nature

SUPPLEMENTARY INFORMATION

https://doi.org/10.1038/s41586-018-0553-9

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Asymmetric α–arylation of amino acids

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Asymmetric α-Arylation of Amino Acids

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Supplementary Information

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General Information

All reactions were performed under a nitrogen atmosphere in flame-dried apparatus, unless stated otherwise. All reagents and chemicals were obtained from chemical suppliers and used without further purification, with the exception of those listed below. THF was distilled from sodium wire under nitrogen using benzophenone as an indicator. DCM and DIPA were distilled from CaH_2 under nitrogen. Et_2O and toluene were collected under argon from an Innovative Technologies PureSolve PS-MP-5 solvent purification system. Et_3N was stored over KOH pellets and used directly. Commercial *n*BuLi solutions were titrated with *N*-benzylbenzamide in anhydrous THF prior to use.[1] Pet.Ether refers to the fractions of petroleum ether boiling between 40 – 60 °C. Acetone/dry ice cooling baths were used to maintain −78 °C.

Thin-layer chromatography (TLC) was performed using pre-coated plates (Macherey-Nagel Polygram SIL G/UV_{254}). Visualisation was achieved by way of UV light (at 254 nm), and either potassium permanganate or 'Seebach' stains (2.50 g phosphomolybdic acid hydrate, 1.00 g $Ce(SO_4)_2{\cdot}4H_2O$, 3.00 mL conc. H_2SO_4, 90.00 mL water). Flash column chromatography was carried out using chromatography grade silica gel (60 Å pore size, 230 – 400 mesh) or using an automated Biotage® Isolera Spektra Four with gradient elution on pre-packed silica gel Biotage® SNAP Ultra columns, with compounds loaded as saturated solutions in DCM.

Nuclear Magnetic Resonance (NMR) spectra (^{1}H NMR and ^{13}C NMR) were recorded on either Bruker Ultrashield 300 (DPX), 400 (Avance III or Avance III HD with CryoProbe Prodigy BBO) or 500 (DRX, Avance II+ or Avance III HD with CryoProbe Prodigy BBO) spectrometers. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of trimethylsilane. Spectra were calibrated using the residual solvent peaks for $CDCl_3$ (δ_H: 7.26 ppm; δ_C: 77.16 ppm), CD_3OD (δ_H: 3.31 ppm; δ_C: 49.00 ppm) and $(CD_3)_2SO$ (δ_H: 2.50 ppm; δ_C: 39.52 ppm) as appropriate.[2] Coupling constants (*J*) are quoted in Hz and are rounded to the nearest 0.1 Hz. Splitting patterns are abbreviated to: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin.), septet (sept.), multiplet (m), broad (br.) or some combination thereof. Major and minor rotameric peaks are denoted by the subscripts $_{(maj)}$ and $_{(min)}$.

Infrared (IR) spectra were recorded on a Thermo Scientific Nicolet iS5 FT-IR spectrometer using an iD5 diamond ATR accessory, with samples applied as neat films. Absorption maxima (ν_{max}) of interest are quoted in wavenumbers (cm^{-1}). High resolution mass spectra (HRMS) were recorded by staff at the Universities of Manchester and Bristol on a Thermo Finnigan MAT95XP, Waters QTOF or Bruker Daltonics MicrOTOF II.

Enantiomeric ratios were determined by chiral HPLC on an Agilent 1260 Infinity using either a Daicel Chiralcel® OD-H or Daicel Chiralpak® AD-H column (4.6 mm x 250 mm x 5 µm) at 25 °C with hexane/IPA as the eluent, or by chiral SFC on a Waters TharSFC system using a Daicel Chiralpak® IA column (4.6 mm x 250 mm x 5 µm) at 40 °C with IPA as the co-solvent.

General Procedures

Procedure 1: *N-Methylamide formation from amino ester hydrochloride*

To an amino ester hydrochloride (1.0 eq.) was added $MeNH_2$ (33% *w/w* solution in EtOH, 7.0 eq.). The mixture was left to stir at room temperature for 48 h before being concentrated *in vacuo*, dissolved in $CHCl_3$ and washed with K_2CO_3 (3.8 M, aq.). The organic layer was separated and the aqueous layer extracted 3 times with $CHCl_3$. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*.

Procedure 2: *Imine formation from amino acid N-methylamide*

To a solution of *N*-methylamide (1.0 eq.) in anhydrous DCM (1.5 M) was added $MgSO_4$ (1.0 eq.) and pivalaldehyde (1.5 eq.). The mixture was left to stir at room temperature for 16 h before being filtered and concentrated *in vacuo*.

Procedure 3a: *N-Chloroformylimidazolidinone formation from N-methylamide (TFA)*

To a solution of amino acid *N*-methylamide (1.0 eq.) in anhydrous DCM (0.75 M) was added pivalaldehyde (1.5 eq.), followed by TFA (1.5 – 5.0 eq.). The reaction mixture was heated to reflux and allowed to stir overnight before being quenched by slow addition of $NaHCO_3$ (sat. aq.) until pH > 9. The organic layer was separated and the aqueous layer extracted 3 times with DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was dissolved in anhydrous DCM (2.0 M) and added dropwise to a solution of triphosgene (0.45 eq.) and 2,6-lutidine (1.2 eq.) in anhydrous DCM (1.0 M) at −78 °C. After 15 min, the reaction mixture was warmed to room temperature and allowed to stir overnight. The reaction was quenched by addition of HCl (1.0 M, aq.). The organic layer was separated and the aqueous layer extracted 3 times with DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*.

Procedure 3b: *N-Chloroformylimidazolidinone formation from N-methylamide (PTSA)*

To a solution of amino acid *N*-methylamide (1.0 eq.) in anhydrous toluene (0.65 M) was added molecular sieves (3 Å), pivalaldehyde (1.1 eq.) and PTSA monohydrate (0.15 eq.). The reaction mixture was heated to reflux and allowed to stir overnight. The reaction mixture was filtered and quenched by slow addition of $NaHCO_3$ (sat. aq.) until pH > 9. The organic layer was separated and the aqueous layer extracted 3 times with DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was dissolved in anhydrous DCM (2.0 M) and added dropwise to a solution of triphosgene (0.45 eq.) and 2,6-lutidine (1.2 eq.) in anhydrous DCM (1.0 M) at −78 °C. After 15 min, the reaction mixture was warmed to room temperature and allowed to stir overnight. The reaction was quenched by addition of HCl (1.0 M, aq.). The organic layer was separated and the aqueous

layer extracted 3 times with DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*.

Procedure 4: *N-Aryl urea formation from N-methylamide imine*

N-Methylamide imine (1.0 eq.), *N*-alkyl-*N*-arylcarbamoyl chloride[3] (1.2 – 1.5 eq.) and DMAP (0.05 eq.) were dissolved in anhydrous solvent (0.2 – 0.25 M). The reaction mixture was stirred at reflux (18 – 88 h) before being cooled to room temperature and diluted with DCM. The mixture was washed 3 times with HCl (1.0 M, aq.), 3 times with $NaHCO_3$ (sat. aq.) and brine. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*.

Procedure 5: *N-Aryl urea formation from N-chloroformylimidazolidinone*

To a solution of *N*-chloroformylimidazolidinone (1.0 eq.) in anhydrous solvent (0.2 – 1.0 M) was added tertiary amine base (2.0 eq.), *N*-alkylaniline (5.0 eq.) and KI (1.1 eq.). The reaction mixture was heated to reflux and left until TLC analysis showed the starting material had been completely consumed. The reaction mixture was cooled to room temperature and quenched with HCl (1.0 M, aq.), the organic layer was separated and the aqueous layer extracted 3 times with DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*.

Procedure 6: *Rearrangement of N-aryl urea*

To a solution of *N*-aryl urea (1.0 eq.) in anhydrous THF (0.1 M) at 0 °C was added dropwise KHMDS (1.0 M in THF, 1.5 eq.). After 15 min, the reaction mixture was warmed to room temperature and allowed to stir for 4 h. The reaction was quenched by dropwise addition of NH_4Cl (sat. aq.) and stirred for 15 min. The organic layer was separated and the aqueous layer extracted 3 times with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*.

Procedure 7: *'Urearrangement' of N-chloroformylimidazolidinone (tandem urea formation / rearrangement)*

To a solution of *N*-chloroformylimidazolidinone (1.0 eq.) and *N*-alkylaniline (1.1 eq.) in anhydrous THF (0.1 M) at −78 °C was added, dropwise, KHMDS (1.0 M in THF, 1.2 eq.) and left to stir for 2 h. The reaction mixture was allowed to warm to 0 °C where it was stirred for a further 30 min before additional KHMDS (1.0 M in THF, 1.2 eq.) was added dropwise. After 15 min, the reaction mixture was warmed to room temperature and allowed to stir overnight. The reaction was quenched by dropwise addition of NH_4Cl (sat. aq.) and stirred for 15 min. The organic layer was separated and the aqueous layer extracted 3 times with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*.

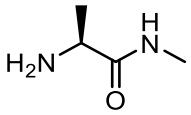
Procedure 8: *Methylation and hydrolysis of rearranged urea to amino acid.*

To a solution of rearranged urea (1.0 eq.) in anhydrous DMF (0.1 M) at 0 °C was added NaH (60% suspension in mineral oil, 1.2 eq.) and left to stir for 30 min before MeI (1.5 eq.) was added dropwise. The reaction mixture was warmed to room temperature and allowed to stir overnight. The reaction was quenched with HCl (1.0 M, aq.) before being extracted 3 times with Et_2O. The combined organic layers were washed twice with brine, before being dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was suspended in HCl (6.0 M, aq.) / EtOH (10:1, 0.2 M) and heated in a microwave reactor at 160 °C for 3 h. The cooled reaction mixture was diluted with water and washed 3 times with DCM before being concentrated *in vacuo*. The resulting crude material was purified by ion-exchange chromatography (Dowex® 50W8-200, 100 – 200 mesh), washing with deionised water before the product was eluted with NH_3 (3.5% *w*/*w*, aq.). The ninhydrin-positive aqueous fractions were combined and concentrated *in vacuo*. The resulting solid was dissolved in MeOH, filtered and concentrated *in vacuo*. Extended drying under high vacuum afforded the amino acid.

Experimental Procedures and Characterisation Data

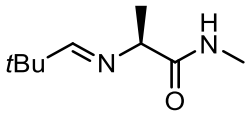
Synthesis of the *N*-Methylamides and Imines

(*S*)-2-Amino-*N*-methylpropanamide (S1)



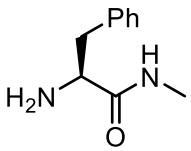
Following general procedure 1, ethanolic $MeNH_2$ (68.00 mL, 547 mmol) was added to L-alanine ethyl ester hydrochloride (12.09 g, 78.7 mmol). The title compound (7.20 g, 70.5 mmol, 90%) was yielded as a pale yellow oil. **S1**: $\mathbf{R_f}$ (4:1 DCM:MeOH): 0.16; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.26 (br. s, 1H, N*H*), 3.48 (q, *J* = 7.0, 1H, C*H*CH_3), 2.80 (d, *J* = 5.0, 3H, NHC*H*$_3$), 1.45 (br. s, 2H, N*H*$_2$), 1.32 (d, *J* = 7.0, 3H, CHC*H*$_3$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 176.4 (*C*=O), 50.9 (*C*HCH$_3$), 25.9 (NH*C*H$_3$), 21.9 (CH*C*H$_3$); **IR**: ν_{max} = 3292, 3099 (N–H), 2971, 2936, 2881 (C–H), 1645 (C=O); **MS** (ESI$^+$, MeOH): *m*/*z* 103 (100%, $[M+H]^+$). Data in agreement with reported values.[4]

(*S*)-2-((2,2-Dimethylpropylidene)amino)-*N*-methylpropanamide (S2)



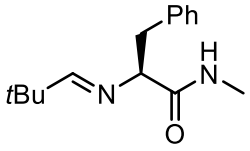
Following general procedure 2, to a solution of *N*-methylamide **S1** (530 mg, 5.19 mmol) in DCM (3.46 mL, 1.5 M) was added $MgSO_4$ (625 mg, 5.19 mmol) and pivalaldehyde (0.85 mL, 7.78 mmol). The title compound (861 mg, 5.06 mmol, 97%) was yielded as a pale yellow oil. **S2**: **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.52 (s, 1H, C*H*C(CH$_3$)$_3$), 6.92 (br. s, 1H, N*H*), 3.68 (q, *J* = 7.0, 1H, C*H*CH$_3$), 2.84 (d, *J* = 4.9, 3H, NHC*H*$_3$), 1.31 (d, *J* = 7.0, 3H, CHC*H*$_3$), 1.07 (s, 9H, C(C*H*$_3$)$_3$); **MS** (ESI$^+$, DCM): *m*/*z* 193 (100%, $[M+Na]^+$). Data in agreement with reported values.[5]

(*S*)-2-Amino-*N*-methyl-3-phenylpropanamide (S3)



Following general procedure 1, ethanolic $MeNH_2$ (37.8 mL, 304 mmol) was added to L-phenylalanine ethyl ester hydrochloride (9.97 g, 43.4 mmol). The title compound (7.60 g, 42.6 mmol, 98%) was yielded as a white solid. **S3**: $\mathbf{R_f}$ (4:1 DCM:MeOH): 0.70; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.33 – 7.29 (m, 2H, Ph*H*), 7.28 – 7.20 (m, 4H, Ph*H* and N*H*), 3.60 (dd, *J* = 9.5, 4.0, 1H, C*H*CH$_A$H$_B$), 3.28 (dd, *J* = 13.7, 4.0, 1H, CHC*H*$_A$H$_B$), 2.81 (d, *J* = 5.0, 3H, NHC*H*$_3$), 2.66 (dd, *J* = 13.7, 9.5, 1H, CHCH$_A$*H*$_B$), 1.34 (br. s, 2H, N*H*$_2$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 175.0 (*C*=O), 138.1 (*C*$_{Ph}$), 129.4 (2×*C*H$_{Ph}$), 128.8 (2×*C*H$_{Ph}$), 126.9 (*C*H$_{Ph}$), 56.6 (NH*C*H$_3$), 41.1 (CH*C*H$_2$), 25.9 (*C*HCH$_2$); **IR**: ν_{max} = 3367, 3304 (N–H), 3072, 3053, 3001, 2925 (C–H), 1657 (C=O); **MS** (ESI$^+$, MeOH): *m*/*z* 179 (100%, $[M+H]^+$). Data in agreement with reported values.[4]

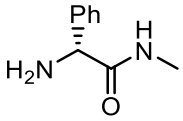
(*S*)-2-((2,2-Dimethylpropylidene)amino)-*N*-methyl-3-phenylpropanamide (S4)



Following general procedure 2, to a solution of *N*-methylamide **S3** (300 mg, 1.68 mmol) in DCM (1.12 mL, 1.5 M) was added $MgSO_4$ (200 mg, 2.49 mmol) and pivalaldehyde (0.27 mL, 2.52 mmol). The title compound (410 mg, 1.66 mmol, 99%) was yielded as a pale yellow oil. **S4**: **^{1}H NMR** (400 MHz, $CDCl_3$):

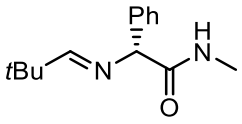
δ_H = 7.26 – 7.20 (m, 2H, Ph*H*), 7.18 – 7.13 (m, 1H, Ph*H*), 7.08 – 7.03 (m, 2H, Ph*H*), 6.90 (br. s, 1H, N*H*), 6.80 (s, 1H, C*H*C$(CH_3)_3$), 3.69 (dd, *J* = 10.6, 3.0, 1H, C*H*CH_AH_B), 3.36 (dd, *J* = 13.4, 3.0, 1H, CHCH_AH_B), 2.86 (d, *J* = 5.0, 3H, NHCH_3), 2.73 (dd, *J* = 13.4, 10.7, 1H, CHCH_AH_B), 0.86 (s, 9H, C(C$H_3)_3$); **MS** (ESI$^+$, DCM): *m*/*z* 269 (100%, $[M+Na]^+$). Data in agreement with reported values.[5]

(*R*)-2-Amino-*N*-methyl-2-phenylacetamide (S5)



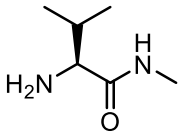
Following general procedure 1, ethanolic $MeNH_2$ (51.90 mL, 417 mmol) was added to D-phenylglycine methyl ester hydrochloride (12.09 g, 60.0 mmol). The title compound (9.30 g, 56.3 mmol, 94%) was yielded as a pale yellow oil. **S5**: $\mathbf{R_f}$ (4:1 DCM:MeOH): 0.68; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.39 – 7.37 (m, 2H, Ph*H*), 7.36 – 7.32 (m, 2H, Ph*H*), 7.30 – 7.26 (m, 1H, Ph*H*), 7.08 (br. s, 1H, N*H*), 4.51 (s, 1H, C*H*Ph), 2.81 (d, *J* = 5.0, 3H, NHCH_3), 1.80 (br. s, 2H, NH_2); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 173.7 (*C*=O), 141.2 (C_{Ph}), 129.0 (2×CH_{Ph}), 128.1 (CH_{Ph}), 127.0 (2×CH_{Ph}), 60.0 (*C*HPh) 26.2 (NH*C*H_3); **IR**: ν_{max} = 3295 (N–H), 3061, 3030, 2940 (C–H), 1650 (C=O); **MS** (ESI$^+$, MeOH): *m*/*z* 165 (100%, $[M+H]^+$). Data in agreement with reported values.[6]

(*R*)-2-((2,2-Dimethylpropylidene)amino)-*N*-methyl-2-phenylacetamide (S6)



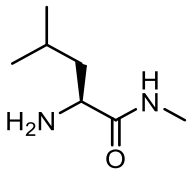
Following general procedure 2, to a solution of *N*-methylamide **S5** (250 mg, 1.52 mmol) in DCM (1.01 mL, 1.5 M) was added $MgSO_4$ (180 mg, 1.50 mmol) and pivalaldehyde (0.25 mL, 2.28 mmol). The title compound (340 mg, 1.46 mmol, 96%) was yielded as a pale yellow oil. **S6**: **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.59 (s, 1H, C*H*C$(CH_3)_3$), 7.37 (d, *J* = 7.7, 2H, Ph*H*), 7.31 (t, *J* = 7.4, 2H, Ph*H*), 7.28 – 7.23 (m, 1H, Ph*H*), 7.00 (br. s, 1H, N*H*), 4.73 (s, 1H, C*H*Ph), 2.85 (d, *J* = 4.9, 3H, NHCH_3), 1.10 (s, 9H, C(C$H_3)_3$); **MS** (ESI$^+$, DCM): *m*/*z* 233 (100%, $[M+H]^+$). Data in agreement with reported values.[5]

(*S*)-2-Amino-*N*,3-dimethylbutanamide (S7)



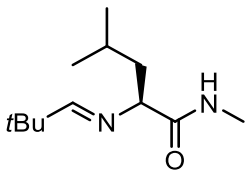
Following general procedure 1, ethanolic $MeNH_2$ (62.40 mL, 501 mmol) was added to L-valine methyl ester hydrochloride (12.11 g, 72.2 mmol). The title compound (8.78 g, 67.4 mmol, 93%) was yielded as a pale yellow oil. **S7**: $\mathbf{R_f}$ (4:1 DCM:MeOH): 0.63; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.26 (br. s, 1H, N*H*), 3.23 (d, *J* = 3.7, 1H, NH_2C*H*CH), 2.82 (d, *J* = 5.0, 3H, NHCH_3), 2.35 – 2.27 (1H, m, C*H*$(CH_3)_2$), 1.23 (br. s, 2H, NH_2), 0.98 (d, *J* = 7.0, 3H, CH(C$H_3)_A(CH_3)_B$), 0.80 (d, *J* = 6.9, 3H, CH$(CH_3)_A$(C$H_3)_B$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 175.1 (*C*=O), 60.3 (NH_2*C*H), 30.9 (*C*H$(CH_3)_2$), 25.8 (NH*C*H_3), 19.9 (CH*C*H_3), 16.1 (CH*C*H_3); **IR**: ν_{max} = 3305, 3089 (N–H), 2959, 2872 (C–H), 1649 (C=O); **MS** (ESI$^+$, MeOH): *m*/*z* 131 (100%, $[M+H]^+$). Data in agreement with reported values.[7]

(*S*)-2-Amino-*N*,4-dimethylpentanamide (S8)



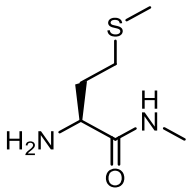
Following general procedure 1, ethanolic $MeNH_2$ (57.60 mL, 462 mmol) was added to L-leucine methyl ester hydrochloride (12.05 g, 66.3 mmol). The title compound (9.15 g, 63.5 mmol, 96%) was yielded as a pale yellow oil. **S8**: **R_f** (4:1 DCM:MeOH): 0.52; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.26 (br. s, 1H, N*H*), 3.37 (dd, *J* = 9.9, 3.3, 1H, $NH_2CHCH_AH_B$), 2.80 (d, *J* = 5.0, 3H, $NHCH_3$), 1.82 – 1.57 (m, 2H, $CHCH_AH_BCH$ and $CH_AH_BCH(CH_3)_2$), 1.36 (br. s, 2H, NH_2), 1.36 – 1.26 (m, 1H, $CHCH_AH_BCH$), 0.94 (d, *J* = 6.2, 3H, $CH(CH_3)_A(CH_3)_B$), 0.92 (3H, d, *J* = 6.1, $CH(CH_3)_A(CH_3)_B$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 176.3 (*C*=O), 53.6 (NH_2CHCH_2), 44.2 (CH_2CH), 25.9 ($NHCH_3$), 25.0 ($CH(CH_3)_2$), 23.6 ($CH(CH_3)_A(CH_3)_B$), 21.4 ($CH(CH_3)_A(CH_3)_B$); **IR**: ν_{max} = 3295, 3090 (N–H), 2955, 2871 (C–H), 1651 (C=O); **MS** (ESI^+, MeOH): *m*/*z* 145 ($[M+H]^+$) (100%).

(*S*)-2-((2,2-Dimethylpropylidene)amino)-*N*,4-dimethylpentanamide (S9)



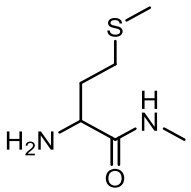
Following general procedure 2, to a solution of *N*-methylamide **S8** (1.00 mg, 6.93 mmol) in DCM (4.62 mL, 1.5 M) was added $MgSO_4$ (850 mg, 7.06 mmol) and pivalaldehyde (1.13 mL, 10.4 mmol). The title compound (1.44 g, 6.79 mmol, 98%) was yielded as a pale yellow oil. **S9**: **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.47 (s, 1H, $CHC(CH_3)_3$), 6.67 (br. s, 1H, N*H*), 3.63 (dd, *J* = 9.9, 3.9, 1H, $CHCH_AH_B$), 2.82 (d, *J* = 5.0, 3H, $NHCH_3$), 1.65 (ddd, *J* = 13.6, 9.6, 3.9, 1H, $CHCH_AH_BCH$), 1.58 (ddd, *J* = 13.8, 9.9, 4.4, 1H, $CHCH_AH_BCH$), 1.47 – 1.37 (m, 1H, $CH_2CH(CH_3)_2$), 1.08 (s, 9H, $C(CH_3)_3$), 0.89 (d, *J* = 6.7, 3H, $CH(CH_3)_A(CH_3)_B$), 0.86 (d, *J* = 6.6, 3H, $CH(CH_3)_A(CH_3)_B$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 174.7 (*C*=O), 173.5 ($CHC(CH_3)_3$), 71.7 ($CHCH_2$), 43.6 ($CHCH_2$), 36.6 ($C(CH_3)_3$), 27.0 ($C(CH_3)_3$), 26.0 ($NHCH_3$), 24.1 ($CH(CH_3)_2$), 23.6 ($CH(CH_3)_A(CH_3)_B$), 21.2 ($CH(CH_3)_A(CH_3)_B$); **HRMS** (ESI^+): *m*/*z* calcd for $C_{12}H_{25}ON_2$ ($[M+H]^+$) 213.1961, found 213.1949.

(*S*)-2-Amino-*N*-methyl-4-(methylthio)butanamide (S10)



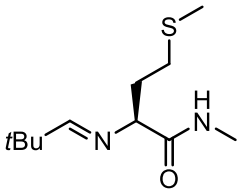
Following general procedure 1, ethanolic $MeNH_2$ (54.00 mL, 434 mmol) was added to L-methionine methyl ester hydrochloride (12.00 g, 62.3 mmol). The title compound (9.40 g, 57.9 mmol, 93%) was yielded as a pale yellow oil. **S10**: **R_f** (4:1 DCM:MeOH): 0.65; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.24 (br. s, 1H, N*H*), 3.49 (dd, *J* = 8.2, 4.5, 1H, $CHCH_AH_B$), 2.82 (d, *J* = 5.0, 3H, $NHCH_3$), 2.60 (t, *J* = 7.3, 2H, $CH_AH_BCH_2SCH_3$), 2.17 (dtd, *J* = 14.2, 7.7, 4.5, 1H, $CHCH_AH_B$), 2.10 (s, 3H, SCH_3), 1.75 (ddt, *J* = 14.1, 8.1, 6.9, 1H, $CHCH_AH_B$), 1.43 (br. s, 2H, NH_2); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 175.2 (*C*=O), 54.4 ($CHCH_2$), 34.2 ($CHCH_2$), 30.8 (CH_2SCH_3), 26.0 (CH_3NH), 15.4 (SCH_3); **IR**: ν_{max} = 3303, 3090 (N–H), 2916 (C–H), 1646 (C=O); **MS** (ESI^+, MeOH): *m*/*z* 163 (100%, $[M+H]^+$). Data in agreement with reported values.[8]

rac-2-Amino-*N*-methyl-4-(methylthio)butanamide (S11)



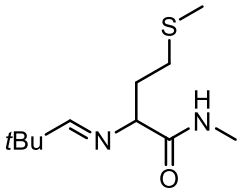
Following general procedure 1, ethanolic $MeNH_2$ (18.10 mL, 145 mmol) was added to DL-methionine methyl ester hydrochloride (4.00 g, 20.8 mmol). The title compound (3.20 g, 19.7 mmol, 95%) was yielded as a pale yellow oil. For full data see compound **S10**.

(*S*)-2-((2,2-Dimethylpropylidene)amino)-*N*-methyl-4-(methylthio)butanamide (S12)



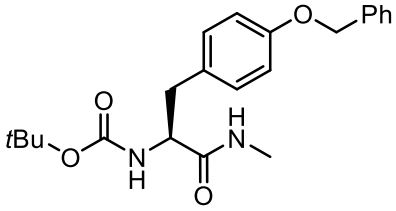
Following general procedure 2, to a solution of *N*-methylamide **S10** (1.10 g, 6.78 mmol) in DCM (1.10 mL, 1.5 M) was added $MgSO_4$ (820 mg, 6.81 mmol) and pivalaldehyde (0.74 mL, 10.2 mmol). The title compound (1.54 g, 6.70 mmol, 99%) was yielded as a pale yellow oil. **S12**: **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.54 (s, 1H, C*H*C$(CH_3)_3$), 6.72 (br. s, 1H, N*H*), 3.73 (dd, *J* = 9.0, 3.9, 1H, C*H*CH_AH_B), 2.84 (d, *J* = 5.0, 3H, NHC*H*$_3$), 2.43 (ddd, *J* = 13.4, 9.1, 4.7, 1H, CH_AH_BC*H*$_{A'}$H$_{B'}$SCH_3), 2.32 (dt, *J* = 13.1, 8.1, 1H, CH_AH_BC$H_{A'}$*H*$_{B'}$SCH_3), 2.19 – 2.12 (tdd, *J* = 9.3, 7.8, 4.5, 1H, CHC*H*$_A$H$_B$CH_2), 2.07 (s, 3H, SC*H*$_3$), 1.91 (dtd, *J* = 13.7, 8.9, 4.7, 1H, CHCH_A*H*$_B$CH_2), 1.09 (s, 9H, C(C*H*$_3$)$_3$); **MS** (ESI$^+$, DCM): *m*/*z* 253 (100%, $[M+Na]^+$). Data in agreement with reported values.[5]

rac-2-((2,2-Dimethylpropylidene)amino)-*N*-methyl-4-(methylthio)butanamide (S13)



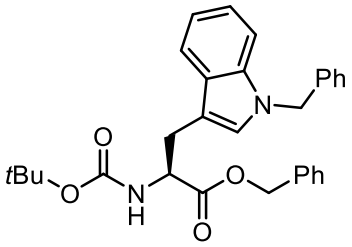
Following general procedure 2, to a solution of *N*-methylamide **S11** (1.60 g, 9.86 mmol) in DCM (6.60 mL, 1.5 M) was added $MgSO_4$ (1.20 g, 9.97 mmol) and pivalaldehyde (1.60 mL, 14.7 mmol). The title compound (2.25 g, 9.75 mmol, 99%) was yielded as a pale yellow oil. For full data see compound **S12**.

tert-Butyl (*S*)-(3-(4-(benzyloxy)phenyl)-1-(methylamino)-1-oxopropan-2-yl)carbamate (S14)



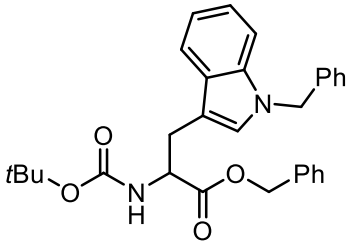
Following a similar method to general procedure 1, ethanolic $MeNH_2$ (1.07 mL, 8.62 mmol, 2.0 eq.) was added to a suspension of L-Boc-Tyr(OBn)-OSu (2.02 g, 4.31 mmol, 1.0 eq.) in EtOH (43.10 mL, 0.1 M) and left to stir for 2 h. The title compound (1.63 g, 4.24 mmol, 98%) was yielded as a white solid without further purification. **S14**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.44 – 7.41 (m, 2H, Ph*H*), 7.40 – 7.36 (m, 2H, Ph*H*), 7.35 – 7.30 (m, 1H, Ph*H*), 7.11 (d, *J* = 8.4, 2H, Ar*H*), 6.93 – 6.89 (m, 2H, Ar*H*), 5.63 (br. s, 1H, N*H*), 5.04 (s, 2H, OCH_2Ph), 5.02 (br. s, 1H, N*H*), 4.22 (br. dd, *J* = 13.5, 7.4, 1H, C*H*CH_AH_B), 3.03 (dd, *J* = 13.4, 5.6, 1H, CHCH_AH$_B$), 2.95 (dd, *J* = 13.6, 7.5, 1H, CHCH_A*H*$_B$), 2.72 (d, *J* = 4.5, 3H, NHCH_3), 1.41 (s, 9H, C(CH_3)$_3$); **MS** (ESI$^+$, DCM): *m*/*z* 385 (100%, $[M+H]^+$). Data in agreement with reported values.[9]

Benzyl 1-benzyl-N_α-(*tert*-butoxycarbonyl)-L-tryptophanate (S15)



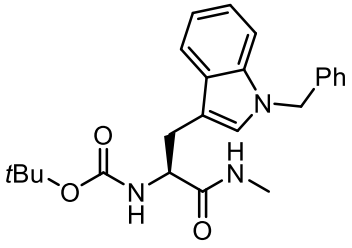
Following the procedure of Wolfe *et al*.,[10] to a cooled (0 °C) solution of N_α-Boc-L-tryptophan (1.00 g, 3.29 mmol, 1.0 eq.) in DMF (3.30 mL, 1.0 M) was added NaH (389 mg, 9.78 mmol, 60% suspension in mineral oil, 3.0 eq.). The solution was stirred for 30 min at 0 °C before BnBr (1.4 mL, 11.83 mmol, 3.6 eq.) was added dropwise. The reaction mixture was warmed to room temperature and allowed to stir for 18 h. The reaction was quenched with NH_4Cl (sat. aq.) and diluted with EtOAc. The organic layer was separated and the aqueous layer extracted 3 times with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 9:1 Pet.Ether:EtOAc) gave the title compound (1.20 g, 2.48 mmol, 75%) as an off-white solid. **S15**: **R_f** (9:1 Pet.Ether:EtOAc): 0.23; **^{1}H NMR** (400 MHz, $CDCl_3$) (major rotamer): δ_H = 7.55 (d, *J* = 7.8, 1H, Ar*H*), 7.33 – 7.19 (m, 9H, Ar*H*), 7.16 (t, *J* = 7.4, 1H, Ar*H*), 7.09 (t, *J* = 7.3, 1H, Ar*H*), 7.02 (d, *J* = 6.3, 2H, Ar*H*), 6.64 (s, 1H, C=C*H*), 5.18 (s, 2H, NCH_2Ph), 5.09 (d, *J* = 12.2, 1H, OCH_AH$_B$Ph), 5.01 (d, *J* = 12.2, 1H, OCH$_A$$H_B$Ph), 4.69 (dt, *J* = 8.3, 5.2, 1H, NHC*H*CH$_2$), 3.35 – 3.23 (m, 2H, CHCH_2), 1.42 (s, 9H, C(CH_3)$_3$); **HRMS** (ESI$^+$): *m/z* calcd for $C_{30}H_{32}O_4N_2Na$ ([M+Na]$^+$) 507.2260, found 507.2280. Data in agreement with reported values.[10]

rac-Benzyl 1-benzyl-N_α-(*tert*-butoxycarbonyl)-tryptophanate (S16)



To a cooled (0 °C) solution of N_α-Boc-DL-tryptophan (2.00 g, 6.57 mmol, 1.0 eq.) in DMF (6.60 mL, 1.0 M) was added NaH (600 mg, 15.0 mmol, 60% suspension in mineral oil, 2.3 eq.). The solution was stirred for 30 min at 0 °C before BnBr (2.80 mL, 23.6 mmol, 3.6 eq.) was added dropwise. The reaction mixture was warmed to room temperature and allowed to stir for 18 h. The reaction was quenched with NH_4Cl (sat. aq.) and diluted with DCM. The organic layer was separated and the aqueous layer extracted 3 times with DCM. The combined organic layers were washed with LiCl (5%, aq.), brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 4:1→2:3 Pet.Ether:EtOAc) gave the title compound (2.84 g, 5.87 mmol, 89%) as an off-white solid. For full data see compound **S15**.

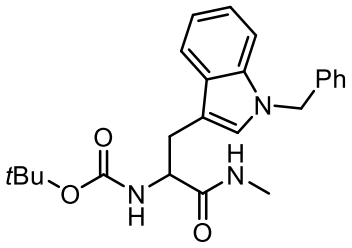
tert-Butyl (*S*)-(*3*-(1-benzyl-1*H*-indol-3-yl)-1-(methylamino)-1-oxopropan-2-yl)carbamate (S17)



Following a similar method to general procedure 1, ethanolic $MeNH_2$ (0.94 mL, 7.52 mmol, 7.0 eq.) was added to ester **S15** (521 mg, 1.08 mmol, 1.0 eq.) and left to stir for 18 h. The title compound (408 mg, 1.00 mmol, 93%) was yielded as a white solid without further purification. **S17**: **^{1}H NMR** (400 MHz, $CDCl_3$):

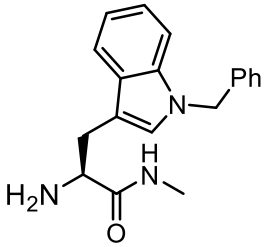
δ_H = 7.66 (d, *J* = 7.8, 1H, Ar*H*), 7.32 – 7.24 (m, 4H, Ar*H*), 7.21 – 7.16 (m, 1H, Ar*H*), 7.16 – 7.12 (m, 1H, Ar*H*), 7.11 – 7.06 (m, 2H, Ar*H*), 6.98 (s, 1H, C=C*H*), 5.68 (br. s, 1H, N*H*), 5.30 – 5.20 (m, 2H, NCH_2Ph), 5.17 (br. s, 1H, N*H*), 4.39 (dd, *J* = 14.3, 7.3, 1H, NHC*H*CH_2), 3.31 (dd, *J* = 14.8, 5.3, 1H, CHCH_AH_B), 3.13 (dd, *J* = 14.5, 7.7, 1H, CHCH_AH_B), 2.61 (d, *J* = 4.9, 3H, NHCH_3), 1.42 (s, 9H, C(CH_3)$_3$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 172.3 (*C*=O), 155.6 (*C*=O), 137.6 (C_{Ar}), 136.7 (C_{Ar}), 128.9 (2×CH_{Ar}), 128.2 (C_{Ar}), 127.8 (CH_{Ar}), 127.3 (C=*C*H), 126.9 (2×CH_{Ar}), 122.2 (CH_{Ar}), 119.6 (CH_{Ar}), 119.3 (CH_{Ar}), 110.2 (*C*=CH), 109.9 (CH_{Ar}), 80.1 (*C*$(CH_3)_3$), 55.4 (*C*HCH_2), 50.0 (NCH_2Ph), 28.7 (CHCH_2), 28.4 (C(*C*H_3)$_3$), 26.2 (NHCH_3); **HRMS** (ESI$^+$): *m/z* calcd for $C_{24}H_{29}O_3N_3Na$ ([M+Na]$^+$) 430.2107, found 430.2104.

rac-tert-Butyl (*3*-(1-benzyl-1*H*-indol-3-yl)-1-(methylamino)-1-oxopropan-2-yl)carbamate (S18)



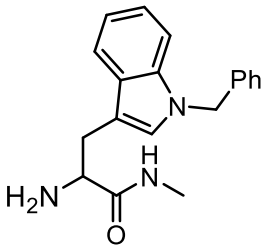
Following a similar method to general procedure 1, ethanolic $MeNH_2$ (5.11 mL, 41.08 mmol, 7.0 eq.) was added to ester **S16** (2.84 g, 5.87 mmol, 1.0 eq.) and left to stir for 18 h. The title compound (2.29 g, 5.62 mmol, 96%) was yielded as a white solid without further purification. For full data see compound **S17**.

(*S*)-2-Amino-3-(1-benzyl-1*H*-indol-3-yl)-*N*-methylpropanamide (S19)



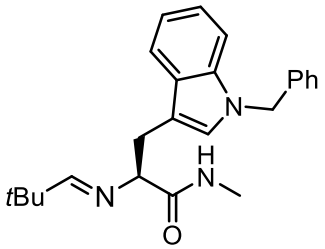
To a solution of *N*-methylamide **S17** (79 mg, 0.194 mmol, 1.0 eq.) in DCM (0.80 mL, 0.24 M) was added TFA (75 µL, 0.969 mmol, 5.0 eq.) dropwise and the reaction mixture was left to stir at room temperature for 18 h. The reaction mixture was concentrated *in vacuo*, redissolved in DCM and washed with $NaHCO_3$ (sat. aq.). The organic layer was separated and the aqueous layer extracted 3 times with DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound (50 mg, 0.163 mmol, 84%) as a yellow solid without further purification. **S19**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.69 (d, *J* = 7.8, 1H, Ar*H*), 7.33 – 7.23 (m, 5H, Ar*H* and N*H*), 7.22 – 7.17 (m, 1H, Ar*H*), 7.16 – 7.08 (m, 3H, Ar*H*), 7.00 (s, 1H, C=C*H*), 5.28 (s, 2H, NCH_2Ph), 3.75 – 3.67 (m, 1H, NH_2C*H*CH_2), 3.39 (dd, *J* = 14.4, 4.0, 1H, CHCH_AH_B), 2.92 (dd, *J* = 14.4, 8.9, 1H, CHCH_AH_B), 2.79 (d, *J* = 5.0, 3H, NHCH_3), 1.46 (br. s, 2H, NH_2); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 175.4 (*C*=O), 137.5 (C_{Ar}), 136.8 (C_{Ar}), 128.9 (2×CH_{Ar}), 128.3 (C_{Ar}), 127.8 (CH_{Ar}), 127.2 (C=*C*H), 126.9 (2×CH_{Ar}), 122.1 (CH_{Ar}), 119.5 (CH_{Ar}), 119.3 (CH_{Ar}), 111.1 (*C*=CH), 109.9 (CH_{Ar}), 55.8 (*C*HCH_2), 50.0 (NCH_2Ph), 30.8 (CHCH_2), 25.9 (NHCH_3); **HRMS** (ESI$^+$): *m/z* calcd for $C_{19}H_{21}ON_3Na$ ([M+Na]$^+$) 330.1576, found 330.1579. Data in agreement with reported values.[4]

rac-2-Amino-3-(1-benzyl-1*H*-indol-3-yl)-*N*-methylpropanamide (S20)



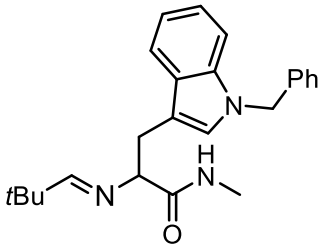
To a solution of *N*-methylamide **S18** (1.52 g, 3.73 mmol, 1.0 eq.) in MeOH (14.00 mL, 0.26 M) was added acetyl chloride (1.40 mL, 19.7 mmol, 5.3 eq.) dropwise and the reaction mixture was left to stir at room temperature for 18 h. The reaction mixture was concentrated *in vacuo*, redissolved in DCM and washed with $NaHCO_3$ (sat. aq.). The organic layer was separated and the aqueous layer extracted 3 times with DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound (1.11 g, 3.61 mmol, 97%) as a pale yellow solid without further purification. For full data see compound **S19**.

(*S*)-3-(1-Benzyl-1*H*-indol-3-yl)-2-((2,2-dimethylpropylidene)amino)-*N*-methylpropanamide (S21)



Following general procedure 2, to a solution of *N*-methylamide **S19** (1.00 g, 3.25 mmol) in DCM (2.20 mL, 1.5 M) was added $MgSO_4$ (400 mg, 3.32 mmol) and pivalaldehyde (0.53 mL, 4.88 mmol). The title compound (12.08 g, 3.22 mmol, 99%) was yielded as a colourless oil. **S21: ^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.64 (ddd, *J* = 7.7, 1.3, 0.8, 1H, Ar*H*), 7.30 – 7.19 (m, 4H, Ar*H*), 7.14 (ddd, *J* = 8.2, 7.0, 1.4, 1H, Ar*H*), 7.12 – 7.03 (m, 3H, Ar*H*), 6.92 (br. q, *J* = 5.0, 1H, N*H*CH_3), 6.82 (s, 1H, C=C*H*), 6.81 (s, 1H, C*H*$C(CH_3)_3$), 5.28 – 5.14 (m, 2H, NCH_2Ph), 3.77 (dd, *J* = 10.1, 3.1, 1H, C*H*CH_AH_B), 3.46 (ddd, *J* = 14.3, 3.1, 0.9, 1H, CHCH_AH_B), 2.92 (dd, *J* = 14.3, 10.1, 1H, $CHCH_AH_B$), 2.84 (d, *J* = 5.0, 3H, NHCH_3), 0.74 (s, 9H, $C(CH_3)_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 173.9 (*C*=O), 173.6 ($CHC(CH_3)_3$), 137.6 (C_{Ar}), 136.6 (C_{Ar}), 128.8 (2×CH_{Ar}), 128.5 (C_{Ar}), 127.7 (CH_{Ar}), 127.2 (C=*C*H), 126.9 (2×CH_{Ar}), 121.8 (CH_{Ar}), 119.8 (CH_{Ar}), 119.1 (CH_{Ar}), 111.2 (*C*=CH), 109.6 (CH_{Ar}), 73.7 ($CHCH_2$), 49.9 (NCH_2Ph), 36.2 ($C(CH_3)_3$), 30.6 ($CHCH_2$), 26.5 ($C(CH_3)_3$), 25.9 (NHCH_3); **IR**: ν_{max} = 3397 (N–H), 3089, 3057, 3030, 2957, 2927, 2865 (C–H), 1667 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{24}H_{30}ON_3$ ($[M+H]^+$) 376.2383, found 376.2386.

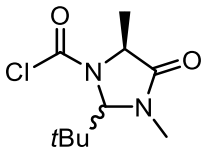
rac-3-(1-Benzyl-1*H*-indol-3-yl)-2-((2,2-dimethylpropylidene)amino)-*N*-methylpropanamide (S22)



Following general procedure 2, to a solution of *N*-methylamide **S20** (460 mg, 2.12 mmol) in DCM (2.00 mL, 1.0 M) was added $MgSO_4$ (255 mg, 2.12 mmol) and pivalaldehyde (0.35 mL, 3.18 mmol). The title compound (786 mg, 2.09 mmol, 99%) was yielded as a colourless oil. For full data see compound **S21**.

Synthesis of *N*-Chloroformylimidazolidinones

(5*S*)-2-(*tert*-Butyl)-3,5-dimethyl-4-oxoimidazolidine-1-carbonyl chloride (S23)

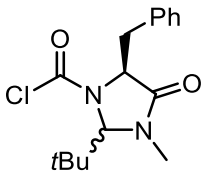


Following general procedure 3a, *N*-methylamide **1** (100 mg, 0.979 mmol), pivalaldehyde (0.12 mL, 1.08 mmol) and TFA (0.15 mL, 1.96 mmol, 2.0 eq.) were reacted to give a crude diastereomeric imidazolidinone (80:20 *trans*:*cis*) which was phosgenated with triphosgene (115 mg, 0.388 mmol) in the presence of 2,6-lutidine (0.12 mL, 1.03 mmol). Purification by flash column chromatography (SiO_2, 99:1 DCM:Acetone) gave isolated diastereomers:

***trans*-S23** (158 mg, 0.679 mmol, 69%) as a white solid: **^{1}H NMR** (400 MHz, $CDCl_3$) (0.55:0.45 rotamers): δ_H = 5.16 (br. s, 0.45H, C*H*C$(CH_3)_{3(min)}$), 5.11 (br. s, 0.55H, C*H*C$(CH_3)_{3(maj)}$), 4.12 (br. s, 1H, C*H*CH_3), 3.03 (br. s, 3H, NC*H*$_3$), 1.73 (br. s, 1.35H, CHC*H*$_{3(min)}$), 1.59 (br. s, 1.65H, CHC*H*$_{3(maj)}$), 1.04 (br. s, 4.95H, C(C*H*$_3)_{3(maj)}$), 1.04 (br. s, 4.05H, C(C*H*$_3)_{3(min)}$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 171.2 (*C*=O$_{(maj)}$), 171.0 (*C*=O$_{(min)}$), 147.6 (*C*=O$_{(min)}$), 145.3 (*C*=O$_{(maj)}$), 83.8 (*C*HC$(CH_3)_{3(maj)}$), 82.7 (*C*HC$(CH_3)_{3(min)}$), 58.5 (*C*HCH$_{3(maj)}$), 57.4 (*C*HCH$_{3(min)}$), 41.4 (*C*$(CH_3)_{3(min)}$), 41.2 (*C*$(CH_3)_{3(maj)}$), 32.3 (N*C*H$_3$), 26.8 (C(*C*H$_3)_{3(maj)}$), 26.4 (C(*C*H$_3)_{3(min)}$), 19.8 (CH*C*H$_{3(min)}$), 15.9 (CH*C*H$_{3(maj)}$); **IR**: ν_{max} = 2969, 2876 (C–H), 1746 (C=O), 1710 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{10}H_{18}O_2N_2Cl$ ([M+H]$^+$) 233.1051, found 233.1049.

***cis*-S23** (40 mg, 0.170 mmol, 18%) as a pale yellow oil: **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 5.07 (s, 1H, C*H*C$(CH_3)_3$), 4.35 (q, *J* = 7.0, 1H, C*H*CH_3), 2.98 (s, 3H, NC*H*$_3$), 1.58 (d, *J* = 7.0, 3H, CHC*H*$_3$), 1.01 (s, 9H, C(C*H*$_3)_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 170.3 (*C*=O), 150.3 (*C*=O), 83.8 (*C*HC$(CH_3)_3$), 58.6 (*C*HCH_3), 38.1 (*C*$(CH_3)_3$), 31.7 (N*C*H$_3$), 26.6 (C(*C*H$_3)_3$), 17.6 (CH*C*H$_3$); **IR**: ν_{max} = 2976, 2877 (C–H), 1746 (C=O), 1708 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{10}H_{18}O_2N_2Cl$ ([M+H]$^+$) 233.1051, found 233.1049.

(2*R*,5*S*)-5-Benzyl-2-(*tert*-butyl)-3-methyl-4-oxoimidazolidine-1-carbonyl chloride (S24)



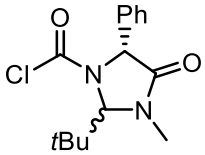
Following a similar method to general procedure 3b, *N*-methylamide **S3** (2.00 g, 11.22 mmol), pivalaldehyde (1.34 mL, 12.34 mmol) and PTSA monohydrate (320 mg, 1.68 mmol) were reacted to give a crude diastereomeric imidazolidinone (60:40 *trans*:*cis*) which was phosgenated with triphosgene (1350 mg, 4.55 mmol) in the presence of pyridine (0.98 mL, 12.13 mmol, 1.2 eq.). Purification by flash column chromatography (SiO_2, 99:1 DCM:Acetone) gave isolated diastereomers:

***trans*-S24** (1048 mg, 3.39 mmol, 30%) as a white solid: **^{1}H NMR** (400 MHz, $CDCl_3$) (0.55:0.45 rotamers): δ_H = 7.22 (br. s, 3H, Ph*H*), 7.17 – 7.15 (m, 2H, Ph*H*), 4.72 (s, 0.55H, C*H*C$(CH_3)_{3(maj)}$), 4.59 (s, 0.45H, C*H*C$(CH_3)_{3(min)}$), 4.45 (br. s, 0.55H, C*H*C$H_AH_{B(maj)}$), 4.42 (br. s, 0.45H, C*H*C$H_AH_{B(min)}$), 3.87 (dd, *J* = 14.1, 4.3, 0.45H, CHC*H*$_A$H$_{B(min)}$), 3.72 (dd, *J* = 14.1, 4.5, 0.55H, CHC*H*$_A$H$_{B(maj)}$), 3.34 (d, *J* = 14.1, 0.45H, CHCH$_A$*H*$_{B(min)}$), 3.26 (d, *J* = 14.2, 0.55H,

$CHCH_AH_{B(maj)}$), 2.87 (s, 1.65H, $NCH_{3(maj)}$), 2.73 (s, 1.35H, $NCH_{3(min)}$), 1.00 (s, 4.95H, $C(CH_3)_{3(maj)}$), 0.92 (s, 4.05H, $C(CH_3)_{3(min)}$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 169.9 (C=$O_{(maj)}$), 169.3 (C=$O_{(min)}$), 147.3 (C=$O_{(min)}$), 146.2 (C=$O_{(maj)}$), 134.4 ($C_{Ph(maj)}$), 134.1 ($C_{Ph(min)}$), 130.2 (2×$CH_{Ph(maj)}$), 130.1 (2×$CH_{Ph(min)}$), 128.5 (2×$CH_{Ph(min)}$), 128.3 (2×$CH_{Ph(maj)}$), 127.6 ($CH_{Ph(min)}$), 127.3 ($CH_{Ph(maj)}$), 83.5 ($CHC(CH_3)_{3(maj)}$), 82.9 ($CHC(CH_3)_{3(min)}$), 63.6 ($CHCH_{2(maj)}$), 62.8 ($CHCH_{2(min)}$), 41.8 ($C(CH_3)_{3(min)}$), 41.7 ($C(CH_3)_{3(maj)}$), 36.7 ($CHCH_{2(min)}$), 32.9 ($CHCH_{2(maj)}$), 32.1 (NCH_3), 26.8 ($C(CH_3)_{3(maj)}$), 26.5 ($C(CH_3)_{3(min)}$); **IR**: ν_{max} = 2968, 2936, 2874 (C–H), 1739 (C=O), 1708 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{16}H_{21}O_2N_2ClNa$ ([M+Na]$^+$) 331.1189, found 331.1197.

***cis*-S24** (687 mg, 2.23 mmol, 20%) as a pale yellow oil: **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.38 (d, *J* = 7.2, 2H, Ph*H*), 7.32 (t, *J* = 7.3, 2H, Ph*H*), 7.28 – 7.24 (m, 1H, Ph*H*), 5.11 (s, 1H, $CHC(CH_3)_3$), 4.52 (dd, *J* = 8.2, 4.7, 1H, $CHCH_AH_B$), 3.24 (dd, *J* = 22.9, 13.9, 1H, $CHCH_AH_B$ and dd, *J* = 23.9, 13.9, 1H, $CHCH_AH_B$), 3.02 (s, 3H, NCH_3), 1.08 (s, 9H, $C(CH_3)_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 169.5 (*C*=O), 150.9 (*C*=O), 136.8 (C_{Ph}), 129.7 (2×CH_{Ph}), 128.7 (2×CH_{Ph}), 127.2 (CH_{Ph}), 83.9 ($CHC(CH_3)_3$), 63.7 ($CHCH_2$), 39.8, ($CHCH_2$), 38.1 ($C(CH_3)_3$), 31.7 (NCH_3), 26.9 ($C(CH_3)_3$); **IR**: ν_{max} = 3087, 3062, 3032, 2968 (C–H), 1740 (C=O), 1711 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{16}H_{21}O_2N_2ClNa$ ([M+Na]$^+$) 331.1189, found 331.1187.

(5*R*)-2-(*tert*-Butyl)-3-methyl-4-oxo-5-phenylimidazolidine-1-carbonyl chloride (S25)

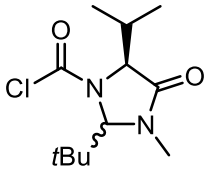


Following general procedure 3b, *N*-methylamide **S5** (2.00 g, 12.18 mmol) and pivalaldehyde (1.46 mL, 13.40 mmol) and PTSA monohydrate (347 mg, 1.83 mmol) were reacted to give a crude diastereomeric imidazolidinone (55:45 *trans*:*cis*) which was phosgenated with triphosgene (1.51 g, 5.10 mmol) in the presence of 2,6-lutidine (1.58 mL, 13.61 mmol). Purification by flash column chromatography (SiO_2, 4:1 Pentane:EtOAc) gave isolated diastereomers:

***trans*-S25** (1.58 g, 5.37 mmol, 44%) as a white solid: **^{1}H NMR** (400 MHz, $CDCl_3$) (0.82:0.18 rotamers): δ_H = 7.40 – 7.32 (m, 3H, Ph*H*), 7.20 (d, *J* = 6.9, 2H, Ph*H*), 5.45 (s, 0.82H, $CHC(CH_3)_{3(maj)}$), 5.38 (s, 0.18H, $CHC(CH_3)_{3(min)}$), 5.07 (s, 0.18H, $CHPh_{(min)}$), 5.03 (s, 0.82H, $CHPh_{(maj)}$), 3.14 (s, 0.54H, $NCH_{3(min)}$), 3.08 (s, 2.46H, $NCH_{3(maj)}$), 1.15 (s, 1.62H, $C(CH_3)_{3(min)}$), 1.09 (s, 7.38H, $C(CH_3)_{3(maj)}$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 169.8 (C=$O_{(min)}$), 169.2 (C=$O_{(maj)}$), 148.8 (C=$O_{(maj)}$), 145.0 (C=$O_{(min)}$), 137.8 ($C_{Ph(maj)}$), 134.9 ($C_{Ph(min)}$), 129.6 – 128.8 (3×CH_{Ph}), 128.1 – 125.7 (2×CH_{Ph}), 83.8 ($CHC(CH_3)_{3(min)}$), 82.8 ($CHC(CH_3)_{3(maj)}$), 66.5 ($CHPh_{(min)}$), 66.1 ($CHPh_{(maj)}$), 41.6 ($C(CH_3)_3$), 32.5 (NCH_3), 26.8 ($C(CH_3)_{3(min)}$), 26.4 ($C(CH_3)_{3(maj)}$); **IR**: ν_{max} = 3066, 3032, 2966, 2924 (C–H), 1713 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{15}H_{19}O_2N_2ClNa$ ([M+Na]$^+$) 317.1033, found 317.1031.

***cis*-S25** (1.50 g, 5.10 mmol, 42%) as a colourless oil: **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.69 (d, *J* = 7.5, 2H, Ph*H*), 7.38 (t, *J* = 7.5, 2H, Ph*H*), 7.30 (t, *J* = 7.2, 1H, Ph*H*), 5.56 (s, 1H, C*H*C$(CH_3)_3$), 5.24 (s, 1H, C*H*Ph), 3.02 (s, 3H, NCH_3), 0.90 (s, 9H, C(C$H_3)_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 167.7 (*C*=O), 151.7 (*C*=O), 133.8 (C_{Ph}), 128.4 (2×CH_{Ph}), 128.0 (CH_{Ph}), 125.8 (2×CH_{Ph}), 84.1 (*C*HC$(CH_3)_3$), 63.8 (*C*HPh), 37.8 (*C*$(CH_3)_3$), 31.6 (NCH_3), 26.4 (C(C$H_3)_3$); **IR**: ν_{max} = 3064, 3034, 2970 (C–H), 1711 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{15}H_{19}O_2N_2ClNa$ ([M+Na]$^+$) 317.1033, found 317.1034.

(5*S*)-2-(*tert*-Butyl)-5-isopropyl-3-methyl-4-oxoimidazolidine-1-carbonyl chloride (S26)

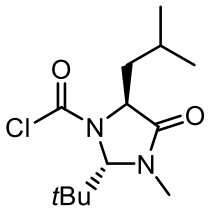


Following general procedure 3b, *N*-methylamide **S7** (135 mg, 1.04 mmol) and pivalaldehyde (0.12 mL, 1.14 mmol) and PTSA monohydrate (30 mg, 0.156 mmol) were reacted to give a crude diastereomeric imidazolidinone (60:40 *trans*:*cis*) which was phosgenated with triphosgene (138 mg, 0.465 mmol) in the presence of 2,6-lutidine (0.14 mL, 1.24 mmol). Purification by flash column chromatography (SiO_2, 3:1 Pet.Ether:EtOAc) gave isolated diastereomers:

***trans*-S26** (143 mg, 0.548 mmol, 53%) as a white solid: **^{1}H NMR** (500 MHz, $CDCl_3$) (0.65:0.35 rotamers): δ_H = 5.14 (s, 1H, C*H*C$(CH_3)_3$), 4.08 (br. s, 0.65H, C*H*CH$(CH_3)_{2(maj)}$), 4.02 (br. s, 0.35H, C*H*CH$(CH_3)_{2(min)}$), 3.06 – 2.90 (m, 4H, NCH_3 and CHC*H*$(CH_3)_2$), 1.23 (d, *J* = 7.0, 3H, CH(C$H_3)_A$$(CH_3)_B$), 1.05 (s, 5.85H, C(C$H_3)_{3(maj)}$), 0.99 (s, 3.15H, C(C$H_3)_{3(min)}$), 0.74 (d, *J* = 6.9, 3H, CH$(CH_3)_A$(C$H_3)_B$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 169.5 (*C*=$O_{(maj)}$), 168.8 (*C*=$O_{(min)}$), 147.7 (*C*=$O_{(min)}$), 145.1 (*C*=$O_{(maj)}$), 83.5 (*C*HC$(CH_3)_{3(maj)}$), 82.8 (*C*HC$(CH_3)_{3(min)}$), 66.5 (*C*HCH$(CH_3)_{2(maj)}$), 65.7 (*C*HCH$(CH_3)_{2(min)}$), 42.1 (*C*$(CH_3)_{3(min)}$), 41.7 (*C*$(CH_3)_{3(maj)}$), 31.8 (NCH_3), 31.4 (*C*H$(CH_3)_{2(min)}$), 26.8 (C(C$H_3)_{3(maj)}$), 26.6 (C(C$H_3)_{3(min)}$), 25.3 (*C*H$(CH_3)_{2(maj)}$), 18.4 (CH(C$H_3)_A$$(CH_3)_{B(min)}$), 18.0 (CH(C$H_3)_A$$(CH_3)_{B(maj)}$), 14.9 (CH$(CH_3)_A$(C$H_3)_B$); **IR**: ν_{max} = 2964, 2936, 2878 (C–H), 1743 (C=O), 1706 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{12}H_{22}O_2N_2Cl$ ([M+H]$^+$) 261.1364, found 261.1359.

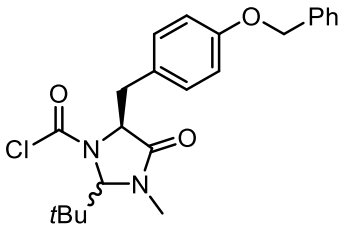
***cis*-S26** (92 mg, 0.353 mmol, 34%) as a white solid: **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 5.07 (s, 1H, C*H*C$(CH_3)_3$), 4.05 (d, *J* = 10.8, 1H, C*H*CH$(CH_3)_2$), 2.97 (s, 3H, NCH_3), 2.05 – 1.93 (m, 1H, CHC*H*$(CH_3)_2$), 1.28 (d, *J* = 6.5, 3H, CH(C$H_3)_A$$(CH_3)_B$), 1.14 (d, *J* = 6.9, 3H, CH$(CH_3)_A$(C$H_3)_B$), 1.04 (s, 9H, C(C$H_3)_3$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 170.2 (*C*=O), 151.9 (*C*=O), 84.6 (*C*HC$(CH_3)_3$), 67.3 (*C*HCH$(CH_3)_2$), 37.5 (*C*$(CH_3)_3$), 32.1 (*C*H$(CH_3)_2$), 31.4 (NCH_3), 26.9 (C(C$H_3)_3$), 20.3 (CH(C$H_3)_A$$(CH_3)_B$), 20.1 (CH$(CH_3)_A$(C$H_3)_B$); **IR**: ν_{max} = 2968, 2936, 2876 (C–H), 1734 (C=O), 1702 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{12}H_{22}O_2N_2Cl$ ([M+H]$^+$) 261.1364, found 261.1361.

(2*S*,5*S*)-2-(*tert*-butyl)-5-isobutyl-3-methyl-4-oxoimidazolidine-1-carbonyl chloride (S27)



Following general procedure 3b, *N*-methylamide **S7** (2.00 g, 17.51 mmol) and pivalaldehyde (2.10 mL, 19.33 mmol) and PTSA monohydrate (500 mg, 2.63 mmol) were reacted to give a crude imidazolidinone which was phosgenated with triphosgene (2.34 g, 7.88 mmol) in the presence of 2,6-lutidine (2.45 mL, 21.04 mmol). Purification by flash column chromatography (SiO_2, 2:1 Pet.Ether:EtOAc) gave the title compound (2.45 g, 8.92 mmol, 51%) as a white solid. **S27**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 5.15 (s, 1H, C*H*C$(CH_3)_3$), 4.17 – 4.10 (m, 1H, NC*H*CH_AH_B), 3.04 (s, 3H, NCH_3), 2.22 (br. s, 1H, CHCH_AH$_B$CH), 1.96 (br. s, 1H, CHCH$_A$$H_B$CH), 1.84 – 1.70 (m, 1H, CH_2C*H*$(CH_3)_2$), 1.04 (s, 9H, C(C$H_3)_3$), 0.93 (d, *J* = 6.7, 3H, CH(C$H_3)_A$$(CH_3)_B$), 0.84 (d, *J* = 6.6, 3H, CH$(CH_3)_A$(C$H_3)_B$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 170.9 (*C*=O), 147.7 (*C*=O$_{(min)}$), 145.3 (*C*=O$_{(maj)}$), 83.5 (*C*HC$(CH_3)_{3(maj)}$), 83.0 (*C*HC$(CH_3)_{3(min)}$), 61.2 (N*C*HC$H_{2(maj)}$), 60.5 (N*C*HC$H_{2(min)}$), 41.8 (*C*$(CH_3)_3$), 39.9 (NCH*C*$H_{2(min)}$), 36.1 (NCH*C*$H_{2(maj)}$), 32.4 (N*C*H_3), 26.8 (C(*C*$H_3)_3$), 24.3 (*C*H$(CH_3)_2$), 23.6 (CH(*C*$H_3)_A$$(CH_3)_B$), 21.9 (CH$(CH_3)_A$(*C*$H_3)_B$); **HRMS** (ESI$^+$): *m/z* calcd for $C_{13}H_{23}O_2N_2ClNa$ ([M+Na]$^+$) 297.1340, found 297.1348.

(5*S*)-5-(4-(benzyloxy)benzyl)-2-(*tert*-butyl)-3-methyl-4-oxoimidazolidine-1-carbonyl chloride (S28)



Following general procedure 3a, *N*-methylamide **S14** (457 mg, 1.19 mmol, 1.0 eq.) and pivalaldehyde (0.19 mL, 1.78 mmol) and TFA (0.46 mL, 5.94 mmol, 5.0 eq.) were reacted to give a crude diastereomeric imidazolidinone (60:40 *trans*:*cis*) which was phosgenated with triphosgene (159 mg, 0.535 mmol) in the presence of 2,6-lutidine (0.17 mL, 1.43 mmol). Purification by flash column chromatography (SiO_2, 99:1 DCM:Acetone) gave:

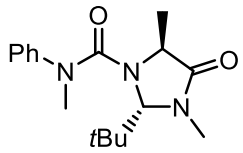
***trans*-S28** (208 mg, 0.501 mmol, 42%) as a white solid: **R_f** (99:1 DCM:Acetone): 0.26; **^{1}H NMR** (400 MHz, $CDCl_3$) (0.55:0.45 rotamers): δ_H = 7.42 (d, *J* = 7.3, 2H, Ph*H*), 7.38 (t, *J* = 7.3, 2H, Ph*H*), 7.35 – 7.29 (m, 1H, Ph*H*), 7.09 (d, *J* = 8.5, 2H, Ar*H*), 6.86 (d, *J* = 8.4, 2H, Ar*H*), 5.06 – 4.98 (m, 2H, OCH_2Ph), 4.74 (s, 0.55H, C*H*C$(CH_3)_{3(maj)}$), 4.61 (s, 0.45H, C*H*C$(CH_3)_{3(min)}$), 4.43 (d, *J* = 2.9, 0.55H, NC$H_{(maj)}$), 4.38 (d, *J* = 3.0, 0.45H, NC$H_{(min)}$), 3.83 (dd, *J* = 14.4, 5.2, 0.45H, CHCH_AH$_{B(min)}$), 3.69 (dd, *J* = 14.4, 4.8, 0.55H, CHCH_AH$_{B(maj)}$), 3.29 (d, *J* = 14.3, 0.45H, CHCH$_A$$H_{B(min)}$), 3.21 (d, *J* = 14.6, 0.55H, CHCH$_A$$H_{B(maj)}$), 2.87 (s, 1.65H, NC$H_{3(maj)}$), 2.73 (s, 1.35H, NC$H_{3(min)}$), 1.01 (s, 4.95H, C(C$H_3)_{3(maj)}$), 0.93 (s, 4.05H, C(C$H_3)_{3(min)}$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 170.0 (*C*=O$_{(maj)}$), 169.4 (*C*=O$_{(min)}$), 158.2 (*C*$_{Ar}$O$_{(min)}$), 158.0 (*C*$_{Ar}$O$_{(maj)}$), 147.4 (*C*=O$_{(min)}$), 146.2 (*C*=O$_{(maj)}$), 137.1 (*C*$_{Ph(maj)}$), 137.0 (*C*$_{Ph(min)}$), 131.3 (2×*C*H$_{Ar(maj)}$), 131.2 (2×*C*H$_{Ar(min)}$), 128.7 (2×*C*H$_{Ph}$), 128.1 (*C*H$_{Ph}$), 127.7 (2×*C*H$_{Ph}$), 126.6 (*C*$_{Ar(maj)}$), 126.2 (*C*$_{Ar(min)}$), 114.9 (2×*C*H$_{Ar(min)}$), 114.7 (2×*C*H$_{Ar(maj)}$), 83.5 (*C*HC$(CH_3)_{3(maj)}$), 82.9 (*C*HC$(CH_3)_{3(min)}$), 70.0 (OCH_2Ph), 63.8 (*C*HC$H_{2(maj)}$), 62.9 (*C*HC$H_{2(min)}$), 41.8 (*C*$(CH_3)_{3(min)}$), 41.7 (*C*$(CH_3)_{3(maj)}$), 35.9

(CH*C*H$_{2(min)}$), 32.2 (N*C*H$_3$), 32.0 (CH*C*H$_{2(maj)}$), 26.8 (C(*C*H$_3$)$_{3(maj)}$) , 26.6 (C(*C*H$_3$)$_{3(min)}$); **IR**: ν_{max} = 3034, 2968, 2929, 2871 (C–H), 1736 (C=O), 1697 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{23}H_{27}O_3N_2ClK$ ([M+K]$^+$) 453.1347, found 453.1357.

***cis*-S28** (128 mg, 0.308 mmol, 26%) as a white solid: **R$_f$** (99:1 DCM:Acetone): 0.21; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.44 (d, *J* = 7.1, 2H, Ph*H*), 7.39 (t, *J* = 7.3, 2H, Ph*H*), 7.35 – 7.31 (m, 1H, Ph*H*), 7.30 (d, *J* = 8.6, 2H, Ar*H*), 6.94 (d, *J* = 8.6, 2H, Ar*H*), 5.10 (s, 1H, C*H*C(CH$_3$)$_3$), 5.05 (s, 2H, OC*H*$_2$Ph), 4.47 (dd, *J* = 8.2, 4.7, 1H, C*H*CH$_A$H$_B$), 3.22 (dd, *J* = 14.0, 8.2, 1H, CHC*H*$_A$H$_B$), 3.16 (dd, *J* = 14.1, 4.6, 1H, CHCH$_A$*H*$_B$), 3.01 (s, 3H, NC*H*$_3$), 1.08 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 169.4 (*C*=O), 158.0 (*C*$_{Ar}$O), 150.9 (*C*=O), 137.1 (*C*$_{Ph}$), 130.8 (2×*C*H$_{Ar}$), 129.1 (*C*$_{Ar}$), 128.7 (2×*C*H$_{Ph}$), 128.1 (*C*H$_{Ph}$), 127.6 (2×*C*H$_{Ph}$), 115.0 (2×*C*H$_{Ar}$), 83.9 (*C*HC(CH$_3$)$_3$), 70.0 (O*C*H$_2$Ph), 63.8 (*C*HCH$_2$), 39.0 (CH*C*H$_2$), 38.1 (*C*(CH$_3$)$_3$), 31.7 (N*C*H$_3$), 26.8 (C(*C*H$_3$)$_3$); **IR**: ν_{max} = 2967 (C–H), 1746 (C=O), 1613 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{23}H_{27}O_3N_2ClK$ ([M+K]$^+$) 453.1347, found 453.1352.

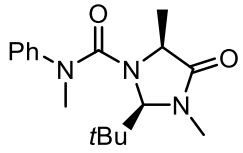
Synthesis of the *N*-Aryl Ureas

(2*S*,5*S*)-2-(*tert*-Butyl)-*N*,3,5-trimethyl-4-oxo-*N*-phenylimidazolidine-1-carboxamide (S29)



To a solution of *trans*-**S23** (1.00 g, 4.30 mmol, 1.0 eq.) in anhydrous MeCN (4.30 mL, 1.0 M) was added Et$_3$N (1.20 mL, 8.59 mmol, 2.0 eq.) and *N*-methylaniline (2.33 mL, 21.49 mmol, 5.0 eq.). The reaction mixture was heated to reflux and left to stir for 18 h. The reaction mixture was cooled to room temperature and quenched with HCl (1.0 M, aq.), the organic layer was separated and the aqueous layer extracted 3 times with DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 Pet.Ether:EtOAc) gave the title compound (1.10 g, 3.63 mmol, 84%) as a pale yellow oil. **S29**: **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.35 (t, *J* = 7.4, 2H, Ph*H*), 7.32 – 7.22 (m, 2H, Ph*H*), 7.18 (t, *J* = 7.1, 1H, Ph*H*), 5.43 (s, 1H, C*H*C(CH$_3$)$_3$), 3.32 (s, 3H, NC*H*$_3$), 2.96 (s, 3H, NC*H*$_3$), 2.87 (br. s, 1H, C*H*CH$_3$), 1.24 (br. s, 3H, CHC*H*$_3$), 0.99 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 173.1 (*C*=O), 158.9 (*C*=O), 144.0 (*C*$_{Ph}$), 129.4 (2×*C*H$_{Ph}$), 125.9 (*C*H$_{Ph}$), 127.2 (2×*C*H$_{Ph}$), 81.6 (*C*HC(CH$_3$)$_3$), 55.8 (*C*HCH$_3$), 40.1 (*C*(CH$_3$)$_3$), 38.7 (N*C*H$_3$), 32.2 (N*C*H$_3$), 26.1 (C(*C*H$_3$)$_3$), 19.9 (CH*C*H$_3$); **IR**: ν_{max} = 2961, 2923, 2851 (C–H), 1707 (C=O), 1652 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{17}H_{25}O_2N_3Na$ ([M+Na]$^+$) 326.1844, found 326.1834.

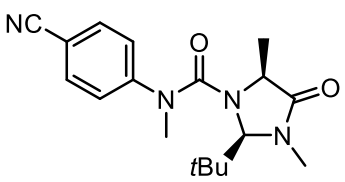
(2*R*,5*S*)-2-(*tert*-Butyl)-*N*,3,5-trimethyl-4-oxo-*N*-phenylimidazolidine-1-carboxamide (S30)



To a solution of *cis*-**S23** (120 mg, 0.516 mmol, 1.0 eq.) in anhydrous DCM (1.00 mL, 0.5 M) was added Et$_3$N (0.11 mL, 0.774 mmol, 1.5 eq.) and *N*-methylaniline (61 µL, 0.567 mmol, 1.1 eq.). The reaction mixture was heated to reflux and left to stir for 18 h. The reaction mixture was cooled to room temperature and quenched with HCl (1.0 M, aq.), the organic layer was separated and the aqueous layer

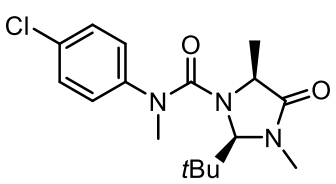
extracted 3 times with DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 EtOAc:Pet.Ether) gave the title compound (152 mg, 0.501 mmol, 97%) as a pale yellow oil. **S30**: **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.43 – 7.38 (m, 2H, Ph*H*), 7.30 – 7.25 (m, 1H, Ph*H*), 7.20 – 7.15 (m, 2H, Ph*H*), 5.60 (s, 1H, C*H*C$(CH_3)_3$), 3.96 (q, *J* = 6.9, 1H, C*H*CH_3), 3.19 (s, 3H, NC*H*$_3$), 2.94 (s, 3H, NC*H*$_3$), 0.98 (s, 9H, C(C*H*$_3)_3$), 0.33 (d, *J* = 6.9, 3H, CHC*H*$_3$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 173.4 (*C*=O), 163.4 (*C*=O), 146.1 (C_{Ph}), 130.2 (2×CH_{Ph}), 127.6 (2×CH_{Ph}), 127.1 (CH_{Ph}), 82.7 (*C*HC$(CH_3)_3$), 59.3 (*C*HCH_3), 41.5 (NCH_3), 36.7 (*C*$(CH_3)_3$), 31.6 (NCH_3), 26.9 (C(*C*$H_3)_3$), 17.4 (CH*C*H_3); **IR**: ν_{max} = 2960, 2927, 2873 (C–H), 1703 (C=O), 1655 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{17}H_{25}O_2N_3Na$ ([M+Na]$^+$) 326.1844, found 326.1854.

(2*R*,5*S*)-2-(*tert*-Butyl)-*N*-(4-cyanophenyl)-*N*,3,5-trimethyl-4-oxoimidazolidine-1-carboxamide (S31)



Following general procedure 5, *cis*-**S23** (85 mg, 0.365 mmol), 4-(methylamino)benzonitrile (241 mg, 1.83 mmol), 2,6-lutidine (85 µL, 0.731 mmol) and KI (67 mg, 0.402 mmol) were reacted in toluene (1.05 mL, 0.35 M) at reflux for 72 h. Purification by flash column chromatography (SiO_2, 4:1→6:1 EtOAc:Pentane) gave the title compound (87 mg, 0.265 mmol, 73%) as a yellow oil. **S31**: **R_f** (4:1 EtOAc:Pentane): 0.21; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.71 – 7.65 (m, 2H, Ar*H*), 7.27 – 7.23 (m, 2H, Ar*H*), 5.50 (s, 1H, C*H*C$(CH_3)_3$), 3.98 (q, *J* = 6.9, 1H, C*H*CH_3), 3.21 (s, 3H, NCH_3), 2.95 (s, 3H, NCH_3), 0.99 (s, 9H, C(C$H_3)_3$), 0.59 (d, *J* = 6.9, 3H, CHCH_3); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 172.5 (*C*=O), 162.8 (*C*=O), 150.3 (C_{Ar}), 134.0 (2×CH_{Ar}), 126.3 (2×CH_{Ar}), 118.2 (*C*≡N), 109.6 (C_{Ar}), 82.8 (*C*HC$(CH_3)_3$), 58.9 (*C*HCH_3), 40.6 (NCH_3), 36.9 (*C*$(CH_3)_3$), 31.7 (NCH_3), 26.9 (C(*C*$H_3)_3$), 17.7 (CH*C*H_3); **IR**: ν_{max} = 2973, 2938, 2874 (C–H), 2227 (C≡N), 1699 (C=O), 1659 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{17}H_{25}O_2N_3Na$ ([M+Na]$^+$) 326.1844, found 326.1834.

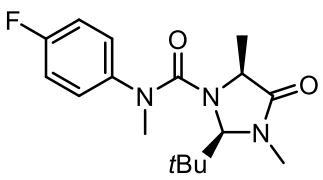
(2*R*,5*S*)-2-(*tert*-Butyl)-*N*-(4-chlorophenyl)-*N*,3,5-trimethyl-4-oxoimidazolidine-1-carboxamide (S32)



Following general procedure 4, imine **S2** (711 mg, 4.18 mmol), *N*-(4-chlorophenyl)-*N*-methylcarbamoyl chloride (1150 mg, 5.64 mmol, 1.35 eq.) and DMAP (26 mg, 0.209 mmol) were dissolved in DCE (17.00 mL, 0.25 M) and reacted for 88 h. Purification by flash column chromatography (SiO_2, 2:1 EtOAc:Pet.Ether), followed by recrystallisation from hexane/EtOAc gave the title compound (718 mg, 2.13 mmol, 51%) as a white solid. **S32**: **R_f** (2:1 EtOAc:Pet.Ether): 0.19; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.39 – 7.32 (m, 2H, Ar*H*), 7.14 – 7.05 (m, 2H, Ar*H*), 5.56 (s, 1H, C*H*C$(CH_3)_3$), 3.92 (q, *J* = 6.9, 1H, C*H*CH_3), 3.13 (s, 3H, NCH_3), 2.92 (s, 3H, NCH_3), 0.96 (s, 9H, C(C$H_3)_3$), 0.44 (d, *J* = 6.9, 3H, CHCH_3); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 173.0 (*C*=O), 163.1 (*C*=O), 144.7 (C_{Ar}), 132.6 (C_{Ar}), 130.3 (2×CH_{Ar}), 128.6 (2×CH_{Ar}), 82.7 (*C*HC$(CH_3)_3$), 59.1 (*C*HCH_3), 41.4 (NCH_3), 36.7 (*C*$(CH_3)_3$), 31.5 (NCH_3),

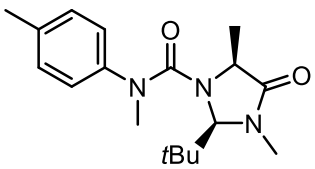
26.9 (C(CH_3)$_3$), 17.7 (CHCH_3); **IR**: ν_{max} = 2975, 2873 (C–H), 1699 (C=O), 1655 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{17}H_{25}O_2N_3Cl$ ([M+H]$^+$) 338.1630, found 338.1632.

(2*R*,5*S*)-2-(*tert*-Butyl)-*N*-(4-fluorophenyl)-*N*,3,5-trimethyl-4-oxoimidazolidine-1-carboxamide (S33)



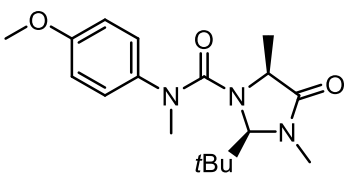
Following general procedure 4, imine **S2** (812 mg, 4.77 mmol), *N*-(4-fluorophenyl)-*N*-methylcarbamoyl chloride (1208 mg, 6.44 mmol, 1.35 eq.) and DMAP (29 mg, 0.238 mmol) were dissolved in DCE (19.00 mL, 0.25 M) and reacted for 88 h. Purification by flash column chromatography (SiO_2, 2:1→5:2 EtOAc:Pet.Ether), followed by recrystallisation from hexane/EtOAc gave the title compound (701 mg, 2.18 mmol, 46%) as a white solid. **S33**: **R_f** (2:1 EtOAc:Pet.Ether): 0.18; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.16 – 7.06 (m, 4H, Ar*H*), 5.59 (s, 1H, C*H*C(CH_3)$_3$), 3.94 (q, *J* = 6.9, 1H, C*H*CH_3), 3.14 (s, 3H, NCH_3), 2.93 (s, 3H, NCH_3), 0.97 (s, 9H, C(CH_3)$_3$), 0.41 (d, *J* = 6.9, 3H, CHCH_3); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 173.1 (*C*=O), 163.3 (*C*=O), 161.3 (d, $^1J_{C–F}$ = 247.9, C_{Ar}F), 142.2 (d, $^4J_{C–F}$ = 3.4, C_{Ar}), 129.2 (d, $^3J_{C–F}$ = 8.3, 2×*C*H$_{Ar}$), 117.1 (d, $^2J_{C–F}$ = 22.6, 2×*C*H$_{Ar}$), 82.7 (*C*HC(CH_3)$_3$), 59.1 (*C*HCH_3), 41.7 (NCH_3), 36.7 (*C*(CH_3)$_3$), 31.5 (NCH_3), 26.9 (C(CH_3)$_3$), 17.7 (CH*C*H_3); **IR**: ν_{max} = 2974, 2874 (C–H), 1702 (C=O), 1655 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{17}H_{25}O_2N_3F$ ([M+H]$^+$) 322.1925, found 322.1914.

(2*R*,5*S*)-2-(*tert*-butyl)-*N*,3,5-trimethyl-4-oxo-N-(*p*-tolyl)imidazolidine-1-carboxamide (S34)



Following general procedure 4, imine **S2** (500 mg, 2.94 mmol), *N*-(*p*-tolyl)-*N*-methylcarbamoyl chloride (647 mg, 3.52 mmol, 1.2 eq.) and DMAP (18 mg, 0.147 mmol) were dissolved in DCE (11.75 mL, 0.25 M) and reacted for 64 h. Purification by flash column chromatography (SiO_2, 4:1 EtOAc:Pet.Ether) gave the title compound (662 mg, 2.09 mmol, 71%) as a white solid. **S34**: **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.20 – 7.16 (m, 2H, Ar*H*), 7.05 – 7.01 (m, 2H, Ar*H*), 5.59 (s, 1H, C*H*C(CH_3)$_3$), 3.94 (q, *J* = 6.9, 1H, C*H*CH_3), 3.14 (s, 3H, NCH_3), 2.92 (s, 3H, NCH_3), 2.34 (s, 3H, CH_3), 0.96 (s, 9H, C(CH_3)$_3$), 0.34 (d, *J* = 6.9, 3H, CHCH_3); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 173.4 (*C*=O), 163.4 (*C*=O), 143.4 (C_{Ar}), 137.0 (C_{Ar}), 130.7 (2×*C*H$_{Ar}$), 127.3 (2×*C*H$_{Ar}$), 82.6 (*C*HC(CH_3)$_3$), 59.2 (*C*HCH_3), 41.6 (NCH_3), 36.7 (*C*(CH_3)$_3$), 31.5 (NCH_3), 26.9 (C(CH_3)$_3$), 21.1 (CH_3), 17.5 (CH*C*H_3); **HRMS** (ESI$^+$): *m/z* calcd for $C_{18}H_{27}O_2N_3Na$ ([M+Na]$^+$) 340.1995, found 340.1998.

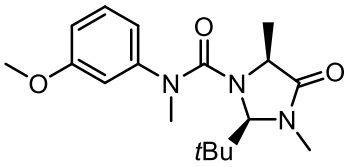
(2*R*,5*S*)-2-(*tert*-butyl)-*N*-(4-methoxyphenyl)-*N*,3,5-trimethyl-4-oxoimidazolidine-1-carboxamide (S35)



Following general procedure 4, imine **S2** (500 mg, 2.94 mmol), *N*-(4-methoxyphenyl)-*N*-methylcarbamoyl chloride (586 mg, 3.52 mmol, 1.2 eq.) and DMAP (18 mg, 0.147 mmol) were dissolved in DCE (11.75 mL, 0.25 M) and reacted for 64 h. Purification by

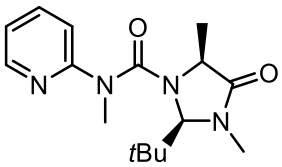
flash column chromatography (SiO_2, 4:1 EtOAc:Pet.Ether) gave the title compound (616 mg, 1.85 mmol, 63%) as an off-white solid. **S35**: **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.08 – 7.03 (m, 2H, Ar*H*), 6.91 – 6.87 (m, 2H, Ar*H*), 5.58 (s, 1H, C*H*C$(CH_3)_3$), 3.92 (q, *J* = 6.8, 1H, C*H*CH_3), 3.79 (s, 3H, OC*H*$_3$), 3.11 (s, 3H, NC*H*$_3$), 2.92 (s, 3H, NC*H*$_3$), 0.95 (s, 9H, C(C*H*$_3)_3$), 0.37 (d, *J* = 6.9, 3H, CHC*H*$_3$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 173.3 (*C*=O), 163.4 (*C*=O), 158.5 (C_{Ar}), 138.8 (C_{Ar}), 128.7 (2×CH_{Ar}), 115.3 (2×CH_{Ar}), 82.6 (*C*HC$(CH_3)_3$), 59.2 (*C*HCH_3), 55.6 (OC*H*$_3$), 41.7 (NC*H*$_3$), 36.6 (*C*$(CH_3)_3$), 31.5 (NC*H*$_3$), 26.9 (C(C*H*$_3)_3$), 17.7 (CH*C*H$_3$); **HRMS** (ESI^+): *m/z* calcd for $C_{18}H_{27}O_3N_3Na$ ($[M+Na]^+$) 356.1945, found 356.1948.

(2*R*,5*S*)-2-(*tert*-butyl)-*N*-(3-methoxyphenyl)-*N*,3,5-trimethyl-4-oxoimidazolidine-1-carboxamide (S36)



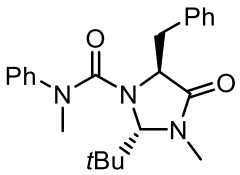
Following general procedure 4, imine **S2** (500 mg, 2.94 mmol), *N*-(3-methoxyphenyl)-*N*-methylcarbamoyl chloride (586 mg, 3.52 mmol, 1.2 eq.) and DMAP (18 mg, 0.147 mmol) were dissolved in DCE (11.75 mL, 0.25 M) and reacted for 64 h. Purification by flash column chromatography (SiO_2, 4:1 EtOAc:Pet.Ether) gave the title compound (605 mg, 1.81 mmol, 62%) as an off-white solid. **S36**: **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.31 – 7.23 (m, 1H, Ar*H*), 6.82 – 6.77 (m, 1H, Ar*H*), 6.77 – 6.73 (m, 1H, Ar*H*), 6.71 – 6.67 (m, 1H, Ar*H*), 5.57 (s, 1H, C*H*C$(CH_3)_3$), 3.97 (q, *J* = 7.1, 1H, C*H*CH_3), 3.77 (m, 3H, OC*H*$_3$), 3.16 (s, 3H, NC*H*$_3$), 2.92 (s, 3H, NC*H*$_3$), 0.97 (s, 9H, C(C*H*$_3)_3$), 0.42 (d, *J* = 6.7, 3H, CHC*H*$_3$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 173.3 (*C*=O), 163.2 (*C*=O), 161.0 (C_{Ar}), 147.2 (C_{Ar}), 130.7 (CH_{Ar}), 119.5 (CH_{Ar}), 113.0 (CH_{Ar}), 112.7 (CH_{Ar}), 82.7 (*C*HC$(CH_3)_3$), 59.2 (*C*HCH_3), 55.5 (OC*H*$_3$), 41.4 (NC*H*$_3$), 36.7 (*C*$(CH_3)_3$), 31.5 (NC*H*$_3$), 26.9 (C(C*H*$_3)_3$), 17.5 (CH*C*H$_3$); **HRMS** (ESI^+): *m/z* calcd for $C_{18}H_{27}O_3N_3Na$ ($[M+Na]^+$) 356.1945, found 356.1942.

(2*R*,5*S*)-2-(*tert*-Butyl)-*N*,3,5-trimethyl-4-oxo-*N*-(pyridin-2-yl)imidazolidine-1-carboxamide (S37)



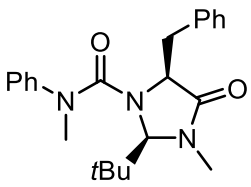
Following general procedure 4, imine **S2** (861 mg, 5.06 mmol), *N*-(pyridin-2-yl)-*N*-methylcarbamoyl chloride (1165 mg, 6.83 mmol, 1.35 eq.) and DMAP (31 mg, 0.253 mmol) were dissolved in DCE (20.00 mL, 0.25 M) and reacted for 88 h. Purification by flash column chromatography (SiO_2, 99:1 EtOAc:MeOH) gave the title compound (652 mg, 2.14 mmol, 42%) as a yellow oil. **S37**: **R_f** (99:1 EtOAc:MeOH): 0.21; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 8.37 (ddd, *J* = 4.9, 1.8, 0.6, 1H, Ar*H*), 7.65 (ddd, *J* = 8.1, 7.6, 2.0, 1H, Ar*H*), 7.06 – 7.00 (m, 2H, Ar*H*), 5.36 (s, 1H, C*H*C$(CH_3)_3$), 4.15 (q, *J* = 7.0, 1H, C*H*CH_3), 3.25 (s, 3H, NC*H*$_3$), 2.94 (s, 3H, NC*H*$_3$), 1.01 (s, 9H, C(C*H*$_3)_3$), 0.78 (d, *J* = 6.9, 3H, CHC*H*$_3$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 172.8 (*C*=O), 163.0 (*C*=O), 158.1 (C_{Ar}), 149.1 (CH_{Ar}), 138.4 (CH_{Ar}), 119.9 (CH_{Ar}), 117.3 (CH_{Ar}), 82.6 (*C*HC$(CH_3)_3$), 58.5 (*C*HCH_3), 37.9 (NC*H*$_3$), 37.1 (*C*$(CH_3)_3$), 31.7 (NC*H*$_3$), 26.8 (C(C*H*$_3)_3$), 17.7 (CH*C*H$_3$); **IR**: ν_{max} = 3053, 2961, 2873 (C–H), 1700 (C=O), 1665 (C=O); **HRMS** (ESI^+): *m/z* calcd for $C_{16}H_{25}O_2N_4$ ($[M+H]^+$) 305.1972, found 305.1969.

(2*S*,5*S*)-5-Benzyl-2-(*tert*-butyl)-*N*,3-dimethyl-4-oxo-*N*-phenylimidazolidine-1-carboxamide (S38)



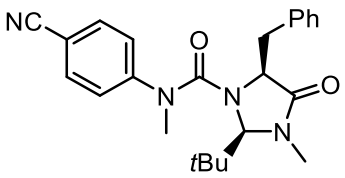
Following general procedure 5, *trans*-**S24** (50 mg, 0.162 mmol), *N*-methylaniline (87 µL, 0.810 mmol), 2,6-lutidine (38 µL, 0.324 mmol) and KI (30 mg, 0.178 mmol) were reacted in DCM/toluene (0.50 mL, 0.32 M, 4:1) at 60 °C for 72 h. Purification by flash column chromatography (SiO_2, 2:1 Pentane:EtOAc) gave the title compound (54 mg, 0.142 mmol, 88%) as a yellow oil. **S38**: **^{1}H NMR** (400 MHz, $CDCl_3$) (major rotamer): δ_H = 7.43 (t, *J* = 7.6, 2H, Ph*H*), 7.38 (d, *J* = 7.6, 2H, Ph*H*), 7.28 – 7.21 (m, 4H, Ph*H*), 7.07 (d, *J* = 6.9, 2H, Ph*H*), 4.92 (s, 1H, C*H*C$(CH_3)_3$), 3.44 (s, 3H, NCH_3), 3.21 – 3.17 (m, 2H, CHCH_AH$_B$ and C*H*CH_AH$_B$), 2.86 (d, *J* = 11.8, 1H, CHC$H_A$$H_B$), 2.57 (s, 3H, NC$H_3$), 0.94 (s, 9H, C(C$H_3$)$_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 171.0 (*C*=O), 158.3 (*C*=O), 144.2 (C_{Ar}), 134.8 (C_{Ar}), 130.2 (2×*C*H$_{Ar}$), 129.8 (2×*C*H$_{Ar}$), 128.1 (2×*C*H$_{Ar}$), 127.1 (*C*H$_{Ar}$), 126.4 (*C*H$_{Ar}$), 125.7 (2×*C*H$_{Ar}$), 82.1 (*C*HC$(CH_3)_3$), 61.1 (*C*HCH$_2$), 40.4 (*C*$(CH_3)_3$), 39.4 (NCH_3), 37.6 (CH*C*H$_2$), 31.8 (NCH_3), 26.4 (C(*C*H_3)$_3$); **IR**: ν_{max} = 3062, 3031, 2965, 2931 (C–H), 1703 (C=O), 1650 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{23}H_{30}O_2N_3$ ([M+H]$^+$) 380.2338, found 380.2321.

(2*R*,5*S*)-5-Benzyl-2-(*tert*-butyl)-*N*,3-dimethyl-4-oxo-*N*-phenylimidazolidine-1-carboxamide (S39)



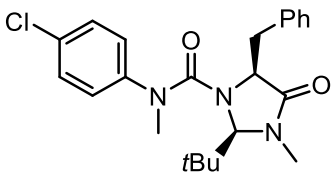
Following general procedure 4, imine **S4** (50 mg, 0.203 mmol), *N*-phenyl-*N*-methylcarbamoyl chloride (52 mg, 0.304 mmol, 1.5 eq.) and DMAP (1 mg, 0.010 mmol) were dissolved in DCE (1.00 mL, 0.2 M) and reacted for 68 h. Purification by flash column chromatography (SiO_2, 2:1→3:2 Pet.Ether:EtOAc) gave the title compound (57 mg, 0.150 mmol, 74%) as a colourless oil. **S39**: **R_f** (3:2 Pet.Ether:EtOAc): 0.18; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.31 (t, *J* = 7.8, 2H, Ph*H*), 7.23 – 7.12 (m, 6H, Ph*H*), 7.05 (d, *J* = 7.1, 2H, Ph*H*), 5.27 (s, 1H, C*H*C$(CH_3)_3$), 4.25 (dd, *J* = 10.7, 3.2, 1H, C*H*CH_AH$_B$), 3.18 (s, 3H, NCH_3), 2.86 (s, 3H, NCH_3), 2.61 (dd, *J* = 14.1, 10.8, 1H, CHCH_AH$_B$), 2.07 (dd, *J* = 14.1, 2.6, 1H, CHC$H_A$$H_B$), 1.04 (s, 9H, C(C$H_3$)$_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 171.7 (*C*=O), 163.2 (*C*=O), 146.0 (C_{Ar}), 137.7 (C_{Ar}), 130.2 (2×*C*H$_{Ar}$), 129.2 (2×*C*H$_{Ar}$), 128.1 (2×*C*H$_{Ar}$), 126.6 (*C*H$_{Ar}$), 126.3 (*C*H$_{Ar}$), 125.9 (2×*C*H$_{Ar}$), 82.3 (*C*HC$(CH_3)_3$), 63.1 (*C*HCH$_2$), 41.3 (NCH_3), 39.3 (CH*C*H$_2$), 37.0 (*C*$(CH_3)_3$), 31.6 (NCH_3), 27.1 (C(*C*H_3)$_3$); **IR**: ν_{max} = 3062, 3029, 2960, 2931, 2872 (C–H), 1704 (C=O), 1655 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{23}H_{29}O_2N_3Na$ ([M+Na]$^+$) 402.2157, found 402.2149.

(2*R*,5*S*)-5-Benzyl-2-(*tert*-butyl)-*N*-(4-cyanophenyl)-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide (S40)



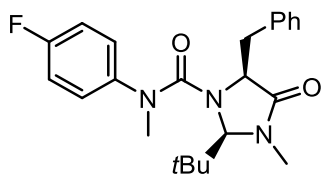
Following general procedure 4, imine **S4** (58 mg, 0.235 mmol), *N*-(4-cyanophenyl)-*N*-methylcarbamoyl chloride (69 mg, 0.353 mmol, 1.5 eq.) and DMAP (1 mg, 0.011 mmol) were dissolved in DCE (1.20 mL, 0.2 M) and reacted for 68 h. Purification by flash column chromatography (SiO_2, 2:1→1:1 Pet.Ether:EtOAc) gave the title compound (80 mg, 0.198 mmol, 84%) as a colourless oil. **S40**: **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.50 (d, *J* = 8.5, 2H, Ar*H*), 7.25 (t, *J* = 7.0, 2H, Ph*H*), 7.19 (t, *J* = 7.2, 1H, Ph*H*), 7.07 (d, *J* = 7.4, 2H, Ph*H*), 6.96 (d, *J* = 8.4, 2H, Ar*H*), 5.22 (s, 1H, C*H*C$(CH_3)_3$), 4.26 (dd, *J* = 8.9, 3.3, 1H, C*H*CH_AH_B), 3.06 (s, 3H, NCH_3), 2.99 – 2.88 (m, 4H, NCH_3 and CHCH_AH_B), 2.47 (dd, *J* = 14.7, 3.1, 1H, CHCH_AH_B), 1.07 (s, 9H, C(CH_3)$_3$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 171.3 (*C*=O), 162.1 (*C*=O), 149.6 (C_{Ar}), 137.6 (C_{Ph}), 133.8 (2×CH_{Ar}), 128.8 (2×CH_{Ph}), 128.4 (2×CH_{Ph}), 126.7 (CH_{Ph}), 123.0 (2×CH_{Ar}), 118.4 (*C*≡N), 108.1 (C_{Ar}), 82.7 (*C*HC$(CH_3)_3$), 62.5 (N*C*HCH_2), 40.0 (CH*C*H_2), 39.8 (N*C*H_3), 37.2 (*C*$(CH_3)_3$), 31.6 (N*C*H_3), 27.1 (C(*C*H_3)$_3$); **IR**: ν_{max} = 3062, 3029, 2969 (C–H), 2225 (C≡N), 1704 (C=O), 1663 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{24}H_{29}O_2N_4$ ([M+H]$^+$) 405.2285, found 405.2285.

(2*R*,5*S*)-5-Benzyl-2-(*tert*-butyl)-*N*-(4-chlorophenyl)-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide (S41)



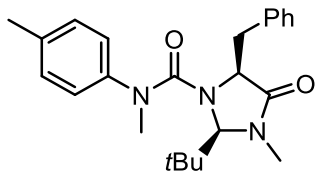
Following general procedure 4, imine **S4** (100 mg, 0.406 mmol), *N*-(4-chlorophenyl)-*N*-methylcarbamoyl chloride (124 mg, 0.609 mmol, 1.5 eq.) and DMAP (3 mg, 0.020 mmol) were dissolved in DCE (2.00 mL, 0.2 M) and reacted for 68 h. Purification by flash column chromatography (SiO_2, 2:1→3:2 Pet.Ether:EtOAc) gave the title compound (135 mg, 0.326 mmol, 80%) as a colourless oil. **S41**: **R_f** (3:2 Pet.Ether:EtOAc): 0.24; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.26 – 7.20 (m, 2H, Ph*H*), 7.20 – 7.14 (m, 3H, Ph*H* and Ar*H*), 7.09 – 7.04 (m, 2H, Ph*H*), 6.99 – 6.93 (m, 2H, Ar*H*), 5.36 (s, 1H, C*H*C$(CH_3)_3$), 4.27 (dd, *J* = 10.2, 2.6, 1H, C*H*CH_AH_B), 3.11 (s, 3H, NCH_3), 2.92 (s, 3H, NCH_3), 2.77 (dd, *J* = 14.8, 10.2, 1H, CHCH_AH_B), 2.14 (dd, *J* = 14.9, 2.7, 1H, CHCH_AH_B), 1.04 (s, 9H, C(CH_3)$_3$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 171.8 (*C*=O), 163.0 (*C*=O), 144.3 (C_{Ar}), 137.8 (C_{Ph}), 132.0 (C_{Ar}), 130.2 (2×CH_{Ar}), 128.8 (2×CH_{Ph}), 128.1 (2×CH_{Ph}), 127.0 (2×CH_{Ar}), 126.4 (CH_{Ph}), 82.4 (*C*HC$(CH_3)_3$), 62.6 (*C*HCH_2), 41.4 (N*C*H_3), 39.8 (CH*C*H_2), 36.9 (*C*$(CH_3)_3$), 31.6 (N*C*H_3), 27.1 (C(*C*H_3)$_3$); **IR**: ν_{max} = 3062, 3029, 2965 (C–H), 1702 (C=O), 1656 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{23}H_{29}O_2N_3Cl$ ([M+H]$^+$) 414.1943, found 414.1945.

(2*R*,5*S*)-5-Benzyl-2-(*tert*-butyl)-*N*-(4-fluorophenyl)-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide (S42)



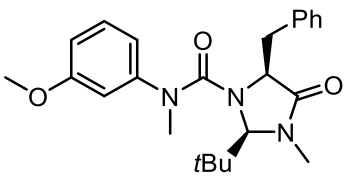
Following general procedure 4, imine **S4** (613 mg, 2.49 mmol), *N*-(4-fluorophenyl)-*N*-methylcarbamoyl chloride (700 mg, 3.73 mmol, 1.5 eq.) and DMAP (15 mg, 0.120 mmol) were dissolved in DCE (2.00 mL, 0.2 M) and reacted for 68 h. Purification by flash column chromatography (SiO_2, 2:1→3:2 Pet.Ether:EtOAc) gave the title compound (445 mg, 1.12 mmol, 45%) as a colourless oil. **S42**: **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.24 – 7.19 (m, 2H, Ph*H*), 7.18 – 7.13 (m, 1H, Ph*H*), 7.09 – 7.01 (m, 4H, Ph*H* and Ar*H*), 6.95 – 6.89 (m, 2H, Ar*H*), 5.37 (s, 1H, C*H*C$(CH_3)_3$), 4.27 (dd, *J* = 10.5, 2.8, 1H, C*H*CH_AH_B), 3.12 (s, 3H, NCH_3), 2.90 (s, 3H, NCH_3), 2.71 (dd, *J* = 14.7, 10.6, 1H, CHCH_AH$_B$), 2.04 (dd, *J* = 14.8, 2.8, 1H, CHC$H_A$$H_B$), 1.04 (s, 9H, C(C$H_3$)$_3$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 171.7 (*C*=O), 163.2 (*C*=O), 160.8 (d, $^1J_{C–F}$ = 247.5, C_{Ar}F), 141.8 (d, $^4J_{C–F}$ = 3.2, C_{Ar}), 137.6 (C_{Ph}), 128.8 (2×*C*H$_{Ph}$), 128.0 (2×*C*H$_{Ph}$), 127.7 (d, $^3J_{C–F}$ = 8.4, 2×*C*H$_{Ar}$), 126.3 (*C*H$_{Ph}$), 116.9 (d, $^2J_{C–F}$ = 22.8, 2×*C*H$_{Ar}$), 82.3 (*C*HC$(CH_3)_3$), 62.6 (*C*HCH$_2$), 41.7 (N*C*H$_3$), 39.6 (CH*C*H$_2$), 36.8 (*C*$(CH_3)_3$), 31.5 (N*C*H$_3$), 27.0 (C(*C*H$_3$)$_3$); **IR**: ν_{max} = 2964, 2248 (C–H), 1701 (C=O), 1651 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{23}H_{28}O_2N_3F$ ([M+H]$^+$) 420.2058, found 420.2042.

(2*R*,5*S*)-5-Benzyl-2-(*tert*-butyl)-*N*,3-dimethyl-4-oxo-*N*-(*p*-tolyl)imidazolidine-1-carboxamide (S43)



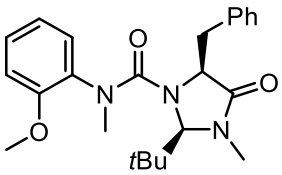
Following general procedure 4, imine **S4** (800 mg, 3.25 mmol), *N*-(*p*-tolyl)-*N*-methylcarbamoyl chloride (895 mg, 4.87 mmol, 1.5 eq.) and DMAP (20 mg, 0.162 mmol) were dissolved in DCE (2.00 mL, 0.2 M) and reacted for 68 h. Purification by flash column chromatography (SiO_2, 2:1→3:2 Pet.Ether:EtOAc) gave the title compound (524 mg, 1.33 mmol, 41%) as a colourless oil. **S43**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H = 7.24 – 7.18 (m, 2H, Ph*H*), 7.17 – 7.12 (m, 1H, Ph*H*), 7.08 – 7.02 (m, 4H, Ph*H* and Ar*H*), 7.00 – 6.96 (m, 2H, Ar*H*), 5.34 (s, 1H, C*H*C$(CH_3)_3$), 4.25 (dd, *J* = 10.7, 3.0, 1H, C*H*CH_AH_B), 3.14 (s, 3H, NCH_3), 2.88 (s, 3H, NCH_3), 2.63 (dd, *J* = 14.5, 10.7, 1H, CHCH_AH$_B$), 2.28 (s, 3H, CH_3), 2.06 (dd, *J* = 14.4, 3.0, 1H, CHC$H_A$$H_B$), 1.04 (s, 9H, C(C$H_3$)$_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 171.9 (*C*=O), 163.3 (*C*=O), 143.2 (C_{Ar}), 137.9 (C_{Ph}), 136.5 (C_{Ar}), 130.7 (2×*C*H$_{Ar}$), 129.1 (2×*C*H$_{Ph}$), 127.9 (2×*C*H$_{Ph}$), 126.2 (*C*H$_{Ph}$), 125.9 (2×*C*H$_{Ar}$), 82.3 (*C*HC$(CH_3)_3$), 62.8 (*C*HCH$_2$), 41.5 (N*C*H$_3$), 39.4 (CH*C*H$_2$), 36.9 (*C*$(CH_3)_3$), 31.6 (N*C*H$_3$), 27.1 (C(*C*H$_3$)$_3$), 21.1 (*C*H$_3$); **IR**: ν_{max} = 2960 (C–H), 1703 (C=O), 1652 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{24}H_{32}O_2N_3$ ([M+H]$^+$) 394.2489, found 394.2482.

(2*R*,5*S*)-5-Benzyl-2-(*tert*-butyl)-*N*-(3-methoxyphenyl)-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide (S44)



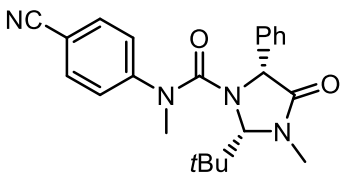
Following general procedure 4, imine **S4** (140 mg, 0.568 mmol), *N*-(3-methoxyphenyl)-*N*-methylcarbamoyl chloride (170 mg, 0.852 mmol, 1.5 eq.) and DMAP (3 mg, 0.028 mmol) were dissolved in toluene (2.85 mL, 0.2 M) and reacted for 68 h. Purification by flash column chromatography (SiO_2, 1:1 Pet.Ether:EtOAc) gave the title compound (123 mg, 0.300 mmol, 53%) as a white solid. **S44**: $\mathbf{R_f}$ (1:1 Pet.Ether:EtOAc): 0.28; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.24 – 7.18 (m, 3H, Ph*H* and Ar*H*), 7.16 – 7.11 (m, 1H, Ph*H*), 7.09 – 7.05 (m, 2H, Ph*H*), 6.71 (t, *J* = 1.9, 1H, Ar*H*), 6.69 (t, *J* = 2.1, 1H, Ar*H*), 6.59 (t, *J* = 2.2, 1H, Ar*H*), 5.31 (s, 1H, C*H*C$(CH_3)_3$), 4.26 (dd, *J* = 10.7, 3.0, 1H, C*H*CH_AH_B), 3.62 (s, 3H, OCH_3), 3.15 (s, 3H, NCH_3), 2.88 (s, 3H, NCH_3), 2.66 (dd, *J* = 14.3, 10.7, 1H, CHCH_AH_B), 2.13 (dd, *J* = 14.3, 2.3, 1H, CHCH_AH_B), 1.04 (s, 9H, C(C$H_3)_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 171.6 (*C*=O), 163.0 (*C*=O), 160.8 (C_{Ar}), 147.0 (C_{Ar}), 137.7 (C_{Ph}), 130.6 (CH_{Ar}), 129.0 (2×CH_{Ph}), 127.9 (2×CH_{Ph}), 126.2 (CH_{Ph}), 117.8 (CH_{Ar}), 112.2 (CH_{Ar}), 111.5 (CH_{Ar}), 82.2 (*C*HC$(CH_3)_3$), 62.8 (*C*HCH_2), 55.2 (O*C*H_3), 41.1 (N*C*H_3), 39.3 (CH*C*H_2), 36.9 (*C*$(CH_3)_3$), 31.5 (N*C*H_3), 27.0 (C(*C*$H_3)_3$); **IR**: ν_{max} = 3062, 3029, 2960, 2873, 2836 (C–H), 1700 (C=O), 1653 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{24}H_{32}O_3N_3$ ([M+H]$^+$) 410.2438, found 410.2434.

(2*R*,5*S*)-5-Benzyl-2-(*tert*-butyl)-*N*-(2-methoxyphenyl)-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide (S45)



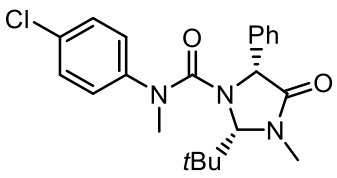
Following general procedure 4, imine **S4** (140 mg, 0.568 mmol), *N*-(2-methoxyphenyl)-*N*-methylcarbamoyl chloride (170 mg, 0.852 mmol, 1.5 eq.) and DMAP (3 mg, 0.028 mmol) were dissolved in toluene (2.85 mL, 0.2 M) and reacted for 68 h. Purification by flash column chromatography (SiO_2, 1:1 Pet.Ether:EtOAc) gave the title compound (143 mg, 0.349 mmol, 61%) as a white solid. **S45**: $\mathbf{R_f}$ (1:1 Pet.Ether:EtOAc): 0.26; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.20 – 7.06 (m, 5H, Ph*H* and Ar*H*), 7.04 (d, *J* = 7.1, 2H, Ph*H*), 6.90 (td, *J* = 7.6, 1.0, 1H, Ar*H*), 6.58 (d, *J* = 8.3, 1H, Ar*H*), 5.50 (s, 1H, C*H*C$(CH_3)_3$), 4.30 (dd, *J* = 11.0, 2.5, 1H, C*H*CH_AH_B), 3.53 (s, 3H, OCH_3), 3.05 (s, 3H, NCH_3), 2.89 (s, 3H, NCH_3), 2.61 (dd, *J* = 15.2, 11.1, 1H, CHCH_AH_B), 1.74 (dd, *J* = 15.3, 2.1, 1H, CHCH_AH_B), 1.01 (s, 9H, C(C$H_3)_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 172.2 (*C*=O), 163.5 (*C*=O), 154.2 (C_{Ar}), 137.8 (C_{Ph}), 133.2 (C_{Ar}), 128.8 (2×CH_{Ph}), 128.6 (CH_{Ar}), 128.5 (CH_{Ar}) 127.7 (2×CH_{Ph}), 125.8 (CH_{Ph}), 121.1 (CH_{Ar}), 112.5 (CH_{Ar}), 82.0 (*C*HC$(CH_3)_3$), 61.4 (*C*HCH_2), 55.0 (O*C*H_3), 39.4 (CH*C*H_2), 39.2 (N*C*H_3), 36.6 (*C*$(CH_3)_3$), 31.4 (N*C*H_3), 26.9 (C(*C*$H_3)_3$); **IR**: ν_{max} = 3063, 3026, 2960, 2873, 2838 (C–H), 1698 (C=O), 1651 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{24}H_{32}O_3N_3$ ([M+H]$^+$) 410.2438, found 410.2428.

(2*R*,5*R*)-2-(*tert*-Butyl)-*N*-(4-cyanophenyl)-*N*,3-dimethyl-4-oxo-5-phenylimidazolidine-1-carboxamide (S46)



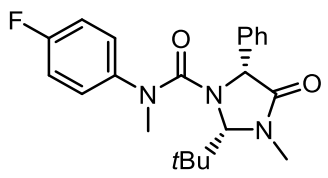
Following general procedure 4, imine **S6** (52 mg, 0.224 mmol), *N*-(4-cyanophenyl)-*N*-methylcarbamoyl chloride (65 mg, 0.336 mmol, 1.5 eq.) and DMAP (1 mg, 0.011 mmol) were dissolved in DCE (1.10 mL, 0.2 M) and reacted for 68 h. Purification by flash column chromatography (SiO_2, 3:2→1:1 Pet.Ether:EtOAc) gave the title compound (76 mg, 0.195 mmol, 87%) as a pale yellow oil. **S46**: $\mathbf{R_f}$ (1:1 Pet.Ether:EtOAc): 0.30; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.36 – 7.29 (m, 2H, Ar*H*), 7.21 – 7.07 (m, 5H, Ph*H*), 7.00 – 6.95 (m, 2H, Ar*H*), 5.46 (s, 1H, C*H*C$(CH_3)_3$), 5.15 (s, 1H, C*H*Ph), 3.10 (s, 3H, NCH_3), 2.95 (s, 3H, NCH_3), 1.01 (s, 9H, C(C$H_3)_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 169.0 (*C*=O), 163.4 (*C*=O), 148.8 (C_{Ar}), 135.5 (C_{Ph}), 133.6 (2×CH_{Ar}), 127.8 (2×CH_{Ph}), 127.2 (CH_{Ph}), 126.3 (2×CH_{Ph}), 125.6 (2×CH_{Ar}), 118.2 (*C*≡N), 109.4 (C_{Ar}), 82.7 (*C*HC$(CH_3)_3$), 65.5 (*C*HPh), 41.0 (NCH_3), 36.8 (*C*$(CH_3)_3$), 31.3 (NCH_3), 26.9 (C(C$H_3)_3$); **IR**: ν_{max} = 3061, 2969, 2932, 2874 (C–H), 2226 (C≡N), 1703 (C=O), 1668 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{23}H_{27}O_2N_4$ ([M+H]$^+$) 391.2129, found 391.2124.

(2*R*,5*R*)-2-(*tert*-Butyl)-*N*-(4-chlorophenyl)-*N*,3-dimethyl-4-oxo-5-phenylimidazolidine-1-carboxamide (S47)



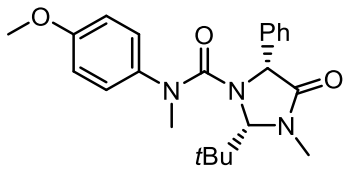
Following general procedure 4, imine **S6** (52 mg, 0.224 mmol), *N*-(4-chlorophenyl)-*N*-methylcarbamoyl chloride (69 mg, 0.336 mmol, 1.5 eq.) and DMAP (1 mg, 0.011 mmol) were dissolved in DCE (1.10 mL, 0.2 M) and reacted for 68 h. Purification by flash column chromatography (SiO_2, 3:2→1:1 Pet.Ether:EtOAc) gave the title compound (63 mg, 0.158 mmol, 70%) as a pale yellow oil. **S47**: $\mathbf{R_f}$ (3:2 Pet.Ether:EtOAc): 0.17; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.14 – 7.09 (m, 3H, Ph*H*), 7.08 – 7.03 (m, 2H, Ph*H*), 6.95 – 6.91 (m, 2H, Ar*H*), 6.85 – 6.80 (m, 2H, Ar*H*), 5.60 (s, 1H, C*H*C$(CH_3)_3$), 5.15 (s, 1H, C*H*Ph), 3.06 (s, 3H, NCH_3), 2.93 (s, 3H, NCH_3), 1.01 (s, 9H, C(C$H_3)_3$); **^{13}C {^{1}H} NMR** (500 MHz, $CDCl_3$): δ_C = 169.4 (*C*=O), 164.1 (*C*=O), 143.3 (C_{Ar}), 135.8 (C_{Ph}), 132.8 (C_{Ar}), 129.8 (2×CH_{Ar}), 128.5 (2×CH_{Ar}), 127.6 (2×CH_{Ph}), 126.6 (CH_{Ph}), 126.1 (2×CH_{Ph}), 82.6 (*C*HC$(CH_3)_3$), 66.0 (*C*HPh), 42.1 (NCH_3), 36.7 (*C*$(CH_3)_3$), 31.2 (NCH_3), 27.0 (C(C$H_3)_3$); **IR**: ν_{max} = 3061, 2970, 2931, 2874 (C–H), 1702 (C=O), 1659 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{22}H_{27}O_2N_3Cl$ ([M+H]$^+$) 400.1786, found 400.1782.

(2*S*,5*R*)-2-(*tert*-Butyl)-*N*-(4-fluorophenyl)-*N*,3-dimethyl-4-oxo-5-phenylimidazolidine-1-carboxamide (S48)



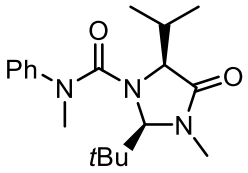
Following general procedure 4, imine **S6** (800 mg, 3.44 mmol), *N*-(4-fluorophenyl)-*N*-methylcarbamoyl chloride (969 mg, 5.16 mmol, 1.5 eq.) and DMAP (21 mg, 0.172 mmol) were dissolved in DCE (17 mL, 0.2 M) and reacted for 63 h. Purification by flash column chromatography (SiO_2, 3:2→1:1 Pet.Ether:EtOAc) gave the title compound (356 mg, 0.158 mmol, 27%) as a white solid. **S48**: **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.14 – 7.11 (m, 2H, Ph*H*), 7.08 – 7.02 (m, 3H, Ph*H*), 6.90 – 6.84 (m, 2H, Ar*H*), 6.68 – 6.62 (m, 2H, Ar*H*), 5.63 (s, 1H, C*H*C$(CH_3)_3$), 5.17 (s, 1H, C*H*Ph), 3.06 (s, 3H, NCH_3), 2.93 (s, 3H, NCH_3), 1.01 (s, 9H, C(C$H_3)_3$); **^{13}C {^{1}H} NMR** (500 MHz, $CDCl_3$): δ_C = 169.5 (*C*=O), 164.3 (*C*=O), 161.3 (d, $^1J_{C–F}$ = 247.2, C_{Ar}F), 140.7 (d, $^4J_{C–F}$ = 3.0, C_{Ar}), 136.0 (C_{Ph}), 129.1 (d, $^3J_{C–F}$ = 8.6, 2×CH$_{Ar}$), 127.5 (2×CH$_{Ph}$), 126.6 (CH$_{Ph}$), 126.0 (2×CH$_{Ph}$), 116.5 (d, $^2J_{C–F}$ = 22.9, 2×CH$_{Ar}$), 82.6 (CHC$(CH_3)_3$), 66.0 (CHPh), 42.4 (NCH$_3$), 36.6 (C(CH$_3)_3$), 31.2 (NCH$_3$), 27.0 (C(CH$_3)_3$); **IR**: ν_{max} = 2972 (C–H), 1704 (C=O), 1658 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{22}H_{26}O_2N_3FNa$ ([M+Na]$^+$) 406.1901, found 406.1894.

(2*S*,5*R*)-2-(*tert*-Butyl)-*N*-(4-methoxyphenyl)-*N*,3-dimethyl-4-oxo-5-phenylimidazolidine-1-carboxamide (S49)



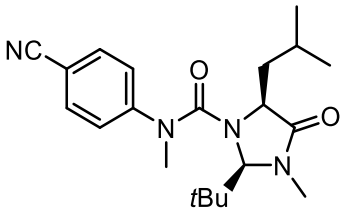
Following general procedure 4, imine **S6** (52 mg, 0.224 mmol), *N*-(4-methoxyphenyl)-*N*-methylcarbamoyl chloride (67 mg, 0.336 mmol, 1.5 eq.) and DMAP (1 mg, 0.011 mmol) were dissolved in DCE (1.10 mL, 0.2 M) and reacted for 68 h. Purification by flash column chromatography (SiO_2, 2:1→1:1 Pet.Ether:EtOAc) gave the title compound (48 mg, 0.121 mmol, 54%) as an off-white solid. **S49**: **R_f** (3:2 Pet.Ether:EtOAc): 0.18; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.16 – 7.09 (m, 2H, Ph*H*), 7.04 – 6.97 (m, 3H, Ph*H*), 6.83 – 6.77 (m, 2H, Ar*H*), 6.49 – 6.42 (m, 2H, Ar*H*), 5.62 (s, 1H, C*H*C$(CH_3)_3$), 5.16 (s, 1H, C*H*Ph), 3.62 (s, 3H, OCH_3), 3.06 (s, 3H, NCH_3), 2.90 (s, 3H, NCH_3), 0.98 (s, 9H, C(C$H_3)_3$); **^{13}C {^{1}H} NMR** (500 MHz, $CDCl_3$): δ_C = 169.7 (*C*=O), 164.2 (*C*=O), 158.3 (C_{Ar}), 137.2 (C_{Ph}), 136.2 (C_{Ar}), 128.6 (2×CH$_{Ar}$), 127.2 (2×CH$_{Ar}$), 126.2 (CH$_{Ph}$), 126.1 (2×CH$_{Ph}$), 114.8 (2×CH$_{Ph}$), 82.5 (CHC$(CH_3)_3$), 65.9 (CHPh), 55.3 (OCH_3) 42.4 (NCH$_3$), 36.5 (C(CH$_3)_3$), 31.2 (NCH$_3$), 26.9 (C(CH$_3)_3$); **IR**: ν_{max} = 3060, 2964, 2934, 2836 (C–H), 1701 (C=O), 1652 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{23}H_{30}O_3N_3$ ([M+H]$^+$) 396.2282, found 396.2279.

(2*R*,5*S*)-2-(*tert*-Butyl)-5-isopropyl-*N*,3-dimethyl-4-oxo-*N*-phenylimidazolidine-1-carboxamide (S50)



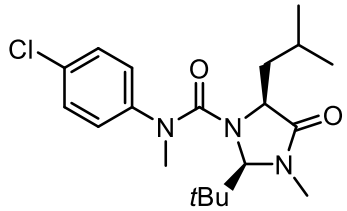
Following general procedure 5, *cis*-**S26** (62 mg, 0.238 mmol), *N*-methylaniline (0.13 mL, 1.19 mmol), Et_3N (66 µL, 0.476 mmol) and KI (43 mg, 0.262 mmol) were reacted in DCM (0.50 mL, 0.48 M) at reflux for 18 h. Purification by flash column chromatography (SiO_2, 3:2 Pentane:EtOAc) gave the title compound (69 mg, 0.208 mmol, 88%) as a white solid. **S50**: **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.36 – 7.31 (m, 2H, Ph*H*), 7.19 – 7.14 (m, 1H, Ph*H*), 6.90 – 6.86 (m, 2H, Ph*H*), 4.41 (s, 1H, C*H*C$(CH_3)_3$), 3.69 (d, *J* = 9.8, 1H, C*H*CH$(CH_3)_2$), 3.14 (s, 3H, NCH_3), 2.58 (s, 3H, NCH_3), 1.85 (dsept., *J* = 10.0, 6.7, 1H, CHC*H*$(CH_3)_2$), 1.18 (d, *J* = 6.5, 3H, CH(C$H_3)_A$$(CH_3)_B$), 1.15 (d, *J* = 6.9, 3H, CH$(CH_3)_A$(C$H_3)_B$), 0.94 (s, 9H, C(C$H_3)_3$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 171.7 (*C*=O), 162.3 (*C*=O), 146.2 (C_{Ph}), 129.8 (2×CH_{Ph}), 125.0 (CH_{Ph}), 122.1 (2×CH_{Ph}), 82.2 (*C*HC$(CH_3)_3$), 66.7 (*C*HCH$(CH_3)_2$), 40.2 (N*C*H_3), 36.8 (*C*$(CH_3)_3$), 32.5 (*C*H$(CH_3)_2$), 30.7 (N*C*H_3), 26.6 (C(*C*$H_3)_3$), 20.8 (CH$(CH_3)_A$(*C*$H_3)_B$), 19.8 (CH(*C*$H_3)_A$$(CH_3)_B$); **IR**: ν_{max} = 2965, 2928, 2873 (C–H), 1699 (C=O), 1660 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{19}H_{29}O_2N_3Na$ ([M+Na]$^+$) 354.2152, found 354.2147.

(2*R*,5*S*)-2-(*tert*-Butyl)-*N*-(4-cyanophenyl)-5-isobutyl-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide (S51)



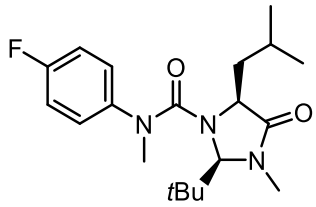
Following general procedure 4, imine **S9** (771 mg, 3.63 mmol), *N*-(4-cyanophenyl)-*N*-methylcarbamoyl chloride (954 mg, 4.90 mmol, 1.35 eq.) and DMAP (22 mg, 0.182 mmol) were dissolved in DCE (18.00 mL, 0.2 M) and reacted for 88 h. Purification by flash column chromatography (SiO_2, 3:2→5:4 Pet.Ether:EtOAc) gave the title compound (632 mg, 1.71 mmol, 47%) as a white solid. **S51**: **R_f** (1:1 Pet.Ether:EtOAc): 0.32; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.66 – 7.60 (m, 2H, Ar*H*), 7.13 – 7.07 (m, 2H, Ar*H*), 5.14 (s, 1H, C*H*C$(CH_3)_3$), 3.97 (dd, *J* = 10.7, 3.3, 1H, NC*H*CH_AH_B), 3.20 (s, 3H, NCH_3), 2.89 (s, 3H, NCH_3), 1.90 – 1.75 (m, 1H, CH_2C*H*$(CH_3)_2$), 1.47 (ddd, *J* = 13.4, 10.8, 5.3, 1H, CHC$H_A$$H_B$CH), 0.99 (s, 9H, C(C$H_3)_3$), 0.89 – 0.79 (m, 1H, CHC$H_A$$H_B$CH), 0.75 (d, *J* = 6.7, 3H, CH(C$H_3)_A$$(CH_3)_B$), 0.72 (d, *J* = 6.6, 3H, CH$(CH_3)_A$(C$H_3)_B$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 171.8 (*C*=O), 162.2 (*C*=O), 150.0 (C_{Ar}), 133.8 (2×CH_{Ar}), 122.9 (2×CH_{Ar}), 118.5 (*C*≡N), 107.5 (C_{Ar}), 82.5 (*C*HC$(CH_3)_3$), 60.6 (N*C*HCH_2), 42.2 (NCH*C*H_2), 39.7 (N*C*H_3), 37.0 (*C*$(CH_3)_3$), 31.6 (N*C*H_3), 27.1 (C(*C*$H_3)_3$), 25.2 (*C*H$(CH_3)_2$), 23.5 (CH(*C*$H_3)_A$$(CH_3)_B$), 21.6 (CH$(CH_3)_A$(*C*$H_3)_B$); **IR**: ν_{max} = 2957, 2927, 2870 (C–H), 2225 (C≡N), 1699 (C=O), 1662 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{21}H_{31}O_2N_4$ ([M+H]$^+$) 371.2442, found 371.2441.

(2*R*,5*S*)-2-(*tert*-Butyl)-*N*-(4-chlorophenyl)-5-isobutyl-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide (S52)



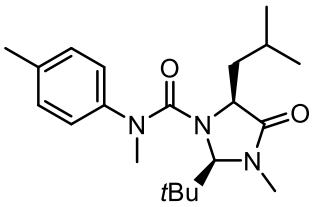
Following general procedure 4, imine **S9** (690 mg, 3.25 mmol), *N*-(4-chlorophenyl)-*N*-methylcarbamoyl chloride (895 mg, 4.39 mmol, 1.35 eq.) and DMAP (20 mg, 0.163 mmol) were dissolved in DCE (16.00 mL, 0.2 M) and reacted for 88 h. Purification by flash column chromatography (SiO_2, 2:1→1:1 Pet.Ether:EtOAc) gave the title compound (558 mg, 1.47 mmol, 45%) as a white solid. **S52**: $\mathbf{R_f}$ (2:1 Pet.Ether:EtOAc): 0.20; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.28 – 7.25 (m, 2H, Ar*H*), 7.00 – 6.97 (m, 2H, Ar*H*), 5.21 (s, 1H, C*H*C$(CH_3)_3$), 3.83 (dd, *J* = 11.3, 3.6, 1H, NC*H*CH_AH_B), 3.06 (s, 3H, NCH_3), 2.79 (s, 3H, NCH_3), 1.79 – 1.60 (m, 1H, CH_2C*H*$(CH_3)_2$), 1.24 (ddd, *J* = 13.4, 11.3, 5.3, 1H, CHCH_AH$_B$CH), 0.90 (s, 9H, C(C$H_3)_3$), 0.65 (d, *J* = 6.6, 3H, CH(C$H_3)_A$$(CH_3)_B$), 0.62 (d, *J* = 6.7, 3H, CH$(CH_3)_A$(C$H_3)_B$), 0.37 (ddd, *J* = 13.1, 9.6, 3.4, 1H, CHC$H_A$$H_B$CH); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 171.9 (*C*=O), 162.9 (*C*=O), 144.5 (C_{Ar}), 131.4 (C_{Ar}), 129.8 (2×*C*H$_{Ar}$), 126.9 (2×*C*H$_{Ar}$), 82.1 (*C*HC$(CH_3)_3$), 60.9 (N*C*HCH_2), 41.4 (NCH*C*H_2), 41.0 (N*C*H_3), 36.6 (*C*$(CH_3)_3$), 31.3 (N*C*H_3), 26.9 (C(*C*$H_3)_3$), 24.7 (*C*H$(CH_3)_2$), 23.5 (CH$(CH_3)_A$(*C*$H_3)_B$), 21.2 (CH(*C*$H_3)_A$$(CH_3)_B$); **IR**: ν_{max} = 2957, 2870 (C–H), 1699 (C=O), 1655 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{20}H_{30}O_2N_3ClNa$ ([M+Na]$^+$) 402.1919, found 420.1920.

(2*R*,5*S*)-2-(*tert*-Butyl)-*N*-(4-fluorophenyl)-5-isobutyl-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide (S53)



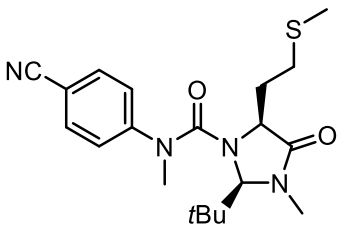
Following general procedure 4, imine **S9** (822 mg, 3.87 mmol), *N*-(4-fluorophenyl)-*N*-methylcarbamoyl chloride (980 mg, 5.23 mmol, 1.35 eq.) and DMAP (24 mg, 0.194 mmol) were dissolved in DCE (19.00 mL, 0.2 M) and reacted for 88 h. Purification by flash column chromatography (SiO_2, 2:1→5:4 Pet.Ether:EtOAc) gave the title compound (667 mg, 1.86 mmol, 48%) as a white solid. **S53**: $\mathbf{R_f}$ (3:2 Pet.Ether:EtOAc): 0.24; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.13 – 7.04 (m, 4H, Ar*H*), 5.31 (s, 1H, C*H*C$(CH_3)_3$), 3.93 (dd, *J* = 11.4, 3.7, 1H, NC*H*CH_AH_B), 3.14 (s, 3H, NCH_3), 2.87 (s, 3H, NCH_3), 1.89 – 1.74 (m, 1H, CH_2C*H*$(CH_3)_2$), 1.31 (ddd, *J* = 13.3, 11.5, 5.1, 1H, CHCH_AH$_B$CH), 0.98 (s, 9H, C(C$H_3)_3$), 0.75 (d, *J* = 6.6, 3H, CH(C$H_3)_A$$(CH_3)_B$), 0.69 (d, *J* = 6.7, 3H, CH$(CH_3)_A$(C$H_3)_B$), 0.37 (ddd, *J* = 13.3, 9.7, 3.6, 1H, CHC$H_A$$H_B$CH); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 172.3 (*C*=O), 163.4 (*C*=O), 160.8 (d, $^1J_{C–F}$ = 246.9, C_{Ar}F), 142.3 (d, $^4J_{C–F}$ = 3.1, C_{Ar}), 127.8 (d, $^3J_{C–F}$ = 8.2, 2×*C*H$_{Ar}$), 116.8 (d, $^2J_{C–F}$ = 22.5, 2×*C*H$_{Ar}$), 82.3 (*C*HC$(CH_3)_3$), 61.2 (N*C*HCH_2), 41.7 (N*C*H_3), 41.6 (NCH*C*H_2), 36.7 (*C*$(CH_3)_3$), 31.5 (N*C*H_3), 27.2 (C(*C*$H_3)_3$), 24.8 (*C*H$(CH_3)_2$), 23.8 (CH$(CH_3)_A$(*C*$H_3)_B$), 21.3 (CH(*C*$H_3)_A$$(CH_3)_B$); **IR**: ν_{max} = 2957, 2871 (C–H), 1700 (C=O), 1656 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{20}H_{31}O_2N_3F$ ([M+H]$^+$) 364.2395, found 364.2393.

(2*R*,5*S*)-2-(*tert*-Butyl)-5-isobutyl-*N*,3-dimethyl-4-oxo-*N*-(*p*-tolyl)imidazolidine-1-carboxamide (S54)



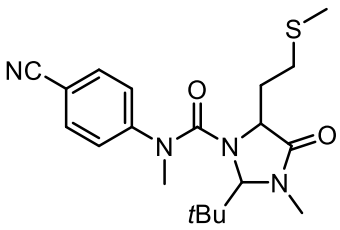
Following general procedure 4, imine **S9** (877 mg, 4.13 mmol), *N*-(*p*-tolyl)-*N*-methylcarbamoyl chloride (1024 mg, 5.58 mmol, 1.35 eq.) and DMAP (25 mg, 0.207 mmol) were dissolved in DCE (21.00 mL, 0.2 M) and reacted for 88 h. Purification by flash column chromatography (SiO_2, 2:1→3:2 Pet.Ether:EtOAc) gave the title compound (505 mg, 1.40 mmol, 34%) as a white solid. **S54**: $\mathbf{R_f}$ (2:1 Pet.Ether:EtOAc): 0.19; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.17 (d, *J* = 8.0, 2H, Ar*H*), 7.00 (d, *J* = 8.3, 2H, Ar*H*), 5.29 (s, 1H, C*H*C$(CH_3)_3$), 3.91 (dd, *J* = 11.3, 3.7, 1H, NC*H*CH_AH_B), 3.14 (s, 3H, NCH_3), 2.85 (s, 3H, NCH_3), 2.34 (s, 3H, CH_3), 1.83 – 1.67 (m, 1H, CH_2C*H*$(CH_3)_2$), 1.24 (ddd, *J* = 13.3, 11.4, 5.3, 1H, CHCH_AH_BCH), 0.97 (s, 9H, C(C$H_3)_3$), 0.72 (d, *J* = 6.6, 3H, CH(C$H_3)_A$$(CH_3)_B$), 0.65 (d, *J* = 6.7, 3H, CH$(CH_3)_A$(C$H_3)_B$), 0.36 (ddd, *J* = 13.3, 9.6, 3.7, 1H, CHCH_AH_BCH); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 172.5 (*C*=O), 163.4 (*C*=O), 143.5 (C_{Ar}), 136.2 (C_{Ar}), 130.5 (2×CH_{Ar}), 126.1 (2×CH_{Ar}), 82.2 (*C*HC$(CH_3)_3$), 61.3 (N*C*HCH_2), 41.4 (N*C*H_3 and NCH*C*H_2), 36.7 (*C*$(CH_3)_3$), 31.4 (N*C*H_3), 27.2 (C(*C*$H_3)_3$), 24.8 (*C*H$(CH_3)_2$), 23.7 (CH$(CH_3)_A$(*C*$H_3)_B$), 21.3 (CH(*C*$H_3)_A$$(CH_3)_B$), 21.0 (*C*$H_3$); **IR**: ν_{max} = 2955, 2869 (C–H), 1702 (C=O), 1652 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{21}H_{34}O_2N_3$ ([M+H]$^+$) 360.2646, found 360.2643.

(2*R*,5*S*)-2-(*tert*-Butyl)-*N*-(4-isocyanophenyl)-*N*,3-dimethyl-5-(2-(methylthio)ethyl)-4-oxoimidazolidine-1-carboxamide (S55)



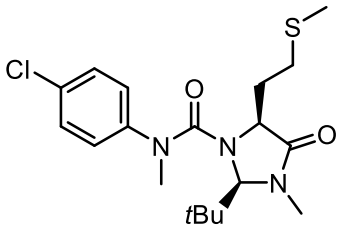
Following general procedure 4, imine **S12** (777 mg, 3.37 mmol), *N*-(4-cyanophenyl)-*N*-methylcarbamoyl chloride (886 mg, 4.55 mmol, 1.35 eq.) and DMAP (21 mg, 0.169 mmol) were dissolved in DCE (17.00 mL, 0.2 M) and reacted for 88 h. Purification by flash column chromatography (SiO_2, 1:1→2:1 EtOAc:Pet.Ether) gave the title compound (585 mg, 1.51 mmol, 45%) as a pale yellow solid. **S55**: $\mathbf{R_f}$ (2:1 EtOAc:Pet.Ether): 0.25; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.68 (d, *J* = 8.5, 2H, Ar*H*), 7.20 (d, *J* = 8.4, 2H, Ar*H*), 5.29 (s, 1H, C*H*C$(CH_3)_3$), 3.89 (dd, *J* = 10.9, 2.0, 1H, C*H*CH_AH_B), 3.19 (s, 3H, NCH_3), 2.90 (s, 3H, NCH_3), 2.72 (ddd, *J* = 12.4, 11.5, 4.8, 1H, CH_AH_BC$H_{A'}H_{B'}$SCH_3), 2.19 (ddd, *J* = 12.6, 10.7, 6.1, 1H, CH_AH_BC$H_{A'}H_{B'}$SCH_3), 1.94 (s, 3H, SCH_3), 1.67 (dtd, *J* = 13.6, 10.9, 4.8, 1H, CHC$H_AH_B$$CH_2$), 0.97 (s, 9H, C(C$H_3)_3$), 0.84 (br. s, 1H, CHC$H_AH_B$$CH_2$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 171.6 (*C*=O), 162.4 (*C*=O), 149.9 (C_{Ar}), 134.0 (2×CH_{Ar}), 125.1 (2×CH_{Ar}), 118.2 (*C*≡N), 109.5 (C_{Ar}), 82.7 (*C*HC$(CH_3)_3$), 61.6 (N*C*HCH_2), 40.4 (N*C*H_3), 37.0 (*C*$(CH_3)_3$), 33.7 (NCH*C*H_2), 31.6 (N*C*H_3), 31.2 (*C*H_2SCH_3), 26.9 (C(*C*$H_3)_3$), 15.8 (S*C*H_3); **IR**: ν_{max} = 2967, 2918, 2873 (C–H), 2227 (C≡N), 1696 (C=O), 1662 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{20}H_{28}O_2N_4SNa$ ([M+Na]$^+$) 411.1825, found 411.1825.

rac-2-(*tert*-Butyl)-*N*-(4-isocyanophenyl)-*N*,3-dimethyl-5-(2-(methylthio)ethyl)-4-oxoimidazolidine-1-carboxamide (S56)



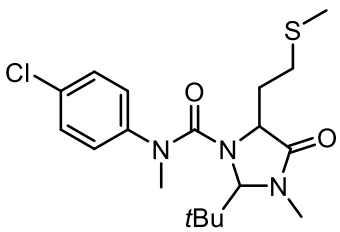
Following general procedure 4, imine **S13** (600 mg, 2.60 mmol), *N*-(4-cyanophenyl)-*N*-methylcarbamoyl chloride (760 mg, 3.91 mmol, 1.5 eq.) and DMAP (16 mg, 0.130 mmol) were dissolved in DCE (13.00 mL, 0.2 M) and reacted for 72 h. Purification by flash column chromatography gave the title compound (486 mg, 1.25 mmol, 48%) as a pale yellow solid. For full data see compound **S55**.

(2*R*,5*S*)-2-(*tert*-Butyl)-*N*-(4-chlorophenyl)-*N*,3-dimethyl-5-(2-(methylthio)ethyl)-4-oxoimidazolidine-1-carboxamide (S57)



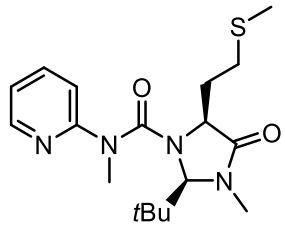
Following general procedure 4, imine **S12** (766 mg, 3.33 mmol), *N*-(4-chlorophenyl)-*N*-methylcarbamoyl chloride (916 mg, 4.49 mmol, 1.35 eq.) and DMAP (20 mg, 0.166 mmol) were dissolved in DCE (16.00 mL, 0.2 M) and reacted for 88 h. Purification by flash column chromatography (SiO_2, 1:1→2:1 EtOAc:Pet.Ether) gave the title compound (607 mg, 1.53 mmol, 46%) as a white solid. **S57**: $\mathbf{R_f}$ (1:1 Pet.Ether:EtOAc): 0.20; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.29 – 7.22 (m, 2H, Ar*H*), 7.04 – 6.98 (m, 2H, Ar*H*), 5.34 (s, 1H, C*H*C$(CH_3)_3$), 3.64 (dd, *J* = 11.4, 2.0, 1H, C*H*CH_AH_B), 3.01 (s, 3H, NCH_3), 2.79 (s, 3H, NCH_3), 2.62 (td, *J* = 12.7, 4.4, 1H, $CH_2CH_AH_BSCH_3$), 1.93 (td, *J* = 12.0, 5.2, 1H, $CH_2CH_AH_BSCH_3$), 1.79 (s, 3H, SCH_3), 1.38 (dtd, *J* = 12.7, 11.6, 4.4, 1H, $CHCH_AH_BCH_2$), 0.84 (s, 9H, C(CH_3)$_3$), 0.42 (tdd, *J* = 12.8, 4.9, 1.7, 1H, $CHCH_AH_BCH_2$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 171.7 (*C*=O), 162.7 (*C*=O), 144.2 (C_{Ar}), 132.5 (C_{Ar}), 130.1 (2×CH_{Ar}), 127.7 (2×CH_{Ar}), 82.1 (*C*HC$(CH_3)_3$), 61.7 (NCHCH_2), 41.2 (NCH_3), 36.4 (*C*$(CH_3)_3$), 33.9 (NCH*C*H_2), 31.1 (NCH_3), 30.7 (*C*H_2SCH_3), 26.6 (C(*C*H_3)$_3$), 15.3 (SCH_3); **IR**: ν_{max} = 2973, 2918, 2873 (C–H), 1694 (C=O), 1656 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{19}H_{28}O_2N_3ClSNa$ ([M+Na]$^+$) 420.1483, found 420.1483.

rac-2-(*tert*-Butyl)-*N*-(4-chlorophenyl)-*N*,3-dimethyl-5-(2-(methylthio)ethyl)-4-oxoimidazolidine-1-carboxamide (S58)



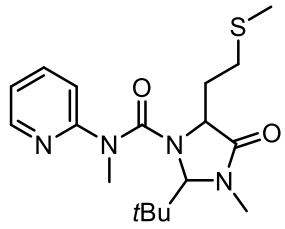
Following general procedure 4, imine **S13** (600 mg, 2.60 mmol), *N*-(4-chlorophenyl)-*N*-methylcarbamoyl chloride (797 mg, 3.91 mmol, 1.5 eq.) and DMAP (16 mg, 0.130 mmol) were dissolved in DCE (13.00 mL, 0.2 M) and reacted for 72 h. Purification by flash column chromatography gave the title compound (508 mg, 1.28 mmol, 49%) as a white solid. For full data see compound **S57**.

(2*R*,5*S*)-2-(*tert*-Butyl)-*N*,3-dimethyl-5-(2-(methylthio)ethyl)-4-oxo-*N*-(pyridin-2-yl)imidazolidine-1-carboxamide (S59)



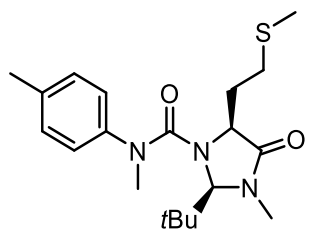
Following general procedure 4, imine **S12** (829 mg, 3.60 mmol), *N*-(pyridin-2-yl)-*N*-methylcarbamoyl chloride (829 mg, 4.86 mmol, 1.35 eq.) and DMAP (22 mg, 0.180 mmol) were dissolved in DCE (18.00 mL, 0.2 M) and reacted for 44 h. Purification by flash column chromatography (SiO_2, 98:2 EtOAc:MeOH) gave the title compound (546 mg, 1.50 mmol, 42%) as a pale yellow solid. **S59**: **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 8.25 – 8.21 (m, 1H, Ar*H*), 7.62 – 7.55 (m, 1H, Ar*H*), 6.96 – 6.92 (m, 1H, Ar*H*), 6.85 (d, *J* = 8.2, 1H, Ar*H*), 4.99 (s, 1H, C*H*C$(CH_3)_3$), 4.02 (dd, *J* = 9.9, 3.5, 1H, C*H*CH_AH_B), 3.12 (s, 3H, NCH_3), 2.81 (s, 3H, NCH_3), 2.69 (ddd, *J* = 13.0, 11.2, 4.9, 1H, $CH_AH_BCH_{A'}H_{B'}SCH_3$), 2.34 (ddd, *J* = 13.0, 10.6, 6.1, 1H, $CH_AH_BCH_{A'}H_{B'}SCH_3$), 1.89 (s, 3H, SC$H_3$), 1.73 (dtd, *J* = 14.8, 10.3, 4.9, 1H, $CHCH_AH_BCH_2$), 1.16 (br. s, 1H, $CHCH_AH_BCH_2$), 0.90 (s, 9H, C$(CH_3)_3$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 171.8 (*C*=O), 162.5 (*C*=O), 157.8 (C_{Ar}), 148.8 (CH_{Ar}), 138.3 (CH_{Ar}), 119.3 (CH_{Ar}), 115.1 (CH_{Ar}), 82.5 (*C*HC$(CH_3)_3$), 60.8 (N*C*HCH_2), 37.3 (N*C*H_3), 37.0 (*C*$(CH_3)_3$), 33.4 (NCH*C*H_2), 31.3 (N*C*H_3), 31.0 (*C*H_2SCH_3), 26.6 (C(*C*$H_3)_3$), 15.4 (S*C*H_3); **IR**: ν_{max} = 2960, 2916, 2873 (C–H), 1696 (C=O), 1667 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{18}H_{29}O_2N_4S$ ($[M+H]^+$) 365.2006, found 365.2003.

rac-2-(*tert*-Butyl)-*N*,3-dimethyl-5-(2-(methylthio)ethyl)-4-oxo-*N*-(pyridin-2-yl)imidazolidine-1-carboxamide (S60)



Following general procedure 4, imine **S13** (600 mg, 2.60 mmol), *N*-(pyridin-2-yl)-*N*-methylcarbamoyl chloride (666 mg, 3.91 mmol, 1.5 eq.) and DMAP (16 mg, 0.130 mmol) were dissolved in DCE (13.00 mL, 0.2 M) and reacted for 72 h. Purification by flash column chromatography gave the title compound (419 mg, 1.15 mmol, 44%) as a pale yellow solid. For full data see compound **S59**.

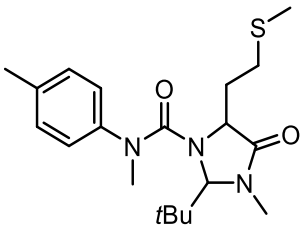
(2*R*,5*S*)-2-(*tert*-Butyl)-*N*,3-dimethyl-5-(2-(methylthio)ethyl)-4-oxo-*N*-(*p*-tolyl)imidazolidine-1-carboxamide (S61)



Following general procedure 4, imine **S12** (815 mg, 3.54 mmol), *N*-(*p*-tolyl)-*N*-methylcarbamoyl chloride (877 mg, 4.78 mmol, 1.35 eq.) and DMAP (22 mg, 0.177 mmol) were dissolved in DCE (18.00 mL, 0.2 M) and reacted for 88 h. Purification by flash column chromatography (SiO_2, 1:1 Pet.Ether:EtOAc) gave the title compound (729 mg, 1.93 mmol, 55%) as a white solid. **S61**: **R_f** (1:1 Pet.Ether:EtOAc): 0.21; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.19 (d, *J* = 8.1, 2H, Ar*H*), 7.04 (d, *J* = 8.2, 2H, Ar*H*), 5.50 (s, 1H, C*H*C$(CH_3)_3$), 3.70 (dd, *J* = 11.5, 2.0, 1H, C*H*CH_AH_B), 3.12 (s, 3H, NCH_3), 2.90 (s, 3H,

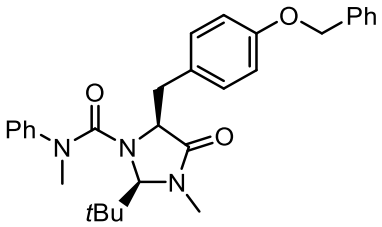
NCH_3), 2.69 (td, J = 12.8, 4.4, 1H, $CH_2CH_AH_BSCH_3$), 2.35 (s, 3H, CH_3), 1.99 (td, J = 12.3, 4.8, 1H, $CH_2CH_AH_BSCH_3$), 1.87 (s, 3H, SCH_3), 1.40 (dtd, J = 13.1, 12.1, 4.5, 1H, $CHCH_AH_BCH_2$), 0.95 (s, 9H, $C(CH_3)_3$), 0.30 (tdd, J = 12.9, 4.6, 1.9, 1H, $CHCH_AH_BCH_2$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 172.4 (*C*=O), 163.3 (*C*=O), 143.1 (C_{Ar}), 137.5 (C_{Ar}), 130.8 (2×CH_{Ar}), 126.8 (2×CH_{Ar}), 82.4 ($CHC(CH_3)_3$), 62.3 ($NCHCH_2$), 41.6 (NCH_3), 36.7 ($C(CH_3)_3$), 34.1 ($NCHCH_2$), 31.5 (NCH_3), 31.4 (CH_2SCH_3), 26.9 ($C(CH_3)_3$), 21.1 (CH_3), 15.3 (SCH_3); **IR**: ν_{max} = 2958, 2918, 2873 (C–H), 1697 (C=O), 1655 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{20}H_{32}O_2N_3S$ ($[M+H]^+$) 378.2210, found 378.2208.

<u>*rac*-2-(*tert*-Butyl)-*N*,3-dimethyl-5-(2-(methylthio)ethyl)-4-oxo-*N*-(*p*-tolyl)imidazolidine-1-carboxamide (S62)</u>



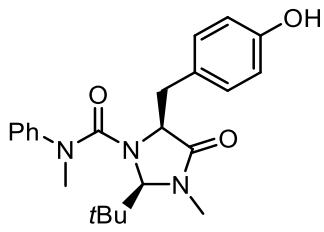
Following general procedure 4, imine **S13** (600 mg, 2.60 mmol), *N*-(*p*-tolyl)-*N*-methylcarbamoyl chloride (717 mg, 3.91 mmol, 1.5 eq.) and DMAP (16 mg, 0.130 mmol) were dissolved in DCE (13.00 mL, 0.2 M) and reacted for 72 h. Purification by flash column chromatography gave the title compound (580 mg, 1.54 mmol, 59%) as a pale yellow solid. For full data see compound **S61**.

<u>(2*R*,5*S*)-5-(4-(Benzyloxy)benzyl)-2-(tert-butyl)-*N*,3-dimethyl-4-oxo-*N*-phenylimidazolidine-1-carboxamide (S63)</u>



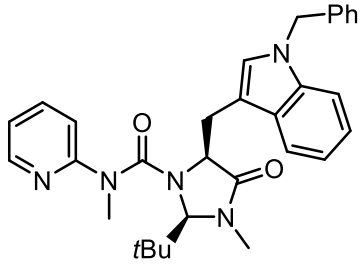
Following general procedure 5, *cis*-**S28** (320 mg, 0.771 mmol), *N*-methylaniline (418 µL, 3.86 mmol, 5.0 eq.), 2,6-lutidine (179 µL, 1.54 mmol) and KI (140 mg, 0.848 mmol) were reacted in DCM/toluene (2.2 mL, 0.35 M, 4:1) at 60 °C for 18 h. Purification by flash column chromatography (SiO_2, 1:1 Pet.Ether:EtOAc) gave the title compound (318 mg, 0.655 mmol, 85%) as a white solid. **S63**: **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.43 (d, J = 7.3, 2H, Ph*H*), 7.38 (t, J = 7.5, 2H, Ph*H*), 7.35 – 7.29 (m, 3H, Ph*H*), 7.18 (t, J = 7.4, 1H, Ph*H*), 7.13 (d, J = 7.1, 2H, Ph*H*), 6.99 (d, J = 8.4, 2H, Ph*H*), 6.85 (d, J = 8.7, 2H, Ph*H*), 5.27 (s, 1H, $CHC(CH_3)_3$), 5.02 (s, 2H, OCH_2Ph), 4.21 (dd, J = 10.7, 3.1, 1H, $CHCH_AH_B$), 3.19 (s, 3H, NCH_3), 2.87 (s, 3H, NCH_3), 2.59 (dd, J = 14.1, 10.7, 1H, $CHCH_AH_B$), 2.06 (dd, J = 14.2, 3.6, 1H, $CHCH_AH_B$), 1.04 (s, 9H, $C(CH_3)_3$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 171.5 (*C*=O), 163.0 (*C*=O), 157.2 ($C_{Ar}O$), 145.9 (C_{Ph}), 137.2 (C_{Ph}), 130.1 (2×CH_{Ar}), 130.0 (2×CH_{Ar}), 129.9 (C_{Ar}), 128.5 (2×CH_{Ph}), 127.8 (CH_{Ph}), 127.5 (2×CH_{Ph}), 126.3 (CH_{Ph}), 125.7 (2×CH_{Ph}), 114.3 (2×CH_{Ar}), 82.1 ($CHC(CH_3)_3$), 69.9 (OCH_2Ph), 63.1 ($CHCH_2$), 41.1 (NCH_3), 38.4 ($CHCH_2$), 36.8 ($C(CH_3)_3$), 31.4 (NCH_3), 26.9 ($C(CH_3)_3$); **IR**: ν_{max} = 3062, 3033, 2959, 2930, 2871 (C–H), 1703 (C=O), 1654 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{30}H_{36}O_3N_3$ ($[M+H]^+$) 486.2751, found 486.2749.

(2*R*,5*S*)-2-(*tert*-Butyl)-5-(4-hydroxybenzyl)-*N*,3-dimethyl-4-oxo-*N*-phenylimidazolidine-1-carboxamide (S64)



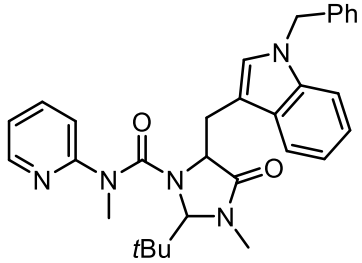
To a solution of urea **S63** (150 mg, 0.309 mmol, 1.0 eq.) in anhydrous THF (3.00 mL, 0.1 M) was added Pd/C (16 mg, 0.015 mmol, 10% *w*/*w*, 0.05 eq.). The suspension was stirred under a hydrogen atmosphere for 18 h. The reaction mixture was filtered over Celite®, washed through with DCM and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 EtOAc:Pet.Ether) gave the title compound (116 mg, 0.294 mmol, 95%) as a white solid. **S64**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.35 (t, *J* = 7.7, 2H, Ph*H*), 7.24 – 7.12 (m, 3H, Ph*H*), 6.76 (d, *J* = 7.9, 2H, Ar*H*), 6.47 (d, *J* = 7.9, 2H, Ar*H*), 5.38 (s, 1H, C*H*C$(CH_3)_3$), 4.22 (dd, *J* = 11.6, 3.6, 1H, C*H*CH_AH_B), 3.21 (s, 3H, NC*H*$_3$), 2.89 (s, 3H, NC*H*$_3$), 2.43 (t, *J* = 12.6, 1H, CHC*H*$_A$H$_B$), 1.84 (d, *J* = 13.4, 1H, CHCH$_A$*H*$_B$), 1.05 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 172.3 (*C*=O), 163.2 (*C*=O), 155.1 (*C*$_{Ar}$O), 145.9 (*C*$_{Ph}$), 130.2 (2×*C*H$_{Ar}$), 130.0 (2×*C*H$_{Ar}$), 127.8 (*C*$_{Ar}$), 126.8 (*C*H$_{Ph}$), 126.3 (2×*C*H$_{Ph}$), 115.3 (2×*C*H$_{Ar}$), 82.5 (*C*HC$(CH_3)_3$), 63.7(*C*HCH$_2$), 41.5 (N*C*H$_3$), 38.3 (CH*C*H$_2$), 36.8 (*C*$(CH_3)_3$), 31.7 (N*C*H$_3$), 27.2 (C(*C*H$_3$)$_3$); **IR**: ν_{max} = 3319 (O–H), 2967, 2247 (C–H), 1683 (C=O), 1653 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{24}H_{29}O_3N_3Na$ ([M+Na]$^+$) 418.2101, found 418.2081.

(2*R*,5*S*)-5-((1-Benzyl-1*H*-indol-3-yl)methyl)-2-(*tert*-butyl)-*N*,3-dimethyl-4-oxo-*N*-(pyridin-2-yl)imidazolidine-1-carboxamide (S65)



Following general procedure 4, imine **S21** (800 mg, 2.13 mmol), *N*-(pyridin-2-yl)-*N*-methylcarbamoyl chloride (543 mg, 3.19 mmol, 1.5 eq.) and DMAP (13 mg, 0.106 mmol, 0.05 eq.) were dissolved in DCE (11.00 mL, 0.2 M) and reacted for 63 h. Purification by flash column chromatography (SiO_2, 3:2→1:1 Pet.Ether:EtOAc) gave the title compound (727 mg, 1.43 mmol, 67%) as a white solid. **S65**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 8.09 – 8.06 (m, 1H, Ar*H*), 7.44 (d, *J* = 7.9, 1H, Ar*H*), 7.39 (ddd, *J* = 8.5, 7.3, 2.0, 1H, Ar*H*), 7.29 – 7.18 (m, 4H, Ar*H*), 7.13 – 7.08 (m, 3H, Ar*H*), 7.07 (s, 1H, C=C*H*), 7.02 – 6.96 (m, 1H, Ar*H*), 6.76 (dd, *J* = 7.2, 5.0, 1H, Ar*H*), 6.39 (d, *J* = 8.3, 1H, Ar*H*), 5.23 (s, 2H, NC*H*$_2$Ph), 5.03 (s, 1H, C*H*C$(CH_3)_3$), 4.43 (dd, *J* = 8.0, 5.4, 1H, C*H*CH_AH_B), 3.18 (dd, *J* = 14.9, 8.0, 1H, CHC*H*$_A$H$_B$), 2.97 (dd, *J* = 5.5, 14.9, 1H, CHCH$_A$*H*$_B$), 2.94 (s, 3H, NC*H*$_3$), 2.69 (s, 3H, NC*H*$_3$), 1.08 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 172.0 (*C*=O), 163.1 (*C*=O), 157.7 (*C*$_{Ar}$), 148.5 (*C*H$_{Ar}$), 138.1 (*C*H$_{Ar}$), 137.8 (*C*$_{Ar}$), 136.6 (*C*$_{Ar}$), 128.8 (2×*C*H$_{Ar}$), 128.3 (*C*$_{Ar}$), 127.7 (*C*H$_{Ar}$), 127.2 (C=*C*H), 127.0 (2×*C*H$_{Ar}$), 121.7 (*C*H$_{Ar}$), 119.5 (*C*H$_{Ar}$), 119.1 (*C*H$_{Ar}$), 117.8 (*C*H$_{Ar}$), 112.3 (*C*H$_{Ar}$), 111.4 (*C*=CH), 109.6 (*C*H$_{Ar}$), 83.0 (*C*HC$(CH_3)_3$), 61.7 (*C*HCH$_2$), 50.1 (N*C*H$_2$Ph), 37.4 (*C*$(CH_3)_3$), 36.1 (N*C*H$_3$), 31.6 (N*C*H$_3$), 29.8 (CH*C*H$_2$), 27.2 (C(*C*H$_3$)$_3$); **IR**: ν_{max} = 2961, 2244 (C–H), 1697 (C=O), 1660 (C=O); **HRMS** (ESI+): *m/z* calcd for $C_{31}H_{35}O_2N_5Na$ ([M+Na]$^+$) 532.2683, found 532.2674.

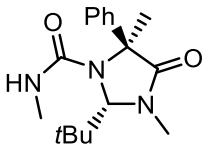
rac-5-((1-Benzyl-1*H*-indol-3-yl)methyl)-2-(*tert*-butyl)-*N*,3-dimethyl-4-oxo-*N*-(pyridin-2-yl)imidazolidine-1-carboxamide (S66)



Following general procedure 4, imine **S22** (563 mg, 1.50 mmol), *N*-(pyridin-2-yl)-*N*-methylcarbamoyl chloride (384 mg, 2.25 mmol, 1.5 eq.) and DMAP (9 mg, 0.075 mmol, 0.05 eq.) were dissolved in DCE (7.50 mL, 0.2 M) and reacted for 72 h. Purification by flash column chromatography gave the title compound (518 mg, 1.02 mmol, 68%) as a white solid. For full data see compound **S65**.

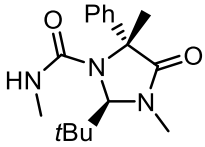
Synthesis of Rearranged Ureas

(2*S*,5*S*)-2-(*tert*-Butyl)-*N*,3,5-trimethyl-4-oxo-5-phenylimidazolidine-1-carboxamide ((*S*) 4-Ala-a)



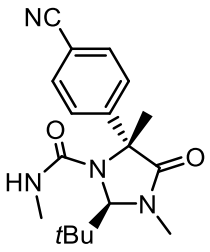
Following general procedure 6, KHMDS (2.47 mL, 2.47 mmol, 1.0 M in THF) was added to a solution of urea **S29** (500 mg, 1.65 mmol) in THF (16.5 mL). The title compound (490 mg, 1.62 mmol, 98%) was yielded as a white solid without further purification. **(*S*) 4-Ala-a**: **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.33 (t, *J* = 7.6, 2H, Ph*H*), 7.25 (t, *J* = 7.3, 1H, Ph*H*), 7.18 (d, *J* = 7.4, 2H, Ph*H*), 5.61 (s, 1H, C*H*C$(CH_3)_3$), 3.86 (br. s, 1H, N*H*CH_3), 3.04 (s, 3H, NC*H*$_3$), 2.28 (d, *J* = 4.8, 3H, NHC*H*$_3$), 1.99 (s, 3H, CC*H*$_3$), 1.05 (s, 9H, C(C*H*$_3)_3$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 172.9 (*C*=O), 158.6 (*C*=O), 141.8 (C_{Ph}), 129.2 (2×CH_{Ph}), 128.3 (CH_{Ph}), 125.2 (2×CH_{Ph}), 80.7 (*C*HC$(CH_3)_3$), 66.0 (*C*CH_3), 38.7 (*C*$(CH_3)_3$), 32.2 (N*C*H_3), 26.9 (NH*C*H_3), 26.8 (C(*C*$H_3)_3$), 23.5 (C*C*H_3); **IR**: ν_{max} = 3415 (N–H), 2960 (C–H), 1698 (C=O), 1656 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{17}H_{26}O_2N_3$ ([M+H]$^+$) 304.2025, found 304.2029; **HPLC**: Chiralcel® OD-H, 25 °C, 0.8 mL/min, Hexane/IPA (80:20), 210 nm, t_R = 6.59 (0.7%), 7.92 (99.3%) min, >99:1 *er*.

(2*R*,5*R*)-2-(*tert*-Butyl)-*N*,3,5-trimethyl-4-oxo-5-phenylimidazolidine-1-carboxamide ((*R*) 4-Ala-a)



Following general procedure 6, KHMDS (0.27 mL, 0.272 mmol, 1.0 M in THF) was added to a solution of urea **S30** (55 mg, 0.181 mmol) in THF (1.80 mL). The title compound (52 mg, 0.172 mmol, 95%) was yielded as a white solid without further purification. **(*R*) 4-Ala-a**: **HPLC**: Chiralcel® OD-H, 25 °C, 0.8 mL/min, Hexane/IPA (80:20), 210 nm, t_R = 6.67 (100%) min, >99:1 *er*. For full data see compound **64**.

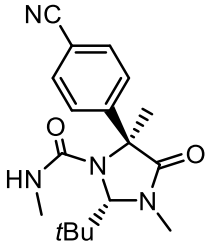
(2*R*,5*R*)-2-(*tert*-Butyl)-5-(4-cyanophenyl)-*N*,3,5-trimethyl-4-oxoimidazolidine-1-carboxamide ((*R*) 4-Ala-b)



Following a similar method to general procedure 6, KHMDS (0.35 mL, 0.350 mmol, 1.0 M in THF, 2.5 eq.) was added to a solution of urea **S31** (46 mg, 0.140 mmol) in THF (1.40 mL). The title compound (44 mg, 0.134 mmol, 96%) was yielded as a white solid without further purification. **(*R*) 4-Ala-b**: **R_f** (1:1 Pet.Ether:EtOAc): 0.10; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.66 – 7.60 (m, 2H, Ar*H*), 7.34 – 7.28 (m, 2H, Ar*H*), 5.61 (s, 1H, C*H*C$(CH_3)_3$), 3.95 (br. s, 1H, N*H*CH_3),

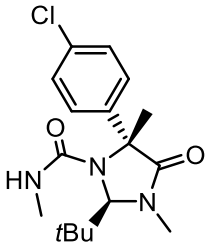
3.04 (s, 3H, NCH_3), 2.36 (d, J = 4.6, 3H, NHCH_3), 2.03 (s, 3H, CCH_3), 1.04 (s, 9H, C(CH_3)$_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 171.7 (*C*=O), 158.1 (*C*=O), 147.2 (C_{Ar}), 132.8 (2×CH_{Ar}), 126.2 (2×CH_{Ar}), 118.4 (*C*≡N), 112.2 (C_{Ar}), 80.7 (*C*HC(CH$_3$)$_3$), 66.2 (*C*CH$_3$), 38.7 (*C*(CH$_3$)$_3$), 32.3 (N*C*H$_3$), 26.9 (NH*C*H$_3$), 26.6 (C(*C*H$_3$)$_3$), 23.9 (C*C*H$_3$); **IR**: ν_{max} = 3401 (N–H), 2962, 2930 (C–H), 2229 (C≡N), 1698 (C=O), 1660 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{18}H_{25}O_2N_4$ ([M+H]$^+$) 329.1972, found 329.1968; **HPLC**: Chiralcel® OD-H, 25 °C, 1.0 mL/min, Hexane/IPA (80:20), 230 nm, t_R = 8.78 (96.4%), 10.25 (3.6%) min, 96:4 *er*.

(2*S*,5*S*)-2-(*tert*-Butyl)-5-(4-cyanophenyl)-*N*,3,5-trimethyl-4-oxoimidazolidine-1-carboxamide ((*S*) 4-Ala-b)



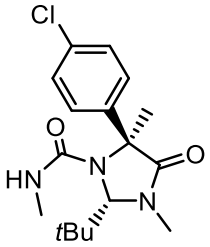
Following general procedure 7, a solution of *trans*-**S23** (200 mg, 0.859 mmol) and 4-(methylamino)benzonitrile (125 mg, 0.945 mmol) in THF (8.60 mL) was treated with 2 portions of KHMDS (2×1.03 mL, 2.06 mmol, 1.0 M in THF). Purification by flash column chromatography gave the title compound (224 mg, 0.682 mmol, 79%) as a white solid. ***(S)* 4-Ala-b**: **HPLC**: Chiralcel® OD-H, 25 °C, 1.0 mL/min, Hexane/IPA (80:20), 230 nm, t_R = 8.89 (3.3%), 10.21 (96.7%) min, 97:3 *er*. For full data see compound **66**.

(2*R*,5*R*)-2-(*tert*-Butyl)-5-(4-chlorophenyl)-*N*,3,5-trimethyl-4-oxoimidazolidine-1-carboxamide ((*R*) 4-Ala-c)



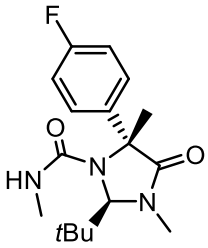
Following general procedure 6, KHMDS (3.19 mL, 3.19 mmol, 1.0 M in THF) was added to a solution of urea **S32** (718 mg, 2.13 mmol) in THF (21.00 mL). Purification by flash column chromatography (SiO_2, 3:2→1:1 Pet.Ether:EtOAc) gave the title compound (675 mg, 2.00 mmol, 94%) as a white solid. ***(R)* 4-Ala-c**: **R_f** (1:1 Pet.Ether:EtOAc): 0.21; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.33 – 7.28 (m, 2H, Ar*H*), 7.15 – 7.10 (m, 2H, Ar*H*), 5.60 (s, 1H, C*H*C(CH$_3$)$_3$), 3.90 (br. s, 1H, N*H*CH$_3$), 3.04 (s, 3H, NC*H*$_3$), 2.37 (d, J = 4.8, 3H, NHC*H*$_3$), 1.98 (s, 3H, CC*H*$_3$), 1.04 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 172.4 (*C*=O), 158.4 (*C*=O), 140.5 (C_{Ar}), 134.3 (C_{Ar}), 129.3 (2×CH_{Ar}), 126.7 (2×CH_{Ar}), 80.6 (*C*HC(CH$_3$)$_3$), 65.7 (*C*CH$_3$), 38.7 (*C*(CH$_3$)$_3$), 32.3 (N*C*H$_3$), 27.0 (NH*C*H$_3$), 26.7 (C(*C*H$_3$)$_3$), 23.8 (C*C*H$_3$); **IR**: ν_{max} = 3426 (N–H), 2983, 2960, 2906, 2874 (C–H), 1705 (C=O), 1656 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{17}H_{25}O_2N_3Cl$ ([M+H]$^+$) 338.1630, found 338.1629; **SFC**: Chiralpak® IA, 125 bar, 40 °C, 4.0 mL/min, 20% co-solvent (IPA), λ_{max}, t_R = 2.09 (99.2%), 4.69 (0.80%) min, >99:1 *er*.

(2*S*,5*S*)-2-(*tert*-Butyl)-5-(4-chlorophenyl)-*N*,3,5-trimethyl-4-oxoimidazolidine-1-carboxamide ((*S*) 4-Ala-c)



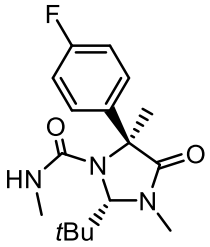
Following a similar method to general procedure 7, a solution of *trans*-**S23** (200 mg, 0.859 mmol) and 4-chloro-*N*-methylaniline (115 µL, 0.945 mmol) in THF (8.60 mL) was treated with 2 portions of KHMDS (2×1.03 mL, 2.06 mmol, 1.0 M in THF). Purification by flash column chromatography gave the title compound (273 mg, 0.808 mmol, 94%) as a white solid. **(*S*) 4-Ala-c**: **HPLC**: Chiralpak® IA, 125 bar, 40 °C, 4.0 mL/min, 20% co-solvent (IPA), λ_{max}, t_R = 2.10 (10.1%), 4.64 (89.9%) min, 90:10 *er*. For full data see compound **68**.

(2*R*,5*R*)-2-(*tert*-Butyl)-5-(4-fluorophenyl)-*N*,3,5-trimethyl-4-oxoimidazolidine-1-carboxamide ((*R*) 4-Ala-d)



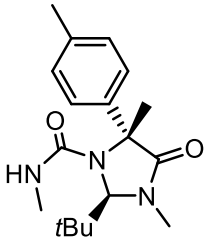
Following general procedure 6, KHMDS (3.11 mL, 3.11 mmol, 1.0 M in THF) was added to a solution of urea **S33** (667 mg, 2.08 mmol) in THF (21.00 mL). Purification by flash column chromatography (SiO_2, 1:1 Pet.Ether:EtOAc) gave the title compound (635 mg, 1.98 mmol, 95%) as a white solid. **(R*)* 4-Ala-d**: **R_f** (1:1 Pet.Ether:EtOAc): 0.23; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.19 – 7.14 (m, 2H, Ar*H*), 7.05 – 6.99 (m, 2H, Ar*H*), 5.60 (s, 1H, C*H*C$(CH_3)_3$), 3.88 (br. s, 1H, N*H*CH_3), 3.05 (s, 3H, NC*H*$_3$), 2.36 (d, *J* = 4.8, 3H, NHC*H*$_3$), 1.99 (s, 3H, CC*H*$_3$), 1.05 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 172.6 (*C*=O), 162.5 (d, $^1J_{C–F}$ = 247.9, C_{Ar}F), 159.5 (*C*=O), 137.7 (d, $^4J_{C–F}$ = 3.2, C_{Ar}), 127.1 (d, $^3J_{C–F}$ = 8.3, 2×*C*H$_{Ar}$), 116.0 (d, $^2J_{C–F}$ = 21.7, 2×*C*H$_{Ar}$), 80.6 (*C*HC$(CH_3)_3$), 65.7 (*C*CH_3), 38.7 (*C*$(CH_3)_3$), 32.3 (NCH_3), 27.0 (NH*C*H_3), 26.7 (C(*C*H_3)$_3$), 23.9 (C*C*H_3); **IR**: ν_{max} = 3428 (N–H), 2962, 2903 (C–H), 1700 (C=O), 1655 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{17}H_{25}O_2N_3F$ ([M+H]$^+$) 322.1918, found 322.1925; **HPLC**: Chiralcel® OD-H, 25 °C, 1.0 mL/min, Hexane/IPA (90:10), 210 nm, t_R = 7.68 (93.2%), 8.82 (6.8%) min, 93:7 *er*.

(2*S*,5*S*)-2-(*tert*-Butyl)-5-(4-fluorophenyl)-*N*,3,5-trimethyl-4-oxoimidazolidine-1-carboxamide ((*S*) 4-Ala-d)



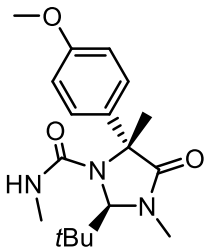
Following a similar method to general procedure 7, a solution of *trans*-**S23** (200 mg, 0.859 mmol) and 4-fluoro-*N*-methylaniline (114 µL, 0.945 mmol) in THF (8.60 mL) was treated with 2 portions of KHMDS (2×1.03 mL, 2.06 mmol, 1.0 M in THF). Purification by flash column chromatography gave the title compound (233 mg, 0.725 mmol, 84%) as a white solid. **(*S*) 4-Ala-d**: **HPLC**: Chiralcel® OD-H, 25 °C, 1.0 mL/min, Hexane/IPA (90:10), 210 nm, t_R = 7.77 (8.0%), 8.81 (92.0%) min, 92:8 *er*. For full data see compound **(*R*) 4-Ala-d**.

(2*R*,5*R*)-2-(*tert*-butyl)-*N*,3,5-trimethyl-4-oxo-5-(*p*-tolyl)imidazolidine-1-carboxamide ((*R)* 4-Ala-i)



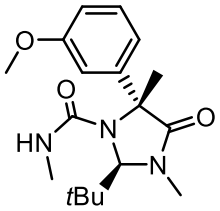
Following general procedure 6, KHMDS (0.17 mL, 0.165 mmol, 1.0 M in THF) was added to a solution of urea **S34** (35 mg, 0.110 mmol) in THF (1.10 mL). Purification by flash column chromatography gave the title compound (33 mg, 0.104 mmol, 94%) as a white solid. **(*R)* 4-Ala-i**

(2*R*,5*R*)-2-(*tert*-butyl)-5-(4-methoxyphenyl)-*N*,3,5-trimethyl-4-oxoimidazolidine-1-carboxamide ((*R)* 4-Ala-j)



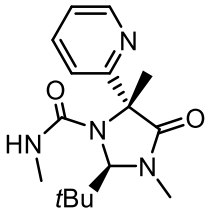
Following general procedure 6, KHMDS (0.26 mL, 0.261 mmol, 1.0 M in THF) was added to a solution of urea **S35** (58 mg, 0.174 mmol) in THF (1.75 mL). Purification by flash column chromatography gave the title compound (52 mg, 0.157 mmol, 90%) as a white solid. **(*R)* 4-Ala-j**

(2*R*,5*R*)-2-(*tert*-butyl)-5-(3-methoxyphenyl)-*N*,3,5-trimethyl-4-oxoimidazolidine-1-carboxamide ((*R)* 4-Ala-k)



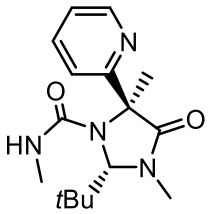
Following general procedure 6, KHMDS (0.19 mL, 0.193 mmol, 1.0 M in THF) was added to a solution of urea **S36** (43 mg, 0.129 mmol) in THF (1.30 mL). Purification by flash column chromatography gave the title compound (39 mg, 0.117 mmol, 91%) as a pale yellow solid. **(*R)* 4-Ala-k**

(2*R*,5*R*)-2-(*tert*-Butyl)-*N*,3,5-trimethyl-4-oxo-5-(pyridin-2-yl)imidazolidine-1-carboxamide ((*R)* 4-Ala-o)



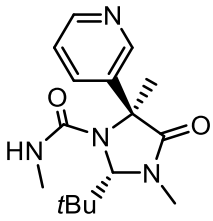
Following general procedure 6, KHMDS (3.16 mL, 3.16 mmol, 1.0 M in THF) was added to a solution of urea **S37** (641 mg, 2.11 mmol) in THF (21.00 mL). Purification by flash column chromatography (SiO_2, 97:3→95:5 DCM:MeOH) gave the title compound (622 mg, 2.04 mmol, 97%) as a white solid. **(*R)* 4-Ala-o**: **R_f** (95:5 DCM:MeOH): 0.34; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 8.55 (ddd, *J* = 4.9, 1.7, 0.9, 1H, Ar*H*), 7.68 – 7.62 (m, 1H, Ar*H*), 7.17 (ddd, *J* = 7.5, 4.9, 1.0, 1H, Ar*H*), 7.10 (d, *J* = 8.0, 1H, Ar*H*), 5.59 (s, 1H, C*H*C$(CH_3)_3$), 4.07 (br. s, 1H, N*H*CH_3), 3.09 (s, 3H, NC*H*$_3$), 2.27 (d, *J* = 4.7, 3H, NHC*H*$_3$), 2.05 (s, 3H, CC*H*$_3$), 1.05 (s, 9H, C(C*H*$_3)_3$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 172.7 (*C*=O), 159.8 (C_{Ar}), 158.5 (*C*=O), 148.8 (C_{Ar}), 137.4 (CH_{Ar}), 122.9 (CH_{Ar}), 120.6 (CH_{Ar}), 80.6 (*C*HC$(CH_3)_3$), 68.1 (*C*CH_3), 38.5 (*C*$(CH_3)_3$), 32.2 (NCH_3), 26.8 (NHCH_3), 26.7 (C(C$H_3)_3$), 22.6 (CCH_3); **IR**: ν_{max} = 3392 (N–H), 2960, 2909 (C–H), 1694 (C=O), 1656 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{16}H_{25}O_2N_4$ ([M+H]$^+$) 305.1972, found 305.1964; **HPLC**: Chiralpak® AD-H, 25 °C, 1.0 mL/min, Hexane/IPA (80:20), 210 nm, t_R = 5.10 (97.9%), 6.59 (2.1%) min, 98:2 *er*.

(2*S*,5*S*)-2-(*tert*-Butyl)-*N*,3,5-trimethyl-4-oxo-5-(pyridin-2-yl)imidazolidine-1-carboxamide ((*S*) 4-Ala-o)



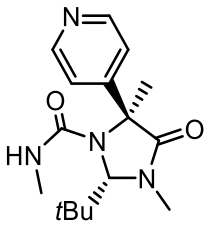
Following a similar method to general procedure 7, a solution of *trans*-**S23** (61 mg, 0.262 mmol) and 2-(methylamino)pyridine (30 µL, 0.288 mmol, 1.1 eq.) in THF (2.60 mL) was treated with 2 portions of KHMDS (2×0.29 mL, 0.577 mmol, 1.0 M in THF, 2.2 eq.). Purification by flash column chromatography (SiO_2, 95:5 EtOAc:MeOH) gave the title compound (75 mg, 0.246 mmol, 94%) as a pale yellow oil. ***(S)* 4-Ala-o**: **HPLC** Chiralpak® AD-H, 25 °C, 1.0 mL/min, Hexane/IPA (80:20), 210 nm, t_R = 5.13 (4.0%), 6.59 (96.0%) min, 96:4 *er*. For full data see compound ***(R)* 4-Ala-o**.

(2*S*,5*S*)-2-(*tert*-Butyl)-*N*,3,5-trimethyl-4-oxo-5-(pyridin-3-yl)imidazolidine-1-carboxamide ((*S*) 4-Ala-n)



Following a similar method to general procedure 7, a solution of *trans*-**S23** (70 mg, 0.301 mmol) and 3-(methylamino)pyridine (34 µL, 0.331 mmol, 1.1 eq.) in THF (3.00 mL) was treated with 2 portions of KHMDS (2×0.33 mL, 0.662 mmol, 1.0 M in THF, 2.2 eq.). Purification by flash column chromatography (SiO_2, 95:5 EtOAc:MeOH) gave the title compound (83 mg, 0.273 mmol, 91%) as a pale yellow oil. ***(S)* 4-Ala-n**: $\mathbf{R_f}$ (95:5 DCM:MeOH): 0.26; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 8.51 (d, *J* = 4.7, 2H, Ar*H*), 7.43 (d, *J* = 8.0, 1H, Ar*H*), 7.25 (dd, *J* = 8.1, 4.8, 1H, Ar*H*), 5.61 (s, 1H, C*H*C$(CH_3)_3$), 4.06 (br. s, 1H, N*H*CH_3), 3.03 (s, 3H, NC*H*$_3$), 2.34 (d, *J* = 4.7, 3H, NHC*H*$_3$), 2.02 (s, 3H, CC*H*$_3$), 1.02 (s, 9H, C(C*H*$_3)_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 172.0 (*C*=O), 158.1 (*C*=O), 149.5 (*C*H$_{Ar}$), 146.9 (*C*H$_{Ar}$), 137.4 (*C*$_{Ar}$), 132.8 (*C*H$_{Ar}$), 123.7 (*C*H$_{Ar}$), 80.6 (*C*HC$(CH_3)_3$), 64.9 (*C*CH$_3$), 38.6 (*C*$(CH_3)_3$), 32.3 (NCH$_3$), 26.9 (NH*C*H$_3$), 26.6 (C(*C*H$_3)_3$), 23.5 (C*C*H$_3$); **IR**: ν_{max} = 3391 (N–H), 2961, 2878 (C–H), 1695 (C=O), 1652 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{16}H_{25}O_2N_4$ ([M+H]$^+$) 305.1972, found 305.1966.

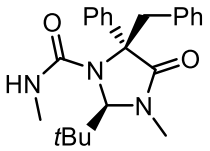
(2*S*,5*S*)-2-(*tert*-Butyl)-*N*,3,5-trimethyl-4-oxo-5-(pyridin-4-yl)imidazolidine-1-carboxamide ((*S*) 4-Ala-m)



Following a similar method to general procedure 7, a solution of *trans*-**S23** (70 mg, 0.301 mmol) and 4-(methylamino)pyridine (36 mg, 0.331 mmol, 1.1 eq.) in THF (3.00 mL) was treated with 2 portions of KHMDS (2×0.33 mL, 0.662 mmol, 1.0 M in THF, 2.2 eq.). Purification by flash column chromatography (SiO_2, 95:5 EtOAc:MeOH) gave the title compound (49 mg, 0.161 mmol, 54%) as a yellow oil. ***(S)* 4-Ala-m**: $\mathbf{R_f}$ (95:5 DCM:MeOH): 0.24; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 8.52 (dd, *J* = 4.6, 1.6, 2H, Ar*H*), 7.05 (dd, *J* = 4.6, 1.6, 2H, Ar*H*), 5.57 (s, 1H, C*H*C$(CH_3)_3$), 3.90 (br. s, 1H, N*H*CH_3), 2.98 (s, 3H, NC*H*$_3$), 2.30 (d, *J* = 4.6, 3H, NHC*H*$_3$), 1.95 (s, 3H, CC*H*$_3$), 0.98 (s, 9H, C(C*H*$_3)_3$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 171.5 (*C*=O),

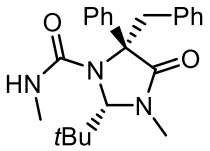
158.1 (*C*=O), 150.9 (C_{Ar}), 150.5 (2×CH_{Ar}), 120.2 (2×CH_{Ar}), 80.7 ($CHC(CH_3)_3$), 65.7 (CCH_3), 38.6 ($C(CH_3)_3$), 32.3 (NCH_3), 26.8 ($NHCH_3$), 26.6 ($C(CH_3)_3$), 23.3 (CCH_3); **IR**: ν_{max} = 3391 (N–H), 2961, 2878 (C–H), 1698 (C=O), 1658 (C=O); **HRMS** (ESI^+): *m/z* calcd for $C_{16}H_{25}O_2N_4$ ($[M+H]^+$) 305.1972, found 305.1966.

(2*R*,5*R*)-5-Benzyl-2-(*tert*-butyl)-*N*,3-dimethyl-4-oxo-5-phenylimidazolidine-1-carboxamide ((*R*) 4-Phe-a)



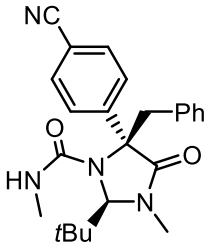
Following general procedure 6, KHMDS (0.22 mL, 0.217 mmol, 1.0 M in THF) was added to a solution of urea **S39** (55 mg, 0.145 mmol) in THF (1.50 mL). Purification by flash column chromatography (SiO_2, 2:1→3:2 Pet.Ether:EtOAc) gave the title compound (54 mg, 0.142 mmol, 98%) as a white solid. ***(R)* 4-Phe-a**: $\mathbf{R_f}$ (1:1 Pet.Ether:EtOAc): 0.29; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.44 – 7.40 (m, 2H, Ph*H*), 7.38 – 7.33 (m, 2H, Ph*H*), 7.33 – 7.23 (m, 6H, Ph*H*), 5.58 (s, 1H, $CHC(CH_3)_3$), 3.89 – 3.81 (m, 2H, CH_AH_BPh and $NHCH_3$), 3.63 (d, *J* = 14.3, 1H, CH_AH_BPh), 2.97 (s, 3H, NCH_3), 2.20 (d, *J* = 4.6, 3H, $NHCH_3$), 0.73 (s, 9H, $C(CH_3)_3$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 171.4 (*C*=O), 159.5 (*C*=O), 141.5 (C_{Ph}), 135.6 (C_{Ph}), 131.6 (2×CH_{Ph}), 129.1 (2×CH_{Ph}), 129.0 (2×CH_{Ph}), 128.2 (CH_{Ph}), 127.8 (CH_{Ph}), 125.6 (2×CH_{Ph}), 81.3 ($CHC(CH_3)_3$), 71.9 (CCH_2Ph), 40.9 (CH_2Ph), 37.7 ($C(CH_3)_3$), 31.9 (NCH_3), 27.1 ($NHCH_3$), 26.5 ($C(CH_3)_3$); **IR**: ν_{max} = 3434 (N–H), 3062, 3031, 2959, 2908 (C–H), 1695 (C=O), 1658 (C=O); **HRMS** (ESI^+): *m/z* calcd for $C_{23}H_{29}O_2N_3Na$ ($[M+Na]^+$) 402.2152, found 402.2149.

(2*S*,5*S*)-5-Benzyl-2-(*tert*-butyl)-*N*,3-dimethyl-4-oxo-5-phenylimidazolidine-1-carboxamide ((*S*) 4-Phe-a)



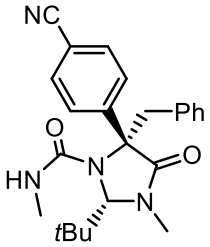
LDA (1.5 eq.) was prepared by dropwise addition of *n*BuLi (0.33 mL, 0.435 mmol, 1.5 eq., 1.5 M in hexanes) to a solution of freshly distilled DIPA (60 µL, 0.435 mmol, 1.5 eq.) in anhydrous THF (1.30 mL, 0.22 M) at 0 °C. After stirring for 15 min, this LDA (0.22 M in THF, 1.5 eq.) was added dropwise to a solution of urea **S38** (110 mg, 0.290 mmol, 1.0 eq.) in anhydrous THF (1.60 mL, 0.18 M) at 0 °C. After 15 min, the reaction mixture was warmed to room temperature and allowed to stir for 4 h. The reaction was quenched by dropwise addition of NH_4Cl (sat. aq.) and stirred for 15 min. The organic layer was separated and the aqueous layer extracted 3 times with EtOAc, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound (108 mg, 0.285 mmol, 98%) as a white solid without further purification. For full data see compound ***(R)* 4-Phe-a**.

(2*R*,5*R*)-5-Benzyl-2-(*tert*-butyl)-5-(4-cyanophenyl)-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide ((*R)* 4-Phe-b)



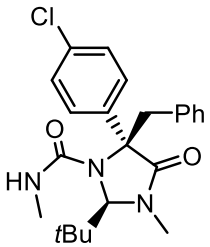
Following general procedure 6, KHMDS (2.28 mL, 2.28 mmol, 1.0 M in THF) was added to a solution of urea **S40** (614 mg, 1.52 mmol) in THF (15.00 mL). Purification by flash column chromatography (SiO_2, 1:1→2:1 EtOAc:Pet.Ether) gave the title compound (522 mg, 1.29 mmol, 85%) as a white solid. **(*R)* 4-Phe-b**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.63 (d, *J* = 8.6, 2H, Ar*H*), 7.43 (d, *J* = 8.6, 2H, Ar*H*), 7.40 – 7.35 (m, 2H, Ph*H*), 7.35 – 7.26 (m, 3H, Ph*H*), 5.57 (s, 1H, C*H*C(CH$_3$)$_3$), 3.85 (br. s, 1H, N*H*CH$_3$), 3.77 (d, *J* = 14.4, 1H, CH_AH$_B$Ph), 3.68 (d, *J* = 14.5, 1H, CH$_A$$H_B$Ph), 2.96 (s, 3H, NC$H_3$), 2.20 (br. d, *J* = 4.6, 3H, NHCH_3), 0.75 (s, 9H, C(CH_3)$_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 170.4 (*C*=O), 158.7 (*C*=O), 146.5 (C_{Ar}), 134.8 (C_{Ph}), 132.6 (2×CH_{Ar}), 131.3 (2×CH_{Ph}), 129.2 (2×CH_{Ph}), 128.2 (CH_{Ph}), 126.6 (2×CH_{Ar}), 118.3 (*C*≡N), 112.0 (C_{Ar}), 81.2 (*C*HC(CH$_3$)$_3$), 72.0 (*C*CH$_2$Ph), 40.8 (*C*H$_2$Ph), 37.7 (*C*(CH$_3$)$_3$), 31.9 (N*C*H$_3$), 27.0 (NH*C*H$_3$), 26.4 (C(*C*H$_3$)$_3$); **IR**: ν_{max} = 3433 (N–H), 2959, 2930 (C–H), 2229 (C≡N), 1694 (C=O), 1664 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{24}H_{28}O_2N_4Na$ ([M+Na]$^+$) 427.2104, found 427.2087; **HPLC**: Chiralcel® OD-H, 25 °C, 1.0 mL/min, Hexane/IPA (80:20), 210 nm, t_R = 9.06 (100%) min, >99:1 *er*.

(2*S*,5*S*)-5-Benzyl-2-(*tert*-butyl)-5-(4-cyanophenyl)-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide ((*S)* 4-Phe-a)



Following general procedure 7, a solution of *trans*-**S24** (100 mg, 0.324 mmol) and 4-(methylamino)benzonitrile (47 mg, 0.356 mmol) in THF (3.20 mL) was treated with 2 portions of KHMDS (2×0.39 mL, 0.777 mmol, 1.0 M in THF). Purification by flash column chromatography gave the title compound (101 mg, 0.250 mmol, 77%) as a white solid. **(*S)* 4-Phe-b**: **HPLC**: t_R = 22.91 (100%) min, >99:1 *er*. For full data see compound **(*R)* 4-Phe-b**.

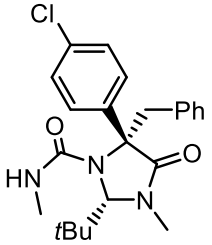
(2*R*,5*R*)-5-Benzyl-2-(*tert*-butyl)-5-(4-chlorophenyl)-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide ((*R)* 4-Phe-c)



Following general procedure 6, KHMDS (2.61 mL, 2.61 mmol, 1.0 M in THF) was added to a solution of urea **S41** (719 mg, 1.74 mmol) in THF (17.00 mL). Purification by flash column chromatography (SiO_2, 1:1→2:1 EtOAc:Pet.Ether) gave the title compound (634 mg, 1.53 mmol, 88%) as a white solid. **(*R)* 4-Phe-c**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.42 – 7.36 (m, 2H, Ph*H*), 7.35 – 7.23 (m, 7H, Ph*H* and Ar*H*), 5.56 (s, 1H, C*H*C(CH$_3$)$_3$), 3.82 (br. s, 1H, N*H*CH$_3$), 3.77 (d, *J* = 14.4, 1H, CH_AH$_B$Ph), 3.63 (d, *J* = 14.4, 1H, CH$_A$$H_B$Ph), 2.96 (s, 3H, NC$H_3$), 2.23 (d, *J* = 4.6, 3H, NHCH_3), 0.75 (s, 9H, C(CH_3)$_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 170.9 (*C*=O), 159.0 (*C*=O), 139.7 (C_{Ar}), 135.1 (C_{Ph}), 134.1 (C_{Ar}), 131.3 (2×CH_{Ph}), 129.0 (2×CH_{Ar}),

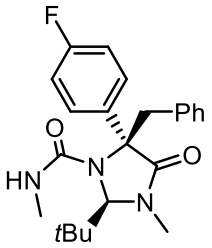
128.9 (2×*C*H$_{Ph}$), 127.9 (*C*H$_{Ph}$), 127.0 (2×*C*H$_{Ar}$), 81.0 (*C*HC(CH$_3$)$_3$), 71.5 (*C*CH$_2$Ph), 40.8 (*C*H$_2$Ph), 37.6 (*C*(CH$_3$)$_3$), 31.8 (N*C*H$_3$), 27.0 (NH*C*H$_3$), 26.4 (C(*C*H$_3$)$_3$); **IR**: ν_{max} = 3435 (N–H), 2959, 1694 (C=O), 1667 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{23}H_{28}O_2N_3ClNa$ ([M+Na]$^+$) 436.1762, found 436.1776; **HPLC**: Chiralcel® OD-H, 25 °C, 1.0 mL/min, Hexane/IPA (80:20), 225 nm, t_R = 6.16 (100%) min, >99:1 *er*.

(2*S*,5*S*)-5-Benzyl-2-(*tert*-butyl)-5-(4-chlorophenyl)-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide ((*S)* 4-Phe-c)



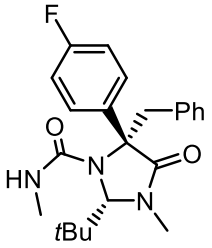
Following general procedure 7, a solution of *trans*-**S24** (100 mg, 0.324 mmol) and 4-chloro-*N*-methylaniline (43 µL, 0.356 mmol) in THF (3.20 mL) was treated with 2 portions of KHMDS (2×0.39 mL, 0.777 mmol, 1.0 M in THF). Purification by flash column chromatography gave the title compound (119 mg, 0.288 mmol, 89%) as a white solid. ***(S)* 4-Phe-c**: **HPLC**: t_R = 6.19 (3.5%), 13.62 (96.5%) min, 97:3 *er*. For full data see compound ***(R)* 4-Phe-c**.

(2*R*,5*R*)-5-Benzyl-2-(*tert*-butyl)-5-(4-fluorophenyl)-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide ((*R)* 4-Phe-d)



Following general procedure 6, KHMDS (2.45 mL, 2.45 mmol, 1.0 M in THF) was added to a solution of urea **S42** (650 mg, 1.64 mmol) in THF (16.00 mL). Purification by flash column chromatography (SiO_2, 1:1→2:1 EtOAc:Pet.Ether) gave the title compound (580 mg, 1.46 mmol, 89%) as a white solid. (*R)* 4-Phe-d: **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.42 – 7.36 (m, 2H, Ph*H*), 7.33 – 7.24 (m, 5H, Ph*H* and Ar*H*), 7.08 – 6.97 (m, 2H, Ar*H*), 5.55 (s, 1H, C*H*C(CH$_3$)$_3$), 3.88 (s, 1H, N*H*CH$_3$), 3.79 (d, *J* = 14.4, 1H, C*H$_A$*H$_B$Ph), 3.60 (d, *J* = 14.3, 1H, CH$_A$*H$_B$*Ph), 2.96 (s, 3H, NC*H*$_3$), 2.23 (d, *J* = 4.7, 3H, NHC*H*$_3$), 0.72 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 171.2 (*C*=O), 162.3 (d, $^1J_{C–F}$ = 248.1, *C*$_{Ar}$F), 159.2 (*C*=O), 137.2 (d, $^4J_{C–F}$ = 3.4, *C*$_{Ar}$), 135.3 (*C*$_{Ph}$), 131.5 (2×*C*H$_{Ph}$), 129.0 (2×*C*H$_{Ph}$), 127.9 (*C*H$_{Ph}$), 127.5 (d, $^3J_{C–F}$ = 8.2, 2×*C*H$_{Ar}$), 115.9 (d, $^2J_{C–F}$ = 21.5, 2×*C*H$_{Ar}$), 81.1 (*C*HC(CH$_3$)$_3$), 71.5 (*C*CH$_2$Ph), 41.1 (*C*H$_2$Ph), 37.7 (*C*(CH$_3$)$_3$), 31.9 (N*C*H$_3$), 27.1 (NH*C*H$_3$), 26.4 (C(*C*H$_3$)$_3$); **IR**: ν_{max} = 3432 (N–H), 2960, 1693 (C=O), 1658 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{23}H_{28}O_2N_3FNa$ ([M+Na]$^+$) 420.2058, found 420.2037; **HPLC**: Chiralcel® OD-H, 25 °C, 1.0 mL/min, Hexane/IPA (80:20), 210 nm, t_R = 5.88 (100%) min, >99:1 *er*.

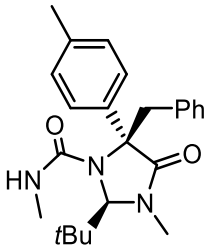
(2*S*,5*S*)-5-Benzyl-2-(*tert*-butyl)-5-(4-fluorophenyl)-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide ((*S)* 4-Phe-d)



Following general procedure 7, a solution of *trans*-**S24** (100 mg, 0.324 mmol) and 4-fluoro-*N*-methylaniline (43 µL, 0.356 mmol) in THF (3.20 mL) was treated with 2 portions of KHMDS (2×0.39 mL, 0.777 mmol, 1.0 M in THF). Purification by flash column chromatography gave an analytical

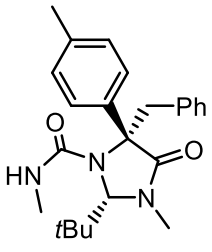
sample for HPLC. **(*S*) 4-Phe-d**: **HPLC**: Chiralcel® OD-H, 25 °C, 1.0 mL/min, Hexane/IPA (80:20), 210 nm, t_R = 5.80 (1.5%), 10.91 (98.5%) min, 99:1 *er*. For full data see compound **(*R*) 4-Phe-d**.

(2*R*,5*R*)-5-Benzyl-2-(*tert*-butyl)-*N*,3-dimethyl-4-oxo-5-(*p*-tolyl)imidazolidine-1-carboxamide ((*R*) 4-Phe-i)



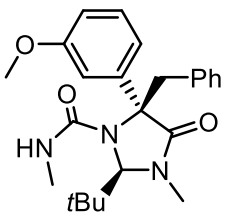
Following general procedure 6, KHMDS (1.91 mL, 1.91 mmol, 1.0 M in THF) was added to a solution of urea **S43** (500 mg, 1.27 mmol) in THF (13.00 mL). Purification by flash column chromatography (SiO_2, 1:1→2:1 EtOAc:Pet.Ether) gave the title compound (400 mg, 1.01 mmol, 80%) as a white solid. **(*R*) 4-Phe-i**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.44 – 7.38 (m, 2H, Ph*H*), 7.32 – 7.23 (m, 3H, Ph*H*), 7.17 (d, *J* = 8.6, 2H, Ar*H*), 7.14 (d, *J* = 8.6, 2H, Ar*H*), 5.55 (s, 1H, C*H*C(CH$_3$)$_3$), 3.87 (br. q, *J* = 4.7, 1H, N*H*CH$_3$), 3.80 (d, *J* = 14.3, 1H, CH_AH$_B$Ph), 3.61 (d, *J* = 14.3, 1H, CH$_A$$H_B$Ph), 2.95 (s, 3H, NC$H_3$), 2.30 (s, 3H, C$H_3$), 2.22 (d, *J* = 4.7, 3H, NHCH_3), 0.72 (s, 9H, C(CH_3)$_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 171.5 (*C*=O), 159.5 (*C*=O), 138.4 (C_{Ar}), 137.9 (C_{Ar}), 135.7 (C_{Ph}), 131.5 (2×CH_{Ph}), 129.7 (2×CH_{Ar}), 128.9 (2×CH_{Ph}), 127.7 (CH_{Ph}), 125.4 (2×CH_{Ar}), 81.2 (*C*HC(CH$_3$)$_3$), 71.7 (*C*CH$_2$Ph), 40.8 (*C*H$_2$Ph), 37.7 (*C*(CH$_3$)$_3$), 31.9 (NCH_3), 27.1 (NH*C*H$_3$), 26.5 (C(*C*H$_3$)$_3$), 21.1 (*C*H$_3$); **IR**: ν_{max} = 3436 (N–H), 2959 (C–H), 1682 (C=O), 1660 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{24}H_{32}O_2N_3Na$ ([M+Na]$^+$) 416.2308, found 416.2302; **HPLC**: Chiralcel® OD-H, 25 °C, 1.0 mL/min, Hexane/IPA (80:20), 210 nm, t_R = 6.70 (100%) min, >99:1 *er*.

(2*S*,5*S*)-5-Benzyl-2-(*tert*-butyl)-*N*,3-dimethyl-4-oxo-5-(*p*-tolyl)imidazolidine-1-carboxamide ((*S*) 4-Phe-i)



Following general procedure 7, a solution of *trans*-**S24** (100 mg, 0.324 mmol) and *N*-methyl-*p*-toluidine (45 µL, 0.356 mmol) in THF (3.20 mL) was treated with 2 portions of KHMDS (2×0.39 mL, 0.777 mmol, 1.0 M in THF). Purification by flash column chromatography gave the title compound (106 mg, 0.269 mmol, 83%) as a white solid. **(*S*) 4-Phe-i**: **HPLC**: Chiralcel® OD-H, 25 °C, 1.0 mL/min, Hexane/IPA (80:20), 210 nm, t_R = 10.32 (100%) min, >99:1 *er*. For full data see compound **(*R*) 4-Phe-i**.

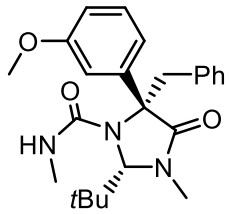
(2*R*,5*R*)-5-Benzyl-2-(*tert*-butyl)-5-(3-methoxyphenyl)-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide ((*R*) 4-Phe-k)



Following general procedure 6, KHMDS (0.16 mL, 0.161 mmol, 1.0 M in THF) was added to a solution of urea **S44** (44 mg, 0.107 mmol) in THF (1.10 mL). Purification by flash column chromatography (SiO_2, 1:1 Pet.Ether:EtOAc) gave the title compound (36 mg, 0.088 mmol, 82%) as a

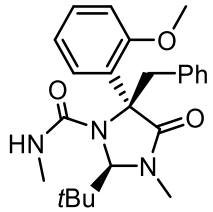
white solid. **(*R*) 4-Phe-k**: **R_f** (1:1 Pet.Ether:EtOAc): 0.24; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.44 – 7.39 (m, 2H, Ph*H*), 7.33 – 7.23 (m, 4H, Ph*H* and Ar*H*), 6.88 – 6.83 (m, 2H, Ar*H*), 6.82 – 6.78 (m, 1H, Ar*H*), 5.55 (s, 1H, C*H*C$(CH_3)_3$), 3.91 (br. q, *J* = 4.9, 1H, N*H*CH_3), 3.83 (d, *J* = 14.3, 1H, C$H_A$$H_B$Ph), 3.78 (s, 3H, OC$H_3$), 3.59 (d, *J* = 14.3, 1H, C$H_A$$H_B$Ph), 2.97 (s, 3H, NC$H_3$), 2.24 (d, *J* = 4.7, 3H, NHCH_3), 0.71 (s, 9H, C(CH_3)$_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 171.3 (*C*=O), 160.1 (C_{Ar}), 159.5 (*C*=O), 143.2 (C_{Ar}), 135.5 (C_{Ph}), 131.6 (2×CH_{Ph}), 130.1 (CH_{Ar}), 128.9 (2×CH_{Ph}), 127.8 (CH_{Ph}), 117.8 (CH_{Ar}), 113.2 (CH_{Ar}), 112.1 (CH_{Ar}), 81.3 (*C*HC$(CH_3)_3$), 71.8 (*C*CH_2Ph), 55.4 (OCH_3), 40.9 (*C*H_2Ph), 37.7 (*C*$(CH_3)_3$), 31.9 (NCH_3), 27.1 (NHCH_3), 26.5 (C(CH_3)$_3$); **IR**: ν_{max} = 3435 (N–H), 3064, 3031, 2958, 2922, 2852 (C–H), 1696 (C=O), 1657 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{24}H_{32}O_3N_3$ ([M+H]$^+$) 410.2438, found 410.2429; **SFC**: Chiralpak® IA, 125 bar, 40 °C, 4.0 mL/min, 20% co-solvent (IPA), λ_{max}, t_R = 4.64 (96.7%), 6.12 (3.3%) min, 97:3 *er*.

(2*S*,5*S*)-5-Benzyl-2-(*tert*-butyl)-5-(3-methoxyphenyl)-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide ((*S*) 4-Phe-k)



Following general procedure 7, a solution of *trans*-**S24** (100 mg, 0.324 mmol) and 3-methoxy-*N*-methylaniline (47 µL, 0.359 mmol) in THF (3.20 mL) was treated with 2 portions of KHMDS (2×0.39 mL, 0.777 mmol, 1.0 M in THF). Purification by flash column chromatography gave the title compound (125 mg, 0.305 mmol, 94%) as a white solid. **(*S*) 4-Phe-k**: **SFC**: Chiralpak® IA, 125 bar, 40 °C, 4.0 mL/min, 20% co-solvent (IPA), λ_{max}, t_R = 5.96 (100%) min, >99:1 *er*. For full data see compound **(*R*) 4-Phe-k**.

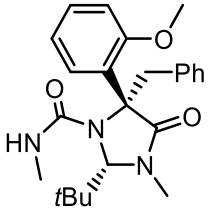
(2*R*,5*R*)-5-Benzyl-2-(*tert*-butyl)-5-(2-methoxyphenyl)-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide ((*R*) 4-Phe-l)



Following general procedure 6, KHMDS (0.17 mL, 0.165 mmol, 1.0 M in THF) was added to a solution of urea **S45** (45 mg, 0.110 mmol) in THF (1.10 mL). Purification by flash column chromatography (SiO_2, 2:1 EtOAc:Pet.Ether) gave the title compound (38 mg, 0.093 mmol, 84%) as a white solid. **(*R*) 4-Phe-l**: **R_f** (2:1 EtOAc:Pet.Ether): 0.24; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.70 (d, *J* = 7.6, 1H, Ar*H*), 7.55 (d, *J* = 7.3, 2H, Ph*H*), 7.31 (t, *J* = 7.3, 2H, Ph*H*), 7.28 – 7.19 (m, 2H, Ph*H* and Ar*H*), 6.92 (td, *J* = 7.7, 0.9, 1H, Ar*H*), 6.82 (d, *J* = 8.1, 1H, Ar*H*), 5.33 (s, 1H, C*H*C$(CH_3)_3$), 3.72 (s, 3H, OCH_3), 3.67 (br. q, *J* = 4.6, 1H, N*H*CH_3), 3.65 (s, 2H, CH_2Ph), 3.03 (s, 3H, NCH_3), 2.07 (d, *J* = 4.6, 3H, NHCH_3), 0.88 (s, 9H, C(CH_3)$_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 172.8 (*C*=O), 159.3 (*C*=O), 156.8 (C_{Ar}), 136.1 (C_{Ph}), 131.7 (2×CH_{Ph}), 129.8 (CH_{Ar}), 128.8 (2×CH_{Ph}), 128.7 (CH_{Ar}), 128.2 (C_{Ar}), 127.6 (CH_{Ph}), 120.5 (CH_{Ar}), 111.7 (CH_{Ar}), 82.6 (*C*HC$(CH_3)_3$), 69.5 (*C*CH_2Ph), 56.5 (OCH_3), 42.6 (*C*H_2Ph), 37.1 (*C*$(CH_3)_3$), 32.2 (NCH_3), 27.1 (C(CH_3)$_3$), 26.8 (NHCH_3); **IR**: ν_{max} = 3435 (N–H), 3064, 3030, 2958, 2922 (C–H), 1692 (C=O),

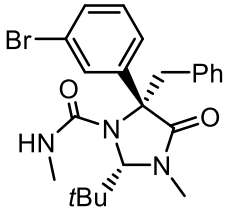
1660 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{24}H_{32}O_3N_3$ ([M+H]$^+$) 410.2438, found 410.2438; **HPLC**: Chiralcel® OD-H, 25 °C, 0.8 mL/min, Hexane/IPA (80:20), 225 nm, t_R = 8.29 (97.6%), 11.86 (2.4%) min, 98:2 *er*.

(2*S*,5*S*)-5-Benzyl-2-(*tert*-butyl)-5-(2-methoxyphenyl)-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide ((*S*) 4-Phe-l)



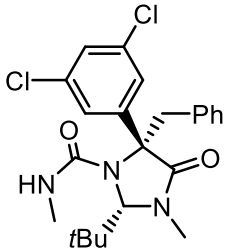
Following general procedure 7, a solution of *trans*-**S24** (100 mg, 0.324 mmol) and 2-methoxy-*N*-methylaniline (49 mg, 0.359 mmol) in THF (3.20 mL) was treated with 2 portions of KHMDS (2×0.39 mL, 0.777 mmol, 1.0 M in THF). Purification by flash column chromatography gave the title compound (74 mg, 0.181 mmol, 56%) as a white solid. **(*S*) 4-Phe-l**: **HPLC**: Chiralcel® OD-H, 25 °C, 0.8 mL/min, Hexane/IPA (80:20), 225 nm, t_R = 8.35 (3.0%), 11.75 (97.0%) min, 97:3 *er*. For full data see compound **(*S*) 4-Phe-l**.

(2*S*,5*S*)-5-Benzyl-5-(3-bromophenyl)-2-(*tert*-butyl)-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide ((*S*) 4-Phe-e)



Following a similar method to general procedure 7, a solution of *trans*-**S24** (535 mg, 1.73 mmol) and 3-bromo-*N*-methylaniline (0.26 mL, 2.08 mmol, 1.2 eq.) in THF (17.00 mL) was treated with 2 portions of KHMDS (2×2.60 mL, 5.19 mmol, 1.0 M in THF, 3.0 eq.). Purification by flash column chromatography (SiO_2, 2:1→9:1 Et_2O:Pet.Ether) gave the title compound (644 mg, 1.40 mmol, 81%) as a white solid. **(*S*) 4-Phe-e**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.56 (t, *J* = 1.9, 1H, Ar*H*), 7.42 (ddd, *J* = 7.9, 1.9, 1.1, 1H, Ar*H*), 7.44 – 7.37 (m, 2H, Ph*H*), 7.35 – 7.27 (m, 3H, Ph*H*), 7.23 (t, *J* = 7.9, 1H, Ar*H*), 7.16 (ddd, *J* = 8.0, 2.0, 1.1, 1H, Ar*H*), 5.57 (s, 1H, C*H*C(CH$_3$)$_3$), 3.84 (br. s, 1H, N*H*CH$_3$), 3.80 (d, *J* = 14.3, 1H, C*H$_A$*H$_B$Ph), 3.60 (d, *J* = 14.4, 1H, CH$_A$*H$_B$*Ph), 2.99 (s, 3H, NC*H*$_3$), 2.26 (d, *J* = 4.7, 3H, NHC*H*$_3$), 0.74 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 170.8 (*C*=O), 159.1 (*C*=O), 143.7 (*C*$_{Ar}$), 135.1 (*C*$_{Ar}$), 131.5 (2×*C*H$_{Ar}$), 131.4 (*C*H$_{Ar}$), 130.5 (*C*H$_{Ar}$), 129.1 (2×*C*H$_{Ar}$), 128.0 (*C*H$_{Ar}$), 124.2 (*C*H$_{Ar}$), 123.2 (*C*$_{Ar}$Br), 81.2 (*C*HC(CH$_3$)$_3$), 71.6 (*C*CH$_2$Ph), 41.0 (*C*H$_2$Ph), 37.7 (*C*(CH$_3$)$_3$), 31.9 (N*C*H$_3$), 27.1 (NH*C*H$_3$), 26.5 (C(*C*H$_3$)$_3$); **HRMS** (ESI$^+$): *m/z* calcd for $C_{23}H_{29}O_2N_3Br$ ([M+H]$^+$) 458.1438, found 458.1431.

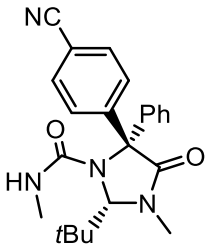
(2*S*,5*S*)-5-Benzyl-5-(3,5-dichlorophenyl)-2-(*tert*-butyl)-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide ((*S*) 4-Phe-f)



Following a similar method to general procedure 7, a solution of *trans*-**S24** (535 mg, 1.73 mmol) and 3,5-dichloro-*N*-methylaniline (366 mg, 2.08 mmol, 1.2 eq.) in THF (17.00 mL) was treated with 2 portions of KHMDS (2×2.60 mL, 5.20 mmol, 1.0 M in THF, 3.0 eq.). Purification by flash column chromatography (SiO_2, 1:1→8:1 Et_2O:Pet.Ether) gave the title compound (653 mg, 1.46 mmol, 84%) as a white solid. **(*S*) 4-Phe-f**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.38

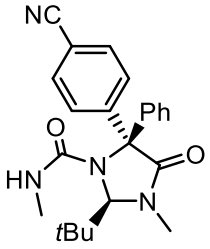
– 7.34 (m, 2H, Ar*H*), 7.33 – 7.26 (m, 4H, Ar*H*), 7.18 (d, *J* = 1.8, 2H, Ar*H*), 5.54 (s, 1H, C*H*C(CH_3)$_3$), 3.97 (br. s, 1H, N*H*CH_3), 3.74 (d, *J* = 14.3, 1H, C$H_A$$H_B$Ph), 3.59 (d, *J* = 14.4, 1H, C$H_A$$H_B$Ph), 2.97 (s, 3H, NC$H_3$), 2.30 (d, *J* = 4.4, 3H, NHCH_3), 0.71 (s, 9H, C(CH_3)$_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 170.3 (*C*=O), 158.7 (*C*=O), 144.8 (C_{Ar}), 135.6 (2×C_{Ar}), 134.8 (C_{Ph}), 131.4 (2×CH_{Ar}), 129.1 (2×CH_{Ar}), 128.5 (CH_{Ar}), 128.1 (CH_{Ar}), 124.5 (2×CH_{Ar}), 81.1 (*C*HC(CH_3)$_3$), 71.5 (*C*CH_2Ph), 41.0 (*C*H_2Ph), 37.7 (*C*(CH_3)$_3$), 31.9 (N*C*H_3), 27.1 (NH*C*H_3), 26.4 (C(*C*H_3)$_3$); **HRMS** (ESI$^+$): *m/z* calcd for $C_{23}H_{28}O_2N_3Cl_2$ ([M+H]$^+$) 448.1553, found 448.1548.

(2*S*,5*S*)-2-(*tert*-Butyl)-5-(4-cyanophenyl)-*N*,3-dimethyl-4-oxo-5-phenylimidazolidine-1-carboxamide ((*S)* 4-Phg-b)



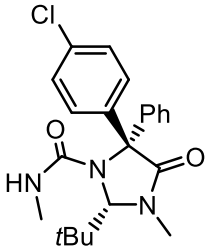
Following general procedure 6, KHMDS (1.97 mL, 1.97 mmol, 1.0 M in THF) was added to a solution of urea **S46** (512 mg, 1.31 mmol) in THF (13.00 mL). Purification by flash column chromatography (SiO_2, 1:1→2:1 EtOAc:Pet.Ether) gave the title compound (404 mg, 1.03 mmol, 79%) as a white solid. **(*S)* 4-Phg-b**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.94 – 7.89 (m, 2H, Ph*H*), 7.60 – 7.54 (m, 2H, Ar*H*), 7.54 – 7.48 (m, 2H, Ph*H*), 7.48 – 7.42 (m, 1H, Ph*H*), 7.15 – 7.09 (m, 2H, Ar*H*), 5.80 (s, 1H, C*H*C(CH_3)$_3$), 3.99 (q, *J* = 4.8, 1H, N*H*CH_3), 3.13 (s, 3H, NCH_3), 2.23 (d, *J* = 4.7, 3H, NHCH_3), 0.93 (s, 9H, C(CH_3)$_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 170.7 (*C*=O), 157.8 (*C*=O), 147.8 (C_{Ar}), 136.0 (C_{Ph}), 132.6 (2×CH_{Ar}), 129.0 (CH_{Ph}), 128.9 (2×CH_{Ph}), 128.3 (2×CH_{Ph}), 127.8 (2×CH_{Ar}), 118.2 (*C*≡N), 112.3 (C_{Ar}), 80.5 (*C*HC(CH_3)$_3$), 72.5 (N*C*Ph), 38.3 (*C*(CH_3)$_3$), 32.1 (N*C*H_3), 26.9 (NH*C*H_3), 26.5 (C(*C*H_3)$_3$); **IR**: ν_{max} = 3428 (N–H), 2969 (C–H), 2228 (C≡N), 1705 (C=O), 1666 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{23}H_{26}O_2N_4$ ([M+H]$^+$) 413.1948, found 413.1952; **HPLC**: Chiralcel® OD-H, 25 °C, 0.8 mL/min, Hexane/IPA (80:20), 225 nm, t_R = 42.31 (81.4%), 47.70 (18.6%) min, 81:19 *er*.

(2*R*,5*R*)-2-(*tert*-Butyl)-5-(4-cyanophenyl)-*N*,3-dimethyl-4-oxo-5-phenylimidazolidine-1-carboxamide ((*R)* 4-Phg-b)



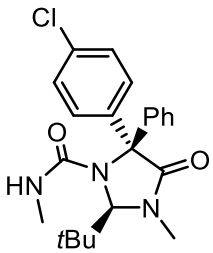
Following general procedure 7, a solution of *trans*-**S25** (100 mg, 0.339 mmol) and 4-(methylamino)benzonitrile (49 mg, 0.373 mmol) in THF (3.40 mL) was treated with 2 portions of KHMDS (2×0.41 mL, 0.814 mmol, 1.0 M in THF). Purification by flash column chromatography gave the title compound (75 mg, 0.197 mmol, 58%) as a white solid. **(*R)* 4-Phg-b**: **HPLC**: Chiralcel® OD-H, 25 °C, 0.8 mL/min, Hexane/IPA (80:20), 225 nm, t_R = 42.53 (95.4%), 47.61 (4.6%) min, 95:5 *er*. For full data see compound **(*S)* 4-Phg-b**.

(2*S*,5*S*)-2-(*tert*-Butyl)-5-(4-chlorophenyl)-*N*,3-dimethyl-4-oxo-5-phenylimidazolidine-1-carboxamide ((*S*) 4-Phg-c)



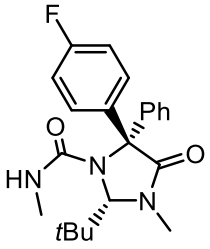
Following general procedure 6, KHMDS (1.73 mL, 1.73 mmol, 1.0 M in THF) was added to a solution of urea **S47** (460 mg, 1.15 mmol) in THF (12.00 mL). Purification by flash column chromatography (SiO_2, 1:1→2:1 EtOAc:Pet.Ether) gave the title compound (404 mg, 1.01 mmol, 88%) as a white solid. **(*S*) 4-Phg-c**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.97 – 7.89 (m, 2H, Ph*H*), 7.51 – 7.45 (m, 2H, Ph*H*), 7.45 – 7.39 (m, 1H, Ph*H*), 7.29 – 7.20 (m, 2H, Ar*H*), 6.93 – 6.88 (m, 2H, Ar*H*), 5.80 (s, 1H, C*H*C(CH$_3$)$_3$), 3.97 (q, *J* = 4.7, 1H, N*H*CH$_3$), 3.13 (s, 3H, NC*H*$_3$), 2.26 (d, *J* = 4.7, 3H, NHC*H*$_3$), 0.92 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 171.3 (*C*=O), 158.3 (*C*=O), 141.2 (C_{Ar}), 136.8 (C_{Ph}), 134.4 (C_{Ar}), 129.1 (2×CH_{Ar}), 128.7 (3×CH_{Ph}), 128.4 (2×CH_{Ar}), 128.3 (2×CH_{Ph}), 80.3 (*C*HC(CH$_3$)$_3$), 72.3 (N*C*Ph), 38.4 (*C*(CH$_3$)$_3$), 32.1 (N*C*H$_3$), 27.1 (NH*C*H$_3$), 26.6 (C(*C*H$_3$)$_3$); **IR**: ν_{max} = 3424 (N–H), 2967 (C–H), 1701 (C=O), 1666 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{22}H_{26}O_2N_3ClNa$ ([M+Na]$^+$) 422.1606, found 422.1620; **HPLC**: Chiralpak® AD-H, 25 °C, 1.0 mL/min, Hexane/IPA (90:10), 210 nm, t_R = 9.62 (86.8%), 14.63 (13.2%) min, 87:13 *er*.

(2*R*,5*R*)-2-(*tert*-Butyl)-5-(4-chlorophenyl)-*N*,3-dimethyl-4-oxo-5-phenylimidazolidine-1-carboxamide ((*R*) 4-Phg-c)



Following general procedure 7, a solution of *trans*-**S25** (100 mg, 0.339 mmol) and 4-chloro-*N*-methylaniline (45 µL, 0.373 mmol) in THF (3.40 mL) was treated with 2 portions of KHMDS (2×0.41 mL, 0.814 mmol, 1.0 M in THF). Purification by flash column chromatography gave the title compound (103 mg, 0.258 mmol, 76%) as a white solid. **(*R*) 4-Phg-c**: **HPLC**: Chiralpak® AD-H, 25 °C, 1.0 mL/min, Hexane/IPA (90:10), 210 nm, t_R = 9.57 (5.7%), 14.51 (94.3%) min, 94:6 *er*. For full data see compound **(*S*) 4-Phg-c**.

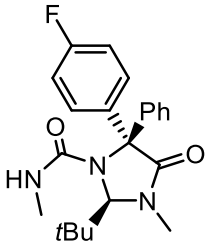
(2*S*,5*S*)-2-(*tert*-Butyl)-5-(4-fluorophenyl)-*N*,3-dimethyl-4-oxo-5-phenylimidazolidine-1-carboxamide ((*S*) 4-Phg-d)



Following general procedure 6, KHMDS (1.56 mL, 1.56 mmol, 1.0 M in THF) was added to a solution of urea **S48** (400 mg, 1.04 mmol) in THF (10.00 mL). Purification by flash column chromatography (SiO_2, 1:1→2:1 EtOAc:Pet.Ether) gave the title compound (339 mg, 0.88 mmol, 85%) as a white solid. **(*S*) 4-Phg-d**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.97 – 7.89 (m, 2H, Ph*H*), 7.51 – 7.45 (m, 2H, Ph*H*), 7.44 – 7.38 (m, 1H, Ph*H*), 7.00 – 6.90 (m, 4H, Ar*H*), 5.80 (s, 1H, C*H*C(CH$_3$)$_3$), 3.96 (q, *J* = 4.8, 1H, N*H*CH$_3$), 3.13 (s, 3H, NC*H*$_3$), 2.25 (d, *J* = 4.7, 3H, NHC*H*$_3$), 0.92 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 171.5 (*C*=O), 162.3 (d, $^1J_{C-F}$ = 249.0, C_{Ar}F), 158.3 (*C*=O), 138.4 (d, $^4J_{C-F}$ = 3.4, C_{Ar}), 137.1 (C_{Ph}), 128.9 (d, $^3J_{C-F}$ = 8.3,

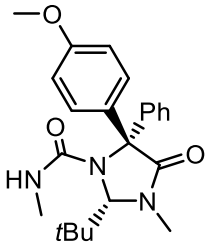
2×*C*H$_{Ar}$), 128.6 (3×*C*H$_{Ph}$), 128.3 (2×*C*H$_{Ph}$), 115.9 (d, $^{2}J_{C-F}$ = 21.8, 2×*C*H$_{Ar}$), 80.3 (*C*HC(CH$_3$)$_3$), 72.3 (NC*C*Ph), 38.4 (*C*(CH$_3$)$_3$), 32.1 (NC*H*$_3$), 27.1 (NH*C*H$_3$), 26.6 (C(*C*H$_3$)$_3$); **IR**: ν_{max} = 3464 (N–H), 2922 (C–H), 1703 (C=O), 1664 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{22}H_{26}O_2N_3FNa$ ([M+Na]$^+$) 406.1901, found 406.1905.

(2*R*,5*R*)-2-(*tert*-Butyl)-5-(4-fluorophenyl)-*N*,3-dimethyl-4-oxo-5-phenylimidazolidine-1-carboxamide ((*R)* 4-Phg-d)



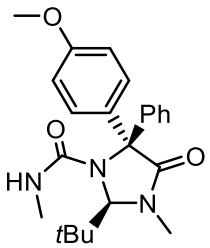
Following general procedure 7, a solution of *trans*-**S25** (100 mg, 0.339 mmol) and 4-fluoro-*N*-methylaniline (45 µL, 0.373 mmol) in THF (3.40 mL) was treated with 2 portions of KHMDS (2×0.41 mL, 0.814 mmol, 1.0 M in THF). Purification by flash column chromatography gave an analytical sample for HPLC. For full data see compound **(*S*) 4-Phg-d**.

(2*S*,5*S*)-2-(*tert*-Butyl)-5-(4-methoxyphenyl)-*N*,3-dimethyl-4-oxo-5-phenylimidazolidine-1-carboxamide ((*S)* 4-Phg-j)



Following general procedure 6, KHMDS (0.13 mL, 0.125 mmol, 1.0 M in THF) was added to a solution of urea **S49** (33 mg, 0.083 mmol) in THF (0.85 mL). Purification by flash column chromatography (SiO_2, 1:1 Pet.Ether:EtOAc) gave the title compound (31 mg, 0.078 mmol, 94%) as a white solid. **(*S)* 4-Phg-j**: **R$_f$** (1:1 Pet.Ether:EtOAc): 0.24; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.94 (d, *J* = 7.1, 2H, Ph*H*), 7.46 (t, *J* = 7.3, 2H, Ph*H*), 7.40 (t, *J* = 7.2, 1H, Ph*H*), 6.87 (d, *J* = 8.9, 2H, Ar*H*), 6.79 (d, *J* = 8.9, 2H, Ar*H*), 5.79 (s, 1H, C*H*C(CH$_3$)$_3$), 3.98 (q, *J* = 4.8, 1H, N*H*CH$_3$), 3.74 (s, 3H, OC*H*$_3$), 3.13 (s, 3H, NC*H*$_3$), 2.26 (d, *J* = 4.7, 3H, NHC*H*$_3$), 0.91 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 171.9 (*C*=O), 159.4 (*C*$_{Ar}$), 158.7 (*C*=O), 137.6 (*C*$_{Ph}$), 134.5 (*C*$_{Ar}$), 128.4 (2×*C*H$_{Ph}$), 128.3 (3×*C*H$_{Ph}$ and 2×*C*H$_{Ar}$), 114.3 (2×*C*H$_{Ar}$), 80.2 (*C*HC(CH$_3$)$_3$), 72.4 (NC*C*Ph), 55.4 (OC*H*$_3$), 38.4 (*C*(CH$_3$)$_3$), 32.1 (NC*H*$_3$), 27.2 (NH*C*H$_3$), 26.6 (C(*C*H$_3$)$_3$); **IR**: ν_{max} = 3452 (N–H), 3062, 2957, 2923, 2853 (C–H), 1703 (C=O), 1666 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{23}H_{29}O_3N_3Na$ ([M+Na]$^+$) 418.2101, found 418.2107; **HPLC**: Chiralcel® OD-H, 25 °C, 0.8 mL/min, Hexane/IPA (90:10), 210 nm, t_R = 14.78 (85.3%), 18.85 (14.7%) min, 85:15 *er*.

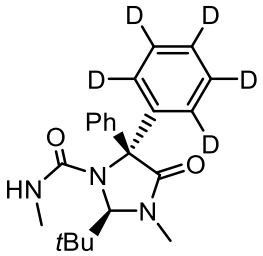
(2*R*,5*R*)-2-(*tert*-Butyl)-5-(4-methoxyphenyl)-*N*,3-dimethyl-4-oxo-5-phenylimidazolidine-1-carboxamide ((*R)* 4-Phg-j)



Following general procedure 7, a solution of *trans*-**S25** (100 mg, 0.339 mmol) and 4-methoxy-*N*-methylaniline (51 mg, 0.373 mmol) in THF (3.40 mL) was treated with 2 portions of KHMDS (2×0.41 mL, 0.814 mmol, 1.0 M in THF). Purification by flash column chromatography gave the title compound (90 mg, 0.228 mmol, 67%) as a white solid. **(*R)* 4-Phg-j**: **HPLC**:

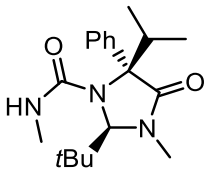
Chiralcel® OD-H, 25 °C, 0.8 mL/min, Hexane/IPA (90:10), 210 nm, t_R = 14.86 (5.2%), 18.81 (94.8%) min, 95:5 *er*. For full data see compound **(*S*) 4-Phg-j**.

(2*R*,5*R*)-2-(*tert*-Butyl)-*N*,3-dimethyl-4-oxo-5-phenyl-5-(phenyl-d_5)imidazolidine-1-carboxamide ((*S*) 4-Phg-p)



Following a similar method to general procedure 7, a solution of *trans*-**S25** (40 mg, 0.136 mmol) and *N*-methylbenzen-d_5-amine (32 mg, 0.271 mmol, 2.0 eq.) in THF (1.4 mL) was treated with 2 portions of KHMDS (2×0.27 mL, 0.271 mmol, 1.0 M in THF, 4.0 eq.). Purification by flash column chromatography (SiO_2, 9:1→1:9 Pet.Ether:EtOAc) gave the title compound (40 mg, 0.109 mmol, 80%) as a white solid. **(*S*) 4-Phg-p**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 8.00 – 7.90 (m, 2H, Ph*H*), 7.52 – 7.44 (m, 2H, Ph*H*), 7.44 – 7.39 (m, 1H, Ph*H*), 5.82 (s, 1H, C*H*C$(CH_3)_3$), 3.93 (q, *J* = 4.7, 1H, N*H*CH_3), 3.14 (s, 3H, NCH_3), 2.18 (d, *J* = 4.8, 3H, NHCH_3), 0.93 (s, 9H, C(CH_3)$_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 171.7 (*C*=O), 158.6 (*C*=O), 142.4 (C_{Ar}), 137.2 (C_{Ph}), 128.9 – 127.6 (m, 4×CH_{Ar} and 5×CH_{Ph}), 126.5 (t, $^1J_{C–D}$ = 24.0, CH_{Ar}), 80.4 (*C*HC$(CH_3)_3$), 72.8 (N*C*Ph), 38.4 (*C*$(CH_3)_3$), 32.1 (NCH_3), 27.0 (NHCH_3), 26.6 (C(*C*H_3)$_3$); **HRMS** (ESI$^+$): *m/z* calcd for $C_{22}H_{22}D_5O_2N_3Na$ ([M+Na]$^+$) 393.2309, found 393.2309.

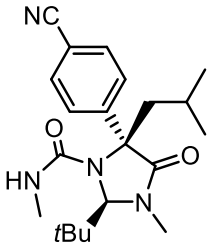
(2*R*,5*R*)-2-(*tert*-Butyl)-5-isopropyl-*N*,3-dimethyl-4-oxo-5-phenylimidazolidine-1-carboxamide ((*R*) 4-Val-a)



LDEA (1.5 eq.) was prepared by dropwise addition of *n*BuLi (0.12 mL, 0.181 mmol, 1.5 eq., 1.5 M in hexanes) to a solution of freshly distilled diethylamine (19 µL, 0.181 mmol, 1.5 eq.) in anhydrous THF (0.50 mL, 0.36 M) at 0 °C. After stirring for 15 min, this LDEA (0.36 M in THF, 1.5 eq.) was added dropwise to a solution of urea **S50** (40 mg, 0.121 mmol, 1.0 eq.) in anhydrous THF (0.70 mL, 0.17 M) at 0 °C. After 15 min, the reaction mixture was warmed to room temperature and allowed to stir for 4 h. The reaction was quenched by dropwise addition of NH_4Cl (sat. aq.) and stirred for 15 min. The organic layer was separated and the aqueous layer extracted 3 times with EtOAc, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound (39 mg, 0.118 mmol, 98%, 91:9 *dr*) as a pale yellow oil without further purification. **(*R*) 4-Val-a**: **^{1}H NMR** (500 MHz, $CDCl_3$) (major diastereomer): δ_H = 7.29 (t, *J* = 7.7, 2H, Ph*H*), 7.22 (t, *J* = 7.3, 1H, Ph*H*), 7.11 (d, *J* = 7.8, 2H, Ph*H*), 5.43 (s, 1H, C*H*C$(CH_3)_3$), 4.42 (br. q, *J* = 4.8, 1H, N*H*CH_3), 3.08 (s, 3H, NCH_3), 2.93 – 2.82 (m, 1H, C*H*$(CH_3)_2$), 2.32 (d, *J* = 4.8, 3H, NHCH_3), 1.34 (d, *J* = 7.1, 3H, CH(CH_3)$_A$$(CH_3)_B$), 1.31 (d, *J* = 6.9, 3H, CH$(CH_3)_A$(CH_3)$_B$), 1.08 (s, 9H, C(CH_3)$_3$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$) (major diastereomer): δ_C = 172.3 (*C*=O), 160.1 (*C*=O), 139.1 (C_{Ph}), 128.7 (2×CH_{Ph}), 128.0 (CH_{Ph}), 126.9 (2×CH_{Ph}), 80.5 (*C*HC$(CH_3)_3$), 73.8 (*C*CH$(CH_3)_2$), 37.6 (*C*$(CH_3)_3$), 33.8 (*C*H$(CH_3)_2$), 31.5 (NCH_3), 27.5 (C(*C*H_3)$_3$), 19.9

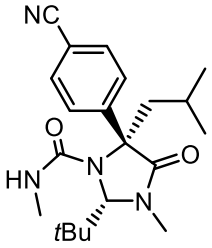
($CH(CH_3)_A(CH_3)_B$), 19.5 ($CH(CH_3)_A(CH_3)_B$); **IR**: ν_{max} = 3391 (N–H), 2962, 2936, 2876 (C–H) 1690 (C=O); **HRMS** (ESI^+): *m/z* calcd for $C_{19}H_{29}O_2N_3Na$ ($[M+Na]^+$) 354.2152, found 354.2150.

(2*R*,5*R*)-2-(*tert*-Butyl)-5-(4-cyanophenyl)-5-isobutyl-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide ((*R)* 4-Leu-b)



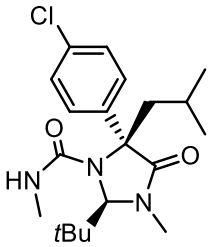
Following general procedure 6, KHMDS (2.60 mL, 2.57 mmol, 1.0 M in THF) was added to a solution of urea **S51** (634 mg, 1.71 mmol) in THF (17.00 mL). Purification by flash column chromatography (SiO_2, 3:2 Pet.Ether:EtOAc) gave the title compound (549 mg, 1.48 mmol, 87%) as a white solid. ***(R)* 4-Leu-b**: $\mathbf{R_f}$ (3:2 Pet.Ether:EtOAc): 0.21; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.63 – 7.58 (m, 2H, Ar*H*), 7.28 – 7.23 (m, 2H, Ar*H*), 5.61 (s, 1H, C*H*C$(CH_3)_3$), 4.12 (br. q, *J* = 4.7, 1H, N*H*CH_3), 3.05 (s, 3H, NC*H*$_3$), 2.47 (dd, *J* = 14.7, 5.2, 1H, CH_AH_BCH), 2.36 (d, *J* = 4.7, 3H, NHC*H*$_3$), 2.16 (dd, *J* = 14.8, 5.3, 1H, CH_AH_BCH), 2.16 – 2.04 (m, 1H, $CH_2CH(CH_3)_2$), 1.14 (d, *J* = 6.4, 3H, $CH(CH_3)_A(CH_3)_B$), 1.10 (d, *J* = 6.5, 3H, $CH(CH_3)_A(CH_3)_B$), 1.08 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 171.1 (*C*=O), 158.9 (*C*=O), 147.4 (C_{Ar}), 132.7 (2×CH_{Ar}), 126.5 (2×CH_{Ar}), 118.4 (*C*≡N), 112.0 (C_{Ar}), 81.3 (*C*HC$(CH_3)_3$), 69.9 (N*C*CH_2), 45.2 (NC*C*H_2), 38.2 (*C*$(CH_3)_3$), 32.1 (N*C*H_3), 27.1 (C(*C*H_3)$_3$), 27.0 (NH*C*H_3), 25.1 ($CH(CH_3)_A(CH_3)_B$), 24.4 ($CH(CH_3)_A(CH_3)_B$), 24.2 (*C*$H(CH_3)_2$); **IR**: ν_{max} = 3432 (N–H), 2958, 2871 (C–H), 2229 (C≡N), 1697 (C=O); **HRMS** (ESI^+): *m/z* calcd for $C_{21}H_{31}O_2N_4$ ($[M+H]^+$) 371.2442, found 371.2441; **HPLC**: Chiralcel® OD-H, 25 °C, 1.0 mL/min, Hexane/IPA (90:10), 254 nm, t_R = 8.31 (100%) min, >99:1 *er*.

(2*S*,5*S*)-2-(*tert*-Butyl)-5-(4-cyanophenyl)-5-isobutyl-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide ((*S)* 4-Leu-b)



Following general procedure 7, a solution of *trans*-**S27** (200 mg, 0.728 mmol) and 4-(methylamino)benzonitrile (106 mg, 0.801 mmol) in THF (7.30 mL) was treated with 2 portions of KHMDS (2×0.87 mL, 1.75 mmol, 1.0 M in THF). Purification by flash column chromatography gave the title compound (208 mg, 0.611 mmol, 84%) as a white solid. ***(S)* 4-Leu-b**: **HPLC**: Chiralcel® OD-H, 25 °C, 1.0 mL/min, Hexane/IPA (90:10), 254 nm, t_R = 11.09 (100%) min, >99:1 *er*. For full data see compound ***(R)* 4-Leu-b**.

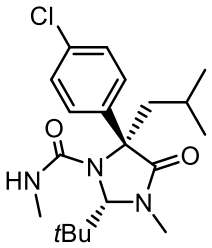
(2*R*,5*R*)-2-(*tert*-Butyl)-5-(4-chlorophenyl)-5-isobutyl-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide ((*R)* 4-Leu-c)



Following general procedure 6, KHMDS (2.14 mL, 2.14 mmol, 1.0 M in THF) was added to a solution of urea **S52** (543 mg, 1.43 mmol) in THF (14.3 mL). Purification by flash column chromatography (SiO_2, 2:1 Pet.Ether:EtOAc) gave the title compound (474 mg, 1.25 mmol, 87%) as a white solid. ***(R)* 4-Leu-c**: $\mathbf{R_f}$ (2:1 Pet.Ether:EtOAc): 0.24; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.31

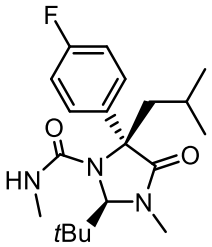
– 7.26 (m, 2H, Ar*H*), 7.10 – 7.05 (m, 2H, Ar*H*), 5.60 (s, 1H, C*H*C(CH$_3$)$_3$), 4.08 (br. q, *J* = 4.9, 1H, N*H*CH$_3$), 3.05 (s, 3H, NC*H*$_3$), 2.41 (dd, *J* = 14.8, 5.4, 1H, C*H*$_A$H$_B$CH), 2.37 (d, *J* = 4.7, 3H, NHC*H*$_3$), 2.16 (dd, *J* = 14.9, 5.2, 1H, CH$_A$*H*$_B$CH), 2.15 – 2.05 (m, 1H, CH$_2$C*H*(CH$_3$)$_2$), 1.13 (d, *J* = 6.4, 3H, CH(C*H*$_3$)$_A$(CH$_3$)$_B$), 1.10 (d, *J* = 6.6, 3H, CH(CH$_3$)$_A$(C*H*$_3$)$_B$), 1.08 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C {^{1}H} NMR** (125 MHz, CDCl$_3$): δ_C = 171.9 (*C*=O), 159.2 (*C*=O), 140.6 (*C*$_{Ar}$), 134.1 (*C*$_{Ar}$), 129.2 (2×*C*H$_{Ar}$), 127.1 (2×*C*H$_{Ar}$), 81.2 (*C*HC(CH$_3$)$_3$), 69.6 (N*C*CH$_2$), 46.3 (NC*C*H$_2$), 38.2 (*C*(CH$_3$)$_3$), 32.1 (N*C*H$_3$), 27.2 (C(*C*H$_3$)$_3$), 27.1 (NH*C*H$_3$), 25.2 (CH(*C*H$_3$)$_A$(CH$_3$)$_B$), 24.4 (CH(CH$_3$)$_A$(*C*H$_3$)$_B$), 24.3 (*C*H(CH$_3$)$_2$); **IR**: ν_{max} = 3431 (N–H), 2958, 2871 (C–H), 1697 (C=O), 1663 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{20}H_{31}O_2N_3Cl$ ([M+H]$^+$) 380.2091, found 380.2099; **HPLC**: Chiralcel® OD-H, 25 °C, 0.8 mL/min, Hexane/IPA (95:5), 225 nm, t_R = 9.88 (100%) min, >99:1 *er*.

(2*S*,5*S*)-2-(*tert*-Butyl)-5-(4-chlorophenyl)-5-isobutyl-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide ((*S)* 4-Leu-c)



Following general procedure 7, a solution of *trans*-**S27** (200 mg, 0.728 mmol) and 4-chloro-*N*-methylaniline (97 µL, 0.801 mmol) in THF (7.30 mL) was treated with 2 portions of KHMDS (2×0.87 mL, 1.75 mmol, 1.0 M in THF). Purification by flash column chromatography gave the title compound (241 mg, 0.634 mmol, 87%) as a white solid. ***(S)* 4-Leu-c**: **HPLC**: Chiralcel® OD-H, 25 °C, 0.8 mL/min, Hexane/IPA (95:5), 225 nm, t_R = 10.94 (100%) min, >99:1 *er*. For full data see compound ***(R)* 4-Leu-c**.

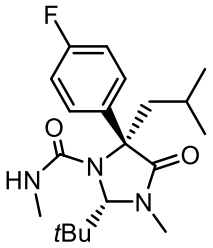
(2*R*,5*R*)-2-(*tert*-Butyl)-5-(4-fluorophenyl)-5-isobutyl-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide ((*R)* 4-Leu-d)



Following general procedure 6, KHMDS (2.62 mL, 2.62 mmol, 1.0 M in THF) was added to a solution of urea **S53** (635 mg, 1.75 mmol) in THF (14.3 mL). Purification by flash column chromatography (SiO_2, 3:1 Pet.Ether:EtOAc) gave the title compound (530 mg, 1.46 mmol, 83%) as a white solid. ***(R)* 4-Leu-d**: **R$_f$** (2:1 Pet.Ether:EtOAc): 0.33; **^{1}H NMR** (500 MHz, CDCl$_3$): δ_H = 7.13 – 7.06 (m, 2H, Ar*H*), 7.02 – 6.95 (m, 2H, Ar*H*), 5.59 (s, 1H, C*H*C(CH$_3$)$_3$), 4.08 (br. q, *J* = 4.9, 1H, N*H*CH$_3$), 3.04 (s, 3H, NC*H*$_3$), 2.39 (dd, *J* = 14.9, 5.4, 1H, C*H*$_A$H$_B$CH), 2.34 (d, *J* = 4.7, 3H, NHC*H*$_3$), 2.16 (dd, *J* = 14.9, 5.2, 1H, CH$_A$*H*$_B$CH), 2.14 – 2.05 (m, 1H, CH$_2$C*H*(CH$_3$)$_2$), 1.11 (d, *J* = 6.4, 3H, CH(C*H*$_3$)$_A$(CH$_3$)$_B$), 1.08 (d, *J* = 6.8, 3H, CH(CH$_3$)$_A$(C*H*$_3$)$_B$), 1.07 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C {^{1}H} NMR** (125 MHz, CDCl$_3$): δ_C = 172.0 (*C*=O), 162.2 (d, $^1J_{C–F}$ = 247.9, *C*$_{Ar}$F), 159.2 (*C*=O), 137.7 (d, $^4J_{C–F}$ = 3.1, *C*$_{Ar}$), 127.5 (d, $^3J_{C–F}$ = 8.2, 2×*C*H$_{Ar}$), 115.9 (d, $^2J_{C–F}$ = 21.6, 2×*C*H$_{Ar}$), 81.1 (*C*HC(CH$_3$)$_3$), 69.4 (N*C*CH$_2$), 45.2 (NC*C*H$_2$), 38.1 (*C*(CH$_3$)$_3$), 32.0 (N*C*H$_3$), 27.1 (C(*C*H$_3$)$_3$), 27.0 (NH*C*H$_3$), 25.1 (CH(*C*H$_3$)$_A$(CH$_3$)$_B$), 24.4 (CH(CH$_3$)$_A$(*C*H$_3$)$_B$), 24.3 (*C*H(CH$_3$)$_2$); **IR**: ν_{max} = 3427 (N–H), 2958, 2871 (C–H), 1696 (C=O), 1662 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for

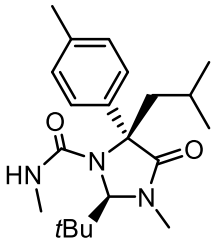
$C_{20}H_{31}O_2N_3F$ ([M+H]$^+$) 364.2395, found 364.2386; **HPLC**: Chiralcel® OD-H, 25 °C, 1.0 mL/min, Hexane/IPA (90:10), 210 nm, t_R = 7.22 (100%) min, >99:1 *er*.

(2*S*,5*S*)-2-(*tert*-Butyl)-5-(4-fluorophenyl)-5-isobutyl-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide ((*S*) 4-Leu-d)



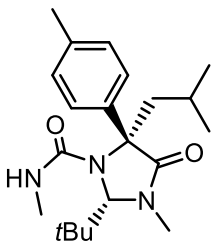
Following general procedure 7, a solution of *trans*-**S27** (200 mg, 0.728 mmol) and 4-fluoro-*N*-methylaniline (96 µL, 0.801 mmol) in THF (7.30 mL) was treated with 2 portions of KHMDS (2×0.87 mL, 1.75 mmol, 1.0 M in THF). Purification by flash column chromatography gave the title compound (201 mg, 0.553 mmol, 76%) as a white solid. **(*S*) 4-Leu-d**: **HPLC**: Chiralcel® OD-H, 25 °C, 1.0 mL/min, Hexane/IPA (90:10), 210 nm, t_R = 8.21 (100%) min, >99:1 *er*. For full data see compound **(*R*) 4-Leu-d**.

(2*R*,5*R*)-2-(*tert*-Butyl)-5-isobutyl-*N*,3-dimethyl-4-oxo-5-(*p*-tolyl)imidazolidine-1-carboxamide ((*R*) 4-Leu-i)



Following general procedure 6, KHMDS (2.07 mL, 2.07 mmol, 1.0 M in THF) was added to a solution of urea **S54** (496 mg, 1.38 mmol) in THF (14.00 mL). Purification by flash column chromatography (SiO_2, 3:1→2:1 Pet.Ether:EtOAc) gave the title compound (402 mg, 1.12 mmol, 81%) as a white solid. **(*R*) 4-Leu-i**: **R_f** (2:1 Pet.Ether:EtOAc): 0.21; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.11 (d, *J* = 8.1, 2H, Ar*H*), 7.01 (d, *J* = 8.4, 2H, Ar*H*), 5.61 (s, 1H, C*H*C(CH$_3$)$_3$), 4.04 (br. q, *J* = 4.8, 1H, N*H*CH$_3$), 3.04 (s, 3H, NC*H*$_3$), 2.37 (dd, *J* = 15.0, 5.8, 1H, C*H*$_A$H$_B$CH), 2.32 (d, *J* = 4.8, 3H, NHC*H*$_3$), 2.28 (s, 3H, C*H*$_3$), 2.21 (dd, *J* = 15.0, 5.1, 1H, CH$_A$*H*$_B$CH), 2.17 – 2.06 (m, 1H, CH$_2$C*H*(CH$_3$)$_2$), 1.12 (d, *J* = 6.5, 3H, CH(C*H*$_3$)$_A$(CH$_3$)$_B$), 1.10 (d, *J* = 6.6, 3H, CH(CH$_3$)$_A$(C*H*$_3$)$_B$), 1.09 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 172.5 (*C*=O), 159.4 (*C*=O), 138.7 (*C*$_{Ar}$), 137.9 (*C*$_{Ar}$), 129.8 (2×*C*H$_{Ar}$), 125.5 (2×*C*H$_{Ar}$), 81.2 (*C*HC(CH$_3$)$_3$), 69.7 (N*C*CH$_2$), 45.0 (NC*C*H$_2$), 38.2 (*C*(CH$_3$)$_3$), 32.1 (N*C*H$_3$), 27.2 (C(*C*H$_3$)$_3$), 27.1 (NH*C*H$_3$), 25.2 (CH(*C*H$_3$)$_A$(CH$_3$)$_B$), 24.4 (CH(CH$_3$)$_A$(*C*H$_3$)$_B$ and *C*H(CH$_3$)$_2$), 21.1 (*C*H$_3$); **IR**: ν_{max} = 3432 (N–H), 2957, 2870 (C–H), 1697 (C=O), 1661 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{21}H_{34}O_2N_3$ ([M+H]$^+$) 360.2646, found 360.2647; **SFC**: Chiralpak® IA, 125 bar, 40 °C, 4.0 mL/min, 20% co-solvent (IPA), λ_{max}, t_R = 1.48 (98.0%), 2.53 (2.0%) min, 98:2 *er*.

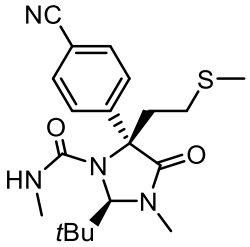
(2*S*,5*S*)-2-(*tert*-Butyl)-5-isobutyl-*N*,3-dimethyl-4-oxo-5-(*p*-tolyl)imidazolidine-1-carboxamide ((*S*) 4-Leu-i)



Following general procedure 7, a solution of *trans*-**S27** (200 mg, 0.728 mmol) and *N*-methyl-*p*-toluidine (101 µL, 0.801 mmol) in THF (7.30 mL) was treated with 2 portions of KHMDS (2×0.87 mL, 1.75 mmol, 1.0 M in THF). Purification by flash column chromatography gave the title compound (167 mg, 0.465 mmol, 64%) as a white solid. **(*S*) 4-Leu-i**: **SFC**: Chiralpak® IA,

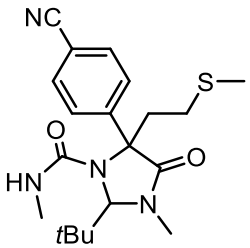
125 bar, 40 °C, 4.0 mL/min, 20% co-solvent (IPA), λ_{max}, t_R = 1.48 (98.3%), 2.51 (1.7%) min, 98:2 *er*. For full data see compound **(*R*) 4-Leu-i**.

(2*R*,5*R*)-2-(*tert*-Butyl)-5-(4-cyanophenyl)-*N*,3-dimethyl-5-(2-(methylthio)ethyl)-4-oxoimidazolidine-1-carboxamide ((*R*) 4-Met-b)



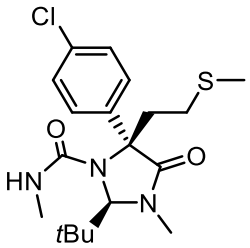
Following general procedure 6, KHMDS (2.23 mL, 2.23 mmol, 1.0 M in THF) was added to a solution of urea **S55** (578 mg, 1.49 mmol) in THF (14.9 mL). Purification by flash column chromatography (SiO_2, 5:1 DCM:EtOAc) gave the title compound (497 mg, 1.28 mmol, 86%) as a pale yellow solid. **(*R*) 4-Met-b**: $\mathbf{R_f}$ (5:1 DCM:EtOAc): 0.27; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.65 – 7.61 (m, 2H, Ar*H*), 7.31 – 7.27 (m, 2H, Ar*H*), 5.58 (s, 1H, C*H*C$(CH_3)_3$), 4.44 (br. q, *J* = 4.8, 1H, N*H*CH_3), 3.06 (s, 3H, NC*H*$_3$), 2.87 – 2.72 (m, 3H, $CH_2CH_2SCH_3$ and $CH_AH_BCH_2SCH_3$), 2.62 – 2.54 (m, 1H, $CH_AH_BCH_2SCH_3$), 2.37 (d, *J* = 4.7, 3H, NHC*H*$_3$), 2.19 (s, 3H, SC*H*$_3$), 1.07 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 170.8 (*C*=O), 158.7 (*C*=O), 145.8 (C_{Ar}), 132.7 (2×*C*H$_{Ar}$), 126.7 (2×*C*H$_{Ar}$), 118.3 (*C*≡N), 112.3 (C_{Ar}), 81.0 (*C*HC$(CH_3)_3$), 38.2 (*C*$(CH_3)_3$), 36.8 (NC*C*H_2), 32.0 (NCH_3), 30.1 (*C*H_2SCH_3), 27.1 (NH*C*H_3), 27.0 (C(*C*$H_3)_3$), 16.1 (S*C*H_3); **IR**: ν_{max} = 3401 (N–H), 2963, 2917 (C–H), 2229 (C≡N), 1695 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{20}H_{29}O_2N_4S$ ([M+H]$^+$) 389.2006, found 389.2006; **HPLC**: Chiralcel® OD-H, 25 °C, 1.0 mL/min, Hexane/IPA (80:20), 236 nm, t_R = 6.52 (100%) min, >99:1 *er*.

rac-2-(*tert*-Butyl)-5-(4-cyanophenyl)-*N*,3-dimethyl-5-(2-(methylthio)ethyl)-4-oxoimidazolidine-1-carboxamide ((*rac*) 4-Met-b)



Following general procedure 6, KHMDS (0.34 mL, 0.336 mmol, 1.0 M in THF) was added to a solution of urea **S56** (87 mg, 0.224 mmol) in THF (2.20 mL). Purification by flash column chromatography gave the title compound (72 mg, 0.185 mmol, 83%) as a pale yellow solid. **(*rac*) 4-Met-b**: **HPLC**: Chiralcel® OD-H, 25 °C, 1.0 mL/min, Hexane/IPA (80:20), 236 nm, t_R = 6.58 (47.3%), 9.18 (52.7%) min, 53:47 *er*. For full data see compound **(*R*) 4-Met-b**.

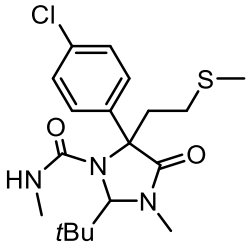
(2*R*,5*R*)-2-(*tert*-Butyl)-5-(4-chlorophenyl)-*N*,3-dimethyl-5-(2-(methylthio)ethyl)-4-oxoimidazolidine-1-carboxamide ((*R*) 4-Met-c)



Following general procedure 6, KHMDS (2.01 mL, 2.01 mmol, 1.0 M in THF) was added to a solution of urea **S57** (533 mg, 1.34 mmol) in THF (13.4 mL). Purification by flash column chromatography (SiO_2, 3:2 Pet.Ether:EtOAc) gave the title compound (460 mg, 1.16 mmol, 86%) as a white solid. **(*R*) 4-Met-c**: $\mathbf{R_f}$ (3:2 Pet.Ether:EtOAc): 0.21; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.33 – 7.28 (m, 2H, Ar*H*), 7.12 – 7.07 (m, 2H, Ar*H*), 5.58 (s, 1H, C*H*C$(CH_3)_3$), 4.30 (br. q, *J* = 4.8, 1H, N*H*CH_3), 3.05 (s, 3H, NC*H*$_3$), 2.88 – 2.68 (m, 3H, $CH_2CH_2SCH_3$ and

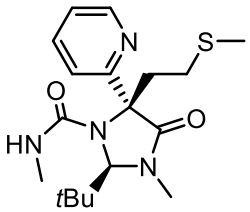
C*H*$_A$H$_B$CH$_2$SCH$_3$), 2.62 – 2.52 (m, 1H, CH$_A$*H*$_B$CH$_2$SCH$_3$), 2.37 (d, *J* = 4.7, 3H, NHC*H*$_3$), 2.18 (s, 3H, SC*H*$_3$), 1.06 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C {^{1}H} NMR** (100 MHz, CDCl$_3$): δ_C = 171.4 (*C*=O), 158.9 (*C*=O), 138.8 (*C*$_{Ar}$), 134.4 (*C*$_{Ar}$), 129.2 (2×*C*H$_{Ar}$), 127.2 (2×*C*H$_{Ar}$), 80.8 (*C*HC(CH$_3$)$_3$), 69.1 (N*C*CH$_2$), 38.1 (*C*(CH$_3$)$_3$), 36.9 (NC*C*H$_2$), 32.0 (N*C*H$_3$), 30.1 (*C*H$_2$SCH$_3$), 27.1 (NH*C*H$_3$), 27.0 (C(*C*H$_3$)$_3$), 16.0 (S*C*H$_3$); **IR**: ν_{max} = 3400 (N–H), 2962, 2916 (C–H), 1694 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for C$_{19}$H$_{29}$O$_2$N$_3$ClS ([M+H]$^+$) 398.1664, found 398.1666; **HPLC**: Chiralcel® OD-H, 25 °C, 1.0 mL/min, Hexane/IPA (90:10), 230 nm, t_R = 7.33 (100%) min, >99:1 *er*.

<u>*rac*-2-(*tert*-Butyl)-5-(4-chlorophenyl)-*N*,3-dimethyl-5-(2-(methylthio)ethyl)-4-oxoimidazolidine-1-carboxamide ((*rac)* 4-Met-c)</u>



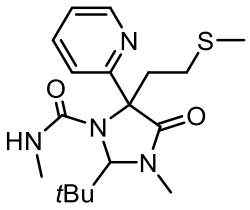
Following general procedure 6, KHMDS (0.27 mL, 0.271 mmol, 1.0 M in THF) was added to a solution of urea **S58** (72 mg, 0.181 mmol) in THF (1.80 mL). Purification by flash column chromatography gave the title compound (58 mg, 0.146 mmol, 81%) as a pale yellow solid. ***(rac)* 4-Met-c**: **HPLC**: Chiralcel® OD-H, 25 °C, 1.0 mL/min, Hexane/IPA (90:10), 230 nm, t_R = 7.30 (50.0%), 9.46 (50.0%) min, 50:50 *er*. For full data see compound ***(R)* 4-Met-c**.

<u>(2*R*,5*R*)-2-(*tert*-Butyl)-*N*,3-dimethyl-5-(2-(methylthio)ethyl)-4-oxo-5-(pyridin-2-yl)imidazolidine-1-carboxamide ((*R)* 4-Met-o)</u>



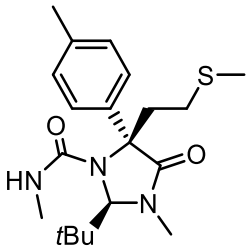
Following general procedure 6, KHMDS (2.06 mL, 2.06 mmol, 1.0 M in THF) was added to a solution of urea **S59** (501 mg, 1.37 mmol) in THF (13.7 mL). Purification by flash column chromatography (SiO_2, 99:1→97:3 EtOAc:MeOH) gave the title compound (450 mg, 1.23 mmol, 90%) as a white solid. ***(R)* 4-Met-o**: **^{1}H NMR** (500 MHz, CDCl$_3$): δ_H = 8.55 (ddd, *J* = 4.8, 1.6, 0.8, 1H, Ar*H*), 7.65 (td, *J* = 7.8, 1.8, 1H, Ar*H*), 7.18 (ddd, *J* = 7.5, 4.9, 0.8, 1H, Ar*H*), 7.02 (d, *J* = 8.0, 1H, Ar*H*), 5.58 (s, 1H, C*H*C(CH$_3$)$_3$), 4.42 (br. q, *J* = 4.9, 1H, N*H*CH$_3$), 3.11 (s, 3H, NC*H*$_3$), 3.00 – 2.83 (m, 3H, CH$_2$C*H*$_2$SCH$_3$ and C*H*$_A$H$_B$CH$_2$SCH$_3$), 2.70 – 2.62 (m, 1H, CH$_A$*H*$_B$CH$_2$SCH$_3$), 2.26 (d, *J* = 4.7, 3H, NHC*H*$_3$), 2.19 (s, 3H, SC*H*$_3$), 1.07 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C {^{1}H} NMR** (125 MHz, CDCl$_3$): δ_C = 171.7 (*C*=O), 158.6 (*C*=O), 158.5 (*C*$_{Ar}$), 148.5 (*C*H$_{Ar}$), 137.5 (*C*H$_{Ar}$), 123.1 (*C*H$_{Ar}$), 121.6 (*C*H$_{Ar}$), 80.7 (*C*HC(CH$_3$)$_3$), 70.7 (N*C*CH$_2$), 38.1 (*C*(CH$_3$)$_3$), 36.6 (NC*C*H$_2$), 32.0 (N*C*H$_3$), 29.9 (*C*H$_2$SCH$_3$), 27.0 (C(*C*H$_3$)$_3$), 26.9 (NH*C*H$_3$), 15.8 (S*C*H$_3$); **IR**: ν_{max} = 3399 (N–H), 2960, 2916 (C–H), 1698 (C=O), 1668 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for C$_{18}$H$_{29}$O$_2$N$_4$S ([M+H]$^+$) 365.2006, found 365.1998; **SFC**: Chiralpak® IA, 125 bar, 40 °C, 4.0 mL/min, 10% co-solvent (IPA), λ_{max}, t_R = 7.80 (100%) min, >99:1 *er*.

rac-2-(*tert*-Butyl)-*N*,3-dimethyl-5-(2-(methylthio)ethyl)-4-oxo-5-(pyridin-2-yl)imidazolidine-1-carboxamide ((*rac)* 4-Met-o)



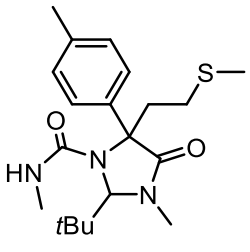
Following general procedure 6, KHMDS (0.80 mL, 0.803 mmol, 1.0 M in THF) was added to a solution of urea **S60** (195 mg, 0.535 mmol) in THF (5.30 mL). Purification by flash column chromatography gave the title compound (168 mg, 0.461 mmol, 86%) as a pale yellow solid. **(*rac)* 4-Met-o**: **SFC**: Chiralpak® IA, 125 bar, 40 °C, 4.0 mL/min, 10% co-solvent (IPA), λ_{max}, t_R = 7.99 (52.1%), 16.39 (47.9%) min, 52:48 *er*. For full data see compound **(*R)* 4-Met-o**.

(2*R*,5*R*)-2-(*tert*-Butyl)-*N*,3-dimethyl-5-(2-(methylthio)ethyl)-4-oxo-5-(*p*-tolyl)imidazolidine-1-carboxamide ((*R)* 4-Met-i)



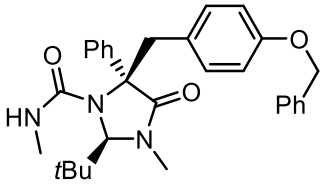
Following general procedure 6, KHMDS (2.86 mL, 2.86 mmol, 1.0 M in THF) was added to a solution of urea **S61** (720 mg, 1.91 mmol) in THF (19.1 mL). Purification by flash column chromatography (SiO_2, 3:2→1:1 Pet.Ether:EtOAc) gave the title compound (527 mg, 1.40 mmol, 73%) as a white solid. **(*R)* 4-Met-i**: **R_f** (1:1 Pet.Ether:EtOAc): 0.26; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.14 (d, *J* = 7.7, 2H, Ar*H*), 7.04 (d, *J* = 7.6, 2H, Ar*H*), 5.60 (s, 1H, C*H*C$(CH_3)_3$), 4.13 (br. q, *J* = 4.1, 1H, N*H*CH_3), 3.06 (s, 3H, NC*H*$_3$), 2.90 – 2.66 (m, 3H, $CH_2CH_2SCH_3$ and $CH_AH_BCH_2SCH_3$), 2.66 – 2.55 (m, 1H, $CH_AH_BCH_2SCH_3$), 2.33 (d, *J* = 4.3, 3H, NHC*H*$_3$), 2.29 (s, 3H, C*H*$_3$), 2.19 (s, 3H, SC*H*$_3$), 1.07 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 172.0 (*C*=O), 159.1 (*C*=O), 138.4 (C_{Ar}), 137.0 (C_{Ar}), 129.9 (2×CH_{Ar}), 125.6 (2×CH_{Ar}), 80.9 (*C*HC$(CH_3)_3$), 69.1 (NCCH_2), 38.2 (*C*$(CH_3)_3$), 36.8 (NC*C*H$_2$), 32.0 (N*C*H$_3$), 30.2 (*C*H_2SCH_3), 27.1 (C(*C*H$_3$)$_3$ and NH*C*H$_3$), 21.1 (*C*H$_3$), 16.0 (S*C*H$_3$); **IR**: ν_{max} = 3400 (N–H), 2960, 2916, 2875 (C–H), 1694 (C=O), 1658 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{20}H_{32}O_2N_3S$ ($[M+H]^+$) 378.2210, found 378.2202; **HPLC**: Chiralcel® OD-H, 25 °C, 1.0 mL/min, Hexane/IPA (90:10), 230 nm, t_R = 8.16 (100%) min, >99:1 *er*.

rac-2-(*tert*-Butyl)-*N*,3-dimethyl-5-(2-(methylthio)ethyl)-4-oxo-5-(*p*-tolyl)imidazolidine-1-carboxamide ((*rac)* 4-Met-i)



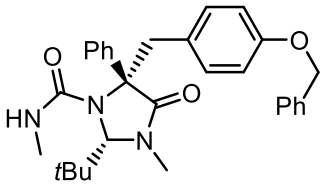
Following general procedure 6, KHMDS (0.23 mL, 0.227 mmol, 1.0 M in THF) was added to a solution of urea **S62** (57 mg, 0.151 mmol) in THF (1.50 mL). Purification by flash column chromatography gave the title compound (37 mg, 0.981 mmol, 65%) as a pale yellow solid. **(*rac*) 4-Met-i**: **HPLC**: Chiralcel® OD-H, 25 °C, 1.0 mL/min, Hexane/IPA (90:10), 230 nm, t_R = 8.21 (49.4%), 9.41 (50.6%) min, 51:49 *er*. For full data see compound **(*R)* 4-Met-i**.

(2*R*,5*R*)-5-(4-(Benzyloxy)benzyl)-2-(*tert*-butyl)-*N*,3-dimethyl-4-oxo-5-phenylimidazolidine-1-carboxamide ((*R)* 4-TyrOBn-a)



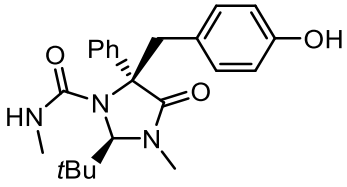
Following a similar method to general procedure 6, KHMDS (0.52 mL, 0.515 mmol, 1.0 M in THF, 2.5 eq.) was added to a solution of urea **S63** (100 mg, 0.206 mmol, 1.0 eq.) in THF (2.00 mL, 0.1 M). Purification by flash column chromatography (SiO_2, 2:1 EtOAc:Pet.Ether) gave the title compound (88 mg, 0.181 mmol, 88%) as a white solid. **(*R)* 4-TyrOBn-a**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.44 – 7.22 (m, 12H, Ph*H* and Ar*H*), 6.91 (d, *J* = 8.2, 2H, Ar*H*), 5.58 (s, 1H, C*H*C$(CH_3)_3$), 5.06 (s, 2H, OCH_2Ph), 3.86 (br. q, *J* = 4.7, 1H, N*H*CH_3), 3.77 (d, *J* = 14.5, 1H, NCCH_AH$_B$), 3.59 (d, *J* = 14.6, 1H, NCCH$_A$$H_B$), 2.97 (s, 3H, NC$H_3$), 2.18 (d, *J* = 4.7, 3H, NHCH_3), 0.76 (s, 9H, C(CH_3)$_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 171.5 (*C*=O), 159.4 (*C*=O), 158.5 (C_{Ar}O), 141.4 (C_{Ph}), 137.0 (C_{Ph}), 132.6 (2×CH_{Ar}), 129.0 (2×CH_{Ph}), 128.7 (2×CH_{Ph}), 128.2 (CH_{Ph}), 128.1 (CH_{Ph}), 127.7 (C_{Ar}), 127.4 (2×CH_{Ph}), 125.6 (2×CH_{Ph}), 115.5 (2×CH_{Ar}), 81.2 (*C*HC$(CH_3)_3$), 71.9 (N*C*CH_2), 70.1 (O*C*H_2Ph), 39.9 (NC*C*H_2), 37.8 (*C*$(CH_3)_3$), 31.9 (N*C*H_3), 27.0 (NH*C*H_3), 26.6 (C(*C*H_3)$_3$); **IR**: ν_{max} = 3432 (N–H), 2958, 2243 (C–H), 1694 (C=O), 1660 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{30}H_{35}O_3N_3Na$ ([M+Na]$^+$) 508.2570, found 508.2555; **HPLC**: Chiralpak® AD-H, 25 °C, 1.0 mL/min, Hexane/IPA (90:10), 210 nm, t_R = 21.48 (99.3%), 52.32 (0.7%) min, >99:1 *er*.

(2*S*,5*S*)-5-(4-(Benzyloxy)benzyl)-2-(*tert*-butyl)-*N*,3-dimethyl-4-oxo-5-phenylimidazolidine-1-carboxamide ((*S)* 4-TyrOBn-a)



Following general procedure 7, a solution of *trans*-**S28** (200 mg, 0.482 mmol) and *N*-methylaniline (57 µL, 0.530 mmol) in THF (4.80 mL) was treated with 2 portions of KHMDS (2×0.58 mL, 1.16 mmol, 1.0 M in THF). Purification by flash column chromatography gave the title compound (222 mg, 0.457 mmol, 95%) as a white solid. **(*S)* 4-TyrOBn-a**: **HPLC**: Chiralpak® AD-H, 25 °C, 1.0 mL/min, Hexane/IPA (90:10), 210 nm, t_R = 51.95 (100%) min, >99:1 *er*. For full data see compound **(*R)* 4-TyrOBn-a**.

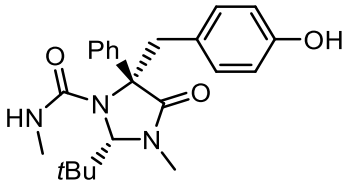
(2*R*,5*R*)-2-(*tert*-Butyl)-5-(4-hydroxybenzyl)-*N*,3-dimethyl-4-oxo-5-phenylimidazolidine-1-carboxamide ((*R)* 4-Tyr-a)



Following a similar method to general procedure 6, KHMDS (1.26 mL, 1.26 mmol, 1.0 M in THF, 5.0 eq.) was added to a solution of urea **S64** (100 mg, 0.253 mmol, 1.0 eq.) in THF (2.50 mL, 0.1 M). Purification by flash column chromatography (SiO_2, 3:1 EtOAc:Pet.Ether) gave the title compound (90 mg, 0.227 mmol, 90%) as a white solid. **(*R)* 4-Tyr-a**: **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.38 – 7.33 (m, 2H, Ph*H*), 7.32 – 7.28 (m, 3H, Ph*H*), 7.28 – 7.25 (m, 2H, Ar*H*), 6.77 – 6.73 (m, 2H, Ar*H*), 6.70 (br. s, 1H, O*H*), 5.61 (s, 1H,

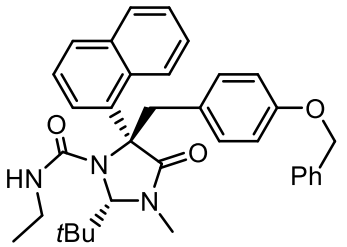
C*H*C(CH$_3$)$_3$), 3.83 (br. q, *J* = 4.0, 1H, N*H*CH$_3$), 3.69 (d, *J* = 14.7, 1H, NCC*H*$_A$H$_B$), 3.64 (d, *J* = 14.7, 1H, NCCH$_A$*H*$_B$), 2.99 (s, 3H, NC*H*$_3$), 2.15 (d, *J* = 4.7, 3H, NHC*H*$_3$), 0.83 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C {^{1}H} NMR** (125 MHz, CDCl$_3$): δ_C = 171.8 (*C*=O), 159.6 (*C*=O), 156.3 (*C*$_{Ar}$O), 141.0 (*C*$_{Ph}$), 132.6 (2×*C*H$_{Ar}$), 129.1 (2×*C*H$_{Ph}$), 128.3 (*C*H$_{Ph}$), 126.6 (*C*$_{Ar}$), 125.7 (2×*C*H$_{Ph}$), 116.0 (2×*C*H$_{Ar}$), 81.5 (*C*HC(CH$_3$)$_3$), 72.2 (N*C*CH$_2$), 39.8 (NC*C*H$_2$), 37.9 (*C*(CH$_3$)$_3$), 32.1 (N*C*H$_3$), 27.1 (NH*C*H$_3$), 26.7 (C(*C*H$_3$)$_3$); **IR**: ν_{max} = 3279 (O–H), 2960, 2540 (C–H), 1692 (C=O), 1644 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{23}H_{29}O_3N_3Na$ ([M+Na]$^+$) 418.2101, found 418.2109; **HPLC**: Chiralcel® AD-H, 25 °C, 1.0 mL/min, Hexane/IPA (80:20), 225 nm, t_R = 5.15 (100%), >99:1 *er*.

(2*S*,5*S*)-2-(*tert*-Butyl)-5-(4-hydroxybenzyl)-*N*,3-dimethyl-4-oxo-5-phenylimidazolidine-1-carboxamide ((*S*) 4-Tyr-a)



To a solution of urea **S64** (50 mg, 0.103 mmol, 1.0 eq.) in EtOH (1.00 mL, 0.1 M) was added Pd/C (6 mg, 0.006 mmol, 10% *w*/*w*, 0.05 eq.). The suspension was stirred under a hydrogen atmosphere for 1 h. The reaction mixture was filtered over Celite®, washed through with DCM and concentrated *in vacuo*. Purification by flash column chromatography gave the title compound (40 mg, 0.101 mmol, 99%) as a white solid. **(*S*) 4-Tyr-a**: **HPLC**: Chiralcel® AD-H, 25 °C, 1.0 mL/min, Hexane/IPA (80:20), 225 nm, t_R = 5.20 (3.0%), 14.36 (97.0%) min, 97:3 *er*. For full data see compound **(*R*) 4-Tyr-a**.

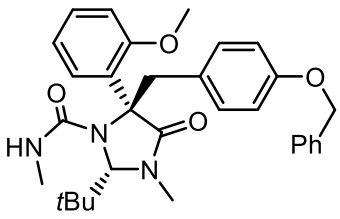
(2*S*,5*R*)-5-(4-(Benzyloxy)benzyl)-2-(*tert*-butyl)-*N*-ethyl-3-methyl-5-(naphthalen-1-yl)-4-oxoimidazolidine-1-carboxamide ((*S*) 4-TyrOBn-h)



Following a similar method to general procedure 7, a solution of *trans*-**S28** (150 mg, 0.362 mmol) and *N*-ethyl-1-naphthylamine (74 mg, 0.432 mmol, 1.2 eq.) in THF (3.60 mL) was treated with 2 portions of KHMDS (2×0.54 mL, 1.08 mmol, 1.0 M in THF, 3.0 eq.). Purification by flash column chromatography gave the title compound (123 mg, 0.224 mmol, 62%) as a white solid. **(*S*) 4-TyrOBn-h**: **^{1}H NMR** (500 MHz, CDCl$_3$): δ_H = 8.14 (d, *J* = 7.4, 1H, Ar*H*), 7.79 – 7.74 (m, 2H, Ar*H*), 7.72 (d, *J* = 8.4, 2H, Ar*H*), 7.49 – 7.44 (m, 1H, Ar*H*), 7.44 – 7.35 (m, 6H, Ar*H*), 7.34 – 7.31 (m, 1H, Ar*H*), 7.29 (t, *J* = 7.4, 1H, Ar*H*), 6.98 (d, *J* = 8.8, 2H, Ar*H*), 5.93 (s, 1H, C*H*C(CH$_3$)$_3$), 5.11 – 5.03 (m, 2H, OC*H*$_2$Ph), 3.97 (d, *J* = 15.6, 1H, NCC*H*$_A$H$_B$), 3.62 (d, *J* = 15.6, 1H, NCCH$_A$*H*$_B$), 3.48 (t, *J* = 5.6, 1H, N*H*CH$_2$), 3.22 (s, 3H, NC*H*$_3$), 2.30 – 2.15 (m, 2H, NHC*H*$_2$CH$_3$), 1.28 (s, 9H, C(C*H*$_3$)$_3$), -0.27 (t, *J* = 7.2, 3H, NHCH$_2$C*H*$_3$); **^{13}C {^{1}H} NMR** (125 MHz, CDCl$_3$): δ_C = 173.3 (*C*=O), 158.2 (*C*$_{Ar}$O), 157.2 (*C*=O), 136.9 (*C*$_{Ar}$), 134.9 (*C*$_{Ar}$), 134.8 (*C*$_{Ar}$), 132.6 (2×*C*H$_{Ar}$), 131.3 (*C*$_{Ar}$), 130.1 (*C*H$_{Ar}$), 129.5 (*C*H$_{Ar}$), 128.7 (2×*C*H$_{Ar}$), 128.2 (*C*$_{Ar}$), 128.1 (2×*C*H$_{Ar}$), 127.5 (2×*C*H$_{Ar}$), 127.0 (*C*H$_{Ar}$), 125.9 (*C*H$_{Ar}$), 124.5 (*C*H$_{Ar}$), 122.5 (*C*H$_{Ar}$), 115.2 (2×*C*H$_{Ar}$), 82.1 (*C*HC(CH$_3$)$_3$), 70.8 (N*C*CH$_2$), 70.1 (O*C*H$_2$Ph), 42.6 (NC*C*H$_2$), 38.4 (*C*(CH$_3$)$_3$), 34.6 (NH*C*H$_2$CH$_3$), 32.2 (N*C*H$_3$), 27.9 (C(*C*H$_3$)$_3$),

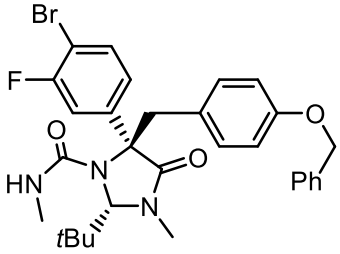
13.5 ($NHCH_2CH_3$); **HRMS** (ESI^+): *m/z* calcd for $C_{35}H_{39}O_3N_3Na$ ($[M+Na]^+$) 572.2884, found 572.2880.

(2*S*,5*R*)-5-(4-(Benzyloxy)benzyl)-2-(*tert*-butyl)-5-(2-methoxyphenyl)-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide ((*S)* 4-TyrOBn-l)



Following a similar method to general procedure 7, a solution of *trans*-**S28** (200 mg, 0.482 mmol) and 2-methoxy-*N*-methylaniline (79 mg, 0.576 mmol, 1.2 eq.) in THF (4.80 mL) was treated with 2 portions of KHMDS (2×0.72 mL, 1.45 mmol, 1.0 M in THF, 3.0 eq.). Purification by flash column chromatography gave the title compound (149 mg, 0.289 mmol, 60%) as a white solid. **(*S)* 4-TyrOBn-l**: **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.70 (d, *J* = 7.8, 1H, Ar*H*), 7.47 (d, *J* = 8.2, 2H, Ar*H*), 7.41 (d, *J* = 7.0, 2H, Ar*H*), 7.37 (t, *J* = 7.5, 2H, Ar*H*), 7.31 (t, *J* = 7.0, 1H, Ar*H*), 7.22 (t, *J* = 7.8, 1H, Ar*H*), 6.96 – 6.89 (m, 3H, Ar*H*), 6.82 (d, *J* = 8.2, 1H, Ar*H*), 5.34 (s, 1H, C*H*C(CH_3)$_3$), 5.06 (s, 2H, OCH_2Ph), 3.72 (s, 3H, OCH_3), 3.67 (br. s, 1H, N*H*CH_3), 3.64 – 3.55 (m, 2H, NCCH_2), 3.03 (s, 3H, NCH_3), 2.06 (d, *J* = 4.7, 3H, NHCH_3), 0.91 (s, 9H, C(CH_3)$_3$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 172.9, 159.3, 158.3, 156.9, 137.0, 132.7, 129.7, 128.7, 128.7, 128.1, 128.0, 127.5, 120.5, 115.2, 111.7, 82.6, 70.1, 69.5, 56.5, 41.7, 37.2, 32.2, 27.2, 26.8; **HRMS** (ESI^+): *m/z* calcd for $C_{31}H_{38}O_4N_3$ ($[M+H]^+$) 516.2857, found 516.2857.

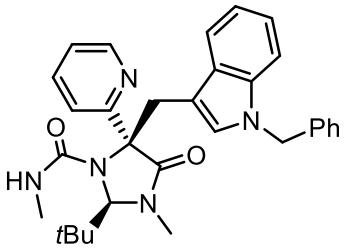
(2*S*,5*R*)-5-(4-(Benzyloxy)benzyl)-5-(4-bromo-3-fluorophenyl)-2-(*tert*-butyl)-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide ((*S)* 4-TyrOBn-g)



Following a similar method to general procedure 7, a solution of *trans*-**S28** (150 mg, 0.362 mmol) and 4-bromo-3-fluoro-*N*-methylaniline (89 mg, 0.436 mmol, 1.2 eq.) in THF (3.60 mL) was treateSd with 2 portions of KHMDS (2×0.54 mL, 1.08 mmol, 1.0 M in THF, 3.0 eq.). Purification by flash column chromatography gave the title compound (194 mg, 0.333 mmol, 92%) as a white solid. **(*S)* 4-TyrOBn-g**: **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.50 (dd, *J* = 8.5, 7.1, 1H, Ar*H*), 7.41 – 7.33 (m, 4H, Ar*H*), 7.33 – 7.27 (m, 3H, Ar*H*), 7.14 (dd, *J* = 10.1, 2.3, 1H, Ar*H*), 6.96 – 6.90 (m, 3H, Ar*H*), 5.57 (s, 1H, C*H*C(CH_3)$_3$), 5.06 (s, 2H, OCH_2Ph), 3.89 (br. s, 1H, N*H*CH_3), 3.66 (d, *J* = 14.6, 1H, NCCH_AH$_B$), 3.56 (d, *J* = 14.8, 1H, NCCH$_A$$H_B$), 2.96 (s, 3H, NC$H_3$), 2.24 (br. s, 3H, NHC$H_3$), 0.77 (s, 9H, C(C$H_3$)$_3$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 170.5 (*C*=O), 159.1 (d, $^1J_{C-F}$ = 248.4, C_{Ar}F), 158.7 (*C*=O), 158.5 (C_{Ar}O), 143.1 (C_{Ar}), 136.7 (C_{Ar}), 133.7 (CH_{Ar}), 132.3 (2×CH_{Ar}), 128.6 (2×CH_{Ar}), 128.0 (CH_{Ar}), 127.3 (2×CH_{Ar}), 126.9 (C_{Ar}), 122.5 (d, $^4J_{C-F}$ = 3.5, CH_{Ar}), 115.5 (2×CH_{Ar}), 114.4 (d, $^2J_{C-F}$ = 24.3, CH_{Ar}), 108.8 (d, $^2J_{C-F}$ = 20.9, C_{Ar}Br), 81.0 (CHC(CH_3)$_3$), 71.5 (NCCH$_2$), 69.9 (OCH$_2$Ph), 39.9 (NCCH$_2$), 37.7 (C(CH_3)$_3$), 31.8 (NCH_3), 27.0 (NHCH_3), 26.4

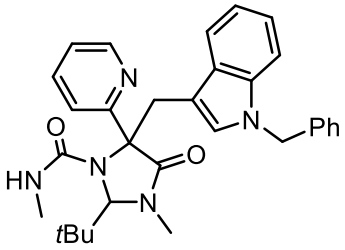
($C(CH_3)_3$); **HRMS** (ESI^+): *m/z* calcd for $C_{30}H_{33}O_3N_3BrFNa$ ($[M+Na]^+$) 604.1582, found 604.1568.

(2*R*,5*R*)-5-((1-Benzyl-1*H*-indol-3-yl)methyl)-2-(*tert*-butyl)-*N*,3-dimethyl-4-oxo-5-(pyridin-2-yl)imidazolidine-1-carboxamide ((*R)* 4-Trp-o)



Following a similar method to general procedure 6, KHMDS (1.72 mL, 1.72 mmol, 1.0 M in THF, 2.5 eq.) was added to a solution of urea **S65** (350 mg, 0.687 mmol, 1.0 eq.) in THF (7.00 mL, 0.1 M). Purification by flash column chromatography (SiO_2, 3:1 EtOAc:Pet.Ether) gave the title compound (315 mg, 0.618 mmol, 90%) as a white solid. ***(R)* 4-Trp-o**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 8.69 – 8.62 (m, 1H, Ar*H*), 8.07 – 7.97 (m, 1H, Ar*H*), 7.62 (td, *J* = 7.8, 1.9, 1H, Ar*H*), 7.39 (s, 1H, C=C*H*), 7.32 – 7.24 (m, 4H, Ar*H*), 7.21 – 7.10 (m, 6H, Ar*H*), 5.69 (s, 1H, C*H*C$(CH_3)_3$), 5.27 (s, 2H, NCH_2Ph), 4.49 (d, *J* = 15.1, 1H, NCCH_AH$_B$), 4.06 (q, *J* = 4.8, 1H, N*H*CH_3), 3.58 (d, *J* = 15.1, 1H, NCCH$_A$$H_B$), 3.07 (s, 3H, NC$H_3$), 1.74 (d, *J* = 4.6, 3H, NHCH_3), 1.01 (s, 9H, C(CH_3)$_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 172.0 (*C*=O), 159.1 (*C*=O and C_{Ar}), 148.5 (*C*H$_{Ar}$), 137.2 (C_{Ar}), 136.9 (*C*H$_{Ar}$), 136.2 (C_{Ar}), 129.9 (C=*C*H), 129.1 (C_{Ar}), 128.9 (2×*C*H$_{Ar}$), 127.9 (*C*H$_{Ar}$), 127.1 (2×*C*H$_{Ar}$), 122.6 (*C*H$_{Ar}$), 122.2 (*C*H$_{Ar}$), 120.8 (*C*H$_{Ar}$), 120.4 (*C*H$_{Ar}$), 119.8 (*C*H$_{Ar}$), 109.7 (*C*H$_{Ar}$), 109.1 (*C*=CH), 81.0 (*C*HC$(CH_3)_3$), 74.0 (N*C*CH$_2$), 50.3 (N*C*H$_2$Ph), 37.9 (*C*$(CH_3)_3$), 32.0 (N*C*H$_3$), 30.4 (NC*C*H$_2$), 26.7 (C(*C*H$_3$)$_3$), 26.3 (NH*C*H$_3$); **IR**: ν_{max} = 3379 (N–H), 2957, 2930 (C–H), 1696 (C=O), 1667 (C=O); **HRMS** (ESI^+): *m/z* calcd for $C_{31}H_{35}O_2N_5Na$ ($[M+Na]^+$) 532.2683, found 532.2684; **SFC**: Chiralpak® IA, 130 bar, 40 °C, 4.0 mL/min, 20% co-solvent (IPA), λ_{max}, t_R = 12.82 (100%) min, >99:1 *er*.

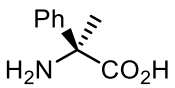
rac-5-((1-Benzyl-1*H*-indol-3-yl)methyl)-2-(*tert*-butyl)-*N*,3-dimethyl-4-oxo-5-(pyridin-2-yl)imidazolidine-1-carboxamide ((*rac)* 4-Trp-o)



Following a similar method to general procedure 6, KHMDS (0.52 mL, 1.72 mmol, 1.0 M in THF, 2.5 eq.) was added to a solution of urea **S66** (105 mg, 0.206 mmol, 1.0 eq.) in THF (2.10 mL, 0.1 M). Purification by flash column chromatography gave the title compound (93 mg, 0.182 mmol, 89%) as a white solid. ***(rac)* 4-Trp-o**: **SFC**: Chiralpak® IA, 130 bar, 40 °C, 4.0 mL/min, 20% co-solvent (IPA), λ_{max}, t_R = 12.98 (49.6%), 18.05 (50.4%) min, 50:50 *er*. For full data see compound ***(R)* 4-Trp-o**.

Hydrolysis to Amino Acids and Hydantoins

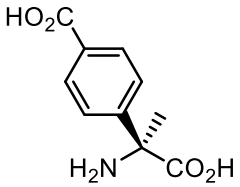
(*S*)-2-Amino-2-phenylpropanoic acid (5-Ala-a)



Urea ***(S)* 4-Ala-a** (48 mg, 0.158 mmol) was suspended in HCl (1.00 mL, 6.0 M, aq.) and heated at 130 °C in a sealed tube for 18 h. The cooled reaction mixture

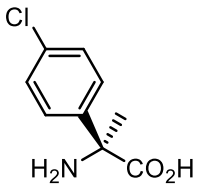
was concentrated *in vacuo* and NaOH (2.0 M, aq.) was added until pH = 14, before being heated at 130 °C in a sealed tube for 42 h. The cooled reaction mixture was concentrated *in vacuo* and HCl (6.0 M, aq.) was added until pH < 3. The crude product was purified according to general procedure 8 to afford the title compound (20 mg, 0.121 mmol, 77%) as a white solid. **5-Ala-a**: **^{1}H NMR** (400 MHz, CD_3OD): δ_H = 7.58 (d, *J* = 7.4, 2H, Ph*H*), 7.43 (t, *J* = 7.3, 2H, Ph*H*), 7.40 – 7.34 (m, 1H, Ph*H*), 1.89 (s, 3H, CH_3); **^{13}C {^{1}H} NMR** (100 MHz, CD_3OD): δ_C = 175.3 (*C*=O), 140.1 (C_{Ph}), 129.9 (2×CH_{Ph}), 129.7 (CH_{Ph}), 127.0 (2×CH_{Ph}), 63.8 (CCH_3), 22.6 (CCH_3); **IR**: ν_{max} = 3062, 2978 (NH_3^+ and C–H), 1593 (COO^- asym.), 1389 (COO^- sym.); **HRMS** (ESI^+): *m/z* calcd for $C_9H_{12}O_2N$ ($[M+H]^+$) 166.0868, found 166.0869. Data in agreement with reported values.[11]

(*S*)-4-(1-amino-1-carboxyethyl)benzoic acid [(*S*)-M4CPG] (5-Ala-b')



Following general procedure 8, NaH (11 mg, 0.275 mmol, 60% suspension) and MeI (20 µL, 0.324 mmol) were added to urea **(*S*) 4-Ala-b** (71 mg, 0.216 mmol) in DMF (2.20 mL). The resulting methylated urea was suspended in HCl/EtOH (1.10 mL, 10:1) and hydrolysed to give the title compound (32 mg, 0.153 mmol, 71%) as a white solid. **5-Ala-b'**: **^{1}H NMR** (500 MHz, CD_3OD): δ_H = 8.00 (d, *J* = 8.0, 2H, Ar*H*), 7.60 (d, *J* = 8.0, 2H, Ar*H*), 1.89 (s, 3H, CH_3); **^{13}C {^{1}H} NMR** (100 MHz, CD_3OD): δ_C = 175.2 (*C*=O), 173.2 (*C*=O), 143.2 (C_{Ar}), 130.9 (C_{Ar}), 130.7 (2×CH_{Ar}), 126.7 (2×CH_{Ar}), 64.0 (CCH_3), 22.9 (CCH_3); **HRMS** (ESI^-): *m/z* calcd for $C_{10}H_{10}O_4N$ ($[M-H]^-$) 208.0610, found 208.0618. Data in agreement with reported values.[12]

(*S*)-2-Amino-2-(4-chlorophenyl)propanoic acid (5-Ala-c)



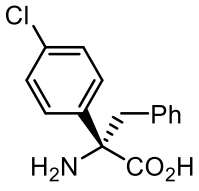
Following general procedure 8, NaH (43 mg, 1.08 mmol, 60% suspension) and MeI (83 µL, 1.33 mmol) were added to urea **(*S*) 4-Ala-c** (300 mg, 0.888 mmol) in DMF (8.90 mL). The resulting methylated urea was suspended in HCl/EtOH (4.45 mL, 10:1) and hydrolysed to give the title compound (147 mg, 0.737 mmol, 83%) as a white solid. **5-Ala-c**: **^{1}H NMR** (500 MHz, CD_3OD): δ_H = 7.57 – 7.53 (m, 2H, Ar*H*), 7.44 – 7.39 (m, 2H, Ar*H*), 1.86 (s, 3H, CH_3); **^{13}C {^{1}H} NMR** (100 MHz, CD_3OD): δ_C = 175.1 (*C*=O), 139.4 (C_{Ar}), 135.5 (C_{Ar}), 129.8 (2×CH_{Ar}), 128.9 (2×CH_{Ar}), 63.6 (CCH_3), 22.8 (CCH_3); **IR**: ν_{max} = 3012, 2979 (NH_3^+ and C–H), 1596 (COO^- asym.), 1390 (COO^- sym.); **HRMS** (ESI^+): *m/z* calcd for $C_9H_{11}O_2N_2Cl$ ($[M+H]^+$) 200.0473, found 200.0467.

(*S*)-2-Amino-2-(4-fluorophenyl)propanoic acid (5-Ala-d)

Following general procedure 8, NaH (56 mg, 1.40 mmol, 60% suspension) and MeI (0.11 mL, 1.75 mmol) were added to urea **(*S*) 4-Ala-d** (375 mg, 1.17 mmol) in DMF (11.70 mL). The resulting methylated urea was suspended in HCl/EtOH (5.85 mL, 10:1) and hydrolysed to give the title compound (175 mg,

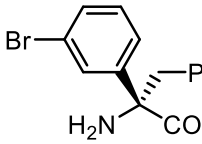
0.955 mmol, 82%) as a white solid. **5-Ala-d**: **^{1}H NMR** (400 MHz, CD_3OD): δ_H = 7.62 – 7.56 (m, 2H, Ar*H*), 7.17 – 7.10 (m, 2H, Ar*H*), 1.87 (s, 3H, CH_3); **^{13}C {^{1}H} NMR** (100 MHz, CD_3OD): δ_C = 175.3 (*C*=O), 164.1 (d, $^{1}J_{C-F}$ = 246.4, C_{Ar}F), 136.7 (d, $^{4}J_{C-F}$ = 3.4, C_{Ar}), 129.4 (d, $^{3}J_{C-F}$ = 8.3, 2×CH_{Ar}), 116.4 (d, $^{2}J_{C-F}$ = 21.9, 2×CH_{Ar}), 63.6 (*C*CH_3), 22.9 (CH_3); **HRMS** (ESI$^-$): *m/z* calcd for $C_9H_9O_2NF$ ([M−H]$^-$) 182.0623, found 182.0623.

(*S*)-2-Amino-2-(4-chlorophenyl)-3-phenylpropanoic acid (5-Phe-c)



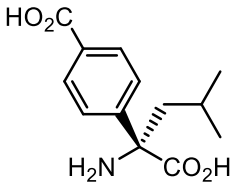
Following general procedure 8, NaH (23 mg, 0.580 mmol, 60% suspension) and MeI (45 µL, 0.724 mmol) were added to urea **(*S*) 4-Phe-c** (200 mg, 0.483 mmol) in DMF (4.80 mL). The resulting methylated urea was suspended in HCl/EtOH (2.40 mL, 10:1) and hydrolysed to give the title compound (103 mg, 0.374 mmol, 77%) as a white solid. **5-Phe-c**: **^{1}H NMR** (500 MHz, CD_3OD): δ_H = 7.64 (d, *J* = 8.5, 2H, Ar*H*), 7.43 (d, *J* = 8.5, 2H, Ar*H*), 7.31 – 7.23 (m, 5H, Ph*H*), 3.71 (d, *J* = 14.1, 1H, C$H_A$$H_B$Ph), 3.44 (d, *J* = 14.1, 1H, C$H_A$$H_B$Ph); **^{13}C {^{1}H} NMR** (125 MHz, $(CD_3)_2SO$): δ_C = 169.1 (*C*=O), 139.1 (C_{Ar}), 135.6 (C_{Ph}), 131.8 (C_{Ar}), 130.7 (2×CH_{Ph}), 128.3 (2×CH_{Ar}), 128.0 (2×CH_{Ph}), 127.6 (2×CH_{Ar}), 126.7 (CH_{Ph}), 66.0 (N*C*CH_2), 43.2 (NC*C*H_2); **HRMS** (ESI$^+$): *m/z* calcd for $C_{15}H_{15}O_2N$ ([M+H]$^+$) 276.0786, found 276.0780.

(*S*)-2-Amino-2-(3-bromophenyl)-3-phenylpropanoic acid (5-Phe-e)



Following general procedure 8, NaH (51 mg, 1.27 mmol, 60% suspension) and MeI (0.10 mL, 1.59 mmol) were added to urea **(*S*) 4-Phe-e** (485 mg, 1.06 mmol) in DMF (10.60 mL). The resulting methylated urea was suspended in HCl/EtOH (5.30 mL, 10:1) and hydrolysed to give the title compound (281 mg, 0.878 mmol, 83%) as a white solid. **5-Phe-e**: **^{1}H NMR** (400 MHz, CD_3OD): δ_H = 7.88 (t, *J* = 1.9, 1H, Ar*H*), 7.64 (dd, *J* = 8.0, 2.0, 1H, Ar*H*), 7.54 (dd, *J* = 7.9, 1.8, 1H, Ar*H*), 7.34 (t, *J* = 8.0, 1H, Ar*H*), 7.31 – 7.20 (m, 5H, Ar*H*), 3.70 (d, *J* = 14.1, 1H, C$H_A$$H_B$Ph), 3.44 (d, *J* = 14.1, 1H, C$H_A$$H_B$Ph); **^{13}C {^{1}H} NMR** (100 MHz, CD_3OD): δ_C = 171.7 (*C*=O), 140.9 (C_{Ar}), 134.1 (C_{Ar}), 131.1 (CH_{Ar}), 130.3 (2×CH_{Ar}), 130.0 (CH_{Ar}), 129.2 (CH_{Ar}), 128.4 (2×CH_{Ar}), 127.3 (CH_{Ar}), 124.8 (CH_{Ar}), 122.2 (C_{Ar}Br), 66.8 (N*C*CH_2), 42.2 (NC*C*H_2); **HRMS** (ESI$^+$): *m/z* calcd for $C_{15}H_{15}O_2NBr$ ([M+H]$^+$) 320.0281, found 320.0281.

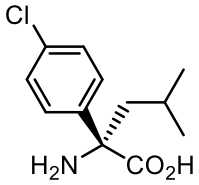
(*S*)-4-(1-Amino-1-carboxy-3-methylbutyl)benzoic acid (5-Leu-b')



Following general procedure 8, NaH (17 mg, 0.425 mmol, 60% suspension) and MeI (33 µL, 0.530 mmol) were added to urea **(*S*) 4-Leu-b** (130 mg, 0.351 mmol) in DMF (3.50 mL). The resulting methylated urea was suspended in HCl/EtOH (1.75 mL, 10:1) and hydrolysed to give the title compound (65 mg, 0.259 mmol, 74%) as a white solid. **5-Leu-b'**: **^{1}H NMR** (400 MHz, CD_3OD): δ_H = 7.98 – 7.94 (m, 2H, Ar*H*), 7.61 – 7.56 (m, 2H, Ar*H*), 2.28 (dd, *J* = 14.7, 6.8, 1H,

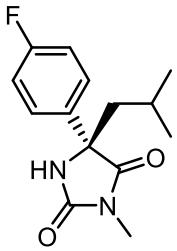
C*H*$_A$H$_B$CH), 2.22 (dd, *J* = 14.7, 5.4, 1H, CH$_A$*H*$_B$CH), 1.90 – 1.73 (m, 1H, CH$_2$C*H*(CH$_3$)$_2$), 1.02 (d, *J* = 6.6, 3H, CH(C*H*$_3$)$_A$(CH$_3$)$_B$), 0.93 (d, *J* = 6.6, 3H, CH(CH$_3$)$_A$(C*H*$_3$)$_B$); **^{13}C {^{1}H} NMR** (100 MHz, CD$_3$OD): δ_C = 174.6 (*C*=O), 174.3 (*C*=O), 143.0 (*C*$_{Ar}$), 138.5 (*C*$_{Ar}$), 130.5 (2×*C*H$_{Ar}$), 126.6 (2×*C*H$_{Ar}$), 67.8 (N*C*CH$_2$), 46.1 (NC*C*H$_2$), 25.5 (*C*H(CH$_3$)$_2$), 25.0 (CH(CH$_3$)$_A$(*C*H$_3$)$_B$), 23.8 (CH(*C*H$_3$)$_A$(CH$_3$)$_B$); **IR**: ν_{max} = 2956, 2932, 2869 (NH_3^+ and C–H), 1596 (COO^- asym.), 1380 (COO^- sym.); **HRMS** (ESI$^+$): *m/z* calcd for $C_{13}H_{18}O_4N$ ([M+H]$^+$) 252.1230, found 252.1226.

(*S*)-2-Amino-2-(4-chlorophenyl)-4-methylpentanoic acid (5-Leu-c)



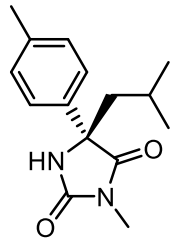
Following general procedure 8, NaH (25 mg, 0.625 mmol, 60% suspension) and MeI (49 µL, 0.787 mmol) were added to urea **(*S*) 4-Leu-c** (200 mg, 0.526 mmol) in DMF (5.30 mL). The resulting methylated urea was suspended in HCl/EtOH (2.60 mL, 10:1) and hydrolysed to give the title compound (97 mg, 0.401 mmol, 76%) as a white solid. **5-Leu-c**: **^{1}H NMR** (400 MHz, CD$_3$OD): δ_H = 7.56 (d, *J* = 8.2, 2H, Ar*H*), 7.39 (d, *J* = 8.1, 2H, Ar*H*), 2.25 (dd, *J* = 14.7, 6.8, 1H, C*H*$_A$H$_B$CH), 2.18 (dd, *J* = 14.7, 5.2, 1H, CH$_A$*H*$_B$CH), 1.82 (hept, *J* = 6.5, 1H, CH$_2$C*H*(CH$_3$)$_2$), 1.02 (d, *J* = 6.5, 3H, CH(C*H*$_3$)$_A$(CH$_3$)$_B$), 0.93 (d, *J* = 6.6, 3H, CH(CH$_3$)$_A$(C*H*$_3$)$_B$); **^{13}C {^{1}H} NMR** (100 MHz, CD$_3$OD): δ_C = 174.2 (*C*=O), 139.7 (*C*$_{Ar}$), 135.2 (*C*$_{Ar}$), 129.6 (2×*C*H$_{Ar}$), 129.0 (2×*C*H$_{Ar}$), 67.3 (N*C*CH$_2$), 46.0 (NC*C*H$_2$), 25.5 (*C*H(CH$_3$)$_2$), 25.0 (CH(CH$_3$)$_A$(*C*H$_3$)$_B$), 23.8 (CH(*C*H$_3$)$_A$(CH$_3$)$_B$); **IR**: ν_{max} = 2960, 2929, 2872 (NH_3^+ and C–H), 1606 (COO^- asym.), 1376 (COO^- sym.); **HRMS** (ESI$^+$): *m/z* calcd for $C_{12}H_{17}O_2NCl$ ([M+H]$^+$) 242.0942, found 242.0932.

(*R*)-5-(4-Fluorophenyl)-5-isobutyl-3-methylimidazolidine-2,4-dione (6-Leu-d)



Urea **(*R*) 4-Leu-d** (436 mg, 1.20 mmol) was suspended in HCl (10.00 mL, 6.0 M, aq.) and heated at 135 °C in a sealed tube for 37 h. The cooled reaction mixture was diluted with water and washed 3 times with DCM. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 3:1 Pet.Ether:EtOAc) gave the title compound (158 mg, 0.598 mmol, 50%) as a white solid. **6-Leu-d**: **R$_f$** (3:1 Pet.Ether:EtOAc): 0.24; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.52 – 7.46 (m, 2H, Ar*H*), 7.37 (br. s, 1H, N*H*), 7.02 – 6.95 (m, 2H, Ar*H*), 2.93 (s, 3H, NC*H*$_3$), 2.03 (dd, *J* = 14.5, 5.5, 1H, C*H*$_A$H$_B$CH), 1.97 (dd, *J* = 14.5, 7.2, 1H, CH$_A$*H*$_B$CH), 1.64 – 1.52 (m, 1H, CH$_2$C*H*(CH$_3$)$_2$), 0.82 (d, *J* = 6.6, 3H, CH(C*H*$_3$)$_A$(CH$_3$)$_B$), 0.78 (d, *J* = 6.7, 3H, CH(CH$_3$)$_A$(C*H*$_3$)$_B$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 175.3 (*C*=O), 162.7 (d, $^1J_{C-F}$ = 247.9, *C*$_{Ar}$F), 157.7 (*C*=O), 134.5 (d, $^4J_{C-F}$ = 2.9, *C*$_{Ar}$), 127.3 (d, $^3J_{C-F}$ = 8.2, 2×*C*H$_{Ar}$), 115.7 (d, $^2J_{C-F}$ = 21.4, 2×*C*H$_{Ar}$), 67.0 (N*C*CH$_2$), 47.7 (NC*C*H$_2$), 24.9 (N*C*H$_3$), 24.8 (*C*H(CH$_3$)$_2$), 24.2 (CH(CH$_3$)$_A$(*C*H$_3$)$_B$), 23.2 (CH(*C*H$_3$)$_A$(CH$_3$)$_B$); **IR**: ν_{max} = 3280 (N–H), 2958, 2872 (C–H), 1773 (C=O), 1704 (C=O); **HRMS** (ESI$^-$): *m/z* calcd for $C_{14}H_{16}O_2N_2F$ ([M−H]$^-$) 263.1190, found 263.1193.

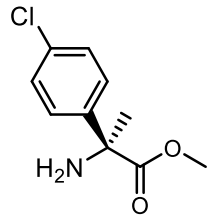
(*R*)-5-Isobutyl-3-methyl-5-(*p*-tolyl)imidazolidine-2,4-dione (6-Leu-i)



Urea **(*R*) 4-Leu-i** (320 mg, 0.890 mmol) was suspended in HCl (10.00 mL, 6.0 M, aq.) and heated at 135 °C in a sealed tube for 37 h. The cooled reaction mixture was diluted with water and washed 3 times with DCM. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 3:1 Pet.Ether:EtOAc) gave the title compound (140 mg, 0.538 mmol, 60%) as an off-white solid. **6-Leu-i**: **R_f** (3:1 Pet.Ether:EtOAc): 0.26; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.45 (d, *J* = 8.3, 2H, Ar*H*), 7.41 (br. s, 1H, N*H*), 7.17 (d, *J* = 8.2, 2H, Ar*H*), 2.98 (s, 3H, NCH_3), 2.33 (s, 3H, CH_3), 2.12 (dd, *J* = 14.5, 5.5, 1H, CH_AH$_B$CH), 2.05 (dd, *J* = 14.5, 7.3, 1H, CH$_A$$H_B$CH), 1.74 – 1.61 (m, 1H, CH_2C*H*$(CH_3)_2$), 0.89 (d, *J* = 6.6, 3H, CH(CH_3)$_A$$(CH_3)_B$), 0.86 (d, *J* = 6.7, 3H, CH$(CH_3)_A$(CH_3)$_B$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 175.5 (*C*=O), 157.8 (*C*=O), 138.1 (C_{Ar}), 135.7 (C_{Ar}), 129.5 (2×CH_{Ar}), 125.3 (2×CH_{Ar}), 67.3 (NCCH_2), 47.3 (NCCH_2), 24.8 (NCH_3 and C*H*$(CH_3)_2$), 24.2 (CH$(CH_3)_A$(CH_3)$_B$), 23.2 (CH(CH_3)$_A$$(CH_3)_B$), 21.1 (C$H_3$); **IR**: ν_{max} = 3270 (N–H), 2956, 2871 (C–H), 1772 (C=O), 1704 (C=O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{15}H_{20}O_2N_2Na$ ([M+Na]$^+$) 283.1417, found 283.1414.

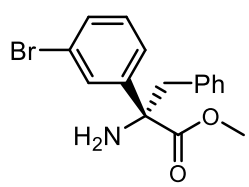
Functionalised Amino Acid Derivatives

Methyl (*S*)-2-amino-2-(4-chlorophenyl)propanoate (8-Ala-c-OMe)



To a suspension of amino acid **5-Ala-c** (100 mg, 0.501 mmol, 1.0 eq.) in anhydrous benzene/MeOH (5.00 mL, 0.1 M, 4:1) was added TMS-diazomethane (0.38 mL, 0.760 mmol, 2.0 M in hexanes, 1.5 eq.). The reaction mixture was left to stir at room temperature for 18 h. The reaction was quenched with acetic acid (0.1 mL) and concentrated *in vacuo*. Purification by flash column chromatography gave the title compound (94 mg, 0.440 mmol, 88%) as a colourless oil. **8-Ala-c-OMe**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.48 – 7.38 (m, 2H, Ar*H*), 7.35 – 7.27 (m, 2H, Ar*H*), 3.70 (s, 3H, OCH_3), 2.08 (s, 2H, NH_2), 1.67 (s, 3H, CCH_3); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 176.3 (*C*=O), 142.6 (C_{Ar}), 133.5 (C_{Ar}), 128.7 (2×CH_{Ar}), 126.8 (2×CH_{Ar}), 60.4 (*C*CH_3), 52.8 (OCH_3), 27.7 (CCH_3); **HRMS** (ESI$^+$): *m/z* calcd for $C_{10}H_{13}O_2NCl$ ([M+H]$^+$) 214.0629, found 214.0638.

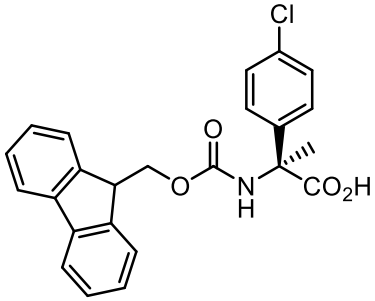
Methyl (*S*)-2-amino-2-(3-bromophenyl)-3-phenylpropanoate (8-Phe-e-OMe)



To a suspension of amino acid **5-Phe-e** (245 mg, 0.764 mmol, 1.0 eq.) in anhydrous benzene/MeOH (7.50 mL, 0.1 M, 4:1) was added TMS-diazomethane (0.57 mL, 1.15 mmol, 2.0 M in hexanes, 1.5 eq.). The reaction mixture was left to stir at room temperature for 18 h. The reaction was quenched with acetic acid (0.1 mL) and concentrated *in vacuo*. Purification by flash

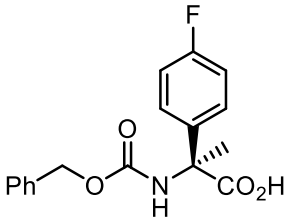
column chromatography gave the title compound (225 mg, 0.673 mmol, 81%) as a colourless oil. **8-Phe-e-OMe**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.77 (t, *J* = 1.9, 1H, Ar*H*), 7.52 (ddd, *J* = 7.9, 1.9, 1.0, 1H, Ar*H*), 7.44 (ddd, *J* = 7.9, 1.9, 1.0, 1H, Ar*H*), 7.30 – 7.20 (m, 4H, Ar*H*), 7.15 – 7.07 (m, 2H, Ar*H*), 3.74 (s, 3H, OCH_3), 3.61 (d, *J* = 13.3, 1H, CH_AH$_B$Ph), 3.08 (d, *J* = 13.3, 1H, CH$_A$$H_B$Ph), 1.84 (s, 2H, N$H_2$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 175.1 (*C*=O), 145.4 (C_{Ar}), 135.8 (C_{Ar}), 130.9 (*C*H$_{Ar}$), 130.5 (2×*C*H$_{Ar}$), 130.0 (*C*H$_{Ar}$), 129.1 (*C*H$_{Ar}$), 128.5 (2×*C*H$_{Ar}$), 127.3 (*C*H$_{Ar}$), 124.5 (*C*H$_{Ar}$), 122.8 (C_{Ar}Br), 64.4 (N*C*CH$_2$), 52.8 (*C*H$_3$), 46.3 (NC*C*H$_2$); **HRMS** (ESI$^+$): *m/z* calcd for $C_{16}H_{17}O_2NBr$ ([M+H]$^+$) 334.0437, found 334.0439.

(*S*)-2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-2-(4-chlorophenyl)propanoic acid (Fmoc-7-Ala-c)



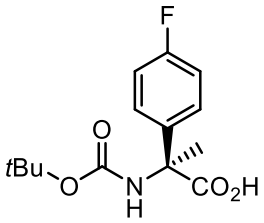
To a suspension of amino acid **5-Ala-c** (120 mg, 0.601 mmol, 1.0 eq.) in DCM (2.00 mL, 0.3 M) was added dropwise *N*-methyl-*N*-trimethylsilyl trifluoroacetamide (0.22 mL, 1.20 mmol, 2.0 eq.). The reaction mixture was heated to reflux and left to stir for 4 h. The reaction mixture was cooled to room temperature and a solution of *N*-(9-fluorenylmethoxycarbonyloxy)succinimide (223 mg, 0.661 mmol, 1.1 eq.) in DCM (1.90 mL, 0.35 M) was added before being left to stir for 16 h. The reaction was quenched with MeOH (1.00 mL) and stirred for 15 min before being concentrated *in vacuo*. The crude residue was taken up in Et_2O and K_2CO_3 (5%, aq.) before the aqueous layer was separated and the organic layer extracted 3 times with K_2CO_3 (5%, aq.). The combined aqueous layers were acidified to pH 2 with HCl (1.0 M, aq.) and extracted 4 times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 99:1→95:5 DCM:MeOH) gave the title compound (167 mg, 0.396 mmol, 66%) as a white solid. **Fmoc-7-Ala-c**: **R_f** (96:4 DCM:MeOH): 0.31; **^{1}H NMR** (500 MHz, $(CD_3)_2SO$): δ_H = 12.93 (br. s, 1H, O*H*), 7.89 (d, *J* = 7.6, 2H, Ar*H*), 7.86 (s, 1H, N*H*), 7.75 (d, *J* = 7.3, 2H, Ar*H*), 7.49 – 7.37 (m, 6H, Ar*H*), 7.34 (t, *J* = 6.1, 2H, Ar*H*), 4.35 – 4.14 (m, 3H, OCH_2CH and OCH$_2$C*H*), 1.76 (s, 3H, CH_3); **^{13}C {^{1}H} NMR** (125 MHz, $(CD_3)_2SO$): δ_C = 173.4 (*C*=O), 154.8 (*C*=O), 143.8 (2×C_{Ar}), 140.7 (2×C_{Ar}), 140.4 (C_{Ar}), 131.9 (C_{Ar}), 128.4 (2×*C*H$_{Ar}$), 127.8 (2×*C*H$_{Ar}$), 127.7 (2×*C*H$_{Ar}$), 127.1 (2×*C*H$_{Ar}$), 125.4 (2×*C*H$_{Ar}$), 120.1 (2×*C*H$_{Ar}$), 65.5 (O*C*H$_2$CH), 61.0 (*C*CH$_3$), 46.7 (OCH$_2$*C*H), 24.2 (C*C*H$_3$); **HRMS** (ESI$^-$): *m/z* calcd for $C_{24}H_{19}O_4NCl$ ([M−H]$^-$) 420.1008, found 420.1005.

(*S*)-2-(((Benzyloxy)carbonyl)amino)-2-(4-fluorophenyl)propanoic acid (Cbz-7-Ala-d)



To a suspension of amino acid **5-Ala-d** (380 mg, 2.07 mmol, 1.0 eq.) in DCM (6.90 mL, 0.3 M) was added dropwise *N*-methyl-*N*-trimethylsilyl trifluoroacetamide (0.77 mL, 4.15 mmol, 2.0 eq.). The reaction mixture was heated to reflux and left to stir for 4 h. The reaction mixture was cooled to room temperature and a solution of *N*-(benzyloxycarbonyloxy)succinimide (569 mg, 2.28 mmol, 1.1 eq.) in DCM (6.50 mL, 0.35 M) was added before being left to stir for 16 h. The reaction was quenched with MeOH (3.50 mL) and stirred for 15 min before being concentrated *in vacuo*. The crude residue was taken up in Et_2O and K_2CO_3 (5%, aq.) before the aqueous layer was separated and the organic layer extracted 3 times with K_2CO_3 (5%, aq.). The combined aqueous layers were acidified to pH 2 with HCl (1.0 M, aq.) and extracted 4 times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 Pet.Ether:EtOAc) gave the title compound (629 mg, 1.98 mmol, 96%) as a white solid. **Cbz-7-Ala-d**: $\mathbf{R_f}$ (2:1 Pet.Ether:EtOAc): 0.26; **^{1}H NMR** (500 MHz, $(CD_3)_2SO$): δ_H = 12.88 (br. s, 1H, O*H*), 7.77 (s, 1H, N*H*), 7.50 (dd, *J* = 8.6, 5.3, 2H, Ar*H*), 7.44 – 7.22 (m, 5H, Ph*H*), 7.15 (t, *J* = 8.7, 2H, Ar*H*), 5.07 – 4.98 (m, 2H, CH_2Ph), 1.78 (s, 3H, CH_3); **^{13}C {^{1}H} NMR** (125 MHz, $(CD_3)_2SO$): δ_C = 174.0 (*C*=O), 161.8 (d, $^1J_{C–F}$ = 243.7, C_{Ar}F), 155.3 (*C*=O), 137.8 (C_{Ar}), 137.4 (C_{Ar}), 128.9 (d, $^3J_{C–F}$ = 8.3, 2×*C*H$_{Ar}$), 128.7 (2×*C*H$_{Ph}$), 128.2 (*C*H$_{Ph}$), 128.0 (2×*C*H$_{Ph}$), 115.0 (d, $^2J_{C–F}$ = 21.3, 2×*C*H$_{Ar}$), 65.7 (*C*H$_2$Ph), 61.4 (*C*CH$_3$), 24.7 (*C*H$_3$); **HRMS** (ESI$^+$): *m/z* calcd for $C_{17}H_{16}O_4NFNa$ ([M+Na]$^+$) 340.0956, found 340.0970.

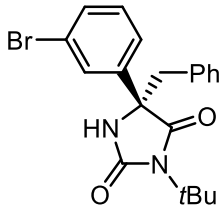
(*S*)-2-((*tert*-Butoxycarbonyl)amino)-2-(4-fluorophenyl)propanoic acid (Boc-7-Ala-d)



To a suspension of amino acid **5-Ala-d** (65 mg, 0.355 mmol, 1.0 eq.) in DCM (1.20 mL, 0.3 M) was added dropwise *N*-methyl-*N*-trimethylsilyl trifluoroacetamide (0.13 mL, 0.701 mmol, 2.0 eq.). The reaction mixture was heated to reflux and left to stir for 4 h. The reaction mixture was cooled to room temperature and a solution of di-*tert*-butyl dicarbonate (85 mg, 0.390 mmol, 1.1 eq.) in DCM (1.10 mL, 0.35 M) was added before being left to stir for 16 h. The reaction was quenched with MeOH (0.60 mL) and stirred for 15 min before being concentrated *in vacuo*. The crude residue was taken up in Et_2O and K_2CO_3 (5%, aq.) before the aqueous layer was separated and the organic layer extracted 3 times with K_2CO_3 (5%, aq.). The combined aqueous layers were acidified to pH 2 with HCl (1.0 M, aq.) and extracted 4 times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography gave the title compound (46 mg, 0.163 mmol, 46%) as a white solid. **Boc-7-Ala-d**: **^{1}H NMR** (500 MHz, $(CD_3)_2SO$): δ_H = 12.77 (br. s, 1H, O*H*), 7.46 (dd, *J* = 8.7, 5.4, 2H, Ar*H*), 7.20 (s, 1H, N*H*), 7.14

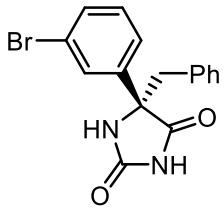
(t, *J* = 8.7, 2H, Ar*H*), 1.73 (s, 3H, C*H*$_3$), 1.35 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C {^{1}H} NMR** (125 MHz, (CD$_3$)$_2$SO): δ_C = 173.8 (*C*=O), 161.2 (d, $^1J_{C-F}$ = 243.2, *C*$_{Ar}$F), 154.3 (*C*=O), 137.8 (*C*$_{Ar}$), 128.4 (d, $^3J_{C-F}$ = 8.2, 2×*C*H$_{Ar}$), 114.4 (d, $^2J_{C-F}$ = 21.2, 2×*C*H$_{Ar}$), 78.3 (*C*(CH$_3$)$_3$), 60.7 (*C*CH$_3$), 28.1 (C(*C*H$_3$)$_3$), 24.5 (*C*H$_3$); **HRMS** (ESI$^+$): *m/z* calcd for $C_{14}H_{18}O_4NFNa$ ([M+Na]$^+$) 306.1112, found 306.1106.

(*S*)-5-Benzyl-5-(3-bromophenyl)-3-(*tert*-butyl)imidazolidine-2,4-dione (6-Phe-e)



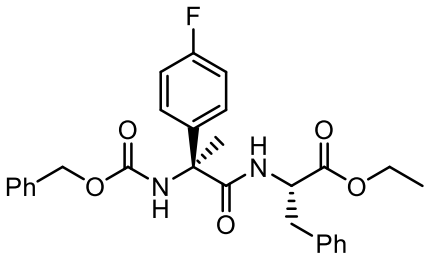
To a solution of amino acid **8-Phe-e-OMe** (33 mg, 0.099 mmol, 1.0 eq.) in DCM (0.40 mL, 0.25 M) was added *tert*-butyl isocyanate (14 µL, 0.123 mmol, 1.2 eq.). The reaction mixture was heated to reflux and left to stir for 18 h before being concentrated *in vacuo*. The crude urea intermediate was redissolved in THF (0.40 mL, 0.25 M) before potassium *tert*-butoxide (13 mg, 0.11 mmol, 1.2 eq.) was added dropwise. The reaction mixture was stirred at room temperature for 18 h before being concentrated *in* vacuo. Purification by flash column chromatography gave the title compound (26 mg, 0.065 mmol, 66%) as a white solid. **6-Phe-e**: **^{1}H NMR** (400 MHz, CD$_3$OD): δ_H = 7.80 (t, *J* = 1.9, 1H, Ar*H*), 7.62 (ddd, *J* = 7.9, 1.9, 1.0, 1H, Ar*H*), 7.49 (ddd, *J* = 7.9, 1.9, 1.0, 1H, Ar*H*), 7.33 – 7.26 (m, 4H, Ar*H*), 7.22 – 7.15 (m, 2H, Ar*H*), 7.07 (s, 1H, N*H*), 3.50 (d, *J* = 13.6, 1H, C*H*$_A$H$_B$Ph), 3.13 (d, *J* = 13.6, 1H, CH$_A$*H*$_B$Ph), 1.37 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C {^{1}H} NMR** (100 MHz, CD$_3$OD): δ_C = 174.3 (*C*=O), 157.9 (*C*=O), 140.9 (*C*$_{Ar}$), 133.9 (*C*$_{Ar}$), 131.5 (*C*H$_{Ar}$), 130.6 (2×*C*H$_{Ar}$), 130.3 (*C*H$_{Ar}$), 129.1 (*C*H$_{Ar}$), 128.6 (2×*C*H$_{Ar}$), 127.7 (*C*H$_{Ar}$), 124.6 (*C*H$_{Ar}$), 123.0 (*C*$_{Ar}$Br), 65.9 (N*C*CH$_2$), 58.1 (*C*(CH$_3$)$_3$), 45.9 (NC*C*H$_2$), 28.4 (C(*C*H$_3$)$_3$); **HRMS** (ESI$^+$): *m/z* calcd for $C_{20}H_{21}O_2N_2BrNa$ ([M+Na]$^+$) 423.0679, found 423.0678.

(*S*)-5-Benzyl-5-(3-bromophenyl)imidazolidine-2,4-dione (6'-Phe-e)



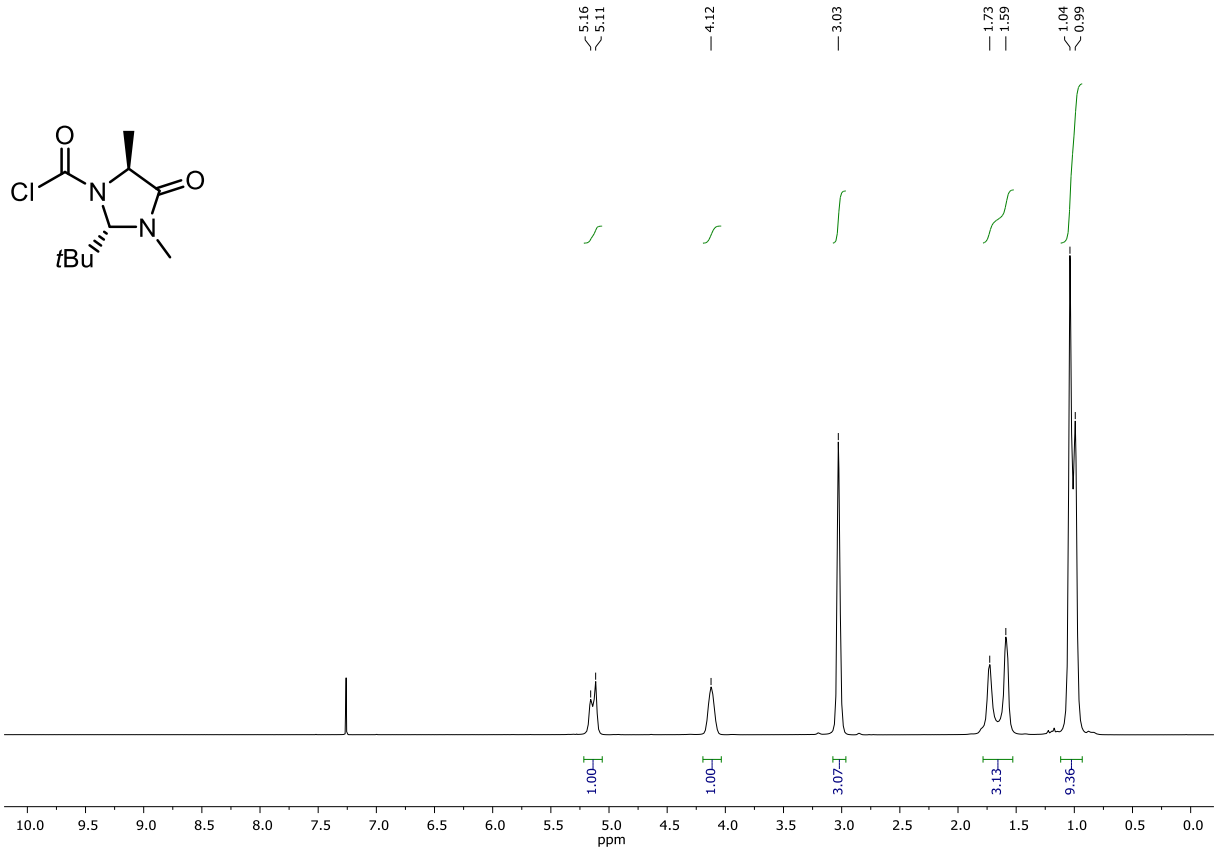
The hydantoin **6-Phe-e** (16 mg, 0.040 mmol, 1.0 eq.) was suspended in HBr (48%, aq.)/acetic acid (0.40 mL, 0.1 M, 1:1) and heated at 120 °C in a sealed tube for 18 h. The cooled reaction mixture was diluted with water and extracted 3 times with EtOAc. The combined organic layers were washed with $NaHCO_3$ (sat. aq.), brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was suspended in DCM, filtered, washed with additional DCM and dried to give the title compound (13 mg, 0.038 mmol, 94%) as a white solid. **6'-Phe-e**: **^{1}H NMR** (400 MHz, CD$_3$OD): δ_H = 7.84 (t, *J* = 1.9, 1H, Ar*H*), 7.67 (ddd, *J* = 7.9, 1.9, 1.0, 1H, Ar*H*), 7.53 (ddd, *J* = 8.0, 2.0, 1.0, 1H, Ar*H*), 7.36 (t, *J* = 8.0, 1H, Ar*H*), 7.30 – 7.20 (m, 5H, Ar*H*), 3.55 (d, *J* = 13.6, 1H, C*H*$_A$H$_B$Ph), 3.08 (d, *J* = 13.6, 1H, CH$_A$*H*$_B$Ph); **^{13}C {^{1}H} NMR** (100 MHz, CD$_3$OD): δ_C = 177.0 (*C*=O), 158.5 (*C*=O), 142.7 (*C*$_{Ar}$), 135.6 (*C*$_{Ar}$), 132.4 (*C*H$_{Ar}$), 131.6 (2×*C*H$_{Ar}$), 131.5 (*C*H$_{Ar}$), 129.8 (*C*H$_{Ar}$), 129.3 (2×*C*H$_{Ar}$), 128.4 (*C*H$_{Ar}$), 125.6 (*C*H$_{Ar}$), 123.7 (*C*$_{Ar}$Br), 70.2 (N*C*CH$_2$), 45.8 (NC*C*H$_2$); **HRMS** (ESI$^+$): *m/z* calcd for $C_{16}H_{13}O_2N_2BrNa$ ([M+Na]$^+$) 367.0053, found 367.0068.

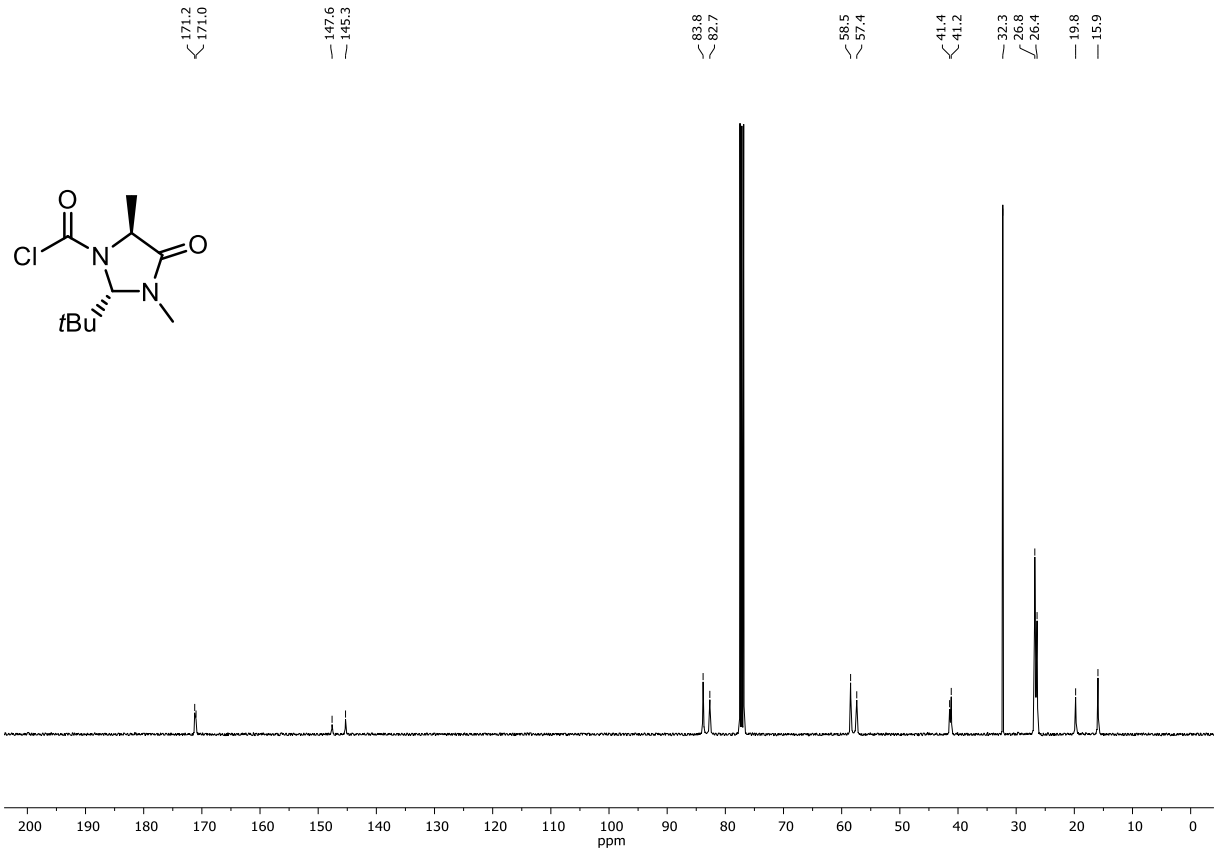
Ethyl ((*S*)-2-(4-fluorophenyl)-2-((phenoxycarbonyl)amino)propanoyl)-L-phenylalaninate (9)

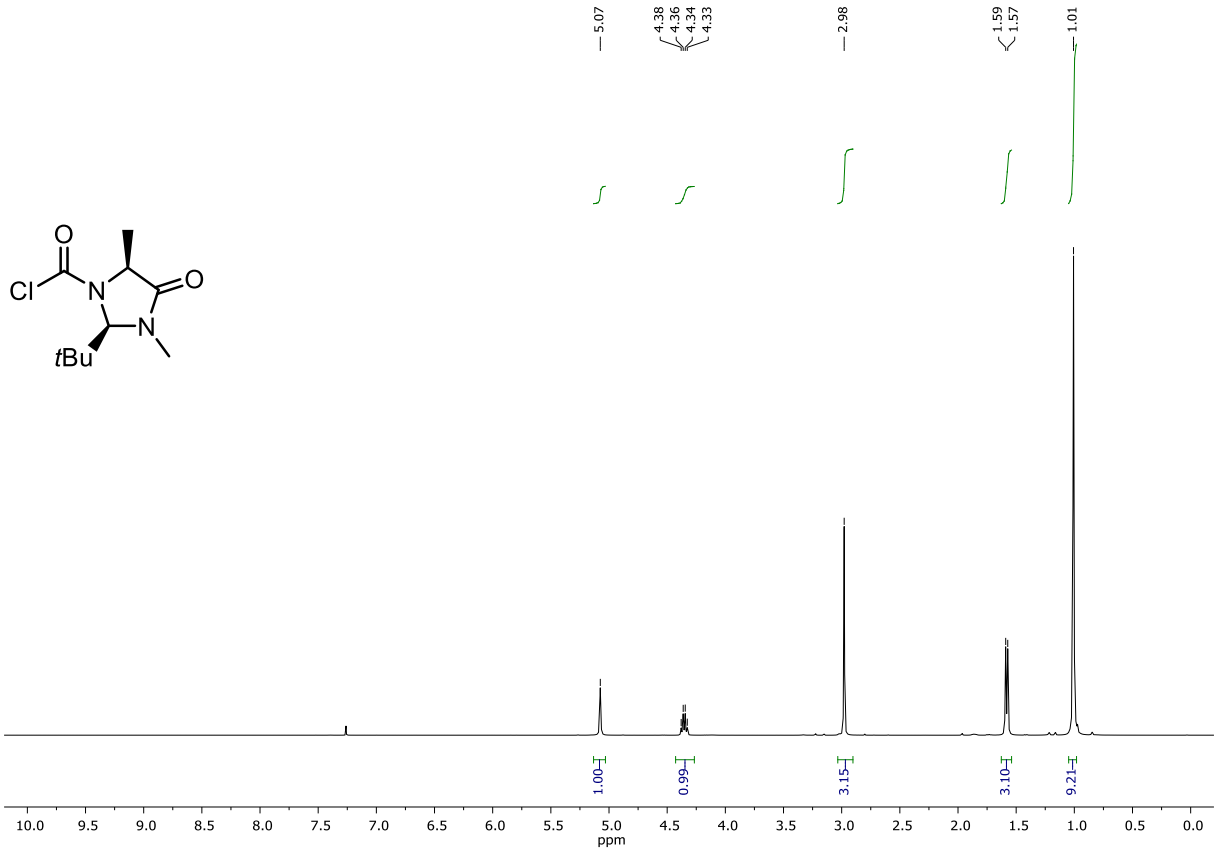


To a solution of carboxylic acid **Cbz-7-Ala-d** (55 mg, 0.173 mmol, 1.0 eq.) in DMF (1.20 mL, 0.14 M) was added K-Oxyma (34 mg, 0.189 mmol, 1.1 eq.). The resulting solution was cooled to 0 °C before EDC·HCl (43 mg, 0.224 mmol, 1.3 eq.) and DIPEA (39 µL, 0.224 mmol, 1.3 eq.) were added. The mixture was allowed to warm to room temperature and stirred for 15 min before L-phenylalanine ethyl ester hydrochloride (44 mg, 0.192 mmol, 1.1 eq.) and DIPEA (0.12 mL, 0.689 mmol, 4.0 eq.) were added. The reaction mixture was left to stir for 72 hours before MTBE and water were added. The organic layer was separated and the aqueous layer extracted 3 times with MTBE. The combined organic layers were washed with $KHSO_4$ (5%, aq.), $NaHCO_3$ (sat. aq.), LiCl (5%, aq.), brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography gave the title compound (79 mg, 0.160 mmol, 92%) as a white solid. **9**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.39 – 7.09 (m, 10H, Ar*H*), 6.98 – 6.84 (m, 4H, Ar*H*), 6.41 (s, 1H, N*H*), 5.85 (br. s, 1H, N*H*), 4.93 (d, *J* = 12.3, 1H, OC$H_A$$H_B$Ph), 4.85 (d, *J* = 12.4, 1H, OC$H_A$$H_B$Ph), 4.63 (td, *J* = 7.1, 5.6, 1H, NHC*H*CH_2Ph), 4.05 – 3.96 (m, 2H, C$H_2$$CH_3$), 3.05 (dd, *J* = 14.0, 5.6, 1H, CHC$H_A$$H_B$Ph), 2.89 (dd, *J* = 14.0, 6.8, 1H, CHC$H_A$$H_B$Ph), 1.71 (s, 3H, CC$H_3$), 1.09 (t, *J* = 7.1, 3H, CH_2CH_3); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 172.7 (*C*=O), 170.8 (*C*=O), 162.3 (d, $^1J_{C–F}$ = 247.5, C_{Ar}F), 154.4 (*C*=O), 136.7 (C_{Ar}), 136.4 (C_{Ar}), 135.6 (C_{Ar}), 129.2 (2×CH_{Ar}), 128.6 (2×CH_{Ar}), 128.5 (2×CH_{Ar}), 128.1 (3×CH_{Ar}), 128.0 (2×CH_{Ar}), 127.2 (CH_{Ar}), 115.7 (d, $^2J_{C–F}$ = 21.6, 2×CH_{Ar}), 66.6 (CH_2CH_3), 61.7 (OCH_2Ph), 61.5 (CCH_3), 53.5 ($CHCH_2$Ph), 37.6 (CHCH_2Ph), 23.9 (CCH_3), 14.1 (CH_2CH_3); **HRMS** (ESI$^+$): *m/z* calcd for $C_{28}H2_9O_5N_2FNa$ ([M+Na]$^+$) 515.1953, found 515.1947.

^{1}H and ^{13}C NMR Spectra



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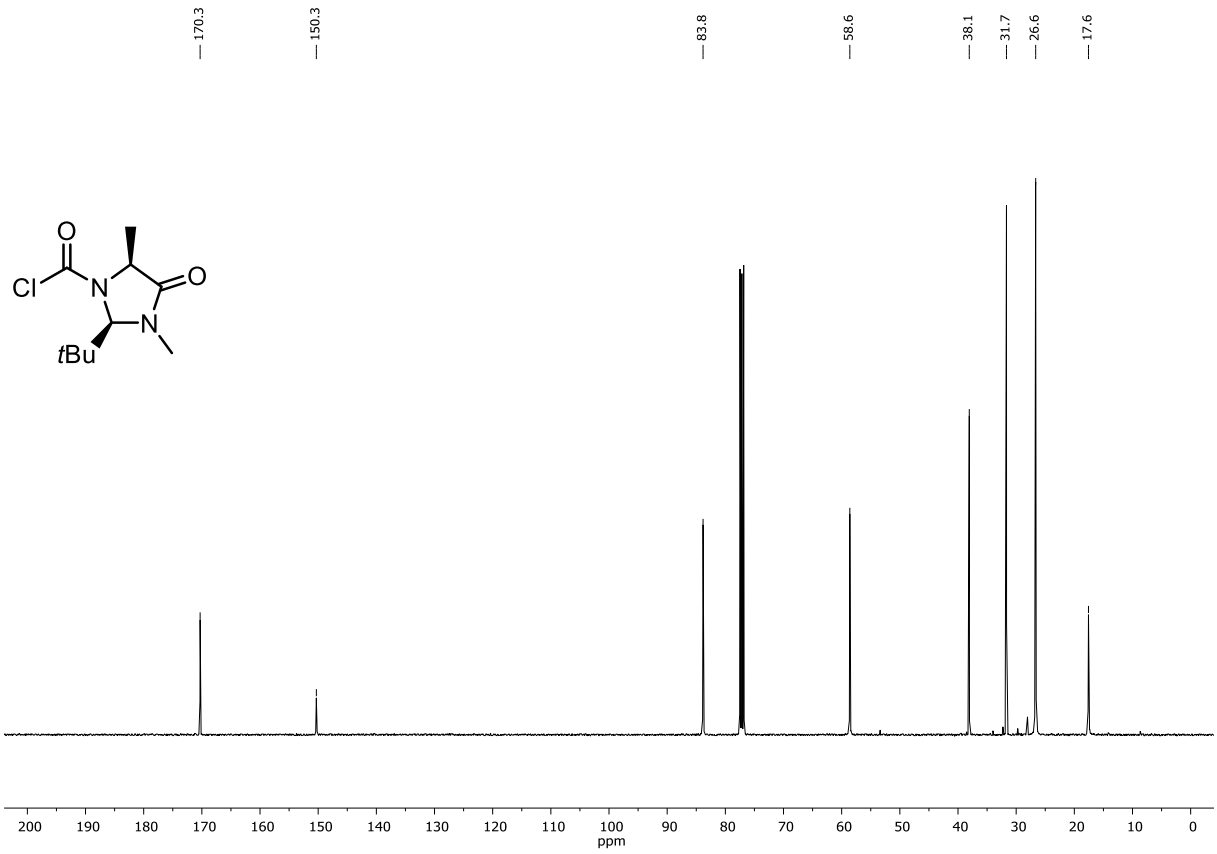
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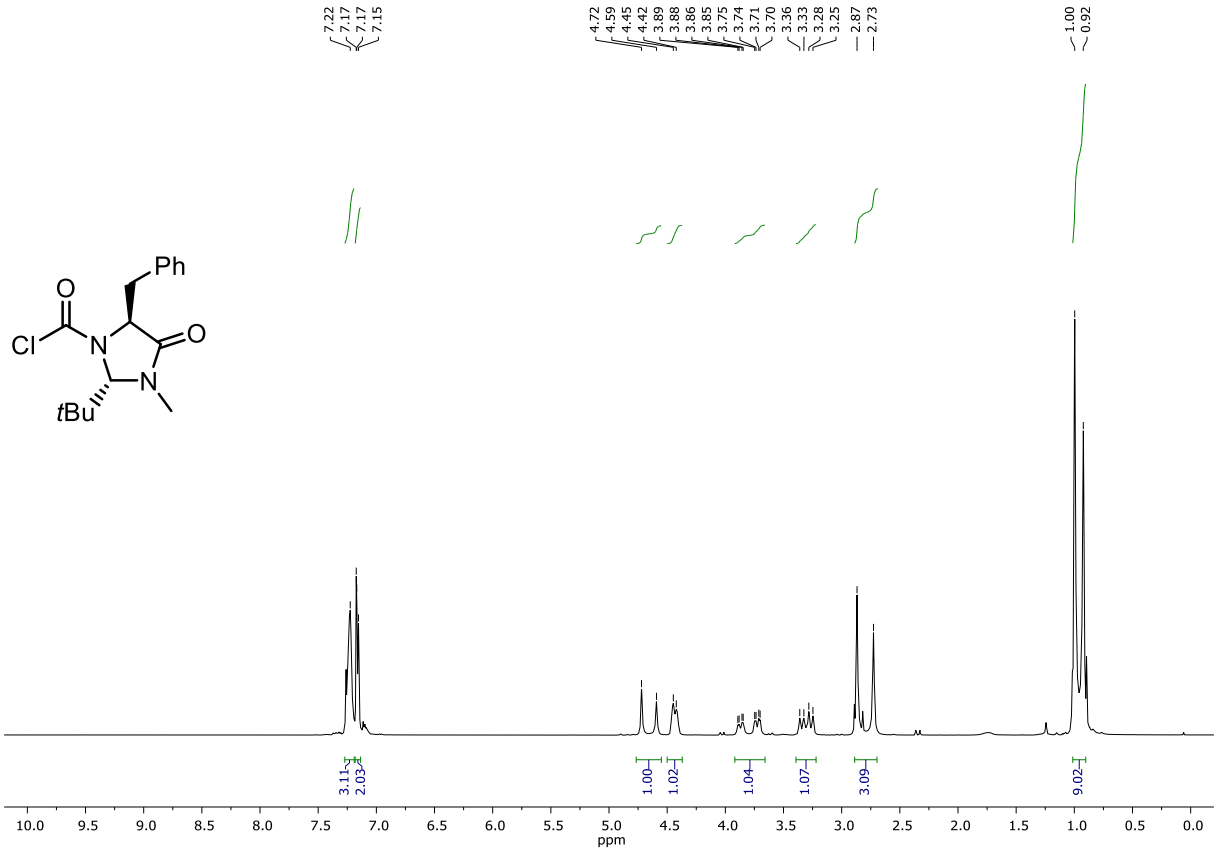
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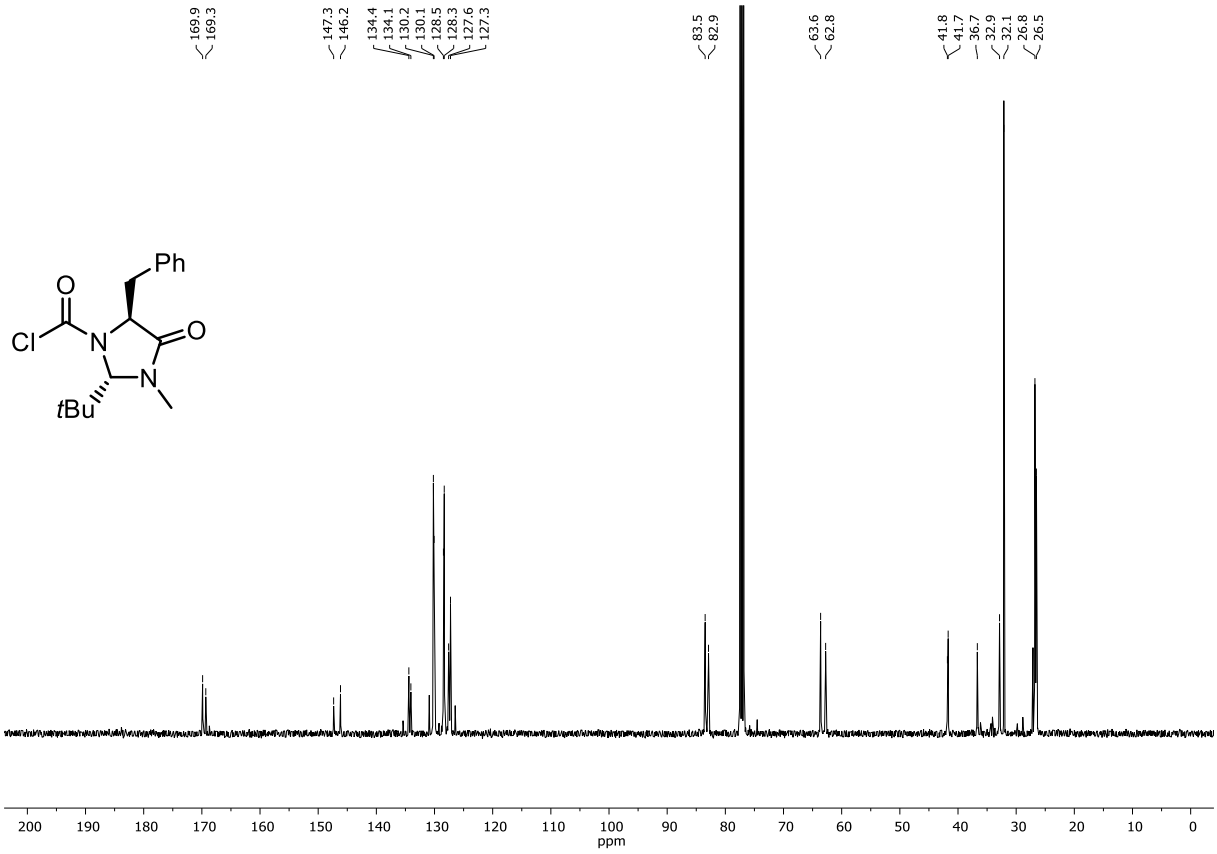
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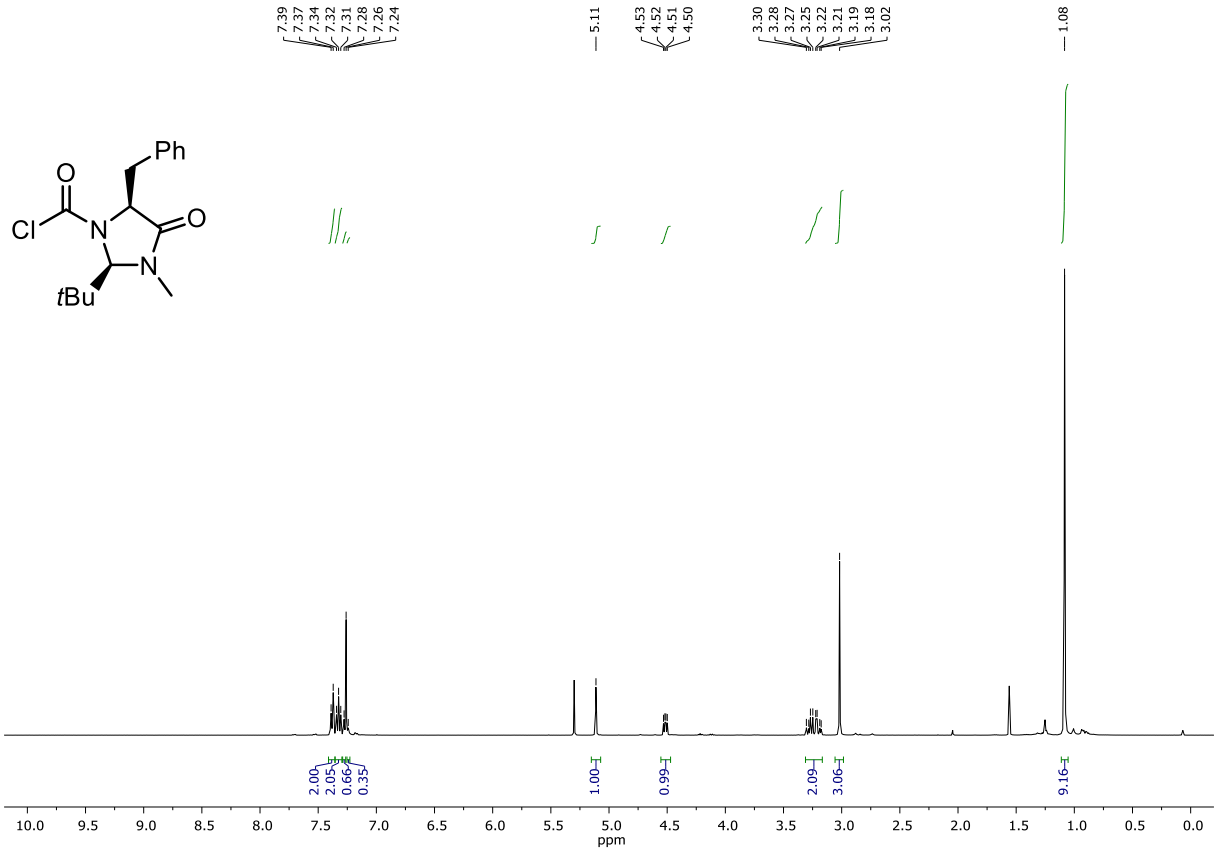
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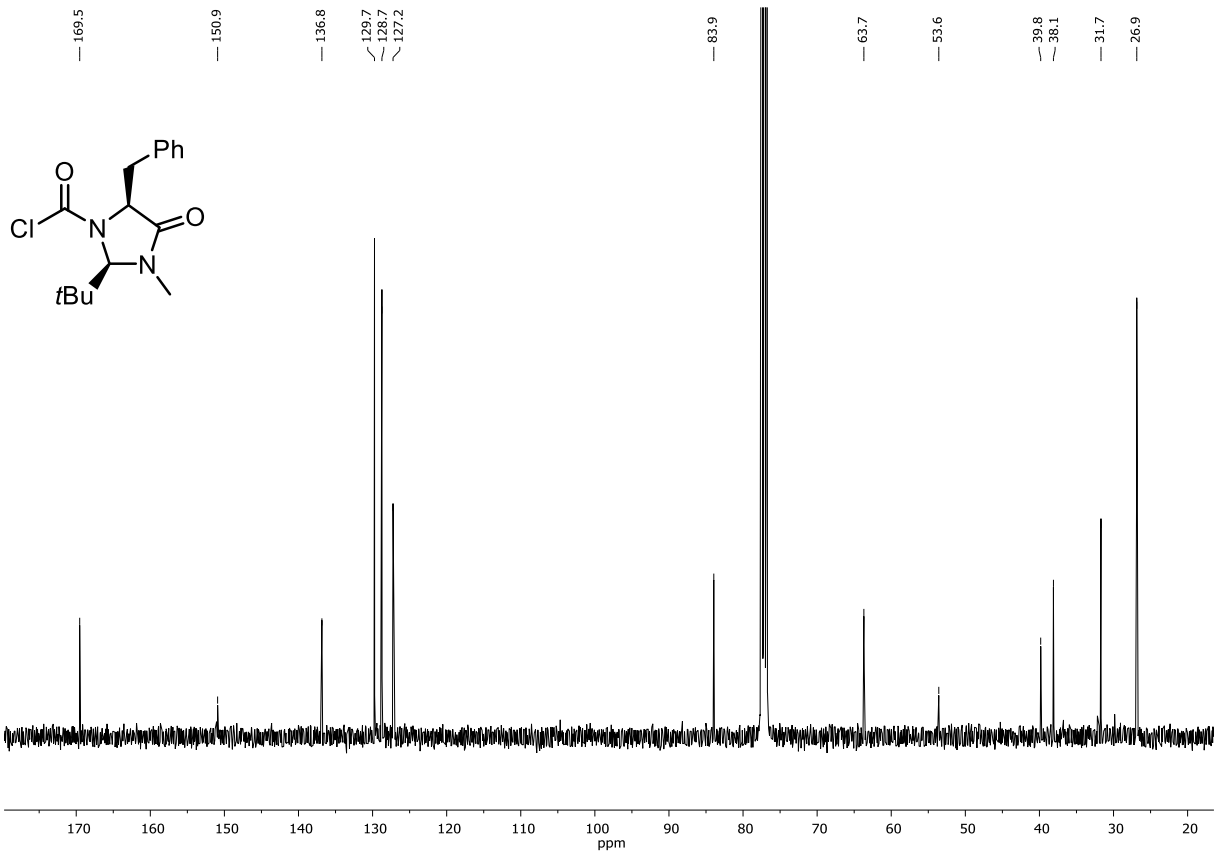
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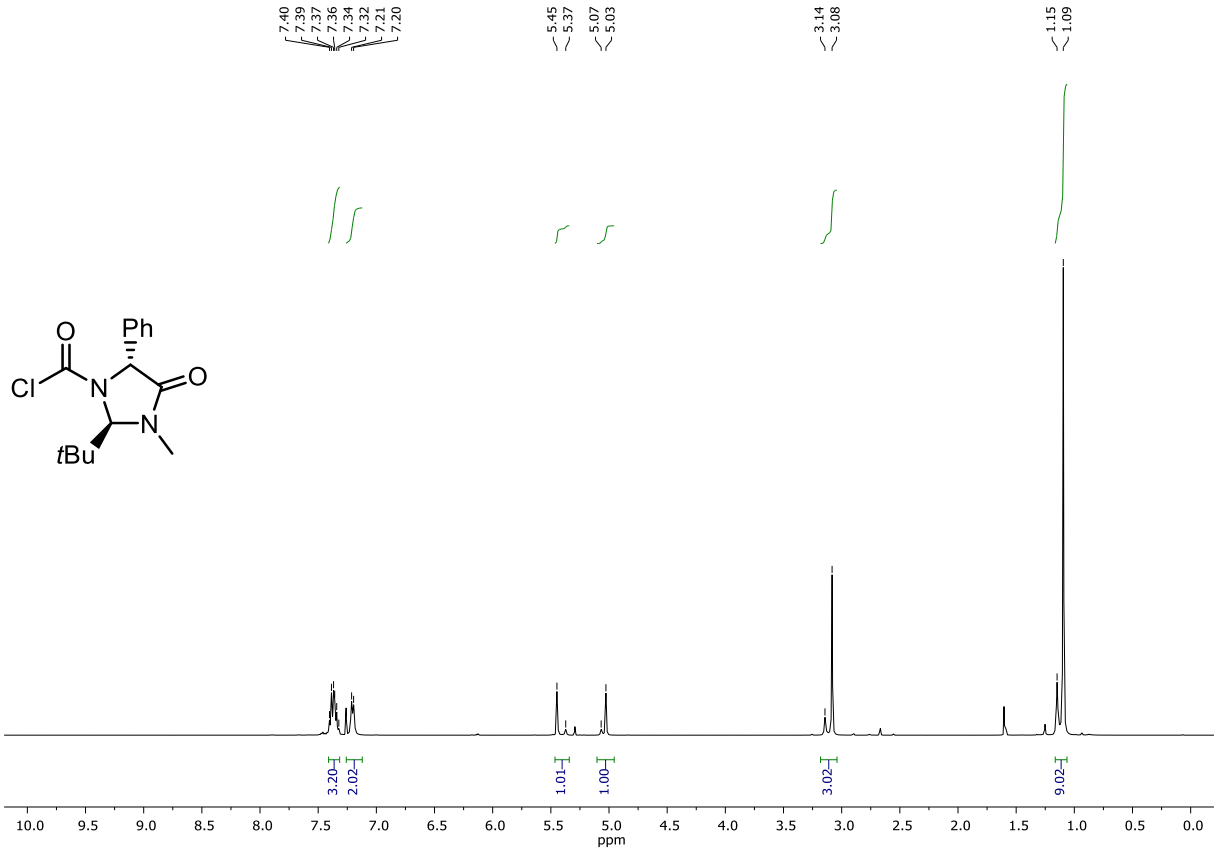
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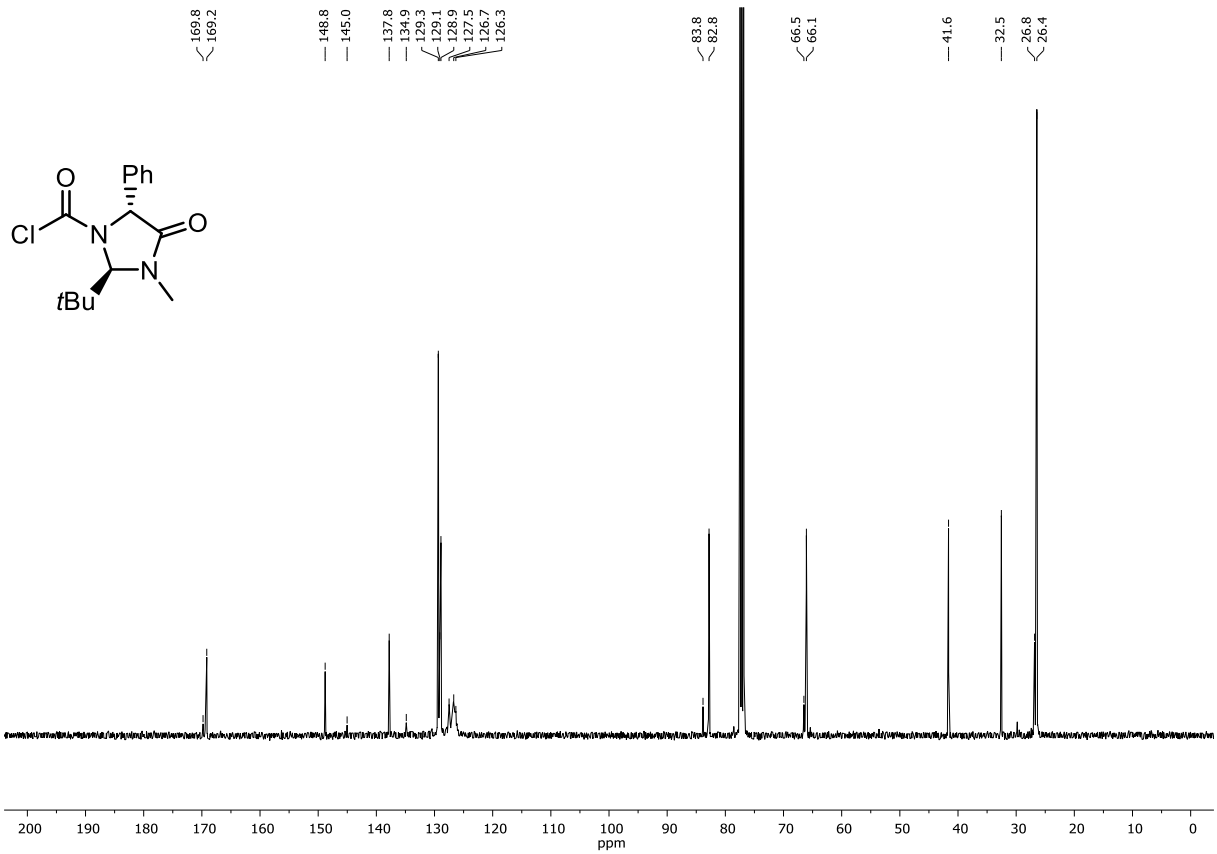
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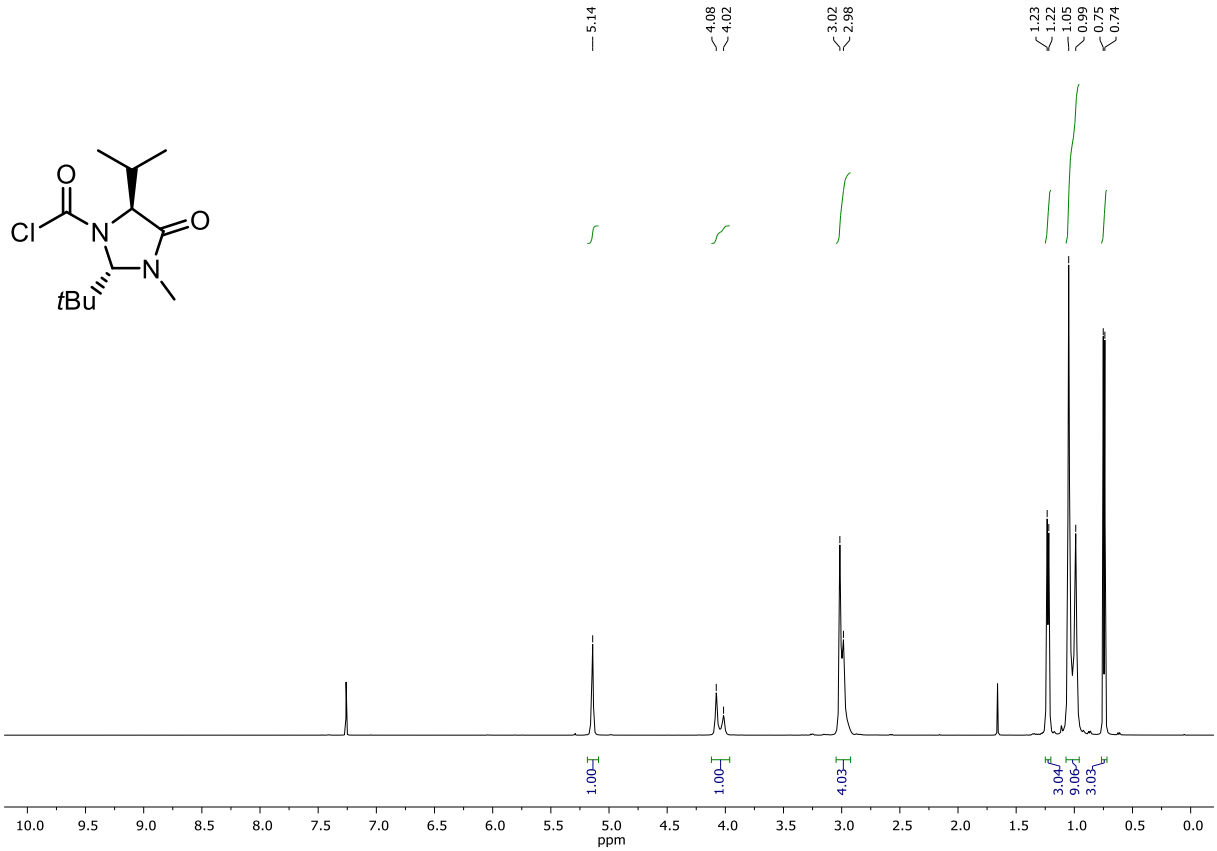
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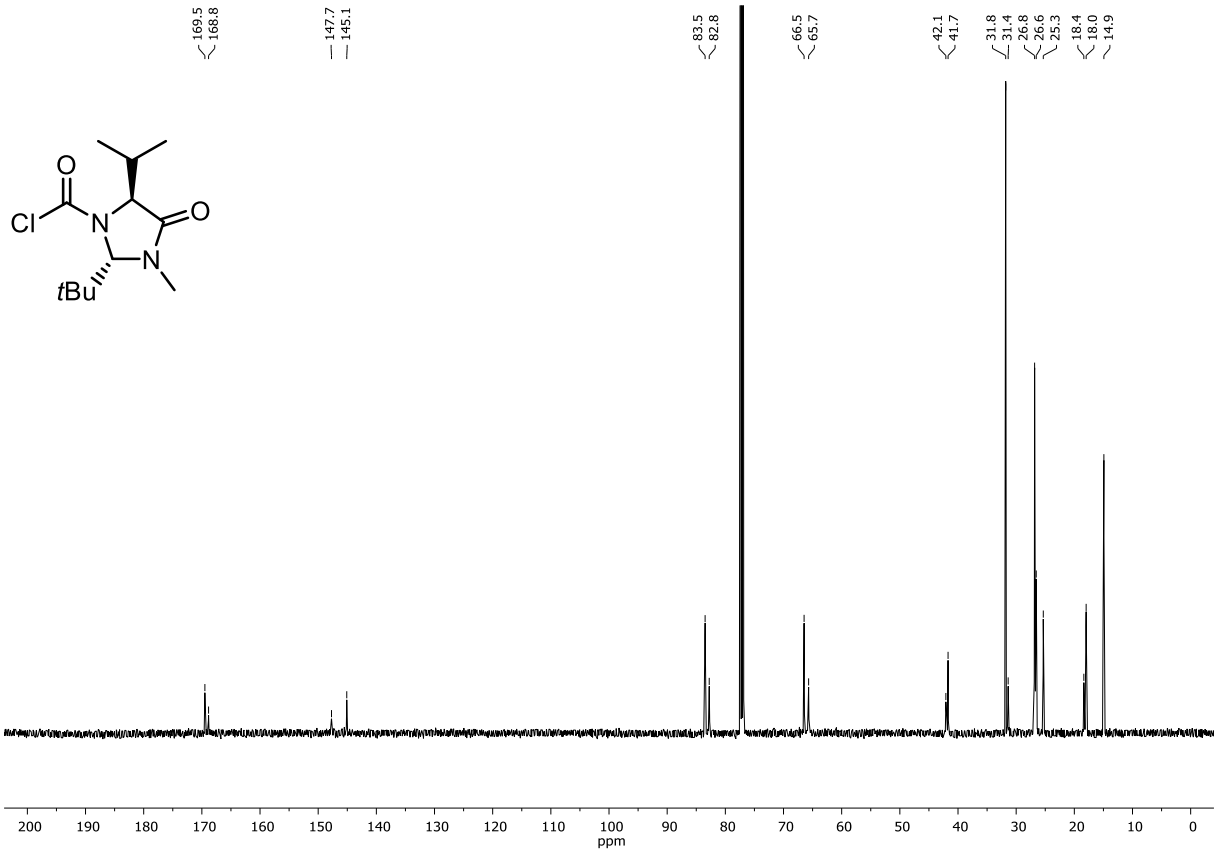
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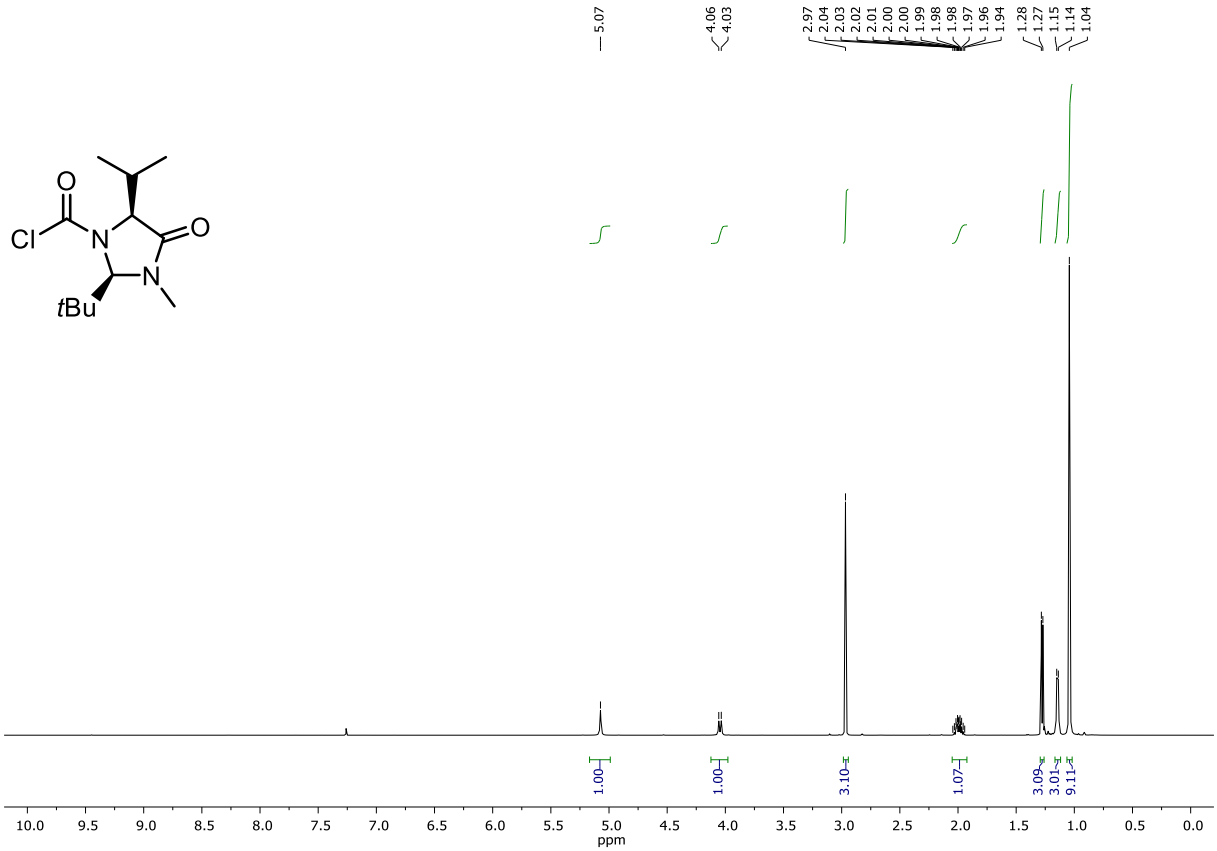
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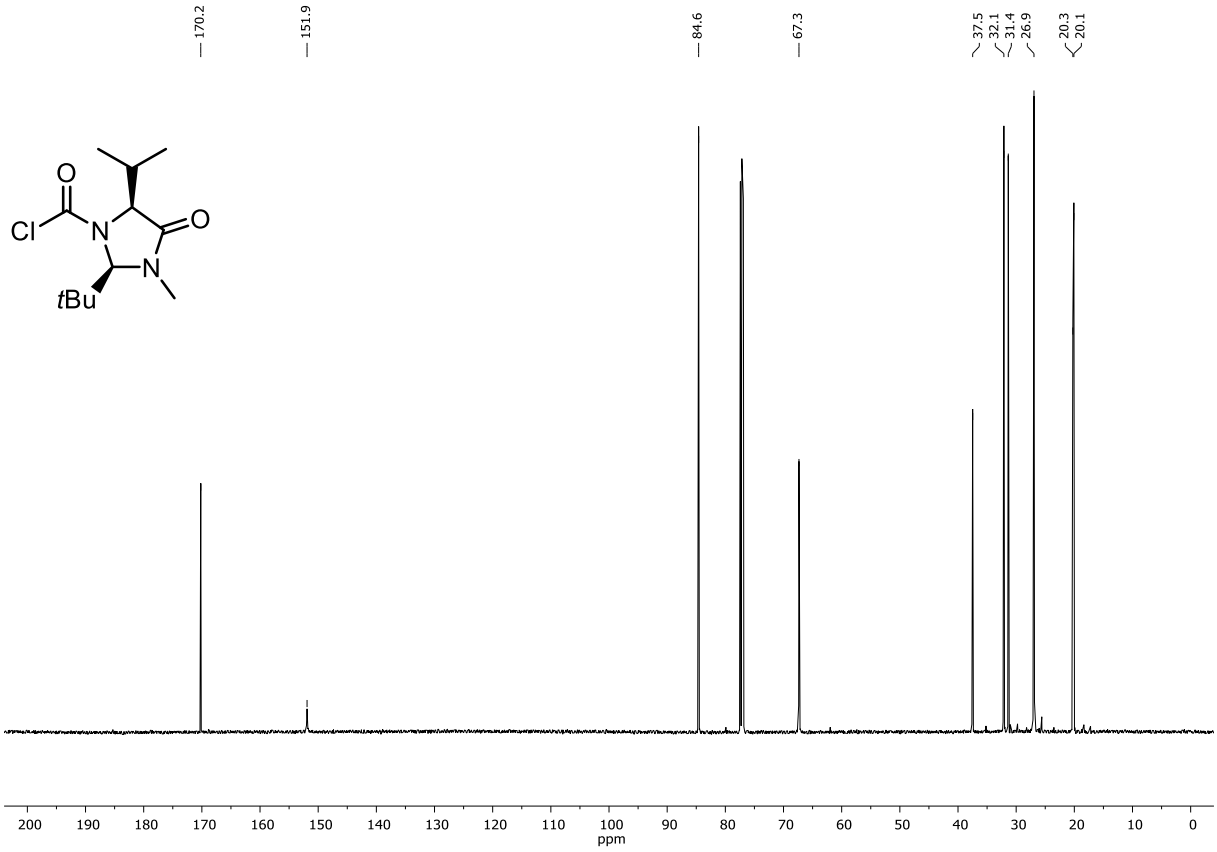
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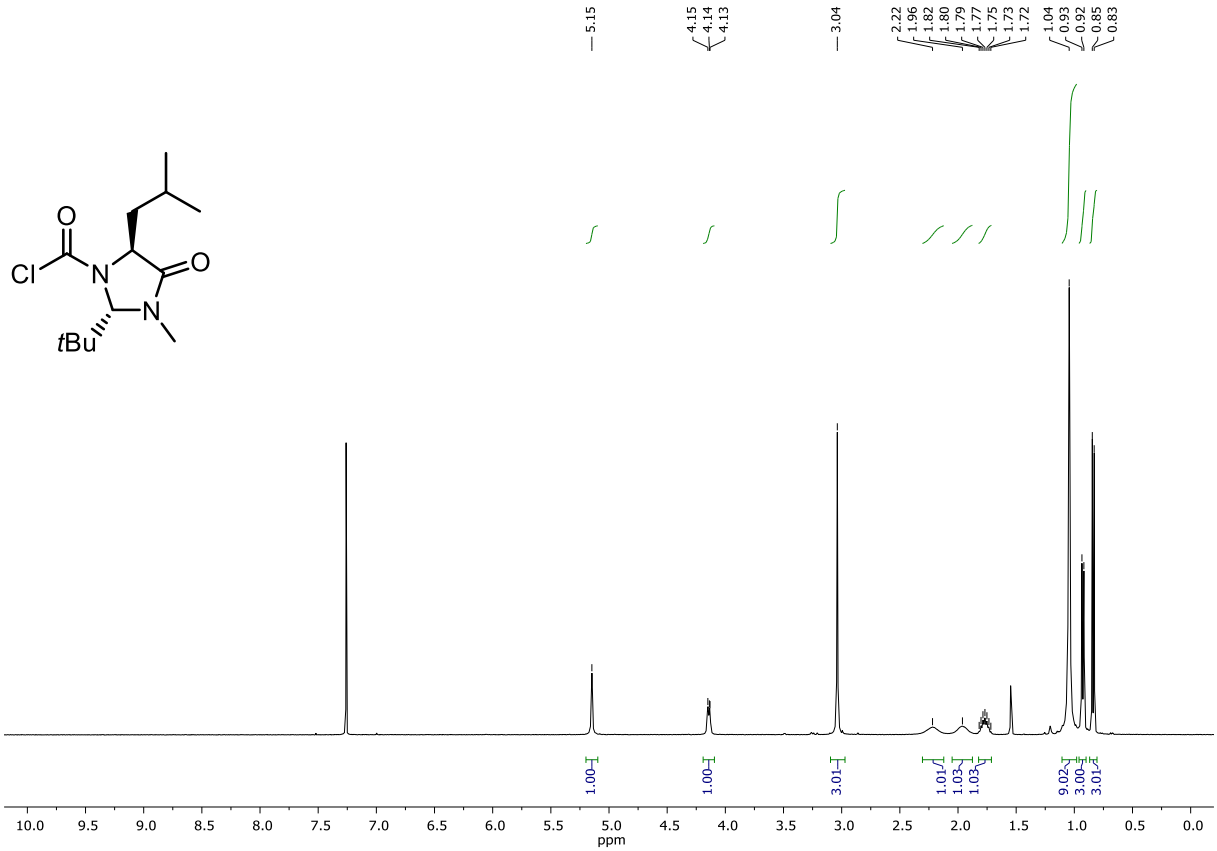
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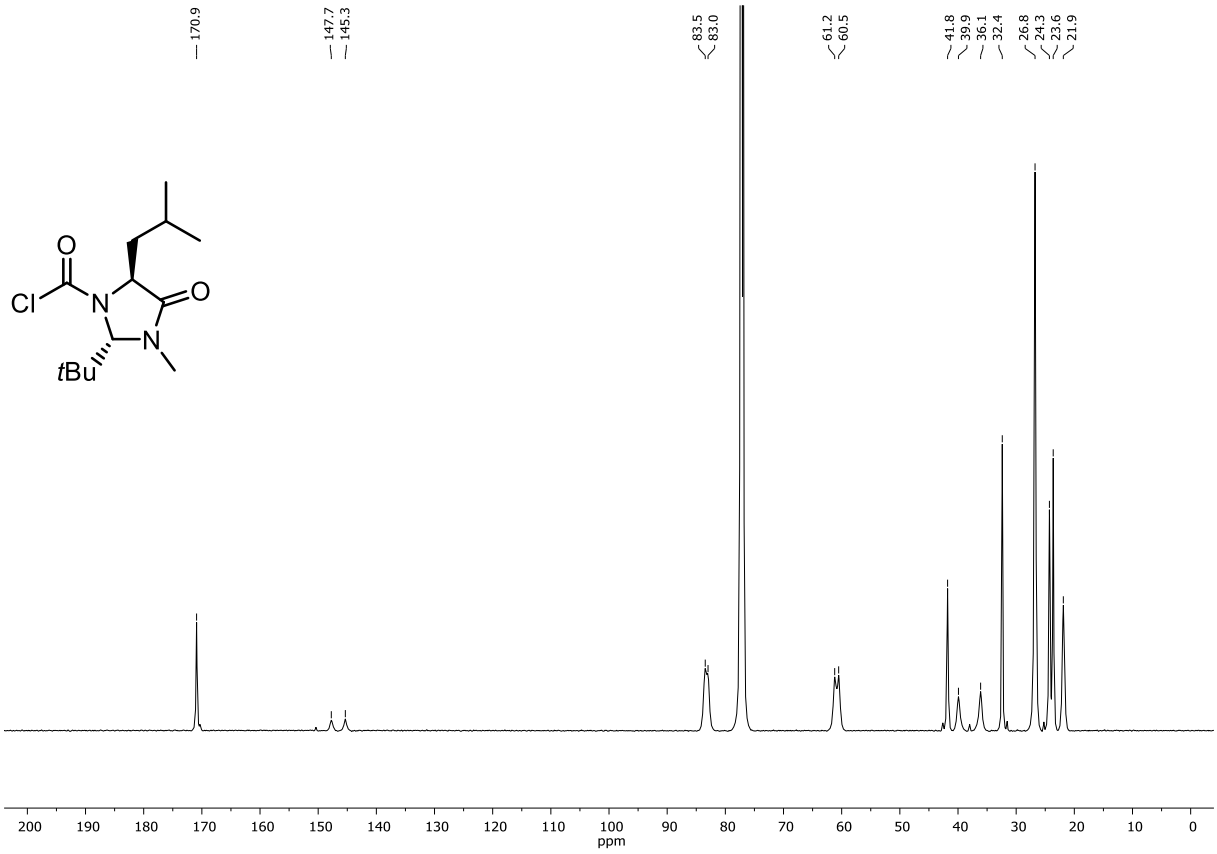
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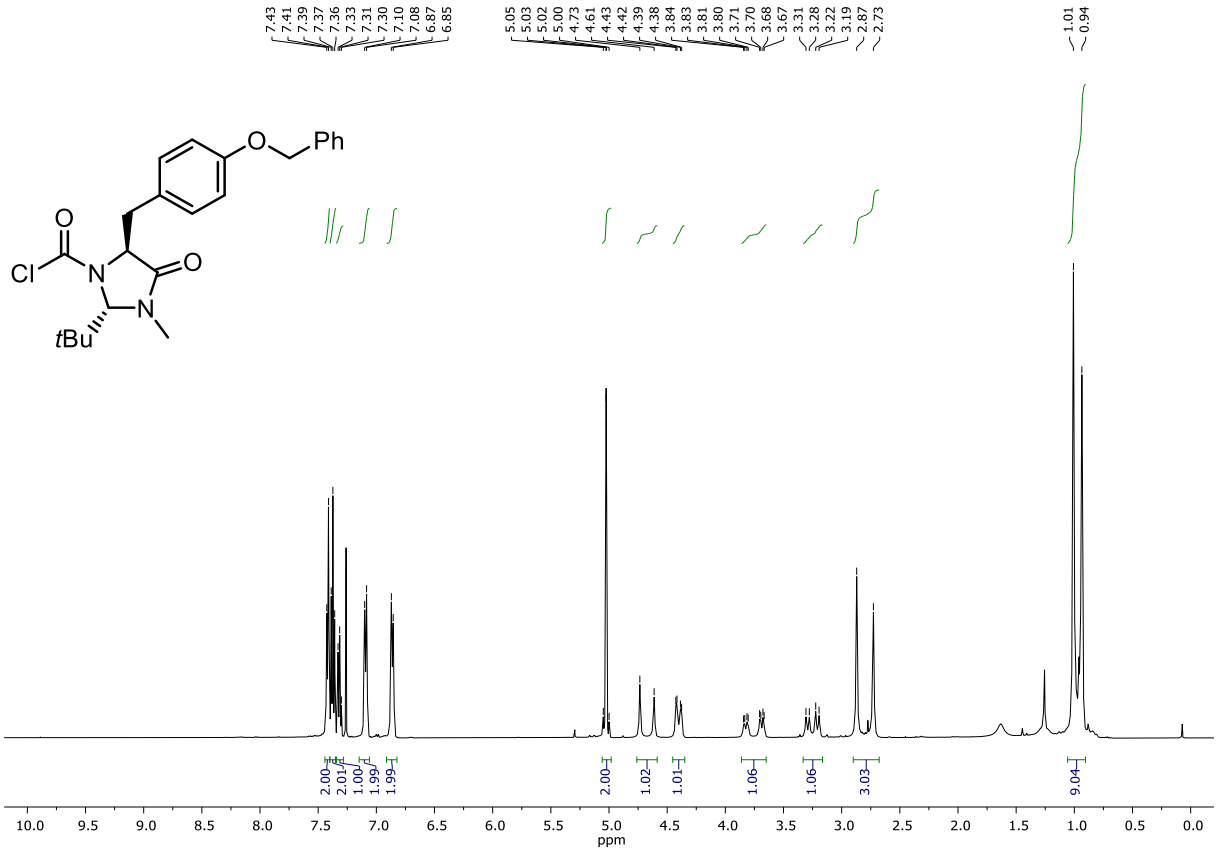
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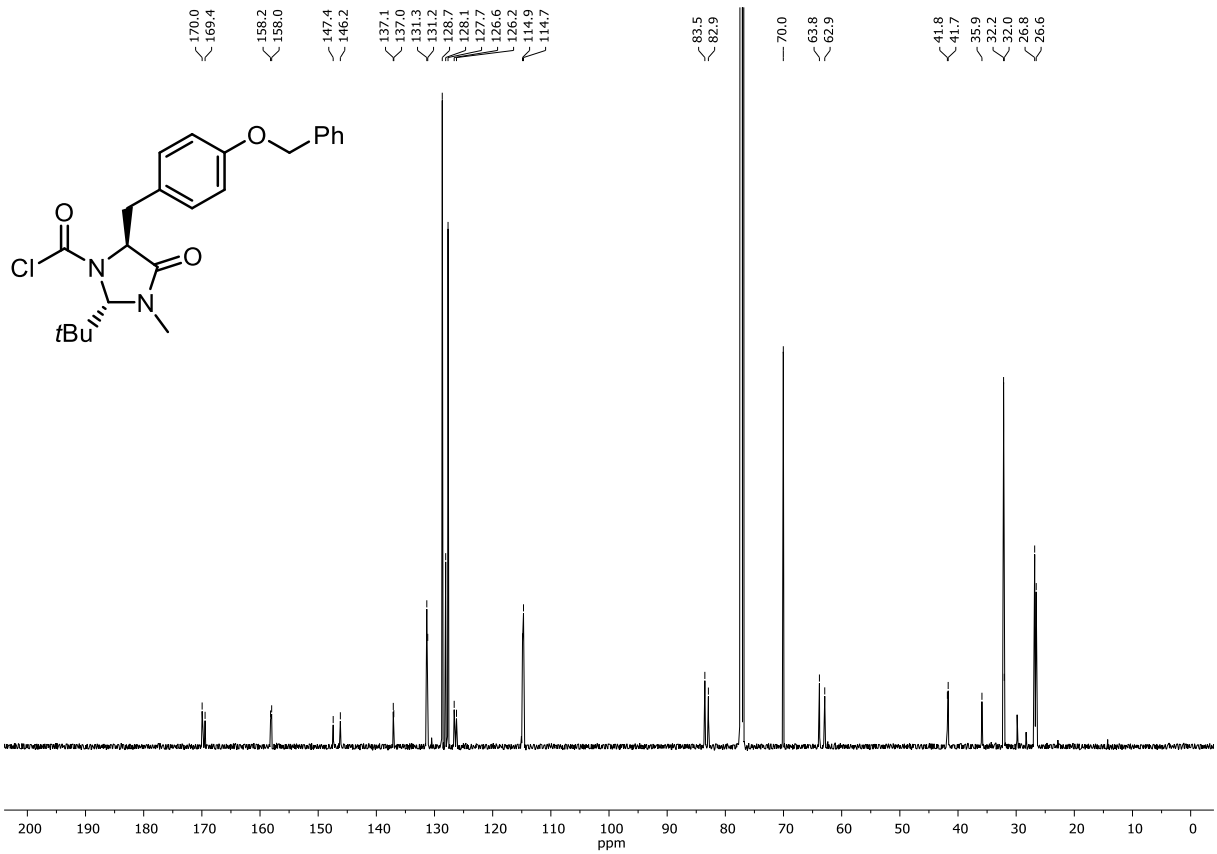
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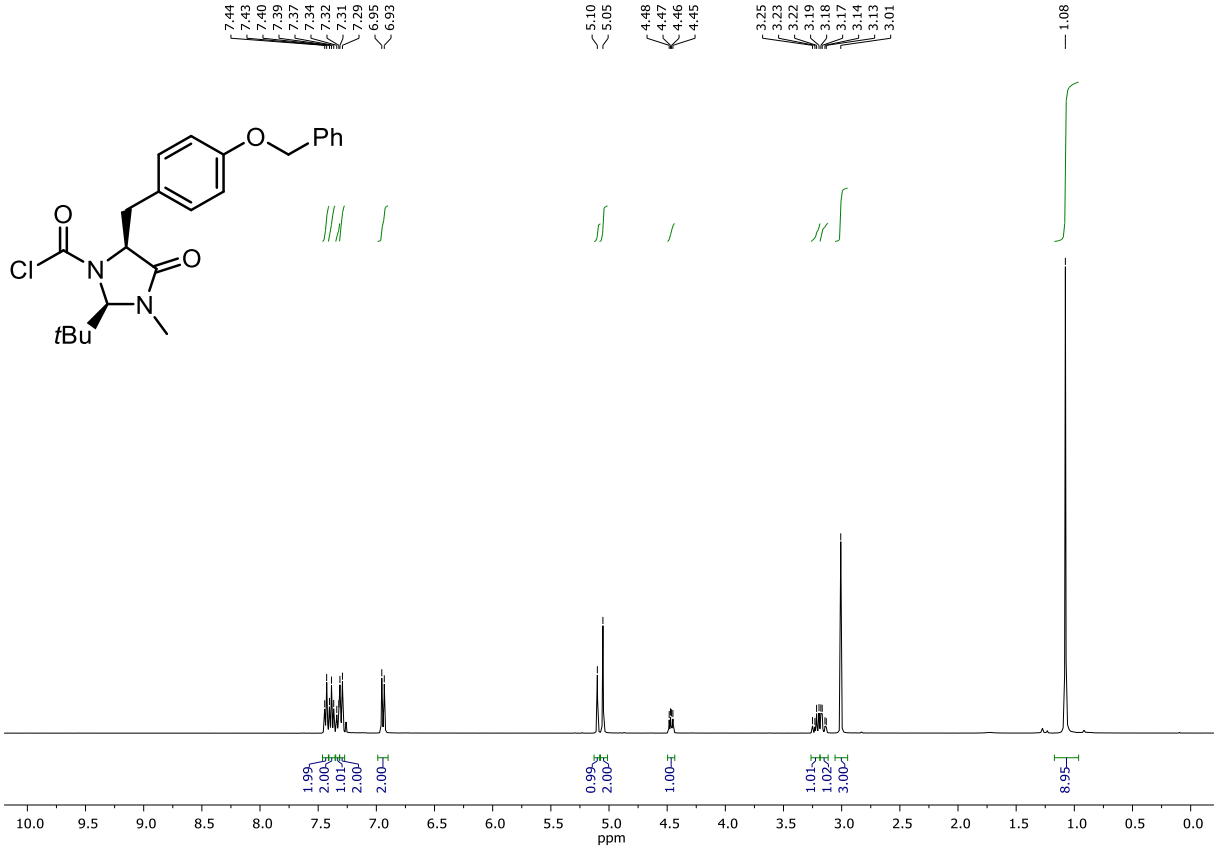
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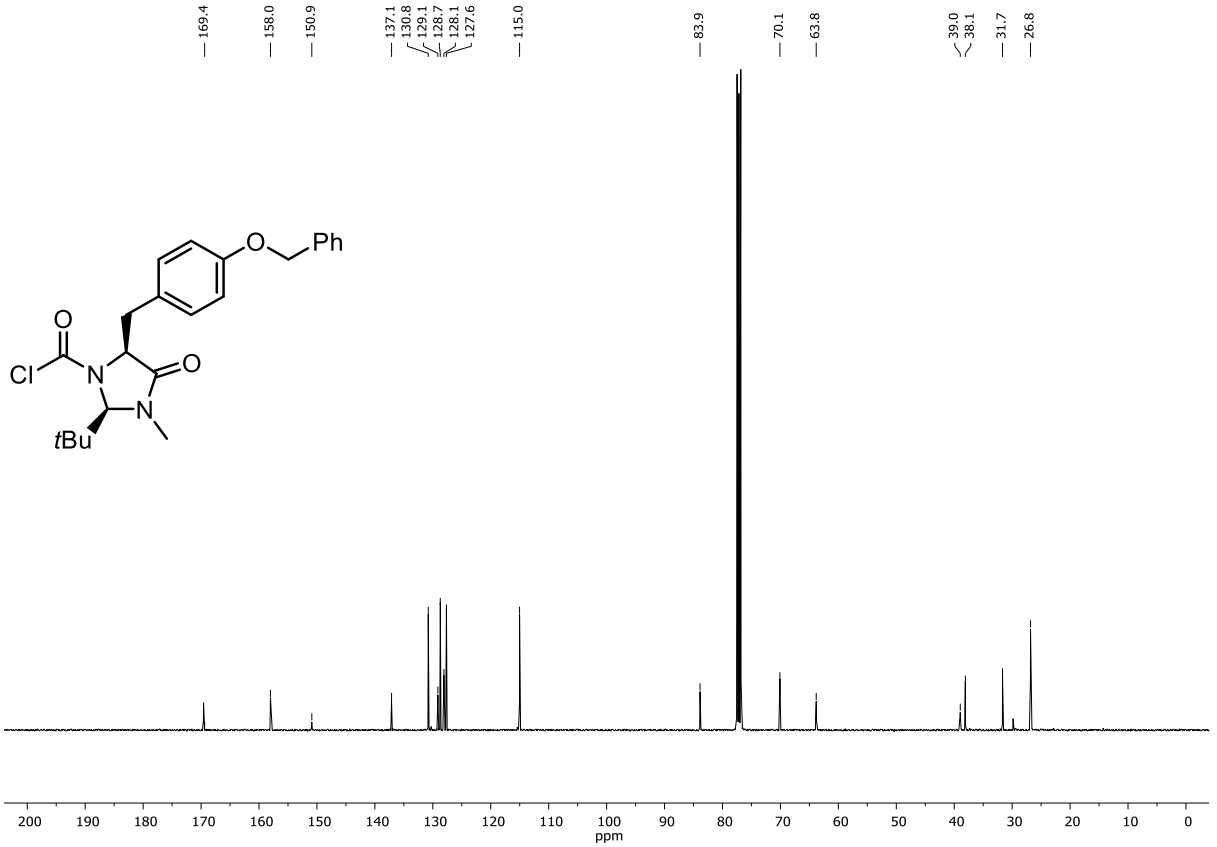
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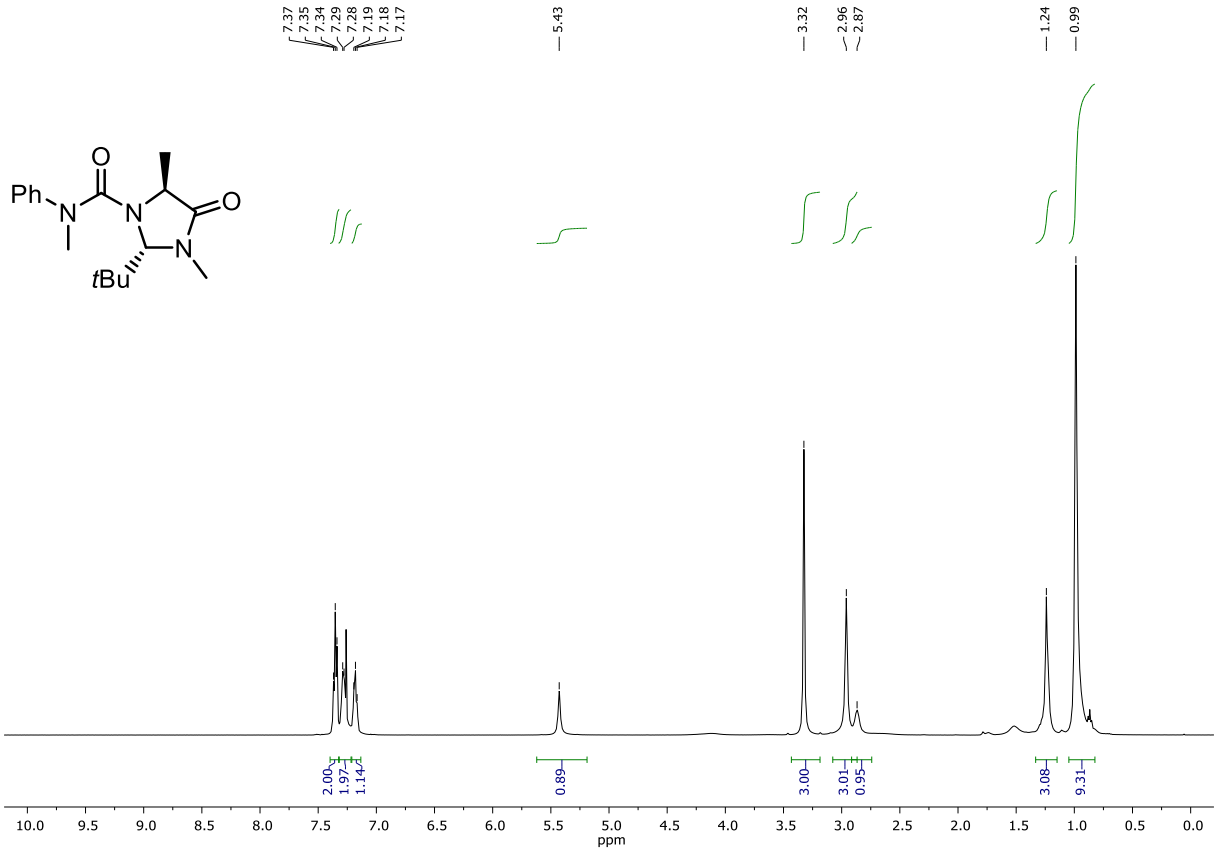
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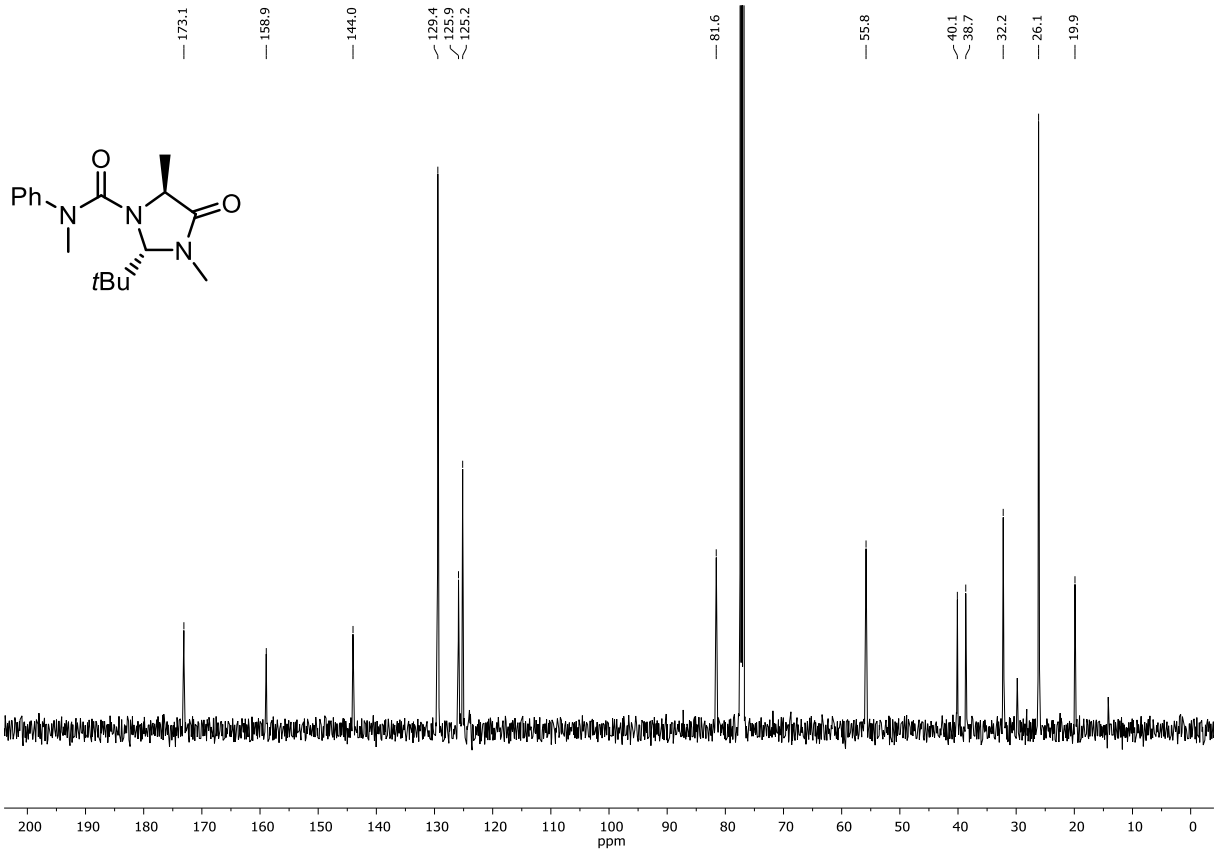
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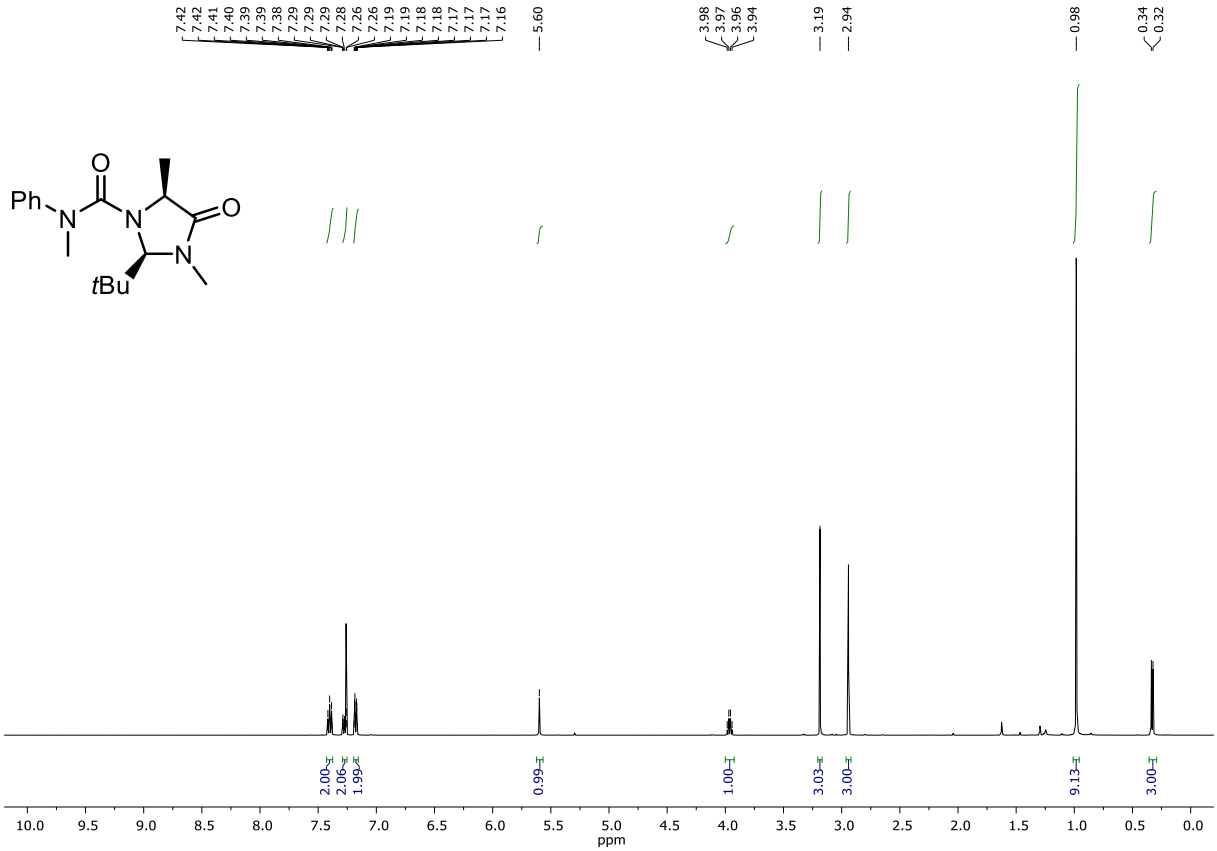
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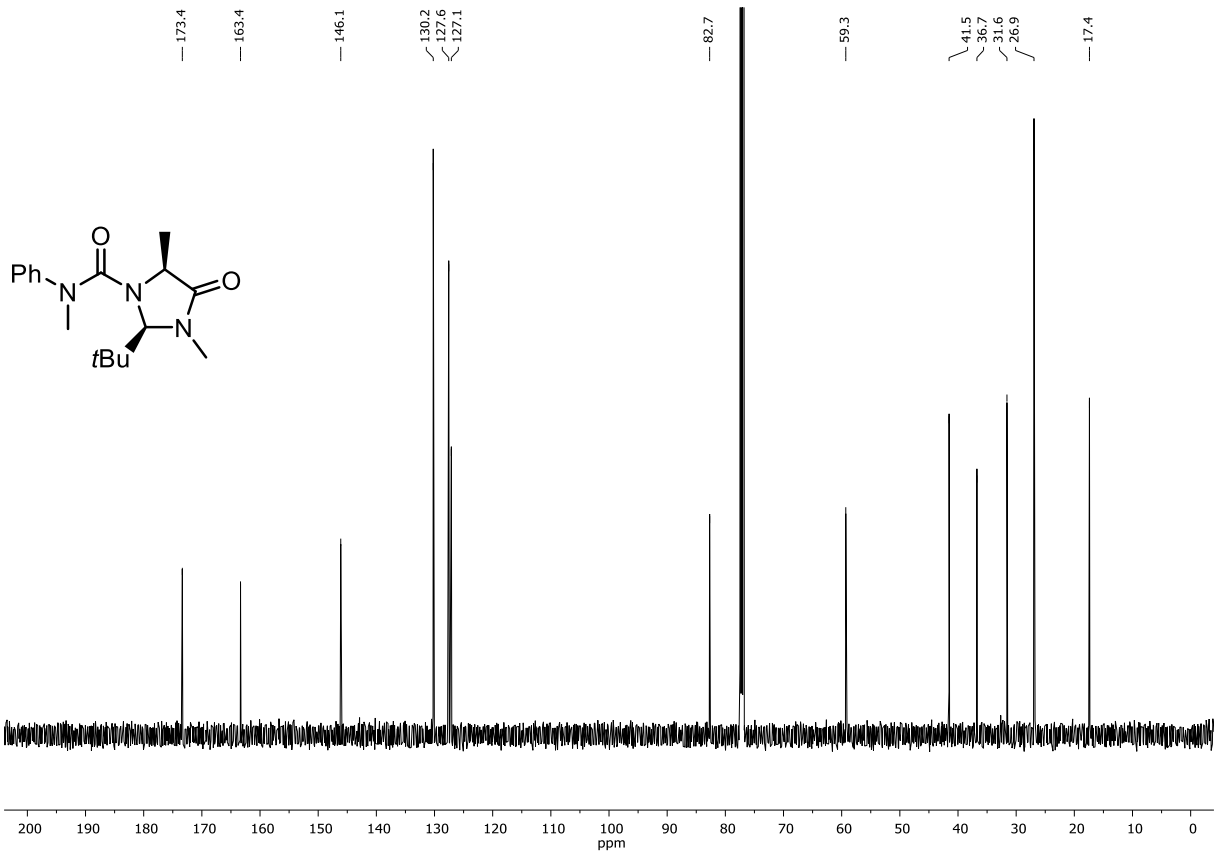
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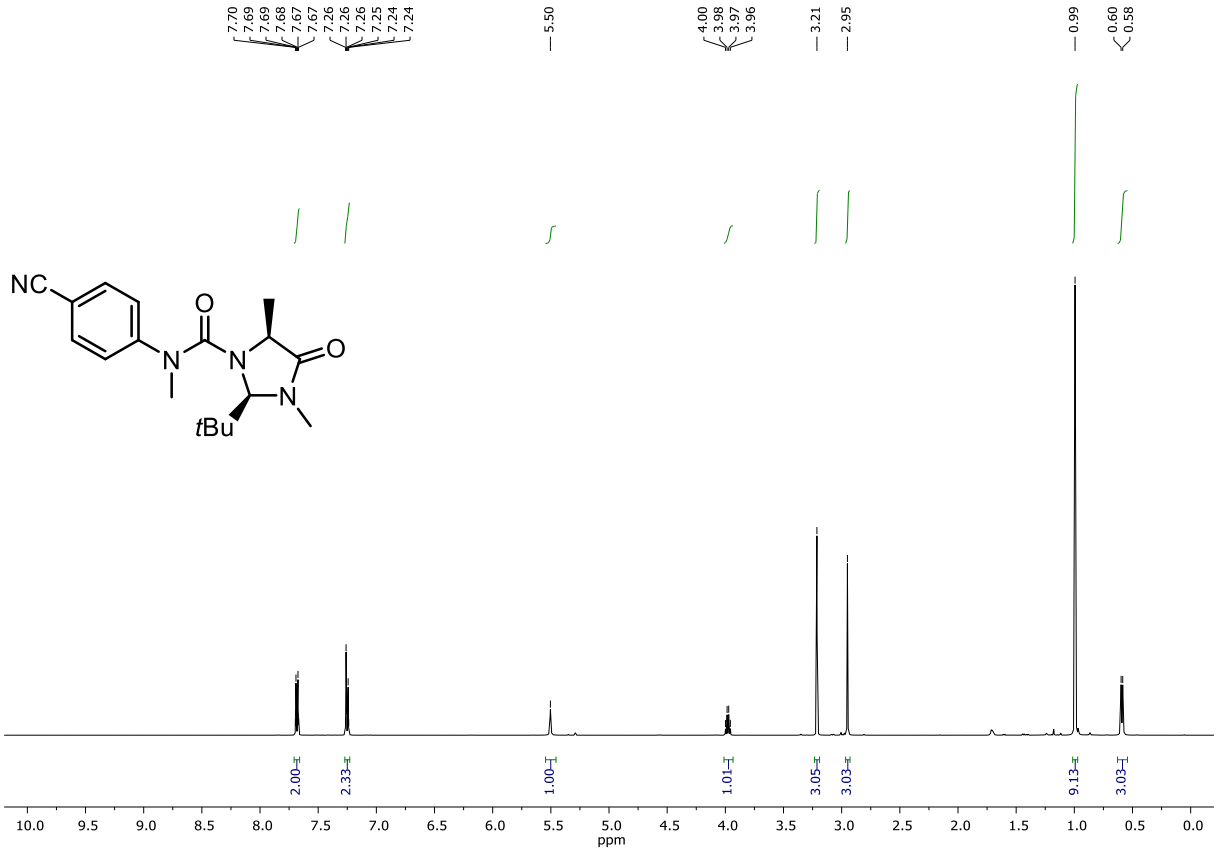
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0.60
0.58
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N
O
N
tBu
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2.33
1.00
1.01
3.05
3.03
9.13
3.03
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9.0
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8.0
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7.0
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6.0
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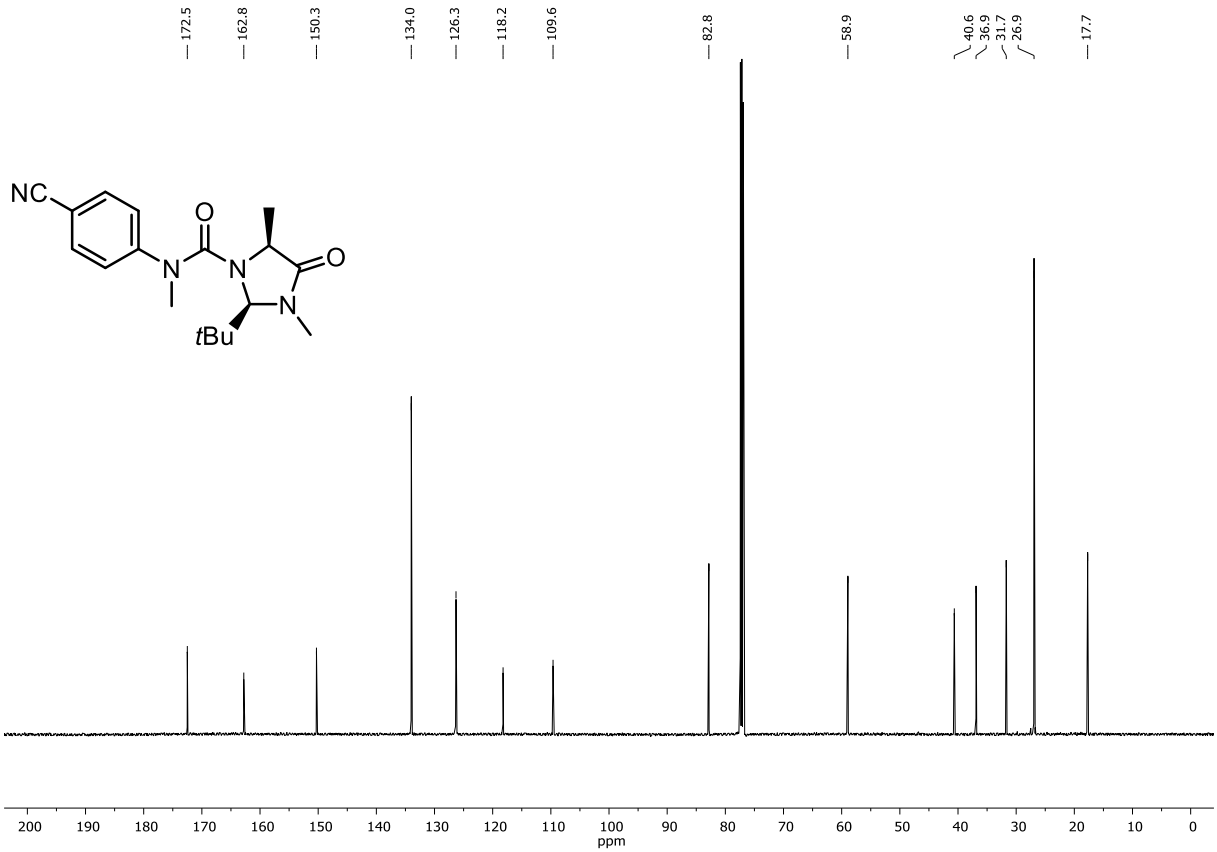
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17.7
NC
O
N
N
O
N
tBu
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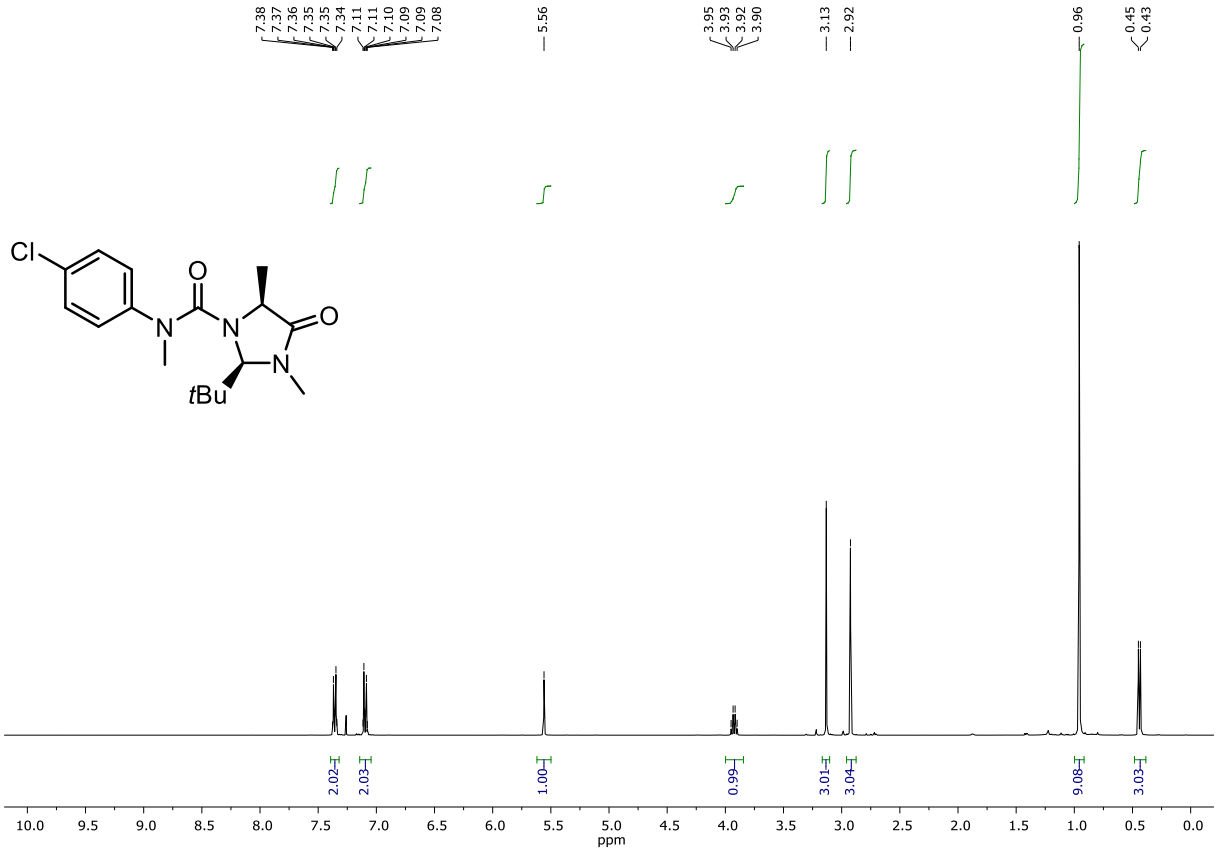
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3.90
3.13
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N
O
N
tBu
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2.03
1.00
0.99
3.01
3.04
9.08
3.03
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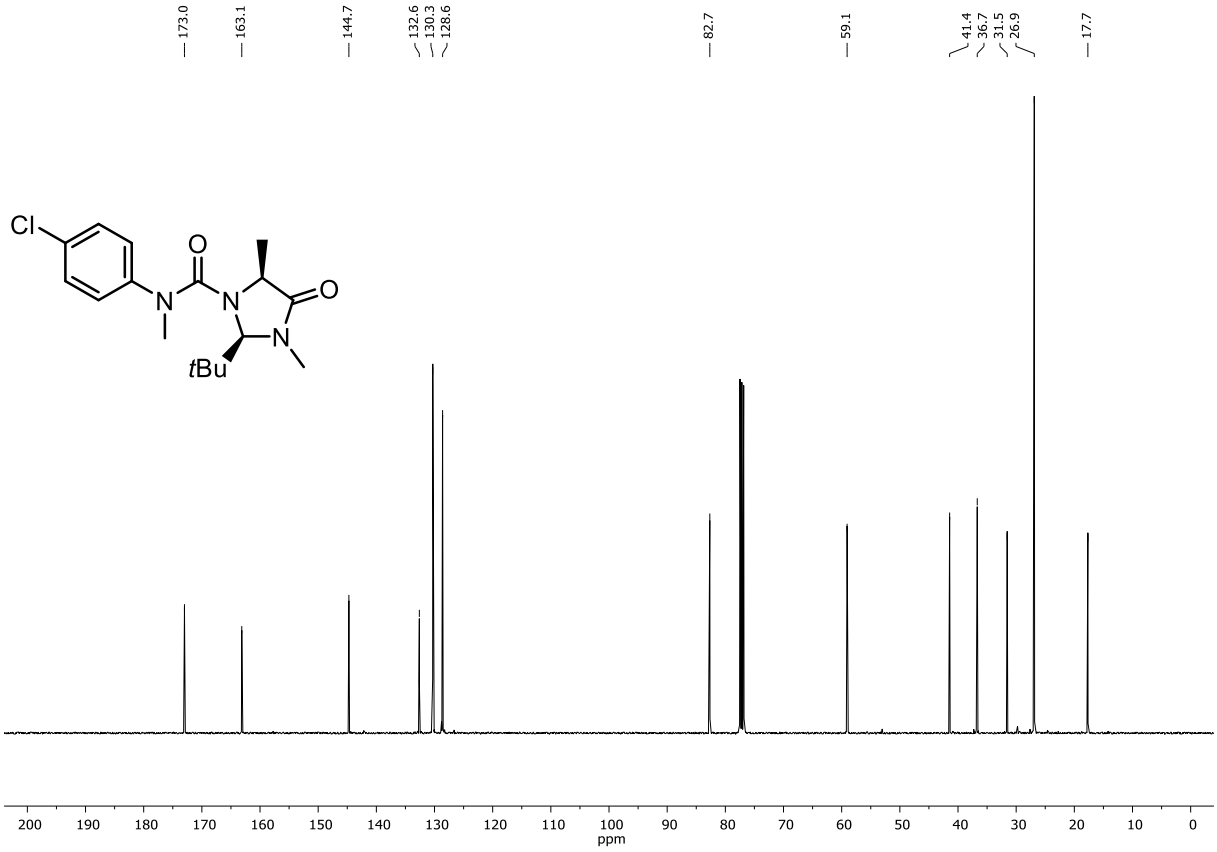
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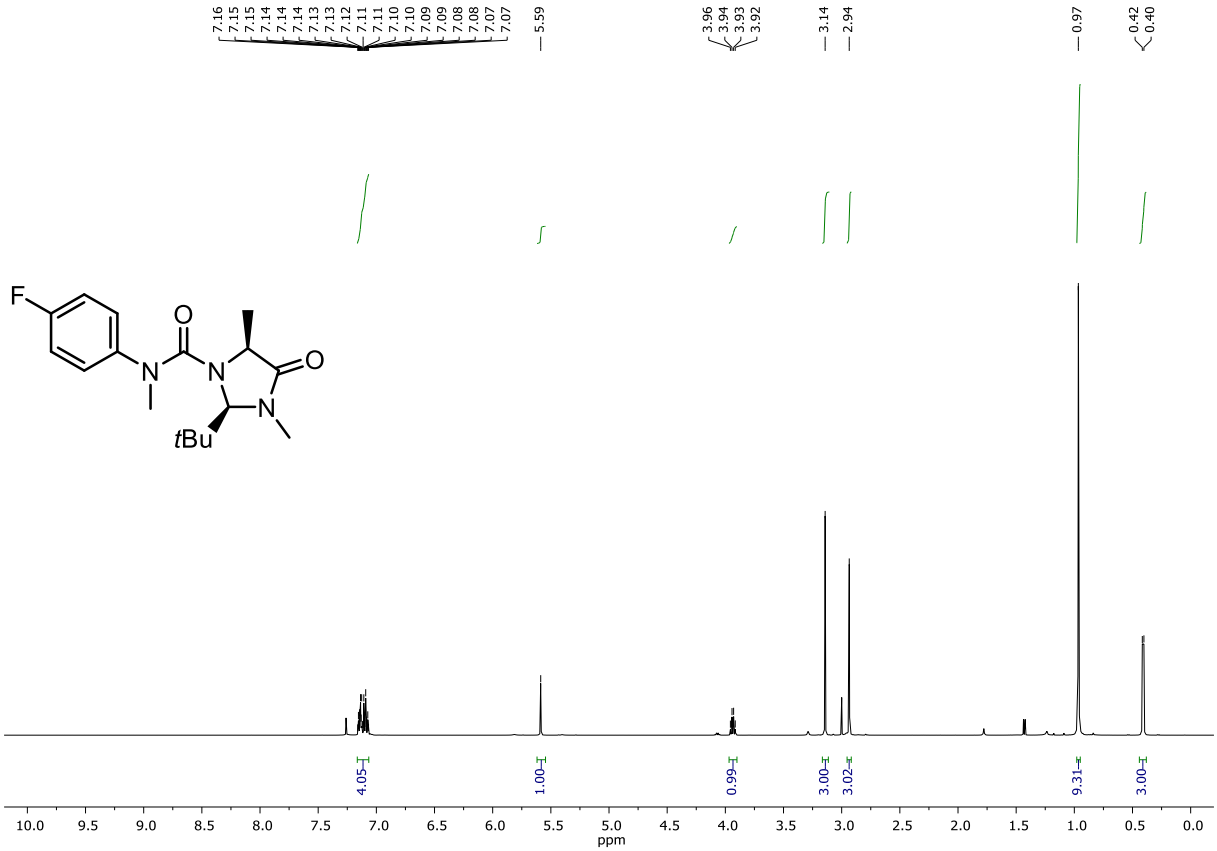
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7.09
7.08
7.08
7.07
7.07
5.59
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3.93
3.92
3.14
2.94
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N
O
N
tBu
4.05
1.00
0.99
3.00
3.02
9.31
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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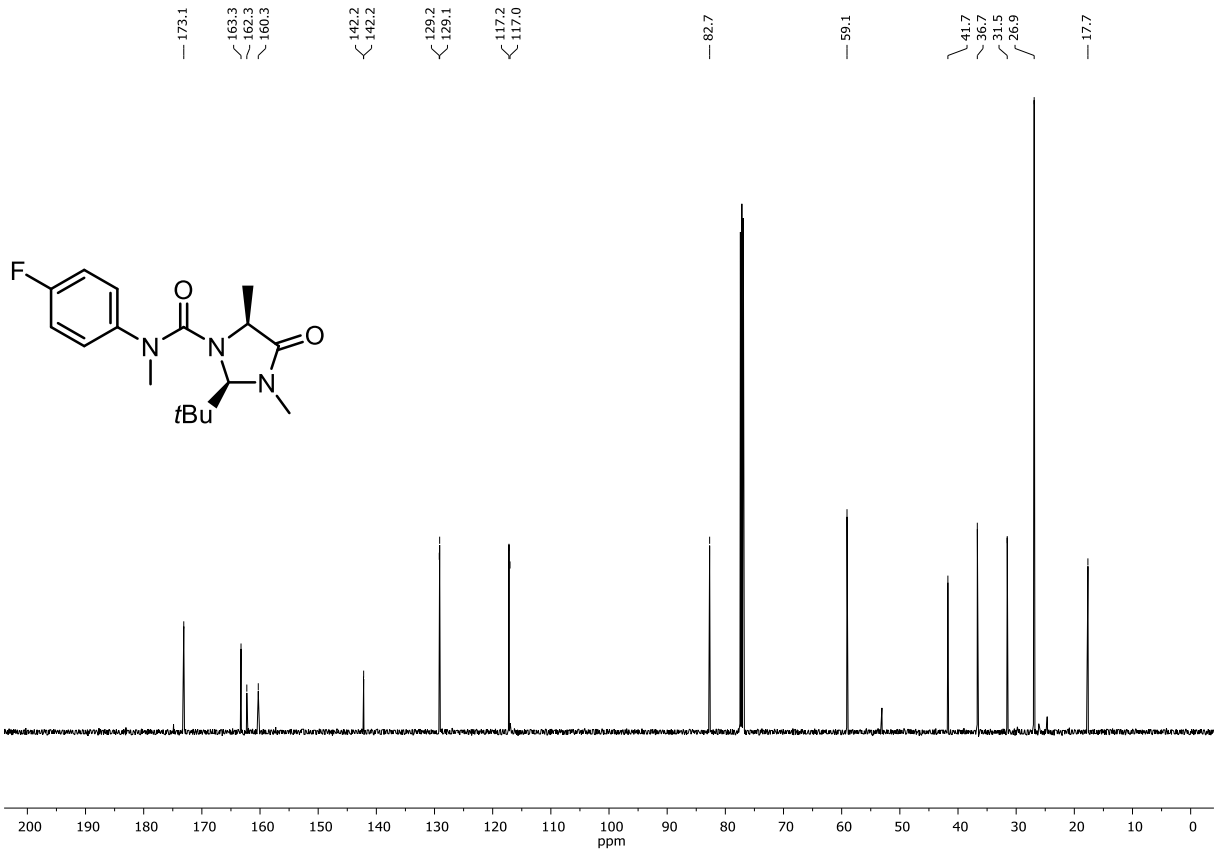
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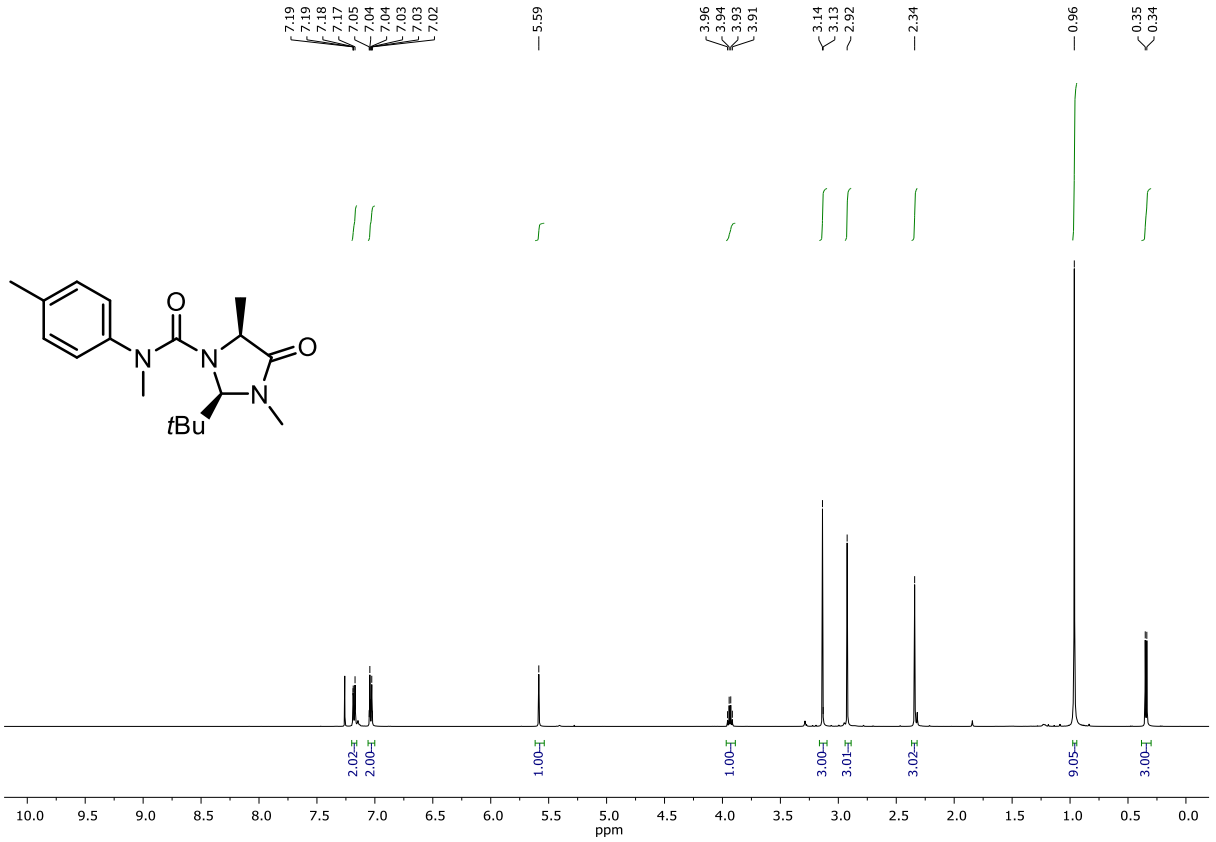
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7.02
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3.13
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N
O
N
tBu
2.02
2.00
1.00
1.00
3.00
3.01
3.02
9.05
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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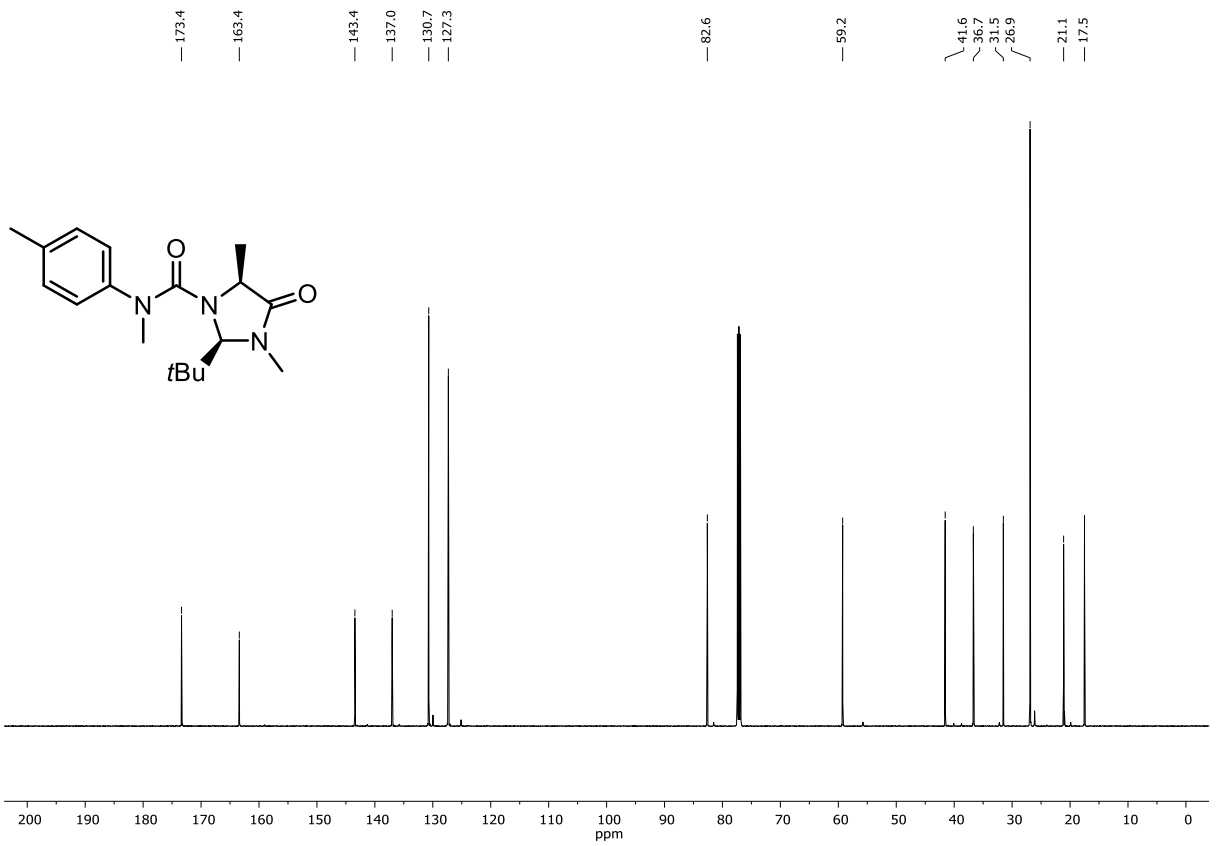
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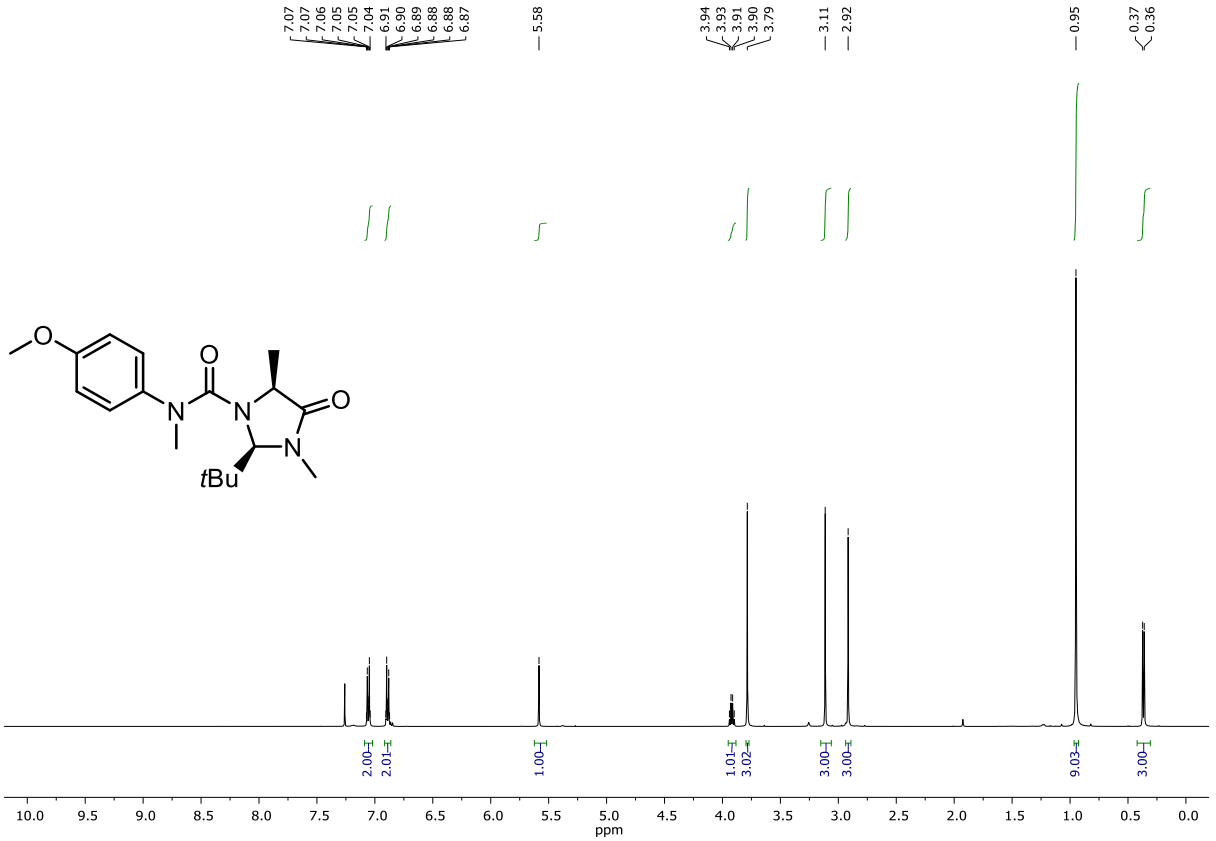
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O
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N
O
N
tBu
2.00
2.01
1.00
1.01
3.02
3.00
3.00
9.03
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10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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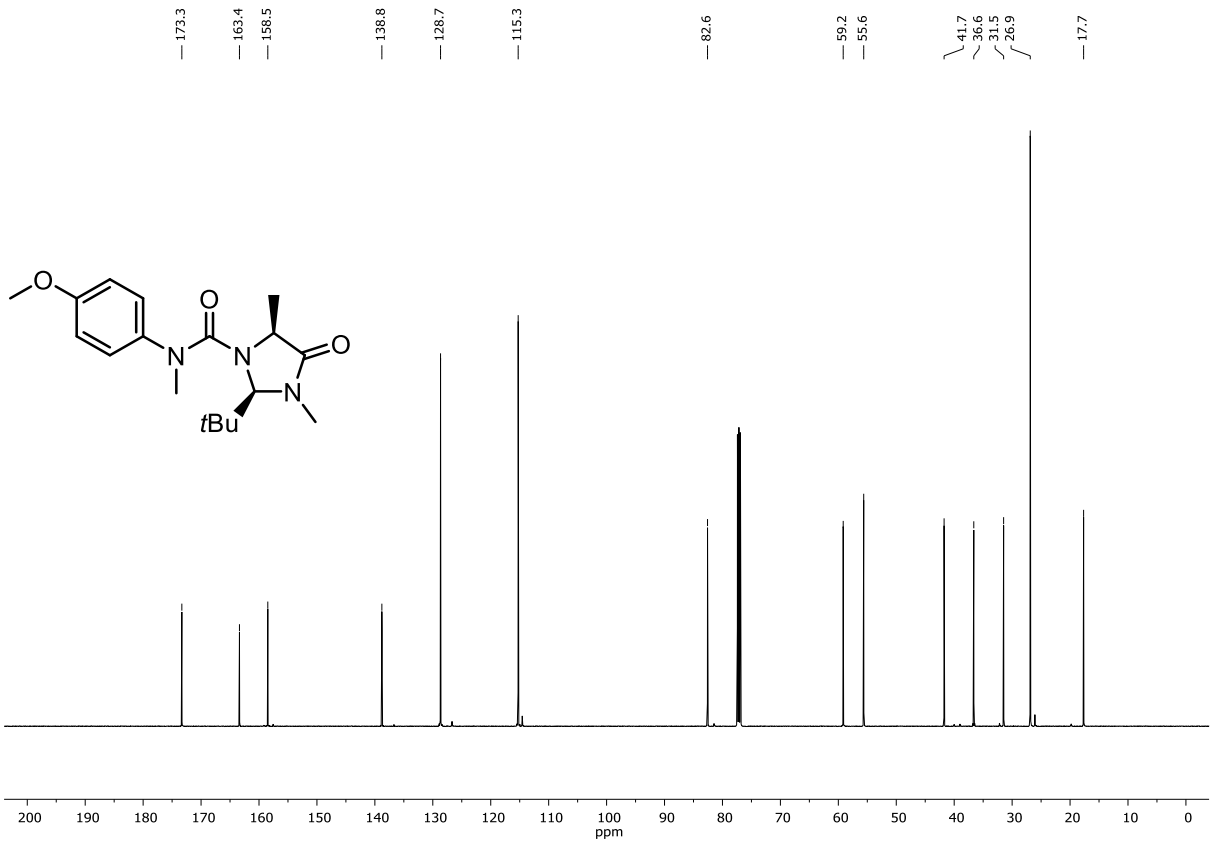
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59.2
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41.7
36.6
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26.9
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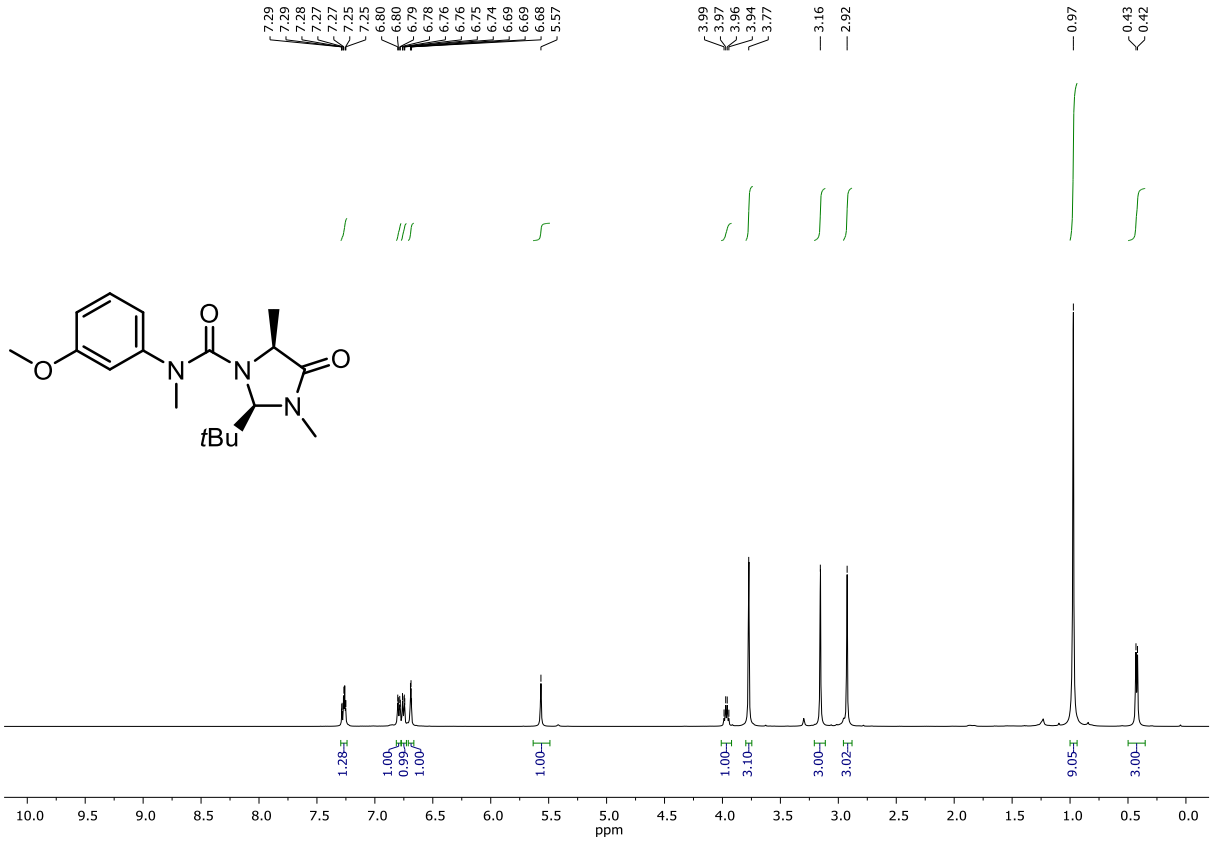
N
tBu
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm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N
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1.00
1.00
1.00
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3.00
3.02
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3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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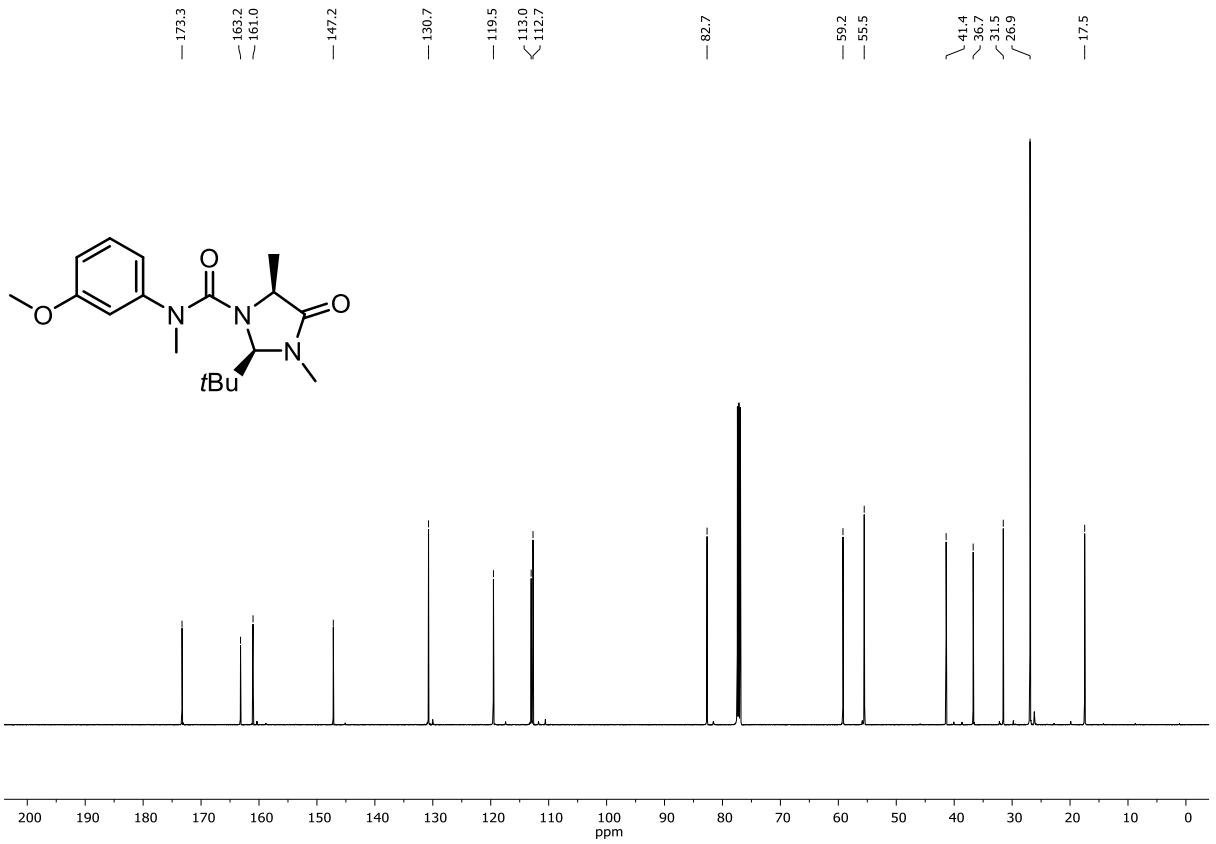
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55.5
41.4
36.7
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N
O
N
tBu
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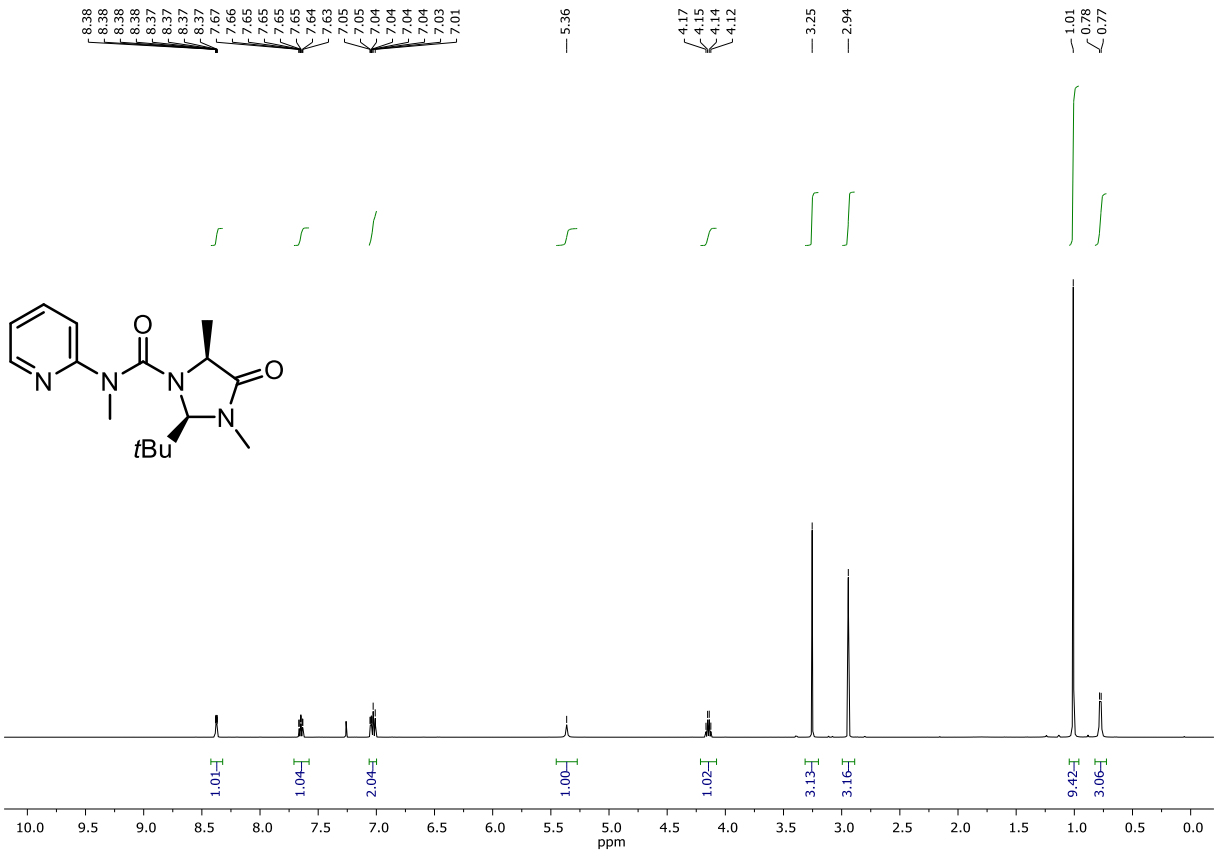
ppm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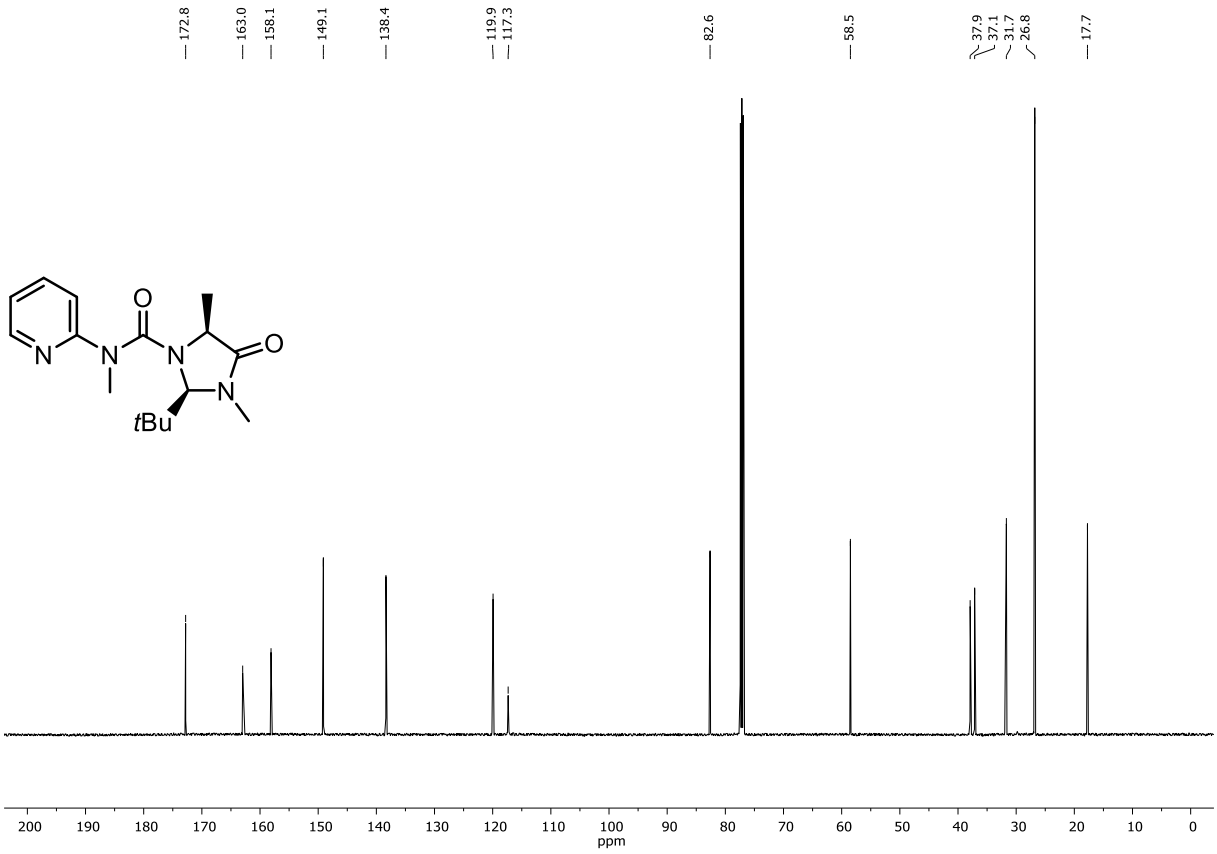
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31.7
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O
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O
N
N
tBu
200
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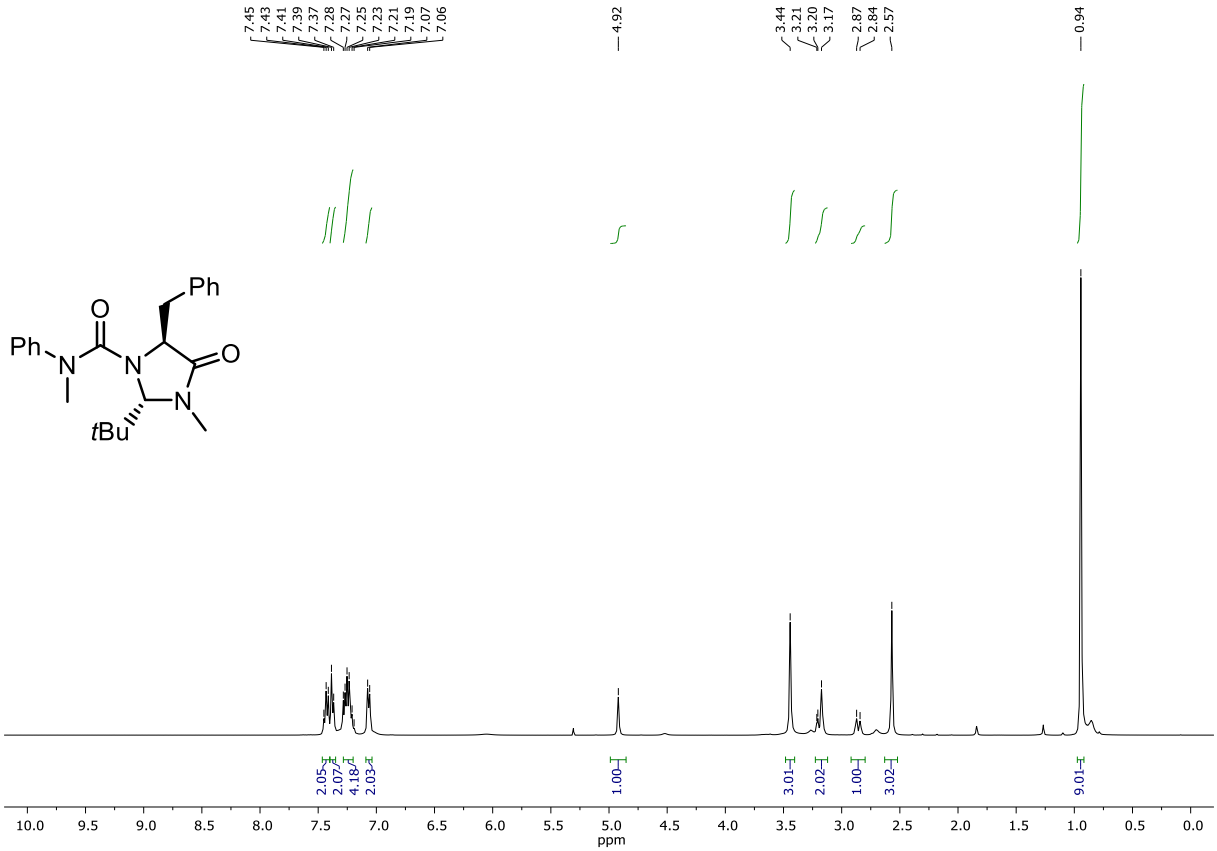
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N
tBu
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2.07
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3.01
2.02
1.00
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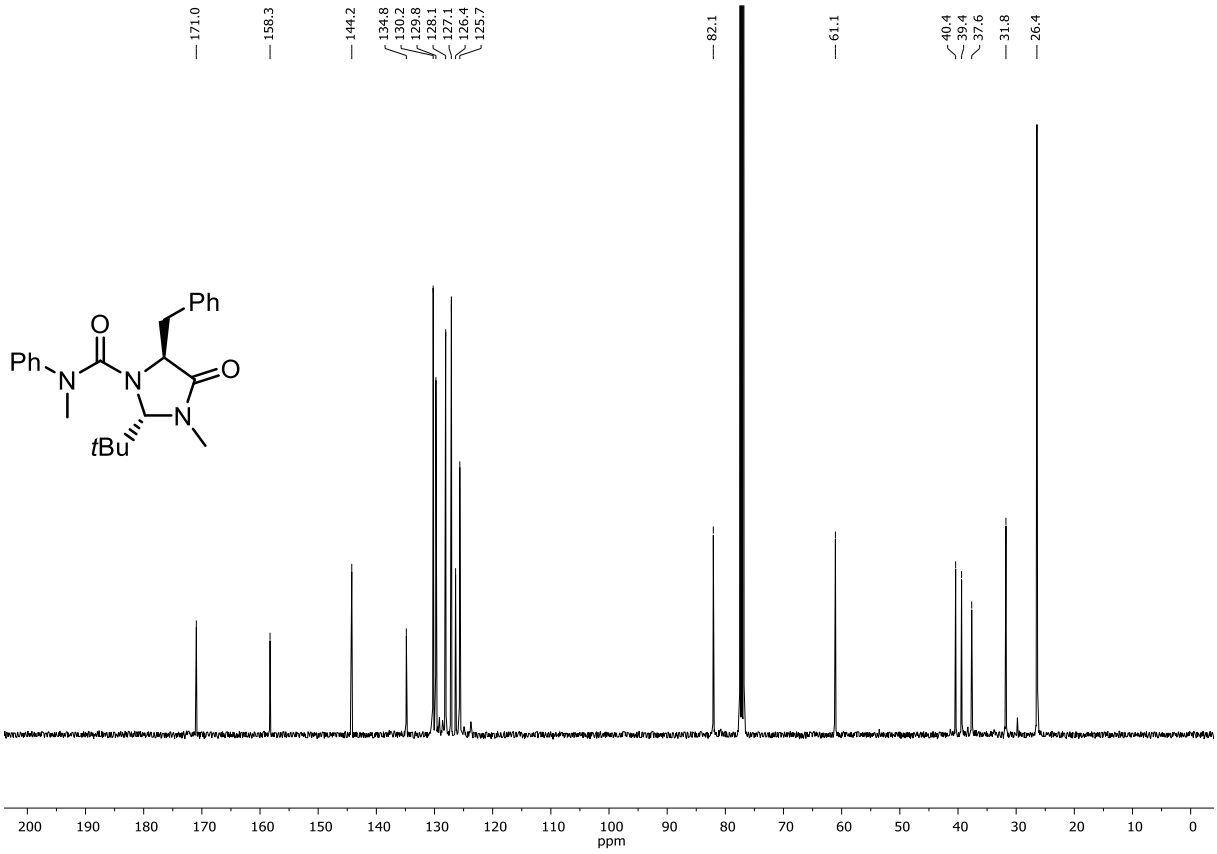
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61.1
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37.6
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Ph
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N
tBu
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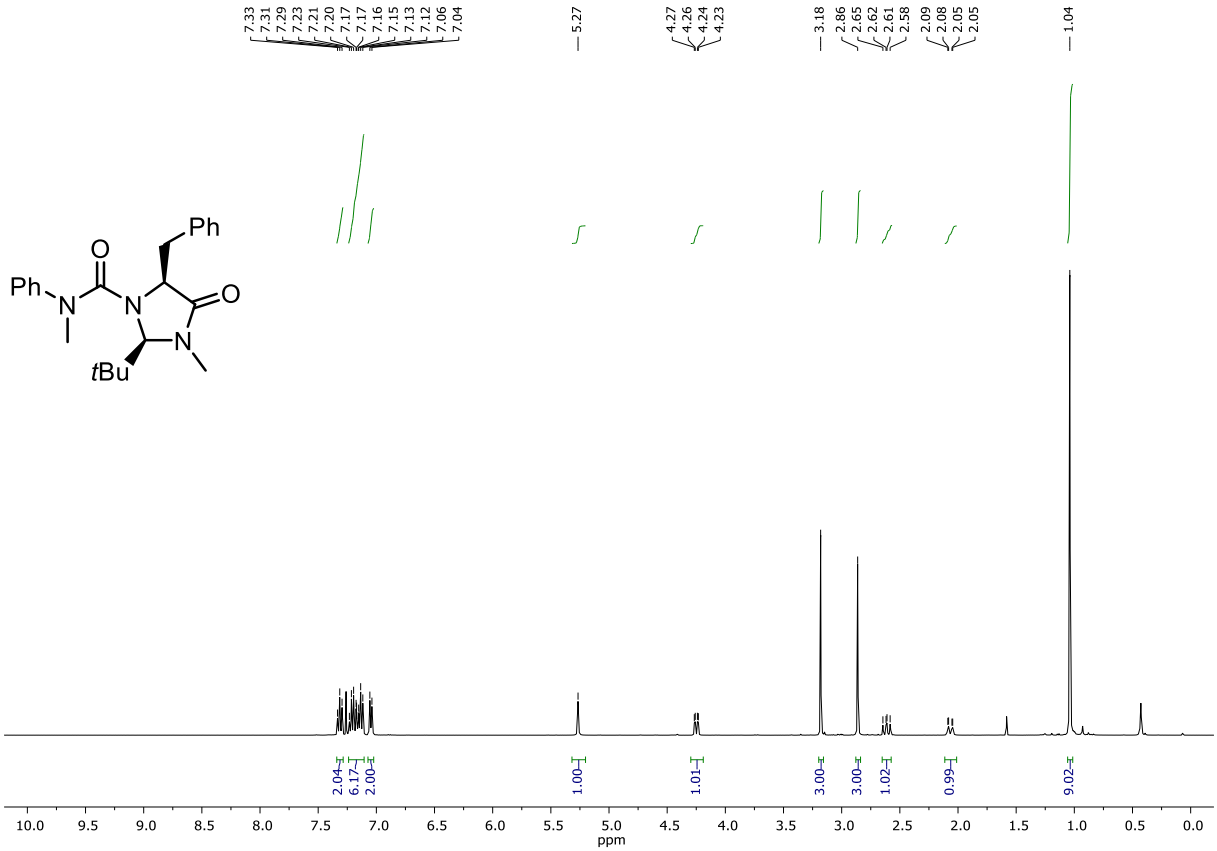
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2.08
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2.05
1.04
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Ph
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N
O
N
tBu
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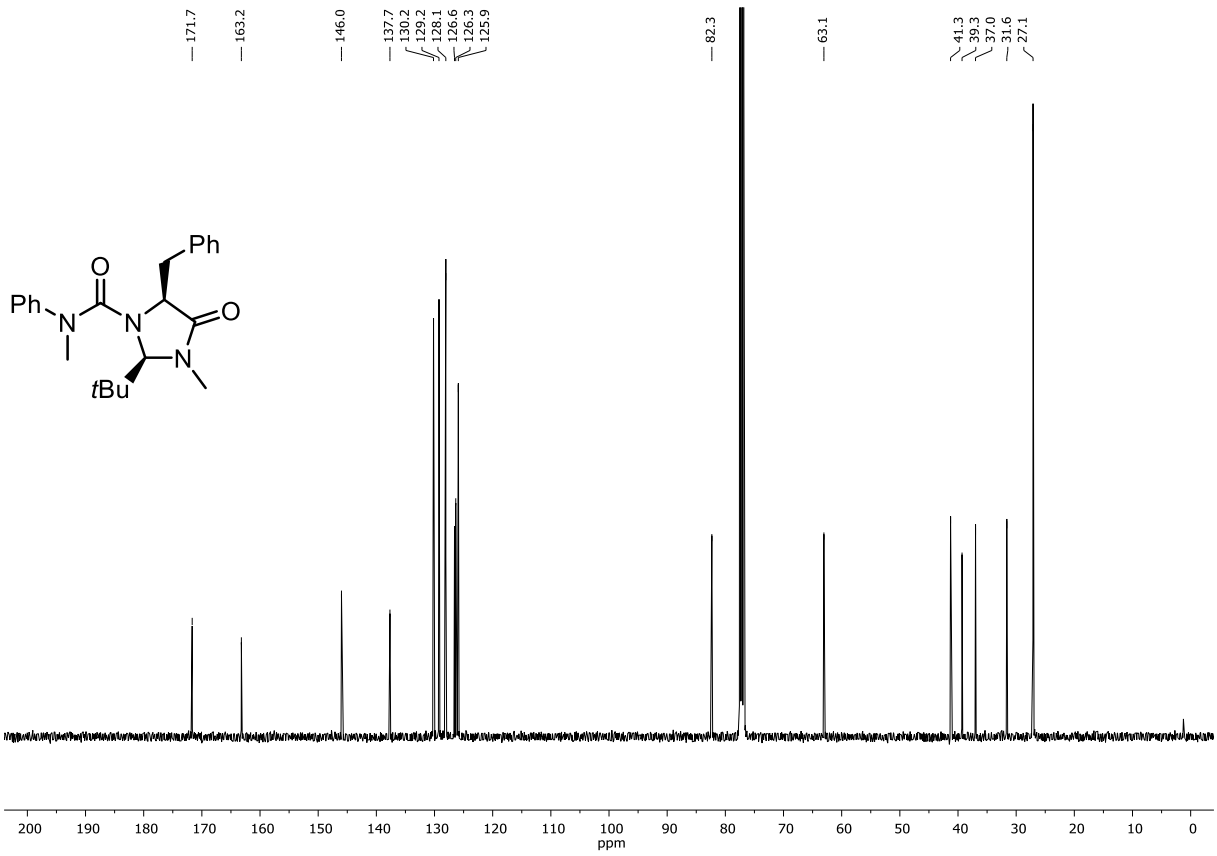
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39.3
37.0
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Ph
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O
N
tBu
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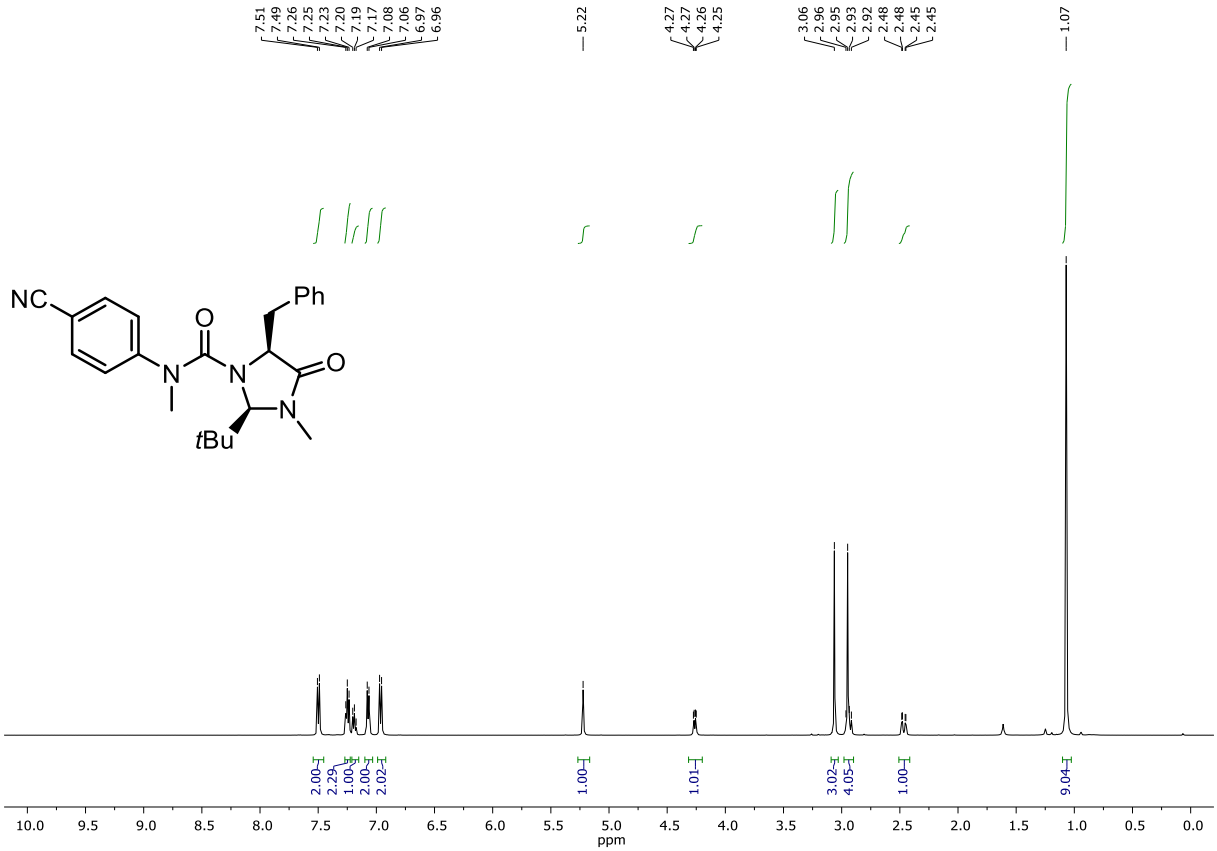
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3.06
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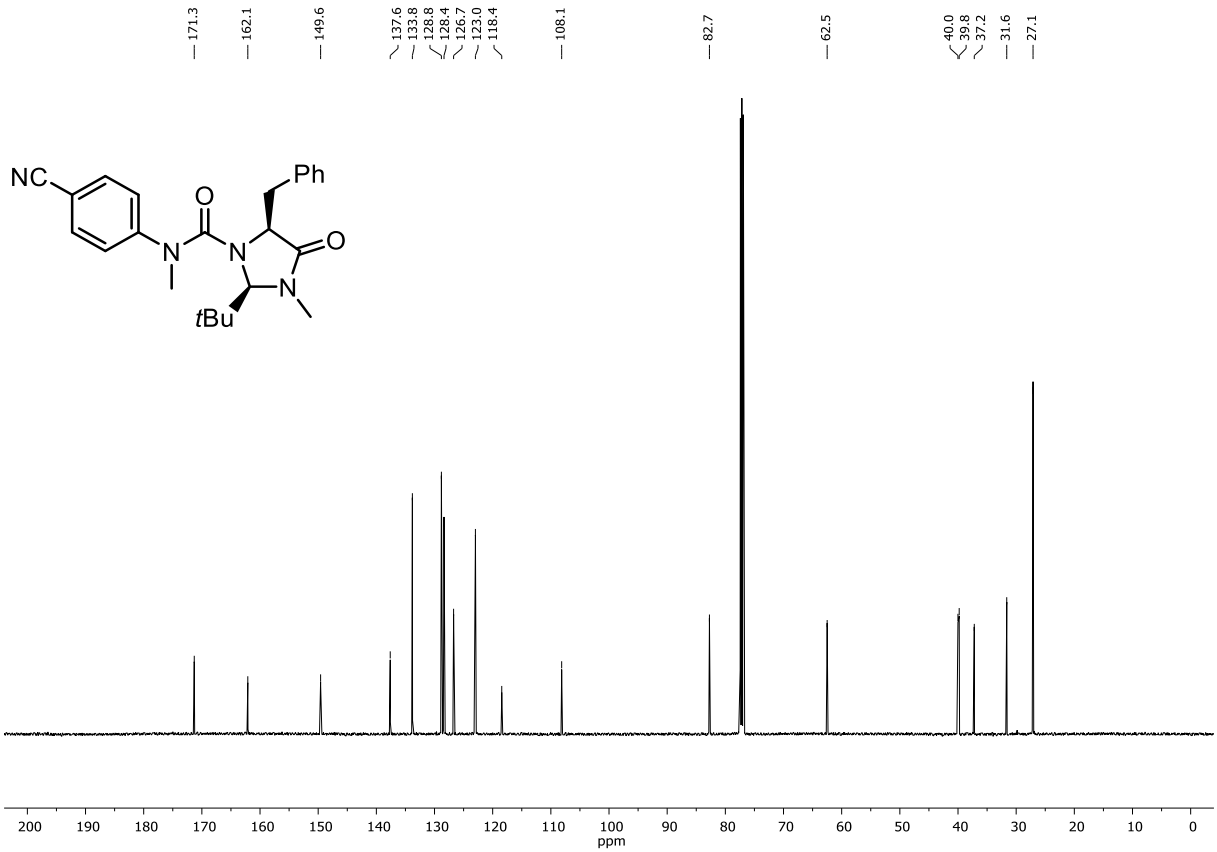
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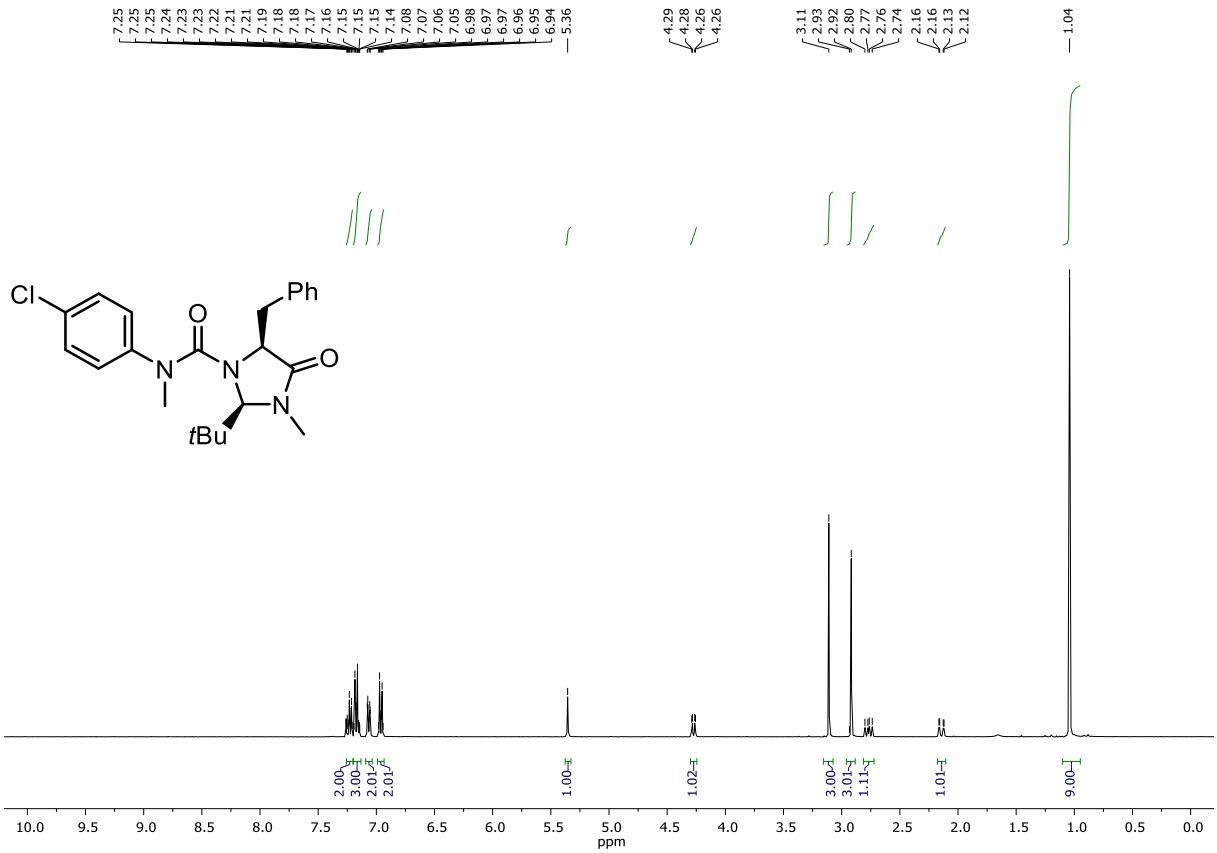
N
tBu
ppm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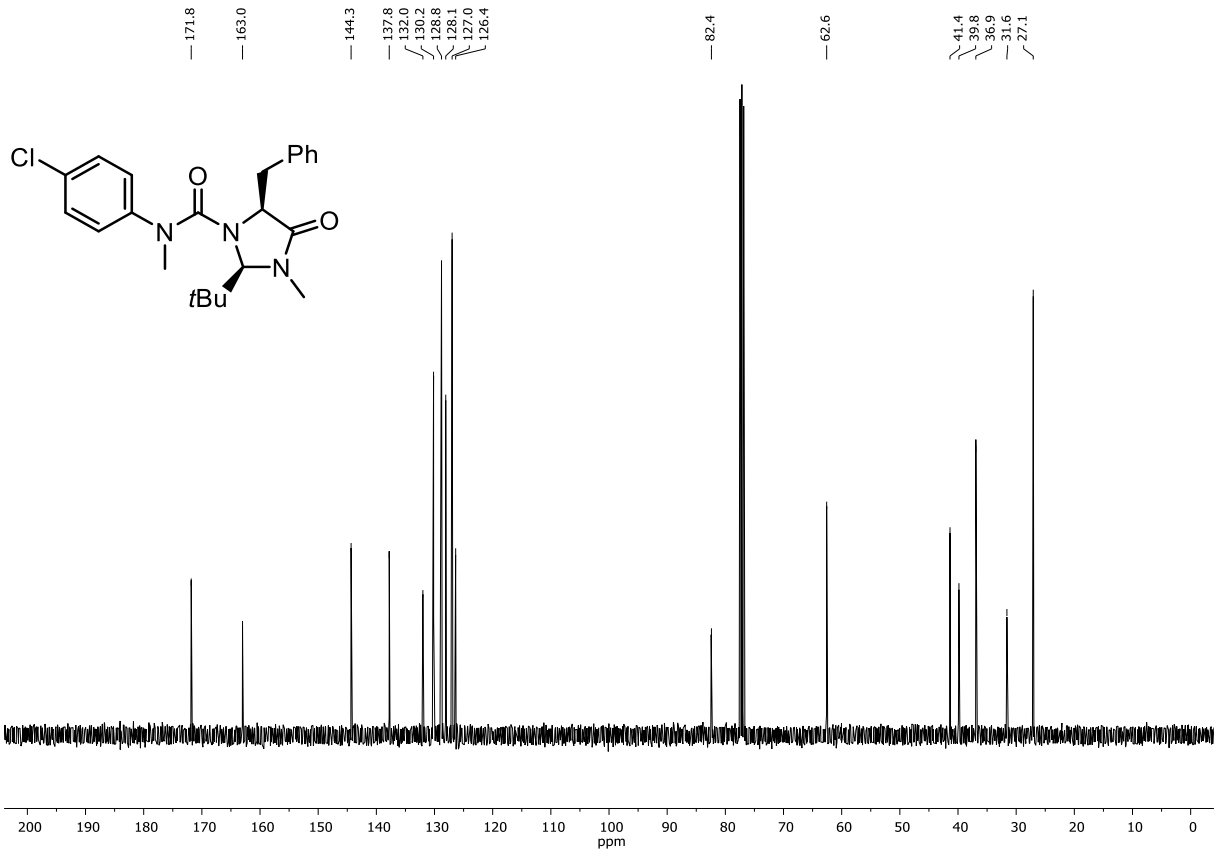
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41.4
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36.9
31.6
27.1
Cl
Ph
O
N
N
O
N
tBu
200
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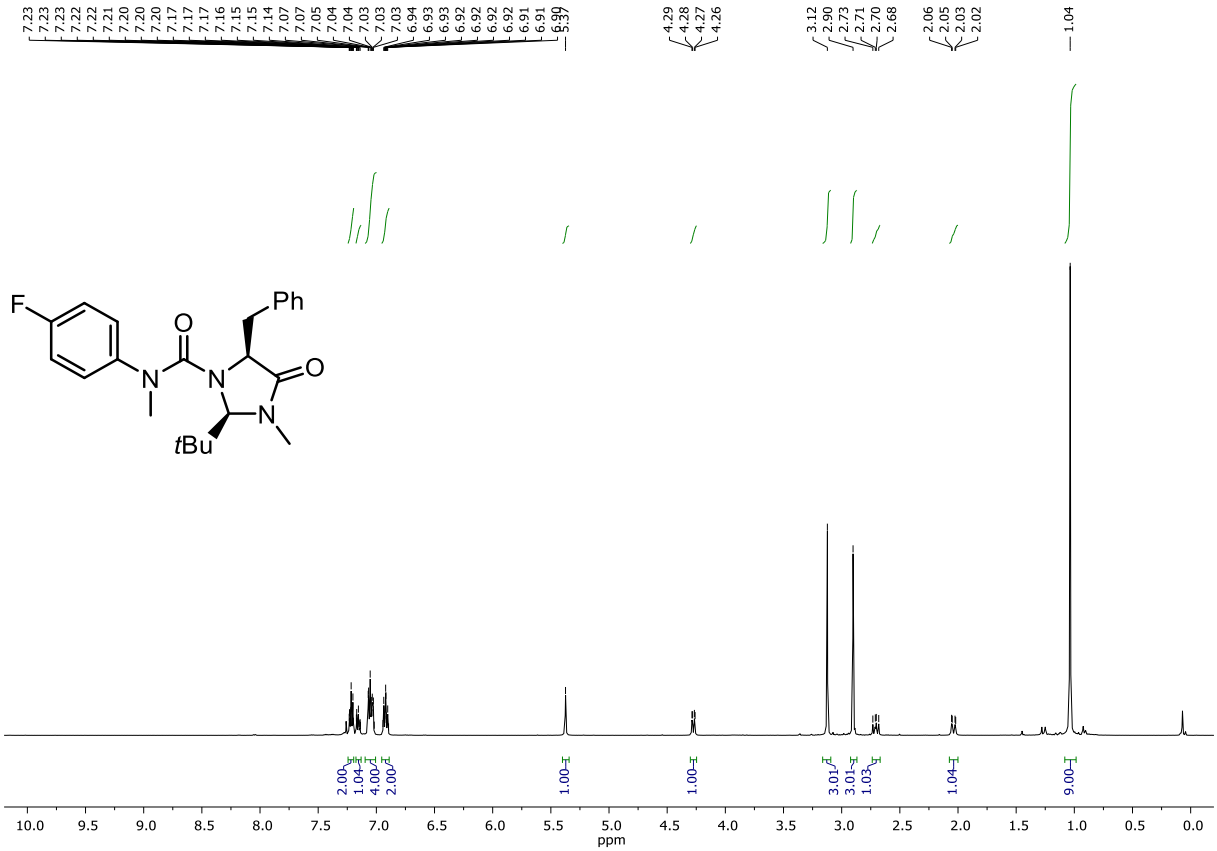
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3.12 2.90 2.73 2.71 2.70 2.68
2.06 2.05 2.03 2.02
1.04
F
O
N
N
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Ph
N
tBu
2.00 1.04 4.00 2.00 1.00 1.00 3.01 3.01 1.03 1.04 9.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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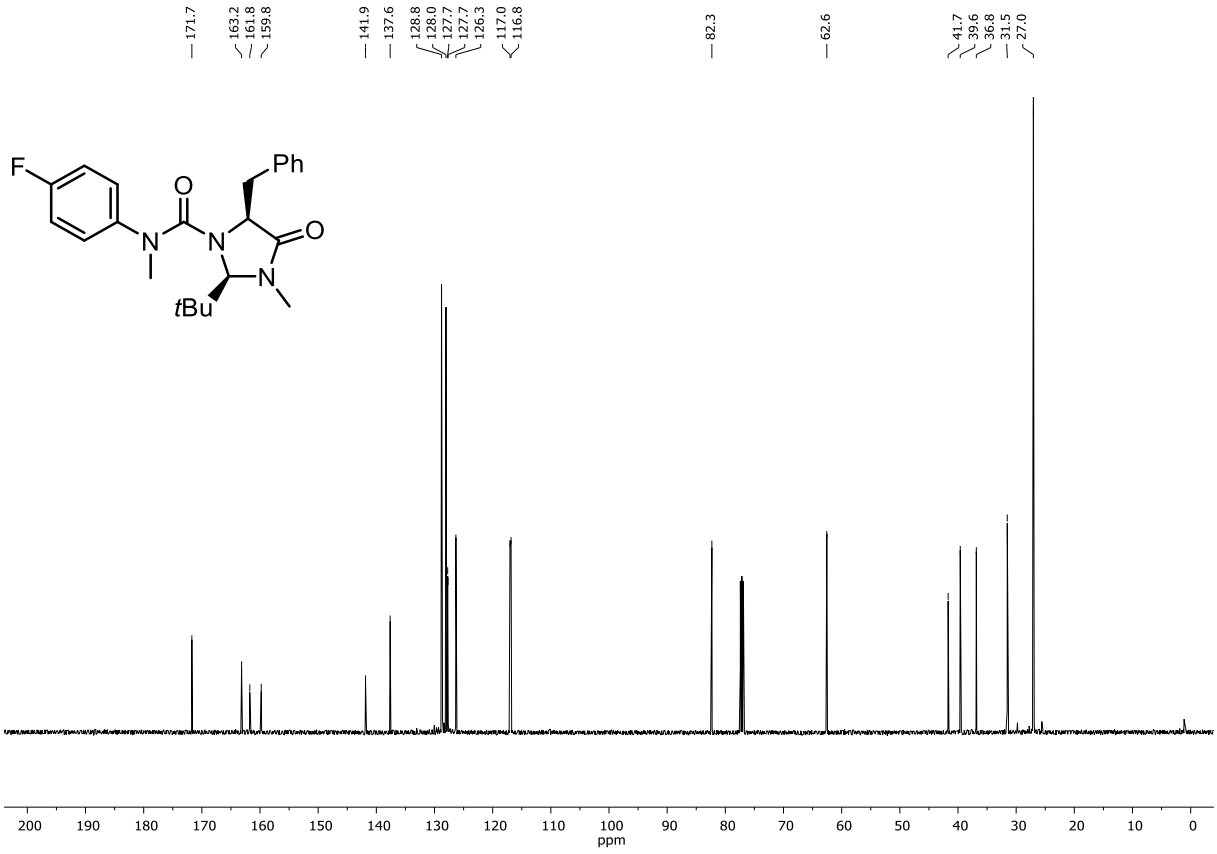
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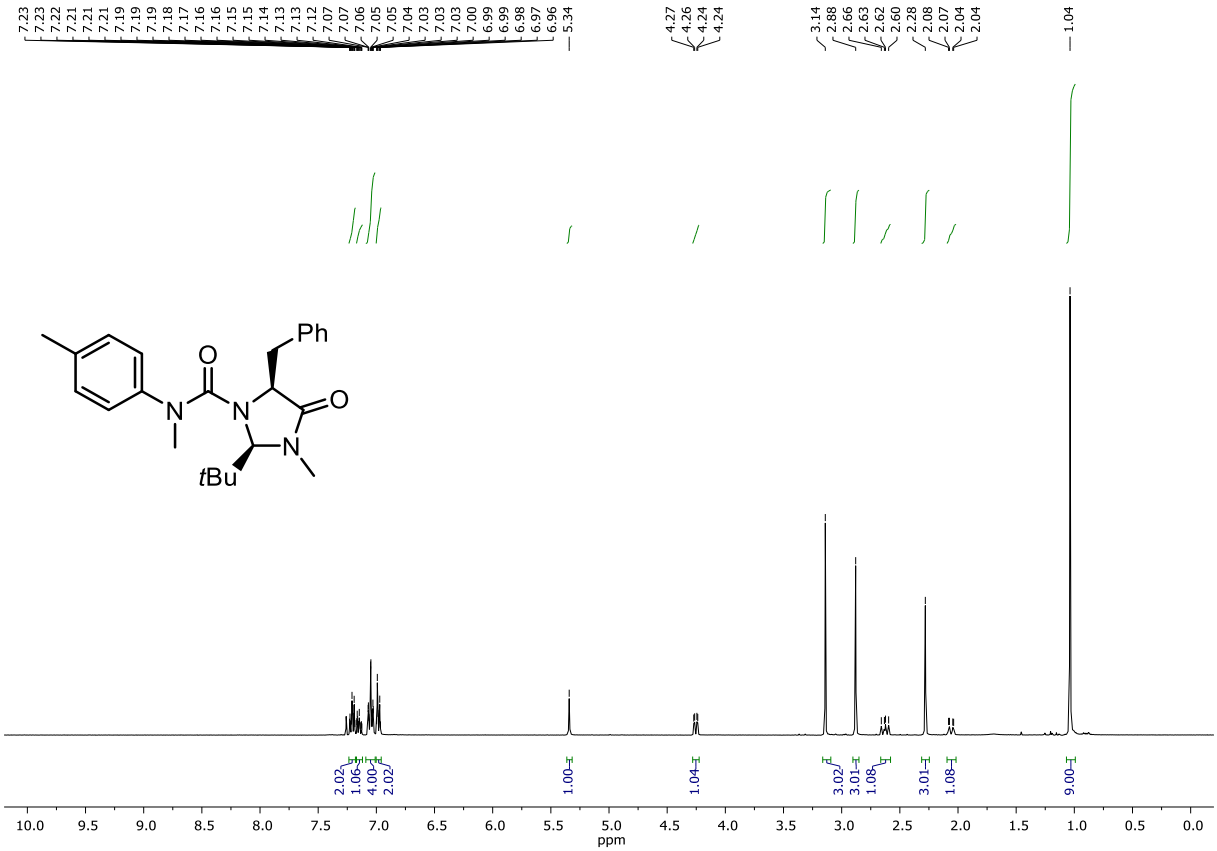
141.9 137.6
128.8 128.0 127.7 127.7 126.3
117.0 116.8
82.3
62.6
41.7 39.6 36.8
31.5
27.0
F
O
N
N
O
Ph
N
tBu
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm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4.27 4.26 4.24 4.24
3.14 2.88 2.66 2.63 2.62 2.60 2.28 2.08 2.07 2.04 2.04
1.04
Ph
O
N
N
O
N
tBu
2.02 1.06 4.00 2.02
1.00
1.04
3.02 3.01 1.08
3.01
1.08
9.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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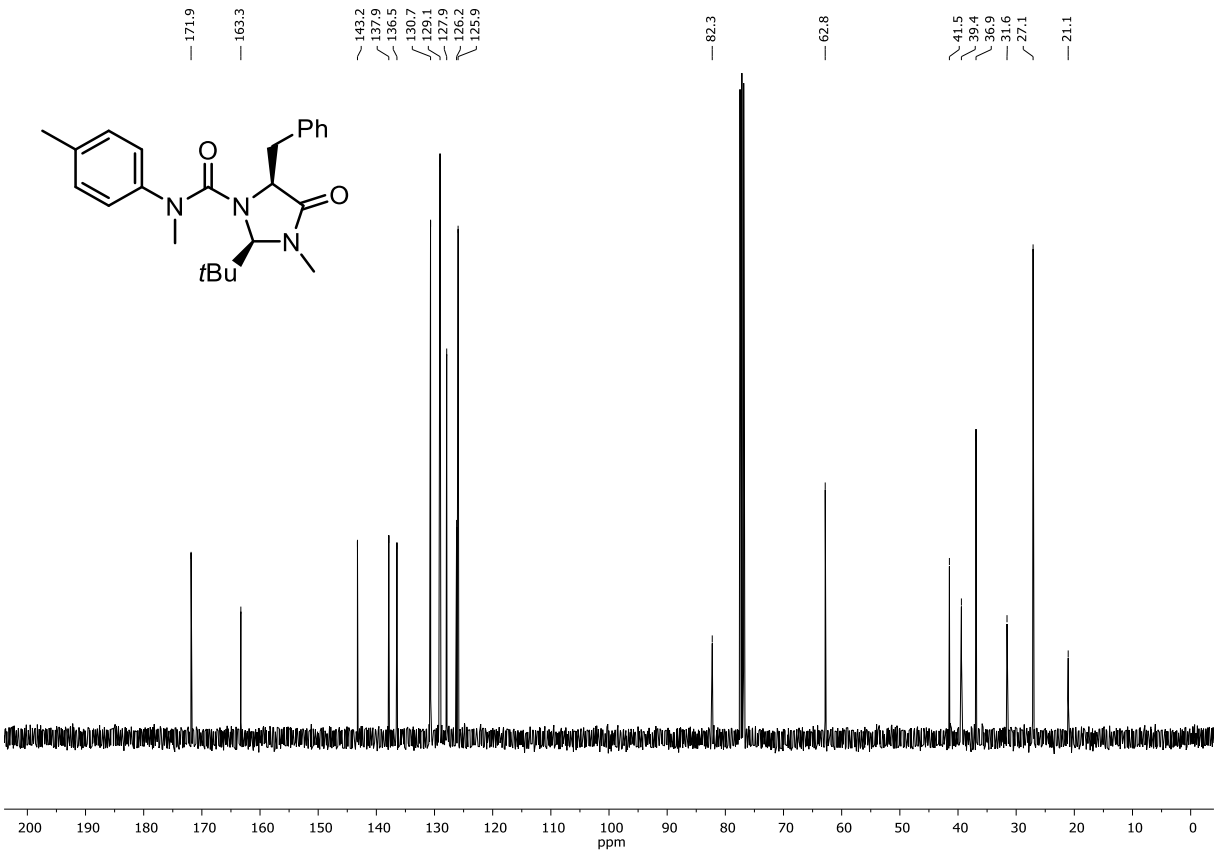
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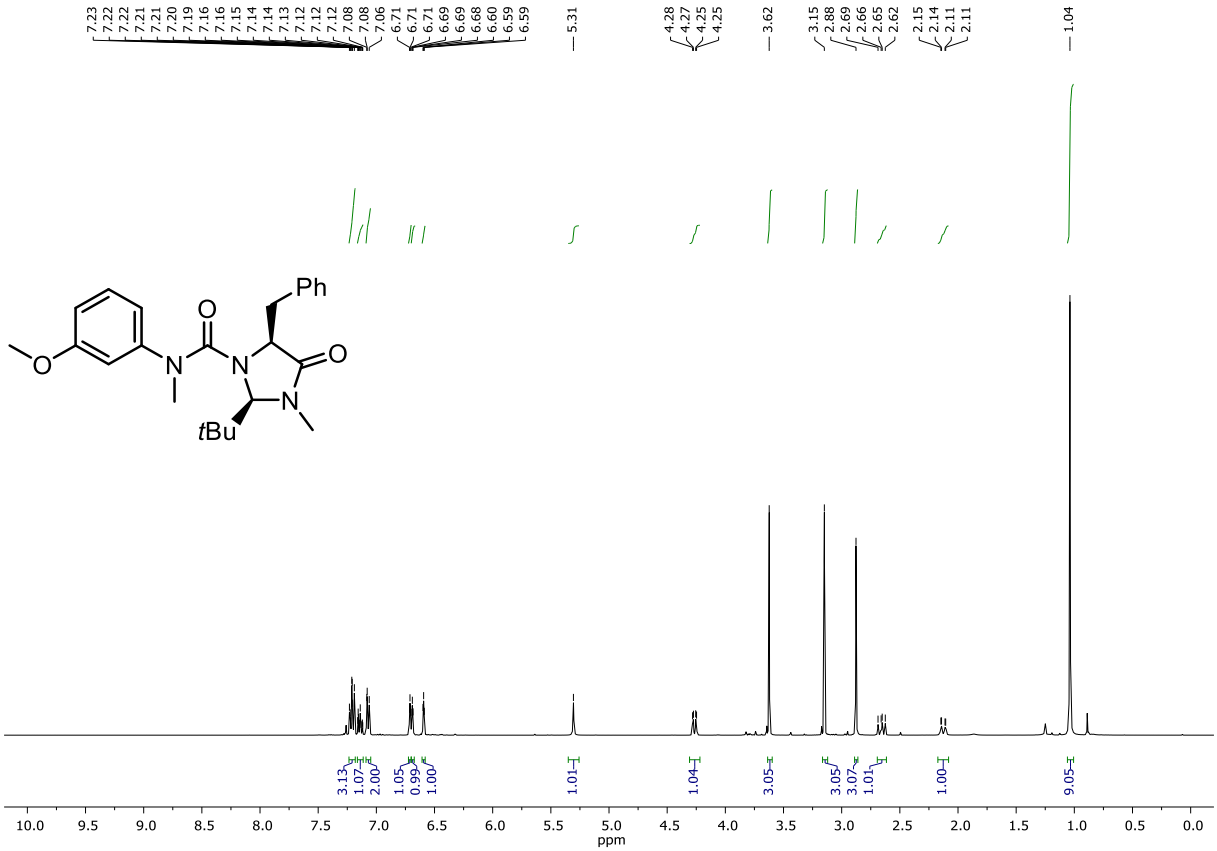
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7.08
7.08
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6.69
6.69
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2.11
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N
N
O
N
O
tBu
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1.01
1.04
3.05
3.05
3.07
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1.00
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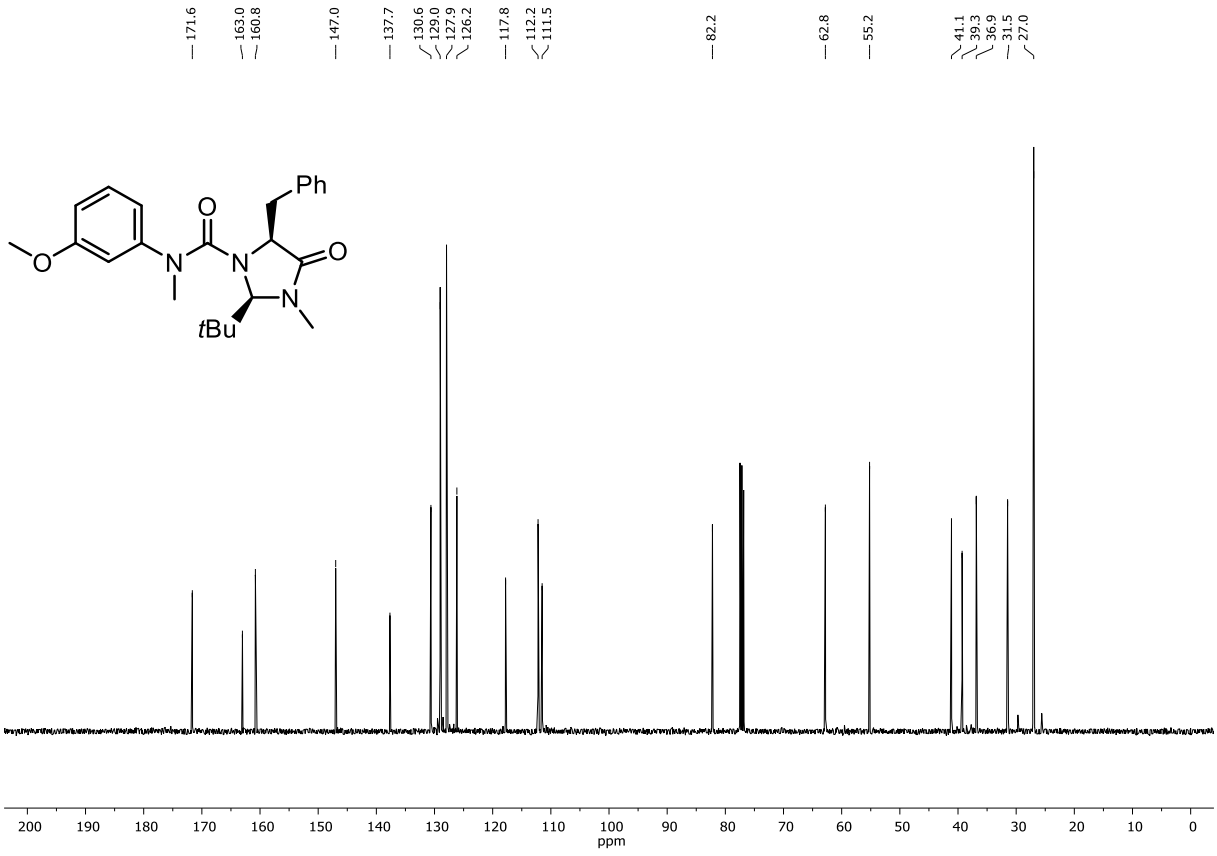
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55.2
41.1
39.3
36.9
31.5
27.0
Ph
O
N
N
O
N
O
tBu
200
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100
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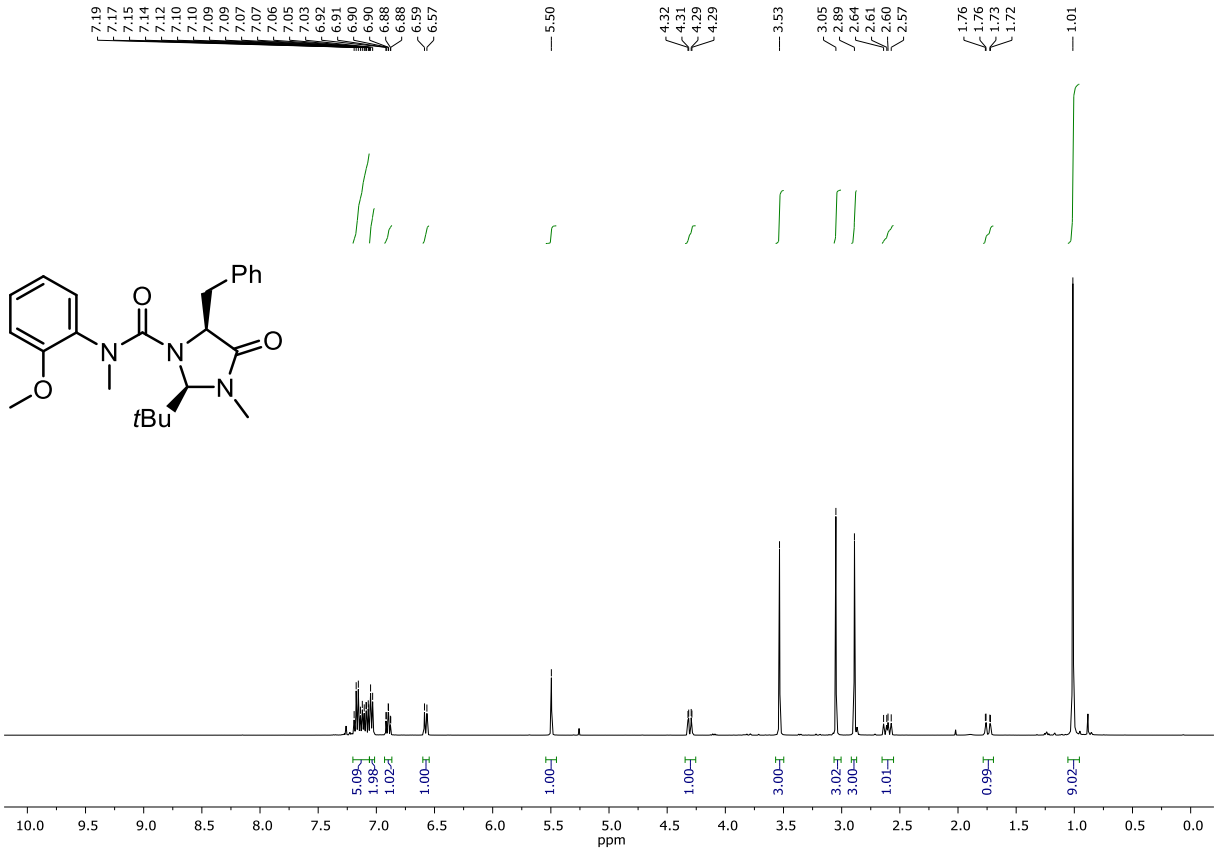
ppm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O
N
tBu
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1.98
1.02
1.00
1.00
1.00
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1.01
0.99
9.02
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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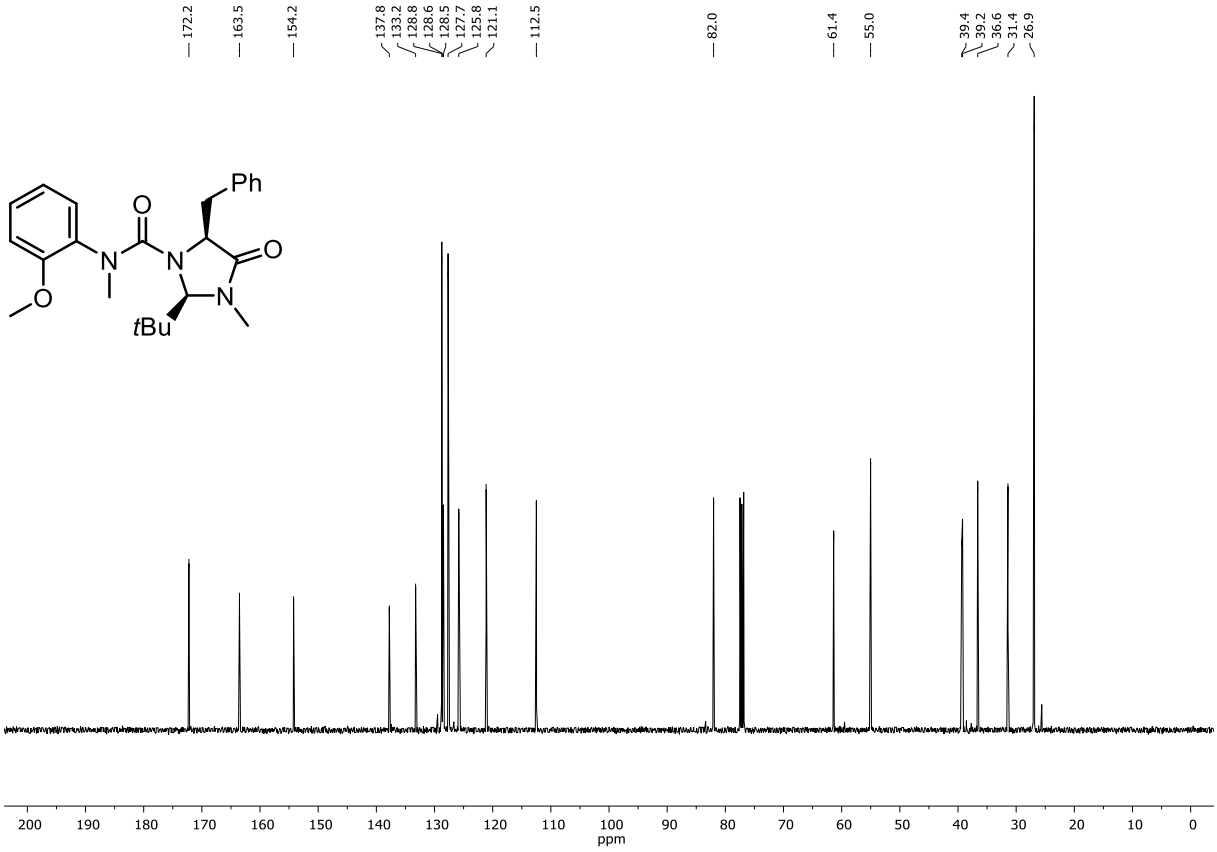
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112.5
82.0
61.4
55.0
39.4
39.2
36.6
31.4
26.9
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N
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O
N
tBu
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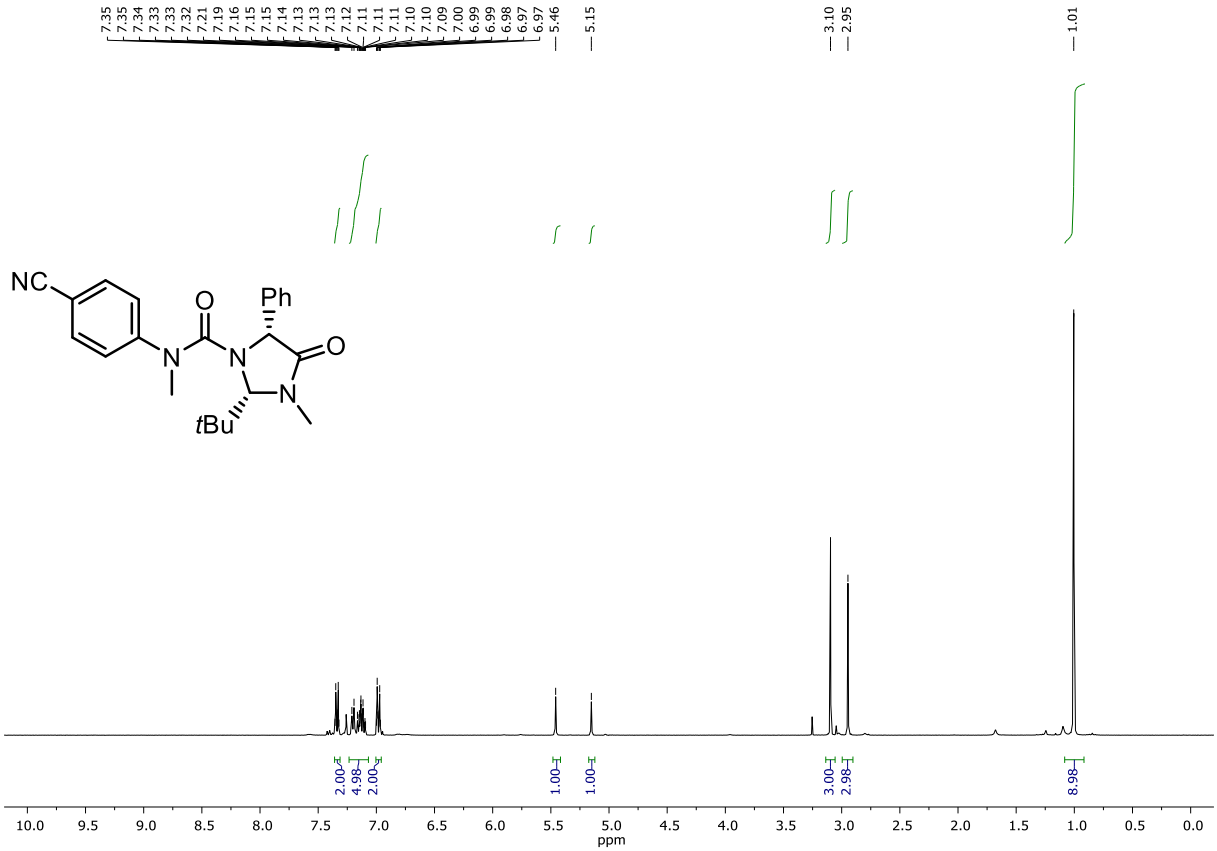
ppm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7.00
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6.98
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6.97
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5.15
3.10
2.95
1.01
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Ph
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N
O
N
tBu
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2.00
1.00
1.00
3.00
2.98
8.98
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9.5
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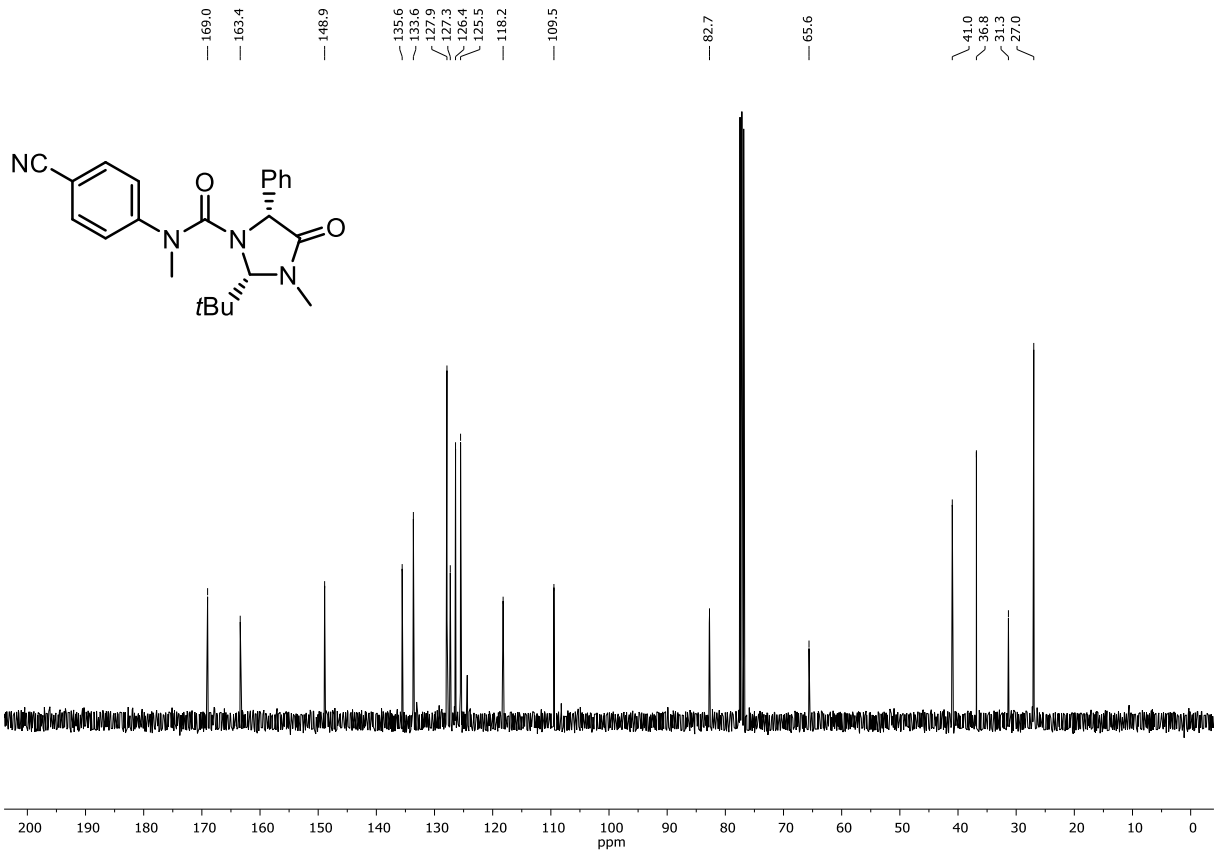
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31.3
27.0
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O
Ph
N
N
O
N
tBu
200
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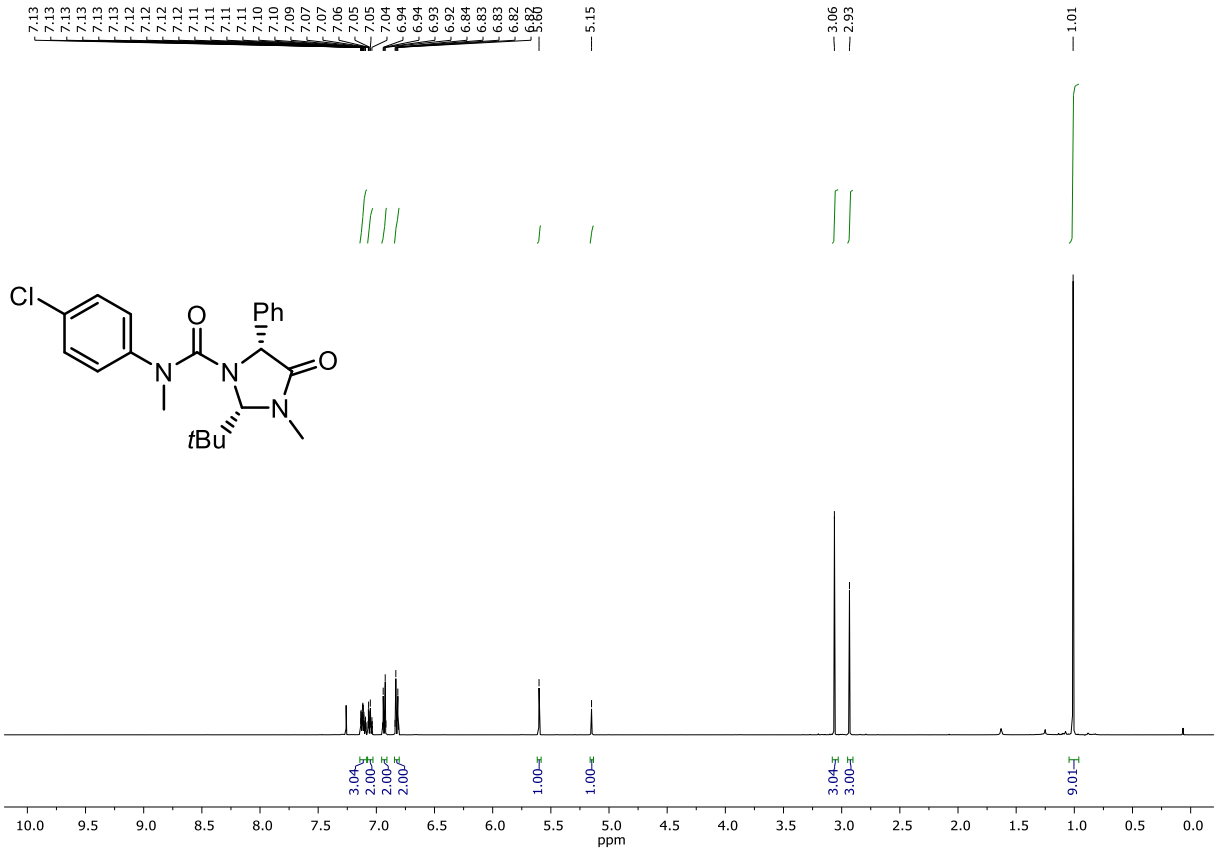
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O
N
tBu
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2.00
2.00
1.00
1.00
3.04
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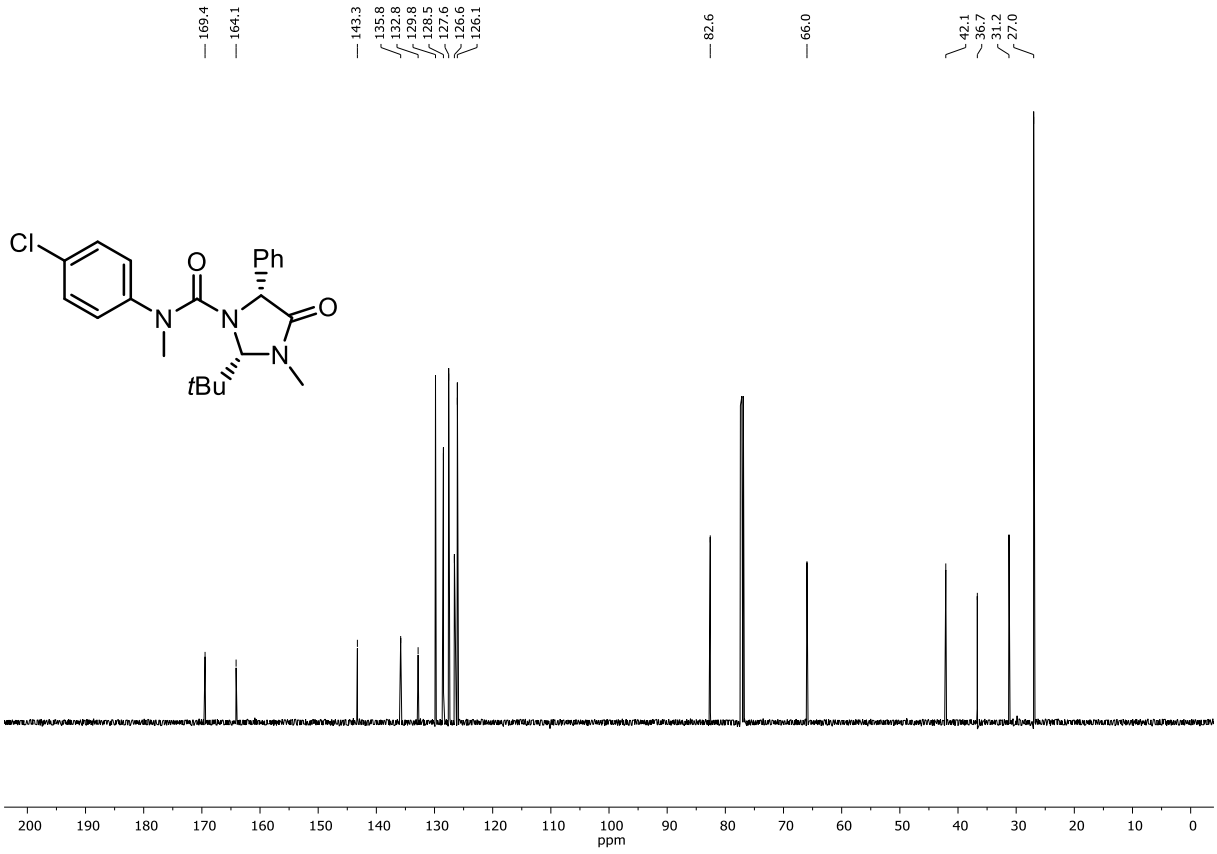
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31.2
27.0
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Ph
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N
O
N
tBu
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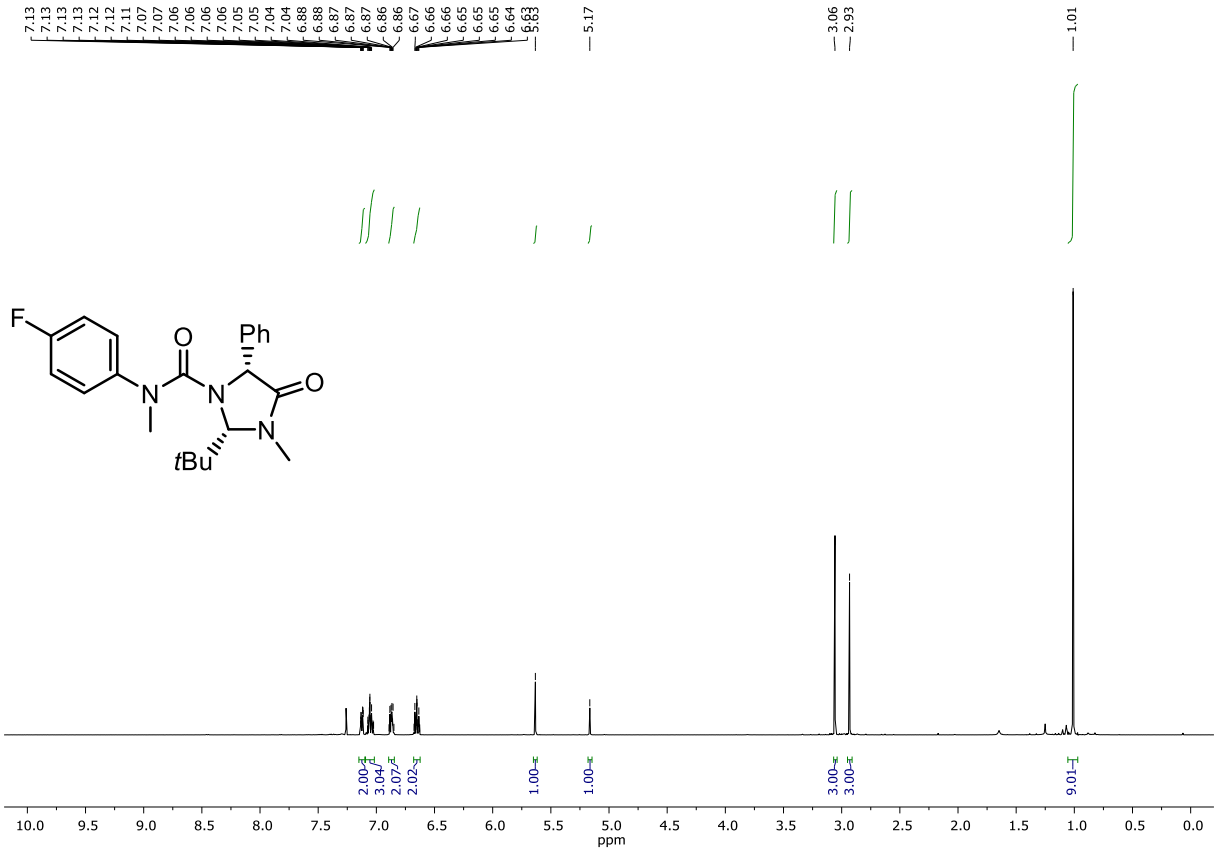
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2.07
2.02
1.00
1.00
3.00
3.00
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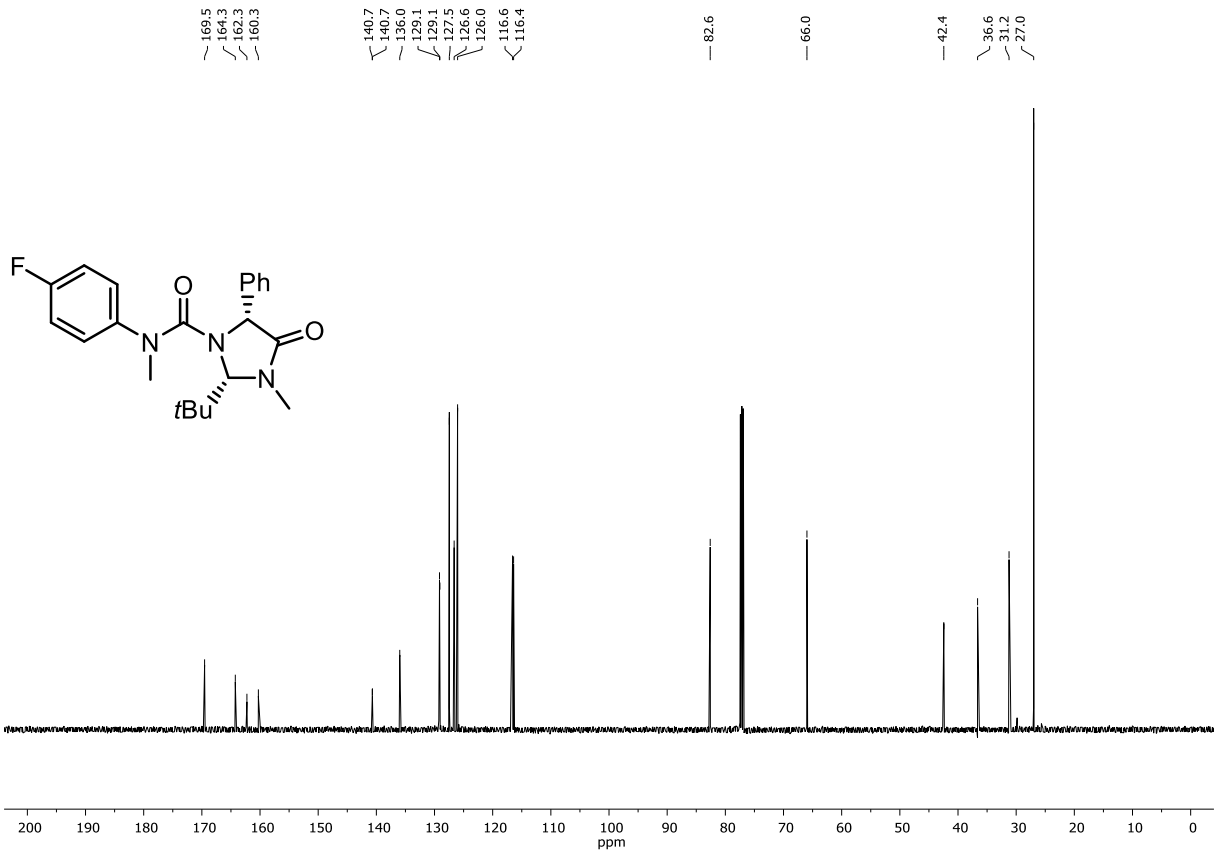
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126.0
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116.4
82.6
66.0
42.4
36.6
31.2
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Ph
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N
tBu
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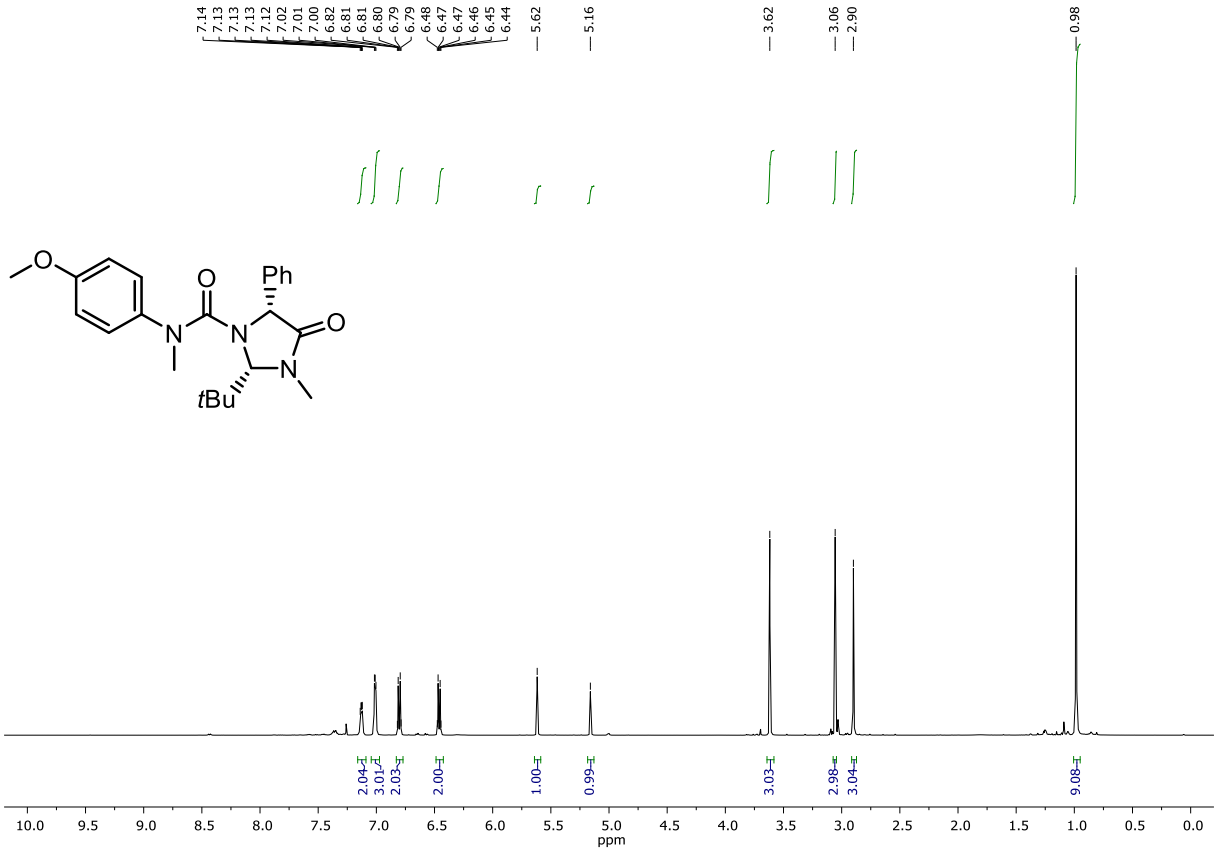
ppm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5.16
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3.06
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O
N
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3.01
2.03
2.00
1.00
0.99
3.03
2.98
3.04
9.08
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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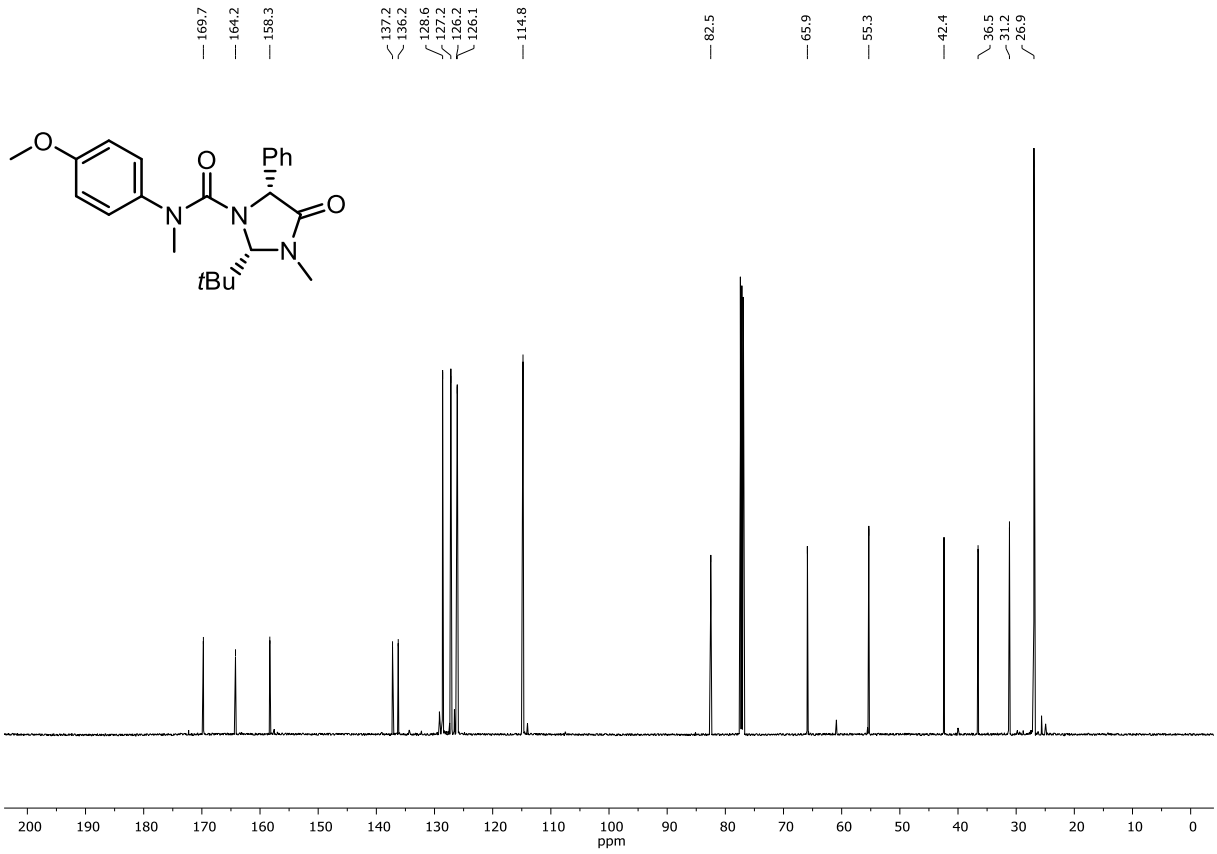
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36.5
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Ph
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N
O
N
tBu
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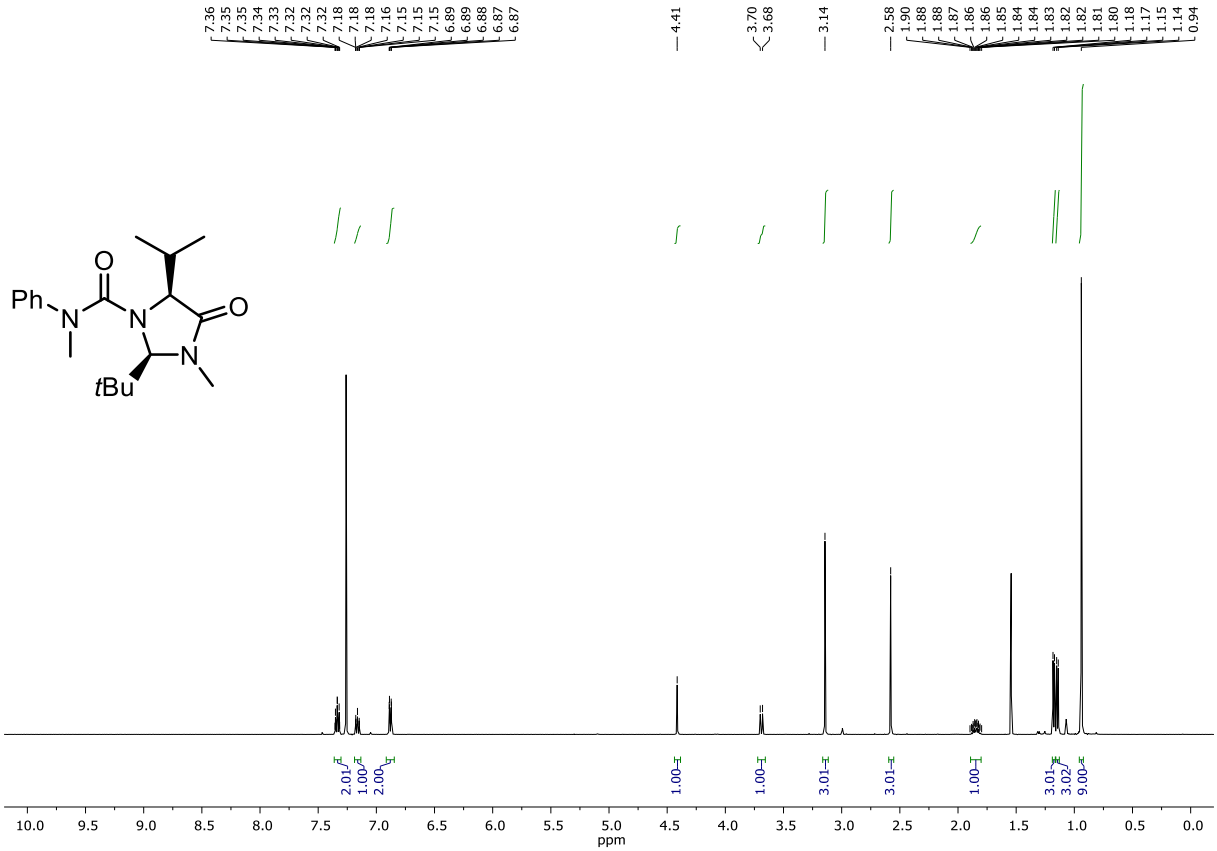
ppm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1.80
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1.17
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O
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tBu
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2.00
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3.01
3.01
1.00
3.01
3.02
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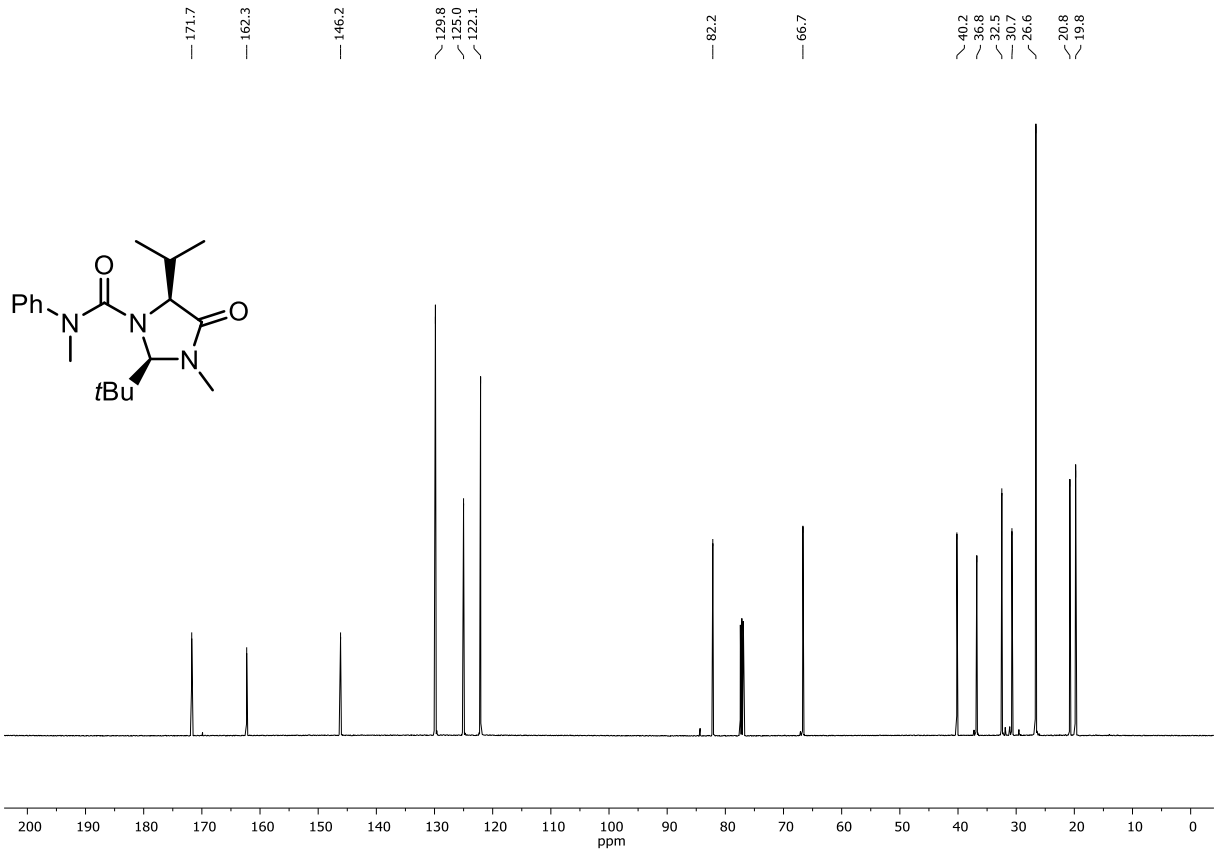
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30.7
26.6
20.8
19.8
Ph
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O
N
O
N
tBu
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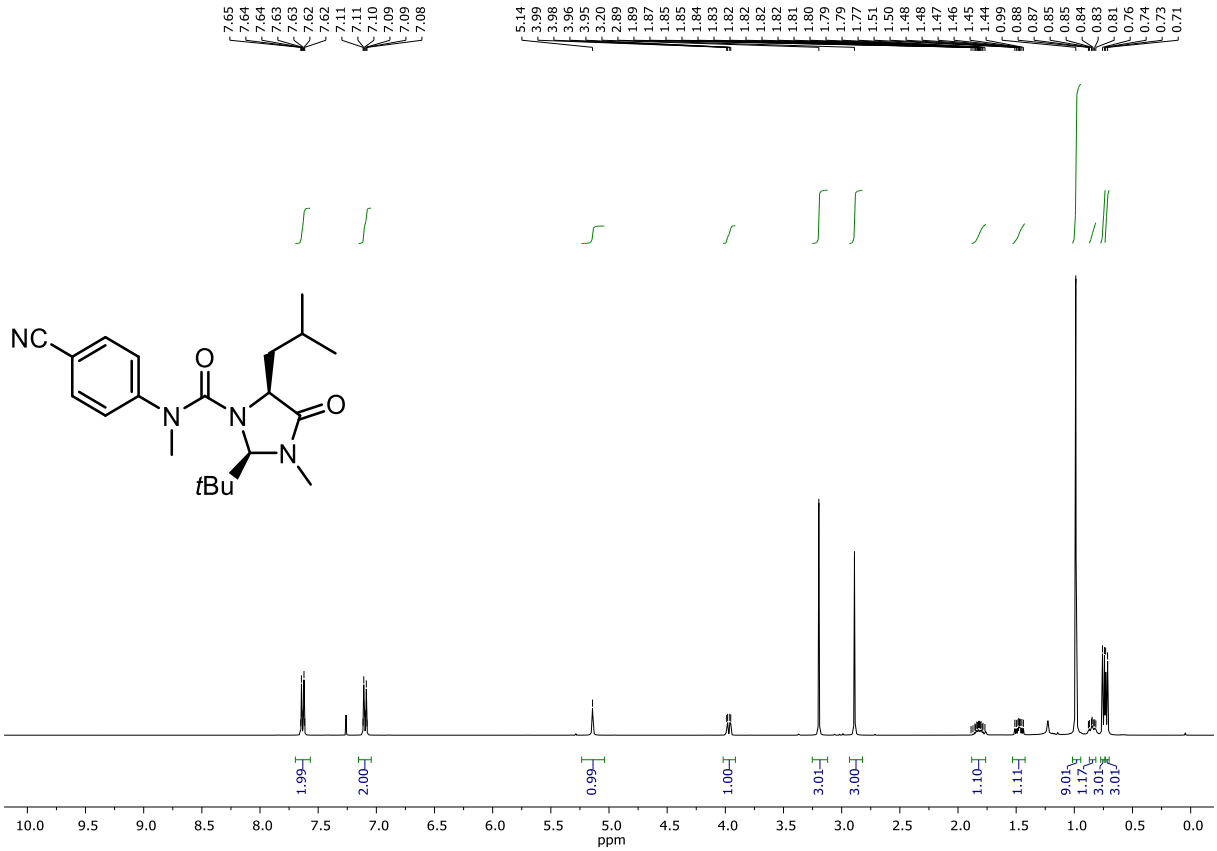
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1.82
1.82
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tBu
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1.00
3.01
3.00
1.10
1.11
9.01
1.17
3.01
3.01
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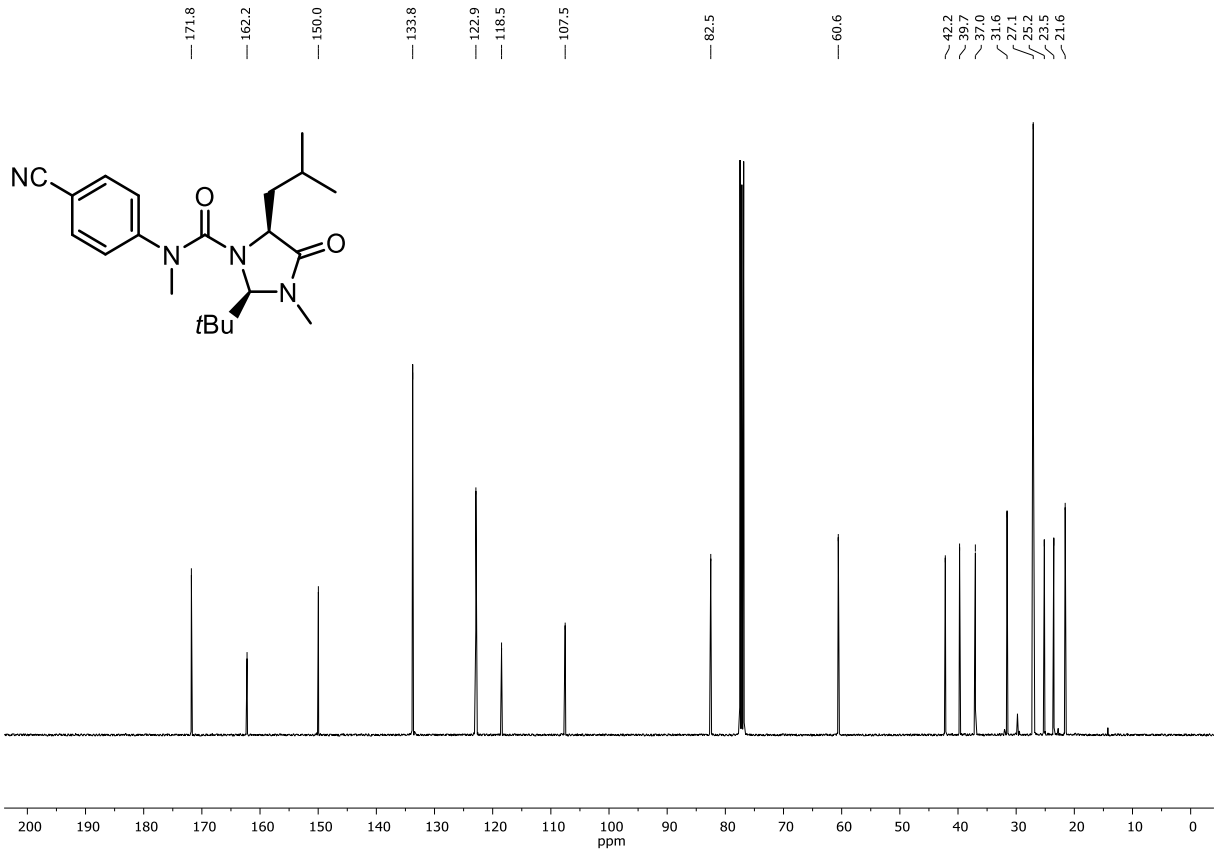
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27.1
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NC
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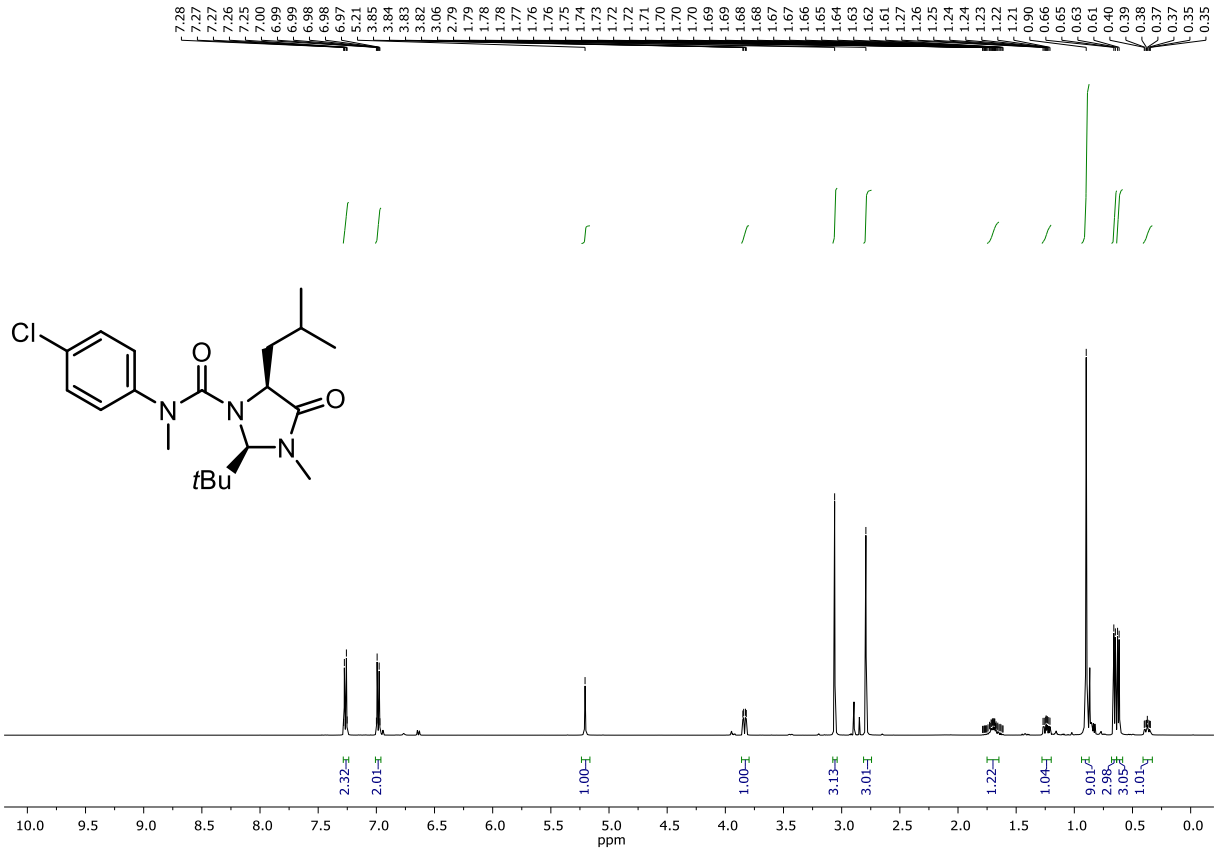
N
tBu
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm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Cl
O
N
N
O
N
tBu
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10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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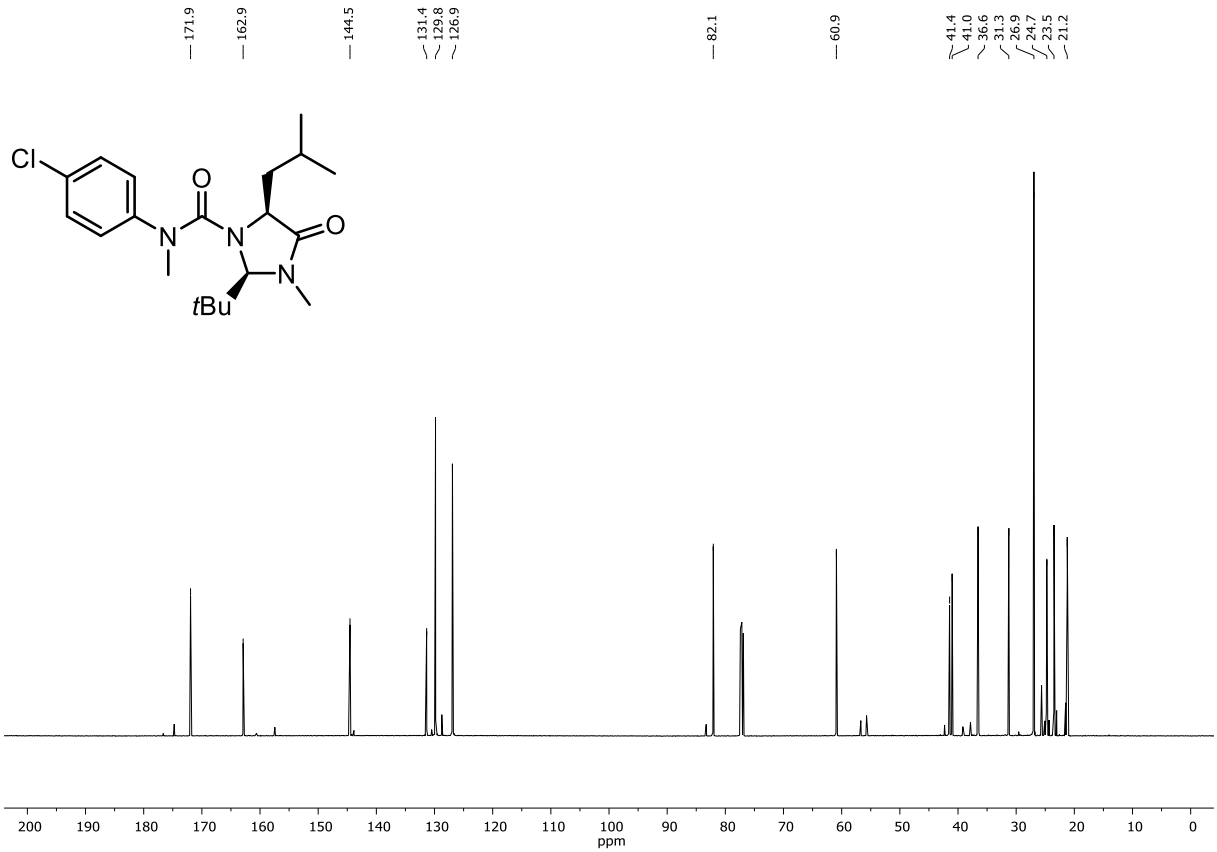
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Cl
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O
N
tBu
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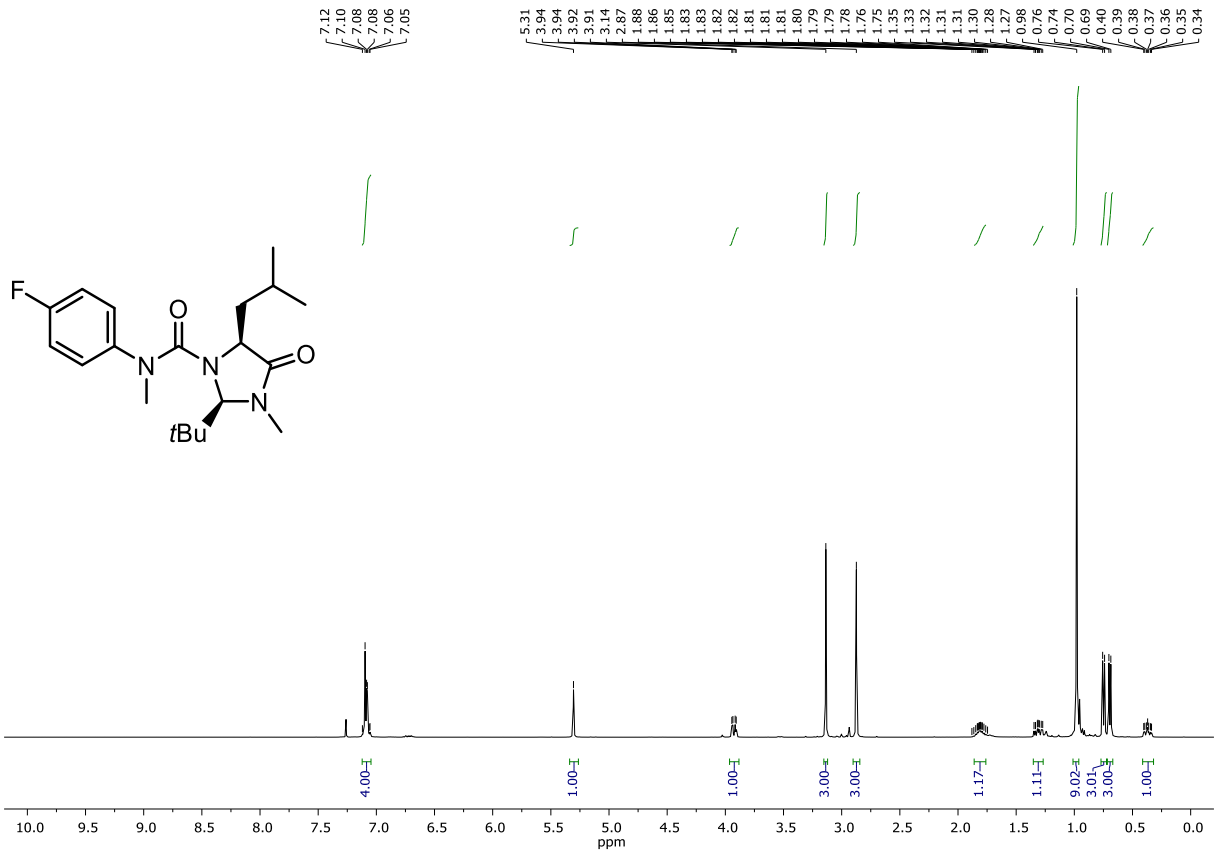
ppm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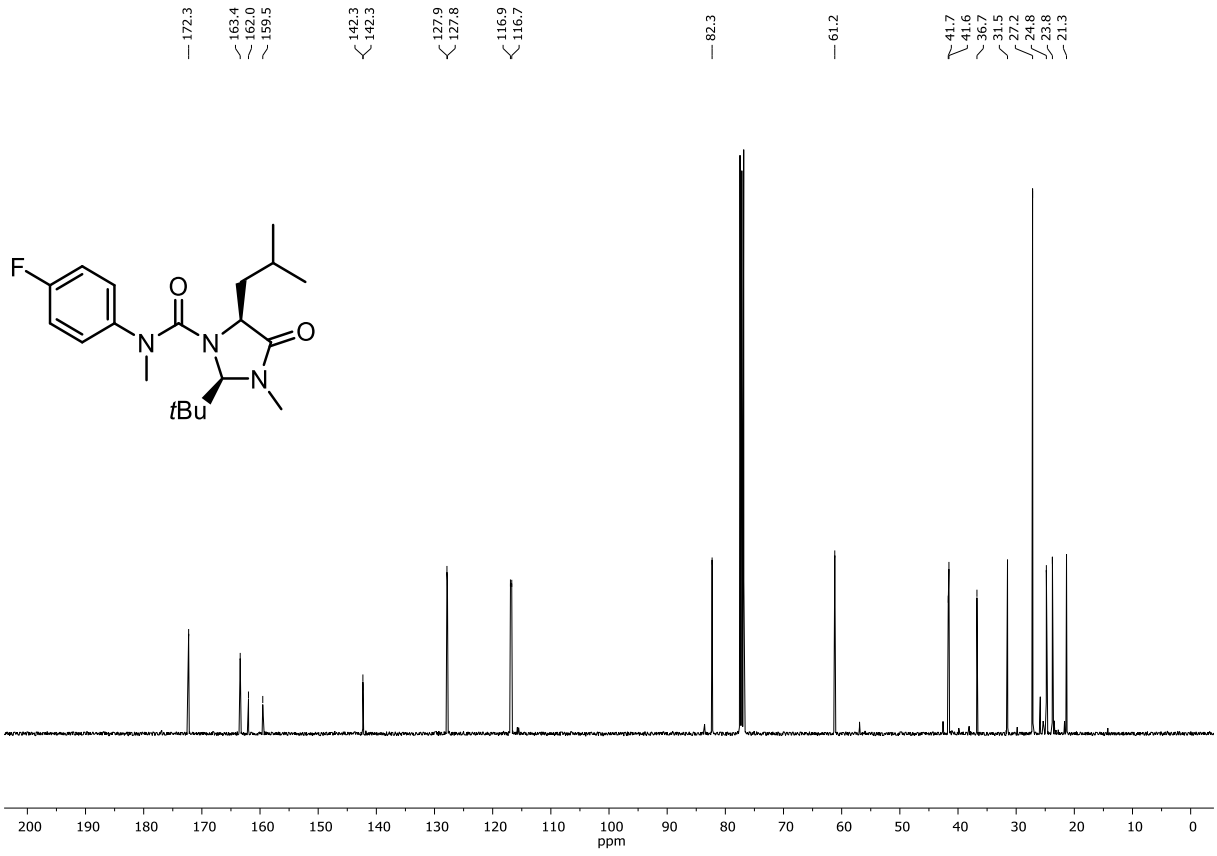
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27.2
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23.8
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N
N
O
N
tBu
200
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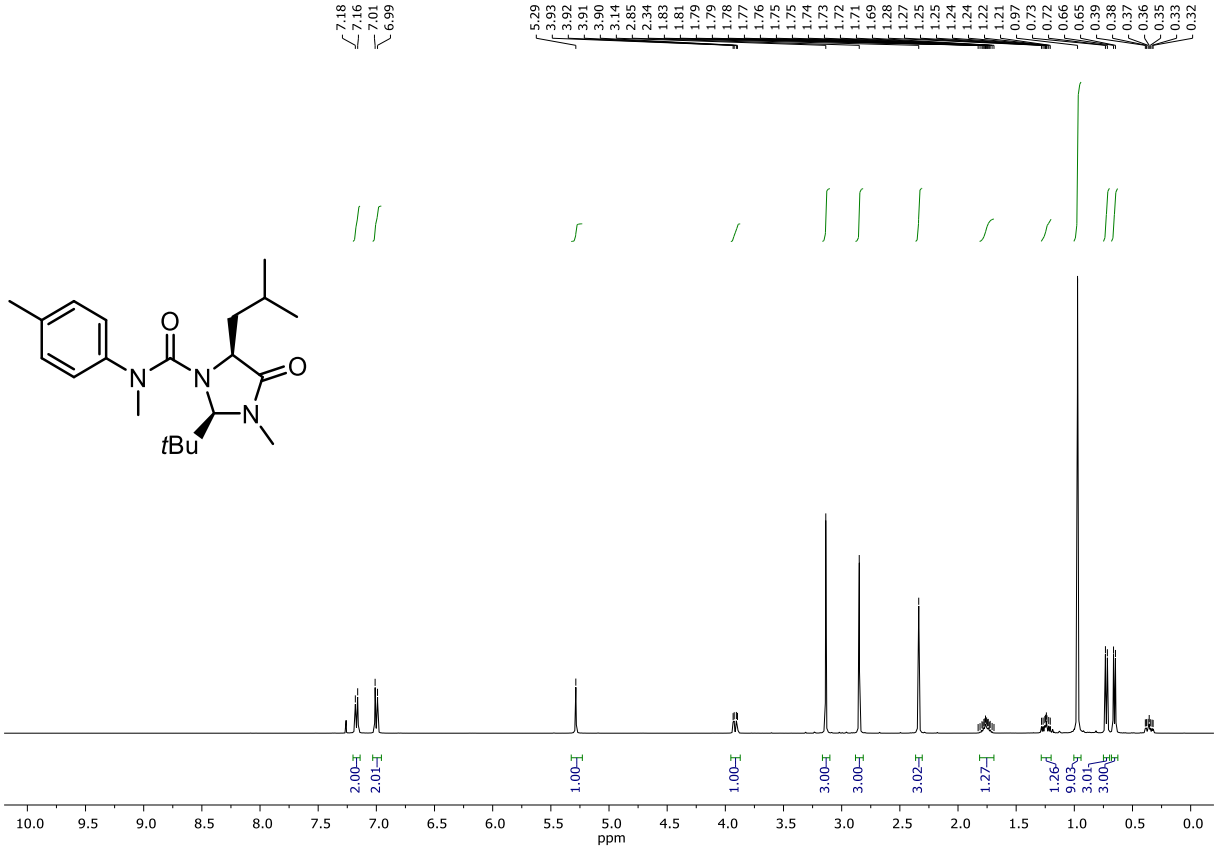
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1.24
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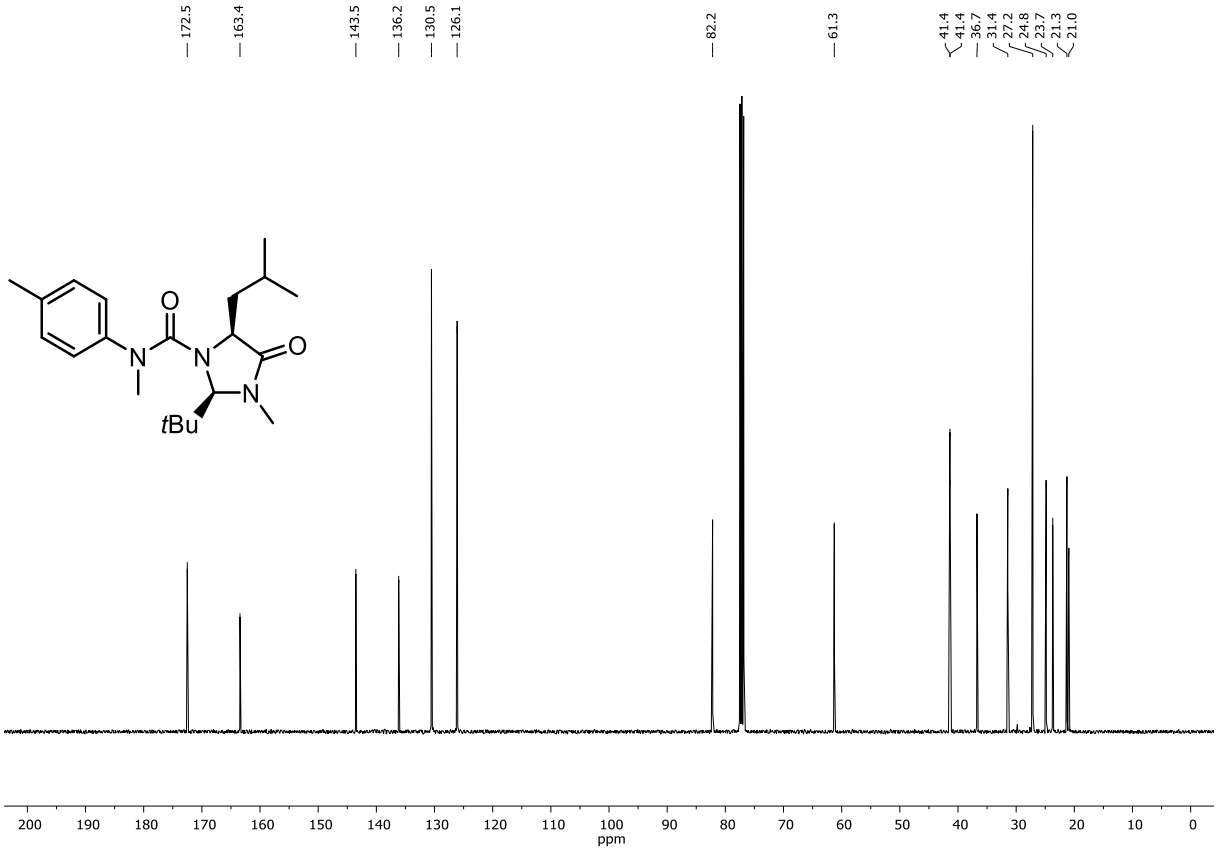
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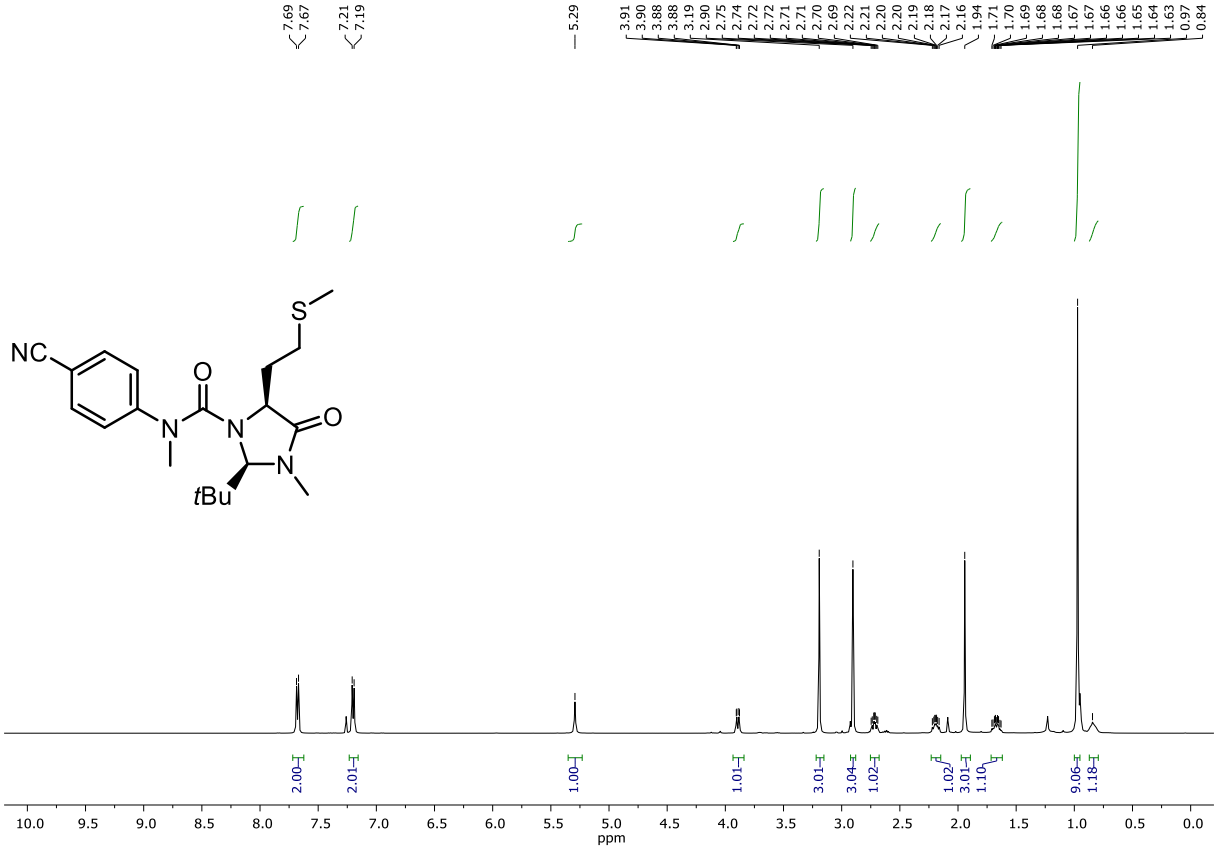
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1.66
1.65
1.64
1.63
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0.84
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N
N
O
S
N
tBu
2.00
2.01
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1.01
3.01
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1.02
3.01
1.10
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1.18
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9.0
8.5
8.0
7.5
7.0
6.5
6.0
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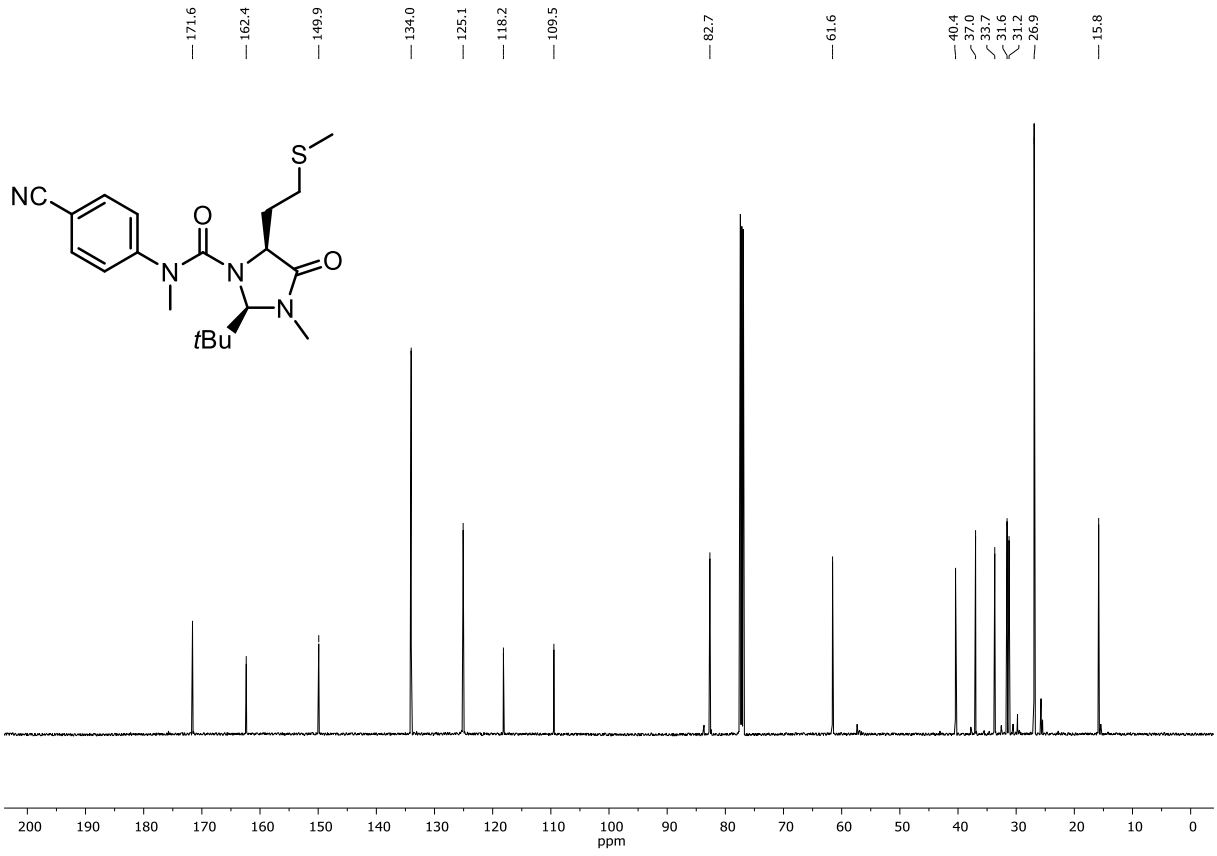
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31.6
31.2
26.9
15.8
NC
O
N
N
O
S
N
tBu
200
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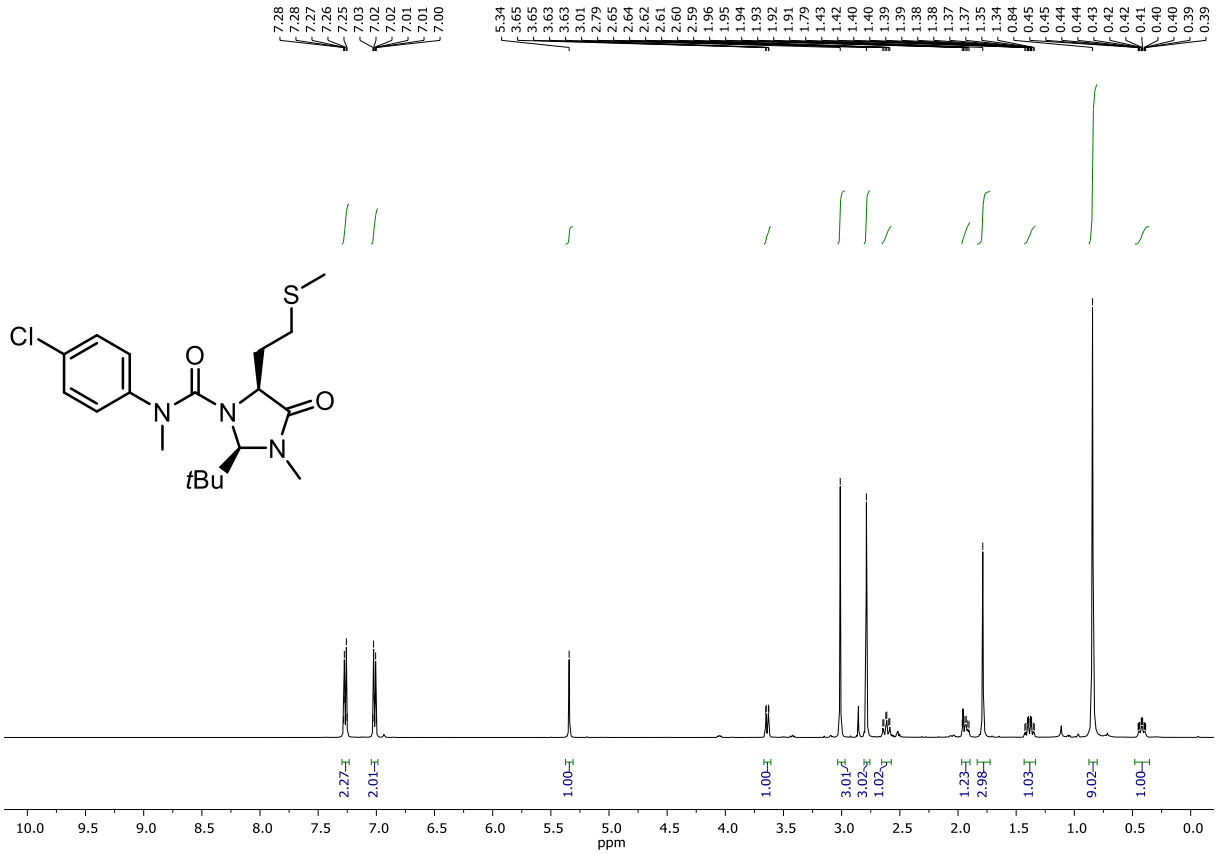
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5.34 3.65 3.65 3.63 3.63 3.01 2.79 2.65 2.64 2.62 2.61 2.60 2.59 1.96 1.95 1.94 1.93 1.92 1.91 1.79 1.43 1.42 1.40 1.40 1.39 1.39 1.38 1.38 1.37 1.37 1.35 1.34 0.84 0.45 0.45 0.44 0.44 0.43 0.42 0.42 0.42 0.41 0.40 0.40 0.39 0.39
Cl
O
N
N
O
S
N
tBu
2.27 2.01 1.00 1.00 3.01 3.02 1.02 1.23 2.98 1.03 9.02 1.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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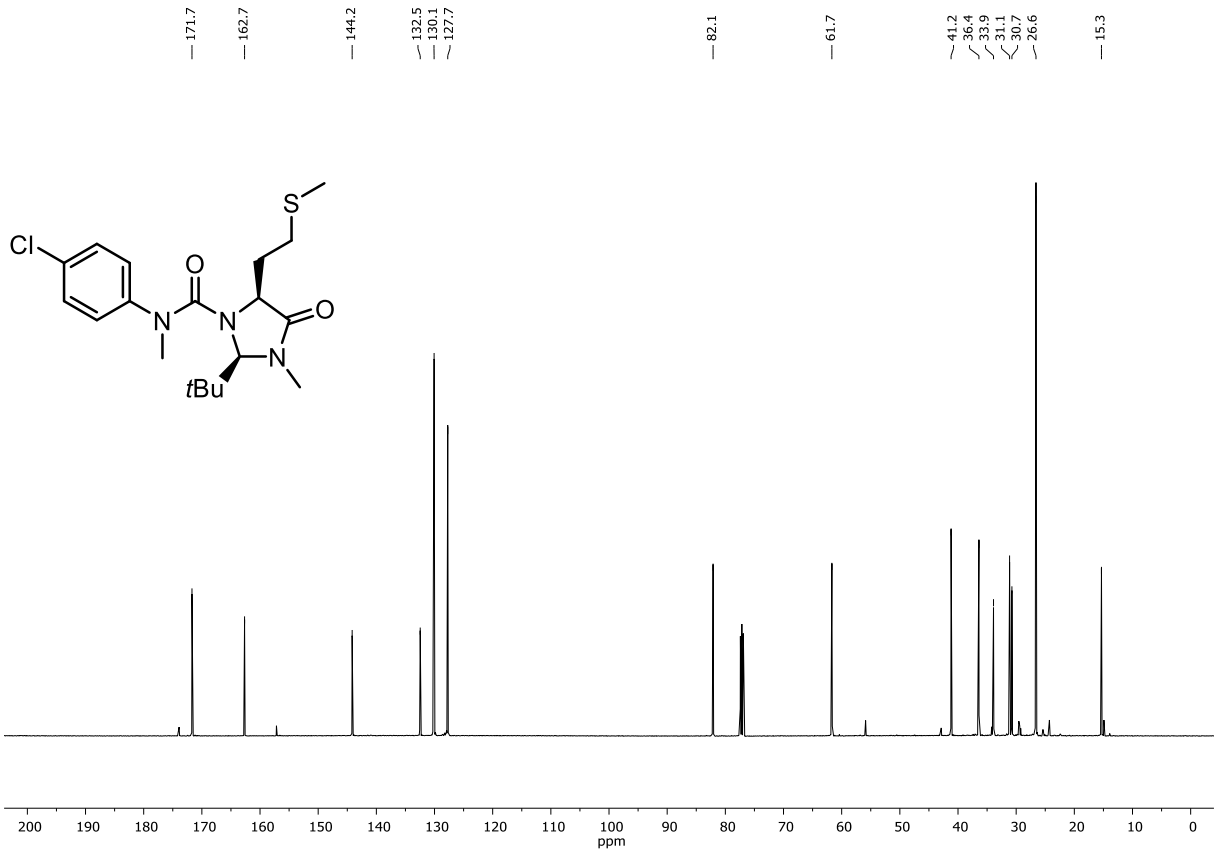
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O
S
N
tBu
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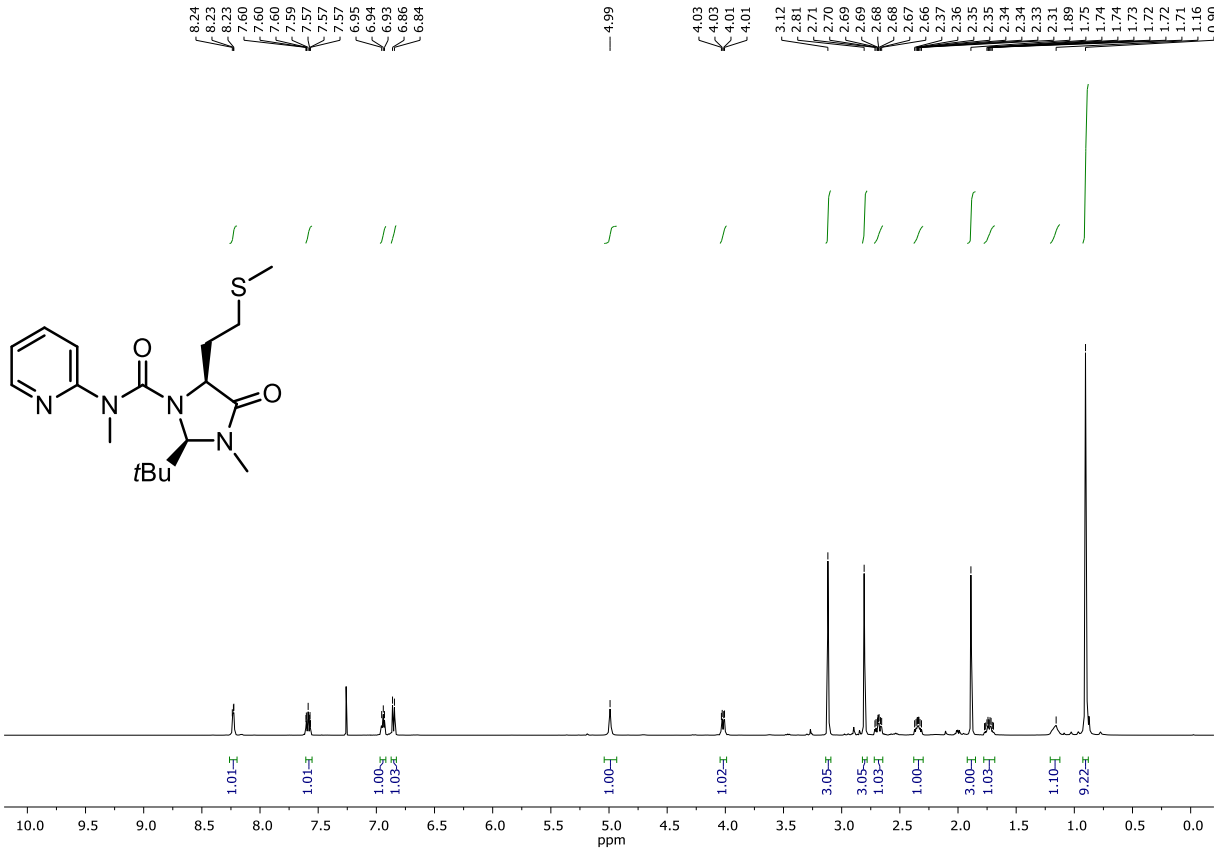
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6.86
6.84
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4.03
4.01
4.01
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2.71
2.70
2.69
2.69
2.68
2.68
2.67
2.66
2.37
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2.31
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1.75
1.74
1.74
1.73
1.72
1.72
1.71
1.16
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N
N
O
N
N
tBu
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1.01
1.00
1.03
1.00
1.02
3.05
3.05
1.03
1.00
3.00
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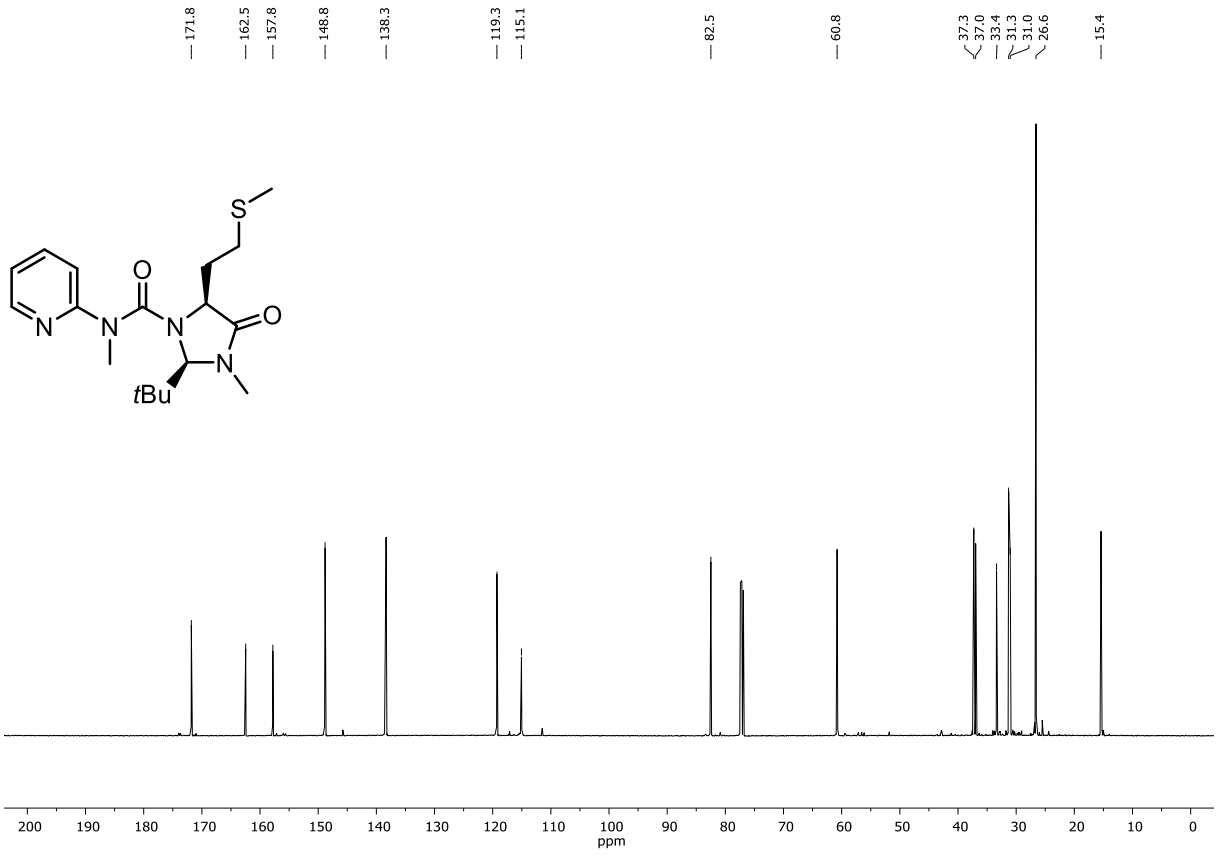
9.22
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm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115.1
82.5
60.8
37.3
37.0
33.4
31.3
31.0
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N
tBu
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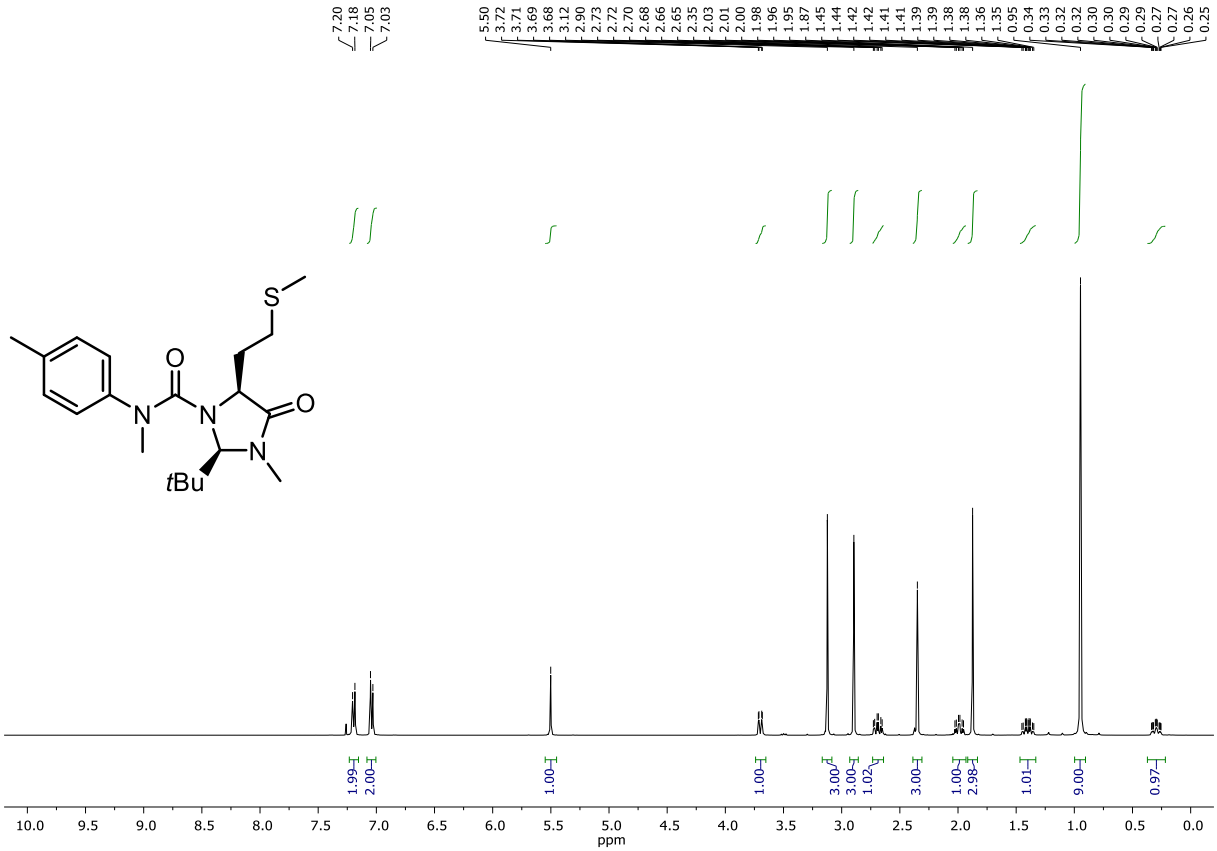
ppm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1.41
1.39
1.39
1.38
1.38
1.36
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0.34
0.33
0.32
0.32
0.30
0.30
0.29
0.29
0.27
0.27
0.26
0.25
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N
O
N
tBu
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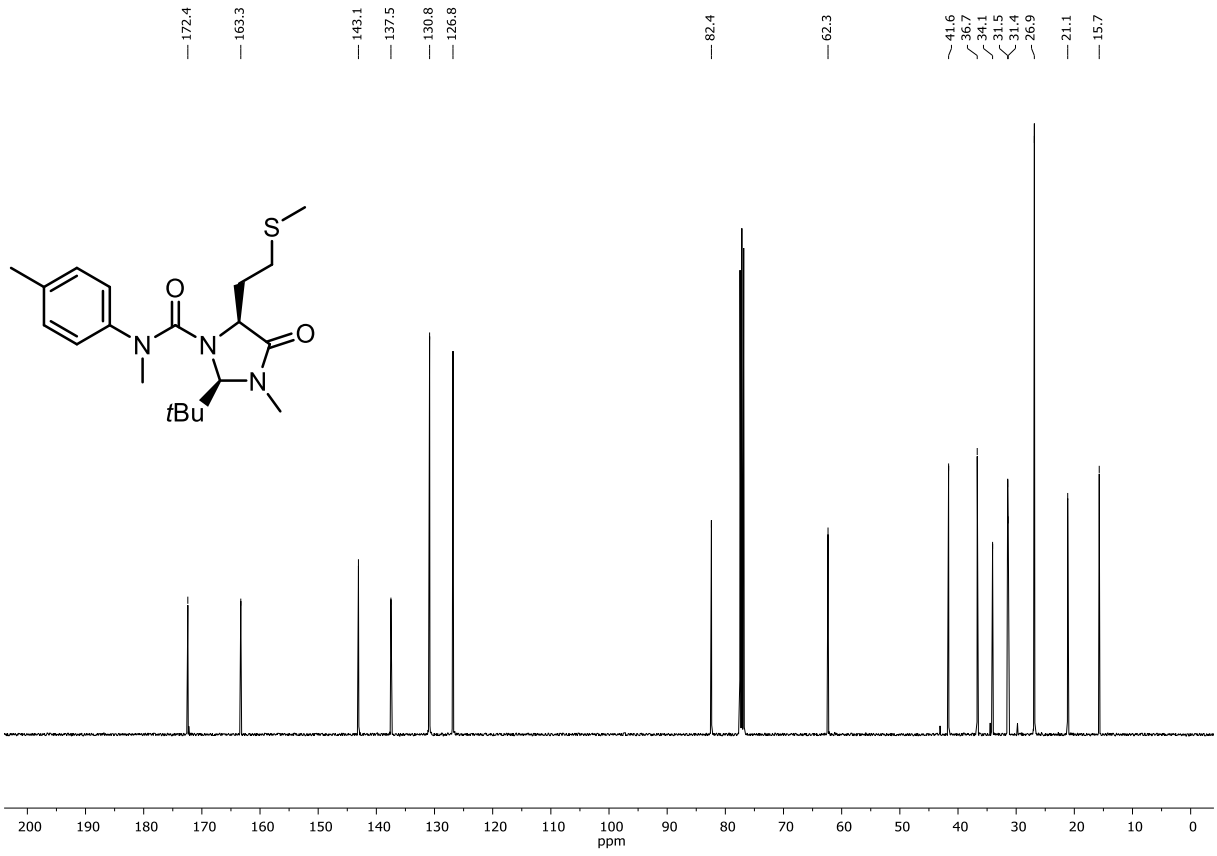
1.00
1.00
3.00
3.00
1.02
3.00
1.00
2.98
1.01
9.00
0.97
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm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31.5
31.4
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S
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O
N
tBu
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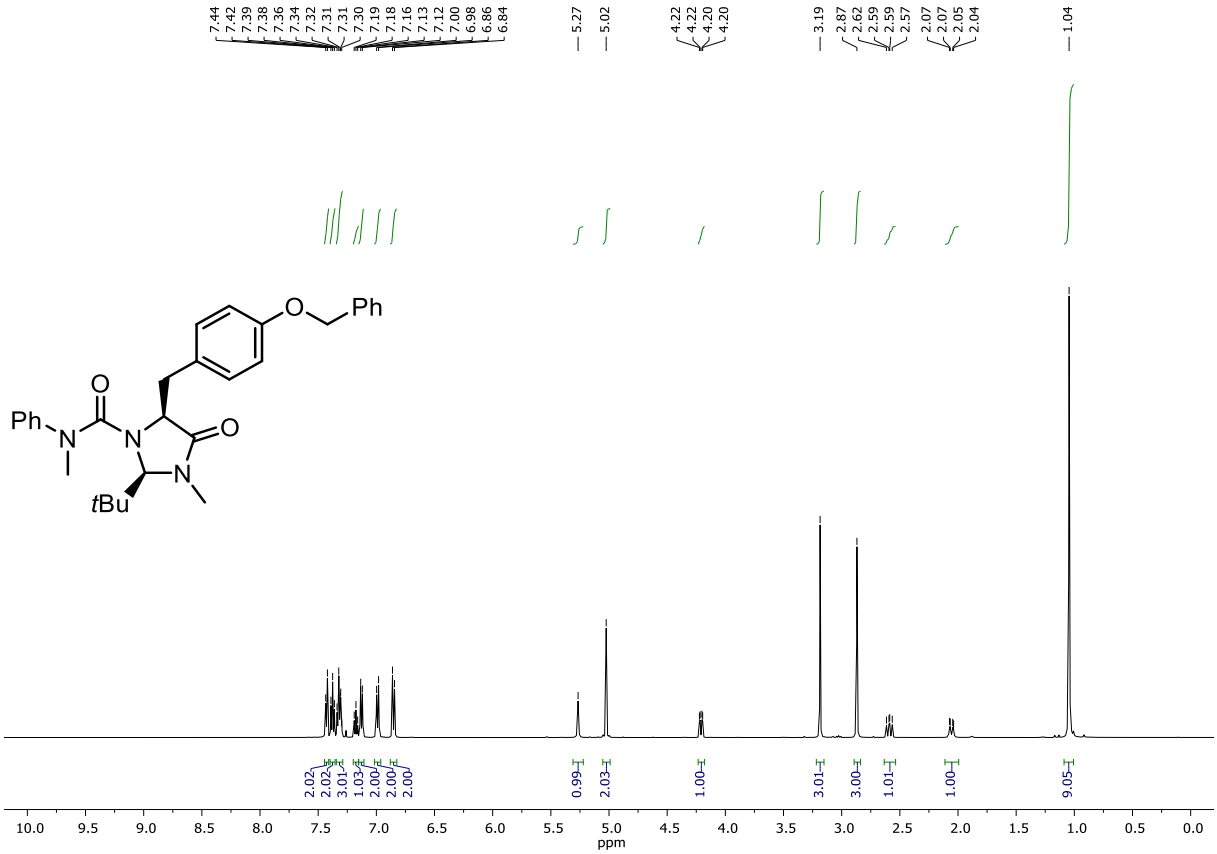
ppm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7.13
7.12
7.00
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6.86
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5.27
5.02
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2.57
2.07
2.07
2.05
2.04
1.04
O
Ph
Ph
N
O
N
O
N
tBu
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2.02
3.01
1.03
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2.00
2.00
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2.03
1.00
3.01
3.00
1.01
1.00
9.05
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9.0
8.5
8.0
7.5
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6.5
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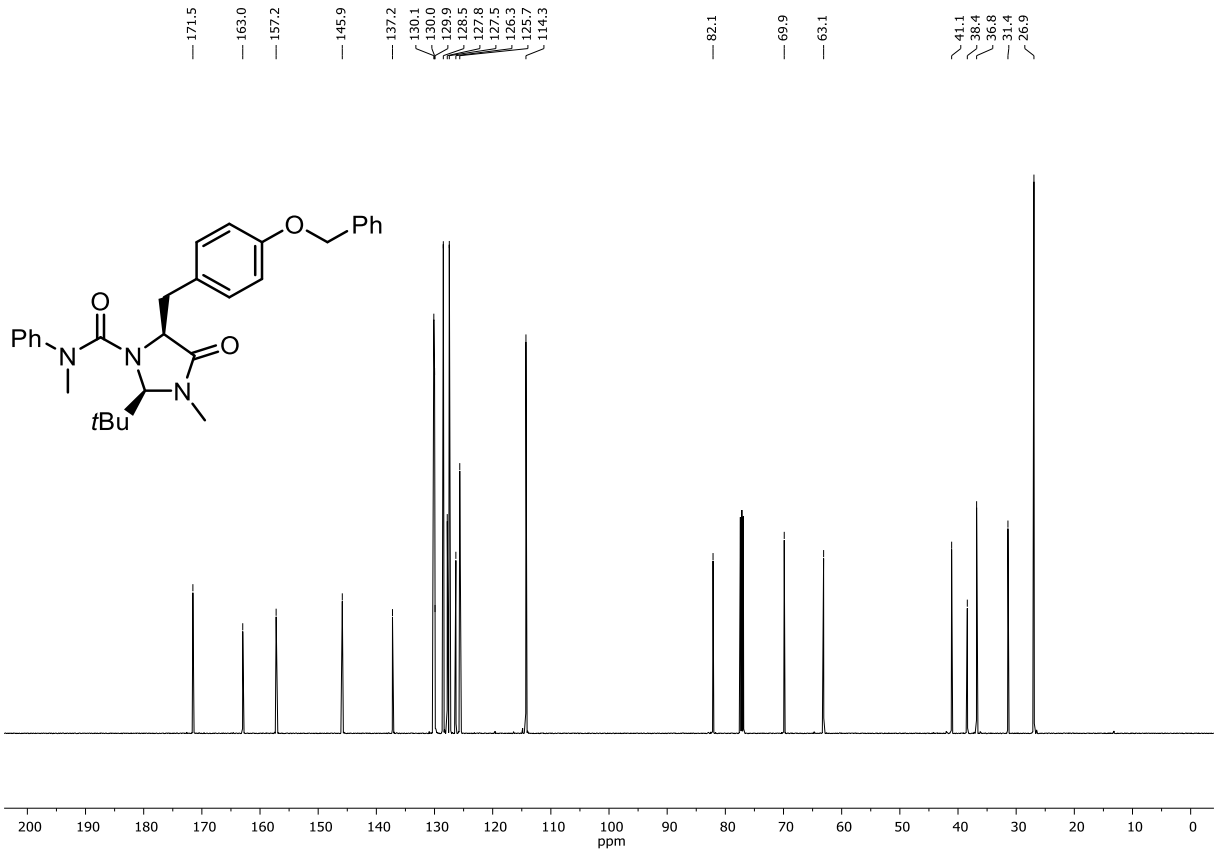
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126.3
125.7
114.3
82.1
69.9
63.1
41.1
38.4
36.8
31.4
26.9
O
Ph
Ph
N
O
N
O
N
tBu
200
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0
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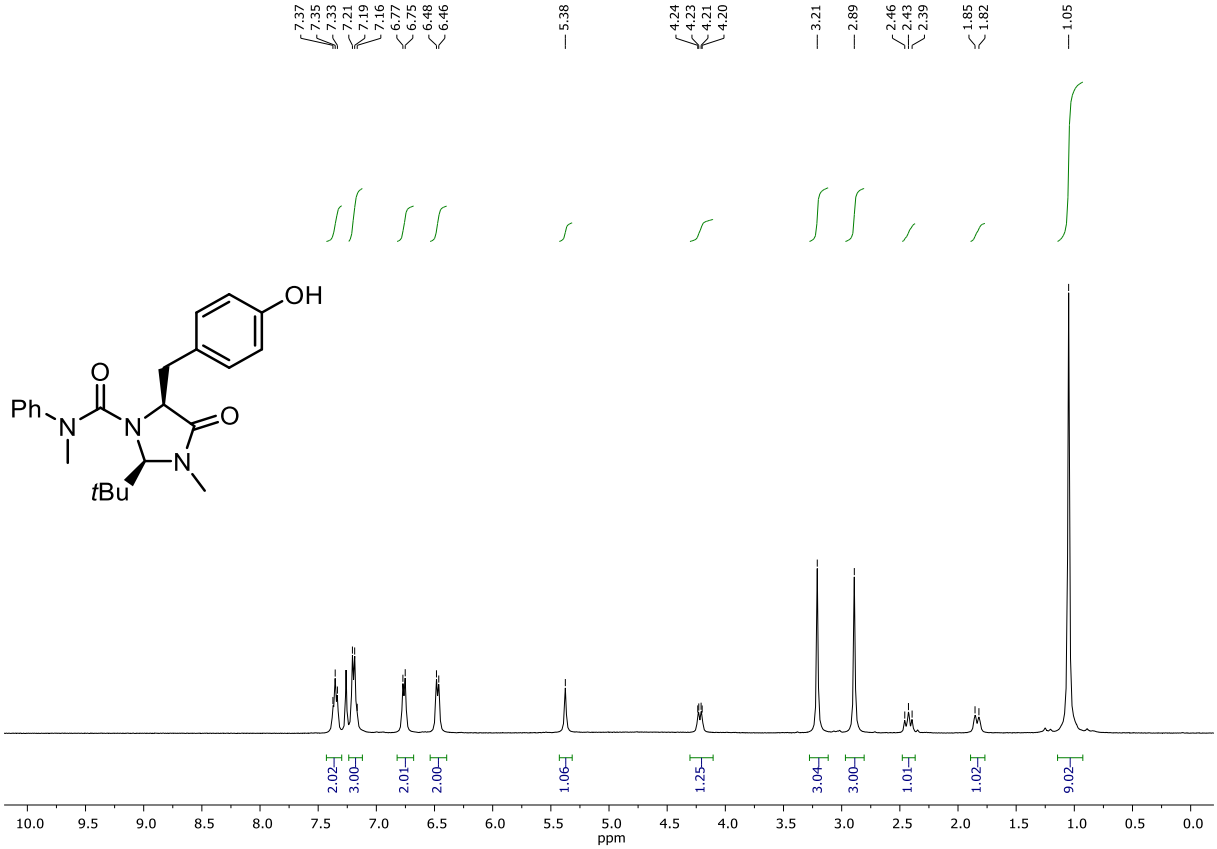
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4.21
4.20
3.21
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2.46
2.43
2.39
1.85
1.82
1.05
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O
Ph
N
N
O
N
tBu
2.02
3.00
2.01
2.00
1.06
1.25
3.04
3.00
1.01
1.02
9.02
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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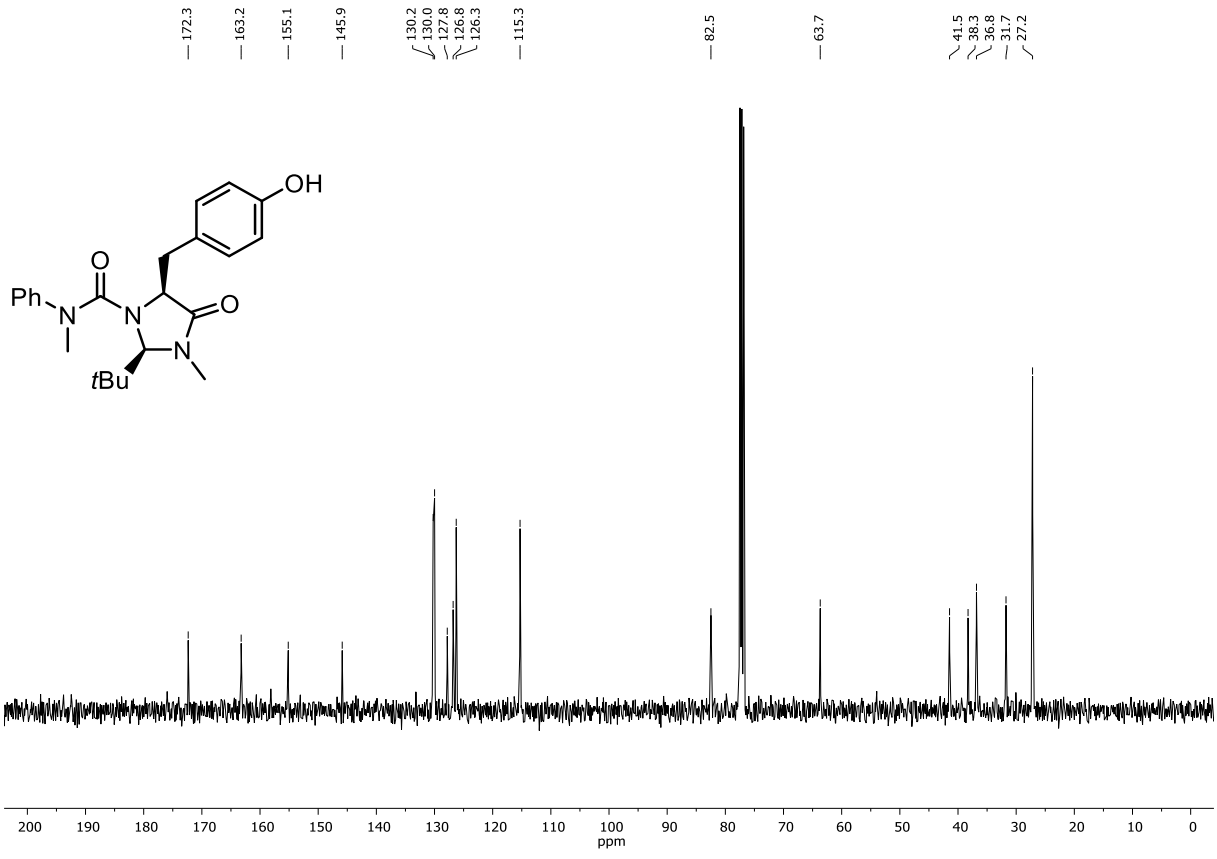
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82.5
63.7
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36.8
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Ph
N
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O
N
tBu
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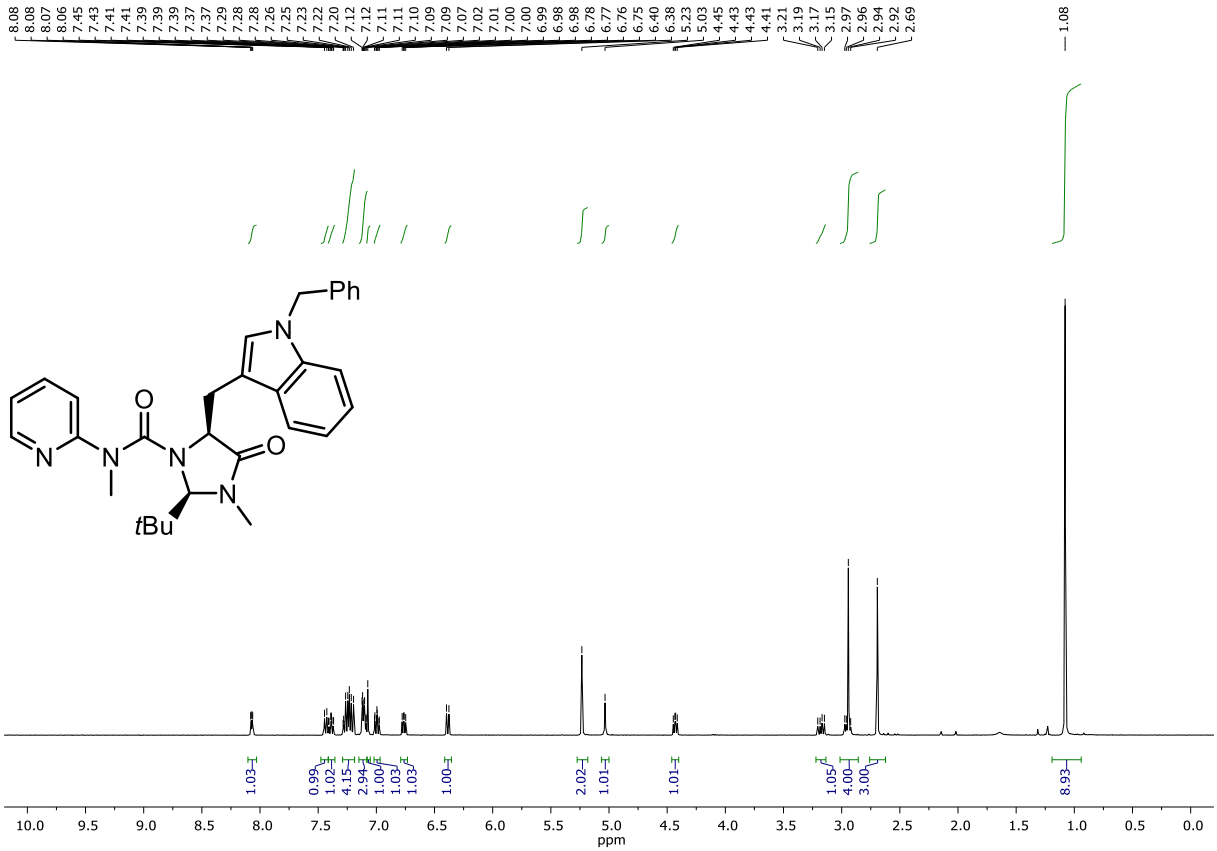
ppm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1.08
Ph
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N
N
O
N
N
tBu
1.03 0.99 1.02 4.15 2.94 1.00 1.03 1.03 1.00 2.02 1.01 1.01 1.05 4.00 3.00 8.93
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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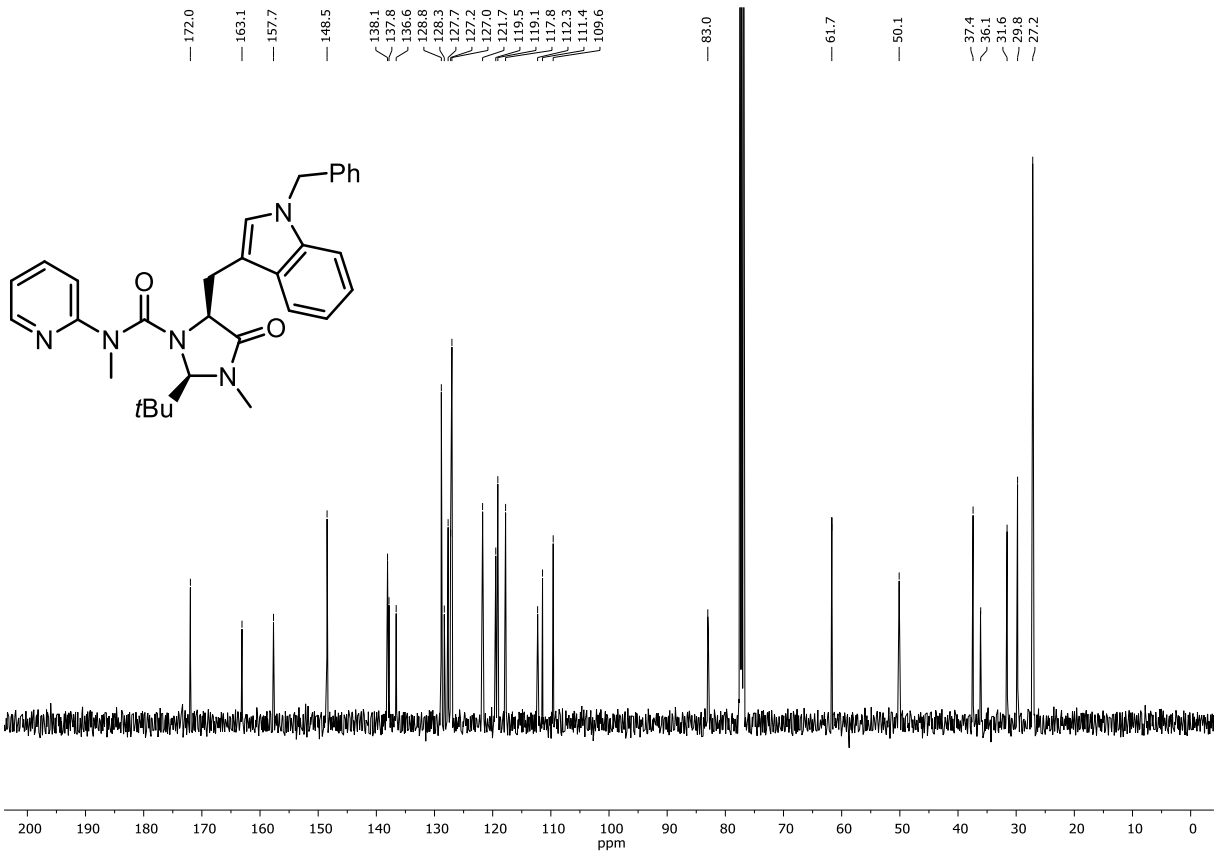
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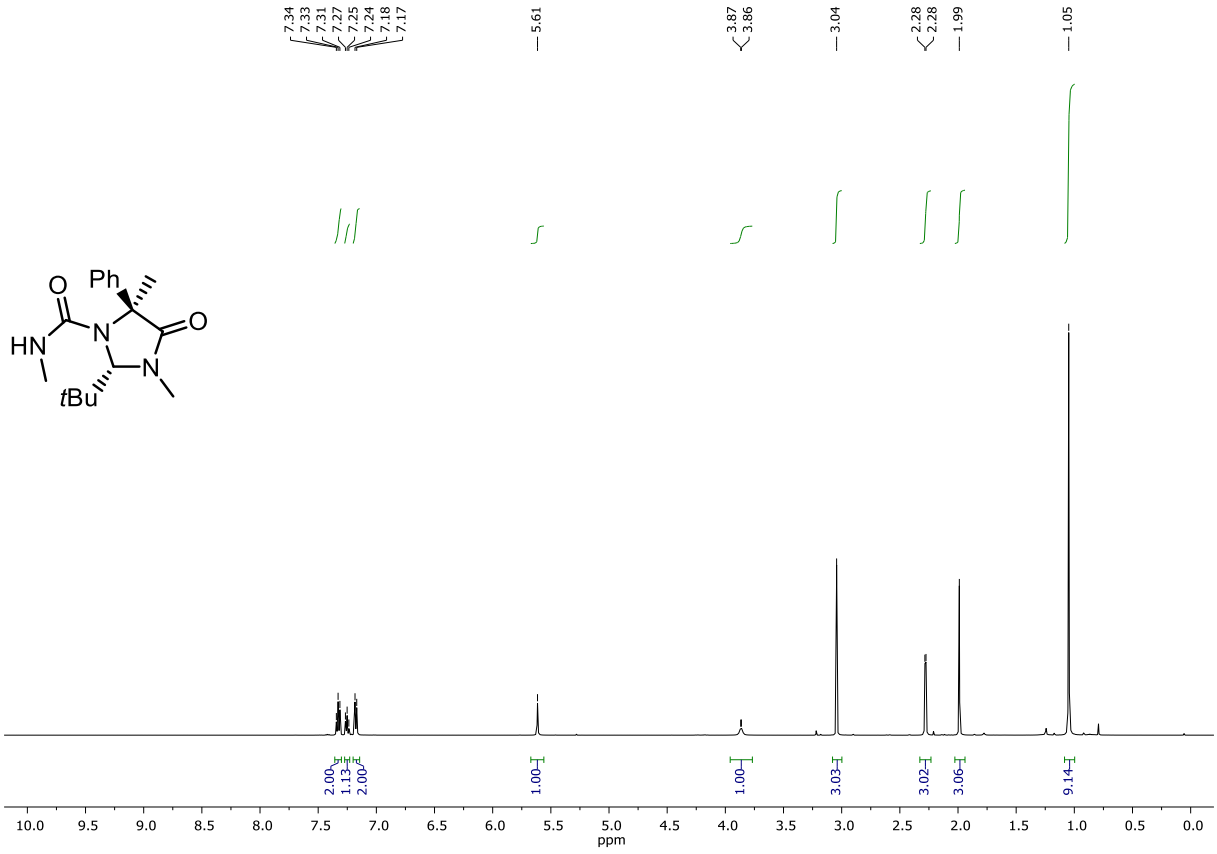
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2.28
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1.05
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O
N
tBu
2.00
1.13
2.00
1.00
1.00
3.03
3.02
3.06
9.14
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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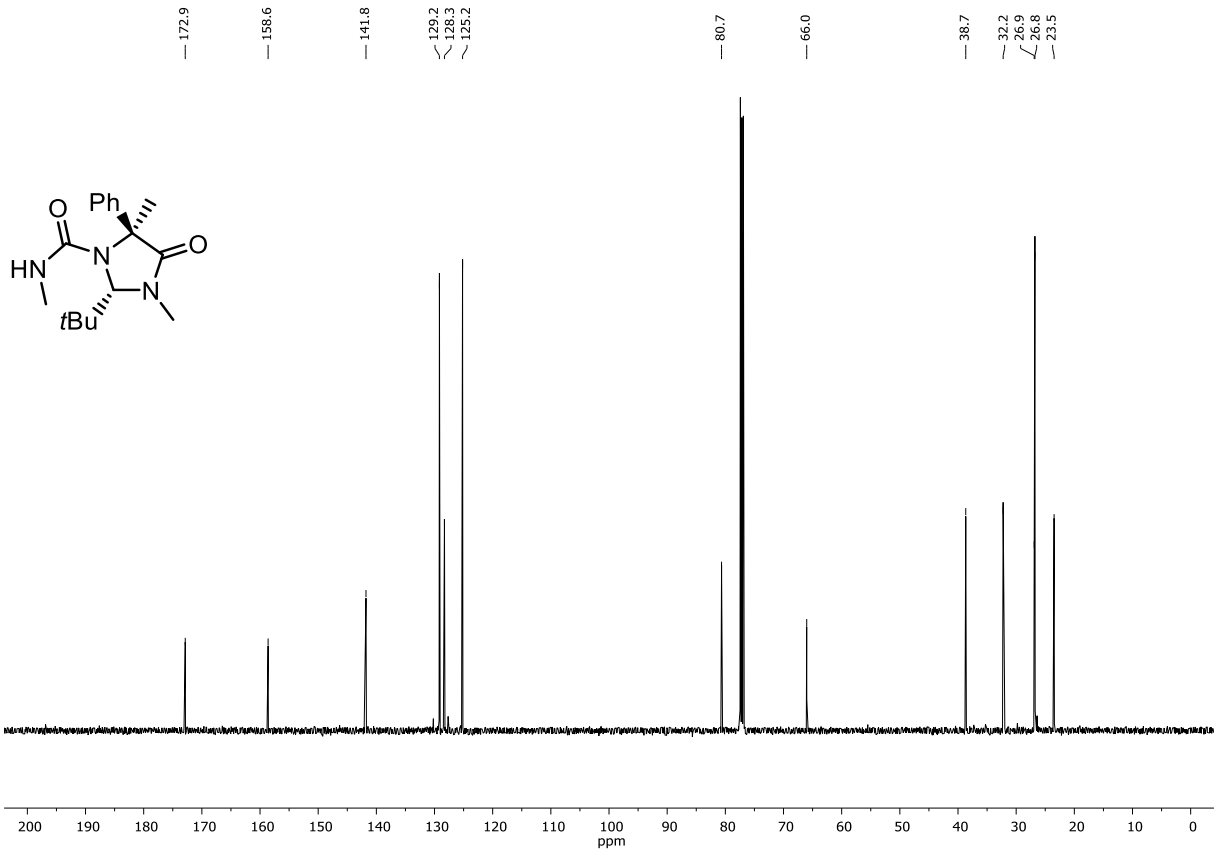
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Ph
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tBu
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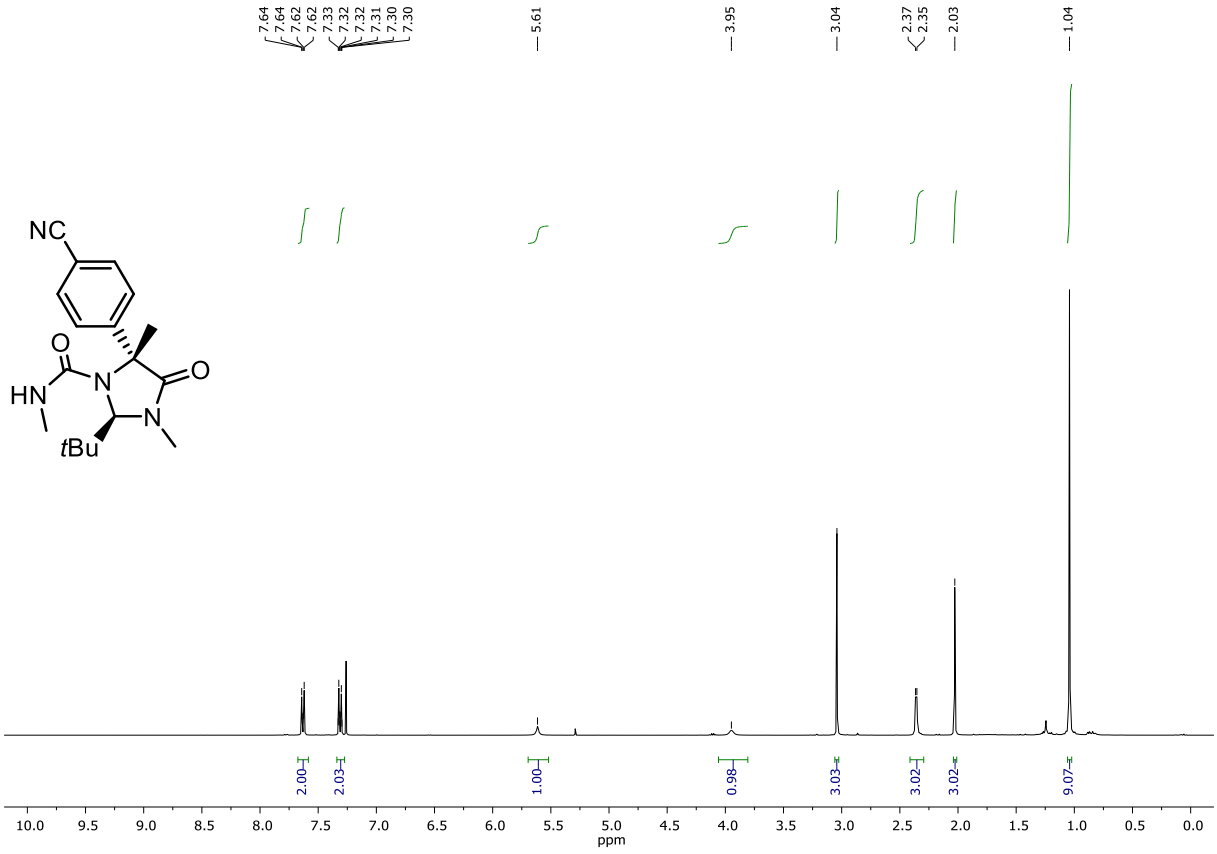
ppm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2.35
2.03
1.04
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N
O
N
tBu
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2.03
1.00
0.98
3.03
3.02
3.02
9.07
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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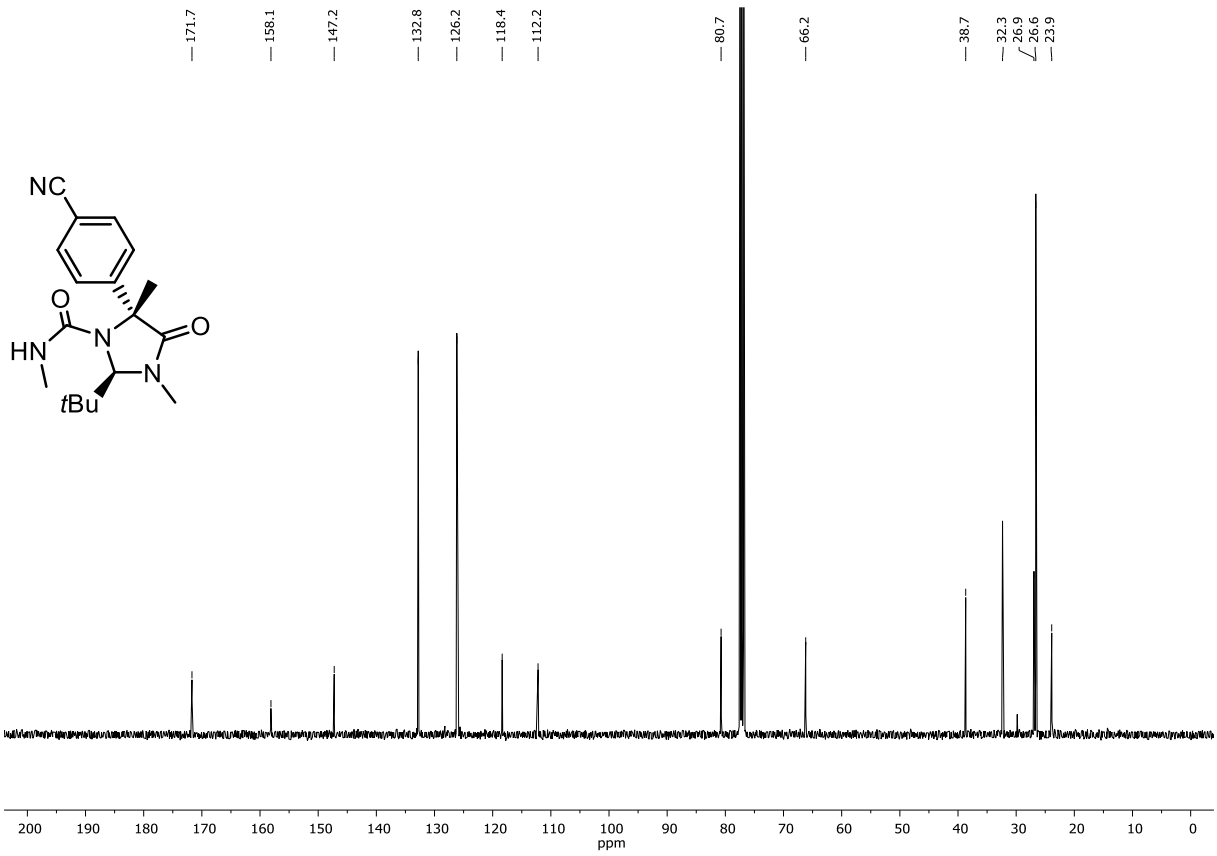
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38.7
32.3
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NC
O
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N
tBu
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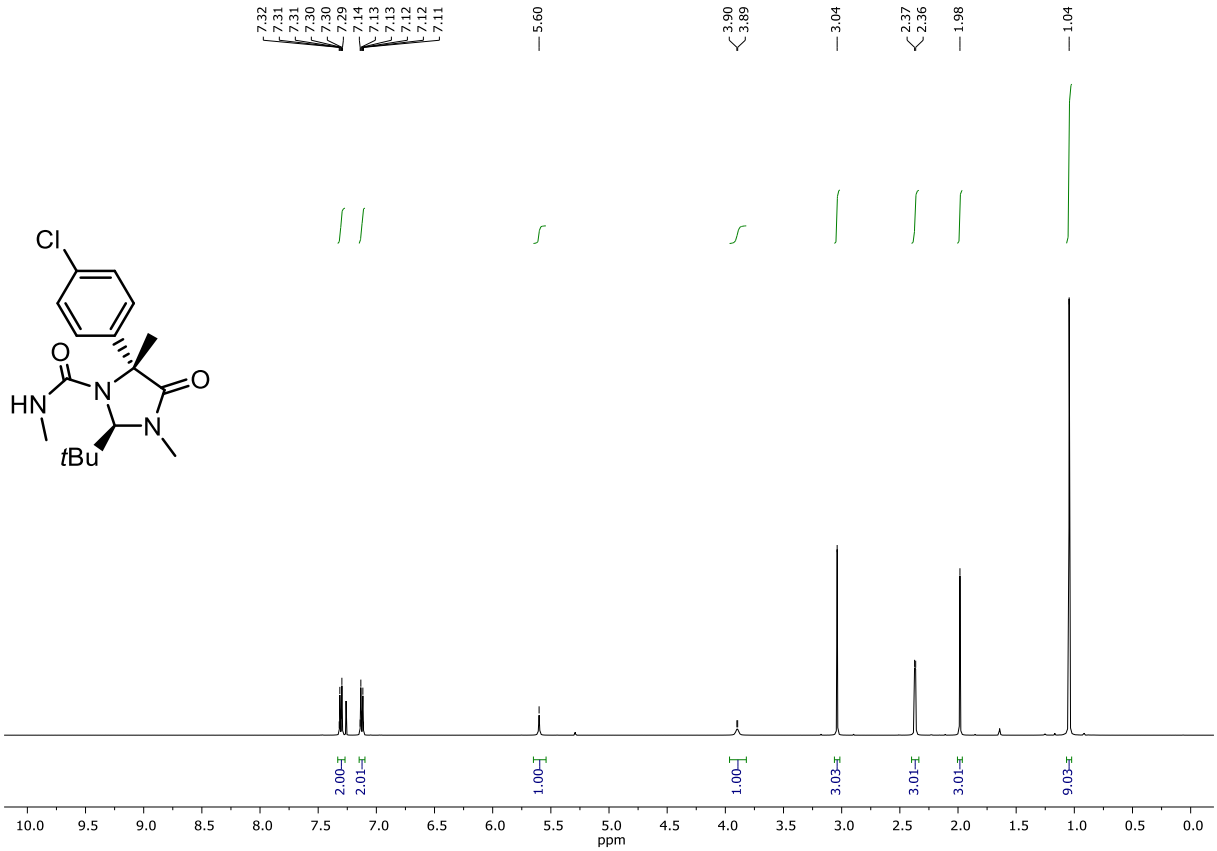
ppm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3.89
3.04
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2.36
1.98
1.04
Cl
O
HN
N
O
N
tBu
2.00
2.01
1.00
1.00
3.03
3.01
3.01
9.03
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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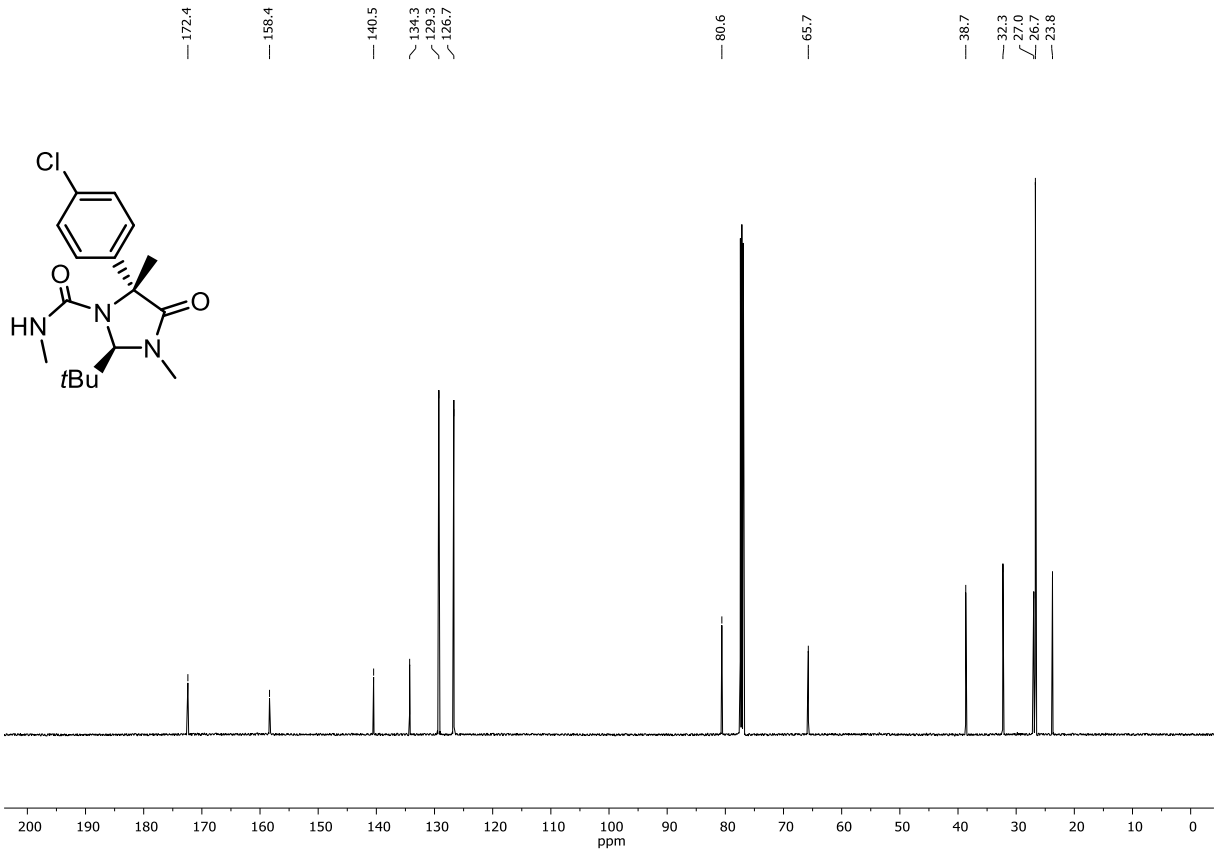
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38.7
32.3
27.0
26.7
23.8
Cl
O
HN
N
O
N
tBu
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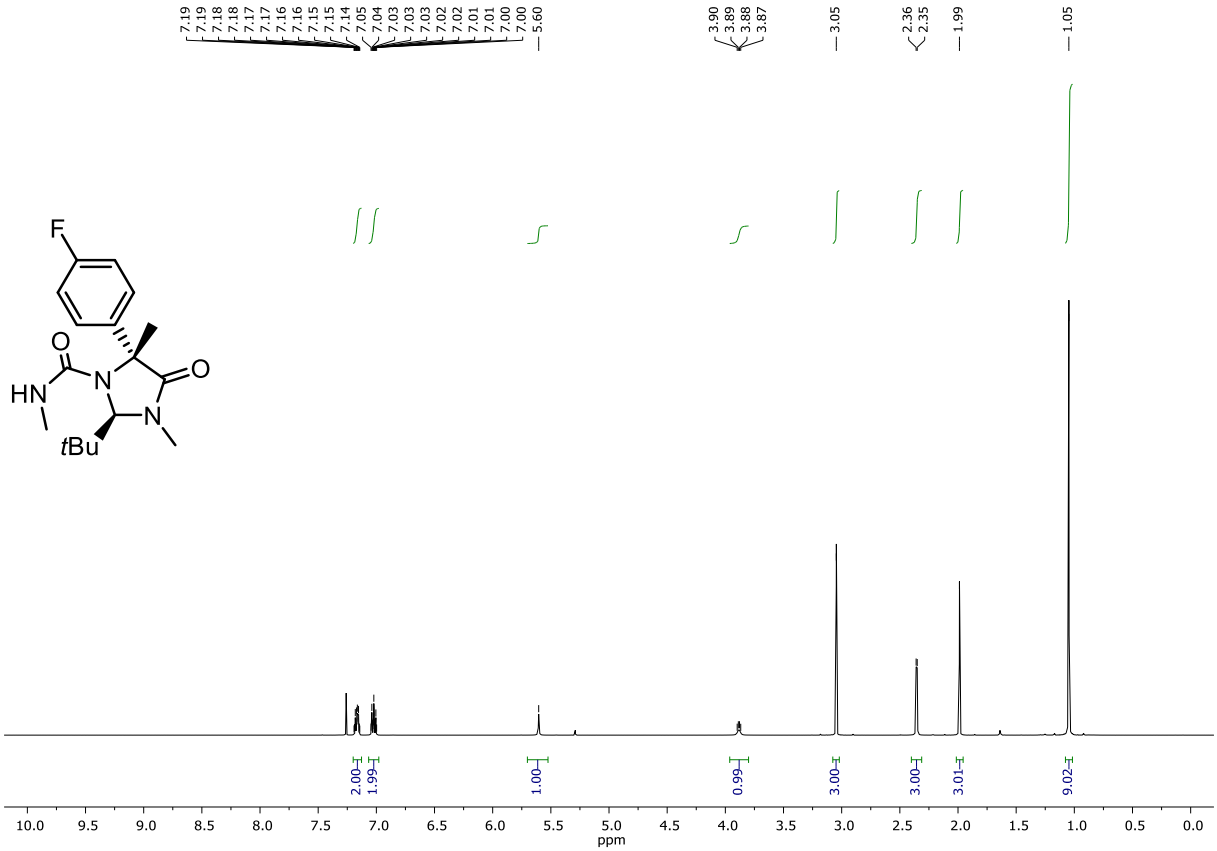
ppm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7.03
7.03
7.03
7.02
7.02
7.01
7.01
7.00
7.00
5.60
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3.89
3.88
3.87
3.05
2.36
2.35
1.99
1.05
F
O
HN
N
O
N
tBu
2.00
1.99
1.00
0.99
3.00
3.00
3.01
9.02
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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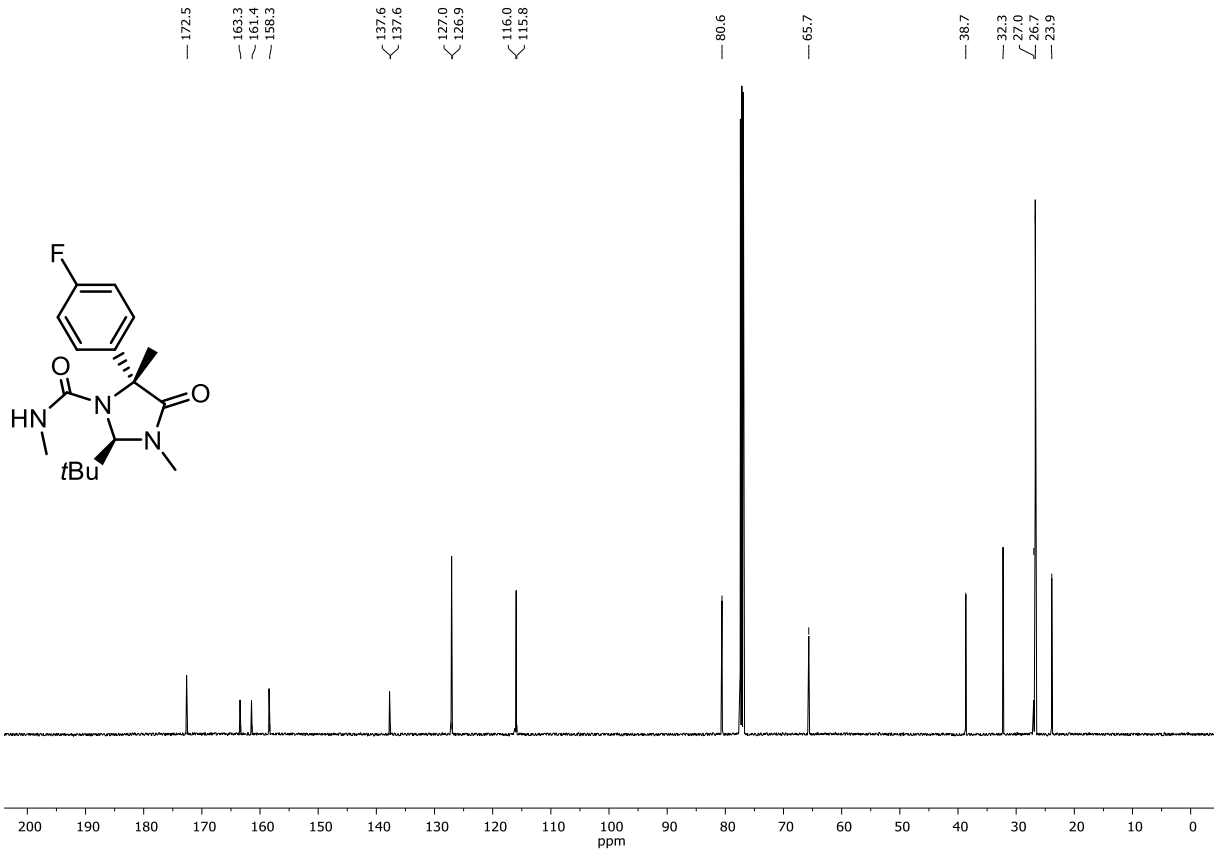
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80.6
65.7
38.7
32.3
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F
O
HN
N
O
N
tBu
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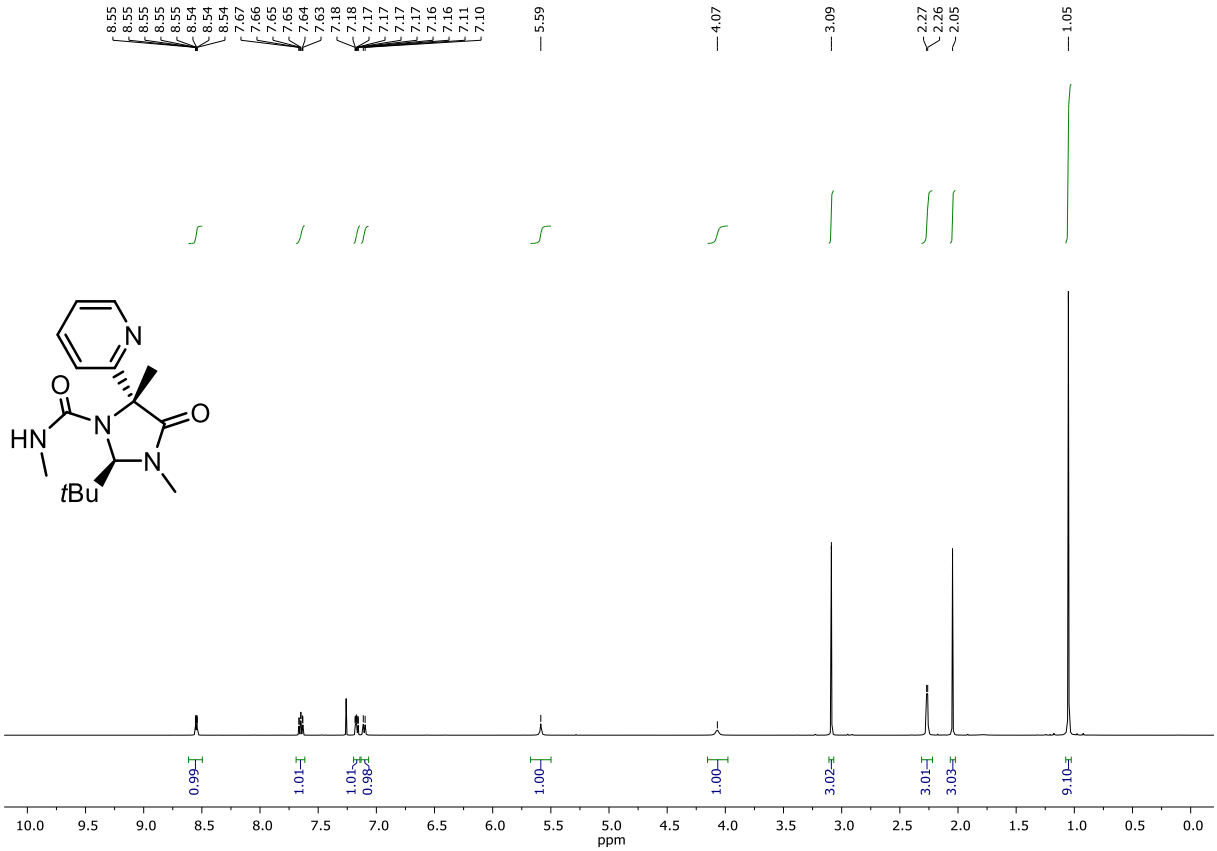
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7.18
7.18
7.17
7.17
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7.16
7.16
7.11
7.10
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4.07
3.09
2.27
2.26
2.05
1.05
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O
N
O
N
N
O
tBu
0.99
1.01
1.01
0.98
1.00
1.00
3.02
3.01
3.03
9.10
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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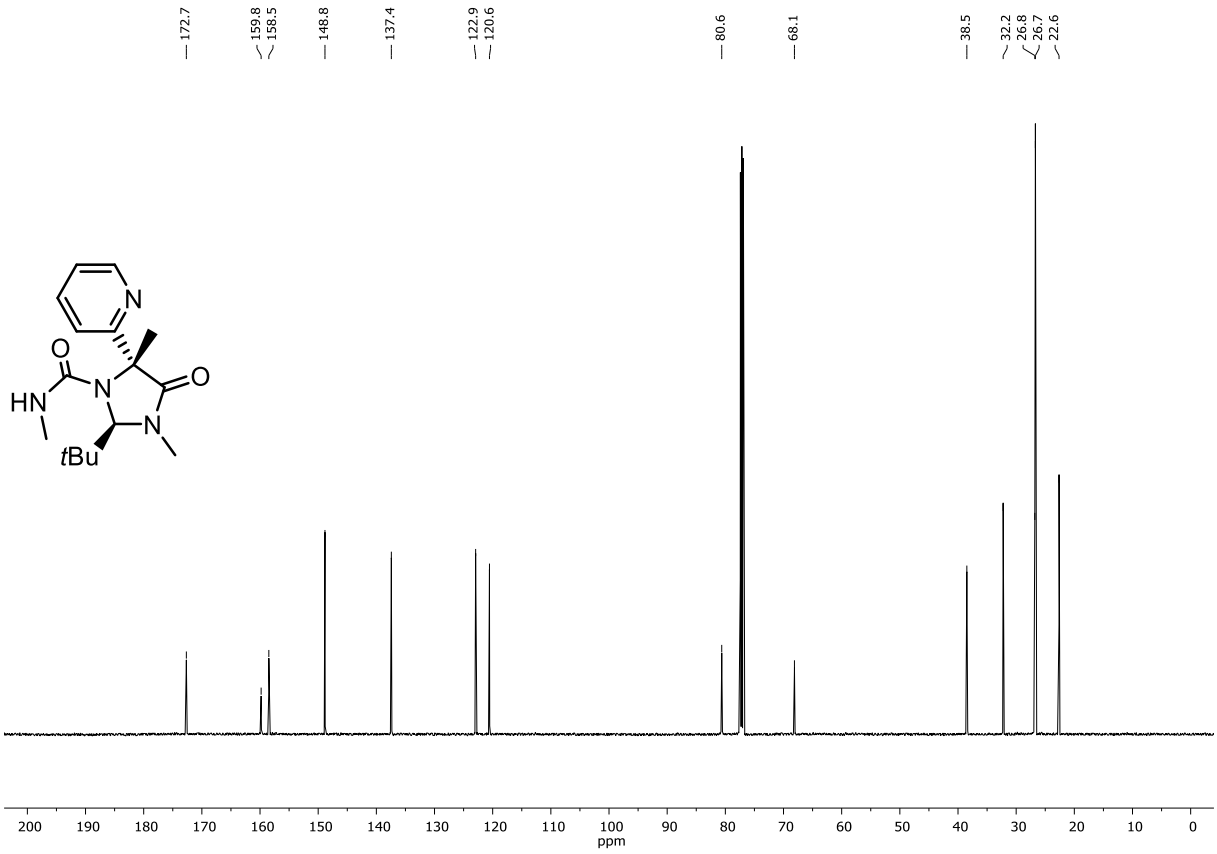
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38.5
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26.8
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N
N
O
tBu
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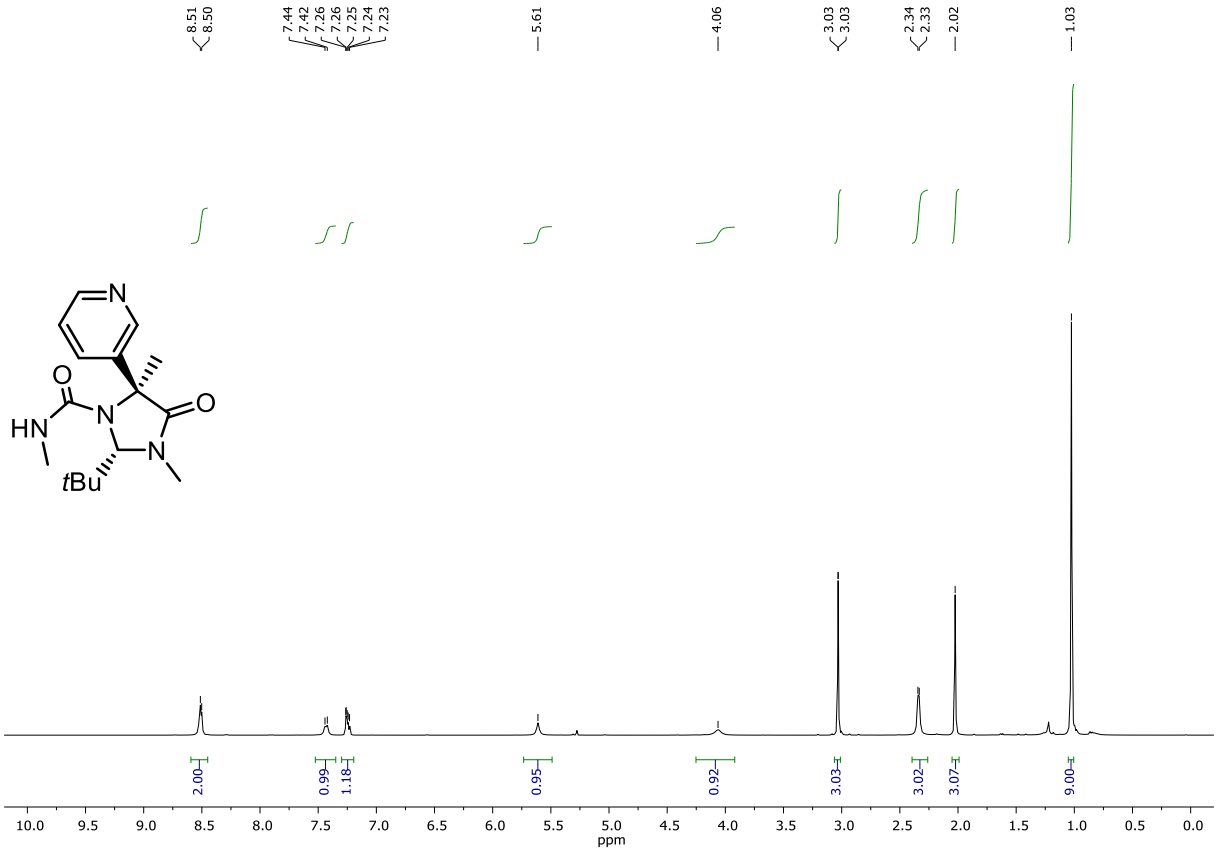
ppm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3.03
2.34
2.33
2.02
1.03
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N
O
N
tBu
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0.99
1.18
0.95
0.92
3.03
3.02
3.07
9.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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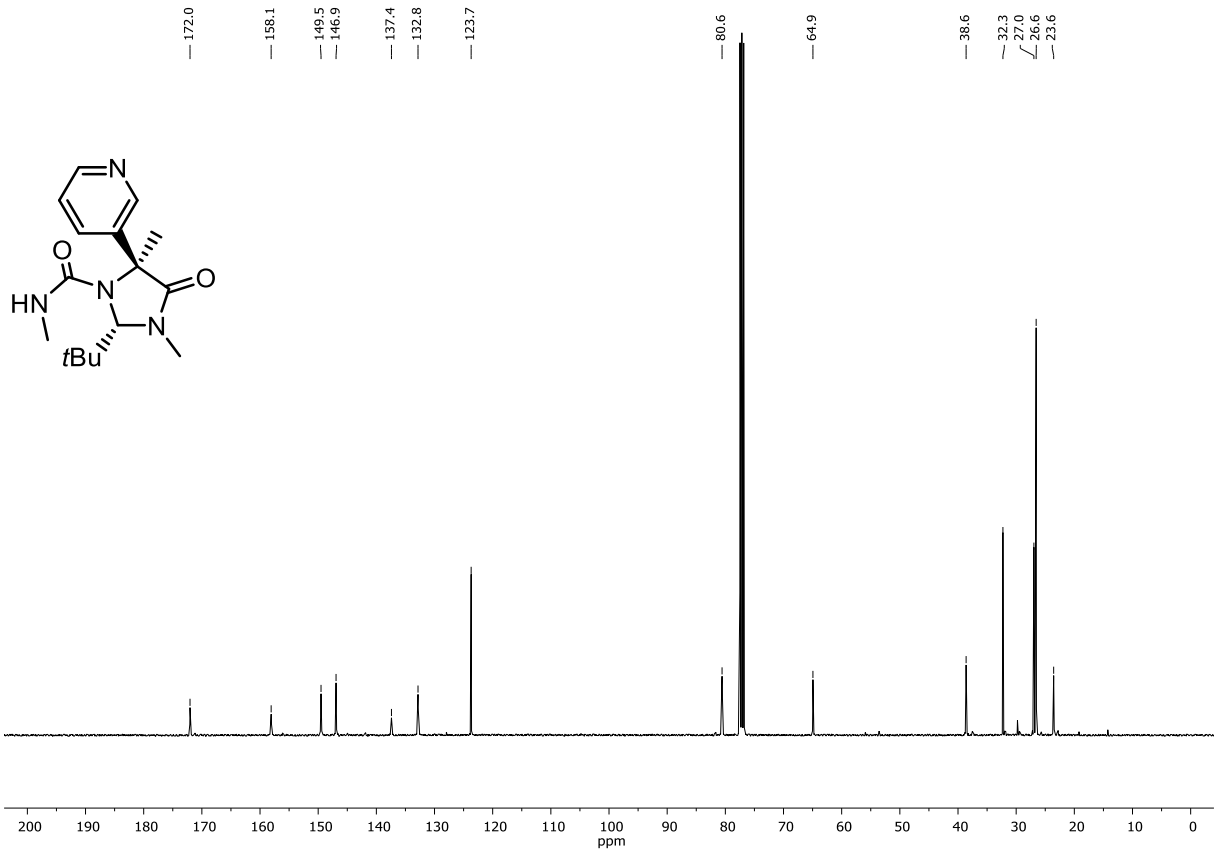
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38.6
32.3
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23.6
HN
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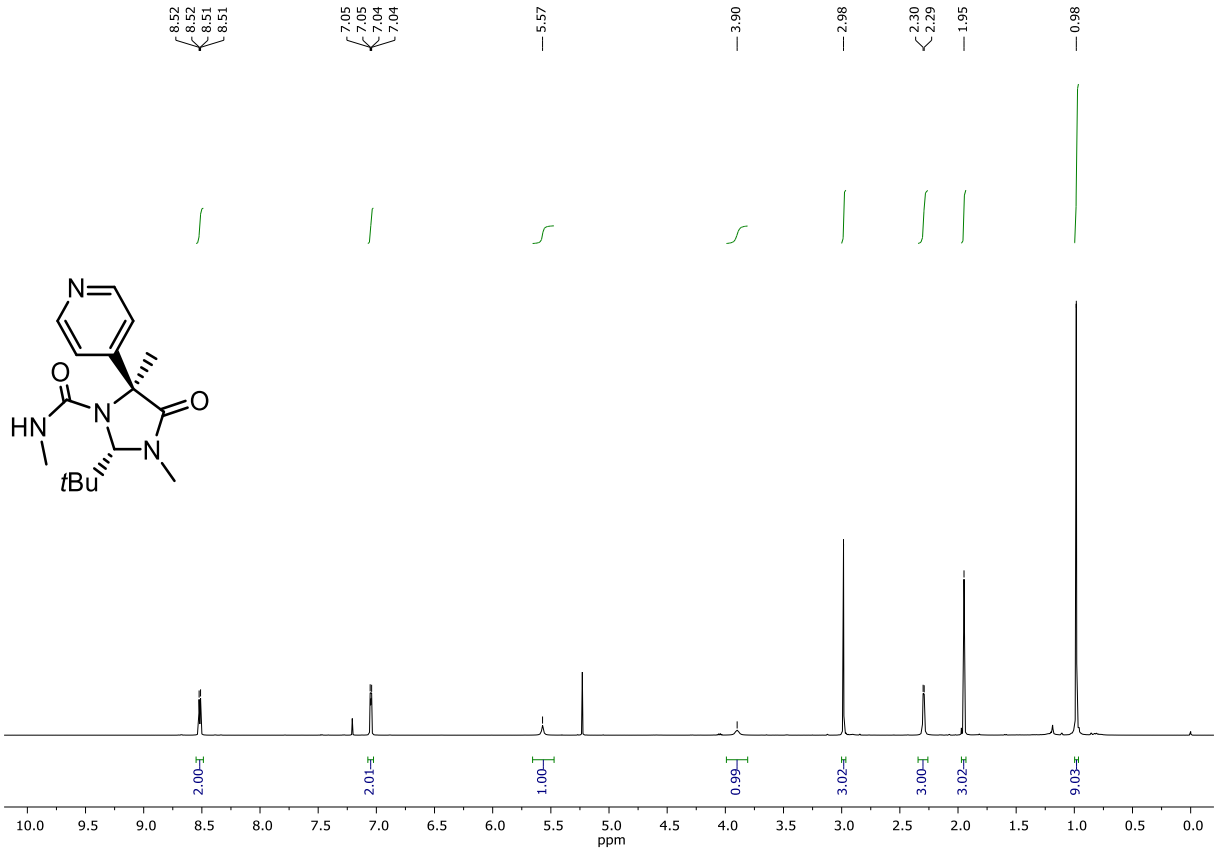
N
O
N
tBu
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm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7.05
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7.04
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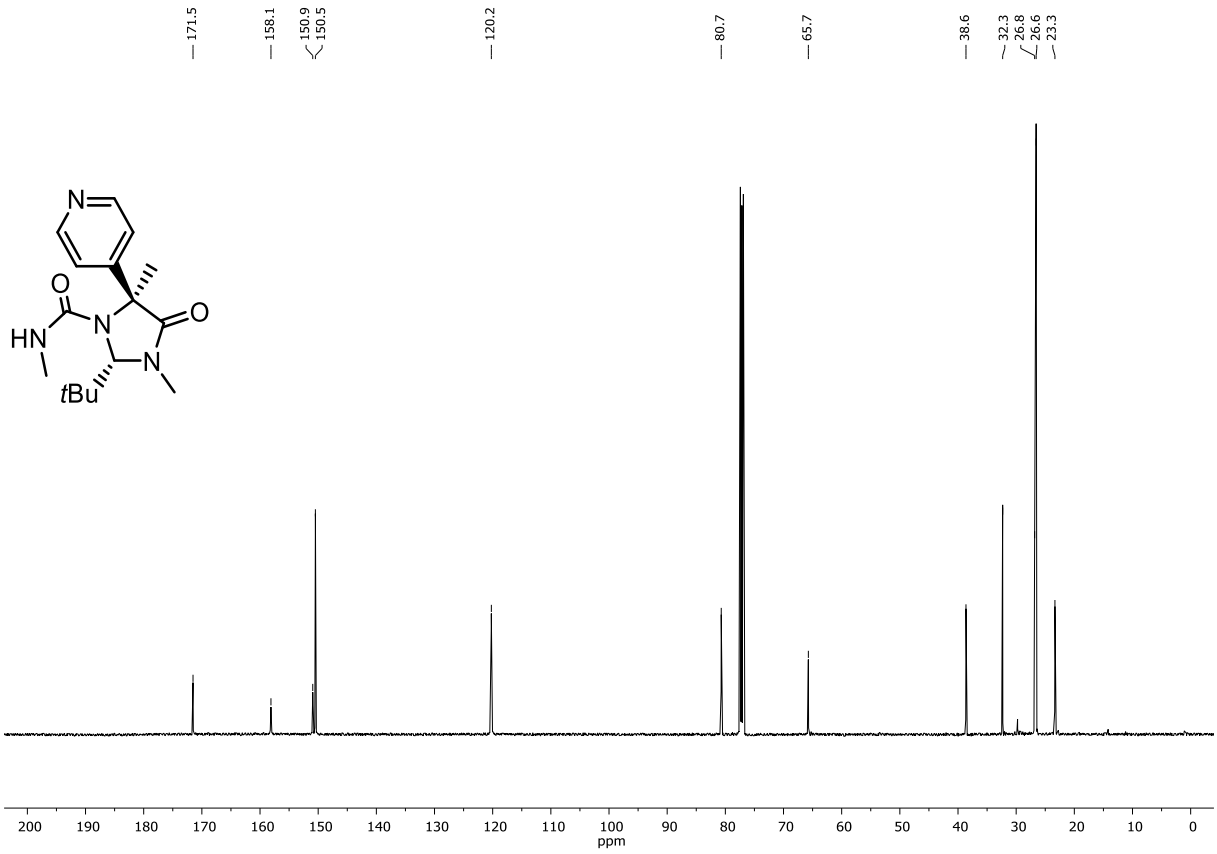
2.30
2.29
1.95
0.98
N
O
HN
N
O
N
tBu
2.00
2.01
1.00
0.99
3.02
3.00
3.02
9.03
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm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32.3
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HN
N
O
N
tBu
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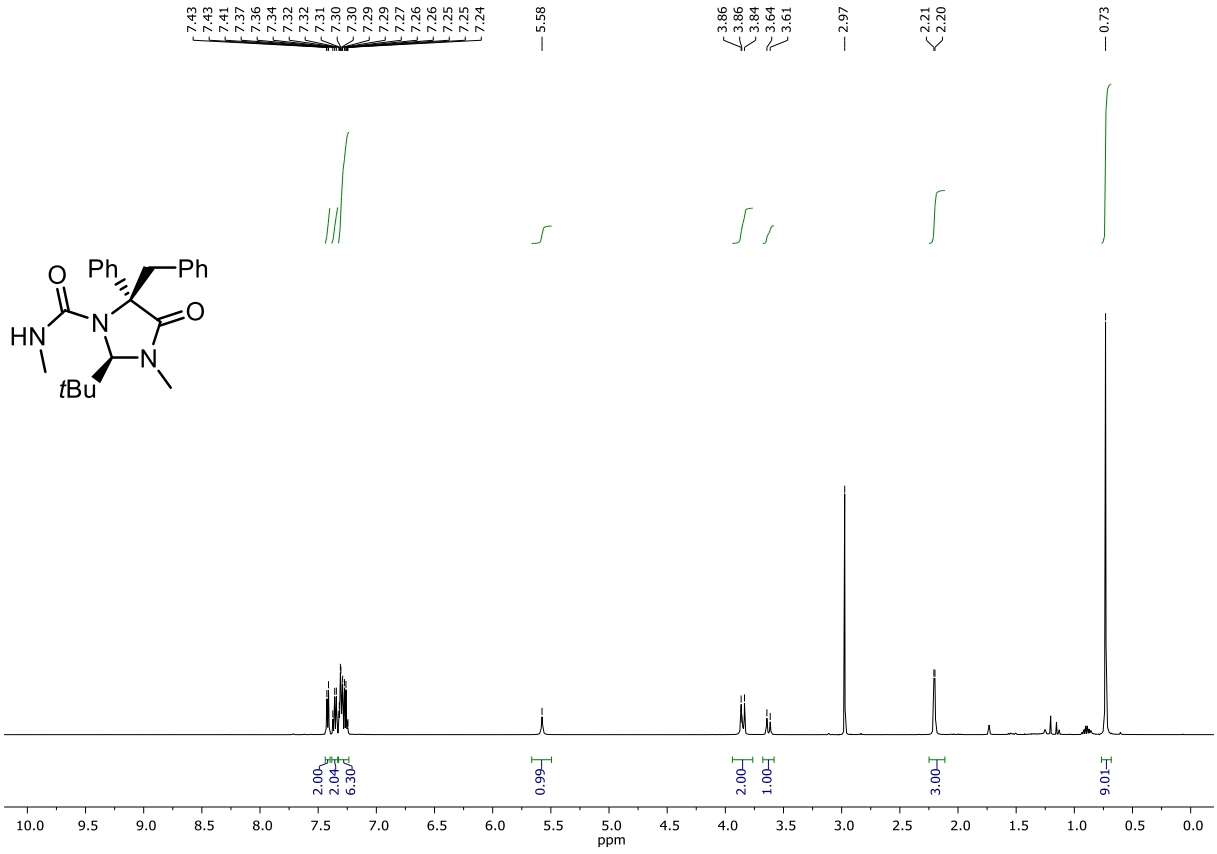
ppm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7.29
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7.25
7.25
7.24
5.58
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3.86
3.84
3.64
3.61
2.97
2.21
2.20
0.73
Ph
Ph
O
HN
N
O
N
tBu
2.00
2.04
6.30
0.99
2.00
1.00
3.00
9.01
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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4.0
3.5
3.0
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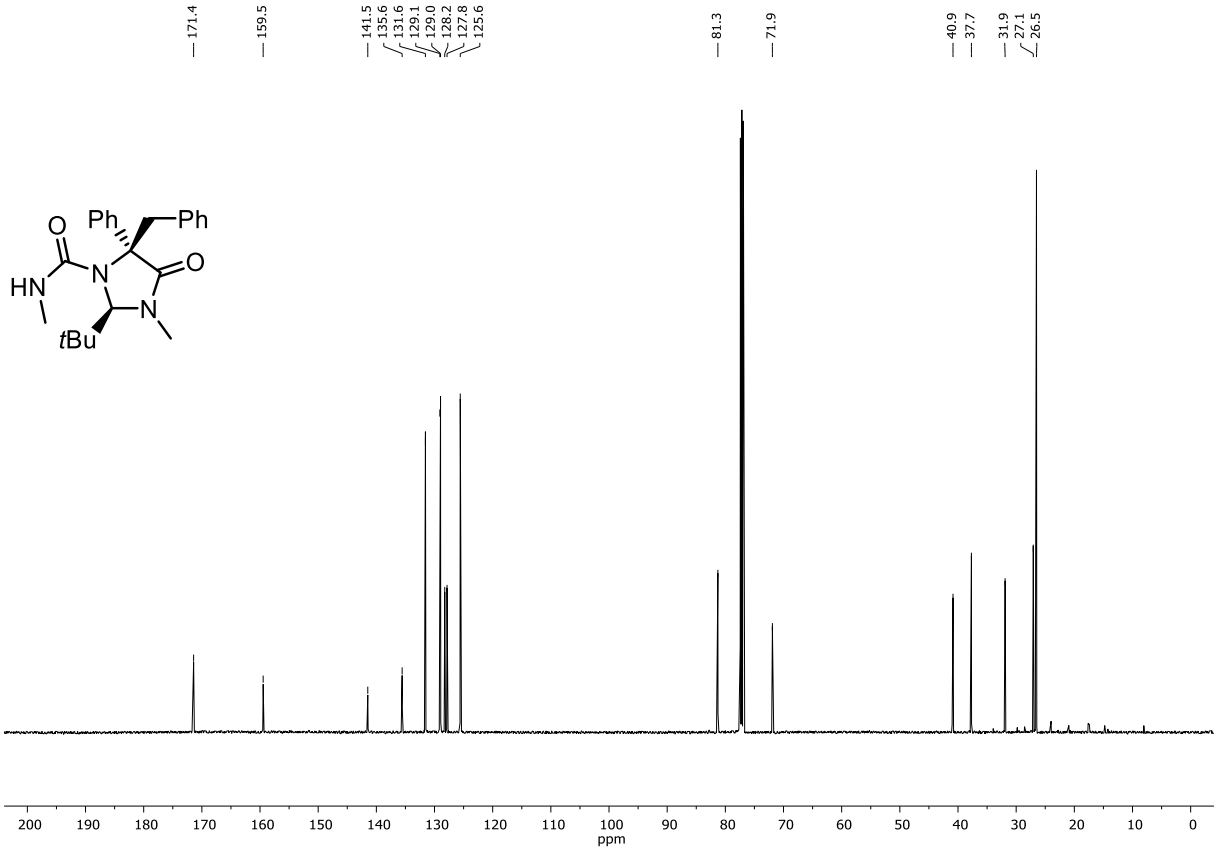
2.0
1.5
1.0
0.5
0.0
ppm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128.2
127.8
125.6
81.3
71.9
40.9
37.7
31.9
27.1
26.5
Ph
Ph
O
HN
N
O
N
tBu
200
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180
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150
140
130
120
110
100
90
80
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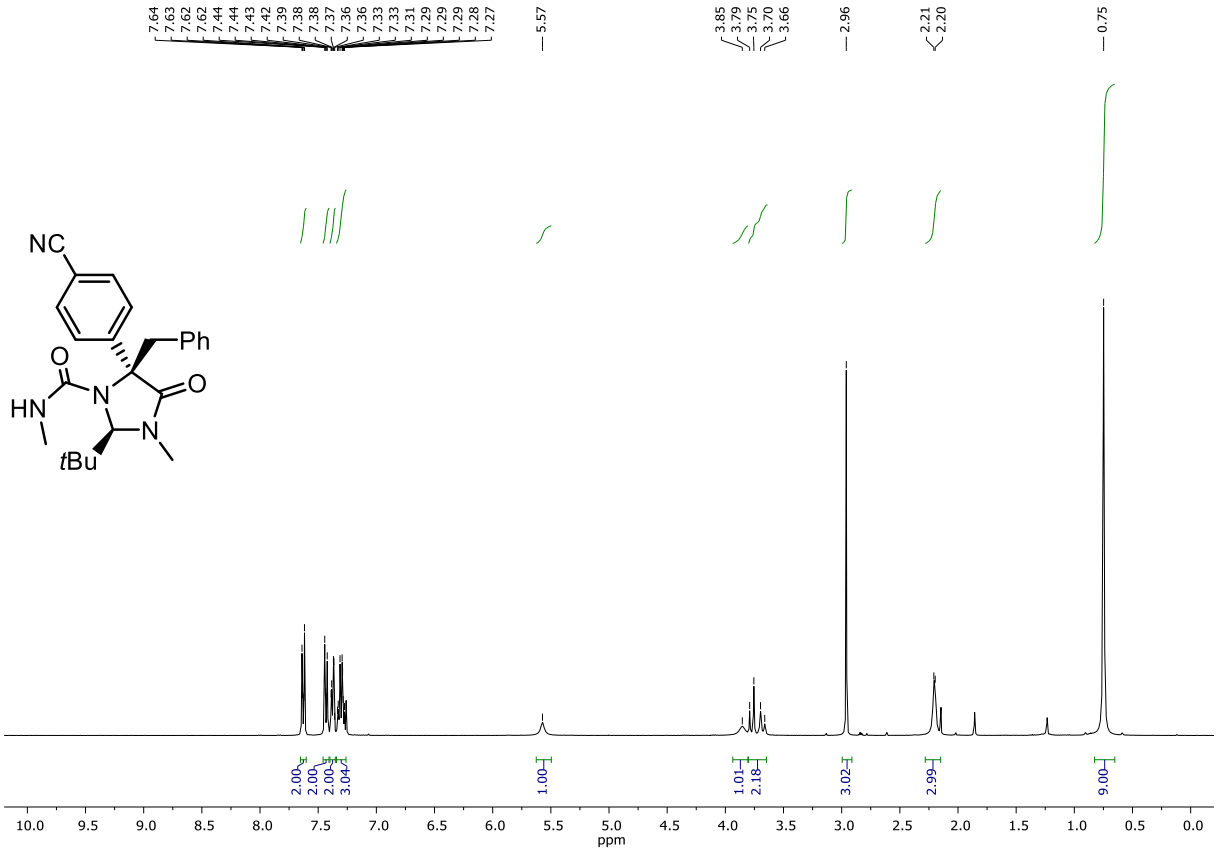
60
50
40
30
20
10
0
ppm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7.29
7.28
7.27
5.57
3.85
3.79
3.75
3.70
3.66
2.96
2.21
2.20
0.75
NC
Ph
O
HN
N
O
N
tBu
2.00
2.00
2.00
3.04
1.00
1.01
2.18
3.02
2.99
9.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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0.5
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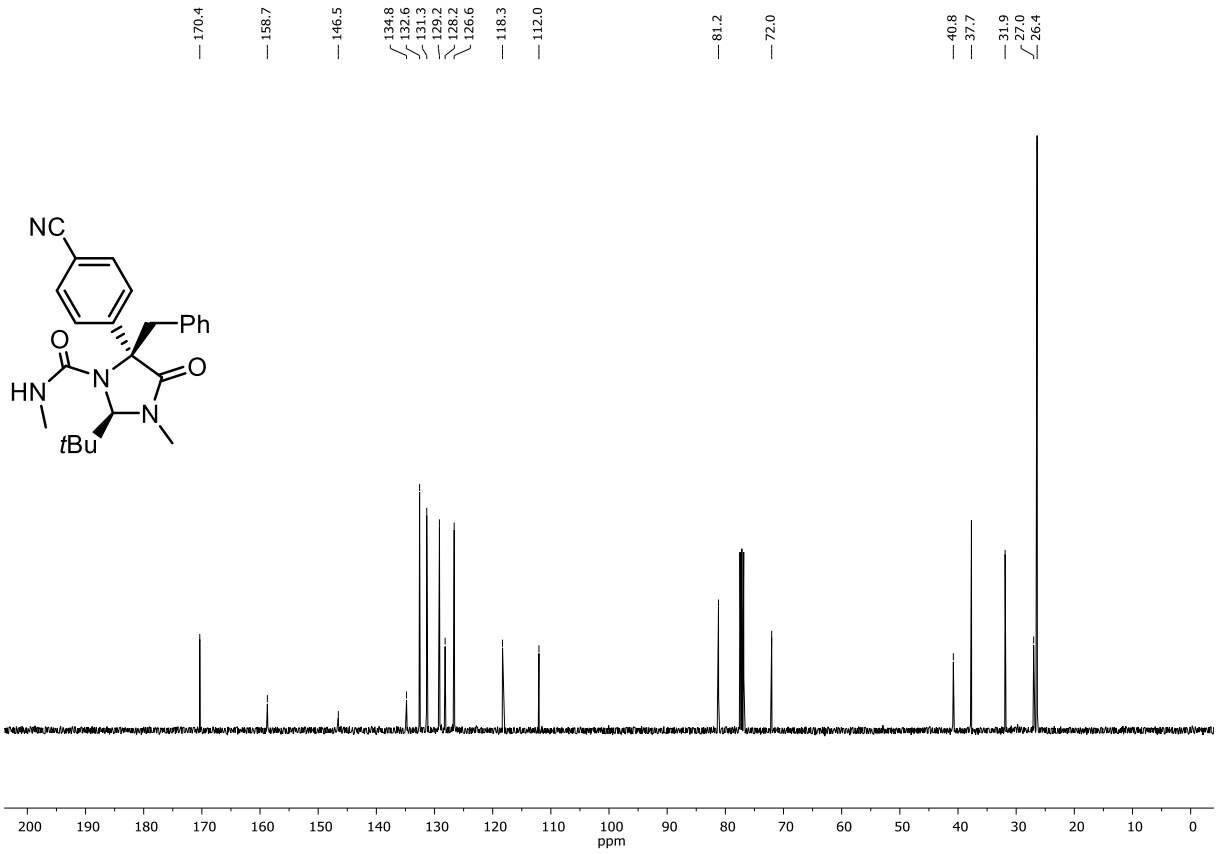
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131.3
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128.2
126.6
118.3
112.0
81.2
72.0
40.8
37.7
31.9
27.0
26.4
NC
Ph
O
HN
N
O
N
tBu
200
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140
130
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110
100
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20
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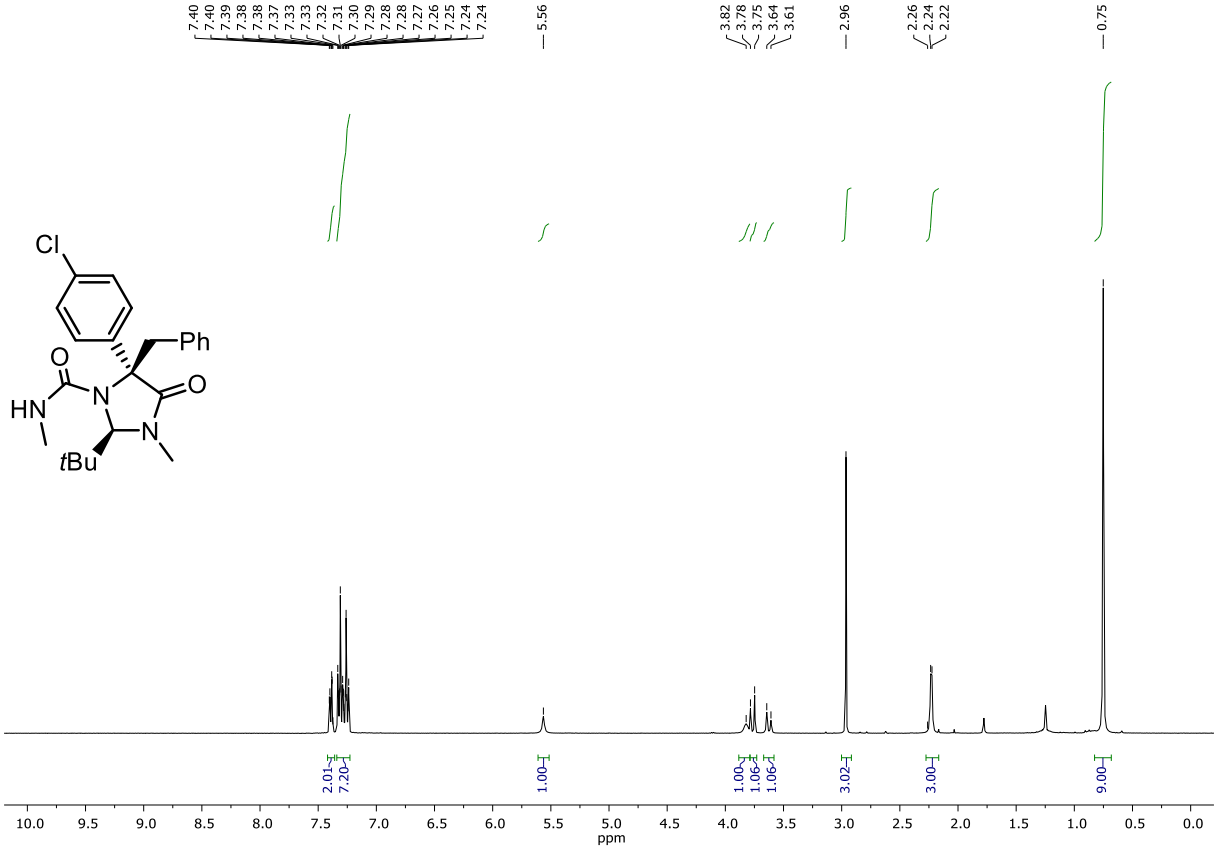
0
ppm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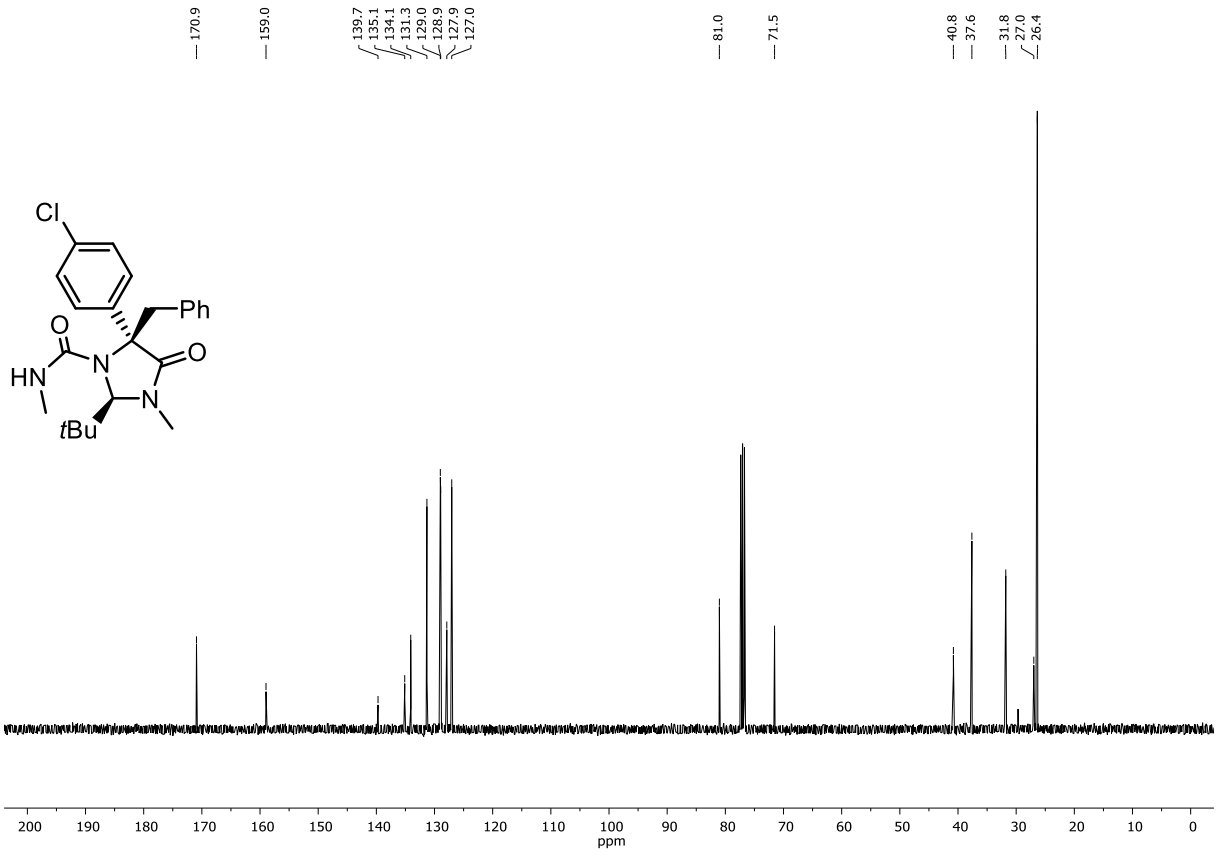
7.29
7.28
7.28
7.27
7.26
7.25
7.24
7.24
5.56
3.82
3.78
3.75
3.64
3.61
2.96
2.26
2.24
2.22
0.75
Cl
Ph
O
HN
N
O
N
tBu
2.01
7.20
1.00
1.00
1.06
1.06
3.02
3.00
9.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm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134.1
131.3
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128.9
127.9
127.0
81.0
71.5
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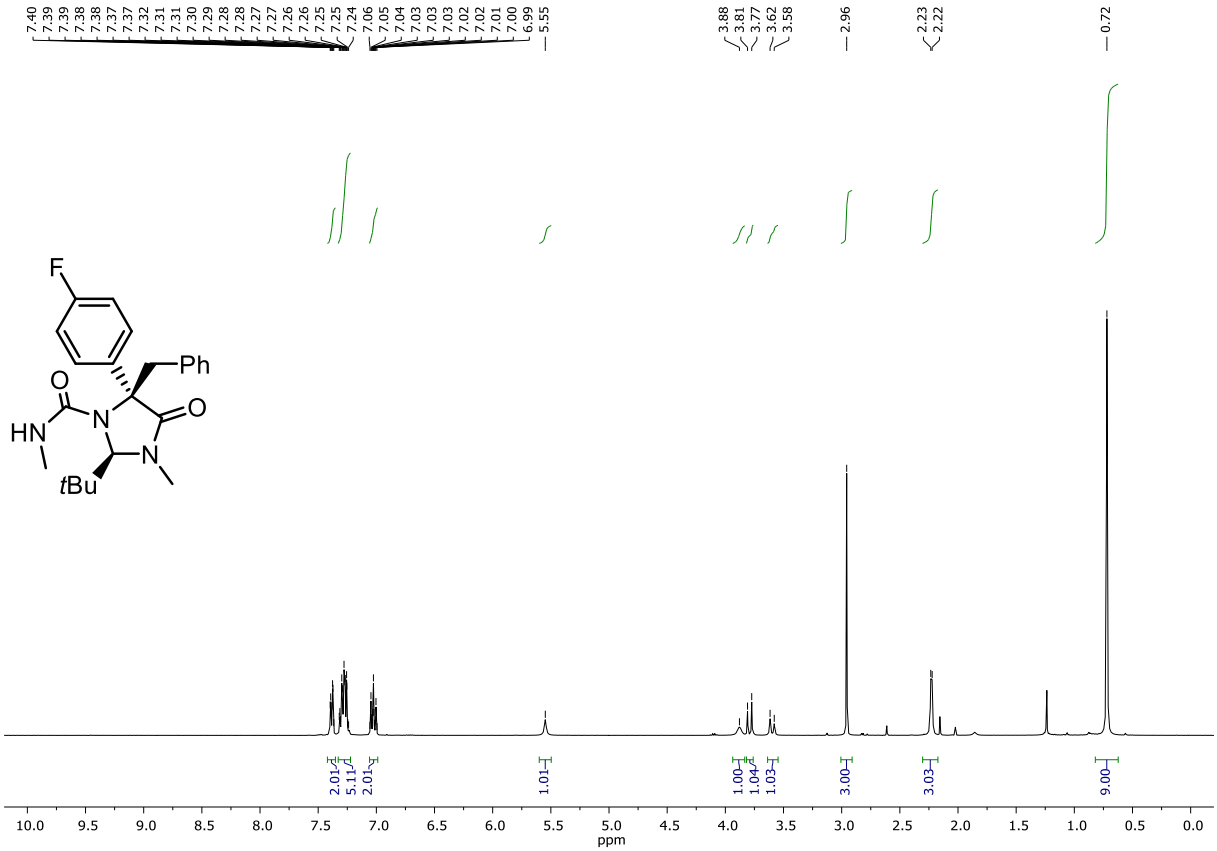
37.6
31.8
27.0
26.4
Cl
Ph
O
HN
N
O
N
tBu
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm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3.88 3.81 3.77 3.62 3.58
2.96
2.23 2.22
0.72
F
Ph
O
HN
N
O
N
tBu
2.01 5.11 2.01 1.01 1.00 1.04 1.03 3.00 3.03 9.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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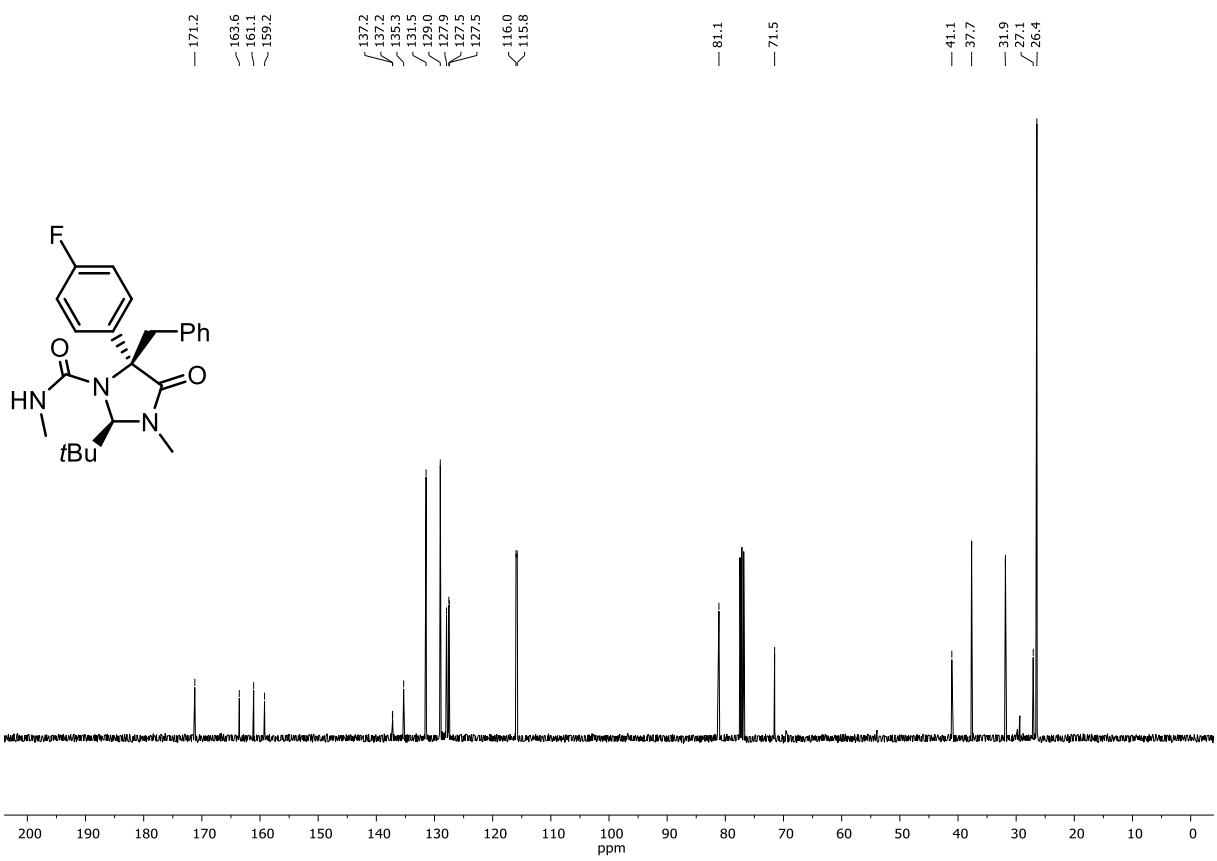
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163.6 161.1 159.2
137.2 137.2 135.3 131.5 129.0 127.9 127.5 127.5
116.0 115.8
81.1
71.5
41.1 37.7
31.9 27.1 26.4
F
Ph
O
HN
N
O
N
tBu
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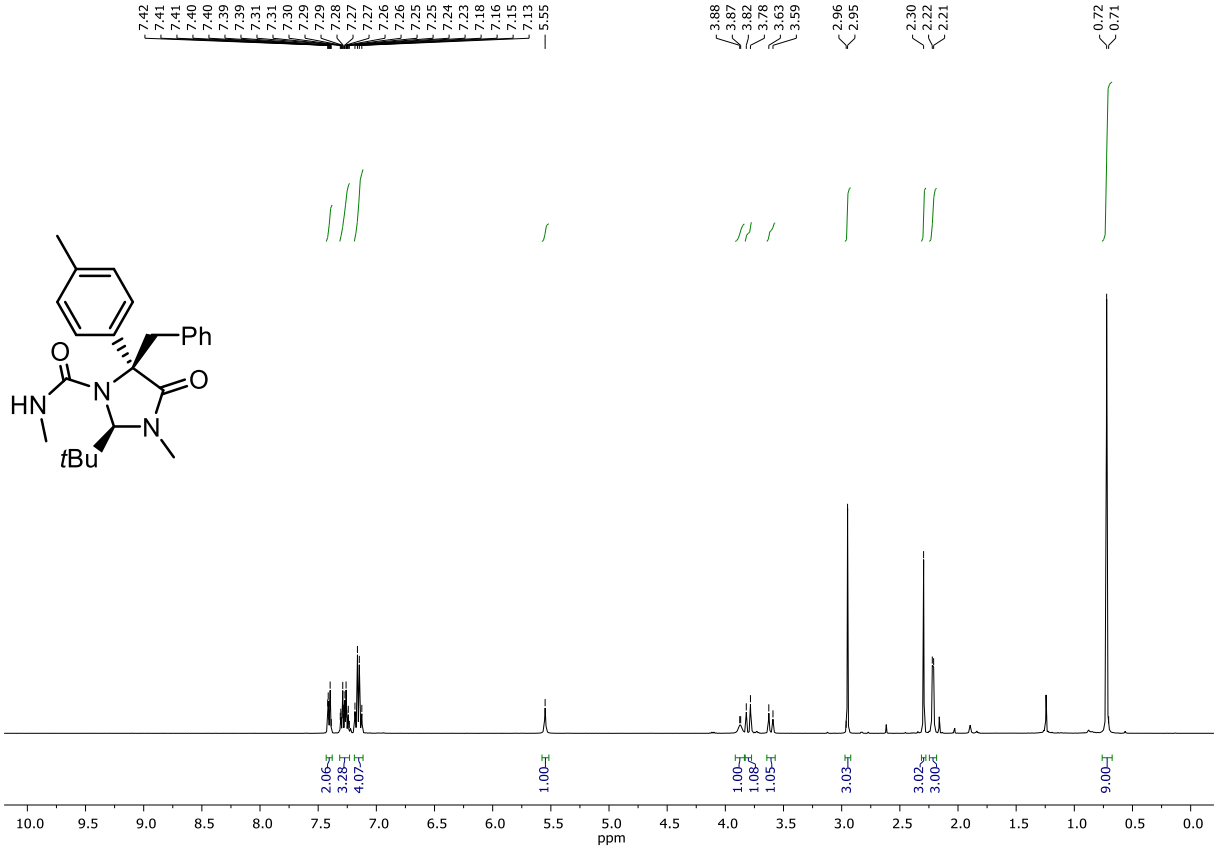
ppm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7.25
7.24
7.23
7.18
7.16
7.15
7.13
5.55
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3.82
3.78
3.63
3.59
2.96
2.95
2.30
2.22
2.21
0.72
0.71
Ph
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HN
N
O
N
tBu
2.06
3.28
4.07
1.00
1.00
1.08
1.05
3.03
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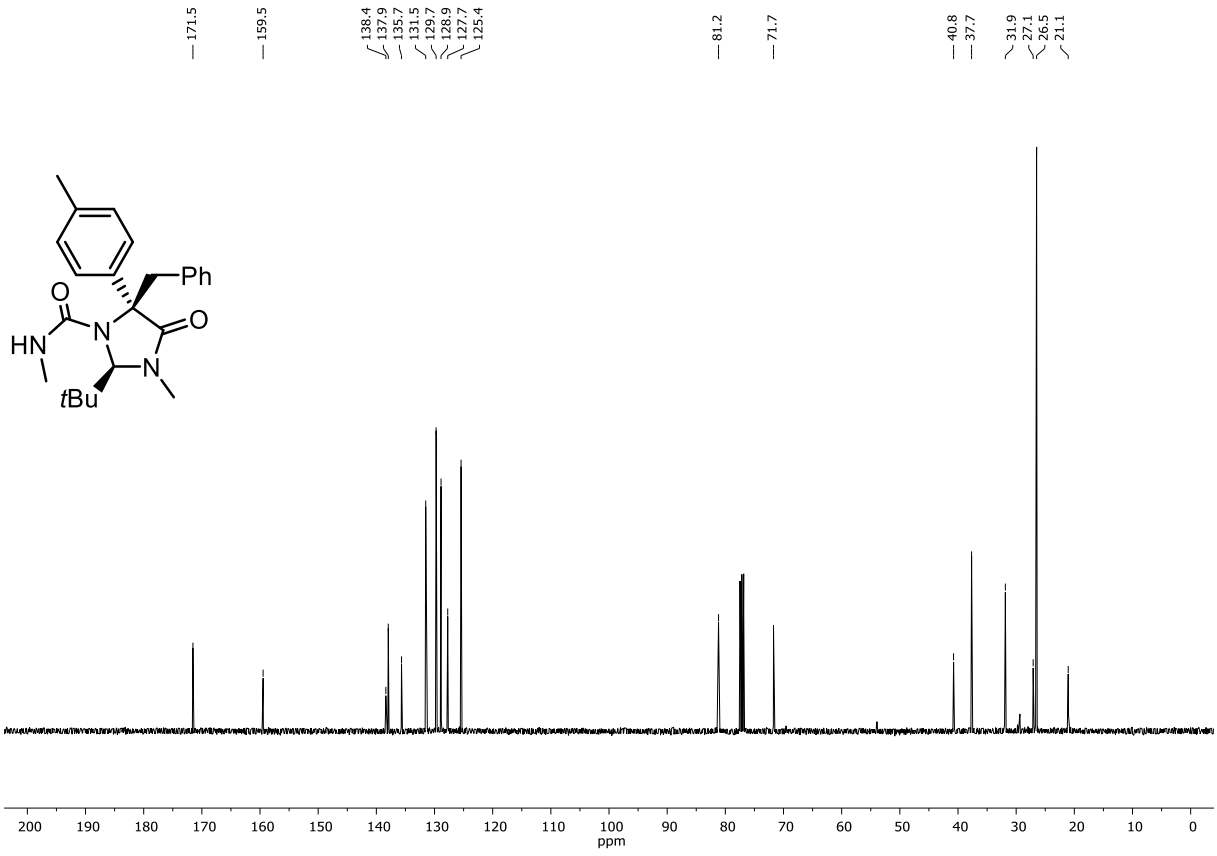
3.00
9.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm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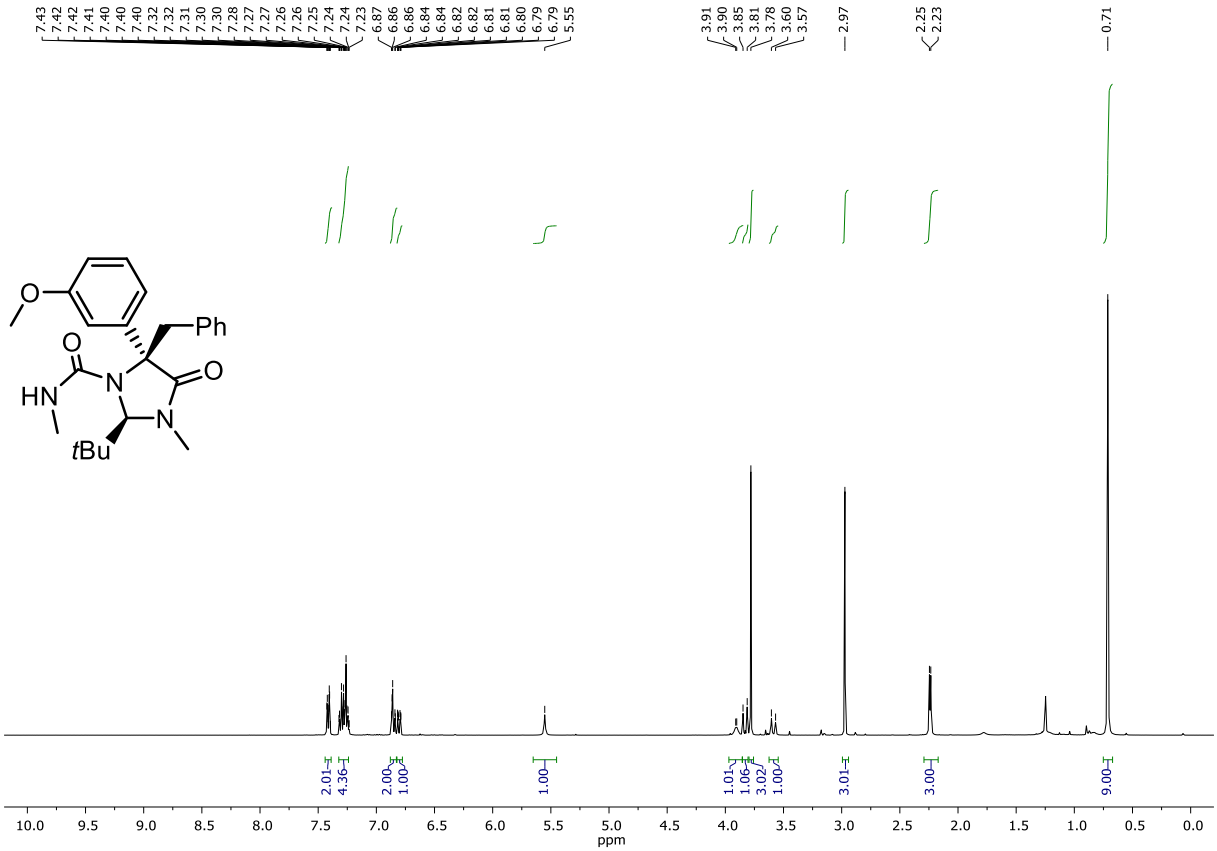
129.7
128.9
127.7
125.4
81.2
71.7
40.8
37.7
31.9
27.1
26.5
21.1
Ph
O
HN
N
O
N
tBu
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm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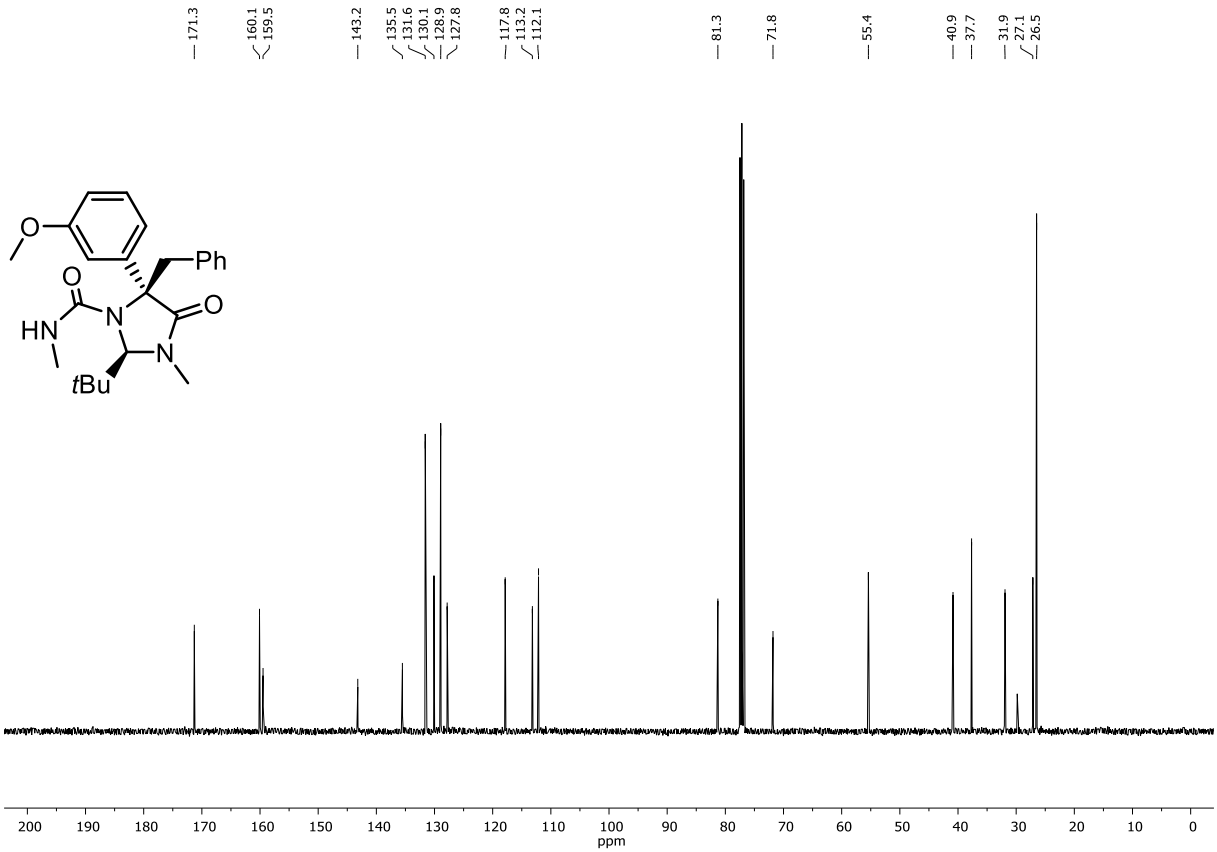
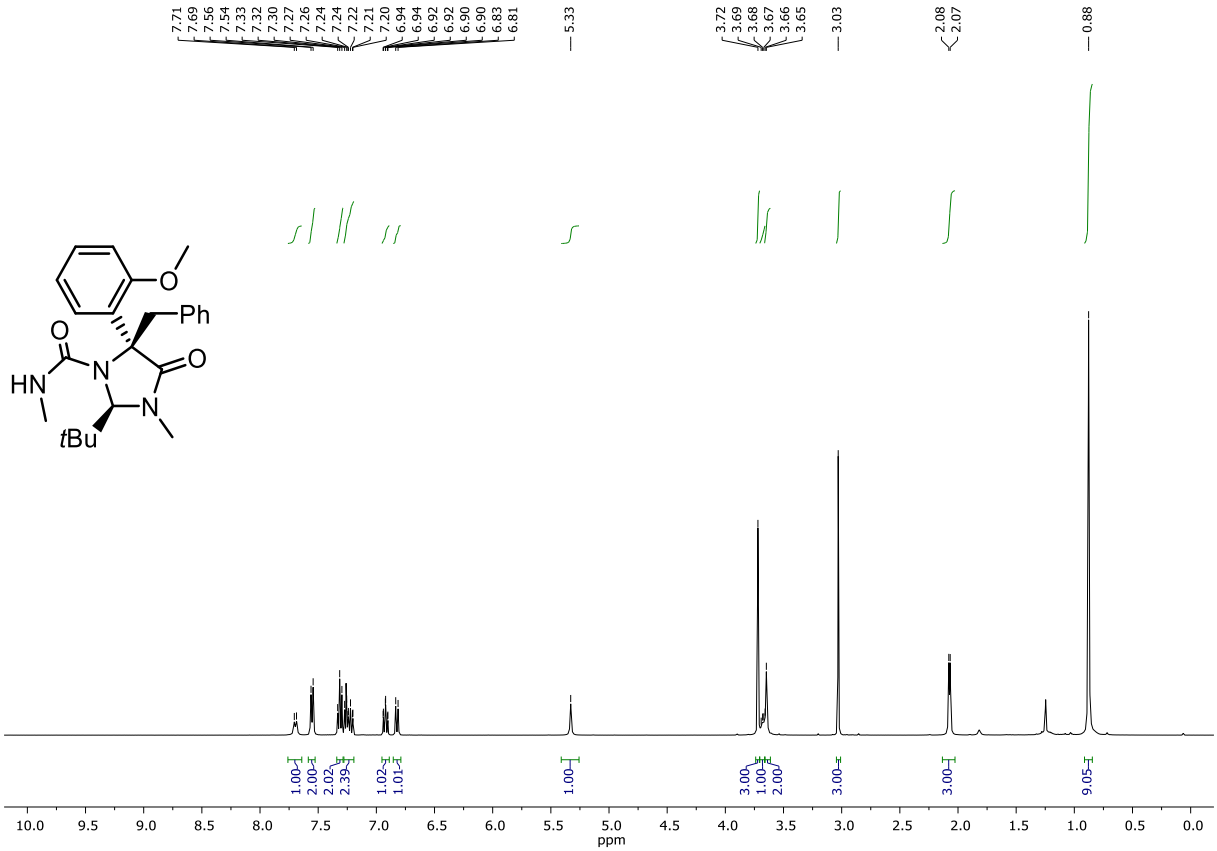
3.91 3.90 3.85 3.81 3.78 3.60 3.57 2.97 2.25 2.23 0.71
O Ph O HN N O N tBu
2.01 4.36 2.00 1.00 1.00 1.01 1.06 3.02 1.00 3.01 3.00 9.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm


171.3 160.1 159.5 143.2 135.5 131.6 130.1 128.9 127.8 117.8 113.2 112.1 81.3 71.8 55.4 40.9 37.7 31.9 27.1 26.5
O Ph O HN N O N tBu
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm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7.20
6.94
6.94
6.92
6.92
6.90
6.90
6.83
6.81
5.33
3.72
3.69
3.68
3.67
3.66
3.65
3.03
2.08
2.07
0.88
O
Ph
O
HN
N
O
N
tBu
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2.00
2.02
2.39
1.02
1.01
1.00
3.00
1.00
2.00
3.00
3.00
9.05
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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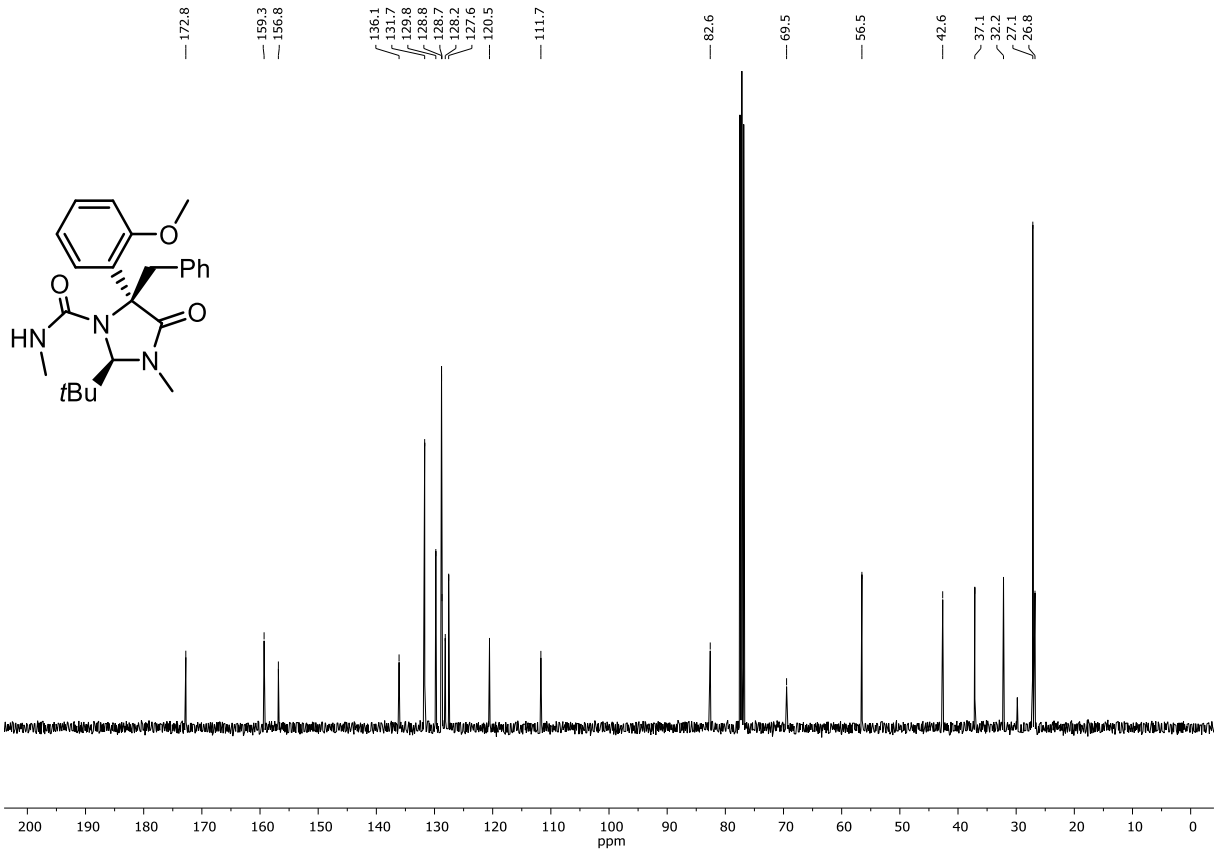
ppm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129.8
128.8
128.7
128.2
127.6
120.5
111.7
82.6
69.5
56.5
42.6
37.1
32.2
27.1
26.8
O
Ph
O
HN
N
O
N
tBu
200
190
180
170
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140
130
120
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100
90
80
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60
50
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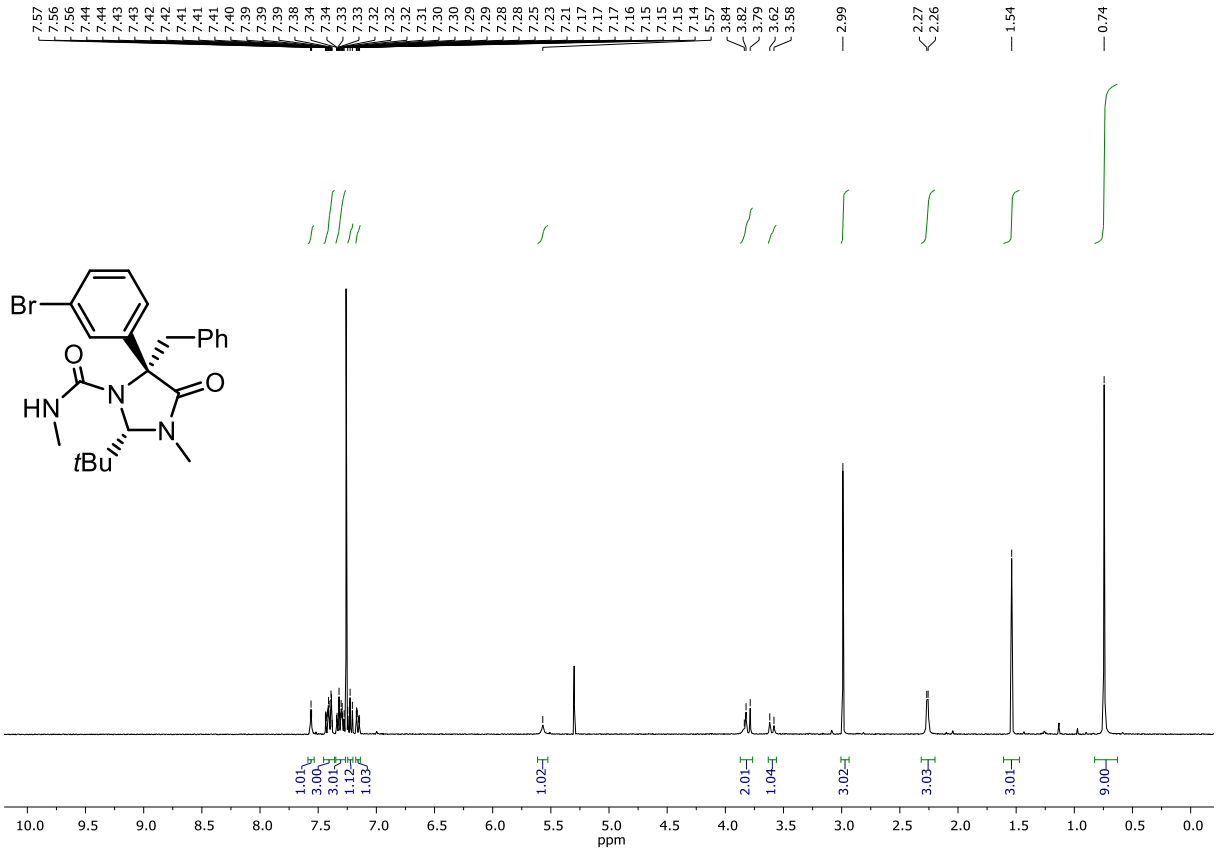
30
20
10
0
ppm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Br
Ph
O
N
O
HN
N
tBu
1.01 3.00 3.01 1.12 1.03 1.02 2.01 1.04 3.02 3.03 3.01 9.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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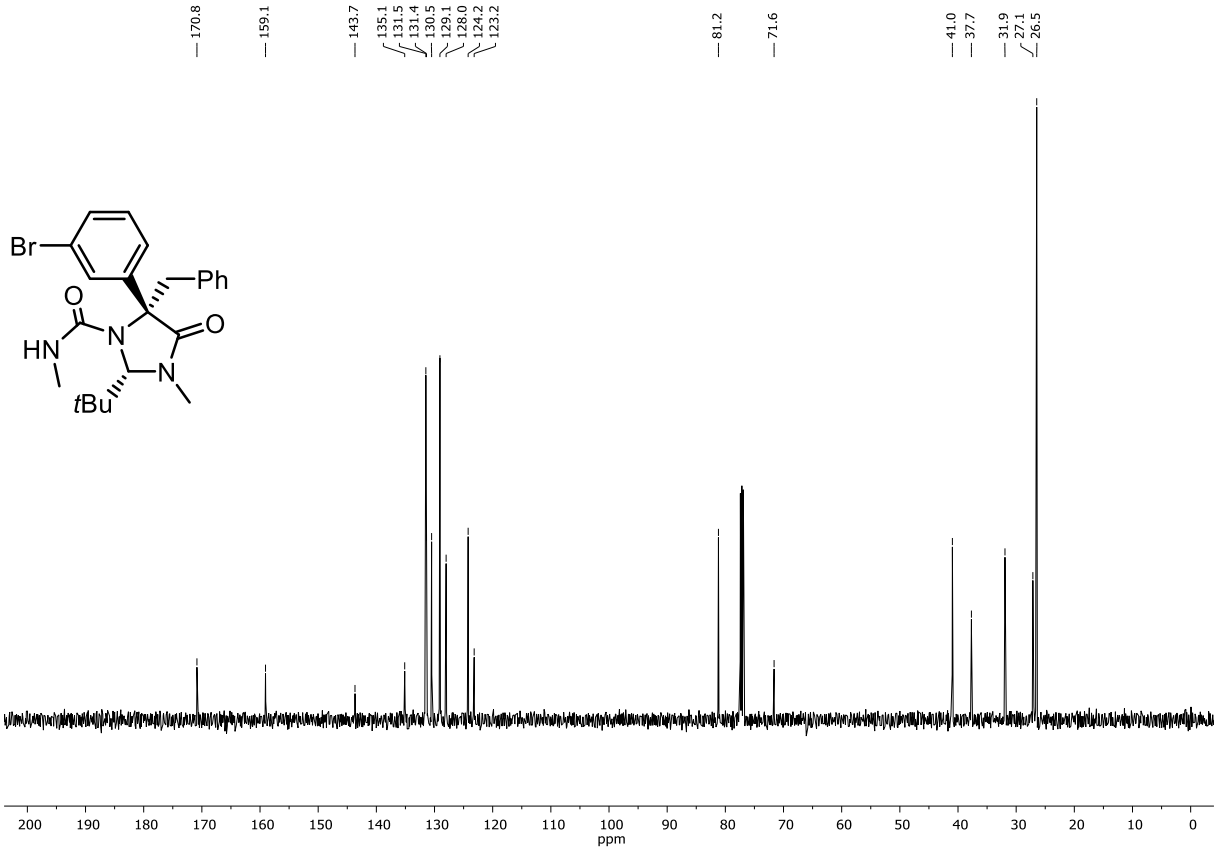
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HN
N
tBu
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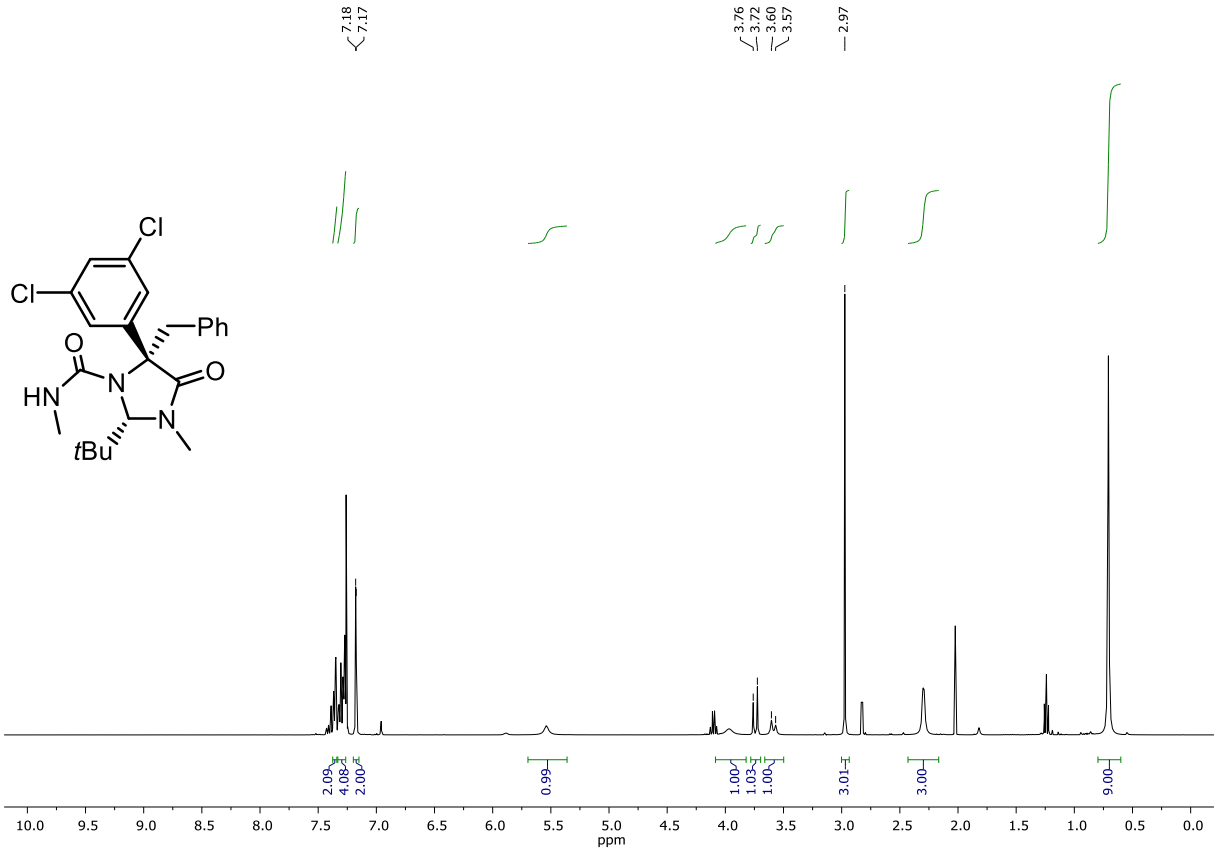
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Cl
Cl
Ph
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HN
N
O
N
tBu
2.09
4.08
2.00
0.99
1.00
1.03
1.00
3.01
3.00
9.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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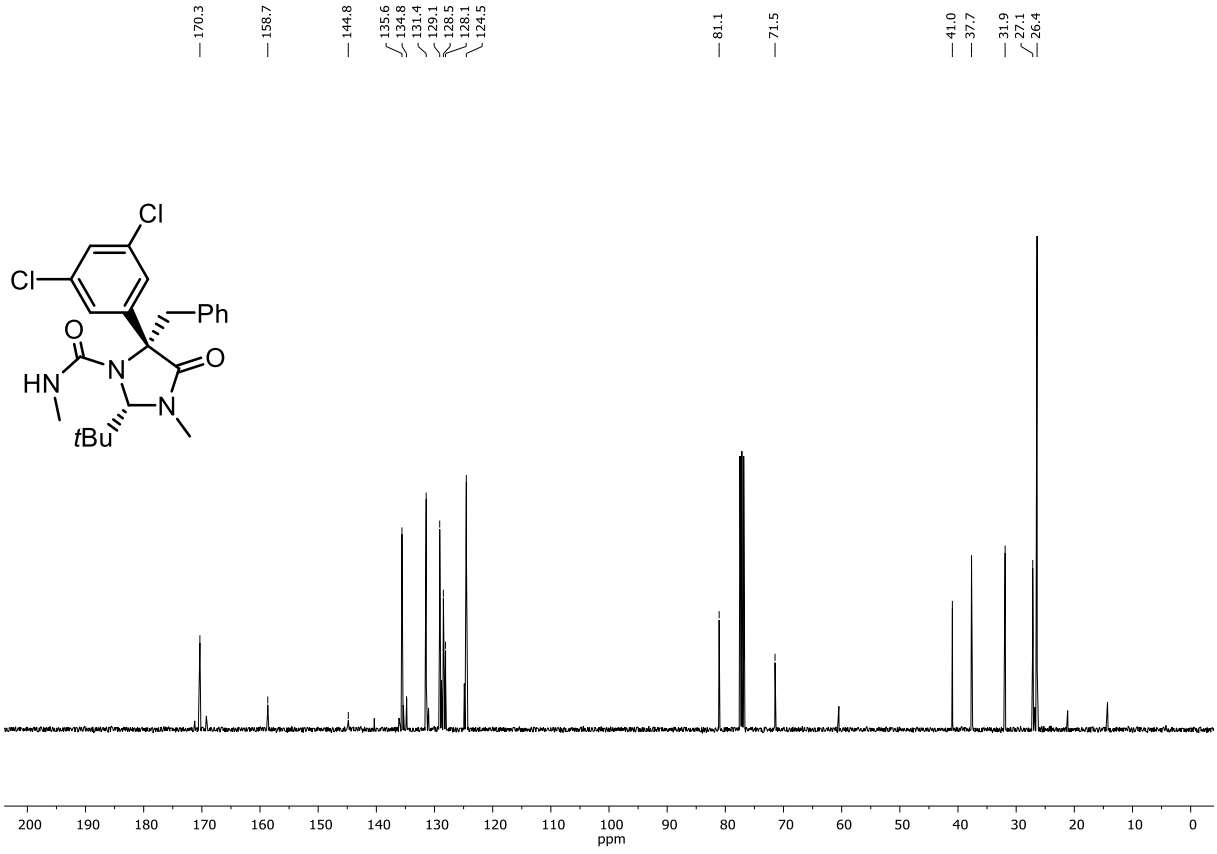
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131.4
129.1
128.5
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124.5
81.1
71.5
41.0
37.7
31.9
27.1
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Cl
Ph
O
HN
N
O
N
tBu
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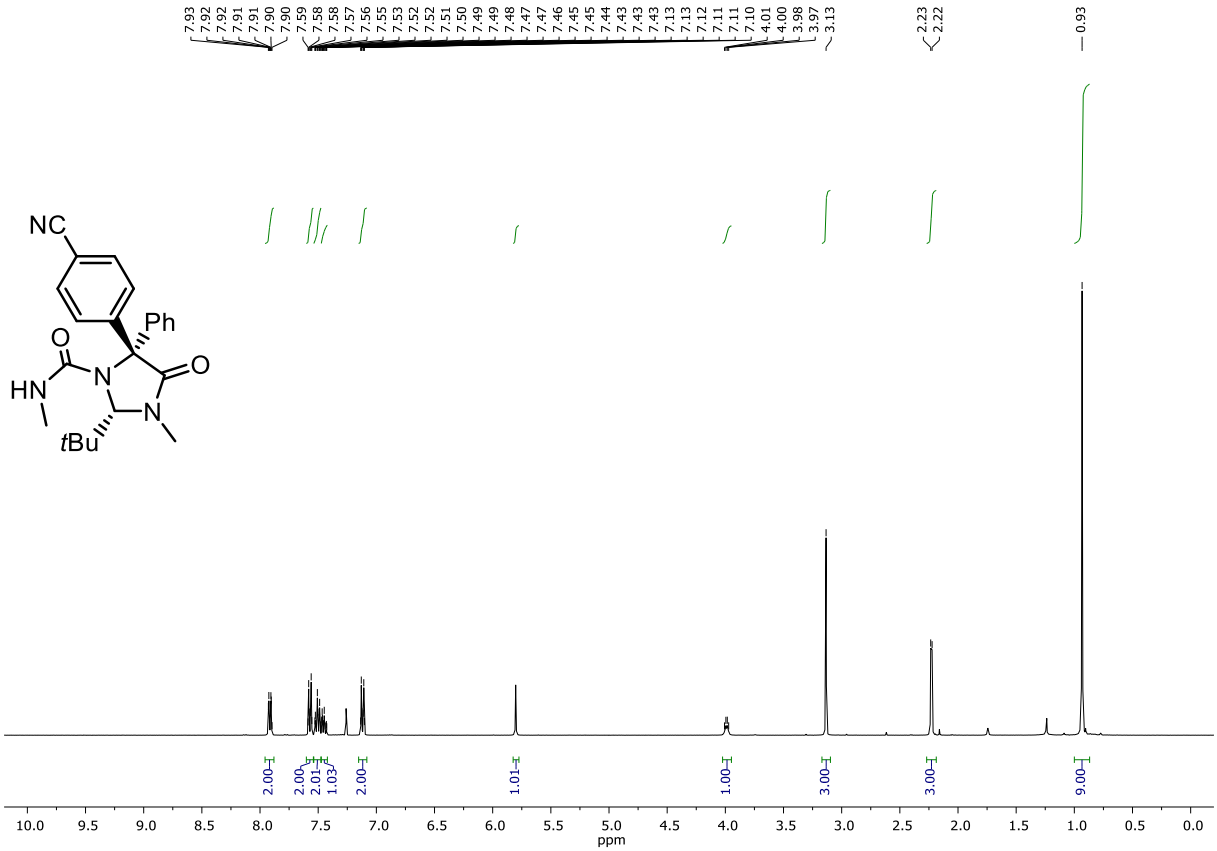
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2.23 2.22
0.93
NC
Ph
O
HN
N
O
N
tBu
2.00 2.00 2.01 1.03 2.00 1.01 1.00 3.00 3.00 9.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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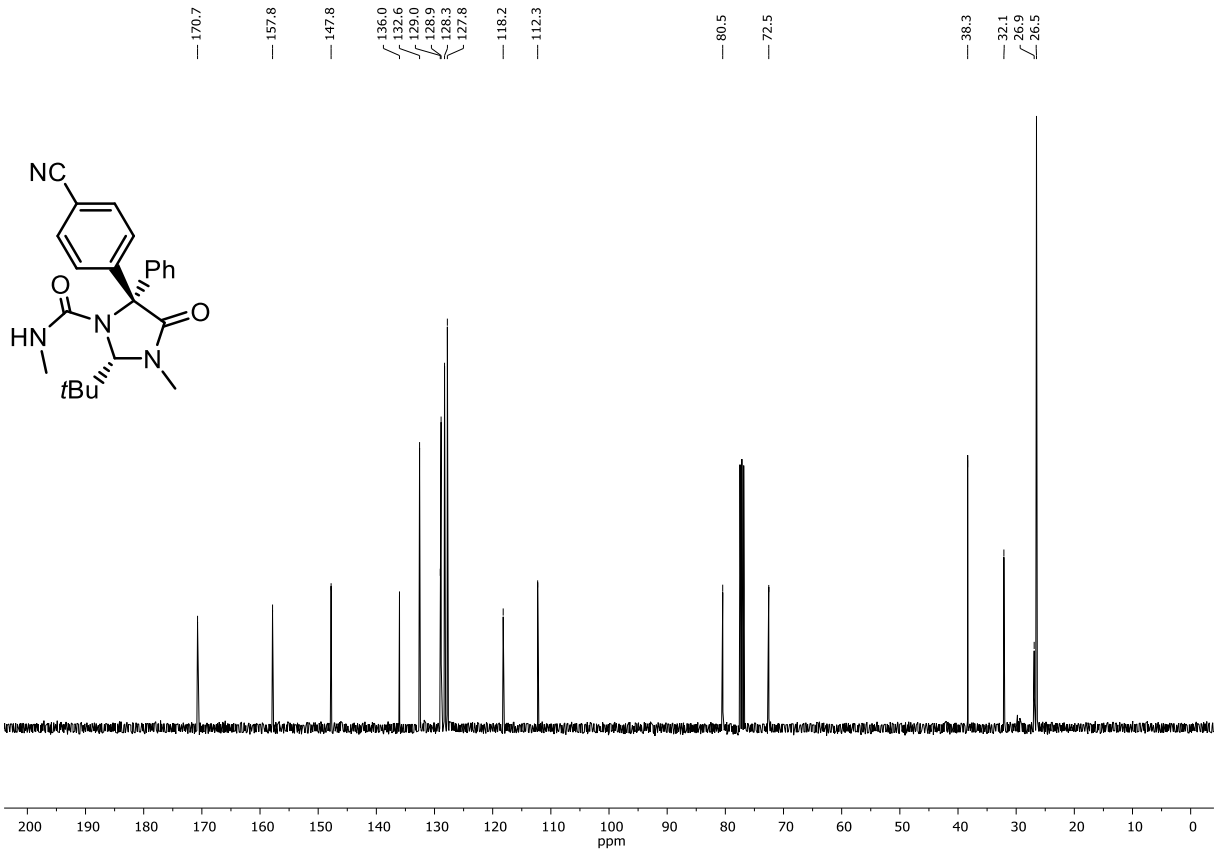
170.7 157.8 147.8 136.0 132.6 129.0 128.9 128.3 127.8 118.2 112.3 80.5 72.5 38.3 32.1 26.9 26.5
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Ph
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O
N
tBu
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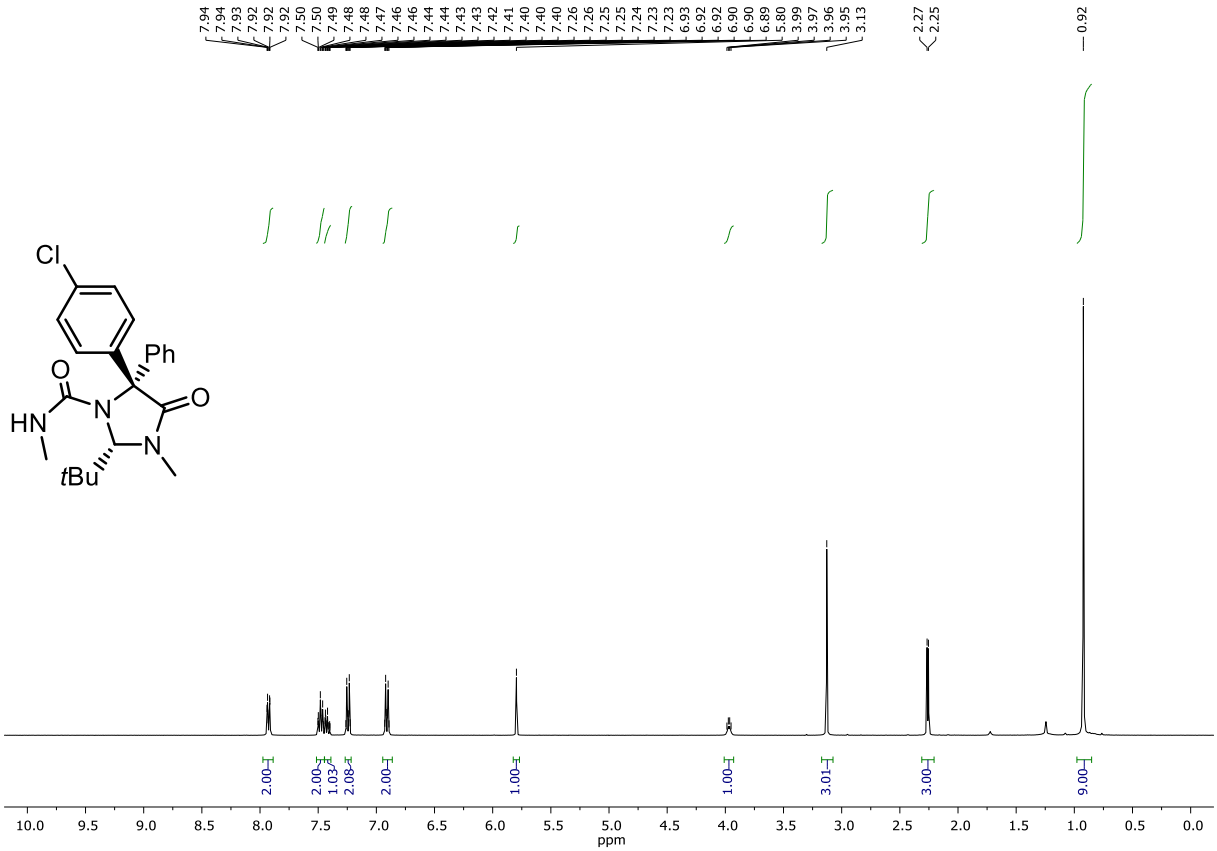
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Cl
Ph
O
HN
N
O
N
tBu
2.00 2.00 1.03 2.08 2.00 1.00 1.00 3.01 3.00 9.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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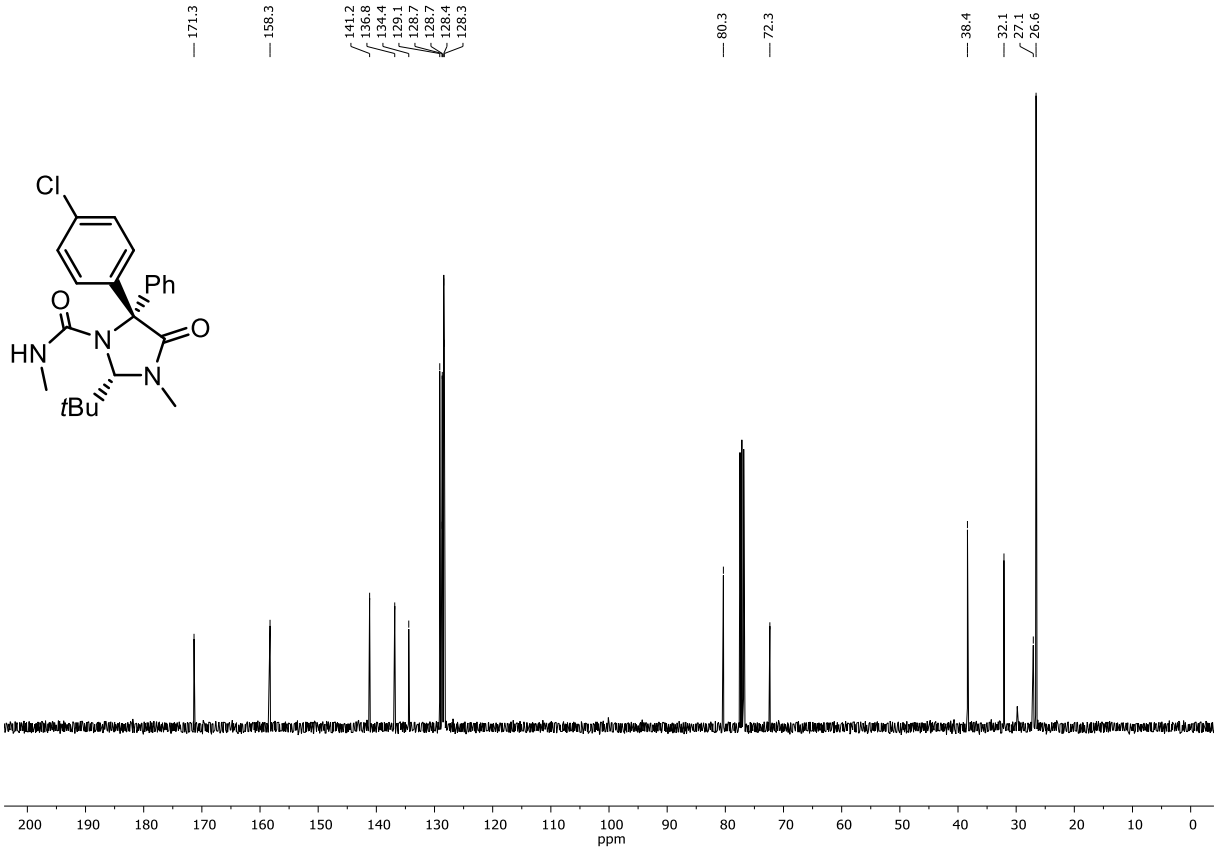
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Cl
Ph
O
HN
N
O
N
tBu
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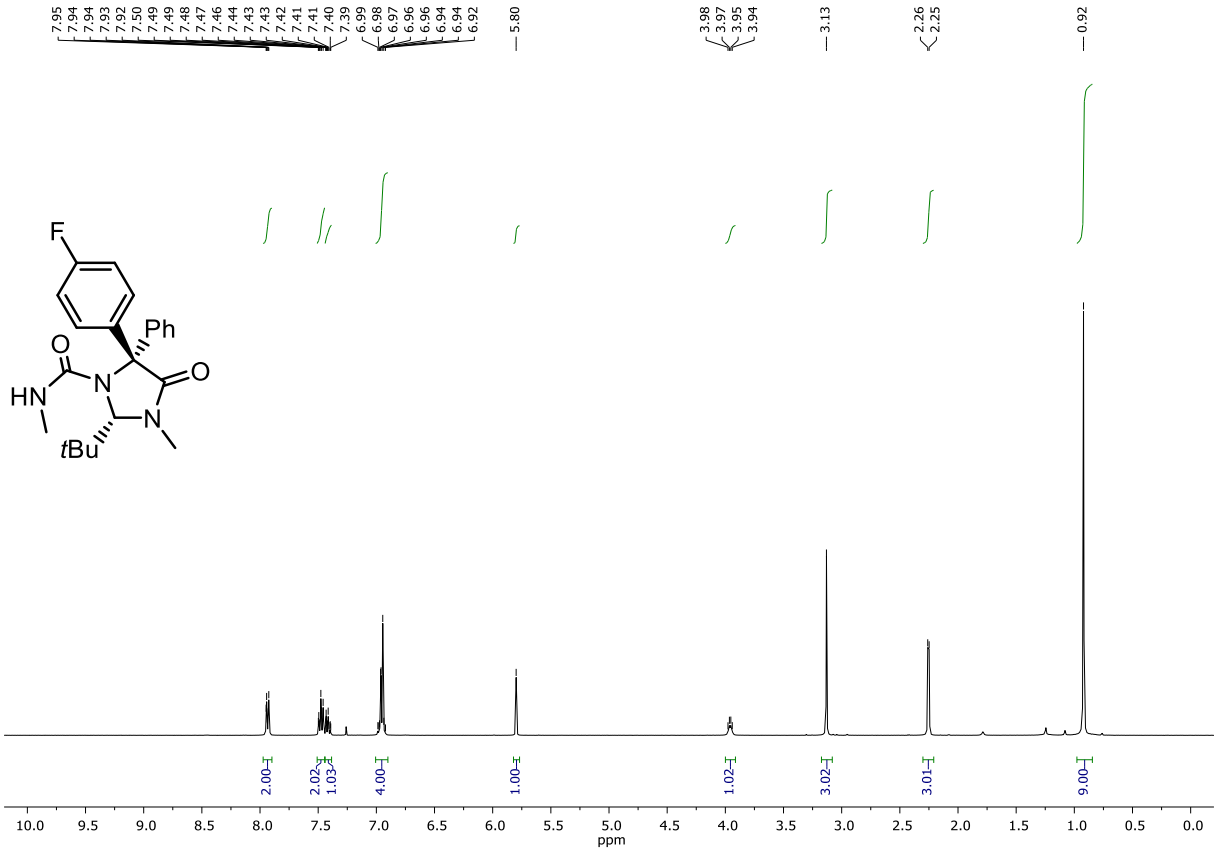
ppm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7.47
7.46
7.44
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7.41
7.41
7.40
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6.98
6.97
6.96
6.96
6.94
6.94
6.92
5.80
3.98
3.97
3.95
3.94
3.13
2.26
2.25
0.92
F
Ph
O
HN
N
O
N
tBu
2.00
2.02
1.03
4.00
1.00
1.02
3.02
3.01
9.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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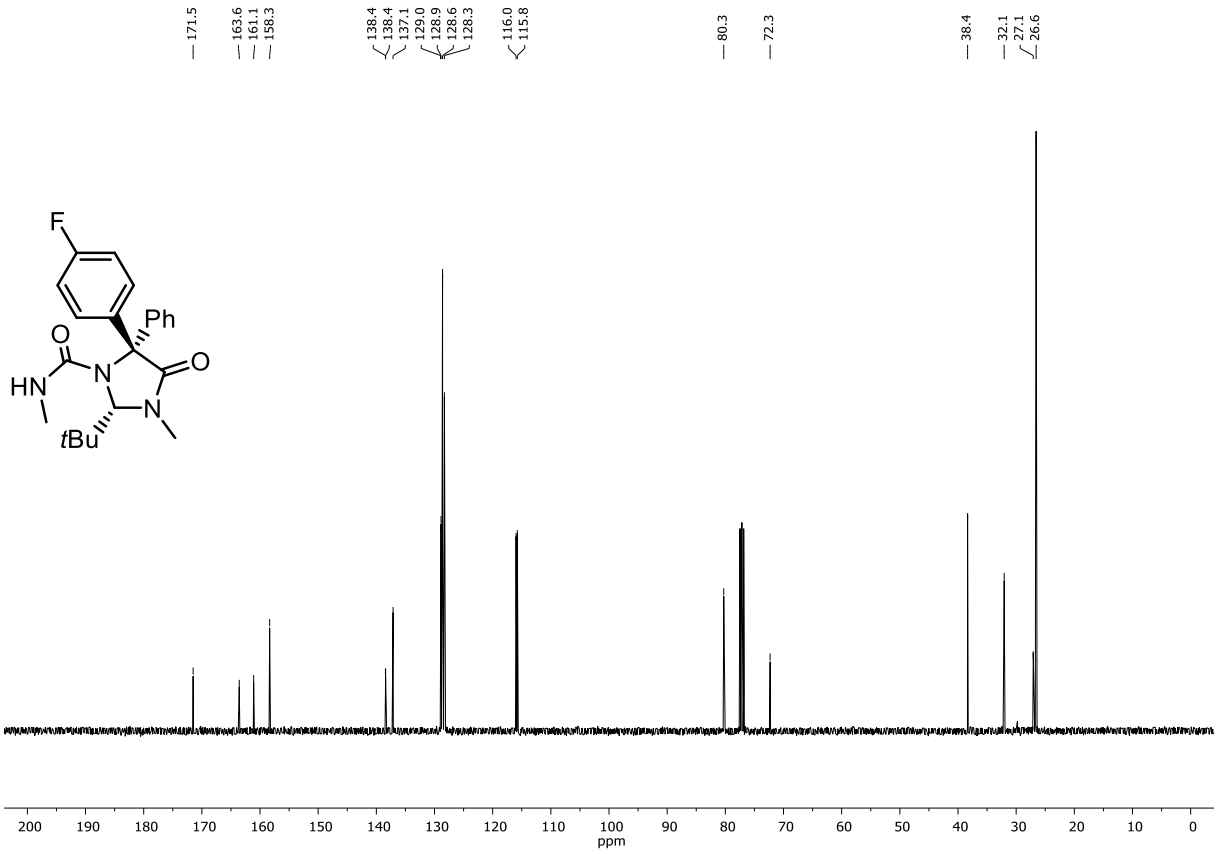
ppm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138.4
137.1
129.0
128.9
128.6
128.3
116.0
115.8
80.3
72.3
38.4
32.1
27.1
26.6
F
Ph
O
HN
N
O
N
tBu
200
190
180
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140
130
120
110
100
90
80
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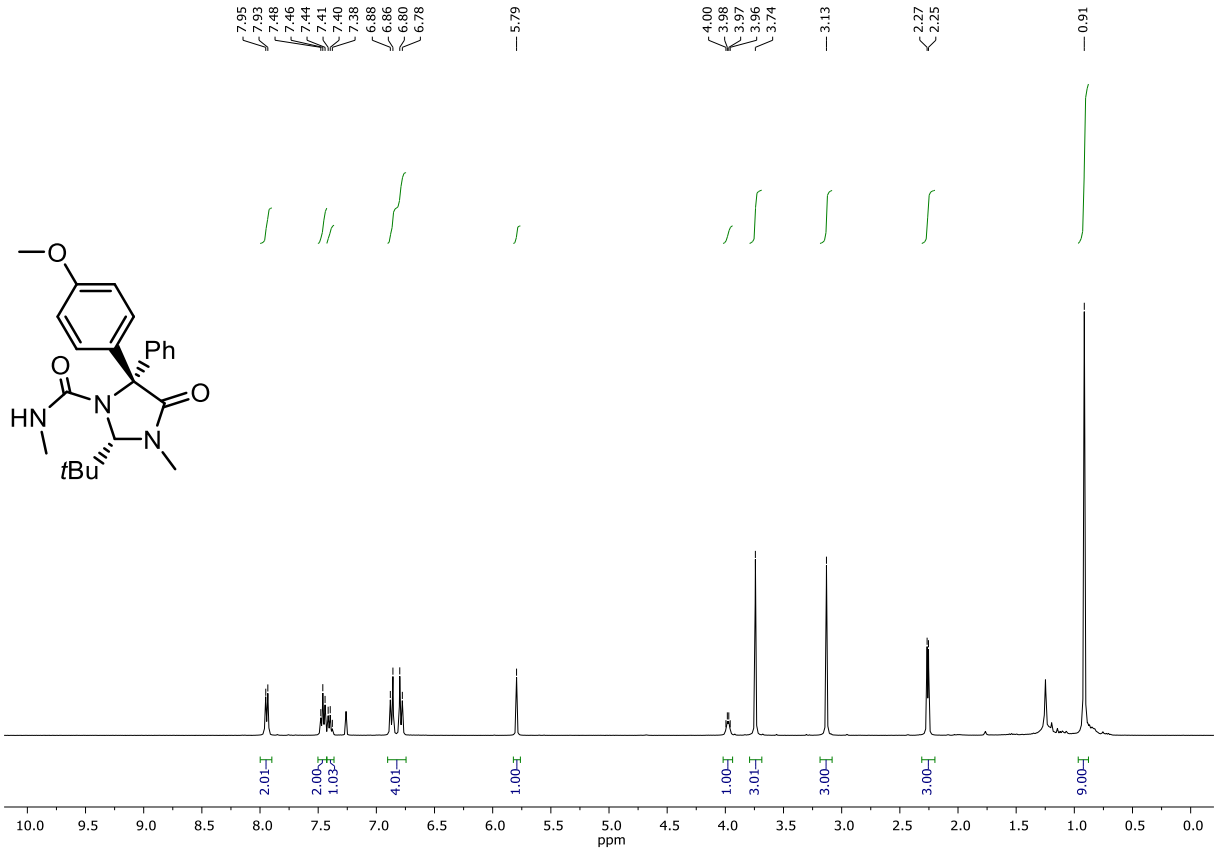
60
50
40
30
20
10
0
ppm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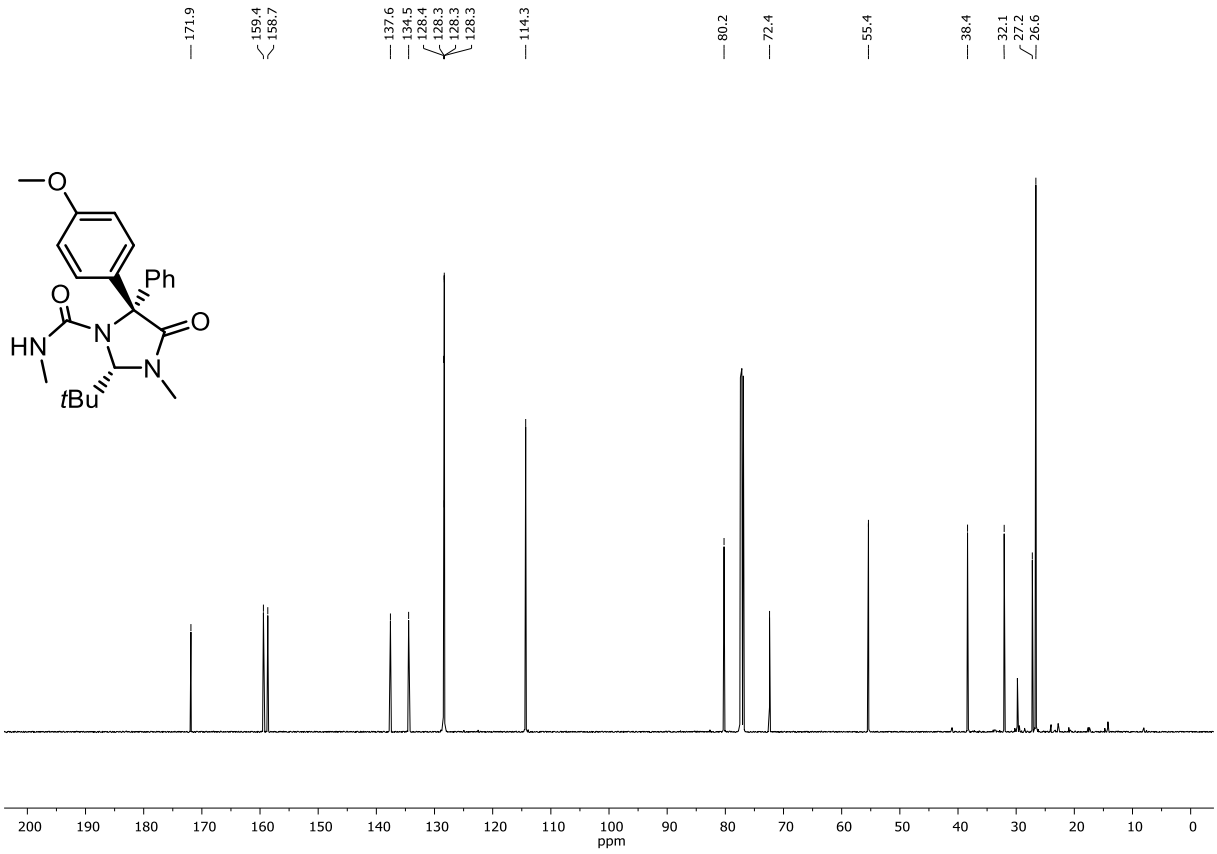
6.86
6.80
6.78
5.79
4.00
3.98
3.97
3.96
3.74
3.13
2.27
2.25
0.91
O
Ph
O
HN
N
O
N
tBu
2.01
2.00
1.03
4.01
1.00
1.00
3.01
3.00
3.00
9.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm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128.4
128.3
128.3
128.3
114.3
80.2
72.4
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38.4
32.1
27.2
26.6
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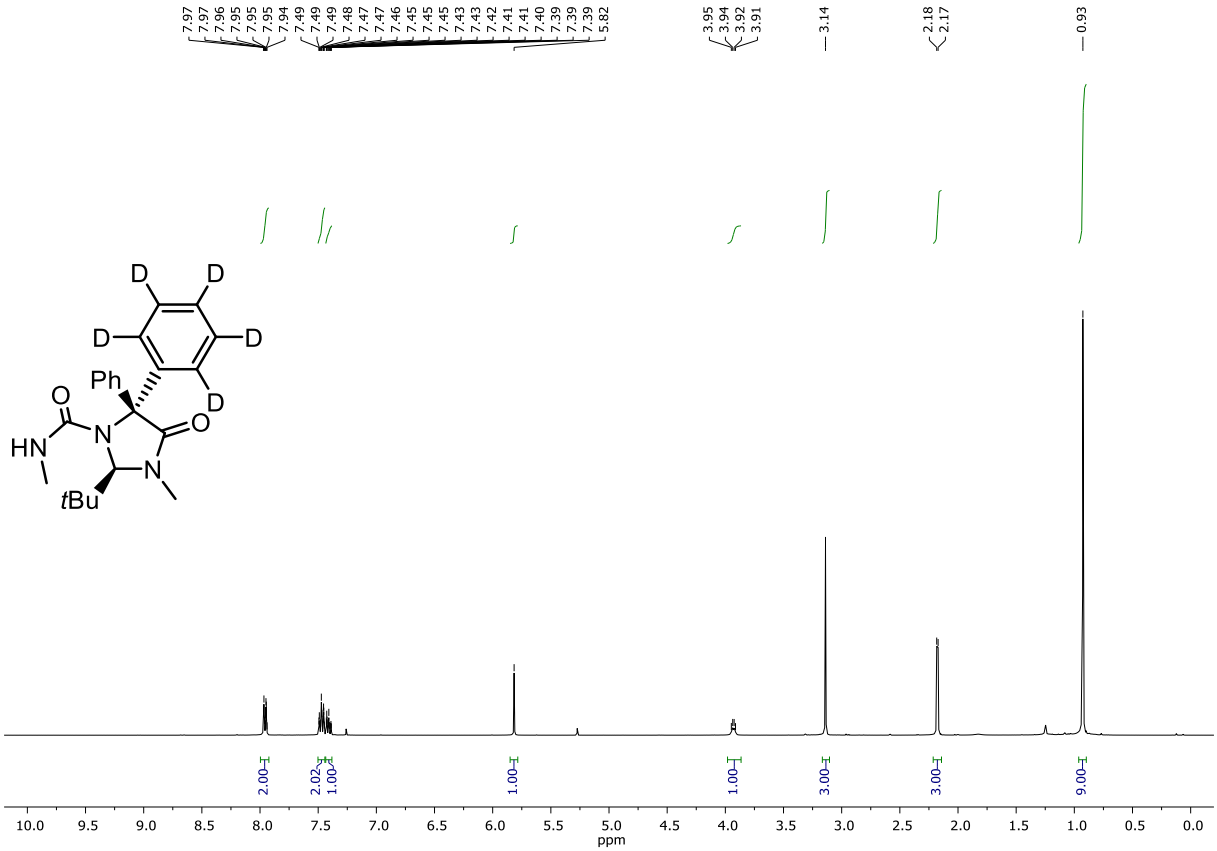
Ph
O
HN
N
O
N
tBu
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm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7.47
7.47
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7.45
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7.42
7.41
7.41
7.40
7.39
7.39
7.39
5.82
3.95
3.94
3.92
3.91
3.14
2.18
2.17
0.93
D
D
D
D
D
Ph
O
HN
N
O
N
tBu
2.00
2.02
1.00
1.00
1.00
3.00
3.00
9.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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4.0
3.5
3.0
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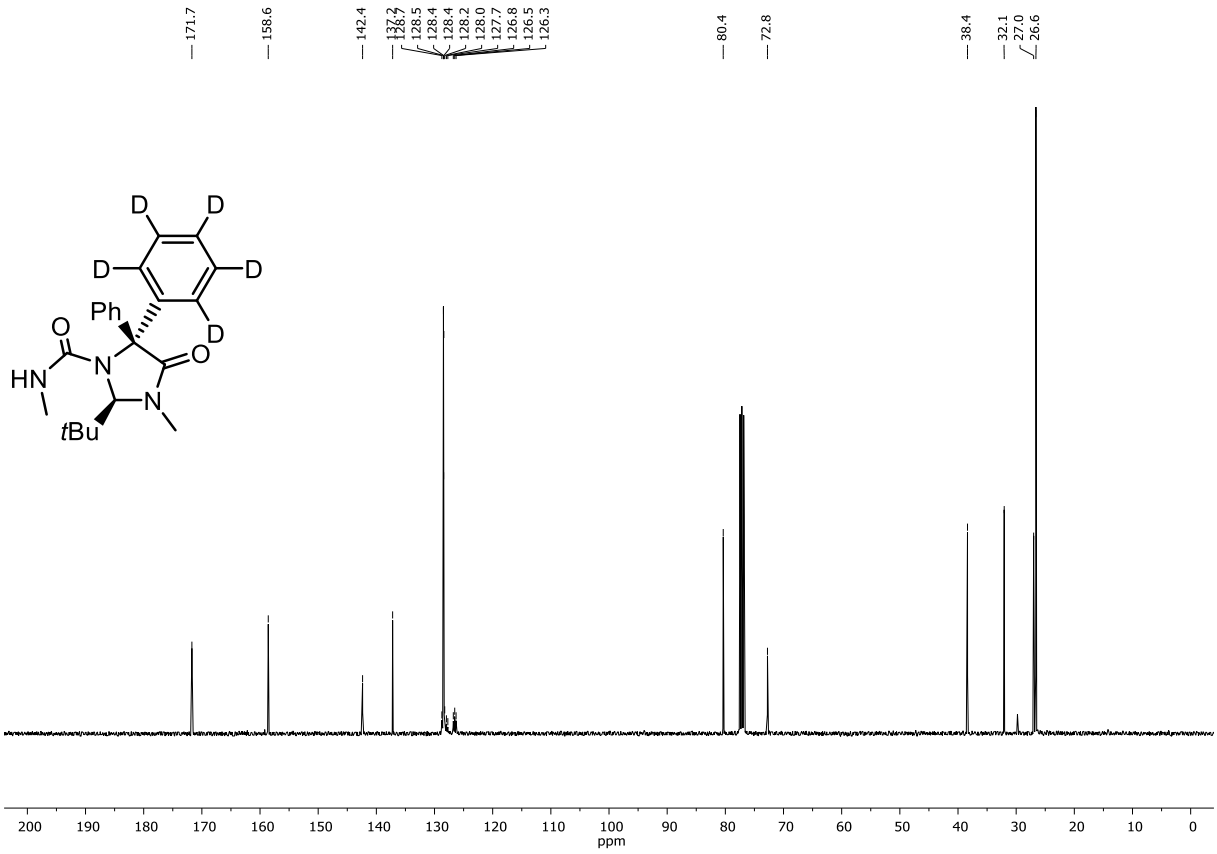
1.0
0.5
0.0
ppm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128.4
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127.7
126.8
126.5
126.3
80.4
72.8
38.4
32.1
27.0
26.6
D
D
D
D
D
Ph
O
HN
N
O
N
tBu
200
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140
130
120
110
100
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60
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20
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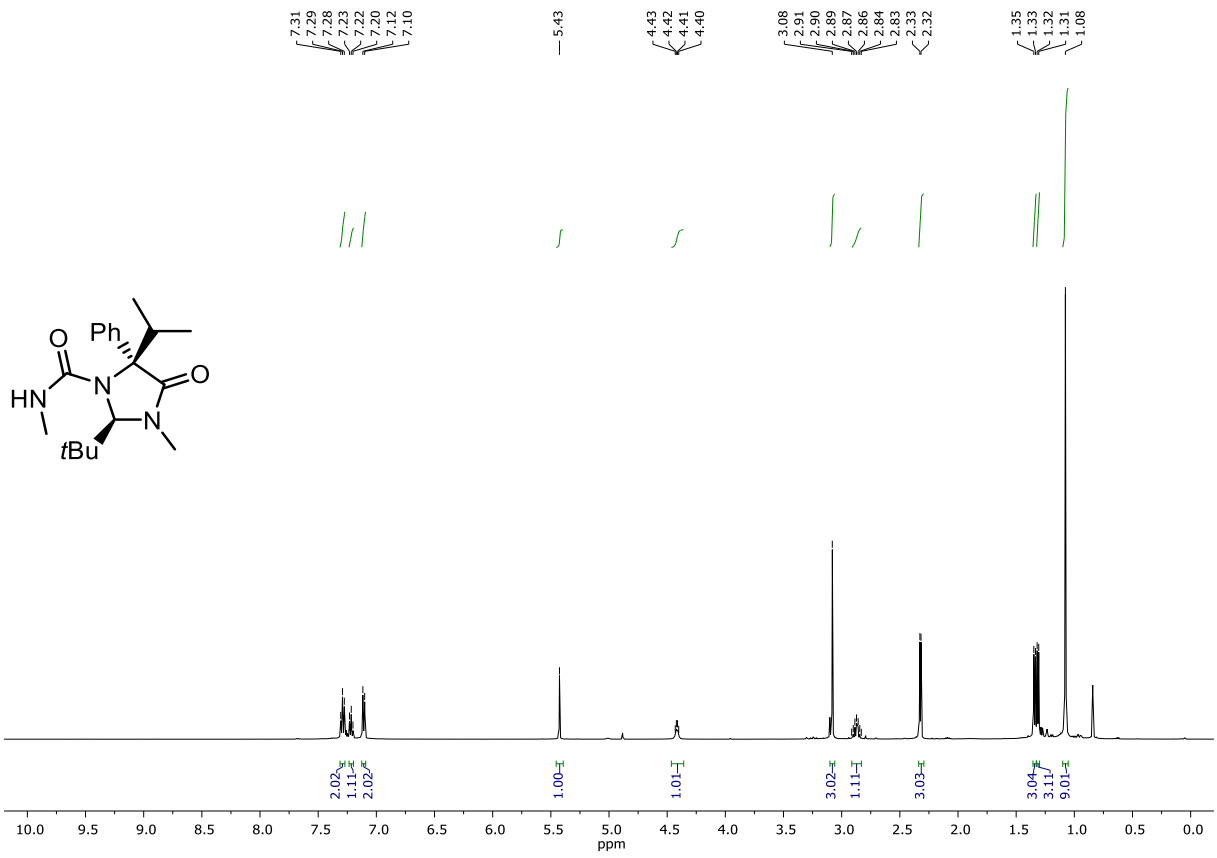
ppm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7.10
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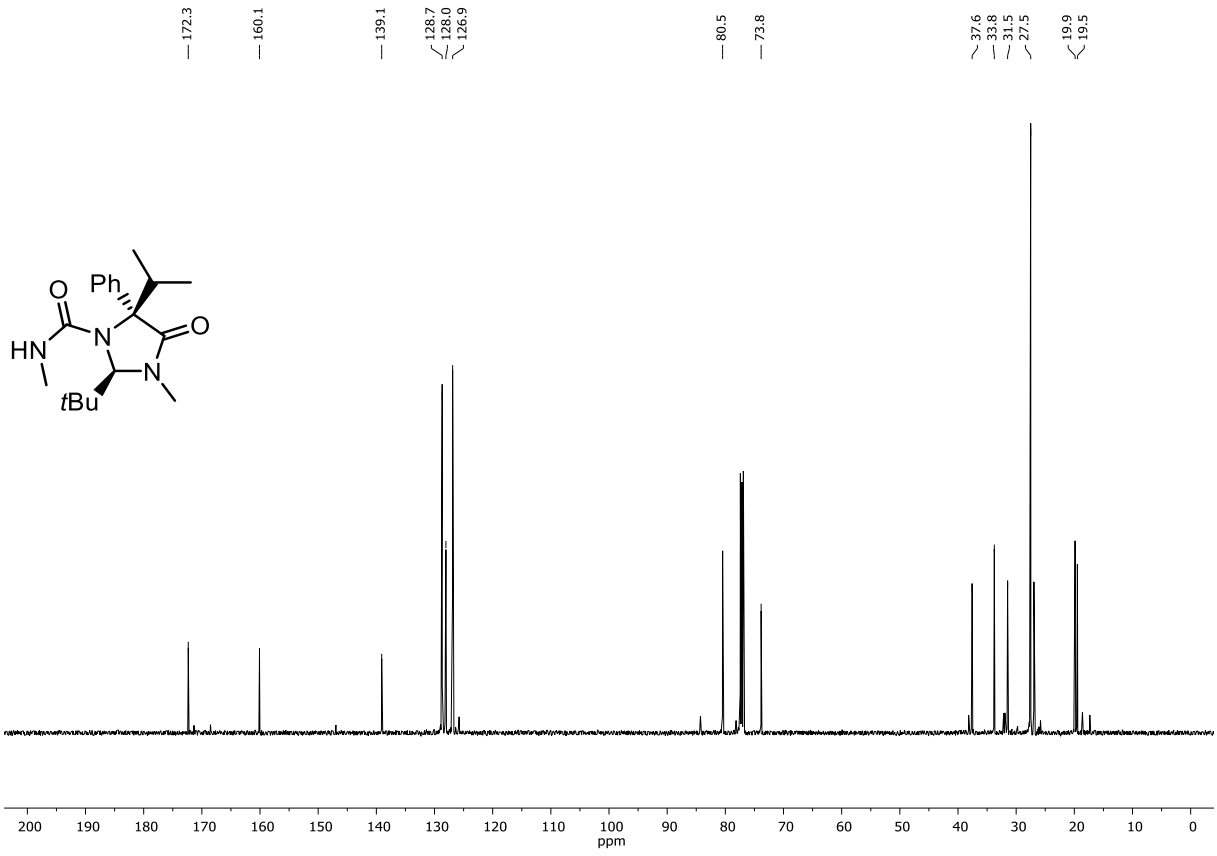
4.43
4.42
4.41
4.40
3.08
2.91
2.90
2.89
2.87
2.86
2.84
2.83
2.33
2.32
1.35
1.33
1.32
1.31
1.08
Ph
O
HN
N
O
N
tBu
2.02
1.11
2.02
1.00
1.01
3.02
1.11
3.03
3.04
3.11
9.01
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm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128.0
126.9
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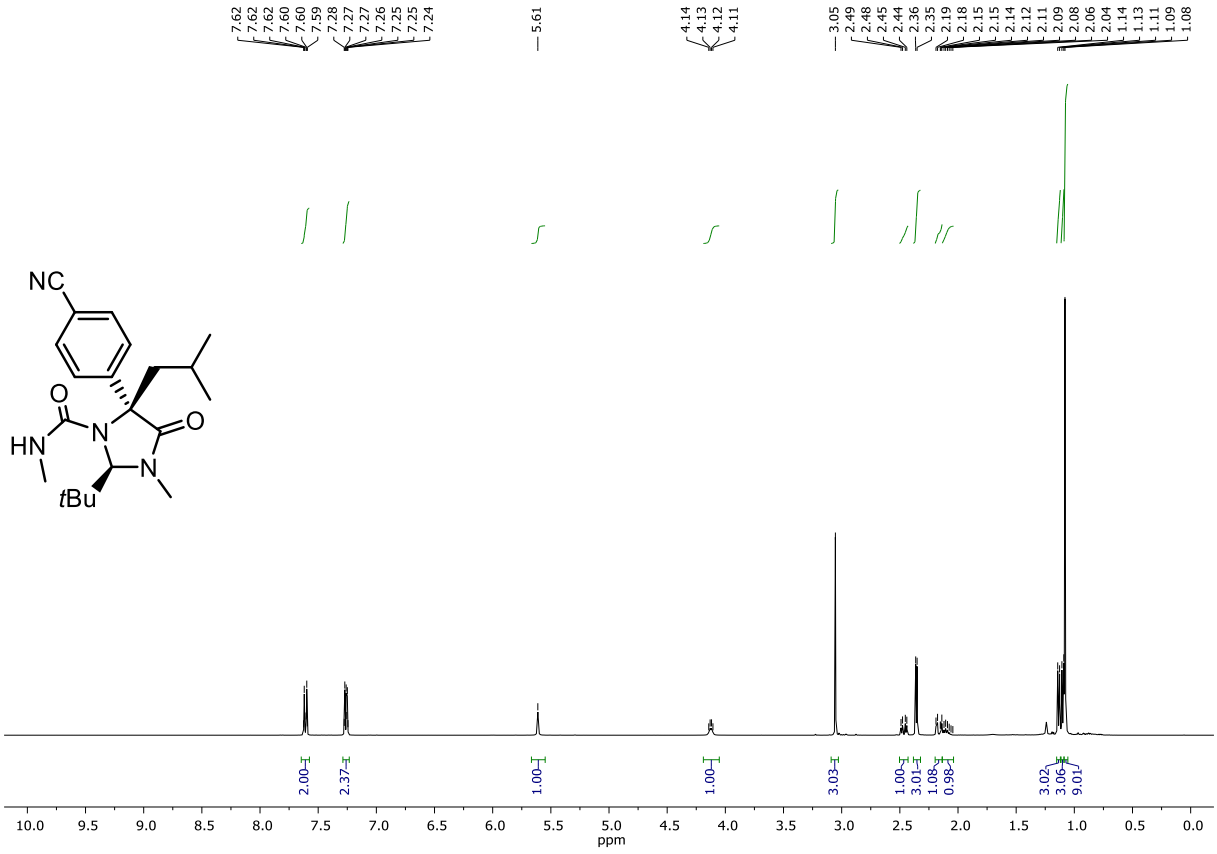
73.8
37.6
33.8
31.5
27.5
19.9
19.5
Ph
O
HN
N
O
N
tBu
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm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7.24
5.61
4.14
4.13
4.12
4.11
3.05
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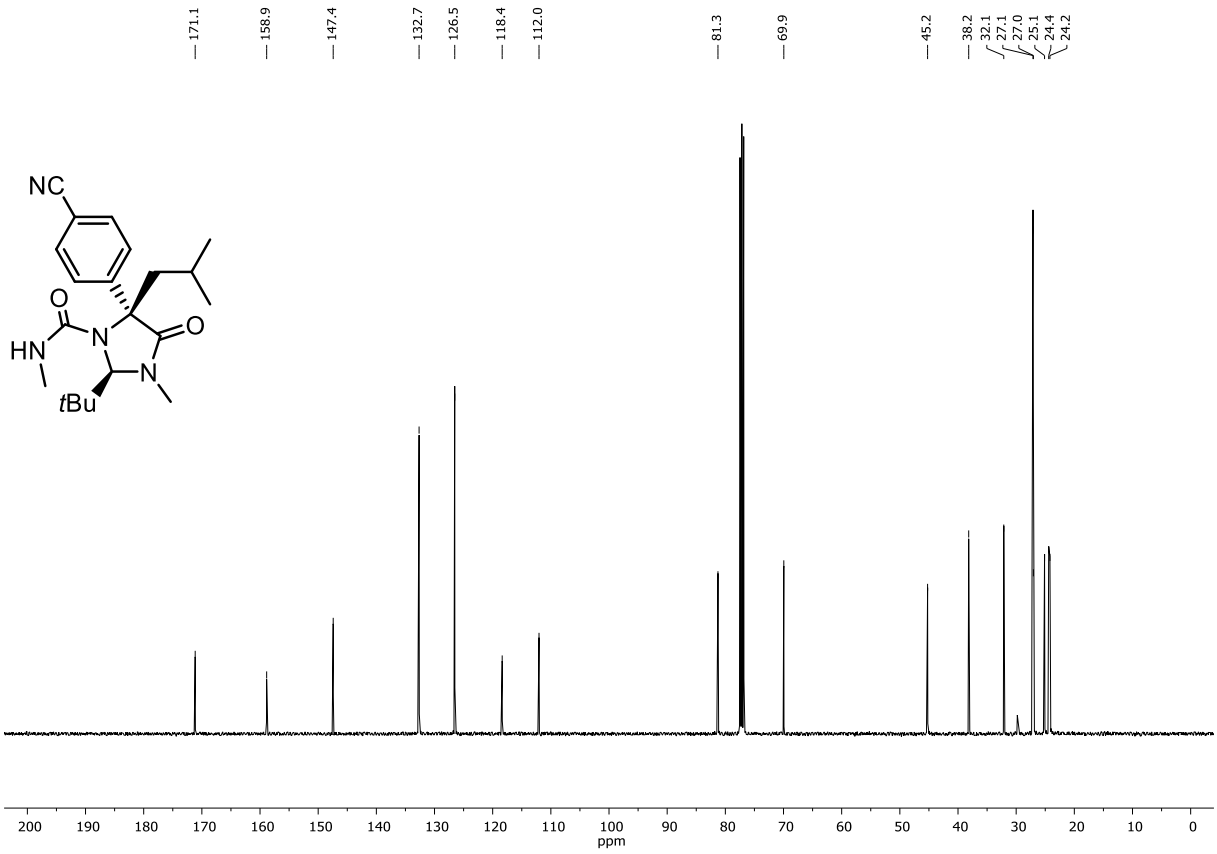
2.48
2.45
2.44
2.36
2.35
2.19
2.18
2.15
2.15
2.14
2.12
2.11
2.09
2.08
2.06
2.04
1.14
1.13
1.11
1.09
1.08
NC
O
HN
N
O
N
tBu
2.00
2.37
1.00
1.00
3.03
1.00
3.01
1.08
0.98
3.02
3.06
9.01
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm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126.5
118.4
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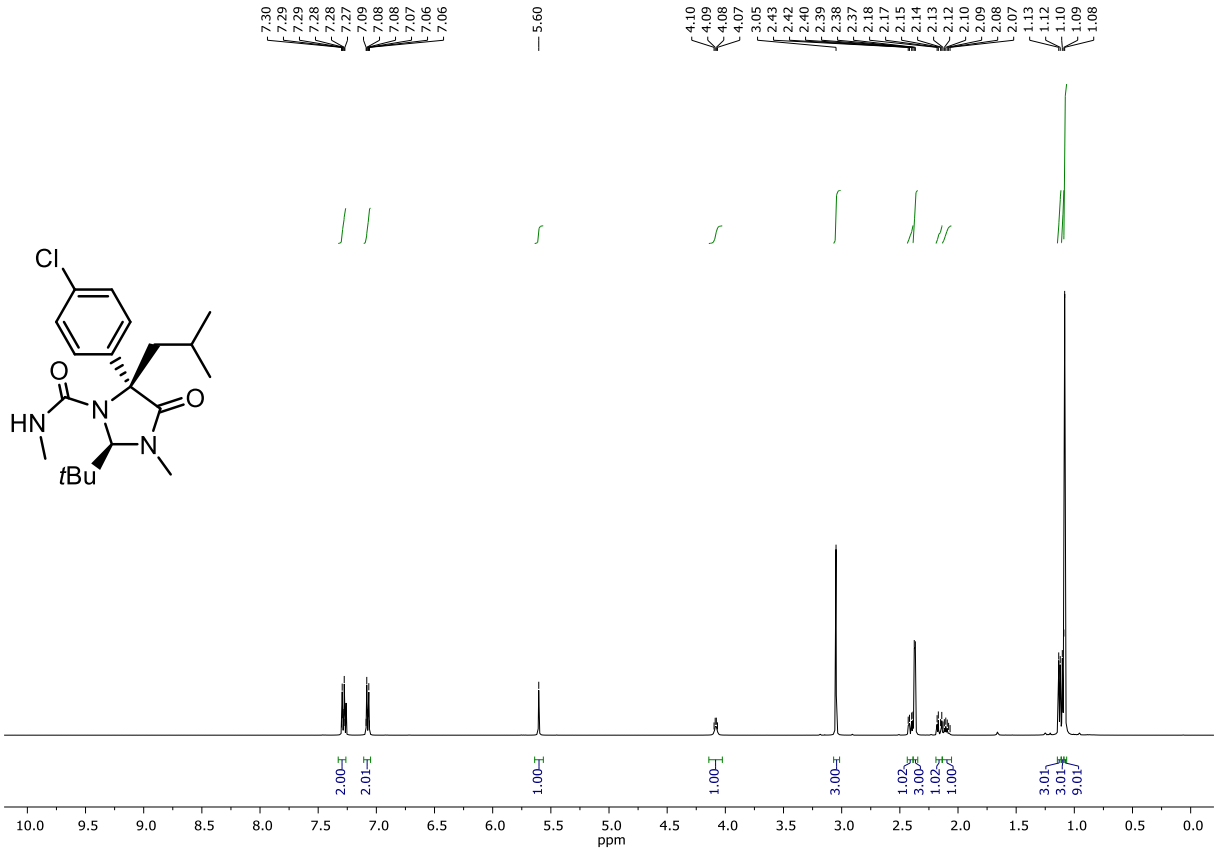
81.3
69.9
45.2
38.2
32.1
27.1
27.0
25.1
24.4
24.2
NC
O
HN
N
O
N
tBu
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm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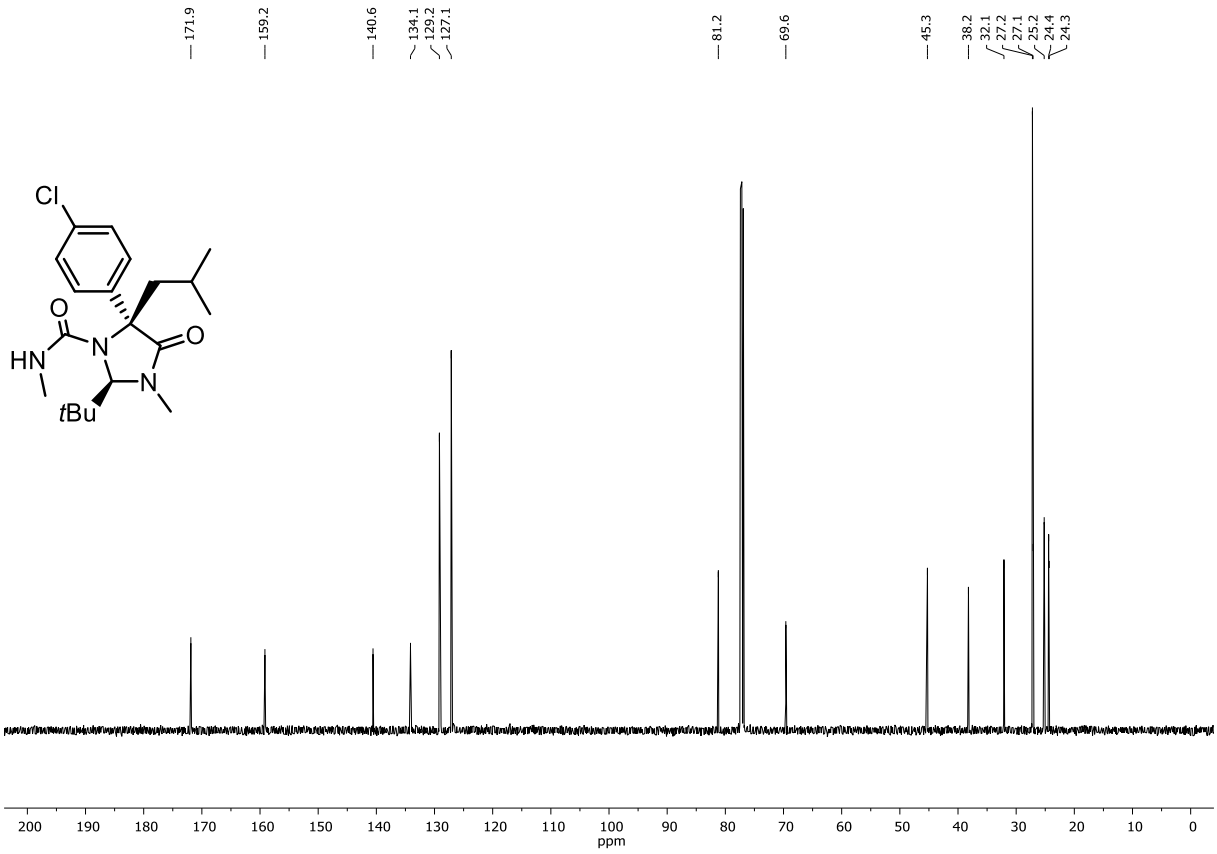
2.14
2.13
2.12
2.10
2.09
2.08
2.07
1.13
1.12
1.10
1.09
1.08
Cl
O
HN
N
O
N
tBu
2.00
2.01
1.00
1.00
3.00
1.02
3.00
1.02
1.00
3.01
3.01
9.01
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm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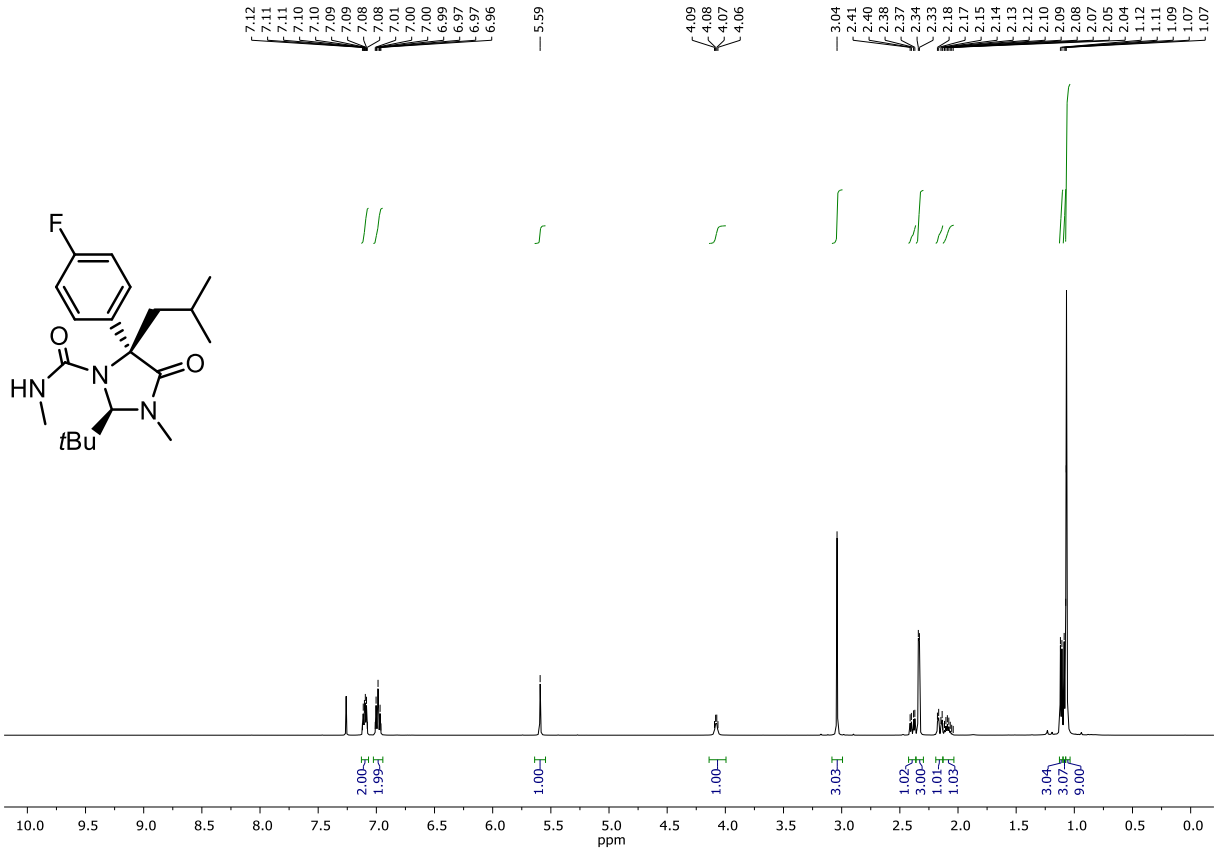
134.1
129.2
127.1
81.2
69.6
45.3
38.2
32.1
27.2
27.1
25.2
24.4
24.3
Cl
O
HN
N
O
N
tBu
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm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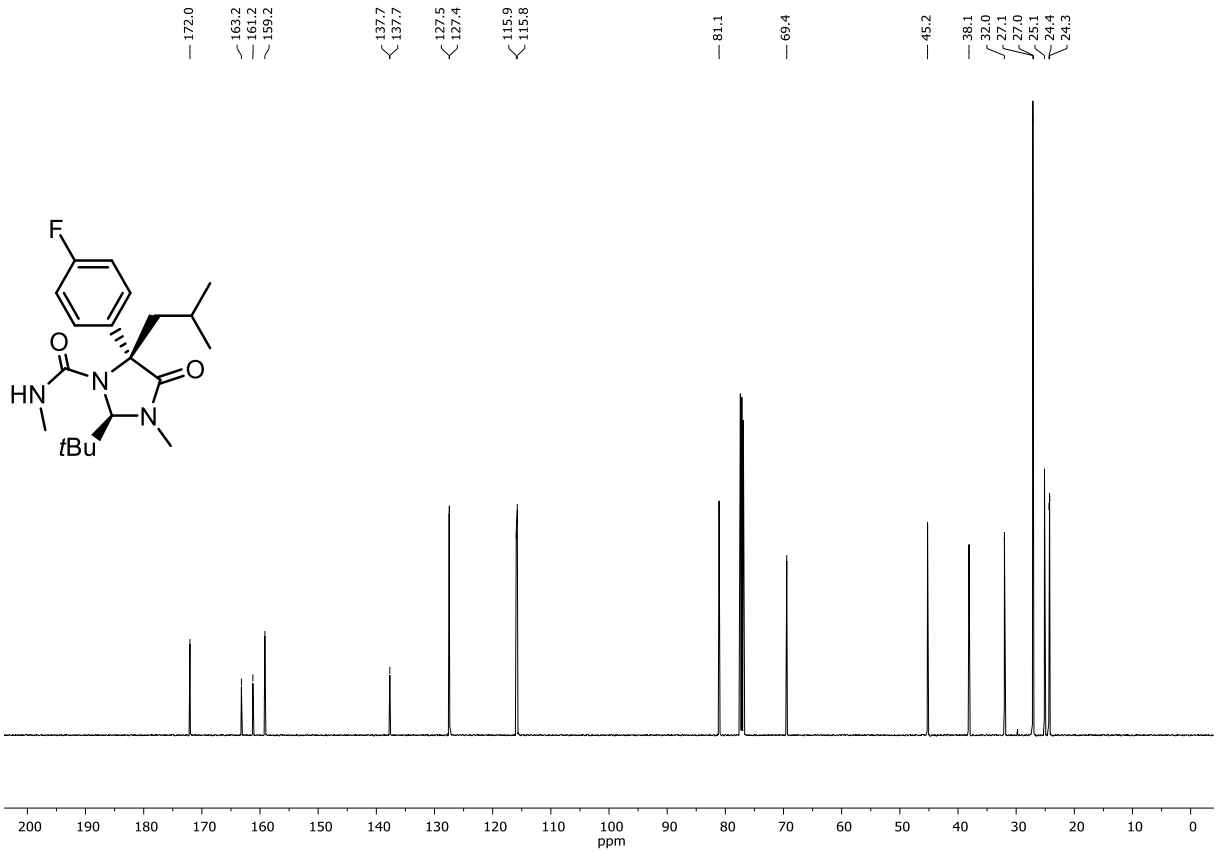
5.59
4.09 4.08 4.07 4.06
3.04 2.41 2.40 2.38 2.37 2.34 2.33 2.18 2.17 2.15 2.14 2.13 2.12 2.10 2.09 2.08 2.07 2.05 2.04 1.12 1.11 1.09 1.07 1.07
F
O
HN
N
O
N
tBu
2.00 1.99 1.00 1.00 3.03 1.02 3.00 1.01 1.03 3.04 3.07 9.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm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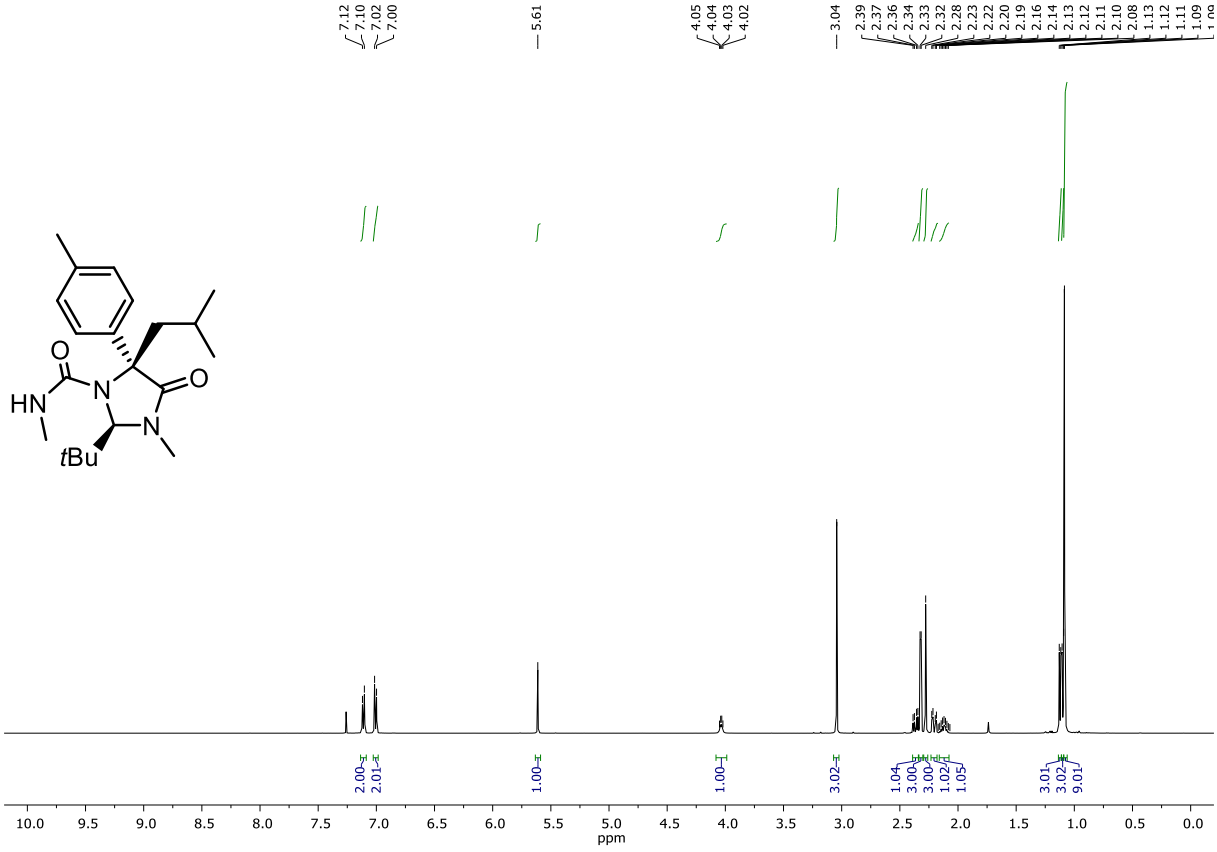
163.2 161.2 159.2
137.7 137.7
127.5 127.4
115.9 115.8
81.1
69.4
45.2
38.1
32.0
27.1
27.0
25.1
24.4
24.3
F
O
HN
N
O
N
tBu
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm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4.03
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2.39
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2.34
2.33
2.32
2.28
2.23
2.22
2.20
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2.16
2.14
2.13
2.12
2.11
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2.08
1.13
1.12
1.11
1.09
2.00
2.01
1.00
1.00
3.02
1.04
3.00
3.00
1.02
1.05
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3.02
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6.5
6.0
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4.5
4.0
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2.0
1.5
1.0
0.5
0.0
ppm
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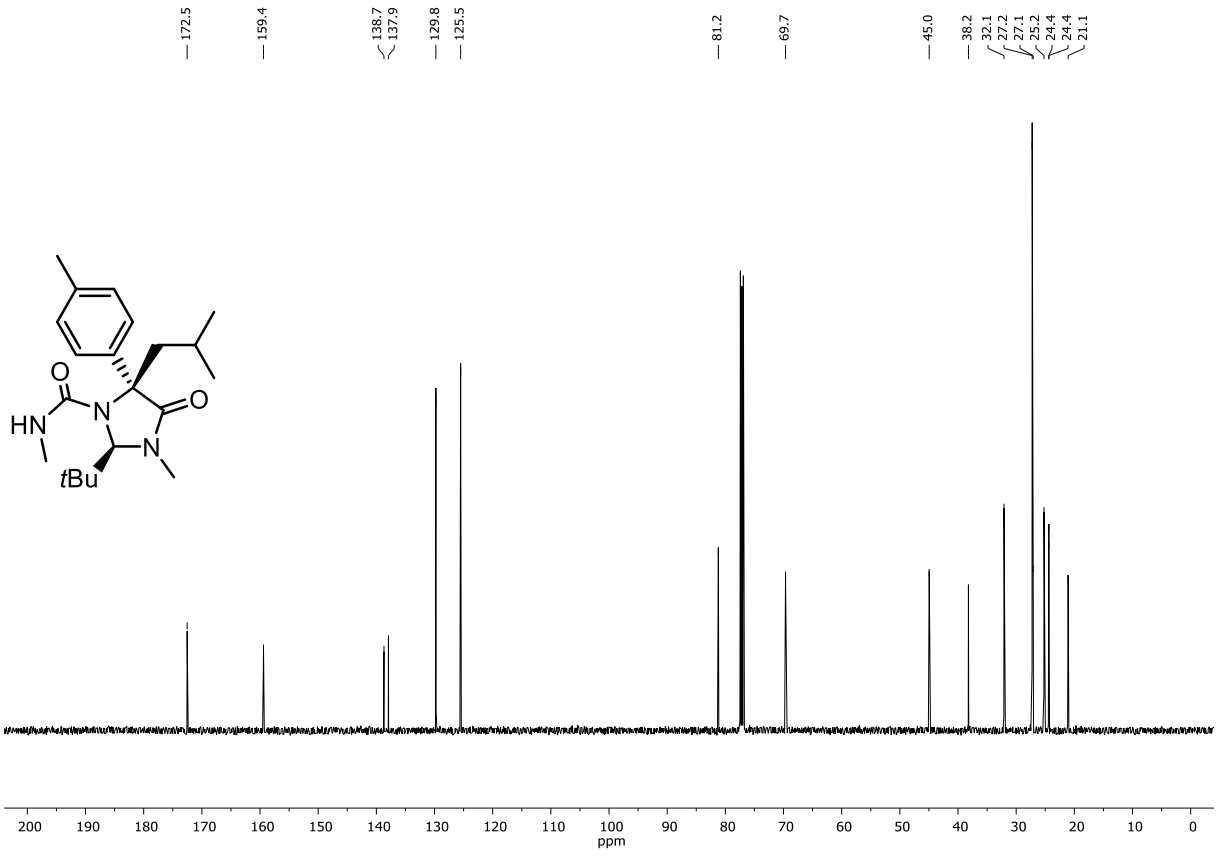
HN
N
O
N
tBu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137.9
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125.5
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69.7
45.0
38.2
32.1
27.2
27.1
25.2
24.4
24.4
21.1
200
190
180
170
160
150
140
130
120
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100
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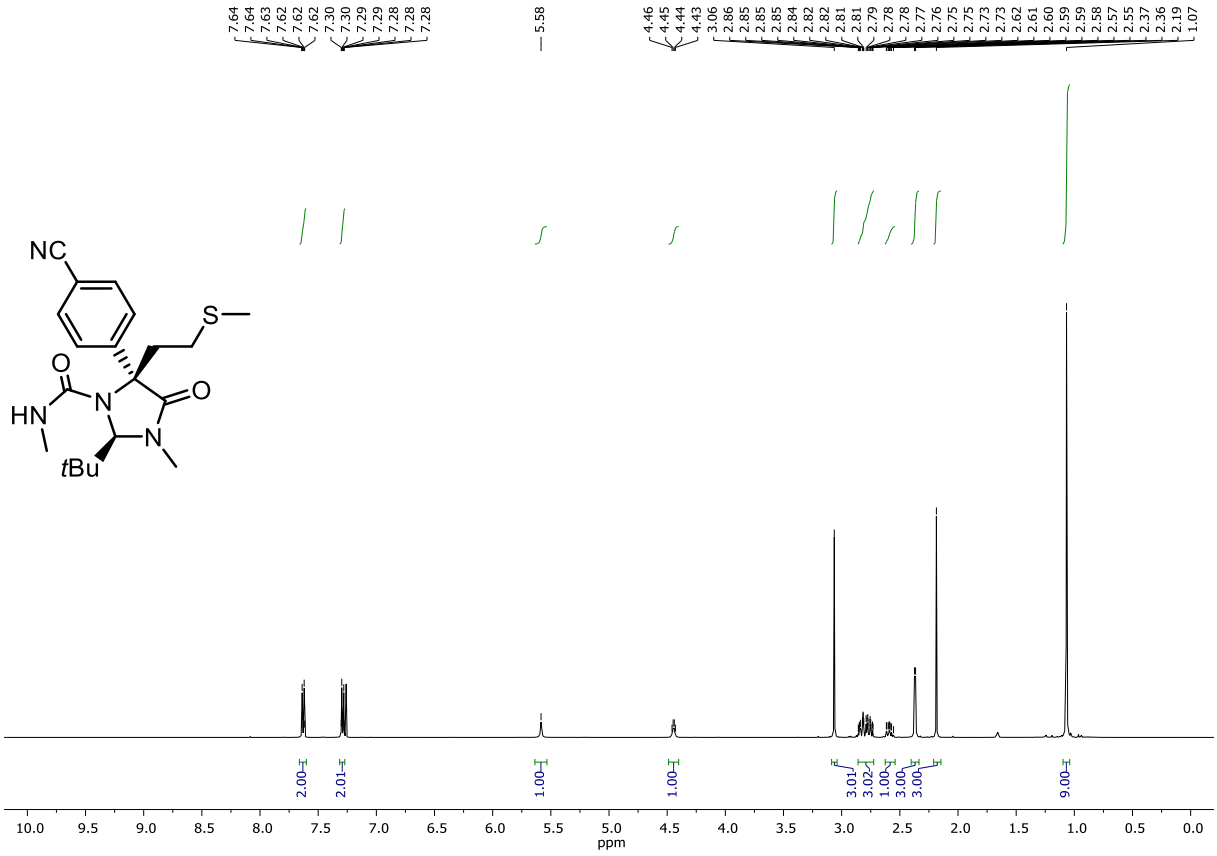
80
70
60
50
40
30
20
10
0
ppm
O
HN
N
O
N
tBu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7.29
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NC
S
O
HN
N
O
N
tBu
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1.00
1.00
3.01
3.02
1.00
3.00
3.00
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9.0
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8.0
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7.0
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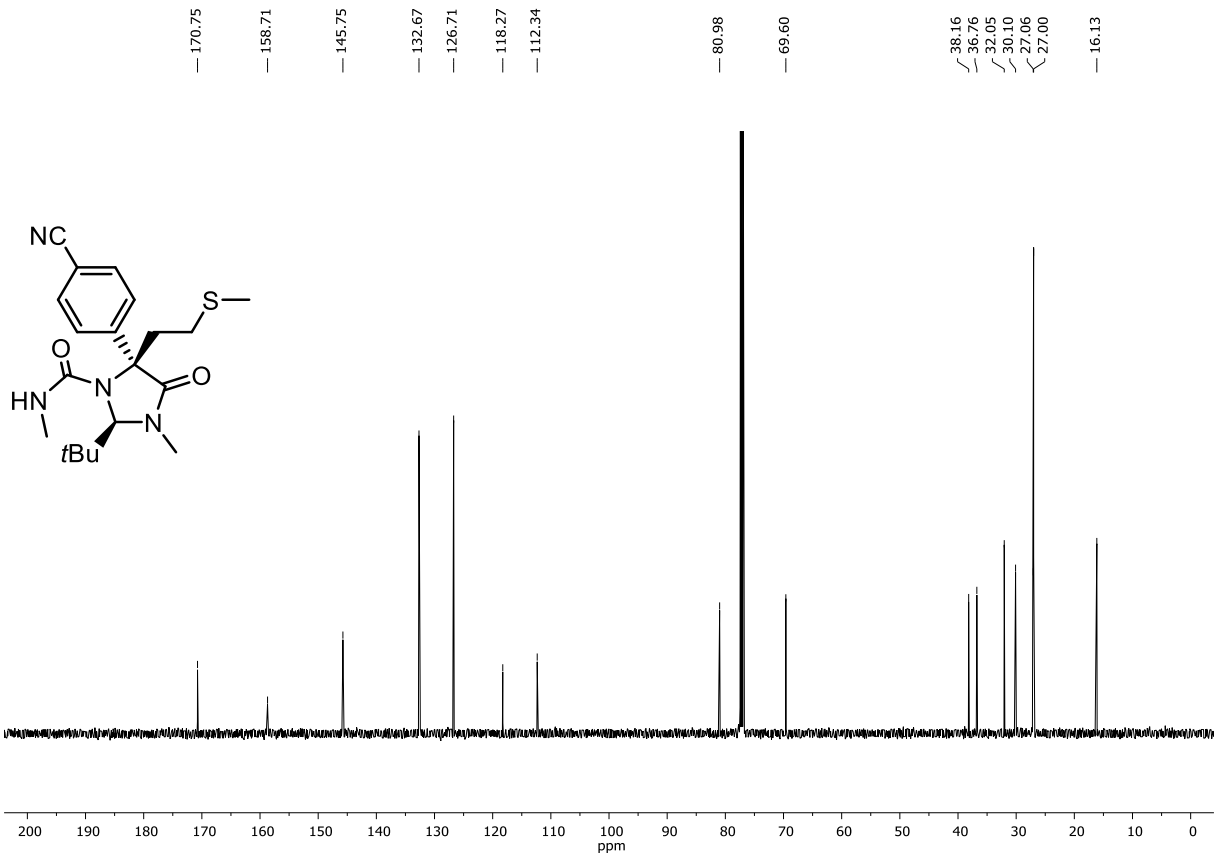
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27.06
27.00
16.13
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S
O
HN
N
O
N
tBu
200
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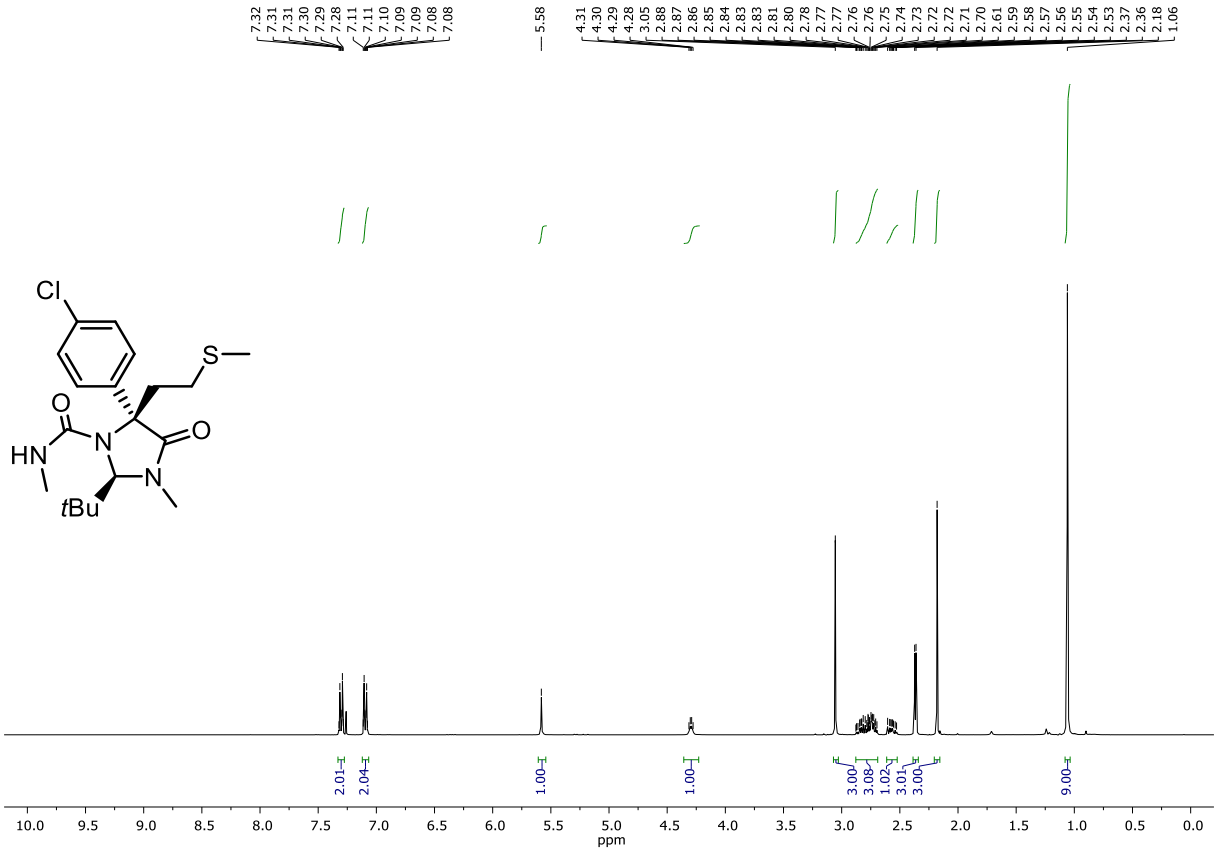
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Cl
S
O
HN
N
O
N
tBu
2.01 2.04 1.00 1.00 3.00 3.08 1.02 3.01 3.00 9.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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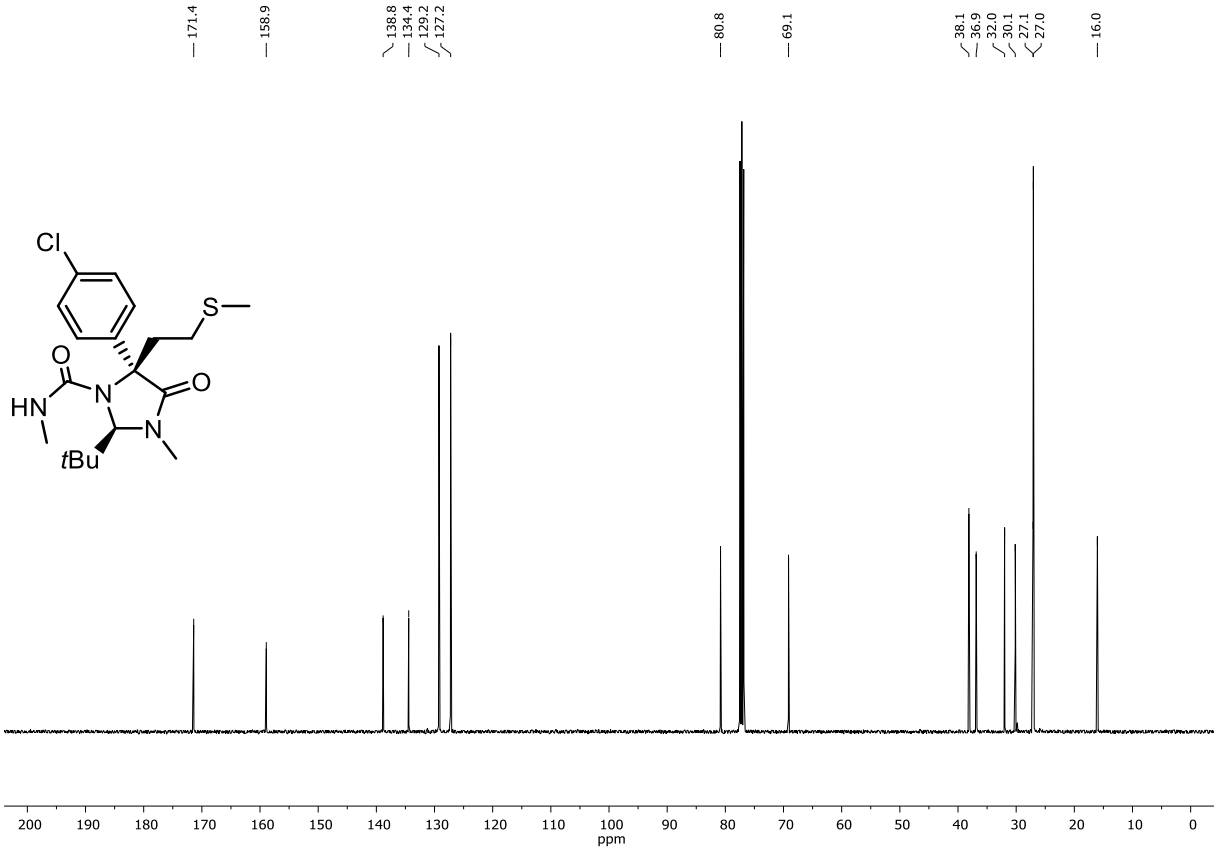
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138.8 134.4 129.2 127.2
80.8
69.1
38.1 36.9 32.0 30.1 27.1 27.0
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Cl
S
O
HN
N
O
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tBu
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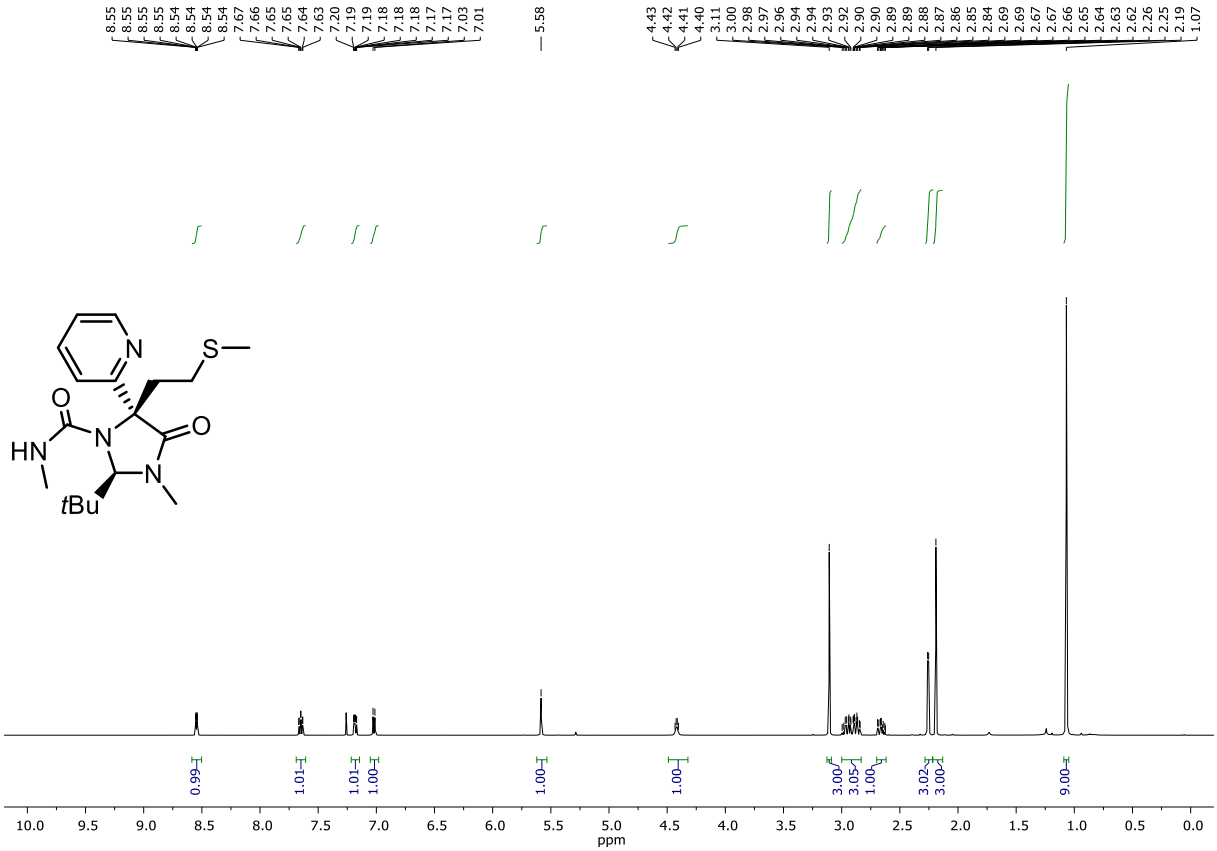
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5.58
4.43 4.42 4.41 4.40 3.11 3.00 2.98 2.97 2.96 2.94 2.94 2.93 2.92 2.90 2.90 2.89 2.89 2.88 2.87 2.86 2.85 2.84 2.69 2.69 2.67 2.67 2.66 2.65 2.64 2.63 2.62 2.26 2.25 2.19 1.07
0.99 1.01 1.01 1.00 1.00 1.00 3.00 3.05 1.00 3.02 3.00 9.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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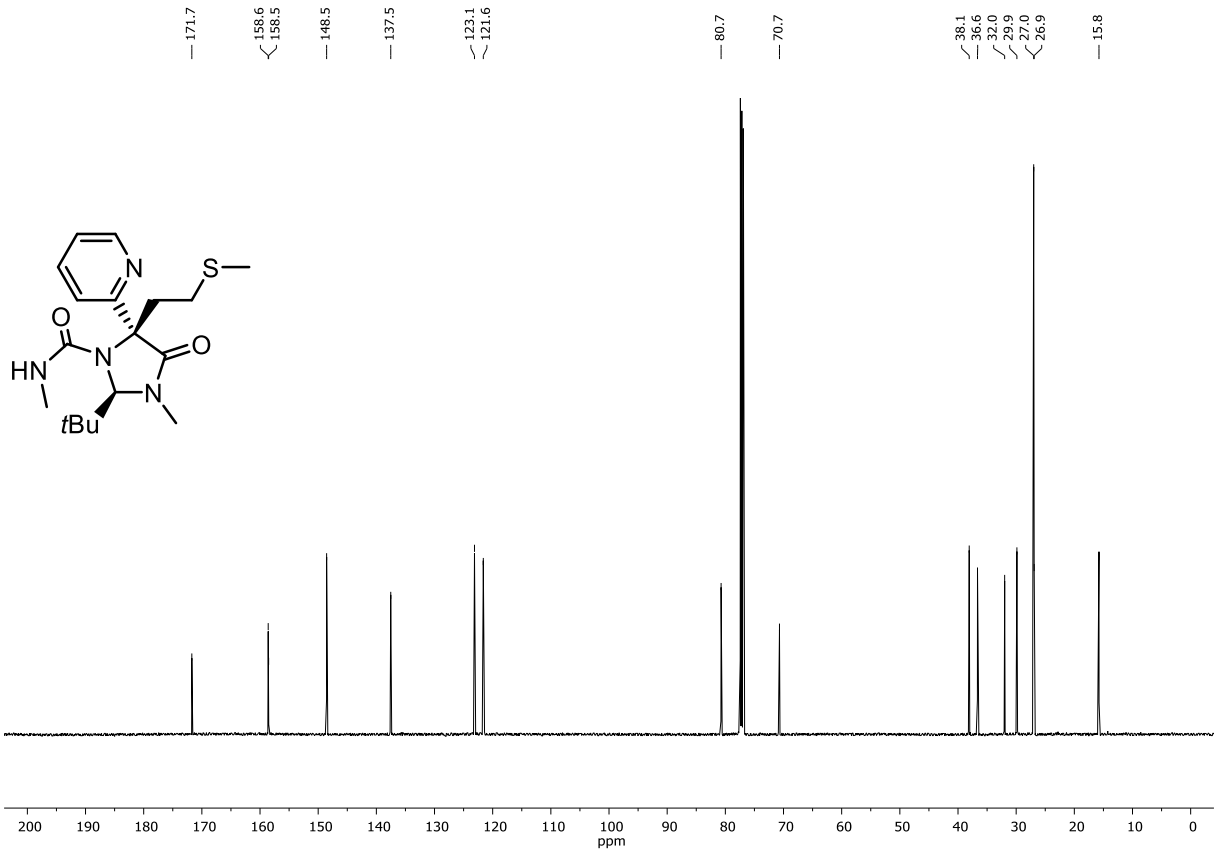
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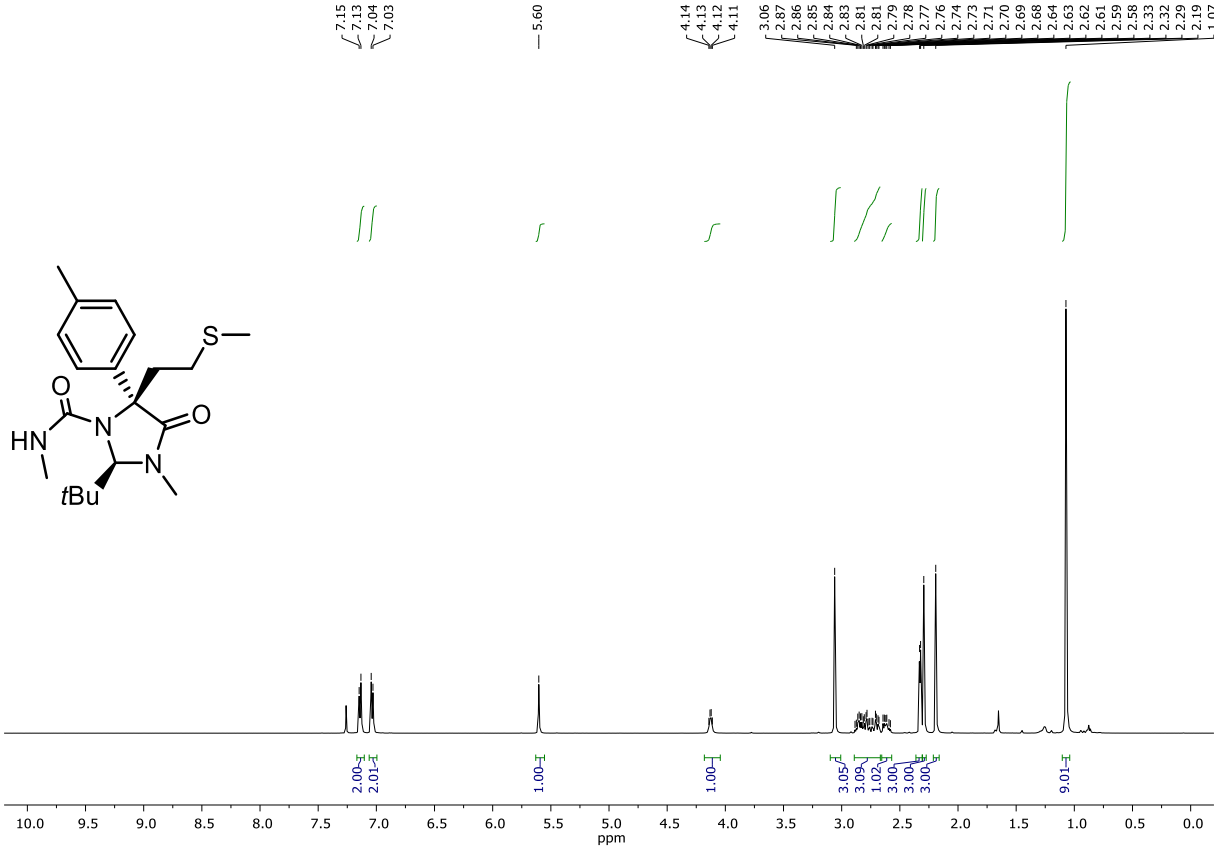
158.6 158.5
148.5
137.5
123.1 121.6
80.7
70.7
38.1 36.6 32.0 29.9 27.0 26.9
15.8
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm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2.81
2.79
2.78
2.77
2.76
2.74
2.73
2.71
2.70
2.69
2.68
2.64
2.63
2.62
2.61
2.59
2.58
2.33
2.32
2.29
2.19
2.00
2.01
1.00
1.00
3.05
3.09
1.02
3.00
3.00
3.00
9.01
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
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0.5
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ppm
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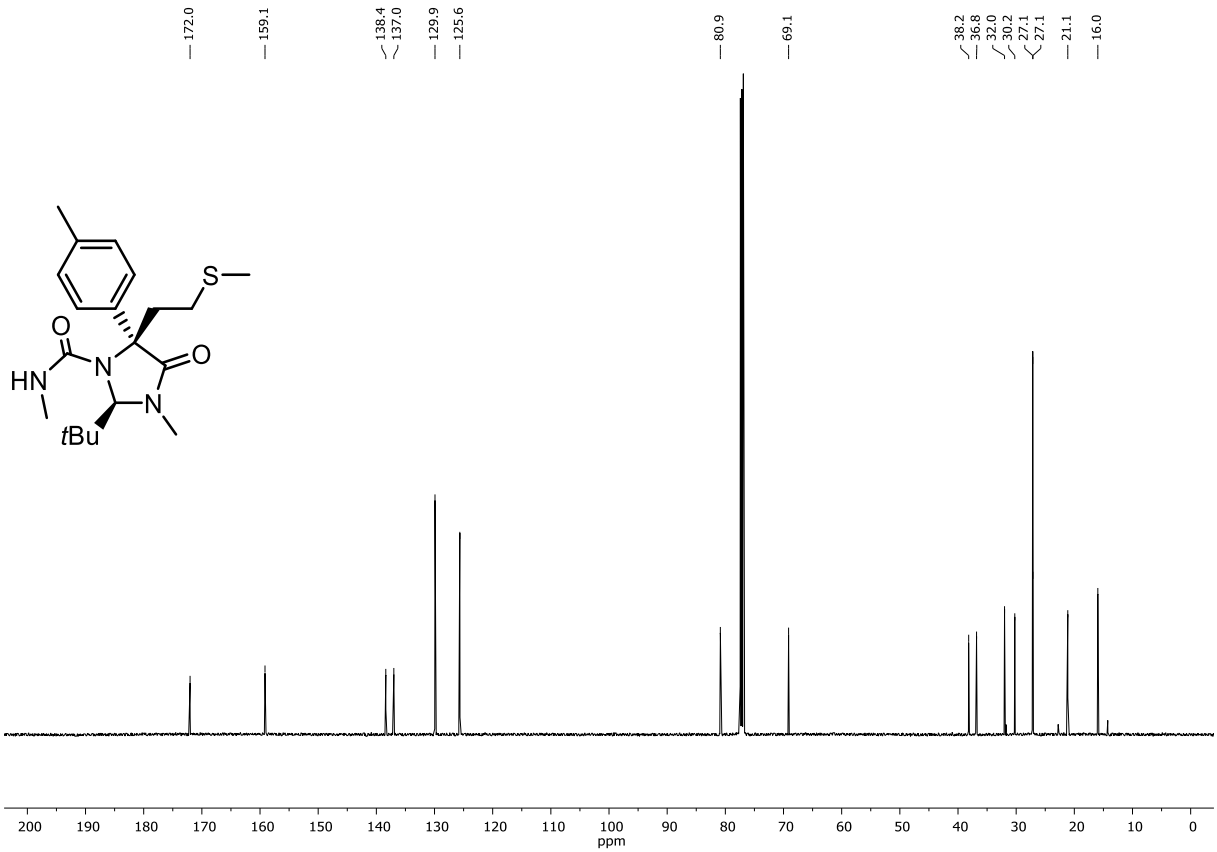
N
O
N
S
tBu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69.1
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36.8
32.0
30.2
27.1
27.1
21.1
16.0
200
190
180
170
160
150
140
130
120
110
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90
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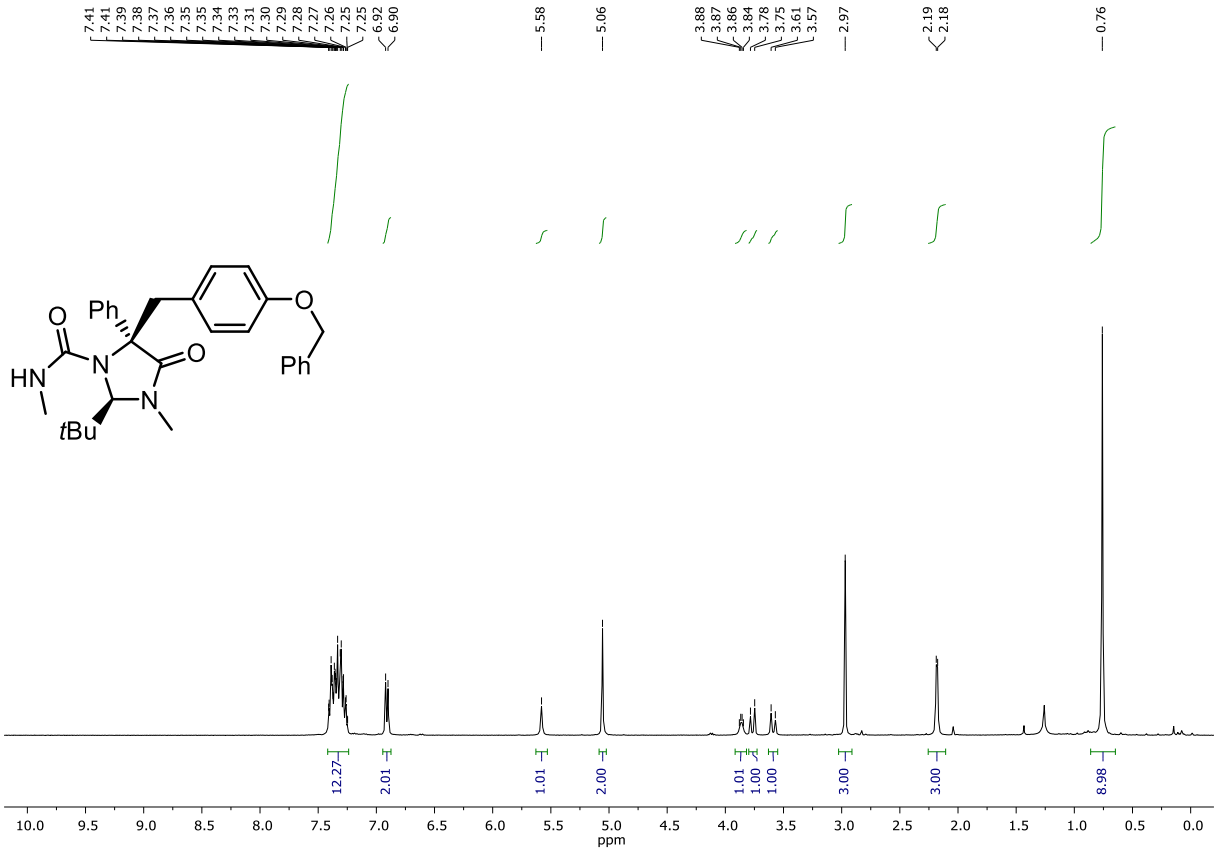
70
60
50
40
30
20
10
0
ppm
O
HN
N
O
N
S
tBu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7.35
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7.33
7.31
7.30
7.29
7.28
7.27
7.26
7.25
7.25
6.92
6.90
5.58
5.06
3.88
3.87
3.86
3.84
3.78
3.75
3.61
3.57
2.97
2.19
2.18
0.76
Ph
O
HN
N
O
N
tBu
O
Ph
12.27
2.01
1.01
2.00
1.01
1.00
1.00
3.00
3.00
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10.0
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8.0
7.5
7.0
6.5
6.0
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1.5
1.0
0.5
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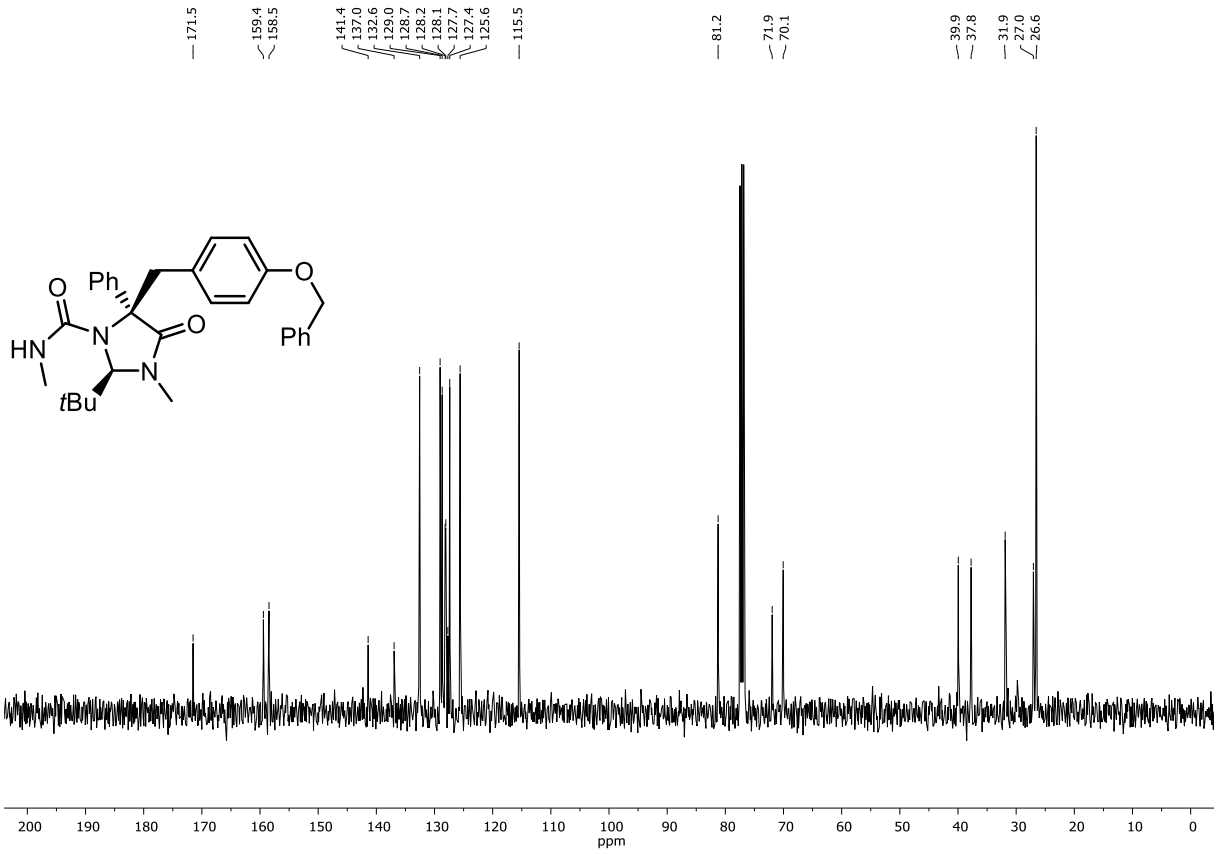
ppm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158.5
141.4
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128.2
128.1
127.7
127.4
125.6
115.5
81.2
71.9
70.1
39.9
37.8
31.9
27.0
26.6
Ph
O
HN
N
O
N
tBu
O
Ph
200
190
180
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140
130
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100
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60
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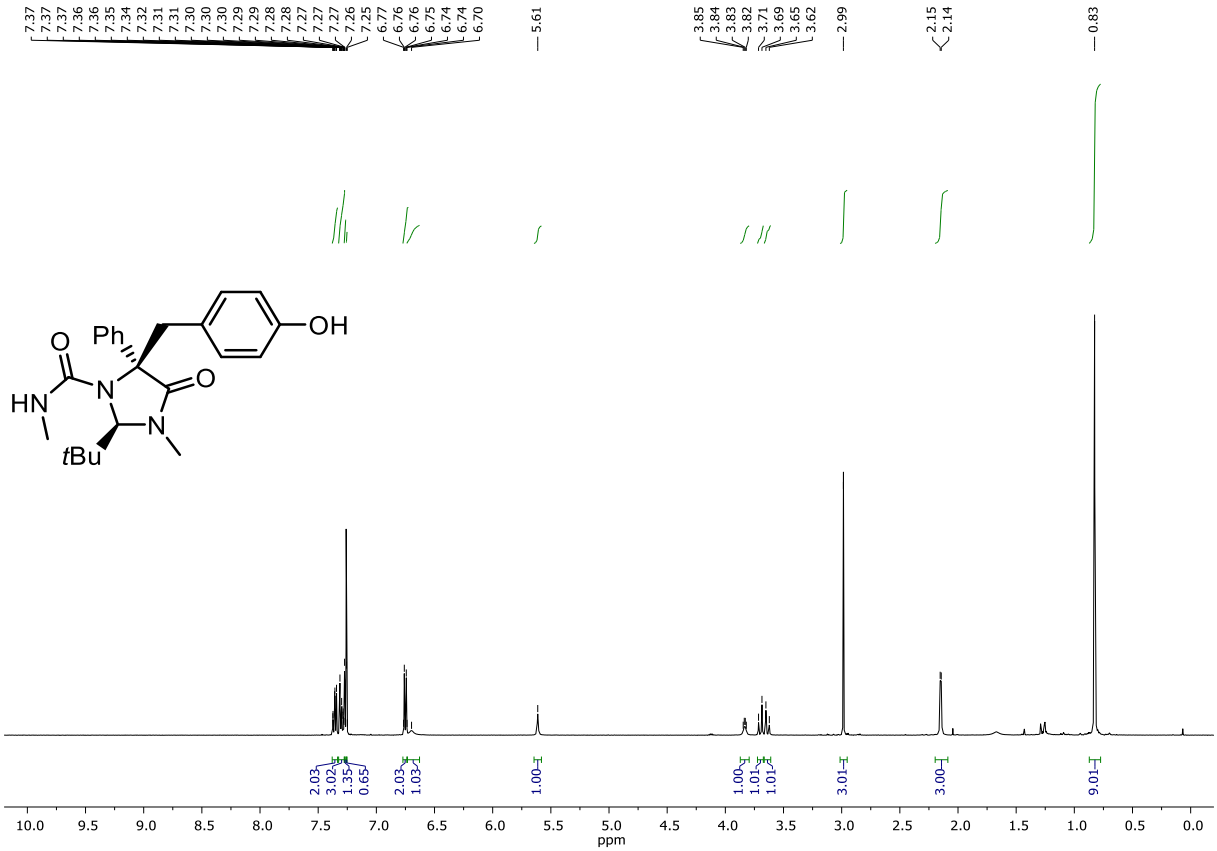
20
10
0
ppm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7.30
7.29
7.29
7.28
7.28
7.27
7.27
7.27
7.26
7.25
6.77
6.76
6.76
6.75
6.74
6.74
6.70
5.61
3.85
3.84
3.83
3.82
3.71
3.69
3.65
3.62
2.99
2.15
2.14
0.83
Ph
OH
O
HN
N
O
N
tBu
2.03
3.02
1.35
0.65
2.03
1.03
1.00
1.00
1.01
1.01
3.01
3.00
9.01
10.0
9.5
9.0
8.5
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6.5
6.0
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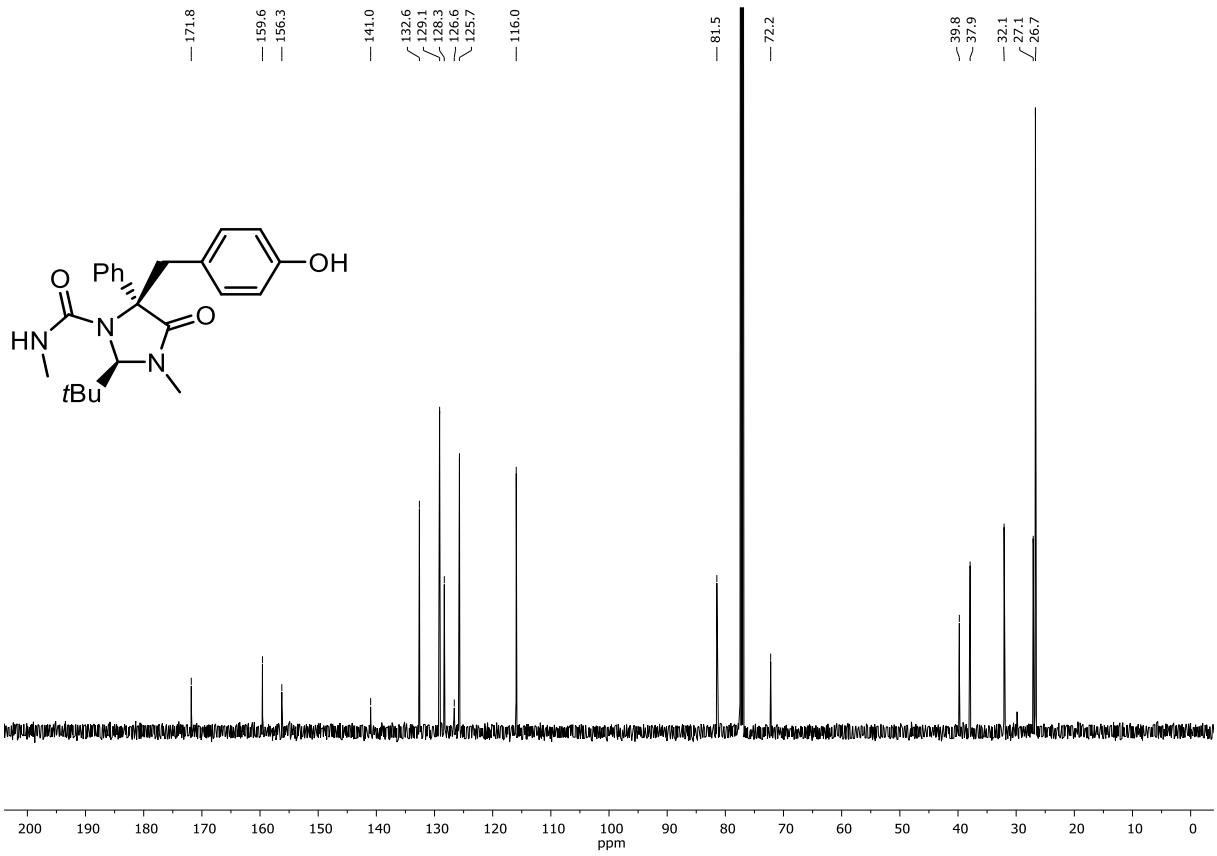
ppm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126.6
125.7
116.0
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72.2
39.8
37.9
32.1
27.1
26.7
Ph
OH
O
HN
N
O
N
tBu
200
190
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140
130
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100
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60
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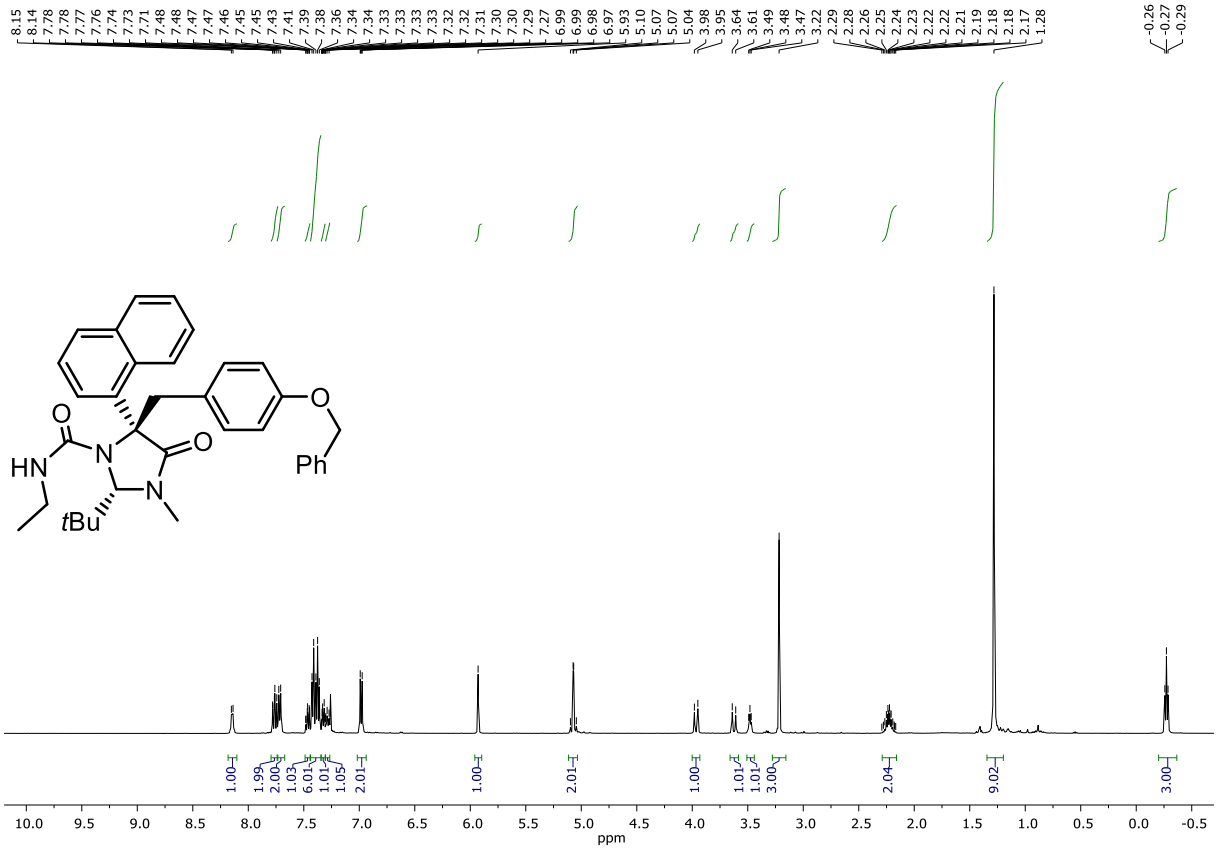
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-0.26 -0.27 -0.29
HN
O
N
O
N
O
O
Ph
tBu
1.00 1.99 2.00 1.03 6.01 1.01 1.05 2.01 1.00 2.01 1.00 1.01 1.01 3.00 2.04 9.02 3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
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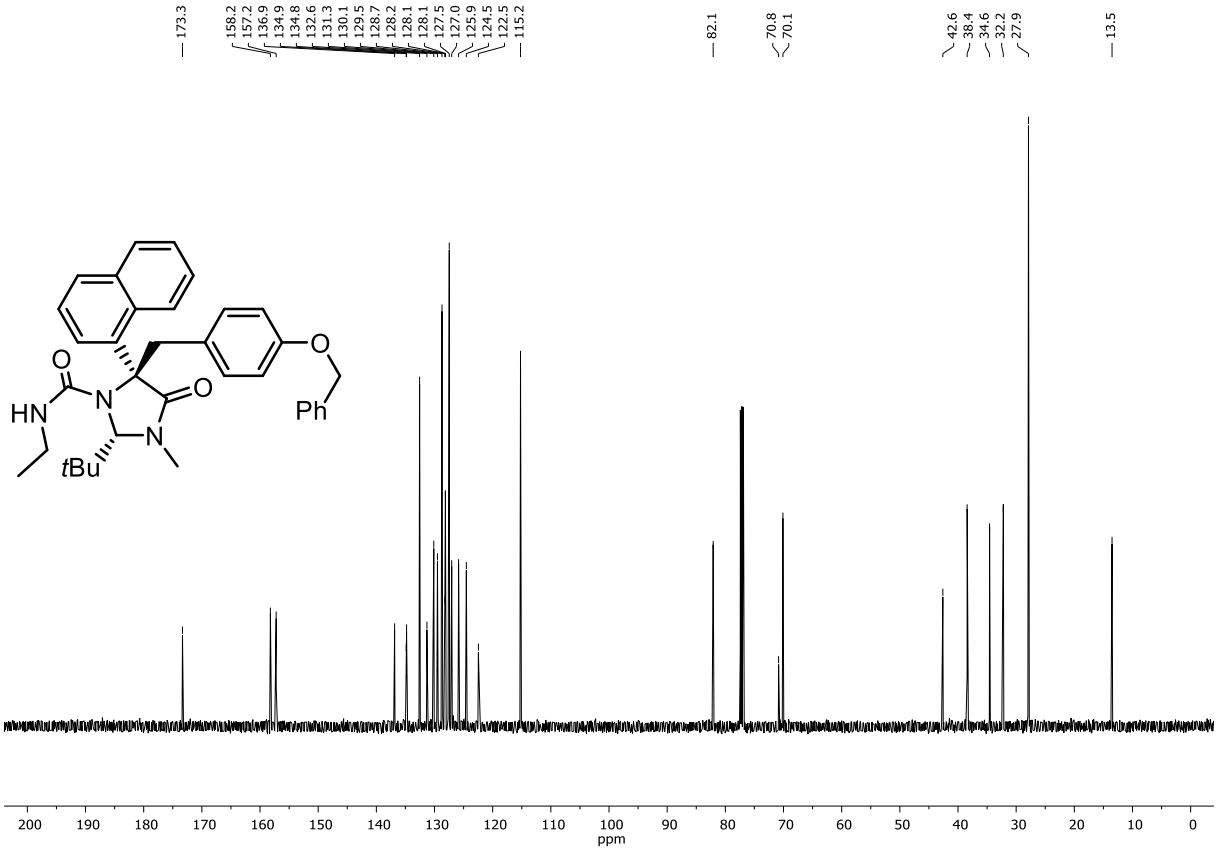
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82.1
70.8 70.1
42.6 38.4 34.6 32.2 27.9
13.5
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N
O
N
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O
Ph
tBu
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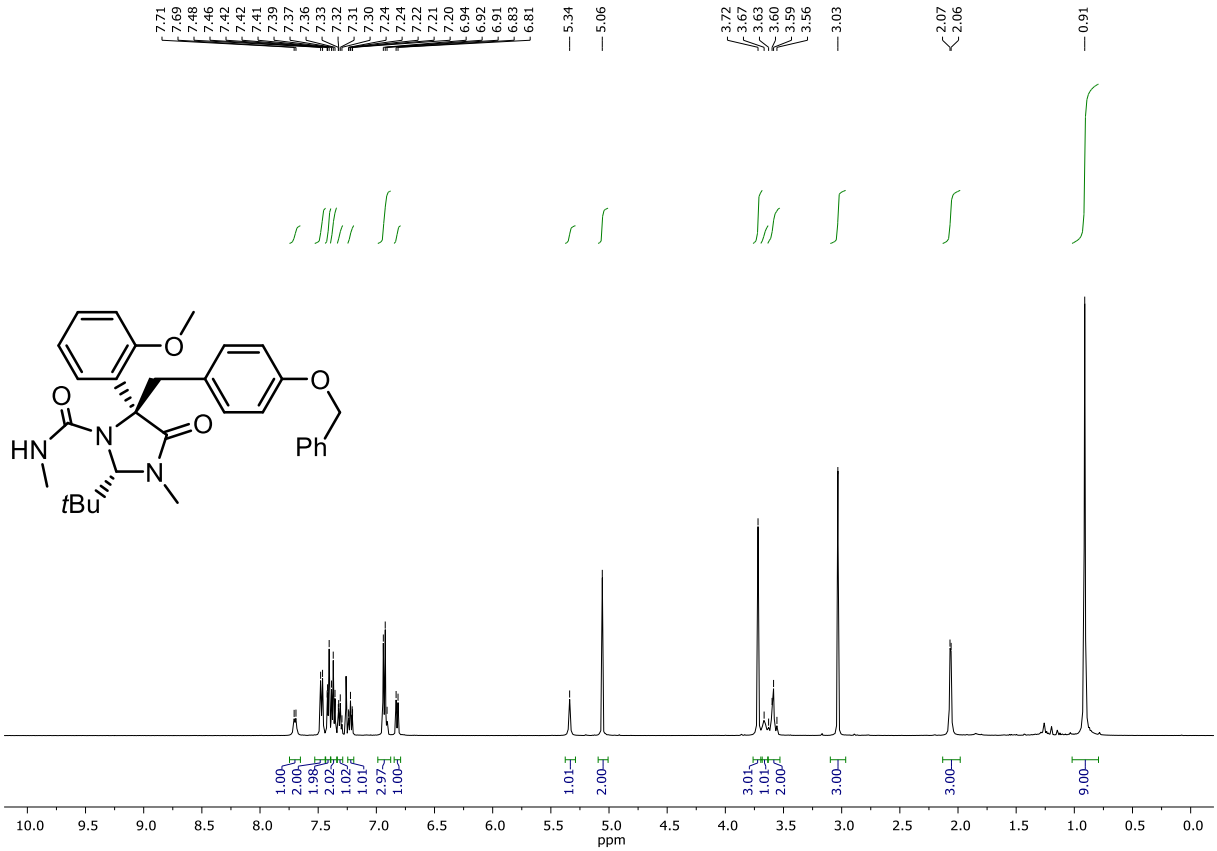
ppm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7.24
7.24
7.22
7.21
7.20
6.94
6.92
6.91
6.83
6.81
5.34
5.06
3.72
3.67
3.63
3.60
3.59
3.56
3.03
2.07
2.06
0.91
O
O
HN
N
O
O
N
Ph
tBu
1.00
2.00
1.98
2.02
1.02
1.01
2.97
1.00
1.01
2.00
3.01
1.01
2.00
3.00
3.00
9.00
10.0
9.5
9.0
8.5
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7.5
7.0
6.5
6.0
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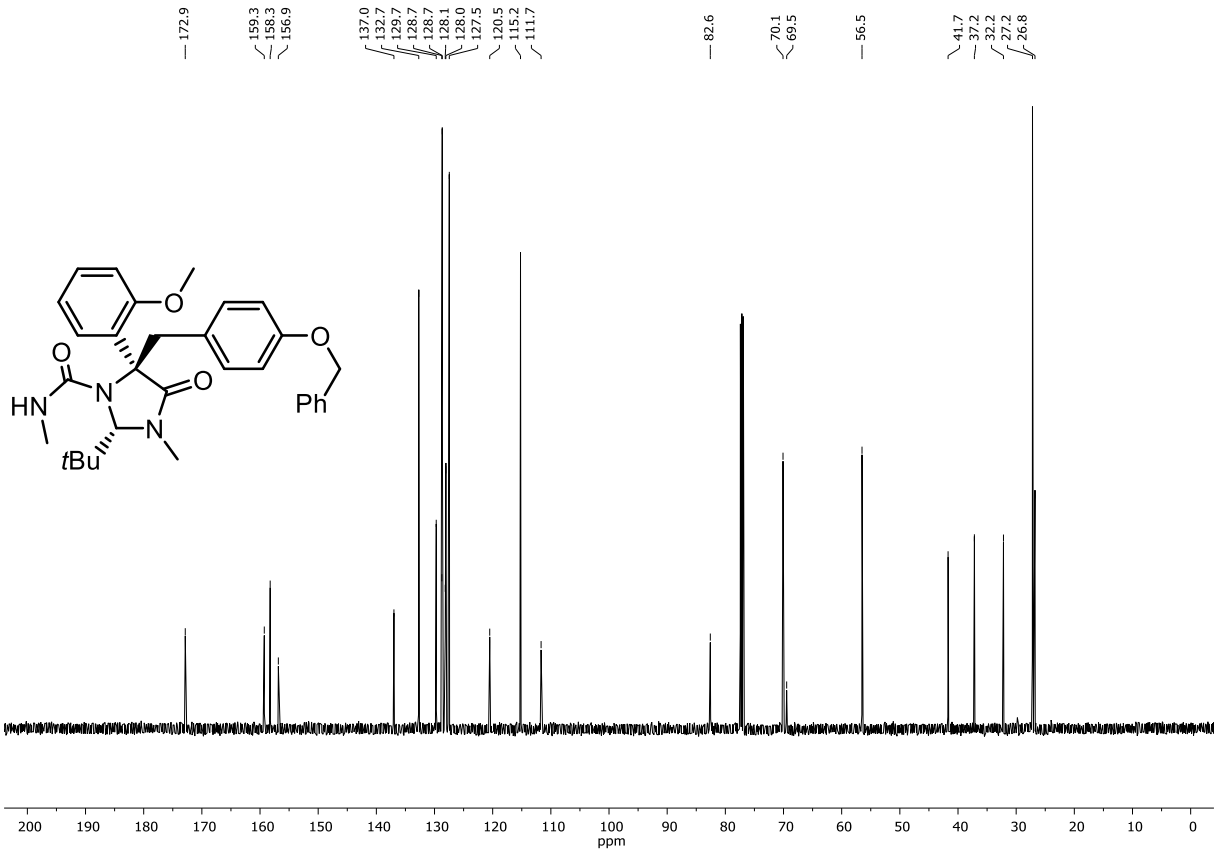
ppm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128.0
127.5
120.5
115.2
111.7
82.6
70.1
69.5
56.5
41.7
37.2
32.2
27.2
26.8
O
O
HN
N
O
O
N
Ph
tBu
200
190
180
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140
130
120
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100
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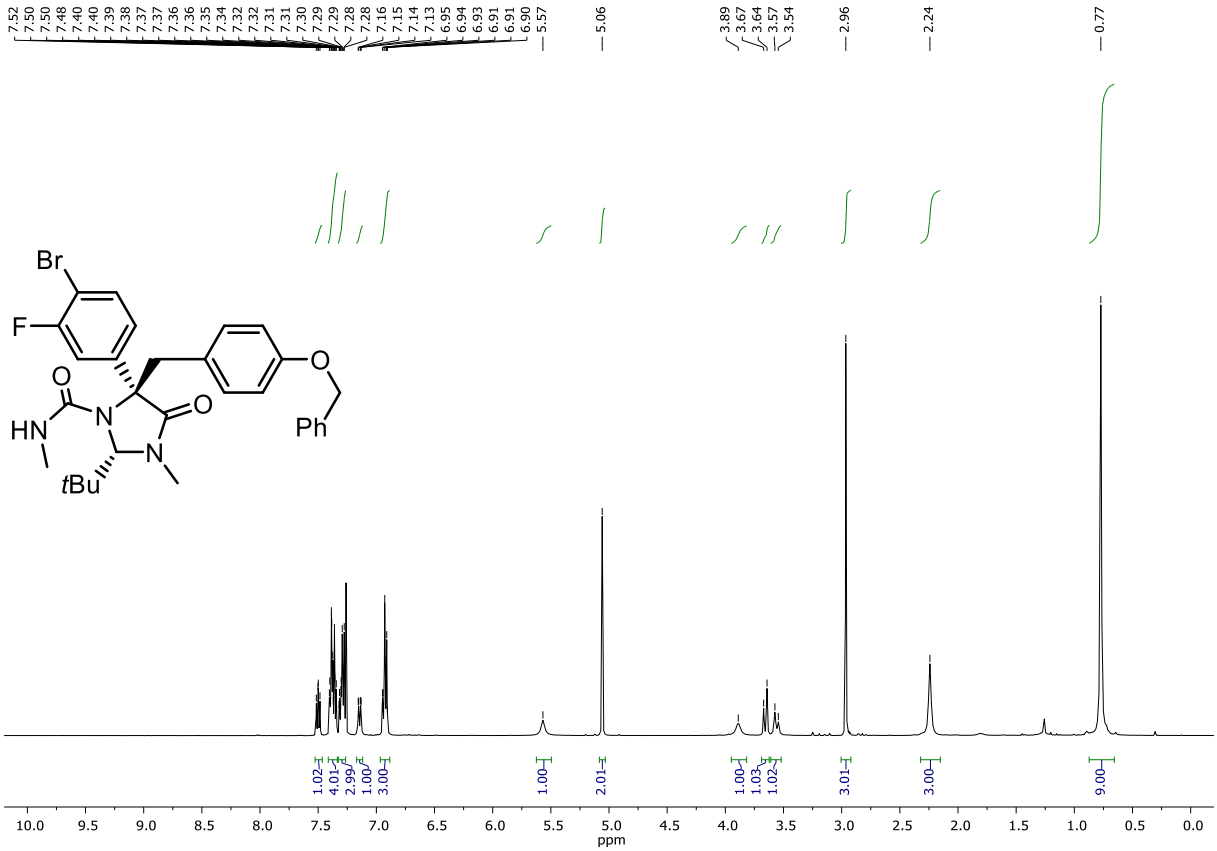
20
10
0
ppm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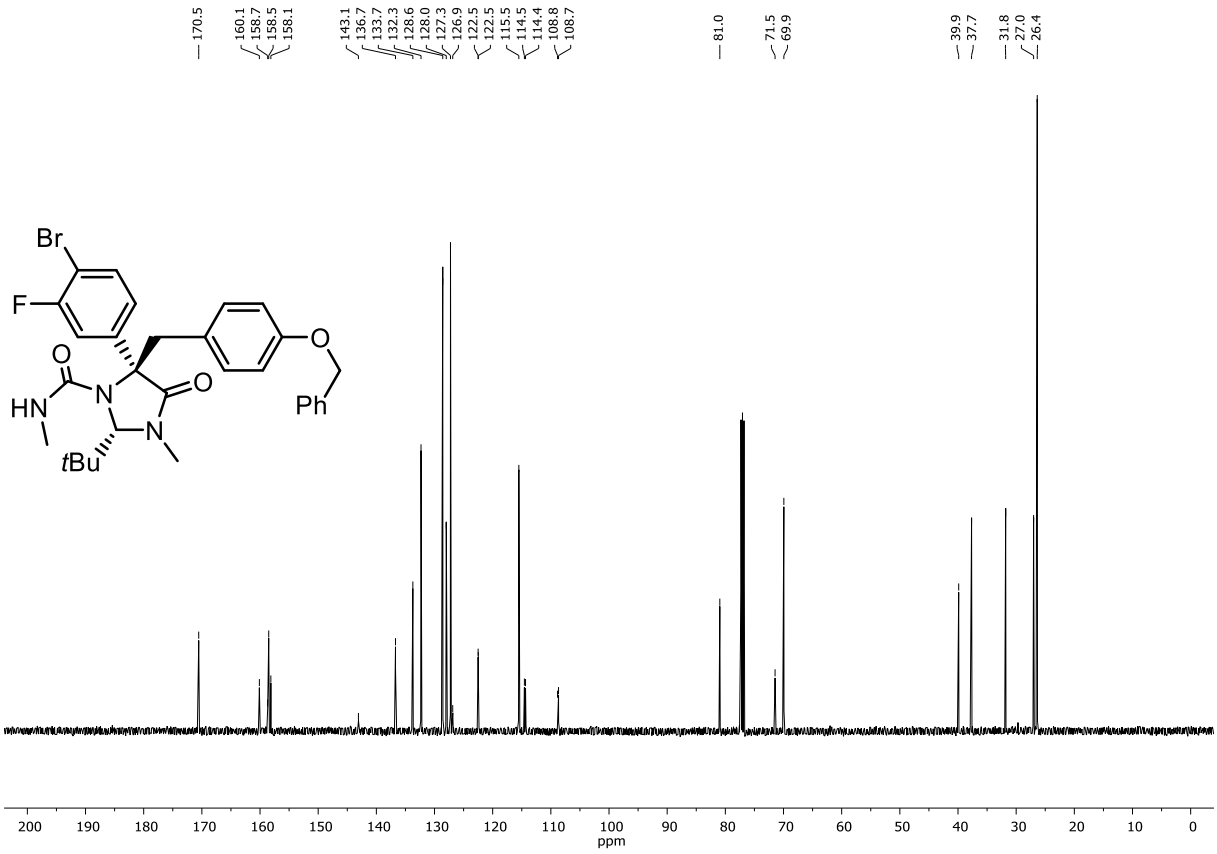
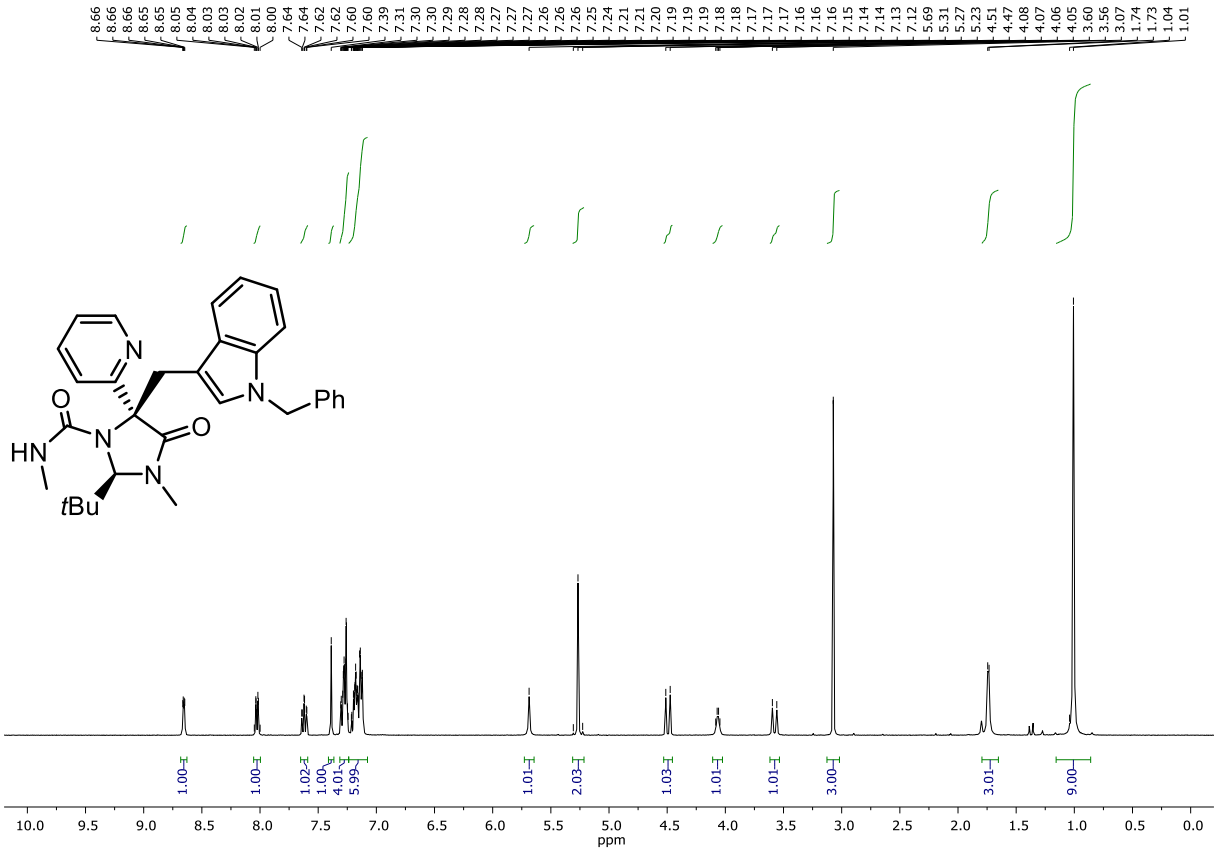
Br
F
O
HN
N
O
N
tBu
O
Ph
1.02 4.01 2.99 1.00 3.00 1.00 2.01 1.00 1.03 1.02 3.01 3.00 9.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm


170.5 160.1 158.7 158.5 158.1 143.1 136.7 133.7 132.3 128.6 128.0 127.3 126.9 122.5 122.5 115.5 114.5 114.4 108.8 108.7 81.0 71.5 69.9 39.9 37.7 31.8 27.0 26.4
Br
F
O
HN
N
O
N
tBu
O
Ph
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm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N
O
HN
N
O
N
N
Ph
tBu
1.00 1.00 1.02 1.00 4.01 5.99 1.01 2.03 1.03 1.01 1.01 3.00 3.01 9.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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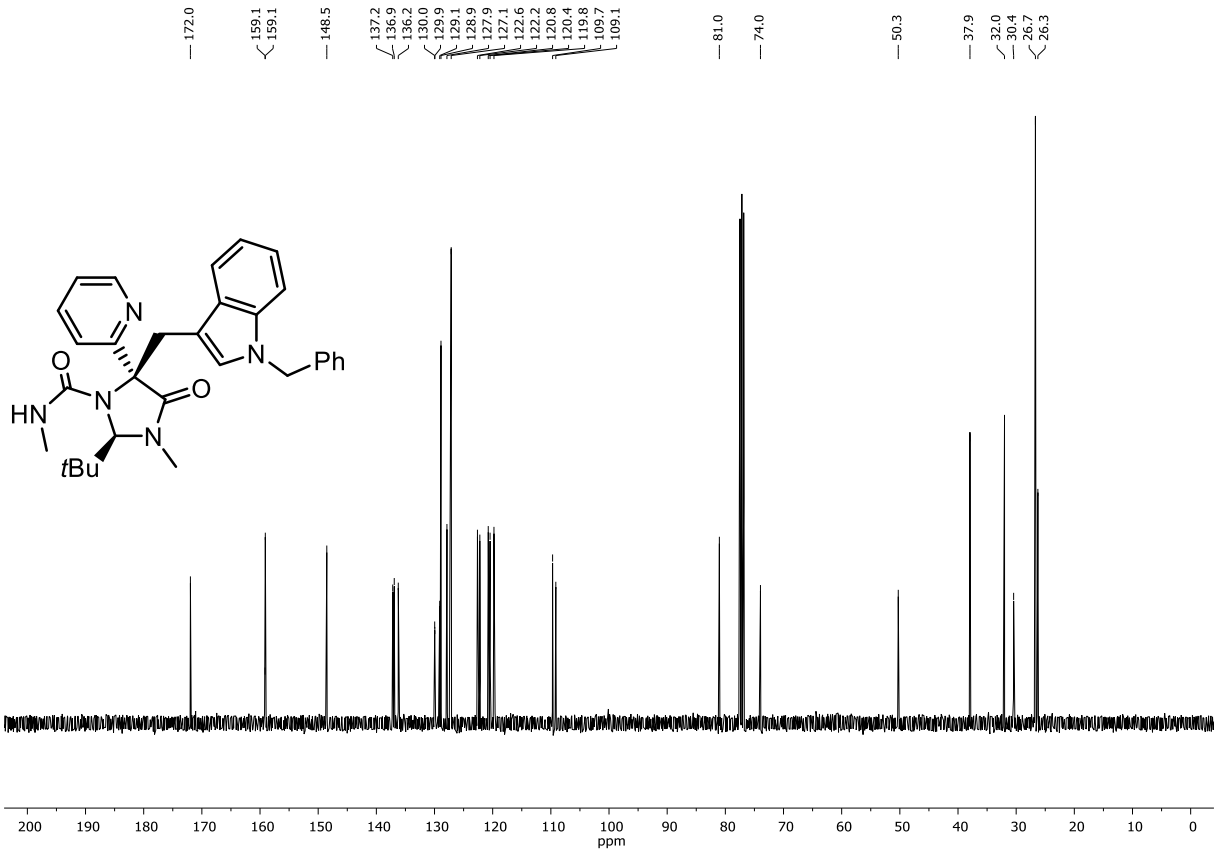
172.0 159.1 159.1 148.5 137.2 136.9 136.2 130.0 129.9 129.1 128.9 127.9 127.1 122.6 122.2 120.8 120.4 119.8 109.7 109.1 81.0 74.0 50.3 37.9 32.0 30.4 26.7 26.3
N
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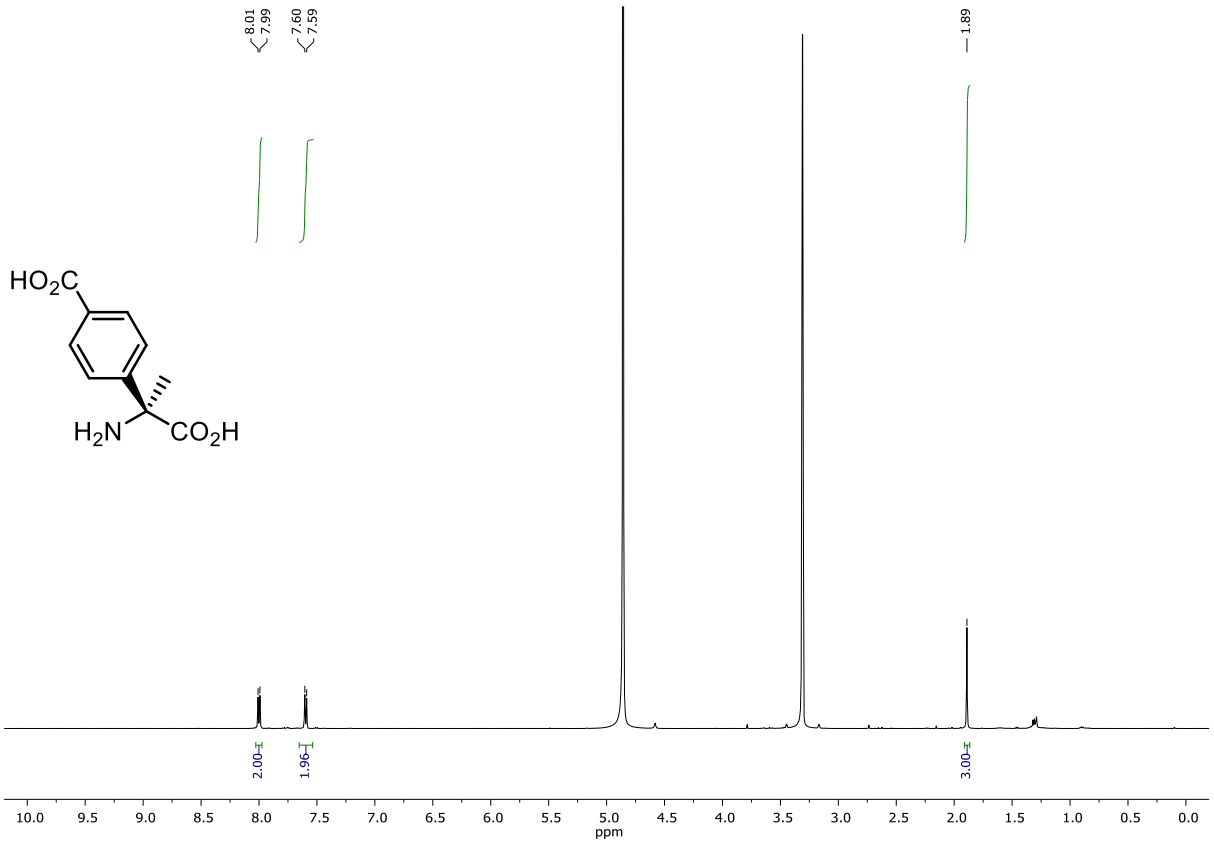
HN
N
O
N
N
Ph
tBu
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm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1.89
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H2N
CO2H
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1.96
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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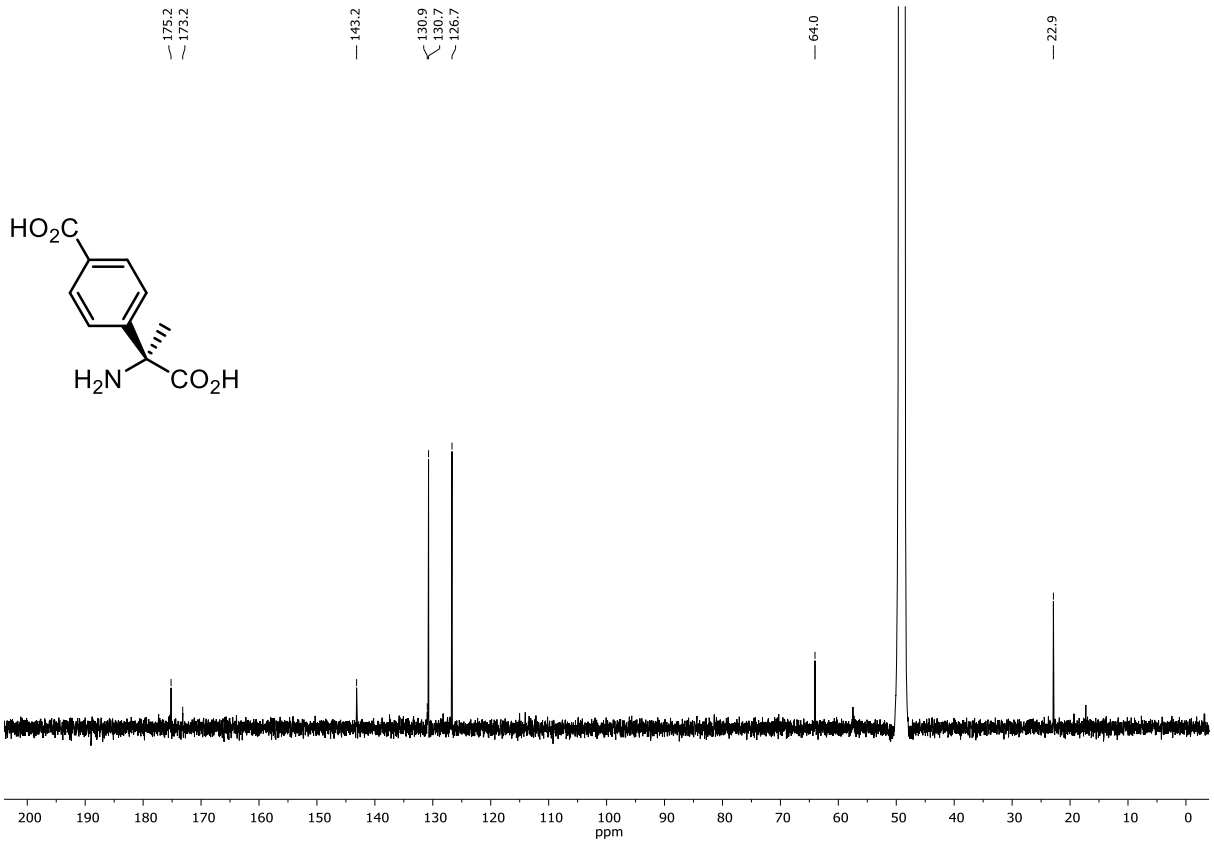
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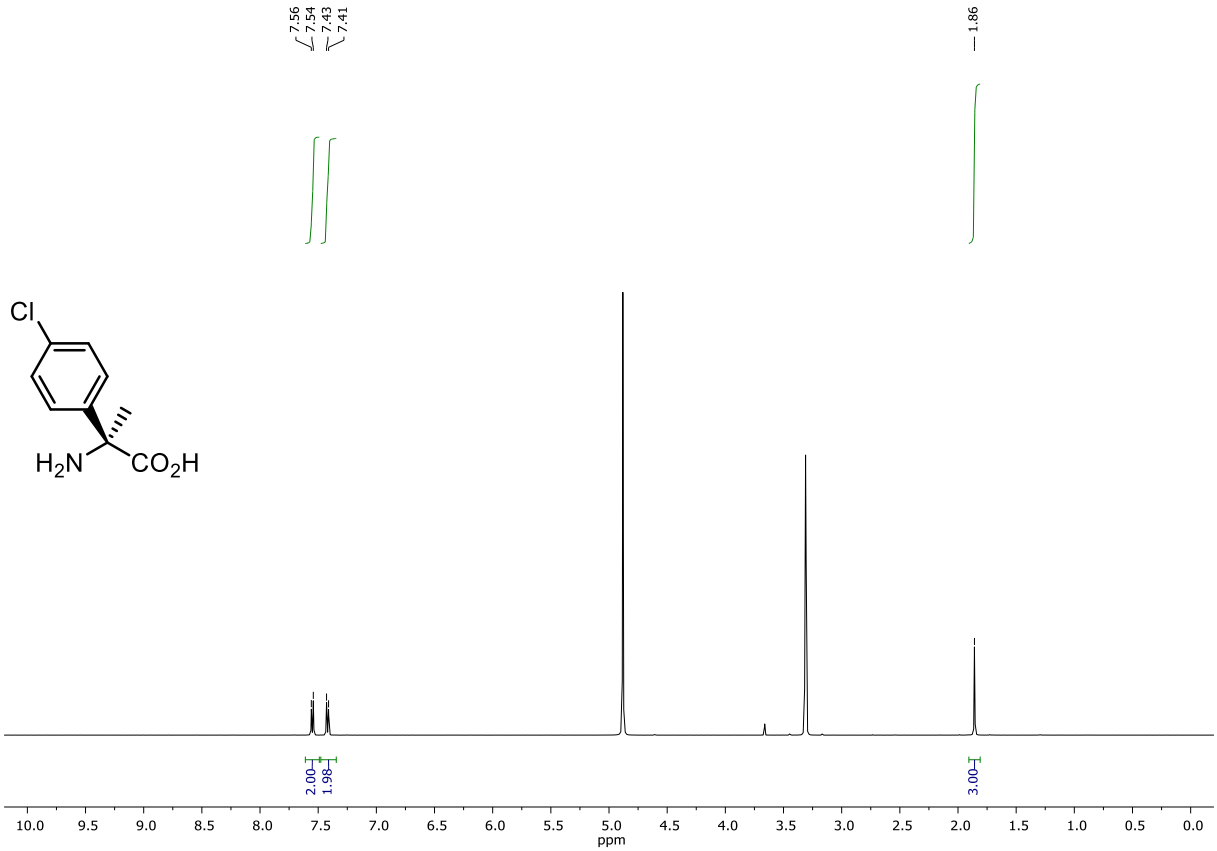
173.2
143.2
130.9
130.7
126.7
64.0
22.9
HO2C
H2N
CO2H
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm


7.56
7.54
7.43
7.41
1.86
Cl
H2N
CO2H
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1.98
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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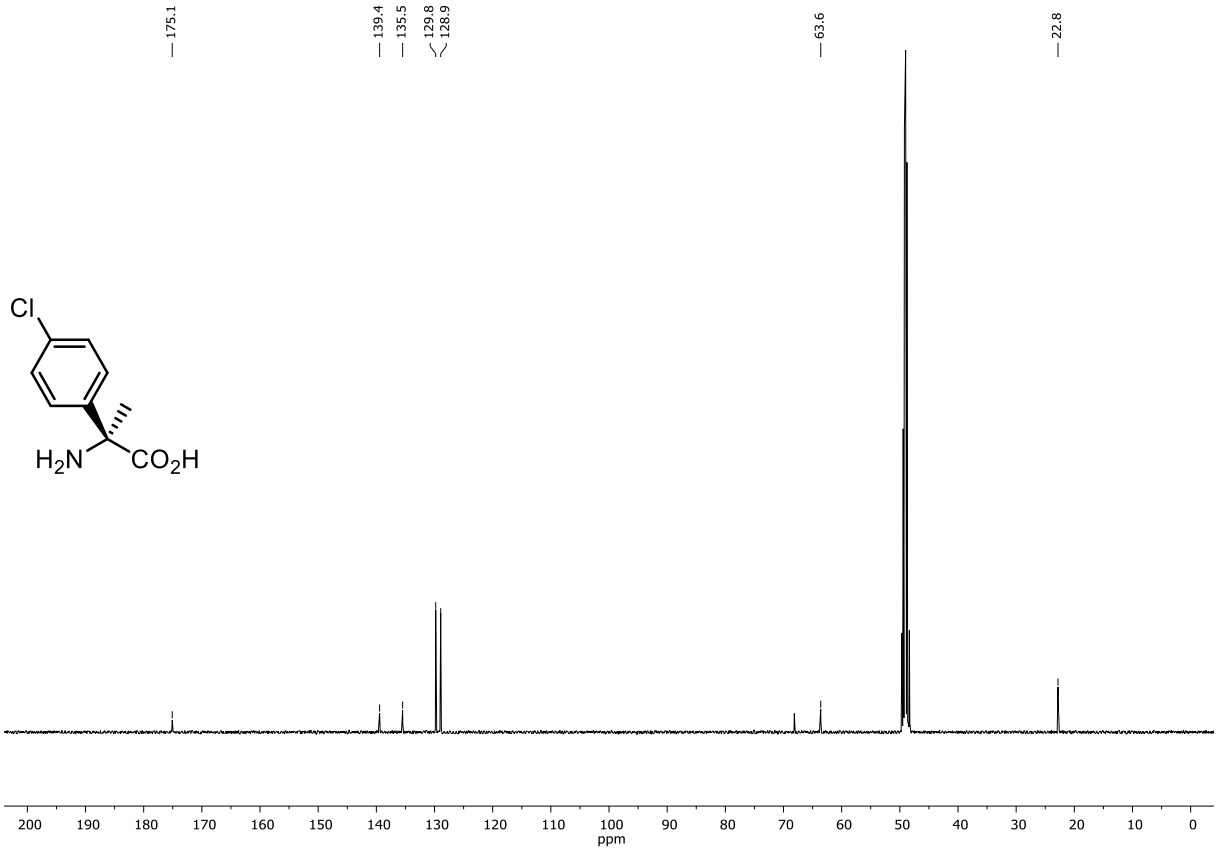
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135.5
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22.8
Cl
H2N
CO2H
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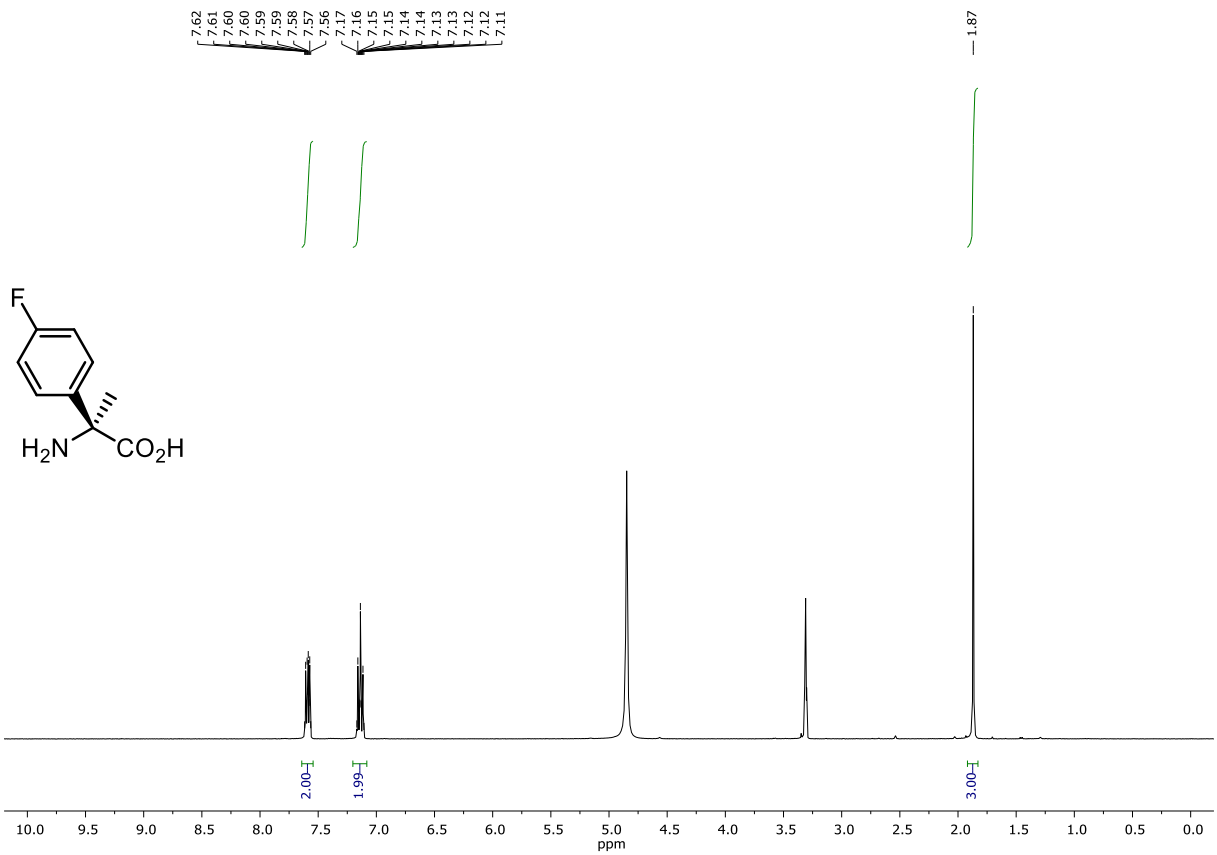
ppm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7.57
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7.15
7.15
7.14
7.14
7.13
7.13
7.12
7.12
7.11
1.87
F
H2N
CO2H
2.00
1.99
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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4.0
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3.0
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1.5
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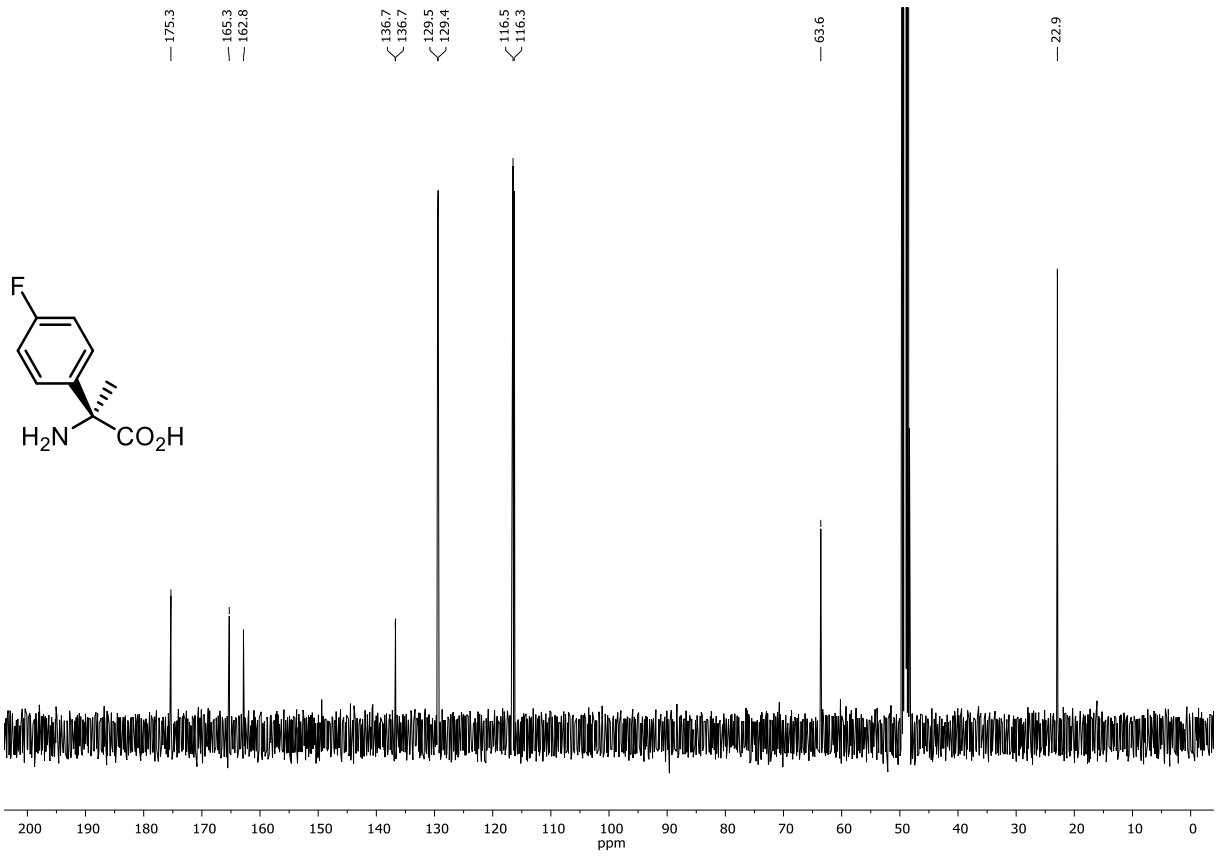
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165.3
162.8
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136.7
129.5
129.4
116.5
116.3
63.6
22.9
F
H2N
CO2H
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
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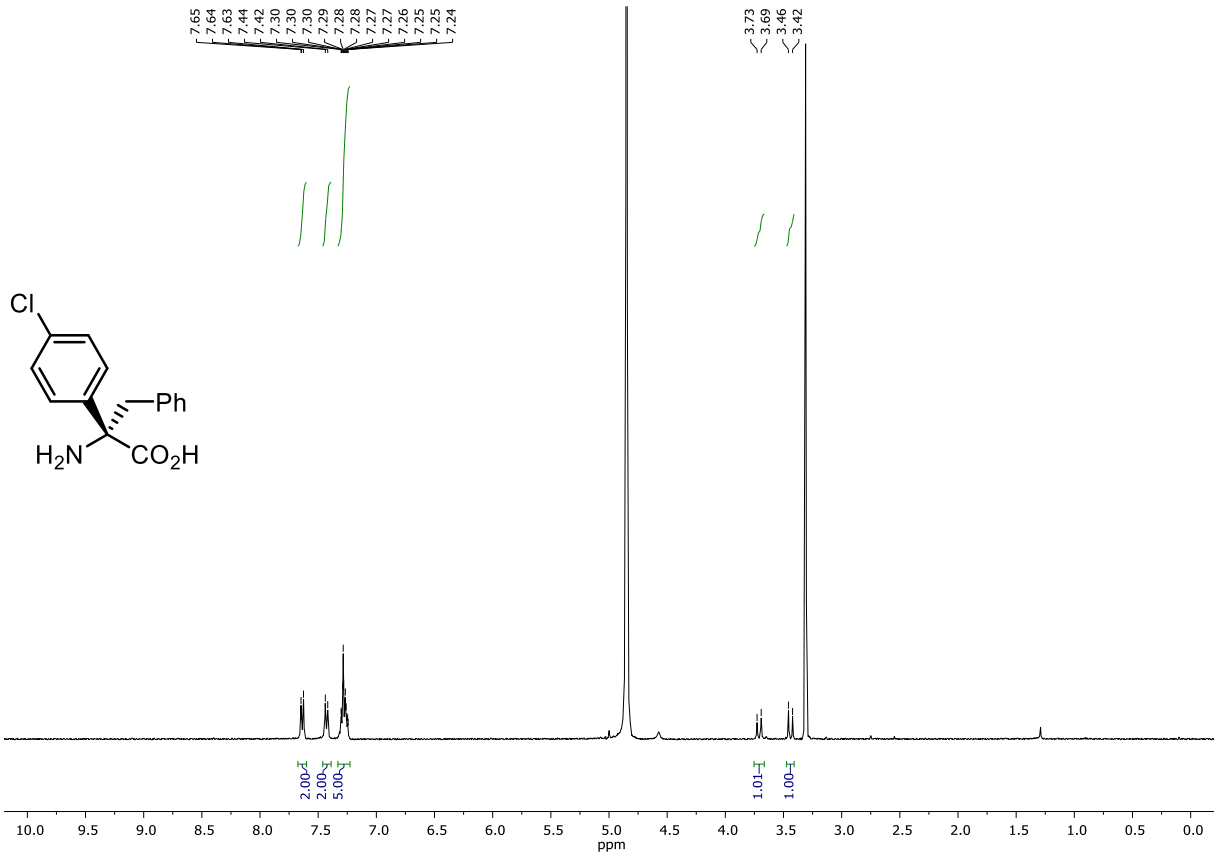
30
20
10
0
ppm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7.30
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7.28
7.27
7.27
7.26
7.25
7.25
7.24
3.73
3.69
3.46
3.42
Cl
Ph
H2N
CO2H
2.00
2.00
5.00
1.01
1.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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4.0
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3.0
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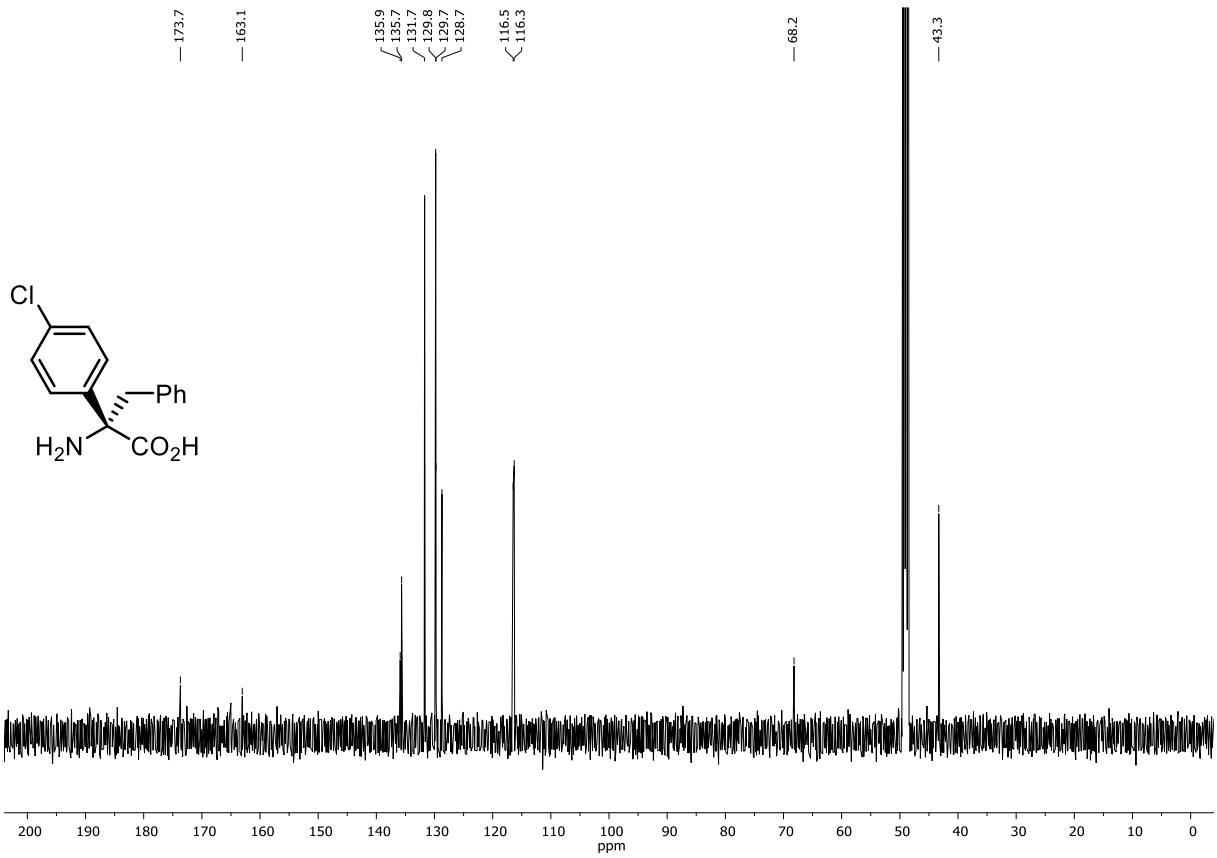
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163.1
135.9
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128.7
116.5
116.3
68.2
43.3
Cl
Ph
H2N
CO2H
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
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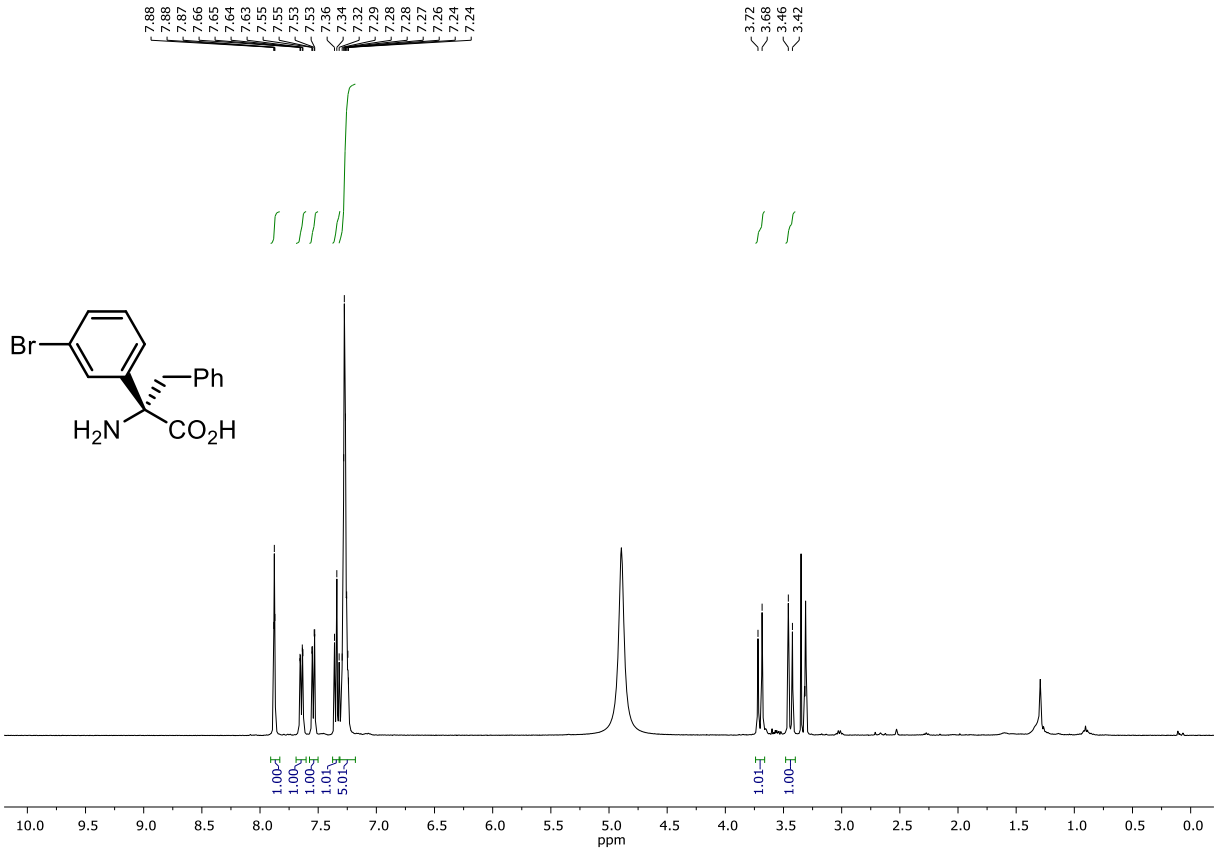
30
20
10
0
ppm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7.34
7.32
7.29
7.28
7.28
7.27
7.26
7.24
7.24
3.72
3.68
3.46
3.42
Br
Ph
H2N
CO2H
1.00
1.00
1.00
1.01
5.01
1.01
1.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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4.0
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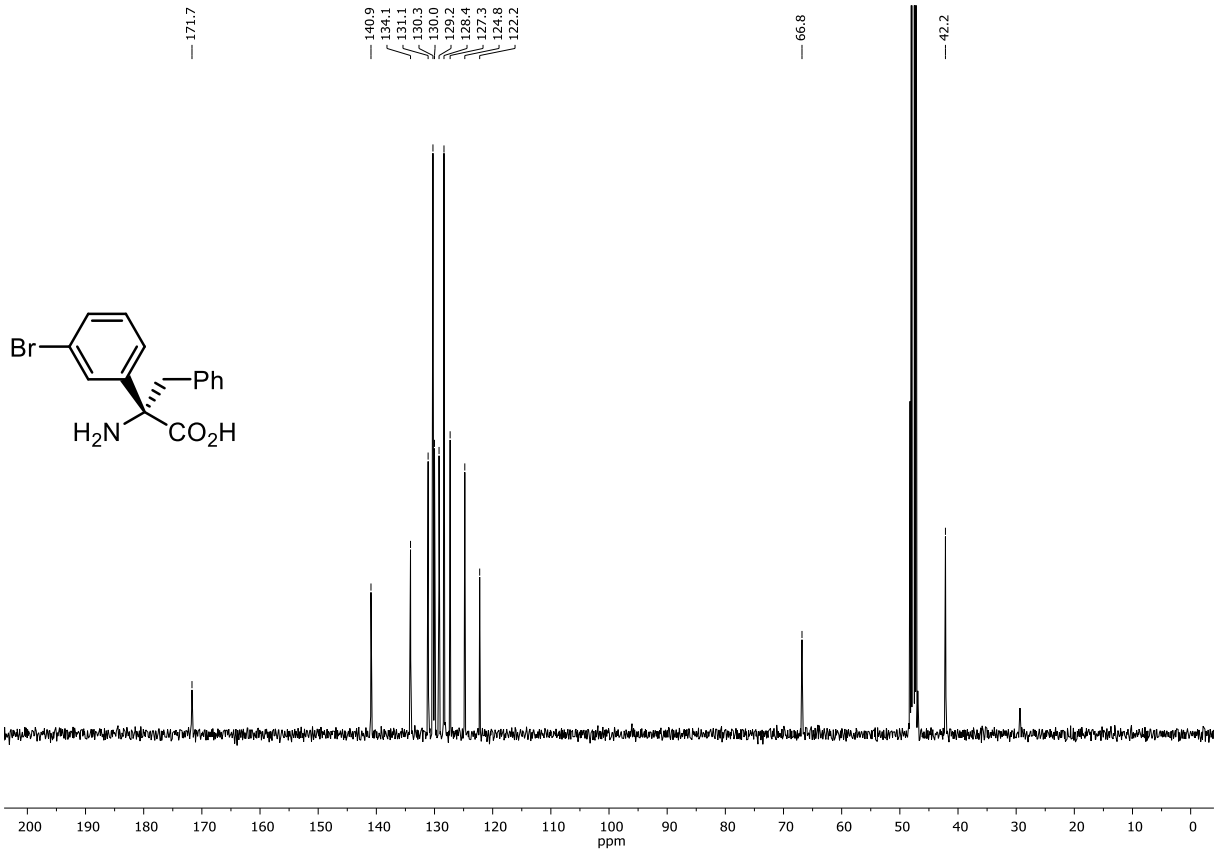
0.0
ppm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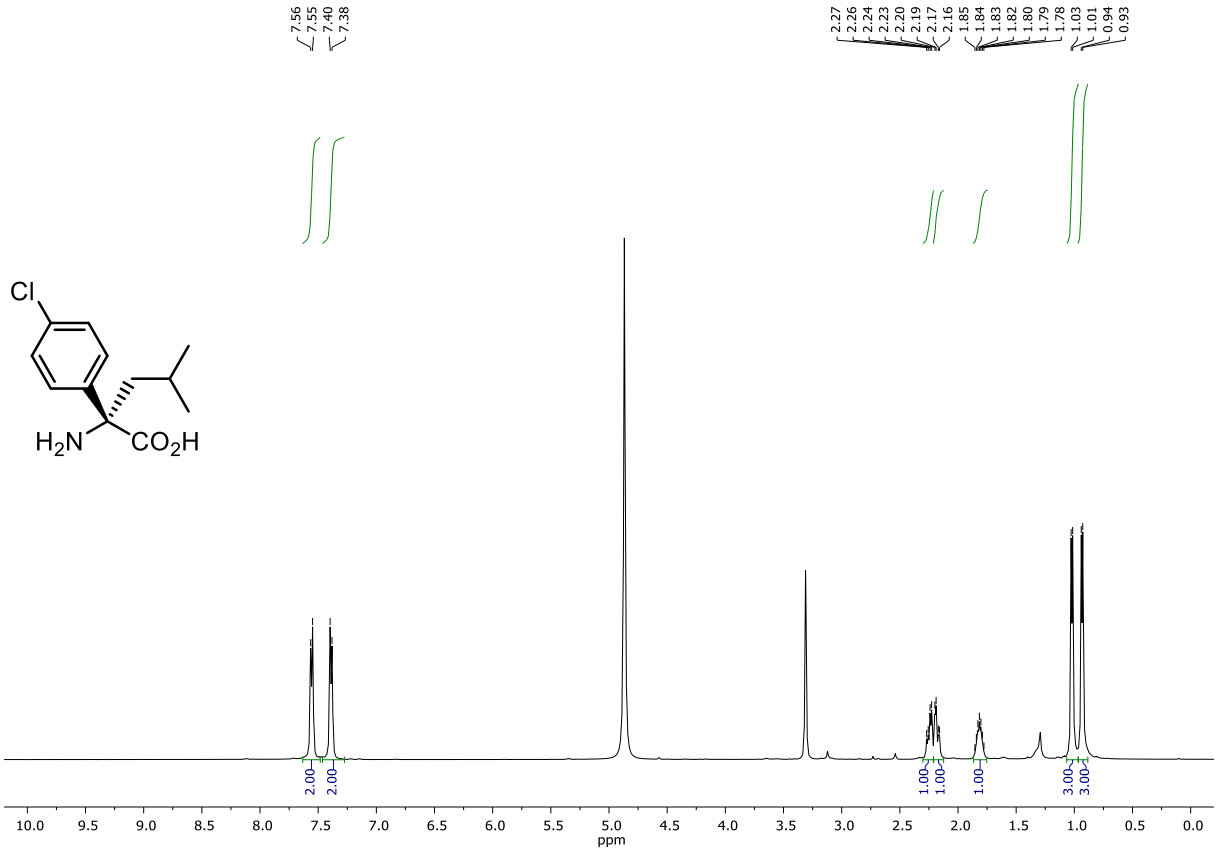
140.9
134.1
131.1
130.3
130.0
129.2
128.4
127.3
124.8
122.2
66.8
42.2
Br
Ph
H2N
CO2H
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm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2.26
2.24
2.23
2.20
2.19
2.17
2.16
1.85
1.84
1.83
1.82
1.80
1.79
1.78
1.03
1.01
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0.93
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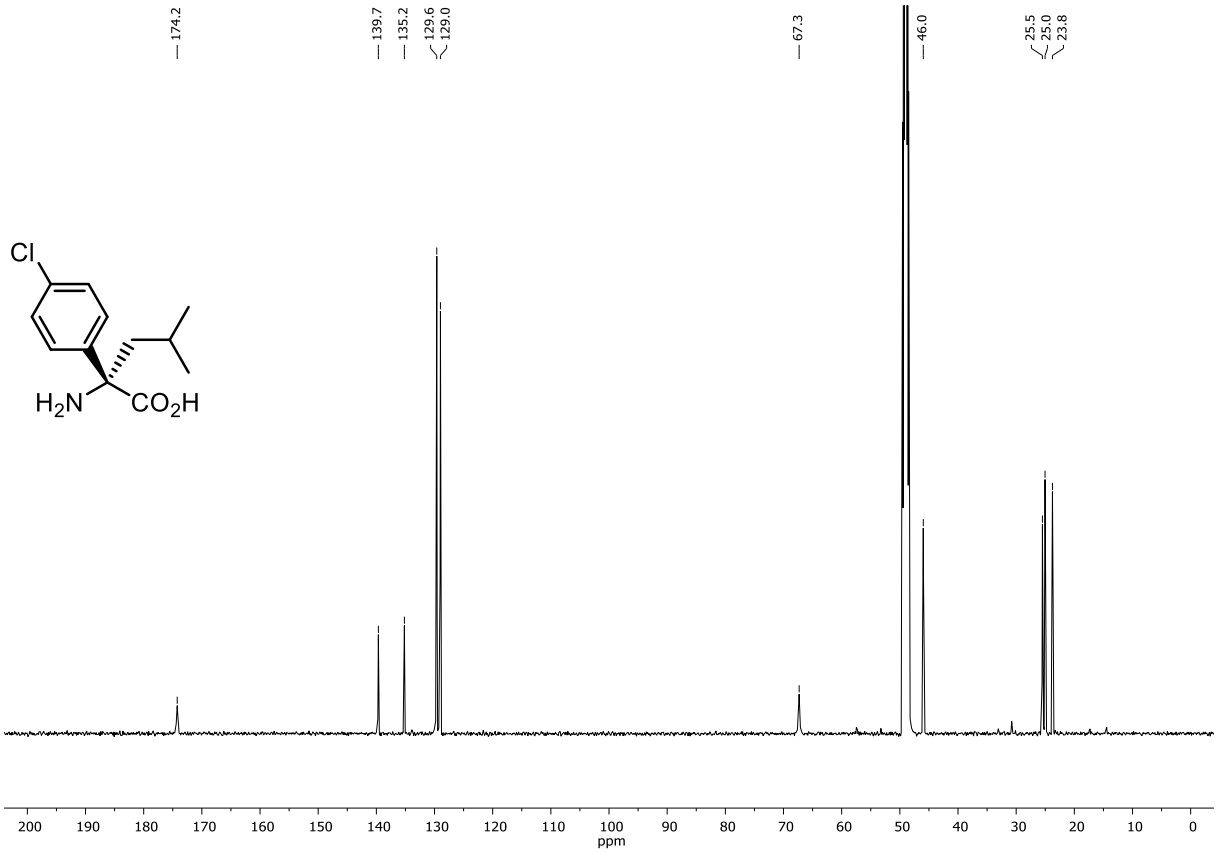
H2N
CO2H
2.00
2.00
1.00
1.00
1.00
3.00
3.00
ppm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139.7
135.2
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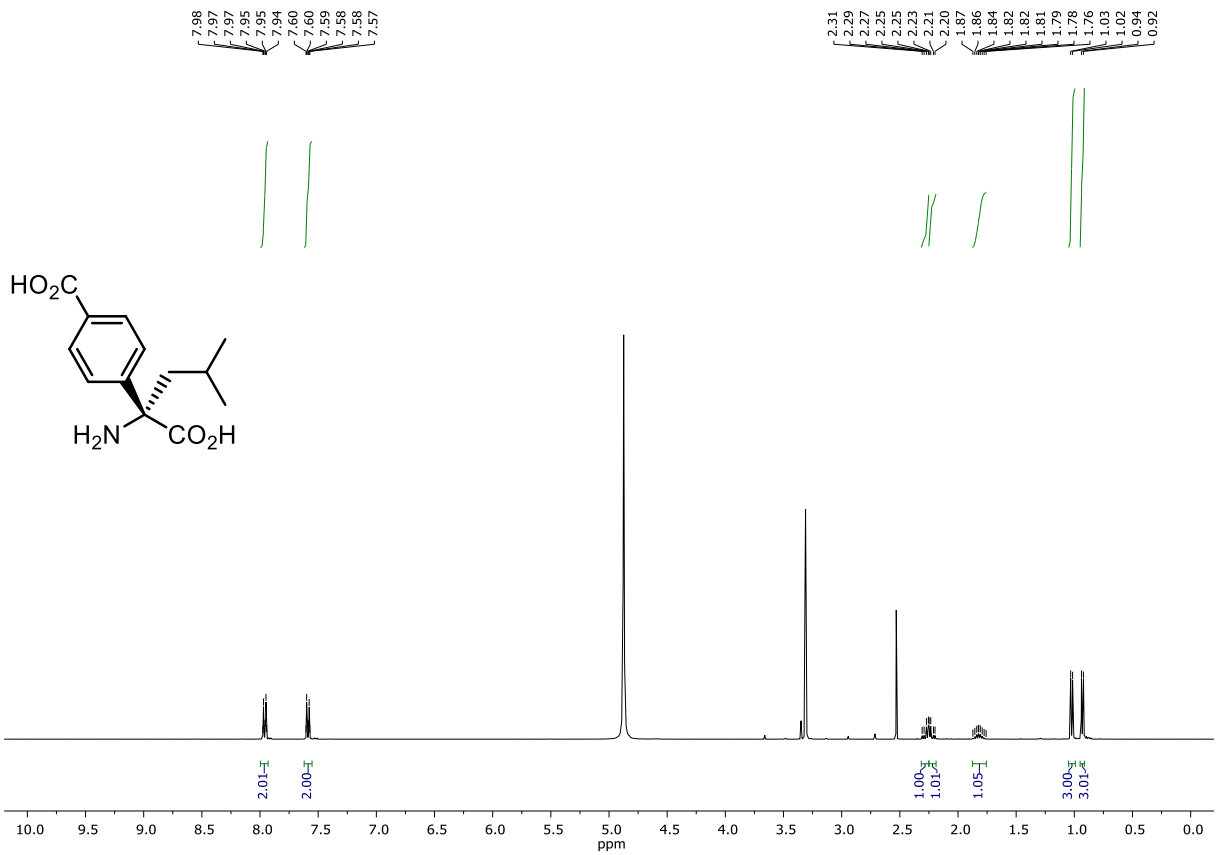
129.0
67.3
46.0
25.5
25.0
23.8
Cl
H2N
CO2H
ppm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7.57
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2.29
2.27
2.25
2.25
2.23
2.21
2.20
1.87
1.86
1.84
1.82
1.82
1.81
1.79
1.78
1.76
1.03
1.02
0.94
0.92
HO2C
H2N
CO2H
2.01
2.00
1.00
1.01
1.05
3.00
3.01
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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5.0
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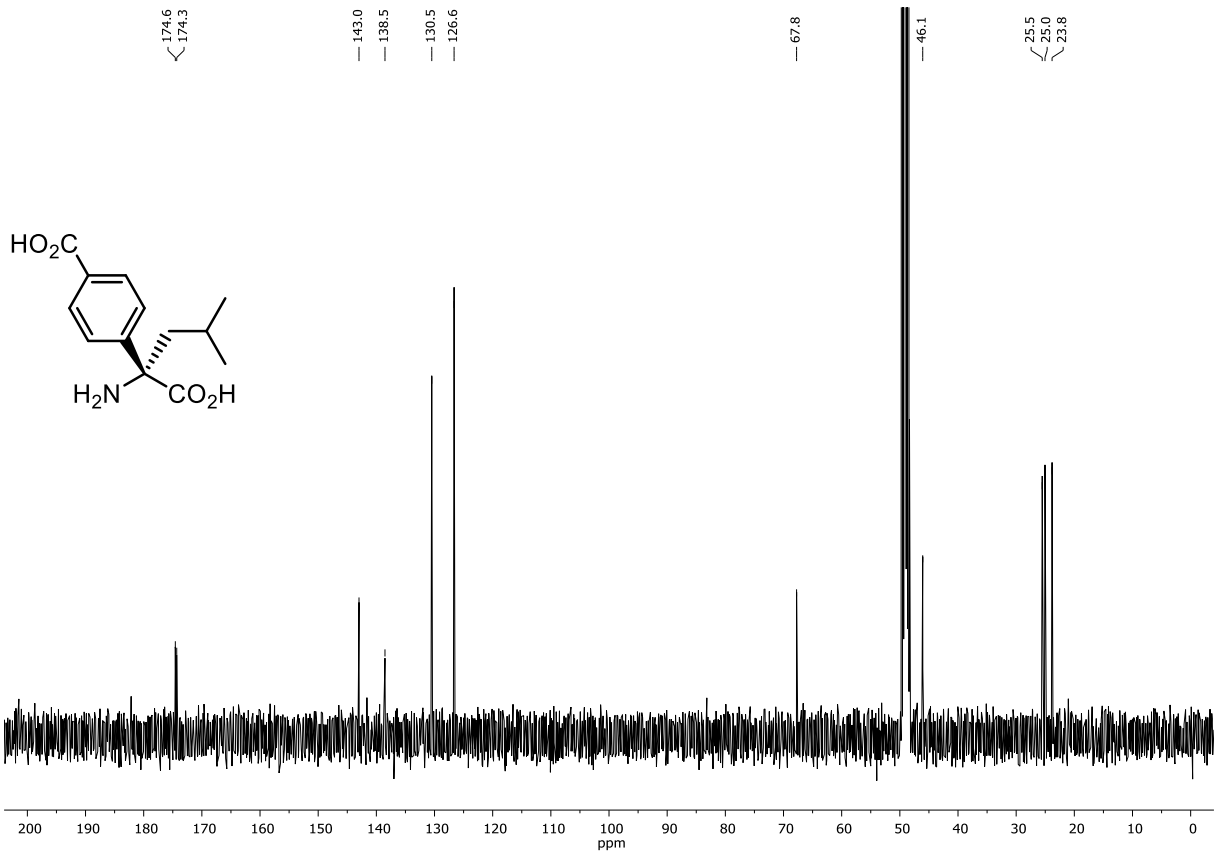
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm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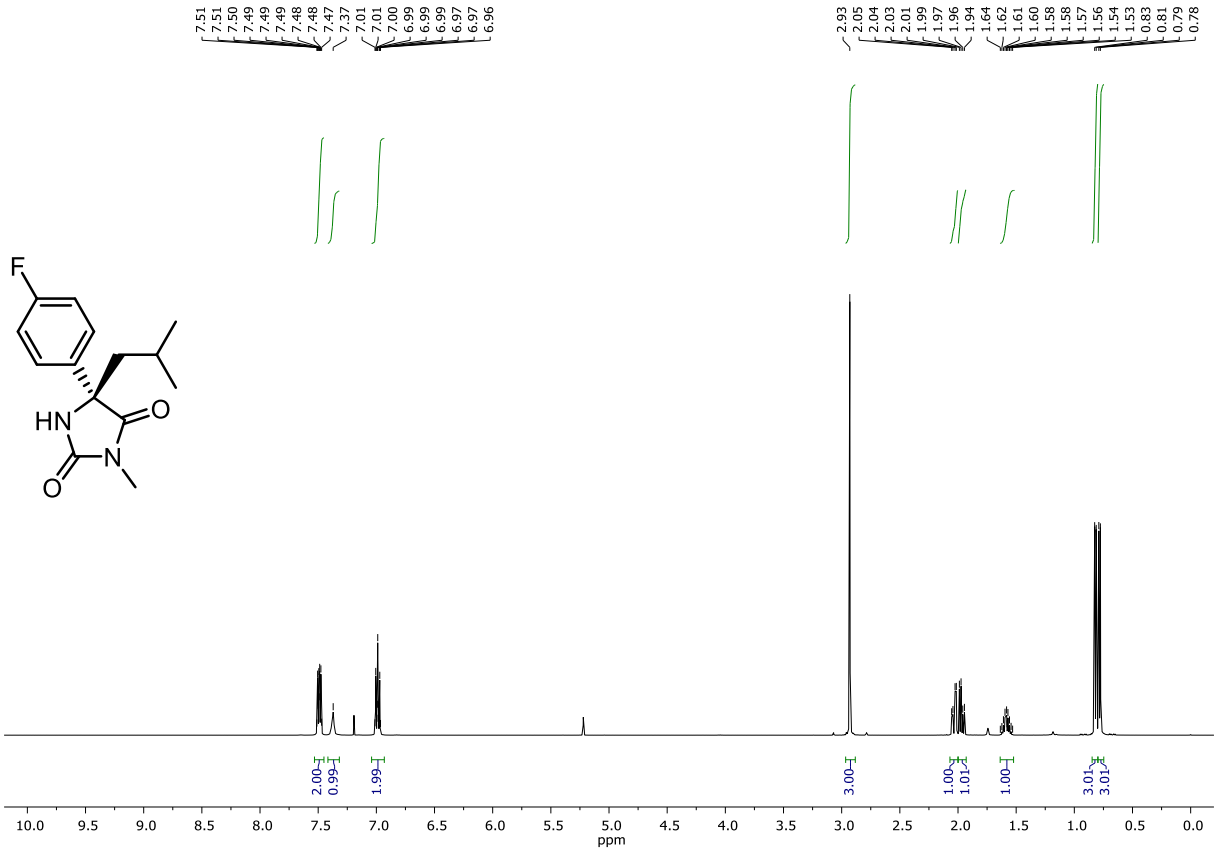
130.5
126.6
67.8
46.1
25.5
25.0
23.8
HO2C
H2N
CO2H
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm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7.01
7.00
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6.99
6.97
6.97
6.96
2.93
2.05
2.04
2.03
2.01
1.99
1.97
1.96
1.94
1.64
1.62
1.61
1.60
1.58
1.58
1.57
1.56
1.54
1.53
0.83
0.81
0.79
0.78
F
HN
O
O
N
2.00
0.99
1.99
3.00
1.00
1.01
1.00
3.01
3.01
10.0
9.5
9.0
8.5
8.0
7.5
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6.5
6.0
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4.0
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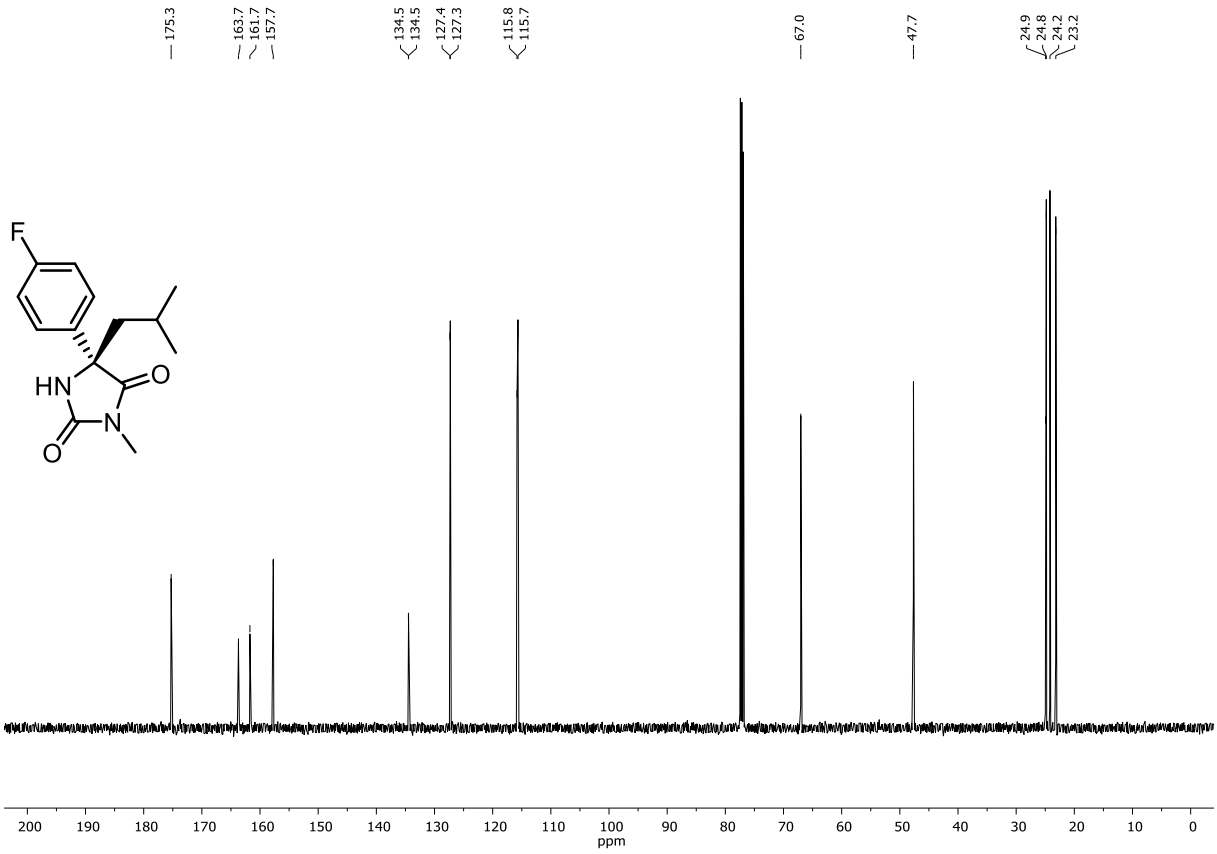
0.5
0.0
ppm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161.7
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134.5
134.5
127.4
127.3
115.8
115.7
67.0
47.7
24.9
24.8
24.2
23.2
F
HN
O
O
N
200
190
180
170
160
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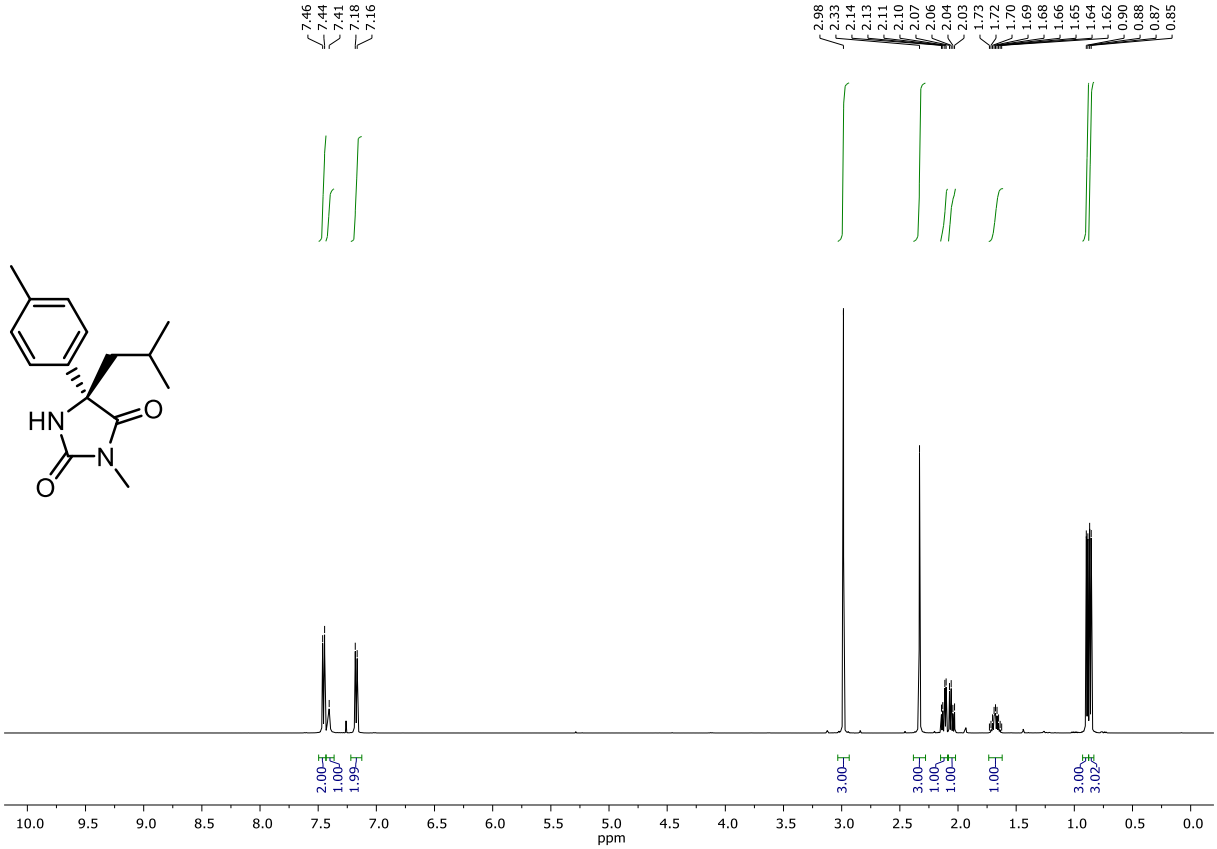
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm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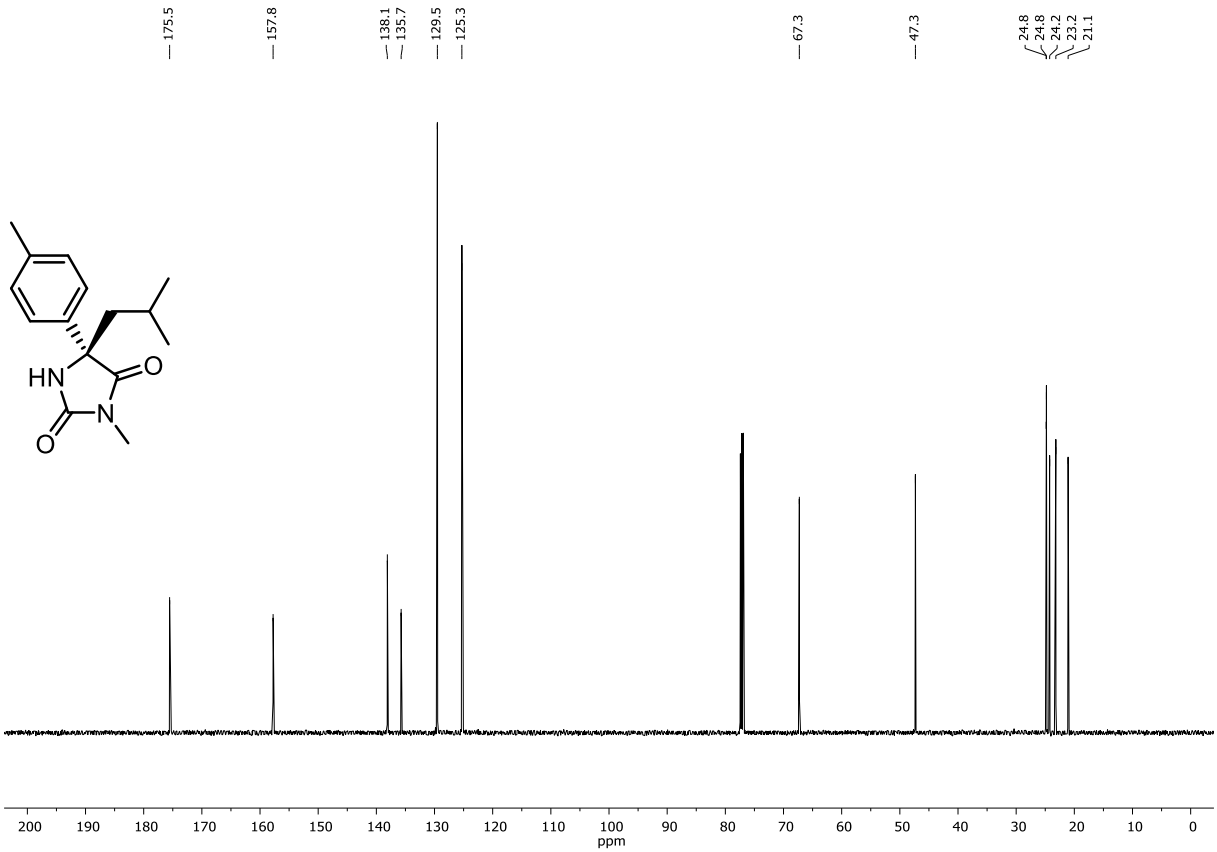
2.33
2.14
2.13
2.11
2.10
2.07
2.06
2.04
2.03
1.73
1.72
1.70
1.69
1.68
1.66
1.65
1.64
1.62
0.90
0.88
0.87
0.85
HN
O
N
O
2.00
1.00
1.99
3.00
3.00
1.00
1.00
1.00
3.00
3.02
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm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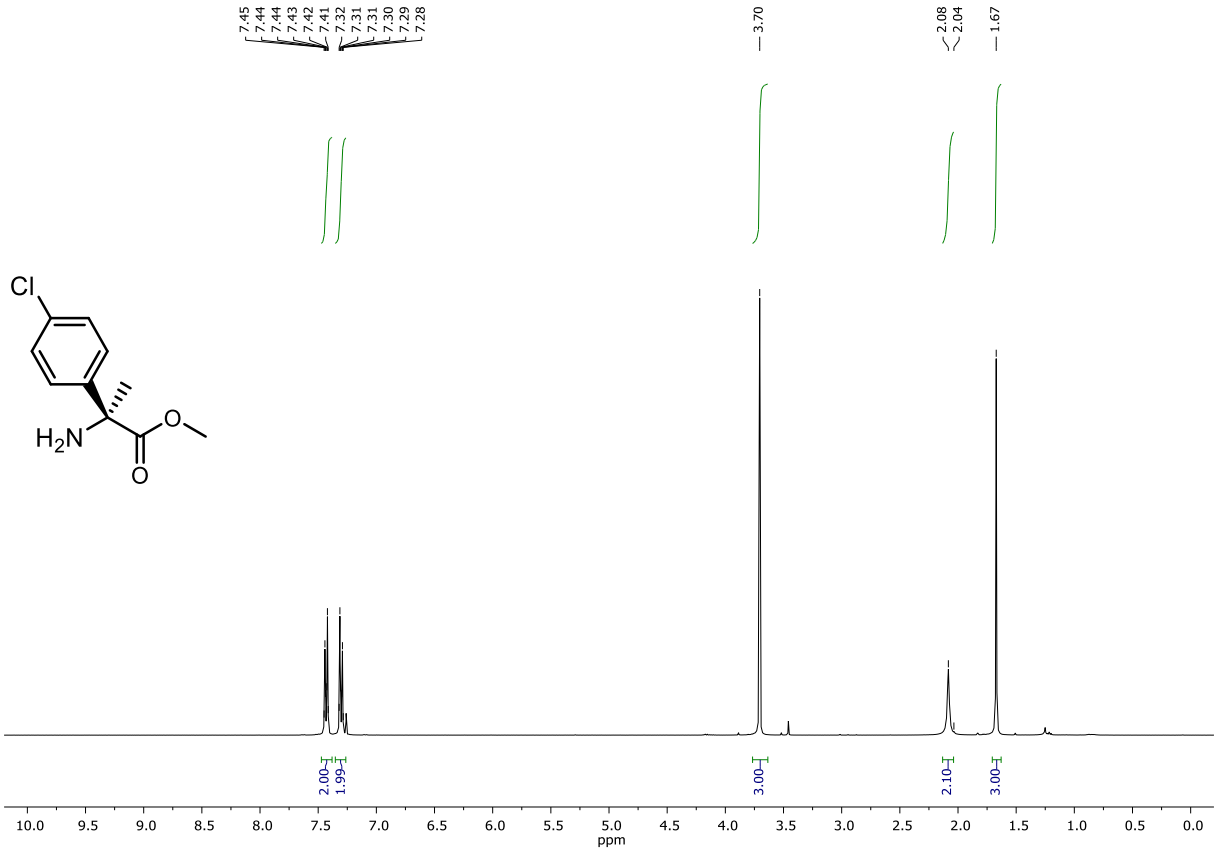
138.1
135.7
129.5
125.3
67.3
47.3
24.8
24.8
24.2
23.2
21.1
HN
O
N
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm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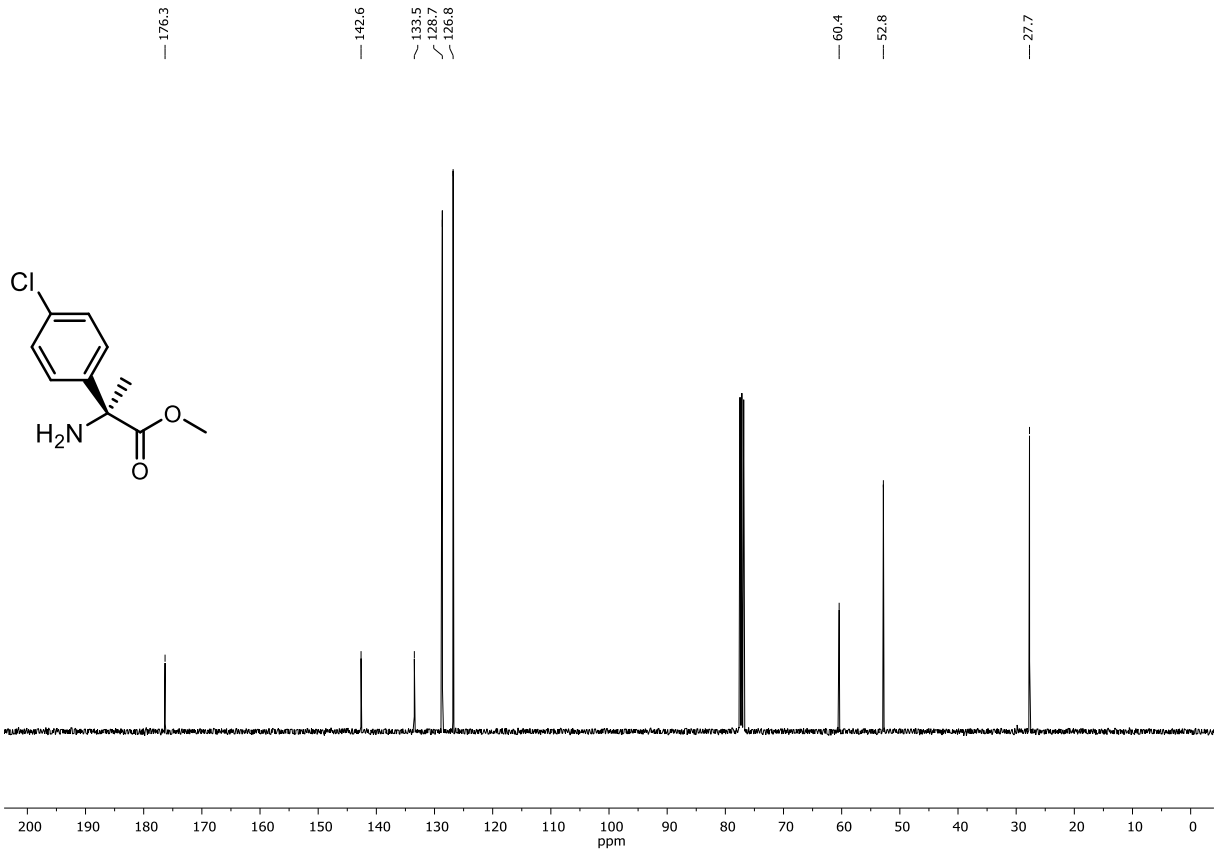
7.32
7.31
7.31
7.30
7.29
7.28
3.70
2.08
2.04
1.67
Cl
H2N
O
O
2.00
1.99
3.00
2.10
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm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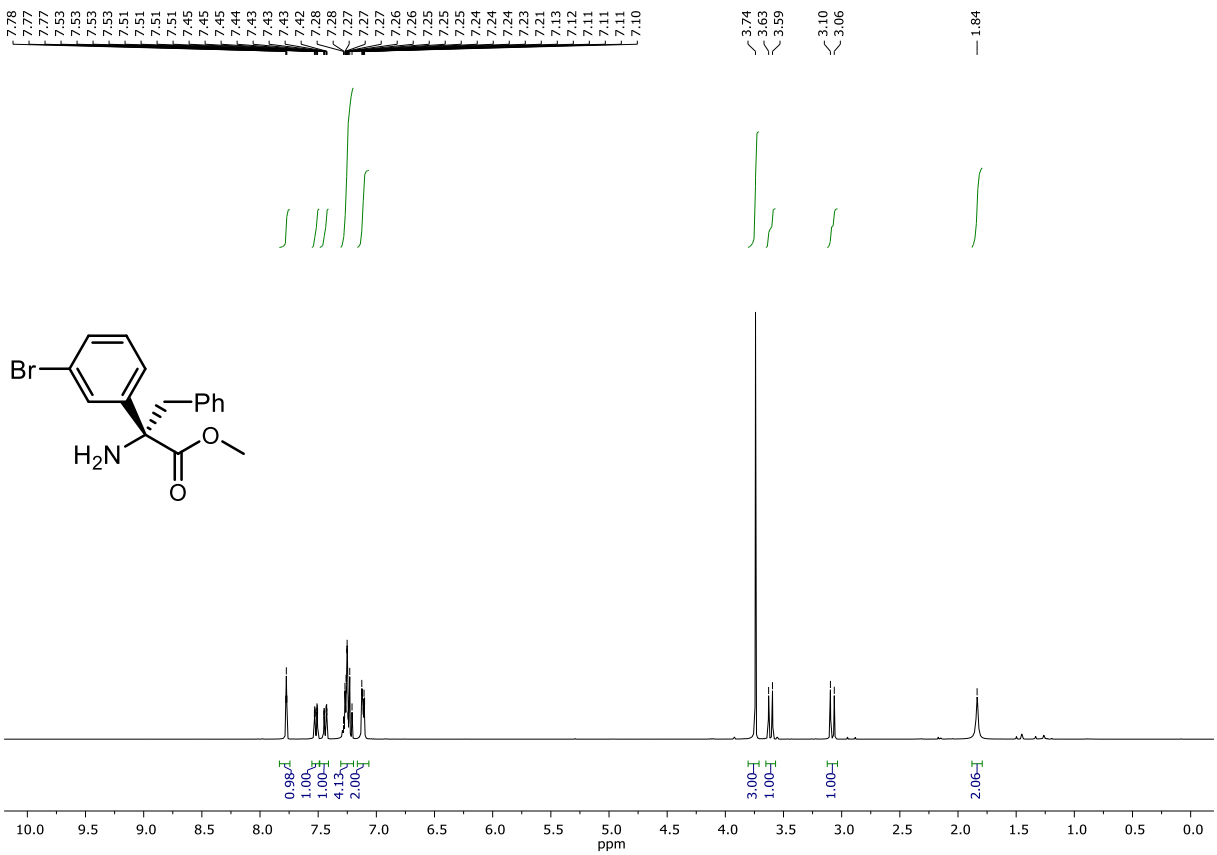
142.6
133.5
128.7
126.8
60.4
52.8
27.7
Cl
H2N
O
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm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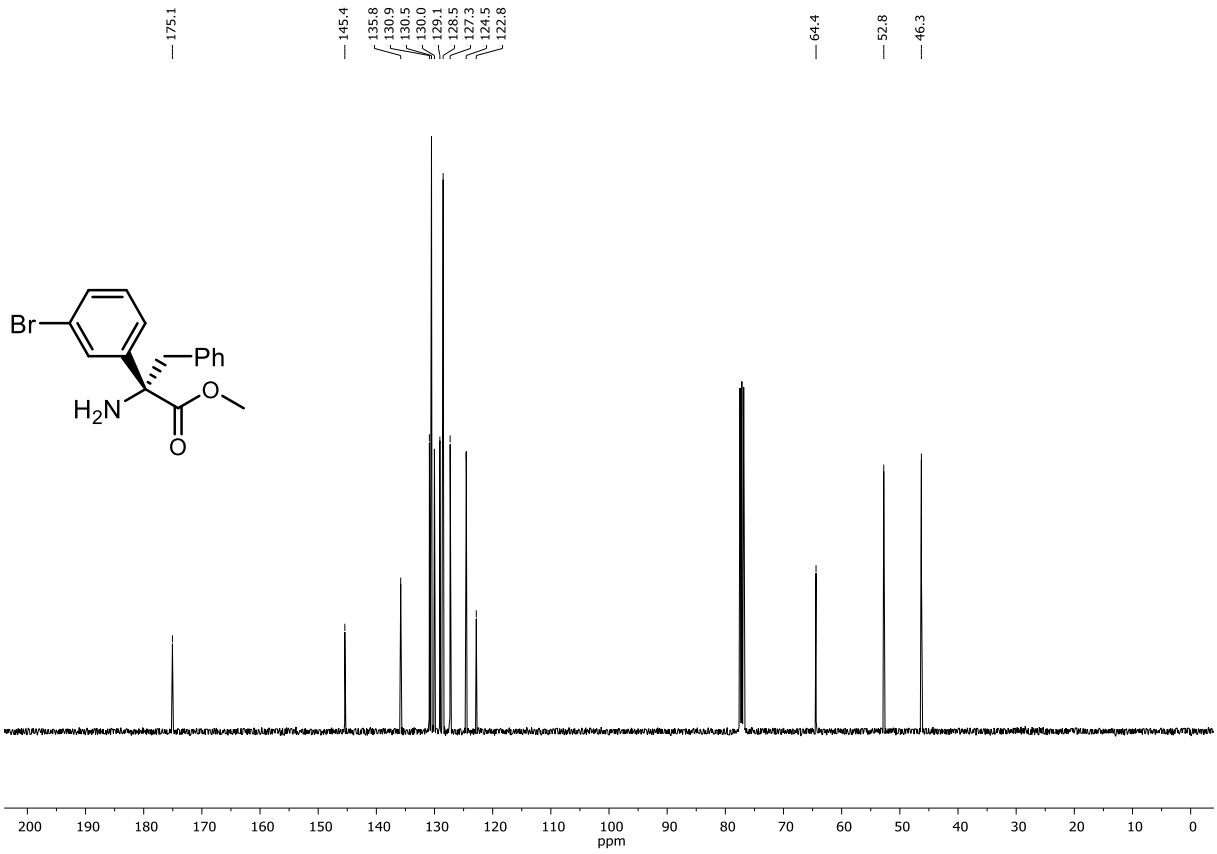
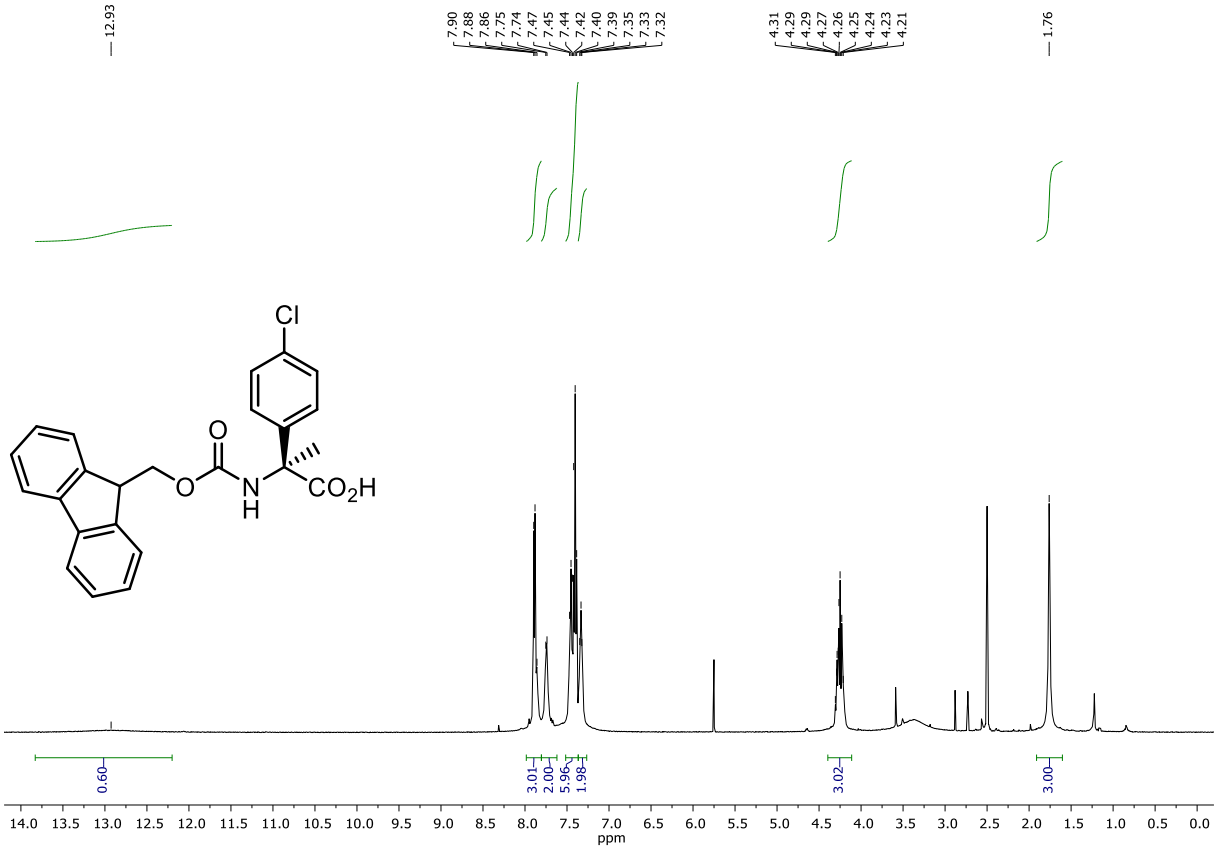
3.74 3.63 3.59
3.10 3.06
1.84
Br
Ph
H2N
O
O
0.98 1.00 1.00 4.13 2.00
3.00 1.00
1.00
2.06
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm


175.1
145.4
135.8 130.9 130.5 130.0 129.1 128.5 127.3 124.5 122.8
64.4
52.8
46.3
Br
Ph
H2N
O
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm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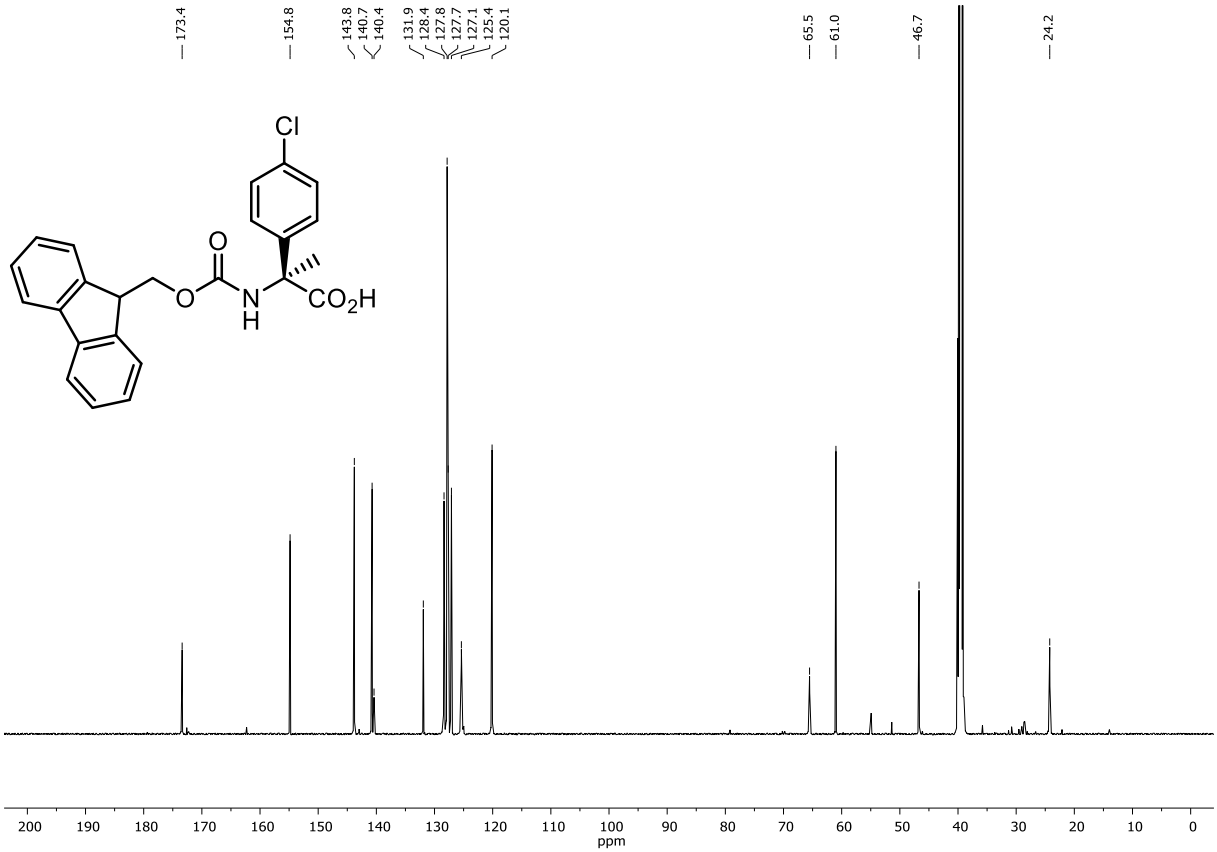
7.40
7.39
7.35
7.33
7.32
4.31
4.29
4.29
4.27
4.26
4.25
4.24
4.23
4.21
1.76
Cl
O
O
N
H
CO2H
0.60
3.01
2.00
5.96
1.98
3.02
3.00
14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm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154.8
143.8
140.7
140.4
131.9
128.4
127.8
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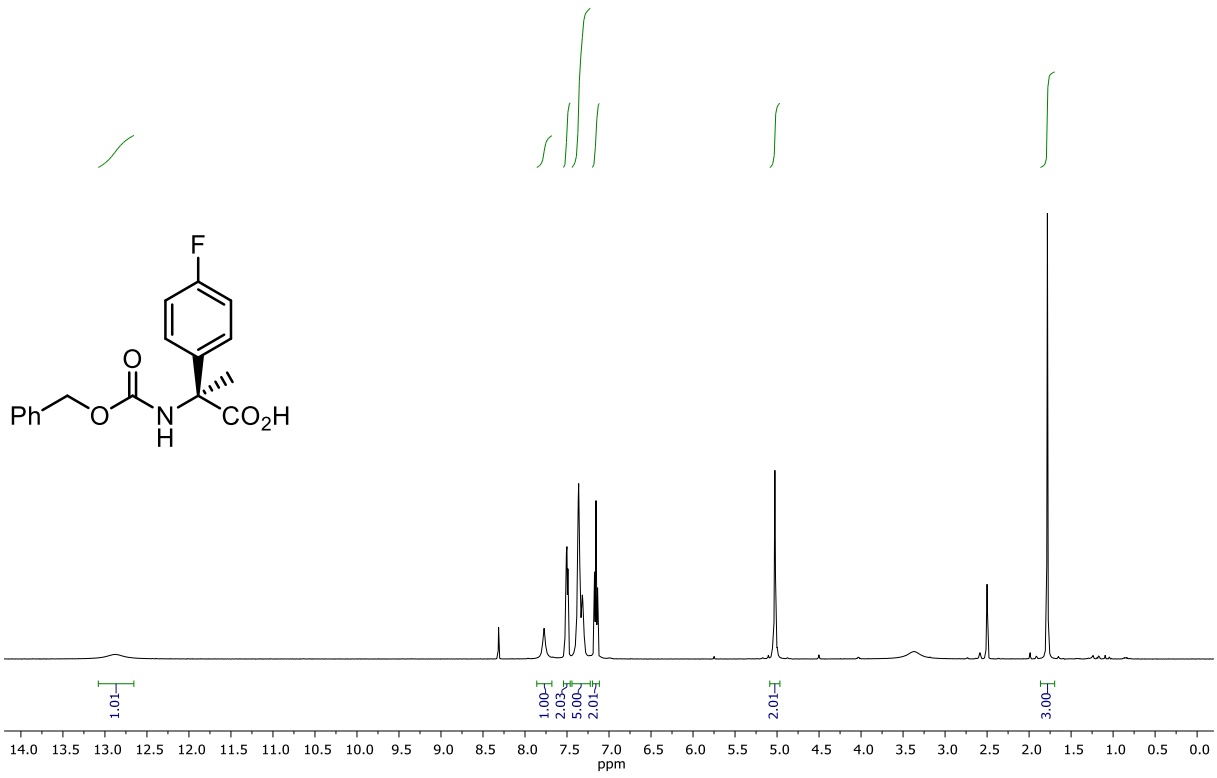
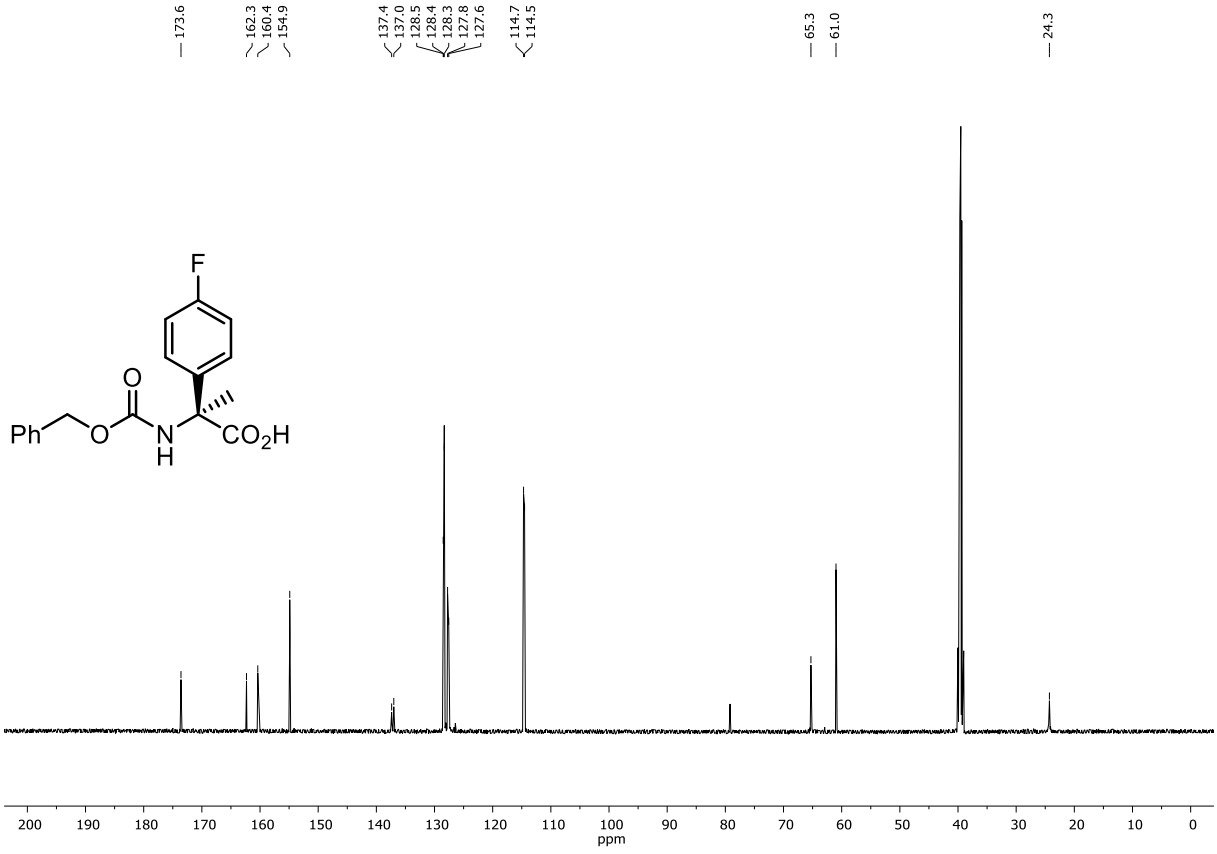
127.1
125.4
120.1
65.5
61.0
46.7
24.2
Cl
O
O
N
H
CO2H
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm


F
O
Ph
O
N
H
CO2H
1.01
1.00
2.03
5.00
2.01
2.01
3.00
14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm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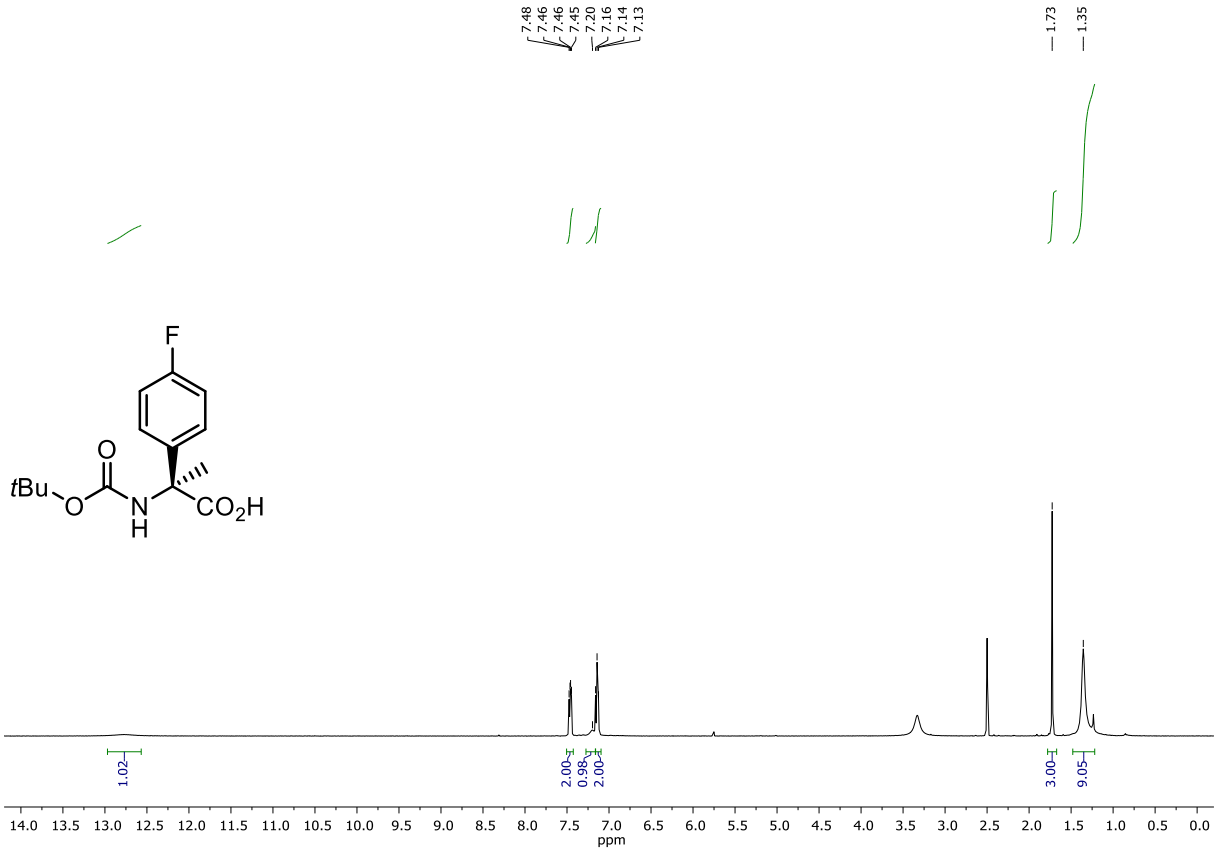
154.9
137.4
137.0
128.5
128.4
128.3
127.8
127.6
114.7
114.5
65.3
61.0
24.3
F
O
Ph
O
N
H
CO2H
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm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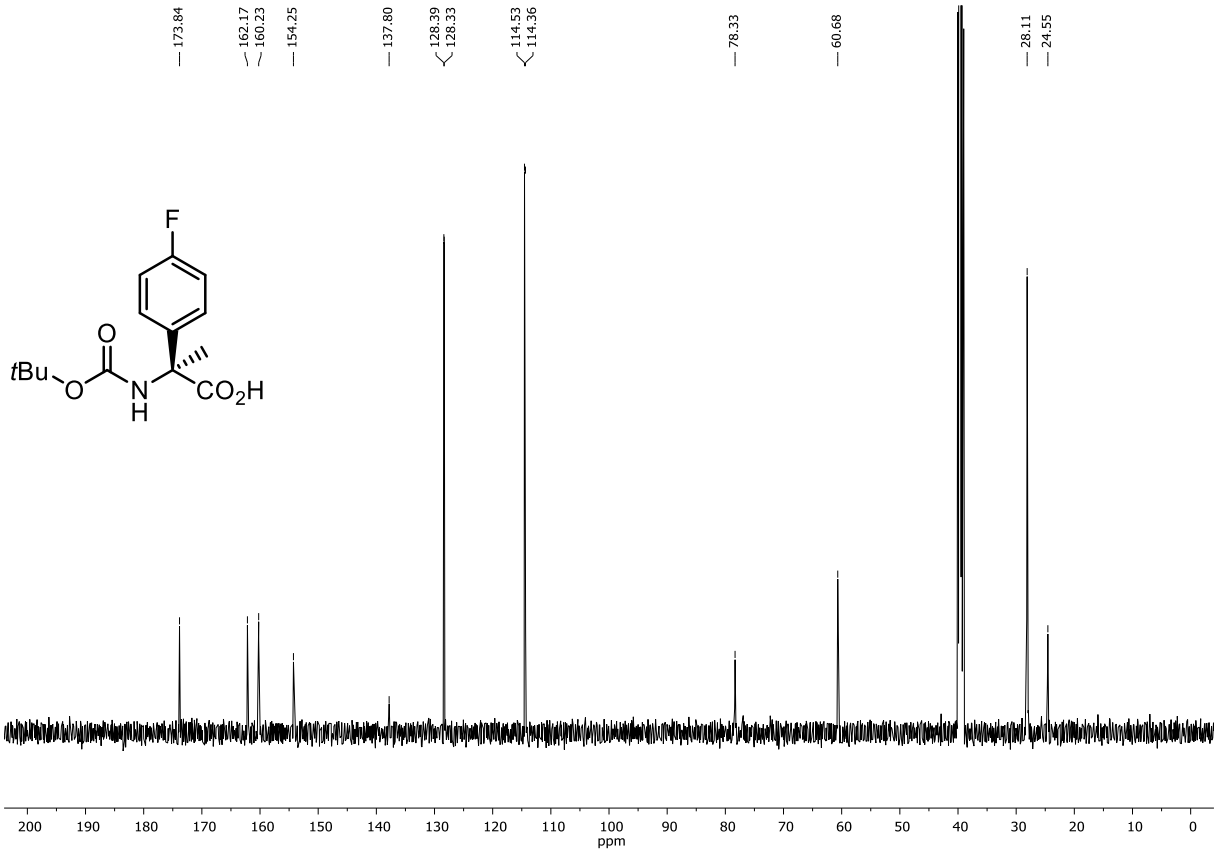
1.35
F
O
tBu
O
N
H
CO2H
1.02
2.00
0.98
2.00
3.00
9.05
14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm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60.68
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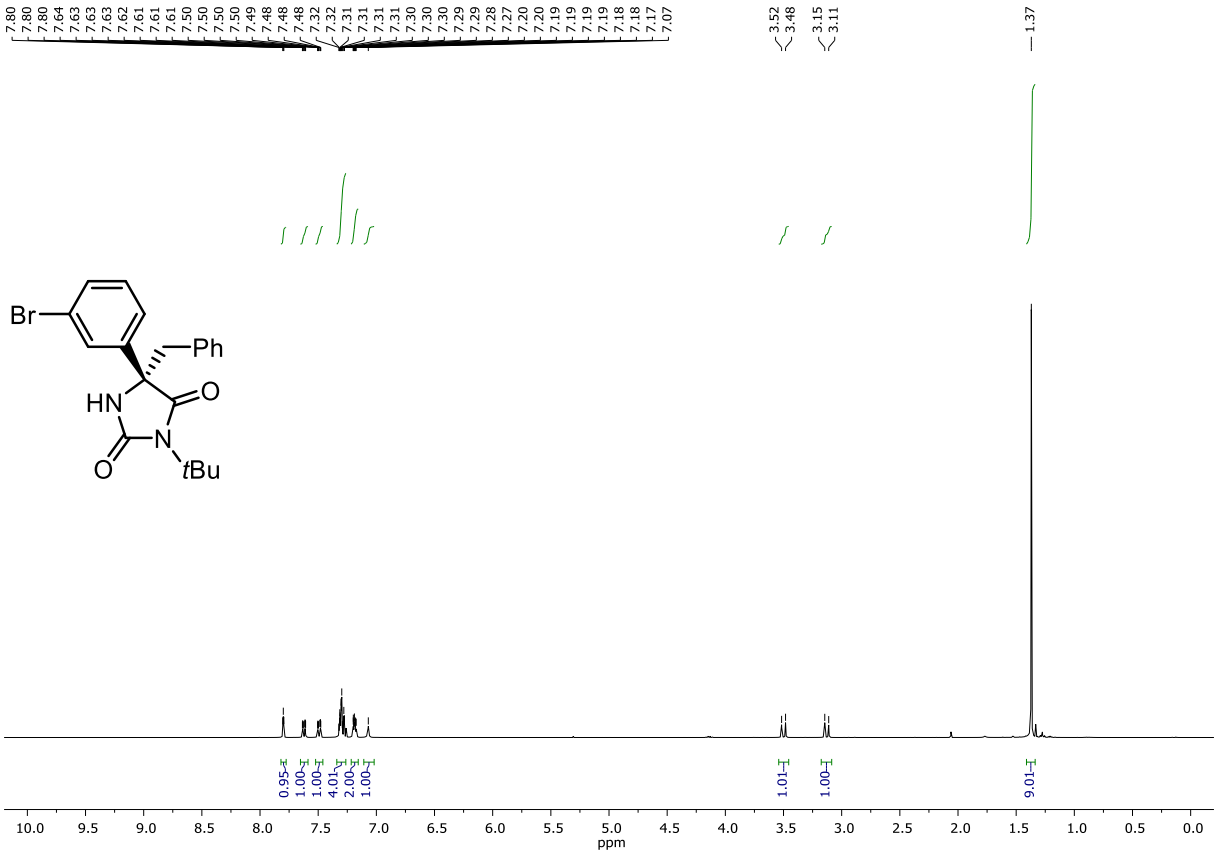
O
tBu
O
N
H
CO2H
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm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7.19
7.18
7.18
7.17
7.07
3.52
3.48
3.15
3.11
1.37
Br
Ph
HN
O
N
O
tBu
0.95
1.00
1.00
4.01
2.00
1.00
1.01
1.00
9.01
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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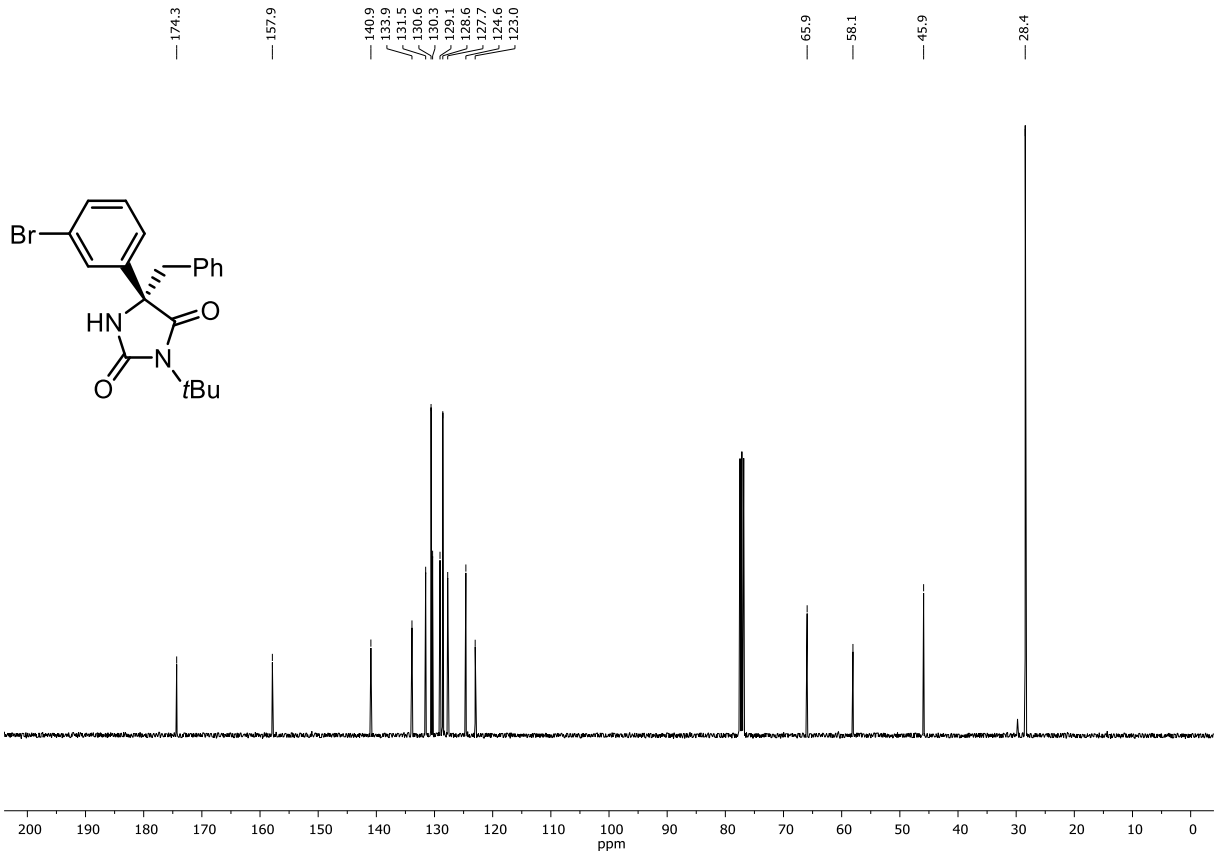
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45.9
28.4
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N
O
tBu
200
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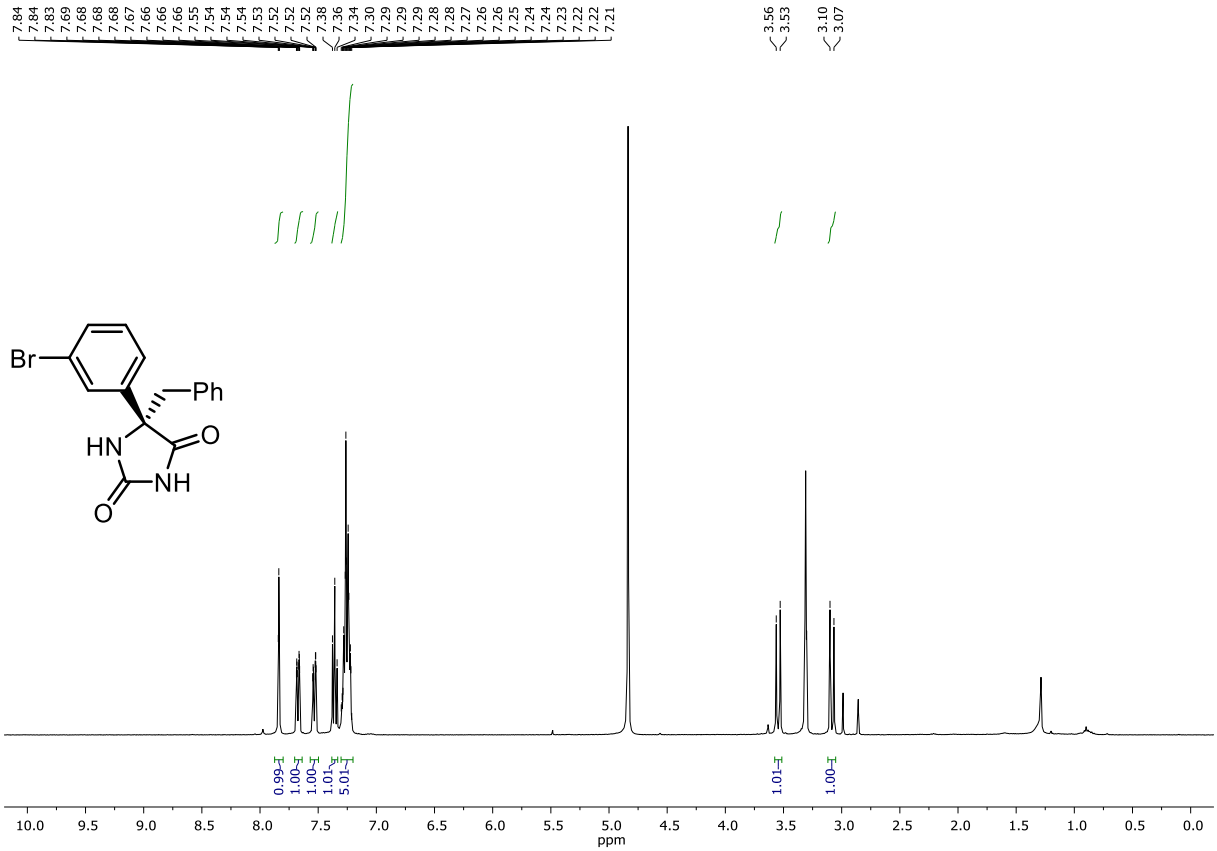
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7.22
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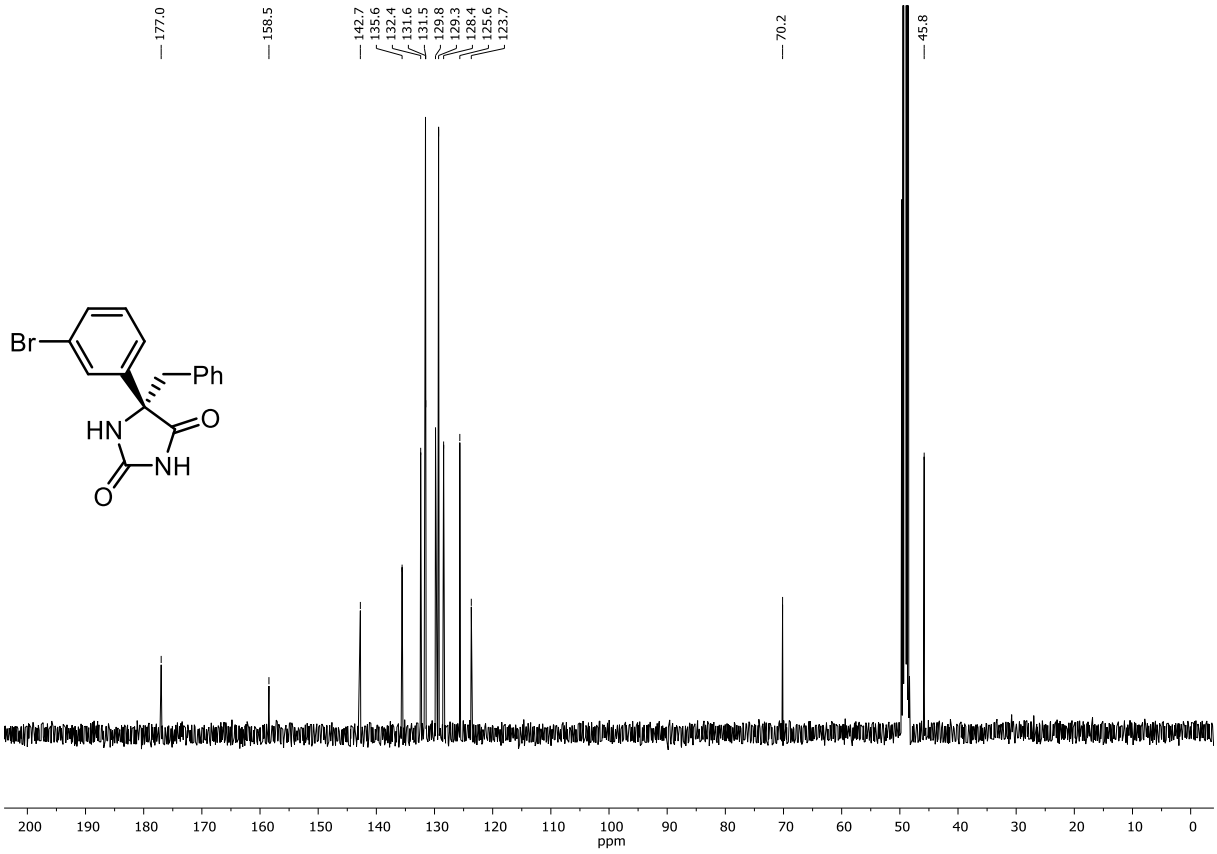
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129.8
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123.7
70.2
45.8
Br
Ph
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O
NH
O
200
190
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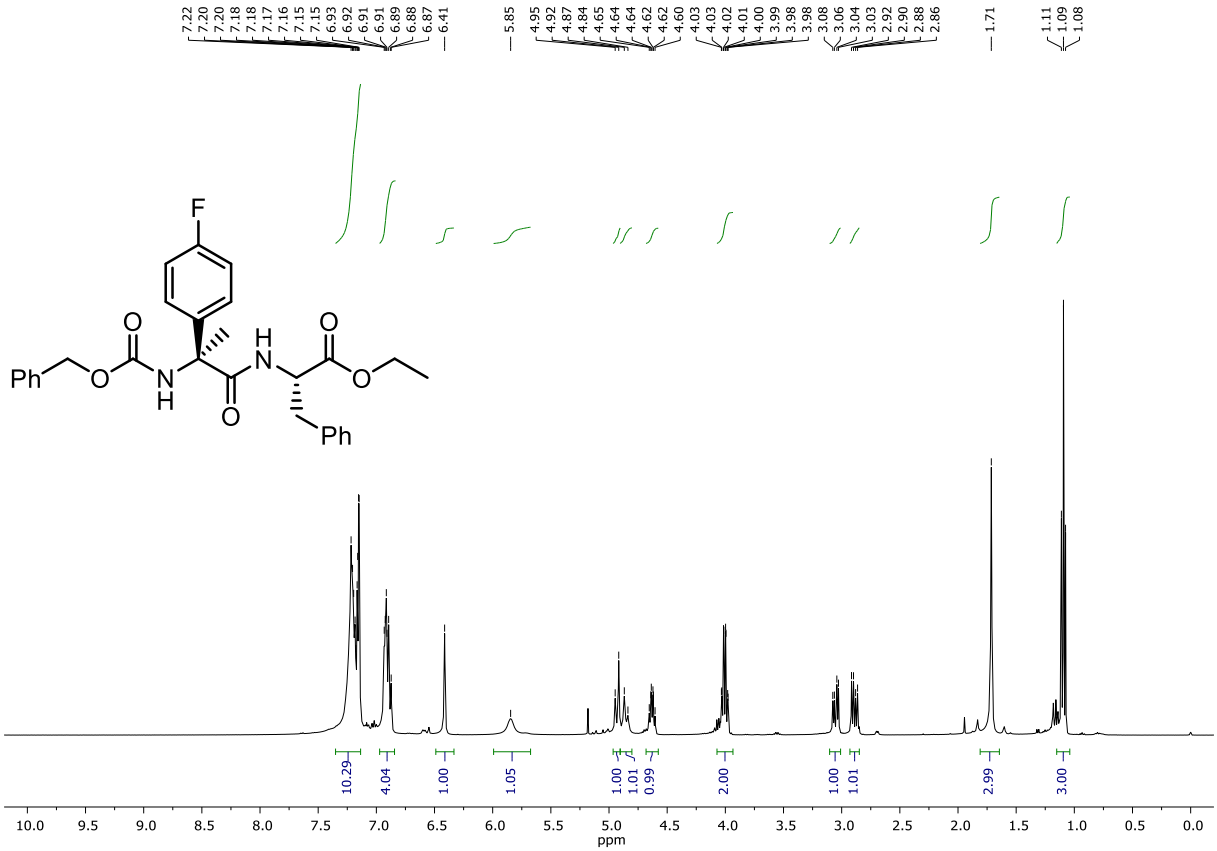
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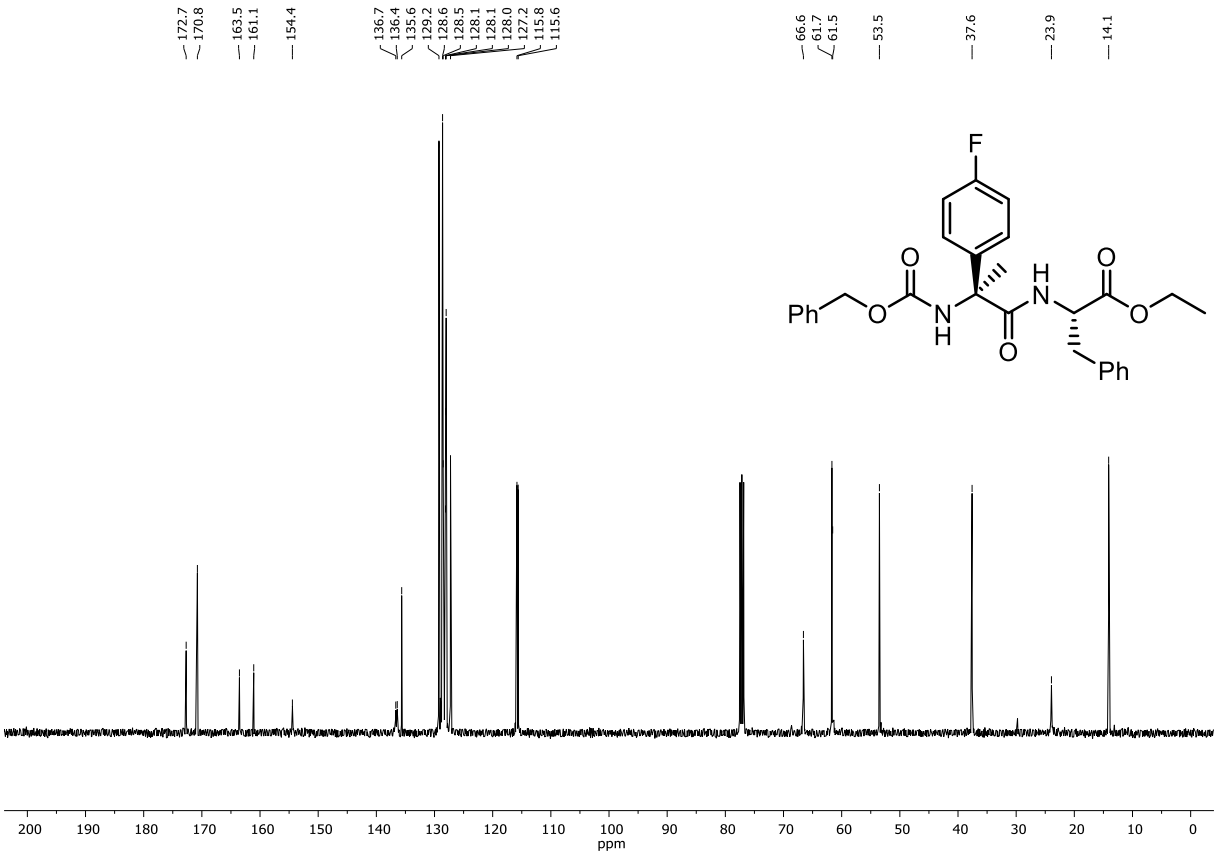
5.85
4.95 4.92 4.87 4.84 4.65 4.64 4.64 4.62 4.62 4.60
4.03 4.03 4.02 4.01 4.00 3.99 3.98 3.98
3.08 3.06 3.04 3.03 2.92 2.90 2.88 2.86
1.71
1.11 1.09 1.08
F
Ph
O
N
H
O
H
N
O
O
Ph
10.29 4.04 1.00 1.05 1.00 1.01 0.99 2.00 1.00 1.01 2.99 3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

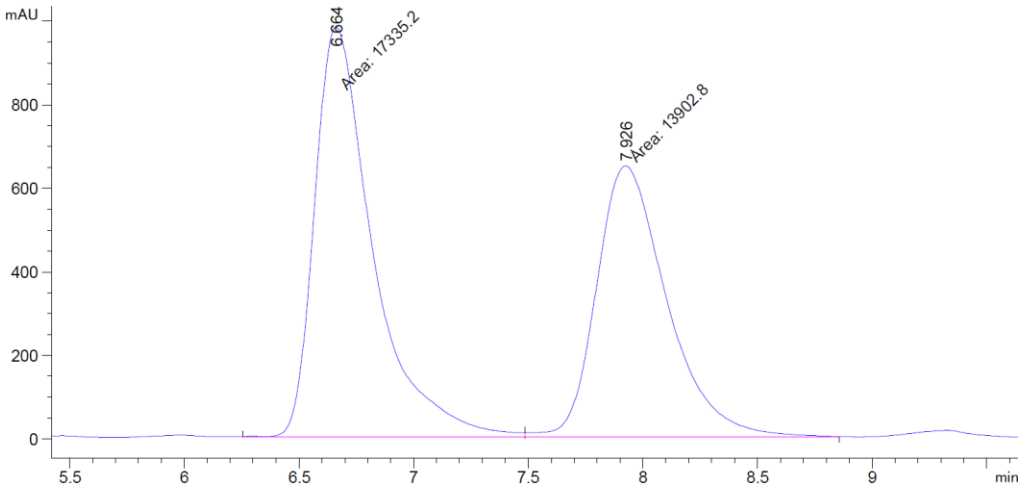

172.7 170.8
163.5 161.1
154.4
136.7 136.4 135.6 129.2 128.6 128.5 128.1 128.1 128.0 127.2 115.8 115.6
66.6 61.7 61.5
53.5
37.6
23.9
14.1
F
Ph
O
N
H
O
H
N
O
O
Ph
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

HPLC and SFC Traces

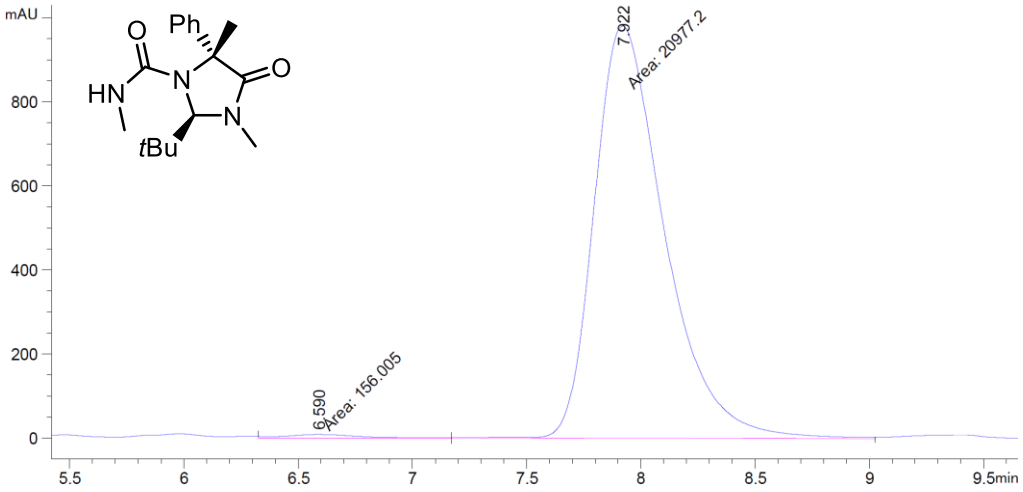
4-Ala-a

Chiral HPLC: Chiralcel® OD-H, 25 °C, 0.8 mL/min, Hexane/IPA (80:20), 210 nm

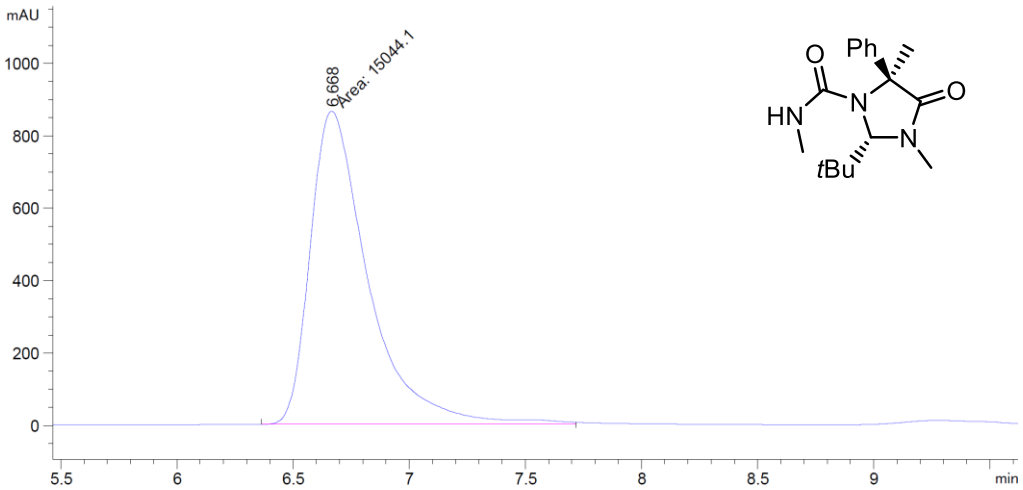
Standard: t_R = 6.66 (55.5%), 7.93 (44.5%) min, 55:45 *er*.



65: t_R = 6.59 (0.7%), 7.92 (99.3%) min, >99:1 *er*.



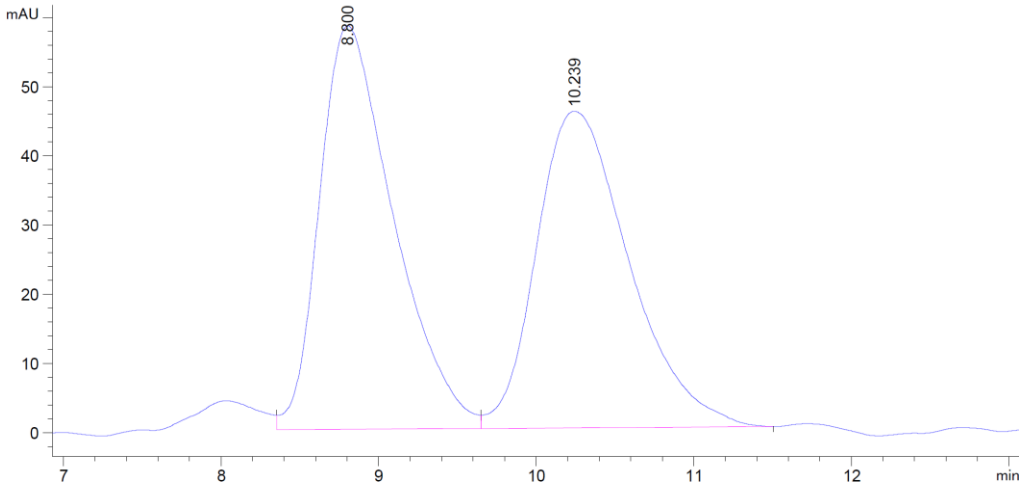
64: t_R = 6.67 (100%) min, >99:1 *er*.



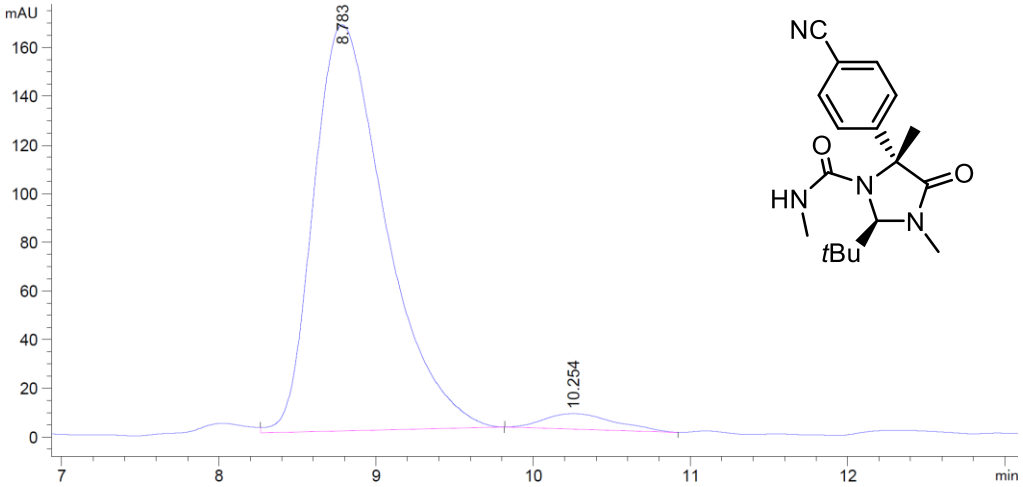
4-Ala-c

Chiral HPLC: Chiralcel® OD-H, 25 °C, 1.0 mL/min, Hexane/IPA (80:20), 230 nm

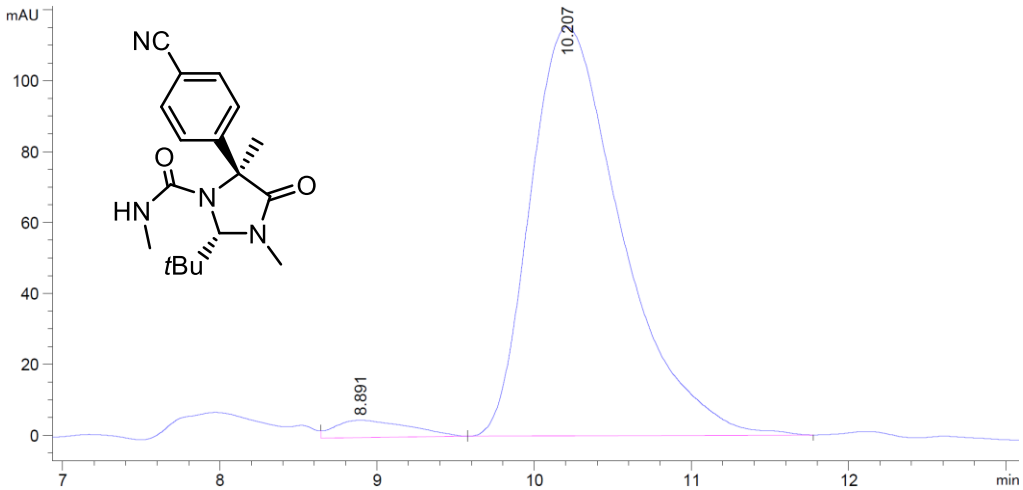
Standard: t_R = 8.80 (50.5%), 10.24 (49.5%) min, 51:49 *er*.



66: t_R = 8.78 (96.4%), 10.25 (3.6%) min, 96:4 *er*.



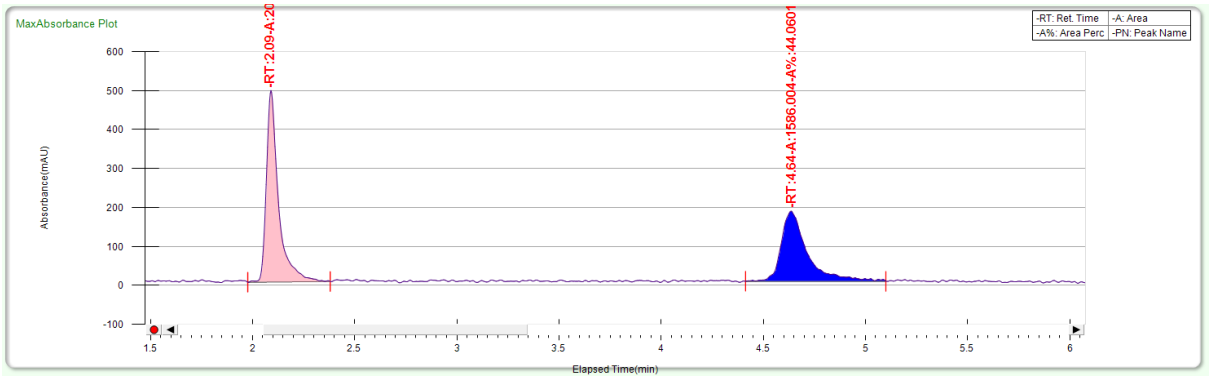
67: t_R = 8.89 (3.3%), 10.21 (96.7%) min, 97:3 *er*.



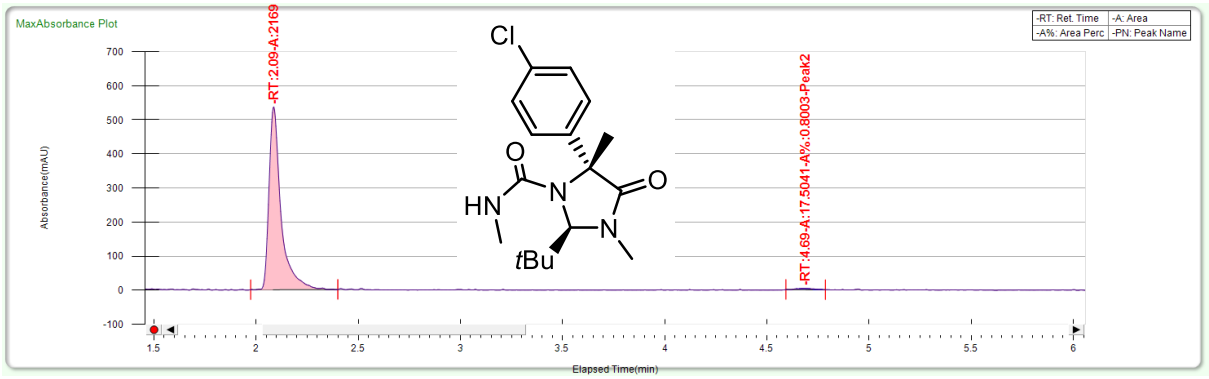
4-Ala-i

Chiral SFC: Chiralpak® IA, 125 bar, 40 °C, 4.0 mL/min, 20% co-solvent (IPA), λ_{max}

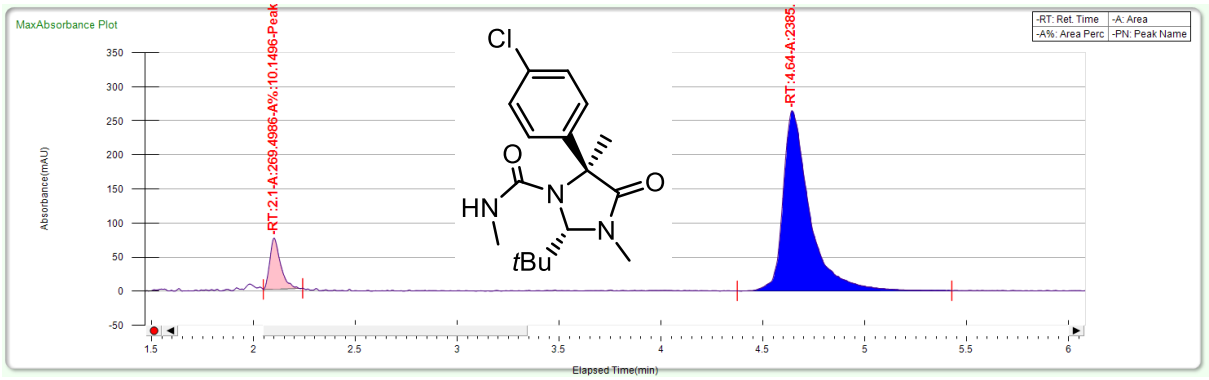
Standard: t_R = 2.09 (55.9%), 4.64 (44.1%) min, 56:44 *er*.



68: t_R = 2.09 (99.2%), 4.69 (0.80%) min, >99:1 *er*.



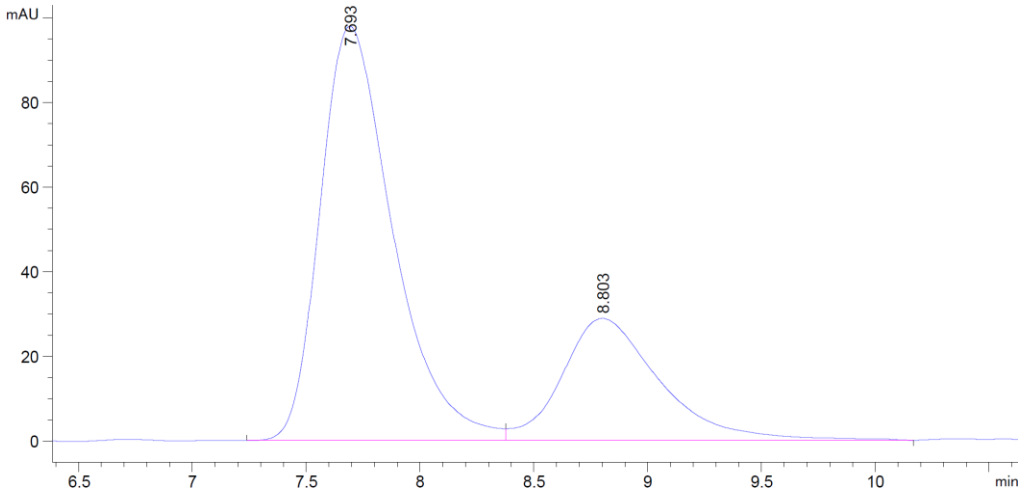
69: t_R = 2.10 (10.1%), 4.64 (89.9%) min, 90:10 *er*.



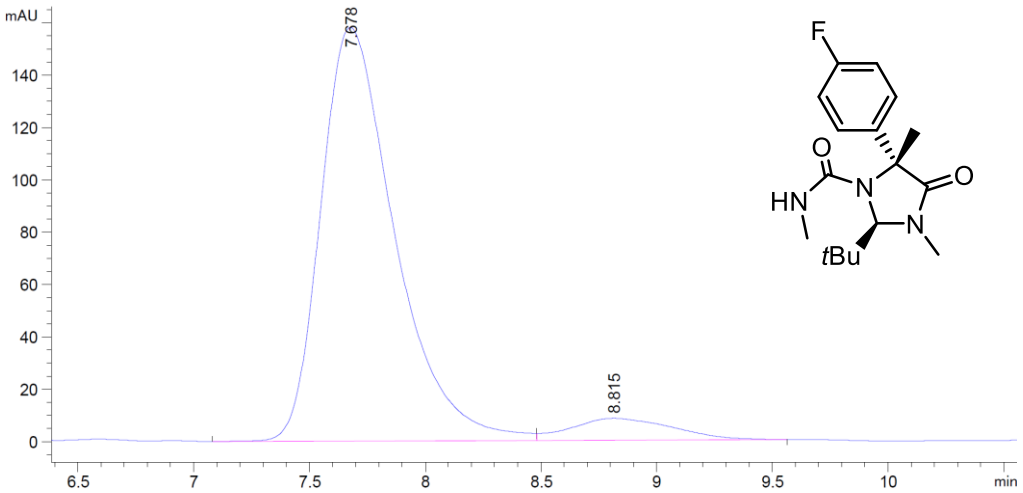
4-Ala-h

Chiral HPLC: Chiralcel® OD-H, 25 °C, 1.0 mL/min, Hexane/IPA (90:10), 210 nm

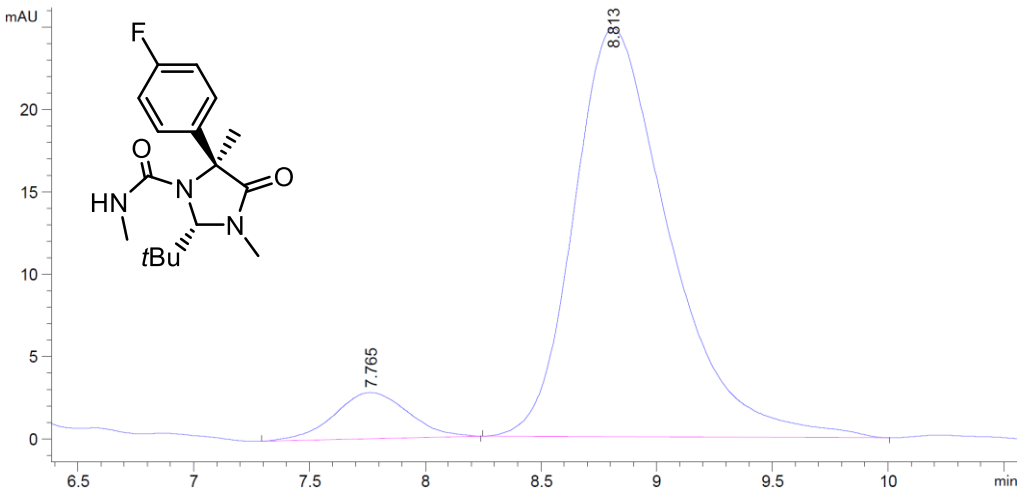
Standard: t_R = 7.69 (71.7%), 8.80 (28.3%) min, 72:28 *er*.



70: t_R = 7.68 (93.2%), 8.82 (6.8%) min, 93:7 *er*.



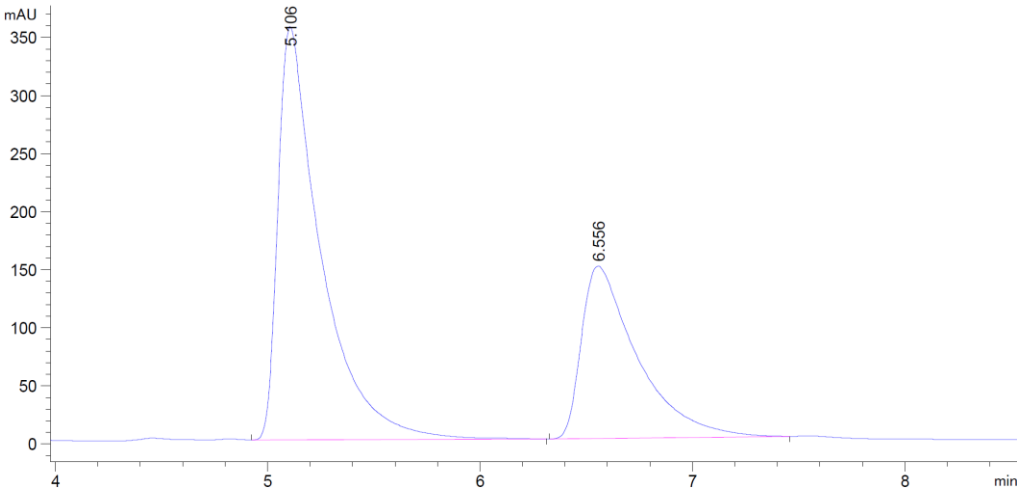
71: t_R = 7.77 (8.0%), 8.81 (92.0%) min, 92:8 *er*.



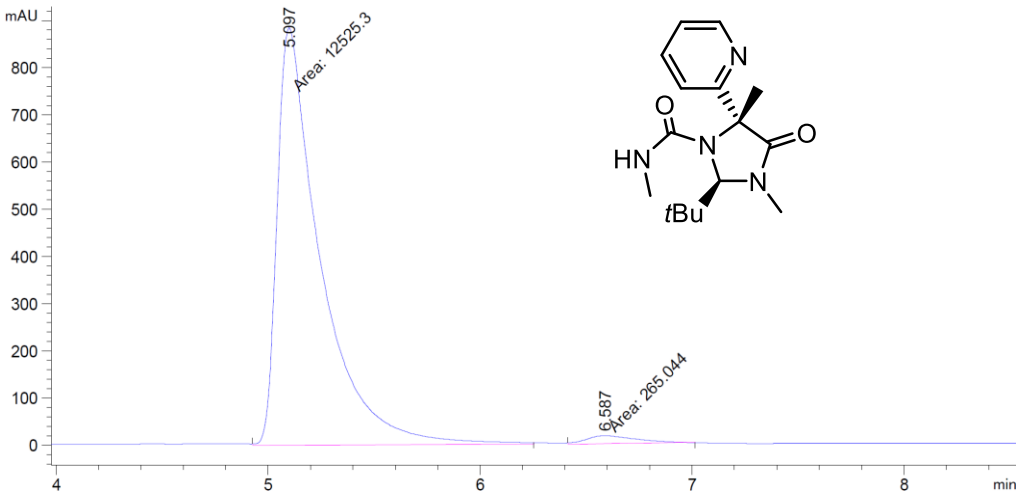
4-Ala-m

Chiral HPLC: Chiralcel® AD-H, 25 °C, 1.0 mL/min, Hexane/IPA (80:20), 210 nm

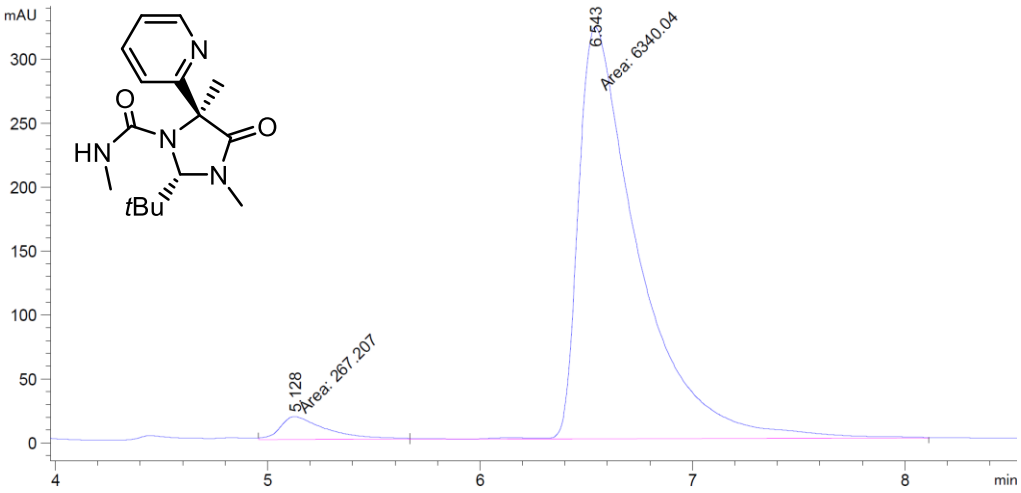
Standard: t_R = 5.11 (64.8%), 6.56 (35.2%) min, 65:35 *er*.



72: t_R = 5.10 (97.9%), 6.59 (2.1%) min, 98:2 *er*.



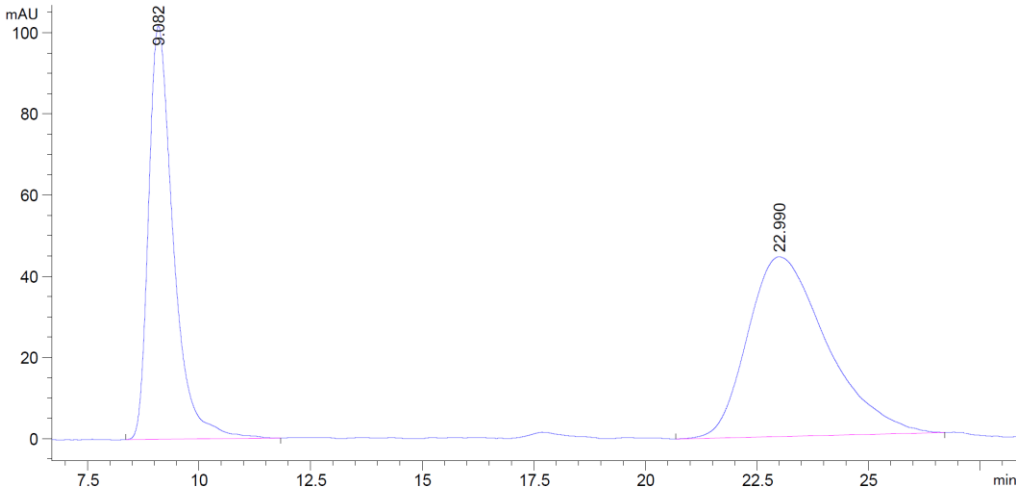
73: t_R = 5.13 (4.0%), 6.59 (96.0%) min, 96:4 *er*.



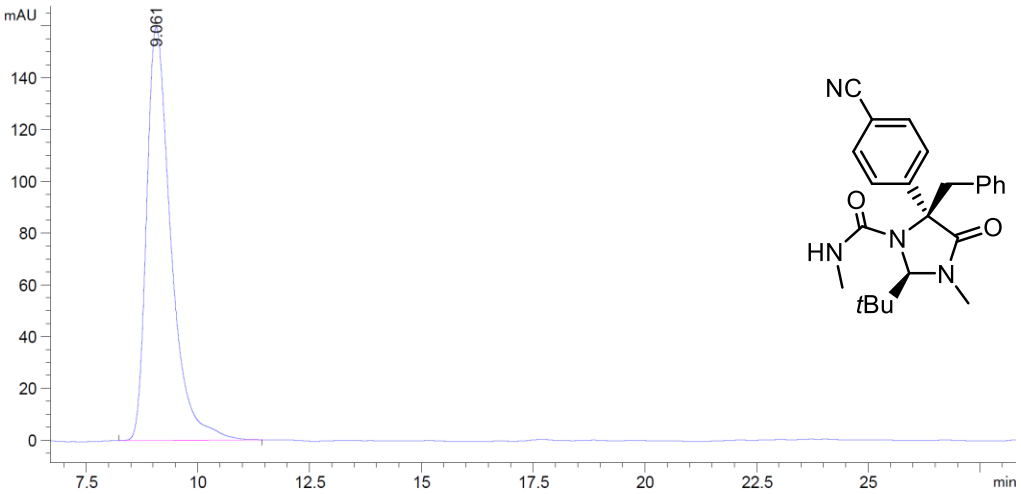
4-Phe-c

Chiral HPLC: Chiralcel® OD-H, 25 °C, 1.0 mL/min, Hexane/IPA (80:20), 210 nm

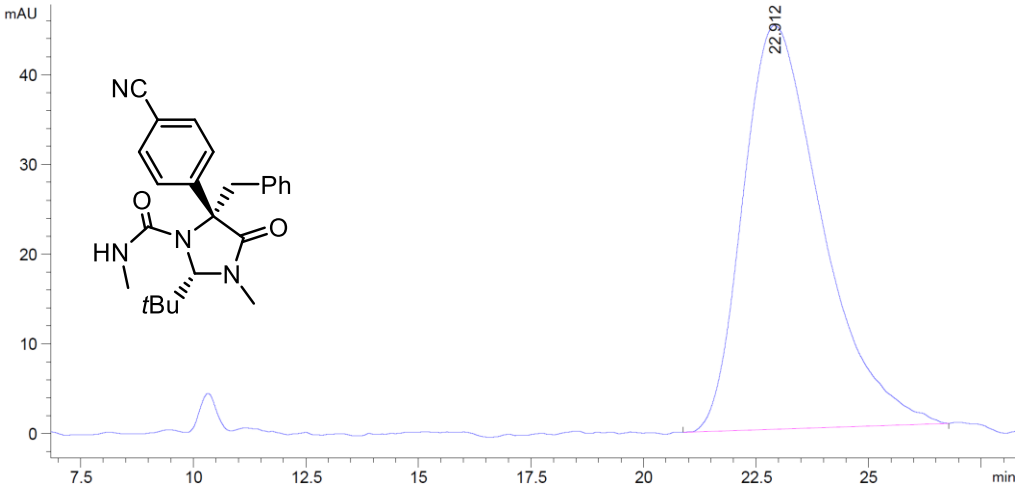
Standard: t_R = 9.08 (41.9%), 22.99 (58.1%) min, 58:42 *er*.



78: t_R = 9.06 (100%) min, >99:1 *er*.



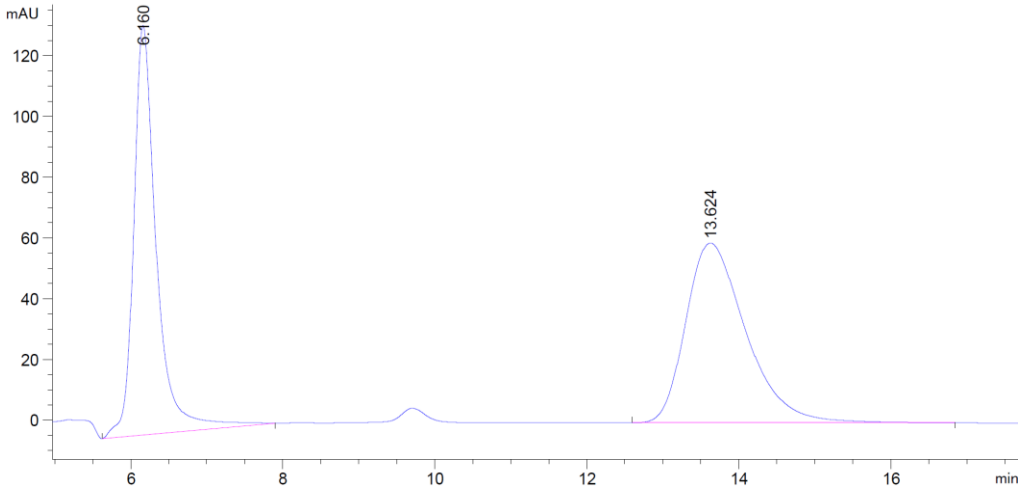
79: t_R = 22.91 (100%) min, >99:1 *er*.



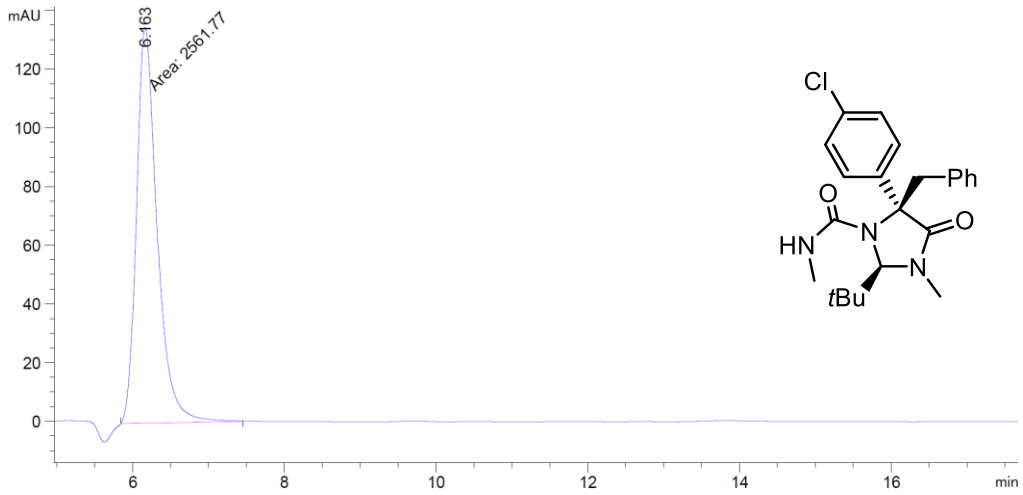
4-Phe-i

Chiral HPLC: Chiralcel® OD-H, 25 °C, 1.0 mL/min, Hexane/IPA (80:20), 225 nm

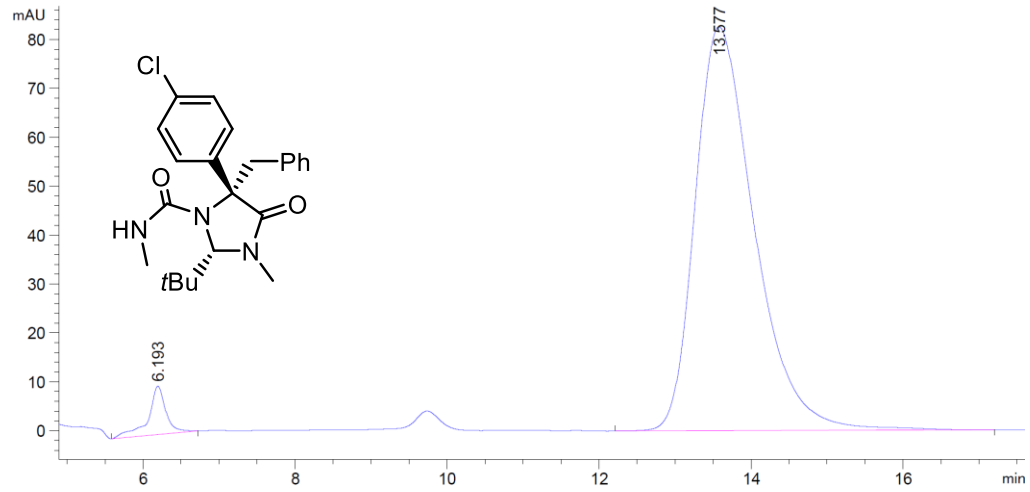
Standard: t_R = 6.16 (46.4%), 13.62 (58.1%) min, 58:42 *er*.



80: t_R = 6.16 (100%) min, >99:1 *er*.



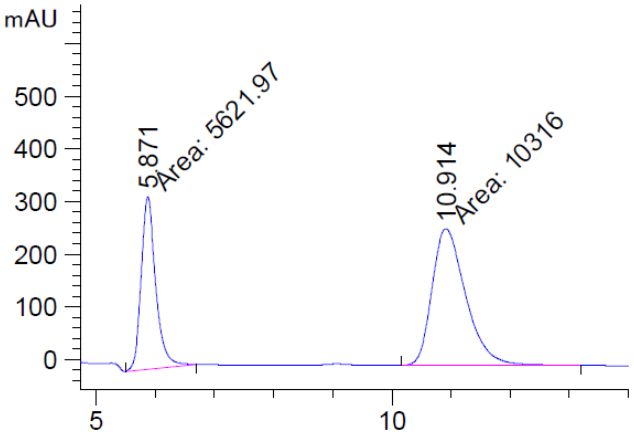
81: t_R = 6.19 (3.5%), 13.62 (96.5%) min, 97:3 *er*.



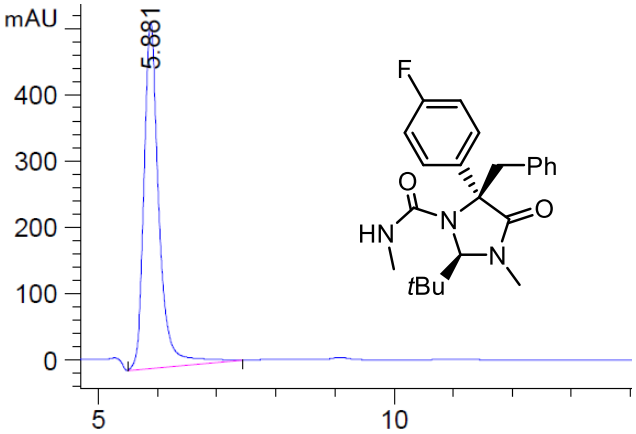
4-Phe-h

Chiral HPLC: Chiralcel® OD-H, 25 °C, 1.0 mL/min, Hexane/IPA (80:20), 210 nm

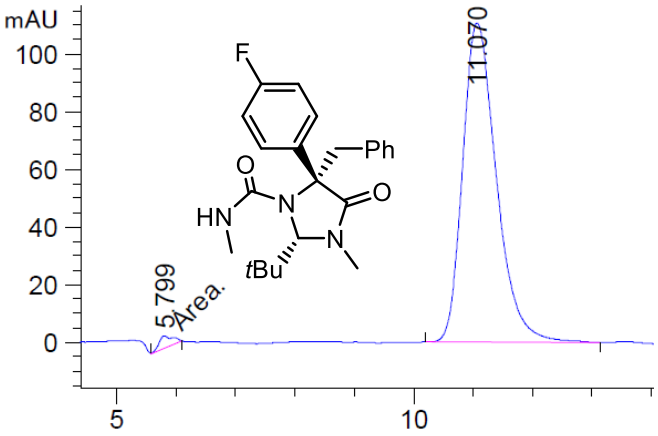
Standard: t_R = 5.87 (35.3%), 10.91 (64.7%) min, 65:35 *er*.



82: t_R = 5.88 (100%) min, >99:1 *er*.



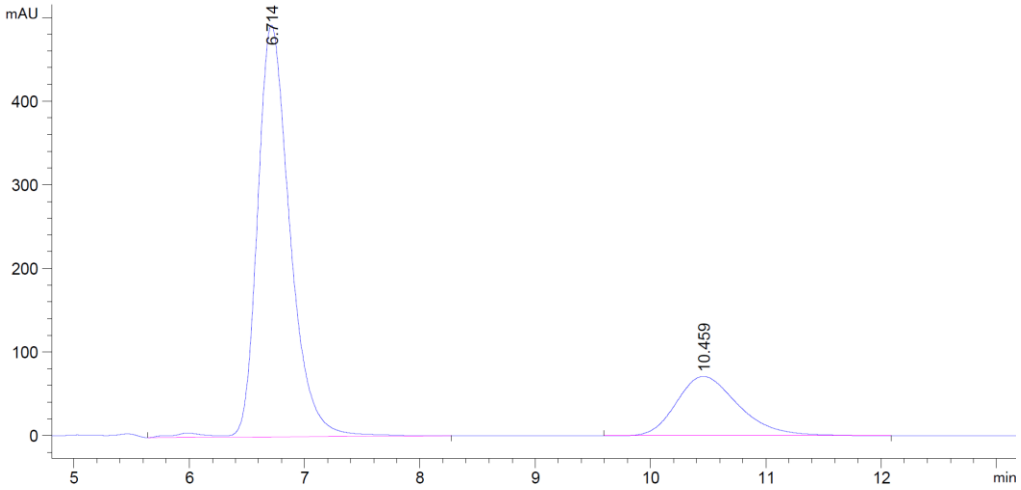
83: t_R = 5.80 (1.5%), 10.91 (98.5%) min, 99:1 *er*.



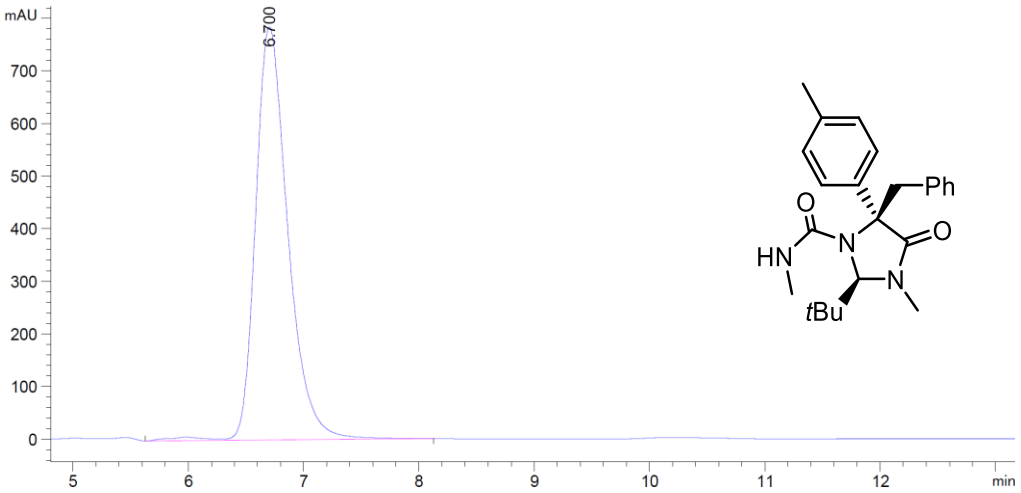
4-Phe-b

Chiral HPLC: Chiralcel® OD-H, 25 °C, 1.0 mL/min, Hexane/IPA (80:20), 210 nm

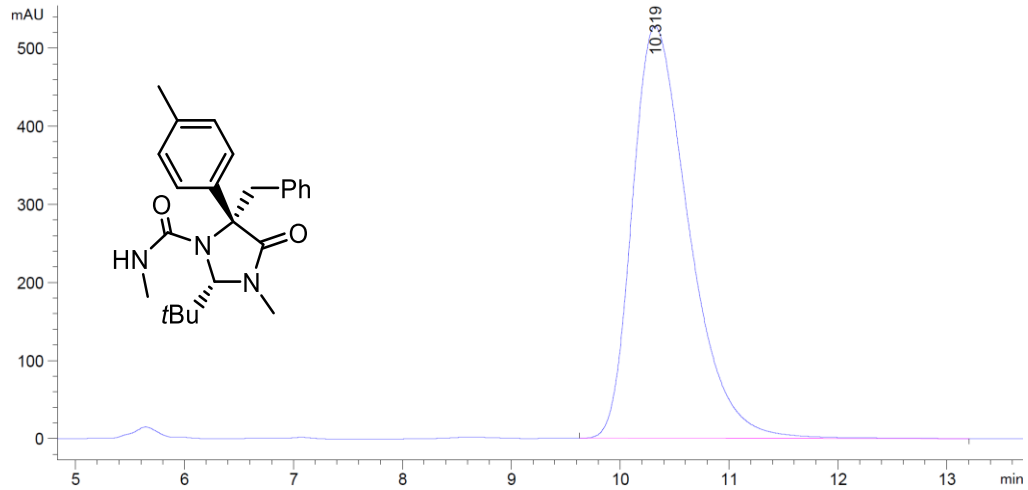
Standard: t_R = 6.71 (78.3%), 10.46 (21.7%) min, 78:22 *er*.



84: t_R = 6.70 (100%) min, >99:1 *er*.



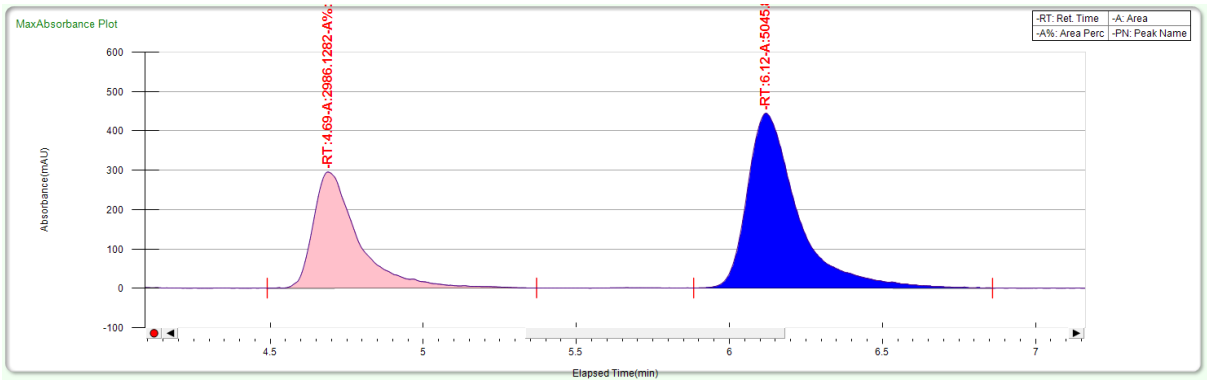
85: t_R = 10.32 (100%) min, >99:1 *er*.



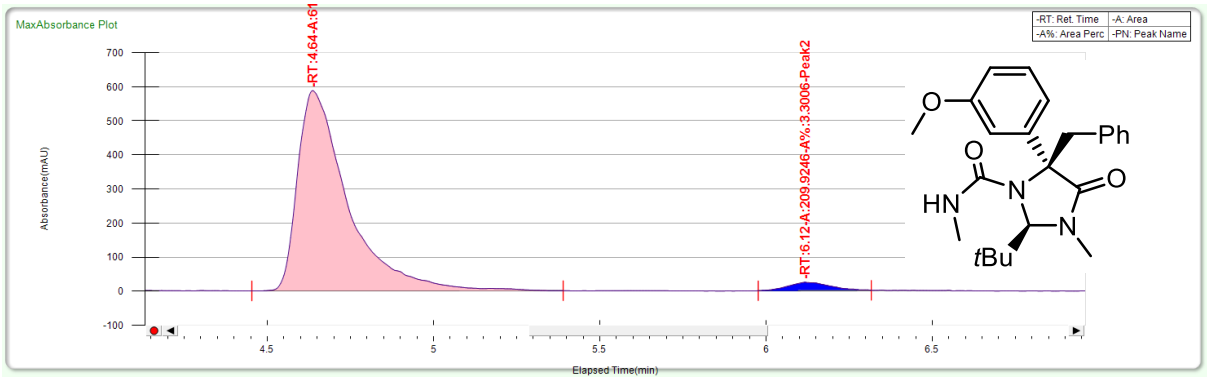
4-Phe-e

Chiral SFC: Chiralpak® IA, 125 bar, 40 °C, 4.0 mL/min, 20% co-solvent (IPA), λ_{max}

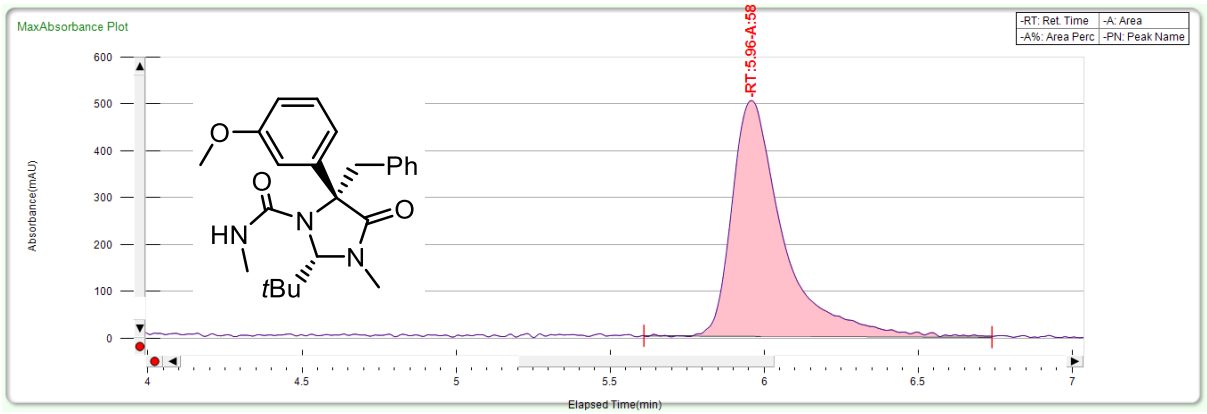
Standard: t_R = 4.69 (37.2%), 6.12 (62.8%) min, 63:37 *er*.



86: t_R = 4.64 (96.7%), 6.12 (3.3%) min, 97:3 *er*.



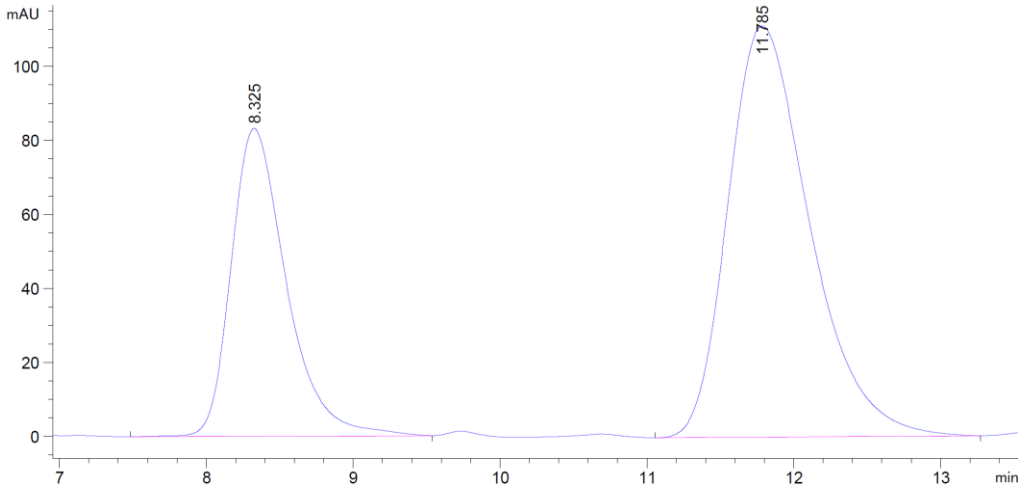
87: t_R = 5.96 (100%) min, >99:1 *er*.



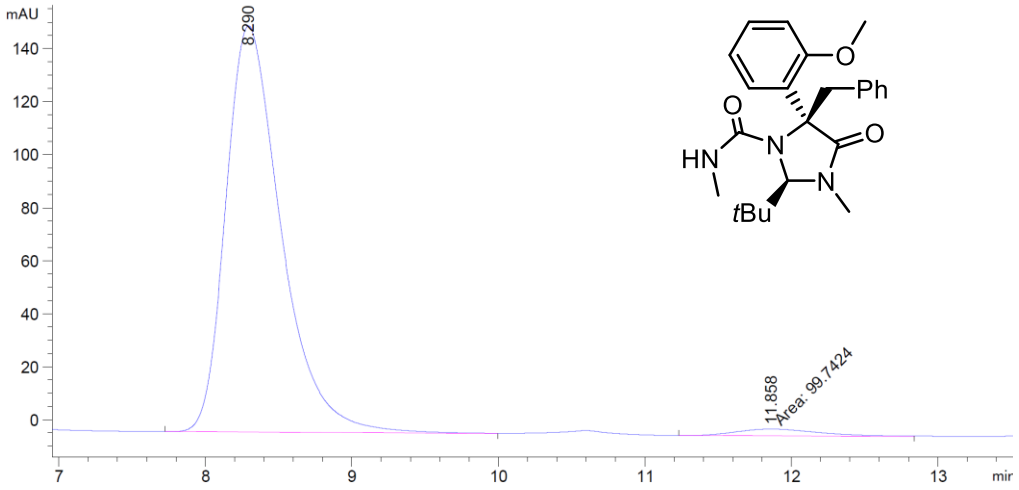
4-Phe-f

Chiral HPLC: Chiralcel® OD-H, 25 °C, 0.8 mL/min, Hexane/IPA (80:20), 225 nm

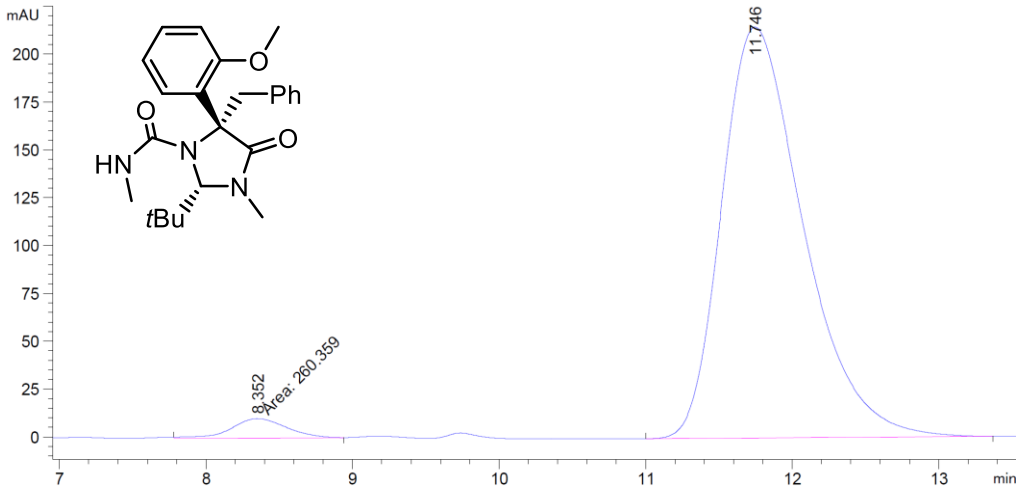
Standard: t_R = 8.33 (33.6%), 11.79 (66.4%) min, 66:33 *er*.



88: t_R = 8.29 (97.6%), 11.86 (2.4%) min, 98:2 *er*.



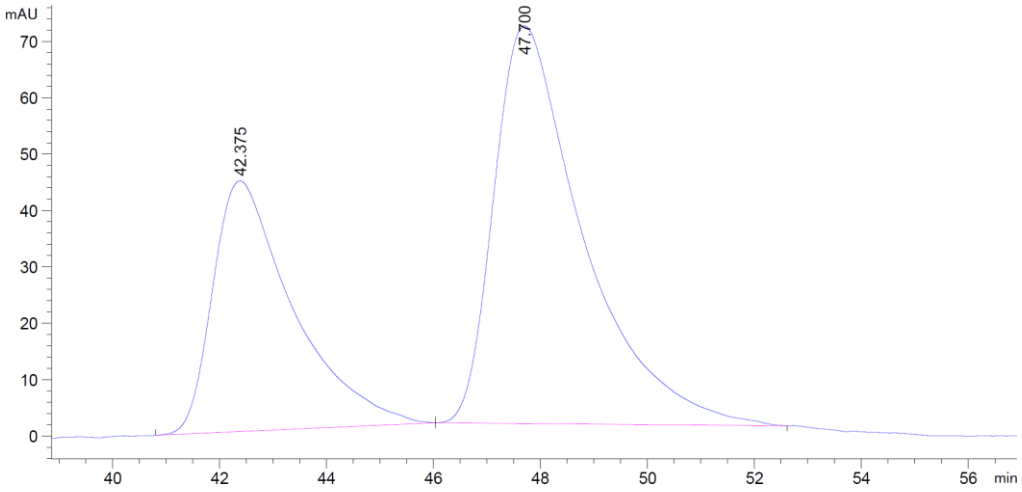
89: t_R = 8.35 (3.0%), 11.75 (97.0%) min, 97:3 *er*.



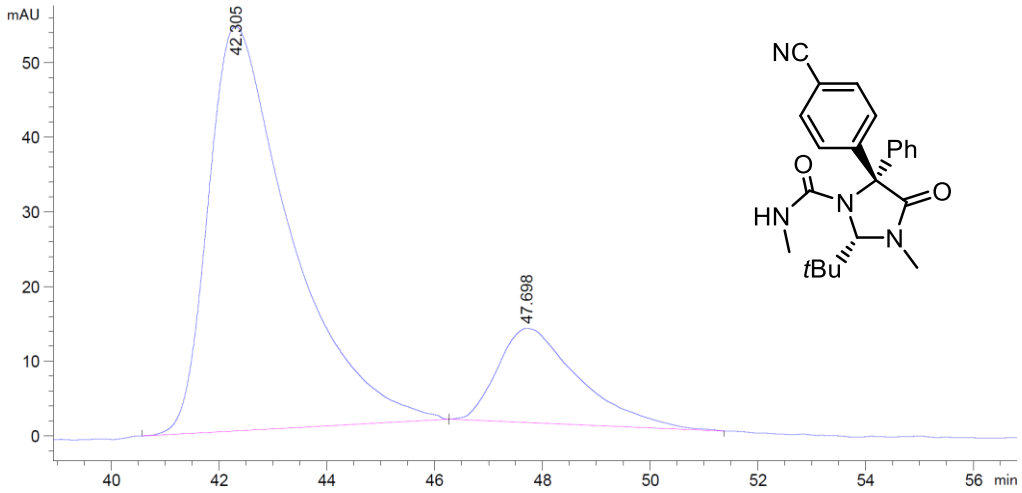
4-Phg-c

Chiral HPLC: Chiralcel® OD-H, 25 °C, 0.8 mL/min, Hexane/IPA (80:20), 225 nm

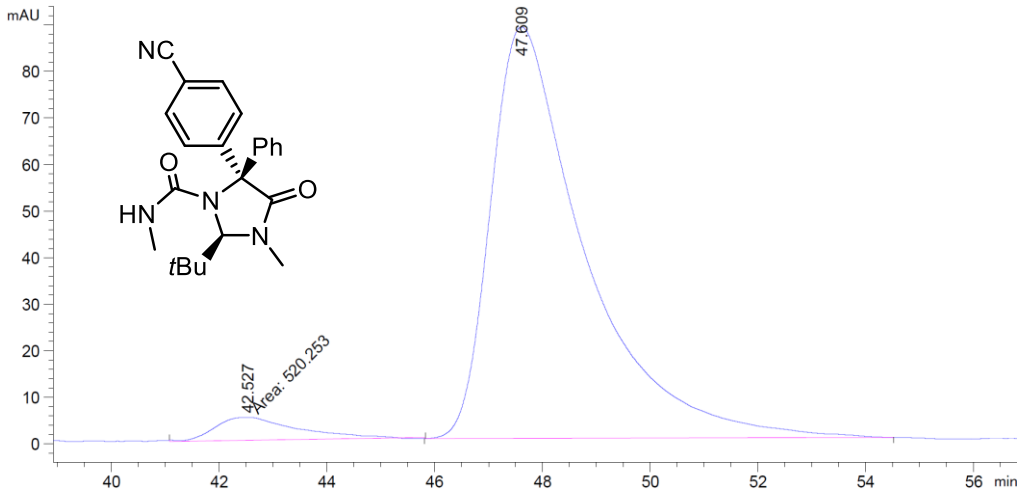
Standard: t_R = 42.38 (36.2%), 47.70 (63.8%) min, 64:36 *er*.



92: t_R = 42.31 (81.4%), 47.70 (18.6%) min, 81:19 *er*.



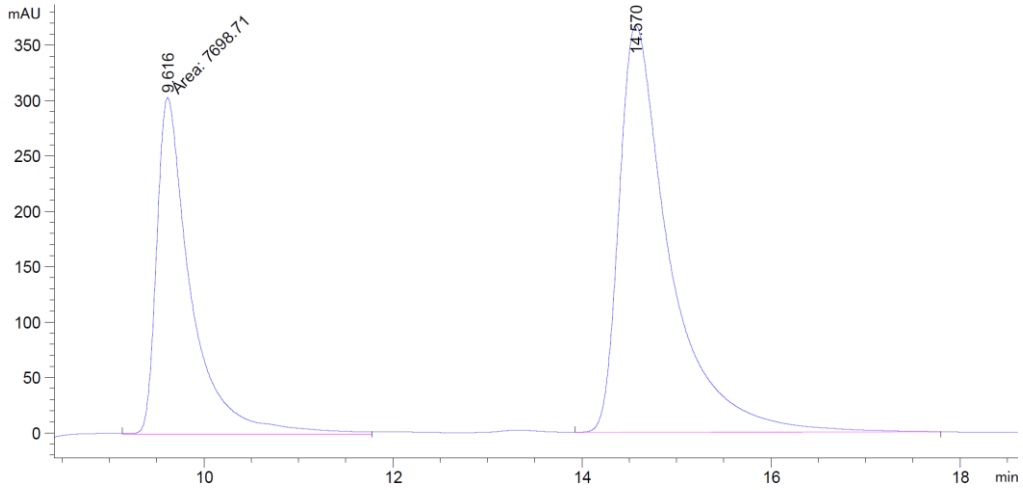
93: t_R = 42.53 (95.4%), 47.61 (4.6%) min, 95:5 *er*.



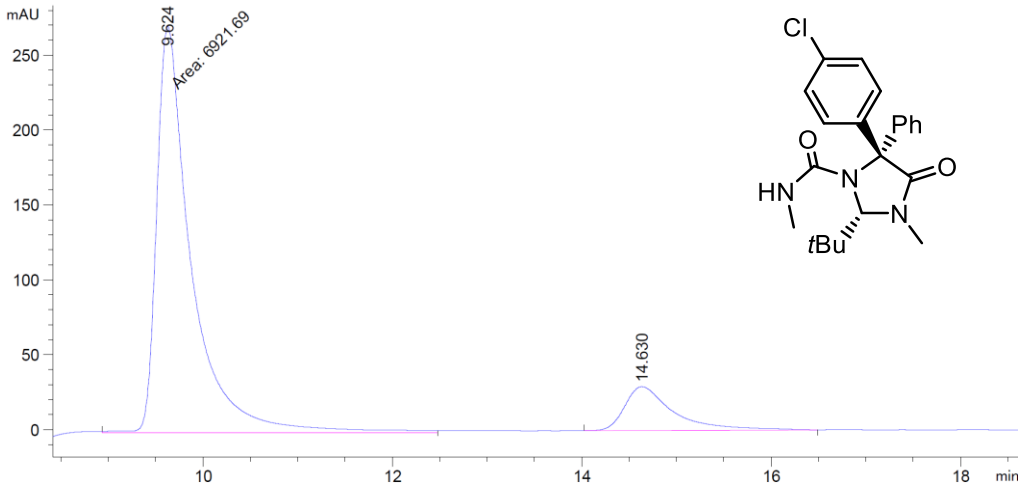
4-Phg-i

Chiral HPLC: Chiralcel® AD-H, 25 °C, 1.0 mL/min, Hexane/IPA (90:10), 210 nm

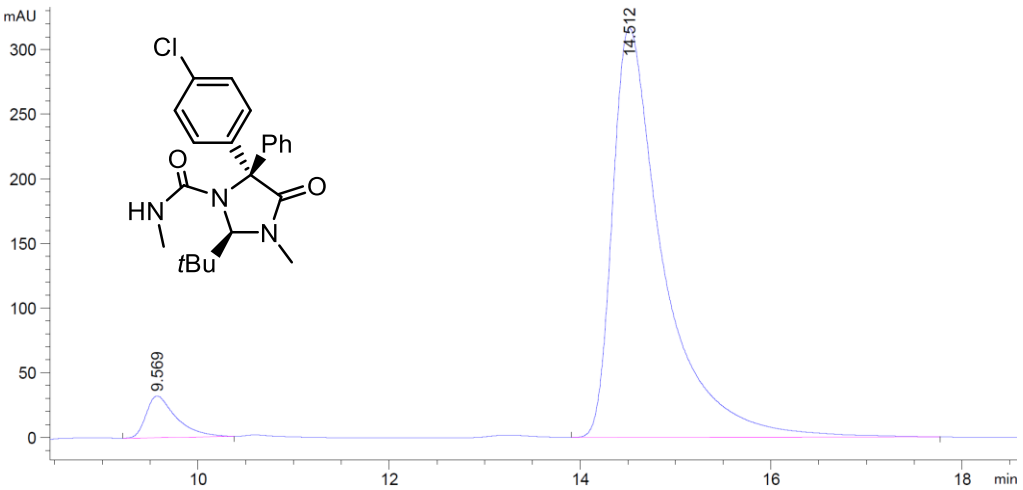
Standard: t_R = 9.62 (36.1%), 14.57 (63.9%) min, 63:37 *er*.



94: t_R = 9.62 (86.8%), 14.63 (13.2%) min, 87:13 *er*.



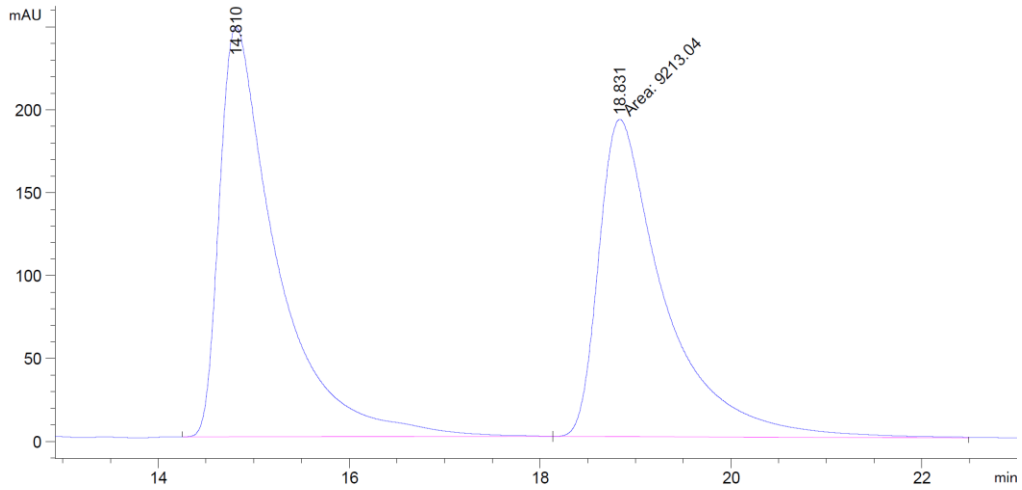
95: t_R = 9.57 (5.7%), 14.51 (94.3%) min, 94:6 *er*.



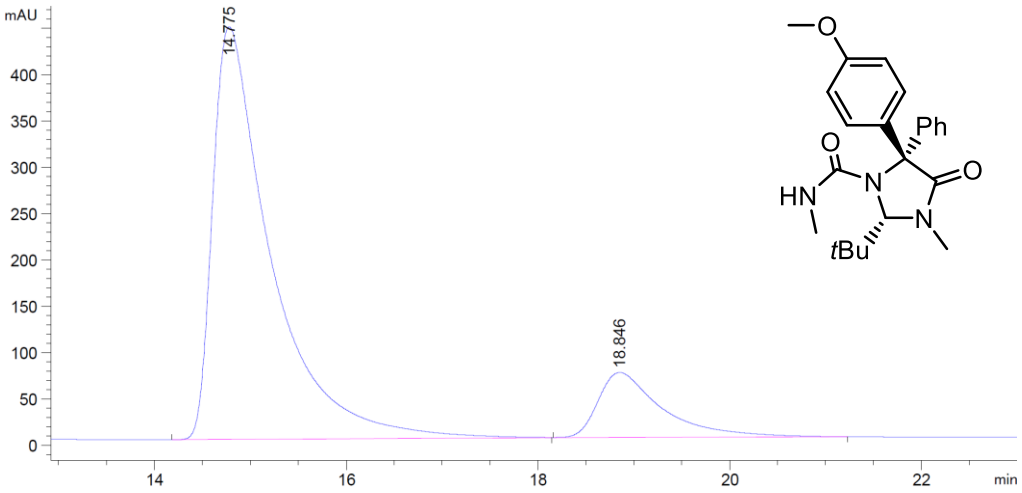
4-Phg-d

Chiral HPLC: Chiralcel® OD-H, 25 °C, 0.8 mL/min, Hexane/IPA (90:10), 210 nm

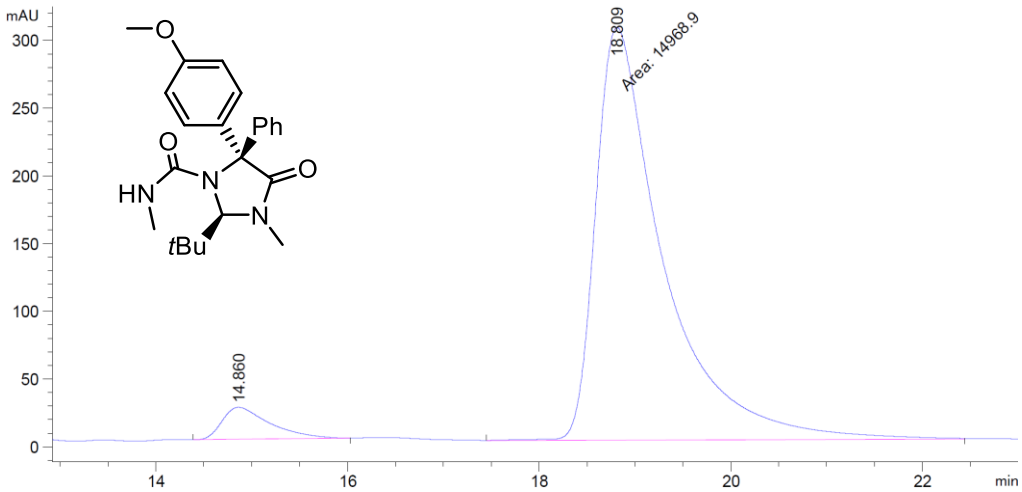
Standard: t_R = 14.81 (52.8%), 18.83 (47.2%) min, 53:47 *er*.



96: t_R = 14.78 (85.3%), 18.85 (14.7%) min, 85:15 *er*.



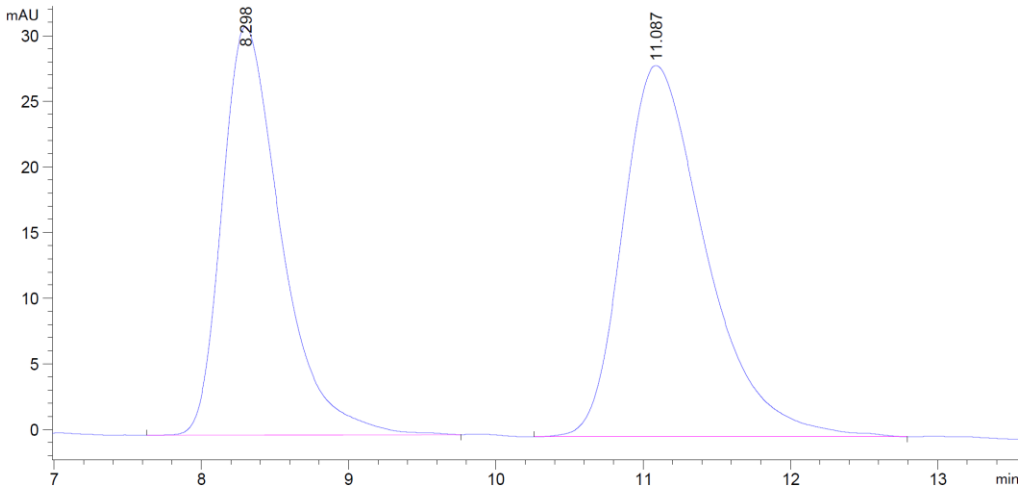
97: t_R = 14.86 (5.2%), 18.81 (94.8%) min, 95:5 *er*.



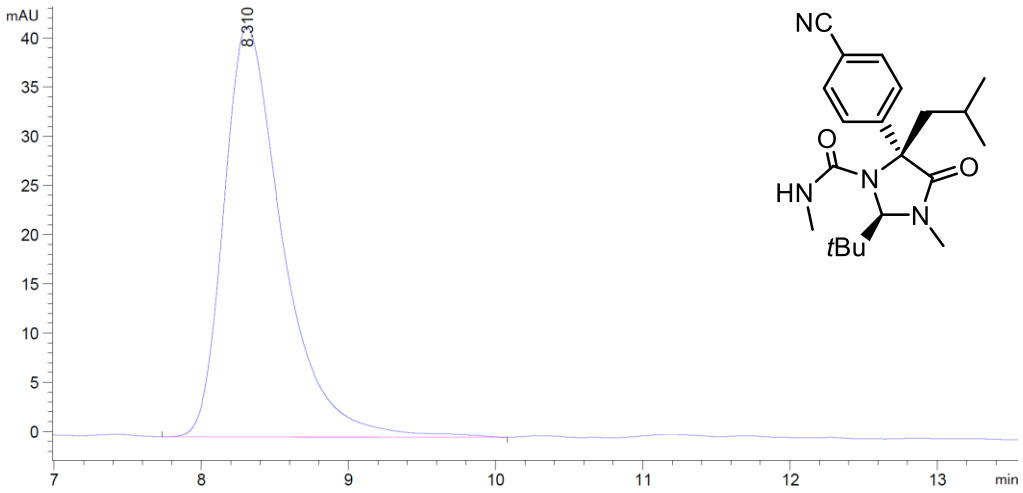
4-Leu-c

Chiral HPLC: Chiralcel® OD-H, 25 °C, 1.0 mL/min, Hexane/IPA (90:10), 254 nm

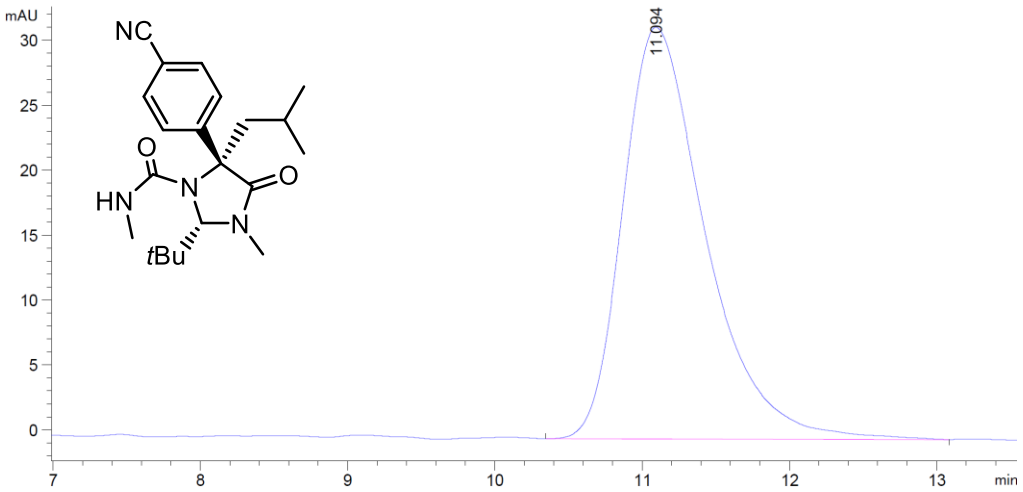
Standard: t_R = 8.30 (43.8%), 11.09 (56.2%) min, 56:44 *er*.



102: t_R = 8.31 (100%) min, >99:1 *er*.



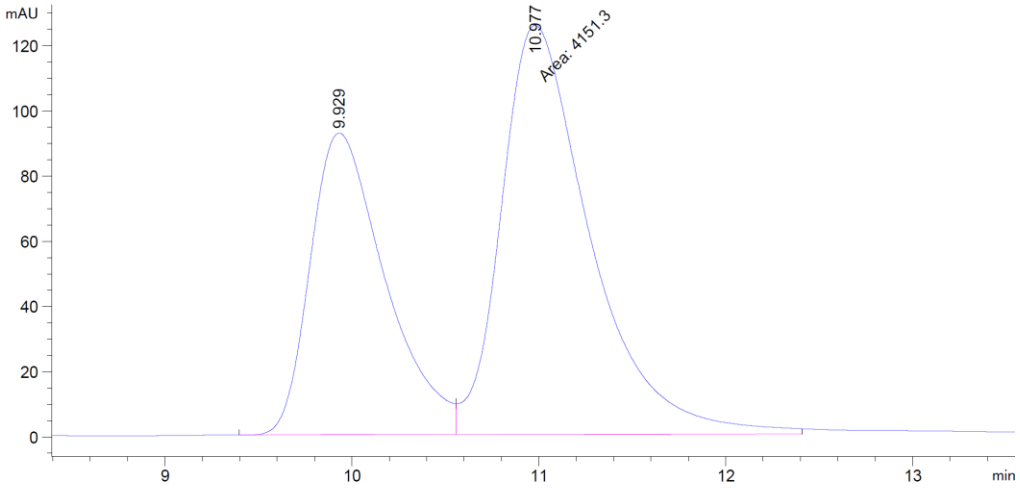
103: t_R = 11.09 (100%) min, >99:1 *er*.



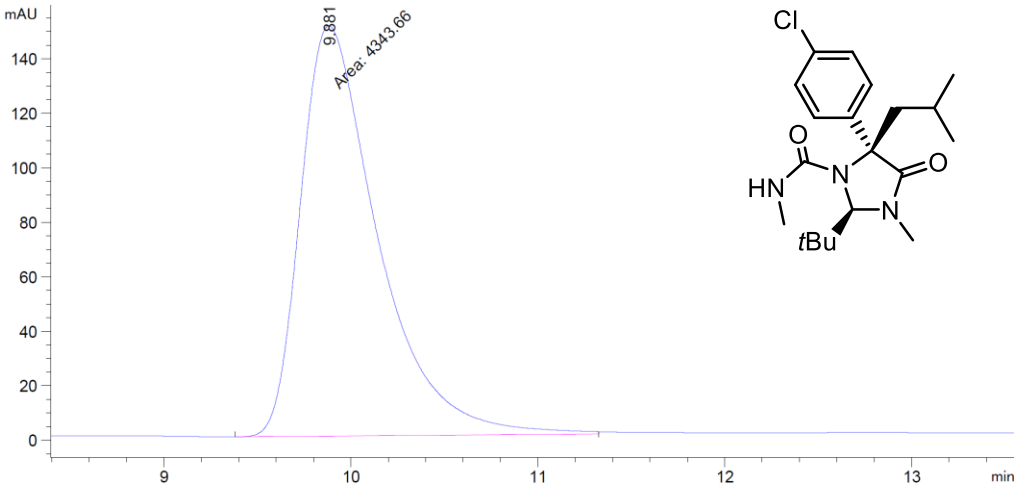
4-Leu-i

Chiral HPLC: Chiralcel® OD-H, 25 °C, 0.8 mL/min, Hexane/IPA (95:5), 225 nm

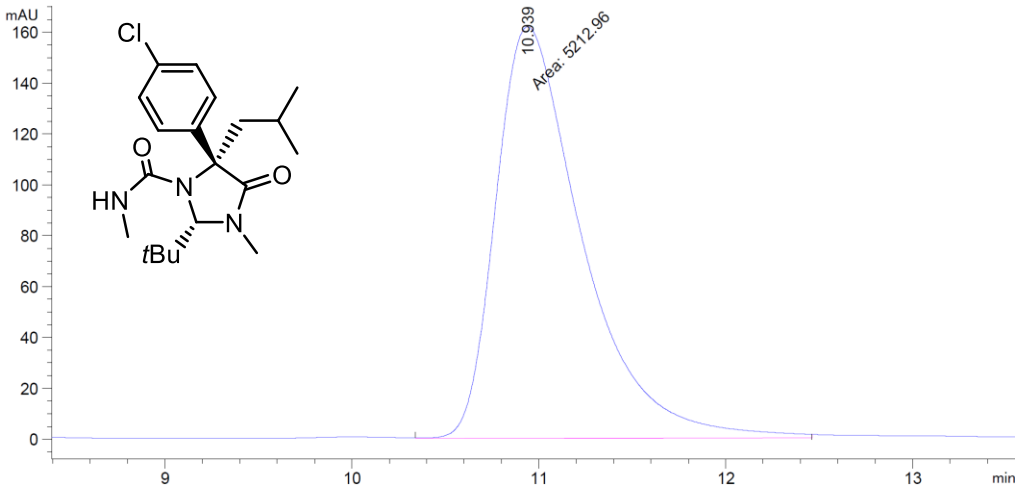
Standard: t_R = 9.93 (38.4%), 10.98 (61.6%) min, 62:38 *er*.



104: t_R = 9.88 (100%) min, >99:1 *er*.



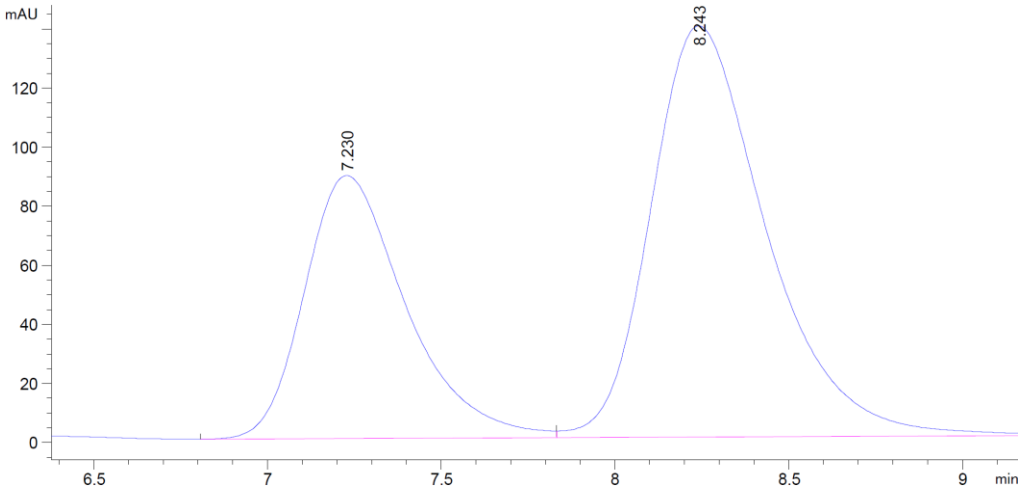
105: t_R = 10.94 (100%) min, >99:1 *er*.



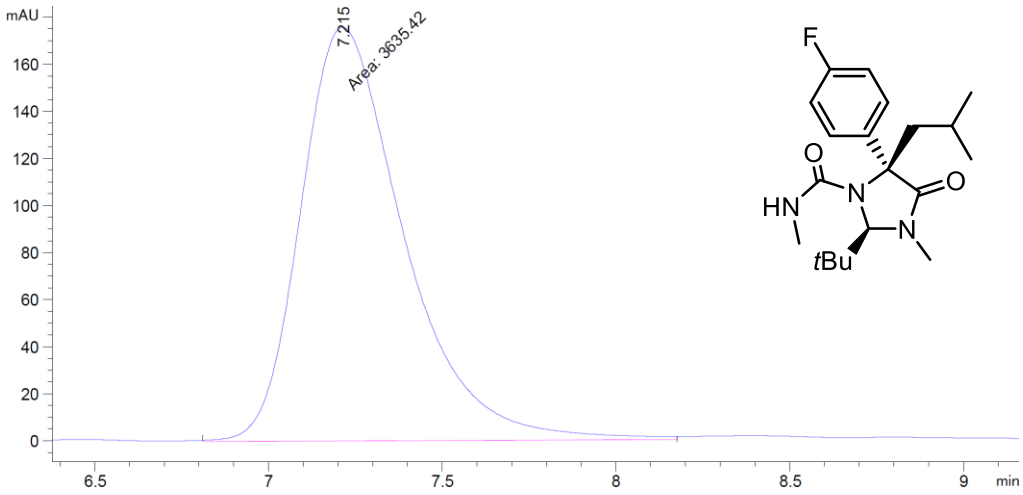
4-Leu-h

Chiral HPLC: Chiralcel® OD-H, 25 °C, 1.0 mL/min, Hexane/IPA (90:10), 210 nm

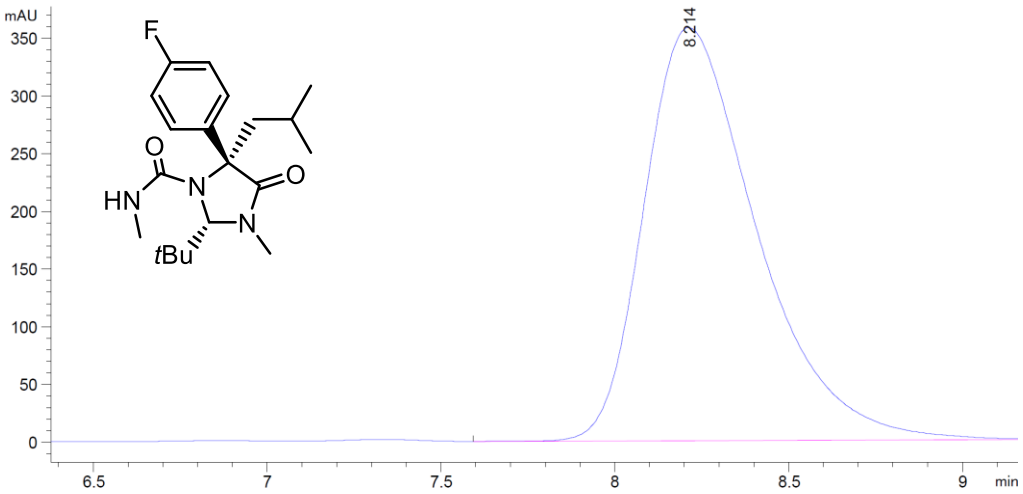
Standard: t_R = 7.23 (36.0%), 8.24 (64.0%) min, 64:36 *er*.



106: t_R = 7.22 (100%) min, >99:1 *er*.



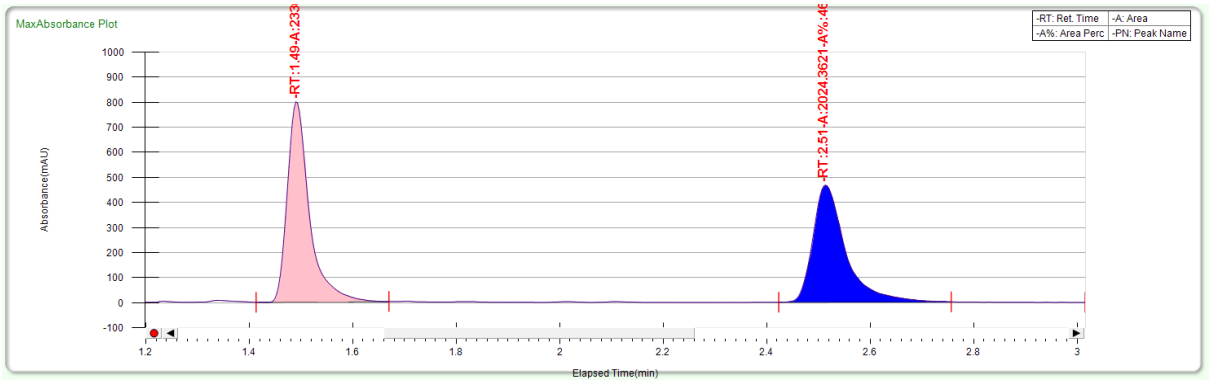
107: t_R = 8.21 (100%) min, >99:1 *er*.



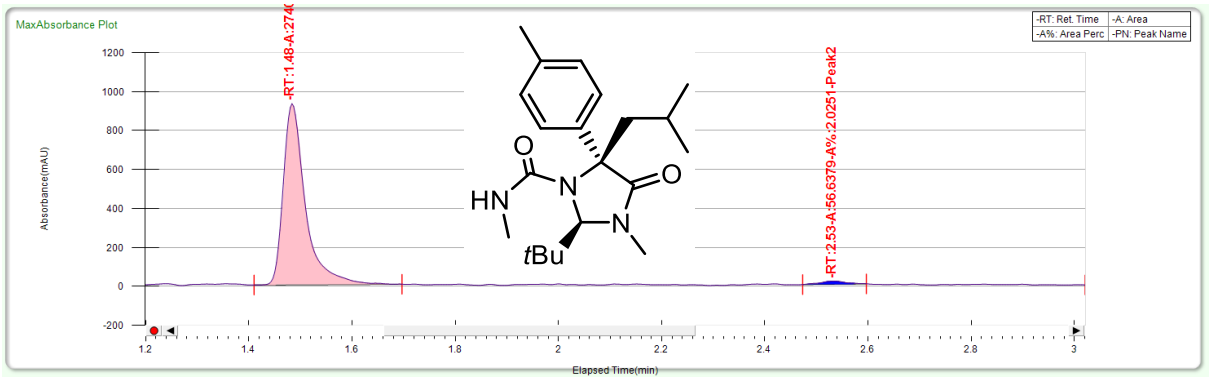
4-Leu-b

Chiral SFC: Chiralpak® IA, 125 bar, 40 °C, 4.0 mL/min, 20% co-solvent (IPA), λ_{max}

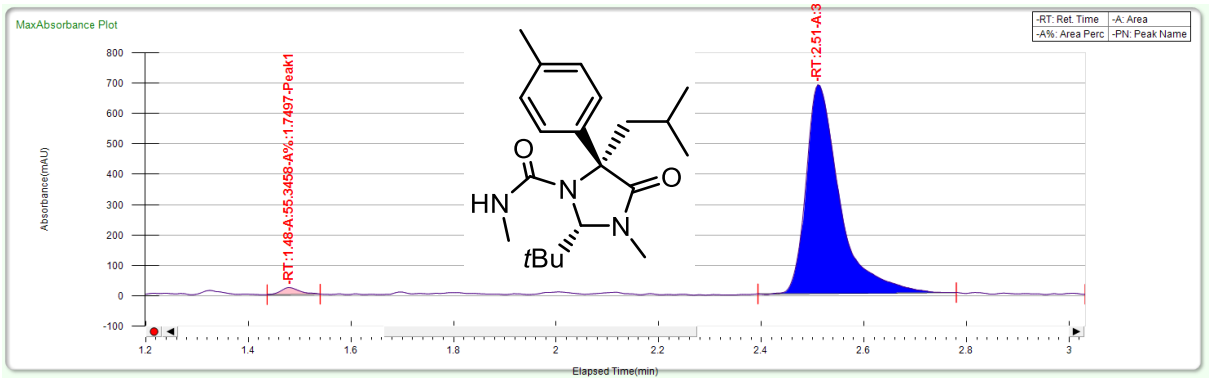
Standard: t_R = 1.49 (53.6%), 2.51 (46.4%) min, 54:46 *er*.



108: t_R = 1.48 (98.0%), 2.53 (2.0%) min, 98:2 *er*.



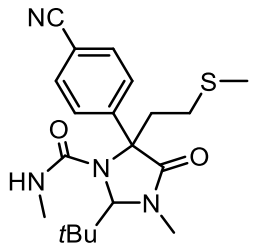
109: t_R = 1.48 (98.3%), 2.51 (1.7%) min, 98:2 *er*.

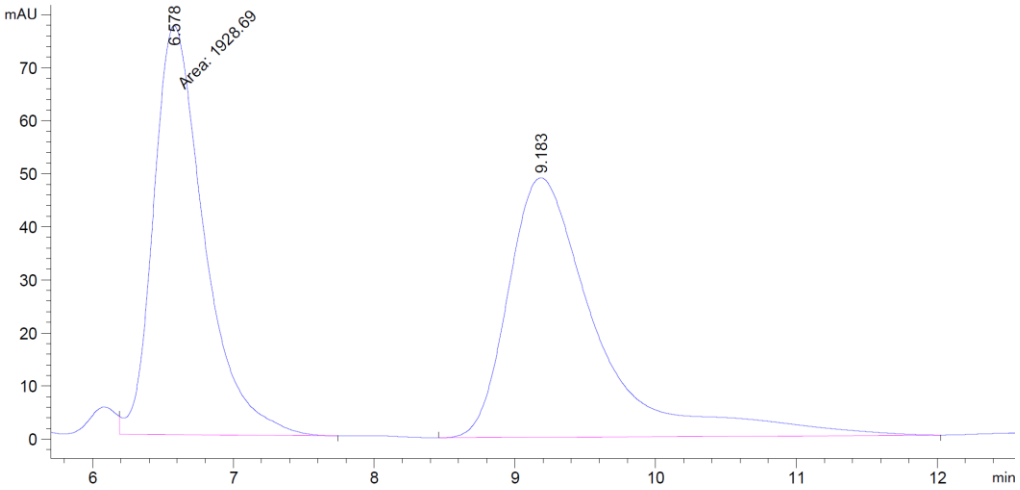


4-Met-c

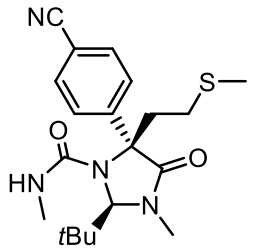
Chiral HPLC: Chiralcel® OD-H, 25 °C, 1.0 mL/min, Hexane/IPA (80:20), 236 nm

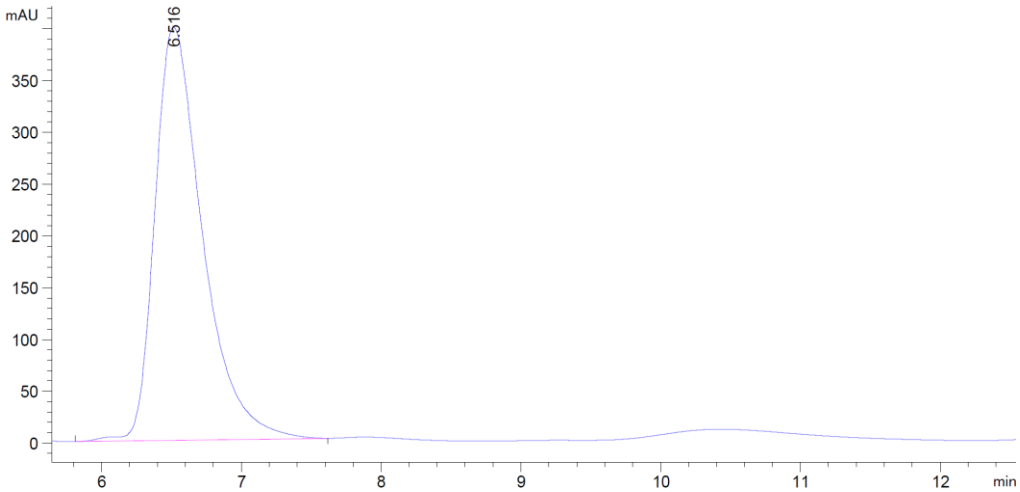
111: t_R = 6.58 (47.3%), 9.18 (52.7%) min, 53:47 *er*.





110: t_R = 6.52 (100%) min, >99:1 *er*.

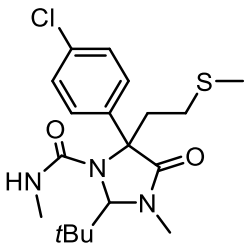


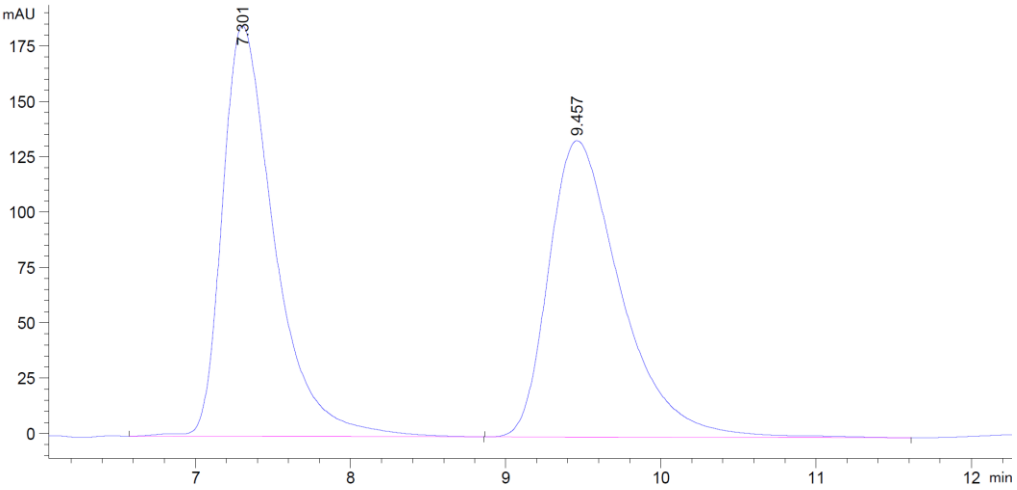


4-Met-i

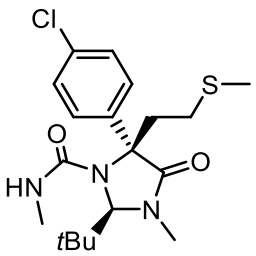
Chiral HPLC: Chiralcel® OD-H, 25 °C, 1.0 mL/min, Hexane/IPA (90:10), 230 nm

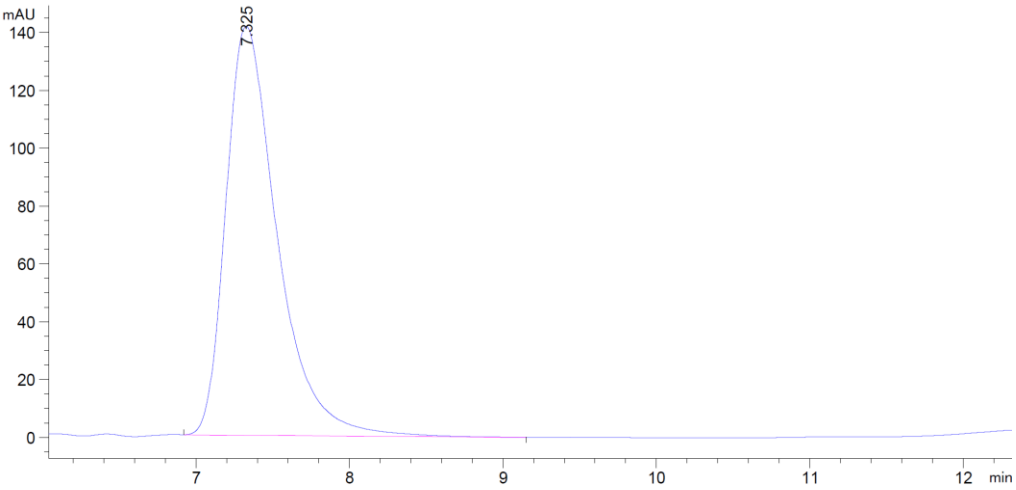
113: t_R = 7.30 (50.0%), 9.46 (50.0%) min, 50:50 *er*.





112: t_R = 7.33 (100%) min, >99:1 *er*.

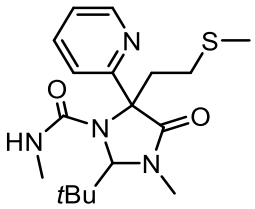


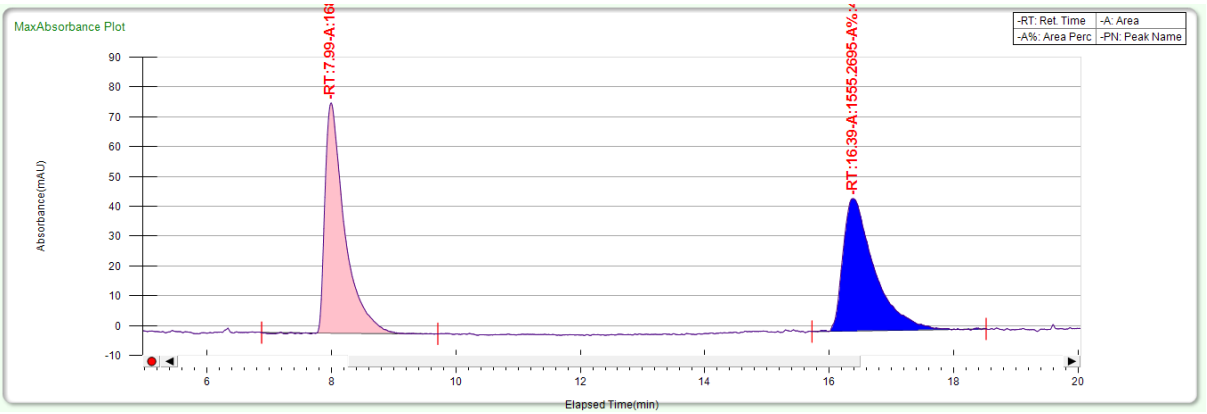


4-Met-m

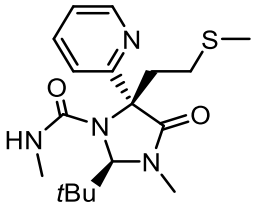
Chiral SFC: Chiralpak® IA, 125 bar, 40 °C, 4.0 mL/min, 10% co-solvent (IPA), λ_{max}

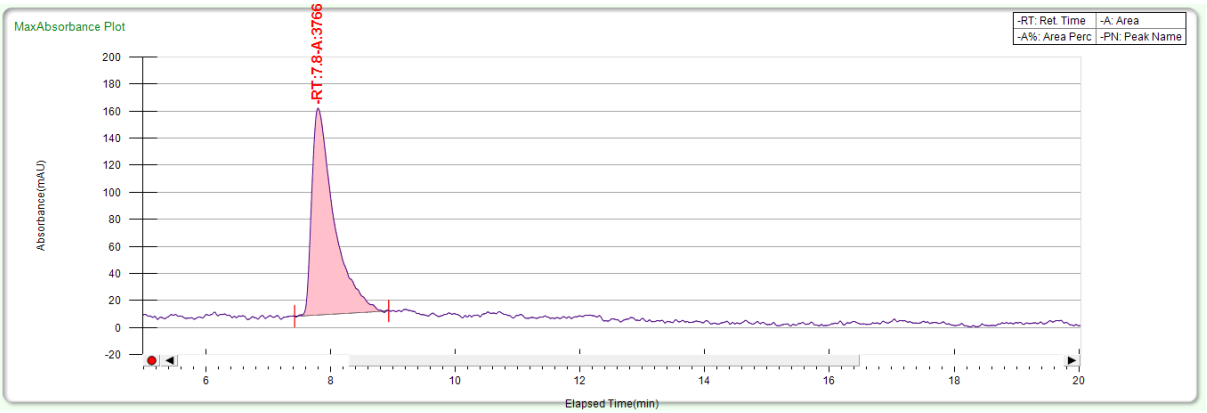
115: t_R = 7.99 (52.1%), 16.39 (47.9%) min, 52:48 *er*.





114: t_R = 7.80 (100%) min, >99:1 *er*.

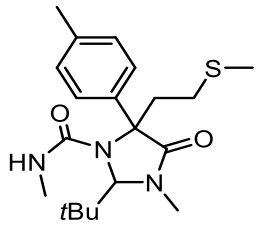


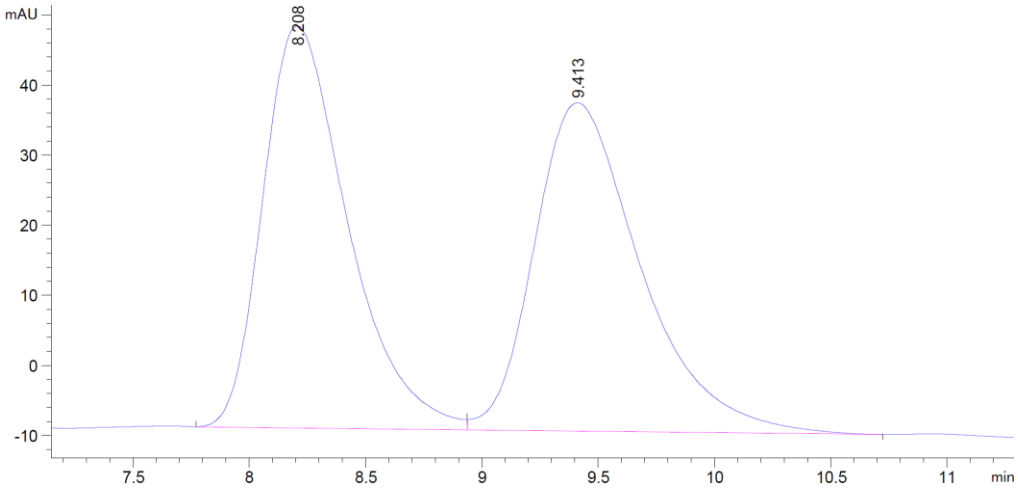


4-Met-b

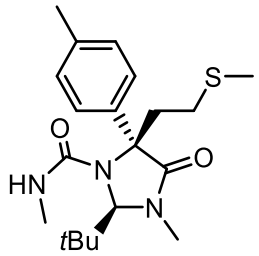
Chiral HPLC: Chiralcel® OD-H, 25 °C, 1.0 mL/min, Hexane/IPA (90:10), 230 nm

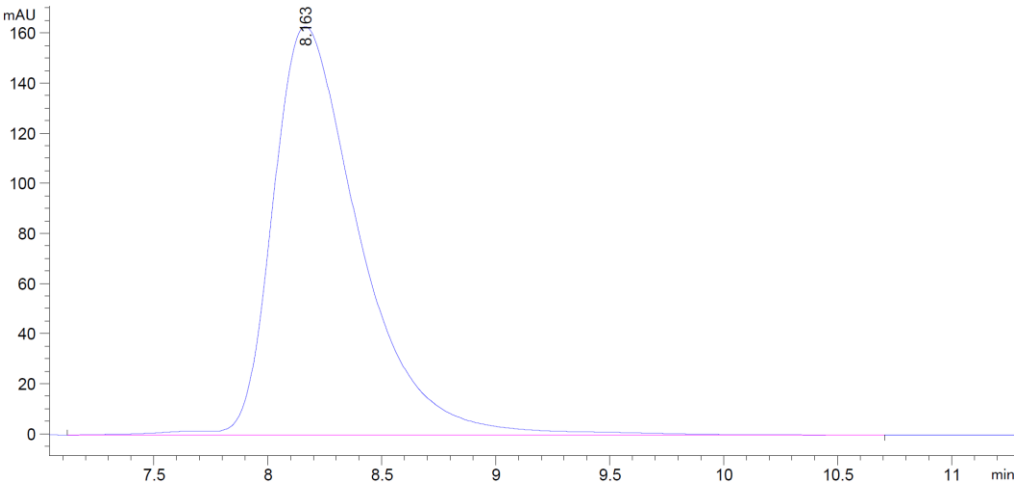
117: t_R = 8.21 (49.4%), 9.41 (50.6%) min, 51:49 *er*.





116: t_R = 8.16 (100%) min, >99:1 *er*.

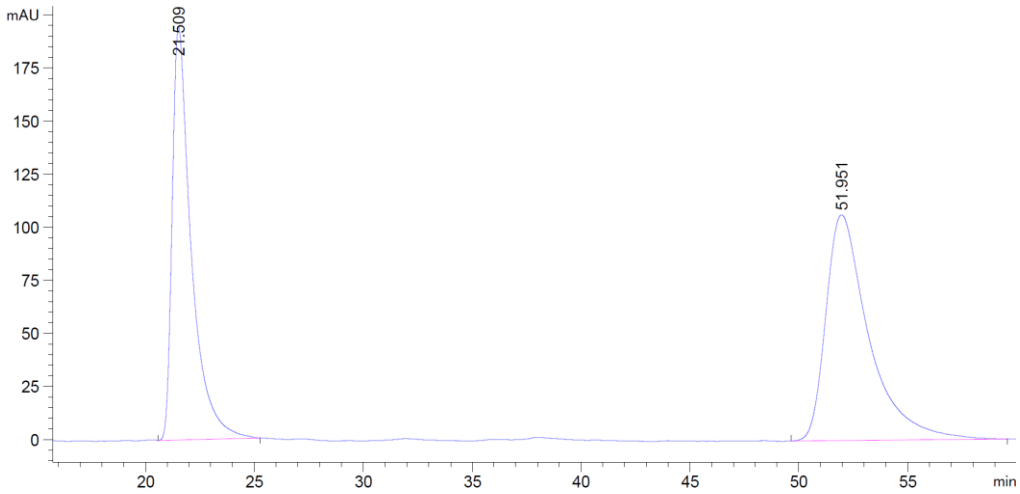




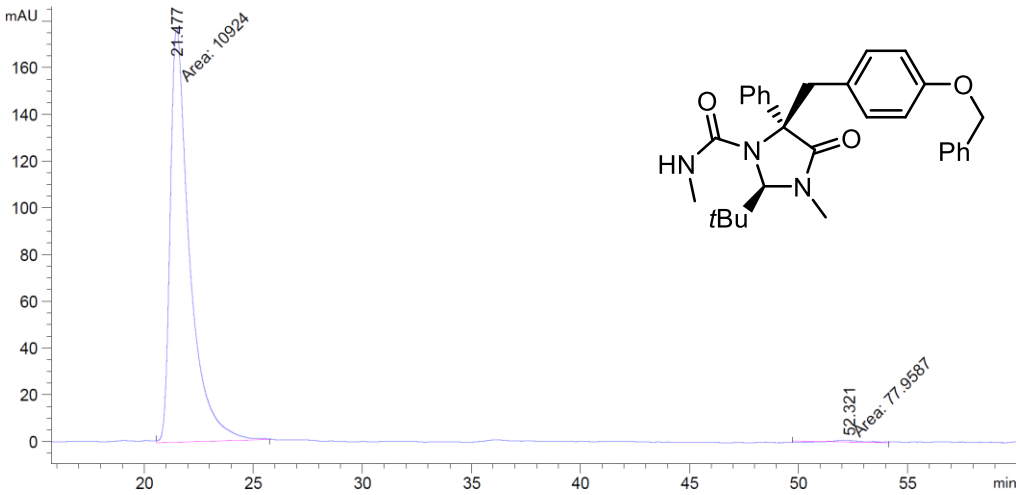
4-TyrOBn-a

Chiral HPLC: Chiralcel® AD-H, 25 °C, 1.0 mL/min, Hexane/IPA (90:10), 210 nm

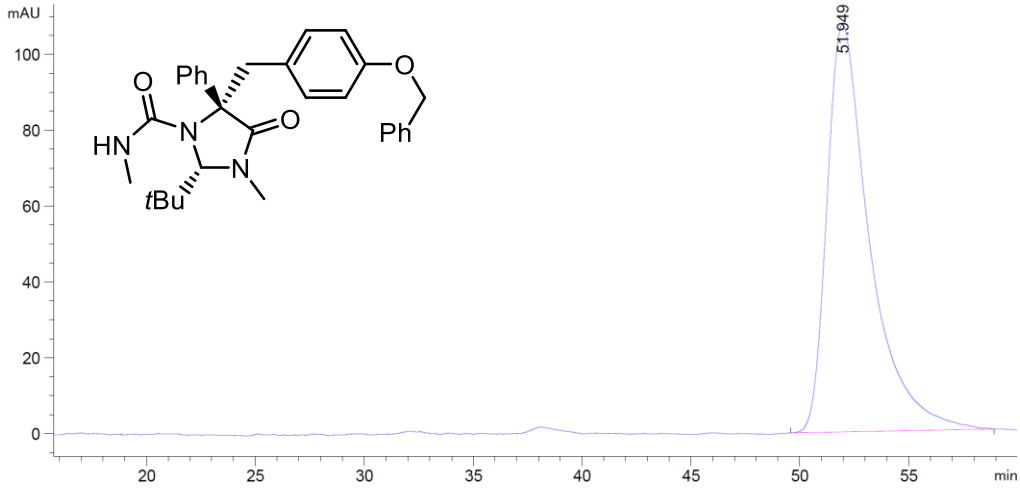
Standard: t_R = 21.51 (44.8%), 51.95 (55.2%) min, 55:45 *er*.



118: t_R = 21.48 (99.3%), 52.32 (0.7%) min, >99:1 *er*.



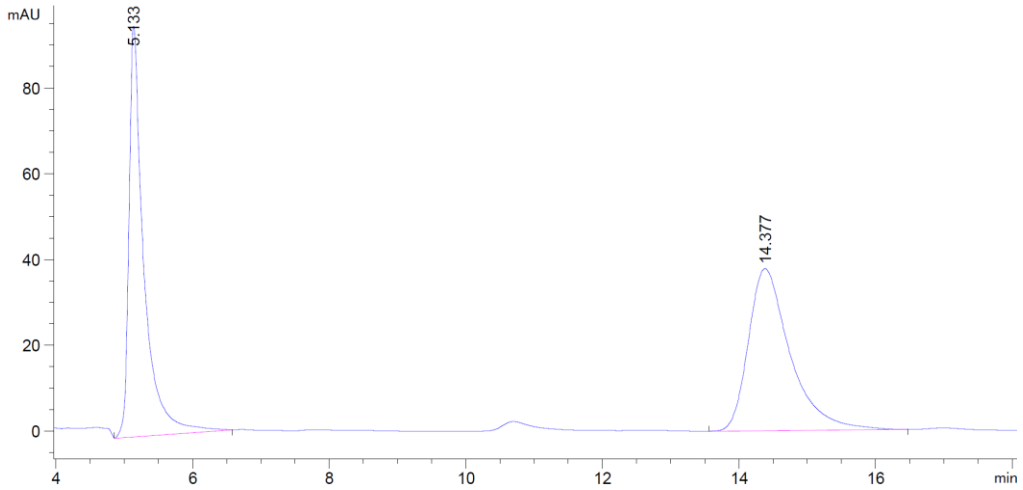
119: t_R = 51.95 (100%) min, >99:1 *er*.



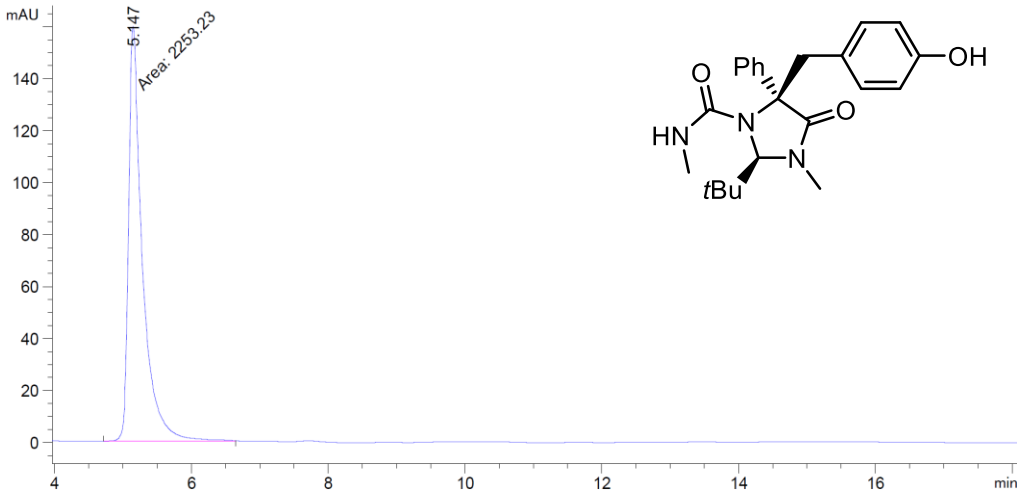
4-Tyr-a

Chiral HPLC: Chiralcel® AD-H, 25 °C, 1.0 mL/min, Hexane/IPA (80:20), 225 nm

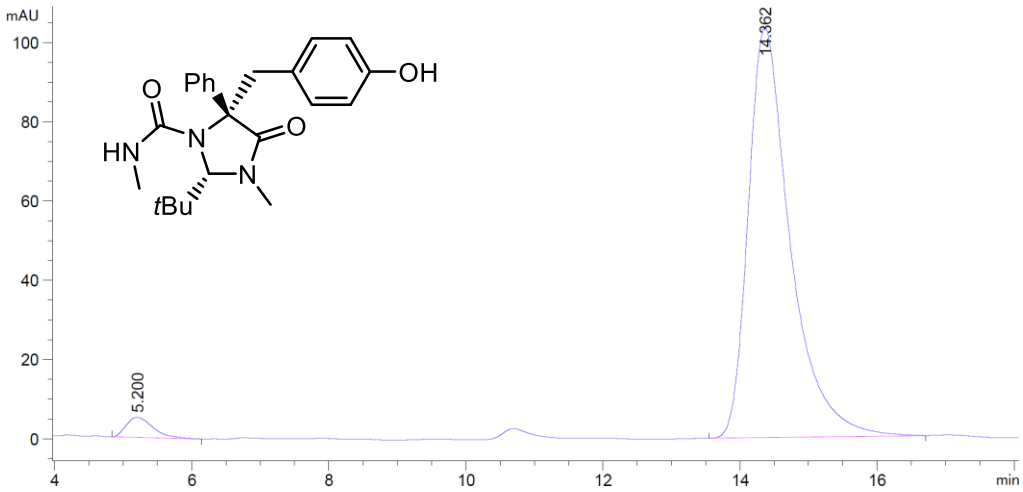
Standard: t_R = 5.13 (47.4%), 14.38 (52.6%) min, 53:47 *er*.



120: t_R = 5.15 (100%), >99:1 *er*.



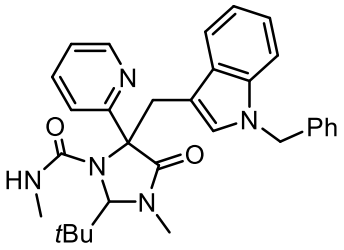
121: t_R = 5.20 (3.0%), 14.36 (97.0%) min, 97:3 *er*.

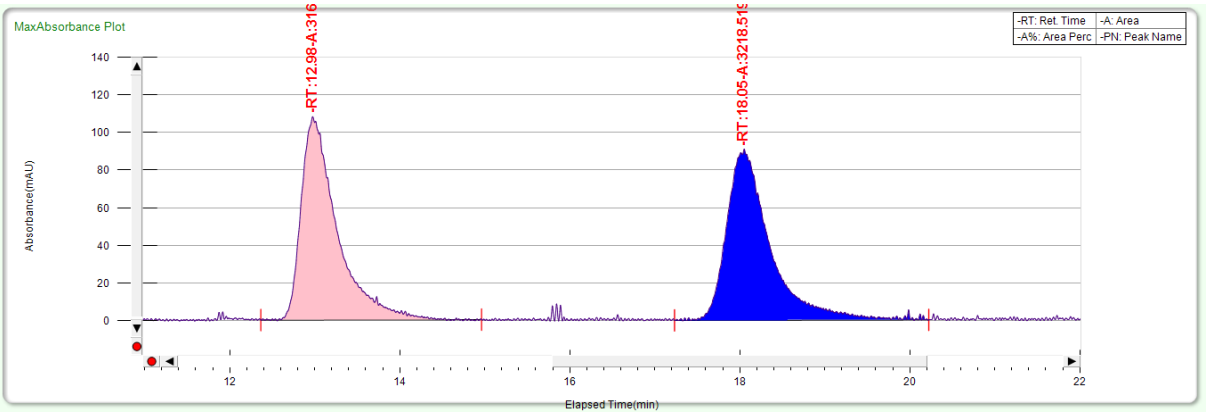


4-Tyr-m

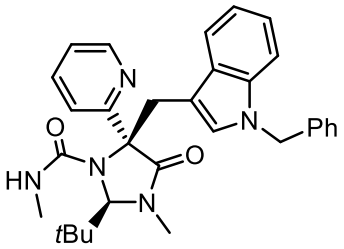
Chiral SFC: Chiralpak® IA, 130 bar, 40 °C, 4.0 mL/min, 20% co-solvent (IPA), λ_{max}

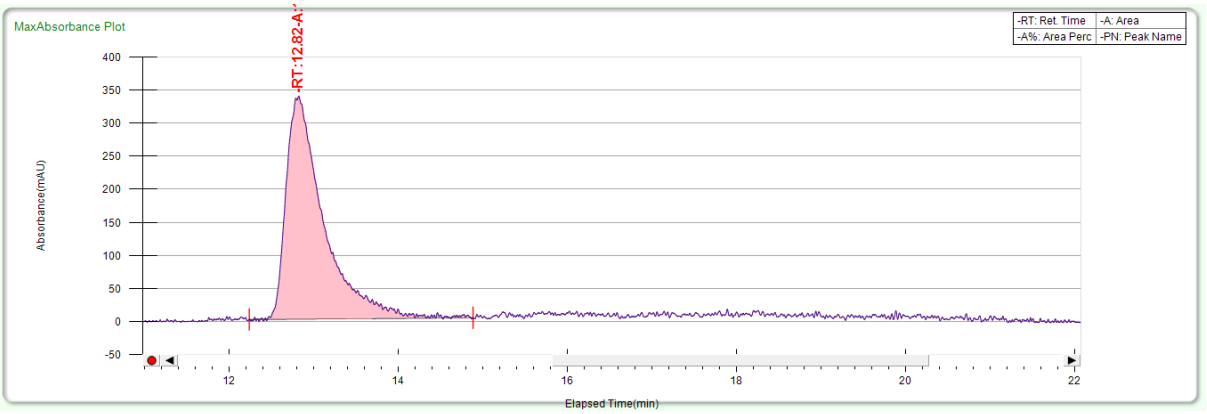
126: t_R = 12.98 (49.6%), 18.05 (50.4%) min, 50:50 *er*.





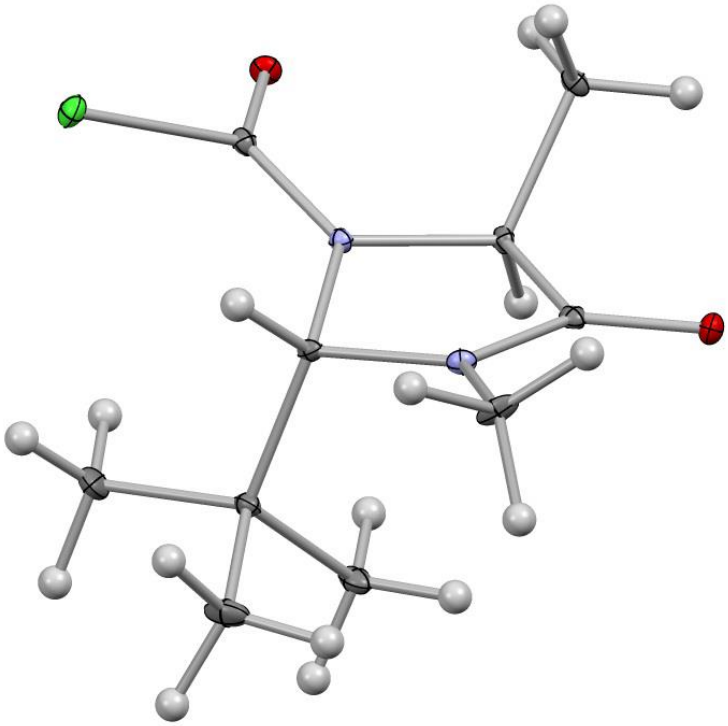
125: t_R = 12.82 (100%) min, >99:1 *er*.





X-Ray Crystallographic Data

Trans Alanine-Derived *N*-Chloroformylimidazolidinone (*trans*-1-Ala)



ORTEP diagram of *trans*-**1-Ala** at 10% probability ellipsoids. Hydrogen atoms included for stereochemical clarity.

Crystal data and Structure Refinement

Empirical formula	$C_{10}H_{17}ClN_2O_2$	
Formula weight	232.71	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal size	0.28 × 0.24 × 0.05 mm^3	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 6.6080(2) Å	α = 90°
	b = 16.0982(6) Å	β = 103.417(3)°
	c = 11.7046(5) Å	γ = 90°
Volume	1211.12(8) $Å^3$	
Z	4	
Density (calculated)	1.276 Mg/m^3	
Absorption coefficient	2.677 mm^{-1}	
F(000)	496	
Theta range for data collection	3.88 to 70.30°	
Index ranges	-7<=h<=8, -18<=k<=12, -11<=l<=14	
Reflections collected	4445	
Independent reflections	3068 [R(int) = 0.0311]	
Completeness to theta = 67.00°	96.2 %	
Absorption correction	Semi-empirical from equivalents	
Maximum and minimum transmission	0.8778 and 0.701261	

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3068 / 1 / 281
Goodness-of-fit on F^2	1.039
Final R indices [I>2sigma(I)]	R1 = 0.0335, wR2 = 0.0801
R indices (all data)	R1 = 0.0367, wR2 = 0.0815
Absolute structure parameter	-0.005(14)
Largest difference peak and hole	0.281 and -0.279 e.Å^{-3}

Atomic coordinates (×10^4) and equivalent isotropic displacement parameters (Å^2×10^3)

U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
C(1)	10301(4)	7354(2)	22(2)	18(1)
C(2)	11275(4)	8610(2)	1006(2)	21(1)
C(3)	11333(4)	7967(2)	1977(2)	19(1)
C(4)	11743(4)	6467(2)	1819(2)	21(1)
C(5)	7923(4)	7211(2)	-391(2)	24(1)
C(6)	6701(4)	7746(3)	293(3)	34(1)
C(7)	7389(5)	6303(3)	-243(4)	46(1)
C(8)	7229(5)	7439(3)	-1701(3)	44(1)
C(9)	11205(5)	8668(2)	-1084(2)	33(1)
C(10)	13390(4)	8065(2)	2880(2)	24(1)
C(11)	9636(3)	624(2)	4906(2)	16(1)
C(12)	8496(4)	1104(2)	2965(2)	17(1)
C(13)	8698(4)	166(2)	2857(2)	17(1)
C(14)	8498(4)	-855(2)	4374(2)	18(1)
C(15)	12020(4)	643(2)	5445(2)	21(1)
C(16)	12660(4)	-106(2)	6242(3)	33(1)
C(17)	12532(5)	1432(3)	6195(3)	41(1)
C(18)	13266(4)	643(3)	4495(3)	32(1)
C(19)	8474(5)	2151(2)	4474(3)	27(1)
C(20)	6737(4)	-169(2)	2037(2)	22(1)
Cl(1)	12195(1)	5666(1)	850(1)	31(1)
Cl(2)	7941(1)	-946(1)	5805(1)	25(1)
N(1)	11107(3)	7192(2)	1290(2)	18(1)
N(2)	10903(3)	8223(2)	-34(2)	22(1)
N(3)	8992(3)	-88(2)	4100(2)	17(1)
N(4)	8897(3)	1315(2)	4104(2)	17(1)
O(1)	12107(3)	6328(1)	2851(2)	25(1)
O(2)	11621(3)	9358(1)	1178(2)	25(1)
O(3)	8320(3)	-1462(1)	3770(2)	22(1)
O(4)	7962(3)	1587(1)	2140(2)	23(1)

Bond lengths (Å)

C(1)-N(2)	1.459(4)	**C(11)-N(4)**	1.464(3)
C(1)-N(1)	1.478(3)	**C(11)-N(3)**	1.482(3)
C(1)-C(5)	1.550(3)	**C(11)-C(15)**	1.555(3)
C(1)-H(1)	1.0000	**C(11)-H(11)**	1.0000
C(2)-O(2)	1.234(4)	**C(12)-O(4)**	1.227(3)
C(2)-N(2)	1.338(4)	**C(12)-N(4)**	1.340(3)
C(2)-C(3)	1.531(4)	**C(12)-C(13)**	1.522(4)
C(3)-N(1)	1.473(3)	**C(13)-N(3)**	1.481(3)
C(3)-C(10)	1.525(3)	**C(13)-C(20)**	1.521(3)
C(3)-H(3)	1.0000	**C(13)-H(13)**	1.0000
C(4)-O(1)	1.196(3)	**C(14)-O(3)**	1.196(4)
C(4)-N(1)	1.342(4)	**C(14)-N(3)**	1.335(4)
C(4)-Cl(1)	1.787(3)	**C(14)-Cl(2)**	1.803(3)
C(5)-C(7)	1.523(5)	**C(15)-C(16)**	1.525(4)
C(5)-C(6)	1.528(4)	**C(15)-C(18)**	1.529(4)
C(5)-C(8)	1.540(4)	**C(15)-C(17)**	1.535(5)
C(6)-H(6A)	0.9800	**C(16)-H(16A)**	0.9800
C(6)-H(6B)	0.9800	**C(16)-H(16B)**	0.9800
C(6)-H(6C)	0.9800	**C(16)-H(16C)**	0.9800
C(7)-H(7A)	0.9800	**C(17)-H(17A)**	0.9800
C(7)-H(7B)	0.9800	**C(17)-H(17B)**	0.9800
C(7)-H(7C)	0.9800	**C(17)-H(17C)**	0.9800
C(8)-H(8A)	0.9800	**C(18)-H(18A)**	0.9800
C(8)-H(8B)	0.9800	**C(18)-H(18B)**	0.9800
C(8)-H(8C)	0.9800	**C(18)-H(18C)**	0.9800
C(9)-N(2)	1.475(4)	**C(19)-N(4)**	1.461(4)
C(9)-H(9A)	0.9800	**C(19)-H(19A)**	0.9800
C(9)-H(9B)	0.9800	**C(19)-H(19B)**	0.9800
C(9)-H(9C)	0.9800	**C(19)-H(19C)**	0.9800
C(10)-H(10A)	0.9800	**C(20)-H(20A)**	0.9800
C(10)-H(10B)	0.9800	**C(20)-H(20B)**	0.9800
C(10)-H(10C)	0.9800	**C(20)-H(20C)**	0.9800

Bond angles (°)

N(2)-C(1)-N(1)	100.2(2)	**H(8A)-C(8)-H(8C)**	109.5	**H(16A)-C(16)-H(16B)**	109.5
N(2)-C(1)-C(5)	113.3(2)	**H(8B)-C(8)-H(8C)**	109.5	**C(15)-C(16)-H(16C)**	109.5
N(1)-C(1)-C(5)	112.9(2)	**N(2)-C(9)-H(9A)**	109.5	**H(16A)-C(16)-H(16C)**	109.5
N(2)-C(1)-H(1)	110.0	**N(2)-C(9)-H(9B)**	109.5	**H(16B)-C(16)-H(16C)**	109.5
N(1)-C(1)-H(1)	110.0	**H(9A)-C(9)-H(9B)**	109.5	**C(15)-C(17)-H(17A)**	109.5
C(5)-C(1)-H(1)	110.0	**N(2)-C(9)-H(9C)**	109.5	**C(15)-C(17)-H(17B)**	109.5
O(2)-C(2)-N(2)	126.2(3)	**H(9A)-C(9)-H(9C)**	109.5	**H(17A)-C(17)-H(17B)**	109.5
O(2)-C(2)-C(3)	124.5(3)	**H(9B)-C(9)-H(9C)**	109.5	**C(15)-C(17)-H(17C)**	109.5
N(2)-C(2)-C(3)	109.2(3)	**C(3)-C(10)-H(10A)**	109.5	**H(17A)-C(17)-H(17C)**	109.5
N(1)-C(3)-C(10)	115.3(2)	**C(3)-C(10)-H(10B)**	109.5	**H(17B)-C(17)-H(17C)**	109.5
N(1)-C(3)-C(2)	100.7(2)	**H(10A)-C(10)-H(10B)**	109.5	**C(15)-C(18)-H(18A)**	109.5
C(10)-C(3)-C(2)	108.0(2)	**C(3)-C(10)-H(10C)**	109.5	**C(15)-C(18)-H(18B)**	109.5
N(1)-C(3)-H(3)	110.8	**H(10A)-C(10)-H(10C)**	109.5	**H(18A)-C(18)-H(18B)**	109.5
C(10)-C(3)-H(3)	110.8	**H(10B)-C(10)-H(10C)**	109.5	**C(15)-C(18)-H(18C)**	109.5
C(2)-C(3)-H(3)	110.8	**N(4)-C(11)-N(3)**	100.07(17)	**H(18A)-C(18)-H(18C)**	109.5
O(1)-C(4)-N(1)	126.6(3)	**N(4)-C(11)-C(15)**	113.6(2)	**H(18B)-C(18)-H(18C)**	109.5
O(1)-C(4)-Cl(1)	118.8(2)	**N(3)-C(11)-C(15)**	112.8(2)	**N(4)-C(19)-H(19A)**	109.5
N(1)-C(4)-Cl(1)	114.50(19)	**N(4)-C(11)-H(11)**	110.0	**N(4)-C(19)-H(19B)**	109.5
C(7)-C(5)-C(6)	108.5(3)	**N(3)-C(11)-H(11)**	110.0	**H(19A)-C(19)-H(19B)**	109.5
C(7)-C(5)-C(8)	108.5(3)	**C(15)-C(11)-H(11)**	110.0	**N(4)-C(19)-H(19C)**	109.5
C(6)-C(5)-C(8)	108.5(3)	**O(4)-C(12)-N(4)**	125.2(3)	**H(19A)-C(19)-H(19C)**	109.5
C(7)-C(5)-C(1)	110.6(3)	**O(4)-C(12)-C(13)**	125.3(3)	**H(19B)-C(19)-H(19C)**	109.5
C(6)-C(5)-C(1)	111.9(2)	**N(4)-C(12)-C(13)**	109.5(2)	**C(13)-C(20)-H(20A)**	109.5
C(8)-C(5)-C(1)	108.7(3)	**N(3)-C(13)-C(20)**	114.9(2)	**C(13)-C(20)-H(20B)**	109.5
C(5)-C(6)-H(6A)	109.5	**N(3)-C(13)-C(12)**	100.7(2)	**H(20A)-C(20)-H(20B)**	109.5
C(5)-C(6)-H(6B)	109.5	**C(20)-C(13)-C(12)**	109.0(2)	**C(13)-C(20)-H(20C)**	109.5
H(6A)-C(6)-H(6B)	109.5	**N(3)-C(13)-H(13)**	110.6	**H(20A)-C(20)-H(20C)**	109.5
C(5)-C(6)-H(6C)	109.5	**C(20)-C(13)-H(13)**	110.6	**H(20B)-C(20)-H(20C)**	109.5
H(6A)-C(6)-H(6C)	109.5	**C(12)-C(13)-H(13)**	110.6	**C(4)-N(1)-C(3)**	120.2(2)
H(6B)-C(6)-H(6C)	109.5	**O(3)-C(14)-N(3)**	127.7(2)	**C(4)-N(1)-C(1)**	128.2(2)
C(5)-C(7)-H(7A)	109.5	**O(3)-C(14)-Cl(2)**	117.9(2)	**C(3)-N(1)-C(1)**	111.4(2)
C(5)-C(7)-H(7B)	109.5	**N(3)-C(14)-Cl(2)**	114.3(2)	**C(2)-N(2)-C(1)**	113.5(2)
H(7A)-C(7)-H(7B)	109.5	**C(16)-C(15)-C(18)**	108.9(3)	**C(2)-N(2)-C(9)**	120.0(3)
C(5)-C(7)-H(7C)	109.5	**C(16)-C(15)-C(17)**	108.1(2)	**C(1)-N(2)-C(9)**	126.4(3)
H(7A)-C(7)-H(7C)	109.5	**C(18)-C(15)-C(17)**	109.4(3)	**C(14)-N(3)-C(13)**	120.5(2)
H(7B)-C(7)-H(7C)	109.5	**C(16)-C(15)-C(11)**	110.1(2)	**C(14)-N(3)-C(11)**	127.8(2)
C(5)-C(8)-H(8A)	109.5	**C(18)-C(15)-C(11)**	111.8(2)	**C(13)-N(3)-C(11)**	111.4(2)
C(5)-C(8)-H(8B)	109.5	**C(17)-C(15)-C(11)**	108.5(2)	**C(12)-N(4)-C(19)**	121.4(2)
H(8A)-C(8)-H(8B)	109.5	**C(15)-C(16)-H(16A)**	109.5	**C(12)-N(4)-C(11)**	113.9(2)
C(5)-C(8)-H(8C)	109.5	**C(15)-C(16)-H(16B)**	109.5	**C(19)-N(4)-C(11)**	124.6(2)

Anisotropic displacement parameters ($Å^2 \times 10^3$)

The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(1)	18(1)	21(2)	14(1)	-1(1)	3(1)	4(1)
C(2)	15(1)	26(2)	23(1)	-2(1)	6(1)	0(1)
C(3)	21(1)	20(2)	17(1)	-5(1)	7(1)	-1(1)
C(4)	20(1)	23(2)	22(1)	-2(1)	7(1)	-4(1)
C(5)	19(1)	29(2)	22(1)	-5(1)	0(1)	1(1)
C(6)	18(1)	47(2)	36(2)	-11(2)	3(1)	1(1)
C(7)	29(2)	35(2)	66(2)	-8(2)	-5(2)	-9(2)
C(8)	30(2)	74(3)	24(2)	-4(2)	-2(1)	9(2)
C(9)	45(2)	42(2)	16(1)	16(1)	15(1)	25(2)
C(10)	24(1)	30(2)	17(1)	-1(1)	3(1)	-5(1)
C(11)	18(1)	15(1)	14(1)	-1(1)	2(1)	1(1)
C(12)	17(1)	19(1)	17(1)	2(1)	6(1)	-3(1)
C(13)	21(1)	17(1)	13(1)	1(1)	6(1)	0(1)
C(14)	17(1)	24(2)	15(1)	3(1)	5(1)	4(1)
C(15)	18(1)	20(1)	23(1)	-1(1)	2(1)	2(1)
C(16)	24(1)	39(2)	31(2)	12(2)	-3(1)	4(1)
C(17)	22(1)	44(2)	49(2)	-23(2)	-7(1)	0(1)
C(18)	18(1)	44(2)	32(1)	3(2)	5(1)	-1(1)
C(19)	39(2)	16(2)	27(1)	-4(1)	8(1)	1(1)
C(20)	28(1)	20(2)	15(1)	-2(1)	1(1)	-6(1)
Cl(1)	41(1)	23(1)	29(1)	-2(1)	10(1)	6(1)
Cl(2)	32(1)	25(1)	20(1)	5(1)	12(1)	2(1)
N(1)	19(1)	20(1)	16(1)	-2(1)	3(1)	0(1)
N(2)	23(1)	26(1)	18(1)	3(1)	5(1)	2(1)
N(3)	20(1)	16(1)	15(1)	-2(1)	5(1)	-1(1)
N(4)	19(1)	14(1)	16(1)	-2(1)	3(1)	0(1)
O(1)	30(1)	29(1)	17(1)	5(1)	6(1)	-1(1)
O(2)	31(1)	18(1)	28(1)	-1(1)	9(1)	0(1)
O(3)	29(1)	15(1)	22(1)	-1(1)	7(1)	0(1)
O(4)	28(1)	22(1)	18(1)	5(1)	6(1)	0(1)

Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$)

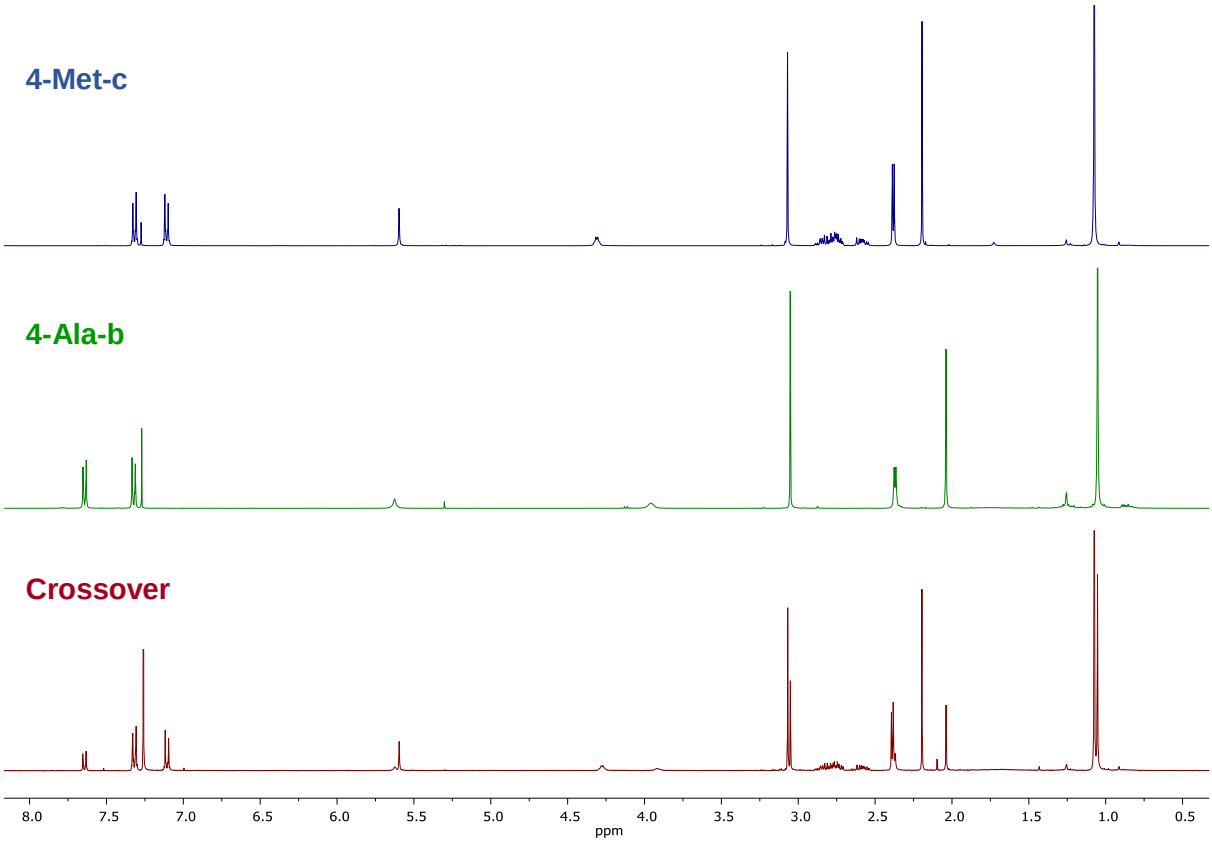
	x	y	z	U(eq)
H(1)	11055	7002	-448	22
H(3)	10130	8044	2351	22
H(6A)	5209	7646	-2	51
H(6B)	7004	8334	192	51
H(6C)	7108	7601	1129	51
H(7A)	7813	6149	588	69
H(7B)	8125	5952	-700	69
H(7C)	5886	6221	-524	69
H(8A)	8125	7155	-2139	66
H(8B)	7339	8041	-1794	66
H(8C)	5783	7265	-2005	66
H(9A)	9913	8952	-1464	50
H(9B)	11580	8269	-1634	50
H(9C)	12323	9077	-851	50
H(10A)	13442	7671	3525	36
H(10B)	13506	8633	3190	36
H(10C)	14545	7953	2507	36
H(11)	8863	613	5546	19
H(13)	9954	24	2556	20
H(16A)	12417	-616	5773	49
H(16B)	11835	-121	6838	49
H(16C)	14140	-64	6629	49
H(17A)	11627	1463	6748	61
H(17B)	12307	1921	5683	61
H(17C)	13989	1414	6631	61
H(18A)	14754	684	4865	47
H(18B)	12846	1117	3970	47
H(18C)	12998	126	4042	47
H(19A)	9564	2531	4351	41
H(19B)	8452	2145	5308	41
H(19C)	7121	2340	4010	41
H(20A)	6868	-770	1950	33
H(20B)	6548	98	1266	33
H(20C)	5533	-49	2365	33

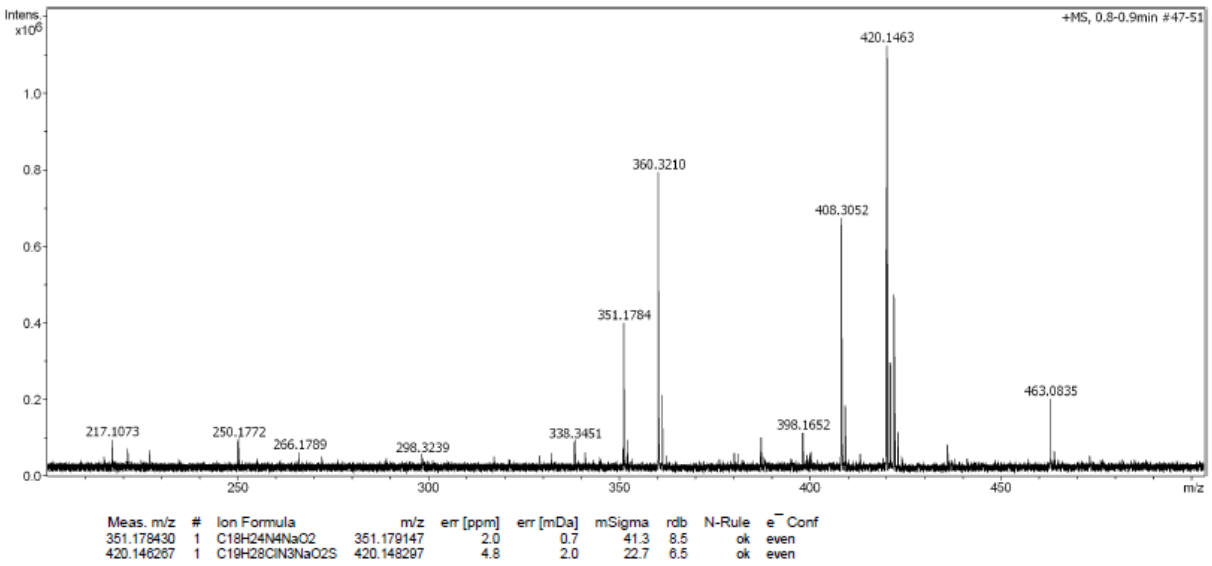
Torsion angles (°)

O(2)-C(2)-C(3)-N(1)	-172.4(3)	**N(2)-C(1)-N(1)-C(3)**	22.7(2)
N(2)-C(2)-C(3)-N(1)	4.4(3)	**C(5)-C(1)-N(1)-C(3)**	-98.1(3)
O(2)-C(2)-C(3)-C(10)	-51.1(4)	**O(2)-C(2)-N(2)-C(1)**	-173.0(3)
N(2)-C(2)-C(3)-C(10)	125.6(2)	**C(3)-C(2)-N(2)-C(1)**	10.3(3)
N(2)-C(1)-C(5)-C(7)	-176.7(3)	**O(2)-C(2)-N(2)-C(9)**	9.6(4)
N(1)-C(1)-C(5)-C(7)	-63.7(3)	**C(3)-C(2)-N(2)-C(9)**	-167.1(2)
N(2)-C(1)-C(5)-C(6)	-55.6(3)	**N(1)-C(1)-N(2)-C(2)**	-20.0(3)
N(1)-C(1)-C(5)-C(6)	57.4(4)	**C(5)-C(1)-N(2)-C(2)**	100.5(3)
N(2)-C(1)-C(5)-C(8)	64.2(3)	**N(1)-C(1)-N(2)-C(9)**	157.1(2)
N(1)-C(1)-C(5)-C(8)	177.2(3)	**C(5)-C(1)-N(2)-C(9)**	-82.3(3)
O(4)-C(12)-C(13)-N(3)	-170.1(2)	**O(3)-C(14)-N(3)-C(13)**	20.9(4)
N(4)-C(12)-C(13)-N(3)	7.0(3)	**Cl(2)-C(14)-N(3)-C(13)**	-56.21(18)
O(4)-C(12)-C(13)-C(20)	-48.9(3)	**O(3)-C(14)-N(3)-C(11)**	-166.3(2)
N(4)-C(12)-C(13)-C(20)	128.2(2)	**Cl(2)-C(14)-N(3)-C(11)**	16.6(3)
N(4)-C(11)-C(15)-C(16)	-178.6(2)	**C(20)-C(13)-N(3)-C(14)**	38.7(4)
N(3)-C(11)-C(15)-C(16)	-65.6(3)	**C(12)-C(13)-N(3)-C(14)**	155.7(2)
N(4)-C(11)-C(15)-C(18)	-57.4(4)	**C(20)-C(13)-N(3)-C(11)**	-135.1(2)
N(3)-C(11)-C(15)-C(18)	55.6(4)	**C(12)-C(13)-N(3)-C(11)**	-18.2(3)
N(4)-C(11)-C(15)-C(17)	63.3(3)	**N(4)-C(11)-N(3)-C(14)**	-151.7(3)
N(3)-C(11)-C(15)-C(17)	176.3(3)	**C(15)-C(11)-N(3)-C(14)**	87.2(3)
O(1)-C(4)-N(1)-C(3)	16.7(4)	**N(4)-C(11)-N(3)-C(13)**	21.6(2)
Cl(1)-C(4)-N(1)-C(3)	-159.82(18)	**C(15)-C(11)-N(3)-C(13)**	-99.4(2)
O(1)-C(4)-N(1)-C(1)	-168.5(3)	**O(4)-C(12)-N(4)-C(19)**	7.8(4)
Cl(1)-C(4)-N(1)-C(1)	14.9(3)	**C(13)-C(12)-N(4)-C(19)**	-169.3(2)
C(10)-C(3)-N(1)-C(4)	42.2(3)	**O(4)-C(12)-N(4)-C(11)**	-176.2(2)
C(2)-C(3)-N(1)-C(4)	158.2(2)	**C(13)-C(12)-N(4)-C(11)**	6.7(3)
C(10)-C(3)-N(1)-C(1)	-133.3(2)	**N(3)-C(11)-N(4)-C(12)**	-17.1(2)
C(2)-C(3)-N(1)-C(1)	-17.4(2)	**C(15)-C(11)-N(4)-C(12)**	103.4(3)
N(2)-C(1)-N(1)-C(4)	-152.4(2)	**N(3)-C(11)-N(4)-C(19)**	158.7(3)
C(5)-C(1)-N(1)-C(4)	86.8(3)	**C(15)-C(11)-N(4)-C(19)**	-80.8(3)

Crossover Experiment

To a solution of **3-Met-c** (0.5 eq.) and **3-Ala-b** (0.5 eq.) in anhydrous THF (0.1 M) at 0 °C was added dropwise KHMDS (1.0 M in THF, 1.5 eq.). After 15 min, the reaction mixture was warmed to room temperature and allowed to stir for 4 h. The reaction was quenched by dropwise addition of HCl (1.0 M, aq.) and stirred for 15 min. The organic layer was separated and the aqueous layer extracted 3 times with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. NMR and mass spectra (shown below) were obtained from the crude product mixture.





Meas. m/z	#	Ion Formula	m/z	err [ppm]	err [mDa]	mSigma	rdb	N-Rule	e⁻ Conf
351.178430	1	C18H24N4NaO2	351.179147	2.0	0.7	41.3	8.5	ok	even
420.146267	1	C19H28ClN3NaO2S	420.148297	4.8	2.0	22.7	6.5	ok	even

In situ IR (ReactIR)

[A background spectrum was obtained in anhydrous THF at −20 °C prior to *in situ* IR analysis]

A solution of **3-Ala** (0.165 mmol, 1.0 eq.) in anhydrous THF (1.65 mL, 0.1 M) was added to a three-neck Schlenk tube equipped with a stirrer bar, ReactIR probe and nitrogen inlet; the remaining neck was used for the addition of reagents. The solution was cooled to −20 °C (using a Thermo Scientific Haake Immersion Cooler EK90) and allowed to stabilise for at least 20 minutes prior to analysis.

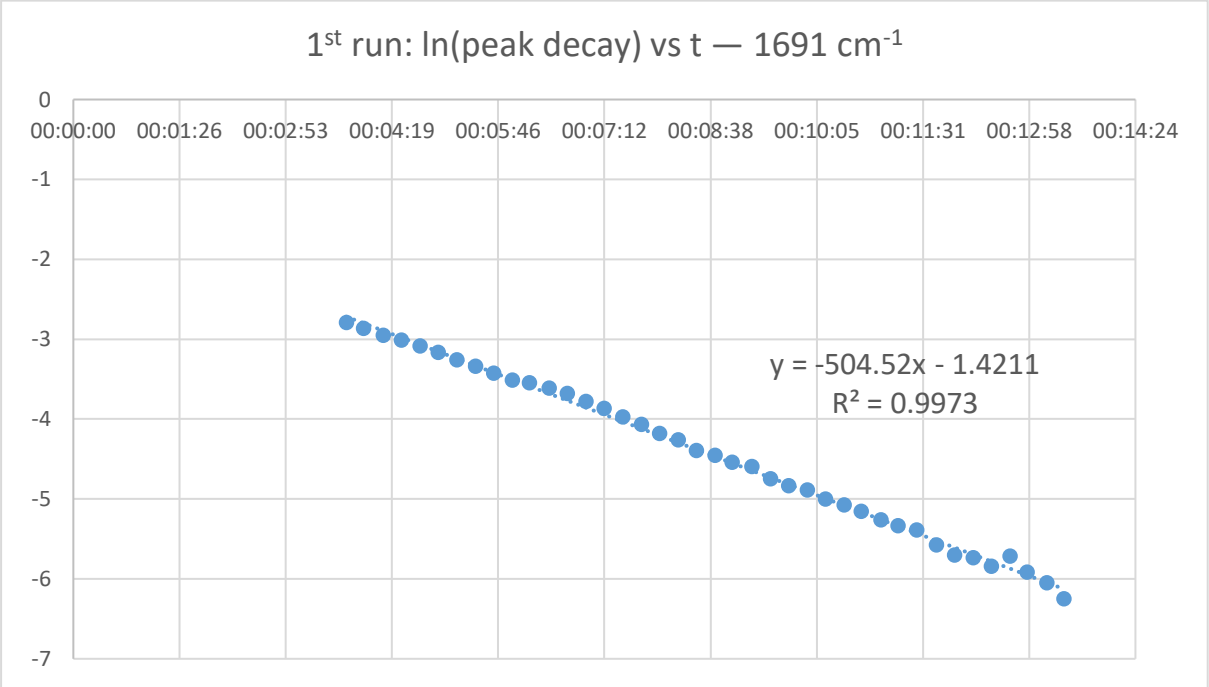
LDA was prepared by dropwise addition of *n*BuLi (0.33 mL, 0.824 mmol, 5.0 eq., 2.5 M in hexanes) to a solution of freshly distilled DIPA (0.12 mL, 0.824 mmol, 5.0 eq.) in anhydrous THF (0.30 mL) at 0 °C. After stirring for 15 min, the LDA solution was cooled to −30 °C.

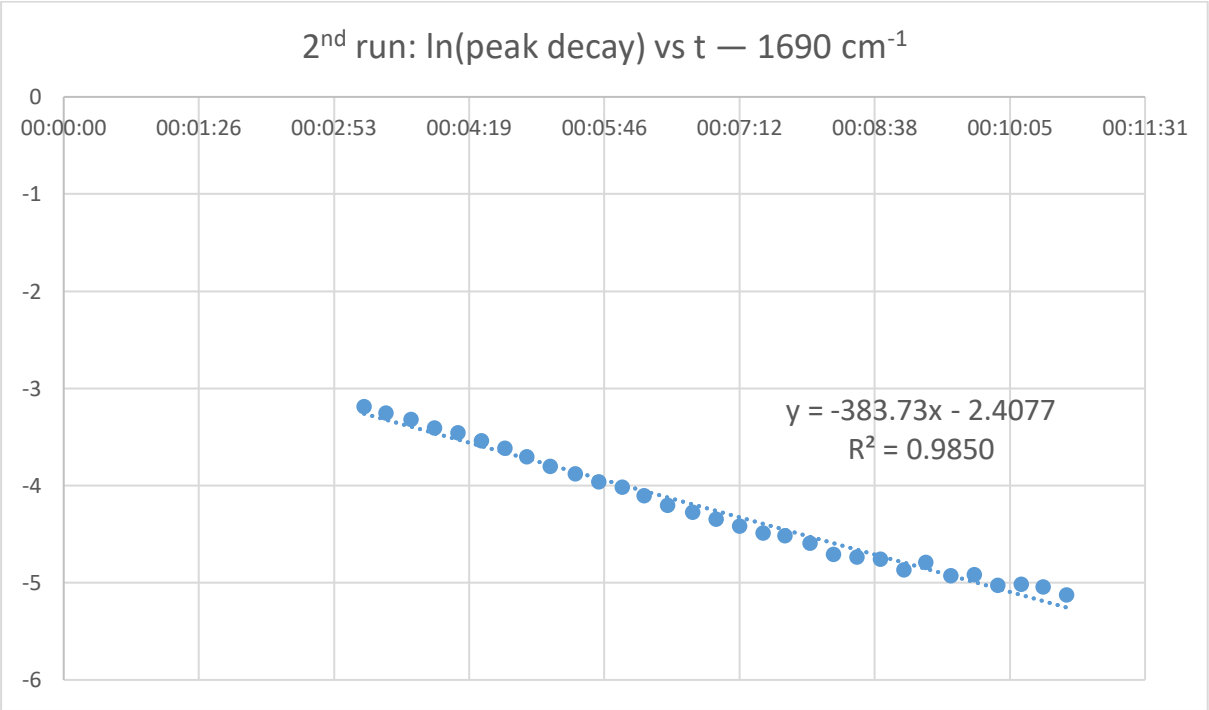
In situ IR analysis was initiated and the cooled LDA (0.74 mL, 0.824 mmol, 5.0 eq.) was added rapidly in a single portion to the solution of **3-Ala**. For electron-rich aryl species **3-Ala-a**, **3-Ala-d**, **3-Ala-i**, **3-Ala-j** and **3-Ala-k** immediate disappearance of the amide and urea carbonyl peaks (at ca. 1710 and 1660 cm^{-1} respectively) was observed, along with formation of a peak at ca. 1630 cm^{-1} corresponding to the enolate carbonyl. Decay of this enolate species was associated with formation of two further peaks at ca. 1690 and 1610 cm^{-1}, attributed to the product anion of **4-Ala,** consistent with rate-determining rearrangement. In the case of electron-deficient aryl species **3-Ala-b** and **3-Ala-c**, the enolate intermediate was not observable, with gradual decay of the starting material instead leading directly to product anion formation – indicating a shift to deprotonation as the rate-determining step. Where possible, rearrangements were monitored until product anion peaks reached a plateau, at which point the reaction was quenched with MeOH (0.70 mL).

Data analysis

For each substrate (with the exception of **3-Ala-j**) a plot of $\ln([P]_\infty - [P])$ vs. time for growth of the product anion peak at ca. 1690 cm^{-1} was constructed. For **3-Ala-j** a plot of $\ln([P] - [P]_{final})$ vs. time for decay of the enolate peak decay at ca. 1630 cm^{-1} was used, as this gave more reliable data owing to the exceptionally slow nature of the reaction. The straight-line section of these curves indicated a period of first-order reactivity with the gradient of the line of best fit providing the rate constant k_{obs}. Hammett plots of log k_{obs} vs. both σ and σ^- were constructed, with a better data fit observed in the case of σ^-. The Hammett plot of log k_{obs} vs. σ^- is consistent with rate-determining deprotonation for electron-deficient rings and rate-determining rearrangement for electron-rich rings. The gradient of the electron-rich domain to the left of the plot, $\rho = +4.5$, is consistent with substantial charge build up on the aryl substituent during the rearrangement.

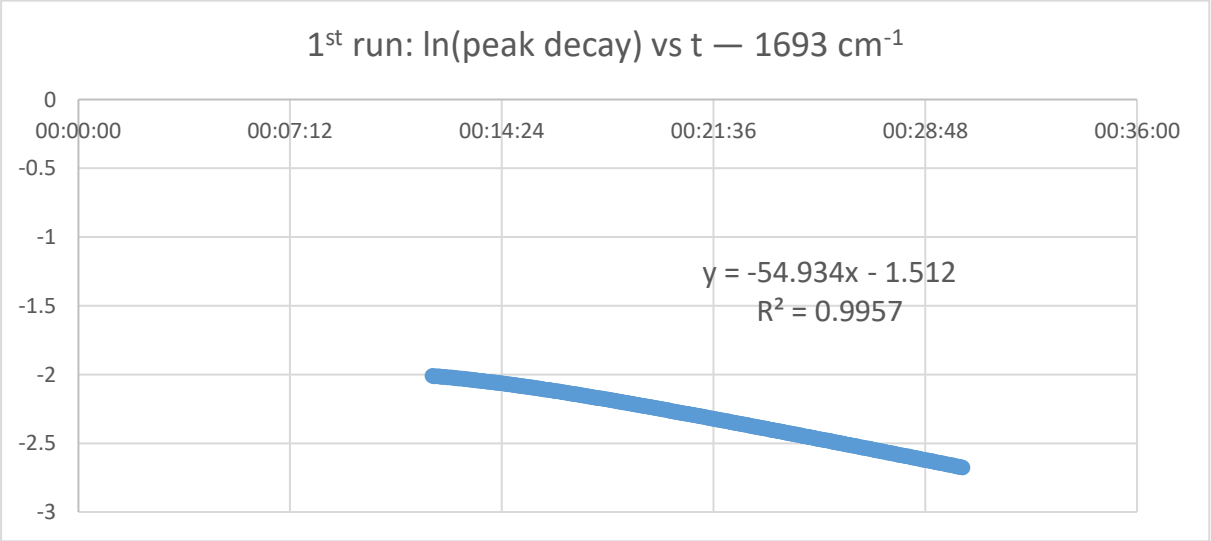
3-Ala-a

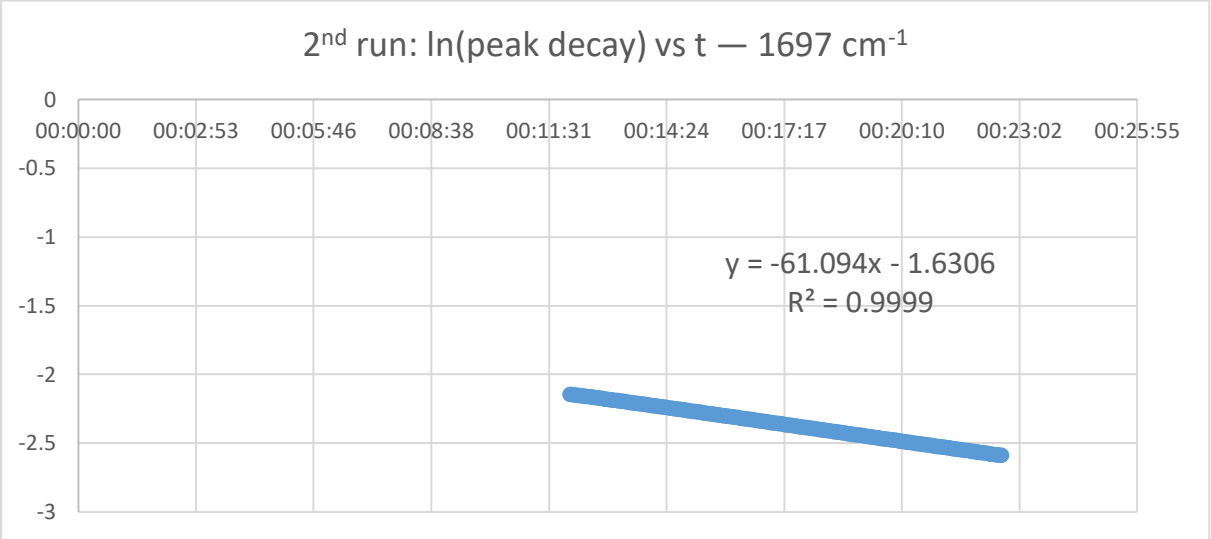


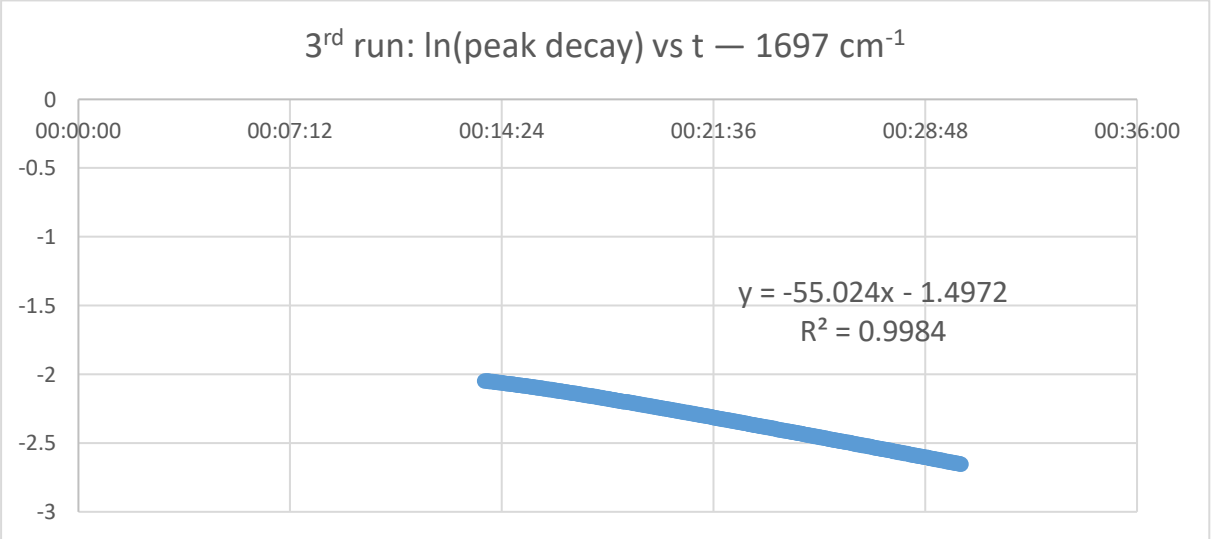


Averaged k_{obs}: (504.52 + 383.73) / 2 = 444.125

3-Ala-b

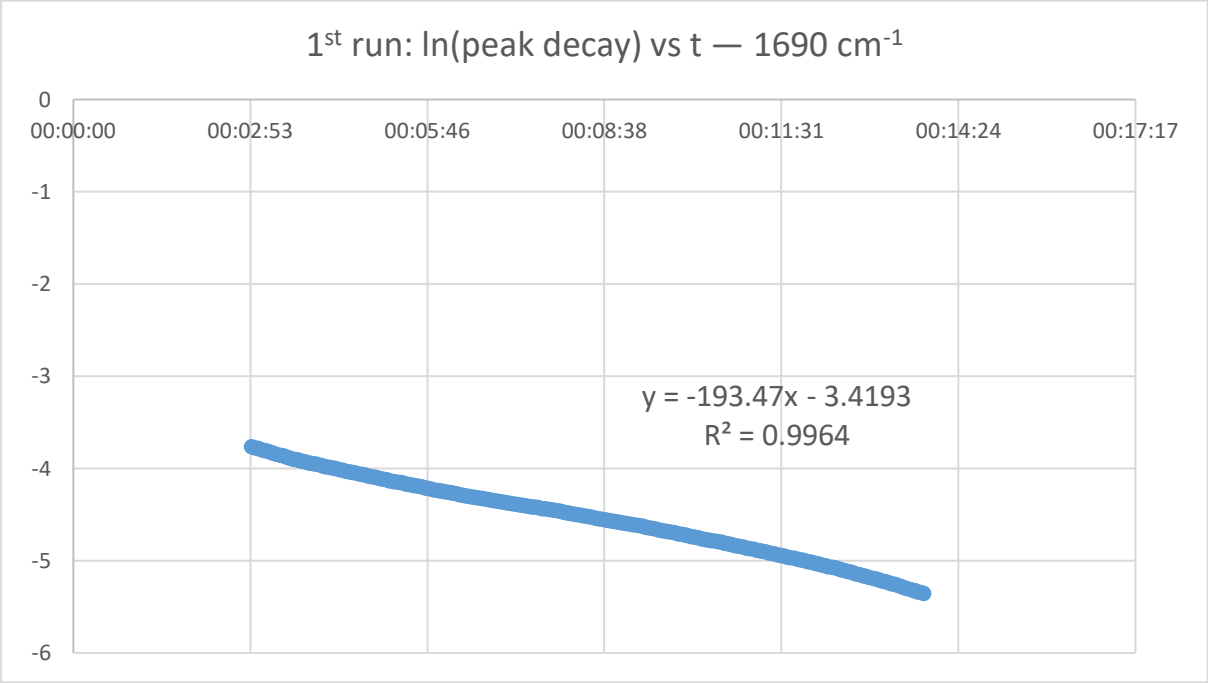


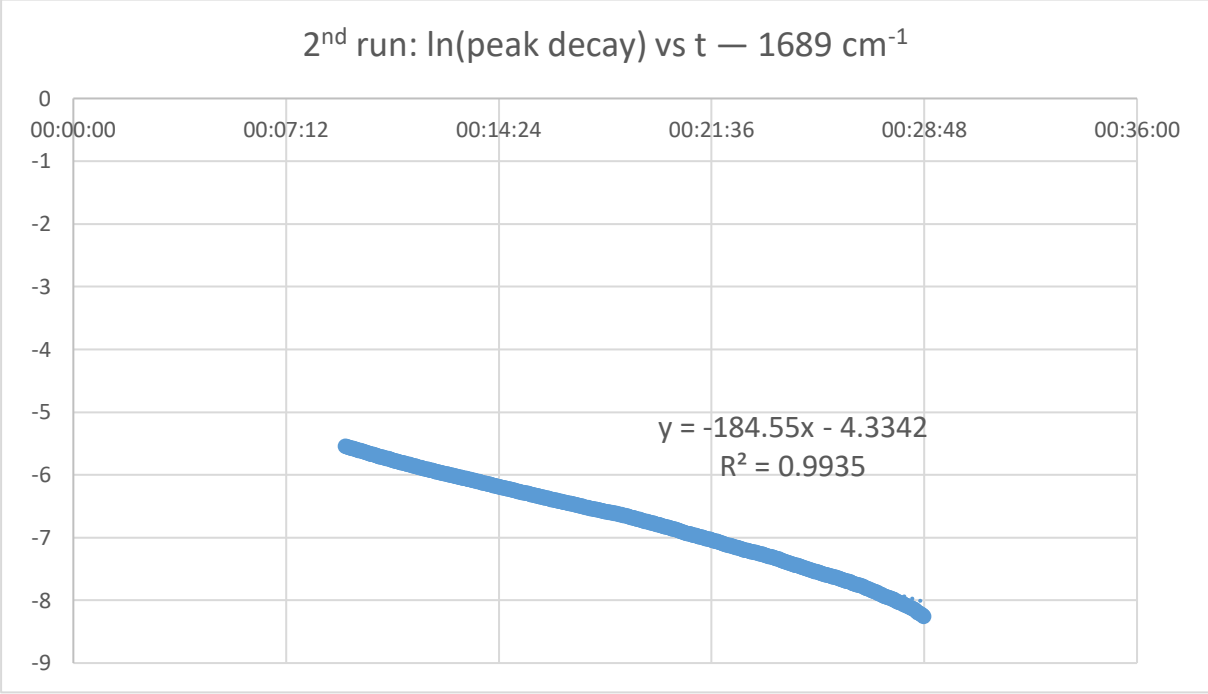




Averaged k_{obs}: (54.934 + 61.094 + 55.024) / 3 = 57.017

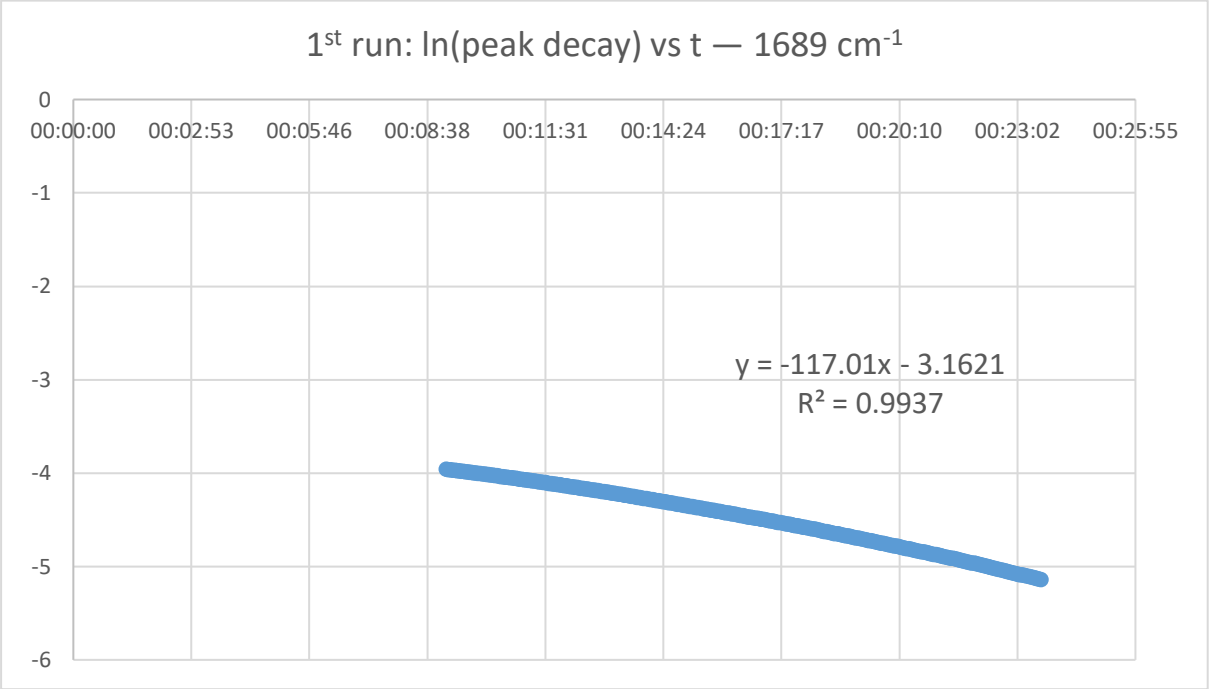
3-Ala-c

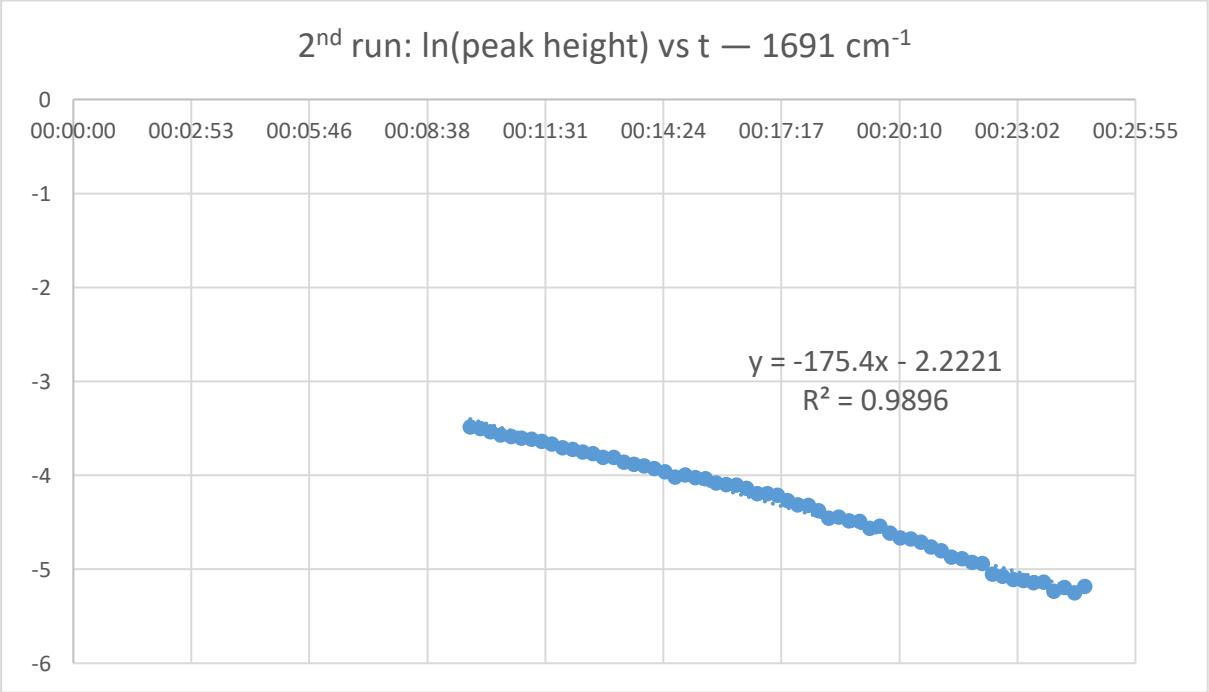




Averaged k_{obs}: (193.47 + 184.55) / 2 = 189.01

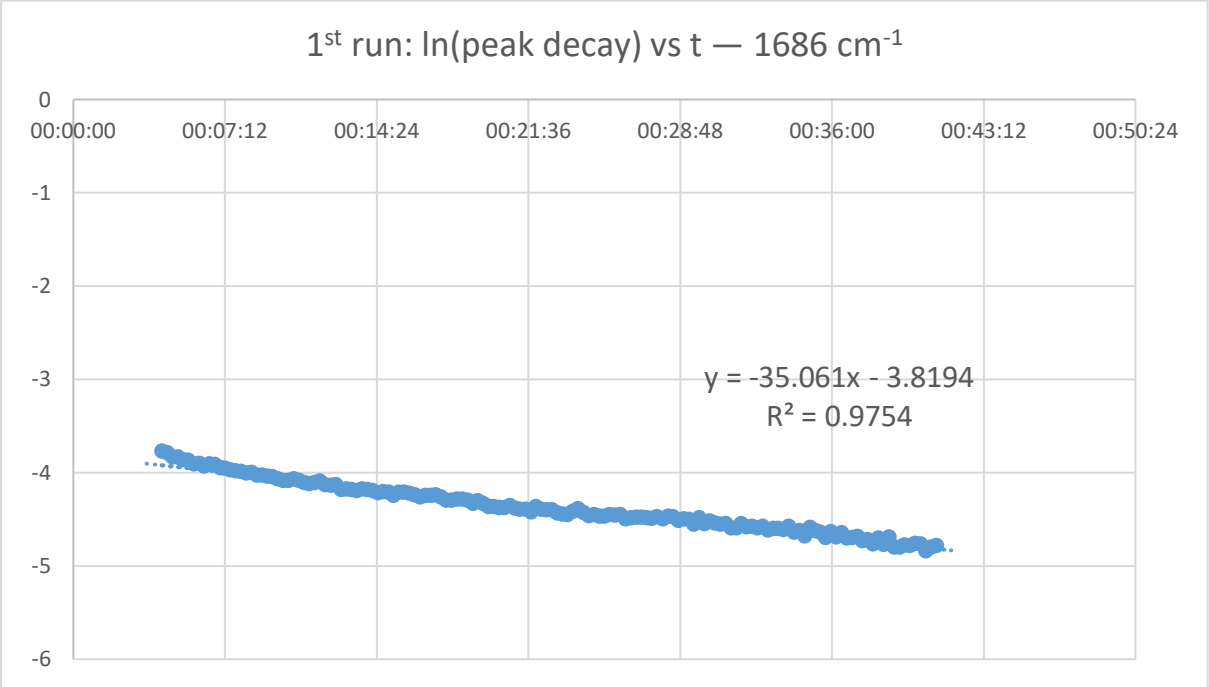
3-Ala-d

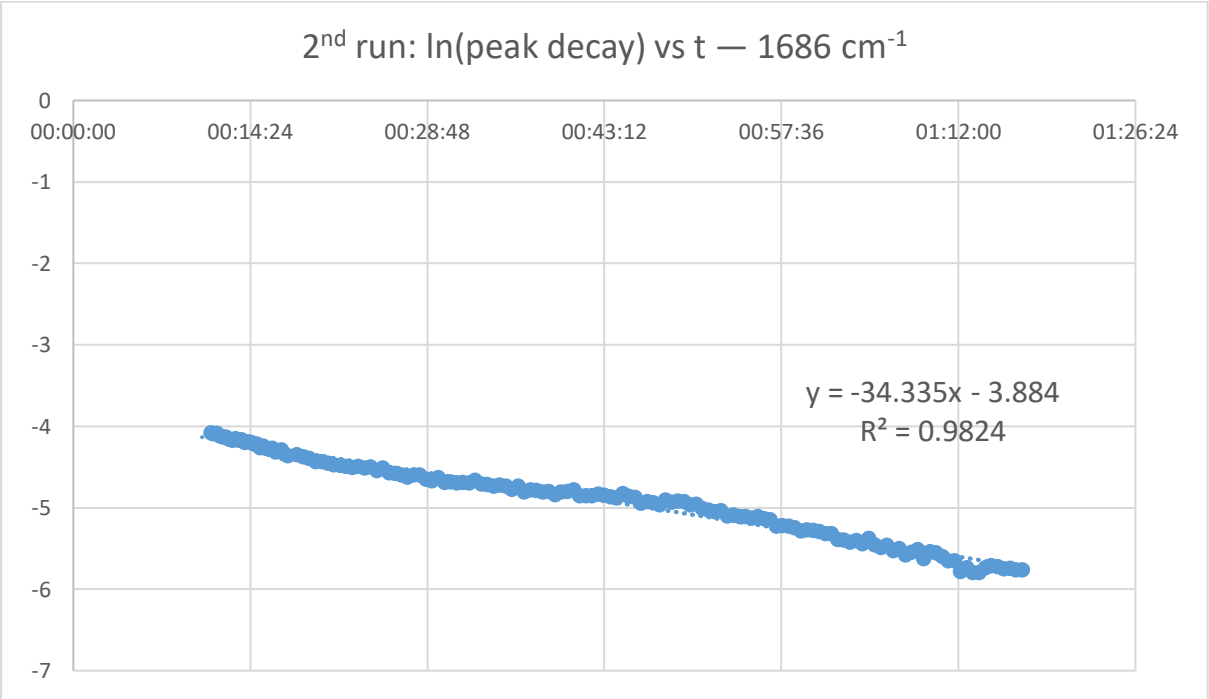




Averaged k_{obs}: (117.01 + 175.40) / 2 = 146.205

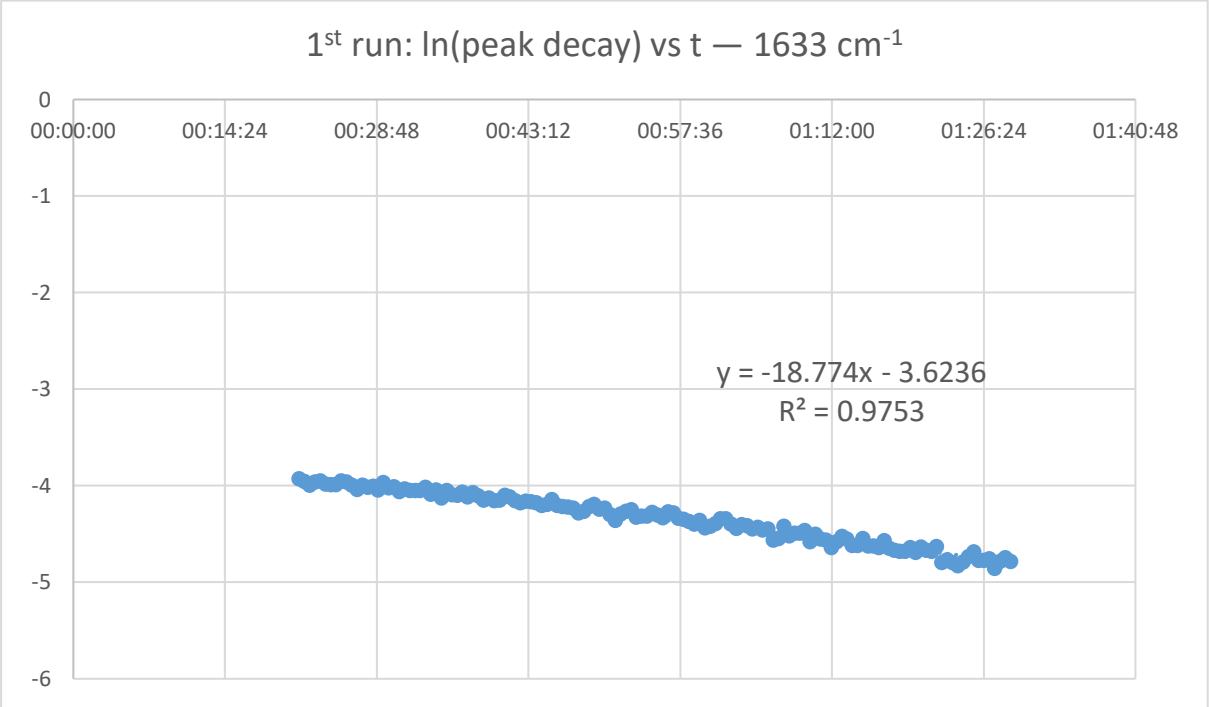
3-Ala-i

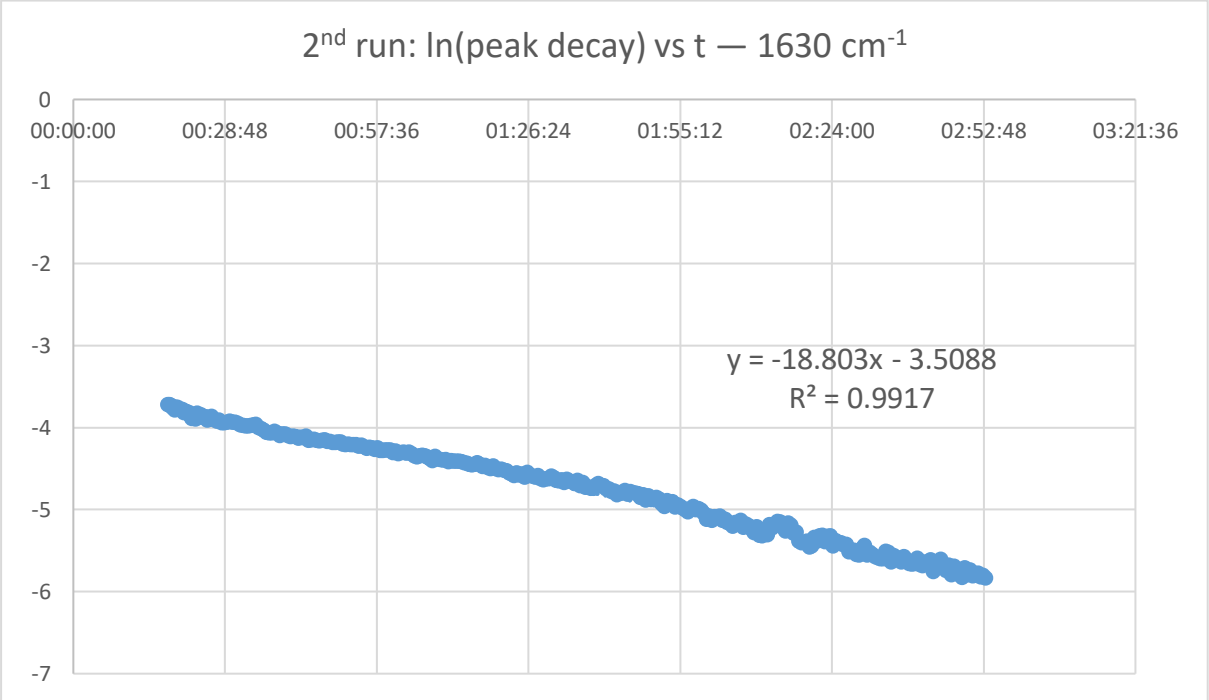




Averaged k_{obs}: (35.061 + 34.335) / 2 = 34.698

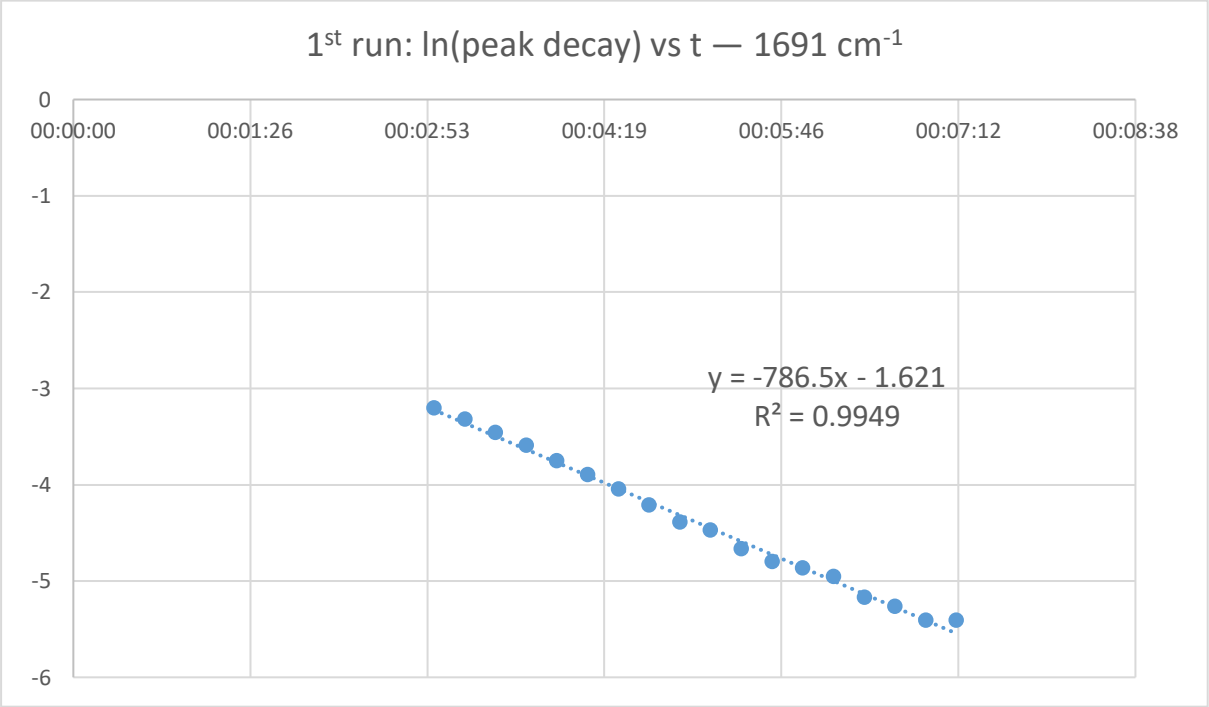
3-Ala-j

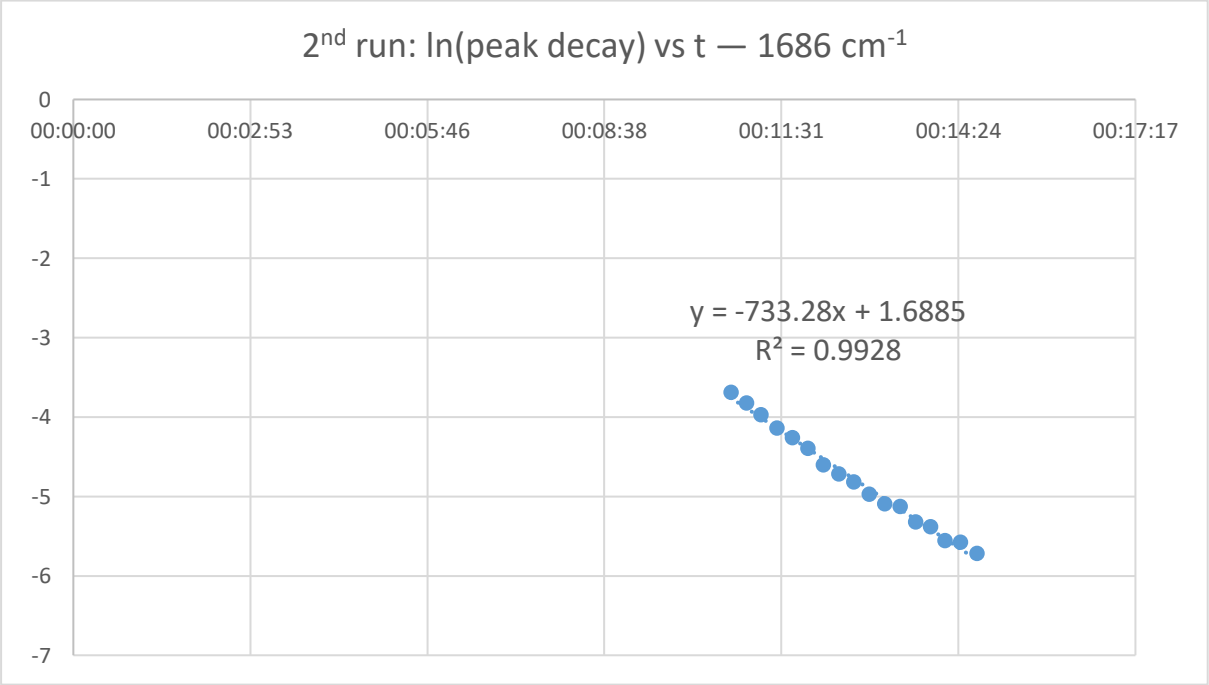




Averaged k_{obs}: (18.774 + 18.803) / 2 = 18.789

3-Ala-k



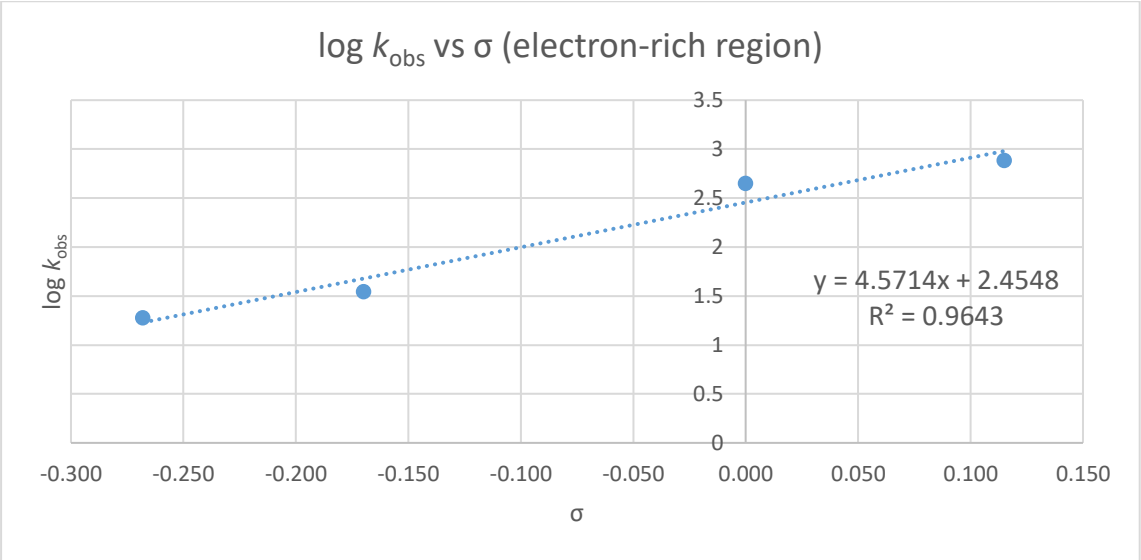


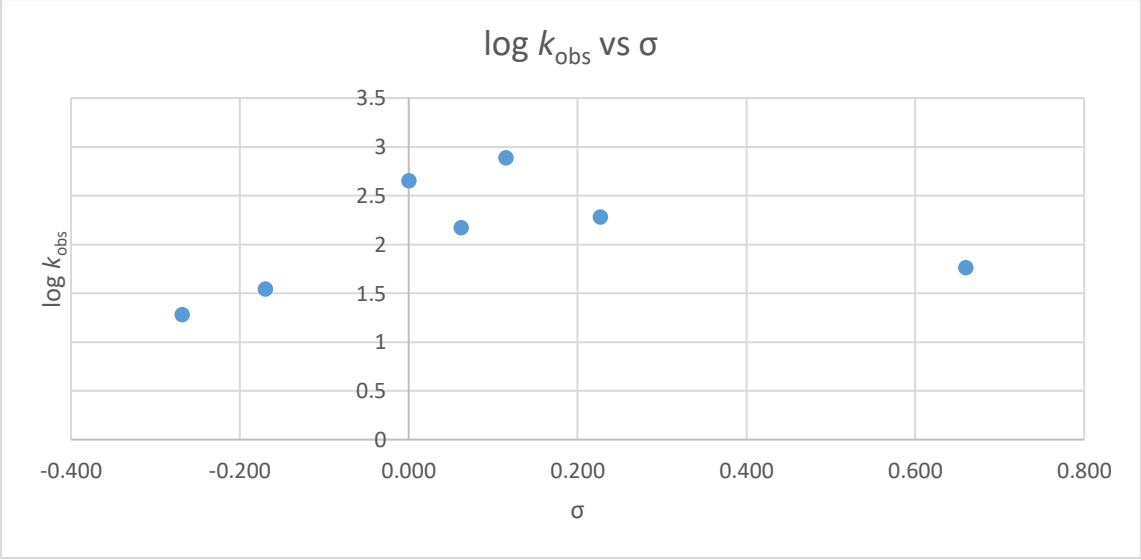
Averaged k_{obs}: (786.50 + 733.28) / 2 = 759.89

Hammett Plots

log k_{obs} vs σ

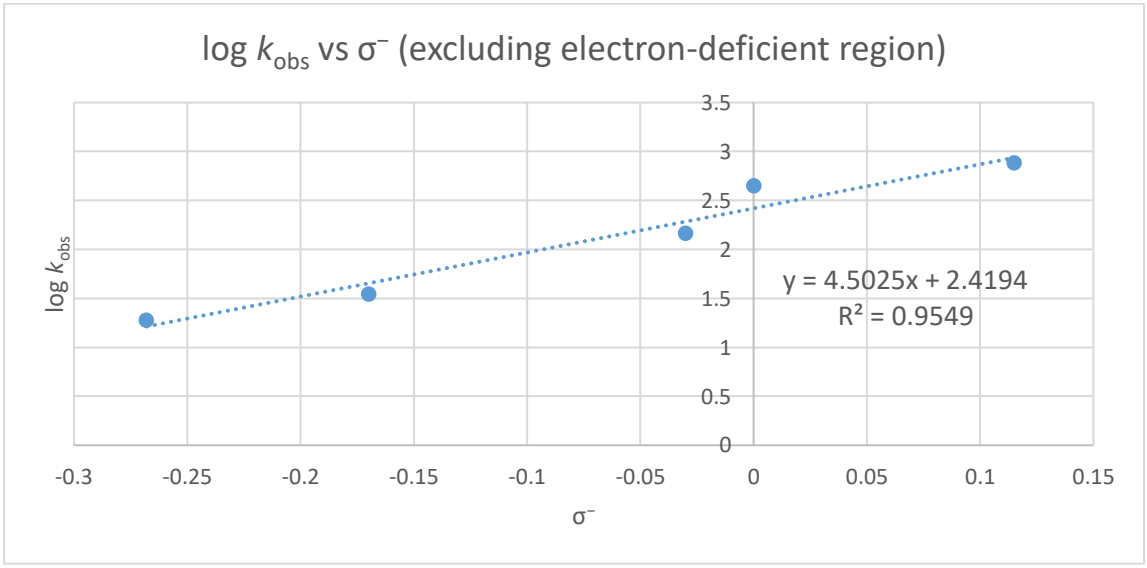
σ	substituent	k_{obs}	log k
-0.268	4-OMe	-18.79	1.273927
-0.170	4-Me	-34.70	1.540329
0.000	H	444.13	2.64751
0.115	3-OMe	759.89	2.880751
0.062	4-F	146.21	2.164977
0.227	4-Cl	189.01	2.276485
0.660	4-CN	-57.02	1.756027

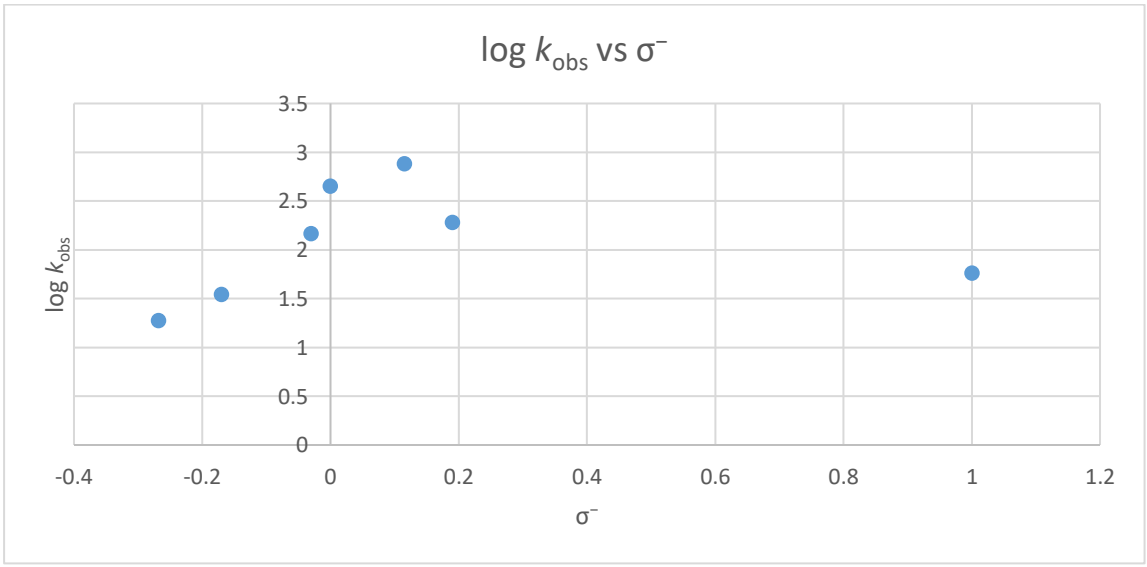




log k_{obs} vs σ⁻

σ_{minus}	substituent	k	log k
-0.268	4-OMe	-18.79	1.273927
-0.170	4-Me	-34.70	1.540329
0.000	H	444.13	2.64751
0.115	3-OMe	759.89	2.880751
-0.030	4-F	146.21	2.164977
0.190	4-Cl	189.01	2.276485
1.000	4-CN	-57.02	1.756027





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