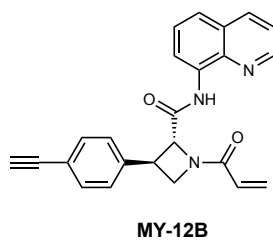
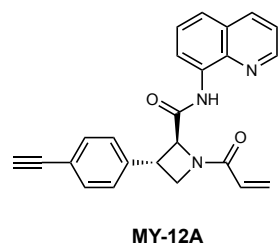
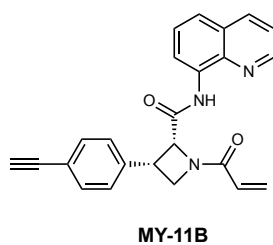
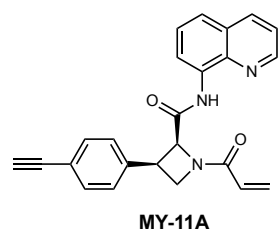
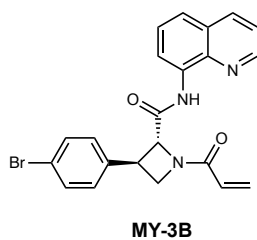
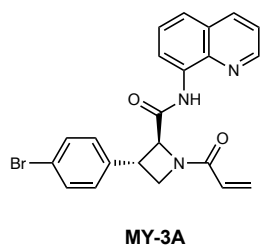
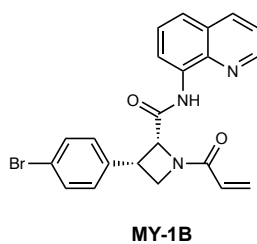
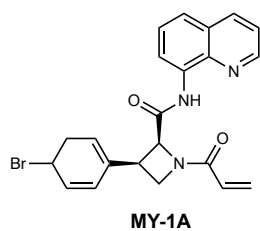


Complexoform-restricted covalent TRMT112 ligands that allosterically agonize METTL5

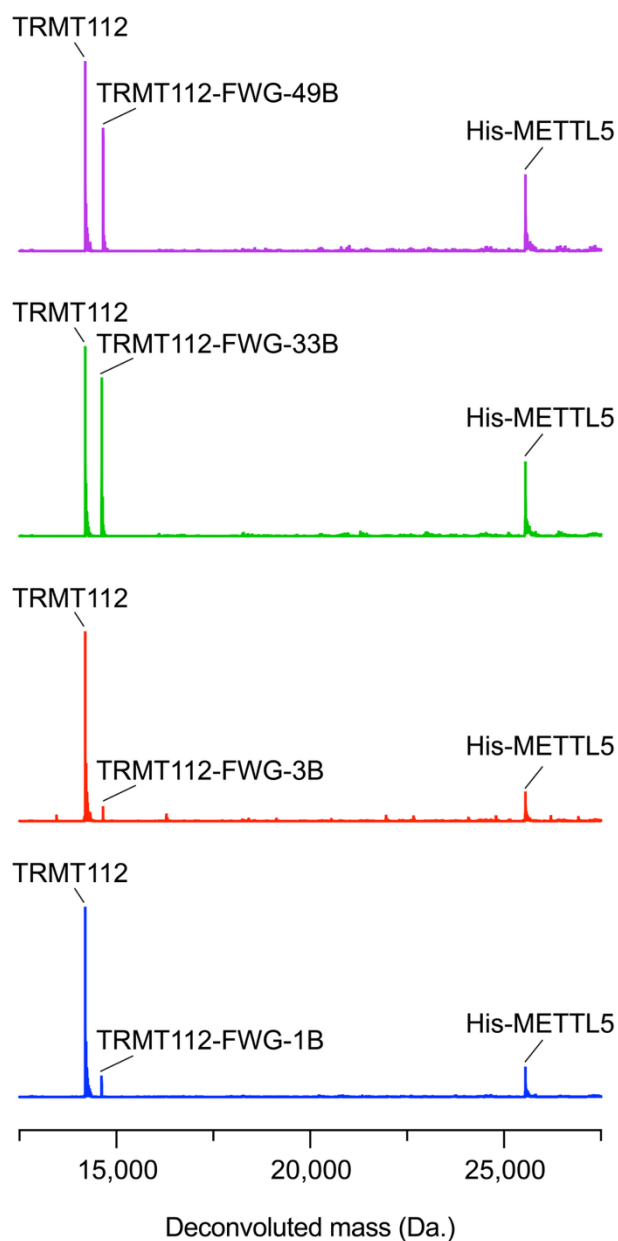
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Table of Content

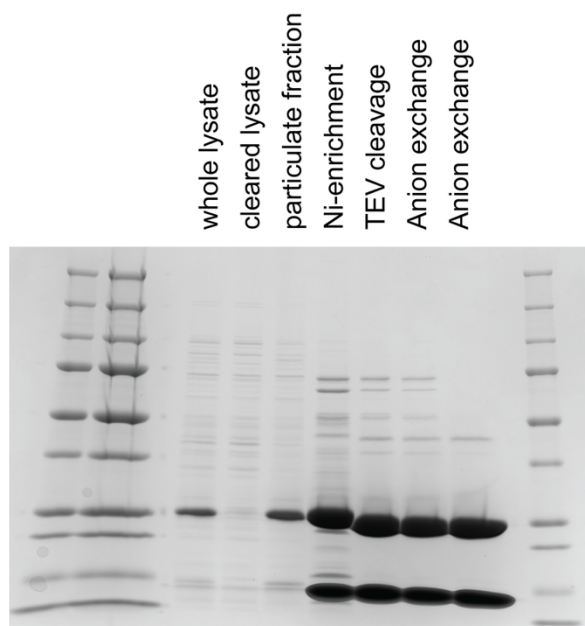
Supplementary Figures	p. 2 – 13
Supplementary Tables	p. 14 – 16
General Methods (Synthesis)	p. 17 – 18
Representative Procedures	p. 19 – 22
Analytical Data for intermediates and FWG-1A/B, FWG-2A/B, FWG-3A/B and FWG-4A/B	p. 23 – 37
Analytical Data for FWG-9A/B and FWG-11A/B	p. 38 – 41
Analytical Data for Intermediates and FWG-33A/B and FWG-49A/B	p. 42 – 48
Analytical Data for Intermediates and FWG-19B, FWG-21B and FWG-23B	p. 49 – 56
Analytical Data for Intermediates and FWG-35B, FWG-41B, FWG-43B, FWG-45B and FWG-47B	p. 57 – 73
Analytical Data for FWG-69B	p. 74
^1H , ^{13}C and ^{19}F NMR Spectra	p. 75 – 128
SFC Traces	p. 129 – 152
References	p. 153



Supplementary Fig. 1: Structures of (MY-1A, 1B, 3A, 3B, 11A, 11B, 12A, and 12B) azetidine acrylamide stereoprobes.



Supplementary Fig. 2: Representative deconvoluted MS of TRMT112:METTL5 with FWG-1B, 3B, 33B and 49B. Purified WT-TRMT112:WT-His-METTL5 complex (0.5 μ M) was treated with FWG-1B^a, 3B^a, 33B^b, or 49B^b (10 μ M) for 60 (^a) and 10 (^b) min, followed by addition of formic acid (0.5%). Data used to calculate $k_{\text{obs}}/[I]$ in Extended Data Fig. 8a.



Supplementary Fig. 3: Coomassie of the purification of tag-free TRMT112:METTL5.

Supplementary Table 1: %-Modified TRMT112:METTTL5 with FWG-1B, 3B, 33B and 49B measured by intact MS. Purified WT-TRMT112:WT-His-METTTL5 complex (0.5 μ M) was treated with FWG-1B, 3B, 33B, or 49B (10 μ M) for 60 (^a) and 10 (^b) min, followed by addition of formic acid (0.5%). The modification of TRMT112 with the ligand was quantified by intact MS. Data used to calculate $k_{\text{obs}}/[I]$ in Extended Data Fig. 8a.

Compound	Replicate	% Modified
FWG-1B ^a	1	10.0
	2	10.2
	3	7.9
FWG-3B ^a	1	7.4
	2	10.2
	3	4.3
FWG-33B ^b	1	45.7
	2	44.7
	3	40.1
FWG-49B ^b	1	38.5
	2	40.4
	3	40.7

Supplementary Table 2: Data collection and refinement statistics (molecular replacement).

TRMT112-METTL5 bound to SAM and FWG-33B PDB ID 9OHL	
Data collection	
Space group	P2 ₁ 2 ₁ 2 ₁
Cell dimensions	
<i>a</i> , <i>b</i> , <i>c</i> (Å)	56.7 70.6 84.6
α , β , γ (°)	90.0 90.0 90.0
Resolution (Å)	47.1-1.30 (1.34-1.30)*
<i>R</i> _{sym}	0.10 (0.94)
<i>R</i> _{pim}	0.04 (0.60)
<i>CC</i> _{1/2}	0.99 (0.33)
<i>I</i> / σ <i>I</i>	9.6 (0.9)
Completeness (%)	93.2 (60.3)
Redundancy	5.8 (3.1)
Refinement	
Resolution (Å)	1.30
No. reflections	80172 (5109)
<i>R</i> _{work} / <i>R</i> _{free}	0.171 / 0.205
No. atoms	
Protein	2596
Ligand/ion	63
Water	722
<i>B</i> -factors	
Protein	14
Ligand/ion	14
Water	32
R.m.s. deviations	
Bond lengths (Å)	0.24
Bond angles (°)	4.31

*Values in parentheses are for highest-resolution shell.

Supplementary Table 3: ORFs used in this manuscript.

WT-TRMT112-FLAG (<i>H. sapiens</i> , codon optimized for mammalian expression)	ATGAAACTGCTGACCCACAACCTGCTCAGCAGCCACG TGCGGGGCGTGGGCAGCAGAGGATTTCCACTGAGACT GCAGGCTACAGAGGTGCGGATCTGCCCCGTCGAGTTC AACCCCAACTTCGTGGCCAGAATGATCCCCAAGGTGG AATGGTCCGCCTTCCTGGAGGCCGCCGACAACCTGAG GCTGATCCAGGTGCCTAAGGGCCCTGTGGAAGGCTAC GAGGAAAACGAGGAATTCCTGCGGACCATGCATCACC TGCTGCTGGAAGTTGAGGTGATCGAGGGAACACTGCA GTGTCCTGAGAGCGGCAGAATGTTCCCTATTTCTAGAG GCATCCCTAATATGCTGCTGAGCGAGGAAGAAACCGA GTCTGGCTCGGGCTCGGGTGATTACAAAGACGATGAC GATAAGTGA
WT-HA-HEMK2 (<i>H. sapiens</i>)	ATGTACCCATACGATGTTCCAGATTACGCTGGTACCAT GGCAGGGGAGAACTTCGCTACGCCGTTCCACGGGCA CGTGGGCGCGCGGCCTTCAGCGACGTGTACGAGCC CGCGGAGGACACGTTTCTGCTTTTGAACGCGCTGGAG GCAGCGGCTGCCGAACCTGGCAGGAGTGGAATATGCC TGGAAGTAGGGTCAGGGTCTGGTGTAGTATCTGCATT CCTAGCCTCTATGATAGGCCCTCAGGCTTTGTACATGT GCACTGATATCAACCCTGAGGCAGCAGCTTGTAACCTA GAGACAGCACGCTGTAACAAAGTTCACATTCAACCAGT TATTACAGATTTGGTCAAAGGCTTGCTACCAAGATTGA CCGAAAAAGTTGATCTTCTGGTGTTTAATCCCCCCTAT GTAGTGACTCCACCTCAAGAGGTAGGAAGTCACGGAA TAGAGGCAGCTTGGGCTGGTGGCAAAAATGGTCGGGA AGTCATGGACAGGTTTTTTCCCTGGTTCCAGATCTCC TTTCACCAAAGGATTATTCTATTTAGTTACCATTAAG AAAACAACCCAGAAGAAATTTTGAAAATAATGAAGACA AAAGGTCTGCAAGGAACCACTGCACTTTCCAGACAAG

	CAGGCCAAGAACTCTTTCAGTCCTCAAGTTCACCAAG TCTTAG
WT-HA-METTL5 (<i>H. sapiens</i>)	ATGTACCCATACGATGTTCCAGATTACGCTGGTACCAT GAAGAAAGTAAGGCTTAAGGAACTAGAGAGTCGCCTG CAACAAGTGGATGGATTTGAAAAGCCCAAGCTACTTCT GGAACAGTATCCTACCAGGCCGCACATTGCAGCATGT ATGCTCTATACAATCCATAACACTTATGATGACATTGAA AATAAAGTCGTTGCAGATCTAGGATGTGGTTGTGGAGT ACTTAGCATCGGAACTGCAATGTTAGGAGCAGGGTTGT GTGTTGGATTTGACATAGATGAAGACGCATTGGAATA TTTAATAGGAATGCAGAAGAGTTTGAGTTAACAAATATT GACATGGTTCAATGTGATGTGTGCTTATTATCTAACAG AATGTCCAAGTCATTCGATACAGTAATTATGAATCCTCC CTTTGGGACCAAAAATAATAAAGGGACAGATATGGCTT TTCTAAAGACTGCTTTGGAAATGGCAAGAACAGCAGTA TATTCCTTACACAAATCCTCAACTAGAGAACATGTTCAA AAGAAAGCTGCAGAATGGAAAATCAAGATAGATATTAT AGCAGAACTTCGATATGACCTGCCAGCATCATACAAGT TTCACAAAAAGAAATCAGTGGACATTGAAGTGGACCTA ATTCGGTTTTTCCTTTTGA
WT-HA-BUD23 (<i>H. sapiens</i>)	ATGTACCCATACGATGTTCCAGATTACGCTGGTACCAT GGCGTCCCGCGGCCGCGTCCGGAGCATGGCGGACC CCCAGAGCTGTTTTATGACGAGACAGAAGCCCGGAAA TACGTTTCGCAACTCACGGATGATTGATATCCAGACCAG GATGGCTGGGCGAGCATTGGAGCTTCTTTATCTGCCA GAGAATAAGCCCTGTTACCTGCTGGATATTGGCTGTGG CACTGGGCTGAGTGGAAGTTATCTGTCAGATGAAGGG CACTATTGGGTGGGCCTGGATATCAGCCCTGCCATGC TGGATGAGGCTGTGGACCGAGAGATAGAGGGAGACCT

	GCTGCTGGGGGATATGGGCCAGGGCATCCCATTCAAG CCAGGCACATTTGATGGTTGCATCAGCATTTCTGCTGT GCAGTGGCTCTGTAATGCTAACAAGAAGTCTGAAAACC CTGCCAAGCGCCTGTACTGCTTTTTTGTCTTCTTTTTT CTGTTCTCGTCCGGGGATCCCGAGCTGTCCTGCAGCT GTACCCTGAGAACTCAGAGCAGTTGGAGCTGATCACA ACCCAGGCCACAAAGGCAGGCTTCTCCGGTGGCATGG TGGTAGACTACCCTAACAGTGCCAAAGCAAAGAAATTC TACCTCTGCTTGTTTTCTGGGCCTTCGACCTTTATACCA GAGGGGCTGAGTGAAAATCAGGATGAAGTTGAACCCA GGGAGTCTGTGTTACCAATGAGAGGTTCCCATTAAG GATGTCGAGGCGGGGAATGGTGAGGAAGAGTCGGGC ATGGGTGCTGGAGAAGAAGGAGCGGCACAGGCGCCA GGGCAGGGAAGTCAGACCTGACACCCAGTACACCGG CCGCAAGCGCAAGCCCCGCTTCTAA
His-METTL5 (<i>H. sapiens</i> , codon optimized for <i>E.</i> <i>coli</i> expression)	ATGCACCACCACCACCACCACGAAAATTTGTATTTCCA GTCAATGAAGAAGGTACGTCTGAAGGAGCTTGAATCC CGTCTTCAGCAAGTGGACGGTTTTTGAGAAACCGAAGC TGTTGCTGGAGCAGTATCCAACGCGCCCGCATATCGC AGCTTGTATGCTGTATACTATCCACAACACCTATGACG ACATTGAGAATAAAGTAGTCGCAGATTTGGGTTGTGGA TGCGGAGTTCTGAGTATCGGGACGGCGATGCTTGGAG CCGGTTTGTGTGTGGGGTTTCGATATCGATGAGGACGC ACTGGAAATTTTAAACCGCAACGCGGAAGAGTTTGAAT TGACTAACATTGACATGGTGCAATGCGACGTTTGTCTT TTAAGTAATCGTATGAGCAAGTCATTTGACACTGTTATT ATGAACCCACCTTTTCGGAATAAAAATAACAAAGGGAC CGATATGGCGTTCCTGAAGACGGCCCTTGAGATGGCC CGCACAGCCGTATATTCCCTTCACAAGAGCTCTACCCG TGAACACGTTTCAGAAGAAAGCCGCTGAGTGGAAGATT

	AAGATTGACATTATCGCTGAGCTTCGTTATGACCTGCC AGCCTCATATAAATTTTCATAAAAAGAAGTCCGTGGATAT TGAAGTTGATTTGATCCGCTTCAGTTTTTGA
TRMT112 (<i>H. sapiens</i> , codon optimized for <i>E.</i> <i>coli</i> expression)	ATGAAGCTGCTGACGCACAATTTACTTTCATCACATGT CCGCGGAGTCGGCTCCCGTGGGTTTCCGCTGCGCTTA CAAGCAACTGAAGTCCGCATCTGTCCTGTCGAATTTAA TCCTAATTTTCGTCGCTCGTATGATCCCAAAGTTGAGT GGAGTGCATTTCTGGAAGCAGCGGACAACCTGCGTCT GATTCAGGTCCCTAAAGGACCTGTCGAAGGATACGAA GAAAACGAAGAATTTTTACGCACCATGCACCATCTGTT ACTGGAAGTCGAGGTGATCGAGGGAACCTTGCAGTGC CCAGAATCTGGGCGCATGTTCCCCATTTCCCGCGGCA TCCCTAACATGCTTCTTTCCGAAGAGGAGACCGAATCT TGA

Supplementary Table 4: Antibodies used in this study.

Primary antibodies	Species	Supplier	Dilution
FLAG® (HRP) (M2)	N/A, monoclonal	Sigma-Aldrich: A8592	1:5,000
β-Actin Antibody (C4)	N/A, monoclonal	Santa Cruz: sc-47778	1:5,000
GAPDH (HRP) (D16H11)	N/A, monoclonal	Cell signaling: 8884	1:2,000
HA (HRP) (6E2)	N/A, monoclonal	Cell signaling: 2999	1:2,000
Vinculin (E1E9V) (HRP)	N/A, monoclonal	Cell signaling: 18799	1:2,000
TRMT112 (F-7)	mouse, monoclonal	Santa Cruz: sc-398481	1:1,000
METTL5	rabbit, polyclonal	Proteintech: 16791-1-AP	1:2,000
BUD23	rabbit, polyclonal	Proteintech: 28192-1-AP	1:3,000
THUMPD3	rabbit, polyclonal	Proteintech: 19807-1-AP	1:2,000
N6AMT1	rabbit, polyclonal	Proteintech: 16211-1-AP	1:1,000
TRMT11	rabbit, polyclonal	Proteintech: 17555-1-AP	1:1,000
THUMPD2 (D1)	mouse, monoclonal	Santa Cruz: sc-393018	1:500
ALKBH8	rabbit, polyclonal	Sigma-Aldrich: HPA061514	1:500
Secondary antibodies	Species	Supplier	Dilution
anti-mouse IgG (HRP)	N/A, monoclonal	Cell signaling: 7076	1:2,000
anti-rabbit IgG (HRP)	N/A, monoclonal	Santa Cruz: sc-2357	1:5,000

Supplementary Table 5: Fractionation of TMT¹⁶-plex into 10 fractions.

Fraction Number	Acetonitrile (%)	Combined into Fraction
1	7.5	1
2	10.0	2
3	12.5	3
4	15.0	4
5	17.5	5
6	20.0	6
7	22.5	7
8	25.0	8
9	27.5	9
10	30.0	10
11	32.5	1
12	35.0	2
13	37.5	3
14	40.0	4
15	42.5	5
16	45.0	6
17	47.5	7
18	50.0	8
19	52.5	9
20	55.0	10
21	57.5	1
22	60.0	2
23	62.5	3
24	65.0	4
25	67.5	5
26	70.0	6
27	72.5	7

28	75.0	8
29	80.0	9
30	95.0	10

Supplementary Table 6: Fractionation of TMT¹⁰-plex into 5 fractions.

Fraction Number	Acetonitrile (%)	Combined into Fraction
1	7.5	1
2	10.0	2
3	12.5	3
4	15.0	4
5	17.5	5
6	20.0	1
7	25.0	2
8	30.0	3
9	35.0	4
10	40.0	5
11	45.0	1
12	50.0	2
13	55.0	3
14	80.0	4
15	95.0	5

Supplementary Table 7: HPLC fractionation gradient for cysteine-directed ABPP.

Time (min)	Acetonitrile (%)	Time (min)	Acetonitrile (%)
0 - 2	0	80 - 85	80
2 - 3	0 - 13	85 - 86	0
3 - 60	13 - 42	86 - 91	0
60 - 61	42 - 100	91 - 94	0 - 13
61 - 65	100	94 - 96	13 - 80
65 - 66	100 - 0	96 - 101	80
66 - 75	0	101 - 102	80 - 0
75 - 78	0 - 13	102 - 115	0
78 - 80	13 - 80		

Supplementary Table 8: 96-well recombination for cysteine-directed ABPP.

A1	A2	...	A12
B1	B2	...	B12
...	...	...	...
H1	H2	...	H12
Fraction 1	Fraction 2	...	Fraction 12
(A1 + B1 + ... + H1)	(A2 + B2 + ... + H2)		(A12 + B12 + ... + H12)

Supplementary Table 9: Fractionation of TMT¹⁶-plex into 3 fractions.

Fraction Number	Acetonitrile (%)	Combined into Fraction
1	7.5	1
2	12.5	2
3	15.0	3
4	20.0	1
5	25.0	2
6	30.0	3
7	35.0	1
8	60.0	2
9	95.0	3

General Methods (Synthesis)

The following commercially available reagents were purchased from Sigma Aldrich: $[\text{Rh}(\text{cod})\text{OH}]_2$, aq. CsOH (50 wt%), $[\text{Rh}(\text{PPh}_3)_3\text{Cl}]$, Cs_2CO_3 , HBpin, KHMDS solution in toluene (0.5 M), THF ($\geq 99.9\%$, anhydrous, inhibitor-free), DMF ($\geq 99.8\%$, anhydrous), Pd/C, pyridine (anhydrous, 99.8%), trifluoroacetic acid, dichloromethane (anhydrous, $\geq 99.8\%$, contains 40-150 ppm amylene as stabilizer), ethyl acetate (anhydrous, 99.8%), *N,N*-diisopropylethylamine ($\geq 99\%$), acryloyl chloride ($\geq 97\%$, contains ~ 400 ppm phenothiazine as stabilizer). (*S*)-Segphos and (*R*)-Segphos were bought from TCI. Boronic acids and esters were bought from Combi-blocks. All listed commercially available reagents were used without further purification. Allyl chloride ($\pm$)-**1** was synthesized according to literature protocols.¹

Preparative thin layer chromatography (prep. TLC) was performed on TLC silica gel 60G F₂₅₄ 25 glass plates (60F-254). Normal phase automated medium-pressure chromatography (MPLC) was performed on Teledyne ISCO CombiFlash NextGen 300+ using RediSep Gold® or Silver® cartridges. Reverse-phase automated medium-pressure chromatography (RP-MPLC) was performed on Teledyne ISCO CombiFlash NextGen 300+ using RediSep Gold® Reverse-phase C18 cartridges. Reverse-phase automated high-pressure chromatography (RP-HPLC) was performed on Teledyne ISCO ACCQPrep HP150 system using a RediSep® Prep C18 Column (20 mm x 150 mm).

Nuclear magnetic resonance (NMR) spectroscopy measurements were carried out at room temperature. NMR spectra were recorded on the following instruments: Bruker AVIII HD 600 MHz NMR (equipped with 5 mm CPQCI and 1.7 mm CPTCI CryoProbes), Bruker AVIII HD 600 MHz NMR (equipped with 5 mm CPDCH CryoProbe), Bruker AV NEO 500 MHz NMR (equipped with 5 mm BBFO Probe) or Bruker AV NEO 399 MHz NMR (equipped with 5 mm BBFO Probe). Chemical shifts (δ) are reported in ppm relative to the residual solvent peak (CHCl_3 , 7.26 ppm for ^1H NMR and 77.16 ppm for ^{13}C NMR) with corresponding coupling constants (*J*) in Hertz (Hz) and apparent multiplicities (i.e., s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, app, or a combination of these multiplicities). The ^{19}F chemical shifts are not referenced.

Mass measurements using high-resolution mass spectrometry (HRMS) were performed on a Waters Xevo G2-XS TOF instrument calibrated against sodium formate clusters and using a LeuEnk lockmass. Expected monoisotopic masses were calculated using MassLynx 4.1 and the *m/z* values for calibrant and lockmass were MassLynx-default values.

Chiral SFC (supercritical fluid chromatography) separations were conducted on a Waters Acquity UPC2 system using Daicel columns as stationary phase and Waters Empower software. Racemic samples of (±)-**3**, (±)-**41**, (±)-**52**, (±)-**55**, (±)-**58** and (±)-**61** were obtained by following **Procedure A** using *rac*-BINAP instead of Segphos. Racemic samples of **FWG-1A/B**, **FWG-2A/B**, **FWG-3A/B**, **FWG-4A/B**, **FWG-9A/B**, **FWG-11A/B**, **FWG-33A/B** and **FWG-49A/B** were obtained by mixing both enantiomers in a 1:1 ratio.

The absolute and relative stereochemistry was initially assigned by analogy to previous literature reports.^{1,2} Our protein co-crystal structure confirms this stereochemistry for **FWG-33B**.

All final compounds were >95% pure by LC-MS (UV) and showed >95% ee, either as intermediates, as final compounds or both.

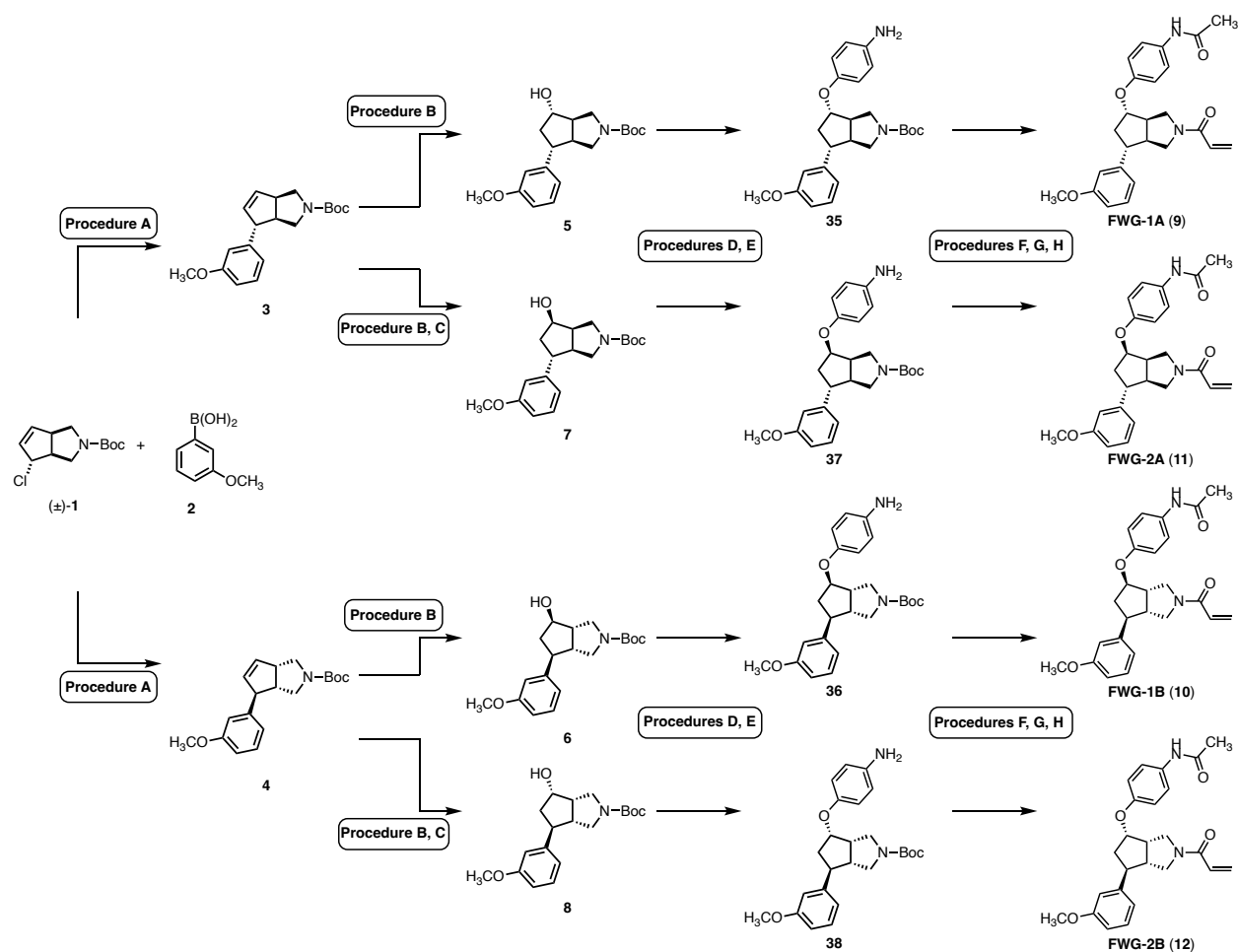


Figure S1: Representative synthesis scheme for bicyclopyrrolidine acrylamides.

Representative synthetic procedures corresponding to the transformations shown in Fig. S1 are found below. Analytical data is provided for specific compounds.

Procedure A

This is a representative procedure on a 4 mmol scale:

[Rh(cod)OH]₂ (45.6 mg, 0.1 mmol, 2.5 mol%) and (*S*)-Segphos (146 mg, 0.24 mmol, 6.0 mol%) were added to a 50 mL round bottom flask, sealed with a rubber septum under a N₂ atmosphere, dissolved in THF (7.2 mL) and stirred at room temperature. CsOH (50 wt% aq. solution, 700 μ L, 4.0 mmol, 1.0 eq) was added and the mixture was heated to 60 $^{\circ}$ C. After 30 min, a solution (or suspension) of boronic acid (or pinacol ester) (12.0 mmol, 3.0 eq) and allylic chloride ($\pm$)-1 (4.0 mmol, 1.0 eq) in THF (8.8 mL) and H₂O (2.0 mL) was added via syringe and the flask was rinsed with THF (2.0 mL). The resulting mixture was then stirred at 60 $^{\circ}$ C overnight. The mixture was then cooled to room temperature before SiO₂ (2 g) was added and the solvents were removed

under reduced pressure. Purification by automated medium pressure liquid chromatography (hexane:EtOAc 100:0 to 60:40) afforded the desired product **3**.

Procedure B

This is a representative procedure on a 2.95 mmol scale:

A mixture of **3** (2.95 mmol, 1.0 eq), Cs₂CO₃ (961 mg, 2.95 mmol, 1.0 eq) and [Rh(PPh₃)₃Cl] (273 mg, 0.295 mmol, 10 mol%) were added to a 25 mL round bottom flask, sealed with a rubber septum under a N₂ atmosphere, suspended in THF (5.9 mL) and stirred at room temperature. HBpin (860 µL, 5.9 mmol, 2.0 eq) were added dropwise and the mixture was stirred at r.t. overnight. The mixture was then cooled to 0 °C. An aq. solution of H₂O₂ (3.0 mL), followed by a 2 N solution of NaOH (7.3 mL) were added and the resulting mixture was stirred for 1 h. The reaction mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (25 mL), dried over MgSO₄ and concentrated under reduced pressure. Purification by automated medium pressure liquid chromatography (hexane:EtOAc 100:0 to 50:50) afforded the desired product **5**.

Procedure C

This is a representative procedure on a 750 µmol scale:

A mixture of **5** (750 µmol, 1.0 eq), PPh₃ (392 mg, 1.5 mmol, 2.0 eq) and 4-nitrobenzoic acid (250 mg, 1.5 mmol, 2.0 eq) were added to a 25 mL round bottom flask, sealed with a rubber septum under a N₂ atmosphere, and dissolved in dry THF (6.0 mL). The solution was cooled to 0 °C and diisopropyl azodicarboxylate (300 µL, 1.5 mmol, 2.0 eq) were added dropwise. The mixture was allowed to reach r.t. overnight. An aq. solution of NaHCO₃ (20 mL) was added. The reaction mixture was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO₄ and concentrated under reduced pressure. Purification by automated medium pressure liquid chromatography (hexane:EtOAc 100:0 to 50:50) afforded a mixture containing the 4-nitrobenzoic ester (LC-MS). This crude mixture was suspended in MeOH (7.0 mL) and H₂O (0.5 mL) in a 25 mL round bottom flask. K₂CO₃ (207 mg, 2.0 eq) was added and the resulting mixture was stirred under an open atmosphere at r.t. overnight. The mixture was concentrated under reduced pressure, resuspended in EtOAc (10 mL), filtered, and concentrated under reduced pressure. Purification by automated medium pressure liquid chromatography (hexane:EtOAc 100:0 to 50:50) afforded the desired product **7**.

Procedure D

This is a representative procedure on a 750 μmol scale:

Caution: This reaction is sensitive to the quality of DMF and exotherms during addition (cooling is required).

A solution of alcohol **6** (750 μmol , 1.0 eq) was stirred in dry DMF (3.8 mL) in a 2-dram vial equipped with a septum under a N_2 atmosphere. The mixture was cooled to 0 $^\circ\text{C}$ and solution of KHMDS in toluene (0.5 M, 2.3 mL, 1.13 mmol, 1.5 eq) was added dropwise. After 10 min, 4-nitrofluorobenzene (95 μL , 900 μmol , 1.2 eq) was added dropwise. The reaction mixture was allowed to reach r.t. overnight. Then, a sat. aq. solution of NaHCO_3 (2 mL), followed by H_2O (3 mL) were added. The mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO_4 and concentrated under reduced pressure. Purification by automated medium pressure liquid chromatography (hexane:EtOAc 100:0 to 50:50) afforded the desired product **32**.

Procedure E

This is a representative procedure on a 100 μmol scale:

Caution: We noticed that extended reaction times (overnight) give lower yields of the desired anilines.

A solution of nitrobenzene **31** (262 μmol , 1.0 eq) in MeOH (5.2 mL) was added to Pd/C (12 mg, 10wt%) in a 10 mL flask, sealed with a rubber septum under a N_2 atmosphere. A balloon filled with H_2 was then attached and bubbled through the reaction mixture for 15 min. The reaction mixture was then sealed and allowed to continue incubating under the H_2 atmosphere for the indicated amount of time. The reaction mixture was then filtered over Celite and concentrated under reduced pressure. The product was either used crude without any additional purification or purified by automated medium pressure liquid chromatography (hexane:EtOAc 100:0 to 30:70) to afford aniline **35**.

Procedure F1

This is a representative procedure on a 50 μmol scale:

Pyridine (140 μL , 1.7 mmol, 35 eq.) and acetic anhydride (95 μL , 1.0 mmol, 20 eq.) were added to aniline **35** (50 μmol , 1.0 eq) in 1-dram vial and the mixture was stirred at r.t. overnight. The reaction mixture was concentrated by blowing an airflow over the solution, diluted with a sat. aq. solution of NaHCO_3 (2 mL) and H_2O (3 mL). The mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO_4 and

concentrated under reduced pressure. The product was used crude without any additional purification step.

Procedure F2

This is a representative procedure on a 50 μmol scale:

A mixture of hexafluorophosphate azabenzotriazole tetramethyl uronium (60 μmol , 1.2 eq) and carboxylic acid (55 μmol , 1.1 eq) and *N,N*-diisopropylethylamine (16 μL , 125 μmol , 2.5 eq) in dichloromethane (330 μL) was stirred for 10 min at r.t. under an open atmosphere in a 1-dram vial. Then, a solution of aniline **35** (50 μmol , 1.0 eq) in dichloromethane (170 μL) was added. The vial was flushed with N_2 and stirred overnight at r.t.. A sat. aq. solution of NaHCO_3 (2 mL) and then H_2O (3 mL) were added. The mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO_4 and concentrated under reduced pressure. The product was used crude without any additional purification step.

Procedure G

This is a representative procedure on a 50 μmol scale:

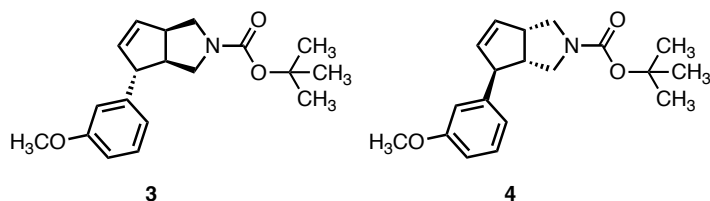
Trifluoroacetic acid (170 μL , 2.2 mmol, 22 eq.) was added to a solution of the crude product from **Procedure F1** or **F2** (100 μmol , 1.0 eq) in dichloromethane (330 μL) in a 1-dram vial. The mixture was stirred for 1 h at r.t.. The reaction mixture was then concentrated under blowing an airflow over the solution, followed by reduced pressure (<5 mbar). The product was used crude without any additional purification step.

Procedure H

This is a representative procedure on a 50 μmol scale (the eluent used in preparative chromatography is provided with the analytical data):

Dichloromethane (500 μL) was added to the crude product from **Procedure G** (50 μmol , 1.0 eq) in a 1-dram vial. *N,N*-diisopropylethylamine (34 μL , 200 μmol , 4 eq) was added, followed by dropwise addition of acryloyl chloride (8 μL , 100 μmol , 2 eq). The vial was flushed with a N_2 atmosphere and stirred for 2 h at r.t.. The reaction mixture was then directly loaded and purified by preparative thin-layer chromatography. Subsequent reverse-phase purification afforded the desired acrylamides.

Synthesis of **3** and **4**



Compound **3** was synthesized according to **Procedure A** (4.0 mmol scale) using 3-methoxyphenylboronic acid and was obtained as a pale-yellow oil (943 mg, 75%) with 99% ee.

The enantiomer **4** was synthesized according to **Procedure A** (4.0 mmol scale; using (*R*)-Segphos) using 3-methoxyphenylboronic acid and was obtained as a pale-yellow oil (916 mg, 73%) with 97% ee.

¹H NMR (600 MHz, CDCl₃, **3**) δ 7.22 (app. t, *J* = 7.9 Hz, 1H), 6.78 – 6.74 (app. dt, *J* = 8.3, 2.3 Hz, 2H), 6.70 (app. t, *J* = 2.1 Hz, 1H), 5.82 (s, 1H), 5.79 – 5.72 (m, 1H), 3.79 (s, 3H), 3.68 (dd, *J* = 11.2, 8.7 Hz, 2H), 3.53 – 3.19 (m, 4H), 2.77 (s, 1H), 1.46 (s, 9H) ppm.

¹H NMR (600 MHz, CDCl₃, **4**) δ 7.22 (app. t, *J* = 7.9 Hz, 1H), 6.79 – 6.74 (m, 2H), 6.70 (app. t, *J* = 2.1 Hz, 1H), 5.82 (dt, *J* = 5.7, 1.8 Hz, 1H), 5.76 (dd, *J* = 5.7, 2.2 Hz, 1H), 3.79 (s, 3H), 3.72 – 3.65 (m, 2H), 3.56 – 3.39 (m, 3H), 3.34 – 3.24 (m, 1H), 2.77 (dtd, *J* = 8.7, 5.9, 2.9 Hz, 1H), 1.46 (s, 9H) ppm.

¹³C NMR (151 MHz, CDCl₃, **3**) 160.0, 154.6, 146.0, 134.6*, 134.2*, 133.7*, 129.7, 119.7, 113.1, 111.7, 79.4, 57.9, 55.3 (3C), 52.5[†], 52.1[†], 51.0[†], 50.2[†], 49.9[†], 49.7[†], 48.8[†], 28.7 (3C) ppm (in total 4 additional rotameric peaks detected).

* rotamers; corresponding to 2C

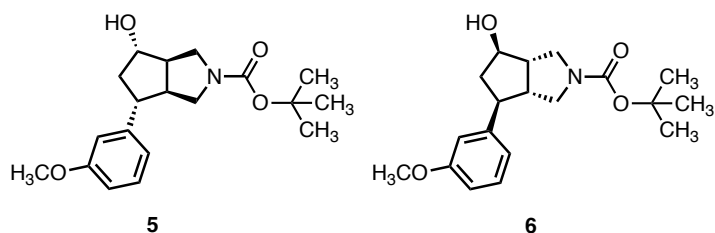
† rotamers; corresponding to 4C

HRMS (**3**) *m/z* calc. for C₁₄H₁₈NO⁺ [M-Boc+2H]⁺ 216.1388 found 216.1392.

HRMS (**4**) *m/z* calc. for C₁₉H₂₅NNaO₃⁺ [M+Na]⁺ 338.1732 found 338.1743.

SFC (Waters UPC2 SFC with a Daicel IA column (3 μm, 4.6x250 mm) under isocratic conditions (3.3 mL/min, 15% MeOH / CO₂, 1600 psi backpressure) at 30 °C) (*t_R* (**3**) = 1.70 min; *t_R* (**4**) = 2.48 min).

Synthesis of **5** and **6**



Compound **5** was synthesized according to **Procedure B** (2.95 mmol scale) and was obtained as a highly viscous pale-yellow oil (501 mg, 51%).

The enantiomer **6** was synthesized according to **Procedure B** (2.75 mmol scale) and was obtained as a colorless oil (440 mg, 48%).

¹H NMR (600 MHz, CDCl₃, **5**) δ 7.23 (app. t, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 6.82 (s, 1H), 6.77 (dd, *J* = 8.2, 2.5 Hz, 1H), 4.18 (s, 1H), 3.80 (s, 3H), 3.61 – 3.23 (m, 4H), 2.81 (s, 2H), 2.67 (dt, *J* = 8.6, 3.8 Hz, 1H), 2.52 (app. h, *J* = 4.2 Hz, 1H), 1.89 (ddd, *J* = 12.9, 11.0, 7.6 Hz, 1H), 1.46 (s, 9H) ppm (OH proton not detected).

¹H NMR (600 MHz, CDCl₃, **6**) 7.23 (app. t, *J* = 7.9 Hz, 1H), 6.89 – 6.84 (m, 1H), 6.82 (app. t, *J* = 2.1 Hz, 1H), 6.78 – 6.72 (m, 1H), 4.17 (dt, *J* = 7.9, 5.5 Hz, 1H), 3.80 (s, 3H), 3.52 (dd, *J* = 11.5, 8.7 Hz, 1H), 3.44 – 3.36 (m, 2H), 3.32 (dd, *J* = 11.5, 6.5 Hz, 1H), 2.88 – 2.74 (m, 2H), 2.67 (tt, *J* = 8.5, 4.9 Hz, 1H), 2.51 (dt, *J* = 12.6, 6.2 Hz, 1H), 2.35 – 2.05 (br. m, 1H), 1.89 (ddd, *J* = 13.1, 10.8, 7.5 Hz, 1H), 1.46 (s, 9H) ppm.

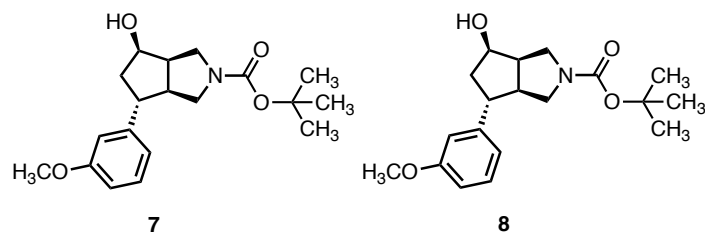
¹³C NMR (151 MHz, CDCl₃, **5**) 159.9, 155.0, 145.6, 129.7, 119.8, 113.5, 111.6, 79.6, 77.9, 55.3, 52.5[†], 51.6[†], 51.0[†], 50.5[†], 50.0[†], 49.7[†], 49.3, 44.7, 28.7 (3C) ppm (in total 2 additional rotameric peaks detected).

[†] rotamers; corresponding to 4C

HRMS (**5**) *m/z* calc. for C₁₄H₂₀NO₂⁺ [M-Boc+2H]⁺ 234.1494 found 234.1500.

HRMS (**6**) *m/z* calc. for C₁₄H₂₀NO₂⁺ [M-Boc+2H]⁺ 234.1494 found 234.1502.

Synthesis of **7** and **8**



Compound **7** was synthesized according to **Procedure C** (750 μ mol scale) and was obtained as a highly colorless oil (170 mg, 68%).

The enantiomer **8** was synthesized according to **Procedure C** (900 μ mol scale) and was obtained as a colorless oil (203 mg, 68%).

¹H NMR (600 MHz, CDCl₃, **7**) δ 7.20 (app. t, J = 7.9 Hz, 1H), 6.79 (d, J = 7.7 Hz, 1H), 6.76 – 6.66 (m, 2H), 4.44 (d, J = 6.9 Hz, 1H), 3.77 (s, 3H), 3.74 – 3.70 (m, 1H), 3.47 (dd, J = 11.2, 7.9 Hz, 1H), 3.41 – 3.03 (m, 4H), 2.87 (dt, J = 9.3, 4.2 Hz, 1H), 2.67 (d, J = 9.9 Hz, 1H), 2.25 (ddd, J = 13.5, 7.5, 3.0 Hz, 1H), 2.05 – 1.95 (m, 1H), 1.44 (s, 9H) ppm.

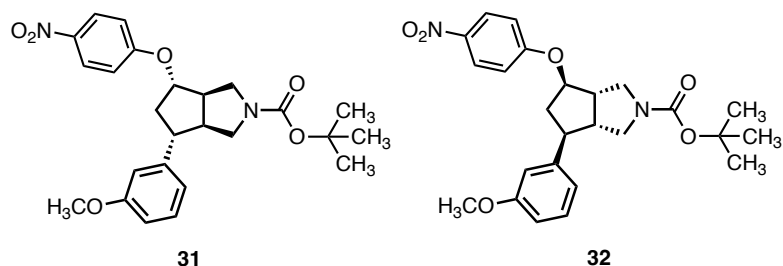
¹H NMR (600 MHz, CDCl₃, **8**) δ 7.23 (app. td, J = 7.6, 1.0 Hz, 1H), 6.81 (d, J = 7.6 Hz, 1H), 6.78 – 6.71 (m, 2H), 4.47 (qd, J = 5.2, 2.9 Hz, 1H), 3.80 (s, 3H), 3.76 – 3.69 (m, 1H), 3.48 (dd, J = 11.2, 8.0 Hz, 1H), 3.40 – 3.31 (m, 2H), 3.15 (dt, J = 10.7, 7.5 Hz, 1H), 2.90 (tt, J = 9.5, 5.1 Hz, 1H), 2.77 – 2.66 (m, 1H), 2.25 (ddd, J = 13.5, 7.4, 2.8 Hz, 1H), 2.11 – 1.95 (br. m, 2H), 1.45 (s, 9H) ppm.

¹³C NMR (151 MHz, CDCl₃, **7**) δ 159.9, 154.9, 146.4, 129.7, 119.7, 113.4, 111.4, 79.5, 73.9, 55.3 (3C), 52.2, 50.8, 49.1, 48.6, 45.4, 44.9, 28.7 (3C) ppm.

HRMS (**7**) m/z calc. for C₁₉H₂₇NNaO₄⁺ [M+Na]⁺ 356.1838 found 356.1851.

HRMS (**8**) m/z calc. for C₁₉H₂₇NNaO₄⁺ [M+Na]⁺ 356.1838 found 356.1838.

Synthesis of **31** and **32**



Compound **31** was synthesized according to **Procedure D** (300 μ mol scale) using 1-fluoro-4-nitrobenzene (1.1 eq) and KHMDS (1.1 eq) and was obtained as a yellow foam (109 mg, 80%).

Compound **32** was synthesized according to **Procedure D** (750 μ mol scale) using 1-fluoro-4-nitrobenzene and was obtained as a yellow foam (294 mg, 86%).

^1H NMR (600 MHz, CDCl_3 , **31**) δ 8.21 (d, J = 9.1 Hz, 2H), 7.25 (app. t, J = 8.5 Hz, 1H), 6.94 (d, J = 9.3 Hz, 2H), 6.86 (d, J = 7.9 Hz, 1H), 6.82 (app. t, J = 2.1 Hz, 1H), 6.78 (dd, J = 8.4, 2.5 Hz, 1H), 4.75 (t, J = 5.9 Hz, 1H), 3.81 (s, 3H), 3.81 – 3.68 (m, 1H), 3.56 – 3.24 (m, 3H), 3.01 – 2.90 (m, 3H), 2.85 (dt, J = 13.9, 6.8 Hz, 1H), 2.10 (ddd, J = 13.8, 10.5, 5.7 Hz, 1H), 1.48 (s, 9H) ppm.

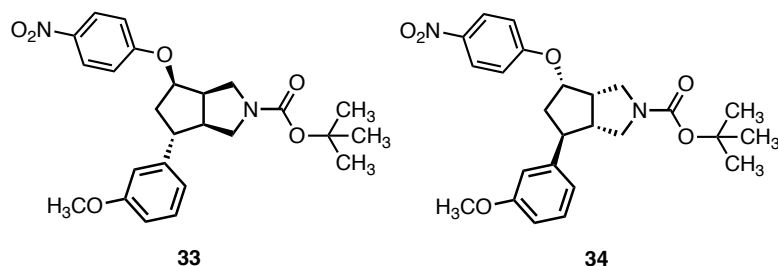
^1H NMR (500 MHz, CDCl_3 , **32**) 8.21 (d, J = 9.2 Hz, 2H), 7.25 (app. t, J = 7.9 Hz, 1H), 6.94 (d, J = 9.3 Hz, 2H), 6.86 (dd, J = 7.8, 1.2 Hz, 1H), 6.81 (t, J = 2.1 Hz, 1H), 6.78 (ddd, J = 8.2, 2.6, 1.0 Hz, 1H), 4.74 (td, J = 6.0, 2.5 Hz, 1H), 3.80 (s, 3H), 3.75 (dd, J = 11.4, 9.2 Hz, 1H), 3.45 (d, J = 11.1 Hz, 1H), 3.37 (ddd, J = 11.6, 6.6, 5.1 Hz, 2H), 3.05 – 2.88 (m, 3H), 2.85 (dt, J = 13.9, 6.9 Hz, 1H), 2.10 (ddd, J = 13.9, 10.0, 5.8 Hz, 1H), 1.48 (s, 9H) ppm.

^{13}C NMR (151 MHz, CDCl_3 , **31**) δ 162.9, 160.1, 154.9, 144.4, 141.7, 129.9, 126.2 (2C), 119.9, 115.4 (2C), 113.6, 111.9, 82.9, 79.9, 55.4 (3C), 50.7, 50.2, 49.3, 49.2, 41.9, 28.7 (3C) ppm (one aliphatic C not detected).

HRMS (**31**) m/z calc. for $\text{C}_{25}\text{H}_{30}\text{N}_2\text{NaO}_6^+$ $[\text{M}+\text{Na}]^+$ 477.2002 found 477.1991.

HRMS (**32**) m/z calc. for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_4^+$ $[\text{M}-\text{Boc}+2\text{H}]^+$ 355.1658 found 355.1671.

Synthesis of **33** and **34**



Compound **33** was synthesized according to **Procedure D** (1.2 mmol scale) using 1-fluoro-4-nitrobenzene and was obtained as a yellow foam (179 mg, 33%) along with unreacted *epi-4* (176 mg, 44%).

Compound **34** was synthesized according to **Procedure D** (500 μ mol scale) using 1-fluoro-4-nitrobenzene and was obtained as a yellow foam (139 mg, 60%).

^1H NMR (600 MHz, CDCl_3 , **33**) δ 8.19 (d, J = 9.2 Hz, 2H), 7.25 (app., J = 7.8 Hz, 1H), 6.96 (d, J = 9.3 Hz, 2H), 6.85 – 6.81 (m, 1H), 6.79 – 6.72 (m, 2H), 5.03 (td, J = 6.3, 2.7 Hz, 1H), 3.81 (s, 3H), 3.74 (dd, J = 11.7, 5.9 Hz, 1H), 3.55 – 3.35 (m, 3H), 3.22 (tt, J = 9.0, 6.1 Hz, 1H), 3.15 (dt, J = 10.7, 8.1 Hz, 1H), 2.92 – 2.78 (m, 1H), 2.47 (ddd, J = 14.1, 7.6, 2.7 Hz, 1H), 2.25 (ddd, J = 14.1, 10.8, 6.2 Hz, 1H), 1.46 (s, 9H) ppm.

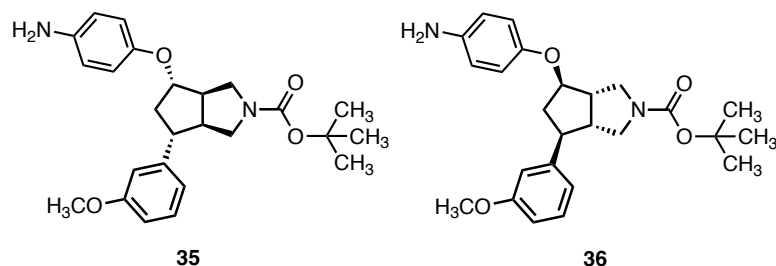
^1H NMR (600 MHz, CDCl_3 , **34**) δ 8.20 (d, J = 9.3 Hz, 2H), 7.26 (app. t, J = 7.8 Hz, 1H), 6.98 (d, J = 9.3 Hz, 2H), 6.84 (d, J = 7.5 Hz, 1H), 6.79 (d, J = 7.7 Hz, 2H), 5.05 (td, J = 6.3, 2.6 Hz, 1H), 3.82 (s, 3H), 3.75 (dt, J = 11.8, 5.6 Hz, 1H), 3.58 – 3.38 (m, 3H), 3.23 (ddd, J = 15.3, 9.0, 6.2 Hz, 1H), 3.16 (dt, J = 10.7, 8.1 Hz, 1H), 2.84 (qd, J = 8.5, 3.2 Hz, 1H), 2.48 (ddd, J = 14.2, 7.6, 2.6 Hz, 1H), 2.27 (ddd, J = 14.1, 10.7, 6.2 Hz, 1H), 1.48 (s, 9H) ppm.

^{13}C NMR (151 MHz, CDCl_3 , **33**) δ 163.1, 160.0, 154.6, 144.8, 141.7, 129.9, 126.1 (2C), 119.6, 115.3 (2C), 113.5, 111.7, 79.7, 79.6, 55.4 (3C), 51.1, 50.9, 48.4, 47.4, 45.3, 41.8, 28.7 (3C) ppm.

HRMS (**33**) m/z calc. for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_4^+$ [$\text{M-Boc}+2\text{H}$] $^+$ 355.1658 found 355.1660.

HRMS (**34**) m/z calc. for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_4^+$ [$\text{M-Boc}+2\text{H}$] $^+$ 355.1658 found 355.1666.

Synthesis of **35** and **36**



Compound **35** was synthesized according to **Procedure E** (262 μ mol scale; 3 h) and was obtained as a pale-brown foam (98 mg, 88%).

Compound **36** was synthesized according to **Procedure E** (225 μ mol scale; 3 h) and was obtained as a pale-brown foam (71 mg, 77%).

^1H NMR (600 MHz, CDCl_3 , **35**) δ 7.23 (s, 1H), 6.87 (d, J = 7.6 Hz, 1H), 6.84 (s, 1H), 6.77 (d, J = 8.1 Hz, 1H), 6.73 (d, J = 8.1 Hz, 2H), 6.64 (d, J = 8.2 Hz, 2H), 4.53 (s, 1H), 3.80 (s, 3H), 3.77 – 3.20 (m, 6H), 3.02 – 2.82 (m, 3H), 2.71 (dt, J = 13.4, 6.5 Hz, 1H), 2.12 – 2.06 (m, 1H), 1.47 (s, 9H) ppm.

^1H NMR (600 MHz, CDCl_3 , **36**) δ 7.23 (s, 1H), 6.87 (d, J = 7.6 Hz, 1H), 6.84 (s, 1H), 6.77 (d, J = 8.2 Hz, 1H), 6.73 (d, J = 8.3 Hz, 2H), 6.65 (d, J = 8.2 Hz, 2H), 4.53 (s, 1H), 3.80 (s, 3H), 3.76 – 3.21 (m, 6H), 2.98 – 2.82 (m, 3H), 2.72 (dt, J = 13.4, 6.6 Hz, 1H), 2.07 (ddt, J = 17.1, 9.5, 4.7 Hz, 1H), 1.47 (s, 9H) ppm.

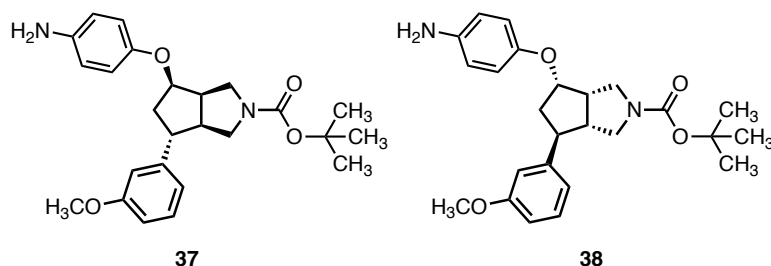
^{13}C NMR (151 MHz, CDCl_3 , **35**) δ 159.9, 154.9, 150.9, 145.1, 140.3, 129.7, 120.0, 117.1 (2C), 116.6 (2C), 113.5*, 113.2*, 112.0*, 111.8*, 83.0, 79.6, 55.3 (3C), 50.7, 50.3, 50.02, 49.97, 49.7, 49.1, 49.0, 42.3, 41.9, 28.6 (3C) ppm (in total for 2 additional rotameric peaks detected).

* rotamers; corresponding to 2C

HRMS (**35**) m/z calc. for $\text{C}_{25}\text{H}_{32}\text{N}_2\text{NaO}_4^+$ $[\text{M}+\text{Na}]^+$ 447.2260 found 447.2274.

HRMS (**36**) m/z calc. for $\text{C}_{25}\text{H}_{32}\text{N}_2\text{NaO}_4^+$ $[\text{M}+\text{Na}]^+$ 447.2260 found 447.2272.

Synthesis of **37** and **38**



Compound **37** was synthesized according to **General Procedure E** (178 μ mol scale; 3 h) and was obtained as a pale-brown foam (72 mg, 88%).

Compound **38** was synthesized according to **General Procedure E** (280 μ mol scale; 3 h) and was obtained as a pale-brown foam (90 mg, 75%).

^1H NMR (600 MHz, CDCl_3 , **37**) δ 7.25 – 7.18 (m, 1H), 6.82 (d, J = 7.6 Hz, 1H), 6.80 – 6.71 (m, 4H), 6.71 – 6.58 (m, 2H), 4.81 (td, J = 6.3, 3.0 Hz, 1H), 3.80 (s, 3H), 3.79 – 3.70 (m, 3H), 3.56 – 3.29 (m, 3H), 3.22 – 2.99 (m, 2H), 2.76 (s, 1H), 2.45 (s, 1H), 2.12 (ddd, J = 13.9, 10.3, 6.2 Hz, 1H), 1.46 (s, 9H) ppm.

^1H NMR (600 MHz, CDCl_3 , **38**) δ 7.25 – 7.16 (m, 1H), 6.82 (d, J = 7.7 Hz, 1H), 6.79 – 6.69 (m, 4H), 6.67 – 6.59 (m, 2H), 4.80 (td, J = 6.2, 3.0 Hz, 1H), 3.80 (s, 3H), 3.78 – 3.74 (m, 1H), 3.57 – 3.23 (m, 5H), 3.13 (ddt, J = 15.7, 8.6, 5.4 Hz, 2H), 2.76 (s, 1H), 2.45 (s, 1H), 2.12 (ddd, J = 13.9, 10.3, 6.2 Hz, 1H), 1.46 (s, 9H) ppm.

^{13}C NMR (151 MHz, CDCl_3 , **37**) δ 159.8, 154.7*, 154.6*, 151.3, 145.9*, 145.7*, 140.0*, 139.7*, 129.7, 119.6, 116.9*, 116.8*, 116.7*, 113.5*, 113.3*, 111.5*, 111.3*, 79.5 † , 79.2, 79.1 † , 55.3 (3C), 51.3 † , 51.2 † , 51.1 † , 50.5 † , 48.3 † , 48.2 † , 48.0 † , 47.2 † , 45.5 † , 45.1 † , 42.2 † , 41.5 † , 28.6 (3C) ppm (in total 13 additional rotameric peaks detected).

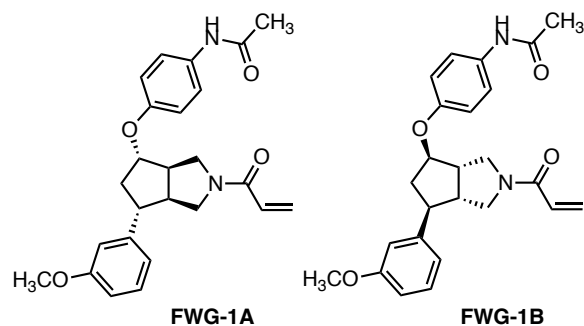
* rotamers; corresponding to 6C

† rotamers; corresponding to 7C

HRMS (**37**) m/z calc. for $\text{C}_{20}\text{H}_{25}\text{N}_2\text{O}_2^+$ [M-Boc+2H] $^+$ 325.1916 found 325.1927.

HRMS (**38**) m/z calc. for $\text{C}_{20}\text{H}_{25}\text{N}_2\text{O}_2^+$ [M-Boc+2H] $^+$ 325.1916 found 325.1919.

Synthesis of **FWG-1A (9)** and **FWG-1B (10)**



Compound **FWG-1A (9)** was synthesized from **35** according to **General Procedure F1** (50 μ mol scale), followed by **General Procedure G** and **General Procedure H** in CH_2Cl_2 and was obtained as a colorless solid (9.1 mg, 43% over 3 steps; prep. TLC hexane/EtOAc 25:75 and RP-HPLC acetonitrile/ H_2O) with 99% ee.

Compound **FWG-1B (10)** was synthesized from **36** according to **General Procedure F1** (150 μ mol scale), followed by **General Procedure G** and **General Procedure H** in CH_2Cl_2 and was obtained as a colorless solid (33 mg, 52% over 3 steps; prep. TLC EtOAc/MeOH 98:2 and RP-HPLC acetonitrile/ H_2O) with 99% ee.

^1H NMR (600 MHz, CDCl_3 , **FWG-1A**) δ 7.46 – 7.35 (m, 2H), 7.27 (s, 1H), 7.25 – 7.20 (m, 1H), 6.87 – 6.74 (m, 5H), 6.53 – 6.32 (m, 2H), 5.81 – 5.60 (m, 1H), 4.71 – 4.57 (m, 1H), 4.02 – 3.85 (m, 1H), 3.80 (s, 3H), 3.78 – 3.45 (m, 3H), 3.12 – 2.73 (m, 4H), 2.15 (s, 3H), 2.14 – 2.06 (m, 1H) ppm.

^1H NMR (600 MHz, CDCl_3 , **FWG-1B**) δ 7.47 – 7.37 (m, 3H), 7.24 (s, 1H), 6.91 – 6.74 (m, 5H), 6.50 – 6.37 (m, 2H), 5.70 (s, 1H), 4.64 (s, 1H), 4.02 – 3.87 (m, 1H), 3.80 (s, 3H), 3.73 – 3.48 (m, 3H), 3.11 – 2.72 (m, 4H), 2.16 (s, 3H), 2.12 (s, 1H) ppm.

^{13}C NMR (151 MHz, CDCl_3 , **FWG-1B**) δ 168.5, 165.1, 160.0, 154.5, 144.5*, 144.3*, 131.6, 129.9, 128.4, 128.3, 122.1, 119.9, 115.9, 113.5*, 113.3*, 112.1, 82.1[†], 81.9[†], 55.4 (3C), 51.2[†], 50.5[†], 50.1[†], 49.5[†], 49.1[†], 48.3[†], 42.3[†], 41.8[†], 24.5 (3C) ppm (in total 5 additional rotameric peaks detected).

* rotamers; corresponding to 7xC

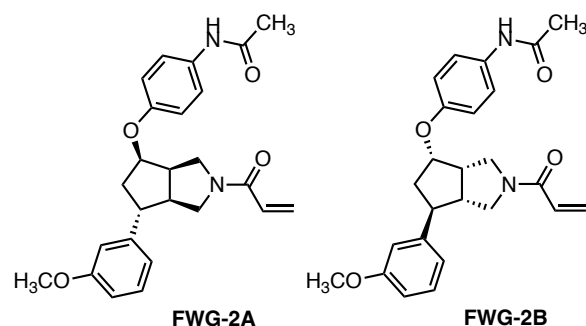
[†] rotamers; corresponding to 2xC

HRMS (FWG-1A) m/z calc. for $C_{25}H_{29}N_2O_4^+$ $[M+H]^+$ 421.2127 and 421.2121.

HRMS (FWG-1B) m/z calc. for $C_{25}H_{29}N_2O_4^+$ $[M+H]^+$ 421.2127 and 421.2128.

SFC (Waters UPC2 SFC with a Daicel IA column (3 μ m, 4.6x250 mm) under isocratic conditions (3.3 mL/min, 45% MeOH / CO₂, 1600 psi backpressure) at 30 °C) (t_R (**FWG-1A**) = 3.02 min; t_R (**FWG-1B**) = 3.64 min).

Synthesis of **FWG-2A (11)** and **FWG-2B (12)**



Compound **FWG-2A (11)** was synthesized from **37** according to **General Procedure F1** (50 μ mol scale), followed by **General Procedure G** and **General Procedure H** in EtOAc and was obtained as a colorless solid (11 mg, 54% over 3 steps; prep. TLC hexane/EtOAc 25:75 and RP-HPLC acetonitrile/H₂O) with >99% ee.

Compound **FWG-2B (12)** was synthesized from **38** according to **General Procedure F1** (100 μ mol scale), followed by **General Procedure G** and **General Procedure H** in EtOAc and was obtained as a colorless solid (18 mg, 56% over 3 steps; prep. TLC EtOAc and RP-HPLC acetonitrile/H₂O) with >99% ee.

¹H NMR (600 MHz, CDCl₃, **FWG-2A**) δ 7.52 – 7.36 (m, 3H), 7.25 – 7.21 (m, 1H), 6.89 – 6.72 (m, 5H), 6.51 – 6.41 (m, 1H), 6.40 – 6.33 (m, 1H), 5.67 (dt, J = 10.0, 2.3 Hz, 1H), 4.92 (dq, J = 6.2, 2.9 Hz, 1H), 4.04 – 3.96 (m, 1H), 3.85 – 3.73 (m, 4H), 3.71 – 3.54 (m, 2H), 3.30 – 3.16 (m, 1H), 3.11 (td, J = 11.3, 5.6 Hz, 1H), 2.93 – 2.79 (m, 1H), 2.51 – 2.41 (m, 1H), 2.23 – 2.10 (m, 4H) ppm.

¹H NMR (600 MHz, CDCl₃, **FWG-2B**) δ 8.06 – 7.83 (m, 1H), 7.41 (dd, J = 8.8, 7.0 Hz, 2H), 7.25 – 7.19 (m, 1H), 6.83 – 6.73 (m, 5H), 6.53 – 6.41 (m, 1H), 6.39 – 6.32 (m, 1H), 5.67 (dd, J = 10.2, 2.1 Hz, 1H), 4.97 – 4.87 (m, 1H), 4.00 (td, J = 12.6, 5.7 Hz, 1H), 3.87 – 3.71 (m, 4H), 3.69 – 3.51 (m, 2H), 3.28 – 3.15 (m, 1H), 3.14 – 3.06 (m, 1H), 2.93 – 2.77 (m, 1H), 2.53 – 2.38 (m, 1H), 2.21 – 2.10 (m, 4H) ppm.

¹³C NMR (151 MHz, CDCl₃, **FWG-2B**) δ 168.6, 164.7*, 164.7*, 160.0*, 159.9*, 154.4*, 154.2*, 144.93*, 144.89*, 131.9, 129.9*, 129.8*, 128.8*, 128.7*, 127.8*, 127.7*, 122.0*, 121.9*, 119.61*, 119.59*, 115.8*, 115.7*, 113.5*, 113.3*, 111.8*, 111.7*, 78.80[†], 78.77[†], 55.35[†], 55.33[†], 51.7[†], 51.6[†], 50.9[†], 49.9[†], 48.7[†], 48.3[†], 48.2[†], 46.5[†], 46.1[†], 45.4[†], 42.2[†], 41.6[†], 24.4 ppm (in total 20 additional rotameric peaks detected).

* rotamers; corresponding to 12xC

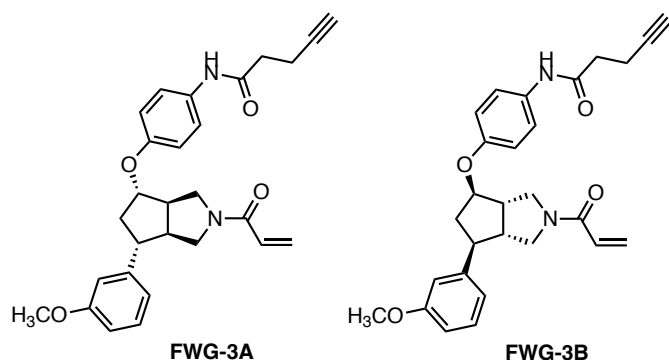
† rotamers; corresponding to 8xC

HRMS (FWG-2A) m/z calc. for $C_{25}H_{29}N_2O_4^+$ $[M+H]^+$ 421.2127 and 421.2121.

HRMS (FWG-2B) m/z calc. for $C_{25}H_{29}N_2O_4^+$ $[M+H]^+$ 421.2127 and 421.2133.

SFC (Waters UPC2 SFC with a Daicel IA column (3 μ m, 4.6x250 mm) under isocratic conditions (3.3 mL/min, 35% MeOH / CO₂, 1600 psi backpressure) at 30 °C) (t_R (**FWG-2A**) = 7.05 min; t_R (**FWG-2B**) = 8.41 min).

Synthesis of **FWG-3A (13)** and **FWG-3B (14)**



Compound **FWG-3A (13)** was synthesized from **35** according to **General Procedure F2** (50 μ mol scale), followed by **General Procedure G** and **General Procedure H** in CH_2Cl_2 and was obtained as a colorless solid (9.0 mg, 39% over 3 steps; prep. TLC hexane/EtOAc 25:75 and RP-HPLC acetonitrile/ H_2O) with >99% ee.

Compound **FWG-3B (14)** was synthesized from **36** according to **General Procedure F2** (100 μ mol scale), followed by **General Procedure G** and **General Procedure H** in EtOAc and was obtained as a colorless solid (26 mg, 56% over 3 steps; prep. TLC EtOAc and RP-HPLC acetonitrile/ H_2O) with 99% ee.

^1H NMR (600 MHz, CDCl_3 , **FWG-3A**) δ 7.50 – 7.38 (m, 3H), 7.25 – 7.19 (m, 1H), 6.90 – 6.74 (m, 5H), 6.51 – 6.32 (m, 2H), 5.74 – 5.67 (m, 1H), 4.69 – 4.57 (m, 1H), 4.01 – 3.86 (m, 1H), 3.83 – 3.78 (m, 3H), 3.78 – 3.44 (m, 3H), 3.13 – 2.98 (m, 1H), 2.96 – 2.72 (m, 3H), 2.66 – 2.53 (m, 4H), 2.18 – 2.08 (m, 1H), 2.05 (t, J = 2.5 Hz, 1H) ppm.

^1H NMR (600 MHz, CDCl_3 , **FWG-3B**) δ 7.88 – 7.80 (m, 1H), 7.44 (app. t, J = 8.5 Hz, 2H), 7.25 – 7.18 (m, 1H), 6.89 – 6.73 (m, 5H), 6.51 – 6.35 (m, 2H), 5.75 – 5.66 (m, 1H), 4.68 – 4.56 (m, 1H), 4.02 – 3.85 (m, 1H), 3.81 – 3.77 (m, 3H), 3.76 – 3.45 (m, 3H), 3.10 – 2.96 (m, 1H), 2.95 – 2.72 (m, 3H), 2.62 – 2.53 (m, 4H), 2.16 – 2.06 (m, 1H), 2.03 (t, J = 2.5 Hz, 1H) ppm.

^{13}C NMR (151 MHz, CDCl_3 , **FWG-3B**) δ 169.3, 165.1*, 165.02*, 159.96*, 160.0*, 154.43*, 154.35*, 144.5*, 144.2*, 131.6*, 131.5*, 129.9*, 129.8*, 128.5*, 128.34*, 128.27*, 128.25*, 122.07*, 122.01*, 119.86*, 119.84*, 116.0*, 115.8*, 113.5*, 113.2*, 112.09*, 112.01*, 83.1 † , 83.0 † , 82.2 † , 81.9 † , 69.67 † , 69.65 † , 55.34 † , 55.32 † , 51.2 † , 50.5 † , 50.4 † , 50.3 † , 50.1 † , 49.4 † , 49.2 † , 49.1 † , 48.3 † , 42.2 † , 41.7 † , 36.1 † , 15.0 ppm (in total 21 additional rotameric peaks detected).

* rotamers; corresponding to ^{13}C

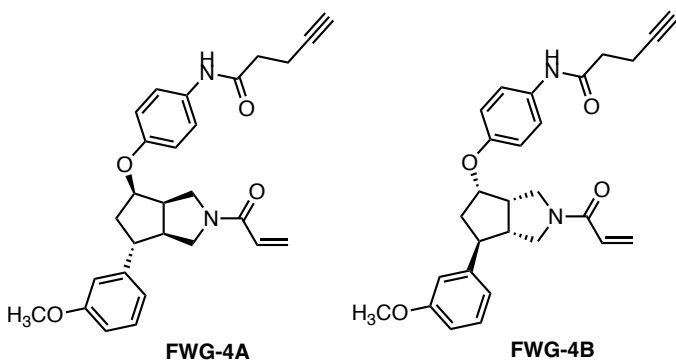
[†] rotamers; corresponding to 11C

HRMS (FWG-3A) m/z calc. for $C_{28}H_{31}N_2O_4^+$ $[M+H]^+$ 459.2284 found 459.2296.

HRMS (FWG-3B) m/z calc. for $C_{28}H_{31}N_2O_4^+$ $[M+H]^+$ 459.2284 found 459.2283.

SFC (Waters UPC2 SFC with a Daicel IA column (3 μ m, 4.6x250 mm) under isocratic conditions (3.3 mL/min, 50% MeOH / CO₂, 1600 psi backpressure) at 30 °C) (t_R (**FWG-3A**) = 3.18 min; t_R (**FWG-3B**) = 4.30 min).

Synthesis of **FWG-4A (15)** and **FWG-4B (16)**



Compound **FWG-4A (15)** was synthesized from **37** according to **General Procedure F2** (50 μ mol scale), followed by **General Procedure G** and **General Procedure H** in EtOAc and was obtained as a colorless solid (15 mg, 64% over 3 steps; prep. TLC hexane/EtOAc 25:75 and RP-HPLC acetonitrile/H₂O) with >99% ee.

Compound **FWG-4B (16)** was synthesized from **34** according to **General Procedure E** (100 μ mol scale; 17 h), followed by **General Procedure F2** (100 μ mol scale), **General Procedure G** and **General Procedure H** in EtOAc and was obtained as a colorless solid (17 mg, 30% over 4 steps; prep. TLC hexane/EtOAc 25:75 and RP-HPLC acetonitrile/H₂O) with >99% ee.

¹H NMR (600 MHz, CDCl₃, **FWG-4A**) δ 8.03 – 7.83 (m, 1H), 7.49 – 7.36 (m, 2H), 7.25 – 7.14 (m, 1H), 6.90 – 6.72 (m, 5H), 6.51 – 6.40 (m, 1H), 6.40 – 6.33 (m, 1H), 5.67 (dt, J = 10.4, 1.6 Hz, 1H), 4.91 (dq, J = 6.2, 3.0 Hz, 1H), 4.07 – 3.94 (m, 1H), 3.85 – 3.73 (m, 4H), 3.70 – 3.53 (m, 2H), 3.32 – 3.16 (m, 1H), 3.15 – 3.06 (m, 1H), 2.95 – 2.77 (m, 1H), 2.65 – 2.54 (m, 4H), 2.51 – 2.40 (m, 1H), 2.25 – 2.09 (m, 1H), 2.02 (dd, J = 3.9, 2.4 Hz, 1H) ppm.

¹H NMR (600 MHz, CDCl₃, **FWG-4B**) δ 8.07 – 7.80 (m, 1H), 7.61 – 7.36 (m, 2H), 7.25 – 7.17 (m, 1H), 6.92 – 6.68 (m, 5H), 6.59 – 6.41 (m, 1H), 6.40 – 6.29 (m, 1H), 5.67 (dt, J = 10.6, 1.4 Hz, 1H), 5.10 – 4.67 (m, 1H), 4.01 (td, J = 11.8, 5.7 Hz, 1H), 3.88 – 3.73 (m, 4H), 3.71 – 3.53 (m, 2H), 3.30 – 3.16 (m, 1H), 3.11 (ddt, J = 15.3, 10.6, 7.9 Hz, 1H), 2.94 – 2.77 (m, 1H), 2.65 – 2.54 (m, 4H), 2.50 – 2.40 (m, 1H), 2.22 – 2.10 (m, 1H), 2.03 – 2.00 (m, 1H) ppm.

¹³C NMR (151 MHz, CDCl₃, **FWG-4B**) δ 169.35*, 169.33*, 164.72*, 164.69*, 160.0*, 159.9*, 154.5*, 154.4*, 144.93*, 144.91*, 131.6*, 131.6*, 130.0*, 129.8*, 128.8*, 128.7*, 127.83*, 127.76*, 122.0*, 121.9*, 119.62*, 119.61*, 115.8*, 115.7*, 113.5*, 113.3*, 111.8*, 111.7*, 83.13[†], 83.08[†], 78.82[†], 78.80[†], 69.64[†], 69.57[†], 55.37[†], 55.35[†], 51.7[†], 51.6[†], 50.9[†], 49.9[†], 48.7[†], 48.3[†],

48.2[†], 46.5[†], 46.1[†], 45.4[†], 42.2[†], 41.6[†], 36.2, 15.0 ppm (in total 24 additional rotameric peaks detected).

* rotamers; corresponding to 14C

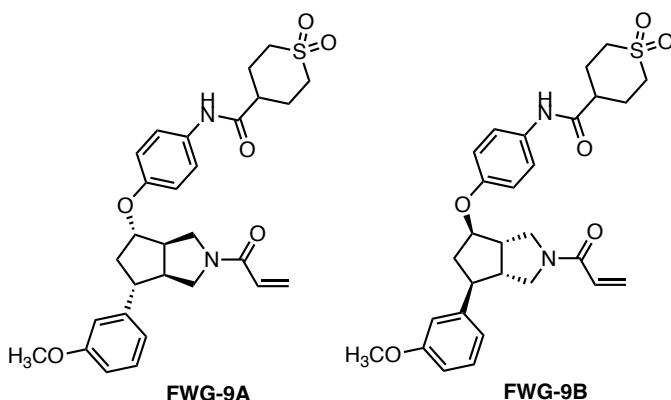
[†] rotamers; corresponding to 10C

HRMS (FWG-4A) m/z calc. for C₂₈H₃₁N₂O₄⁺ [M+H]⁺ 459.2284 found 459.2277.

HRMS (FWG-4B) m/z calc. for C₂₈H₃₁N₂O₄⁺ [M+H]⁺ 459.2284 found 459.2290.

SFC (Waters UPC2 SFC with a Daicel IA column (3 μm, 4.6x250 mm) under isocratic conditions (3.3 mL/min, 35% IPA / CO₂, 1600 psi backpressure) at 30 °C) (t_R (**FWG-4A**) = 7.78 min; t_R (**FWG-4B**) = 8.56 min).

Synthesis of **FWG-9A (39)** and **FWG-9B (17)**



Compound **FWG-9A (39)** was synthesized from **35** according to **General Procedure F2** (50 μ mol scale), followed by **General Procedure G** and **General Procedure H** in CH_2Cl_2 and was obtained as a colorless solid (19 mg, 69% over 3 steps; prep. TLC EtOAc/MeOH 95:5 and RP-HPLC acetonitrile/ H_2O) with >99% ee.

Compound **FWG-9B (17)** was synthesized from **36** according to **General Procedure F2** (50 μ mol scale), followed by **General Procedure G** and **General Procedure H** in EtOAc and was obtained as a colorless solid (17 mg, 63% over 3 steps; prep. TLC EtOAc/MeOH 95:5 and RP-HPLC acetonitrile/ H_2O) with >99% ee

^1H NMR (600 MHz, CDCl_3 , **FWG-9A**) δ 7.94 – 7.77 (m, 1H), 7.42 (dd, J = 8.8, 5.6 Hz, 2H), 7.25 – 7.18 (m, 1H), 6.94 – 6.71 (m, 5H), 6.54 – 6.33 (m, 2H), 5.79 – 5.66 (m, 1H), 4.62 (dt, J = 7.0, 3.5 Hz, 1H), 4.01 – 3.87 (m, 1H), 3.86 – 3.78 (m, 3H), 3.77 – 3.47 (m, 3H), 3.43 – 3.33 (m, 2H), 3.10 – 2.73 (m, 6H), 2.60 (td, J = 8.1, 4.1 Hz, 1H), 2.49 – 2.41 (m, 2H), 2.37 (ddt, J = 11.2, 8.1, 3.8 Hz, 2H), 2.17 – 2.05 (m, 1H) ppm.

^1H NMR (600 MHz, CDCl_3 , **FWG-9B**) δ 8.06 – 7.86 (m, 1H), 7.46 – 7.37 (m, 2H), 7.25 – 7.19 (m, 1H), 6.90 – 6.73 (m, 5H), 6.52 – 6.32 (m, 2H), 5.80 – 5.67 (m, 1H), 4.61 (td, J = 6.1, 2.1 Hz, 1H), 3.98 – 3.85 (m, 1H), 3.83 – 3.78 (m, 3H), 3.77 – 3.46 (m, 3H), 3.40 – 3.32 (m, 2H), 3.11 – 2.89 (m, 4H), 2.88 – 2.80 (m, 1H), 2.79 – 2.69 (m, 1H), 2.60 (qt, J = 7.4, 3.8 Hz, 1H), 2.51 – 2.41 (m, 2H), 2.40 – 2.30 (m, 2H), 2.20 – 2.06 (m, 1H) ppm.

^{13}C NMR (151 MHz, CDCl_3 , **FWG-9B**) δ 171.21*, 171.16*, 165.1*, 165.0*, 160.1*, 160.0*, 154.72*, 154.68*, 144.4*, 144.1*, 131.2*, 130.0*, 129.9*, 128.5*, 128.4*, 128.34*, 128.31*, 122.27*, 122.2*, 119.84*, 119.82*, 116.03*, 115.97*, 113.6*, 113.4*, 112.02*, 111.98*, 82.14 † ,

82.10[†], 55.37[†], 55.36[†], 51.1[†], 50.5[†], 50.4[†], 50.3[†], 50.1[†], 49.83[†], 49.80[†], 49.6[†], 49.2[†], 49.03[†], 49.00[†], 48.2[†], 42.3[†], 41.7[†], 40.9[†], 27.4 (2C) ppm (in total 22 additional rotameric peaks detected).

* rotamers; corresponding to 14C

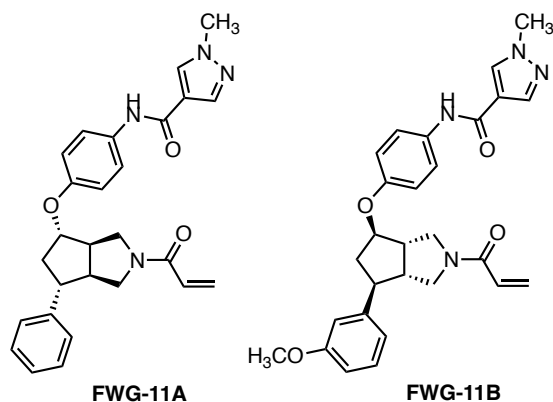
[†] rotamers; corresponding to 11C

HRMS (FWG-9A) m/z calc. for C₂₉H₃₅N₂O₆S⁺ [M+H]⁺ 539.2216 found 539.2228.

HRMS (FWG-9B) m/z calc. for C₂₉H₃₅N₂O₆S⁺ [M+H]⁺ 539.2216 found 539.2225.

SFC (Waters UPC2 SFC with a Daicel IK column (3 μm, 4.6x250 mm) under isocratic conditions (3.3 mL/min, 50% MeOH / CO₂, 1600 psi backpressure) at 30 °C) (t_R (**FWG-9B**) = 14.92 min; t_R (**FWG-9A**) = 16.52 min).

Synthesis of **FWG-11A (40)** and **FWG-11B (18)**



Compound **FWG-11A (40)** was synthesized from **35** according to **Procedure F2** (50 μ mol scale), followed by **Procedure G** and **Procedure H** in EtOAc and was obtained as a colorless solid (6.0 mg, 25% over 3 steps; prep. TLC EtOAc/MeOH 95:5 and RP-HPLC acetonitrile/H₂O) with 99% ee.

Compound **FWG-11B (18)** was synthesized from **32** according to **Procedure E** (100 μ mol scale, 2h), followed by **Procedure F2**, **Procedure G** and **Procedure H** in EtOAc and was obtained as a colorless solid (24 mg, 49% over 4 steps; prep. TLC EtOAc/MeOH EtOAc/MeOH 95:5 and RP-MPLC acetonitrile/H₂O) with >99% ee.

¹H NMR (600 MHz, CDCl₃, **FWG-11A**) δ 7.92 (s, 1H), 7.83 (s, 1H), 7.65 – 7.55 (m, 1H), 7.50 (t, J = 8.3 Hz, 2H), 7.25 – 7.19 (m, 1H), 6.92 – 6.74 (m, 5H), 6.53 – 6.34 (m, 2H), 5.71 (ddd, J = 15.3, 8.8, 3.5 Hz, 1H), 4.68 – 4.60 (m, 1H), 4.06 – 3.88 (m, 4H), 3.87 – 3.78 (m, 3H), 3.78 – 3.43 (m, 3H), 3.13 – 2.98 (m, 1H), 2.96 – 2.73 (m, 3H), 2.13 (tdd, J = 13.8, 10.1, 5.6 Hz, 1H) ppm.

¹H NMR (600 MHz, CDCl₃, **FWG-11B**) δ 8.01 – 7.81 (m, 3H), 7.50 (t, J = 9.7 Hz, 2H), 7.25 – 7.17 (m, 1H), 6.91 – 6.72 (m, 5H), 6.52 – 6.33 (m, 2H), 5.76 – 5.67 (m, 1H), 4.66 – 4.58 (m, 1H), 4.11 – 3.87 (m, 4H), 3.84 – 3.79 (m, 3H), 3.77 – 3.40 (m, 3H), 3.12 – 2.95 (m, 1H), 2.95 – 2.70 (m, 3H), 2.11 (qd, J = 13.2, 5.7 Hz, 1H) ppm.

¹³C NMR (151 MHz, CDCl₃, **FWG-11B**) δ 165.1*, 165.0*, 160.8, 160.04*, 159.97*, 154.5*, 154.4*, 144.5*, 144.2*, 138.3*, 138.2*, 132.3, 131.6*, 131.5*, 129.9*, 129.8*, 128.5*, 128.4*, 128.3 (2C), 122.5*, 122.4*, 119.88*, 119.86*, 119.2, 116.0*, 115.9*, 113.5*, 113.2*, 112.1*, 112.0*, 82.2[†], 81.9[†], 55.4, 51.2, 50.5[†], 50.4[†], 50.3[†], 50.1[†], 49.5[†], 49.2[†], 49.0[†], 48.3[†], 42.3[†], 41.7[†], 39.5 ppm (in total 19 additional rotameric peaks detected).

* rotamers; corresponding to 13C

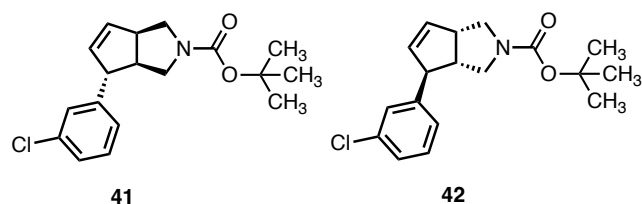
† rotamers; corresponding to 6C

HRMS (FWG-11A) m/z calc. for $C_{28}H_{31}N_4O_4^+$ $[M+H]^+$ 487.2345 found 487.2343.

HRMS (FWG-11B) m/z calc. for $C_{28}H_{31}N_4O_4^+$ $[M+H]^+$ 487.2345 found 487.2361.

SFC (Waters UPC2 SFC with a Daicel IK column (3 μ m, 4.6x250 mm) under isocratic conditions (3.3 mL/min, 50% MeOH / CO₂, 1600 psi backpressure) at 30 °C) (t_R (**FWG-11A**) = 3.35 min; t_R (**FWG-11B**) = 4.53 min).

Synthesis of **41** and **42**



Compound **41** was synthesized according to **Procedure A** (2.0 mmol scale) using 3-chlorophenylboronic acid) and was obtained as a colorless oil (506 mg, 79%) with 96% ee.

The enantiomer **42** was synthesized according to **Procedure A** (2.0 mmol scale; using (*R*)-Segphos) and 3-chlorophenylboronic acid) and was obtained as a colorless oil (543 mg, 85%) with 98% ee.

¹H NMR (600 MHz, CDCl₃, **41**) δ 7.22 (app. t, *J* = 7.7 Hz, 1H), 7.20 – 7.17 (m, 1H), 7.13 (app. t, *J* = 1.9 Hz, 1H), 7.04 (d, *J* = 7.5 Hz, 1H), 5.86 (s, 1H), 5.79 – 5.62 (m, 1H), 3.68 (dd, *J* = 11.3, 8.7 Hz, 2H), 3.63 – 3.19 (m, 4H), 2.74 (s, 1H), 1.46 (s, 9H) ppm.

¹H NMR (600 MHz, CDCl₃, **42**) δ 7.22 (app. t, *J* = 7.6 Hz, 1H), 7.18 (app. dt, *J* = 8.0, 1.6 Hz, 1H), 7.13 (app. t, *J* = 1.9 Hz, 1H), 7.04 (app. dt, *J* = 7.3, 1.6 Hz, 1H), 5.85 (s, 1H), 5.74 (dd, *J* = 6.0, 2.4 Hz, 1H), 3.68 (dd, *J* = 11.4, 8.6 Hz, 2H), 3.56 – 3.20 (m, 4H), 2.74 (s, 1H), 1.46 (s, 9H) ppm.

¹³C NMR (151 MHz, CDCl₃, **42**) δ 154.6, 146.4, 135.2*, 134.8*, 134.6, 133.5*, 133.2*, 130.0, 127.4, 126.8, 125.5, 79.4, 57.5[†], 52.4[†], 52.0[†], 50.9[†], 50.1[†], 49.7[†], 48.7[†], 28.6 (3C) ppm (in total 4 additional rotameric peaks detected).

* rotamers; corresponding to 2C

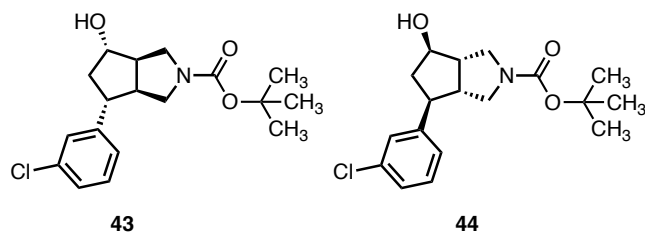
[†] rotamers; corresponding to 5C

HRMS (**41**) *m/z* calc. for C₁₃H₁₅ClN⁺ [M-Boc+2H]⁺ 220.0893 found 220.0896.

HRMS (**42**) *m/z* calc. for C₁₃H₁₅ClN⁺ [M-Boc+2H]⁺ 220.0893 found 220.0895.

SFC (Waters UPC2 SFC with a Daicel IG column (3 μm, 4.6x250 mm) under isocratic conditions (3.3 mL/min, 25% MeOH / CO₂, 1600 psi backpressure) at 30 °C) (*t_R* (**41**) = 1.88 min; *t_R* (**42**) = 2.60 min).

Synthesis of **43** and **44**



Compound **43** was synthesized according to **Procedure B** (1.55 mmol scale) and was obtained as a highly viscous colorless oil (164 mg, 31%).

The enantiomer **44** was synthesized according to **Procedure B** (1.65 mmol scale) and was obtained as a colorless oil (284 mg, 51%).

¹H NMR (600 MHz, CDCl₃, **43**) δ 7.29– 7.12 (m, 4H; overlapping with CHCl₃ peak), 4.19 (s, 1H), 3.63 – 3.16 (m, 4H), 2.88 – 2.75 (m, 2H), 2.68 (s, 1H), 2.53 (dt, *J* = 13.0, 5.9 Hz, 1H), 1.93 – 1.80 (m, 1H), 1.47 (s, 9H) ppm (OH not detected).

¹H NMR (500 MHz, CDCl₃, **44**) δ 7.30 – 7.10 (m, 4H; overlapping with CHCl₃ peak), 4.16 (s, 1H), 3.65 – 3.13 (m, 4H), 2.87 – 2.74 (m, 2H), 2.68 (t, *J* = 8.2 Hz, 1H), 2.51 (dt, *J* = 12.8, 6.1 Hz, 1H), 1.86 (td, *J* = 11.8, 7.2 Hz, 1H), 1.46 (s, 9H) ppm (OH not detected).

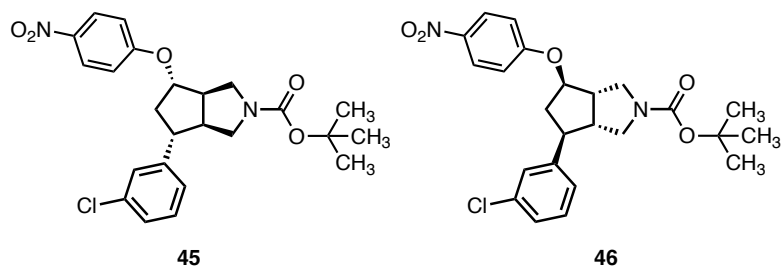
¹³C NMR (126 MHz, CDCl₃, **44**) 155.0, 146.1, 134.5, 130.0, 127.6, 126.7, 125.7, 79.7, 77.6, 52.3[†], 51.6[†], 51.0[†], 50.8[†], 50.5[†], 49.7[†], 48.9, 44.5, 28.6 (3C) ppm (in total 2 additional rotameric peaks detected).

[†] rotamers; corresponding to 4C

HRMS (**43**) *m/z* calc. for C₁₃H₁₇ClNO⁺ [M-Boc+2H]⁺ 238.0999 found 238.1005.

HRMS (**44**) *m/z* calc. for C₁₃H₁₇ClNO⁺ [M-Boc+2H]⁺ 238.0999 found 238.0996.

Synthesis of **45** and **46**



Compound **45** was synthesized according to **Procedure D** (200 μ mol scale) using 1-fluoro-4-nitrobenzene and was obtained as a yellow foam (81 mg, 88%).

Compound **46** was synthesized according to **Procedure D** (440 μ mol scale) using 1-fluoro-4-nitrobenzene and was obtained as a yellow foam (152 mg, 75%).

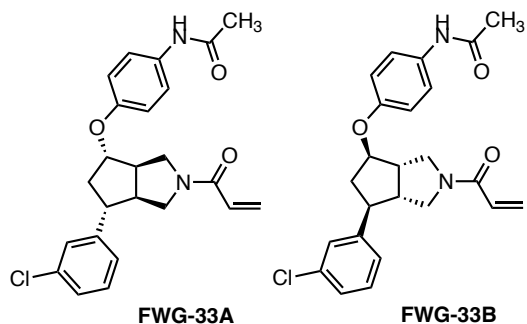
^1H NMR (600 MHz, CDCl_3 , **45**) δ 8.20 (d, J = 9.1 Hz, 2H), 7.31 – 7.18 (m, 3H), 7.14 (d, J = 7.5 Hz, 1H), 6.94 (d, J = 8.7 Hz, 2H), 4.76 (s, 1H), 3.76 (s, 1H), 3.50 – 3.28 (m, 3H), 3.11 – 2.75 (m, 4H), 2.08 (ddd, J = 15.0, 10.2, 5.3 Hz, 1H), 1.48 (s, 9H) ppm.

^1H NMR (500 MHz, CDCl_3 , **46**) δ 8.20 (d, J = 9.2 Hz, 2H), 7.30 – 7.18 (m, 3H), 7.14 (dt, J = 7.5, 1.5 Hz, 1H), 6.94 (d, J = 9.2 Hz, 2H), 4.76 (td, J = 5.8, 2.4 Hz, 1H), 3.76 (t, J = 10.4 Hz, 1H), 3.49 – 3.30 (m, 3H), 3.06 – 2.76 (m, 4H), 2.08 (ddd, J = 13.8, 10.2, 5.4 Hz, 1H), 1.48 (s, 9H) ppm.

^{13}C NMR (126 MHz, CDCl_3 , **46**) δ 162.7, 154.8, 144.9, 141.7, 134.7, 130.2, 127.6, 127.2, 126.2 (2C), 125.8, 115.3 (2C), 82.7, 80.0, 50.4, 50.1, 49.6, 49.2, 48.9, 41.7, 28.6 (3C) ppm.

HRMS (**46**) m/z calc. for $\text{C}_{19}\text{H}_{20}\text{ClN}_2\text{O}_3^+$ [M-Boc+2H] $^+$ 359.1162 found 359.1160.

Synthesis of **FWG-33A (28)** and **FWG-33B (22)**



Compound **FWG-33A (28)** was synthesized from **45** according to **Procedure E** (100 μ mol scale; 30 min with 5 wt% Pd/C), followed by **Procedure F1**, **Procedure G** and **Procedure H** in EtOAc and was obtained as a colorless solid (13 mg, 31% over 4 steps; prep. TLC EtOAc and RP-MPLC acetonitrile/H₂O) with 97% ee.

Compound **FWG-33B (22)** was synthesized from **46** according to **Procedure E** (150 μ mol scale; 90 min with 5 wt% Pd/C), followed by **Procedure F1**, **Procedure G** and **Procedure H** in EtOAc and was obtained as a colorless solid (26 mg, 40% over 4 steps; prep. TLC EtOAc and RP-HPLC acetonitrile/H₂O) with >99% ee.

¹H NMR (600 MHz, CDCl₃, **FWG-33A**) δ 7.52 – 7.36 (m, 3H), 7.27 (app. t, J = 1.9 Hz, 1H), 7.26 – 7.19 (m, 2H), 7.17 – 7.09 (m, 1H), 6.90 – 6.77 (m, 2H), 6.56 – 6.30 (m, 2H), 5.76 – 5.68 (m, 1H), 4.75 – 4.53 (m, 1H), 4.09 – 3.87 (m, 1H), 3.81 – 3.41 (m, 3H), 3.18 – 2.74 (m, 4H), 2.16 (s, 3H), 2.13 – 2.06 (m, 1H) ppm.

¹H NMR (600 MHz, CDCl₃, **FWG-33B**) δ 7.84 – 7.72 (m, 1H), 7.50 – 7.34 (m, 2H), 7.33 – 7.16 (m, 3H; overlapping with CHCl₃ peak), 7.15 – 7.07 (m, 1H), 6.90 – 6.73 (m, 2H), 6.56 – 6.27 (m, 2H), 5.78 – 5.62 (m, 1H), 4.73 – 4.54 (m, 1H), 4.11 – 3.82 (m, 1H), 3.79 – 3.38 (m, 3H), 3.20 – 2.59 (m, 4H), 2.14 (s, 3H), 2.12 – 2.04 (m, 1H) ppm.

¹³C NMR (151 MHz, CDCl₃, **FWG-33B**) δ 168.6, 165.1*, 165.0*, 154.2*, 154.1*, 145.0*, 144.9*, 134.7*, 134.6*, 131.9*, 131.8*, 130.2*, 130.1*, 128.4*, 128.3*, 127.7*, 127.6*, 127.2*, 127.1*, 125.84*, 125.81*, 122.2* (2C), 122.1* (2C), 115.9* (2C), 115.8* (2C), 82.0[†], 81.7[†], 51.2[†], 50.5[†], 50.4[†], 50.1[†], 50.0[†], 49.3[†], 49.1[†], 48.87[†], 48.85[†], 48.3[†], 42.1[†], 41.6[†], 24.4 ppm (in total 18 additional rotameric peaks detected).

* rotamers; corresponding to ¹³C

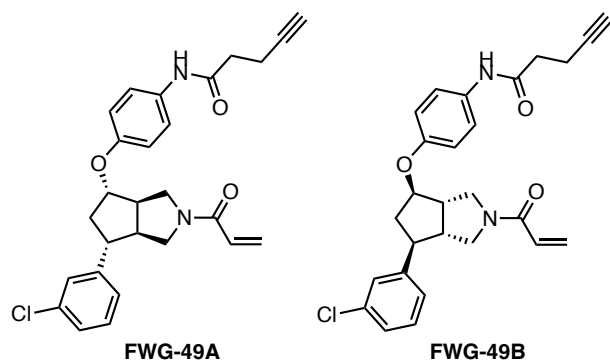
[†] rotamers; corresponding to 7C

HRMS (FWG-33A) m/z calc. for $C_{24}H_{26}ClN_2O_3^+$ $[M+H]^+$ 425.1632 found 425.1645.

HRMS (FWG-33B) m/z calc. for $C_{24}H_{26}ClN_2O_3^+$ $[M+H]^+$ 425.1632 found 425.1635.

SFC (Waters UPC2 SFC with a Daicel IA column (3 μ m, 4.6x250 mm) under isocratic conditions (3.3 mL/min, 45% MeOH / CO₂, 1600 psi backpressure) at 30 °C) (t_R (**FWG-33A**) = 3.15 min; t_R (**FWG-33B**) = 3.90 min).

Synthesis of **FWG-49A (29)** and **FWG-49B (30)**



Compound **FWG-49A (29)** was synthesized from **45** according to **Procedure E** (75 μ mol scale; 30 min with 5 wt% Pd/C), followed by **Procedure F2**, **Procedure G** and **Procedure H** in EtOAc and was obtained as a colorless solid (14 mg, 40% over 4 steps; prep. TLC EtOAc and RP-MPLC acetonitrile/H₂O) with 98% ee.

Compound **FWG-49B (30)** was synthesized from **46** according to **Procedure E** (100 μ mol scale; 30 min with 5 wt% Pd/C), followed by **Procedure F2**, **Procedure G** and **Procedure H** in EtOAc and was obtained as a colorless solid (20 mg, 44% over 4 steps; prep. TLC EtOAc and RP-MPLC acetonitrile/H₂O) with 98% ee.

¹H NMR (600 MHz, CDCl₃, **FWG-49A**) δ 7.71 – 7.61 (m, 1H), 7.51 – 7.38 (m, 2H), 7.32 – 7.17 (m, 3H; overlapping with CHCl₃ peak), 7.17 – 7.06 (m, 1H), 6.87 – 6.79 (m, 2H), 6.51 – 6.33 (m, 2H), 5.81 – 5.62 (m, 1H), 4.70 – 4.59 (m, 1H), 4.09 – 3.87 (m, 1H), 3.82 – 3.42 (m, 3H), 3.16 – 2.73 (m, 4H), 2.66 – 2.51 (m, 4H), 2.13 – 2.06 (m, 1H), 2.04 (s, 1H) ppm.

¹H NMR (600 MHz, CDCl₃, **FWG-49B**) δ 7.63 (s, 1H), 7.54 – 7.39 (m, 2H), 7.27 (app. t, J = 1.9 Hz, 1H), 7.25 – 7.18 (m, 2H), 7.16 – 7.06 (m, 1H), 6.95 – 6.70 (m, 2H), 6.53 – 6.36 (m, 2H), 5.83 – 5.63 (m, 1H), 4.71 – 4.56 (m, 1H), 4.03 – 3.86 (m, 1H), 3.80 – 3.40 (m, 3H), 3.18 – 2.75 (m, 4H), 2.70 – 2.50 (m, 4H), 2.14 – 2.06 (m, 1H), 2.04 (t, J = 2.5 Hz, 1H) ppm.

¹³C NMR (151 MHz, CDCl₃, **FWG-49B**) δ 169.3, 165.1*, 165.0*, 154.3, 145.02*, 144.95*, 134.7, 131.6*, 131.5*, 130.2*, 130.1*, 128.4*, 128.3*, 127.7*, 127.6*, 127.2*, 127.1*, 125.9, 122.1, 116.0*, 115.9*, 83.0, 82.1[†], 81.8[†], 69.8, 51.3[†], 50.5[†], 50.4[†], 50.2[†], 50.0[†], 49.3[†], 49.1[†], 48.9, 48.4[†], 42.1[†], 41.6[†], 36.2, 15.0 ppm (in total 14 additional rotameric peaks detected).

* rotamers; corresponding to 8C

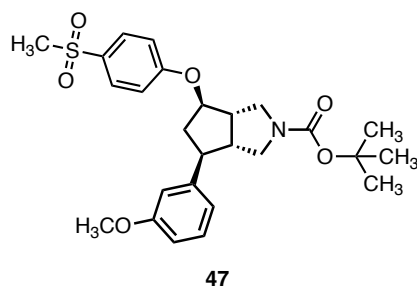
[†] rotamers; corresponding to 6C

HRMS (FWG-49A) m/z calc. for $C_{27}H_{28}ClN_2O_3^+$ $[M+H]^+$ 463.1788 found 463.1800.

HRMS (FWG-49B) m/z calc. for $C_{27}H_{28}ClN_2O_3^+$ $[M+H]^+$ 463.1788 found 463.1787.

SFC (Waters UPC2 SFC with a Daicel IBN column (3 μ m, 4.6x100 mm) under isocratic conditions (3.3 mL/min, 60% MeOH / CO₂, 1600 psi backpressure) at 30 °C) (t_R (**FWG-49B**) = 1.24 min; t_R (**FWG-49A**) = 1.60 min).

Synthesis of **47**

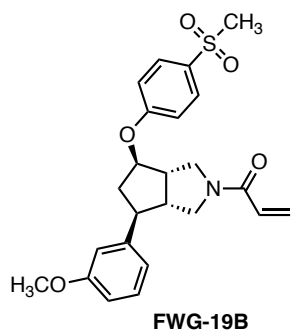


Compound **47** was synthesized according to **Procedure D** (150 μ mol scale; *modification*: aryl fluoride and alcohol were pre-mixed) using 1-fluoro-4-(methylsulfonyl)benzene (44 mg, 60%; purified by MPLC hexane/EtOAc 100:0 to 30:70 and prep. TLC hexane/EtOAc 50:50).

^1H NMR (500 MHz, CDCl_3 , **47**) δ 7.86 (d, J = 8.9 Hz, 2H), 7.24 (app. t, J = 8.0 Hz, 1H), 7.00 (d, J = 8.9 Hz, 2H), 6.86 (app. dt, J = 7.7, 1.2 Hz, 1H), 6.81 (app. t, J = 2.1 Hz, 1H), 6.79 – 6.74 (m, 1H), 4.73 (td, J = 6.0, 2.4 Hz, 1H), 3.80 (s, 3H), 3.74 (app. t, J = 10.3 Hz, 1H), 3.44 (d, J = 11.6 Hz, 1H), 3.36 (app. p, J = 5.6 Hz, 2H), 3.03 (s, 3H), 3.00 – 2.87 (m, 3H), 2.83 (dt, J = 13.9, 7.0 Hz, 1H), 2.08 (ddd, J = 13.7, 10.1, 5.7 Hz, 1H), 1.47 (s, 9H) ppm.

HRMS (**47**) m/z calc. for $\text{C}_{26}\text{H}_{33}\text{NNaO}_6\text{S}^+$ $[\text{M}+\text{Na}]^+$ 510.1926 found 510.1937.

Synthesis of **FWG-19B** (**17**)

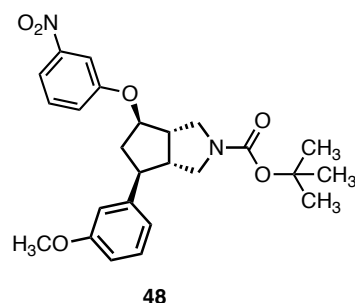


Compound **FWG-19B** (**17**) was synthesized from **47** according to **Procedure G** (85 μ mol scale) and **Procedure H** in EtOAc and was obtained as a colorless solid (32 mg, 84% over 2 steps; prep. TLC hexane/EtOAc 33:67).

^1H NMR (600 MHz, CDCl_3 , **FWG-19B**) δ 7.87 (d, J = 8.9 Hz, 2H), 7.24 (app. t, J = 8.1 Hz, 1H), 7.00 (d, J = 8.9 Hz, 2H), 6.87 – 6.82 (m, 1H), 6.81 – 6.74 (m, 2H), 6.48 – 6.37 (m, 2H), 5.71 (t, J = 6.1 Hz, 1H), 4.77 (s, 1H), 4.09 – 3.95 (m, 1H), 3.79 (s, 3H), 3.71 – 3.46 (m, 3H), 3.22 – 2.79 (m, 7H), 2.30 – 2.08 (m, 1H) ppm.

HRMS (**FWG-19B**) m/z calc. for $\text{C}_{24}\text{H}_{28}\text{NO}_5\text{S}^+$ $[\text{M}+\text{H}]^+$ 442.1688 found 442.1684.

Synthesis of **48**

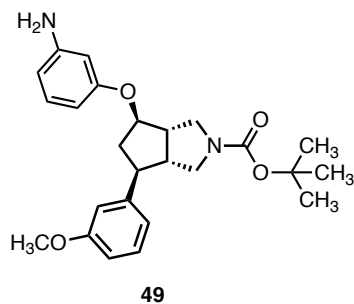


A mixture of **8** (150 μ mol, 1.0 eq), PPh_3 (59 mg, 225 μ mol, 1.5 eq) and 3-nitrophenol (31 mg, 225 μ mol, 1.5 eq) were added 2-dram vial equipped with septum under a N_2 atmosphere, and dissolved in dry THF (1.5 mL). The solution was cooled to 0 $^\circ\text{C}$ and diisopropyl azodicarboxylate (45 μL , 225 μmol , 1.5 eq) was added dropwise. The mixture was allowed to reach r.t. overnight. A sat. aq. solution of NaHCO_3 (2 mL) and H_2O (2 mL) were added. The reaction mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over MgSO_4 and concentrated under reduced pressure. Purification by automated medium pressure liquid chromatography (hexane:EtOAc 100:0 to 20:80) afforded **48** as colorless oil (37 mg, 54%).

^1H NMR (600 MHz, CDCl_3 , **48**) δ 7.83 (ddd, J = 8.2, 2.1, 0.9 Hz, 1H), 7.71 (app. t, J = 2.3 Hz, 1H), 7.44 (app. t, J = 8.2 Hz, 1H), 7.24 (d, J = 7.9 Hz, 1H), 7.22 – 7.20 (m, 1H), 6.87 (d, J = 7.7 Hz, 1H), 6.82 (app. t, J = 2.1 Hz, 1H), 6.81 – 6.75 (m, 1H), 4.72 (td, J = 6.0, 2.7 Hz, 1H), 3.81 (s, 3H), 3.75 (dd, J = 11.4, 9.3 Hz, 1H), 3.46 (d, J = 11.5 Hz, 1H), 3.38 (td, J = 11.0, 8.2 Hz, 2H), 3.05 – 2.89 (m, 3H), 2.85 (ddd, J = 13.9, 7.6, 6.2 Hz, 1H), 2.09 (ddd, J = 13.8, 10.3, 5.8 Hz, 1H), 1.48 (s, 9H) ppm.

HRMS (**48**) m/z calc. for $\text{C}_{25}\text{H}_{30}\text{N}_2\text{NaO}_6^+$ $[\text{M}+\text{Na}]^+$ 477.2002 found 477.2012.

Synthesis of **49**

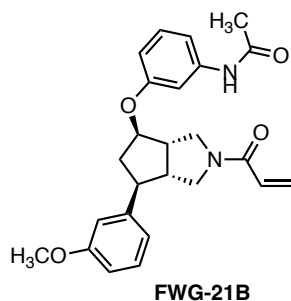


Compound **49** was synthesized according to **Procedure E** (82 μ mol scale; 16 h) and was obtained as a pale-brown foam (23 mg, 65%).

^1H NMR (500 MHz, CDCl_3 , **49**) δ 7.23 (d, J = 7.9 Hz, 1H), 7.06 (app. t, J = 8.0 Hz, 1H), 6.88 (d, J = 7.7 Hz, 1H), 6.84 (app. t, J = 2.1 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 6.38 – 6.20 (m, 3H), 4.62 (s, 1H), 4.10 (br. s, 2H), 3.81 (s, 3H), 3.57 – 3.22 (m, 4H), 2.87 (s, 3H), 2.76 (dt, J = 13.5, 6.6 Hz, 1H), 2.10 (s, 1H). 1.48 (s, 9H) ppm.

HRMS (**49**) m/z calc. for $\text{C}_{25}\text{H}_{33}\text{N}_2\text{O}_4^+$ $[\text{M}+\text{H}]^+$ 425.2440 found 425.2445.

Synthesis of **FWG-21B (18)**

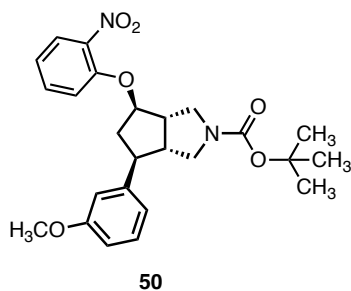


Compound **FWG-21B (18)** was synthesized from **49** according to **Procedure F1** (50 μ mol scale), followed by **Procedure G** and **Procedure H** in EtOAc and was obtained as a colorless solid (14 mg, 66% over 3 steps; prep. TLC hexane/EtOAc 33:67).

^1H NMR (500 MHz, CDCl_3 , **FWG-21B**) δ 7.74 – 7.42 (m, 1.4H), 7.26 – 7.22 (m, 1H), 7.19 (app. *t*, J = 8.1 Hz, 1H), 7.02 (s, 0.6H), 6.85 (app. dt, J = 7.7, 1.2 Hz, 1H), 6.81 (app. *t*, J = 2.4 Hz, 1H), 6.78 (d, J = 8.3 Hz, 1H), 6.62 (d, J = 8.2 Hz, 1H), 6.56 – 6.33 (m, 2H), 5.71 (*t*, J = 6.2 Hz, 1H), 4.65 (td, J = 6.1, 2.1 Hz, 1H), 4.01 (d, J = 10.6 Hz, 1H), 3.80 (s, 3H), 3.56 (s, 3H), 3.15 – 2.62 (m, 5H), 2.18 (s, 3H), 2.13 (ddd, J = 12.9, 6.7, 4.1 Hz, 1H) ppm.

HRMS (FWG-21B) m/z calc. for $\text{C}_{25}\text{H}_{29}\text{N}_2\text{O}_4^+$ $[\text{M}+\text{H}]^+$ 421.2127 found 421.2121.

Synthesis of **50**

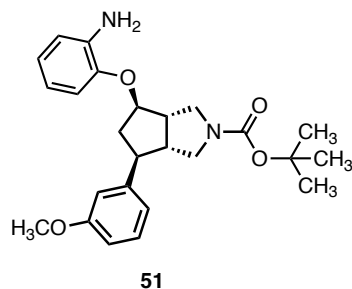


Compound **50** was synthesized according to **Procedure D** (150 μ mol scale) using 1-fluoro-2-nitrobenzene (28 mg, 41%; purified by MPLC hexane/EtOAc 100:0 to 40:60).

^1H NMR (600 MHz, CDCl_3 , **50**) δ 7.83 (dd, J = 8.0, 1.7 Hz, 1H), 7.50 (ddd, J = 8.2, 7.5, 1.7 Hz, 1H), 7.24 (app. t, J = 7.9 Hz, 1H), 7.10 – 6.99 (m, 2H), 6.88 (app. dt, J = 7.7, 1.2 Hz, 1H), 6.83 (app. t, J = 2.1 Hz, 1H), 6.78 (ddd, J = 8.2, 2.6, 0.9 Hz, 1H), 4.79 (td, J = 5.8, 2.5 Hz, 1H), 3.81 (s, 3H), 3.73 (dd, J = 11.4, 9.4 Hz, 1H), 3.44 (d, J = 11.4 Hz, 1H), 3.34 (ddd, J = 11.3, 6.7, 4.4 Hz, 2H), 3.12 – 3.00 (m, 1H), 2.98 – 2.89 (m, 2H), 2.84 (ddd, J = 13.7, 7.6, 6.2 Hz, 1H), 2.18 (ddd, J = 13.8, 9.9, 5.5 Hz, 1H), 1.47 (s, 9H) ppm.

HRMS (**50**) m/z calc. for $\text{C}_{25}\text{H}_{31}\text{N}_2\text{O}_6^+$ $[\text{M}+\text{H}]^+$ 455.2182 found 455.2180.

Synthesis of **51**

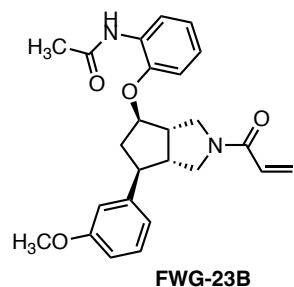


Compound **51** was synthesized according to **Procedure E** (62 μ mol scale; 16 h) and was obtained as a colorless foam (22 mg, 84%).

^1H NMR (600 MHz, CDCl_3 , **51**) δ 7.23 (app. t, J = 7.8 Hz, 1H), 6.88 (d, J = 7.7 Hz, 1H), 6.83 (t, J = 2.0 Hz, 1H), 6.81 – 6.70 (m, 5H), 4.66 (s, 1H), 4.20 (br. s, 1H), 3.80 (s, 3H), 3.73 – 3.25 (m, 4H), 3.04 – 2.87 (m, 3H), 2.80 (dt, J = 13.4, 6.6 Hz, 1H), 2.15 (ddd, J = 13.8, 10.7, 6.0 Hz, 1H), 1.48 (s, 9H) (one NH not detected) ppm.

HRMS (**51**) m/z calc. for $\text{C}_{25}\text{H}_{32}\text{N}_2\text{NaO}_4^+$ $[\text{M}+\text{Na}]^+$ 447.2260 found 447.2258.

Synthesis of **FWG-23B** (**19**)

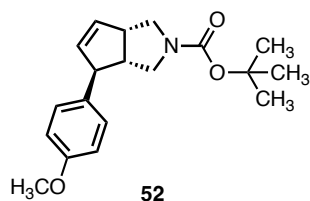


Compound **FWG-23B** (**19**) was synthesized from **51** according to **Procedure F1** (50 μ mol scale), followed by **Procedure G** and **Procedure H** in EtOAc and was obtained as a colorless solid (11 mg, 54% over 3 steps; prep. TLC hexane/EtOAc 33:67).

^1H NMR (500 MHz, CDCl_3 , **FWG-23B**) δ 8.36 (d, J = 8.5 Hz, 1H), 7.65 (s, 1H), 7.29 – 7.22 (m, 1H), 7.02 (td, J = 7.8, 1.8 Hz, 1H), 6.97 (td, J = 7.8, 1.5 Hz, 1H), 6.86 (dt, J = 7.6, 1.2 Hz, 1H), 6.84 – 6.75 (m, 3H), 6.41 (d, J = 6.7 Hz, 2H), 5.71 (d, J = 8.3 Hz, 1H), 4.74 (s, 1H), 4.09 – 3.89 (m, 1H), 3.80 (s, 3H), 3.64 – 3.50 (m, 3H), 3.14 – 2.92 (m, 3H), 2.85 (dt, J = 13.7, 6.8 Hz, 1H), 2.19 (s, 4H) ppm.

HRMS (**FWG-23B**) m/z calc. for $\text{C}_{25}\text{H}_{29}\text{N}_2\text{O}_4^+$ $[\text{M}+\text{H}]^+$ 421.2127 found 421.2124.

Synthesis of **52**



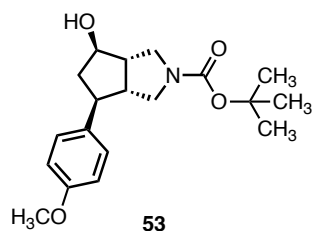
Compound **52** was synthesized according to **Procedure A** (1.0 mmol scale; using (*R*)-Segphos and 4-methoxyphenylboronic acid) and was obtained as a colorless oil (248 mg, 79%) with 99% ee.

¹H NMR (600 MHz, CDCl₃, **52**) δ 7.07 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 5.80 (d, *J* = 5.6 Hz, 1H), 5.77 – 5.73 (m, 1H), 3.79 (s, 3H), 3.73 – 3.60 (m, 2H), 3.55 – 3.18 (m, 4H), 2.72 (td, *J* = 8.5, 4.1 Hz, 1H), 1.46 (s, 9H) ppm.

HRMS (**52**) *m/z* calc. for C₁₄H₁₈NO⁺ [M-Boc+2H]⁺ 216.1388 found 216.1390.

SFC (Waters UPC2 SFC with a Daicel IG column (3 μm, 4.6x250 mm) under isocratic conditions (3.3 mL/min, 25% MeOH / CO₂, 1600 psi backpressure) at 30 °C) (*t_R* (**52**) = 2.76 min; *t_R* (*ent*-**52**) = 3.11 min).

Synthesis of **53**

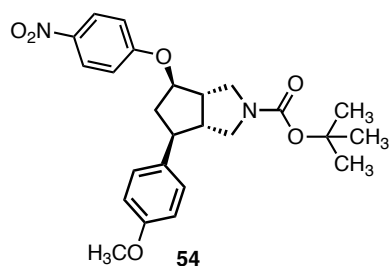


Compound **53** was synthesized according to **Procedure B** (750 μ mol scale; *modification*: the reaction was performed with 5 mol% $[\text{Rh}(\text{PPh}_3)_3\text{Cl}]$ at 50 $^\circ\text{C}$) and was obtained as a viscous colorless oil (64 mg, 30%).

^1H NMR (600 MHz, CDCl_3 , **53**) δ 7.18 (d, J = 8.3 Hz, 2H), 6.95 – 6.77 (m, 2H), 4.16 (s, 1H), 3.79 (s, 3H), 3.64 – 3.23 (m, 4H), 2.91 – 2.57 (m, 3H), 2.49 (dt, J = 12.9, 5.9 Hz, 1H), 2.27 (br. s, 1H), 1.94 – 1.75 (m, 1H), 1.46 (s, 9H) ppm.

HRMS (**53**) m/z calc. for $\text{C}_{14}\text{H}_{20}\text{NO}_2^+$ $[\text{M-Boc}+2\text{H}]^+$ 234.1494 found 234.1496.

Synthesis of **54**

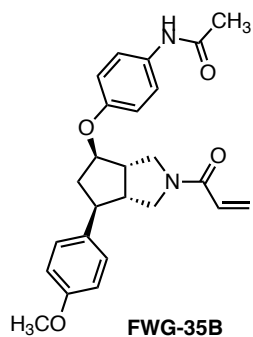


Compound **54** was synthesized according to **Procedure D** (180 μ mol scale) using 1-fluoro-4-nitrobenzene (1.2 eq) and KHMDS (1.5 eq) and was obtained as a yellow foam (60 mg, 73%).

^1H NMR (500 MHz, CDCl_3 , **54**) δ 8.20 (d, J = 9.0 Hz, 2H), 7.18 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 9.2 Hz, 2H), 6.86 (d, J = 8.1 Hz, 2H), 4.73 (td, J = 6.1, 2.5 Hz, 1H), 3.79 (s, 4H), 3.50 – 3.28 (m, 3H), 3.05 – 2.68 (m, 4H), 2.12 – 2.02 (m, 1H), 1.48 (s, 9H) ppm.

HRMS (**54**) m/z calc. for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_4^+$ [M-Boc+2H] $^+$ 355.1658 found 355.1666.

Synthesis of **FWG-35B (23)**

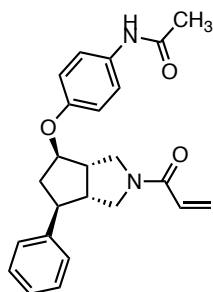


Compound **FWG-35B (23)** was synthesized from **54** according to **Procedure E** (125 μ mol scale; 20 h), followed by **Procedure F1**, **Procedure G** and **Procedure H** in EtOAc and was obtained as a colorless solid (20 mg, 37% over 4 steps; prep. TLC EtOAc and RP-MPLC acetonitrile/H₂O).

¹H NMR (500 MHz, CDCl₃, **FWG-35B**) δ 7.65 – 7.56 (m, 1H), 7.41 (dd, J = 9.0, 6.9 Hz, 2H), 7.23 – 7.14 (m, 2H), 6.91 – 6.78 (m, 4H), 6.53 – 6.34 (m, 2H), 5.70 (ddd, J = 14.2, 9.0, 3.2 Hz, 1H), 4.72 – 4.52 (m, 1H), 4.05 – 3.86 (m, 1H), 3.81 – 3.78 (m, 3H), 3.77 – 3.41 (m, 3H), 3.15 – 2.66 (m, 4H), 2.14 (s, 3H), 2.11 – 2.04 (m, 1H) ppm.

HRMS (FWG-35B) m/z calc. for C₂₅H₂₉N₂O₄⁺ [M+H]⁺ 421.2127 found 421.2128.

Synthesis of **FWG-41B (24)**



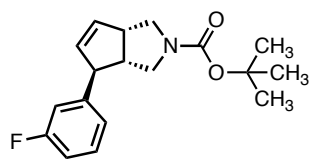
FWG-41B

Compound **FWG-41B (24)** was synthesized from **46** according to **Procedure E** (100 μ mol scale; 18 h with 20 wt% Pd/C), followed by **Procedure F1**, **Procedure G** and **Procedure H** in EtOAc and was obtained as a colorless solid (8 mg, 21% over 4 steps; prep. TLC EtOAc and RP-MPLC acetonitrile/H₂O).

¹H NMR (500 MHz, CDCl₃, **FWG-41B**) δ 7.44 – 7.38 (m, 2H), 7.33 (app. t, J = 7.5 Hz, 2H), 7.29 – 7.15 (m, 4H; overlapping with CHCl₃), 6.88 – 6.80 (m, 2H), 6.48 – 6.35 (m, 2H), 5.77 – 5.65 (m, 1H), 4.65 (s, 1H), 4.07 – 3.43 (m, 4H), 3.12 – 2.69 (m, 4H), 2.19 – 2.08 (m, 4H) ppm.

HRMS (FWG-41B) m/z calc. for C₂₄H₂₇N₂O₃⁺ [M+H]⁺ 391.2022 found 391.2020.

Synthesis of **55**



55

Compound **55** was synthesized according to **Procedure A** (1.0 mmol scale; using (*R*)-Segphos and 3-fluorophenylboronic acid pinacol ester) and was obtained as a colorless oil (262 mg, 86%) with 98% ee.

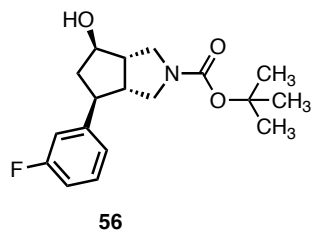
¹H NMR (400 MHz, CDCl₃, **55**) δ 7.31 – 7.19 (m, 1H), 7.01 – 6.78 (m, 3H), 5.85 (d, *J* = 5.6 Hz, 1H), 5.79 – 5.72 (m, 1H), 3.76 – 3.62 (m, 2H), 3.62 – 3.07 (m, 4H), 2.75 (s, 1H), 1.46 (s, 9H) ppm.

¹⁹F NMR {1H} (376 MHz, CDCl₃, **55**) δ -115.82 (s, 1F) ppm.

HRMS (**55**) *m/z* calc. for C₁₃H₁₅FN⁺ [M-Boc+2H]⁺ 204.1189 found 204.1189.

SFC (Waters UPC2 SFC with a Daicel IG column (3 μm, 4.6x100 mm) under isocratic conditions (3.3 mL/min, 25% MeOH / CO₂, 1600 psi backpressure) at 30 °C) (*t_R* (*ent*-**55**) = 0.74 min; *t_R* (**55**) = 0.90 min).

Synthesis of **56**



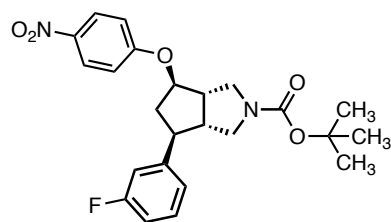
Compound **56** was synthesized according to **Procedure B** (800 μ mol scale) and was obtained as a viscous colorless oil (114 mg, 44%).

^1H NMR (400 MHz, CDCl_3 , **56**) δ 7.22 (app. t, J = 7.2 Hz, 1H), 7.01 (dd, J = 7.7, 1.2 Hz, 1H), 6.97 (app. dt, J = 10.3, 2.1 Hz, 1H), 6.89 (app. td, J = 8.5, 2.6 Hz, 1H), 4.15 (q, J = 6.1 Hz, 1H), 3.62 – 3.27 (m, 4H), 3.13 (br. s, 0.6H, OH), 2.85 – 2.63 (m, 3H), 2.50 (dt, J = 12.9, 6.3 Hz, 1H), 2.15 (br. s, 0.4H, OH), 1.86 (ddd, J = 13.0, 10.6, 7.4 Hz, 1H), 1.45 (s, 9H) ppm.

^{19}F NMR {1H} (376 MHz, CDCl_3 , **56**) δ -115.69 (s, 1F) ppm.

HRMS (**56**) m/z calc. for $\text{C}_{13}\text{H}_{17}\text{FNO}^+$ [M-Boc+2H] $^+$ 222.1294 found 222.1295.

Synthesis of **57**



57

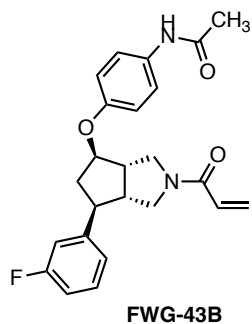
Compound **57** was synthesized according to **Procedure D** (300 μ mol scale) using 1-fluoro-4-nitrobenzene (1.2 eq) and KHMDS (1.5 eq) and was obtained as a pale-yellow foam (96 mg, 71%).

^1H NMR (400 MHz, CDCl_3 , **57**) δ 8.23 – 8.16 (m, 2H), 7.32 – 7.23 (m, 1H), 7.06 – 7.01 (m, 1H), 7.00 – 6.88 (m, 4H), 4.76 (td, J = 5.8, 2.4 Hz, 1H), 3.76 (dd, J = 11.4, 9.3 Hz, 1H), 3.50 – 3.29 (m, 3H), 3.07 – 2.77 (m, 4H), 2.07 (ddt, J = 18.1, 9.7, 4.8 Hz, 1H), 1.47 (s, 9H).
ppm.

^{19}F NMR {1H} (376 MHz, CDCl_3 , **57**) δ -115.30 (s, 1F) ppm.

HRMS (**57**) m/z calc. for $\text{C}_{19}\text{H}_{20}\text{FN}_2\text{O}_3^+$ [M-Boc+2H] $^+$ 343.1458 found 343.1460.

Synthesis of **FWG-43B (25)**



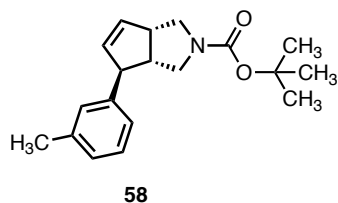
Compound **FWG-43B (25)** was synthesized from **57** according to **Procedure E** (100 μ mol scale; 1 h), followed by **Procedure F1**, **Procedure G** and **Procedure H** in EtOAc and was obtained as a colorless solid (24 mg, 58% over 4 steps; prep. TLC EtOAc and RP-MPLC acetonitrile/H₂O).

¹H NMR (400 MHz, CDCl₃, **FWG-43B**) δ 7.55 – 7.38 (m, 3H), 7.31 – 7.20 (m, 1H; overlapping with CHCl₃), 7.15 – 6.82 (m, 5H), 6.52 – 6.29 (m, 2H), 5.79 – 5.60 (m, 1H), 4.76 – 4.55 (m, 1H), 4.03 – 3.86 (m, 1H), 3.81 – 3.43 (m, 3H), 3.14 – 2.65 (m, 4H), 2.15 (s, 3H), 2.12 – 2.03 (m, 1H) ppm.

¹⁹F NMR {1H} (376 MHz, CDCl₃, **FWG-43B**) δ -115.20 (s, 1F, 0.6F), -115.40 (s, 0.4F) ppm.

HRMS (FWG-43B) m/z calc. for C₂₄H₂₆FN₂O₃⁺ [M+H]⁺ 409.1927 found 409.1930

Synthesis of **58**



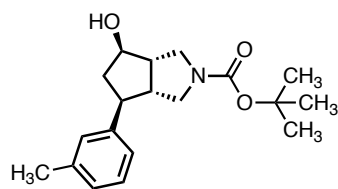
Compound **58** was synthesized according to **Procedure A** (1.0 mmol scale; using (*R*)-Segphos and 3-methylphenylboronic acid pinacol ester) and was obtained as a colorless oil (253 mg, 85%) with 97% ee.

¹H NMR (500 MHz, CDCl₃, **58**) δ 7.19 (t, *J* = 7.5 Hz, 1H), 7.06 – 7.01 (m, 1H), 6.96 (d, *J* = 8.7 Hz, 2H), 5.88 – 5.81 (m, 1H), 5.79 – 5.74 (m, 1H), 3.68 (dd, *J* = 11.2, 8.7 Hz, 2H), 3.58 – 3.19 (m, 4H), 2.77 (s, 1H), 2.33 (s, 3H), 1.47 (s, 9H) ppm.

HRMS (**58**) *m/z* calc. for C₁₄H₁₈N⁺ [M-Boc+2H]⁺ 200.1439 found 200.1441.

SFC (Waters UPC2 SFC with a Daicel IA column (3 μm, 4.6x100 mm) under isocratic conditions (3.3 mL/min, 3% MeOH / CO₂, 1600 psi backpressure) at 30 °C) (*t_R* (*ent*-**58**) = 1.41 min; *t_R* (**58**) = 1.63 min).

Synthesis of **59**



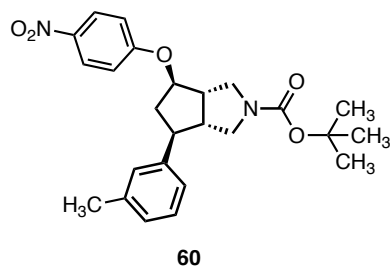
59

Compound **59** was synthesized according to **Procedure B** (800 μ mol scale) and was obtained as a viscous colorless oil (126 mg, 50%).

^1H NMR (500 MHz, CDCl_3 , **59**) δ 7.20 (app. t, J = 7.5 Hz, 1H), 7.13 – 6.99 (m, 3H), 4.17 (s, 1H), 3.66 – 3.22 (m, 4H), 2.90 – 2.43 (m, 5H), 2.34 (s, 3H), 1.89 (td, J = 11.8, 7.5 Hz, 1H), 1.47 (s, 9H) ppm.

HRMS (**59**) m/z calc. for $\text{C}_{14}\text{H}_{20}\text{NO}^+$ [M-Boc+2H] $^+$ 218.1545 found 218.1544

Synthesis of **60**

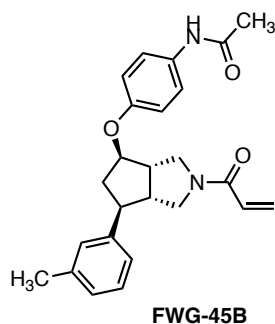


Compound **60** was synthesized according to **Procedure D** (350 μ mol scale) using 1-fluoro-4-nitrobenzene (1.2 eq) and KHMDS (1.5 eq) and was obtained as a pale-yellow foam (103 mg, 67%).

^1H NMR (500 MHz, CDCl_3 , **60**) δ 8.20 (d, J = 9.2 Hz, 2H), 7.22 (app. t, J = 7.5 Hz, 1H), 7.12 – 7.02 (m, 3H), 6.94 (d, J = 9.2 Hz, 2H), 4.75 (td, J = 6.0, 2.5 Hz, 1H), 3.76 (dd, J = 11.4, 9.3 Hz, 1H), 3.45 (d, J = 11.5 Hz, 1H), 3.38 (ddd, J = 15.3, 11.4, 6.5 Hz, 2H), 3.02 – 2.78 (m, 4H), 2.35 (s, 3H), 2.11 (ddd, J = 13.6, 10.2, 5.7 Hz, 1H), 1.49 (s, 9H) ppm.

HRMS (**60**) m/z calc. for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_3^+$ [M-Boc+2H] $^+$ 339.1709 found 339.1710.

Synthesis of **FWG-45B**

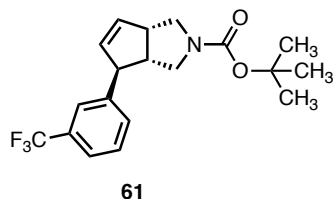


Compound **FWG-45B** (**26**) was synthesized from **60** according to **Procedure E** (100 μ mol scale; 2 h), followed by **Procedure F1**, **Procedure G** and **Procedure H** in EtOAc and was obtained as a colorless solid (11 mg, 28% over 4 steps; prep. TLC EtOAc and RP-MPLC acetonitrile/H₂O).

¹H NMR (500 MHz, CDCl₃, **FWG-45B**) δ 7.47 – 7.36 (m, 2H), 7.28 – 7.17 (m, 2H), 7.11 – 7.02 (m, 3H), 6.90 – 6.82 (m, 2H), 6.49 – 6.37 (m, 2H), 5.75 – 5.65 (m, 1H), 4.64 (s, 1H), 3.96 (s, 1H), 3.85 – 3.42 (m, 3H), 3.10 – 2.72 (m, 4H), 2.34 (s, 3H), 2.16 (s, 3H), 2.14 – 2.08 (m, 1H) ppm.

HRMS (**FWG-45B**) m/z calc. for C₂₅H₂₉N₂O₃⁺ [M+H]⁺ 405.2178 found 405.2178.

Synthesis of **61**



Compound **61** was synthesized according to **Procedure A** (1.0 mmol scale; using (*R*)-Segphos and 3-trifluoromethylphenylboronic acid pinacol ester) and was obtained as a colorless oil (304 mg, 86%) with 98% ee.

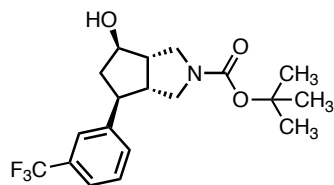
¹H NMR (400 MHz, CDCl₃, **61**) δ 7.49 – 7.46 (m, 1H), 7.44 – 7.38 (m, 2H), 7.37 – 7.32 (m, 1H), 5.89 (d, *J* = 5.5 Hz, 1H), 5.82 – 5.66 (m, 1H), 3.77 (s, 1H), 3.70 (dd, *J* = 11.3, 8.7 Hz, 1H), 3.61 – 3.18 (m, 4H), 2.75 (s, 1H), 1.46 (s, 9H) ppm.

¹⁹F NMR {1H} (376 MHz, CDCl₃, **61**) δ -65.20 (s, 3F) ppm.

HRMS (**61**) *m/z* calc. for C₁₄H₁₅F₃N⁺ [M-Boc+2H]⁺ 254.1157 found 254.1156.

SFC (Waters UPC2 SFC with a Daicel IG column (3 μm, 4.6x100 mm) under isocratic conditions (3.3 mL/min, 5% IPA / CO₂, 1600 psi backpressure) at 30 °C) (*t_R* (*ent*-**61**) = 1.17 min; *t_R* (**61**) = 1.42 min).

Synthesis of **62**



62

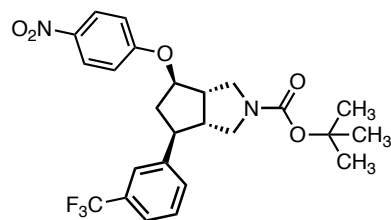
Compound **62** was synthesized according to **Procedure B** (800 μ mol scale) and was obtained as a viscous colorless oil (114 mg, 49%).

¹H NMR (400 MHz, CDCl₃, **62**) δ 7.51 (s, 1H), 7.48 – 7.35 (m, 3H), 4.17 (q, J = 6.0 Hz, 1H), 3.65 – 3.01 (m, 5H), 2.92 – 2.64 (m, 3H), 2.53 (dt, J = 13.2, 6.5 Hz, 1H), 1.88 (ddd, J = 13.1, 10.6, 7.4 Hz, 1H), 1.45 (s, 9H) ppm.

¹⁹F NMR {1H} (376 MHz, CDCl₃, **62**) δ - 65.18 (s, 3F) ppm.

HRMS (**62**) m/z calc. for C₁₄H₁₇F₃NO⁺ [M-Boc+2H]⁺ 272.1262 found 272.1264.

Synthesis of **63**



63

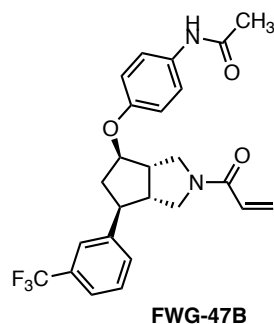
Compound **63** was synthesized according to **Procedure D** (250 μ mol scale) using 1-fluoro-4-nitrobenzene (1.2 eq) and KHMDS (1.5 eq) and was obtained as a pale-yellow foam (101 mg, 82%).

^1H NMR (400 MHz, CDCl_3 , **63**) δ 8.20 (d, J = 8.7 Hz, 2H), 7.56 – 7.42 (m, 4H), 6.94 (d, J = 8.9 Hz, 2H), 4.79 (t, J = 5.8 Hz, 1H), 3.77 (s, 1H), 3.61 – 3.26 (m, 3H), 3.12 – 2.81 (m, 4H), 2.11 (ddd, J = 14.6, 9.9, 5.1 Hz, 1H), 1.48 (s, 9H) ppm.

^{19}F NMR {1H} (376 MHz, CDCl_3 , **63**) δ -62.53 (s, 3F) ppm.

HRMS (**63**) m/z calc. for $\text{C}_{20}\text{H}_{20}\text{F}_3\text{N}_2\text{O}_3^+$ [M-Boc+2H] $^+$ 393.1426 found 393.1429.

Synthesis of **FWG-47B** (**27**)



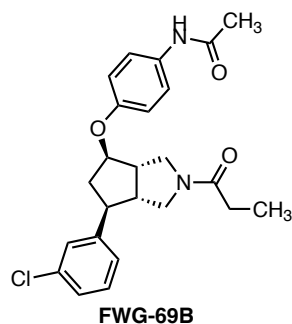
Compound **FWG-47B** (**27**) was synthesized from **63** according to **Procedure E** (100 μ mol scale; 2 h), followed by **Procedure F1**, **Procedure G** and **Procedure H** in EtOAc and was obtained as a colorless solid (31 mg, 69% over 4 steps; prep. TLC EtOAc and RP-MPLC acetonitrile/H₂O).

¹H NMR (400 MHz, CDCl₃, **FWG-47B**) δ 7.65 – 7.38 (m, 7H), 6.91 – 6.77 (m, 2H), 6.57 – 6.33 (m, 2H), 5.71 (q, J = 7.0 Hz, 1H), 4.73 – 4.60 (m, 1H), 4.12 – 3.88 (m, 1H), 3.83 – 3.46 (m, 3H), 3.16 – 2.88 (m, 3H), 2.87 – 2.72 (m, 1H), 2.14 (s, 3H), 2.13 – 2.04 (m, 1H) ppm.

¹⁹F NMR {1H} (376 MHz, CDCl₃, **FWG-47B**) δ -65.16 (s, 1.1F), -65.19 (s, 1.9F) ppm.

HRMS (**FWG-47B**) m/z calc. for C₂₅H₂₆F₃N₂O₃ + [M+H]⁺ 405.2178 found 405.2178.

Synthesis of **FWG-69B** (**31**)



Compound **FWG-69** (**31**) was synthesized from **46** according to **Procedure E** (75 μ mol scale; 45 min with 10 wt% Pd/C), followed by **Procedure F2**, **Procedure G** and **Procedure H** (using propanoyl chloride instead of acroyl chloride) in CH_2Cl_2 and was obtained as a colorless solid (10 mg, 32% over 4 steps; prep. TLC EtOAc and RP-HPLC acetonitrile/ H_2O).

^1H NMR (600 MHz, CDCl_3 , **FWG-69B**) δ 7.41 (t, J = 9.3 Hz, 2H), 7.31 – 7.27 (m, 2H), 7.26 – 7.18 (m, 2H), 7.15 – 7.08 (m, 1H), 6.93 – 6.75 (m, 2H), 4.74 – 4.50 (m, 1H), 3.98 – 3.74 (m, 1H), 3.72 – 3.33 (m, 3H), 3.19 – 2.69 (m, 4H), 2.46 – 2.01 (m, 2H), 2.17 – 2.14 (m, 3H), 2.12 – 2.04 (m, 1H), 1.17 (q, J = 7.6 Hz, 3H) ppm.

^{13}C NMR (151 MHz, CDCl_3 , **FWG-69B**) δ 173.2*, 173.0*, 168.4, 154.4*, 154.3*, 145.1*, 145.0*, 134.8*, 134.7*, 131.6*, 131.5*, 130.2*, 130.1*, 127.7*, 127.6*, 127.2*, 127.1*, 125.9*, 125.8*, 122.2* (2C), 122.1* (2C), 116.0* (2C), 115.9* (2C), 82.2 † , 81.9 † , 51.3 † , 50.5 † , 50.02 † , 49.98 † , 49.20 † , 49.15 † , 48.98 † , 48.96 † , 48.5, 42.2 † , 41.7 † , 28.2 † , 28.1 † , 24.52 † , 24.50 † , 9.21 † , 9.15 † ppm.

* rotamers; corresponding to 13C

† rotamers; corresponding to 9C

HRMS (FWG-69B) m/z calc. for $\text{C}_{24}\text{H}_{28}\text{ClN}_2\text{O}_3$ $^+$ $[\text{M}+\text{H}]^+$ 427.1788 found 427.1796.

NMR Spectra

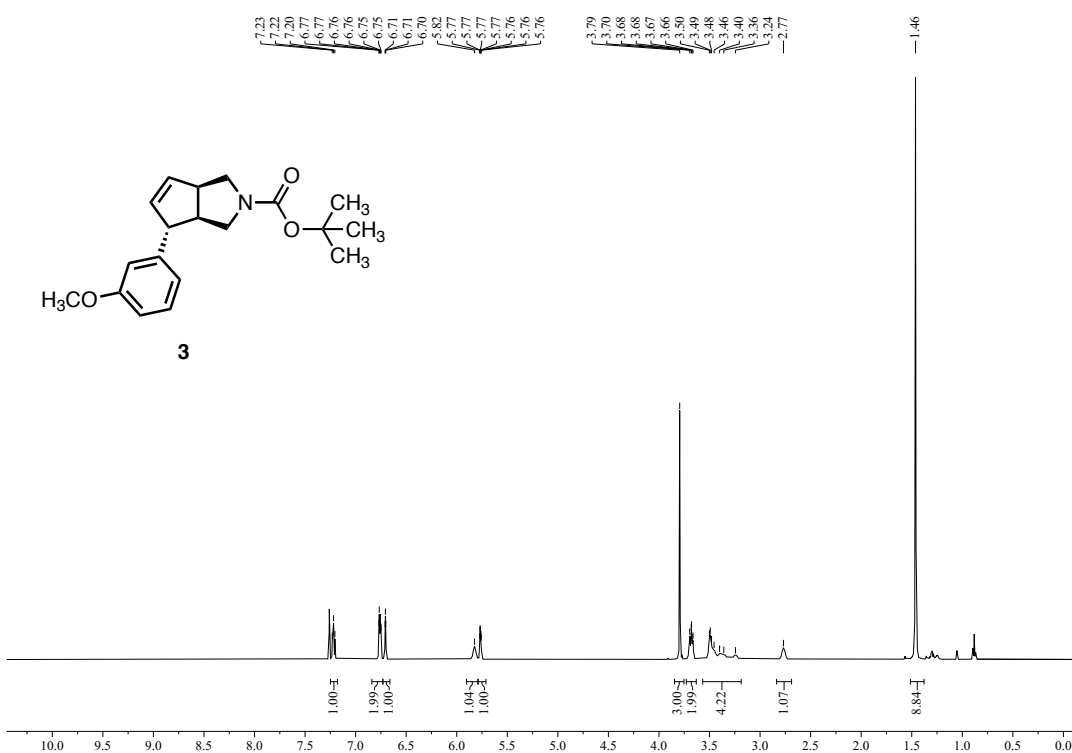


Figure S2: ¹H NMR (600 MHz, CDCl₃) of **3**.

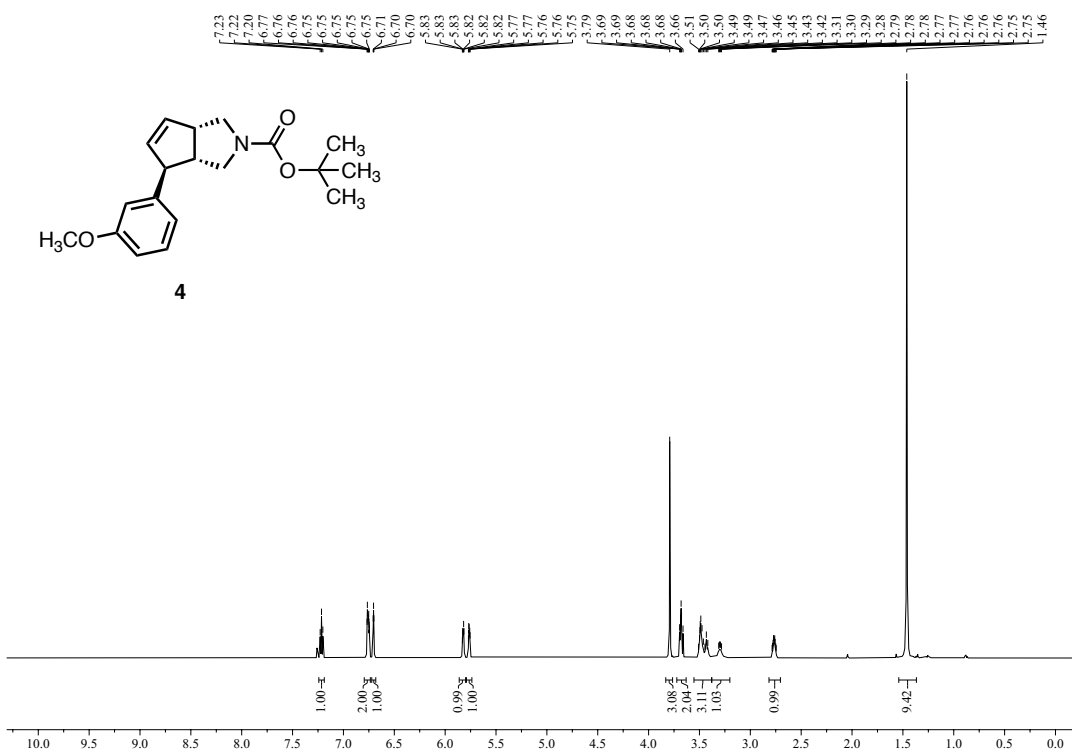


Figure S3: ¹H NMR (600 MHz, CDCl₃) of **4**.

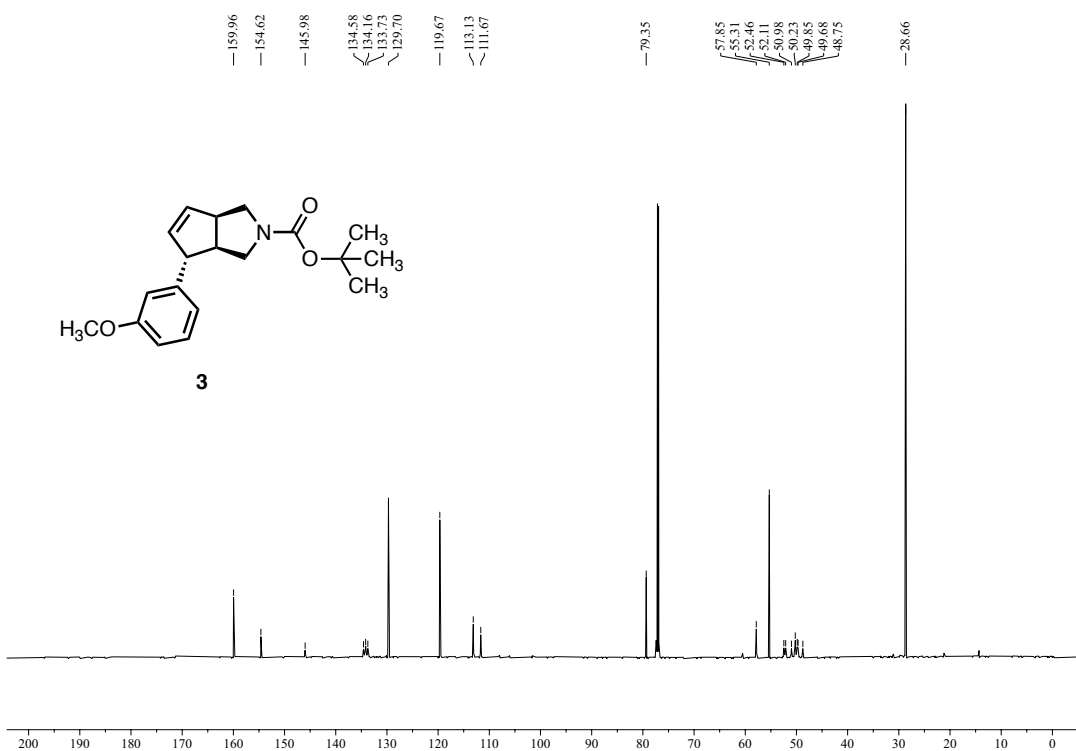
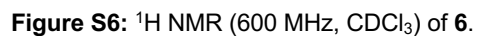
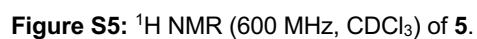


Figure S4: ¹³C NMR (151 MHz, CDCl₃) of **3**.



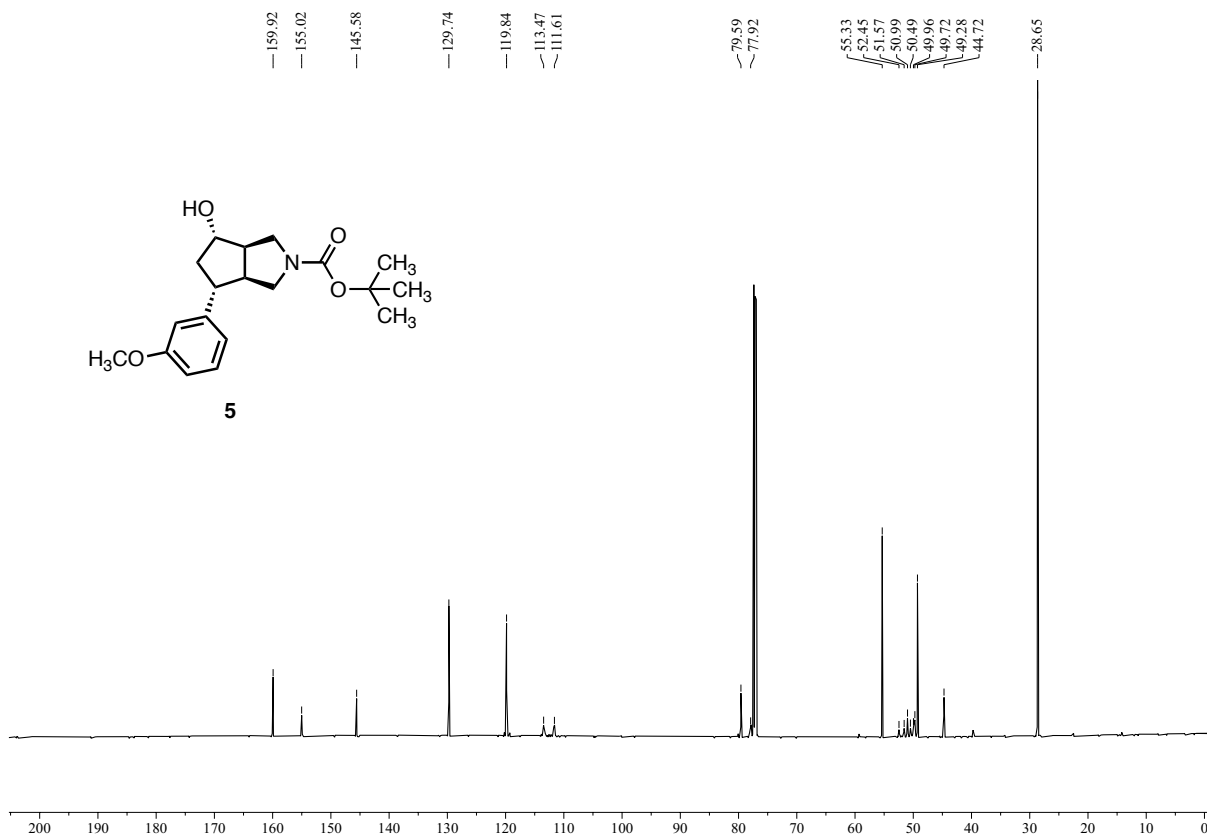


Figure S7: ^{13}C NMR (151 MHz, CDCl_3) of **5**.

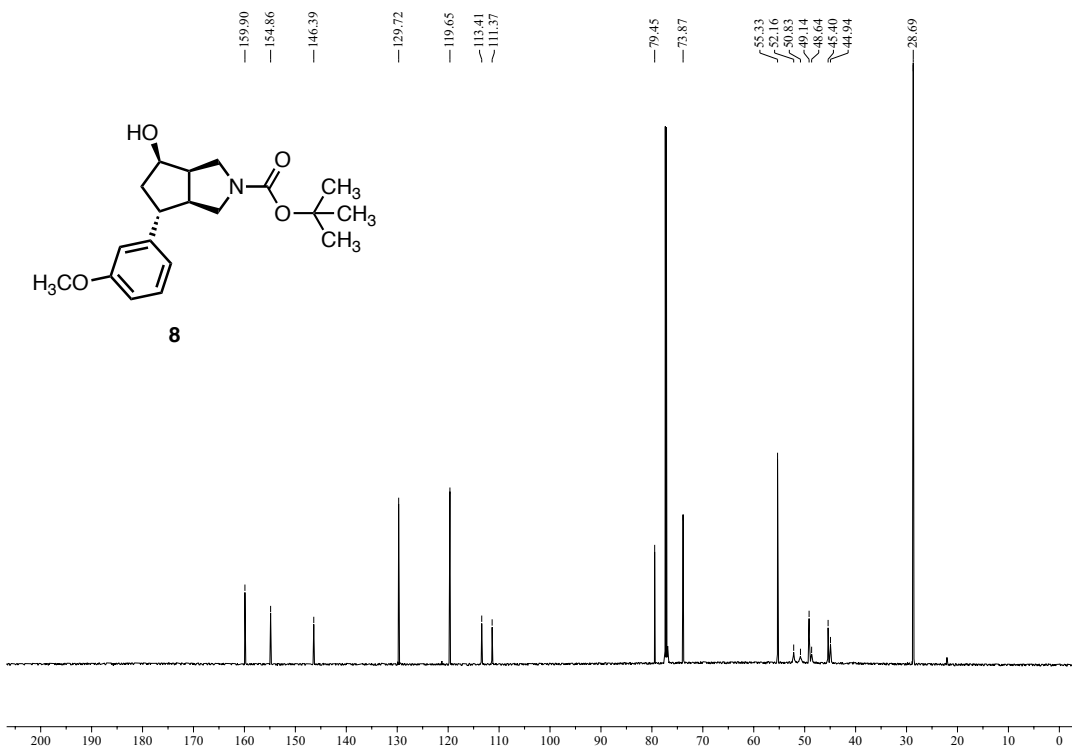


Figure S10: ^{13}C NMR (151 MHz, CDCl_3) of **8**.

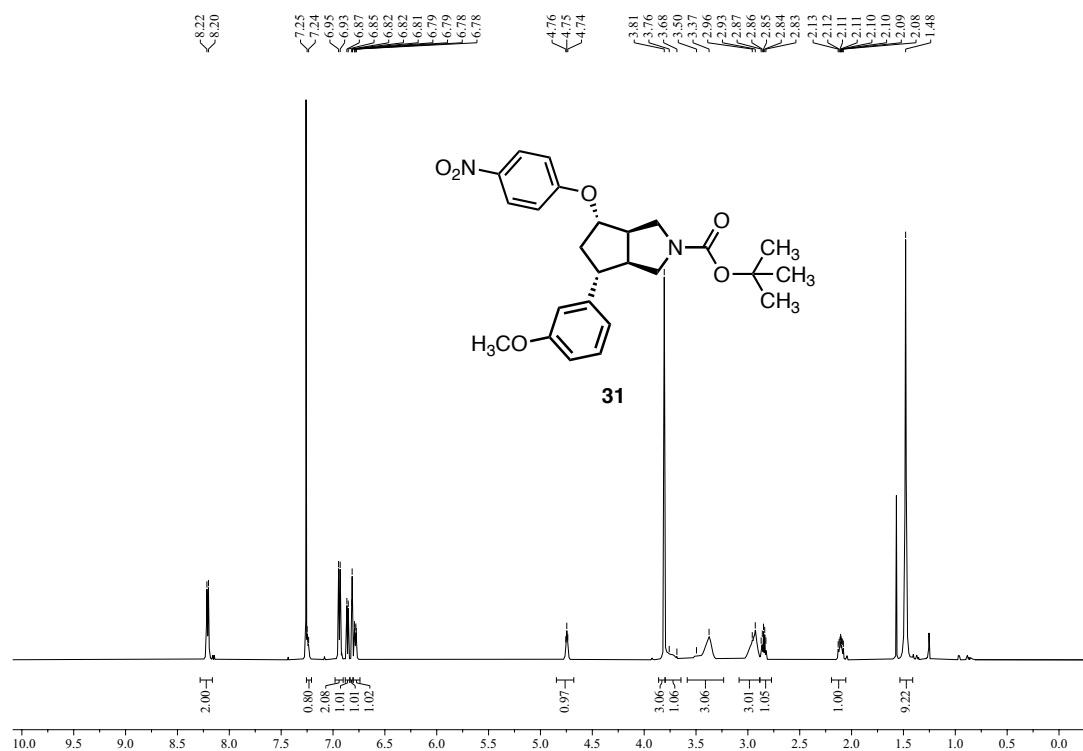


Figure S11: ^1H NMR (600 MHz, CDCl_3) of **31**.

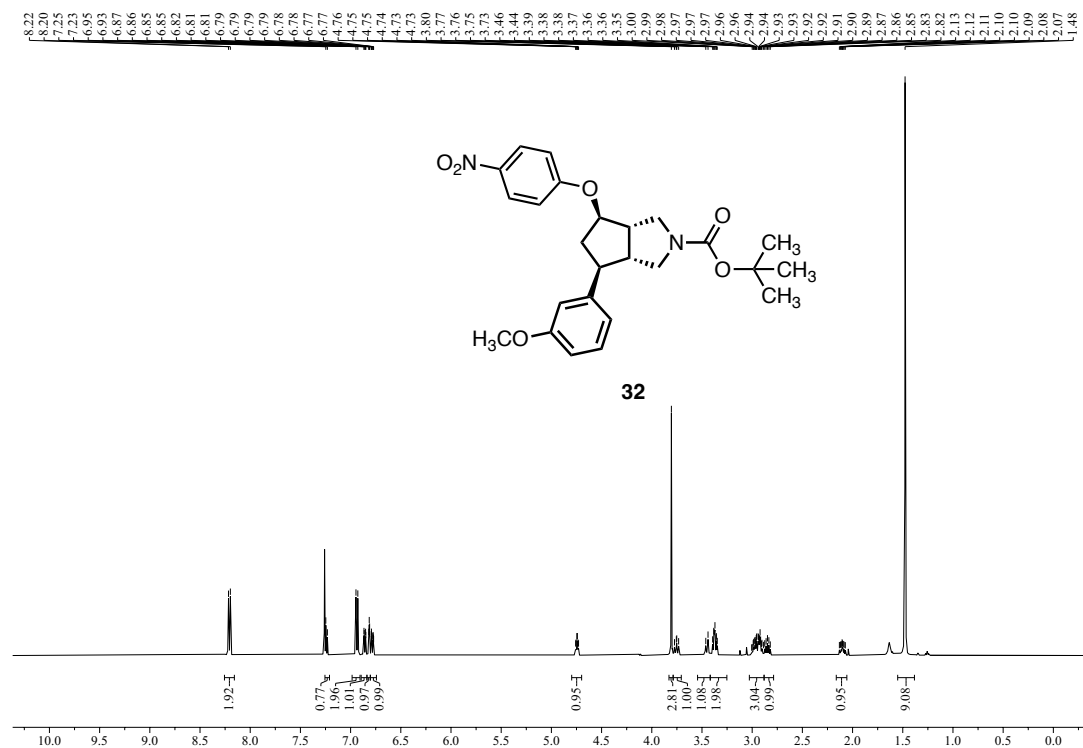


Figure S12: ^1H NMR (500 MHz, CDCl_3) of **32**.

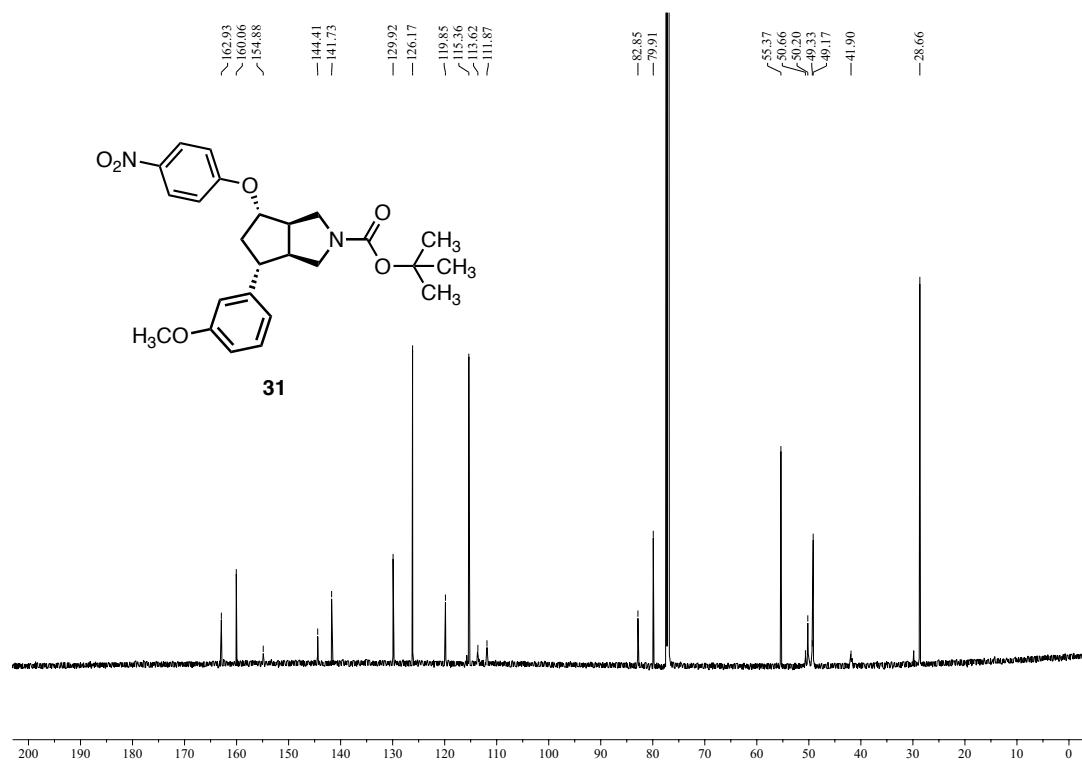


Figure S13: ¹³C NMR (151 MHz, CDCl₃) of **31**.

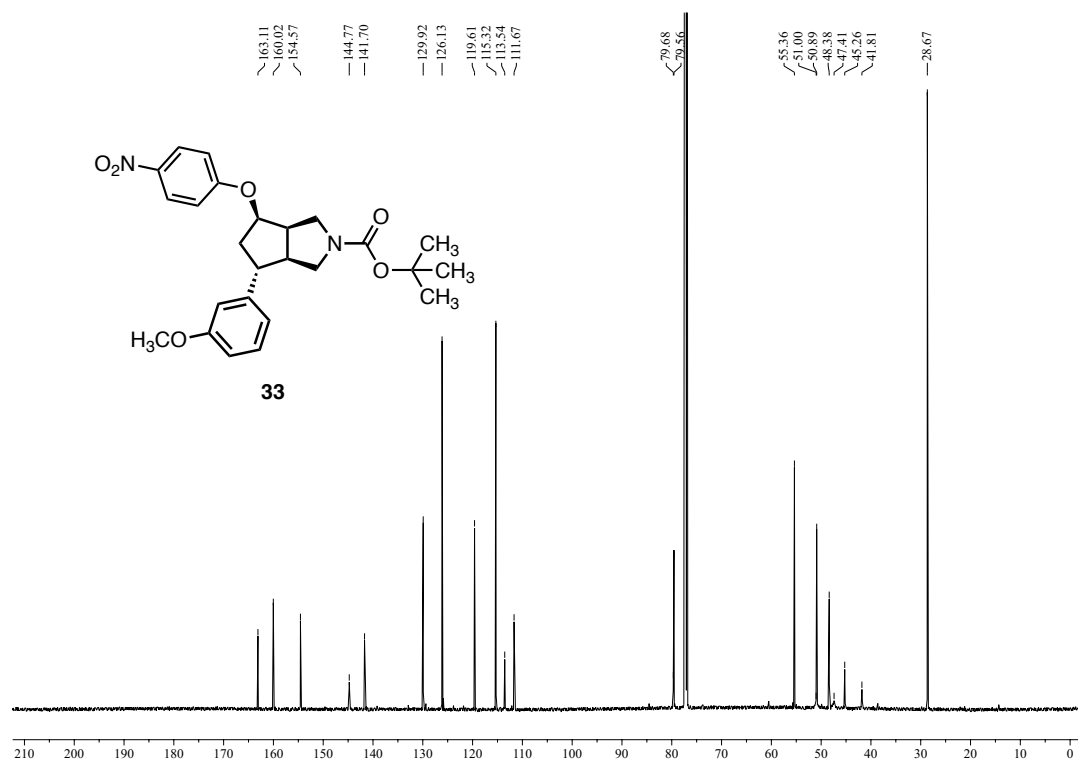


Figure S16: ^{13}C NMR (151 MHz, CDCl_3) of **33**.

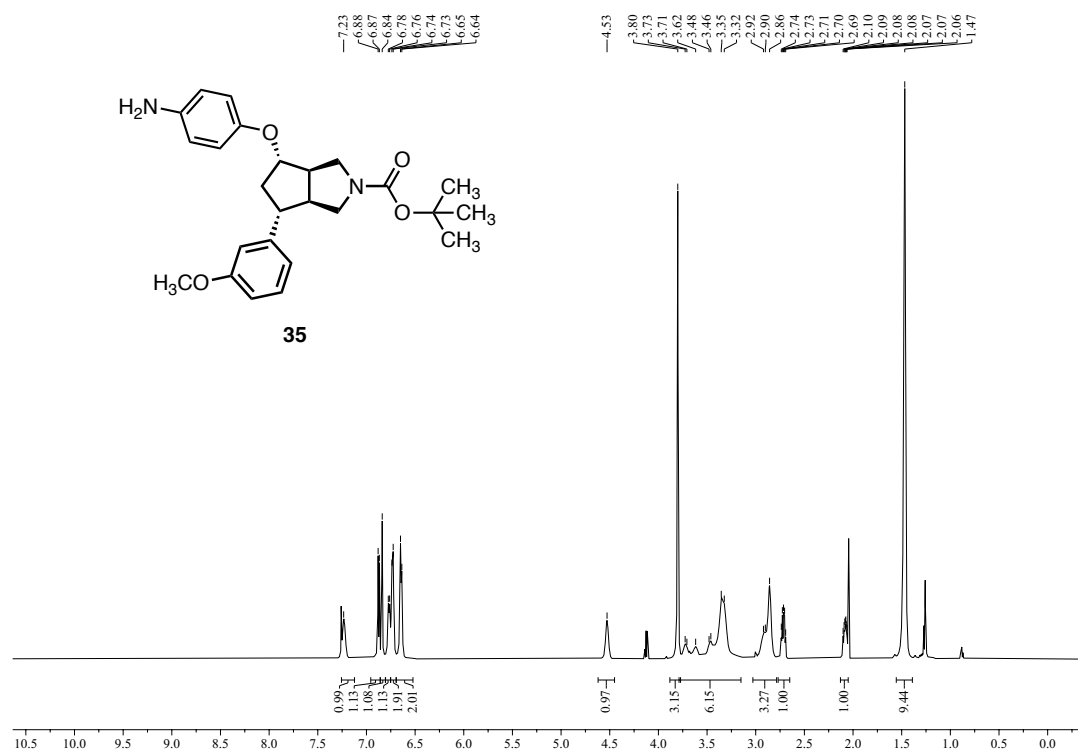


Figure S17: ¹H NMR (600 MHz, CDCl₃) of **35**.

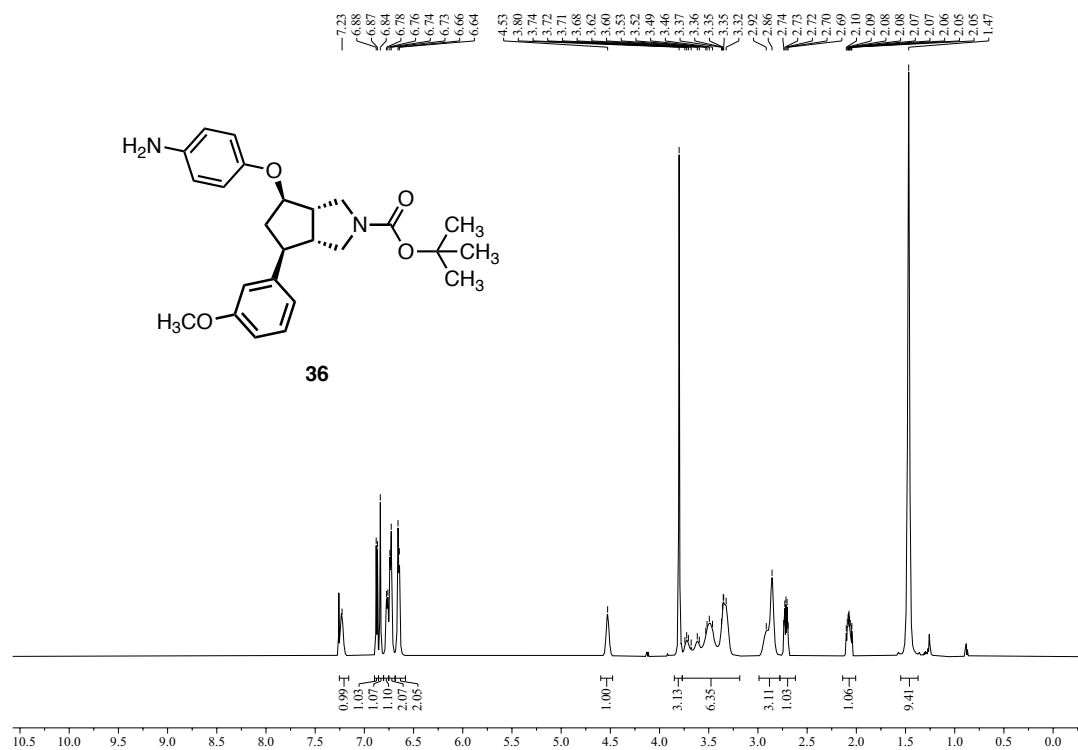


Figure S18: ¹H NMR (600 MHz, CDCl₃) of **36**.

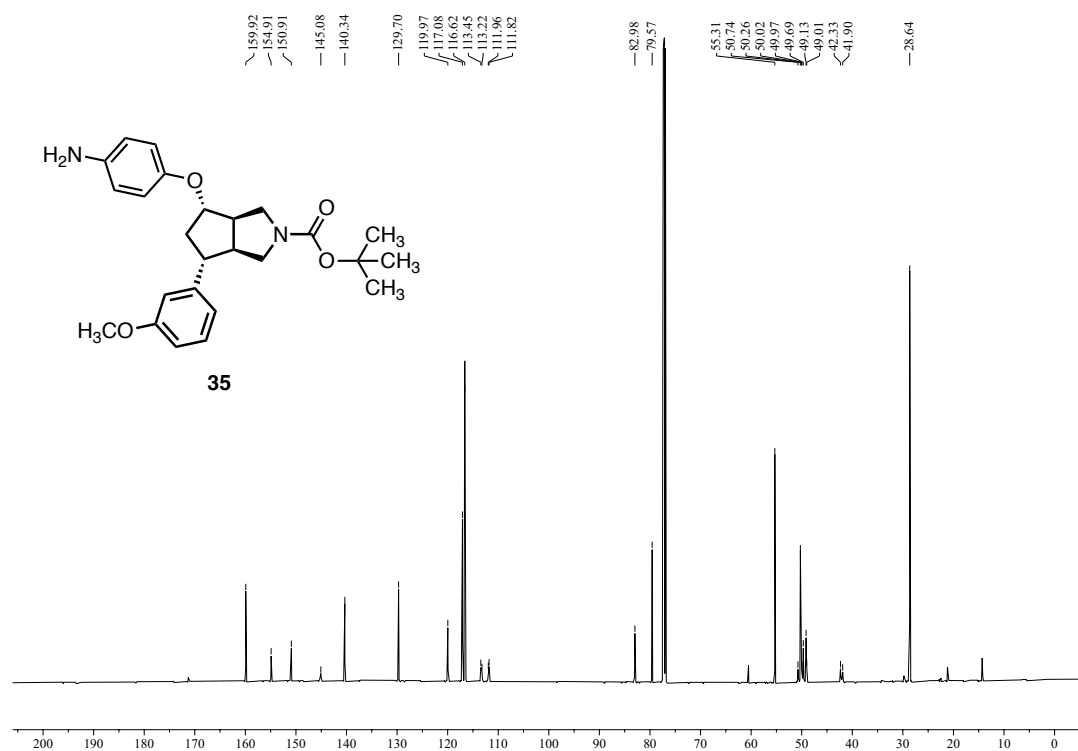


Figure S19: ^{13}C NMR (151 MHz, CDCl_3) of **35**.

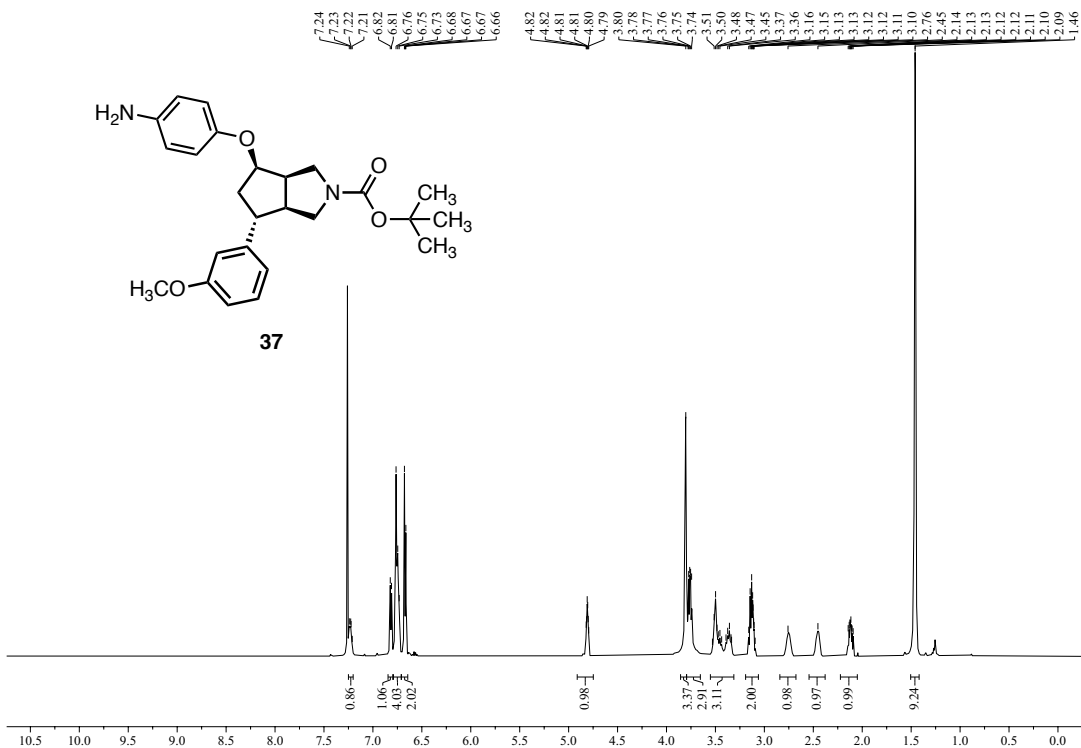


Figure S20: ¹H NMR (600 MHz) of **37**.

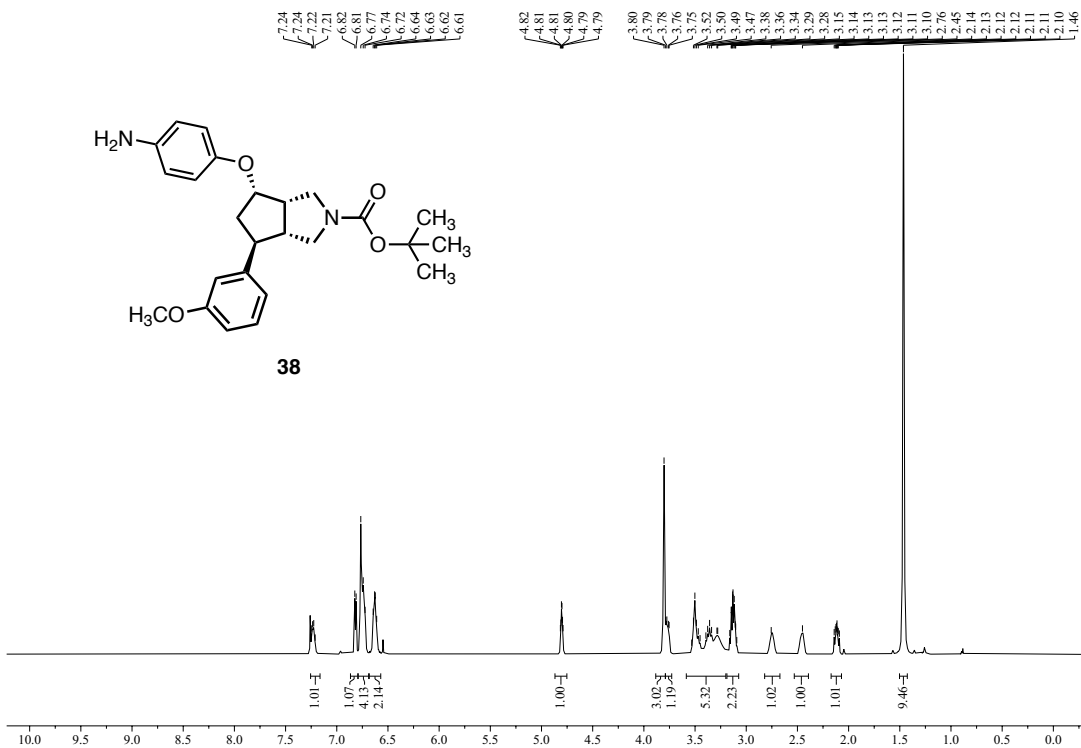


Figure S21: ¹H NMR (600 MHz, CDCl₃) of **38**.

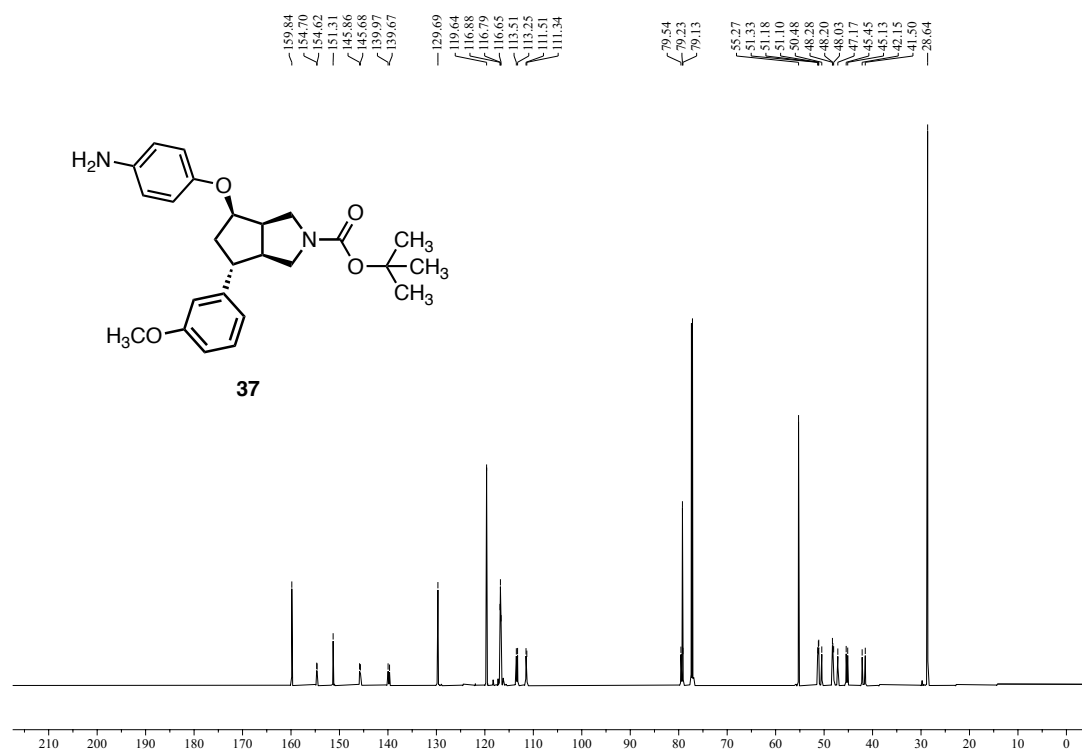
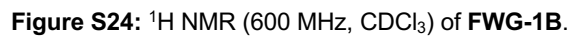
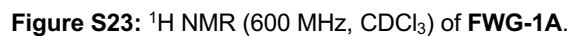


Figure S22: ^{13}C NMR (151 MHz, CDCl_3) of **37**.



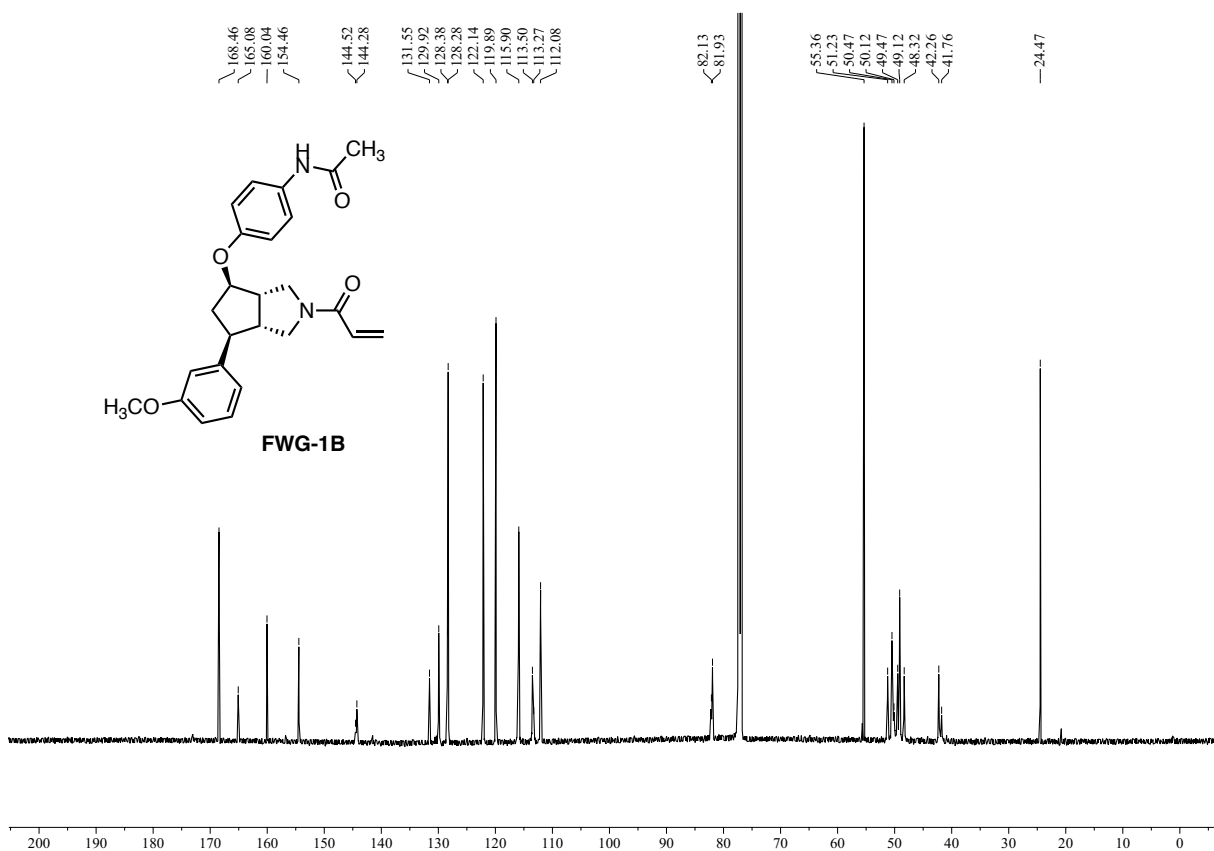


Figure S25: ¹³C NMR (151 MHz, CDCl₃) of **FWG-1B**.

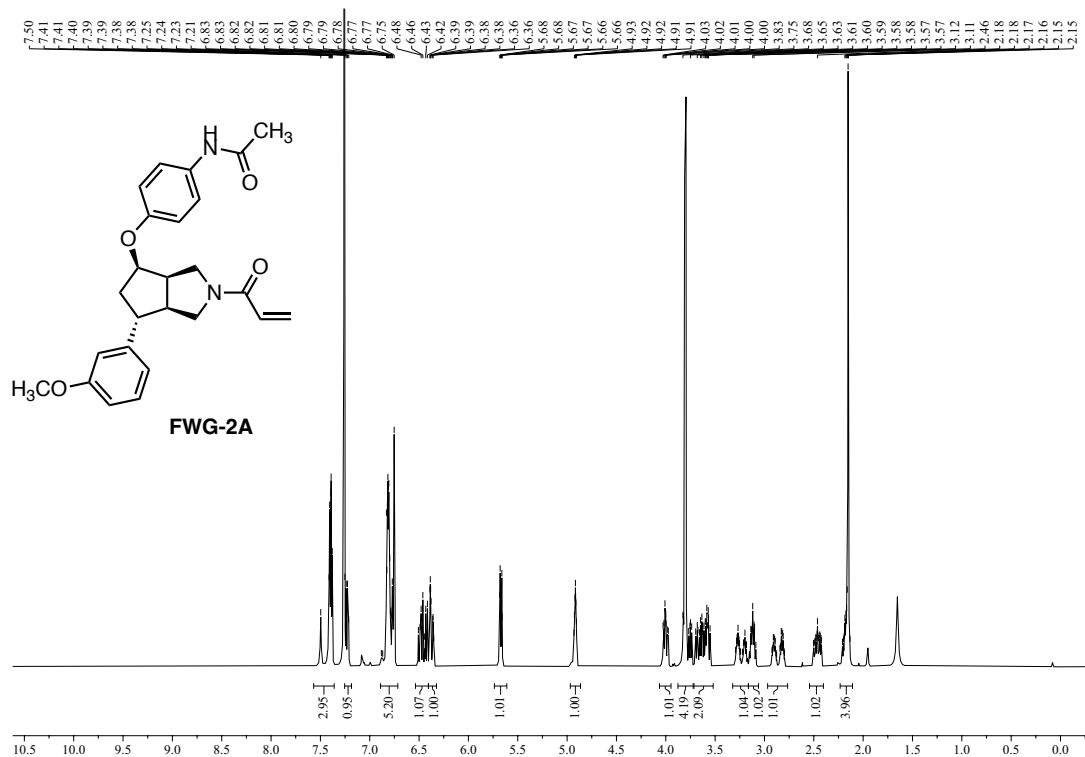


Figure S26: ¹H NMR (600 MHz, CDCl₃) of **FWG-2A**.

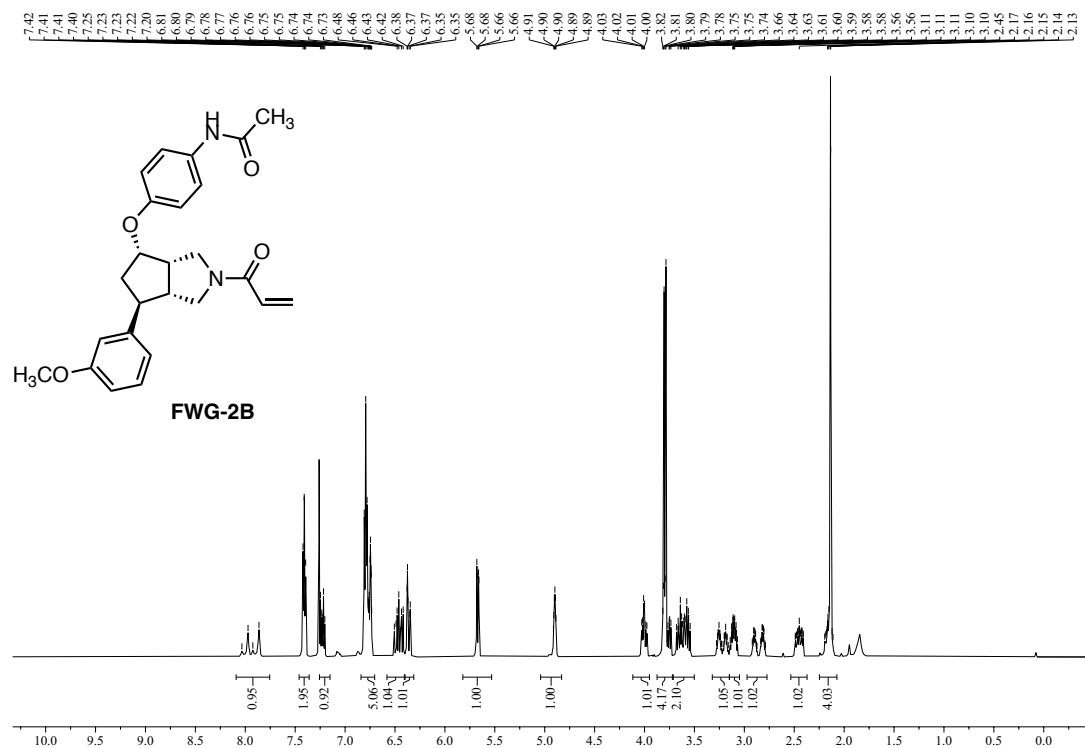


Figure S27: ¹H NMR (600 MHz, CDCl₃) of **FWG-2B**.

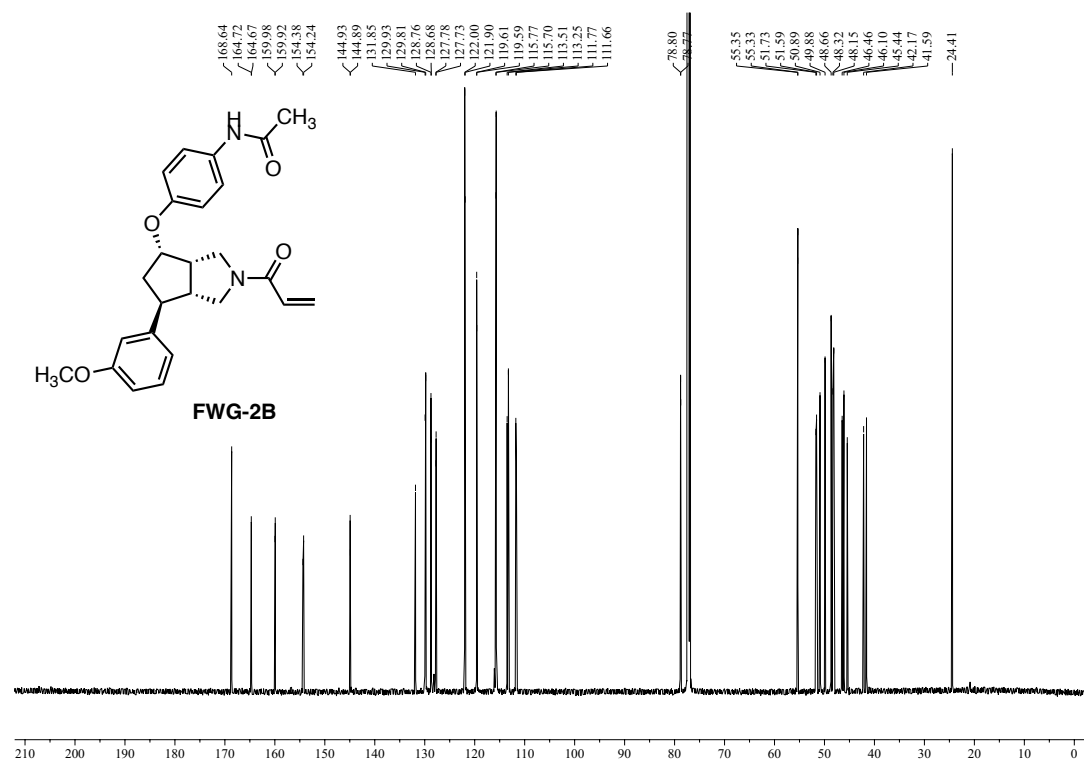
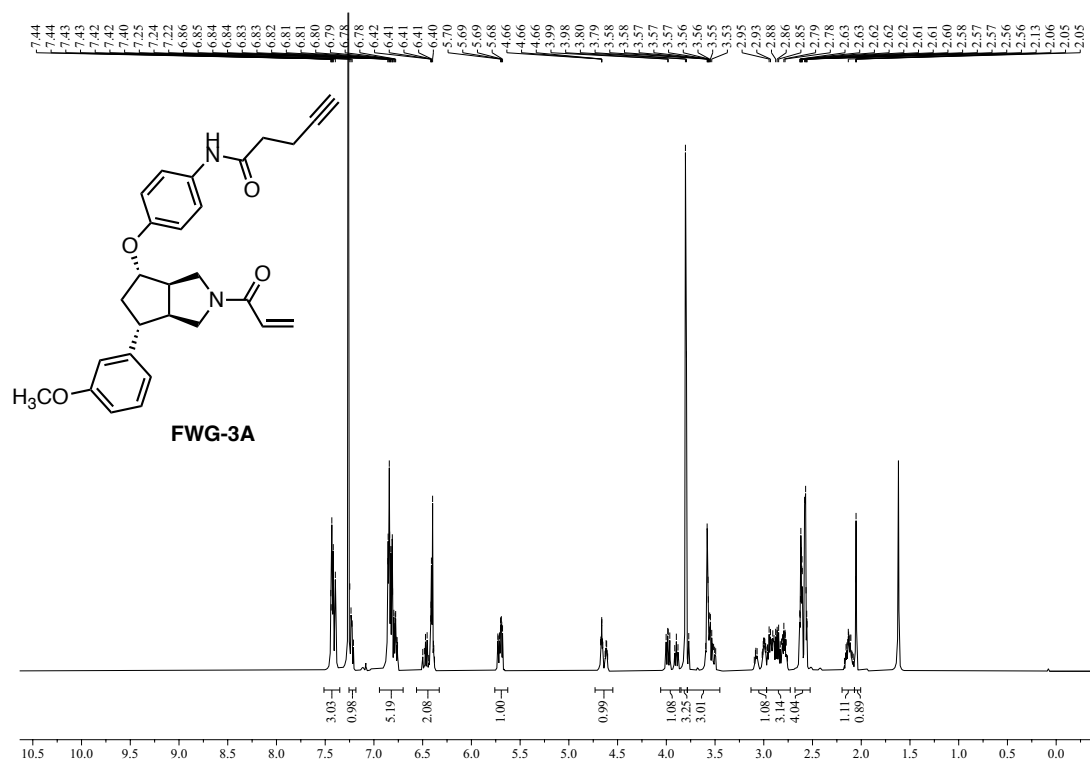


Figure S28: ¹³C NMR (151 MHz, CDCl₃) of **FWG-2B**.



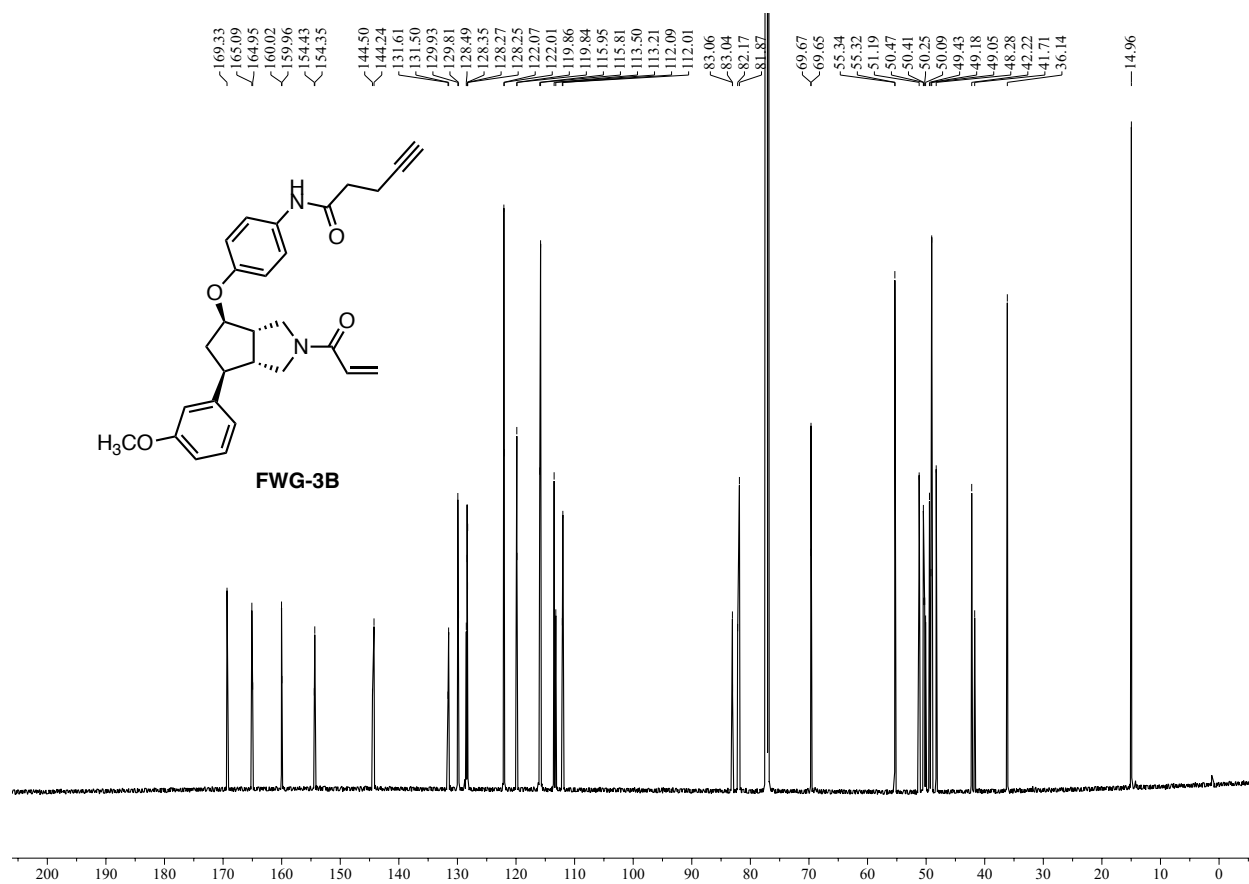


Figure S31: ¹³C NMR (151 MHz, CDCl₃) of **FWG-3B**.

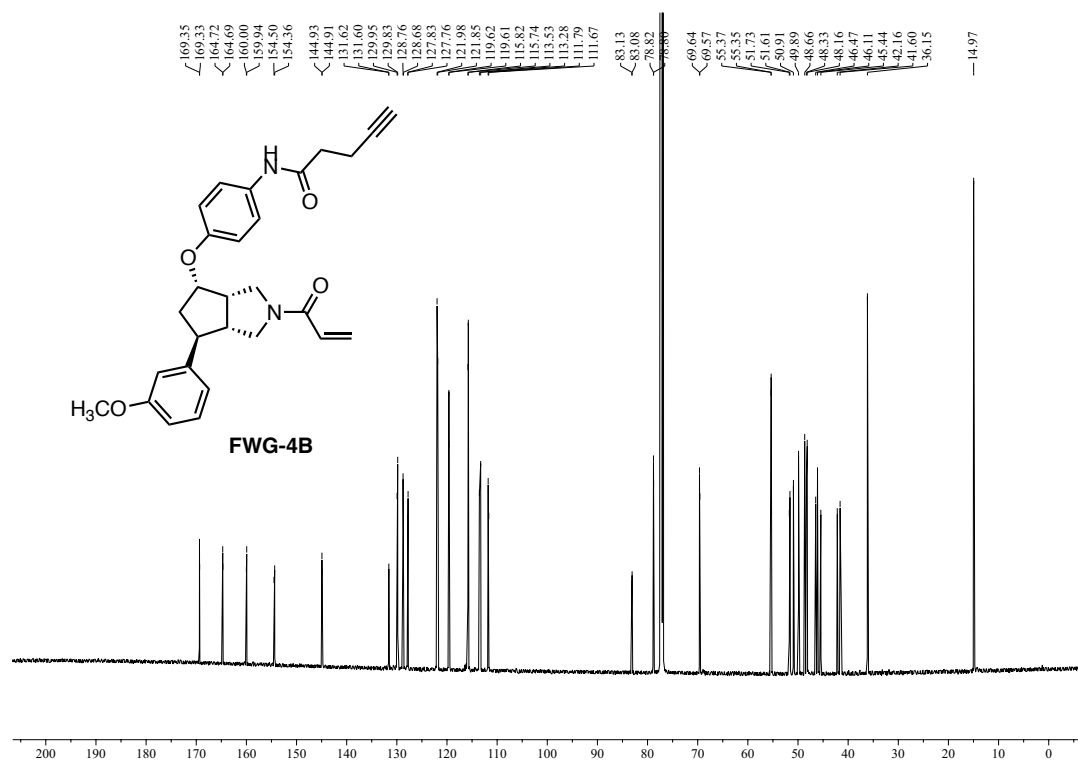


Figure S34: ¹³C NMR (151 MHz, CDCl₃) of **FWG-4B**.

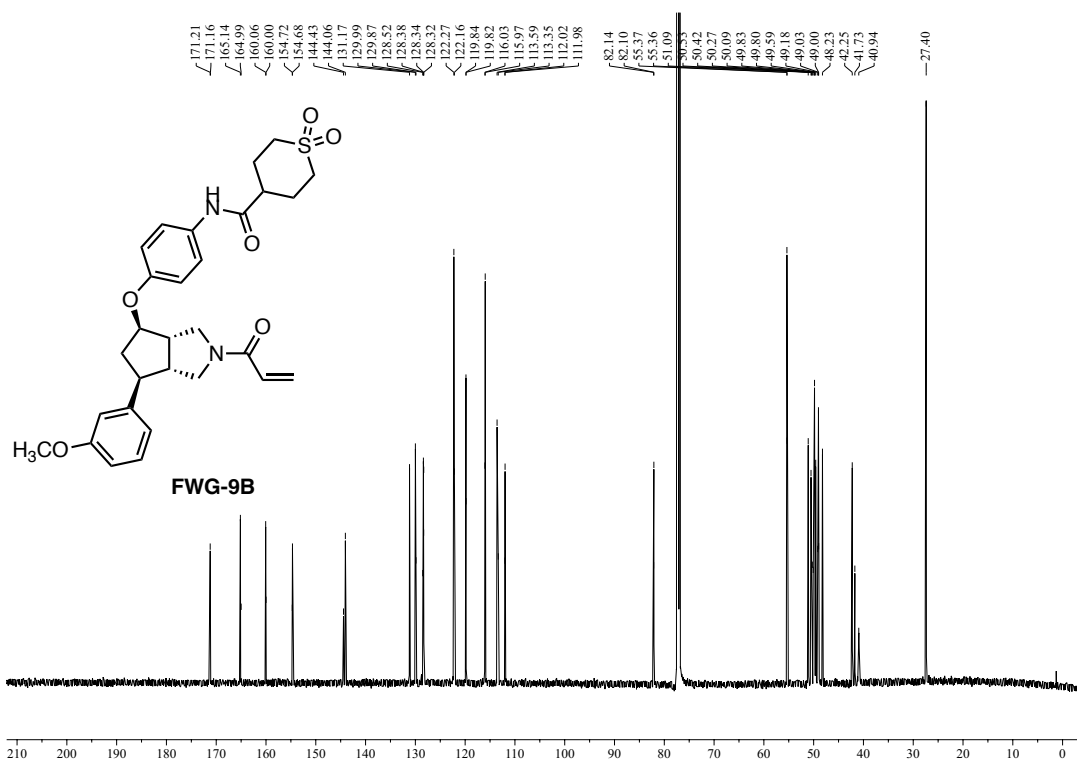


Figure S37: ^{13}C NMR (151 MHz, CDCl_3) of **FWG-9B**.

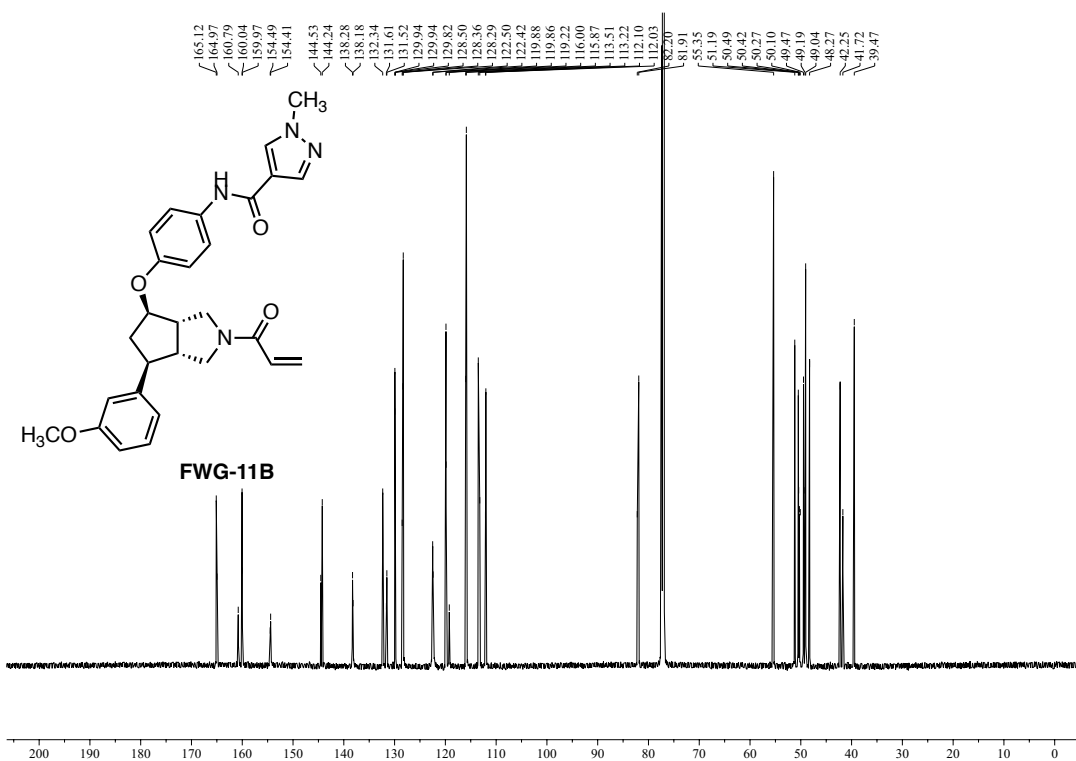


Figure S40: ¹³C NMR (151 MHz, CDCl₃) of **FWG-11B**.

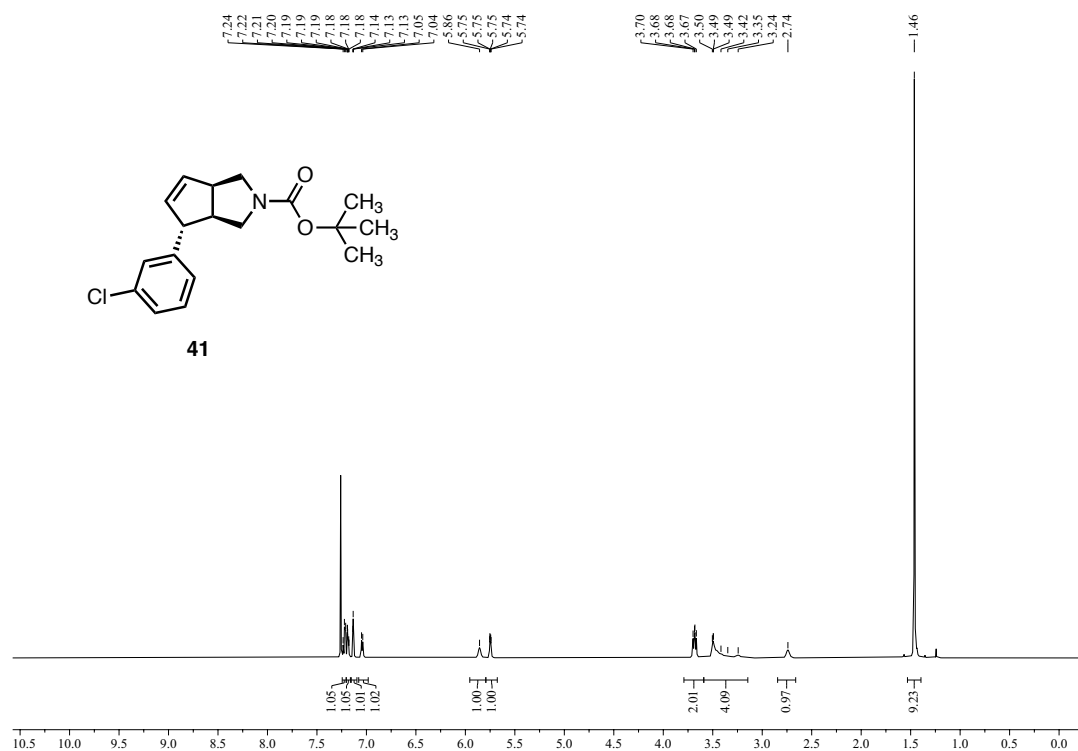


Figure S41: ^1H NMR (600 MHz, CDCl_3) of **41**.

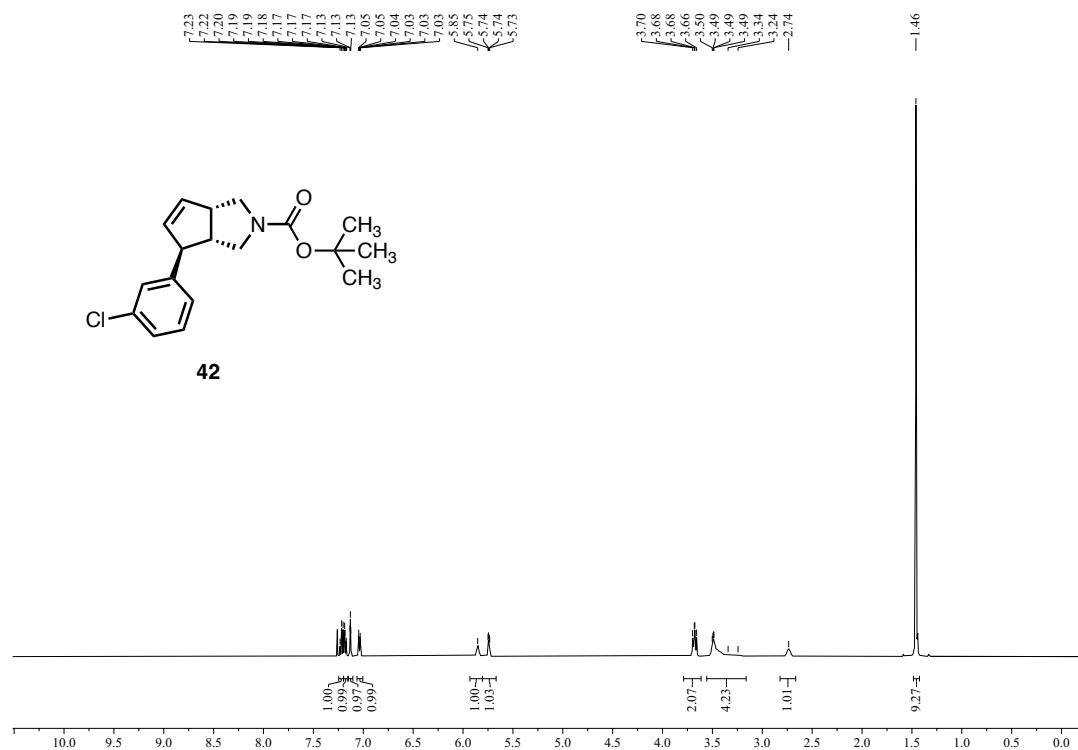


Figure S42: ^1H NMR (600 MHz, CDCl_3) of **42**.

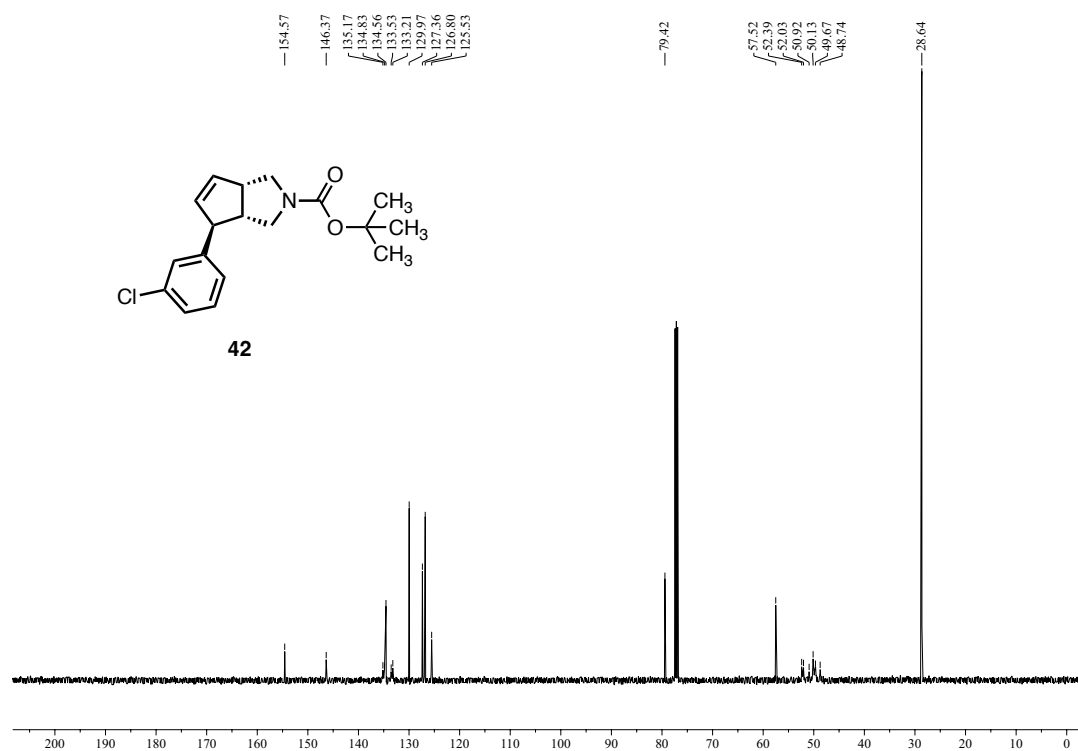


Figure S43: ¹³C NMR (151 MHz, CDCl₃) of **42**.

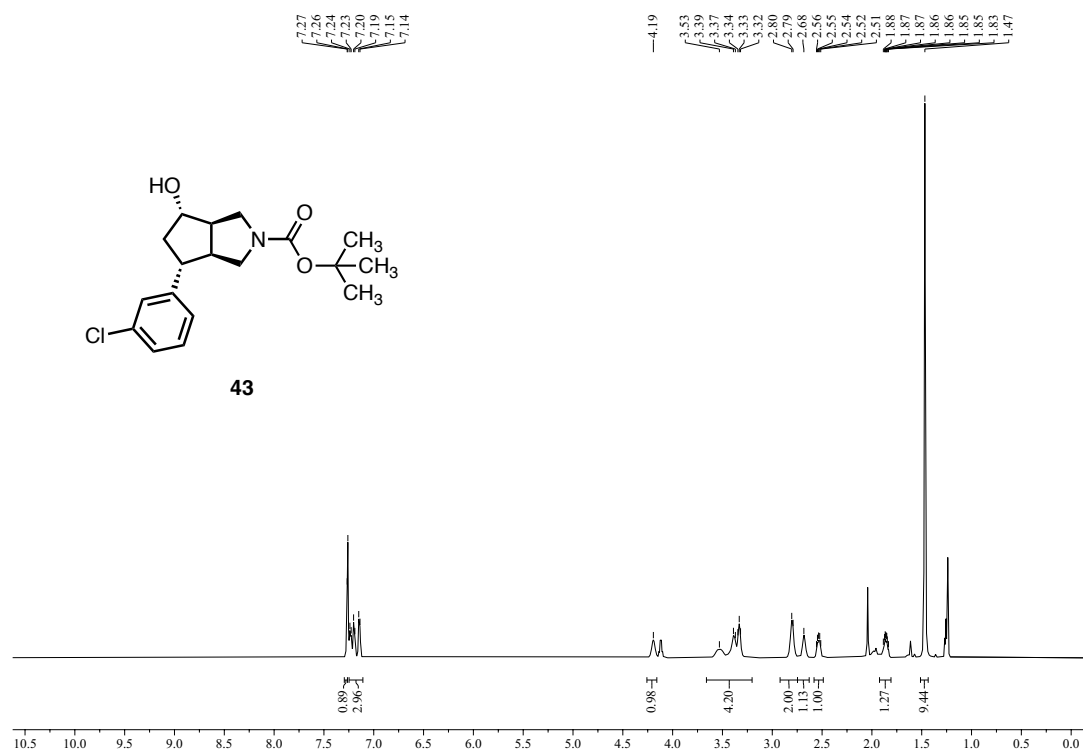


Figure S44: ¹H NMR (600 MHz, CDCl₃) of **43** (spectra contains a small amount of EtOAc).

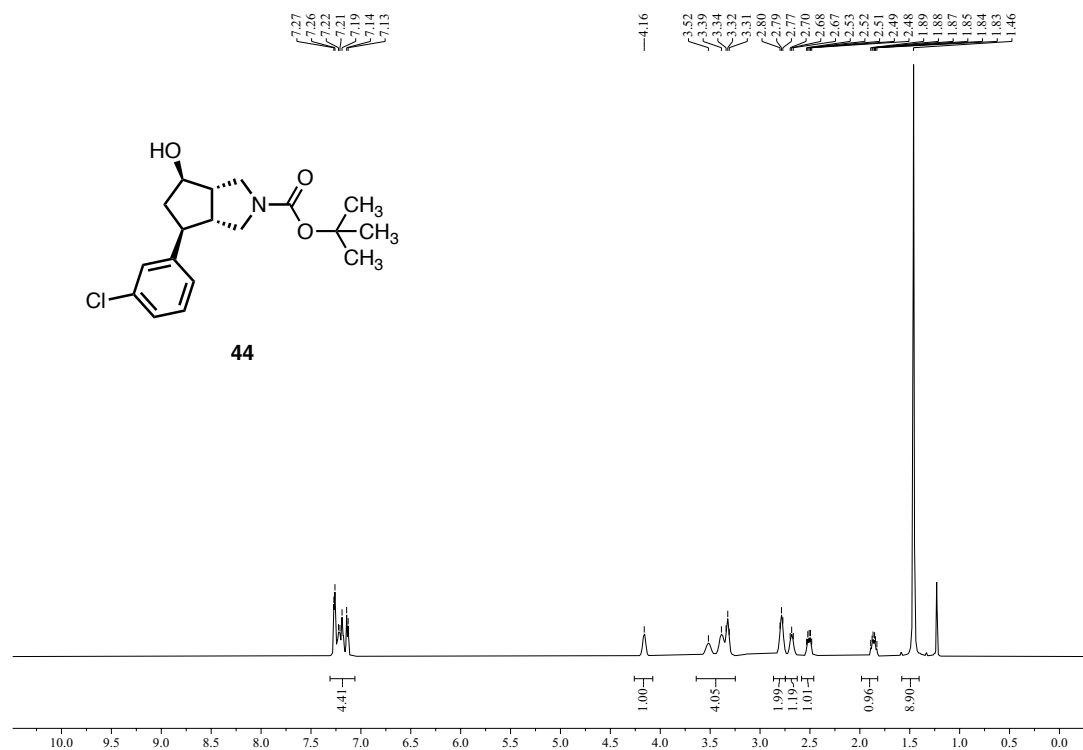


Figure S45: ¹H NMR (500 MHz, CDCl₃) of **44**.

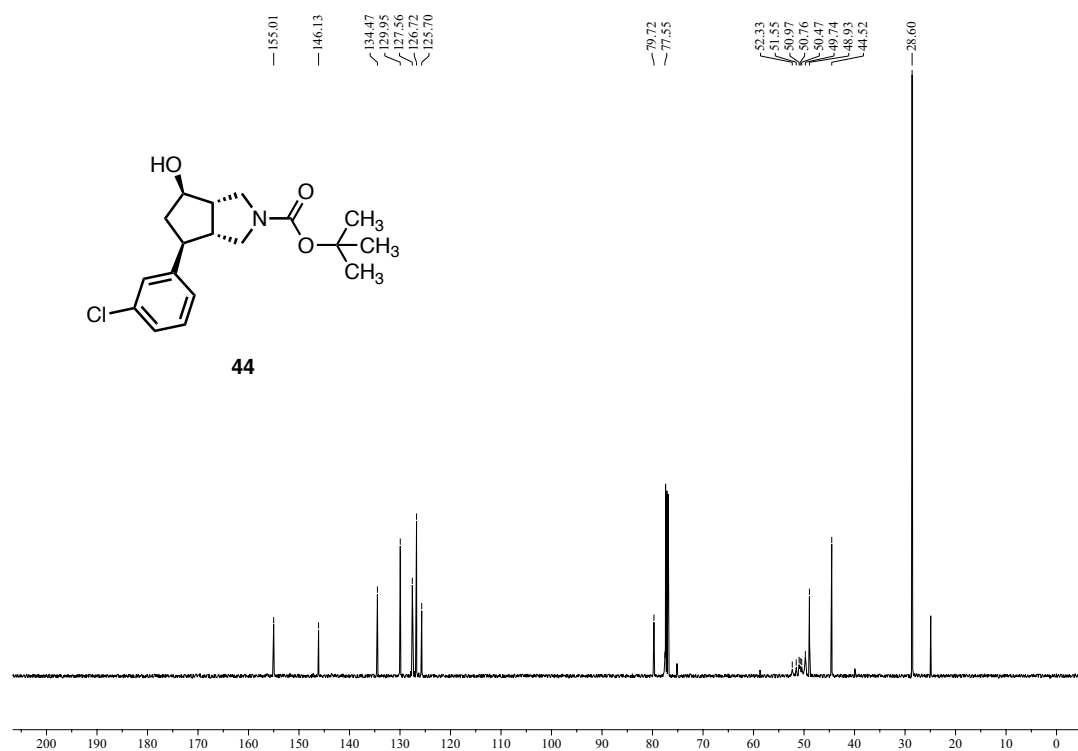


Figure S46: ¹³C NMR (126 MHz, CDCl₃) of **44**.

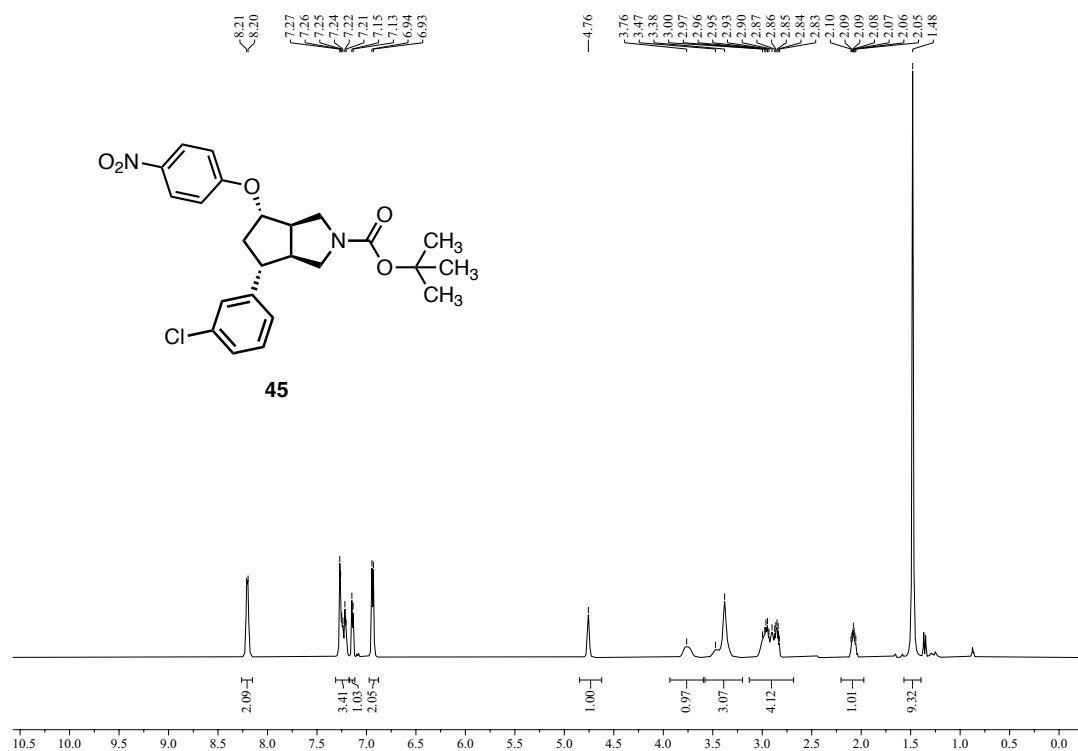


Figure S47: ¹H NMR (600 MHz, CDCl₃) of **45**.

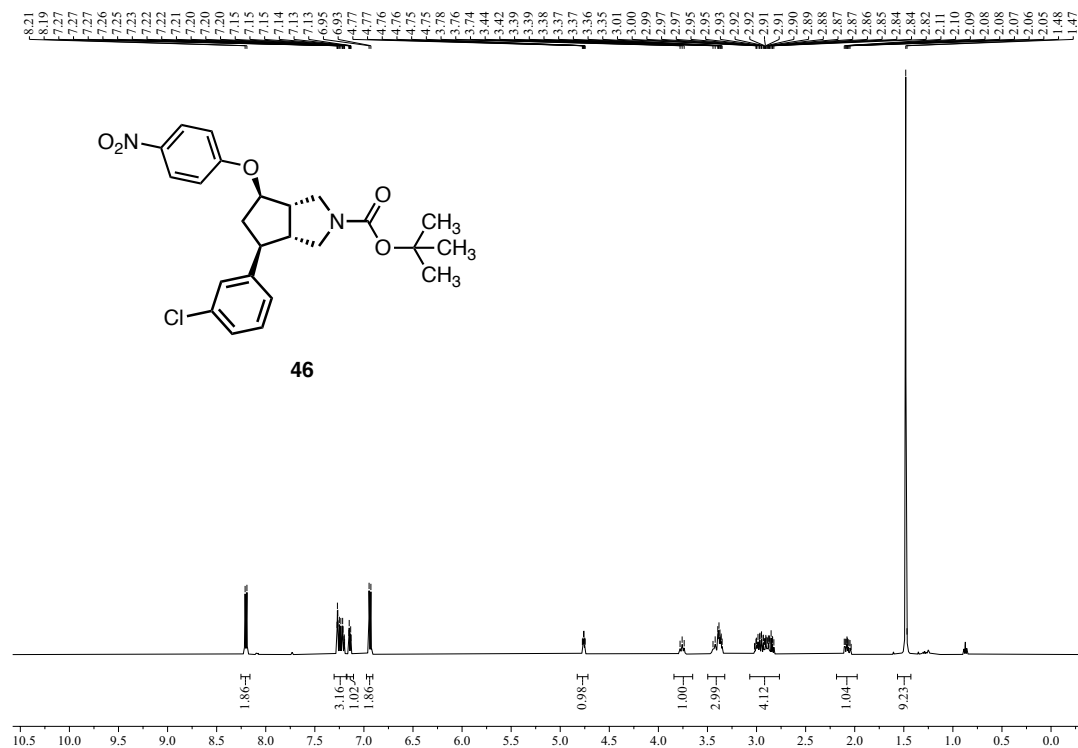


Figure S48: ¹H NMR (500 MHz, CDCl₃) of **46**.

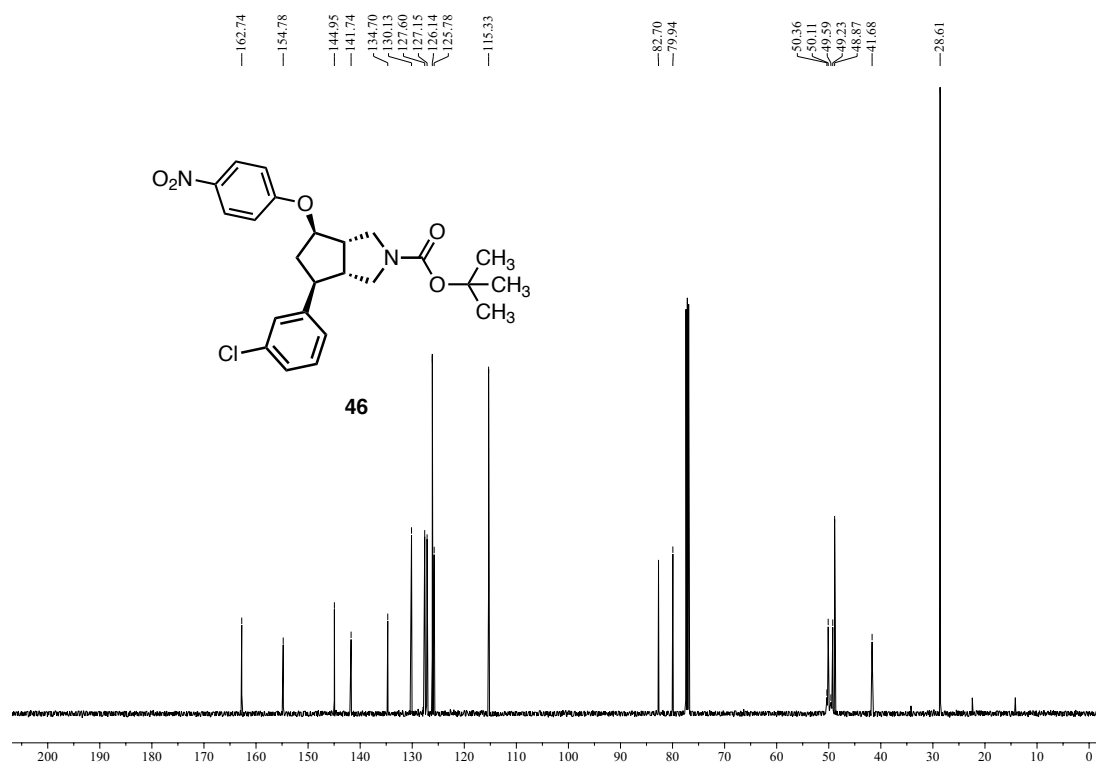


Figure S49: ^{13}C NMR (126 MHz, CDCl_3) of **46**.

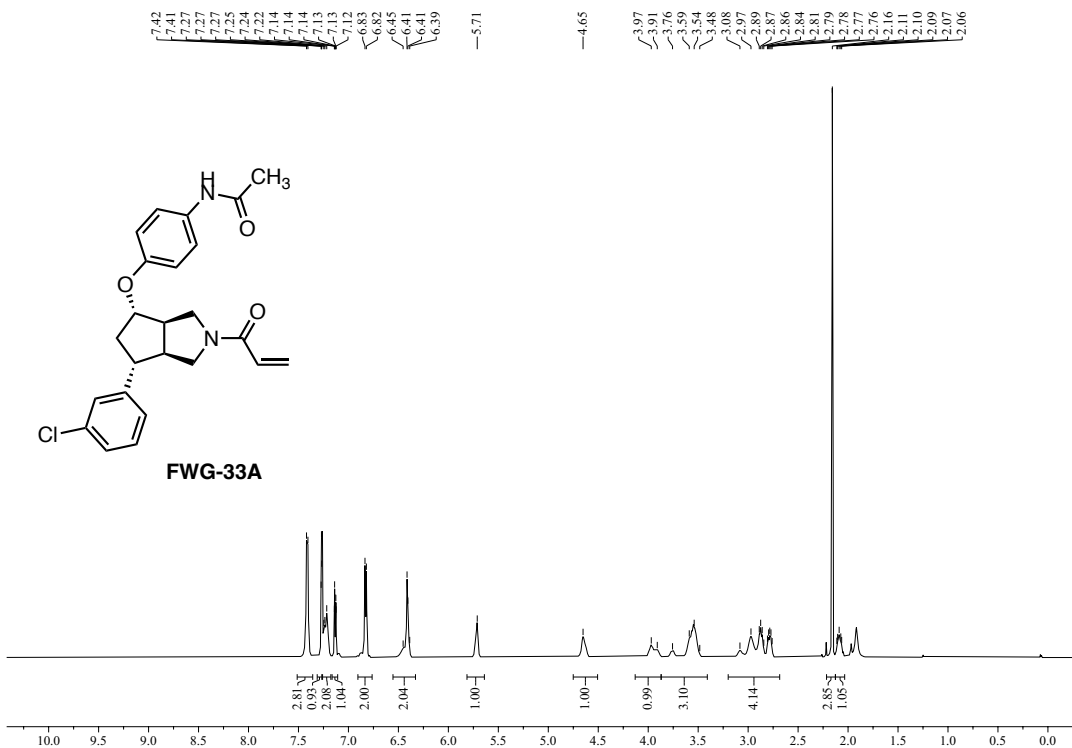


Figure S50: ^1H NMR (600 MHz, CDCl_3) of **FWG-33A**.

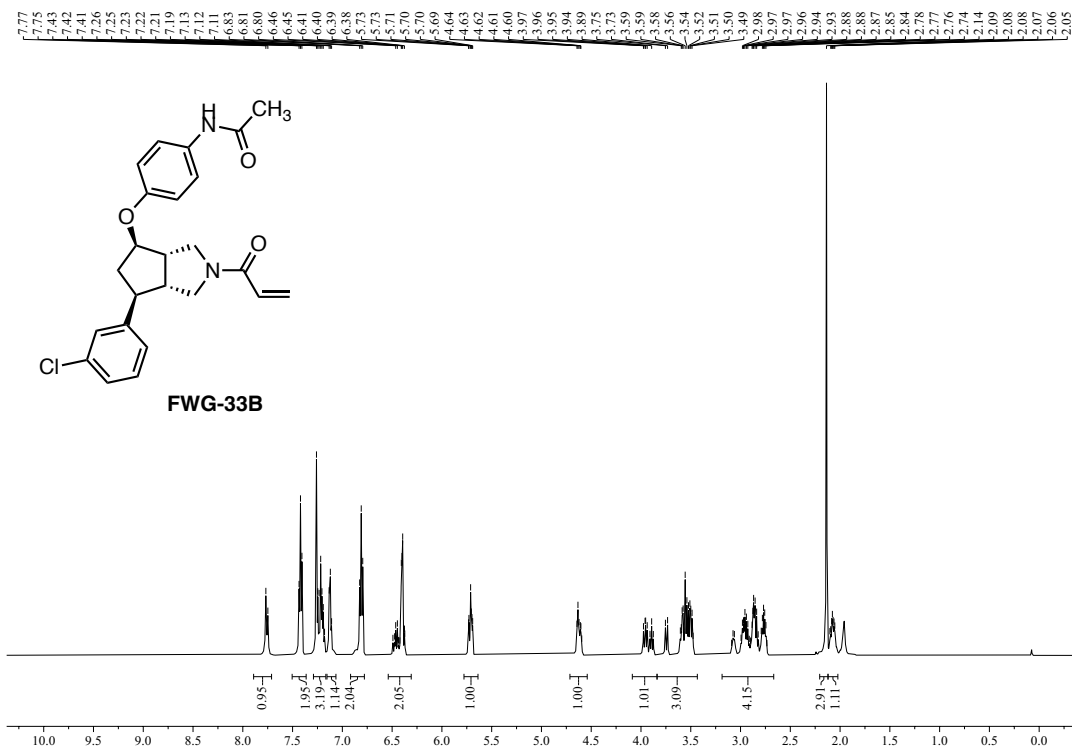


Figure S51: ^1H NMR (600 MHz, CDCl_3) of **FWG-33B**.

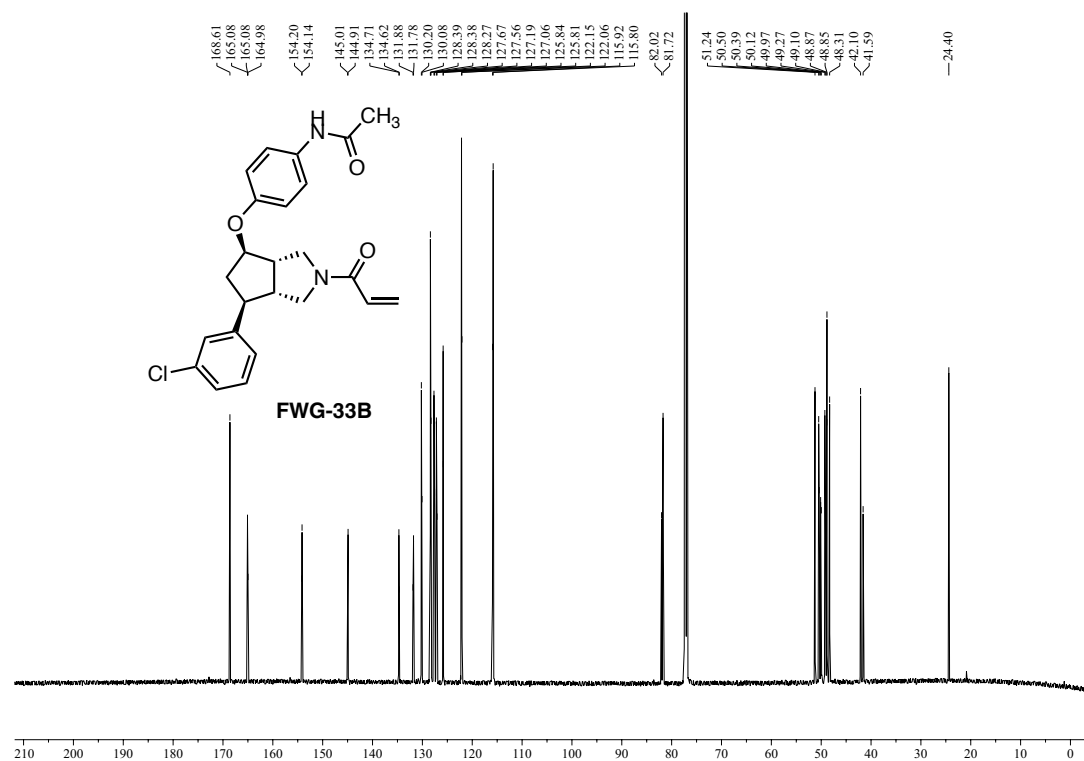


Figure S52: ¹³C NMR (151 MHz, CDCl₃) of **FWG-33B**.

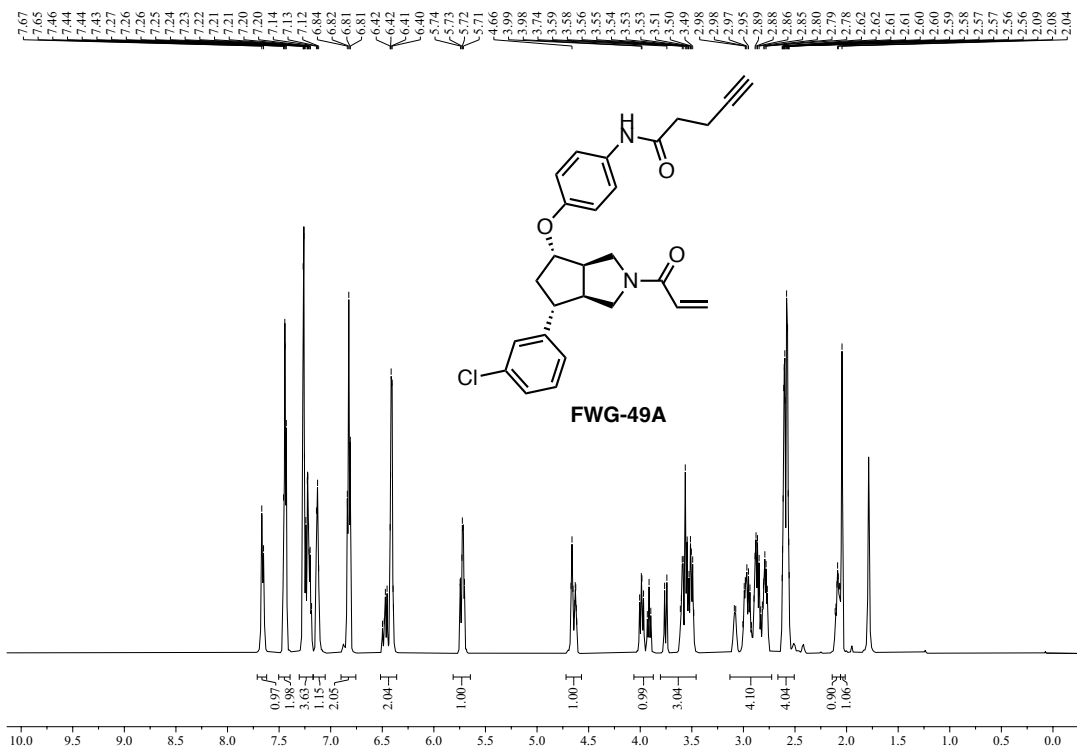


Figure S53: ¹H NMR (600 MHz, CDCl₃) of **FWG-49A**.

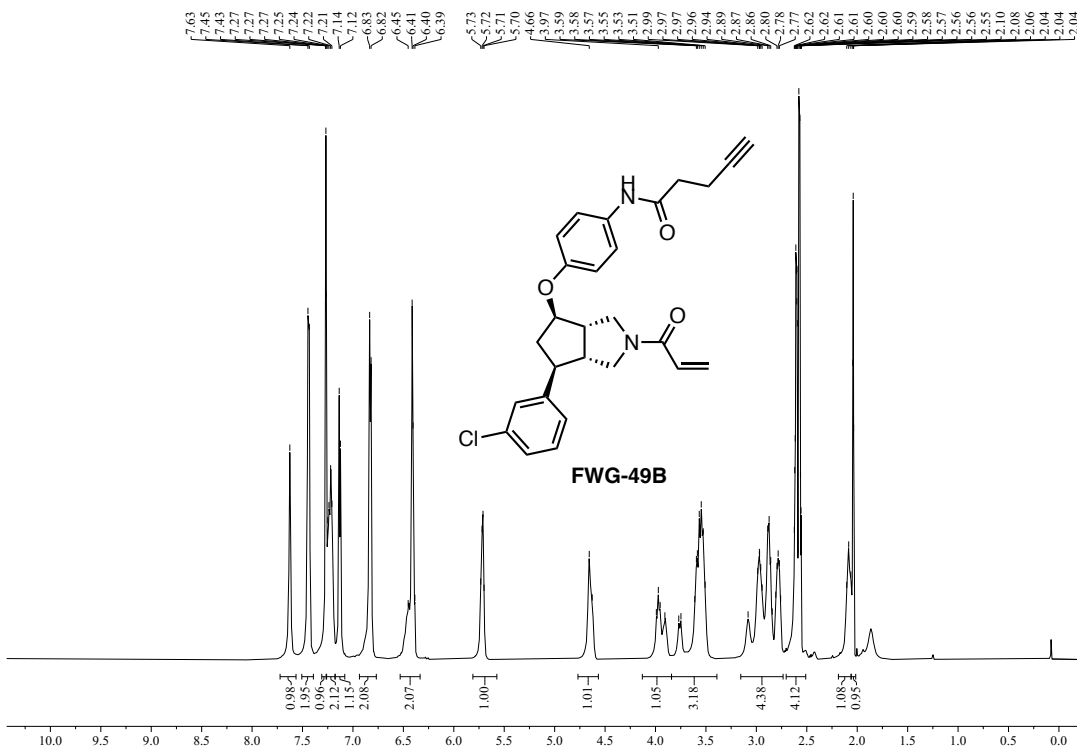


Figure S54: ¹H NMR (600 MHz, CDCl₃) of **FWG-49B**.

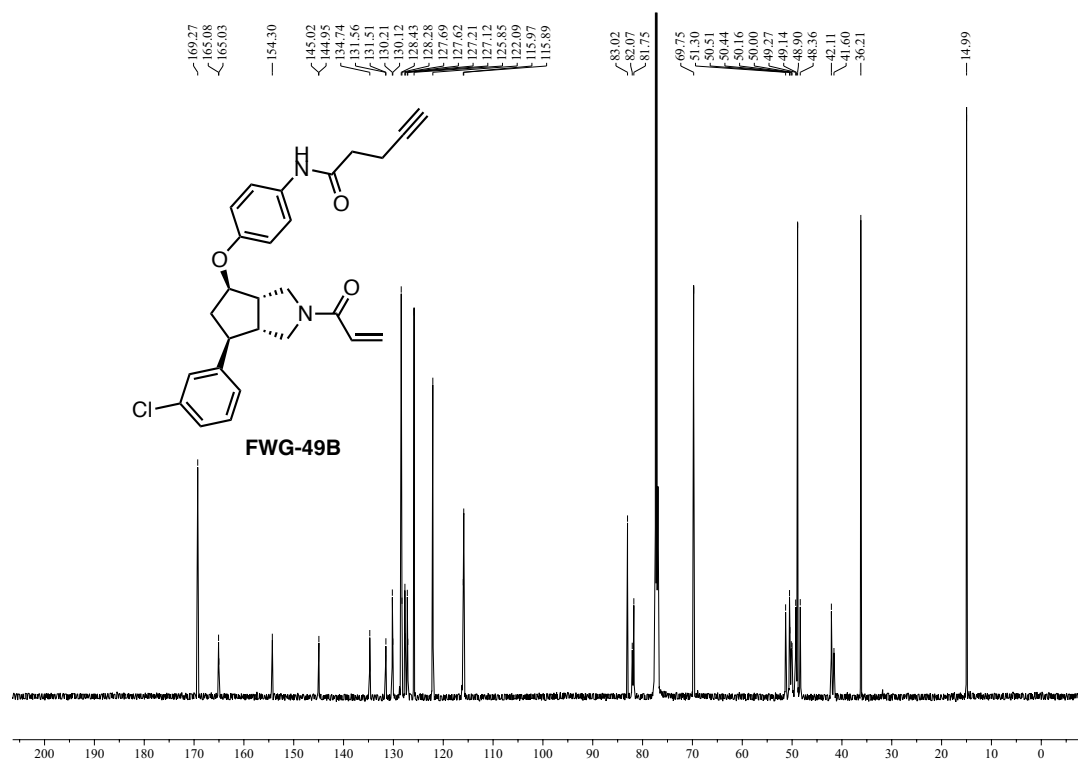


Figure S55: ¹³C NMR (600 MHz, CDCl₃) of **FWG-49B**.

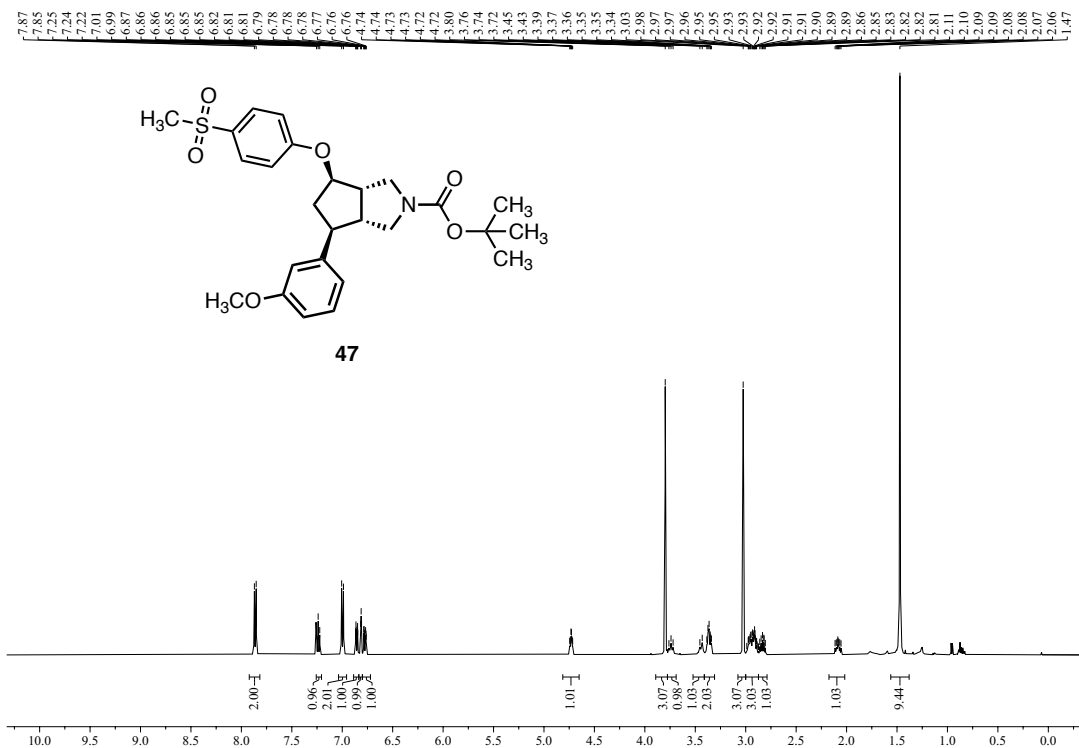


Figure S56: ¹H NMR (500 MHz, CDCl₃) of **47**.

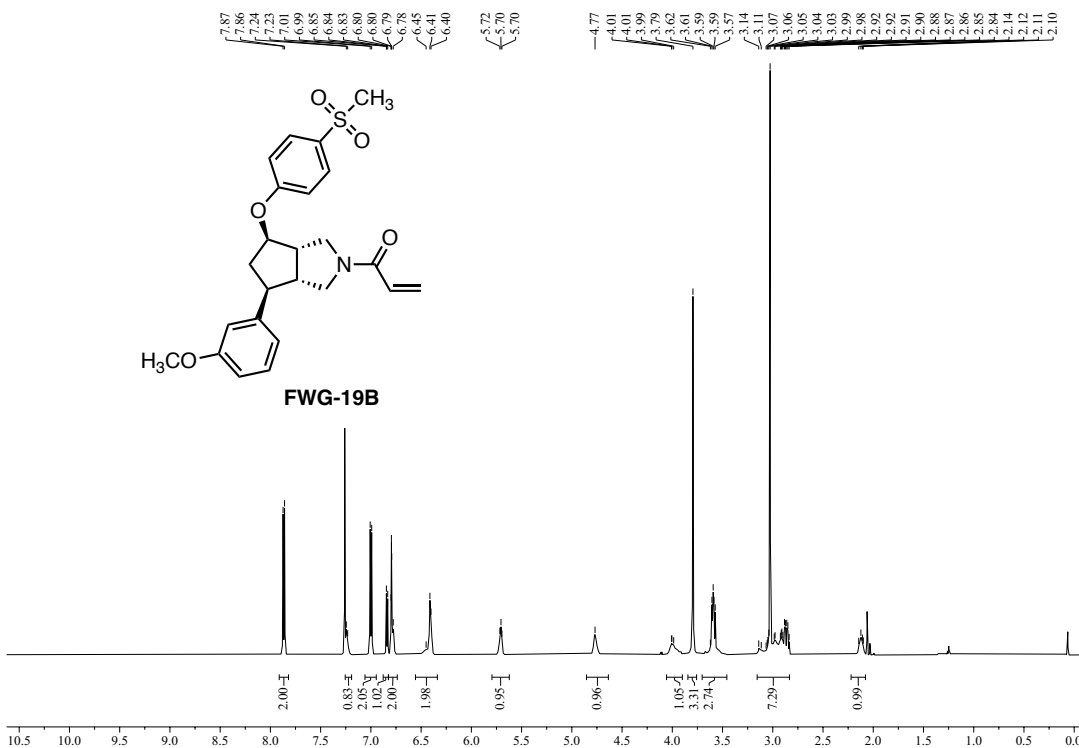


Figure S57: ¹H NMR (500 MHz, CDCl₃) of **FWG-19B**.

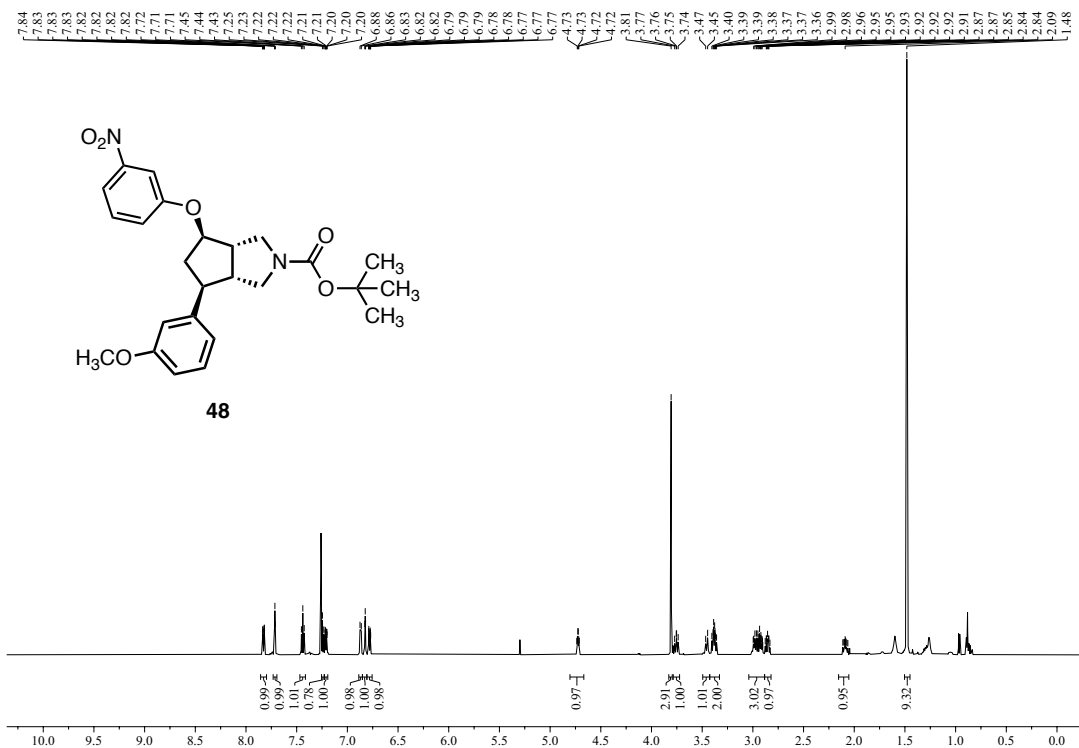


Figure S58: ¹H NMR (600 MHz, CDCl₃) of **48**.

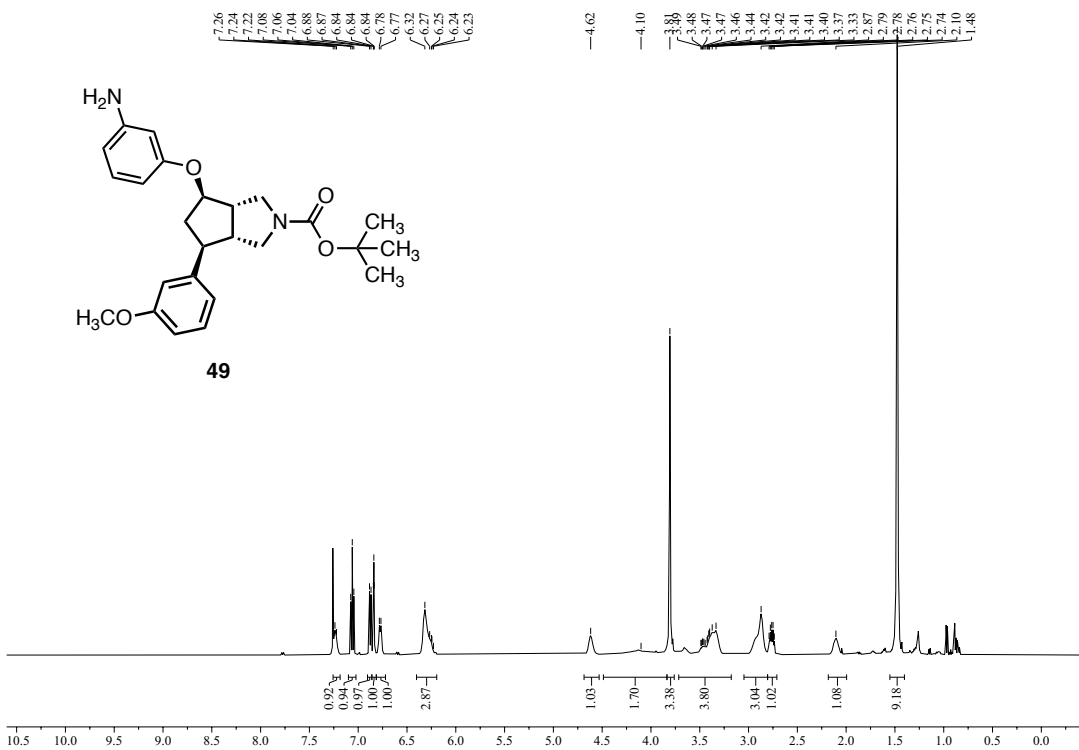


Figure S59: ¹H NMR (500 MHz, CDCl₃) of **49**.

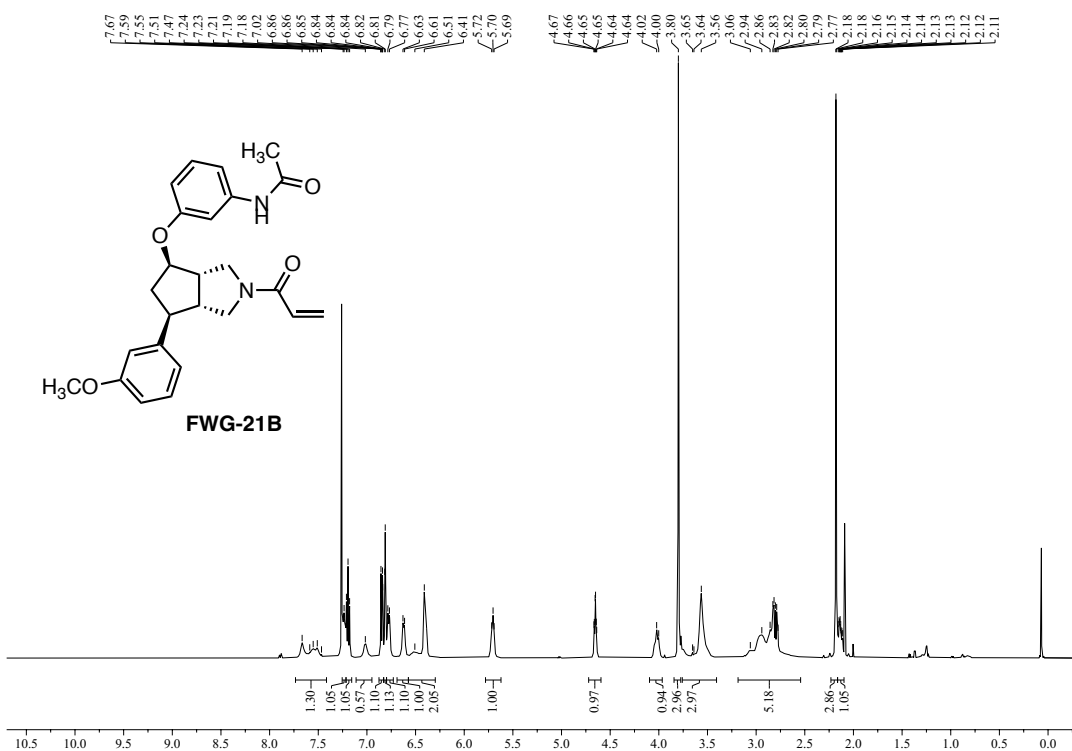


Figure S60: ¹H NMR (500 MHz, CDCl₃) of **FWG-21B**.

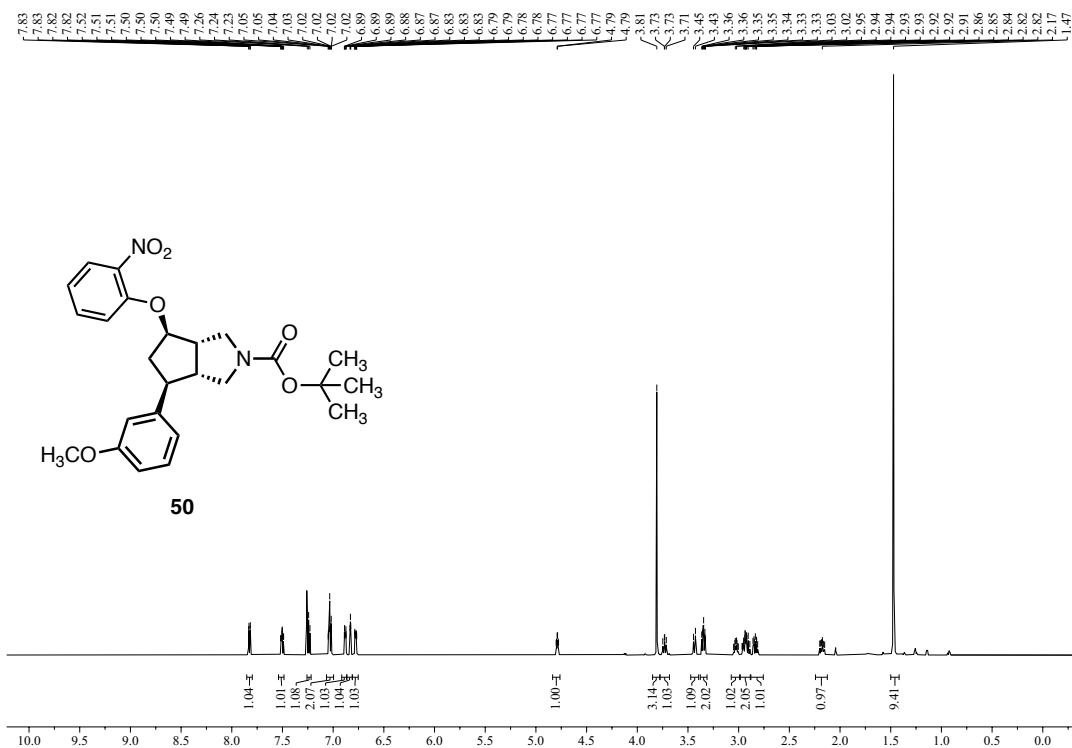


Figure S61: ¹H NMR (600 MHz, CDCl₃) of **50**.

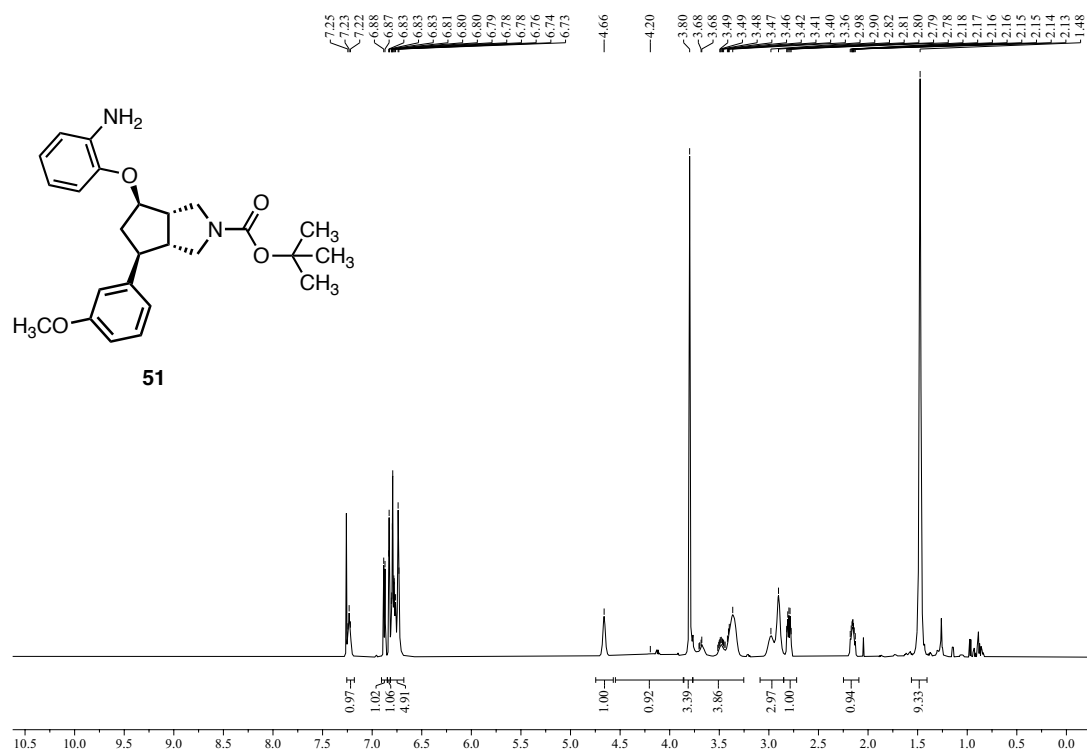


Figure S62: ¹H NMR (600 MHz, CDCl₃) of **51**.

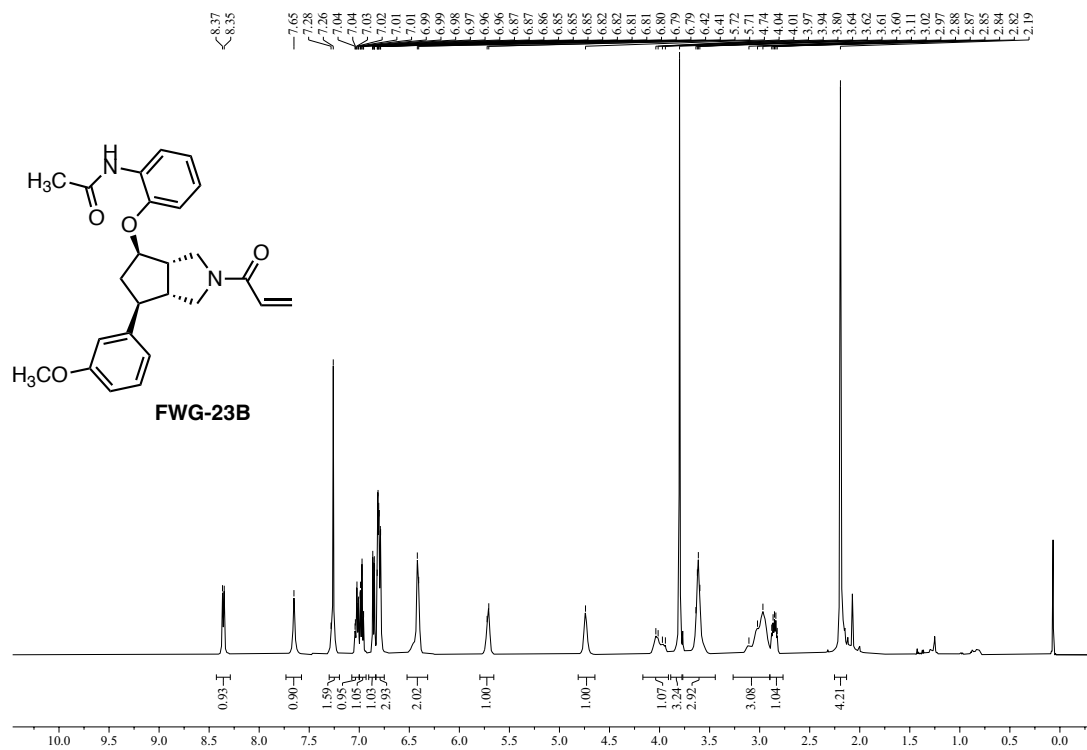
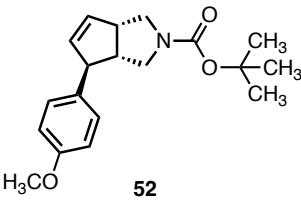


Figure S63: ¹H NMR (500 MHz, CDCl₃) of **FWG-23B**.



53

COc1ccc(cc1)[C@H]2C[C@@H](O)[C@H](C3OC(C)(C)C(C)O3)O2

53

1H NMR spectrum (CDCl₃) of compound **53**. The x-axis represents chemical shift in ppm, ranging from 0.0 to 10.0. The spectrum shows several peaks with corresponding integration values:

- 7.19, 7.17, 6.89, 6.87, 6.86, 6.85 (aromatic protons, integration 1.96)
- 4.16, 3.79, 3.55, 3.53, 3.50, 3.40, 3.35, 3.32, 3.31, 3.30, 3.29, 3.28 (sugar protons, integration 2.00)
- 2.76, 2.68, 2.67, 2.66, 2.65, 2.65, 2.64, 2.63, 2.61, 2.61, 2.59, 2.49, 2.47 (tert-butyl methyls, integration 0.97)
- 1.87, 1.86, 1.85, 1.84, 1.84, 1.83, 1.82, 1.82, 1.46 (tert-butyl methyls, integration 3.00)
- 1.87, 1.86, 1.85, 1.84, 1.84, 1.83, 1.82, 1.82, 1.46 (tert-butyl methyls, integration 3.93)
- 2.76, 2.68, 2.67, 2.66, 2.65, 2.65, 2.64, 2.63, 2.61, 2.61, 2.59, 2.49, 2.47 (tert-butyl methyls, integration 2.91)
- 1.87, 1.86, 1.85, 1.84, 1.84, 1.83, 1.82, 1.82, 1.46 (tert-butyl methyls, integration 1.05)
- 2.76, 2.68, 2.67, 2.66, 2.65, 2.65, 2.64, 2.63, 2.61, 2.61, 2.59, 2.49, 2.47 (tert-butyl methyls, integration 0.56)
- 1.87, 1.86, 1.85, 1.84, 1.84, 1.83, 1.82, 1.82, 1.46 (tert-butyl methyls, integration 0.96)
- 2.76, 2.68, 2.67, 2.66, 2.65, 2.65, 2.64, 2.63, 2.61, 2.61, 2.59, 2.49, 2.47 (tert-butyl methyls, integration 9.11)

115

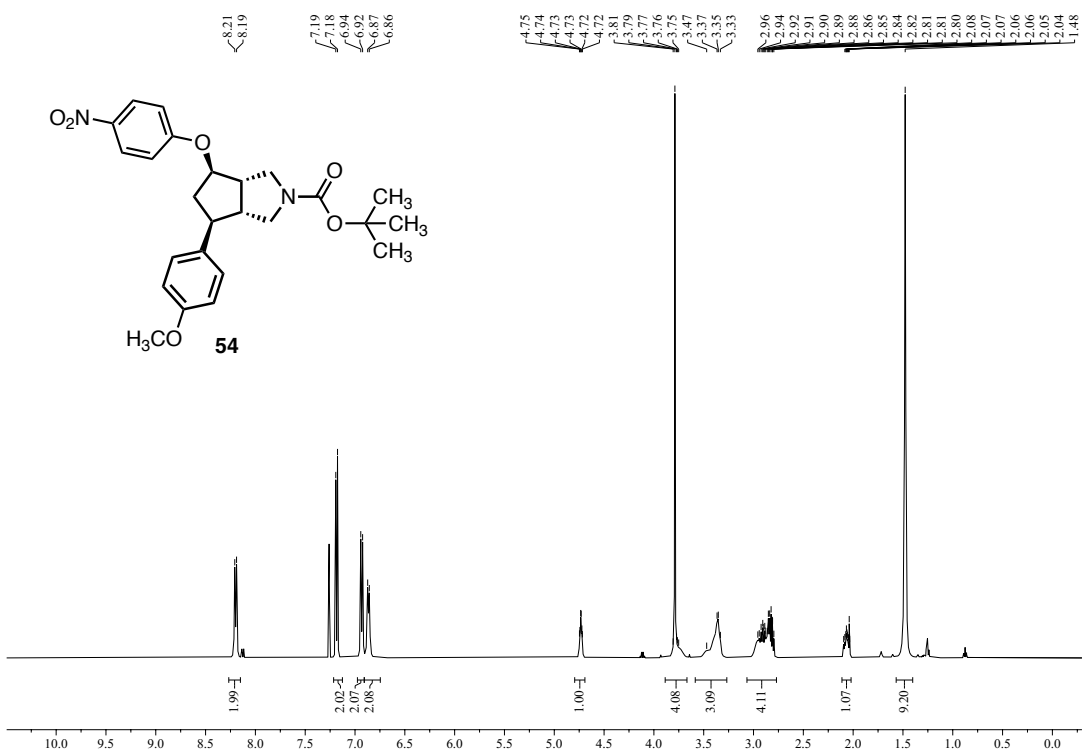


Figure S66: ¹H NMR (500 MHz, CDCl₃) of **54**.

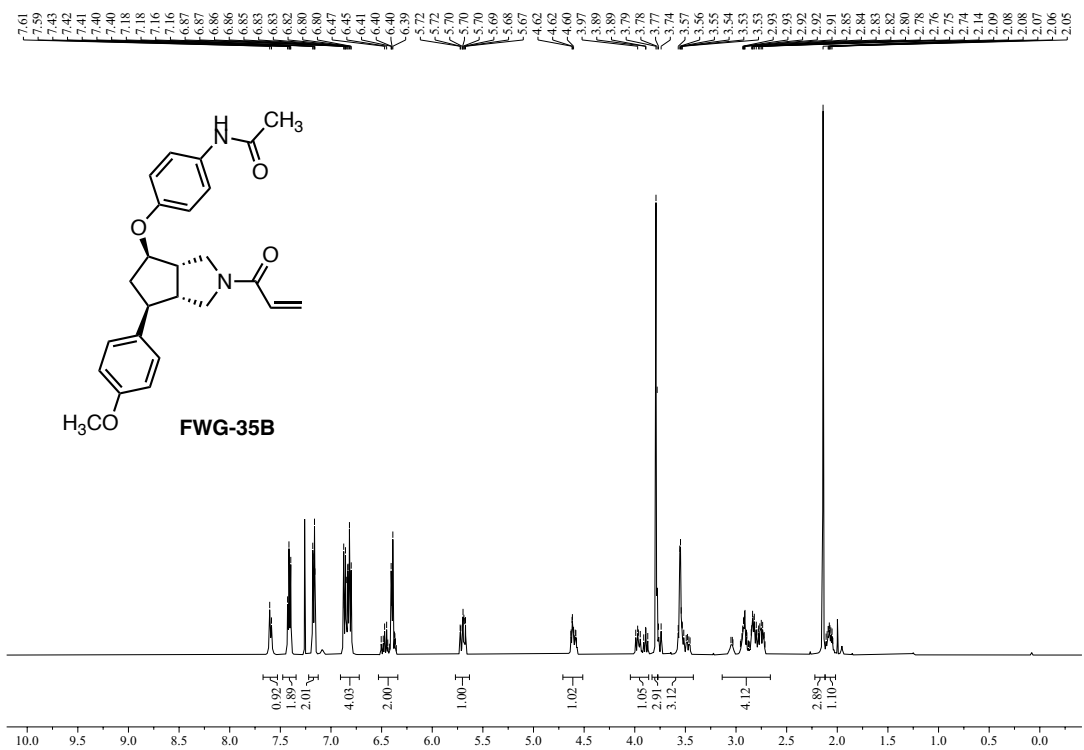


Figure S67: ¹H NMR (500 MHz, CDCl₃) of **FWG-35B**.

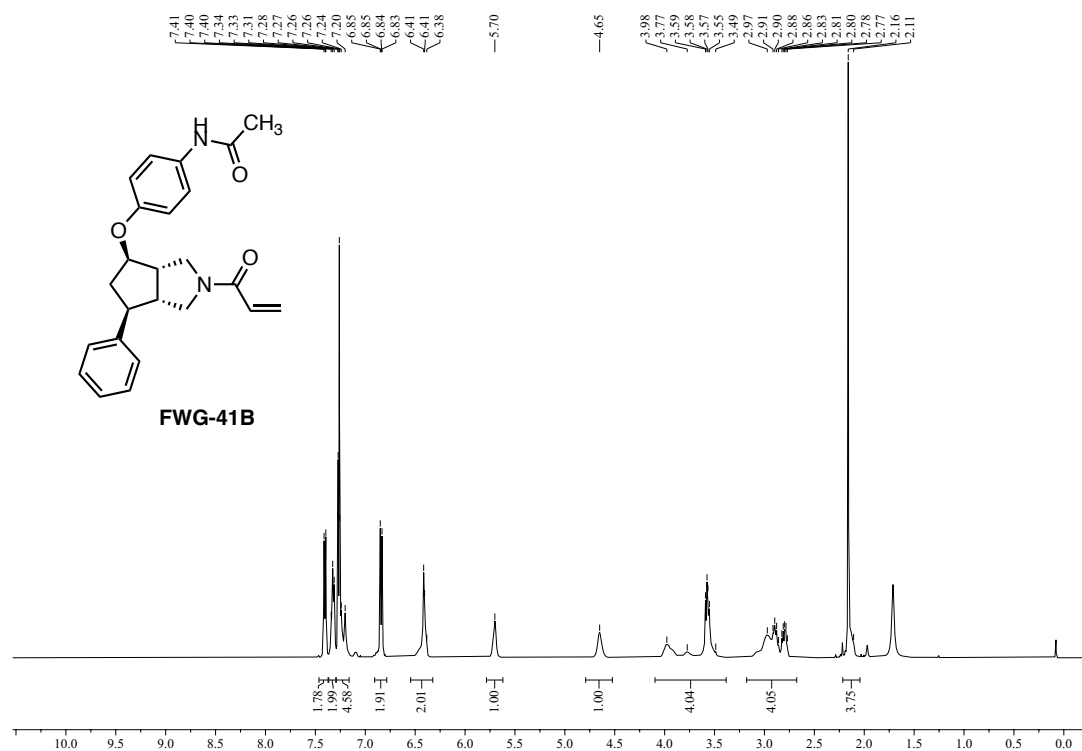


Figure S68: ^1H NMR (500 MHz, CDCl_3) of **FWG-41B**.

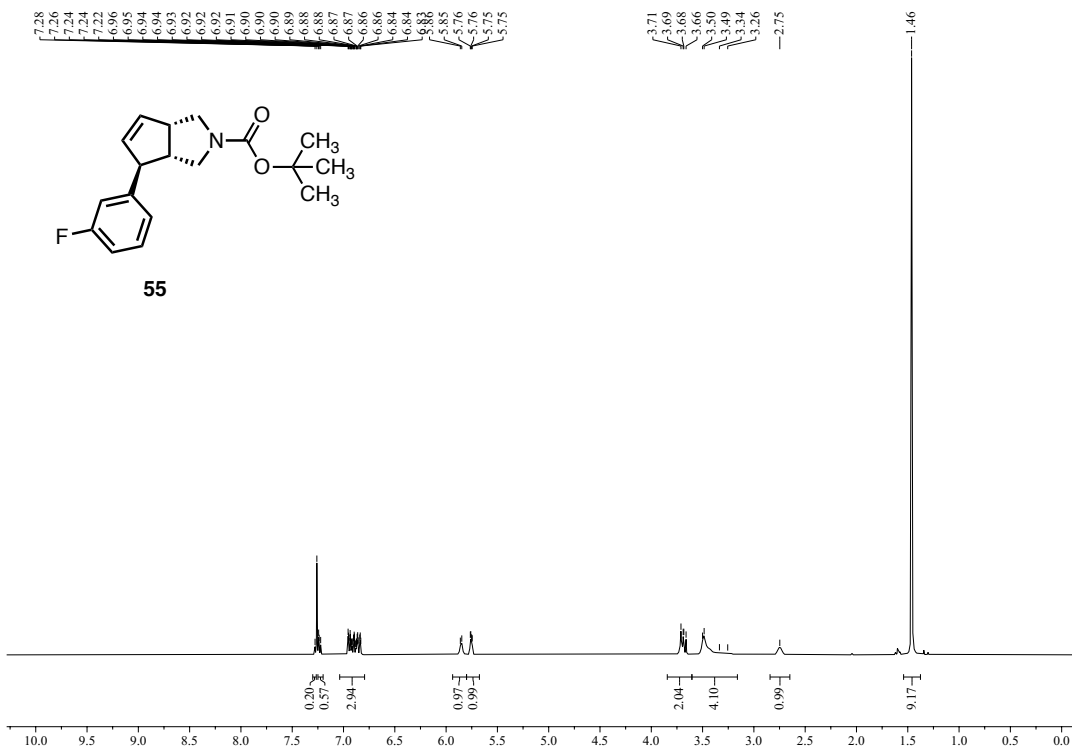


Figure S69: ¹H NMR (400 MHz, CDCl₃) of **55**.

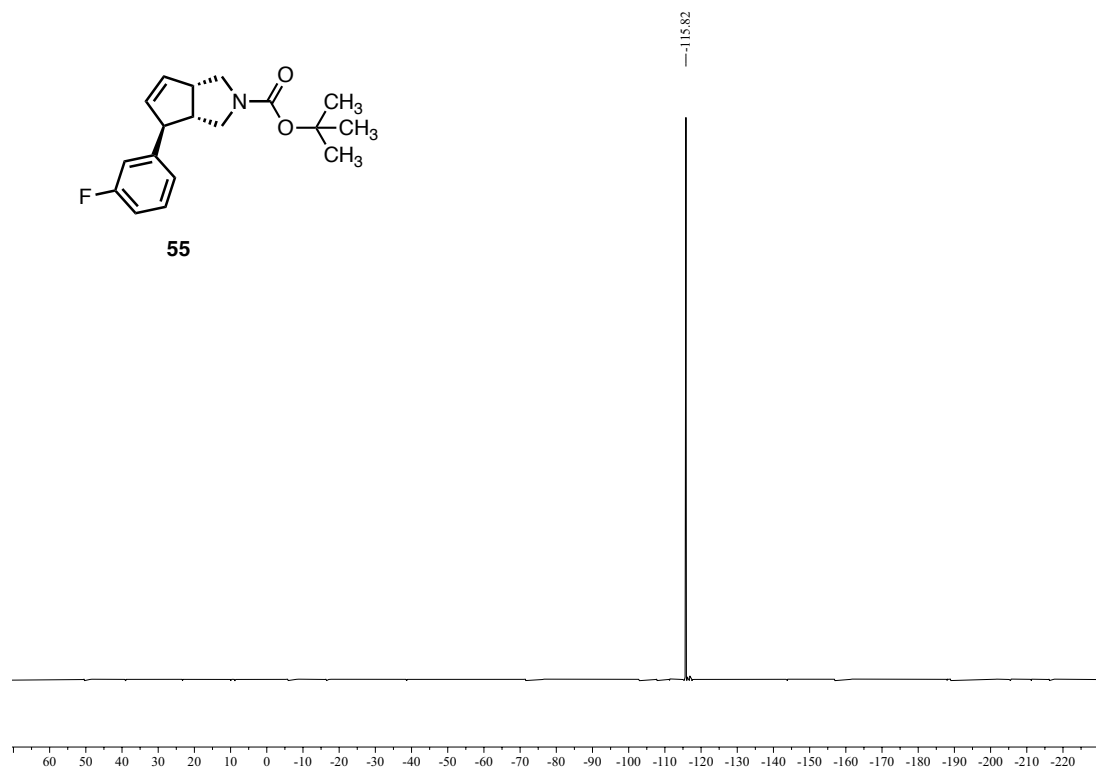


Figure S70: ¹⁹F NMR {¹H} (376 MHz, CDCl₃) of **55**.

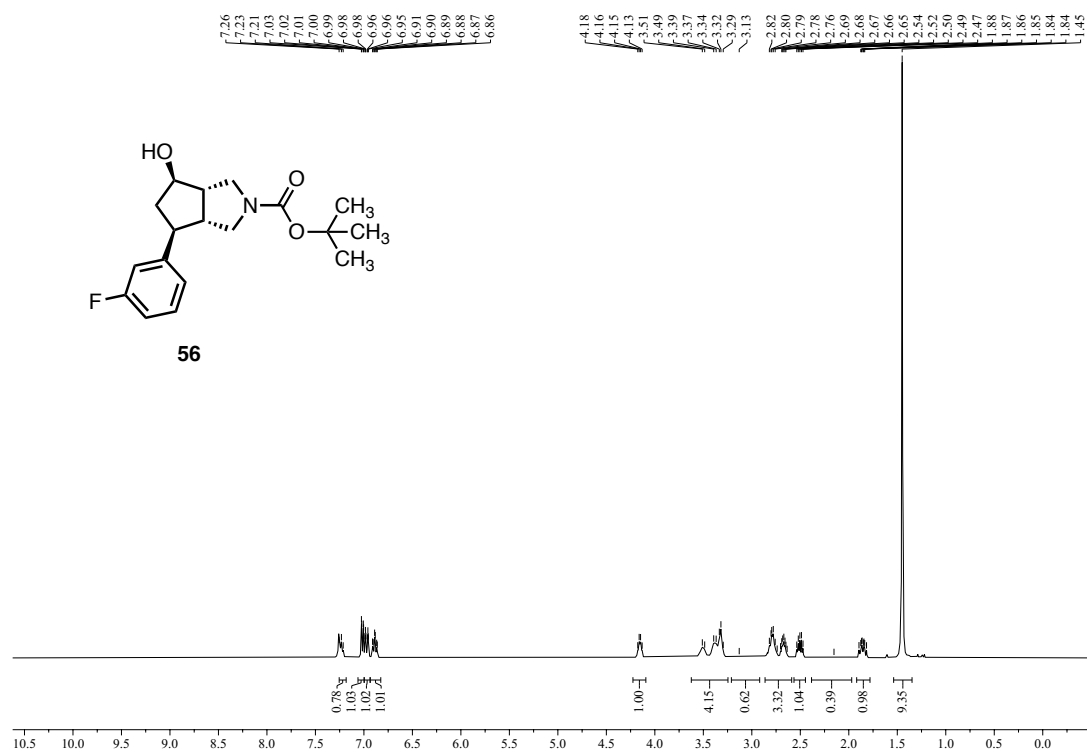


Figure S71: ¹H NMR (400 MHz, CDCl₃) of **56**.

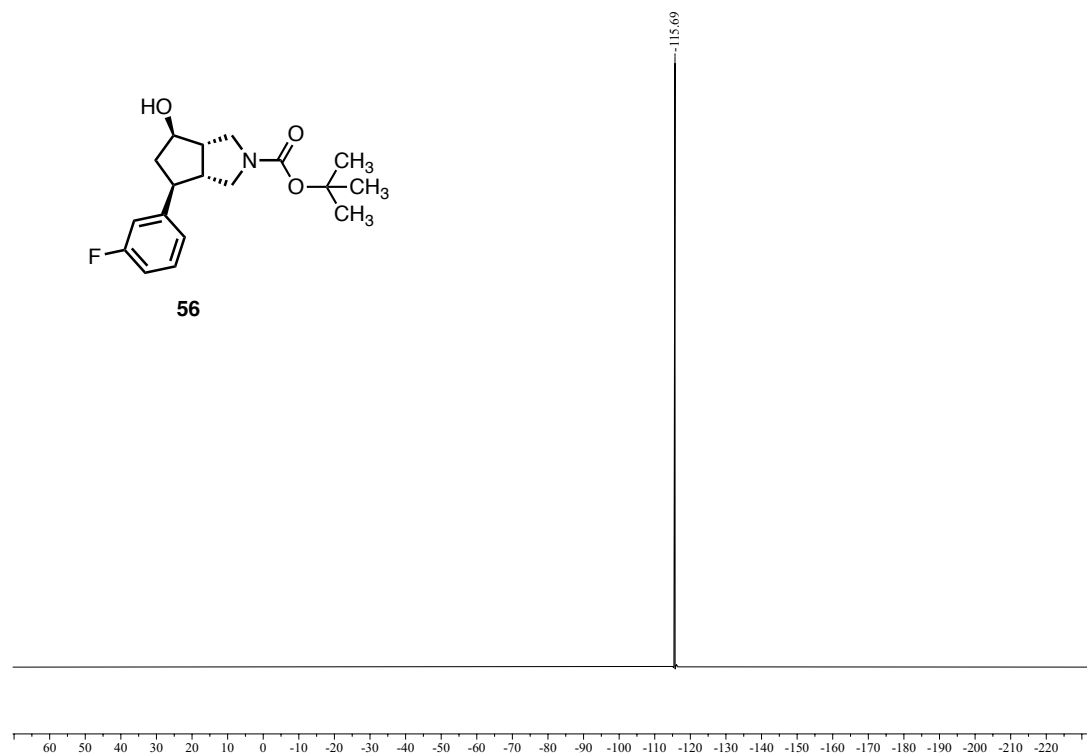


Figure S72: ¹⁹F NMR {¹H} (376 MHz, CDCl₃) of **56**.

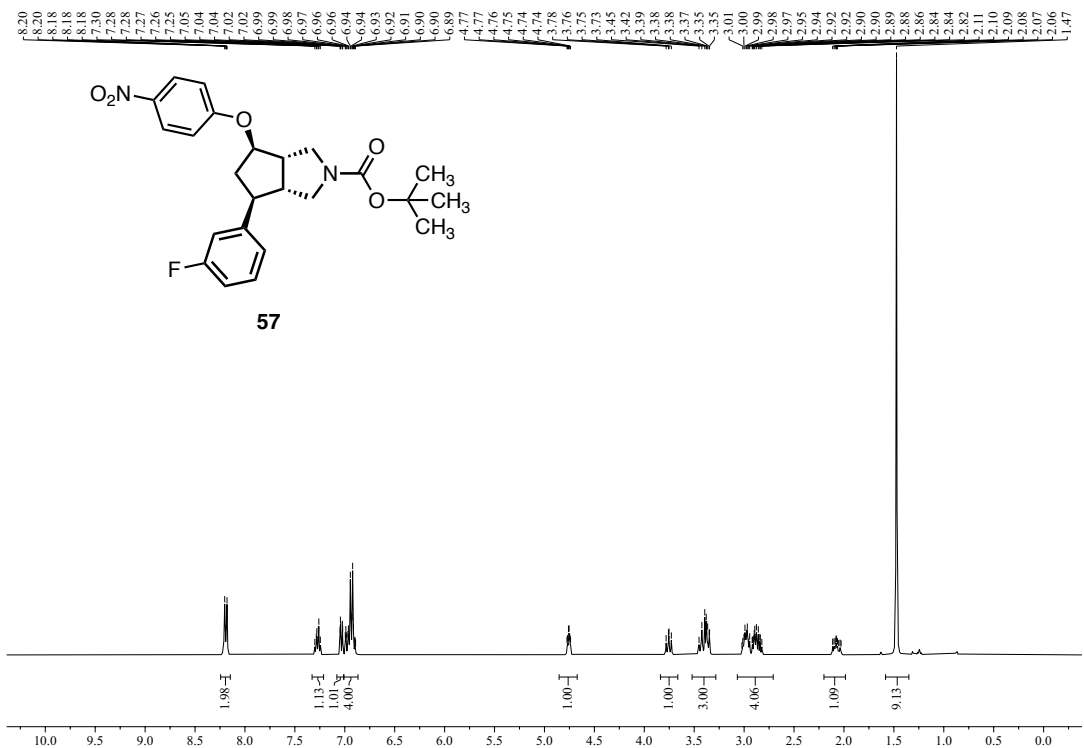


Figure S73: ¹H NMR (400 MHz, CDCl₃) of **57**.

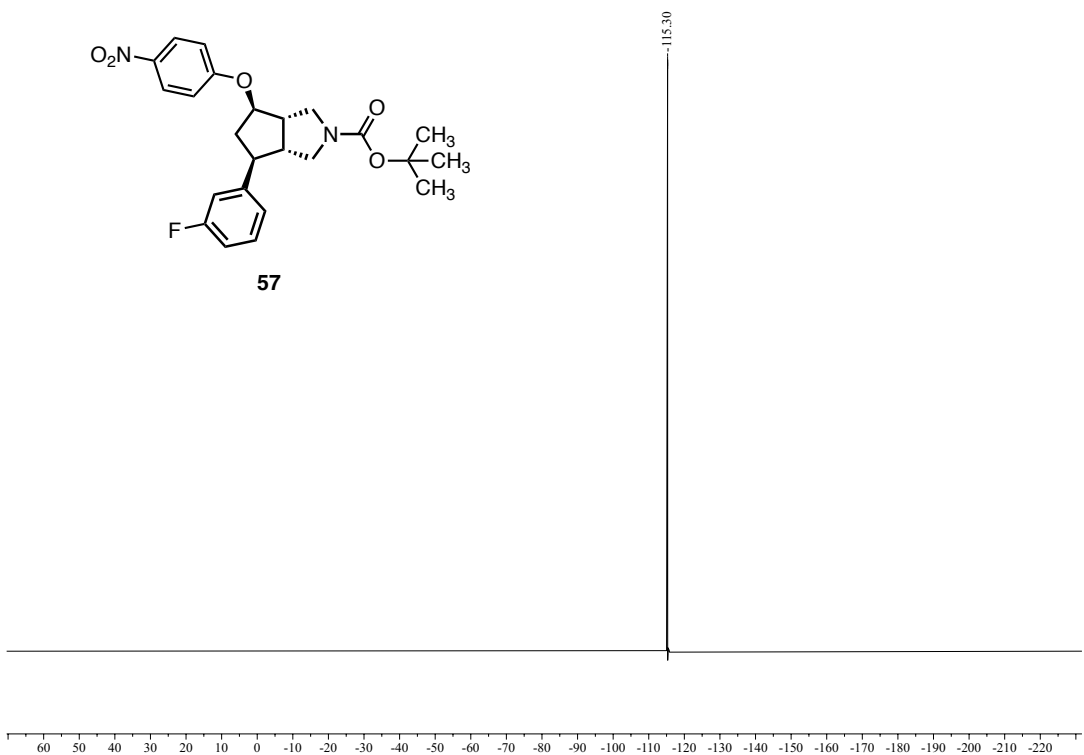


Figure S74: ¹⁹F NMR {¹H} (376 MHz, CDCl₃) of **57**.

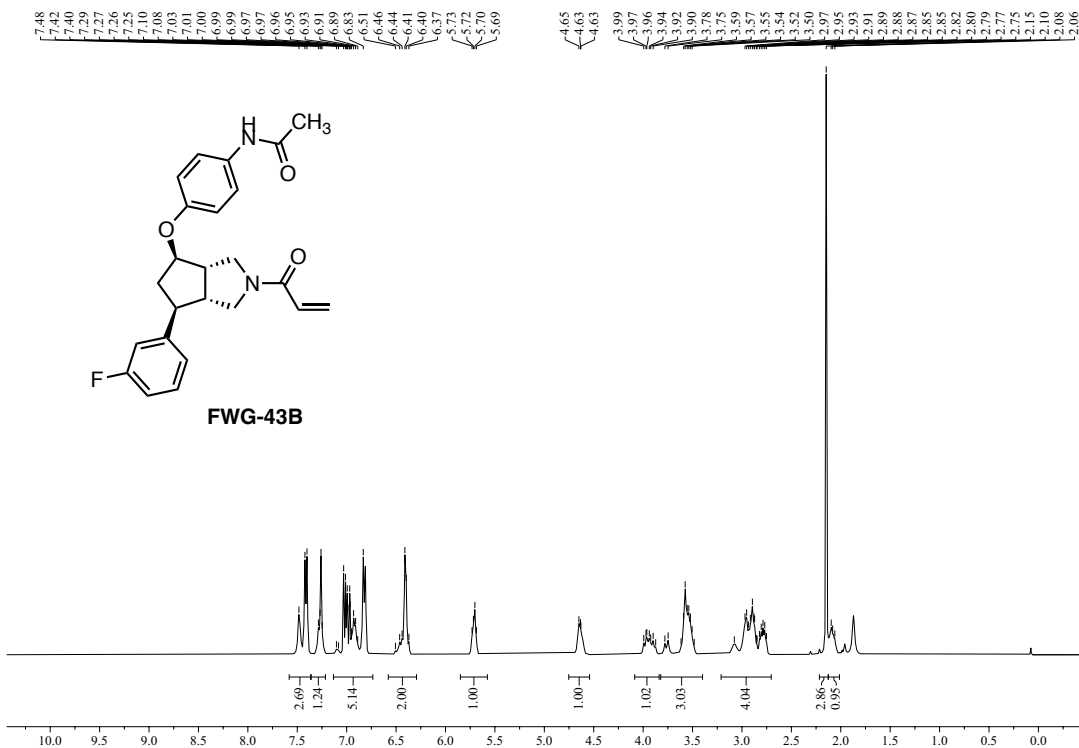


Figure S75: ¹H NMR (400 MHz, CDCl₃) of **FWG-43B**.

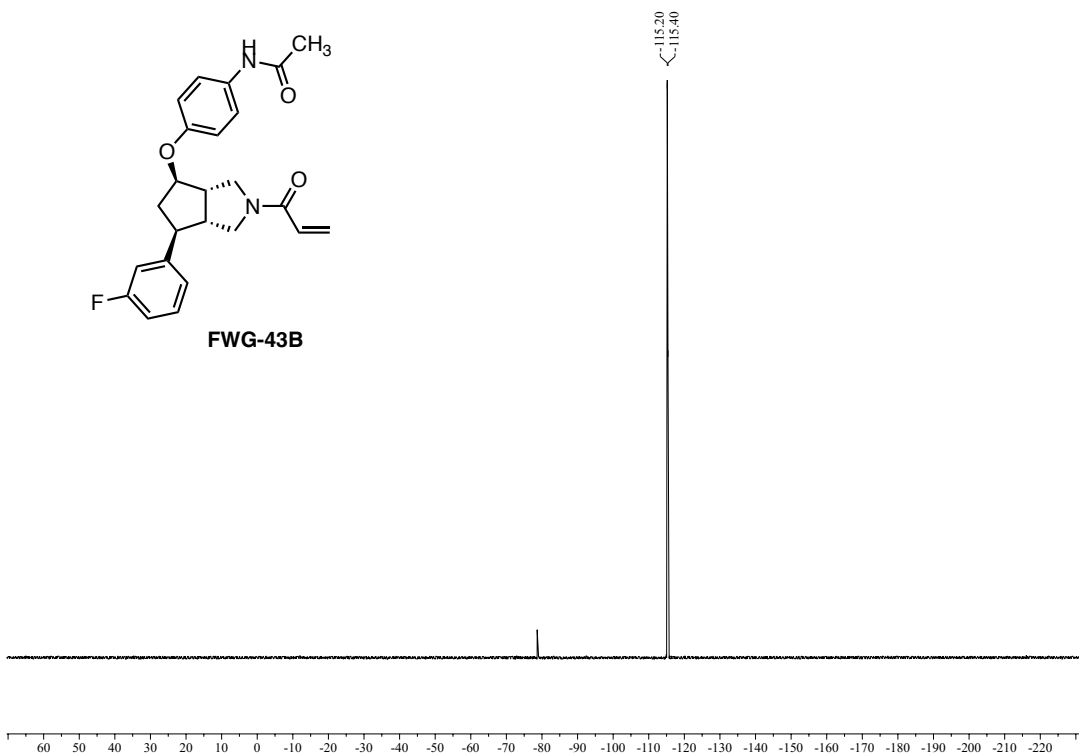


Figure S76: ¹⁹F NMR {¹H} (376 MHz, CDCl₃) of **FWG-43B**.

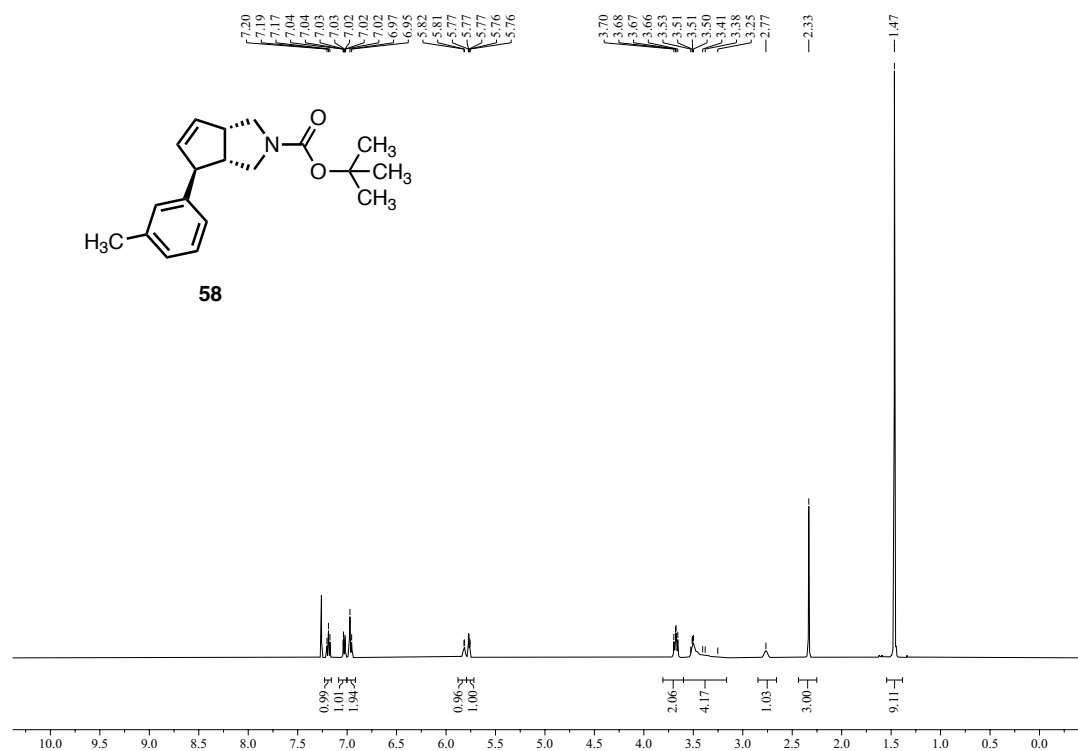


Figure S77: ¹H NMR (500 MHz, CDCl₃) of **58**.

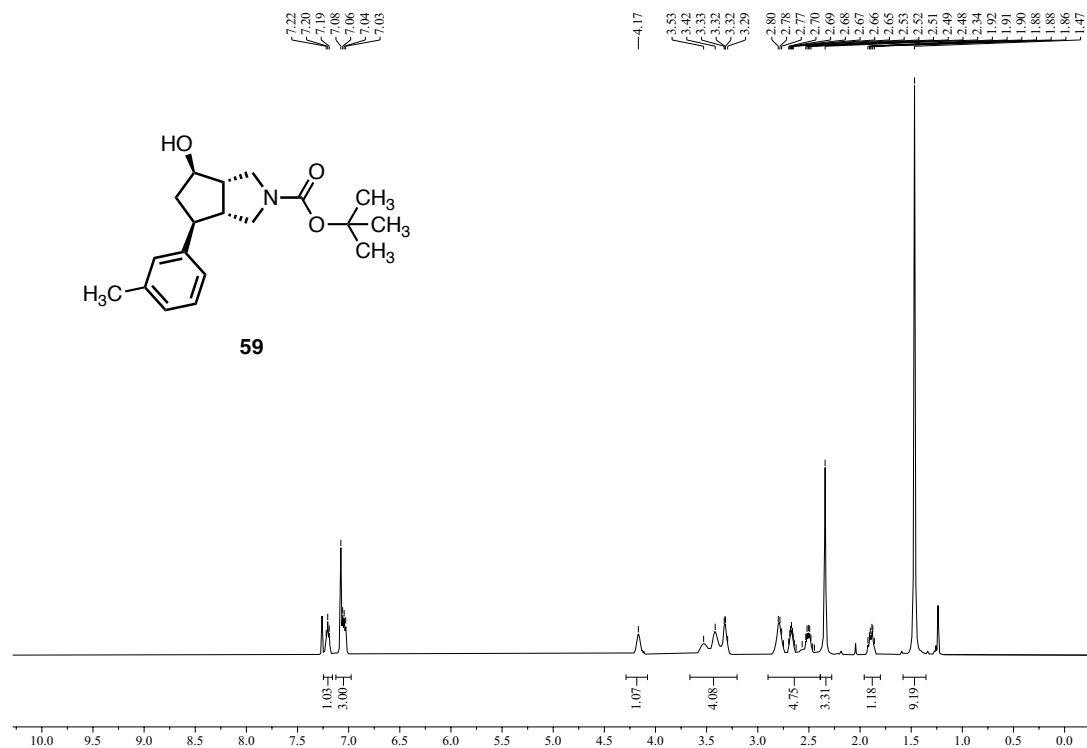


Figure S78: ¹H NMR (500 MHz, CDCl₃) of **59**.

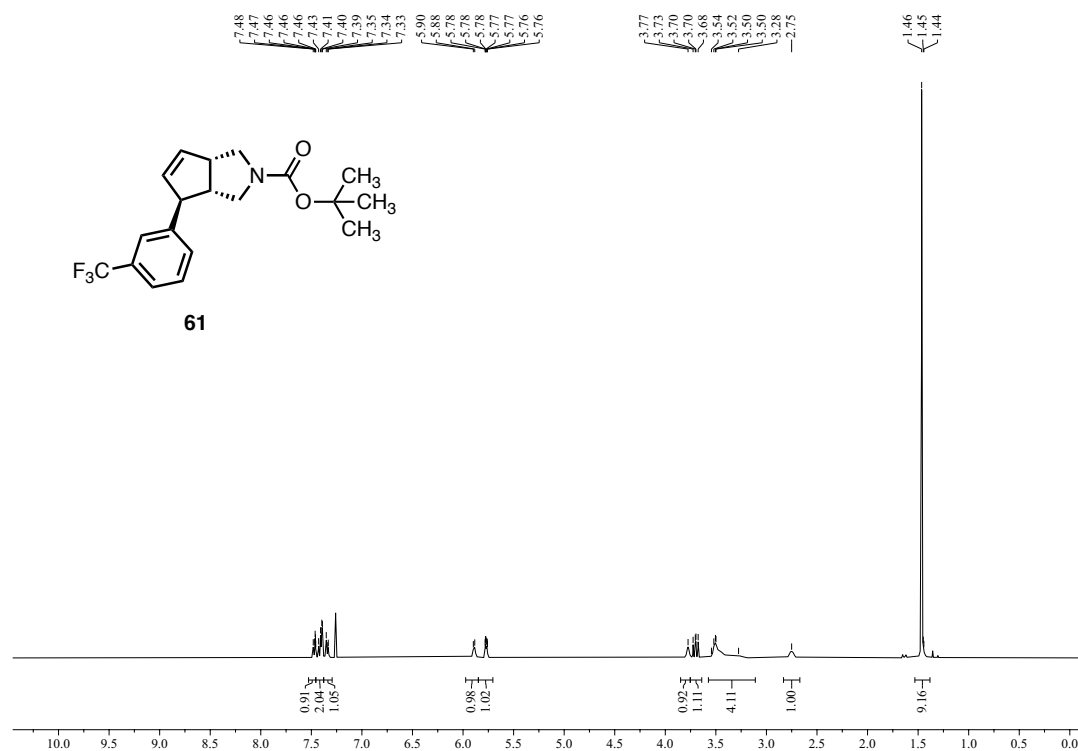


Figure S81: ¹H NMR (400 MHz, CDCl₃) of **61**.

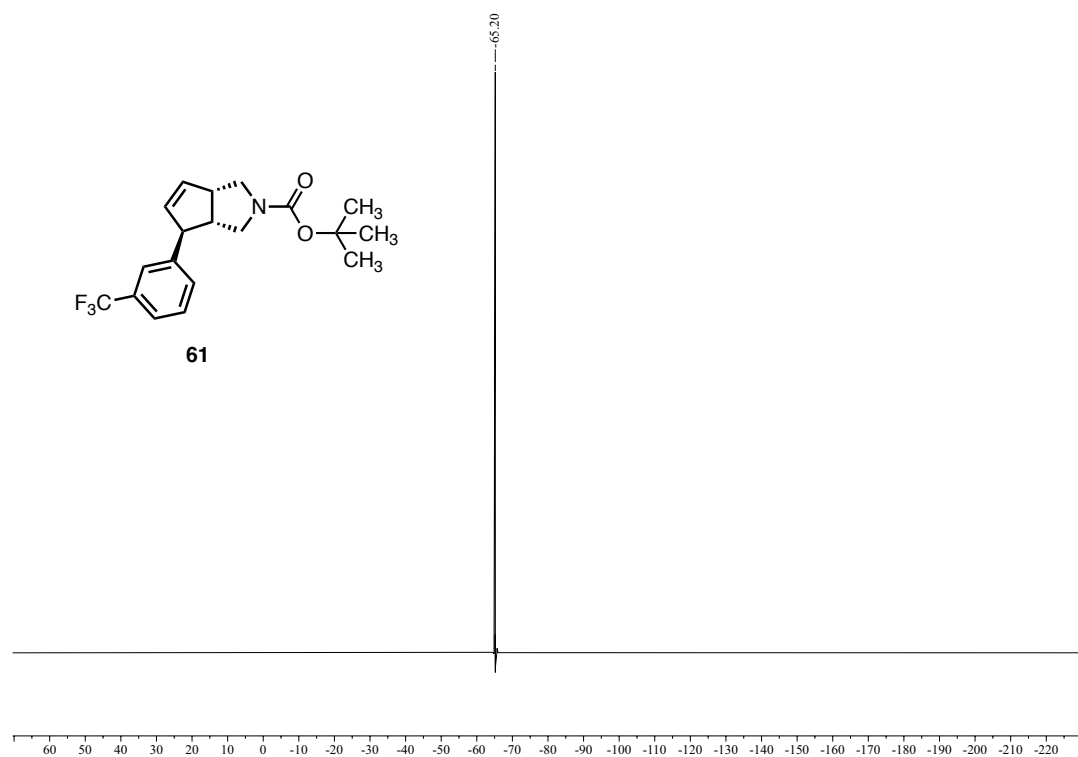


Figure S82: ¹⁹F NMR {¹H} (376 MHz, CDCl₃) of **61**.

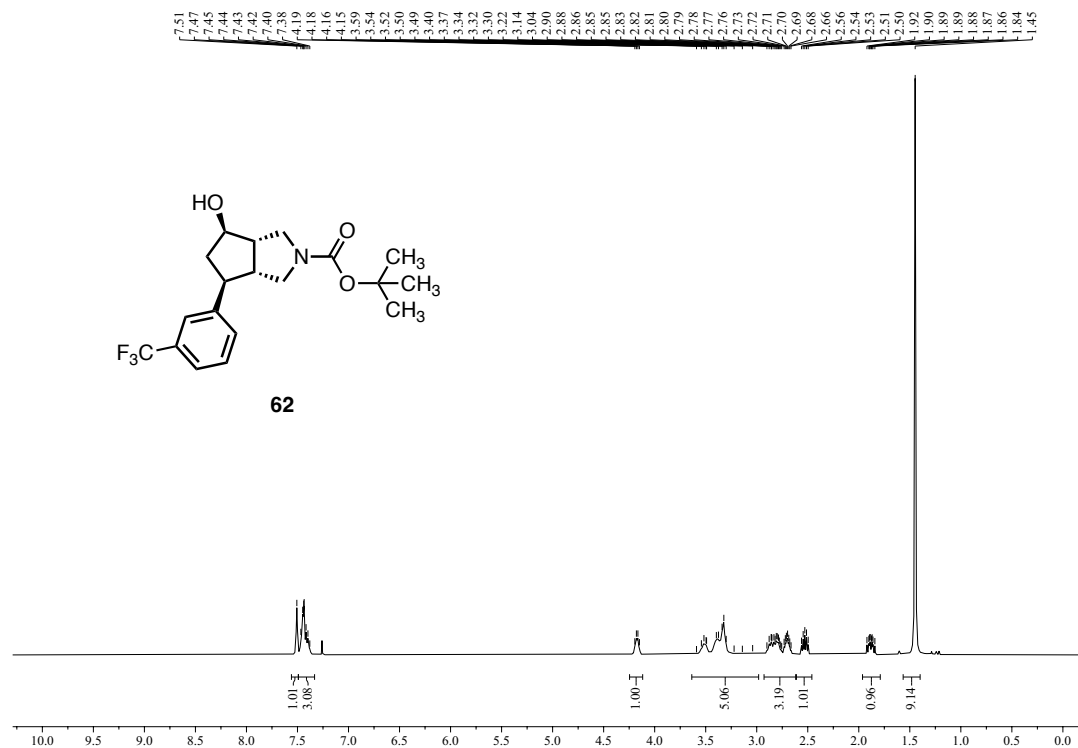


Figure S83: ¹H NMR (400 MHz, CDCl₃) of **62**.

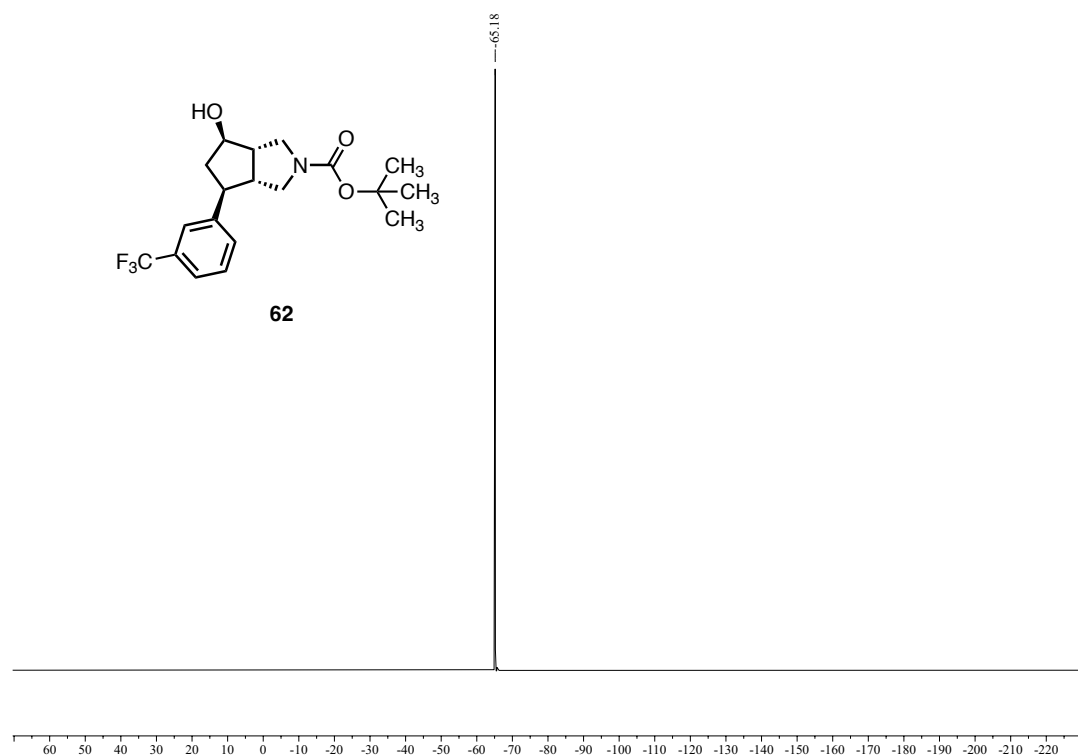


Figure S84: ¹⁹F NMR {¹H} (376 MHz, CDCl₃) of **62**.

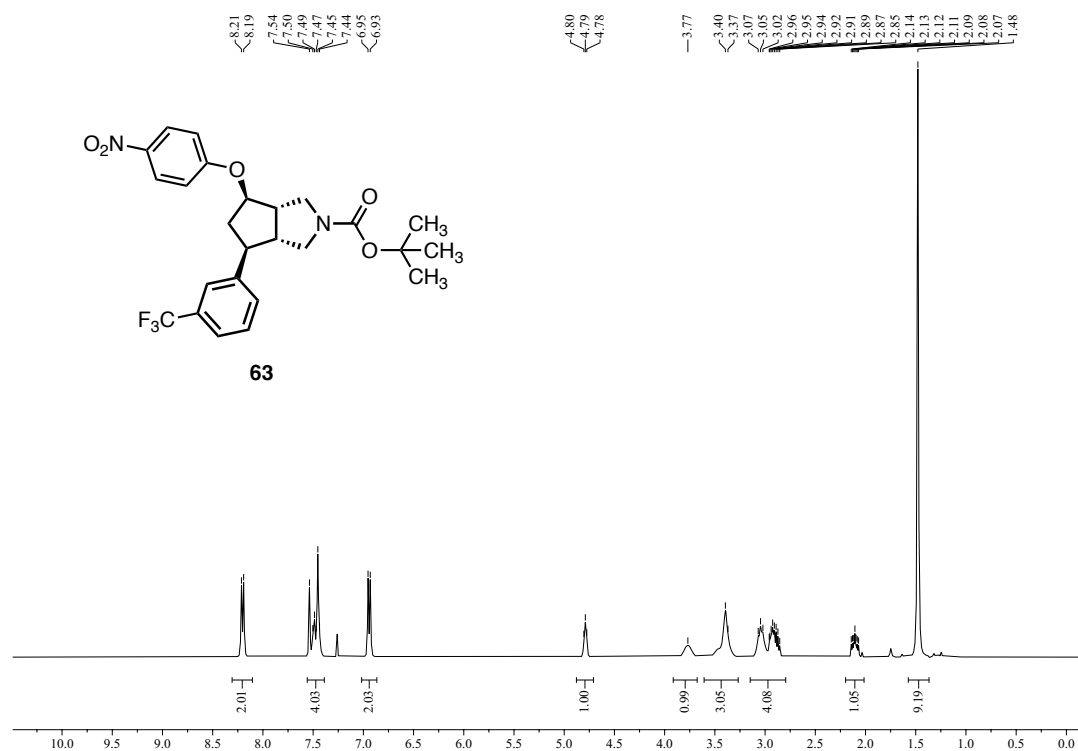


Figure S85: ¹H NMR (400 MHz, CDCl₃) of **63**.

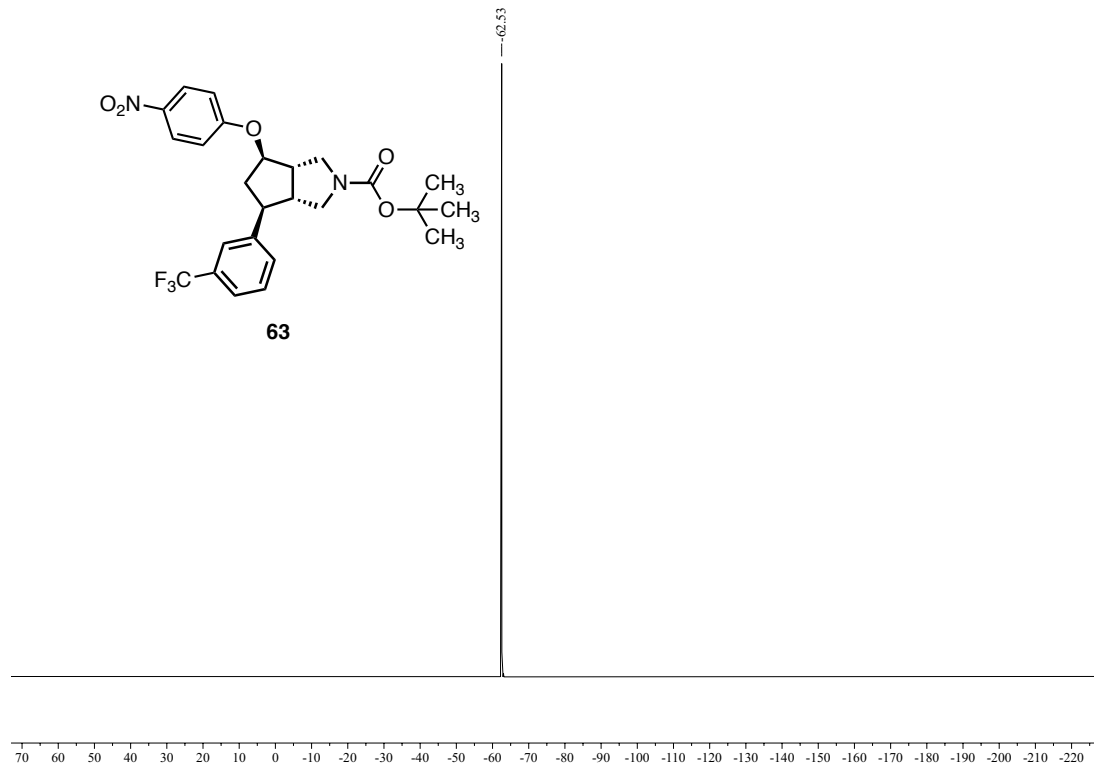


Figure S86: ¹⁹F NMR {¹H} (376 MHz, CDCl₃) of **63**.

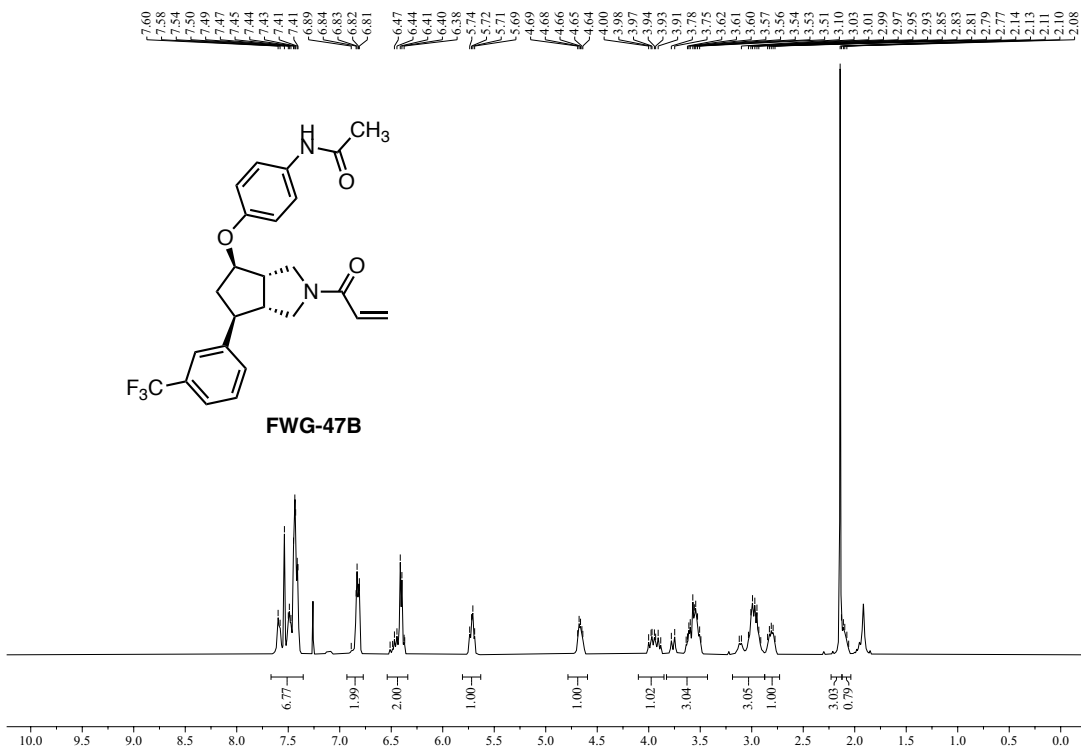


Figure S87: ^1H NMR (400 MHz, CDCl_3) of **FWG-47B**.

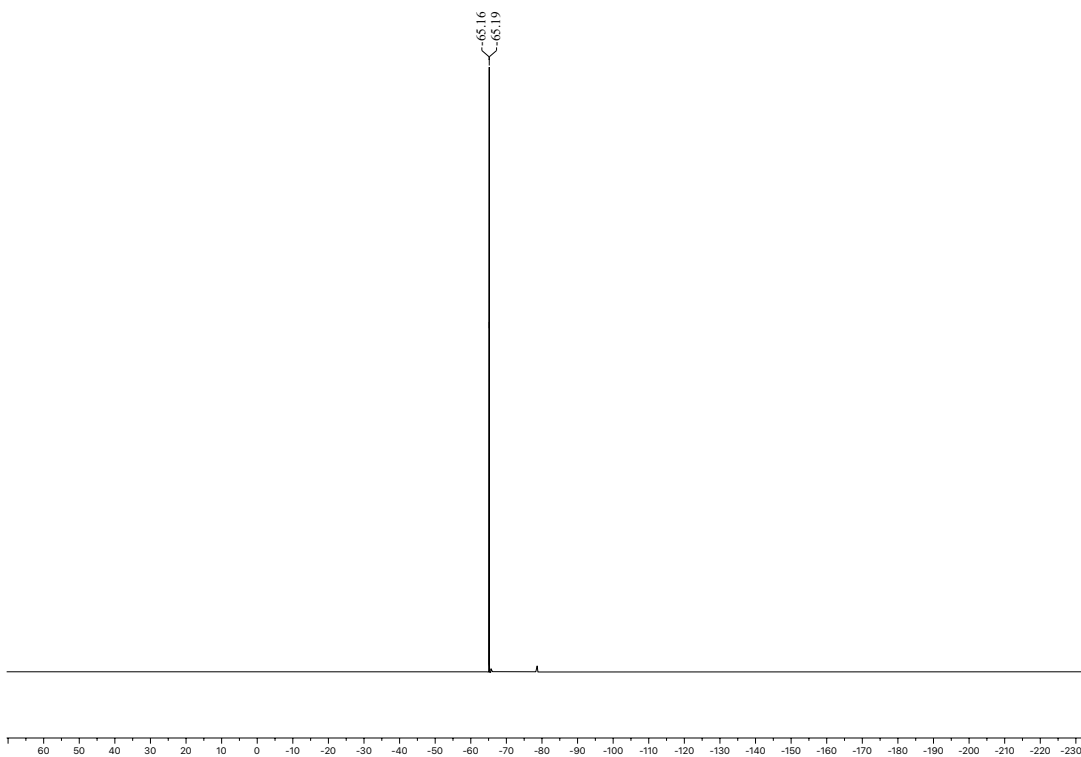


Figure S88: ^{19}F NMR (^1H) (376 MHz, CDCl_3) of **FWG-47B**.

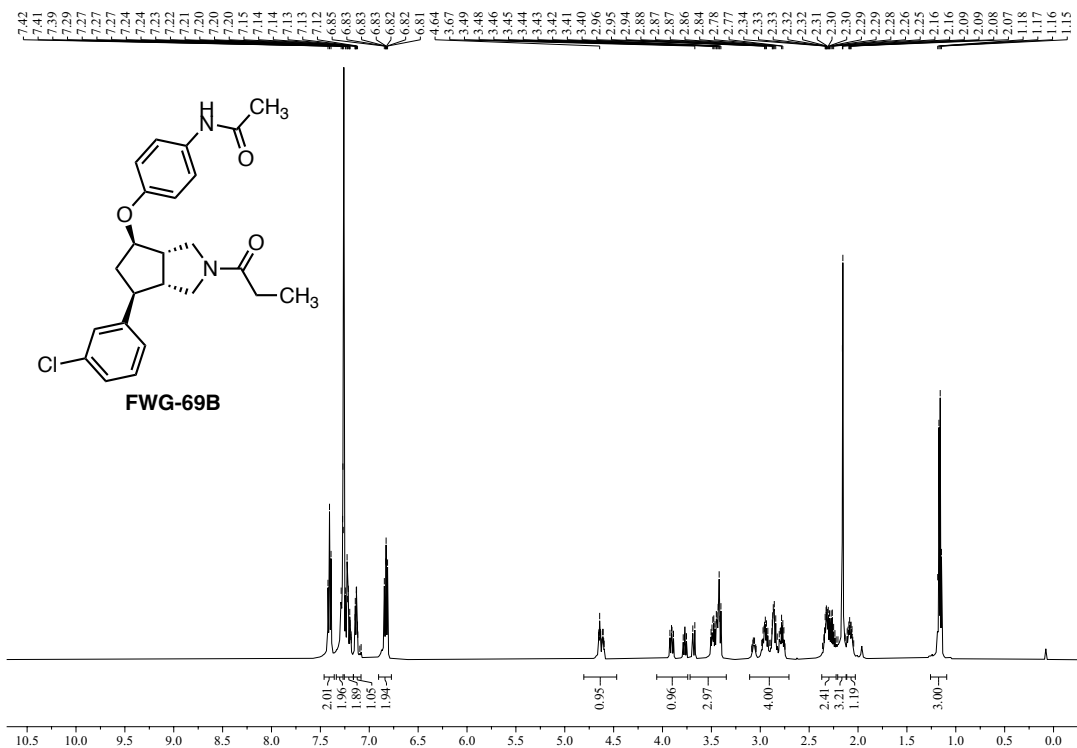


Figure S89: ¹H NMR (600 MHz, CDCl₃) of **FWG-69B**.

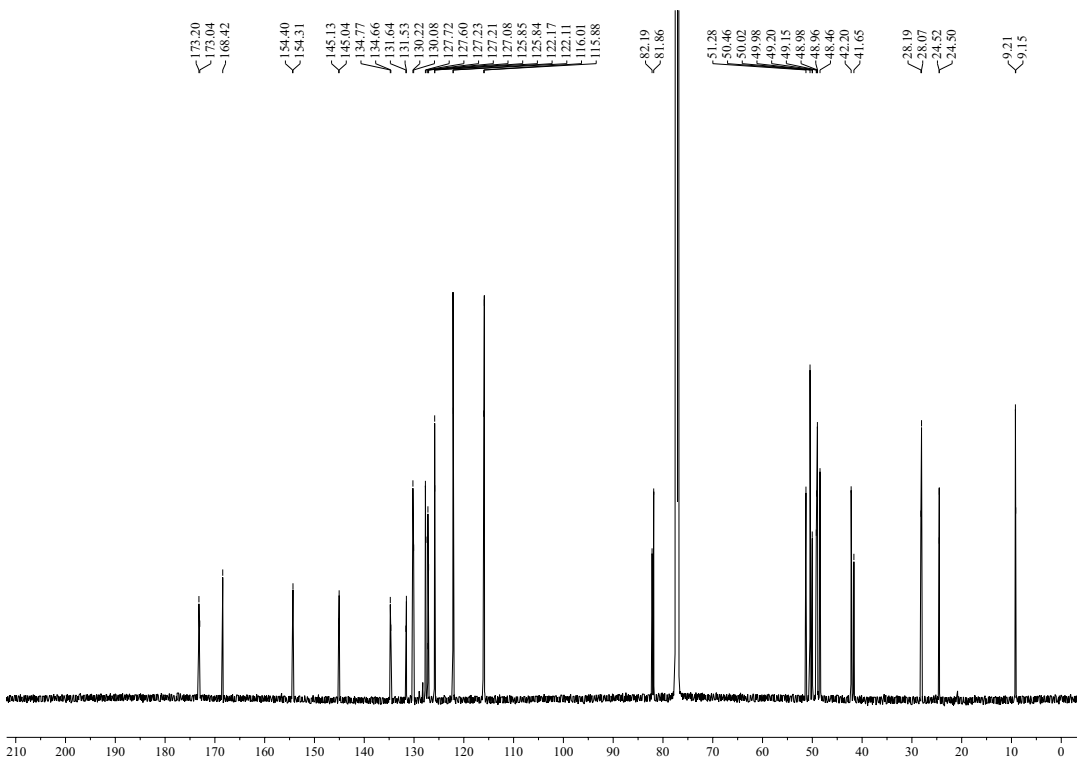


Figure S90: ¹³C NMR (151 MHz, CDCl₃) of **FWG-69B**.

SFC

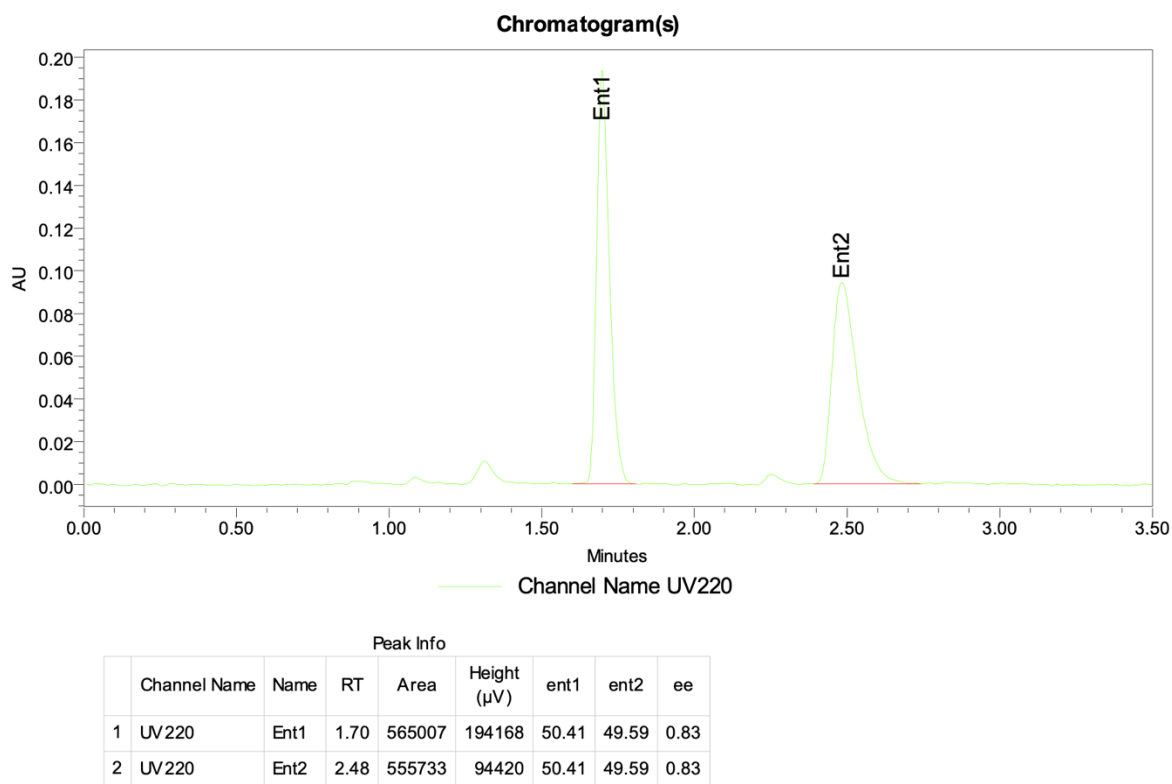


Figure S91: SFC trace of (±)-**3**.

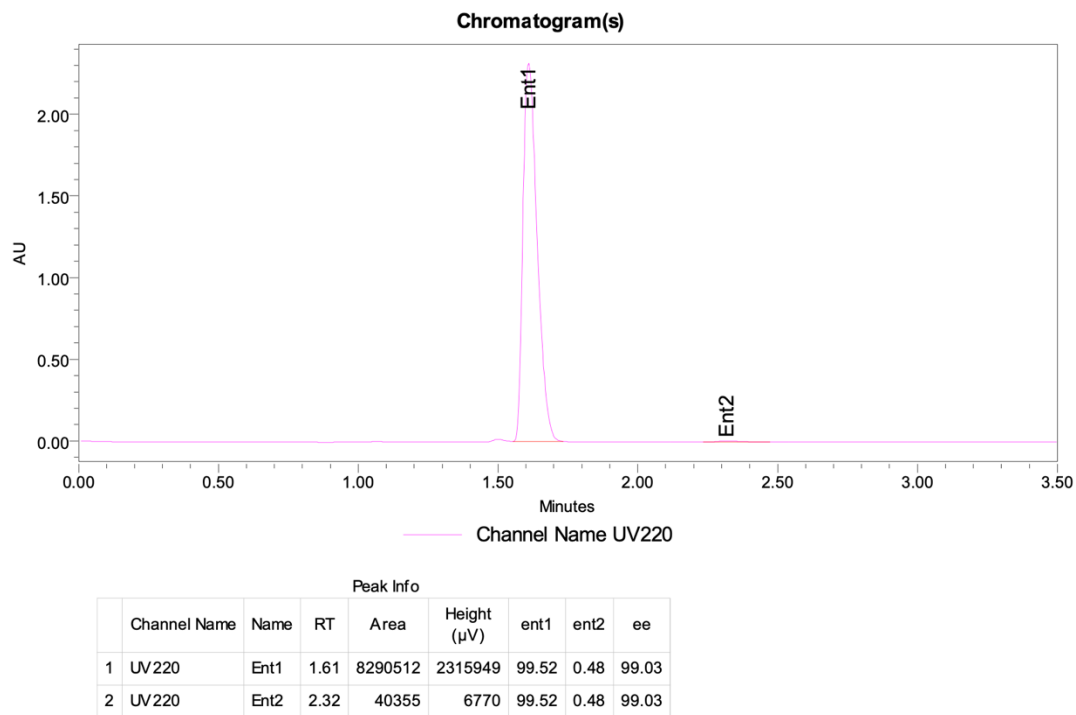


Figure S92: SFC trace of **3**.

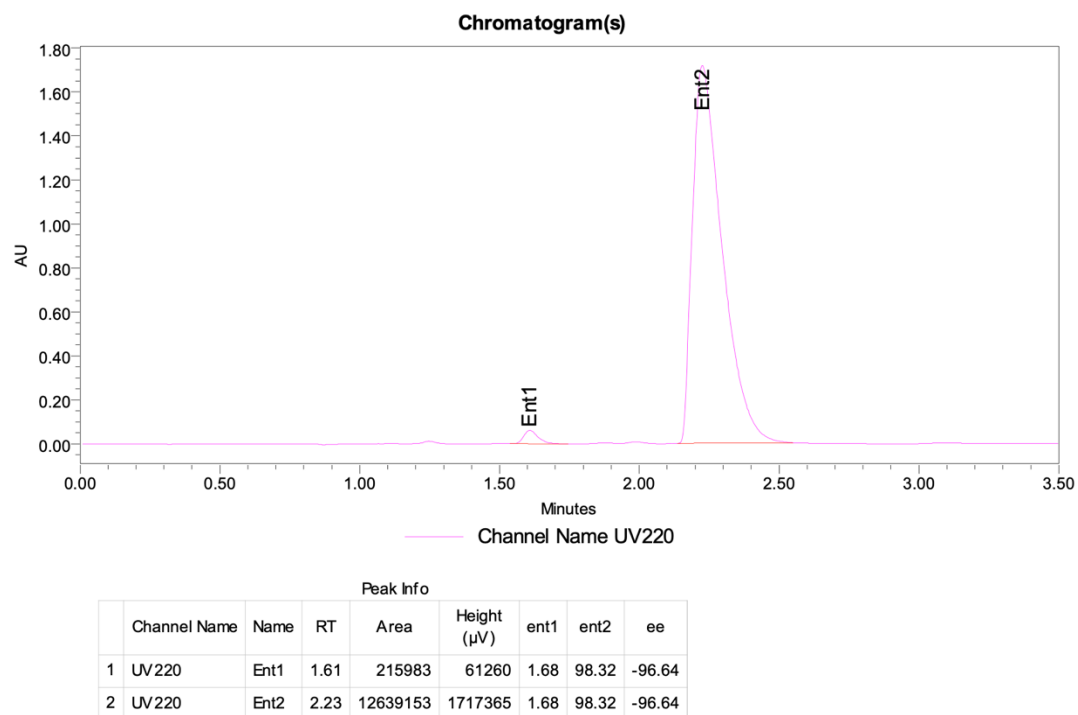
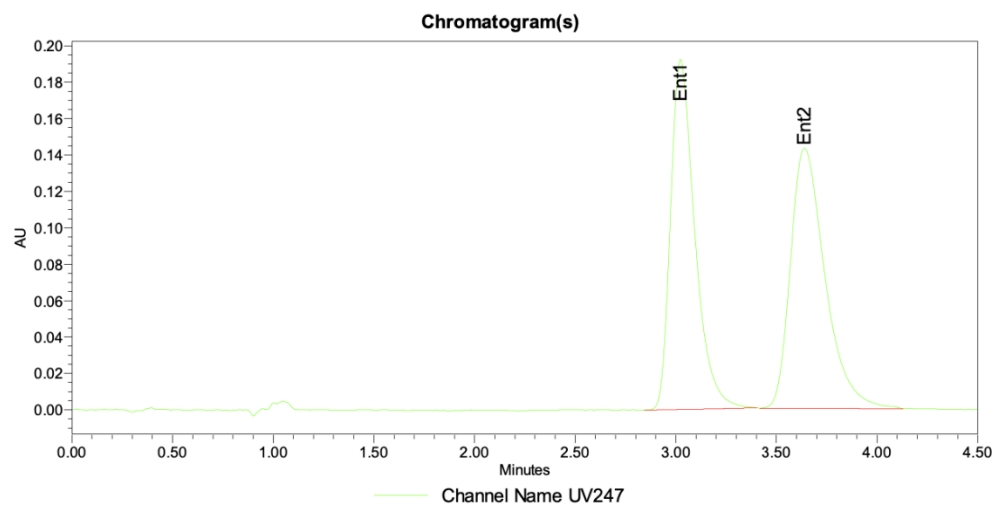
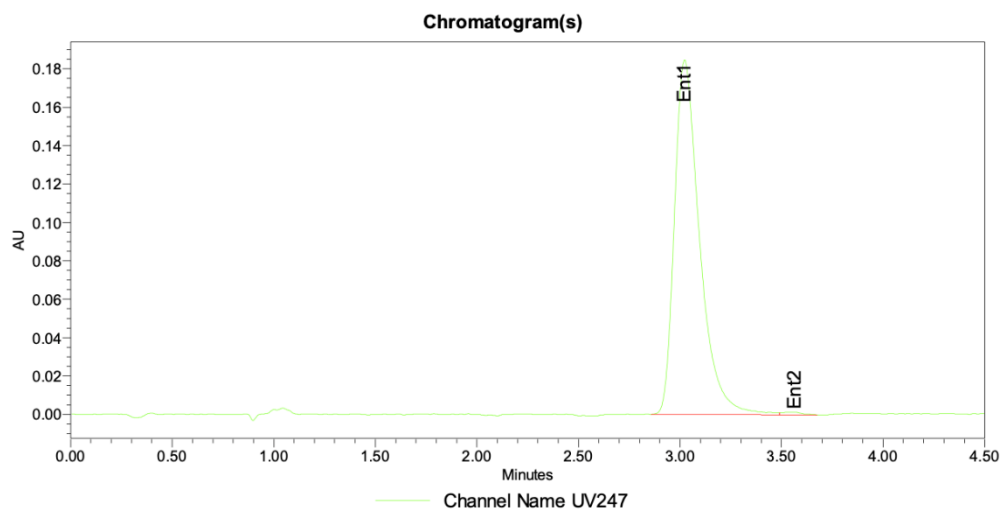


Figure S93: SFC trace of **4**.



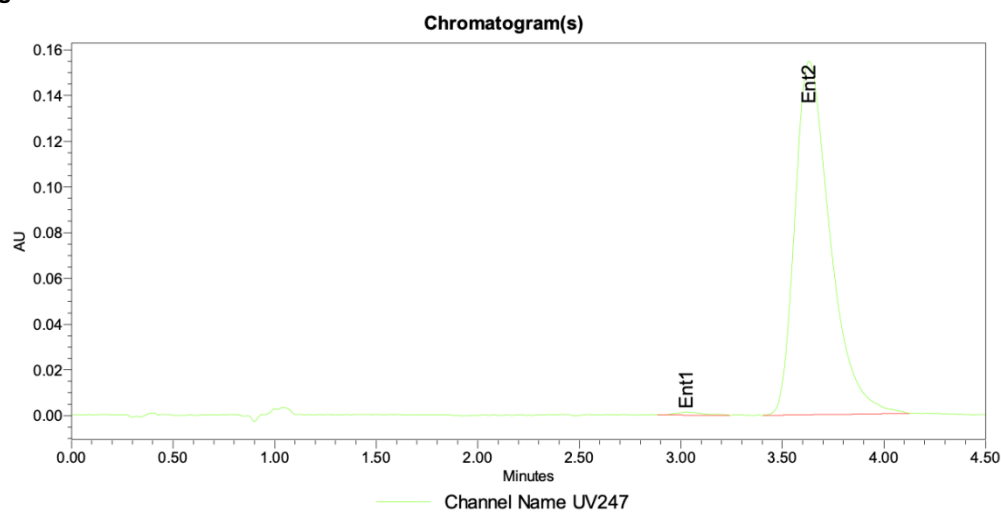
Peak Info							
	Channel Name	Name	RT	Area	Height (μV)	ent1	ent2
1	UV247	Ent1	3.02	1617203	192319	48.67	51.33
2	UV247	Ent2	3.64	1705807	142926	48.67	51.33

Figure S94: SFC trace of an equimolar mixture of **FWG-1A** and **FWG-1B**.



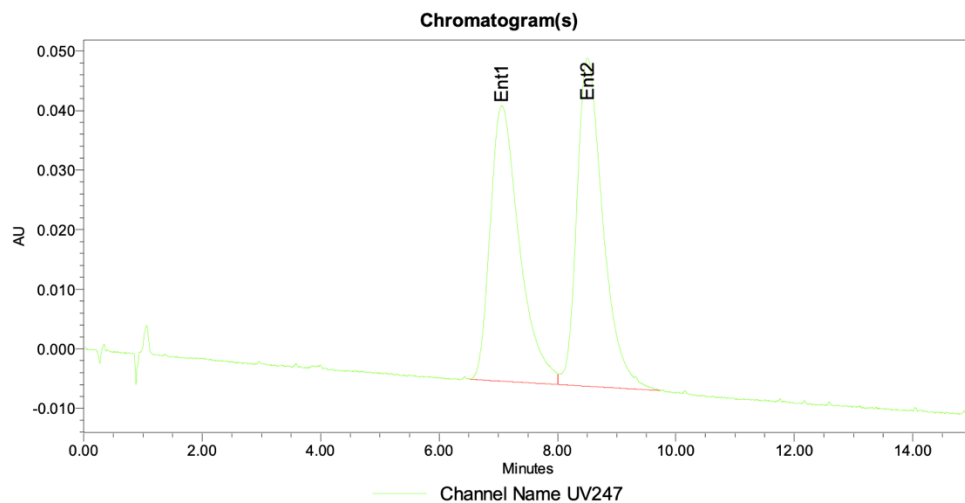
Peak Info							
Channel Name	Name	RT	Area	Height (μV)	ent1	ent2	ee
1 UV247	Ent1	3.02	1599391	184797	99.38	0.62	98.76
2 UV247	Ent2	3.57	9959	1468	99.38	0.62	98.76

Figure S95: SFC trace of **FWG-1A**.



Peak Info							
Channel Name	Name	RT	Area	Height (μV)	ent1	ent2	ee
1 UV247	Ent1	3.03	12120	1381	0.65	99.35	-98.71
2 UV247	Ent2	3.63	1863267	154661	0.65	99.35	-98.71

Figure S96: SFC trace of **FWG-1B**.



Peak Info							
	Channel Name	Name	RT	Area	Height (μV)	ent1	ent2
1	UV247	Ent1	7.05	1582516	46267	48.40	51.60
2	UV247	Ent2	8.51	1686977	55090	48.40	51.60

Figure S97: SFC trace of an equimolar mixture of **FWG-2A** and **FWG-2B**.

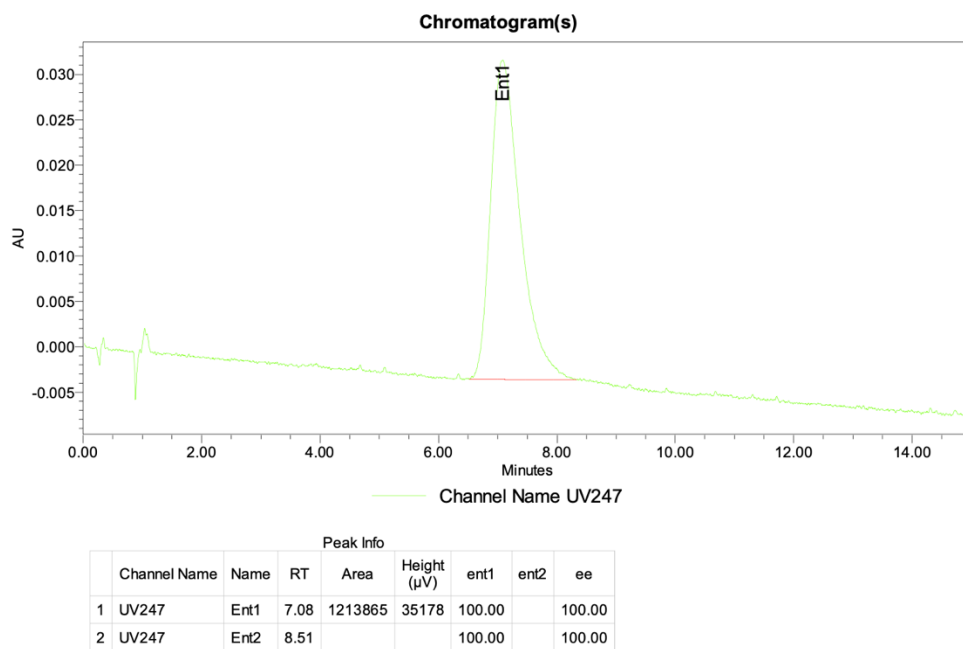


Figure S98: SFC trace of **FWG-2A**.

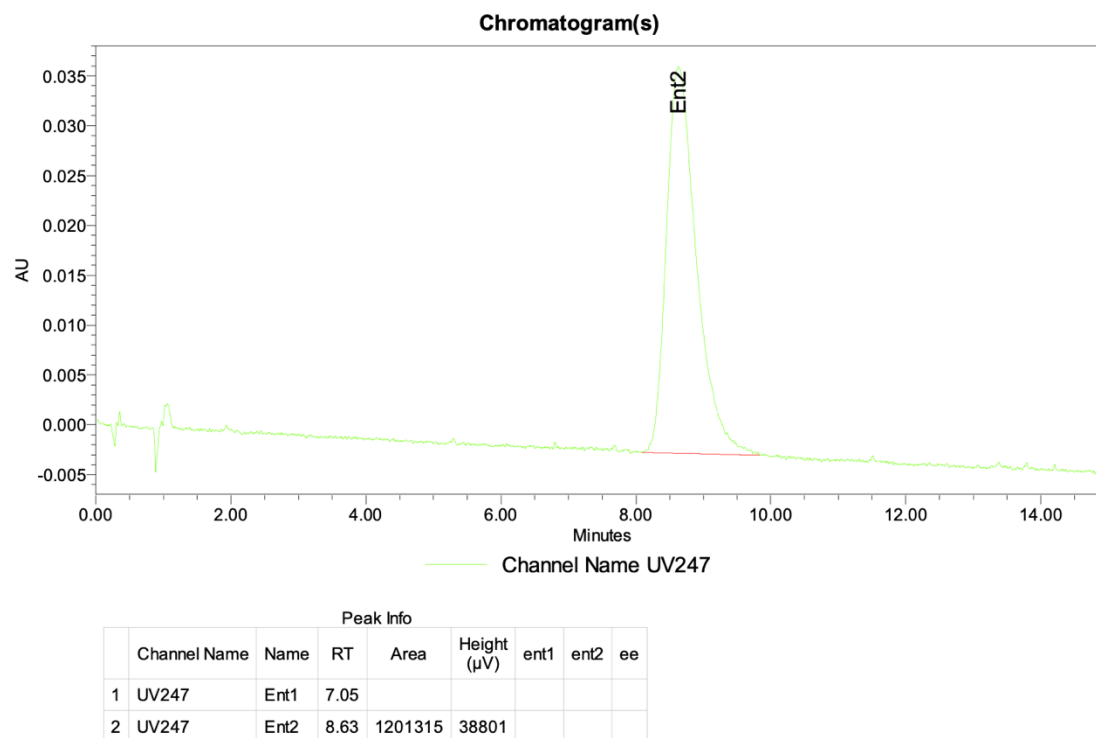


Figure S99: SFC trace of **FWG-2B**.

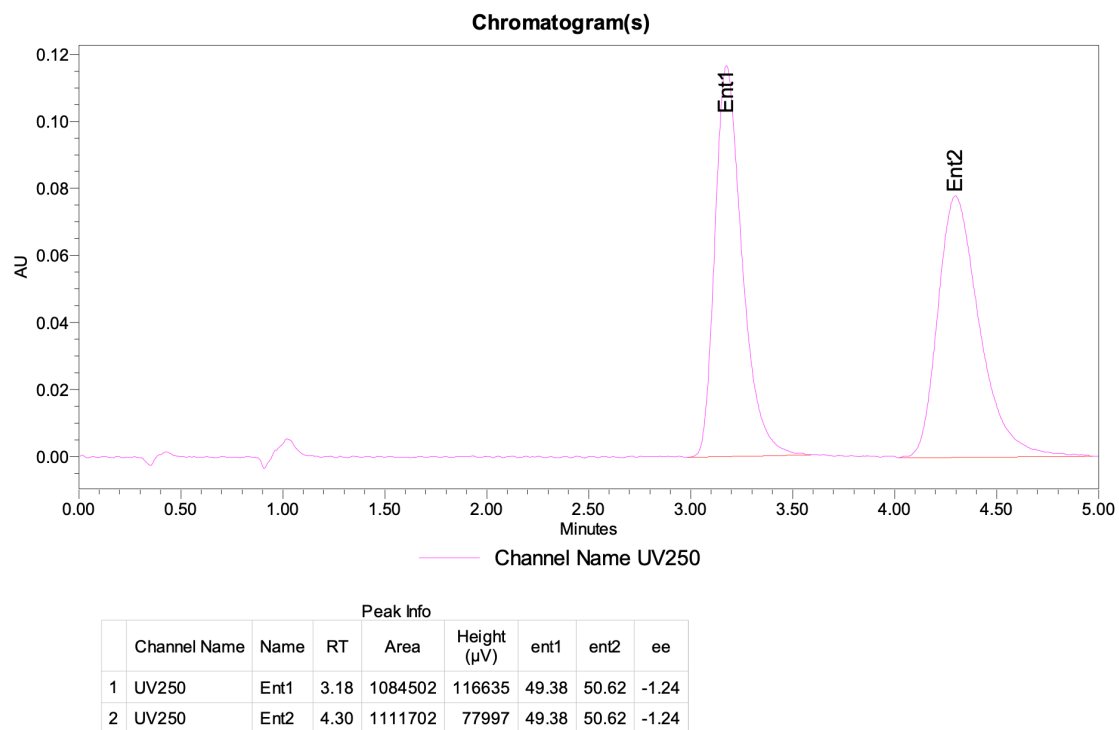


Figure S100: SFC trace of an equimolar mixture of **FWG-3A** and **FWG-3B**.

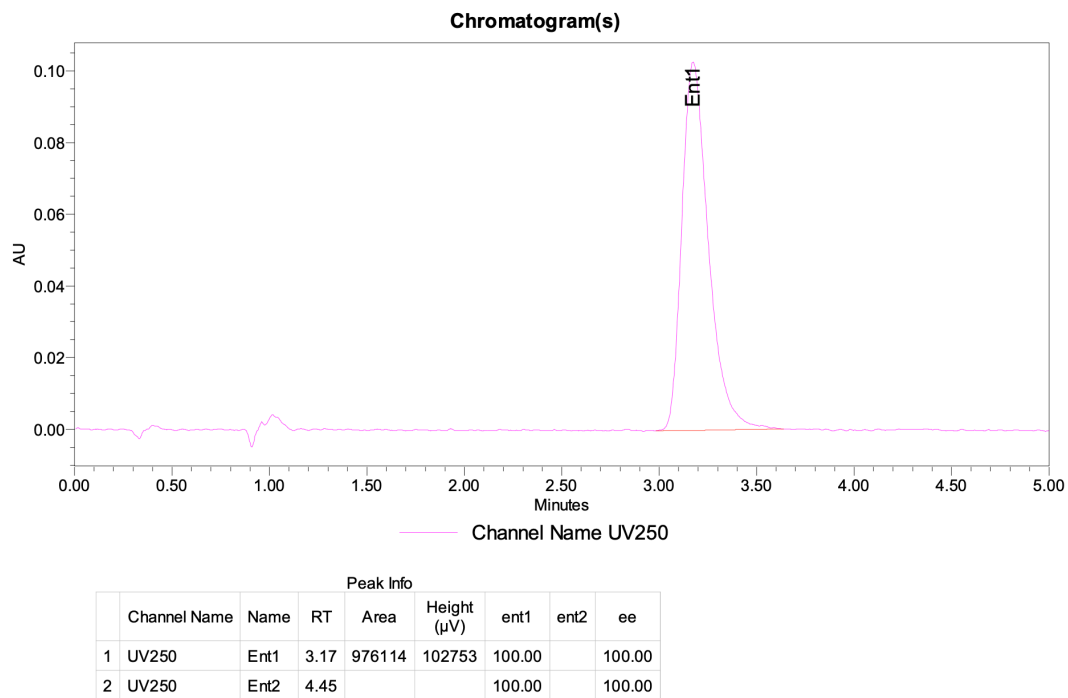


Figure S101: SFC trace of FWG-3A.

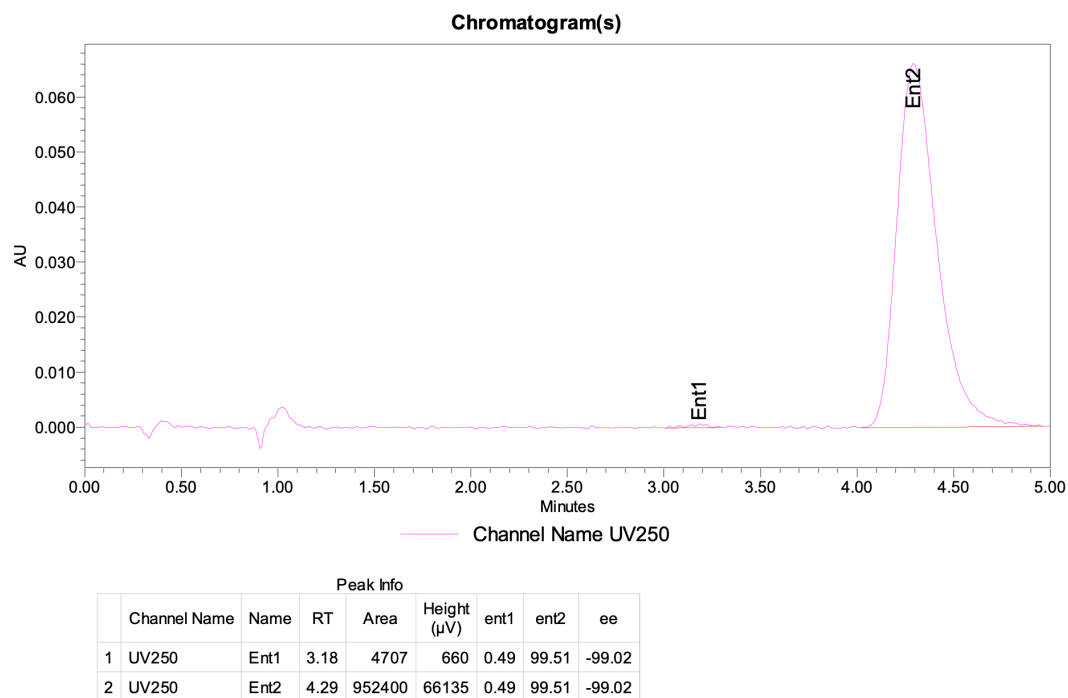


Figure S102: SFC trace of FWG-3B.

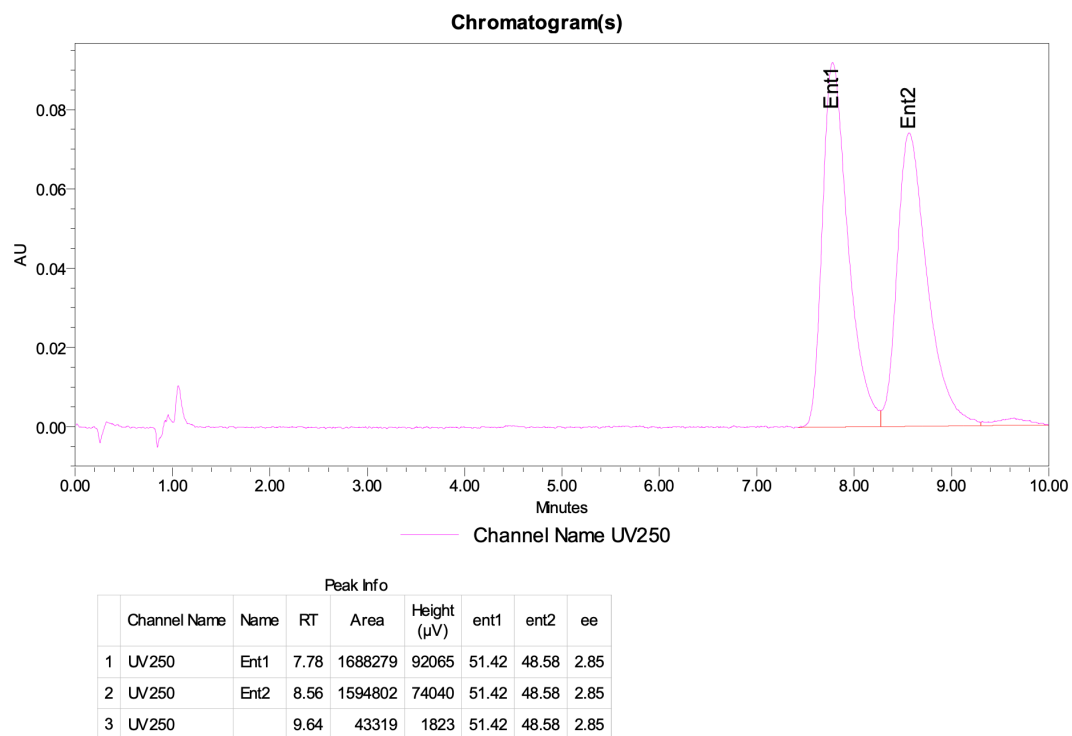


Figure S103: SFC trace of an equimolar mixture of **FWG-4A** and **FWG-4B**.

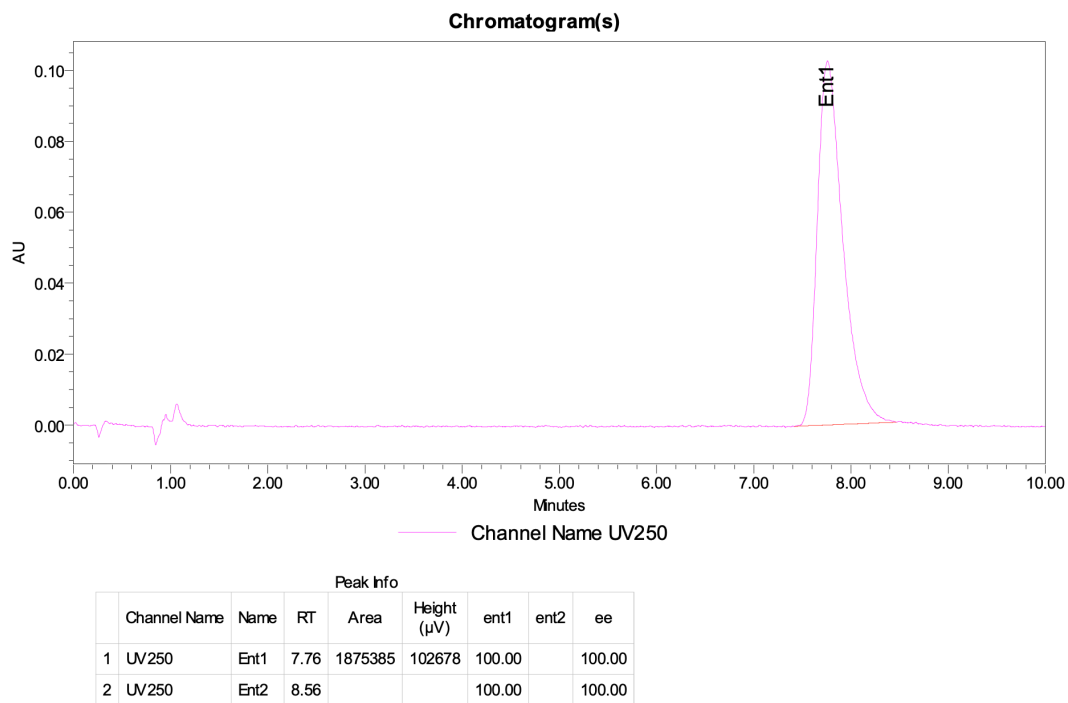


Figure S104: SFC trace of FWG-4A.

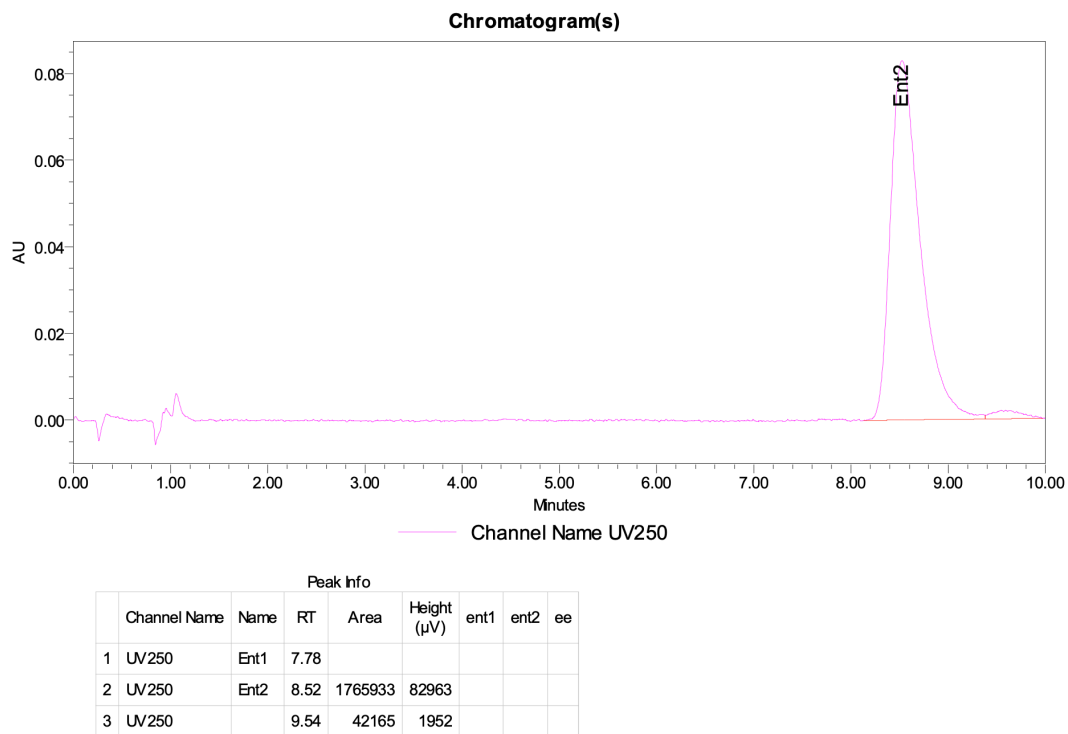


Figure S105: SFC trace of FWG-4B.

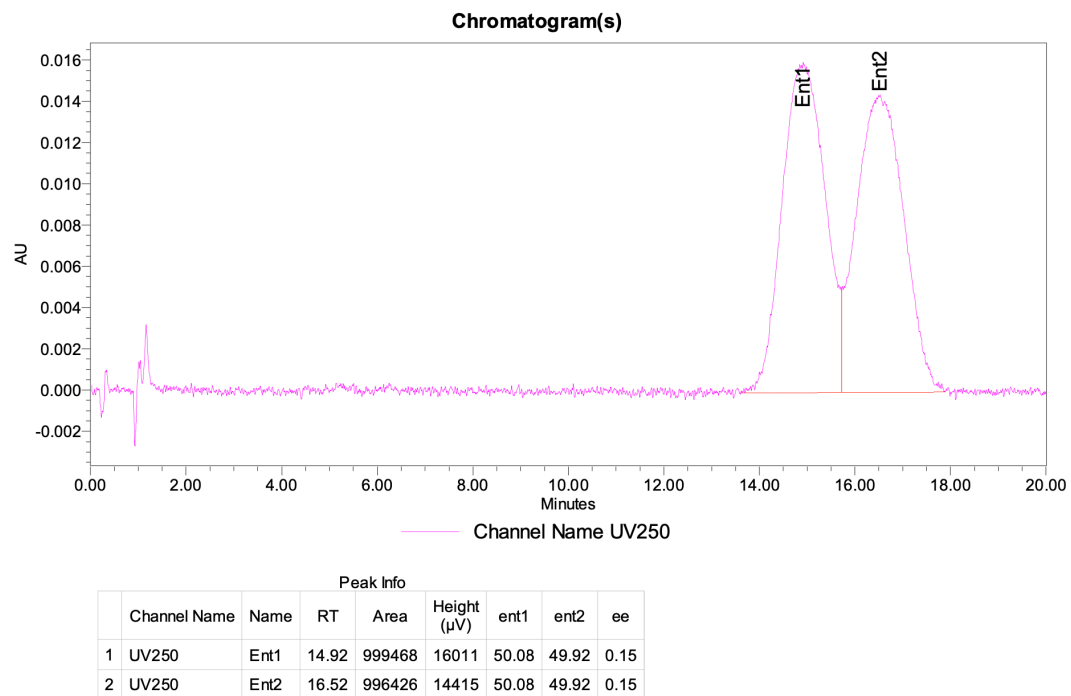


Figure S106: SFC trace of SFC trace of an equimolar mixture of **FWG-9A** and **FWG-9B**.

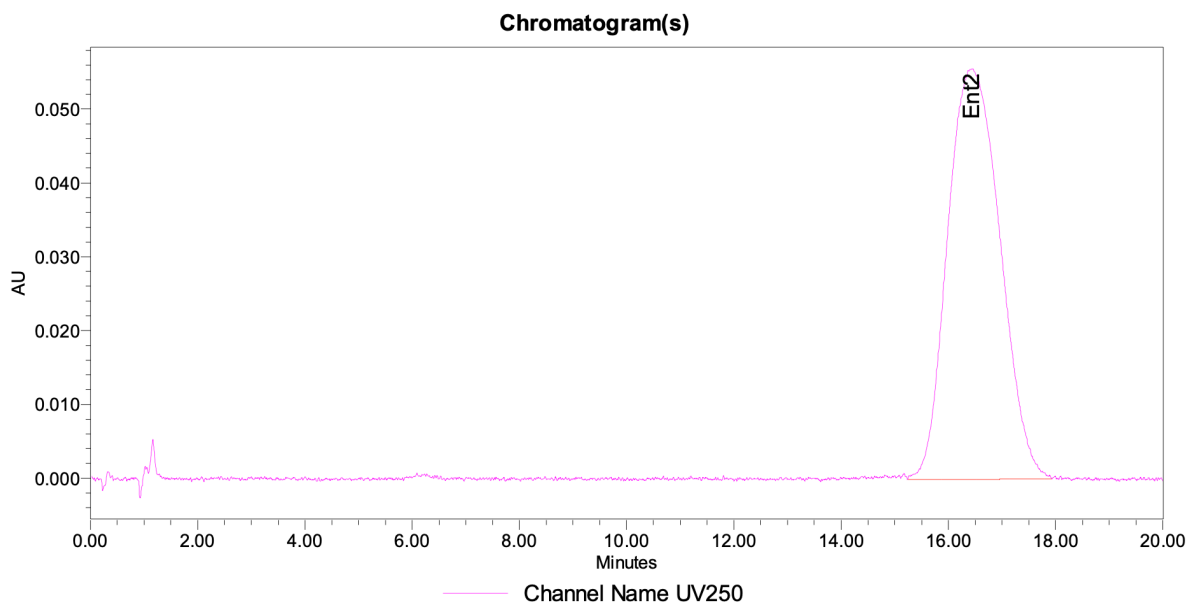


Figure S107: SFC trace of **FWG-9A**.

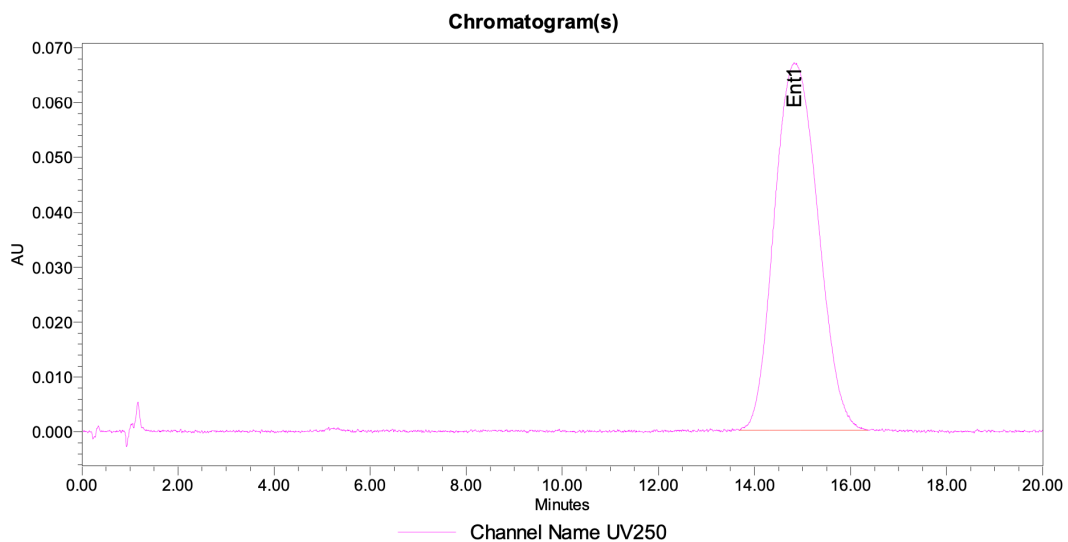


Figure S108: SFC trace of **FWG-9B**.

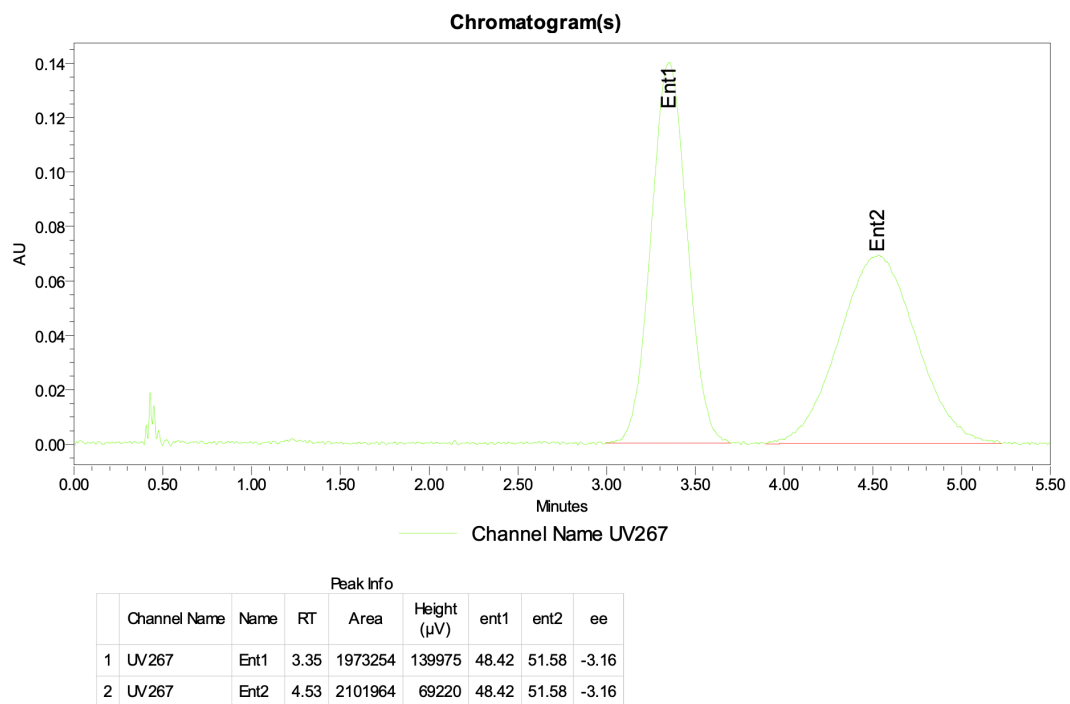


Figure S109: SFC trace of SFC trace of an equimolar mixture of **FWG-11A** and **FWG-11B**.

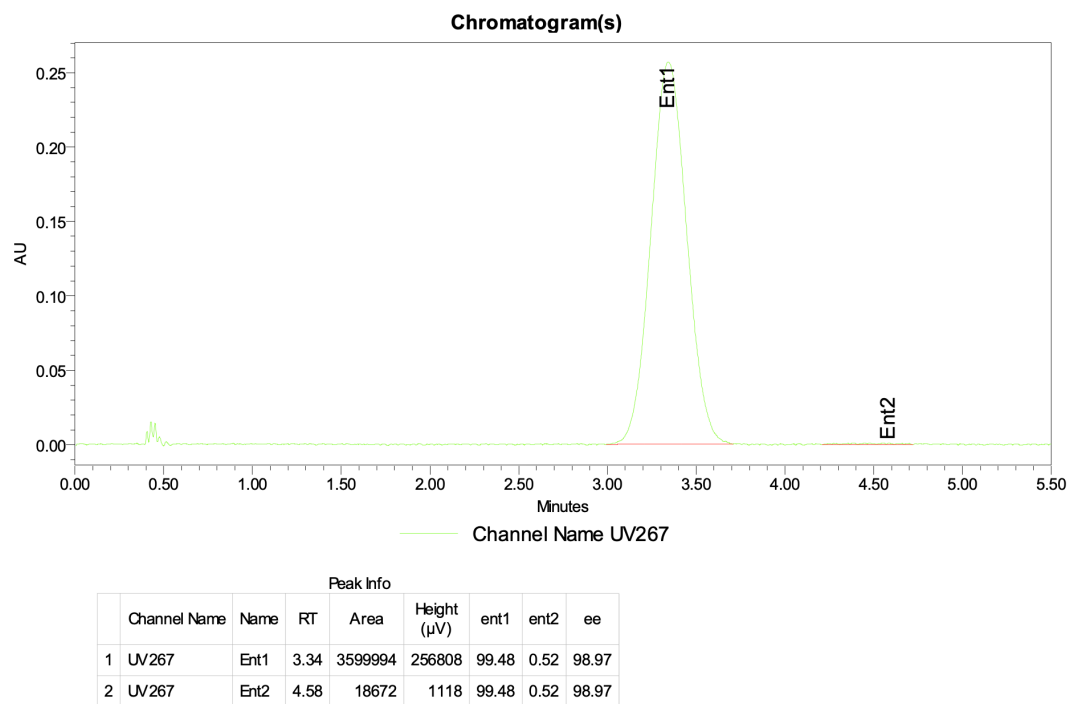


Figure S110: SFC trace of FWG-11A.

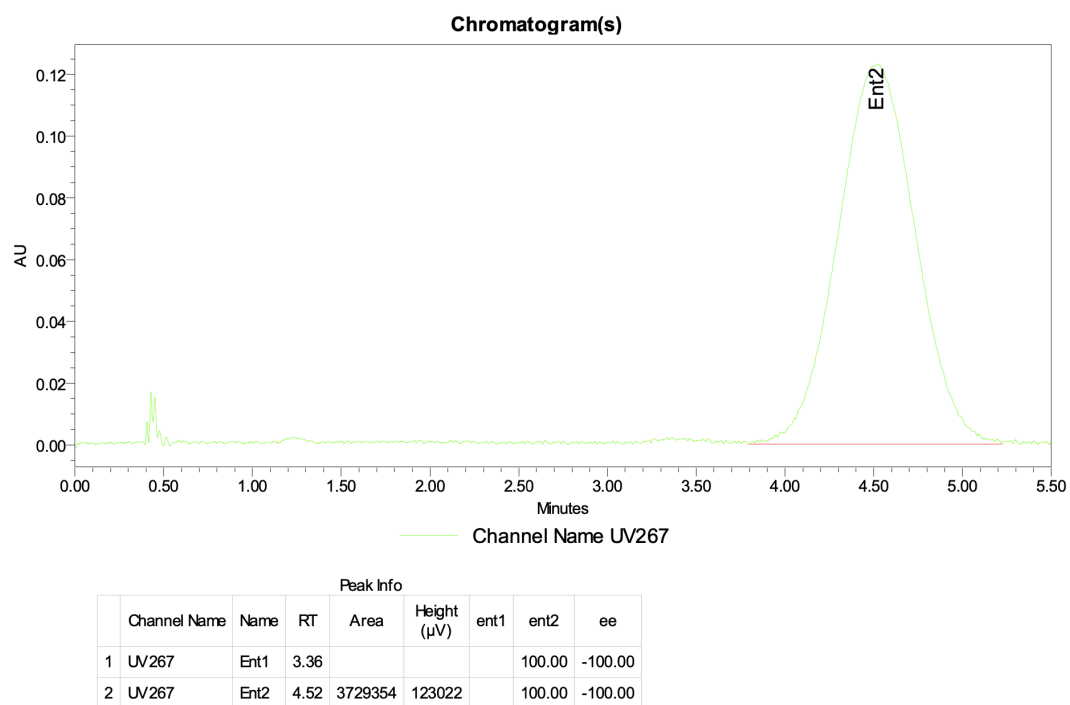
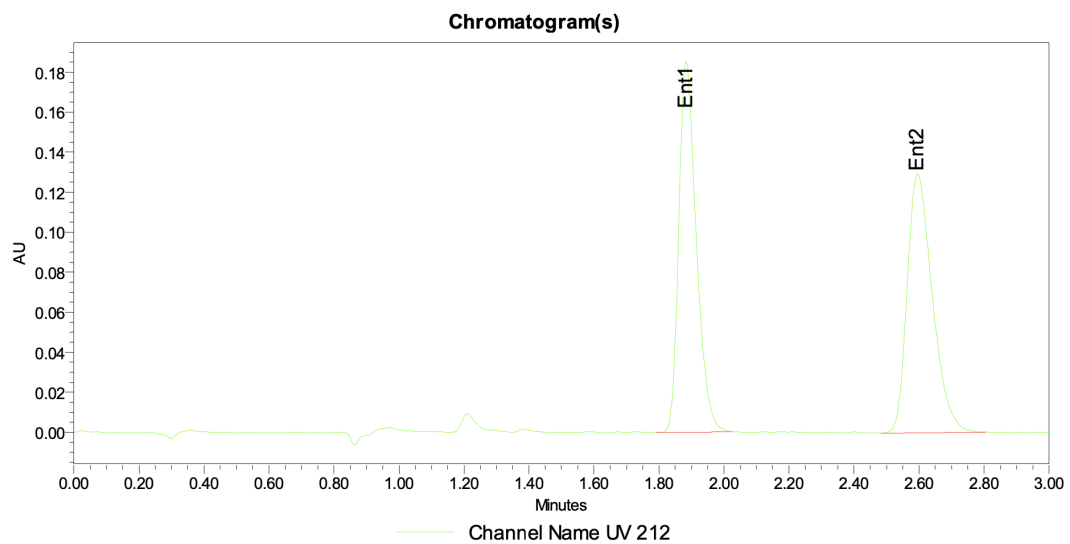


Figure S111: SFC trace of FWG-11B.



Peak Info							
	Channel Name	Name	RT	Area	Height (μV)	ent1	ent2
1	UV 212	Ent1	1.88	694154	185279	50.02	49.98
2	UV 212	Ent2	2.60	693725	129470	50.02	49.98

Figure S112: SFC trace of (±)-**41**.

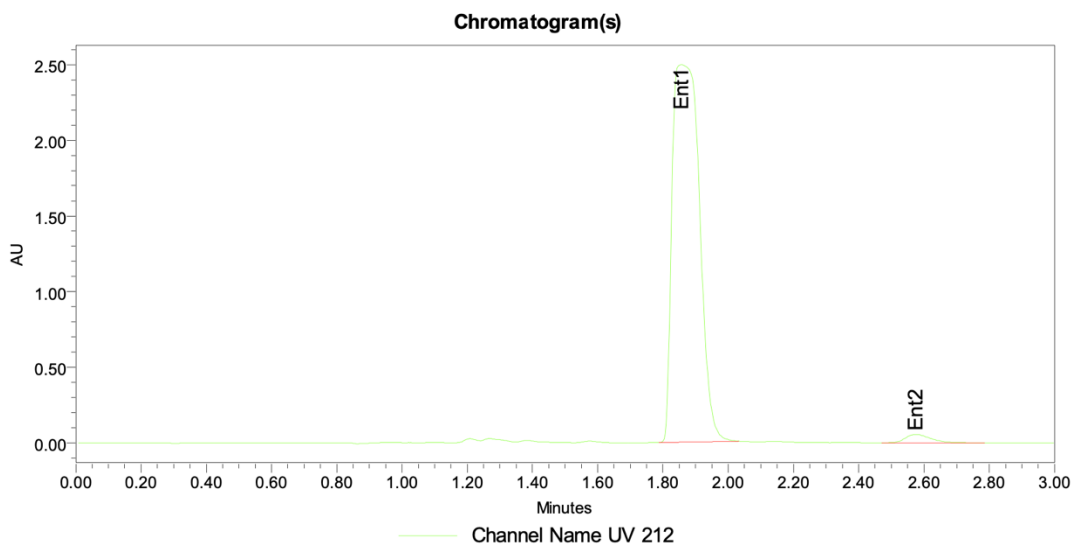


Figure S113: SFC trace of **41**.

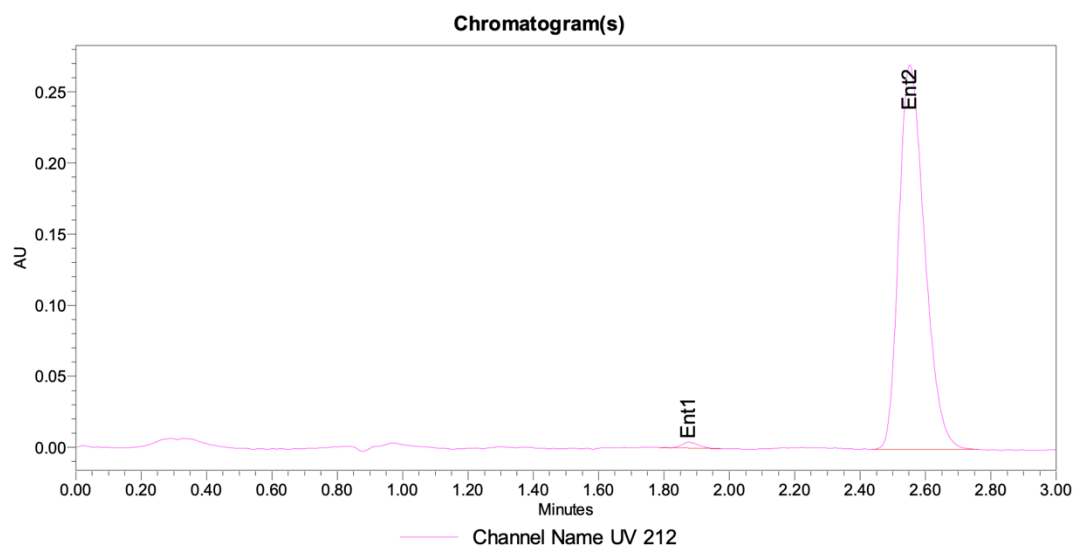


Figure S114: SFC trace of **42**.

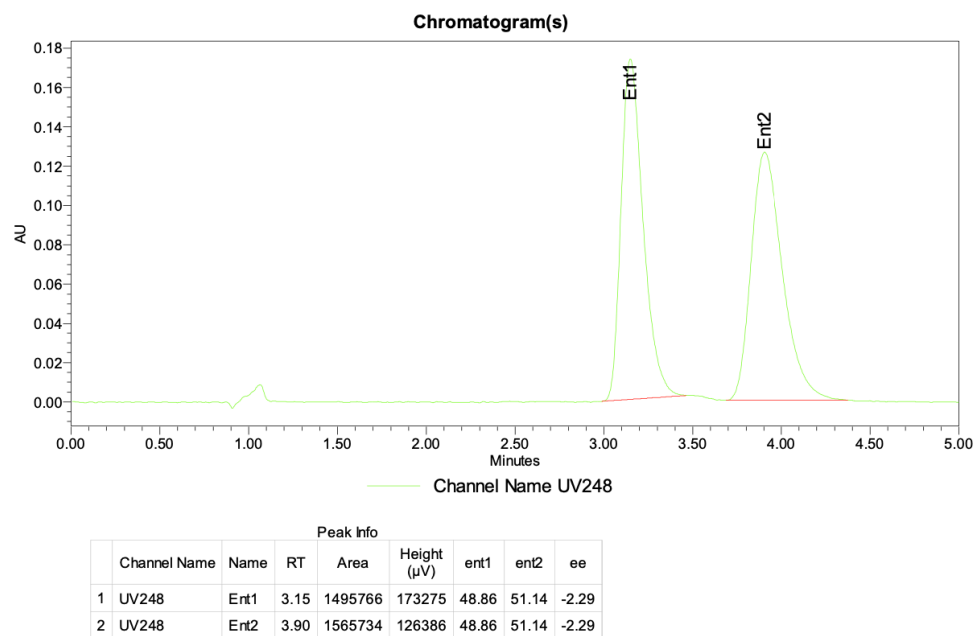


Figure S115: SFC trace of SFC trace of equimolar mixture of **FWG-33A** and **FWG-33B**.

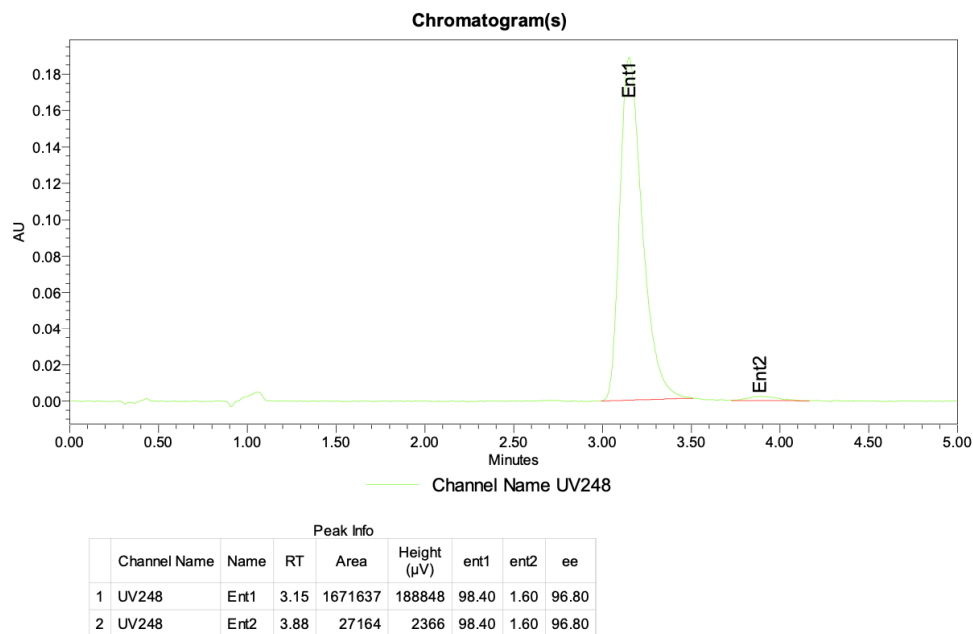


Figure S116: SFC trace of **FWG-33A**.

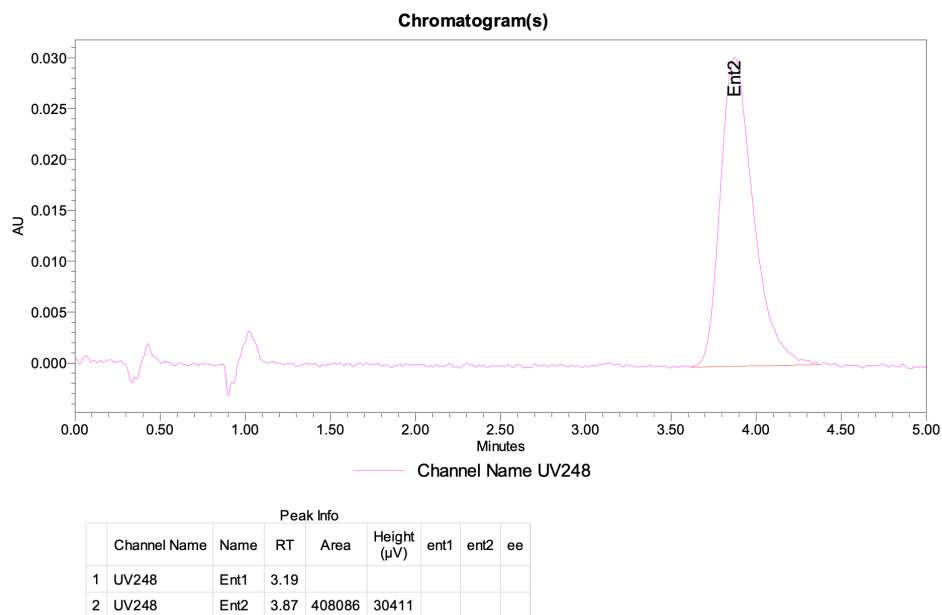
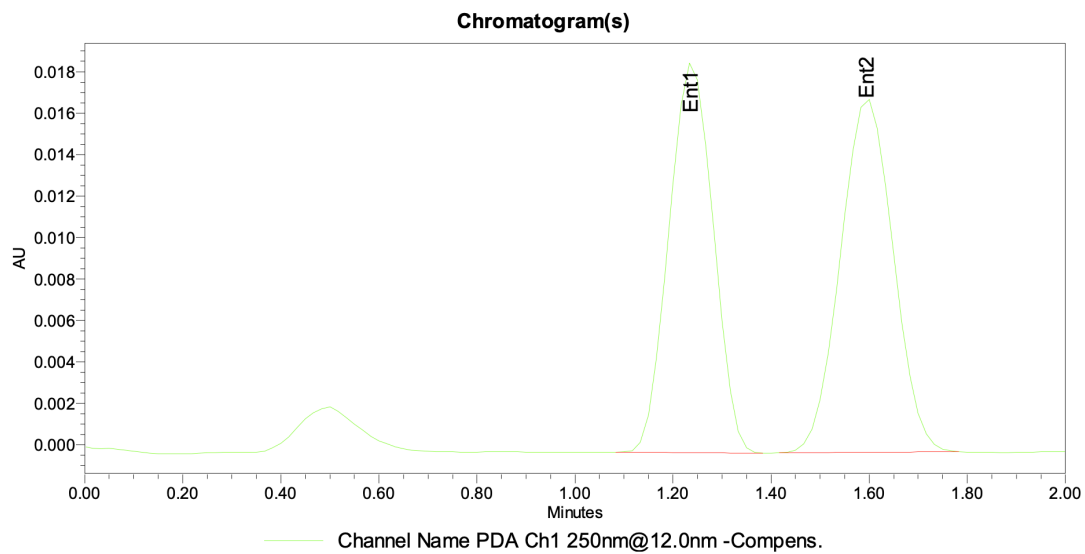
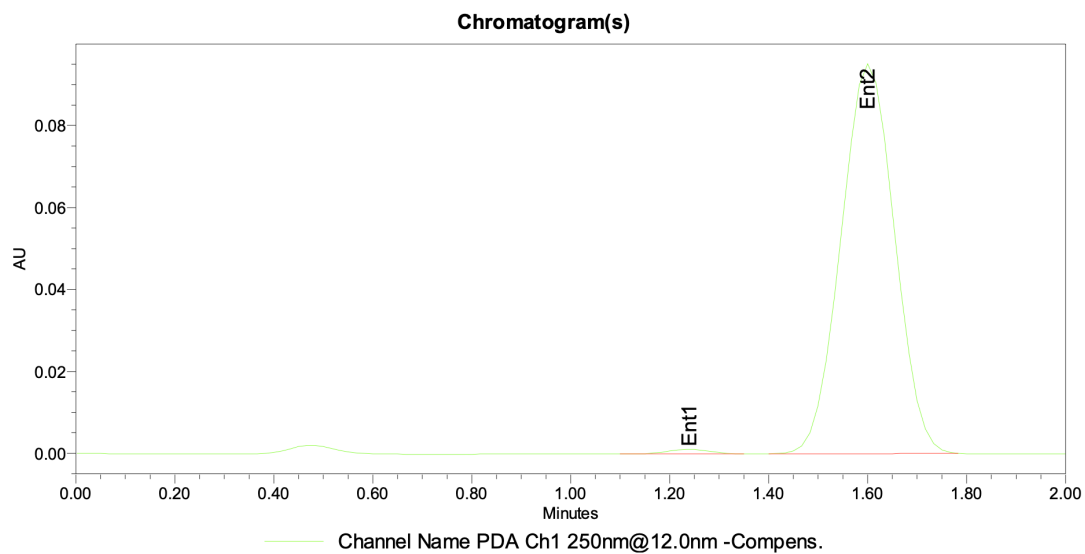


Figure S117: SFC trace of **FWG-33B**.



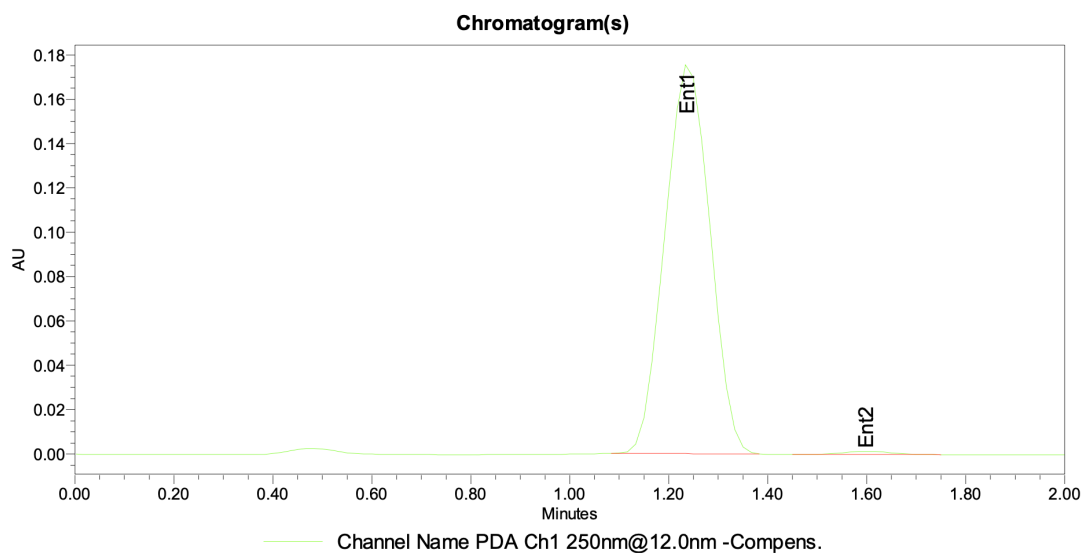
		Peak Info						
	Channel Name	Name	RT	Area	Height (μV)	ent1	ent2	ee
1	PDA Ch1 250nm@12.0nm -Compens.	Ent1	1.24	118046	18715	48.03	51.97	-3.95
2	PDA Ch1 250nm@12.0nm -Compens.	Ent2	1.60	127747	17026	48.03	51.97	-3.95

Figure S118: SFC trace of SFC trace of equimolar mixture of **FWG-49A** and **FWG-49B**.



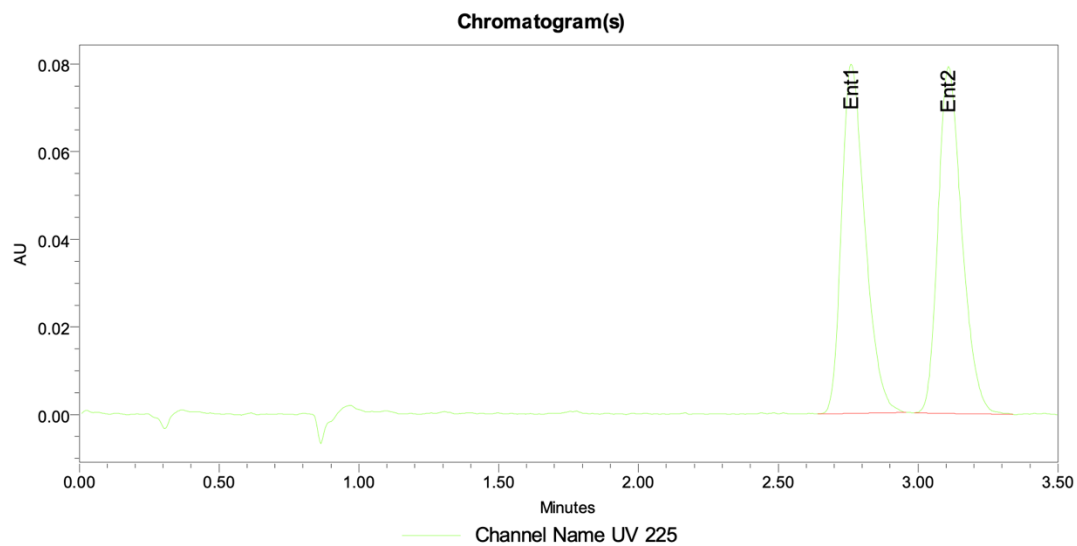
Peak Info								
	Channel Name	Name	RT	Area	Height (μV)	ent1	ent2	ee
1	PDA Ch1 250nm@12.0nm -Compens.	Ent1	1.24	7086	1129	0.98	99.02	-98.04
2	PDA Ch1 250nm@12.0nm -Compens.	Ent2	1.60	714950	94976	0.98	99.02	-98.04

Figure S119: SFC trace of FWG-49A.



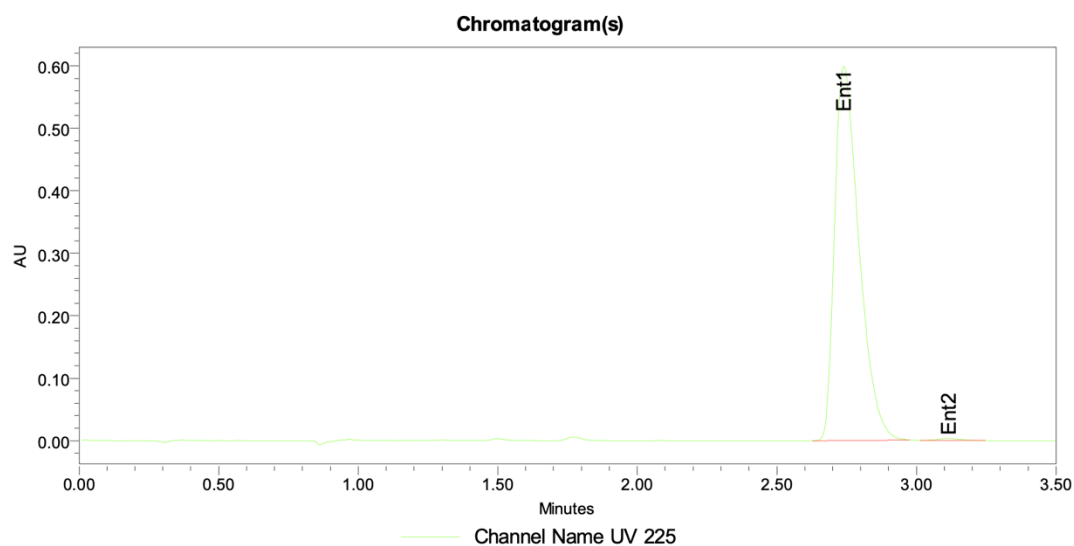
Peak Info								
	Channel Name	Name	RT	Area	Height (μV)	ent1	ent2	ee
1	PDA Ch1 250nm@12.0nm -Compens.	Ent1	1.24	1109681	175059	99.12	0.88	98.23
2	PDA Ch1 250nm@12.0nm -Compens.	Ent2	1.60	9886	1365	99.12	0.88	98.23

Figure S120: SFC trace of FWG-49B.



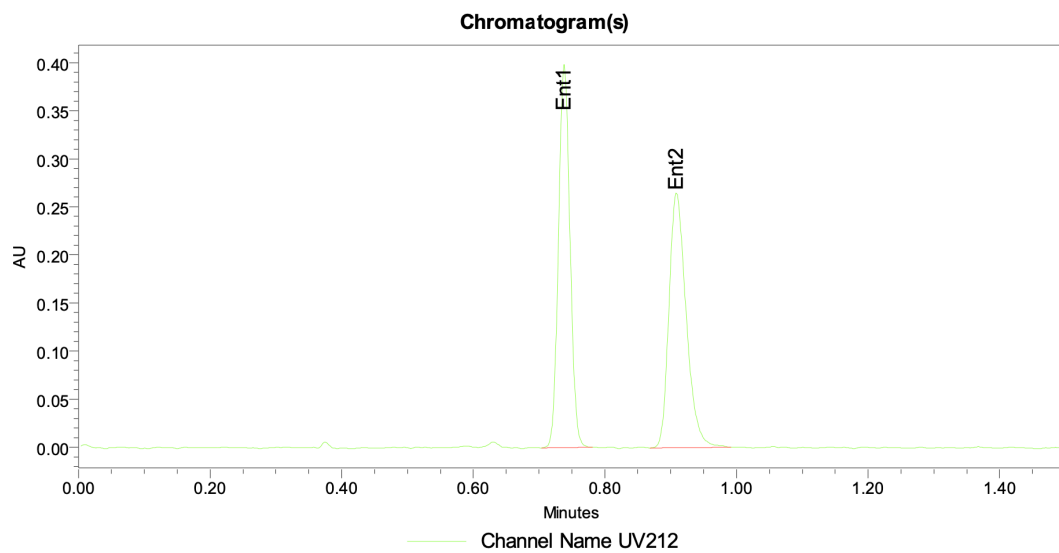
Peak Info								
	Channel Name	Name	RT	Area	Height (μV)	ent1	ent2	ee
1	UV 225	Ent1	2.76	464750	79732	49.85	50.15	-0.29
2	UV 225	Ent2	3.11	467479	79179	49.85	50.15	-0.29

Figure S121: SFC trace of (±)-52.



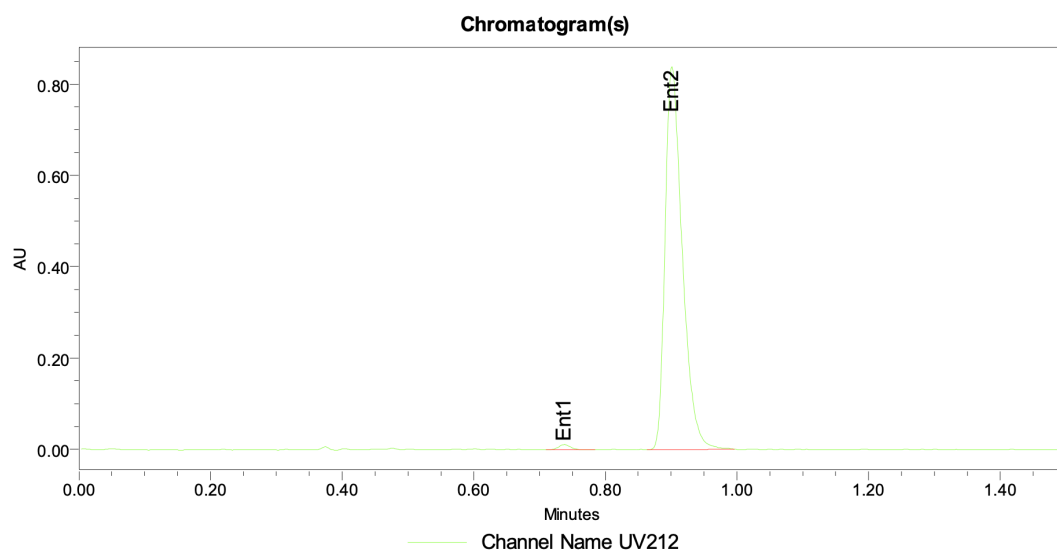
Peak Info								
	Channel Name	Name	RT	Area	Height (μV)	ent1	ent2	ee
1	UV 225	Ent1	2.74	3642586	599048	99.53	0.47	99.06
2	UV 225	Ent2	3.12	17151	3115	99.53	0.47	99.06

Figure S122: SFC trace of 52.



Peak Info							
	Channel Name	Name	RT	Area	Height (μV)	ent1	ent2
1	UV212	Ent1	0.74	481464	398384	50.07	49.93
2	UV212	Ent2	0.91	480191	264996	50.07	49.93

Figure S123: SFC trace of **55**.



Peak Info							
	Channel Name	Name	RT	Area	Height (μV)	ent1	ent2
1	UV212	Ent1	0.74	15092	11612	0.98	99.02
2	UV212	Ent2	0.90	1517881	839311	0.98	99.02

Figure S124: SFC trace of **55**.

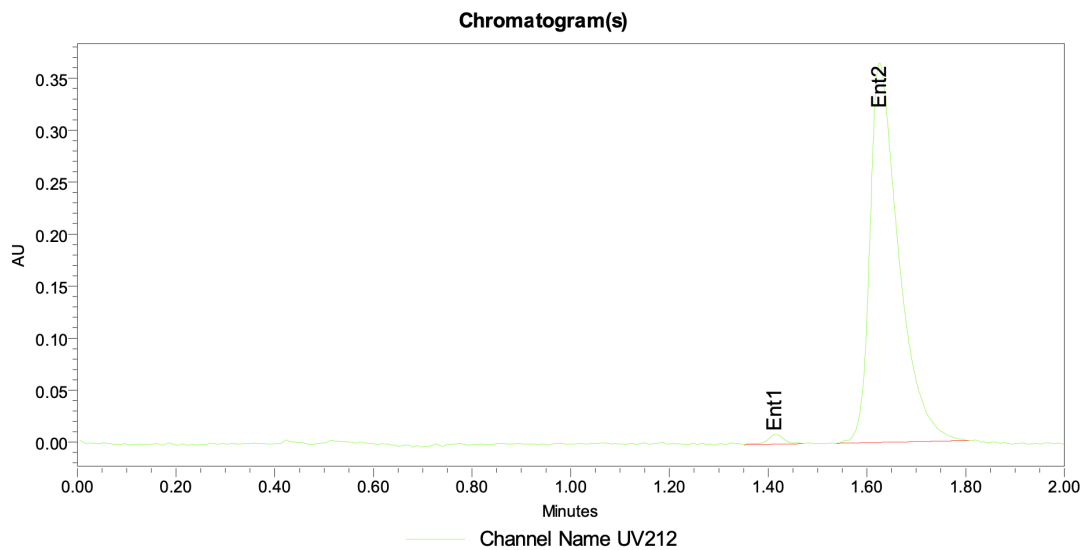


Figure S125: SFC trace of (±)-58.

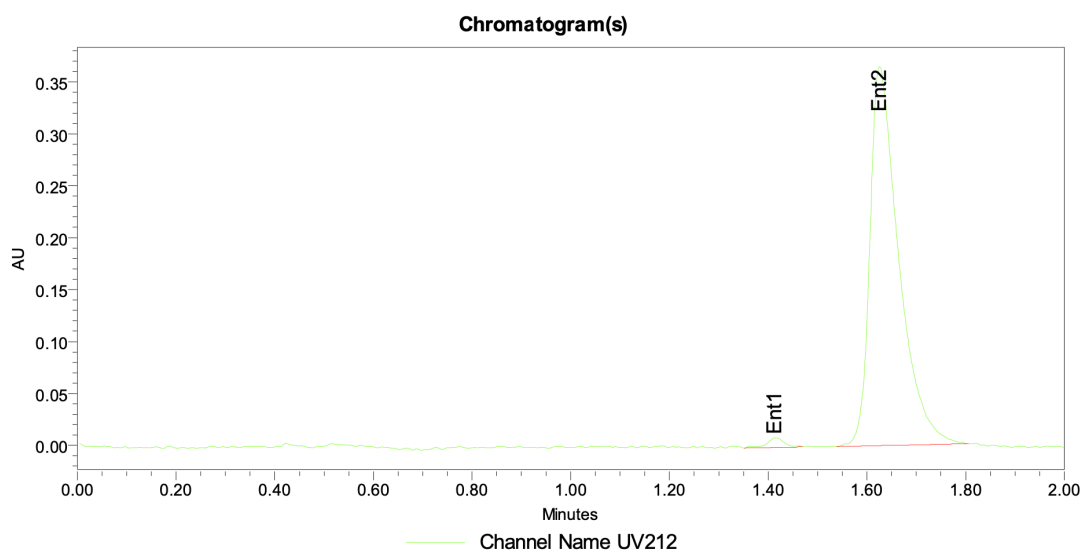
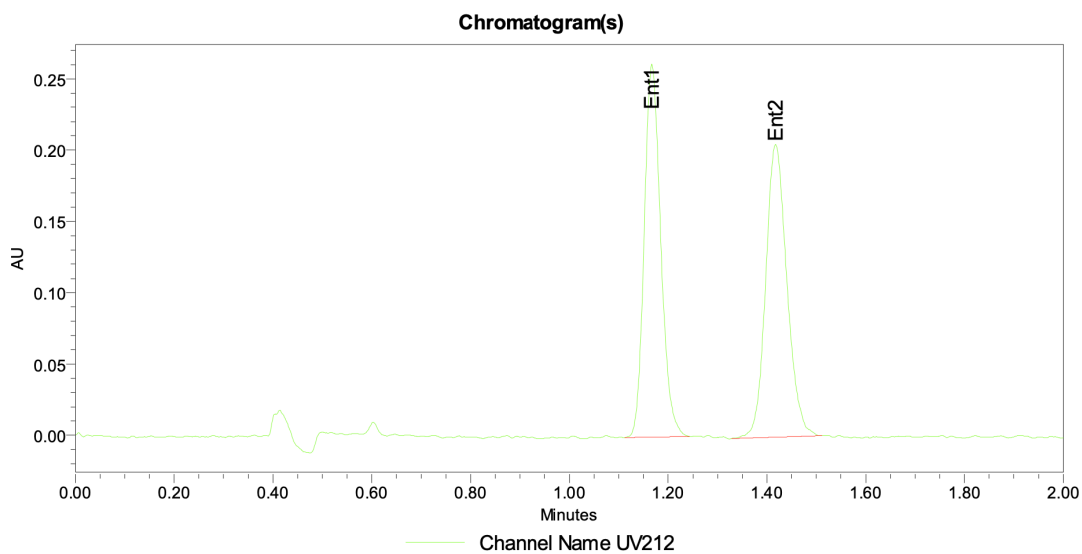
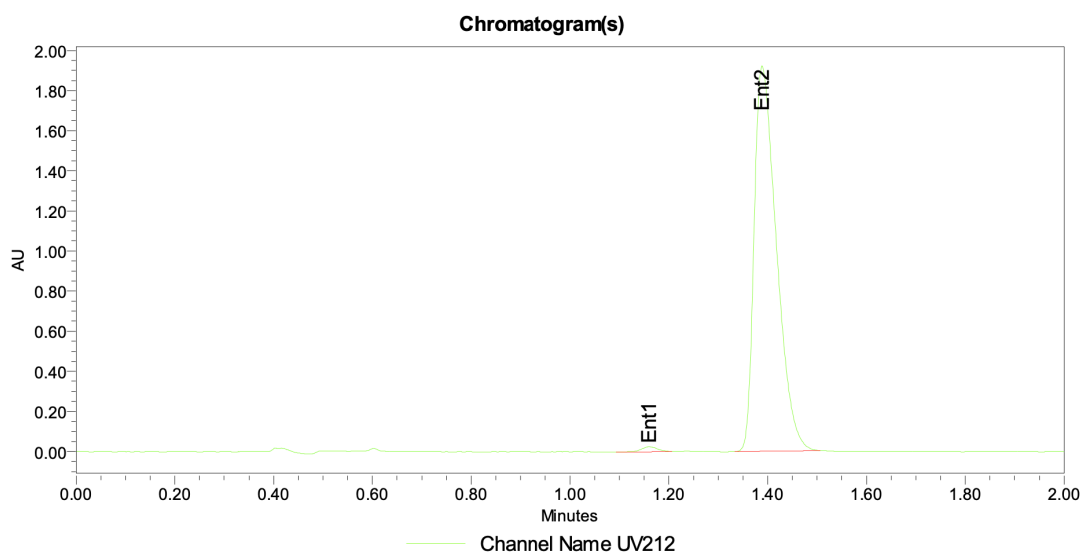


Figure S126: SFC trace of 58.



Peak Info							
	Channel Name	Name	RT	Area	Height (μV)	ent1	ent2
1	UV212	Ent1	1.17	606916	261793	49.75	50.25
2	UV212	Ent2	1.42	613025	205324	49.75	50.25

Figure S127: SFC trace of (±)-**61**.



Peak Info							
	Channel Name	Name	RT	Area	Height (μV)	ent1	ent2
1	UV212	Ent1	1.16	56898	24684	0.94	99.06
2	UV212	Ent2	1.39	6010575	1921909	0.94	99.06

Figure S128: SFC trace of **61**.

References

1. Goetzke, F. W., Mortimore, M. & Fletcher, S. P. Enantio- and Diastereoselective Suzuki–Miyaura Coupling with Racemic Bicycles. *Angew. Chem. Int. Ed.* **58**, 12128–12132 (2019).
2. Mishra, S., Modicom, F. C. T., Dean, C. L. & Fletcher, S. P. Catalytic asymmetric synthesis of carbocyclic C-nucleosides. *Commun. Chem.* **5**, 154 (2022).