High-Throughput Experimentation Enabling Rapid Process Optimization of an RSV Drug Candidate

Xavier Jusseau,[1] Ed Cleator,[1] William M. Maton,[1] Qinghao Chen,[1] Robert Geertman,[1] Yuanyuan Yuan,[2] Xiaowei Wang,[3] Haojuan Wei,[2] Florian Medina,[1,] Massimo Giannerini [1,*]*

[1] Chemical Process Research and Development, Janssen Pharmaceutica, Turnhoutseweg 30, 2340 Beerse, Belgium
[2] Changzhou SynTheAll Pharmaceutical Co., Ltd., 589 North Yulong Road, XinBei District, Changzhou 213127, China
[3] Shanghai SynTheAll Pharmaceutical Co., Ltd., 90 Delin Road, Waigaoqiao Free Trade Zone, Shanghai 200131, China

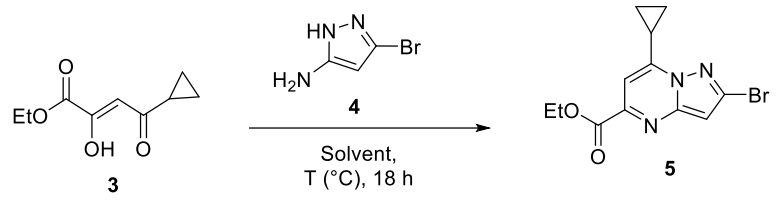
Supporting Information

I] General procedure for HTE screening:

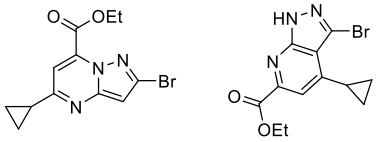
All screening experiments described were carried out under a nitrogen atmosphere filled glove box. Solvents were purchased from Sigma Aldrich, anhydrous, sure-seal quality, and used without further purification. Biphenyl (0.2 equivalent to limiting reagent) was used as internal standard for all screenings, introduced as stock solution with the corresponding starting materials. Reactions were run in vials contained in 96-well aluminum reactor block. Once reaction mixtures were prepared, stirring bar was added to each vial, and reactor top was screw on with two Silicon/rubber mats and one PFA mat to avoid any leakage (all reactors and mats were bought from Analytical Sales & Services). Reactor block was then placed in a tumble stirrer at the desired temperature for overnight. Once cooled down, reaction mixtures were diluted with ACN (two times the amount of solvent used for the reaction) and let to stir at room temperature for few minutes to homogenize. Finally, a representative aliquot was analyzed by HPLC at 220 nm.

II] HTE screening for the Pyrazolopyrimidine core 5:

Scheme S1: Pyrazolopyrimidine core 5 synthesis with putative isomers structures.



Isomers



Putative structures of the two isomers of compound **5** observed (proposals based on MS and ^{1}H-NMR data)

Full data sets obtained across the 3 screenings performed are listed in the SuppInfo_Screening_Data excel file.

- 1st screening: CentralCore S1
- 2nd screening: CentralCore S2
- 3rd screening: CentralCore S3

- Screening conditions, first screening:
  Substrate: 30.0 µmol **4**, 39.0 µmol **3** and 6.0 µmol **IS** in each vial
  Additive: 2.0 equiv., 10.0 equiv. H_2O or 0.2 X Activated 4A-MS in each vial or not
  Base or Acid: 1.0 equiv. or 3.0 equiv. Base or acid in each vial or not
  Solvent: 94.0 µL EtOH (20.0 L/kg) in each vial
  T: 30 °C
  Time: 18 h

Additive	Base or Acid	TFA	TCA	DIPEA	MeNCy2	N/A
2.0 equiv. H2O	1.0 equiv.					
	3.0 equiv.					
10.0 equiv. H2O	1.0 equiv.					
	3.0 equiv.					
0.2 X Activated 4A-MS	1.0 equiv.					
	3.0 equiv.					
N/A	1.0 equiv.					
	3.0 equiv.					

- Screening conditions, second screening:
  Substrate: 50.0 µmol **4**, 65.0 µmol **3** and 10.0 µmol **IS** in each vial
  Acid: 1.0 equiv. to 0.1 equiv. TFA in each vial or not
  Additive: 15.0 equiv., 30.0 equiv. H_2O or 50.0 equiv. H_2O in each vial or not
  Solvent: 160 µL EtOH (20.0 L/kg) in each vial
  T: 30 °C
  Time: 18 h

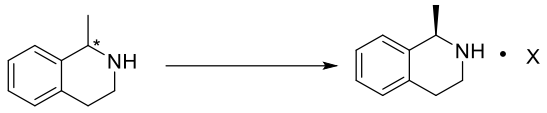
Additive	TFA				
	1.0 eq.	0.5 eq.	0.3 eq.	0.1 eq.	N/A
N/A					
15.0 equiv. H2O					
30.0 equiv. H2O					
50.0 equiv. H2O					

- Screening conditions, third screening:
  Substrate: 30.0 µmol **4**, 39.0 µmol **3** and 6.0 µmol **IS** in each vial
  Base or Acid: 1.5 equiv., 3.0 equiv. or 5.0 equiv. Base or acid in each vial or not

Additives: 2.0 equiv., 10.0 equiv. H_2O or 0.2 X Activated 4A-MS in each vial
Solvent: 94.0 µL EtOH (10.0 L/kg) in each vial
T: 70 °C
Time: 18 h

Additive	Base	TEA	DIPEA	MeNCy2	NMethylMorpholine	1-MeImidazole	DABCO	TFA	MSA	CSA	TCA	N/A
2.0 equiv. H_2O	5.0 equiv.											
	3.0 equiv.											
	1.5 equiv.											
10.0 equiv. H_2O	5.0 equiv											
	3.0 equiv.											
	1.5 equiv.											
0.2 X Activated 4A-MS	5.0 equiv.											
	3.0 equiv.											
	1.5 equiv.											

III] HTE screening for the resolution of the chiral Amine 8:



Rac-8

Full data sets obtained across the 2 screenings performed are listed in the SuppInfo_Screening_Data excel file. Only heterogeneous samples were analyzed, after filtration both solid and ML were analyzed.

- 1st screening: Resolution S1
- 2nd screening: Resolution S2

- Screening conditions, first screening:
  Substrate: 250 µmol ***rac*-8** in each vial
  Acid: 150 µmol Chiral Acid in each vial
  Solvent: 368.0 µL Solvent (20.0 L/kg) in each vial
  T: 45 °C for 1 h, and then 20 to 25 °C for 18 h
  Time: 45 °C for 1 h, and then 20 to 25 °C for 18 h

	1	2	3	4	5	6	7	8	9	10	11	12
	13	14	15	16	17	18	19	20	21	22	23	24

MTBE	**A**												
Toluene	**B**												
IPAc	**C**												
IPA	**D**												
MeCN	**E**												
THF	**F**												

Location	Name	CAS
1	L-(−)-Malic acid	97-67-6
2	L-(+)-Tartaric acid	87-69-4
3	(1S)-(+)-10-Camphorsulfonic acid	3144-16-9
4	(1R)-(−)-10-Camphorsulfonic acid	35963-20-3
5	(+)-O,O′-Di-p-toluoyl-D-tartaric acid	32634-68-7
6	L-Cysteine	52-90-4
7	(−)-O,O′-Di-p-toluoyl-L-tartaric acid	32634-66-5
8	L-(+)-Mandelic acid	17199-29-0
9	(+)-2,3-Dibenzoyl-D-tartaric acid	17026-42-5
10	L-Lactic acid	79-33-4
11	Dibenzoyl-L-Tartaric acid	2743-38-6
12	Dipivaolyl-L-tartaric acid	65259-81-6
13	Abietic acid	514-10-3
14	L-Pyroglutamic acid	98-79-3
15	D-Pyroglutamic acid	4042-36-8
16	L-Histidine	71-00-1
17	(+)-Naproxen	22204-53-1
18	L-Isoleucine	73-32-5
19	L-Proline	147-85-3
20	(-)-Di-p-anisoyl-L-tartarid acid	50583-51-2
21	L-Glutamic acid	56-86-0
22	trans-4-Hydroxy-L-proline	51-35-4
23	L-Phenylalanine	63-91-2
24	L-Tyrosine	60-18-4

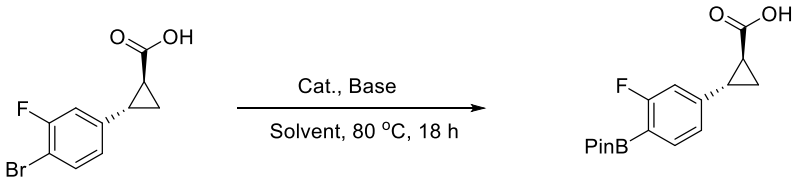
- Screening conditions, second screening:
  Substrate: 300 μmol ***rac*-8** in each vial
  Chiral Acid: 300 μmol Chiral Acid in each vial
  Solvent: 442.0 μL Solvent (10.0 L/kg) in each vial
  T: 45 °C for 1 h, and then 20 to 25 °C for 18 h
  Time: 45 °C for 1 h, and then 20 to 25 °C for 18 h

		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
		13	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
MTBE	**A**												
Toluene	**B**												
IPAc	**C**												
IPA	**D**												
MeCN	**E**												

THF	**F**												
MeOH	**G**												
EtOH	**H**												

Location	Name	CAS
1	(1S)-(+)-10-Camphorsulfonic acid	3144-16-9
2	L-Cysteine	52-90-4
3	L-(+)-Mandelic acid	17199-29-0
4	L-Threonine	72-19-5
5	Abietic acid	514-10-3
6	L-Pyroglutamic acid	98-79-3
7	L-Valine	72-18-4
8	L-Histidine	71-00-1
9	(+)-Naproxen	22204-53-1
10	L-Isoleucine	73-32-5
11	L-Proline	147-85-3
12	(1S)-(-)-Camphanic acid	13429-83-9
13	(S)-2-Acetoxy-2-phenylacetic acid	7322-88-5
14	trans-4-Hydroxy-L-proline	51-35-4
15	L-Phenylalanine	63-91-2
16	L-Tyrosine	60-18-4
17	L-Lactic acid	79-33-4
18	L-Alanine	56-41-7
19	L-Asparagine	70-47-3
20	L-Glutamine	56-85-9
21	L-Isoleucine	73-32-5
22	L-Lysine	56-87-1
23	L-Methionine	63-68-3
24	L-2-Phenylglycine	2935-35-5

IV] HTE screening for the Borylation of 14:



14 **19**

Full data sets obtained across the 3 screenings performed are listed in the SuppInfo_Screening_Data excel file.

- 1st screening: Borylation S1
- 2nd screening: Borylation S2
- 3rd screening: Borylation S3

- Screening conditions, first screening:
  Substrate: 20.0 µmol **14**, 24.0 µmol **B_2Pin_2** and 4.0 µmol **IS** in each vial
  Catalyst: 5.0 mol% $Pd(OAc)_2$ in each vial
  Ligand: 10.0 mol% P source in each vial
  Base: 60.0 µmol KOAc in each vial
  Solvent: 104.0 µL Solvent (20.0 L/kg) in each vial
  T: 80 °C
  Time: 18 h

		1	2	3	4	5	6	7	8	9	10	11	12
2-MeTHF	**A**												
	B												
	C												
	D												/
Toluene	**E**												
	F												
	G												
	H												/

A1	Ph_3P
A2	dppb
A3	(*o*-tol)$_3$P
A4	DPEPhos
A5	dppf
A6	*t*BuXPhos
A7	dtbpf
A8	Ph_2CyP
A9	Cy_3P-HBF_4
A10	XantPhos
A11	Ph_2P(*t*Bu)
A12	(*t*Bu)$_2$PMe-HBF_4
B1	*t*Bu$_3$P-HBF_4
B2	(2-furyl)$_3$P
B3	Cy_2P($_o$-Tol)
B4	JohnPhos
B5	XPhos
B6	Ph_2DavePhos
B7	SPhos
B8	dcpp-HBF_4
B9	Ad_2nBuP
B10	RuPhos
B11	AmgenPhos
B12	(*R*)-BINAP
C1	dppp
C2	dppe
C3	$(C_6F_5)_3P$
C4	dpppe
C5	RockPhos
C6	MorDalPhos
C7	DavePhos
C8	MePhos
C9	*t*BuMePhos
C10	dippf

C11	*N*-XantPhos
C12	(*o*-anisyl)$_3$P
D1	(*R*)-Tol-BINAP
D2	(2,4,6-MeO$_3$Phenyl)$_3$P
D3	Ph$_2$P-CH$_2$CH$_2$-(2-Pyr)
D4	BrettPhos
D5	BippyPhos
D6	SPhos-SO$_3$Na
D7	Me$_4$-*t*BuXPhos
D8	(4-CF$_3$Phenyl)$_3$P
D9	Pd(dppf)Cl$_2$
D10	Pd(Ph$_3$P)$_2$Cl$_2$
D11	Pd(dtbpf)Cl$_2$

- Screening conditions, Second screening:
  Substrate: 25.0 µmol **14**, 30.0 µmol **B$_2$Pin$_2$** and 5.0 µmol **IS** in each vial
  Catalyst: 2.0 mol% Pd(OAc)$_2$ in each vial
  Ligand: 4.0 mol% P source in each vial
  Base: 75.0 µmol Base in each vial
  Solvent: 130.0 µL Solvent (20.0 L/kg) in each vial
  T: 80 °C
  Time: 18 h

			1	2	3	4	5	6	7	8	9	10	11	12
2-MeTHF	**KOAc**	**A**												
		B												
	DIPEA	**C**												
		D												
Toluene	**KOAc**	**E**												
		F												
	DIPEA	**G**												
		H												

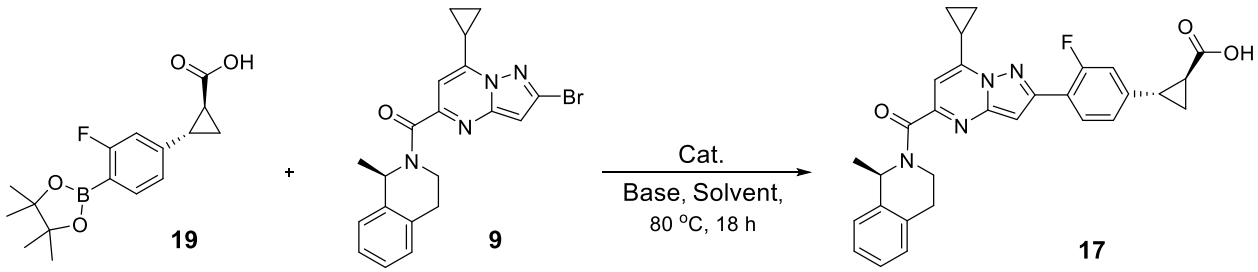
A1	Ph$_3$P
A2	(o-tol)$_3$P
A3	DPEPhos
A4	Pd(dppf)Cl$_2$
A5	Pd(dtbpf)Cl$_2$
A6	Ph$_2$CyP
A7	XantPhos
A8	Ph$_2$P(*t*Bu)
A9	*t*Bu$_3$P-HBF$_4$
A10	XPhos
A11	SPhos
A12	dcpp-HBF$_4$
B1	Ad$_2$*n*BuP
B2	RuPhos
B3	AmgenPhos
B4	(*R*)-BINAP
B5	dpppe
B6	MePhos
B7	dippf

B8	*N*-XantPhos
B9	(*o*-anisyl)$_3$P
B10	(*R*)-Tol-BINAP
B11	SPhos-SO_3Na
B12	(4-CF3Phenyl)$_3$P

- Screening conditions, Third screening:
  Substrate: 25.0 µmol **14**, 27.5 µmol **B_2Pin_2** and 5.0 µmol **IS** in each vial
  Catalyst: 1.0 mol% $Pd(OAc)_2$ in each vial
  Ligand: 2.0 mol% monodentate P ligand or 1.0 mol% bidentate P ligand (Pd: P = 1:2) in each vial
  Base: 62.5 µmol KOAc or KOPiv in each vial
  Solvent: 96.0 µL Solvent (15.0 L/kg) in each vial
  T: 80 °C
  Time: 18 h

		Ph_3P	$Ph_2P(tBu)$	XPhos	SPhos	Ad_2nBuP	RuPhos	AmgenPhos	dippf	*N*-XantPhos	(*o*-anisyl)$_3$P	SPhos-SO_3Na	(4-CF3Phenyl)$_3$P
Toluene	KOAc												
	KOPiv												
THF	KOAc												
	KOPiv												
2-MeTHF	KOAc												
	KOPiv												
IPAc	KOAc												
	KOPiv												

V] HTE screening for the Palladium catalysed Suzuki step between 19 and 9:



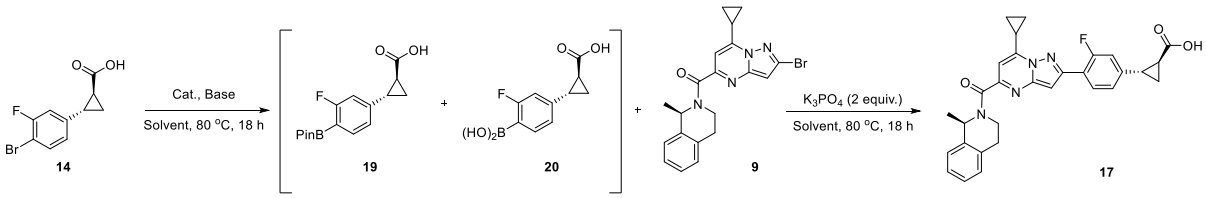
Full data set obtained across the screening performed is listed in the SuppInfo_Screening_Data excel file.

- 1st screening: Suzuki S1

- Screening conditions, First screening:
  Substrate: 25.0 µmol **9**, 30.0 µmol **19** and 5.0 µmol **IS** in each vial
  Catalyst: 1.0 mol% $Pd(OAc)_2$ in each vial
  Ligand: 2.0 mol% P source in each vial
  Base: 37.5 µmol Base in each vial
  Solvent: 103.0 µL solvent (10.0 L/kg) with 31.0 µL H_2O (3.0 L/kg) in each vial
  T: 80 °C
  Time: 18 h

		Ph_3P	$Ph_2P(tBu)$	XPhos	SPhos	Ad_2nBuP	RuPhos	AmgenPhos	dippf	*N*-XantPhos	(*o*-anisyl)$_3$P	SPhos-SO_3Na	(4-CF3Phenyl)$_3$P
Toluene	K_3PO_4												
	K_2CO_3												
THF	K_3PO_4												
	K_2CO_3												
2-MeTHF	K_3PO_4												
	K_2CO_3												
IPAc	K_3PO_4												
	K_2CO_3												

VI] HTE screening for the Palladium catalysed telescope sequence Borylation/Suzuki:



Full data set obtained across the screening performed is listed in the SuppInfo_Screening_Data excel file.

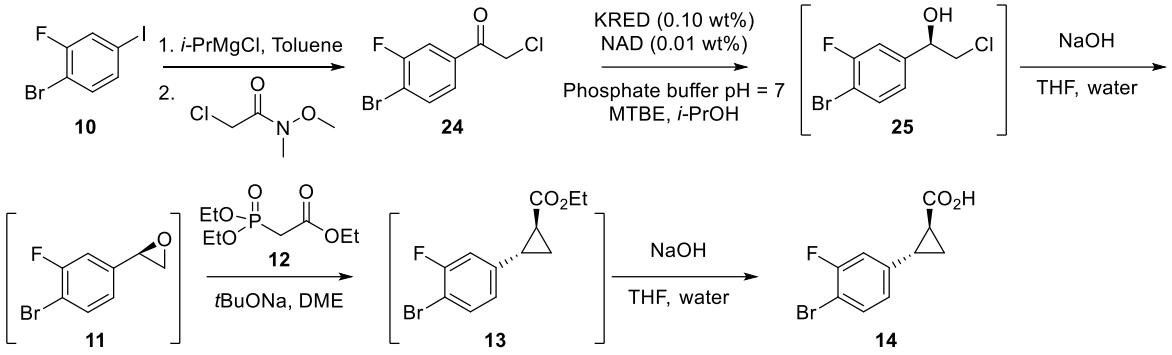
- 1st screening: Telescope S1

- Screening conditions, First screening:
  Borylation reaction:
  Substrate: 25.0 µmol **14**, 27.5 µmol **B_2Pin_2** and 5.0 µmol **IS** in each vial
  Catalyst: 1.0 mol% $Pd(OAc)_2$ in each vial
  Ligand: 2.0 mol% monodentate P ligand or 1.0 mol% bidentate P ligand (Pd: P = 1:2) in each vial
  Base: 62.5 µmol KOAc or KOPiv in each vial
  Solvent: 96.0 µL Solvent (15.0 L/kg) in each vial

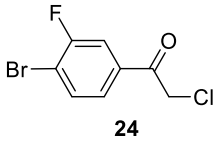
T: 80 °C
Time: 18 h
Suzuki reaction:
Substrate: 22.5 µmol **9** in each vial
Base: 50.0 µmol K_3PO_4 in each vial
Solvent: 32.0 µL (5.0 L/kg) Solvent and 26.0 µL (4.0 L/kg) H_2O in each vial
T: 80 °C
Time: 18 h

		Ph_3P	$Ph_2P(tBu)$	XPhos	SPhos	Ad_2nBuP	RuPhos	AmgenPhos	dippf	*N*-XantPhos	(*o*-anisyl)$_3$P	SPhos-SO_3Na	(4-CF3Phenyl)$_3$P
Toluene	KOAc												
	KOPiv												
THF	KOAc												
	KOPiv												
2-MeTHF	KOAc												
	KOPiv												
IPAc	KOAc												
	KOPiv												

VII] Synthesis of (1*S*,2*S*)-2-(4-bromo-3-fluorophenyl)cyclopropane-1-carboxylic acid 14:



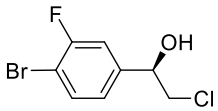
Scheme 1: Scale-up synthesis of (1*S*,2*S*)-2-(4-bromo-3-fluorophenyl)cyclopropane-1-carboxylic acid **14** from -bromo-2-fluoro-4-iodobenzene **10**.



24

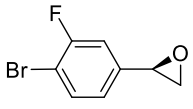
To a reactor under nitrogen was charged 1-bromo-2-fluoro-4-iodobenzene **10** (79.8 mol, 24.0 kg, 1.00 equiv.), and anhydrous toluene (109 L). The reaction mixture was cooled down to -40 °C then isopropyl magnesium chloride (2.0 *M* in THF, 87.7 mol, 43.0 kg, 1.10 equiv.) was charged over 2.5h. Upon reaction completion, the reaction mixture was further cooled down to -78 °C. Then a solution of 2-chloro-N-methoxy-N-methylacetamide (87.7 mol, 12.0 kg, 1.10 equiv.) in anhydrous toluene (37 L) was charged over 2h, then the reaction mixture was warmed up to 25 °C over 2 h. Upon reaction completion, the reaction mixture was cooled to 5 °C and quenched by addition of aqueous citric acid (10 wt%, 90 kg) over 2.6 h to reach pH = 6-7. Water (120 L) was added and the mixture was extracted with MTBE (257 L) at 25 °C. The organic layer was washed with sodium sulfate (10 wt%, 188 kg) and the phase were separated. The organic layer was treated with diatomite (13 kg) and filtered. The resulting Toluene-THF-MTBE solution was concentrated under vacuum to remove MTBE and THF, then switched to isopropyl alcohol (60 L). The solution was cooled down to 30°C, seeded then further cooled to 20 °C over 2 h then water (86 L) was slowly added over 2h. The suspension was stirred for 4 h then filtered. The resulting solid was washed twice with water (48 L) and dried for 18h at 40 °C under

vacuum to afford 1-(4-bromo-3-fluorophenyl)-2-chloroethan-1-one **24** (15.8 kg, yield 79 %) as a white solid. **^{1}H NMR** (400 MHz, 298 K, d6-DMSO): δ 7.94 (d, *J* =6.8 Hz, 1H, Ar-H), 7.92 (dd, *J* = 7.2, 2.0 Hz, 1H, Ar-H), 7.74 (dd, *J* = 8.0, 2.0 Hz, 1H, Ar-H), 5.20 (s, 2H, CH_2) ppm.**^{13}C NMR** (100 MHz, 298 K, d6-DMSO): δ 190.1 (d, *J* = 2.0 Hz), 158.3 (d, *J* = 245 Hz), 135.6 (d, *J* = 6.0 Hz), 134.2, 125.7 (d, *J* = 2.0 Hz), 116.2 (d, *J* = 23.0 Hz), 114.5 (d, *J* = 21 Hz), 47.7 ppm. **^{19}F NMR** (376.5 MHz, 298 K, d6-DMSO): δ -106.8 ppm.



25

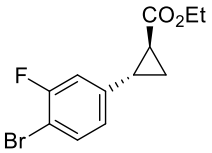
To a reactor under nitrogen was charged 1-(4-bromo-3-fluorophenyl)-2-chloroethan-1-one **24** (199.3 mol, 30.0 kg, 1.00 equiv.), MTBE (45 L), isopropyl alcohol (42 L), and water (46 L). The reaction mixture was warmed up to 40 °C then a phosphate buffer pH = 7.0, made of, potassium phosphate dibasic trihydrate (57 mol, 13.0 kg, 0.48 equiv.), potassium phosphate monobasic (37 mol, 5.0 kg, 0.31 equiv.), and sodium thiosulfate pentahydrate (1.2 mol, 0.3 kg, 0.01 equiv.) in water (472 L) containing KRED enzyme (3.1 kg, 0.10 wt%) and NAD co-factor (0.31 kg, 0.01 wt%) was charged over 1.5 h. Upon reaction completion, the reaction mixture was cooled to 25 °C and concentrated under vacuum to remove acetone. DCM (453 L) and diatomite (36 kg) were added, and the resulting biphasic mixture was filtered. The organic layer was separated, concentrated under vacuum and solvent was switched to THF (120 L) to afford (*R*)-1-(4-bromo-3-fluorophenyl)-2-chloroethan-1-ol **25** (22.0 wt%, 136 kg, 99.9 % e.e., 99 % yield) as a solution in THF.



11

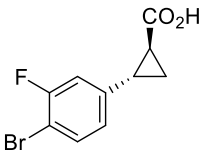
To a reactor under nitrogen was charged (*R*)-1-(4-bromo-3-fluorophenyl)-2-chloroethan-1-ol **25** (117.5 mol, 22.0 wt%, 136 kg, 1.00 equiv.) as a THF a solution and THF (56 L). The reaction mixture was warmed up to 25 °C then aqueous sodium hydroxide (15 wt%, 227.5 mol, 41.0 kg, 1.94 equiv.) was dosed over 3 h. Upon reaction completion, the reaction mixture was cooled to 15 °C and aqueous acetic acid (10.0

wt%, 40.0 kg) was added to reach pH = 7-8. Water (88 L) was added and the reaction mixture was extracted twice with ethyl acetate (2x150 L). The combined organic layers were washed with aqueous sodium sulphate (5.0 wt%, 162 kg) then concentrated under vacuum and solvent was switched to 1,2-dimethoxyethane (100 L) to afford (*R*)-2-(4-bromo-3-fluorophenyl)oxirane **11** (21.9 wt%, 115 kg, 99.9 % e.e. yield 98 %) as a solution in 1,2-dimethoxyethane.



13

To a reactor under nitrogen was charged sodium *tert*-butoxide (239.3 mol, 23.0 kg, 2.1 equiv.) and 1,2-dimethoxyethane (800 L). The reaction mixture was warmed up to 25 °C and ethyl 1-(diethoxyphosphoryl)acetate (240.9 mol, 54.0 kg, 2.10 equiv.) was dosed over 1 h, followed by the addition of (*R*)-2-(4-bromo-3-fluorophenyl)oxirane **11** (21.9 wt%, 115.5 mol, 115 kg, 1.00 equiv.) as 1,2-dimethoxyethane solution over 1.5 h, then the mixture was warmed up to 80 °C. Upon reaction completion, the reaction mixture was cooled to 25 °C and quenched by the slow addition of acetic acid (100 mol, 6.0 kg, 0.90 equiv.). Water (206 L) was added and the reaction mixture was extracted with heptane (250 L). The phases were separated then the aqueous layer was extracted with ethyl acetate (250 L). The organic layers were combined, concentrated under vacuum and solvent was switched to THF (84 L) to afford ethyl (1*S*,2*S*)-2-(4-bromo-3-fluorophenyl)cyclopropane-1-carboxylate **13** (29.7 wt%, 106 kg, 95 % yield) as a solution in THF.



14

To a reactor under nitrogen was charged ethyl (1*S*,2*S*)-2-(4-bromo-3-fluorophenyl)cyclopropane-1-carboxylate **13** (29.7 wt%, 109.4 mol, 106 kg, 1.00 equiv.) as a THF solution. The reaction mixture was warmed up to 25 °C and aqueous sodium hydroxide (15.0 wt%, 322.5 mol, 86.0 kg, 3.00 equiv.) was charged. Upon reaction completion, water (270 L) was added followed by DCM (205 L). The phases were separated, and the aqueous layer was acidified to pH = 6-7 at 25°C with aqueous

hydrochloric acid (2.0 *M*, 52.0 kg). The reaction mixture was seeded then further acidified to pH = 2-3 at 25 °C with aqueous hydrochloric acid (2.0 *M*, 120 kg). The suspension was stirred for 5 h then filtered. The resulting solid was washed with water (70 L) and dried for 18 h at 50 °C under vacuum to afford (1*S*,2*S*)-2-(4-bromo-3-fluorophenyl)cyclopropane-1-carboxylic acid **14** (25.2 kg, 89. 0 % yield) as a whit solid. **^{1}H NMR** (400 MHz, 298 K, d6-DMSO): δ 12.37 (s, 1H, OH), 7.56 (m, 1H, Ar-H), 7.21 (d, *J* = 10.4 Hz, 1H, Ar-H), 7.00 (t, *J* = 8.0 Hz, 1H, Ar-H), 2.47-2.37 (m, 1H, CH), 1.92-1.80 (m, 1H, CH), 1.49-1.31 (m, 2H, CH_2) ppm. **^{13}C NMR** (100 MHz, 298 K, d6-DMSO): δ 173.5, 158.3 (d, *J* = 243 Hz), 143.2 (d, *J* = 8.0 Hz), 133.1, 123.9 (d, *J* = 3.0 Hz), 114.2 (d, *J* = 24.0 Hz), 105.1 (d, *J* = 21.0 Hz), 24.53, 24.50, 17.0 ppm. **^{19}F NMR** (376.5 MHz, 298 K, d6-DMSO): δ -108.6 ppm. All analytical data were aligned with reported literature: McCoull, W.; Bailey, A.; Barton, P.; Birch, A. M.; Brown, A. J. H.; Butler, H. S.; Boyd, S.; Butlin, R. J.; Chappell, B.; Clarkson, P.; Collins, S.; Davies, R. M. D.; Ertan, A.; Hammond, C. D.; Holmes, J. L.; Lenaghan, C.; Midha, A.; Morentin-Gutierrez, P.; Moore, J. E.; Raubo, P.; Robb, G. Indazole-6-phenylcyclopropylcarboxylic Acids as Selective GPR120 Agonists with in Vivo Efficacy. *J. Med. Chem.* **2017** *60*, 3187-3197.

VIII] NMR spectra of isolated intermediates:

Ethyl 4-cyclopropyl-2-hydroxy-4-oxobut-2-enoate 3:

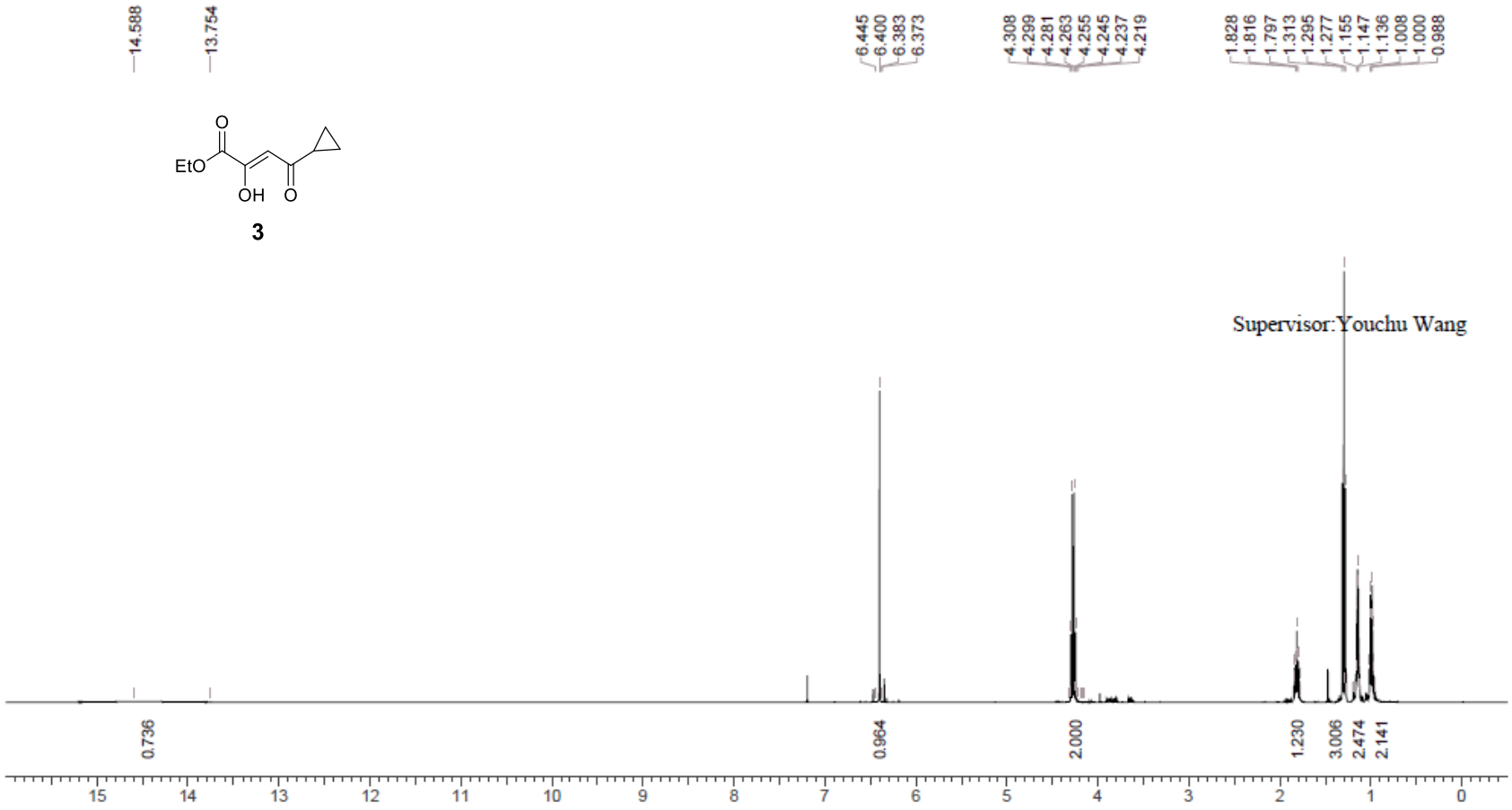


Figure S1. ^{1}H NMR of (*Z*)-4-cyclopropyl-2-hydroxy-4-oxobut-2-enoate **3** in $CDCl_3$.

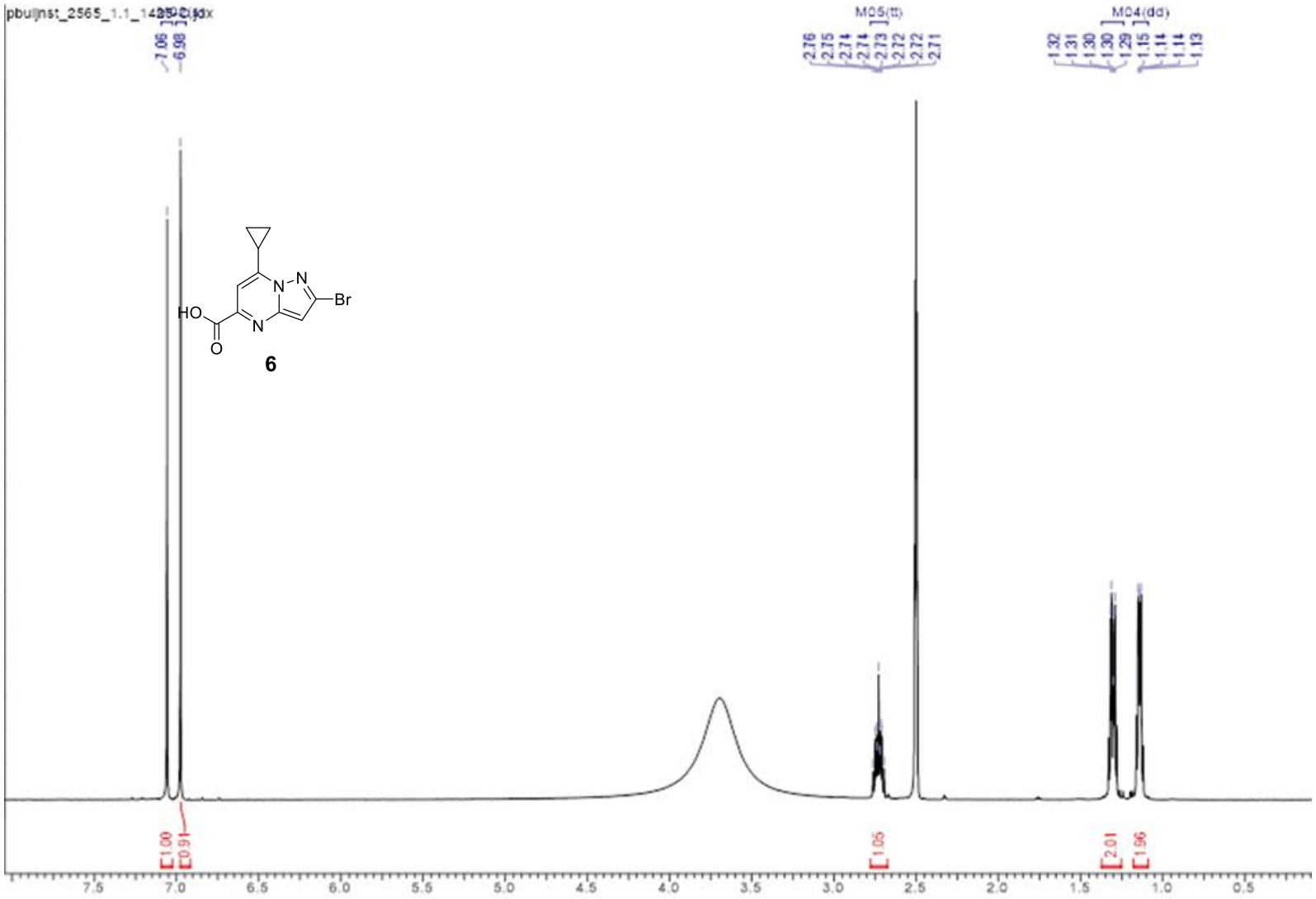


Figure S2. ^{1}H NMR of bromo-7-cyclopropylpyrazolo[1,5-a]pyrimidine-5-carboxylic acid **6** in d6-DMSO.

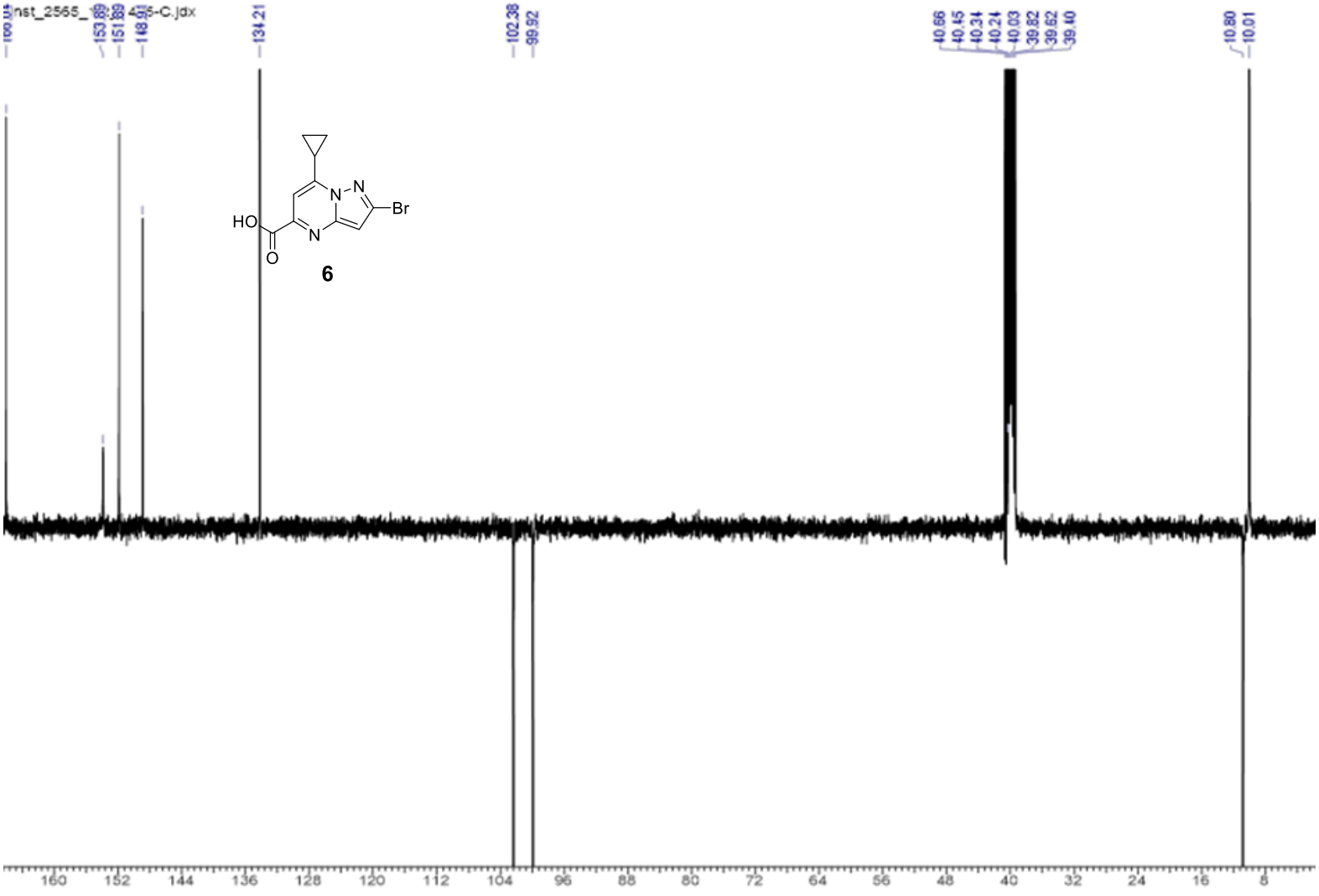


Figure S3. ^{13}C NMR of bromo-7-cyclopropylpyrazolo[1,5-*a*]pyrimidine-5-carboxylic acid **6** in d6-DMSO.

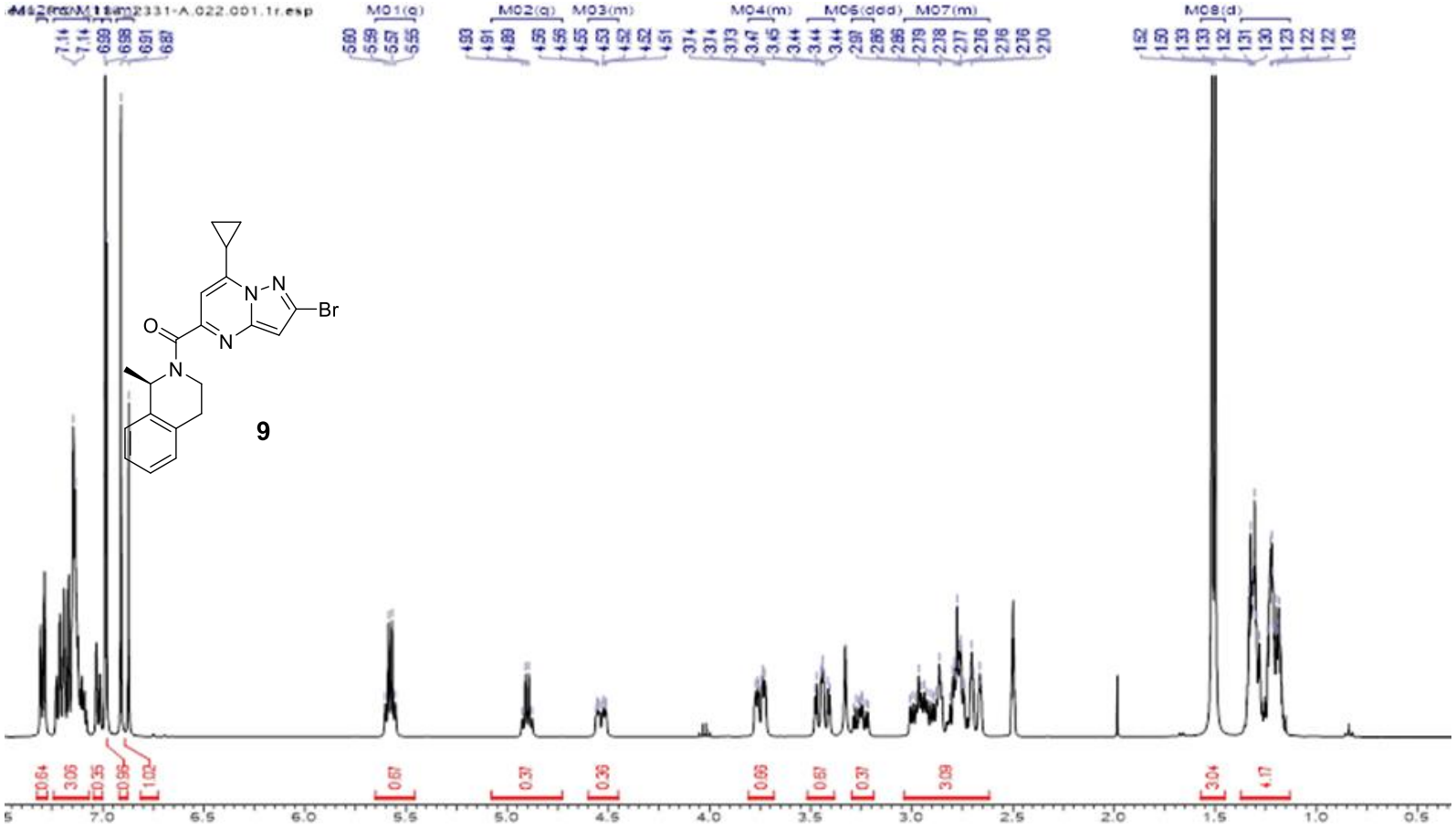


Figure S4. ^{1}H NMR of (*R*)-(2-bromo-7-cyclopropylpyrazolo[1,5-*a*]pyrimidin-5-yl)(1-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl)methanone **9** in d6-DMSO.

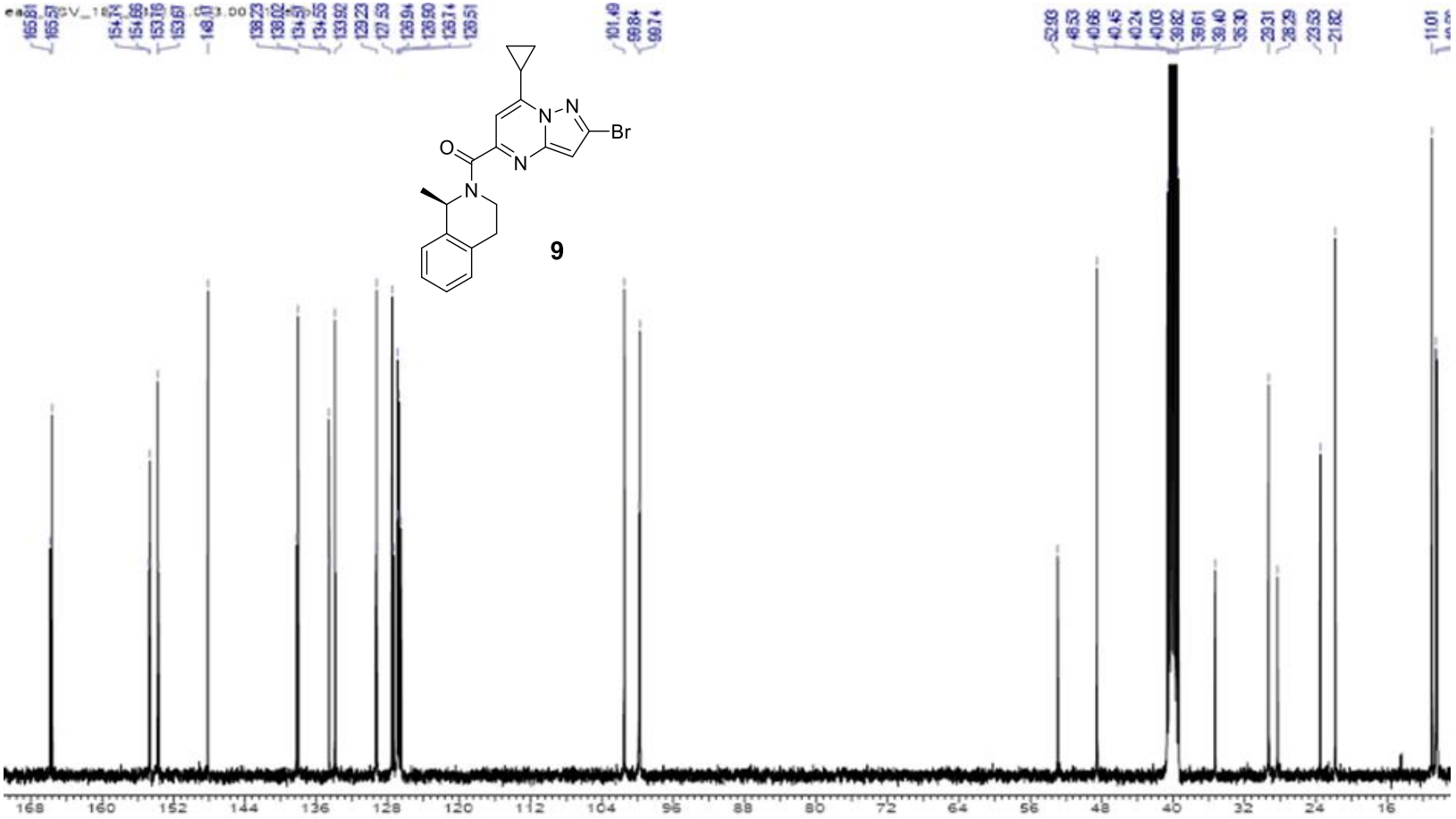


Figure S5. ^{13}C NMR of (*R*)-(2-bromo-7-cyclopropylpyrazolo[1,5-*a*]pyrimidin-5-yl)(1-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl)methanone **9** in d6-DMSO.

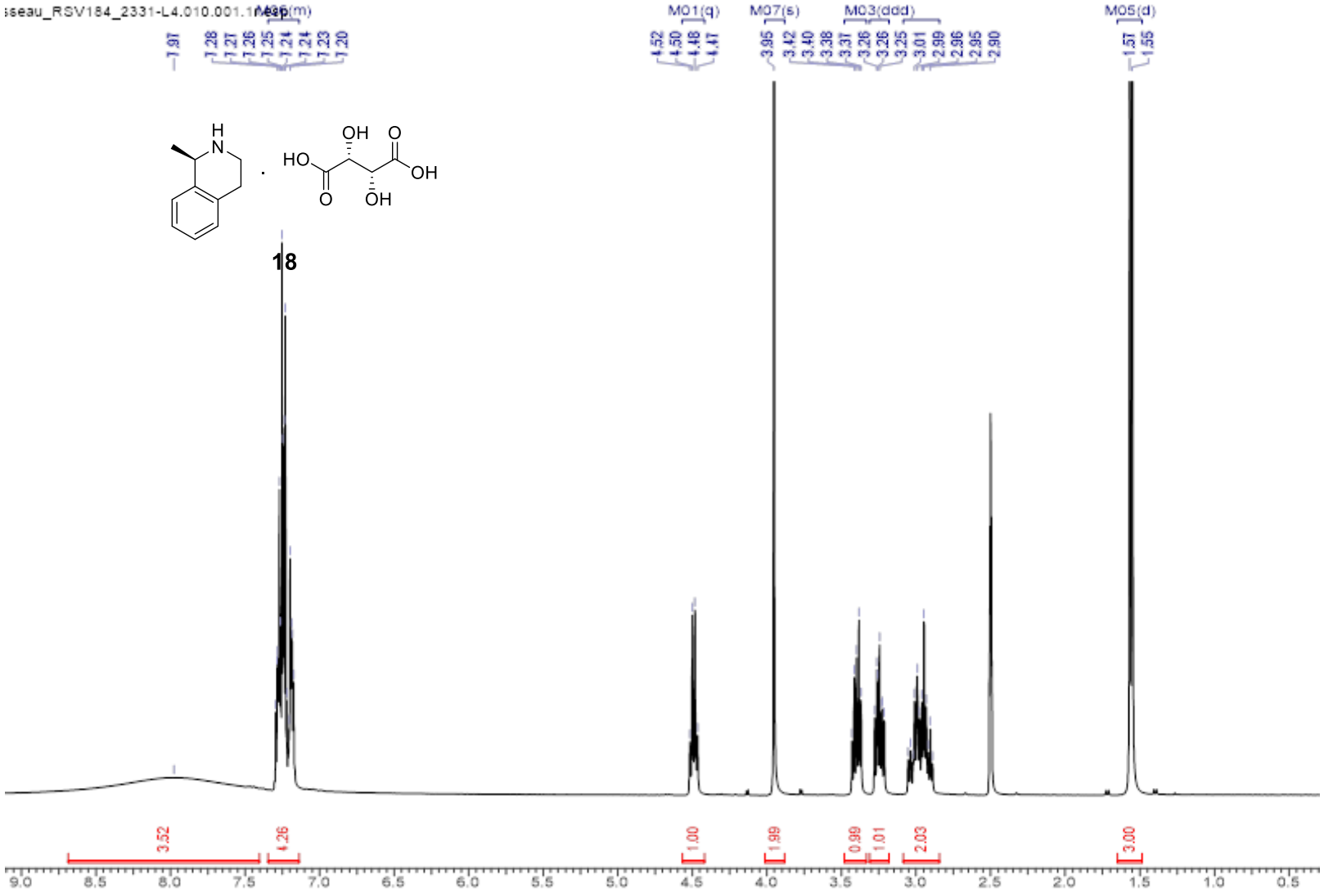


Figure S6. ^{1}H NMR of (*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline mono-(*L*)-tartrate **18** in d6-DMSO.

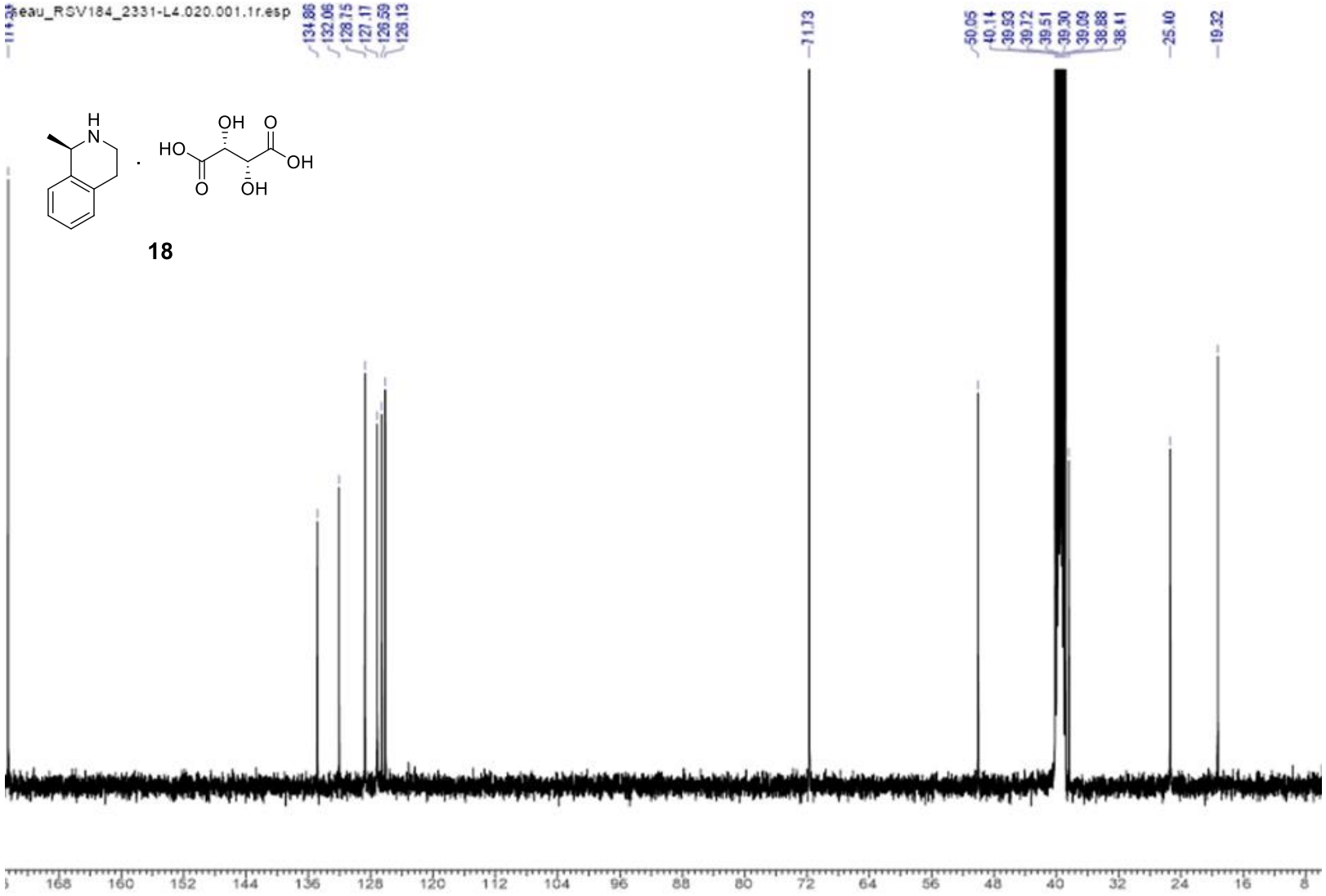


Figure S7. ^{13}C NMR of (*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline mono-(*L*)-tartrate **18** in d6-DMSO.

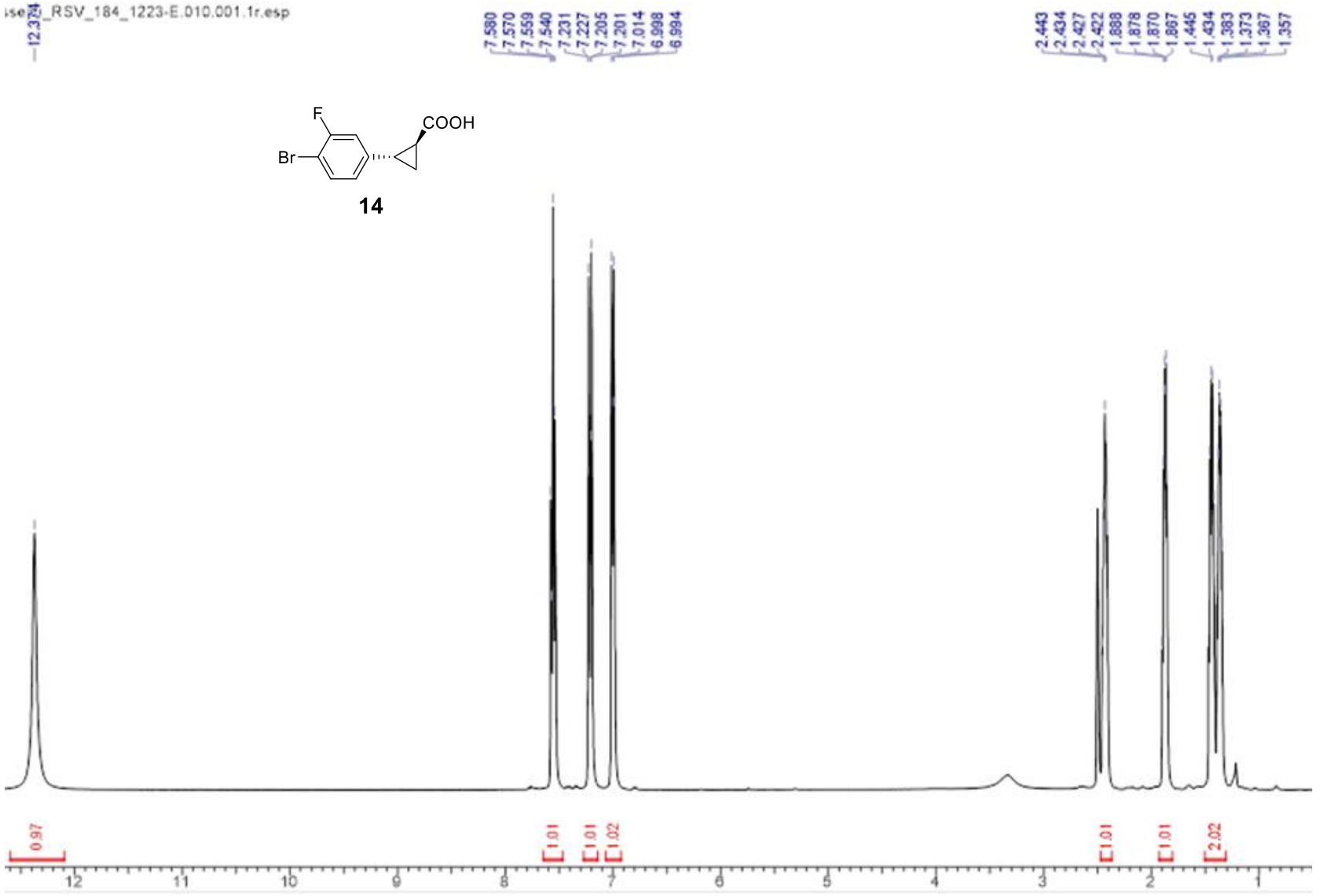


Figure S8. ^{1}H NMR of (1*S*,2*S*)-2-(4-bromo-3-fluorophenyl)cyclopropanecarboxylic acid **14** in d6-DMSO.

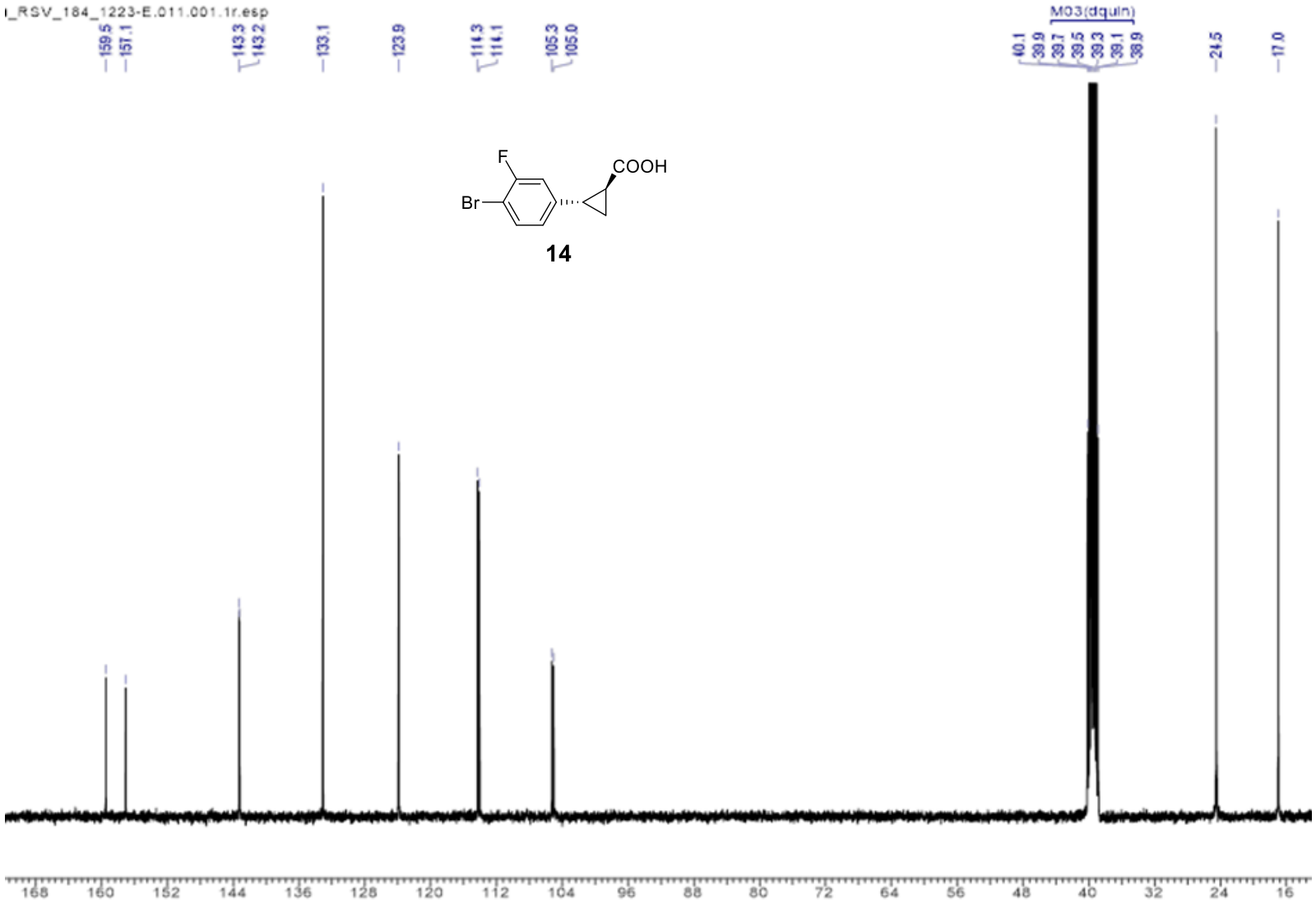


Figure S9. ^{13}C NMR of (1*S*,2*S*)-2-(4-bromo-3-fluorophenyl)cyclopropanecarboxylic acid **14** in d6-DMSO.

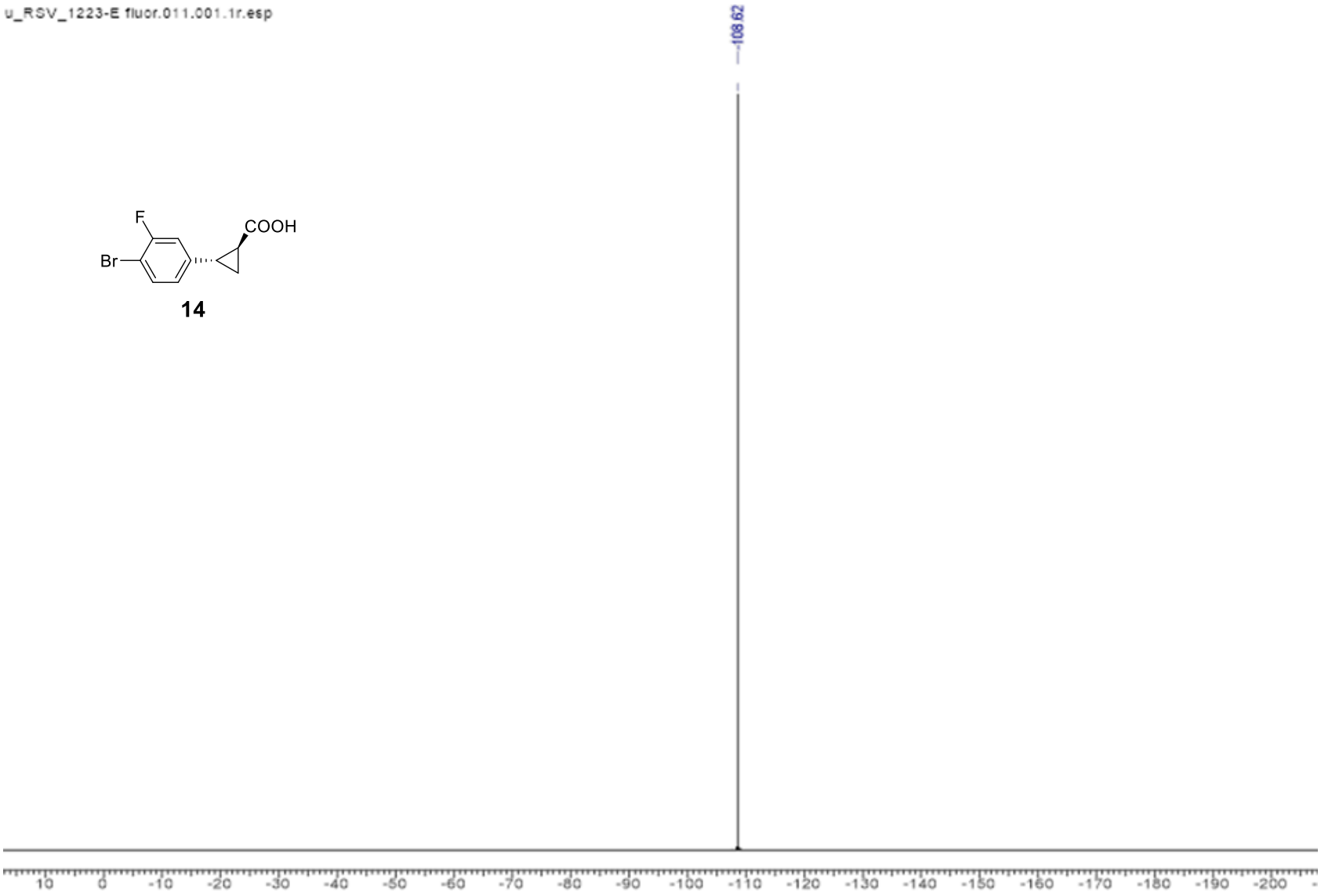


Figure S10. ^{19}F NMR of (1*S*,2*S*)-2-(4-bromo-3-fluorophenyl)cyclopropanecarboxylic acid **14** in d6-DMSO.

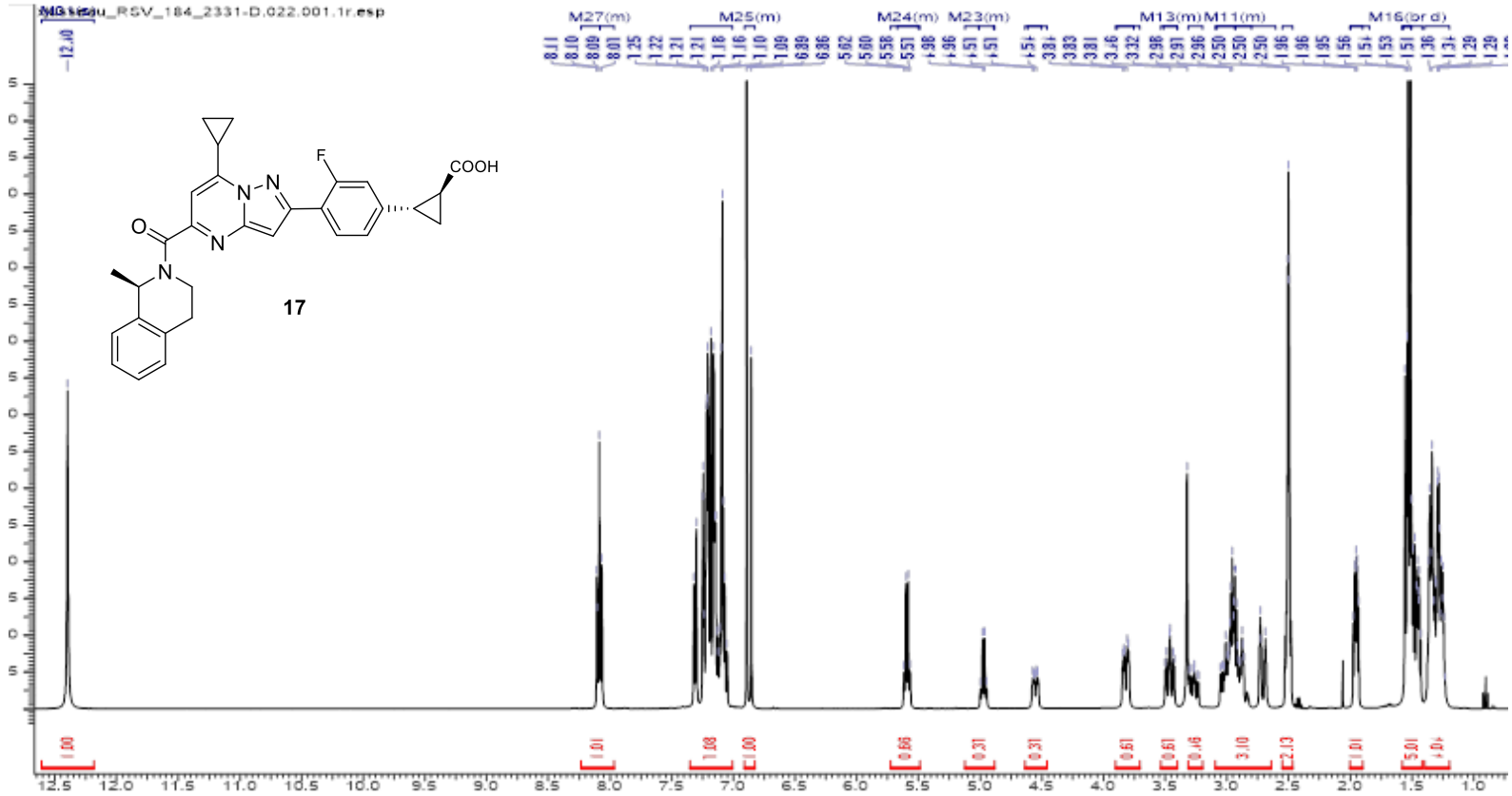


Figure S11. ^{1}H NMR of (1*S*,2*S*)-2-[4-(7-cyclopropyl-5-[[(1*R*)-1-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl]pyrazolo[1,5-*a*]pyrimidin-2-yl)-3-fluorophenyl]cyclopropanecarboxylic acid **17** in d6-DMSO.

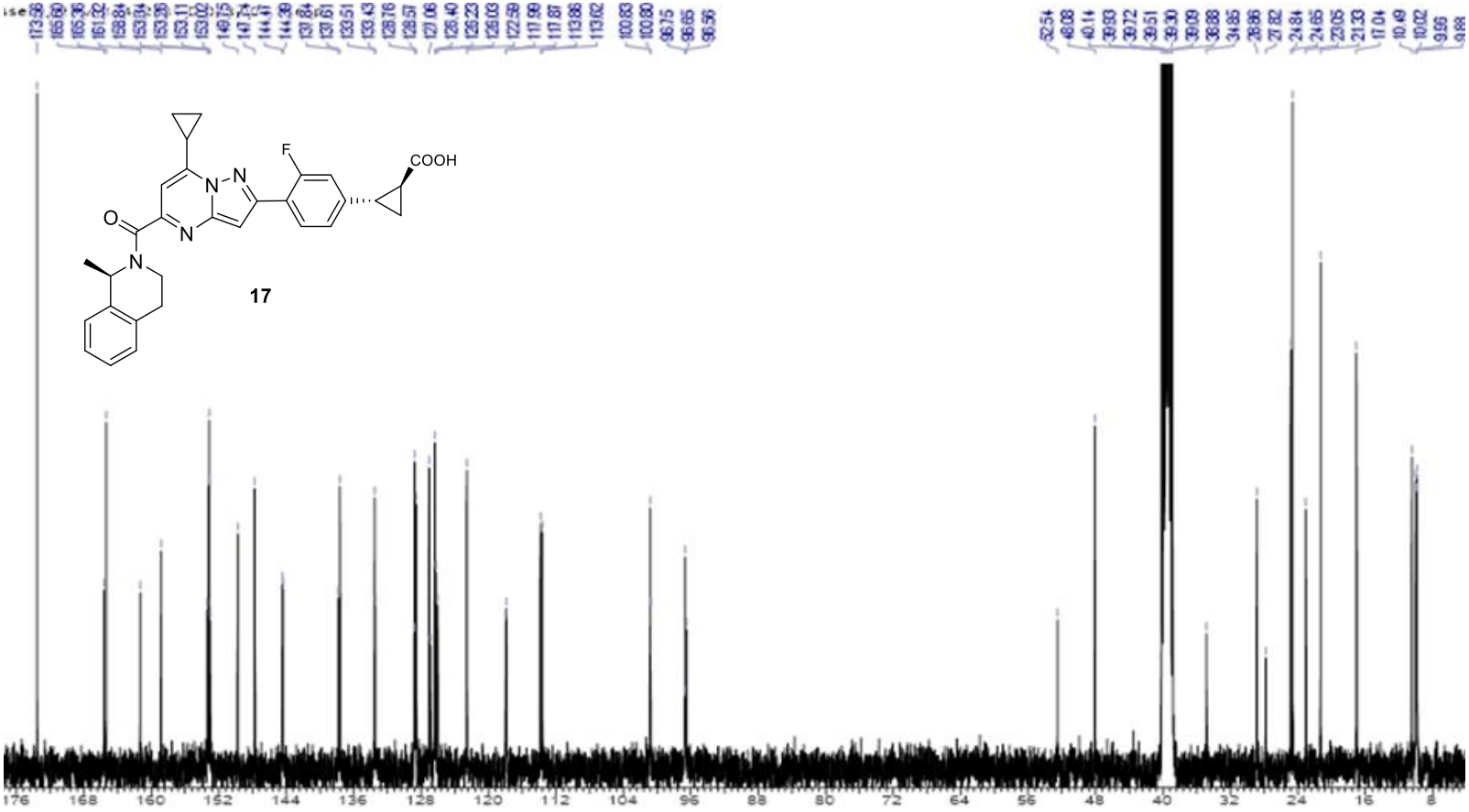


Figure S12. ^{13}C NMR of (1*S*,2*S*)-2-[4-(7-cyclopropyl-5-[[(1*R*)-1-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl]pyrazolo[1,5-*a*]pyrimidin-2-yl)-3-fluorophenyl]cyclopropanecarboxylic acid **17** in d6-DMSO.

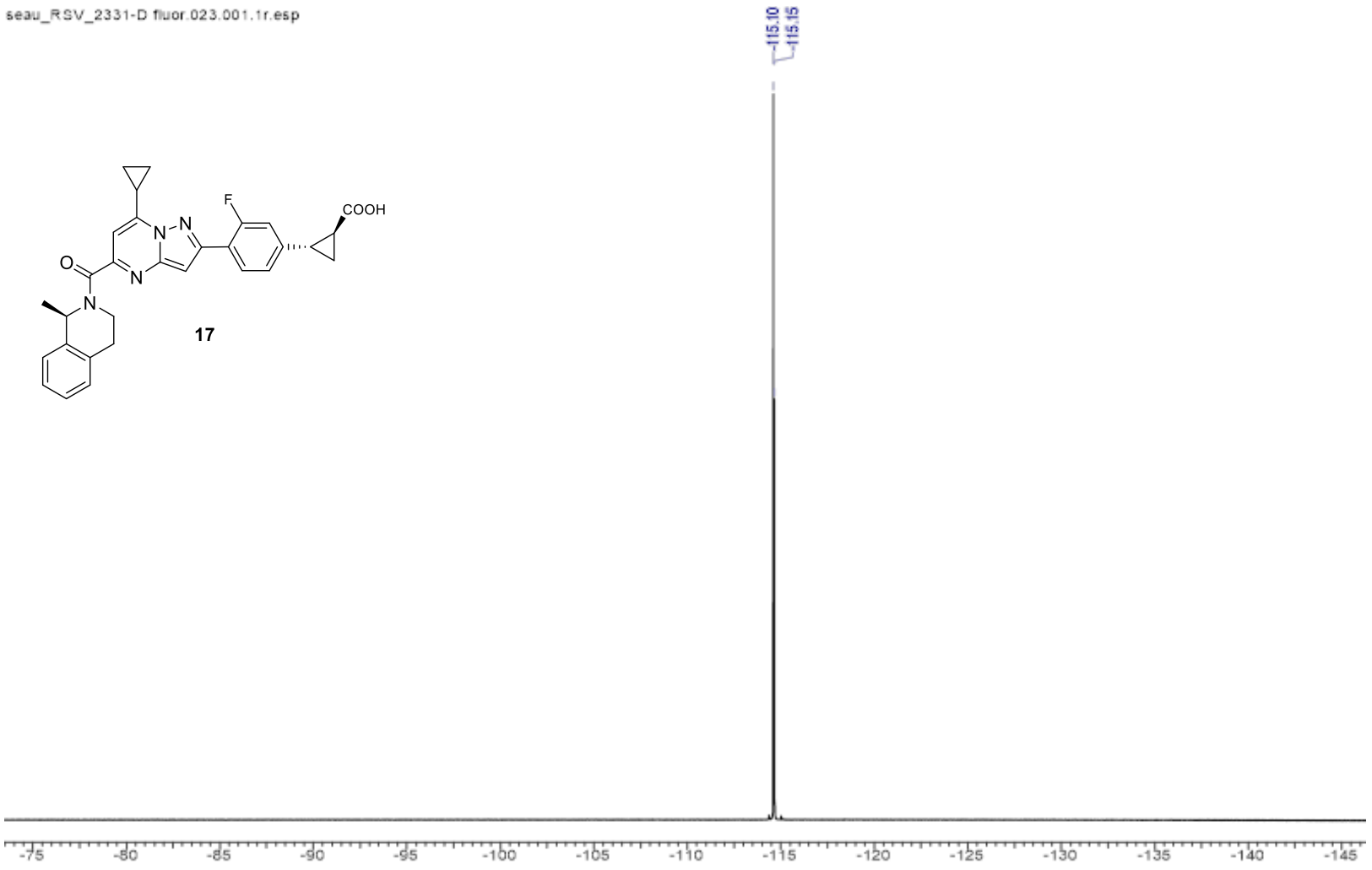


Figure S13. ^{19}F NMR of (1*S*,2*S*)-2-[4-(7-cyclopropyl-5-[[(1*R*)-1-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl]pyrazolo[1,5-*a*]pyrimidin-2-yl)-3-fluorophenyl]cyclopropanecarboxylic acid **17** in d6-DMSO.

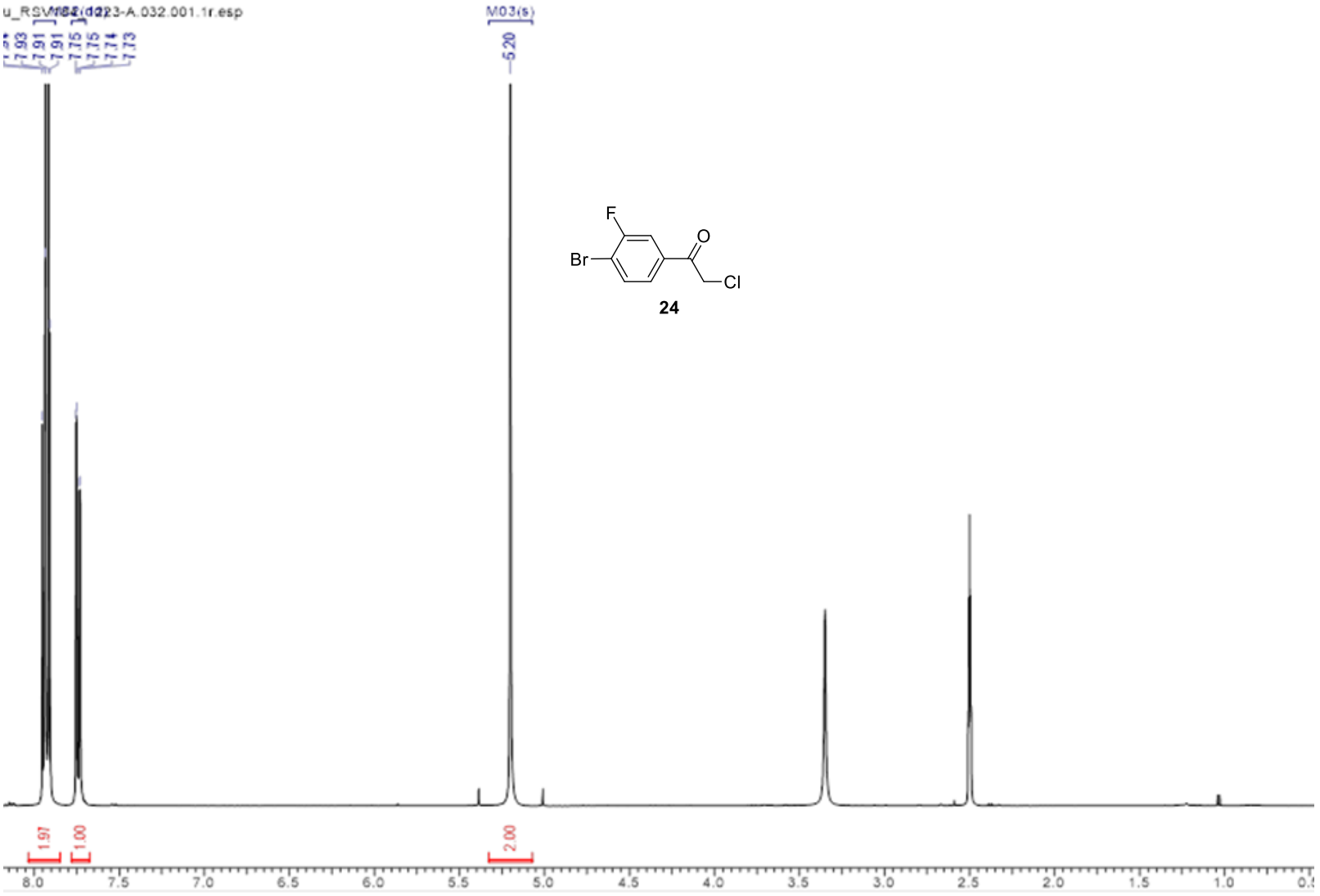


Figure S14. ^{1}H NMR of (1-(4-bromo-3-fluorophenyl)-2-chloroethan-1-one **24** in d6-DMSO.

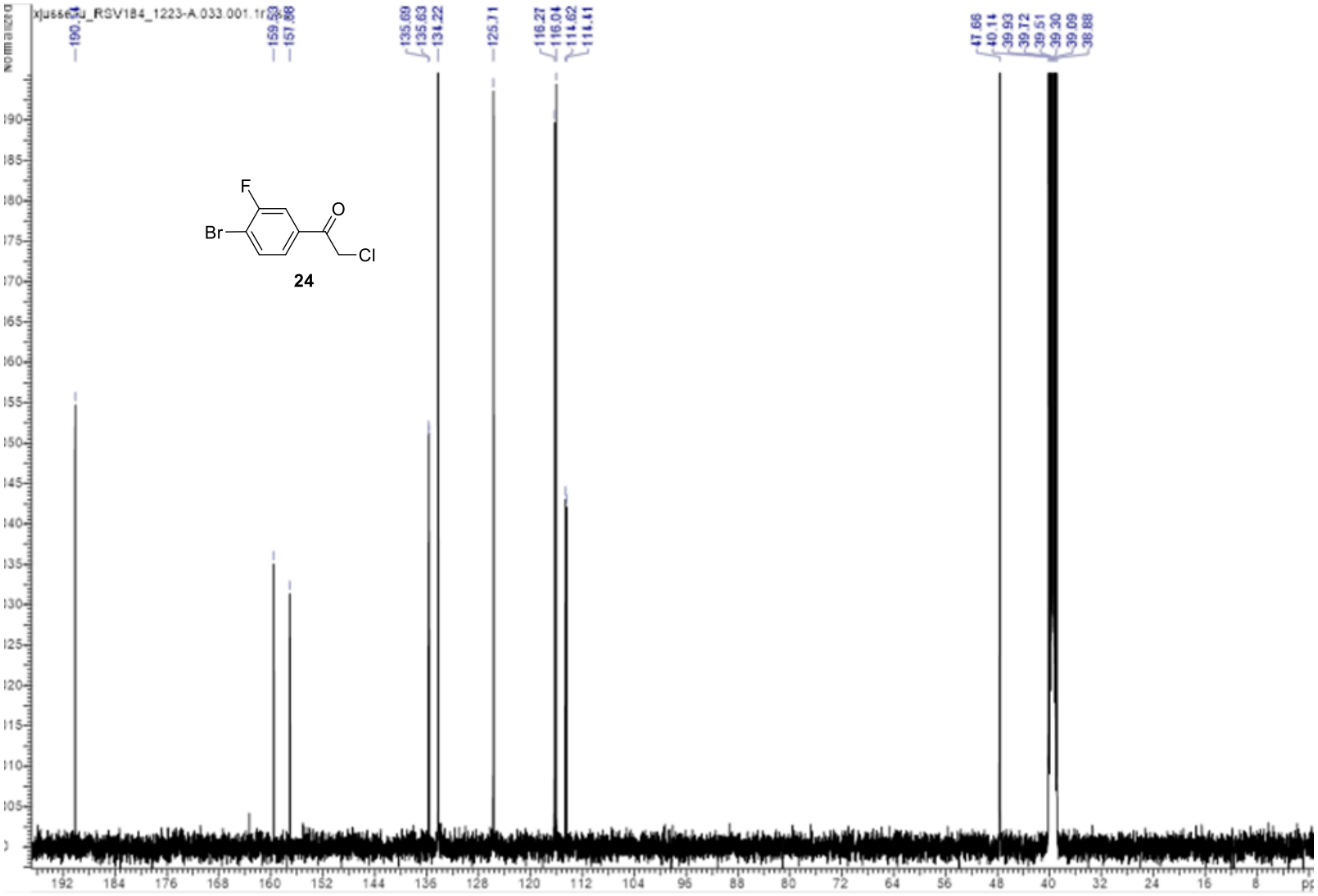


Figure S15. ^{13}C NMR of (1-(4-bromo-3-fluorophenyl)-2-chloroethan-1-one **24** in d6-DMSO.

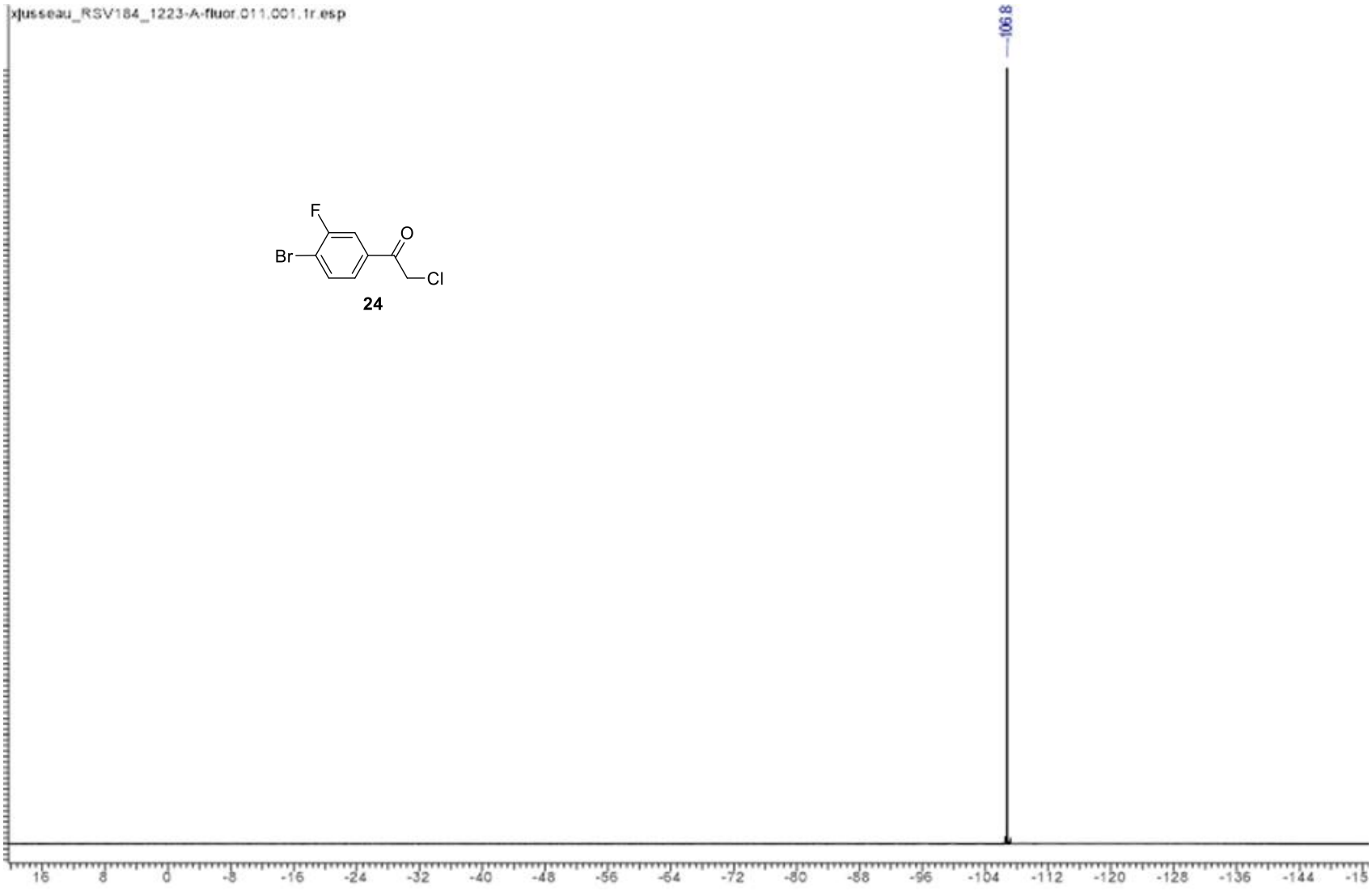
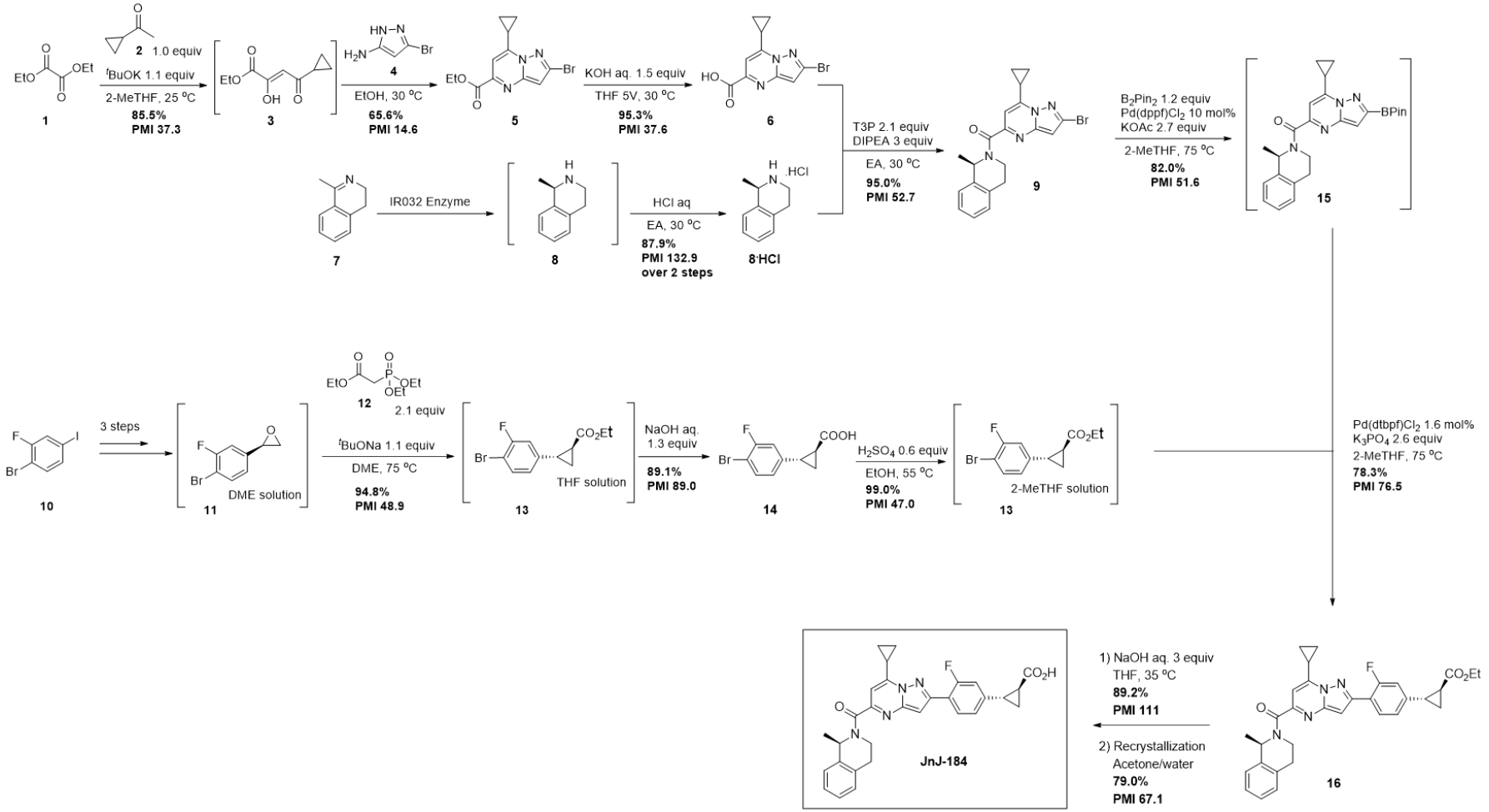


Figure S16. ^{19}F NMR of (1-(4-bromo-3-fluorophenyl)-2-chloroethan-1-one **24** in d6-DMSO.

IX] Original and new synthesis route description (PMI included):

Scheme S2: Original process synthesis route.



Scheme S3: New synthesis route with new steps in blue.