Electronic Supplementary Information

Rapid Construction of Substituted 3-Amino-1,5-Benzothiazepin-4(5*H*)-One Dipeptide Scaffolds Through an Ugi-4CR – Ullmann Cross-Coupling Sequence

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Contents

1. General Information

Thin-layer chromatography (TLC) was performed on glass plates pre-coated with silica gel 60F254 (Merck, Darmstadt, Germany) using the mentioned solvent systems. Visualization of the products on TLC plates was realized using UV light (254 nm) and $KMnO_4$ spray. Purification of organic molecules was performed via silica gel column chromatography (Davisil LC60A, 40−63 µm). Mass spectrometry (MS) was performed on a Micromass Q-Tof Micro spectrometer with electrospray ionization (ESI). High-resolution electrospray mass spectrometry (HRMS) data were recorded with a Micromass QTOF-micro system. Mass spectra were recorded with a LC-MS triple-quadrupole system. Data collection and spectrum analysis were done with Masslynx software. Analytical RP-HPLC was performed using a Waters 717plus autosampler, a Waters 1525 binary HPLC pump, and a Waters 2487 dual absorbance wavelength detector (Milford, MA) on a Grace (Deerfield, IL) Vydac RP C18 column (25 cm × 4.6 mm × 5 µm) using UV detection at 215 nm or an Agilent 1100 Series system (Waldbronn, Germany) with a SUPELCO Discovery BIO Wide Pore® (Bellefonte, PA, USA) RP C-18 column (15 cm x 2.1 mm, 3 µm) using UV detection at 215 nm. The mobile phase was a mixture of water and acetonitrile both containing 0.1% TFA (v/v). The used gradient runs from 3 to 100% acetonitrile in 20 minutes at a flow rate of 1 mL/min for the Waters system or 0.3 mL/min for the Agilent system. Preparative RP-HPLC purification was done on a Gilson (Middleton, WI) HPLC system with Gilson 322 pumps, controlled by the software package Unipoint and a reversed phase C18 column (DiscoveryBIO SUPELCO Wide Pore C18 column, 25 cm × 2.21 cm, 5 µm) using a mixture of water and acetonitrile (both containing 0.1% TFA v/v) as mobile phase. The gradient of the mobile phase was chosen according to the retention time of the desired product on the analytical HPLC. All fractions were lyophilized using a Flexy-Dry lyophilizer (FTS Systems, Warminster, PA). ^{1}H and ^{13}C NMR spectra (298 K) were recorded at 250 MHz and 63 MHz on a Bruker Avance DRX 250 spectrometer or at 500 MHz and 126 MHz respectively on a Bruker Avance II 500 spectrometer. Chemical shifts are in parts per million (ppm). Tetramethylsilane (TMS) or residual solvent signals were used as internal standard. The solvent used is mentioned in all cases, and the abbreviations used are as follows: s (singlet), br s (broad singlet), d (doublet), dd (double doublet), t (triplet), t* (pseudo triplet), q (quadruplet), and m (multiplet). The assignments were made using one- dimensional (1D) ^{1}H and ^{13}C spectra or two-dimensional (2D) HSQC, HMBC and COSY spectra. Specific rotations were measured on a polarimeter polartronic M Schmidt-Haensch using a 5 cm cell in standard conditions (MeOH / 20 °C / 589.3 nm^{air} / 589.44 nm^{vac}). All commercial reagents and solvents were used without further purification, unless otherwise stated. DMF was dried over microwave activated 4 Å molecular sieves, degassed with a gaseous N_2 flow and stored under argon atmosphere.

2. General Ugi-4CR Procedure for Compounds **19a-g**

In a flame-dried round-bottom flask were combined N^{α}-Boc-L-Cys(Trt)-OH (1 equiv, 2.2 mmol, 1.00 g), *o*-iodoaniline (1 equiv), aldehyde (1 equiv), and *tert*-butyl isocyanide (1 equiv) in MeOH (1.0 M) at room temperature. The flask was closed with a rubber septum, evacuated/backfilled with argon (3 cycles), and the reaction mixture was stirred for 24 hours at room temperature. The reaction conversion was monitored by RP-HPLC and TLC analysis. Upon reaction completion (± 24 hours), the volatiles were removed *in vacuo*. The resulting crude reaction product was dissolved in EtOAc and the organic layer was washed with a saturated aqueous $NaHCO_3$ solution (3x), a 20 wt.% aqueous citric acid solution (3x), and a saturated aqueous NaCl solution (3x). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude Ugi-4CR products **19a-g** were finally purified via silica gel column chromatography (EtOAc/*n*-hexane gradient).

3. General *S*-Trityl Deprotection Procedure for Compounds **20a-g**

To a solution of the *S*-trityl-protected Ugi-4CR dipeptide (1.00 equiv, 1.00 mmol) and triethylsilane (1.15 equiv) in CH_2Cl_2 (0.1 M), TFA (6% v/v) was added dropwise with a polytetrafluoroethylene (PTFE) syringe. The reaction mixture was stirred for 15 minutes and subsequently quenched with a saturated aqueous $NaHCO_3$ solution until pH 8-9 was reached. Both layers were separated, and the aqueous layer was extracted two times more with CH_2Cl_2. The combined organic layers were washed with a saturated aqueous NaCl solution (3x). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude *S*-trityl deprotected Ugi-4CR products **20a-g** were finally purified via silica gel column chromatography to yield white solids in all cases (EtOAc/*n*-hexane gradient).

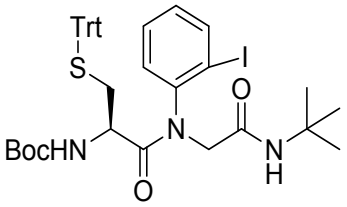
4. General Intramolecular CuI-Catalyzed C-S Ullmann Cyclization Procedure for Compounds **21a-g**

In a flame-dried round-bottom flask were combined the *S*-trityl deprotected Ugi-4CR product (1.0 equiv, 0.1 mmol), CuI (0.1 equiv), Cs_2CO_3 (2.0 equiv), and *N*,*N*-dimethyl glycine (0.2 equiv). The flask was closed with a rubber septum and evacuated/backfilled with argon (3 cycles). Dry and degassed DMF (0.03 M) was added via a syringe at room temperature. The mixture was left stirring for 4 hours at 80 °C under argon atmosphere. The reaction conversion was monitored by RP-HPLC and TLC analysis. Upon reaction completion (± 4 hours), the mixture was cooled to room temperature, filtered through dicalite and subsequently washed with methanol. After filtration, the volatiles were removed *in vacuo*. The resulting crude reaction product was partitioned between EtOAc and H_2O. Both layers were separated, and the aqueous layer was extracted two times more with EtOAc. The combined organic layers were washed with a saturated aqueous NaCl solution (3x). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude 1,5-benzothiazepin-4(5*H*)-one dipeptidomimetics **21a-g** were finally purified via silica gel column chromatography (EtOAc/*n*-hexane gradient).

5. Characterization of Compounds

5.1 Ugi-4CR Products 19a-g

Tert-butyl (R)-(1-((2-(tert-butylamino)-2-oxoethyl)(2-iodophenyl-amino)-1-oxo-3(tritylthio)propan-2-yl) carbamate **19a**



Yield: 84%

Chemical Formula: $C_{39}H_{44}IN_3O_4S$

Molecular Weight: 777.76

TLC: R_f = 0.26 (*n*-Hexane/EtOAc 7:4 v/v)

RP-HPLC (Agilent): t_{ret} = 22.8 min

RP-HPLC (VWR Hitachi): t_{ret} = 4.01 min

$[\alpha]_D$: -41.3 ° (*c* 2.52 mg/mL, MeOH)

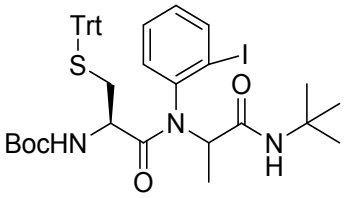
MS (ES+): $[M+Na]^+$ m/z 801

HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{39}H_{44}IN_3O_4SNa$ 800.1990; found 800.2004

^{1}H NMR ($CDCl_3$, 250 MHz, 298 K, rotamers ± 60:40) δ 1.17 (s, 3H, *t*Bu), 1.25 (s, 6H, *t*Bu), 1.32 (s, 5H, *t*Bu), 1.34 (s, 4H, *t*Bu), 1.90 (dd, 0.5H, *J* = 11.8 Hz, *J* = 5.2 Hz, CH^{β} L-Cys), 2.21 (dd, 0.5H, *J* = 12.3 Hz, *J* = 9.7 Hz, $CH^{\beta'}$ L-Cys), 2.37 (dd, 0.5H, *J* = 11.8 Hz, *J* = 5.1 Hz, CH^{β} L-Cys), 2.50 (dd, 0.5H, *J* = 12.4 Hz, *J* = 3.5 Hz, $CH^{\beta'}$ L-Cys), 3.16 (d, 0.4H, *J* = 14.8 Hz, CH^{α} Gly), 3.32 (d, 0.6H, *J* = 15.6 Hz, CH^{α} Gly), 3.99 (m, 0.5H, CH^{α} L-Cys), 4.19 (m, 0.5H, CH^{α} L-Cys), 4.77 (m, 1.6H, $CH^{\alpha'}$ Gly + *N*H Boc), 5.44 (d, 0.4H, *J* = 8.6 Hz, *N*H Boc), 6.26 (br s, 0.5H, *N*H amide), 6.40 (br s, 0.5H, *N*H amide), 6.94-7.83 (m, 19H, CH aromatic region)

^{13}C NMR ($CDCl_3$, 63 MHz, 298 K, rotamers) δ 28.37, 28.80, 32.77, 35.15, 50.25, 50.43, 51.51, 54.08, 54.83, 66.41, 66.84, 79.83, 79.97, 126.90, 127.02, 128.12, 128.24, 129.61, 130.10, 130.67, 130.84, 131.58, 140.61, 140.75, 142.98, 143.12, 144.39, 154.21, 155.41, 167.12, 170.94, 171.61

Tert-butyl ((2R)-1-((1-(tert-butylamino)-1-oxopropan-2-yl)(2-iodophenyl)amino)-1-oxo-3-(tritylthio) propan-2-yl)carbamate **19b**



Yield: 88%

Chemical Formula: $C_{40}H_{46}IN_3O_4S$

Molecular Weight: 791.79

MS (ES+): $[M+Na]^+$ m/z 814

Diastereomer 1

RP-HPLC (VWR Hitachi): t_{ret} = 4.16 min

TLC: R_f = 0.17 (*n*-Hexane/EtOAc 7:4 v/v)

$[\alpha]_D$: -32.9 ° (*c* 5.90 mg/mL, MeOH)

HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{40}H_{46}IN_3O_4SNa$ 814.2146; found 814.2188

^{1}H NMR ($CDCl_3$, 250 MHz, 298 K, rotamers ± 2:1) δ 0.99 (d, 2H, *J* = 7.0 Hz, CH_3^{β} Ala), 1.15-1.38 (m, 18H, *t*Bu region), 1.44 (d, 1H, *J* = 7.0 Hz, CH_3^{β} Ala), 1.73 (dd, 0.3 H, *J* = 11.9 Hz, *J* = 5.0 Hz, CH_2^{β} L-Cys), 2.44 (m, 1.7H, CH_2^{β} L-Cys), 3.95 (m, 0.8H, CH^{α} L-Cys), 4.14 (m, 0.2H, CH^{α} L-Cys), 4.27 (q, 0.3H, *J* = 6.9 Hz, CH^{α} Ala), 4.61 (m, 0.7H, CH^{α} Ala), 4.67 (d, 0.6H, *J* = 9.1 Hz, *N*H Boc), 5.53 (d, 0.4H, *J* = 8.4 Hz, *N*H Boc), 5.99 (br s, 0.7H, *N*H amide), 6.33 (br s, 0.3H, *N*H amide), 7.03-7.38 (m, 18H, CH aromatic region), 7.81 (d, 1H, *J* = 7.8 Hz, CH aromatic region)

^{13}C NMR ($CDCl_3$, 63 MHz, 298 K, rotamers) δ 13.99, 16.94, 28.29, 28.43, 28.59, 34.36, 34.64, 50.91, 51.33, 51.54, 51.66, 56.69, 66.72, 79.72, 102.04, 126.67, 127.92, 129.61, 129.43, 129.61, 129.85, 130.35, 130.61, 132.05, 139.88, 140.40, 144.29, 144.52, 154.19, 169.32, 170.59, 171.09, 172.05

Diastereomer 2

RP-HPLC (VWR Hitachi): t_{ret} = 4.27 min

TLC: R_f = 0.22 (*n*-Hexane/EtOAc 7:4 v/v)

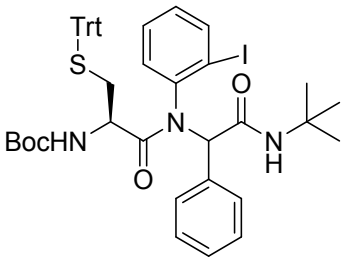
$[\alpha]_D$: +20.0 ° (*c* 5.80 mg/mL, MeOH)

HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{40}H_{46}IN_3O_4SNa$ 814.2146; found 814.2156

^{1}H NMR ($CDCl_3$, 250 MHz, 298 K) δ 0.87 (d, 3H, *J* = 7 Hz, CH_3^{β} Ala), 1.17 (s, 9H, *t*Bu), 1.37 (s, 9H, *t*Bu), 1.75 (dd, 1H, *J* = 11.9 Hz, *J* = 5.6 Hz, CH^{β} L-Cys), 2.17 (dd, 1H, *J* = 11.9 Hz, *J* = 4.3 Hz, $CH^{\beta'}$ L-Cys), 4.22 (m, 1H, CH^{α} L-Cys), 4.88 (q, 1H, *J* = 7.1 Hz, CH^{α} Ala), 5.60 (d, 1H, *J* = 8.5 Hz, *N*H Boc), 6.45 (br s, 1H, *N*H amide), 6.95-7.30 (m, 18H, CH aromatic region), 7.78 (d, 1H, *J* = 7.9 Hz, CH aromatic region)

^{13}C NMR ($CDCl_3$, 63 MHz, 298 K) δ 13.28, 28.43, 35.09, 51.33, 54.86, 66.12, 79.66, 103.18, 126.61, 127.89, 129.44, 129.60, 130.56, 130.86 139.30, 139.74, 140.22, 144.24, 154.27, 170.08, 171.10

Tert-butyl ((2R)-1-((2-(tert-butylamino)-2-oxo-1-phenylethyl)(2-iodophenyl)amino)-1-oxo-3-(tritylthio)propan-2-yl)carbamate **19c**



Yield: 80%

Chemical Formula: $C_{45}H_{48}IN_3O_4S$

Molecular Weight: 853.86

MS (ES+): $[M+Na]^+$ m/z 876

Diastereomer 1

RP-HPLC (VWR Hitachi): t_{ret} = 4.15 min

TLC: R_f = 0.15 (*n*-Hexane/EtOAc 7:3 v/v)

$[\alpha]_D$: -15.8 ° (*c* 0.63 mg/mL, MeOH)

HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{45}H_{48}IN_3O_4SNa$ 876.2302; found 876.2291

^{1}H NMR ($CDCl_3$, 250 MHz, 298 K, rotamers) δ 1.17, 1.20, 1.28, 1.35 (m, 18H, *t*Bu region), 2.30 (dd, 1H, *J* = 12.1 Hz, *J* = 8.6 Hz, CH^{β} L-Cys), 2.51 (dd, 1H, *J* = 12.2 Hz, *J* = 4.8 Hz, $CH^{\beta'}$ L-Cys), 4.05 (m, 1H, CH^{α} L-Cys), 4.86 (d, 1H, *J* = 10.0 Hz, *N*H Boc), 5.48 (s, 1H, CH^{α} phenylglycine), 5.88 (s, 1H, *N*H amide), 6.81-7.74 (m, 24H, CH aromatic region)

^{13}C NMR ($CDCl_3$, 63 MHz, 298 K, rotamers) δ 28.51, 34.33, 51.24, 51.82, 66.62, 67.06, 68.80, 79.82, 102.43, 126.63, 127.93, 129.61, 131.16, 133.34, 139.60, 140.53, 144.59, 146.85, 154.50, 168.70, 171.64

Diastereomer 2

RP-HPLC (VWR Hitachi): t_{ret} = 4.26 min

TLC: R_f = 0.20 (*n*-Hexane/EtOAc 7:3 v/v)

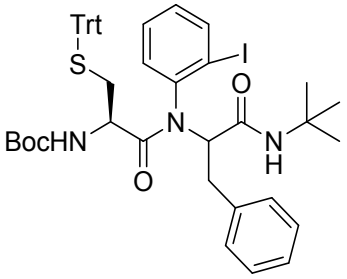
$[\alpha]_D$: -13.1 ° (*c* 1.07 mg/mL, MeOH)

HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{45}H_{48}IN_3O_4SNa$ 876.2302; found 876.2296

^{1}H NMR ($CDCl_3$, 250 MHz, 298 K) δ 1.21 (s, 9H, *t*Bu), 1.34 (s, 9H, *t*Bu), 1.97 (dd, 1H, *J* = 11.9 Hz, *J* = 6.6 Hz, CH^{β} L-Cys), 2.24 (dd, 1H, *J* = 11.9 Hz, *J* = 4.3 Hz, $CH^{\beta'}$ L-Cys), 4.14 (m, 1H, CH^{α} L-Cys), 5.45 (d, 1H, *J* = 8.8, *N*H Boc), 5.81 (m, 2H, CH^{α} phenylglycine + *N*H amide), 6.78-7.51 (m, 24H, CH aromatic region)

^{13}C NMR ($CDCl_3$, 63 MHz, 298 K) δ 28.51, 35.13, 51.43, 65.39, 66.15, 79.54, 103.84, 126.52, 127.27, 127.93, 129.56, 130.16, 131.41, 131.79, 131.79, 132.23 132.66, 139.23, 139.81, 140.50, 144.46, 156.34, 168.22, 171.10

Tert-butyl ((2R)-1-((1-(tert-butylamino)-1-oxo-3-phenylpropan-2-yl)(2-iodophenyl)amino)-1-oxo-3-(tritylthio)propan-2-yl)carbamate **19d**



Yield: 51%

Chemical Formula: $C_{46}H_{50}IN_3O_4S$

Molecular Weight: 867.89

MS (ES+): $[M+Na]^+$ m/z 890

Diastereomer 1

RP-HPLC (VWR Hitachi): t_{ret} = 4.31 min

TLC: R_f = 0.13 (Petroleum Ether/EtOAc 2:1 v/v)

$[\alpha]_D$: -96.0 ° (*c* 0.83 mg/mL, MeOH)

HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{46}H_{50}IN_3O_4SNa$ 890.2459; found 890.2496

^{1}H NMR ($CDCl_3$, 250 MHz, 298 K, rotamers) δ 1.16 (s, 9H, *t*Bu), 1.37 (s, 9H, *t*Bu), 2.51 (m, 3.2H, CH_2^{β} L-Cys + CH^{β} Phe), 2.93 (dd, 0.8H, *J* = 12.6 Hz, *J* = 5.0 Hz, CH^{β} Phe), 4.09 (m, 1H, CH^{α} L-Cys), 4.48 (dd, 1H, *J* = 10.6 Hz, *J* = 5.0 Hz, CH^{α} Phe), 4.81 (d, 1H, *J* = 9.5 Hz, *N*H Boc), 5.97 (br s, 1H, *N*H amide), 7.08-7.40 (m, 23H, CH aromatic region), 7.87 (d, 1H, *J* = 8.1 Hz, CH aromatic region)

^{13}C NMR ($CDCl_3$, 63 MHz, 298 K) δ 28.37, 34.44, 35.64, 50.84, 51.24, 64.85, 66.64, 79.64, 102.33, 126.63, 127.90, 128.50, 129.51, 129.62, 130.58, 132.58, 132.54, 136.99, 139.59, 141.29, 144.60, 154.10, 169.21, 172.00

Diastereomer 2

RP-HPLC (VWR Hitachi): t_{ret} = 4.39 min

TLC: R_f = 0.20 (Petroleum Ether/EtOAc 2:1 v/v)

$[\alpha]_D$: -131.0 ° (*c* 2.00 mg/mL, MeOH)

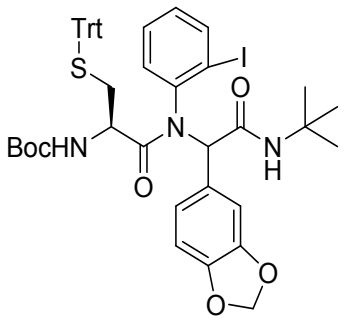
HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{46}H_{50}IN_3O_4SNa$ 890.2459; found 890.2496

^{1}H NMR ($CDCl_3$, 250 MHz, 298 K, rotamers) δ 1.09 (s, 9H, *t*Bu), 1.45 (s, 9H, *t*Bu), 1.83 (m, 1.2H, CH^{β} L-Cys), 2.23 (dd, 0.8H, *J* = 11.9 Hz, *J* = 4.1 Hz, CH^{β} L-Cys), 2.56 (m, 2H, CH^{β} Phe), 4.26 (m, 1H, CH^{α} L-Cys),

4.81 (dd, 1H, *J* = 9.3 Hz, *J* = 6.2 Hz, CH$^{\alpha}$ Phe), 5.63 (d, 1H, *J* = 8.5 Hz, *N*H Boc), 5.86 (br s, 1H, *N*H amide), 7.06 -7.44 (m, 23H, CH aromatic region), 7.87 (d, 1H, *J* = 7.9 Hz, CH aromatic region)

^{13}C NMR ($CDCl_3$, 63 MHz, 298 K) δ 28.28, 28.43, 34.80, 34.97, 51.19, 51.33, 61.44, 68.70, 79.48, 103.84, 126.52, 127.86, 128.33, 129.48, 130.59, 131.74, 136.92, 139.87, 144.35, 154.28, 168.19, 170.77

Tert-butyl ((2R)-1-((1-(benzo[d][1,3]dioxol-5-yl)-2-(tert-butylamino)-2-oxoethyl)(2-iodophenyl)amino)-1-oxo-3-(tritylthio)propan-2-yl)carbamate **19e**



Yield: 46%

Chemical Formula: $C_{46}H_{48}IN_3O_6S$

Molecular Weight: 897.87

MS (ES+): $[M+Na]^+$ m/z 921

Diastereomer 1

RP-HPLC (VWR Hitachi): t_{ret} = 4.09 min

TLC: R_f = 0.21 (Petroleum Ether/EtOAc 2:1 v/v)

[α]$_D$: -71.1 ° (*c* 10.07 mg/mL, MeOH)

HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{46}H_{48}IN_3O_6SNa$ 920.2201; found 920.2260

^{1}H NMR ($CDCl_3$, 250 MHz, 298 K, rotamers) δ 1.15 (s, 3H, *t*Bu), 1.21 (s, 6H, *t*Bu), 1.28 (s, 6H, *t*Bu), 1.36 (s, 3H, *t*Bu), 2.31 (dd, 1H, *J* = 12.1 Hz, *J* = 8.3 Hz, CH$^{\beta}$ L-Cys), 2.50 (dd, 1H, *J* = 12.2 Hz, *J* = 4.8 Hz, CH$^{\beta'}$ L-Cys), 4.12 (m, 1H, CH$^{\alpha}$ L-Cys), 4.84 (d, 1H, *J* = 9.2 Hz, *N*H Boc), 5.36 (s, 1H, CH$^{\alpha}$ methylenedioxyphenyl), 5.76 (m, 3H, CH_2 methylenedioxyphenyl + *N*H amide), 6.41-7.63 (m, 22H, CH aromatic region)

^{13}C NMR ($CDCl_3$, 63 MHz, 298 K, rotamers) δ 28.30, 28.42, 28.57, 34.41, 51.14, 51.69, 66.45, 66.59, 79.67, 101.09, 107.46, 111.24, 125.58, 126.60, 127.00, 127.28, 127.88, 128.15, 129.24, 129.61, 1230.26, 131.12, 133.37, 138.85, 139.64, 140.09, 140.53, 144.60, 147.00, 147.77, 154.42, 168.41, 171.43

Diastereomer 2

RP-HPLC (VWR Hitachi): t_{ret} = 4.17 min

TLC: R_f = 0.26 (Petroleum Ether/EtOAc 2:1 v/v)

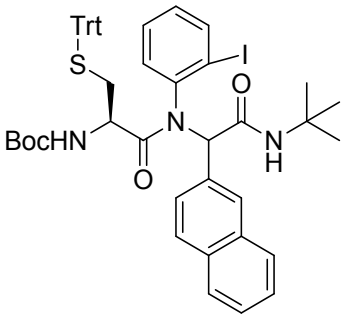
[α]$_D$: -20.1 ° (*c* 2.78 mg/mL, MeOH)

HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{46}H_{48}IN_3O_6SNa$ 920.2201; found 920.2265

^{1}H NMR ($CDCl_3$, 250 MHz, 298 K, rotamers) δ 1.20 (s, 9H, *t*Bu), 1.33 (s, 9H, *t*Bu), 1.93 (dd, 1H, *J* = 11.7 Hz, *J* = 6.2 Hz, CH^{β} L-Cys), 2.22 (dd, 1H, *J* = 11.8 Hz, *J* = 3.7 Hz, $CH^{\beta'}$ L-Cys), 4.13 (m, 1H, CH^{α} L-Cys), 5.45 (d, 1H, *J* = 8.6 Hz, *N*H Boc), 5.75 (m, 4H, CH^{α} methylenedioxyphenyl + CH_2 methylenedioxyphenyl + *N*H amide), 6.42-7.59 (m, 22H, CH aromatic region)

^{13}C NMR ($CDCl_3$, 63 MHz, 298 K, rotamers) δ 28.73-28.84, 35.44, 51.71, 51.96, 65.05, 66.44, 79.76, 101.38, 104.24, 107.80, 111.78, 125.67, 126.15, 127.59, 128.20, 129.29, 129.88, 130.57, 132.51, 140.21, 144.78, 147.21, 148.11, 154.59, 168.49, 171.25

Tert-butyl ((2R)-1-((2-(tert-butylamino)-1-(naphthalen-2-yl)-2-oxoethyl)(2-iodophenyl)amino)-1-oxo-3-(tritylthio)propan-2-yl)carbamate **19f**



Yield: 44%

Chemical Formula: $C_{49}H_{50}IN_3O_4S$

Molecular Weight: 903.92

MS (ES+): $[M+Na]^+$ m/z 926

Diastereomer 1

RP-HPLC (VWR Hitachi): t_{ret} = 4.30 min

TLC: R_f = 0.24 (*n*-hexane/EtOAc 7:4 v/v)

$[\alpha]_D$: -9.0 ° (*c* 0.67 mg/mL, MeOH)

HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{49}H_{50}IN_3O_4SNa$ 926.2459; found 926.2484

^{1}H NMR ($CDCl_3$, 250 MHz, 298 K, rotamers ± 2:1) δ 1.26 (s, 3H, *t*Bu), 1,29 (s, 6H, *t*Bu), 1.37 (s, 6H, *t*Bu), 1.46 (s, 3H, *t*Bu), 2.42 (dd, 1H, *J* = 12.1 Hz, *J* = 8.4 Hz, CH^{β} L-Cys), 2.61 (dd, 1H, *J* = 12.1 Hz, *J* = 4.9 Hz, $CH^{\beta'}$ L-Cys), 4.18 (m, 0.8H, CH^{α} L-Cys), 4.32 (m, 0.2H, CH^{α} L-Cys), 4.94 (d, 1H, *J* = 8.75 Hz, *N*H Boc), 5.73 (s, 1H, CH^{α} naphthylglycine), 5.78 (br s, 1H, *N*H amide), 6.83-7.84 (m, 26H, CH aromatic region)

^{13}C NMR ($CDCl_3$, 63 MHz, 298 K, rotamers) δ 28.32, 28.58, 34.49, 34.77, 51.09, 51.72, 66.17, 66.58, 66.91, 79.62, 102.58, 126.03, 126.58, 127.88, 129.16, 129.46, 129.63, 130.18, 131.59, 132.46, 133.00, 133.46, 139.55, 140.54, 144.34, 144.63, 154.37, 168.35, 171.41

Diastereomer 2

RP-HPLC (VWR Hitachi): t_{ret} = 4.38 min

TLC: R_f = 0.26 (*n*-hexane/EtOAc 7:4 v/v)

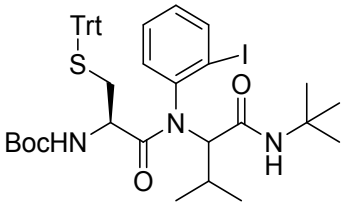
$[\alpha]_D$: +12.0 ° (*c* 0.33 mg/mL, MeOH)

HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{49}H_{50}IN_3O_4SNa$ 926.2459; found 926.2485

^{1}H NMR ($CDCl_3$, 250 MHz, 298 K) δ 1.29 (s, 9H, *t*Bu), 1.42 (s, 9H, *t*Bu), 2.06 (dd, 1H, *J* = 11.9 Hz, *J* = 6.6 Hz, CH^{β} L-Cys), 2.36 (dd, 1H, *J* = 12.1 Hz, *J* = 4.4 Hz, $CH^{\beta'}$ L-Cys), 4.24 (m, 1H, CH^{α} L-Cys), 5.54 (d, 1H, *J* = 8.9 Hz, *N*H Boc), 5.87 (br s, 1H, *N*H amide), 6.05 (s, 1H, CH^{α} naphthylglycine), 6.81-7.76 (m, 26H, CH aromatic region)

^{13}C NMR ($CDCl_3$, 63 MHz, 298 K) δ 28.41, 28.54, 35.18, 51.38, 51.72, 65.51, 79.44, 126.02, 126.52, 127.44, 127.88, 128.08, 128.92, 129.57, 130.19, 131.68, 132.20, 132.53, 133.01, 139.85, 144.49, 154.29, 168.11, 171.04

Tert-butyl ((2R)-1-((1-(tert-butylamino)-3-methyl-1-oxobutan-2-yl)(2-iodophenyl)amino)-1-oxo-3-(tritylthio)propan-2-yl)carbamate **19g**



Yield: 52%

Chemical Formula: $C_{42}H_{50}IN_3O_4S$

Molecular Weight: 819.26

MS (ES+): $[M+Na]^+$ m/z 842

Diastereomer 1

RP-HPLC (VWR Hitachi): t_{ret} = 4.12 min

TLC: R_f = 0.26 (Petroleum Ether/EtOAc 2:1 v/v)

$[\alpha]_D$: +26.5 ° (*c* 2.87 mg/mL, MeOH)

HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{42}H_{50}IN_3O_4SNa$ 842.2459; found 842.2477

^{1}H NMR ($CDCl_3$, 250 MHz, 298 K) δ 0.80 (d, 3H, *J* = 6.5 Hz, CH_3^{γ} Val), 0.87 (d, 3H, *J* = 6.5 Hz, $CH_3^{\gamma'}$ Val), 1.18 (s, 9H, *t*Bu), 1.39 (s, 9H, *t*Bu), 1.77 (dd, 1H, *J* = 11.7 Hz, *J* = 6.0 Hz, CH^{β} L-Cys), 2.09 (m, 1H, CH^{β} Val), 2.18 (dd, 1H, *J* = 11.7 Hz, *J* = 4.5 Hz, $CH^{\beta'}$ L-Cys), 4.25 (m, 1H, CH^{α} L-Cys), 4.35 (d, 1H, *J* = 10.7 Hz, CH^{α} Val), 5.58 (d, 1H, *J* = 8.5 Hz, *N*H Boc), 5.76 (s, 1H, *N*H amide), 7.08-7.32 (m, 18H, CH aromatic region), 7.78 (dd, 1H, *J* = 8.0 Hz, *J* = 1.1 Hz, CH aromatic region)

^{13}C NMR ($CDCl_3$, 63 MHz, 298 K) δ 19.22, 20.07, 28.48, 29.90, 35.43, 51.78, 66.00, 67.53, 79.52, 103.42, 126.52, 127.88, 128.97, 129.45, 129.57, 130.16, 140.46, 144.32, 154.29, 167.06, 171.75

Diastereomer 2

RP-HPLC (VWR Hitachi): t_{ret} = 4.30 min

TLC: R_f = 0.29 (Petroleum Ether/EtOAc 2:1 v/v)

$[\alpha]_D$: +12.9 ° (*c* 0.47 mg/mL, MeOH)

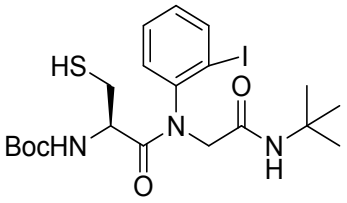
HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{42}H_{50}IN_3O_4SNa$ 842.2459; found 842.2484

^{1}H NMR ($CDCl_3$, 250 MHz, 298 K, rotamers) δ 0.77 (m, 6H, CH_3^{γ} Val + $CH_3^{\gamma'}$ Val), 1.25 (s, 9H, *t*Bu), 1.40 (s, 9H, *t*Bu), 1.75 (dd, 1H, *J* = 11.7 Hz, *J* = 6.0 Hz, CH^{β} L-Cys), 2.23 (dd, 1H, *J* = 11.7 Hz, ^3J = 4.5 Hz, $CH^{\beta'}$ L-Cys), 2.45 (m, 1H, CH^{β} Val), 3.35 (d, 1H, *J* = 10.4 Hz, CH^{α} Val), 4.01 (m, 0.3H, CH^{α} L-Cys), 4.19 (m, 0.7H, CH^{α} L-Cys), 5.41 (d, 1H, J = Hz, *N*H Boc), 5.52 (d, 1H, *J* = 8.5 Hz, *N*H Boc), 6.89-7.28 (m, 18H, CH aromatic region), 7.44 (s, 0.8H, *N*H amide), 7.52 (s, 0.2H, *N*H amide), 7.76 (dd, 1H, *J* = 8.0 Hz, *J* = 1.1 Hz, CH aromatic region)

^{13}C NMR ($CDCl_3$, 63 MHz, 298 K, rotamers) δ 19.72, 21.99, 27.80, 28.55-29.01, 35.12, 51.69, 51.19, 52.91, 66.36, 79.94, 81.10, 101.91, 126.83, 129.76, 129.86, 130.02, 130.38, 140.43, 140.92, 144.08, 144.56, 154.61, 169.87, 172.41

5.2 *S*-trityl Deprotected Ugi-4CR Products 20a-g

(R)-tert-butyl (1-((2-(tert-butylamino)-2-oxoethyl)(2-iodophenyl)amino)-3-mercapto-1-oxopropan-2-yl)carbamate **20a**



Yield: 82%

Chemical Formula: $C_{20}H_{30}IN_3O_4S$

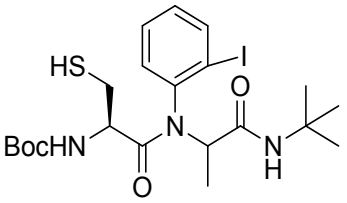
Molecular Weight: 535.44

TLC: R_f = 0.20 (*n*-Hexane/EtOAc 3:1 v/v)

RP-HPLC (Agilent): t_{ret} = 18.1 min

MS (ES+): $[M+Na]^+$ m/z 558

Tert-butyl ((2R)-1-((1-(tert-butylamino)-1-oxopropan-2-yl)(2-iodophenyl)amino)-3-mercapto-1-oxopropan-2-yl)carbamate **20b**



Yield: 79%

Chemical Formula: $C_{21}H_{32}IN_3O_4S$

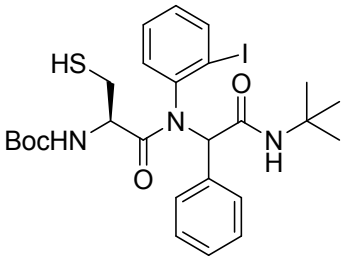
Molecular Weight: 549.47

TLC: R_f = 0.14 and 0.21 (*n*-Hexane/EtOAc 3:1 v/v)

RP-HPLC (VWR Hitachi): t_{ret} = 3.24 and 3.29 min

MS (ES+): $[M+Na]^+$ m/z 572

Tert-butyl ((2R)-1-((2-(tert-butylamino)-2-oxo-1-phenylethyl)(2-iodophenyl)amino)-3-mercapto-1-oxopropan-2-yl)carbamate **20c**



Yield: 73%

Chemical Formula: $C_{26}H_{34}IN_3O_4S$

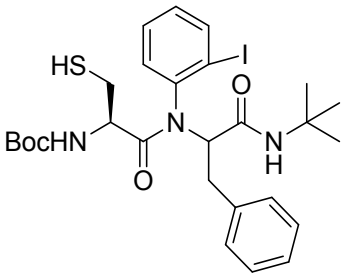
Molecular Weight: 611.54

TLC: R_f = 0.19 and 0.24 (*n*-Hexane/EtOAc 3:1 v/v)

RP-HPLC (VWR Hitachi): t_{ret} = 3.46 and 3.54 min

MS (ES+): $[M+Na]^+$ m/z 634

Tert-butyl ((2R)-1-((1-(tert-butylamino)-1-oxo-3-phenylpropan-2-yl)(2-iodophenyl)amino)-3-mercapto-1-oxopropan-2-yl)carbamate **20d**



Yield: 64%

Chemical Formula: $C_{27}H_{36}IN_3O_4S$

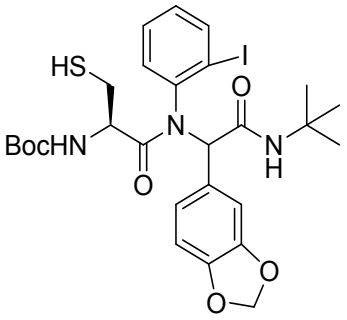
Molecular Weight: 625.57

TLC: R_f = 0.22 and 0.32 (*n*-Hexane/EtOAc 3:1 v/v)

RP-HPLC (VWR Hitachi): t_{ret} = 3.56 and 3.60 min

MS (ES+): $[M+Na]^+$ m/z 648

Tert-butyl ((2R)-1-((1-(benzo[d][1,3]dioxol-5-yl)-2-(tert-butylamino)-2-oxoethyl)(2-iodophenyl)amino)-3-mercapto-1-oxopropan-2-yl)carbamate **20e**



Yield: 68%

Chemical Formula: $C_{27}H_{34}IN_3O_6S$

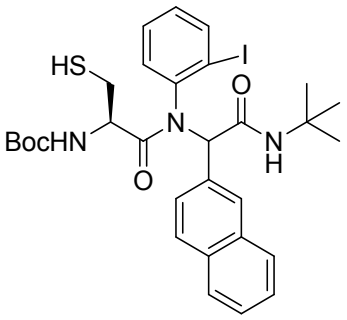
Molecular Weight: 655.55

TLC: R_f = 0.21 and 0.24 (*n*-hexane/EtOAc 3:1 v/v)

RP-HPLC (VWR Hitachi): t_{ret} = 3.32 and 3.40 min

MS (ES+): $[M+Na]^+$ m/z 678

Tert-butyl ((2R)-1-((2-(tert-butylamino)-1-(naphthalen-2-yl)-2-oxoethyl)(2-iodophenyl)amino)-3-mercapto-1-oxopropan-2-yl)carbamate **20f**



Yield: 72%

Chemical Formula: $C_{30}H_{36}IN_3O_4S$

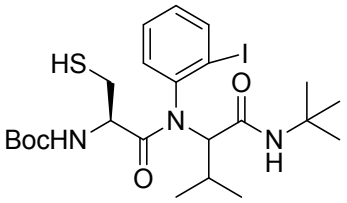
Molecular Weight: 661.60

TLC: R_f = 0.31 and 0.35 (*n*-Hexane/EtOAc 2:1 v/v)

RP-HPLC (VWR Hitachi): t_{ret} = 3.64 and 3.71 min

MS (ES+): $[M+Na]^+$ m/z 684

Tert-butyl ((2R)-1-((1-(tert-butylamino)-3-methyl-1-oxobutan-2-yl)(2-iodophenyl)amino)-3-mercapto-1-oxopropan-2-yl)carbamate **20g**



Yield: 63%

Chemical Formula: $C_{23}H_{36}IN_3O_4S$

Molecular Weight: 577.52

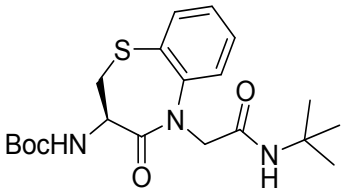
TLC: R_f = 0.24 and 0.29 (*n*-Hexane/EtOAc 2:1 v/v)

RP-HPLC (VWR Hitachi): t_{ret} = 3.38 and 3.44 min

MS (ES+): $[M+Na]^+$ m/z 600

5.3 1,5-Benzothiazepin-4(5*H*)-one Dipeptidomimetics 21a-g

(R)-tert-butyl (5-(2-(tert-butylamino)-2-oxoethyl)-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-3-yl)carbamate **21a**



Yield: 78%

Chemical Formula: $C_{20}H_{29}N_3O_4S$

Molecular Weight: 407.53

TLC: R_f = 0.35 (Petroleum Ether/EtOAc 1:1 v/v)

RP-HPLC (Agilent): t_{ret} = 16.2 min

RP-HPLC (VWR Hitachi): t_{ret} = 2.69 min

$[\alpha]_D$: -200.2 ° (*c* 14.73 mg/mL, MeOH)

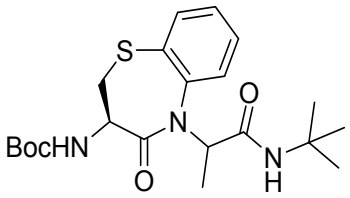
MS (ES+): $[M+Na]^+$ m/z 430

HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{20}H_{29}N_3O_4S$ 408,1952; found 408.1968

^{1}H NMR ($CDCl_3$, 500 MHz, 298 K) δ 1.27 (s, 9H, *t*Bu), 1.39 (s, 9H, *t*Bu), 2.92 (t*, 1H, *J* = 11.4 Hz, CH^{β} BT), 3.77 (dd, 1H, *J* = 11.1 Hz, *J* = 6.7 Hz, $CH^{\beta'}$ BT), 4.21 (d, 1H, *J* = 16.5 Hz, CH^{α} Gly), 4.41 (m, 1H, CH^{α} BT), 4.79 (d, 1H, *J* = 16.5 Hz, $CH^{\alpha'}$ Gly), 5.61 (d, 1H, *J* = 7.8 Hz, *N*H Boc), 6.75 (br s, 1H, *N*H amide), 7.28 (dd, 1H, *J* = 7.5 Hz, *J* = 1.3 Hz, CH aromatic), 7.37 (m, 1H, CH aromatic), 7.47 (m, 1H, CH aromatic), 7.67 (dd, 1H, *J* = 7.7 Hz, *J* = 1.4 Hz, CH aromatic)

^{13}C NMR ($CDCl_3$, 125 MHz, 298 K) δ 28.48, 28.84, 39.10, 50.97, 51.96, 53.67, 80.49, 124.60, 126.79, 128.37, 131.49, 136.01, 144.59, 154.77, 166.77, 171.30

Tert-butyl ((3R)-5-(1-(tert-butylamino)-1-oxopropan-2-yl)-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-3-yl)carbamate **21b**



Yield: 72%

Chemical Formula: $C_{21}H_{31}N_3O_4S$

Molecular weight: 421.56

MS (ES+): $[M+Na]^+$ m/z 444

(R,R)-diastereomer

RP-HPLC (VWR Hitachi): t_{ret} = 3.02 min

TLC: R_f = 0.20 (Petroleum Ether/EtOAc 2:1 v/v)

$[\alpha]_D$: -213.8.0 ° (*c* 0.53 mg/mL, MeOH)

HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{21}H_{31}N_3O_4SNa$ 444.1927; found 444.1896

^{1}H NMR (DMSO-d_6, 500 MHz, 303 K) δ 1.06 (s, 9H, *t*Bu), 1.34 (s, 9H, *t*Bu), 1.40 (d, 3H, *J* = 6.8 Hz, CH_3^{β} Ala), 3.02 (t*, 1H, *J* = 11.8 Hz, CH^{β} BT), 3.41 (dd, 1H, *J* = 11.3 Hz, *J* = 7.1 Hz, $CH^{\beta'}$ BT), 3.96 (m, 1H, CH^{α} BT), 4.69 (q, 1H, *J* = 6.8 Hz, CH^{α} Ala), 6.52 (br s, 1H, *N*H amide), 7.33-7.67 (m, 5H, CH aromatic region + *N*H Boc)

^{13}C NMR ($CDCl_3$, 125 MHz, 298 K) δ 16.84, 28.35, 39.14, 51.55, 58.34, 80.50, 125.47, 127.87, 128.78, 131.20, 135.90, 143.83, 154.70, 168.52, 171.11

(R,S)-diastereomer

RP-HPLC (VWR Hitachi): t_{ret} = 3.14 min

TLC: R_f = 0.29 (Petroleum Ether/EtOAc 2:1 v/v)

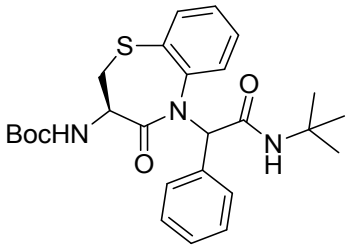
$[\alpha]_D$: -198.9 ° (*c* 0.63 mg/mL, MeOH)

HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{21}H_{31}N_3O_4SNa$ 444.1927; found 444.1905

^{1}H NMR (DMSO-d_6, 500 MHz, 298 K) δ 0.94 (d, 3H, *J* = 7.3 Hz, CH_3^{β} Ala), 1.30 (s, 9H, *t*Bu), 1.33 (s, 9H, *t*Bu), 2.98 (t*, 1H, *J* = 11.8 Hz, CH^{β} BT), 3.39 (dd, 1H, *J* = 11.4, *J* = 6.9 Hz, $CH^{\beta'}$ BT), 3.98 (m, 1H, CH^{α} BT), 5.14 (q, 1H, *J* = 7.5 Hz, CH^{α} Ala), 7.11 (br s, 1H, *N*H amide), 7.37-7.69 (m, 5H, CH aromatic region + *N*H Boc)

^{13}C NMR ($CDCl_3$, 125 MHz, 298 K) δ 14.26, 28.44-28.82, 38.17, 51.49, 57.03, 80.51, 126.00, 128.15, 128.75, 130.93, 135.85, 142.91, 154.92, 170.41, 171.46

Tert-butyl ((3R)-5-(2-(tert-butylamino)-2-oxo-1-phenylethyl)-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-3-yl)carbamate **21c**



Yield: 46%

Chemical Formula: $C_{26}H_{33}N_3O_4S$

Molecular Weight: 483.63

MS (ES+): $[M+Na]^+$ m/z 506

Diastereomer 1

RP-HPLC (VWR Hitachi): t_{ret} = 3.33 min

TLC: R_f = 0.22 (*n*-Hexane /EtOAc 7:4 v/v)

$[\alpha]_D$: -354.5 ° (*c* 3.30 mg/mL, MeOH)

HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{26}H_{33}N_3O_4SNa$ 506.2084; found 506.2064

^{1}H NMR ($CDCl_3$, 500 MHz, 298 K) δ 1.19 (s, 9H, *t*Bu), 1.41 (s, 9H, *t*Bu), 2.92 (t*, 1H, *J* = 11.0 Hz, CH^{β} BT), 3.80 (dd, 1H, *J* = 11.0 Hz, *J* = 7.0 Hz, $CH^{\beta'}$ BT), 4.49 (m, 1H, CH^{α} BT), 5.56 (dd, 1H, *J* = 7.9 Hz, *N*H Boc), 6.06 (s, 1H, CH^{α} phenylglycine), 6.43 (br s, 1H, *N*H amide), 7.13-7.36 (m, 8H, CH aromatic region), 7.65 (dd, 1H, *J* = 7.5 Hz, *J* = 1.7, CH aromatic)

^{13}C NMR ($CDCl_3$, 125 MHz, 298 K) δ 28.45, 28.50, 38.75, 51.40, 68.02, 126.39, 128.32, 128.50, 128.64, 128.79, 129.73, 130.72, 135.74, 154.83, 167.48, 171.40

Diastereomer 2

RP-HPLC (VWR Hitachi): t_{ret} = 3.42 min

TLC: R_f = 0.26 (*n*-Hexane /EtOAc 7:4 v/v)

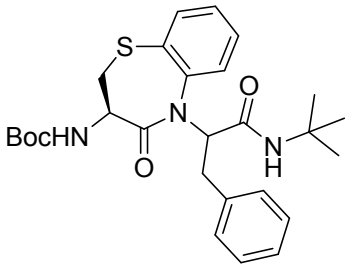
$[\alpha]_D$: -88.9 ° (*c* 0.90 mg/mL, MeOH)

HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{26}H_{33}N_3O_4SNa$ 506.2084; found 506.2073

^{1}H NMR ($CDCl_3$, 500 MHz, 298 K) δ 1.41 (s, 9H, *t*Bu), 1.45 (s, 9H, *t*Bu), 2.84 (t*, 1H, *J* = 11.0 Hz, CH^{β} BT), 3.73 (m, 1H, $CH^{\beta'}$ BT), 4.38 (m, 1H, CH^{α} BT), 5.62 (d, 1H, *J* = 7.3 Hz, *N*H Boc), 6.06 (s, 1H, s, CH^{α} phenylglycine), 6.35 (br s, 1H, *N*H amide), 7.07-7.57 (m, 9H, CH aromatic region)

^{13}C NMR ($CDCl_3$, 125 MHz, 298 K) δ 28.45, 28.84, 38.56, 51.63, 67.22, 80.57, 127.70, 128.47, 129.68, 130.27, 134.00, 135.28, 143.00, 154.85, 168.76, 171.72

Tert-butyl ((3R)-5-(1-(tert-butylamino)-1-oxo-3-phenylpropan-2-yl)-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-3-yl)carbamate **21d**



Yield: 61%

Chemical Formula: $C_{27}H_{35}N_3O_4S$

Molecular Weight: 497.65

MS (ES+): $[M+H]^+$ m/z 498

Diastereomer 1

RP-HPLC (VWR Hitachi): t_{ret} = 3.41 min

TLC: R_f = 0.31 (Petroleum Ether/EtOAc 3:1 v/v)

HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{27}H_{35}N_3O_4SNa$ 520.2241; found 520.2213

^{1}H NMR ($CDCl_3$, 500 MHz, 298 K) δ 0.96 (s, 9H, *t*Bu), 1.42 (s, 9H, *t*Bu), 2.87 (t*, 1H, *J* = 11.3 Hz, CH^{β} BT), 3.17 (dd, 1H, *J* = 13.1 Hz, *J* = 4.5 Hz, CH^{β} Phe), 3.74 (m, 2H, $CH^{\beta'}$ BT + $CH^{\beta'}$ Phe), 4.38 (m, 1H, CH^{α} BT), 5.36 (dd, 1H, *J* = 9.0 Hz, *J* = 4.5 Hz, CH^{α} Phe), 5.52 (d, 1H, *J* = 8.1 Hz, *N*H Boc), 5.87 (br s, 1H, *N*H amide), 7.21-7.65 (m, 9H, CH aromatic region)

^{13}C NMR ($CDCl_3$, 125 MHz, 298 K) δ 28.42-28.82, 38.32, 39.53, 51.32, 61.77, 63.86, 80.59, 112.64, 121.03, 125.87, 126.83, 128.05, 128.70, 128.91, 129.92, 131.23, 136.10, 138.61, 143.62, 154.76, 168.71, 171.57

Diastereomer 2

RP-HPLC (VWR Hitachi): t_{ret} = 3.52 min

TLC: R_f = 0.36 (Petroleum Ether/EtOAc 3:1 v/v)

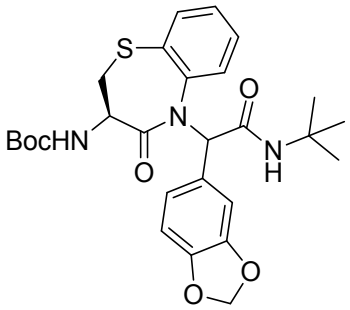
$[\alpha]_D$: -119.0 ° (*c* 2.10 mg/mL, MeOH)

HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{27}H_{35}N_3O_4SNa$ 520.2241; found 520.2216

^{1}H NMR ($CDCl_3$, 500 MHz, 298 K) δ 1.35 (s, 9H, *t*Bu), 1.41 (s, 9H, *t*Bu), 2.77 (t*, 1H, *J* = 11.3 Hz, CH^{β} BT), 3.01 (m, 1H, CH^{β} Phe), 3.34 (dd, 1H, *J* = 14.1 Hz, *J* = 6.2 Hz, $CH^{\beta'}$ Phe), 3.63 (dd, 1H, *J* = 11.1 Hz, *J* = 6.8 Hz, $CH^{\beta'}$ BT), 4.27 (m, 1H, CH^{α} BT), 4.86 (m, 1H, CH^{α} Phe), 5.49 (d, 1H, *J* = 8.1 Hz, *N*H Boc), 6.81 (br s, 1H, *N*H amide), 7.03-7.56 (m, 9H, CH aromatic region)

^{13}C NMR ($CDCl_3$, 125 MHz, 298 K) δ 28.45-28.80, 34.30, 38.61, 51.73, 65.60, 80.51, 126.19, 126.99, 128.87, 129.64, 130.98, 135.77, 138.07, 143.51, 154.86, 169.01, 172.09

Tert-butyl ((3R)-5-(1-(benzo[d][1,3]dioxol-5-yl)-2-(tert-butylamino)-2-oxoethyl)-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-3-yl)carbamate **21e**



Yield: 51%

Chemical Formula: $C_{27}H_{33}N_3O_6S$

Molecular Weight: 527.64

MS (ES+): $[M+H]^+$ m/z 528

Diastereomer 1

RP-HPLC (VWR Hitachi): t_{ret} = 3.17 min

TLC: R_f = 0.31 (*n*-Hexane/EtOAc 3:2 v/v)

$[\alpha]_D$: -16.6 ° (*c* 1.57 mg/mL, MeOH)

HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{27}H_{33}N_3O_6SNa$ 550.1982; found 550.1962

^{1}H NMR ($CDCl_3$, 500 MHz, 298 K) δ 1.21 (s, 9H, *t*Bu), 1.41 (s, 9H, *t*Bu), 2.90 (t*, 1H, *J* = 11.2 Hz, CH^{β} BT), 3.79 (m, 1H, $CH^{\beta'}$ BT), 4.44 (m, 1H, CH^{α} BT), 5.55 (d, 1H, *J* = 7.9 Hz, *N*H Boc), 5.90 (s, 1H, CH^{α} methylenedioxyphenyl), 5.97 (m, 2H, CH_2 methylenedioxyphenyl), 6.44 (br s, 1H, *N*H amide), 6.76-7.65 (m, 7H, CH aromatic region)

^{13}C NMR ($CDCl_3$, 125 MHz, 298 K) δ 28.52, 38.67, 51.36, 67.99, 80.49, 101.42, 108.34, 109.52, 122.64, 126.54, 128.58, 130.68, 135.73, 143.66, 147.72, 154.80, 167.55, 171.34

Diastereomer 2

RP-HPLC (VWR Hitachi): t_{ret} = 3.24 min

TLC: R_f = 0.36 (*n*-Hexane/EtOAc 3:2 v/v)

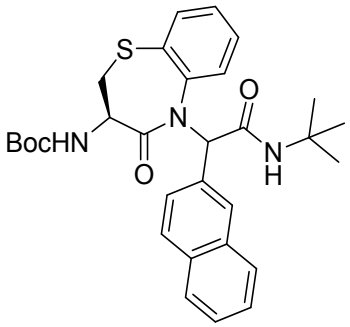
$[\alpha]_D$: -151.3 ° (*c* 3.77 mg/mL, MeOH)

HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{27}H_{33}N_3O_6SNa$ 550.1982; found 550.1978

^{1}H NMR ($CDCl_3$, 500 MHz, 298 K) δ 1.41 (s, 9H, *t*Bu), 1.44 (s, 9H, *t*Bu), 2.81 (t*, 1H, *J* = 11.1 Hz, CH^{β} BT), 3.73 (m, 1H, $CH^{\beta'}$ BT), 4.35 (m, 1H, CH^{α} BT), 5.59 (d, 1H, *J* = 7.1 Hz, *N*H Boc), 5.87 (m, 2H, CH_2 methylenedioxyphenyl), 5.94 (s, 1H, CH^{α} methylenedioxyphenyl), 6.25 (br s, 1H, *N*H amide), 6.60-7.62 (m, 7H, CH aromatic region)

^{13}C NMR ($CDCl_3$, 125 MHz, 298 K) δ 28.47-28.86, 38.59, 51.53, 66.74, 80.39, 101.32, 108.05, 110.22, 123.74, 127.89, 128.14, 128.54, 130.19, 135.27, 143.03, 147.67, 154.72, 168.52, 171.37

Tert-butyl ((3R)-5-(2-(tert-butylamino)-1-(naphthalen-2-yl)-2-oxoethyl)-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-3-yl)carbamate **21f**



Yield: 49%

Chemical Formula: $C_{30}H_{35}N_3O_4S$

Molecular Weight: 533.69

RP-HPLC (VWR Hitachi): t_{ret} = 3.42 and 3.52 min

MS (ES+): $[M+Na]^+$ m/z 556

Diastereomer 1 (only major peak isolated)

RP-HPLC (VWR Hitachi): t_{ret} = 3.52 min

TLC: R_f = 0.38 (*n*-hexane/EtOAc 3:2 v/v)

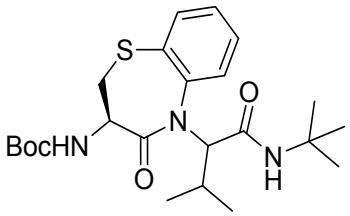
$[\alpha]_D$: -320.0 ° (*c* 0.80 mg/mL, MeOH)

HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{30}H_{35}N_3O_4SNa$ 556.2241; found 556.2229

^{1}H NMR ($CDCl_3$, 500 MHz, 298 K) δ 1.40 (s, 9H, *t*Bu), 1.46 (s, 9H, *t*Bu), 2.85 (t*, 1H, *J* = 11.0 Hz, CH^{β} BT), 3.75 (dd, 1H, *J* = 10.9 Hz, *J* = 6.8 Hz, $CH^{\beta'}$ BT), 4.40 (m, 1H, CH^{α} BT), 5.61 (d, 1H, *J* = 7.5 Hz, *N*H Boc), 6.19 (br s, 2H, CH^{α} naphthylglycine + *N*H amide), 6.99-7.77 (m, 11H, CH aromatic region)

^{13}C NMR ($CDCl_3$, 125 MHz, 298 K) δ 28.64, 29.08, 38.84, 51.69, 52.42, 67.13, 80.48, 126.52, 126.82, 127.81, 128.04, 128.23, 128.47, 128.61, 129.28, 130.28, 131.80, 133.06, 133.11, 135.35, 143.11, 154.84, 168.65, 171.60

Tert-butyl ((3R)-5-(1-(tert-butylamino)-3-methyl-1-oxobutan-2-yl)-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-3-yl)carbamate **21g**



Yield: 31%

Chemical Formula: $C_{23}H_{35}N_3O_4S$

Molecular Weight: 449.61

MS (ES+): $[M+H]^+$ m/z 450

Diastereomer 1

RP-HPLC (VWR Hitachi): t_{ret} = 3.17 min

TLC: R_f = 0.31 (Petroleum Ether/EtOAc 3:1 v/v)

$[\alpha]_D$: -170.8 ° (*c* 0.43 mg/mL, MeOH)

HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{23}H_{35}N_3O_4SNa$ 472.2241; found 472.2248

^{1}H NMR ($CDCl_3$, 500 MHz, 298 K) δ 1.06 (m, 15H, CH_3^{γ} Val + $CH_3^{\gamma'}$ Val + *t*Bu), 1.41 (s, 9H, *t*Bu), 2.74 (m, 1H, CH^{β} Val), 2.89 (t*, 1H, *J* = 11.2 Hz, CH^{β} BT), 3.73 (dd, 1H, *J* = 11.0 Hz, *J* = 6.7 Hz, $CH^{\beta'}$ BT), 4.41 (m, 1H, CH^{α} BT), 4.71 (d, 1H, *J* = 9.6 Hz, CH^{α} Val), 5.48 (d, 1H, *J* = 7.9 Hz, *N*H Boc), 6.22 (br s, 1H, *N*H amide), 7.24-7.63 (m, 4H, CH aromatic region)

^{13}C NMR ($CDCl_3$, 125 MHz, 298 K) δ 19.16, 21.46, 28.57, 29.66, 39.39, 51.55, 51.79, 80.60, 125.69, 127.54, 128.58, 131.31, 136.14, 144.12, 154.89, 167.78, 172.80

Diastereomer 2

RP-HPLC (VWR Hitachi): t_{ret} = 3.35 min

TLC: R_f = 0.34 (Petroleum Ether/EtOAc 3:1 v/v)

$[\alpha]_D$: -225.0 ° (*c* 0.53 mg/mL, MeOH)

HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{23}H_{35}N_3O_4SNa$ 472.2241; found 472.2250

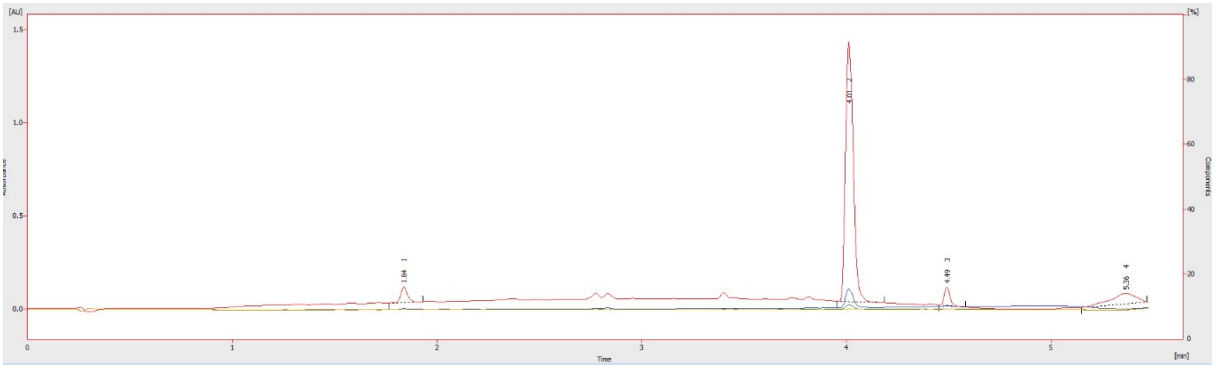
^{1}H NMR ($CDCl_3$, 500 MHz, 298 K) δ 0.67 (d, 3H, *J* = 6.4 Hz, CH_3^{γ} Val), 1.00 (d, 3H, *J* = 6.4 Hz, $CH_3^{\gamma'}$ Val), 1.38 (s, 9H, *t*Bu), 1.41 (s, 9H, *t*Bu), 2.18 (m, 1H, CH^{β} Val), 2.83 (t*, 1H, *J* = 11.3 Hz, CH^{β} BT), 3.69 (dd, 1H, *J* = 10.4 Hz, *J* = 6.5 Hz, $CH^{\beta'}$ BT), 4.31 (m, 1H, CH^{α} BT), 4.46 (d, 1H, *J* = 11.4 Hz, CH^{α} Val), 5.46 (d, 1H, *J* = 15.4 Hz, *N*H Boc), 6.66 (br s, 1H, *N*H amide), 7.24-8.02 (m, 4H, CH aromatic region)

^{13}C NMR ($CDCl_3$, 125 MHz, 298 K) δ 19.43, 20.05, 26.29, 28.26, 28.62, 38.52, 51.52, 51.64, 68.88, 80.13, 126.92, 128.06, 130.36, 135.84, 142.57, 154.48, 169.64, 172.71

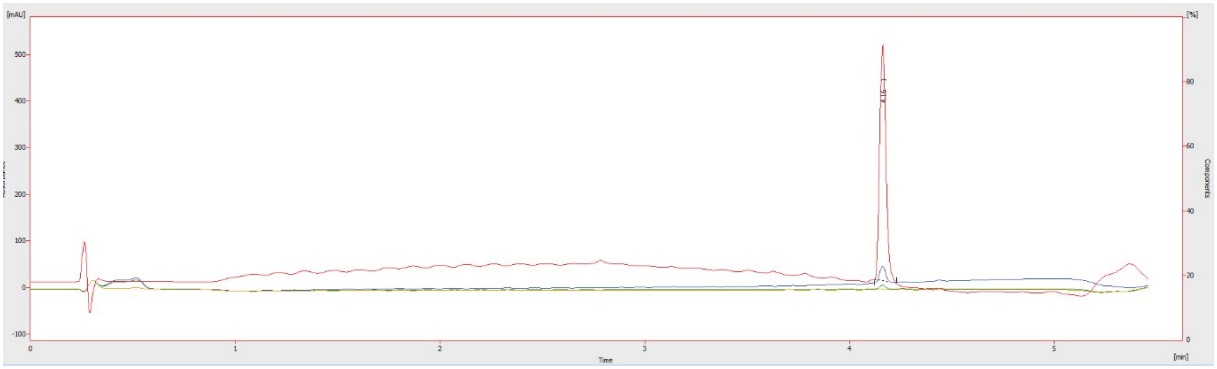
6. RP-HPLC Chromatograms

6.1 Ugi-4CR Products 19a-g

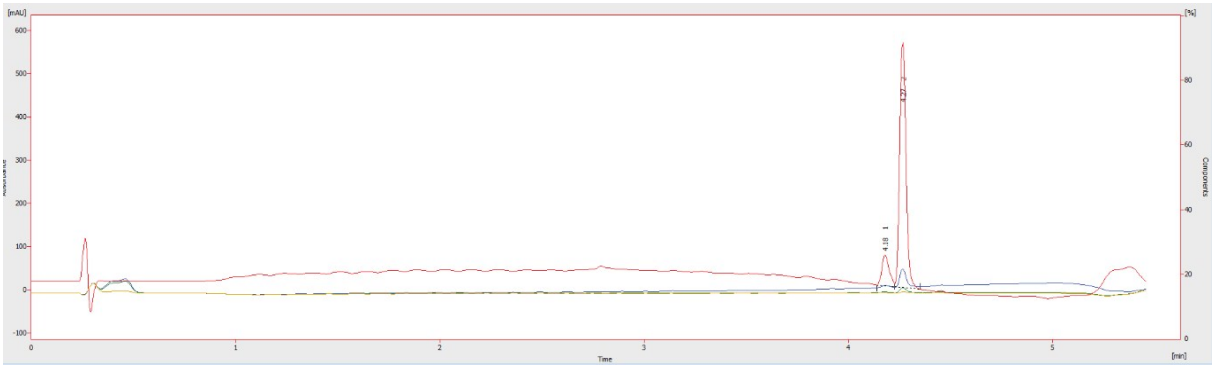
RP-HPLC **19a**



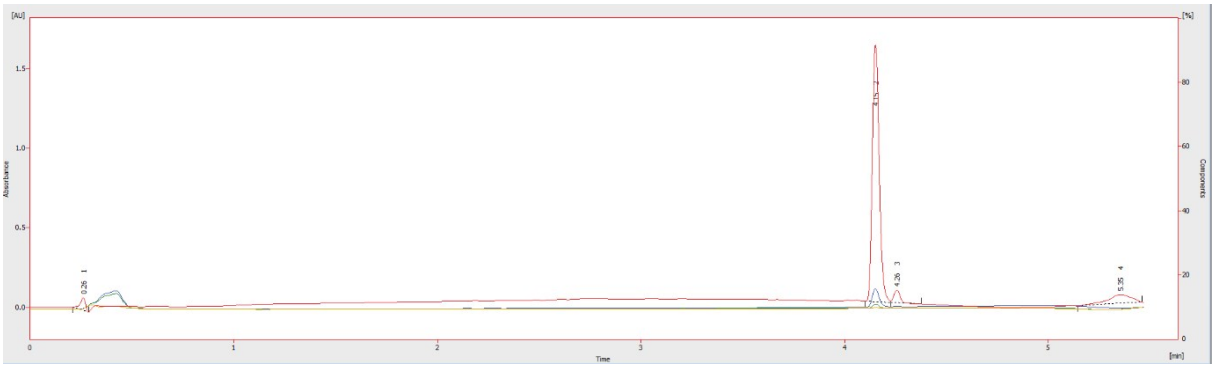
RP-HPLC **19b** *Diastereomer 1*



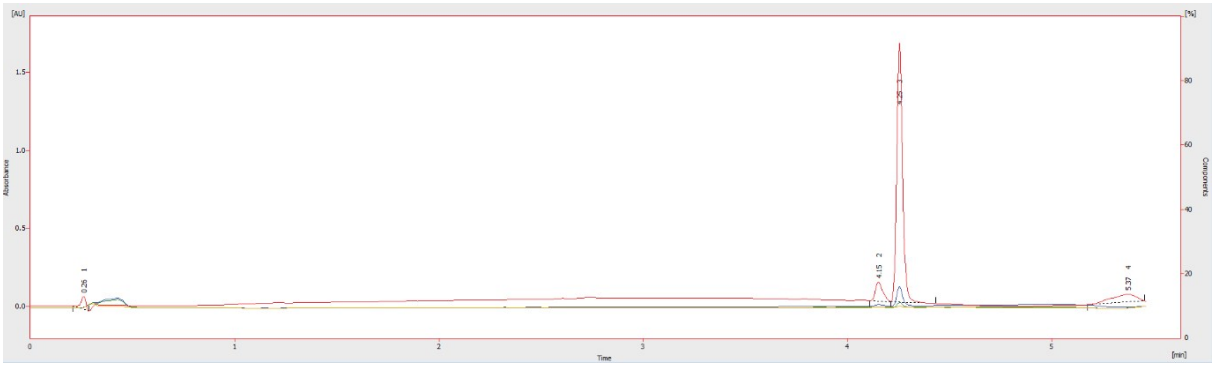
RP-HPLC **19b** *Diastereomer 2*



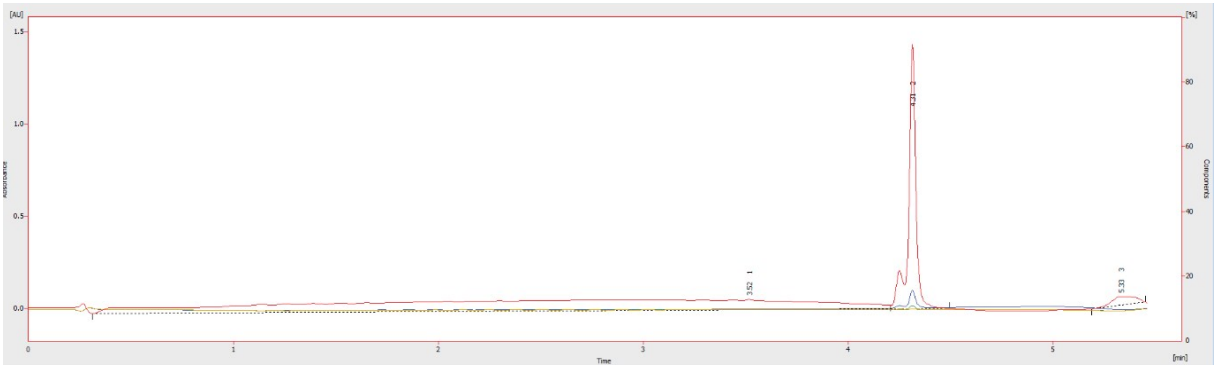
RP-HPLC **19c** *Diastereomer 1*



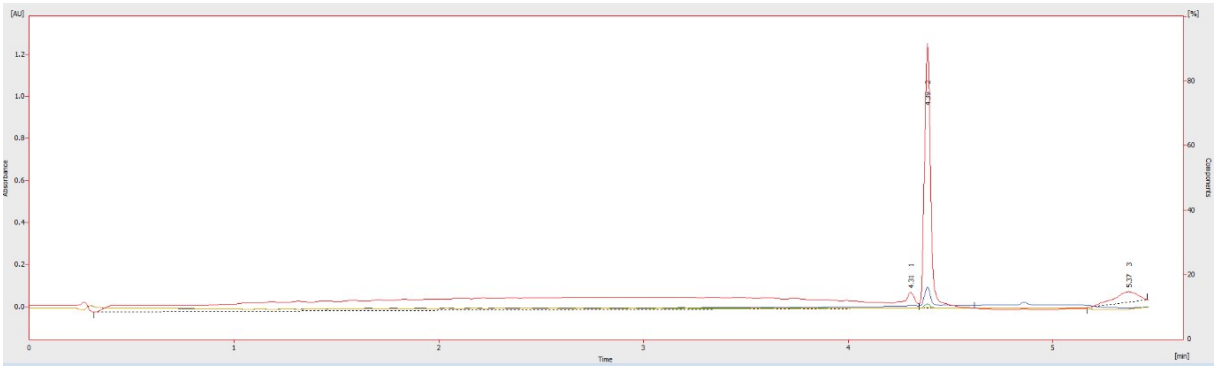
RP-HPLC **19c** *Diastereomer 2*



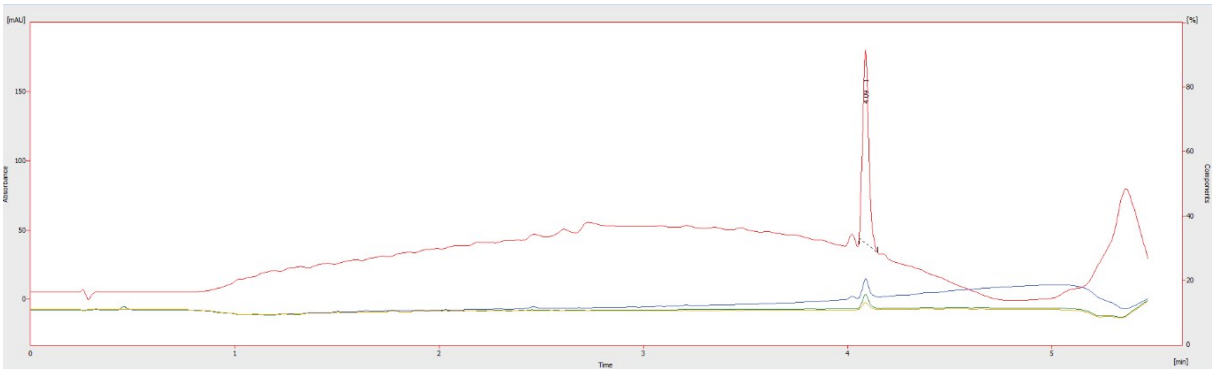
RP-HPLC **19d** *Diastereomer 1*



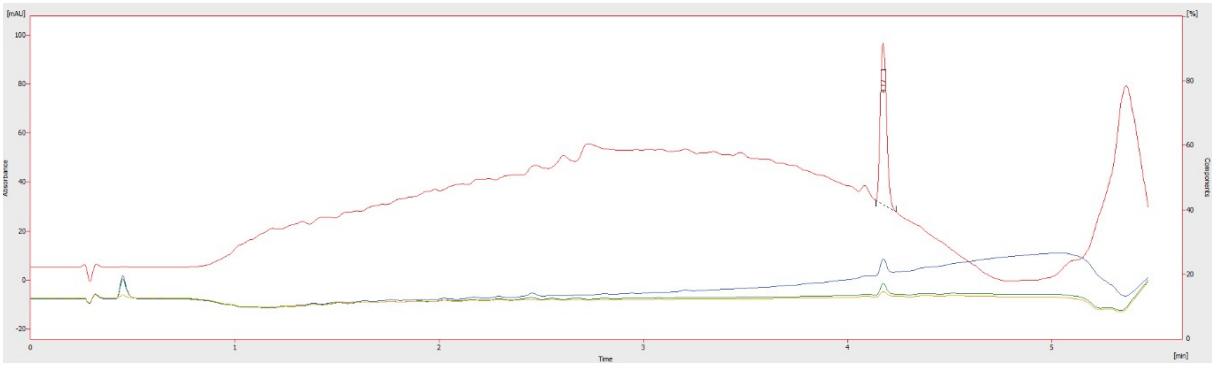
RP-HPLC **19d** *Diastereomer 2*



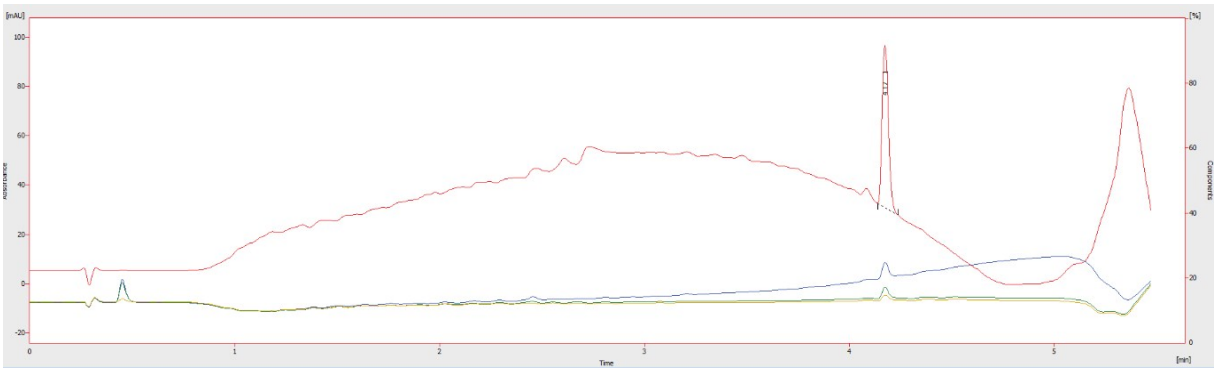
RP-HPLC **19e** *Diastereomer 1*



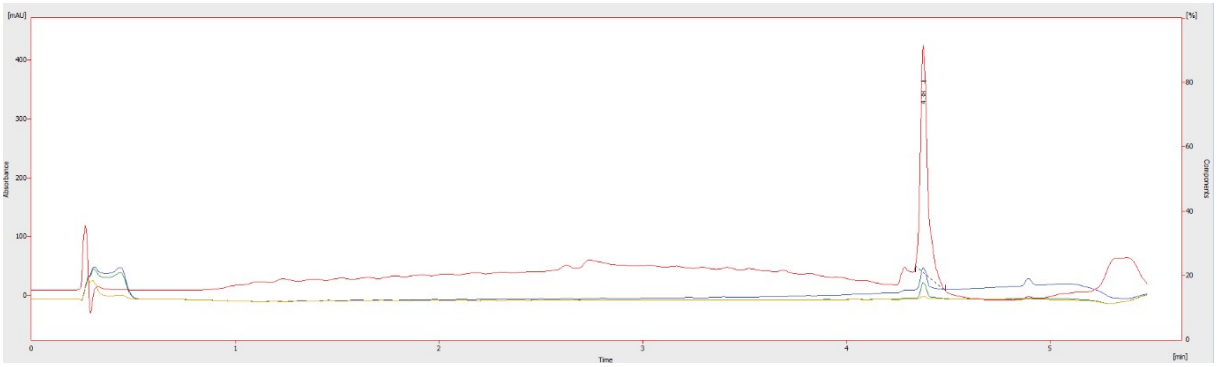
RP-HPLC **19e** *Diastereomer 2*



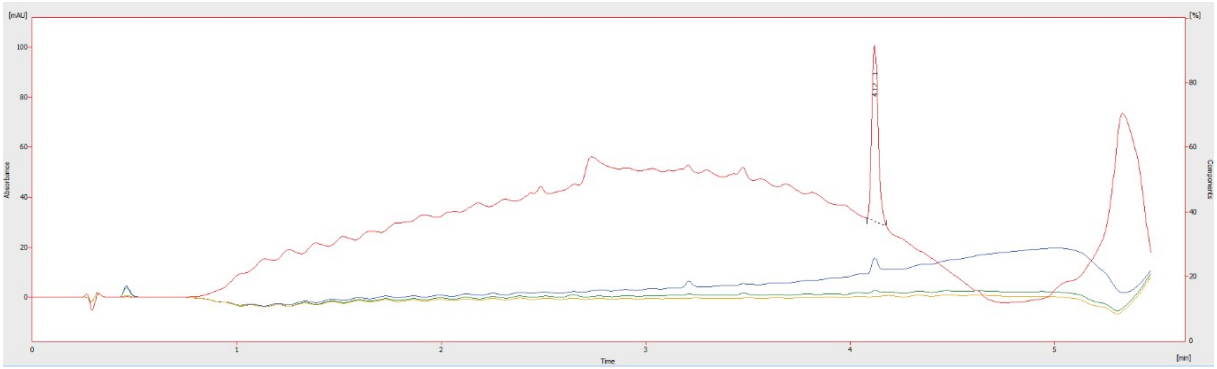
RP-HPLC **19f** *Diastereomer 1*



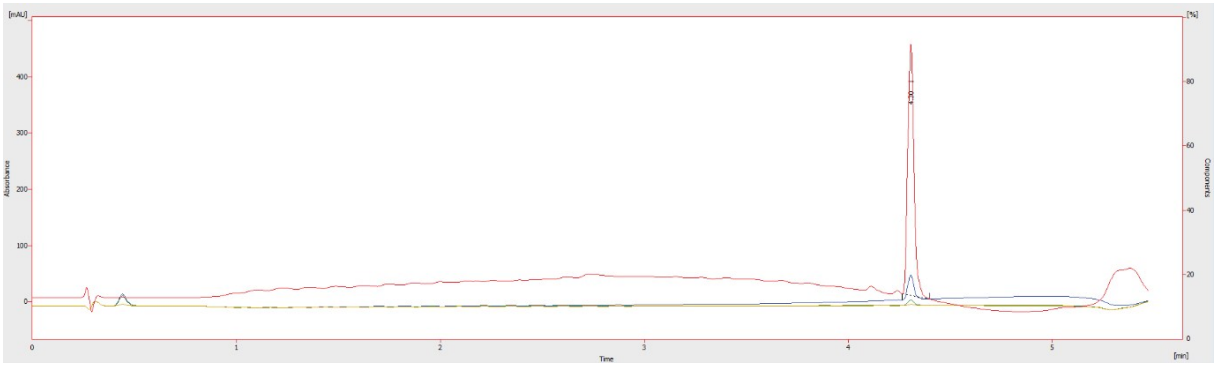
RP-HPLC **19f** *Diastereomer 2*



RP-HPLC **19g** *Diastereomer 1*

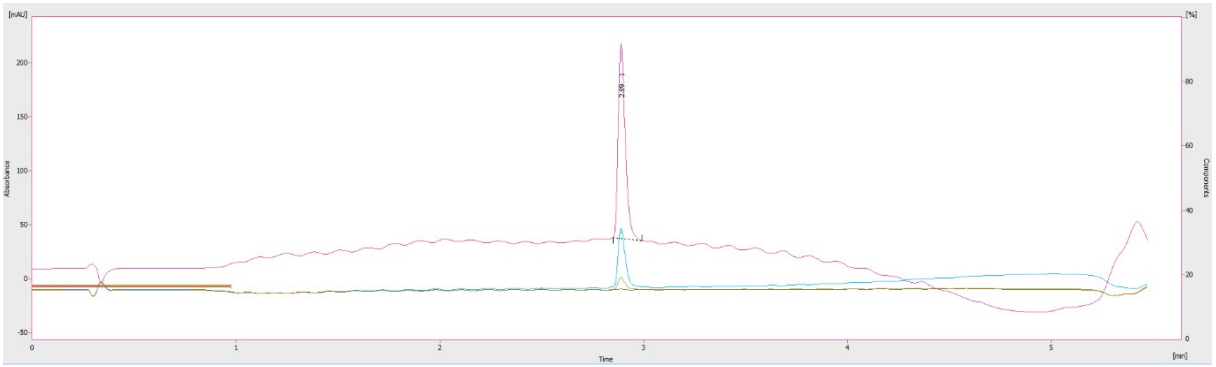


RP-HPLC **19g** *Diastereomer 2*

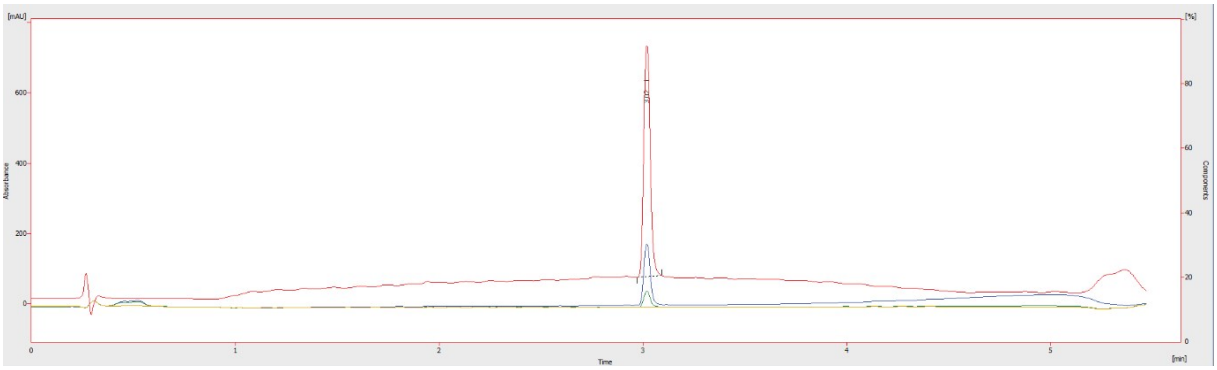


6.2 1,5-Benzothiazepin-4(5*H*)-one Dipeptidomimetics 21a-g

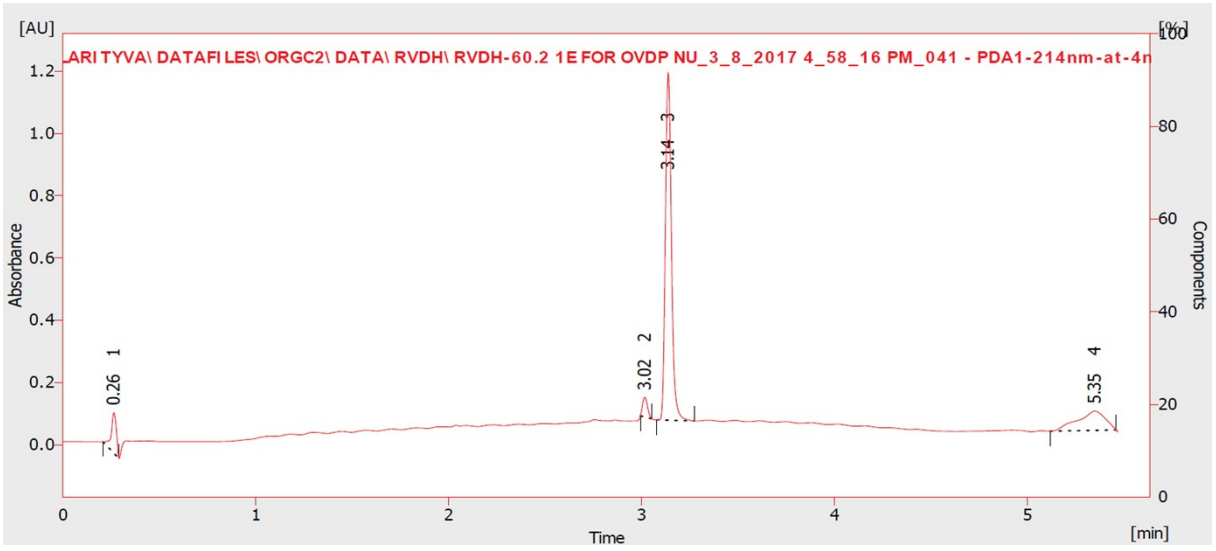
RP-HPLC **21a**



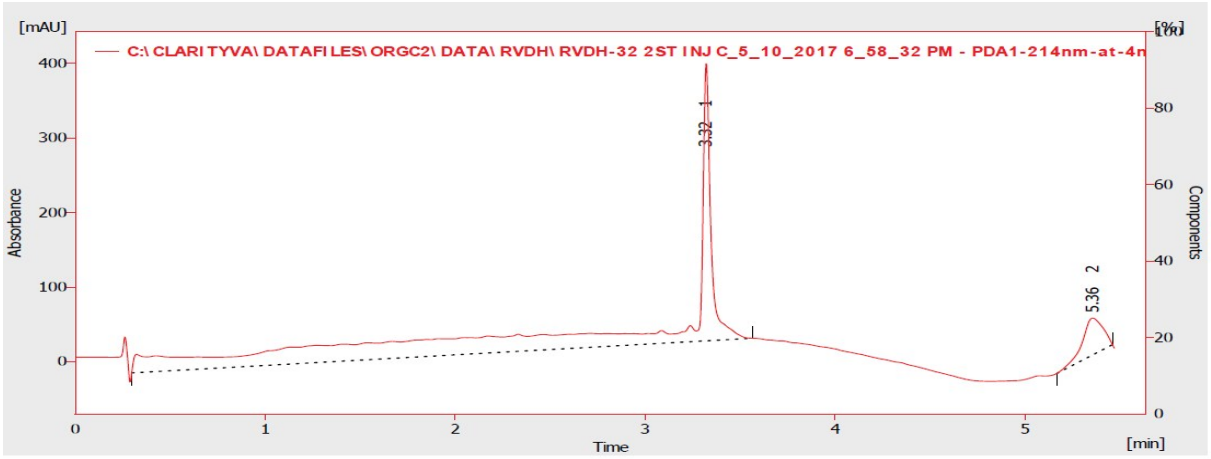
RP-HPLC **21b** *(R,R)-diastereomer*



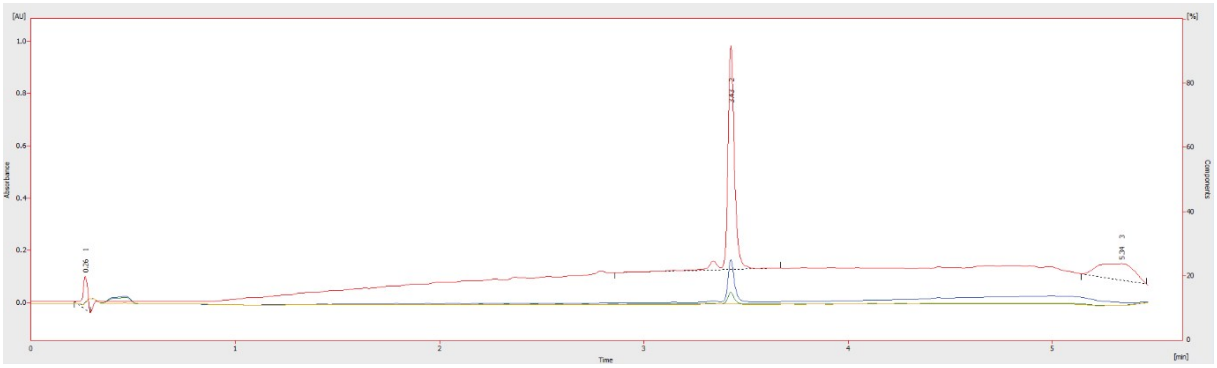
RP-HPLC **21b** *(R,S)-diastereomer*



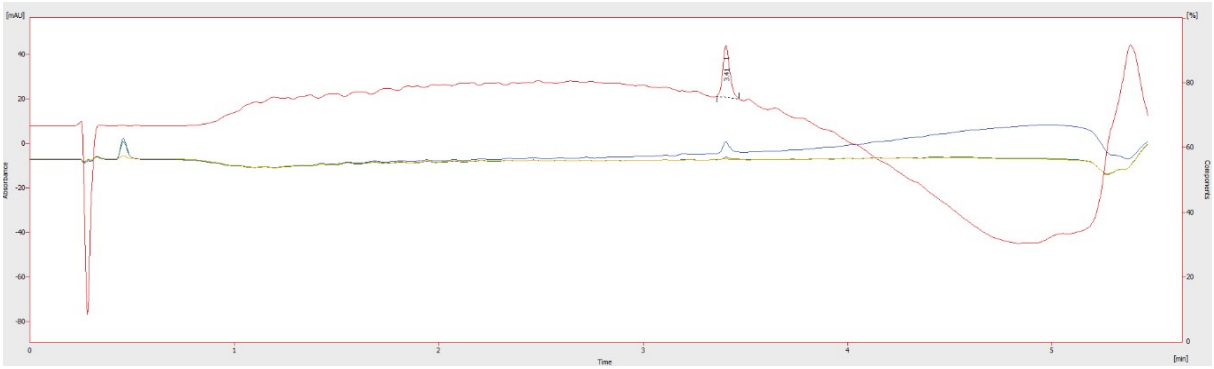
RP-HPLC **21c** *Diastereomer 1*



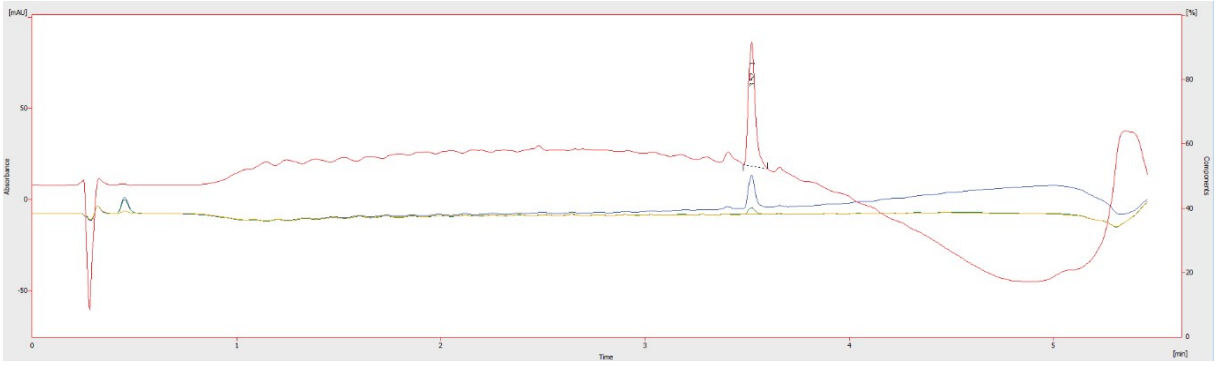
RP-HPLC **21c** *Diastereomer 2*



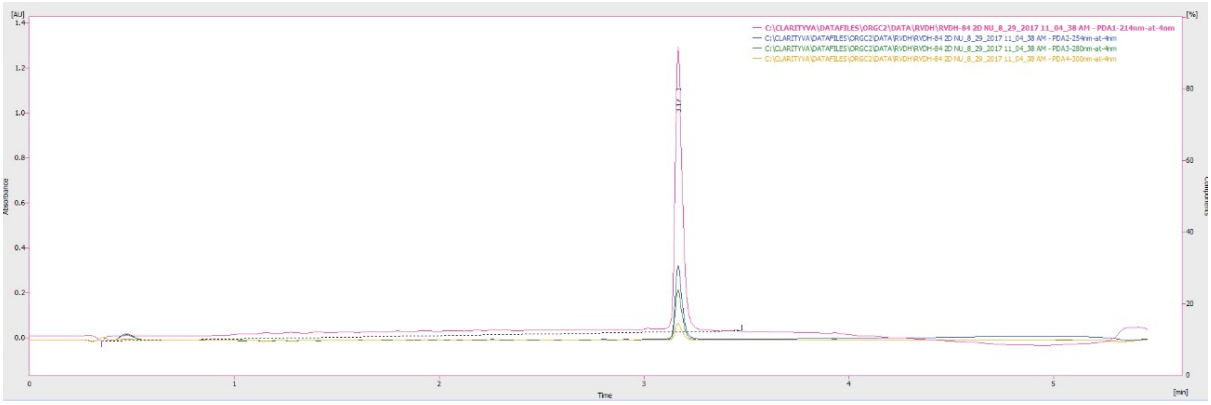
RP-HPLC **21d** *Diastereomer 1*



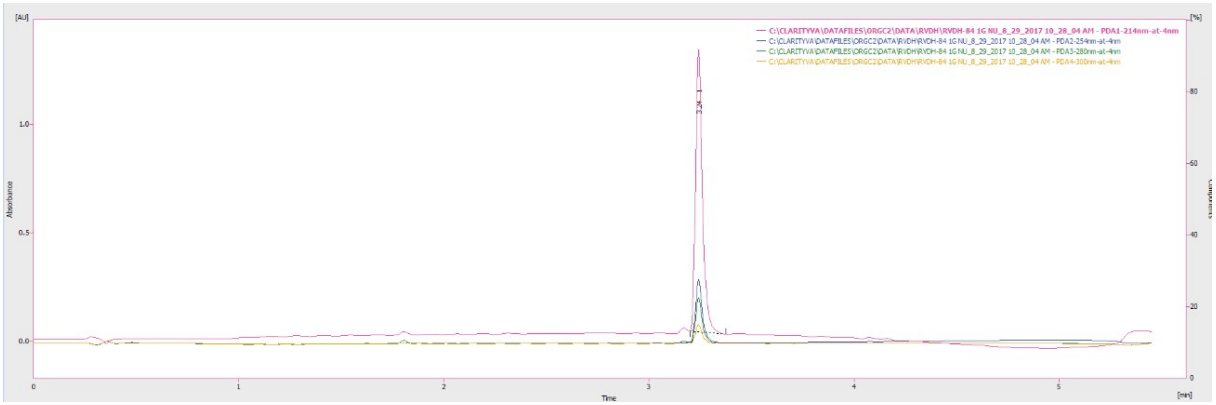
RP-HPLC **21d** *Diastereomer 2*



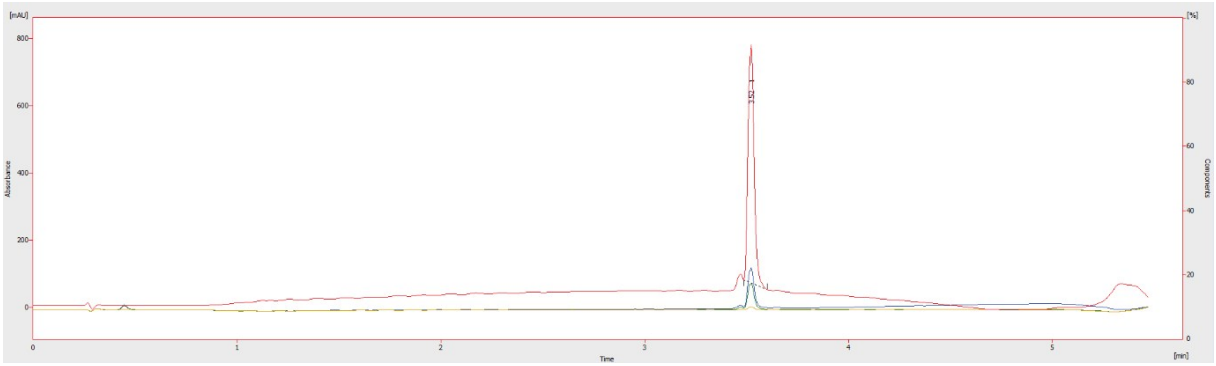
RP-HPLC **21e** *Diastereomer 1*



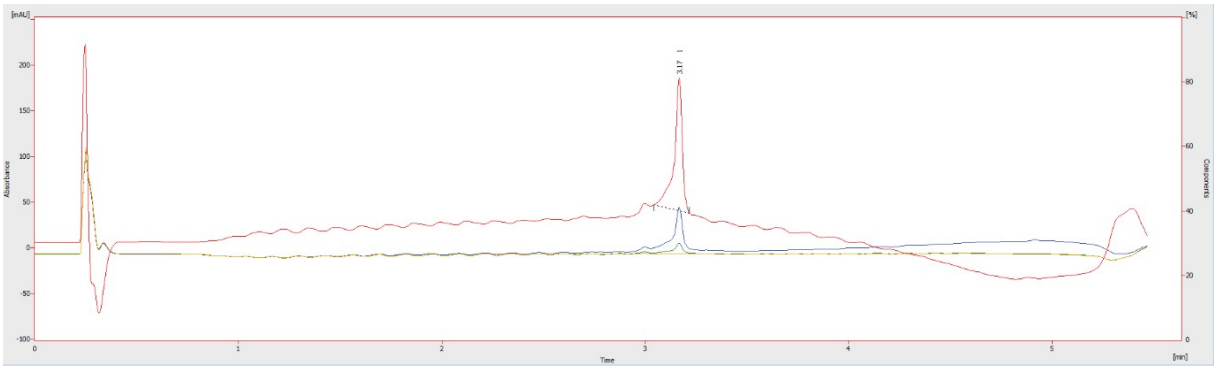
RP-HPLC **21e** *Diastereomer 2*



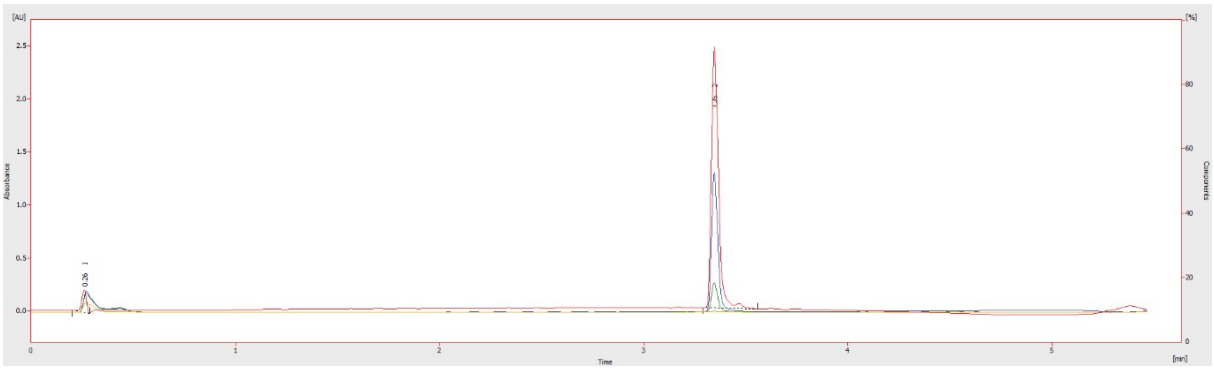
RP-HPLC **21f** *Diastereomer 1* (only major peak isolated)



RP-HPLC **21g** *Diastereomer 1*



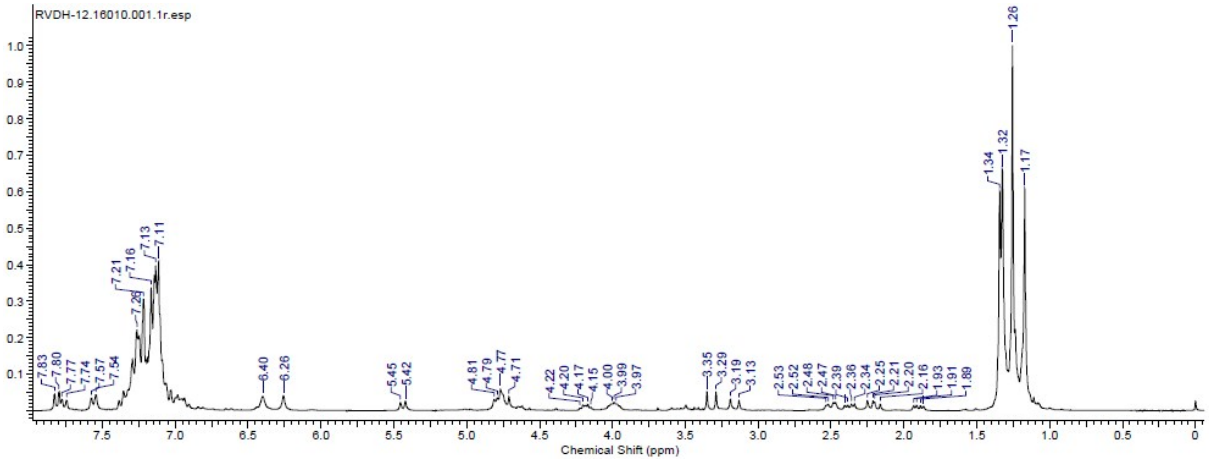
RP-HPLC **21g** *Diastereomer 2*



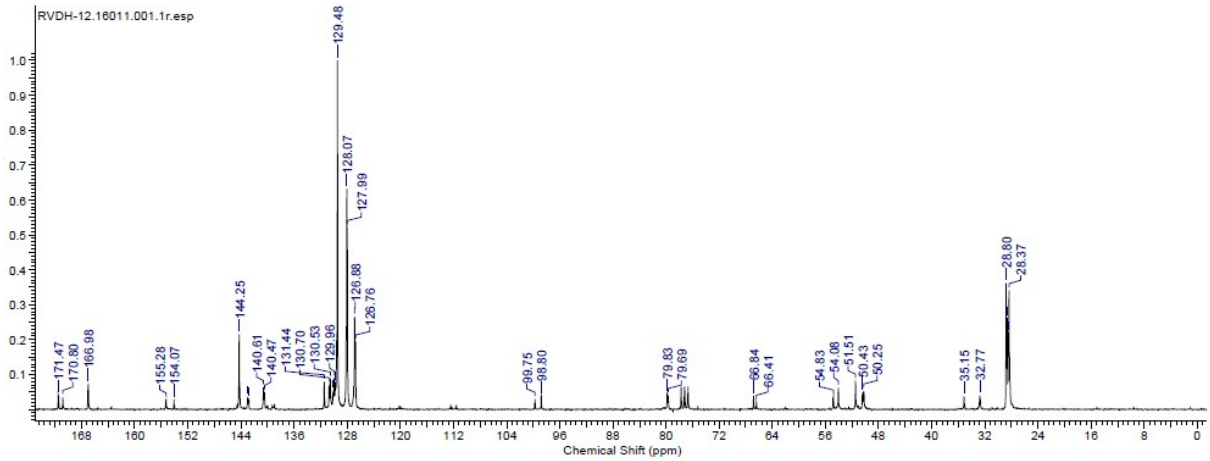
7. NMR Spectral Data

7.1 Ugi-4CR Products 19a-g

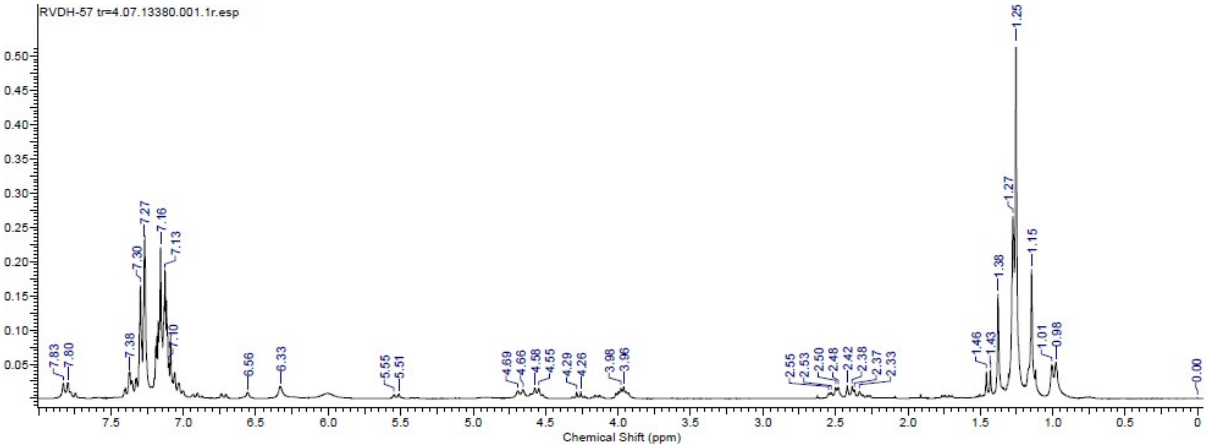
^{1}H NMR ($CDCl_3$, 250 MHz, 298 K, rotamers) **19a**



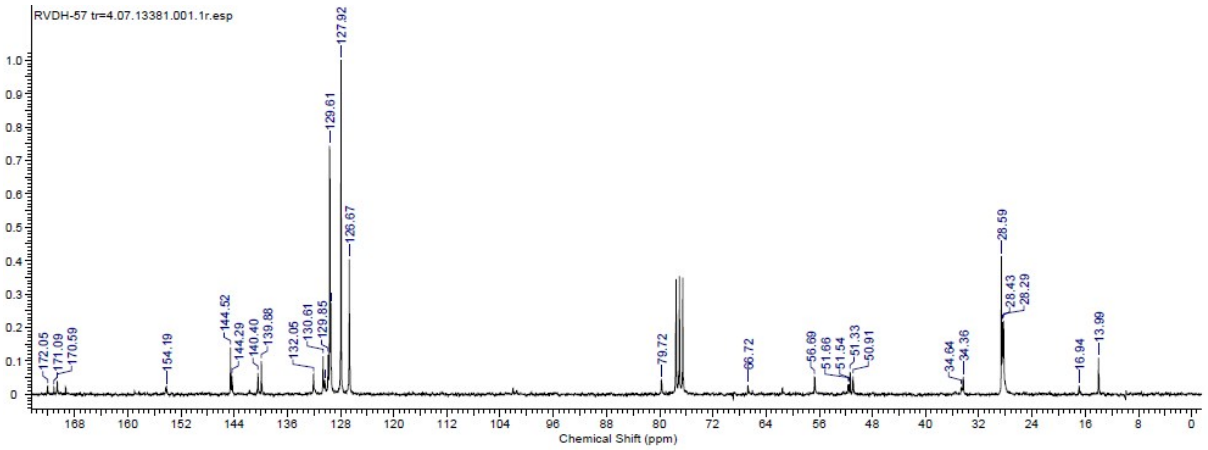
^{13}C NMR ($CDCl_3$, 63 MHz, 298 K, rotamers) **19a**



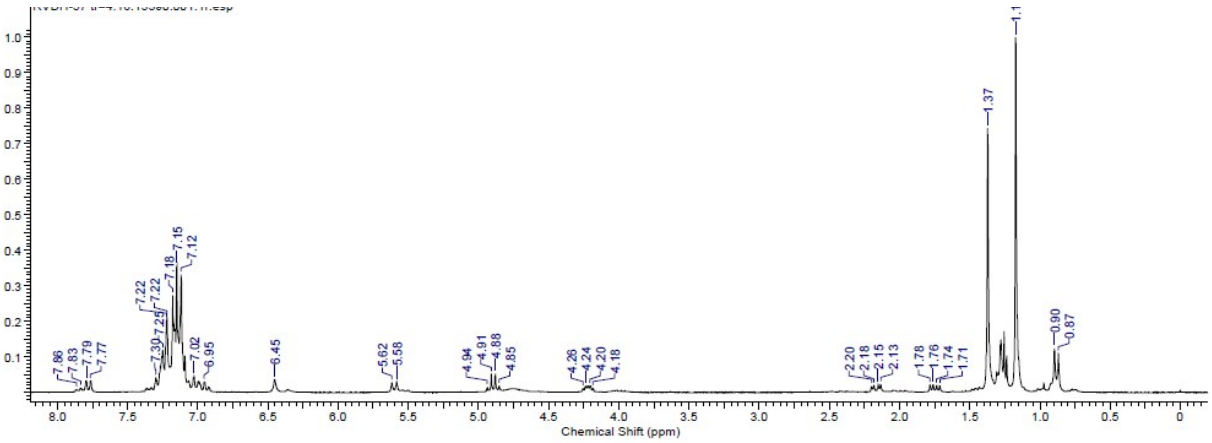
^{1}H NMR ($CDCl_3$, 250 MHz, 298 K, rotamers) **19b** *Diastereomer 1*



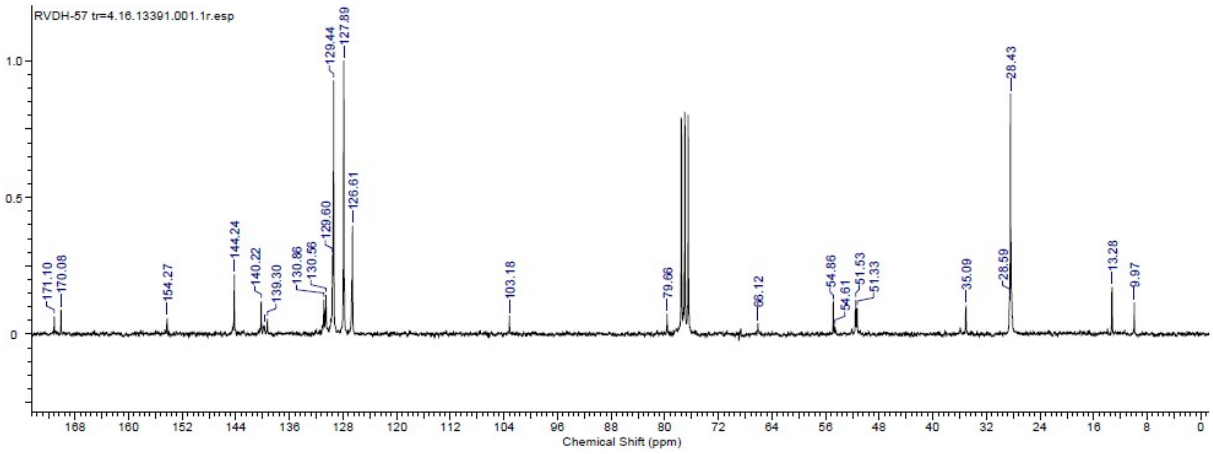
^{13}C NMR ($CDCl_3$, 63 MHz, 298 K, rotamers) **19b** *Diastereomer 1*



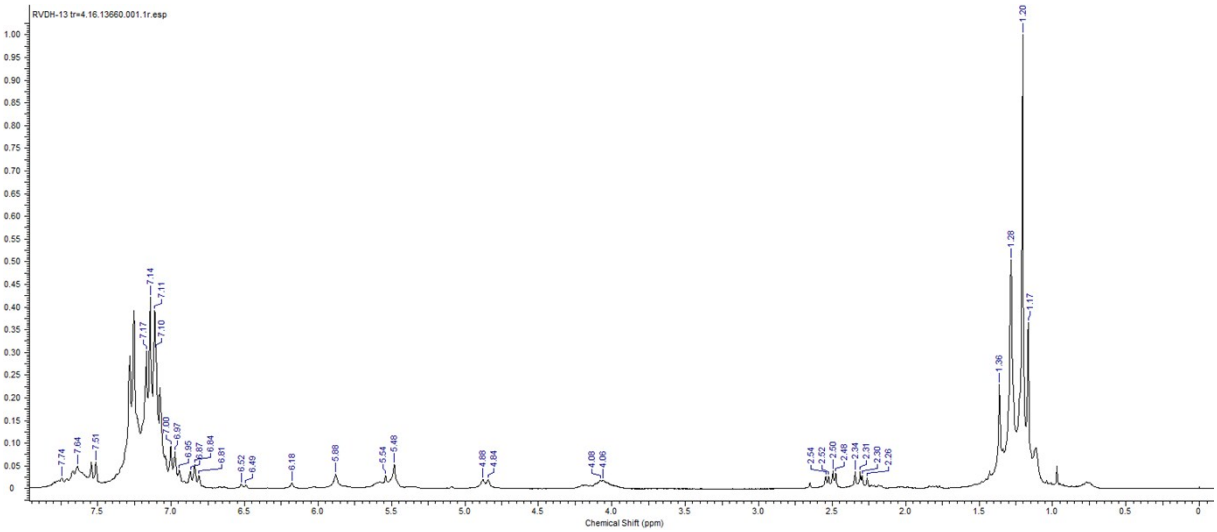
^{1}H NMR ($CDCl_3$, 250 MHz, 298 K) **19b** *Diastereomer 2*



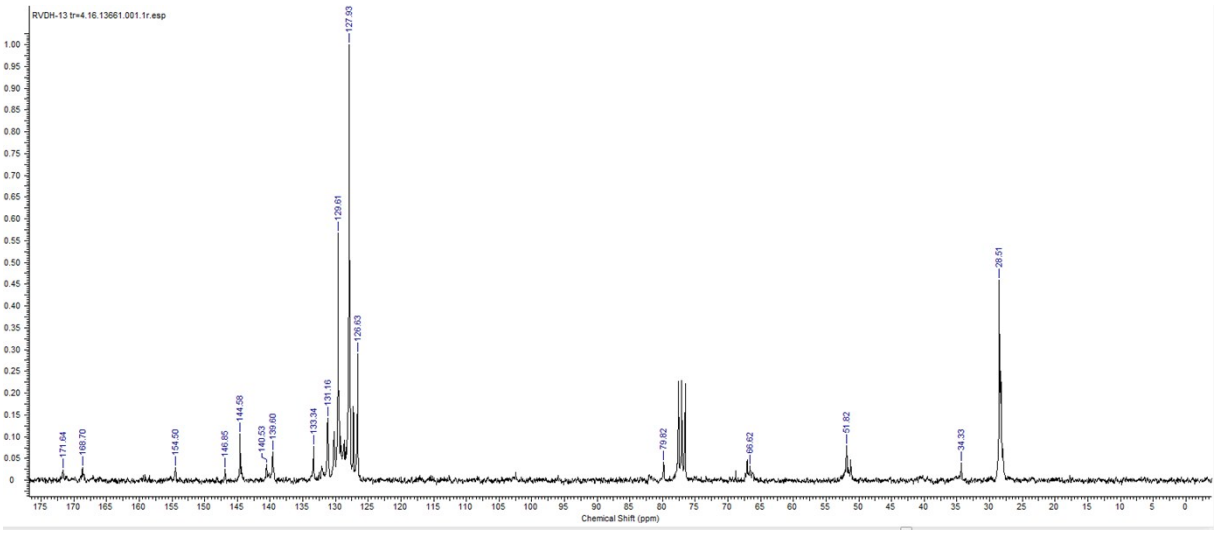
^{13}C NMR ($CDCl_3$, 63 MHz, 298 K) **19b** *Diastereomer 2*



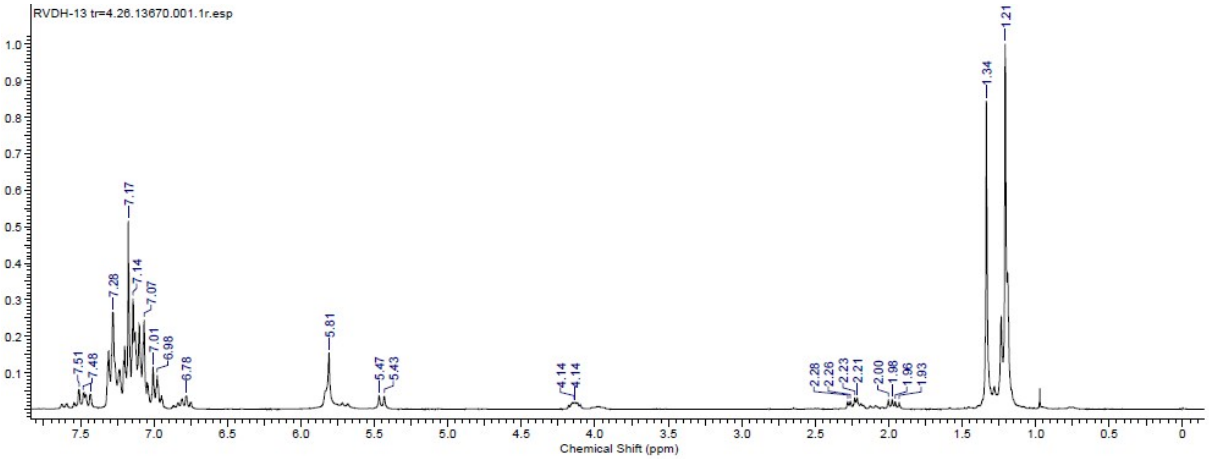
^{1}H NMR ($CDCl_3$, 250 MHz, 298 K, rotamers) **19c** *Diastereomer 1*



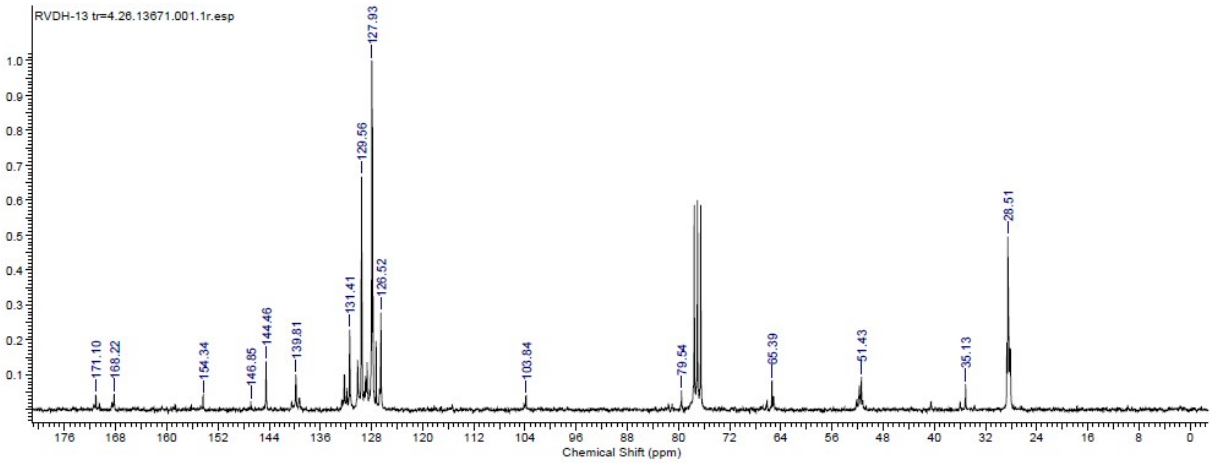
^{13}C NMR ($CDCl_3$, 63 MHz, 298 K, rotamers) **19c** *Diastereomer 1*



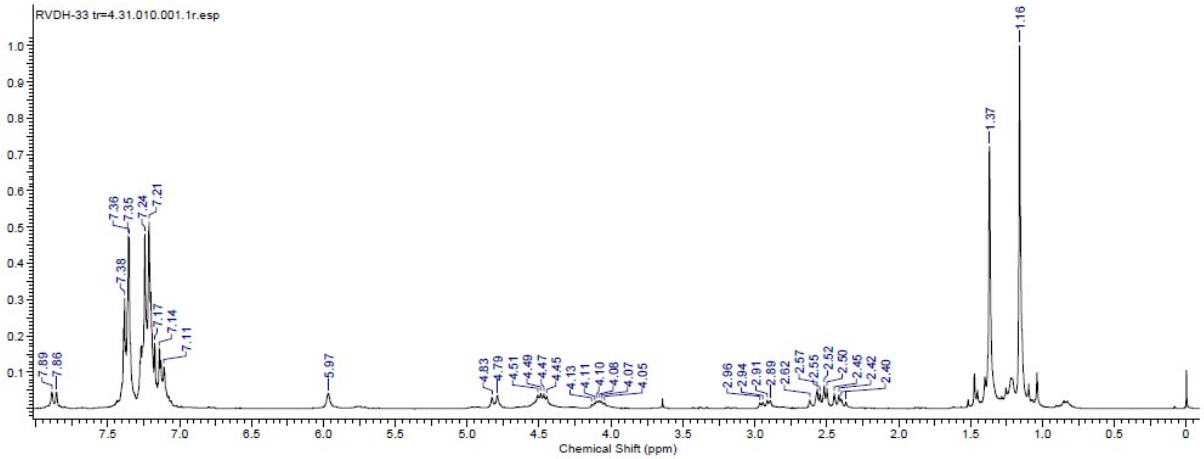
^{1}H NMR ($CDCl_3$, 250 MHz, 298 K) **19c** *Diastereomer 2*



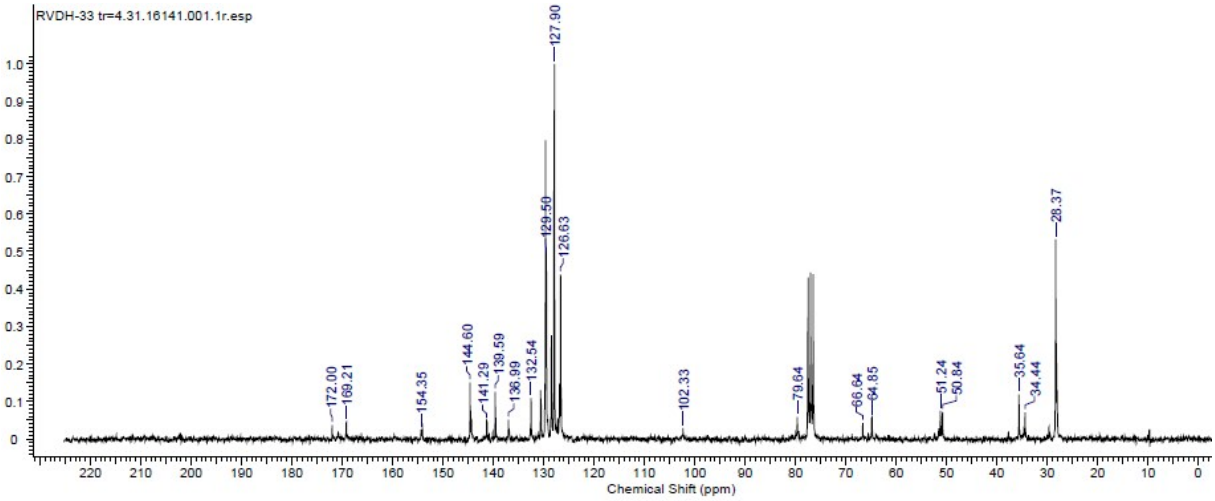
^{13}C NMR ($CDCl_3$, 63 MHz, 298 K) **19c** *Diastereomer 2*



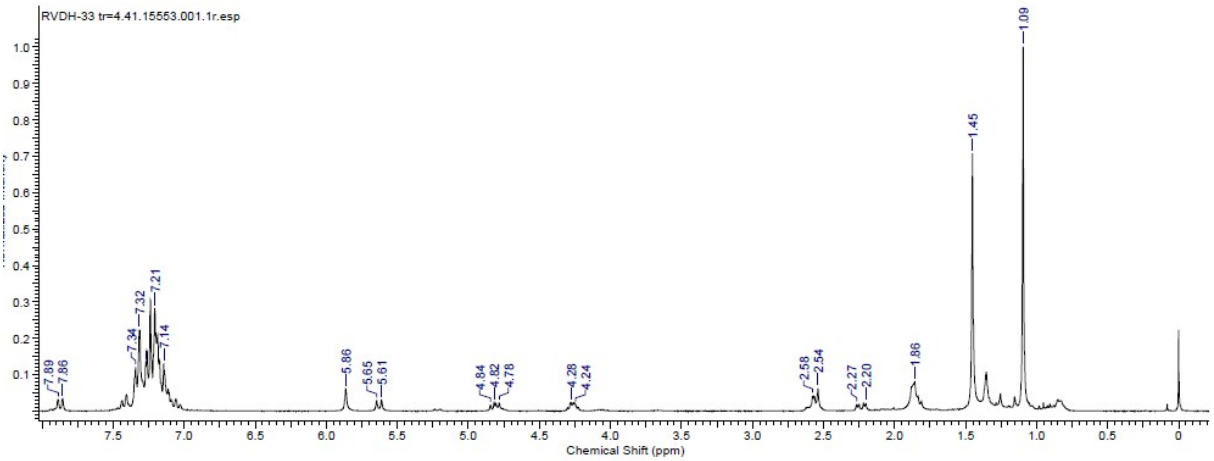
^{1}H NMR ($CDCl_3$, 250 MHz, 298 K, rotamers) **19d** *Diastereomer 1*



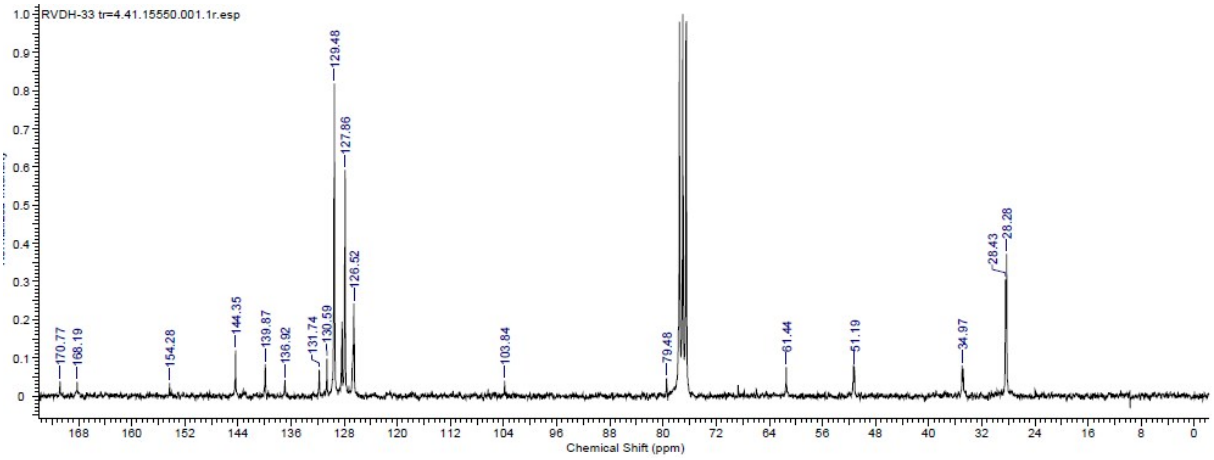
^{13}C NMR ($CDCl_3$, 63 MHz, 298 K) **19d** *Diastereomer 1*



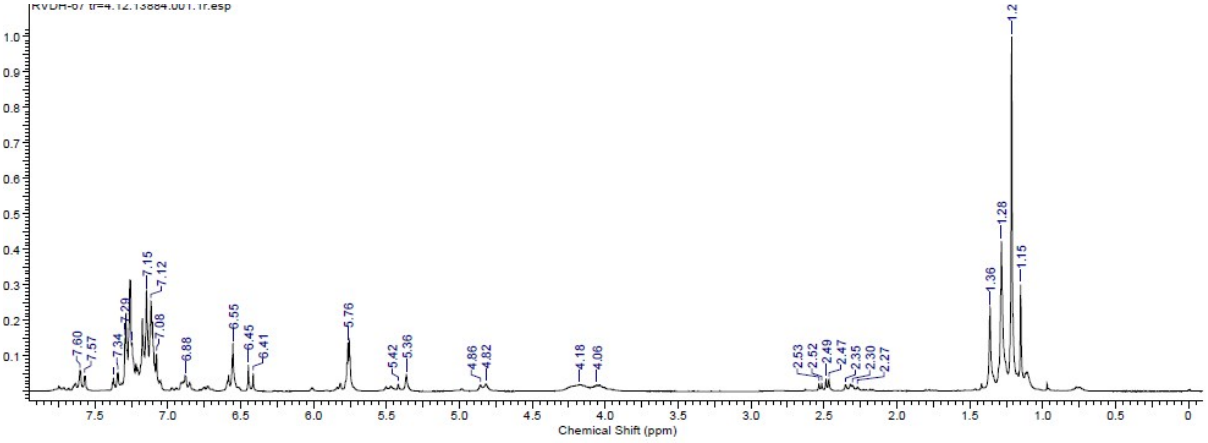
^{1}H NMR ($CDCl_3$, 250 MHz, 298 K, rotamers) **19d** *Diastereomer 2*



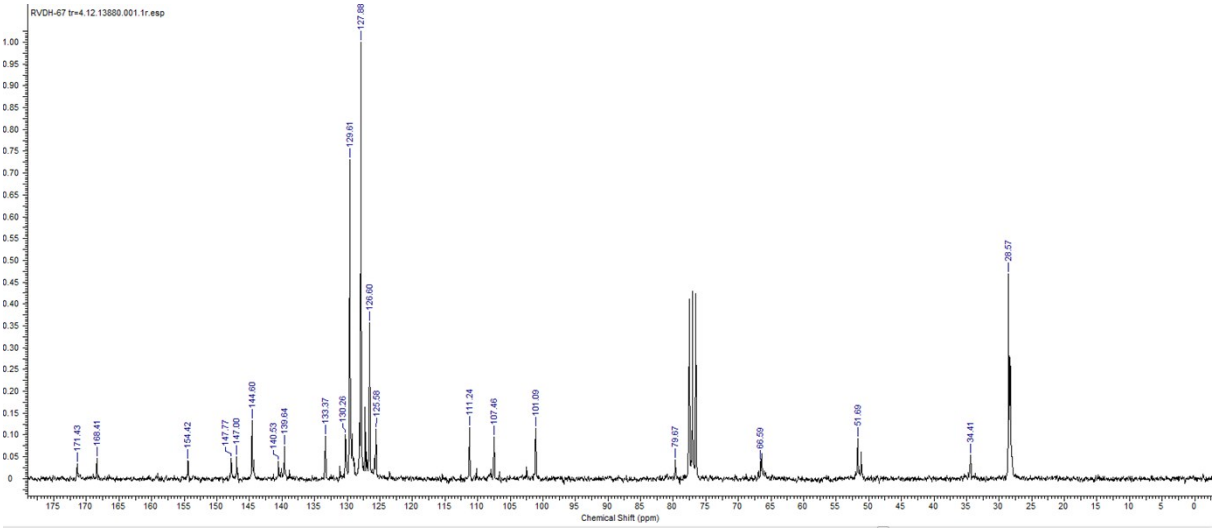
^{13}C NMR ($CDCl_3$, 63 MHz, 298 K) **19d** *Diastereomer 2*



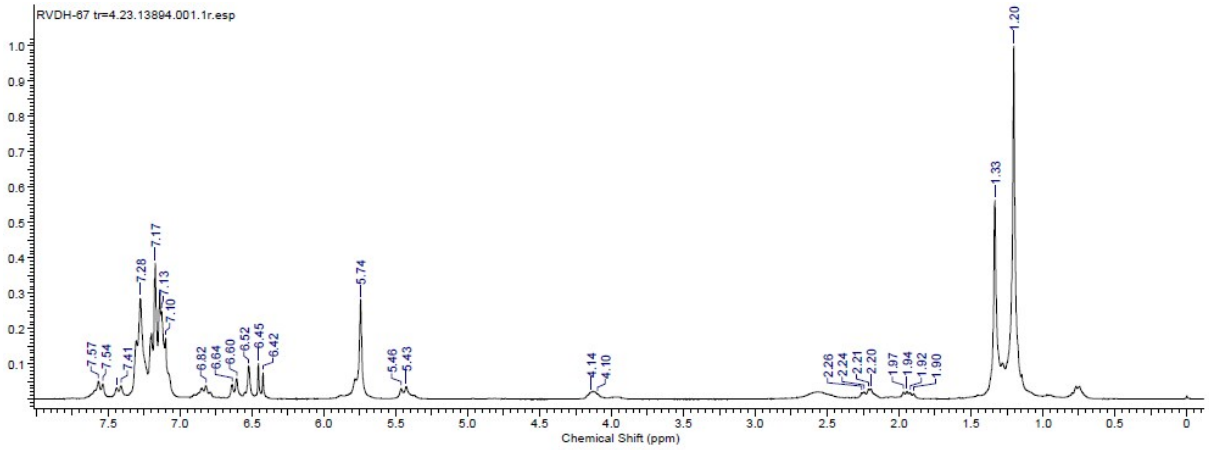
^{1}H NMR ($CDCl_3$, 250 MHz, 298 K, rotamers) **19e** *Diastereomer 1*



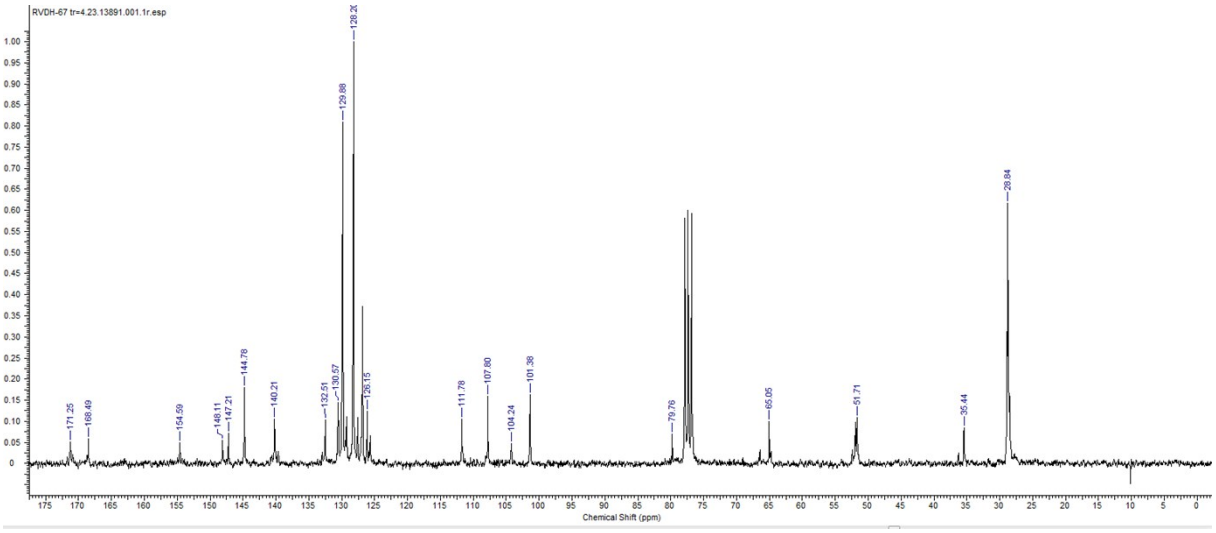
^{13}C NMR ($CDCl_3$, 63 MHz, 298 K, rotamers) **19e** *Diastereomer 1*



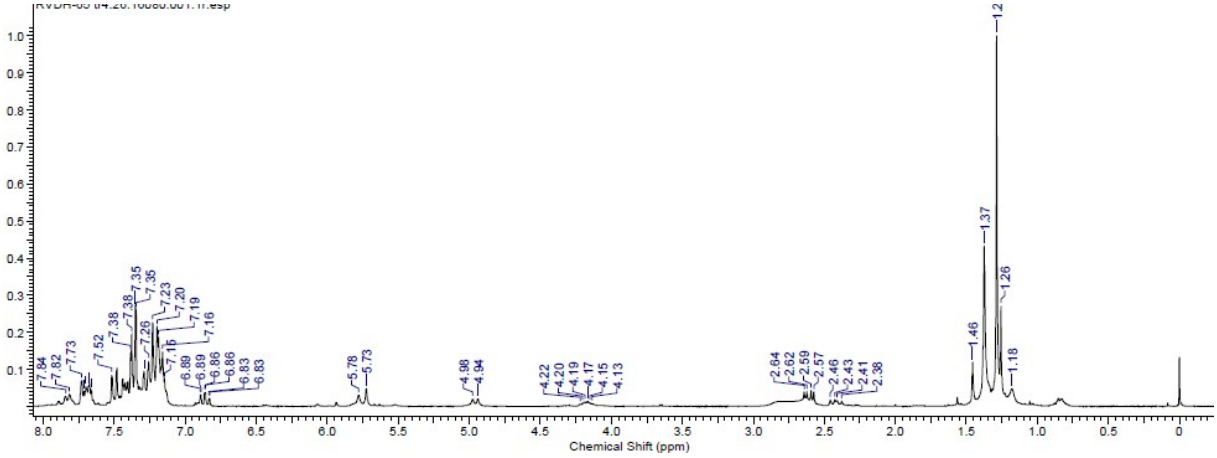
^{1}H NMR ($CDCl_3$, 250 MHz, 298 K, rotamers) **19e** *Diastereomer 2*



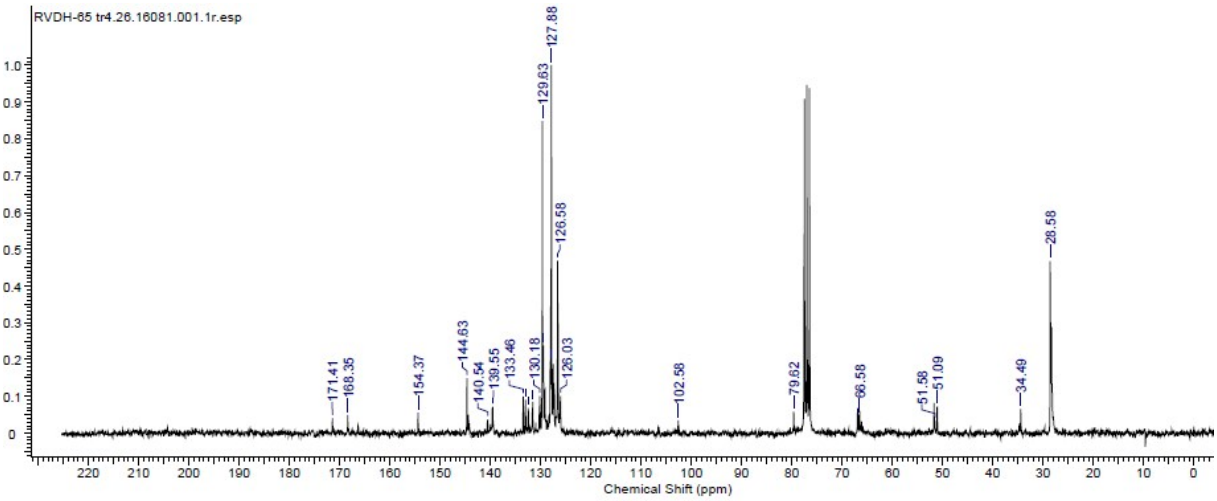
^{13}C NMR ($CDCl_3$, 63 MHz, 298 K, rotamers) **19e** *Diastereomer 2*



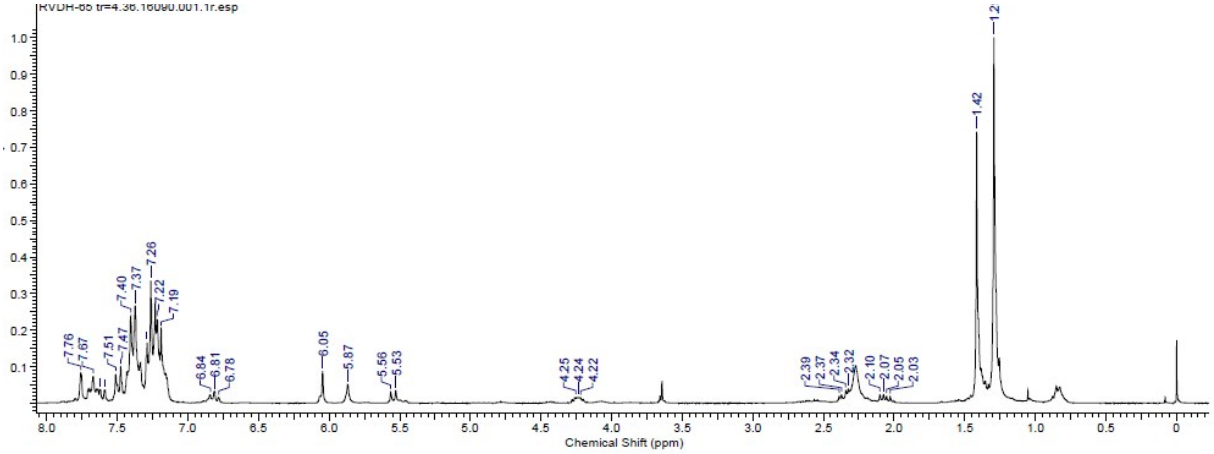
^{1}H NMR ($CDCl_3$, 250 MHz, 298 K, rotamers) **19f** *Diastereomer 1*



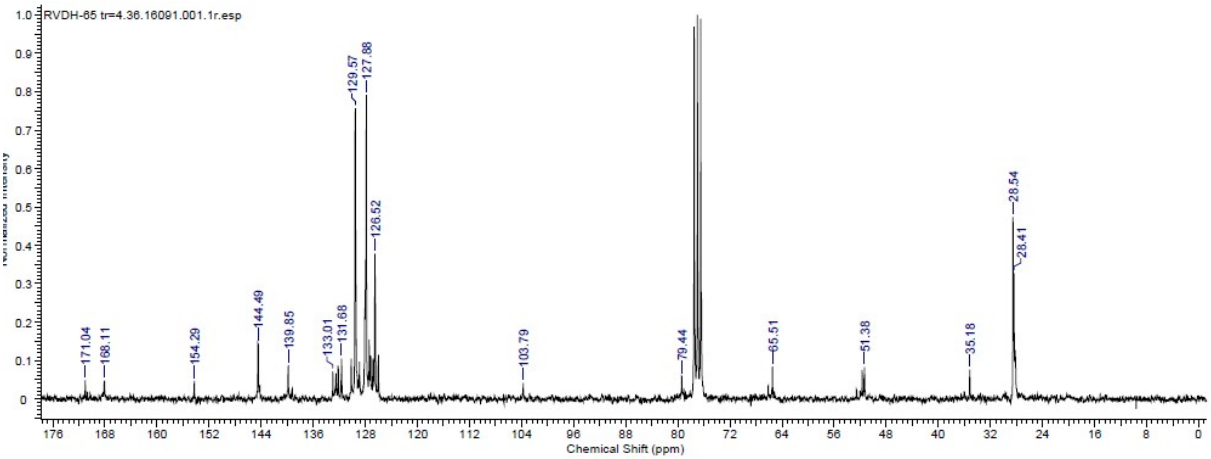
^{13}C NMR ($CDCl_3$, 63 MHz, 298 K, rotamers) **19f** *Diastereomer 1*



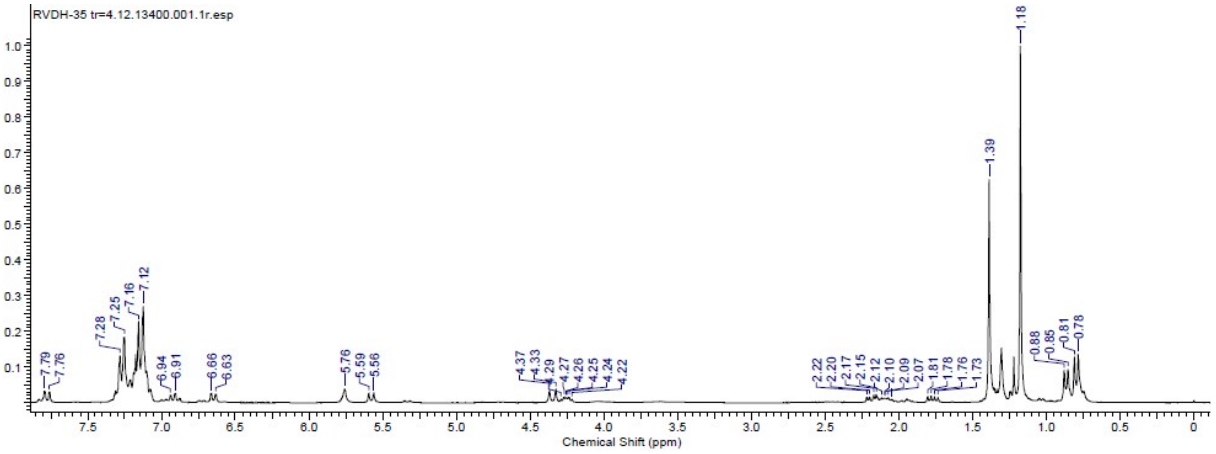
^{1}H NMR ($CDCl_3$, 250 MHz, 298 K) **19f** *Diastereomer 2*



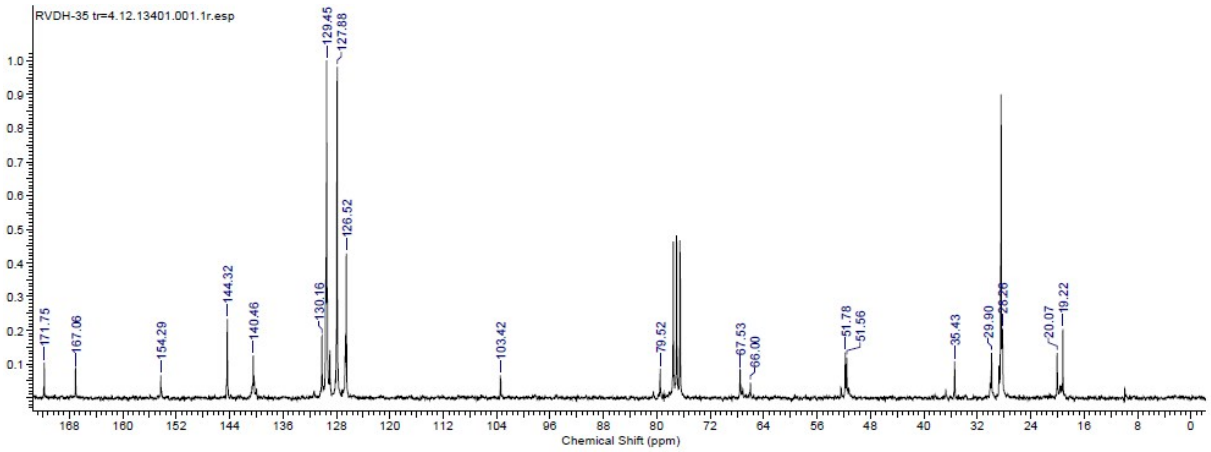
^{13}C NMR ($CDCl_3$, 63 MHz, 298 K) **19f** *Diastereomer 2*



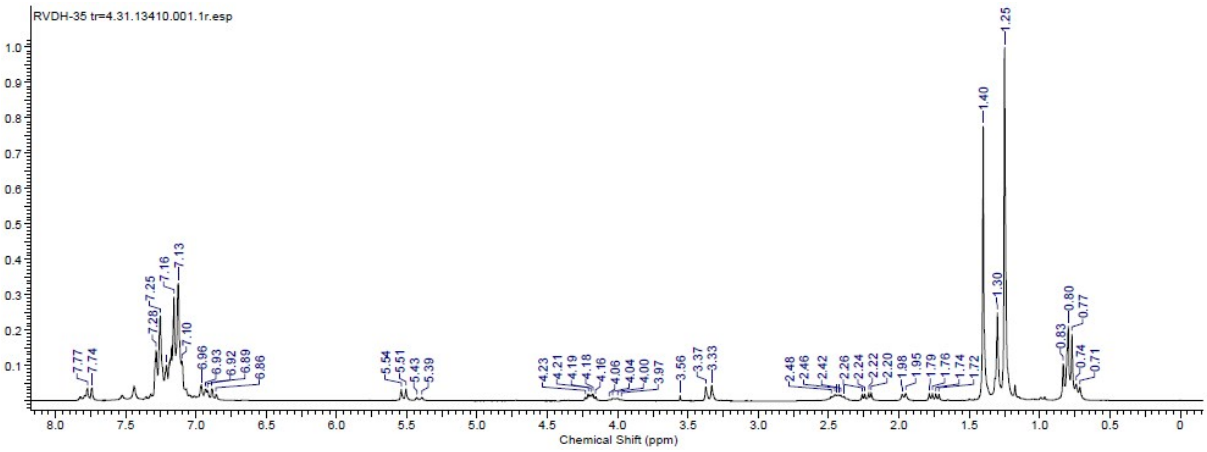
^{1}H NMR ($CDCl_3$, 250 MHz, 298 K) **19g** *Diastereomer 1*



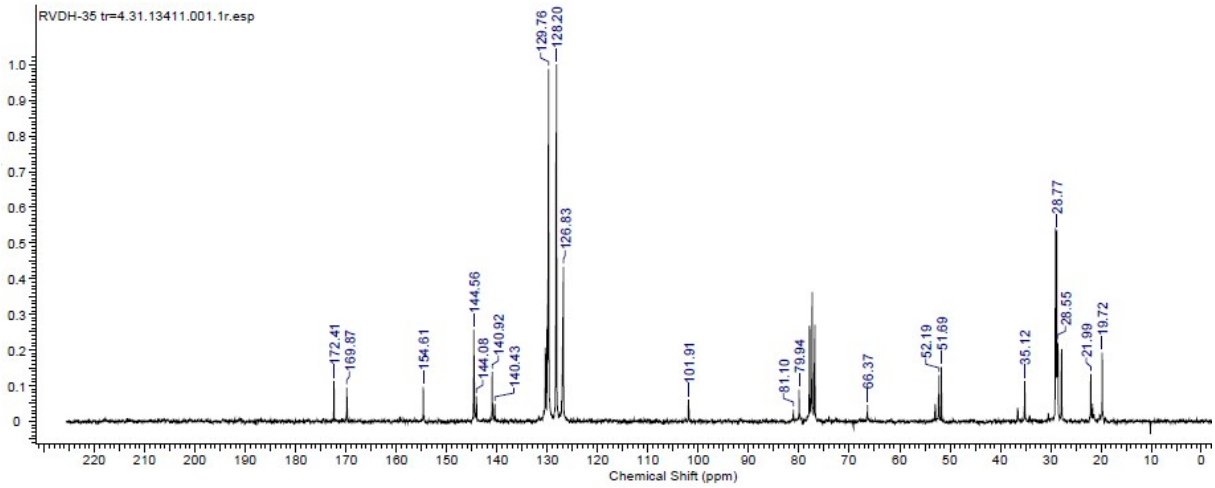
^{13}C NMR ($CDCl_3$, 63 MHz, 298 K) **19g** *Diastereomer 1*



^{1}H NMR ($CDCl_3$, 250 MHz, 298 K, rotamers) **19g** *Diastereomer 2*

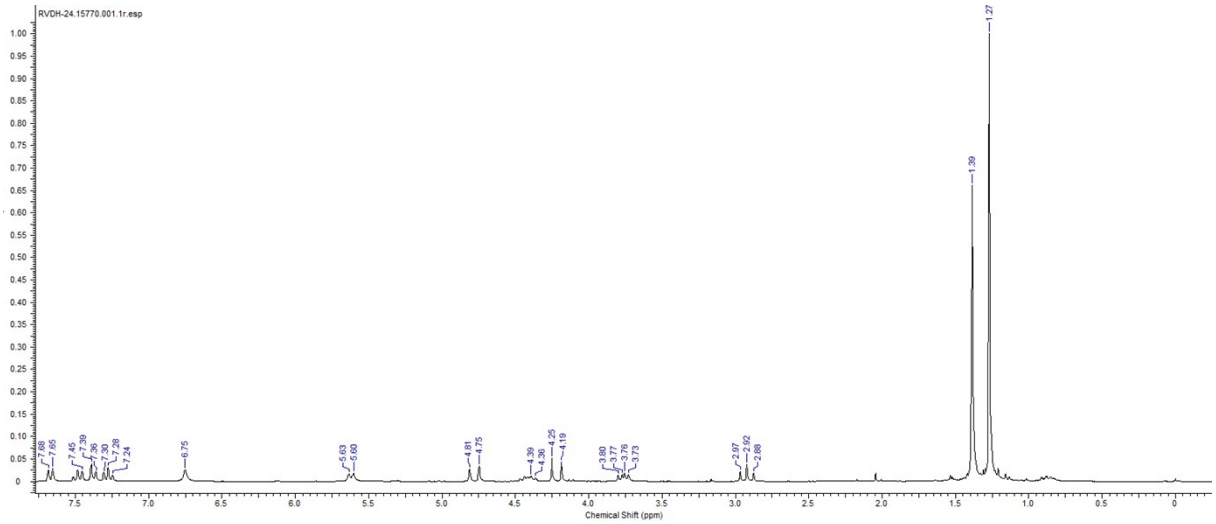


^{13}C NMR ($CDCl_3$, 63 MHz, 298 K, rotamers) **19g** *Diastereomer 2*

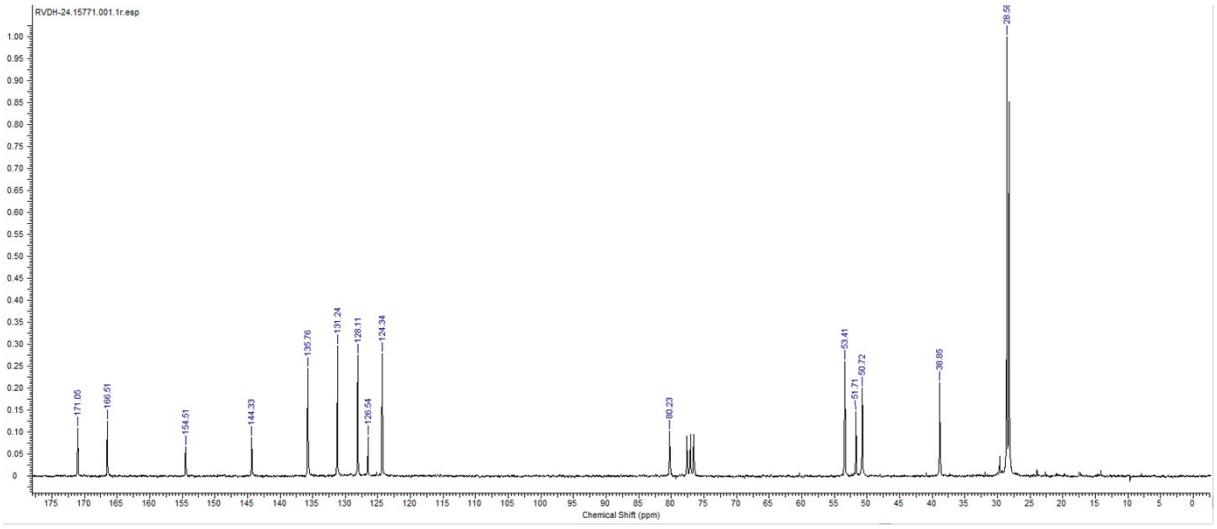


7.2 1,5-Benzothiazepin-4(5*H*)-one Dipeptidomimetics 21a-*g*

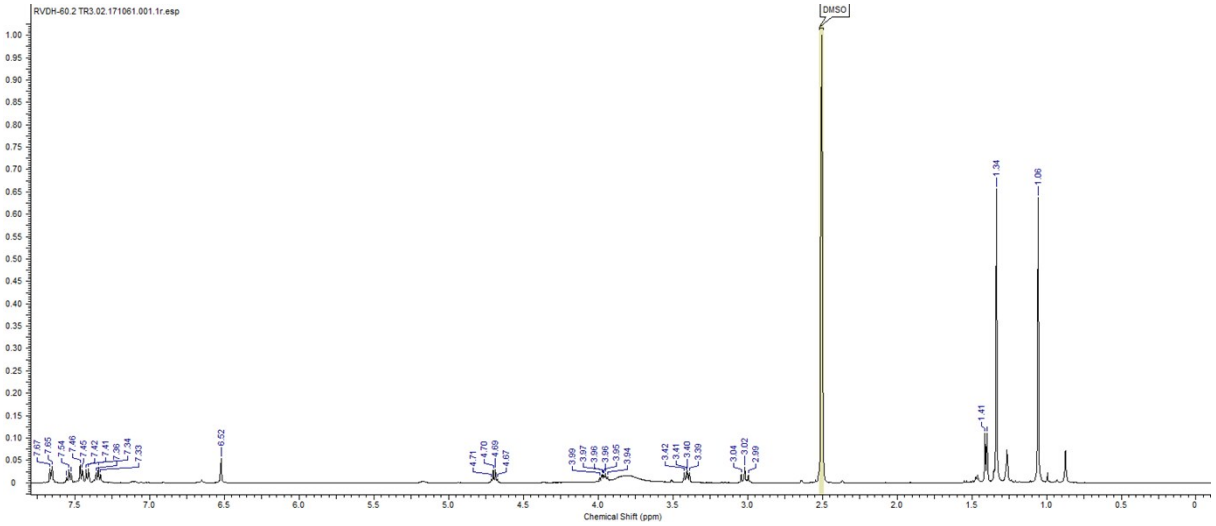
^{1}H NMR ($CDCl_3$, 500 MHz, 298 K) **21a**



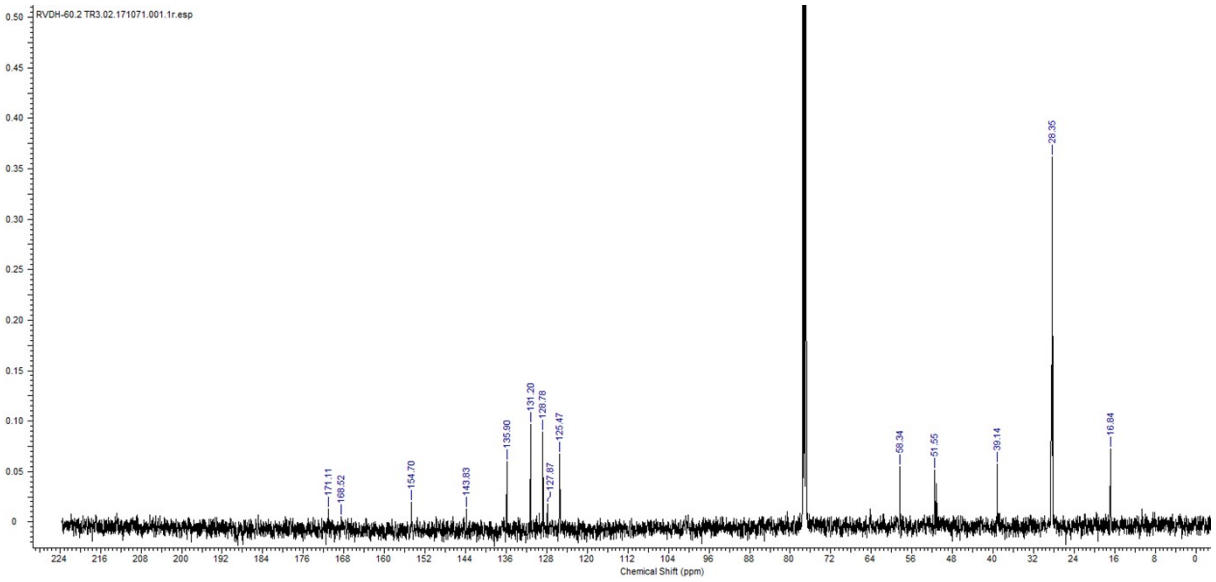
^{13}C NMR ($CDCl_3$, 125 MHz, 298 K) **21a**



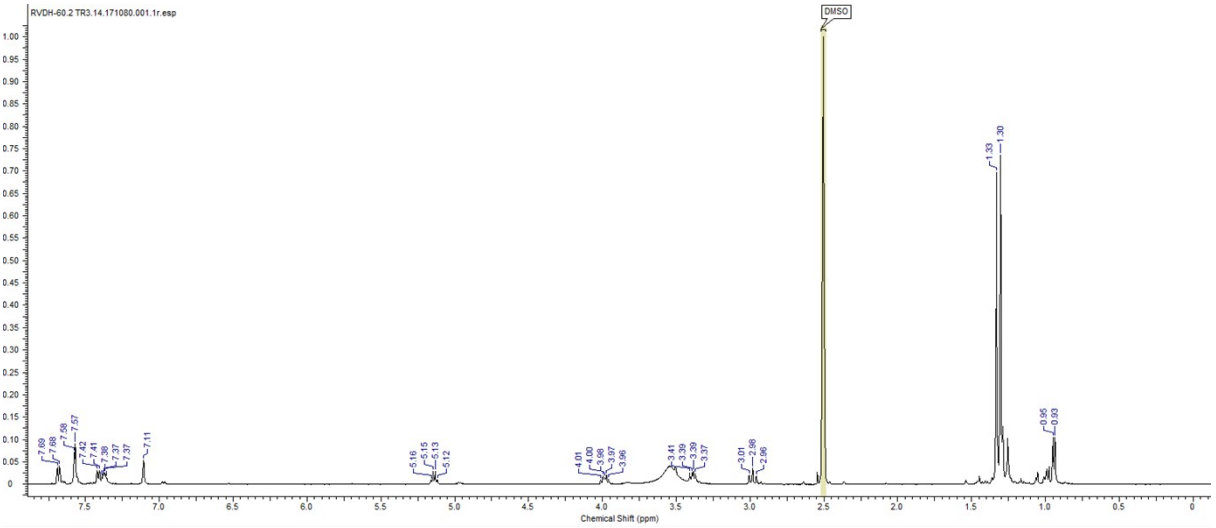
^{1}H NMR (DMSO-d_6, 500 MHz, 303 K) **21b** *(R,R)-diastereomer*



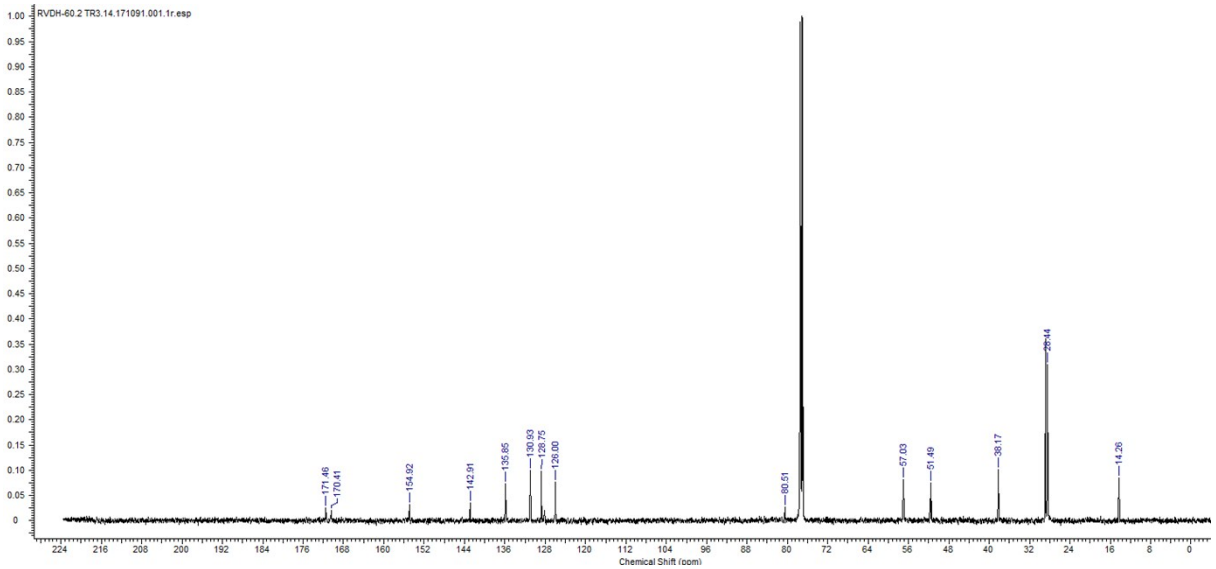
^{13}C NMR ($CDCl_3$, 125 MHz, 298 K) **21b** *(R,R)-diastereomer*



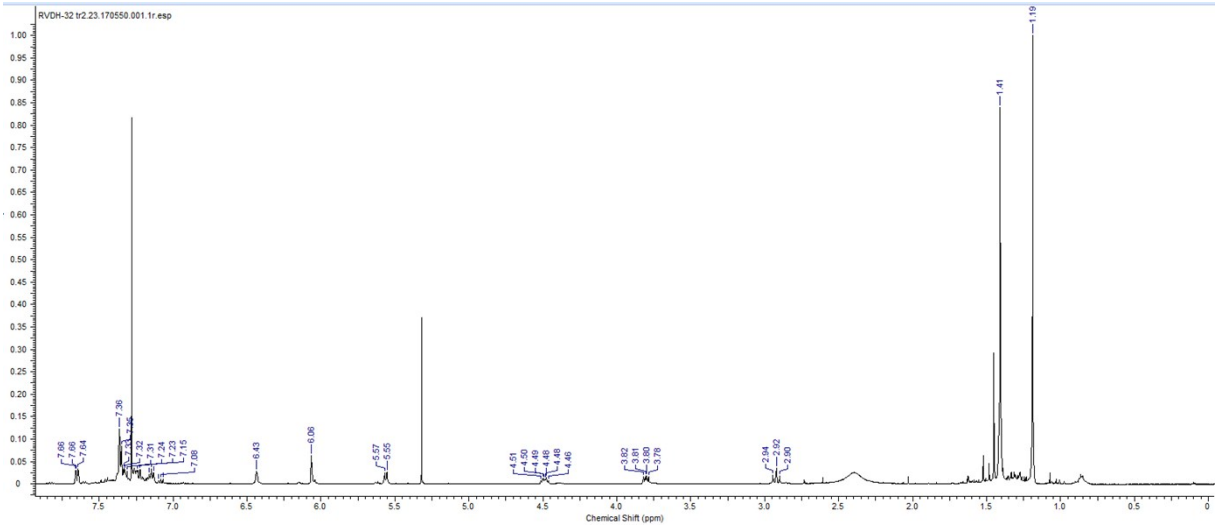
^{1}H NMR (DMSO-d_6, 500 MHz, 298 K) **21b** *(R,S)-diastereomer*



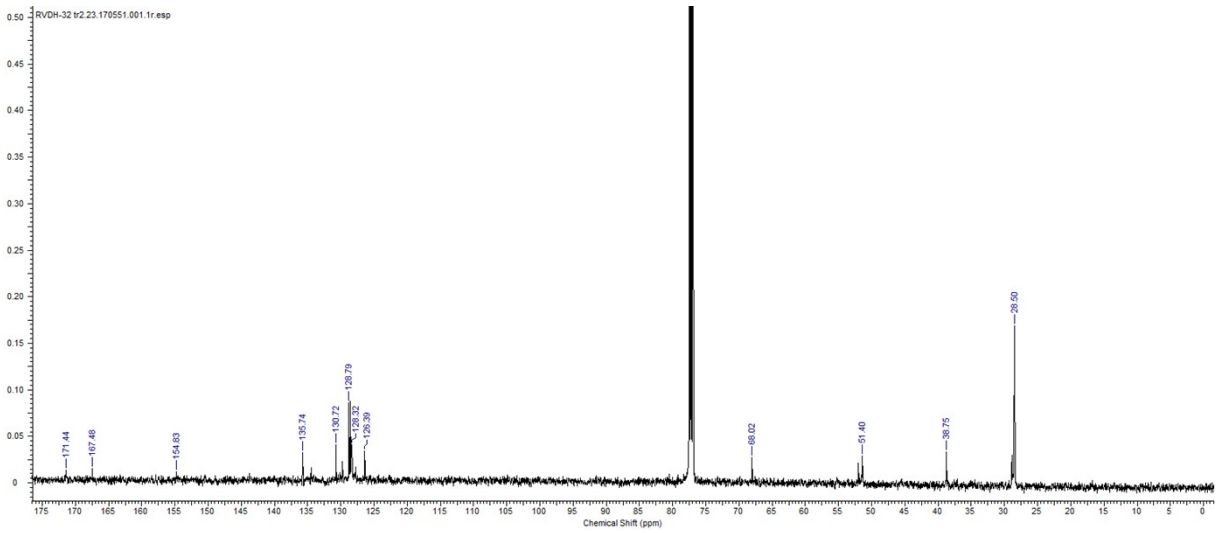
^{13}C NMR ($CDCl_3$, 125 MHz, 298 K) **21b** *(R,S)-diastereomer*



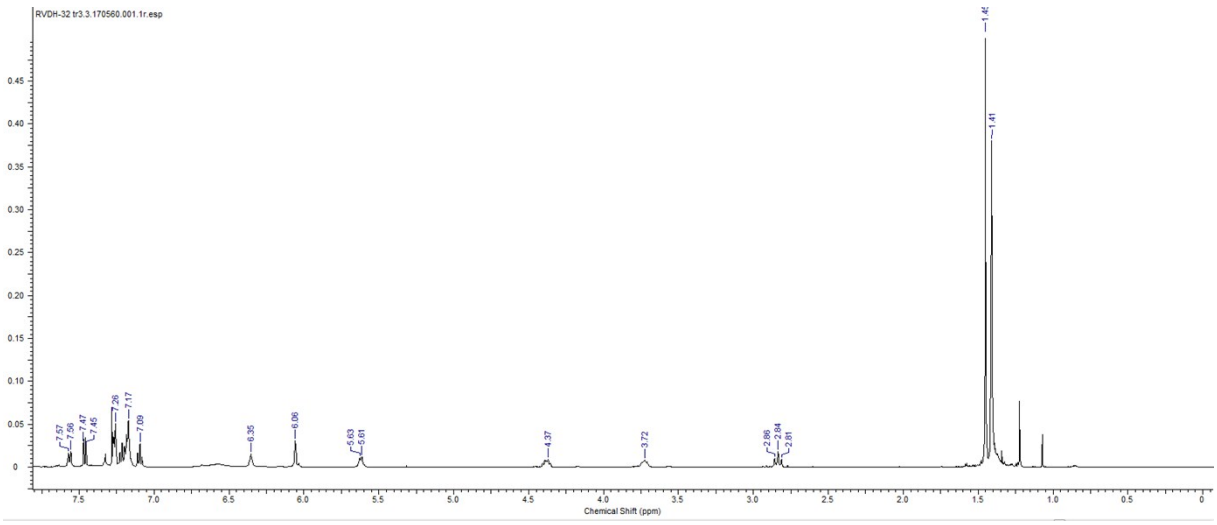
^{1}H NMR ($CDCl_3$, 500 MHz, 298 K) **21c** *Diastereomer 1*



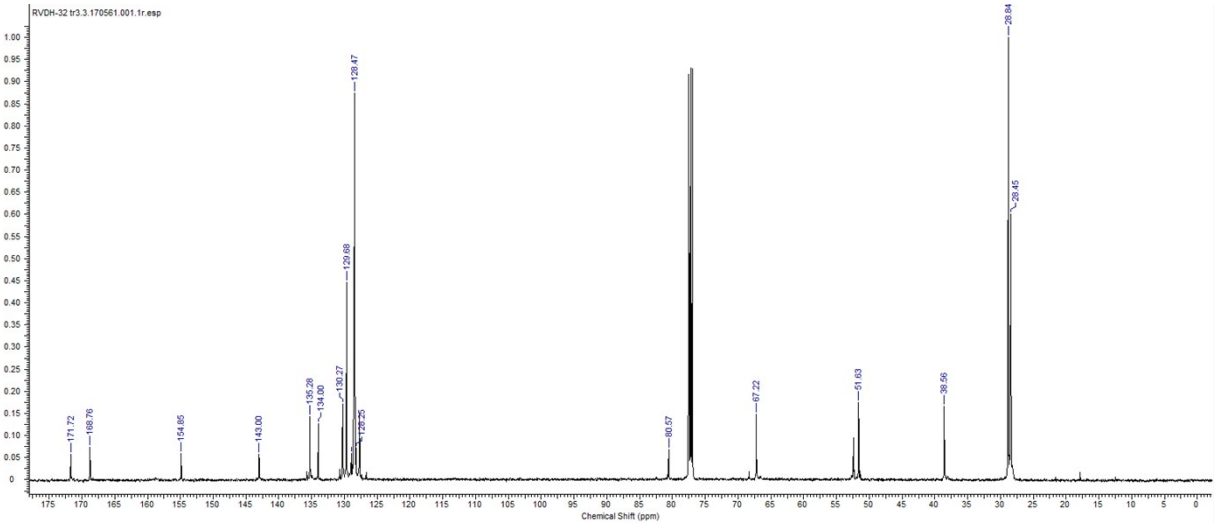
^{13}C NMR ($CDCl_3$, 125 MHz, 298 K) **21c** *Diastereomer 1*



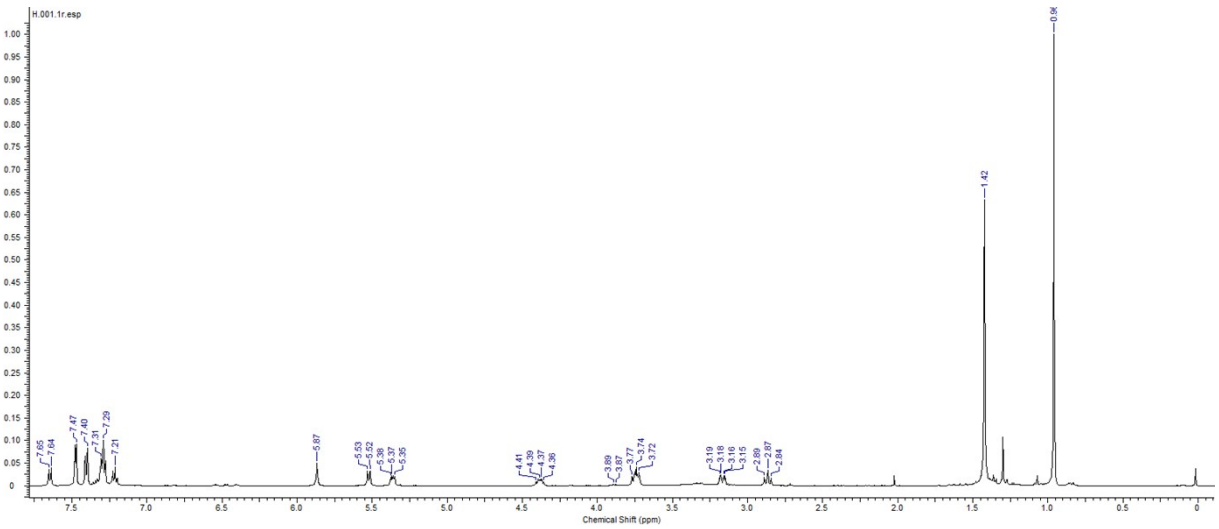
^{1}H NMR ($CDCl_3$, 500 MHz, 298 K) **21c** *Diastereomer 2*



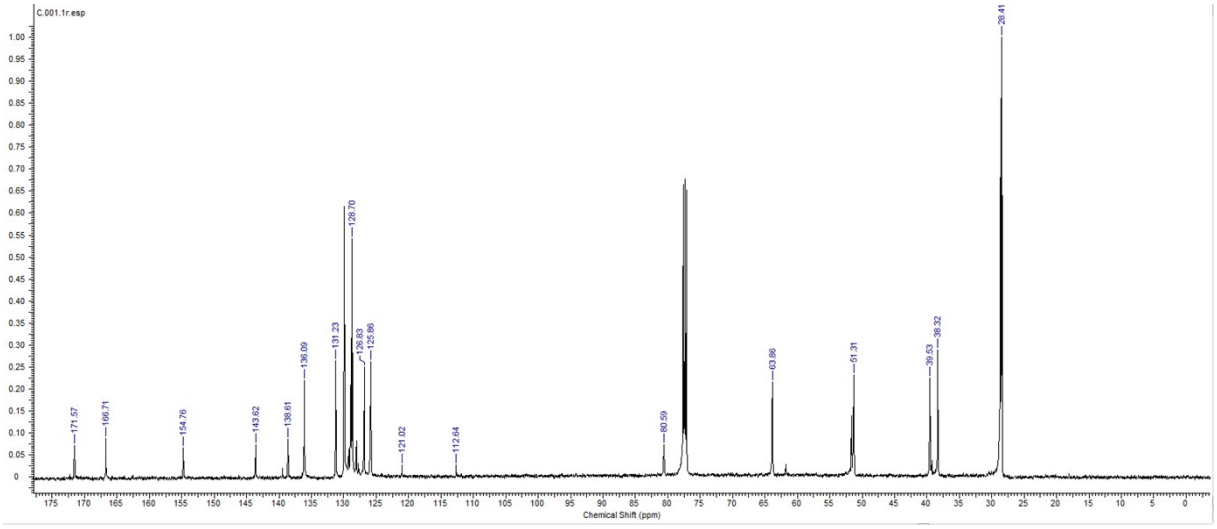
^{13}C NMR ($CDCl_3$, 125 MHz, 298 K) **21c** *Diastereomer 2*



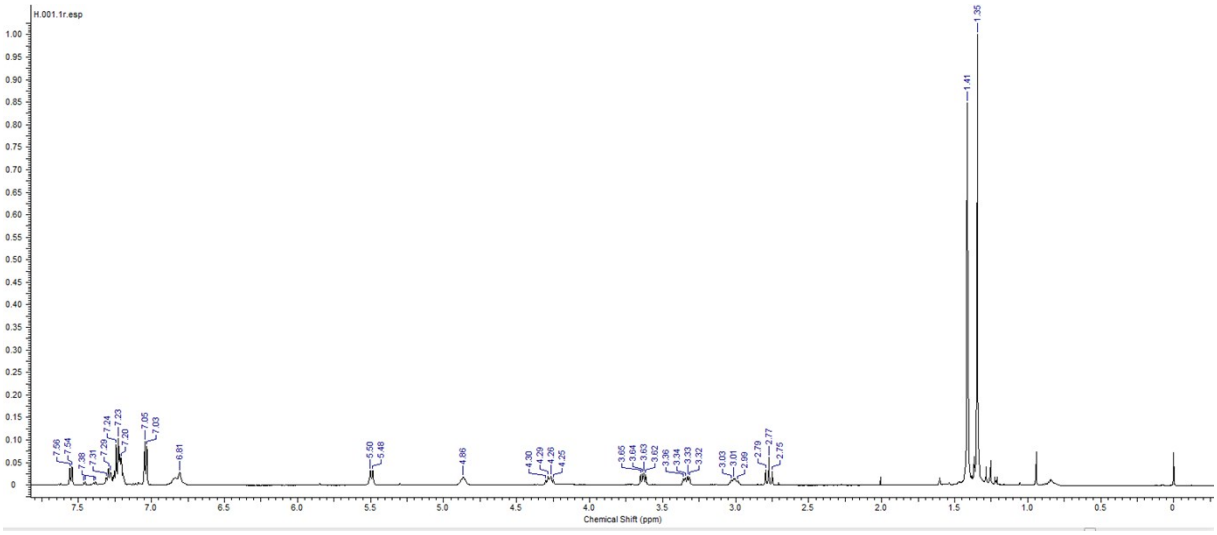
^{1}H NMR ($CDCl_3$, 500 MHz, 298 K) **21d** *Diastereomer 1*



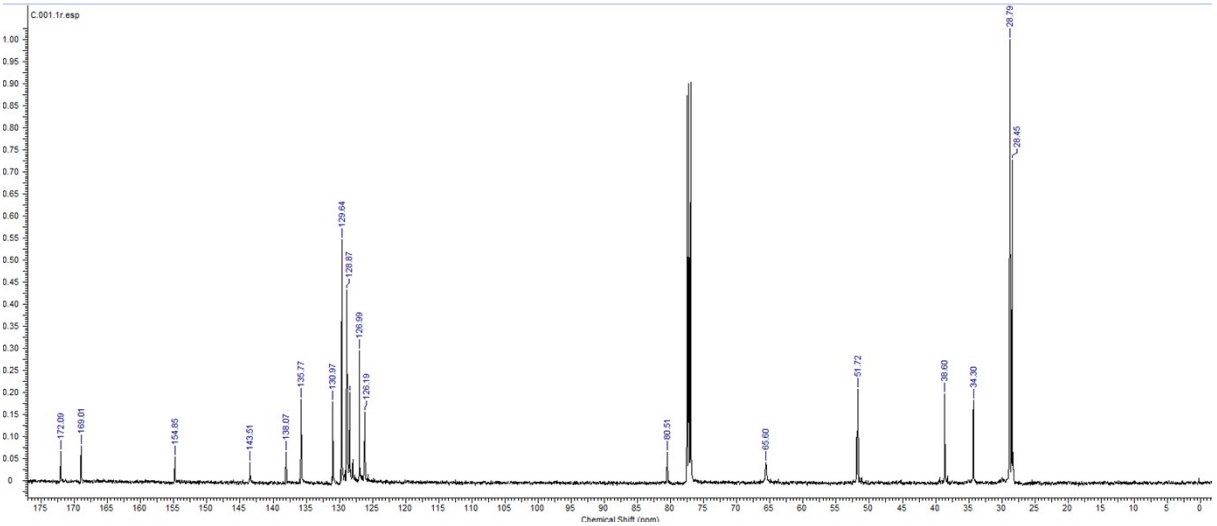
^{13}C NMR ($CDCl_3$, 125 MHz, 298 K) **21d** *Diastereomer 1*



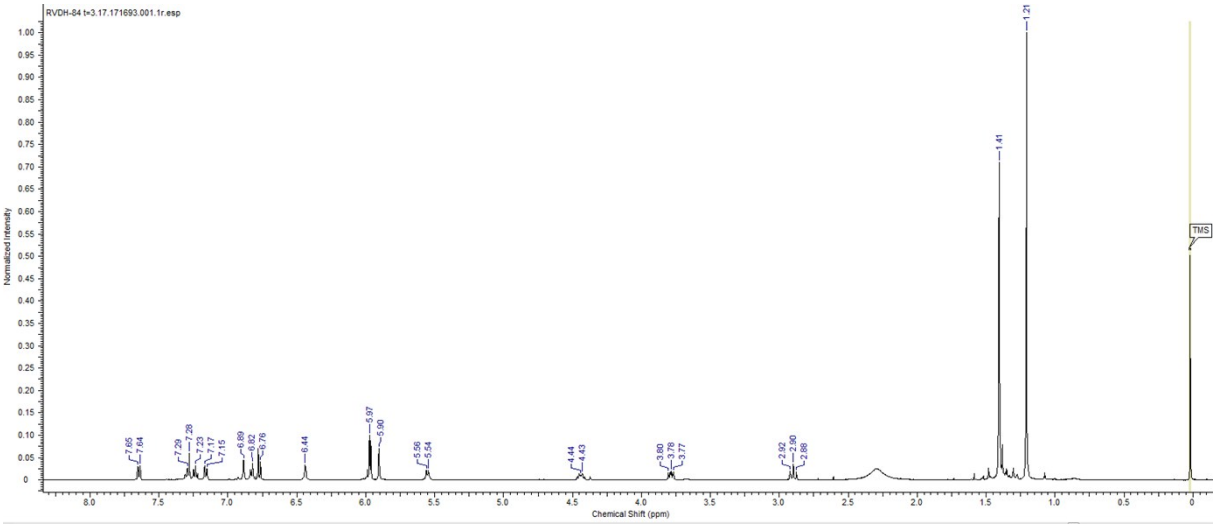
^{1}H NMR ($CDCl_3$, 500 MHz, 298 K) **21d** *Diastereomer 2*



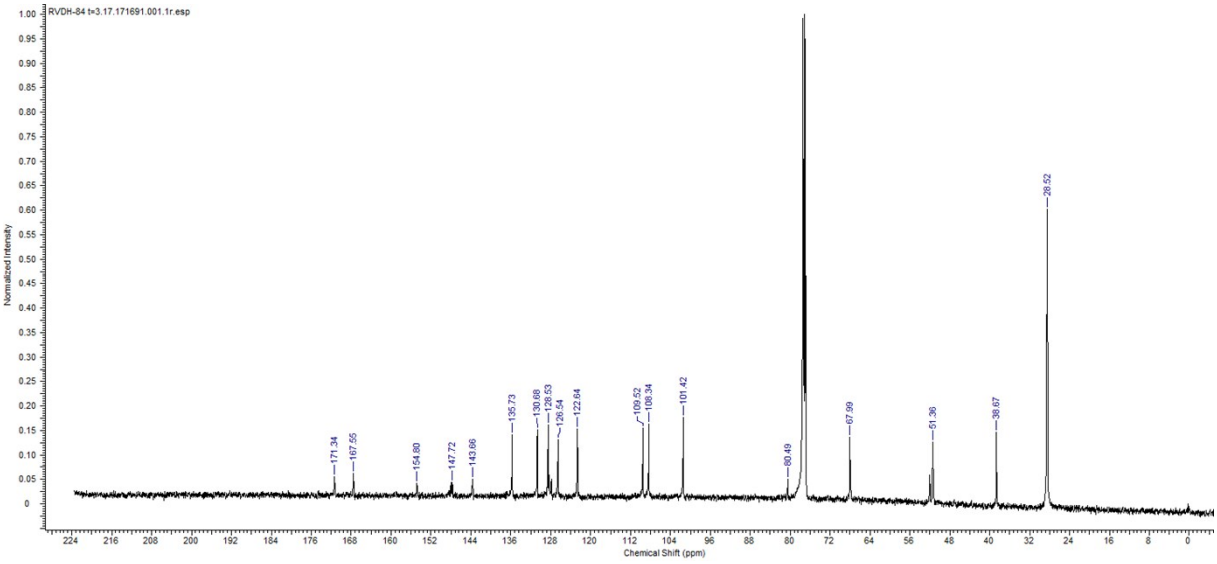
^{13}C NMR ($CDCl_3$, 125 MHz, 298 K) **21d** *Diastereomer 2*



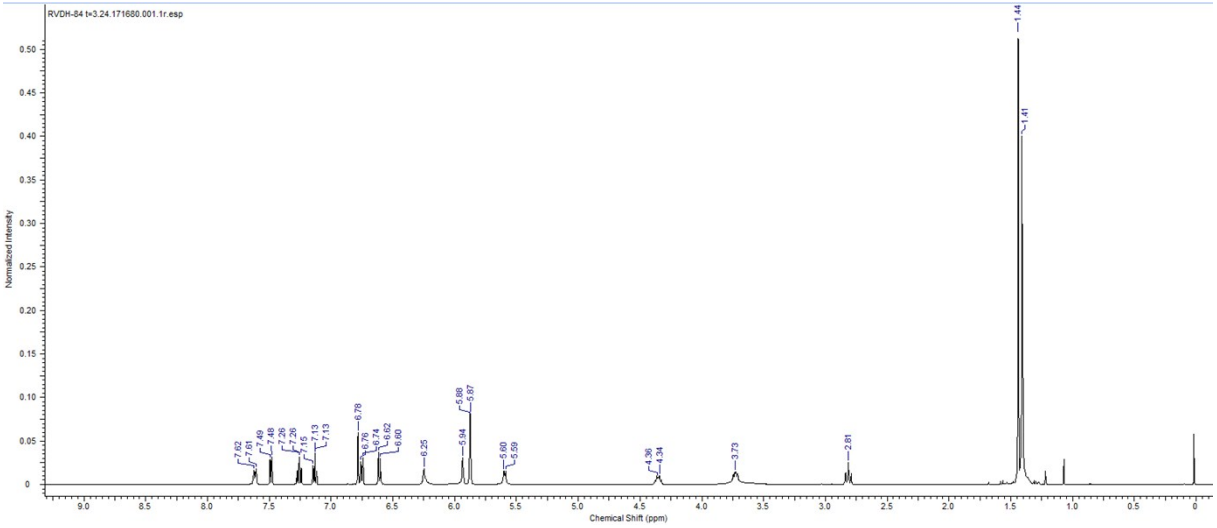
^{1}H NMR ($CDCl_3$, 500 MHz, 298 K) **21e** *Diastereomer 1*



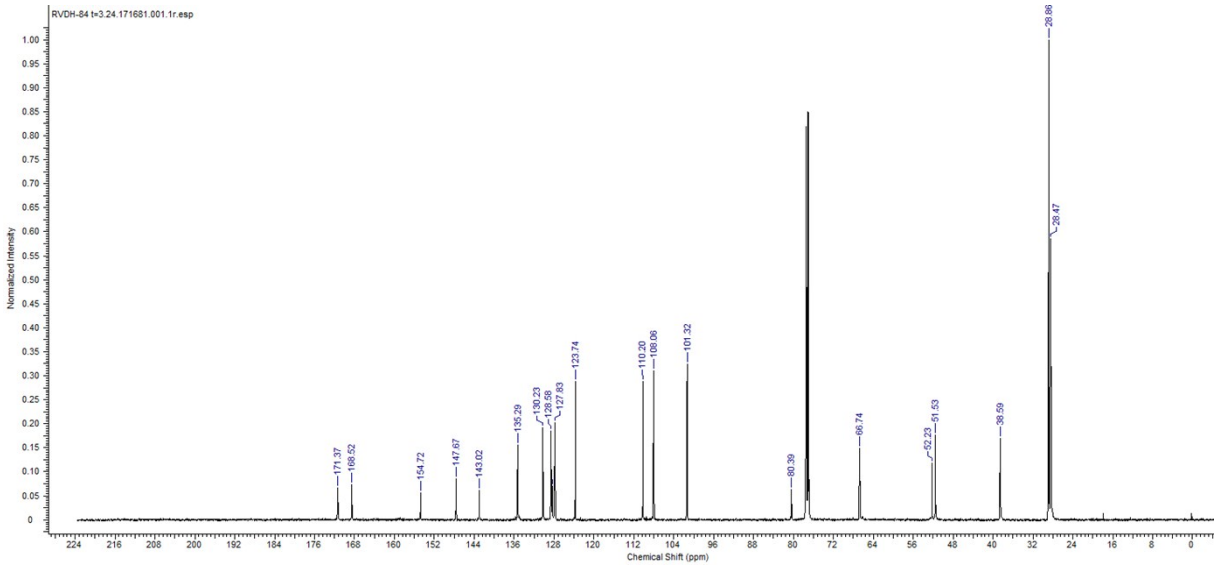
^{13}C NMR ($CDCl_3$, 125 MHz, 298 K) **21e** *Diastereomer 1*



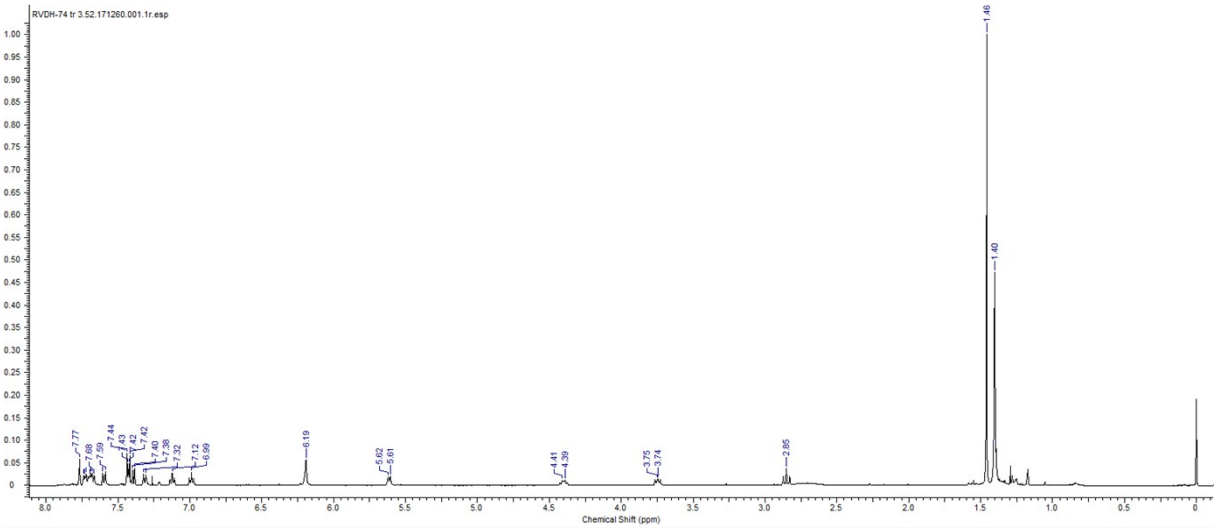
^{1}H NMR ($CDCl_3$, 500 MHz, 298 K) **21e** *Diastereomer 2*



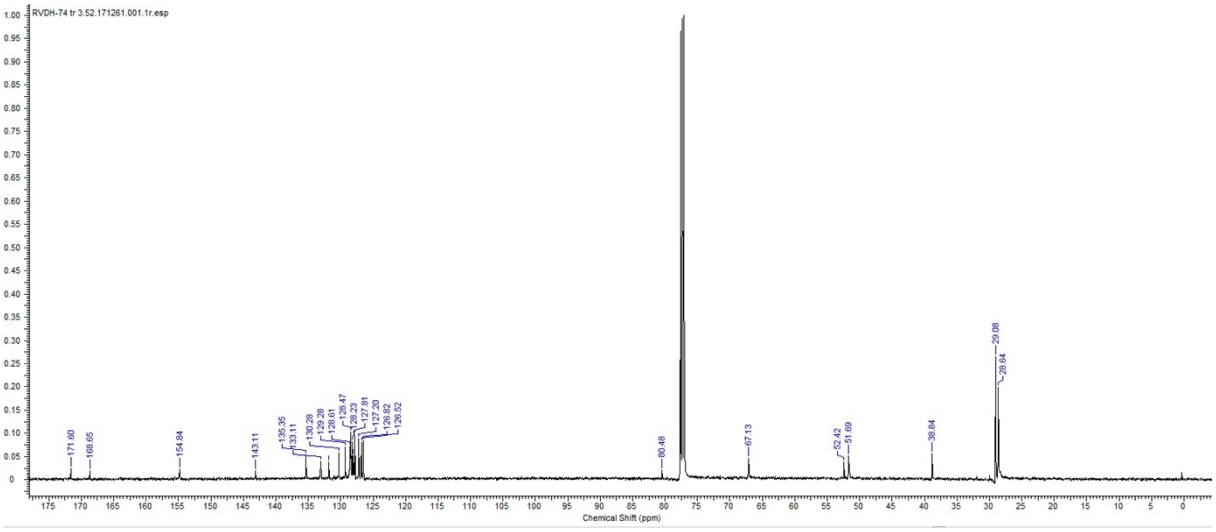
^{13}C NMR ($CDCl_3$, 125 MHz, 298 K) **21e** *Diastereomer 2*



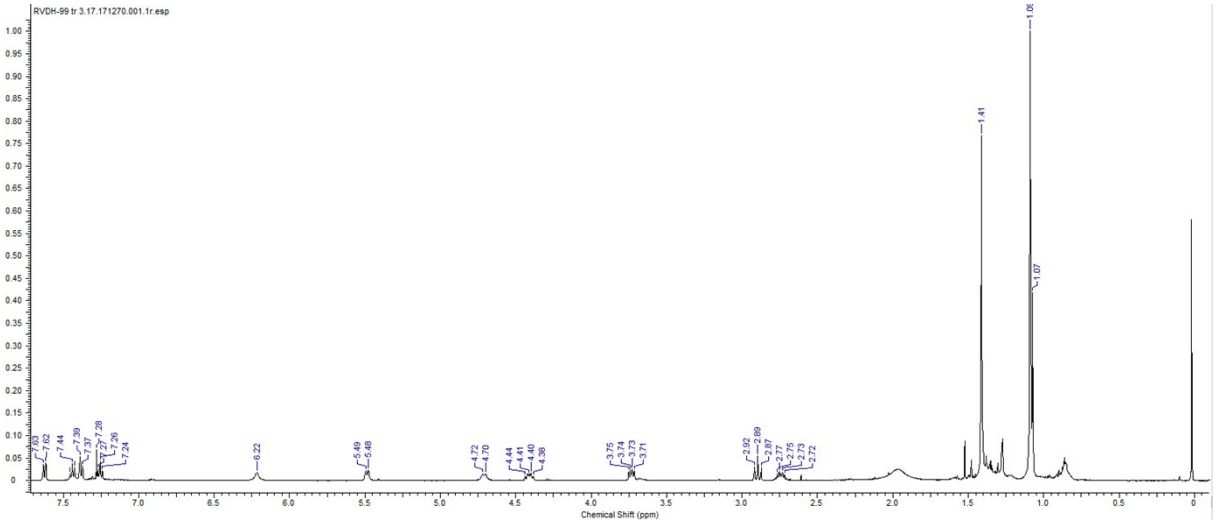
^{1}H NMR ($CDCl_3$, 500 MHz, 298 K) **21f** *Diastereomer 1* (only major peak isolated)



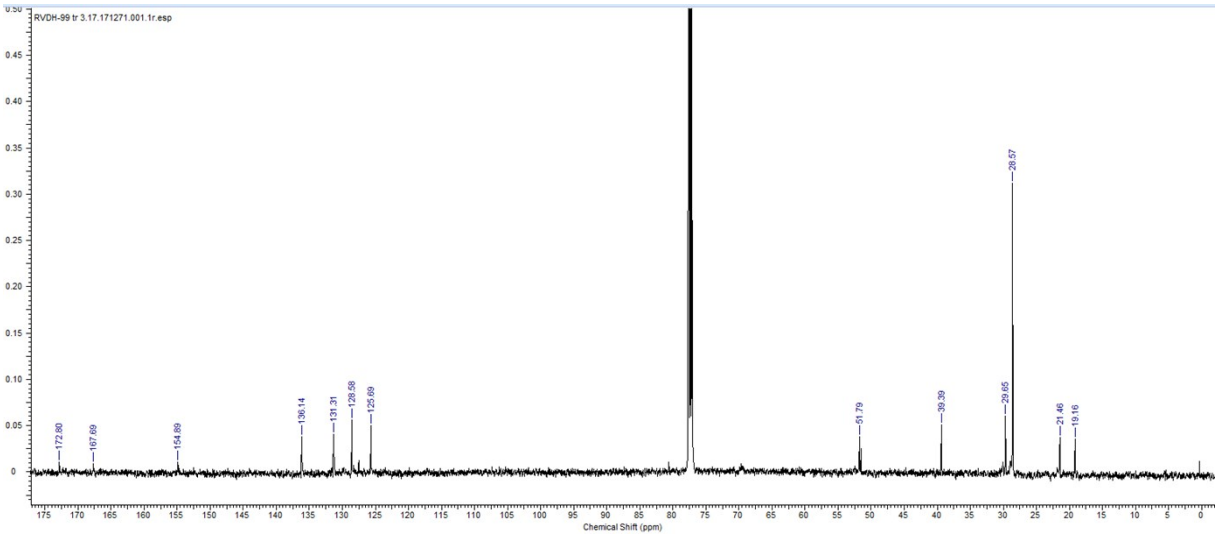
^{13}C NMR ($CDCl_3$, 125 MHz, 298 K) **21f** *Diastereomer 1* (only major peak isolated)



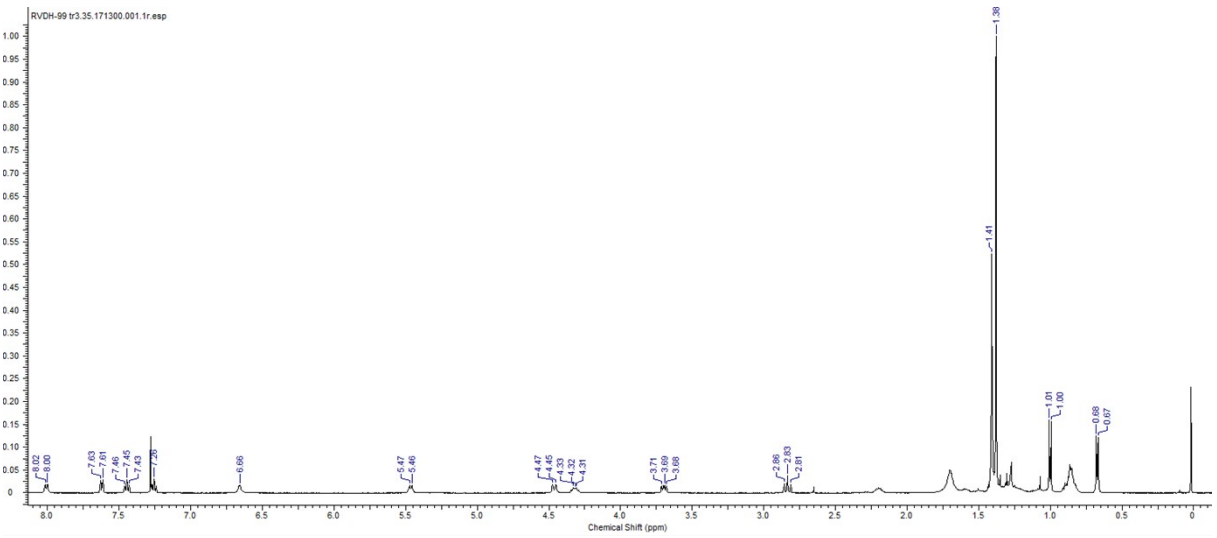
^{1}H NMR ($CDCl_3$, 500 MHz, 298 K) **21g** *Diastereomer 1*



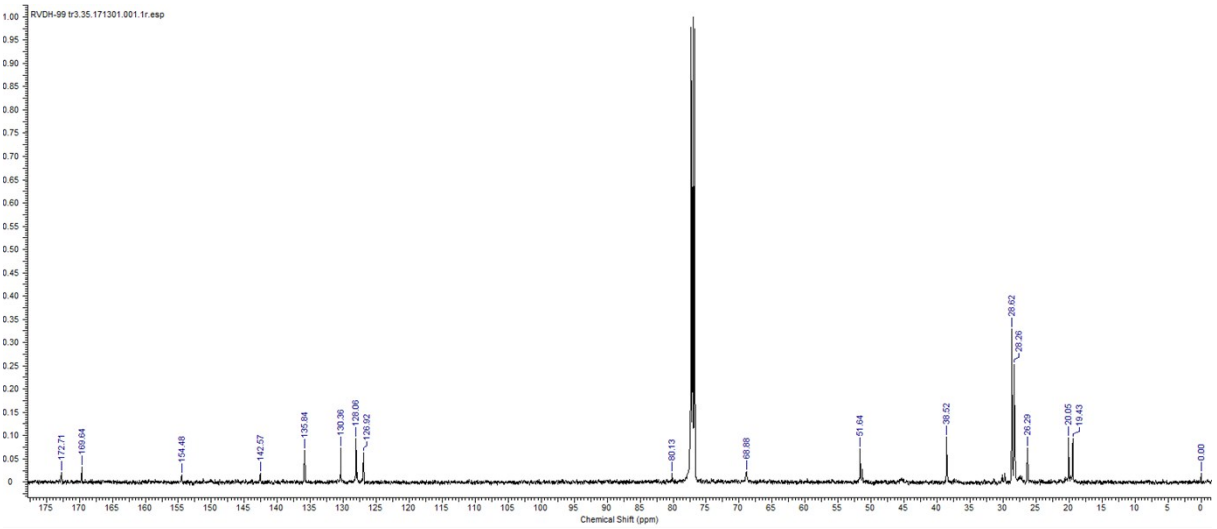
^{13}C NMR ($CDCl_3$, 125 MHz, 298 K) **21g** *Diastereomer 1*



^{1}H NMR ($CDCl_3$, 500 MHz, 298 K) **21g** *Diastereomer 2*



^{13}C NMR ($CDCl_3$, 125 MHz, 298 K) **21g** *Diastereomer 2*

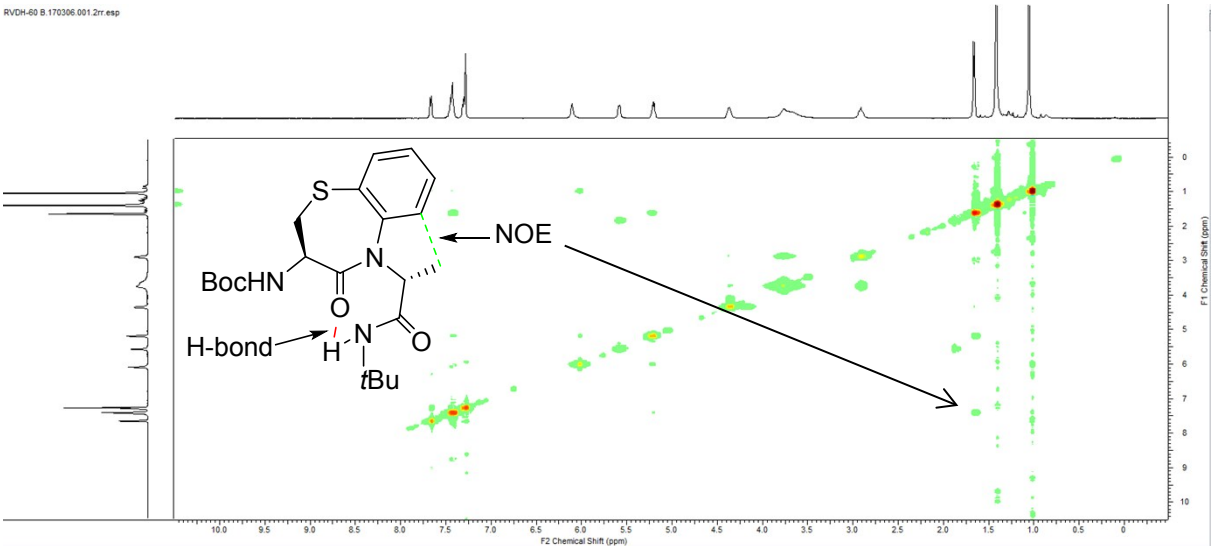


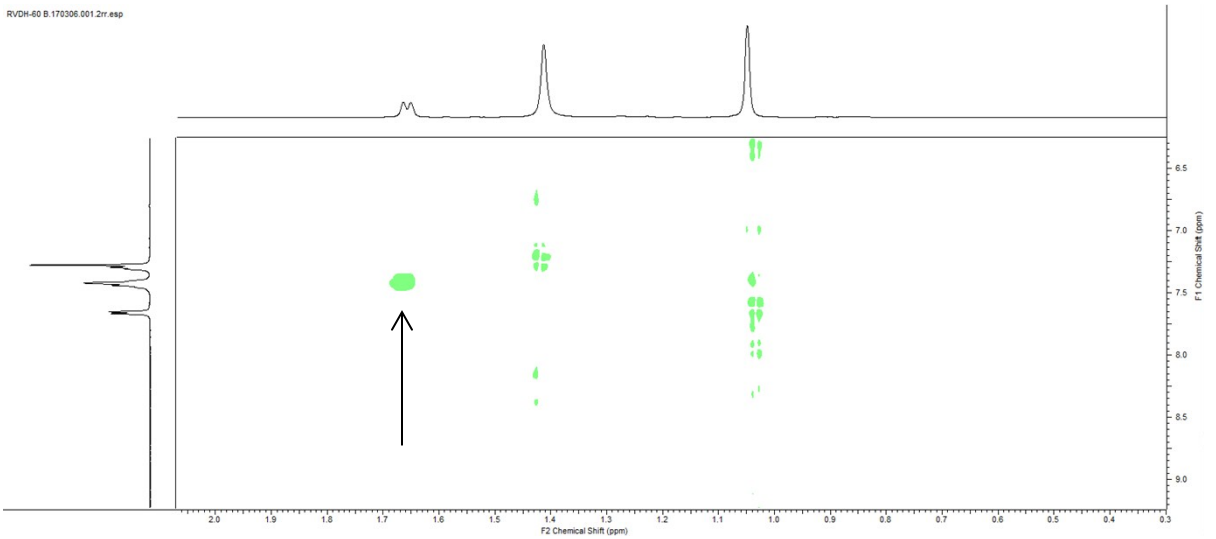
8. Conformational NMR Analysis

8.1 2D ^{1}H NOESY Studies

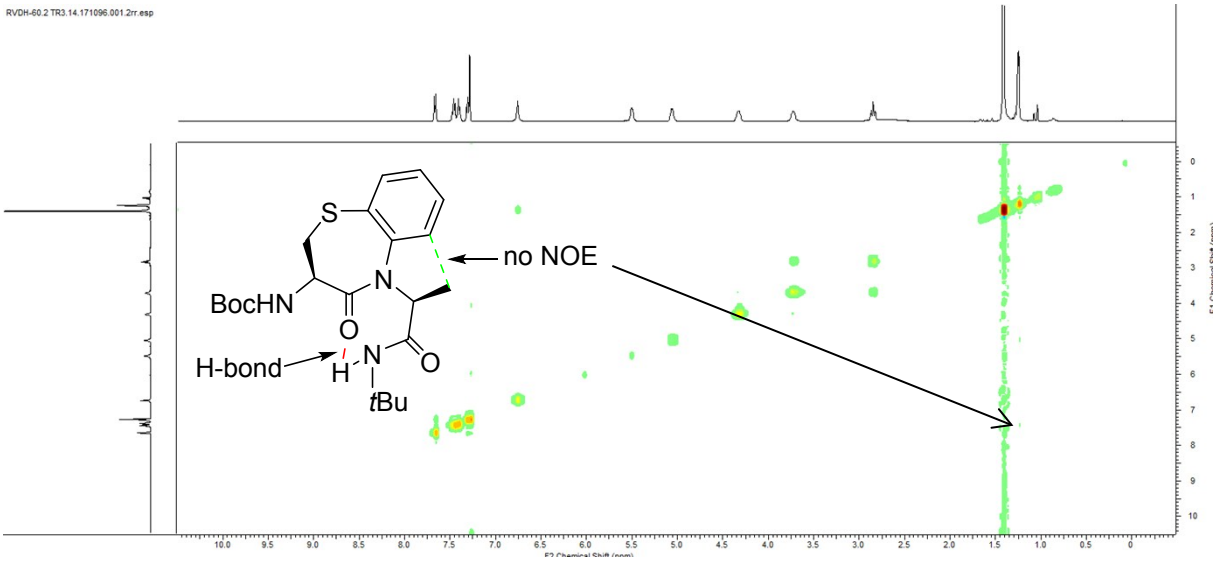
The individual stereochemistry of both (*R*,*S*)- and (*R*,*R*)-**21b** was assigned via 2D ^{1}H NOESY studies. For (*R*,*R*)-**21b**, an indicative NOE correlation was observed between the CH_3^{β} group of the '(*R*)-Ala residue' and the H-6 of the aromatic benzothiazepinone ring (a distance of 2.8 Å was found in the lowest energy conformer by MM). This distinct NOE signal was absent for (*R*,*S*)-**21b** (MM 5.0 Å in the lowest energy conformer).

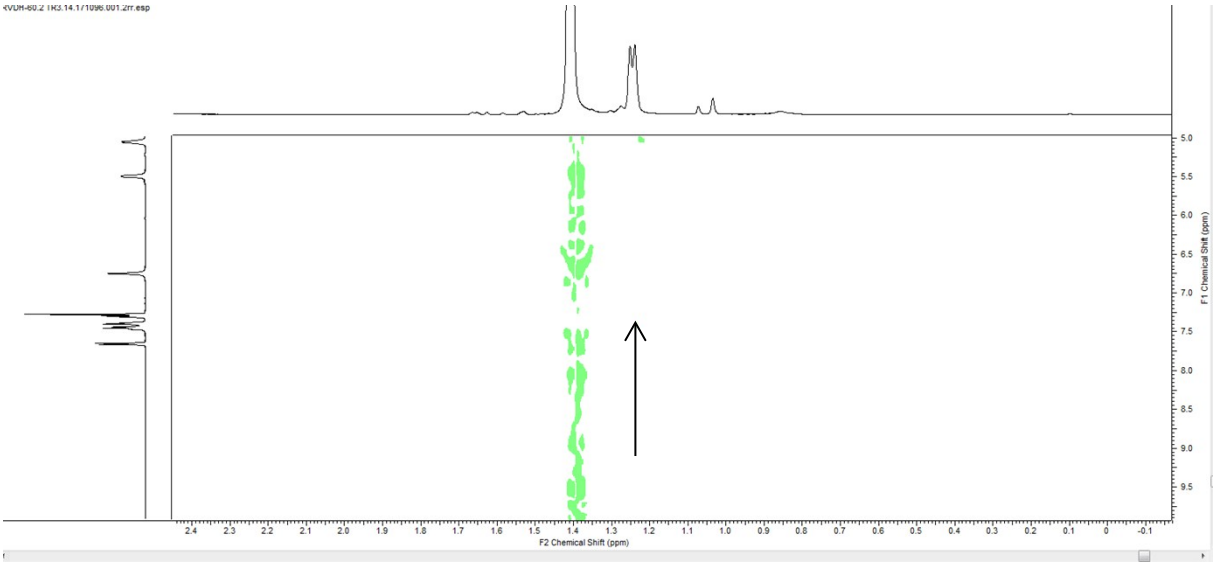
^{1}H-^{1}H NOESY NMR ($CDCl_3$, 500 MHz, 298 K) (*R*,*R*)-**21b**





^{1}H-^{1}H NOESY NMR ($CDCl_3$, 500 MHz, 298 K) (*R*,*S*)-**21b**

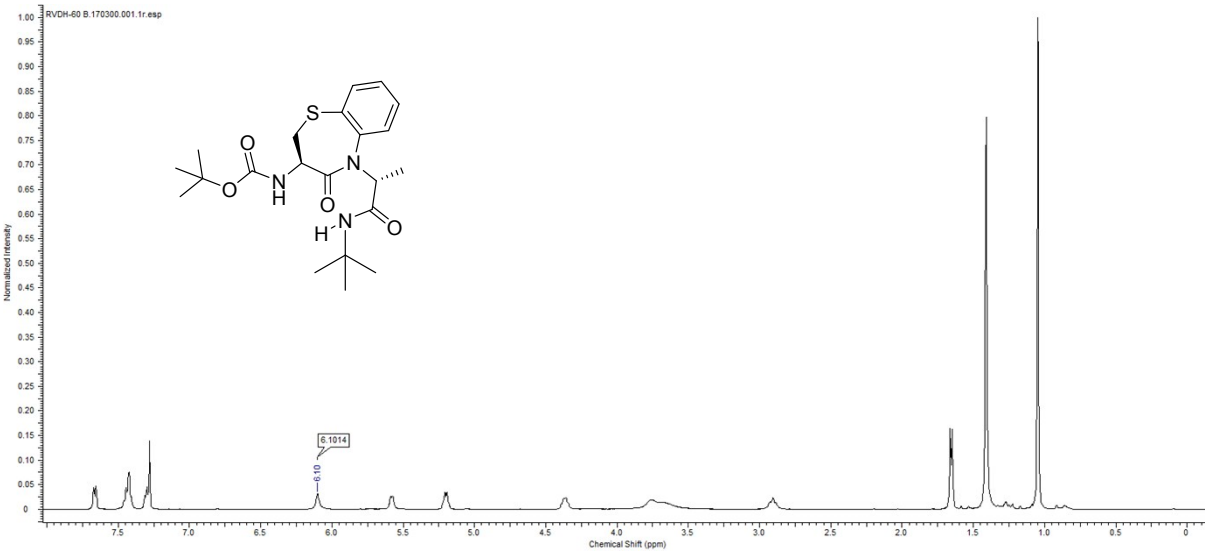




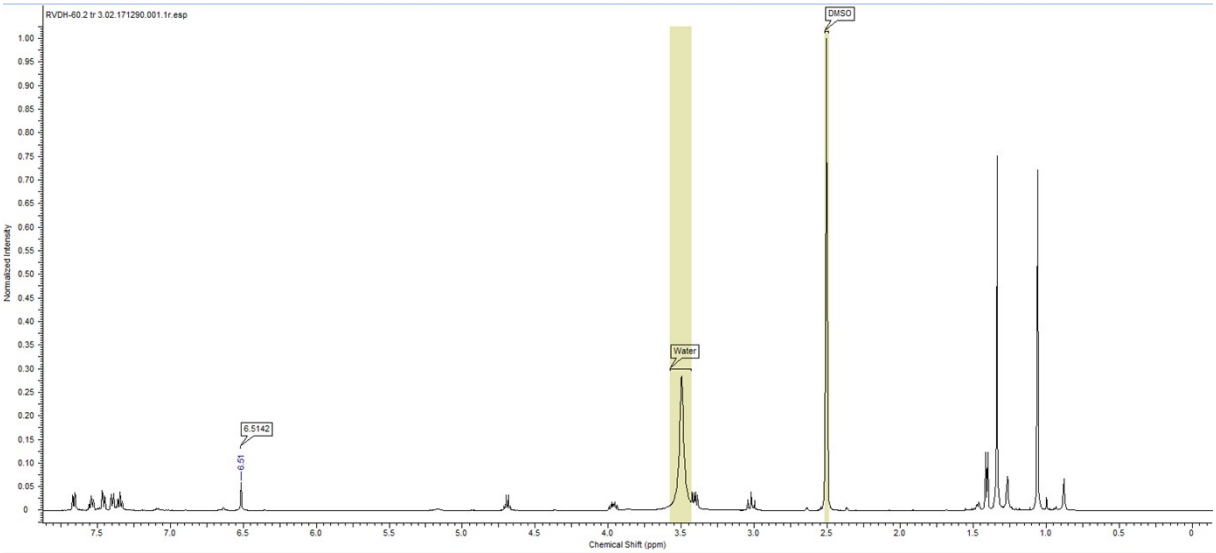
8.2 $CDCl_3$ to DMSO-d_6 Solvent Switch

^{1}H NMR spectra of (*R*,*S*)- and (*R*,*R*)-**21b** were measured in $CDCl_3$ and DMSO-d_6 to evaluate the effect of switching from a non-hydrogen bond-forming solvent to a strong hydrogen bond-forming solvent on the chemical shift value of the *N*H-*tert*-butylamide proton. Both amide resonances of, respectively, (*R*,*S*)- and (*R*,*R*)-**21b** were only weakly influenced upon the solvent switch from $CDCl_3$ to DMSO-d_6 resulting in small differences in chemical shift values of, respectively, 0.35 and 0.41 ppm.

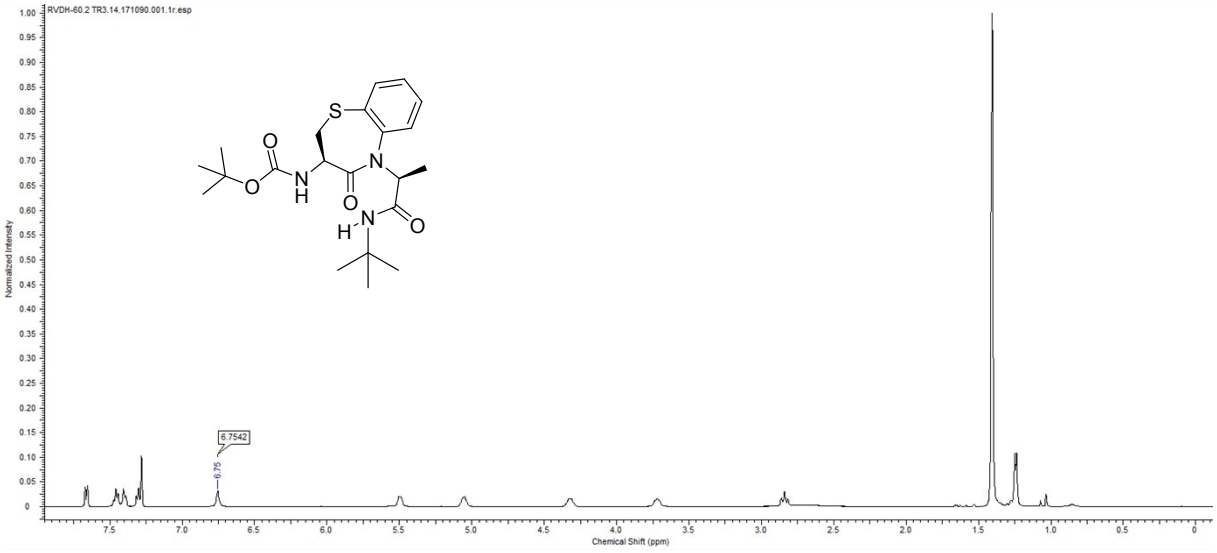
^{1}H NMR ($CDCl_3$, 500 MHz, 298 K) (*R*,*R*)-**21b**



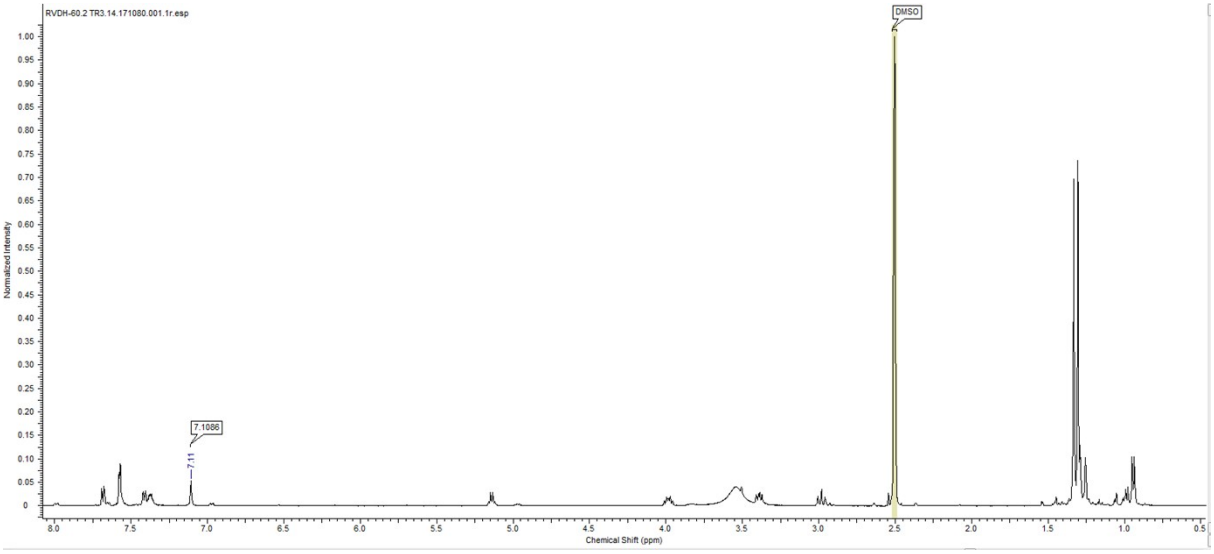
^{1}H NMR (DMSO-d_6, 500 MHz, 298 K) (*R*,*R*)-**21b**



^{1}H NMR ($CDCl_3$, 500 MHz, 298 K) (*R*,*S*)-**21b**



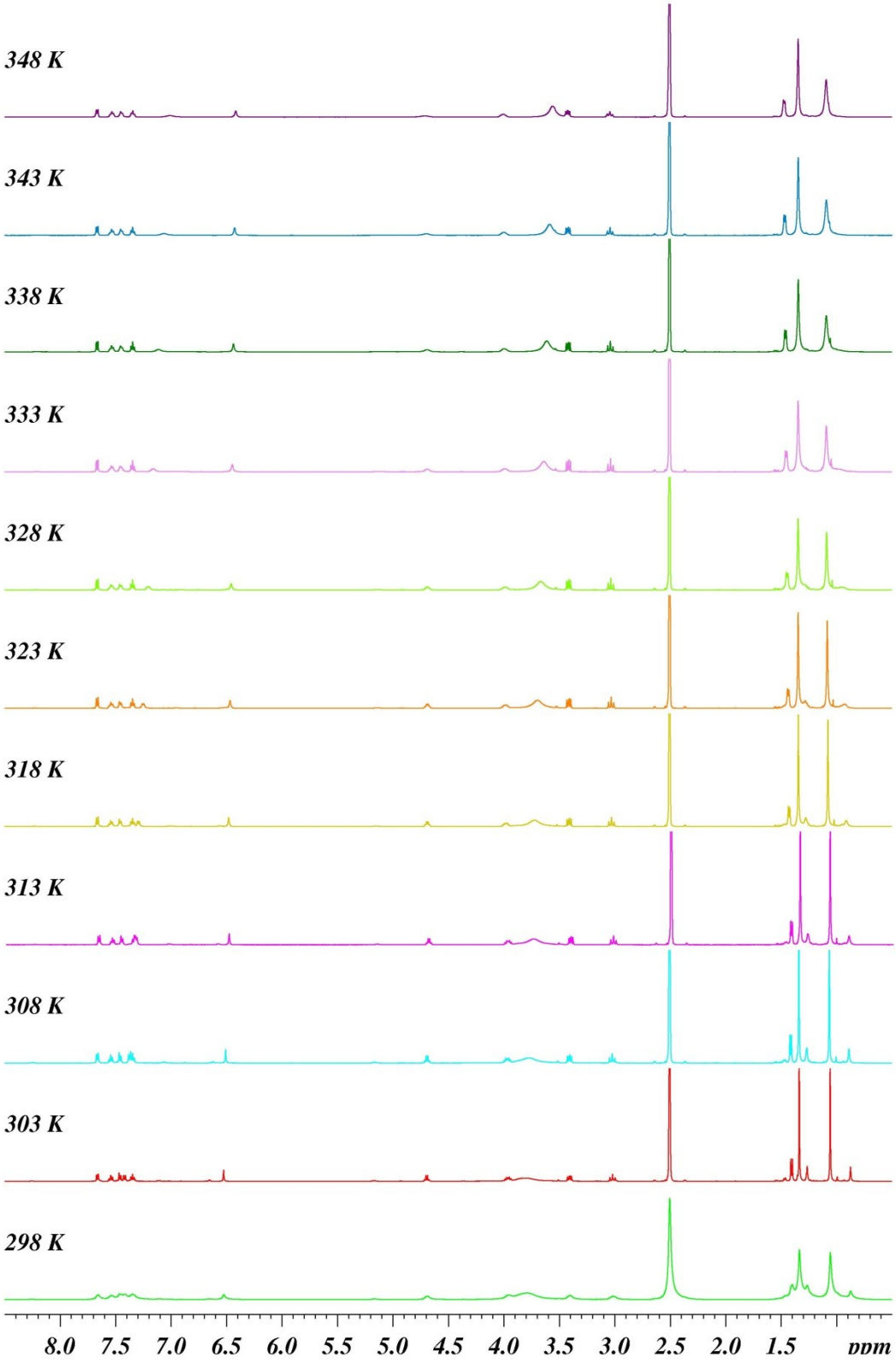
^{1}H NMR (DMSO-d_6, 500 MHz, 298 K) (*R*,*S*)-**21b**



8.3 Temperature-Dependent ^{1}H NMR Study

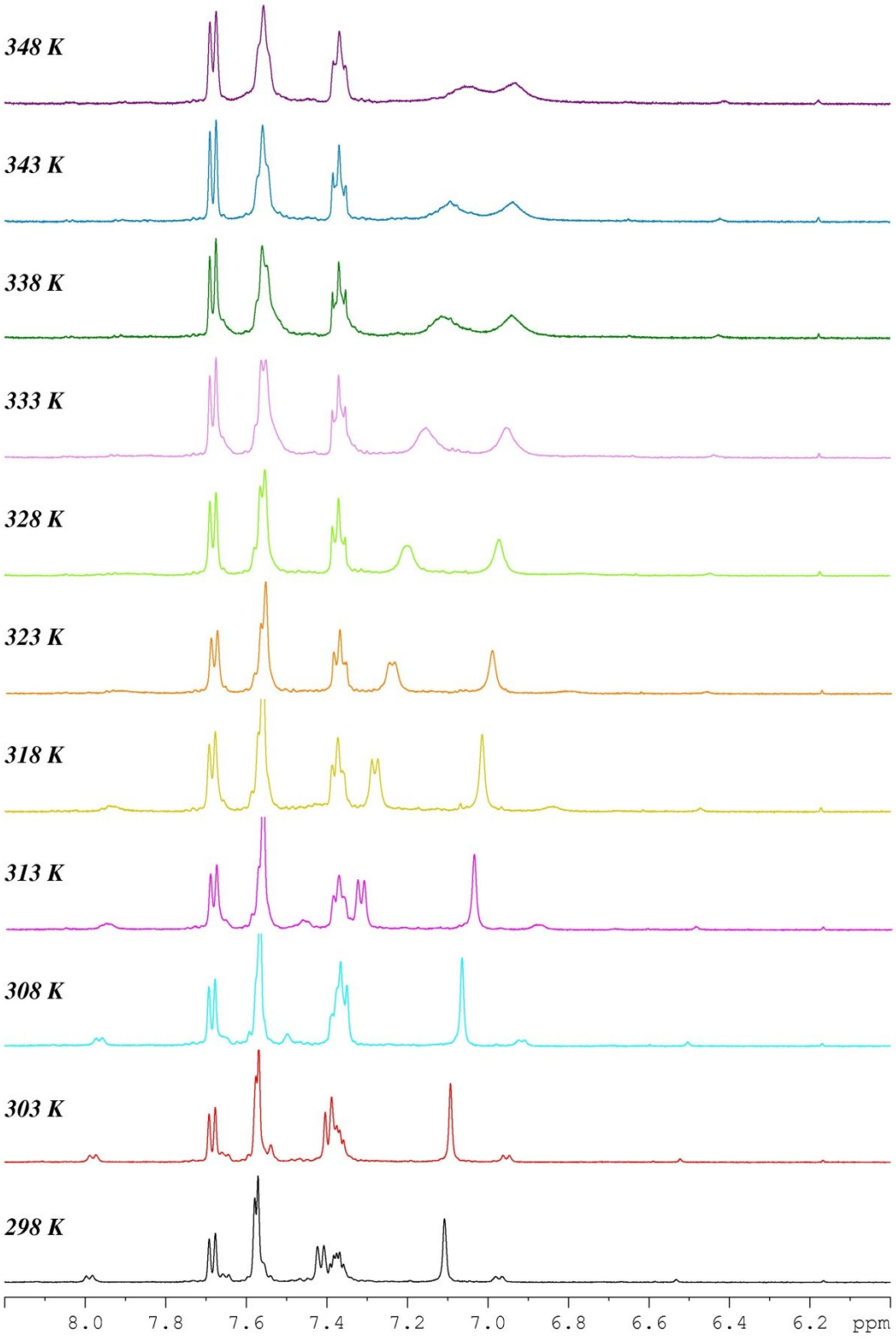
Unlike intermolecular hydrogen bonds, intramolecular hydrogen bonds are only slightly affected by the temperature of the system.[1, 2] Samples of (*R*,*S*)- and (*R*,*R*)-**21b** were then heated in DMSO-d_6 (temperature range between 298 K and 348 K, with temperature increments of 5 K) to examine the effect of temperature increase on the chemical shift of the *N*H-*tert*-butylamide proton. Only coefficients between 0 and -4 ppb/K are generally accepted for solvent-shielded amide protons involved in intramolecular hydrogen bonds.[2, 3] Given the fact that this criterion has been set for cyclic peptides or peptides with longer sequences, in small peptides a thermal coefficient less negative than -4.6 ppb/K has been suggested as a criterion for identifying the solvent-shielded amide protons.[1] For (*R*,*S*)- and (*R*,*R*)-**21b**, it was observed that the chemical shift resonances of the *N*H-*tert*-butylamide proton shifted linearly, resulting in temperature coefficients of, respectively, -3.6 and -2.2 ppb/K. Hence, the calculated amide proton temperature coefficients for (*R*,*S*)- and (*R*,*R*)-**21b** were supporting the presence of an intramolecular hydrogen bond , a common characteristic of γ- and β-turns. These experimental results were consistent with the molecular modeling of both (*R*,*S*)- and (*R*,*R*)-diastereomers of mimic **21b**.

^{1}H NMR (DMSO-d_6, 500 MHz, $\Delta\delta/\Delta T$ = - 2.2 ppb/K) (*R*,*R*)-**21b**




348 K
343 K
338 K
333 K
328 K
323 K
318 K
313 K
308 K
303 K
298 K
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4
6.2
ppm

^{1}H NMR (DMSO-d_6, 500 MHz, $\Delta\delta/\Delta T$ = - 3.6 ppb/K) (*R*,*S*)-**21b**

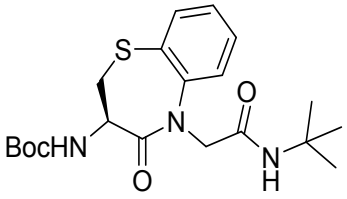

348 K
343 K
338 K
333 K
328 K
323 K
318 K
313 K
308 K
303 K
298 K
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4
6.2
ppm

9. Molecular Modeling

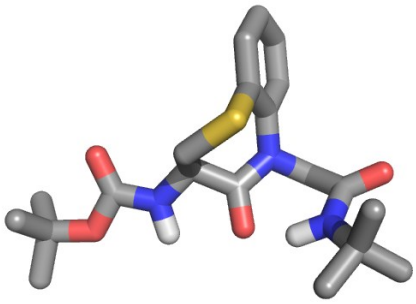
The effect of the second stereocenter on the overall turn-inducing properties of the 1,5-benzothiazepin-4(5*H*)-one dipeptidomimetics **21a-g** was explored via *in silico* structural calculations. The conformational preferences were investigated by molecular modeling using *Molecular Operating Environment* (MOE).[1] The built-in *Conformational Search* module was used to monitor the conformational preferences of the molecules. The MMFF94x force field was used, which was parameterized for gas phase small organic molecules in medicinal chemistry. This force field was implemented to use the Born solvation model. The *LowModeMD* method was applied to sample small ring conformations. While the iteration limit was set at 25000, the rejection limit was set at 1000, meaning that if after 1000 iterations no unique conformation was found, the calculation was stopped. The RMSD limit was set at 0.25 kcal/mol/A, with a maximum energy window of 7 kcal/mol.

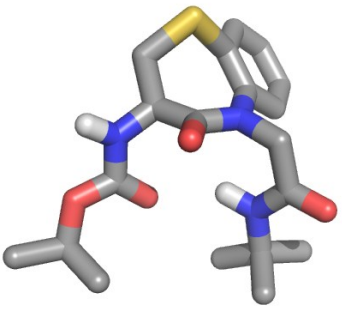
Lowest energy γ- and β-turn conformations for all diastereomers **21a-g**, relative to the lowest energy γ-turn conformation (0.00 kcal.mol^{-1}).

[1] *Molecular Operating Environment (MOE)*, 2013.08; Chemical Computing Group ULC, 1010 Sherbooke St. West, Suite #910, Montreal, QC, Canada, H3A 2R7, **2017**.



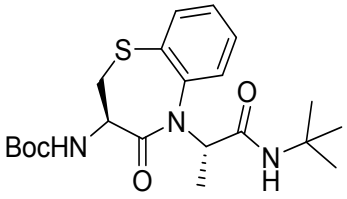
21a



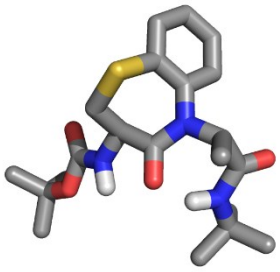


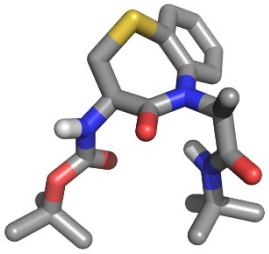
Lowest energy γ-turn conformer: 0.00 kcal.mol^{-1}

Lowest energy β-turn conformer: 3.40 kcal.mol^{-1}



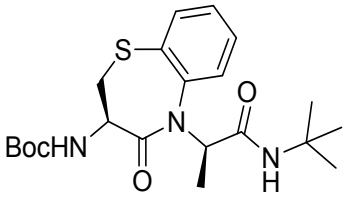
(*R*,*S*)-**21b**



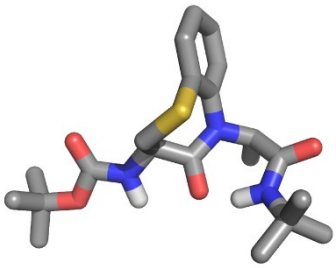


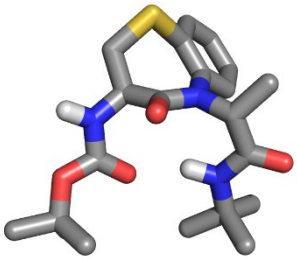
Lowest energy γ-turn conformer: 0.00 kcal.mol^{-1}

Lowest energy β-turn conformer: 3.20 kcal.mol^{-1}



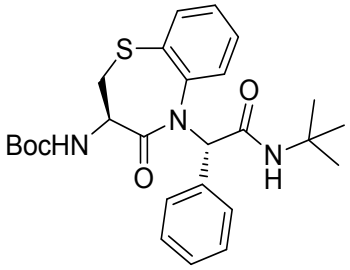
(*R*,*R*)-**21b**



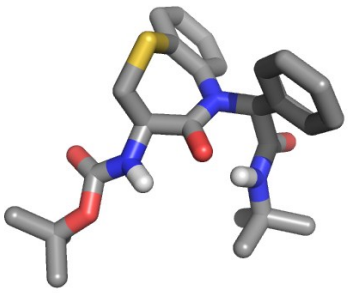


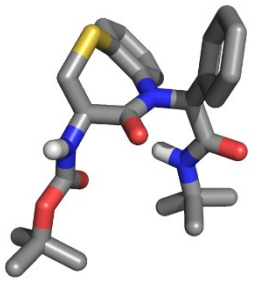
Lowest energy γ-turn conformer: 0.00 kcal.mol^{-1}

Lowest energy β-turn conformer: 3.04 kcal.mol^{-1}

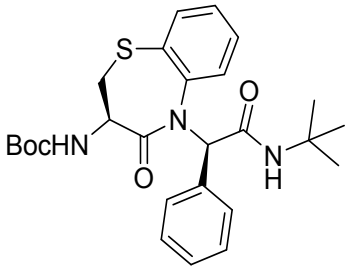


(*R*,*S*)-**21c**

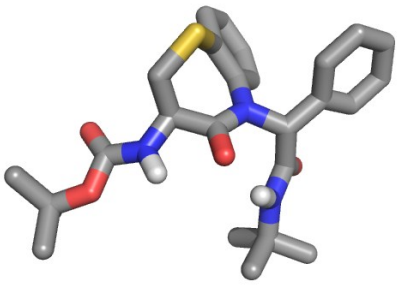


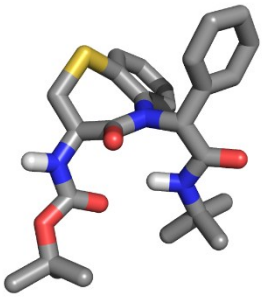


Lowest energy γ-turn conformer: 0.00 kcal.mol^{-1} Lowest energy β-turn conformer: 3.02 kcal.mol^{-1}

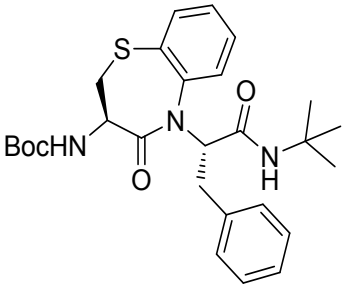


(*R*,*R*)-**21c**

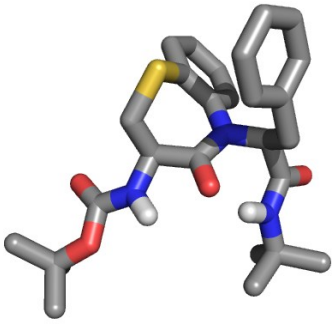


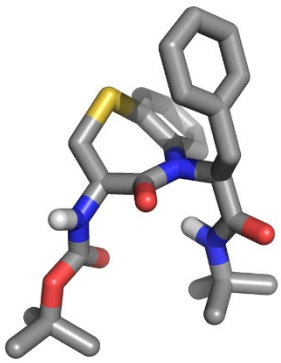


Lowest energy γ-turn conformer: 0.00 kcal.mol^{-1} Lowest energy β-turn conformer: 1.95 kcal.mol^{-1}

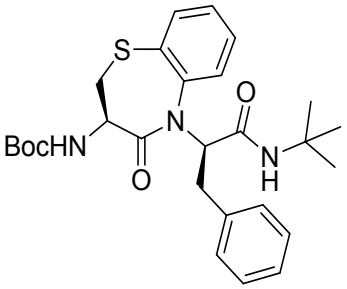


(*R*,*S*)-**21d**

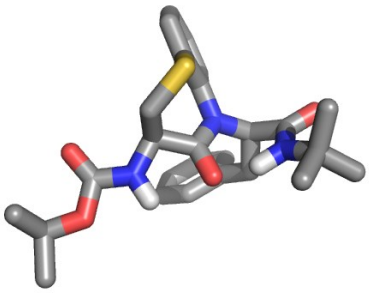


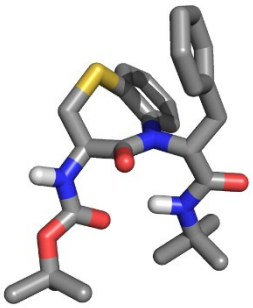


Lowest energy γ-turn conformer: 0.00 kcal.mol^{-1} Lowest energy β-turn conformer: 3.02 kcal.mol^{-1}

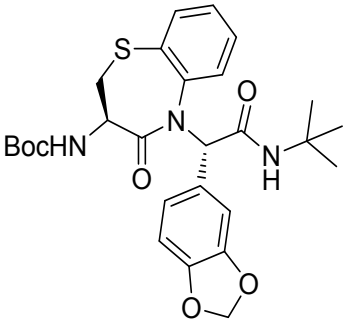


(*R*,*R*)-**21d**

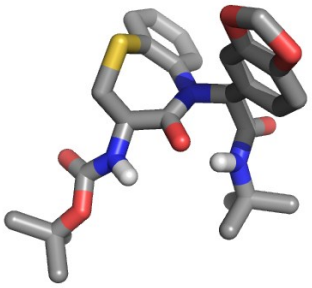


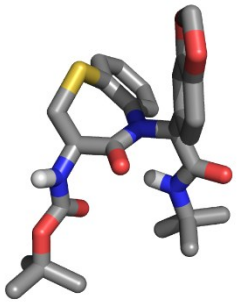


Lowest energy γ-turn conformer: 0.00 kcal.mol^{-1} Lowest energy β-turn conformer: 3.60 kcal.mol^{-1}

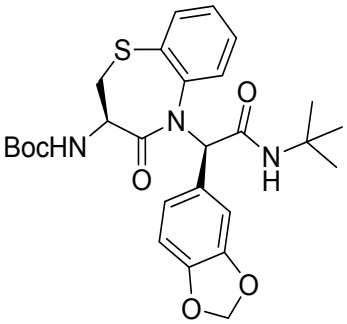


(*R*,*S*)-**21e**

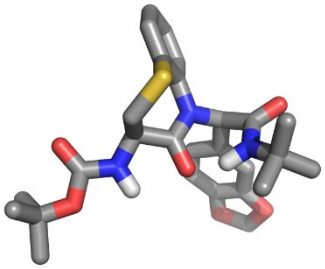


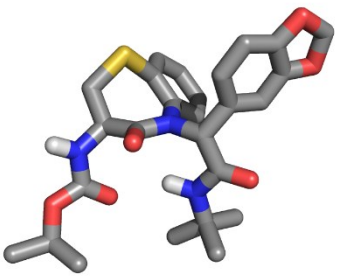


Lowest energy γ-turn conformer: 0.00 kcal.mol^{-1} Lowest energy β-turn conformer: 2.80 kcal.mol^{-1}

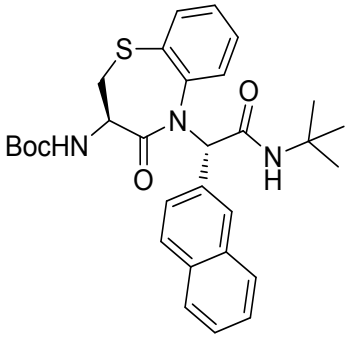


(*R*,*R*)-**21e**

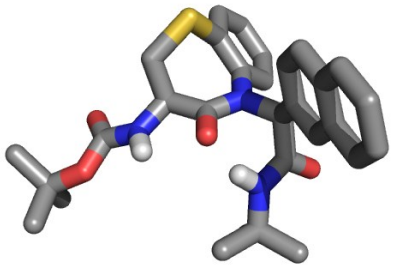


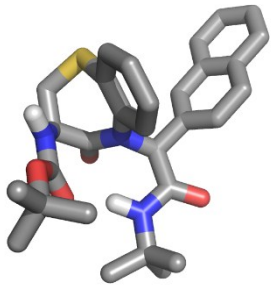


Lowest energy γ-turn conformer: 0.00 kcal.mol^{-1} Lowest energy β-turn conformer: 1.96 kcal.mol^{-1}



(*R*,*S*)-**21f**





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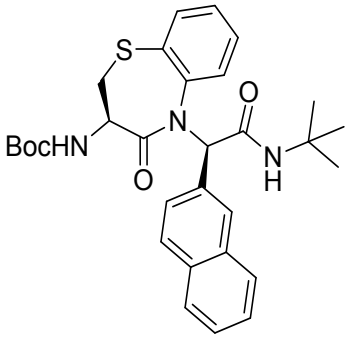
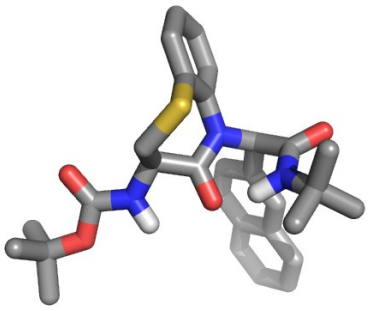
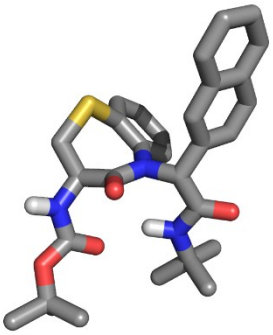
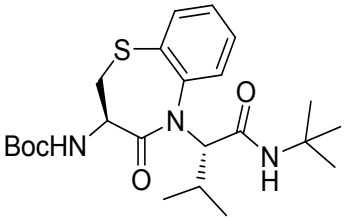


(*R*,*R*)-**21f**

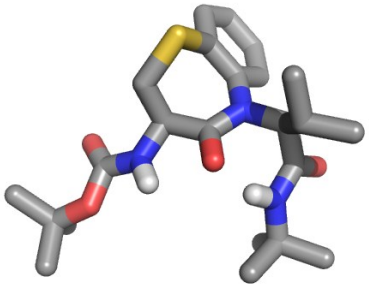




Lowest energy γ-turn conformer: 0.00 kcal.mol^{-1} Lowest energy β-turn conformer: 2.02 kcal.mol^{-1}

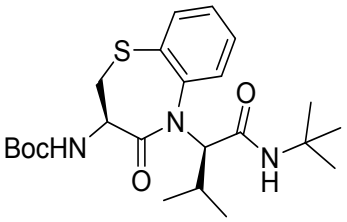


(*R*,*S*)-**21g**

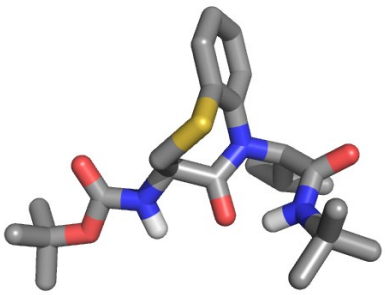


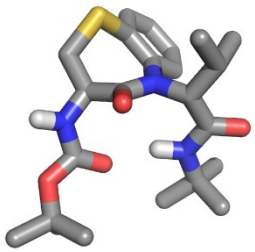
Lowest energy γ-turn conformer: 0.00 kcal.mol^{-1}

Lowest energy β-turn conformer: not observed



(*R*,*R*)-**21g**





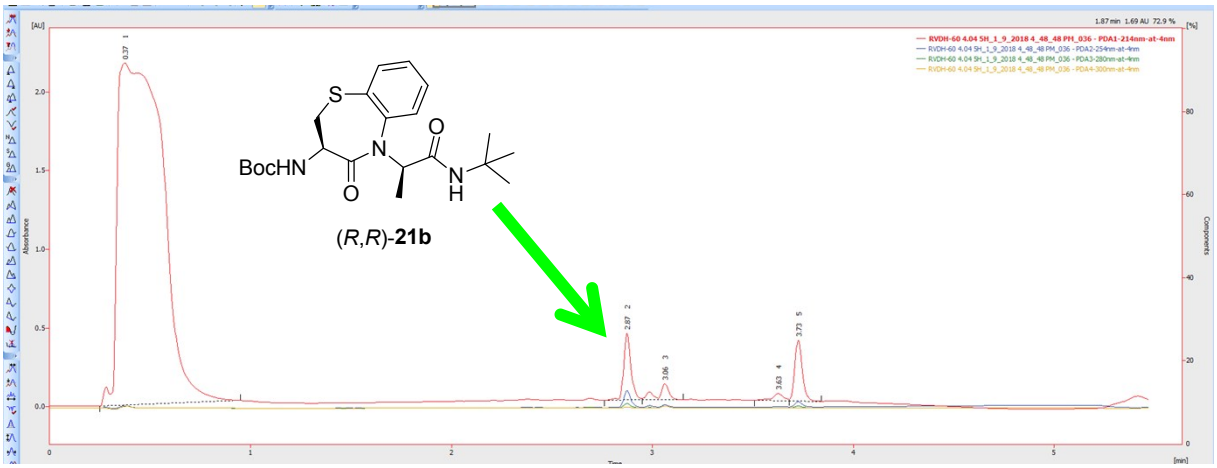
Lowest energy γ-turn conformer: 0.00 kcal.mol^{-1}

Lowest energy β-turn conformer: 5.60 kcal.mol^{-1}

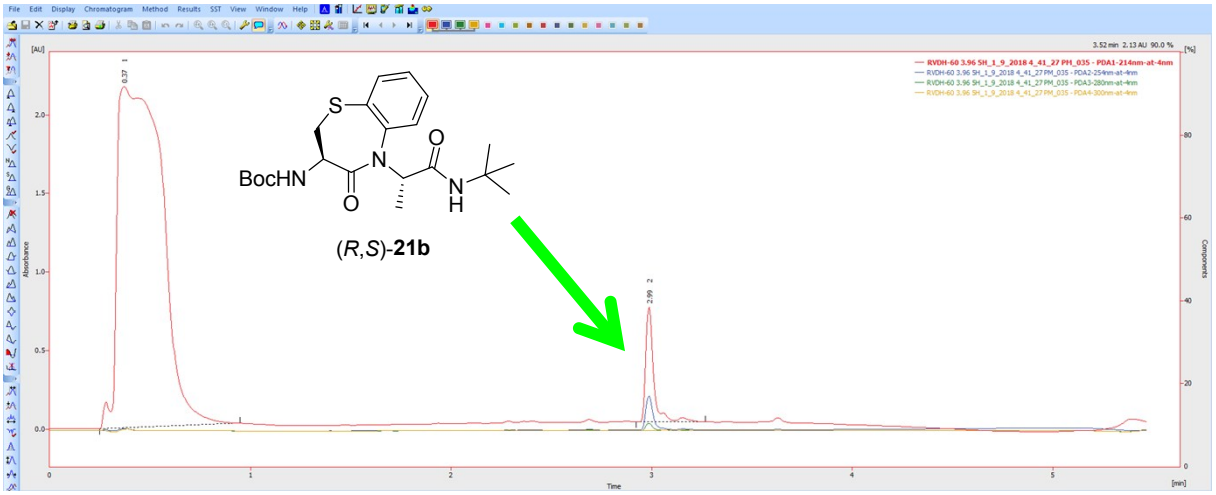
10. Separate C-S Ullmann Coupling of (*R*,*R*)- and (*R*,*S*)-**20b**

After *S*-trityl deprotection of Ugi-4CR products **19b**, both (*R*,*R*)- and (*R*,*S*)-diastereomers of **20b** were successfully separated and purified via silica gel column chromatography. In a next step, these diastereomers of **20b** were separately subjected to the C-S Ullmann coupling to detect any energetically favored formation of one diastereomer of **21b**. After 5 hours of reaction time using the previously described reaction conditions for the intramolecular CuI-catalyzed C-S Ullmann condensation, RP-HPLC analysis revealed that for the (*R*,*R*)-diastereomer of **20b** several unidentified side products were observed during the CuI-catalyzed cyclization into (*R*,*R*)-**21b**, whereas reaction of (*R*,*S*)-**20b** resulted in a clean RP-HPLC conversion into (*R*,*S*)-**21b**.

RP-HPLC chromatogram of the reaction of (*R*,*R*)-**20b** into (*R*,*R*)-**21b** after 5 hours of reaction time:



RP-HPLC chromatogram of the reaction of (*R*,*S*)-**20b** into (*R*,*S*)-**21b** after 5 hours of reaction time:



11. References

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2. K. Van Rompaey, S. Ballet, C. Tömböly, R. De Wachter, K. Vanommeslaeghe, M. Biesemans, R. Willem and D. Tourwé, *Eur. J. Org. Chem.*, 2006, **2006**, 2899-2911.
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