Supporting Information

Scalable synthesis of favipiravir via conventional and continuous flow chemistry

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General information

Analytical Thin-layer chromatography carried out on silica plates (silica gel 60 F254, Merck) using UV-light, ninhydrin and $KMnO_4$ for visualization. Eluting solvents are reported as ratio by volume.

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 as solvent on a Bruker 500 NMR spectrometer operated at 500 MHz, 125MHz, and 202 MHz. Chemical shifts (δ) were reported in part per million (ppm), The coupling constants J are given in Hertz (Hz). The spin multiplicities are reported as follows: s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublet, t = triplet, m = multiplet. High resolution mass spectra (HRMS) were recorded on micrOTOF mass spectrometer using the ESI technique.

Continues flow reactions were performed on Vapourtec R series RS-300 flow reactor using fixed bed reactor (diameter: 15 mm) or rapid mixing large volume reactor (diameter: 3.2 mm, volume: 10 mL).

High Performance Liquid Chromatography (HPLC) data were recorded on Dionex™ UltiMate™ 3000 UHPLC using Kinetex® 2.6 μm C18 100 Å (75 X 3 mm)

Operating systems: mobile phase A: 0.1% formic acid in water
mobile phase B: 0.1% formic acid in acetonitrile
flow rate 0.5 mL/min

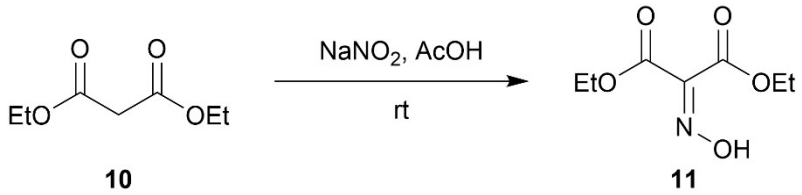
Method A: 0-10 min 0.2%B, 10-13 min gradient 0.2–95%B, 13-16 min gradient 95–0.2%B, 16-25 min 0.2%B.

Method B: 0-10 min 10%B, 10-15 min gradient 10–95%B, 15-20 min gradient 95–10%B, 20-25 min 10%B.

Method C: 0-25 min 10%B, 25-30 min gradient 10–95%B, 30-35 min gradient 95–10%B, 35-40 min 10%B

Optimization and scale-up of the synthesis of compounds

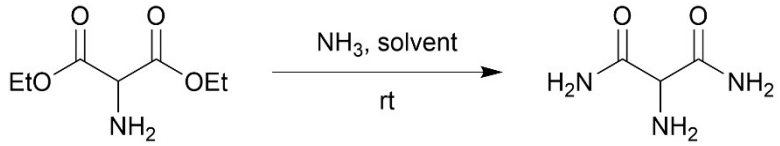
Table S.1 Optimization and scale-up of the synthesis of diethyl oximinomalonate (**11**).



10 **11**

Entry	$NaNO_2$ (eq.)	AcOH (eq.)	Time (h)	Scale (g)	Conversion (%)	Yield[a] (%)
1	2	3.42	16	12.25	87	85
2	3	4.57	24	12.25	92	83
3	3	4.57	24	105.63	94	89

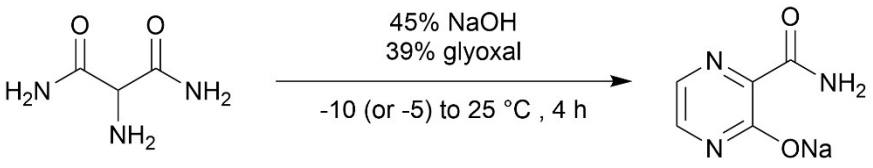
Table S.2 Optimization and scale-up of the synthesis of 2-aminomalonamide (**2**).



12 **2**

Entry	Reagent	Time	Scale (g)	yield (%)
1	2N NH_3 in MeOH	overnight	34	-
2	28% NH_3 in water	overnight	1	98.5
3	28% NH_3 in water	overnight	25	98
4	28% NH_3 in water	overnight	60	98
5	28% NH_3 in water	10 h	100	99

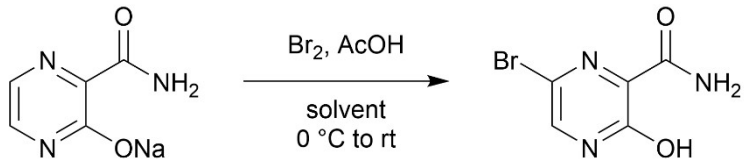
Table S.3 Optimization and scale-up of the synthesis of sodium 2-carbamoylpyrazine-3-hydroxylate (**13**).



2 **13**

Entry	NaOH (eq.)	Solvent	Temp (°C)	Scale (g)	Yield (%)
1	1.25	H_2O	-10 to 25	0.1	19
2	1.1	H_2O	-10 to 25	3	57
3	1.25	H_2O	-10 to 25	3	86
4	1.25	H_2O	-10 to 25	15	81
5	1.25	H_2O	-5 to 25	75	75

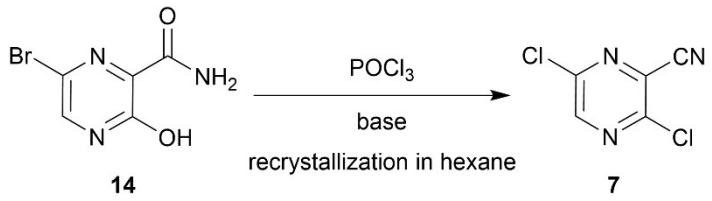
Table S.4 Optimization and scale-up of the synthesis of 3-hydroxy-6-bromopyrazine-2-carboxamid (**14**) in batch process.



13 **14**

Entry	Solvent	AcOH (eq)	Time (min)	Scale (g)	Yield (%)
1	MeOH:ACN 1:4	-	60	1	6
2	ACN	1.2	20	1	38
3	ACN	2	60	1	33
4	ACN	1.2	60	10	36

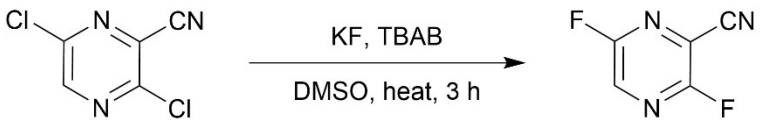
Table S.5 Optimization and scale-up of the synthesis of 3,6-dichloropyrazine-2-carbonitrile (**7**).



14 **7**

Entry	Base	Temp. (°C)	Time (h)	Scale (g)	Yield (%)
1	DIEA	70 to 100	6	1.4	68
2	DIEA	70 to 100	6	24.3	45
3	Pyridine	70 to 100	5.5	1.4	64
4	Pyridine	60 to 100	6	24.3	62

Table S.6 Optimization and scale-up of the synthesis of 3,6-difluoropyrazine-2-carbonitrile (**15**).

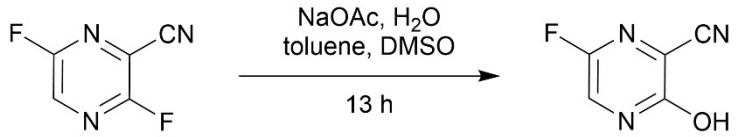


7 **15**

Entry	Temp (° C)	KF (eq.)	DMSO (mL/mmol)	Scale (g)	Conversion (%)[a]
1	60	3	1	0.34	48
2	80	3	1	0.34	32
3	100	3	1	0.34	7
4	60	4	1	0.34	31
5	60	5	1	0.34	93
6	60	5	2	10.43	100
7[b]	60	5	2	10.43	100

[a] According to NMR integration, [b] using 300 mL hastelloy reactor (stirring speed 500 rpm).

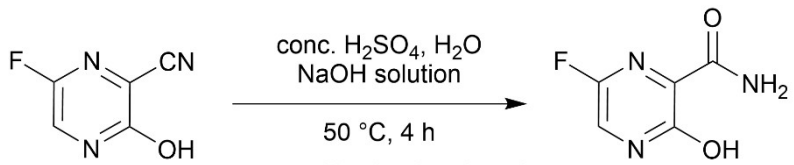
Table S.7 Optimization and scale-up of the synthesis of 6-fluoro-3-hydroxypyrazine-2-carbonitrile (**16**).



15 **16**

Entry	Time (h)	Scale (g)	Extraction	Yield (%)
1	20	2.82	Ether	quant
2	13	7.76	EtOAc	55
3	13	14.10	Ether	quant

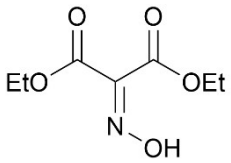
Table S.8 Optimization and scale-up of the synthesis of 6-fluoro-3-hydroxypyrazine-2-carboxamide (**1**, Favipiravir).



16 **1**

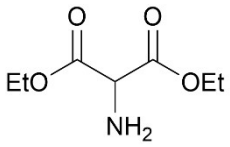
Entry	Scale (g)	Yield (%)
1	0.32	34
2	2.78	49
3	3.48	80
4	13.90	61

Synthesis and characterization of compounds



11

Preparation of diethyl oximinomalonate (11): Glacial acetic acid (172.4 mL, 3014 mmol) was added to diethyl malonate (100 mL, 659.5 mmol). The solution was cooled to -10 °C, then a solution of sodium nitrite (136.5 g, 1978.5 mmol) in water (215.5 mL) was slowly added dropwise over a period of 2 h. After stirring for 24 h at room temperature, the reaction was twice extracted with diethyl ether (450 mL). The combined organic layers were washed with 10% $NaHCO_3$ (5 x 200 mL) (pH of aqueous solution ~8), dried over anhydrous sodium sulfate, and evaporated to obtain a yellow oil of diethyl oximinomalonate (110.8 g, 89%). R_f 0.39 (Hexane/EtOAc, 6:4, stain potassium permanganate); ^{1}H NMR (500 MHz, DMSO-d_6): δ 13.30 (s, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.7, 160.1, 144.0, 62.6, 62.3, 13.8, 13.7; HRMS (ESI): *m/z* calcd for = $C_7H_{11}NO_5Na$ $[M+Na]^+$ 212.0535, found 212.0516.



12

Preparation of diethyl 2-aminomalonate (12):

Batch process to prepare diethyl 2-aminomalonate: diethyl oximinomalonate (5 g, 26.5 mmol) and 10% Palladium on carbon (0.038 g, 5 wt. %) were suspended in ethanol (20 mL) under the atmosphere of hydrogen (1 atm, room temperature) for 24 h. The Pd catalyst was filtrated off, and the filtrate was evaporated to obtain a crude product as a yellow oil. The crude was diluted in ethyl acetate (50 mL) and extracted with 10% HCl. The aqueous solution was adjusted to pH 9 by adding $NaHCO_3$, extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate and evaporated to give a yellow oil of diethyl 2-aminomalonate (1.85 g, 40%).

Continuous flow chemistry process to prepare diethyl 2-aminomalonate: The solution of diethyl 2-aminomalonate (10 g, 52.9 mmol) in ethanol (100 mL, 0.53 M) was prepared in a feed vessel. Diethyl 2-aminomalonate solution was pumped at a flow rate of approximately 1.159 mL/min (1 equiv) and hydrogen gas was pumped at a flow rate of approximately 88.5 scc/min (6 equiv). Reactant and hydrogen gas were combined in a fixed bed reactor (diameter: 15 mm) containing 0.24 mol/g Pd on Silica (SiliaCat Pt0 | R820-100) (5 g) at 60 °C and 5 bars for 7 minutes. After running the flow reactor for 12 min. (steady state time), the outlet was collected directly to a vessel for 81 min. The solution was evaporated to obtain a yellow oil of diethyl 2-aminomalonate (7.96 g, 96%). The product was used in the next step without further purification. R_f 0.24 (Hexane/EtOAc, 6:4, stain potassium permanganate); ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.09-4.16 (m, 5H), 2.15 (br s, 2H), 1.18 (t, J = 7.1 Hz, 6H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.9 (2C), 61.1 (2C), 58.4, 13.9 (2C); HRMS (ESI): *m/z* calcd for $C_7H_{13}NO_4Na$ $[M+Na]^+$ 198.0742, found 198.0747.

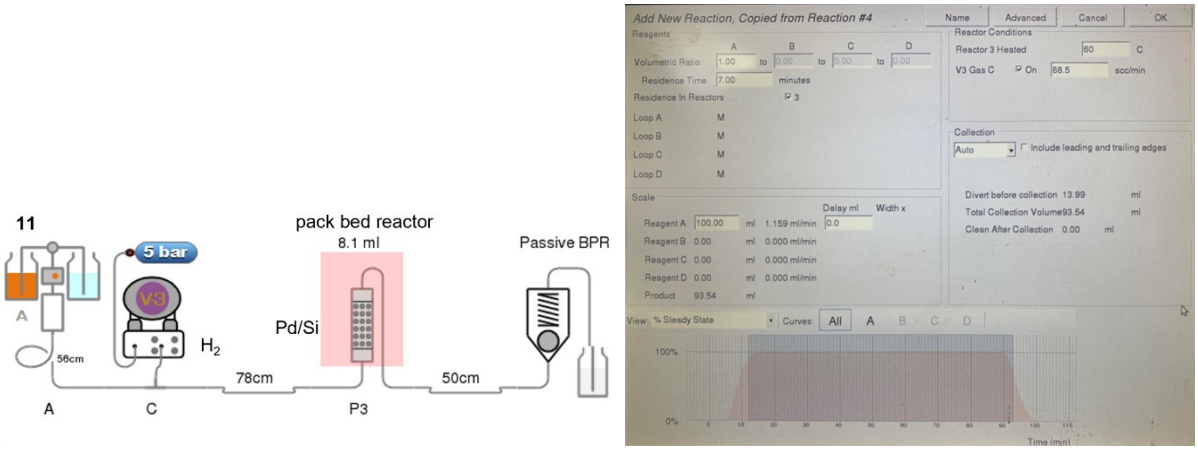
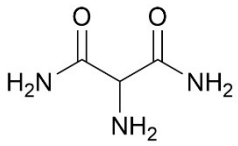


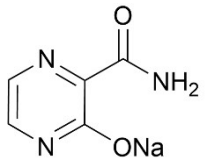
Diagram and example of the detailed setup for the continuous flow reaction.



2

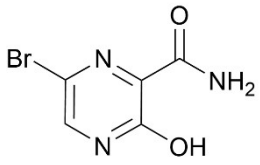
Preparation of 2-aminomalonamide (2): Diethyl 2-aminomalonate (100 g, 570.8 mmol) in a flat bottom flask was charged with 28% ammonia in aqueous solution (500 mL). The reaction was stirred at room temperature for 10 h. Then, the reaction was evaporated and dried under vacuum to obtain a yellow solid of 2-aminomalonamide (66 g, 99%). R_f 0.10 (DCM/MeOH, 8:2, stain

potassium permanganate); ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.46 (br s, 2H), 7.27 (br s, 2H), 3.78 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 172.1 (2C), 58.2; HRMS (ESI): *m/z* calcd for $C_3H_7N_3O_2Na$ $[M+Na]^+$ 140.0436, found 140.0460; HPLC R_t = 0.80 min (method B).



13

Preparation of sodium 2-carbamoylpyrazine-3-hydroxylate (13): 45% NaOH solution (2.8 mL, 32 mmol) was cooled to -10 °C. 2-aminomalonamind (3 g, 25.6 mmol) was suspended in NaOH solution. Then, 39% glyoxal (3.6 mL, 32 mmol) was added dropwise to the suspension over a period of 15 min. The mixture was stirred at -5 °C for 1 h, then at room temperature for 3 h. The reaction was cooled to below 5 °C, filtrated, and washed with 80% aqueous solution of acetonitrile (5 mL) and acetonitrile (5 mL) to obtain sodium 2-carbamoylpyrazine-3-hydroxylate as a light yellow solid (3.57 g, 86%). R_f 0.25 (DCM/MeOH, 8:2, stain ninhydrin); ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.93 (br s, 1H), 7.85 (d, *J* = 2.2 Hz, 1H), 7.31 (d, *J* = 2.2 Hz, 1H), 7.16 (br s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.2, 167.9, 146.1, 133.0, 125.6; HRMS (ESI): *m/z* calcd for $C_5H_4N_3O_2Na_2$ $[M+Na]^+$ 184.0099, found 184.0096; HPLC R_t = 0.73 min (method B).



14

Preparation of 3-hydroxy-6-bromopyrazine-2-carboxamide (14):

Batch process to prepare 3-hydroxy-6-bromopyrazine-2-carboxamide: The suspension of sodium 2-carbamoylpyrazine-3-hydroxylate (10 g, 61.68 mmol) in acetonitrile (7.5 mL) and methanol (12.5 mL) was cooled to 0 °C. The solution of Br_2 (3.18 mL, 61.68 mmol) and glacial acetic acid (4.23 mL, 74.02 mmol) in acetonitrile (5 mL) was added dropwise to a suspension. The reaction was stirred at room temperature for 1 h. Then, the reaction was charged with 10% NaS_2O_3 (10 mL) and evaporated to remove solvents. The crude product was extracted with ethyl acetate (3

x 200 mL). The combined organic layers were dried over anhydrous sodium sulfate and evaporated to obtain 3-hydroxy-6-bromopyrazine-2-carboxamide as a yellow solid (4.9 g, 36%).

Continuous flow chemistry process to prepare 3-hydroxy-6-bromopyrazine-2-carboxamide: The suspension of sodium 2-carbamoylpyrazine-3-hydroxylate (1 g, 6.168 mmol) in methanol (62 mL, ~10 mL/mmol) (feed 1) and Br_2 (0.95 mL, 18.504 mmol) in acetonitrile (62 mL, 0.3 mM) (feed 2) were prepared in separate feed vessels. Feed 1 and 2 were pumped at a flow rate of approximately 9.09 mL/min. Both feeds were combined in rapid mixing large volume reactor (diameter: 3.2 mm, volume: 10 mL) at 30 °C for 33 sec. After running the flow reactor for 54 sec. (steady state time), the outlet was collected directly to a vessel containing 10% $Na_2S_2O_3$ (35 mL) and 9% $NaHCO_3$ (35 mL) for 6 min and 31 sec. The mixture was evaporated to remove organic solvents and adjusted to pH 3 by adding 0.5 M HBr (~30 mL), then extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over anhydrous sodium sulfate and evaporated to obtain 3-hydroxy-6-bromopyrazine-2-carboxamide as a yellow solid (0.82 g, 64%). R_f 0.52 (DCM/MeOH, 8:2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.48 (br s, 1H), 8.49 (s, 1H), 7.58 (br s, 1H), 5.86 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.7, 161.5, 150.8, 128.0, 126.7; HRMS (ESI): *m/z* calcd for $C_5H_4BrN_3O_2Na$ $[M+Na]^+$ 239.9385, found 239.9417; HPLC R_t = 1.90 min (method B).

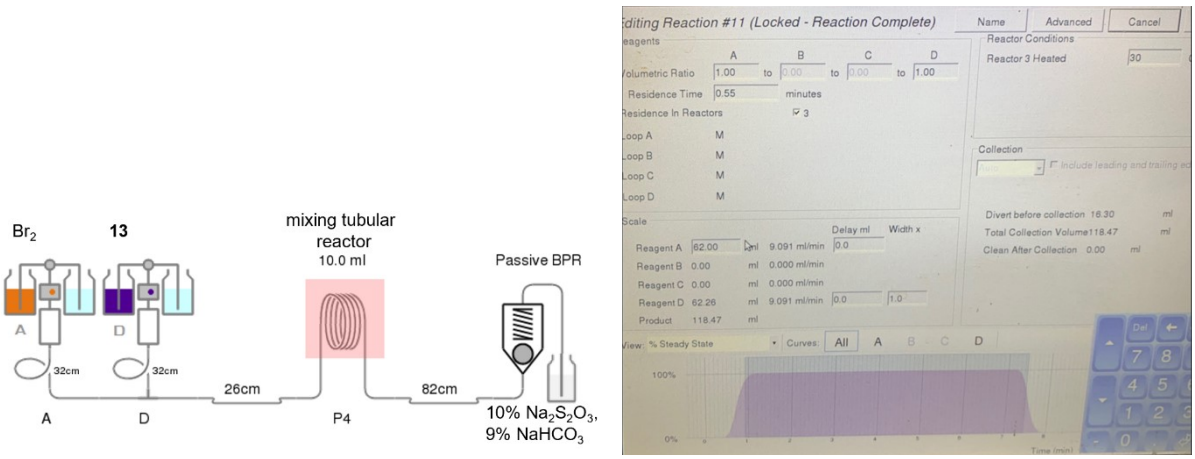
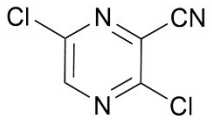
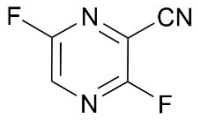


Diagram and example of the detailed setup for the continuous flow reaction.



7

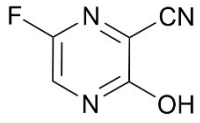
Preparation of 3,6-dichloropyrazine-2-carbonitrile (7): 3-hydroxy-6-bromopyrazine-2-carboxamide (24.3 g, 111.5 mmol) was added $POCl_3$ (72.9 mL, 780.2 mmol). The mixture was stirred at 70 °C for 30 min until the mixture became homogeneous. Then, the mixture was cooled to room temperature, and pyridine (26.9 mL, 334.4 mmol) was added dropwise over a period of 1 h (keeping a temperature below 60 °C). The reaction was stirred at 60 °C for 1 h, 80 °C for 1 h, and 100 °C for 4 h. The reaction was cooled to room temperature, then poured to cool water (750 mL) and vigorously stirred for 1 h. The mixture was extracted with ethyl acetate (5 x 150 mL). The combined organic layers were washed with brine solution (3 x 100 mL) and dried over anhydrous sodium sulfate and evaporated to give the crude product as black solid. The crude was suspended in hexane (500 mL), heated to reflux for 30 min, and filtrated. The filtrate residue was refluxed in hexane (500 mL) and filtrated again. The combined filtrate was evaporated to obtain a yellow solid of 3,6-dichloropyrazine-2-carbonitrile (12.13 g, 62%). R_f 0.35 (DCM); ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.03 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 149.2, 148.3, 146.6, 128.4, 113.7; HPLC R_t = 14.65 min (method C).



15

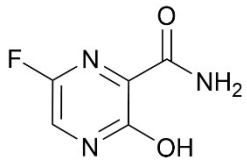
Preparation of 3,6-difluoropyrazine-2-carbonitrile (15): The mixture of 3,6-dichloropyrazine-2-carbonitrile (10.4 g, 60 mmol) and tetrabutylammonium bromide (3.9 g, 12 mmol) in a PFA reaction vessel was added anhydrous dimethyl sulfoxide (120 mL). The mixture of anhydrous potassium fluoride (17.4 g, 300 mmol) in anhydrous dimethyl sulfoxide (120 mL) was added to the suspension. The reaction was stirred at 60 °C for 3 h under nitrogen atmosphere. The cooled reaction was added water (60 mL) and stirred for 15 min, then added water (60 mL) and stirred for 5 min. The mixture was adjusted to pH 1.6 by adding concentrate hydrochloric acid (~14 mL) and extracted with diethyl ether (3 x 200 mL). The combined organic layers were washed with 5% brine solution, dried over anhydrous sodium sulfate, and evaporated to obtain 3,6-difluoropyrazine-2-carbonitrile as a black oil (8.3 g, 98%). R_f 0.45 (Hexane/EtOAc, 9:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.34 (dd, *J* = 8.1, 1.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.7 (dd, *J* = 257.5, 2.8 Hz), 156.6 (dd, *J* = 256.9, 2.9 Hz), 135.9 (dd, *J* = 41.7, 11.2 Hz), 113.9 (dd, *J* = 35.8, 11.2

Hz), 110.6 (d, *J* = 9.1 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ -77.18 (d, *J* = 37.1 Hz), -81.12 (d, *J* = 37.1 Hz); HPLC R_t = 4.24 min (method C).



16

Preparation of 6-fluoro-3-hydroxypyrazine-2-carbonitrile (16): The solution of 3,6-difluoropyrazine-2-carbonitrile (14.1 g, 100 mmol) in toluene (80 mL) was added dimethyl sulfoxide (80 mL), water (50 mL), and sodium acetate (27.2 g, 200 mmol). The mixture was stirred at 50 °C for 13 h. The cooled reaction was added concentrate hydrochloric acid (~13 mL) to adjust the pH to ~2.5, then added water (50 mL) and extracted with diethyl ether (7 x 250 mL). The combined organic layers were washed with water (500 mL), 10% brine solution (200 mL), then dried over anhydrous sodium sulfate, and evaporated to obtain a yellow solid of 6-fluorop-3-hydroxypyrazine-2-carbonitrile (14.8 g, quantitative). R_f 0.35 (DCM/MeOH, 9:1); ^{1}H NMR (500 MHz, DMSO-d_6): δ 13.71 (br s, 1H), 8.52 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 160.3, 153.3, 152.3 (d, *J* = 239.7Hz), 114.3 (2C); ^{19}F NMR (470 MHz, DMSO-d_6): δ -82.0 (s, 1F); HPLC R_t = 5.45 min (method A).

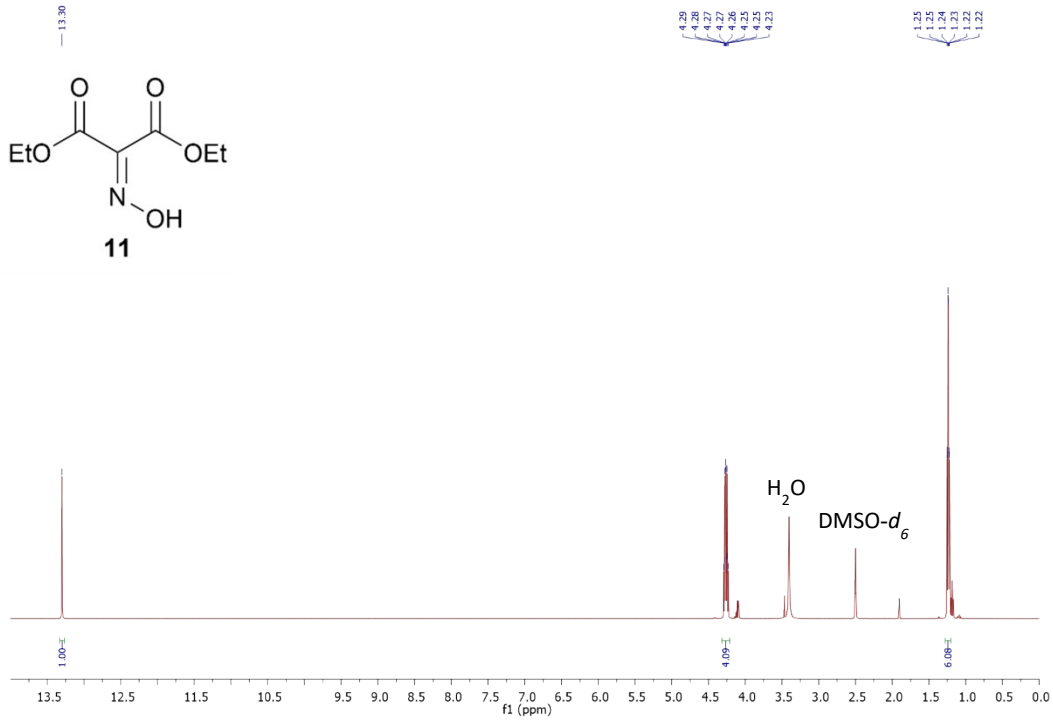


1

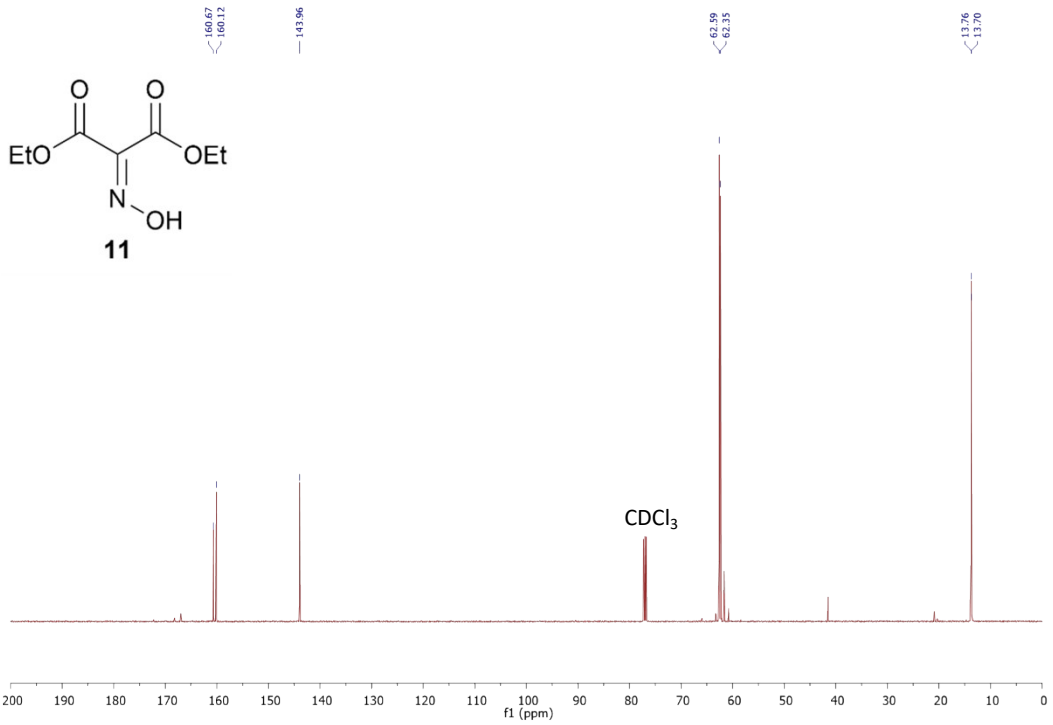
Preparation of 6-fluoro-3-hydroxypyrazine-2-carboxamide (1, Favipiravir): 6-fluoro-3-hydroxypyrazine-2-carbonitrile (13.9 g, 100 mmol) was added concentrated sulfuric acid (32 mL) and stirred at 50 °C for 4 h. The reaction was cooled to 3 °C, then water (180 mL) was slowly added to the reaction over a period time of 20 min and stirred at a temperature below 10 °C for 20 min. After stirring, 28% aqueous NaOH (40 mL) was added dropwise to the reaction over a period time of 15 min and stirred at a temperature below 10 °C for a further 30 min. The precipitate was filtrated and dried under vacuum to obtain a mixture of product and sulfate salt as an orange solid. The solid mixture was extracted with acetone (2 x 100 mL). The combined organic layers were evaporated to obtain an orange solid. The solid was dissolved in acetone (30

mL/g) added activated charcoal (30 wt. %). Then, the suspension was heated to reflux for 30 min, filtrated to remove charcoal, and evaporated to give a light-yellow solid. The product was crystallized by dissolved in ethanol (17 mL/g), reflux for 1 h, cooled to 4 °C and then filtrated to obtain an off-white solid of favipiravir (9.6 g, 61%). R_f 0.63 (DCM/MeOH, 9:1); ^{1}H NMR (500 MHz, DMSO-d_6): δ 13.40 (br s, 1H), 8.74 (br s, 1H), 8.51 (br s, 1H), 8.49 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.7, 159.7, 152.4 (d, J = 243.6 Hz), 135.8, 122.1; ^{19}F NMR (470 MHz, DMSO-d_6): δ -92.8 (s, 1F).; HPLC R_t = 4.58 min (method A).

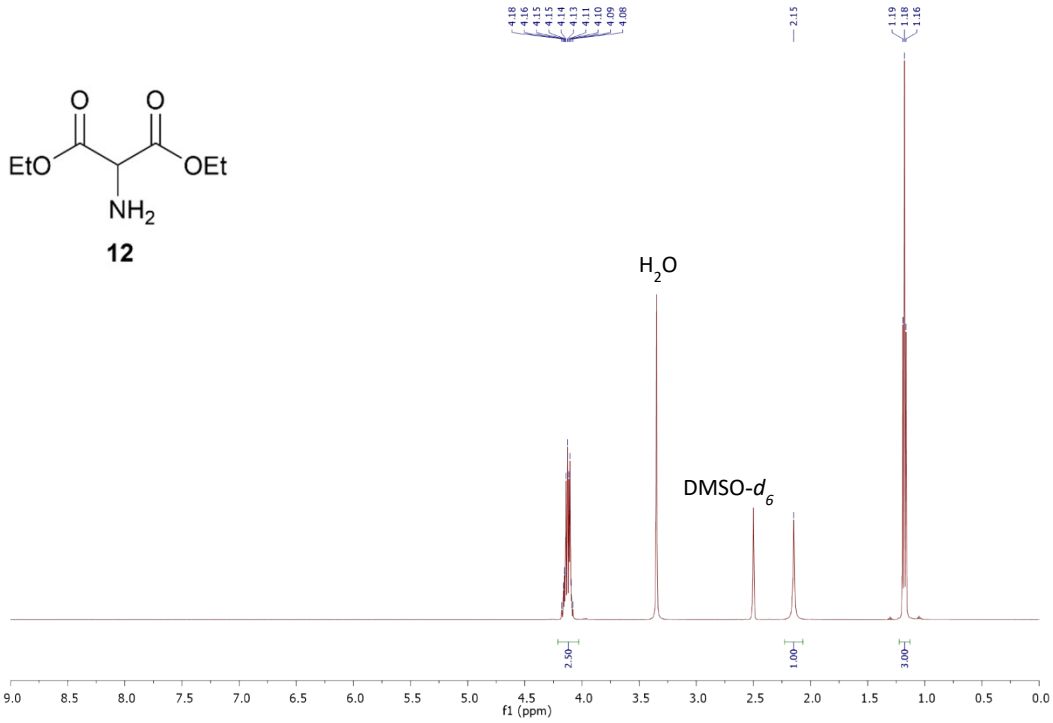
^{1}H, ^{13}C and ^{19}F NMR of compounds



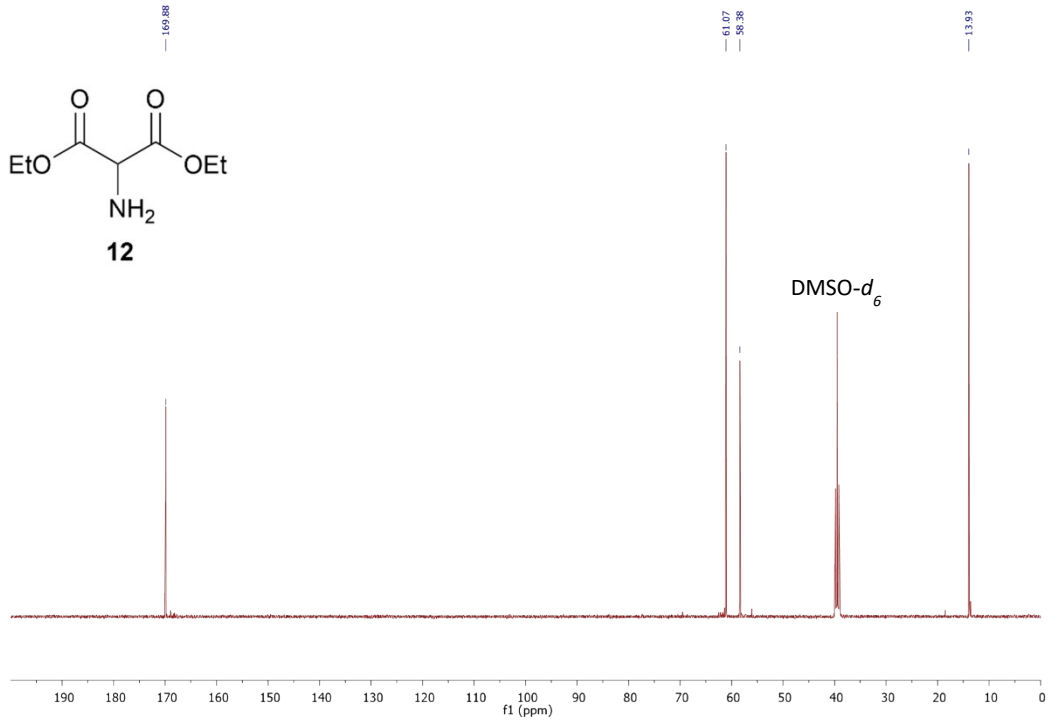
^{1}H NMR (DMSO-d_6) spectrum of diethyl oximinomalonate (**11**).



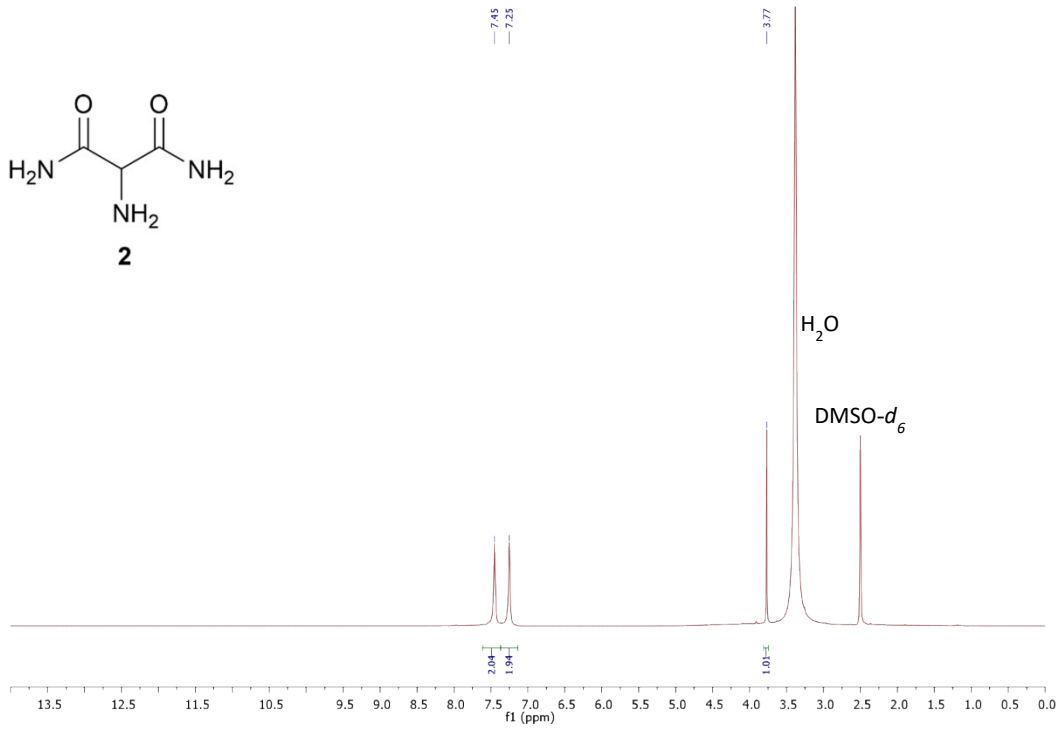
^{13}C NMR ($CDCl_3$) spectrum of diethyl oximinomalonate (**11**).



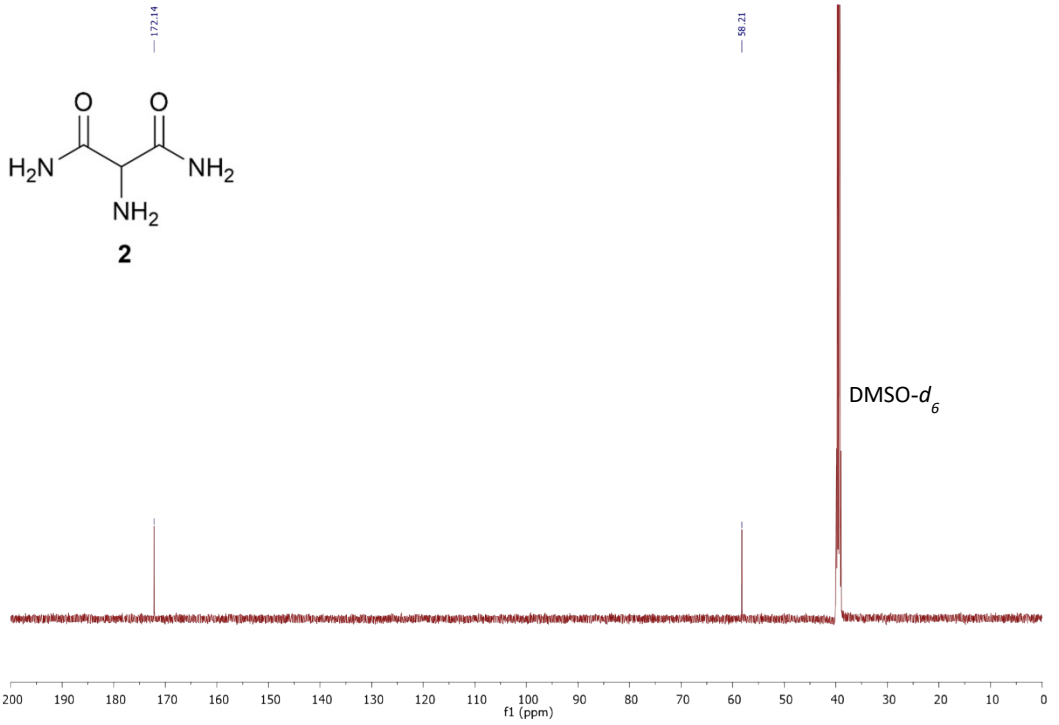
^{1}H NMR (DMSO-d_6) spectrum of 2-aminomalonate (**12**).



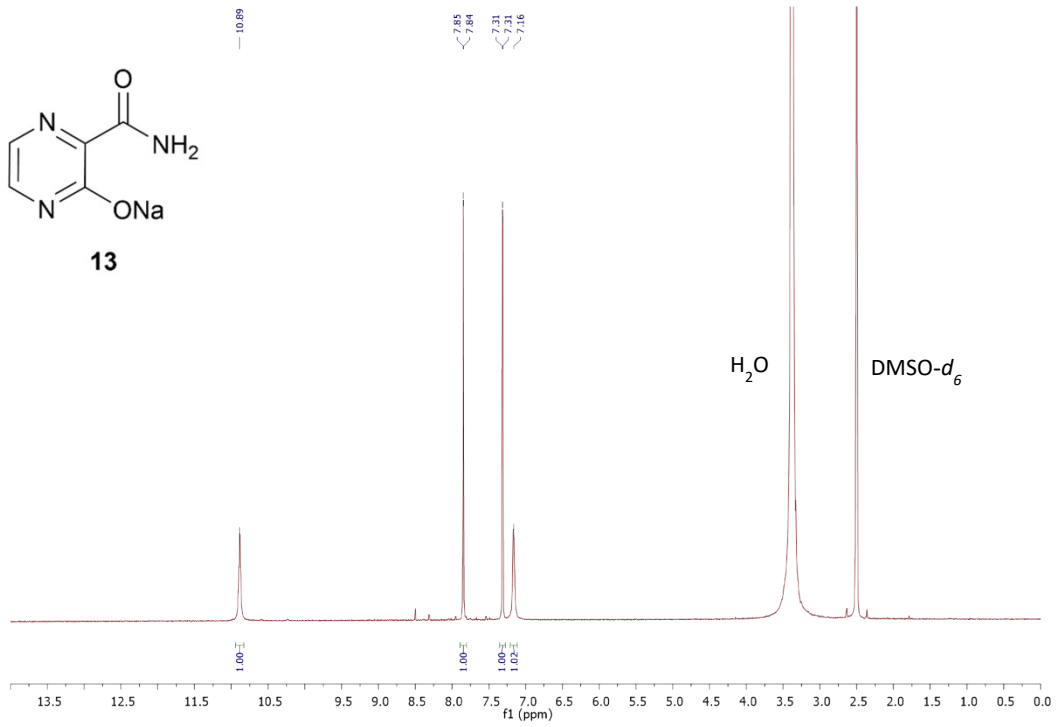
^{13}C NMR (DMSO-d_6) spectrum of 2-aminomalonate (**12**).



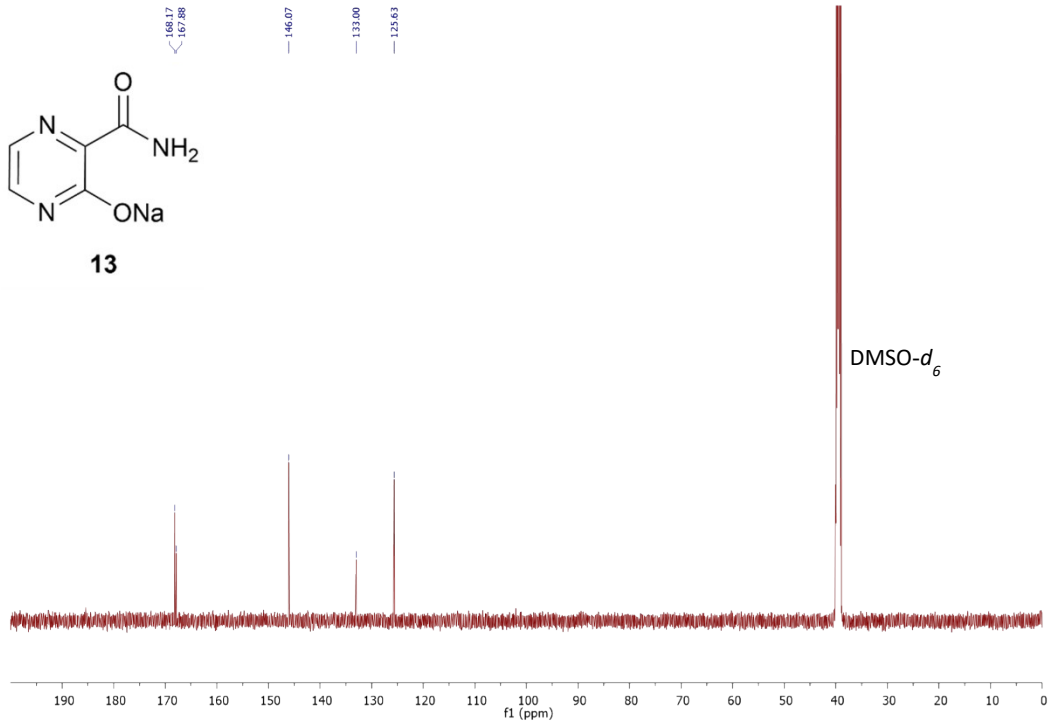
^{1}H NMR (DMSO-d_6) spectrum of 2-aminomalonamide (**2**).



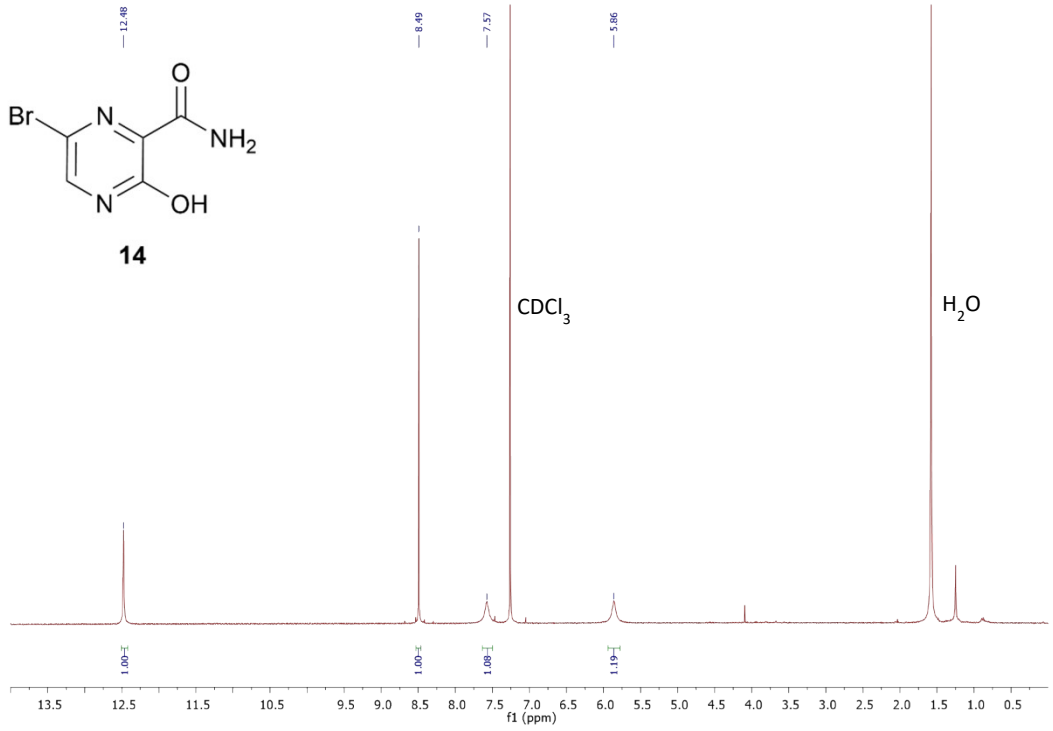
^{13}C NMR (DMSO-d_6) spectrum of 2-aminomalonamide (**2**).



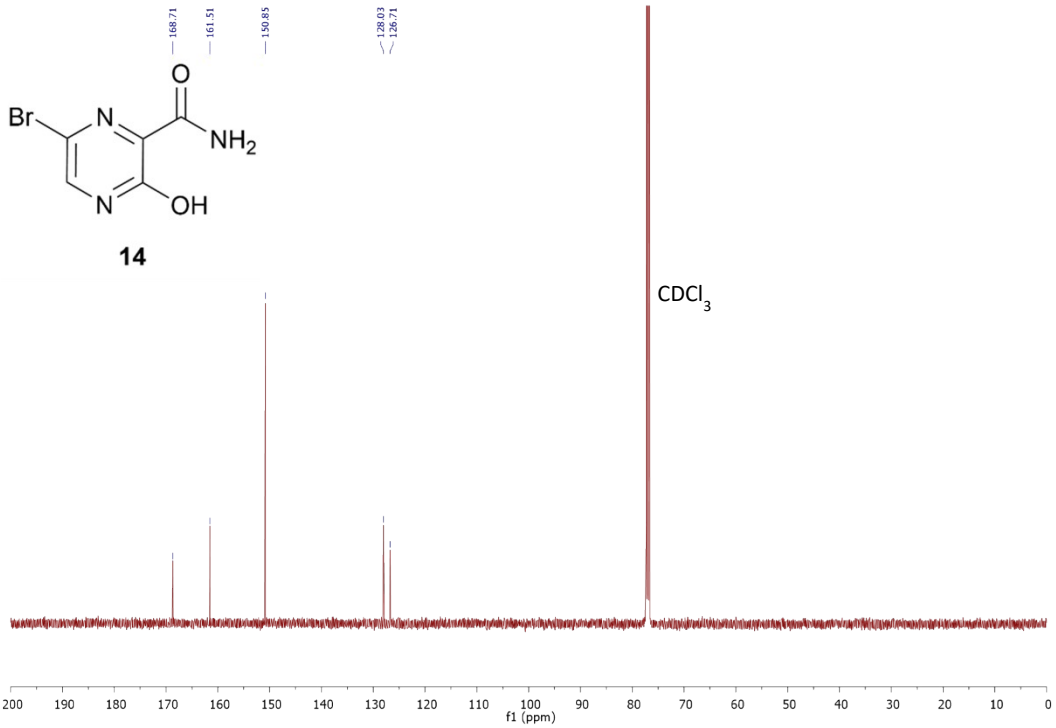
^{1}H NMR (DMSO-d_6) spectrum of sodium 2-carbamoylpyrazine-3-hydroxylate (**13**).



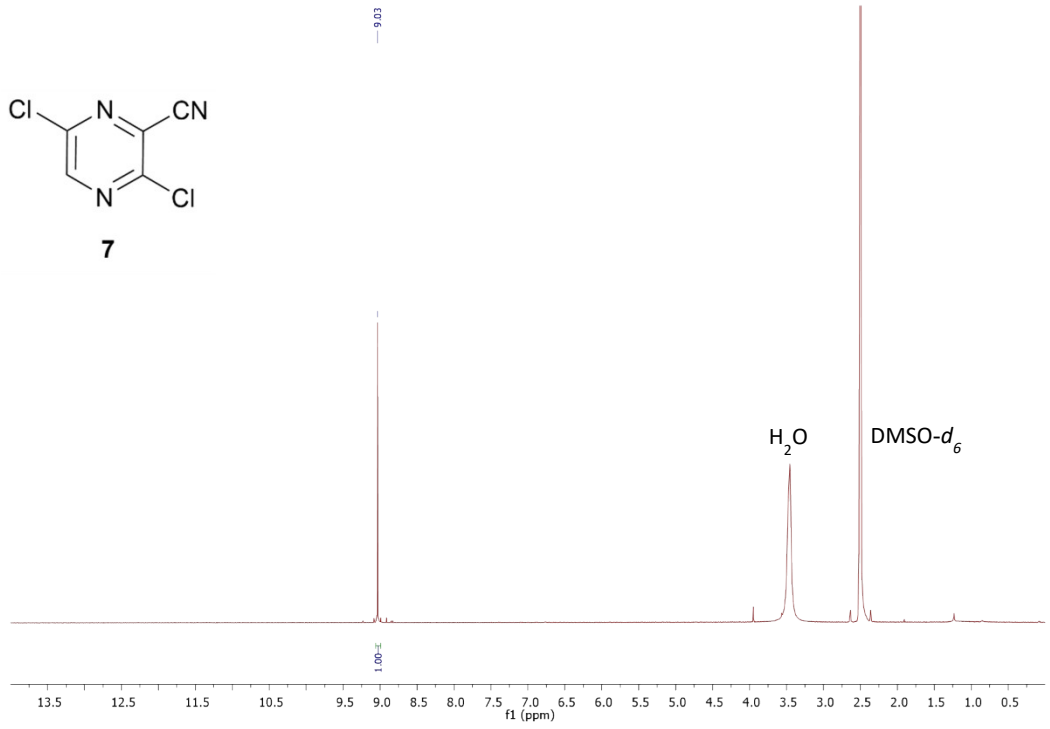
^{13}C NMR (DMSO-d_6) spectrum of sodium 2-carbamoylpyrazine-3-hydroxylate (**13**).



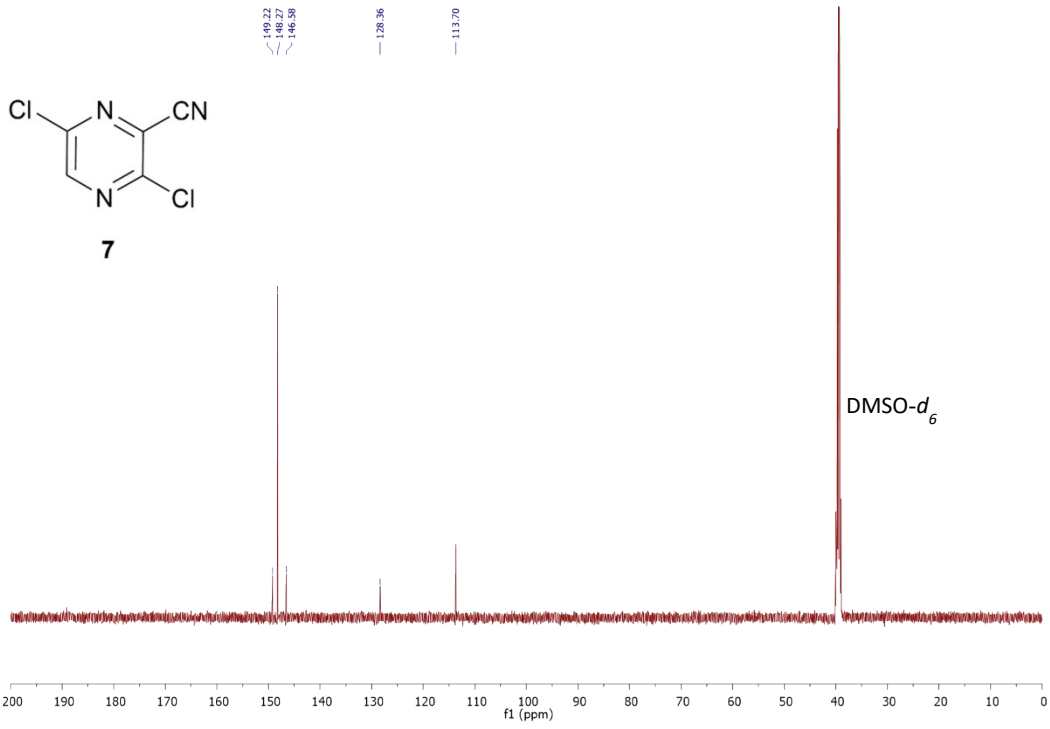
^{1}H NMR ($CDCl_3$) spectrum of 3-hydroxy-6-bromopyrazine-2-carboxamide (**14**).



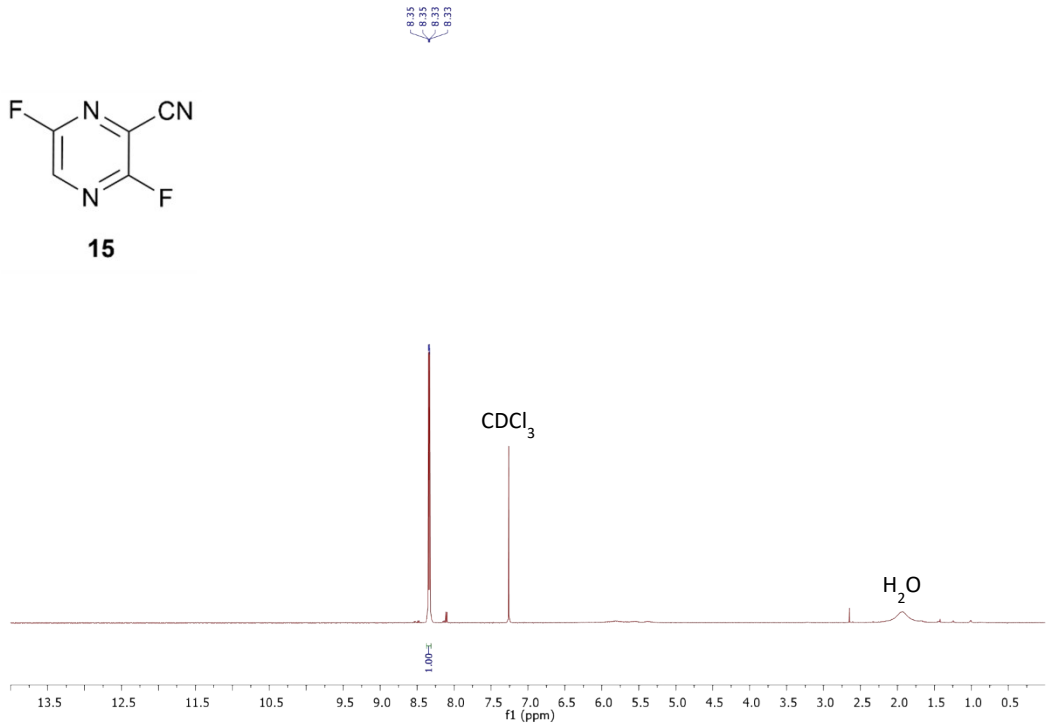
^{13}C NMR ($CDCl_3$) spectrum of 3-hydroxy-6-bromopyrazine-2-carboxamide (**14**).



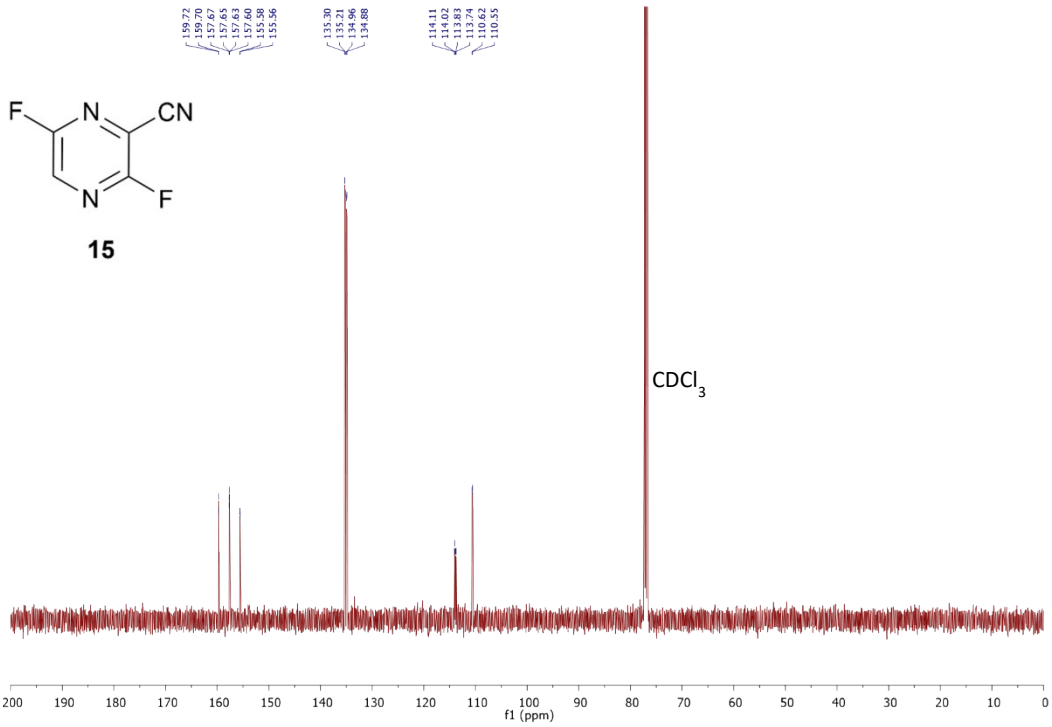
^{1}H NMR (DMSO-d_6) spectrum of 3,6-dichloropyrazine-2-carbonitrile (**7**).



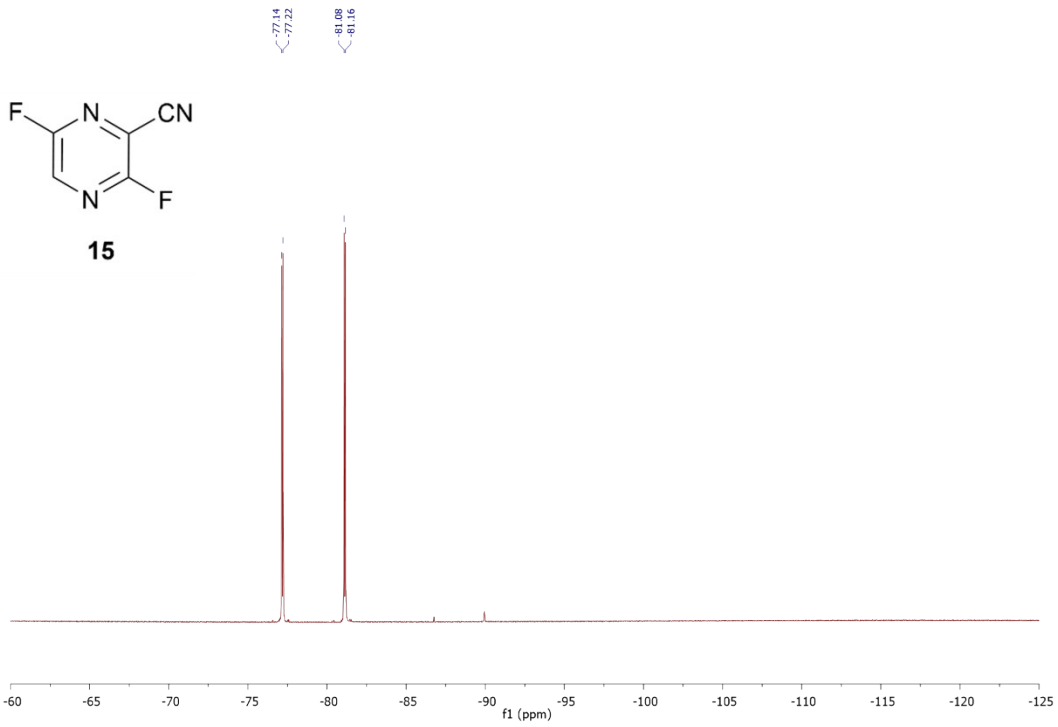
^{13}C NMR (DMSO-d_6) spectrum of 3,6-dichloropyrazine-2-carbonitrile (**7**).



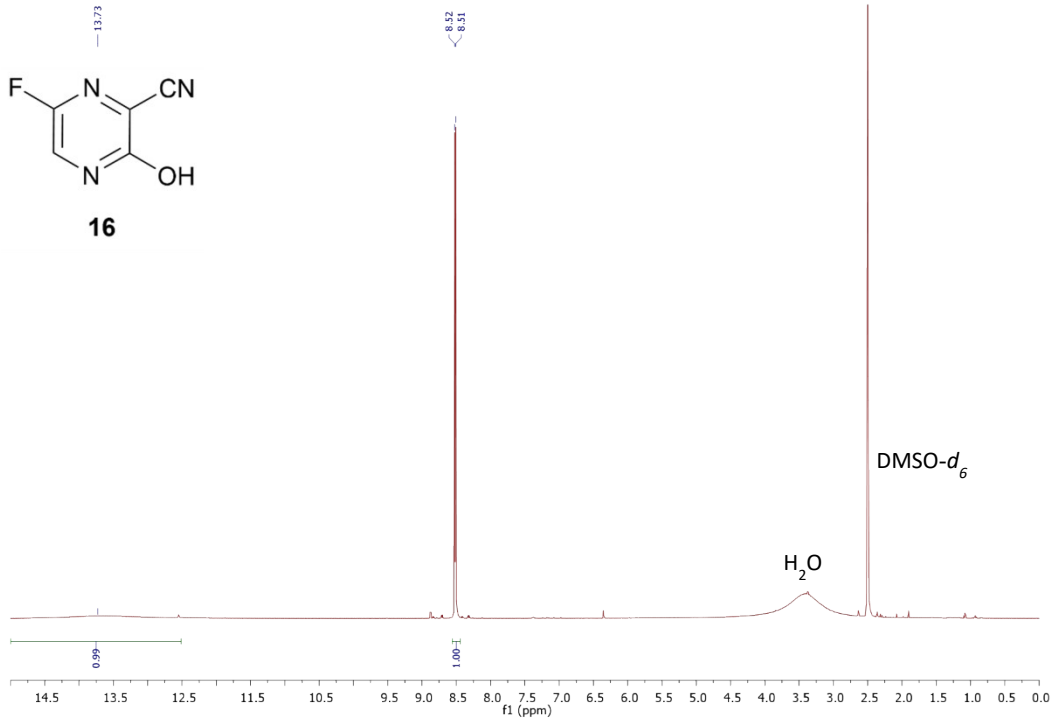
^{1}H NMR ($CDCl_3$) spectrum of 3,6-difluoropyrazine-2-carbonitrile (**15**).



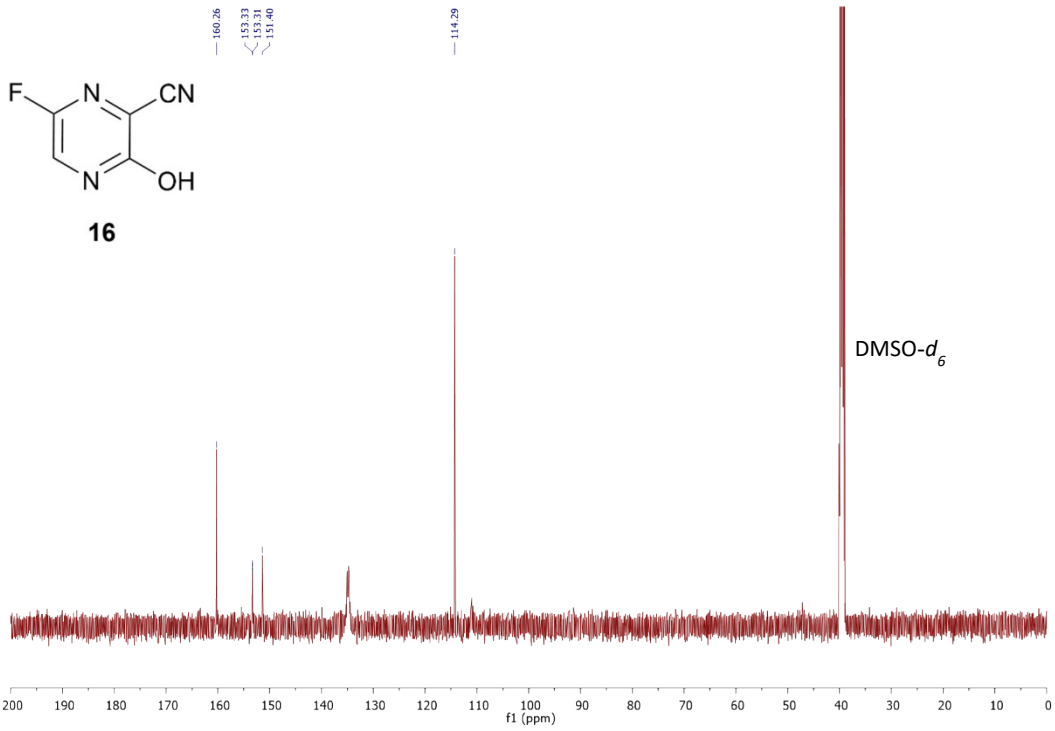
^{13}C NMR ($CDCl_3$) spectrum of 3,6-difluoropyrazine-2-carbonitrile (**15**).



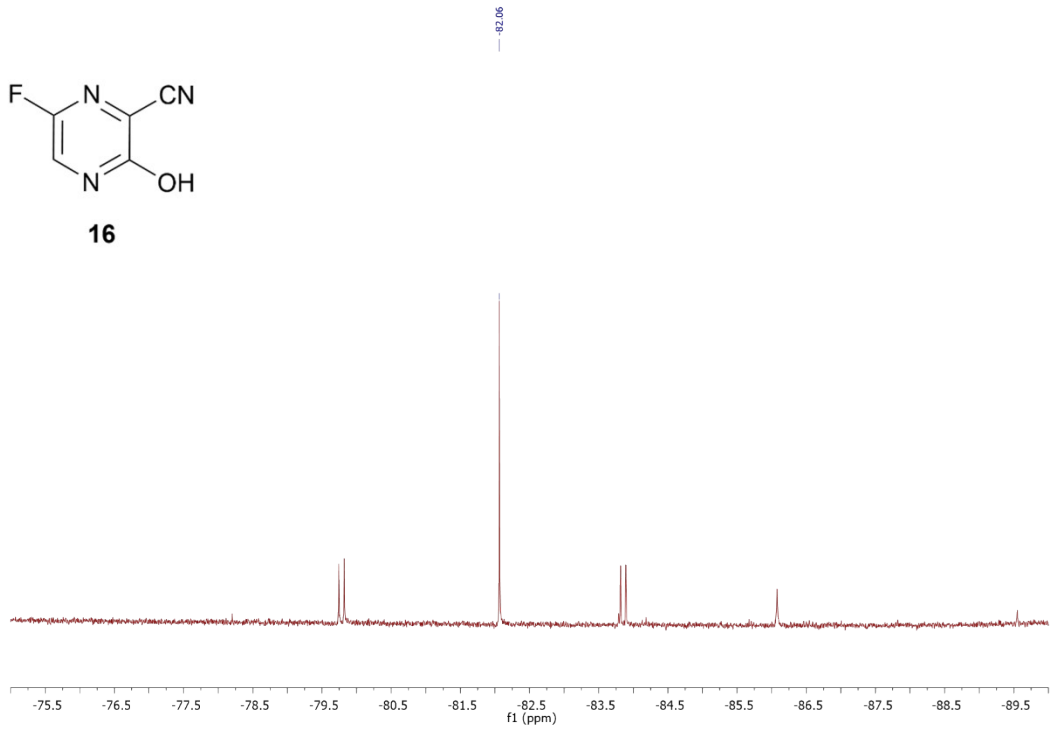
^{19}F NMR ($CDCl_3$) spectrum of 3,6-difluoropyrazine-2-carbonitrile (**15**).



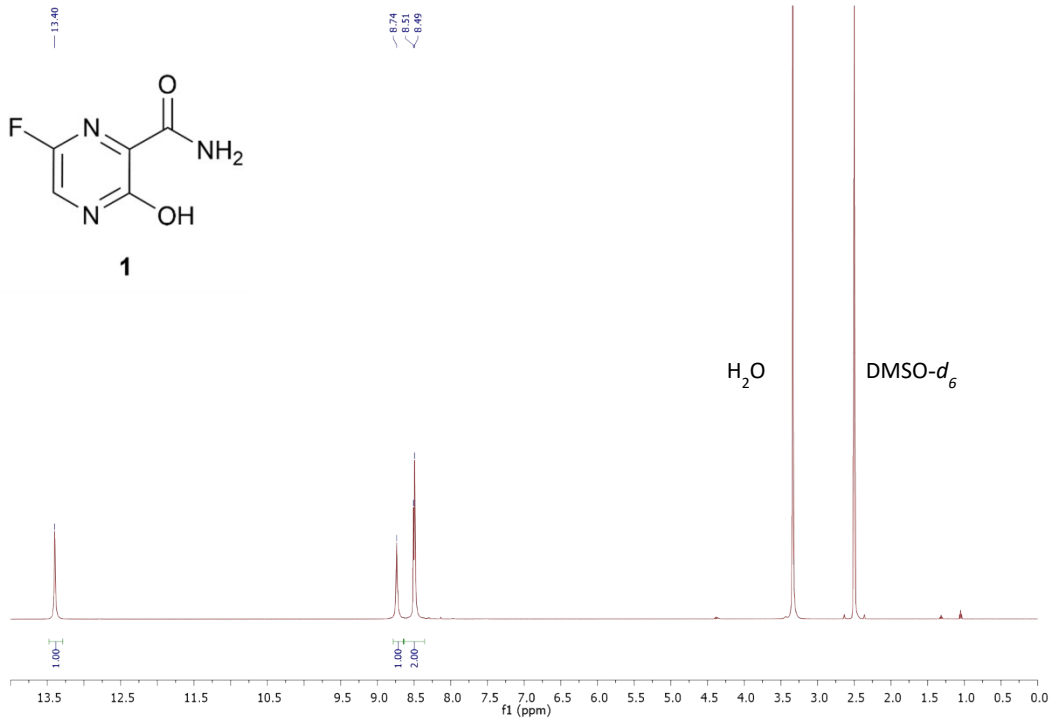
^{1}H NMR (DMSO-d_6) spectrum of 6-fluoro-3-hydroxypyrazine-2-carbonitrile (**16**).



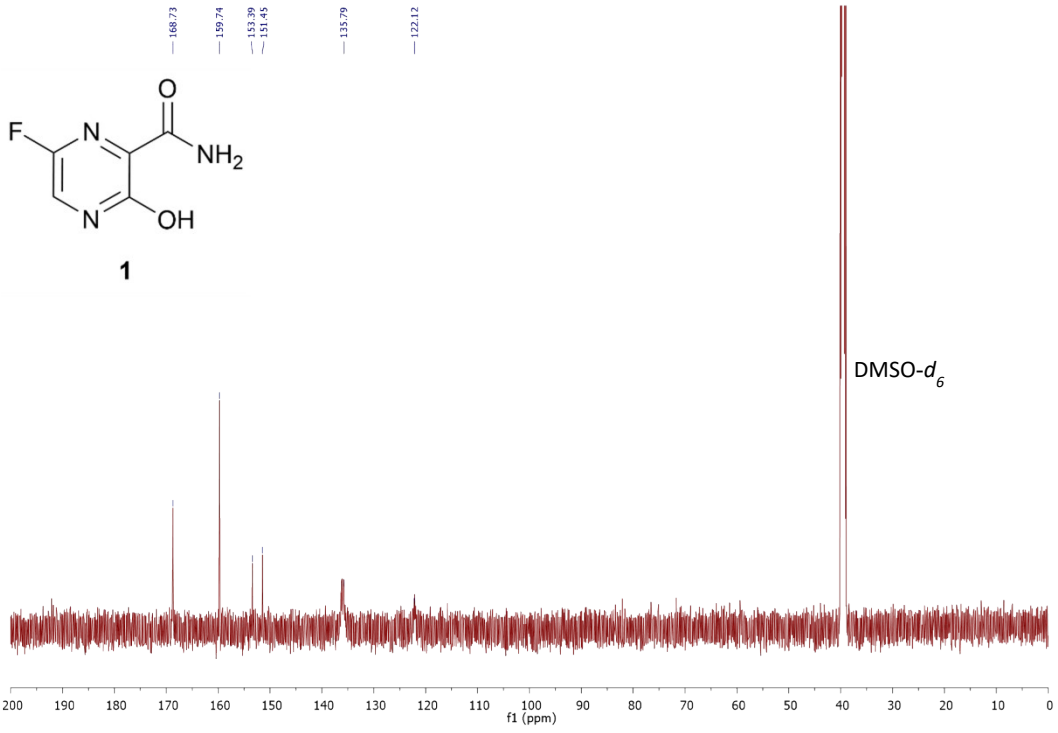
^{13}C NMR (DMSO-d_6) spectrum of 6-fluoro-3-hydroxypyrazine-2-carbonitrile (**16**).



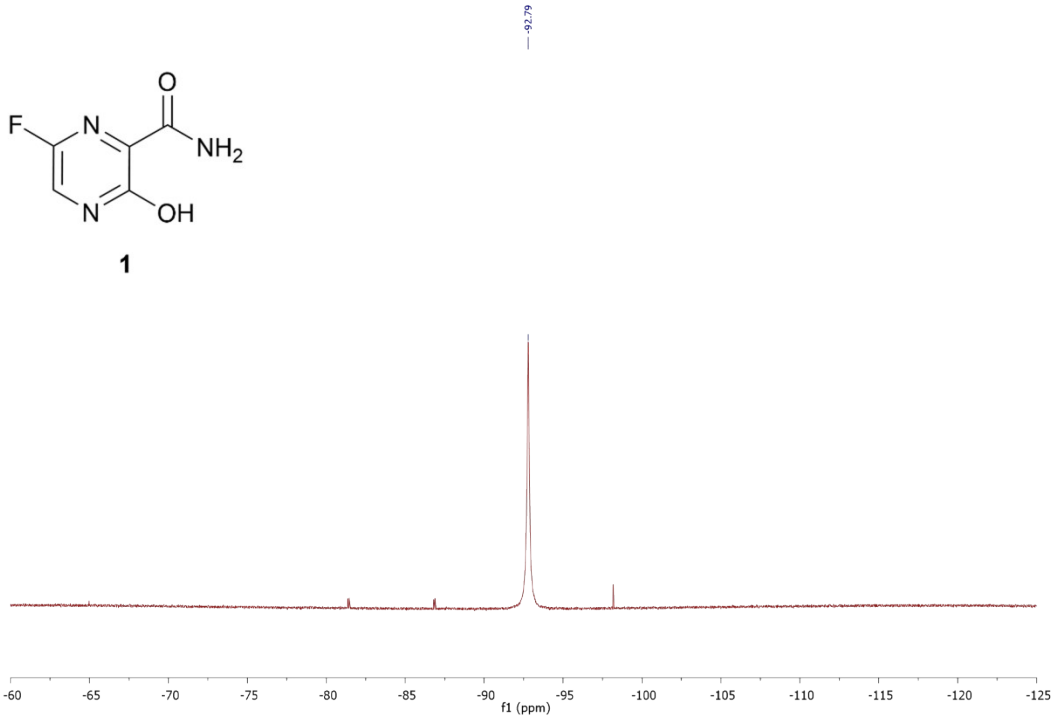
^{19}F NMR (DMSO-d_6) spectrum of 6-fluoro-3-hydroxypyrazine-2-carbonitrile (**16**).



^{1}H NMR (DMSO-d_6) spectrum of 6-fluoro-3-hydroxypyrazine-2-carboxamide (**1**).



^{13}C NMR (DMSO-d_6) spectrum of 6-fluoro-3-hydroxypyrazine-2-carboxamide (**1**).



^{19}F NMR (DMSO-d_6) spectrum of 6-fluoro-3-hydroxypyrazine-2-carboxamide (**1**).

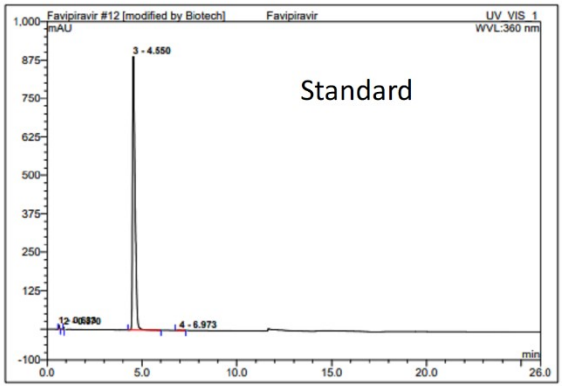
Purity determination of favipiravir

Ultra High Performance Liquid Chromatographs (HPLC) analysis

The purity of standard favipiravir (Toronto Research Chemicals (TRC), Canada) and our favipiravir were analyzed by UHPLC (general information, method A). The results showed 99.24% purity of standard favipiravir and 98.88% purity of our favipiravir.

(A)

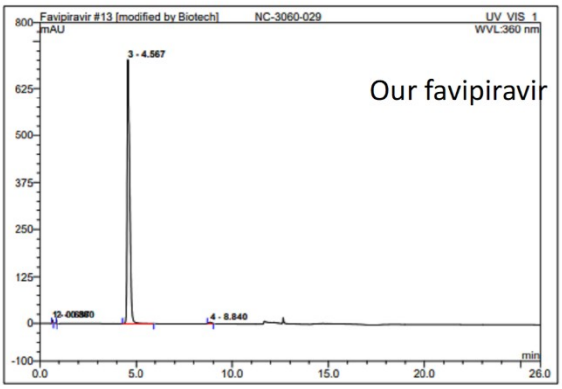
Sample Name:	Favipiravir	Injection Volume:	10.0
Vial Number:	GA1	Channel:	UV_VIS_1
Sample Type:	unknown	Wavelength:	360.0
Control Program:	2020 HPLC C6 Favipiravir 05 mL 9908W 00:	Bandwidth:	4
Quantif. Method:	Training	Dilution Factor:	1.0000
Recording Time:	7/14/2020 8:59	Sample Weight:	1.0000
Run Time (min):	26.00	Sample Amount:	1.0000



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	0.63	n.a.	12.314	0.647	0.49	n.a.	BMB*
2	0.87	n.a.	7.992	0.267	0.20	n.a.	BMB*
3	4.55	n.a.	889.312	132.271	99.24	n.a.	BMB
4	6.97	n.a.	0.504	0.103	0.08	n.a.	BMB
Total:			910.122	133.289	100.00	0.000	

(B)

Sample Name:	NC-3060-029	Injection Volume:	10.0
Vial Number:	GA2	Channel:	UV_VIS_1
Sample Type:	unknown	Wavelength:	360.0
Control Program:	2020 HPLC C6 Favipiravir 05 mL 9908W 00:	Bandwidth:	4
Quantif. Method:	Training	Dilution Factor:	1.0000
Recording Time:	7/14/2020 9:26	Sample Weight:	1.0000
Run Time (min):	26.00	Sample Amount:	1.0000



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	0.64	n.a.	7.946	0.359	0.33	n.a.	BMB*
2	0.86	n.a.	9.685	0.306	0.28	n.a.	BMB*
3	4.57	n.a.	702.791	108.208	98.88	n.a.	BMB*
4	8.84	n.a.	3.300	0.558	0.51	n.a.	BMB*
Total:			723.721	109.432	100.00	0.000	

Figure S.1 (A) UHPLC spectra of standard favipiravir (TRC Canada). (B) UHPLC spectra of our favipiravir.

Moisture determination

The water content of favipiravir was measured using Karl-Fischer titration. The results showed the average water content of favipiravir was 0.13% (specification: not more than 1.0%).

Table S.9 Water content analysis of favipiravir by Karl-Fischer titration.

Sample	water content	
	ppm	%
1	1126.4	0.11
2	1401.3	0.14
3	1253.6	0.13
Average	1260.4	0.13

Heavy metal determination

Heavy metal analysis of favipiravir was performed by inductively coupled plasma mass spectrometer (ICP-MS). The total heavy metal of favipiravir was 1.288 ppm (specification: not more than 10 ppm).

Table S.10 Heavy metal analysis of favipiravir by ICP-MS.

Entry	Test item	LOQ (ppm)	Result (ppm)
1	Arsenic (As)	0.050	<0.050
2	Cadmium (Cd)	0.050	<0.050
3	Cobalt (Co)	0.050	<0.050
4	Lead (Pb)	0.050	0.475
5	Nickel (Ni)	0.050	0.813
5	Palladium (Pd)	0.050	<0.050
6	Vanadium (V)	0.500	<0.500
7	Mercury (Hg)	0.005	<0.005
Total Heavy Metal			1.288

Single crystal X-ray diffraction (SC-XRD)

Number CCDC 2106319

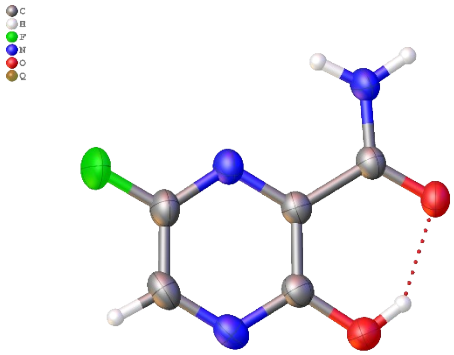


Figure S.2 X-ray crystal structure of favipiravir.