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Supplementary Materials for

Decarboxylative borylation

Chao Li, Jie Wang, Lisa M. Barton, Shan Yu, Maoqun Tian, David S. Peters, Manoj Kumar, Antony W. Yu, Kristen A. Johnson, Arnab K. Chatterjee, Ming Yan, Phil S. Baran*

*Corresponding author. Email: pbaran@scripps.edu

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SUPPLEMENTARY MATERIALS

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General Information

Tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF), acetonitrile (CH_3CN) and dichloromethane (CH_2Cl_2) were obtained by passing the previously degassed solvents through activated alumina columns. Purity and source of reagents were listed on Page S19. Reagents were used as received without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous material, unless otherwise stated. Reactions were monitored by GC/MS, LC/MS, and thin layer chromatography (TLC). TLC was performed using 0.25 mm E. Merck silica plates (60F-254), using short-wave UV light as visualizing agent, as well as potassium permanganate ($KMnO_4$) or ceric ammonium molybdate (CAM) and heat as developing agents. NMR spectra were recorded on Bruker DRX-600, DRX-500, or DPX-400 instruments and were calibrated using residual undeuterated solvent (^1H: δ 7.26 for $CDCl_3$, δ 3.31 for MeOH-d_4, δ 3.58, 1.73 for THF-d_8, δ 2.50 for DMSO-d_6, δ 2.05 for acetone-d_6; ^{13}C: δ 77.16 for $CDCl_3$, δ 49.0 for MeOH-d_4, δ 67.6, 25.5 for THF-d_8, δ 39.50 for DMSO-d_6, δ 29.84 for acetone-d_6). The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Column chromatography was performed using E. Merck silica gel (60, particle size 0.043-0.063 mm), and preparative TLC was performed on 0.25 mm E. Merck silica plates (60F-254). High resolution mass spectra (HRMS) were recorded on an Agilent LC/MSD TOF mass spectrometer by electrospray ionization time of flight reflectron experiments. Preparative high performance liquid chromatography (HPLC) was performed using an Agilent SD-1 prepstar system equipped with Phenomenex Gemini 10 μm C18 column with dimension 200 × 50 mm. Melting points were recorded on a Fisher-Johns 12-144 melting point apparatus and are uncorrected. All X-ray diffraction data were collected and analyzed by the UCSD small molecule X-ray facility. The deactivated silica gel (35 wt% H_2O) was prepared by mixing silica gel and deionized water, followed by vigorous shaking until a fluffy powder was observed.

Purity and Source of Reagents

Reagents (Purity)	Sources	Catalog Numbers
$NiCl_2$•$6H_2O$ (*ReagentPlus*®, >99%)	Sigma-Aldrich®	223387
MeLi in Et_2O (1.6 M)	Sigma-Aldrich®	197343
$MgBr_2$•OEt_2 (99%)	Sigma-Aldrich®	225959
B_2pin_2 (99%)	Oakwood Chemical®	019250
4,4′-di-*tert*-butyl-2,2′-dipyridine (di-*t*Bubipy, 98%)	Sigma-Aldrich®	515477
4,4′-dimethoxy-2,2′-bipyridine (di-MeObipy, 97%)	Sigma-Aldrich®	536040
N-hydroxyphthalimide (>98%)	Alfa Aesar®	A13862
N,N′-diisopropylcarbodiimide (DIC, >99%)	Oakwood Chemical®	M02889
4-dimethylaminopyridine (DMAP, 99%)	Acros Organics®	148275000

General Procedure for the Synthesis of Redox-active Esters (RAEs) (General Procedure A)

A round bottom flask was charged with carboxylic acid (1.0 equiv.), *N*-hydroxyphthalimide (NHPI, 1.0 equiv.) or tetrachloro-*N*-hydroxyphthalimide (TCNHPI, 1.0 equiv.), and DMAP (0.1 equiv.). CH_2Cl_2 (0.2 M) was added, followed by *N*,*N'*-diisopropylcarbodiimide (DIC, 1.1 equiv.), both at room temperature (RT). The mixture was allowed to stir until all the acid was consumed (as indicated by TLC). The resulting mixture was quickly filtered and the solid residue was rinsed with more CH_2Cl_2. The filtrate was concentrated *in vacuo* and purified by flash column chromatography to afford the corresponding redox-active ester (RAE), which was used without further purification unless otherwise noted.

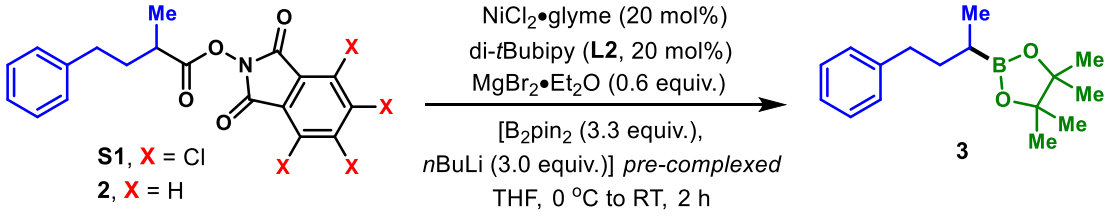
Note: Some RAEs that are prone to hydrolysis on silica gel during column chromatography were purified by recrystallization or column chromatography using deactivated silica gel (35 wt% H_2O).

Optimization Details

All reactions were screened based on 0.1 mmol scale.

*The optimization started with **S1**. TCNHPI esters were used in the initial screening since earlier conditions indicated better performance than NHPI esters (NHPI esters were used in the optimized conditions in the end, vide infra):*

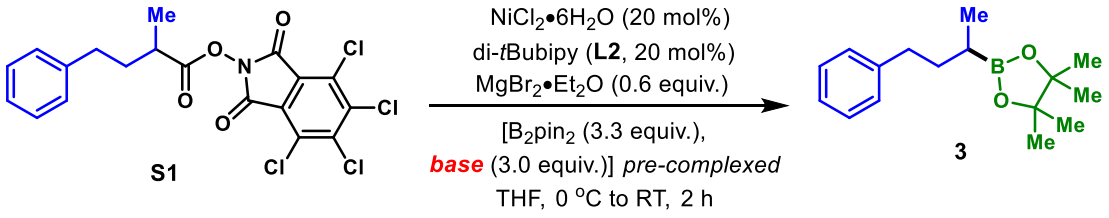
Table S1. Comparison of NHPI and TCNHPI esters.



RAEs	Yield*
X = H	31%
X = Cl	***45%***

*Yields determined by GC-FID with dodecane as internal standard.

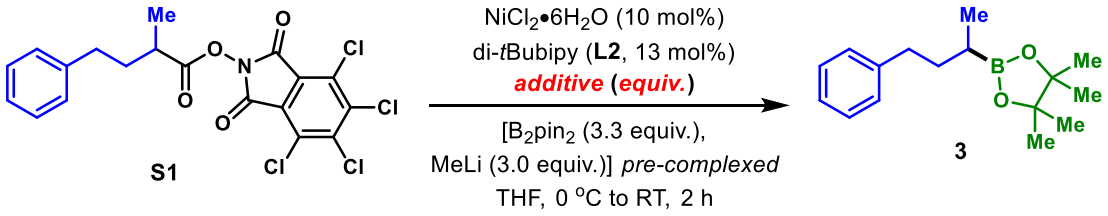
Table S2. Screening of bases.



Base	Yield*
w/o base	0
MeLi	***58% (54%†)***
MeLi·LiBr	***58%***
*n*BuLi	45%
*t*BuLi	36%
MeMgBr	11%
MeMgBr (w/o $MgBr_2$)	7%
EtMgBr	10%
EtOK	0
*t*BuOK	0
MeOLi	0
NaHMDS	0
KHMDS	0
LiHMDS	0
KF	0
CsF	0

*Yields determined by GC-FID with dodecane as internal standard. †Isolated yield.

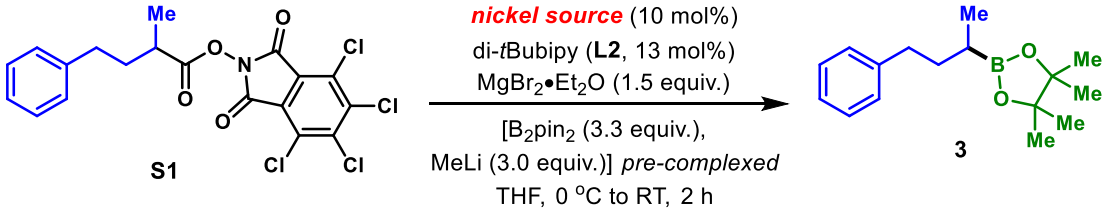
Table S3. Screening of additives.



Additive (equiv.)	Yield*
w/o	4%
$Mg(OAc)_2$ (1.5 equiv.)	< 1%
$Mg(acac)_2$ (1.5 equiv.)	< 1%
$MgCl_2$ (1.5 equiv.)	13%
$MgSO_4$ (1.5 equiv.)	< 1%
LiBr (3.0 equiv.)	34%
$ZnCl_2$ (1.5 equiv.)	14%
$MgBr_2 \cdot OEt_2$ (0.2 equiv.)	23%
$MgBr_2 \cdot OEt_2$ (0.6 equiv.)	53%
$MgBr_2 \cdot OEt_2$ (1.0 equiv.)	64%
$MgBr_2 \cdot OEt_2$ (1.5 equiv.)	***67% (63%†)***
$MgBr_2 \cdot OEt_2$ (2.0 equiv.)	66%
$MgBr_2 \cdot OEt_2$ (2.5 equiv.)	57%

*Yields determined by GC-FID with dodecane as internal standard. †Isolated yield.

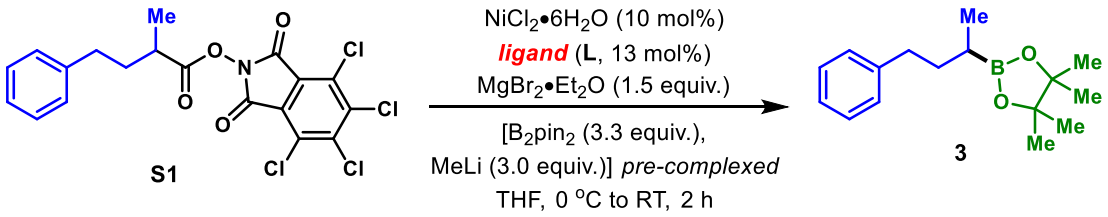
Table S4. Screening of nickel catalysts.



Nickel source	Yield*
$NiCl_2 \cdot 6H_2O$	***67% (63%†)***
$NiCl_2 \cdot$glyme	58%
$NiBr_2 \cdot$glyme	63%
NiI_2	14%
$Ni(acac)_2 \cdot 2H_2O$	17%
$Ni(ClO_4)_2$	3%
$Ni(PCy)_3Cl_2$	4%
w/o nickel	0

*Yields determined by GC-FID with dodecane as internal standard. †Isolated yield.

Table S5. Screening of ligands.



Ligand	Yield*
L2	***67% (63%†)***
L2 (20 mol%)	57%
L1	51%
L3	23%
L4	26%
L5	4%
L6	0
L7	13%
L8	11%
L9	17%
L10	0
L11	0
L12	1%
L13	1%
L14	0
L15	1%
L16	1%
w/o ligand	0

*Yields determined by GC-FID with dodecane as internal standard. †Isolated yield.

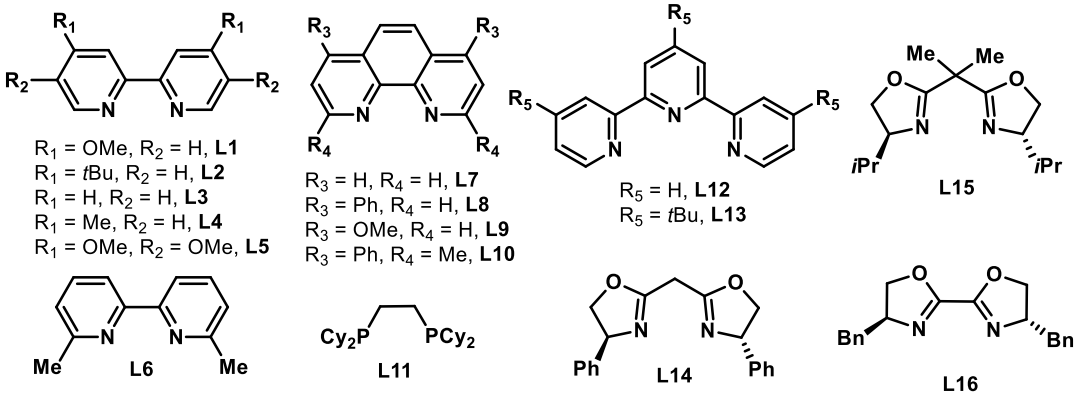
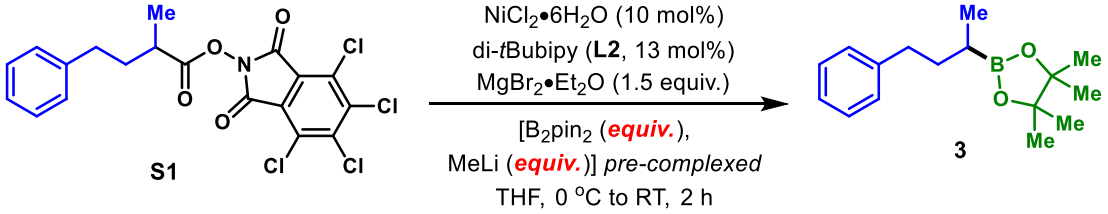


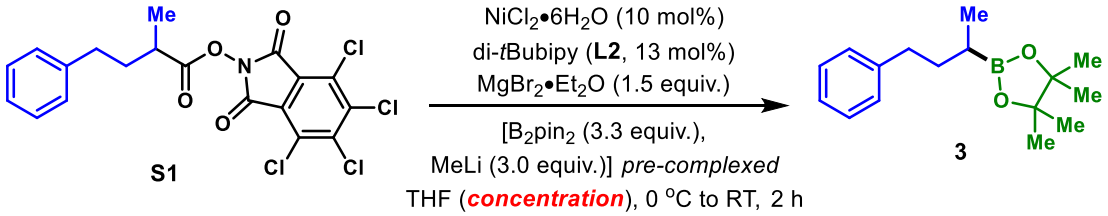
Table S6. Optimization of [B_2pin_2Me]Li complexation.



B_2pin_2 (equiv.), MeLi (equiv.)	Yield*
B_2pin_2 (2.2 equiv.), MeLi (2.0 equiv.)	51%
B_2pin_2 (2.75 equiv.), MeLi (2.5 equiv.)	65%
B_2pin_2 (3.3 equiv.), MeLi (3.0 equiv.)	***67% (63%†)***
B_2pin_2 (3.85 equiv.), MeLi (3.5 equiv.)	60%
B_2pin_2 (4.4 equiv.), MeLi (4.0 equiv.)	57%

*Yields determined by GC-FID with dodecane as internal standard. †Isolated yield.

Table S7. Screening of reaction concentration.

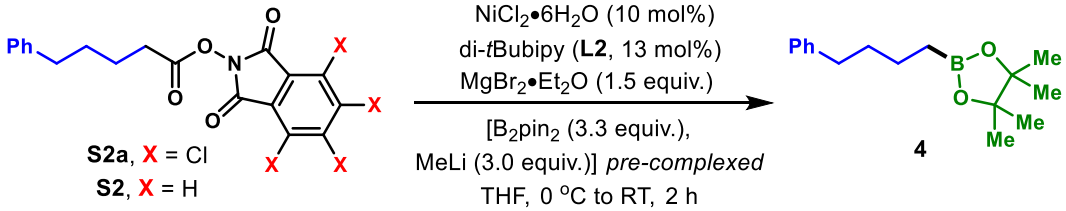


Concentration	Yield*
0.025 M	44%
0.033 M	58%
0.05 M	***67%***
0.10 M	***67% (63%†)***
0.15 M	65%

*Yields determined by GC-FID with dodecane as internal standard. †Isolated yield.

*However, under the aforementioned optimized conditions for **S1**, decarboxylative borylation of **S2a** proceeded in lower yield than the NHPI ester of **S2**.*

Table S8. Comparison of NHPI and TCNHPI esters of a primary acid.

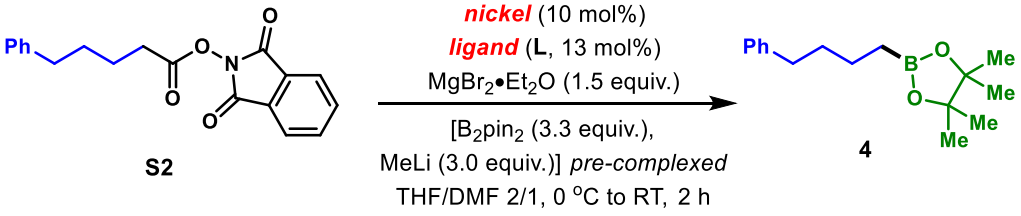


RAEs	Yield*
X = H	***39%***
X = Cl	28%

*Yields determined by GC-FID with dodecane as internal standard.

*In order to identify a more general set of conditions, further optimization efforts were undertaken on the NHPI ester **S2**.*

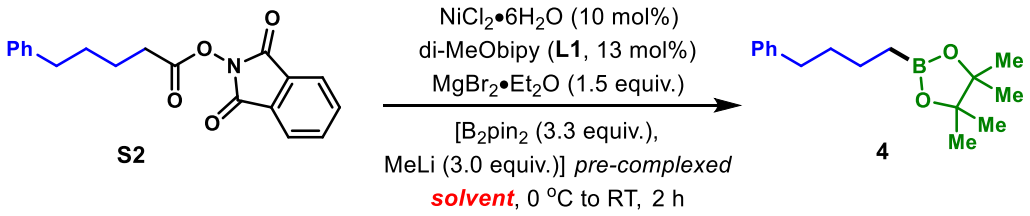
Table S9. Screening of nickel catalysts.



Nickel/ligand	Yield*
$NiCl_2·6H_2O$/L1	***67% (65%†)***
$NiCl_2·6H_2O$/**L2**	28%
$NiCl_2·6H_2O$/**L4**	32%
$NiCl_2·6H_2O$/**L5**	55%
$NiCl_2$·glyme/**L1**	53%
$NiBr_2$·glyme/**L1**	64%
$Ni(OAc)_2·4H_2O$/**L1**	61%
$Ni(acac)_2$/**L1**	46%
$Ni(ONO_3)_2·6H_2O$/**L1**	58%

*Yields determined by GC-FID with dodecane as internal standard. †Isolated yield.

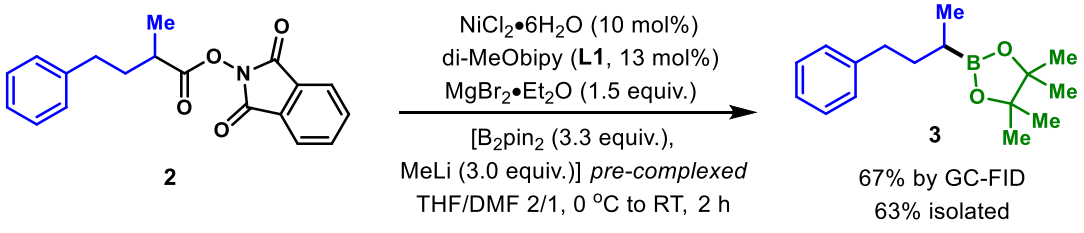
Table S10. Screening of solvents.



Solvent	Yield*
THF (0.4 mL)	54%
DMF (0.4 mL)	44%
THF/DMF (0.2/0.2 mL)	***67%***
THF/DMF (0.4/0.2 mL)	***67% (65%†)***
THF/DMF (0.6/0.2 mL)	***67%***
THF/DMF (1.0/0.2 mL)	62%
THF/DMF (1.4/0.2 mL)	57%
dioxane/DMF (0.4/0.2 mL)	41%
glyme/DMF (0.4/0.2 mL)	49%
diglyme/DMF (0.4/0.2 mL)	43%
Et_2O/DMF (0.4/0.2 mL)	38%
THF/DMA (0.4/0.2 mL)	39%
THF/CH_3CN (0.4/0.2 mL)	8%
THF/HMPA (0.4/0.2 mL)	63%
THF/DMPU (0.4/0.2 mL)	45%
THF/DMSO (0.4/0.2 mL)	10%
THF/NMP (0.4/0.2 mL)	45%

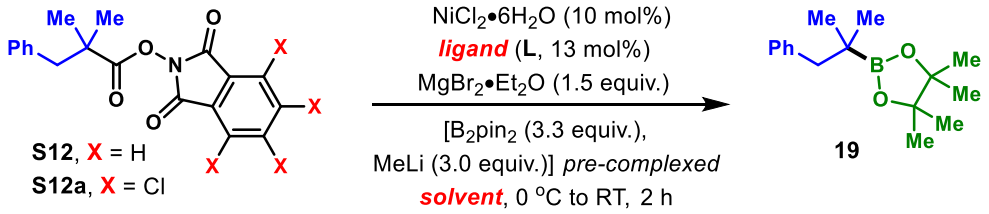
*Yields determined by GC-FID with dodecane as internal standard. †Isolated yield.

*This optimized set of condition for the decarboxylative borylation of **S2** (1° RAE) was more general, and was also suitable for **2** (2° RAE).*



Further screening indicated that employing THF as sole solvent gave the best yield for tertiary carboxylic acids (3° RAEs).

Table S11. Optimization on tertiary RAEs.



X	Ligand	Solvent	Yield*
H	**L2**	THF (0.4 mL)	26%
H	***L1***	***THF (0.4 mL)***	***74% (68%†)***
H	**L1**	THF/DMF (0.4/0.2 mL)	66%
H	**L5**	THF (0.4 mL)	62%
Cl	**L2**	THF (0.4 mL)	70%
Cl	**L1**	THF (0.4 mL)	52%

*Yields determined by GC-FID with dodecane as internal standard. †Isolated yield.

General Procedure for Nickel Catalyzed Decarboxylative Borylation

Part I. Preparation of $NiCl_2$•$6H_2O$/Ligand Stock Solution or Suspension

(1) Suspension A: $NiCl_2$•$6H_2O$/di-MeObipy (**L1**) in THF (0.025 M).

A screw-capped culture tube charged with $NiCl_2$•$6H_2O$ (23.8 mg, 0.1 mmol) and 4,4′-dimethoxy-2,2′-bipyridine (**L1**, 28.1 mg, 0.13 mmol) was evacuated and backfilled with argon for three times. THF (4.0 mL) was added and the resulting mixture was stirred at room temperature overnight (or until no granular $NiCl_2$•$6H_2O$ was observed) to afford a pale green suspension.

(2) Suspension B: $NiCl_2$•$6H_2O$/di-MeObipy (**L1**) in DMF (0.05 M).

A screw-capped culture tube charged with $NiCl_2$•$6H_2O$ (23.8 mg, 0.1 mmol) and 4,4′-dimethoxy-2,2′-bipyridine (**L1**, 28.1 mg, 0.13 mmol) was evacuated and backfilled with argon for three times. DMF (2.0 mL) was added and the resulting mixture was stirred at room temperature overnight to afford a pale green suspension.

(3) Suspension C: $NiCl_2$•$6H_2O$/di-*t*Bubipy (**L2**) in THF (0.025 M).

A screw-capped culture tube charged with $NiCl_2$•$6H_2O$ (23.8 mg, 0.1 mmol) and 4,4′-di-*tert*-butyl-2,2′-bipyridine (**L2**, 34.8 mg, 0.13 mmol) was evacuated and backfilled with argon for three times. THF (4.0 mL) was added and the resulting mixture was stirred at room temperature overnight (or until no granular $NiCl_2$•$6H_2O$ was observed) to afford a pale green suspension.

(4) Solution D: $NiCl_2$•$6H_2O$/di-*t*Bubipy (**L2**) in DMF (0.05 M).

A screw-capped culture tube charged with $NiCl_2$•$6H_2O$ (23.8 mg, 0.1 mmol) and 4,4′-di-*tert*-butyl-2,2′-bipyridine (**L2**, 34.8 mg, 0.13 mmol) was evacuated and backfilled with argon for three times. DMF (2.0 mL) was added and the resulting mixture was stirred at room temperature for 2 h to afford a green solution.

Note: All the solutions or suspensions kept under argon can be used for two weeks without appreciable deterioration in reaction yields.

Part II. Preparation of [B_2pin_2Me]Li Complex

To a solution of B_2pin_2 (168 mg, 0.66 mmol) in THF (0.6 mL) was added MeLi (0.38 mL, 1.6 M in Et_2O, 0.6 mmol) at 0 °C under argon. The reaction mixture was warmed to room temperature and stirred for 1 h to afford a suspension (sometimes a clear solution was observed).

Note: The resulting mixture can be stored under constant stirring for 12 hours without appreciable deterioration.

Part III. Nickel Catalyzed Decarboxylative Borylation

General Procedure B

A screw-capped culture tube charged with redox-active ester (0.2 mmol, 1.0 equiv.) and $MgBr_2$•OEt_2 (77 mg, 0.3 mmol, 1.5 equiv.) was evacuated and backfilled with argon for three times. THF (0.8 mL) was added, and the mixture was stirred until no granular $MgBr_2$•OEt_2 was observed (*ca.* 10 min, sonication could promote this process) before suspension B [0.4 mL, $NiCl_2$•$6H_2O$ (10 mol%)/di-MeObipy (13 mol%) in DMF], or solution D [0.4 mL, $NiCl_2$•$6H_2O$ (10 mol%)/di-*t*Bubipy (13 mol%) in DMF] was added via a syringe. The resulting mixture was stirred vigorously until no visible solid was observed on the bottom of the reaction vessel (*ca.* 10 min, sonication could promote this process). This mixture was cooled to 0 °C before a suspension of [B_2pin_2Me]Li in THF (3.0 equiv., 1.1 mL) was added in one portion (*note: do not add it dropwise!*). After stirring for 1 h at 0 °C, the reaction was warmed to room temperature and stirred for another 1 h before quenching with 0.1 N HCl (10 mL). The resulting mixture was extracted with Et_2O or EtOAc (3 mL×2). The combined organic layers were concentrated *in vacuo*, and the crude product was purified by flash column chromatography. For acid labile substrates, the reaction was alternatively quenched with saturated aqueous NH_4Cl (10 mL).

General Procedure C

A screw-capped culture tube charged with redox-active ester (0.2 mmol, 1.0 equiv.) and $MgBr_2$•OEt_2 (77 mg, 0.3 mmol, 1.5 equiv.) was evacuated and backfilled with argon for three times. Suspension A [0.8 mL, $NiCl_2$•$6H_2O$ (10 mol%)/di-MeObipy (13 mol%) in THF] or C **[**(0.8 mL, $NiCl_2$•$6H_2O$ (10 mol%)/di-*t*Bubipy (13 mol%) in THF] was added via a syringe. The mixture was stirred vigorously at room temperature until no granular $MgBr_2$•OEt_2 was observed (*ca.*10 min, sonication could promote this process). This suspension was cooled to 0 °C before a suspension of [B_2pin_2Me]Li was added in one portion (*note: do not add it dropwise!*). After stirring for 1 h at 0 °C, the reaction was warmed to room temperature and stirred for another 1 h. The reaction mixture was diluted with Et_2O (10 mL), filtered through a short pad of silica gel and celite (top layer: celite, bottom layer: silica gel, v/v celite:silica gel = 1:1), and washed with Et_2O (50 mL). The filtrate was concentrated, and the crude product was purified by flash column chromatography.

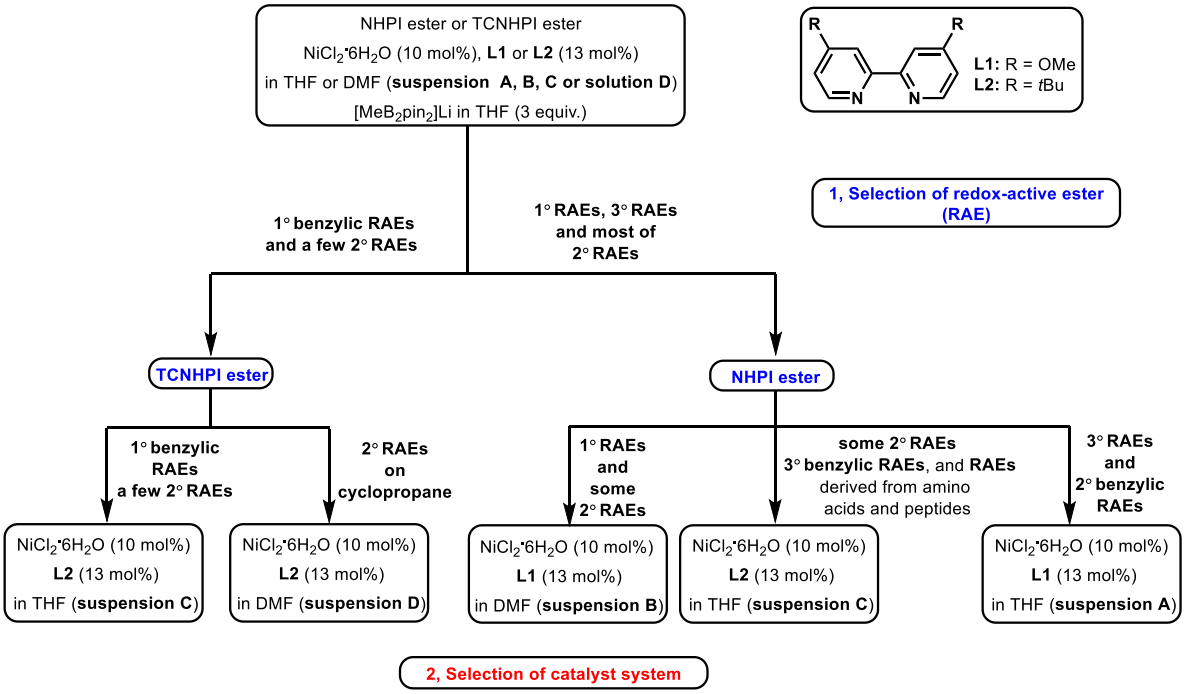
For polar substrates, such as peptides, the reaction was quenched either with 0.1 N HCl (10 mL) or saturated aqueous NH_4Cl (10 mL) followed by extraction with EtOAc (3 mL×2). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by flash column chromatography.

Note:

1. *Addition of THF to solid $MgBr_2$•OEt_2 is* ***exothermic****.*
2. *Addition of [B_2pin_2Me]Li to the reactiom mixture is* ***exothermic****.*

Guide for Selecting Reaction Conditions

Based on the substrates examined, a flow chart is presented herein to guide the selection of optimal conditions for each substrate:



Graphical Supporting Information for Nickel Catalyzed Decarboxylative Borylation

Part I. $NiCl_2$•$6H_2O$/Ligand Stock Solution or Suspension

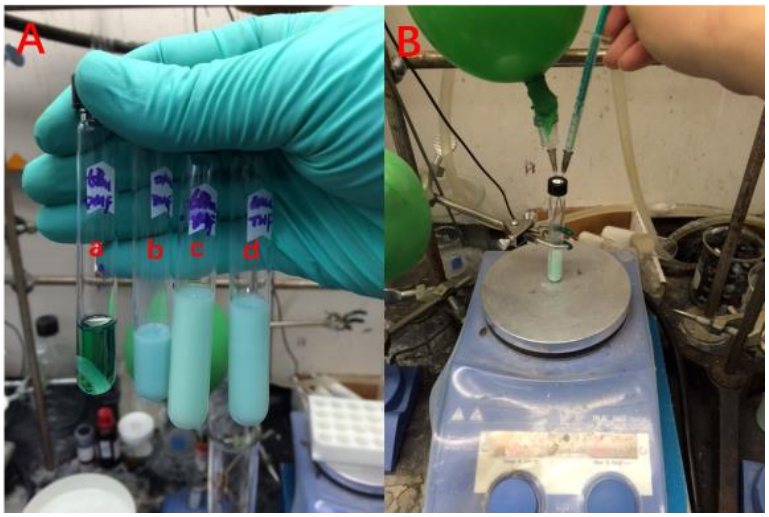


Figure S1. (Left) $NiCl_2$•$6H_2O$/ligand stock solution and suspensions: (a) $NiCl_2$•$6H_2O$/di-*t*Bubipy in DMF (0.05 M), (b) $NiCl_2$•$6H_2O$/di-MeObipy in DMF (0.05 M), (c) $NiCl_2$•$6H_2O$/di-*t*Bubipy in THF (0.025 M), (d) $NiCl_2$•$6H_2O$/di-MeObipy in THF (0.025M). **(Right)** The suspensions were used under stirring.

Part II. Preparation of [B_2pin_2Me]Li Complex

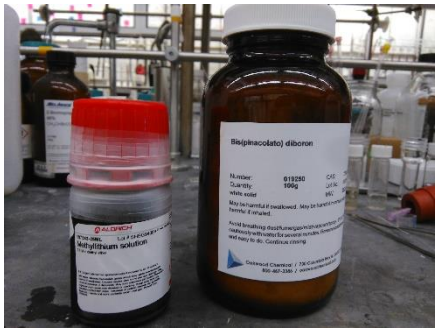


Figure S2. (Above) MeLi (1.6 M in Et_2O) and B_2pin_2

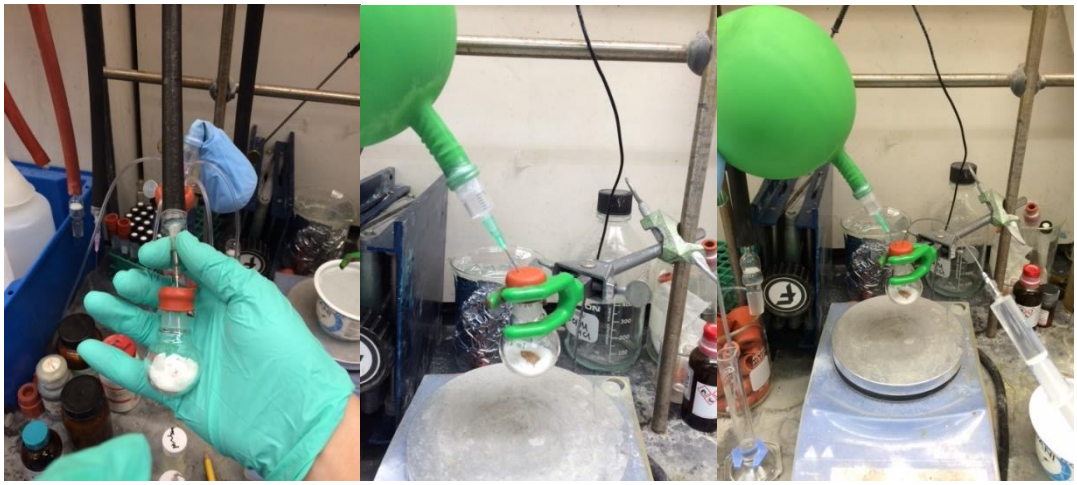


Figure S3. (Left) A flask containing B_2pin_2 was evacuated. **(Center)** The flask was backfilled with argon. **(Right)** THF was added.

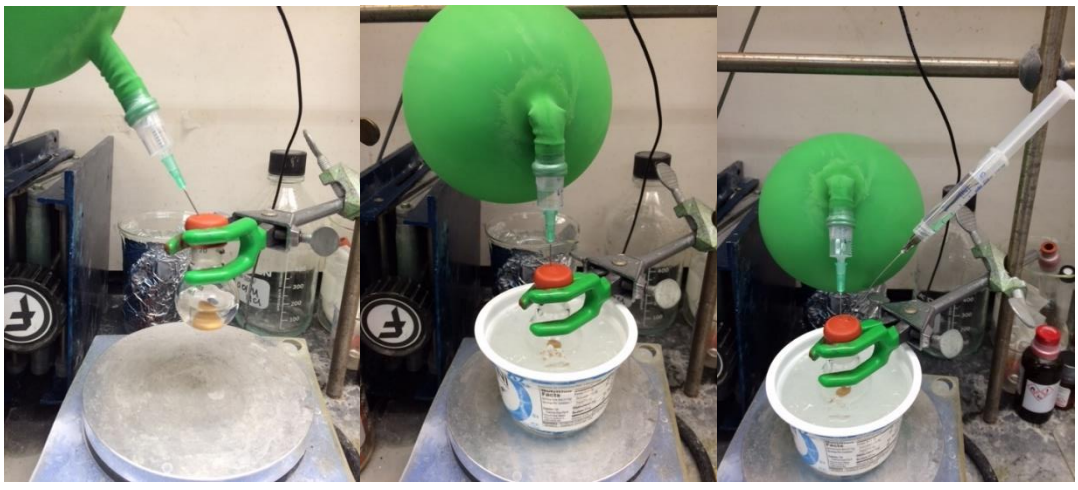


Figure S4. (Left) After addition of THF, the mixture was stirred until all B_2pin_2 dissolved. **(Center)** The solution was cooled to 0 °C. **(Right)** MeLi (1.6 M in Et_2O) was added dropwise.

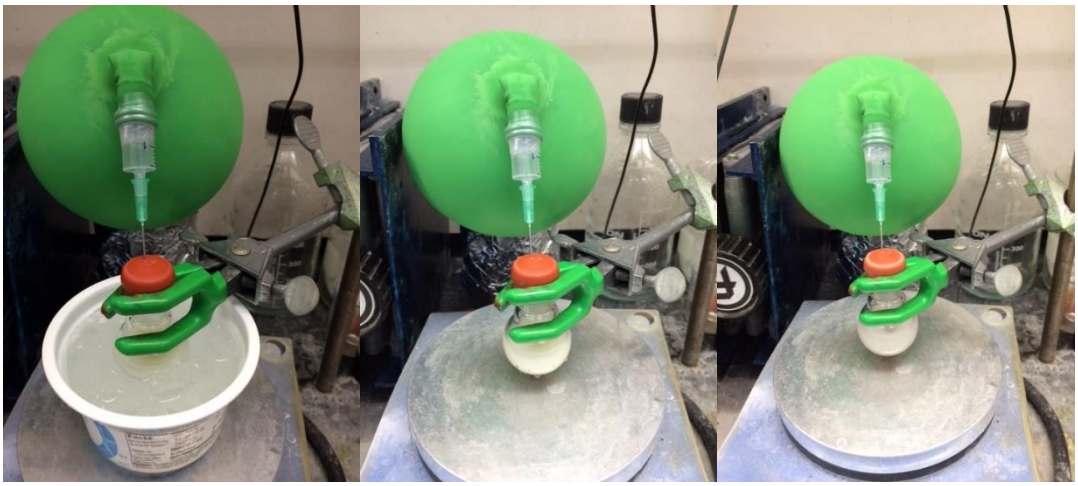


Figure S5. (Left) After addition of MeLi, a white suspension was obtained. **(Center)** The suspension was warmed to room temperature. **(Right)** After stirring for 1 h at room temperature.

Part III. Nickel Catalyzed Decarboxylative Borylation (Genernal Procedure B)

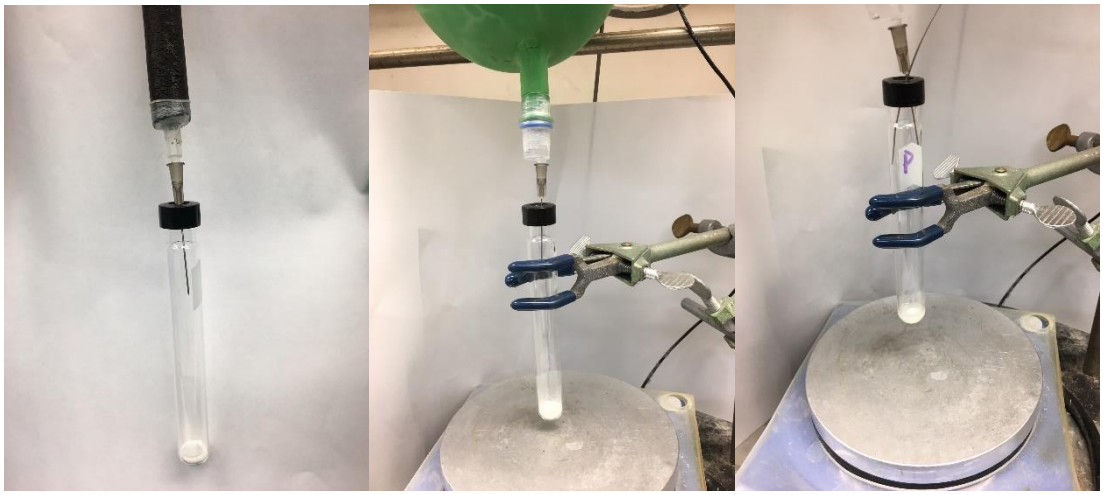


Figure S6. (Left) $MgBr_2$•OEt_2 was added to a screw-capped culture tube containing NHPI ester (**S2**, 0.2 mmol), and the tube was evacuated. **(Center)** The tube was backfilled with argon. **(Right)** THF was added.

Figure S7. (Left) The mixture was stirred at room temperature until no granular $MgBr_2$•OEt_2 was observed (*ca.* 10 min). **(Center)** Sonication could accelerate this process (*this was optional*). **(Right)** No solid was observed at the bottom of the tube.

Figure S8. (Left) The suspension of $NiCl_2$•$6H_2O$/di-MeObipy in DMF (0.05 M) was added. **(Center)** The mixture was stirred at room temperature until no granular $MgBr_2$•OEt_2 was observed (*ca.* 10 min). **(Right)** Sonication could accelerate this process (*this is optional*).

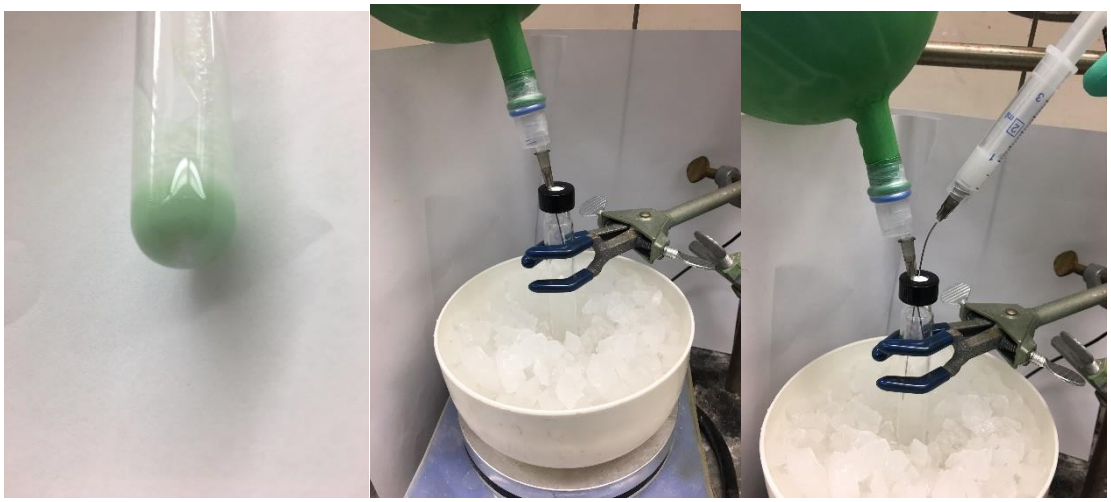


Figure S9. (Left) No solid was observed at the bottom of the culture tube. **(Center)** The resulting mixture was cooled to 0 °C. **(Right)** [B_2pin_2Me]Li complex was added at 0 °C.

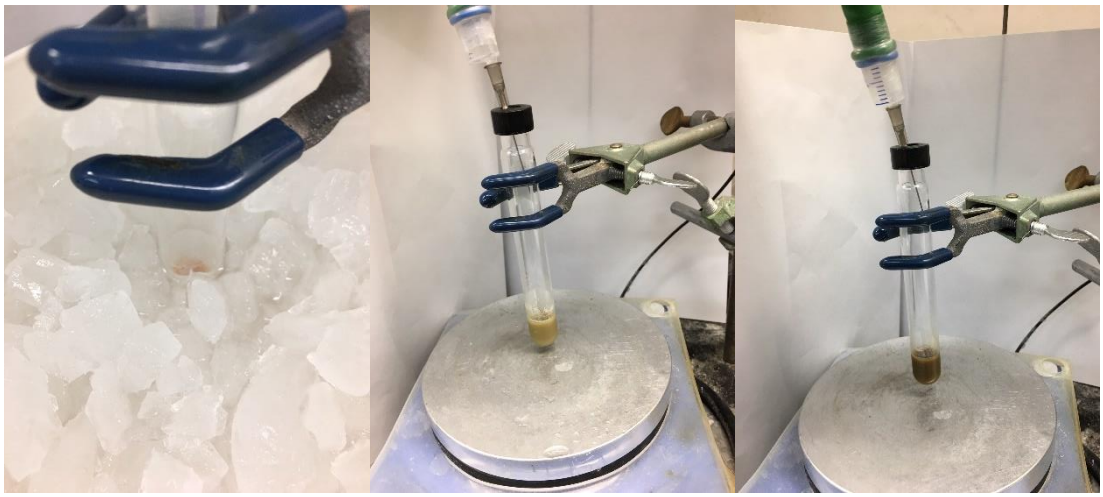


Figure S10. (Left) After addition of $[B_2pin_2Me]Li$, the resulting mixture was stirred at 0 °C for 1 h. **(Center)** The reaction mixture was warmed to room temperature and stirred for another 1 h. **(Right)** After 1 h stirring at room temperature.

Figure S11. (Left) The reaction was quenched with 0.1 N HCl. **(Center)** After the addition of HCl. **(Right)** Et_2O was added.

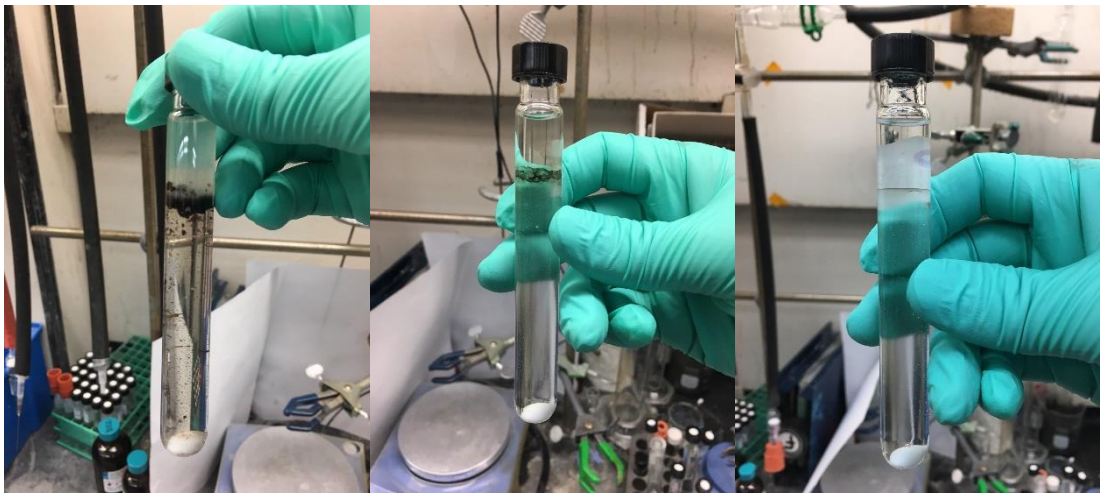


Figure S12. (Left) After the addition of Et_2O, the tube was capped and shaken. **(Center)** First extraction. **(Right)** Second extraction.

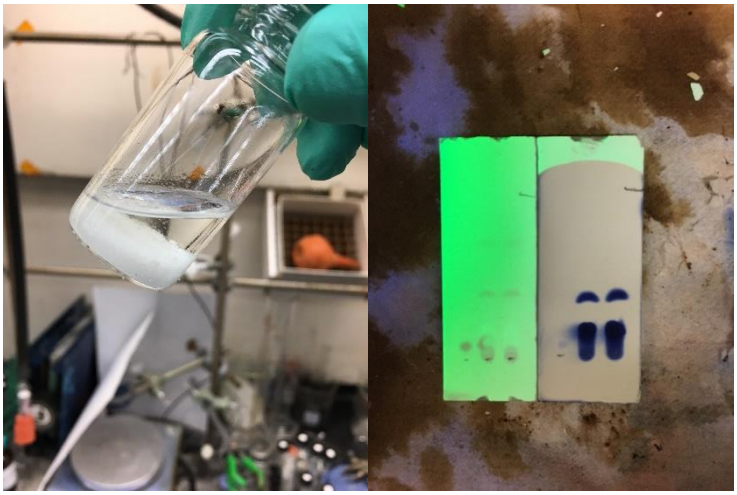


Figure S13. (Left) The combined organic layers were dried over anhydrous Na_2SO_4. **(Right)** TLC of the reaction mixture (1:20 EtOAc:hexanes). Lane 1: starting material; Lane 2: co-spot of starting material and reaction mixture; Lane 3: reaction mixture (the top spot was the desired product).

Part IV. Nickel Catalyzed Decarboxylative Borylation (Generral Procedure C)

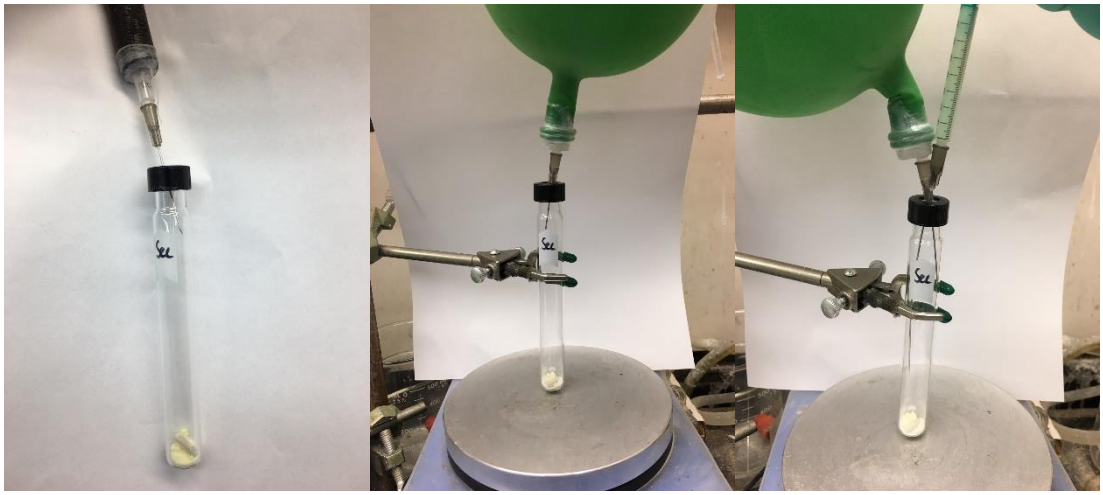


Figure S14. (Left) $MgBr_2$•OEt_2 was added to a screw-capped culture tube containing NHPI ester (**S7**, 0.2 mmol), and the tube was evacuated. **(Center)** The tube was backfilled with argon. **(Right)** The suspension of $NiCl_2$•$6H_2O$/di-*t*Bubipy in THF (0.025 M) was added.

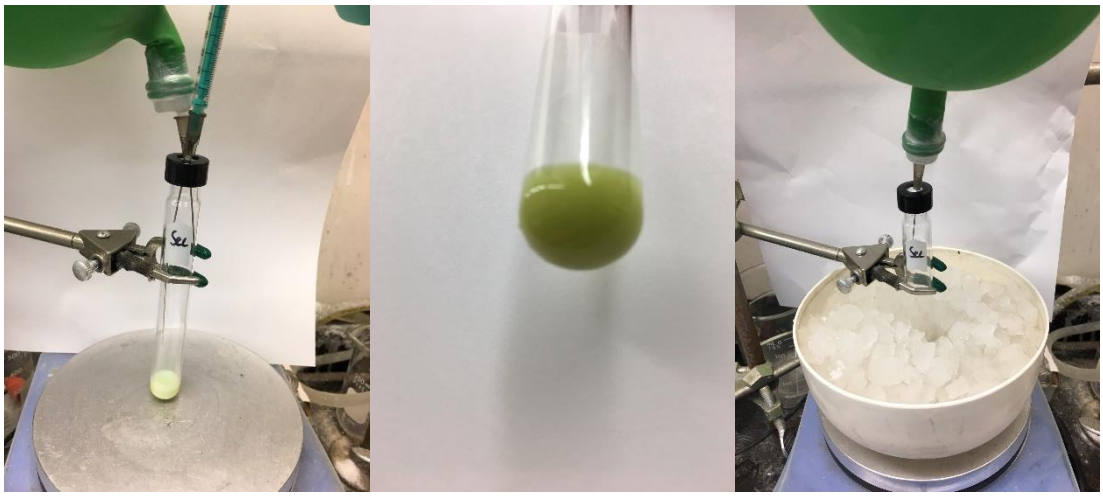


Figure S15. (Left) After addition of $NiCl_2$•$6H_2O$/di-*t*Bubipy in THF. **(Center)** The mixture was stirred at room temperature until no granular $MgBr_2$•OEt_2 was observed (*ca.* 10 min). **(Right)** The resulting mixture was cooled to 0 °C.

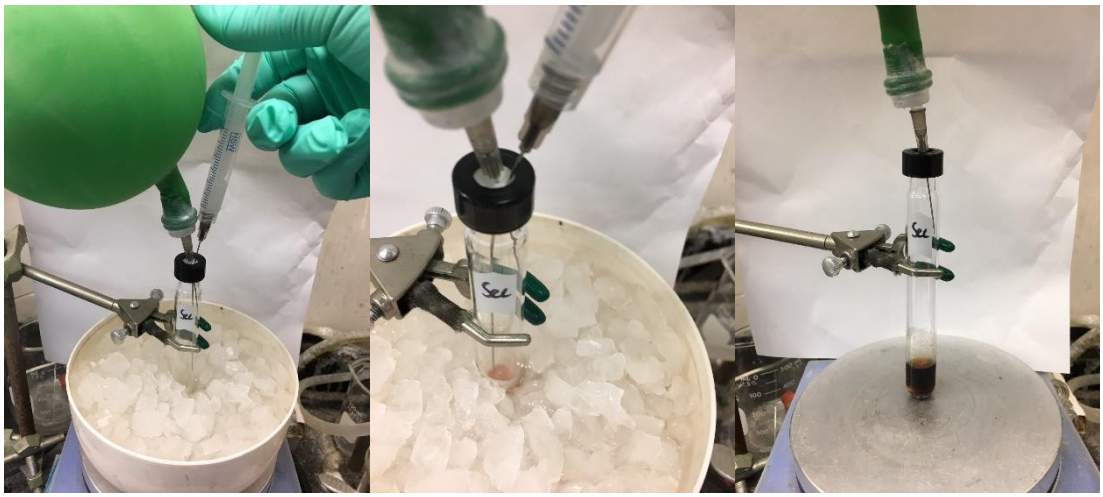


Figure S16. (Left) [B_2pin_2Me]Li complex was added at 0 °C. **(Center)** After the addition of [B_2pin_2Me]Li, the resulting mixture was stirred at 0 °C for 1 h. **(Right)** The reaction mixture was warmed to room temperature and stirred for another 1 h.

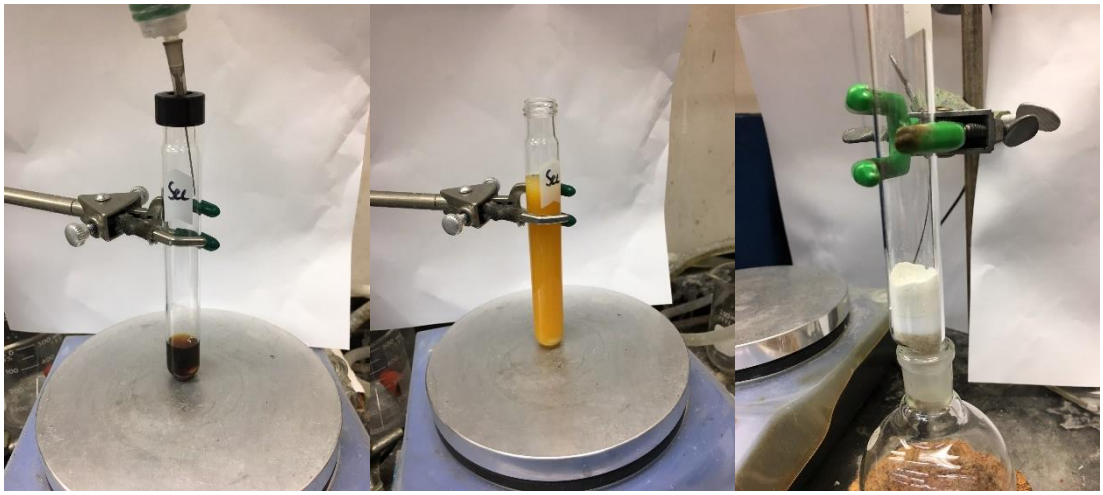


Figure S17. (Left) After 1 h stirring at room temperature. **(Center)** The reaction mixture was diluted with Et_2O. **(Right)** A short pad of silica gel and celite (top layer: celite, middle layer: silica gel, bottom layer: sand).

Figure S18. (Left) The diluted mixture was filtered through a short pad of silica gel and celite. **(Center)** The filtrate. **(Right)** TLC of the reaction mixture (1:20 EtOAc:hexanes). Lane 1: starting material; Lane 2: co-spot of starting material and reaction mixture; Lane 3: reaction mixture (the top spot was the desired product).

For polar substrates, such as peptides, the reaction was quenched either with 0.1 N HCl (10 mL) or saturated aqueous NH_4Cl (10 mL) followed by extraction with EtOAc (3 mL×2). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by flash column chromatography.

General Procedure for Gram Scale Nickel Catalyzed Decarboxylative Borylation (Ibuprofen)

The gram scale procedure was adapted from **General Procedure C**. A flame-dried round bottom fask charged with B_2pin_2 (2.57 g, 10.1 mmol, 3.3 equiv.) was evacuated and backfilled with argon for three times. THF (9.2 mL) was added, and the clear solution was cooled to 0 °C when MeLi (5.8 mL, 1.6 M in Et_2O, 9.3 mmol, 3.0 equiv.) was added dropwise. The reaction mixture was then warmed to room temperature and stirred for 1 h.

The NHPI redox-active ester of ibuprofen **S16** (1.08 g, 3.07 mmol, 1.0 equiv.) and $MgBr_2$•OEt_2 (792 mg, 3.07 mmol, 1.0 equiv.) were sequentially added to another flame-dried round-bottom flask. This flask was evacuated and backfilled with argon for three times and was cooled to 0 °C. THF (12 mL) was added, followed by a suspension of $NiCl_2$•$6H_2O$ (73 mg, 0.31 mmol, 10 mol%) and di-MeObipy (**L1**, 86 mg, 0.40 mmol, 13 mol%) in THF (12 mL), The resulting mixture was sonicated until there was no visible solid on the bottom of the flask. The mixture was then cooled to 0 °C before a suspension of $[B_2pin_2Me]Li$ in THF was added in one portion. After stirring for 1 h at 0 °C, the reaction mixture was warmed to room temperature and stirred for another 1 h.

The reaction mixture was then poured into Et_2O (100 mL), and the flask was rinsed with additional Et_2O (100 mL). The resulting mixture was filtered through a plug of silica gel and celite (top layer: celite, bottom layer: silica gel, v/v celite:silica gel = 1:1), the solid residue was washed with Et_2O (350 mL), and the filtrate was concentrated *in vacuo*. Purification by flash column chromatography (silica gel, hexanes to 1:30 Et_2O: hexanes) furnished the product (709 mg, 80%) as a colorless oil.

Note:

*1, Addition of THF to solid $MgBr_2$•OEt_2 is **exothermic**.*

*2, Addition of $[B_2pin_2Me]Li$ to the reactiom mixture is **exothermic**.*

Graphical Supporting Information for Gram Scale Nickel Catalyzed Decarboxylative Borylation (Ibuprofen)

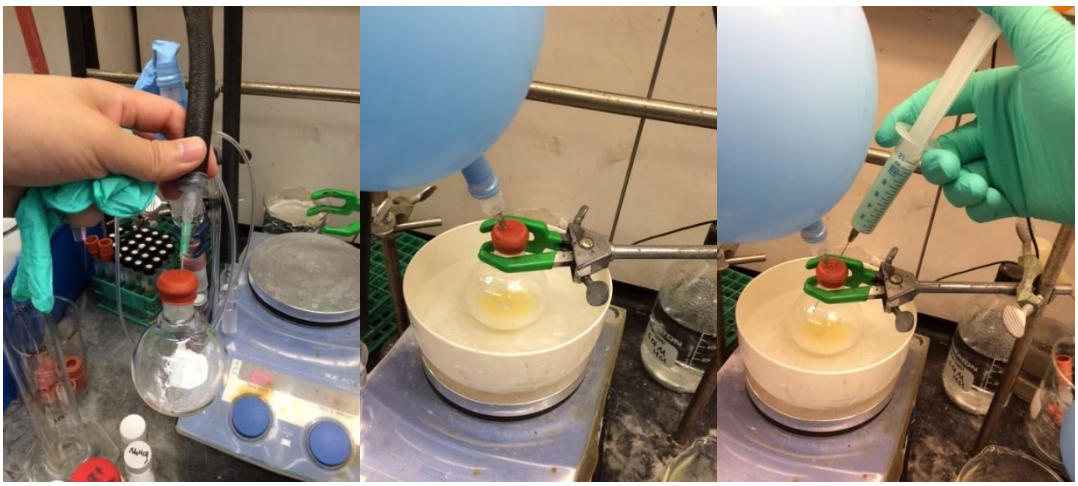


Figure S19. (Left) A flask containing NHPI ester of ibuprofen and $MgBr_2$•OEt_2 powder was evacuated and backfilled with argon. **(Center)** THF was added at 0 °C. **(Right)** The suspension of $NiCl_2$•$6H_2O$ and di-MeObipy in THF was added, and the reaction mixture was sonicated until no granular $MgBr_2$•Et_2O was observed.

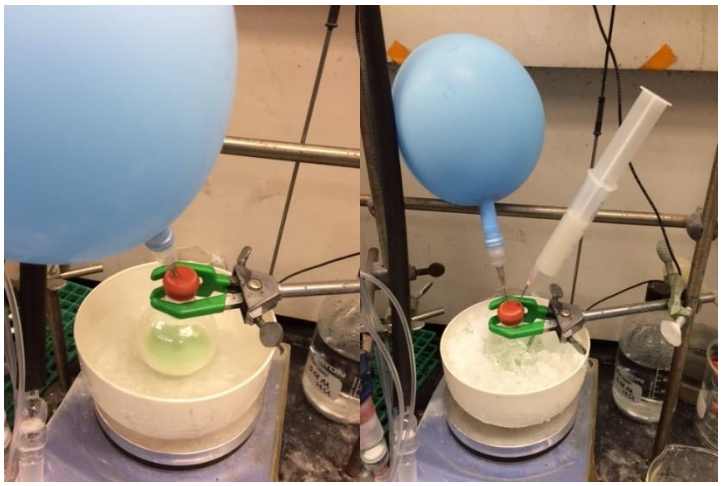


Figure S20. (Left) The reaction mixture was sonicated until no solid left on the bottom, and was then cooled to 0 °C. **(Right)** The $[B_2pin_2Me]Li$ complex in THF was added.

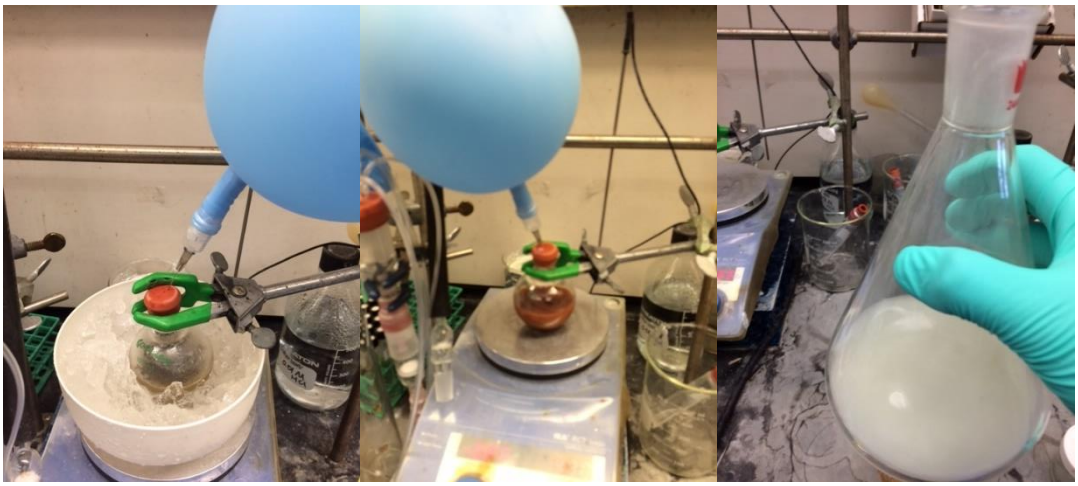


Figure S21. (Left) After addition of [B_2pin_2Me]Li complex. **(Center)** The resulting mixture was stirred at 0 °C for 1 h and at room temperature for another 1 h. **(Right)** The reaction mixture was poured onto Et_2O.

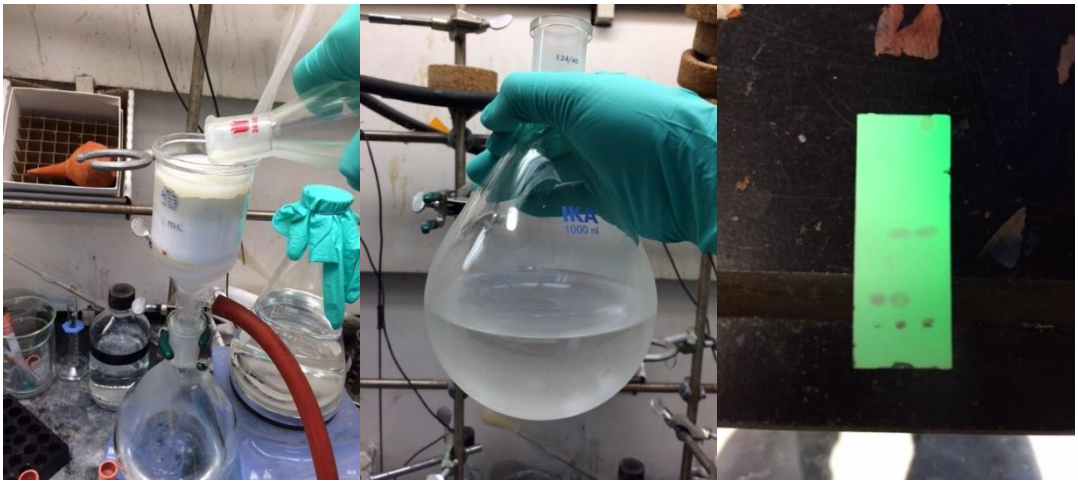


Figure S22. (Left) The diluted mixture was filtered through a pad of silica gel and celite, washed with Et_2O. **(Center)** After filtration. **(Right)** TLC of the reaction mixture (1:9 EtOAc:hexanes) under UV. (Lane 1: starting material; Lane 2: co-spot of starting material and reaction mixture; Lane 3: reaction mixture).

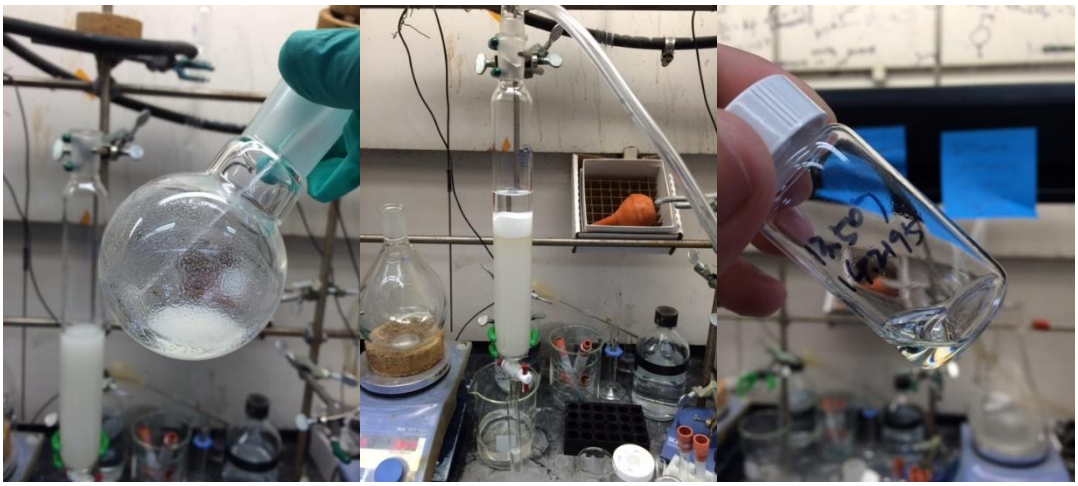
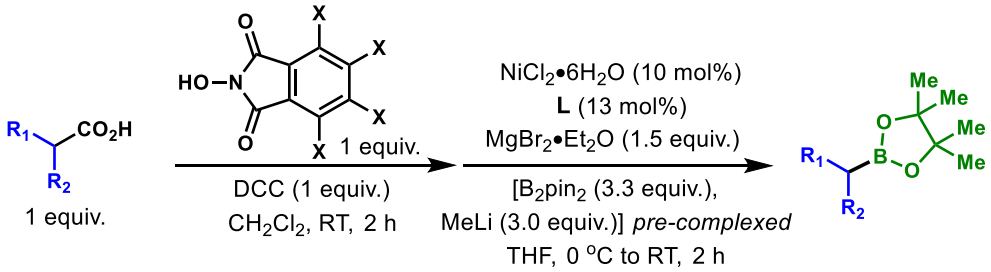


Figure S23. (Left) After concentration. **(Center)** The residue was purified by flash column chromatography. **(Right)** The desired product.

General Procedure for *in situ* Nickel Catalyzed Decarboxylative Borylation of Alkyl Carboxylic Acids (General Procedure D)



A screw-capped culture tube equipped with a stir bar was charged with alkyl carboxylic acid (0.2 mmol, 1.0 equiv.), *N*-hydroxyphthalimide or tetrachloro-*N*-hydroxyphthalimide (0.2 mmol, 1.0 equiv.) and *N,N'*-dicyclohexylcarbodiimide (0.2 mmol, 1.0 equiv.). The tube was then evacuated and backfilled with argon for three times. CH_2Cl_2 (2.0 mL) was added and the resulting mixture was stirred at room temperature for 2 h before the volatiles were removed *in vacuo*. $MgBr_2$•OEt_2 (77 mg, 0.3 mmol, 1.5 equiv.) was added. The tube was evacuated and backfilled with argon for three times. Suspension A [0.8 mL, $NiCl_2$•$6H_2O$ (10 mol%)/**L1** (13 mol%) in THF] or suspension C [0.8 mL, $NiCl_2$•$6H_2O$ (10 mol%)/**L2** (13 mol%) in THF] was added. The mixture was stirred vigorously at room temperature for 10 min (or until no granular $MgBr_2$•OEt_2 was observed) and was subsequently cooled to 0 °C before a suspension of [B_2pin_2Me]Li in THF (1.1 mL) was added in one portion (*note: do not add it dropwise!*). After stirring at that temperature for 1 h, the reaction was warmed to room temperature and stirred for another 1 h. The reaction mixture was then quenched with 0.1 N HCl (10 mL) and extracted with Et_2O (5 mL×2). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by column chromatography to afford the desired product.

Graphical Supporting Information for *in situ* Nickel Catalyzed Decarboxylative Borylation of Alkyl Carboxylic Acids (General Procedure D)

Figure S24. (Left) A screw-capped culture tube equipped with a stir bar was charged with 2-methyl-4-phenylbutanoic acid (0.2 mmol, 1.0 equiv.), tetrachloro-*N*-hydroxy-phthalimide (0.2 mmol, 1.0 equiv.), and *N*,*N*′-dicyclohexylcarbodiimide (0.2 mmol, 1.0 equiv.). **(Center)** The tube was evacuated and backfilled with argon for three times. **(Right)** CH_2Cl_2 was added.

Figure S25. (Left) After addition of CH_2Cl_2. **(Center)** After stirring at room temperature for 2 h. **(Right)** The reaction mixture was concentrated to dryness *in vacuo*.

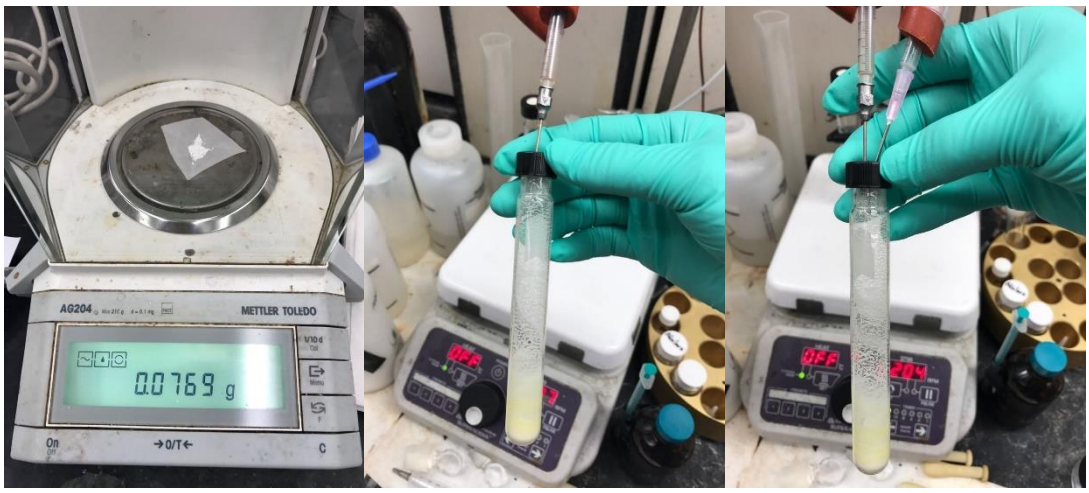


Figure S26. (Left) $MgBr_2$•OEt_2. **(Center)** $MgBr_2$•OEt_2 was added to the crude TCNHPI ester. **(Right)** The tube was evacuated and backfilled with argon for three times.

Figure S27. (Left) Suspension C [0.8 mL, $NiCl_2$•$6H_2O$ (10 mol%)/**L2** (13 mol%) in THF] was added. **(Center)** The mixture was stirred vigorously at room temperature until no granular $MgBr_2$•OEt_2 was observed (*ca.* 10 min). **(Right)** [B_2pin_2Me]Li complex was added in one portion at 0 °C.

Figure S28. (Left) After addition of [B_2pin_2Me]Li complex, the mixture was stirred at 0 °C for 1 h. **(Center)** The mixture was stirred at room temperature for another 1 h. **(Right)** The reaction mixture was quenched with 0.1 N HCl (10 mL) and extracted with Et_2O (5 mL×2).

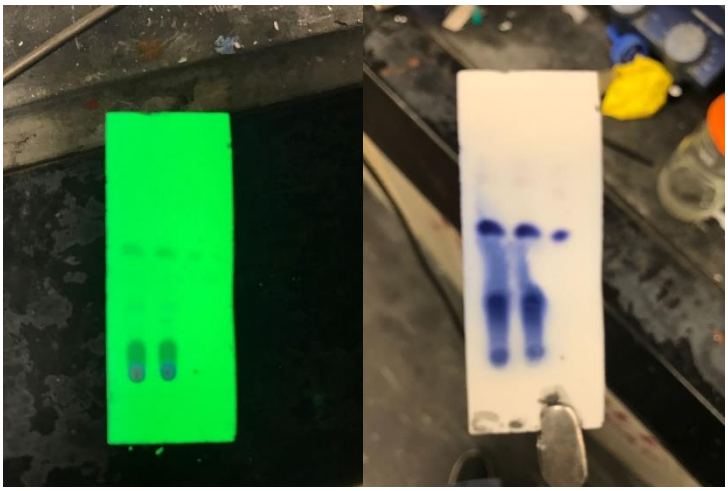


Figure S29. (Left) TLC of the reaction mixture (1:9 EtOAc:hexanes). Lane 1: reaction mixture; Lane 2: co-spot of reaction mixture and pure product; Lane 3: pure product. **(Right)** The same TLC after staining with CAM.

Examples of *in situ* Nickel Catalyzed Decarboxylative Borylation of Alkyl Carboxylic Acids

This *in situ* procedure was demonstrated on seven alkyl carboxylic acids following *General Procedure D*.

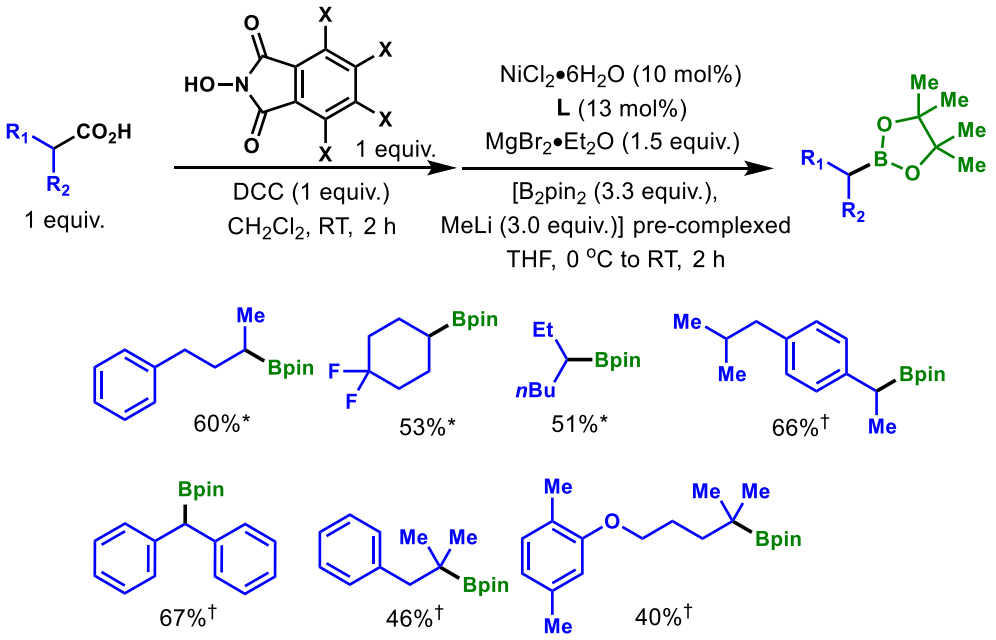


Figure S30. Examples of *in situ* nickel catalyzed decarboxylative borylation. *X = Cl, **L** = di-*t*Bubipy (**L2**). †X = H, **L** = di-MeObipy (**L1**).

Note: General Procedure D is less effective for primary carboxylic acids (typically ~ 20% yield).

General Procedure for Nickel Catalyzed Decarboxlyative Borylation with 2.5 mol% Nickel Catalyst.

Part I. Preparation of $NiCl_2$•$6H_2O$/Ligand Stock Solution or Suspension

(1) Suspension E: $NiCl_2$•$6H_2O$/di-MeObipy (**L1**) in THF (6.25 mM).

A screw-capped culture tube charged with $NiCl_2$•$6H_2O$ (23.8 mg, 0.1 mmol) and 4,4′-dimethoxy-2,2′-bipyridine (**L1**, 28.1 mg, 0.13 mmol) was evacuated and backfilled with argon for three times. THF (16.0 mL) was added and the resulting mixture was stirred at room temperature overnight (or until no granular $NiCl_2$•$6H_2O$ was observed) to afford a pale green suspension.

(2) Solution F: $NiCl_2$•$6H_2O$/di-MeObipy (**L1**) in DMF (12.5 mM).

A screw-capped culture tube charged with $NiCl_2$•$6H_2O$ (23.8 mg, 0.1 mmol) and 4,4′-dimethoxy-2,2′-bipyridine (**L1**, 28.1 mg, 0.13 mmol) was evacuated and backfilled with argon for three times. DMF (8.0 mL) was added and the resulting mixture was stirred at room temperature overnight to afford a light green solution.

(3) Suspension G: $NiCl_2$•$6H_2O$/di-*t*Bubipy (**L2**) in THF (6.25 mM).

A screw-capped culture tube charged with $NiCl_2$•$6H_2O$ (23.8 mg, 0.1 mmol) and 4,4′-di-*tert*-butyl-2,2′-bipyridine (**L2**, 34.8 mg, 0.13 mmol) was evacuated and backfilled with argon for three times. THF (16.0 mL) was added and the resulting mixture was stirred at room temperature overnight (or until no granular $NiCl_2$•$6H_2O$ was observed) to afford a pale green suspension.

Note: All the solutions or suspensions kept under argon can be used for two weeks without appreciable deterioration in reaction yields.

Part II. Nickel Catalyzed Decarboxlyative Borylation

Decarboxylative borylation of redox-active esters with 2.5 mol% nickel loading followed General Procedure B/C with Suspension E/Solution F/Suspension G.

Examples of Nickel Catalyzed Decarboxylative Borylation with 2.5 mol% Nickel

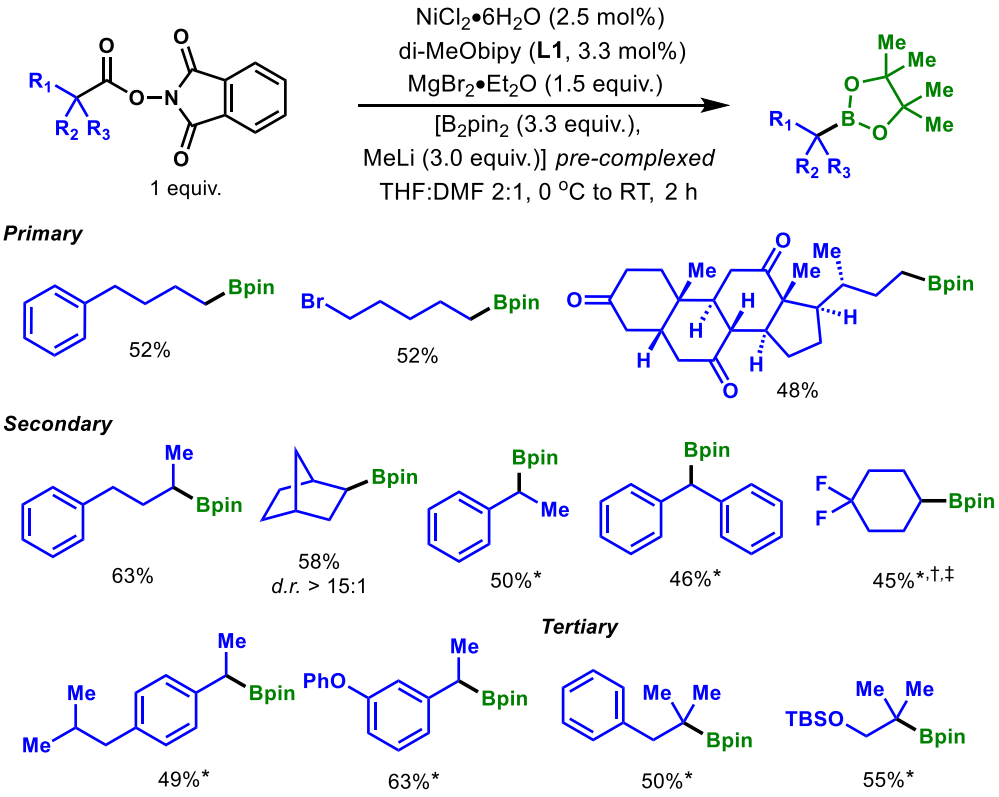


Figure S31. Examples of nickel catalyzed decarboxylative borylation with 2.5 mol% nickel. *Using THF as solvent. †Using **L2** (di-*t*Bubipy) as ligand and THF as solvent. ‡Using TCNHPI redox-active ester.

Troubleshooting and Frequently Asked Questions (FAQs):

Part I. Redox-active Ester Synthesis

Question 1:

Some polar redox-active esters (RAEs), such as those derived from amino acids or peptides, are very prone to hydrolysis on silica gel. How can I isolate them?

Answer:

Purification by flash column chromatography using deactivated silica gel (35 wt% H_2O) is recommended.

Question 2:

How does the retention factor of the products change when using deactivated silica gel (35 wt. % H_2O)?

Answer:

The adsorption capacity of deactivated silica gel (35 wt% H_2O) is lower than the normal silica gel. Thus, a less polar eluent should be used compared to normal.

Part II. Preparation of $NiCl_2$•$6H_2O$/Ligand Stock Solution or Suspension

Question 1:

$NiCl_2$•$6H_2O$ has very low solubility in THF in the presence of di-MeObipyl (**L1**) or di-*t*Bubipyl (**L2**). How do I proceed?

Answer:

The complexes of $NiCl_2$•$6H_2O$/**L1** and $NiCl_2$•$6H_2O$/**L2** do not dissolve well in THF. However, a very good suspension of such complexes can be afforded after vigorous stirring overnight. ***Tips:*** It is much easier to get good suspensions (4 – 6 h), if the culture tube was placed at the edge of a stir plate (with a stirring rate of 500 – 800 rpm) instead of the center (see below).

Question 2:

How can I make sure that I have added the precise amount of $NiCl_2$•$6H_2O$/**L1** or $NiCl_2$•$6H_2O$/**L2** as these complexes do not fully dissolve in THF?

Answer:

The precise amount of catalyst complexes can be drawn out from a "homogeneous" suspension under vigorous stirring.

Question 3:

If there are precipitates in catalyst suspensions A, B, or C, can I still use them?

Answer:

Yes, they can be still used after stirring.

Part III. Preparation of [B_2pin_2Me]Li Complex

Question 1:

Do I have to use 3.0 equiv. of [B_2pin_2Me]Li?

Answer:

2.5 equiv. of [B_2pin_2Me]Li also works fine for most of the subtrates. Addition of more than 3.0 equiv. of [B_2pin_2Me]Li, nevertheless, does not help the borylation reaction.

Question 2:

How can I monitor the [B_2pin_2Me]Li complex formation?

Answer:

It is very hard to monitor the formation of [B_2pin_2Me]Li complex, but we have determined that the reaction between MeLi and B_2pin_2 is completed in 1 h. If the reaction is run for less than 30 min, unreacted MeLi could destroy some base sensitive substrates (such as Fmoc protected amino acids), leading to lower yields.

Question 3:

If I get a clear solution of [B_2pin_2Me]Li instead of a white suspension after stirring for 1 h, what can I do?

Answer:

In a few cases, we have also obtained a clear solution after stirring for 1 h. It was found that both clear solution and white suspension worked fine for the borylation reaction.

Question 4:

How long can I keep the suspension of [B_2pin_2Me]Li in THF?

Answer:

The suspension of [B_2pin_2Me]Li in THF can be kept at room temperature for 12 h under stirring. A lower yield was observed if the suspension was left for more than 12 h. This complex is not very stable under air and should thus be kept under an inert atmosphere.

Part IV. Nickel Catalyzed Decarboxlyative Borylation

Question 1:

If I only have a small amount of carboxylic acid material, which condition would you suggest to try first?

Answer:

A flow chart is provided on page S32 to guide the selection of optimal conditions for

different structural classes of substrates.

Question 2:

Have you tried any other magnesium salts for this reaction?

Answer:

During our initial screening, we examined several magnesium salts, such as $MgCl_2$, $Mg(OAc)_2$, $Mg(acac)_2$, $MgSO_4$, *etc*., among which $MgBr_2$•OEt_2 gave the best yield.

Question 3:

Can I change the amount of $MgBr_2$•OEt_2 to increase the yield?

Answer:

Generally, more than 2.0 equiv. or less than 1.2 equiv. of $MgBr_2$•OEt_2 led to diminished yields. However, for the 2° benzylic RAEs, 1.0 equiv. proved to be sufficient for the borylation reaction.

Question 4:

Can I use granular $MgBr_2$•OEt_2 in this reaction?

Answer:

Granular $MgBr_2$•OEt_2 can be used in this reaction, but longer stirring time (until no granular $MgBr_2$•OEt_2 was observed) was required before the addition of $[B_2pin_2Me]Li$ complex. $MgBr_2$•OEt_2 powder is therefore highly recommended.

Question 5:

If there is granular $MgBr_2$•OEt_2 left after stirring for 15 min, what can I do?

Answer:

Sonicate the mixture or stir for longer periods of time.

Question 6:

Can I add the $[B_2pin_2Me]Li$ complex at room temperature?

Answer:

This borylation reaction is ***exothermic***. The reaction temperature would increase a lot if $[B_2pin_2Me]Li$ complex was added at room temperature, leading to lower yields.

Question 7:

How do you monitor the reaction?

Answer:

We monitor the reaction by TLC (UV visualization or staining based on redox-active esters). Reactions on all substrates examined herein (> 40 examples) were completed in 1 h at 0 °C and another 1 h at room temperature. Longer reaction time generally lead to lower yield. Shorter reaction time is recommended for substrates that are conceivably unstable under the reaction conditions.

Question 8:

How can I detect the pinacol alkylboronate esters (alkyl-Bpin) on TLC?

Answer:

Most of the pinacol alkylboronate esters are sensitive to ceric ammonium molybdate (CAM, Hanessian's stain) and potassium permanganate ($KMnO_4$). You can also detect the product *via* UV visualization if your product is UV active. GC/MS and LC/MS are also recommended.

Question 9:

What other possible byproduct were observed in this reaction?

Answer:

We occasionally observed hydrodecarboxylation, decarboxylative dimerization or the hydrolysis (to carboxylic acids) of RAEs.

Question 10:

Is there any indicative color change during the reaction?

Answer:

The color of the coupling reaction varies for different substrates. Normally, we observed a color change from green to yellow, brown, or black after addition of the $[B_2pin_2Me]Li$ complex.

Question 11:

Can I purify the pinacol alkylboronate esters (alkyl-Bpin) on preparative TLC?

Answer:

The pinacol alkylboronate esters are not very stable on preparative TLC due to possible oxidation of C–B bond or hydrolytic cleavage of pinacol esters. Usually, we purify the products using flash column chromatography with gradient elution. Some pinacol α-aminoboronate esters were purified by flash column chromatography with gradient elution using deactivated silica gel (35 wt% H_2O).

Question 12:

Are the pinacol alkylboronate esters bench-stable?

Answer:

Most of the pinacol alkylboronate esters we made can be stored under air at room temperature for two weeks without appreciable decomposition. Normally, we store them under argon at –20 °C.

Question 13:

If the desired product was contaminated with some phthlimide after column, what can I do to remove it and get the pure product?

Answer:

Most of the pinacol alkylboronate esters can be dissolved in hexanes, but phthlimide

can not. Thus one can dissolve the product in hexanes and filter it through celite to remove the phthlimide.

Question 14:

Although I am able to obtain some product, the yield is not satisfactory for my purposes. How should I optimize the reaction?

Answer:

For further optimization, we recommend the following:

1. Screen the four nickel catalytic systems first (suspension A, B, C and solution D).
2. If NHPI ester does not work well, try TCNHPI redox-active ester.
3. Try a higher loading of nickel precatalyst.
4. If suspension B or solution D work better than suspension A or C, one can also try to use DMA instead of DMF.

Part V Nickel Catalyzed *in situ* Decarboxlyative Borylation of Alkyl Carboxylic Acids

Question 1

Can I use DIC instead of DCC as coupling reagent in this *in situ* coupling reaction?

Answer:

We have tried both of them and found that DCC gave better yield than DIC.

Question 2

When is the *in situ* protocol applicable?

Answer:

The protocol is suitable for secondary and tertiary carboxylic acids. Lower yields were obtained for primary substrates. Also, the quality of DCC was found to be critical.

Part VI. Deprotection of Pinacol Alkylboronate Esters

Question 1

Are the alkyl boronic acids stable?

Answer:

1. Alkyl boronic acids on tertiary carbon are prone to oxidation. We only obtained the corresponding alcohols instead of desired boronic acids after column chromatography or preparative TLC.

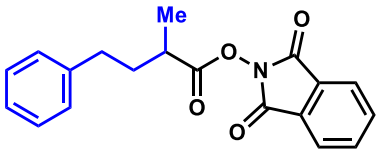
2. Alkyl boronic acids on primary and secondary carbon are relatively stable and can survive quick purifications.

3. α-Amino boronic acids containing electron-withdrawing protecting group on amine are relatively stable.

4. Alkyl boronic acids are prone to dimerization and trimerization, but they can generally be stabilized through addition of water.

Experimental Procedures and Characterization Data for Redox-active Esters

Compound 2



2

1,3-dioxoisoindolin-2-yl 2-methyl-4-phenylbutanoate (2)

On 8.75 mmol scale, General Procedure A was followed with 2-methyl-4-phenylbutanoic acid. Purification by flash column chromatography (silica gel, 1:9 EtOAc:hexanes) afforded **2** (2.31 g, 82 %).

Physical state: colorless oil;

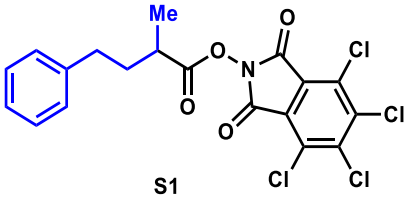
R_f = 0.60 (silica gel, 3:7 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.92 – 7.88 (m, 2H), 7.81 – 7.78 (m, 2H), 7.32 – 7.29 (m, 2H), 7.27 – 7.25 (m, 2H), 7.22 – 7.20 (m, 1H), 2.90 – 2.74 (m, 3H), 2.20 – 2.14 (m, 1H), 1.96 – 1.90 (m, 1H), 1.40 (d, *J* = 7.2 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.7, 162.2, 141.3, 134.9, 129.2, 128.7, 128.6, 126.2, 124.1, 36.7, 35.7, 33.1, 17.2 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{19}H_{18}NO_4$ $[M+H]^+$ 324.1230; found 324.1230.

Compound S1



S1

4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl 2-methyl-4-phenylbutanoate (S1)

On 13.0 mmol scale, General Procedure A was followed with 2-methyl-4-phenylbutanoic acid. Purification by flash column chromatography (silica gel, 1:10 EtOAc:hexanes) afforded a yellow solid which was recrystallized from CH_2Cl_2/MeOH

to afford **S1** (4.12 g, 69 %).

Physical state: white solid;

m.p. = 80 – 81 °C;

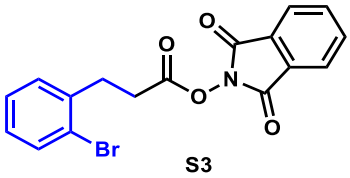
R_f = 0.63 (silica gel, 1:4 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.32 – 7.28 (m, 2H), 7.26 – 7.19 (m, 3H), 2.89 – 2.72 (m, 3H), 2.20 – 2.13 (m, 1H), 1.95 – 1.88 (m, 1H), 1.39 (d, *J* = 8.4 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.3, 157.8, 141.1, 141.0, 130.6, 128.6, 126.3, 124.9, 36.6, 35.5, 33.1, 17.3 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{19}H_{14}Cl_4NO_4$ $[M+H]^+$ 459.9671; found 459.9659.

Compound S3



S3

1,3-dioxoisoindolin-2-yl 3-(2-bromophenyl)propanoate (S3)

On 5.0 mmol scale, General Procedure A was followed with 3-(2-bromophenyl) propanoic acid. Purification by flash column chromatography (silica gel, 1:9 EtOAc:hexanes) afforded **S3** (1.63 g, 87 %).

Physical state: white solid;

m.p. = 158 – 160 °C;

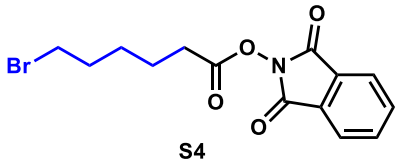
R_f = 0.36 (silica gel, 1:4 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.90 – 7.87 (m, 2H), 7.80 – 7.77 (m, 2H), 7.56 (dd, *J* = 1.2 Hz, 7.8 Hz, 1H), 7.34 (dd, *J* = 7.8 Hz, 1.8 Hz, 1H), 7.28 (dt, *J* = 7.8 Hz, 1.2 Hz, 1H), 7.12 (dt, *J* = 7.8 Hz, 1.8 Hz, 1H), 3.21 (t, *J* = 7.2 Hz, 2H), 3.02 (t, *J* = 7.2 Hz, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 168.8, 162.0, 138.5, 134.9, 133.1, 130.1, 129.0, 128.7, 127.9, 124.4, 124.1, 31.2, 31.0 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{17}H_{13}BrNO_4$ $[M+H]^+$ 374.0022; found 374.0022.

Compound S4



S4

1,3-dioxoisoindolin-2-yl 6-bromohexanoate (S4)

On 5.0 mmol scale, General Procedure A was followed with 6-bromohexanoic acid. Purification by flash column chromatography (silica gel, 1:10 EtOAc:hexanes) afforded **S4** (1.52 g, 89%).

Physical state: white solid;

m.p. = 60 – 62 °C;

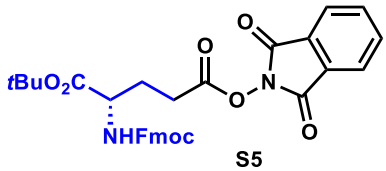
R_f = 0.45 (silica gel, 1:4 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.89 – 7.86 (m, 2H), 7.79 – 7.77 (m, 2H), 3.42 (t, J = 7.2 Hz, 2H), 2.68 (t, J = 7.2 Hz, 2H), 1.94 – 1.89 (m, 2H), 1.84 – 1.79 (m, 2H), 1.63 – 1.57 (m, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 169.4, 162.0, 134.9, 129.0, 124.1, 33.3, 32.3, 30.9, 27.5, 24.0 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{14}H_{15}BrNO_4$ $[M+H]^+$ 340.0179; found 340.0178.

Compound S5



S5

1-(*tert*-butyl) 5-(1,3-dioxoisoindolin-2-yl) (((9*H*-fluoren-9-yl)methoxy)carbonyl)-*L* glutamate (S5)

On 3.0 mmol scale, General Procedure A was followed with Fmoc-Glu-O*t*Bu. Purification by flash column chromatography (silica gel, 1:3 EtOAc:hexanes) afforded **S5** (1.53 g, 89%).

Physical state: white foam;

R_f = 0.49 (silica gel, 1:4 EtOAc:hexanes);

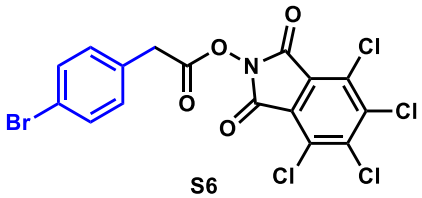
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.90 – 7.86 (m, 2H), 7.80 – 7.76 (m, 4H), 7.67 – 7.61 (m, 2H), 7.42 – 7.38 (m, 2H), 7.31 (dt, *J* = 7.2 Hz, 1.2 Hz, 2H), 5.52 (br d, *J* = 7.8 Hz, 1H), 4.50 (dd, *J* = 10.8 Hz, 7.2 Hz, 1H), 4.39 – 4.36 (m, 2H), 4.23 (t, *J* = 7.2 Hz, 1H), 2.82 – 2.77 (m, 1H), 2.73 – 2.67 (m, 1H), 2.40 – 2.34 (m, 1H), 2.15 – 2.09 (m, 1H), 1.50 (s, 9H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.6, 169.1, 162.0, 156.2, 143.9, 141.5, 134.9, 129.0, 127.9, 127.2, 125.4, 125.2, 124.2, 120.1, 83.1, 67.2, 53.7, 47.4, 28.1, 28.0, 27.6 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{32}H_{30}N_2NaO_8$ $[M+Na]^+$ 593.1894; found 593.1895;

[a]$_D^{20}$ = +5.4 (c 1.0, $CHCl_3$).

Compound S6



S6

4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl 2-(4-bromophenyl)acetate (S6)

On 5.0 mmol scale, General Procedure A was followed with 2-(4-bromophenyl)acetic acid. After completion of the reaction, reaction mixture was fitered through a short pad of silica gel and washed with EtOAc/hexanes (1:8). The filtrate was concentrated, and **S6** was obtained after recrystallization with CH_2Cl_2/MeOH (1.52 g, 61%).

Physical state: pale yellow solid;

m.p. = 212 – 213 °C;

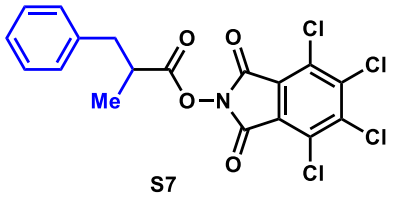
***R*$_f$** = 0.57 (silica gel, 1:4 EtOAc:hexanes);

^{1}H NMR (600 MHz, DMSO-*d*$_6$): δ 7.61 – 7.59 (m, 2H), 7.37 – 7.35 (m, 2H), 4.25 (s, 2H) ppm;

^{13}C NMR (151 MHz, DMSO-*d*$_6$): δ 167.7, 157.5, 139.3, 131.7, 131.6, 131.6, 129.0, 125.2, 120.9, 35.8 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{16}H_7BrCl_4NO_4$ $[M+H]^+$ 495.8307; found 495.8323.

Compound S7



S7

4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl 2-methyl-3-phenylpropanoate (S7)

On 5.0 mmol scale, General Procedure A was followed with 2-methyl-3-phenylpropanoic acid. Purification by flash column chromatography (silica gel, 1:10 EtOAc:hexanes) afforded a yellow solid which was recrystallized from CH_2Cl_2/MeOH to afford **S7** (1.45 g, 65%).

Physical state: pale yellow solid;

m.p. = 127 – 128 °C

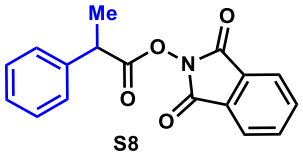
R_f = 0.63 (silica gel, 1:4 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35 – 7.32 (m, 2H), 7.28 – 7.23 (m, 3H), 3.25 (dd, *J* = 13.8 Hz, 6.6 Hz, 1H), 3.14 – 3.08 (m, 1H), 2.82 (dd, *J* = 13.8 Hz, 7.8 Hz, 1H), 1.34 (d, *J* = 7.2 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 171.9, 157.7, 141.2, 137.8, 130.6, 129.2, 128.8, 127.0, 124.9, 39.3, 39.0,16.6 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{18}H_{12}Cl_4NO_4$ $[M+H]^+$ 445.9515; found 445.9516.

Compound S8



S8

1,3-dioxoisoindolin-2-yl 2-phenylpropanoate (S8)

On 5.0 mmol scale, General Procedure A was followed with 2-phenylpropanoic acid. Purification by flash column chromatography (silica gel, 1:10 EtOAc:hexanes) afforded **S8** (1.19 g, 81%).

Physical state: colorless oil;

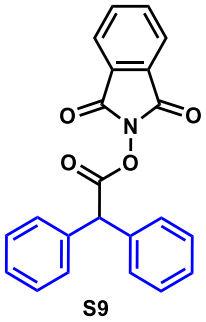
***R*$_f$** = 0.21 (silica gel, 1:4 EtOAc:hexanes);

^{1}H NMR (600 MHz, CDCl$_3$): δ 7.87 – 7.85 (m, 2H), 7.79 – 7.76 (m, 2H), 7.43 – 7.39 (m, 4H), 7.34 – 7.31 (m, 1H), 4.13 (q, *J* = 7.2 Hz, 1H), 1.68 (d, *J* = 7.2 Hz, 3H) pm;

^{13}C NMR (151 MHz, CDCl$_3$): δ 170.9, 162.0, 138.5, 134.9, 129.1, 129.1, 127.9, 127.7, 124.1, 43.1, 19.1 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{17}H_{14}NO_4$ $[M+H]^+$ 296.0917; found 296.0920.

Compound S9



S9

1,3-dioxoisoindolin-2-yl 2,2-diphenylacetate (S9)

On 1.5 mmol scale, General Procedure A was followed with diphenylacetic acid. Purification by flash column chromatography (silica gel, 1:4 EtOAc:hexanes) afforded **S9** (0.46 g, 86%).

Physical state: white solid;

m.p. = 135 – 137 °C;

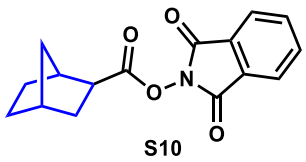
***R*$_f$** = 0.33 (silica gel, 1:4 EtOAc:hexanes)

^{1}H NMR (600 MHz, CDCl$_3$): δ 7.89 – 7.86 (m, 2H), 7.80 – 7.77 (m, 2H), 7.42 – 7.37 (m, 8H), 7.34 – 7.31 (m, 2H), 5.42 (s, 1H) ppm;

^{13}C NMR (151 MHz, CDCl$_3$): δ 169.2, 162.0, 136.9, 134.9, 129.1, 129.0, 128.9, 128.0, 124.1, 54.2 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{22}H_{16}NO_4$ $[M+H]^+$ 358.1074; found 358.1078.

Compound S10



S10

1,3-dioxoisoindolin-2-yl-bicyclo[2.2.1]heptane-2-carboxylate (S10)

On 3.0 mmol scale, General Procedure A was followed with bicyclo[2.2.1]heptane-2-carboxylic acid (mixture of *exo*/*endo* isomers). Purification by flash column chromatography (silica gel, 1:19 to 1:9 EtOAc:hexanes) afforded **S10** (0.75 g, 88%) as mixture of *exo*/*endo* isomers.

Physical state: white solid;

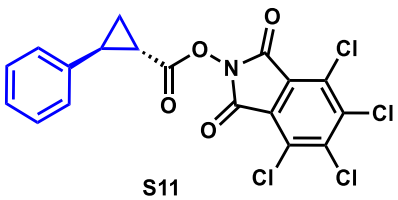
R_f = 0.41 (silica gel, 1:4 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.90 – 7.86 (m, 2H), 7.80 – 7.77 (m, 2H), 3.15 – 3.11 (m, 0.82H), 2.81 (br s, 0.82H), 2.77 (br d, *J* = 4.2 Hz, 0.18 H), 2.70 (dd, *J* = 9.6 Hz, 6.0 Hz, 0.18H), 2.38 (br t, *J* = 4.2 Hz, 0.18 H), 2.35 – 2.33 (br, m, 0.82H), 2.00 – 1.96 (m, 0.18H), 1.86 – 1.81 (m, 0.82H), 1.74 – 1.70 (m, 0.82H), 1.63 – 1.67 (m, 3.28H), 1.51 – 1.44 (m, 1.64H), 1.38 – 1.25 (m, 1.26H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ171.5, 162.3, 134.8, 129.2, 124.0, 43.4, 41.0, 40.5, 37.0, 32.7, 29.0, 24.9 ppm (*major isomer*); 172.3, 162.3, 134.8, 129.2, 124.0, 43.7, 41.7, 36.7, 36.2, 34.6, 29.5, 28.6 ppm (*minor isomer*).

HRMS (ESI-TOF, *m/z*): Calcd for $C_{16}H_{16}NO_4$ $[M+H]^+$ 286.1074; found 286.1071.

Compound S11



S11

4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl *trans*-2-phenylcyclopropane-1-carboxylate (S11)

On 3.0 mmol scale, General Procedure A was followed with *trans*-2-

phenylcyclopropane-1-carboxylic acid. Upon complete consumption of starting material as indicated by TLC, the reaction mixture was filtered through celite, washed with CH_2Cl_2 (100 mL), and concentrated under reduced pressure. The crude product was purified by crystallization (CH_2Cl_2/MeOH) to afford **S11** (949 mg, 71%).

Physical state: pale yellow needles;

m.p. = 203 – 205 °C;

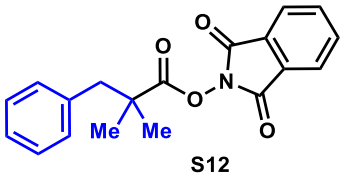
R_f = 0.48 (silica gel, 1:9 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34 – 7.31 (m, 2H), 7.28 – 7.25 (m, 1H), 7.18 – 7.16 (m, 2H), 2.80 – 2.77 (m, 1H), 2.22 – 2.19 (m, 1H), 1.84 (dt, *J* = 10.2 Hz, 5.4 Hz, 1H), 1.69 – 1.66 (m, 1H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 169.4, 157.7, 141.2, 138.3, 130.6, 128.8, 127.4, 126.5, 124.8, 28.8, 21.0, 18.6 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{18}H_{10}Cl_4NO_4$ $[M+H]^+$ 443.9358; found 443.9356.

Compound S12



S12

1,3-dioxoisoindolin-2-yl 2,2-dimethyl-3-phenylpropanoate (S12)

On 5.0 mmol scale, General Procedure A was followed with 2, 2-dimethyl-3-phenylpropanoic acid. Purification by flash column chromatography (silica gel, 1:10 EtOAc:hexanes) afforded **S12** (1.36 g, 84%).

Physical state: white solid;

m.p. = 70 – 72 °C;

R_f = 0.45 (silica gel, 1:4 EtOAc:hexanes);

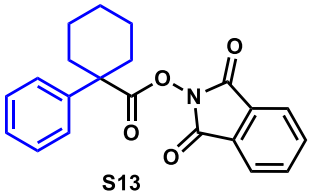
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.92 – 7.88 (m, 2H), 7.81 – 7.78 (m, 2H), 7.36 – 7.31 (m, 4H), 7.29 – 7.26 (m, 1H), 3.10 (s, 2H), 1.40 (s, 6H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 173.7, 162.2, 136.5, 134.8, 130.6, 129.1, 128.3, 127.0,

124.0, 45.8, 43.3, 25.0 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{19}H_{18}NO_4$ $[M+H]^+$ 324.1230; found 324.1232.

Compound S13



S13

1,3-dioxoisoindolin-2-yl 1-phenylcyclohexane-1-carboxylate (S13)

On 5.0 mmol scale, General Procedure A was followed with 2-phenylpropanoic acid. Purification by flash column chromatography (silica gel, 1:9 EtOAc:hexanes) afforded **S13** (1.64 g, 81%).

Physical state: white solid;

m.p. = 108 – 109 °C;

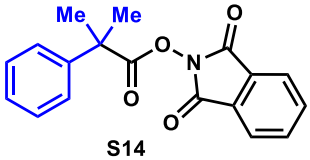
R_f = 0.39 (silica gel, 1:4 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.87 – 7.84 (m, 2H), 7.78 – 7.75 (m, 2H), 7.54 – 7.52 (m, 2H), 7.44 – 7.41 (m, 2H), 7.34 – 7.31 (m, 1H), 2.64 (br d, J = 13.2 Hz, 2H), 1.89 – 1.73 (m, 7H), 1.37 – 1.30 (m, 1H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 171.8, 162.2, 142.3, 134.8, 129.2, 128.9, 127.7, 126.1, 124.0, 51.3, 35.5, 25.6, 23.6 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{21}H_{20}NO_4$ $[M+H]^+$ 350.1387; found 350.1387.

Compound S14



S14

1,3-dioxoisoindolin-2-yl 2-methyl-2-phenylpropanoate (S14)

On 5.0 mmol scale, General Procedure A was followed with 2-methyl-2-phenylpropanoic acid. Purification by flash column chromatography (silica gel, 1:8

EtOAc:hexanes) afforded **S14** (1.32 g, 85%).

Physical state: white solid;

m.p. = 73 – 74 °C;

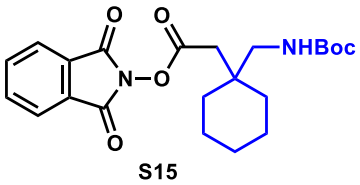
R_f = 0.36 (silica gel, 1:4 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.88 – 7.85 (m, 2H), 7.79 – 7.75 (m, 2H), 7.51 – 7.49 (m, 2H), 7.44 – 7.41 (m, 2H), 7.34 – 7.31 (m, 1H), 1.79 (s, 6H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 173.4, 162.1, 142.7, 134.8, 129.1, 128.8, 127.5, 125.9, 124.0 46.5, 27.0 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{18}H_{16}NO_4$ $[M+H]^+$ 310.1074; found 310.1082.

Compound S15



S15

1,3-dioxoisoindolin-2-yl-2-(1-(((*tert*-butoxycarbonyl)amino)methyl)cyclohexyl) acetate (S15)

On 0.44 mmol scale, General Procedure A was followed with *N*-Boc-gabapentin. Purification by flash column chromatography (silica gel, 1:5 EtOAc:hexanes) afforded **S15** (165 mg, 85%).

Physical state: white solid;

m.p. = 76 – 79 °C;

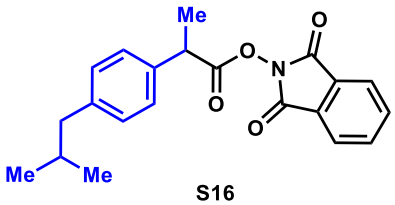
R_f = 0.32 (silica gel, 1:5 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.90 – 7.87 (m, 2H), 7.82 – 7.77 (m, 2H), 4.95 (br t, *J* = 7.2 Hz, 1H), 3.38 (d, *J* = 6.6 Hz, 2H), 2.63 (s, 2H), 1.65 – 1.43 (m, 10H), 1.44 (s, 9H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 168.3, 162.1, 156.6, 135.0, 129.0, 124.2, 79.3, 46.9, 39.1, 37.8, 33.9, 28.5, 26.0, 21.6 ppm;

HRMS (ESI-TOF, m/z): Calcd for $C_{22}H_{29}N_2O_6$ $[M+H]^+$ 417.2020; found 417.2022.

Compound S16



S16

1,3-dioxoisoindolin-2-yl-2-(4-isobutylphenyl)propanoate (S16)

On 5.0 mmol scale, General Procedure A was followed with ibuprofen. Purification by flash column chromatography (silica gel, 1:9 EtOAc:hexanes) afforded **S16** (1.48 g, 84%).

Physical state: colorless solid;

m.p. = 67 – 68 °C;

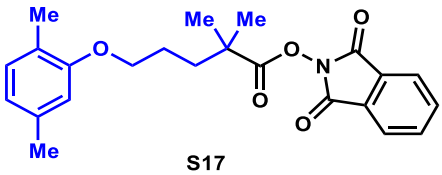
R_f = 0.42 (silica gel, 1:4 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.87 – 7.85 (m, 2H), 7.79 – 7.76 (m, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 4.10 (q, J = 7.2 Hz, 1H), 2.48 (d, J = 7.2 Hz, 2H), 1.91 – 1.84 (m, 1H), 1.67 (d, J = 7.2 Hz, 3H), 0.91 (d, J = 6.6 Hz, 6H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 171.1, 162.0, 141.4, 135.7, 134.8, 129.8, 129.1, 127.4, 124.0, 45.2, 42.7, 30.3, 22.5, 19.2 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{21}H_{22}NO_4$ $[M+H]^+$ 352.1543; found 352.1544.

Compound S17



S17

1,3-dioxoisoindolin-2-yl 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoate (S17)

On 1.0 mmol scale, General Procedure A was followed with gemfibrozil. Purification by flash column chromatography (silica gel, 1:25 EtOAc:hexanes) afforded **S17** (0.33 g, 84%).

Physical state: white solid;

m.p. = 65 – 67 °C;

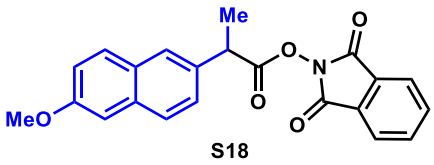
R_f = 0.50 (silica gel, 1:4 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.90 – 7.87 (m, 2H), 7.80 – 7.77 (m, 2H), 7.01 (d, *J* = 7.8 Hz, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 6.66 (s, 1H), 4.02 (t, *J* = 6.0 Hz, 2H), 2.32 (s, 3H), 2.20 (s, 3H), 1.95 – 2.00 (m, 4H), 1.46 (s, 6H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 173.9, 162.2, 157.1, 136.6, 134.8, 130.4, 129.2, 124.0, 123.8, 120.8, 112.1, 67.9, 42.1, 37.5, 31.7, 25.3, 25.1, 21.5, 15.9 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{23}H_{26}NO_5$ $[M+H]^+$ 396.1805; found 396.1803.

Compound S18



S18

1,3-dioxoisoindolin-2-yl 2-(6-methoxynaphthalen-2-yl)propanoate (S18)

On 5.0 mmol scale, General Procedure A was followed with naproxen. Purification by flash column chromatography (silica gel, 1:7 EtOAc:hexanes) afforded **S18** (1.65 g, 88%).

Physical state: white solid;

m.p. = 110 – 111 °C;

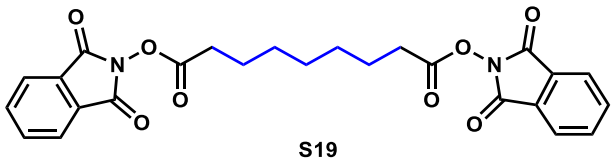
R_f = 0.53 (silica gel, 2:3 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.86 (br s, 2H), 7.80 – 7.75 (m, 5H), 7.49 (dd, *J* = 8.4 Hz, 1.8 Hz, 1H), 7.17 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 7.14 (d, *J* = 2.4 Hz, 1H), 4.26 (q, *J* = 7.2 Hz, 1H), 3.92 (s, 3H), 1.75 (d, *J* = 7.2 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 171.1, 162.0, 158.0, 134.9, 134.1, 133.6, 129.6, 129.1, 127.7, 126.5, 126.0, 124.1, 119.3, 105.8, 55.5, 43.1, 19.2 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{22}H_{18}NO_5$ $[M+H]^+$ 376.1179; found 376.1183.

Compound S19



S19

bis(1,3-dioxoisoindolin-2-yl) nonanedioate (S19)

On 5.0 mmol scale, General Procedure A was followed with azelaic acid (5.0 mmol, 1.0 equiv.), NHPI (10 mmol, 2.0 equiv.), DIC (11 mmol, 2.2 equiv.) and DMAP (1 mmol, 0.2 equiv.). Purification by flash column chromatography (silica gel, 1:10 EtOAc:CH_2Cl_2) afforded **S19** (1.52 g, 64%).

Physical state: white solid;

m.p. = 103 – 105 °C;

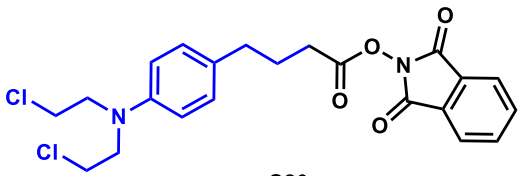
R_f = 0.55 (silica gel, 1:1 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.90 – 7.87 (m, 4H), 7.81 – 7.78 (m, 4H), 2.69 (t, J = 4.8 Hz, 4H), 1.85 – 1.80 (m, 4H), 1.53 – 1.48 (m, 4H), 1.45 – 1.42 (m, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 169.1, 161.5, 134.3, 128.5, 123.5, 30.5, 28.1, 28.0, 24.1 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{25}H_{23}N_2O_8$ $[M+H]^+$ 479.1449; found 479.1451.

Compound S20



S20

1,3-dioxoisoindolin-2-yl 4-(4-(bis(2-chloroethyl)amino)phenyl)butanoate (S20)

On 1.0 mmol scale, General Procedure A was followed with chlorambucil. Purification by flash column chromatography (silica gel, 1:4 EtOAc:hexanes) afforded **S20** (431 mg, 96%).

Physical state: yellow oil;

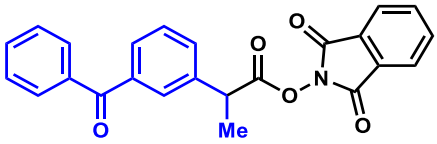
R_f = 0.23 (silica gel, 1:4 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.91 – 7.87 (m, 2H), 7.81 – 7.77 (m, 2H), 7.12 (d, *J* = 8.5 Hz, 2H), 6.65 (d, *J* = 9.0 Hz, 2H), 3.66 (AB t, *J* = 6.7 Hz, 4H), 3.63 (BA t, *J* = 6.7 Hz, 4H), 2.67 (dt, *J* = 7.5 Hz, 16 Hz, 4H), 2.09 – 2.02 (m, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 169.6, 162.1, 144.7, 134.9, 130.0, 129.9, 129.1, 124.1, 112.4, 53.8, 40.7, 33.6, 30.3, 26.6 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{22}H_{23}Cl_2N_2O_4$ $[M+H]^+$ 449.1029; found 449.1009.

Compound S21



S21

1,3-dioxoisoindolin-2-yl 2-(3-benzoylphenyl)propanoate (S21)

On 5.0 mmol scale, General Procedure A was followed with ketoprofen. Purification by flash column chromatography (silica gel, 1:3 EtOAc:hexanes) afforded **S21** (1.91 g, 96%).

Physical state: white solid;

m.p. = 118 – 120 °C;

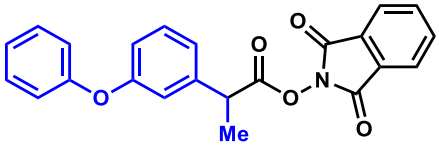
***R*$_f$** = 0.45 (silica gel, 1:2 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 5.5 Hz, 3.1 Hz, 2H), 7.86 – 7.83 (m, 3H), 7.80–7.76 (m, 3H), 7.68 – 7.65 (m, 1H), 7.60 (ddt, *J* = 8.7 Hz, 7.0 Hz, 1.3 Hz, 1H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.52 – 7.48 (m, 2H), 4.20 (q, *J* = 7.2 Hz, 1H), 1.71 (d, *J* = 7.2 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 196.4, 170.6, 161.9, 138.7, 138.4, 137.5, 134.9, 132.7, 131.7, 130.3, 129.8, 129.5, 129.1, 129.1, 128.5, 124.1, 43.0, 19.0 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{24}H_{18}NO_5$ $[M+H]^+$ 400.1179; found 400.1181.

Compound S22



S22

1,3-dioxoisoindolin-2-yl 2-(3-phenoxyphenyl)propanoate (S22)

On 5.0 mmol scale, General Procedure A was followed with fenoprofen. Purification by flash column chromatography (silica gel, 1:8 EtOAc:hexanes) afforded **S22** (1.83 g, 94%).

Physical state: colorless oil;

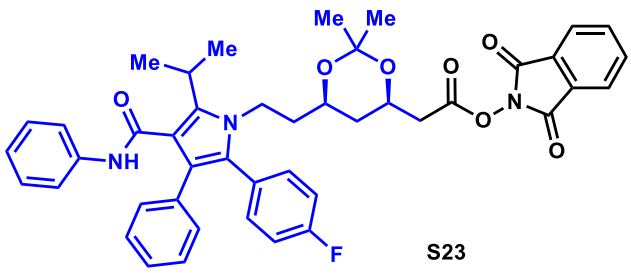
R_f = 0.50 (silica gel, 1:4 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.89 – 7.85 (m, 2H), 7.79 – 7.76 (m, 2H), 7.37 – 7.33 (m, 3H), 7.16 (dt, *J* = 7.8 Hz, 1.2 Hz, 1H), 7.13 – 7.10 (m, 1H), 7.09 (t, *J* = 2.4 Hz, 1H), 7.07 – 7.04 (m, 2H), 6.95 (ddd, *J* = 7.8 Hz, 2.4 Hz, 0.6 Hz, 1H), 4.09 (q, *J* = 7.2 Hz, 1H). 1.67 (d, *J* = 7.2 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.6, 161.9, 157.8, 157.1, 140.3, 134.9, 130.3, 129.9, 129.1, 124.1, 123.5, 122.5, 119.2, 118.4, 118.2, 42.9, 19.0 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{23}H_{18}NO_5$ $[M+H]^+$ 388.1179; found 388.1178.

Compound S23



S23

1,3-dioxoisoindolin-2-yl 2-((4*R*,6*R*)-6-(2-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (S23)

On 0.5 mmol scale, General Procedure A was followed with acetone ketal of

atorvastatin (Lipitor). Purification by flash column chromatography (silica gel, 1:2 EtOAc:hexanes) afforded **S23** (0.35 g, 95%).

Physical state: yellow foam;

R_f = 0.35 (silica gel, 1:2 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.90 – 7.87 (m, 2H), 7.81 – 7.77 (m, 2H), 7.21 – 7.15 (m, 9H), 7.08 (d, *J* = 8.4 Hz, 2H), 7.02 – 6.97 (m, 3H), 6.88 (br s, 1H), 4.33 – 4.28 (m, 1H), 4.14 – 4.07 (m, 1H), 3.89 – 3.84 (m, 1H), 3.75 – 3.71 (m, 1H), 3.61 – 3.56 (m, 1H), 2.85 (dd, *J* = 15.6 Hz, 6.6 Hz, 1H), 2.69 (dd, *J* = 15.0 Hz, 6.6 Hz, 1H), 1.76 – 1.70 (m, 2H), 1.55 – 1.53 (m, 7H), 1.40 (s, 3H), 1.35 (s, 3H), 1.18 (dd, *J* = 12.0 Hz, 5.4 Hz, 1H) ppm;

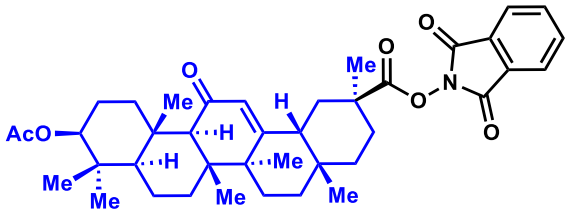
^{13}C NMR (151 MHz, $CDCl_3$): δ 166.9, 164.9, 162.4 (d, *J* = 247.8 Hz), 161.9, 141.6, 138.5, 134.9, 134.8, 133.3 (d, *J* = 8.0 Hz), 130.6, 129.0, 128.9, 128.8, 128.4, 128.3 (d, *J* = 3.6 Hz), 126.7, 124.1, 123.6, 121.9, 119.7, 115.5 (d, *J* = 21.3 Hz), 99.2, 66.4, 65.6, 40.9, 38.4, 38.1, 35.8, 29.9, 26.2, 21.9, 21.7, 19.7 ppm;

^{19}F NMR (376 MHz, $CDCl_3$): δ −113.9 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{44}H_{43}FN_3O_7$ $[M+H]^+$ 744.3080; found 744.3061.

$[\alpha]_D^{20}$ = +25.1 (c 1.0, $CHCl_3$).

Compound S24



S24

1,3-dioxoisoindolin-2-yl (2*S*,4a*S*,6a*S*,6b*R*,8a*R*,10*S*,12a*S*,12b*R*,14b*R*)-10-acetoxy-2,4a,6a,6b,9,9,12a-heptamethyl-13-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-icosahydropicene-2-carboxylate (S24)

On 1.0 mmol scale, General Procedure A was followed with acetyl enoxolone.

Purification by flash column chromatography (silica gel, 1:5 EtOAc:hexanes) afforded **S24** (0.49 g, 75%).

Physical State: white solid;

m.p. = 264 °C;

R_f = 0.57 (silica gel, 2:3 EtOAc:hexanes);

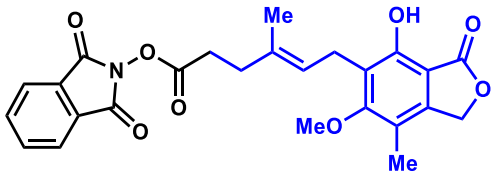
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.89 – 7.86 (m, 2H), 7.80 – 7.77 (m, 2H), 5.76 (s, 1H), 4.51 (dd, *J* = 11.8 Hz, 4.6 Hz, 1H), 2.79 (dt, *J* = 13.7 Hz, 3.7 Hz, 1H), 2.45 (ddd, *J* = 13.7 Hz, 4.3 Hz, 1.7 Hz, 1H), 2.35 (s, 1H), 2.15 – 2.11 (m, 1H), 2.11 – 2.00 (m, 2H), 2.04 (s, 3H), 1.86 (td, *J* = 13.7 Hz, 4.7 Hz, 1H), 1.79 (t, *J* = 13.7 Hz, 1H), 1.74 – 1.55 (m, 4H), 1.51 – 1.40 (m, 4H), 1.43 (s, 3H), 1.37 (s, 3H), 1.20 (ddd, *J* = 13.8 Hz, 4.6 Hz, 2.4 Hz, 1H), 1.15 (s, 3H), 1.14 (s, 3H), 1.10 – 1.01 (m, 3H), 0.90 (s, 3H), 0.87 (s, 6H), 0.80 (dd, *J* = 11.9 Hz, 1.8 Hz, 1H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 200.0, 172.7, 171.1, 168.5, 162.2, 134.8, 129.2, 129.0, 124.0, 80.8, 61.9, 55.2, 47.9, 45.5, 44.0, 43.3, 41.3, 38.9, 38.2, 37.4, 37.1, 32.9, 32.0, 31.6, 28.5, 28.2, 28.1, 26.6, 26.6, 23.7, 23.4, 21.5, 18.8, 17.5, 16.8, 16.6 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{40}H_{52}NO_7$ $[M+H]^+$ 658.3738; found 658.3736;

$[\alpha]_D^{20}$ = +191.0 (c 1.0, $CHCl_3$).

Compound S25



S25

1,3-dioxoisoindolin-2-yl (*E*)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoate (S25)

On 1.0 mmol scale, General Procedure A was followed with mycophenolic acid. Purification by flash column chromatography (silica gel, 1:4 EtOAc:hexanes) afforded **S25** (0.36 g, 78%).

Physical state: white solid;

m.p. = 126 – 128 °C;

R_f = 0.40 (silica gel, 1:3 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.88 – 7.85 (m, 2H), 7.79 – 7.77 (m, 2H), 7.68 (s, 1H), 5.34 (t, *J* = 7.2 Hz, 1H), 5.19 (s, 2H), 3.77 (s, 3H), 3.42 (d, *J* = 6.6 Hz, 2H), 2.76 (t, *J* = 7.8 Hz, 2H), 2.45 (t, *J* = 7.8 Hz, 2H), 2.15 (s, 3H), 1.85 (s, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 173.0, 169.3, 163.8, 162.0, 153.8, 144.2, 134.9, 133.1, 129.0, 124.1, 123.9, 122.0, 116.8, 106.5, 70.2, 61.2, 34.1, 29.9, 22.8, 16.2, 11.7 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{25}H_{24}NO_8$ $[M+H]^+$ 466.1496; found 466.1499.

The preparation and spectral data of the following RAEs have been reported (*22-26*).

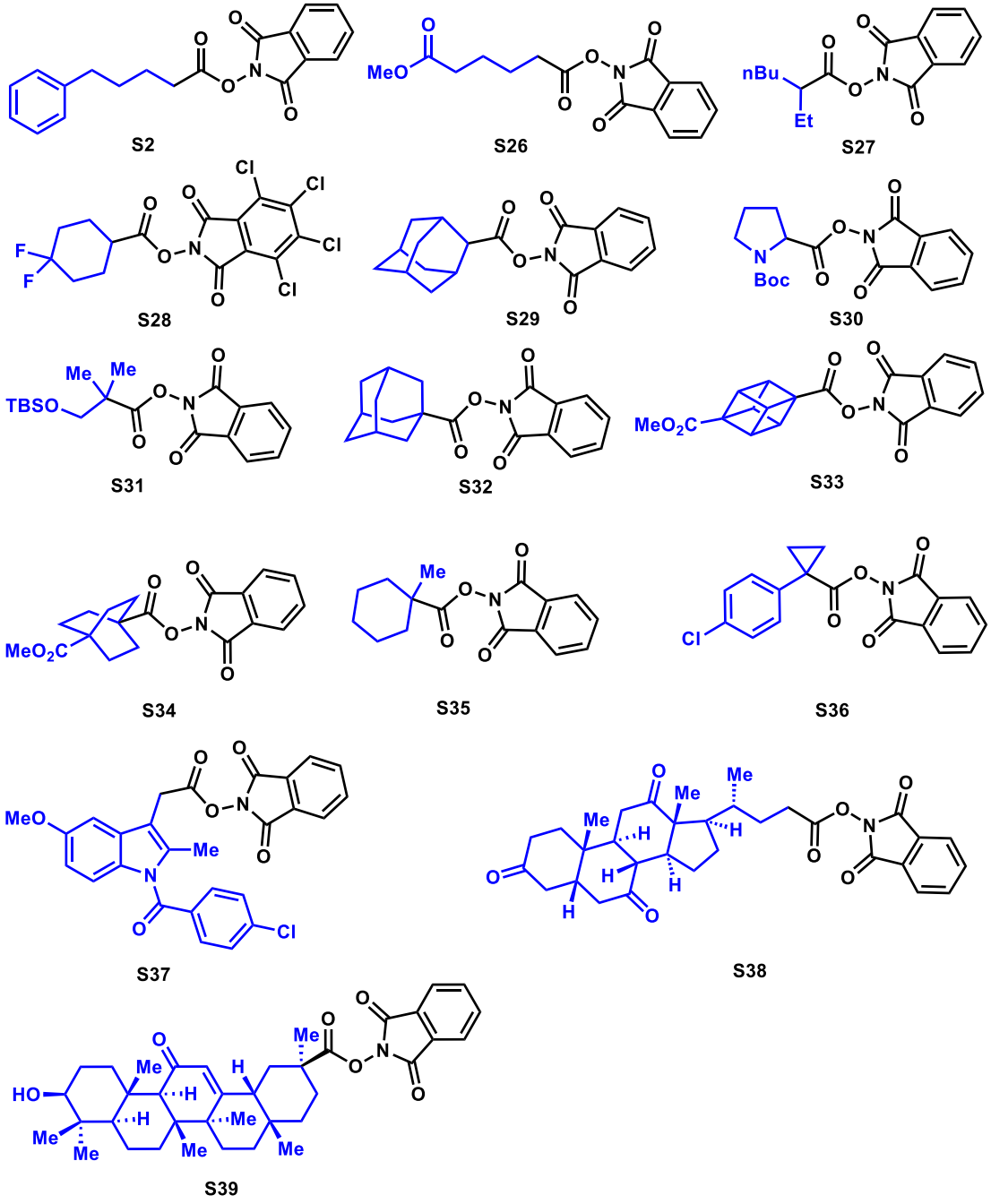
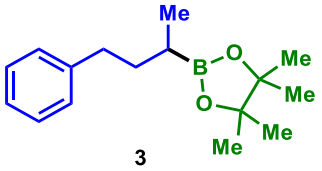


Figure S32. Structures of **S2**, **S26-S39**.

Experimental Procedure and Characterization Data for Borylation Products

Compound 3



3

4,4,5,5-tetramethyl-2-(4-phenylbutan-2-yl)-1,3,2-dioxaborolane (3)

On 0.2 mmol scale, General Procedure B was followed with NHPI ester (**2**) and suspension B ($NiCl_2$•$6H_2O$/di-MeObipy in DMF). Purification by flash column chromatography (silica gel, hexanes to 1:35 Et_2O:hexanes) afforded **3** (32.7 mg, 63%).

Physical state: colorless oil;

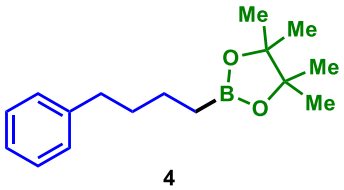
R_f = 0.49 (silica gel, 1:12 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28 – 7.25 (m, 2H), 7.20 – 7.14 (m, 3H), 2.66 – 2.58 (m, 2H), 1.82 – 1.76 (m, 1H), 1.62 – 1.57 (m, 1H), 1.25 (s, 12H), 1.10 – 1.05 (m, 1H), 1.02 (d, J = 7.2 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 143.2, 128.6, 128.3, 125.6, 83.0, 35.5, 35.4, 25.0, 24.9, 15.7 ppm;

Spectroscopic data matches that reported in the literature (*10*).

Compound 4



4

4,4,5,5-tetramethyl-2-(4-phenylbutyl)-1,3,2-dioxaborolane (4)

On 0.2 mmol scale, General Procedure B was followed with NHPI ester (**S2**) and solution B ($NiCl_2$•$6H_2O$/di-MeObipy in DMF). Purification by flash column chromatography (silica gel, hexanes to 1:30 Et_2O: hexanes) afforded **4** (34.0 mg, 65%).

Physical state: colorless oil;

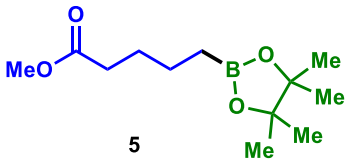
***R**f* = 0.50 (silica gel, 1:12 EtOAc: Hexane);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28 – 7.25 (m, 2H), 7.18 – 7.15 (m, 3H), 2.61 (t, *J* = 7.8 Hz, 2H), 1.66 – 1.61 (m, 2H), 1.50 – 1.45 (m, 2H), 1.24 (s, 12H), 0.82 (t, *J* = 7.8 Hz, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 143.1, 128.5, 128.3, 125.6, 83.0, 35.9, 34.3, 25.0, 23.9 ppm;

Spectroscopic data matches that reported in the literature (*55*).

Compound 5



5

Methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentanoate (5)

On 0.2 mmol scale, General Procedure B was followed with NHPI ester (**S26**) and solution B ($NiCl_2$•$6H_2O$/di-MeObipy in DMF). Purification by flash column chromatography (silica gel, hexanes to 1:100 CH_2Cl_2:hexanes) afforded **5** (25.2 mg, 52%).

Physical state: colorless oil;

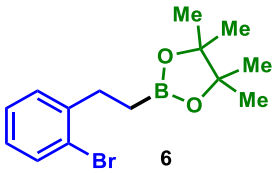
***R**f* = 0.55 (silica gel, 1:6 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 3.64 (s, 3H), 2.29 (t, *J* = 7.2 Hz, 2H), 1.64 – 1.59 (m, 2H), 1.45 – 1.40 (m, 2H), 1.23 (s, 12H), 0.78 (t, *J* = 7.8 Hz, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.4, 83.1, 51.6, 34.1, 27.7, 25.0, 23.8 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{12}H_{24}BO_4$ $[M+H]^+$ 243.1762; found 243.1765.

Compound 6



6

2-(2-bromophenethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6)

On 0.2 mmol scale, General Procedure B was followed with NHPI ester (**S3**) and solution B ($NiCl_2$•$6H_2O$/di-MeObipy in DMF). Purification by flash column chromatography (silica gel, hexanes to 1:30 Et_2O:hexanes) afforded **6** (34.3 mg, 55%).

Physical state: colorless oil;

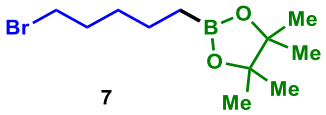
***R**f* = 0.55 (silica gel, 1:12 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.50 (d, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.02 (t, *J* = 7.8 Hz, 1H), 2.84 (t, *J* = 7.8 Hz, 2H), 1.24 (s, 12H), 1.15 (t, *J* = 7.8 Hz, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 143.7, 132.8, 129.9, 127.4, 127.4, 124.5, 83.3, 30.6, 25.0 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{14}H_{21}BBrO_2$ $[M+H]^+$ 313.0798; found 313.0799.

Compound 7



7

2-(5-bromopentyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7)

On 0.2 mmol scale, General Procedure B was followed with NHPI ester (**S4**) and solution B ($NiCl_2$•$6H_2O$/di-MeObipy in DMF). Purification by flash column chromatography (silica gel, hexanes to 1:30 Et_2O:hexanes) afforded **7** (36.0 mg, 65%).

Physical state: colorless oil;

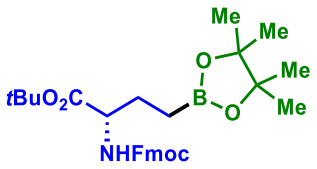
***R**f* = 0.55 (silica gel, 1:12 EtOAc:hexanes)

^{1}H NMR (600 MHz, $CDCl_3$): δ 3.40 (t, *J* = 7.2 Hz, 2H), 1.88 – 1.83 (m, 2H), 1.45 – 1.42 (m, 4H), 1.24 (s, 12H), 0.80 – 0.77 (m, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 83.1, 34.2, 32.8, 31.0, 25.0, 23.4 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{11}H_{23}BBrO_2$ $[M+H]^+$ 277.0969; found 277.0968.

Compound 8



8

***tert*-butyl 2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate (8)**

On 0.2 mmol scale, General Procedure B was followed with NHPI ester (**S5**) and solution B ($NiCl_2$•$6H_2O$/di-MeObipy in DMF). Purification by flash column chromatography (silica gel, 1:12 EtOAc:hexanes to 1:6 EtOAc:hexanes to 1:4 EtOAc:hexanes) afforded **8** (37.6 mg, 37%).

Physical state: colorless oil;

***R*$_f$** = 0.40 (silica gel, 1:4 EtOAc:hexanes)

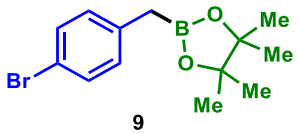
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.2 Hz, 2H), 7.61 (d, *J* = 7.2 Hz, 2H), 7.41 – 7.38 (m, 2H), 7.33 – 7.30 (m, 2H), 5.53 (d, *J* = 8.4 Hz, 1H), 4.34 – 4.24 (m, 2H), 4.23 – 4.19 (m, 2H), 1.97 – 1.91 (m, 1H), 1.84 – 1.78 (m, 1H), 1.47 (s, 9H), 1.23 (s, 12H), 0.89 – 0.78 (m, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 171.8, 156.2, 144.2, 144.1, 141.4, 127.8, 127.2, 125.3, 120.1, 83.5, 81.9, 67.0, 56.1, 47.4, 28.2, 27.0, 25.0, 24.9 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{29}H_{38}BNNaO_6$ $[M+Na]^+$ 530.2684; found 530.2685;

$[\alpha]_D^{20}$ = +2.3 (c 0.35, $CHCl_3$).

Compound 9



9

2-(4-bromobenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (9)

On 0.2 mmol scale, General Procedure C was followed with TCNHPI ester (**S6**) and suspension C ($NiCl_2$•$6H_2O$/di-*t*Bubipy in THF). Purification by flash column chromatography (silica gel, 1:40 to 1:20 Et_2O:hexanes) afforded **9** (30.5 mg, 51%).

Physical State: colorless oil;

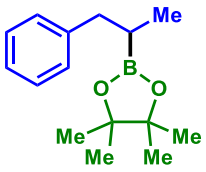
R_f = 0.30 (silica gel, 1:19 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35 – 7.33 (m, 2H), 7.06 – 7.04 (m, 2H), 2.23 (s, 2H), 1.23 (s, 12H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 137.8, 131.4, 130.9, 118.7, 83.7, 24.9 ppm;

Spectroscopic data matches that reported in the literature (*13*).

Compound 10



10

4,4,5,5-tetramethyl-2-(1-phenylpropan-2-yl)-1,3,2-dioxaborolane (10)

On 0.2 mmol scale, General Procedure C was followed with TCNHPI ester (**S7**) and suspension C ($NiCl_2$•$6H_2O$/di-*t*Bubipy in THF). Purification by flash column chromatography (silica gel, hexanes to 1:35 Et_2O:hexanes) afforded **10** (33.1 mg, 67%).

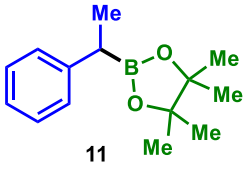
Physical state: colorless oil;

R_f = 0.53 (silica gel, 1:12 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.26 – 7.13 (m, 5H), 2.81 (dd, J = 13.8 Hz, 7.8 Hz, 1H), 2.54 (dd, J = 13.8 Hz, 7.8 Hz, 1H), 1.41 – 1.34 (m, 1H), 1.19 (s, 6H), 1.18 (s, 6H), 0.97 (d, J = 7.8 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 142.5, 129.0, 128.1, 125.7, 83.1, 39.1, 24.9, 15.3 ppm; Spectroscopic data matches that reported in the literature (*56*).

Compound 11



11

4,4,5,5-tetramethyl-2-(1-phenylethyl)-1,3,2-dioxaborolane (11)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (**S8**) and suspension A ($NiCl_2$•$6H_2O$/di-MeObipy in THF). 1.0 equiv. of $MgBr_2$•OEt_2 was used in this case. Purification by flash column chromatography (silica gel, hexanes to 1:30 Et_2O:hexanes) afforded **11** (33.8 mg, 73%).

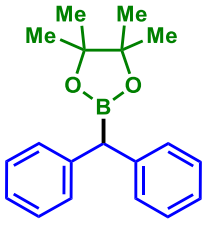
Physical State: colorless oil;

***R**$_f$* = 0.33 (silica gel, 1:19 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 – 7.21 (m, 4H), 7.15 – 7.12 (m, 1H), 2.44 (q, *J* = 7.8 Hz, 1H), 1.33 (d, *J* = 7.8 Hz, 3H), 1.21 (s, 6H), 1.20 (s, 6H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 145.1, 128.4, 127.9, 125.2, 83.4, 24.8, 24.7, 17.2 ppm; Spectroscopic data matches that reported in the literature (*10*).

Compound 12



12

2-benzhydryl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (12)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (**S9**) and suspension A ($NiCl_2$•$6H_2O$/di-MeObipy in THF). Purification by flash column

chromatography (silica gel, hexanes to 1:30 Et_2O:hexanes) afforded **12** (41.0 mg, 70%).

Physical State: colorless oil;

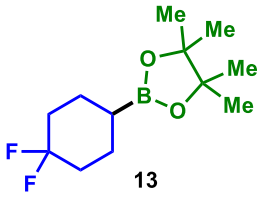
R_f = 0.41 (silica gel, 1:9 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30 – 7.25 (m, 8H), 7.19 – 7.15 (m, 2H), 3.88 (s, 1H), 1.24 (s, 12H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 142.2, 129.2, 128.5, 125.7, 83.9, 24.7 ppm;

Spectroscopic data matches that reported in the literature (*57*).

Compound 13



13

2-(4,4-difluorocyclohexyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (13)

On 0.2 mmol scale, General Procedure C was followed with TCNHPI ester (**S28**) and suspension C ($NiCl_2$•$6H_2O$/di-*t*Bubipy in THF). Purification by flash column chromatography (silica gel, hexanes to 1:45 Et_2O:hexanes) afforded **13** (23.0 mg, 47%).

Physical state: colorless oil;

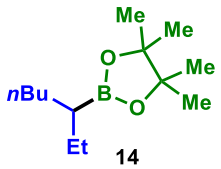
R_f = 0.45 (silica gel, 1:9 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 2.02 – 1.95 (m, 2H), 1.82-1.78 (m, 2H), 1.75 – 1.58 (m, 4H), 1.23 (s, 12H), 1.00 – 0.96 (m, 1H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 123.9 (t, J = 239.9 Hz), 83.4, 34.5 (t, J = 23.3 Hz), 24.9, 24.4 (t, J = 4.6 Hz) ppm;

HRMS (ESI-TOF, *m/z*): High-resolution mass spectra data could not be obtained for this compound.

Compound 14



14

2-(heptan-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (14)

On 0.2 mmol scale, General Procedure C was followed with TCNHPI ester (**S27**) and suspension C ($NiCl_2$•$6H_2O$/di-*t*Bubipy in THF). Purification by flash column chromatography (silica gel, hexanes to 1:40 Et_2O:hexanes) afforded **14** (25.6 mg, 57%).

Physical state: colorless oil;

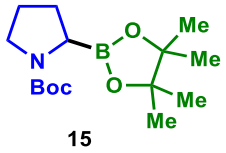
R_f = 0.42 (silica gel, 1:19 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 1.45 – 1.22 (m, 20H), 0.90 – 0.86 (m, 7H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 82.9, 31.7, 30.8, 25.0, 24.4, 23.1, 14.3, 13.9 ppm;

Spectroscopic data matches that reported in the literature (*58*).

Compound 15



15

***tert*-Butyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidine-1-carboxylate (15)**

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (**S30**) and suspension C ($NiCl_2$•$6H_2O$/di-*t*Bubipy in THF). Purification by flash column chromatography (first flash column chromatography: deactivated silica gel, hexanes to 1:9 EtOAc:hexanes; second flash column chromatography: deactivated silica gel, CH_2Cl_2) afforded **15** (39.2 mg, 66%).

Physical State: colorless oil;

R_f = 0.45 (silica gel, 1:4 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 3.42 – 2.99 (m, 3H), 2.09 – 1.65 (m, 4H), 1.43 (s, 9H),

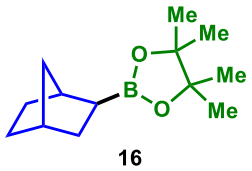
1.26 – 1.22 (m, 12H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 155.1, 83.6, 79.1, 46.1, 28.7, 27.9, 27.3 25.2, 25.0, 24.6 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{15}H_{29}BNO_4$ $[M+H]^+$ 298.2184; found 298.2179;

$[\alpha]_D^{20}$ = 0 (c 0.3, $CHCl_3$).

Compound 16



16

2-(Bicyclo[2.2.1]heptan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (16)

On 0.2 mmol scale, General Procedure B was followed with NHPI ester (**S10**, mixture of *endo*/*exo*) and solution B ($NiCl_2$•$6H_2O$/di-MeObipy in DMF). Purification by flash column chromatography (silica gel, hexanes to 1:40 Et_2O:hexanes to 1:20 Et_2O:hexanes) afforded **16** (24.4 mg, 55%, *exo*/*endo* = 10:1).

Physical state: colorless oil;

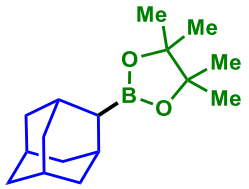
***R*$_f$** = 0.38 (silica gel, 1:19 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 2.28 – 2.27 (m, 1H), 2.22 – 2.21 (m, 1H), 1.56 – 1.44 (m, 3H), 1.37 – 1.33 (m, 1H), 1.26 – 1.21 (m, 14H), 1.20 – 1.14 (m, 2H), 0.89 – 0.86 (m, 1H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 82.9, 38.9, 38.3, 36.8, 32.4, 32.3, 29.4, 24.9 ppm (*exo*); 83.0, 41.1, 39.1, 37.2, 32.3, 30.0, 28.0, 25.1, 25.0 ppm (*endo*);

Spectroscopic data matches that reported in the literature (*11*).

Compound 17



17

2-Adamantan-2-yl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (17)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (**S29**) and suspension A ($NiCl_2$•$6H_2O$/di-MeObipy in THF). Purification by flash column chromatography (silica gel, hexanes to 1:30 Et_2O:hexanes) afforded **17** (30.9 mg, 59%).

Physical state: colorless oil;

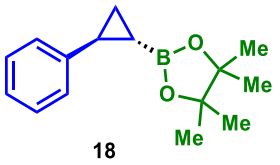
R_f = 0.55 (silica gel, 1:9 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 2.06 – 2.04 (m, 2H), 1.90 – 1.67 (m, 12H), 1.37 – 1.35 (m, 1H), 1.25 (s, 12H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 82.9, 39.5, 37.9, 36.4, 29.5, 28.4, 28.3, 25.0 ppm;

Spectroscopic data matches that reported in the literature (*10*).

Compound 18



18

***trans*-4,4,5,5-tetramethyl-2-(2-phenylcyclopropyl)-1,3,2-dioxaborolane (18)**

On 0.2 mmol scale, General Procedure B was followed with TCNHPI ester (**S11**) and solution D ($NiCl_2$•$6H_2O$/di-*t*Bubipy in DMF). Purification by flash column chromatography (silica gel, hexanes to 1:30 Et_2O:hexanes) afforded **18** (11.3 mg, 23%, *d.r.* > 20:1).

Physical State: colorless oil;

R_f = 0.48 (silica gel, 1:9 EtOAc:hexanes);

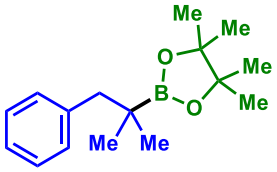
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.25 – 7.22 (m, 2H), 7.15 – 7.11 (m, 1H), 7.09 – 7.06

(m, 2H), 2.10 (dt, J = 7.8 Hz, 5.4 Hz, 1H), 1.25 (s, 6H), 1.24 (s, 6H), 1.17 – 1.14 (m, 1H), 1.02 – 0.99 (m, 1H), 0.32 – 0.29 (m, 1H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 143.5, 128.4, 125.8, 125.7, 83.3, 24.9, 24.8, 22.0, 15.2 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{15}H_{22}BO_2$ $[M+H]^+$ 245.1707; found 245.1714.

Compound 19



19

4,4,5,5-tetramethyl-2-(2-methyl-1-phenylpropan-2-yl)-1,3,2-dioxaborolane (19)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (**S12**) and suspension A ($NiCl_2$•$6H_2O$/di-MeObipy in THF). Purification by flash column chromatography (silica gel, hexanes to 1:30 Et_2O:hexanes) afforded **19** (35.3 mg, 68%).

Physical State: colorless solid;

m.p.= 36 – 37 °C;

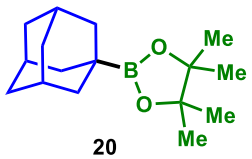
***R*$_f$** = 0.50 (silica gel, 1:12 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24 – 7.19 (m, 4H), 7.17 – 7.14 (m, 1H), 2.61 (s, 2H), 1.21 (s, 12H), 0.94 (s, 6H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 140.6, 130.3, 127.8,125.8, 83.24, 46.5, 24.9 ppm.

Spectroscopic data matches that reported in the literature (*10*).

Compound 20



20

2-Adamantan-1-yl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (20)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (**S32**) and

suspension C ($NiCl_2$•$6H_2O$/di-*t*Bubipy in THF). Purification by flash column chromatography (silica gel, 1:60 Et_2O:hexanes to 1:40 Et_2O:hexanes) afforded **20** (29.2 mg, 56%).

Physical State: white amorphous solid;

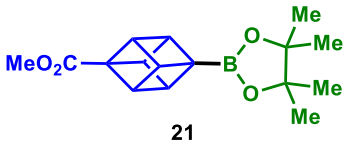
R_f = 0.60 (silica gel, 1:9 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 1.84 (br s, 3H), 1.75 (br t, *J* = 3.6 Hz, 12H), 1.20 (s, 12H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 82.7, 38.1, 37.6, 27.7, 24.8 ppm;

Spectroscopic data matches that reported in the literature (*10*).

Compound 21



21

Methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cubane-1-carboxylate (21)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (**S33**) and suspension A ($NiCl_2$•$6H_2O$/di-MeObipy in THF). Purification by flash column chromatography (silica gel, hexanes to 1:15:15 Et_2O:CH_2Cl_2:hexanes) afforded **21** (26.2 mg, 45%).

Physical State: white solid;

m.p.= 152 – 155 °C;

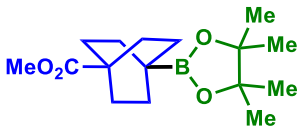
R_f = 0.45 (silica gel, 1:6 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.30 – 4.28 (m, 3H), 4.03 – 4.01 (m, 3H), 3.70 (s, 3H), 1.26 (s, 12H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.8, 83.4, 55.4, 51.6, 50.0, 45.2, 24.9 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{16}H_{22}BO_4$ $[M+H]^+$ 289.1606; found 289.1607.

Compound 22



22

Methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)bicyclo[2.2.2]octane-1-carboxylate (22)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (**S34**) and suspension C ($NiCl_2$•$6H_2O$/di-*t*Bubipy in THF). Purification by flash column chromatography (silica gel, hexanes to 1:9 Et_2O:hexanes) afforded **22** (31.1 mg, 53%).

Physical State: colorless solid;

Sublimation at 100 °C;

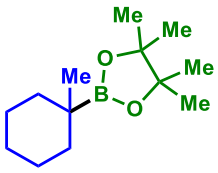
R_f = 0.39 (silica gel, 1:5 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 3.62 (s, 3H), 1.72 – 1.65 (m, 6H), 1.62 – 1.54 (m, 6H), 1.19 (s, 12H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 179.0, 83.0, 51.7, 38.6, 27.9, 26.7, 24.8 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{16}H_{28}BO_4$ $[M+H]^+$ 295.2075; found 295.2077.

Compound 23



23

4,4,5,5-tetramethyl-2-(1-methylcyclohexyl)-1,3,2-dioxaborolane (23)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (**S35**) and suspension A ($NiCl_2$•$6H_2O$/di-MeObipy in THF). Purification by flash column chromatography (silica gel, hexanes to 1:30 Et_2O:hexanes) afforded **23** (27.8 mg, 62%).

Physical State: colorless oil;

R_f = 0.50 (silica gel, 1:12 EtOAc:hexanes);

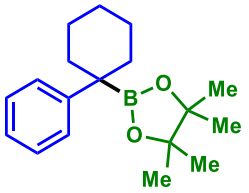
^{1}H NMR (600 MHz, $CDCl_3$): δ 1.84 – 1.80 (m, 2H), 1.64 – 1.57 (m, 3H), 1.29 – 1.21

(m, 14H), 1.16 – 1.08 (m, 1H), 0.92 – 0.87 (m, 5H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 82.9, 37.2, 26.6, 26.0, 25.7, 24.8 ppm;

Spectroscopic data matches that reported in the literature (*10*).

Compound 24



24

4,4,5,5-tetramethyl-2-(1-phenylcyclohexyl)-1,3,2-dioxaborolane (24)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (**S13**) and suspension C ($NiCl_2$•$6H_2O$/di-*t*Bubipy in THF). Purification by flash column chromatography (silica gel, hexanes to 1:30 Et_2O:hexanes) afforded **24** (28.5 mg, 50%).

Physical State: white solid;

m.p. = 87 – 88 °C;

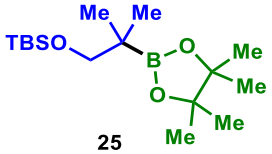
***R**$_f$* = 0.60 (silica gel, 1:9 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36 – 7.34 (m, 2H), 7.29 – 7.26 (m, 2H), 7.13 – 7.11 (m, 1H), 2.36 – 2.32 (m, 2H), 1.82 – 1.78 (m, 2H), 1.70 – 1.66 (m, 1H), 1.49 – 1.38 (m, 4H), 1.21 – 1.14 (m, 1H), 1.17 (s, 12H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 147.6, 128.2, 126.3, 125.1, 83.4, 35.0, 26.4, 25.9, 25.7 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{18}H_{28}BO_2$ $[M+H]^+$ 287.2177; found 287.2184.

Compound 25



25

***tert*-butyldimethyl(2-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-**

yl)propoxy)silane (25)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (**S31**) and suspension A ($NiCl_2$•$6H_2O$/di-MeObipy in THF). Purification by flash column chromatography (silica gel, hexanes to 1:30 Et_2O:hexanes) afforded **25** (41.2 mg, 66%).

Physical State: colorless oil;

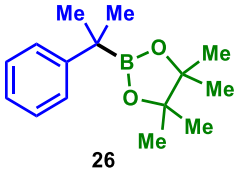
R_f = 0.40 (silica gel, 1:12 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 3.39 (s, 2H), 1.22 (s, 12H), 0.90 (s, 6H), 0.88 (s, 9H), 0.01 (s, 6H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 83.0, 72.0, 26.1, 24.9, 21.4, 18.5, –5.34 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{16}H_{36}BO_3Si$ $[M+H]^+$ 315.2521; found 315.2523.

Compound 26



26

4,4,5,5-tetramethyl-2-(2-phenylpropan-2-yl)-1,3,2-dioxaborolane (26)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (**S14**) and suspension C ($NiCl_2$•$6H_2O$/di-*t*Bubipy in THF). Purification by flash column chromatography (silica gel, hexanes to 1:30 Et_2O:hexanes) afforded **26** (23.3 mg, 47%).

Physical State: colorless oil;

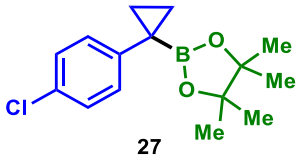
R_f = 0.51 (silica gel, 1:9 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.33 – 7.27 (m, 4H), 7.15 – 7.12 (m, 1H), 1.35 (s, 6H), 1.20 (s, 12H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 148.8, 128.2, 126.4, 125.1, 83.4, 25.7, 24.7 ppm;

Spectroscopic data matches that reported in the literature (*59*).

Compound 27



27

2-(1-(4-chlorophenyl)cyclopropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (27)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (**S36**) and suspension A ($NiCl_2$•$6H_2O$/di-MeObipy in THF). Purification by flash column chromatography (silica gel, hexanes to 1:30 Et_2O:hexanes) afforded **27** (32.9 mg, 59%).

Physical State: white solid;

m.p. = 83 – 85 °C;

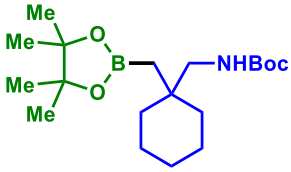
***R**f* =** 0.37 (silica gel, 1:19 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.19 (s, 4H), 1.21 (s, 12H), 1.11 (dd, *J* = 6.0 Hz, 3.6 Hz, 2H), 0.87 (dd, *J* = 6.0 Hz, 3.6 Hz, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 143.5, 131.0, 130.5, 128.2, 83.6, 24.7, 13.6 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{15}H_{21}BClO_2$ $[M+H]^+$ 279.1318; found 279.1319.

Compound 28



28

***tert*-butyl ((1-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)cyclohexyl) methyl)carbamate (28)**

On 0.1 mmol scale, General Procedure B was followed with NHPI ester (**S15**) and solution B ($NiCl_2$•$6H_2O$/di-MeObipy in DMF). Purification by flash column chromatography (silica gel, 1:20 EtOAc:hexanes) afforded **28** (22.5 mg, 64%).

Physical State: white solid;

m.p. = 92 – 96 °C;

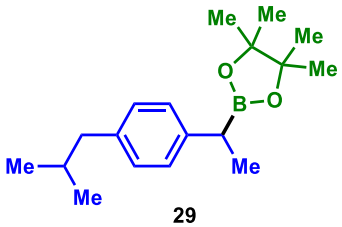
***R**f* =** 0.28 (silica gel, 1:20 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.32 (br s, 1H), 3.08 (d, *J* = 6.0 Hz, 2H), 1.52 – 1.41 (m, 4H), 1.43 (s, 9H), 1.38 – 1.31 (m, 6H), 1.25 (s, 12H), 0.81 (s, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 156.5, 83.4, 78.7, 50.0, 36.7, 36.3, 28.6, 26.4, 25.0, 21.9 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{19}H_{37}BNO_4$ $[M+H]^+$ 354.2810; found 354.2809.

Compound 29



29

2-(1-(4-isobutylphenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (29)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (**S16**) and suspension A ($NiCl_2$•$6H_2O$/di-MeObipy in THF, 1.0 equiv. of $MgBr_2$•OEt_2 was used in this case). Purification by flash column chromatography (silica gel, hexanes to 1:30 Et_2O:hexanes) afforded **29** (43.0 mg, 75%).

Physical State: colorless oil;

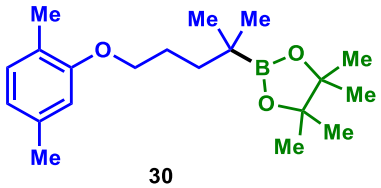
***R*$_f$** = 0.59 (silica gel, 1:9 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.12 – 7.10 (m, 2H), 7.04 – 7.02 (m, 2H), 2.42 (d, *J* = 7.2 Hz, 2H), 2.40 (q, *J* = 7.2 Hz, 1H), 1.79 – 1.88 (m, 1H), 1.31 (d, *J* = 7.2 Hz, 3H), 1.21 (s, 6H), 1.20 (s, 6H), 0.89 (d, *J* = 6.6 Hz, 6H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 142.1, 138.4, 129.2, 127.6, 83.4, 45.2, 30.4, 24.8, 24.7, 22.6, 17.2 ppm;

Spectroscopic data matches that reported in the literature (*60*).

Compound 30



30

2-(5-(2,5-dimethylphenoxy)-2-methylpentan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (30)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (**S17**) and suspension A ($NiCl_2$•$6H_2O$/di-MeObipy in THF). Purification by flash column chromatography (silica gel, hexanes to 1:30 Et_2O:hexanes) afforded **30** (36.3 mg, 55%).

Physical State: colorless solid;

m.p. = 59 – 61 °C;

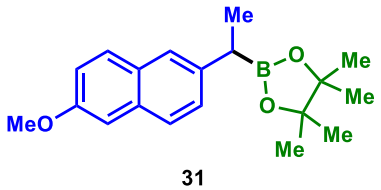
R_f = 0.60 (silica gel, 1:12 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.99 (d, J = 7.8 Hz, 1H), 6.64 (d, J = 7.2 Hz, 1H), 6.62 (s, 1H), 3.92 (t, J = 6.6 Hz, 2H), 2.30 (s, 3H), 2.18 (s, 3H), 1.78 – 1.73 (m, 2H), 1.41 – 1.44 (m, 2H), 1.23 (s, 12H), 0.96 (s, 6H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 157.3, 136.5, 130.4, 123.8, 120.6, 112.2, 83.1, 68.8, 37.4, 26.6, 25.0, 24.9, 21.6, 16.0 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{20}H_{34}BO_3$ $[M+H]^+$ 333.2595; found 333.2598.

Compound 31



31

2-(1-(6-methoxynaphthalen-2-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (31)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (**S18**) and

suspension A ($NiCl_2$•$6H_2O$/di-MeObipy in THF, 1.0 equiv. of $MgBr_2$•OEt_2 was used in this case). Purification by flash column chromatography (silica gel, hexanes to 1:25 Et_2O:hexanes) afforded **31** (50.0 mg, 80%).

Physical State: white solid;

m.p. = 82 – 84 °C;

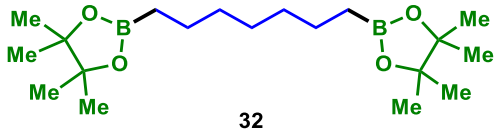
R_f = 0.62 (silica gel, 1:4 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.64 – 7.67 (m, 2H), 7.57 (s, 1H), 7.35 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.09 – 7.11 (m, 2H), 3.90 (s, 3H), 2.57 (q, *J* = 7.2 Hz, 1H), 1.41 (d, *J* = 7.2 Hz, 3H), 1.21 (s, 6H), 1.20 (s, 6H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 157.1, 140.3, 132.8, 129.5, 129.1, 127.8, 126.7, 125.3, 118.5, 105.8, 83.5, 55.4, 24.8, 24.8, 17.1 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{19}H_{26}BO_3$ $[M+H]^+$ 313.1969; found 313.1970.

Compound 32



32

1,7-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)heptane (32)

On 0.2 mmol scale, General Procedure B was followed with NHPI ester (**S19**) and solution B [$NiCl_2$•$6H_2O$ (20 mol%)/di-MeObipy (26 mol%) in DMF]. Purification by flash column chromatography (silica gel, hexanes to 1:20 Et_2O:hexanes) afforded **32** (26.5 mg, 38%).

Physical State: colorless oil;

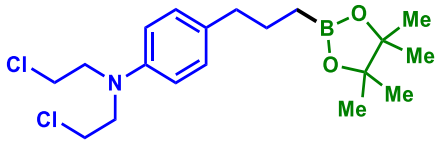
R_f = 0.45 (silica gel, 1:8 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 1.41 – 1.36 (m, 4H), 1.29 – 1.24 (m, 6H), 1.24 (s, 24H), 0.75 (t, *J* = 7.8 Hz, 4H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 83.0, 32.5, 29.4, 25.0, 24.2 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{19}H_{39}B_2O_4$ $[M+H]^+$ 353.3029; found 353.3030.

Compound 33



33

***N*,*N*-bis(2-chloroethyl)-4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl) aniline (33)**

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (**S20**) and suspension A ($NiCl_2$•$6H_2O$/di-MeObipy in THF). Purification by flash column chromatography (silica gel, hexanes to 1:19 EtOAc:hexanes) afforded **33** (20.7 mg, 27%).

Physical State: yellow oil;

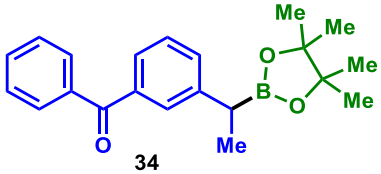
***R*$_f$** = 0.36 (silica gel, 1:9 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.09 – 7.04(m, 2H), 6.63 – 6.59 (m, 2H), 3.69 (t, *J* = 7.1 Hz, 4H), 3.61 (t, *J* = 7.1 Hz, 4H), 2.54 – 2.48 (t, *J* = 7.8 Hz, 2H), 1.68 (p, *J* = 7.8 Hz, 2H), 1.24 (s, 12H), 0.81 (t, *J* = 7.8 Hz, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 144.2, 132.2, 129.9, 112.2, 83.1, 53.8, 40.7, 37.6, 26.5, 25.0 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{19}H_{31}BCl_2NO_2$ $[M+H]^+$ 386.1819; found 386.1815.

Compound 34



34

phenyl (3-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)phenyl) methanone (34)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (**S21**) and suspension A ($NiCl_2$•$6H_2O$/di-MeObipy in THF, 1.0 equiv. of $MgBr_2$•OEt_2 was used in

this case). Purification by flash column chromatography (silica gel, hexanes to 1:15 EtOAc:hexanes) afforded **34** (51.9 mg, 77%).

Physical State: colorless oil;

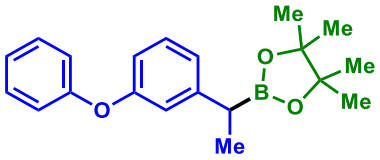
R_f = 0.45 (silica gel, 1:6 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.81 (dd, *J* = 8.2 Hz, 1.4 Hz, 2H), 7.66 (t, *J* = 1.8 Hz, 1H), 7.58 (tt, *J* = 7.2 Hz, 1.4 Hz, 2H), 7.50 – 7.44 (m, 3H), 7.37 (t, *J* = 7.6 Hz, 1H), 2.51 (q, *J* = 7.8 Hz, 1H), 1.35 (d, *J* = 7.8 Hz, 3H), 1.21 (s, 6H), 1.21 (s, 6H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 197.2, 145.4, 138.0, 137.7, 132.4, 132.2, 130.3, 129.7, 128.4, 128.3, 127.2, 83.6, 24.8, 24.8, 17.1 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{21}H_{26}BO_3$ $[M+H]^+$ 337.1969; found 337.1971.

Compound 35



35

4,4,5,5-tetramethyl-2-(1-(3-phenoxyphenyl)ethyl)-1,3,2-dioxaborolane (35)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (**S22**) and suspension A ($NiCl_2$•$6H_2O$/di-MeObipy in THF, 1.0 equiv. of $MgBr_2$•OEt_2 was used in this case). Purification by flash column chromatography (silica gel, hexanes to 1:30 Et_2O:hexanes) afforded **35** (52.6 mg, 81%).

Physical State: colorless oil;

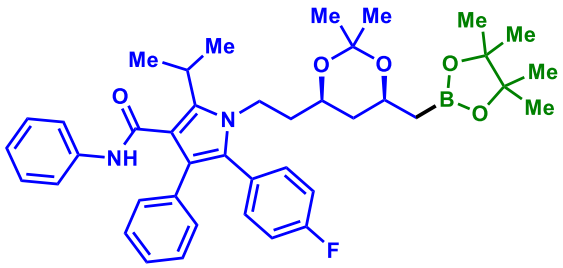
R_f = 0.50 (silica gel, 1:12 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.32 (t, *J* = 7.8 Hz, 2H), 7.22 (t, *J* = 7.8 Hz, 1H), 7.07 (t, *J* = 7.8 Hz, 1H), 7.01 (d, *J* = 7.2 Hz, 2H), 6.97 (d, *J* = 7.2 Hz, 1H), 6.91 (t, *J* = 1.8 Hz, 1H), 6.79 (dd, *J* = 7.8 Hz, 2.4 Hz, 1H), 2.42 (q, *J* = 7.8 Hz, 1H), 1.31 (d, *J* = 7.8 Hz, 3H), 1.20 (s, 6H), 1.19 (s, 6H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 157.7, 157.2, 147.3, 129.7, 129.6, 123.0, 123.0, 118.8, 118.7, 115.9, 83.5, 24.8, 24.7, 17.0 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{20}H_{26}BO_3$ $[M+H]^+$ 325.1969; found 325.1970.

Compound 36



36

1-(2-((4*R*,6*S*)-2,2-dimethyl-6-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)-1,3-dioxan-4-yl)ethyl)-5-(4-fluorophenyl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (36)

On 0.2 mmol scale, General Procedure B was followed with NHPI ester (**S23**) and solution B ($NiCl_2$•$6H_2O$/di-MeObipy in DMF). Purification by flash column chromatography (silica gel, hexanes to 1:9 EtOAc:hexanes) afforded **36** (77.4 mg, 57%).

Physical State: white foam;

***R*$_f$** = 0.52 (silica gel, 1:4 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.21 – 7.14 (m, 9H), 7.07 (br d, *J* = 8.4 Hz, 2H), 7.00 – 6.97 (m, 3H), 6.85 (br s, 1H), 4.08 – 4.03 (m, 1H), 4.00 – 3.96 (m, 1H), 3.85 – 3.80 (m, 1H), 3.69 – 3.65 (m, 1H), 3.60 – 3.55 (m, 1H), 1.68 – 1.64 (m, 2H), 1.55 (d, *J* = 1.8 Hz, 3H), 1.53 (d, *J* = 1.8 Hz, 3H), 1.34 (dt, *J* = 13.2 Hz, 1.2 Hz, 1H), 1.34 (s, 3H), 1.30 (s, 3H), 1.23 (s, 12H), 1.08 – 1.03 (m, 2H), 0.98 – 0.94 (m, 1H) ppm;

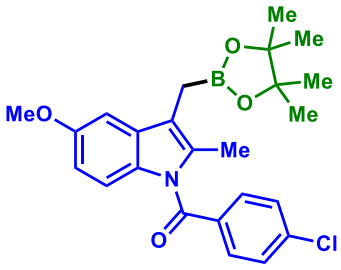
^{13}C NMR (151 MHz, $CDCl_3$): δ 165.0, 162.4 (d, *J* = 247.6 Hz), 141.7, 138.6, 134.8, 134.5, 133.3 (d, *J* = 8.2 Hz), 130.7, 128.9, 128.8, 128.5, 128.4 (d, *J* = 3.8 Hz), 126.7, 123.8, 123.6, 121.8, 119.7, 115.4 (d, *J* = 21.3 Hz), 98.6, 83.3, 66.7, 66.7, 41.0, 38.4, 38.3, 30.3, 26.2, 24.9, 24.9, 21.9, 21.7, 20.0 ppm;

^{19}F NMR (376 MHz, $CDCl_3$): δ −114.1 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{41}H_{51}BFN_2O_5$ $[M+H]^+$ 681.3870; found 681.3870;

$[\alpha]_D^{20}$ = +4.0 (c 0.68, $CHCl_3$).

Compound 37



37

(4-chlorophenyl)(5-methoxy-2-methyl-3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)-1H-indol-1-yl)methanone (37)

On 0.1 mmol scale, General Procedure C was followed with NHPI ester (**S37**) and suspension A ($NiCl_2$•$6H_2O$/di-MeObipy in THF). Purification by flash column chromatography (silica gel, hexanes to 1:17 EtOAc:hexanes) afforded **37** (22.1 mg, 50%).

Physical State: yellow oil;

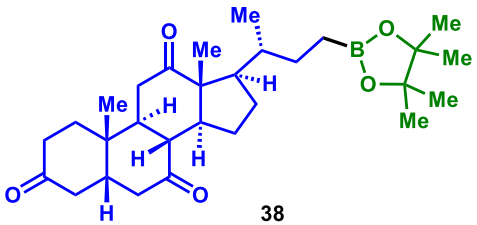
R_f = 0.5 (silica gel, 1:4 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.64 (dt, *J* = 9.0 Hz, 1.8 Hz, 2H), 7.45 (m, dt, *J* = 8.4 Hz, 1.8 Hz, 2H), 6.96 – 6.93 (m, 2H), 6.64 (dd, *J* = 9.0 Hz, 2.6 Hz, 1H), 3.84 (s, 3H), 2.29 (s, 3H), 2.18 (s, 2H), 1.23 (s, 12H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 168.3, 156.0, 138.8, 134.7, 133.2, 132.0, 131.2, 131.1, 129.1, 116.7, 115.0, 111.3, 101.7, 83.7, 55.8, 29.9, 25.0, 13.9 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{24}H_{28}BClNO_4$ $[M+H]^+$ 440.1794; found 440.1794.

Compound 38



38

(5*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-yl)dodecahydro-3*H*-cyclopenta[*a*]phenanthrene-

3,7,12(2*H*,4*H*)-trione (38)

On 0.2 mmol scale, General Procedure B was followed with NHPI ester (**S38**) and solution B ($NiCl_2$•$6H_2O$/di-MeObipy in DMF). Purification by flash column chromatography (silica gel, hexanes to 1:5 EtOAc:hexanes) afforded **38** (63.0 mg, 65%).

Physical State: white solid;

R_f = 0.40 (silica gel, 1:3 EtOAc:hexanes);

m.p. = 230 – 232 °C;

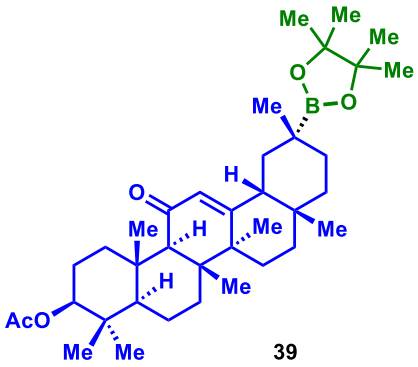
^{1}H NMR (600 MHz, $CDCl_3$): δ 2.92 – 2.82 (m, 3H), 2.35 – 2.19 (m, 6H), 2.14 – 2.09 (m, 2H), 2.05 – 1.94 (m, 4H), 1.80 – 1.85 (m, 1H), 1.56 – 1.63 (m, 2H), 1.39 (s, 3H), 1.35 – 1.12 (m, 16 H), 1.06 (s, 3H), 0.87 – 0.81 (m, 4H), 0.68 – 0.62 (m, 1H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 212.1, 209.2, 208.9, 83.0, 57.1, 51.9, 49.2, 47.0, 45.8, 45.7, 45.1, 42.9, 38.8, 38.2, 36.6, 36.1, 35.4, 29.4, 27.8, 25.4, 25.0, 24.9, 22.1, 18.6, 12.0 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{29}H_{45}BO_5$ $[M+H]^+$ 485.3433; found 485.3435.

$[\alpha]_D^{20}$ = +16.9 (c 0.62, $CHCl_3$).

Compound 39



39

(3*S*,4a*R*,6a*R*,6b*S*,8a*R*,11*S*,12a*R*,14a*R*,14b*S*)-4,4,6a,6b,8a,11,14b-heptamethyl-14-oxo-11-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,14,14a,14b-icosahydropicen-3-yl acetate (39)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (**S24**) and suspension A ($NiCl_2$•$6H_2O$/di-MeObipy in THF). Purification by flash column chromatography (silica gel, 1:12:3 EtOAc:hexanes:CH_2Cl_2) afforded **39** (82.0 mg, 69%, *d. r.* = 11.8:1).

Physical State: colorless film;

***R*$_f$** = 0.34 (silica gel, 1:5 EtOAc:hexanes);

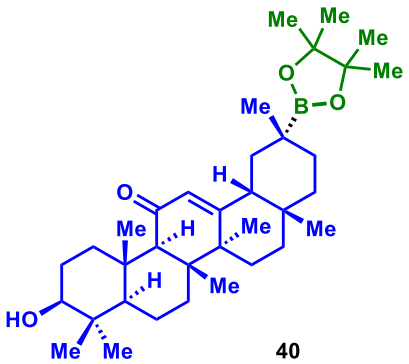
^{1}H NMR (600 MHz, $CDCl_3$): *Major isomer* δ 5.57 (s, 1H), 4.51 (dd, *J* = 11.8 Hz, 4.7 Hz, 1H), 2.79 (dt, *J* = 13.7 Hz, 3.6 Hz, 1H), 2.35 (s, 1H), 2.20 (ddd, *J* = 13.3 Hz, 4.4 Hz, 1.7 Hz, 1H), 2.12 (td, *J* = 13.7 Hz, 4.6 Hz, 1H), 2.04 (s, 3H), 1.96 (t, *J* = 13.6 Hz, 1H), 1.80 (td, *J* = 13.7 Hz, 4.6 Hz, 1H), 1.75 – 1.38 (m, 7H), 1.37 (s, 3H), 1.27 – 1.13 (m, 5H), 1.20 (d, *J* = 1.8 Hz, 12H), 1.15 (s, 3H), 1.12 (s, 3H), 1.02 (td, *J* = 13.5 Hz, 3.6 Hz, 1H), 0.99 (s, 3H), 0.94 (ddt, *J* = 13.7 Hz, 4.5 Hz, 2.2 Hz, 1H), 0.87 (s, 6H), 0.84 (s, 3H), 0.81 – 0.76 (m, 1H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): *Major isomer* δ 200.1, 171.14, 171.12, 128.3, 83.0, 80.8, 61.8, 55.2, 45.5, 45.3, 43.6, 38.9, 38.5, 38.2, 37.1, 34.2, 32.9, 32.7, 29.1, 28.2, 27.8, 26.7, 26.6, 24.8, 24.7, 23.7, 23.4, 21.5, 18.9, 17.7, 17.6, 16.8, 16.6 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{37}H_{60}BO_5$ $[M+H]^+$ 595.4528; found 595.4520;

$[\alpha]_D^{20}$ = +65.8 (c 1.0, $CHCl_3$).

Compound 40



40

(2*S*,4a*R*,6a*S*,6b*R*,8a*R*,10*S*,12a*S*,12b*R*,14b*R*)-10-hydroxy-2,4a,6a,6b,9,9,12a-heptamethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,14b-octadecahydropicen-13(2*H*)-one (40)

On 0.2 mmol scale, General Procedure C was followed with NHPI ester (**S39**) and suspension A ($NiCl_2$•$6H_2O$/di-MeObipy in THF). Purification by flash column chromatography (silica gel, first flash column chromatography: 1:5.7 to 1:4 EtOAc:hexanes; second flash column chromatography, 1:6:3 to 2:6:3 EtOAc:hexanes:CH_2Cl_2) afforded **40** (72.1 mg, 65%, *d.r.* = 11.3:1).

Physical State: colorless film;

***R*$_f$** = 0.46 (silica gel, 3:7 EtOAc:hexanes);

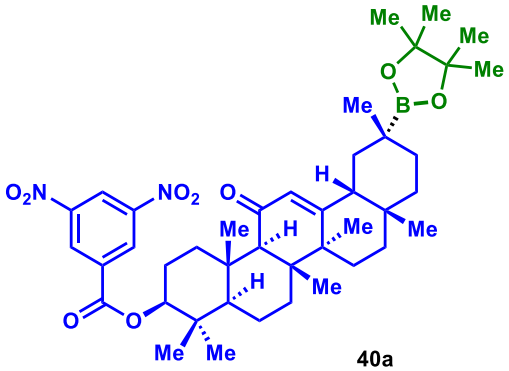
^{1}H NMR (600 MHz, $CDCl_3$): *Major isomer* δ 5.59 (s, 1H), 3.27 – 3.18 (m, 1H), 2.81 (dt, *J* = 13.5 Hz, 3.6 Hz, 1H), 2.36 (s, 1H), 2.22 (ddd, *J* = 13.5 Hz, 4.5 Hz, 1.7 Hz, 1H), 2.14 (td, *J* = 13.7 Hz, 4.6 Hz, 1H), 1.99 (t, *J* = 13.6 Hz, 1H), 1.83 (td, *J* = 13.7 Hz, 4.7 Hz, 1H), 1.74 – 1.58 (m, 4H), 1.55 (td, *J* = 13.8 Hz, 4.0 Hz, 1H), 1.51 – 1.35 (m, 2H), 1.41 (s, 3H), 1.33 – 1.15 (m, 7H), 1.22 (s, 6H), 1.22 (s, 6H), 1.15 (s, 3H), 1.15 (s, 3H), 1.02 (s, 3H), 1.01 (s, 3H), 1.00 – 0.94 (m, 1H), 0.86 (s, 3H), 0.82 (s, 3H), 0.71 (dd, *J* = 11.8 Hz, 1.9 Hz, 1H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): *Major isomer* δ 200.3, 171.1, 128.3, 83.0, 79.0, 61.9, 55.2, 45.5, 45.3, 43.6, 39.31, 39.27, 38.5, 37.2, 34.2, 33.0, 32.7, 29.1, 28.3, 27.8, 27.5, 26.7, 26.6, 24.8, 24.7, 23.5, 18.9, 17.7, 16.5, 15.7 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{35}H_{58}BO_4$ $[M+H]^+$ 553.4422; found 553.4423;

$[\alpha]_D^{20}$ = +73.4 (c 1.0, $CHCl_3$).

Compound 40a



40a

(3*S*,4a*R*,6a*R*,6b*S*,8a*R*,11*S*,12a*R*,14a*R*,14b*S*)-4,4,6a,6b,8a,11,14b-heptamethyl-14-oxo-11-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,14,14a,14b-icosahydropicen-3-yl 3,5-dinitrobenzoate (40a)

A culture tube charged with **40** (30 mg, 0.054 mmol, 1.0 equiv.), 3,5-dinitrobenzoyl chloride (50 mg, 0.22 mmol, 4.1 equiv.), and DMAP (1.3 mg, 0.011 mmol, 0.2 equiv.). CH_2Cl_2 (0.3 mL) and Et_3N (30 μL, 0.22 mmol, 4.1 equiv.) were added, and the resulting mixture was stirred for 1 h at room temperature. The mixture was loaded directly onto a silica gel column for purification by flash column chromatography (1:11 EtOAc: hexanes) to afford **40a** (39.0 mg, 96%, *d.r.* = 11.3:1). The pure product was crystallized from hexanes/CH_2Cl_2.

Physical State: pale yellow solid (major isomer is a white solid);

m.p. decompose at 295 °C;

R_f = 0.45 (silica gel, 1:5.7 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): *Major isomer* δ 9.22 (t, *J* = 2.2 Hz, 1H), 9.13 (d, *J* = 2.2 Hz, 2H), 5.60 (s, 1H), 4.88 (dd, *J* = 11.9 Hz, 4.7 Hz, 1H), 2.92 (dt, *J* = 13.7 Hz, 3.6 Hz, 1H), 2.40 (s, 1H), 2.26 – 2.19 (m, 1H), 2.13 (td, *J* = 13.7 Hz, 4.5 Hz, 1H), 1.98 (t, *J* = 13.6 Hz, 1H), 1.95 – 1.87 (m, 1H), 1.87 – 1.75 (m, 2H), 1.74 – 1.59 (m, 3H), 1.56 – 1.48 (m, 2H), 1.45 (dt, *J* = 12.8 Hz, 3.1 Hz, 1H), 1.40 (s, 3H), 1.30 – 1.09 (m, 5H), 1.23 (s, 3H), 1.21 (s, 6H), 1.21 (s, 6H), 1.16 (s, 3H), 1.08 (s, 3H), 1.00 (s, 3H), 0.97 (s, 3H),

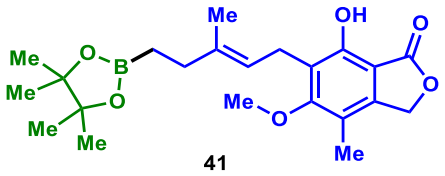
0.97 – 0.94 (m, 1H), 0.89 (dd, J = 11.8 Hz, 1.9 Hz, 1H), 0.86 (s, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): *Major isomer* δ 199.9, 171.4, 162.3, 148.8, 134.8, 129.5, 128.3, 122.4, 84.3, 83.1, 61.7, 55.3, 45.6, 45.3, 43.6, 38.9, 38.6, 38.5, 37.1, 34.2, 32.8, 32.7, 29.2, 28.5, 27.8, 26.7, 26.6, 24.8, 24.7, 23.8, 23.4, 18.9, 17.7, 17.6, 17.2, 16.6 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{42}H_{60}BN_2O_9$ $[M+H]^+$ 747.4386; found 747.4385;

$[\alpha]_D^{20}$ = +60.5 (c 1.0, $CHCl_3$).

Compound 41



41

(*E*)-7-hydroxy-5-methoxy-4-methyl-6-(3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-2-en-1-yl)isobenzofuran-1(3*H*)-one (41)

On 0.2 mmol scale, General Procedure B was followed with NHPI ester (**S25**) and solution B ($NiCl_2$•$6H_2O$/di-MeObipy in DMF). Purification by flash column chromatography (silica gel, hexanes to 1:6:6 EtOAc:hexanes:CH_2Cl_2) afforded **41** (37.0 mg, 46%).

Physical State: white solid;

m.p. = 122 – 124 °C;

***R*$_f$** = 0.40 (silica gel, 1:2 EtOAc:hexanes);

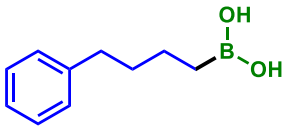
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.64 (s, 1H), 5.21 – 5.18 (m, 3H), 3.75 (s, 3H), 3.37 (d, J = 6.6 Hz, 2H), 2.13 (s, 3H), 2.08 (t, J = 7.8 Hz, 2H), 1.77 (s, 3H), 1.17 (s, 12H), 0.86 (t, J = 7.8 Hz, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 173.1, 163.9, 153.8, 143.9, 137.8, 122.8, 120.6, 116.8, 106.4, 83.0, 70.1, 61.1, 33.6, 24.9, 22.7, 16.3, 11.7 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{22}H_{32}BO_6$ $[M+H]^+$ 403.2286; found 403.2289.

Experimental Procedure and Characterization Data for Boronic Acids

Compound 4a



4a

(4-phenylbutyl)boronic acid (4a)

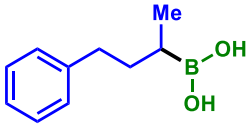
Pinacol boronate ester **4** (70 mg, 0.27 mmol) was dissolved in CH_2Cl_2 (5 mL) under argon and the solution was cooled to −78 °C in a dry ice/acetone bath. BCl_3 (0.81 mL, 1.0 M in CH_2Cl_2, 3.0 equiv.) was added dropwise, after which the mixture was stirred for 1 h at −78 °C. The mixture was then allowed to warm up to room temperature, and the volatiles were removed *in vacuo*. Anhydrous methanol (5 mL) was added and the resulting mixture was stirred for 10 minutes when methanol was removed *in vacuo*. An additional portion of methanol (5 mL) was added; the mixture was stirred for 10 minutes before it was concentrated *in vacuo*. This process was repeated for another three times. The resulting crude product was then purified with preparative TLC to afford **4a** as a white solid (41.8 mg, 87%).

^{1}H NMR (600 MHz, DMSO-d_6/D_2O 100/1): δ 7.28 – 7.22 (m, 2H), 7.15 (ddt, J = 13.9 Hz, 6.9 Hz, 1.5 Hz, 3H), 2.56 – 2.51 (m, 2H), 1.51 (tt, J = 7.8, 6.7 Hz, 2H), 1.38 – 1.28 (m, 2H), 0.60 (t, J = 7.9 Hz, 2H);

^{13}C NMR (151 MHz, DMSO-d_6/D_2O 100/1): δ 142.6, 128.3, 128.3, 125.6, 35.3, 34.2, 24.0, 15.3 (br);

HRMS (ESI-TOF) Calcd for $C_{10}H_{16}BO_2$ $[M+H]^+$ 179.1238; found 179.1236.

Compound 3a



3a

(4-phenylbutan-2-yl)boronic acid (3a)

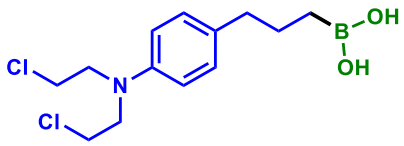
Pinacol boronate ester **3** (30 mg, 0.12 mmol) was dissolved in CH_2Cl_2 (2 mL) under argon and the solution was cooled to −78 °C in a dry ice/acetone bath. BCl_3 (0.36 mL, 1.0 M in CH_2Cl_2, 3.0 equiv.) was added dropwise, after which the mixture was stirred for 1 h at −78 °C. The mixture was then allowed to warm up to room temperature, and the volatiles were removed *in vacuo*. Anhydrous methanol (5 mL) was added and the resulting mixture was stirred for 10 minutes before methanol was removed *in vacuo*. An additional portion of methanol (5 mL) was added; the mixture was stirred for 10 minutes before it was concentrated *in vacuo*. This process was repeated for another three times. The resulting crude product was then purified with preparative TLC to afford **4a** as a white solid (15.4 mg, 75%).

^{1}H NMR (600 MHz, DMSO-*d*$_6$/D$_2$O 100/1): δ 7.24 (t, *J* = 7.6 Hz, 2H), 7.18 – 7.10 (m, 3H), 2.53 – 2.48 (m, 2H), 1.74 – 1.63 (m, 1H), 1.42 (ddt, *J* = 13.0 Hz, 9.9 Hz, 6.5 Hz, 1H), 0.90 (d, *J* = 7.2 Hz, 3H), 0.89 – 0.81 (m, 1H) ppm;

^{13}C NMR (151 MHz, DMSO-*d*$_6$/D$_2$O 100/1): δ 143.0, 128.3, 125.6, 35.7, 35.1, 20.3 (br), 16.4 ppm;

HRMS (ESI-TOF) Calcd for $C_{10}H_{16}BO_2$ $[M+H]^+$ 179.1238; found 179.1232.

Compound 33a



33a

(3-(4-(bis(2-chloroethyl)amino)phenyl)propyl)boronic acid (33a)

Pinacol boronate ester **33** (76.2 mg, 0.2 mmol) was dissolved in CH_2Cl_2 (1 mL) under argon and the solution was cooled to −78 °C in a dry ice/acetone bath. BCl_3 (0.79 mL, 1.0 M in CH_2Cl_2, 4.0 equiv.) was added dropwise, after which the mixture was stirred for 1 h at −78 °C. The mixture was then allowed to warm up to room temperature, and the volatiles were removed *in vacuo*. Anhydrous methanol (2 mL) was added and the resulting mixture was stirred for 10 minutes when methanol was removed *in vacuo*. An additional portion of methanol (2 mL) was added; the mixture was stirred for 10 minutes before it was concentrated *in vacuo*. This process was repeated for another three times. Purification of the resulting residue by preparative reverse-phase HPLC (20 – 80% CH_3CN/H_2O over 30 min, both CH_3CN and H_2O containing 0.1% TFA) afforded **33a** (27 mg, 50%) as a colorless oil.

^{1}H NMR (600 MHz, DMSO-*d*$_6$/D$_2$O 10/1): δ 7.00 (d, *J* = 12.6 Hz, 2H), 6.65 (d, *J* = 12.6 Hz, 2H), 3.71 – 3.65 (m, 8H), 2.39 (t, *J* = 7.8 Hz, 2H), 1.58 – 1.53 (m, 2H), 0.59 (t, *J* = 8.4 Hz, 2H) ppm;

^{13}C NMR (151 MHz, DMSO-*d*$_6$/D$_2$O 10/1): δ 144.2, 130.9, 129.3, 111.8, 52.3, 41.2, 37.2, 26.6 ppm;

HRMS (ESI-TOF) Calcd for $C_{13}H_{21}BCl_2NO_2$ $[M+H]^+$ 304.1037; found 304.1030.

Synthesis of Ixazomib (Ninlaro)

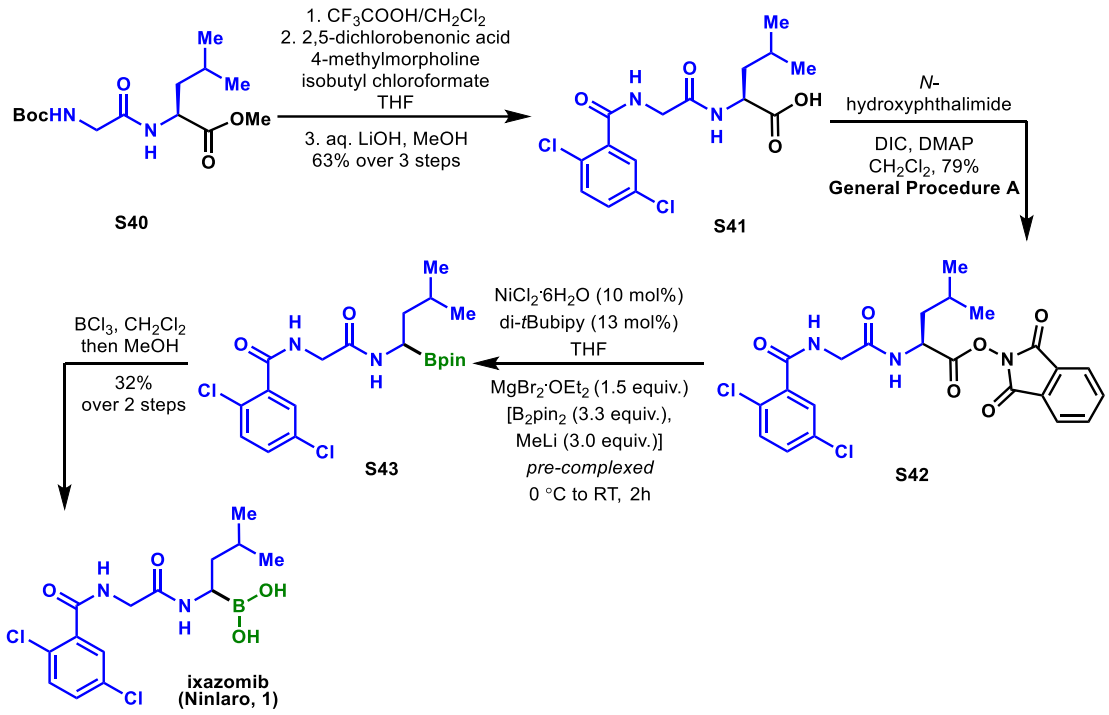
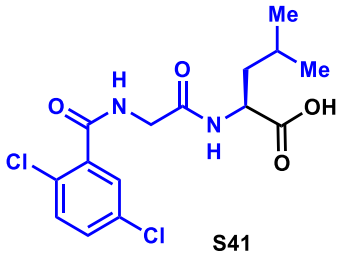


Figure S33. Synthesis of ixazomib (Ninlaro).

Compound S41



(2,5-dichlorobenzoyl)glycylleucine (S41)

Removal of Boc: To a solution of Boc-Gly-Leu-OMe (*61*) (**S40**, 3.1 g, 10.36 mmol) in CH_2Cl_2 (30 mL) was added TFA (15 mL) at room temperature, the reaction mixture was stirred for 1 h before concentration *in vacuo*. The residue was used directly in the next step.

Amide bond formation: To a solution 2,5-dichlorobenonic acid (2.94 g, 15.4 mmol) in THF (70 mL) was added 4-methylmorpholine (4.0 mL, 35.9 mmol) at –15 °C, the reaction mixture was stirred for 10 min at that temperature. To the resulting white

suspension was added isobutyl chloroformate (2.0 mL, 15.4 mmol) dropwise and the mixture was stirred for another 30 min at –15 °C. The crude TFA salt (from the deprotection step) in THF (35 mL) was added slowly at the same temperature. The reaction mixture was warmed up to room temperature and stirred for 6 h. The resulting mixture was diluted with EtOAc (100 mL), washed with water (100 mL), sat. aqueous $NaHCO_3$ (100 mL), and brine (100 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (silica, 3:2 Hexane/EtOAc) afforded the desired ester which was directly used in next step without further purification.

Hydrolysis of methyl ester: To a solution of the aforementioned ester in THF (50 mL) was added aqueous LiOH (1 M, 50 mL). The reaction mixture was stirred at room temperature for 2 h and was then washed with EtOAc (60 mL). The aqueous layer was acidified with 1 N HCl (65 mL) and extracted with EtOAc (100 mL). The organic layer was washed with brine (100 mL) whereby the aqueous layers were back-extracted with EtOAc (100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. To the residue was added CH_2Cl_2 (30 mL) when the desired product **S41** precipitated out and was collected by filtration (2.31 g, 63% over 3 steps).

m.p. = 137 – 138 °C;

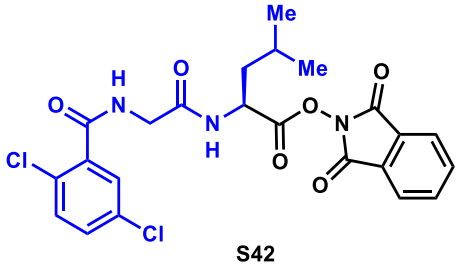
^{1}H NMR (600 MHz, MeOH-*d*$_4$): δ 7.63 (dd, *J* = 1.8 Hz, 0.6 Hz, 1H), 7.45 – 7.48 (m, 2H), 4.50 (dd, *J* = 9.6 Hz, 5.4 Hz, 1H), 4.08 (dd, *J* = 37.8 Hz, 16.8 Hz, 2H), 1.79 – 1.72 (m, 1H), 1.70 – 1.62 (m, 2H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H) ppm;

^{13}C NMR (151 MHz, MeOH-*d*$_4$): δ 175.8, 170.9, 168.7, 138.4, 134.0, 132.6, 132.3, 130.6, 130.2, 52.1, 43.6, 41.9, 26.0, 23.4, 21.9 ppm;

HRMS (ESI-TOF) Calcd for $C_{15}H_{19}Cl_2N_2O_4$ $[M+H]^+$ 361.0716; found 361.0706;

$[\alpha]_D^{20}$ = −14.0 (c 1.0, MeOH).

Compound S42



S42

1,3-dioxoisoindolin-2-yl (2,5-dichlorobenzoyl)glycylleucinate (S42)

On 2.0 mmol scale, General Procedure A was followed with **S37**. Purification by flash column chromatography (deactivated silica gel, 3:7 EtOAc:hexanes) afforded **S42** (940 mg, 79%).

Physical state: white solid;

m.p. = 164 °C;

R_f = 0.55 (silica gel, 3:2 EtOAc:hexanes);

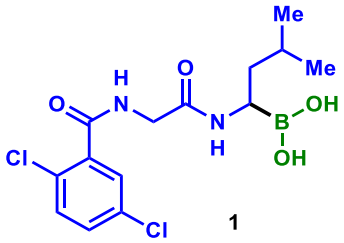
^{1}H NMR (600 MHz, THF-*d*$_8$): δ 8.05 (br s, 1H), 7.99 – 7.97 (m, 1H), 7.91 – 7.89 (m, 2H), 7.87 – 7.85 (m, 2H), 7.58 (dd, *J* = 2.4 Hz, 0.5 Hz, 1H), 7.42 – 7.38 (m, 2H), 5.10 – 5.06 (m, 1H), 4.14 (dd, *J* = 16.8 Hz, 6.0 Hz, 1H), 3.99 (dd, *J* = 16.8 Hz, 6.0 Hz, 1H), 1.92 – 1.83 (m, 2H), 1.80 – 1.75 (m, 1H), 1.02 (d, *J* = 6.0 Hz, 3H), 1.00 (d, *J* = 6.0 Hz, 3H) ppm;

^{13}C NMR (151 MHz, THF-*d*$_8$): δ 170.5, 169.4, 166.0, 162.4, 139.2, 135.9, 133.5, 132.3, 131.5, 130.7, 130.5, 130.2, 124.7, 49.7, 43.6, 42.3, 25.8, 23.4, 22.1 ppm;

HRMS (ESI-TOF) Calcd for $C_{23}H_{22}Cl_2N_3O_6$ $[M+H]^+$ 506.0880; found 506.0875;

$[\alpha]_D^{20}$ = −1.0 (c 1.0, THF).

Compound 1



1

On 0.2 mmol scale, General Procedure C was followed using suspension C ($NiCl_2$•$6H_2O$/di-*t*Bubipy in THF) with **S42**. Flash column chromatography (silica gel, hexanes to 2:3 EtOAc:hexanes to 4:1 EtOAc:hexanes) afforded pinacol aminoboronate ester **S43** which was directly used in the next step without further purification.

The pinacol aminoboronate ester **S43** was dissolved in CH_2Cl_2 (5 mL) under argon and the solution was cooled to −78 °C in a dry ice/acetone bath. BCl_3 (0.6 mL, 1.0 M in CH_2Cl_2, 3.0 equiv.) was added dropwise, after which the mixture was stirred for 1 h at −78 °C. The mixture was then allowed to warm up to room temperature, and the volatiles were removed *in vacuo*. Anhydrous methanol (5 mL) was added and the mixture was stirred for 10 minutes when the methanol was removed *in vacuo*. An additional portion of methanol (5 mL) was added; the mixture was stirred for 10 minutes before it was concentrated *in vacuo*. This process was repeated for another three times. The resulting residue was then purified by preparative reverse-phase HPLC (10 – 60% CH_3CN/H_2O over 35 min, both CH_3CN and H_2O containing 0.1% TFA) to afford ixazomib (Ninlaro) (**1**, 23.0 mg, 32% over 2 steps).

^{1}H NMR (600 MHz, MeOH-*d*$_4$): δ 7.60 (br t, *J* = 1.5 Hz, 1H), 7.49 – 7.47 (m, 2H), 4.24 (s, 2H), 2.79 (t, *J* = 7.6 Hz, 1H), 1.68 (ddt, *J* = 14.7 Hz, 13.0 Hz, 6.4 Hz, 1H), 1.38 (tdd, *J* = 13.8 Hz, 10.4 Hz, 5.9 Hz, 2H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H);

^{13}C NMR (151 MHz, MeOH-*d*$_4$): δ 175.6, 168.8, 138.0, 134.0, 132.7, 132.5, 130.7, 130.2, 44.7 (br, α to boron), 40.9, 40.2, 27.1, 23.7, 22.4.

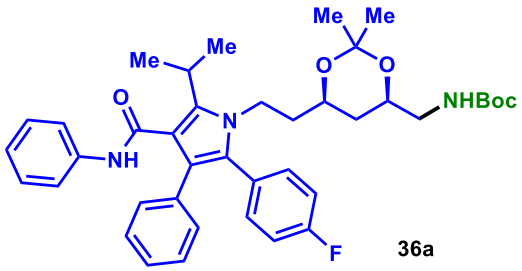
HRMS (ESI-TOF, *m/z*): Calcd for $C_{14}H_{18}BCl_2N_2O_3$ $[M-H_2O+H]^+$ 343.0782; found

343.0779;

[α]D^{20} = −0.6 (c 1.0, MeOH).

Decarboxylative Borylation Enabled Late-stage Diversification of Lipitor

Compound 36a



36a

***tert*-butyl (((4*R*,6*R*)-6-(2-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)carbamate (36a)**

A solution of *O*-methylhydroxylamine (63 μL, 2.8 M in THF, 6.0 equiv.) was diluted with THF (1 mL). *n*BuLi (72 μL, 2.45 M in hexanes, 6.0 equiv.) was added at –78 °C, and the resulting mixture was stirred for 1 h at that temperature. A solution of pinacol boronate **36** (20 mg, 0.03 mmol, 1.0 equiv.) in THF (1 mL) was added dropwise at –78 °C. After warming up to room temperature, the reaction mixture was heated to 65 °C and stirred for 36 h. Upon cooling to room temperature, Boc_2O (66 mg, 10.0 equiv.) was added. The resulting mixture was stirred at room temperature for 1 h before the volatiles were removed *in vacuo*. Purification of the resulting residue by preparative TLC (silica gel, 15:1 CH_2Cl_2:Et_2O) afforded **36a** (10.7 mg, 54%) as colorless oil.

Physical state: colorless oil;

R_f = 0.40 (silica gel, 3:1 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24 – 7.09 (m, 9H), 7.07 (d, *J* = 8.0 Hz, 2H), 7.04 – 6.94 (m, 3H), 6.86 (s, 1H), 4.84 (s, 1H), 4.07 (ddd, *J* = 15.3 Hz, 10.7 Hz, 5.1 Hz, 1H), 3.82 (ddt, *J* = 15.1 Hz, 10.3 Hz, 6.5 Hz, 2H), 3.66 (tt, *J* = 8.2 Hz, 3.6 Hz, 1H), 3.57 (p, *J* = 7.2 Hz, 1H), 3.24 (d, *J* = 8.7 Hz, 1H), 2.98 (ddd, *J* = 13.8 Hz, 6.8 Hz, 5.1 Hz, 1H), 1.70-1.63 (m, 2H), 1.53 (d, *J* = 7.1 Hz, 6H), 1.44 (s, 9H), 1.34 (s, 3H), 1.31 (s, 3H), 1.27 – 1.20 (m, 1H), 1.07 (q, *J* = 12.0 Hz, 1H) ppm;

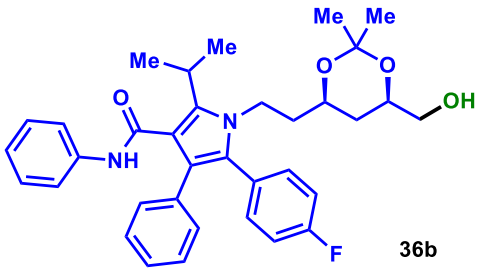
^{13}C NMR (151 MHz, $CDCl_3$): δ 164.9, 162.4 (d, *J* = 247.9 Hz), 156.2, 141.6, 138.5, 134.8, 133.3 (d, *J* = 8.1 Hz), 130.6, 128.9, 128.8, 128.5, 128.4 (d, *J* = 3.5 Hz), 126.7, 123.6, 121.9, 119.7, 115.5 (d, *J* = 21.3 Hz), 98.8, 79.6, 68.2, 66.3, 45.4, 41.0, 38.3, 33.4, 30.5, 30.0, 28.5, 26.2, 21.9, 21.7, 20.0 ppm;

^{19}F NMR (376 MHz, $CDCl_3$): δ −113.9 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{40}H_{49}FN_3O_5$ $[M+H]^+$ 670.3651; found 670.3646;

$[\alpha]_D^{20}$ = −2.0 (c 0.74, $CHCl_3$).

Compound 36b



36b

5-(4-fluorophenyl)-1-(2-((4*R*,6*R*)-6-(hydroxymethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (36b)

To a solution of **36** (50 mg, 0.073 mmol, 1.0 equiv.) in THF/H_2O (1:1, 0.73 mL) at room temperature open to air was added $NaBO_3 \cdot 4H_2O$ (56 mg, 0.37 mmol, 5.1 equiv.). The mixture was stirred vigorously for 3 h before H_2O (10 mL) was added. The resulting mixture was extracted with EtOAc (10 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, 2:3 EtOAc:hexanes) afforded **36b** (40 mg, 86%).

m.p. = 166 – 170 °C;

***R*$_f$ =** 0.27 (silica gel, 2:3 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.21 – 7.15 (m, 9H), 7.07 (d, *J* = 8.0 Hz, 2H), 7.02 – 6.96 (m, 3H), 6.86 (s, 1H), 4.13 – 4.05 (m, 1H), 3.92 – 3.81 (m, 2H), 3.73 – 3.66 (m,

1H), 3.61 – 3.52 (m, 2H), 3.45 (dd, *J* = 11.4 Hz, 6.1 Hz, 1H), 1.74 – 1.61 (m, 2H), 1.54 (s, 3H), 1.53 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H), 1.74 – 1.61 (m, 2H) ppm;

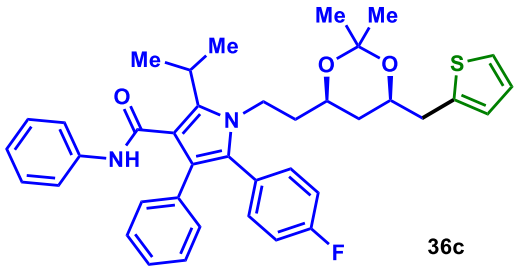
^{13}C NMR (151 MHz, $CDCl_3$): δ 164.9, 162.4 (d, *J* = 247.6 Hz), 141.7, 138.5, 134.8, 133.3 (d, *J* = 8.0 Hz), 130.6, 128.9, 128.8, 128.5, 128.4 (d, *J* = 3.5 Hz), 126.7, 123.6, 121.9, 119.7, 115.5 (d, *J* = 21.4 Hz), 98.9, 69.4, 66.2, 66.0, 41.0, 38.3, 31.9, 30.0, 26.2, 21.9, 21.7, 20.0 ppm;

^{19}F NMR (376 MHz, acetone-d_6): δ −114.0 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{35}H_{40}FN_2O_4$ $[M+H]^+$ 571.2966; found 571.2963;

$[\alpha]_D^{20}$ = −4.6 (c 1.0, $CHCl_3$).

Compound 36c



36c

1-(2-((4*R*,6*R*)-2,2-dimethyl-6-(thiophen-2-ylmethyl)-1,3-dioxan-4-yl)ethyl)-5-(4-fluorophenyl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (36c)

To a solution of thiophene (23 μL, 0.29 mmol) in THF (1.0 mL) was added *n*BuLi (0.1 mL, 2.5 M in hexanes, 0.25 mmol) at –78 °C. The resulting mixture was warmed to room temperature and stirred for 1 h when 0.33 mL (4.1 equiv.) of the resulting yellow solution was transferred to a reaction tube. A solution of **36** (12.4 mg, 0.018 mmol, 1.0 equiv.) in THF (0.3 mL) was added dropwise at –78 °C. The resulting mixture was stirred at the same temperature for 1.5 h when a solution of *N*-bromosuccinimide (14.4 mg, 0.081 mmol, 4.5 equiv.) in THF (0.3 mL) was added. After stirring for 1 h at the same temperature, the reaction was quenched with sat. aqueous $Na_2S_2O_3$ (1 mL) before warming up to room temperature. The resulting mixture was extracted with EtOAc (1 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and

concentrated *in vacuo*. Purification by flash column chromatography (silica gel, 1:9 EtOAc:hexanes) followed by preparative TLC (silica gel, 1:6 EtOAc:hexanes) afforded **36c** (6.5 mg, 56%).

Physical state: white foam;

R_f = 0.61 (silica gel, 2:3 EtOAc:hexanes);

^{1}H NMR (600 MHz, acetone-*d*$_6$): δ 8.29 (br s, 1H), 7.45 (d, *J* =7.8 Hz, 2H), 7.30 – 7.27 (m, 2H), 7.24 (dd, *J* = 5.4 Hz, 1.2 Hz, 1H), 7.20 (t, *J* = 7.8 Hz, 2H), 7.13 – 7.09 (m, 6H), 7.08 – 7.05 (m, 1H), 6.99 – 6.96 (m, 1H), 6.92 (dd, *J* = 5.4 Hz, 3.6 Hz, 1H), 6.85 – 6.84 (m, 1H), 4.11 – 4.06 (m, 1H), 4.05 – 4.00 (m, 1H), 3.91 – 3.86 (m, 1H), 3.85 – 3.81 (m, 1H), 3.43 – 3.39 (m, 1H), 2.93 – 2.90 (m, 1H), 2.87 – 2.83 (m, 1H), 1.75 – 1.63 (m, 2H), 1.47 (d, *J* = 1.2 Hz, 3H), 1.45 (d, *J* = 1.2 Hz, 3H), 1.36 (dt, *J* = 12.6 Hz, 3.0 Hz, 1H), 1.36 (s, 3H), 1.28 (s, 3H) 1.05 – 0.99 (m, 1H) ppm;

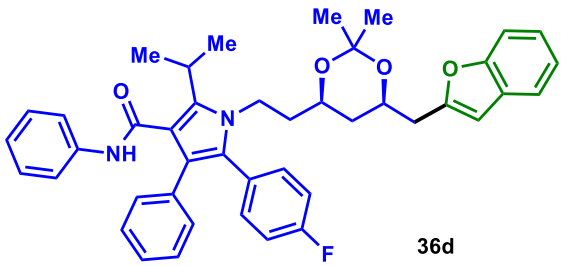
^{13}C NMR (151 MHz, acetone-*d*$_6$): δ 166.4, 163.1 (d, *J* = 245.6 Hz), 140.9, 140.6, 139.4, 136.1, 134.5 (d, *J* = 8.2 Hz), 130.8, 129.9 (d, *J* = 3.3 Hz), 129.3, 128.9, 128.6, 127.3, 126.70, 126.65, 124.9, 123.8, 122.4, 120.2, 118.0, 116.0 (d, *J* = 21.6 Hz), 99.2, 70.2, 67.3, 41.3, 39.1, 37.3, 36.5, 30.5, 26.9 22.4, 22.3, 20.1 ppm;

^{19}F NMR (376 MHz, acetone-*d*$_6$): δ −114.9 ppm;

HRMS (ESI-TOF) Calcd for $C_{39}H_{42}FN_2O_3S$ $[M+H]^+$ 637.2895; found 637.2892;

$[\alpha]_D^{20}$ = + 19.2 (c 0.5, $CHCl_3$).

Compound 36d



36d

1-(2-((4*R*,6*R*)-6-(benzofuran-2-ylmethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-5-(4-fluorophenyl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (36d)

To a solution of 2,3-benzofuran (30 μL, 0.27 mmol) in THF (1.0 mL) was added *n*BuLi (0.1 mL, 2.5 M in hexanes, 0.25 mmol) at –78 °C. The resulting mixture was warmed to room temperature and stirred for 1 h when 0.33 mL (4.1 equiv.) of the resulting yellow solution was transferred to a reaction tube. A solution of **36** (12.0 mg, 0.018 mmol, 1.0 equiv.) in THF (0.3 mL) was added dropwise at –78 °C. The resulting mixture was stirred at the same temperature for 1 h when a solution of *N*-bromosuccinimide (14.4 mg, 0.081 mmol, 4.5 equiv.) in THF (0.3 mL) was added. After stirring for 1 h at the same temperature, the reaction was quenched with sat. aqueous $Na_2S_2O_3$ (1 mL) before warming up to room temperature. The resulting mixture was extracted with EtOAc (1 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, 1:9 EtOAc:hexanes) followed by preparative TLC (silica gel, 1:9 EtOAc:hexanes) afforded **36d** (6.1 mg, 52%).

Physical state: colorless oil;

R_f = 0.64 (silica gel, 2:3 EtOAc:hexanes);

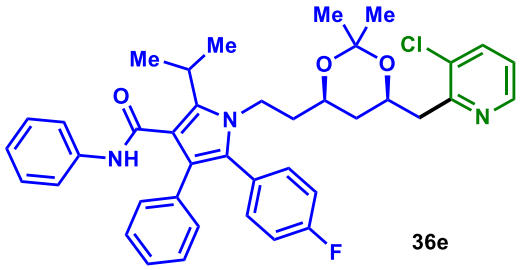
^{1}H NMR (600 MHz, acetone-d_6): δ 8.29 (br s, 1H), 7.54 – 7.52 (m, 1H), 7.44 (d, *J* = 7.8 Hz, 2H), 7.45 – 7.42 (m, 1H), 7.31 – 7.27 (m, 2H), 7.24 – 7.17 (m, 4H), 7.13 – 7.05 (m, 7H), 6.99 – 6.96 (m, 1H), 6.58 (dd, *J* = 1.2 Hz, 0.6 Hz, 1H), 4.29 – 4.24 (m, 1H), 4.11 – 4.06 (m, 1H), 3.91 – 3.85 (m, 2H), 3.44 – 3.37 (m, 1H), 2.93 (dd, *J* = 15.6 Hz, 6.6 Hz, 1H), 2.79 (dd, *J* = 15.6 Hz, 6.6 Hz, 1H), 1.76 – 1.65 (m, 2H), 1.46 (s, 3H), 1.45 (s, 3H), 1.51 – 1.46 (m, 1H), 1.39 (d, *J* = 0.6 Hz, 3H), 1.27 (d, *J* = 0.6 Hz, 3H), 1.14 – 1.08 (m, 1H) ppm;

^{13}C NMR (151 MHz, acetone-d_6): δ 166.4, 163.1 (d, *J* = 245.7 Hz), 156.5, 155.5, 140.6, 139.4, 136.1, 134.5 (d, *J* = 8.3 Hz), 130.8, 129.9 (d, *J* = 3.3 Hz), 129.9, 129.3, 128.9, 128.6, 126.7, 124.2, 123.8, 123.4, 122.4, 121.3, 120.2, 120.1, 118.0, 116.0 (d, *J* = 21.6 Hz), 111.4, 104.6, 99.3, 68.1, 67.3, 41.3, 39.1, 37.0, 36.2, 30.4, 26.9, 22.4, 22.3, 20.1 ppm;

^{19}F NMR (376 MHz, acetone-d_6): δ −115.0 ppm;

HRMS (ESI-TOF) Calcd for $C_{43}H_{44}FN_2O_4$ $[M+H]^+$ 671.3280; found 671.3274; $[\alpha]_D^{20}$ = +28.5 (c 0.5, $CHCl_3$).

Compound 36e



36e

1-(2-((4*R*,6*S*)-6-((3-chloropyridin-2-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-5-(4-fluorophenyl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (36e)

To a screw-capped culture tube was added $Pd_2(dba)_3$ (1.9 mg, 0.0022 mmol, 0.1 equiv.), *p*-anisyldiphenylphosphine (3.7 mg, 0.0132 mmol, 0.6 equiv.), 2,3-dichloropyridine (32.6 mg, 0.22 mmol, 10 equiv.), and K_3PO_4 (47 mg, 0.22 mmol, 10 equiv.). This tube was then evacuated and backfilled with argon for three times. 1,4-dioxane (0.4 mL) was then added via a syringe and the resulting mixture was stirred at room temperature for 5 minutes. A deoxygenated solution of **36** (15.0 mg, 0.022 mmol, 1.0 equiv.) in dioxane (0.6 mL) was added followed by degassed deionic water (0.5 mL). The reaction mixture was heated at 100 °C for 15 h, after which it was cooled to room temperature and treated with brine (4 mL). The resulting mixture was extracted with EtOAc (2 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, 1:6 to 3:7 EtOAc:hexanes) and preparative TLC (silica gel, 1:3 EtOAc:hexanes) afforded **36e** (7.9 mg, 54%).

Physical state: colorless oil;

$\mathbf{R_f}$ = 0.38 (silica gel, 3:7 EtOAc:hexanes);

^{1}H NMR (600 MHz, acetone-d_6): δ 8.45 (dd, *J* = 4.8 Hz, 1.8 Hz, 1H), 8.30 (br s, 1H), 7.79 (dd, *J* = 8.4 Hz, 1.8 Hz, 1H), 7.45 (d, *J* = 7.8 Hz, 2H), 7.30 – 7.25 (m, 3H), 7.20

(t, *J* = 7.8 Hz, 2H), 7.12 – 7.05 (m, 7H), 6.99 – 6.96 (m, 1H), 4.46 – 4.41 (m, 1H), 4.11 – 4.06 (m, 1H), 3.91 – 3.86 (m, 1H), 3.85 – 3.81 (m, 1H), 3.44 – 3.39 (m, 1H), 3.13 (dd, *J* = 14.4 Hz, 6.6 Hz, 1H), 2.88 (dd, *J* = 14.4 Hz, 7.2 Hz, 1H), 1.76 – 1.64 (m, 2H), 1.47 (d, *J* = 0.6 Hz, 3H), 1.45 (d, *J* = 0.6 Hz, 3H), 1.38 (dt, *J* = 12.6 Hz, 2.4 Hz, 1H), 1.34 (s, 3H), 1.24 (s, 3H), 1.16 – 1.10 (m, 1H) ppm;

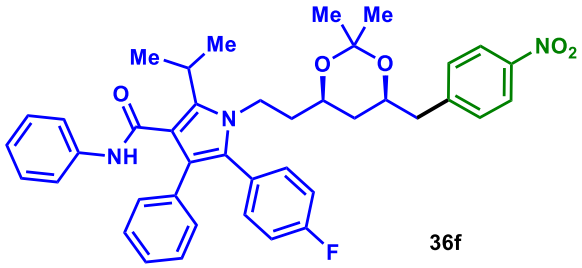
^{13}C NMR (151 MHz, acetone-*d*$_6$): δ 166.4, 163.1 (d, *J* = 245.5 Hz), 156.2, 148.3, 140.6, 139.3, 137.6, 136.2, 134.5 (d, *J* = 8.3 Hz), 132.2, 130.8, 129.9 (d, *J* = 3.3 Hz), 129.3, 128.9, 128.6, 126.7, 123.8, 123.8, 122.4, 120.2, 118.0, 116.0 (d, *J* = 21.6 Hz), 99.2, 68.7, 67.3, 42.3, 41.3, 39.2, 37.0, 30.5, 26.9, 22.4, 22.3, 20.1 ppm;

^{19}F NMR (376 MHz, acetone-*d*$_6$): δ −114.9 ppm;

HRMS (ESI-TOF) Calcd for $C_{40}H_{42}ClFN_3O_3$ $[M+H]^+$ 666.2893; found 666.2884;

$[\alpha]_D^{20}$ = +26.2 (c 0.5, $CHCl_3$).

Compound 36f



36f

1-(2-((4*R*,6*S*)-2,2-dimethyl-6-(4-nitrobenzyl)-1,3-dioxan-4-yl)ethyl)-5-(4-fluorophenyl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (36f)

To a screw-capped culture tube was added $Pd_2(dba)_3$ (1.9 mg, 0.0022 mmol, 0.1 equiv.), *p*-anisyldiphenylphosphine (3.7 mg, 0.0132 mmol, 0.6 equiv.), 1-chloro-4-nitrobenzene (35 mg, 0.22 mmol, 10 equiv.), and K_3PO_4 (47 mg, 0.22 mmol, 10 equiv.). This tube was evacuated and backfilled with argon for three times. 1,4-dioxane (0.4 mL) was added via a syringe and the resulting mixture was stirred at room temperature for 5 minutes. A deoxygenated solution of **36** (15.0 mg, 0.022 mmol, 1.0 equiv.) in dioxane (0.6 mL) was added followed by degassed deionic water (0.5 mL). The reaction mixture

was heated to 100 °C for 15 h after which it was cooled to room temperature and treated with brine (4 mL). The resulting mixture was extracted with EtOAc (2 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, 1:9 to 1:3 EtOAc:hexanes) followed by preparative TLC (silica gel, 1:4 EtOAc:hexanes) afforded **36f** (10.5 mg, 72%).

Physical state: yellow oil;

R_f = 0.45 (silica gel, 3:7 EtOAc:hexanes);

^{1}H NMR (600 MHz, acetone-d_6): δ 8.28 (br s, 1H), 8.15 (dt, *J* = 9.0 Hz, 1.8 Hz, 2H), 7.51 (dt, *J* = 9.0 Hz, 1.8 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.30 – 7.27 (m, 2H), 7.20 (t, *J* = 7.8 Hz, 2H), 7.14 – 7.10 (m, 6H), 7.09 – 7.05 (m, 1H), 6.99 – 6.96 (m, 1H), 4.17 – 4.13 (m, 1H), 4.11 – 4.06 (m,1H), 3.92 – 3.87 (m, 1H), 3.85 – 3.81 (m, 1H), 3.44 – 3.37 (m, 1H), 2.87 (dd, *J* = 13.8 Hz, 7.2 Hz, 1H), 2.81 (dd, *J* = 13.8 Hz, 7.2 Hz, 1H), 1.73 – 1.65 (m, 2H), 1.46 (d, *J* = 0.6 Hz, 3H), 1.45 (d, *J* = 0.6 Hz, 3H), 1.36 (dt, *J* = 12.6 Hz, 2.4 Hz, 1H), 1.32 (s, 3H), 1.25 (s, 3H), 1.09 – 1.03 (m, 1H) ppm;

^{13}C NMR (151 MHz, acetone-d_6): δ 166.4, 163.1 (d, *J* = 245.5 Hz), 147.6, 147.5, 140.5, 139.4, 136.1, 134.5 (d, *J* = 8.3 Hz), 131.4, 130.8, 129.9 (d, *J* = 3.8 Hz), 129.3, 128.9, 128.7, 126.7, 123.9, 123.8, 122.4, 120.2, 118.0, 116.0 (d, *J* = 21.4 Hz), 99.2, 69.8, 67.3, 42.9, 41.2, 39.1, 36.7, 30.4, 26.9, 22.4, 22.3, 20.1 ppm;

^{19}F NMR (376 MHz, acetone-d_6): δ −114.9 ppm;

HRMS (ESI-TOF) Calcd for $C_{41}H_{43}FN_3O_5$ $[M+H]^+$ 676.3181; found 676.3182;

$[\alpha]_D^{20}$ = + 10.8 (c 0.5, $CHCl_3$).

Synthesis of Borono-vancomycin Analog

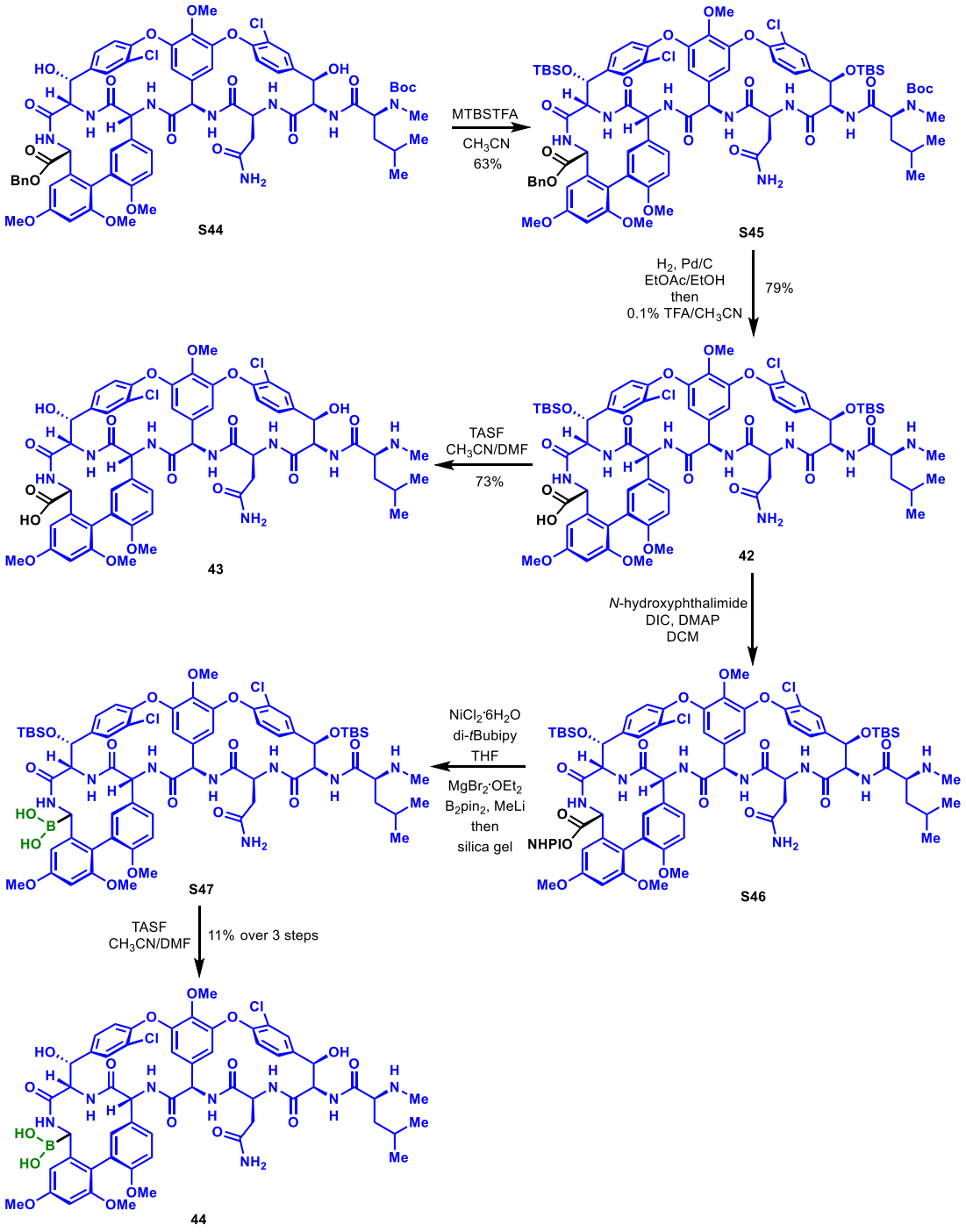
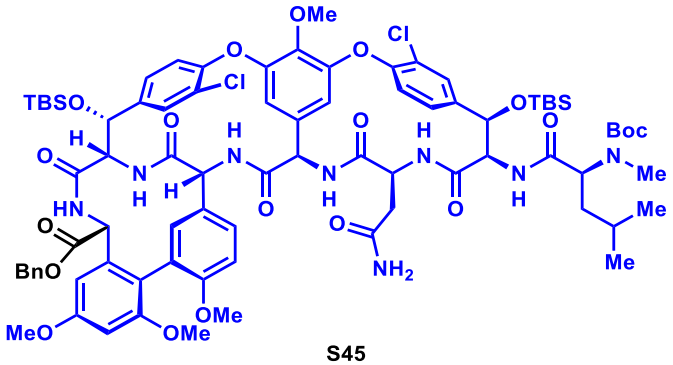


Figure S34. Synthesis of **42**, **43** and **44**.

Compound S45



S45

To **S44** [synthesized according to literature report (*38*, *62*)] **(**600 mg, 0.43 mmol, 1.0 equiv.) in CH_3CN (5.1 mL) was added *N*-*tert*-butyldimethylsilyl-*N*-methyltrifluoroacetamide (MTBSTFA, 2.4 mL, 10.2 mmol, 23.7 equiv.), the resulting mixture was heated to 50 °C. After 30 h, the reaction mixture was poured onto a mixture of sat. aqueous citric acid (50 mL)/EtOAc (20 mL) and stirred vigorously at room temperature for 12 h. The organic layer was separated and washed with sat. aqueous $NaHCO_3$ (50 mL) and brine (50 mL). The aqueous layers were then back-extracted with EtOAc (20 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, 1:1 to 4:1 EtOAc:hexanes) and preparative TLC (7:93 MeOH/CH_2Cl_2) afforded the desired product **S45** (440 mg, 63%).

Physical state: white film;

***R*$_f$** = 0.31 (silica gel, 7:93 MeOH/CH_2Cl_2);

^{1}H NMR (600 MHz, acetone-*d*$_6$): δ 9.43 (br s, 1H), 7.94 (d, *J* = 6.5 Hz, 1H), 7.57 (dd, *J* = 8.3 Hz, 1.9 Hz, 1H), 7.53 (br s, 3H), 7.49 (s, 1H), 7.46 (s, 1H), 7.45 (s, 1H), 7.43 – 7.33 (m, 4H), 7.26 (d, *J* = 8.3 Hz, 1H), 7.19 (d, *J* = 8.3 Hz, 1H), 7.08 (s, 1H), 7.03 (d, *J* = 8.7 Hz, 1H), 6.77 (d, *J* = 9.9 Hz, 1H), 6.73 (s, 1H), 6.67 (d, *J* = 2.3 Hz, 1H), 6.45 (br s, 1H), 6.31 (d, *J* = 2.3 Hz, 1H), 5.94 (br s, 1H), 5.85 (s, 1H), 5.58 (d, *J* = 4.9 Hz, 1H), 5.54 (s, 1H), 5.51(s, 1H), 5.39 (d, *J* = 12.3 Hz, 1H), 5.23 (d, *J* = 12.3 Hz, 1H), 5.20 (br s, 1H), 5.10 (br s, 1H), 4.96 (d, *J* = 6.5 Hz, 1H), 4.67 (d, *J* = 5.2 Hz, 1H), 4.63 (t, *J* = 7.2 Hz, 1H), 4.42 (d, *J* = 11.7 Hz, 1H), 4.18 (s, 3H), 3.68 (s, 3H), 3.67 (s, 3H), 3.59 (s,

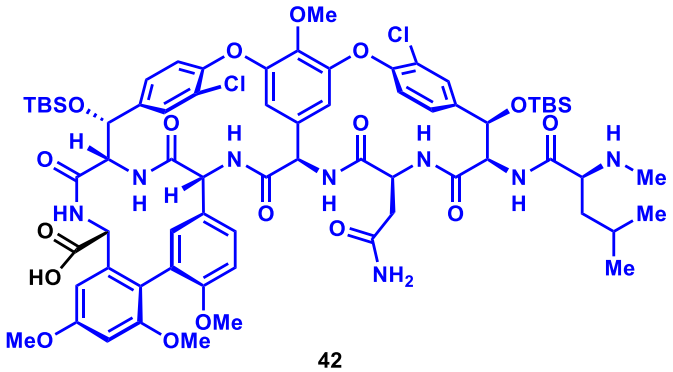
3H), 2.83 (s, 3H), 2.59 (d, J = 16.5 Hz, 1H), 2.42 (d, J = 16.3 Hz, 1H), 2.09 (s, 1H), 1.66 – 1.57 (m, 2H), 1.53 (s, 9H), 1.54 – 1.48 (m, 2H), 1.00 (s, 9H), 0.92 (s, 9H), 0.92 (d, J = 6.5 Hz, 3H) 0.86 (d, J = 6.5 Hz, 3H), 0.17 (s, 6H), 0.13 (s, 3H), 0.12 (s, 3H) ppm;

^{13}C NMR (151 MHz, acetone-d_6): δ 172.3, 171.7, 171.34, 171.31, 171.1, 170.8, 168.9, 168.0, 161.1, 159.9, 158.1, 156.9, 154.5, 153.0, 151.54, 151.51, 141.5, 140.0, 138.4, 137.0, 136.9, 136.2, 135.7, 130.0, 129.34, 129.30, 129.0, 128.3, 127.9, 127.6, 126.1, 125.4, 124.7, 124.1, 122.1, 113.8, 106.5, 106.1, 105.4, 99.6, 80.3, 74.6, 74.0, 67.2, 64.3, 61.5, 60.0, 57.5, 56.5, 56.2, 56.1, 55.7, 55.4, 55.2, 52.0, 38.1, 37.2, 28.9, 28.6, 26.5, 26.3, 25.7, 23.7, 23.3, 22.8, 19.15, 19.13, –4.4, –4.6, –4.71, –4.78.

HRMS (ESI-TOF, *m/z*): Calcd for $C_{81}H_{103}Cl_2N_8O_{19}Si_2$ $[M+H]^+$ 1617.6249; found 1617.6248.

Note: The loading amount of material for preparative TLC is crucial for separation [no more than 15 mg per PTLC plate (20 cm × 20 cm, 0.5 mm)].

Compound 42



42

To a solution of **S45** (600 mg, 0.37 mmol) in EtOH/EtOAc (4/1, 50 mL) was added Pd/C (240 mg, 5% Pd/C, 50% wetted powder); the resulting black suspension was stirred under a hydrogen atmosphere at room temperature for 12 h. The reaction mixture was then filtered through celite and washed with EtOH/EtOAc (4:1, 150 mL). The filtrate was concentrated under reduced pressure. The resulting residue was purified by

preparative reverse-phase HPLC (85%–100% CH_3CN/H_2O over 30 min, 100% CH_3CN for 30 min, both CH_3CN and H_2O containing 0.1% TFA) to afford **42** (450 mg, 79%) as a TFA salt.

Note: The Boc group was found to have cleaved during the purification process.

Physical state: pale yellow film;

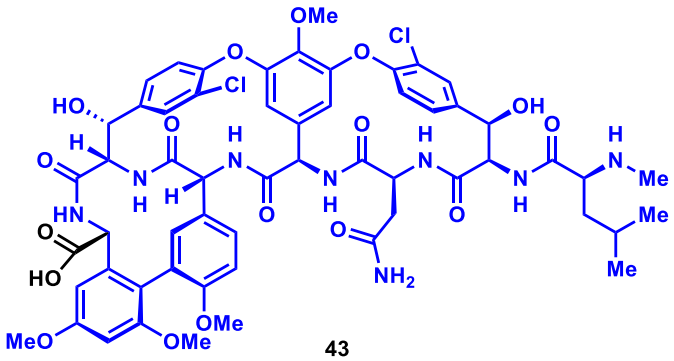
^{1}H NMR (600 MHz, methanol-*d*$_4$): δ 8.68 (d, *J* = 5.4 Hz, 1H), 7.60 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 7.48 (br s, 1H), 7.42 (br s, 1H), 7.37 (d, *J* = 8.4 Hz, 1H) 7.40 – 7.35 (br m, 1H), 7.10 (d, *J* = 9.0 Hz, 1H), 7.04 – 7.02 (m, 2H), 6.68 (d, *J* = 2.4 Hz, 1H), 6.58 (d, *J* = 2.4 Hz, 1H), 6.39 (br s, 2H), 5.77 (d, *J* = 1.2 Hz, 1H), 5.65 (br s, 1H), 5.46 (s, 1H), 5.37 (s, 1H), 5.30 (br s, 1H), 4.80 (s, 1H), 4.60 (d, *J* = 5.4 Hz, 1H), 4.23 (s, 3H), 4.10 (br s, 1H), 3.93 – 3.90 (m, 1H), 3.87 (s, 3H), 3.73 (s, 3H), 3.67 (s, 3H), 2.83 (s, 3H), 2.83 – 2.78 (m, 1H), 2.42 (dd, *J* = 16.8 Hz, 5.4 Hz, 1H), 1.89 – 1.82 (m, 1H), 1.79 – 1.74 (m, 2H), 0.98 – 0.93 (m, 24H), 0.15 (s, 3H), 0.15 (s, 3H), 0.13 (s, 3H), 0.12 (s, 3H) ppm;

^{13}C NMR (600 MHz, methanol-*d*$_4$): δ 175.3, 174.0, 172.3, 171.9, 171.8, 171.4, 170.4, 169.4, 169.2, 162.0, 160.4, 159.0, 155.2, 154.2, 153.3, 152.1, 142.2, 140.0, 139.4, 137.3, 136.8, 135.4, 130.6, 129.2, 128.46, 128.52, 128.0, 127.2, 126.1, 125.2, 124.9, 122.5, 114.1, 107.3, 106.7, 106.4, 99.4, 74.9, 65.0, 62.5, 62.4, 61.1, 58.2, 56.6, 56.1, 56.0, 55.6, 52.4, 40.8, 37.0, 33.2, 26.8, 26.5, 25.3, 23.7, 22.0, 19.7, 19.5, –4.3, –4.5, –4.65, –4.68 ppm;

^{19}F NMR (376 MHz, methanol-*d*$_4$): δ −77.2 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{69}H_{89}Cl_2N_8O_{17}Si_2$ $[M+H]^+$ 1427.5256; found 1427.5258.

Compound 43



43

To a solution of **42** (15.0 mg, 0.0097 mmol, 1.0 equiv.) in CH_3CN (1.5 mL) was added a solution of tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) in DMF (120 μL, 1.0 M, 12.4 equiv.). The resulting mixture was stirred at room temperature for 1.5 h before it was concentrated to a final volume of *ca.* 0.1 mL under reduced pressure. This residue was purified by preparative reverse-phase HPLC (30%–45% CH_3CN/H_2O over 40 min, both CH_3CN and H_2O containing 0.1% TFA) to afford **43** (9.3 mg, 73%) as a TFA salt.

Physical state: white film;

^{1}H NMR (600 MHz, methanol-*d*$_4$) δ 9.01 (d, *J* = 6.4 Hz, 0.6H), 8.73 (d, *J* = 5.8 Hz, 0.4H), 7.86 (d, *J* = 8.8 Hz, 1H), 7.75 (d, *J* = 2.1 Hz, 1H), 7.65 (d, *J* = 8.5 Hz, 1H), 7.64 (d, *J* = 2.1 Hz, 1H) 7.61 (ddd, *J* = 8.5 Hz, 2.2 Hz, 0.9 Hz, 1H), 7.21 (d, *J* = 8.5 Hz, 1H), 7.09 (d, *J* = 2.3 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 6.68 (d, *J* = 2.3 Hz, 1H), 6.51 (d, *J* = 2.2 Hz, 1H), 6.13 (br s, 1H), 6.06 (s, 1H), 5.87 (s, 1H), 5.40 (dd, *J* = 2.2 Hz, 1.0 Hz, 1H), 5.37 (s, 1H), 5.27 (d, *J* = 3.5 Hz, 1H), 4.78 (s, 1H), 4.65 (s, 1H), 4.27 (dd, *J* = 9.6 Hz, 1.9 Hz, 1H), 4.18 (s, 1H), 4.11 (s, 3H), 4.02 (t, *J* = 7.2 Hz, 1H), 3.86 (s, 3H), 3.66 (s, 3H), 3.63 (s, 3H), 3.03 (d, *J* = 15.7 Hz, 1H), 2.76 (s, 3H), 2.03 (dd, *J* = 15.7 Hz, 10.4 Hz, 1H), 1.90 (dt, *J* = 14.0 Hz, 7.2 Hz, 1H), 1.69 – 1.57 (m, 2H), 0.88 (d, *J* = 6.4 Hz, 3H), 0.85 (d, *J* = 6.4 Hz, 3H).

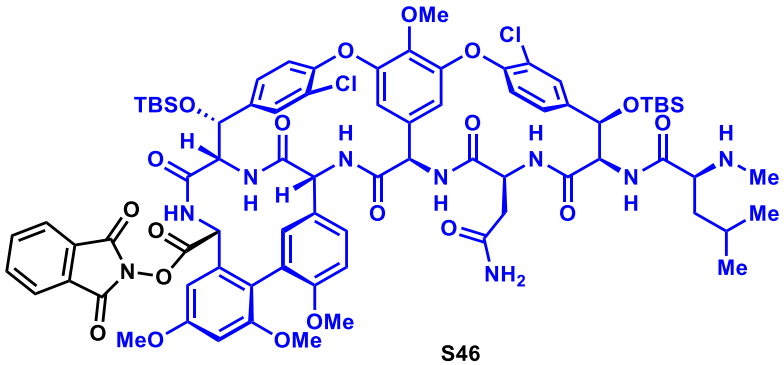
^{13}C NMR (600 MHz, methanol-*d*$_4$): δ 175.8, 174.6, 172.8, 171.7, 170.0, 169.9, 169.4, 169.0, 161.9, 160.4, 158.7, 154.2, 153.0, 152.3, 151.1, 142.7, 141.7, 138.1, 136.8, 136.7, 136.6, 130.2, 129.01, 128.95, 128.9, 128.5, 127.6, 127.3, 125.33, 125.27, 124.8, 122.4,

113.8, 109.8, 106.7, 106.3, 99.2, 74.3, 73.4, 63.9, 62.1, 61.9, 59.5, 58.5, 56.6, 56.3, 56.2, 56.0, 55.2, 53.0, 52.9, 40.2, 38.7, 36.4, 33.0, 25.5, 23.2, 22.8 ppm;

^{19}F NMR (376 MHz, methanol-*d*$_4$): δ −76.9 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{57}H_{61}Cl_2N_8O_{17}$ $[M+H]^+$ 1199.3526; found 1199.3521.

Compound S46



S46

To a suspension of **42** (45 mg, 0.029 mmol, 1.0 equiv.), *N*-hydroxyphthalimide (26 mg, 0.16 mmol, 5.5 equiv.), and *N*,*N*-dimethylpyridin-4-amine (0.4 mg, 0.0033 mmol, 0.11 equiv.) in CH_2Cl_2 (0.5 mL) was added *N*,*N*′-diisopropylcarbodiimide (25 µL, 0.16 mmol, 5.5 equiv.). The reaction mixture was stirred at room temperature for 1 h before AcOH (10 µL) was added. The resulting mixture was stirred for another 2 h and was subjected to flash column chromatography directly [silica gel, column: *d* 1.6 cm × *l* 7.5 cm, 3:2 EtOAc:hexanes (200 mL) to 1:19 MeOH:CH_2Cl_2 (120 mL)]. The combined fractions eluted with MeOH-CH_2Cl_2 were concentrated under reduced pressure, and the residue (31 mg) was used in next step without further purification.

Note:

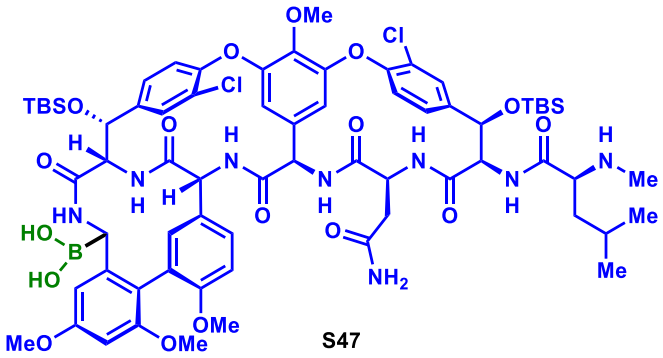
*(1) LC/MS indicated that the desired redox-active ester (**S46**) only eluted with MeOH/CH_2Cl_2. Nonpolar impurities, such as 1,3-diisopropylurea, were found to elute with EtOAc/hexanes.*

(2) Additional amounts of DMAP or longer reaction time have deleterious effects on

the reaction yield.

*(3) This redox-active ester (**S46**) was rather unstable and should be used in next step within 3 h after purification. Alternatively, it can be stored at –20 °C.*

Compound S47



S47

A screw-capped culture tube containing **S46** (31 mg), $MgBr_2$•OEt_2 powder (38 mg, 0.15 mmol) was evacuated and backfilled with argon for three times. Suspension C (0.4 mL, $NiCl_2$•$6H_2O$/di-*t*Bubipy in THF) was added next and the mixture was stirred vigorously at room temperature for 15 min (or sonicated until no granular $MgBr_2$•OEt_2 was observed). The resulting suspension was cooled to 0 °C, and the suspension of [B_2pin_2Me]Li in THF (0.55 mL) was added in one portion. After stirring for 1 h, the reaction mixture was diluted with CH_2Cl_2 (5 mL), filtered through a short pad of silica gel and celite, washed with 5% MeOH/CH_2Cl_2 (50 mL). The filtrate was concentrated under reduced pressure, and the residue was subjected to flash column chromatography directly [silica gel, column: *d* 1.6 cm × *l* 7.5 cm, 1:1 EtOAc:hexanes (200 mL) to 1:19 MeOH:CH_2Cl_2 (120 mL)]. The MeOH/CH_2Cl_2 elution was concentrated under reduced pressure, and the residue (16 mg) was used in next step without further purification.

Note:

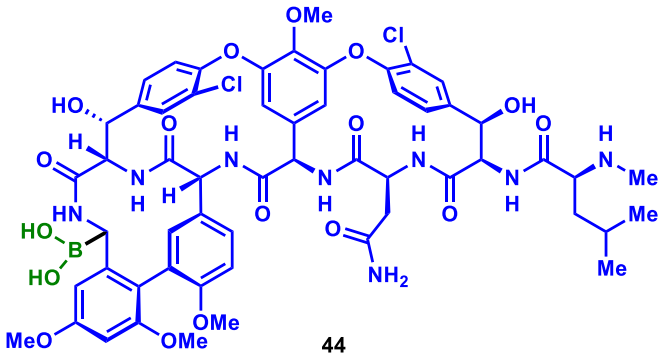
(1) The pinacol ester was found to hydrolyze during the reaction based on LC/MS analysis.

*(2) LC/MS indicated that **S47** only eluted with MeOH/CH_2Cl_2 based on LC/MS analysis.*

Nonpolar impurities, such as B_2pin_2, were found to elute with EtOAc/hexanes.

(3) Not all impurities can be removed through flash chromatography in this step; instead the unpure materials were carried forward to the next step.

Compound 44



44

To a solution of **S47** (16 mg) in CH_3CN (1.3 mL) was added a solution of tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) in DMF (120 μL, 1.0 M). The mixture was stirred at room temperature for 1.5 h and was concentrated to a final volume of *ca.* 0.3 mL under reduced pressure. The residue was purified by preparative reverse-phase HPLC (20%–50% CH_3CN/H_2O over 30 min, both CH_3CN and H_2O containing 0.1% TFA) to afford **44** (4.1 mg, 11% over 3 steps) as a TFA salt.

Note: This compound was not stable in neat condition due to its propensity toward polymerization. Therefore, the purified compound was dissolved immediately. Solutions in MeOH were used for HRMS; solutions in MeOH-d_4 were used for for NMR study; solutions in DMSO were used for biological studies.

Physical state: white film;

^{1}H NMR (600 MHz, methanol-d_4): δ 9.05 (d, J = 6.6 Hz, 1H), 7.65 – 7.58 (m, 4H), 7.31 (d, J = 9.0 Hz, 1H), 7.30 (d, J = 9.6 Hz, 1H), 7.15 (dd, J = 9.0 Hz, 1.8 Hz, 1H), 6.97 – 6.91 (m, 2H), 6.81 (s, 1H), 6.52 (d, J = 2.4 Hz, 1H), 5.81 (d, J = 5.4 Hz, 1H), 5.69 (s, 1H), 5.65 (s, 1H), 5.54 (s, 1H), 5.35 (d, J = 3.6 Hz, 1H), 5.07 (br s, 1H), 5.04

(d, *J* = 6.6 Hz, 1H), 4.43 (s, 1H), 4.32 (d, *J* = 5.4 Hz, 1H), 4.14 (s, 3H), 4.03 (t, *J* = 7.2 Hz, 1H), 3.87 (s, 3H), 3.68 (s, 3H), 3.65 (s, 3H), 2.96 (d, *J* = 15.6, 1H), 2.77 (s, 3H), 2.34 (dd, *J* = 16.2 Hz, 9.0 Hz, 1H), 1.86 – 1.82 (m, 1H), 1.79 – 1.73 (m, 1H), 1.86 – 1.71 (m, 1H), 1.01 (d, *J* = 6.0 Hz, 3H), 0.98 (d, *J* = 6.0 Hz, 3H) ppm;

^{11}B NMR (500 MHz, methanol-*d*$_4$): δ −0.87 (s) ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{56}H_{62}BCl_2N_8O_{17}$ $[M+H]^+$ 1199.3698; found 1199.3698.

Experimental Procedure for Antibiotic Evaluation of 43, 44, Vancomycin and Vancomycin Aglycon.

Antibiotic susceptibilities were determined using the Clinical and Laboratory Standards Institute broth microdilution method (*63*). Briefly, antibiotics were prepared as 2-fold dilutions in 96-well plates containing cation-adjusted Mueller-Hinton broth (*S. aureus* strains) or brain-heart infusion broth (*Enterococcus* strains). Stock solutions of antibiotics were made in dimethyl sulfoxide (DMSO). Wells were inoculated from a fresh plate scrape diluted to a final concentration of 5×10^5 CFU/mL and incubated at 37 °C. Growth observed visually at 20 h. All MICs are an average of at least three independent determinations.

Table S12. Antibacterial evaluation of a boronic acid vancomycin analog.

Compd.	*S. aureus*[*]	MRSA[†]	*E. faecium*[‡]	*E. faecalis*[§]	*E. faecalis*[¶]
vancomycin	0.5	0.5	>64	>64	16
vancomycin aglycon	1	1	>64	>64	32
43	2	2	>64	>64	8
44	16	16	>64	>64	16

[*] *Staphylococcus aureus* (ATCC 25923)

[†] *Staphylococcus aureus* (methicillin resistant, ATCC 43300)

[‡] *Enterococcus faecium* (Van A, ATCC BAA-2317)

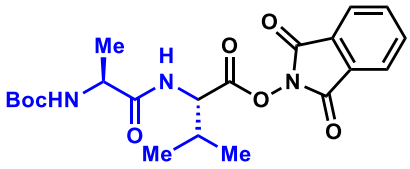
[§] *Enterococcus faecalis* (VanA, BM4166)

[¶] *Enterococcus faecalis* (VanB, ATCC 51299)

*Note: compound **44** was not very stable in H_2O at 37 °C under air. Under such conditions, ca. 20% of **44** was found to have decomposed after 24 h as indicated by LC/MS analysis (254 nM UV detector).*

Probing the Stereoselectivity on Peptide Substrates

Compound S48



S48

1,3-dioxoisoindolin-2-yl (*tert*-butoxycarbonyl)-*L*-alanyl-*L*-valinate (S48)

N-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC, 422 mg, 2.2 mmol, 1.1 equiv.) was added into a solution of Boc-*L*-Ala-*L*-Val-OH (2.0 mmol, 1.0 equiv.) and NHPI (359 mg, 2.2 mmol, 1.1 equiv.) in CH_2Cl_2 (30 mL) at –10 °C. After stirring for 1 h at room temperature, the mixture was washed with water and the aqueous phase was extracted with CH_2Cl_2 for three times. The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, 3:7 EtOAc:hexanes) afforded **S48** (591 mg, 62%).

Physical state: white foam;

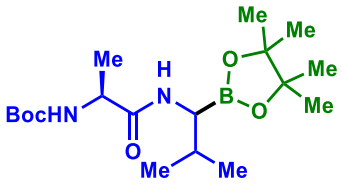
***R*$_f$** = 0.36 (silica gel, 2:3 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 5.5 Hz, 3.1 Hz, 2H), 7.79 (dd, *J* = 5.5 Hz, 3.1 Hz, 2H), 6.93 – 6.79 (br, 1H), 5.02 – 4.88 (m, 2H), 4.28 – 4.14 (br, s, 1H), 2.48 – 2.32 (m, 1H), 1.44 (s, 9H), 1.38 (d, *J* = 7.0 Hz, 3H), 1.10 (d, *J* = 6.9 Hz, 3H), 1.08 (d, *J* = 6.9 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.6, 168.4, 161.6, 155.9, 135.0, 129.0, 124.2, 80.5, 55.6, 50.0, 31.8, 28.4, 18.9, 17.5 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{21}H_{28}N_3O_7$ $[M+H]^+$ 434.1922; found 434.1930.

Compound 45



45

***tert*-butyl ((2*S*)-1-((2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-yl)amino)-1-oxopropan-2-yl)carbamate (45)**

On 0.2 mmol scale, General Procedure C was followed with suspension C ($NiCl_2$•$6H_2O$/di-*t*Bubipy in THF). Flash column chromatography (silica gel, 3:7 EtOAc:hexanes) afforded **45** as a mixture of inseparable diastereomers (50 mg, *d.r.* = 1:1, 67%)

Physical state: colorless oil;

R_f = 0.22 (silica gel, 3:7 EtOAc:hexanes);

^{1}H NMR (600 MHz, C_6D_6): δ 6.77 (s, 1H), 6.73 (s, 1H), 5.56 (s, 1H), 5.37 (s, 1H), 4.23 (s, 1H), 4.11 (s, 1H), 3.05 (s, 2H), 2.10 – 2.04 (m, 2H), 1.41 (s, 9H), 1.40 (s, 9H), 1.25 – 0.92 (m, 42H) ppm;

^{13}C NMR (151 MHz, C_6D_6): δ 174.7, 174.2, 156.0, 155.9, 82.8, 82.6, 79.4, 74.7, 49.1, 49.0, 37.0, 30.3, 28.4, 25.3, 25.3, 25.2, 25.0, 20.73, 20.68, 20.0, 19.9, 17.9, 17.7 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{18}H_{36}BN_2O_5$ $[M+H]^+$ 371.2712; found 371.2710.

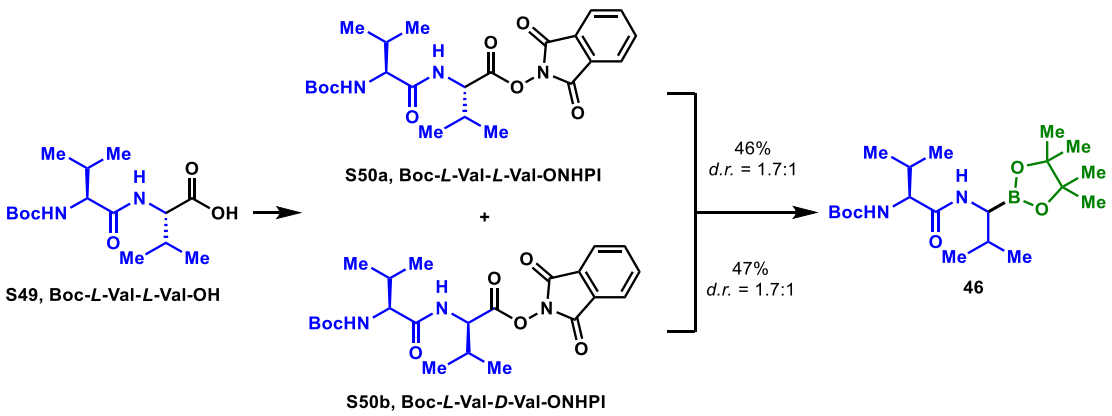
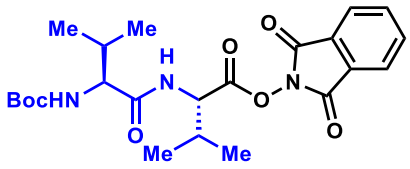


Figure S35. Synthesis of **46**.

On a 2.0 mmol scale, General Procedure A was followed with Boc-*L*-Val-*L*-Val-OH (**S49**). Purification by flash column chromatography (silica gel, 1:3 EtOAc:hexanes) afforded **S50a** (187 mg, 20%) and **S50b** (395 mg, 43%).

Compound S50a



S50a, Boc-*L*-Val-*L*-Val-ONHPI

1,3-dioxoisoindolin-2-yl (*tert*-butoxycarbonyl)-*L*-valyl-*L*-valinate (S50a)

Physical state: white foam;

***R*$_f$** = 0.40 (silica gel, 1:2 EtOAc:hexanes);

^{1}H NMR (600 MHz, CDCl$_3$): δ 7.90 – 7.88 (m, 2H), 7.81 – 7.79 (m, 2H), 6.48 (br d, *J* = 8.8 Hz, 1H), 5.09 (br d, *J* = 8.4 Hz, 1H), 4.98 (dd, *J* = 8.8 Hz, 5.1 Hz, 1H), 3.91 (dd, *J* = 8.7 Hz, 6.8 Hz, 1H), 2.43-2.38 (m, 1H), 2.14 (br s, 1H), 1.43 (s, 9H), 1.11 (t, *J* = 6.3 Hz, 6H), 0.97 (dd, *J* = 16.5 Hz, 6.8 Hz, 6H) ppm;

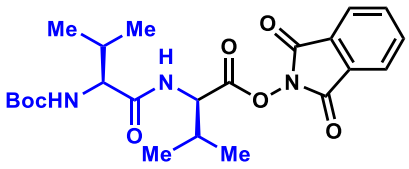
^{13}C NMR (151 MHz, CDCl$_3$): δ 171.9, 168.4, 161.6, 156.1, 135.0, 129.0, 124.2, 80.2, 60.4, 55.6, 31.7, 30.6, 28.4, 19.4, 18.9, 18.2, 17.7 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{18}H_{24}N_3O_5$ $[M\text{-Boc}+H]^+$ 362.1710; found

362.1705;

[α]$_D^{20}$ = −31.8 (c 0.96, $CHCl_3$).

Compound S50b



S50b, Boc-*L*-Val-*D*-Val-ONHPI

1,3-dioxoisoindolin-2-yl (*tert*-butoxycarbonyl)-*L*-valyl-*L*-valinate (S50b)

Physical state: white foam;

***R*$_f$** = 0.4 (silica gel, 1:2 EtOAc:hexanes);

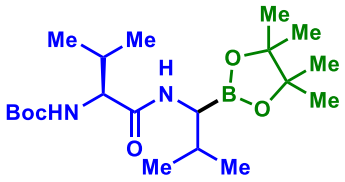
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.87 – 7.85 (m, 2H), 7.79 – 7.77 (m, 2H), 6.60 (br d, *J* = 8.8 Hz, 1H), 5.15 (d, *J* = 8.9 Hz, 1H), 4.96 (dd, *J* = 8.8 Hz, 5.2 Hz, 1H), 3.92 (dd, *J* = 8.8 Hz, 6.8 Hz, 1H), 2.41 – 2.36 (m, 1H), 2.10 (br s, 1H), 1.42 (s, 9H), 1.09 (dd, *J* = 6.9 Hz, 4.6 Hz, 6H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.0, 168.4, 161.6, 156.1, 134.9, 128.9, 124.1, 80.1, 60.3, 55.6, 31.6, 30.6, 28.4, 19.4, 18.9, 18.2, 17.7 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{18}H_{24}N_3O_5$ $[M\text{-Boc}+H]^+$ 362.1710; found 362.1714;

[α]$_D^{20}$ = −31.2 (c 1.0, $CHCl_3$).

Compound 46



46

***tert*-butyl ((*S*)-3-methyl-1-(((*S*)-2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)amino)-1-oxobutan-2-yl)carbamate (46)**

*From **S50a**:*

On 0.2 mmol scale, General Procedure C was followed with suspension C ($NiCl_2$•$6H_2O$/di-*t*Bubipy in THF) from **S50a** (1.0 equiv. of $MgBr_2$•Et_2O was used in this case). Purification by flash column chromatography (silica gel, 1:3 EtOAc:hexanes) afforded **46** as a mixture of inseparable diastereomers (37.1 mg, *d.r.* = 1.7 : 1, 47%)

*From **S50b**:*

On 0.2 mmol scale, General Procedure C was followed with suspension C ($NiCl_2$•$6H_2O$/di-*t*Bubipy in THF) from **S50b** (1.0 equiv. of $MgBr_2$•Et_2O was used in this case). Purification by flash column chromatography (silica gel, 1:3 EtOAc: hexanes) afforded **46** as a mixture of inseparable diastereomers (36.5 mg, *d.r.* = 1.7 : 1, 46%).

Physical state: colorless oil;

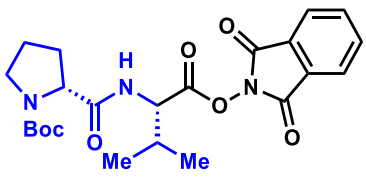
***R**_f* = 0.30 (silica gel, 1:2 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.30 (br d, *J* = 5.5 Hz, 0.78H), 6.22 (br s, 0.22H), 5.10 (br d, *J* = 8.7 Hz, 1H), 3.92 – 3.86 (m, 1H), 3.03 (br s, 1H), 2.10 (br s, 1H), 1.96 – 1.90 (m, 1H), 1.42 (s, 9H), 1.28 – 1.16 (m, 12H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 6H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.48 (minor), 172.46, 155.92, 83.37, 79.91, 59.57 (minor), 59.25, 44.96 (br), 31.10, 31.02 (minor), 30.01, 29.91 (minor), 28.51, 28.44, 25.18, 25.12, 25.10 (minor), 25.03 (minor), 24.97, 20.42, 20.37 (minor), 20.12, 20.03, 19.35, 19.21 (minor), 18.13 (minor), 17.90 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{20}H_{40}BN_2O_5$ $[M+H]^+$ 399.3025; found 399.3028.

Compound S51



S51

***tert*-butyl (*R*)-2-(((*S*)-1-((1,3-dioxoisoindolin-2-yl)oxy)-3-methyl-1-oxobutan-2-yl) carbamoyl)pyrrolidine-1-carboxylate (S51)**

On 1.0 mmol scale (based on Boc-*L*-Pro-*L*-Leu-OH), the same procedure as in the synthesis of **S48** was used. Purification by flash column chromatography (silica gel, 1:2 EtOAc:hexanes) afforded **S51** (308 mg, 67%).

Physical state: white foam;

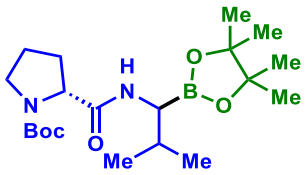
R_f = 0.4 (silica gel, 1:1 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.88 – 7.85 (m, 2H), 7.87 (br s, 0.6H), 7.79 – 7.77 (m, 2H), 6.63 (s, 0.4H), 4.99 – 4.88 (m, 1H), 4.37 – 4.30 (m, 1H), 3.61 – 3.21 (m, 2H), 2.47 (br s, 0.4H), 2.43 – 2.37 (m, 1H), 2.16 (br s, 0.6H), 2.03 – 1.76 (m, 3H), 1.51 – 1.39 (m, 9H), 1.12 – 1.03 (m, 6H); (complex spectrum was observed due to mixture of rotamers);

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.7, 172.0, 168.4, 161.6, 156.3, 154.9, 140.9, 137.2, 134.9, 130.1, 129.0, 124.1, 115.6, 110.4, 81.4, 80.7, 61.3, 59.5, 55.7, 55.1, 47.0, 31.5, 28.5, 27.1, 24.8, 19.0, 17.5; (complex spectrum was observed due to mixture of rotamers);

HRMS (ESI-TOF, *m/z*): Calcd for $C_{18}H_{22}N_3O_5$ $[M\text{-Boc}+H]^+$ 360.1554; found 360.1554.

Compound 47



47

***tert*-butyl 2-(((*S*)-2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl) carbamoyl)pyrrolidine-1-carboxylate (47)**

On 0.28 mmol scale, General Procedure C was followed with **S51** and suspension C ($NiCl_2$•$6H_2O$/di-*t*Bubipy in THF). Purification by flash column chromatography (silica gel, 2:1 EtOAc:hexanes) afforded **47** as a mixture of diastereomers (70.5 mg, *d.r.* =

2.6:1, 63%). Diastereomeric ratio was determined by ^{1}H NMR and NOESY in DMSO-d_6 at 65 °C.

Physical state: colorless oil;

R_f = 0.30 (silica gel, 2:1 EtOAc:hexanes);

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.37 (s, 0.72H), 8.28 (s, 0.28H), 4.25 (dd, J = 8.5, 2.8 Hz, 1H), 3.44 – 3.35 (m, 1H), 3.34 – 3.27 (m, 1H), 2.46 (t, J = 5.3 Hz, 0.28H), 2.40 (t, J = 4.7 Hz, 0.72H), 2.19 – 2.05 (m, 1H), 1.89 – 1.74 (m, 4H), 1.39 (s, 9H), 1.13 (s, 3.36H), 1.12 (s, 8.64H), 0.93 – 0.85 (m, 6H) ppm;

^{13}C NMR (126 MHz, DMSO-d_6): δ 174.9, 153.0, 80.6 (minor), 80.4, 78.5, 57.5 (minor), 57.3, 46.2, 28.9 (minor), 28.7, 27.8, 27.7, 24.9 (minor), 24.8, 24.7, 20.1, 20.0 (minor), 19.2 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{20}H_{38}BN_2O_5$ $[M+H]^+$ 397.2868; found 397.2864.

Stereoselective Synthesis of Bortezomib (Velcade)

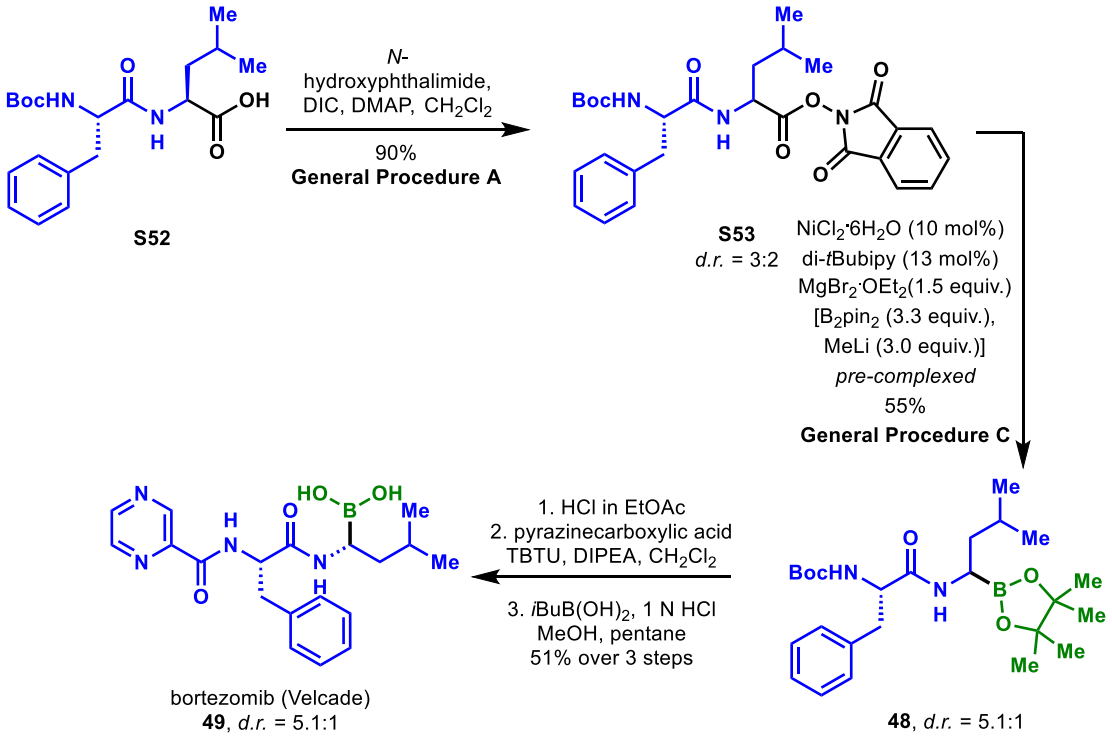
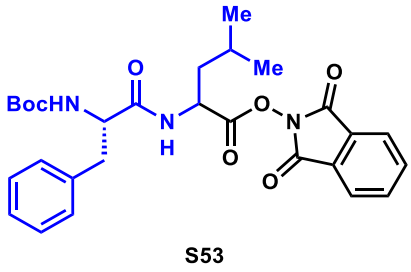


Figure S36. Synthesis of bortezomib (Velcade).

Compound S53



1,3-dioxoisoindolin-2-yl (*tert*-butoxycarbonyl)-*L*-phenylalanylleucinate (S53)

On 3.0 mmol scale, General Procedure A was followed with Boc-*L*-Phe-*L*-Leu-OH (*64*) (**S62**). Purification by flash column chromatography (deactivated silica gel, 1:5.6 EtOAc:hexanes) afforded **S53** as a mixture of inseparable diastereomers (1.42 g, *d.r.* = 3:2, 90%). Diastereomeric ratio was determined by ^{1}H NMR and NOESY.

Physical state: White foam;

R_f = 0.50 (silica gel, 2:3 EtOAc:hexanes);

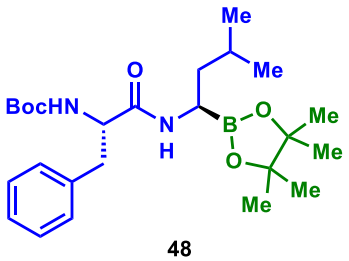
^{1}H NMR (600 MHz, methanol-d_4): *Minor isomer:* δ 7.94 – 7.89 (m, 4H), 7.29 – 7.15 (m, 5H), 4.78 (dd, *J* = 9.5 Hz, 5.8 Hz, 1H), 4.39 – 4.35 (m, 1H), 3.05 (dd, *J* = 13.7 Hz, 7.2 Hz, 1H), 2.90 (dd, *J* = 13.6 Hz, 8.1 Hz, 1H), 1.76 – 1.70 (m, 2H), 1.54 – 1.50 (m, 1H), 1.38 (s, 9H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H) ppm;

Major isomer: δ 7.94 – 7.89 (m, 4H), 7.29 – 7.15 (m, 5H), 4.92 (dd, *J* = 9.6 Hz, 6.0 Hz, 1H), 4.39 – 4.35 (m, 1H), 3.13 (dd, *J* = 14.4 Hz, 5.4 Hz, 1H), 2.84 (dd, *J* = 13.8 Hz, 9.0 Hz, 1H), 1.89 – 1.83 (m, 3H), 1.37 (s, 9H), 1.02 (d, *J* = 6.0 Hz, 3H), 0.99 (d, *J* = 6.0 Hz, 3H) ppm;

^{13}C NMR (151 MHz, methanol-d_4): *Minor isomer:* δ 174.4, 170.4, 163.1, 157.3, 138.3, 136.3, 135.5, 130.4, 130.1, 129.5, 127.7, 124.9, 124.0, 80.7, 57.4, 50.2, 41.2, 39.6, 28.6, 28.4, 25.7, 25.5, 23.2, 21.7 ppm; *Major isomer:* δ 174.6, 170.4, 163.1, 157.6, 138.4, 136.4, 135.5, 130.4, 130.1, 129.4, 127.6, 124.9, 124.0, 80.6, 57.1, 50.2, 41.5, 39.1, 28.6, 28.4, 25.7, 25.5, 23.2, 21.8 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{23}H_{26}N_3O_5$ $[M\text{-Boc}+H]^+$ 424.1867; found 424.1871.

Compound 48



48

***tert*-butyl ((*S*)-1-(((*R*)-3-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) butyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (48)**

On 0.6 mmol scale, General Procedure C was followed with suspension C ($NiCl_2$•$6H_2O$/di-*t*Bubipy in THF) and **S53**. The reaction was started from −15 °C and warmed to room temperature over 3 h. Flash column chromatography (silica gel, 1:9 EtOAc:hexanes to 1:4 EtOAc:hexanes) afforded **48**, which was dissolved in hexanes

and filtered through celite. The filtrate was concentrated *in vacuo* to afford **48** as a mixture of inseparable diastereomers (151 mg, *d.r.* = 5.1 : 1, 55%).

Physical state: Pale yellow oil;

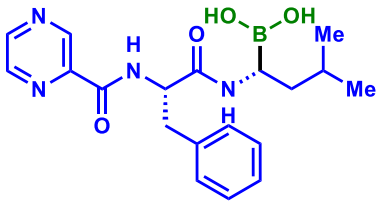
R_f = 0.50 (silica gel, 2:3 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): *Major isomer:* δ 7.31 – 7.26 (m, 2H), 7.24 – 7.21 (m, 3H), 6.19 (br s, 1H), 5.00 (br s, 1H), 4.35 (q, *J* = 7.3 Hz, 1H), 3.10 – 3.02 (m, 2H), 2.98 (ddd, *J* = 8.8 Hz, 6.3 Hz, 4.4 Hz, 1H), 1.49 – 1.42 (m, 1H), 1.39 (s, 9H), 1.37 – 1.35 (m, 2H), 1.24 (s, 6H), 1.23 (s, 6H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): *Major isomer:* δ 172.6, 155.5, 134.4, 129.6, 128.8, 127.1, 83.0, 80.3, 54.8, 39.9, 38.3, 28.4, 25.6, 25.1, 25.0, 23.3, 22.0 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{25}H_{42}BN_2O_5$ $[M+H]^+$ 461.3181; found 461.3179.

Compound 49



bortezomib (Velcade); **49**

(3-methyl-1-((*S*)-3-phenyl-2-(pyrazine-2-carboxamido)propanamido)butyl)boronic acid (49)

Bortezomib (**49**) was synthesized from **48** using the literature procedure (*19*) with slight modifications.

Boc deprotection: To a screw-capped culture tube charged with **48** (151 mg, 0.33 mmol) was added HCl in EtOAc (14 wt%) at 0 °C, and the reaction mixture was stirred at 0 °C for 3 h and room temperature for an additional 1 h. The reaction mixture was concentrated to dryness and the resulting solid was washed with hexanes. The desired product was afforded as a white solid and was used in next step without further purification.

Esterification: CH_2Cl_2 (1.2 mL, 0.5 M) was added to a screw-capped culture tube containing the hydrochloride salt obtained from the previous step. The mixture was cooled to 0 °C. Diisopropylethylamine (0.15 mL, 0.86 mmol) was added dropwise, and the reaction mixture was stirred for 5 min. 2-Pyrazine carboxylic acid (56 mg, 0.45 mmol) was then added to the solution in one portion. *o*-(Benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU, 118 mg, 0.37 mmol) was then added to the reaction mixture which was stirred at 0 °C for 2 h and room temperature for additional 1 h. The reaction mixture was then concentrated *in vacuo*. The crude residue was dissolved in EtOAc (10 mL) and transferred to a separatory funnel. The organic layer was washed with deionic H_2O (2 × 10 mL), 1% phosphoric acid (2 × 10 mL), 2% K_2CO_3 (2 × 10 mL), and brine (2 × 10 mL) successively. Each aqueous layer was back-extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The resulting pale yellow foam was carried on to the next step without further purification.

Boronate ester exchange: Pentane (0.8 mL) and MeOH (0.8 mL) were added to a screw-capped culture tube containing the pinacol boronate obtained from the previous step. 2-Methylpropaneboronic acid (125 mg, 1.2 mmol) was then added to the solution. 1 N aq. HCl (0.6mL) was added to the reaction mixture, and the resulting biphasic solution was stirred vigorously for 16 h. Stirring was then stopped and the biphasic mixture was allowed to separate. The aqueous layer was washed with pentane (2 × 10 mL) and was then concentrated *in vacuo*. The resulting film was partitioned between CH_2Cl_2 and 1 N aq. NaOH (10 mL). The aqueous layer was washed with CH_2Cl_2 (3 × 10 mL) and the organic phase was back-extracted with 1 N aq. NaOH (2 × 10 mL). 1 N aq. HCl was added to the combined aqueous layers until the pH = 6 when the desired product was extracted into the organic layer with CH_2Cl_2 (3 × 10 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was dissolved in EtOAc (2 mL), and the solution was subsequently concentrated

in vacuo. To the residue was then added hexanes (2 mL), and the suspension was concentrated *in vacuo* to afford the product **49** (64 mg, *d.r.* = 5.1 :1, 51% over 3 steps).

Physical state: white solid;

^{1}H NMR (600 MHz, $CD_3CN:D_2O$ = 4:1): *Major isomer:* δ 9.10 (d, *J* = 1.8 Hz, 1H), 8.74 (d, *J* = 2.4 Hz, 1H)), 8.61 (dd, *J* = 2.4 Hz, 1.8 Hz, 1H), 7.26 – 7.22 (m, 4H), 7.20 – 7.17 (m, 1H), 4.78 (dd, *J* = 8.4 Hz, 6.0 Hz, 1H), 3.19 (dd, *J* = 13.8 Hz, 6.0 Hz, 1H), 3.07 (dd, *J* = 13.8 Hz, 8.2 Hz, 1H), 2.93 (dd, *J* = 10.2 Hz, 5.4 Hz, 1H), 1.44 – 1.33 (m, 2H), 1.26 – 1.21 (m, 1H), 0.80 (d, *J* = 6.6 Hz, 3H), 0.78 (d, *J* = 6.6 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CD_3CN:D_2O$ = 4:1): *Major isomer:* 172.4, 164.5, 148.7, 145.0, 144.7, 144.4, 137.7, 130.4, 129.5, 127.8, 54.9, 40.2, 40.2 (br s), 38.5, 25.9, 23.6, 22.0 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{19}H_{24}BN_4O_3$ $[M–H_2O+H]^+$ 367.1936; found 367.1950.

Synthesis of Elastase Inhibitor 50

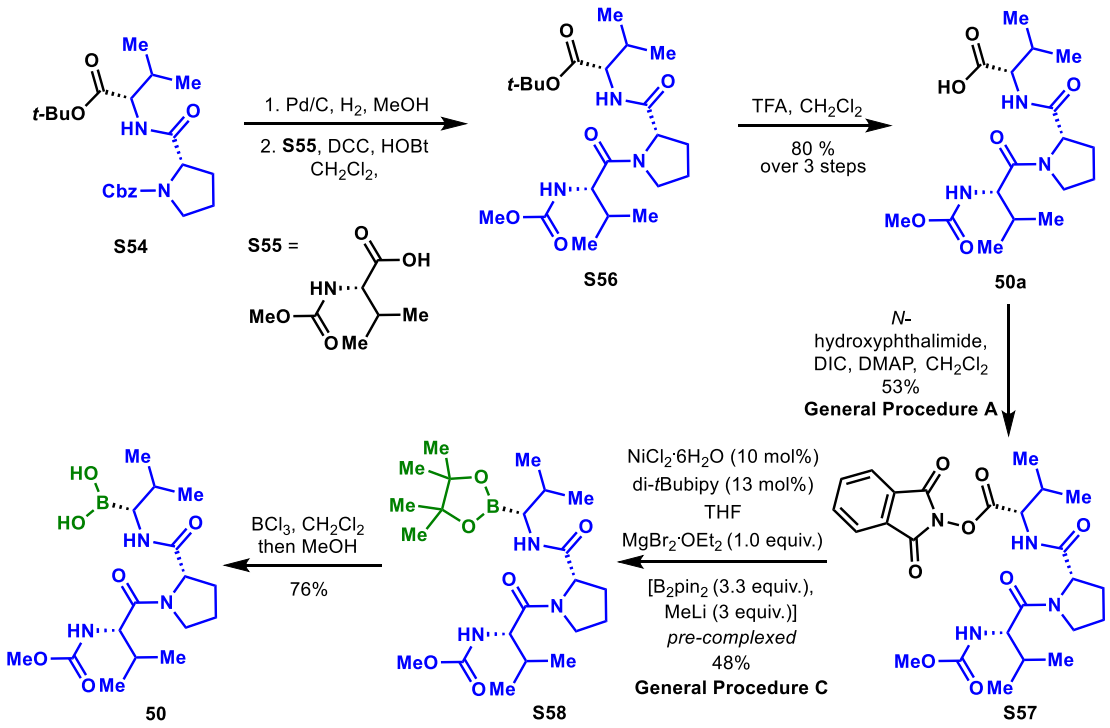
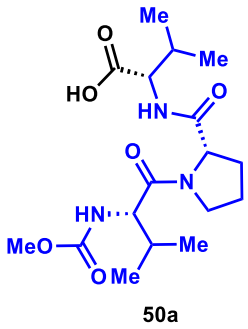


Figure S37. Synthesis of **50** and **50a**.

Compound 50a



(methoxycarbonyl)-*L*-valyl-*L*-prolyl-*L*-valine (50a)

Cbz deprotection: A 100 mL flask equipped with a stirrer bar was charged with Z-*L*-Pro-*L*-Val-O*t*Bu (*65*) (**S54**, 2.55 g, 6.3 mmol), 10% Pd/C (128 mg, 5 wt%), and MeOH (30 mL). The flask was then evacuated and backfilled with H_2 from a balloon for three times. The mixture was stirred at room temperature for 6 h and was filtered through a short pad of celite which was then rinsed with MeOH (10 mL). The filtrate was concentrated *in vacuo* to give the corresponding amine as colorless oil.

Amide bond formation: The aforementioned amine was treated successively with **S55** (1.1 g, 6.3 mmol, 1.0 equiv.), HOBt•H_2O (96 mg, 0.07 mmol, 0.11 equiv.), and CH_2Cl_2 (25 mL). The resulting solution was cooled to 0 °C before DCC (1.43 g, 6.9 mmol, 1.1 equiv.) was added. The reaction mixture was allowed to stir at 0 °C for 30 min and then at room temperature overnight. The reaction mixture was filtrered through a pad of celite; the filtrate was redissolved in EtOAc and washed with 0.1 N aq. HCl, 0.1 M aq. NH_4OH, and brine successively. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give **S56** (2.2 g) as colorless oil, which was used in the next step without further purification.

tBu deprotection: In a 25 mL flask equipped with a stirrer bar, **S56** (428 mg, 1.0 mmol) was dissolved in CH_2Cl_2 (3 mL). TFA (3 mL) was added and the resulting solution was allowed to stir at room temperature for 5 h. After the volatiles were removed *in vacuo*, the crude mixture was purified by flash column chromatography (silica gel, 2:1 EtOAc:hexanes) to furnish **50a** (359 mg, 80% over 3 steps).

Physical state: white foam;

$\boldsymbol{R_f}$ = 0.35 (silica gel, 1:2 hexanes: EtOAc);

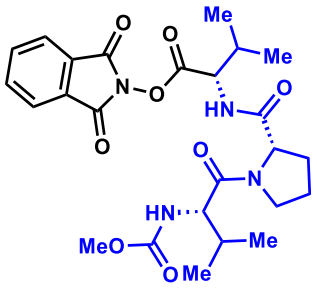
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43 (br d, *J* = 8.4 Hz, 2H), 6.17 (d, *J* = 9.0 Hz, 1H), 4.64 (dd, *J* = 7.8 Hz, 3.0 Hz, 1H), 4.48 (dd, *J* = 8.4 Hz, 4.0 Hz, 1H), 4.29 (t, *J* = 8.4 Hz, 1H), 3.84 (dd, *J* = 16.8 Hz, 8.4 Hz, 1H), 3.69 – 3.63 (m, 4H), 2.33 – 2.29 (m, 1H), 2.20 – 2.10 (m, 2H), 2.03 – 1.92 (m, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 7.2 Hz, 3H), 0.89 (d, *J* = 7.2 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.5, 173.5, 171.1, 157.8, 60.6, 58.1, 57.8, 52.5, 48.3, 31.4, 31.2, 27.7, 25.2, 19.4, 19.0, 18.1, 17.8 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{17}H_{30}N_3O_6$ $[M+H]^+$ 372.2129; found 372.2126;

$[\alpha]_D^{20}$ = −62.9 (c 0.79, $CHCl_3$)

Compound S57



S57

1,3-dioxoisoindolin-2-yl (methoxycarbonyl)-*L*-valyl-*L*-prolylvalinate (S57)

On 2.34 mmol scale, General Procedure A was followed with (methoxycarbonyl)-*L*-valyl-*L*-prolyl-*L*-valine. Purification by flash column chromatography (silica gel, 1:1 EtOAc:hexanes) furnished **S57** (640 mg, 53 %).

Physical state: white foam;

***R*$_f$** = 0.40 (silica gel, 1:2 hexanes: EtOAc);

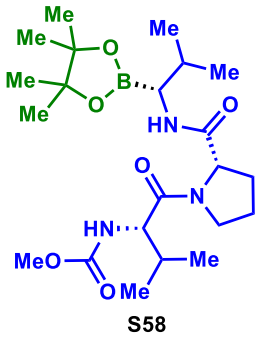
^{1}H NMR (600 MHz, CDCl$_3$) δ 7.88 – 7.84 (m, 2H), 7.78 – 7.75 (m, 2H), 7.50 (d, *J* = 8.4 Hz, 1H), 5.61 (d, *J* = 9.2 Hz, 1H), 4.84 (dd, *J* = 8.5 Hz, 5.0 Hz, 1H), 4.61 (dd, *J* = 8.1 Hz, 3.0 Hz, 1H), 4.29 (dd, *J* = 9.3 Hz, 6.9 Hz, 1H), 3.79 – 3.72 (m, 1H), 3.63 (s, 3H), 3.64 – 3.61 (m, 1H), 2.41 – 2.30 (m, 2H), 2.17 (dt, *J* = 12.3 Hz, 9.1 Hz, 1H), 2.01 – 1.96 (m, 2H), 1.95 – 1.89 (m, 1H), 1.07 (d, *J* = 7.2 Hz, 3H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H) ppm;

^{13}C NMR (151 MHz, CDCl$_3$) δ 172.5, 171.2, 168.4, 161.7, 157.3, 134.9, 129.0, 124.1, 60.0, 57.7, 56.0, 52.4, 48.0, 31.6, 31.4, 27.4, 25.3, 19.5, 18.8, 17.8, 17.7 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{25}H_{33}N_4O_8$ $[M+H]^+$ 517.2293; found 517.2289;

$[\alpha]_D^{20}$ = −61.0 (c 1.0, $CHCl_3$).

Compound S58

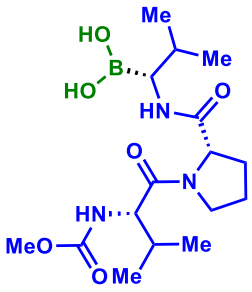


S58

methyl ((*S*)-3-methyl-1-((*S*)-2-(((*R*)-2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)carbamoyl)pyrrolidin-1-yl)-1-oxobutan-2yl)-carbamate (S58)

On 0.33 mmol scale, General Procedure C was followed with suspension C ($NiCl_2$•$6H_2O$/di-*t*Bubipy in THF). $MgBr_2$•Et_2O (1.0 equiv.) was used in this case. Purification by flash column chromatography (silica gel, 2:3 EtOAc:hexanes to 20:1 CH_2Cl_2:MeOH) furnished **S58** (72 mg, 48%) as slightly yellow oil.

Compound 50



50

((*R*)-1-((*S*)-1-((methoxycarbonyl)-*L*-valyl)pyrrolidine-2-carboxamido)-2-methylpropyl)boronic acid (50)

Aminoboronate ester **S58** (24 mg, 0.053 mmol) was dissolved in CH_2Cl_2 (2 mL) under argon; the solution was cooled to −78 °C with a dry ice/acetone bath when BCl_3 (0.16 mL, 1.0 M in CH_2Cl_2, 3.0 equiv.) was added dropwise, after which the mixture was stirred for 1 h at −78 °C. The reaction was then allowed to warm up to room temperature, and the volatiles were removed *in vacuo*. Anhydrous methanol (4 mL) was added and the resulting mixture was stirred for 10 minutes prior to concentration *in vacuo*. The

resulting residue was treated with methanol (4 mL) for 10 minutes and was concentrated *in vacuo*. This process was repeated for three times. The resulting crude product was then purified by preparative reverse-phase HPLC (10−40% CH_3CN/H_2O over 25 min, both CH_3CN and H_2O containing 0.1% TFA) and lyophilized to afford **50** as a white floppy powder (15.0 mg, 76%).

Physical state: white powder;

^{1}H NMR (600 MHz, methanol-*d*$_4$): δ 4.61 (dd, *J* = 8.4 Hz, 6.0 Hz, 1H), 4.17 (d, *J* = 7.8 Hz, 1H), 3.97–3.93 (m, 1H), 3.75–3.71 (m, 1H), 3.64 (s, 3H), 2.33–2.24 (m, 2H), 2.19–2.13 (m, 1H), 2.08–1.98 (m, 3H), 1.80–1.74 (m, 1H), 1.05 (d, *J* = 6.6 Hz, 3H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H) ppm;

^{13}C NMR (151 MHz, methanol-*d*$_4$): δ 179.3, 173.5, 159.4, 59.7, 57.9, 52.7, 31.7, 31.0, 29.8, 26.2, 21.4, 21.2, 19.6, 18.8 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{16}H_{29}BN_3O_5$ $[M-H_2O+H]^+$ 354.2195; found 354.2189;

$[\alpha]_D^{20}$ = −81.1 (c 0.44, MeOH).

Synthesis of Elastase Inhibitors 51 and 52

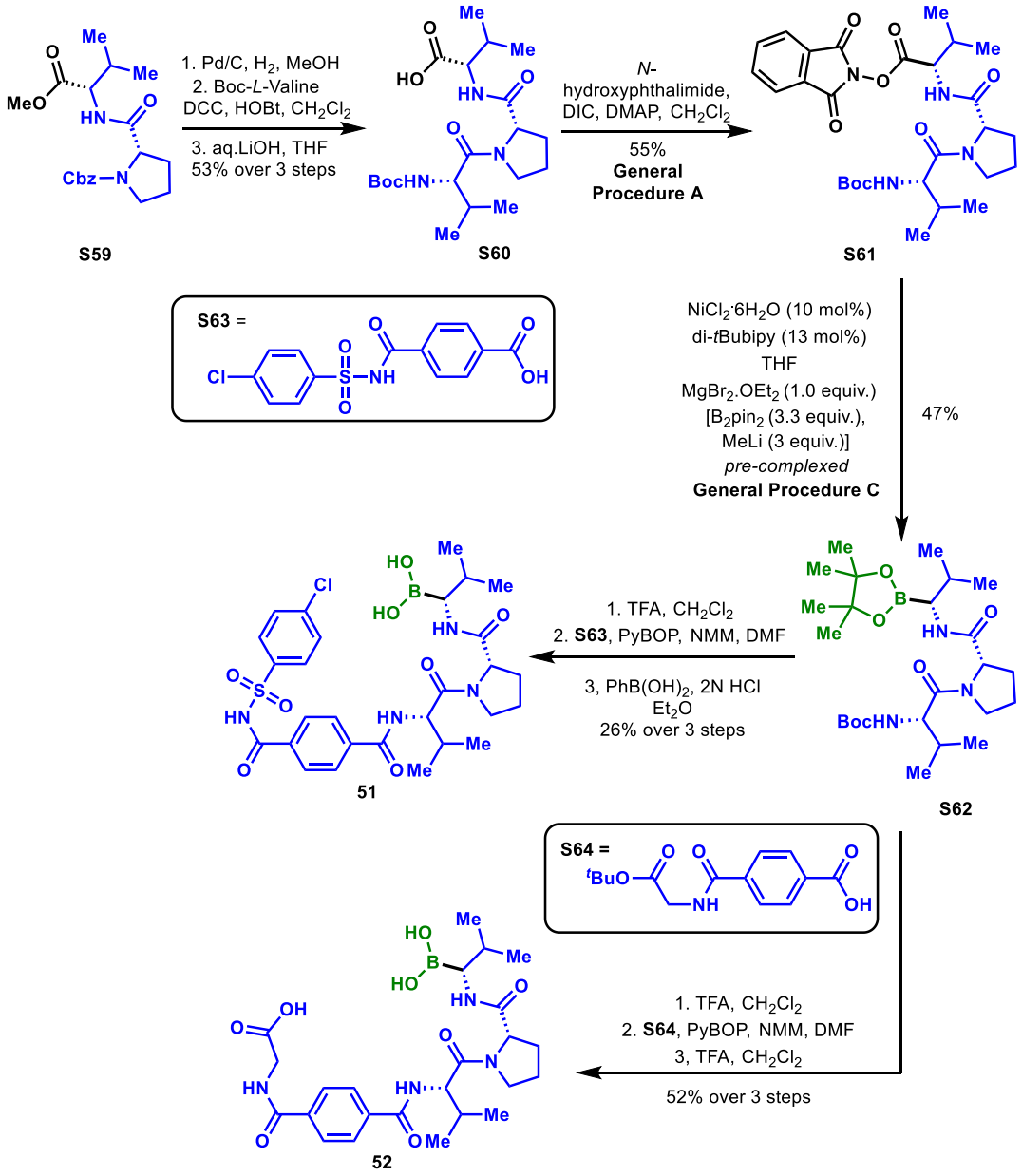
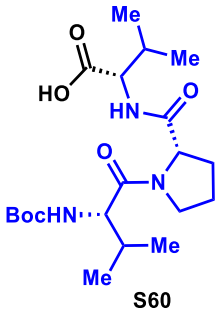


Figure S38. Synthesis of **51** and **52**.

Compound S60



S60

(*tert*-butoxycarbonyl)-*L*-valyl-*L*-prolyl-*L*-valine (S60)

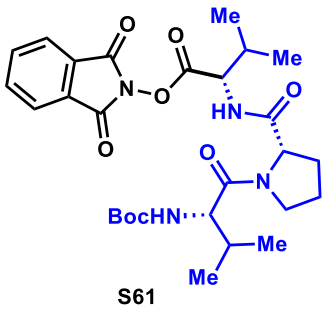
Cbz deprotection: A 100 mL flask equipped with a stirrer bar was charged with *Z*-*L*-Pro-*L*-Val-OMe (*66*) (**S59**, 1.95 g, 5.4 mmol), 10% Pd/C (98 mg, 5 wt%), and MeOH (25 mL). This flask was then evacuated and backfilled with H_2 from a balloon for three times. The reaction mixture was stirred at room temperature for 6 h and was filtered through a thin pad of celite which was then rinsed with MeOH (10 mL). The filtrate was concentrated *in vacuo* to give the corresponding amine as colorless oil.

Amide bond formation: The aforementioned amine was treated sequentially with Boc-*L*-Valine (1.17 g, 5.4 mmol, 1.0 equiv.), HOBt•H_2O (83 mg, 0.61 mmol, 0.11 equiv.), and CH_2Cl_2 (25 mL). The resulting solution was cooled to 0 °C before DCC (1.23 g, 6.0 mmol, 1.1 equiv.) was added. The reaction mixture was allowed to stir at 0 °C for 30 min and then at room temperature overnight. The resulting mixture was filtered through a pad of celite; the filtrate was concentrated *in vacuo*, redissolved in EtOAc, and washed with 0.1N aq. HCl, 0.1 M aq. NH_4OH, and brine successively. The organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by flash column chromatography (silica gel, 2:1 EtOAc:hexanes) to give Boc-*L*-Val-*L*-Pro-*L*-Val-OMe (1.32 g) as a colorless oil.

Hydrolysis of ester: A 25 mL flask equipped with a stirrer bar was charged with Boc-*L*-Val-*L*-Pro-*L*-Val-OMe (1.32 g) and THF (3 mL). LiOH (4 mL, 1 M aqueous solution) was added and the resulting solution was allowed to stir vigorously at room temperature

for 12 h. 1 N HCl was added to the reaction mixture until pH = 2–3 and the mixture was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give **S60** (1.24 g, 53% over 3 steps) as a white foam, which was used in the next step without further purification.

Compound S61



S61

1,3-dioxoisoindolin-2-yl (*tert*-butoxycarbonyl)-*L*-valyl-*L*-prolylvalinate (S61)

On 10.0 mmol scale, General Procedure A was followed with Boc-*L*-valyl-*L*-prolyl-*L*-valine (**S60**). Purification by flash column chromatography (silica gel, 1:1 EtOAc:hexanes) furnished **S61** (4.7g, 84%).

Physical state: white foam;

R_f = 0.50 (silica gel, 1:2 hexane: EtOAc);

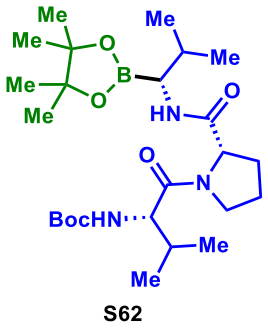
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.88 – 7.85 (m, 2H), 7.79 – 7.76 (m, 2H), 7.50 (d, *J* = 8.4 Hz, 1H), 5.28 (d, *J* = 9.6 Hz, 1H), 4.84 (dd, *J* = 8.4 Hz, 4.8 Hz, 1H), 4.62 (dd, *J* = 7.8 Hz, 3.0 Hz, 1H), 4.28 (dd, *J* = 9.6 Hz, 6.6 Hz, 1H), 3.71 – 3.77 (m, 1H), 3.60 (dt, *J* = 8.4 Hz, 3.6 Hz, 1H), 2.43 – 2.39 (m, 1H), 2.37 – 2.31 (m, 1H), 2.11 – 2.19 (m, 1H), 1.88 – 2.02 (m, 3H), 1.41 (s, 9H), 1.08 (d, *J* = 6.6 Hz, 3H), 1.07 (d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 7.2 Hz, 3H), 0.92 (d, *J* = 7.2 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.9, 171.1, 168.3, 161.7, 156.0, 134.9, 129.0, 124.1, 79.7, 60.0, 57.0, 56.1, 47.9, 31.60, 31.56, 28.5, 27.1, 25.4, 19.7, 18.9, 17.8, 17.6 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{28}H_{39}N_4O_8$ $[M+H]^+$ 559.2762; found 559.2757.

$[\alpha]_D^{20}$ = −86.2 (c 1.0, $CHCl_3$).

Compound S62



S62

***tert*-butyl ((*S*)-3-methyl-1-((*S*)-2-(((*R*)-2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)carbamoyl)pyrrolidin-1-yl)-1-oxobutan-2-yl)carbamate (S62)**

On 1.1 mmol scale, General Procedure C was followed with **S61** and suspension C ($NiCl_2$•$6H_2O$/di-*t*Bubipy in THF), 1.0 equiv. of $MgBr_2$•Et_2O was used in this case. Purification by flash column chromatography (silica gel, 2:3 EtOAc:hexanes to 3:1 EtOAc:hexanes) furnished **S62** (257 mg, 47%).

Physical state: slight yellow oil;

R_f = 0.65 (silica gel, 1:2 hexanes: EtOAc);

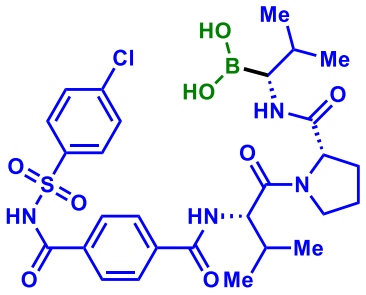
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.08 (br s, 1H), 5.22 (d, *J* = 9.3 Hz, 1H), 4.66 (dd, *J* = 8.2 Hz, 2.6 Hz, 1H), 4.28 (dd, *J* = 9.3 Hz, 6.0 Hz, 1H), 3.70 (q, *J* = 8.7 Hz, 1H), 3.56 (ddd, *J* = 9.7 Hz, 8.1 Hz, 3.7 Hz, 1H), 2.97 – 2.86 (m, 1H), 2.41–2.38 (m, 1H), 2.19 – 2.11 (m, 1H), 2.01 – 1.94 (m, 2H), 1.94 – 1.80 (m, 2H), 1.43 (s, 9H), 1.25 (d, *J* = 5.4 Hz, 12H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.8, 171.8, 156.0, 83.3, 79.8, 59.0, 56.9, 47.7, 31.6, 29.8, 28.5, 27.0, 25.3, 25.2, 25.1, 20.6, 20.3, 19.7, 17.5 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{25}H_{47}BN_3O_6$ $[M+H]^+$ 496.3552; found 496.3550.

$[\alpha]_D^{20}$ = −73.6 (c 1.0, $CHCl_3$).

Compound 51



51

(1-((*S*)-1-((4-(((4-chlorophenyl)sulfonyl)carbamoyl)benzoyl)-*L*-valyl)pyrrolidine-2-carboxamido)-2-methylpropyl)boronic acid (51)

Boc deprotection: In a screw-capped culture tube equipped with a stir bar, **S62** (55 mg, 0.11 mmol) was dissolved in CH_2Cl_2 (1 mL). TFA (1 mL) was added at 0 °C and the resulting solution was allowed to stir at 0 °C for 2 h. The volatiles were removed *in vacuo* using a rotary evaporator (water bath temperature < 25 °C), and the residue was used in next step without purification.

Esterification: Benzoic acid **S63** (45 mg, 0.13 mmol, 1.2 equiv.) and PyBOP (69 mg, 0.13 mmol, 1.2 equiv.) were then added and the mixture was dissolved in DMF (2.0 mL). *N*-methyl morpholine (49 μL, 0.45 mmol, 4.0 equiv.) was added and the reaction was allowed to stir at room temperature for 3 h. The mixture was then diluted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by flash column chromatography (silica gel, 10:1 CH_2Cl_2:MeOH) to give the pinacol boronate of **51** (69 mg) contaminated with some tripyrrolidinophosphine oxide. This mixture was used in the next step without further purification.

Boronate ester exchange: In a screw-capped culture tube equipped with a stir bar, the aforementioned mixture (53 mg) and $PhB(OH)_2$ (14 mg) was dissolved in Et_2O (3 mL). 2 N HCl (3 mL) was added and the resulting biphasic mixture was allowed to stir vigorously at room temperature for 36 h when it was extracted with EtOAc (5 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo*.

The resulting residue was purified by preparative reverse-phase HPLC (20–80% CH_3CN/H_2O over 35 min, both CH_3CN and H_2O containing 0.1% TFA) and lyophilized to afford **51** (14.0 mg, 26% for 3 steps).

Physical state: white powder;

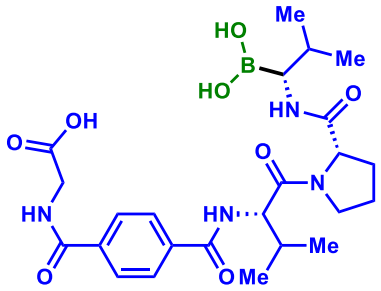
^{1}H NMR (600 MHz, methanol-*d*$_4$): δ 8.10 (d, *J* = 8.4 Hz, 2H), 7.94 – 7.90 (m, 4H), 7.66 (d, *J* = 9.0 Hz, 2H), 4.64 (dd, *J* = 8.4 Hz, 3.6 Hz, 1H), 4.61 (d, *J* = 9.6 Hz, 1H), 4.12 (dt, *J* = 9.6 Hz, 6.6 Hz, 1H), 3.82 (dt, *J* = 9.6 Hz, 6.6 Hz, 1H), 2.38 – 2.31 (m, 2H), 2.25-2.19 (m, 2H), 2.14 – 2.02 (m, 2H), 1.82 – 1.77 (m, 1H), 1.16 (d, *J* = 6.6 Hz, 3H), 1.10 (d, *J* = 7.2 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H) ppm;

^{13}C NMR (151 MHz, methanol-*d*$_4$): δ 179.2, 173.0, 169.1, 166.9, 141.3, 139.5, 139.4, 135.9, 131.2, 130.3, 129.5, 128.9, 59.0, 57.9, 31.8, 31.1, 29.8, 26.3, 21.4, 21.2, 19.6, 19.5 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{28}H_{35}BClN_4O_7S$ $[M\text{-}H_2O+H]^+$ 617.2003; found 617.2002.

$[\alpha]_D^{20}$ = −72.2 (c 0.36, MeOH).

Compound 52



52

(4-(((2*S*)-1-((2*S*)-2-((1-borono-2-methylpropyl)carbamoyl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)carbamoyl)benzoyl)glycine (52)

Boc deprotection: In a screw-capped culture tube equipped with a stir bar, **S62** (55 mg, 0.11 mmol) was dissolved in CH_2Cl_2 (1 mL). TFA (1 mL) was added at 0 °C and the resulting solution was allowed to stir at 0 °C for 2 h. The volatiles were removed *in vacuo* using a rotary evaporator (water bath temperature < 25 °C), and the residue was used in next step without purification.

Esterification: Benzoic acid **S64** (37 mg, 0.13 mmol, 1.2 equiv.) and PyBOP (69 mg, 0.13 mmol, 1.2 equiv.) were then added and the mixture was dissolved in DMF (2.0 mL). *N*-methyl morpholine (49 μL, 0.45 mmol, 4.0 equiv.) was added and the reaction was allowed to stir at room temperature for 3 h. The mixture was then diluted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by flash column chromatography (silica gel, 10:1 CH_2Cl_2: MeOH) to give the pinacol boronate (63 mg) which was used in the next step without further purification.

Global deprotection: In a culture tube equipped with a stir bar, the aforementioned pinacol boronic ester (32 mg) was dissolved in CH_2Cl_2 (1 mL). TFA (1 mL) was added at 0 °C and the resulting solution was allowed to stir at room temperature overnight. The volatiles were removed *in vacuo* using a rotary evaporator (water bath temperature < 25 °C), and the residue was purified by preparative reverse-phase HPLC (20–80% CH_3CN/H_2O over 40 min, both CH_3CN and H_2O containing 0.1% TFA) and lyophilized

to afford **52** (13.0 mg, 52% over 3 steps).

Physical state: white powder;

^{1}H NMR (600 MHz, methanol-*d*$_4$): δ 7.96 – 7.90 (m, 4H), 4.66 – 4.59 (m, 2H), 4.16 – 4.07 (m, 3H), 3.83 (dt, *J* = 10.1 Hz, 6.8 Hz, 1H), 2.40 – 2.29 (m, 2H), 2.26 – 2.16 (m, 2H), 2.14 – 2.02 (m, 2H), 1.82 – 1.72 (m, 1H), 1.17 (d, *J* = 6.7 Hz, 3H), 1.12 (d, *J* = 6.7 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H) ppm;.

^{13}C NMR (151 MHz, methanol-*d*$_4$): δ 179.3, 173.1, 173.0, 169.50, 169.48, 138.1, 138.0, 128.8, 128.6, 59.0, 58.0, 42.3, 31.8, 31.1, 29.8, 26.3, 21.4, 21.2, 19.6, 19.5 ppm;

HRMS (ESI-TOF, *m/z*): Calcd for $C_{24}H_{34}BN_4O_7$ $[M\text{-}H_2O+H]^+$ 501.2515; found 501.2516;

$[\alpha]_D^{20}$ = –97.3 (c 0.26, MeOH).

Stereochemistry Assignment of the Peptidic Boronic Acids 50, 51 and 52

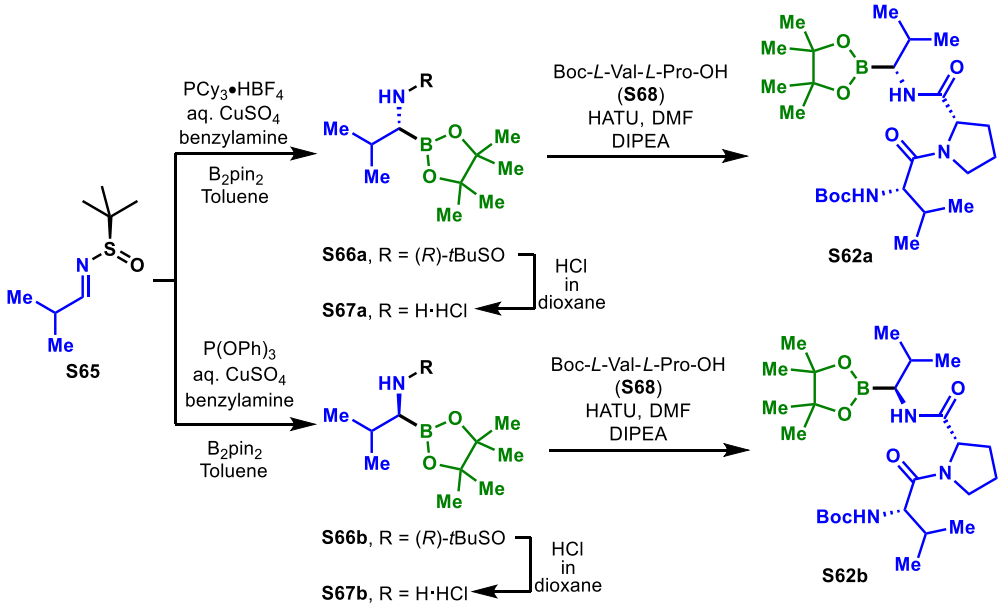
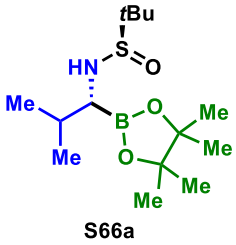


Figure S39. Synthesis of **S62a** and **S62b**.

The pinacol α-amino boronate **S66a**/**S66b** was prepared using the literature procedure (*67*) with slight modifications.

Compound S66a

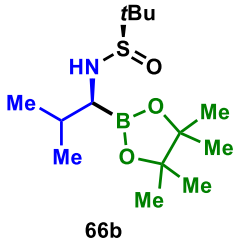


(*R*)-2-methyl-N-((*R*)-2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)propane-2-sulfinamide (S66a)

A culture tube equipped with a stir bar was charged sequentially with PCy_3•HBF_4 (12 mg, 0.033 mmol, 1.2 mol%) , toluene (0.55 mL), aqueous $CuSO_4$ (1.1 mL, 0.03 M, 1.2 mol%) and benzylamine (15.3 μL, 0.14 mmol, 5 mol%). The mixture was stirred for 10 min at the room temperature when a solution of aldimine **S65** (480 mg, 2.74 mmol, 1.0 equiv.) in toluene (5.0 mL) was added, followed by B_2pin_2 (1.39 g, 5.5 mmol, 2.0 equiv.). The mixture was stirred vigorously for 14 h, diluted with EtOAc and filtered

through a silica gel plug eluting with EtOAc. The filtrate was concentrated and purified by flash column chromatography (silica gel, 1:3 EtOAc:hexanes) to give **S66a** (1.07 g, *d.r.* > 20:1) that was contaminated with impurities originating from B_2pin_2 which could be removed in the next step.

Compound S66b



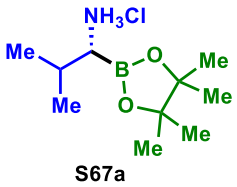
66b

(*R*)-2-methyl-N-((*S*)-2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)propane-2-sulfinamide (S66b)

To a culture tube equipped with a stir bar were added a solution of $P(OPh)_3$ (0.33 mL, 0.1 M in toluene, 1.2 mol%), aqueous $CuSO_4$ (1.1 mL, 0.03 M, 1.2 mol%), and benzylamine (15.3 μL, 0.14 mmol, 5 mol%) sequentially. The mixture was stirred for 10 min, after which a solution of aldimine **S65** (480 mg, 2.74 mmol, 1.0 equiv.) in toluene (5.0 mL) and B_2pin_2 (1.39 g, 5.5 mmol, 2.0 equiv.) were added sequentially. The mixture was stirred vigorously for 14 h, diluted with EtOAc, and filtered through a silica gel plug eluting with EtOAc. The filtrate was concentrated *in vacuo*, and purified by flash column chromatography (silica gel, 1:3 EtOAc:hexanes) to give **S66b** (857 mg, *d.r.* = 6.1:1) contaminated with impurities originating from B_2pin_2 which could be removed in the next step.

The α-boronic amine hydrochloride **S67a**/**S67b** was prepared using the literature procedure (*19*)

Compound S67a



S67a

(*R*)-2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-amine hydrochloride (S67a)

S66a (190 mg, contaminated with B_2pin_2 impurities) was dissolved in 1,4-dioxane (1.2 mL) and methanol (0.1 mL) under argon. HCl (80 μL, 4.0 M in 1,4-dioxane) was added at room temperature and the resulting mixture was stirred at the same temperature before the volatiles were removed *in vacuo*. The resulting solid was triturated with a 2:1 mixture of hexanes and Et_2O to give **S67a** (48 mg, 42 % over 2 steps).

Physical state: white solid;

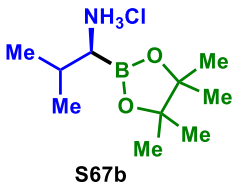
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.23 (s, 3H), 2.79 (br s, 1H), 2.26 (pd, *J* = 6.9 Hz, 4.8 Hz, 1H), 1.28 (br s, 12H), 1.11 (d, *J* = 7.0 Hz, 3H), 1.10 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 85.2, 44.4 (br), 29.3, 25.2, 24.8, 20.4, 19.9.

HRMS (ESI-TOF, *m/z*): Calcd for $C_{10}H_{23}BNO_2$ $[M+H]^+$ 200.1816; found 200.1812.

$[\alpha]_D^{20}$ = −3.0 (c 1.0, $CHCl_3$).

Compound S67b



S67b

(*S*)-2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-amine hydrochloride (S67b)

S66b (350 mg, contaminated with Bpin impurities) was dissolved in 1,4-dioxane (2.4 mL) and methanol (0.2 mL) under argon. HCl (0.16 mL, 4.0 M in 1,4-dioxane) was added at room temperature and the resulting mixture was stirred at the same temperature before the volatiles were removed *in vacuo*. The resulting solid was triturated with a 2:1 mixture of hexanes and Et_2O to give **S67b** (94 mg, 37% over 2 steps).

Physical state: white solid;

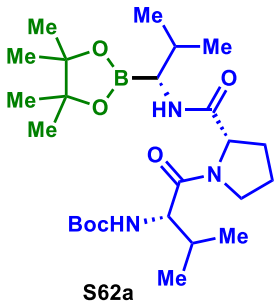
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.25 (s, 3H), 2.80 (q, *J* = 5.6 Hz, 1H), 2.26 (pd, *J* = 6.9 Hz, 4.9 Hz, 1H), 1.28 (br s, 12H), 1.12 (d, *J* = 7.2 Hz, 3H), 1.11 (d, *J* = 7.2 Hz, 3H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 85.2, 44.5 (br), 29.3, 25.2, 24.8, 20.4, 19.9;

HRMS (ESI-TOF, *m/z*): Calcd for for $C_{10}H_{23}BNO_2$ $[M+H]^+$ 200.1816; found 200.1817;

$[\alpha]_D^{20}$ = +2.7 (c 1.0, $CHCl_3$).

Compound S62a



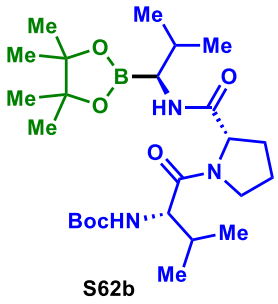
S62a

To a culture tube charged with Boc-*L*-Val-*L*-Pro-OH (**S68**, 34 mg, 0.11 mmol, 1.2 equiv.) and 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU, 44 mg, 0.12 mmol, 1.3 equiv.) was added DMF (0.5 mL), followed by diisopropylethylamine (45 µL, 0.26 mmol, 2.9 equiv.). **S67a** (21 mg, 0.089 mmol) in DMF (1.0 mL) was added dropwise at 0 °C. After the completion of addition, the reaction was kept stirring at room temperature for 1 h. The mixture was diluted with Et_2O, washed with brine, dried over anhydrous Na_2SO_4, concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 1:1 EtOAc:hexanes to 3:1 EtOAc:hexanes) to give **S62a** (32.3 mg, 73%) as a colorless

oil.

*The NMR spectra of **S62a** are in agreements with those of **S62** prepared via decarboxylative borylation. This confirms the configuration of the stereocenter α to boron in **S62** to be R.*

Compound S62b



S62b

To a culture tube charged with Boc-*L*-Val-*L*-Pro-OH (**S68**, 26 mg, 0.083 mmol, 1.2 equiv.) and 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU, 34 mg, 0.089 mmol, 1.3 equiv.) was added DMF (0.5 mL), followed by diisopropylethylamine (35 µL, 0.2 mmol, 2.9 equiv.). **S67b** (16 mg, 0.068 mmol, 1.0 equiv.) in DMF (1.0 mL) was added dropwise at 0 °C. After the completion of addition, the reaction was kept stirring at room temperature for 1 h. The mixture was diluted with Et_2O, washed with brine, dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by flash column chromatography (silica gel, 1:1 EtOAc:hexanes to EtOAc) to give **S62b** (22 mg, 65%) as a colorless oil.

Physical state: colorless oil;

R_f = 0.60 (silica gel, 1:2 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.08 (br s, 1H), 5.21 (d, *J* = 9.3 Hz, 1H), 4.65 (dd, *J* = 8.2 Hz, 2.3 Hz, 1H), 4.28 (dd, *J* = 9.4 Hz, 6.1 Hz, 1H), 3.70 (td, *J* = 9.4 Hz, 7.1 Hz, 1H), 3.56 (ddd, *J* = 9.6 Hz, 8.1 Hz, 3.4 Hz, 1H), 2.94 (td, *J* = 5.7 Hz, 2.6 Hz, 1H), 2.39 (ddd, *J* = 12.8 Hz, 6.1 Hz, 2.6 Hz, 1H), 2.14 – 2.05 (m, 1H), 1.98 (dtd, *J* = 12.3 Hz, 6.8 Hz, 3.5 Hz, 2H), 1.88 (tdd, *J* = 11.3 Hz, 9.0 Hz, 5.8 Hz, 2H), 1.42 (s, 9H), 1.21 (d, *J* = 6.3

Hz, 12H), 1.00 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.8 Hz, 6H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$) δ 172.9, 171.8, 156.0, 83.1, 79.8, 59.0, 56.9, 47.7, 45.5, 31.6, 29.8, 28.5, 27.2, 25.2, 25.12, 25.10, 20.4, 20.3, 19.9, 17.7 ppm.

*The NMR spectra of **S62b** differ from those of **S62**.*

Elastase Inhibition Assay

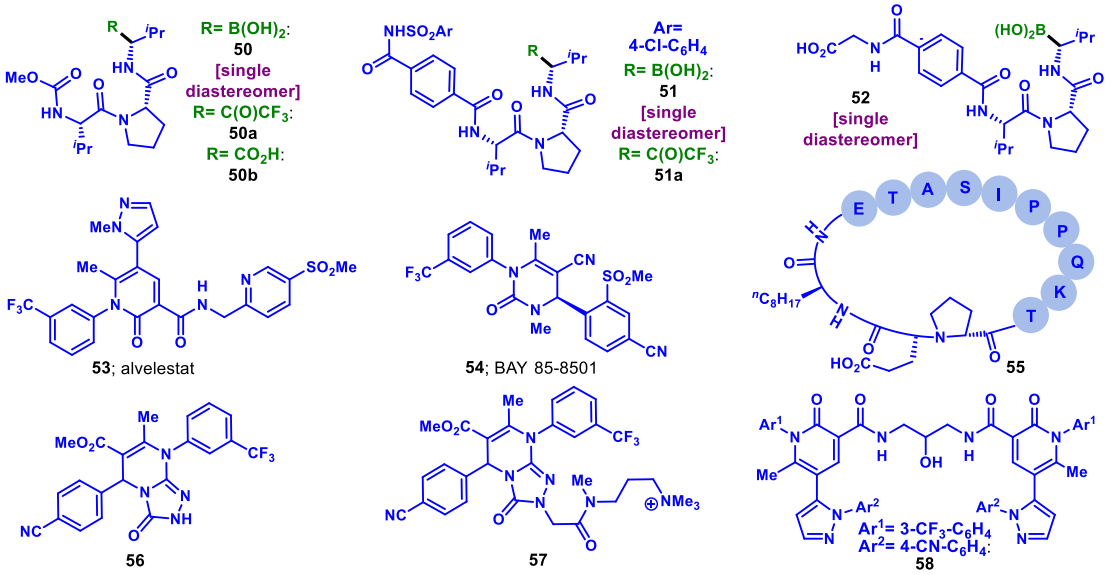


Figure S40. Strutures of selected elastase inhibitors.

Materials and methods:

Compounds **50**–**58**, **50a**, **50b**, and **51a** were subjected to this assay.

Serially diluted compounds in DMSO were dispensed into a 384-well black opaque plate by Echo dispenser. 0.1 μg/mL human neutrophil elastase (EPC, Catalog# SE563, Owensville, MS) or human sputum diluted with assay buffer (100 mM HEPES, 500 mM NaCl, 0.02% Tween 20) was added into the 384-well plate, and was incubated with different compounds at different concentrations for 30 minutes at room temperature. The final concentration of DMSO in the reaction was 0.1%. Elastase substrate MeOSuc-AAPV-AMC (Bachem, Catalog # I-1270, Torrance, CA) of 100 μM final concentration was then added into the reaction system just before enzyme kinetics were read on PheraSTAR plate reader at excitation of 380 nm and emission of 460 nm with a 3-minutes interval for 30 minutes in total. Slope of fluorescence intensity vs. time representing the V_{max} of enzyme activity was calculated with MARS software. %relative inhibition was calculated as:

$$\frac{Slope_{DMSO} - Slope_{inhibitor}}{Slope_{DMSO}} \times 100\%$$

IC_{50} was calculated based on the % relative inhibition curve using log(agonist) *vs.*

response (three parameters) method with Prism software. All experiments were performed in triplicate for at least three independent times. The IC_{50} results of all experiments are shown as the average of triplicates with error bar indicating standard deviation as indicated in individual figures. For compounds **51**, **52**, and **58**, the assay above was repeated with 2.5, 25, 50 and 100 μM of elastase substrate (MeOSuc-AAPV-AMC) and Ki/nM values were calculated based on these results using the mixed model (*68*).

Quantification of elastase concentration in human sputum:

Human sputum was purchased from Discovery Life Sciences (Los Osos, CA). Human sputum was diluted 1:10 in volume with assay buffer (100 mM HEPES, 500 mM NaCl, 0.02% Tween 20) followed by vigorous vortexing. The 1:10 diluted human sputum was further diluted into 1:30, 1:90, 1:270, 1:810, and 1:2430. The elastase concentration was determined by elastase inhibition assay as described above. Specifically, a series of standards of human neutrophil elastase (starting at 2 μg/mL and further diluted 1:2 in volume) were prepared in the assay buffer. The samples and standards were plated in a 384-well black solid bottom plate; the substrate MeOSuc-AAPV-AMC of 100 μM final concentration was then added into the reaction system just before enzyme kinetics were read on PheraSTAR plate reader as mentioned above. The slope of enzymatic kinetic reading was calculated by MARS software. The elastase levels of the human sputum were calculated based on the standard curve.

Table S13. IC_{50} and LipE of selected elastase inhibitors.

Compound	*Purified NHE*		*CF sputum*		*COPD sputum*	
	IC_{50}/nM	LipE	IC_{50}/nM	LipE	IC_{50}/nM	LipE
50–$B(OH)_2$	0.27±0.02	8.37	0.51±0.04	8.09	0.274±0.004	8.36
50a–$C(O)CF_3$	134.9±12.2	4.57	358.3±54.5	4.15	178.9±15.0	4.45
50b–CO_2H	Not Active	N.A.	N.A.	N.A	N.A.	N.A.
51–$B(OH)_2$	0.030±0.002	7.33	0.096±0.002	6.83	0.0223±0.0006	7.46
51a–$C(O)CF_3$	289.8±32.1	1.95	833.4±220.5	1.49	282.2±23.1	1.96
52–$B(OH)_2$	0.015±0.001	10.1	0.043±0.002	9.62	0.0127±0.0008	10.2
53	2.62±0.39	7.32	4.08±0.39	7.11	2.98±0.82	7.22
54	0.031±0.002	6.76	0.40±0.04	5.87	0.024±0.003	6.85
55	0.093±0.008	18.6	0.48±0.03	17.8	0.051±0.004	18.8
56	1.34±0.13	4.59	2.68±0.04	4.29	1.12±0.04	4.67
57	0.99±0.13	9.46	2.04±0.08	9.16	0.97±0.14	9.45
58	0.0111±0.0002	5.04	202.8±31.2	0.77	16.23±2.13	1.87

Note: (1) Average ± SD, n=3 plotted, representative of 3 independent, triplicate experiments. A non-linear, 3-parameter log inhibitor curve was used to calculate the IC_{50} values. Curve fit statistics: purified HNE, $R^2 \geq 0.95$, CF patient sputum, $R^2 \geq 0.93$, COPD patient sputum, $R^2 \geq 0.93$.

(2) LipE value is calculated based on the formula $LipE = pIC_{50} - logP$ where $pIC_{50} = -logIC_{50}$ and logP is calculated using SEURAT software (69).

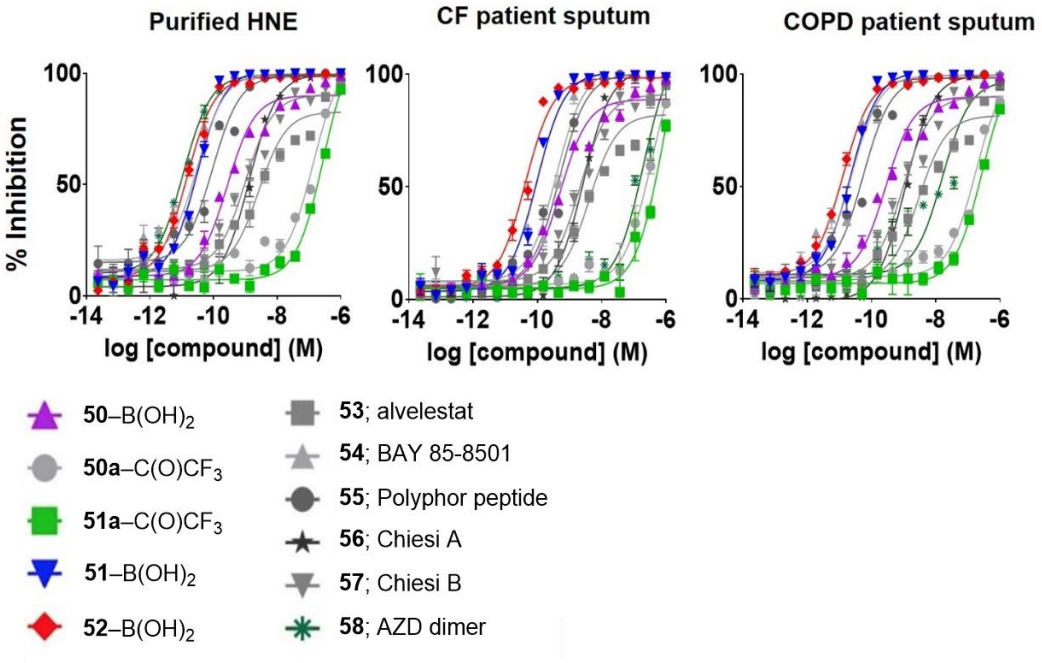


Figure S41. Inhibitory activity of selected elastase inhibitors.

Table S14. Ki values of **51**, **52** and **53**.

Compound	**51**	**52**	**58**
Ki/nM	0.034	0.0037	0.0027
Standard deviation	0.002	0.0005	0.0029

Note: Measurements were performed in 3 replicates and average values were reported.

Time Dependence of Elastase Inhibition

Method:

The procedure for the elastase inhibition assay (Page S164-166) was followed with slight modifications. 0.1 μg/mL human neutrophil elastase was incubated with a range of concentrations of inhibitors for 5, 15, 30 and 60 minutes before substrate MeOSuc-AAPV-AMC of 100 μM final concentration was added. Enzyme kinetics were read on PheraSTAR plate reader and IC_{50} was calculated with the method described above.

Table S15. Result of time dependence experiment.

Compound	**51**		**52**		**58**	
	IC_{50}/nM	Standard deviation	IC_{50}/nM	Standard deviation	IC_{50}/nM	Standard deviation
5 min	0.027	0.002	0.0040	0.0015	0.011	0.002
15 min	0.030	0.007	0.0047	0.0009	0.0040	0.0011
30 min	0.037	0.005	0.0042	0.0015	0.0026	0.0003
60 min	0.026	0.010	0.0042	0.00076	0.00029	0.00021

Note: Measurements were performed in 3 replicates and average values were reported.

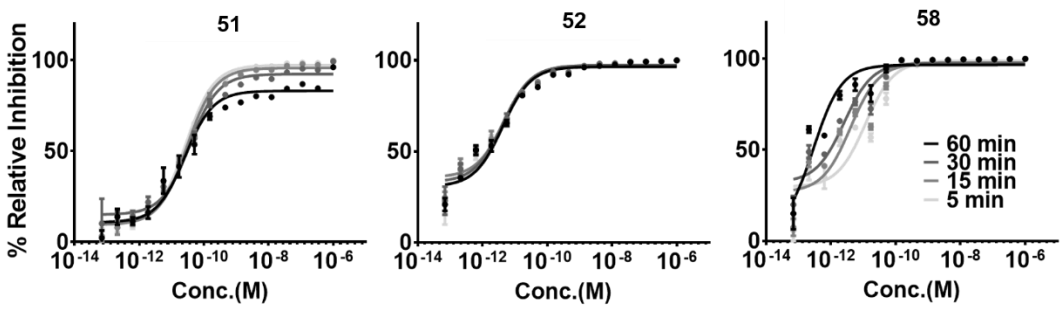


Figure S42. Time dependence curves of **51**, **52** and **58**.

Plasma Stability Assay

Materials:

1) Compounds **50**, **50a**, **51**, **51a** and **52** were tested. Propantheline was used as the reference compound in this assay; all stock solutions were stored at –40°C before use.

2) **Test system**: CD-1 Mouse Plasma from a minimum of 20 male individuals were obtained from BioreclamationIVT (Catalog #: MSEPLEDTA2-M; Batch #: MSE244515). EDTA-K2 was used as the anticoagulant.

Procedure:

The frozen plasma was thawed in a water bath at 37 °C prior to the experiments. The plasma was centrifuged at 4000 rpm for 5 min and the clots were removed if necessary. The pH was adjusted to 7.4 ± 0.1 as necessary. An intermediate solution (1 mM) was prepared and a 100 μM dosing solution was prepared by diluting 10 μL of the intermediate solution with 90 μL 45% MeOH/H_2O. Duplicate of test samples were made by mixing 98 μL of blank plasma with 2 μL of dosing solution (100 μM) to achieve the final concentration of 2 μM. Samples were incubated at 37 °C. At each time point (0, 10, 30, 60, and 120 min), 400 μL of stop solution (consisting of 200 ng/mL tolbutamide and 20 ng/mL buspirone in 50% MeOH/CH_3CN) was added to precipitate protein under thorough mixing. The sample plates were then centrifuged at 4,000 rpm for 10 min. An aliquot of supernatant (100 μL) was transferred from each well and mixed with 200 of μL ultrapure water. The samples were shaken at 800 rpm for about 10 min before LC-MS/MS analysis.

Data analysis: The % remaining of test compound after incubation in plasma was calculated using following equation:

$$\% \text{ Remaining} = 100 \times (P_{AR} \text{ at } T_n / P_{AR} \text{ at } T_0)$$

where P_{AR} is the peak area ratio of analyte versus internal standard (IS) and The appointed incubation time points are T_0 (0 min), T_n (n=0, 10, 30, 60, 120 min).

LC-MS/MS condition: Each compound was analyzed by LC/MS using an ACE 5-phenyl 50×2.1 mm column (Part No. ACE-125-0502) with 0.1% formic acid in water and 0.1% formic acid in acetonitrile as the mobile phases. Tobultamide was used as the internal standard. Data collected were processed by Analyst 1.6.2 software and MultiQuant 3.0.2 software.

Table S16. Result of plasma stability assay.

Compound	Species / Matrix	Time Point (min)	% Remaining (mean)
50	CD-1 Mouse Plasma	0	100.0
		10	100.5
		30	105.2
		60	88.0
		120	76.7
50a	CD-1 Mouse Plasma	0	100.0
		10	101.7
		30	98.8
		60	100.0
		120	92.5
51	CD-1 Mouse Plasma	0	100.0
		10	90.0
		30	79.4
		60	84.1
		120	90.3
51a	CD-1 Mouse Plasma	0	100.0
		10	99.0
		30	109.1
		60	99.5
		120	106.6
52	CD-1 Mouse Plasma	0	100.0
		10	116.1
		30	104.8
		60	96.4
		120	79.2
Propantheline	CD-1 Mouse Plasma	0	100.0
		10	76.8
		30	39.1
		60	21.7
		120	7.7

Mouse Liver Microsomal Metabolic Stability Assay

Materials:

1) Compounds **50**, **50a**, **51**, **51a**, and **52** were tested in this assay. Testosterone, Dichlofenac, and Propafenone were used as control.

2) **Buffers:**

1. 100 mM potassium phosphate buffer, pH 7.4.
2. 10 mM $MgCl_2$

3) **Compound Dilution:**

Intermediate solution was prepared by diluting 5 μL of compound or control stock solution (10 mM in DMSO) with DMSO (45 μL) and 1:1 methanol/water (450 μL) (concentration=100 μM, 45% MeOH). Working solution was prepared by diluting 50 μL of the intermediate solution with 450 μL of 100 mM potassium phosphate buffer, pH=7.4 (centration= 10 μM, 4.5%MeOH).

4) **NADPH regenerating system** (final Isocitric dehydrogenase concentration = 1 unit/mL at incubation) comprised:

β-Nicotinamide adenine dinucleotide phosphate acquired from Sigma (Catalog # N0505), isocitric acid from Sigma (Cat. No. I1252) and isocitric dehydrogenase from Sigma (Catalog # I2002).

5) **Liver microsome solution** (final concentration of 0.5 mg protein/mL) was prepared using Mouse liver microsomes from Xenotech (Catalog # M1000, Lot # 1310028).

6) **Stop solution**: Cold acetonitrile containing 100 ng/mL Tolbutamide and 100 ng/mL Labetalol as internal standards (IS)

Procedure:

10 μL/well of compound working solution or control working solution was added to all plates (T0, T5, T10, T20, T30, T60, NCF60) except the matrix blank. 80 μL/well of microsome solution was added to every plate. The mixtures of microsome solution and compound were incubated at 37 °C for about 10 min. 10 μL/well of NADPH regenerating system (pre-warmed to 37 °C) was then added to every plate to start the reaction. The plates were incubated for the durations indicated (matrix blank: 1 h; T60: 1 h; T30: 31 min; T20: 40 min; T10 50min; T5: 55min). For NCF60 (abbreviation of no co-factor) no NADPH regenerating system was added, but was replaced by 10 μL/well of potassium phosphate buffer (100 mM, pH 7.4); the resulting mixture was incubated at 37 °C for 1 h.

The reactions were then terminated with the stop solution (cold at 4 °C) containing 100 ng/mL Tolbutamide and 100 ng/mL Labetalol (300 μL/well). The sampling plates were shaken for approximately 10 minutes, then were centrifuged at 4000 rpm for 20 min at 4 °C. While centrifuging, 8 new 96 well plates were loaded with 300 μL of HPLC grade water. 100 μL of supernatant was finally added to 300 μL of HPLC grade water and mixed for LC/MS/MS analysis.

Apricot pipetting robot was used for all additions, mixing, and transformations described above in 96-well plate format.

Data Analysis

The equation of first order kinetics was used to calculate $T_{1/2}$ and $Cl_{int(mic)}$:

$$C_t = C_o \bullet e^{-k_e \bullet t}$$

$$\text{when } C_t = \frac{1}{2} C_o,\ T_{1/2} = \frac{ln2}{k_e} = 0.693/k_e$$

$$CL_{int(mic)} = \frac{0.693}{in\ \ vitro\ \ T_{1/2}} \bullet \left(\frac{1}{\frac{mg}{mL}\ \ microsomal\ \ protein\ \ in\ \ reaction\ \ system} \right)$$

$$CL_{int(liver)} = CL_{int(mic)} \bullet \left(\frac{mg\ \ microsomes}{g\ \ liver} \right) \bullet \left(\frac{g\ \ liver}{Kg\ \ body\ \ weight} \right)$$

Table S17. Result of mouse liver microsomal metabolic stability assay.

Compounds	MLM 0.5						
	R^2	$T_{1/2}$ (min)	$CL_{int(mic)}$ (μL/min/mg)	$CL_{int(liver)}$ (mL/min/kg)	Extraction ratio	Remaining (T=60min)	Remaining (*NCF=60min)
50	0.8919	> 145	< 9.6	< 38.0	< 0.3	78.5%	99.0%
50a	0.6722	> 145	< 9.6	< 38.0	< 0.3	92.9%	82.3%
51	0.2713	> 145	< 9.6	< 38.0	< 0.3	85.8%	95.0%
51a	0.9190	71.6	19.4	76.6	0.5	52.2%	91.7%
52	0.4436	> 145	< 9.6	< 38.0	< 0.3	78.9%	103.6%
Testosterone	0.9992	2.3	597.4	2365.5	1.0	0.0%	70.3%
Diclofenac	0.9820	51.0	27.2	107.6	0.5	43.0%	88.0%
Propafenone	0.9858	1.3	1.3	4188.4	1.0	0.2%	84.3%

Notes: *1) * NCF: the abbreviation of no co-factor. No NADPH regenerating system was added into NCF samples (replaced by buffer) during the 60 min-incubation, if the NCF remaining is less than 60%, then Non-NADPH dependent occurs.*

2) R^2 is the correlation coefficient of the linear regression for the determination of kinetic constant.

3) $T_{1/2}$ is half-life and $CL_{int\ (mic)}$ is the intrinsic clearance.

4) $\frac{mg\ \ microsomes}{g\ \ liver} = 45mg/g$ for five species.

5) $\frac{g\ \ liver\ \ weight}{Kg\ \ body\ \ weight} = 88g/Kg$ for mouse.

6) Hepatic blood clearance (CLH) = $\frac{CLint(liver)\times\ Qh}{CLint(liver)+Qh}$

Hepatic extraction ratio (EH) = $\frac{CLH}{QH}=\frac{Clint(liver)}{Clint(liver)+Qh}$

Whereby Qh(mL/min/Kg liver） = 90.0 mL/min/Kg for mouse liver

Kinetic Solubility Test

Materials:

Compounds **50**, **50a**, **51**, **51a**, and **52** were tested.

Procedure:

The stock solution of each compound (10 µL; 10 mM in DMSO) was diluted with phosphate buffer solution (490 µL; 50mM, pH 6.8). The resulting mixture was shaken for 24 h. Samples were then filtered. Kinetic solubility was then determined by UV spectroscopy [calibrated by a standard curve (1, 20, and 200 µM)].

Table S18. Result of kinetic solubility test.

Compound	Kinetic Solubility pH=6.8 (µg/mL)	Kinetic Solubility pH=6.8 (µM)
50	>74.25	>200.00
50a	>84.69	>200.00
51	>126.99	>200.00
51a	119.75	174.28
52	>103.67	>200.00

***Caco-2* Permeability Assay**

Materials:

1) ***Caco-2* culture**: Caco-2 cells purchased from ATCC were seeded onto polyethylene membranes (PET) in 96-well BD Insert plates at 1 x 105 cells/ cm^2, and refreshed medium every 4~5 days until to the 21st to 28th day for confluent cell monolayer formation.

2) **Compound information**: compounds **51** and **51a** were subjected to the assay. Digoxin, fenoterol, and propranol were used as standards respectively.

Transport method:

The transport buffer used in the study was HBSS with 10 mM HEPES at pH 7.40±0.05. Compounds were tested at 2 μM bi-directionally in duplicates. Digoxin was tested at 10 μM bi-directionally in a duplicate, while fenoterol and propranolol were tested at 2 μM in A(apical) to B (basolateral) direction in duplicates. The final DMSO concentration was adjusted to less than 1%. The plate was incubated for 2 hours in a CO_2 incubator at 37±1°C, with 5% CO_2 at saturated humidity without shaking. All samples, after mixing with acetonitrile containing internal standard, were centrifuged at 4000 rpm for 20 min. Subsequently,100 μL supernatant solution was diluted with 100 μL distilled water for LC/MS/MS analysis. Concentrations of test and control compounds in starting solution, donor solution, and receiver solution were quantified by LC/MS/MS methodologies, using peak area ratio of analyte/internal standard. After transport assay, lucifer yellow rejection assay was applied to determine the *Caco*-2 cell monolayer integrity. All data presented herein have passed this test.

Data analysis: The apparent permeability coefficient Papp (cm/s) was calculated using the equation:

$$P_{app} = \left(\frac{dC_r}{dt}\right) \bullet V_r/(A \bullet C_0)$$

Where $\frac{dC_r}{dt}$ is the cumulative concentration of compound in the receiver chamber as a function of time (μM/s); V_r is the solution volume in the receiver chamber (0.075 mL on the apical side, 0.25 mL on the basolateral side); A is the surface area for the transport, *i.e.* 0.0804 cm^2 for the area of the monolayer; C_0 is the initial concentration in the donor chamber (μM).

The efflux ratio was calculated using the equation:

$$\text{Efflux ratio } = P_{app}(BA)/P_{app}(AB)$$

Percent recovery was calculated using the equation:

$$\%\ \ Recovery = 100\times[(V_r \bullet C_r) + (V_d \bullet C_d)]/(V_d \bullet C_0)$$

Where V_d is the volume in the donor chambers (0.075 mL on the apical side, 0.25 mL on the basolateral side); C_d and C_r are the final concentrations of transport compound in donor and receiver chambers, respectively.

LC/MS conditions: Each compound was analyzed by LC/MS using an ACE 5-phenyl 50×2.1 mm column (Part No. ACE-125-0502) with 0.1% formic acid in water and 0.1% formic acid in acetonitrile as the mobile phases. Tobultamide was used as the internal standard. Data collected were processed by Analyst 1.6.2 software and MultiQuant 3.0.2 software.

Table S19. Result of *Caco-2* permeability assay.

Compound ID	Mean P_{app} (10^{-6} cm/s)		Efflux Ratio	Mean Recovery %	
	A to B	B to A		A to B	B to A
Fenoterol	0.24	ND	–	93.38	ND
Propranolol	19.76	ND	–	69.25	ND
Digoxin	<0.02	8.50	>364.02	<91.21	100.33
51	<0.16	0.61	>3.91	<88.25	99.12
51a	<0.08	<0.12	NA	<74.15	<90.87

Note:

1) For digoxin and test compound, the signal responses in receiver samples were lower than the limit of quantification. For the convenience of calculating P_{app} values, 50 was used as the peak area of analyte in receiver samples instead.

2) The permeation was assessed over a 120-minute incubation at 37±1°C and 5% CO_2 with saturated humidity.

X-ray Crystallographic Data for Compound 28

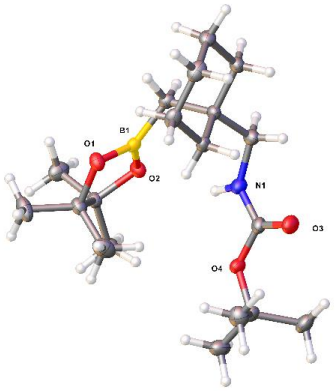


Table S20. Crystal data and structure refinement for **28**.

Identification code	CCDC 1525341	
Empirical formula	C19 H36 B N O4	
Molecular formula	C19 H36 B N O4	
Formula weight	353.30	
Temperature	100.0 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	a = 10.7315(3) Å	α= 90°.
	b = 17.6585(4) Å	β= 106.9990(10)°.
	c = 11.5200(3) Å	γ = 90°.
Volume	2087.69(9) $Å^3$	
Z	4	
Density (calculated)	1.124 Mg/m^3	
Absorption coefficient	0.076 mm^{-1}	
F(000)	776	
Crystal size	0.271 x 0.235 x 0.096 mm^3	
Crystal color, habit	Colorless Block	
Theta range for data collection	1.984 to 26.372°.	
Index ranges	-13<=h<=13, -21<=k<=22, -13<=l<=11	
Reflections collected	12673	
Independent reflections	4204 [R(int) = 0.0267, R(sigma) = 0.0283]	
Completeness to theta = 25.000°	99.2 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.2602 and 0.2254	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	4204 / 1 / 237
Goodness-of-fit on F^2	1.037
Final R indices [I>2sigma(I)]	R1 = 0.0370, wR2 = 0.0864
R indices (all data)	R1 = 0.0481, wR2 = 0.0930
Extinction coefficient	n/a
Largest diff. peak and hole	0.237 and -0.182 e.Å^{-3}

Table S21. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **28**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	2318(1)	4420(1)	7581(1)	23(1)
O(2)	2956(1)	4269(1)	5870(1)	22(1)
O(3)	6389(1)	6345(1)	7273(1)	31(1)
O(4)	6591(1)	5063(1)	7124(1)	24(1)
N(1)	4742(1)	5613(1)	6117(1)	24(1)
C(1)	1826(1)	5540(1)	6073(1)	20(1)
C(2)	2753(1)	6228(1)	6467(1)	19(1)
C(3)	3413(1)	6238(1)	7846(1)	21(1)
C(4)	2445(1)	6376(1)	8570(1)	26(1)
C(5)	1683(1)	7106(1)	8181(1)	30(1)
C(6)	1011(1)	7117(1)	6820(1)	26(1)
C(7)	1977(1)	6966(1)	6102(1)	23(1)
C(8)	3792(1)	6222(1)	5784(1)	24(1)
C(9)	4321(1)	3150(1)	6337(1)	30(1)
C(10)	3087(1)	3521(1)	6447(1)	21(1)
C(11)	3087(1)	3720(1)	7760(1)	23(1)
C(12)	4431(1)	3916(1)	8595(1)	36(1)
C(13)	1903(1)	3069(1)	5750(1)	31(1)
C(14)	2430(2)	3135(1)	8346(1)	37(1)
C(15)	5948(1)	5733(1)	6875(1)	22(1)
C(16)	7909(1)	5038(1)	7985(1)	24(1)
C(17)	8841(1)	5505(1)	7504(1)	32(1)
C(18)	7874(1)	5297(1)	9228(1)	34(1)
C(19)	8248(1)	4204(1)	7998(1)	34(1)
B(1)	2381(1)	4735(1)	6520(1)	19(1)

X-ray Crystallographic Data for Compound 38

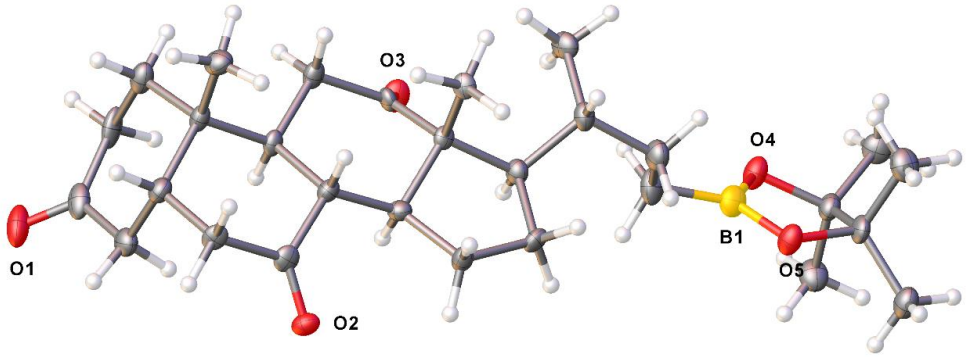


Table S22. Crystal data and structure refinement for **38**.

Identification code	CCDC 1525343	
Empirical formula	C29 H45 B O5	
Molecular formula	C29 H45 B O5	
Formula weight	484.46	
Temperature	100.0 K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 6.6785(3) Å	α= 90°.
	b = 17.0629(7) Å	β= 90°.
	c = 23.2325(10) Å	γ = 90°.
Volume	2647.4(2) $Å^3$	
Z	4	
Density (calculated)	1.215 Mg/m^3	
Absorption coefficient	0.634 mm^{-1}	
F(000)	1056	
Crystal size	0.25 x 0.015 x 0.015 mm^3	
Crystal color, habit	colorless needle	
Theta range for data collection	3.213 to 63.732°.	
Index ranges	-7<=h<=7, -19<=k<=19, -25<=l<=25	
Reflections collected	20442	
Independent reflections	4221 [R(int) = 0.0549]	
Completeness to theta = 63.732°	98.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.5192 and 0.4394	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4221 / 0 / 323	

Goodness-of-fit on F^2	1.075
Final R indices [I>2sigma(I)]	R1 = 0.0564, wR2 = 0.1220
R indices (all data)	R1 = 0.0679, wR2 = 0.1268
Absolute structure parameter	0.01(13)
Extinction coefficient	n/a
Largest diff. peak and hole	0.248 and -0.234 e.$Å^{-3}$

Table S23. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for compound **38**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	2096(6)	10257(2)	5416(2)	38(1)
O(2)	-1462(5)	7135(2)	5092(1)	21(1)
O(3)	5151(5)	6632(2)	6661(2)	25(1)
O(4)	9138(5)	2949(2)	6288(1)	26(1)
O(5)	6214(5)	2453(2)	5929(1)	25(1)
C(1)	-1639(8)	8353(3)	6986(2)	26(1)
C(2)	-168(7)	8502(3)	6494(2)	18(1)
C(3)	1254(8)	9169(3)	6685(2)	26(1)
C(4)	2731(7)	9438(3)	6227(2)	30(1)
C(5)	1697(8)	9661(3)	5679(2)	28(1)
C(6)	116(8)	9100(3)	5473(2)	25(1)
C(7)	-1299(8)	8791(3)	5953(2)	22(1)
C(8)	-2675(7)	8147(3)	5703(2)	19(1)
C(9)	-1479(7)	7414(3)	5570(2)	19(1)
C(10)	-329(7)	7097(2)	6080(2)	18(1)
C(11)	1039(7)	7747(2)	6333(2)	17(1)
C(12)	2308(7)	7445(3)	6842(2)	20(1)
C(13)	3336(7)	6674(2)	6691(2)	17(1)
C(14)	1896(7)	6029(2)	6512(2)	15(1)
C(15)	911(7)	6368(3)	5954(2)	18(1)
C(16)	-65(8)	5646(3)	5690(2)	21(1)
C(17)	1308(7)	4955(3)	5852(2)	19(1)
C(18)	2860(7)	5259(3)	6293(2)	20(1)
C(19)	3387(7)	4655(3)	6757(2)	22(1)
C(20)	4188(8)	3878(3)	6506(2)	28(1)

C(21)	6196(8)	3927(3)	6192(2)	30(1)
C(22)	320(7)	5857(3)	6980(2)	18(1)
C(23)	4823(7)	4968(3)	7220(2)	24(1)
C(24)	10715(8)	2254(3)	5515(2)	31(1)
C(25)	9609(8)	2158(3)	6088(2)	23(1)
C(26)	11001(7)	1779(3)	6523(2)	27(1)
C(27)	7260(8)	1212(3)	5529(2)	29(1)
C(28)	7503(8)	1774(3)	6028(2)	24(1)
C(29)	6772(8)	1394(3)	6583(2)	31(1)
B(1)	7194(9)	3105(3)	6125(3)	26(1)

X-ray Crystallographic Data for compound 40a

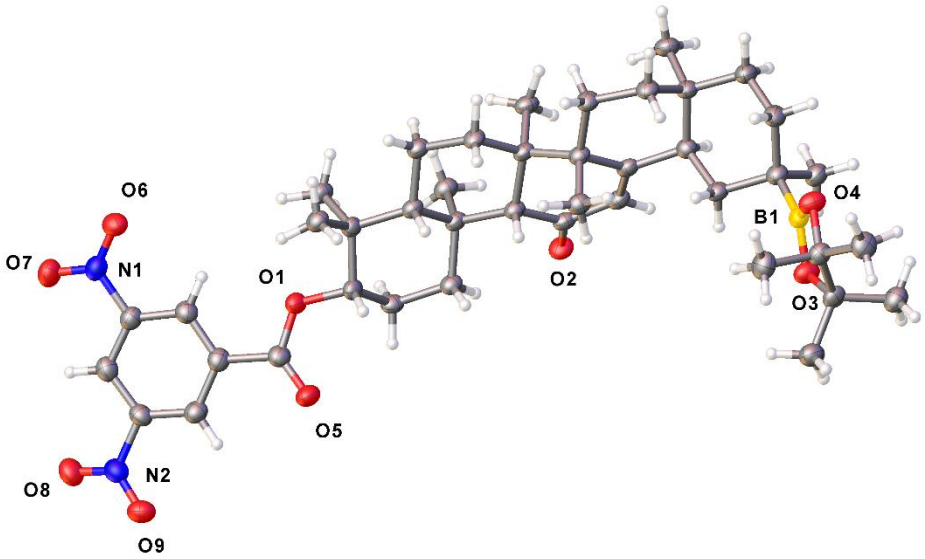


Table S24. Crystal data and structure refinement for **40a**.

Identification code	CCDC 1533051	
Empirical formula	C42 H59 B N2 O9	
Molecular formula	C42 H59 B N2 O9	
Formula weight	746.72	
Temperature	100 K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 7.2593(3) Å	α= 90°.
b = 13.7343(6) Å	β= 90°.	
c = 39.6303(19) Å	γ = 90°.	
Volume	3951.2(3) $Å^3$	
Z	4	
Density (calculated)	1.255 Mg/m^3	
Absorption coefficient	0.702 mm^{-1}	
F(000)	1608	
Crystal size	0.473 x 0.035 x 0.031 mm^3	
Crystal color, habit	Colorless Needle	
Theta range for data collection	2.230 to 68.501°.	
Index ranges	-8<=h<=8, -16<=k<=16, -47<=l<=37	
Reflections collected	59234	

Independent reflections	7157 [R(int) = 0.0968, R(sigma) = 0.0578]
Completeness to theta = 68.000°	99.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.3201 and 0.2131
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7157 / 0 / 499
Goodness-of-fit on F^2	1.019
Final R indices [I>2sigma(I)]	R1 = 0.0400, wR2 = 0.0828
R indices (all data)	R1 = 0.0580, wR2 = 0.0872
Absolute structure parameter	0.18(11)
Extinction coefficient	0.00055(9)
Largest diff. peak and hole	0.261 and -0.179 e.$Å^{-3}$

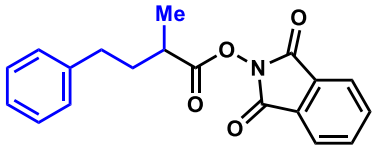
Table S25. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **40a**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

x	y	z	U(eq)	
O(1)	2305(2)	4809(2)	4801(1)	33(1)
O(2)	4688(2)	687(2)	4023(1)	35(1)
O(3)	6171(3)	135(2)	2098(1)	36(1)
O(4)	3528(3)	89(2)	1785(1)	36(1)
O(5)	4969(3)	5604(2)	4694(1)	41(1)
O(6)	-1984(3)	5995(2)	5616(1)	42(1)
O(7)	-979(3)	6787(2)	6052(1)	46(1)
O(8)	5160(3)	8130(2)	6030(1)	48(1)
O(9)	6714(3)	8080(2)	5562(1)	44(1)
N(1)	-762(3)	6409(2)	5774(1)	37(1)
N(2)	5413(3)	7845(2)	5739(1)	39(1)
C(1)	2000(3)	2214(2)	4188(1)	27(1)
C(2)	3891(4)	2694(2)	4261(1)	30(1)
C(3)	3853(4)	3409(2)	4555(1)	30(1)
C(4)	2441(4)	4197(2)	4500(1)	30(1)
C(5)	464(3)	3815(2)	4436(1)	28(1)
C(6)	586(3)	3057(2)	4146(1)	26(1)
C(7)	-1301(3)	2667(2)	4035(1)	30(1)
C(8)	-1165(3)	2199(2)	3690(1)	29(1)
C(9)	254(3)	1364(2)	3670(1)	26(1)

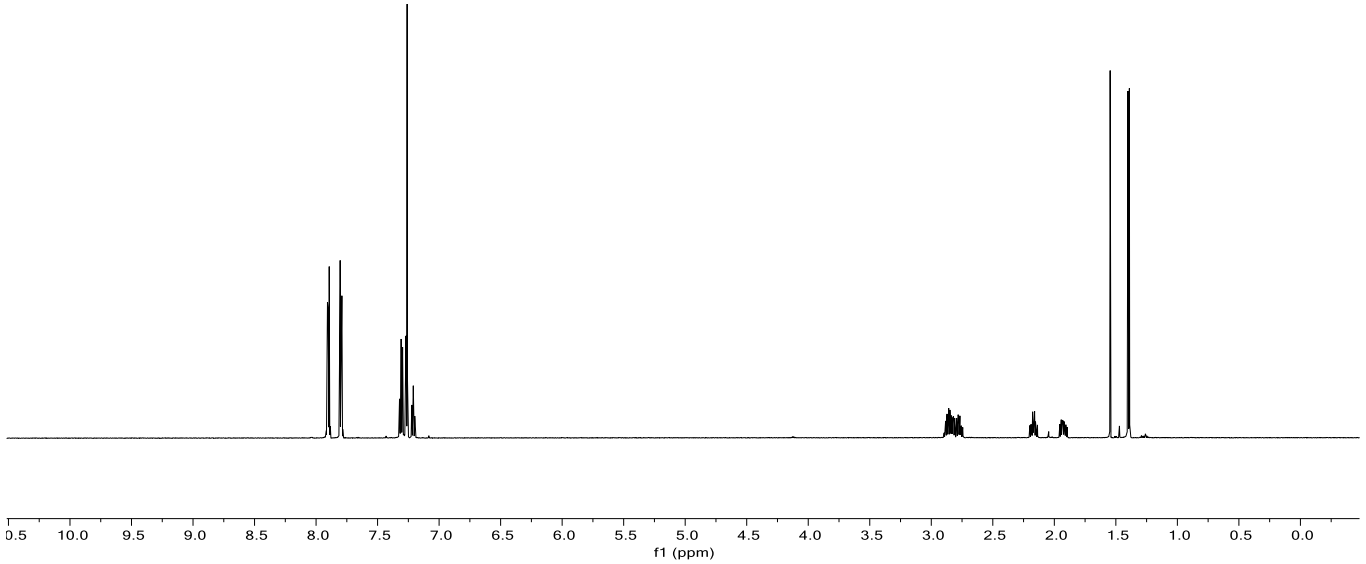
C(10)	2121(3)	1687(2)	3837(1)	26(1)
C(11)	3484(3)	842(2)	3812(1)	28(1)
C(12)	3344(3)	202(2)	3516(1)	30(1)
C(13)	2054(3)	266(2)	3276(1)	27(1)
C(14)	663(3)	1103(2)	3288(1)	27(1)
C(15)	-1171(3)	871(3)	3100(1)	32(1)
C(16)	-938(3)	240(2)	2788(1)	32(1)
C(17)	114(3)	-713(2)	2863(1)	30(1)
C(18)	2082(3)	-443(2)	2981(1)	27(1)
C(19)	3299(3)	-58(2)	2690(1)	31(1)
C(20)	3369(4)	-728(2)	2376(1)	31(1)
C(21)	1372(4)	-948(3)	2266(1)	34(1)
C(22)	202(4)	-1355(3)	2548(1)	35(1)
C(23)	1540(4)	1498(2)	4476(1)	32(1)
C(24)	-381(4)	3414(2)	4764(1)	33(1)
C(25)	-716(4)	4685(2)	4326(1)	33(1)
C(26)	-565(4)	480(2)	3860(1)	32(1)
C(27)	1585(4)	1955(2)	3093(1)	31(1)
C(28)	-876(4)	-1283(3)	3140(1)	37(1)
C(29)	4425(4)	-1674(2)	2451(1)	36(1)
C(30)	6665(4)	515(2)	1765(1)	32(1)
C(31)	4747(4)	767(2)	1611(1)	33(1)
C(32)	7639(4)	-295(3)	1577(1)	40(1)
C(33)	7951(4)	1372(3)	1810(1)	42(1)
C(34)	4576(4)	610(3)	1237(1)	42(1)
C(35)	4072(4)	1783(3)	1705(1)	44(1)
C(36)	3602(4)	5471(2)	4862(1)	33(1)
C(37)	3127(4)	6043(2)	5173(1)	33(1)
C(38)	1423(4)	5938(2)	5330(1)	33(1)
C(39)	1071(4)	6483(2)	5617(1)	33(1)
C(40)	2350(4)	7097(2)	5761(1)	36(1)
C(41)	4009(4)	7182(2)	5594(1)	33(1)
C(42)	4432(4)	6679(2)	5302(1)	34(1)
B(1)	4378(4)	-162(3)	2084(1)	31(1)

NMR Spectra

Compound 2 ^{1}H NMR

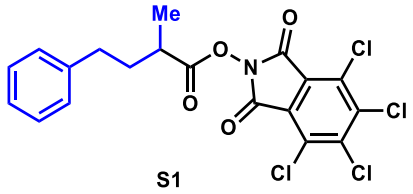


2

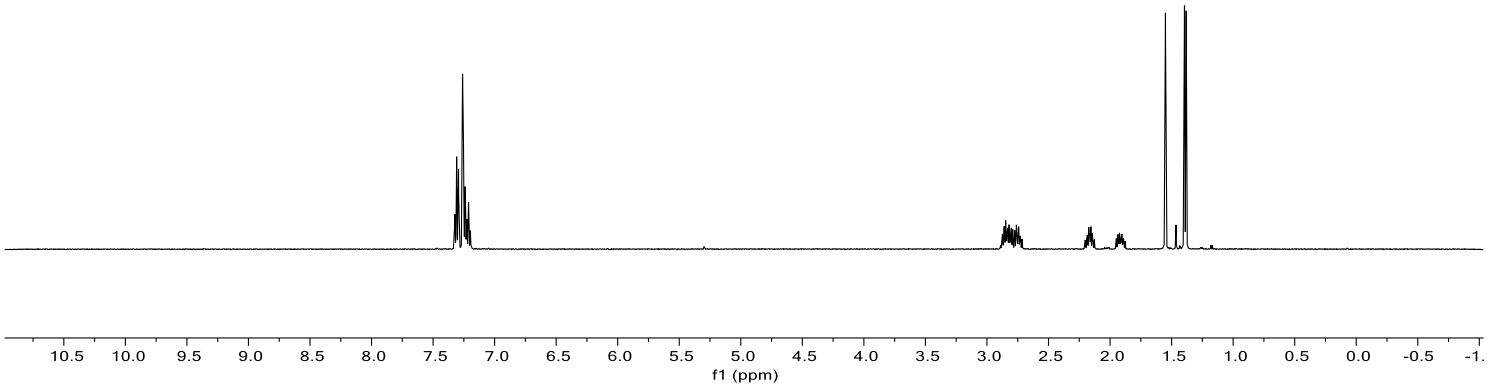


Compound 2 ^{13}C NMR

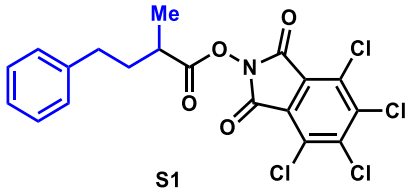
Compound S1 ^{1}H NMR



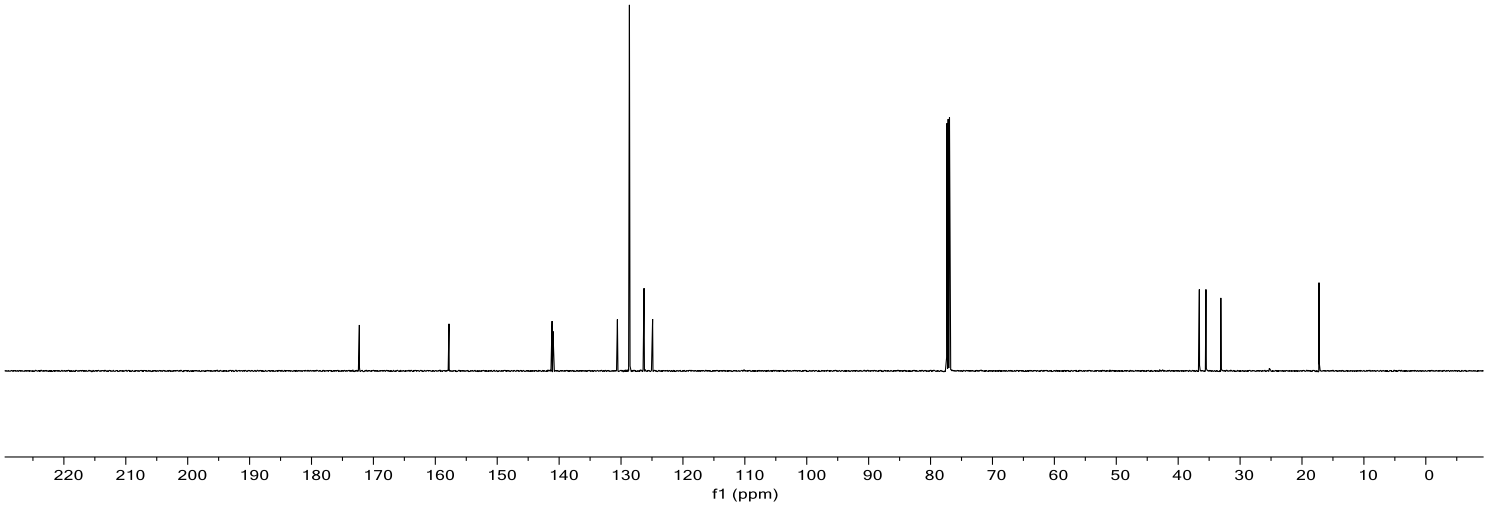
S1



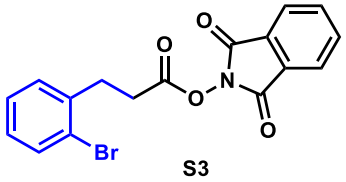
Compound S1 ^{13}C NMR



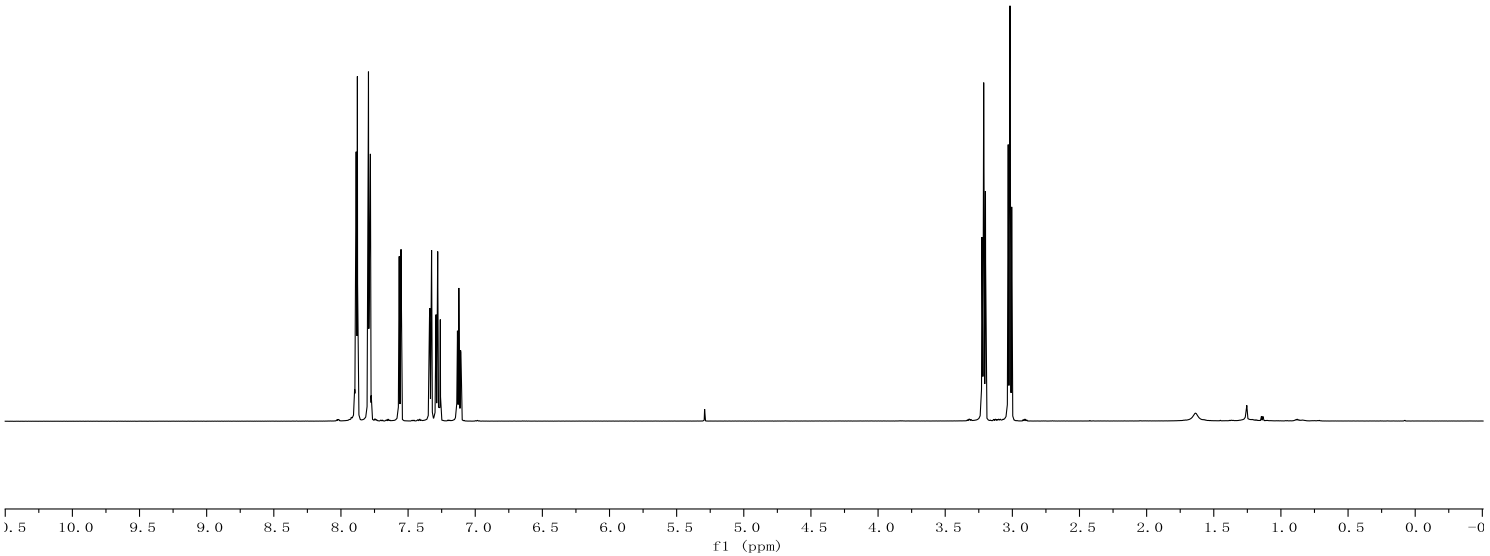
S1



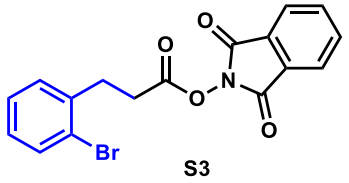
Compound S3 ^{1}H NMR



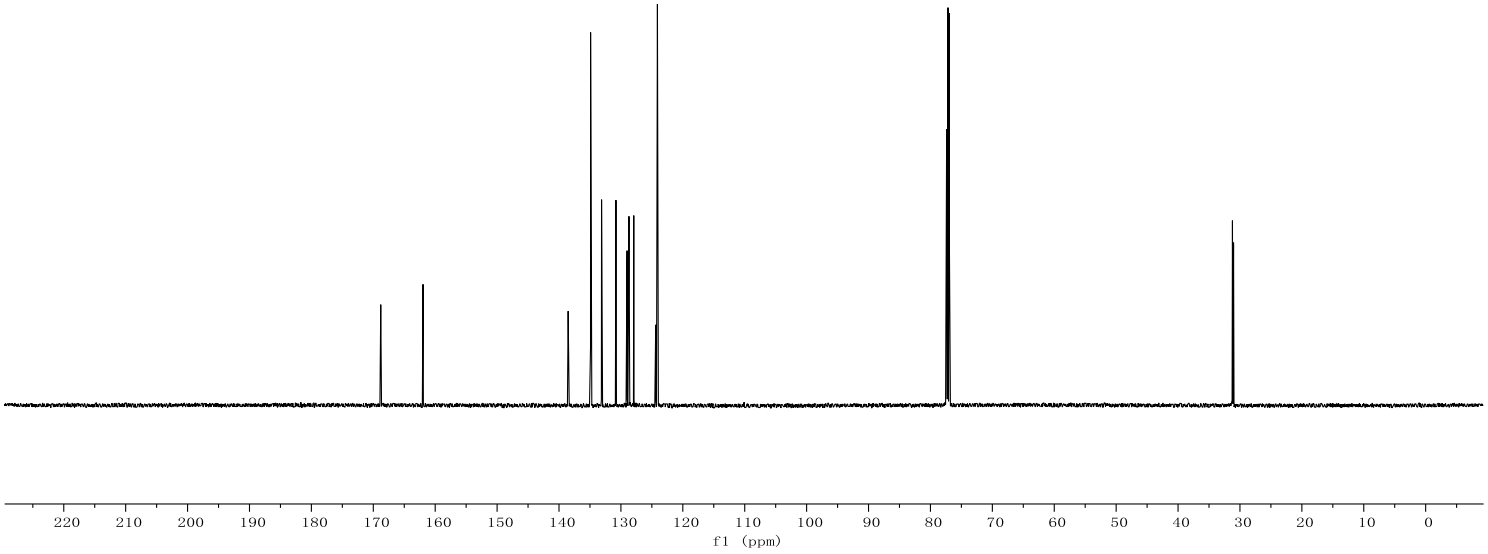
S3



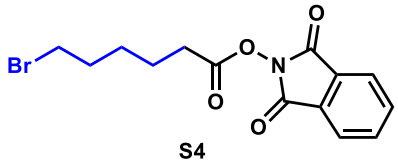
Compound S3 ^{13}C NMR



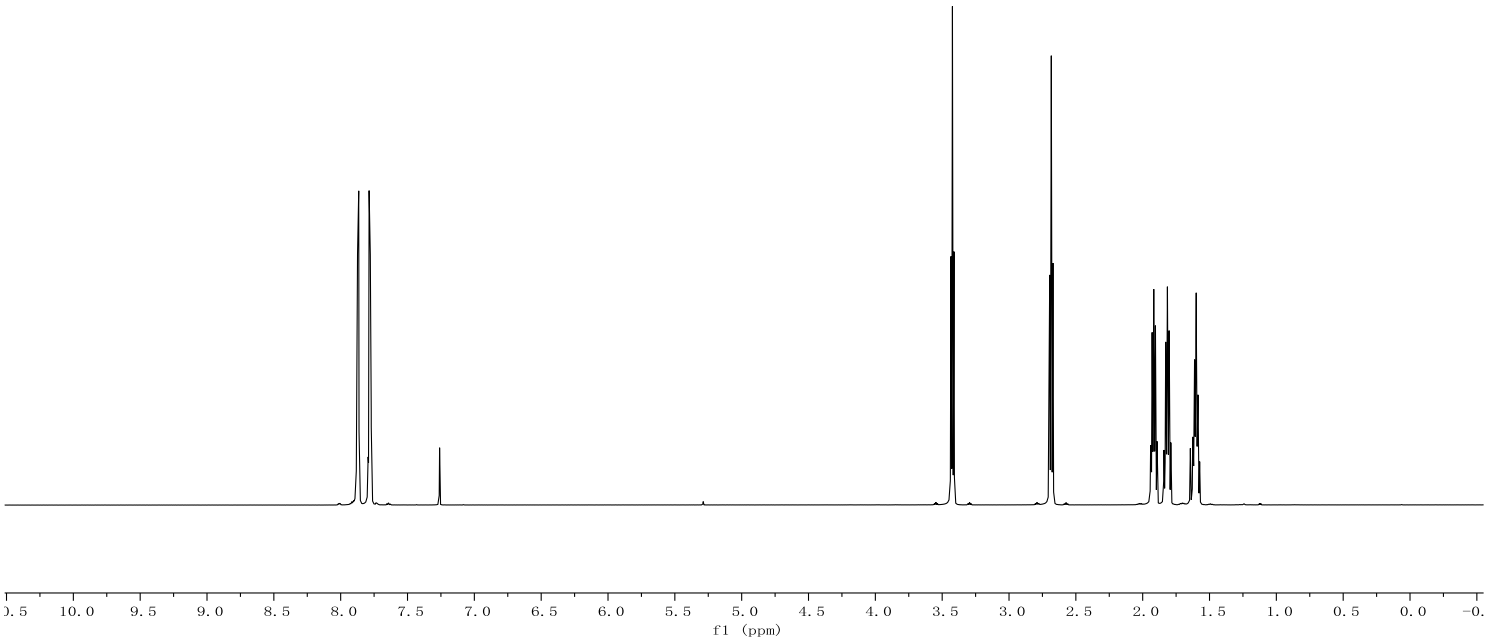
S3



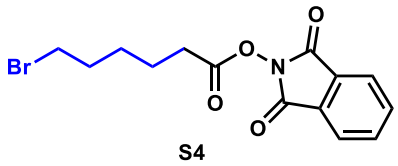
Compound S4 ^{1}H NMR



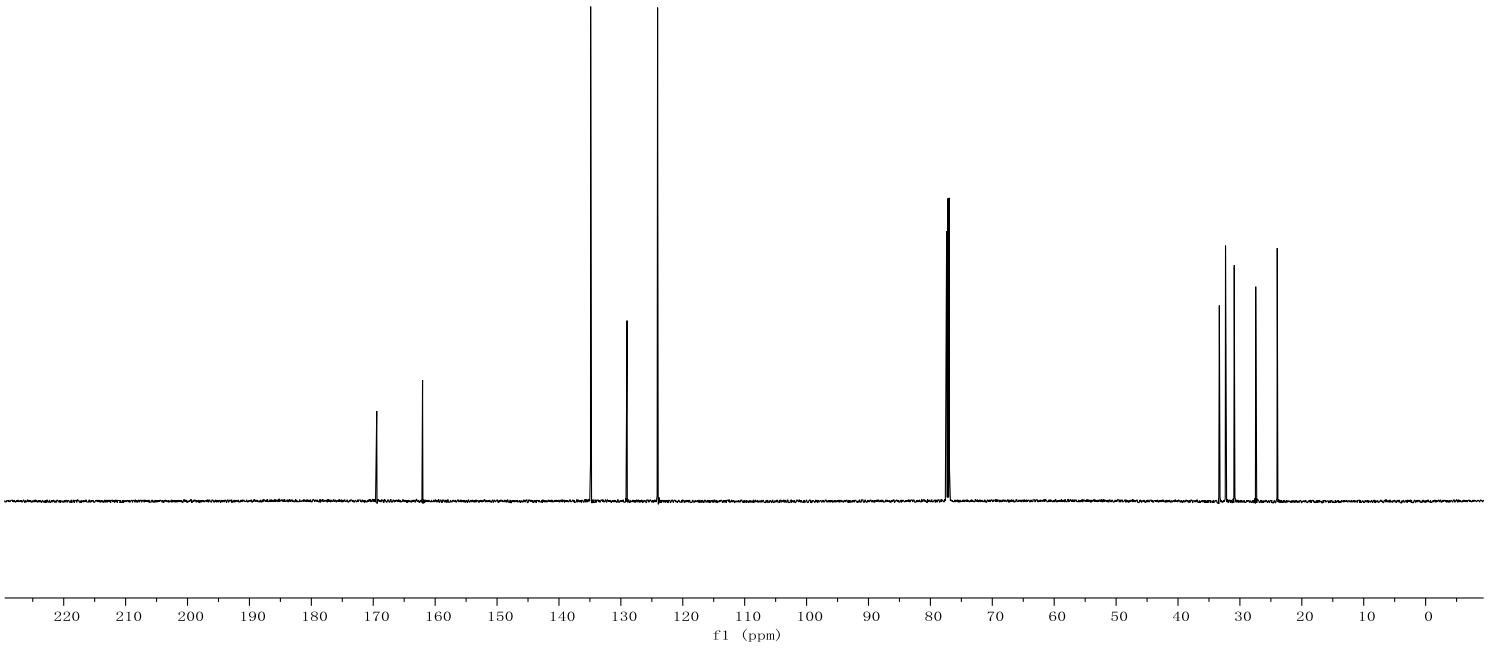
S4



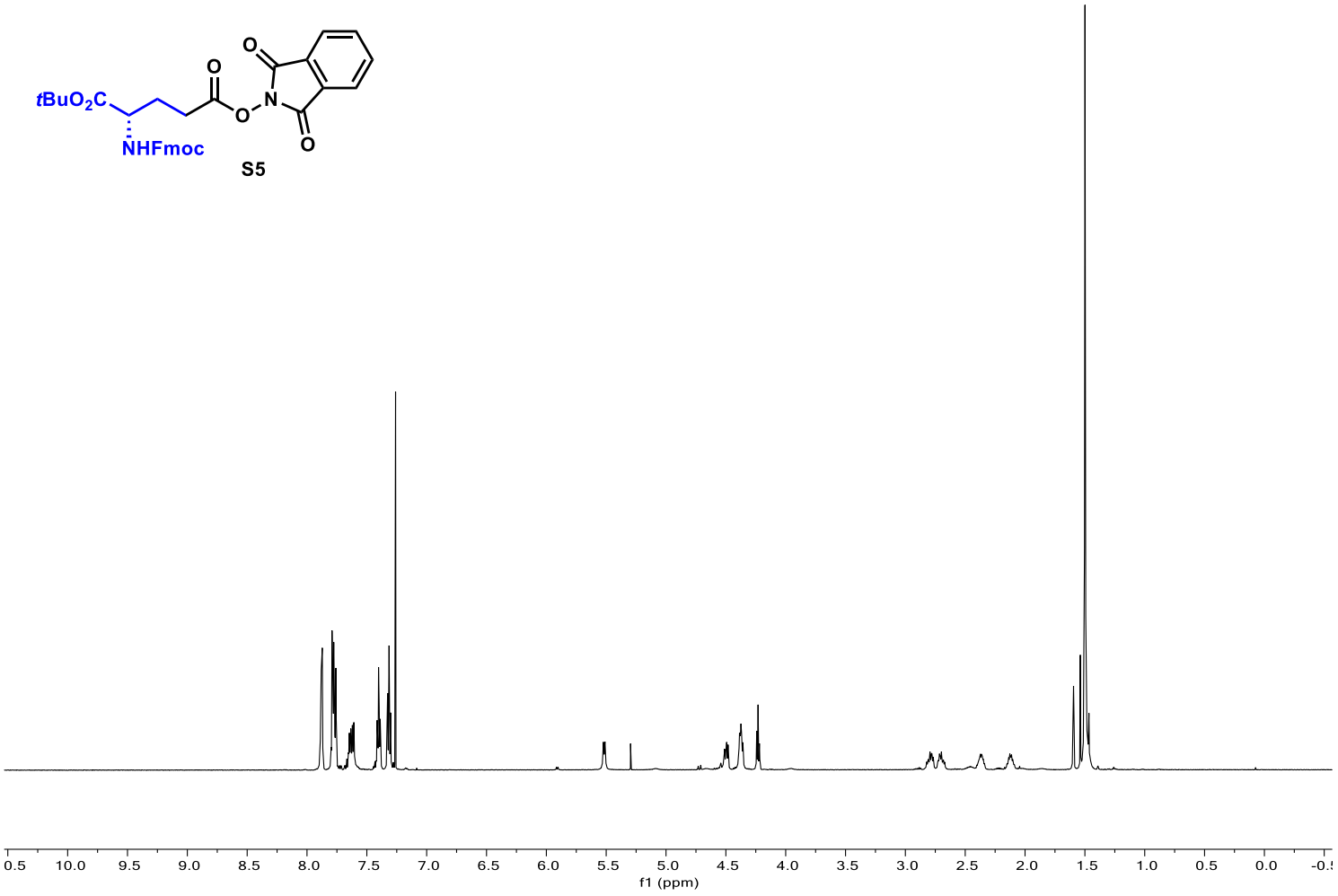
Compound S4 ^{13}C NMR



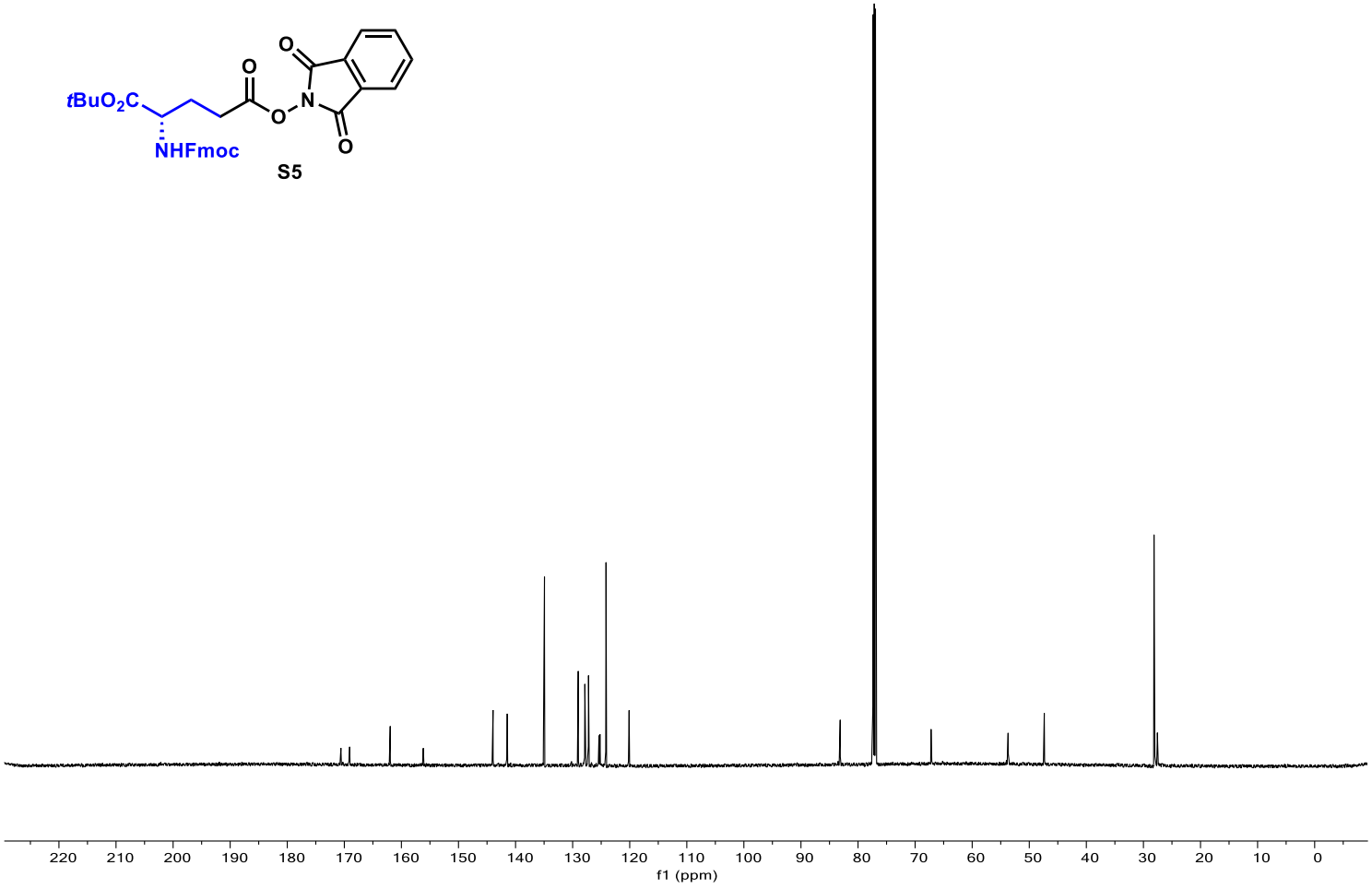
S4



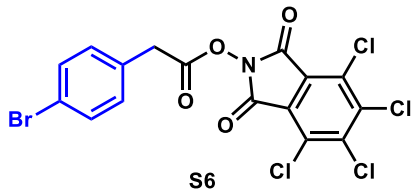
Compound S5 ^{1}H NMR



Compound S5 ^{13}C NMR

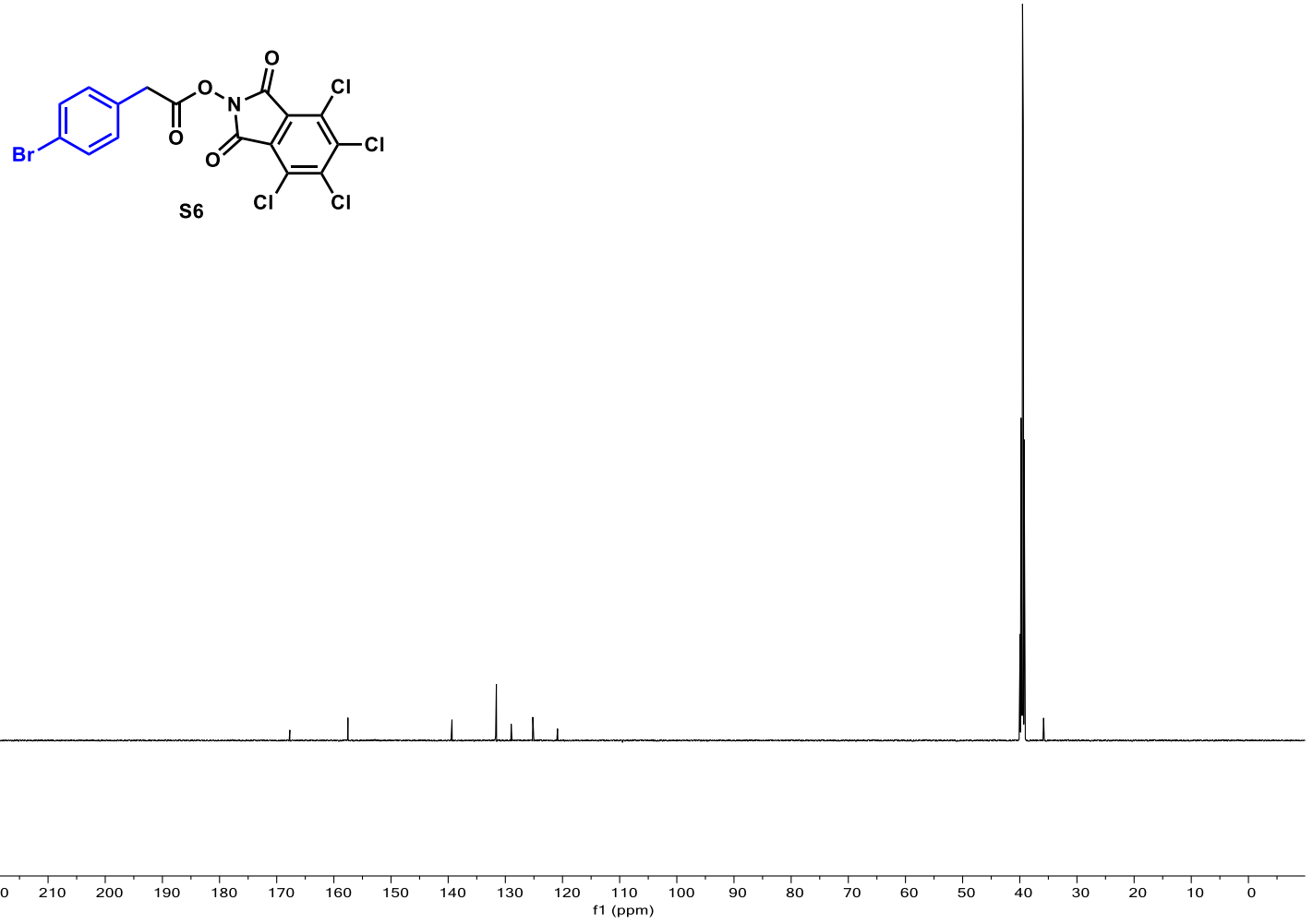


Compound S6 ^{1}H NMR

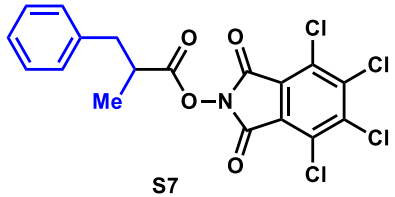


S6

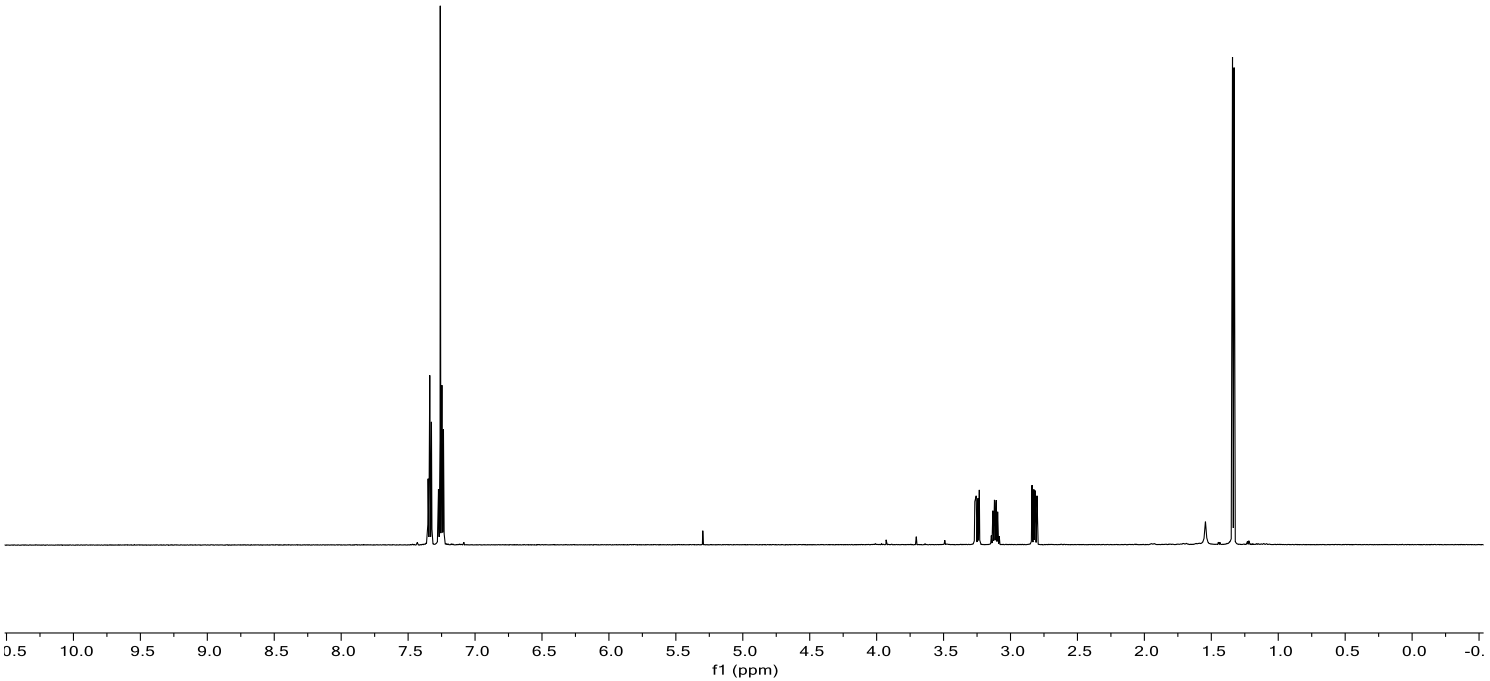
Compound S6 ^{13}C NMR



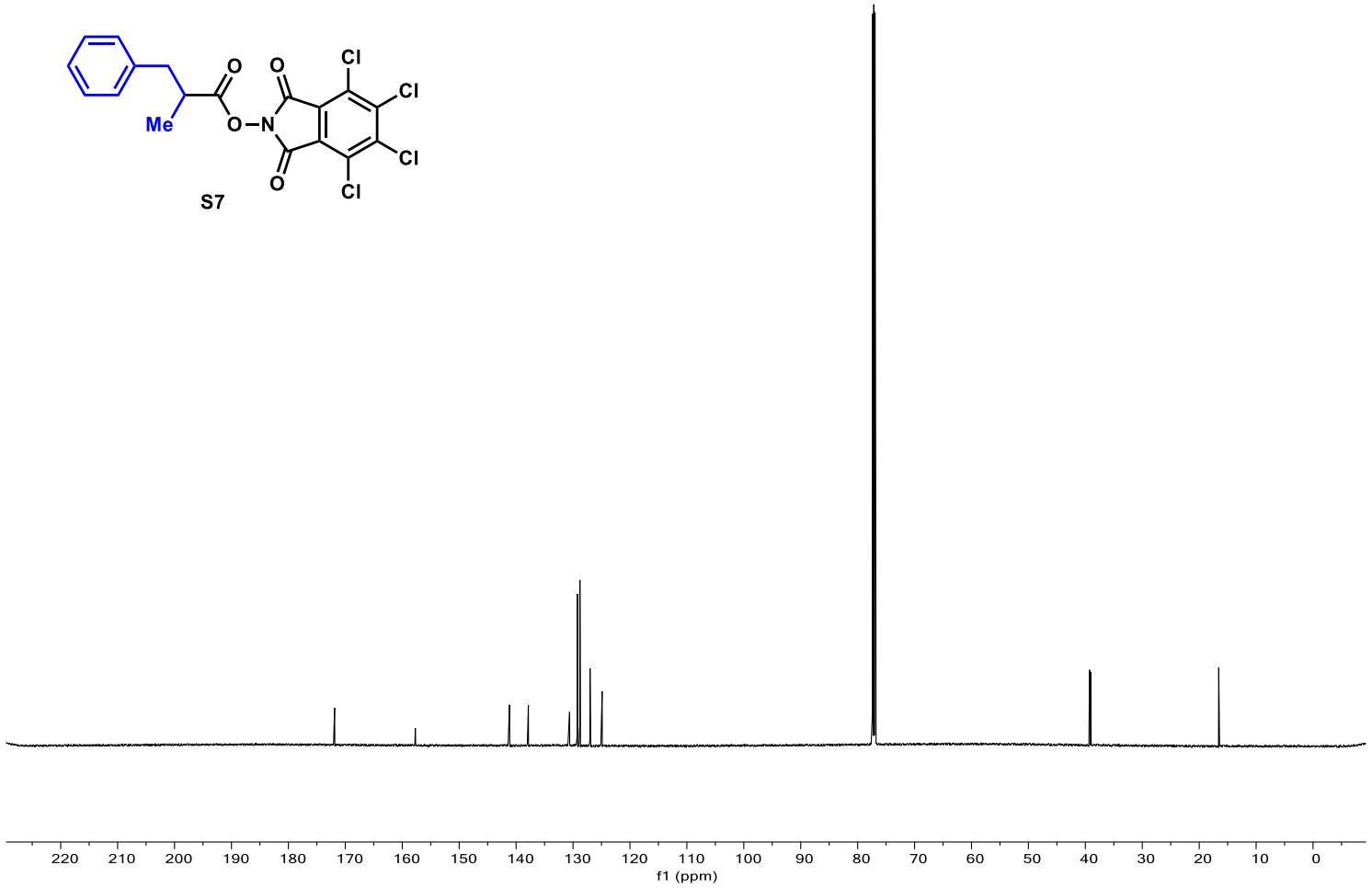
Compound S7 ^{1}H NMR



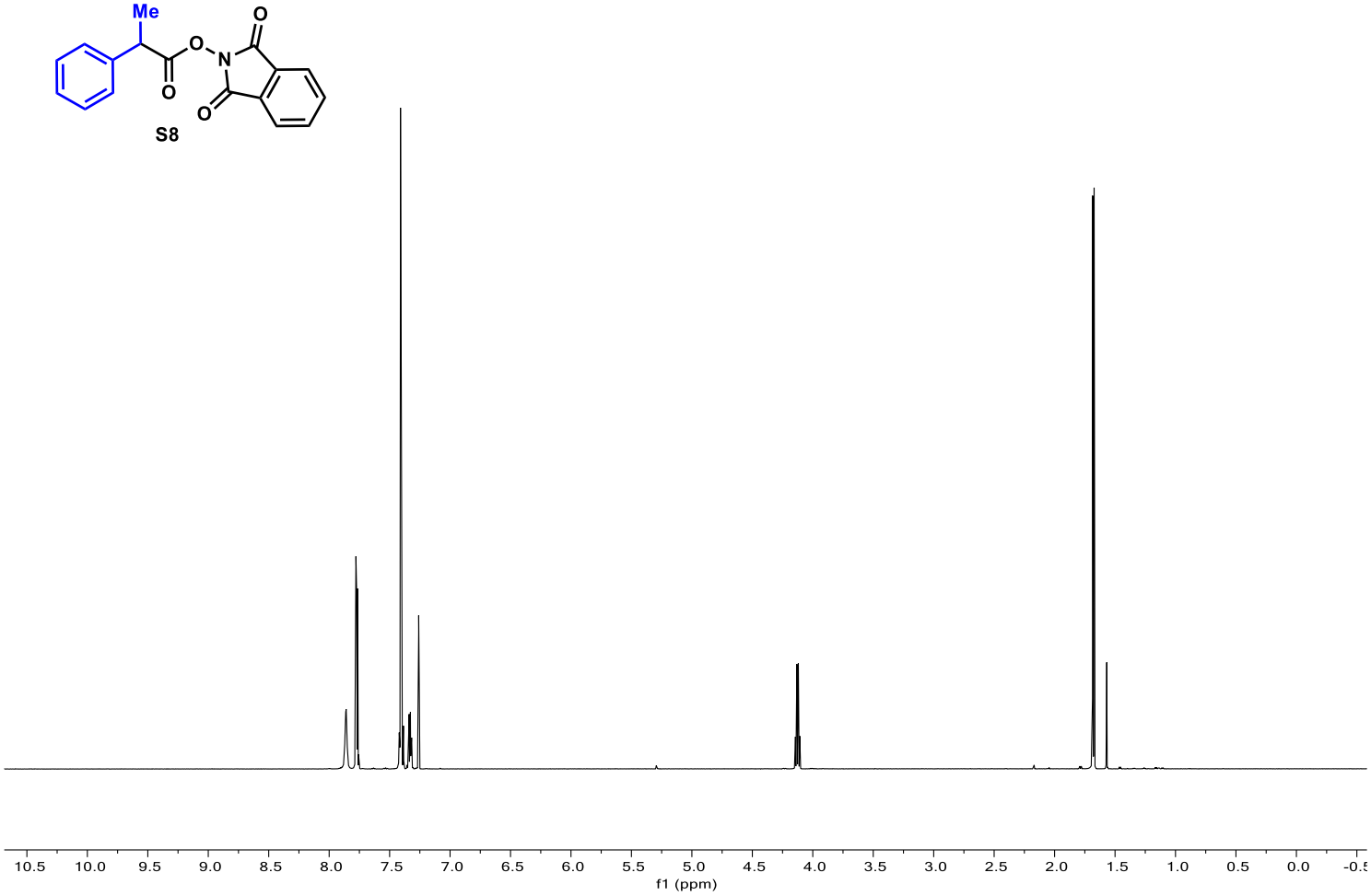
S7



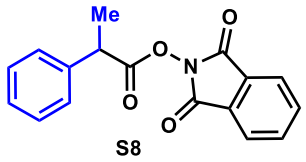
Compound S7 ^{13}C NMR



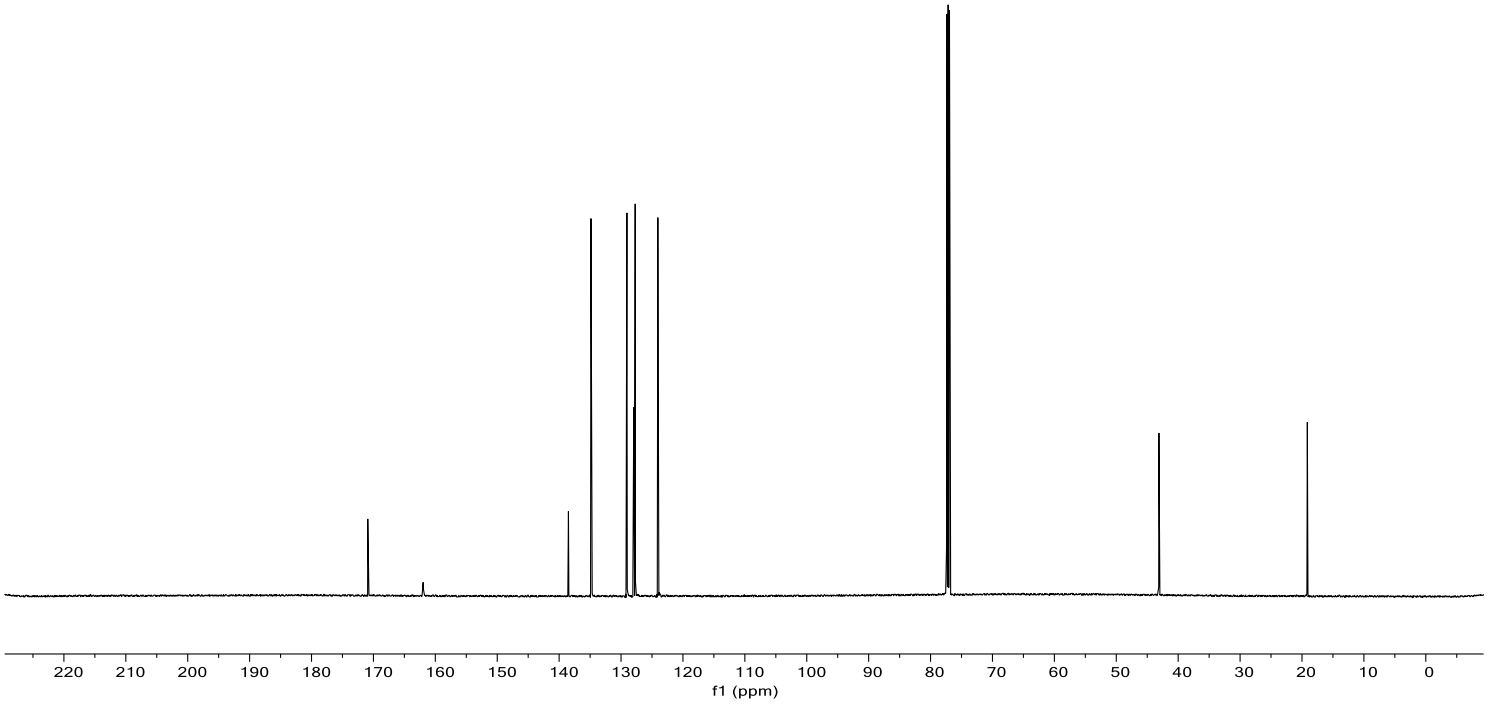
Compound S8 ^{1}H NMR



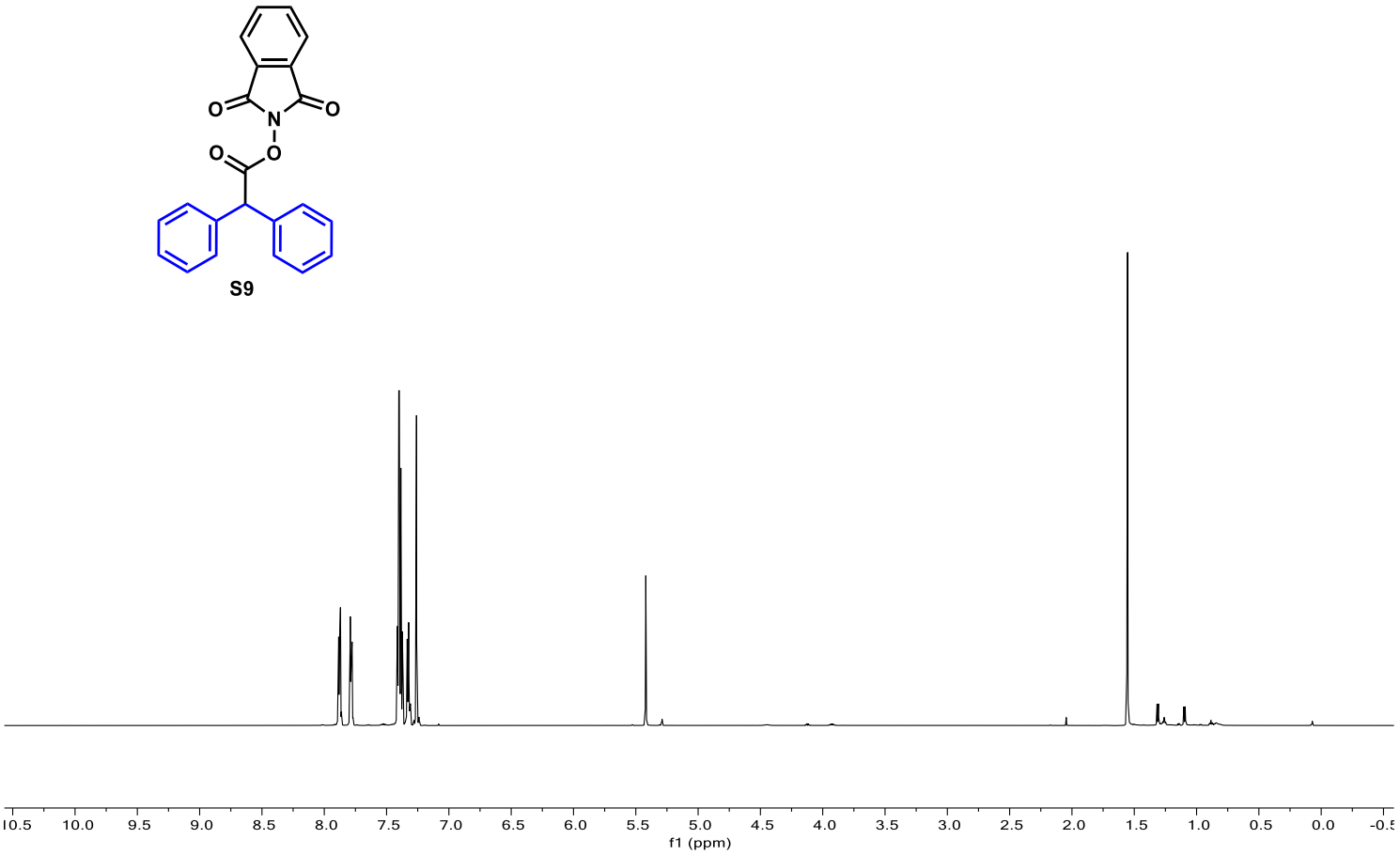
Compound S8 ^{13}C NMR



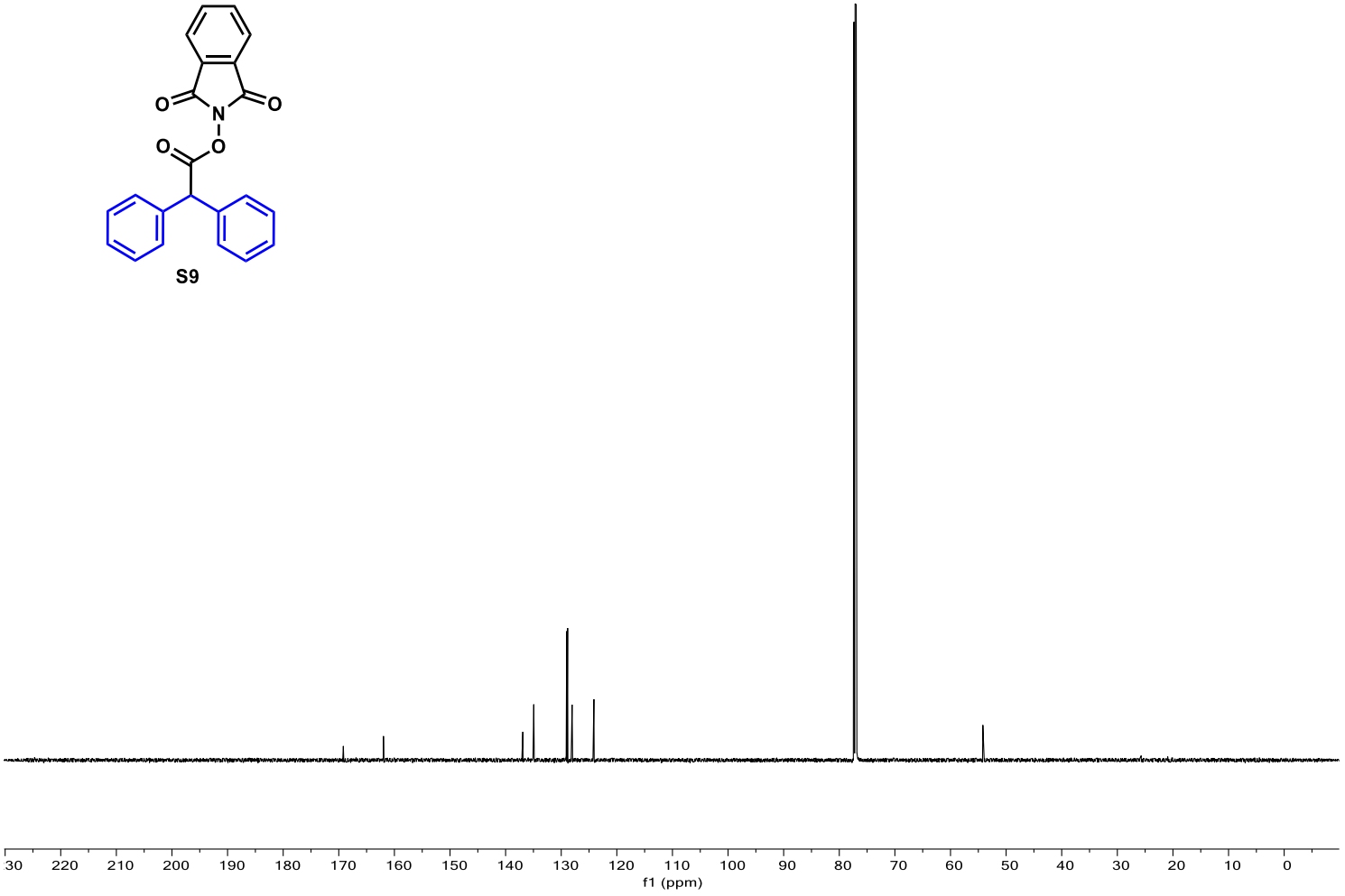
S8



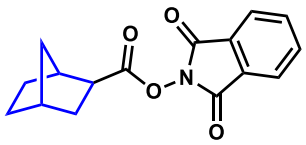
Compound S9 ^{1}H NMR



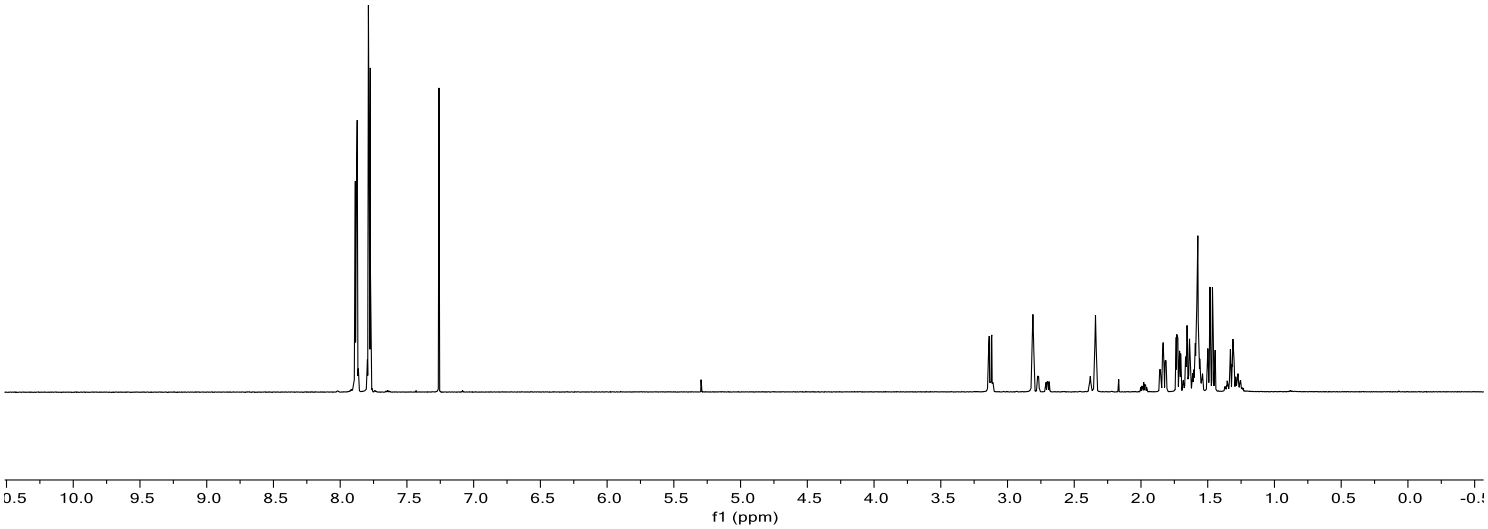
Compound S9 ^{13}C NMR



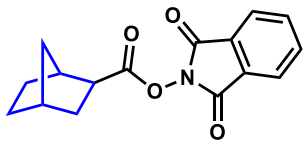
Compound S10 ^{1}H NMR



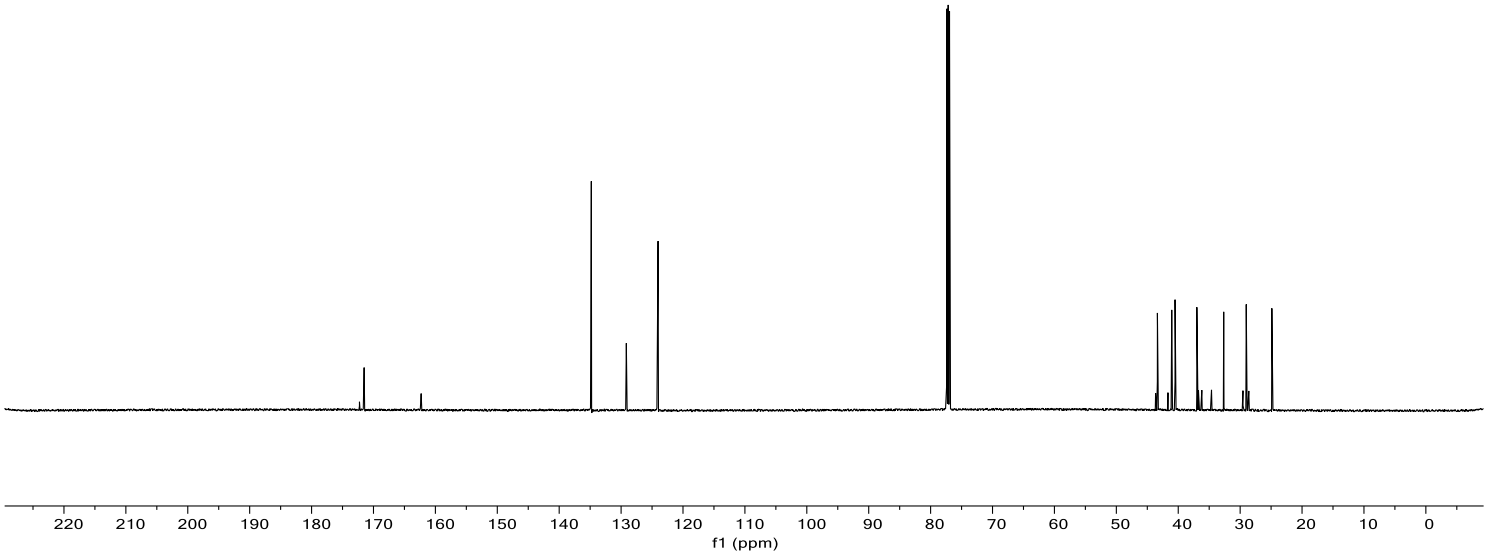
S10, mxiture of *exo* and *endo*



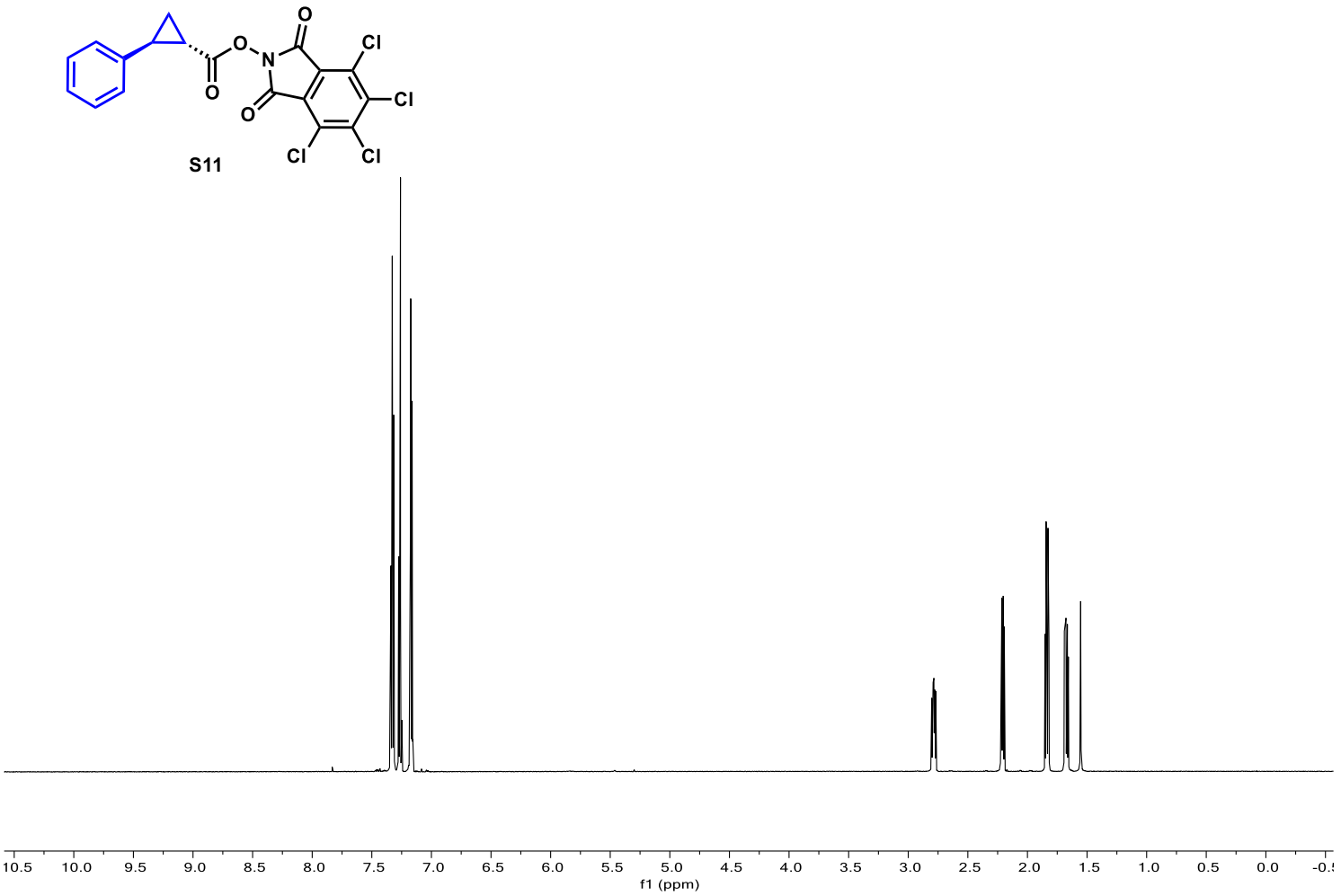
Compound S10 ^{13}C NMR



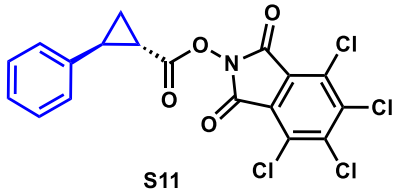
S10, mxiture of *exo* and *endo*



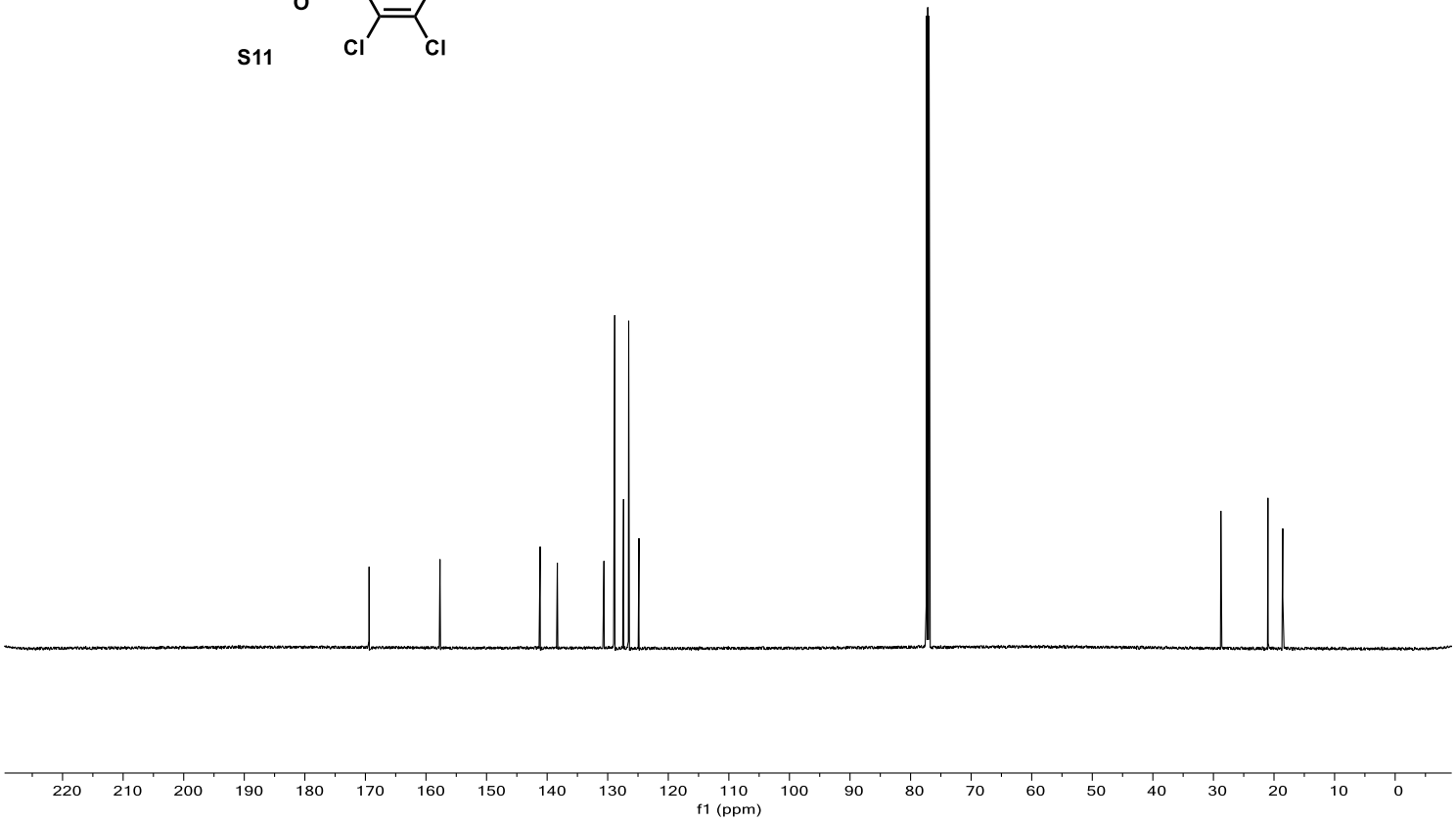
Compound S11 ^{1}H NMR



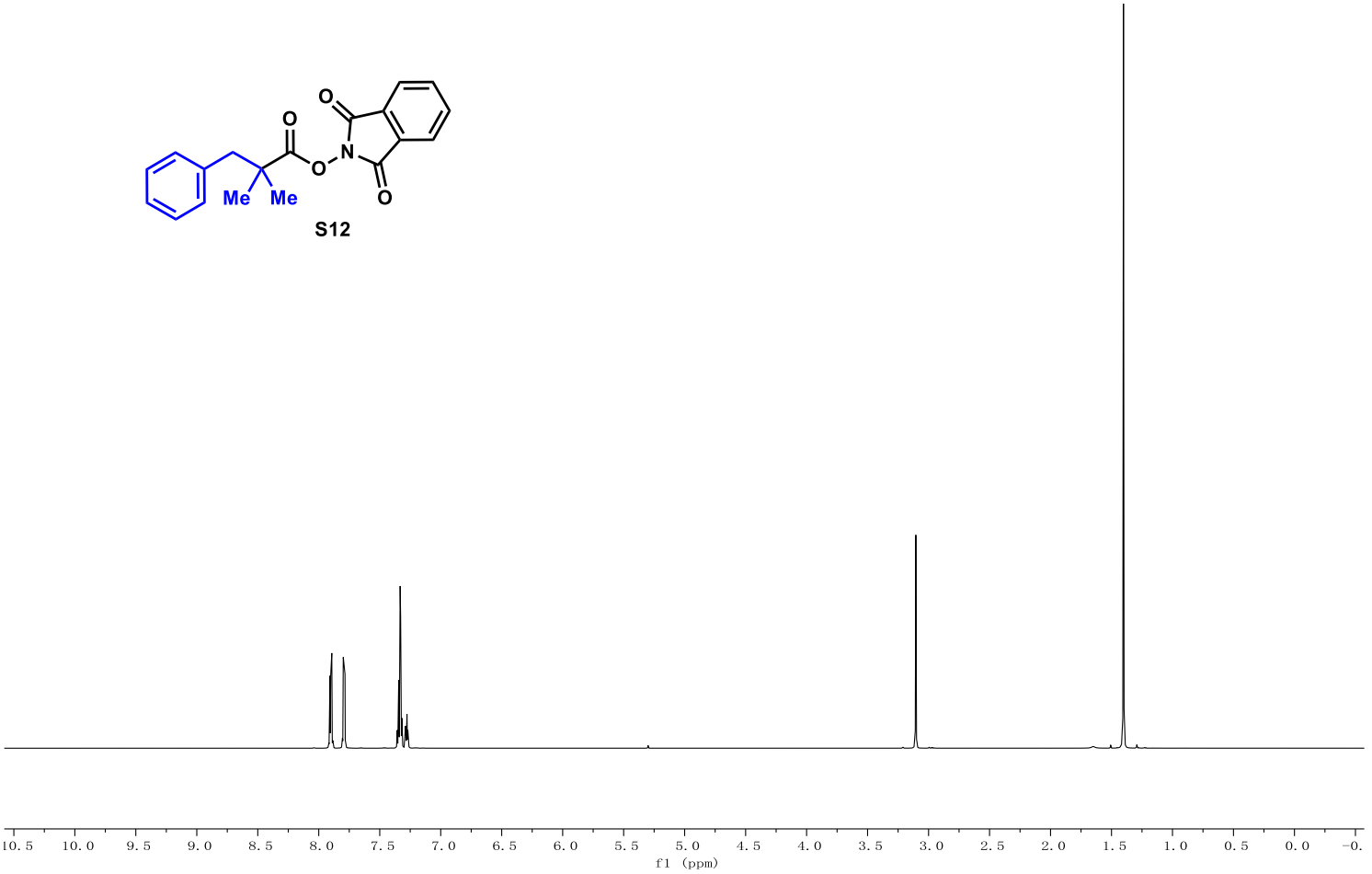
Compound S11 ^{13}C NMR



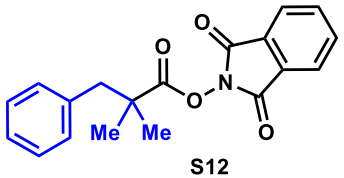
S11



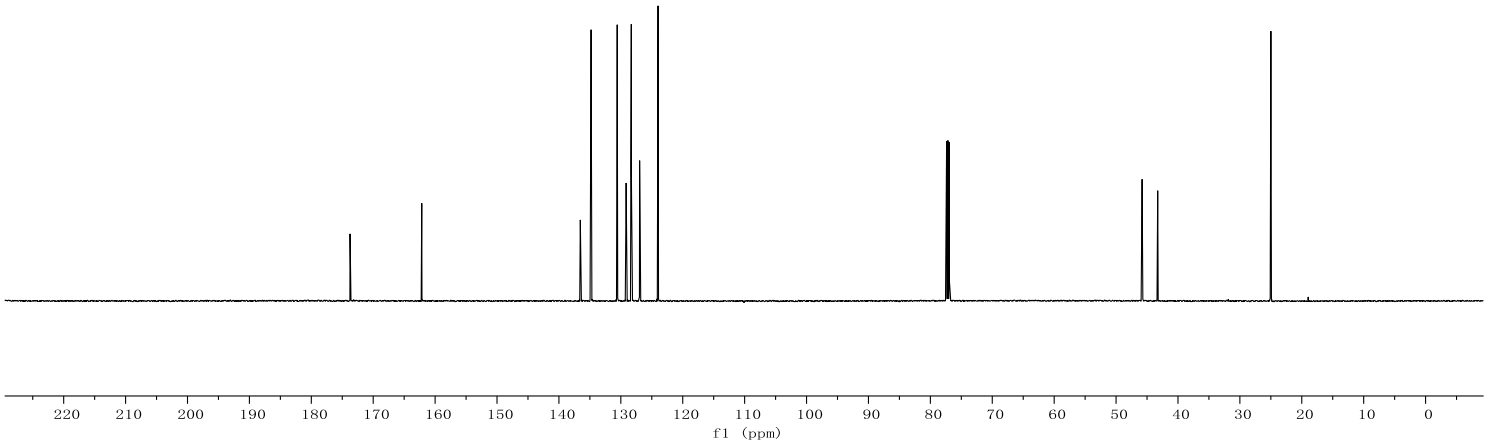
Compound S12 ^{1}H NMR



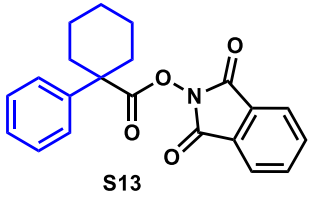
Compound S12 ^{13}C NMR



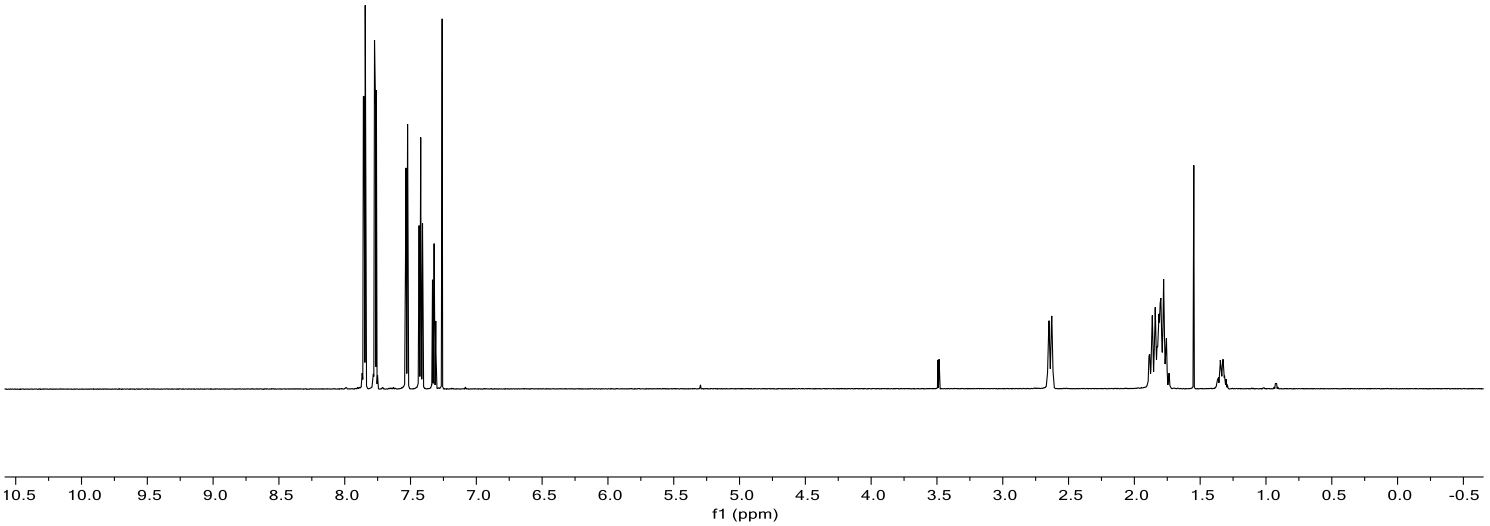
S12



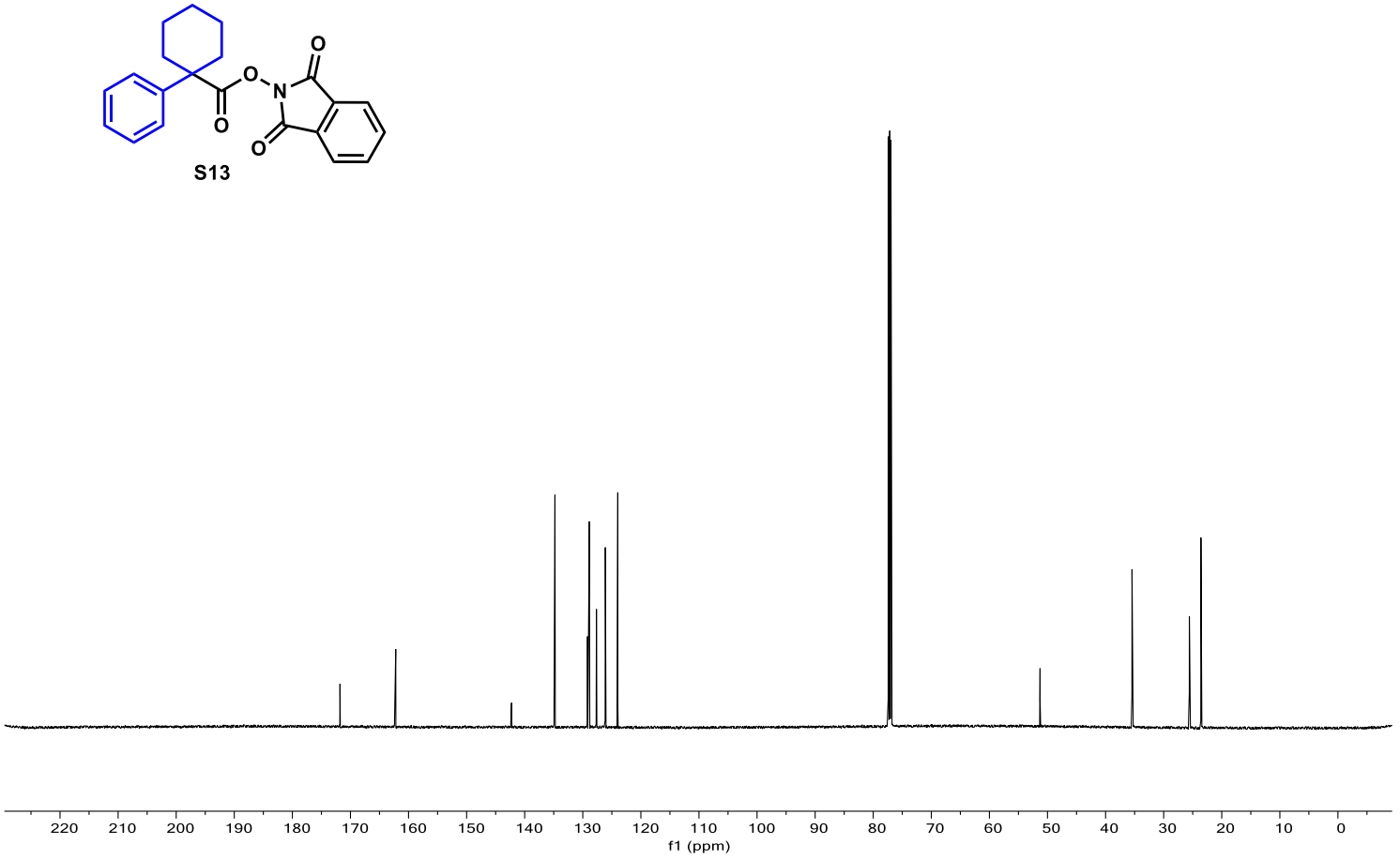
Compound S13 ^{1}H NMR



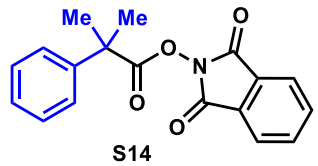
S13



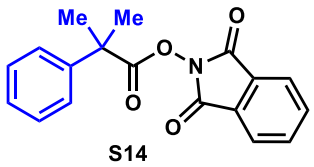
Compound S13 ^{13}C NMR



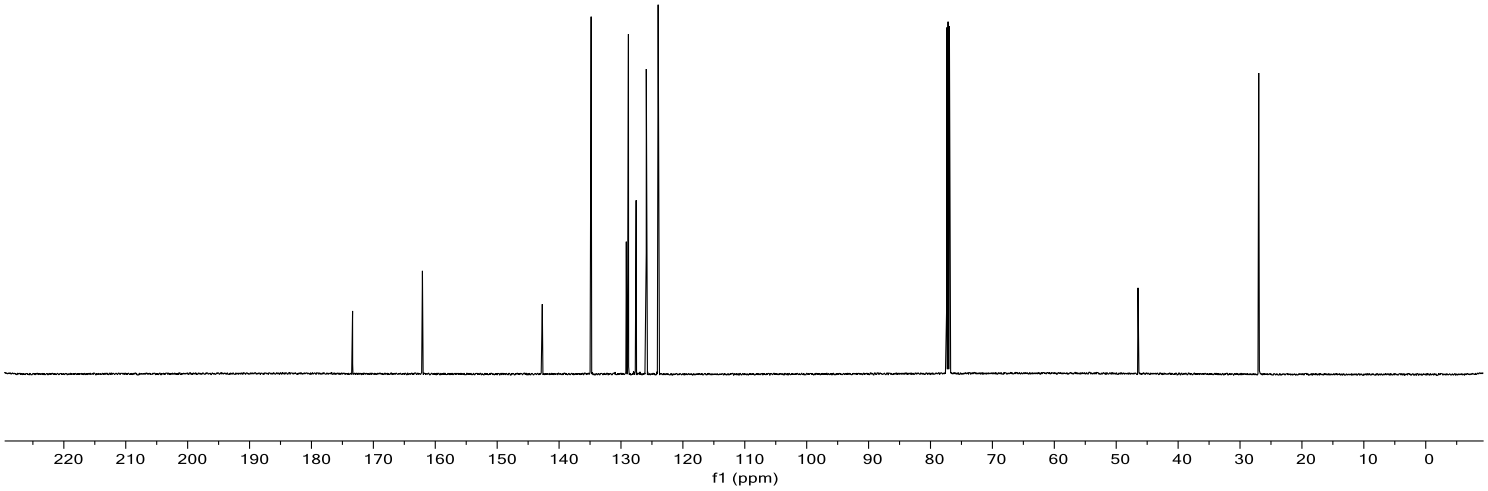
Compound S14 ^{1}H NMR



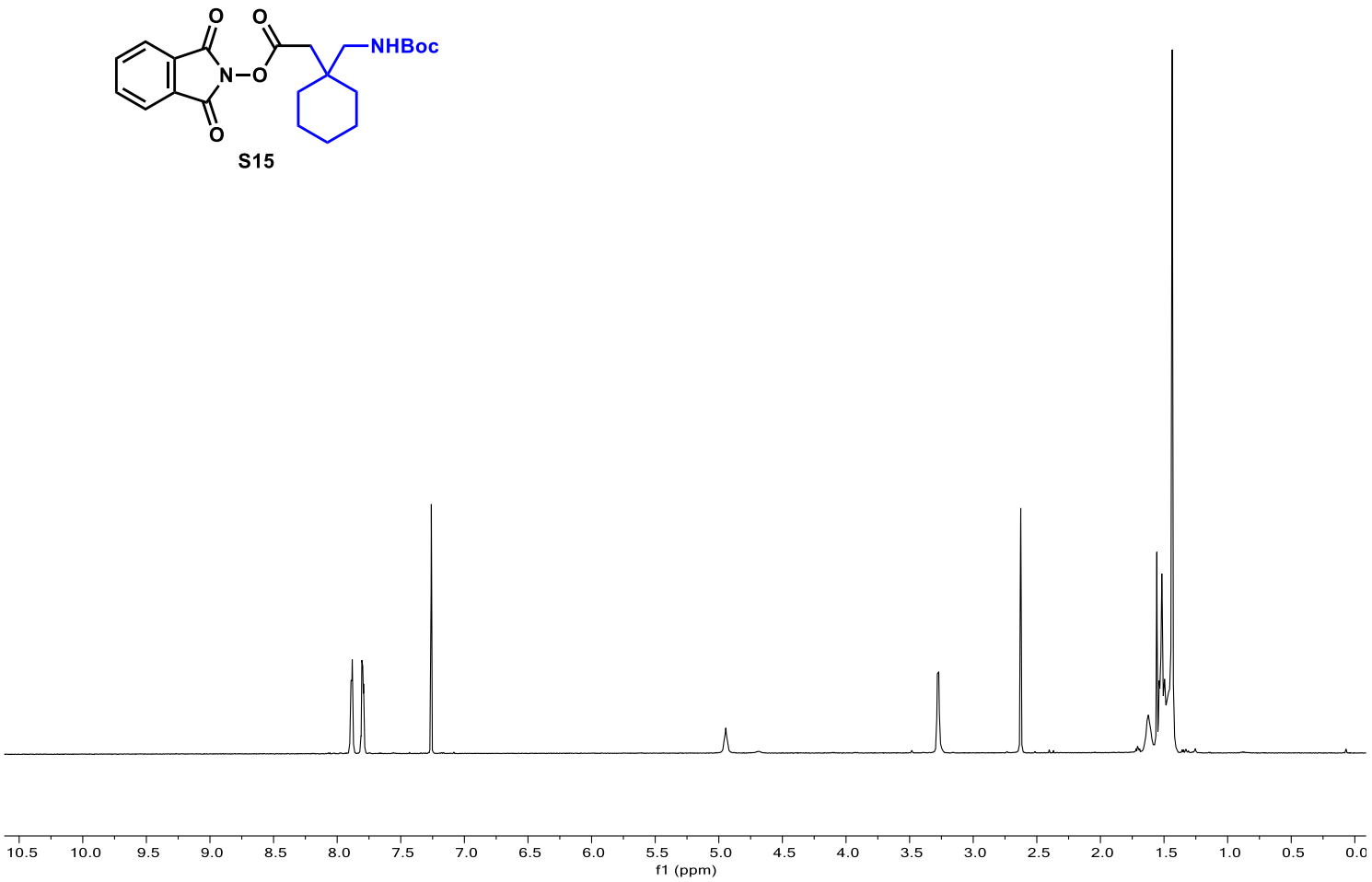
Compound S14 ^{13}C NMR



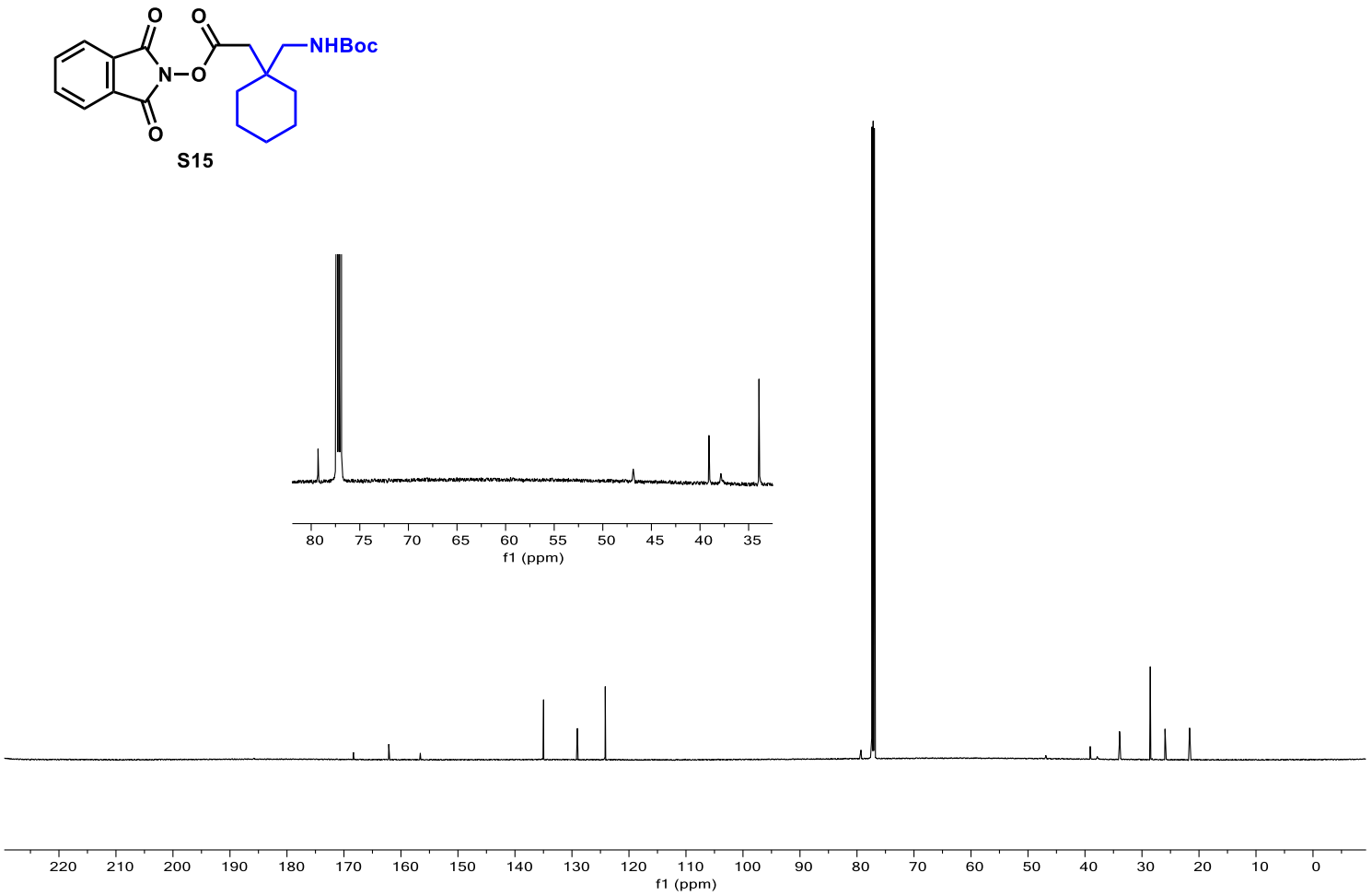
S14



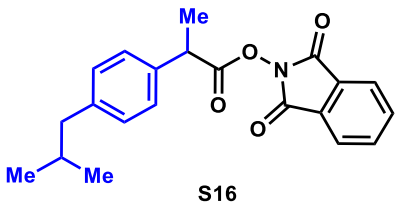
Compound S15 ^{1}H NMR



Compound S15 ^{13}C NMR

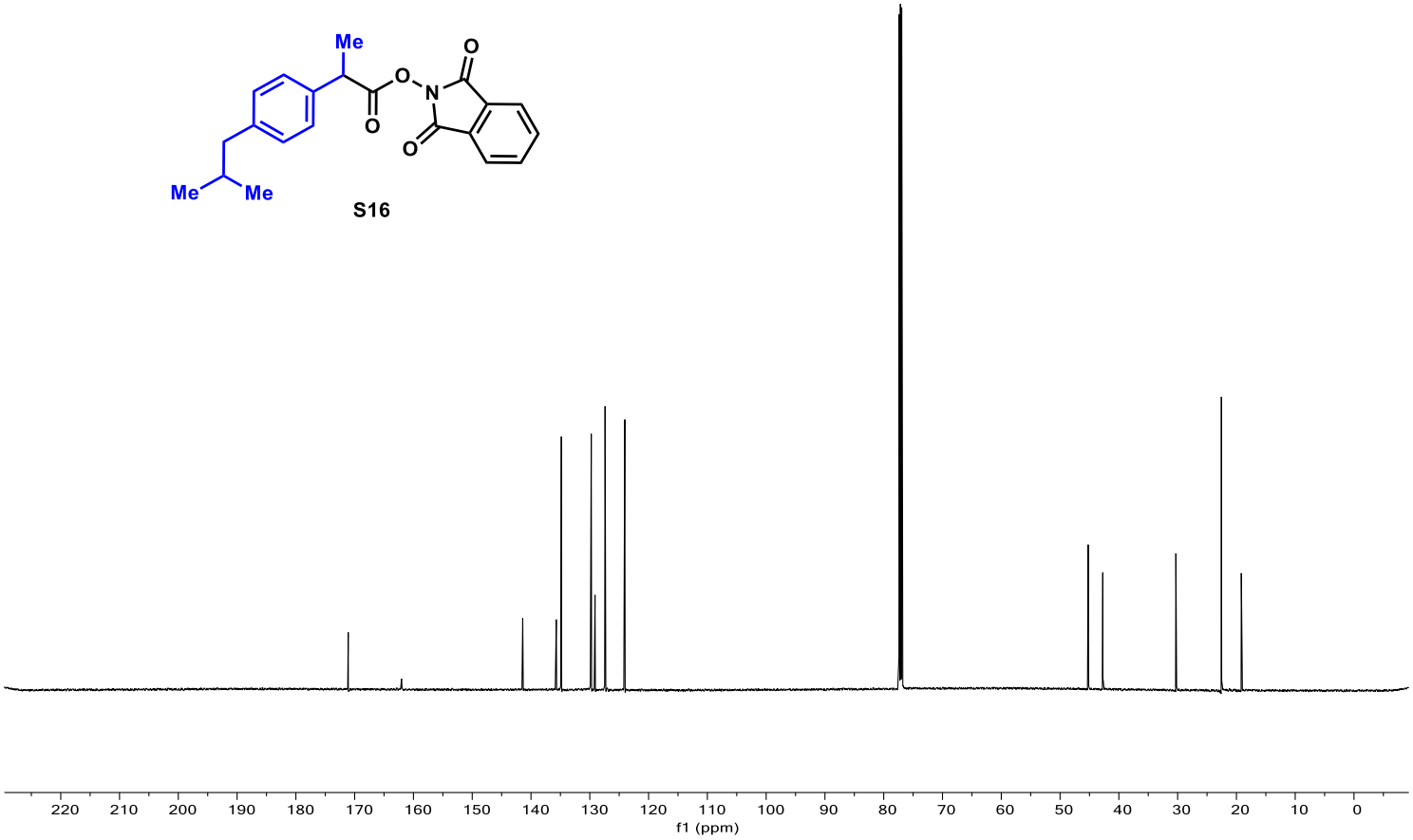


Compound S16 ^{1}H NMR

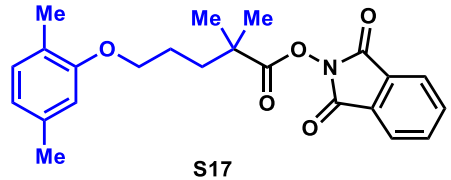


S16

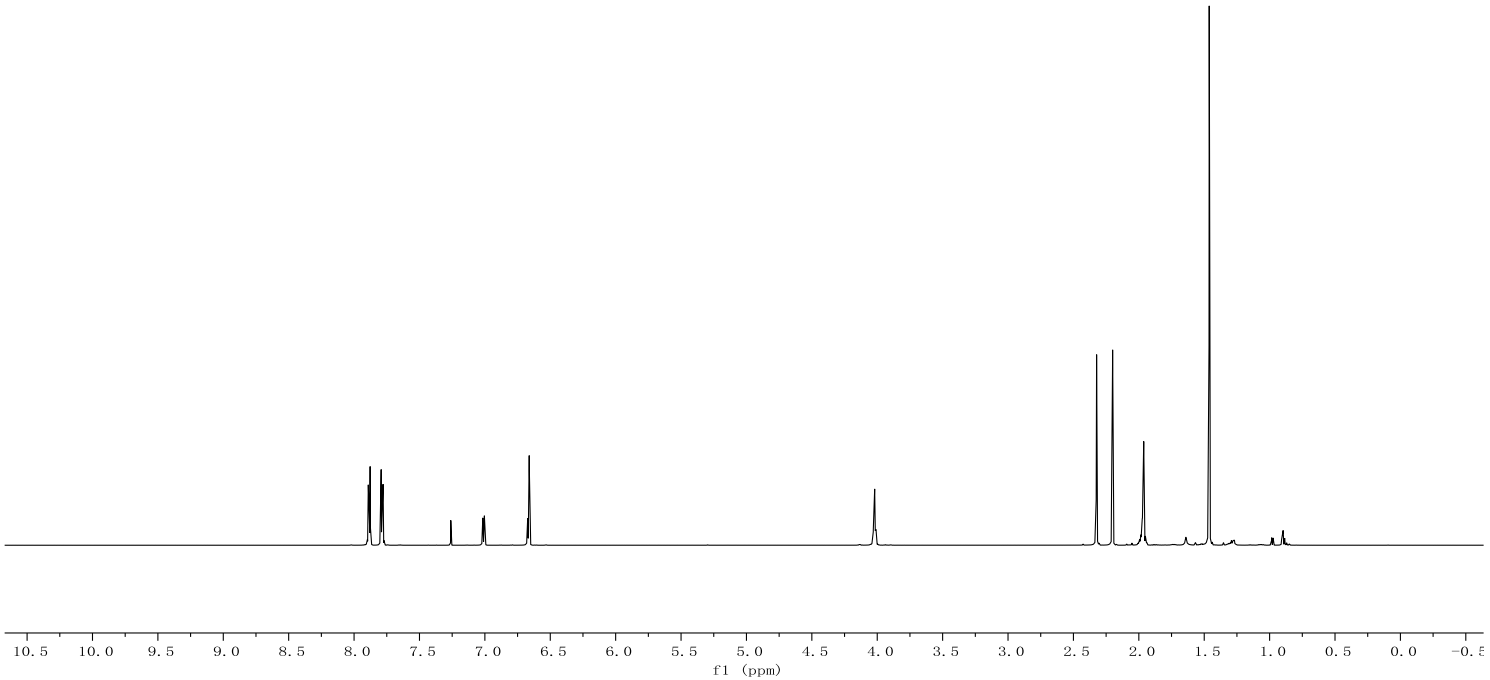
Compound S16 ^{13}C NMR



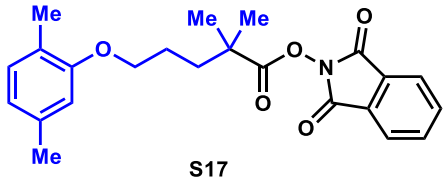
Compound S17 ^{1}H NMR



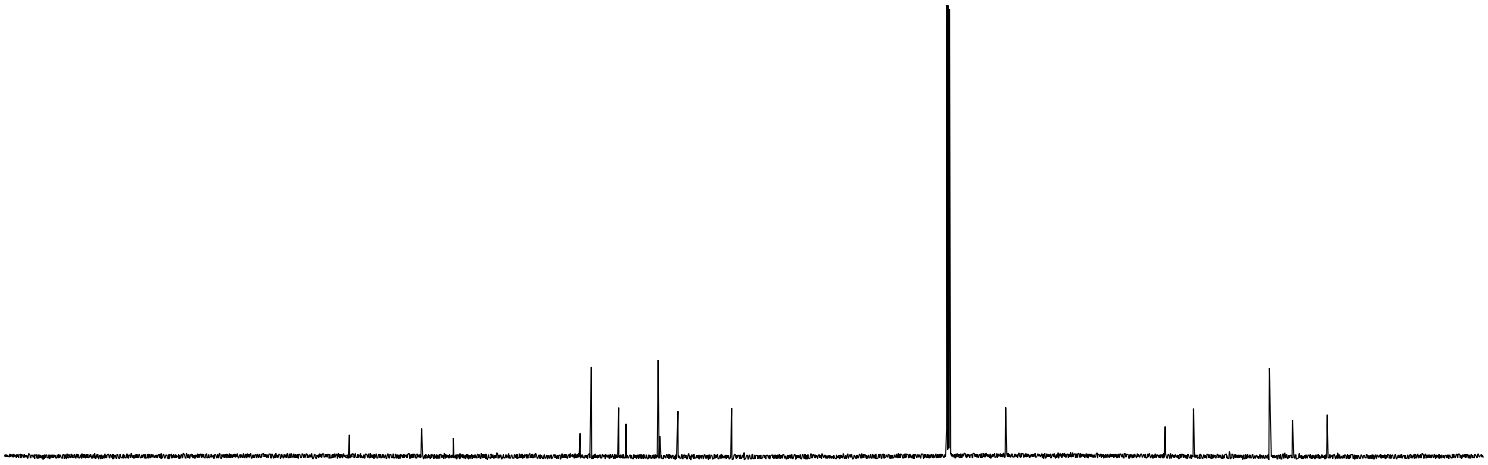
S17



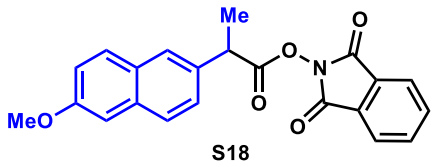
Compound S17 ^{13}C NMR



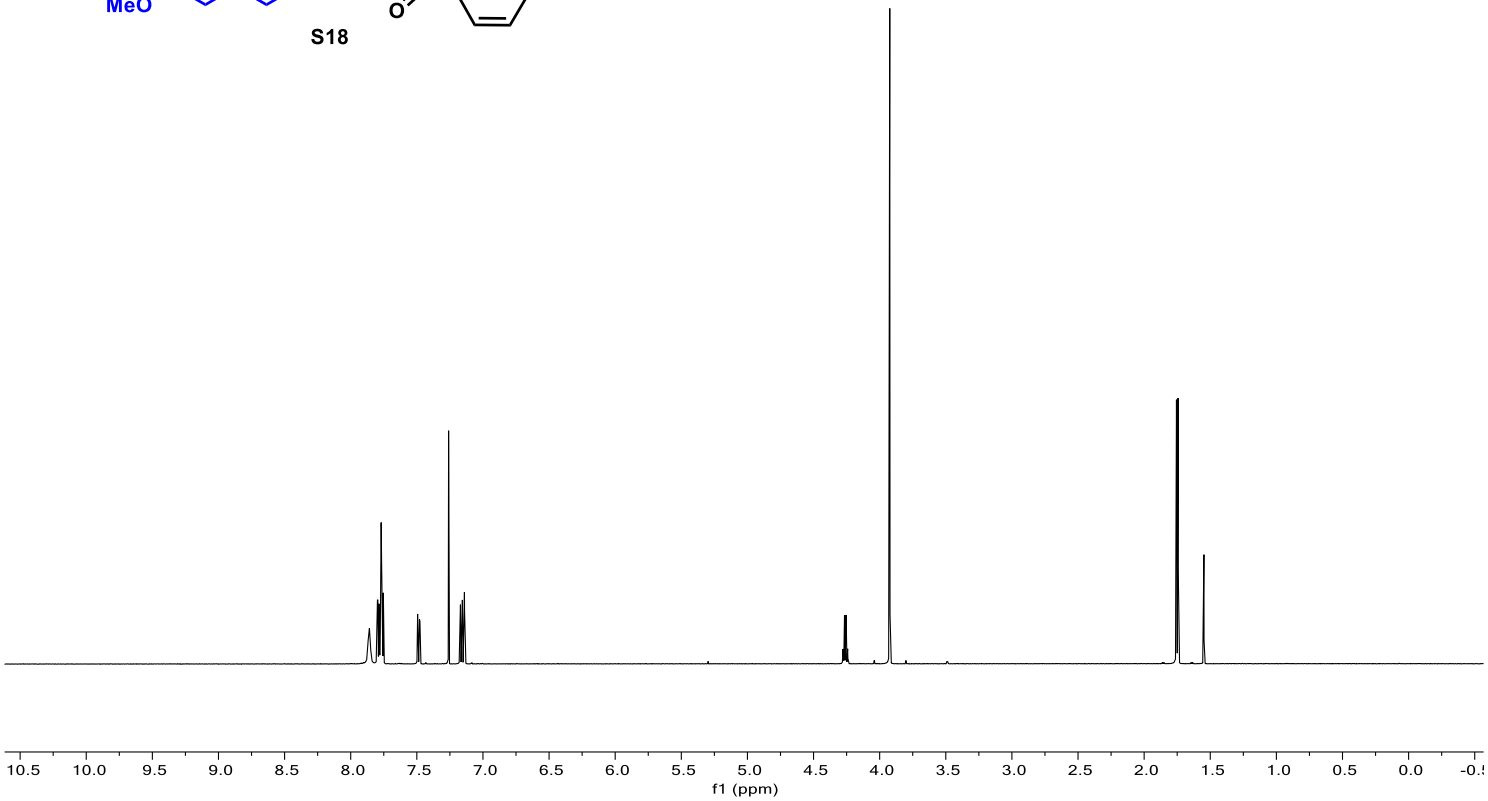
S17



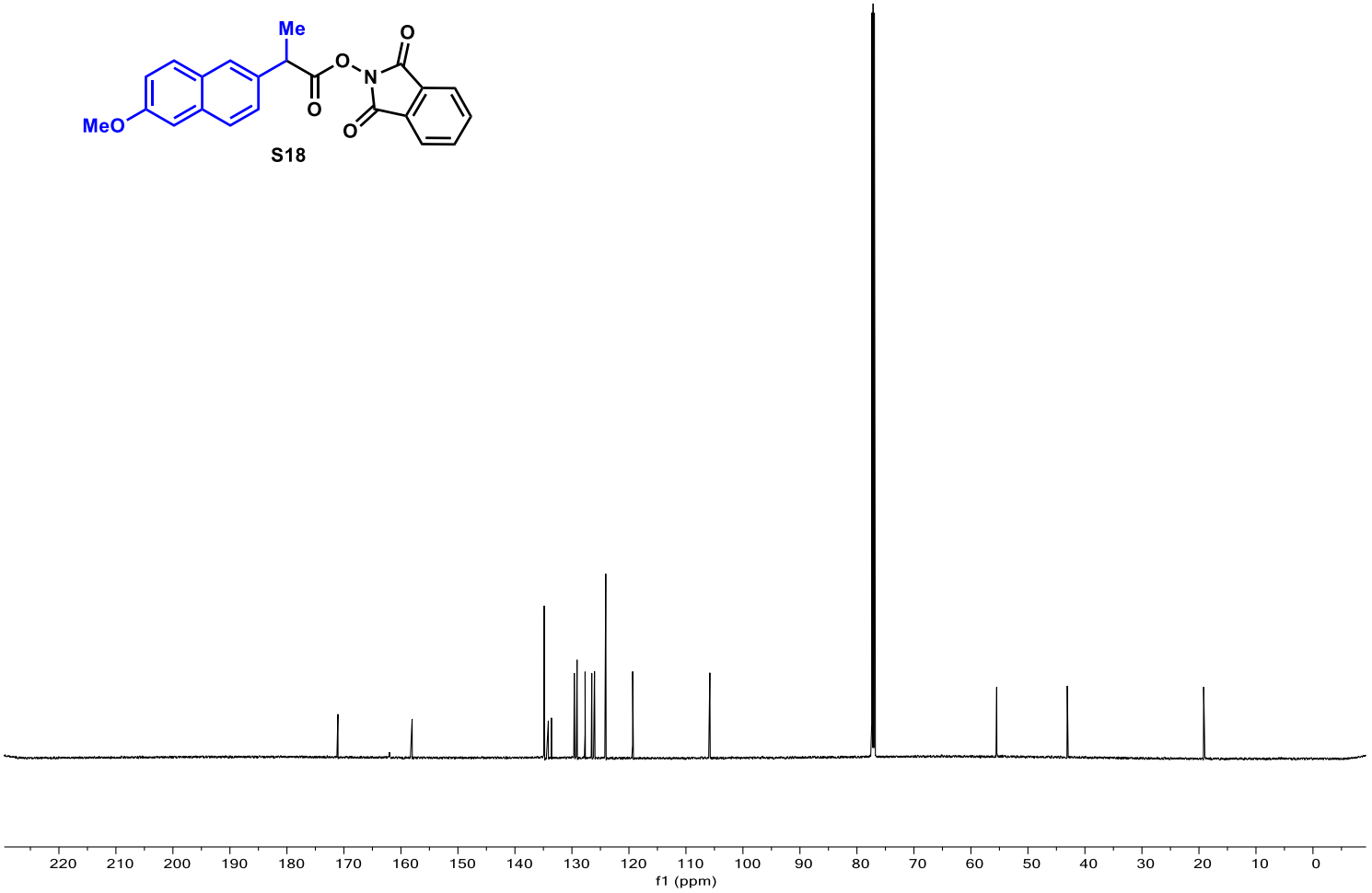
Compound S18 ^{1}H NMR



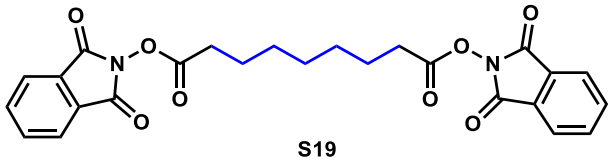
S18



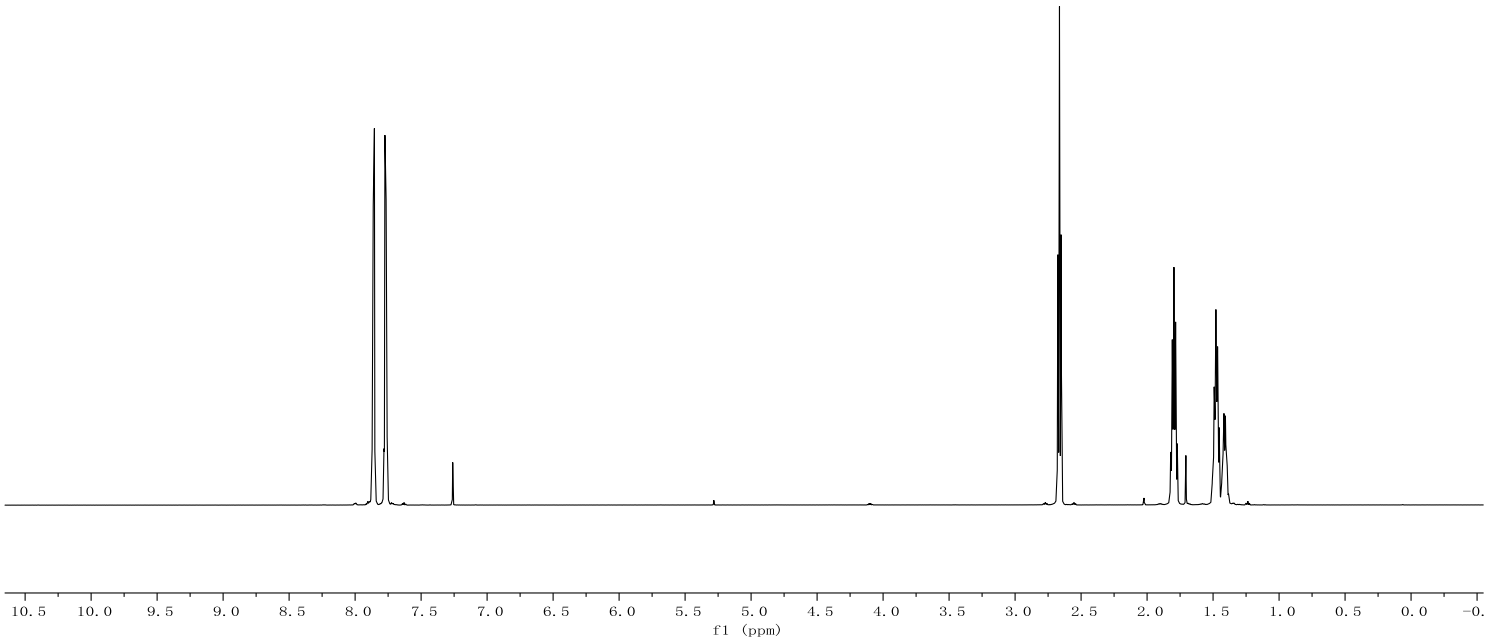
Compound S18 ^{13}C NMR



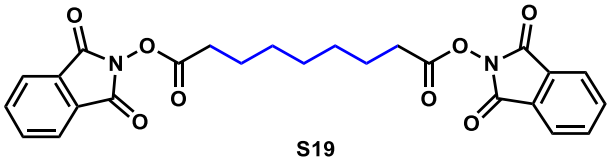
Compound S19 ^{1}H NMR



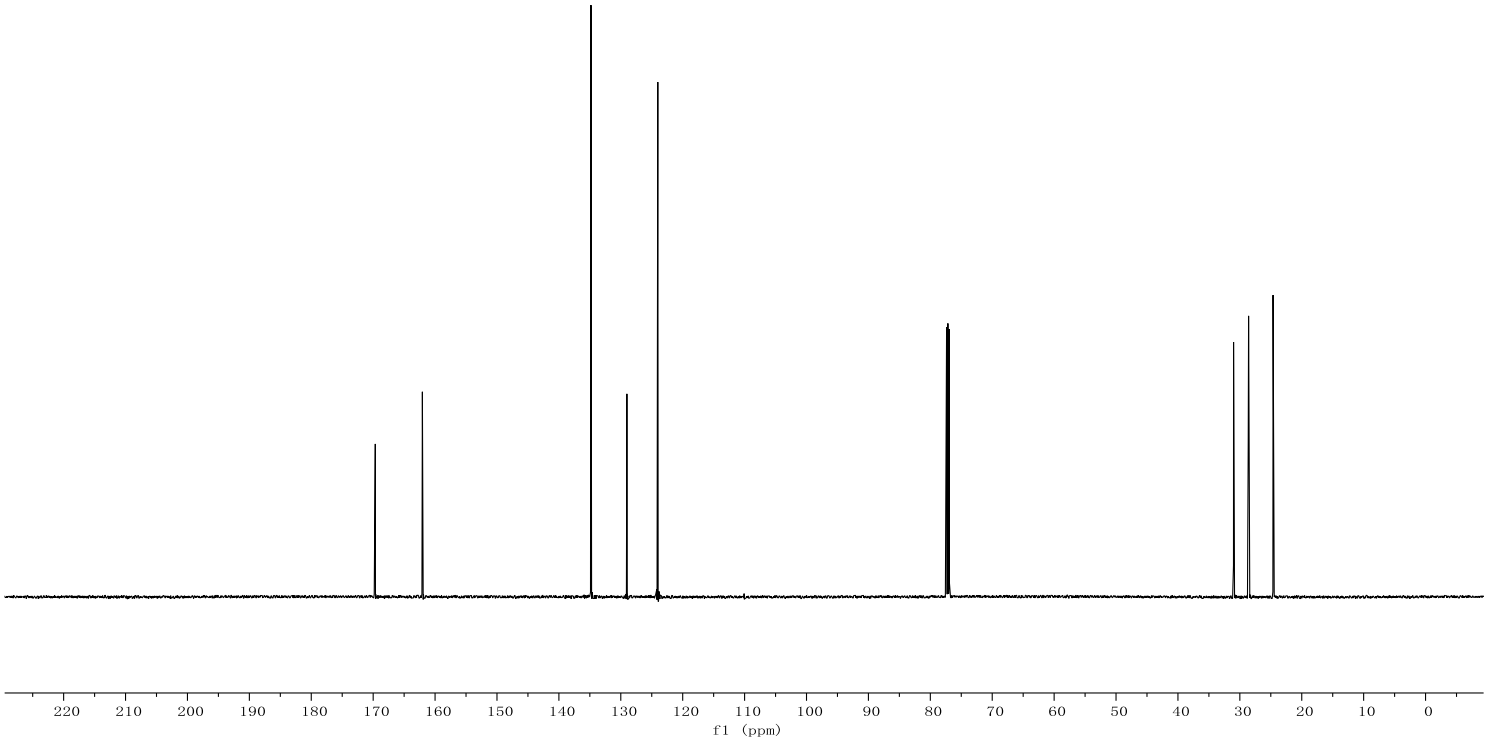
S19



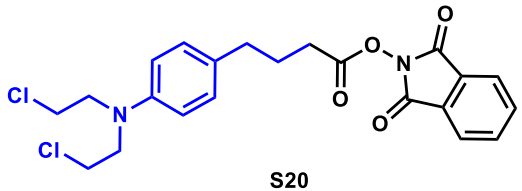
Compound S19 ^{13}C NMR



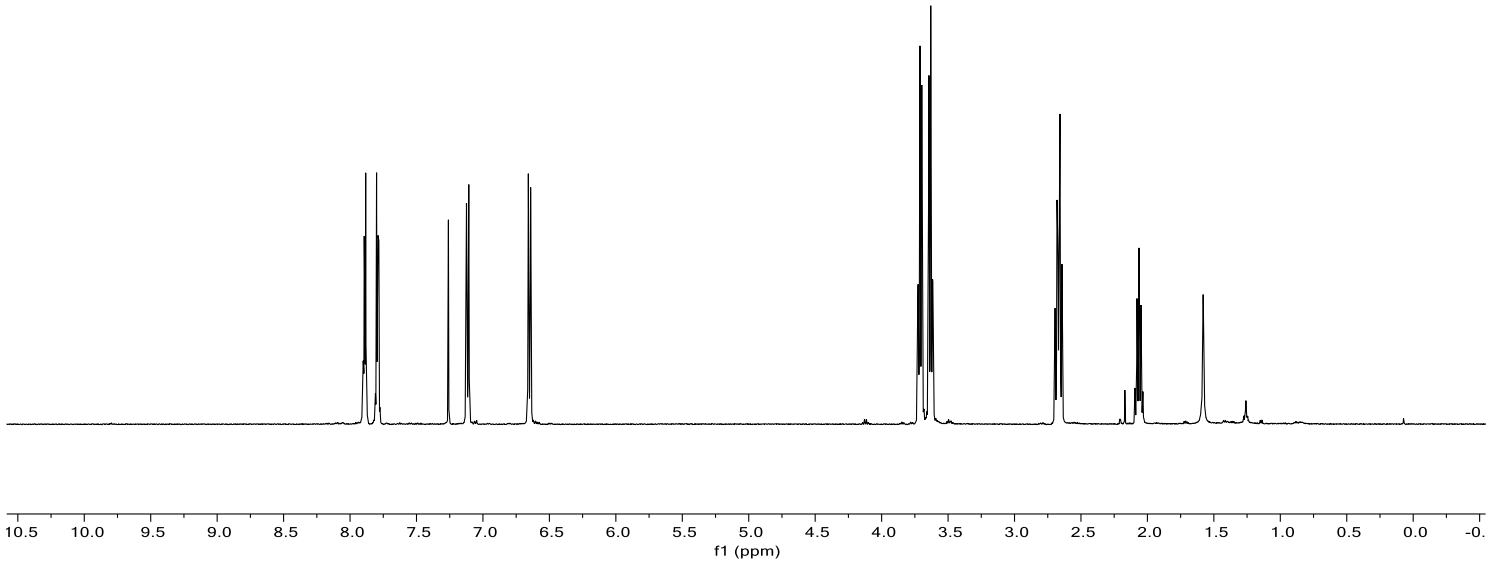
S19



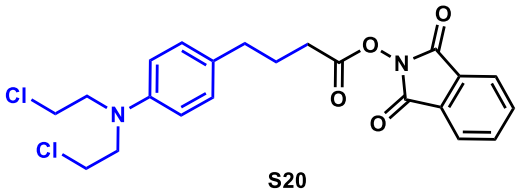
Compound S20 ^{1}H NMR



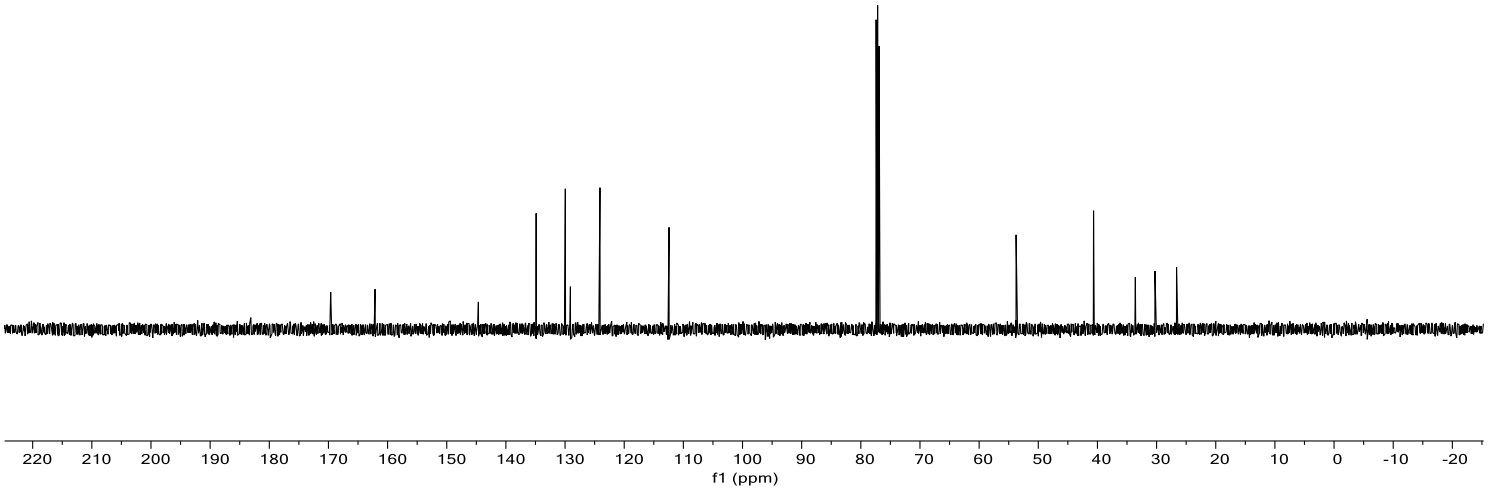
S20



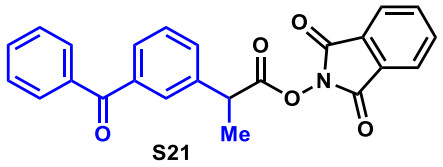
Compound S20 ^{13}C NMR



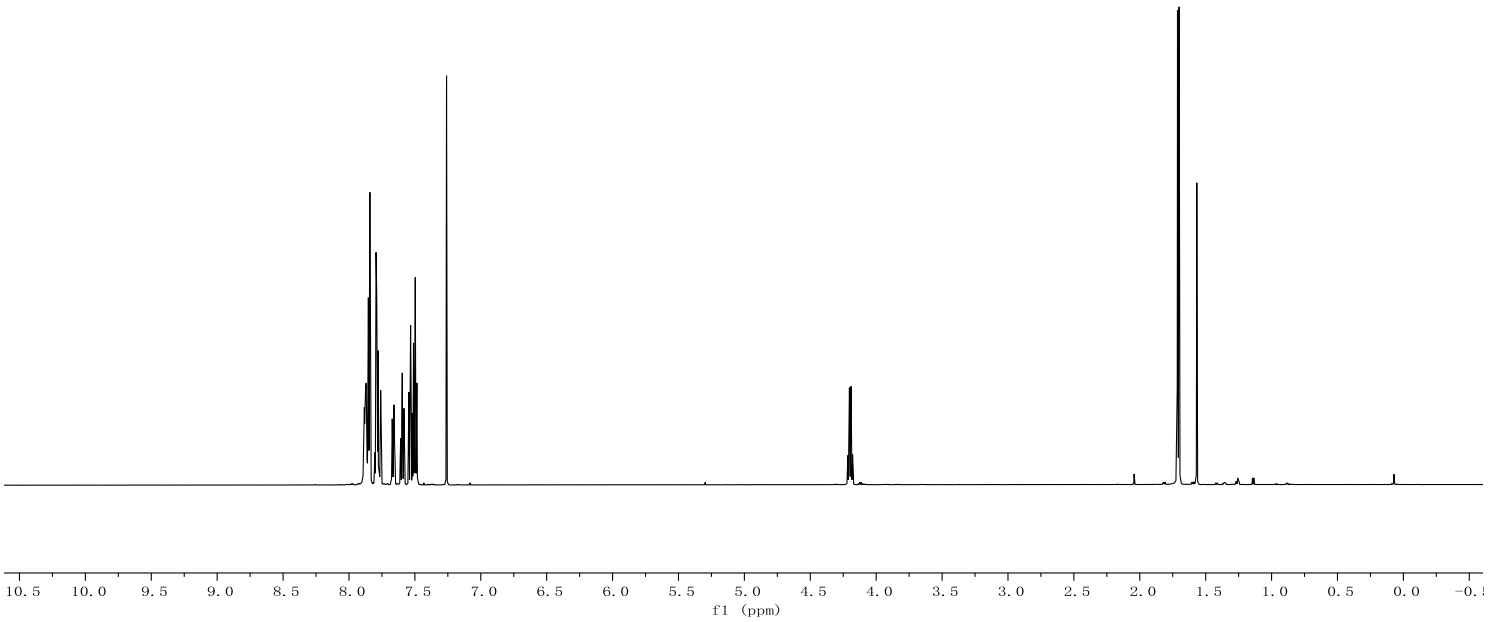
S20



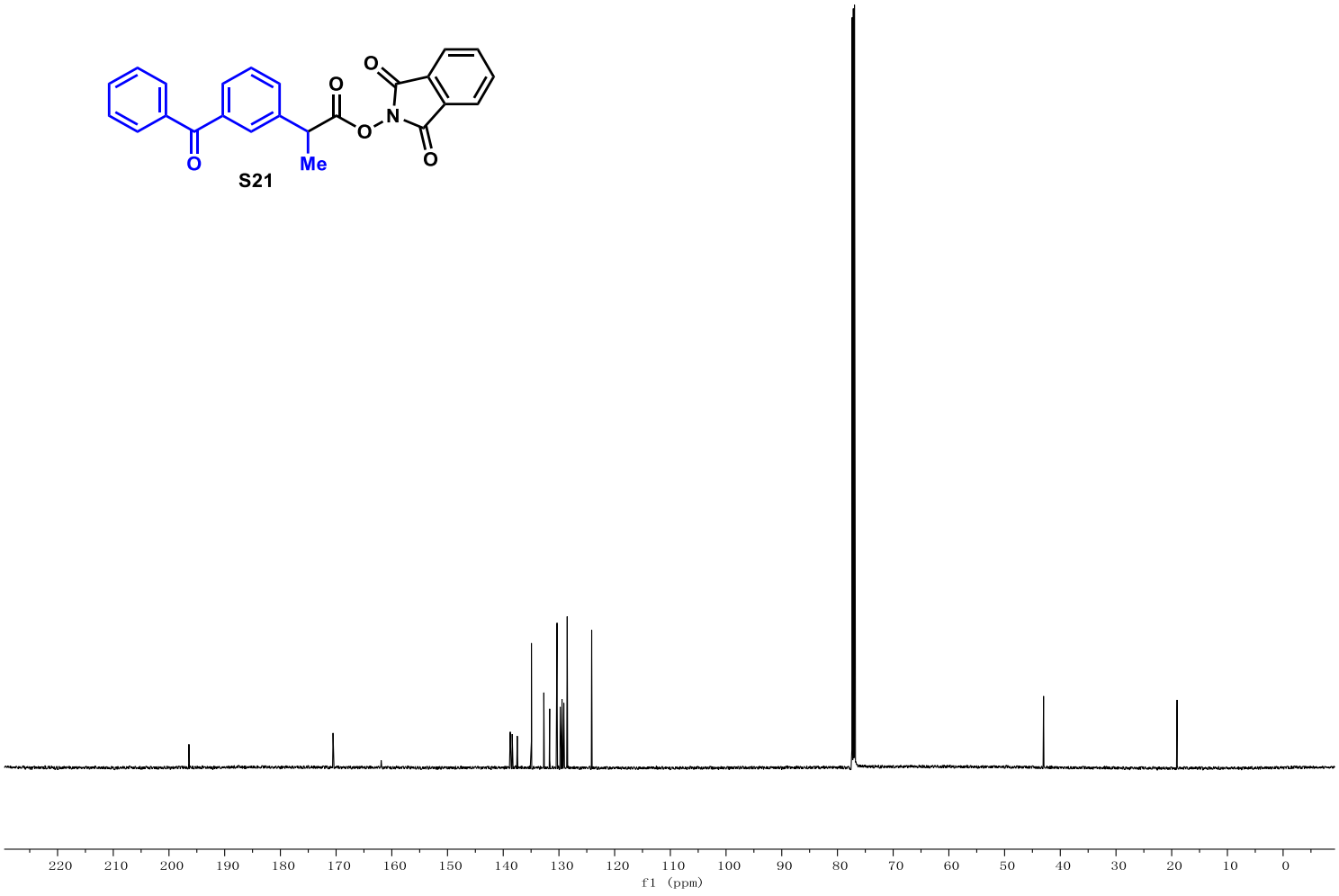
Compound S21 ^{1}H NMR



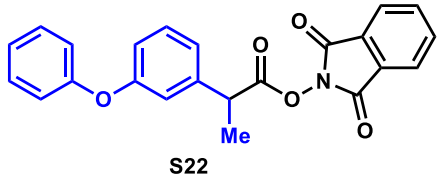
S21



Compound S21 ^{13}C NMR

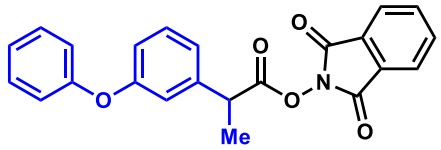


Compound S22 ^{1}H NMR

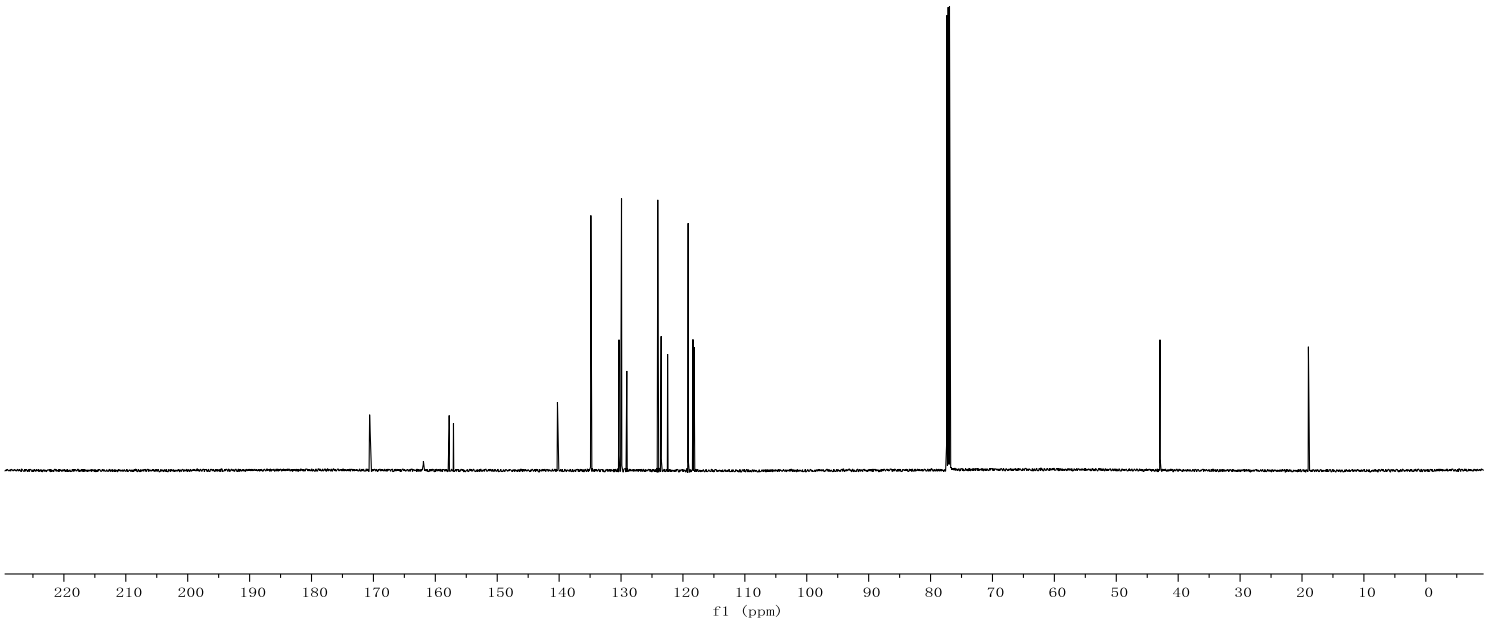


S22

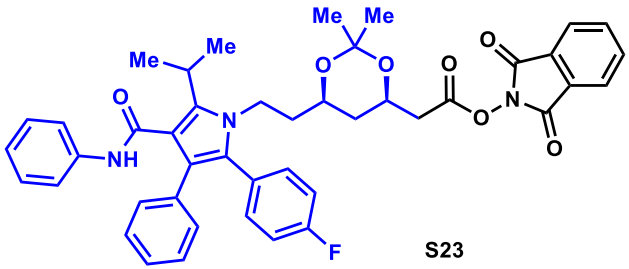
Compound S22 ^{13}C NMR



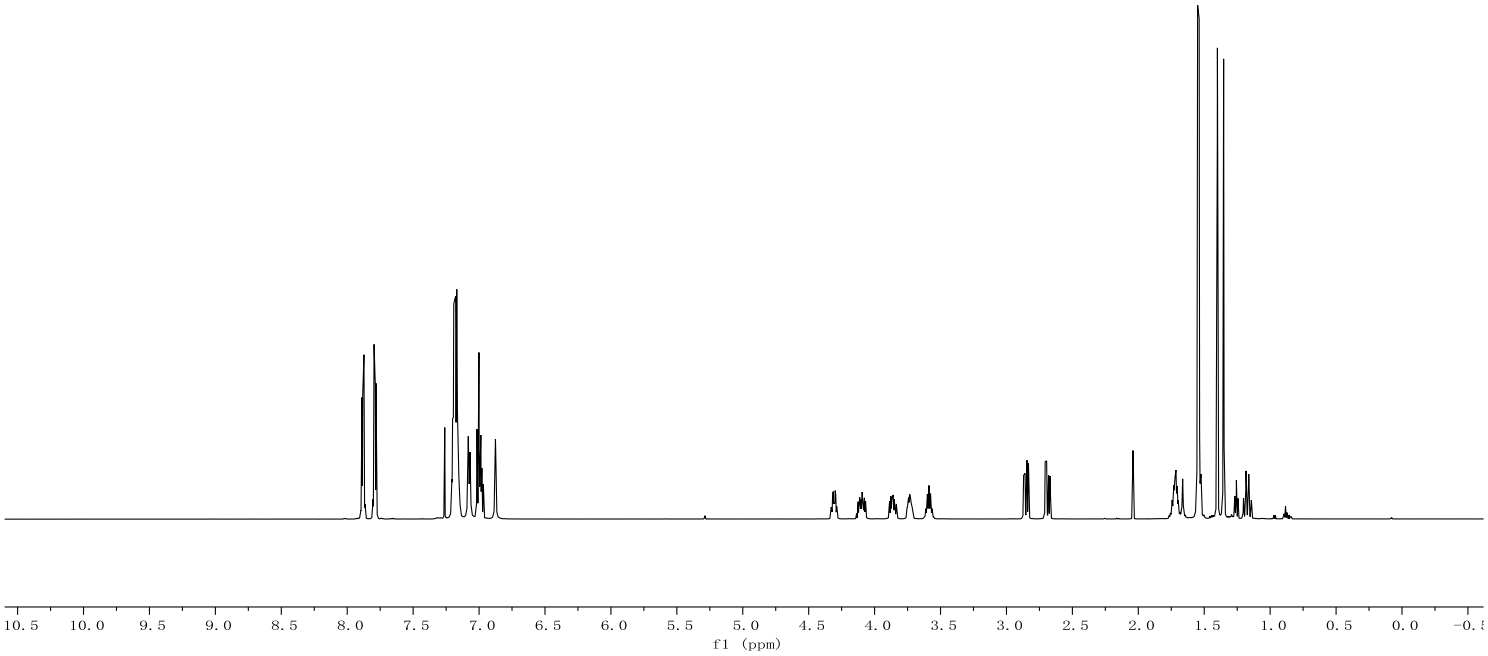
S22



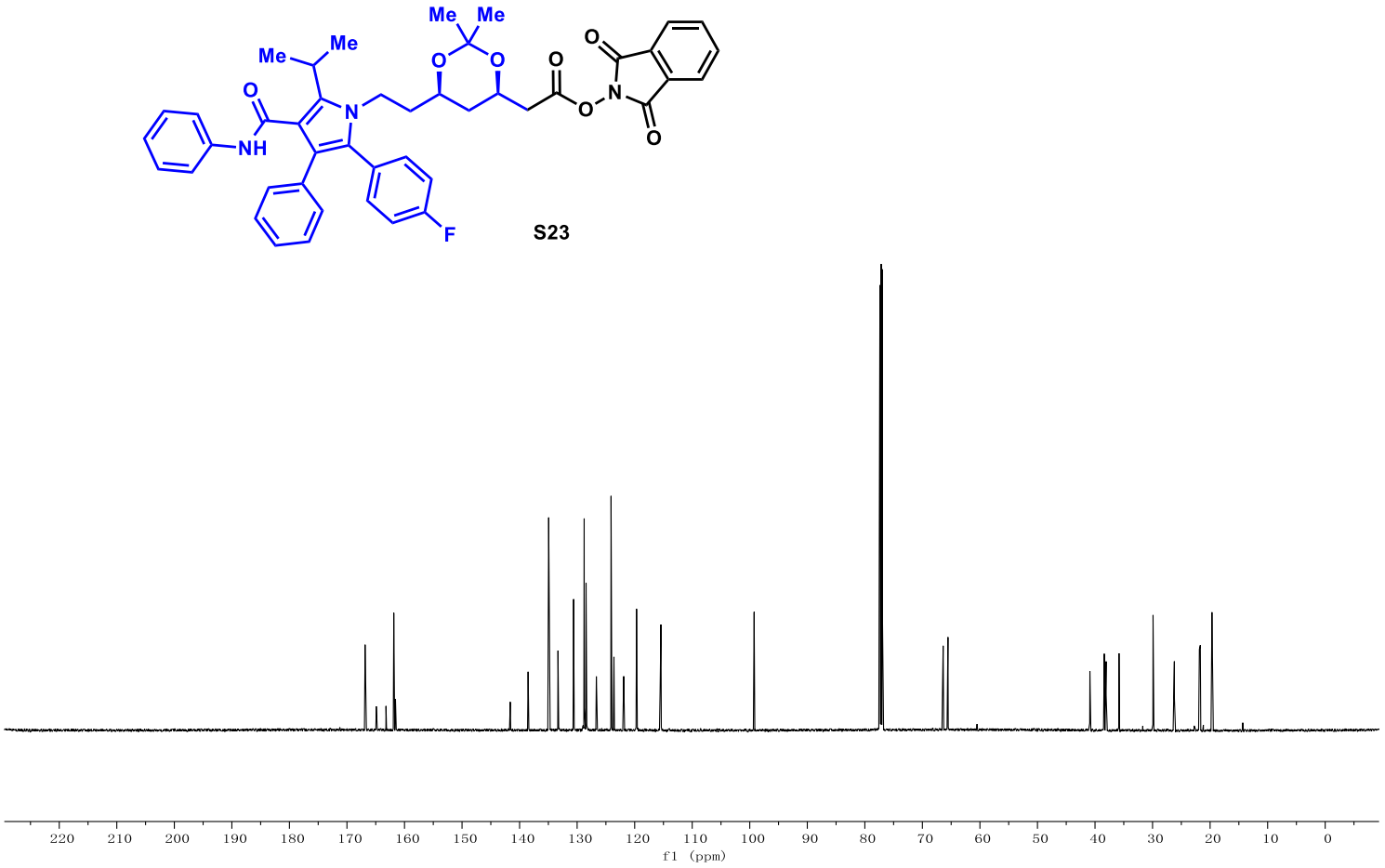
Compound S23 ^{1}H NMR



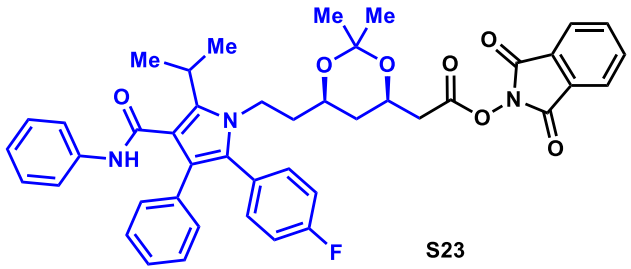
S23



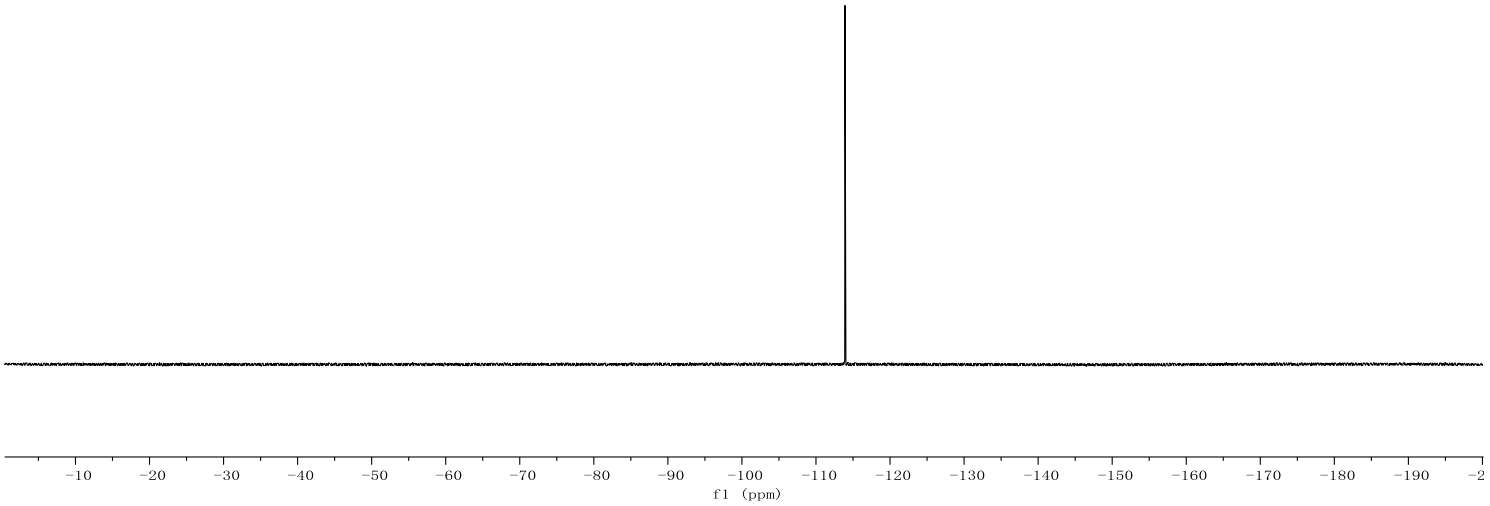
Compound S23 ^{13}C NMR



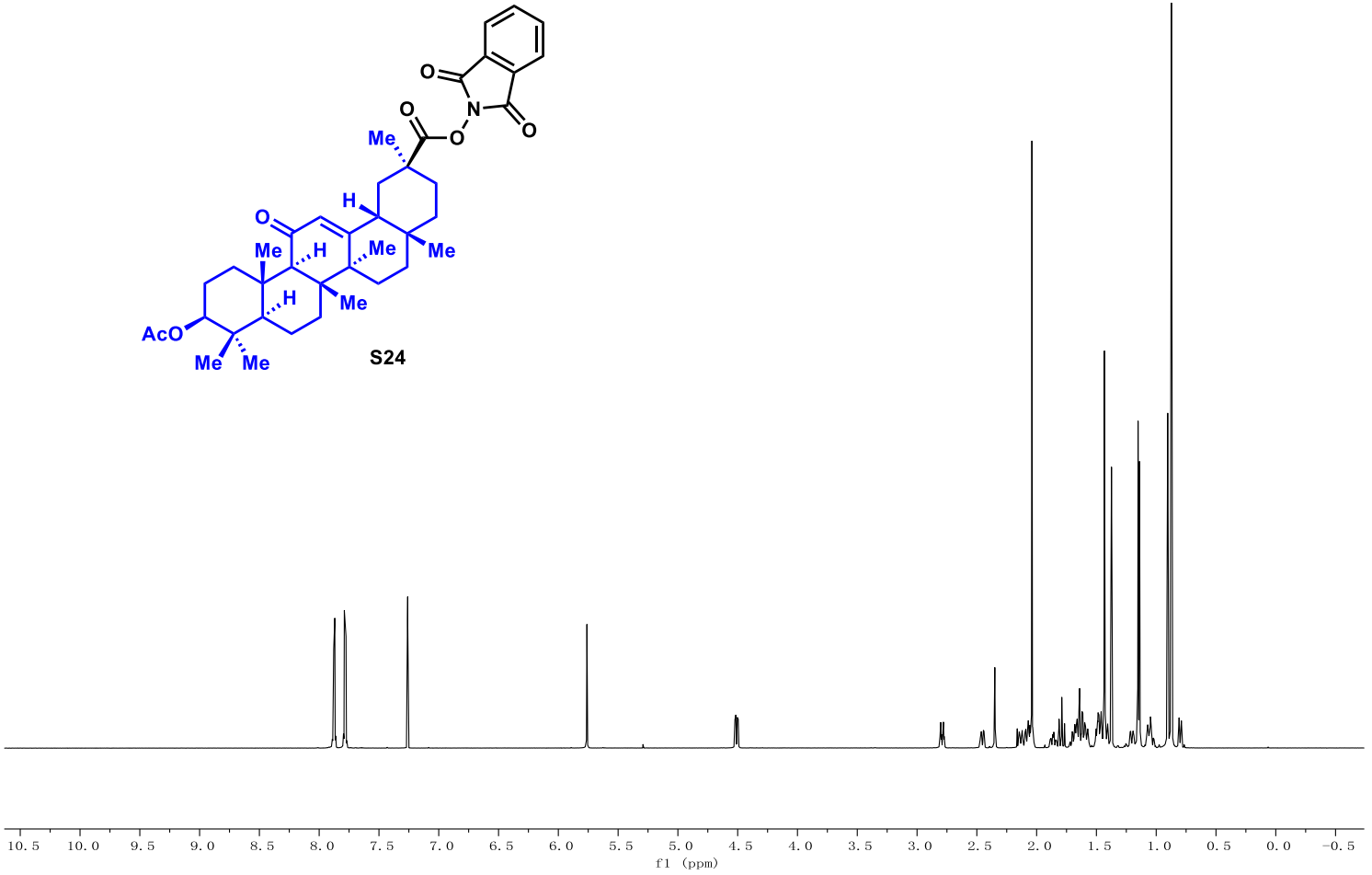
Compound S23 ^{19}F NMR



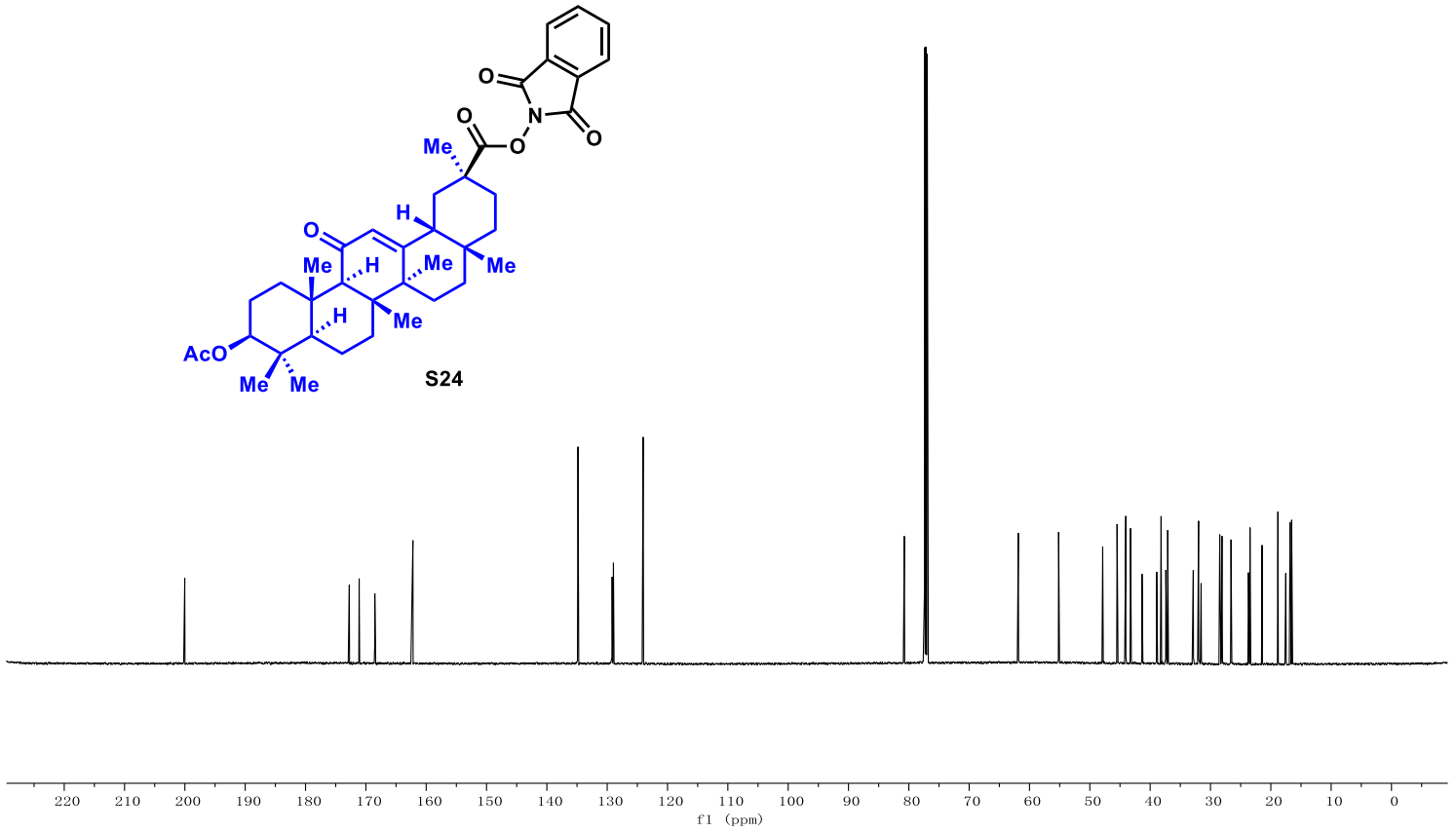
S23



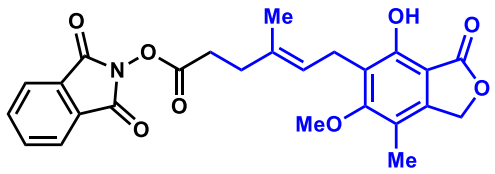
Compound S24 ^{1}H NMR



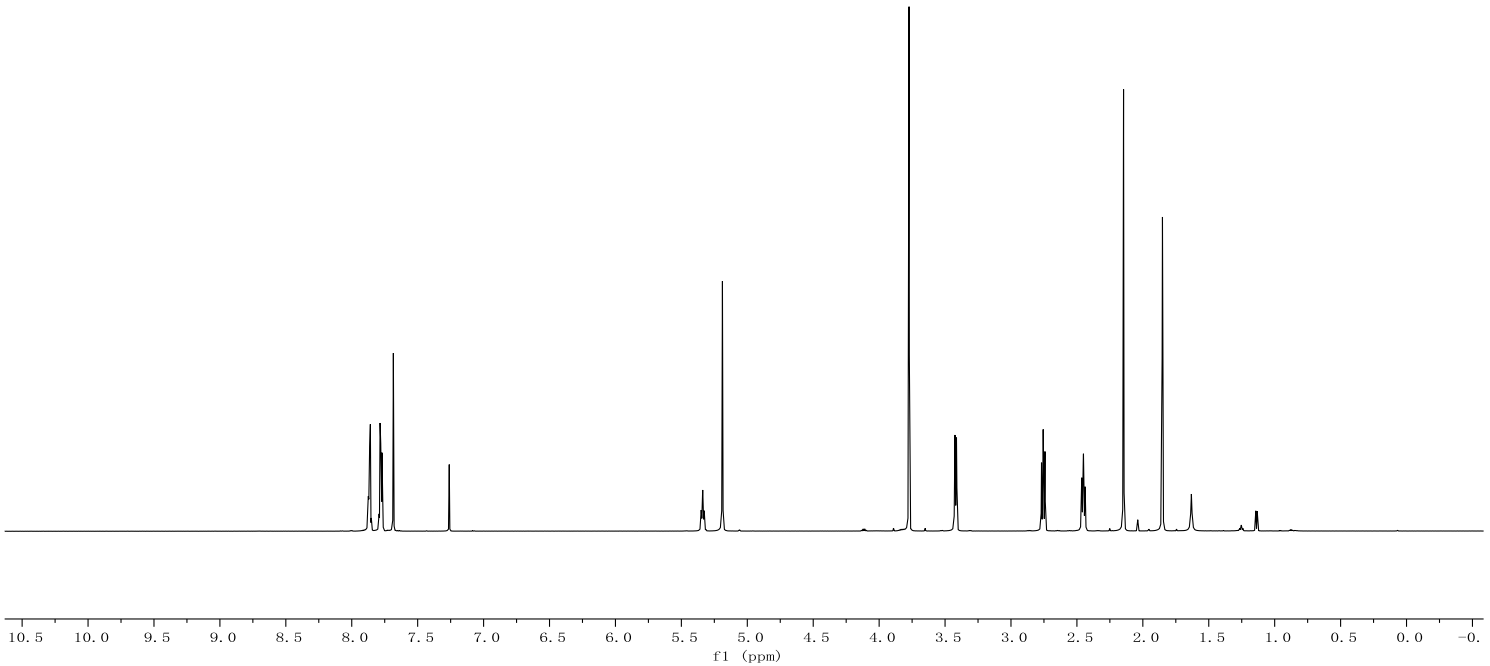
Compound S24 ^{13}C NMR



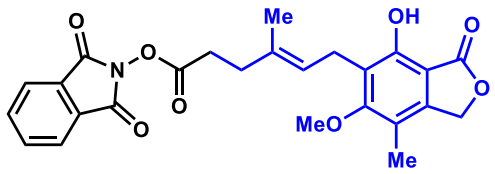
Compound S25 ^{1}H NMR



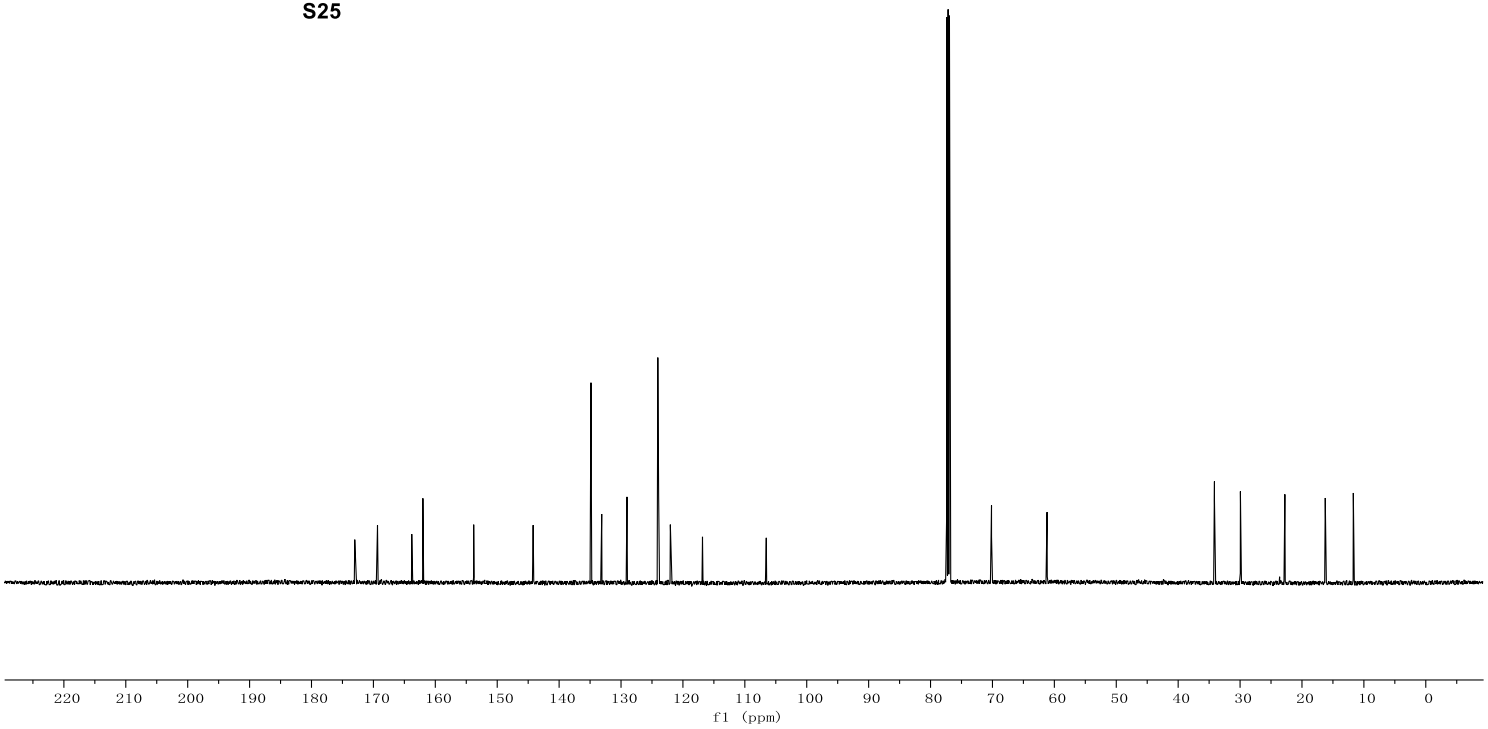
S25



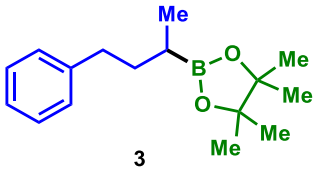
Compound S25 ^{13}C NMR



S25

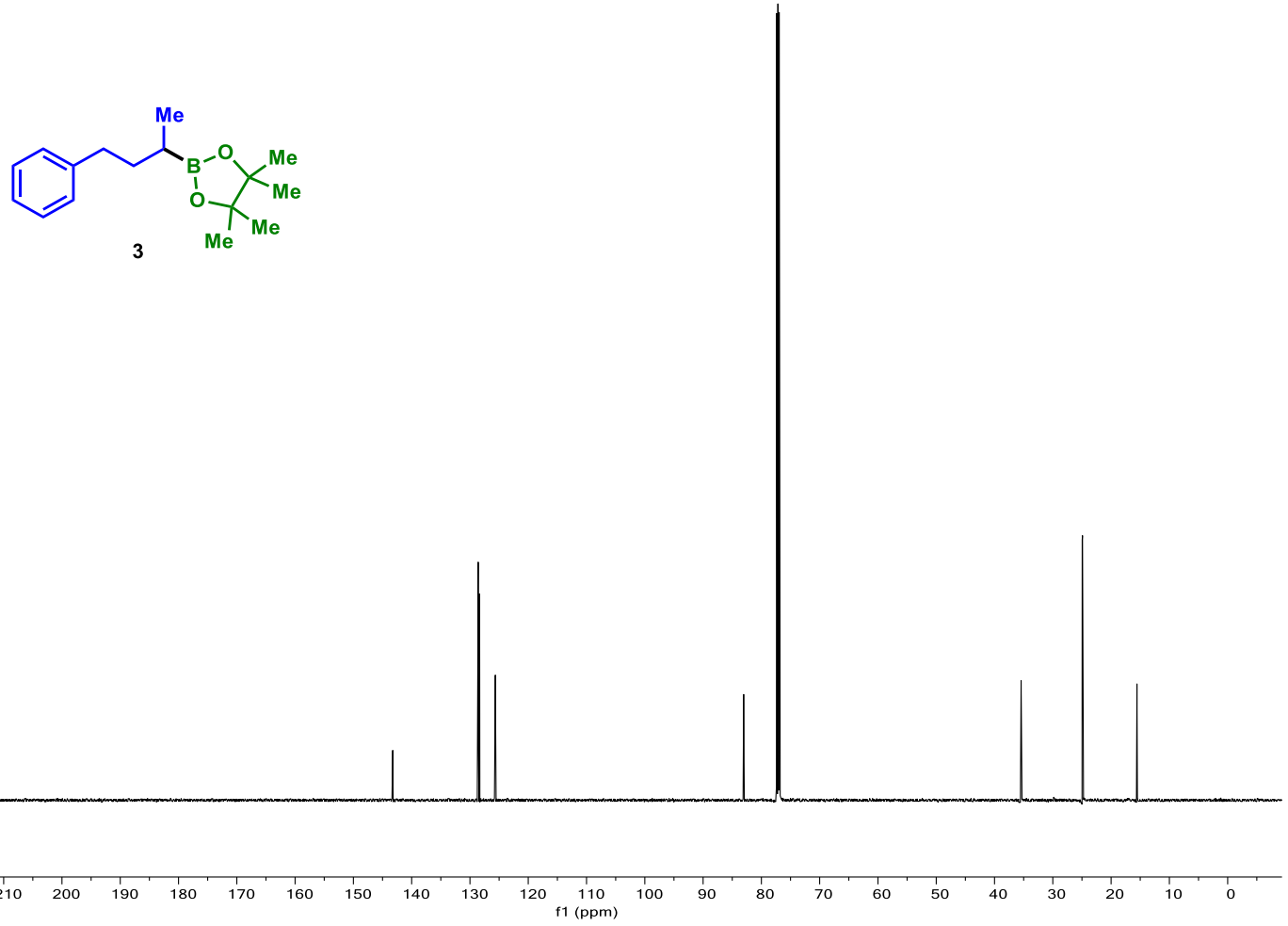


Compound 3 ^{1}H NMR

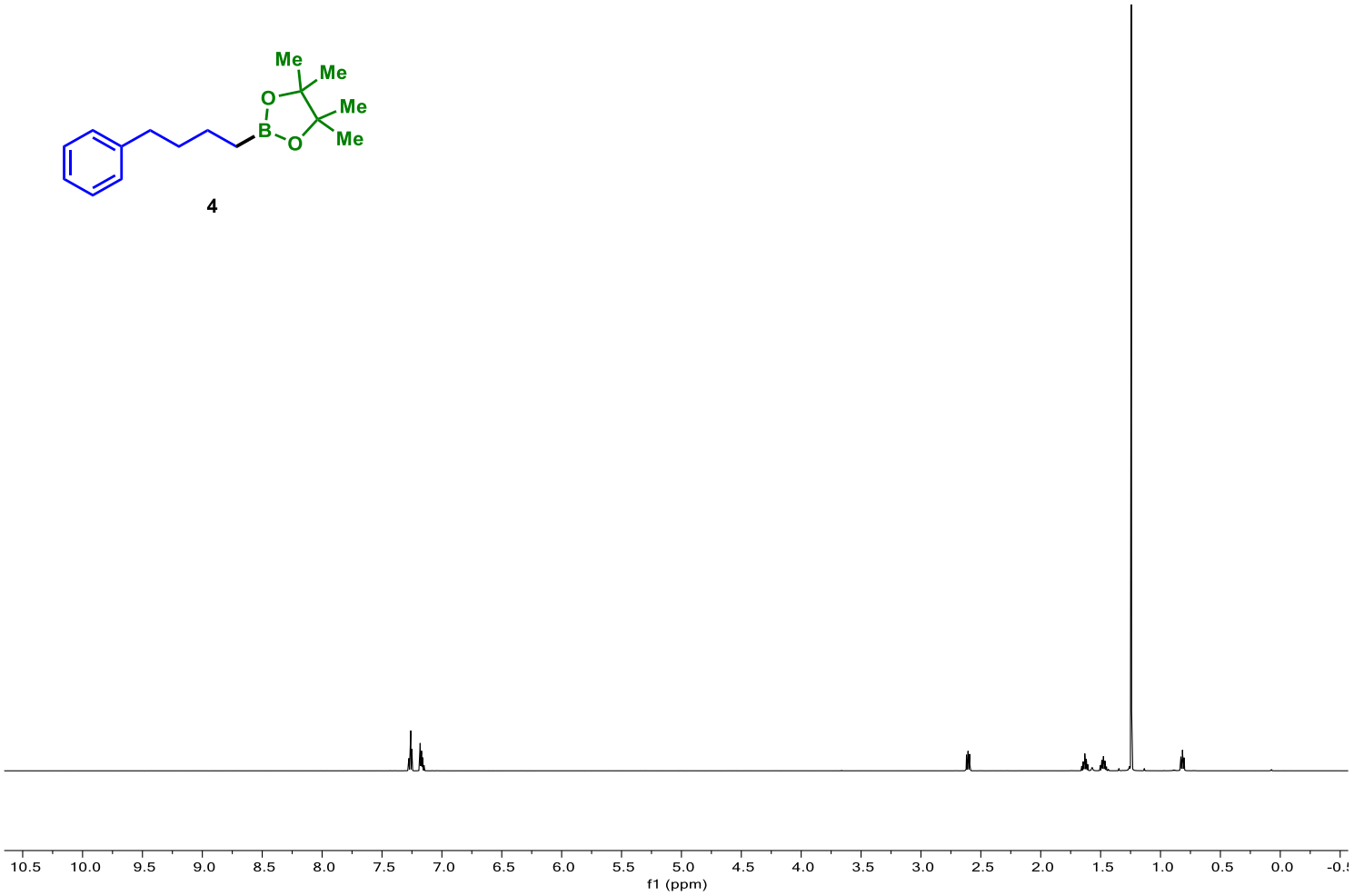


3

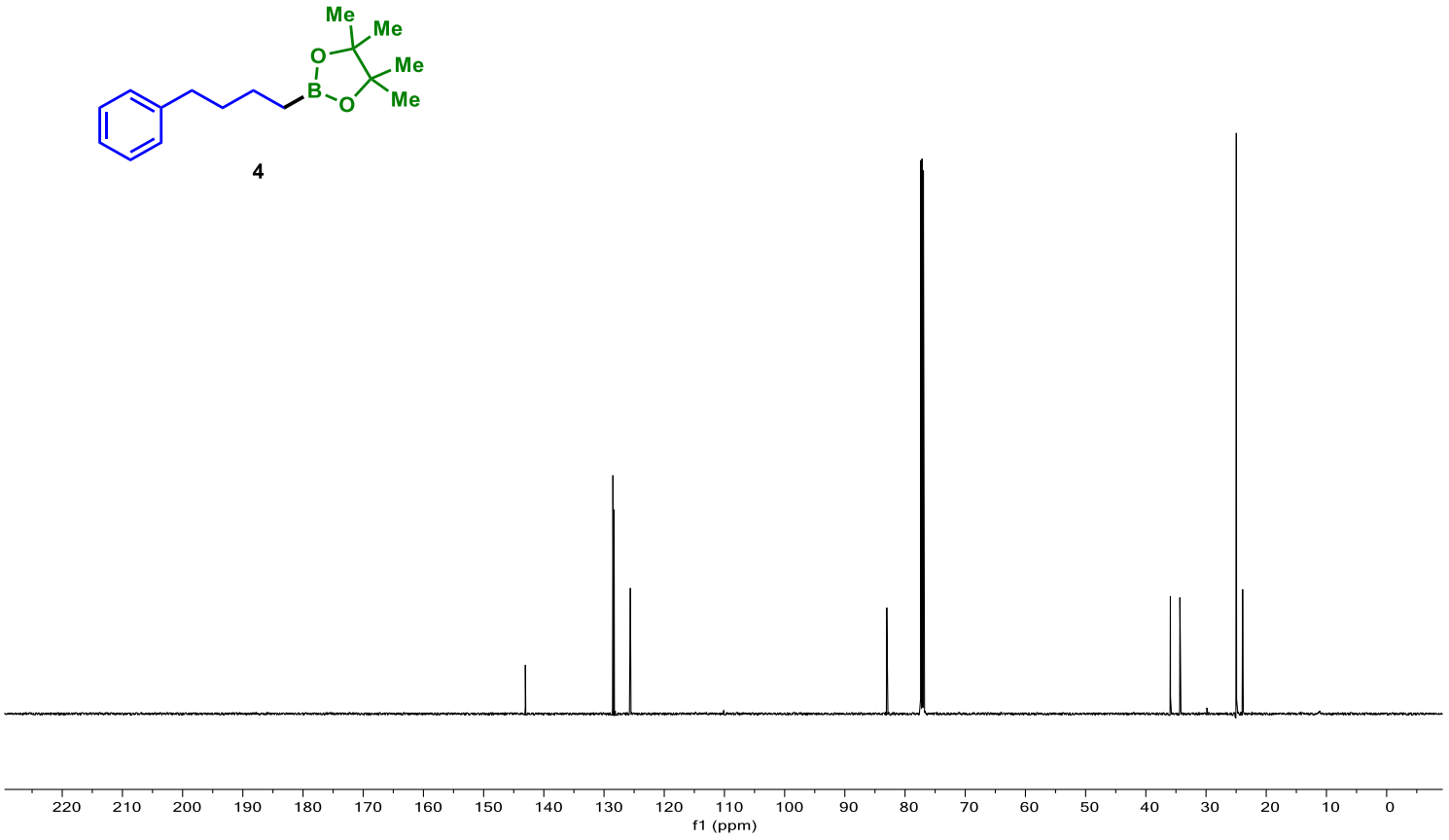
Compound 3 ^{13}C NMR



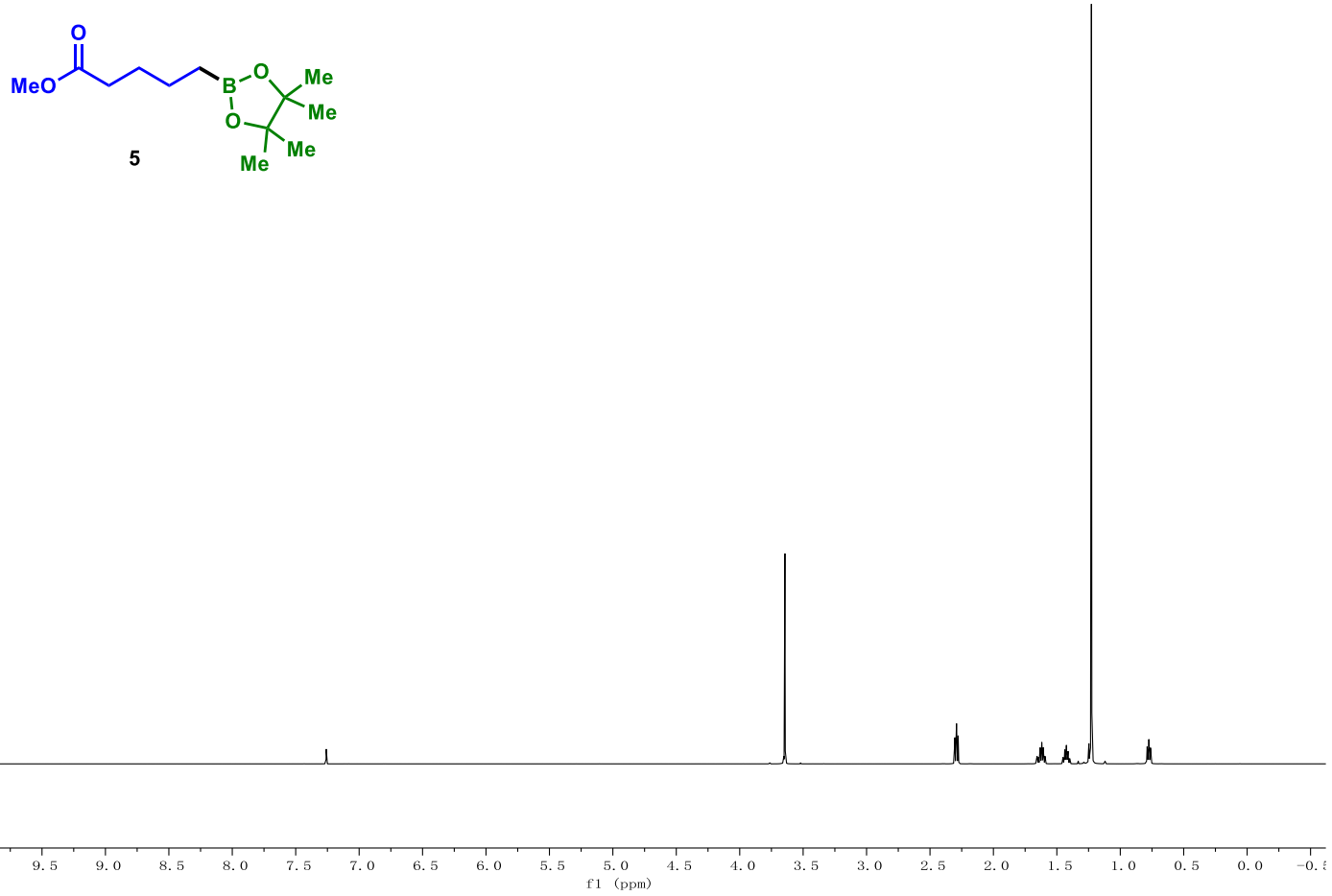
Compound 4 ^{1}H NMR



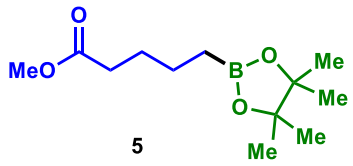
Compound 4 ^{13}C NMR



Compound 5 ^{1}H NMR

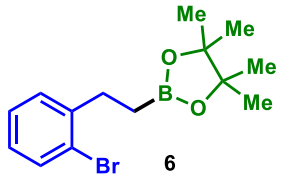


Compound 5 ^{13}C NMR



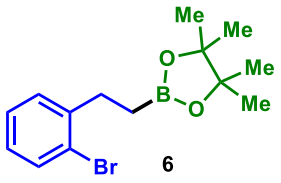
5

Compound 6 ^{1}H NMR

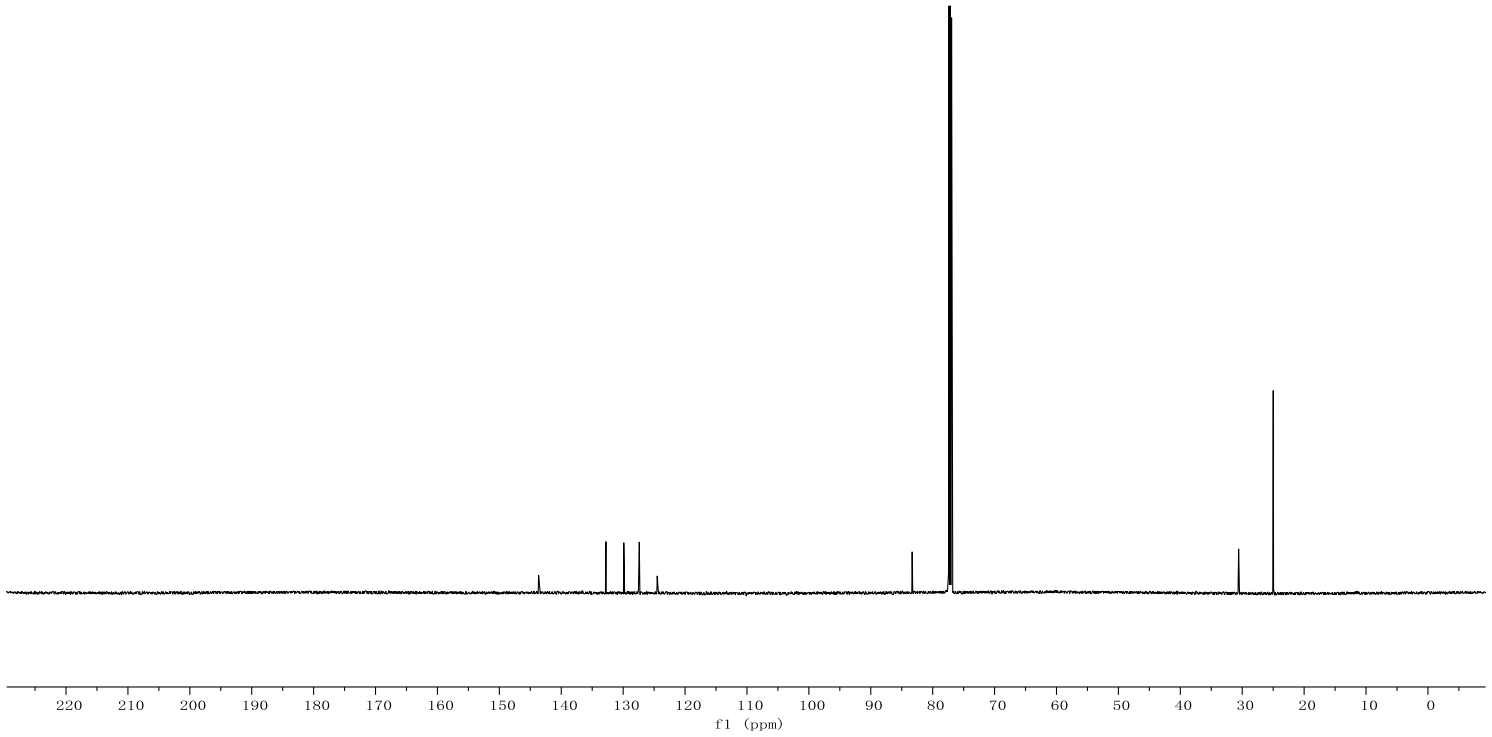


6

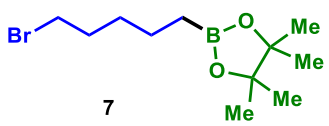
Compound 6 ^{13}C NMR



6

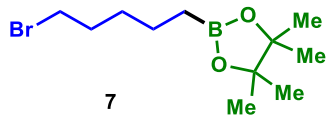


Compound 7 ^{1}H NMR



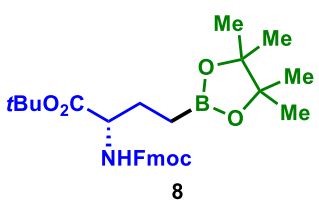
7

Compound 7 ^{13}C NMR



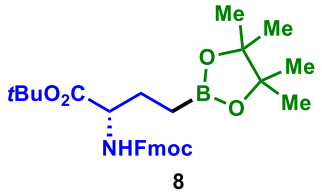
7

Compound 8 ^{1}H NMR



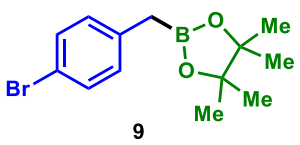
8

Compound 8 ^{13}C NMR



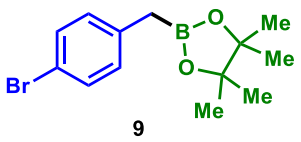
8

Compound 9 ^{1}H NMR



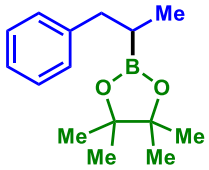
9

Compound 9 ^{13}C NMR



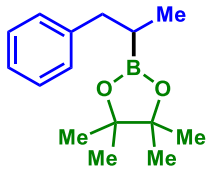
9

Compound 10 ^{1}H NMR

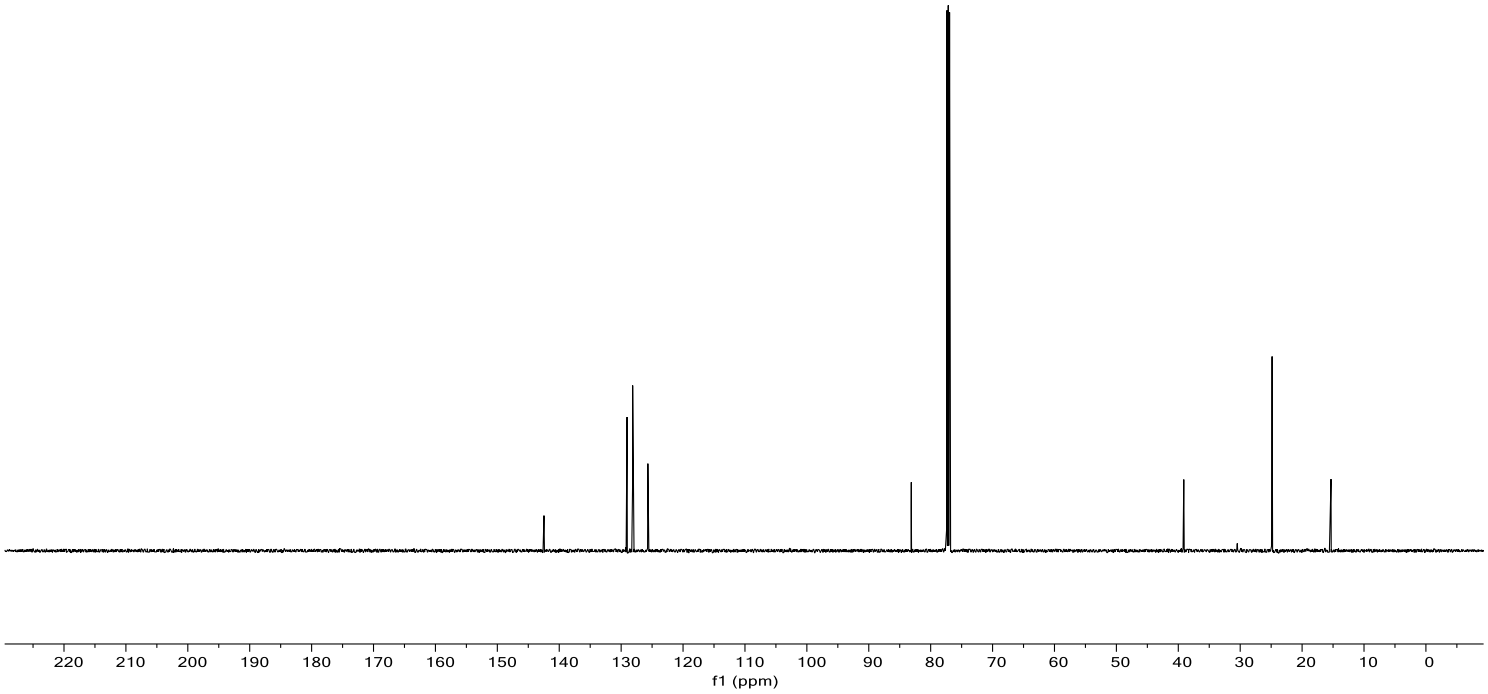


10

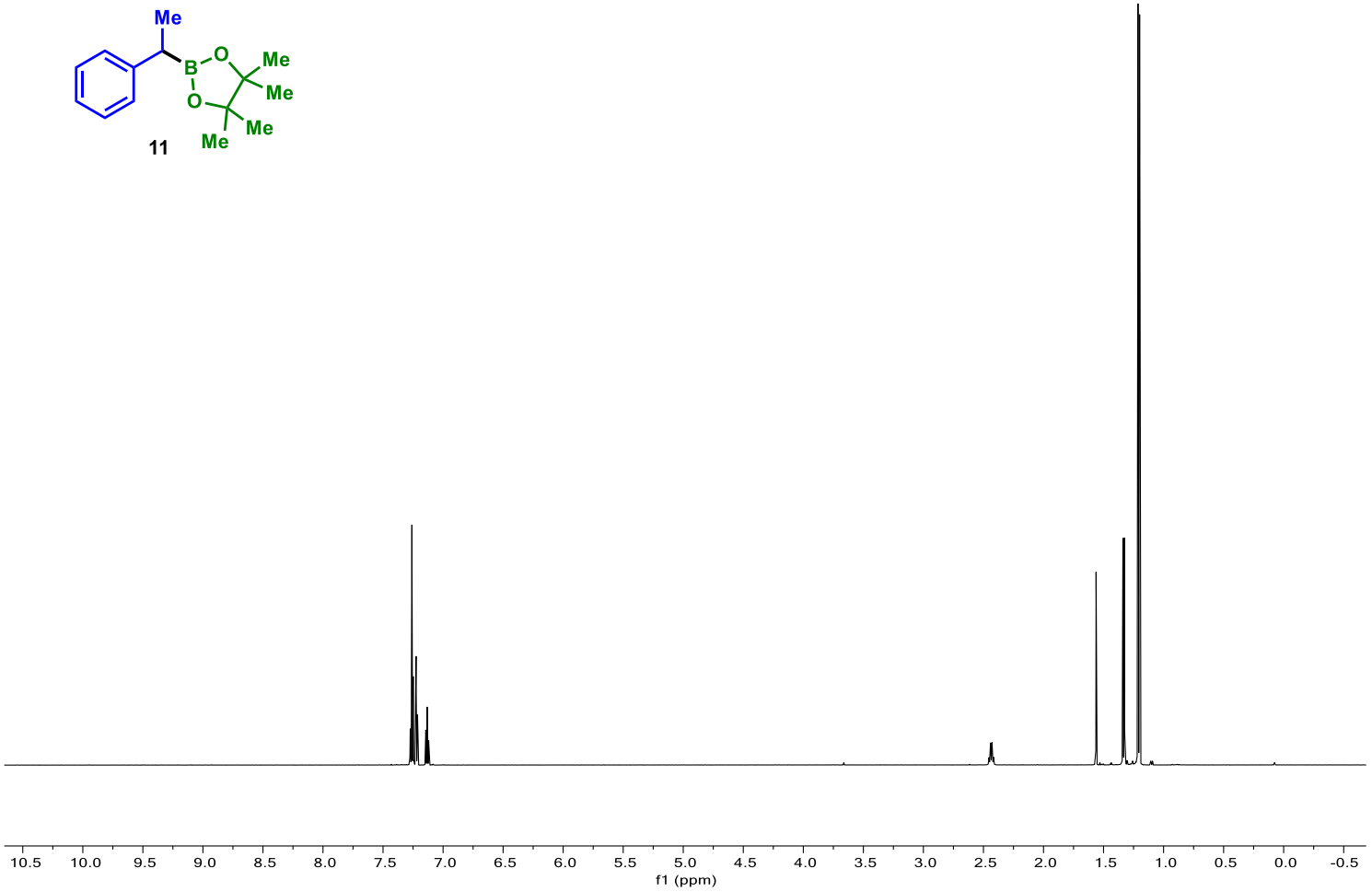
Compound 10 ^{13}C NMR



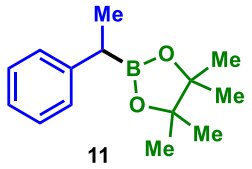
10



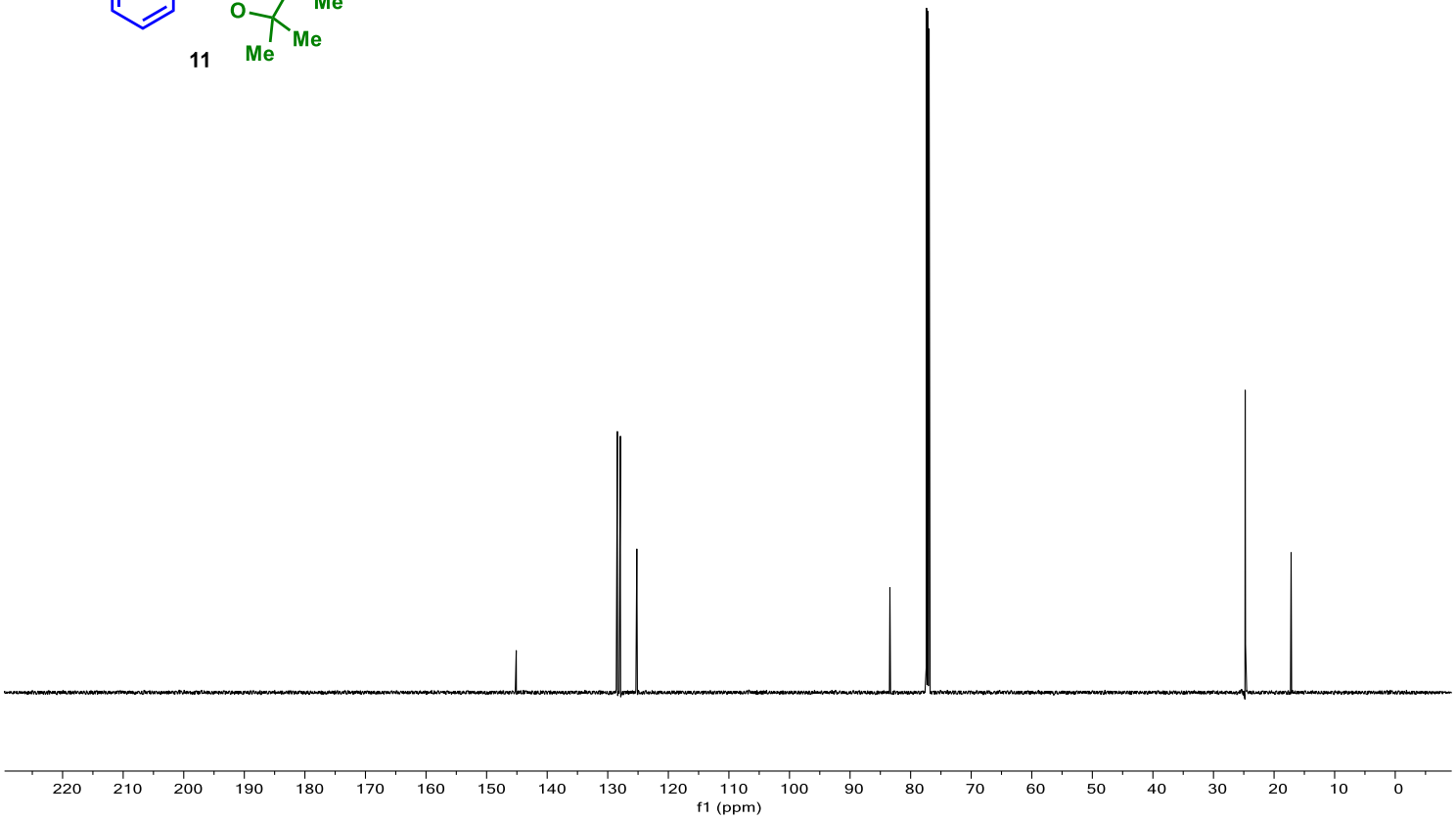
Compound 11 ^{1}H NMR



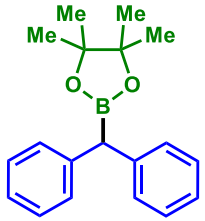
Compound 11 ^{13}C NMR



11

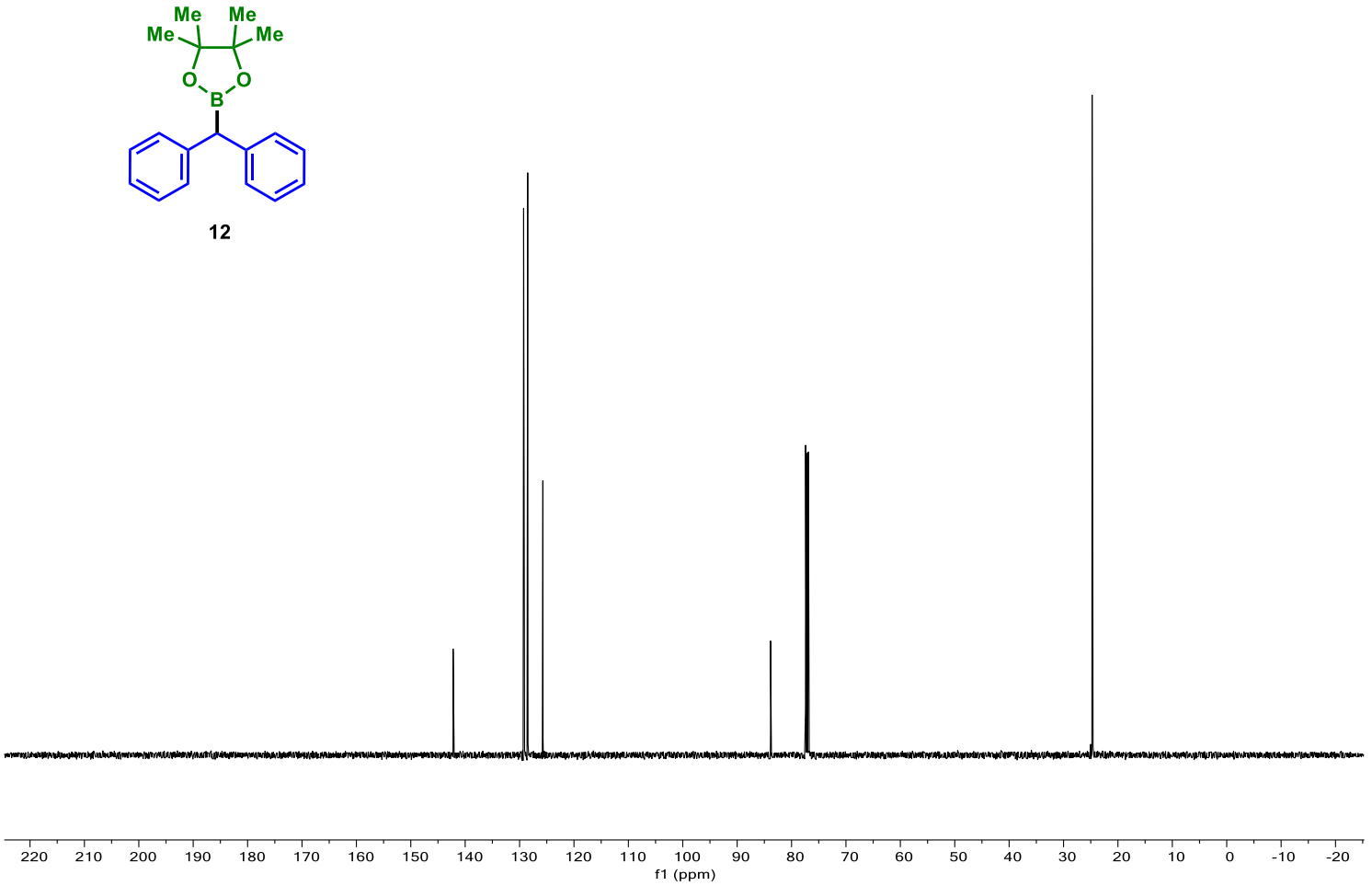


Compound 12 ^{1}H NMR

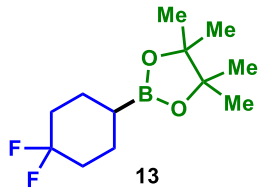


12

Compound 12 ^{13}C NMR

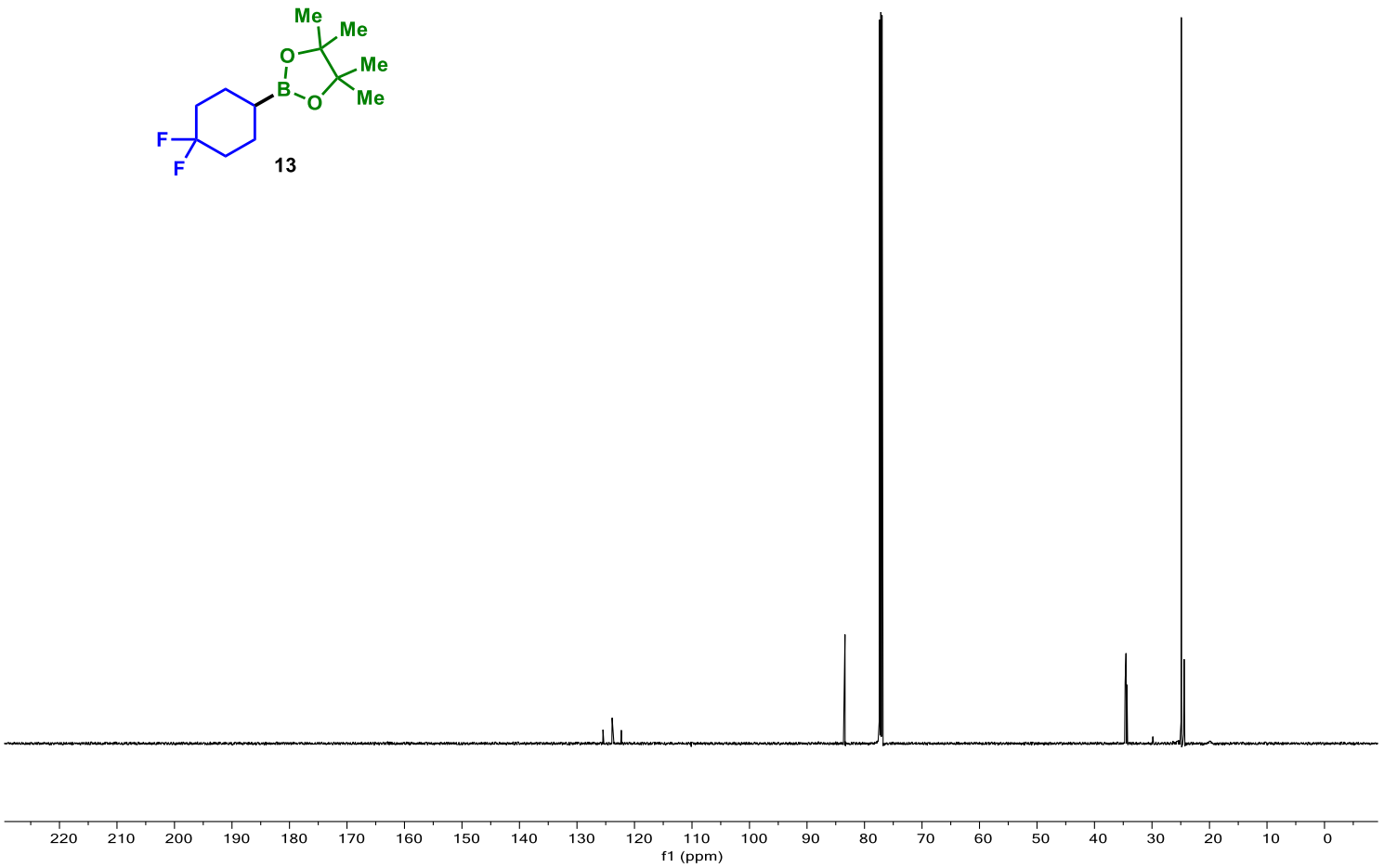


Compound 13 ^{1}H NMR

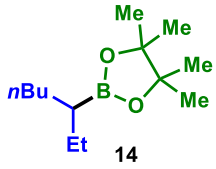


13

Compound 13 ^{13}C NMR

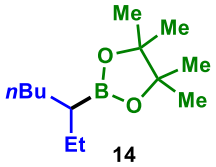


Compound 14 ^{1}H NMR

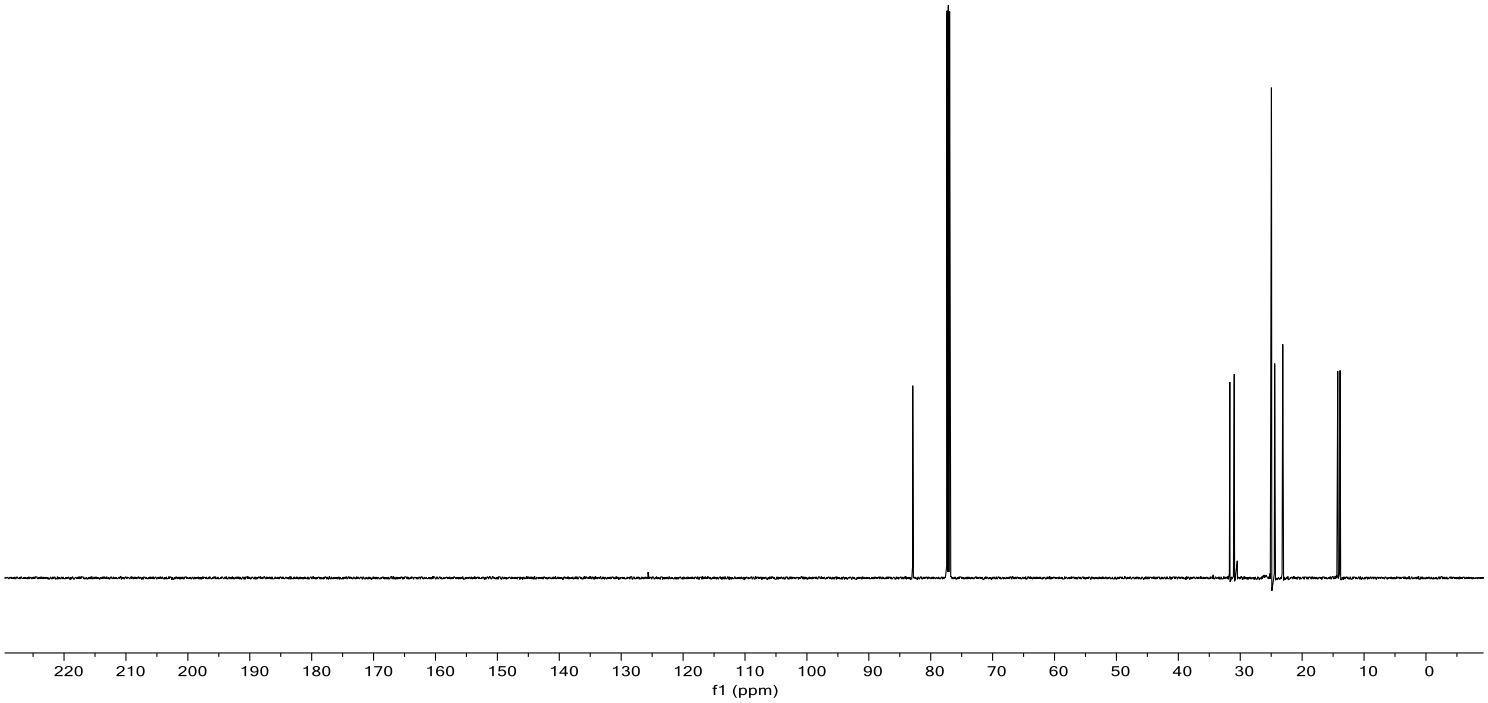


14

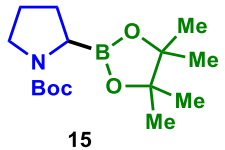
Compound 14 ^{13}C NMR



14

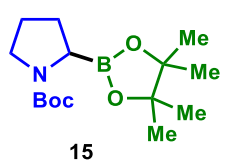


Compound 15 ^{1}H NMR



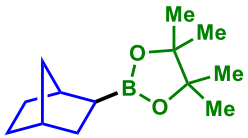
15

Compound 15 ^{13}C NMR



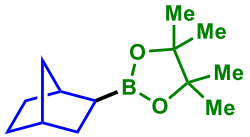
15

Compound 16 ^{1}H NMR



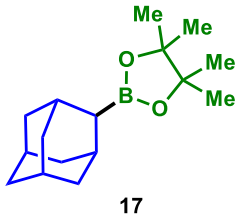
16, *exo*:*endo* = 10:1

Compound 16 ^{13}C NMR



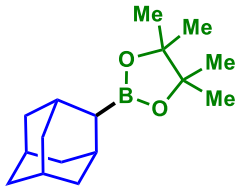
16, *exo*:*endo* = 10:1

Compound 17 ^{1}H NMR

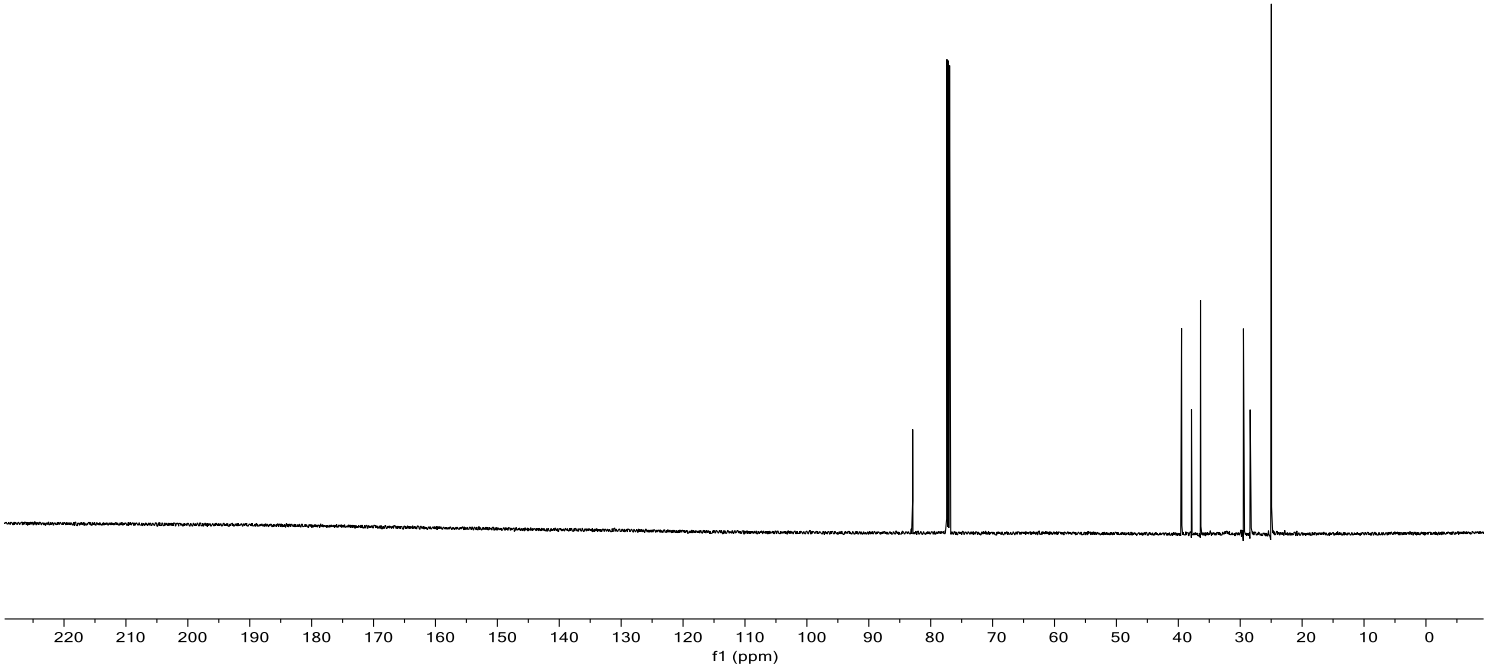


17

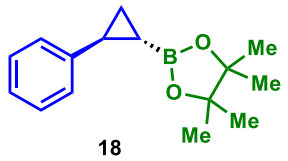
Compound 17 ^{13}C NMR



17

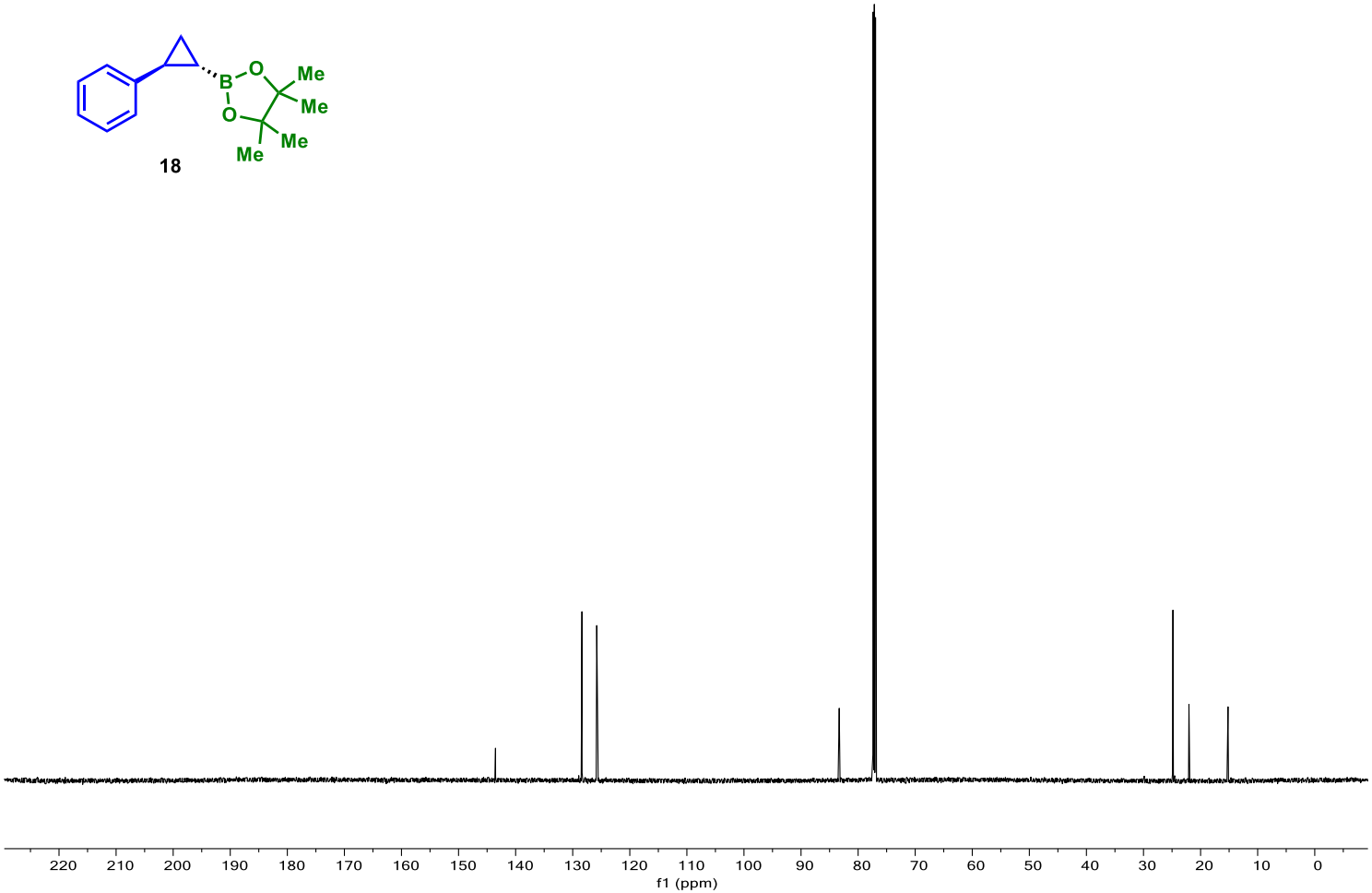


Compound 18 ^{1}H NMR

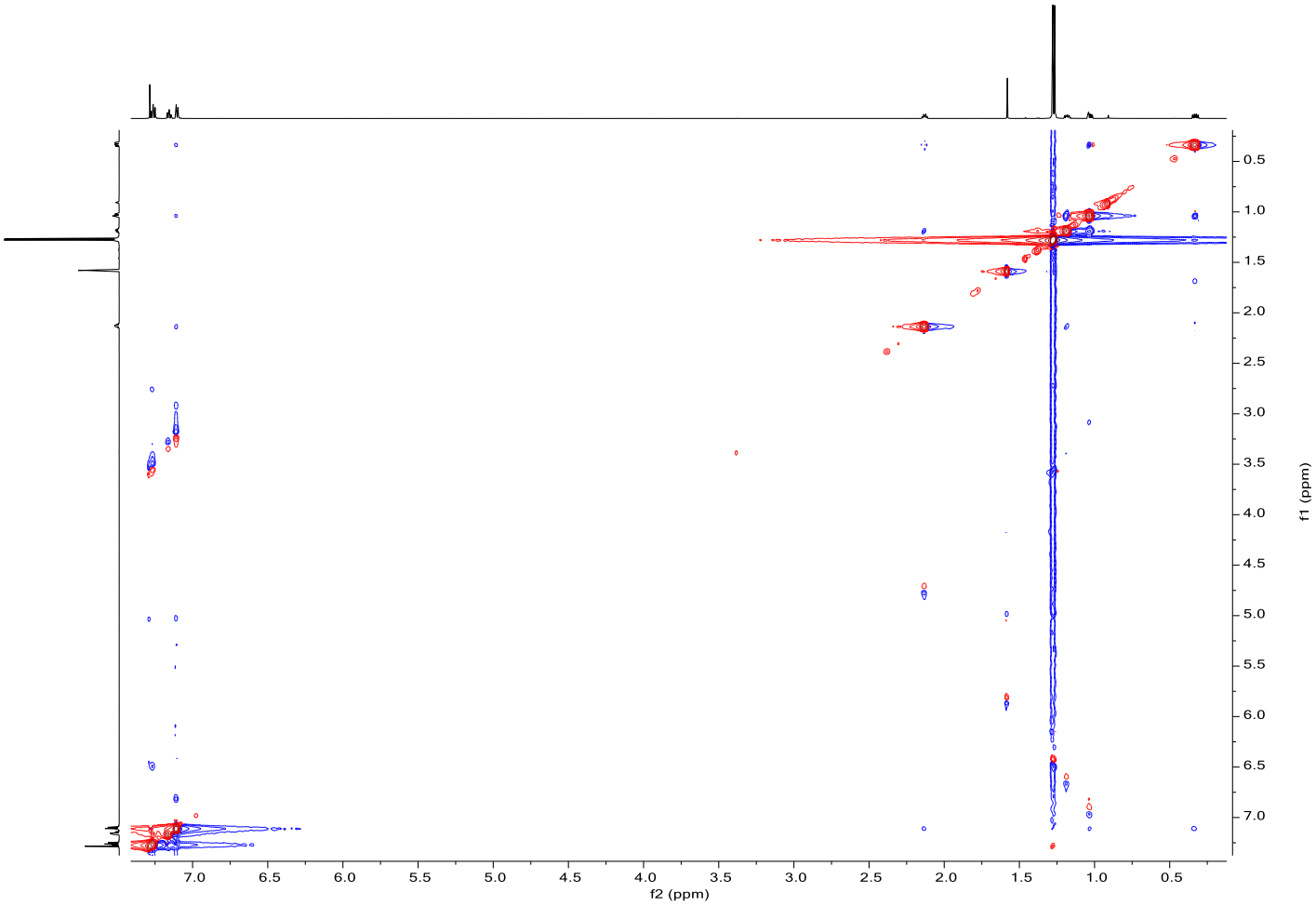


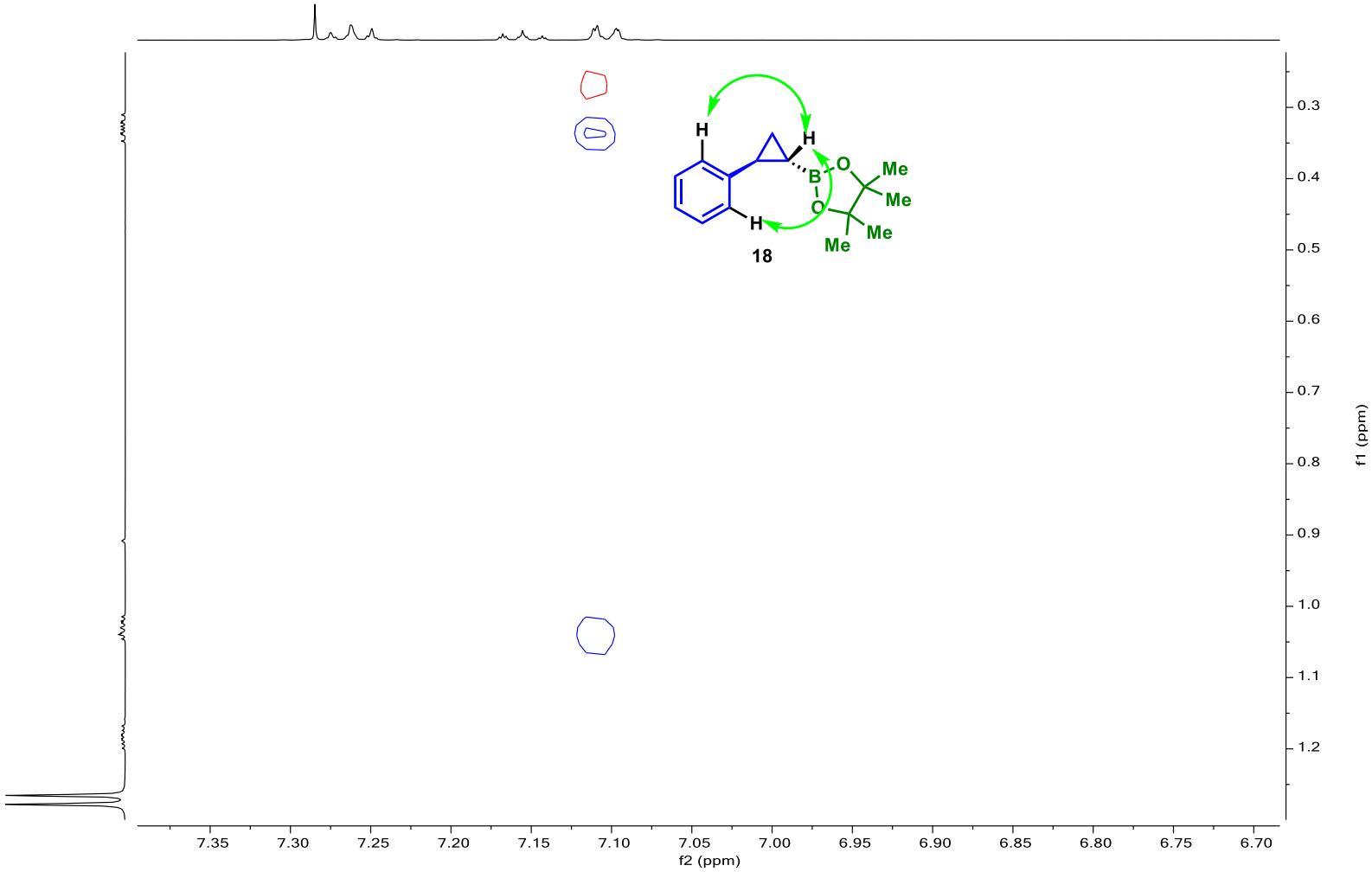
18

Compound 18 ^{13}C NMR

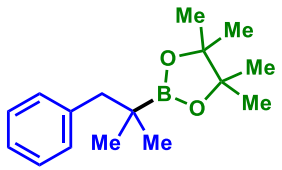


Compound 18 2D NOESY



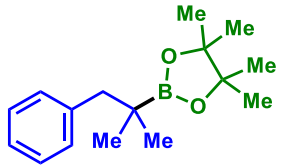

H
H
H
B
O
O
Me
Me
Me
Me
18
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
f1 (ppm)
7.35
7.30
7.25
7.20
7.15
7.10
7.05
7.00
6.95
6.90
6.85
6.80
6.75
6.70
f2 (ppm)

Compound 19 ^{1}H NMR



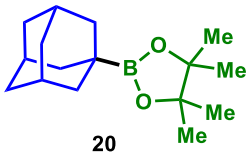
19

Compound 19 ^{13}C NMR



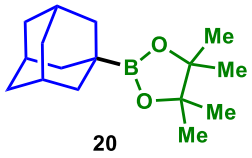
19

Compound 20 ^{1}H NMR



20

Compound 20 ^{13}C NMR



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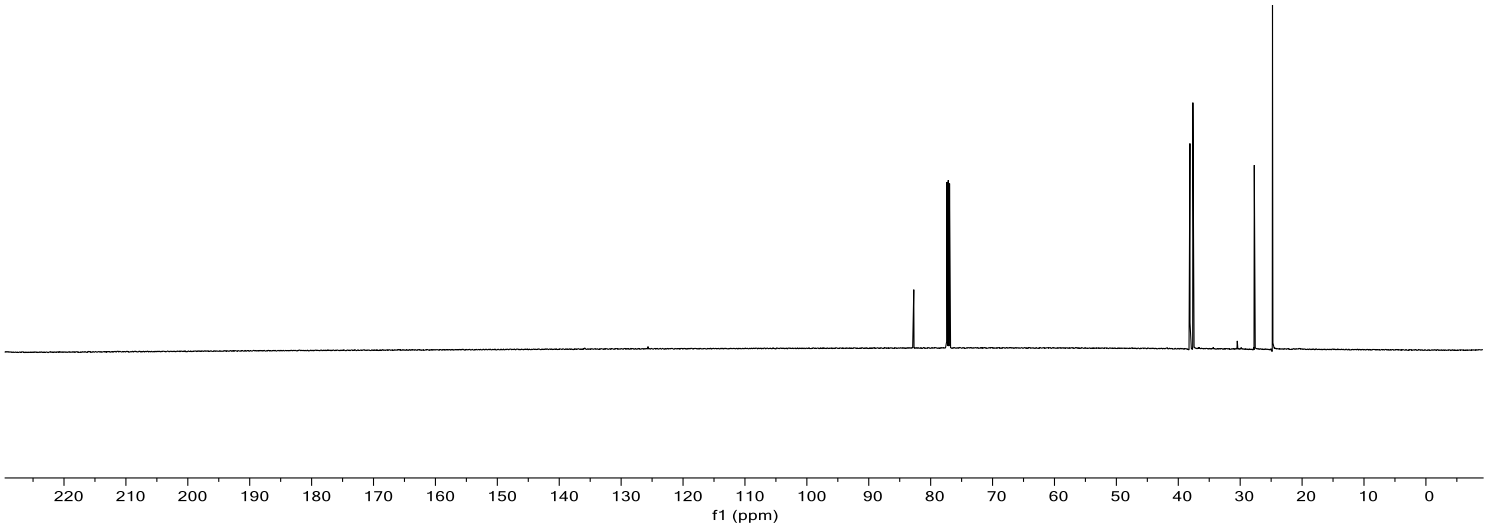
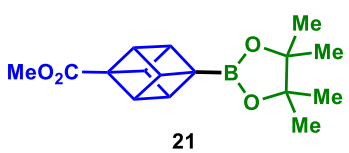
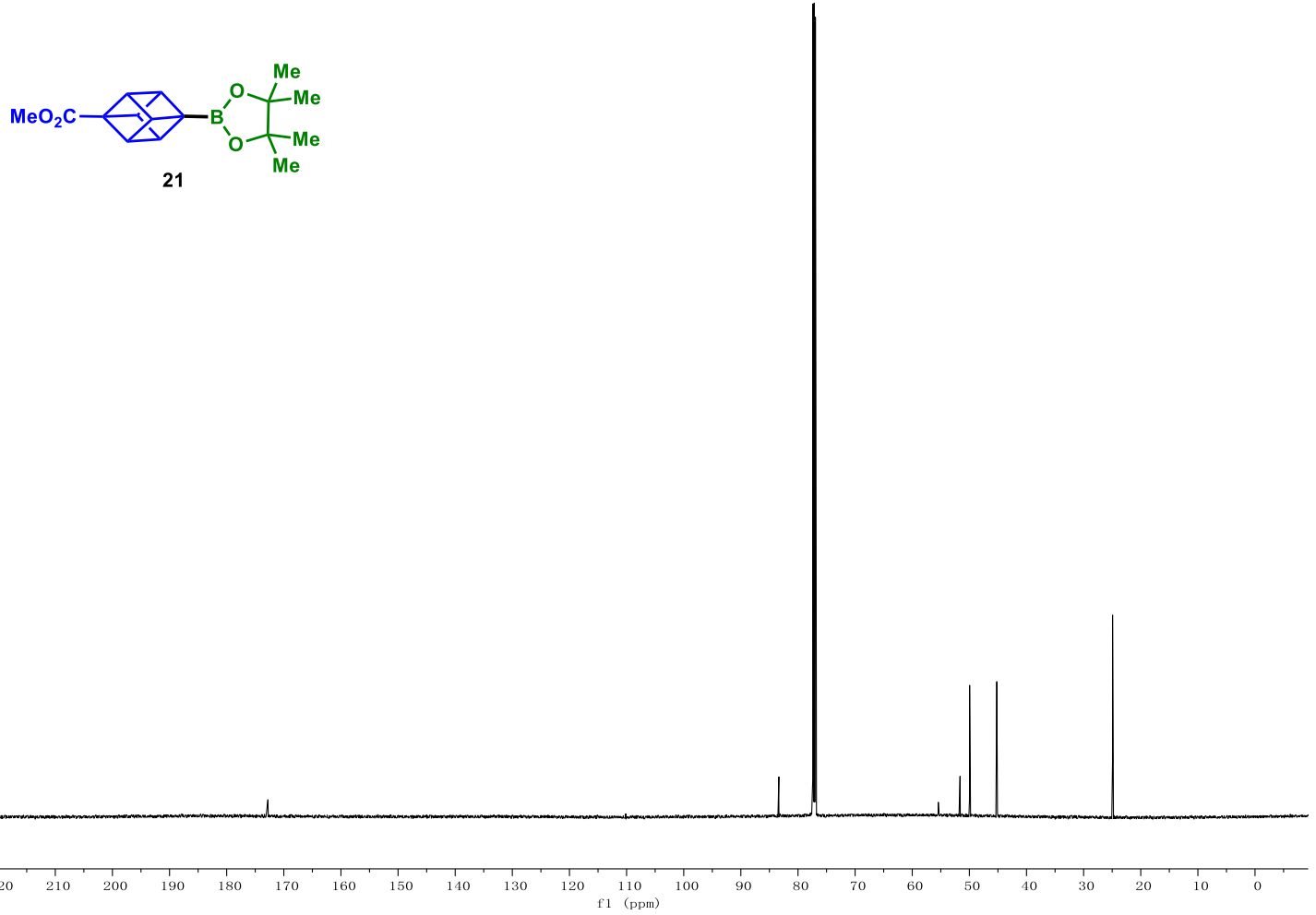


Compound 21 ^{1}H NMR

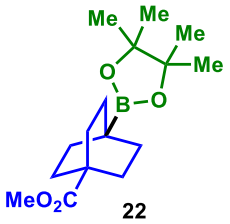


21

Compound 21 ^{13}C NMR



Compound 22 ^{1}H NMR



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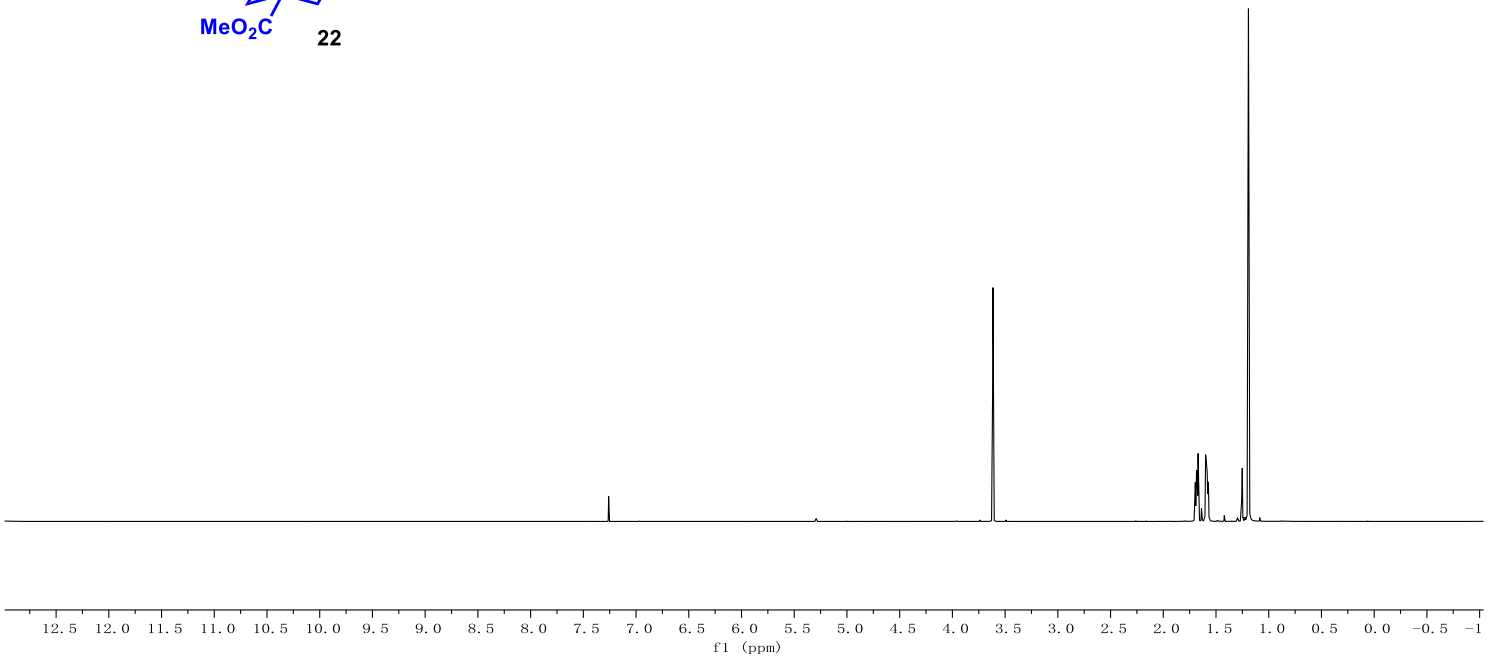
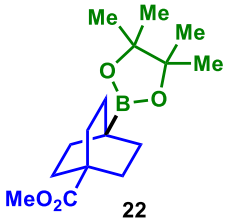


Compound 22 ^{13}C NMR



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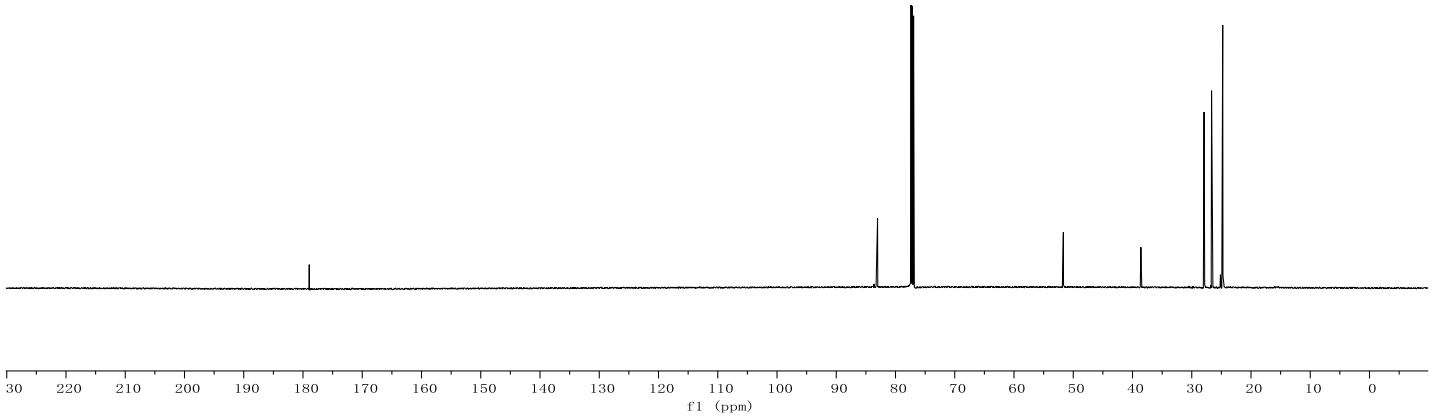
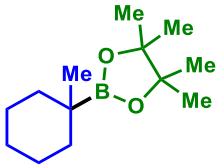
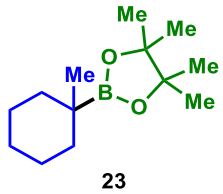


Compound 23 ^{1}H NMR



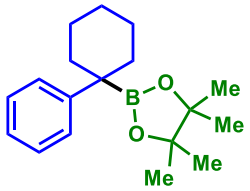
23

Compound 23 ^{13}C NMR



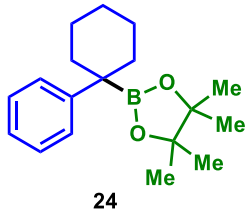
23

Compound 24 ^{1}H NMR



24

Compound 24 ^{13}C NMR



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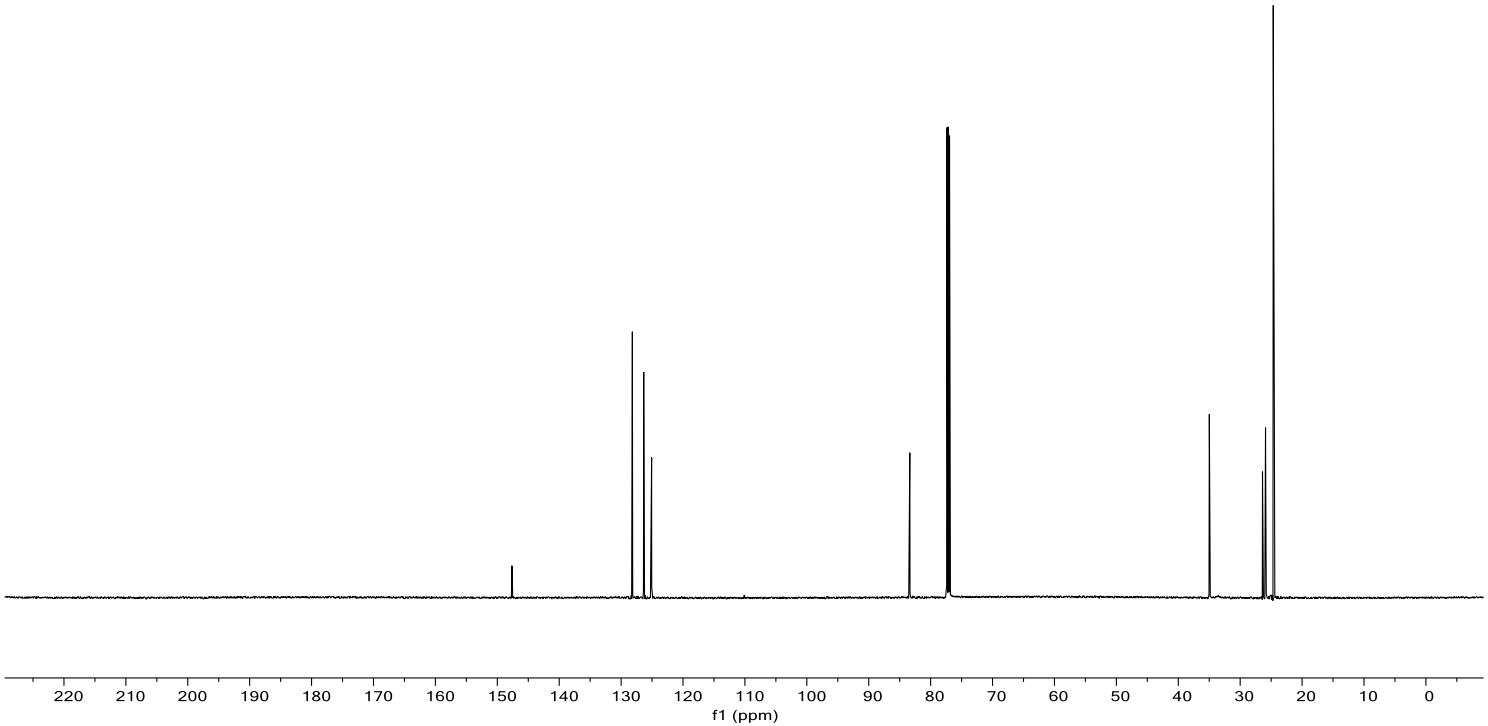
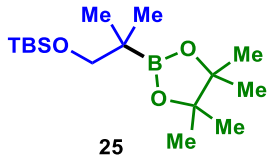
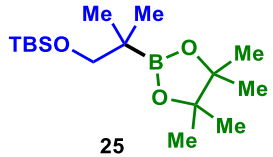


Compound 25 ^{1}H NMR



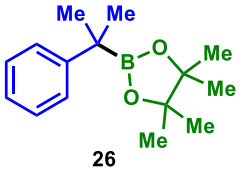
25

Compound 25 ^{13}C NMR



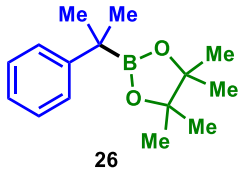
25

Compound 26 ^{1}H NMR

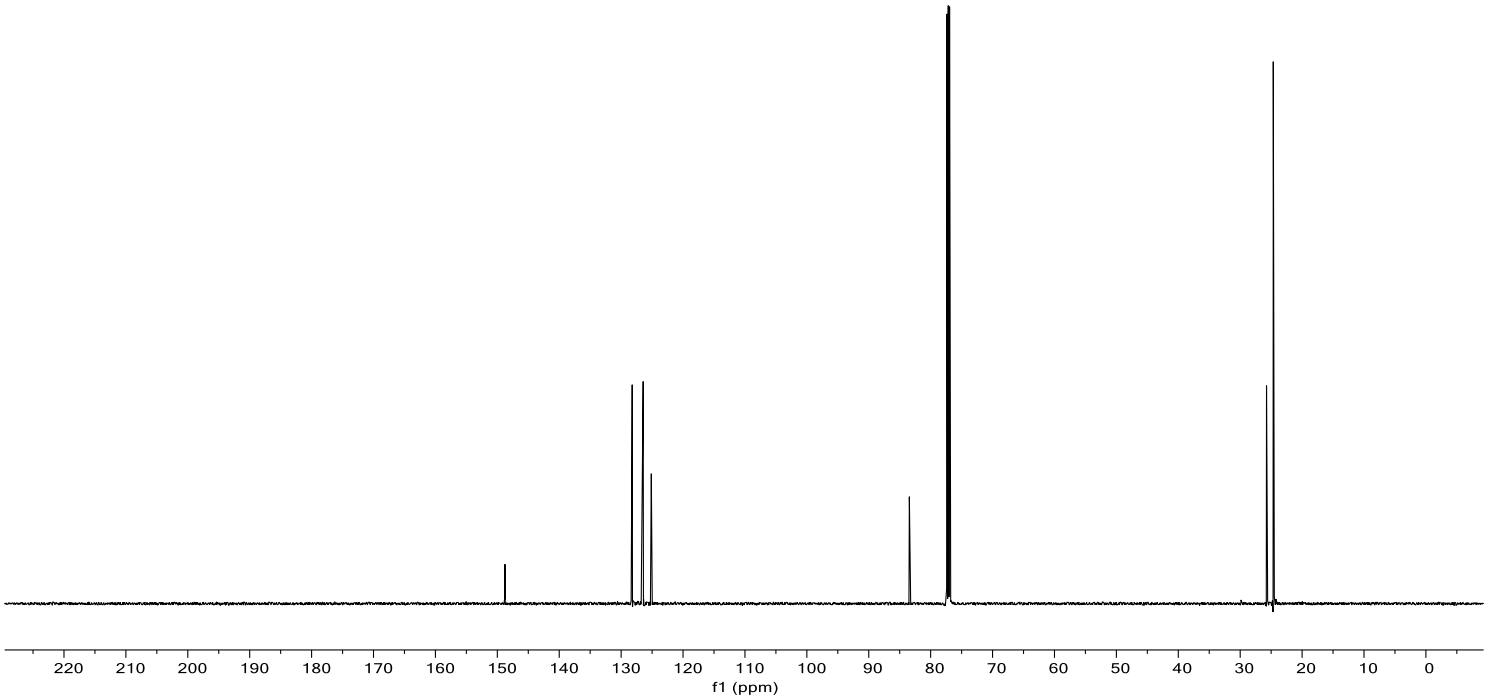


26

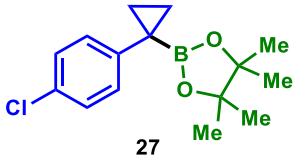
Compound 26 ^{13}C NMR



26

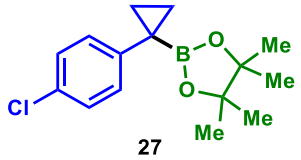


Compound 27 ^{1}H NMR



27

Compound 27 ^{13}C NMR



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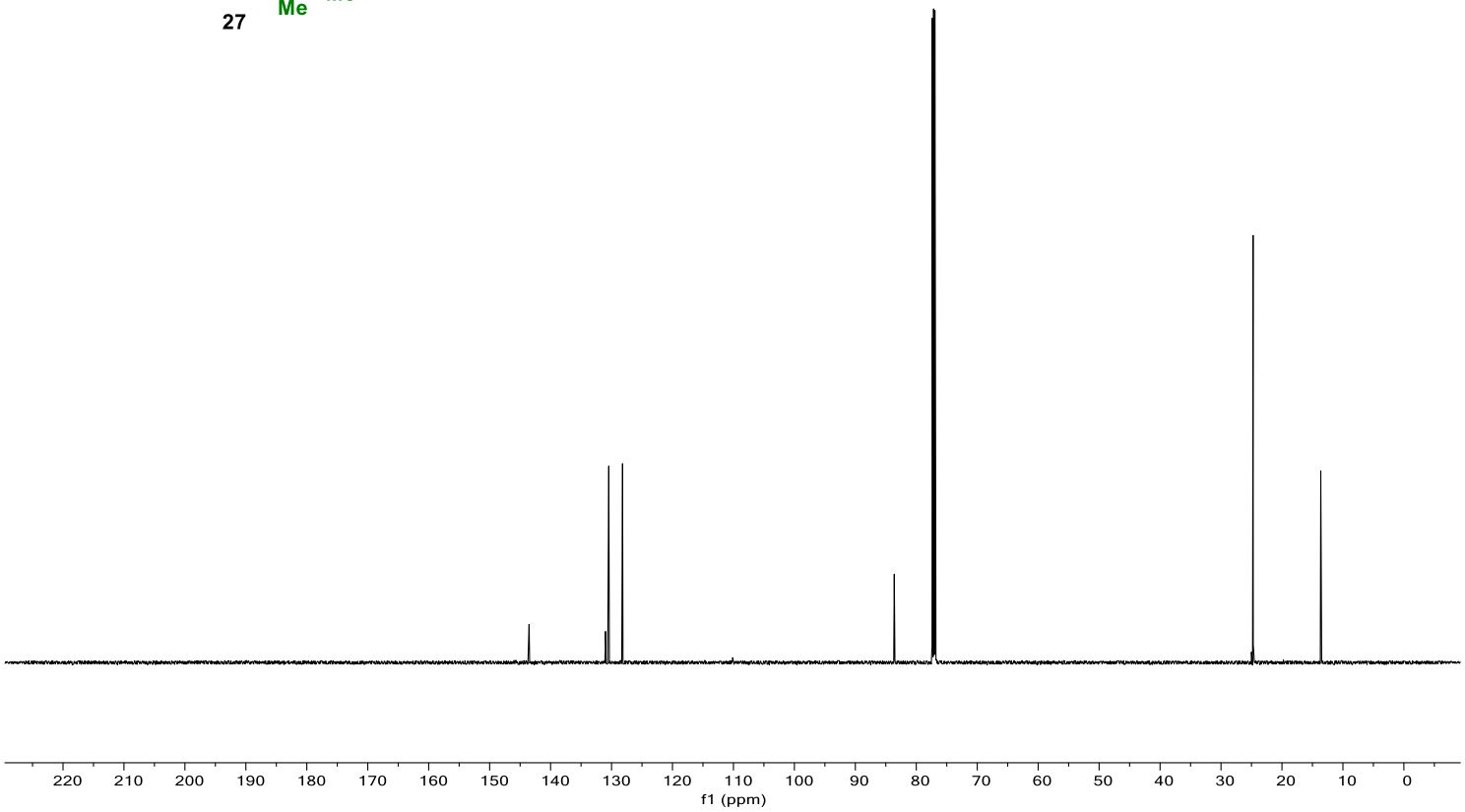
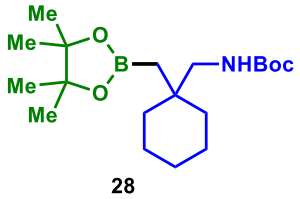
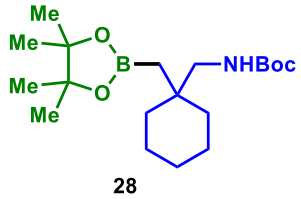


Compound 28 ^{1}H NMR



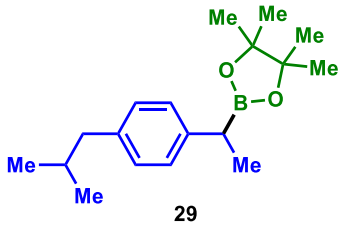
28

Compound 28 ^{13}C NMR



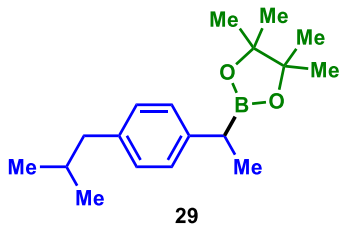
28

Compound 29 ^{1}H NMR



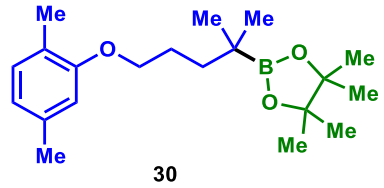
29

Compound 29 ^{13}C NMR



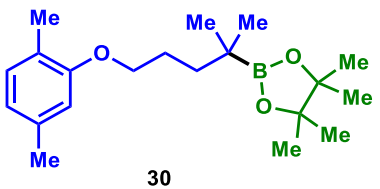
29

Compound 30 ^{1}H NMR



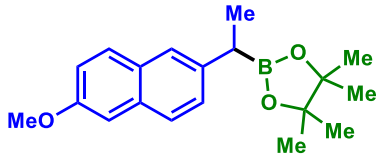
30

Compound 30 ^{13}C NMR



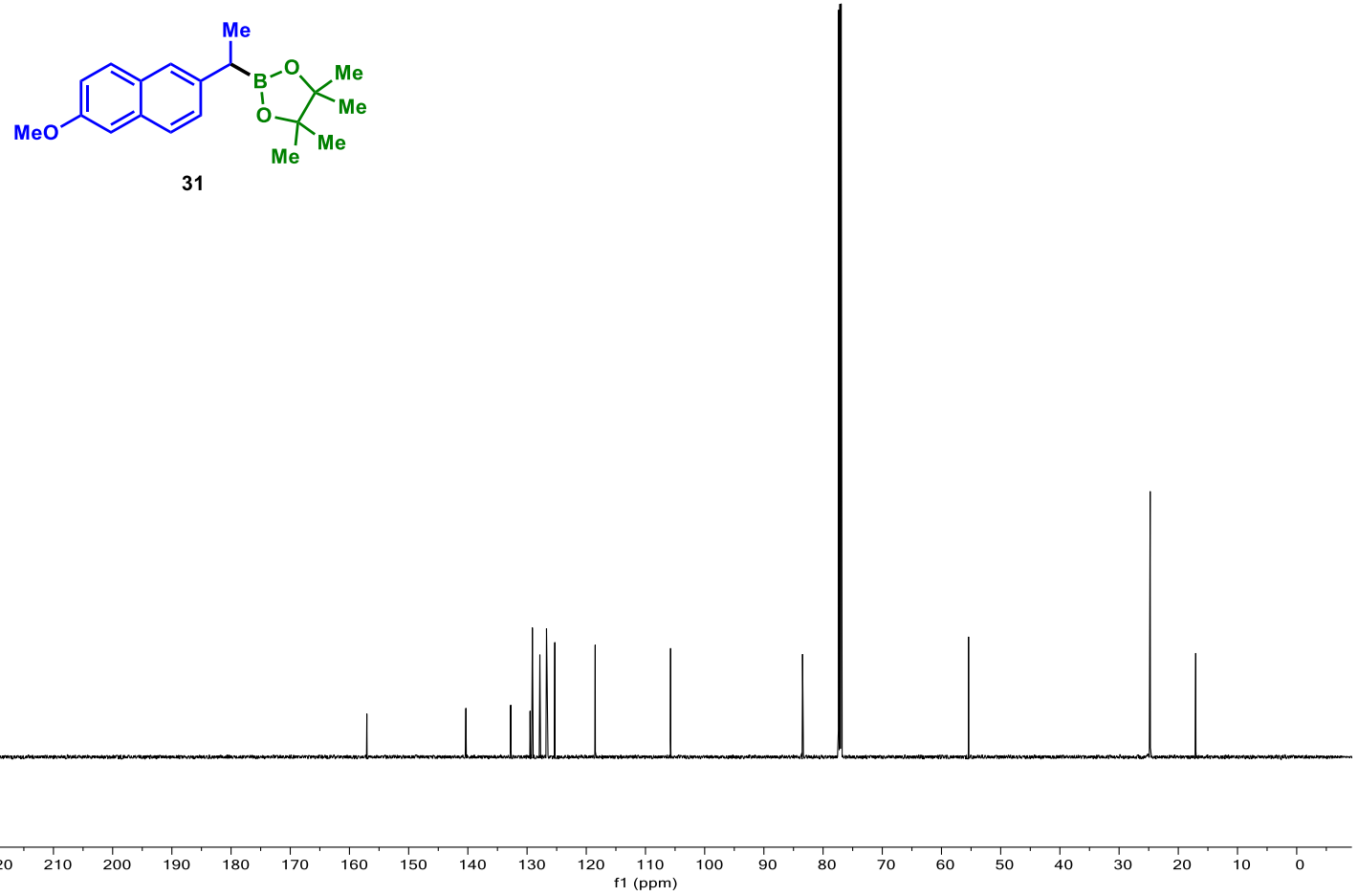
30

Compound 31 ^{1}H NMR



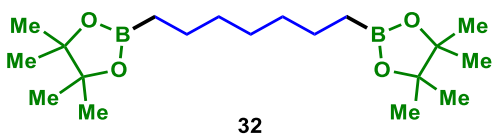
31

Compound 31 ^{13}C NMR



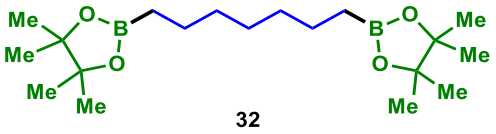
31

Compound 32 ^{1}H NMR



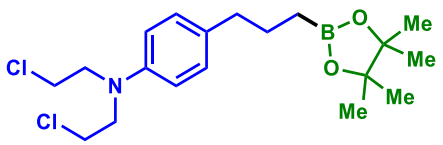
32

Compound 32 ^{13}C NMR



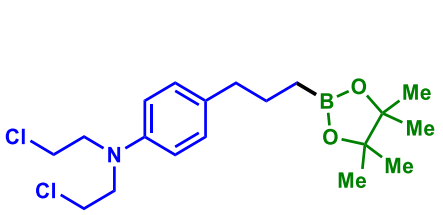
32

Compound 33 ^{1}H NMR



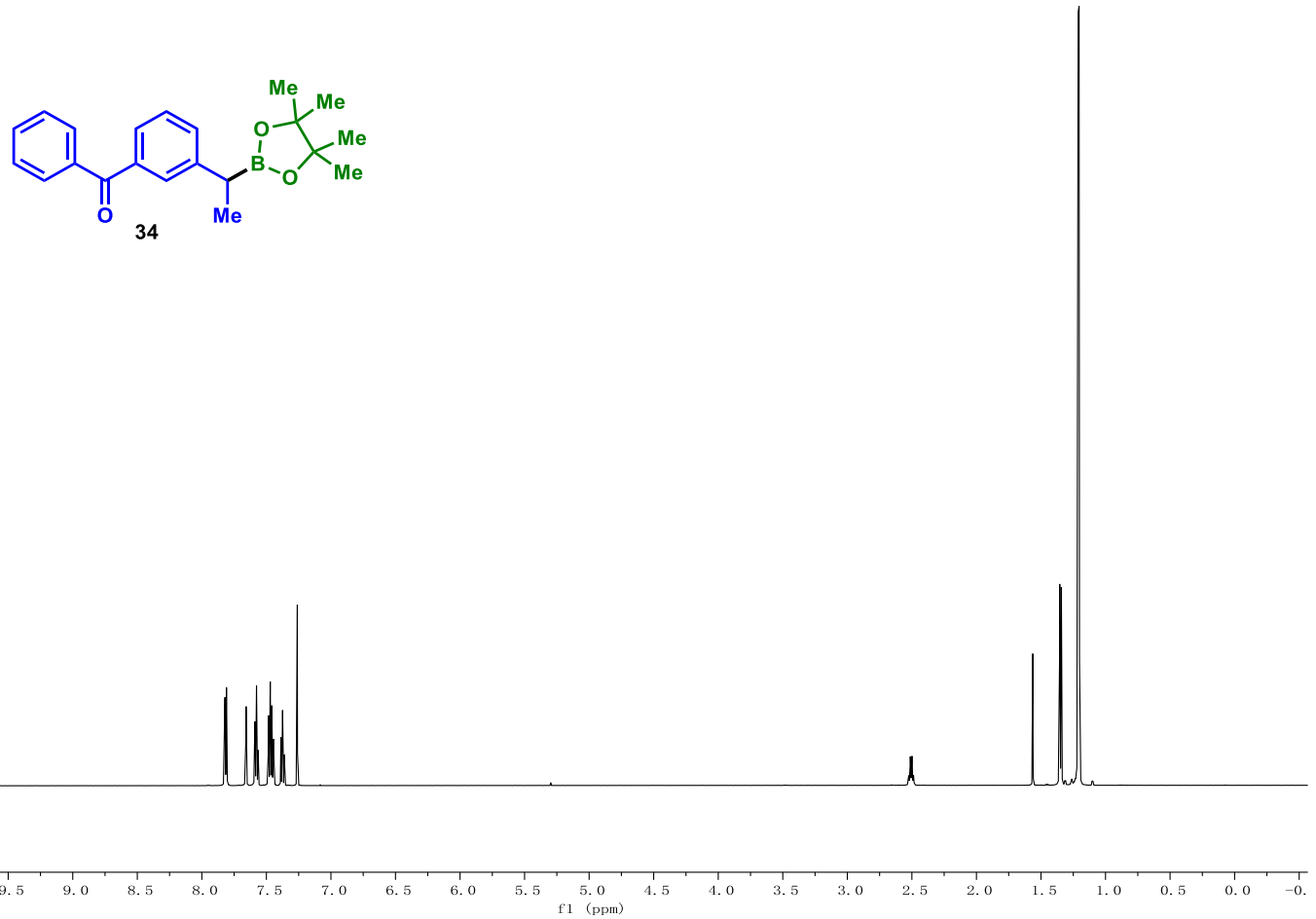
33

Compound 33 ^{13}C NMR

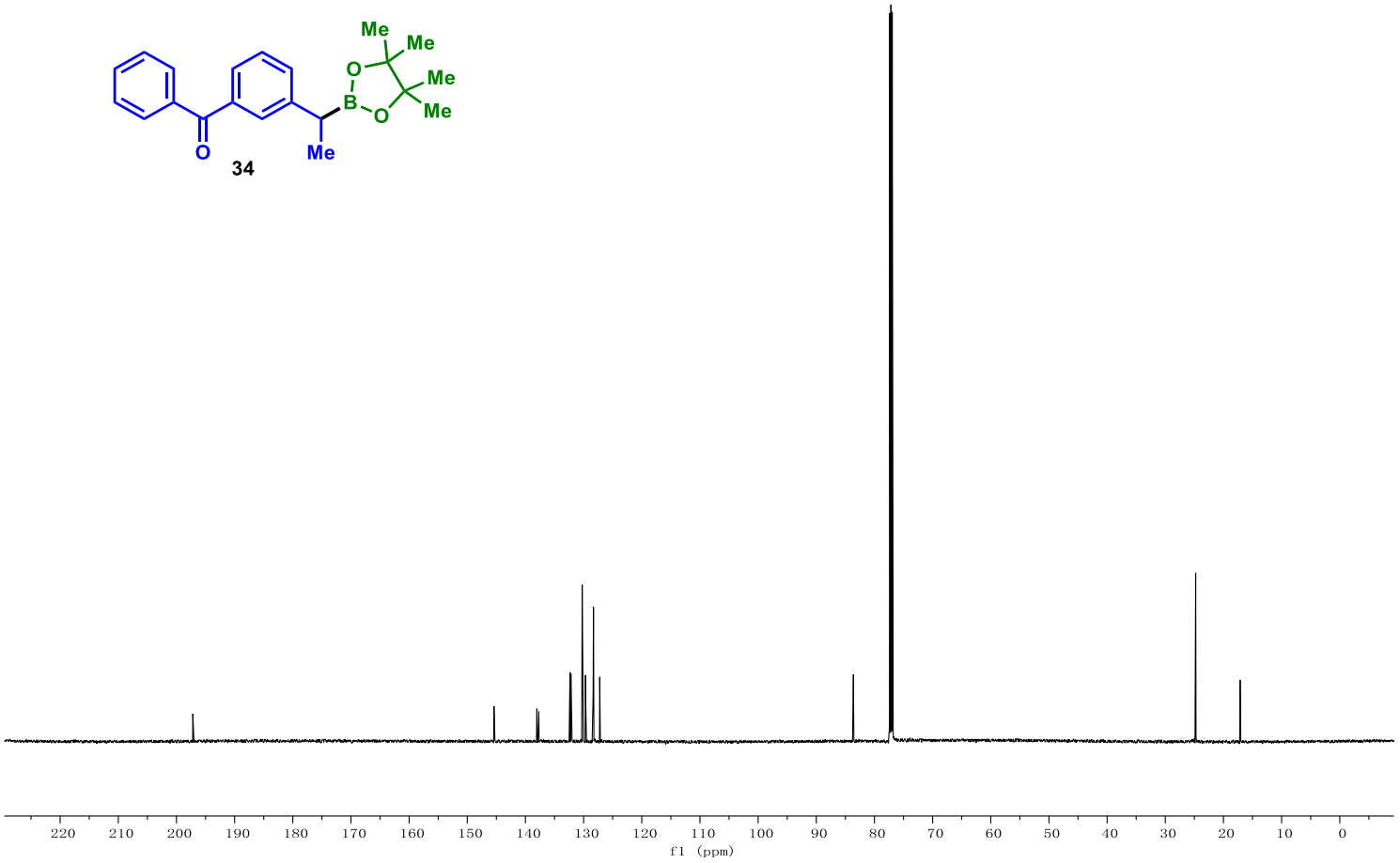


33

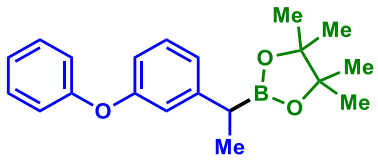
Compound 34 ^{1}H NMR



Compound 34 ^{13}C NMR

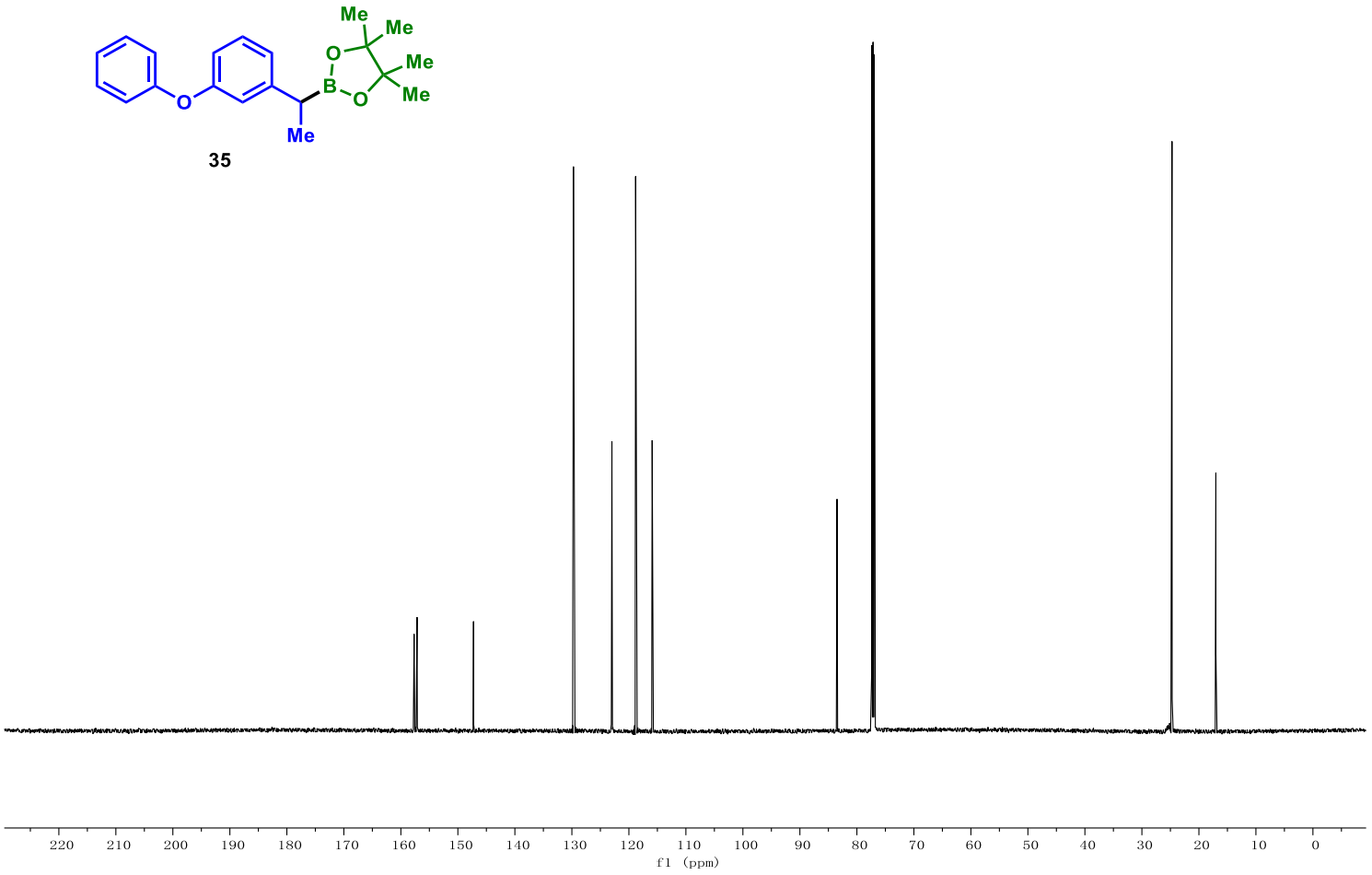


Compound 35 ^{1}H NMR

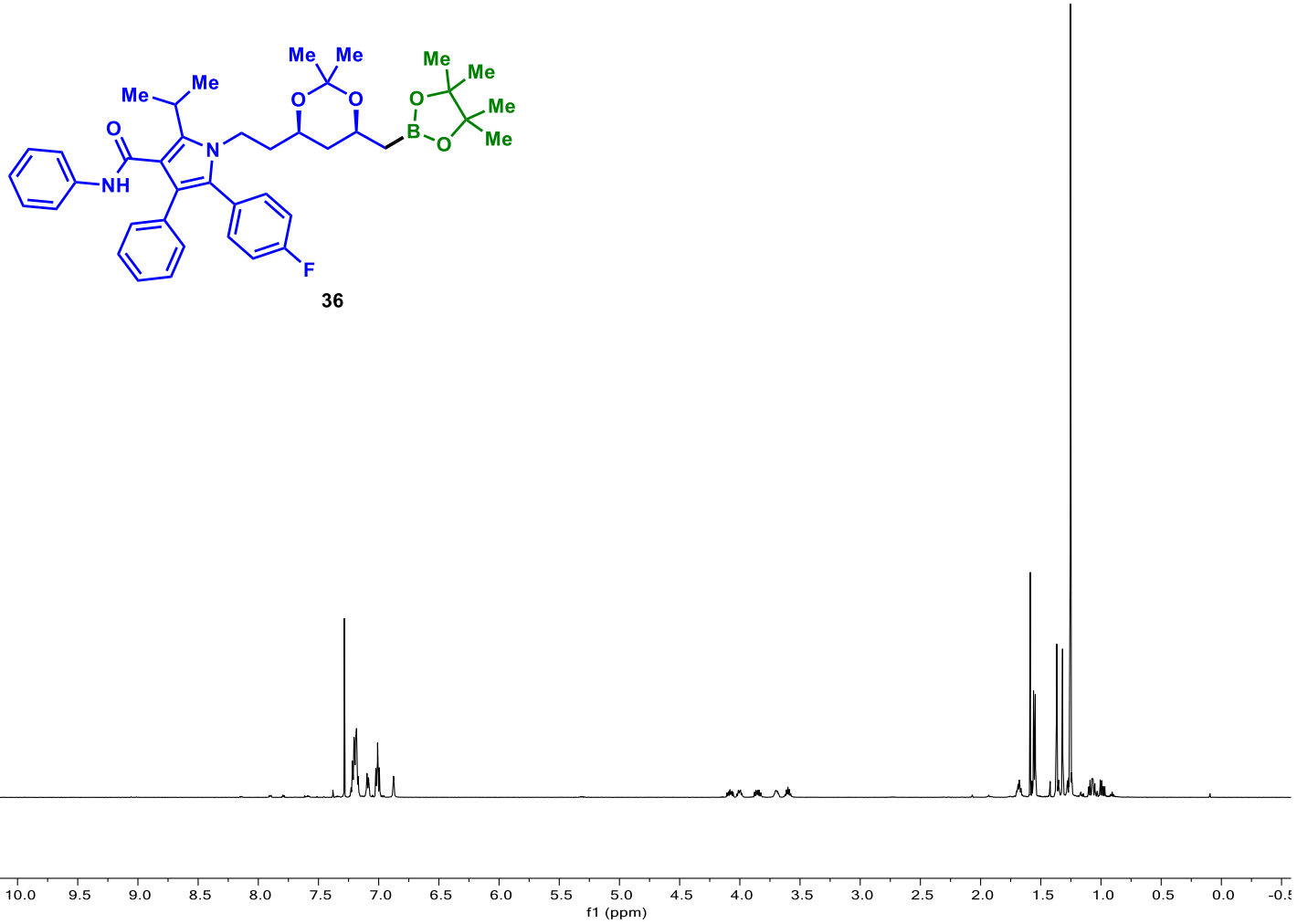


35

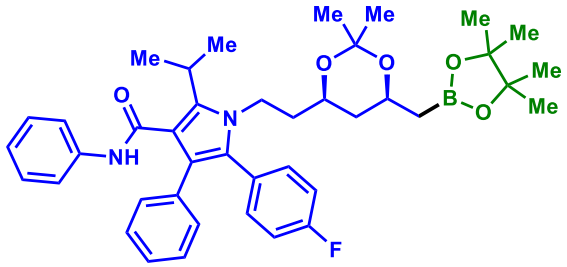
Compound 35 ^{13}C NMR



Compound 36 ^{1}H NMR

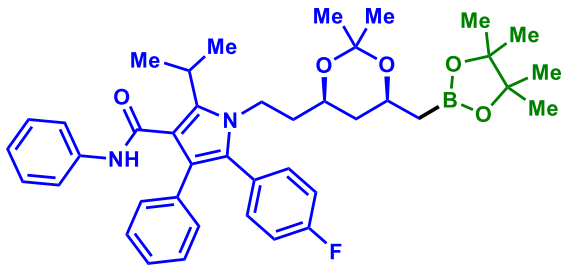


Compound 36 ^{13}C NMR

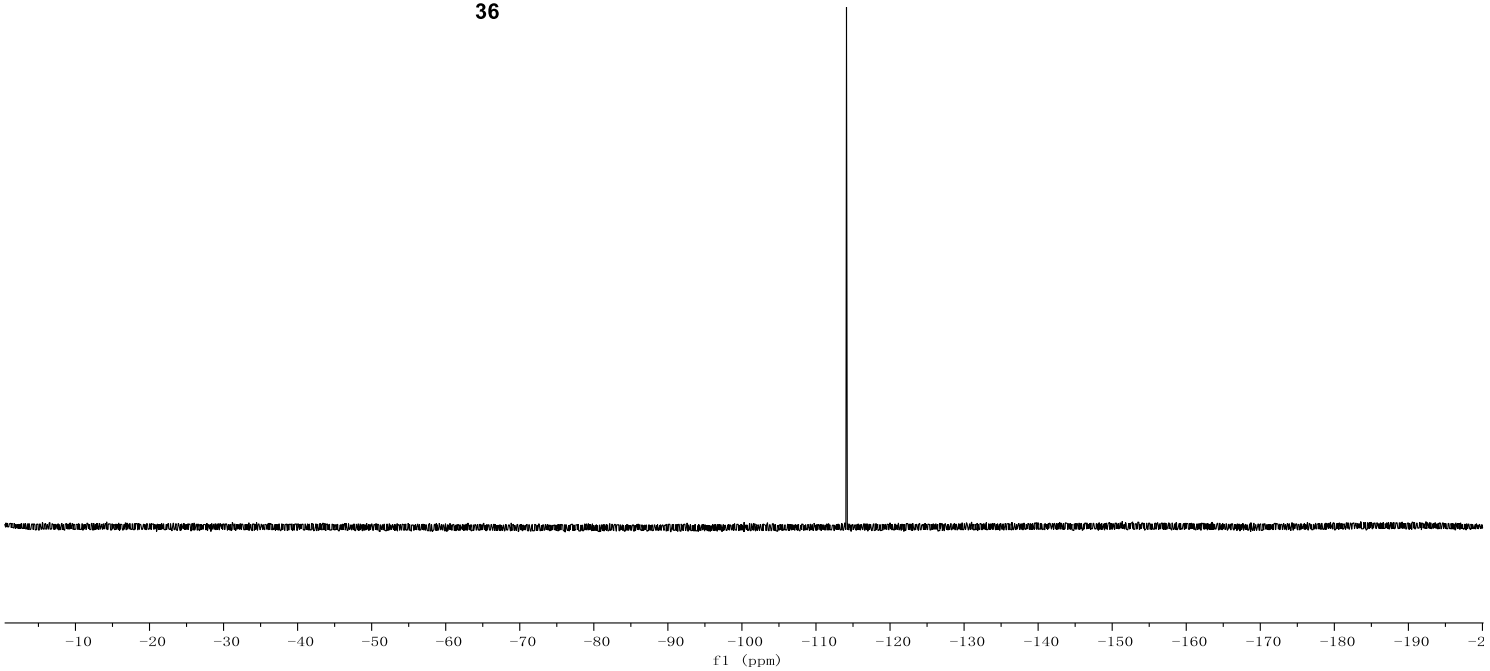


36

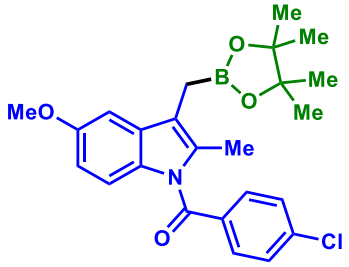
Compound 36 ^{19}F NMR



36

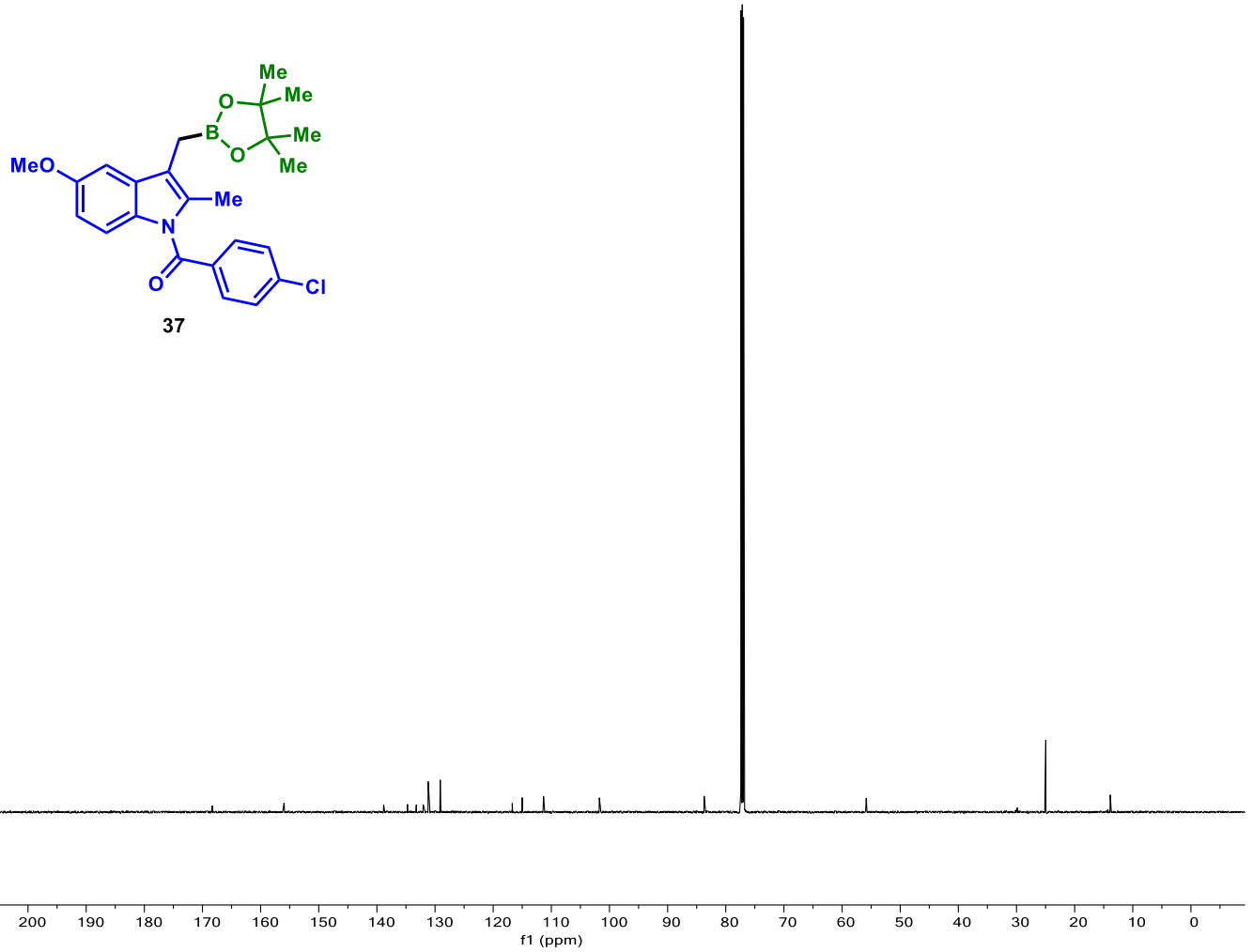


Compound 37 ^{1}H NMR

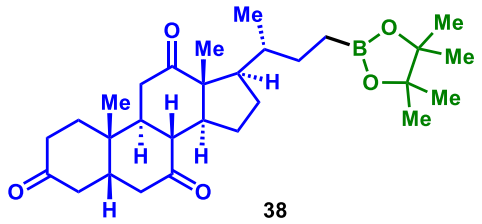


37

Compound 37 ^{13}C NMR

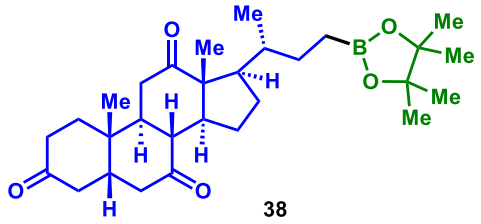


Compound 38 ^{1}H NMR



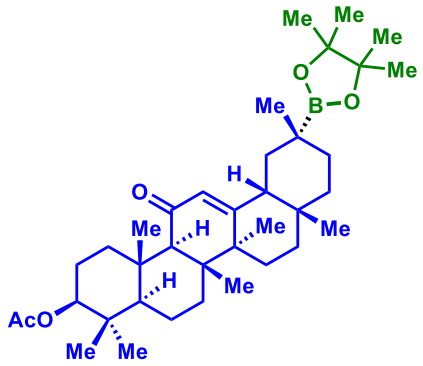
38

Compound 38 ^{13}C NMR



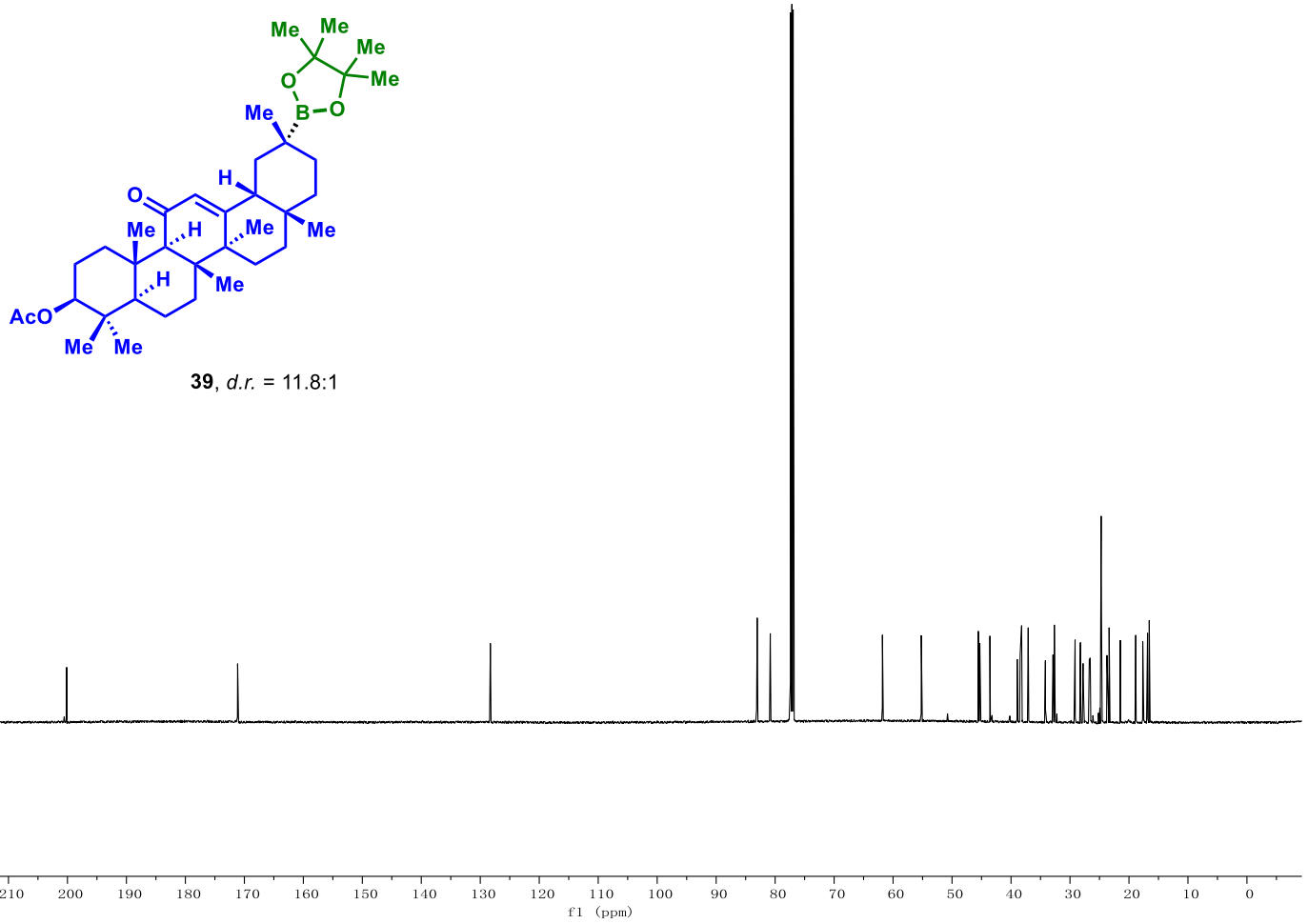
38

Compound 39 ^{1}H NMR



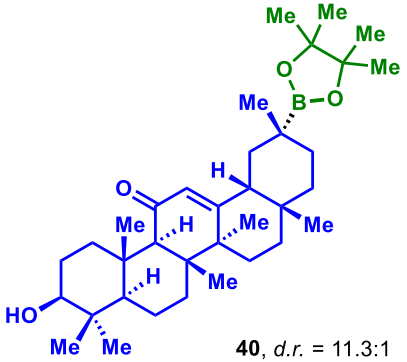
39, *d.r.* = 11.8:1

Compound 39 ^{13}C NMR



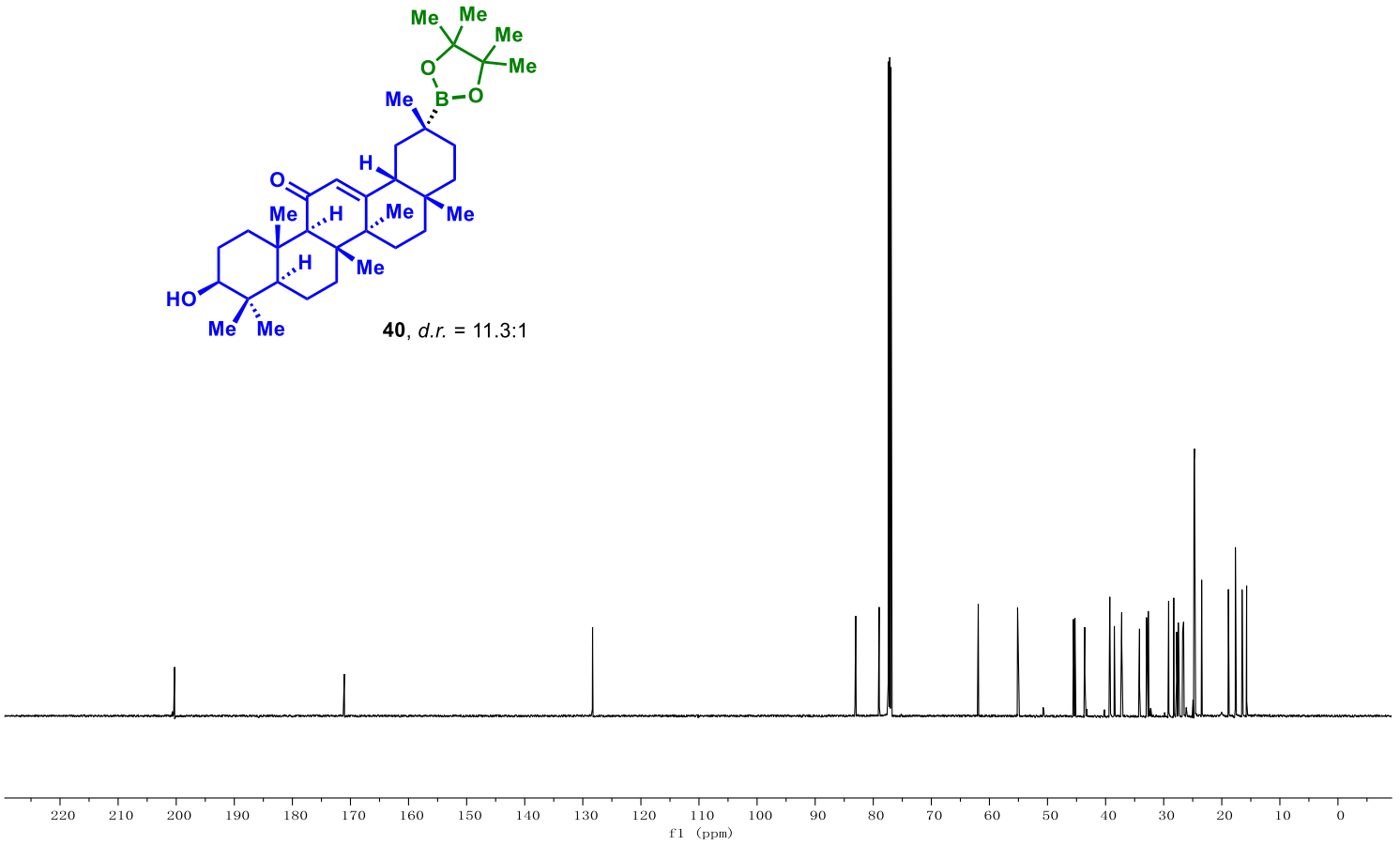
39, *d.r.* = 11.8:1

Compound 40 ^{1}H NMR

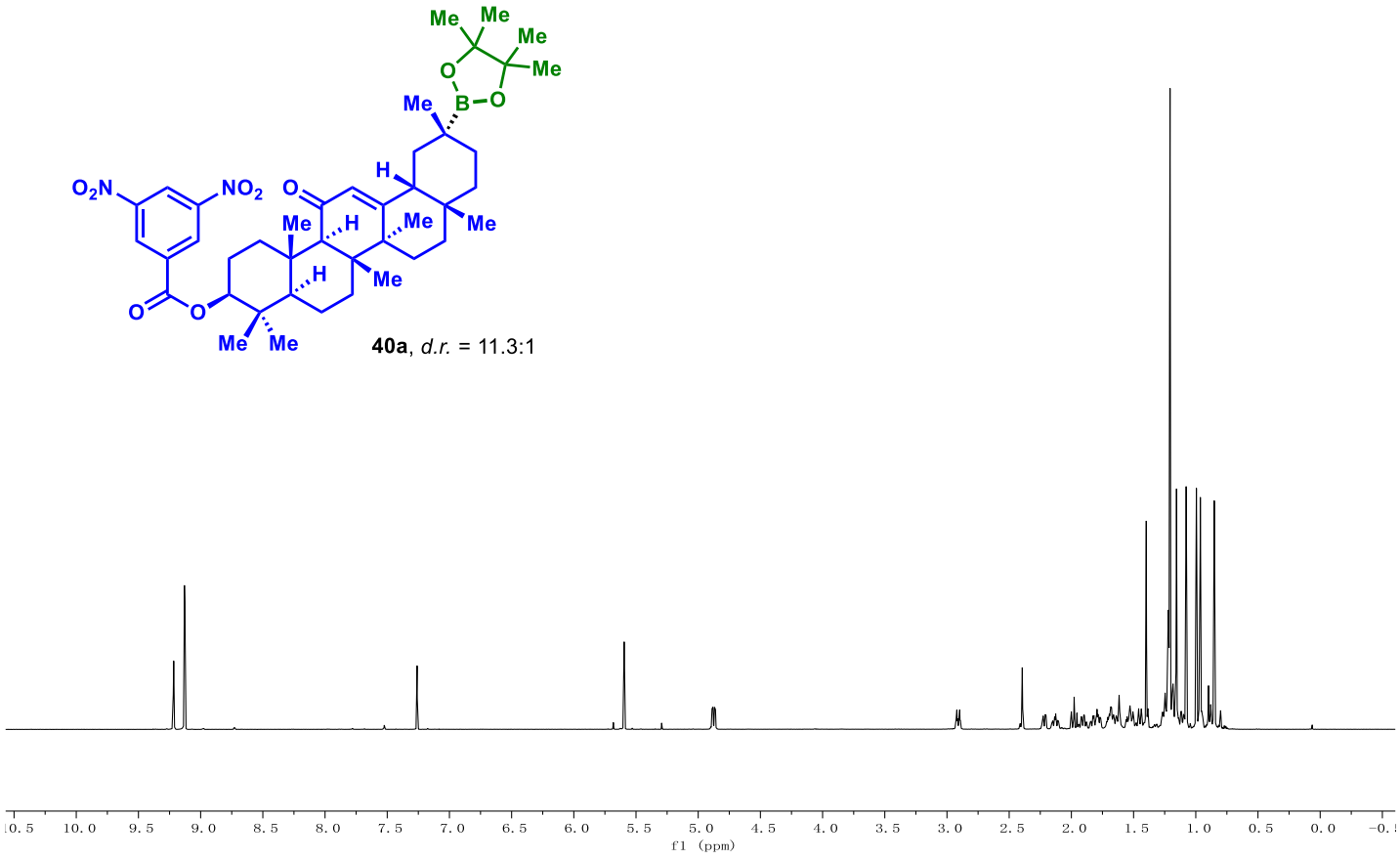


40, *d.r.* = 11.3:1

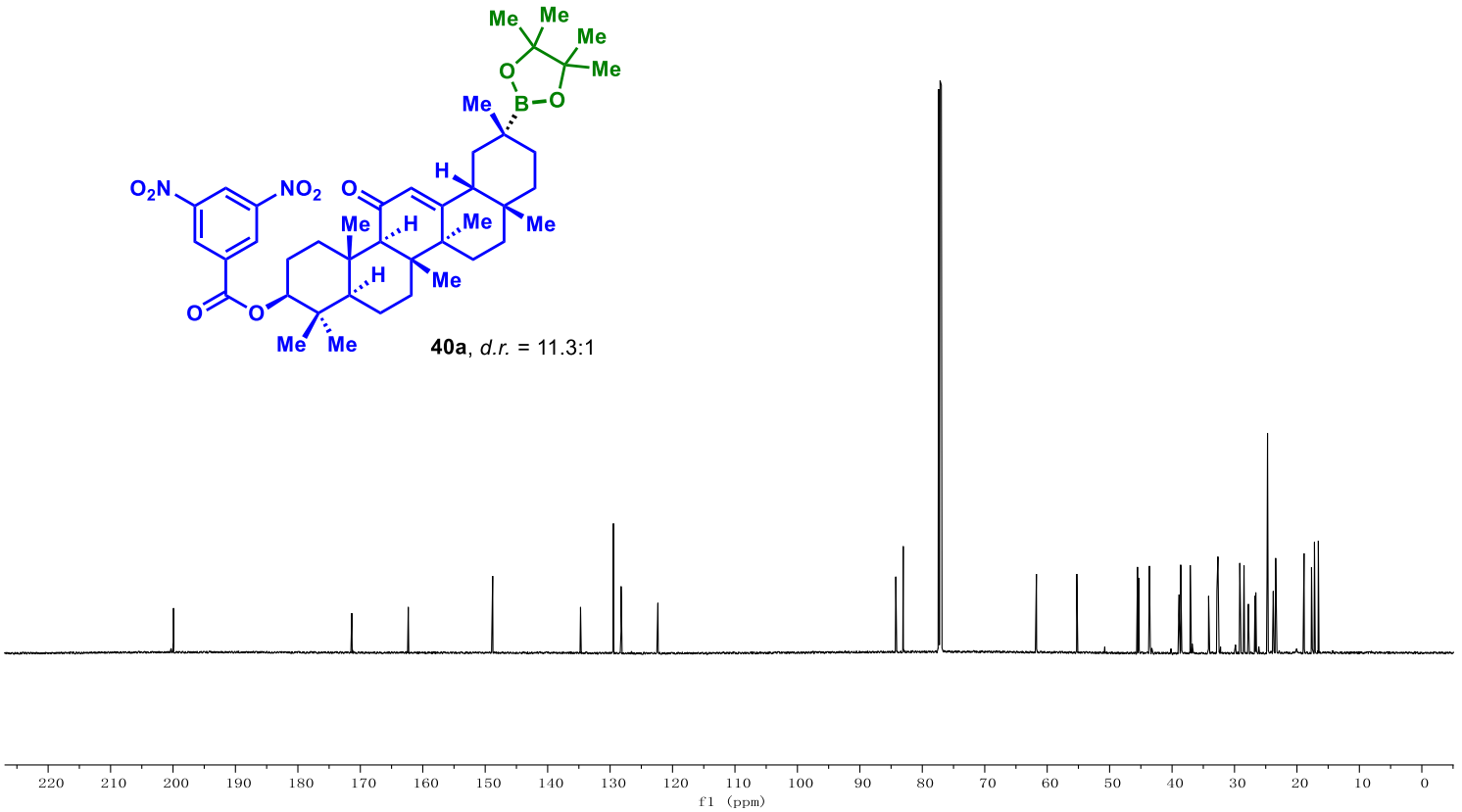
Compound 40 ^{13}C NMR



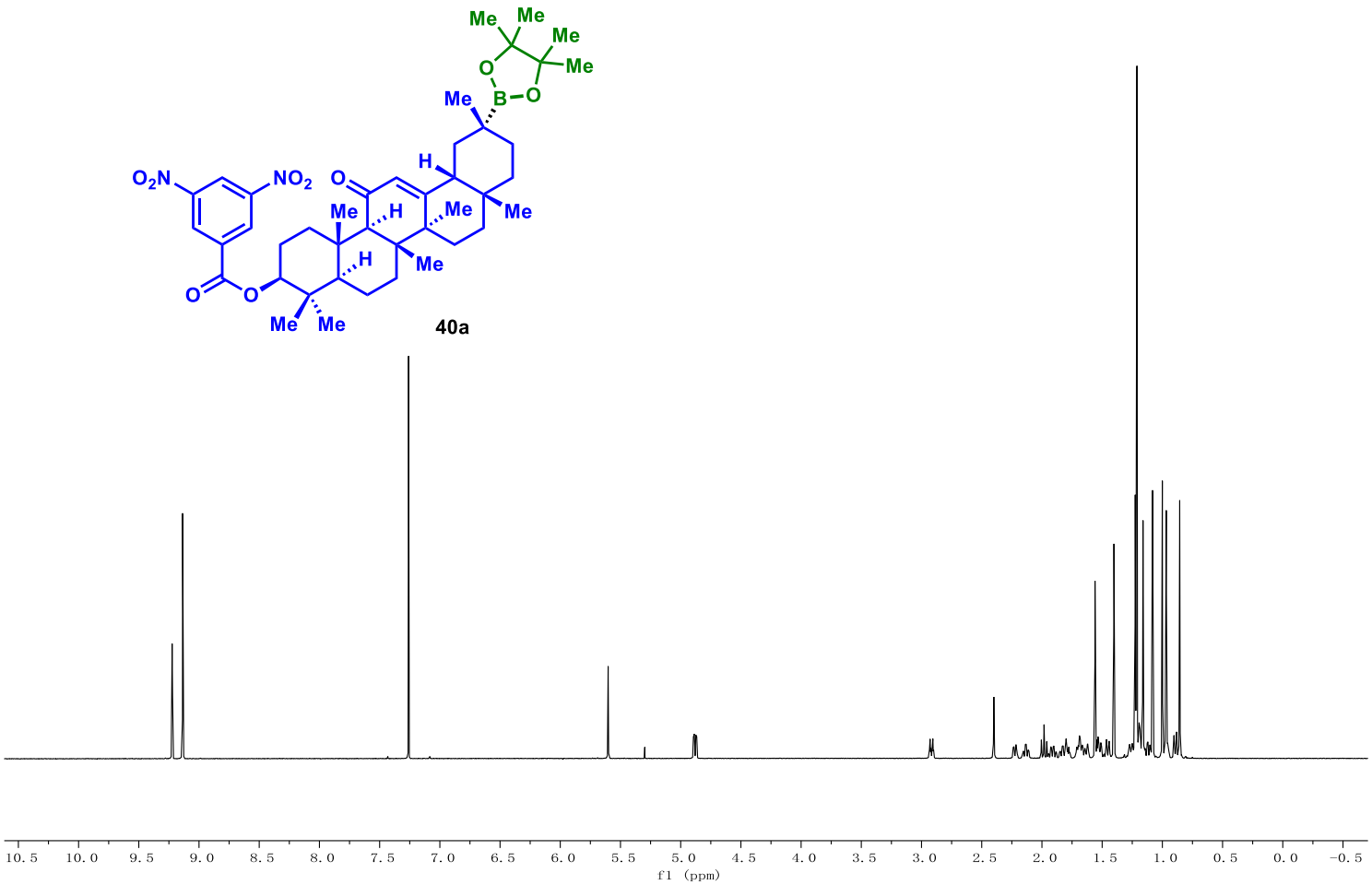
Compound 40a ^{1}H NMR



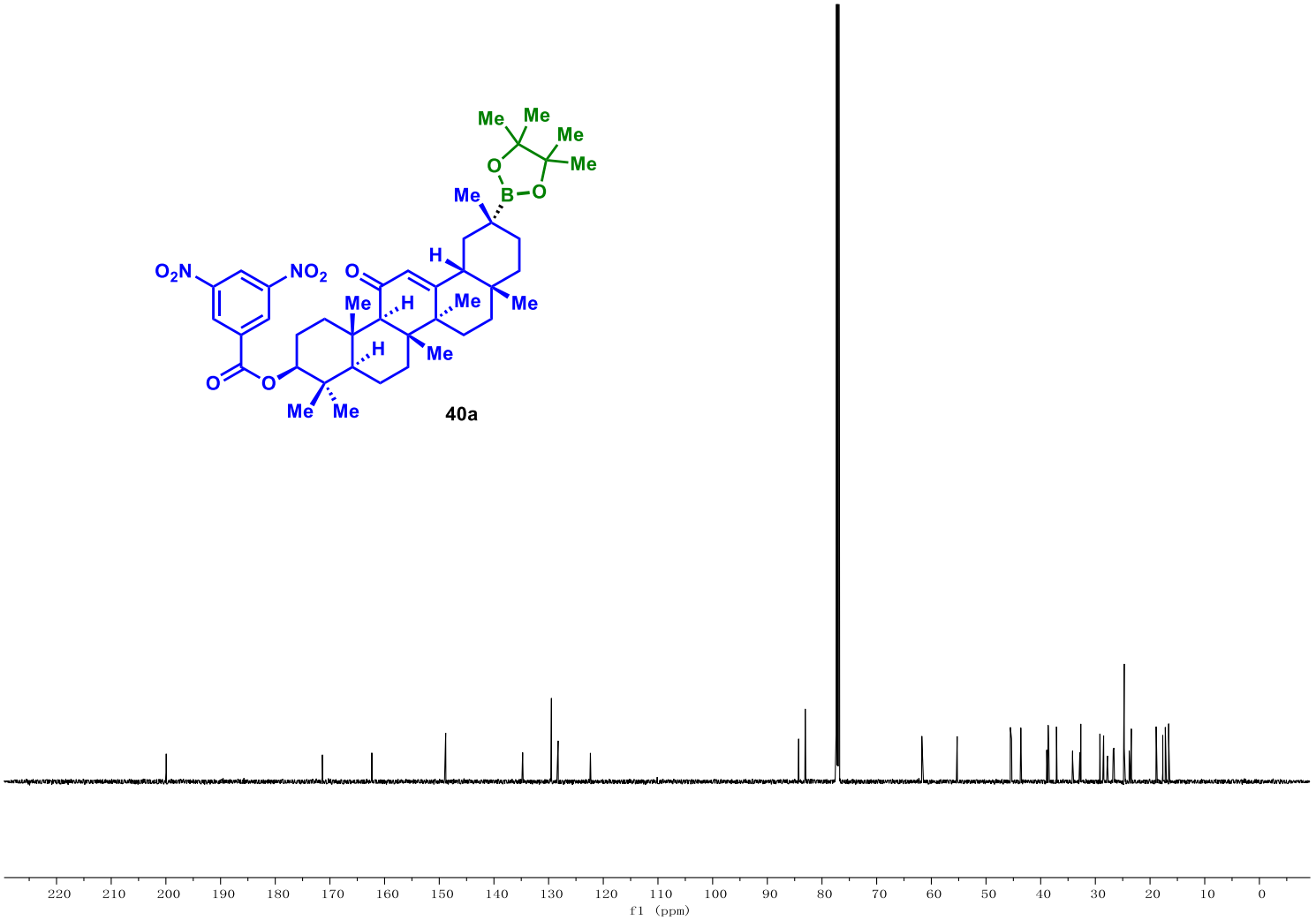
Compound 40a ^{13}C NMR



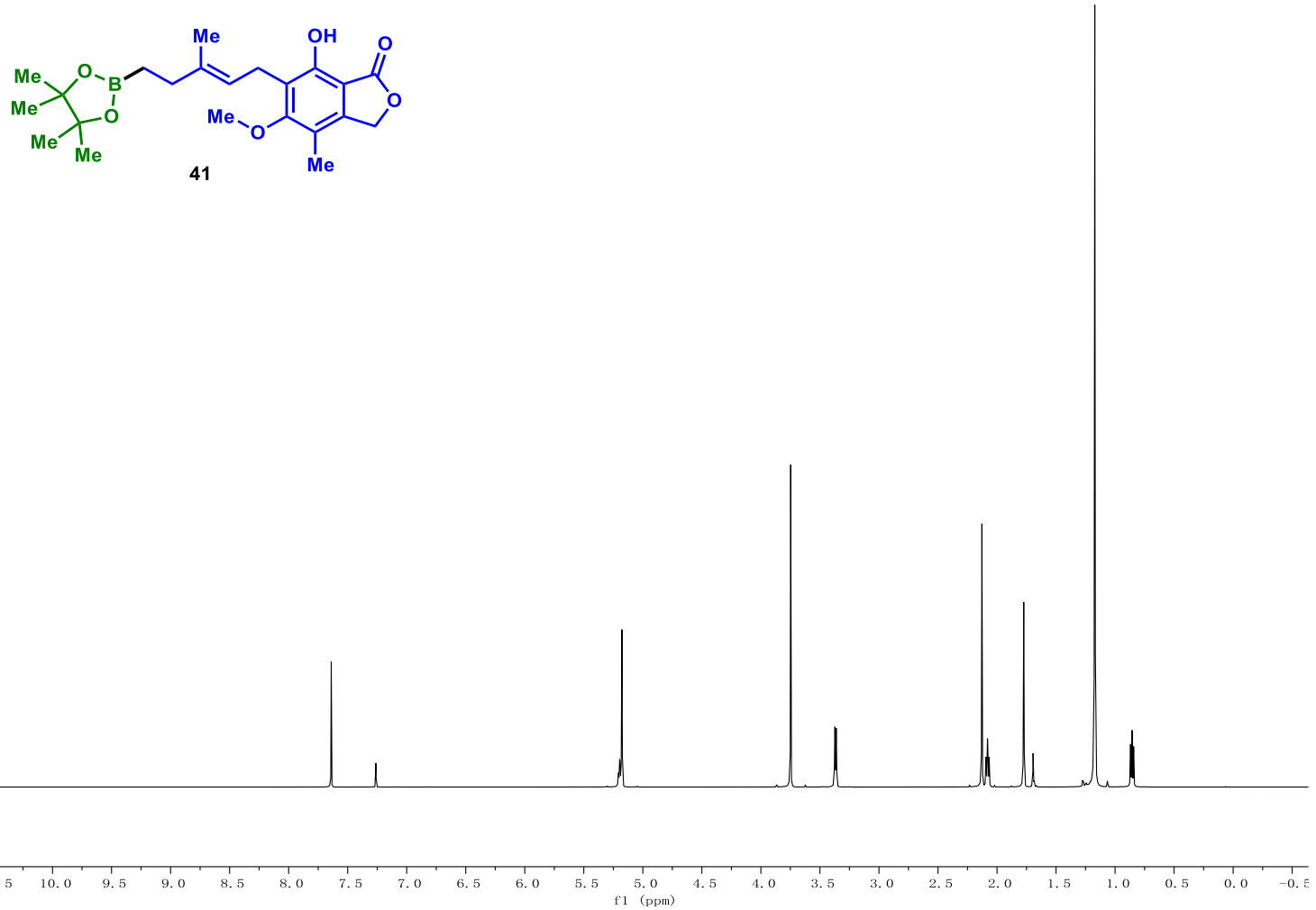
Compound 40a (crystal) ^{1}H NMR



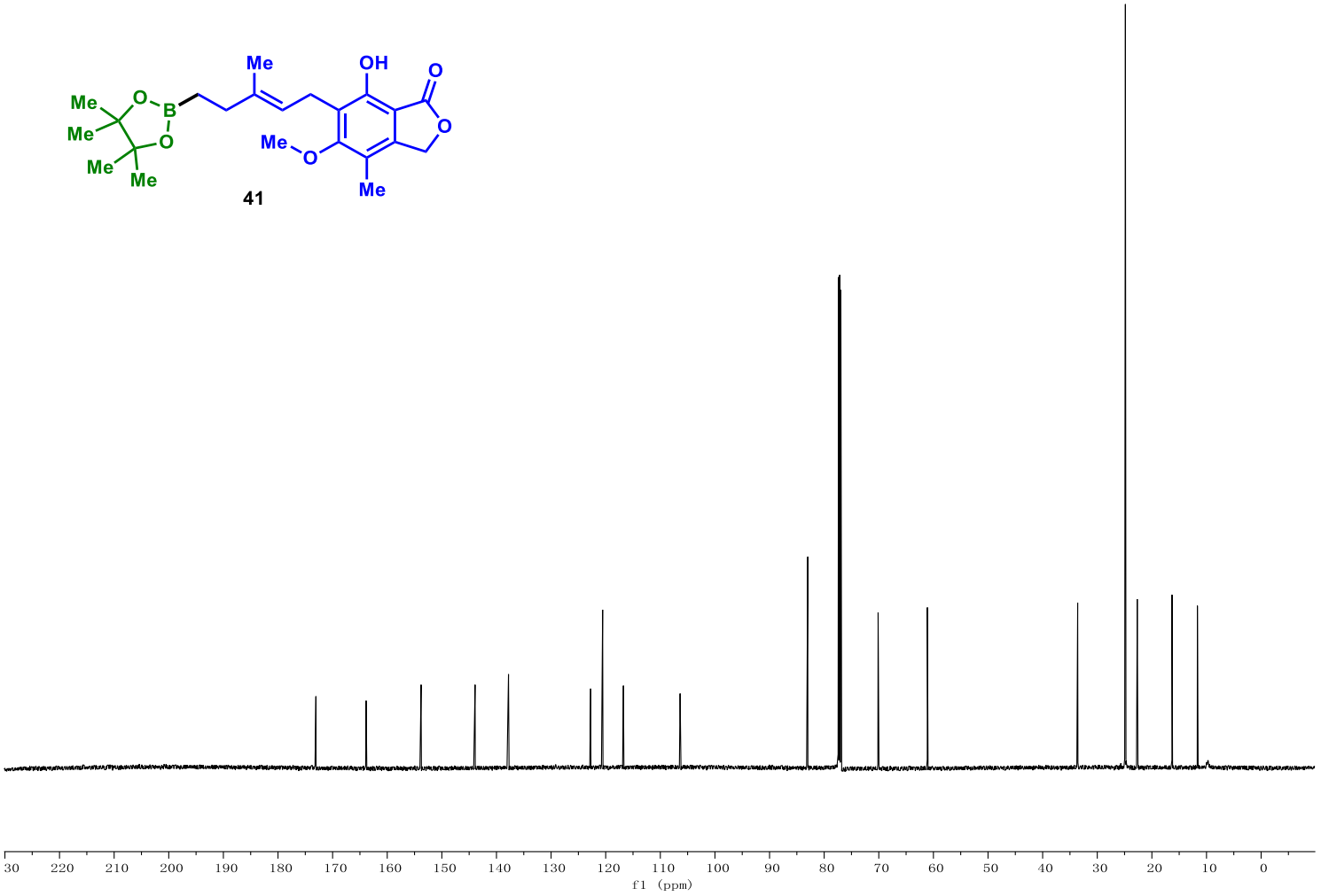
Compound 40a (crystal) ^{13}C NMR



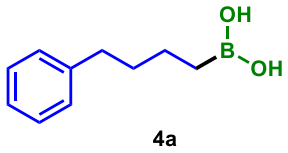
Compound 41 ^{1}H NMR



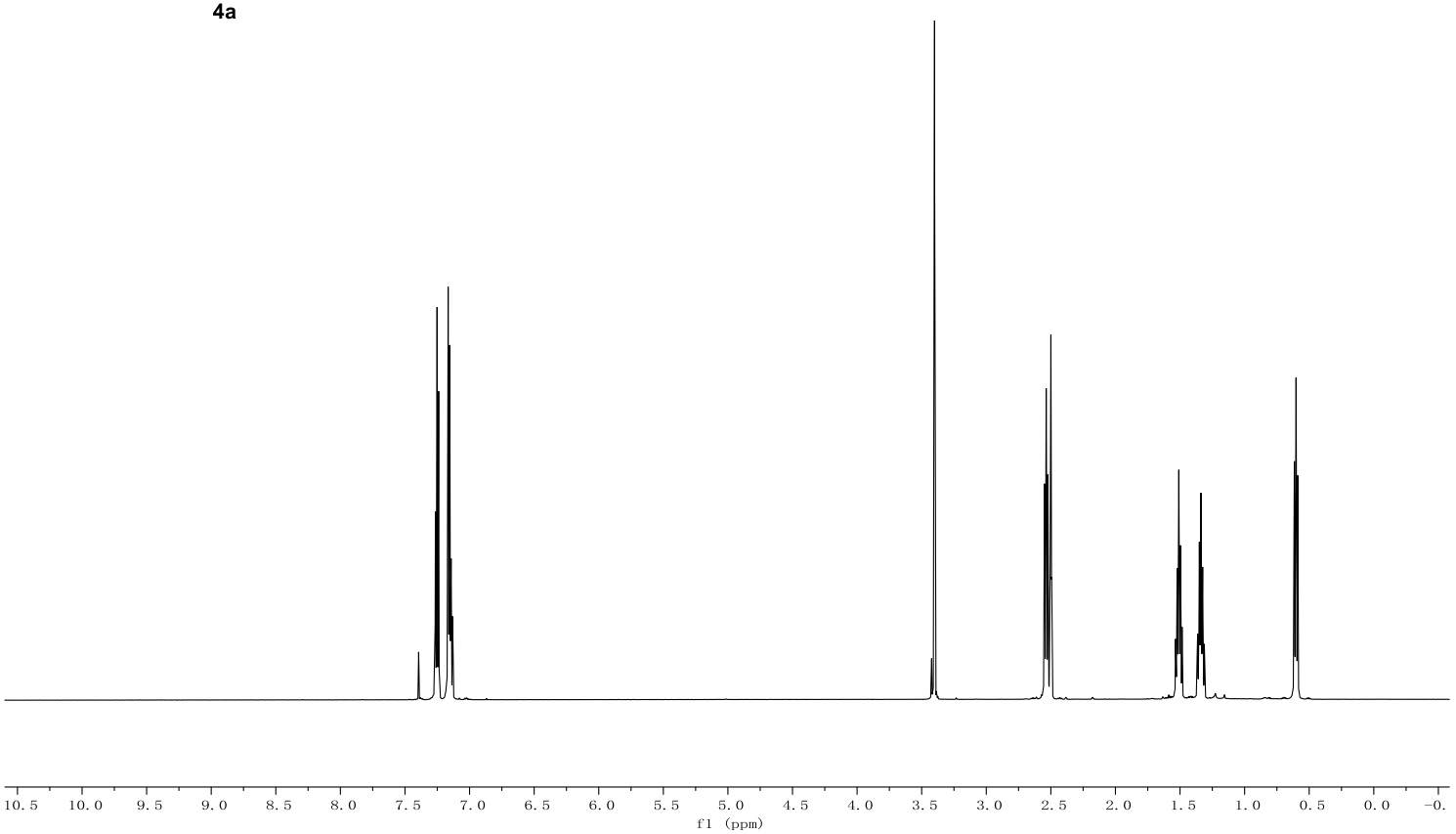
Compound 41 ^{13}C NMR



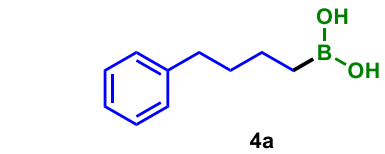
Compound 4a ^{1}H NMR



4a

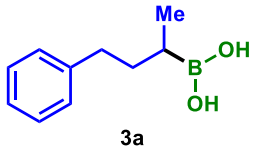


Compound 4a ^{13}C NMR

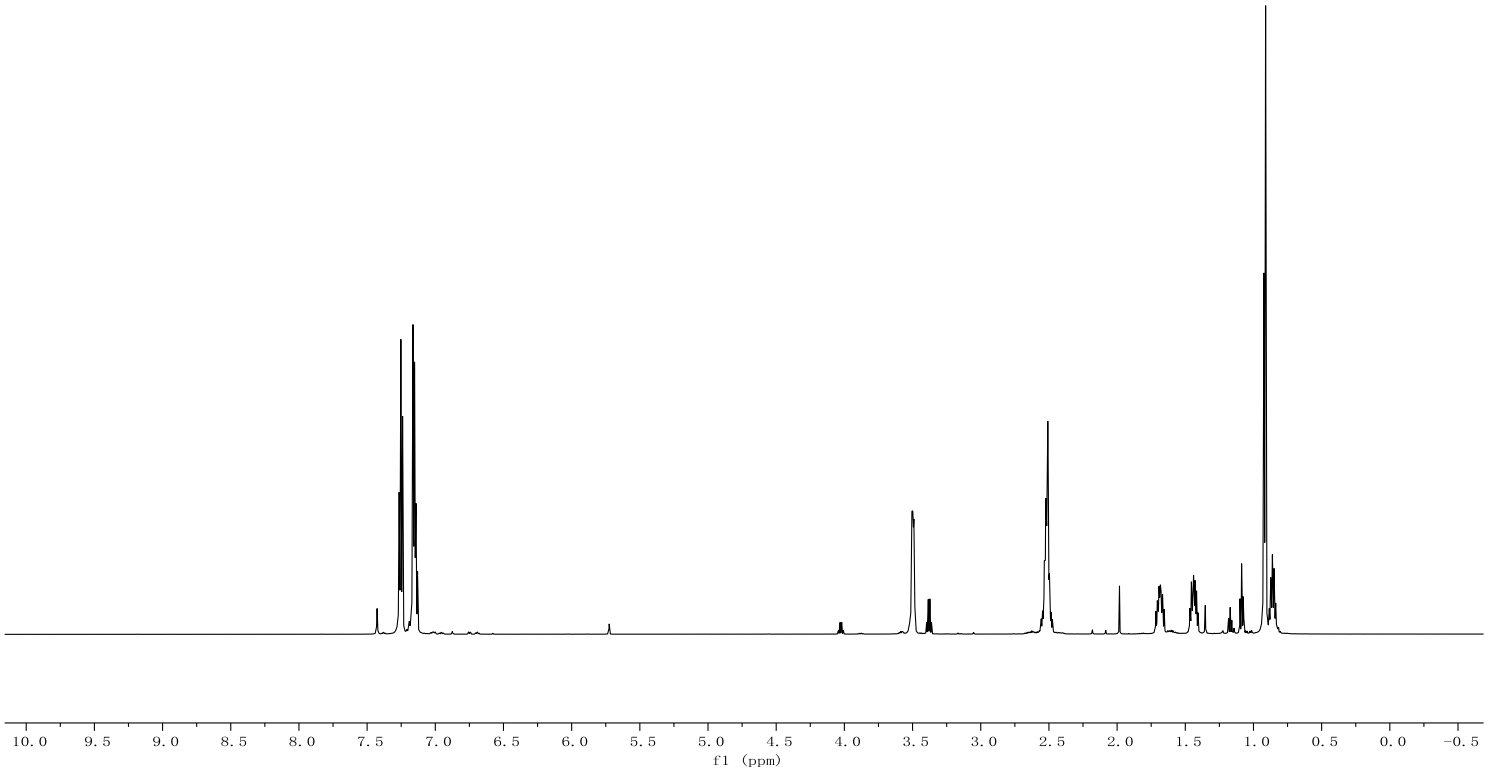


4a

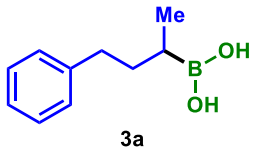
Compound 3a ^{1}H NMR



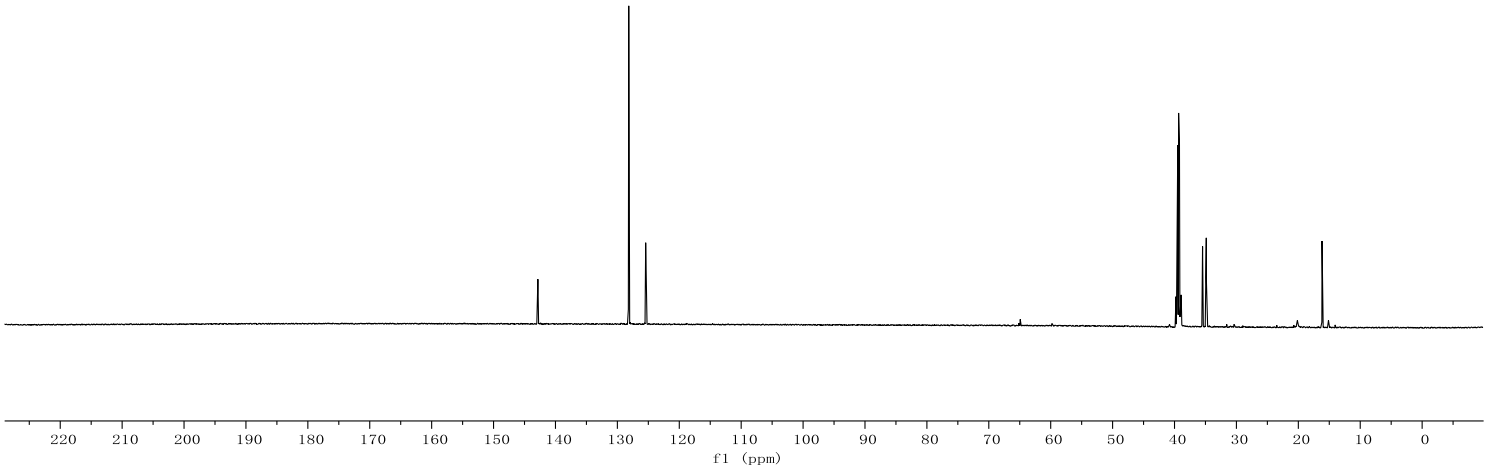
3a



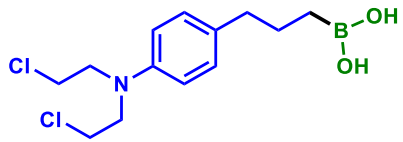
Compound 3a ^{13}C NMR



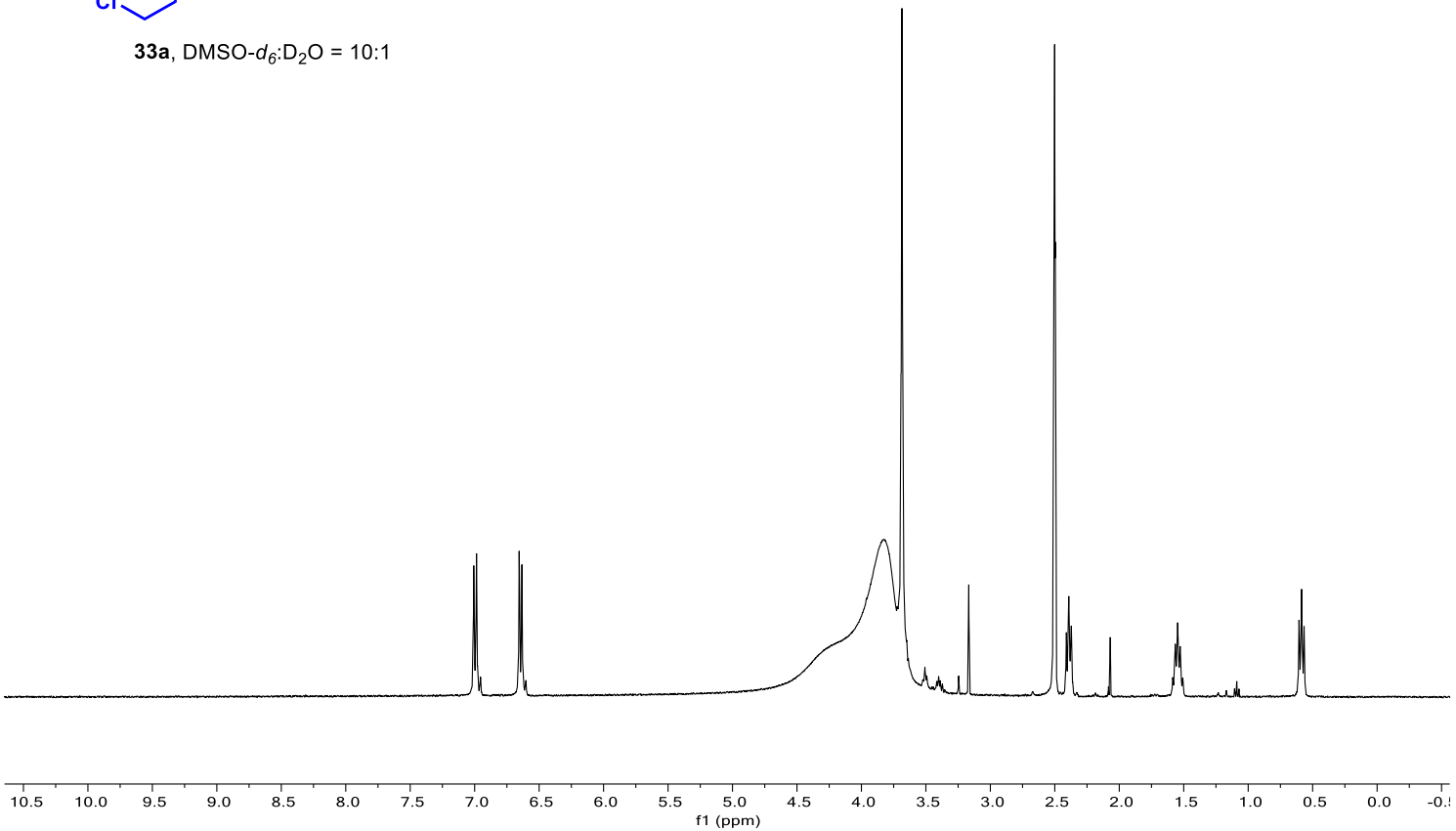
3a



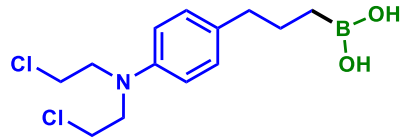
Compound 33a ^{1}H NMR



33a, DMSO-d_6:D_2O = 10:1

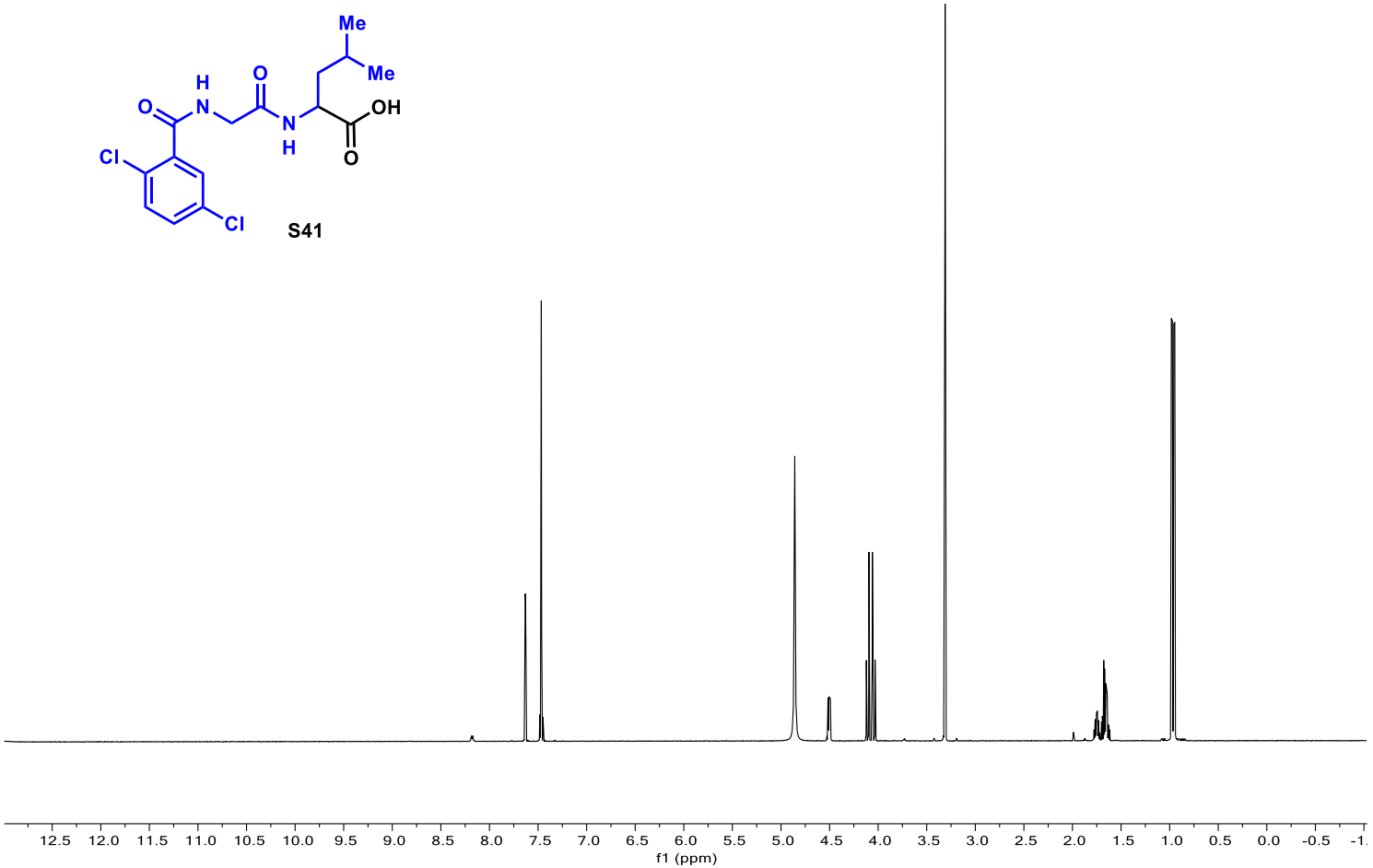


Compound 33a ^{13}C NMR

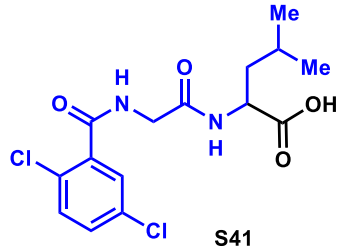


33a, DMSO-d_6:D_2O = 10:1

Compound S41 ^{1}H NMR

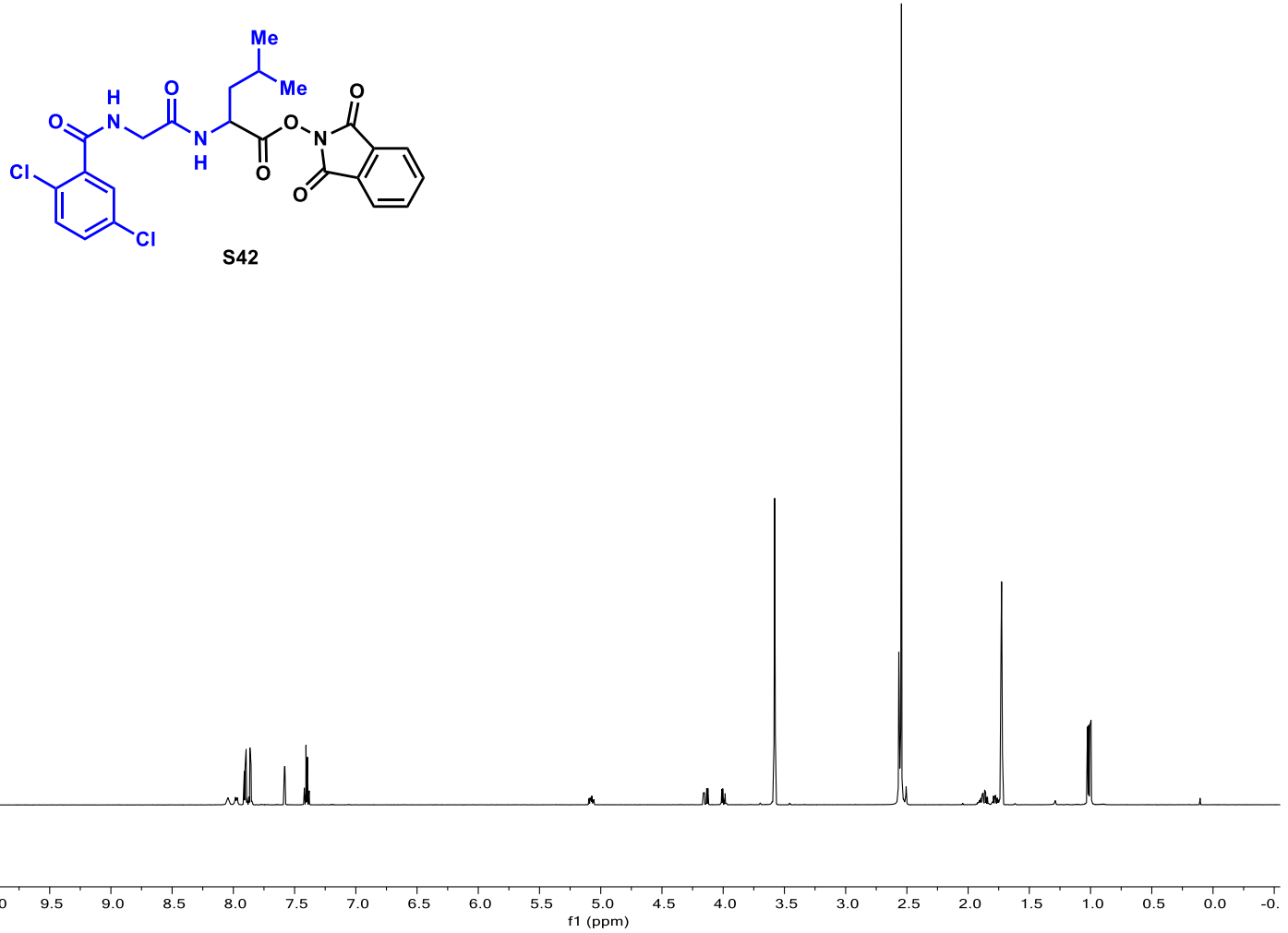


Compound S41 ^{13}C NMR

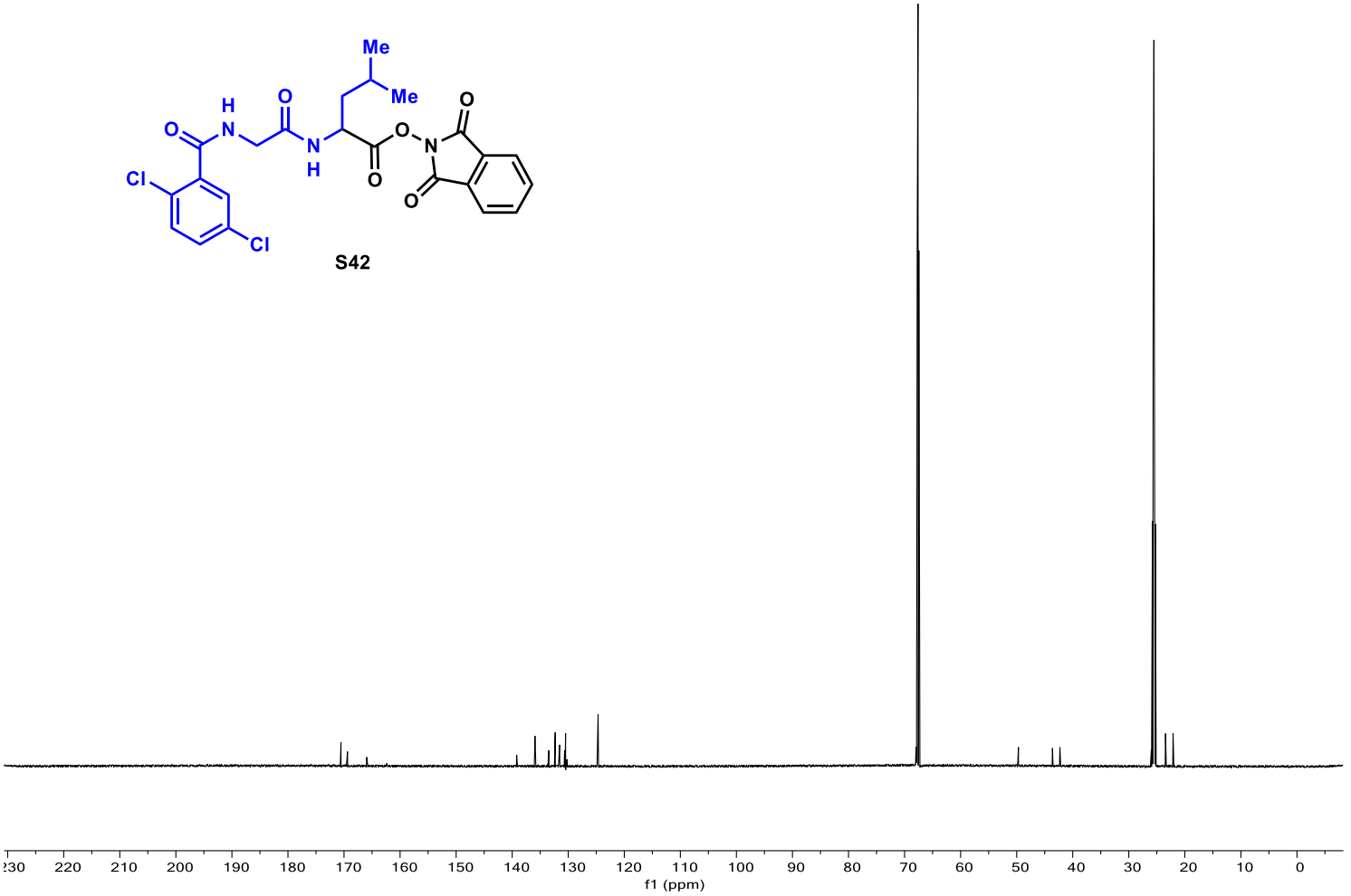


S41

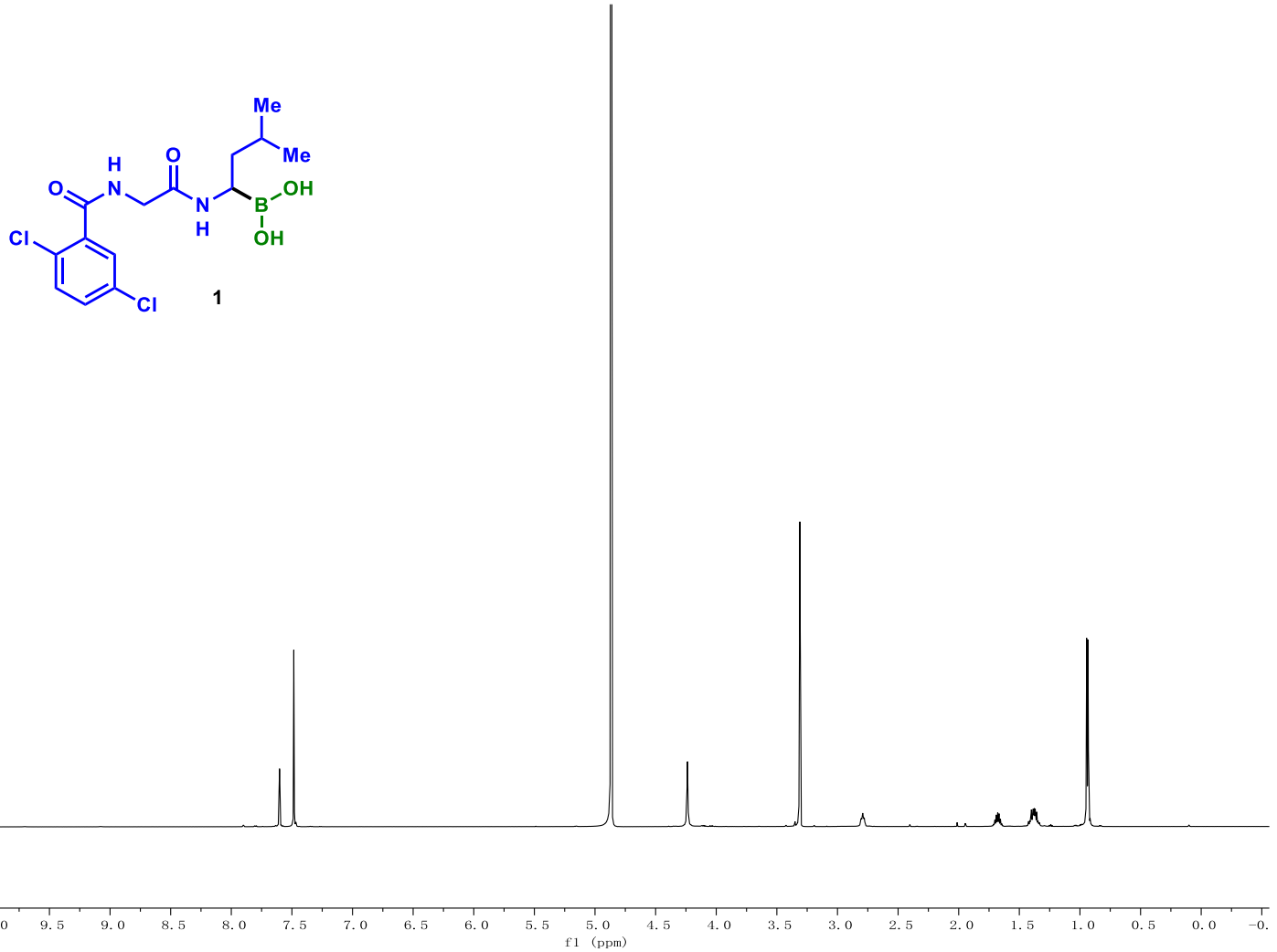
Compound S42 ^{1}H NMR



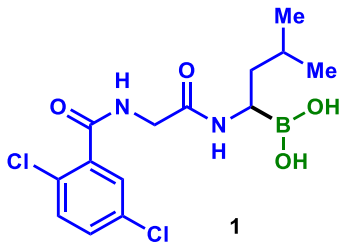
Compound S42 ^{13}C NMR



Compound 1 ^{1}H NMR

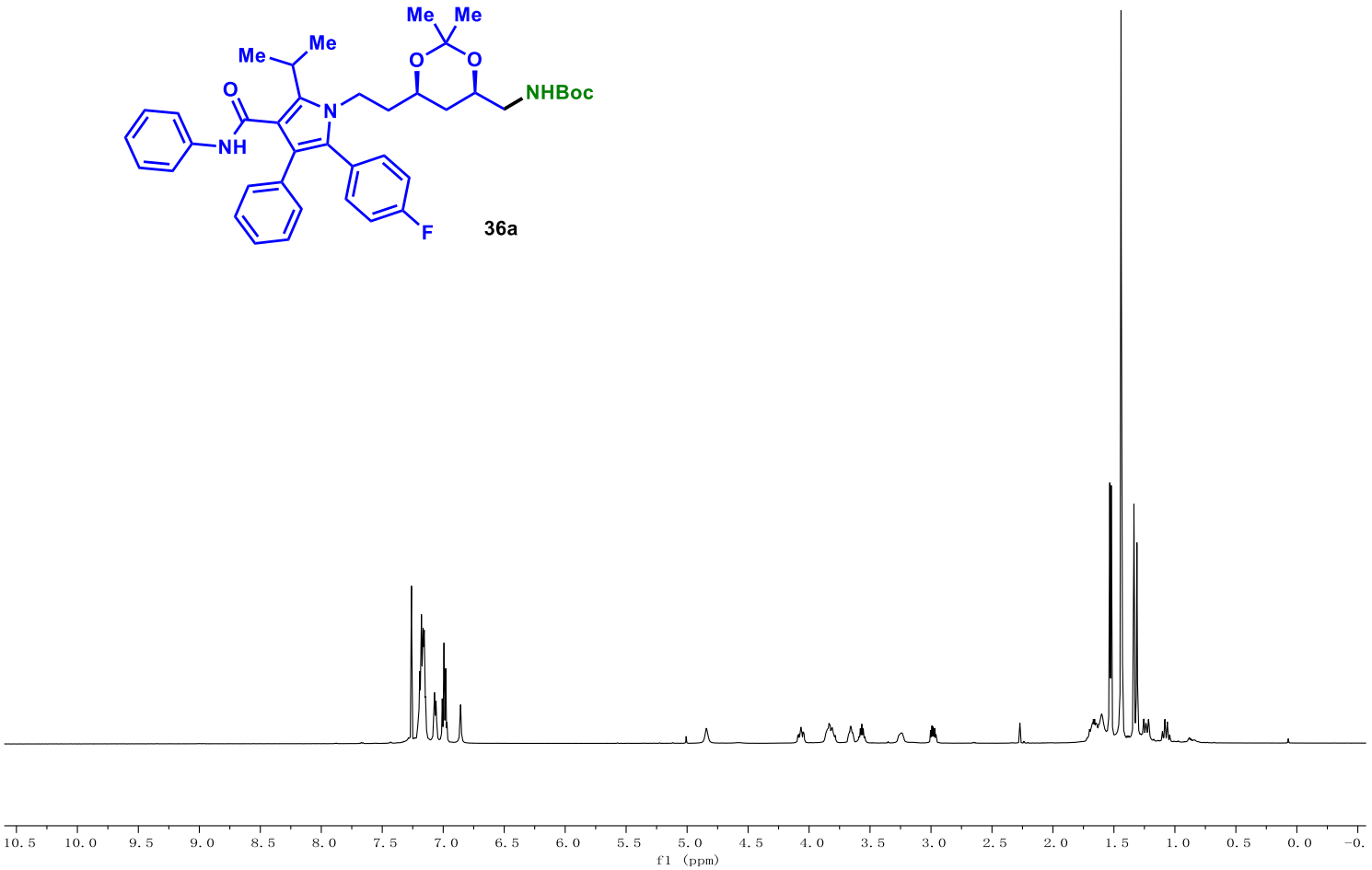


Compound 1 ^{13}C NMR

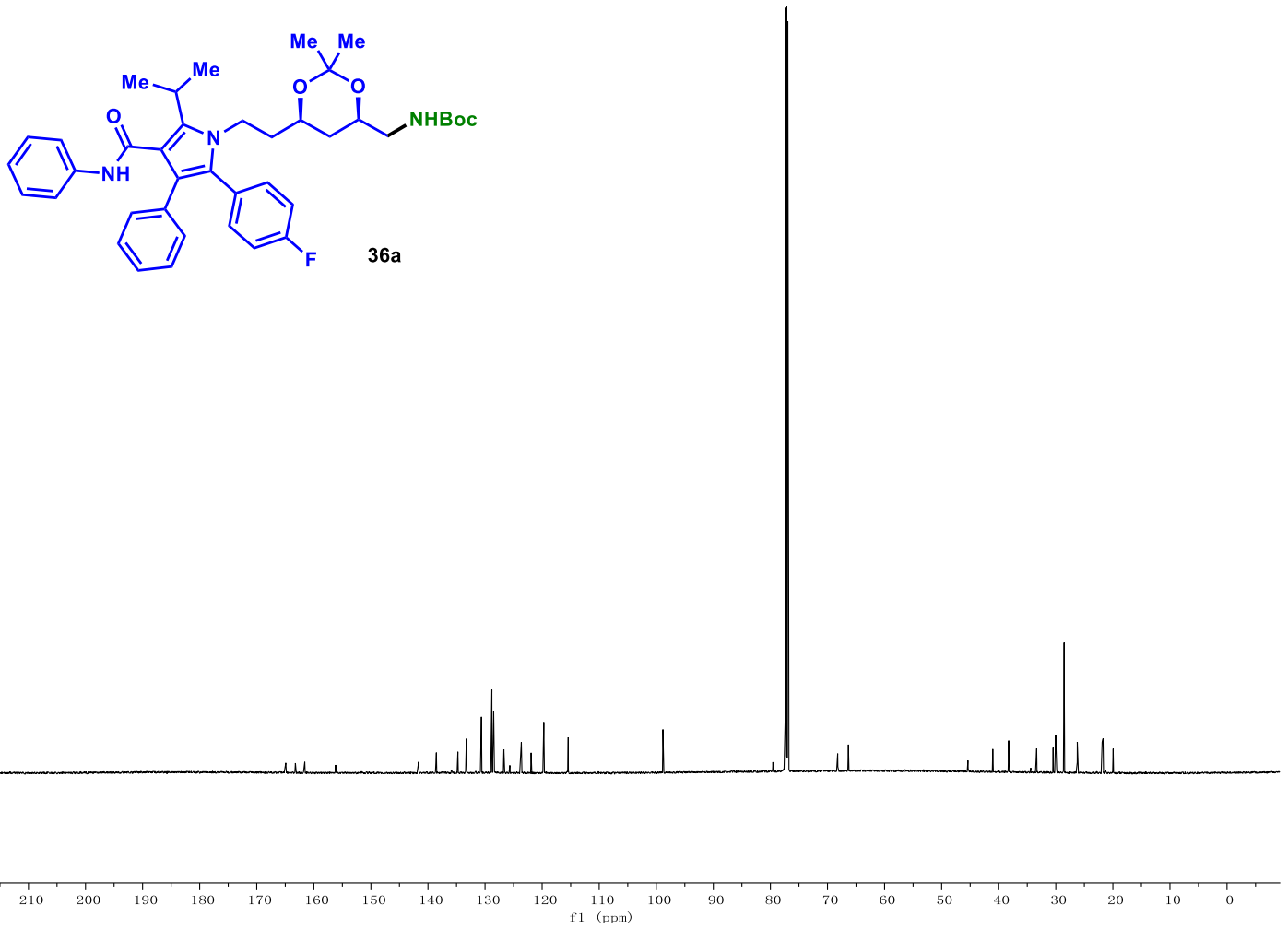


1

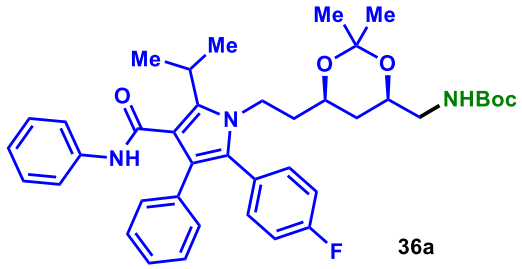
Compound 36a ^{1}H NMR



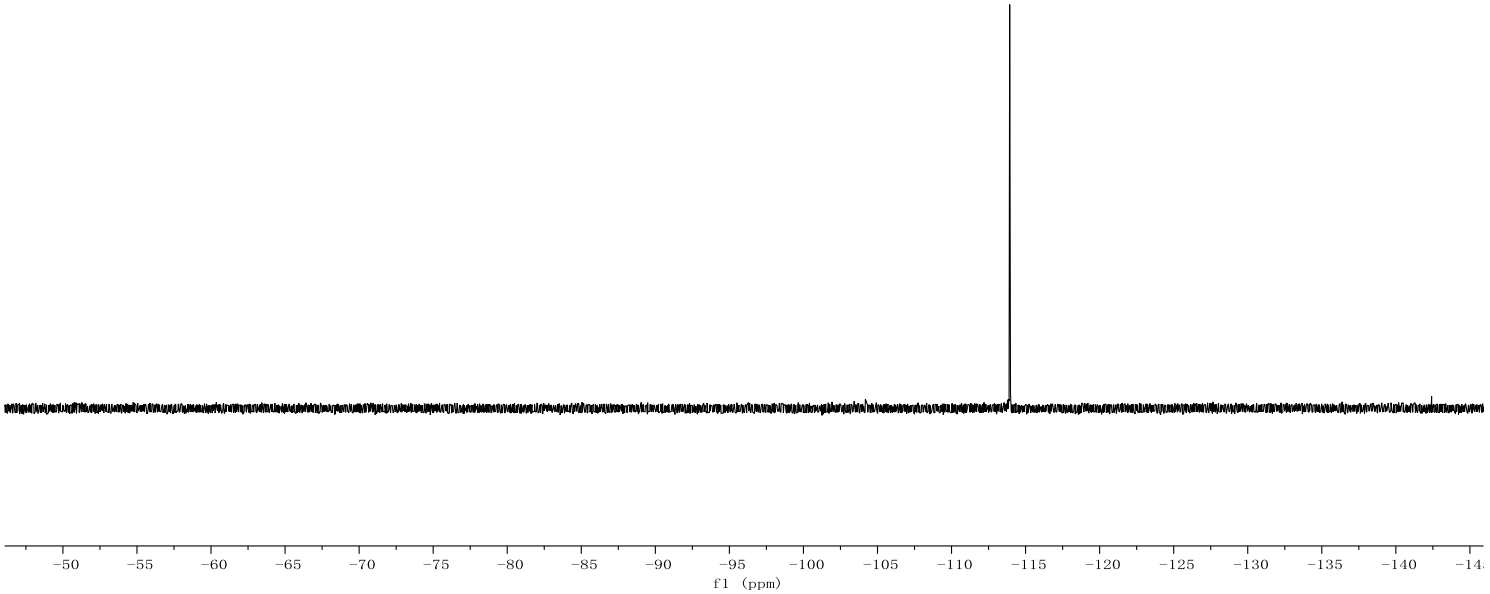
Compound 36a ^{13}C NMR



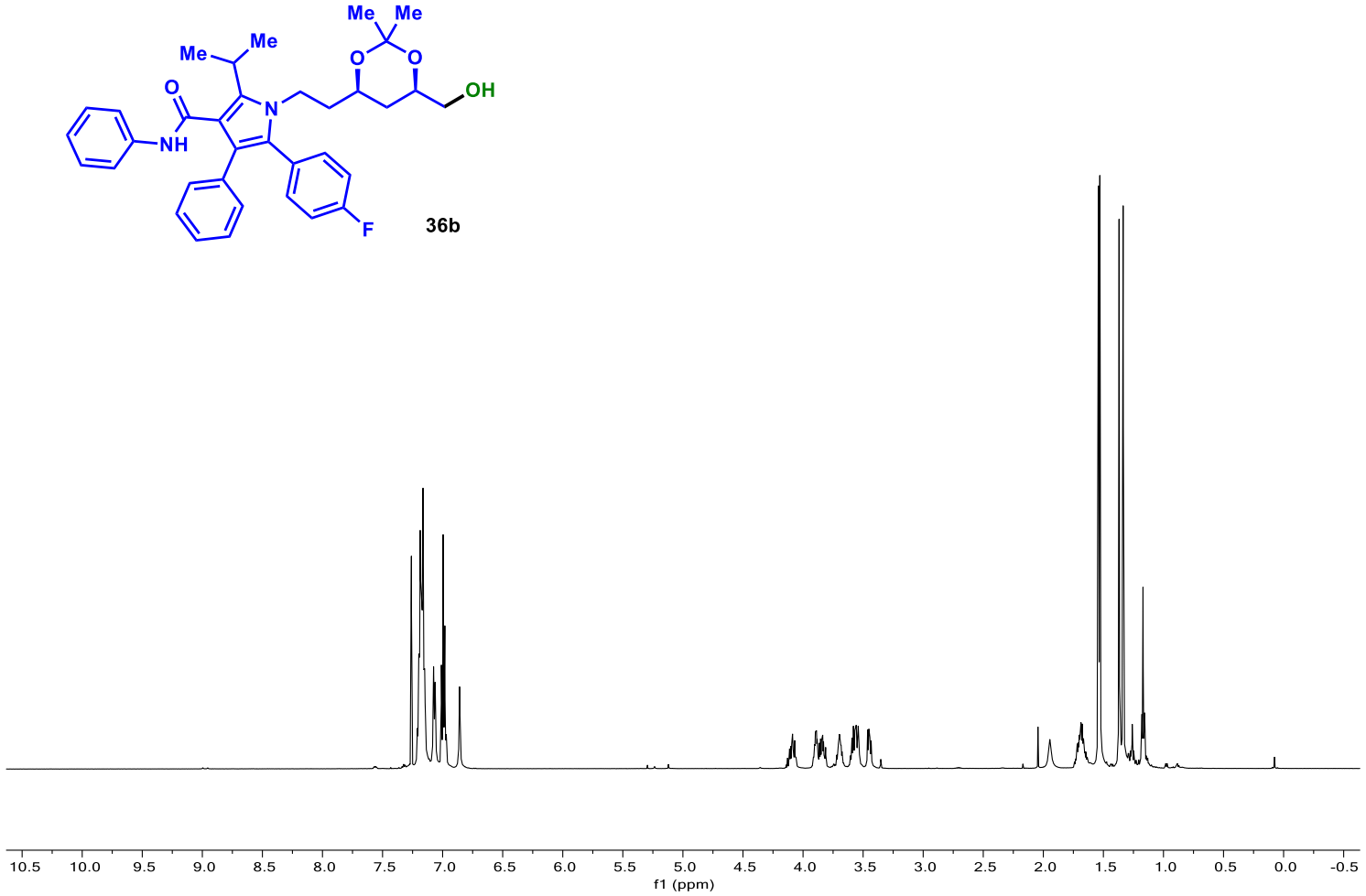
Compound 36a ^{19}F NMR



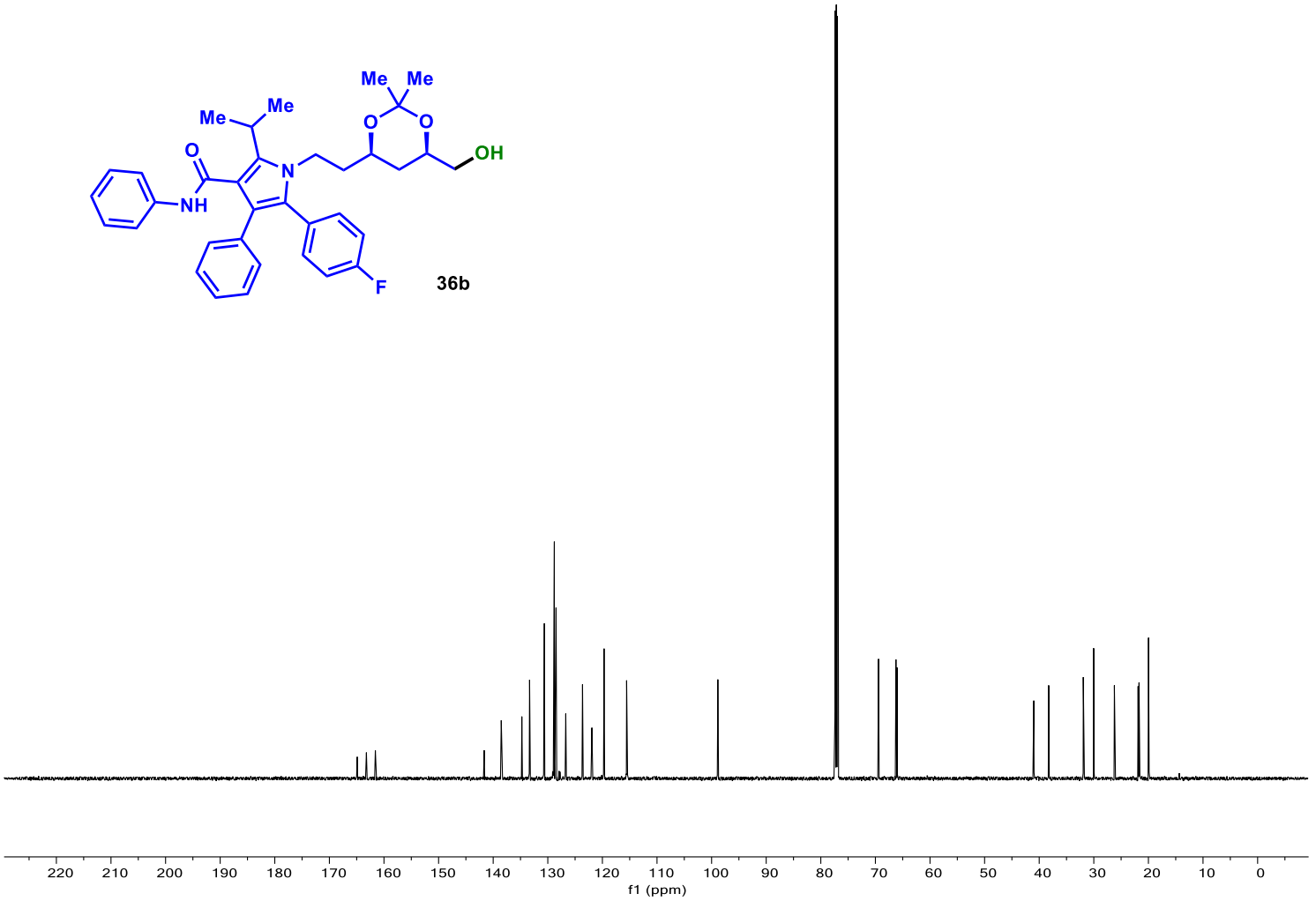
36a



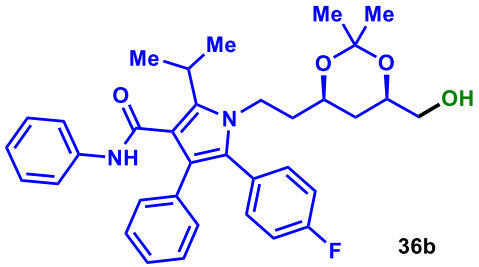
Compound 36b ^{1}H NMR



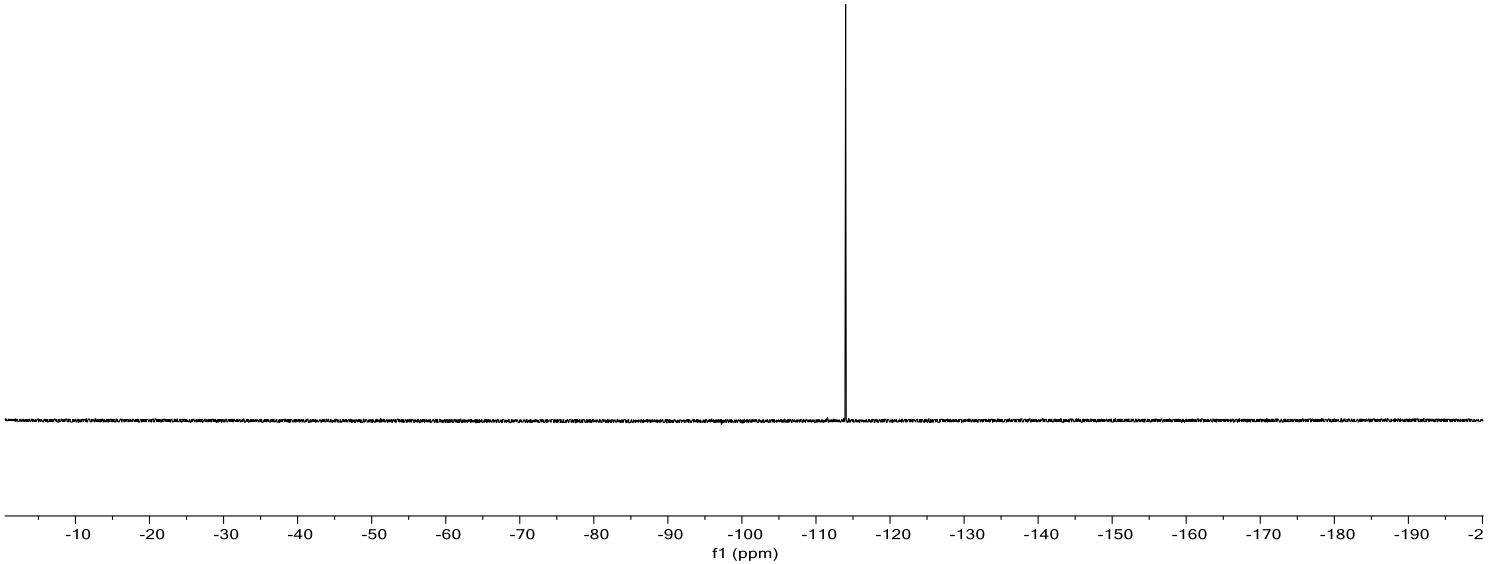
Compound 36b ^{13}C NMR



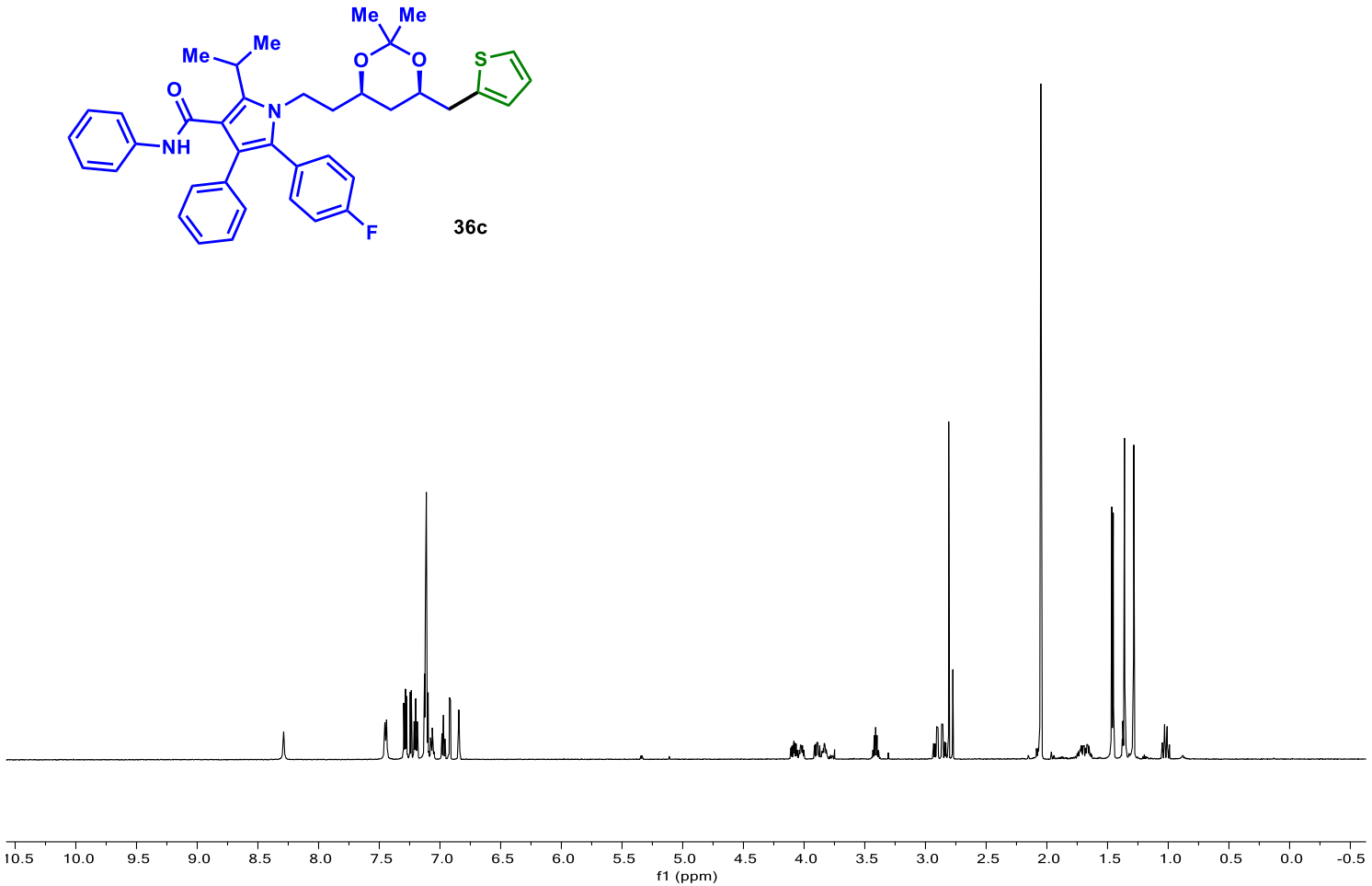
Compound 36b ^{19}F NMR



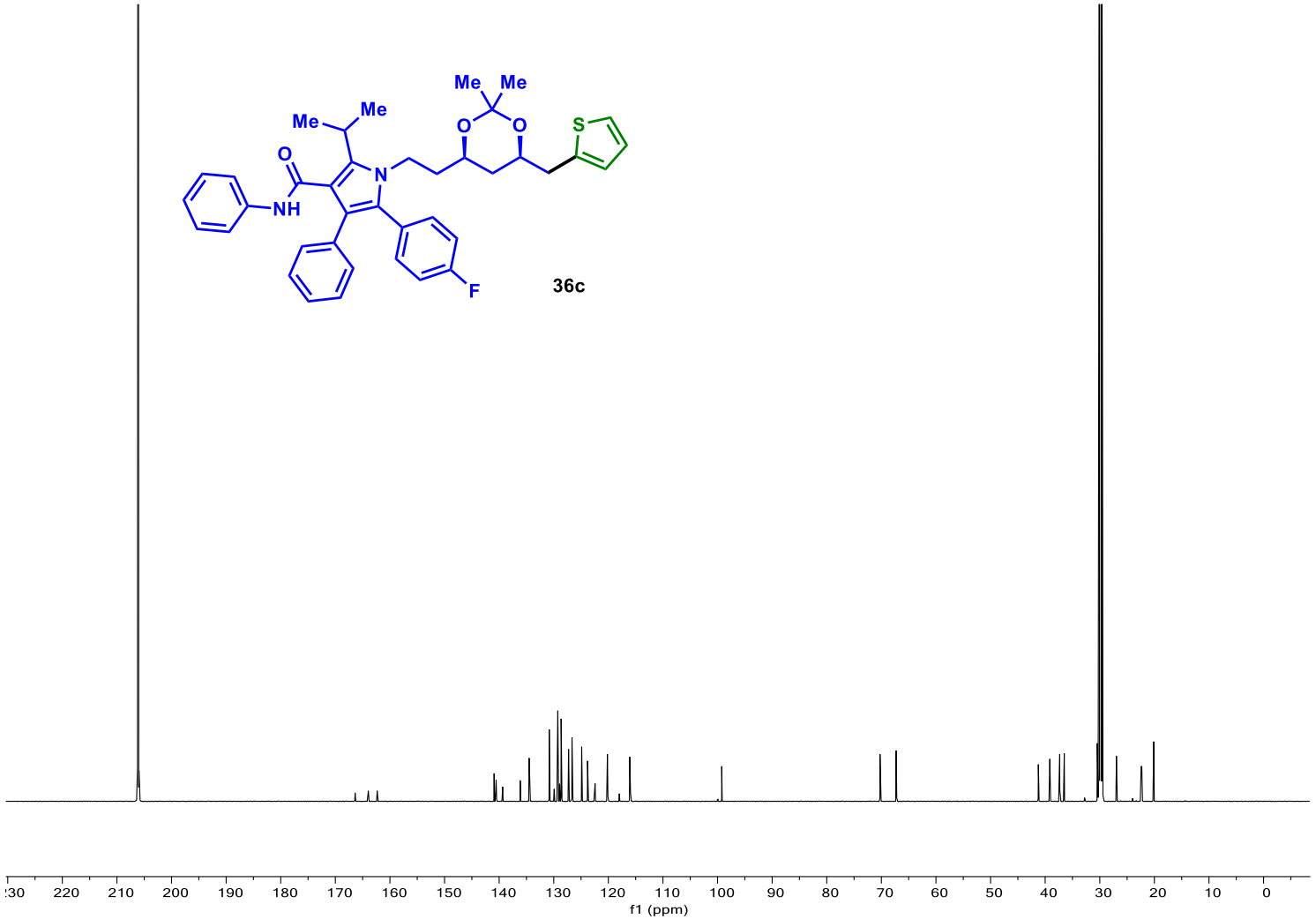
36b



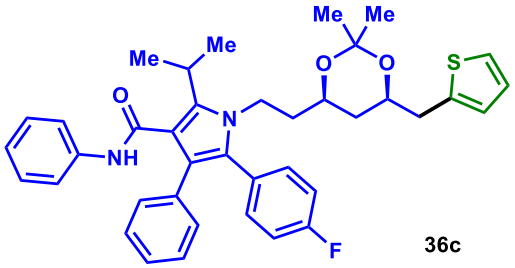
Compound 36c ^{1}H NMR



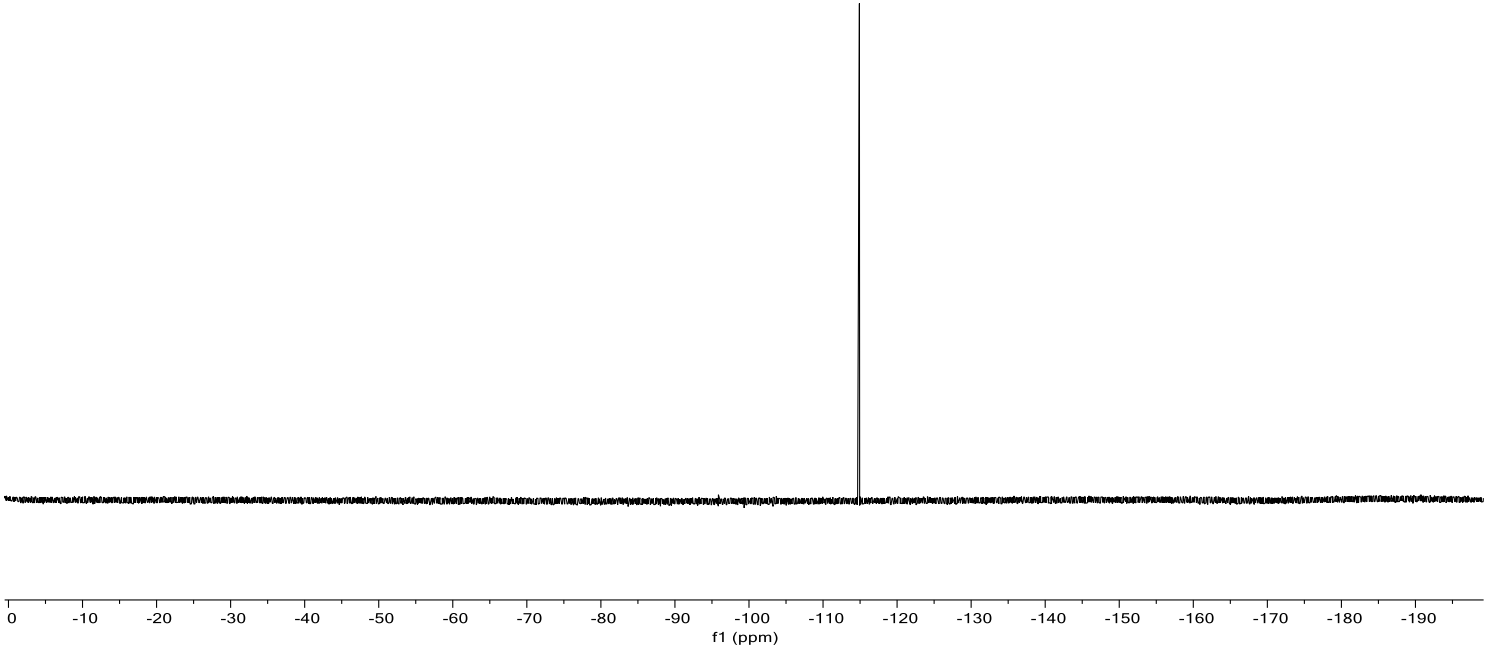
Compound 36c ^{13}C NMR



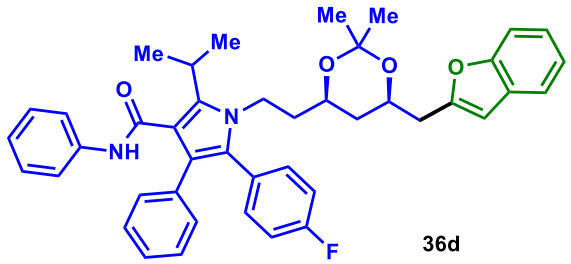
Compound 36c ^{19}F NMR



36c

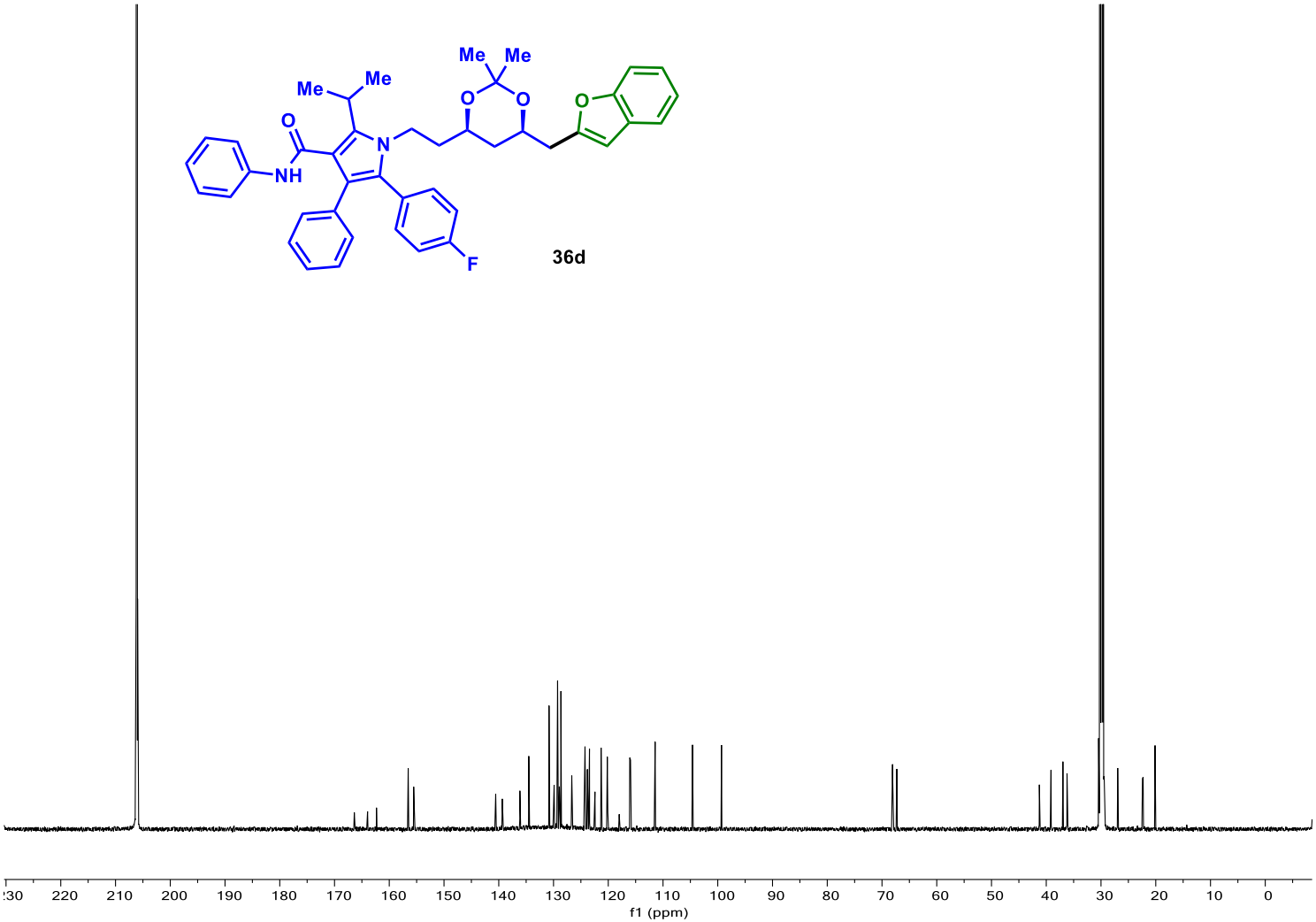


Compound 36d ^{1}H NMR

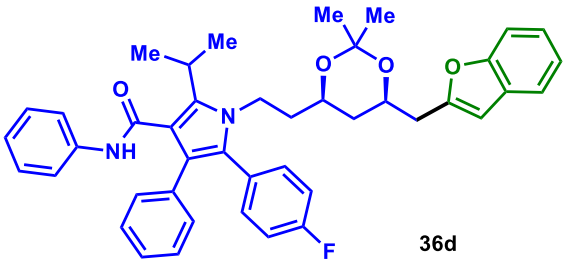


36d

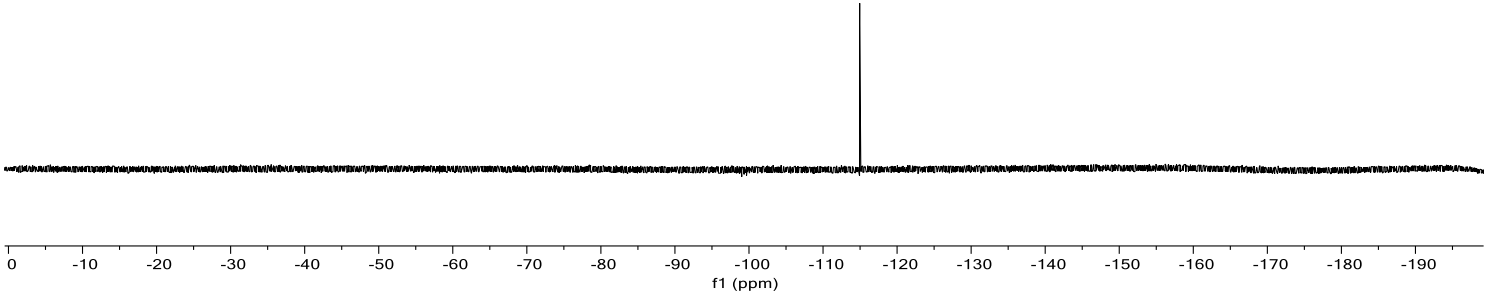
Compound 36d ^{13}C NMR



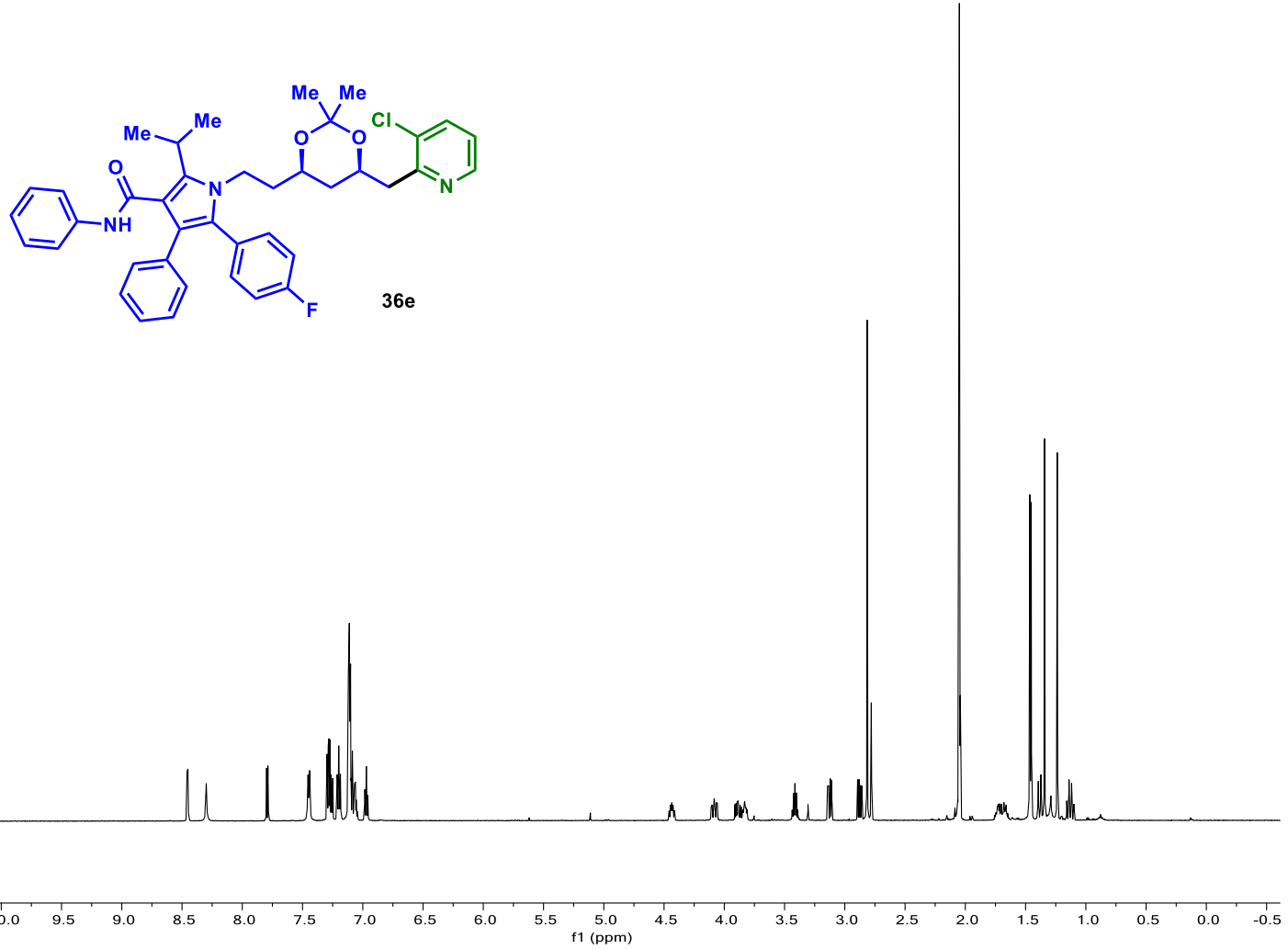
Compound 36d ^{19}F NMR



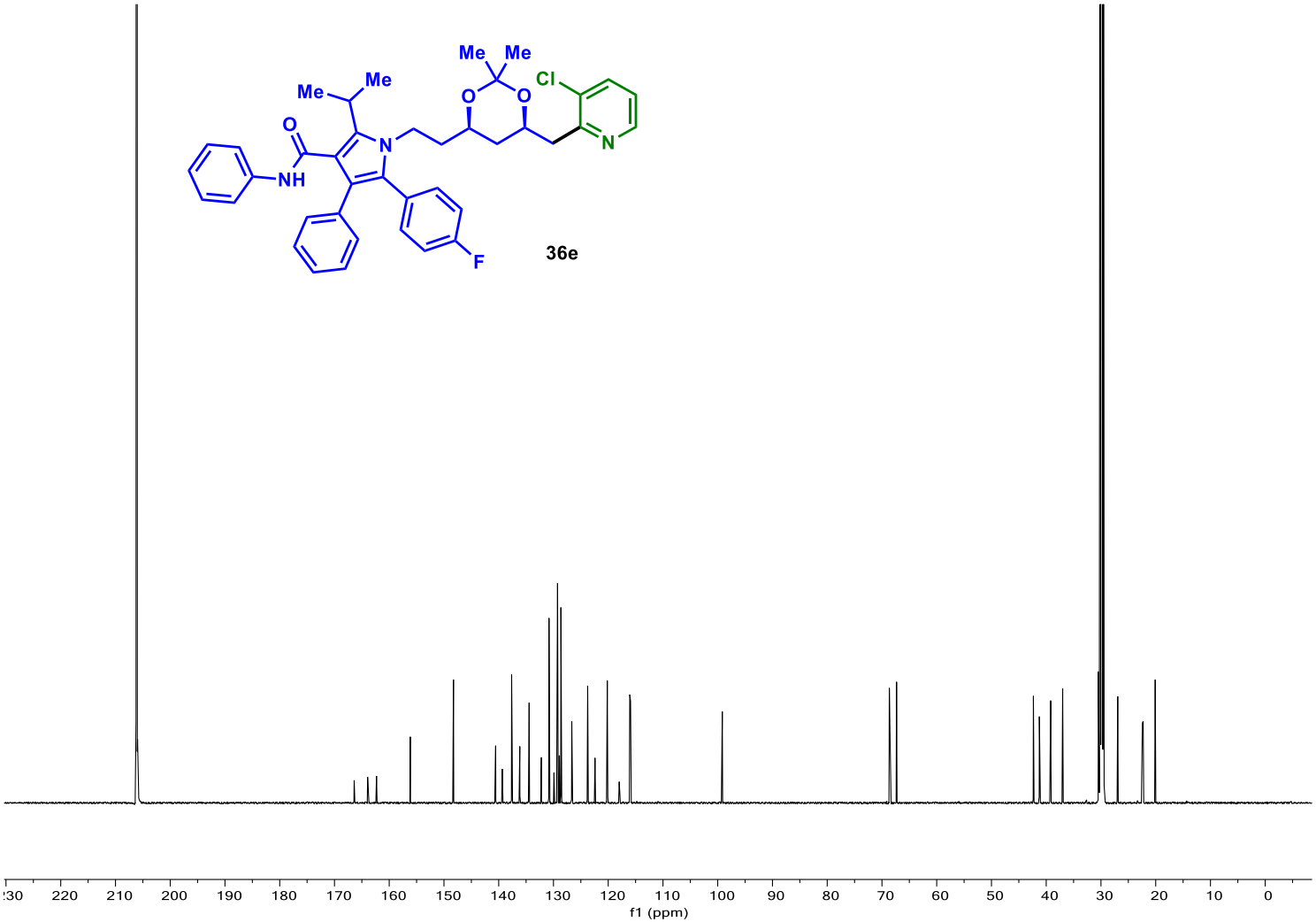
36d



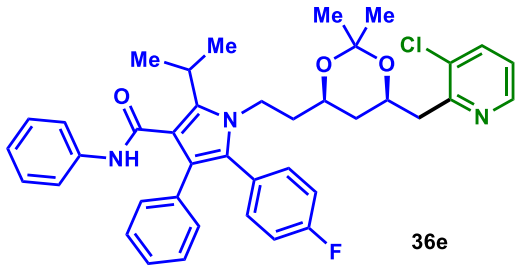
Compound 36e ^{1}H NMR



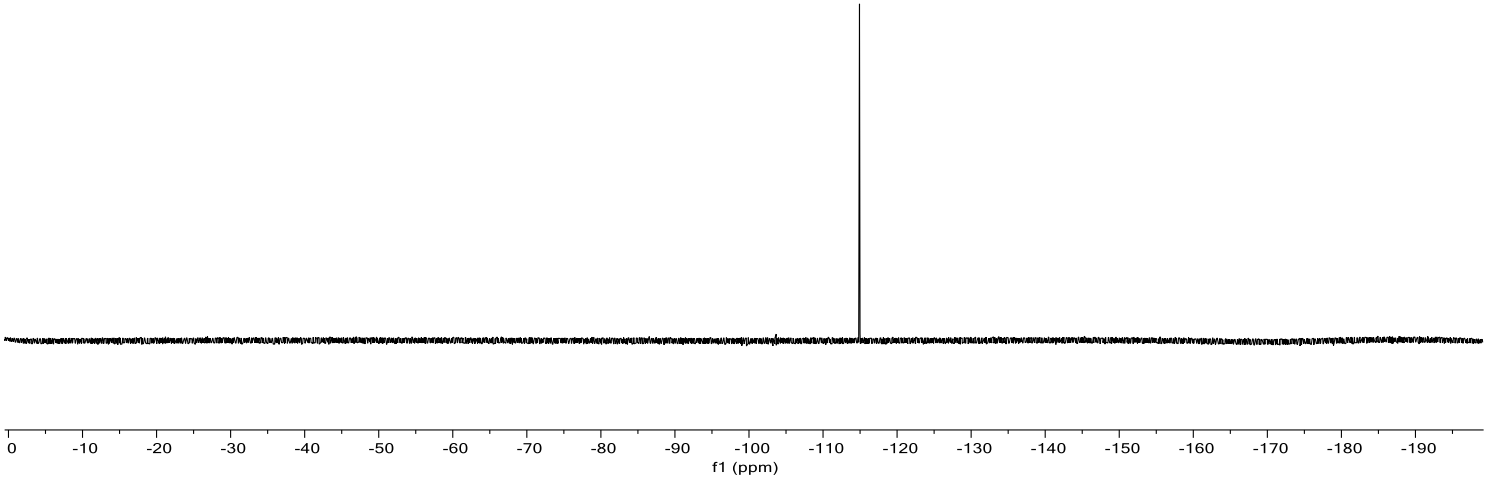
Compound 36e ^{13}C NMR



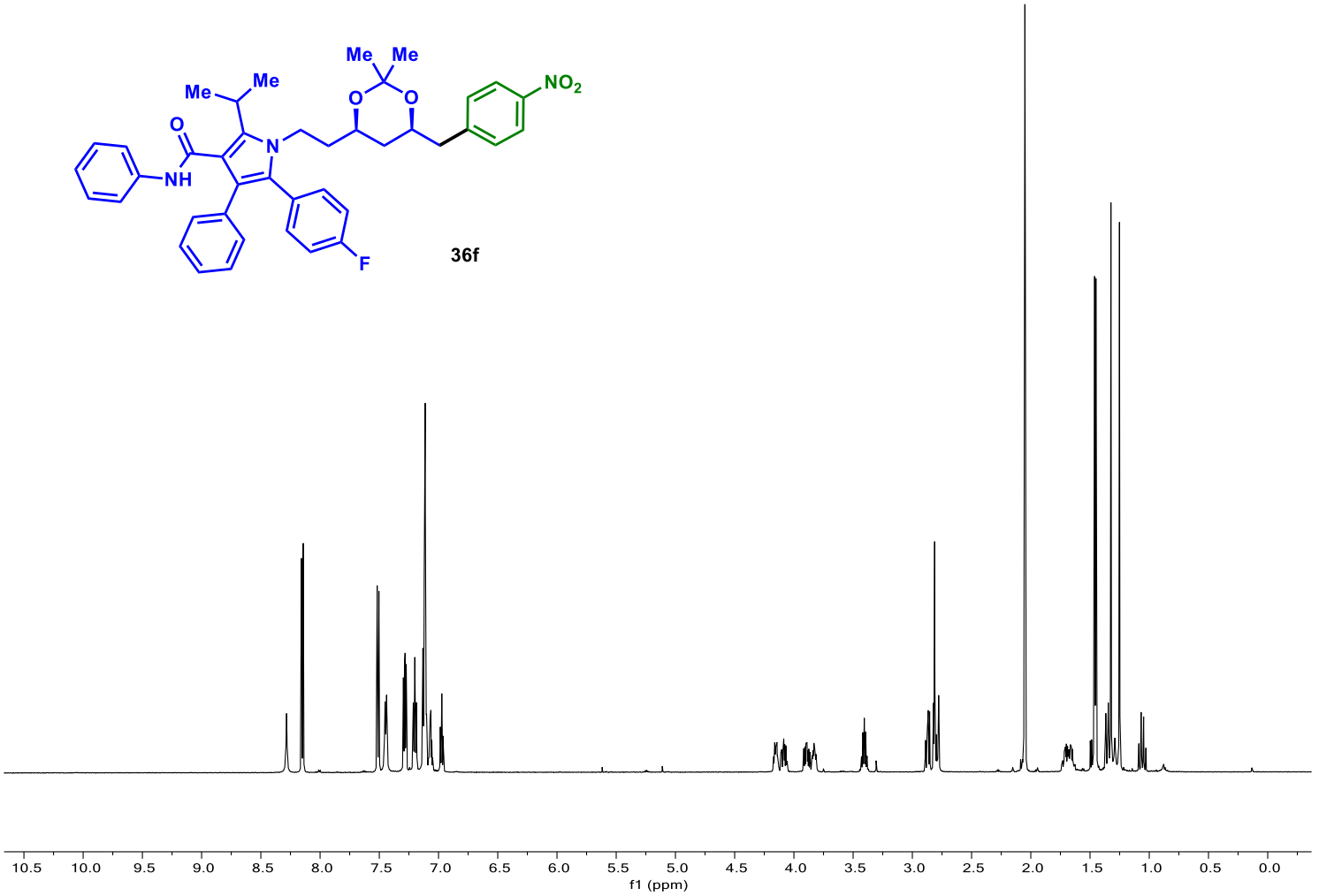
Compound 36e ^{19}F NMR



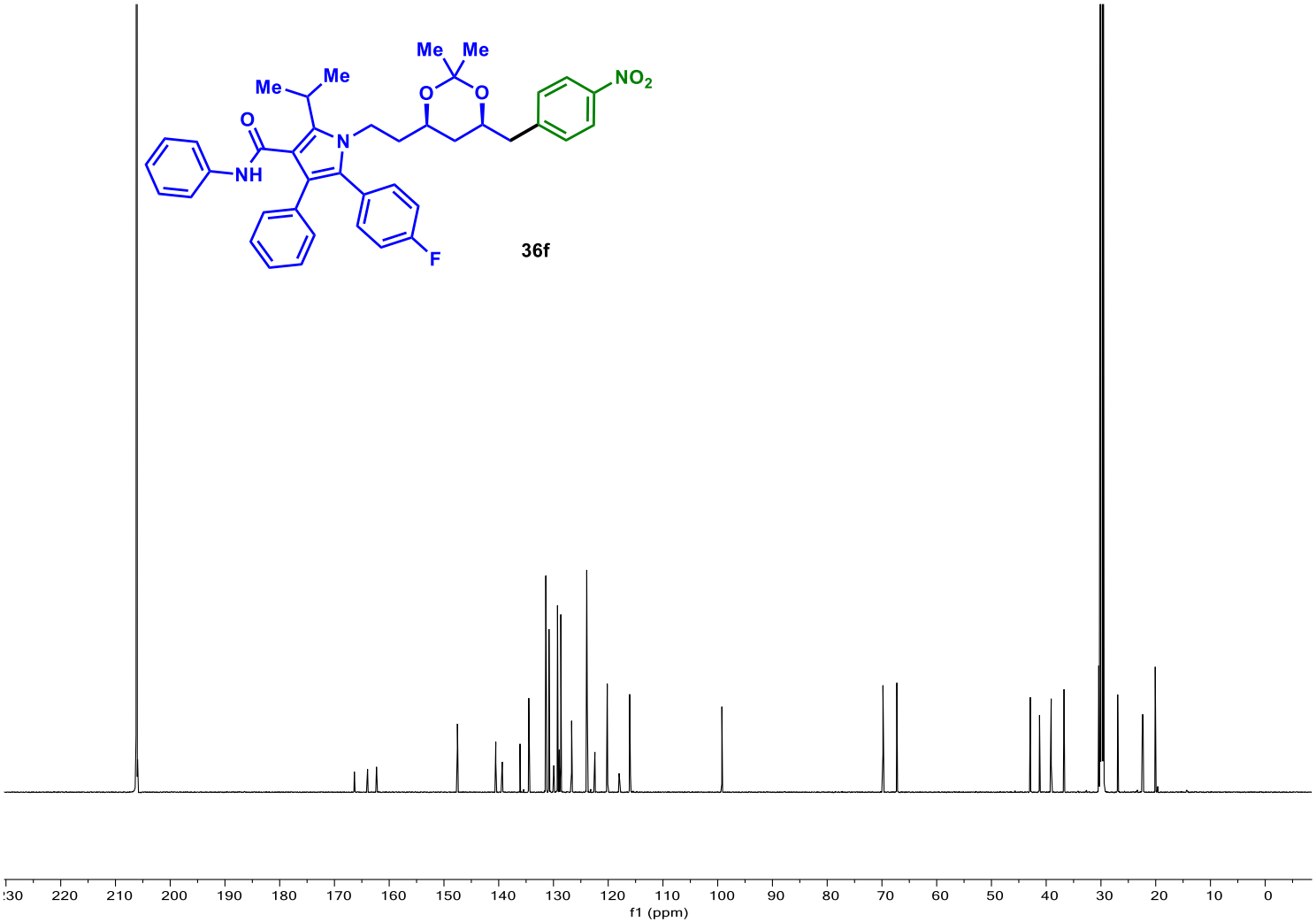
36e



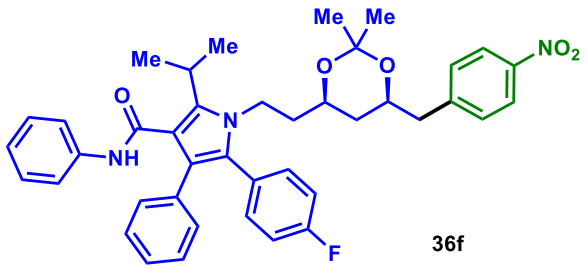
Compound 36f ^{1}H NMR



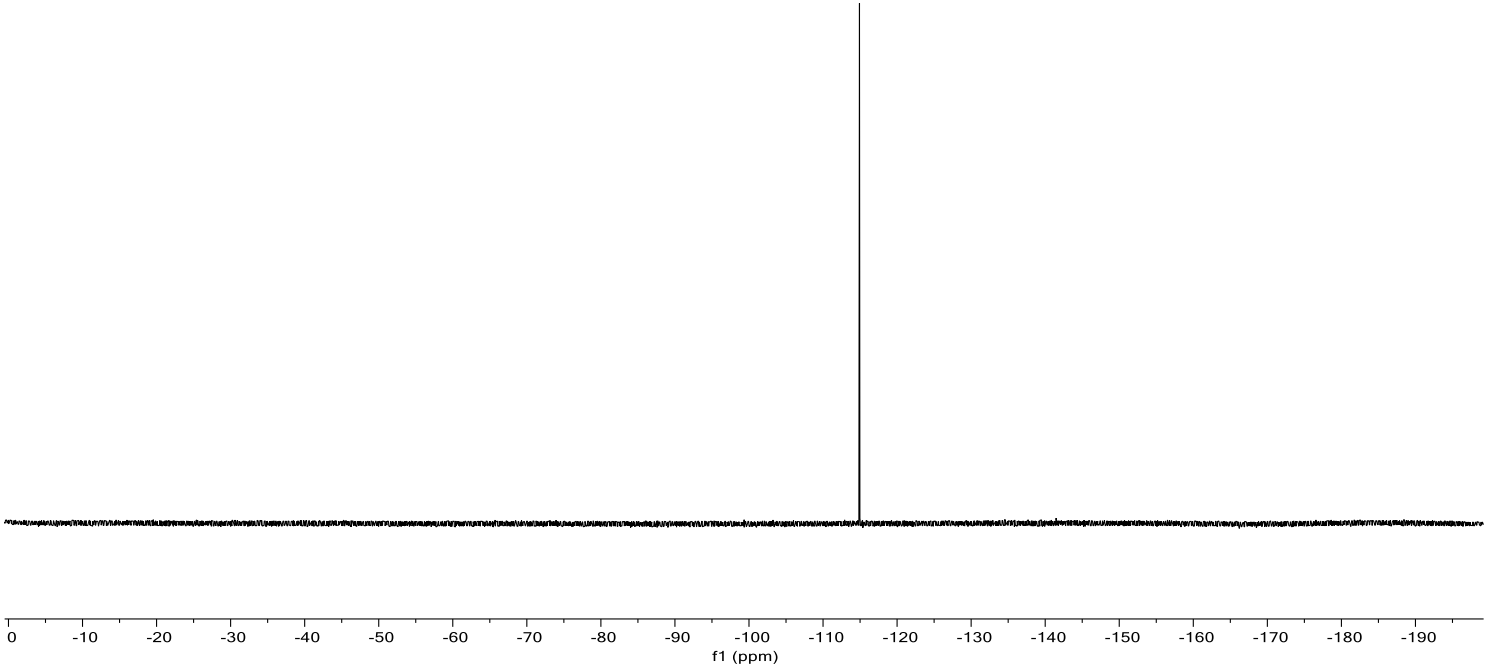
Compound 36f ^{13}C NMR



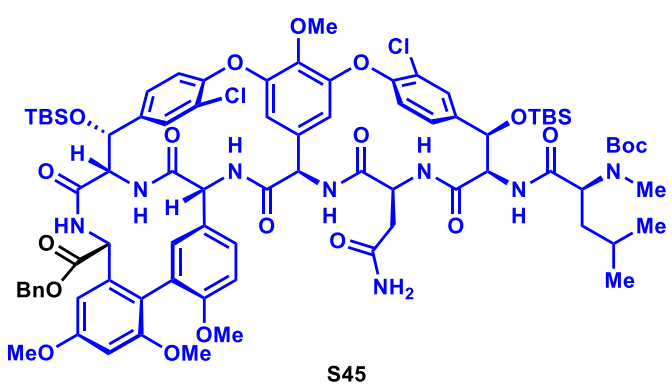
Compound 36f ^{19}F NMR



36f

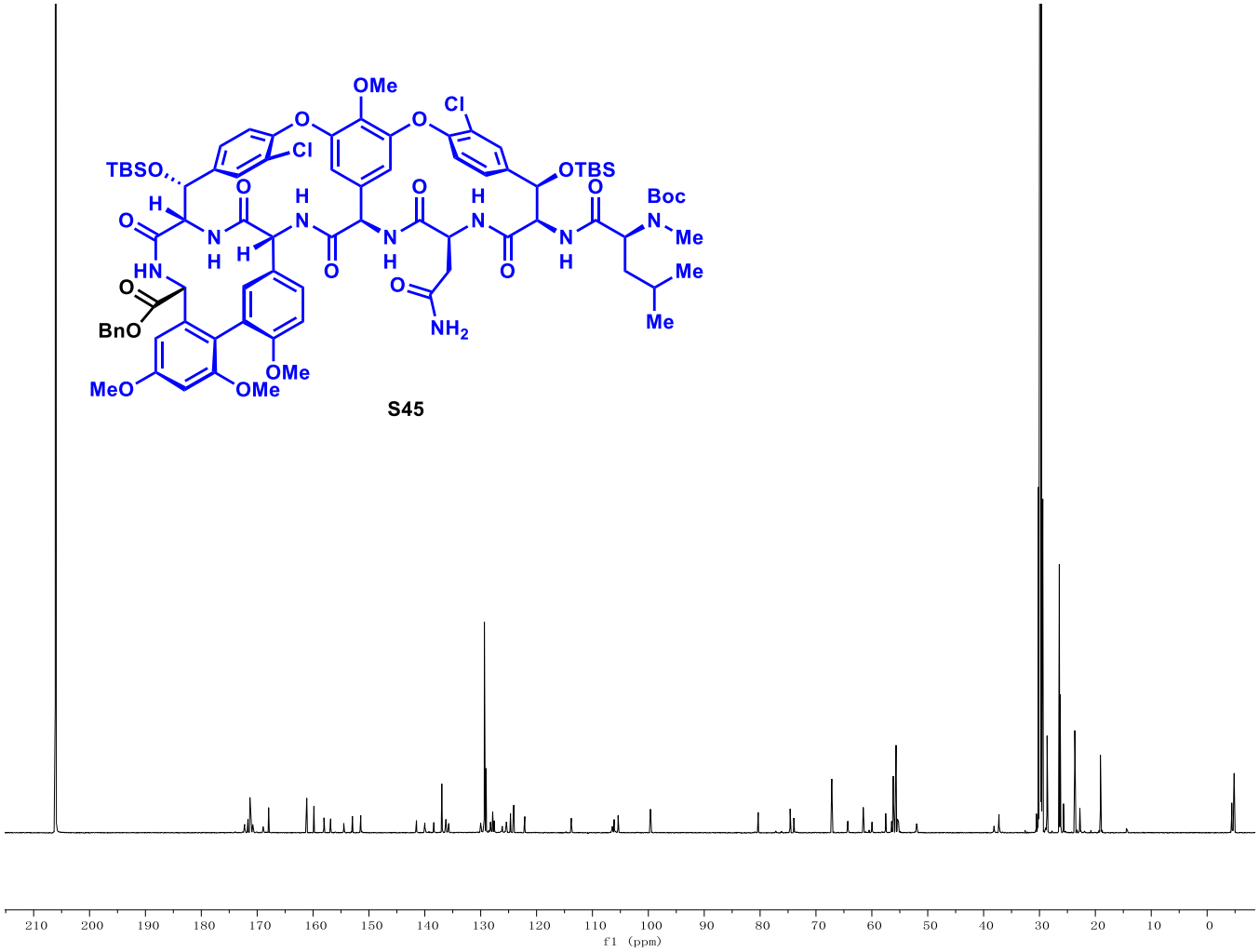


Compound S45 ^{1}H NMR

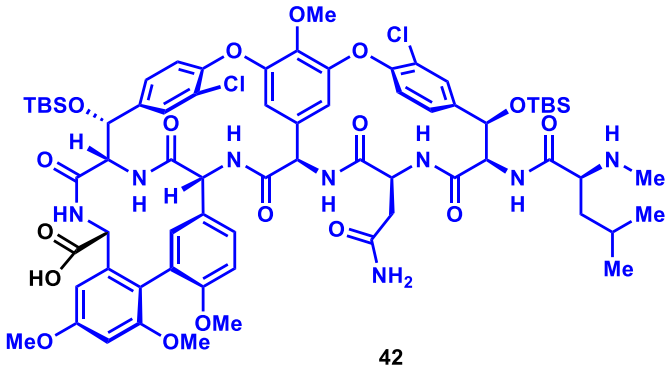


S45

Compound S45 ^{13}C NMR

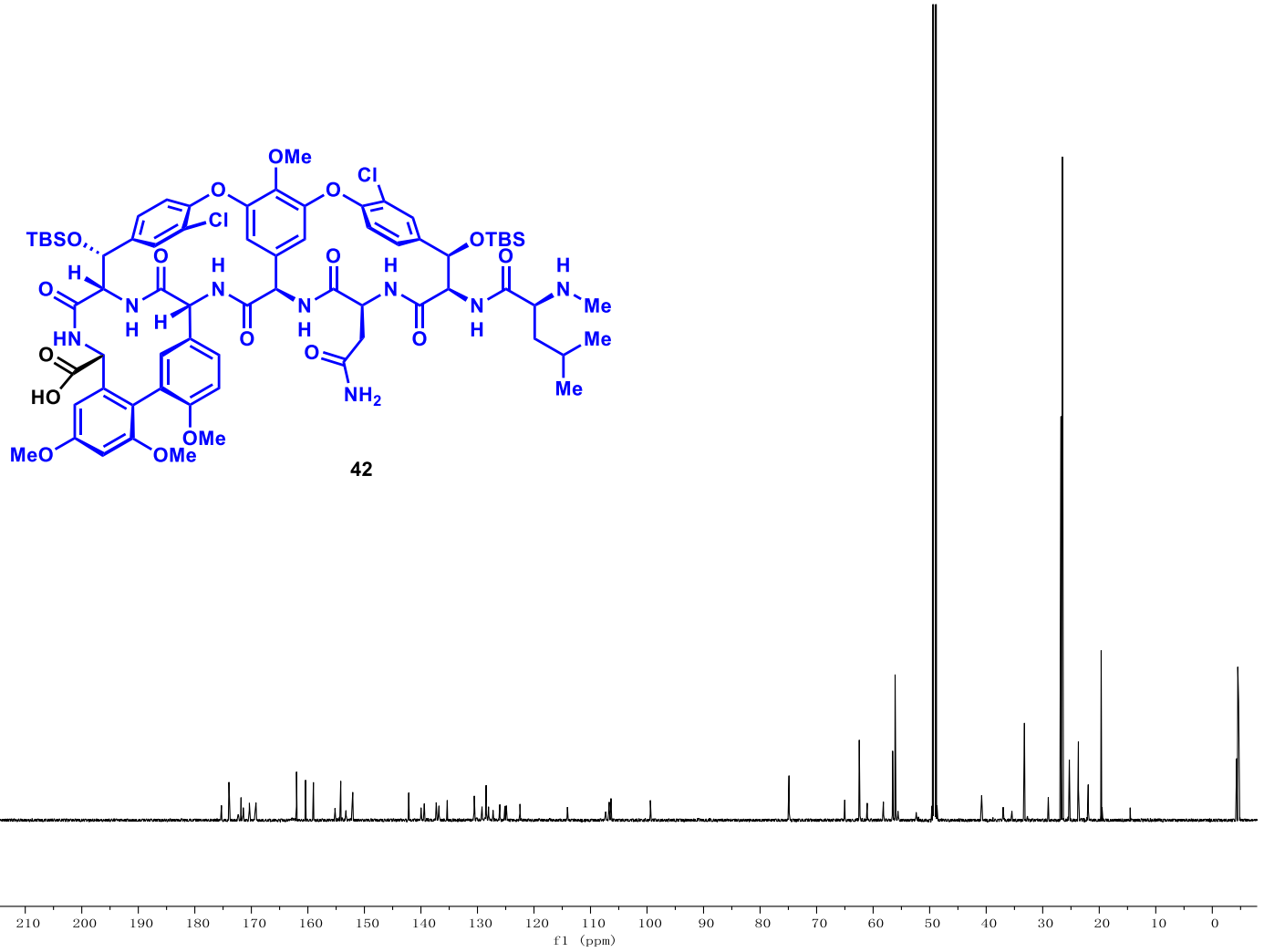


Compound 42 (TFA salt) ^{1}H NMR

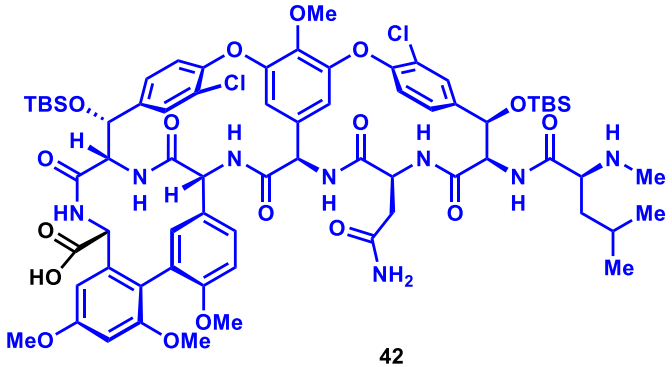


42

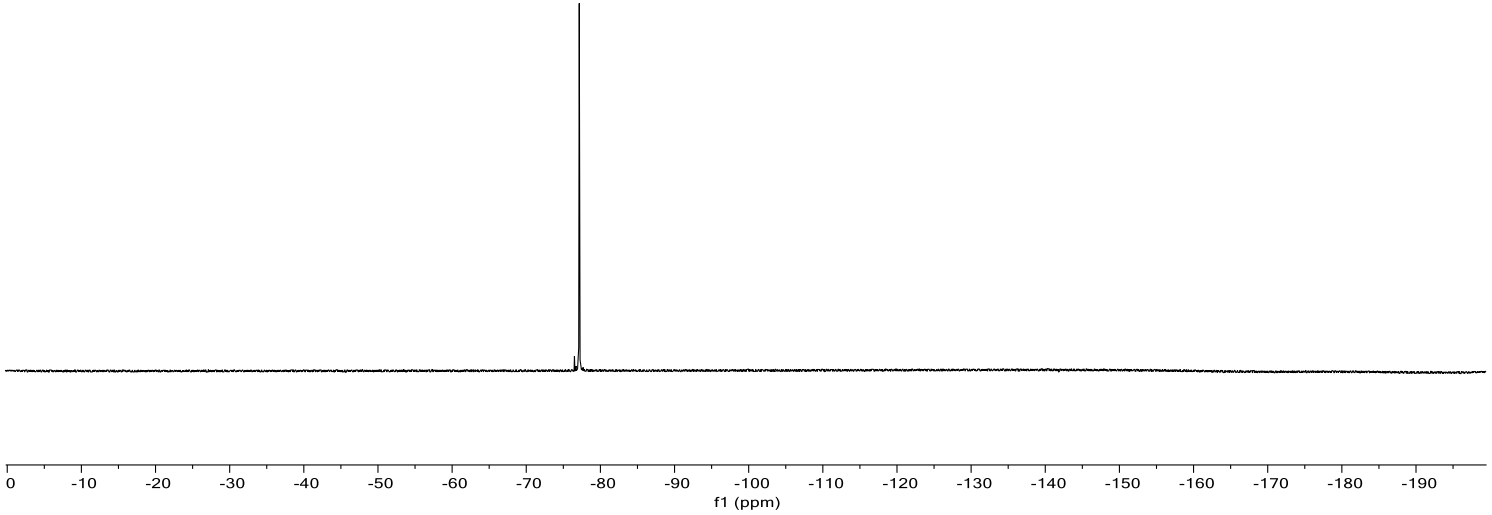
Compound 42 (TFA salt) ^{13}C NMR



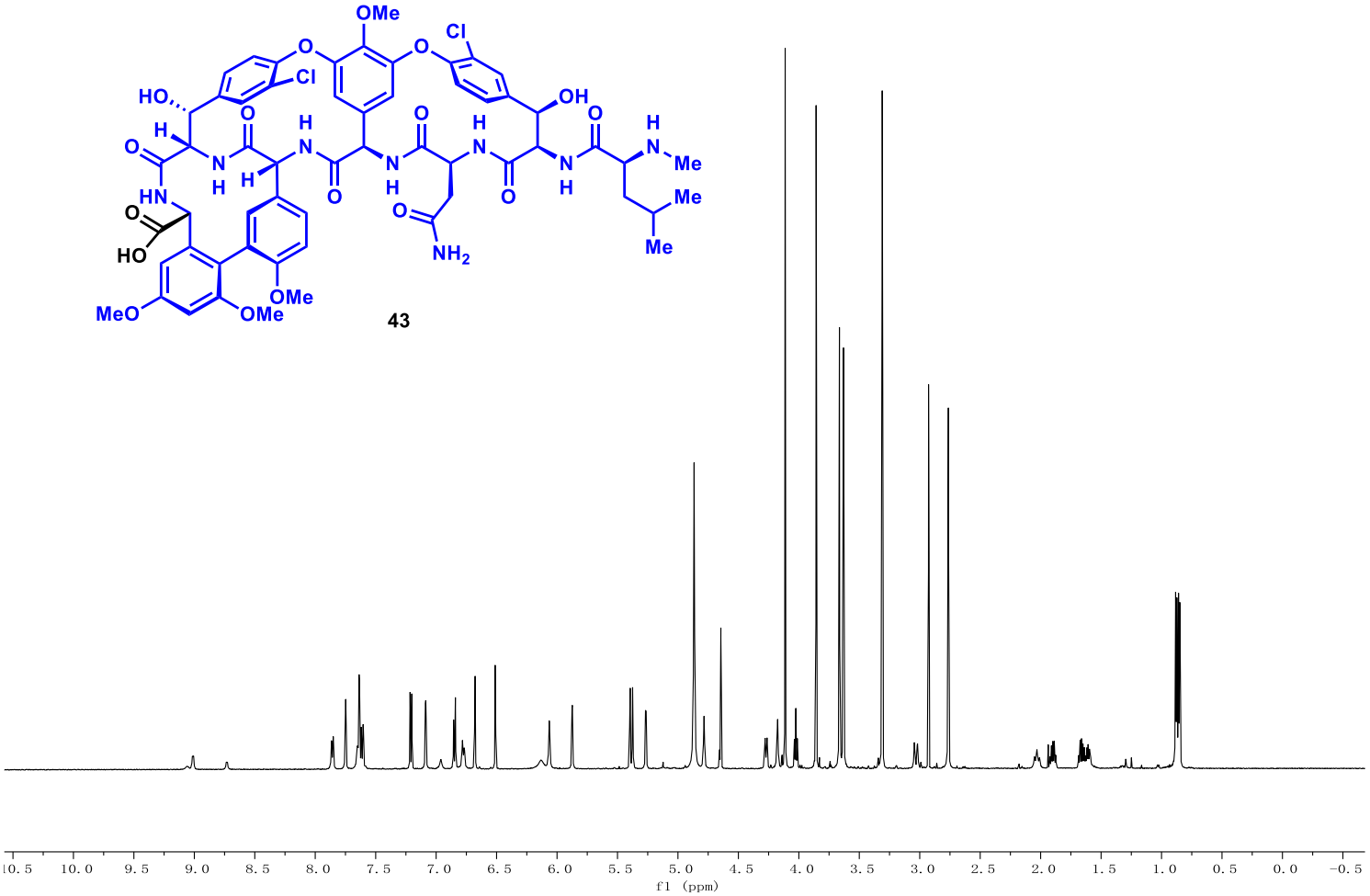
Compound 42 (TFA salt) ^{19}F NMR



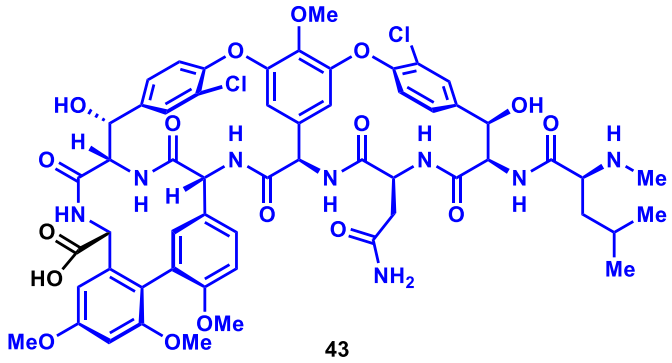
42



Compound 43 (TFA salt) ^{1}H NMR

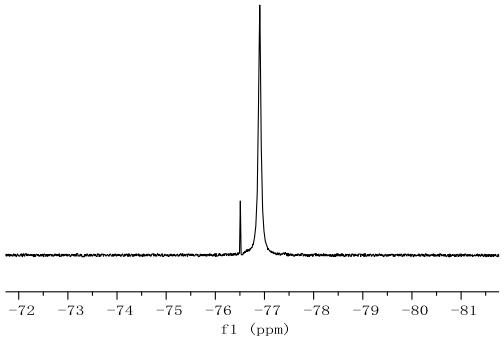


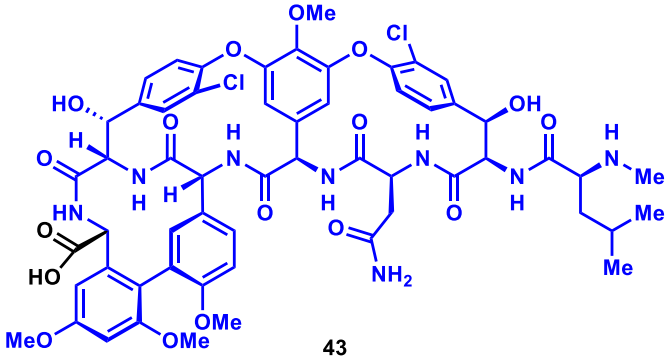
Compound 43 (TFA salt) ^{13}C NMR



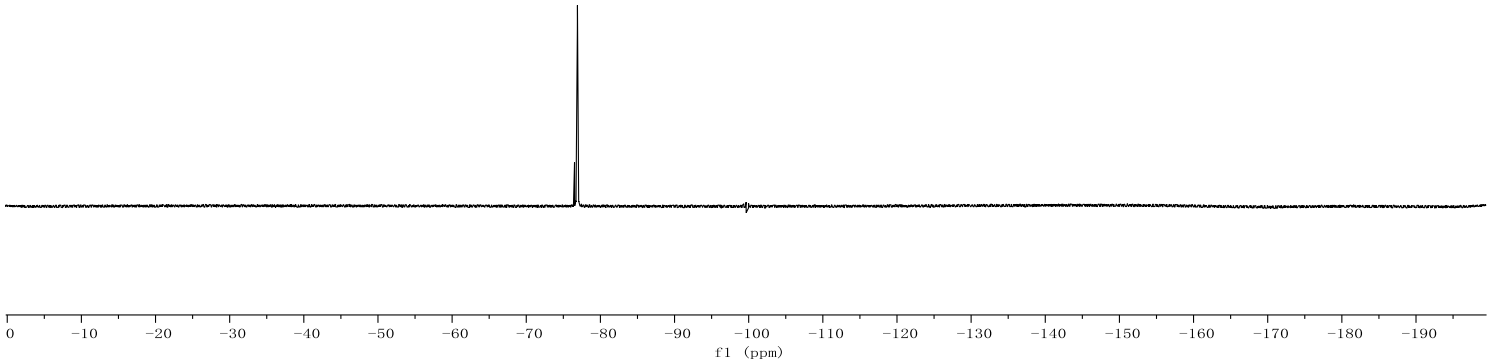
43

Compound 43 (TFA salt) ^{19}F NMR

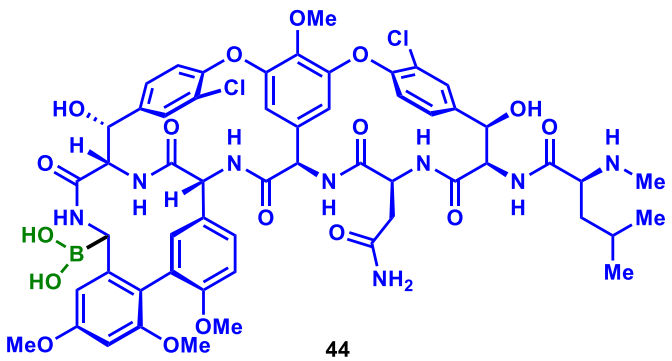




43

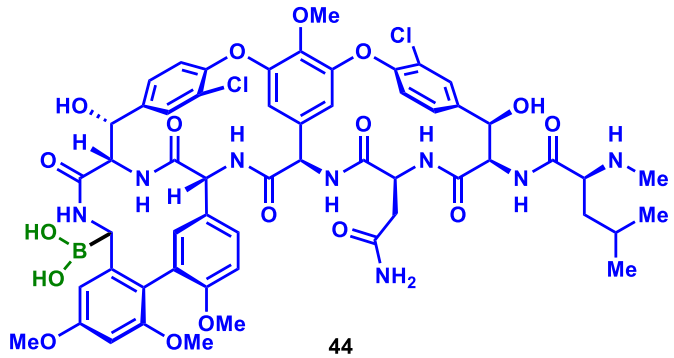


Compound 44 (TFA salt) ^{1}H NMR

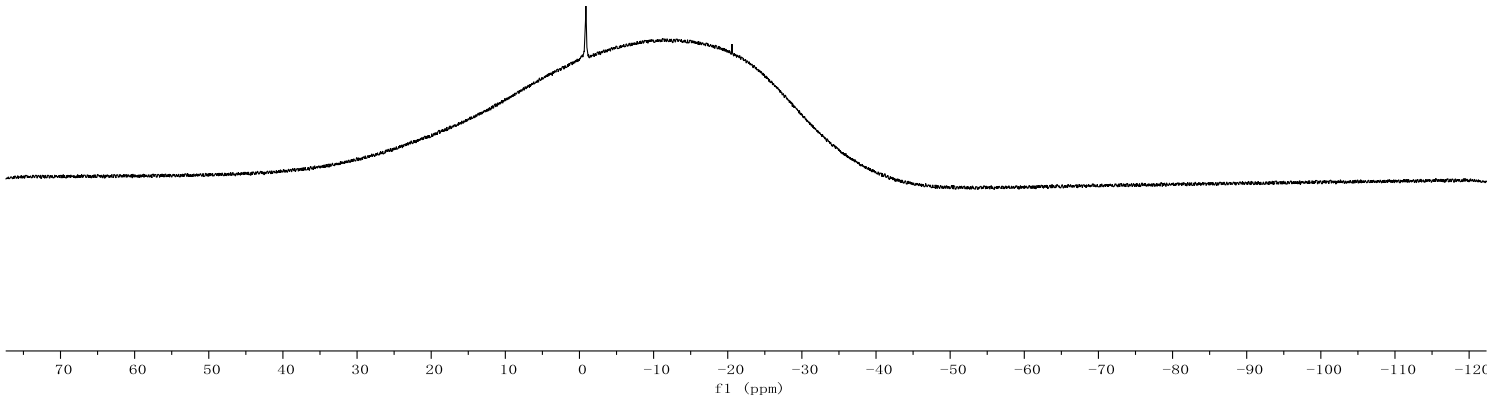


44

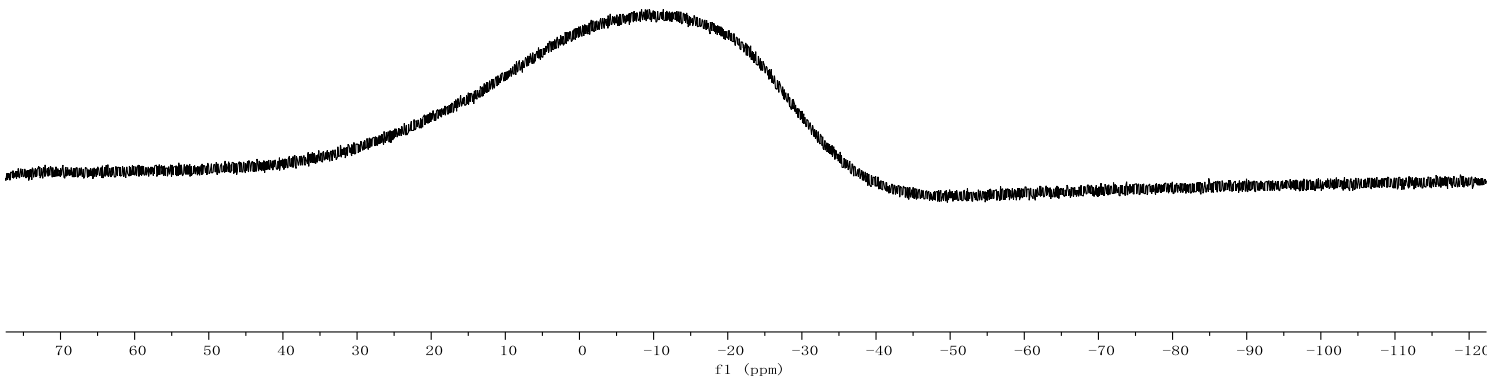
Compound 44 (TFA salt) ^{11}B NMR



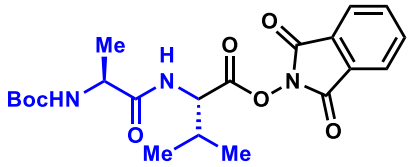
44



Compound 44 ^{11}B NMR-backgroud

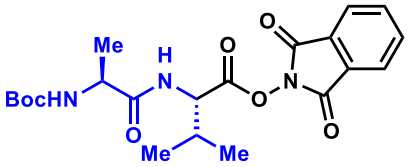


Compound S48 ^{1}H NMR

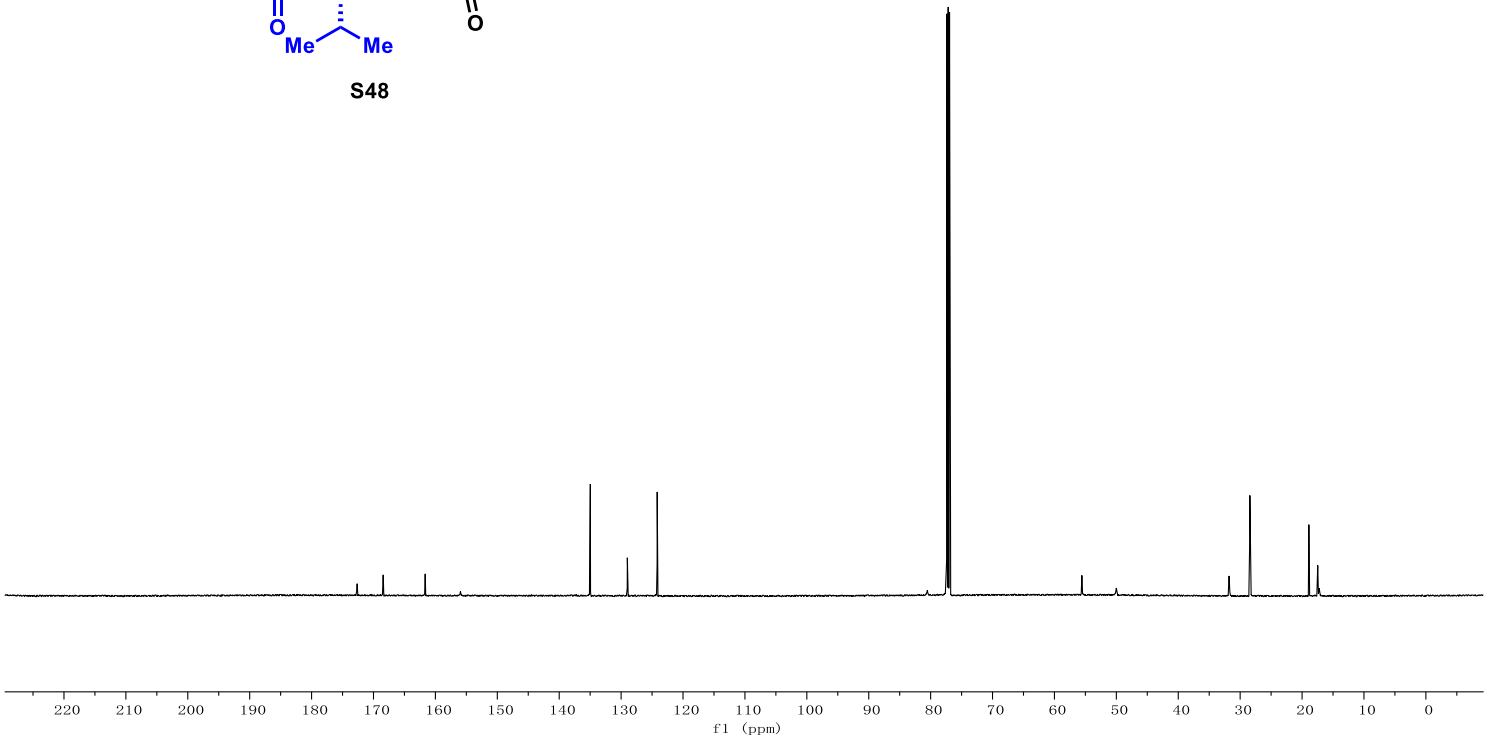


S48

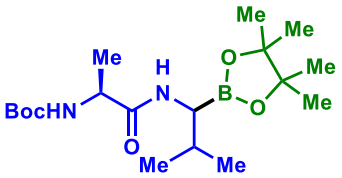
Compound S48 ^{13}C NMR



S48

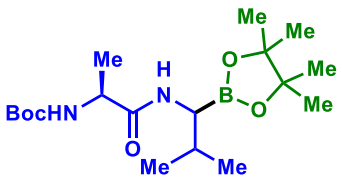


Compound 45 ^{1}H NMR



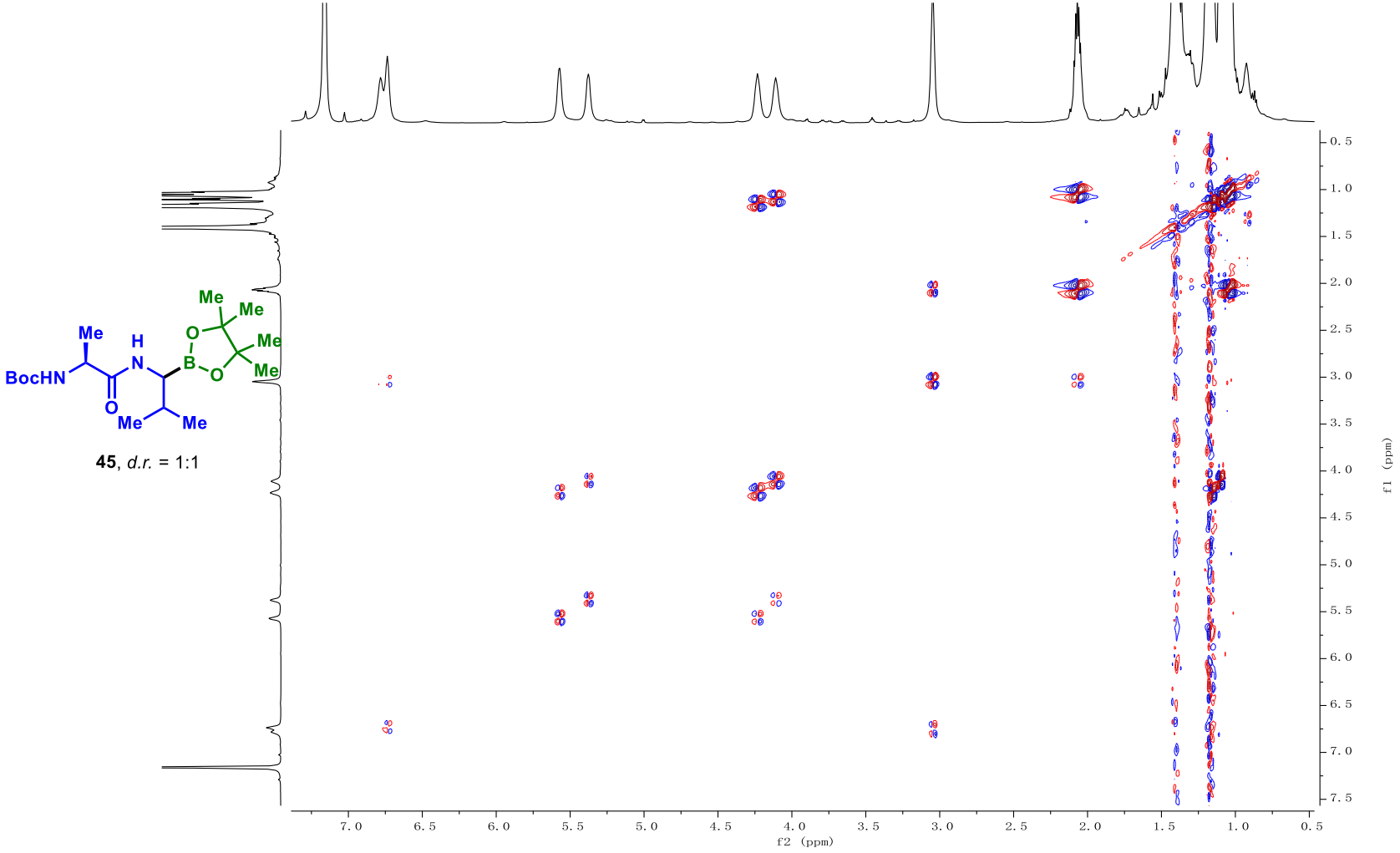
45, *d.r.* = 1:1

Compound 45 ^{13}C NMR

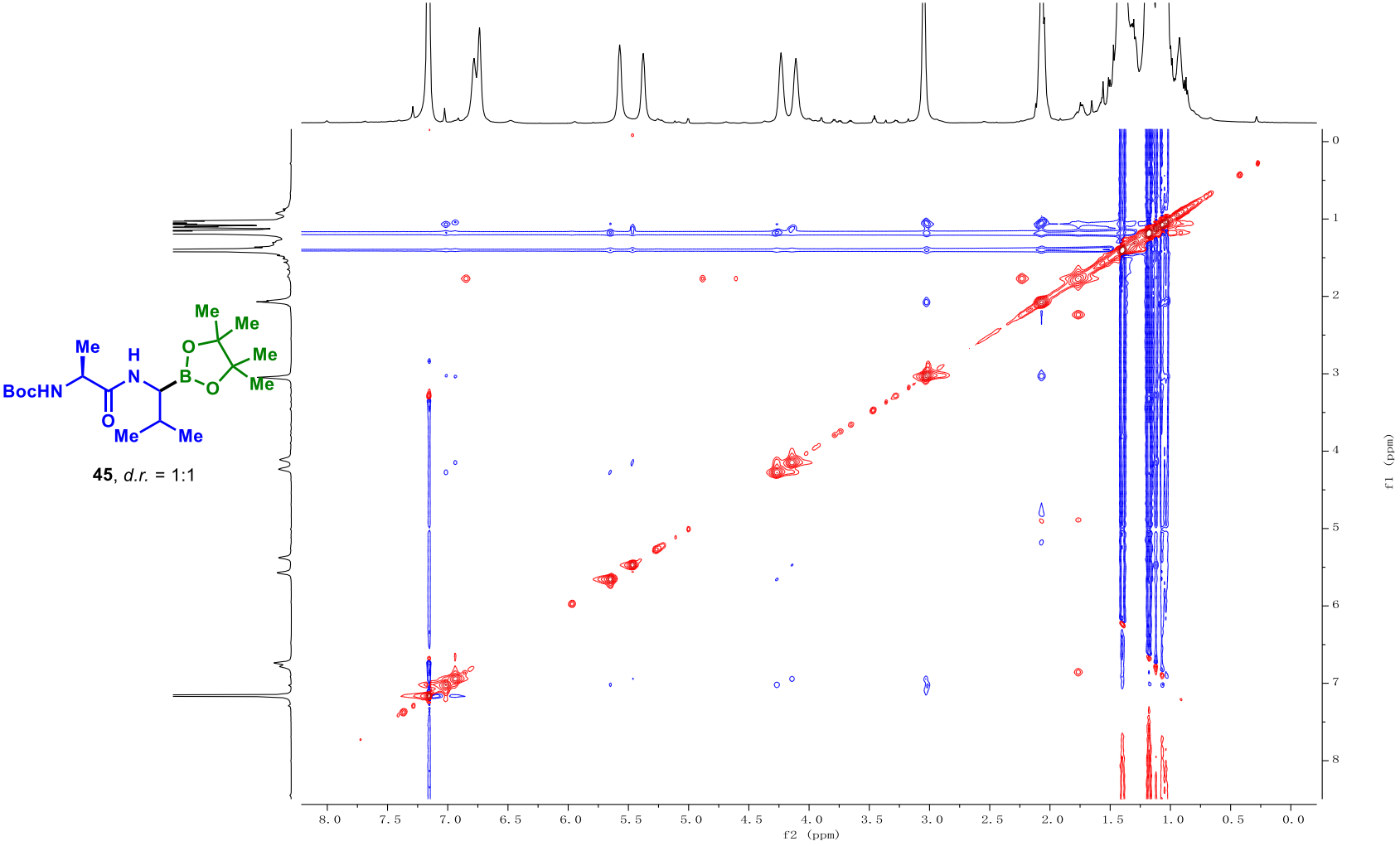


45, *d.r.* = 1:1

Compound 45 COSY

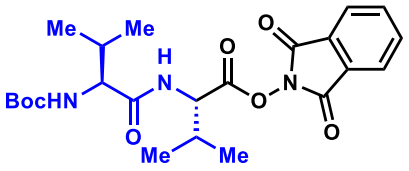


Compound 45 2D NOESY



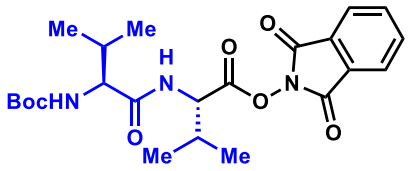
45, *d.r.* = 1:1

Compound S50a ^{1}H NMR



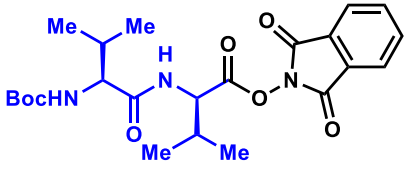
S50a, Boc-*L*-Val-*L*-Val-ONHPI

Compound S50a ^{13}C NMR



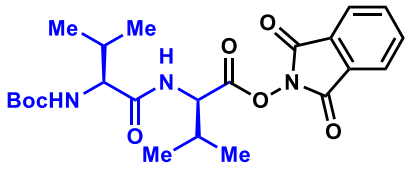
S50a, Boc-*L*-Val-*L*-Val-ONHPI

Compound S50b ^{1}H NMR

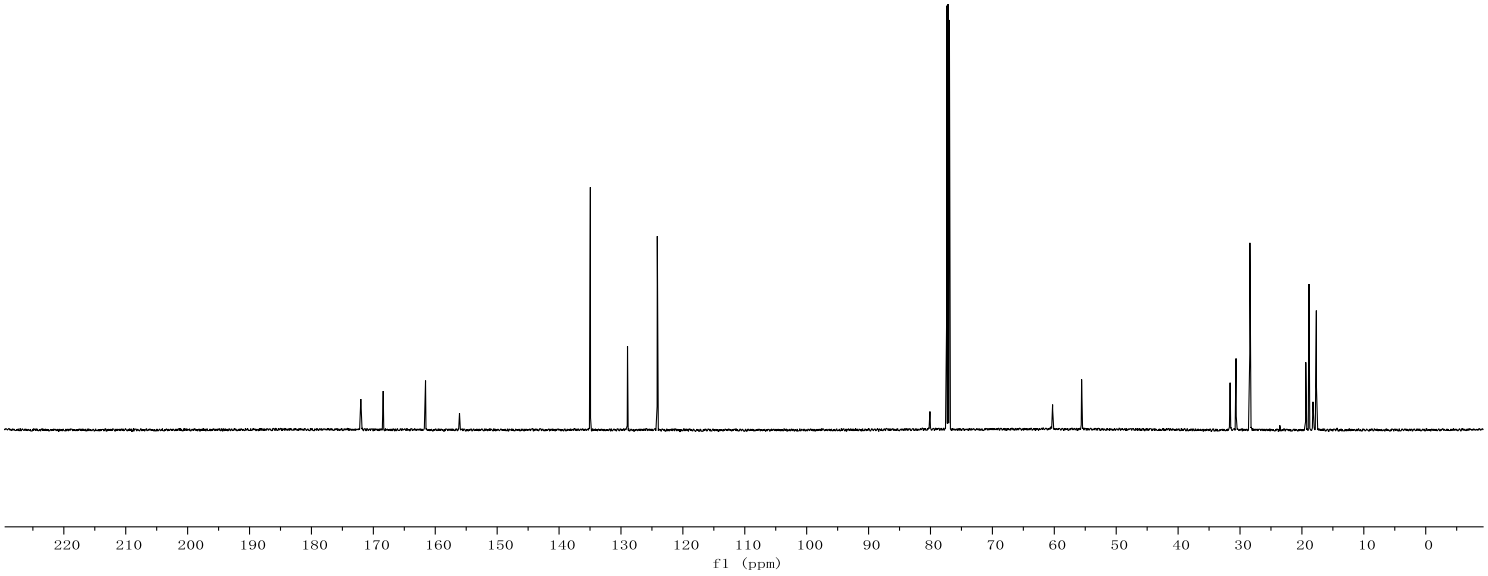


S50b, Boc-*L*-Val-*D*-Val-ONHPI

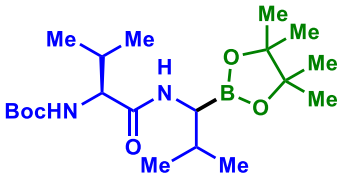
Compound S50b ^{13}C NMR



S50b, Boc-*L*-Val-*D*-Val-ONHPI

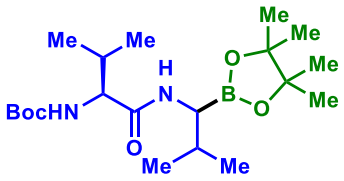


Compound 46 ^{1}H NMR



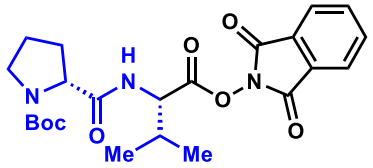
46, *d.r.* = 1.7:1

Compound 46 ^{13}C NMR

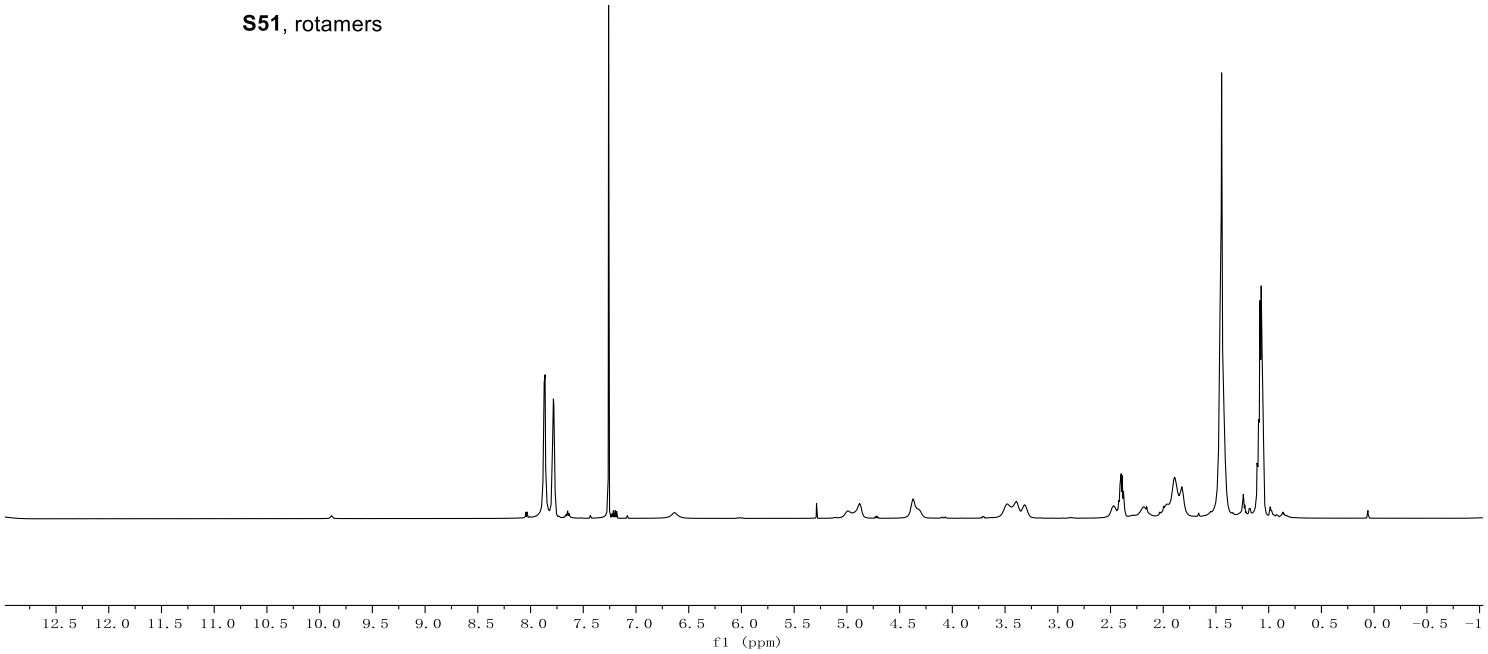


46, *d.r.* = 1.7:1

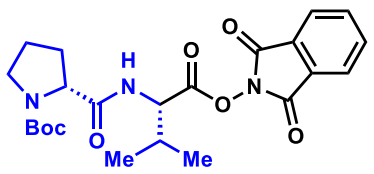
Compound S51 ^{1}H NMR



S51, rotamers

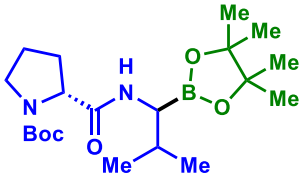


Compound S51 ^{1}H NMR



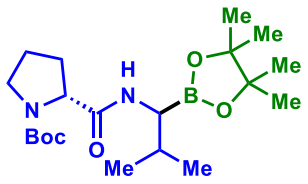
S51, rotamers

Compound 47 ^{1}H NMR



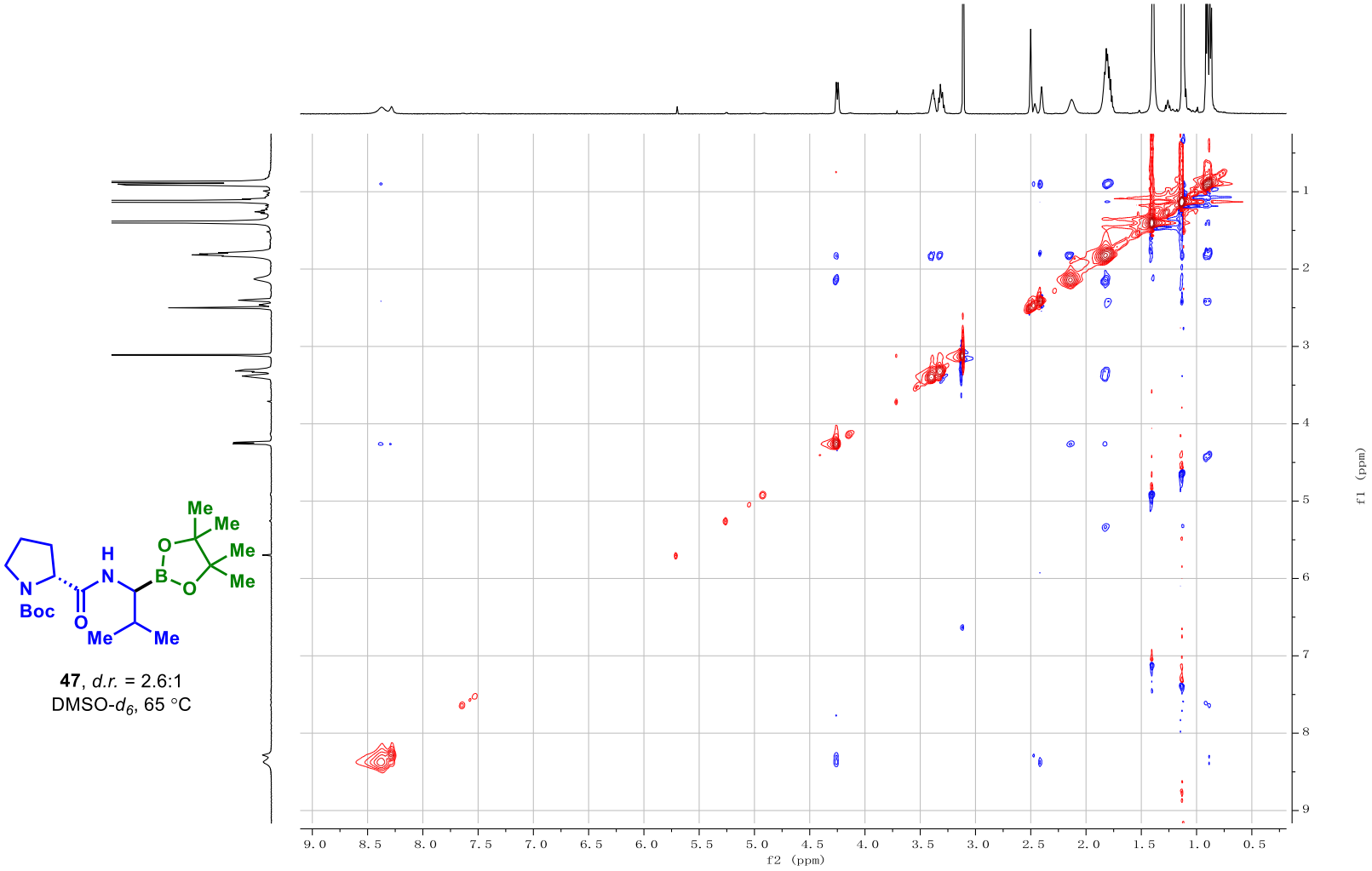
47, *d.r.* = 2.6:1
DMSO-d_6, 65 °C

Compound 47 ^{13}C NMR



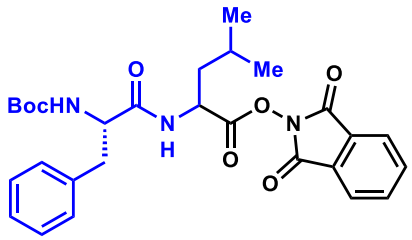
47, *d.r.* = 2.6:1
DMSO-d_6, 65 °C

Compound 47 2D NOESY



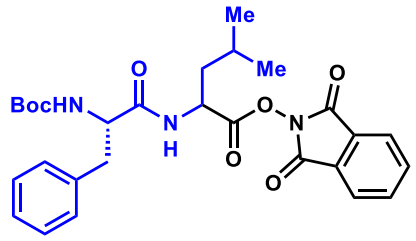
47, *d.r.* = 2.6:1
DMSO-d_6, 65 °C

Compound S53 ^{1}H NMR



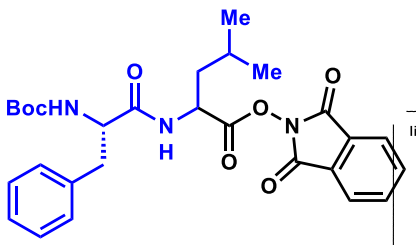
S53, *d.r.* = 3:2

Compound S53 ^{13}C NMR

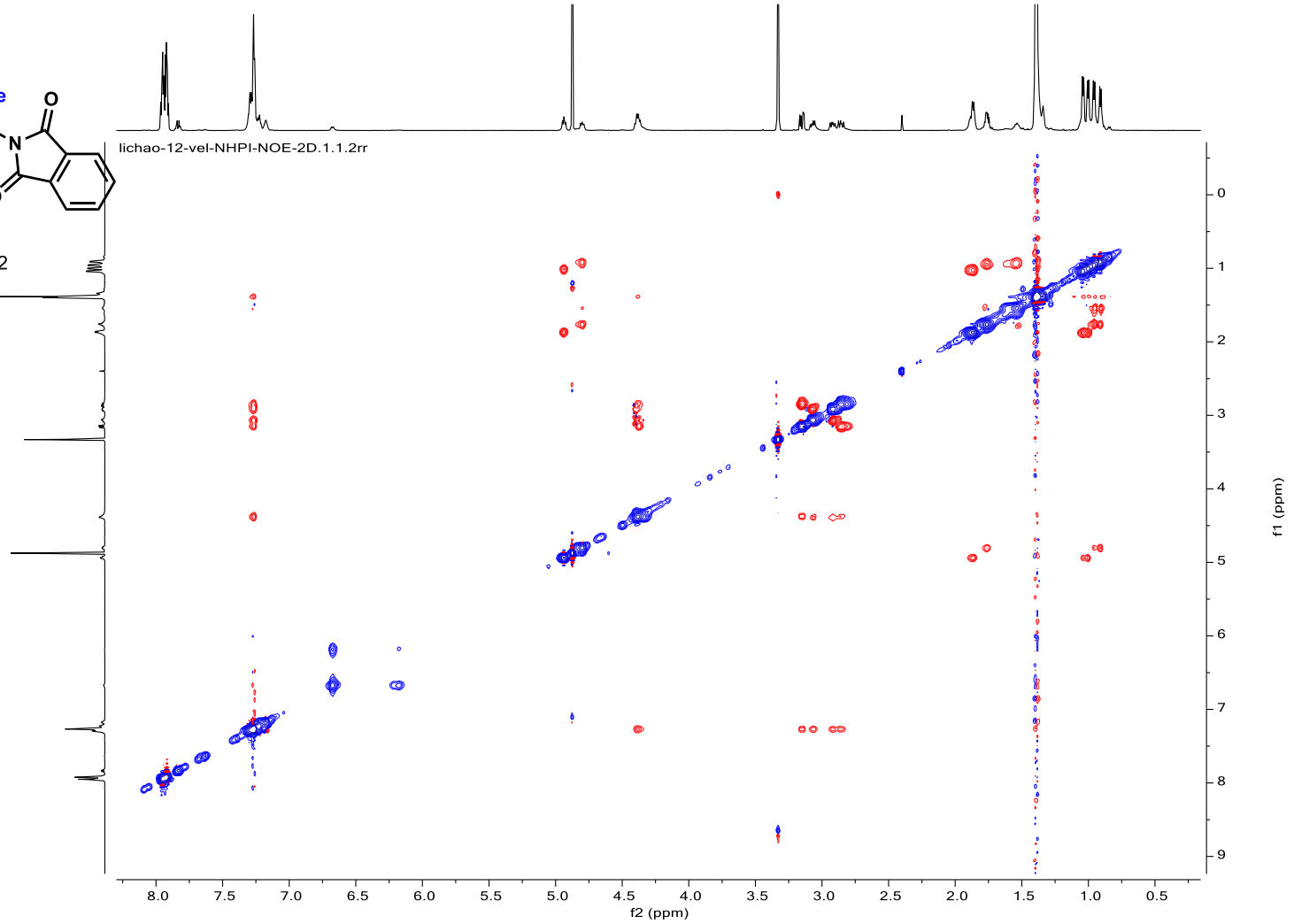


S53, *d.r.* = 3:2

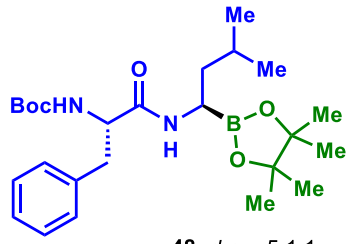
Compound S53 2D NOESY



S53, *d.r.* = 3:2

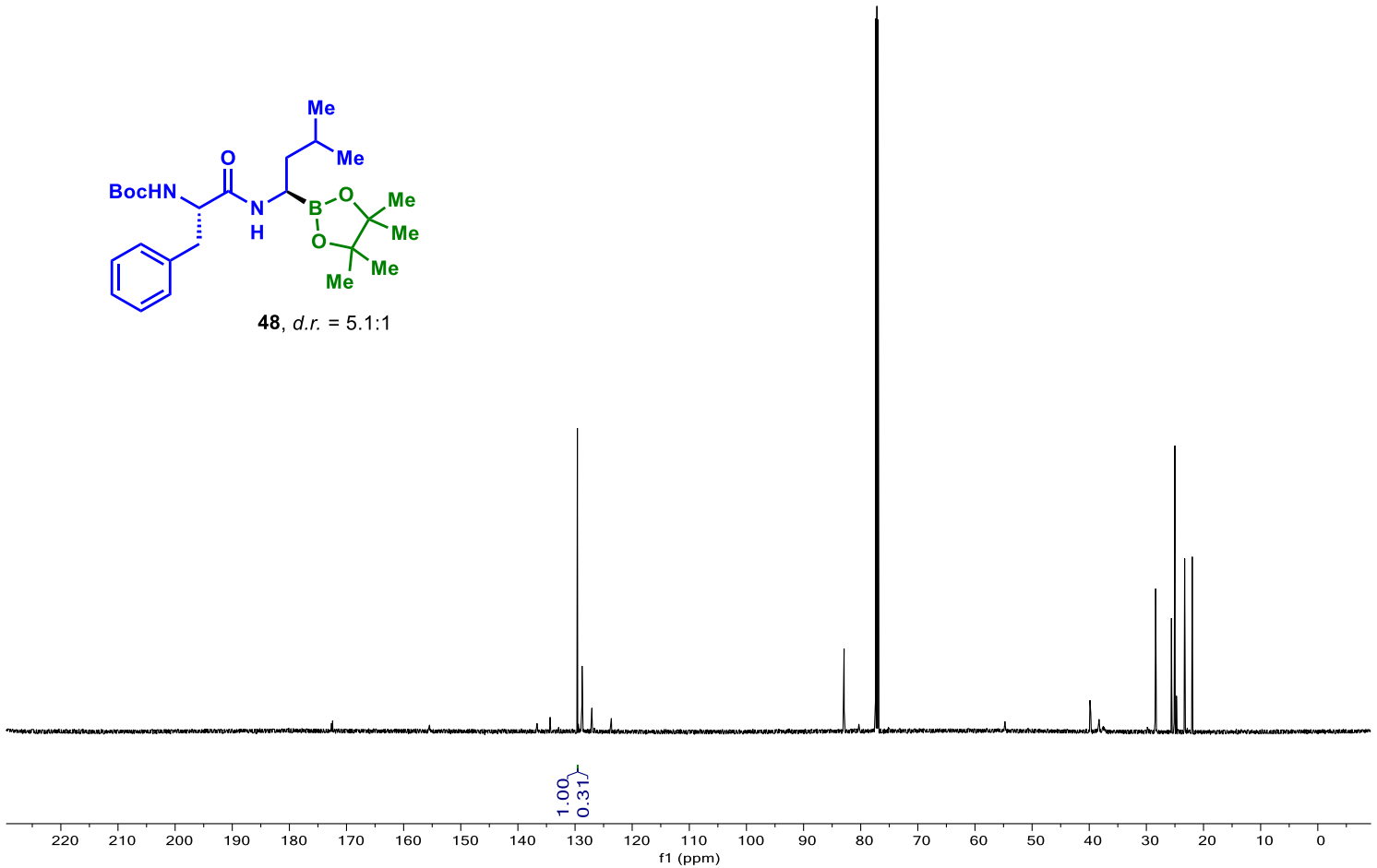


Compound 48 ^{1}H NMR

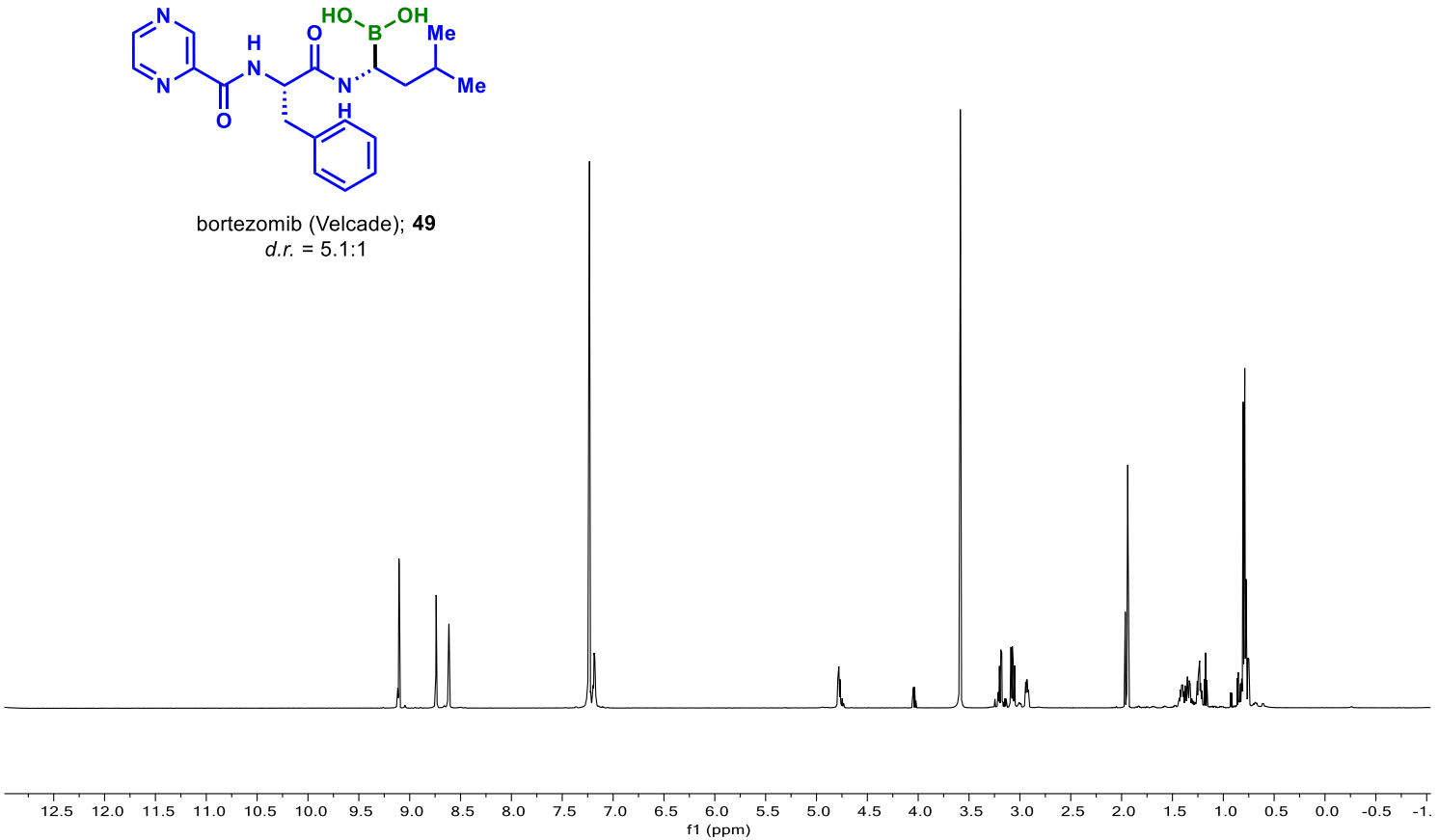


48, *d.r.* = 5.1:1

Compound 48 ^{13}C NMR

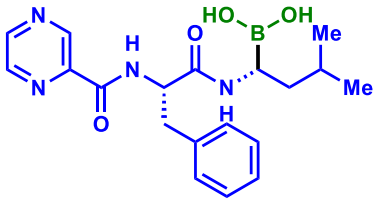


Compound 49 ^{1}H NMR



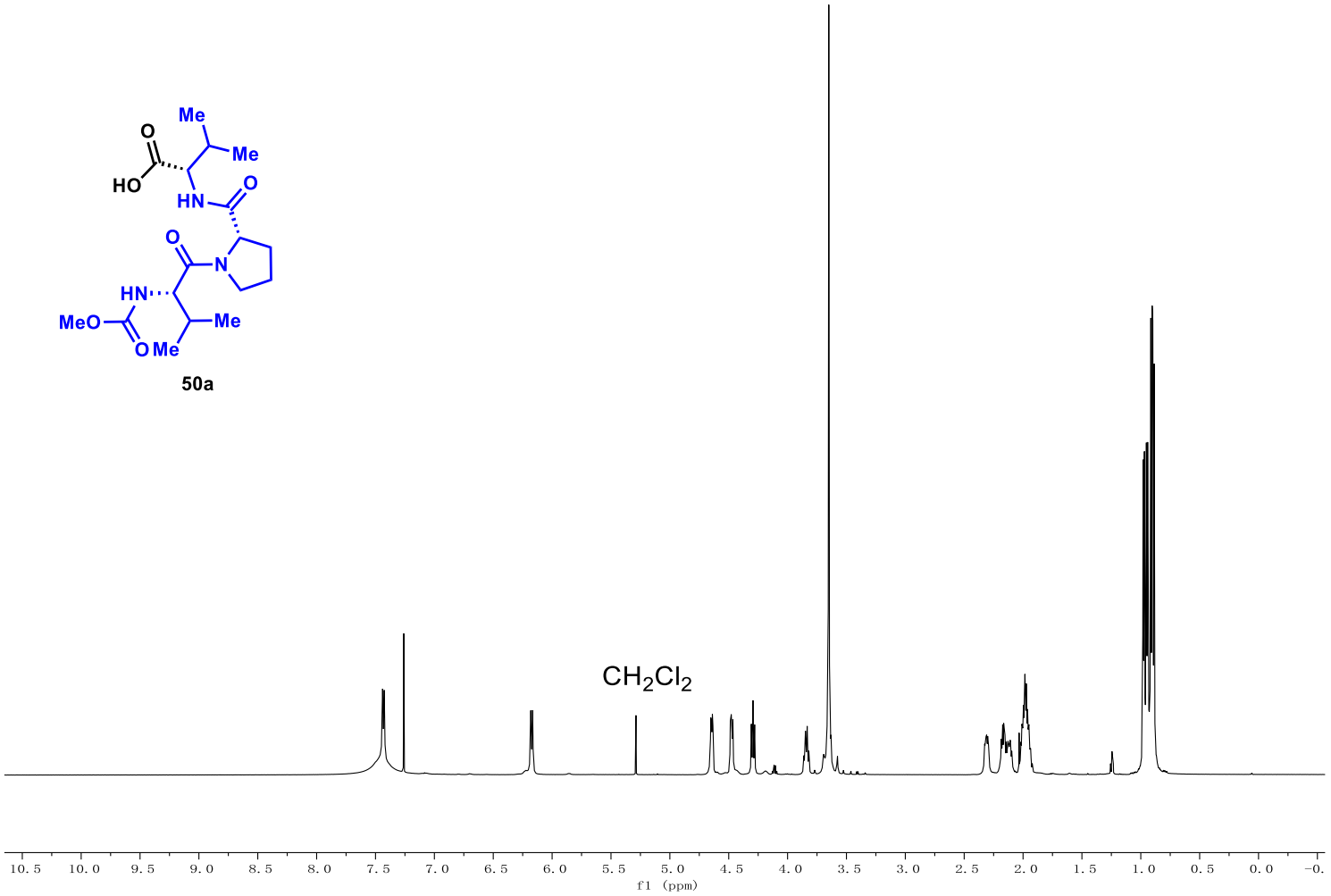
bortezomib (Velcade); **49**
d.r. = 5.1:1

Compound 49 ^{13}C NMR

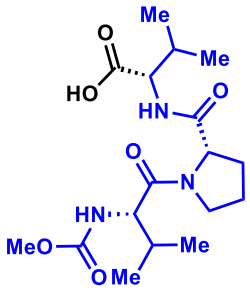


bortezomib (Velcade); **49**
d.r. = 5.1:1

Compound 50a ^{1}H NMR

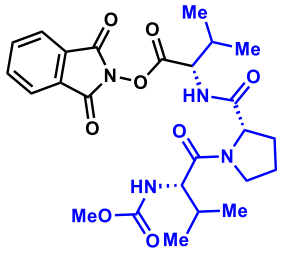


Compound 50a ^{13}C NMR

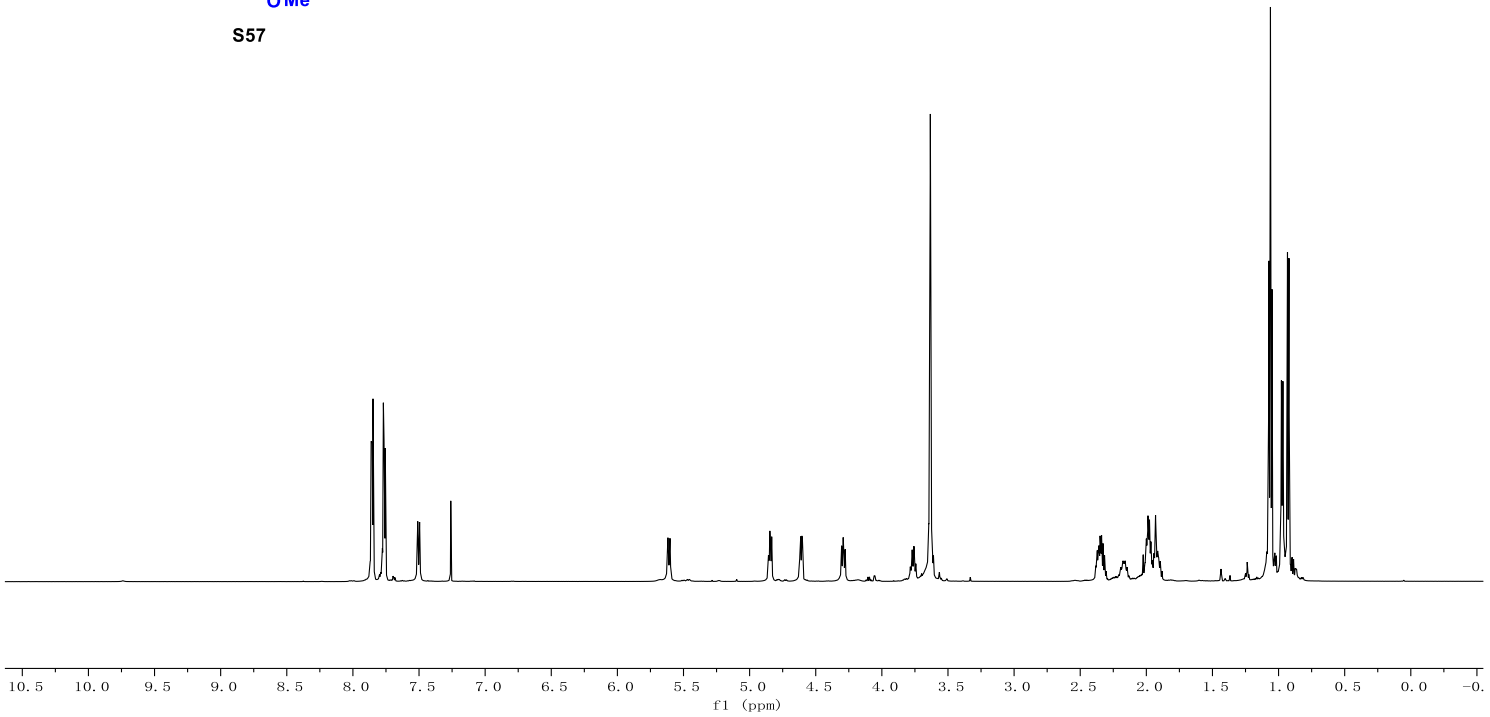


50a

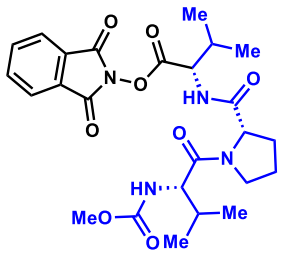
Compound S57 ^{1}H NMR



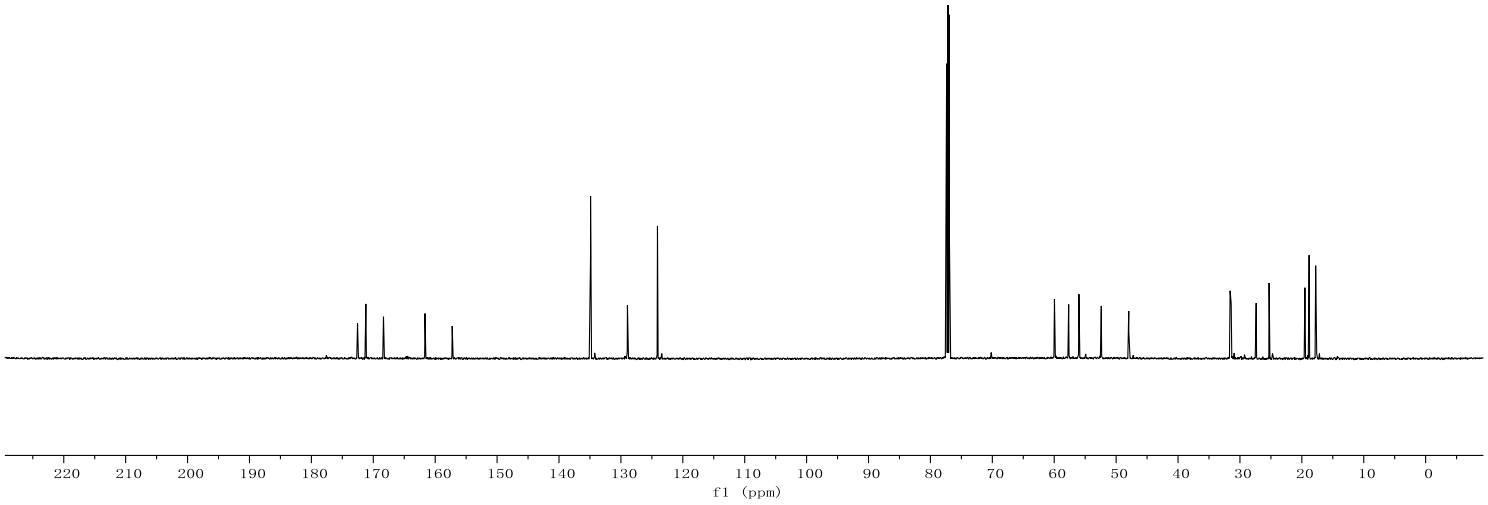
S57



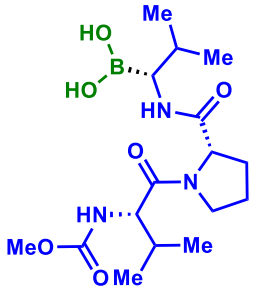
Compound S57 ^{13}C NMR



S57

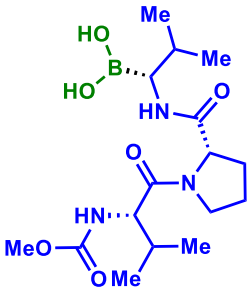


Compound 50 ^{1}H NMR



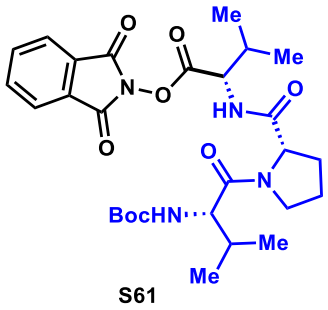
50

Compound 50 ^{13}C NMR



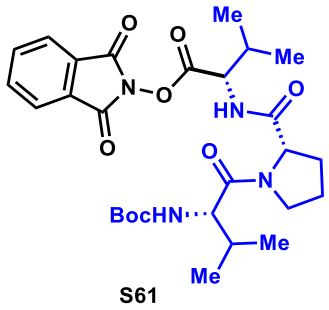
50

Compound S61 ^{1}H NMR

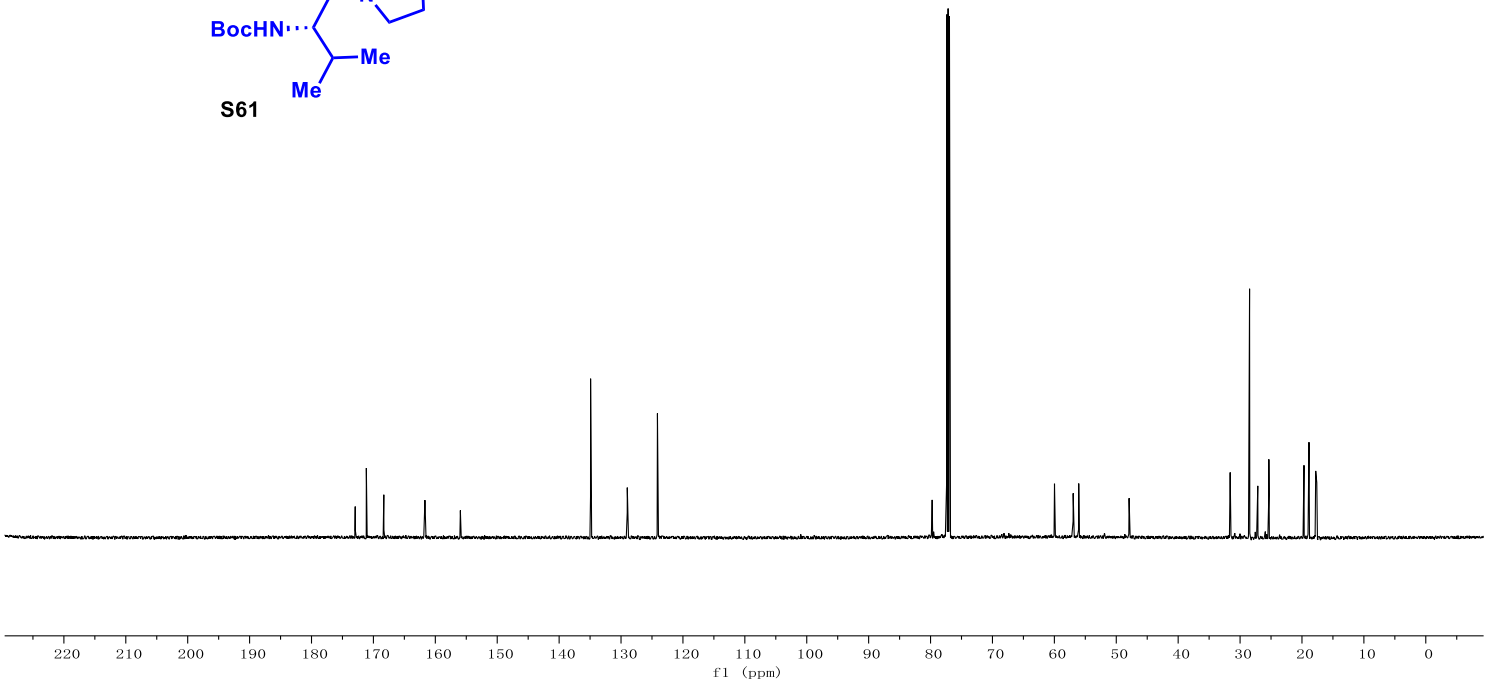


S61

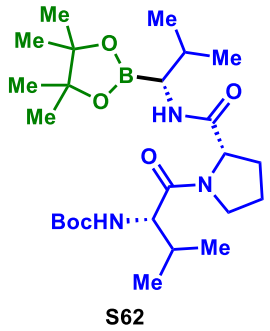
Compound S61 ^{13}C NMR



S61

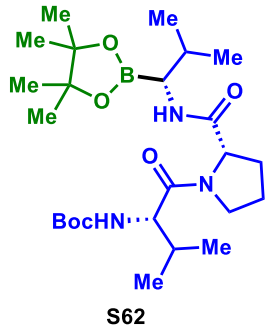


Compound S62 ^{1}H NMR



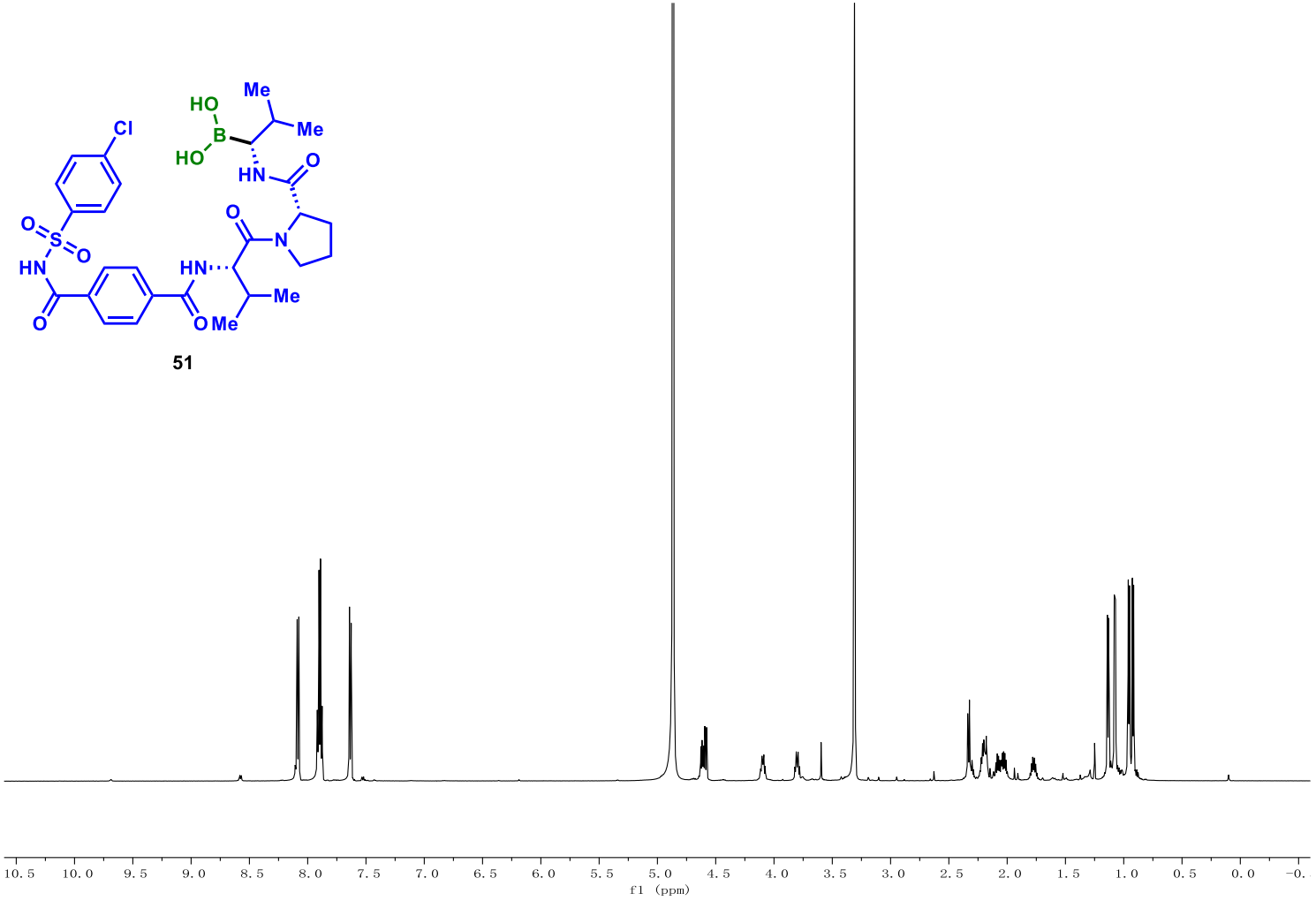
S62

Compound S62 ^{13}C NMR

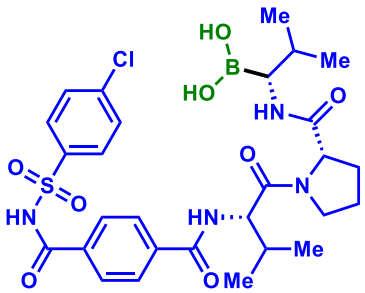


S62

Compound 51 ^{1}H NMR

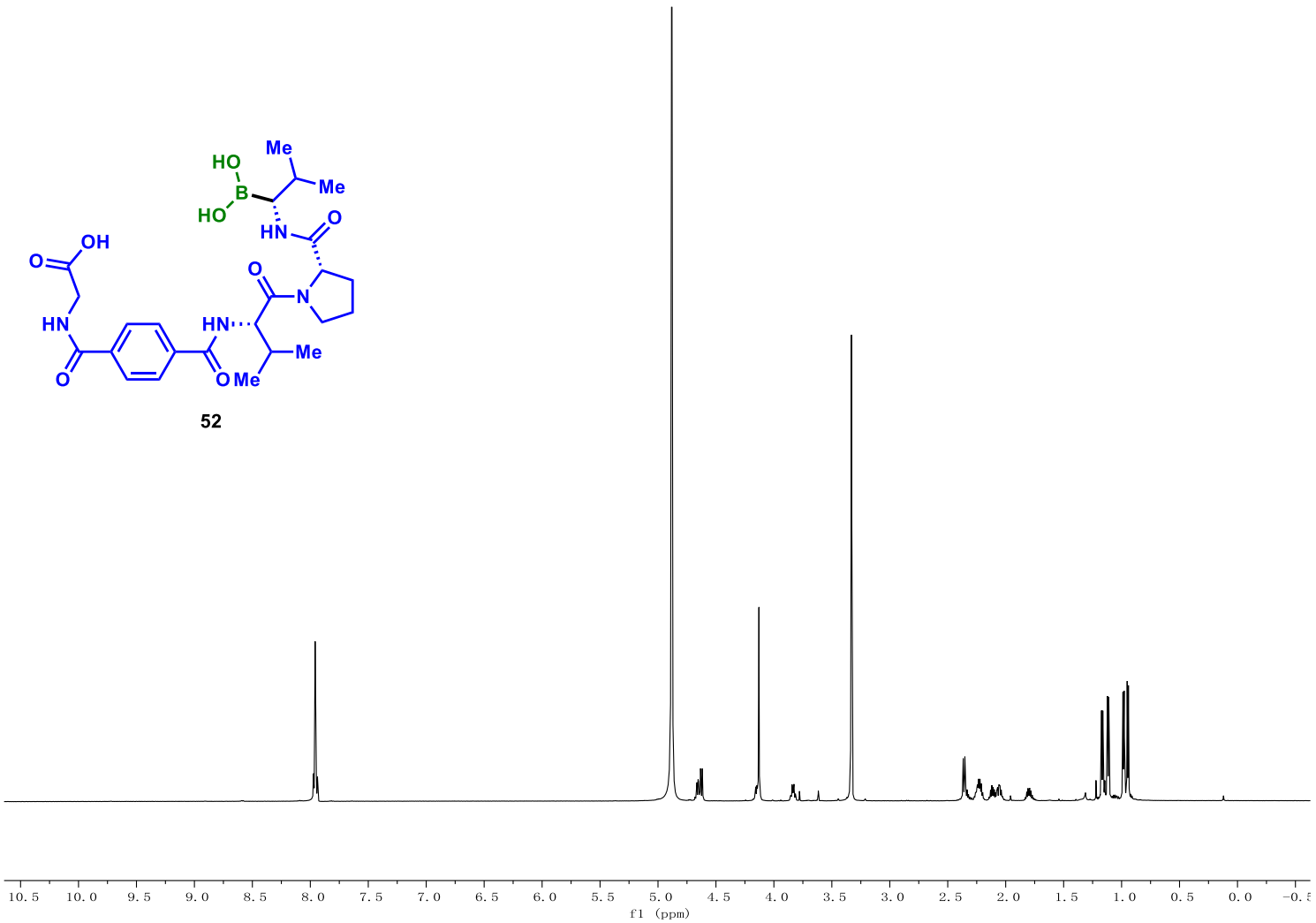


Compound 51 ^{13}C NMR

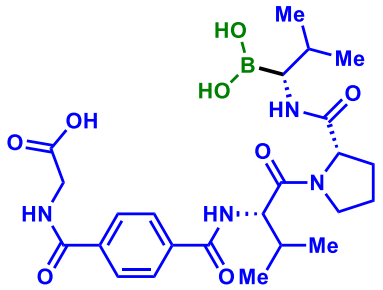


51

Compound 52 ^{1}H NMR

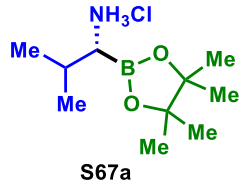


Compound 52 ^{13}C NMR



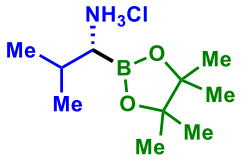
52

Compound S67a ^{1}H NMR

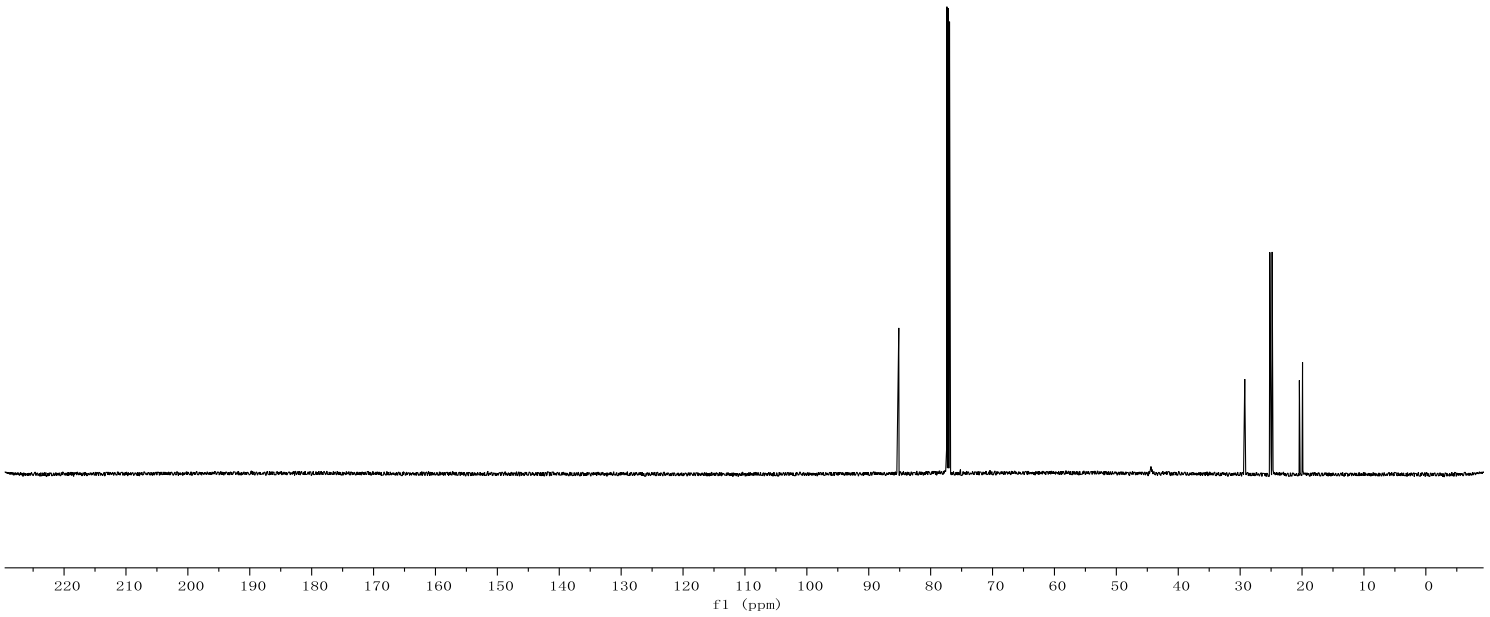


S67a

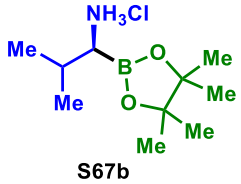
Compound S67a ^{13}C NMR



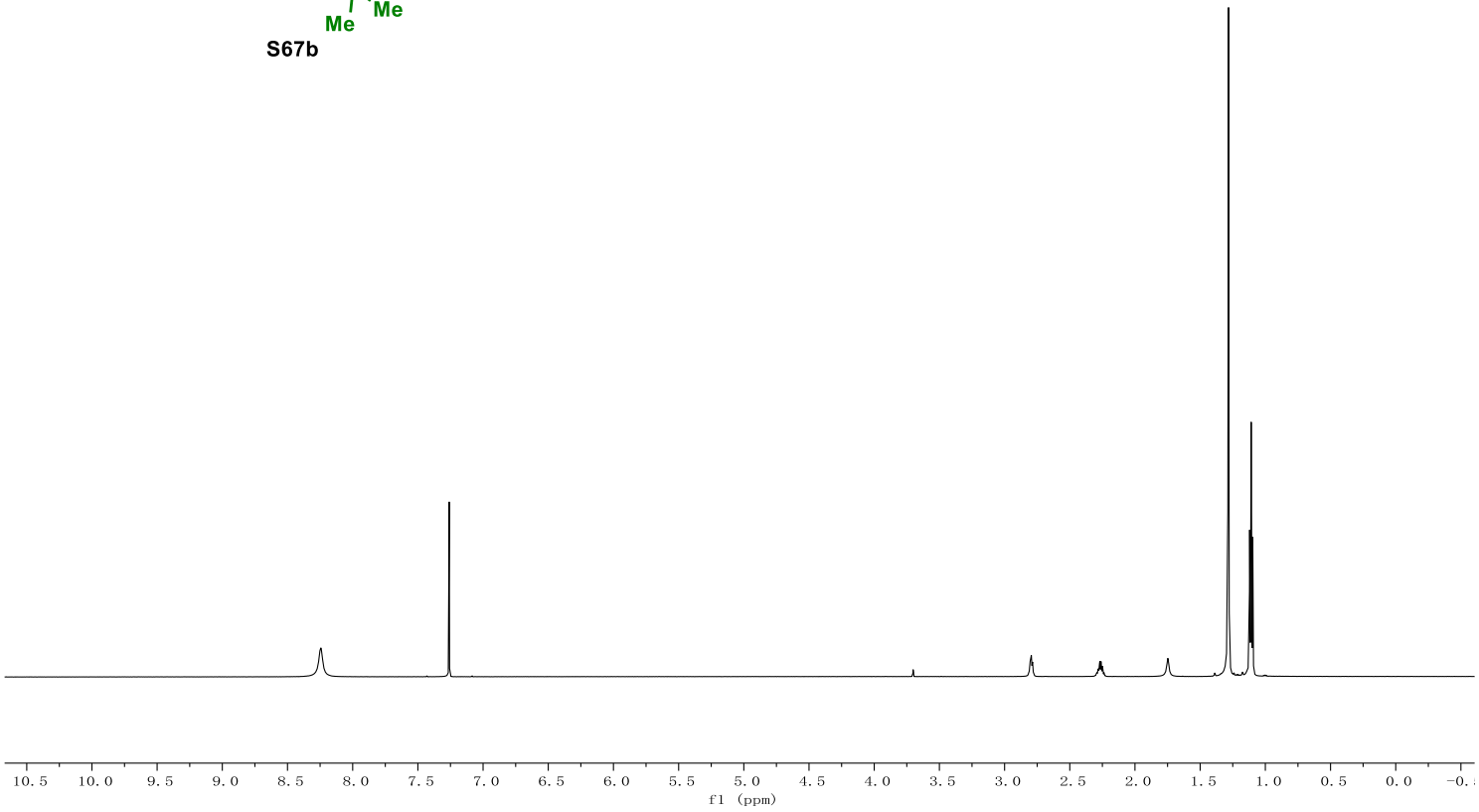
S67a



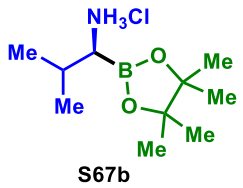
Compound S67b ^{1}H NMR



S67b

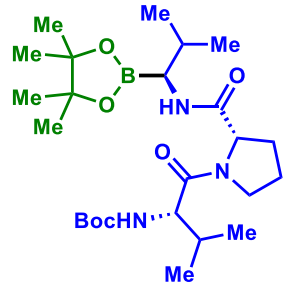


Compound S67b ^{13}C NMR



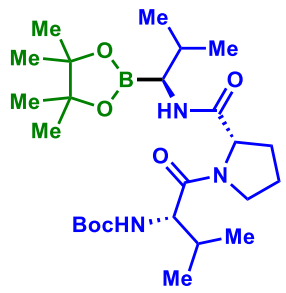
S67b

Compound S62b ^{1}H NMR



S62b, *d.r.* = 6:1

Compound S62b ^{13}C NMR



S62b, *d.r.* = 6:1

References

1. A. Suzuki, Cross-coupling reactions of organoboranes: An easy way to construct C-C bonds (Nobel Lecture). *Angew. Chem. Int. Ed.* **50**, 6722–6737 (2011). doi:10.1002/anie.201101379 Medline

2. W. L. A. Brooks, B. S. Sumerlin, Synthesis and applications of boronic acid-containing polymers: From materials to medicine. *Chem. Rev.* **116**, 1375–1397 (2016). doi:10.1021/acs.chemrev.5b00300 Medline

3. S. D. Bull, M. G. Davidson, J. M. H. van den Elsen, J. S. Fossey, A. T. A. Jenkins, Y.-B. Jiang, Y. Kubo, F. Marken, K. Sakurai, J. Zhao, T. D. James, Exploiting the reversible covalent bonding of boronic acids: Recognition, sensing, and assembly. *Acc. Chem. Res.* **46**, 312–326 (2013). doi:10.1021/ar300130w Medline

4. P. C. Trippier, C. McGuigan, Boronic acids in medicinal chemistry: Anticancer, antibacterial and antiviral applications. *MedChemComm* **1**, 183 (2010). doi:10.1039/c0md00119h

5. A. Draganov, D. Wang, B. Wang, The future of boron in medicinal chemistry: Therapeutic and diagnostic applications. In *Atypical Elements in Drug Design*, J. Schwarz, Ed. (Springer, 2014), pp. 1–27. doi:10.1007/7355_2014_65

6. C. Ballatore, D. M. Huryn, A. B. Smith 3rd, Carboxylic acid (bio)isosteres in drug design. *ChemMedChem* **8**, 385–395 (2013). doi:10.1002/cmdc.201200585 Medline

7. R. Smoum, A. Rubinstein, V. M. Dembitsky, M. Srebnik, Boron containing compounds as protease inhibitors. *Chem. Rev.* **112**, 4156–4220 (2012). doi:10.1021/cr608202m Medline

8. H. C. Brown, *Hydroboration* (Benjamin/Cummings, 1980).

9. C. M. Vogels, S. A. Westcott, Recent advances in organic synthesis using transition metal-catalyzed hydroborations. *Curr. Org. Chem.* **9**, 687–699 (2005). doi:10.2174/1385272053765060

10. A. S. Dudnik, G. C. Fu, Nickel-catalyzed coupling reactions of alkyl electrophiles, including unactivated tertiary halides, to generate carbon-boron bonds. *J. Am. Chem. Soc.* **134**, 10693–10697 (2012). doi:10.1021/ja304068t Medline

11. T. C. Atack, R. M. Lecker, S. P. Cook, Iron-catalyzed borylation of alkyl electrophiles. *J. Am. Chem. Soc.* **136**, 9521–9523 (2014). doi:10.1021/ja505199u Medline

12. R. B. Bedford, P. B. Brenner, E. Carter, T. Gallagher, D. M. Murphy, D. R. Pye, Iron-catalyzed borylation of alkyl, allyl, and aryl halides: Isolation of an iron(I) boryl complex. *Organometallics* **33**, 5940–5943 (2014). doi:10.1021/om500847j

13. C.-T. Yang, Z.-Q. Zhang, H. Tajuddin, C.-C. Wu, J. Liang, J.-H. Liu, Y. Fu, M. Czyzewska, P. G. Steel, T. B. Marder, L. Liu, Alkylboronic esters from copper-catalyzed borylation

of primary and secondary alkyl halides and pseudohalides. *Angew. Chem. Int. Ed.* **51**, 528–532 (2012). doi:10.1002/anie.201106299 Medline

14. H. Ito, K. Kubota, Copper(I)-catalyzed boryl substitution of unactivated alkyl halides. *Org. Lett.* **14**, 890–893 (2012). doi:10.1021/ol203413w Medline

15. H. C. Brown, T. E. Cole, Organoboranes. 31. A simple preparation of boronic esters from organolithium reagents and selected trialkoxyboranes. *Organometallics* **2**, 1316–1319 (1983). doi:10.1021/om50004a009

16. K. S. Lee, A. R. Zhugralin, A. H. Hoveyda, Efficient C-B bond formation promoted by N-heterocyclic carbenes: Synthesis of tertiary and quaternary B-substituted carbons through metal-free catalytic boron conjugate additions to cyclic and acyclic α,β-unsaturated carbonyls. *J. Am. Chem. Soc.* **131**, 7253–7255 (2009). doi:10.1021/ja902889s Medline

17. J. A. Schiffner, K. Müther, M. Oestreich, Enantioselective conjugate borylation. *Angew. Chem. Int. Ed.* **49**, 1194–1196 (2010). doi:10.1002/anie.200906521 Medline

18. P. Andrés, G. Ballano, M. I. Calaza, C. Cativiela, Synthesis of α-aminoboronic acids. *Chem. Soc. Rev.* **45**, 2291–2307 (2016). doi:10.1039/C5CS00886G Medline

19. M. A. Beenen, C. An, J. A. Ellman, Asymmetric copper-catalyzed synthesis of α-amino boronate esters from *N*-*tert*-butanesulfinyl aldimines. *J. Am. Chem. Soc.* **130**, 6910–6911 (2008). doi:10.1021/ja800829y Medline

20. I. A. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, C-H activation for the construction of C-B bonds. *Chem. Rev.* **110**, 890–931 (2010). doi:10.1021/cr900206p Medline

21. E. J. Olhava, M. D. Danca, U.S. patent 7442830 (2008).

22. T. Qin, J. Cornella, C. Li, L. R. Malins, J. T. Edwards, S. Kawamura, B. D. Maxwell, M. D. Eastgate, P. S. Baran, A general alkyl-alkyl cross-coupling enabled by redox-active esters and alkylzinc reagents. *Science* **352**, 801–805 (2016). doi:10.1126/science.aaf6123 Medline

23. J. Cornella, J. T. Edwards, T. Qin, S. Kawamura, J. Wang, C.-M. Pan, R. Gianatassio, M. Schmidt, M. D. Eastgate, P. S. Baran, Practical Ni-catalyzed aryl-alkyl cross-coupling of secondary redox-active esters. *J. Am. Chem. Soc.* **138**, 2174–2177 (2016). doi:10.1021/jacs.6b00250 Medline

24. J. Wang, T. Qin, T.-G. Chen, L. Wimmer, J. T. Edwards, J. Cornella, B. Vokits, S. A. Shaw, P. S. Baran, Nickel-catalyzed cross-coupling of redox-active esters with boronic acids. *Angew. Chem. Int. Ed.* **55**, 9676–9679 (2016). doi:10.1002/anie.201605463 Medline

25. F. Toriyama, J. Cornella, L. Wimmer, T.-G. Chen, D. D. Dixon, G. Creech, P. S. Baran, Redox-active esters in Fe-catalyzed C-C coupling. *J. Am. Chem. Soc.* **138**, 11132–11135 (2016). doi:10.1021/jacs.6b07172 Medline

26. T. Qin, L. R. Malins, J. T. Edwards, R. R. Merchant, A. J. E. Novak, J. Z. Zhong, R. B. Mills, M. Yan, C. Yuan, M. D. Eastgate, P. S. Baran, Nickel-catalyzed barton decarboxylation and Giese reactions: A practical take on classic transforms. *Angew. Chem. Int. Ed.* **56**, 260–265 (2017). doi:10.1002/anie.201609662 Medline

27. T. Hatakeyama, T. Hashimoto, Y. Kondo, Y. Fujiwara, H. Seike, H. Takaya, Y. Tamada, T. Ono, M. Nakamura, Iron-catalyzed Suzuki-Miyaura coupling of alkyl halides. *J. Am. Chem. Soc.* **132**, 10674–10676 (2010). doi:10.1021/ja103973a Medline

28. R. B. Bedford, P. B. Brenner, E. Carter, T. W. Carvell, P. M. Cogswell, T. Gallagher, J. N. Harvey, D. M. Murphy, E. C. Neeve, J. Nunn, D. R. Pye, Expedient iron-catalyzed coupling of alkyl, benzyl and allyl halides with arylboronic esters. *Chemistry* **20**, 7935–7938 (2014). doi:10.1002/chem.201402174 Medline

29. R. Al Hussainy, J. Verbeek, D. van der Born, A. H. Braker, J. E. Leysen, R. J. Knol, J. Booij, J. K. D. M. Herscheid, Design, synthesis, radiolabeling, and in vitro and in vivo evaluation of bridgehead iodinated analogues of *N*-2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl-*N*-(pyridin-2-yl)cyclohexanecarboxamide (WAY-100635) as potential SPECT ligands for the 5-HT_{1A} receptor. *J. Med. Chem.* **54**, 3480–3491 (2011). doi:10.1021/jm1009956 Medline

30. P. Lassalas, B. Gay, C. Lasfargeas, M. J. James, V. Tran, K. G. Vijayendran, K. R. Brunden, M. C. Kozlowski, C. J. Thomas, A. B. Smith 3rd, D. M. Huryn, C. Ballatore, Structure property relationships of carboxylic acid isosteres. *J. Med. Chem.* **59**, 3183–3203 (2016). doi:10.1021/acs.jmedchem.5b01963 Medline

31. J. Schmidt, J. Choi, A. T. Liu, M. Slusarczyk, G. C. Fu, A general, modular method for the catalytic asymmetric synthesis of alkylboronate esters. *Science* **354**, 1265–1269 (2016). doi:10.1126/science.aai8611 Medline

32. Y. Xi, J. F. Hartwig, Diverse asymmetric hydrofunctionalization of aliphatic internal alkenes through catalytic regioselective hydroboration. *J. Am. Chem. Soc.* **138**, 6703–6706 (2016). doi:10.1021/jacs.6b02478 Medline

33. G. A. Molander, N. Ellis, Organotrifluoroborates: Protected boronic acids that expand the versatility of the Suzuki coupling reaction. *Acc. Chem. Res.* **40**, 275–286 (2007). doi:10.1021/ar050199q Medline

34. S. N. Mlynarski, A. S. Karns, J. P. Morken, Direct stereospecific amination of alkyl and aryl pinacol boronates. *J. Am. Chem. Soc.* **134**, 16449–16451 (2012). doi:10.1021/ja305448w Medline

35. A. Bonet, M. Odachowski, D. Leonori, S. Essafi, V. K. Aggarwal, Enantiospecific sp^2-sp^3 coupling of secondary and tertiary boronic esters. *Nat. Chem.* **6**, 584–589 (2014). doi:10.1038/nchem.1971 Medline

36. S. Laulhé, J. M. Blackburn, J. L. Roizen, Selective and serial Suzuki-Miyaura reactions of polychlorinated aromatics with alkyl pinacol boronic esters. *Org. Lett.* **18**, 4440–4443 (2016). doi:10.1021/acs.orglett.6b02323 Medline

37. V. M. Dembitsky, M. Srebnik, Synthesis and biological activity of α-aminoboronic acids, amine-carboxyboranes and their derivatives. *Tetrahedron* **59**, 579–593 (2003). doi:10.1016/S0040-4020(02)01618-6

38. J. J. McAtee, S. L. Castle, Q. Jin, D. L. Boger, Synthesis and evaluation of vancomycin and vancomycin aglycon analogues that bear modifications in the residue 3 asparagine. *Bioorg. Med. Chem. Lett.* **12**, 1319–1322 (2002). doi:10.1016/S0960-894X(02)00130-0 Medline

39. F. J. Brown, D. W. Andisik, P. R. Bernstein, C. B. Bryant, C. Ceccarelli, J. R. Damewood Jr., P. D. Edwards, R. A. Earley, S. Feeney, R. C. Green, B. Gomes, B. J. Kosmider, R. D. Krell, A. Shaw, G. B. Steelman, R. M. Thomas, E. P. Vacek, C. A. Veale, P. A. Tuthill, P. Warner, J. C. Williams, D. J. Wolanin, S. A. Woolson, Design of orally active, non-peptidic inhibitors of human leukocyte elastase. *J. Med. Chem.* **37**, 1259–1261 (1994). doi:10.1021/jm00035a004 Medline

40. C. A. Veale, P. R. Bernstein, C. M. Bohnert, F. J. Brown, C. Bryant, J. R. Damewood Jr., R. Earley, S. W. Feeney, P. D. Edwards, B. Gomes, J. M. Hulsizer, B. J. Kosmider, R. D. Krell, G. Moore, T. W. Salcedo, A. Shaw, D. S. Silberstein, G. B. Steelman, M. Stein, A. Strimpler, R. M. Thomas, E. P. Vacek, J. C. Williams, D. J. Wolanin, S. Woolson, Orally active trifluoromethyl ketone inhibitors of human leukocyte elastase. *J. Med. Chem.* **40**, 3173–3181 (1997). doi:10.1021/jm970250z Medline

41. P. R. Bernstein, B. C. Gomes, B. J. Kosmider, E. P. Vacek, J. C. Williams, Nonpeptidic inhibitors of human leukocyte elastase. 6. Design of a potent, intratracheally active, pyridone-based trifluoromethyl ketone. *J. Med. Chem.* **38**, 212–215 (1995). doi:10.1021/jm00001a028 Medline

42. J. P. Burkhart, J. R. Koehl, S. Mehdi, S. L. Durham, M. J. Janusz, E. W. Huber, M. R. Angelastro, S. Sunder, W. A. Metz, P. W. Shum, T.-M. Chen, P. Bey, R. J. Cregge, N. P. Peet, Inhibition of human neutrophil elastase. 3. An orally active enol acetate prodrug. *J. Med. Chem.* **38**, 223–233 (1995). doi:10.1021/jm00002a003 Medline

43. P. D. Edwards, D. W. Andisik, C. A. Bryant, B. Ewing, B. Gomes, J. J. Lewis, D. Rakiewicz, G. Steelman, A. Strimpler, D. A. Trainor, P. A. Tuthill, R. C. Mauger, C. A. Veale, R. A. Wildonger, J. C. Williams, D. J. Wolanin, M. Zottola, Discovery and biological activity of orally active peptidyl trifluoromethyl ketone inhibitors of human neutrophil elastase. *J. Med. Chem.* **40**, 1876–1885 (1997). doi:10.1021/jm960819g Medline

44. K. Hemmi, I. Shima, K. Imai, H. Tanaka, European patent EP0494071 (1992).

45. T. Kinoshita, I. Nakanishi, A. Sato, T. Tada, True interaction mode of porcine pancreatic elastase with FR136706, a potent peptidyl inhibitor. *Bioorg. Med. Chem. Lett.* **13**, 21–24 (2003). doi:10.1016/S0960-894X(02)00852-1 Medline

46. F. von Nussbaum, V. M.-J. Li, Neutrophil elastase inhibitors for the treatment of (cardio)pulmonary diseases: Into clinical testing with pre-adaptive pharmacophores. *Bioorg. Med. Chem. Lett.* **25**, 4370–4381 (2015). doi:10.1016/j.bmcl.2015.08.049 Medline

47. F. von Nussbaum, V. M.-J. Li, S. Allerheiligen, S. Anlauf, L. Bärfacker, M. Bechem, M. Delbeck, M. F. Fitzgerald, M. Gerisch, H. Gielen-Haertwig, H. Haning, D. Karthaus, D. Lang, K. Lustig, D. Meibom, J. Mittendorf, U. Rosentreter, M. Schäfer, S. Schäfer, J. Schamberger, L. A. Telan, A. Tersteegen, Freezing the bioactive conformation to boost potency: The identification of BAY 85-8501, a selective and potent inhibitor of human neutrophil elastase for pulmonary diseases. *ChemMedChem* **10**, 1163–1173 (2015). doi:10.1002/cmdc.201500131 Medline

48. F. O. Gombert *et al.*., patent application WO2015096873 (2015).

49. T. J. Blench *et al.*., patent application WO2013037809 (2013).

50. L. Bergström, M. Lundkvist, H. Lönn, P. Sjö, patent application WO2008030158 (2008).

51. M. D. Shultz, The thermodynamic basis for the use of lipophilic efficiency (LipE) in enthalpic optimizations. *Bioorg. Med. Chem. Lett.* **23**, 5992–6000 (2013). doi:10.1016/j.bmcl.2013.08.030 Medline

52. A. Zervosen, R. Herman, F. Kerff, A. Herman, A. Bouillez, F. Prati, R. F. Pratt, J.-M. Frère, B. Joris, A. Luxen, P. Charlier, E. Sauvage, Unexpected tricovalent binding mode of boronic acids within the active site of a penicillin-binding protein. *J. Am. Chem. Soc.* **133**, 10839–10848 (2011). doi:10.1021/ja200696y Medline

53. M. Groll, C. R. Berkers, H. L. Ploegh, H. Ovaa, Crystal structure of the boronic acid-based proteasome inhibitor bortezomib in complex with the yeast 20S proteasome. *Structure* **14**, 451–456 (2006). doi:10.1016/j.str.2005.11.019 Medline

54. A. F. Kisselev, W. A. van der Linden, H. S. Overkleeft, Proteasome inhibitors: An expanding army attacking a unique target. *Chem. Biol.* **19**, 99–115 (2012). doi:10.1016/j.chembiol.2012.01.003 Medline

55. M. D. Greenhalgh, S. P. Thomas, Chemo-, regio-, and stereoselective iron-catalysed hydroboration of alkenes and alkynes. *Chem. Commun.* **49**, 11230–11232 (2013). doi:10.1039/c3cc46727a Medline

56. Y. Wen, J. Xie, C. Deng, C. Li, Selective synthesis of alkylboronates by copper(I)-catalyzed borylation of allyl or vinyl arenes. *J. Org. Chem.* **80**, 4142–4147 (2015). doi:10.1021/jo502606x Medline

57. S. Roesner, C. A. Brown, M. Mohiti, A. P. Pulis, R. Rasappan, D. J. Blair, S. Essafi, D. Leonori, V. K. Aggarwal, Stereospecific conversion of alcohols into pinacol boronic esters using lithiation-borylation methodology with pinacolborane. *Chem. Commun.* **50**, 4053–4055 (2014). doi:10.1039/C4CC00993B Medline

58. J. Yi, J.-H. Liu, J. Liang, J.-J. Dai, C.-T. Yang, Y. Fu, L. Liu, Alkylboronic esters from palladium- and nickel-catalyzed borylation of primary and secondary alkyl bromides. *Adv. Synth. Catal.* **354**, 1685–1691 (2012). doi:10.1002/adsc.201200136

59. J. Hu, H. Sun, W. Cai, X. Pu, Y. Zhang, Z. Shi, Nickel-catalyzed borylation of aryl- and benzyltrimethylammonium salts via C-N bond cleavage. *J. Org. Chem.* **81**, 14–24 (2016). doi:10.1021/acs.joc.5b02557 Medline

60. A. Chen, L. Ren, C. M. Crudden, Catalytic asymmetric hydrocarboxylation and hydrohydroxymethylation. A two-step approach to the enantioselective functionalization of vinylarenes. *J. Org. Chem.* **64**, 9704–9710 (1999). doi:10.1021/jo9914216

61. T. Furukawa, T. Akutagawa, H. Funatani, T. Uchida, Y. Hotta, M. Niwa, Y. Takaya, Cyclic dipeptides exhibit potency for scavenging radicals. *Bioorg. Med. Chem.* **20**, 2002–2009 (2012). doi:10.1016/j.bmc.2012.01.050 Medline

62. D. L. Boger, S. Miyazaki, O. Loiseleur, R. T. Beresis, S. L. Castle, J. H. Wu, Q. Jin, Thermal atropisomerism of aglucovancomycin derivatives: Preparation of (*M*,*M*,*M*)- and (*P*,*M*,*M*)-aglucovancomycins. *J. Am. Chem. Soc.* **120**, 8920–8926 (1998). doi:10.1021/ja981928i

63. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically—Ninth Edition* (Clinical and Laboratory Standards Institute, 2012).

64. S. Kokinaki, L. Leondiadis, N. Ferderigos, A novel and efficient method for cleavage of phenacylesters by magnesium reduction with acetic acid. *Org. Lett.* **7**, 1723–1724 (2005). doi:10.1021/ol050209n Medline

65. T. Miyazawa, S. Hiramatsu, Y. Tsuboi, T. Yamada, S. Kuwata, Studies of unusual amino acids and their peptides. XVII. The synthesis of peptides containing *N*-carboxymethyl amino acids. II. *Bull. Chem. Soc. Jpn.* **58**, 1976–1982 (1985). doi:10.1246/bcsj.58.1976

66. J. Liu, K. R. West, C. R. Bondy, J. K. M. Sanders, Dynamic combinatorial libraries of hydrazone-linked pseudo-peptides: Dependence of diversity on building block structure and chirality. *Org. Biomol. Chem.* **5**, 778–786 (2007). doi:10.1039/b617217b Medline

67. A. W. Buesking, V. Bacauanu, I. Cai, J. A. Ellman, Asymmetric synthesis of protected α-amino boronic acid derivatives with an air- and moisture-stable Cu(II) catalyst. *J. Org. Chem.* **79**, 3671–3677 (2014). doi:10.1021/jo500300t Medline

68. R. A. Copeland, *Evaluation of Enzyme Inhibitors in Drug Discovery: A Guide for Medicinal Chemists and Pharmacologists* (Wiley, 2005).

69. S. A. Wildman, G. M. Crippen, Prediction of physicochemical parameters by atomic contributions. *J. Chem. Inf. Comput. Sci.* **39**, 868–873 (1999). doi:10.1021/ci990307l