Supplementary Information

An Environmentally Responsible 3-pot, 5-step Synthesis of the Antitumor Agent Sonidegib using ppm Levels of Pd Catalysis

Balaram S. Takale,*[a] Ruchita R. Thakore,[a] Fan Yi Kong[a,b] and Bruce H. Lipshutz*[a]

[a]Department of Chemistry and Biochemistry, University of California, Santa Barbara, California 93106, USA
[b]Upper Canada College, 220 Lonsdale Ave., Toronto, ON M2N 6X5, Canada

Table of Contents

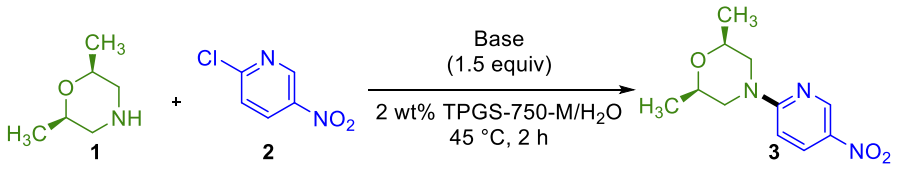
1. General information

Reagents were purchased from Sigma-Aldrich, Combi-Blocks, Alfa Aeser, or Acros Organics and used without further purification. Palladium acetate was supplied generously by Johnson Matthey. ^{1}H and ^{13}C NMR spectra were recorded on either a Varian Unity Inova 400 MHz (400 MHz for ^{1}H, 100 MHz for ^{13}C), a Varian Unity Inova 500 MHz (500 MHz for ^{1}H, 125 MHz for ^{13}C) or on a Varian Unity Inova 600 MHz spectrometer (600 MHz for ^{1}H); DMSO-d_6, CD_3OD, CD_3CN and $CDCl_3$ were used as solvent. Residual peaks for $CHCl_3$ in $CDCl_3$ (1 H = 7.26 ppm, ^{13}C = 77.20 ppm), $(CH_3)_2SO$ in $(CD_3)_2SO$ (1 H = 2.50 ppm, ^{13}C = 39.52 ppm), CH_3CN in CD_3CN (^{1}H = 1.98 ppm, ^{13}C = 0.49 and 117.47 ppm) or MeOH in MeOD (^{1}H = 4.78 ppm, ^{13}C = 49.00 ppm) have been assigned. The chemical shifts are reported in ppm, the coupling constants *J* value are given in Hz. The peak patterns are indicated as follows: bs, broad singlet; s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet. Thin layer chromatography (TLC) was performed using Silica Gel 60 F254 plates (Merck, 0.25 mm thick). Flash chromatography was done in glass columns using Silica Gel 60 (EMD, 40-63 μm). GCMS data were recorded on a 5975C Mass Selective Detector, coupled with a 7890A Gas Chromatograph (Agilent Technologies). Brij-30 is purchased from across organics (Catalog AC216725000). The desired 2 wt % of Brij-30 solution in HPLC water (which was degassed with argon prior to use) was prepared by dissolving 2 g of Brij-30 solid to 98 g of HPLC water and stored under argon.

2. Procedures for the synthesis of sonidegib *via* Route 1

2.1 S_NAr reaction

2.1.1 Screening of base

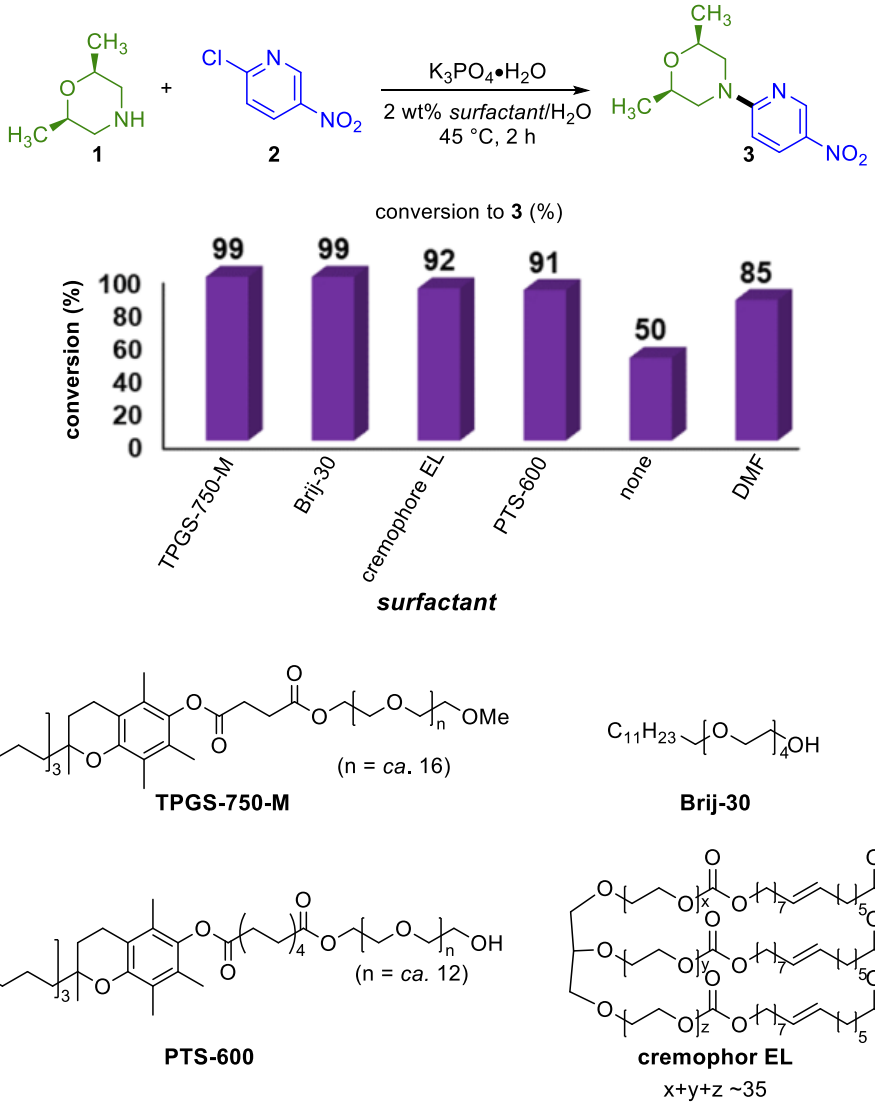


entry	base (1.5 equiv)	conversion to **3** (%)[b]
1	$K_3PO_4.H_2O$	>99
2	Et_3N	91
3	K_2CO_3	89
4[c]	$K_3PO_4.H_2O$	45

[a]Reaction conditions: 0.5 mmol of **1**, 0.5 mmol of **2**, 0.75 mmol of base, stirred at 45 °C for 2.0 h; [b]Determined by GC-MS; [c]reaction at room temperature for 24 h.

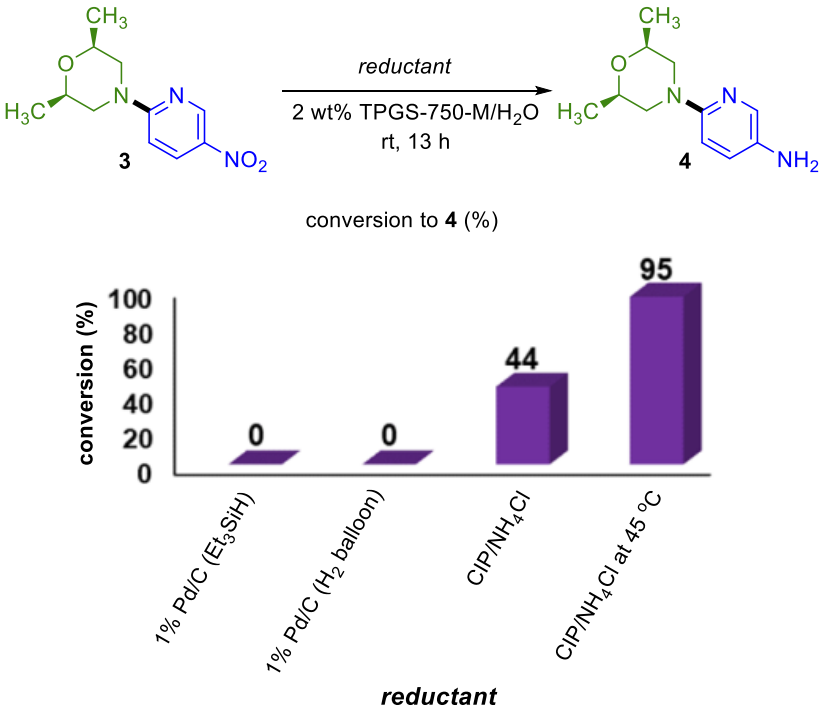
In a 1-dram vial, (2*S*,6*R*)-2,6-dimethylmorpholine **1** (0.5 mmol), 2-chloro-5-nitropyridine **2** (0.5 mmol), and base (0.75 mmol) were added. Aqueous 2 wt % TPGS-750-M solution (1.0 mL) was then added, and the vial was stirred at rt or 45 °C until completion (as monitored by TLC or GC-MS). The products were then separated by filtration, vacuum dried to give free flowing yellow powder in quantitative yield.

2.1.2 Screening of surfactants



In a 1-dram vial, (2*S*,6*R*)-2,6-dimethylmorpholine **1** (0.5 mmol), 2-chloro-5-nitropyridine **2** (0.5 mmol), and $K_3PO_4•H_2O$ (0.75 mmol) were added. Aqueous 2 wt % surfactant solution or water or DMF (1.0 mL) was added, and the vial was stirred at stirred 45 °C for 2 h. The products were then separated by filtration, vacuum dried to give free flowing yellow powder in quantitative yield.

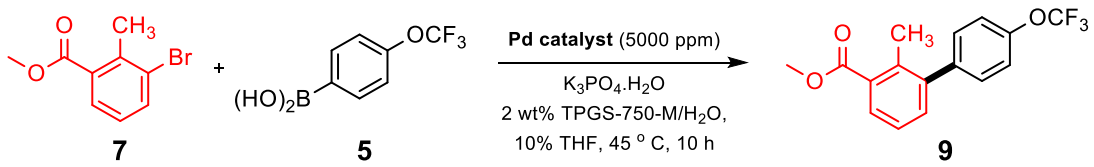
2.2 Reduction of the nitro group



In a 1-dram vial, (2*S*,6*R*)-2,6-dimethyl-4-(5-nitropyridin-2-yl)morpholine **3** (0.5 mmol), and reducing system (1 wt % Pd/C (1.0 mol%)/ H_2 balloon or 1 wt % Pd/C (1.0 mol %)/ Et_3SiH (3.0 equiv) or CIP (5.0 equiv)/NH_4Cl (3.0 equiv) was added. Aqueous 2 wt % Brij-30 solution (1.0 mL) was then added, and the vial was stirred at rt or 45 °C until completion (as monitored by TLC or GC-MS). The reaction mixture was then extracted with EtOAc (3 x 1 mL), and the combined organic layers were evaporated to give crude product as a purple colored oil, which was analysed by GC-MS, and used subsequently without further purification.

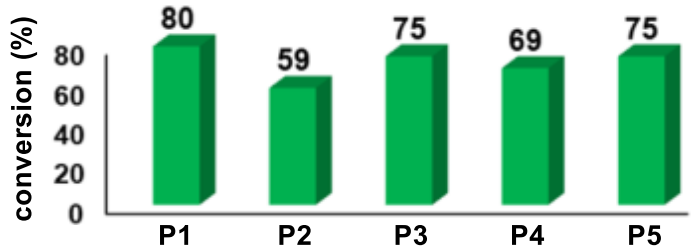
2.3 Suzuki-Miyaura coupling

2.3.1 Screening of palladium catalysts



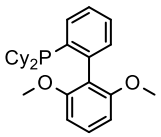
7 5 9

conversion to **9** (%)

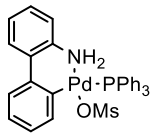


Pd catalyst

P1 = $Pd(OAc)_2$: PPh_3 (1:3)
P2 = $Pd(OAc)_2$: SPhos (1:2)
P3 = PPh_3-Pd-G3
P4 = $Pd(PPh_3)_4$
P5 = $Pd(PPh_3)_2Cl_2$



SPhos



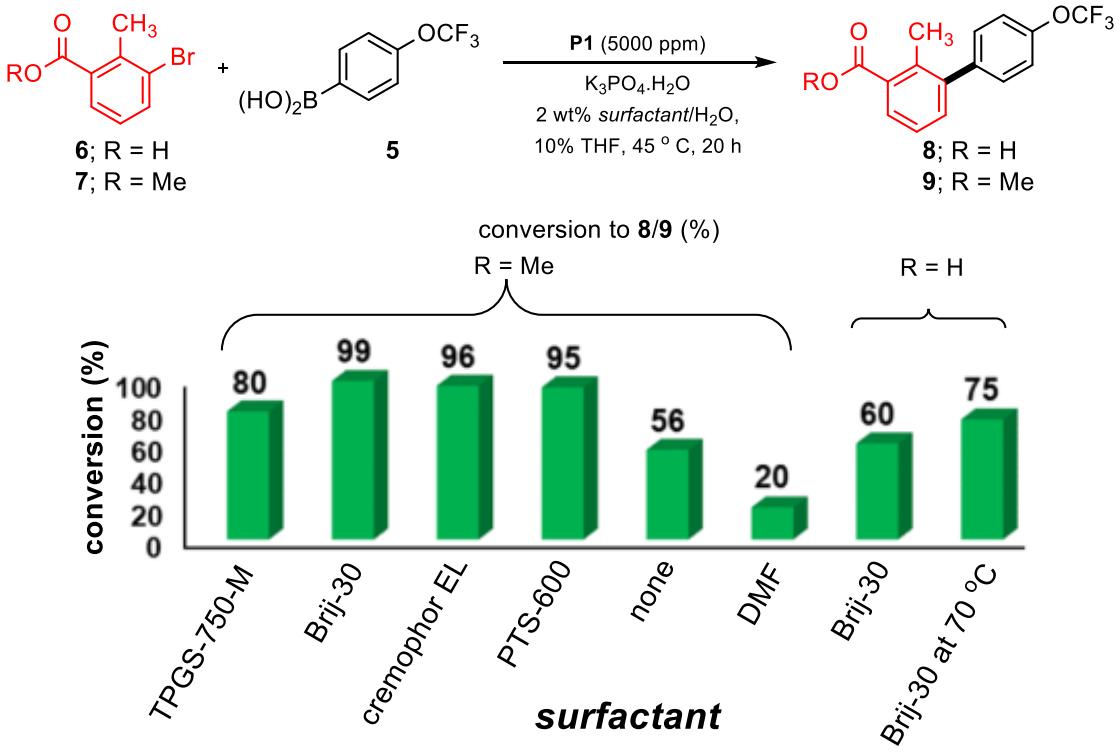
Ph_3P-Pd-G3

Preparation of a stock solution for a 0.5 mmol scale reaction. The stock solution was prepared by dissolving 5.0 mol % of $Pd(OAc)_2$ and 15 mol % of PPh_3 in 1.0 mL of THF and stirred for 15 min at rt under an inert atmosphere. From this stock solution, 100 μL (corresponds to 5000 ppm) of solution was used for Suzuki-Miyaura couplings.

Coupling reaction. In a 1-dram vial, aryl bromide **7** (0.5 mmol), boronic acid **5**, (0.55 mmol), and K_3PO_4•H_2O (0.75 mmol) were added. The vial was evacuated and backfilled with argon (this process was repeated 3 times). Catalyst stock solution as prepared above (100 μL = 5000 ppm of Pd) was then added before addition of the

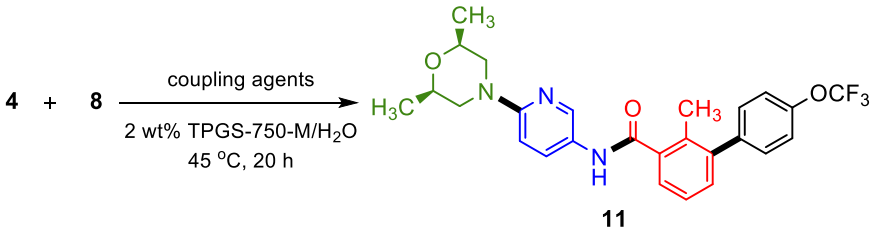
aqueous 2 wt % TPGS-750-M/H_2O (0.9 mL) solution. The vial was quickly closed with a screw cap and stirred at 45 °C for 10 h. The reaction mixture was then extracted with EtOAc (3 x 1 mL). The organic solvents were removed under vacuum to give a pale-yellow oil which was then analysed for conversion using GC-MS.

2.3.2 Screening of surfactants



A similar procedure mentioned in **Section 2.3.1** was followed by choosing a different surfactant system or solvent.

2.4 Amide coupling



11

entry	coupling reagent	yield of **11** (%)[b]
1	COMU/ 2,6-lutidine	40
2	HATU/ *i*-Pr_2EtN	43
3	HOBt/ *i*-Pr_2EtN	25
4[c]	DCC/ DMAP	61

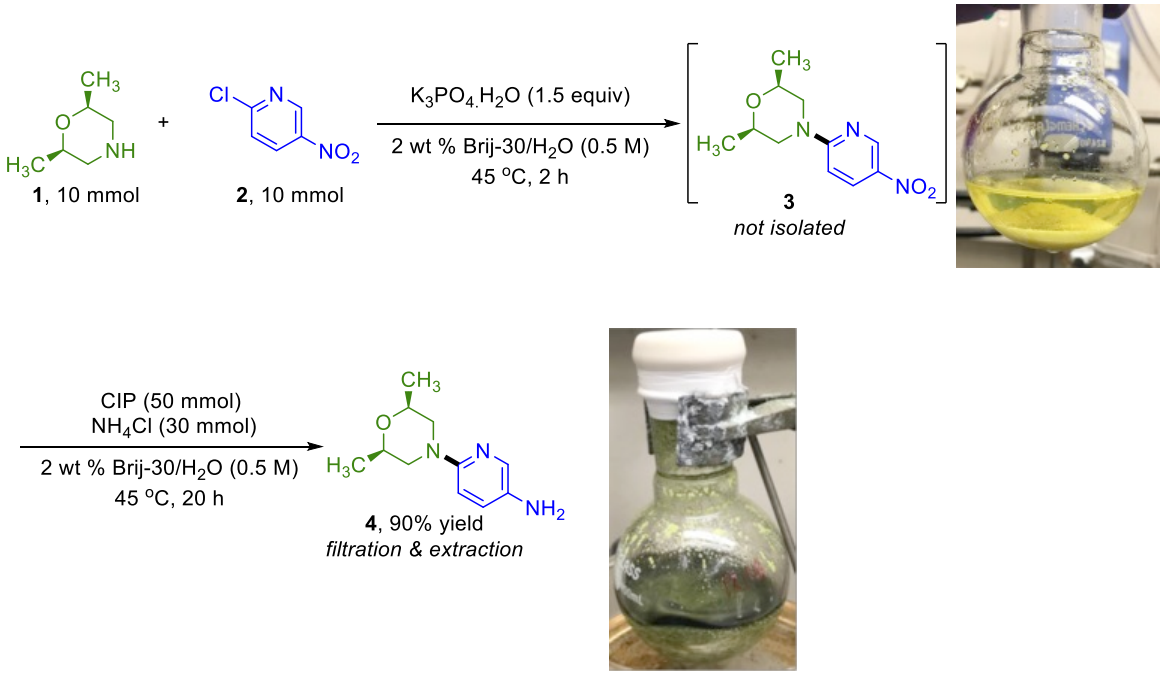
[a]Reaction conditions: 0.6 mmol of **4**, 0.5 mmol of **8**, 1.2 equiv of coupling reagent (COMU/ HATU/ HOBt) or 2.0 equiv DCC, 2.0 equiv base (2,6-lutidine, *i*-Pr_2EtN, or 10% DMAP; [b]Isolated yield.

Procedure (a): In a 1-dram vial, carboxylic acid **8** was added (0.5 mmol) followed by 2 wt % TPGS-750-M/H_2O (1.0 ml) and base (2.0 equiv). The vial was screw capped and stirred for ~5 - 10 min, after which the amine **4** (1.2 equiv) was added followed by coupling reagent (1.2 equiv). The reaction was stirred at 45 °C for 20 h. The reaction mixture was then extracted with EtOAc (3 x 1 mL). The organic solvents were then removed under vacuum to give crude material which was then purified by column chromatography to give pure product **11**.

Procedure (b): In a 1-dram vial, carboxylic acid **8**, amine **4** (1.2 equiv), and 10% DMAP were added followed by 2 wt % TPGS-750-M/H_2O (1.0 mL). The vial was screw capped and stirred for at 45 °C for 10 min. At this stage, 0.5 equiv of DCC was added and the stirring was continued for 1 h (this process was repeated 3 times for an additional 1.5 equiv DCC). Finally, the reaction mixture was stirred for another 15-16 h. The reaction mixture was then extracted with EtOAc (3 x 1 mL). The organic solvents were removed under vacuum to give crude material which was then purified by column chromatography to give pure product **11**.

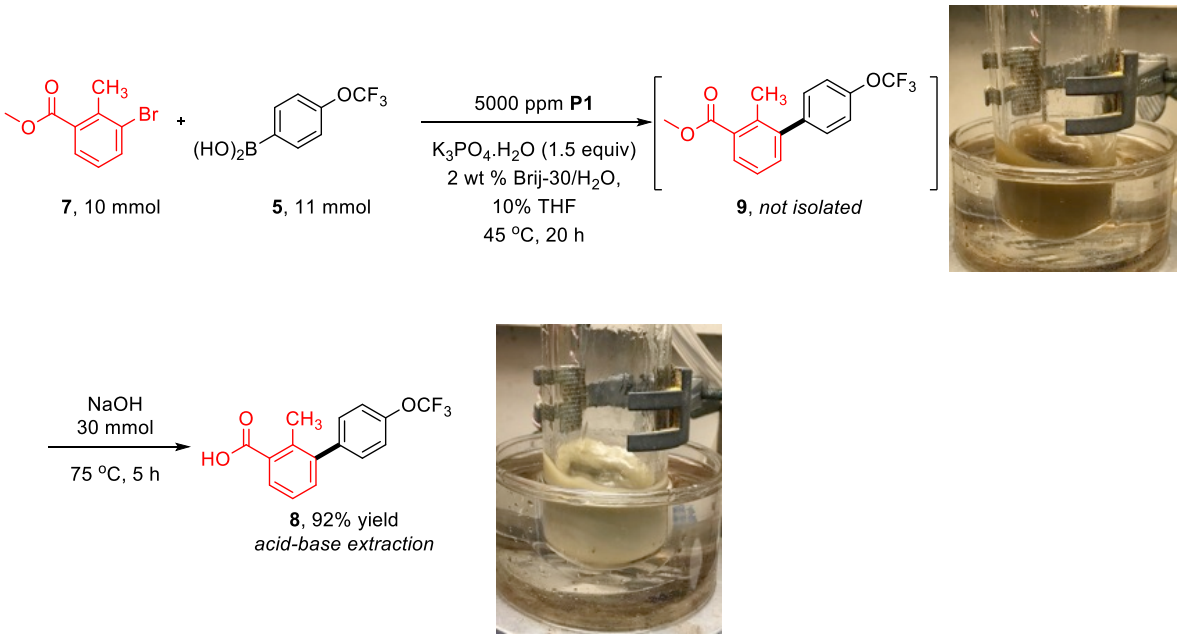
2.5 Large scale one-pot reaction

2.5.1 Synthesis of intermediate 4



In a 100.0 mL round bottom flask, (2*S*,6*R*)-2,6-dimethylmorpholine **1** (10.0 mmol), 2-chloro-5-nitropyridine **2** (10.0 mmol), and K_3PO_4•H_2O (1.5 equiv) were added. Aqueous 2 wt % Brij-30/H_2O solution (20 mL) was added, and the round bottom flask was capped with a rubber septum and the reaction was stirred at stirred 45 °C for 2 h allowing the formation of S_NAr product **3** (yellow solid). Later in the same pot, CIP (50.0 mmol) and NH_4Cl (30.0 mmol) were added and the reaction was stirred at 45 °C for 20 h. The product was then separated through filtration followed by extraction using EtOAc (4 x 15 mL). The extracts were combined and then evaporated to give pure amine **4** as a purple colored oil in 90% yield which was analysed by GC-MS.

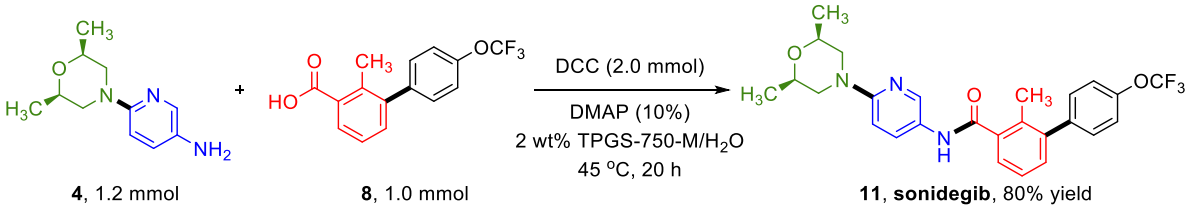
2.5.2 Synthesis of intermediate 8



Preparation of stock solution for a 10.0 mmol scale reaction. The stock solution was prepared by dissolving 5000 ppm of $Pd(OAc)_2$ and 15000 of PPh_3 in 2.0 mL of THF and then stirred for 15 min at rt under inert atmosphere. This stock solution was used for large scale Suzuki-Miyaura couplings.

In a 150 mL Schlenk tube, aryl bromide **7** (10.0 mmol), boronic acid **5**, (11.0 mmol), and $K_3PO_4•H_2O$ (1.5 equiv) were added. The flask was evacuated and backfilled with argon (this process was repeated 3 times). Catalyst stock solution as prepared above (2.0 mL = 5000 ppm of Pd) was then added before addition of aqueous 2 wt % Brij-30/H_2O (18.0 mL) solution. The reaction was allowed to stir at 45 °C for 20 h under argon (monitored by TLC). Later in the same reaction pot, 30.0 mmol of NaOH was added and the reaction was stirred at 75 °C for 5.0 h (monitored by TLC). The reaction mixture was then acidified using 2 M HCl (pH = 2) in an ice bath to get crude product, which was recrystallized from ethanol (~50 mL) to provide a white solid (92% yield).

2.5.3 Amide coupling: Route 1

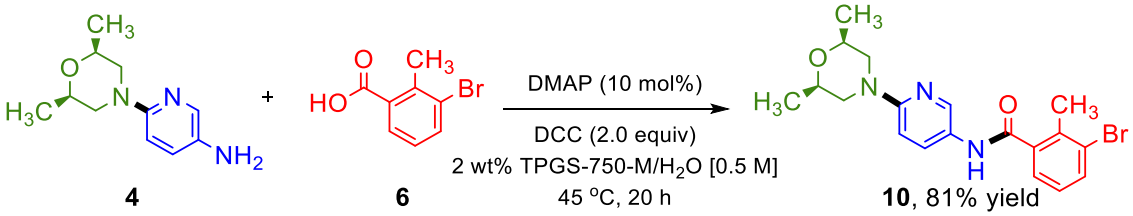


4, 1.2 mmol **8**, 1.0 mmol **11**, **sonidegib**, 80% yield

In a 10 mL round bottom flask, carboxylic acid **8** (1.0 mmol), amine **4** (1.0 mmol), and 10% DMAP were added followed by 2 wt % TPGS-750-M/H_2O (2.0 ml). The vial was screw capped and stirred for at 45 °C for 10 min. At this stage 0.5 equiv of DCC was added and the stirring was continued for 1 h (this process was repeated 3 times for an additional 1.5 equiv DCC). Finally, the reaction mixture was stirred for another 15-16 h (monitored by TLC). The reaction mixture was then extracted with EtOAc (3 x 1 mL). The organic solvents were removed under vacuum to give crude material which was then purified by column chromatography to give pure product **11** in 80% yield.

3. Procedures for the synthesis of sonidegib *via* Route 2:

3.1 Amide coupling

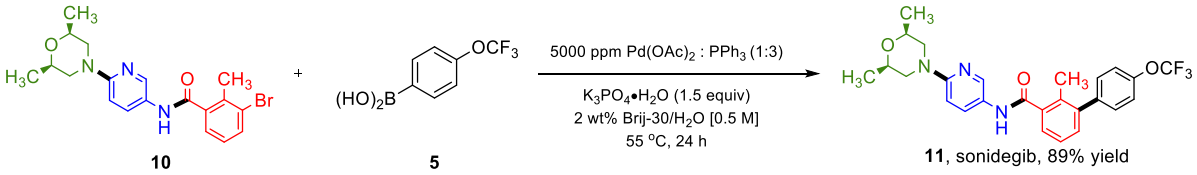


4 **6** **10**, 81% yield

In a 1-dram screw cap glass vial, carboxylic acid **6** (1.0 mmol), amine **4** (1.2 mmol), and 10% DMAP were added followed by 2 wt % TPGS-750-M/H_2O (2.0 ml). The vial was screw capped and stirred for at 45 °C for 10 min. At this stage 0.5 equiv of DCC was added and the stirring was continued for 1 h (this process was repeated 3 times for an additional 1.5 equiv DCC). Finally, the reaction mixture was stirred for another

15-16 h (monitored by TLC). The reaction mixture was then extracted with EtOAc (3 x 1 mL). The organic solvent was removed under vacuum to give crude material which was then purified by column chromatography to give pure product **10** in 81% yield.

3.2 Late stage Suzuki-Miyaura coupling



In a 1-dram vial, aryl bromide **10** (0.5 mmol), boronic acid **5**, (0.55 mmol), and $K_3PO_4•H_2O$ (1.5 equiv) were added. The vial was evacuated and backfilled with argon (this process was repeated 3 times). Catalyst stock solution as prepared above (100 μL = 5000 ppm of Pd) was then added before addition of aqueous 2 wt % Brij-30/H_2O (1.0 mL) solution. The vial was quickly closed with a screw cap, and stirred at 55 °C for 24 h (monitored by TLC). The reaction mixture was then extracted with EtOAc (4 x 1 mL). The organic solvents were combined and then removed under vacuum and the crude material was purified by column chromatography to give pure product **11** in 89% yield.

4. E Factor calculations

$$\text{E Factor} = \frac{\text{(g) of waste}}{\text{(g) of product}} = \frac{0.988}{0.216} = 4.57$$

Micellar conditions

$$\text{E Factor} = \frac{\text{(g) of waste}}{\text{(g) of product}} = \frac{5.100}{0.183} = 27.9$$

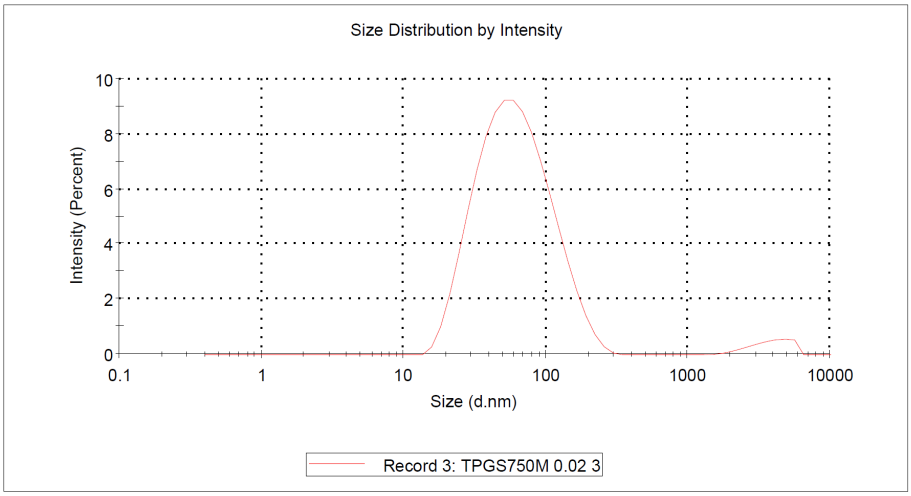
literature conditions

5. Dyanamic light scattering (DLS) charts of TPGS-750-M and Brij-30 in water

Results

		Size (d.nm):	% Intensity:	St Dev (d.n...
Z-Average (d.nm): 51.02	Peak 1:	68.86	96.8	41.42
PdI: 0.280	Peak 2:	3890	3.2	1120
Intercept: 0.907	Peak 3:	0.000	0.0	0.000

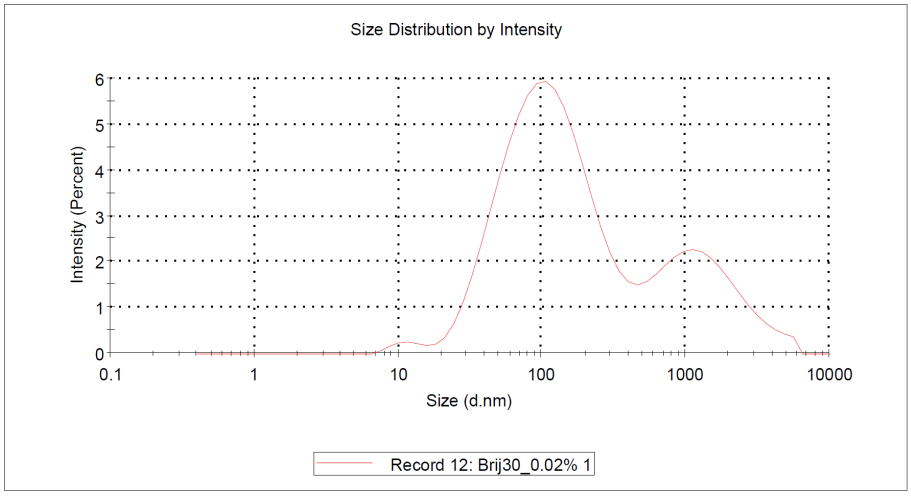
Result quality : Good



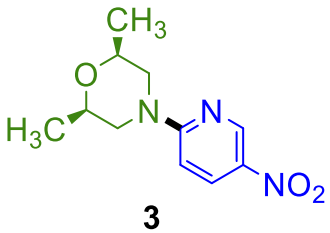
Results

		Size (d.nm):	% Intensity:	St Dev (d.n...
Z-Average (d.nm): 104.9	Peak 1:	132.7	72.9	96.42
PdI: 0.686	Peak 2:	1516	25.9	1068
Intercept: 0.938	Peak 3:	11.67	1.1	2.463

Result quality : Good



6. Compound characterization data

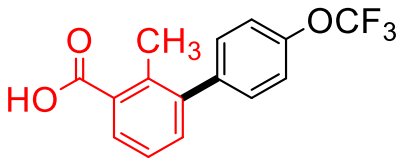


3

(2S,6R)-2,6-Dimethyl-4-(5-nitropyridin-2-yl)morpholine: yellow solid.

^{1}H NMR (500 MHz, chloroform-*d*) δ 9.03 (s, 1H), 8.21 (d, *J* = 9.5 Hz, 1H), 7.28 (s, 0H), 6.57 (d, *J* = 9.5 Hz, 2H), 4.30 (d, *J* = 11.8 Hz, 5H), 3.68 (s, 1H), 2.86 – 2.51 (m, 3H), 1.28 (s, 5H).

^{13}C NMR (126 MHz, chloroform-d) δ 160.14, 146.36, 135.16, 133.03, 104.58, 71.51, 50.16, 18.85.

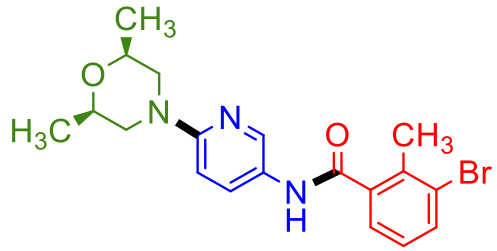


8

2-Methyl-4'-(trifluoromethoxy)-[1,1'-biphenyl]-3-carboxylic acid: white solid,

^{1}H NMR (500 MHz, chloroform-*d*) δ 8.06 (d, *J* = 7.8 Hz, 1H), 7.55 – 7.02 (m, 7H), 3.68 (s, 0H), 2.51 (s, 2H), 1.27 (s, 0H).

^{13}C NMR (126 MHz, chloroform-*d*) δ 173.48, 148.46, 142.62, 140.04, 137.94, 134.25, 130.77, 130.74, 129.97, 125.50, 18.73.

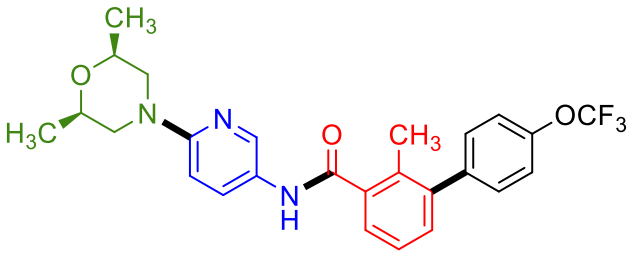


10

3-Bromo-N-(6-((2*R*,6*S*)-2,6-dimethylmorpholino)pyridin-3-yl)-2-methylbenzamide: white solid

^{1}H NMR (500 MHz, chloroform-*d*) δ 8.20 (s, 1H), 8.02 (d, *J* = 8.8 Hz, 1H), 7.65 (d, *J* = 7.7 Hz, 1H), 7.46 – 7.32 (m, 2H), 7.12 (t, *J* = 7.7 Hz, 1H), 6.67 (d, *J* = 9.0 Hz, 1H), 4.01 (d, *J* = 12.3 Hz, 2H), 3.81 – 3.64 (m, 2H), 2.61 – 2.44 (m, 5H), 1.35 – 1.21 (m, 6H).

^{13}C NMR (126 MHz, chloroform-*d*) δ 167.51, 156.86, 140.11, 138.41, 135.81, 134.34, 131.30, 127.21, 126.86, 125.65, 125.40, 106.92, 71.55, 51.15, 20.13, 19.01.



11

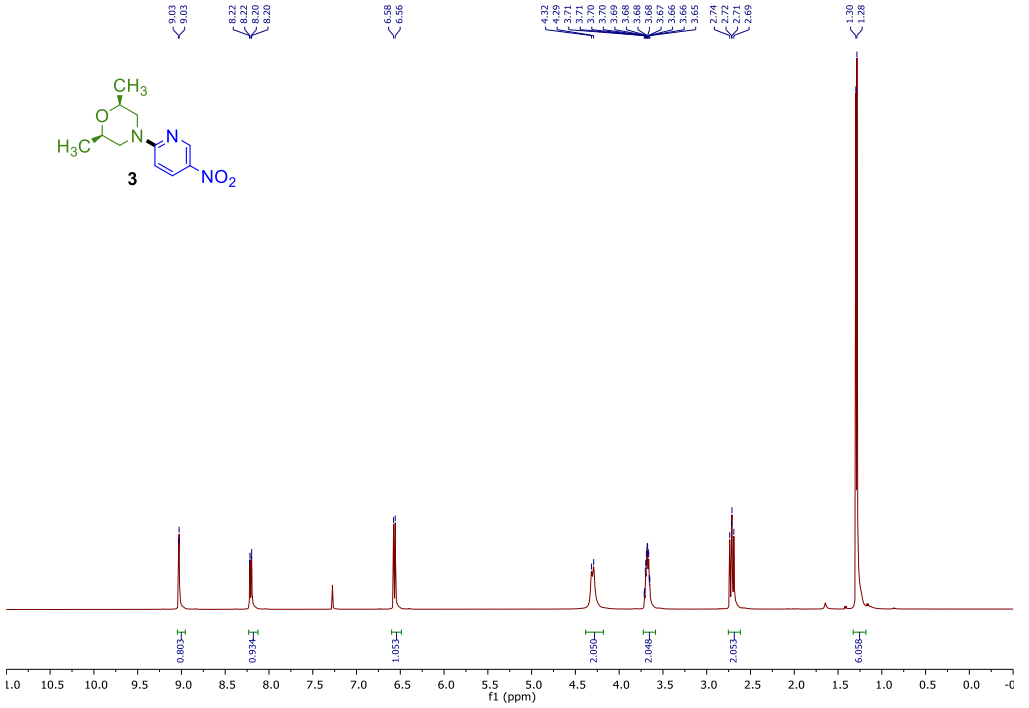
***N*-(6-((2*R*,6*S*)-2,6-Dimethylmorpholino)pyridin-3-yl)-2-methyl-4'-(trifluoromethoxy)-[1,1'-biphenyl]-3-carboxamide**: light pink solid

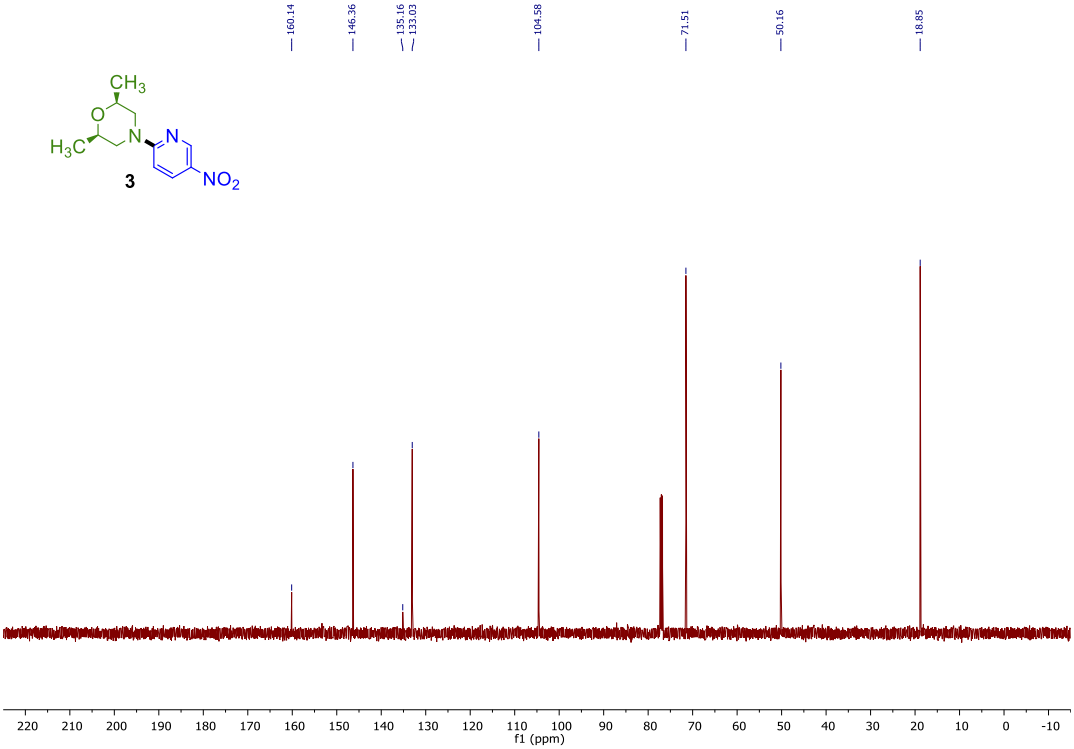
^{1}H NMR (500 MHz, chloroform-*d*) δ 8.22 (d, *J* = 2.7 Hz, 1H), 8.03 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.69 (s, 1H), 7.47 – 7.42 (m, 1H), 7.33 – 7.24 (m, 6H), 6.66 (d, *J* = 9.1 Hz, 1H), 3.99 (d, *J* = 12.2 Hz, 2H), 3.73 (ddt, *J* = 10.0, 6.2, 3.2 Hz, 2H), 2.55 – 2.46 (m, 2H), 2.31 (s, 3H), 1.27 (d, *J* = 6.2 Hz, 6H).

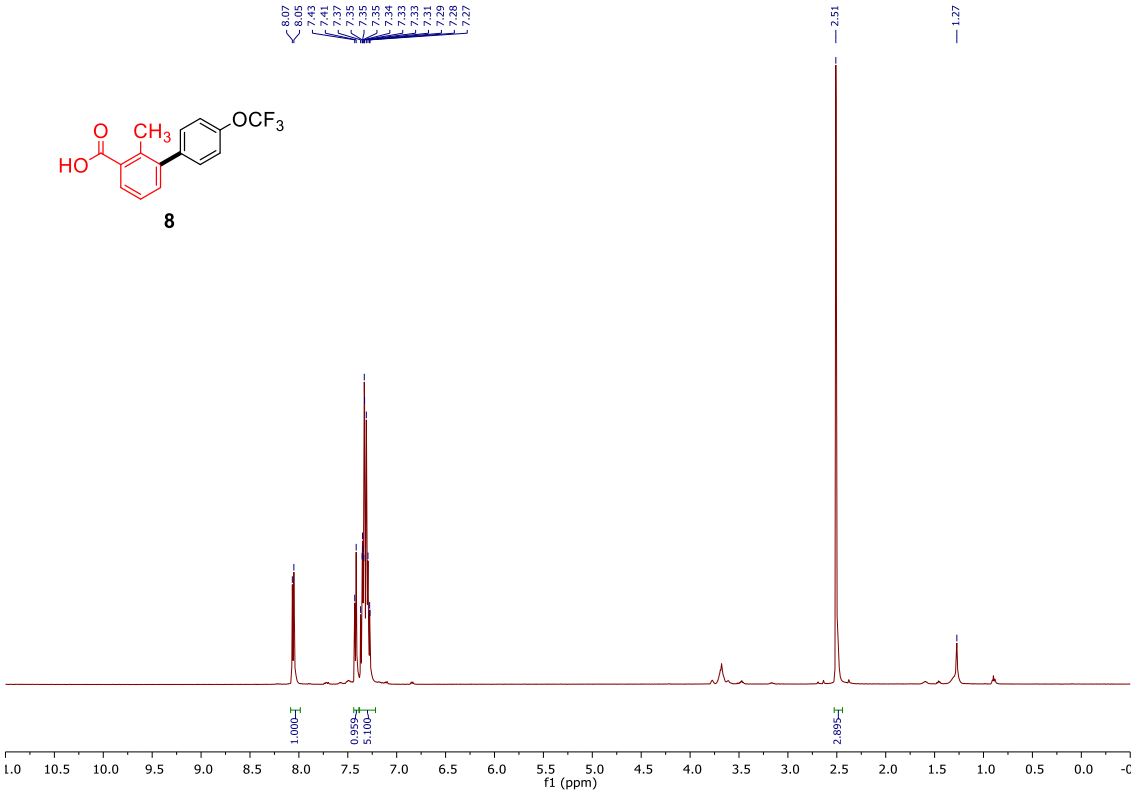
^{13}C NMR (126 MHz, chloroform-*d*) δ 168.72, 156.80, 148.46, 142.20, 140.18, 139.85, 137.57, 133.41, 131.62, 131.38, 130.60, 126.05, 125.84, 125.68, 120.72, 106.97, 71.55, 51.19, 18.98, 17.62.

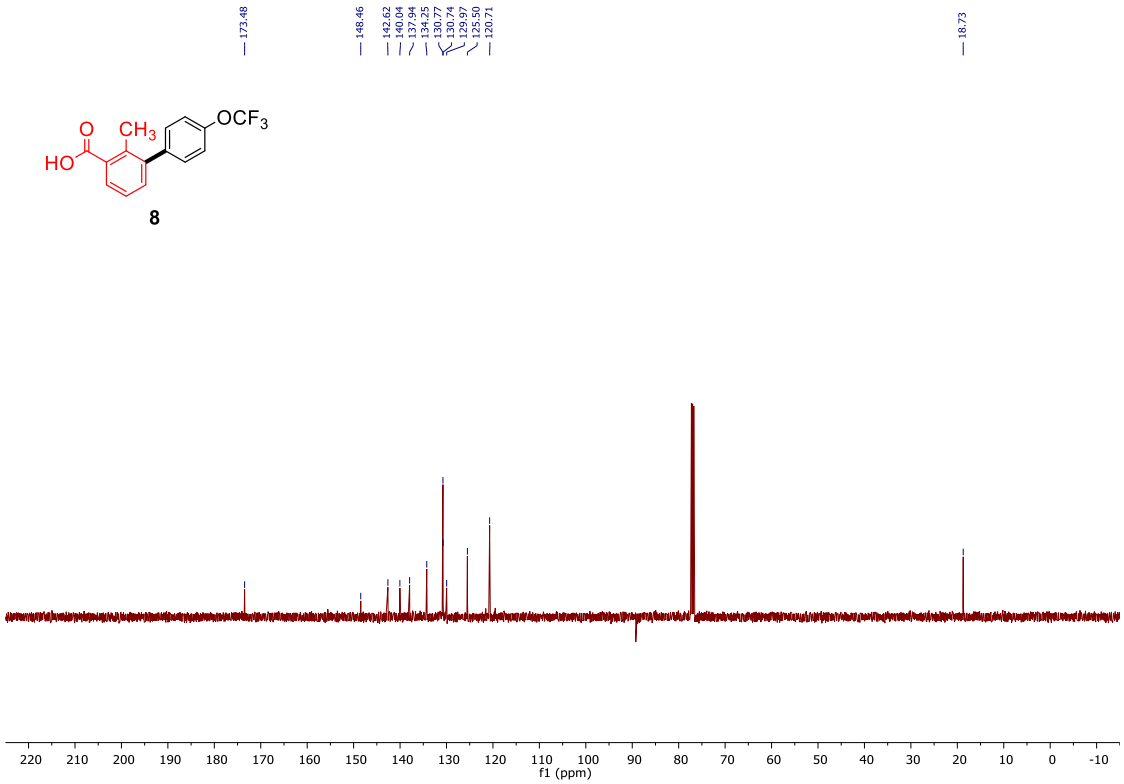
HRMS: $C_{26}H_{26}F_3N_3O_3Na$ ESI-MS [M+Na] calcd: 508.1824; found: 508.1810.

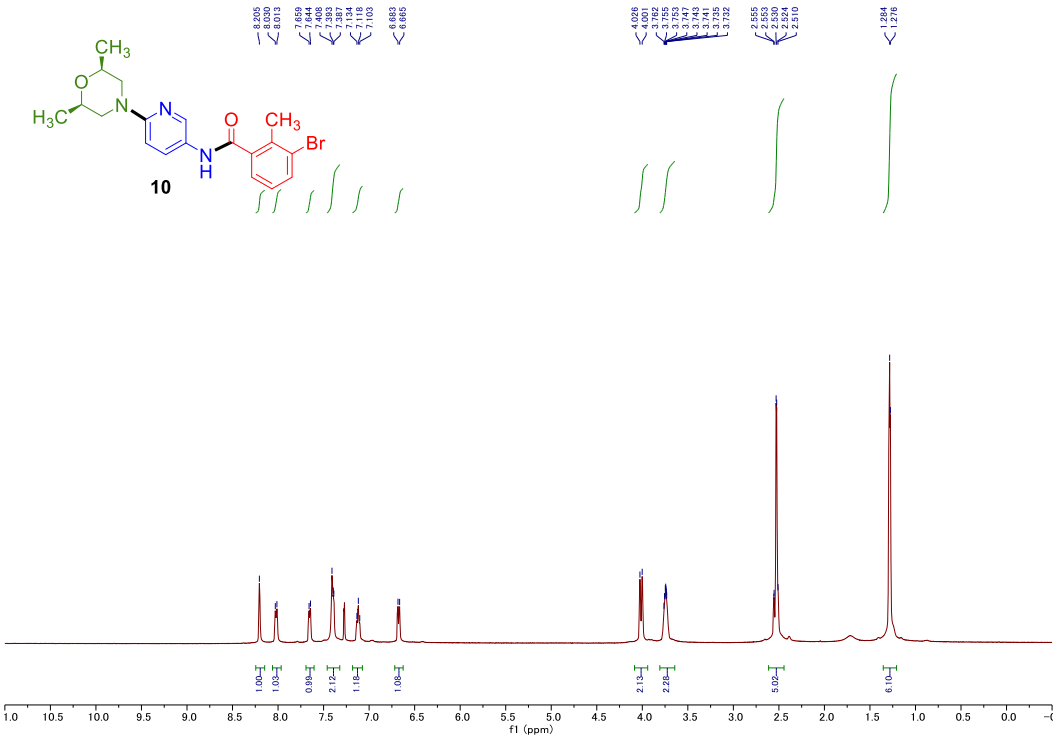
7. NMR spectra’s

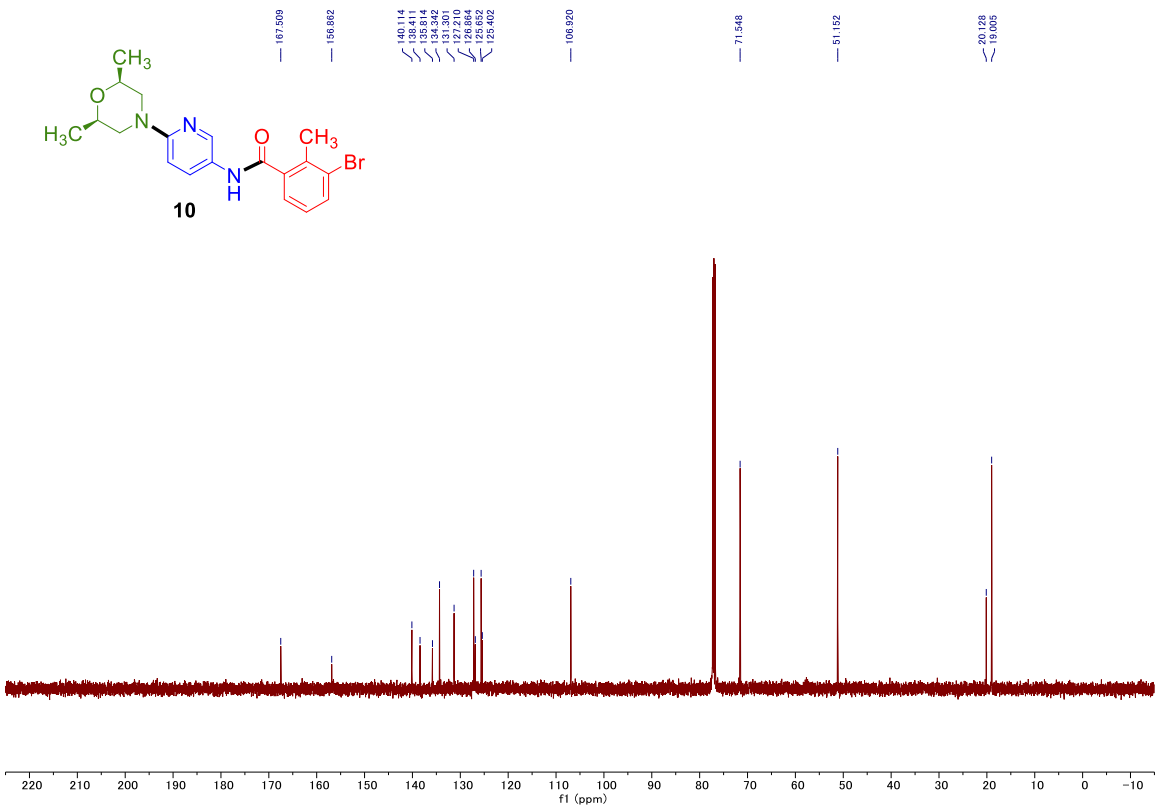


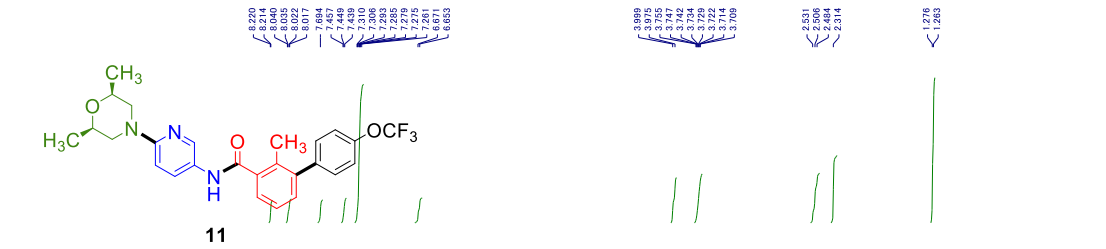



8.07
8.05
7.43
7.41
7.37
7.35
7.35
7.35
7.34
7.33
7.33
7.31
7.29
7.28
7.27
2.51
1.27
O
CH3
OCF3
HO
8
1.000
0.959
5.100
2.895
f1 (ppm)


173.48
148.46
142.62
140.04
137.94
134.25
130.77
130.74
129.97
125.50
120.71
18.73
O
CH3
OCF3
HO
8
f1 (ppm)

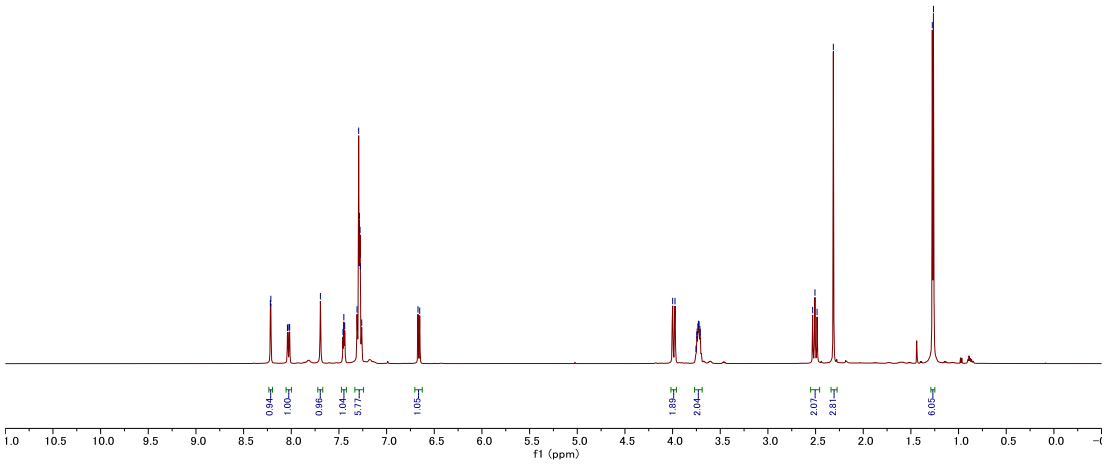

8.205
8.030
8.015
7.659
7.644
7.406
7.393
7.387
7.114
7.116
7.103
6.883
6.866
4.026
4.001
3.762
3.755
3.753
3.747
3.744
3.741
3.735
3.732
2.555
2.553
2.530
2.524
2.510
1.284
1.276
CH3
O
H3C
N
N
O
CH3
Br
N
H
10
1.00
1.03
0.99
2.12
1.18
1.08
2.13
2.28
5.02
6.10
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


167.509
156.862
140.114
138.411
135.814
134.342
133.301
127.210
126.864
125.652
125.402
106.920
71.548
51.152
20.128
19.605
CH3
O
H3C
N
N
O
CH3
Br
N
H
10
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)

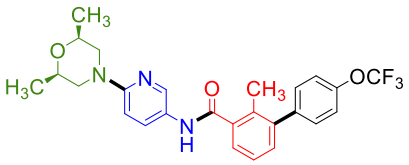

8.220
8.214
8.040
8.035
8.022
8.017
7.604
7.457
7.449
7.439
7.310
7.306
7.293
7.285
7.278
7.275
7.261
6.671
6.653
3.999
3.975
3.755
3.747
3.742
3.734
3.729
3.723
3.714
3.709
2.531
2.506
2.484
2.314
1.276
1.263

CH3
O
H3C
N
N
O
CH3
OCF3
N
H

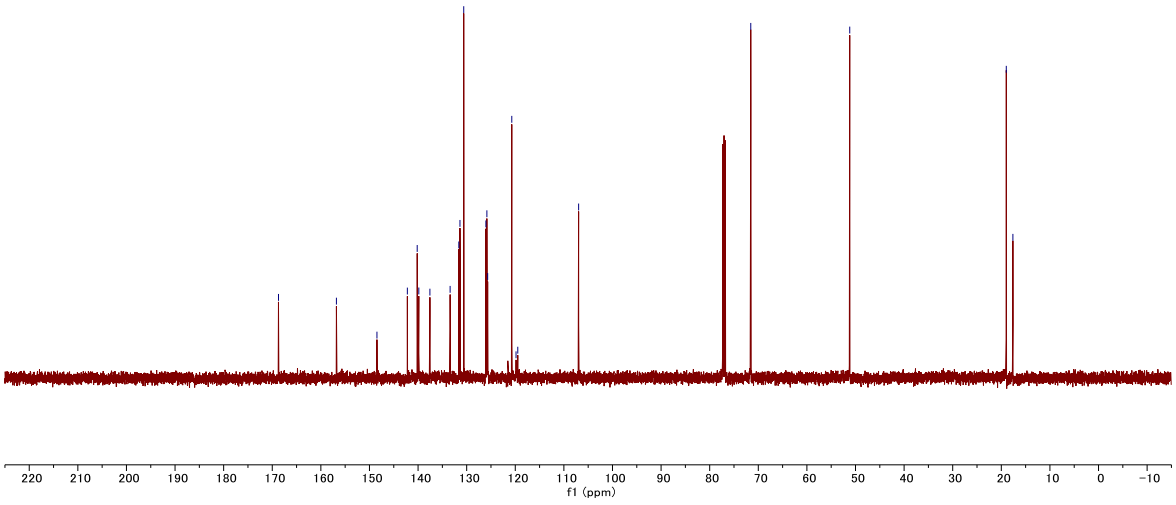
11


0.94
1.00
0.98
1.04
5.77
1.05
1.89
2.04
2.07
2.81
6.05
1.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


168.719
156.801
148.461
142.205
140.179
139.846
137.567
133.406
131.617
131.381
130.805
126.047
125.843
125.681
120.718
119.844
119.485
106.966
71.548
51.185
18.977
17.616


CH3
O
H3C
N
N
O
CH3
OCF3
N
H

11


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)