m, N-H), 1676 (s, C=O), 1586 (m, C=C), 1510 (s, N-H)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 8.06 (1H, s), 7.96 (1H, d, *J* = 5.2 Hz), 7.55 - 7.57 (1H, m), 7.29 - 7.40 (9H, m), 7.25 (2H, d, *J* = 7.3 Hz), 5.57 (1H, br s), 5.13 (2H, s), 4.58 (1H, dd, *J* = 7.2, 6.4 Hz), 3.18 (2H, dd, *J*=7.2, 3.5 Hz)

^{13}C NMR (126 MHz, $CDCl_3$): δ_c =169.9, 156.8, 152.3, 140.3, 136.0, 135.8, 129.3, 129.1, 128.8, 128.6, 128.4, 128.0, 127.3, 116.6, 109.9, 67.5, 51.7, 39.2

HRMS (ESI+): found $[M + H]^+$ 391.1775, $C_{22}H_{23}N_4O_3^+$ required 391.1770

1.3.4.2. Benzyl (1-(3H-imidazo[4,5-c]pyridin-2-yl)-2-phenylethyl)carbamate (15)



A solution of benzyl (1-((4-aminopyridin-3-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate **15a** (375 mg, 0.960 mmol, 1.0 eq.) was stirred in acetic acid (4 mL, 0.6 M) at 40 °C for 2h. The reaction was neutralised with saturated aqueous sodium carbonate and extracted with ethyl acetate (3 x 25 mL). The combined organic fractions were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude compound was purified by flash column chromatography on silica eluting with methanol (0-30%) in ethyl acetate to yield the title compound **15** as a clear liquid (292 mg, 0.780 mmol, 82%).

R_f = 0.64 (10% MeOH in EtOAc)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -35.8 (c = 0.5 in $CHCl_3$)

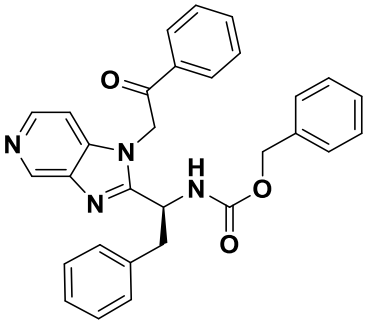
IR: ν_{max} = 3219 (m, N-H), 2882 (m, C-H), 1684 (s, C=O), 1621 (m, C=C), 1586 (m, C=C), 1560 (s, N-H)

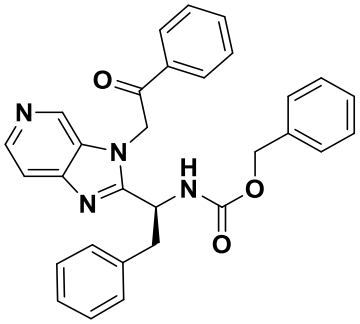
^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 8.91 (1H, s), 8.31 (1H, d, *J* = 5.8 Hz), 7.51 (1H, d, *J* = 5.8 Hz), 7.27 - 7.30 (3H, m), 7.21 - 7.26 (5H, m), 7.16 (2H, dd, *J* = 6.6, 2.9 Hz), 6.05 (1H, d, *J* = 7.0 Hz), 5.32 (1H, q, *J* = 7.0 Hz), 5.06 (1H, d, *J* = 12.2 Hz), 5.01 (1H, d, *J* = 12.2 Hz), 3.38 - 3.54 (2H, m)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 159.0, 156.7, 143.6, 139.1, 137.1, 136.9, 136.1, 135.8, 129.2, 128.8, 128.5, 128.3, 127.9, 127.2, 110.2, 67.3, 51.9, 39.5

HRMS (ESI+): found $[M + H]^+$ 373.1671, $C_{22}H_{21}N_4O_2^+$ required 373.1665

1.3.4.3. Benzyl (1-(1-(2-oxo-2-phenylethyl)-1H-imidazo[4,5-c]pyridin-2-yl)-2-phenylethyl)carbamate (16a) and Benzyl (1-(3-(2-oxo-2-phenylethyl)-3H-imidazo[4,5-c]pyridin-2-yl)-2-phenylethyl)carbamate (17a)





Following General Procedure 5: benzyl (1-(3H-imidazo[4,5-c]pyridin-2-yl)-2-phenylethyl)carbamate **15** (200 mg, 0.53 mmol), 2-bromoacetophenone (128 mg, 0.64 mmol) and potassium carbonate (74 mg, 0.53 mmol) in acetone (2.5 mL) were used. The crude product was purified by flash column chromatography eluting with methanol (0-30%) in ethyl acetate to yield the title compound **16a & 17a** as a yellow solid (79.6 mg, 0.16 mmol, 30%).

R_f = 0.61 & 0.68 (30% MeOH in EtOAc)

$[\alpha]_D^{20}$ = +37.3(c = 0.3 in $CHCl_3$)

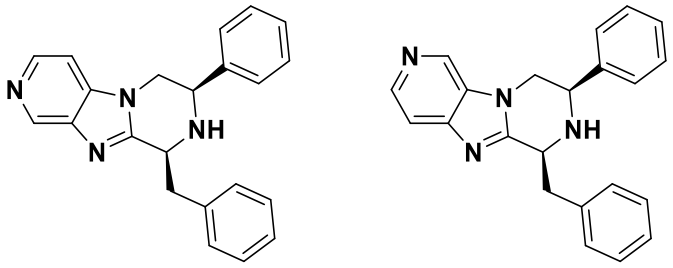
IR: ν_{max} = 3031 (m, N-H), 2928 (m, C-H), 1694 (s, C=O), 1610 (m, C=C), 1581 (m, C=C), 1527 (m, C=C), 1494 (m, C=C)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 9.14 (1H, s), 8.60 (1H, s), 8.50 (1H, d, *J* = 5.5 Hz), 8.43 (1H, d, *J* = 5.5 Hz), 7.99 (4H, d, *J* = 7.3 Hz), 7.72 - 7.74 (2H, m), 7.71 (1H, dt, *J* = 2.7, 1.3 Hz), 7.58 (4H, td, *J* = 7.7, 3.5 Hz), 7.29 - 7.33 (6H, m), 7.24 - 7.27 (6H, m), 7.14 - 7.21 (8H, m), 7.10 (1H, d, *J* = 5.5 Hz), 5.71 (2H, t, *J* = 4.3 Hz), 5.59 - 5.68 (2H, m), 5.48 (1H, d, *J* = 14.6 Hz), 5.45 (1H, d, *J* = 15.0 Hz), 5.11 (2H, dd, *J* = 18.0, 7.6 Hz), 4.91 - 4.99 (2H, m), 4.84 (1H, d, *J* = 12.5 Hz), 4.79 (1H, d, *J* = 12.5 Hz), 3.51 (1H, dd, *J* = 14.0, 6.7 Hz), 3.41 - 3.48 (3H, m)

^{13}C NMR (126 MHz, $CDCl_3$): δ_H = 190.9, 190.8, 157.7, 156.1, 155.9, 155.9, 147.4, 142.7, 142.5, 142.4, 140.4, 139.5, 136.5, 136.4, 135.9, 135.9, 134.6, 134.6, 133.8, 133.8, 133.0, 132.9, 129.4, 129.3, 129.2, 129.2, 128.7, 128.7, 128.5, 128.5, 128.2, 128.2, 128.1, 128.1, 127.7, 127.7, 127.1, 127.0, 114.5, 105.0, 67.0, 67.0, 49.5, 49.4, 49.2, 40.7, 40.6

HRMS (ESI+): found $[M + H]^+$ 491.2103, $C_{30}H_{27}N_4O_3^+$ required 491.2083

1.3.4.4. (7R,9S)-9-benzyl-7-phenyl-6,7,8,9-tetrahydropyrido[3',4':4,5]imidazo[1,2-a]pyrazine (16) and (6S,8R)-6-benzyl-8-phenyl-6,7,8,9-tetrahydropyrido[4',3':4,5]imidazo[1,2-a]pyrazine (17)



Following General Procedure 6: benzyl (1-(1-(2-oxo-2-phenylethyl)-1H-imidazo[4,5-c]pyridin-2-yl)-2-phenylethyl)carbamate **16a** and benzyl (1-(3-(2-oxo-2-phenylethyl)-3H-imidazo[4,5-c]pyridin-2-yl)-2-phenylethyl)carbamate **17a** (44.0 mg, 89.7 µmol), ammonium formate (170 mg, 2.69 mmol) and palladium dihydroxide (13.0 mg, 17.9 µmol) in methanol and water (1 mL, 3:1 v:v,) were used. The crude product was purified by flash column chromatography eluting with ethyl acetate (0-40%) in 40-60 petroleum ether to yield the title compounds **16** & **17** as a yellow solid (30.0 mg, 89.3 µmol, 90%).

R_f = 0.22 & 0.28 (30% MeOH in EtOAc)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = 0.0 (c = 0.2 in MeOH)

IR: ν_{max} = 2972 (m, C-H), 2900 (m, C-H), 1643 (m, C=N), 1615 (m, C=C), 1546 (m, C=C)

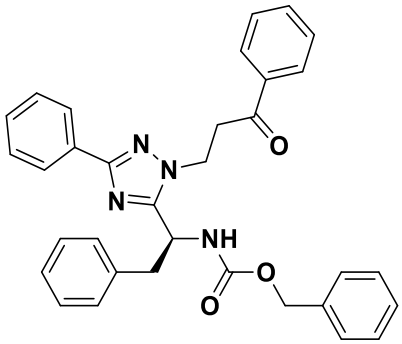
^{1}H NMR (500 MHz, CD_3OD): δ_H = 9.44 (2H, s), 8.61 - 8.69 (2H, m), 8.24 - 8.34 (2H, m), 7.83 (4H, dd, *J* = 7.5, 2.3 Hz), 7.51 - 7.61 (10H, m), 7.36 - 7.43 (4H, m), 7.29 - 7.34 (2H, m), 5.55 (2H, ddd, *J* = 14.3, 8.9, 5.2 Hz), 5.18 - 5.27 (2H, m), 4.99 - 5.10 (4H, m), 4.00 - 4.17 (2H, m), 3.69 (2H, ddd, *J* = 14.8, 8.9, 2.9 Hz)

^{13}C NMR (126 MHz, CD_3OD): δ_C = 159.6, 156.4, 154.3, 145.9, 141.4, 136.5, 136.2, 136.1, 135.4, 135.3, 134.0, 133.7, 131.8, 131.0, 130.8, 130.3, 130.2, 129.9, 129.7, 129.7, 129.6, 129.0, 129.0, 118.5, 110.8, 59.3, 59.2, 58.9, 58.8, 48.0, 47.8, 38.2, 38.1

HRMS (ESI+): found $[M + H]^+$ 341.1772, $C_{22}H_{21}N_4^+$ required 341.1766

1.4. Efficient synthesis of 7-membered saturated rings.

1.4.1. Benzyl (S)-(1-(1-(3-oxo-3-phenylpropyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (18)



Following General Procedure 5: benzyl (1-(1H-indol-2-yl)-2-phenylethyl)carbamate **6a** (100 mg, 0.25 mmol), 3-chloropropiophenone (46 mg, 0.28 mmol) and potassium carbonate (35 mg, 0.25 mmol) in acetone (1 mL), was used eluting with 20% ethyl acetate in 40-60 petroleum ether to yield the title compound **18** as a white solid (124 mg, 0.23 mmol, 93%).

R_f = 0.25 (20% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = +13.5 (c = 0.3 in $CHCl_3$)

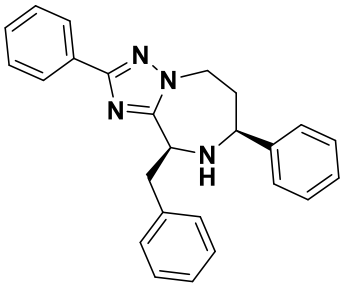
IR: ν_{max} = 3030 (m, C-H), 1697 (s, C=O), 1600 (m,, C=C), 1524 (m, N-H)

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.07 (2H, dd, *J* = 8.0, 1.5 Hz), 7.87 (2H, d, *J* = 7.5 Hz), 7.59 (1H, tt, *J* = 7.2, 1.5 Hz), 7.40 - 7.50 (5H, m), 7.30 - 7.39 (5H, m), 7.23 (2H, t, *J* = 7.5 Hz), 7.16 (3H, d, *J* = 7.5 Hz), 5.81 (1H, d, *J* = 8.6 Hz), 5.34 (1H, td, *J* = 8.6, 6.3 Hz), 5.16 (1H, d, *J* = 12.3 Hz), 5.10 (1H, d, *J* = 12.3 Hz), 4.23 (2H, t, *J* = 6.8 Hz), 3.36 - 3.51 (2H, m), 3.25 (1H, dd, *J* = 12.9, 8.6 Hz), 2.89 (1H, dt, *J* = 18.1, 7.0 Hz)

^{13}C NMR (101 MHz, $CDCl_3$): δ_C =196.7, 161.4, 155.8, 155.6, 136.4, 136.2, 136.1, 133.4, 130.9, 129.5, 129.2, 128.7, 128.6, 128.5, 128.5, 128.2, 128.1, 128.0, 127.1, 126.3, 67.0, 48.8, 43.0, 41.7, 37.9

HRMS (ESI+): found $[M + H]^+$ 531.2395, $C_{33}H_{31}N_4O_3^+$ required 531.2396

1.4.2. (7S,9S)-9-benzyl-2,7-diphenyl-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[1,5-a][1,4]diazepine (19)



Following the protocol for the ring closure, benzyl (S)-(1-(1-(2-oxo-2-phenylethyl)-5-phenyl-1H-imidazol-2-yl)-2-phenylethyl)carbamate **18** (75.0 mg, 141 µmol), ammonium formate (267 mg, 4.24 mmol) and palladium dihydroxide (19.8 mg, 28.3 µmol) in methanol and water (1 mL, 3:1 v:v,) was used eluting with 30% ethyl acetate in 40-60 petroleum ether to yield the title compound **19** as a white solid (10.6 mg, 27.9 µmol, 20%).

R_f = 0.78 (30% EtOAc in hexane)

$[\alpha]_D^{20}$ = +103.1 (c = 0.1 in MeOH)

IR: ν_{max} = 2925 (m, C-H), 1684 (m, C=N), 1604 (m, C=C), 1482 (m, C=C)

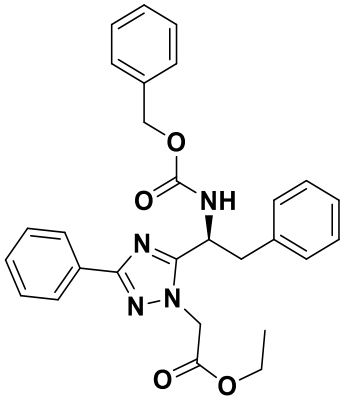
^{1}H NMR (400 MHz, CD_3OD): δ_H = 8.08 (2H, dd, *J* = 7.9), 7.65 (2H, d, *J* = 7.6 Hz), 7.41 - 7.58 (8H, m), 7.34 (2H, t, *J* = 7.3 Hz), 7.25 (1H, d, *J* = 7.3 Hz), 5.27 (1H, dd, *J* = 10.5, 1.9 Hz), 5.07 (1H, d, *J* = 11.4, 3.4 Hz), 4.80 (1H, dd, *J* = 13.4, 3.4 Hz), 4.68 (1H, dd, *J* = 13.4, 11.4), 3.98 (1H, dd, *J* = 13.0, 10.5 Hz), 3.57 (1H, dd, *J* = 13.0, 1.9 Hz), 2.33 - 2.50 (2H, m)

^{13}C NMR (101 MHz, CD_3OD): δ_C = 161.9, 152.6, 138.7, 137.1, 132.0, 131.3, 131.2, 130.8, 130.7, 129.9, 129.6, 128.6, 128.4, 127.4, 68.0, 57.5, 37.0, 34.4 – 1C obscured by MeOD peak

HRMS (ESI+): found $[M + H]^+$ 381.2079, $C_{25}H_{25}N_4^+$ required 381.2079

1.5. Efficient Synthesis of single chiral centres.

1.5.1. Ethyl (S)-2-(5-(1-(((benzyloxy)carbonyl)amino)-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-1-yl)acetate (21)



Following General Procedure 5: benzyl ((3-phenyl-1H-1,2,4-triazol-5-yl)methyl)carbamate **6a** (900 mg, 2.26 mmol), ethyl 2-bromoacetate (300 µL, 2.71 mmol) and potassium carbonate (312 mg, 2.26 mmol) in DMF (3 mL) were used. The crude product was purified by flash column chromatography eluting with 20% ethyl acetate in 40-60 petroleum ether to yield the title compound **20** as a white solid (1.08 g, 2.25 mmol, 99%).

R_f = 0.42 (10% EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -14.6 (c = 0.1 in $CHCl_3$)

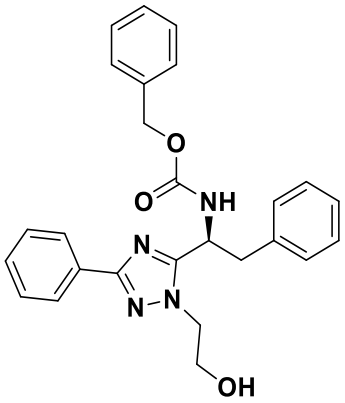
IR: ν_{max} = 3675 (m, N-H), 2988 (s, C-H), 2901 (s, C-H), 1743 (s, C=O), 1697 (s, C=O), 1406 (m, C=C), 1394 (m, C=C), 1382 (m, C=C)

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.08 (2H, dd, *J* = 8.0, 1.5 Hz), 7.39 - 7.49 (4H, m), 7.28 - 7.37 (7H, m), 7.16 (2H, dd, *J* = 7.5, 1.4 Hz), 5.59 (1H, d, *J* = 8.5 Hz), 5.09 (1H, d, *J* = 12.3 Hz), 5.04 (1H, t, *J* = 7.5 Hz), 5.03 (2H, d, *J* = 12.3 Hz), 4.92 (1H, d, *J* = 17.7 Hz), 4.53 (1H, d, *J* = 17.7 Hz), 4.19 (2H, q, *J* = 7.0 Hz), 3.37 (1H, dd, *J* = 14.0, 7.5 Hz), 3.30 (1H, dd, *J* = 14.0, 7.5 Hz), 1.25 (3H, t, *J* = 7.0 Hz)

^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 166.9, 166.8, 161.4, 156.8, 136.3, 136.0, 130.6, 129.3, 129.3, 128.7, 128.5 (C11 & 18), 128.5, 128.2, 127.9, 127.1, 126.4, 67.1, 62.2, 49.5, 48.6, 40.8, 14.0

HRMS (ESI+): found $[M + H]^+$ 485.2189, $C_{28}H_{29}N_4O_4^+$ required 285.2189

1.5.2. Benzyl (S)-(1-(1-(2-hydroxyethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (22)



To a stirred solution of ethyl (S)-2-(5-(1-(((benzyloxy)carbonyl)amino)-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-1-yl)acetate **20** (700 mg, 1.44 mmol, 1.0 eq.) in ethanol (9.0 mL, 0.2 M) at 0 °C, was added lithium borohydride (2.63 mL, 2.63 mmol, 1.8 eq.). The reaction was stirred at room temperature for 18 h before it was quenched with a saturated aqueous solution of ammonium chloride (10 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic fractions were washed with brine (10 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure. The resultant crude compound was purified by flash column chromatography on silica eluting with ethyl acetate (0-100%) in 40-60 petroleum ether to yield the title compound **21** as a white solid (578 mg, 1.31 mmol, 91%).

R_f = 0.57 (50% EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = +53.3 (c = 0.2 in $CHCl_3$)

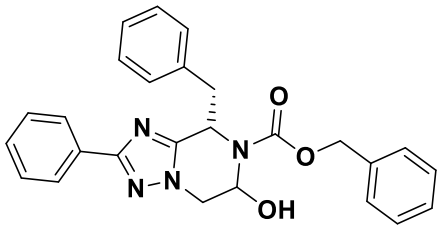
IR: ν_{max} = 3676 (m, O-H), 2988 (s, C-H), 2901 (s, C-H), 1697 (m, C=O), 1406 (m, C=C), 1394 (m, C=C), 1382 (m, C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 8.16 (1H, d, *J* = 8.5 Hz), 7.99 (2H, d, *J* = 7.0 Hz), 7.46 (2H, t, *J* = 7.0 Hz), 7.40 (1H, t, *J* = 7.0 Hz), 7.30 - 7.34 (2H, m), 7.24 - 7.29 (5H, m), 7.18 - 7.23 (3H, m), 5.13 (1H, ddd, *J* = 9.8, 8.5, 5.2 Hz), 5.10 (1H, t, *J* = 5.3 Hz), 4.95 (1H, d, *J* = 12.8 Hz), 4.90 (2H, d, *J* = 12.8 Hz), 4.42 (1H, ddd, *J* = 14.1, 8.9, 5.0 Hz), 4.16 (1H, dt, *J* = 14.1, 4.1 Hz), 3.71 - 3.78 (1H, m), 3.61 - 3.65 (1H, m), 3.23 (1H, dd, *J* = 13.7, 9.8 Hz), 3.15 (1H, dd, *J* = 13.7, 5.2 Hz)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 159.7, 157.7, 155.9, 137.9, 136.9, 131.1, 129.4, 129.0, 128.7, 128.3, 128.1, 127.7, 127.4, 126.4, 125.6, 65.4, 59.7, 50.5, 48.0, 38.6

HRMS (ESI+): found $[M + H]^+$ 443.2071, , $C_{26}H_{27}N_4O_3^+$ required 443.2083

1.5.3. Benzyl 8-benzyl-6-hydroxy-2-phenyl-5,6-dihydro-[1,2,4]triazolo[1,5-a]pyrazine-7(8H)-carboxylate (23)



A stirred solution of ethyl (S)-2-(5-(1-(((benzyloxy)carbonyl)amino)-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-1-yl)acetate **21** (300 mg, 0.681 mmol, 1.0 eq.) and 2-iodoxybenzoic acid (570 mg, 2.03 mmol, 3.0 eq.) in ethyl acetate (7.0 mL, 0.1 M) was heated to reflux for 12 hours. The reaction mixture was filtered through Celite®, and then extracted with ethyl acetate (3 x 20 mL). The combined organic fractions were washed brine (10 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure. The resultant crude compound was purified by flash column chromatography on silica eluting with ethyl acetate (0-100%) in 40-60 petroleum ether to yield the title compound **22** as a white solid (298 mg, 0.681 mmol, 99%).

R_f = 0.50 & 0.61 (50% EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = +4.0 (c = 0.1 in $CHCl_3$)

IR: ν_{max} = 2962 (m, C-H), 1709 (s, C=O)

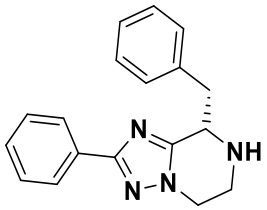
^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 8.07 - 8.17 (6H, m), 7.62 (1H, tt, *J* = 7.4 Hz), 7.29 - 7.54 (13H, m), 7.19 - 7.27 (6H, m), 7.15 (2H, t, *J*=7.9 Hz), 6.64 (2H, d, *J* = 7.0 Hz), 6.37 - 6.39 (1H, m), 5.75 (1 H, t, *J* = 0.9 Hz), 5.71 (1H, t, *J* = 3.1 Hz), 5.61 (1H, dd, *J* = 4.4, 2.7 Hz), 5.39 (2H, s), 5.04 (1H, d, *J*=11.7), 4.51 (1H, d, *J* = 11.7), 4.34 (2H, s), 4.01 (2H, d, *J* = 13.4 Hz), 3.53 3.65 (1H, m), 3.44 (2H, s), 3.19 (1H, dd, *J*=13.7, 2.7 Hz), 2.35 (1 H, dd, *J*=13.4, 3.1 Hz)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 170.2, 170.2, 162.2, 162.1, 151.7, 151.7, 137.6, 137.0, 135.4, 135.4, 133.7, 130.8, 130.7, 130.2, 130.1, 129.9, 129.4, 129.4, 129.3, 128.9, 128.8, 128.6, 128.4, 128.3, 128.5,

128.5, 127.4, 127.4, 126.4, 126.4, 74.9, 73.7, 68.6, 68.3, 53.4, 53.4, 51.5, 51.1, 49.4, 49.4 – ratio of diastereomers 1:1

HRMS (ESI+): found $[M + H]^+$ 441.1926, $C_{26}H_{25}N_4O_3^+$ required 441.1927

1.5.4. (S)-8-benzyl-2-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (24)



Following General Procedure 6: benzyl 8-benzyl-6-hydroxy-2-phenyl-5,6-dihydro-[1,2,4]triazolo[1,5-a]pyrazine-7(8H)-carboxylate **22** (38.0 mg mg, 86.3 µmol), ammonium formate (163 mg, 2.59 mmol) and palladium (12.1 mg, 17.3 µmol) in methanol and water (1 mL, 3:1 v:v) was used eluting with ethyl acetate to yield the title compound **23** as a yellow solid (19.5 mg, 67.2 µmol, 78%).

R_f = 0.31 (60% EtOAc in hexane)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -97.2 (c = 0.1 in MeOH)

IR: ν_{max} = 2922 (m, C-H), 2850 (m, C-H), 1633 (w, C=C), 1491 (m, C=C)

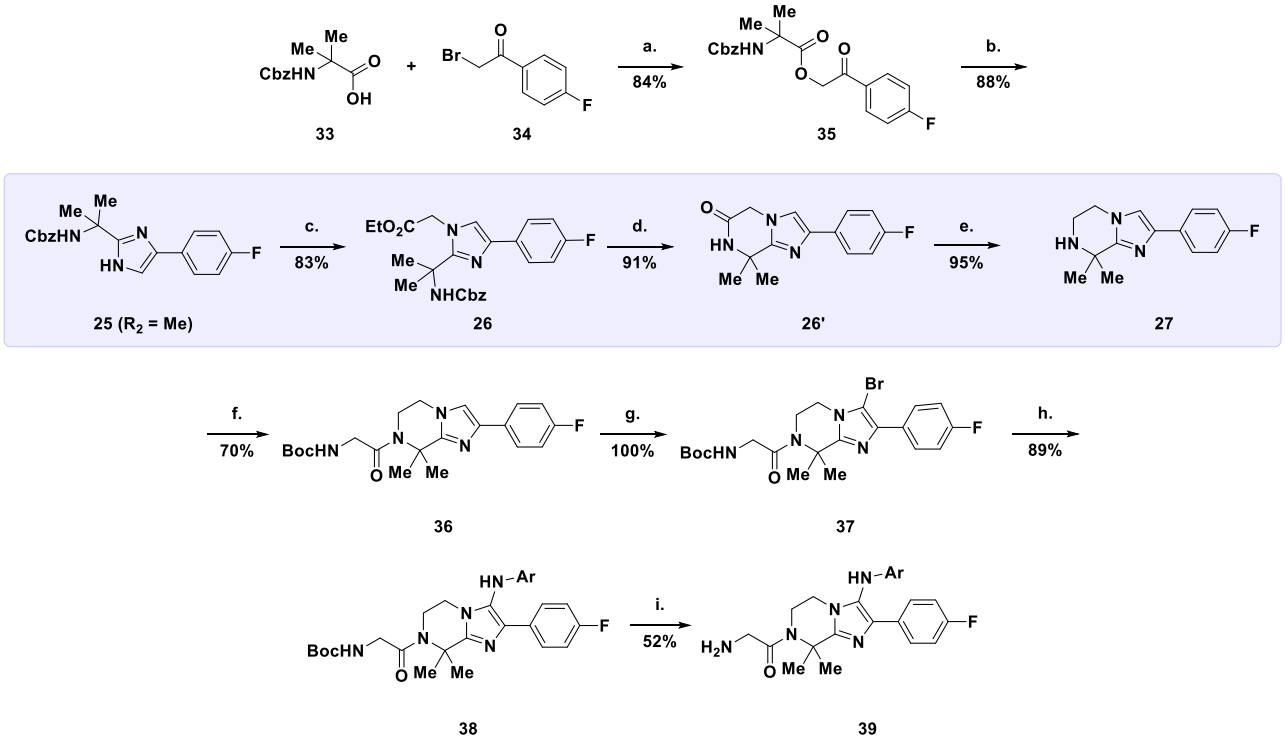
^{1}H NMR (500 MHz, CD_3OD): δ_H = 8.10 (2H, m), 7.45 - 7.52 (7H, m), 7.42 (1H, *J* = 3.5, 2.9 Hz), 5.16 (1H, dd, *J* = 10.2, 4.3 Hz), 4.62 (1H, ddd, *J* = 13.7, 5.1, 2.4 Hz), 4.53 (1H, ddd, *J* = 13.7, 10.9, 5.2 Hz), 3.97 (1H, dd, *J* = 15.1, 4.3 Hz), 3.90 (1H, ddd, *J* = 13.4, 5.2, 2.4 Hz), 3.76 (1H, ddd, *J* = 13.6, 10.9, 5.1 Hz), 3.25 (1 H, dd, *J* = 15.1, 10.2 Hz)

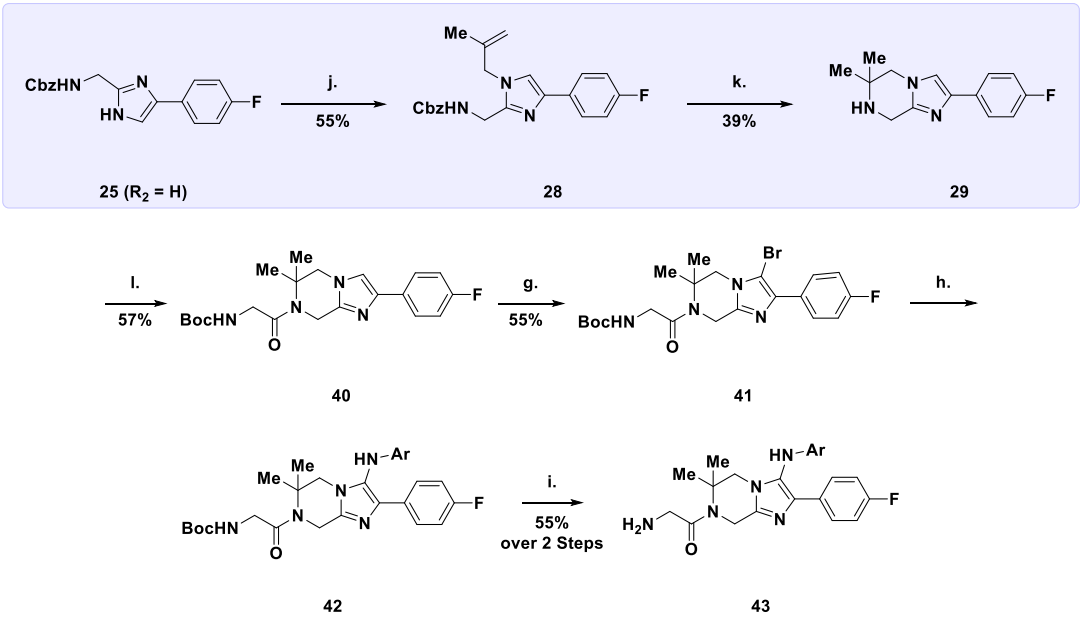
^{13}C NMR (126 MHz, CD_3OD): δ_C = 164.0, 151.2, 135.5, 131.8, 131.3, 131.0, 130.8, 130.1, 129.6, 127.7, 57.0, 44.9, 42.6, 38.2

HRMS (ESI+): found $[M + H]^+$ 291.1622, $C_{18}H_{19}N_4$ required 291.1610.

1.6. Ganaplacide Analogue

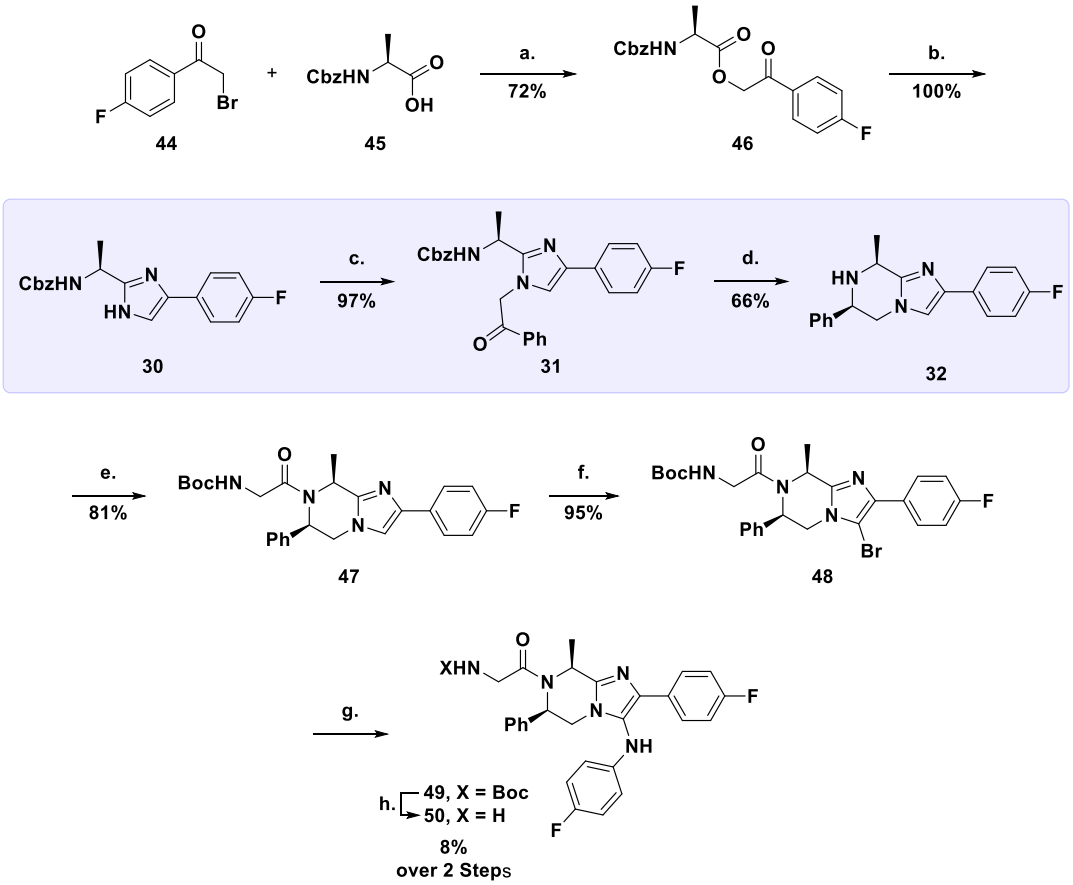
1.6.1. Full Schemes





Scheme 1: The synthetic route used for the SAR studies carried out in the lead optimisation of second-generation antimalarial agents:[22] a. K_2CO_3, DMF, rt, 84% **35**; b. NH_4OAC, toluene, reflux, 88% **25**; c. ethyl 2-bromoacetate, Cs_2CO_3, DMF, rt, 83% **26**; d. Pd/C, H_2 (1 atm), MeOH, rt, 91%, **26'**; e. BH_3·THF, THF, reflux, 95%, **27**; f. N-Boc-glycine, HATU, DIPEA, CH_2Cl_2, rt, 70%, **36**; g. Br_2, AcOH, DCM, rt, 100%

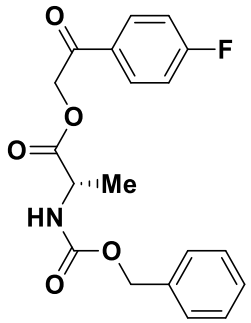
37, 55% ; h. $ArNH_2$, $Pd_2(dba)_3$, xantphos, Cs_2CO_3, dioxane, 150 °C, 89% **38**; i. TFA, DCM, rt, 52% **39**, 55% (2 steps) **43**; j. methallyl chloride, K_2CO_3, KI, DMF, rt, 55%, **28**; k. AcOH/MsOH (6:1), 210 °C, 39% **29**; l. N-Boc-glycine, HATU, DIPEA, DMF, rt, 57% **40**.



Scheme 2: Synthesis of Ganaplacide analogue: a. K_2CO_3, DMF, 4h, rt, 72%, **46**; b. NH_4OAc, toluene, 4h, reflux, 100%, **30**; c. 2-bromoacetopheone, K_2CO_3, acetone, 97%, **31**; d. $NH_4{\cdot}CO_2H$, $Pd(OH_2)/C$ (20 mol %), MeOH:H_2O (3:1 v/v), 66%, **32**; e. N-Boc-glycine, HATU, DIPEA, DMF, 12h, rt, 81%, **47**; f. Br_2, AcOH, CH_2Cl_2, 30min, rt, 95%, **48**; g. p-$FPhNH_2$, $Pd_2(dba)_3$, xantphos, Cs_2CO_3, dioxane, 12h, 150 ºC, **49**; h. TFA, CH_2Cl_2, 1h, rt, 8% (2 steps), **50**.

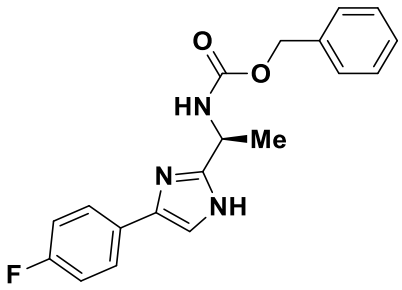
1.6.2. Efficient Synthesis of Ganaplacide Analogue

1.6.2.1. 2-(4-fluorophenyl)-2-oxoethyl ((benzyloxy)carbonyl)-L-alaninate (46)



To a stirred solution of 2-bromo-1-(4-fluorophenyl)ethanone **44** (2.49 g, 11.5 mmol, 1.0 eq.) in DMF (21.4 mL, 0.5 M) was added Z-*L*-Alanine **45** (2.84 g, 12.7 mmol, 1.1 eq.) and potassium carbonate (1.90 g, 13.8 mmol, 1.2 eq.). The reaction mixture was then stirred at room temperature for 4 hours. Upon completion the reaction mixture was quenched with water and extracted wit ethyl acetate (2 x 50 mL). The combined organic fractions were washed with water (50 mL), brine (50 mL) and dried ($MgSO_4$) before the solvent was removed under reduced pressure to yield the crude compound as a white solid (2.96 g, 8.22 mmol, 72%). The title compound **46** was reacted on without further purification.

1.6.2.2. Benzyl (S)-(1-(4-(4-fluorophenyl)-1H-imidazol-2-yl)ethyl)carbamate (30)



A solution of 2-(4-fluorophenyl)-2-oxoethyl ((benzyloxy)carbonyl)-L-alaninate **46** (2.96 g, 8.22 mmol, 1.0 eq.) and ammonium acetate (8.88 g, 115, mmol, 15 eq.) in toluene (43 mL, 0.2 M) was heated to reflux for 4 hours. After complete consumption of starting material, the reaction mixture was concentrated under reduced pressure. The residue was suspended in water (50 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic fractions were washed with brine (50 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield the crude compound as an orange solid (2.79 g, 8.22 mmol, 100%). The title compound **30** was reacted on without further purification.

R_f = 0.18 (30% EtOAc in 40-60 petroleum ether)

IR: ν_{max} = 3215 (m, N–H), 1684 (s, C=O), 1494, 1453 (m, C=C)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -0.795 (c = 0.2 in $CHCl_3$)

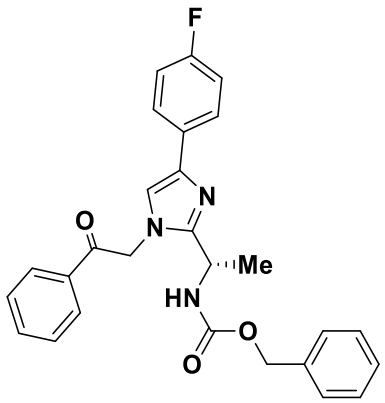
^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.83 (1H, s), 7.54 (2H, dd, *J* = 8.6, 5.4 Hz), 7.45–7.31 (5H, m), 7.05 (1H, s), 7.01 (2H, tt, *J* = 8.8, 3.0 Hz), 6.41 (1H, d, *J* = 7.3 Hz), 5.10 (1H, d, *J* = 12.4 Hz), 5.01 (1H, d, *J* = 12.4 Hz), 4.96 (1H, q, *J* = 7.4 Hz), 1.63 (3H, d, *J* = 6.9 Hz).

^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 175.4, 162.1 (d, *J* = 244.0 Hz), 156.9, 149.9, 136.1, 128.6, 128.5, 128.2, 128.0, 127.8, 126.6 (d, *J* = 8.0 Hz), 115.7 (d, *J* = 21.7 Hz), 67.1, 44.9, 21.4

HRMS (ESI+): found $[M + H]^+$ 340.1455, $C_{19}H_{19}FN_3O_2^+$ required 340.1456

This data is in accordance with that previously reported.[22]

1.6.2.3. Benzyl (S)-(1-(4-(4-fluorophenyl)-1-(2-oxo-2-phenylethyl)-1H-imidazol-2-yl)ethyl)carbamate (31)



Following General Procedure 5: benzyl (*S*)-(1-(4-(4-fluorophenyl)-1H-imidazol-2-yl)ethyl)carbamate **30** (2.90 g, 8.55 mmol), 2-bromoacetophenone (2.75 g, 13.8 mmol) and potassium carbonate (1.59 mg, 11.5 mmol) in acetone (10 mL) were used. The crude product was purified by flash column chromatography eluting with ethyl acetate (30%) in 40-60 petroleum ether to yield the title compound **31** as a white solid (3.80 g, 8.31 mmol, 97%, 72% - over 3 steps).

R_f = 0.24 (30% EtOAc in 40-60 petroleum ether)

IR: ν_{max} = 3285 (m, N–H), 1702 (s, C=O), 1498, 1450 (m, C=C)

$[\alpha]_D^{20}$ = -52.7 (c = 0.4 in $CHCl_3$)

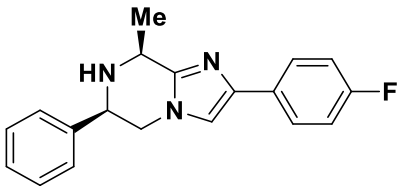
^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.01 (2H, d, *J* = 7.3 Hz), 7.75–7.69 (2H, m), 7.69–7.63 (1H), 7.54 (2H, t, *J* = 7.7 Hz), 7.35–7.21 (5H, m), 7.08–7.00 (3H, m), 5.70 (1H, d, *J* = 18.3 Hz), 5.49 (1H, d, *J* = 18.3 Hz), 5.39 (1H, d, *J* = 8.9 Hz), 5.00 (1H, d, *J* = 12.2 Hz), 4.87–4.78 (2H, m), 1.66 (3H, d, *J* = 6.8 Hz)

^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 192.3, 162.1 (d, *J* = 244.5 Hz), 155.9, 149.5, 140.0, 136.3, 134.5, 134.3, 130.5, 129.2, 128.6, 128.3, 128.0, 126.7 (d, *J* = 7.9 Hz), 116.6, 115.5 (d, *J* = 22.5), 67.0, 52.2, 43.0, 20.4

^{19}F NMR (376 MHz, $CDCl_3$): δ_F = –116.09

HRMS (ESI+): found $[M + H]^+$ 458.1874, $C_{27}H_{25}FN_3O_3^+$ required 458.1870

1.6.2.4. (6R,8S)-2-(4-fluorophenyl)-8-methyl-6-phenyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine (32)



Following General Procedure 6: benzyl (*S*)-(1-(4-(4-fluorophenyl)-1-(2-oxo-2-phenylethyl)-1H-imidazol-2-yl)ethyl)carbamate **31** (2.18 g, 4.76 mmol), ammonium formate (9.00 g, 143 mmol) and palladium dihydroxide (436 mg, 0.62 mmol) in methanol and water (47.6 mL, 3:1 v:v,) were used. The crude product was purified by flash column chromatography eluting with ethyl acetate (35%) in hexane to yield the title compound **32** as a white solid (3.14 g, 3.14 mmol, 66%).

R_f = 0.10 (35% EtOAc in 40-60 petroleum ether)

IR: ν_{max} = 3285 (m, N–H), 1702 (s, C=O), 1498, 1450 (m, C=C)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -21.6 (c = 0.1 in $CHCl_3$)

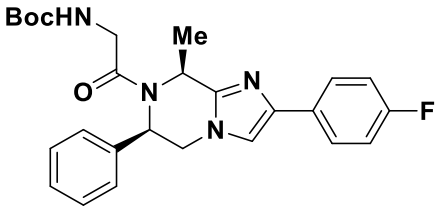
^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.79–7.69 (2H, m), 7.51 – 7.45 (2H, m), 7.44 – 7.32 (3H, m), 7.14 – 6.99 (3H, m), 4.39 – 4.27 (2H, m), 4.09 (1H, dd, *J* = 11.7, 3.9 Hz), 4.05 – 3.95 (1H, m), 1.68 (3H, d, *J* = 6.5 Hz)

^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 162.0 (d, *J* = 244.9 Hz), 147.5, 140.4, 139.9, 130.8 (d, *J* = 3.0 Hz), 129.1, 128.7, 127.1, 126.6 (d, *J* = 7.9 Hz), 115.5 (d, *J* = 21.5), 113.3, 58.4, 52.1, 51.4, 20.3

^{19}F NMR (376 MHz, $CDCl_3$): δ_F = –116.27

HRMS (ESI+): found $[M + H]^+$ 308.1558, $C_{19}H_{19}FN_3^+$ required 308.1558

1.6.2.5. tert-butyl (2-((6R,8S)-2-(4-fluorophenyl)-8-methyl-6-phenyl-5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)-2-oxoethyl)carbamate (47)



To a stirred solution of (6*R*,8*S*)-2-(4-fluorophenyl)-8-methyl-6-phenyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine **32** (3.66 g, 9.76 mmol, 1.0 eq.) and *N*-Boc-glycine (2.23 g, 12.7 mmol, 1.3 eq.) in DMF (40 mL, 0.25M) was added *N*,*N*-diisopropylethylamine (2.60 mL, 14.6 mmol, 1.5 eq.) and HATU (5.54 g, 14.6 mmol, 1.5 eq.). The reaction mixture was stirred at room temperature for 4 days, before further dilution with dichloromethane (50 mL). The organic layer was washed with water (50 mL), saturated aqueous sodium hydrogen carbonate solution (50 mL), brine (30 mL) and dried ($MgSO_4$) before being concentrated under reduced pressure. The resultant crude compound was purified by flash column chromatography on silica eluting with ethyl acetate (0-100%) in 40-60 petroleum ether to yield the title compound **47** as a yellow solid (3.66 g, 7.88 mmol, 81%).

R_f = 0.12 (30% EtOAc in 40-60 petroleum ether)

IR: ν_{max} = 3336 (m, N–H), 2980 (m, C-H), 1703 (s, C=O), 1650 (S, C=N), 1496, 1454 (m, C=C)

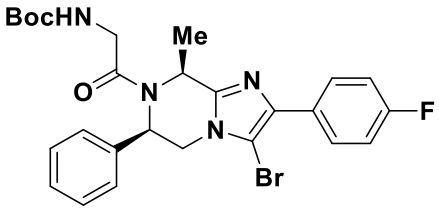
$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = +0.74 (c = 0.1 in $CHCl_3$)

^{1}H NMR (500 MHz, d^6-DMSO, 100 °C): δ_H = 7.76 (2H, dd, *J* = 8.0, 5.8 Hz), 7.62 (1H, s), 7.29 (3H, dt, *J* = 13.9, 6.8 Hz), 7.23 (2H, d, *J* = 7.4 Hz), 7.14 (2 H, t, *J* = 8.7 Hz), 6.45 - 6.58 (1H, m), 5.37 (1H, q, *J* = 6.8 Hz), 4.79 (1H, d, *J* = 13.5 Hz), 4.39 (1H, dd, *J* = 13.5, 4.4 Hz), 4.08 (2H, d, *J* = 5.6 Hz), 3.62 (1H, d, *J* = 6.1 Hz), 1.44 (9H, s), 1.16 (3H, d, *J* = 6.8 Hz)

^{13}C NMR (126 MHz, d^6-DMSO, 100 °C): δ_C = 167.9, 162.4 (d, *J* = 221.6. Hz), 158.4, 148.2, 143.4, 141.2, 128.8, 128.0, 127.5, 127.3, 126.6 (d, *J* = 7.8 Hz), 1261, 115.4 (d, *J* = 21.8 Hz), 114.8, 100.3, 82.9, 78.7, 72.9, 60.0, 44.7, 28.6, 27.8

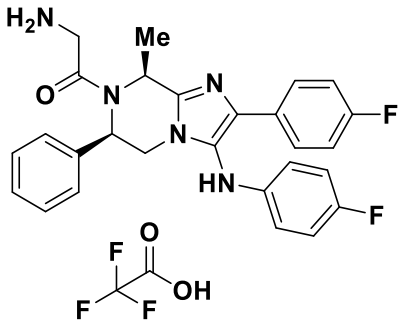
HRMS (ESI+): found $[M + H]^+$ 487.2114, $C_{26}H_{29}FN_4O_3Na^+$ required 487.2121

1.6.2.6. tert-butyl (2-((6R,8S)-3-bromo-2-(4-fluorophenyl)-8-methyl-6-phenyl-5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)-2-oxoethyl)carbamate (48)



To a stirred solution of *tert*-butyl (2-((6*R*,8*S*)-2-(4-fluorophenyl)-8-methyl-6-phenyl-5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)-2-oxoethyl)carbamate **47** (515 mg, 1.11 mmol, 1.0 eq.) in dichloromethane (11 mL, 0.25 M) was added a solution of bromine (0.06 mL, 1.22 mmol, 1.1 eq.) in acetic acid (2 mL). The reaction mixture was stirred for 30 minutes at room temperature. Upon completion, the reaction mixture was concentrated under reduced pressure with the temperature maintained below 20 °C. The residue was neutralised with a saturated aqueous solution of sodium hydrogen carbonate (10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic fractions were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield the title compound **48** as an orange solid (575 mg, 1.06 mmol, 95%). The title compound **48** was reacted on without further purification.

1.6.2.7. 2-amino-1-((6R,8S)-2-(4-fluorophenyl)-3-((4-fluorophenyl)amino)-8-methyl-6-phenyl-5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)ethan-1-one. TFA salt (50)



A solution of caesium carbonate (360 mg, 1.10 mmol, 2.0 eq.), xantphos (32.0 mg, 55.0 µmol, 0.1 eq.) and tris(dibenzylideneacetone)dipalladium(0) (25.0 mg, 28.0 µmol, 0.05 eq.) in dioxane were stirred at room temperature for 5 minutes before the addition of *tert*-butyl (2-((6R,8S)-2-(4-fluorophenyl)-8-methyl-6-phenyl-5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)-2-oxoethyl)carbamate **48** (300 mg, 0.55 mmol, 1.0 eq.). The resulting solution was degassed for 15 minutes, then stirred at 120 °C under nitrogen for 8 hours. Upon completion, the reaction was filtered to remove solid, then concentrated under reduced pressure. The resultant crude compound was purified by flash column chromatography on silica eluting with ethyl acetate (0-100%) in 40-60 petroleum ether to yield a mixture of *tert*-butyl (2-((6*R*,8*S*)-2-(4-fluorophenyl)-3-((4-fluorophenyl)amino)-8-methyl-6-phenyl-5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)-2-oxoethyl)carbamate **49** and the dehalogenated product **47** as a white solid (110 mg). The mixture was carried through to the final deprotection.

The mixture (110mg) was treated with 20% TFA in dichloromethane (1 mL). Upon completion, the resulting mixture was concentrated under reduced pressure. The resulting residue was purified by reverse phase HPLC (5-95% acetonitrile in water) to yield the title product **50** as a TFA salt (24.7 mg, 0.0421 mmol, 8%).

HPLC R_t = 9.759 min (5-95% acetonitrile in water over 15 mins)

IR: ν_{max} = 2935 (m, C-H), 1665 (s, C=O), 1506, 1426 (m, C=C)

$[\alpha]_D^{20}$ = +1.36 (c = 0.1 in $CHCl_3$)

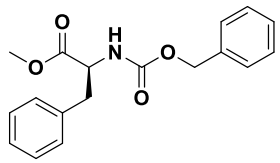
^{1}H NMR (500 MHz, d^6-DMSO, 100 °C): δ_H = 7.84 (3H, dd, *J* = 7.4, 5.2 Hz), 7.30 (3H, br s), 7.17 (2H, d, *J* = 2.9 Hz), 7.10 (2H, t, *J* = 8.7 Hz), 6.98 (2H, *J* = 8.7 Hz), 6.68 (2H, d, *J* = 4.4 Hz), 5.38 (1H, br s), 4.49 (3H, d, *J* = 13.6 Hz), 3.97 – 4.22 (2H, m), 1.21 (3H, d, *J* = 6.0 Hz)

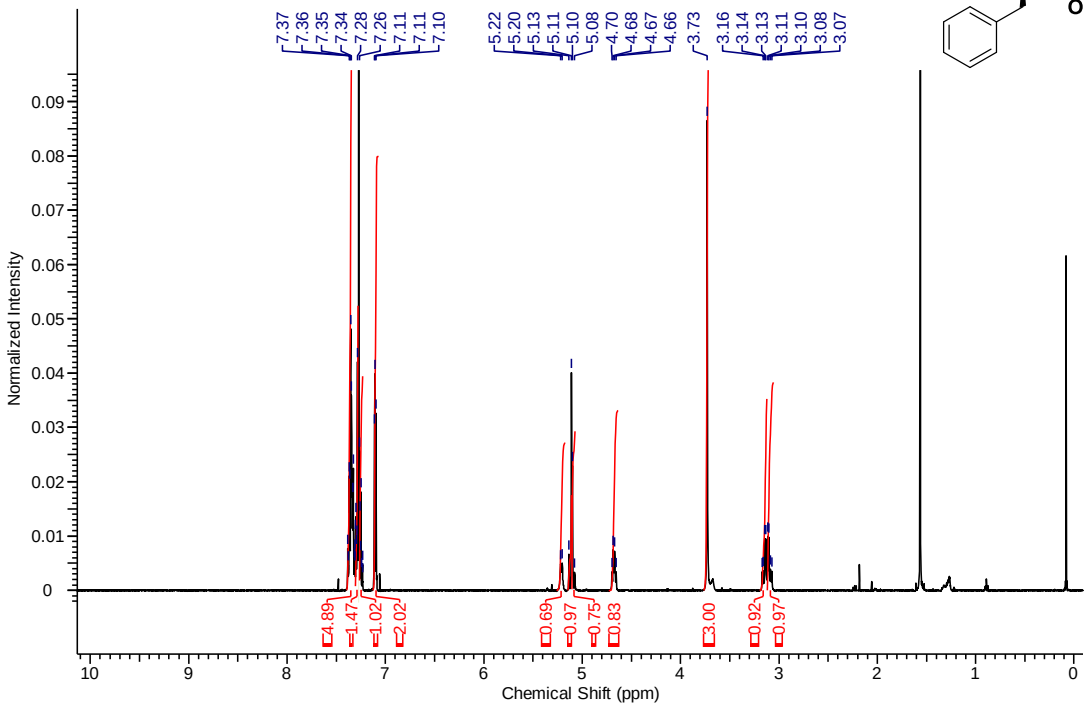
^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 166.6, 165.1 (d, *J* = 207 Hz), 154.7 (d, *J* = 179 Hz), 149.7, 143.0, 139.5, 138.0, 130.7, 128.9, 128.3, 127.5, 127.4, 125.5, 116.1 (d, *J* = 22.4 Hz), 115.3 (d, *J* = 21.3 Hz), 114.8 (d, *J* = 7.3 Hz), 75.8, 72.2, 62.2, 48.5, 28.6

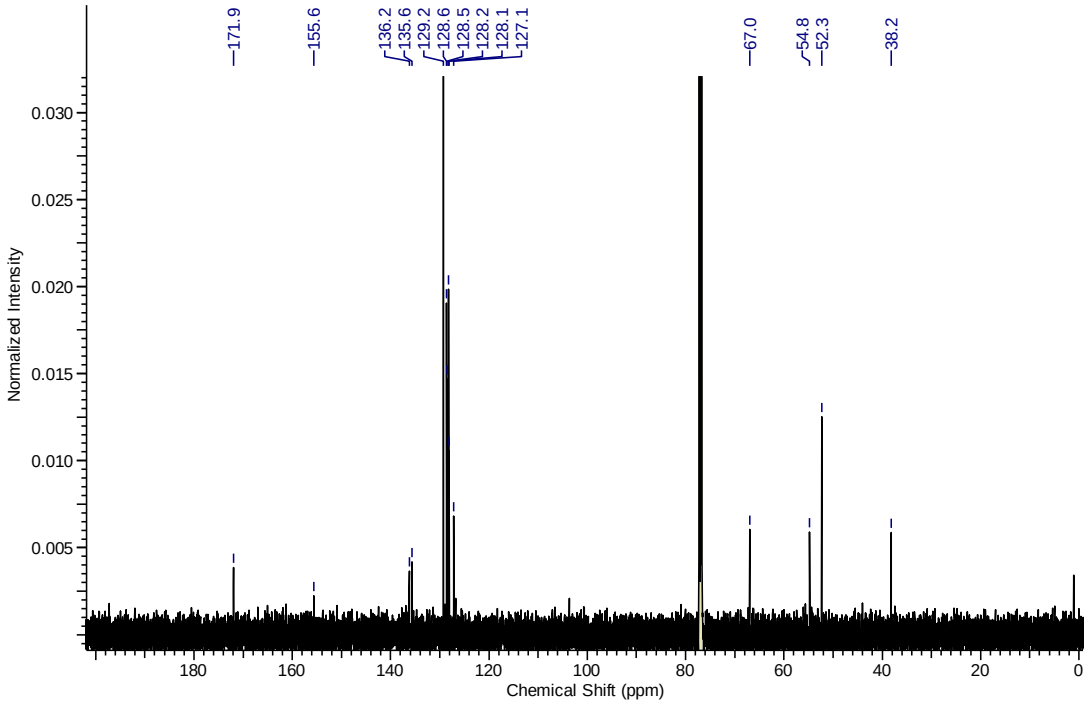
HRMS (ESI+): found $[M + H]^+$ 474.2096, $C_{27}H_{26}F_2N_4O^+$ required 474.2100

2. NMR Spectra

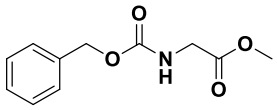
Methyl((benzyloxy)carbonyl)-L- phenylalaninate (2a)

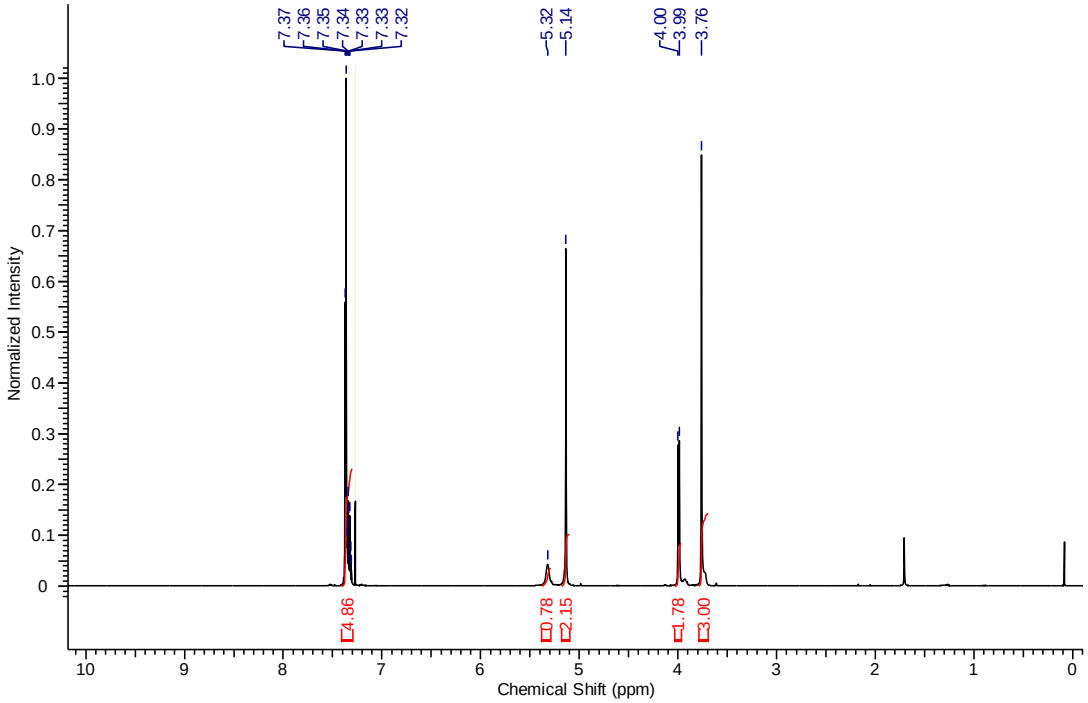


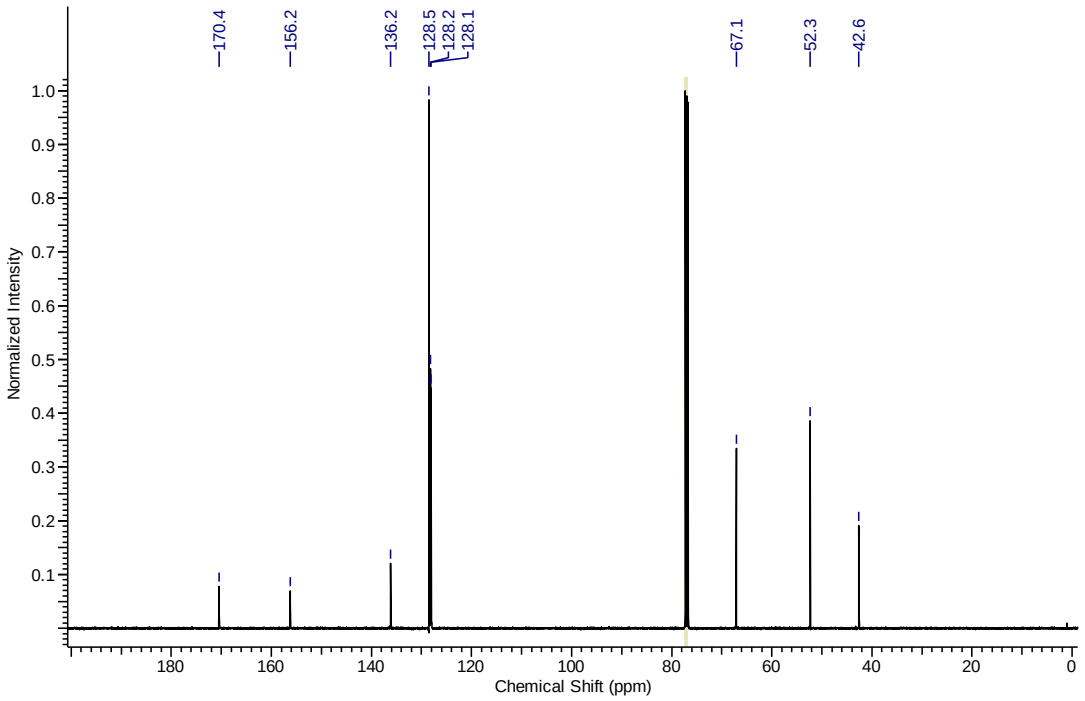




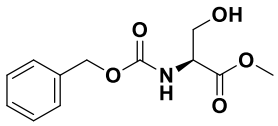
Methyl ((benzyloxy)carbonyl)glycinate (2b)

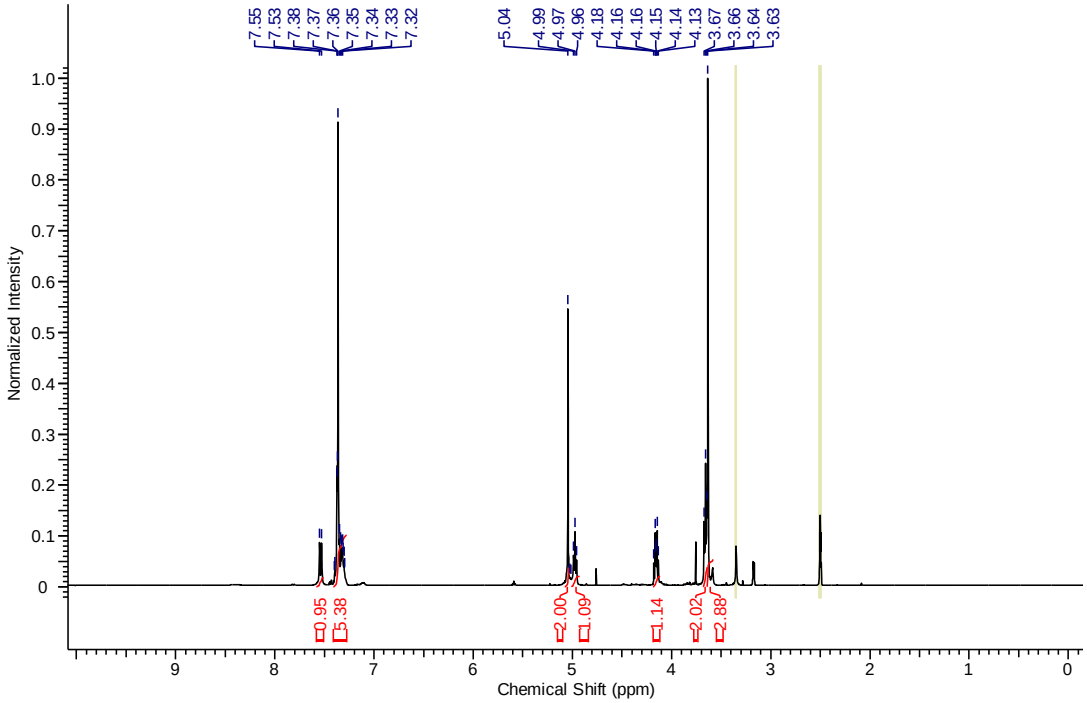


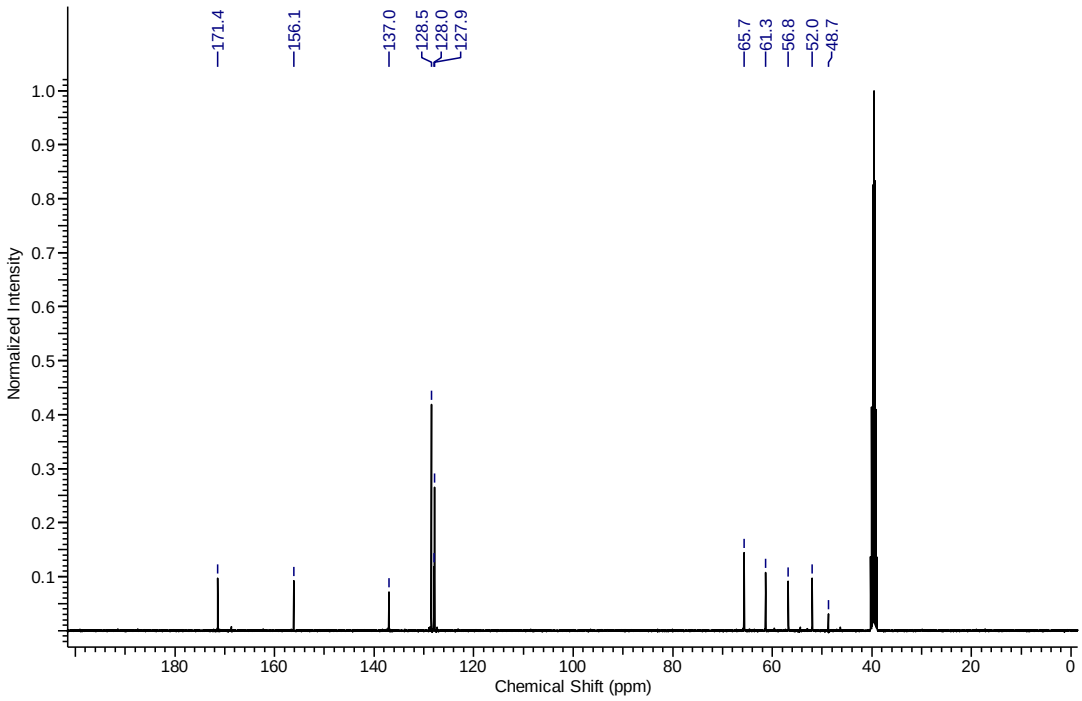




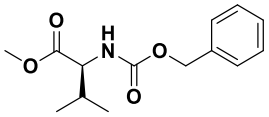
Methyl ((benzyloxy)carbonyl)-L-serinate (2c)

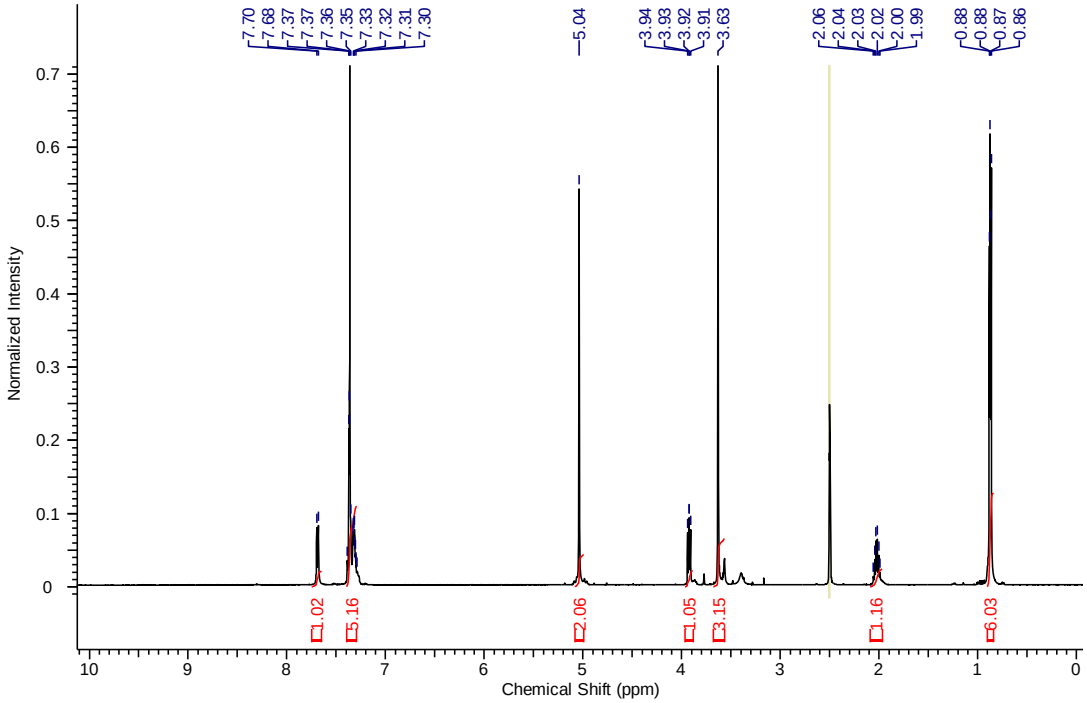


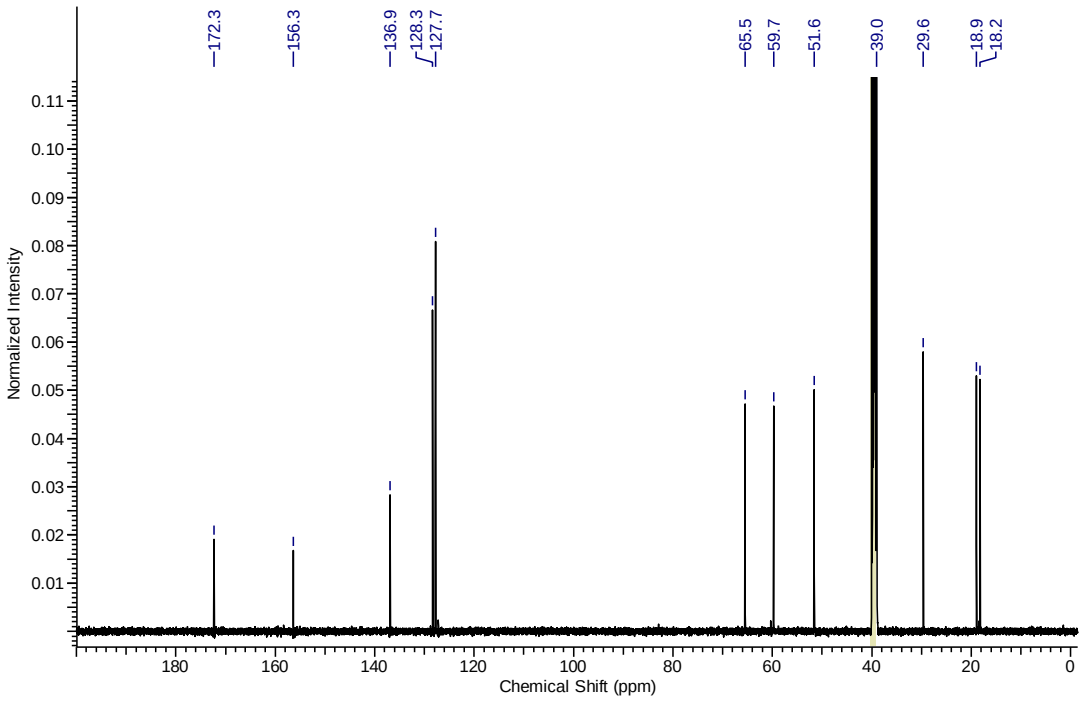




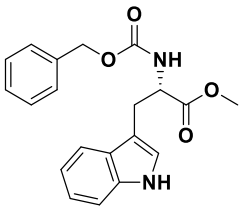
Methyl ((benzyloxy)carbonyl)-L-valinate (2d)

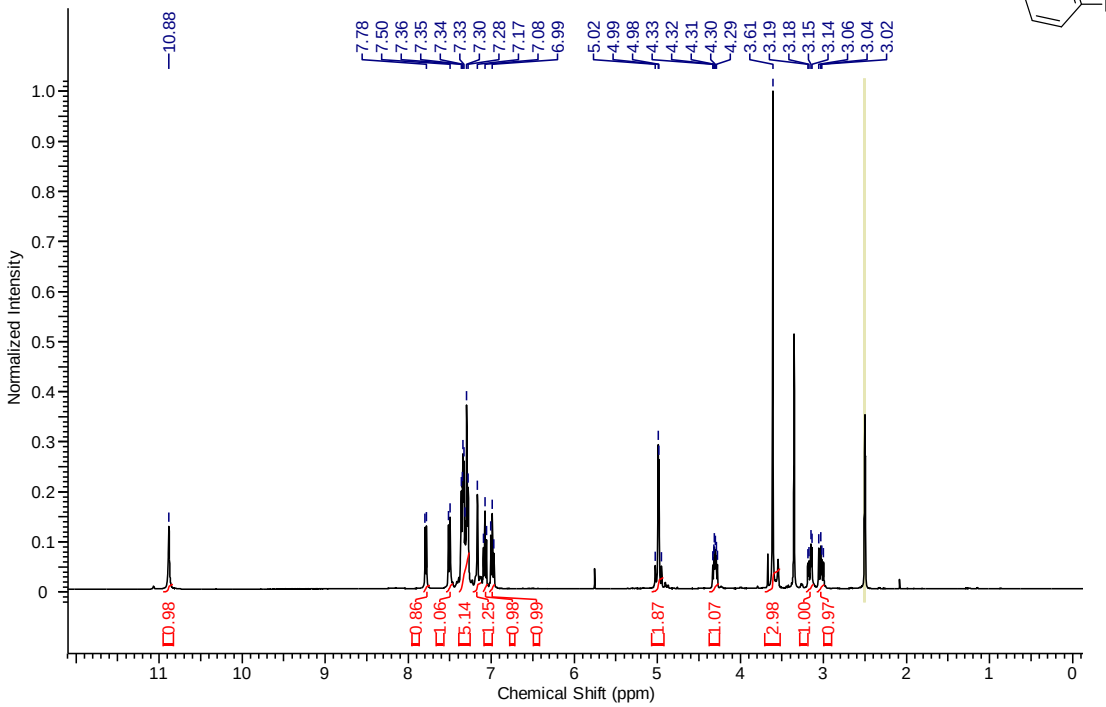


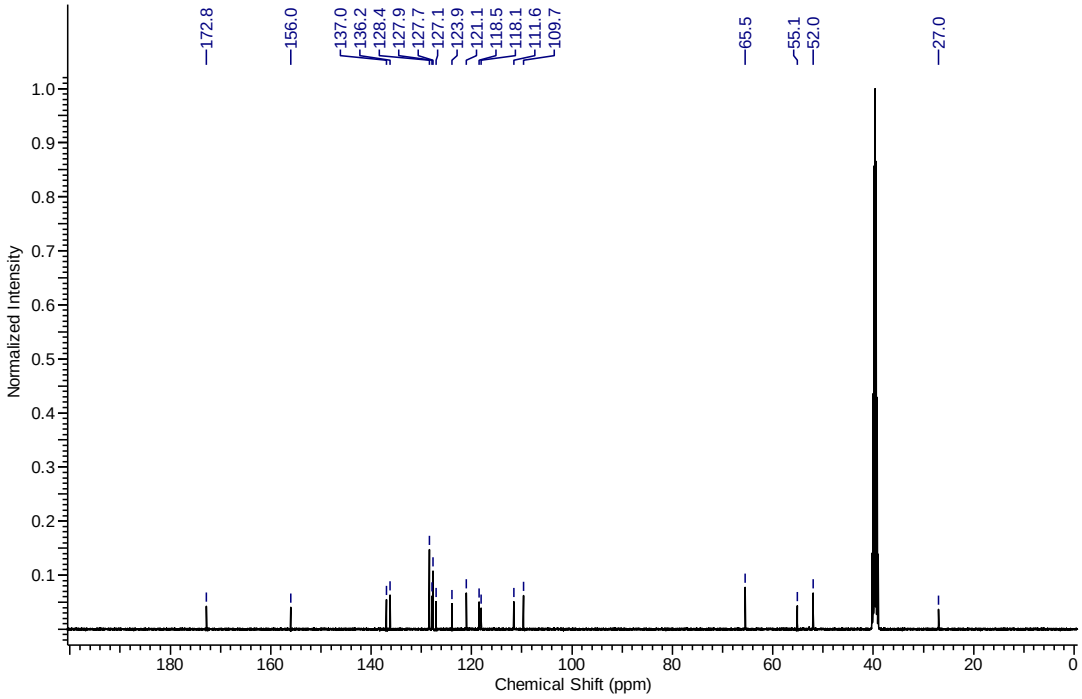




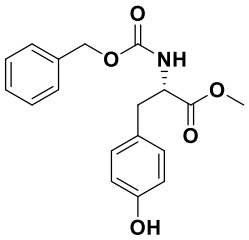
Methyl ((benzyloxy)carbonyl)-L-tryptophanate (2e)

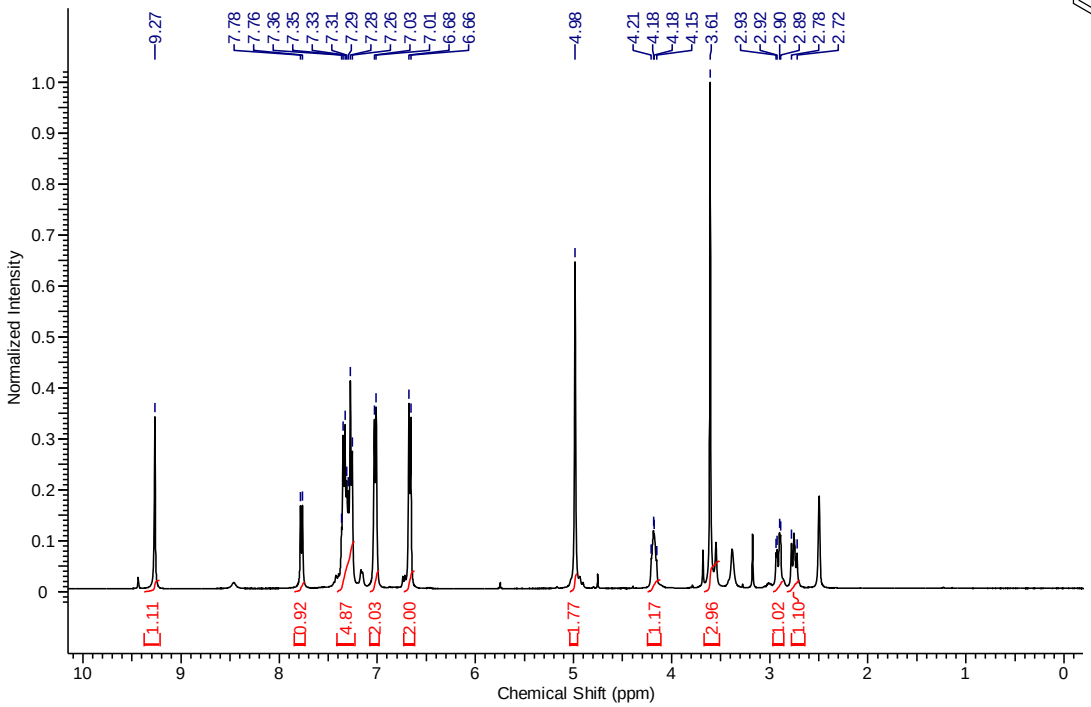


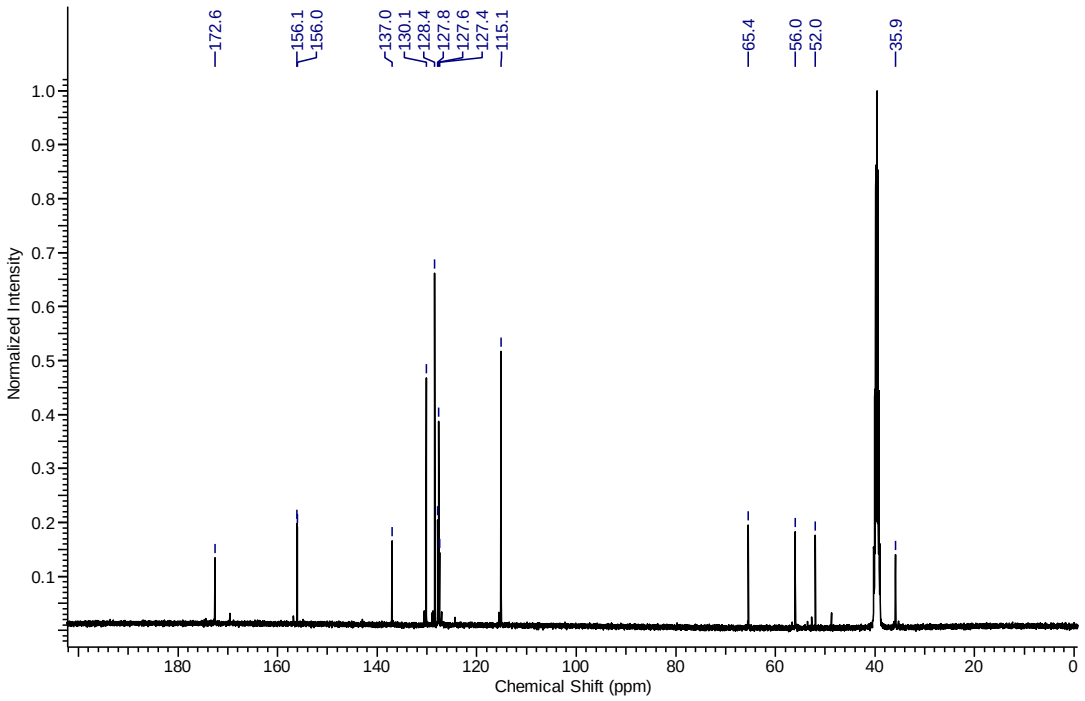




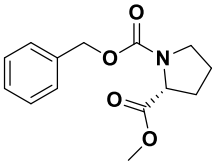
Methyl ((benzyloxy)carbonyl)-L-tyrosinate (2f)

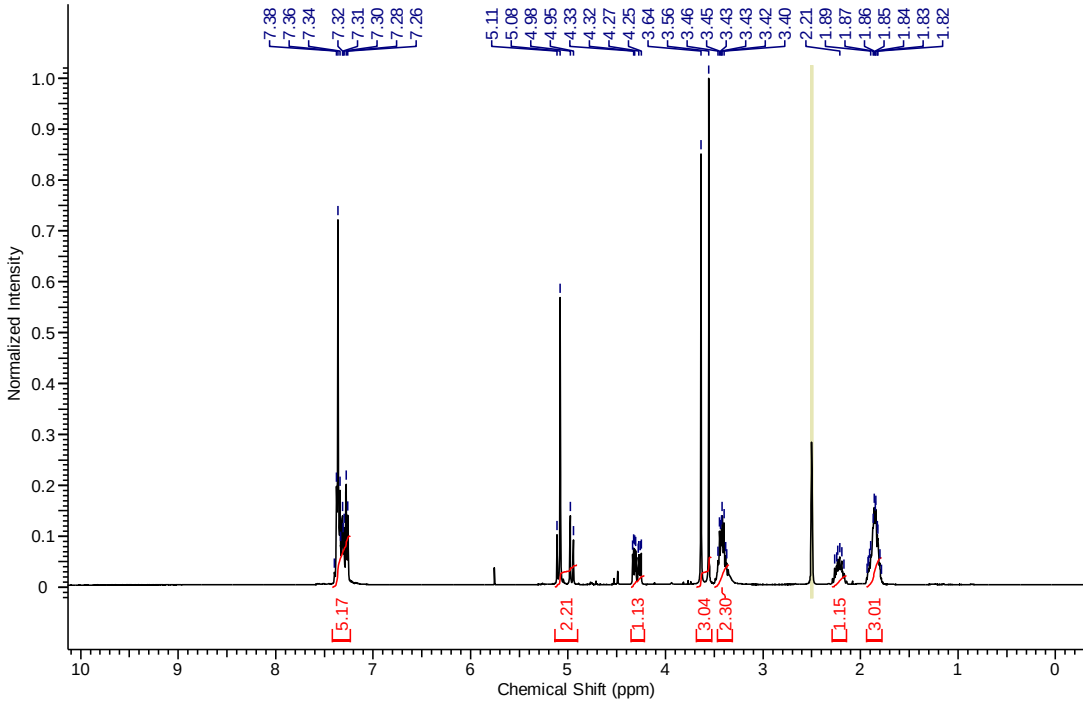


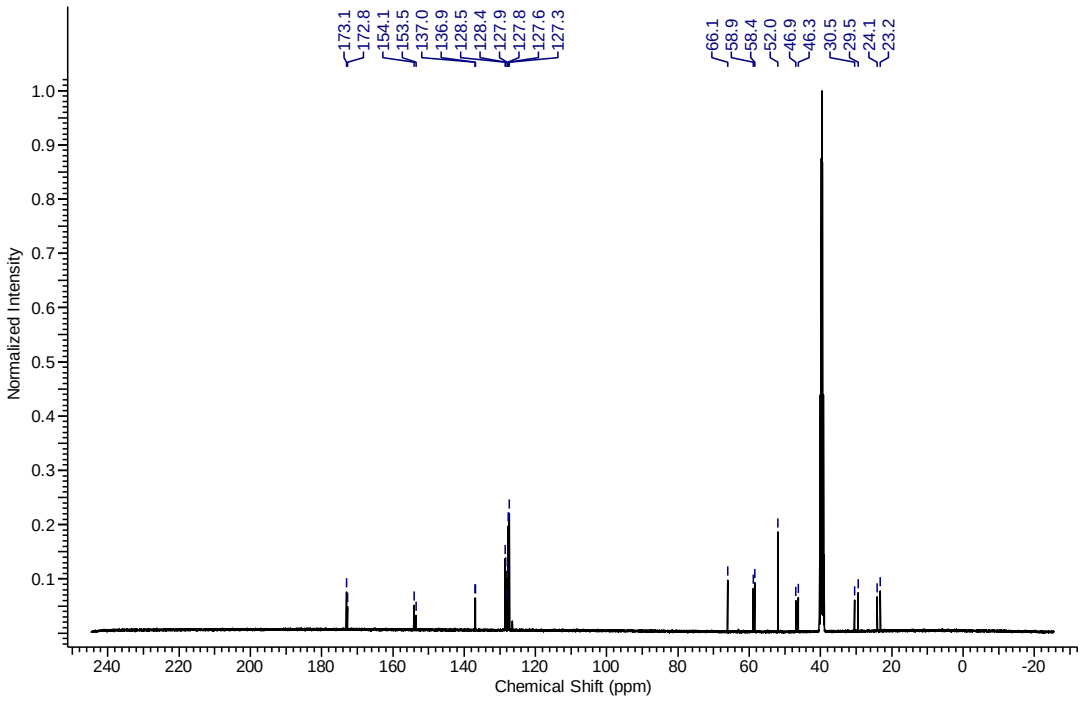




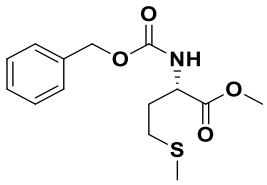
Methyl ((benzyloxy)carbonyl)-L-prolinate (2g)

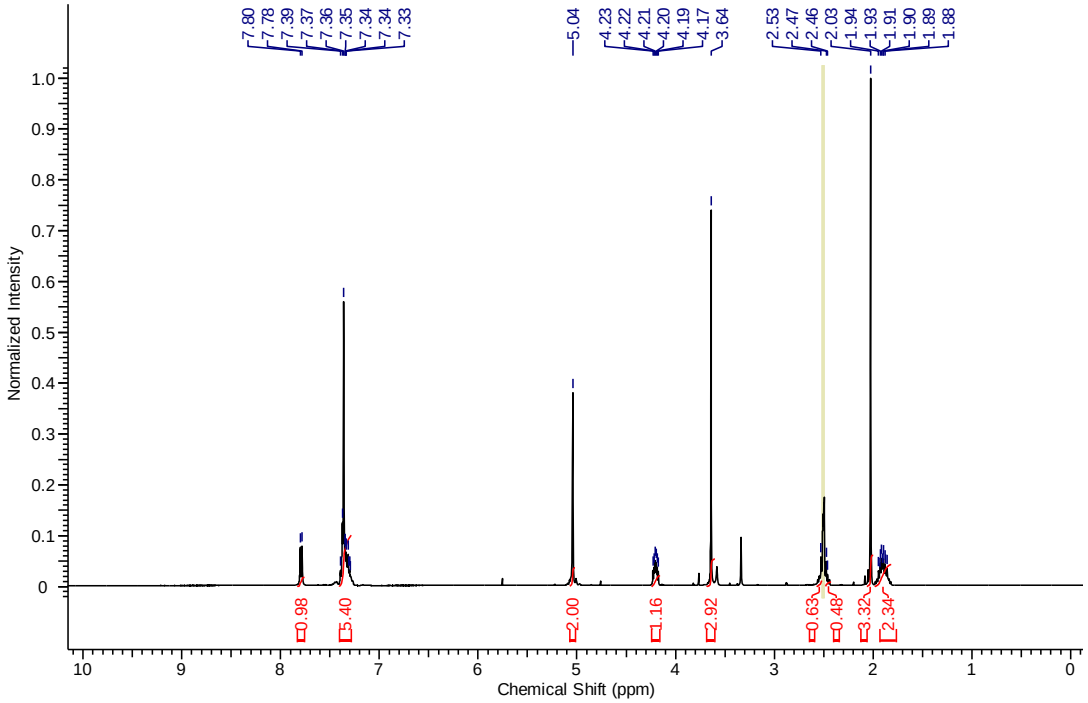


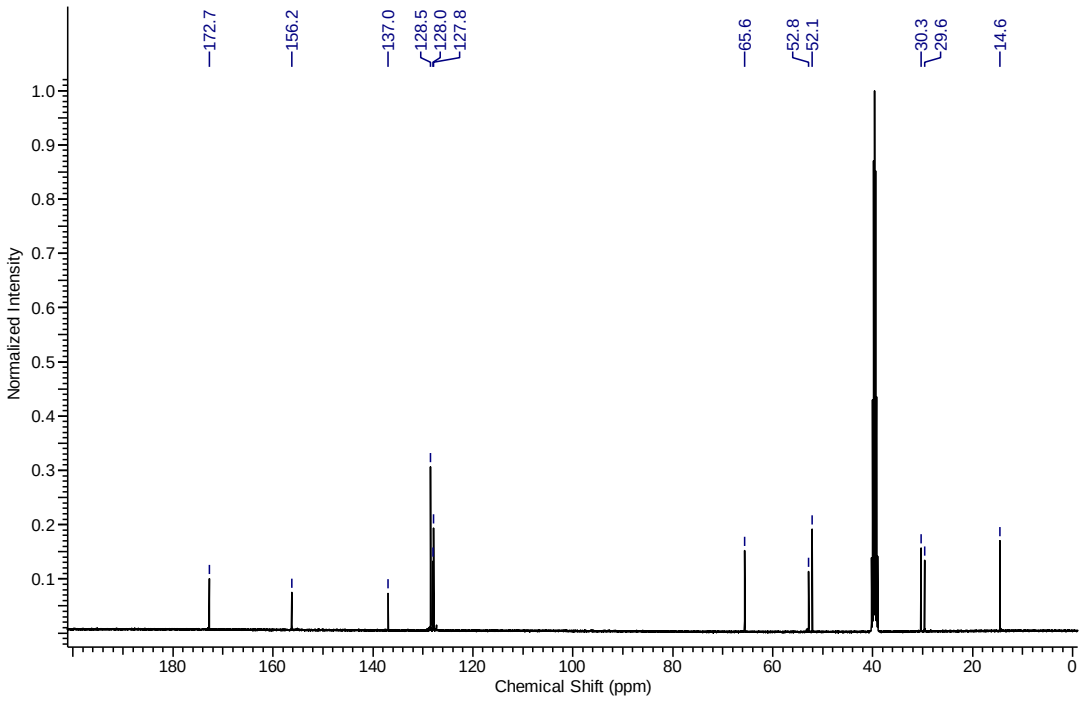




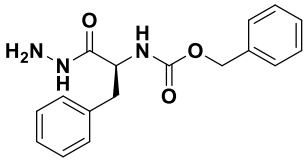
Methyl ((benzyloxy)carbonyl)-L-methioninate (2h)

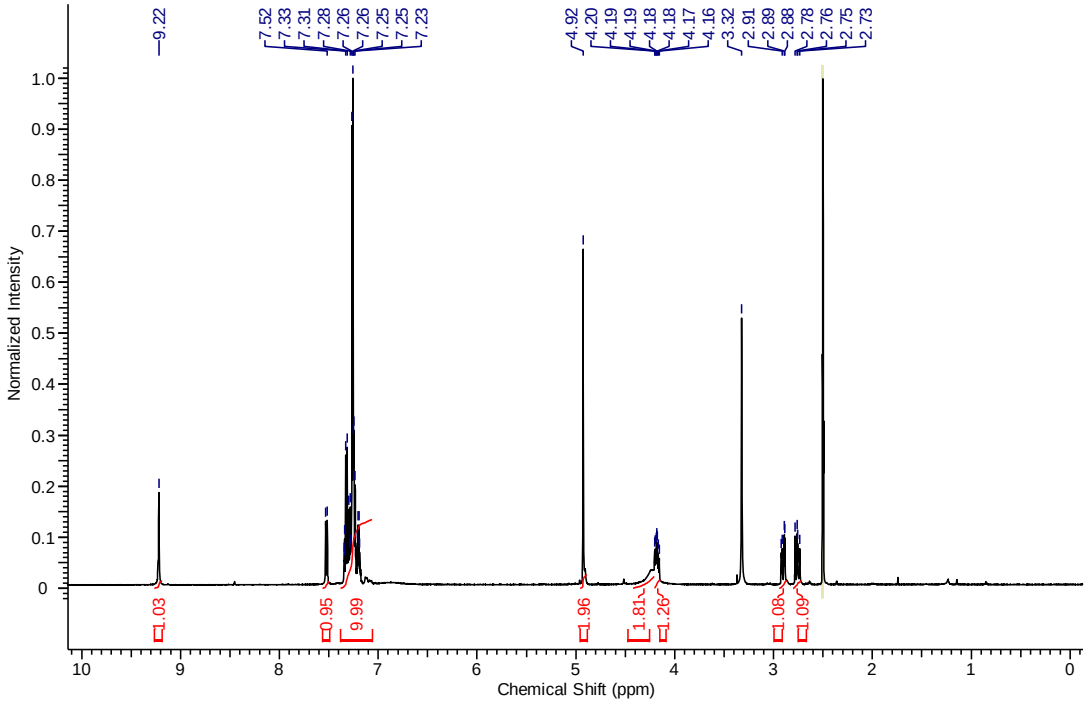


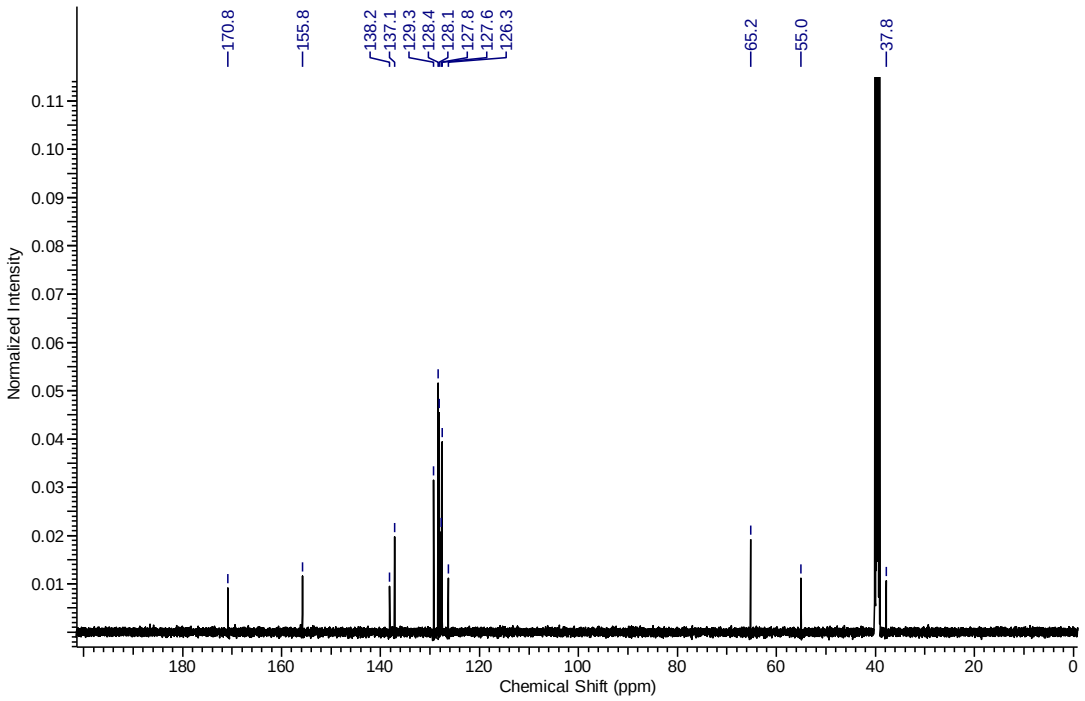




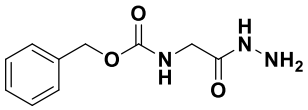
Benzyl (S)-(1-hydrazinyl-1-oxo-3-phenylpropan-2-yl)carbamate (3a)

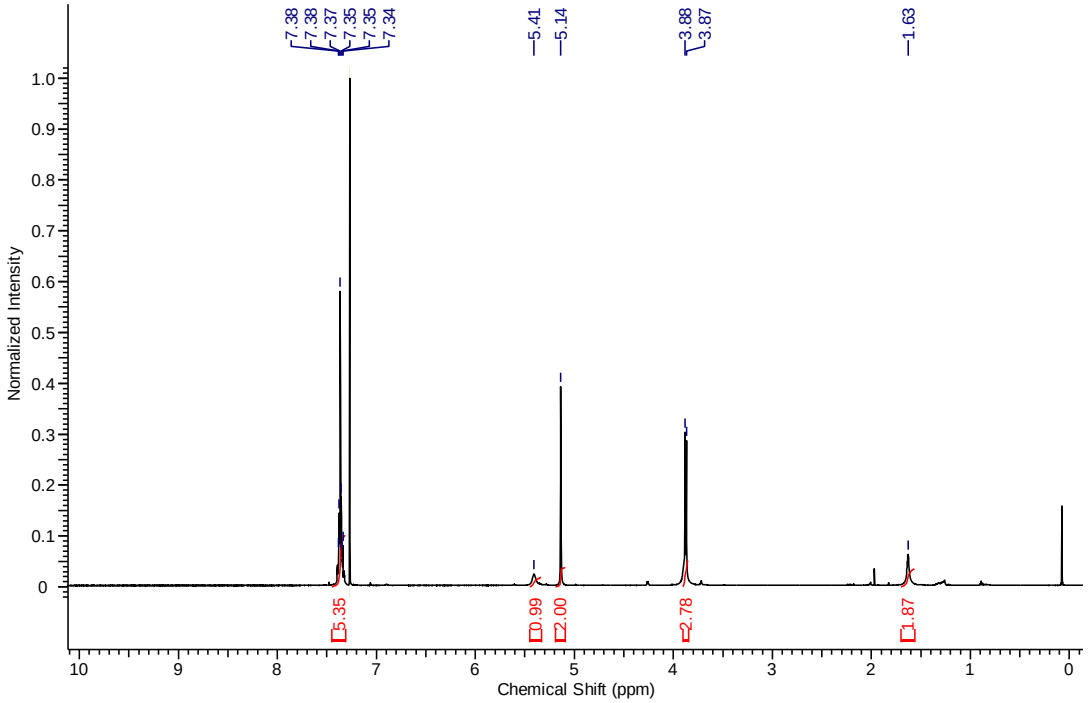


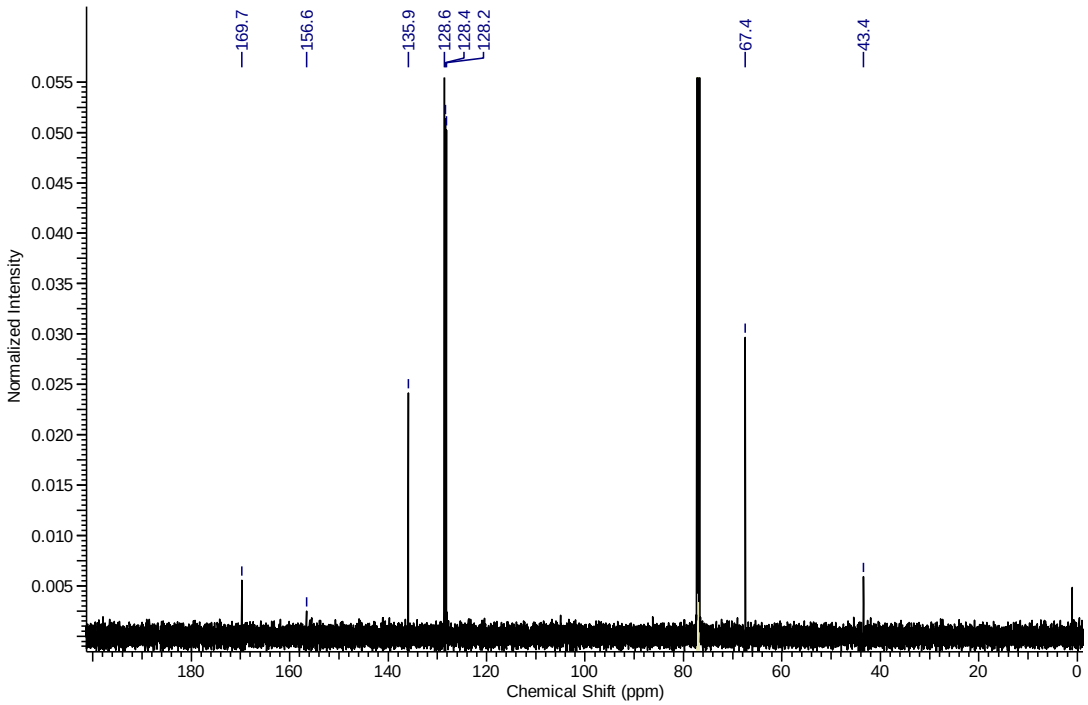




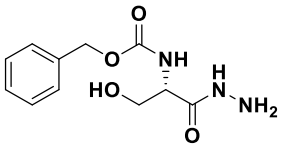
Benzyl (2-hydrazinyl-2-oxoethyl)carbamate (3b)

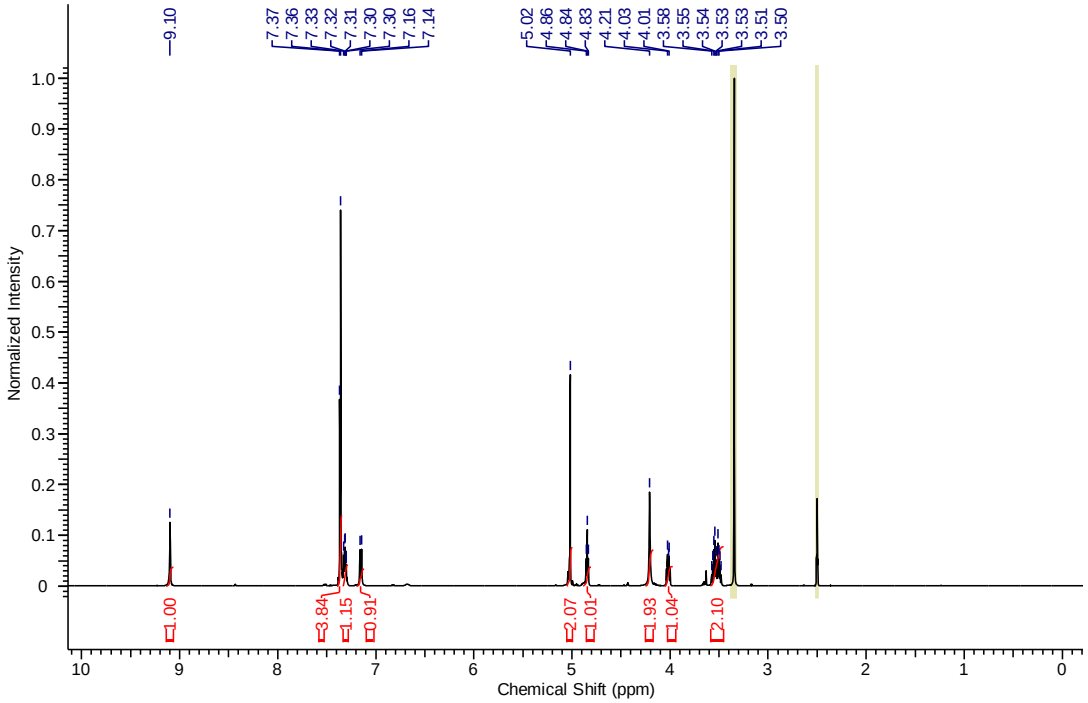


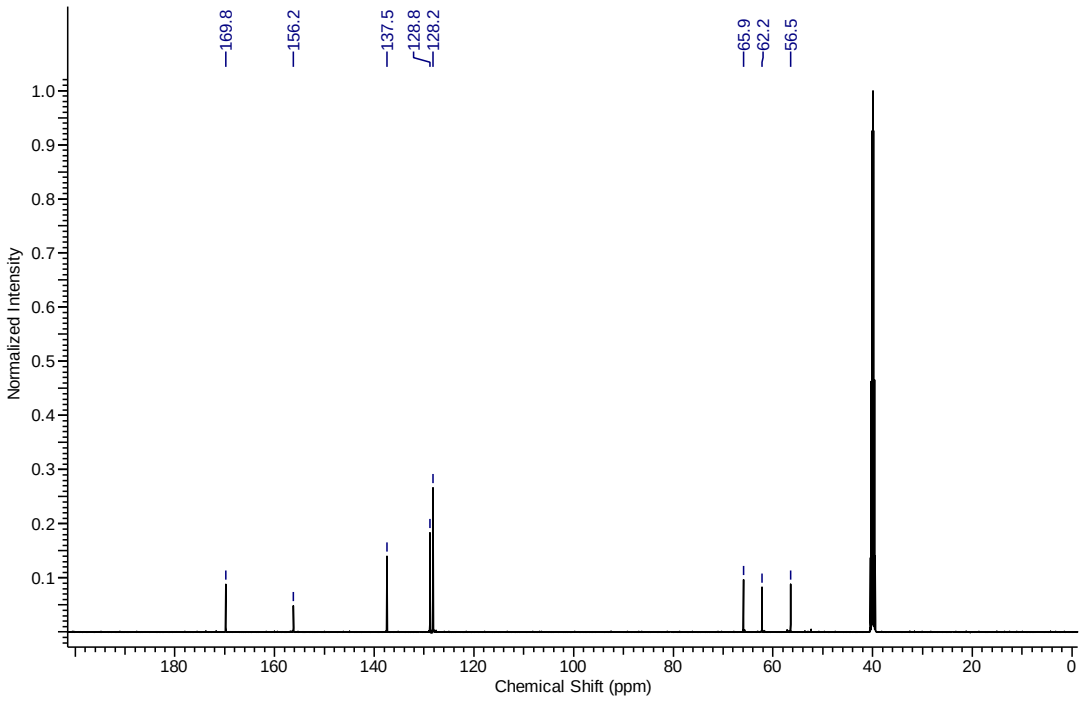




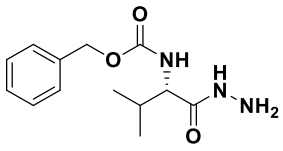
Benzyl (S)-(1-hydrazinyl-3-hydroxy-1-oxopropan-2-yl)carbamate (3c)

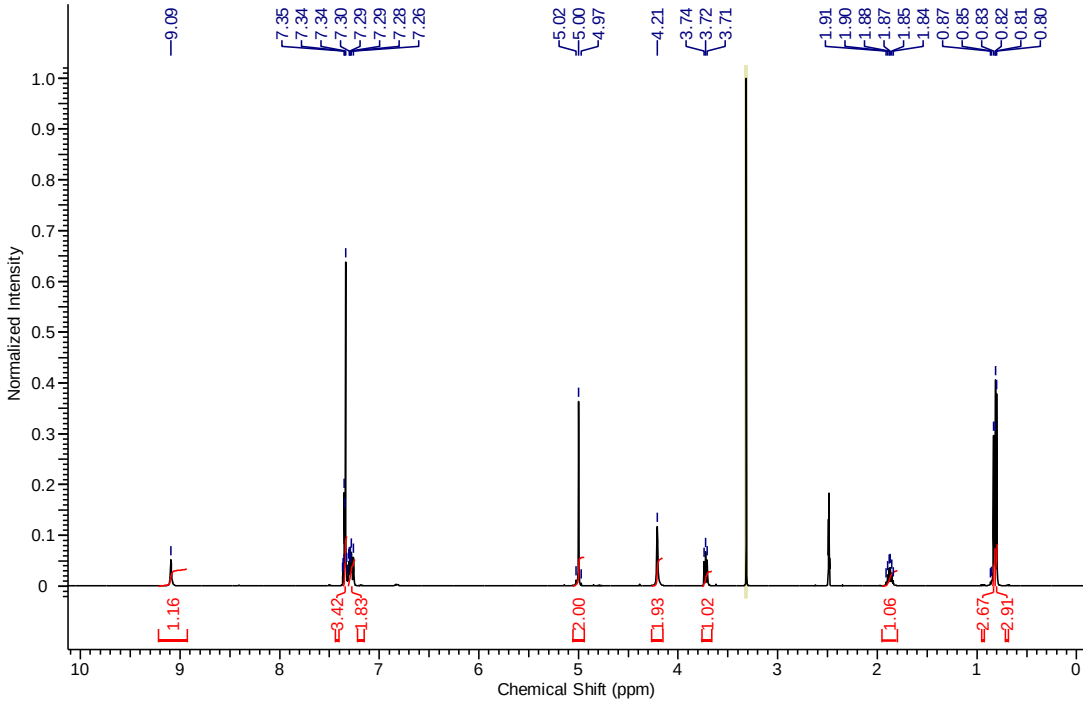


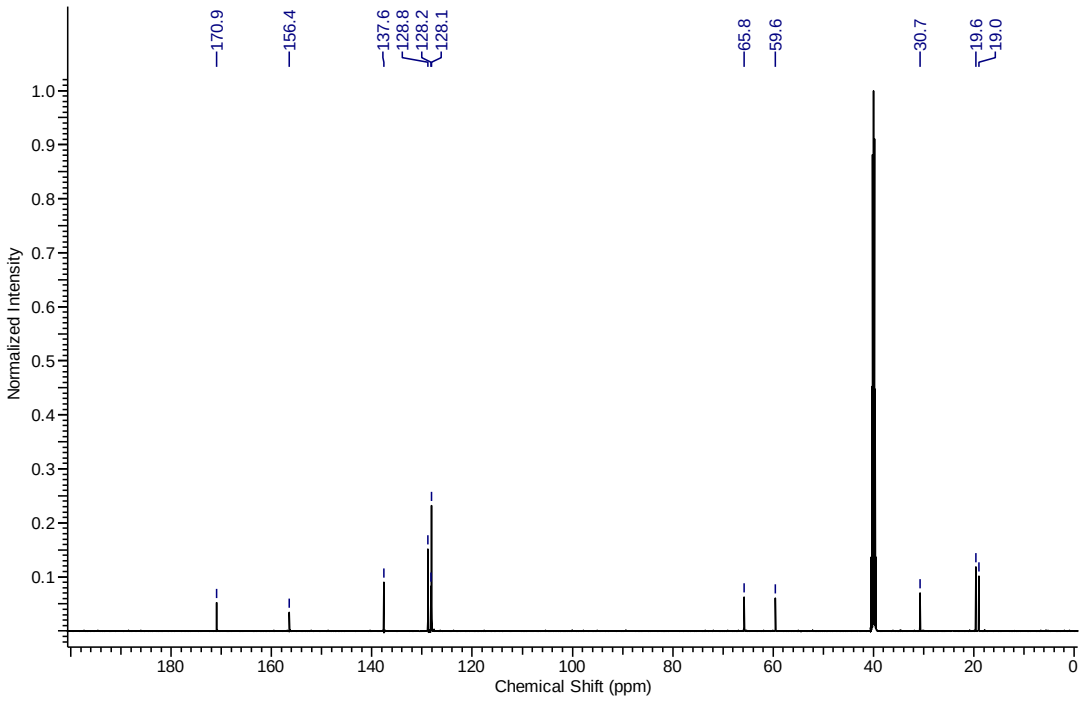




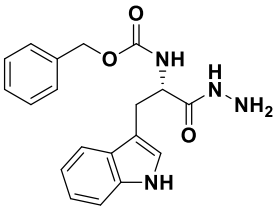
Benzyl (S)-(1-hydrazinyl-3-methyl-1-oxobutan-2-yl)carbamate (3d)

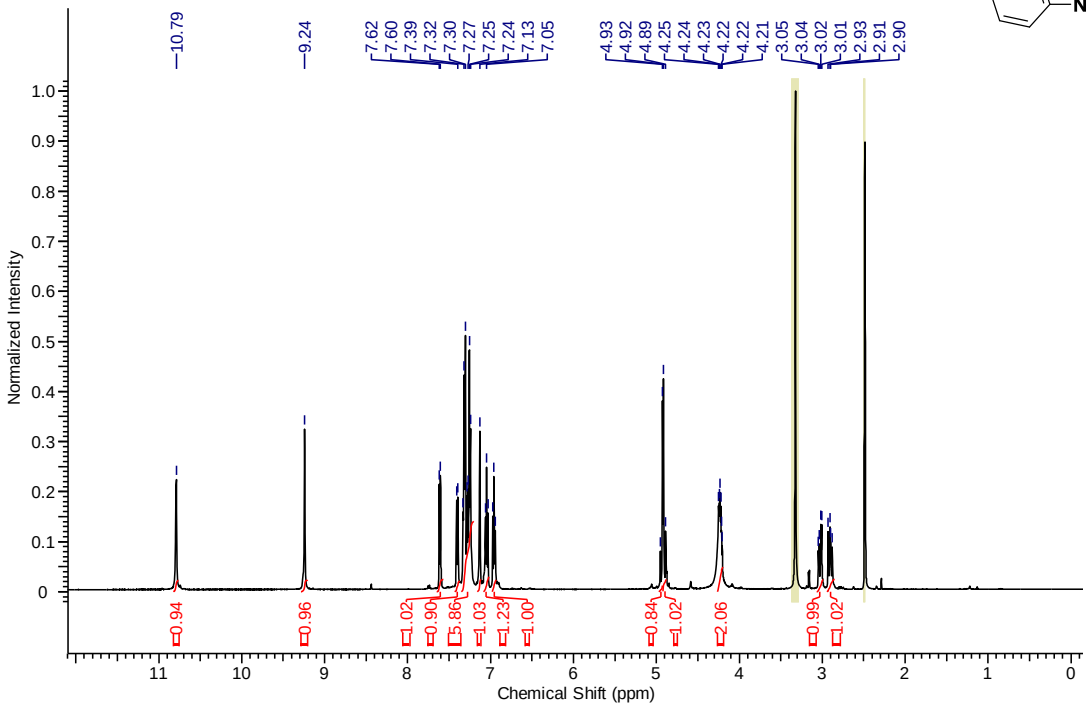


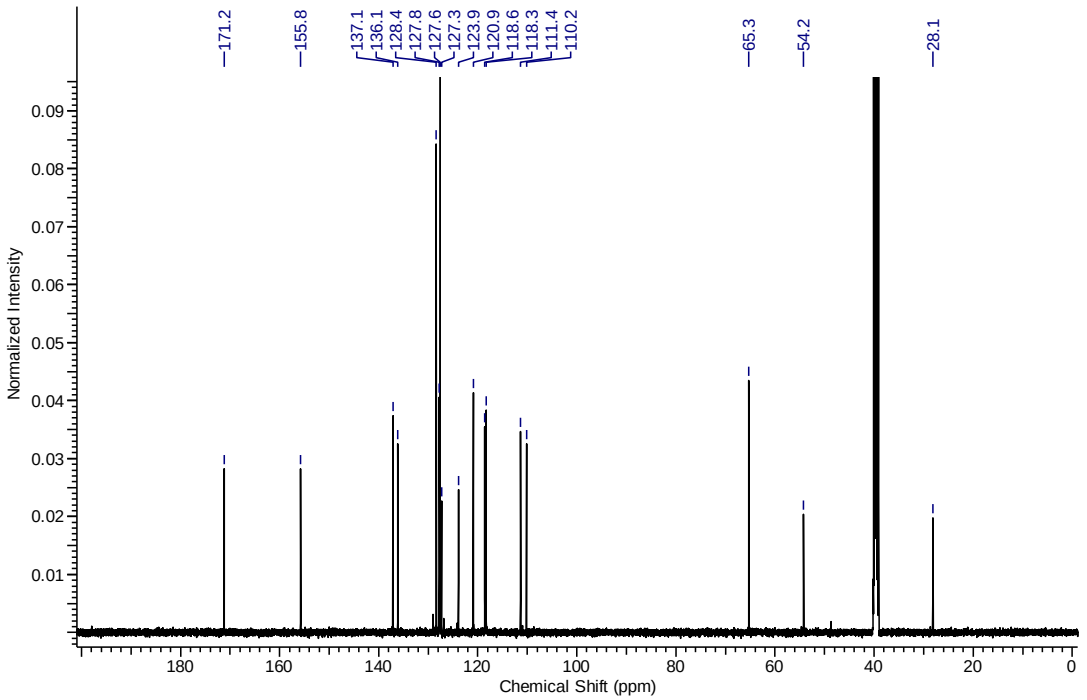




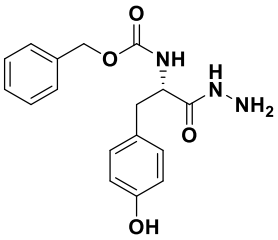
Benzyl (S)-(1-hydrazinyl-3-(1H-indol-3-yl)-1-oxopropan-2-yl)carbamate (3e)

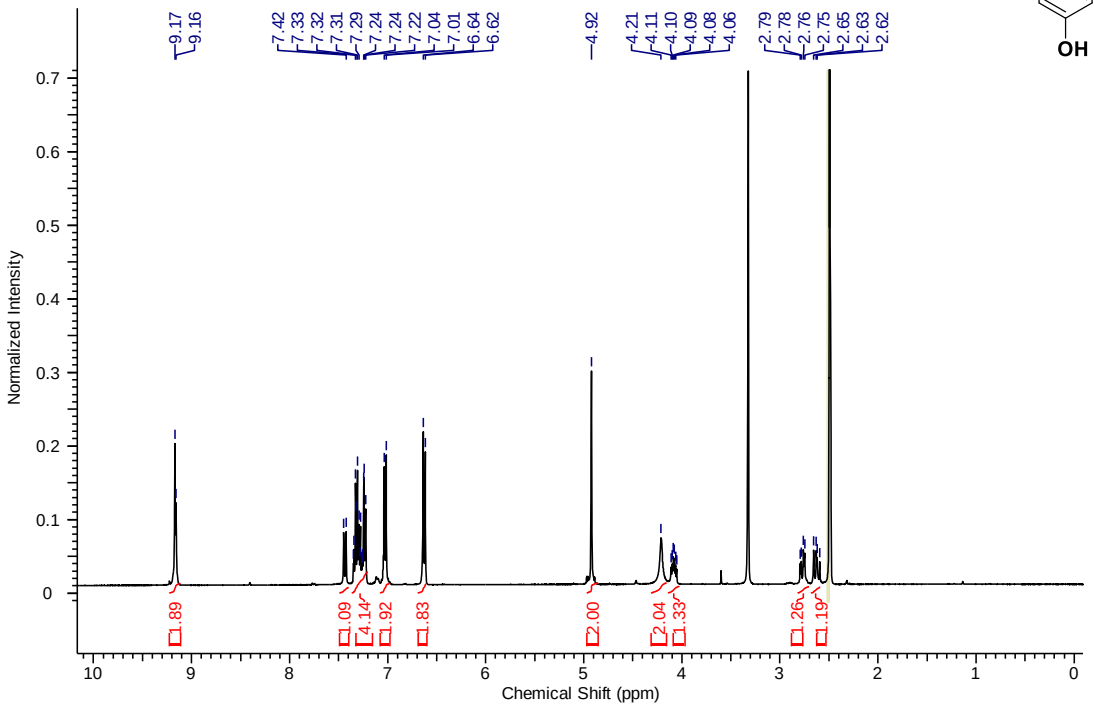


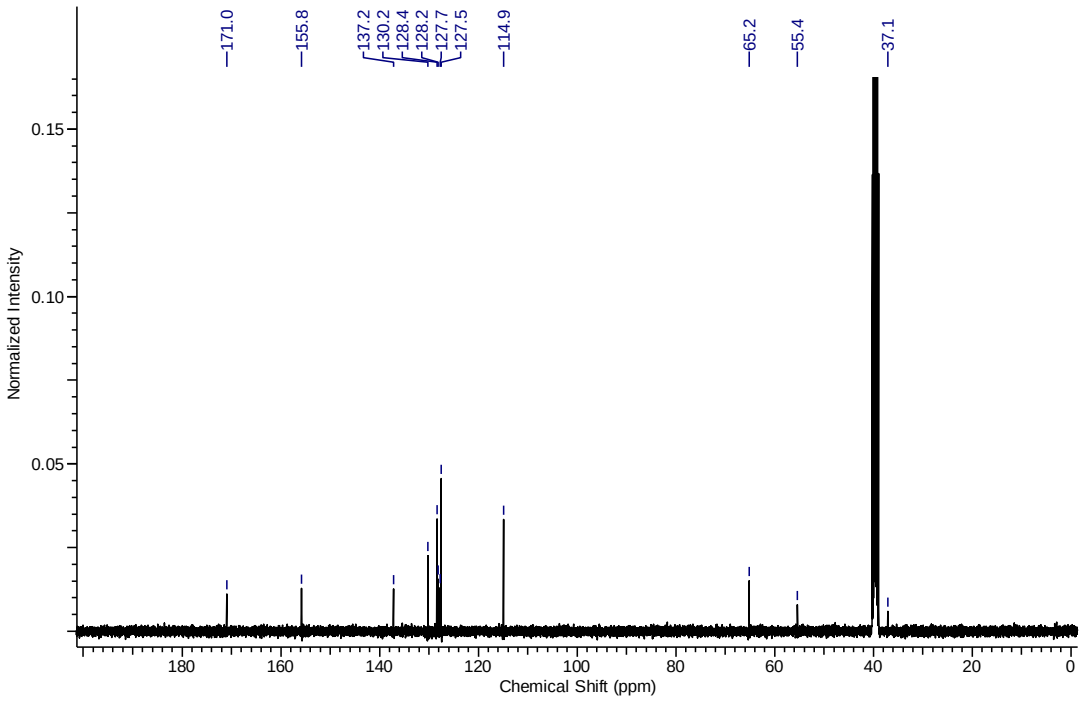




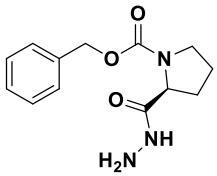
Benzyl (S)-(1-hydrazinyl-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)carbamate (3f)

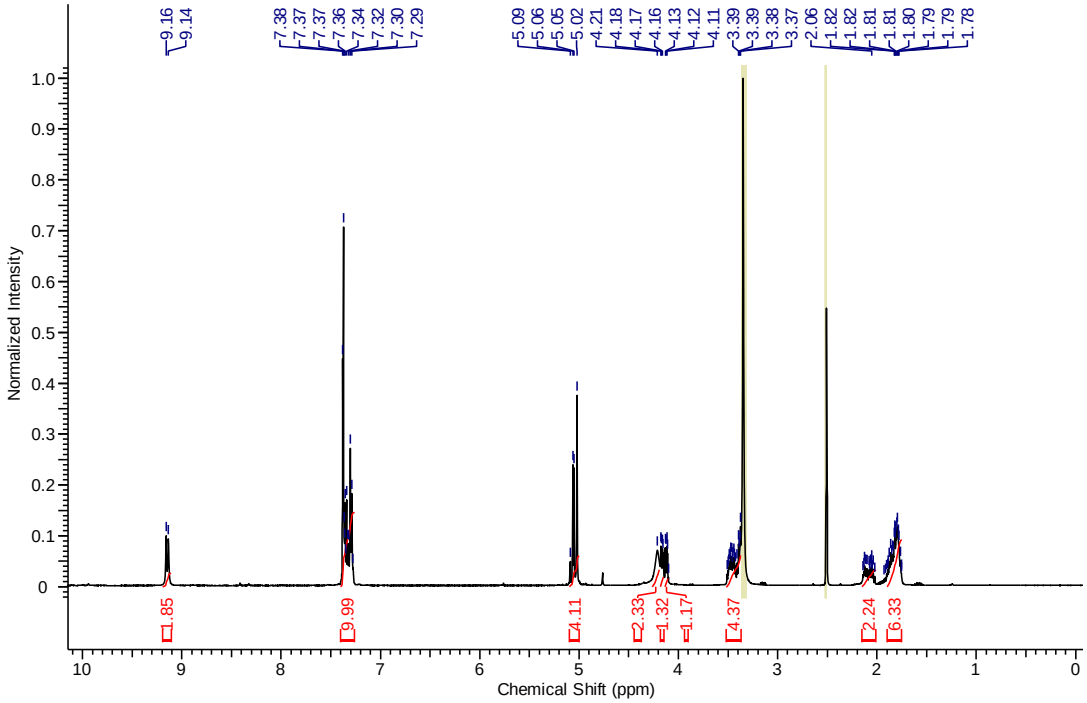


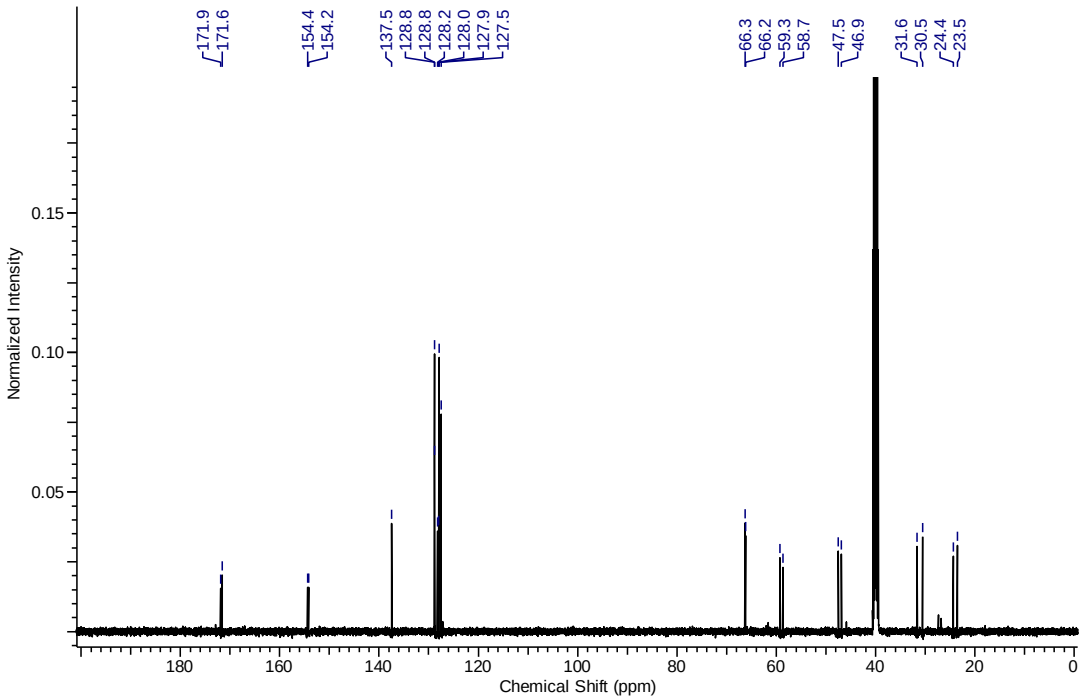




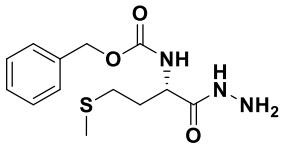
Benzyl (S)-2-(hydrazinecarbonyl)pyrrolidine-1-carboxylate (3g)

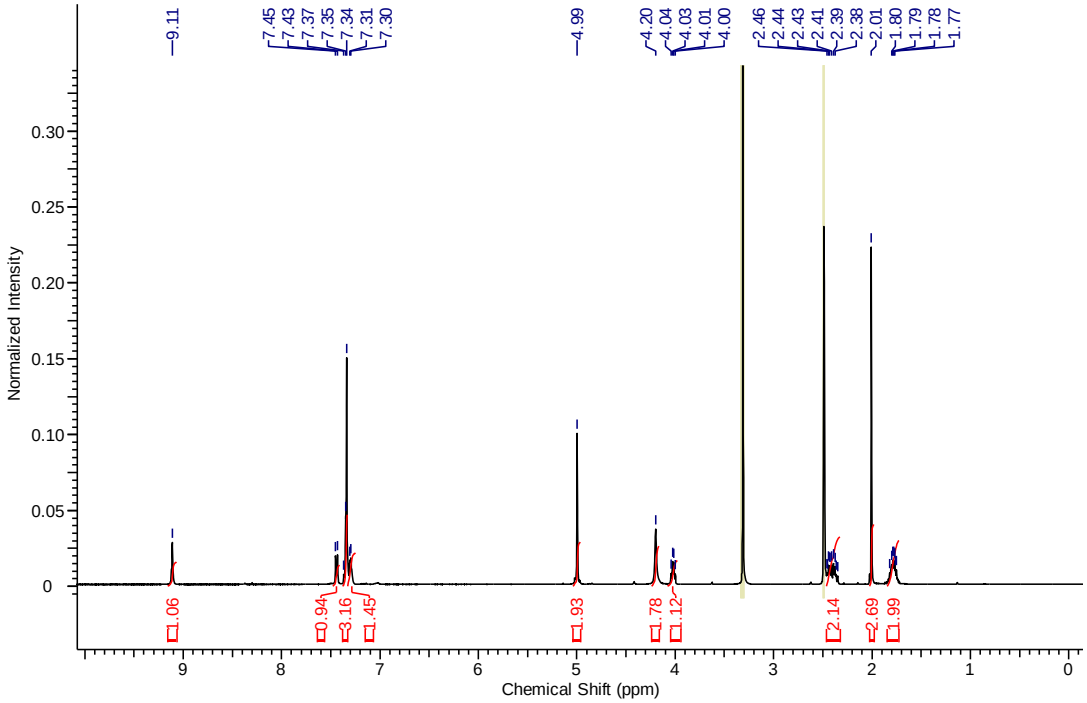


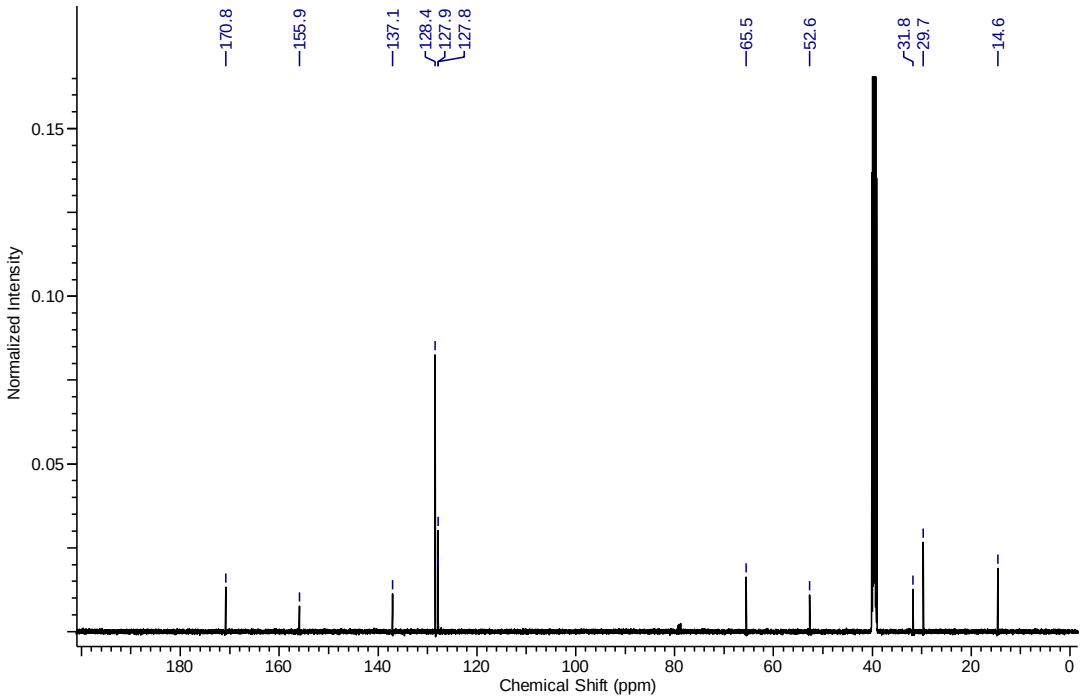




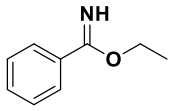
Benzyl (S)-(1-hydrazinyl-4-(methylthio)-1-oxobutan-2-yl)carbamate (3h)

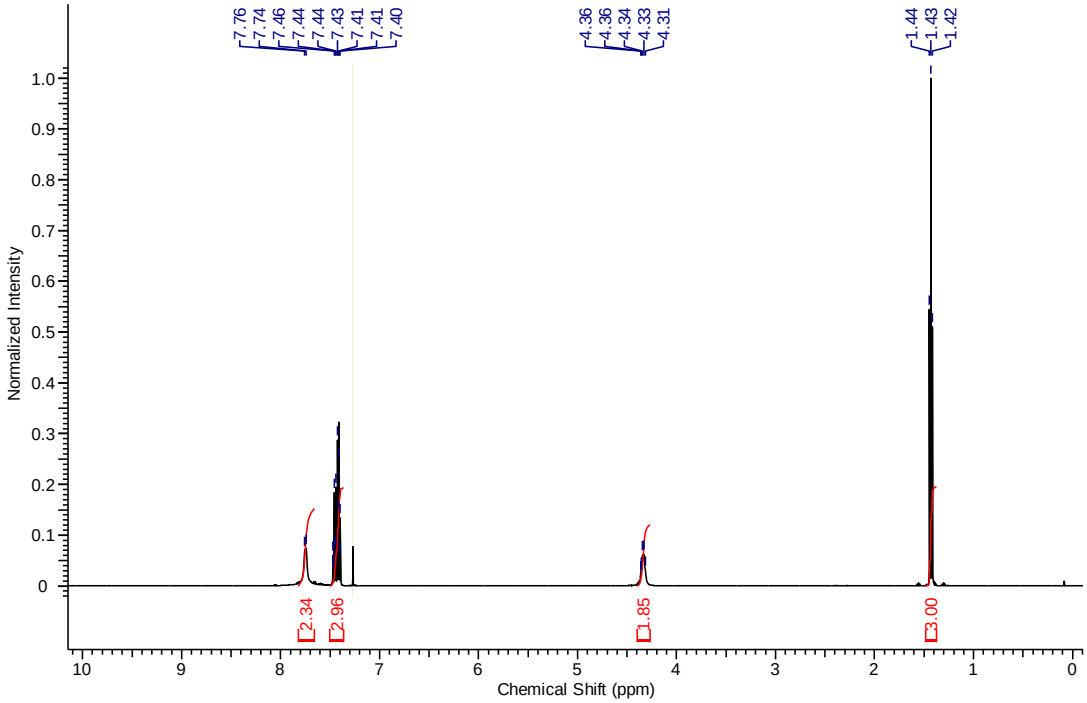


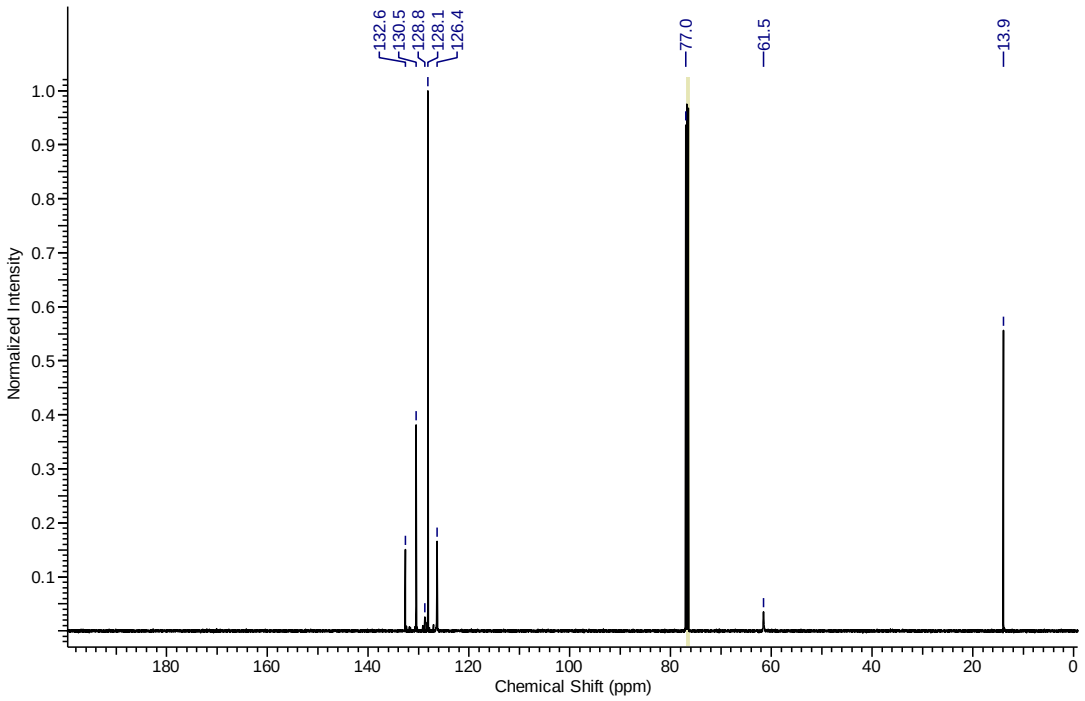




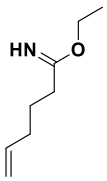
Ethyl benzimidate (5a)

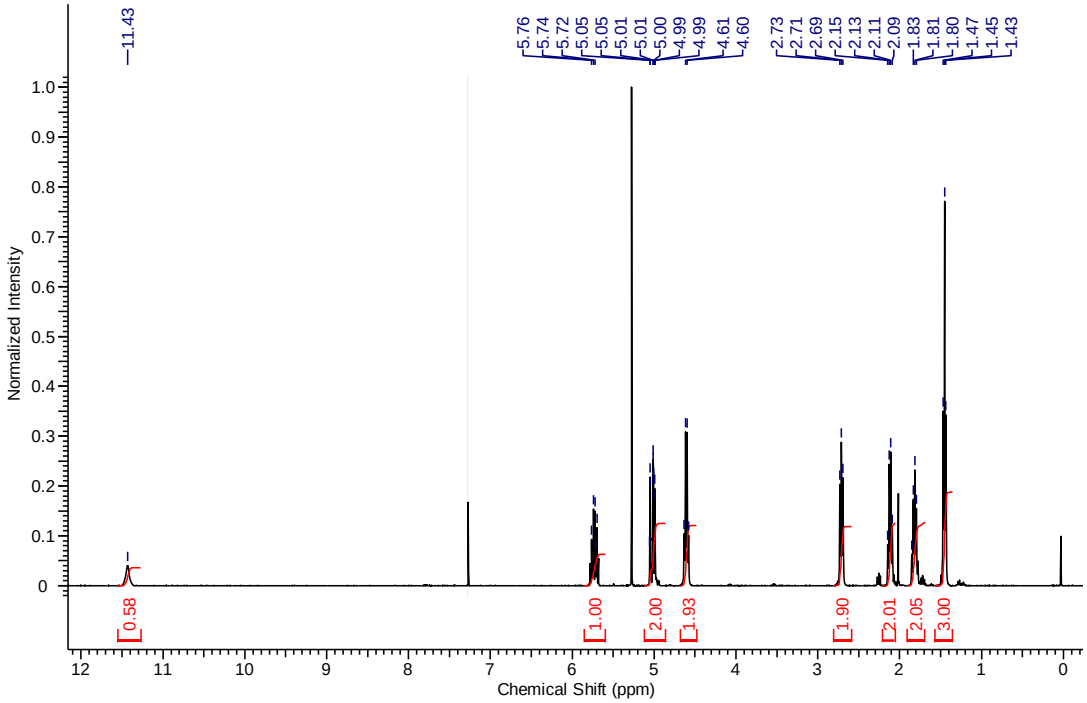


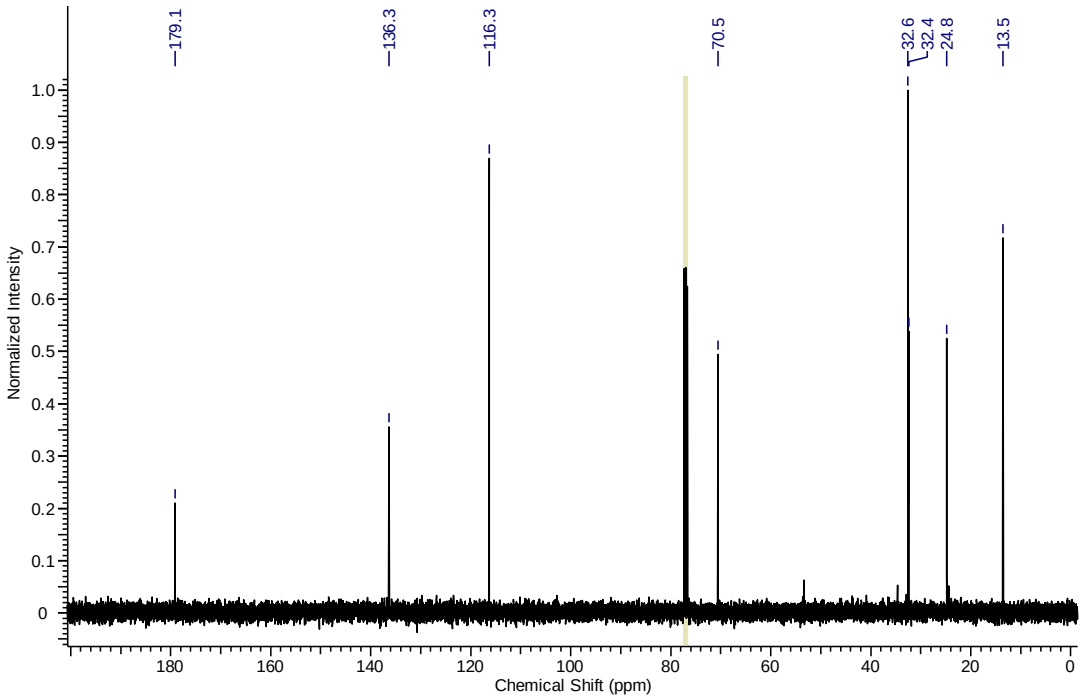




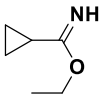
Ethyl hex-5-enimidate (5b)

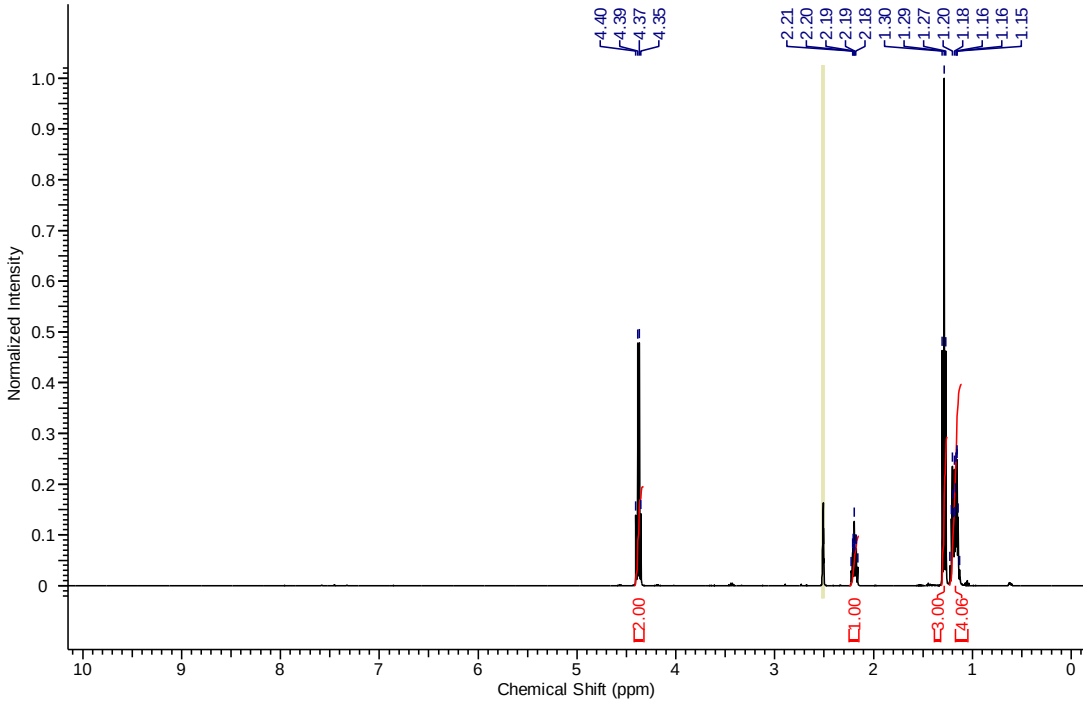


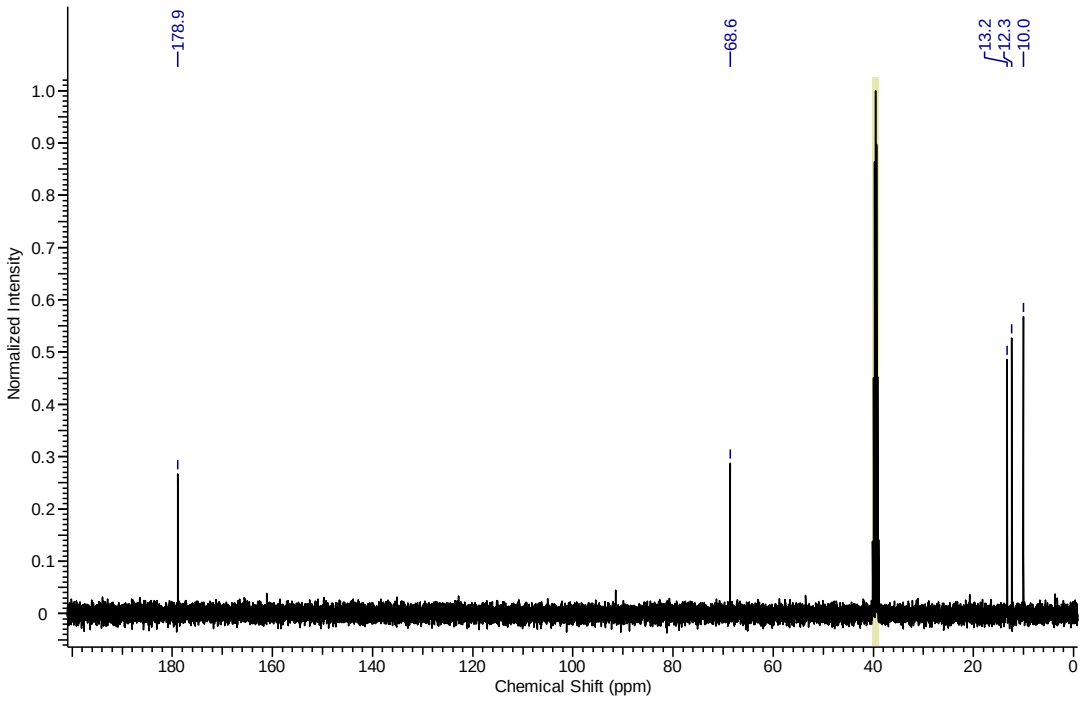




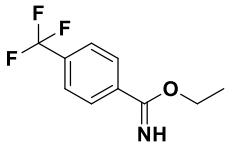
Cyclopropane carbimidate (5c)

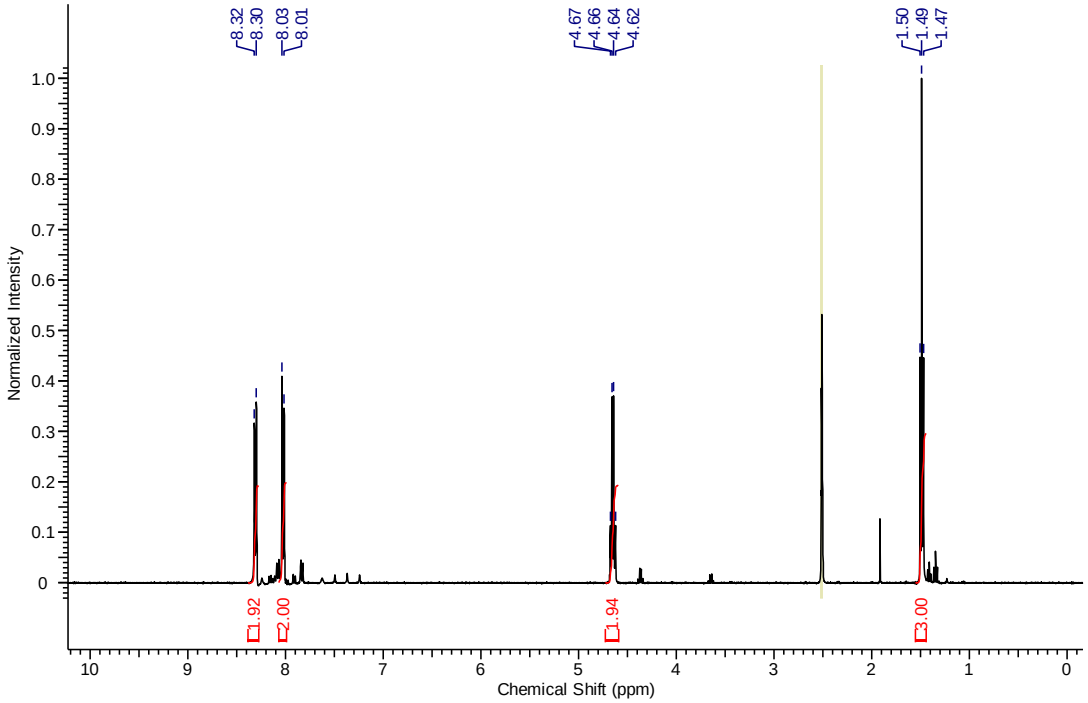


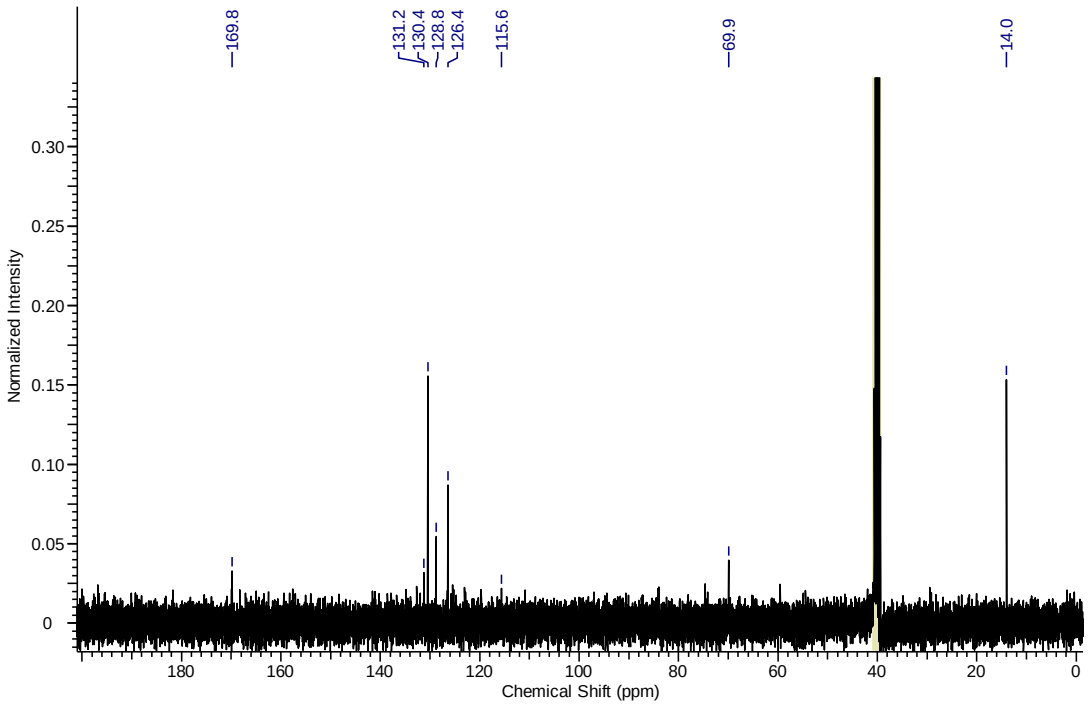




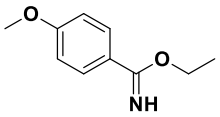
Ethyl 4-(trifluoromethyl)benzimidate (5d)

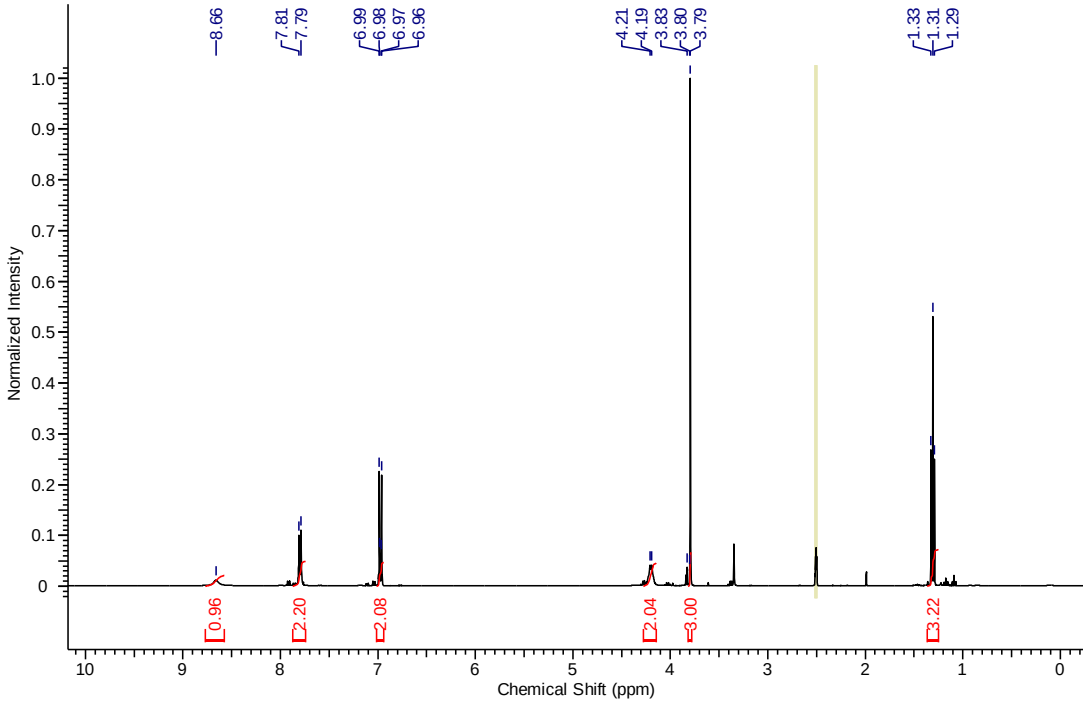


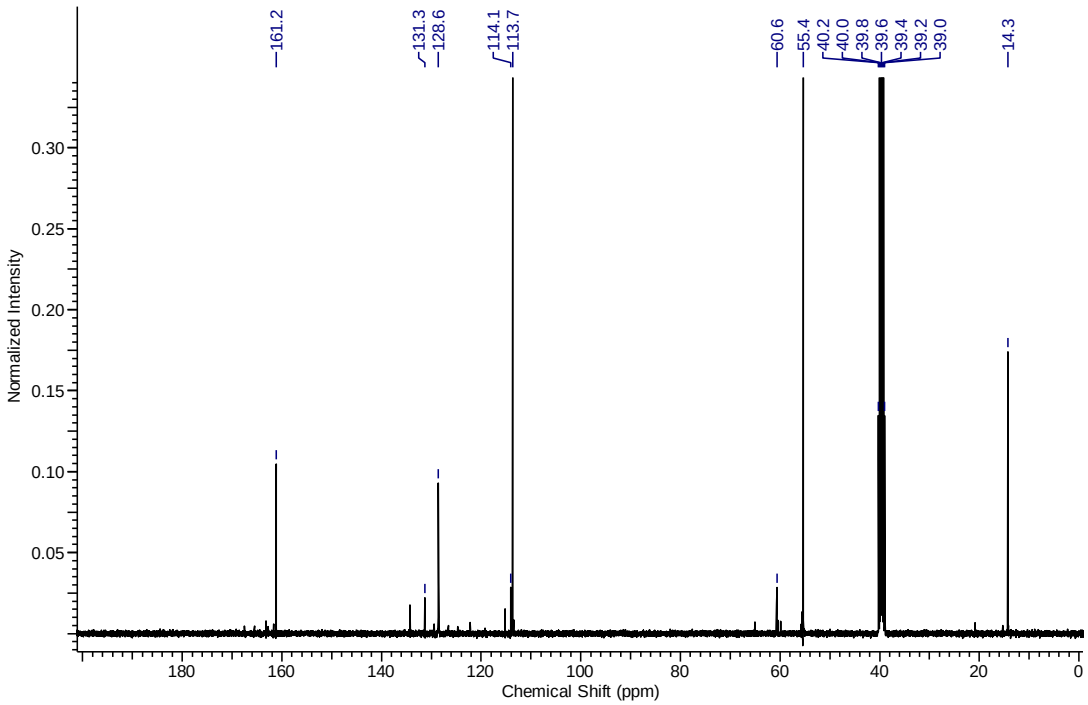




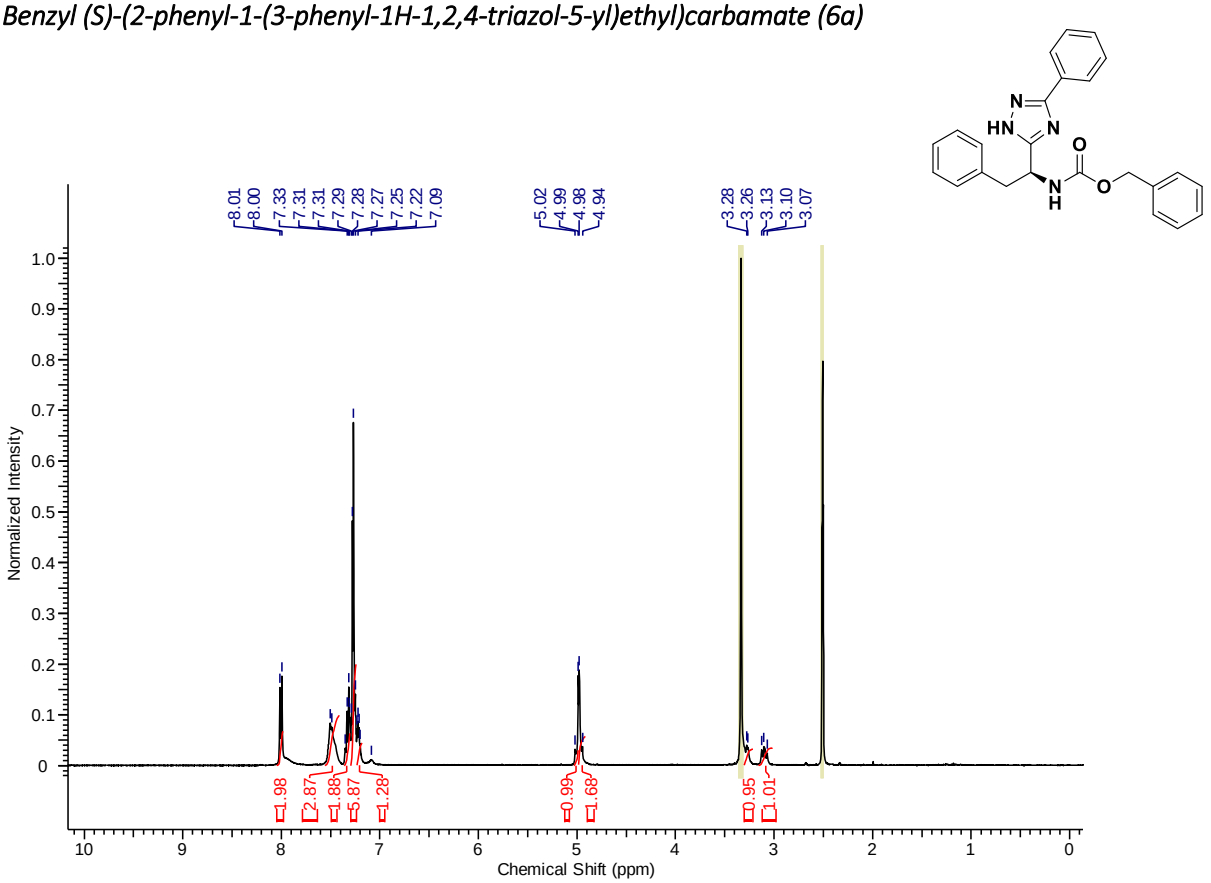
Ethyl 4-methoxybenzimidate (5e)

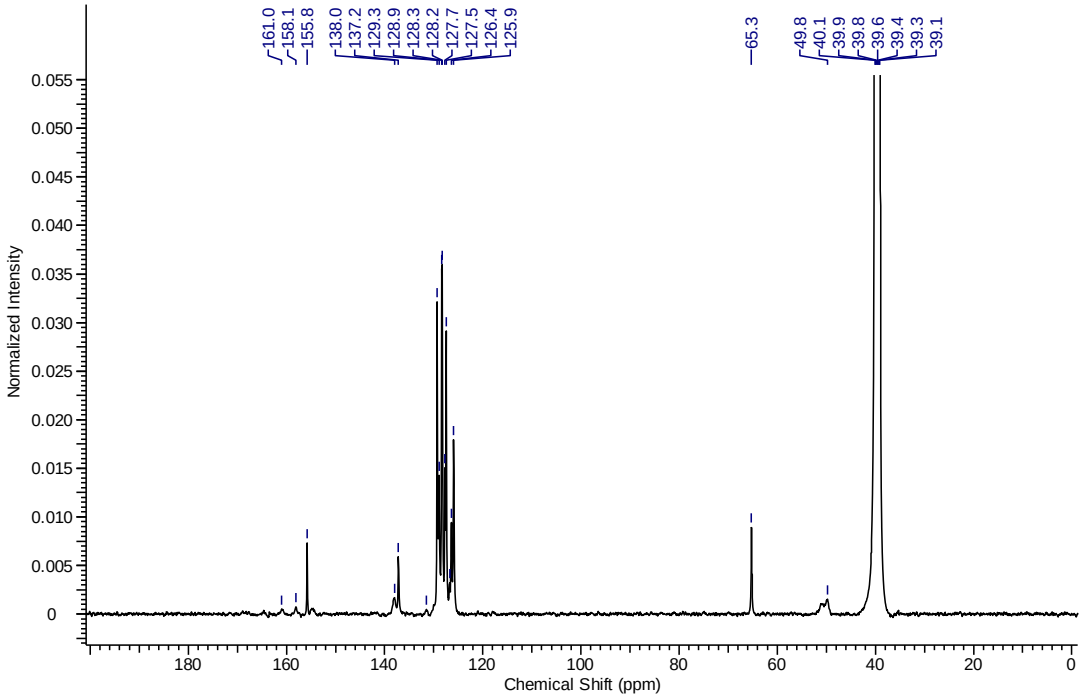




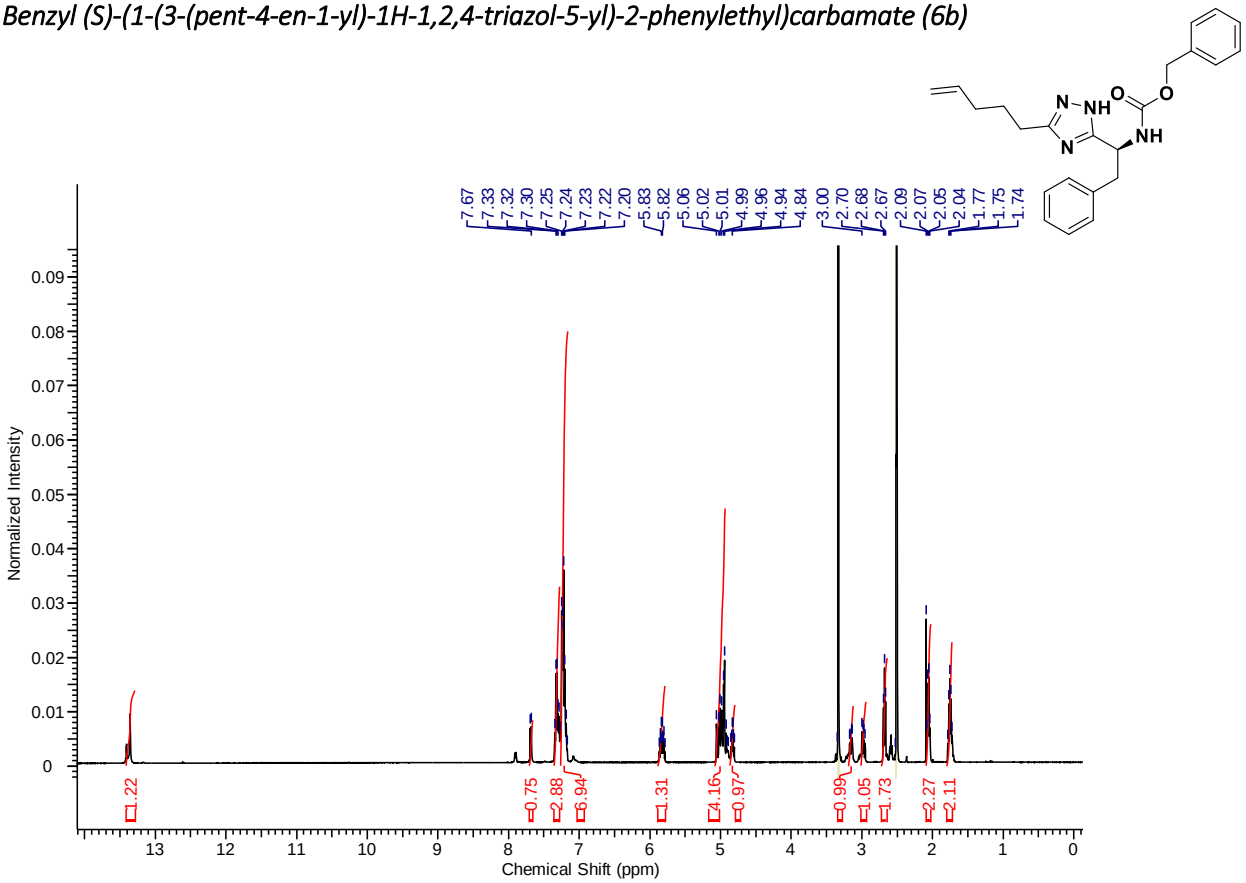


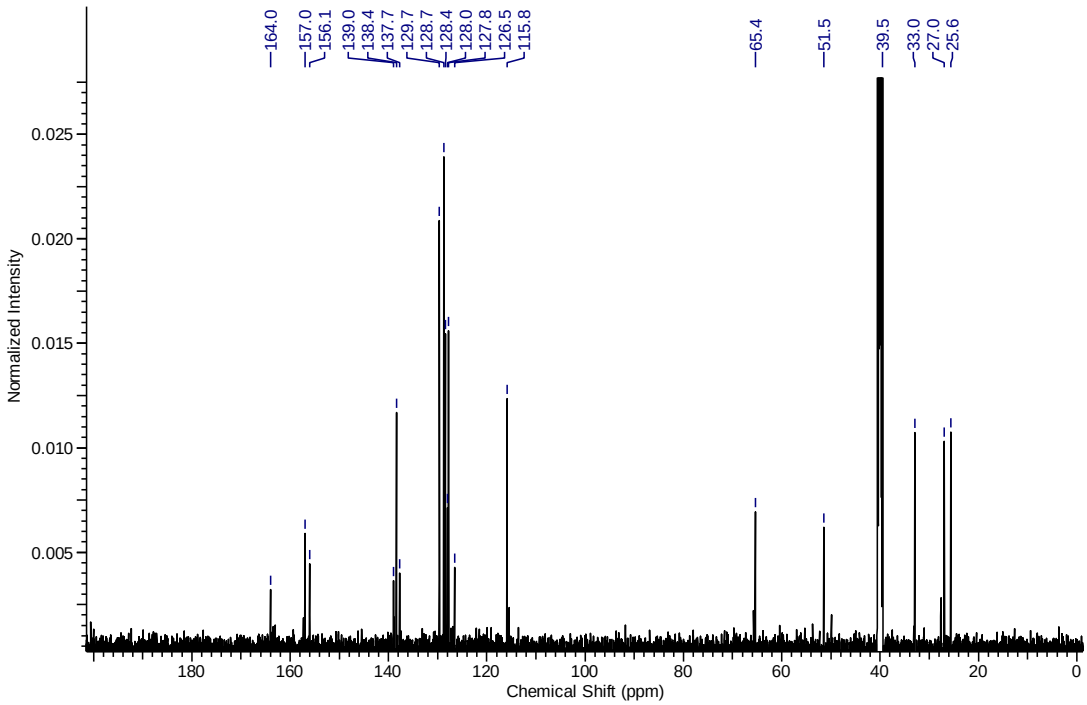
Benzyl (S)-(2-phenyl-1-(3-phenyl-1H-1,2,4-triazol-5-yl)ethyl)carbamate (6a)



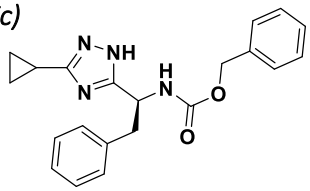


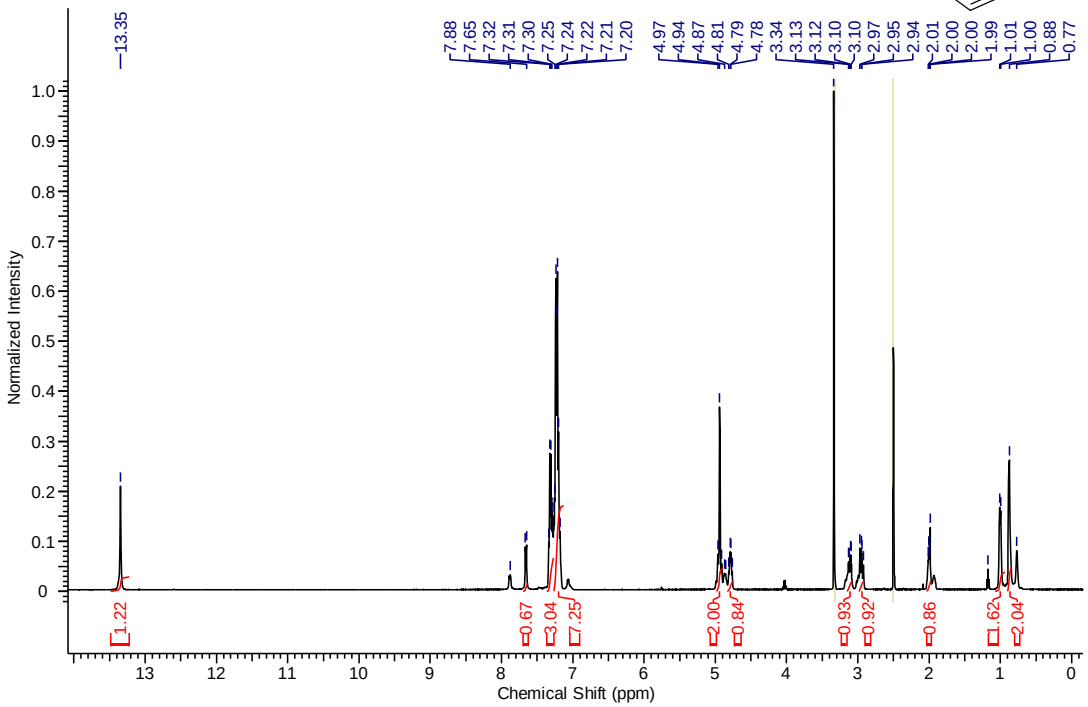
Benzyl (S)-(1-(3-(pent-4-en-1-yl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (6b)

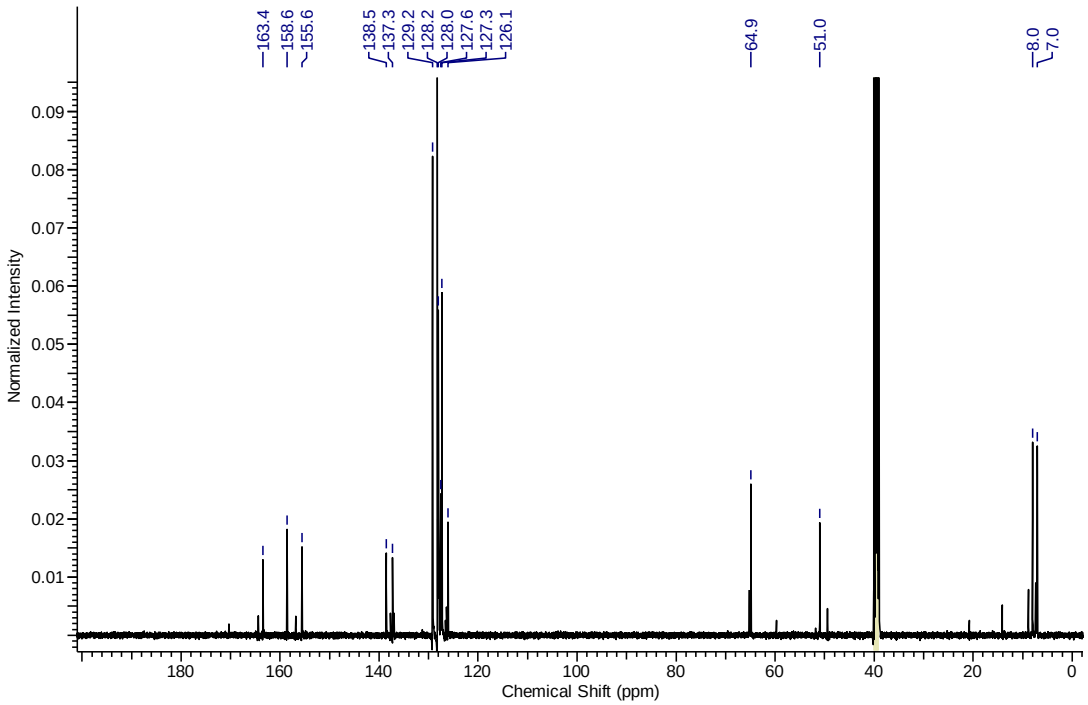




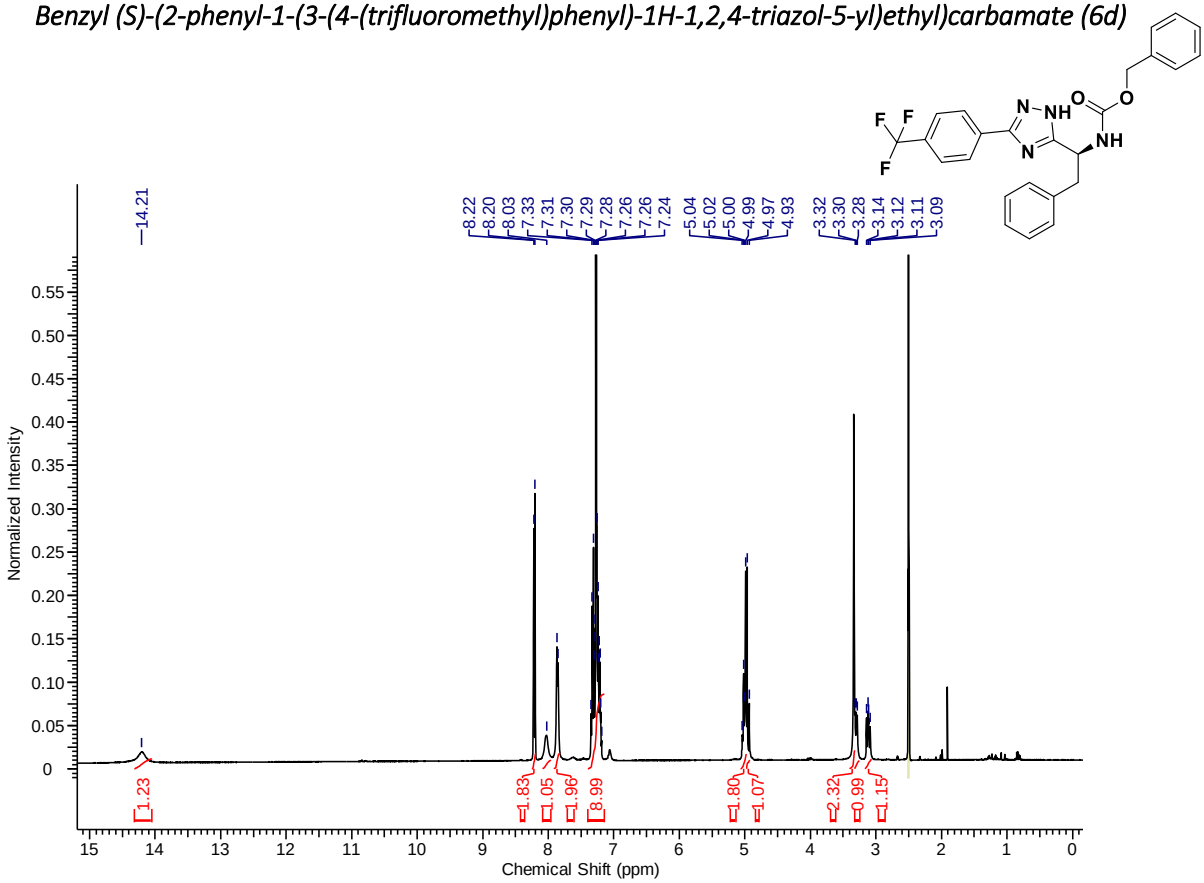
Benzyl (S)-(1-(3-cyclopropyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (6c)

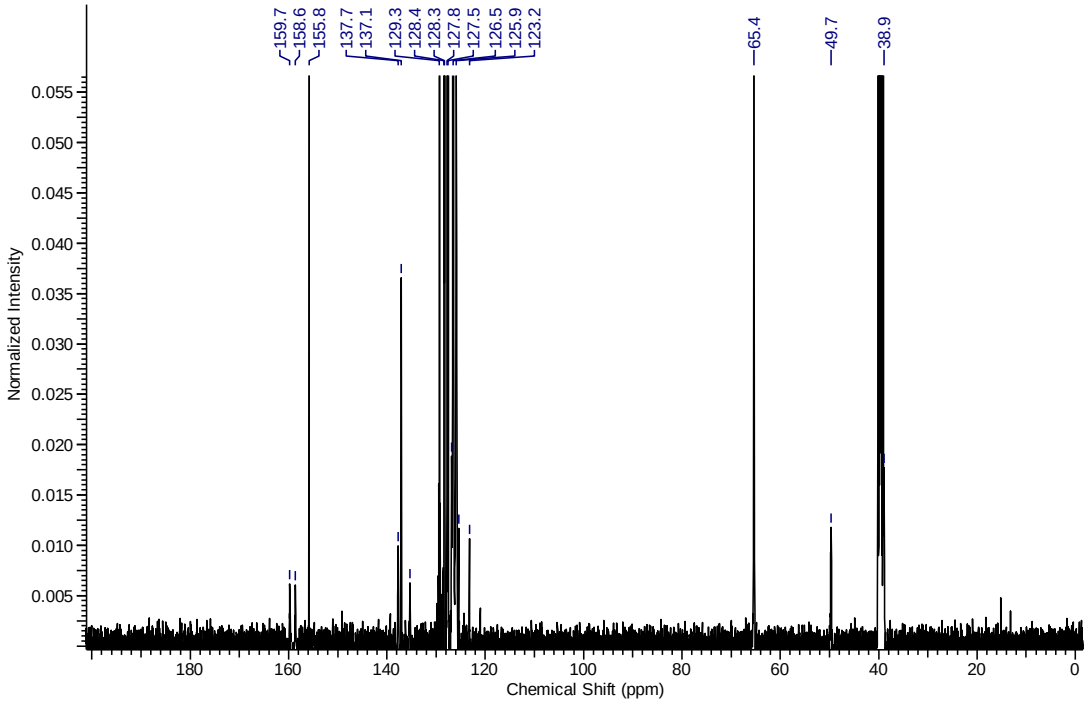




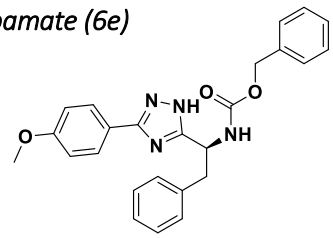


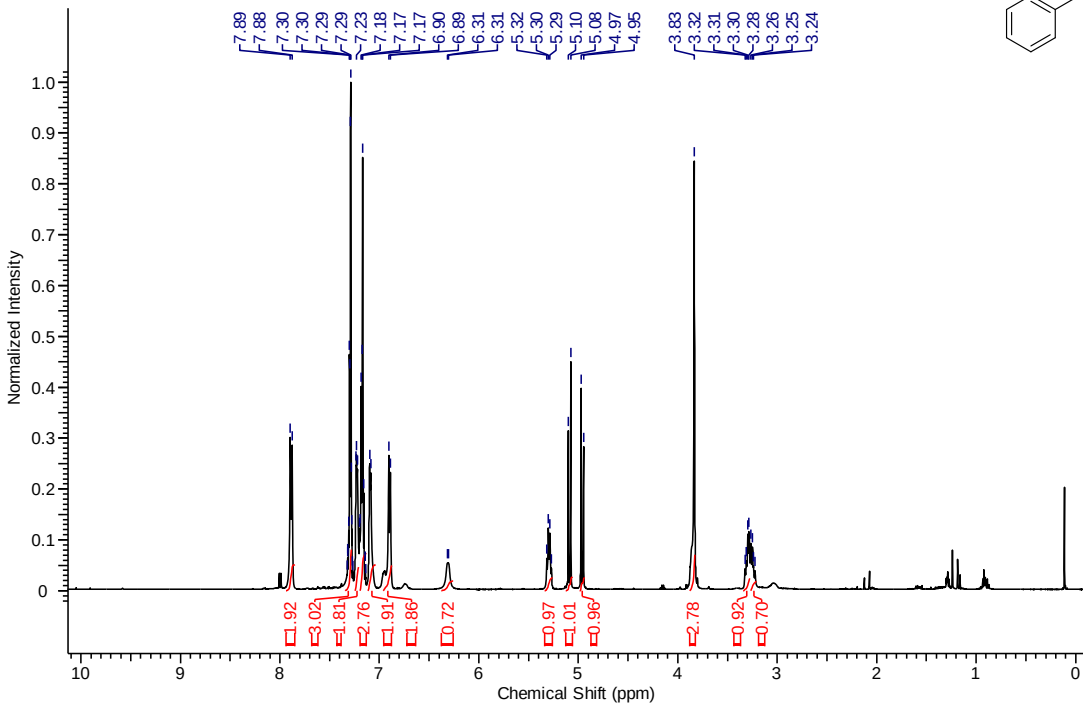
Benzyl (S)-(2-phenyl-1-(3-(4-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-5-yl)ethyl)carbamate (6d)

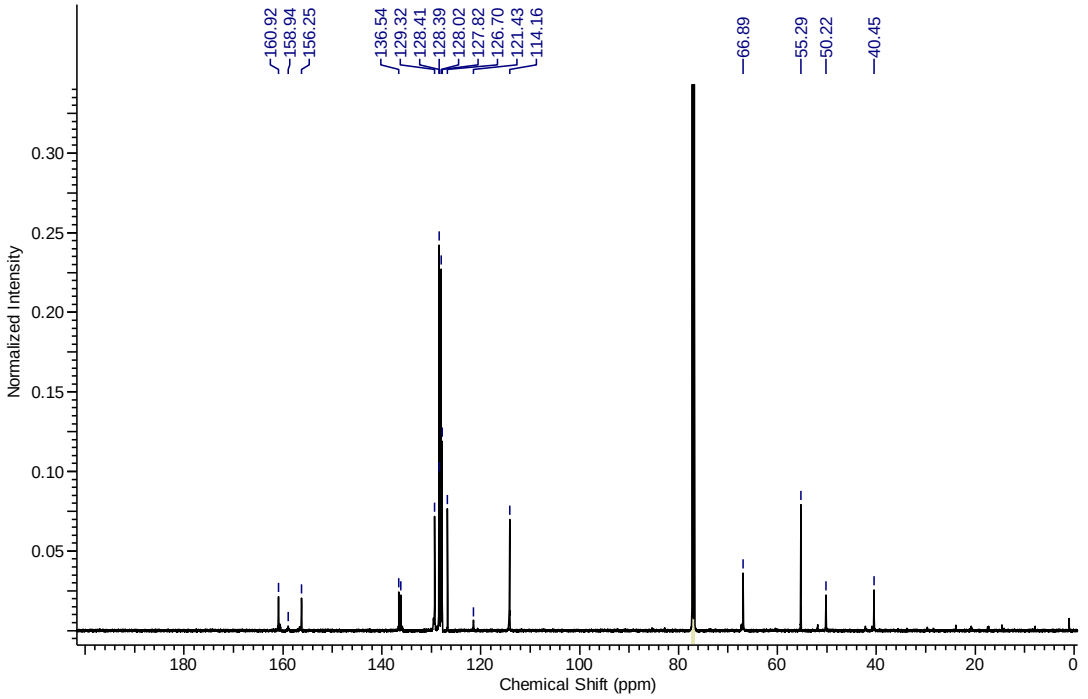




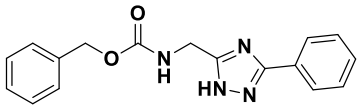
Benzyl (S)-(1-(3-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (6e)

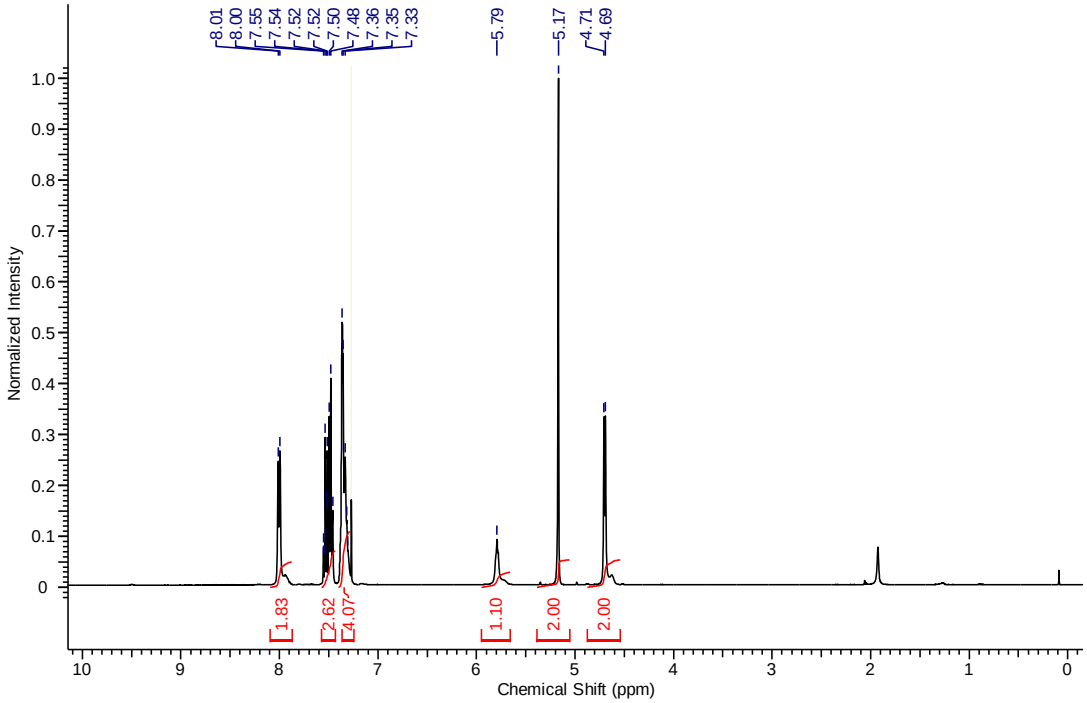


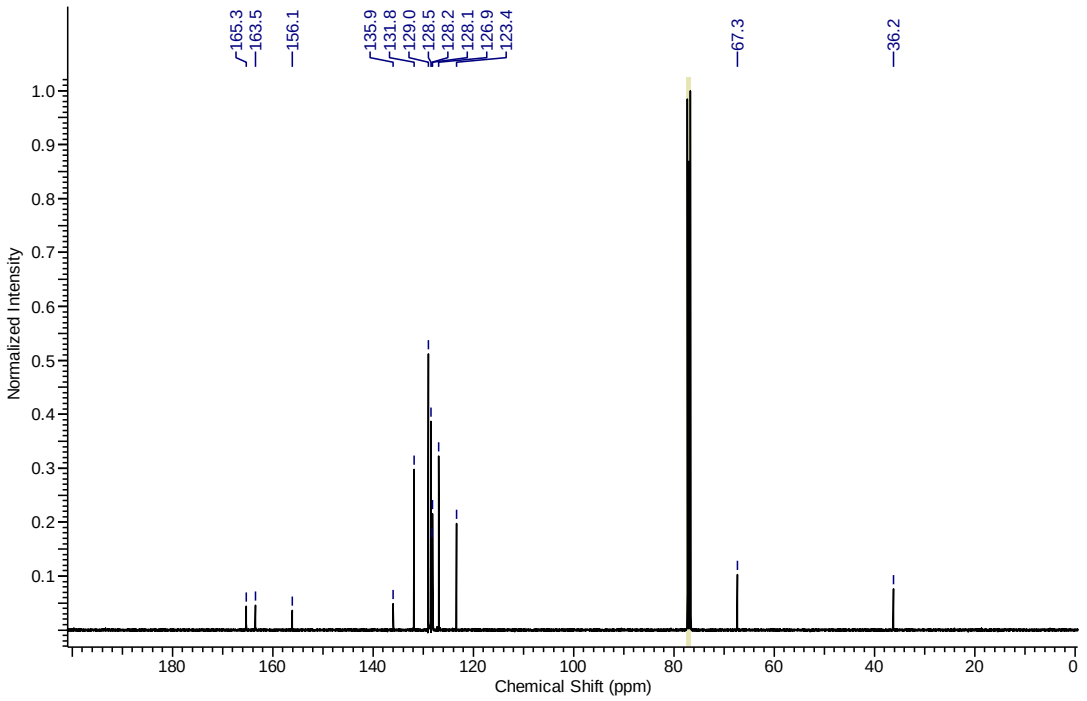




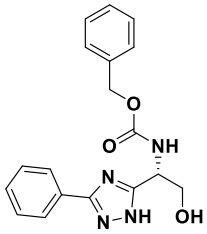
Benzyl ((3-phenyl-1H-1,2,4-triazol-5-yl)methyl)carbamate (6f)

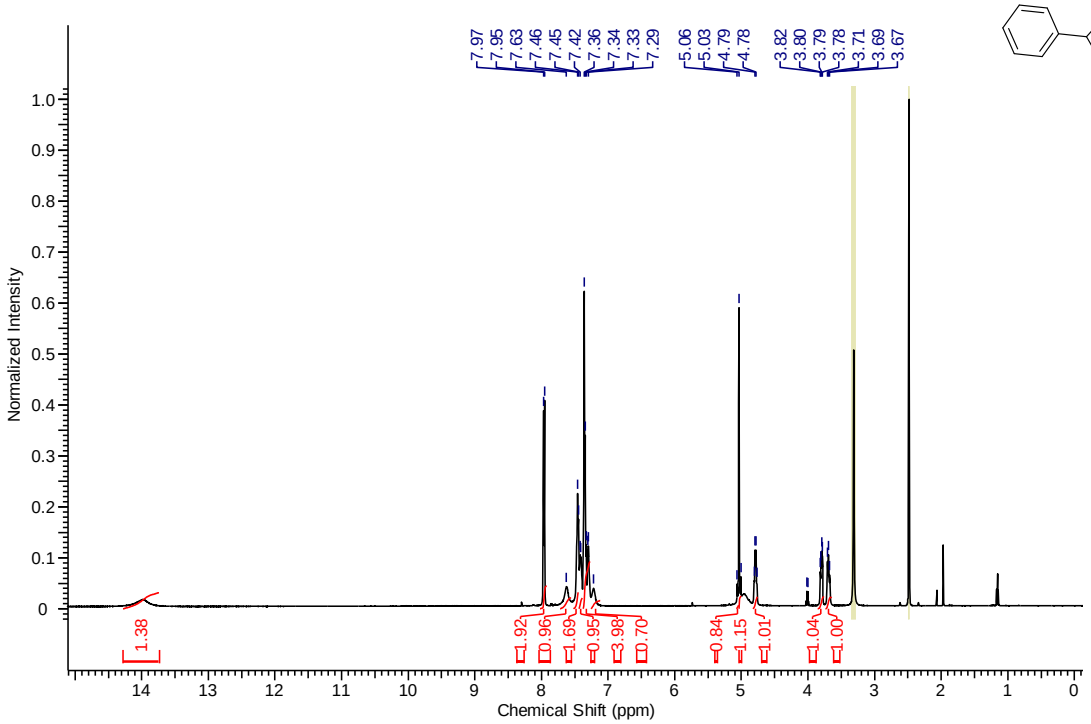


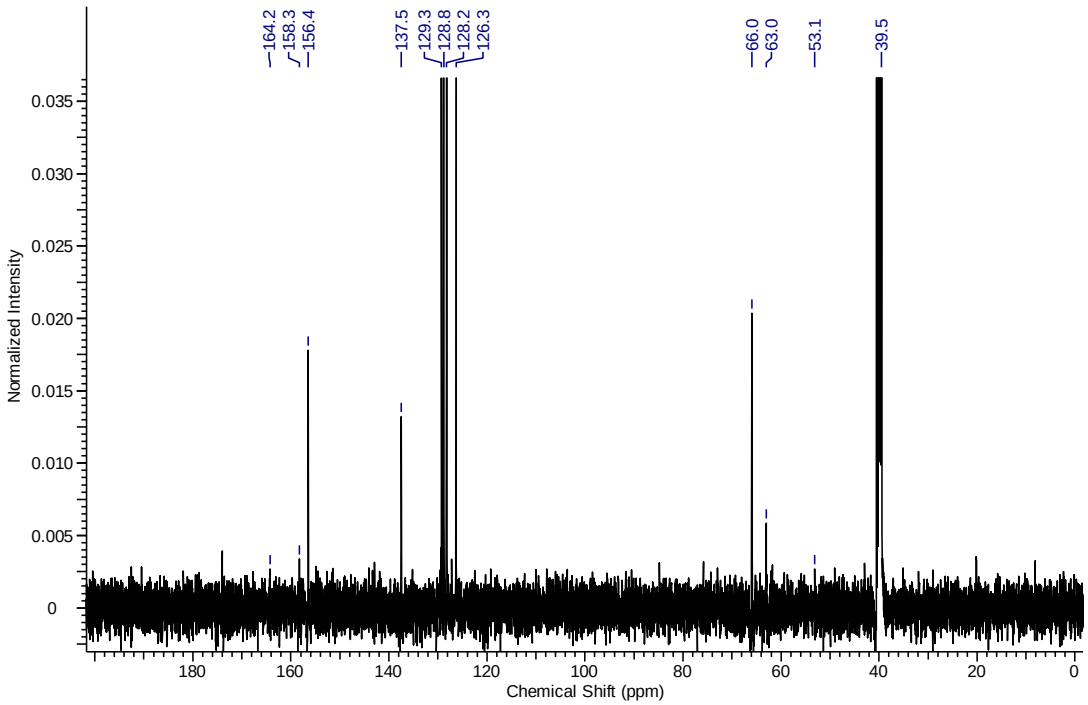




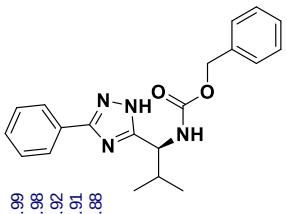
Benzyl (S)-(2-hydroxy-1-(3-phenyl-1H-1,2,4-triazol-5-yl)ethyl)carbamate (6g)

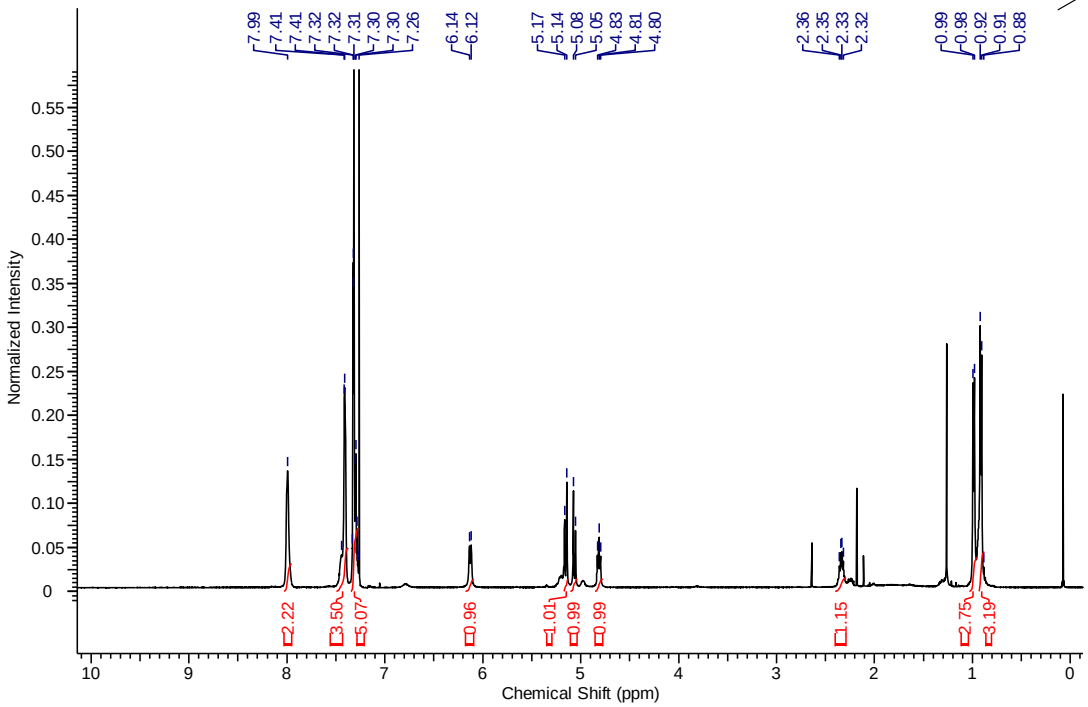


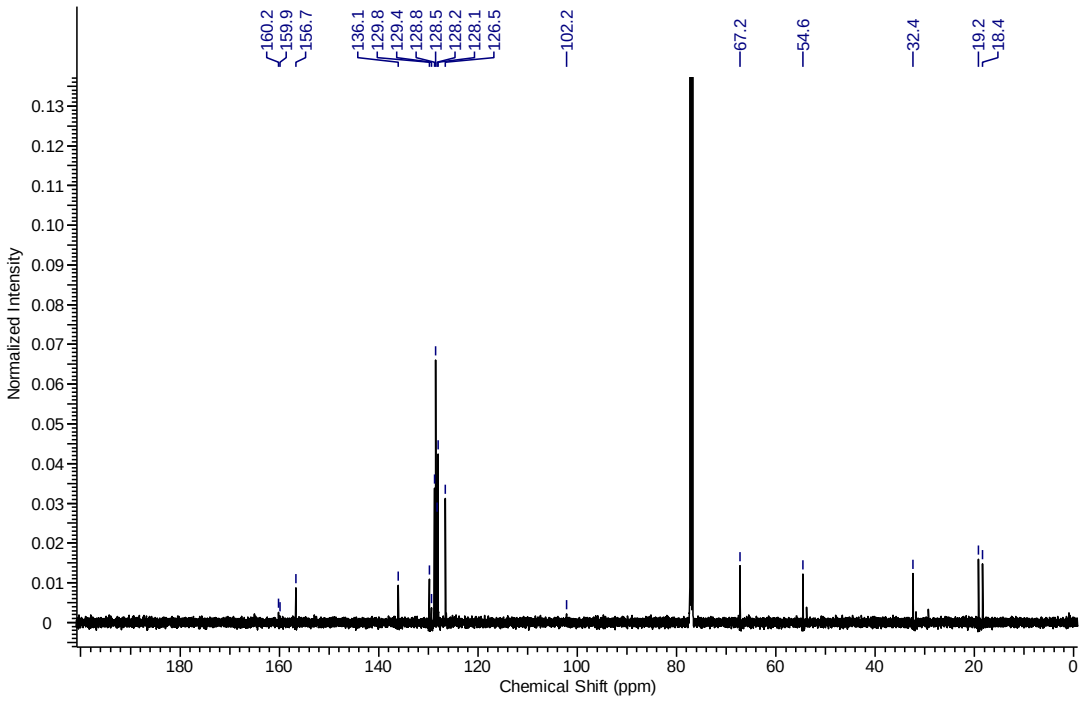




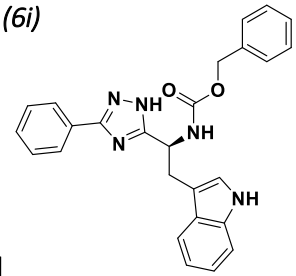
Benzyl (S)-(2-methyl-1-(3-phenyl-1H-1,2,4-triazol-5-yl)propyl)carbamate (6h)

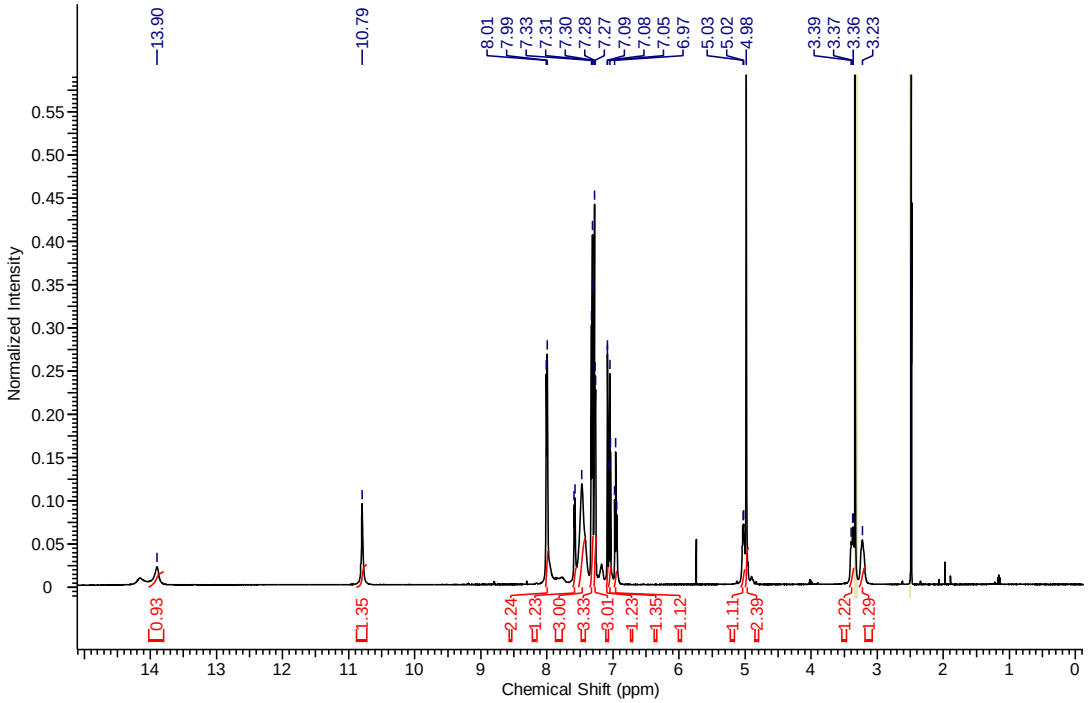


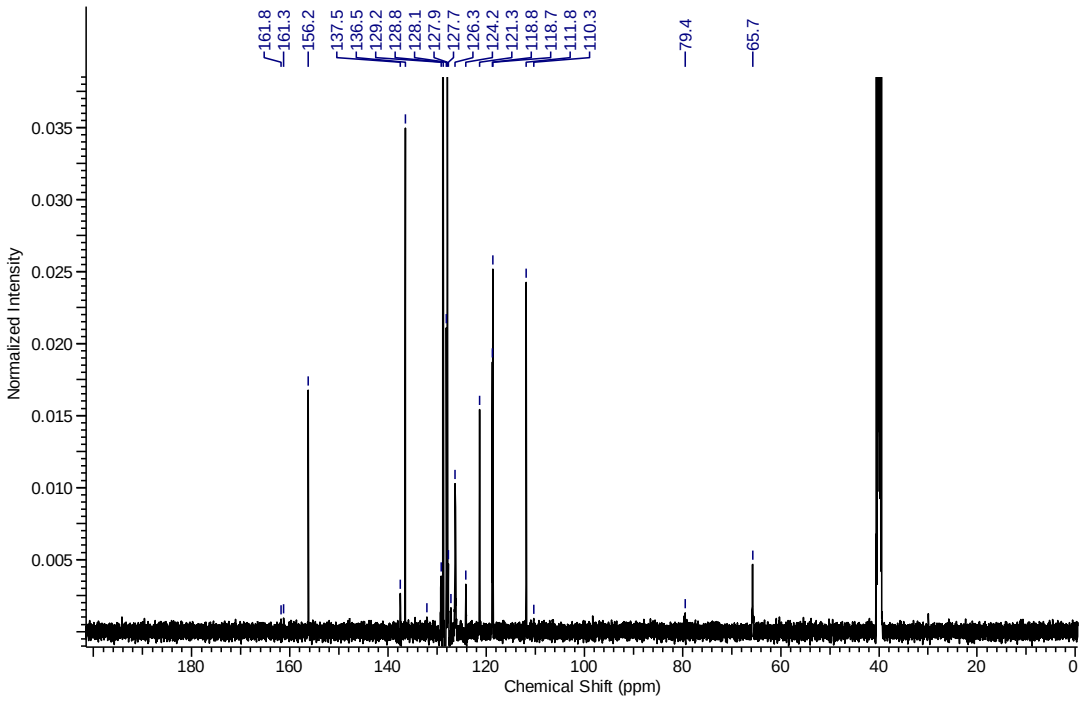




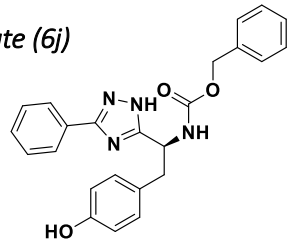
Benzyl (S)-(2-(1H-indol-3-yl)-1-(3-phenyl-1H-1,2,4-triazol-5-yl)ethyl)carbamate (6i)

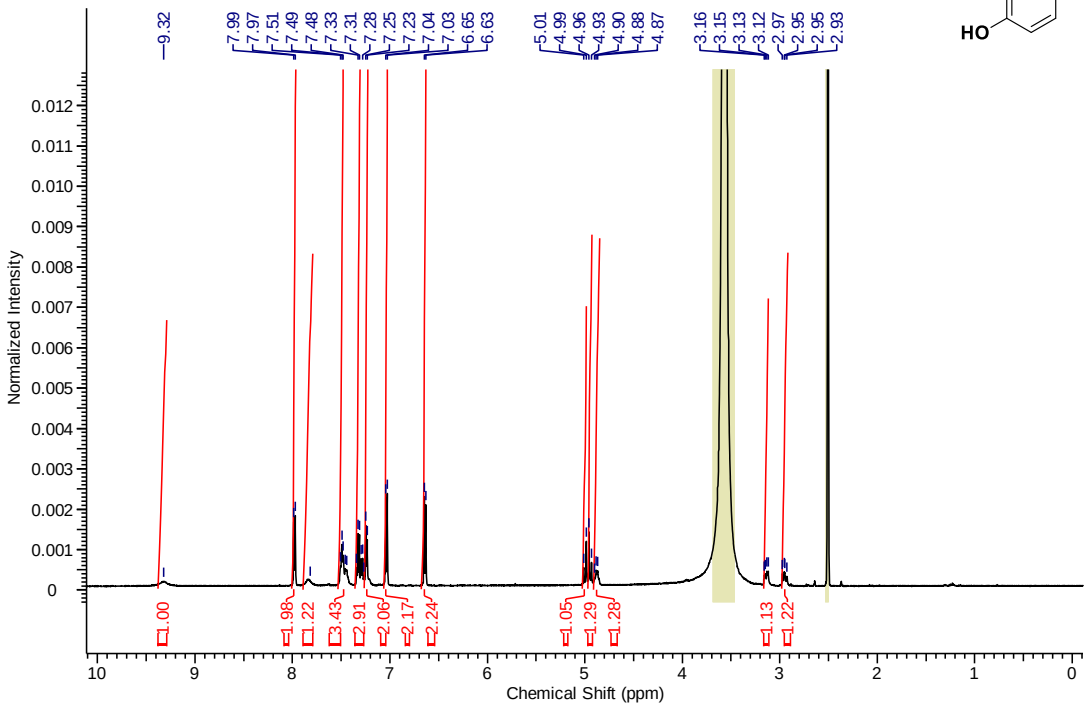


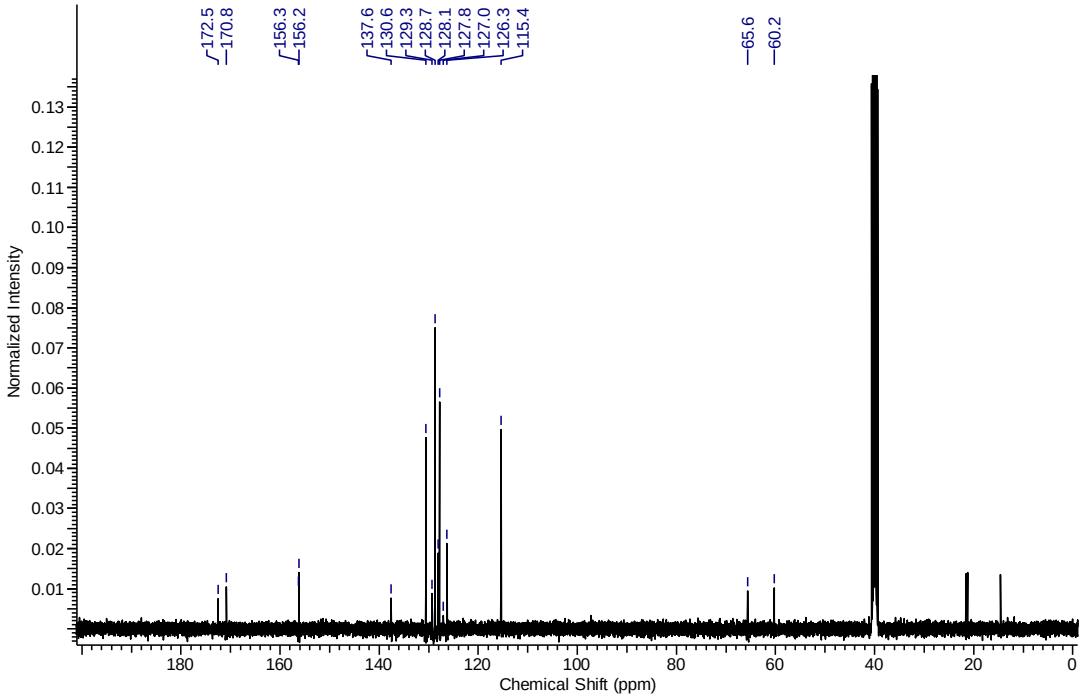




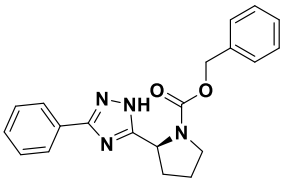
Benzyl (S)-(2-(4-hydroxyphenyl)-1-(3-phenyl-1H-1,2,4-triazol-5-yl)ethyl)carbamate (6j)

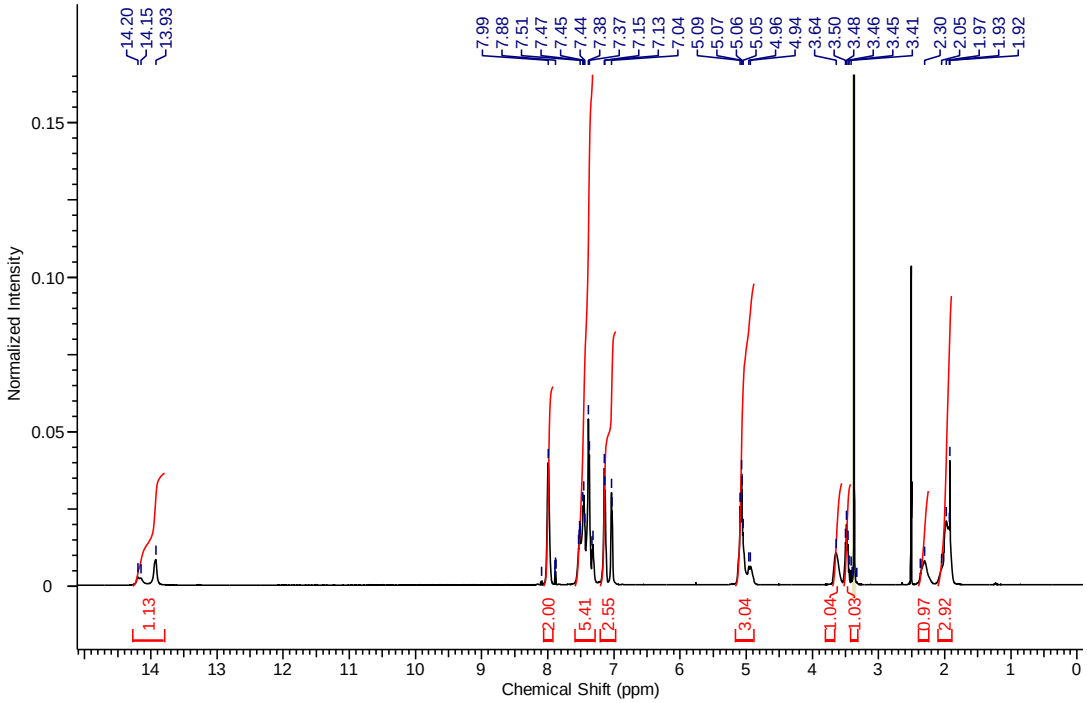


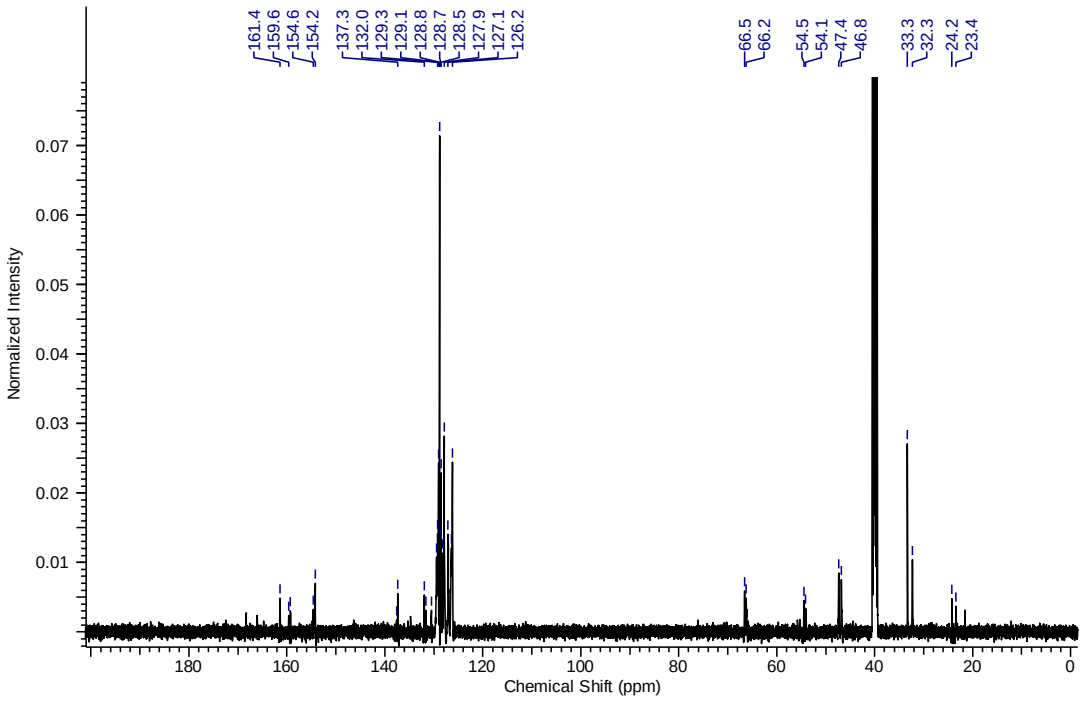




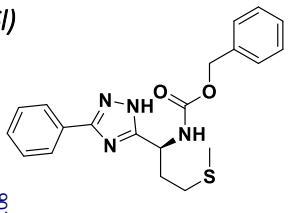
Benzyl (S)-2-(3-phenyl-1H-1,2,4-triazol-5-yl)pyrrolidine-1-carboxylate (6k)

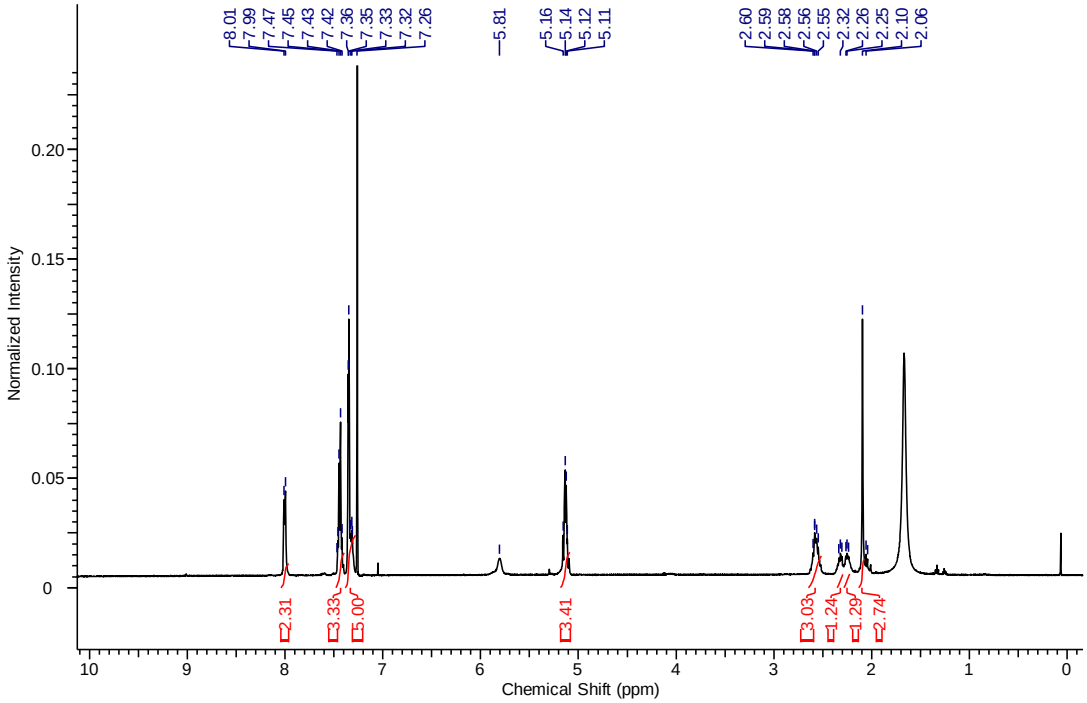


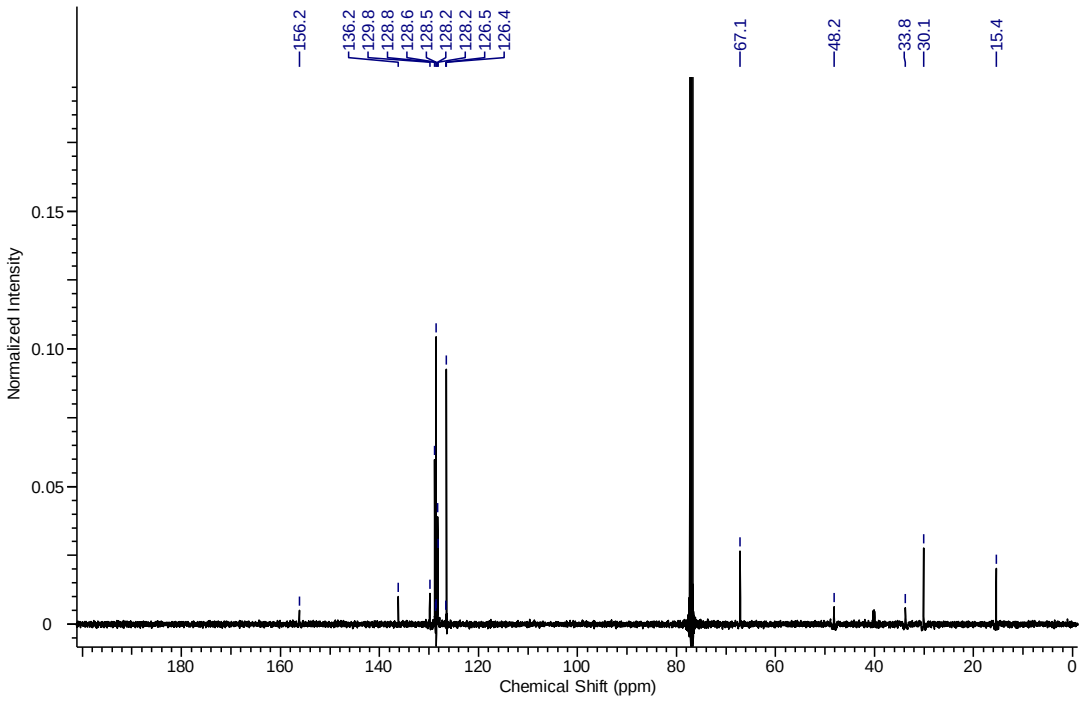




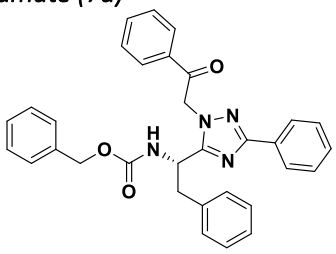
Benzyl (S)-(3-(methylthio)-1-(3-phenyl-1H-1,2,4-triazol-5-yl)propyl)carbamate (6l)

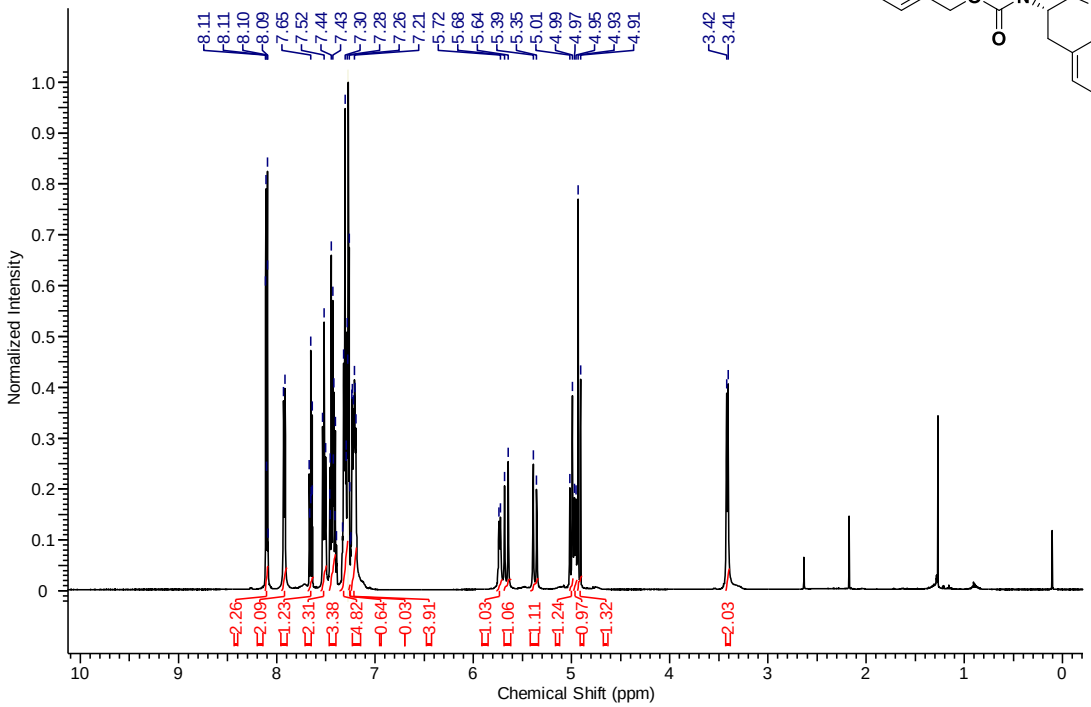


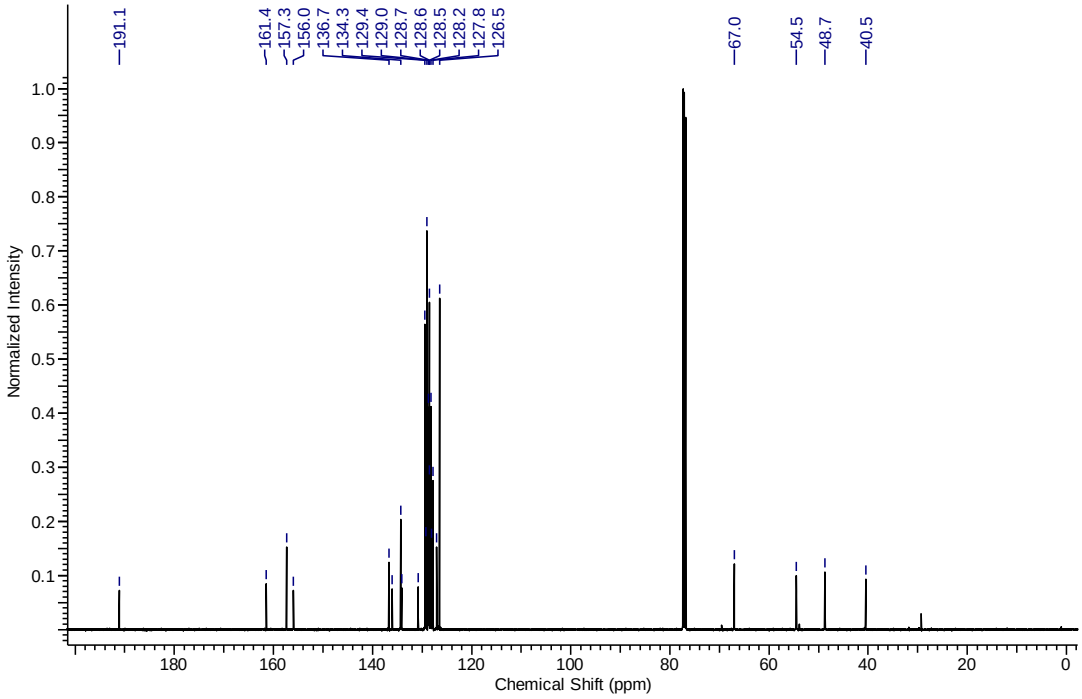




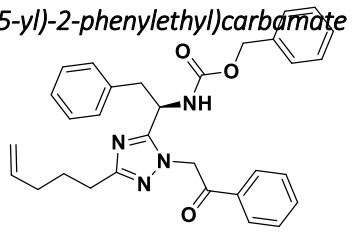
Benzyl ((1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)methyl)carbamate (7a)

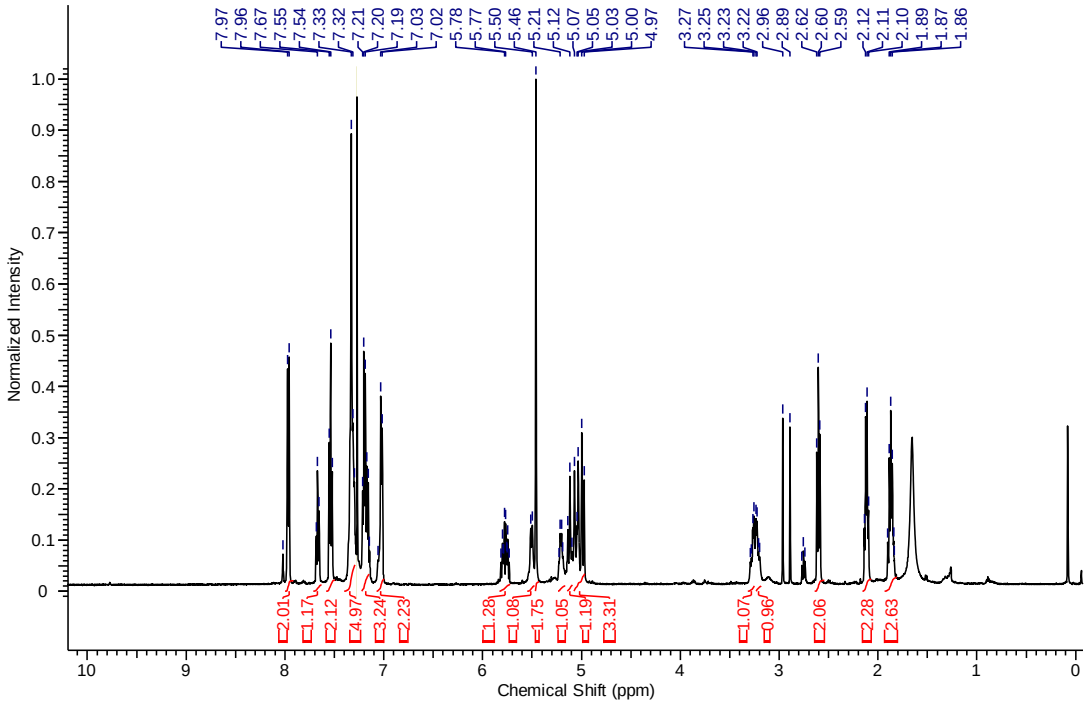


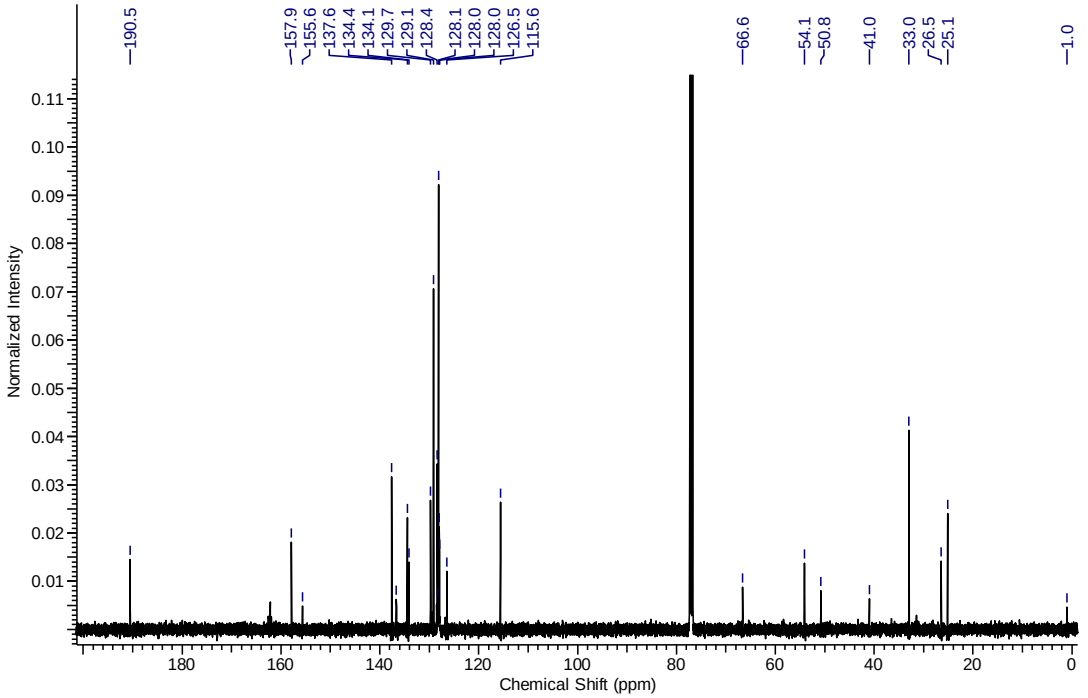




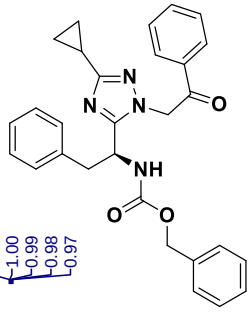
Benzyl (S)-(1-(1-(2-oxo-2-phenylethyl)-3-(pent-4-en-1-yl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (7b)

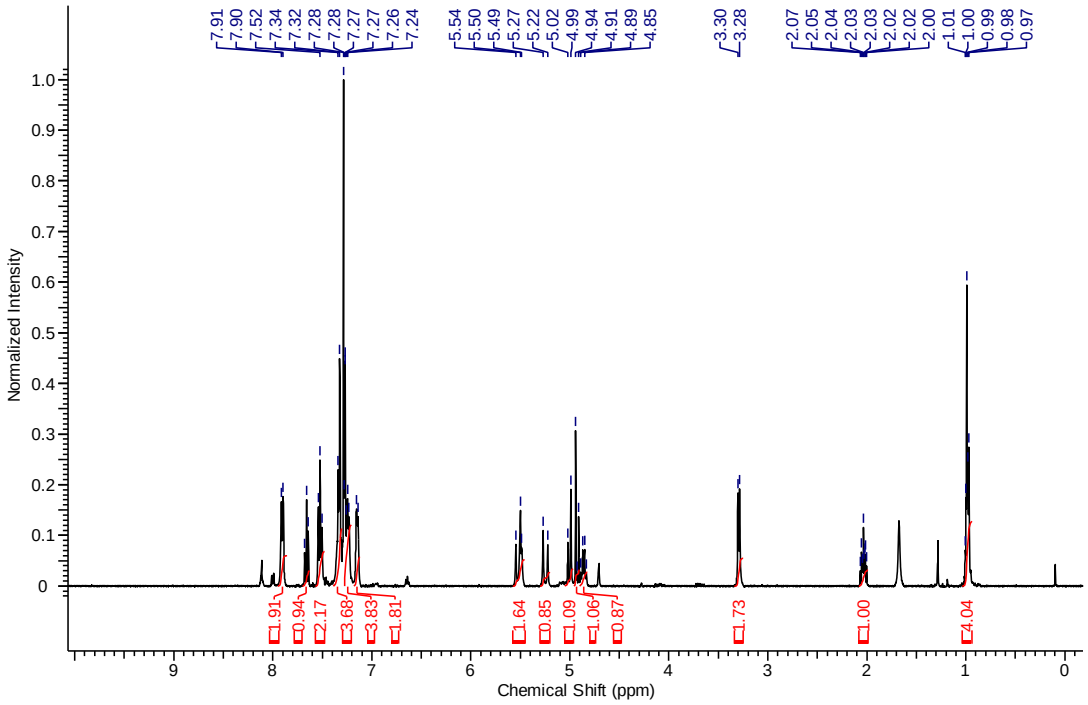


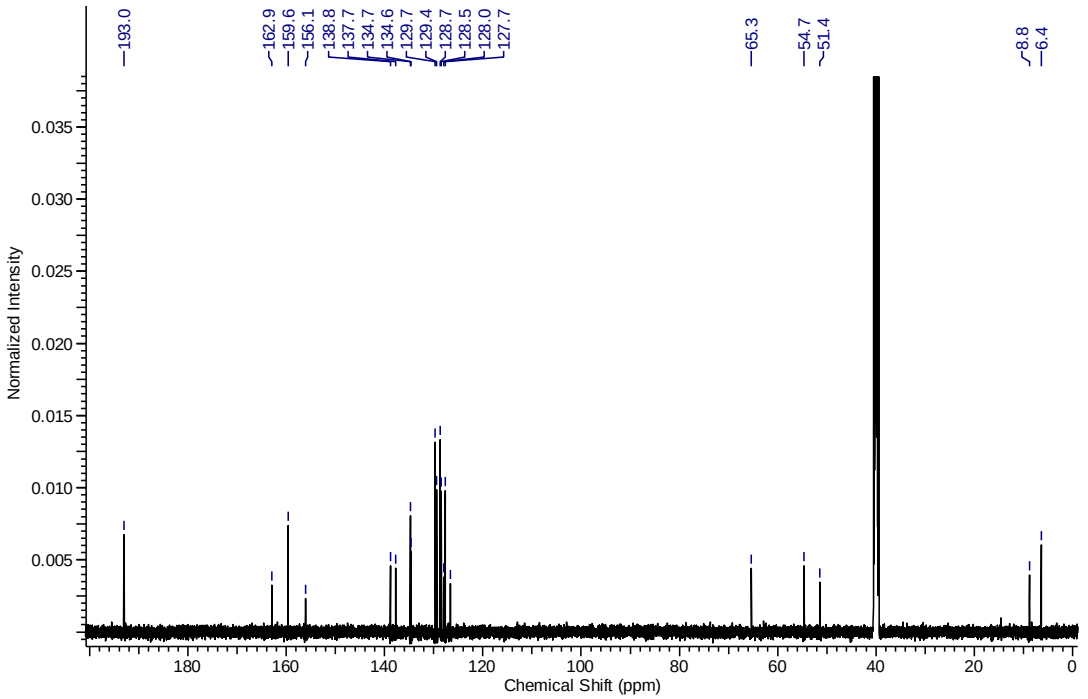




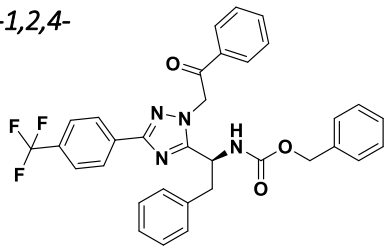
(S)-Benzyl 1-(3-cyclopropyl-1-(2-oxo-2-phenylethyl)-1H-1,2,4-triazol-5-yl)-2-phenylethylcarbamate (7c)

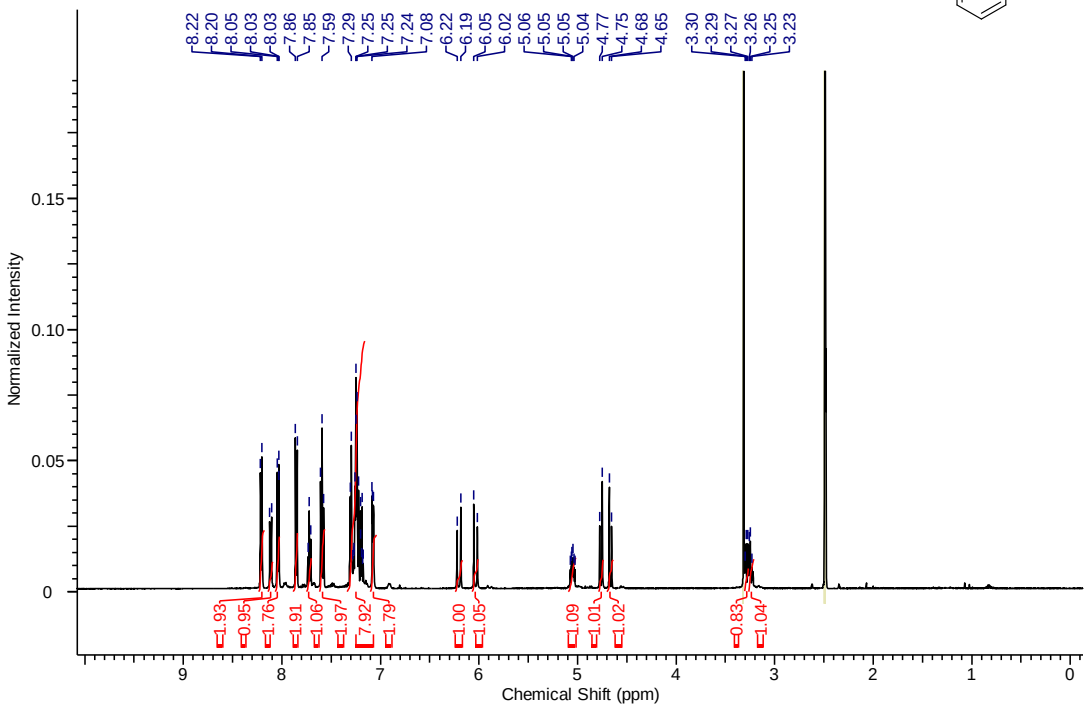


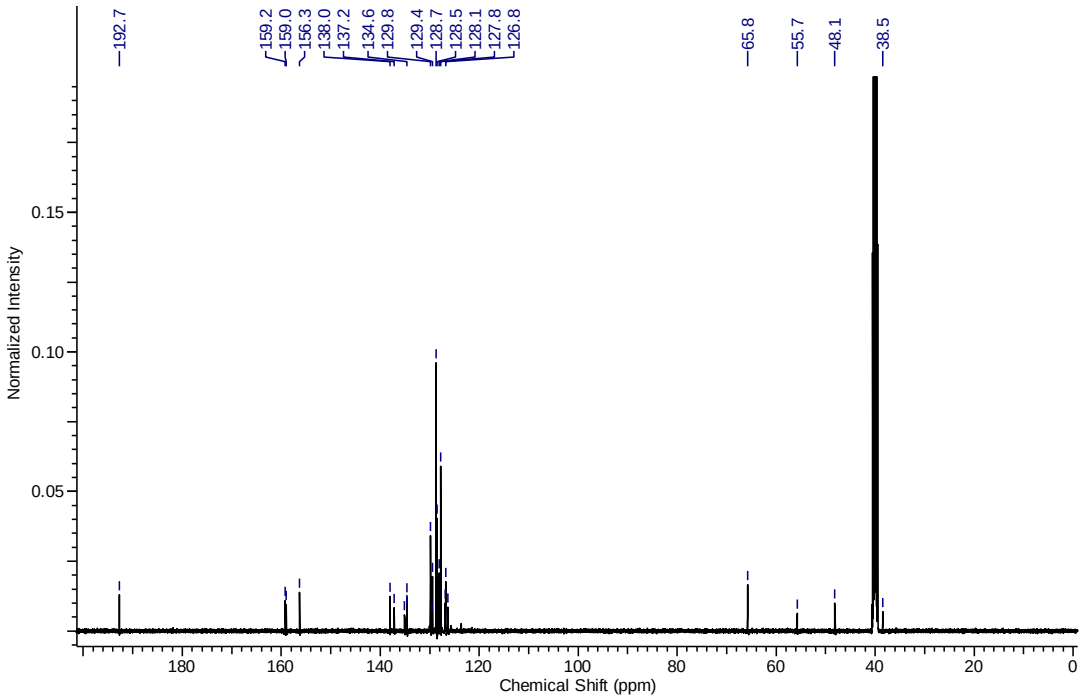




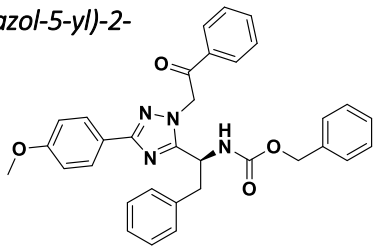
Benzyl (S)-(1-(1-(2-oxo-2-phenylethyl)-3-(4-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (7d)

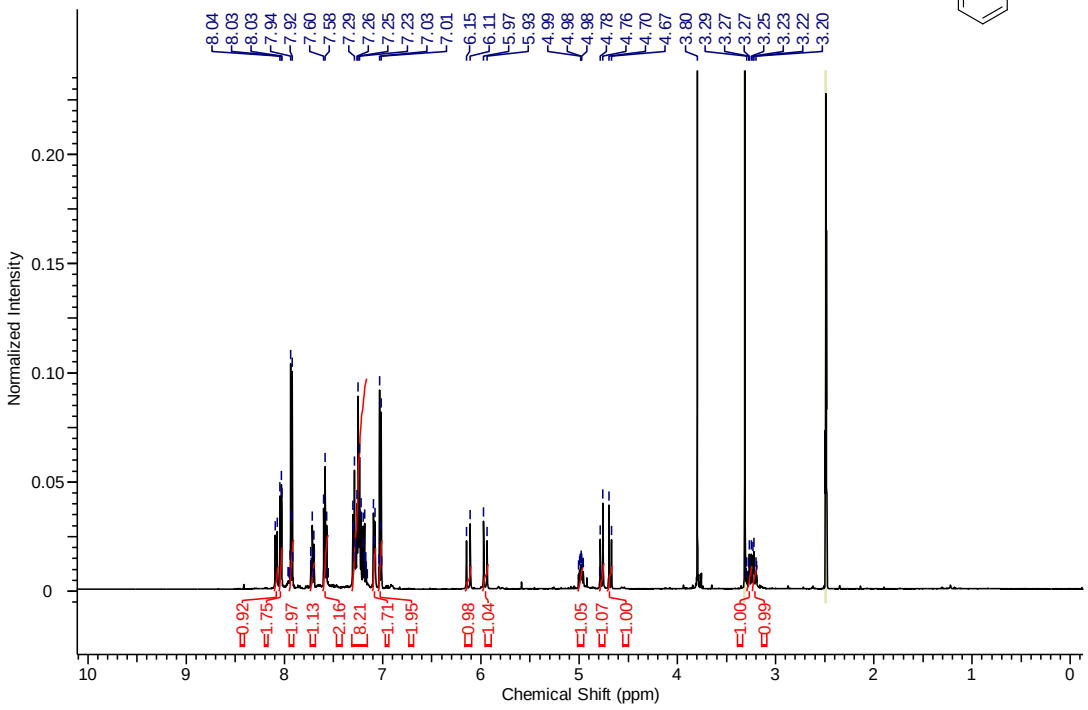


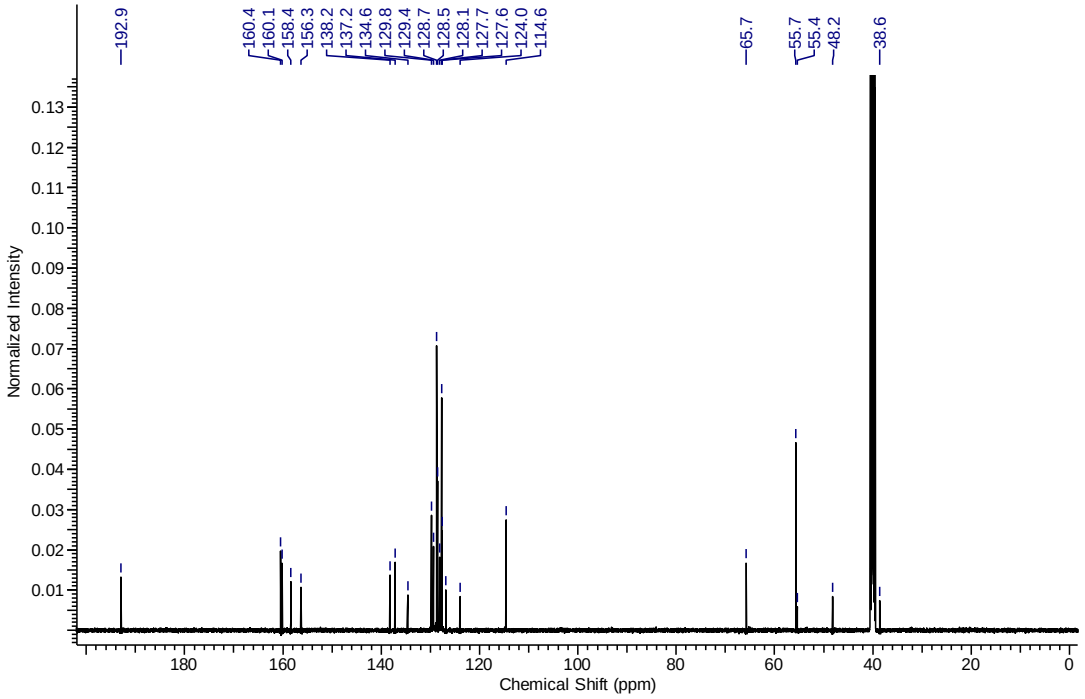




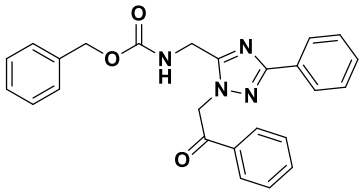
Benzyl (S)-(1-(3-(4-methoxyphenyl)-1-(2-oxo-2-phenylethyl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (7e)

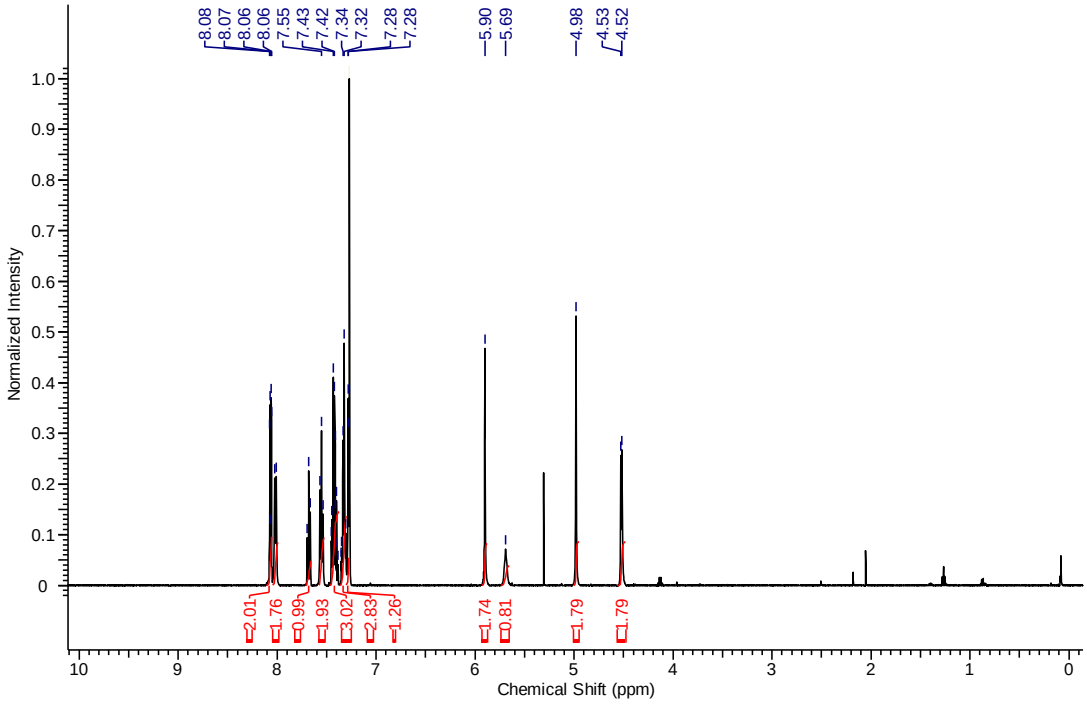


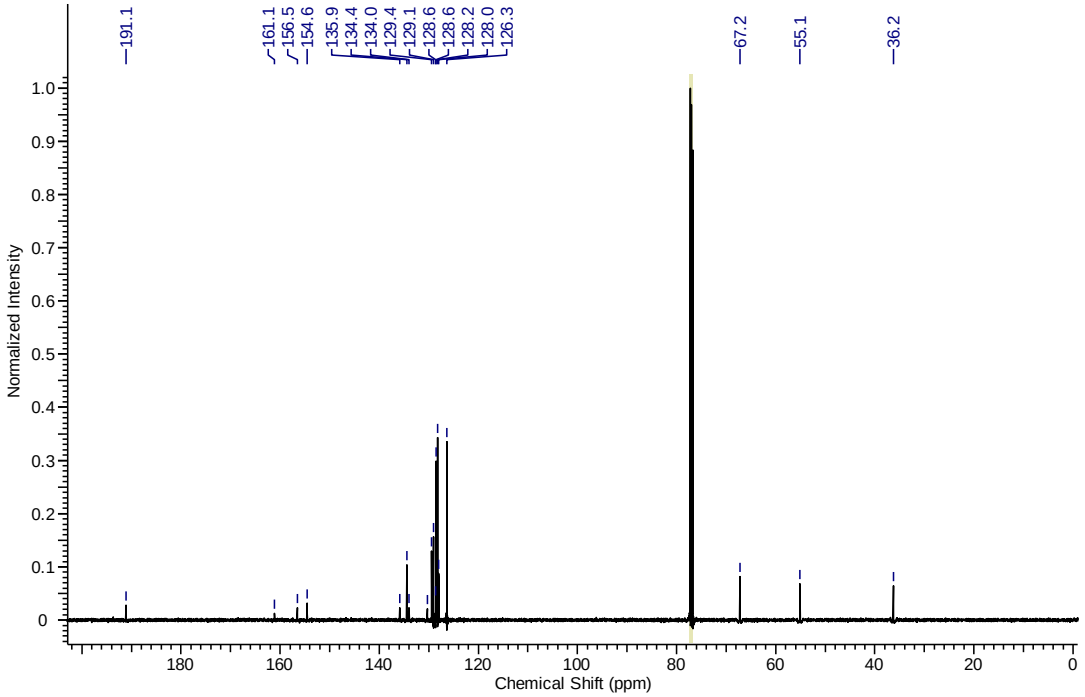




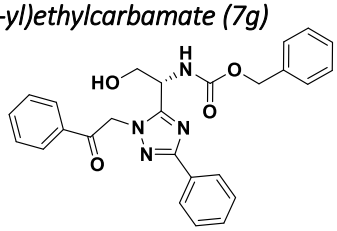
Benzyl ((1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)methyl) Carbamate (7f)

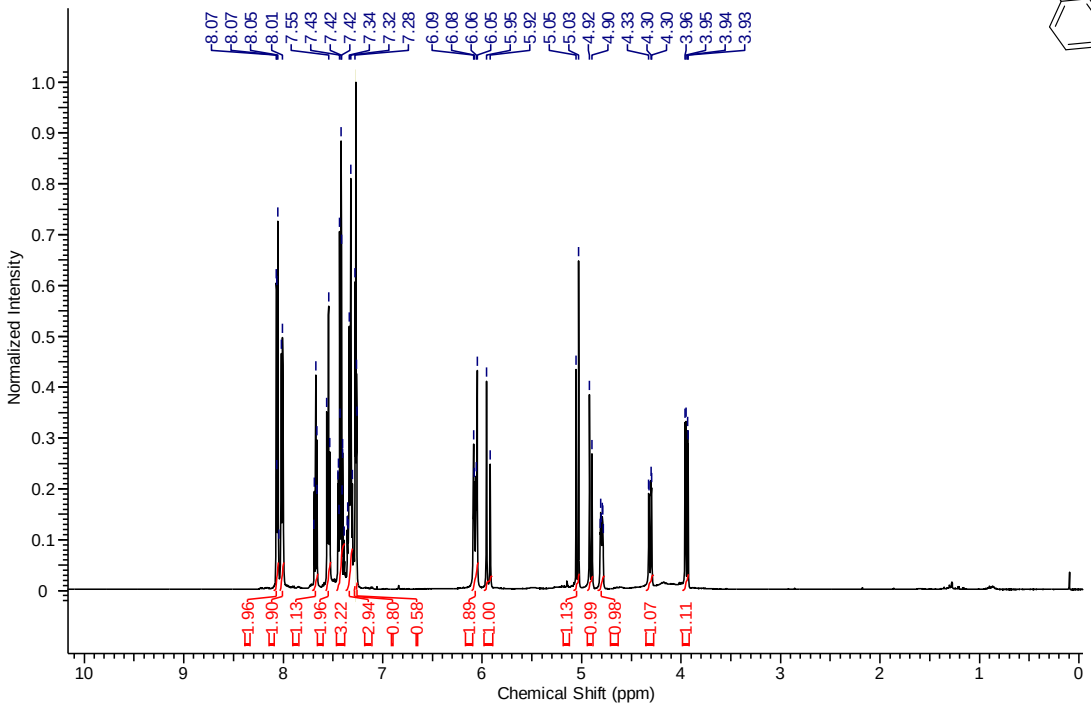


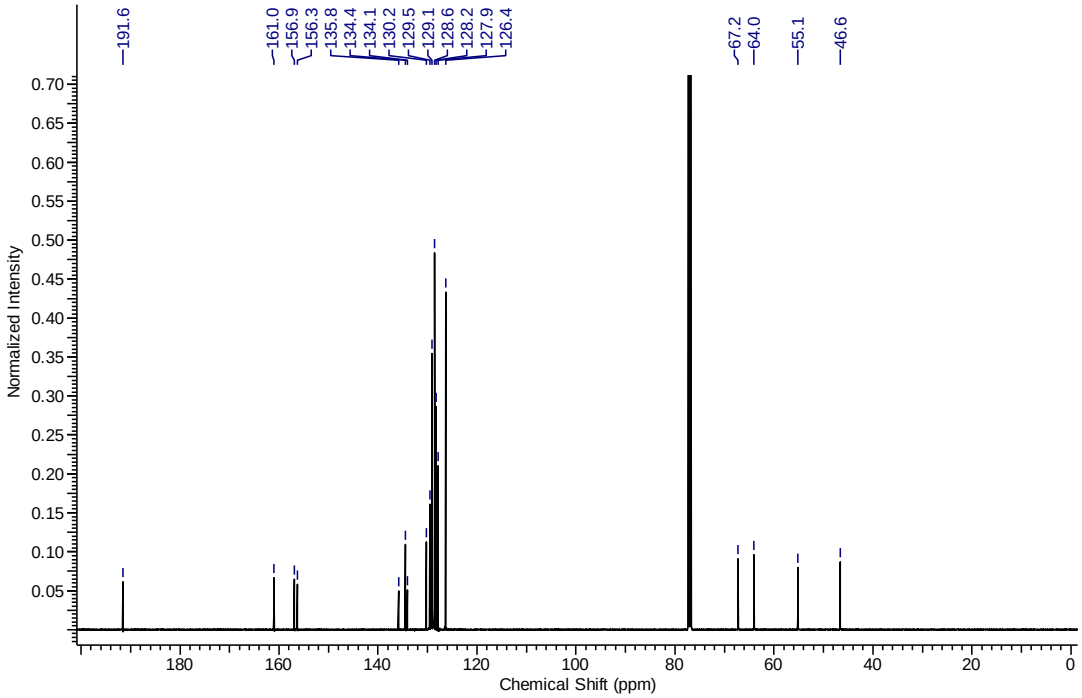




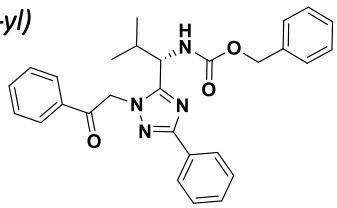
(S)-benzyl 2-hydroxy-1-(1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)ethylcarbamate (7g)

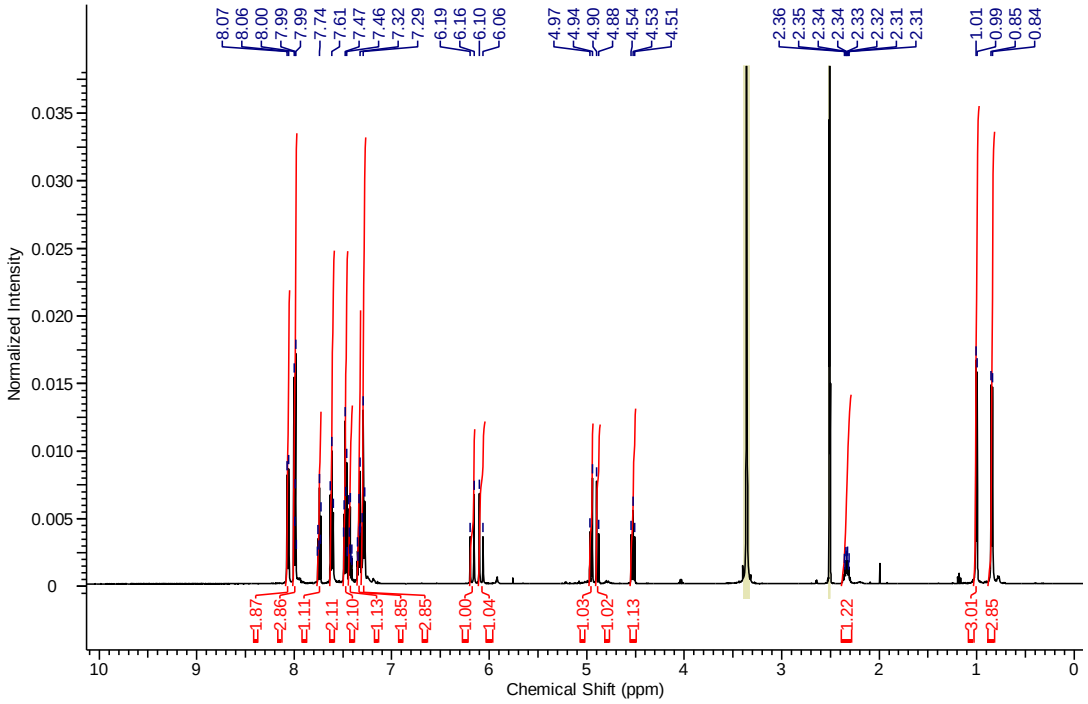


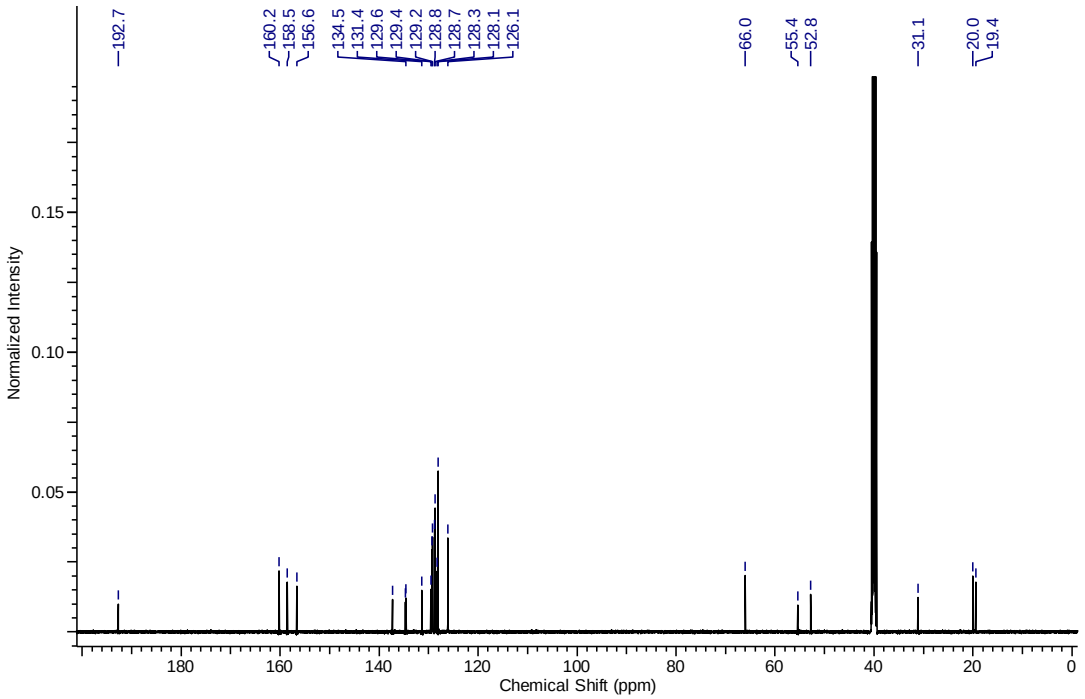




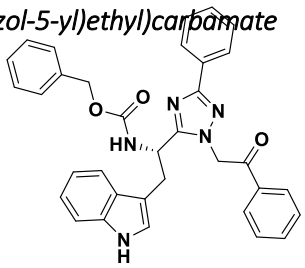
Benzyl (S)-(2-methyl-1-(1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl) propyl)carbamate (7h)

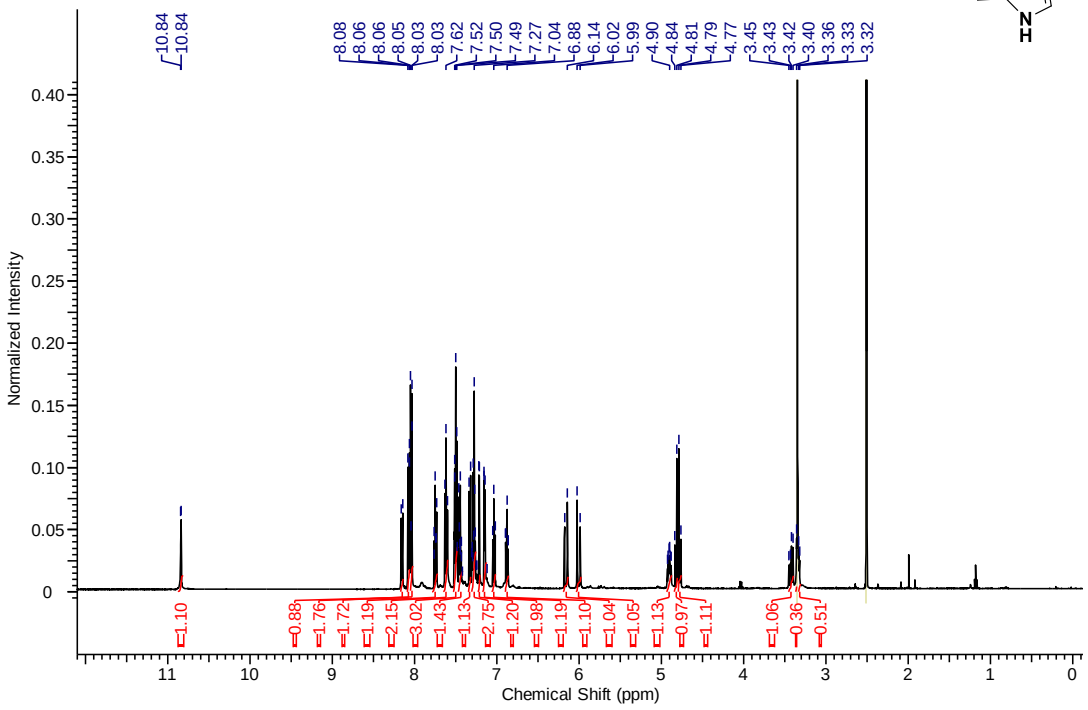


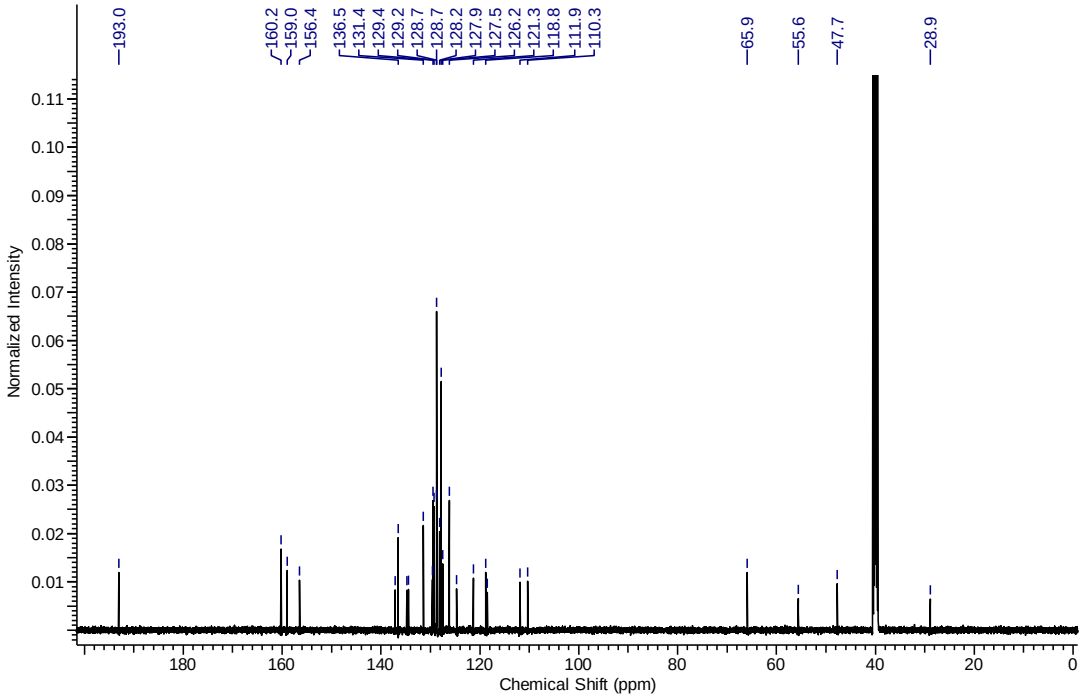




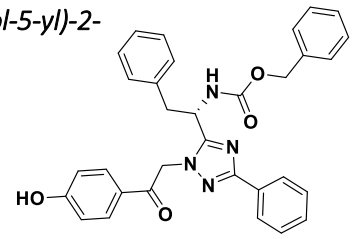
Benzyl (S)-(2-(1H-indol-3-yl)-1-(1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)ethyl)carbamate (7i)

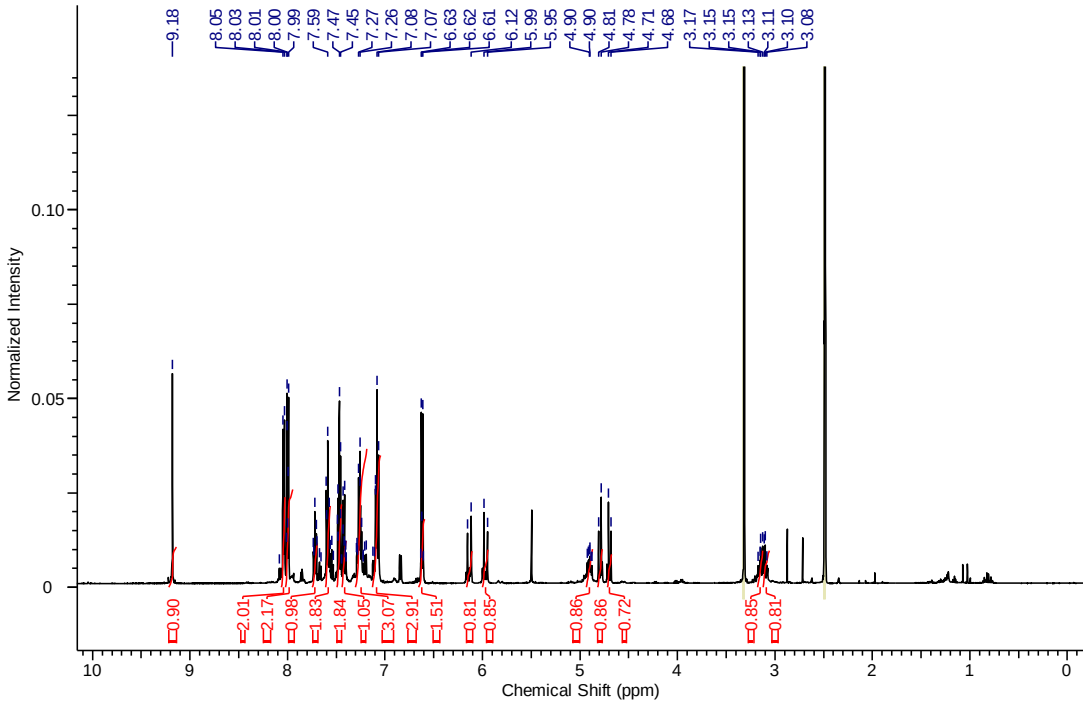


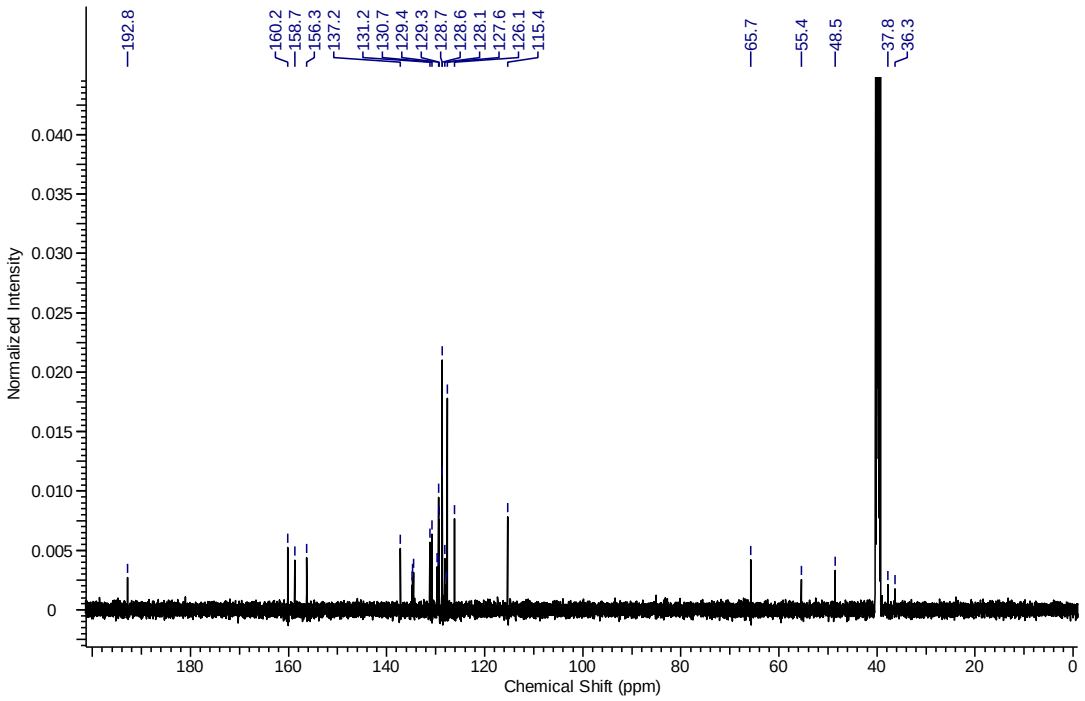




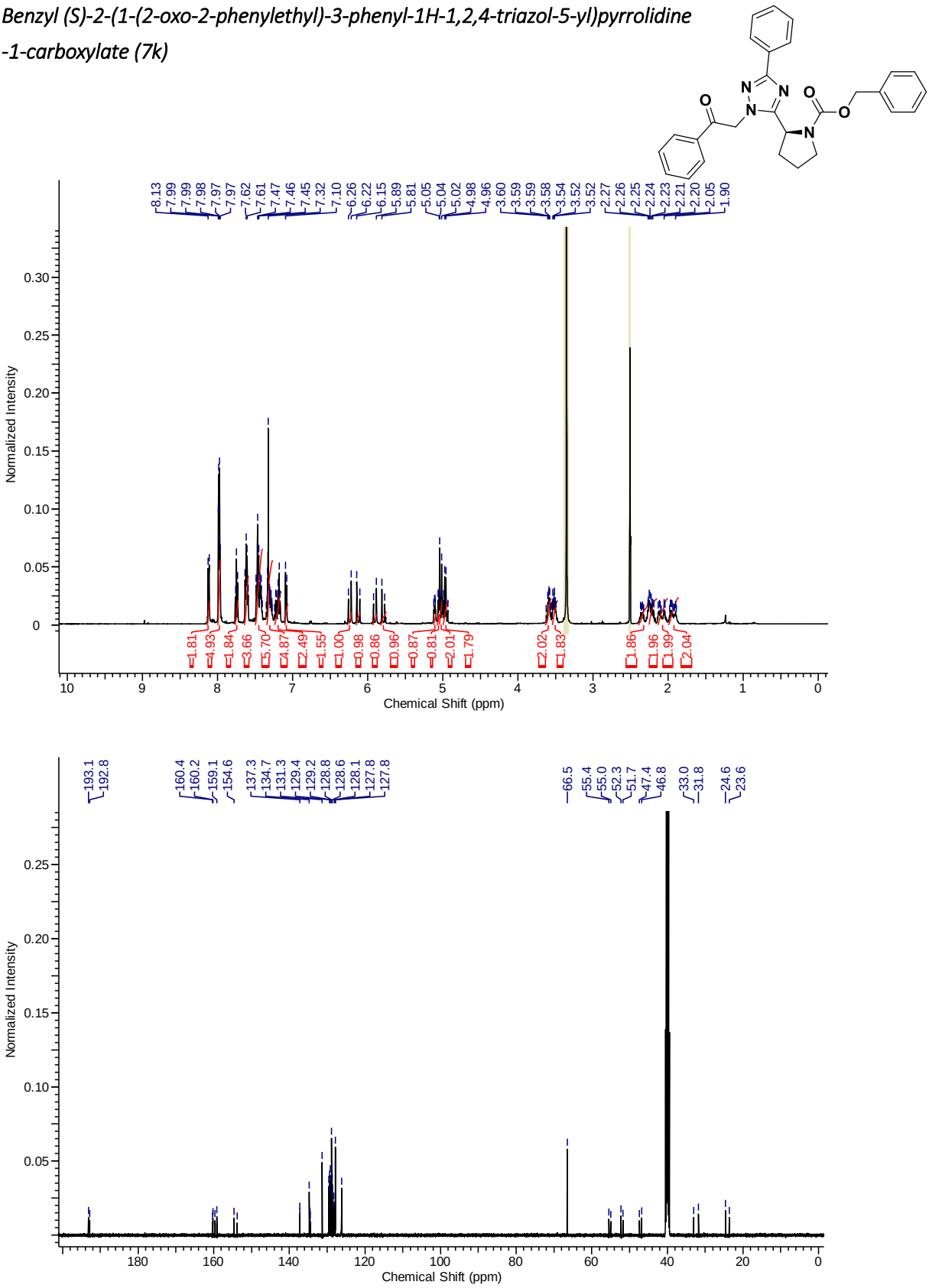
Benzyl (S)-(1-(1-(2-(4-hydroxyphenyl)-2-oxoethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (7j)



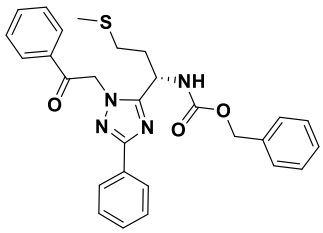


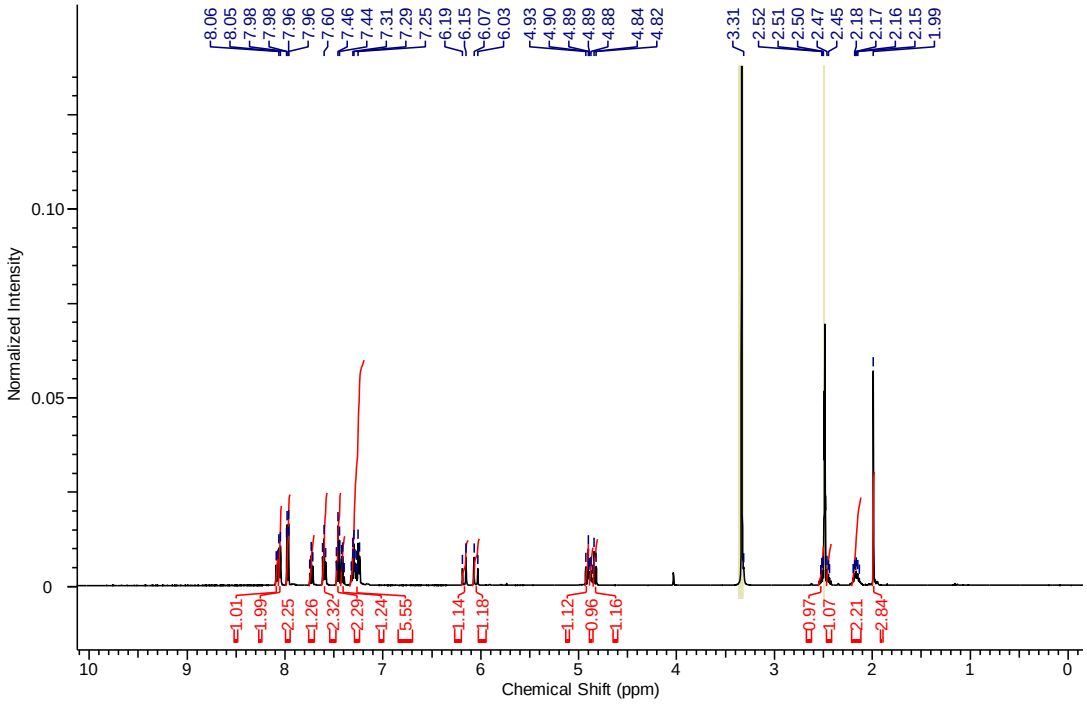


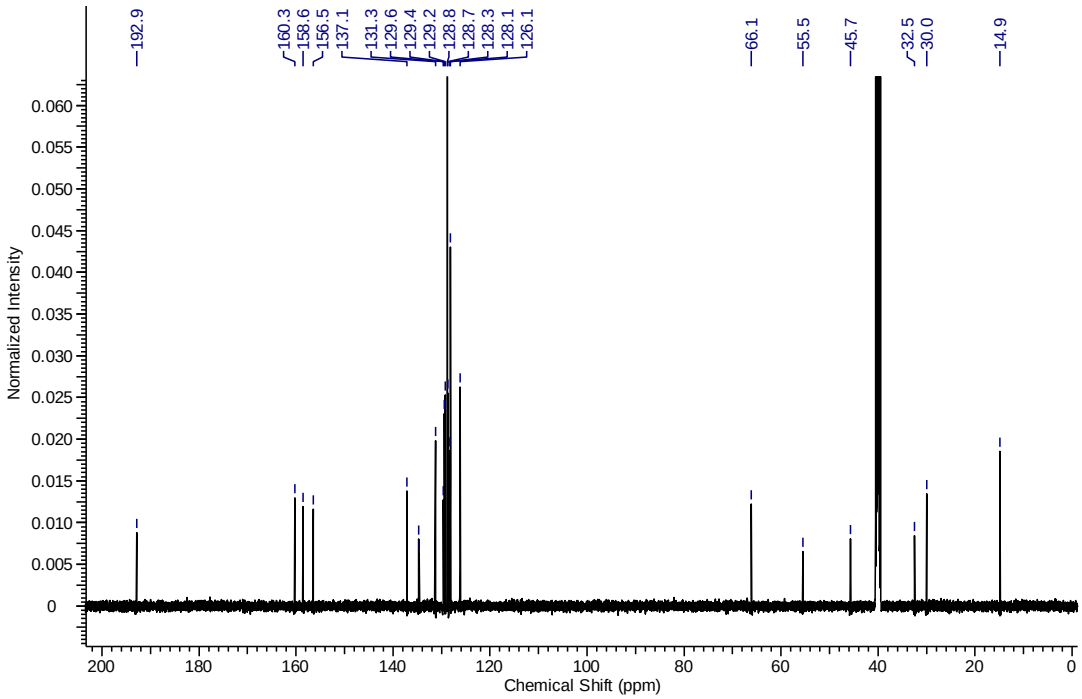
Benzyl (S)-2-(1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)pyrrolidine -1-carboxylate (7k)



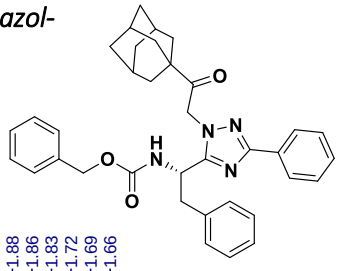
Benzyl (S)-(3-(methylthio)-1-(1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4 -triazol-5-yl)propyl)carbamate (7l)

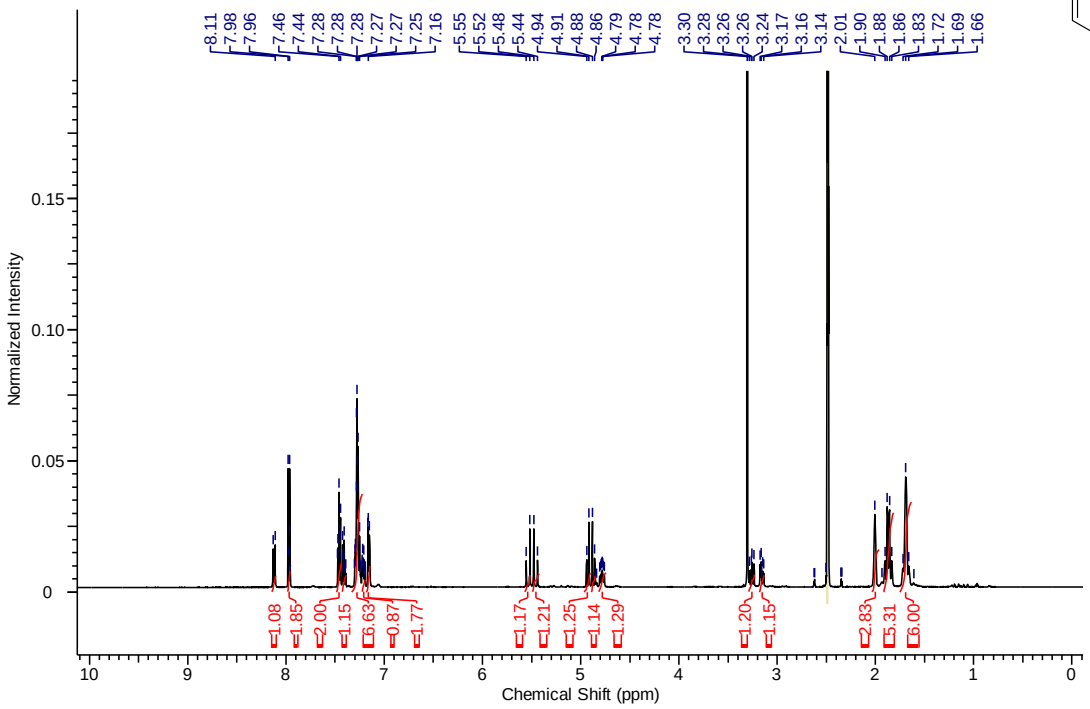


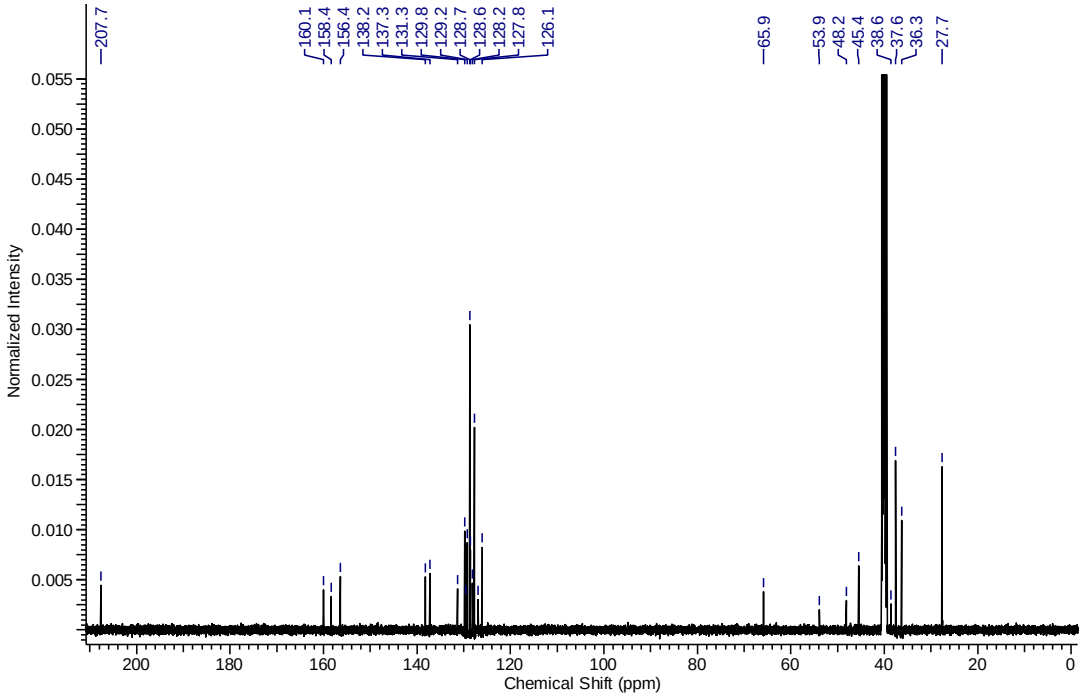




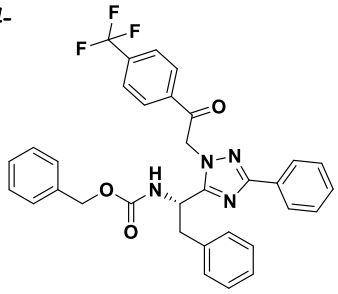
(S)-benzyl-1-(1-(2-oxo-2-((1R,3R)-adamant-1-yl)ethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethylcarbamate (7m)

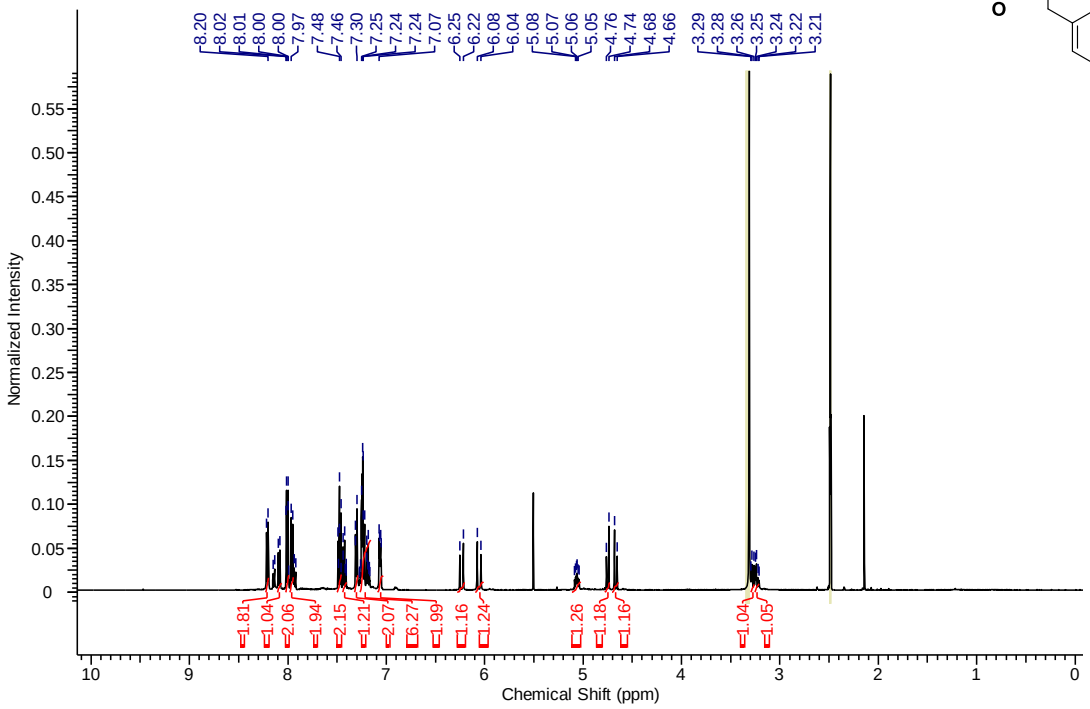


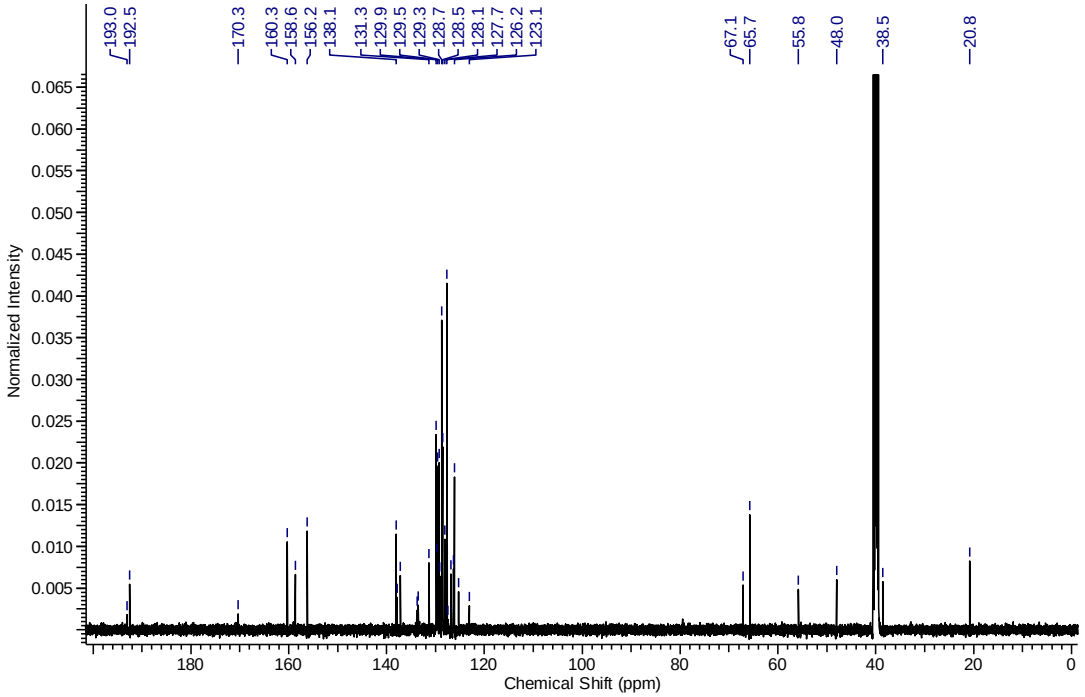




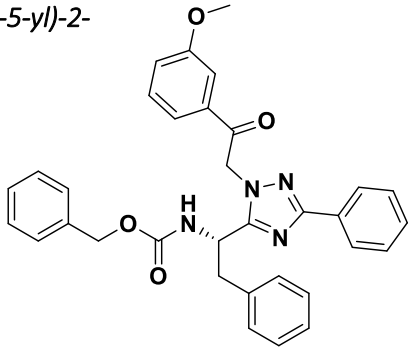
(S)-benzyl 1-(1-(2-oxo-2-(4-(trifluoromethyl)phenyl)ethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethylcarbamate (7n)

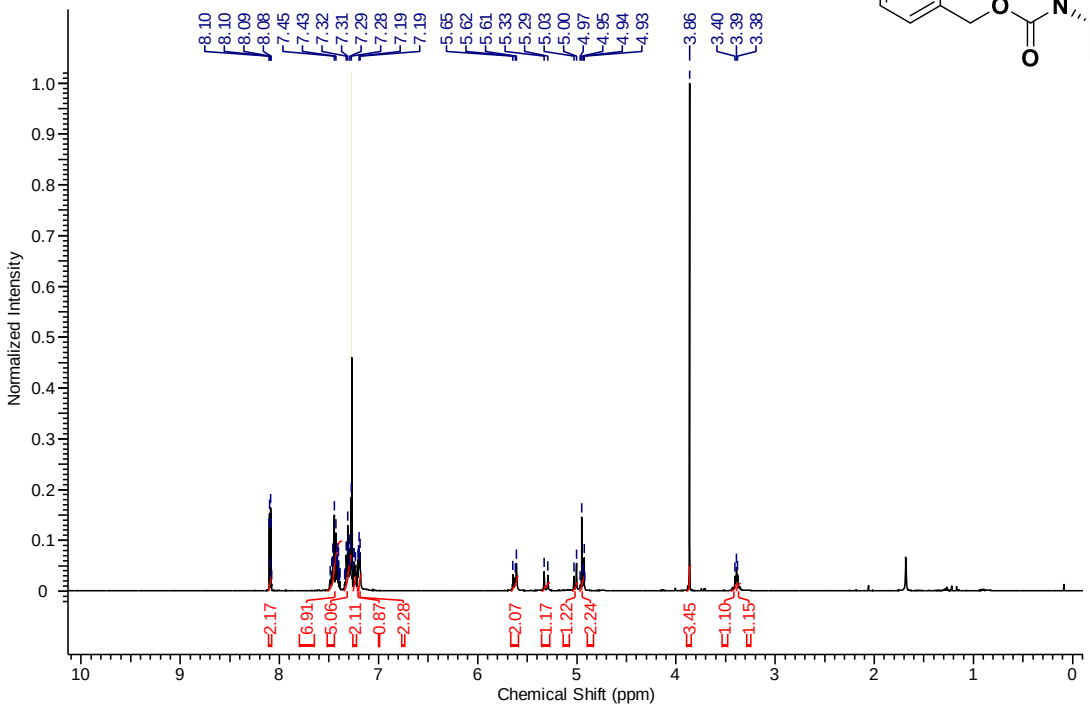


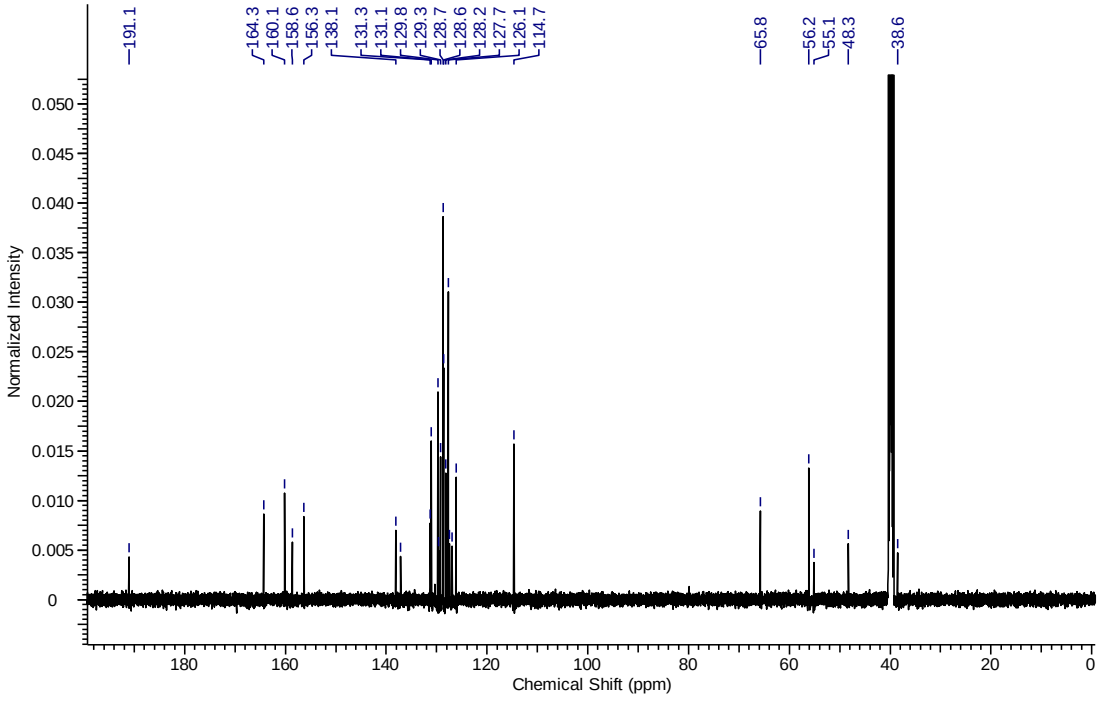




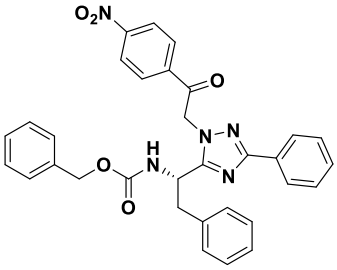
Benzyl (S)-(1-(1-(2-(3-methoxyphenyl)-2-oxoethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (7o)

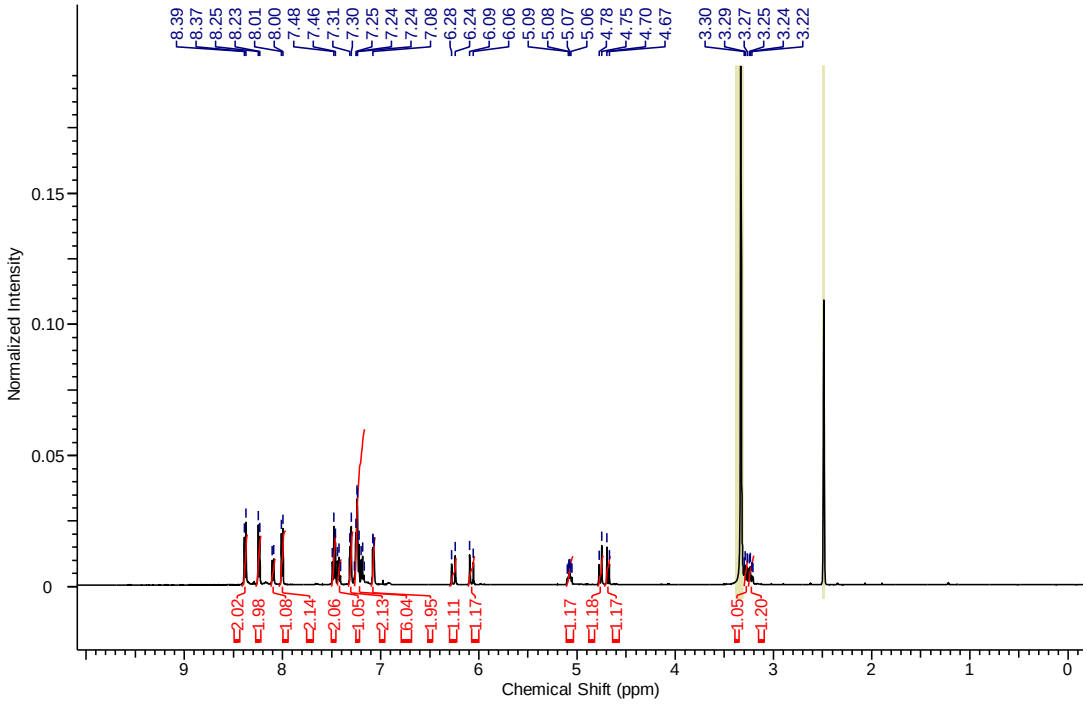


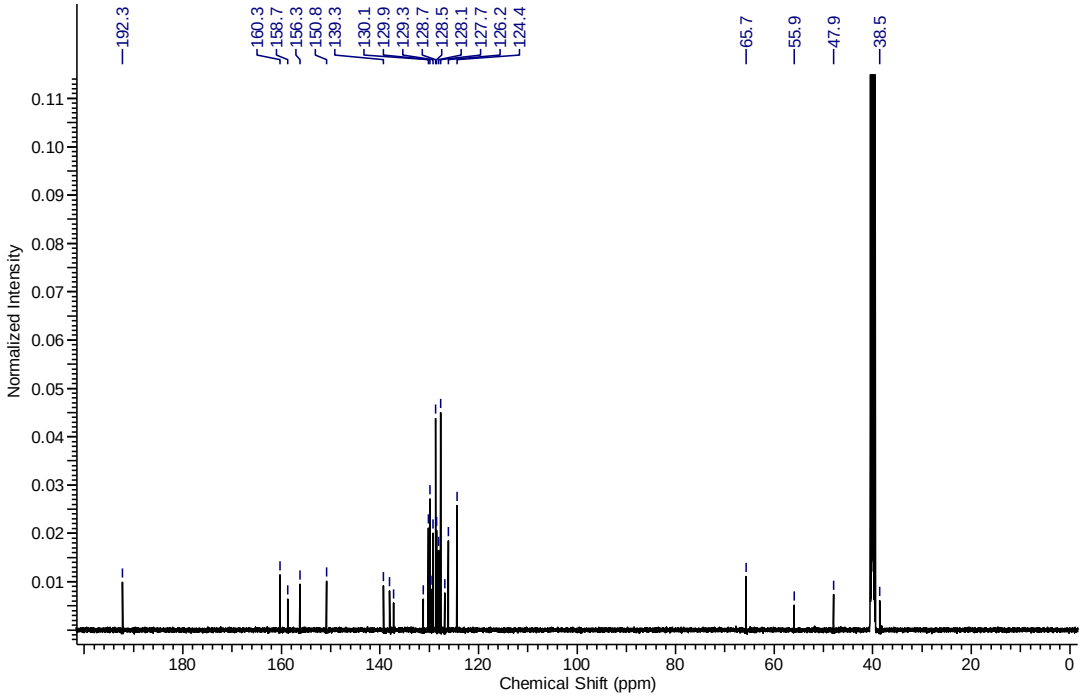




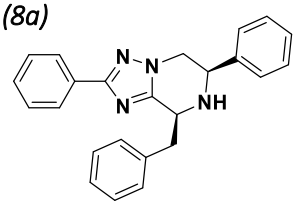
Benzyl (S)-(1-(1-(2-(4-nitrophenyl)-2-oxoethyl)-3-phenyl-1H-1,2,4-triazol-5-yl) -2-phenylethyl)carbamate (7p)

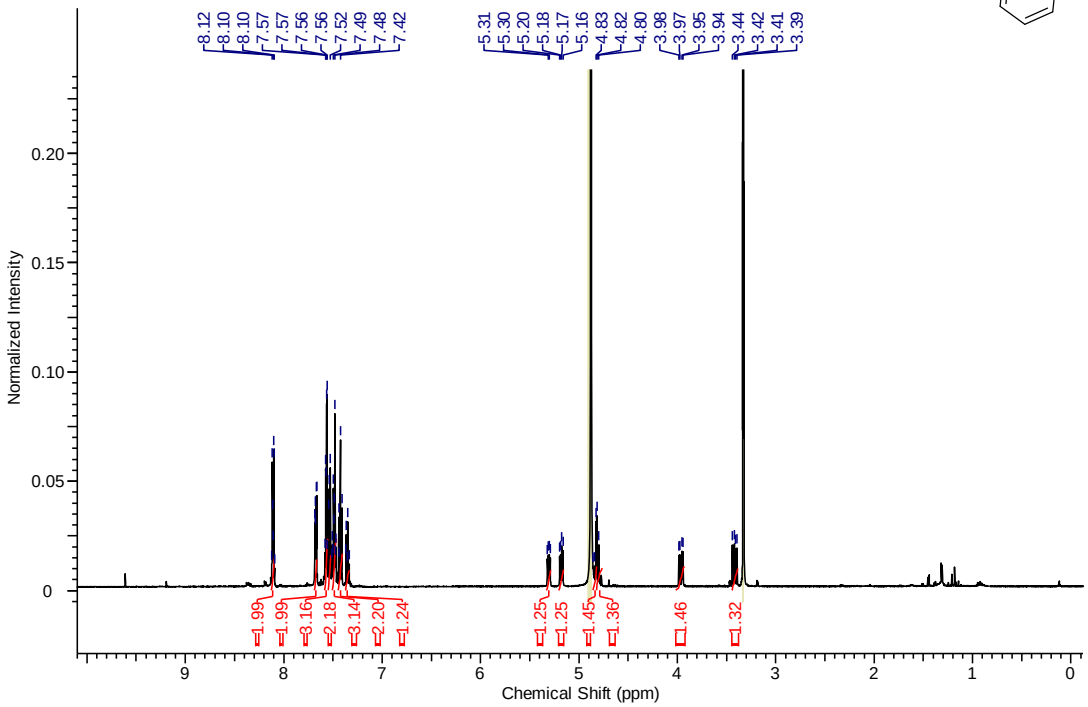


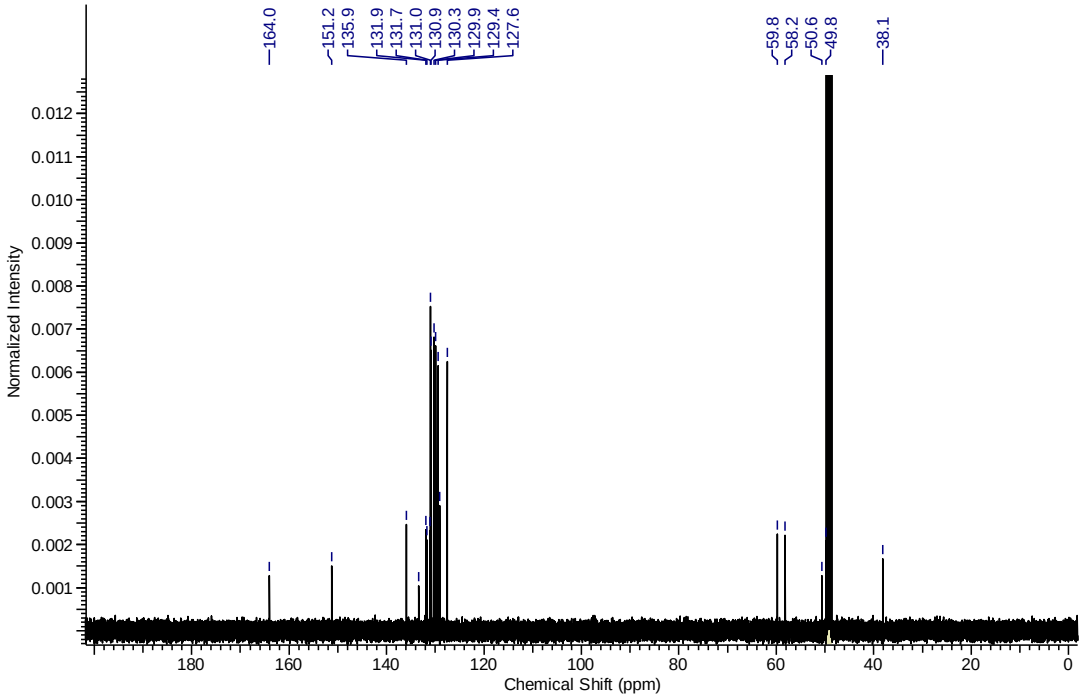




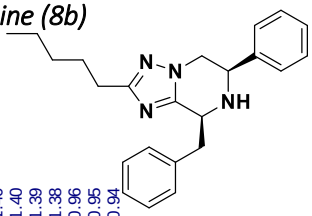
(6R,8S)-8-benzyl-2,6-diphenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (8a)

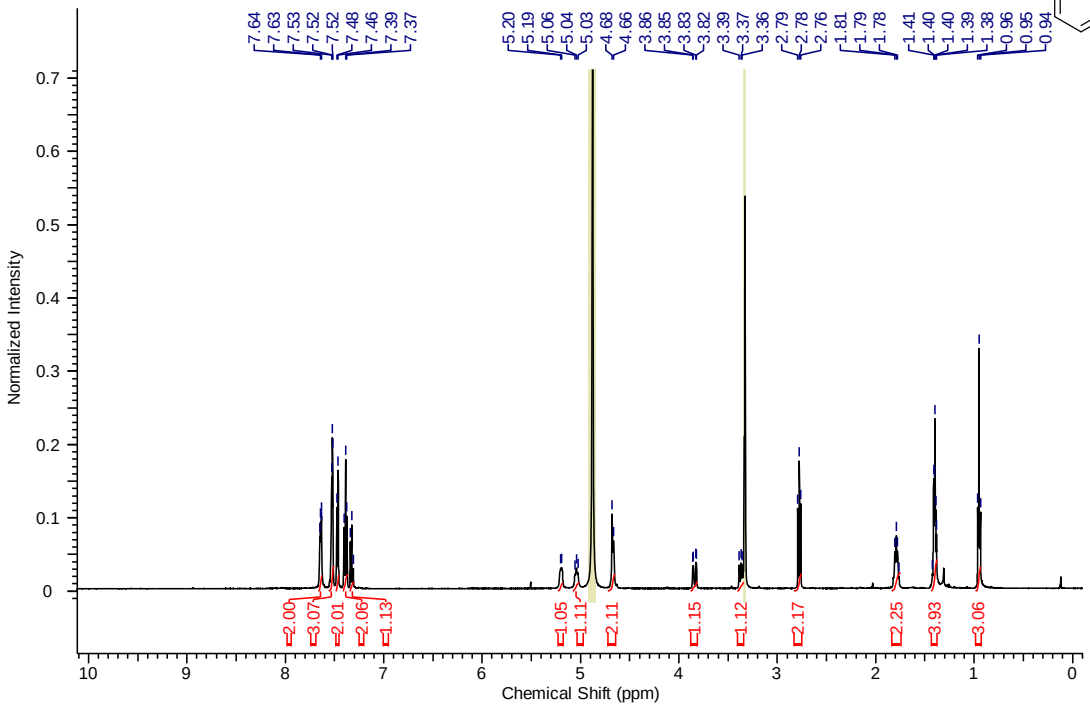


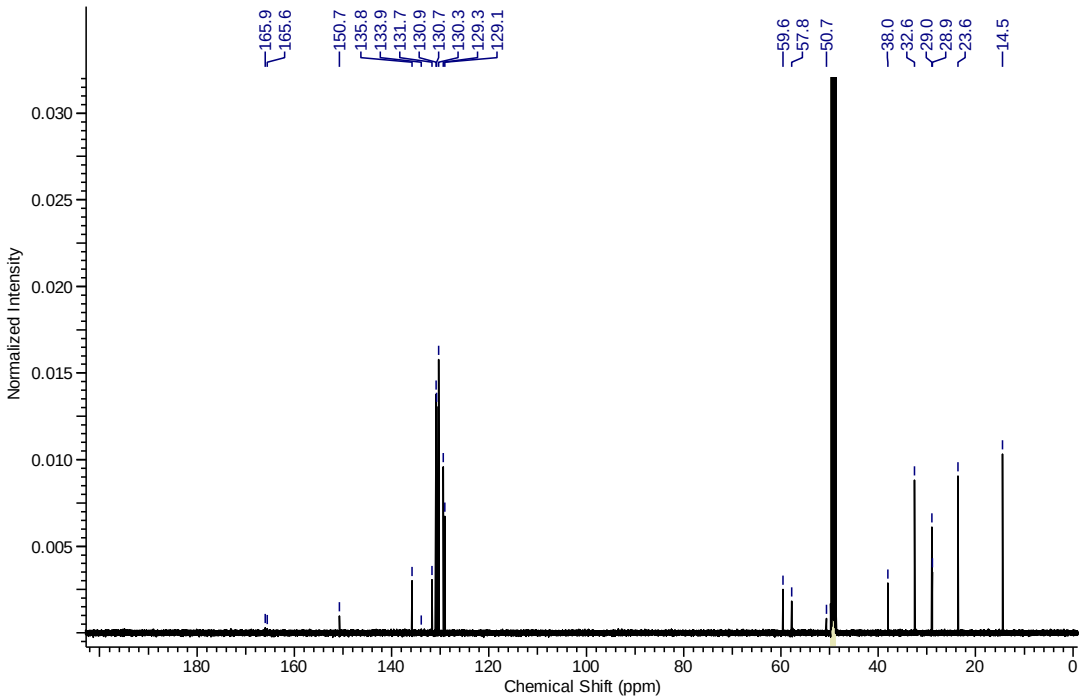




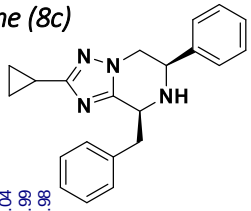
(6R,8S)-8-benzyl-2-pentyl-6-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (8b)

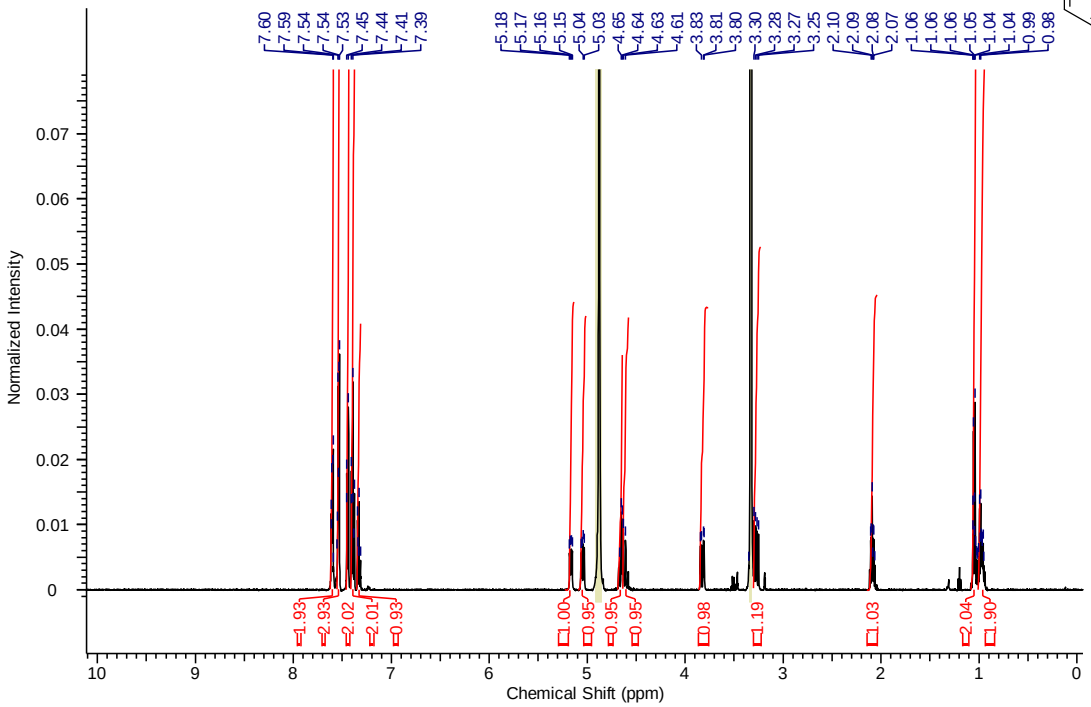


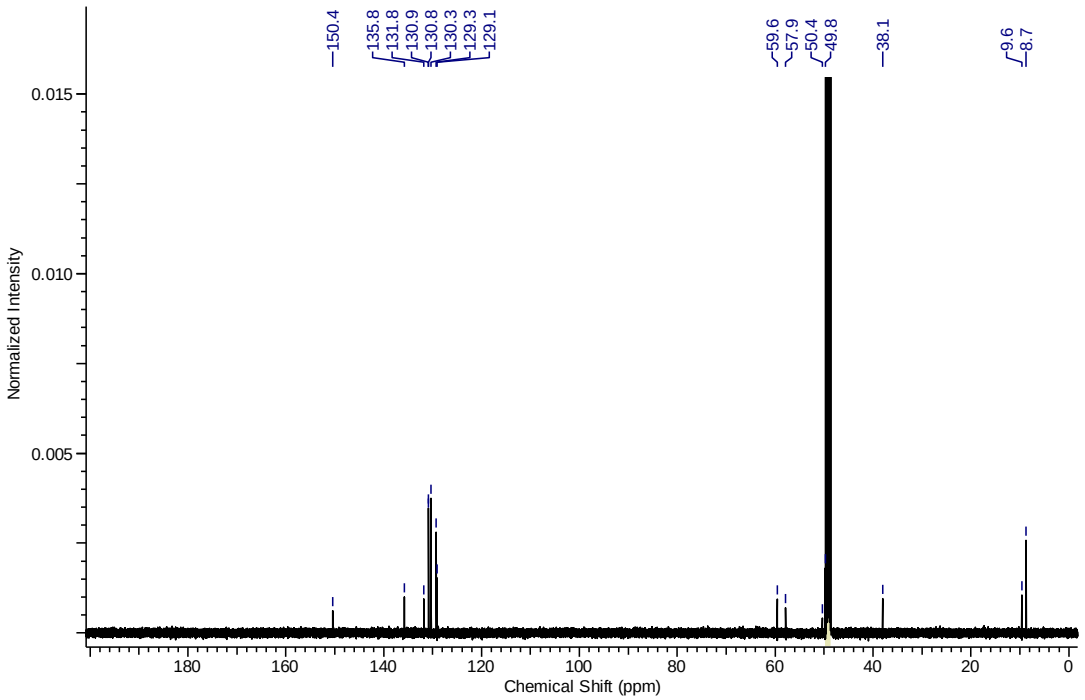




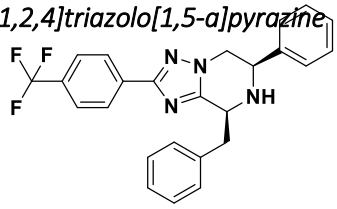
(6R,8S)-8-benzyl-6-cyclopropyl-6-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (8c)

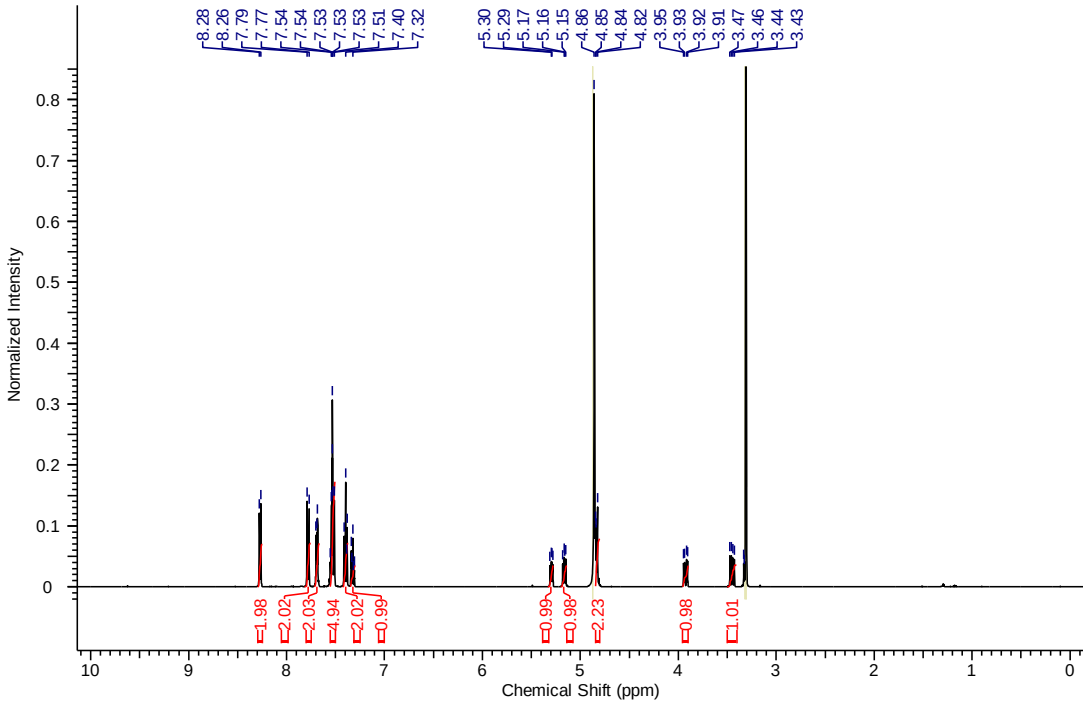


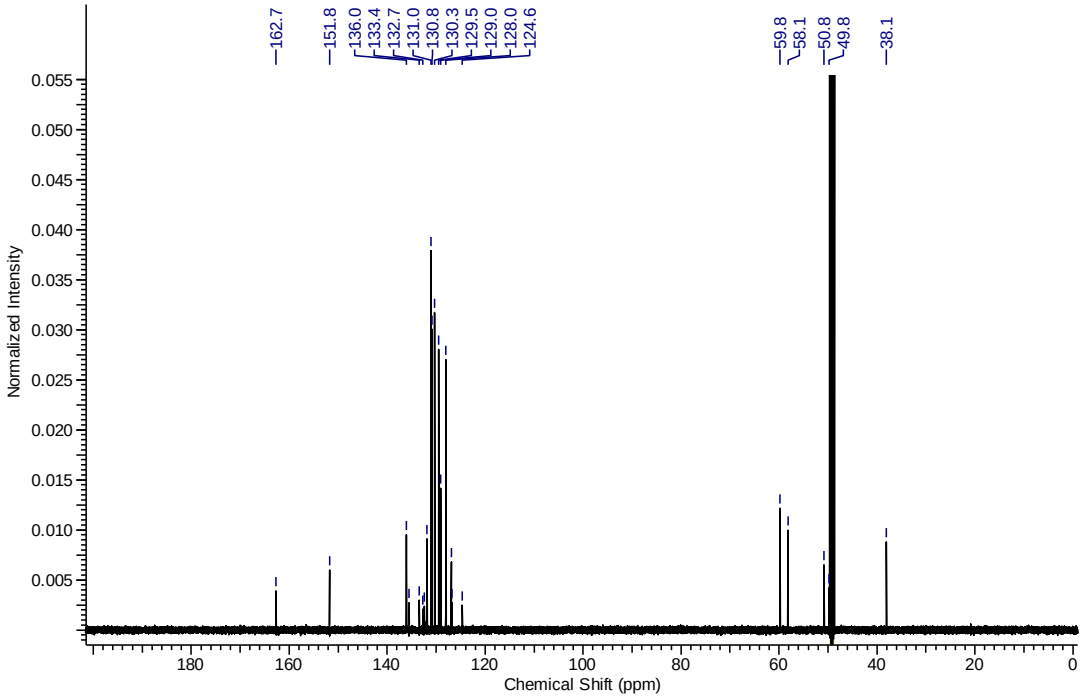




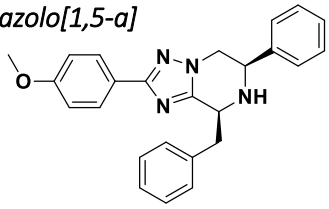
(6R,8S)-8-benzyl-6-phenyl-2-(4-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (8d)

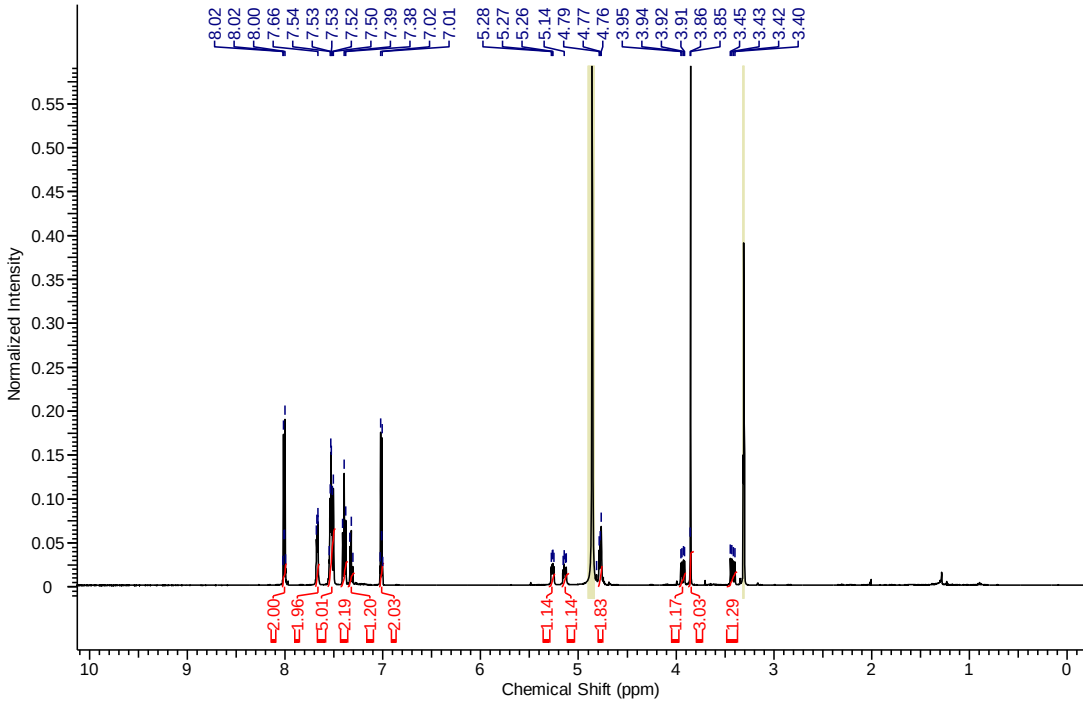


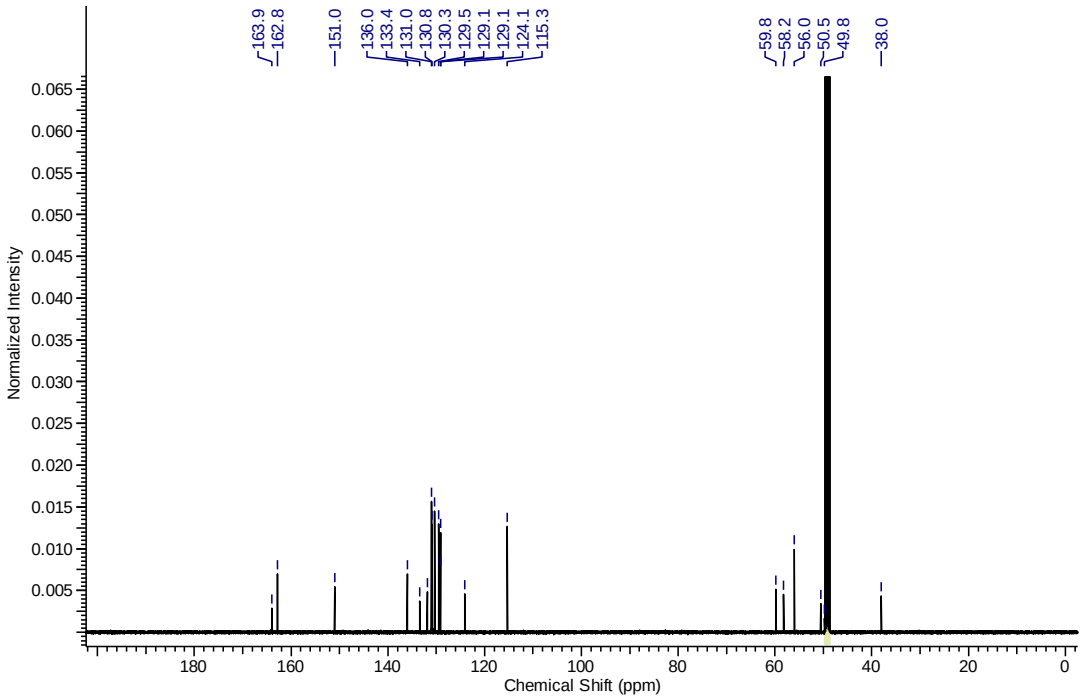




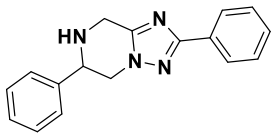
(6R,8S)-8-benzyl-2-(4-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a] Pyrazine (8e)

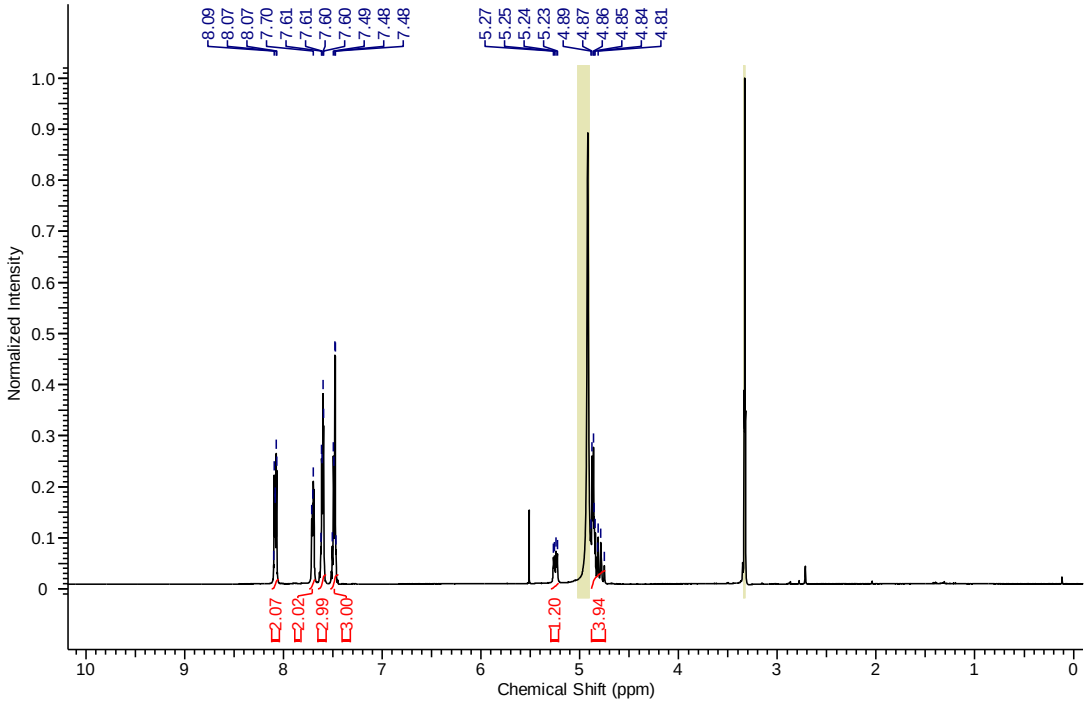


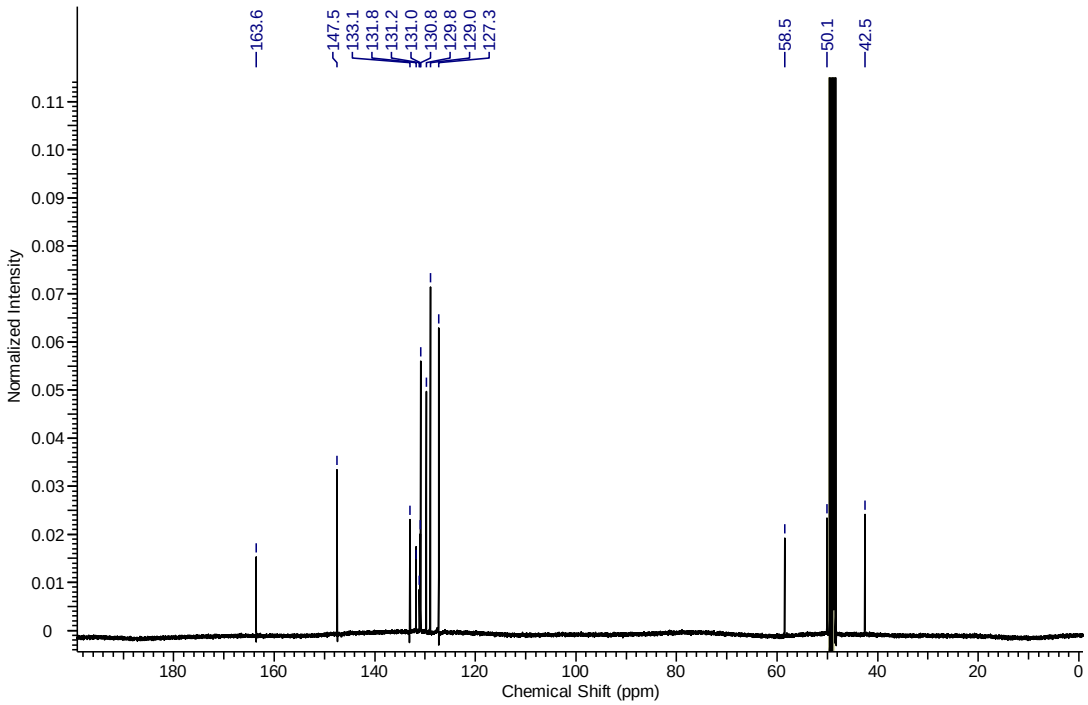




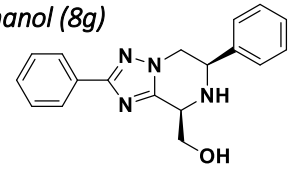
2,6-diphenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (8f)

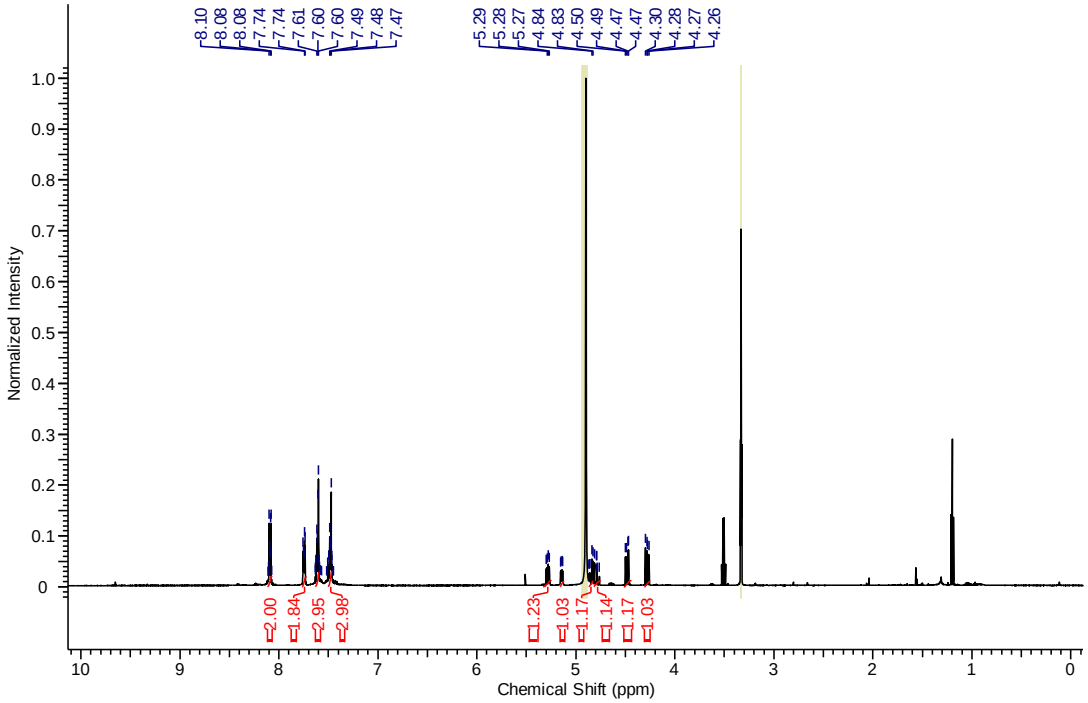


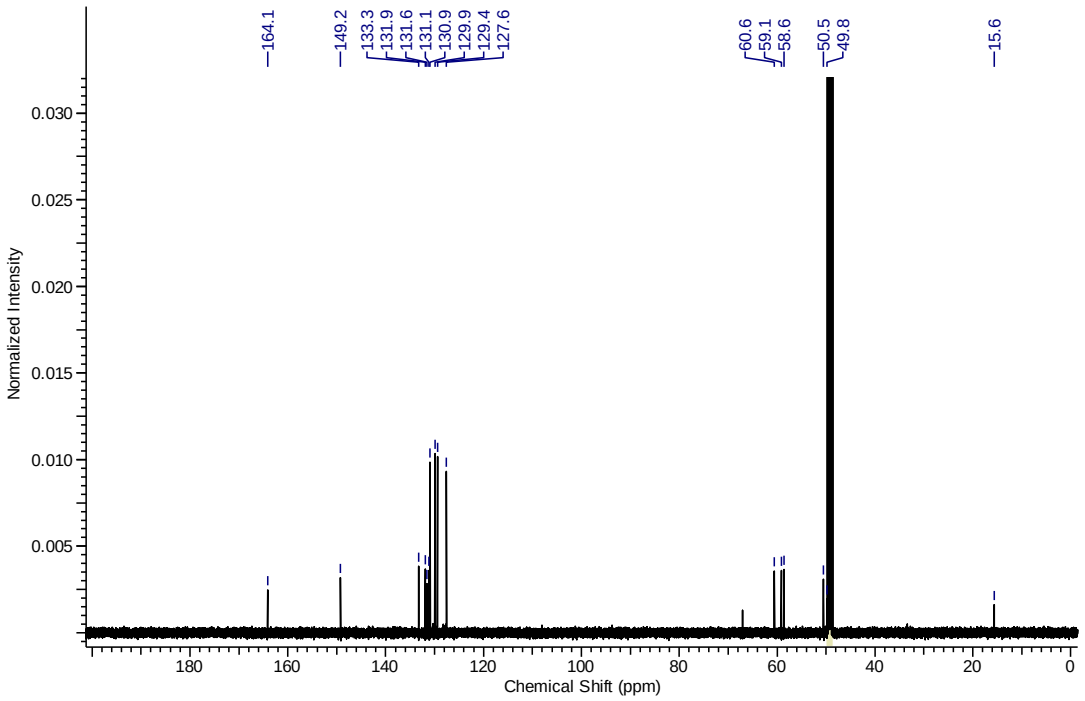




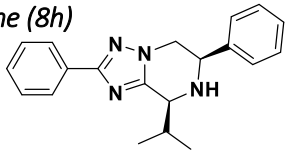
((6R,8R)-2,6-diphenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazin-8-yl)methanol (8g)

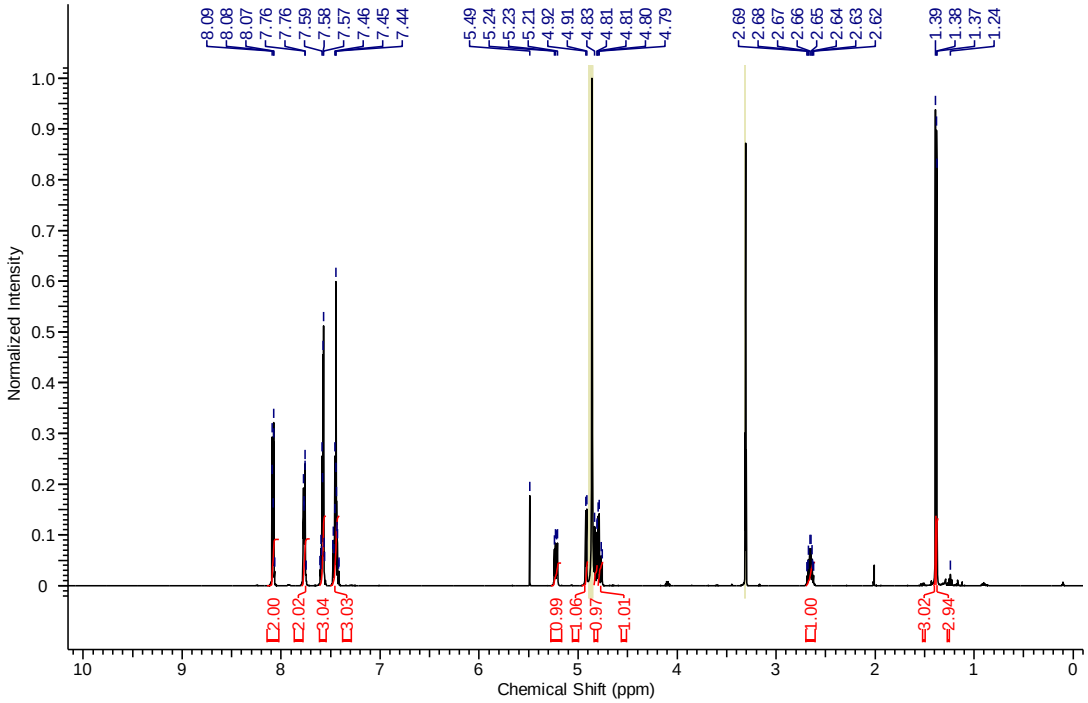


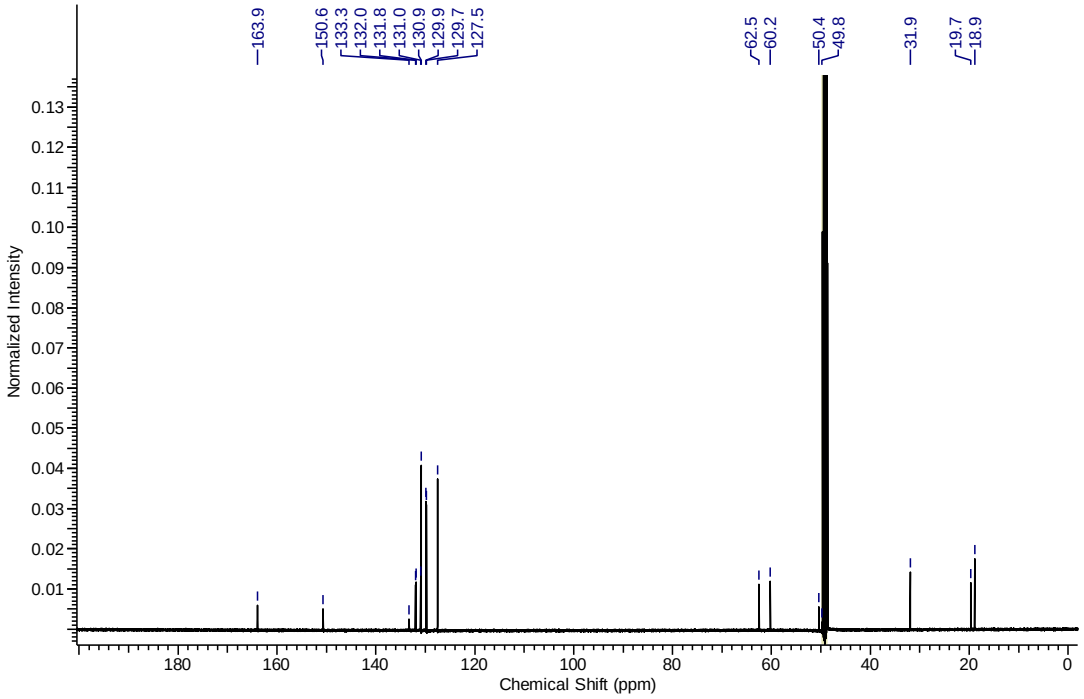




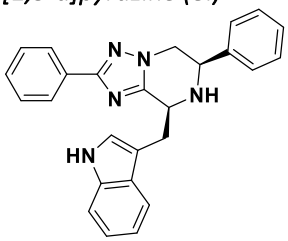
(6R,8S)-8-isopropyl-2,6-diphenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (8h)

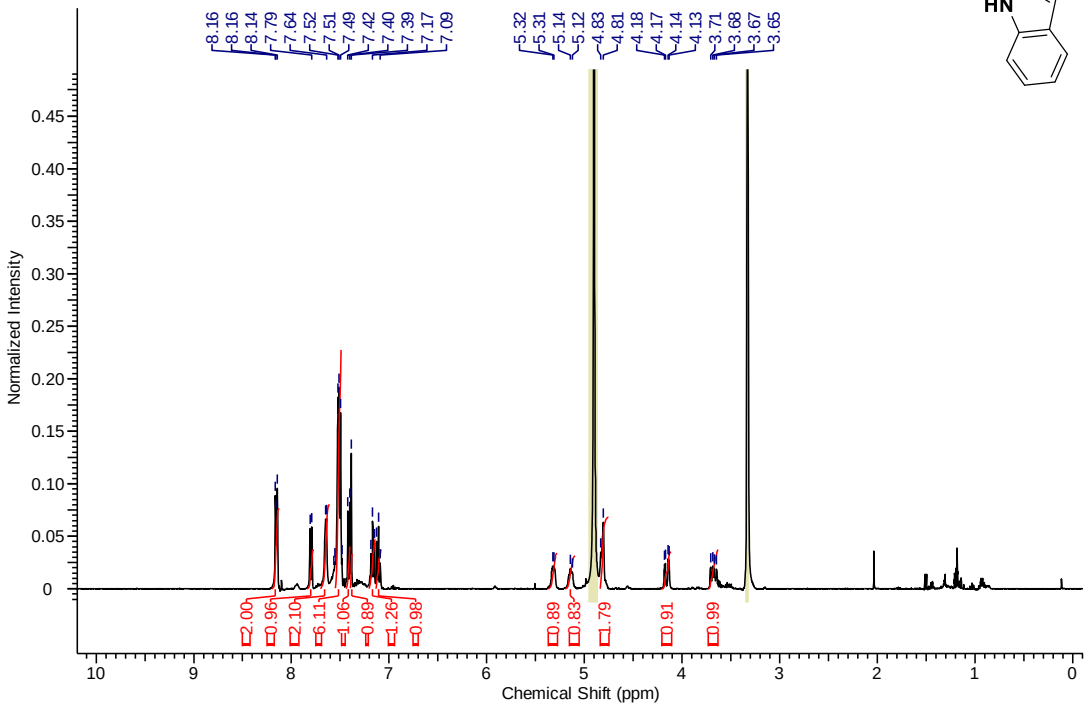


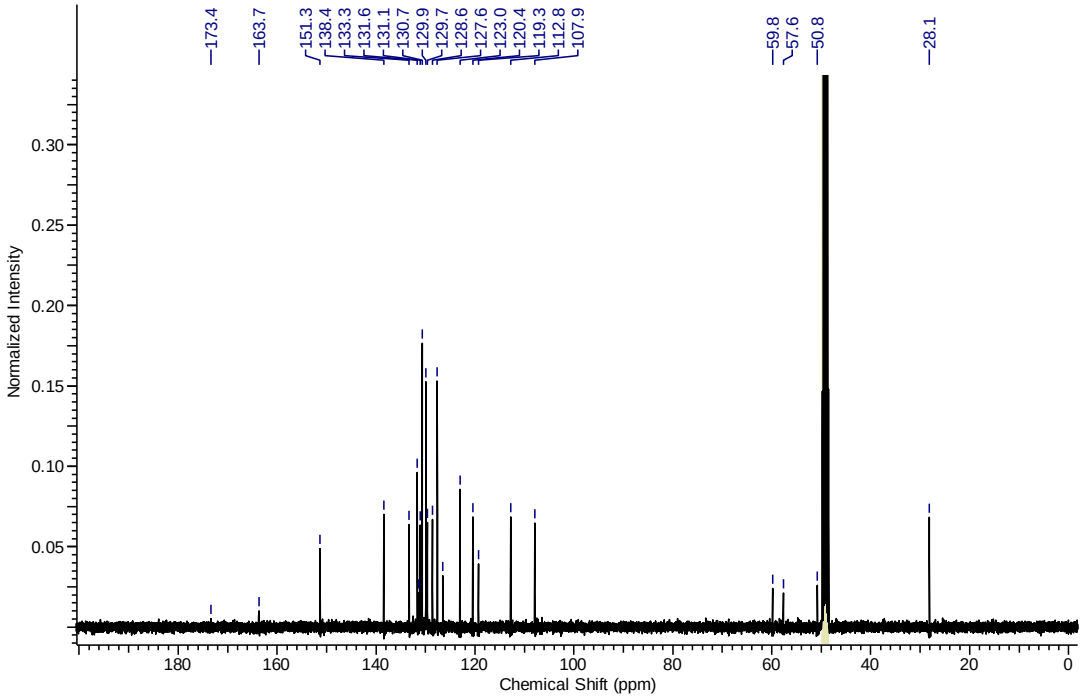




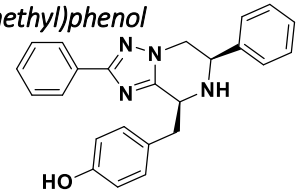
(6R,8S)-8-((1H-indol-3-yl)methyl)-2,6-diphenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (8i)

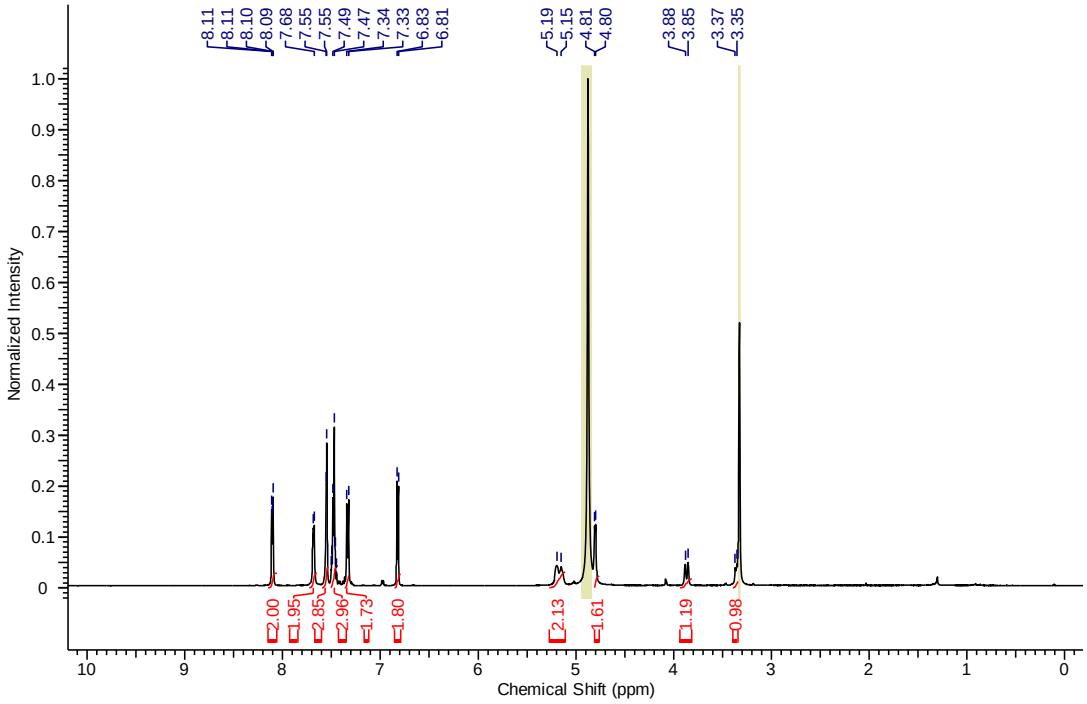


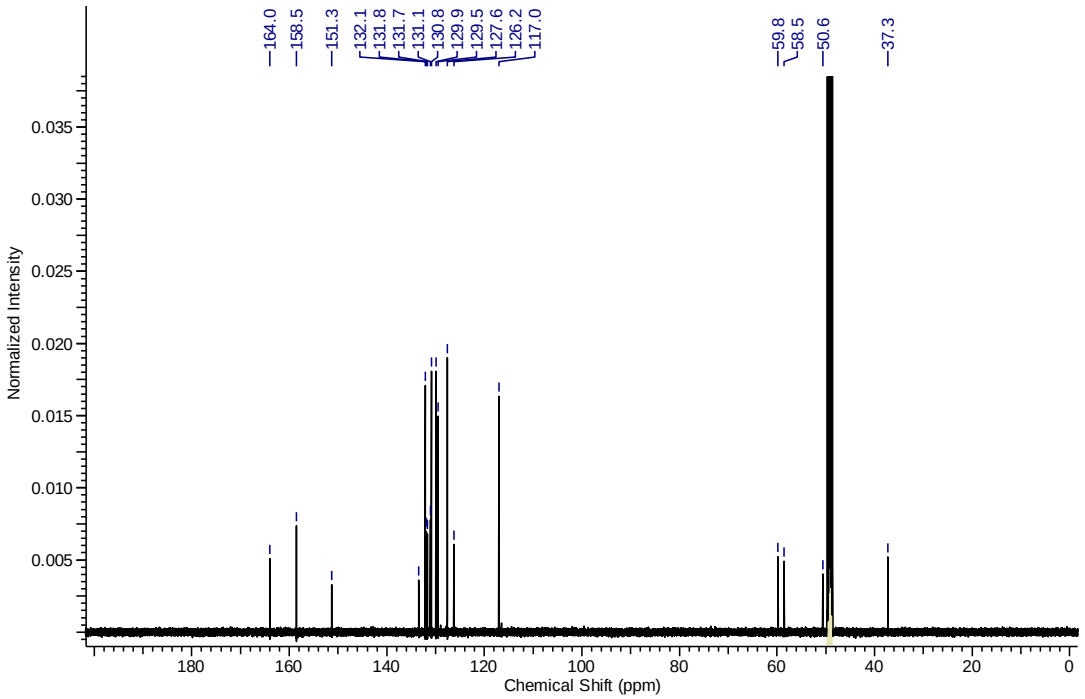




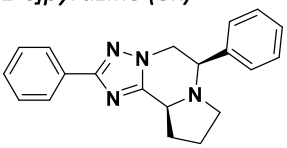
4-(((6R,8S)-2,6-diphenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazin-8-yl)methyl)phenol (8j)

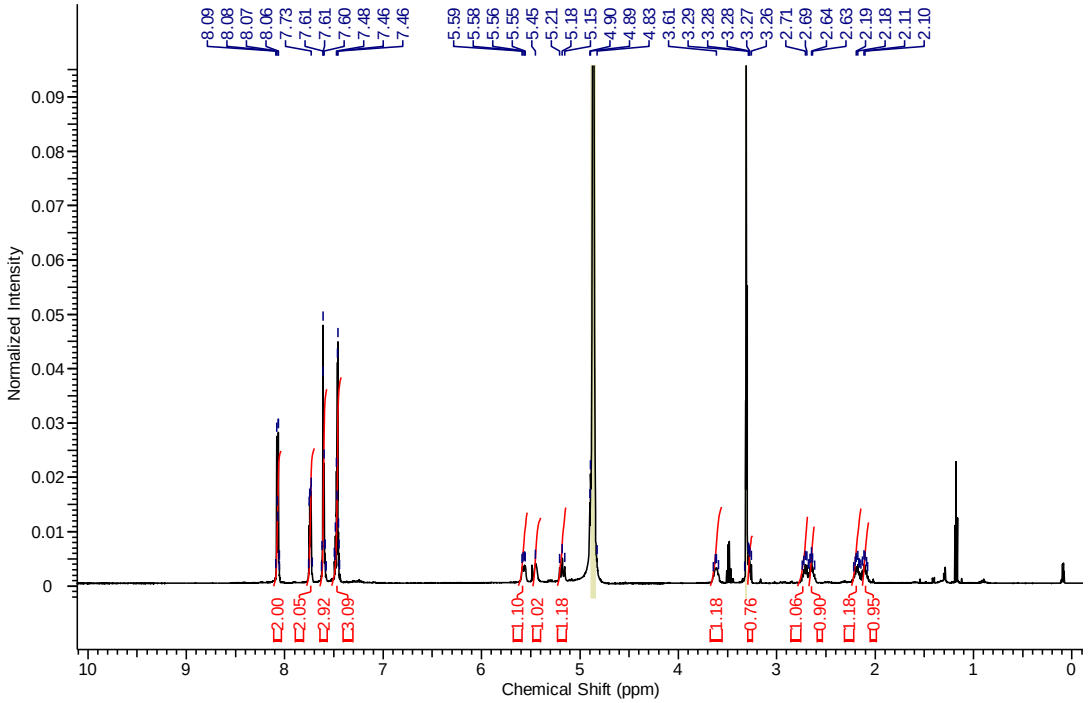


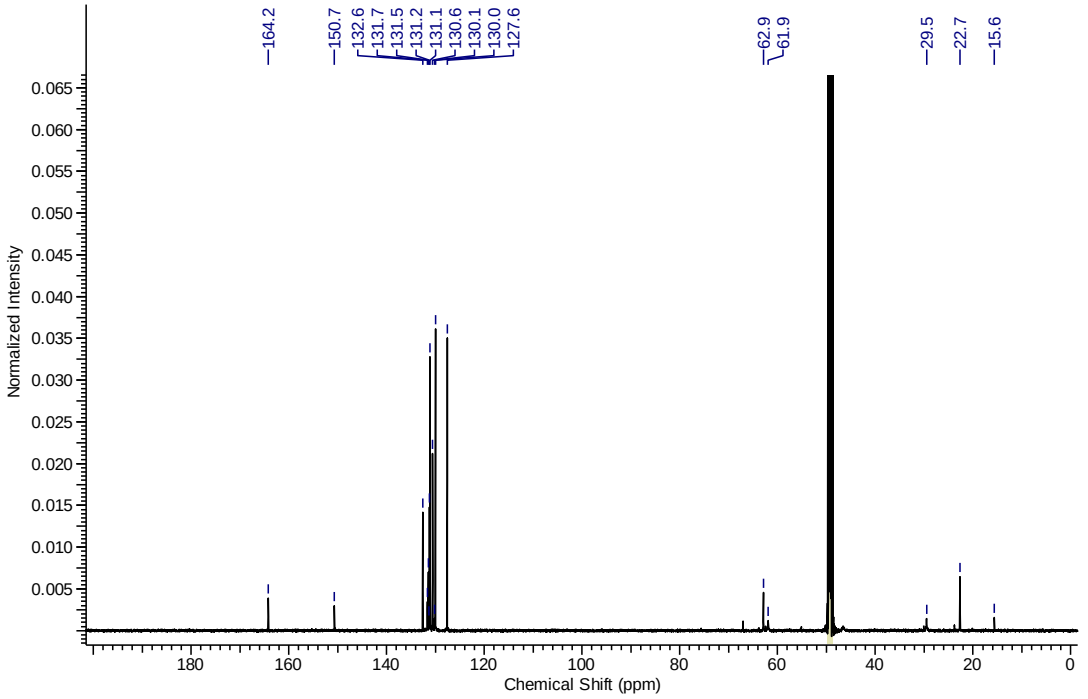




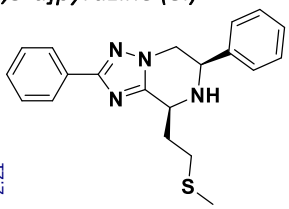
(6R,10aS)-2,6-diphenyl-5,6,8,9,10,10a-hexahydropyrrolo[1,2-a][1,2,4]triazolo[5,1-c]pyrazine (8k)

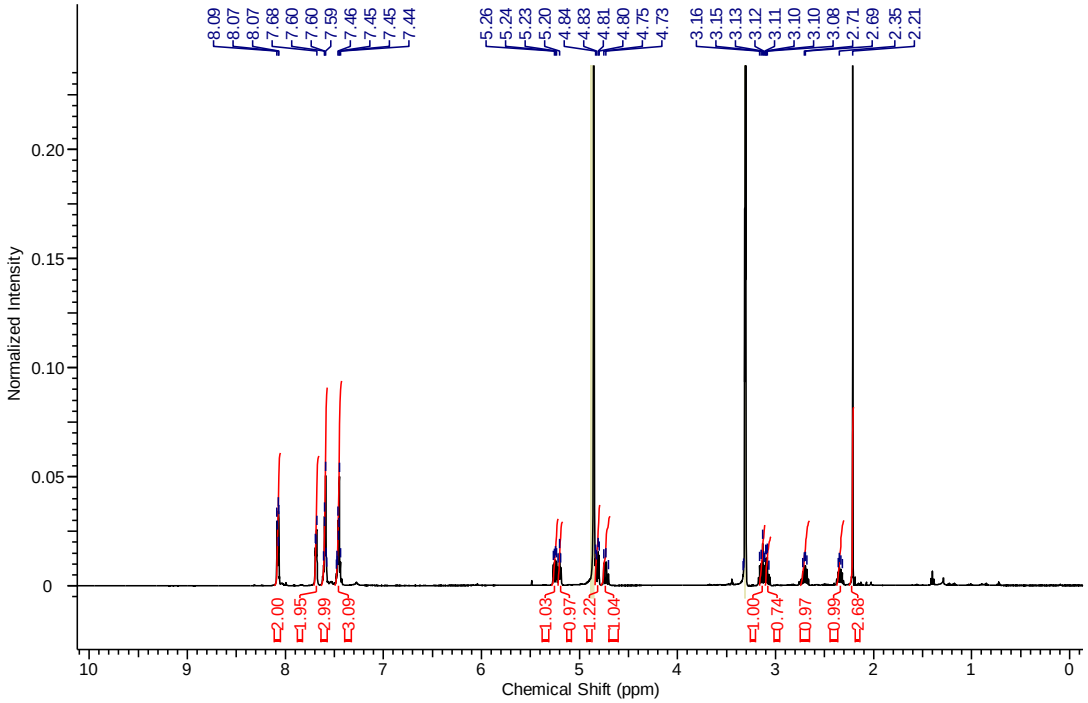


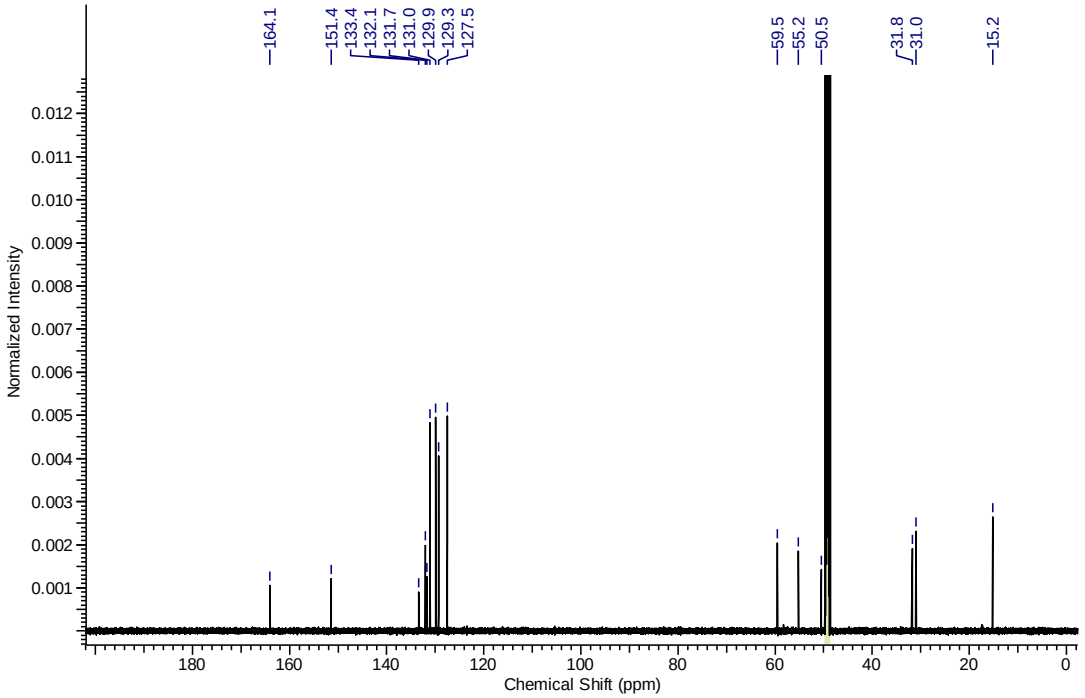




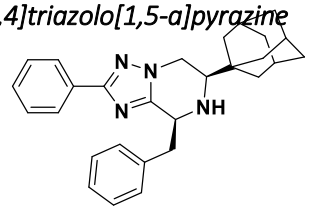
(6R,8S)-8-(2-(methylthio)ethyl)-2,6-diphenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (8l)

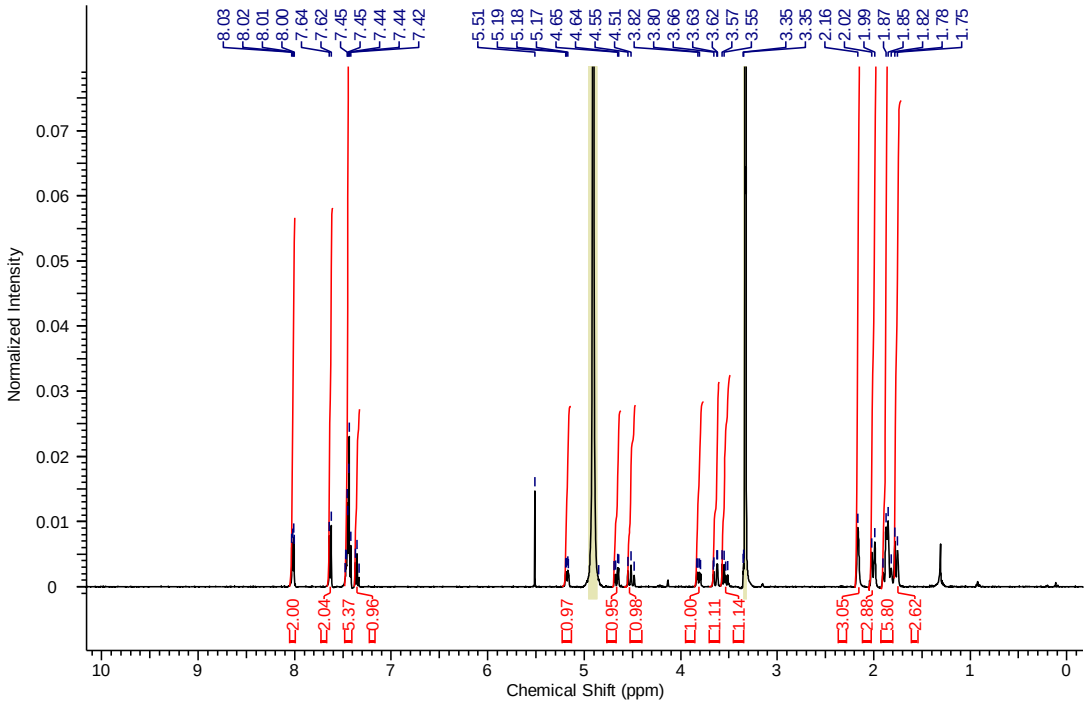


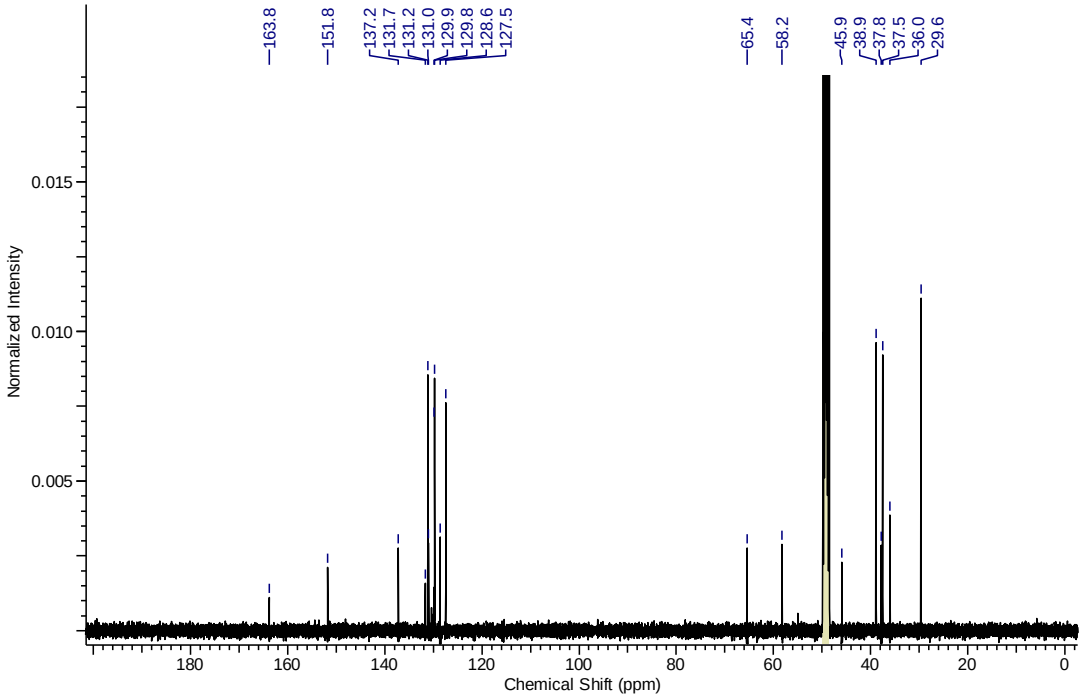




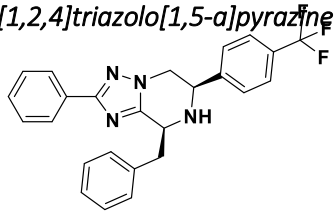
(6R,8S)-6-((1r,3R)-adamantan-1-yl)-8-benzyl-2-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (8m)

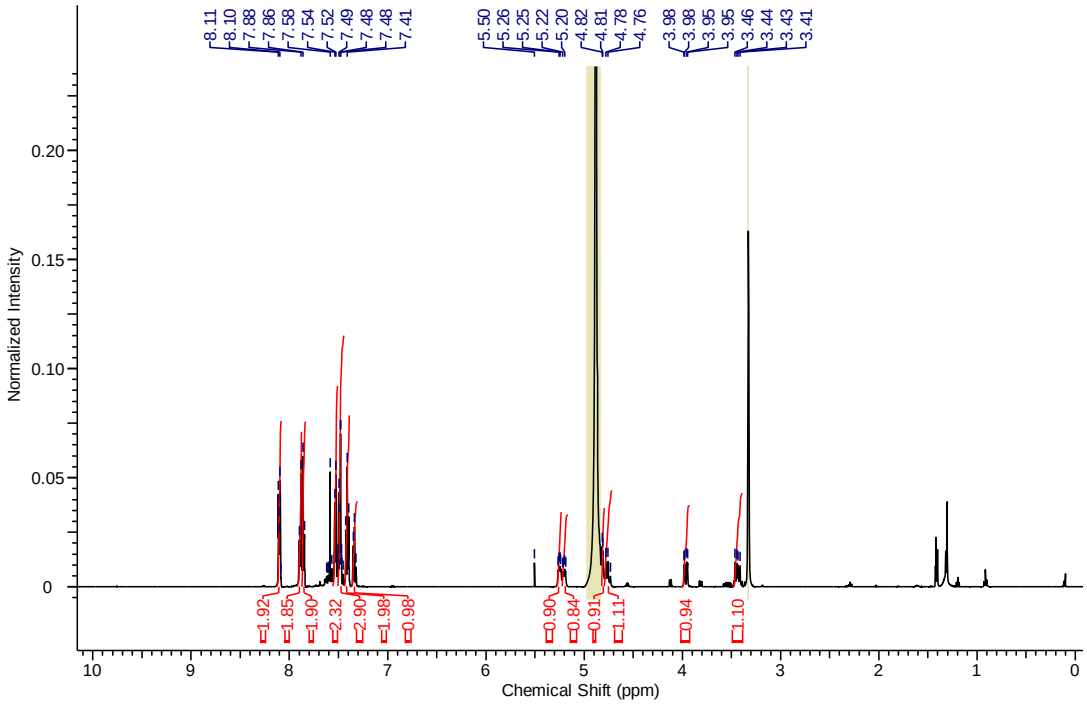


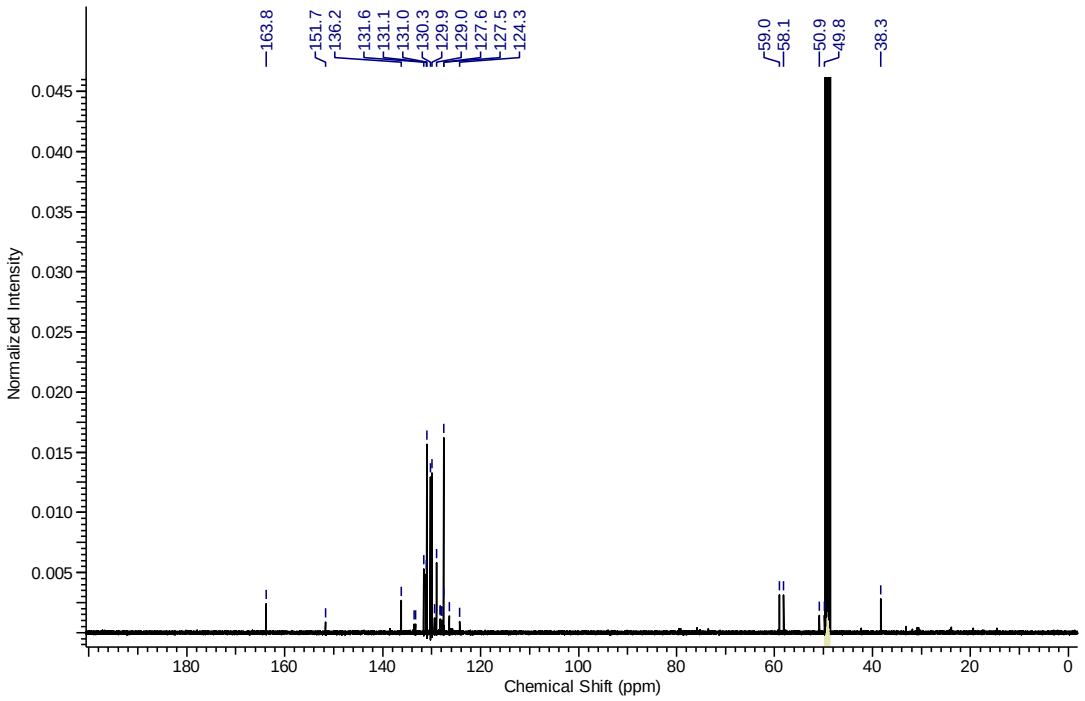




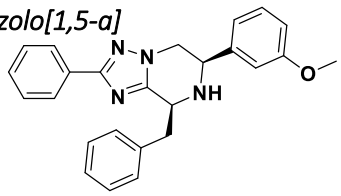
(6R,8S)-8-benzyl-2-phenyl-6-(4-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (8n)

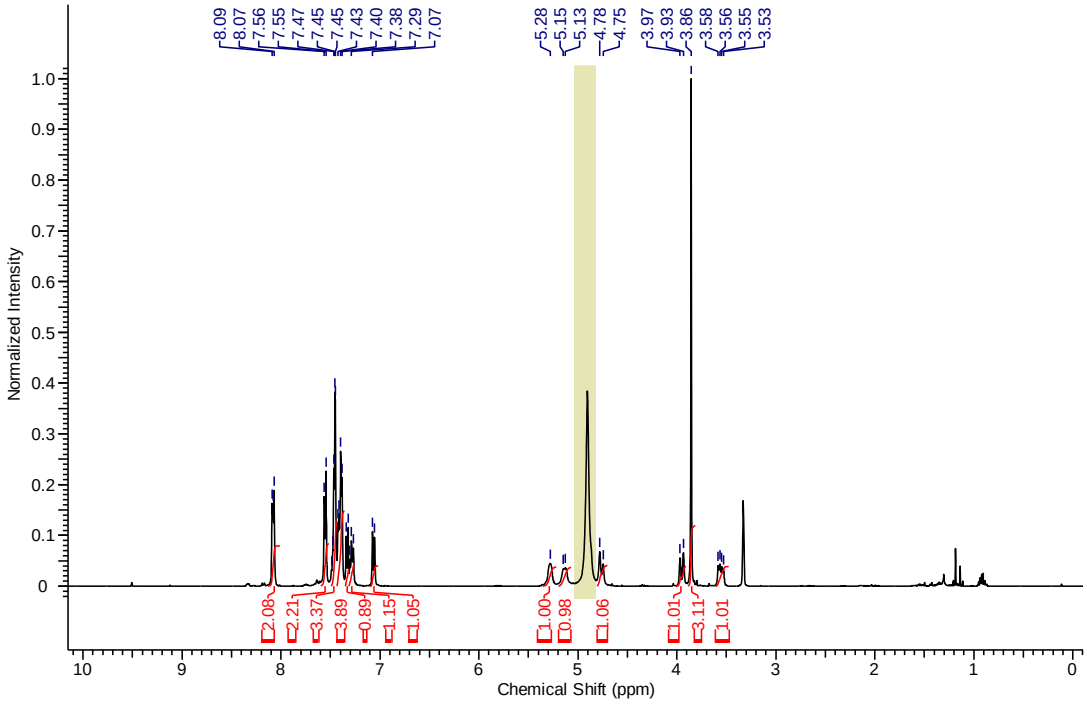


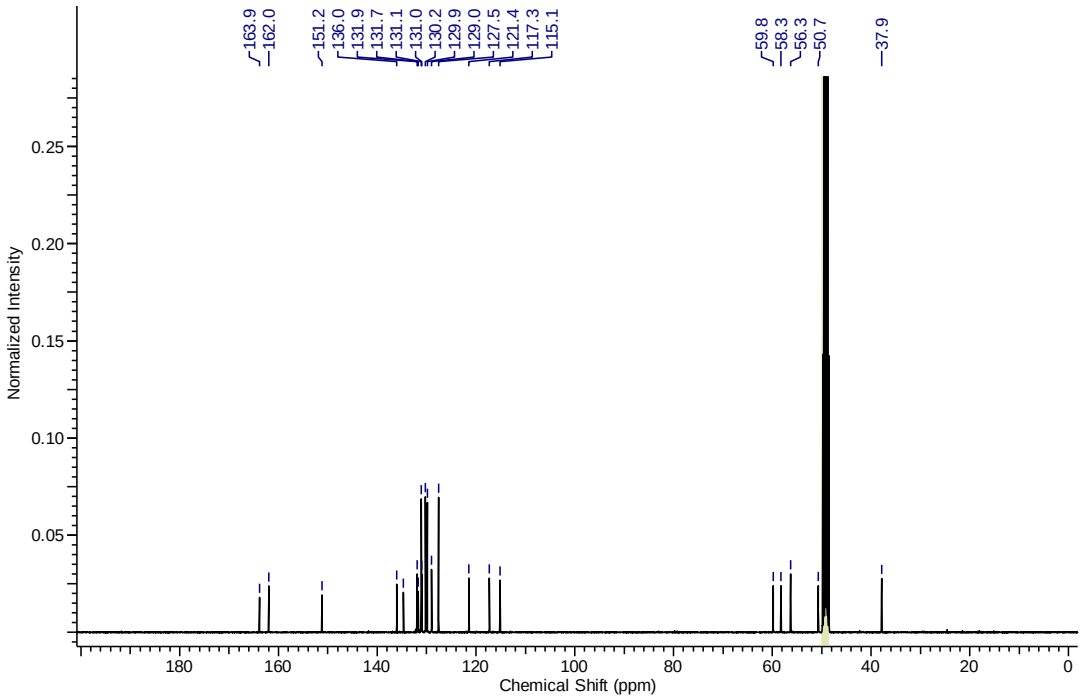




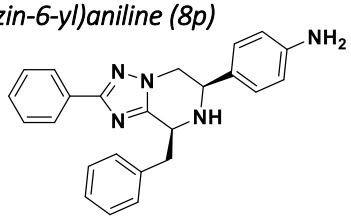
(6R,8S)-8-benzyl-6-(3-methoxyphenyl)-2-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]
Pyrazine (8o)

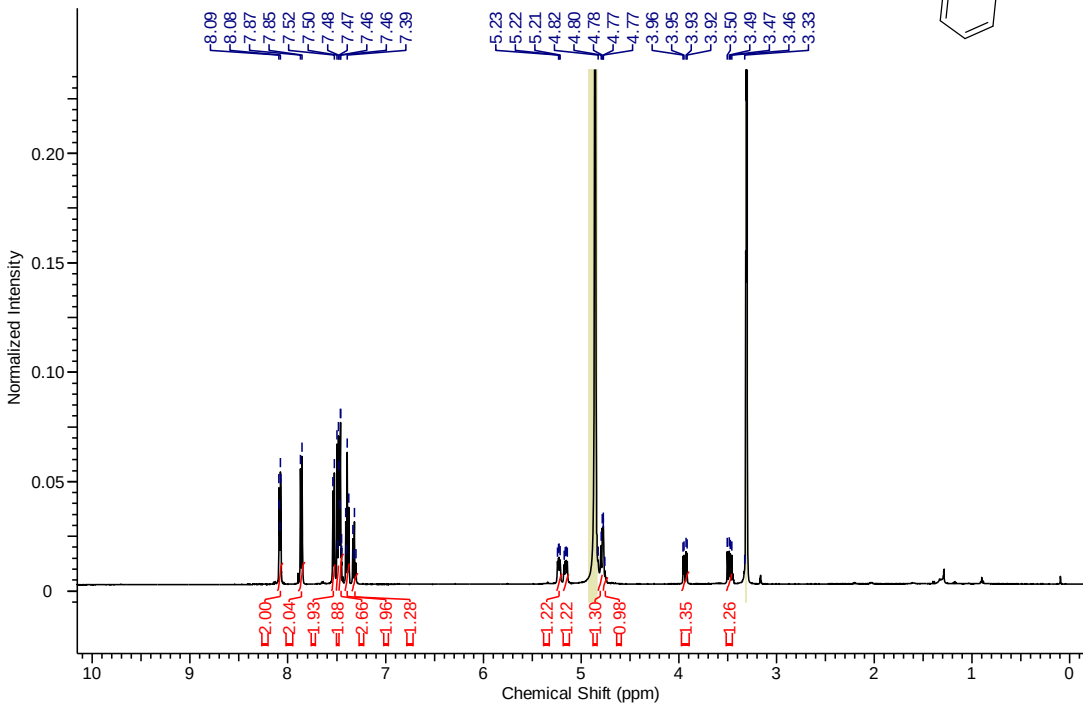


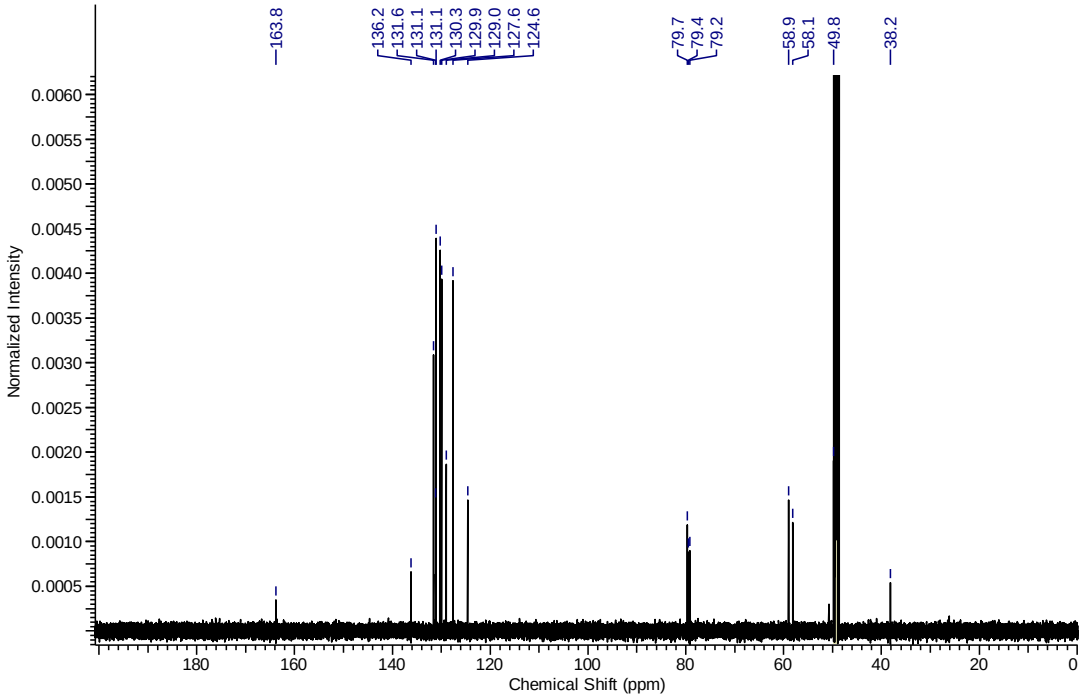




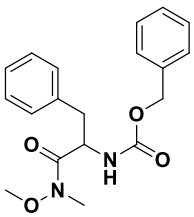
4-((6R,8S)-8-benzyl-2-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazin-6-yl)aniline (8p)

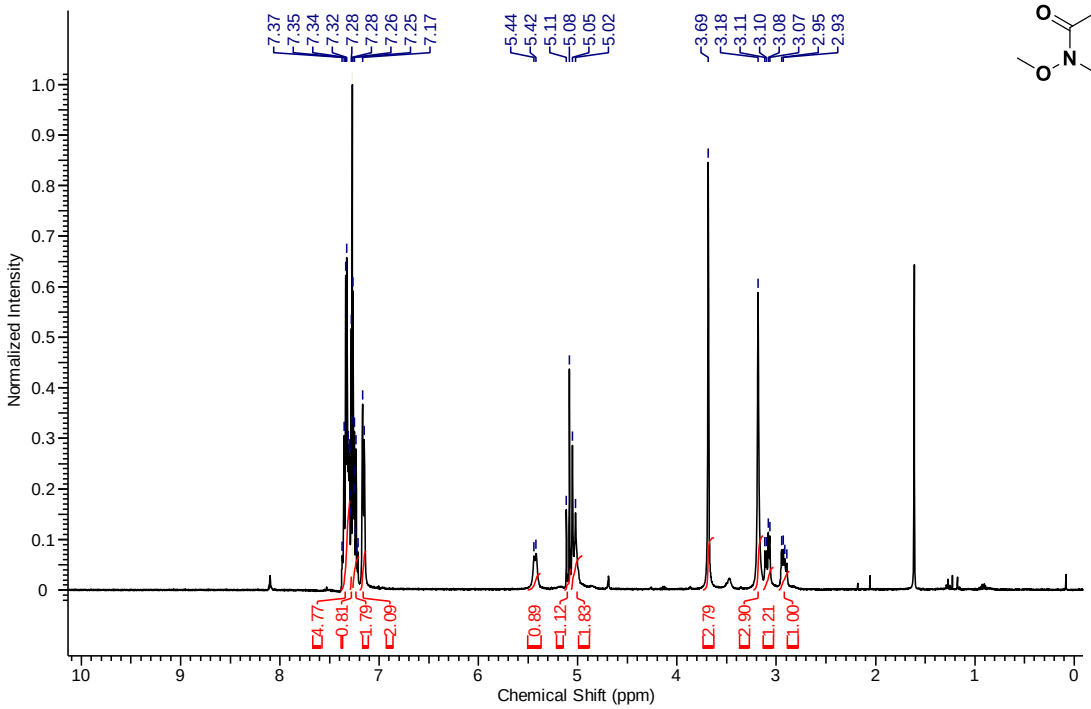


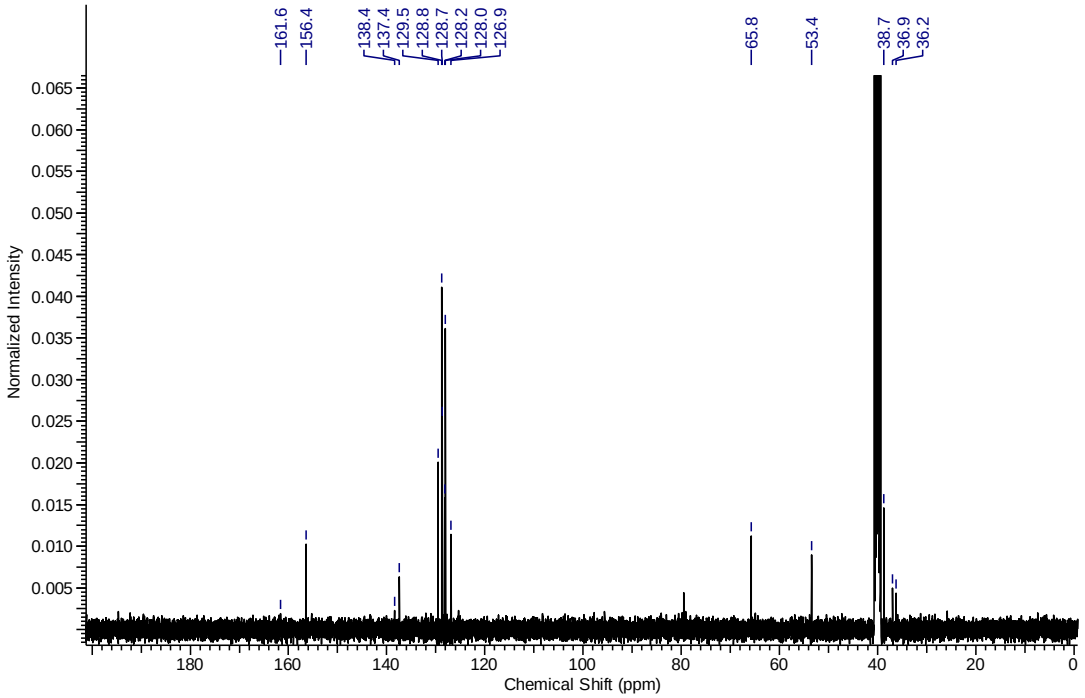




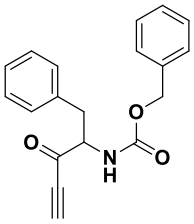
Benzyl (1-(methoxy(methyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (9a)

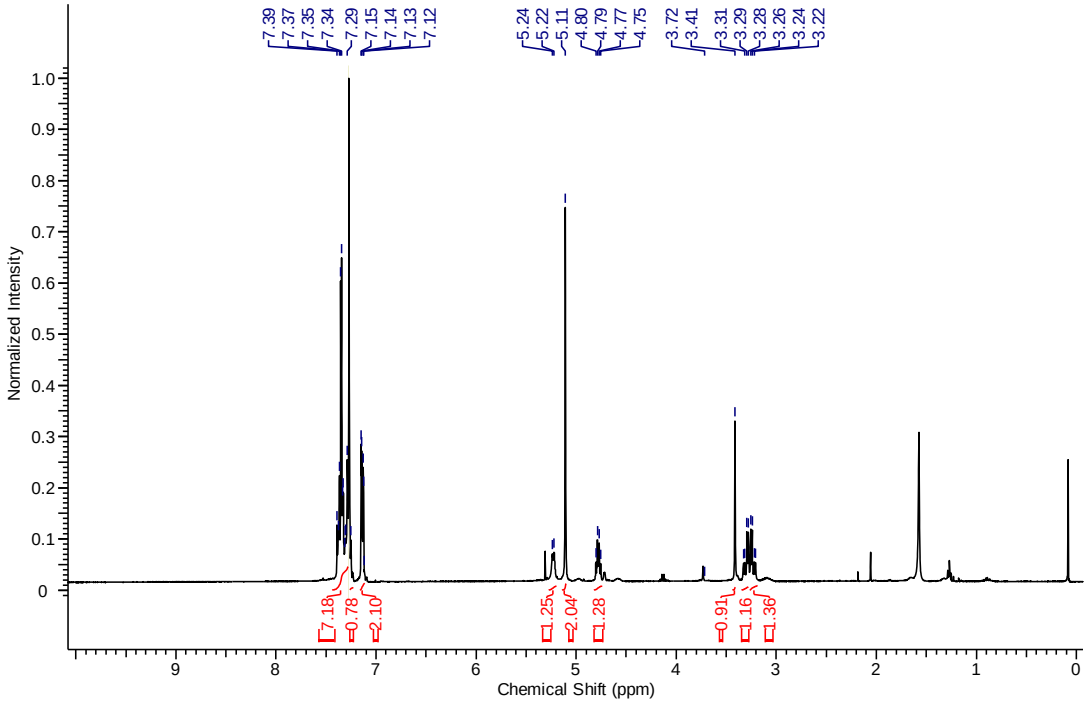


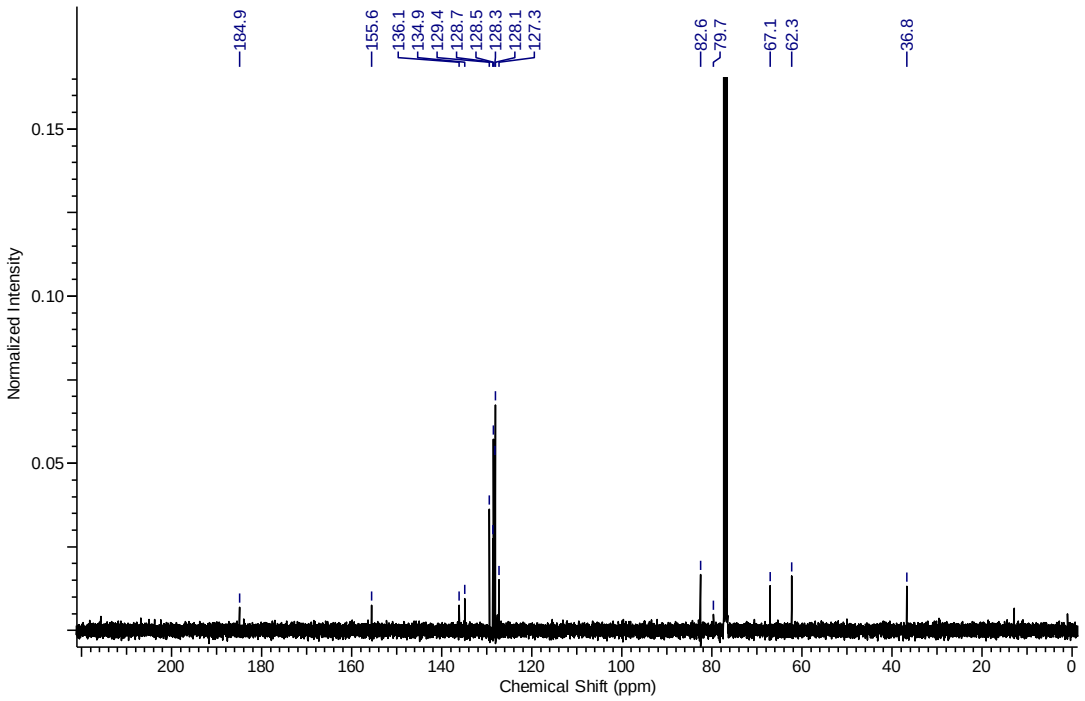




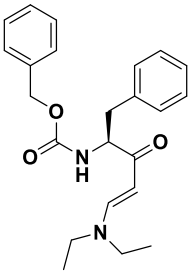
Benzyl (3-oxo-1-phenylpent-4-yn-2-yl)carbamate (9b)

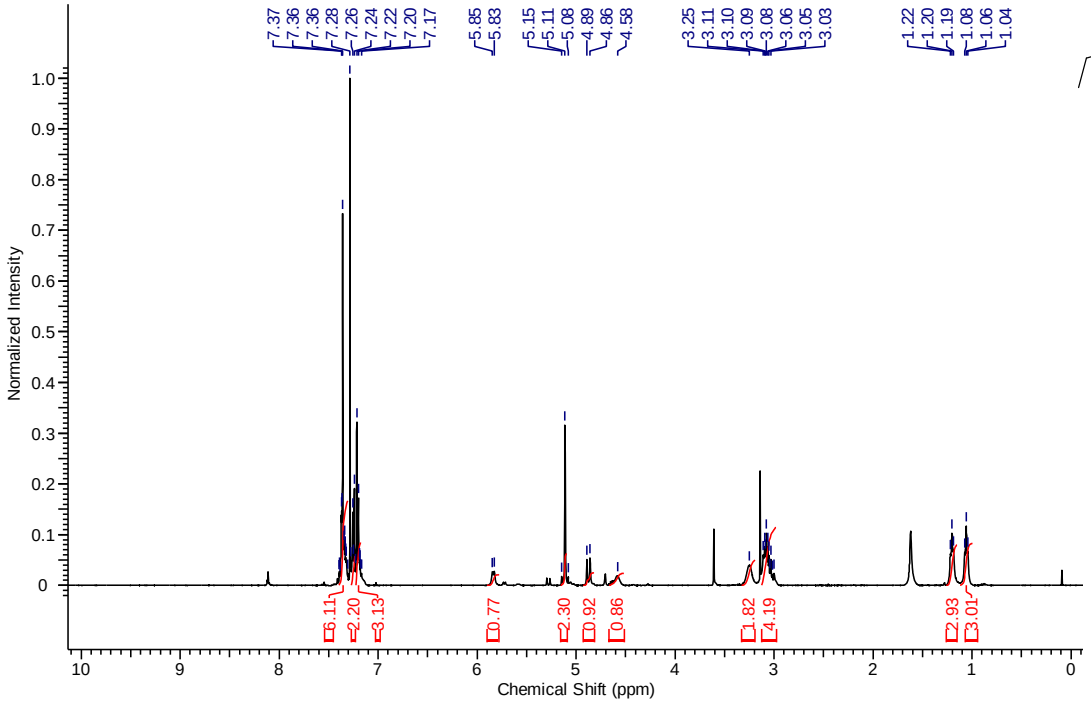


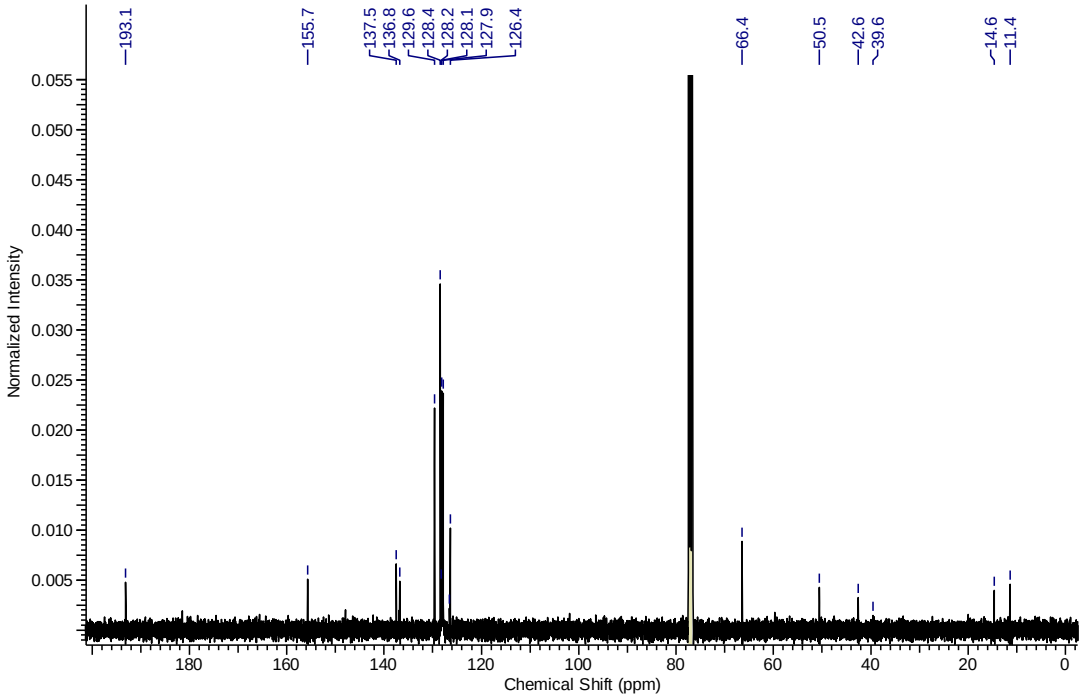




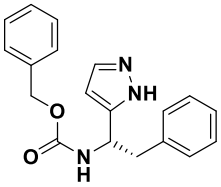
Benzyl (S)-(5-(diethylamino)-3-oxo-1-phenylpent-4-en-2-yl)carbamate (9c)

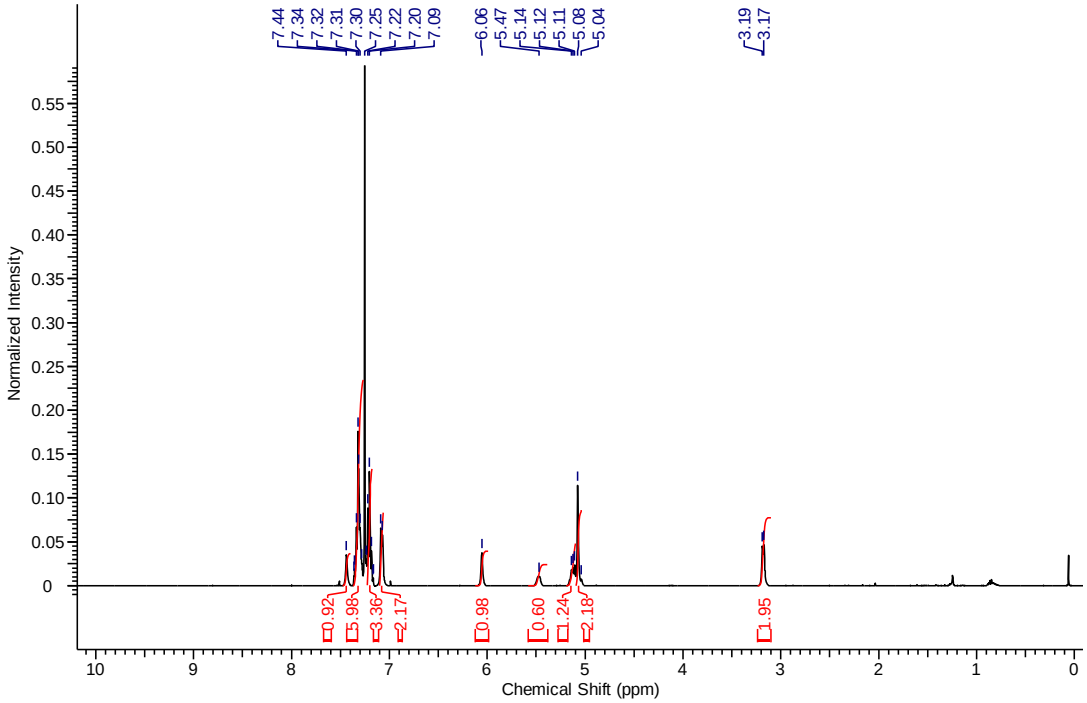


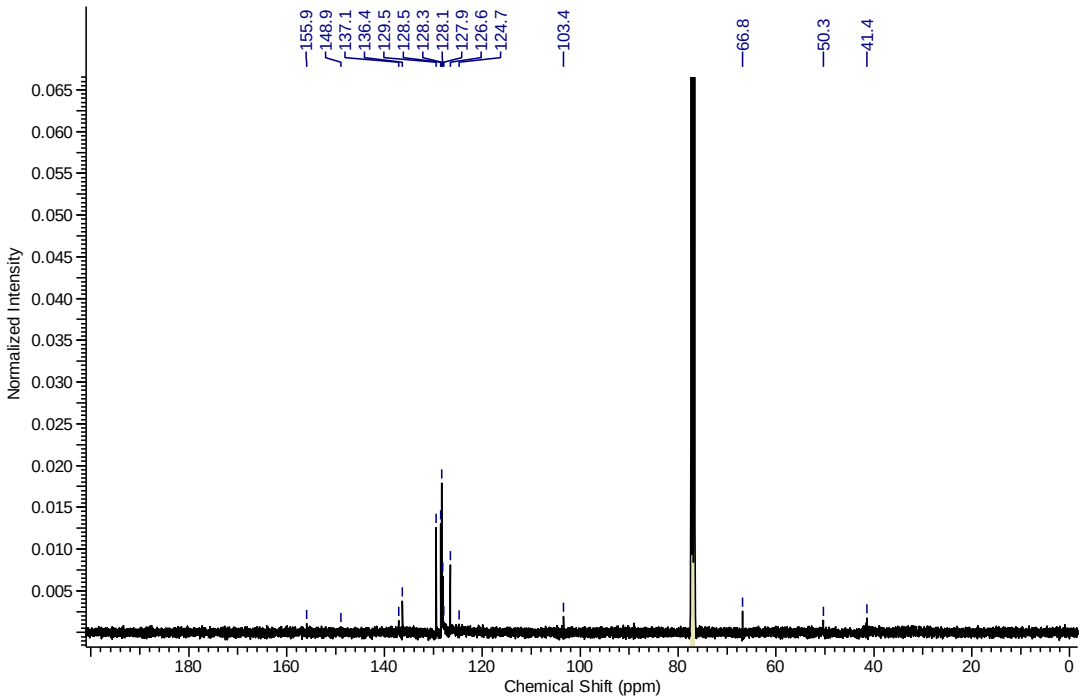




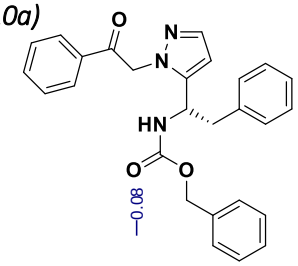
Benzyl (S)-(2-phenyl-1-(1H-pyrazol-5-yl)ethyl)carbamate (9)

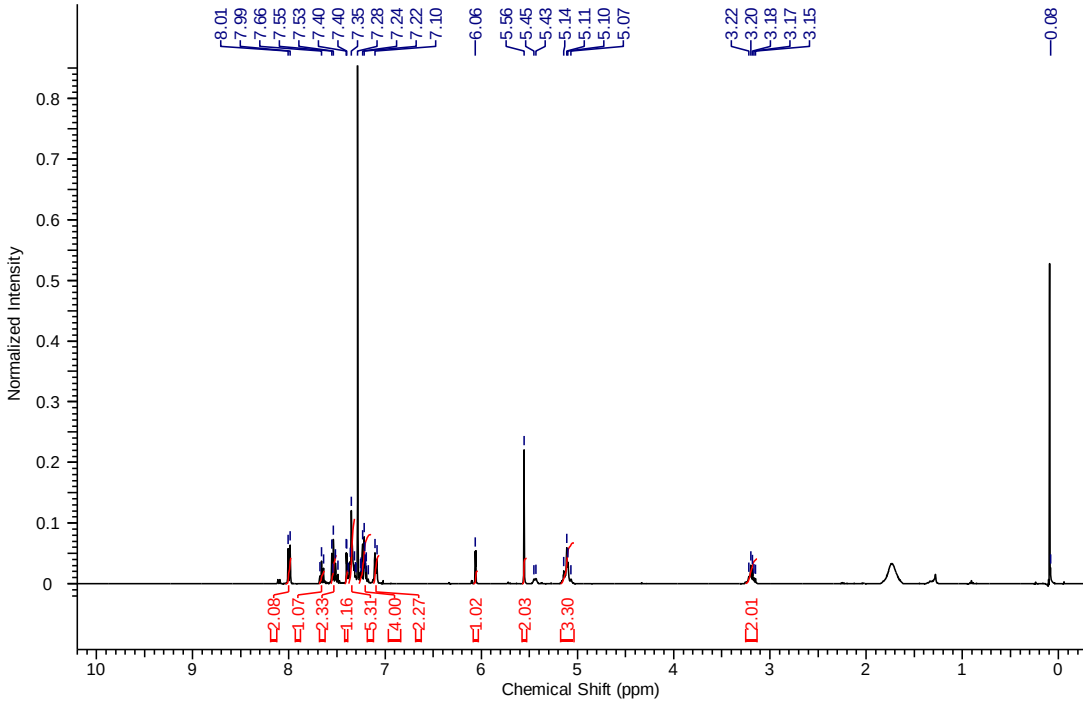


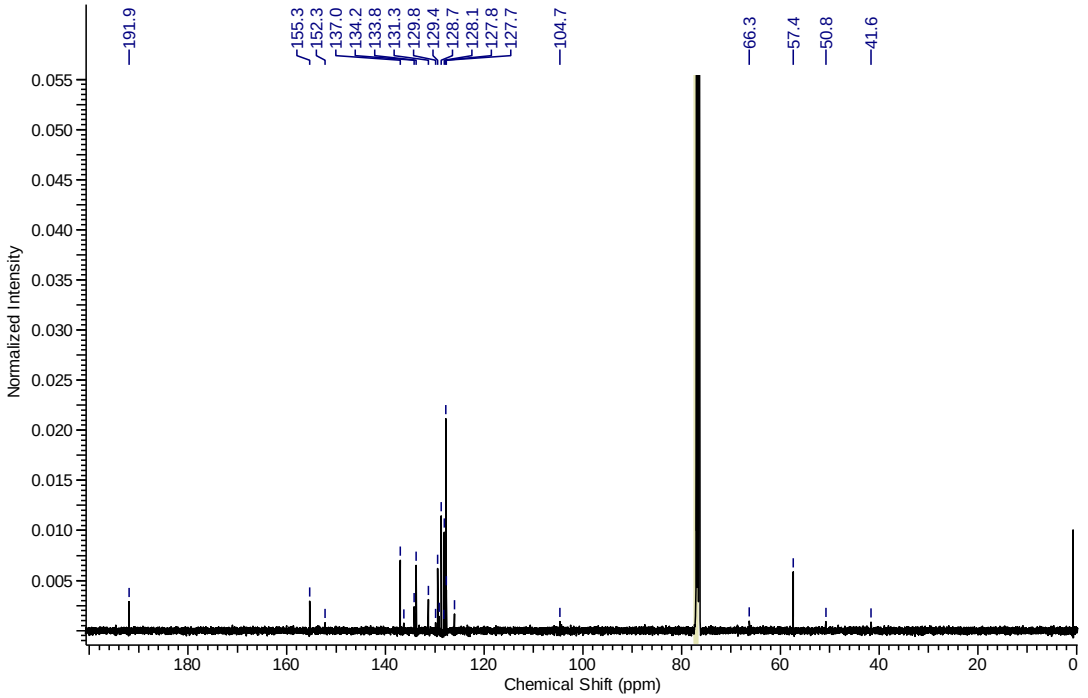




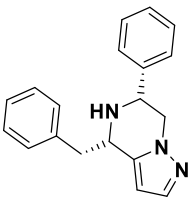
Benzyl (1-(1-(2-oxo-2-phenylethyl)-1H-pyrazol-5-yl)-2-phenylethyl)carbamate (10a)

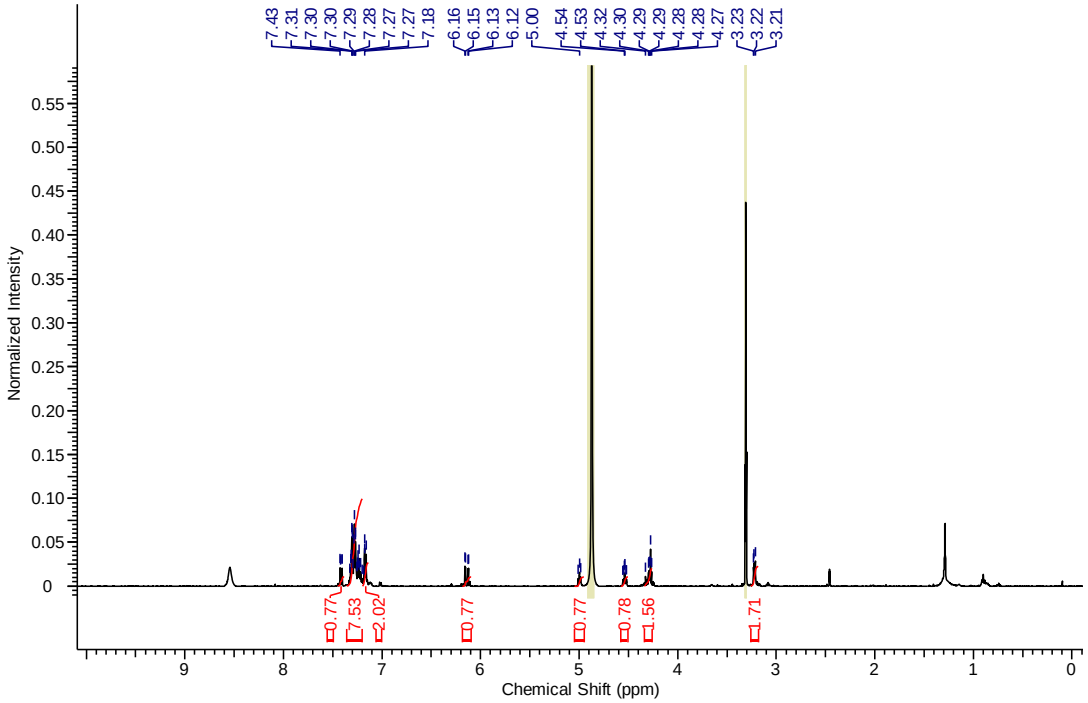


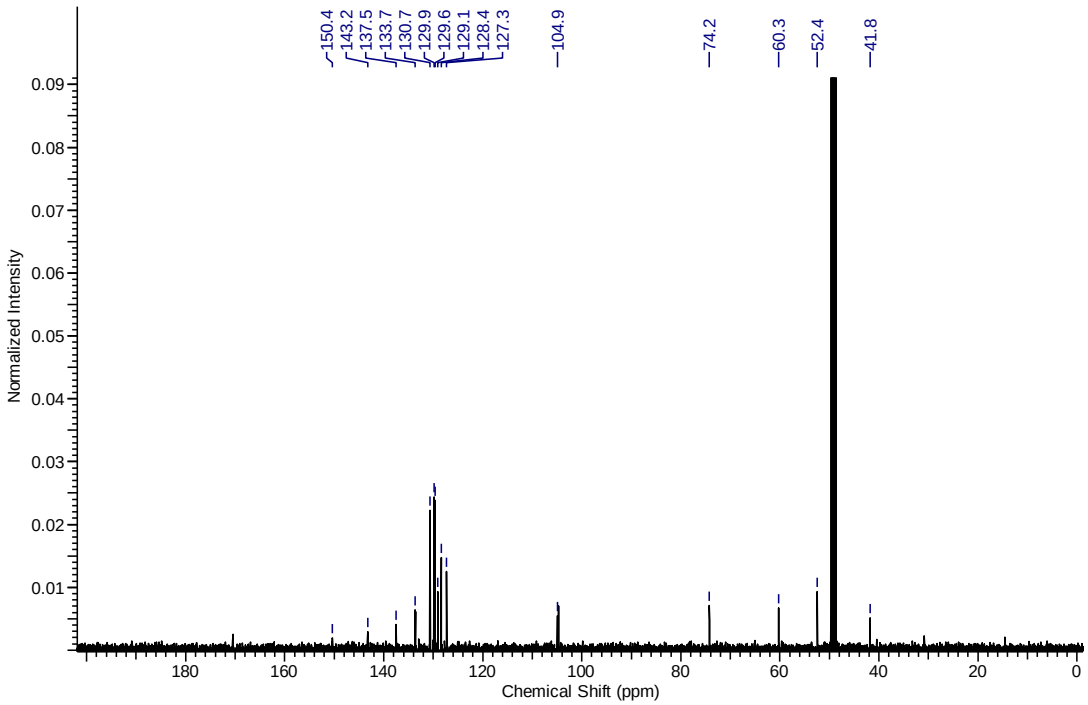




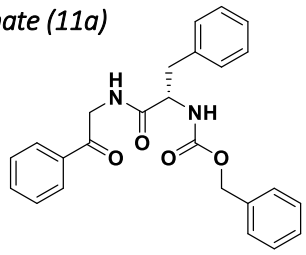
(4S,6R)-4-benzyl-6-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine (10)

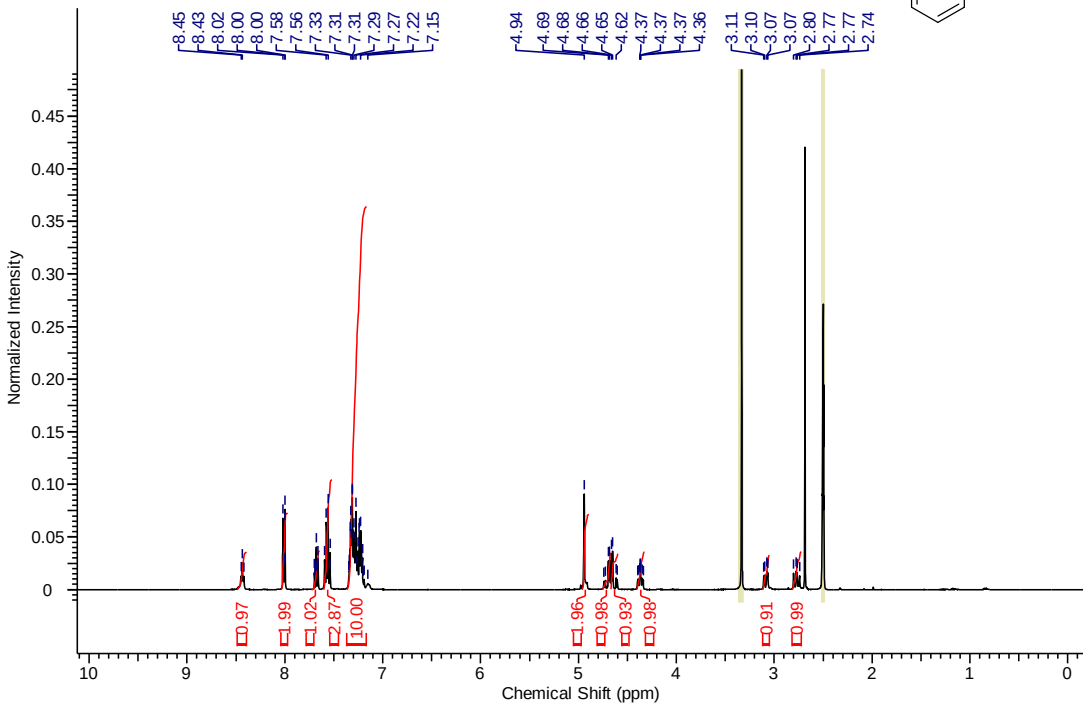


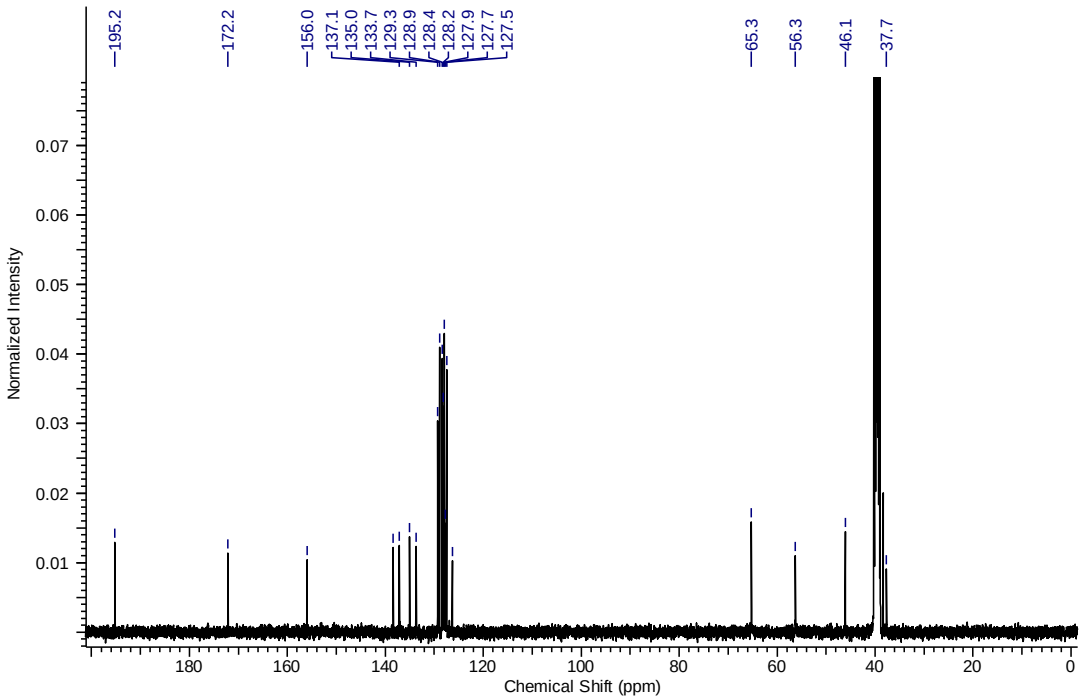




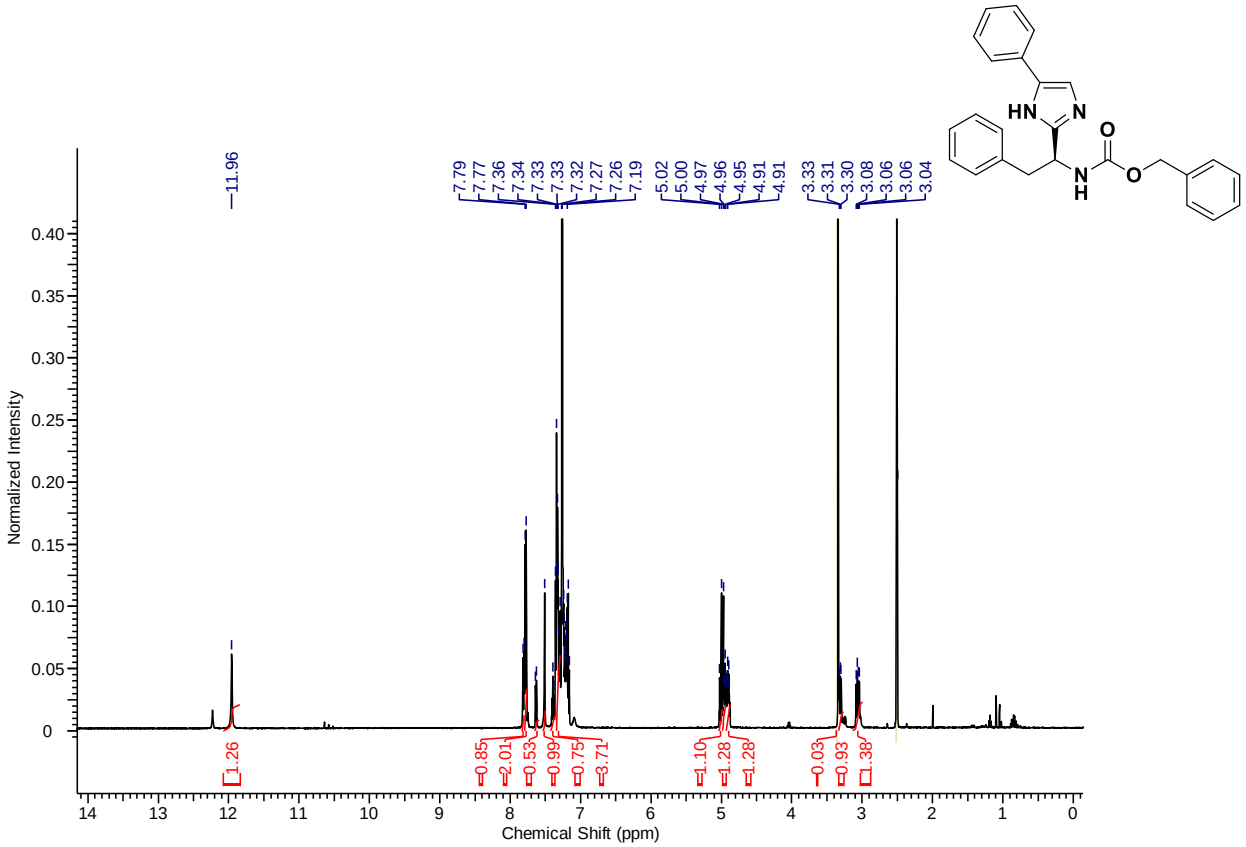
Benzyl (S)-(1-oxo-1-((2-oxo-2-phenylethyl)amino)-3-phenylpropan-2-yl)carbamate (11a)

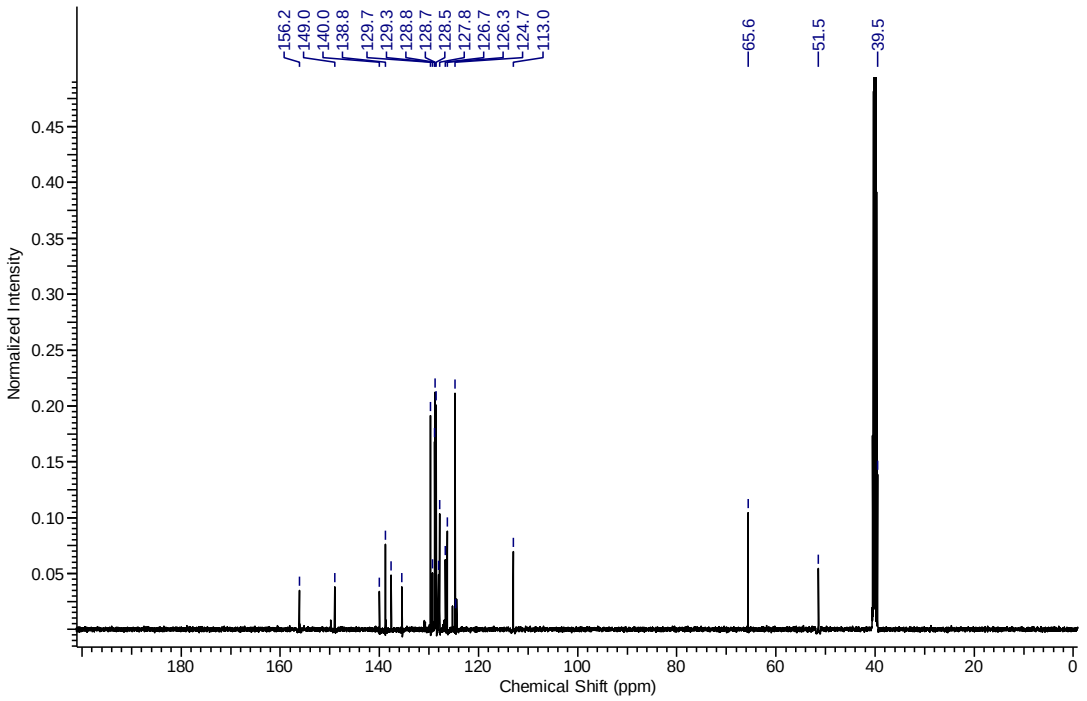




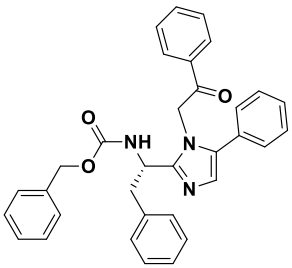


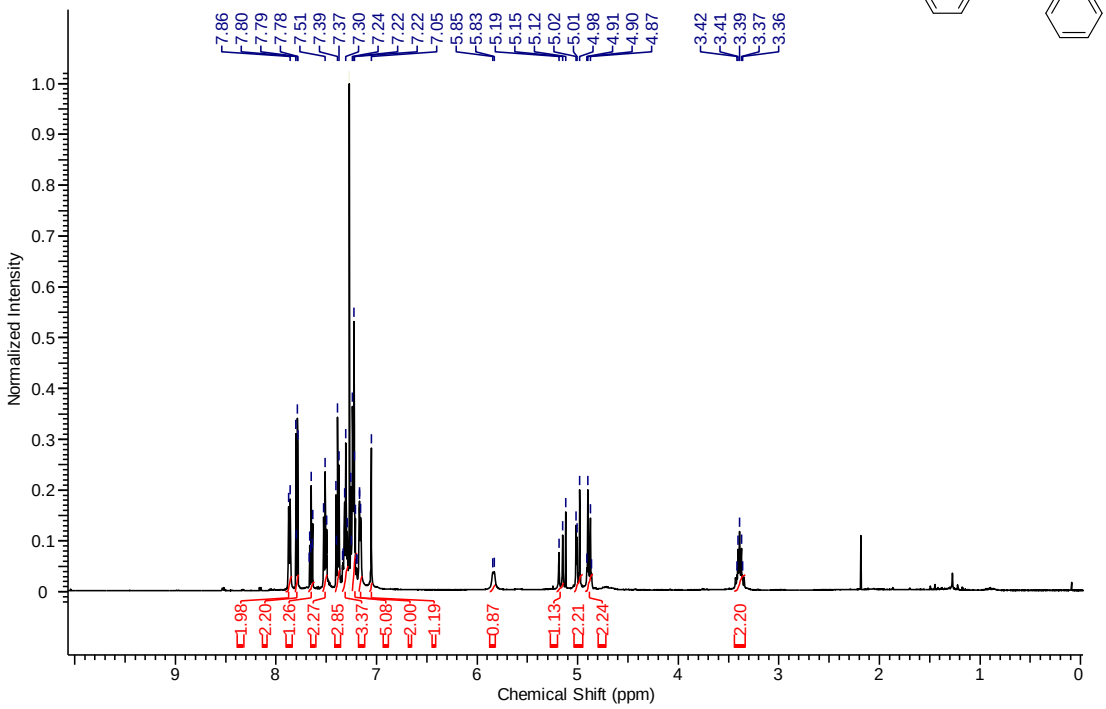
Benzyl (S)-(2-phenyl-1-(5-phenyl-1H-imidazol-2-yl)ethyl)carbamate (11)

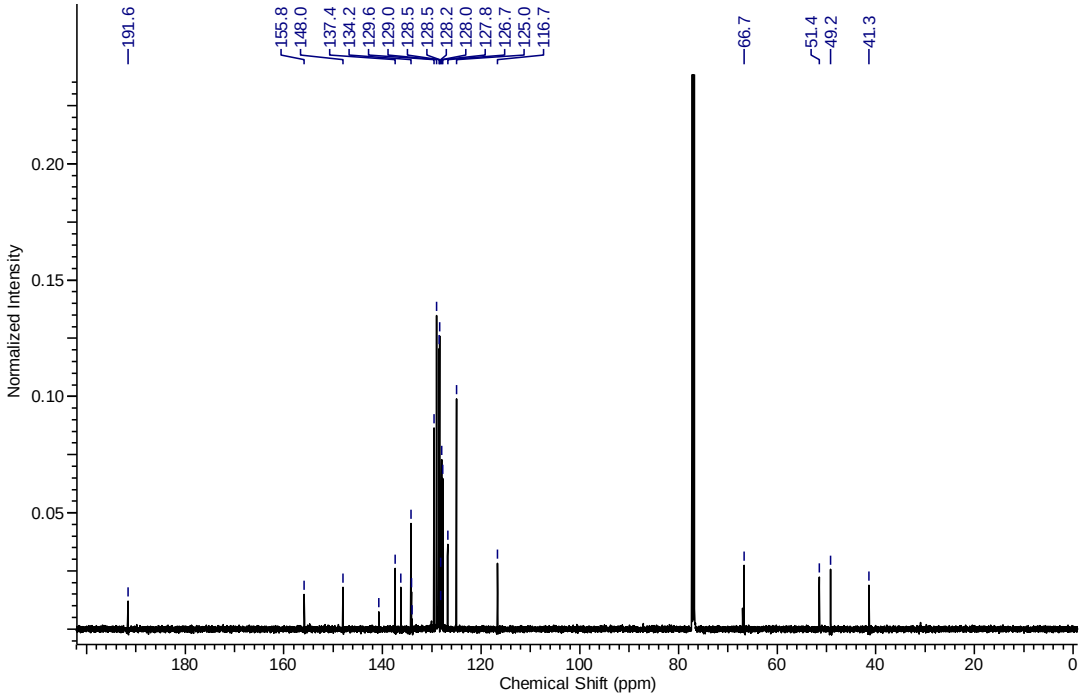




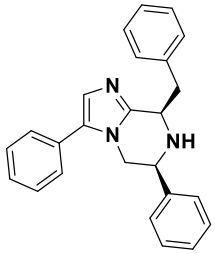
Benzyl (S)-(1-(1-(2-oxo-2-phenylethyl)-5-phenyl-1H-imidazol-2-yl)-2phenylethyl) Carbamate (12a)

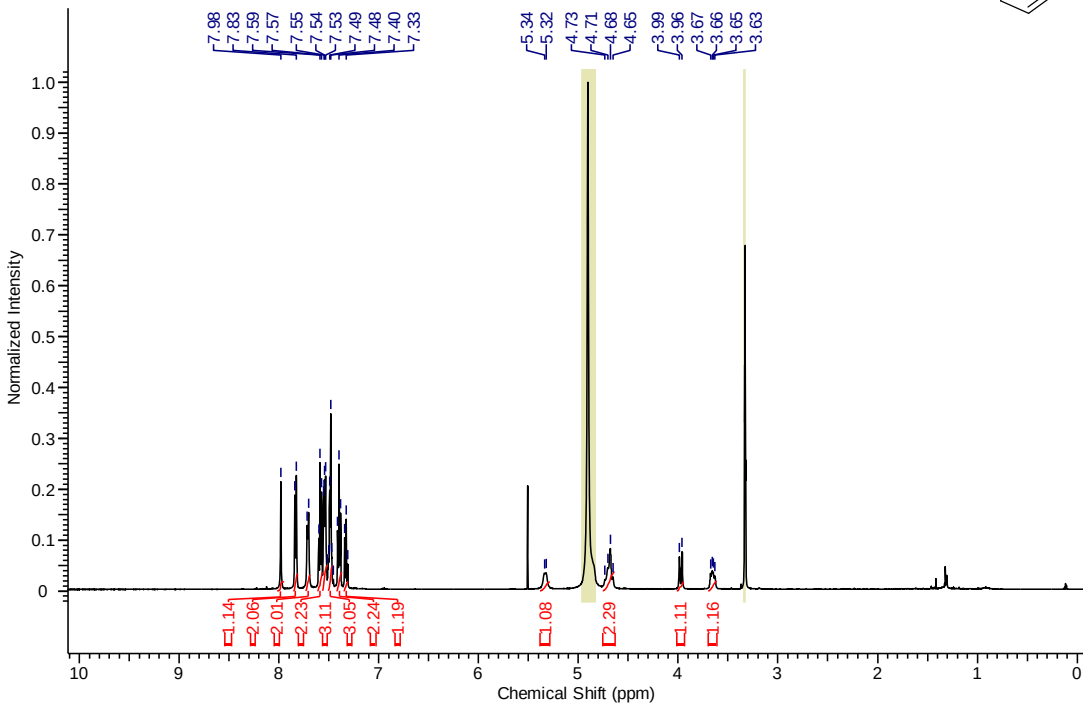


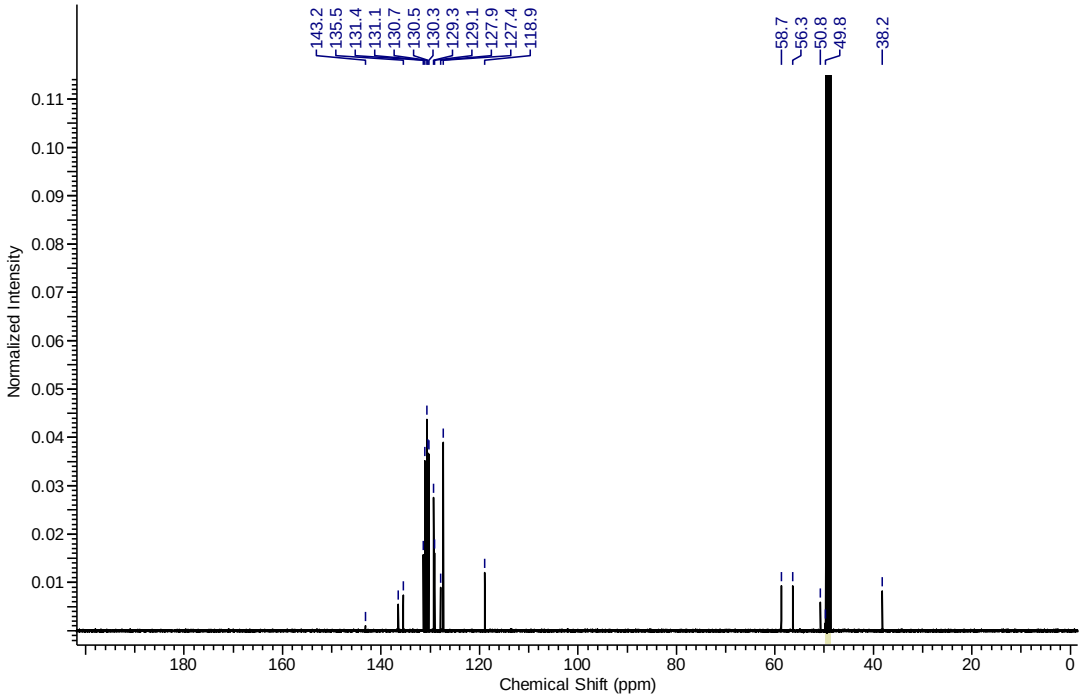




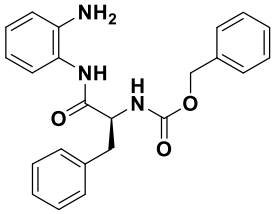
(6S,8R)-8-benzyl-3,6-diphenyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine (12)

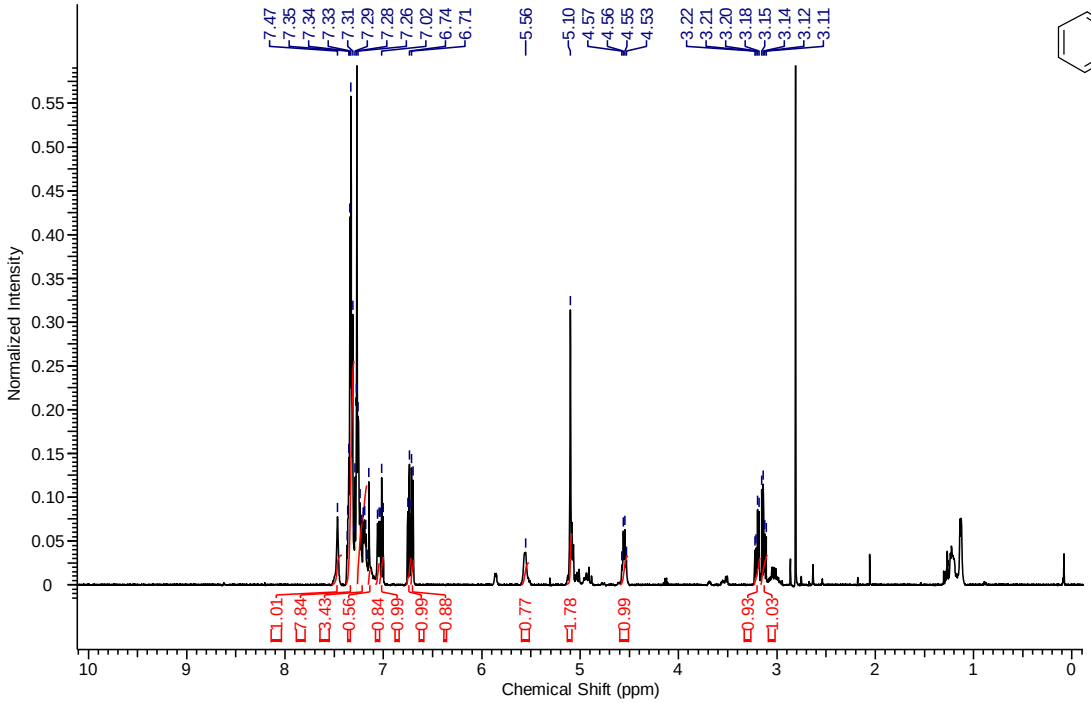


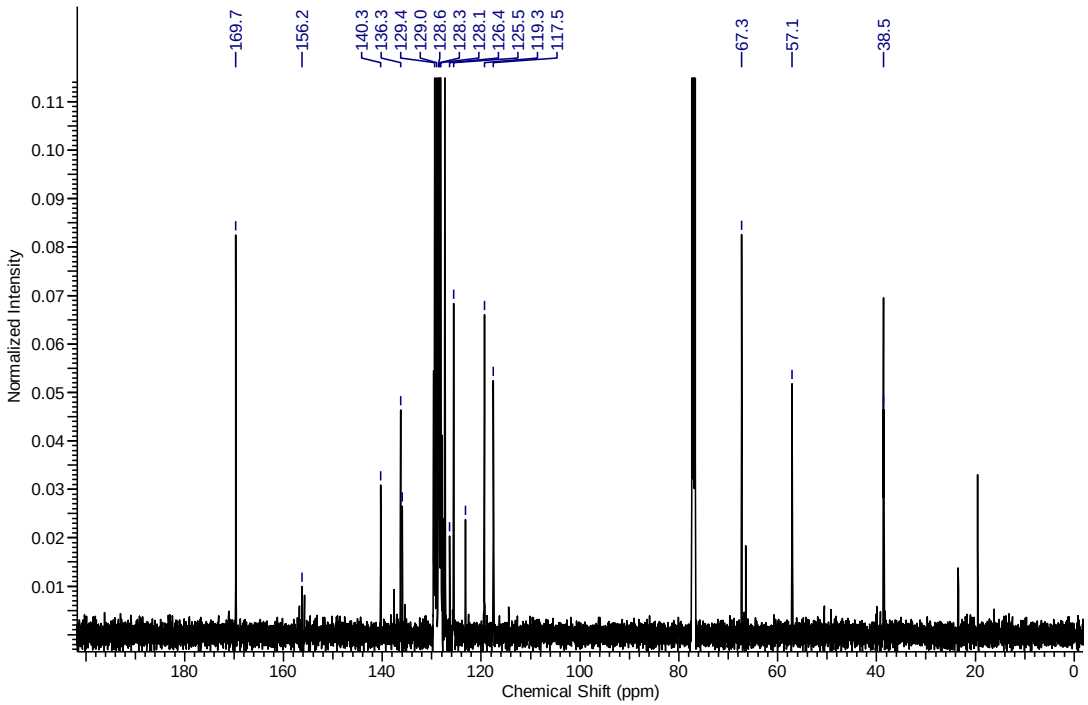




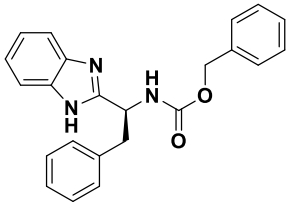
Benzyl (1-((2-aminophenyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (13a)

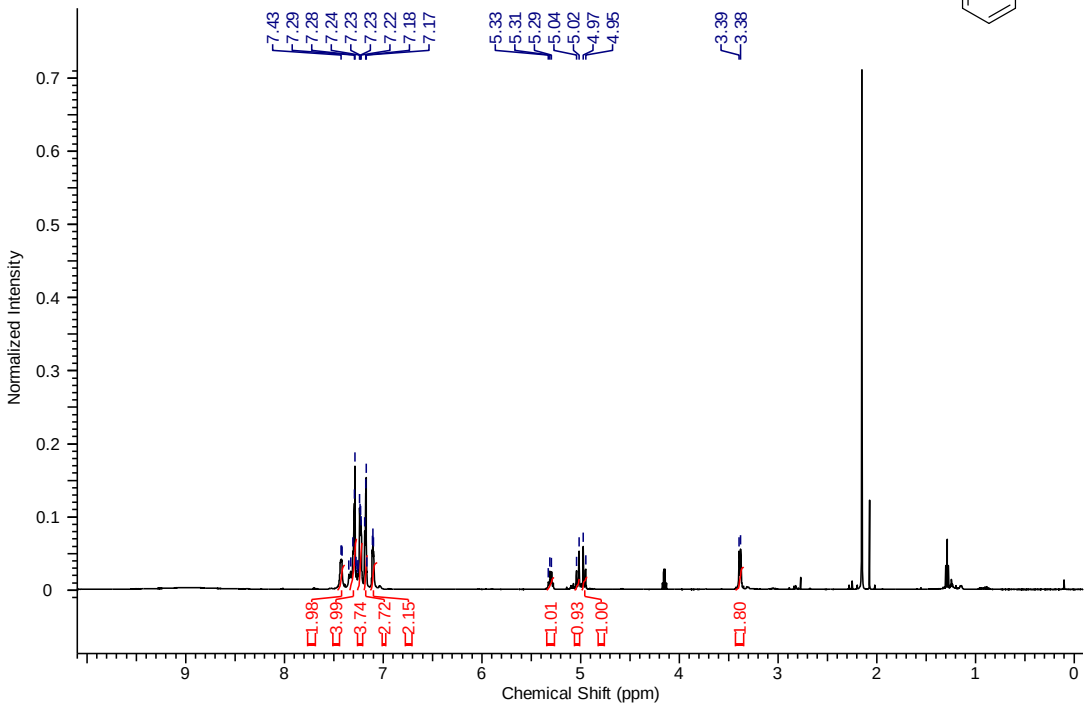


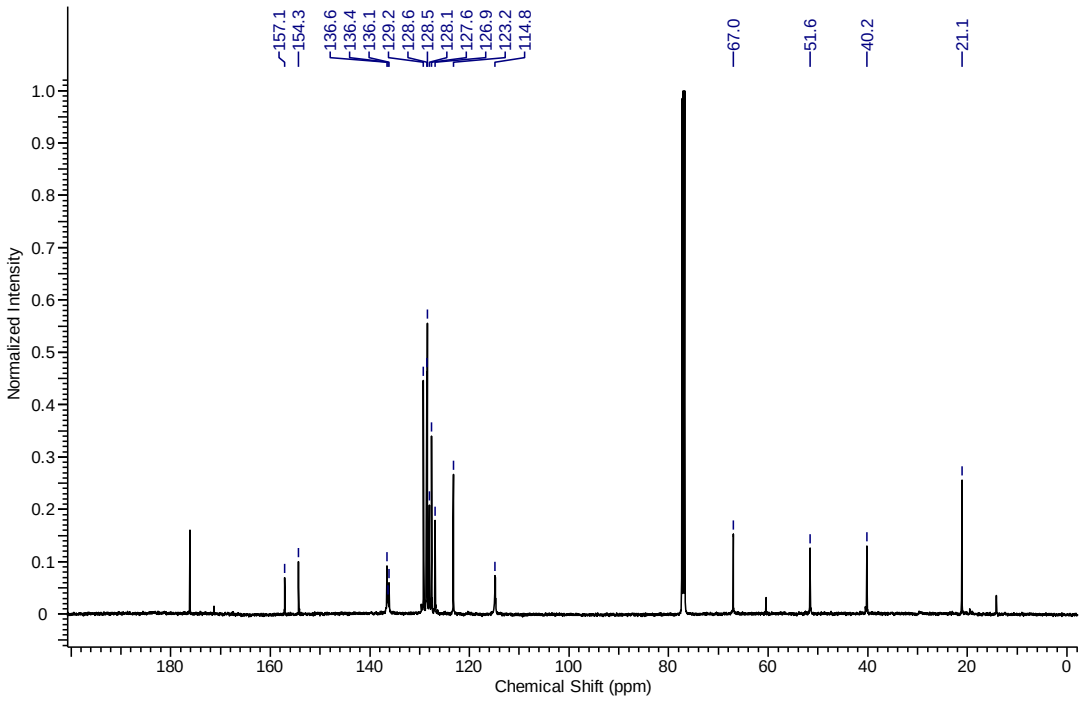




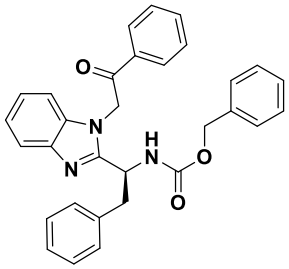
Benzyl (1-(1H-benzo[d]imidazol-2-yl)-2-phenylethyl)carbamate (13)

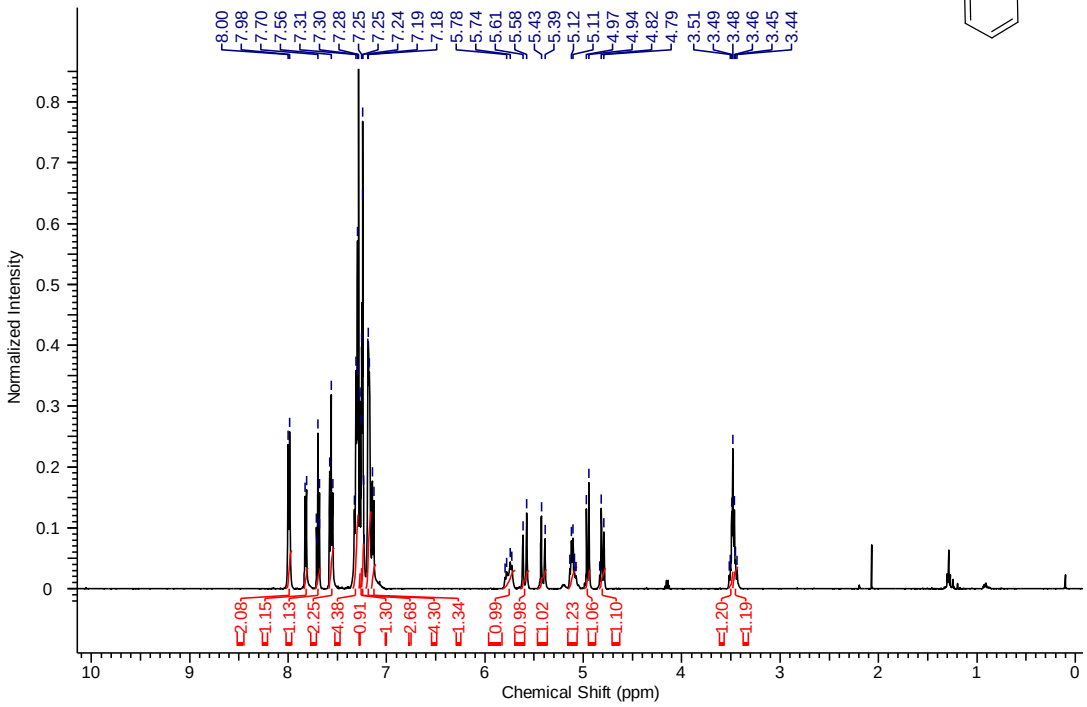


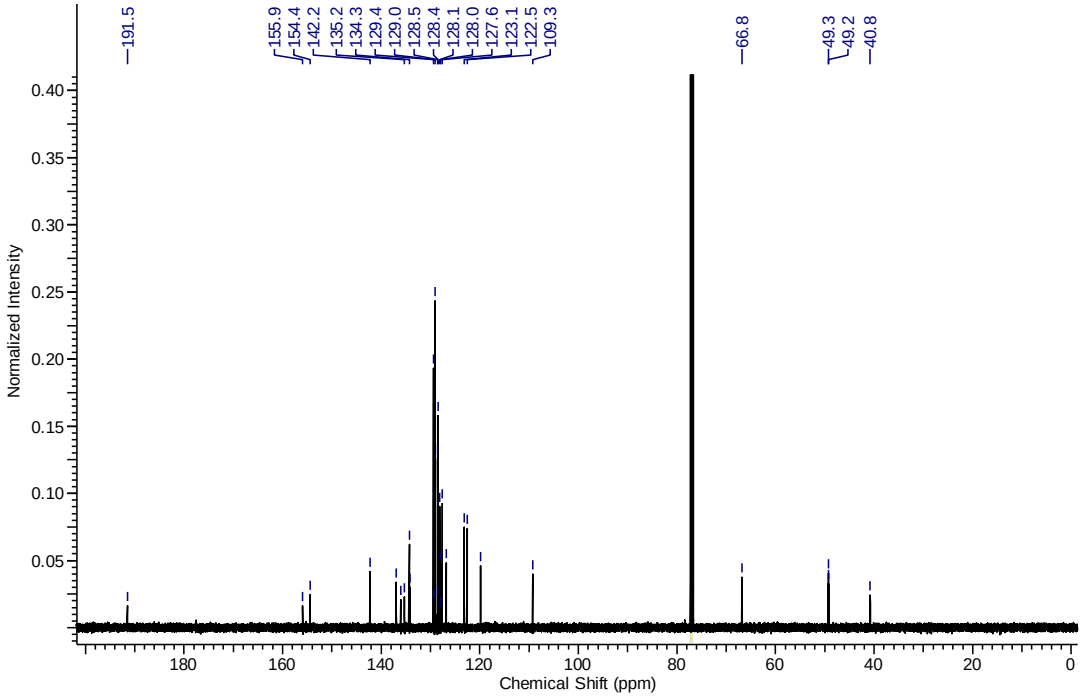




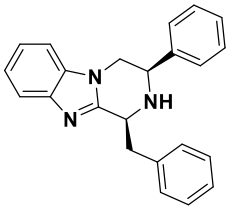
Benzyl (1-(1-(2-oxo-2-phenylethyl)-1H-benzo[d]imidazol-2-yl)-2-phenyl ethyl)carbamate (14a)

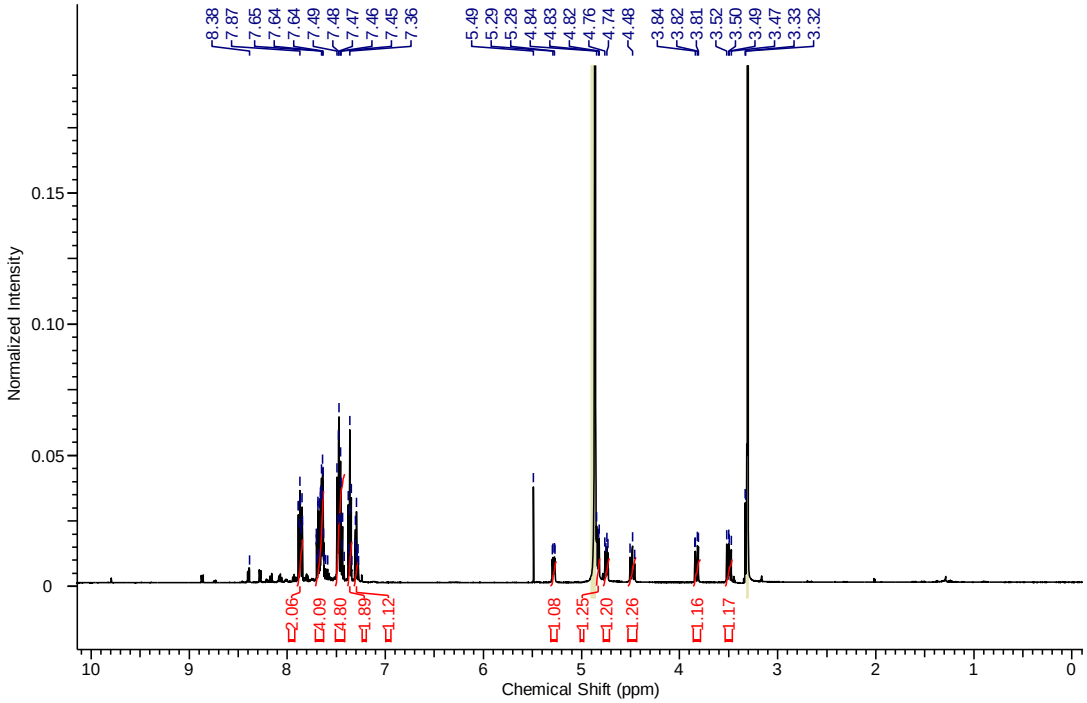


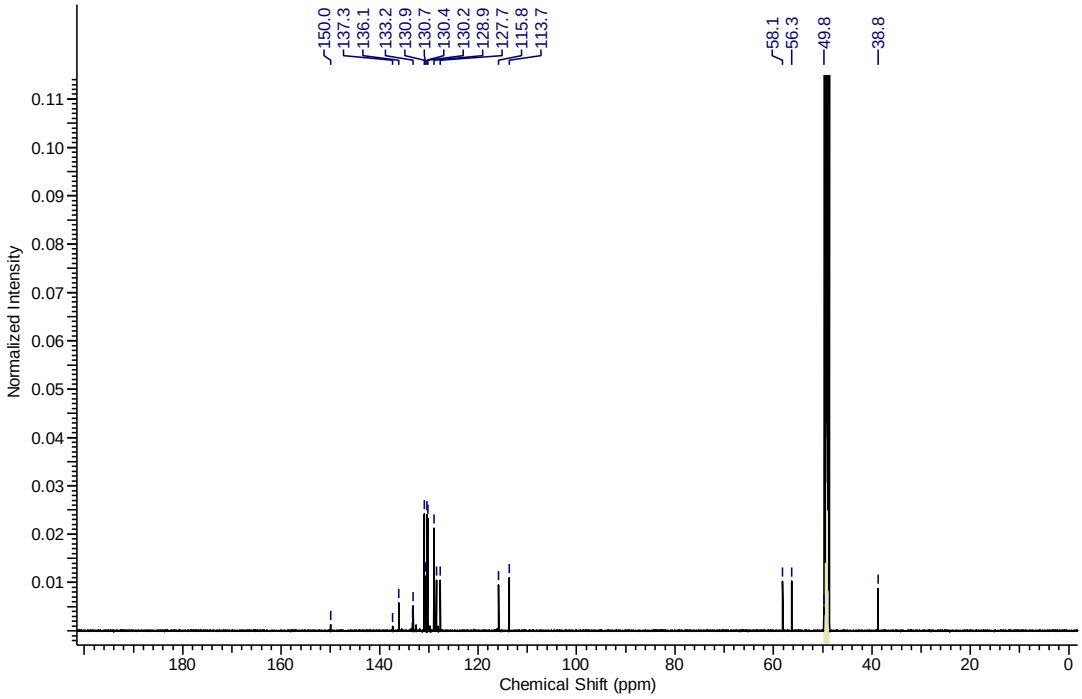




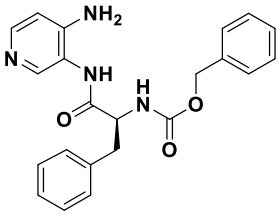
(1S,3R)-1-benzyl-3-phenyl-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazine (14)

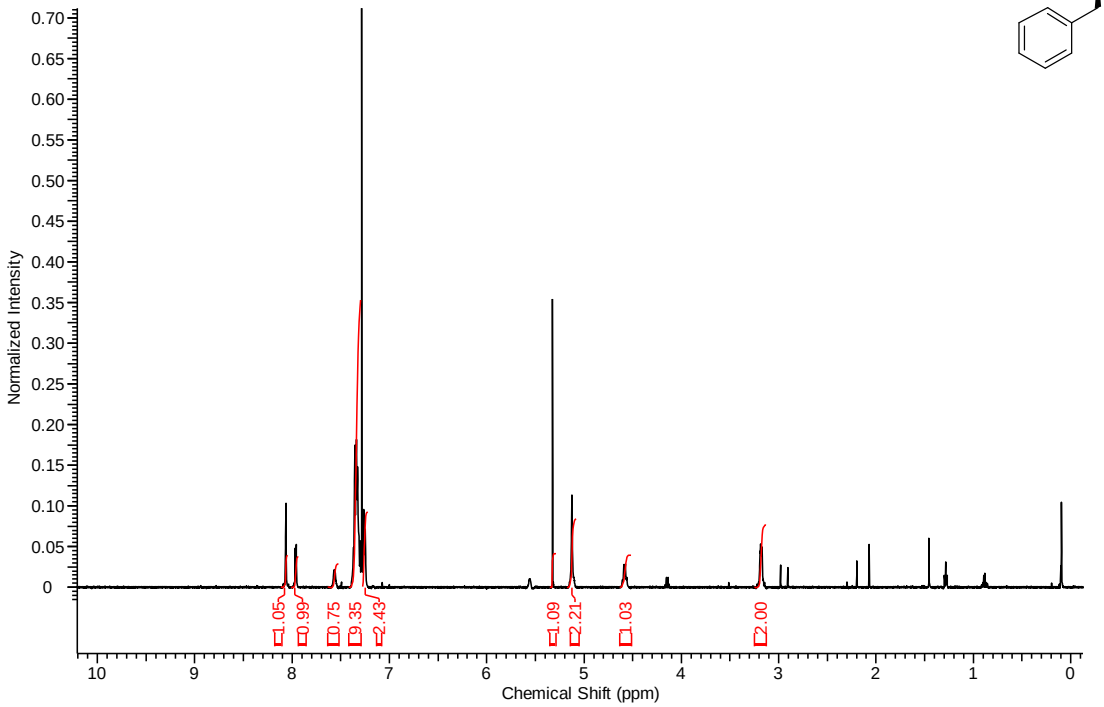


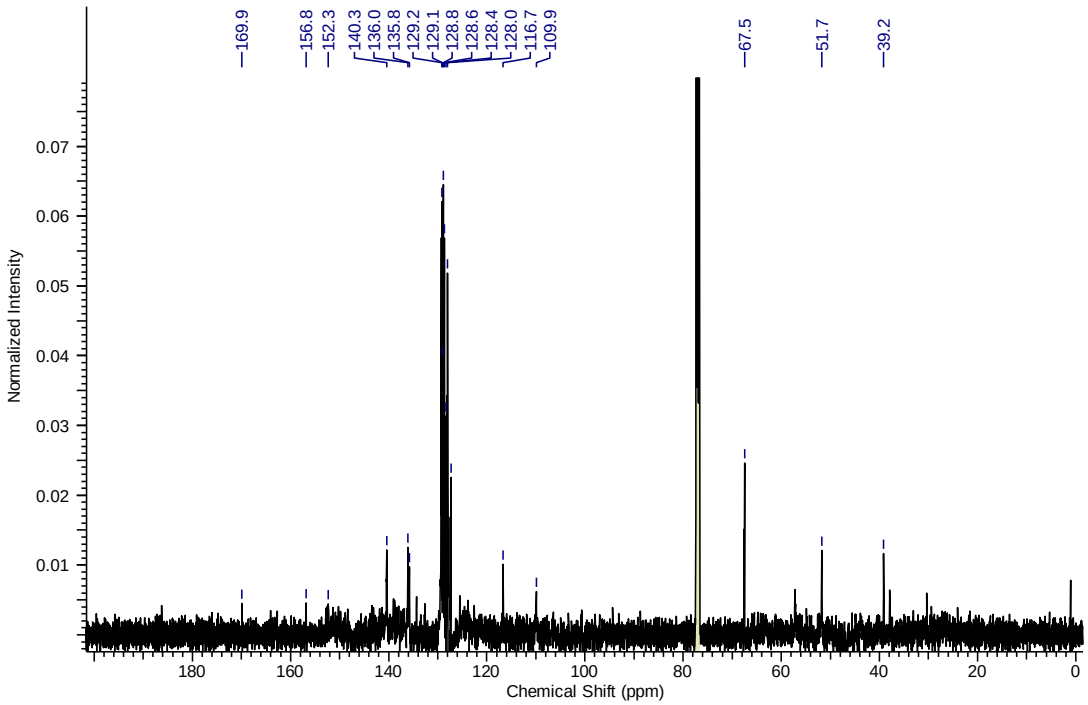




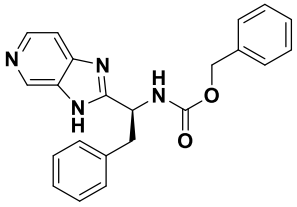
Benzyl (1-((4-aminopyridin-3-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (15a)

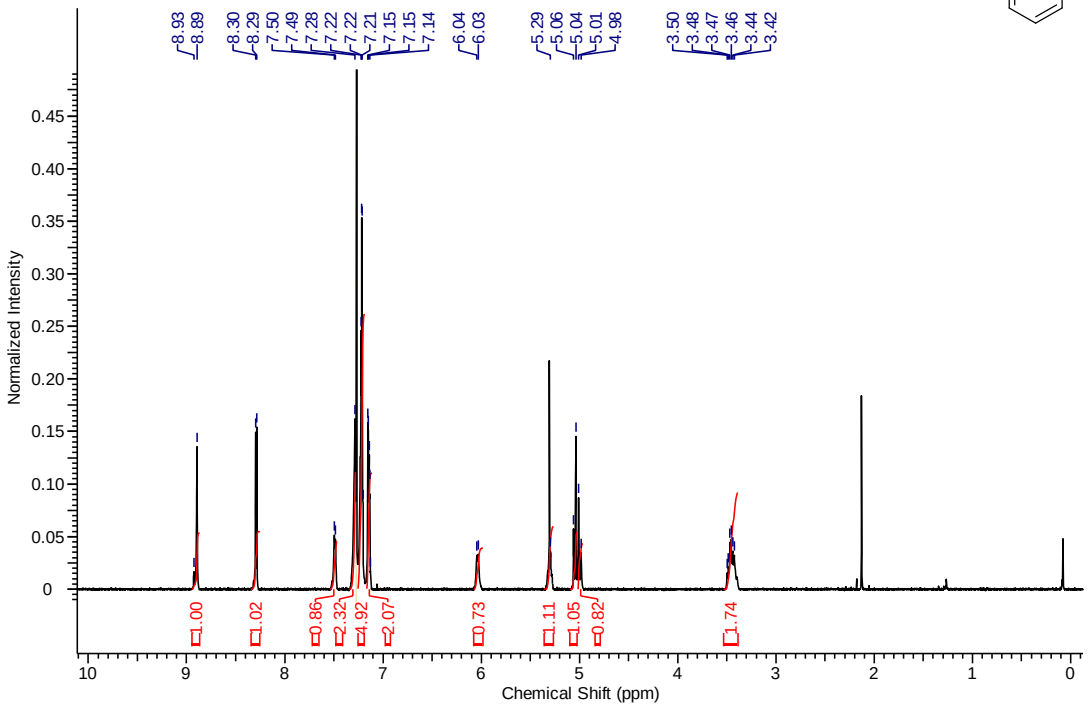


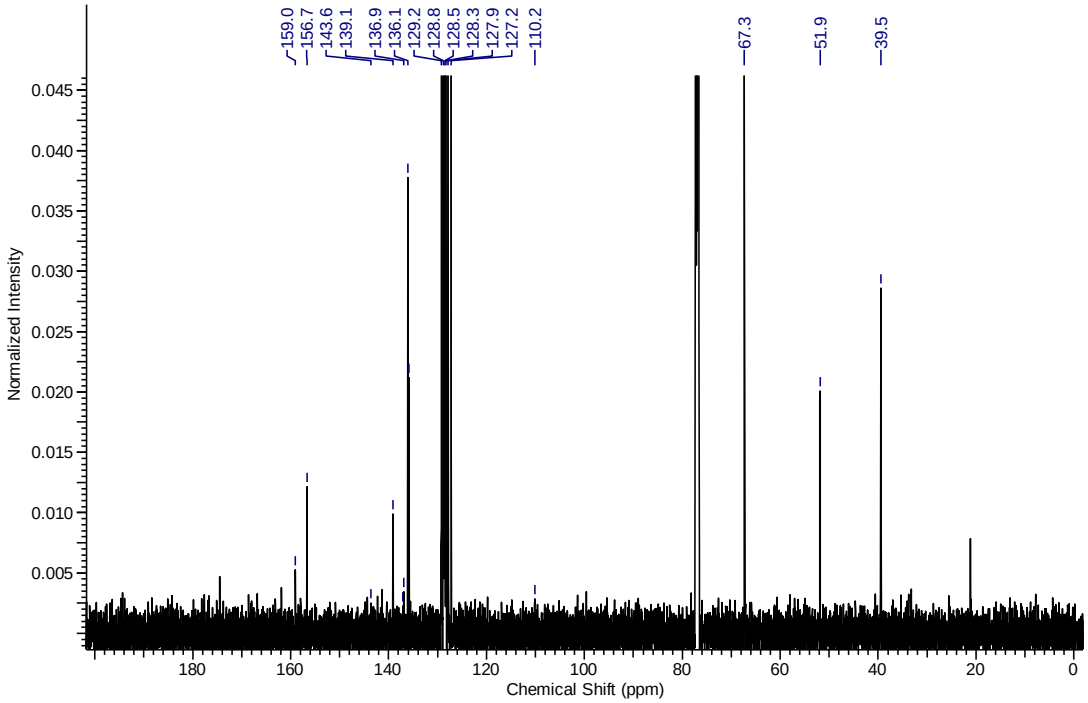




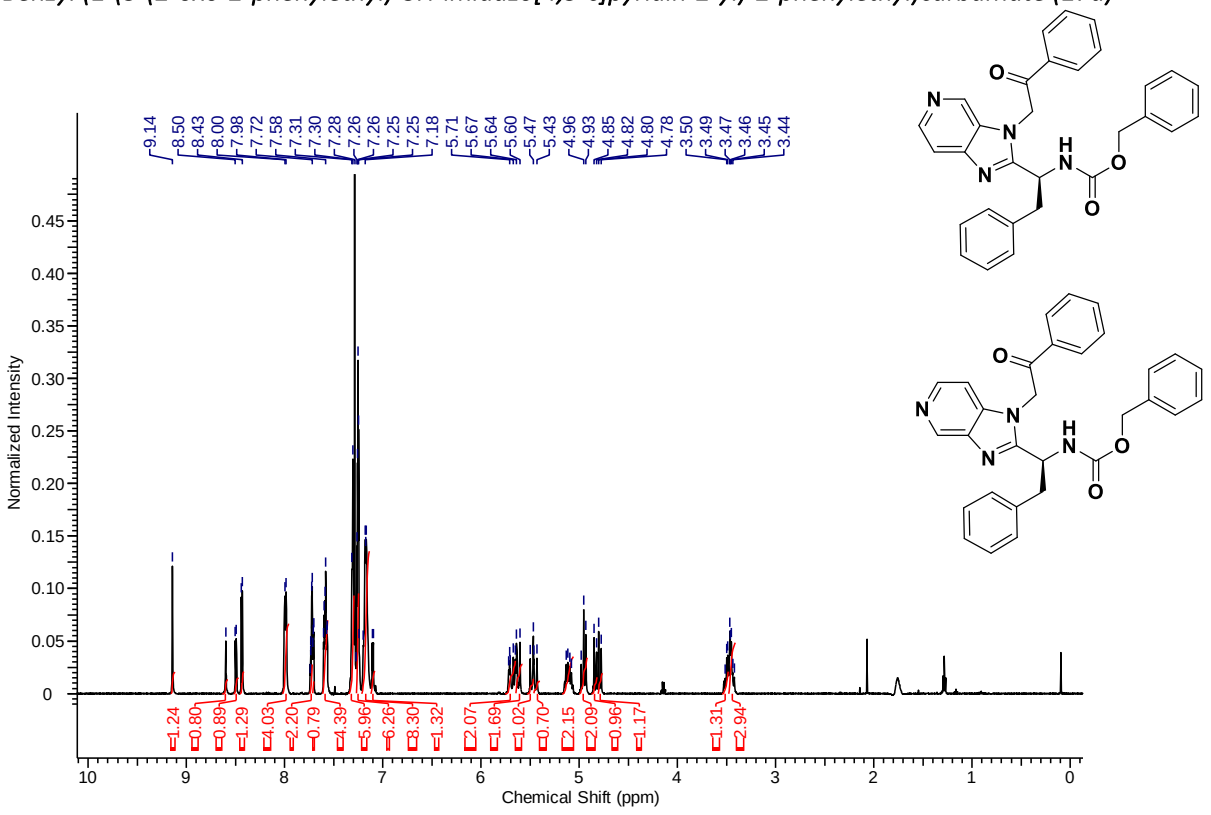
Benzyl (1-(3H-imidazo[4,5-c]pyridin-2-yl)-2-phenylethyl)carbamate (15)

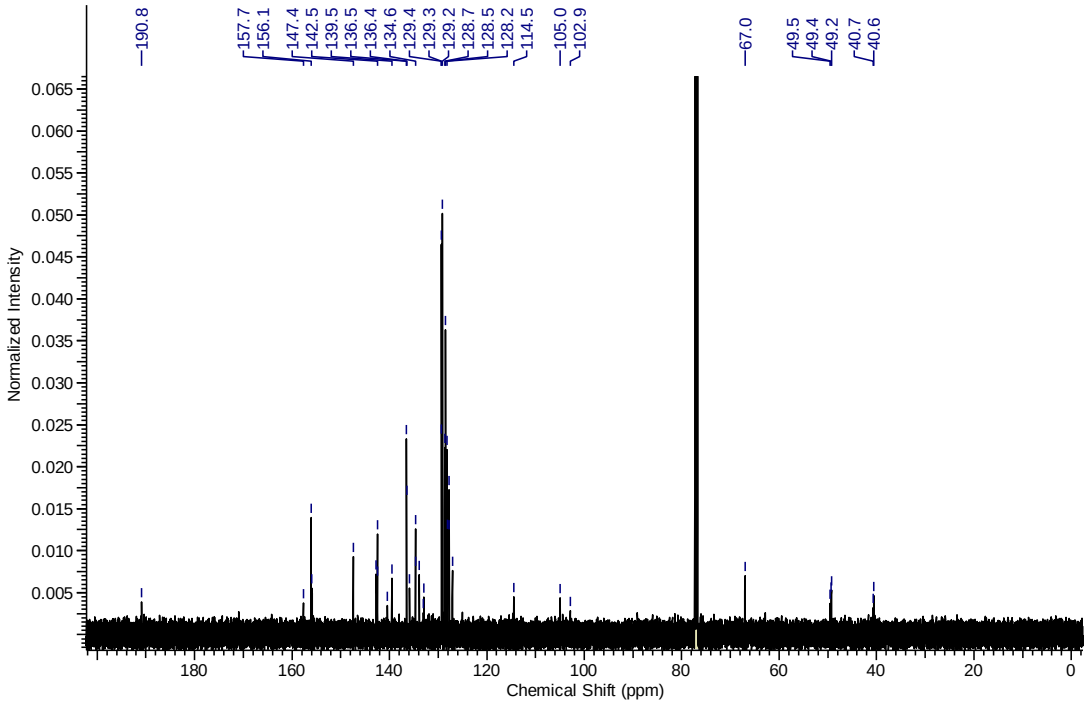




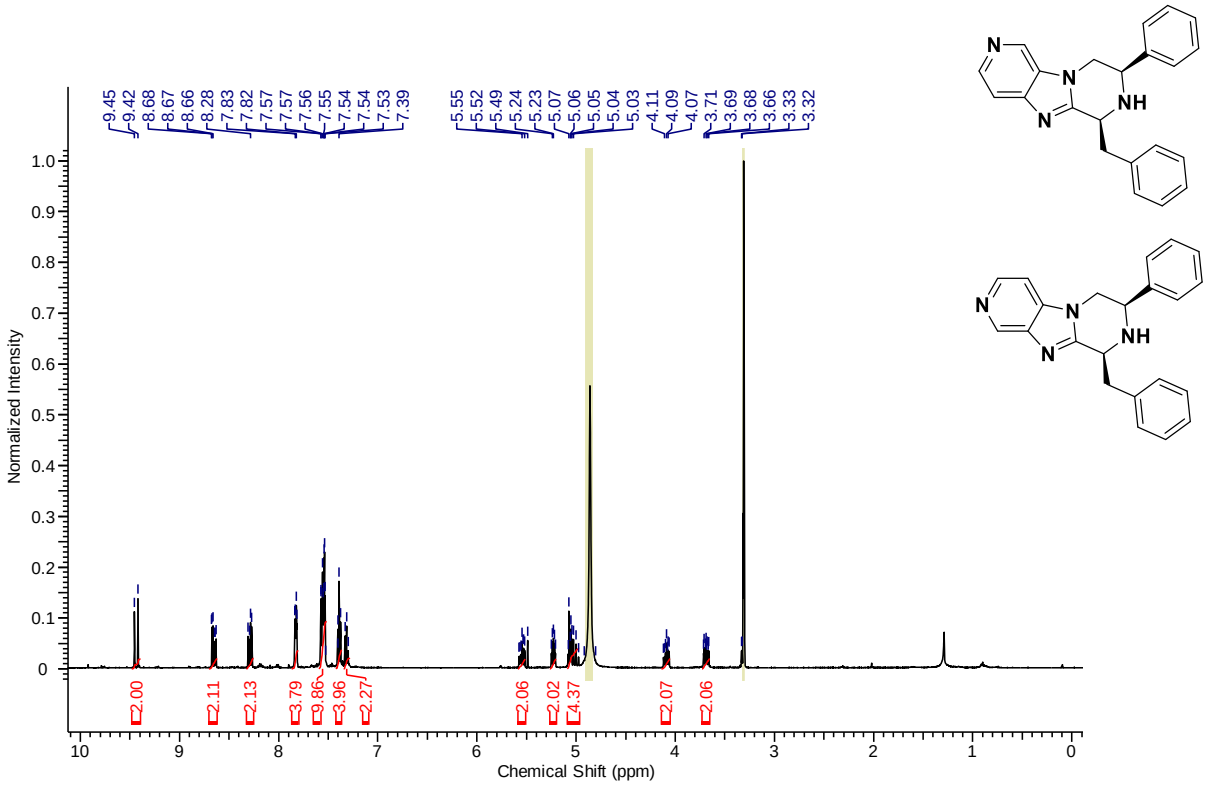


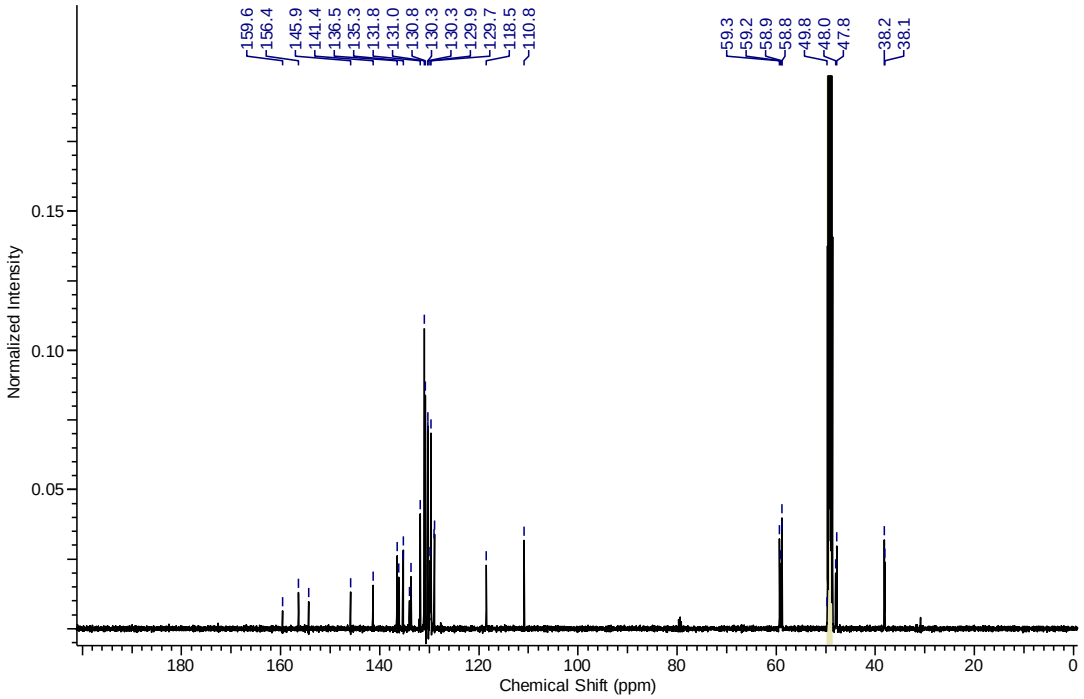
Benzyl (1-(1-(2-oxo-2-phenylethyl)-1H-imidazo[4,5-c]pyridin-2-yl)-2-phenylethyl)carbamate (16a) and Benzyl (1-(3-(2-oxo-2-phenylethyl)-3H-imidazo[4,5-c]pyridin-2-yl)-2-phenylethyl)carbamate (17a)



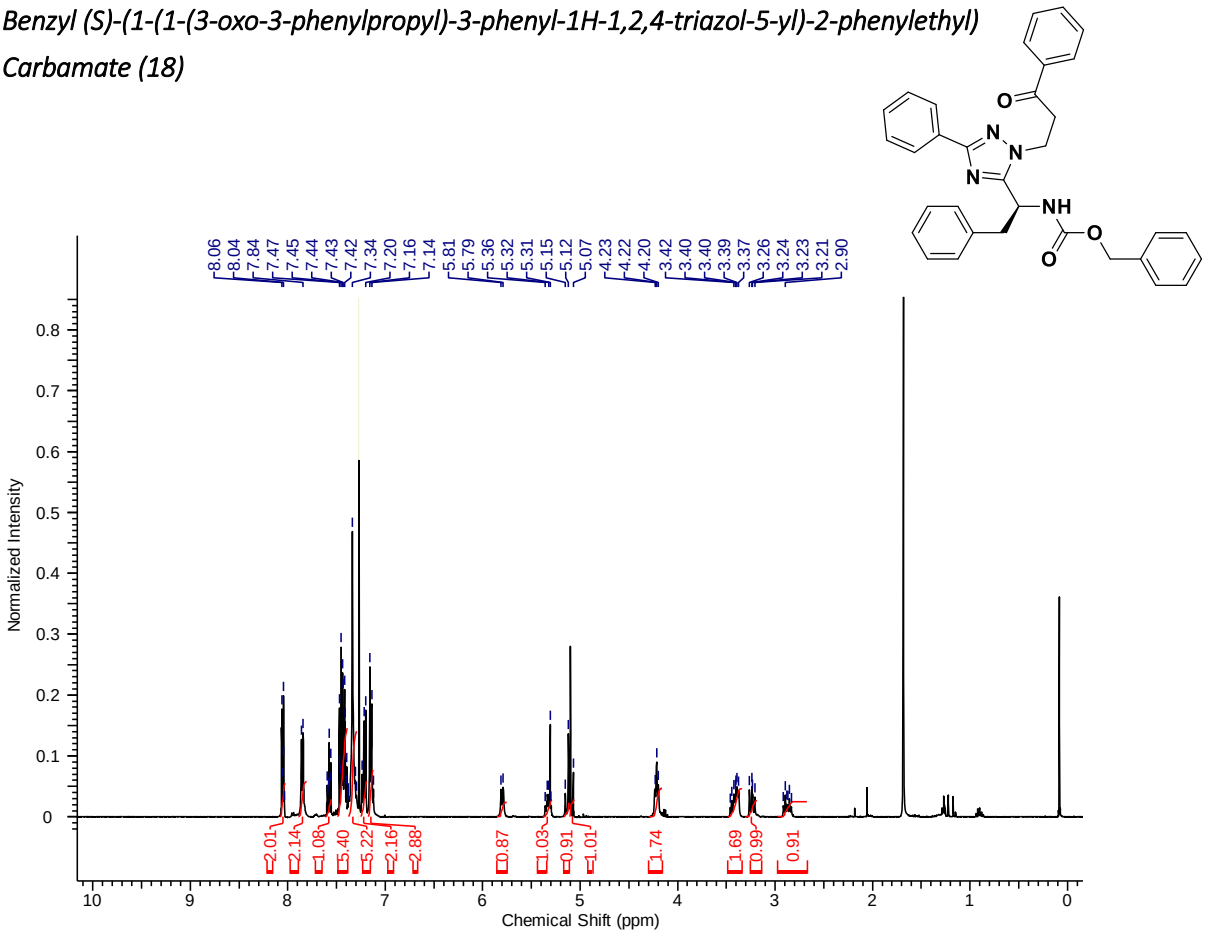


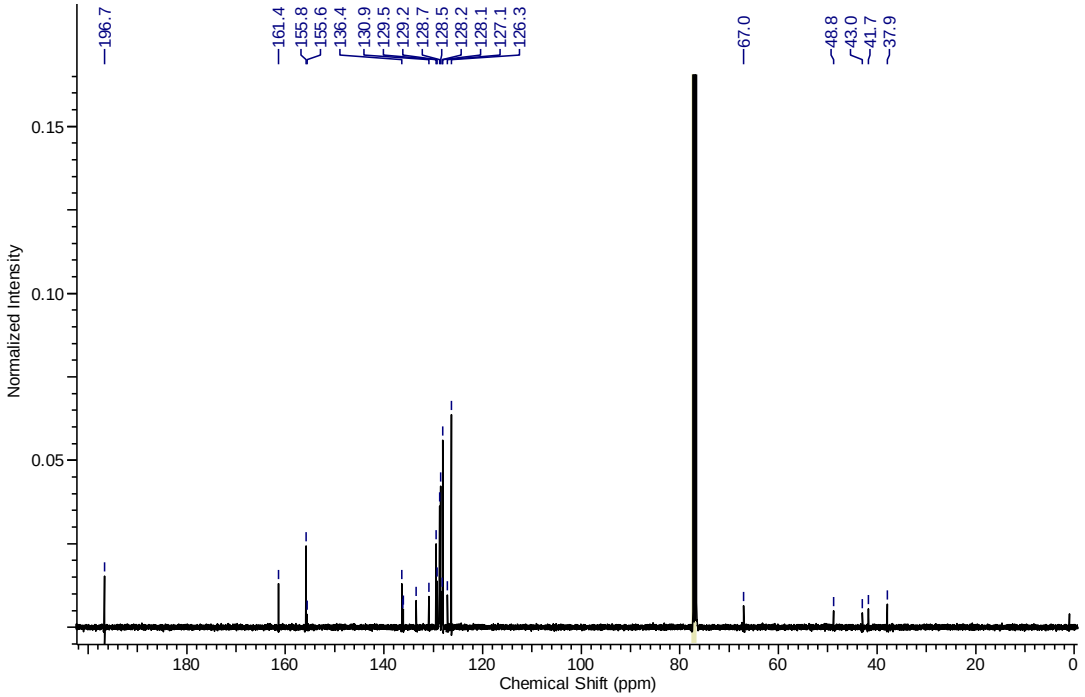
(7R,9S)-9-benzyl-7-phenyl-6,7,8,9-tetrahydropyrido[3',4':4,5]-imidazo[1,2-a]pyrazine (16) and (6S,8R)-6-benzyl-8-phenyl-6,7,8,9-tetrahydropyrido[4',3':4,5]imidazo[1,2-a]pyrazine (17)



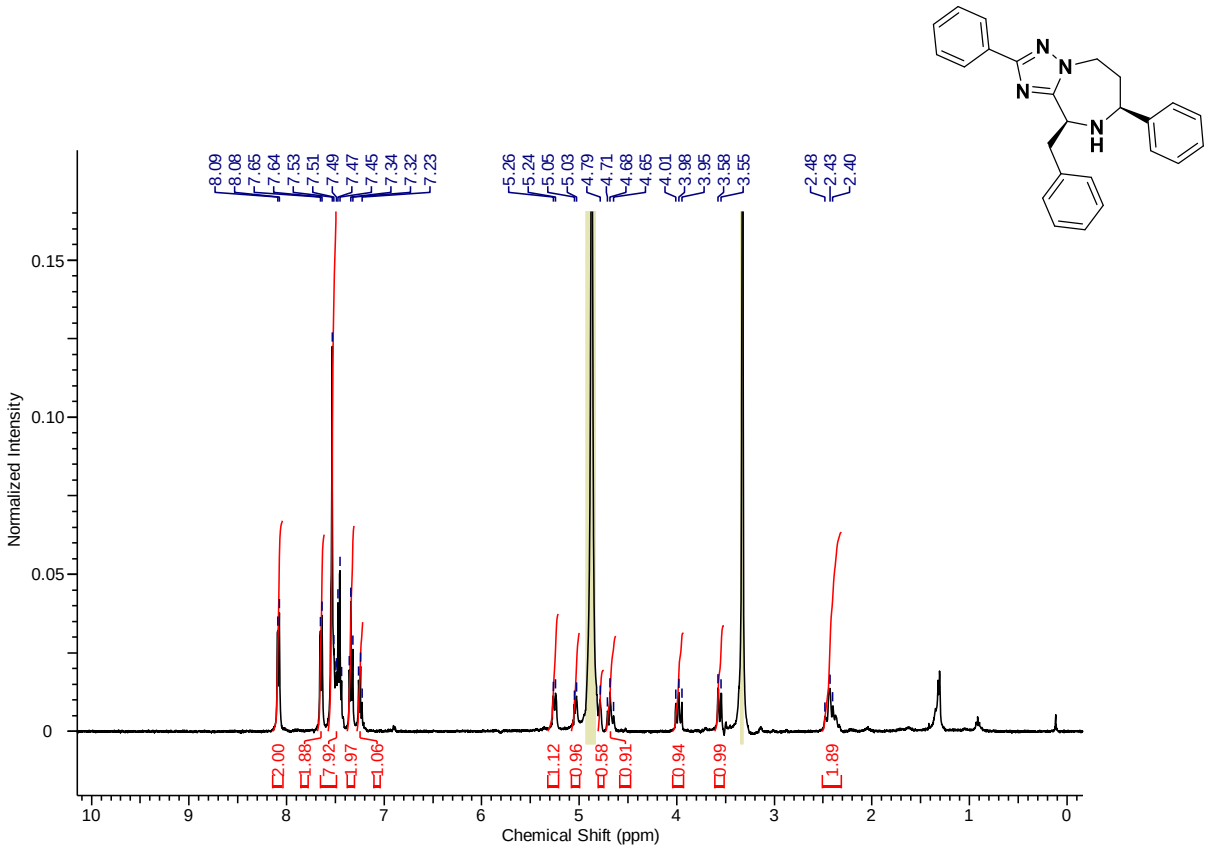


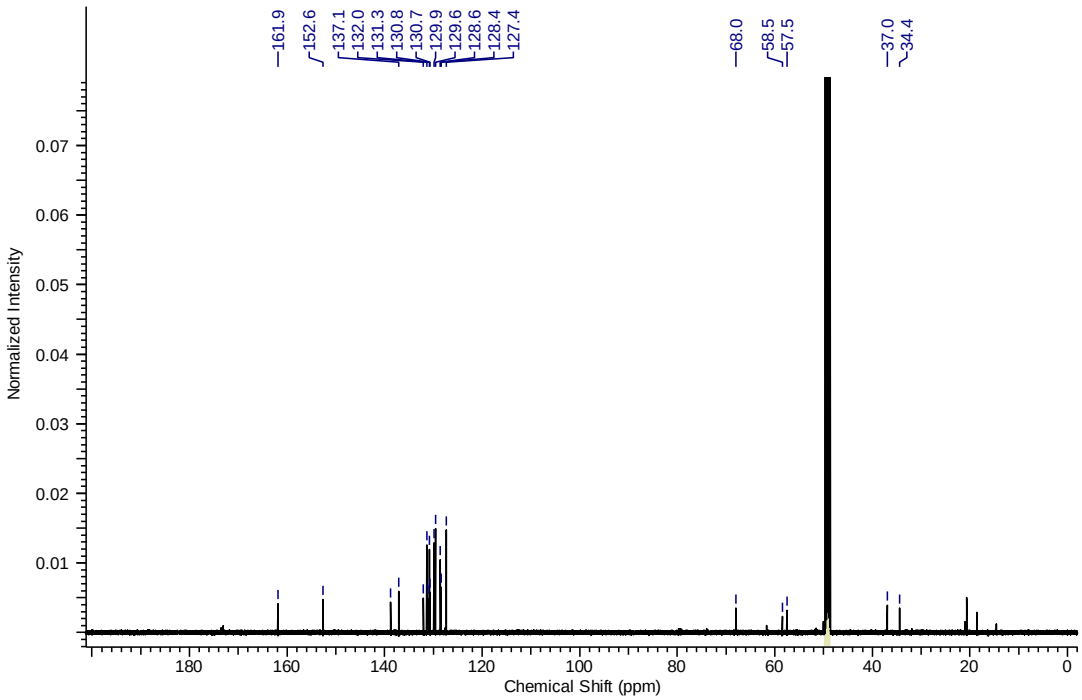
Benzyl (S)-(1-(1-(3-oxo-3-phenylpropyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl) Carbamate (18)



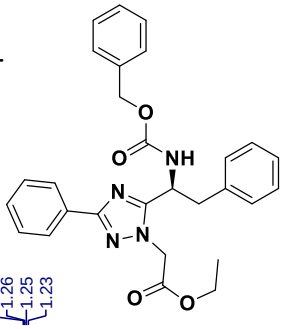


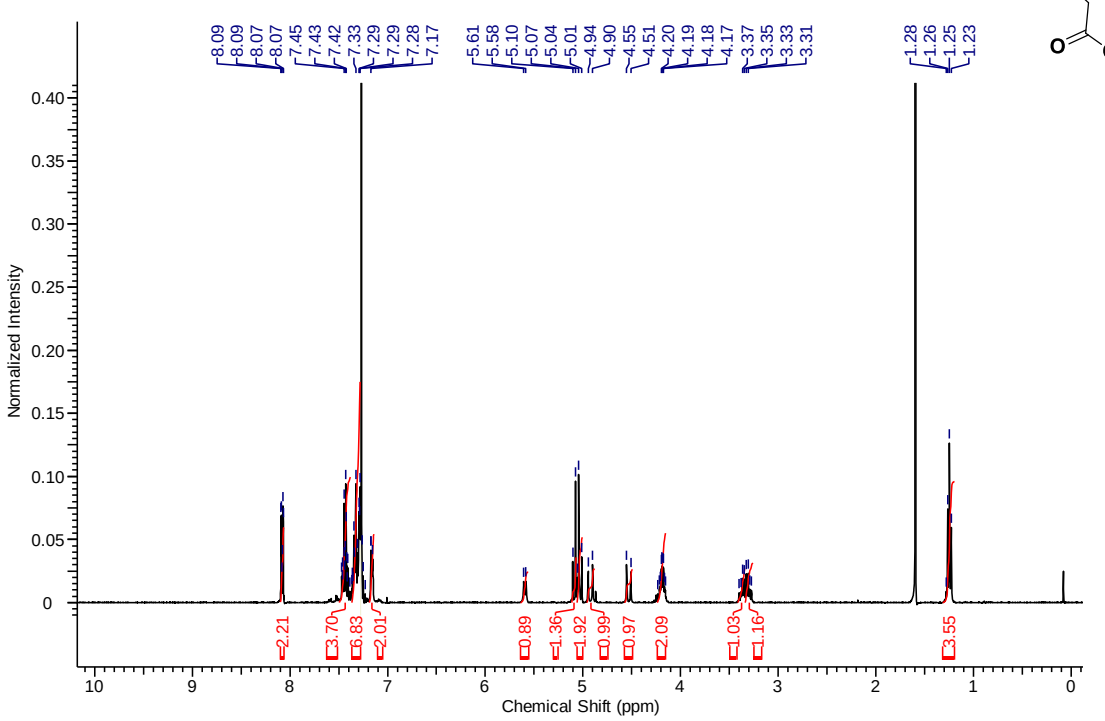
(7S,9S)-9-benzyl-2,7-diphenyl-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[1,5-a][1,4]diazepine (19)

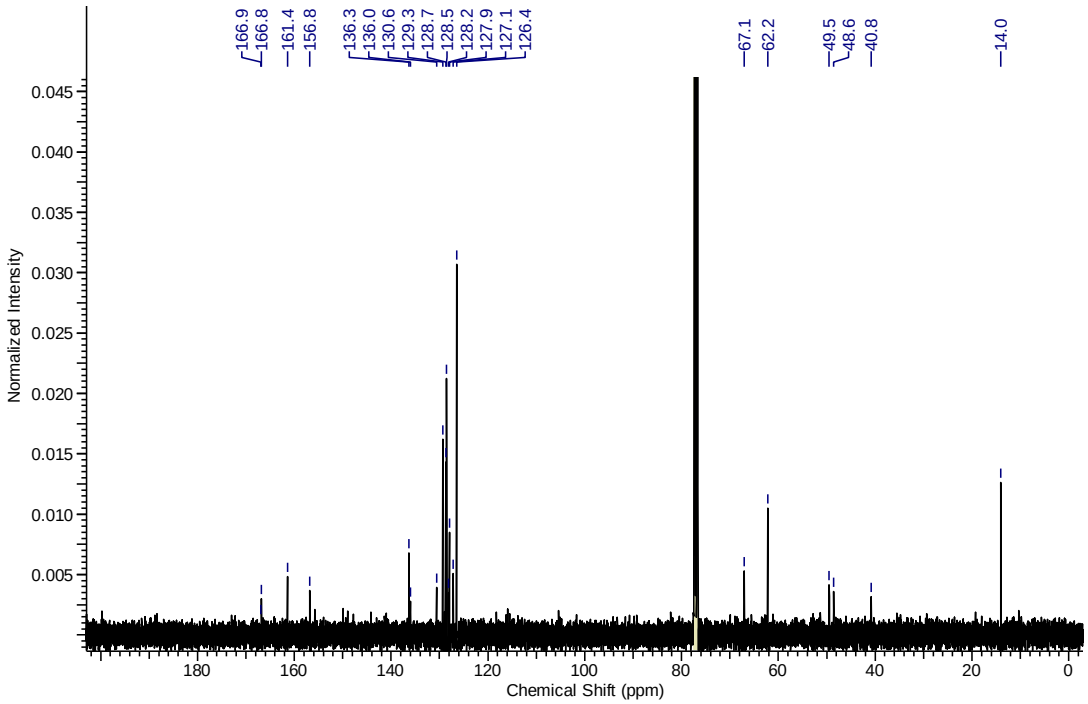




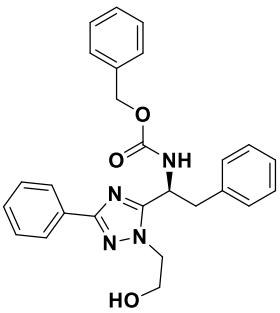
Ethyl (S)-2-(5-(1-(((benzyloxy)carbonyl)amino)-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-1-yl)acetate (21)

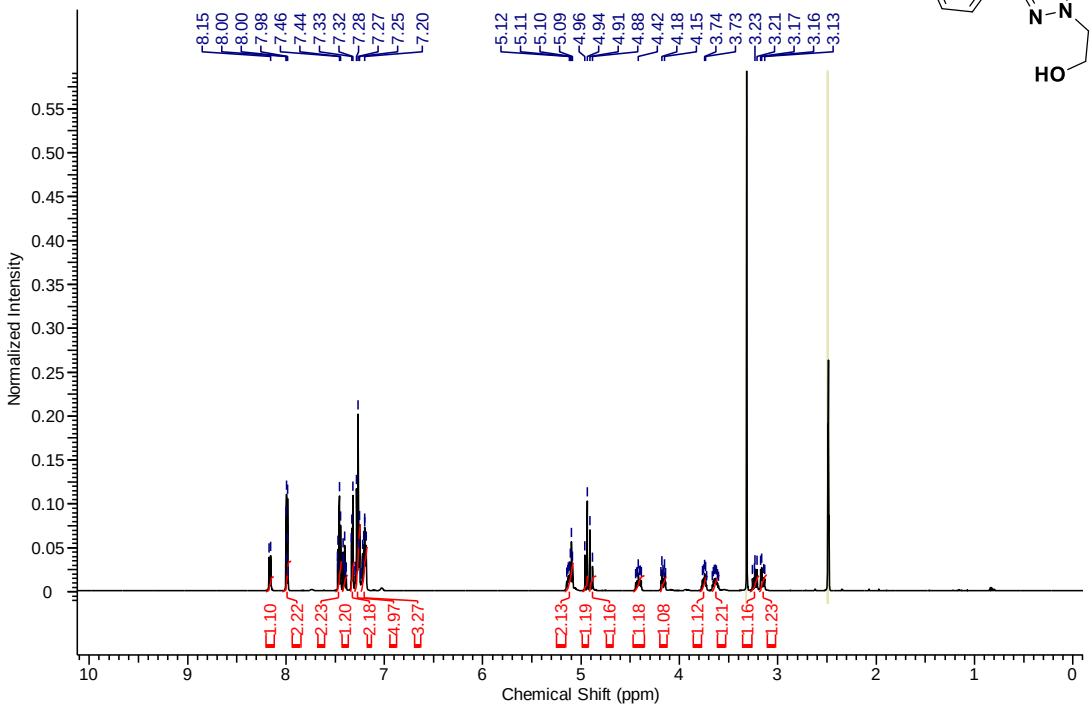


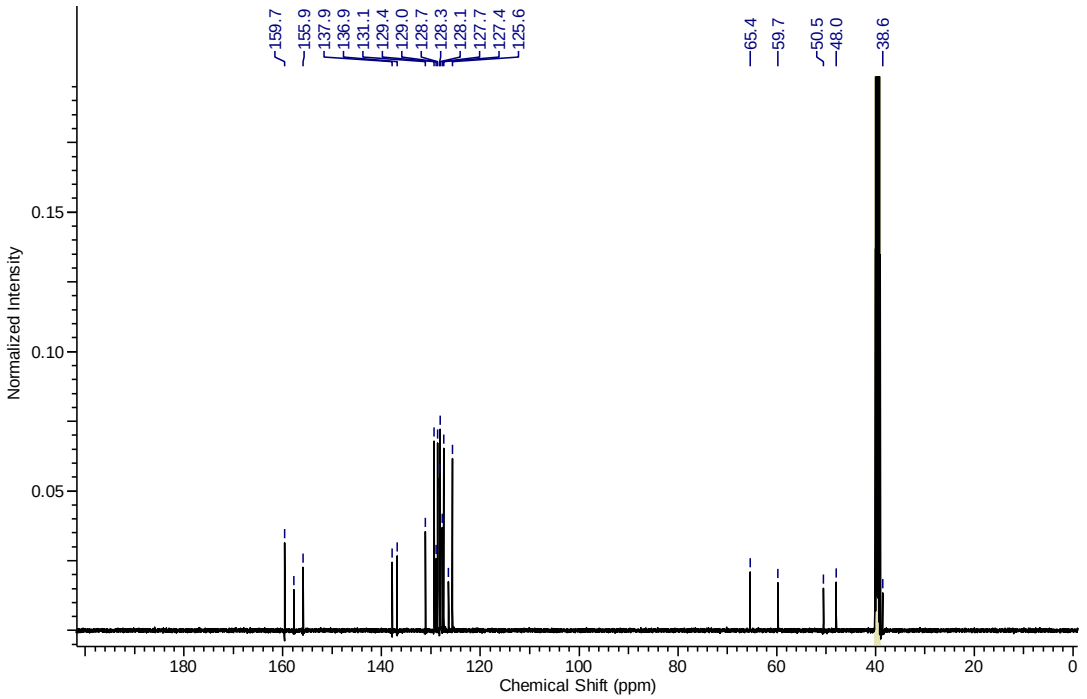




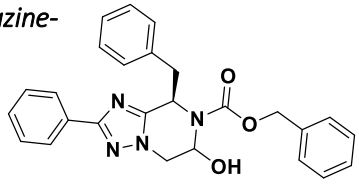
Benzyl (S)-(1-(1-(2-hydroxyethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl) carbamate (22)

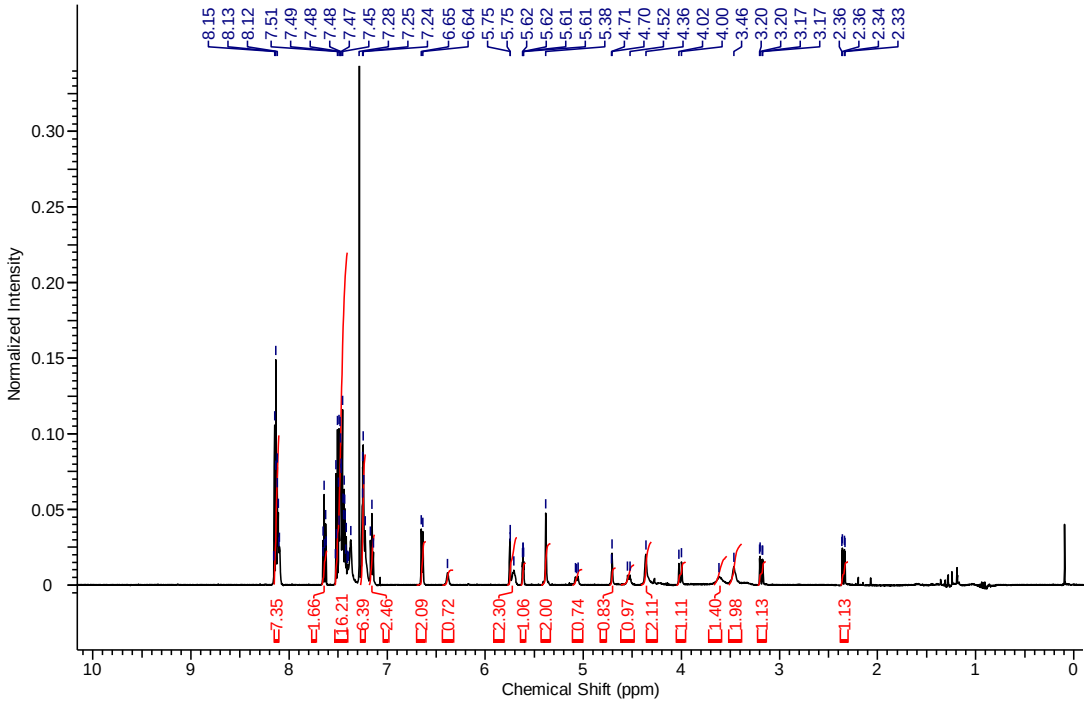


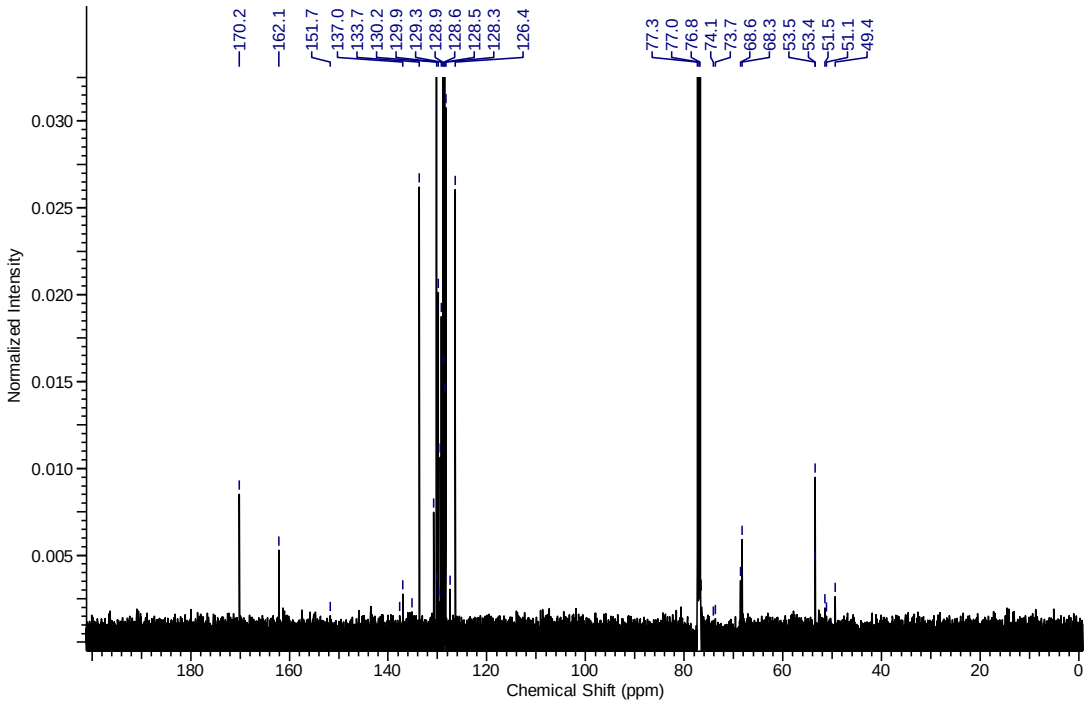




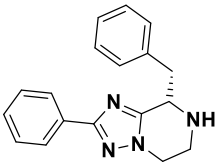
Benzyl 8-benzyl-6-hydroxy-2-phenyl-5,6-dihydro-[1,2,4]triazolo[1,5-a]pyrazine-7(8H)-carboxylate (23)

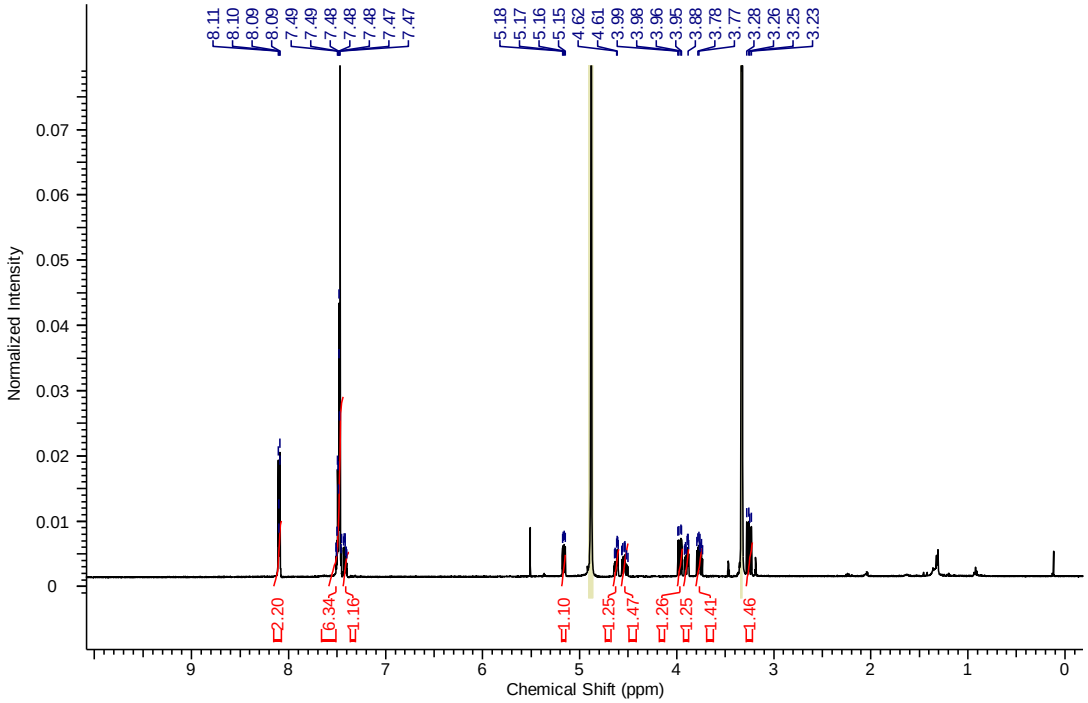


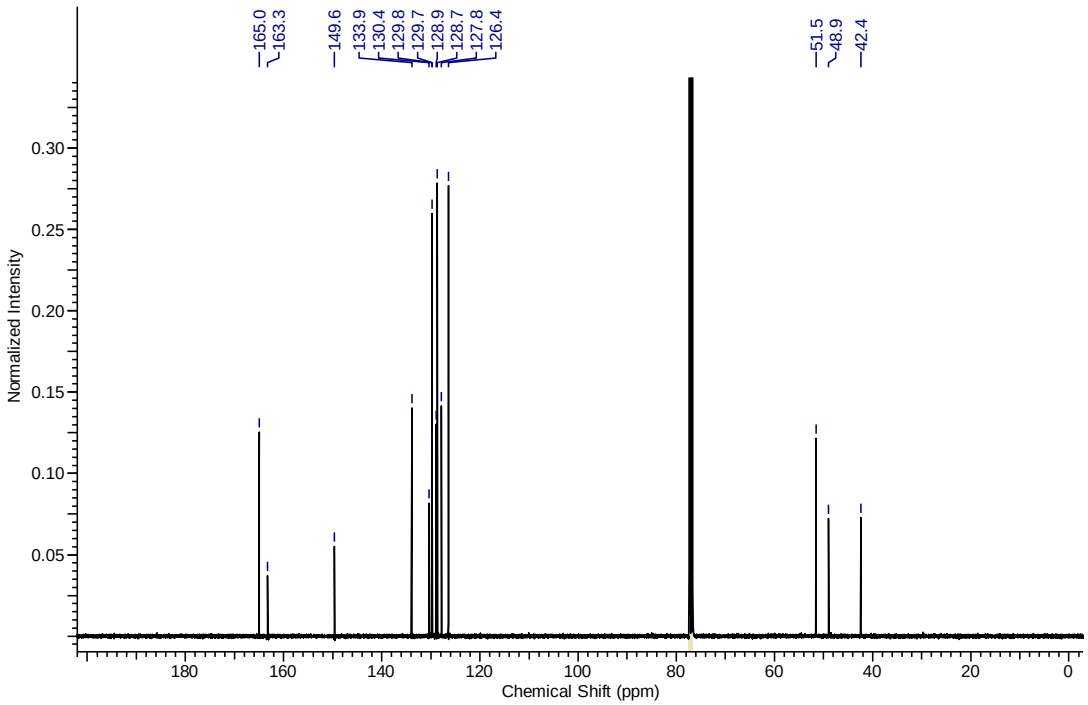




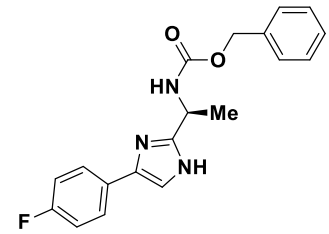
(S)-8-benzyl-2-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (24)

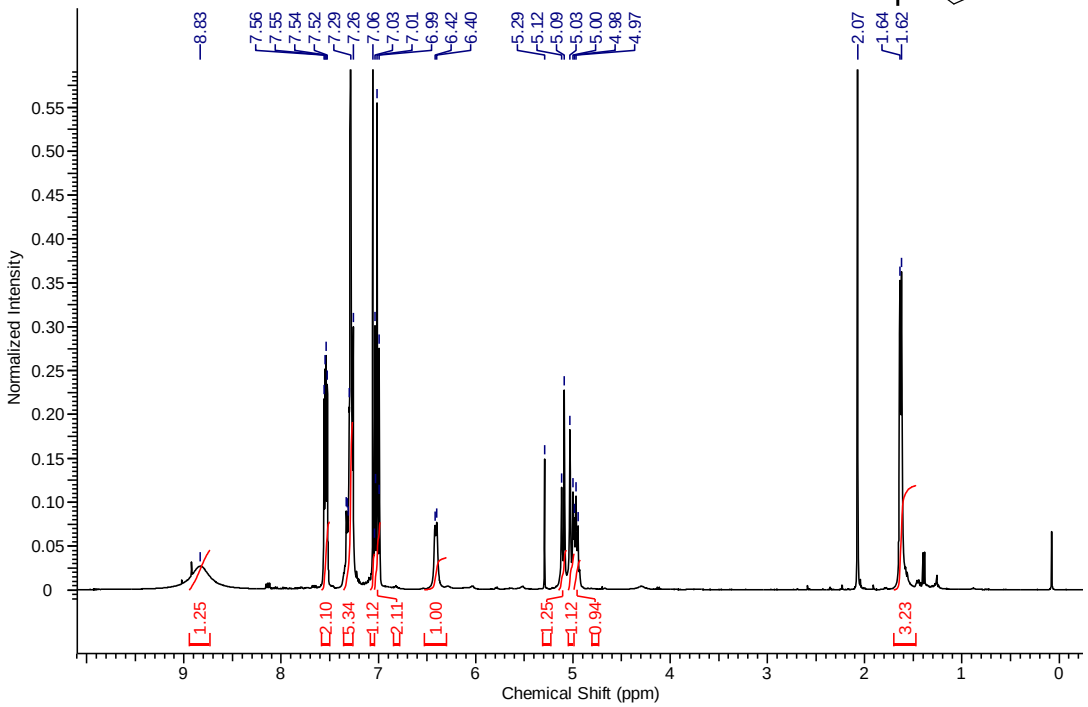


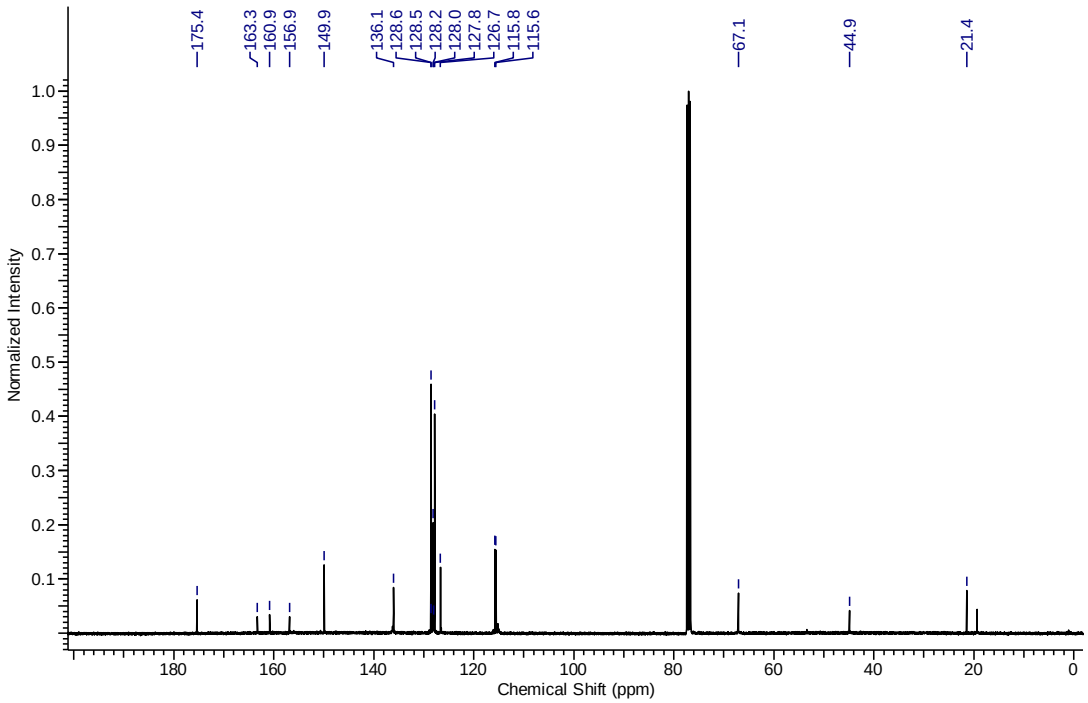




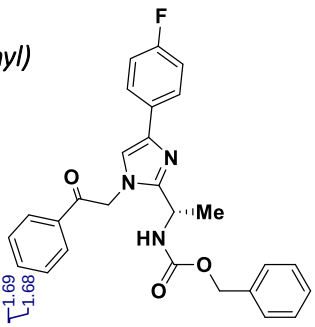
Benzyl (S)-(1-(4-(4-fluorophenyl)-1H-imidazol-2-yl)ethyl)carbamate (30)

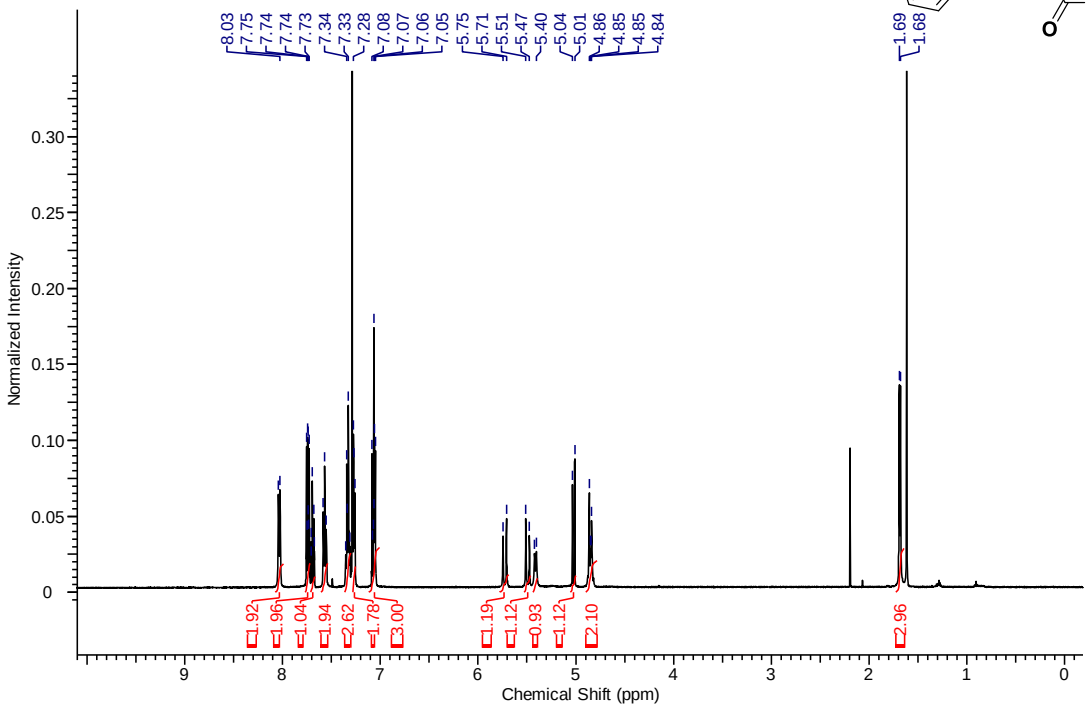


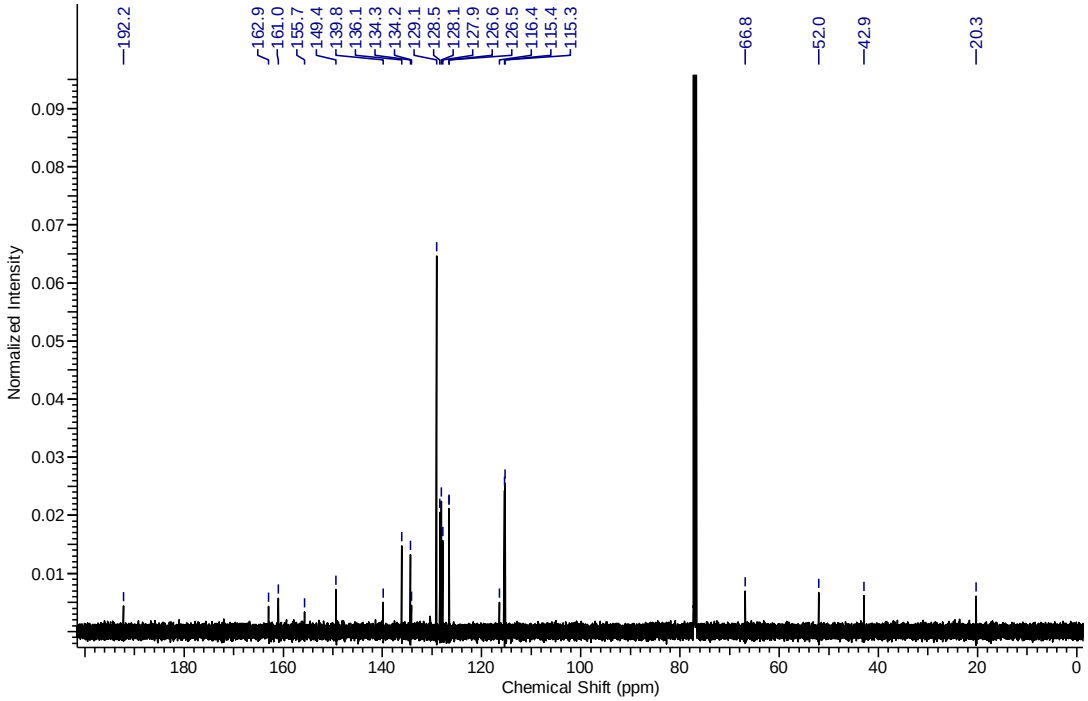




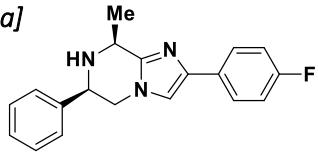
Benzyl (S)-(1-(4-(4-fluorophenyl)-1-(2-oxo-2-phenylethyl)-1H-imidazol-2-yl)ethyl) carbamate (31)

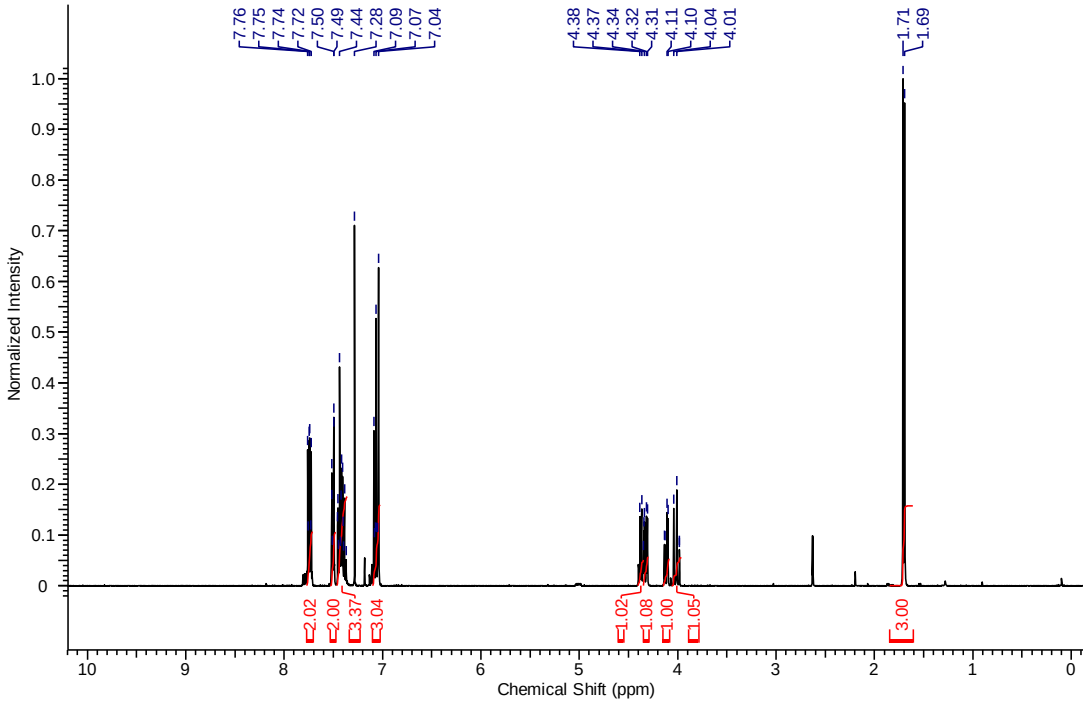


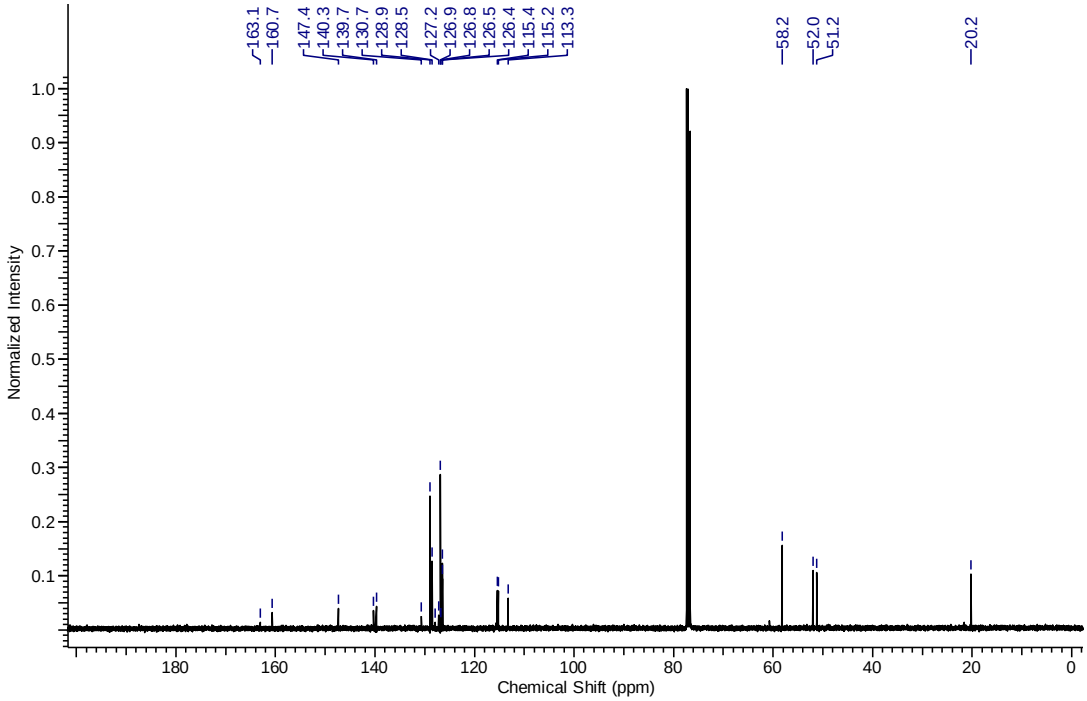




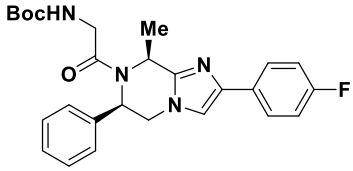
(6R,8S)-2-(4-fluorophenyl)-8-methyl-6-phenyl-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine (32)

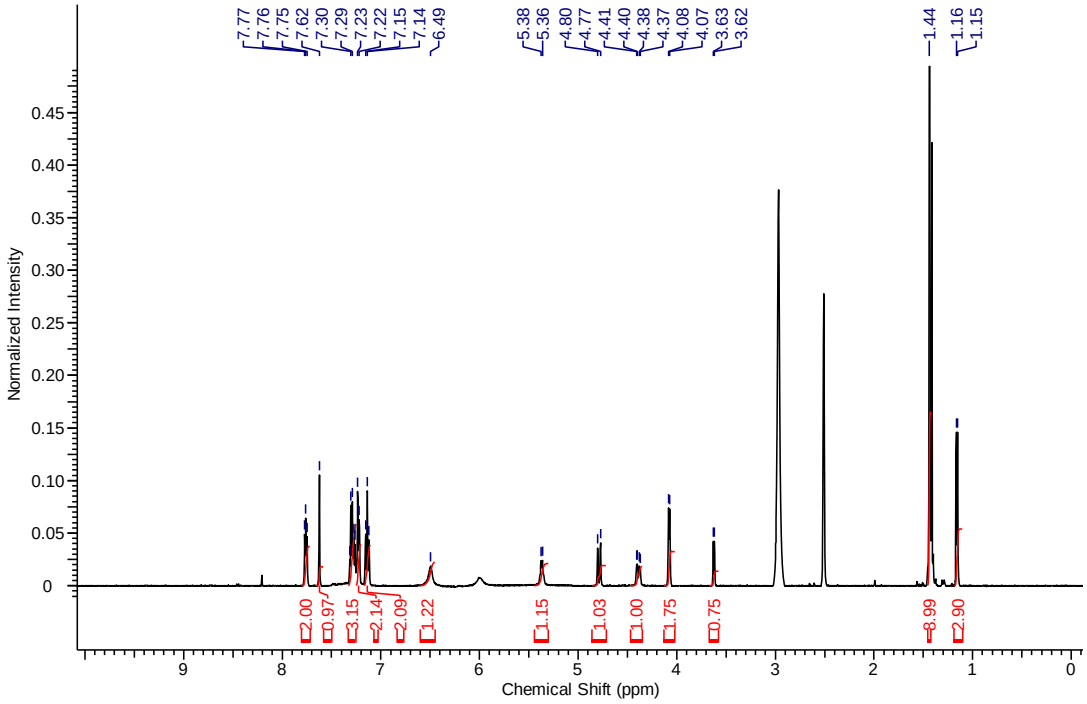


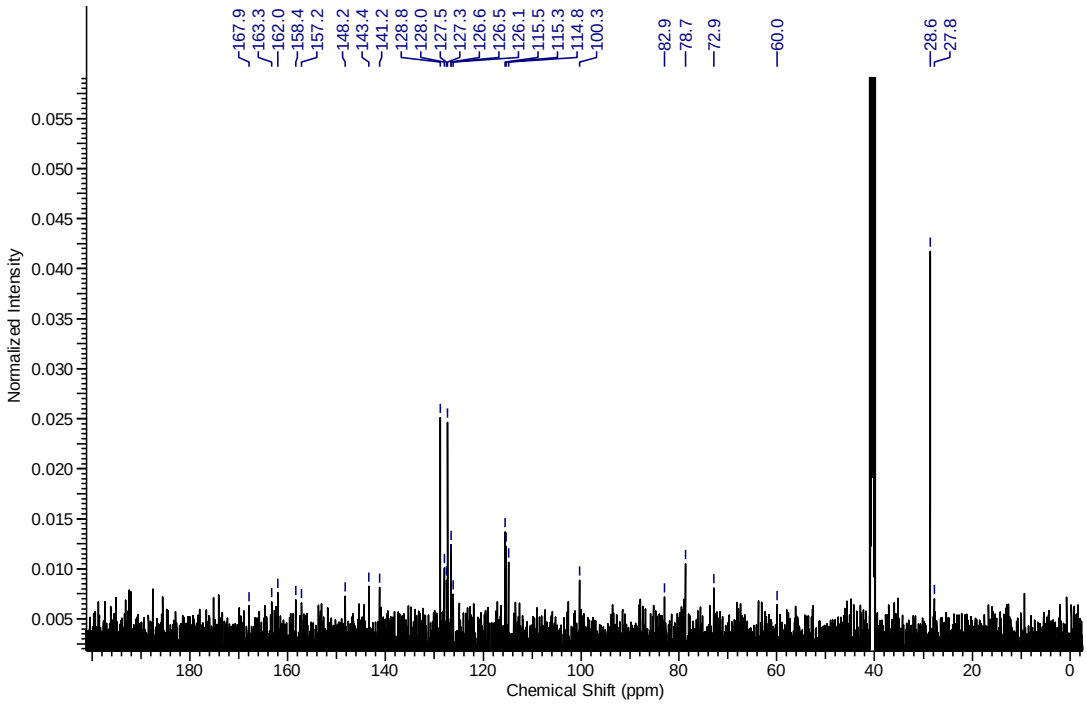




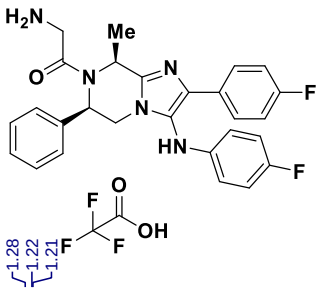
tert-butyl (2-((6R,8S)-2-(4-fluorophenyl)-8-methyl-6-phenyl-5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)-2-oxoethyl)carbamate (47)

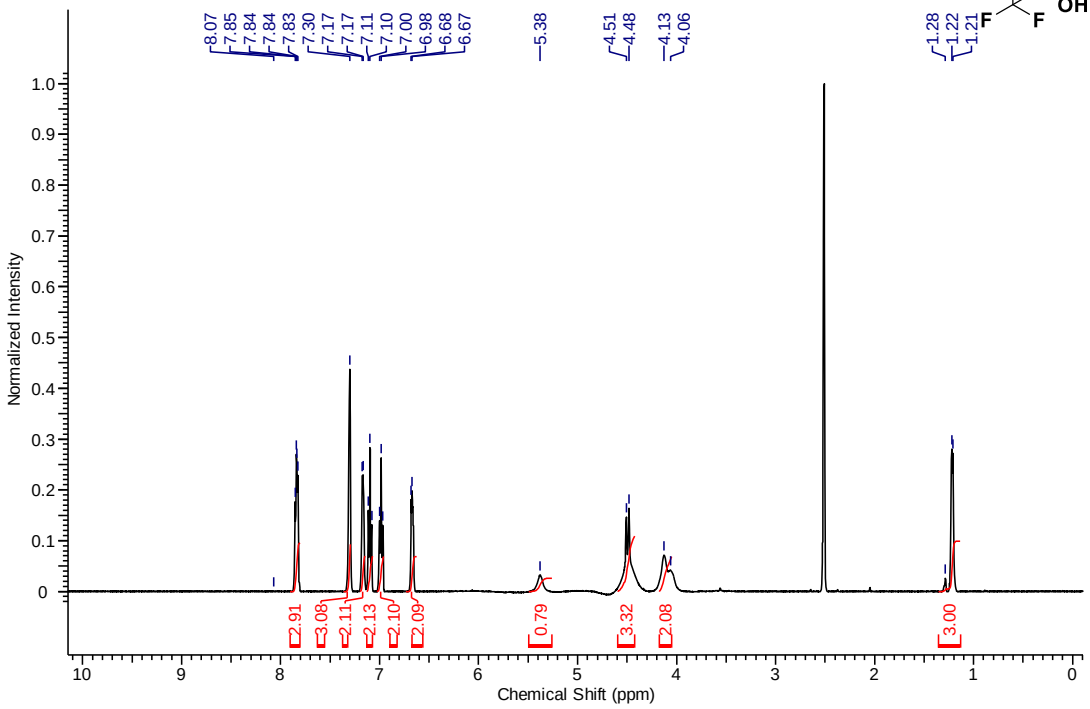


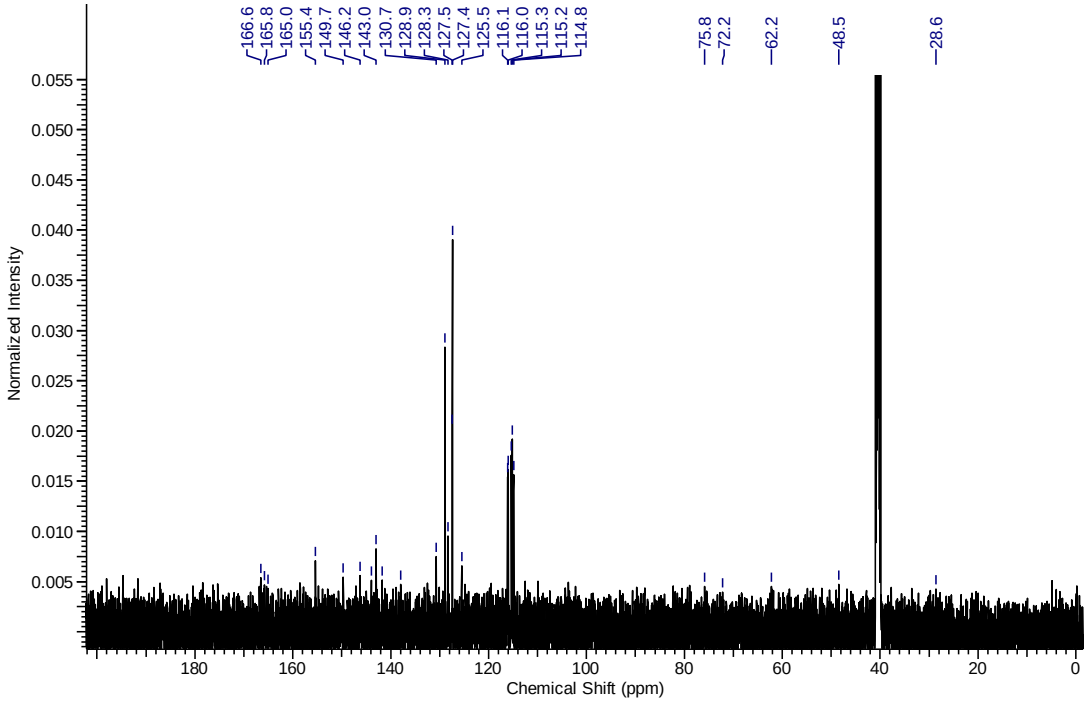




2-amino-1-((6R,8S)-2-(4-fluorophenyl)-3-((4-fluorophenyl)amino)-8-methyl-6-phenyl-5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)ethan-1-one. TFA salt (50)





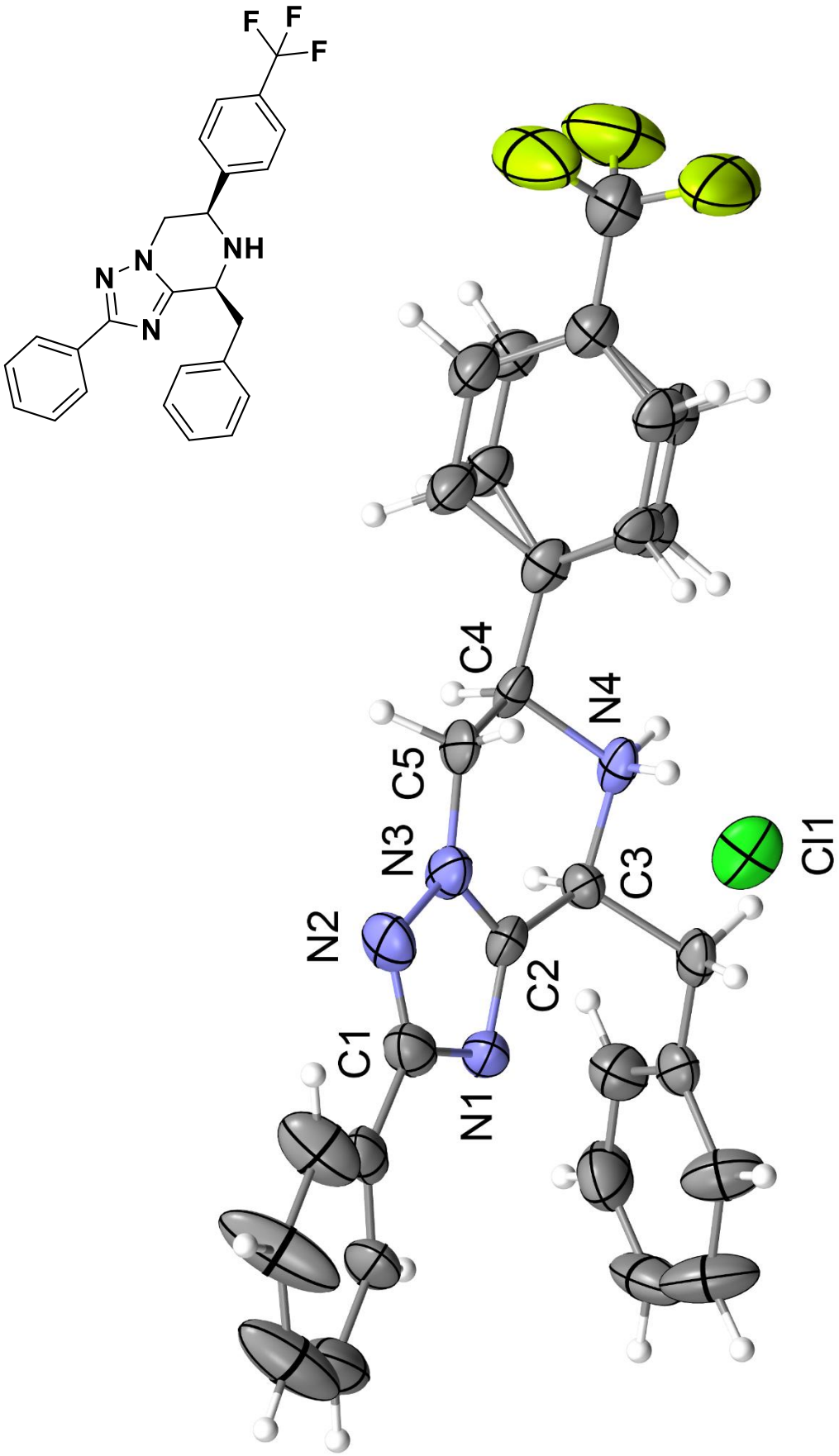


3. Crystallographic Data

CCDC number[23]	1914926
Cambridge data number	DS_B1_0025
Chemical formula	$C_{25}H_{22}ClF_3N_4$
Formula weight	470.91
Temperature / K	180(2)
Crystal system	monoclinic
Space group	$P2_1$
a / Å	5.6933(4)
b / Å	12.7845(10)
c / Å	15.7666(13)
α / °	90
β / °	99.160(7)
γ / °	90
Unit-cell volume / Å^3	1132.95(15)
Z	2
Calc. density / g cm^{-3}	1.380
F(000)	488
Radiation type	CuKα
Absorption coefficient / mm^{-1}	1.887
Crystal size / mm^3	0.68 x 0.42 x 0.005
2-Theta range / degrees	5.68-133.54
Completeness to max 2-theta	0.992
No. of reflections measured	10800
No. of independent reflections	3903
R_{int}	0.1006
No. parameters / restraints	335 / 49
Final *R*1 values ($I > 2\sigma(I)$)	0.0854
Final *wR*(F^2) values (all data)	0.1503
Goodness-of-fit on F^2	1.039
Largest difference peak & hole / e Å^{-3}	0.549, -0.477
Flack parameter	0.01(3)

Single crystal X-ray diffraction was carried out at 180(2) K on a Bruker D8-Quest PHOTON-100 diffractometer equipped with an Incoatec IμS Cu microsource (λ_{ave} = 1.5418 Å). Structures were solved using *SHELXT* and refined using full-matrix least squares on F^2 using *SHELXL* (ver. 2018/1). The absolute structure was determined from the Flack parameter, obtained by the Parsons method from 654 quotients. The crystals were plates with *ca* 5 micron thickness. To achieve significant diffracted intensity, a large plate was chosen, which exceeded the beam diameter in its major dimensions. This produced reasonable intensity to 0.84 Å resolution ($I/\sigma(I)$ falling below 3 around 0.9 Å). This crystal shape is not ideal, and the R_{int} value is correspondingly higher than might otherwise be seen. For the available crystals, however, the result is good, especially for the absolute structure, which is of principal interest.

SHELXT: Sheldrick, Acta Cryst. A71 (2015) 3-8.
SHELXL: Sheldrick, Acta Cryst. C71 (2015) 3-8.
Quotient method: Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259.


F
F
F
NH
N
N
N
C4
N4
C5
N3
C3
Cl1
N2
C2
C1
N1

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[23] "CCDC 1914926 contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service," can be found under www.ccdc.cam.ac.uk/structures, **2019**.