

SUPPLEMENTARY MATERIAL

Synthesis of *bis*-furyl-pyrrolo[3,4-*b*]pyridin-5-ones *via* Ugi-Zhu Reaction and *In Vitro* Activity Assays Against Human SARS-CoV-2 and *In Silico* Studies on its main Proteins

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1. Spectra

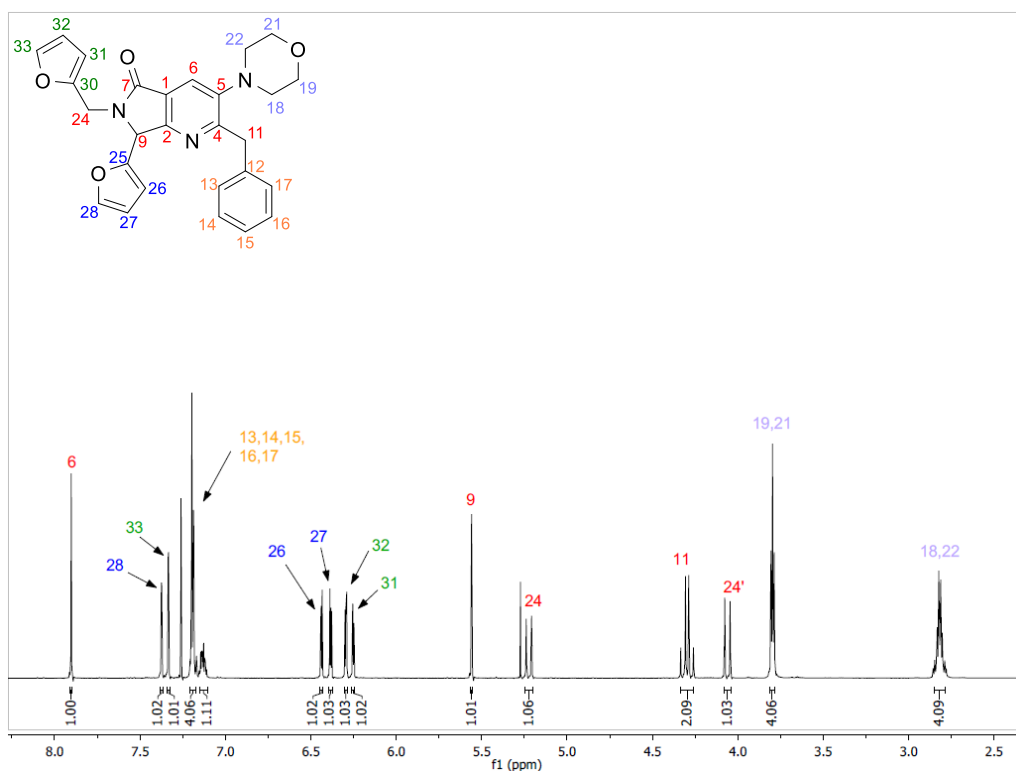


Figure S1. ¹H NMR spectrum of the compound 1a

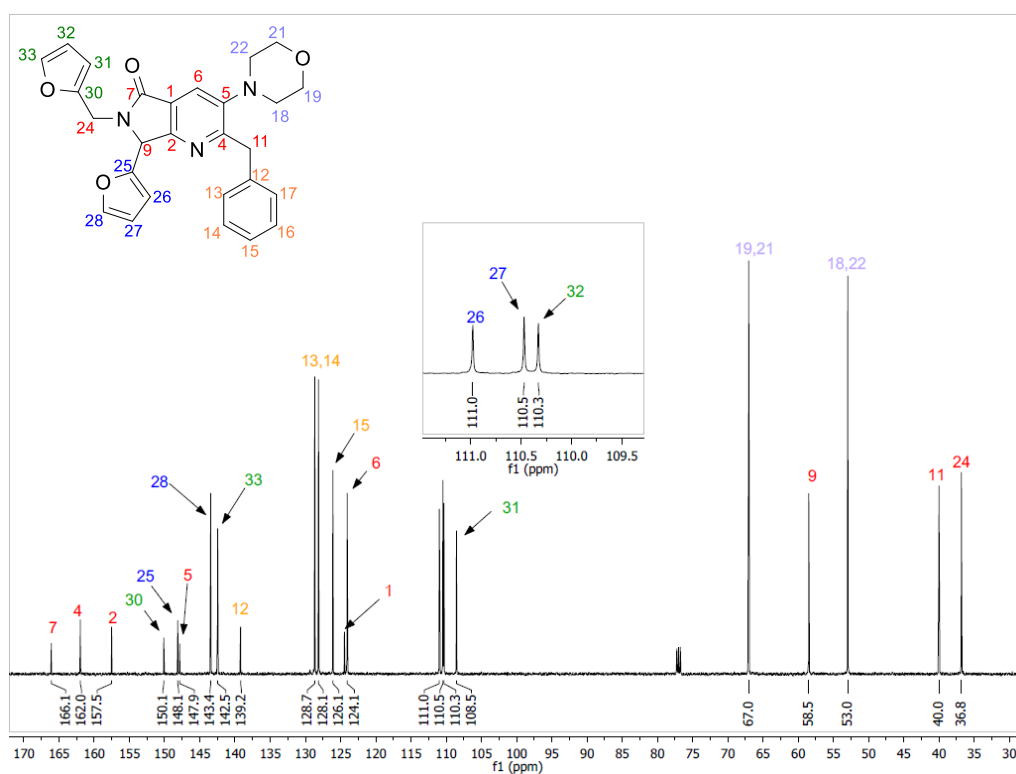


Figure S2. ¹³C NMR spectrum of the compound 1a

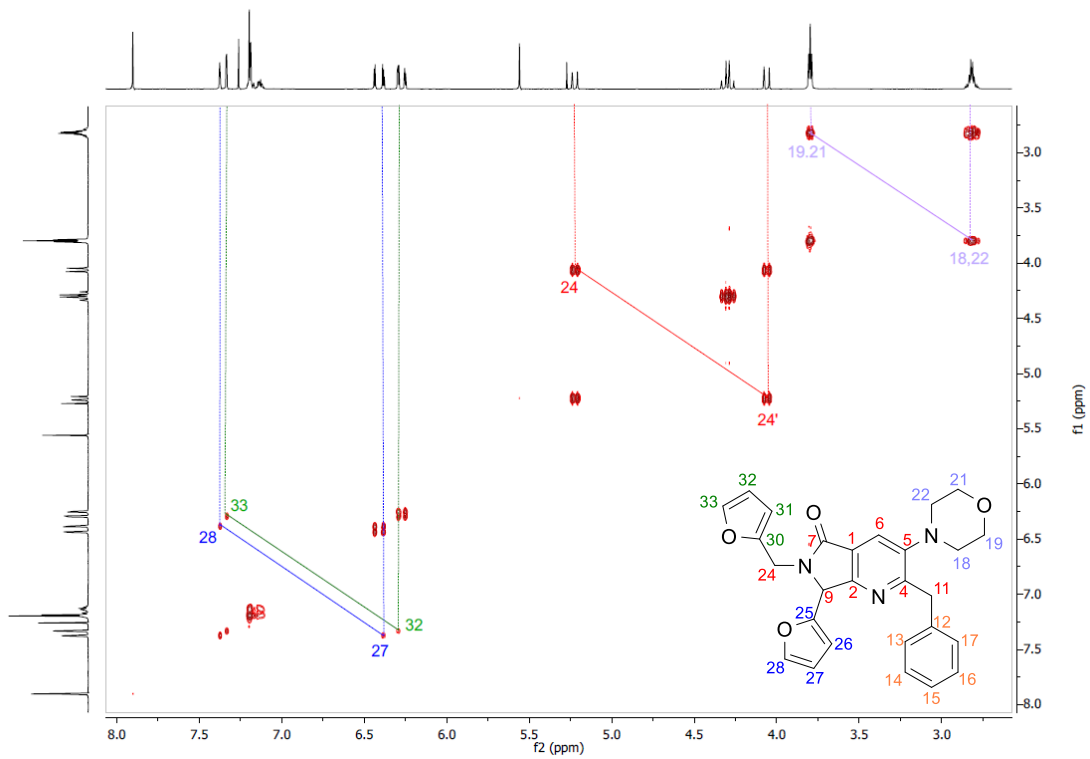


Figure S3. COSY spectrum of the compound 1a

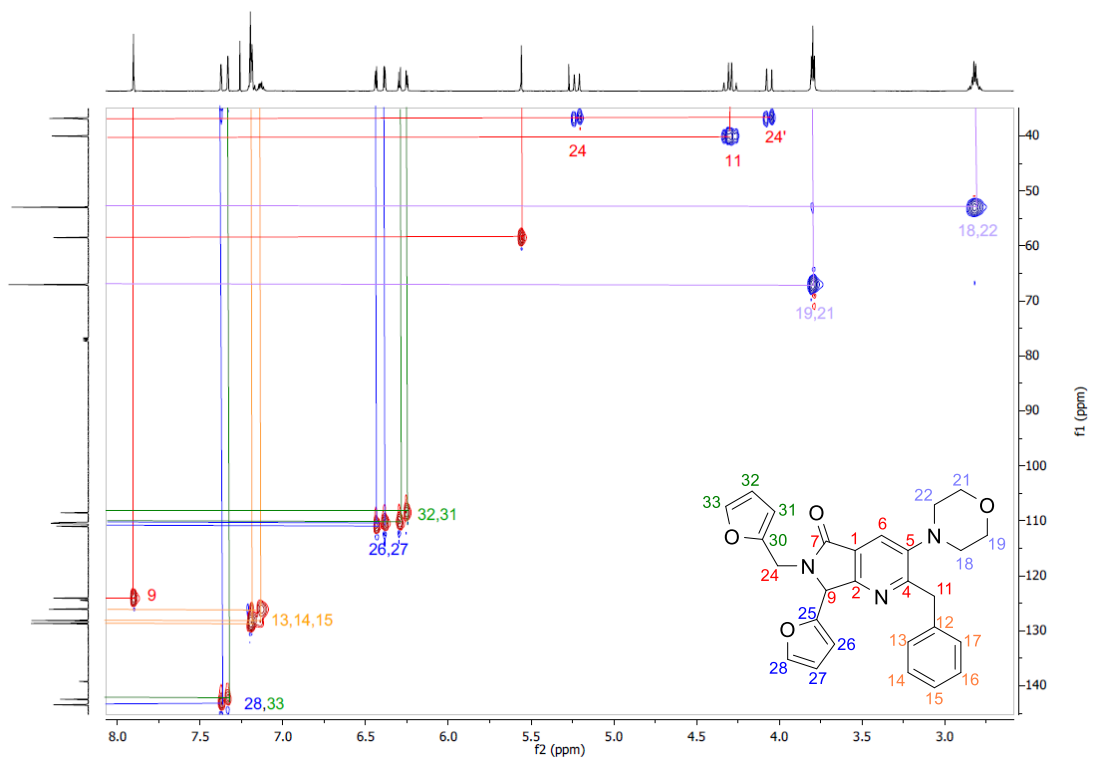


Figure S4. HSQC (^1H , ^{13}C) spectrum of the compound 1a

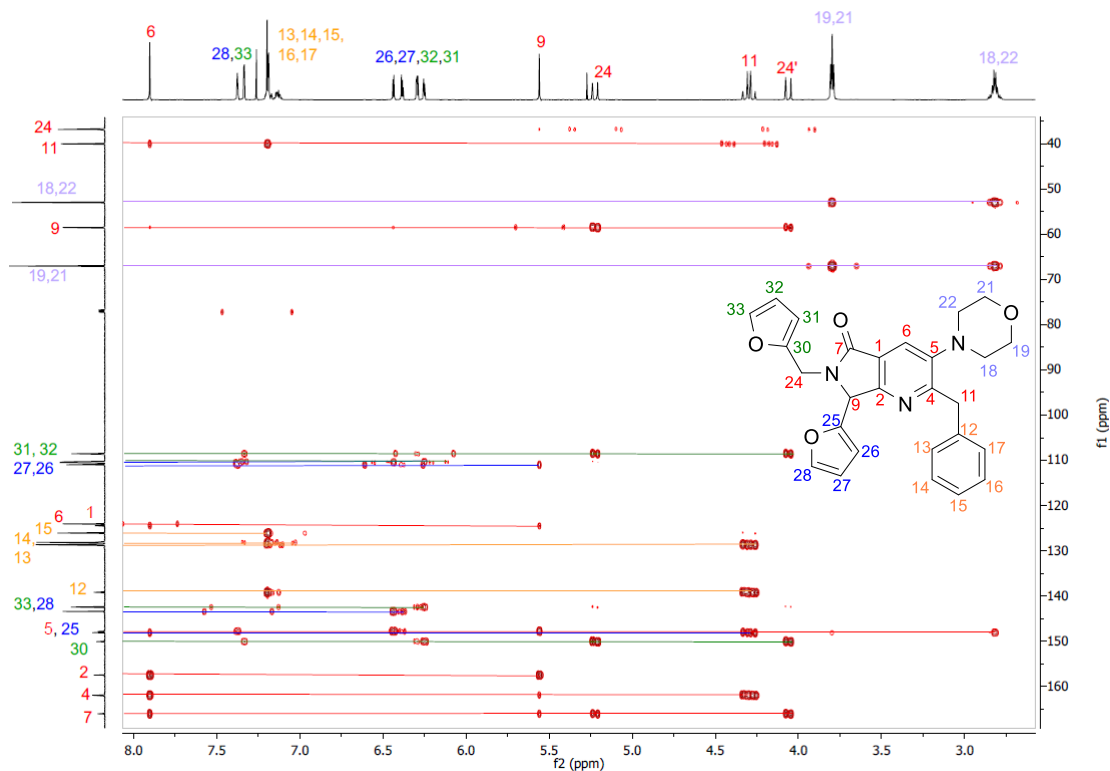
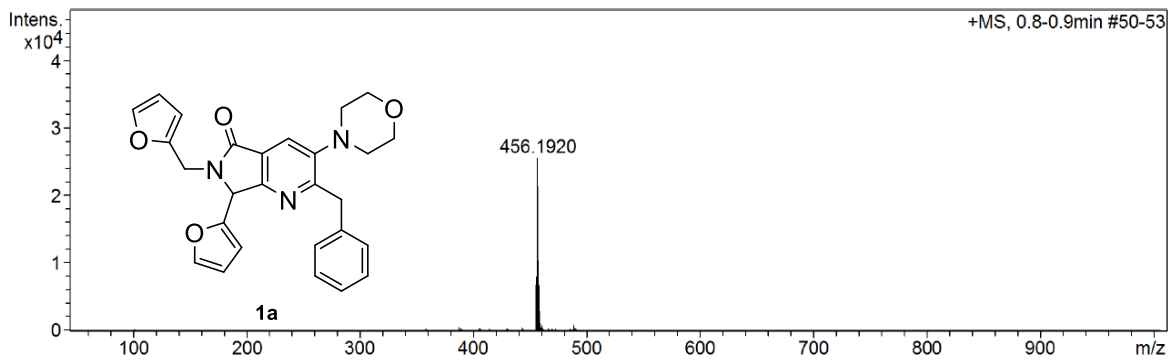


Figure S5. HMBC (^1H , ^{13}C) spectrum of the compound **1a**



Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	3.0 Bar
Focus	Active	Set Capillary	4500 V	Set Dry Heater	210 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	10.0 l/min
Scan End	1000 m/z	Set Charging Voltage	0 V	Set Divert Valve	Source
		Set Corona	0 nA	Set APCI Heater	0 °C

Meas. m/z	#	Ion Formula	Sum Formula	m/z	err [ppm]	mSigma	# Sigma
456.1920	1	C ₂₇ H ₂₆ N ₃ O ₄	C ₂₇ H ₂₆ N ₃ O ₄	456.1918	0.5	6.4	2

Figure S6. HRMS spectrum of the compound **1a**

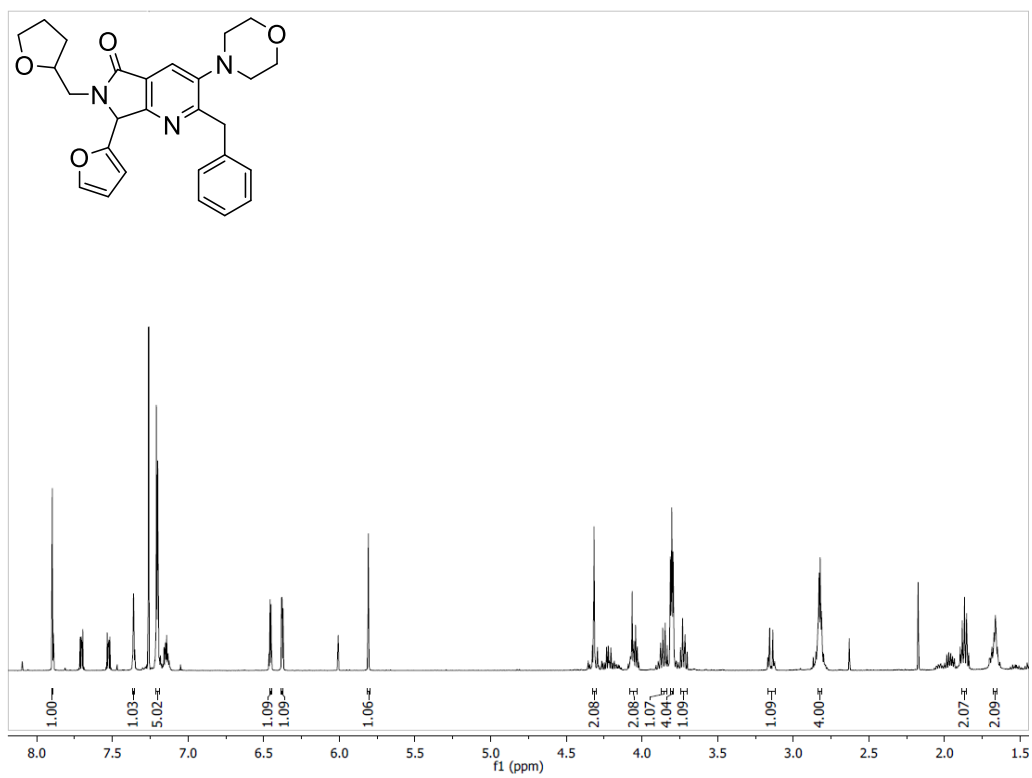


Figure S7. ¹H NMR spectrum of the compound **1b**

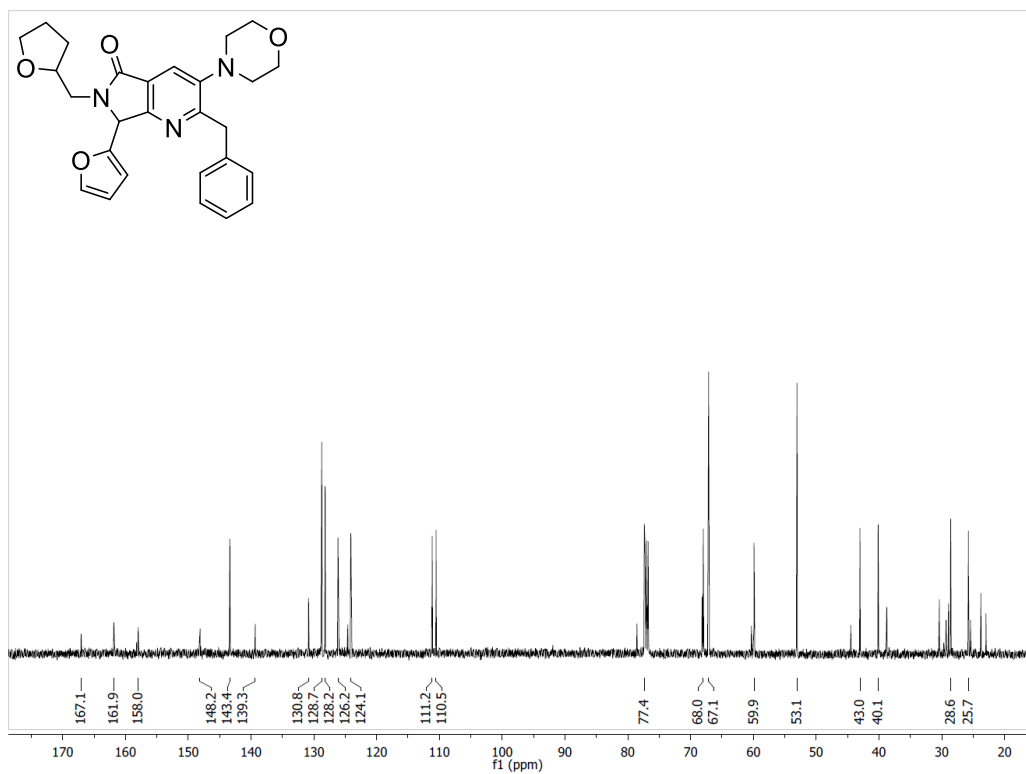
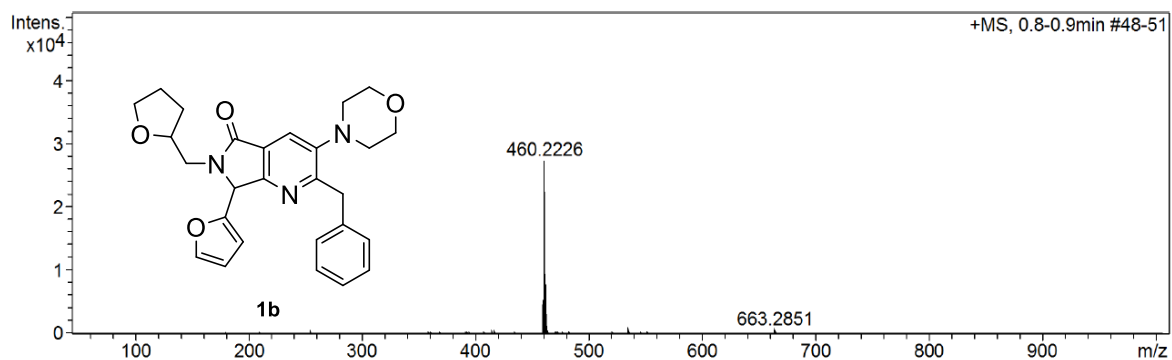


Figure S8. ¹³C NMR spectrum of the compound **1b**



Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	3.0 Bar
Focus	Active	Set Capillary	4500 V	Set Dry Heater	210 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	10.0 l/min
Scan End	1000 m/z	Set Charging Voltage	0 V	Set Divert Valve	Source
		Set Corona	0 nA	Set APCI Heater	0 °C

Meas. m/z	#	Ion Formula	Sum Formula	m/z	err [ppm]	mSigma	# Sigma
460.2226	1	C ₂₇ H ₃₀ N ₃ O ₄	C ₂₇ H ₂₉ N ₃ O ₄	460.2231	1.1	21.2	1

Figure S9. HRMS spectrum of the compound **1b**

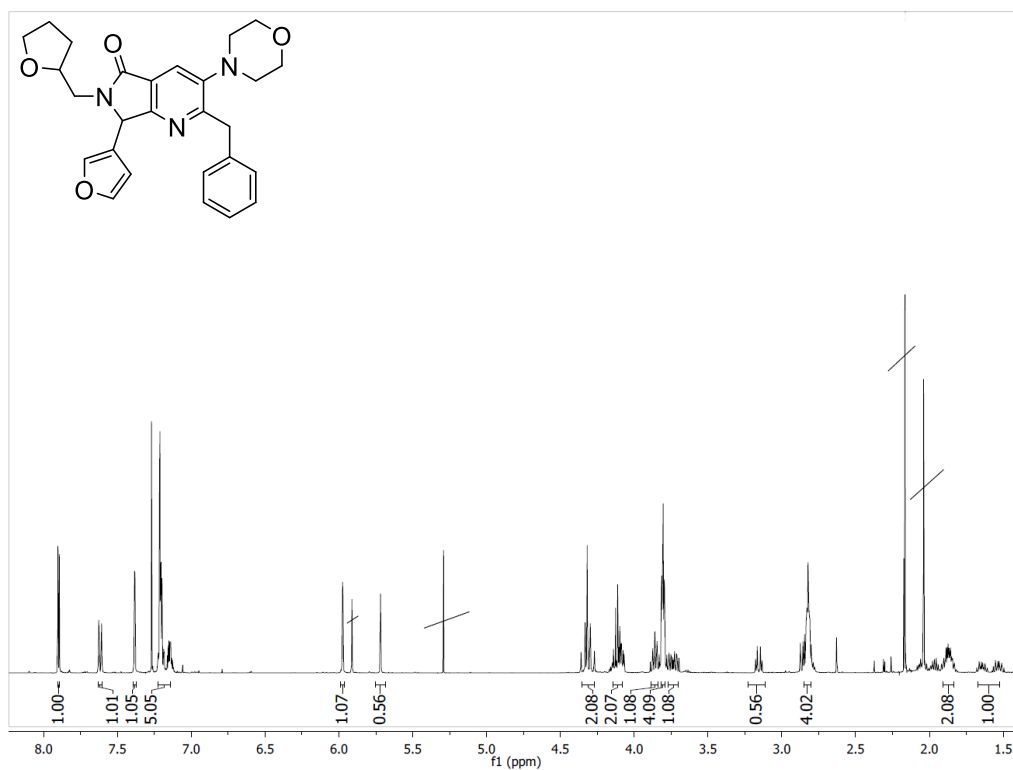


Figure S10. ¹H NMR spectrum of the compound **1c**

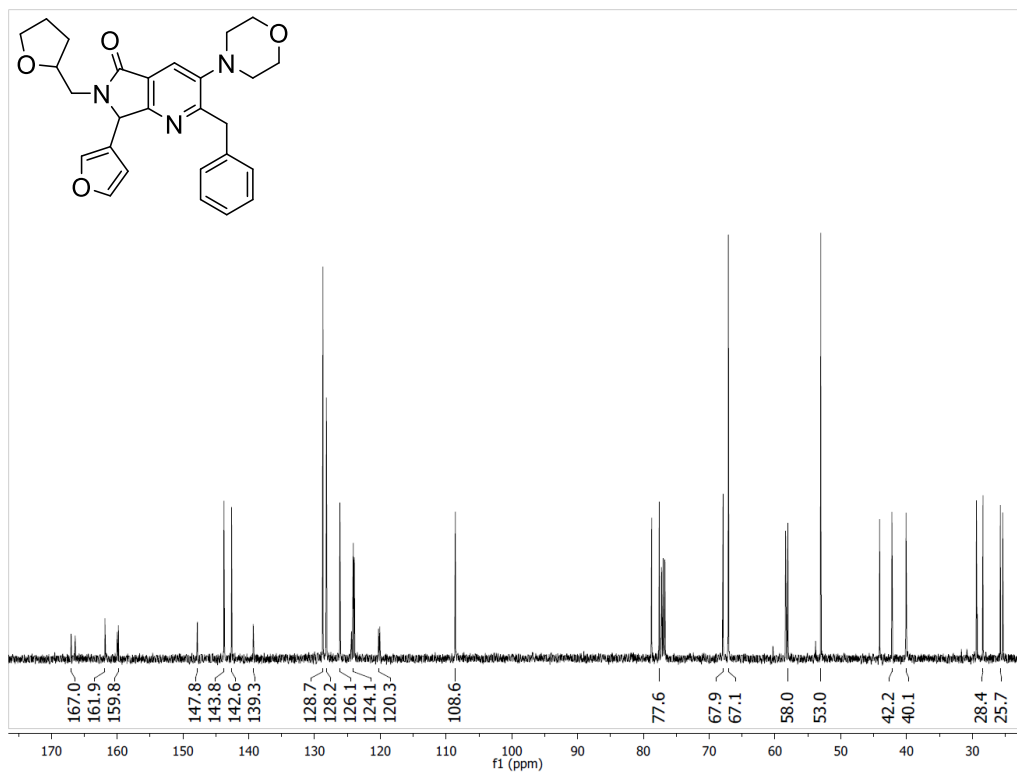
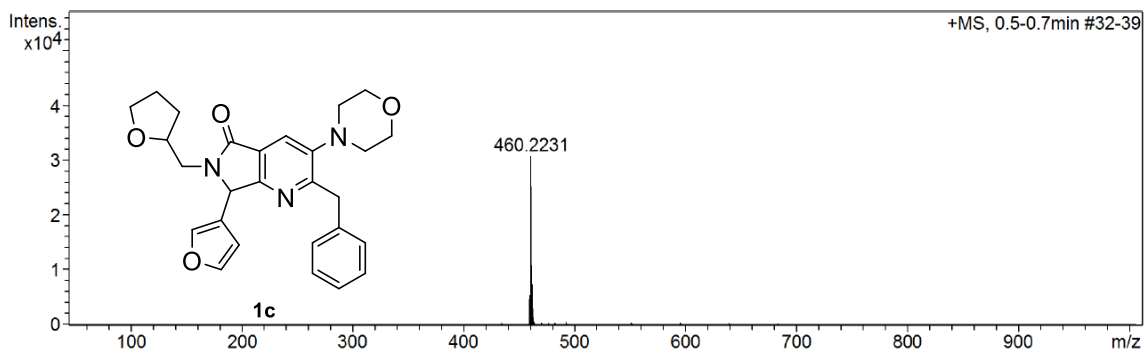


Figure S11. ¹³C NMR spectrum of the compound 1c



Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	3.0 Bar
Focus	Active	Set Capillary	4500 V	Set Dry Heater	210 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	10.0 l/min
Scan End	1000 m/z	Set Charging Voltage	0 V	Set Divert Valve	Source
		Set Corona	0 nA	Set APCI Heater	0 °C

Meas. m/z	#	Ion Formula	Sum Formula	m/z	err [ppm]	mSigma	# Sigma
460.2231	1	C ₂₇ H ₃₀ N ₃ O ₄	C ₂₇ H ₂₉ N ₃ O ₄	460.2231	0.1	5.8	1

Figure S12. HRMS spectrum of the compound 1c

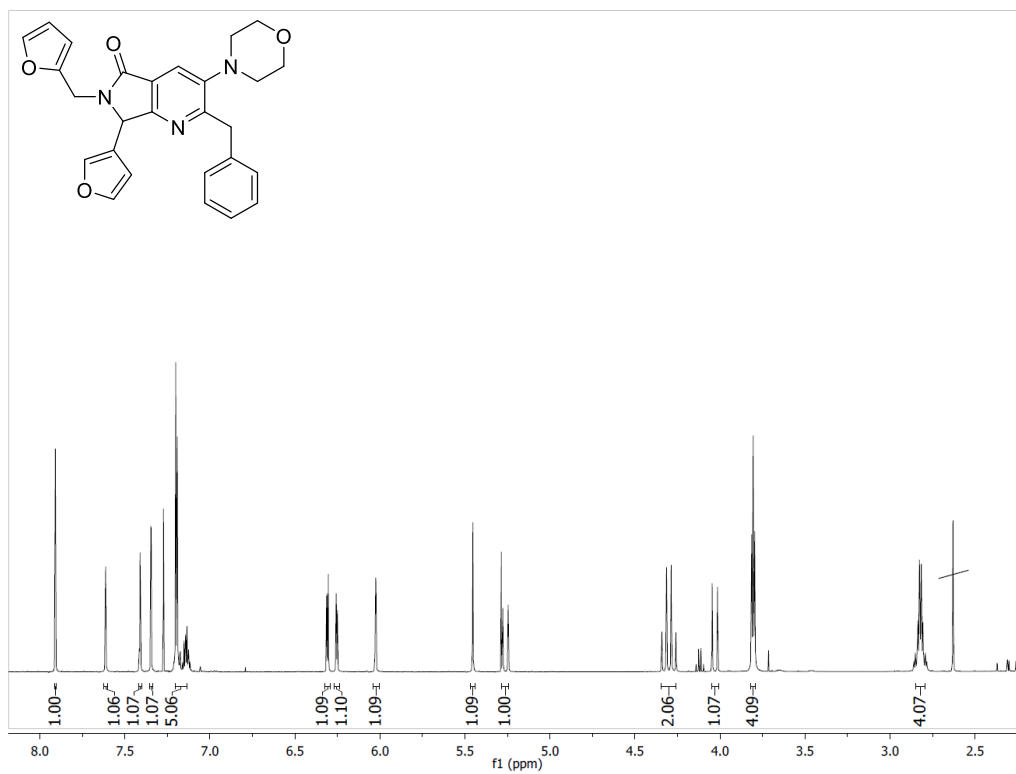


Figure S13. ¹H NMR spectrum of the compound 1d

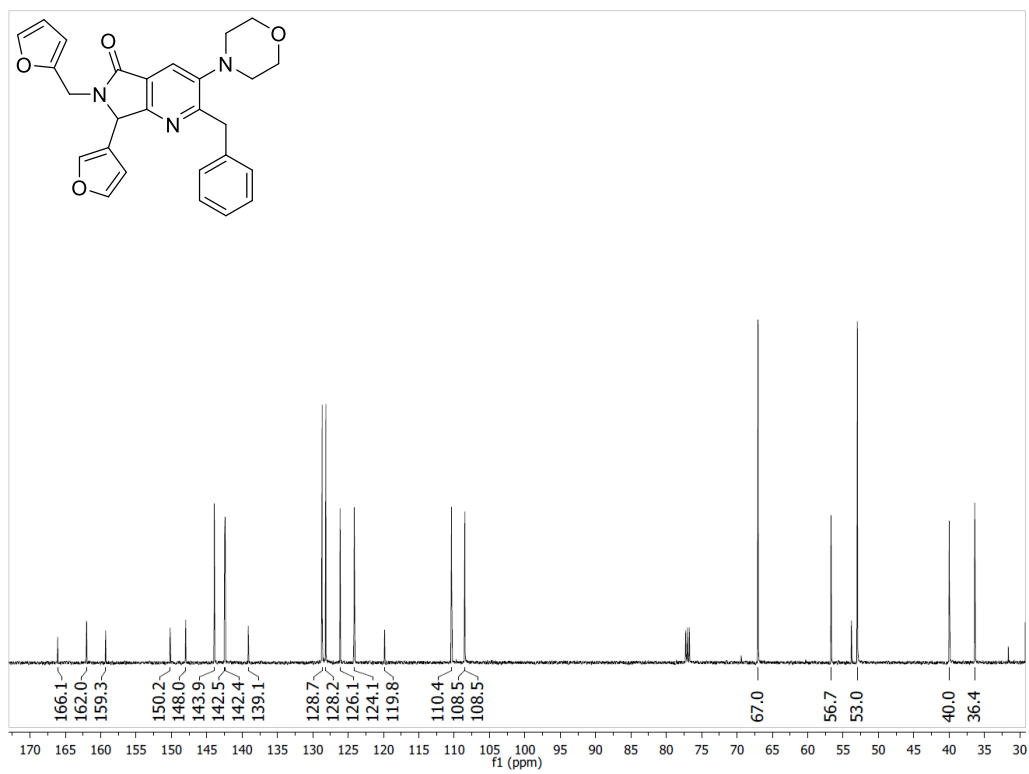
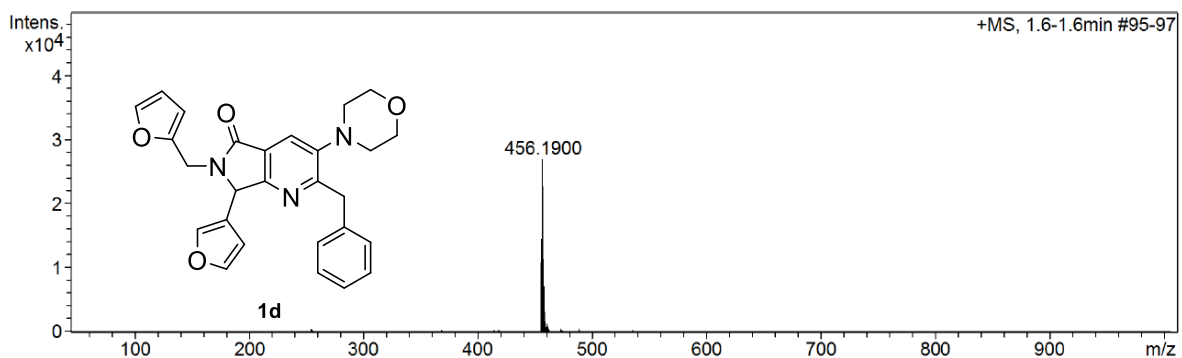


Figure S14. ¹³C NMR spectrum of the compound 1d



Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	3.0 Bar
Focus	Active	Set Capillary	4500 V	Set Dry Heater	210 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	10.0 l/min
Scan End	1000 m/z	Set Charging Voltage	0 V	Set Divert Valve	Source
		Set Corona	0 nA	Set APCI Heater	0 °C

Meas. m/z	#	Ion Formula	Sum Formula	m/z	err [ppm]	mSigma	# Sigma
456.1900	1	C ₂₈ H ₂₂ N ₇	C ₂₈ H ₂₁ N ₇	456.1931	6.9	11.0	1
	2	C ₂₇ H ₂₆ N ₃ O ₄	C ₂₇ H ₂₅ N ₃ O ₄	456.1918	-4.0	11.5	2

Figure S15. HRMS spectrum of the compound **1d**

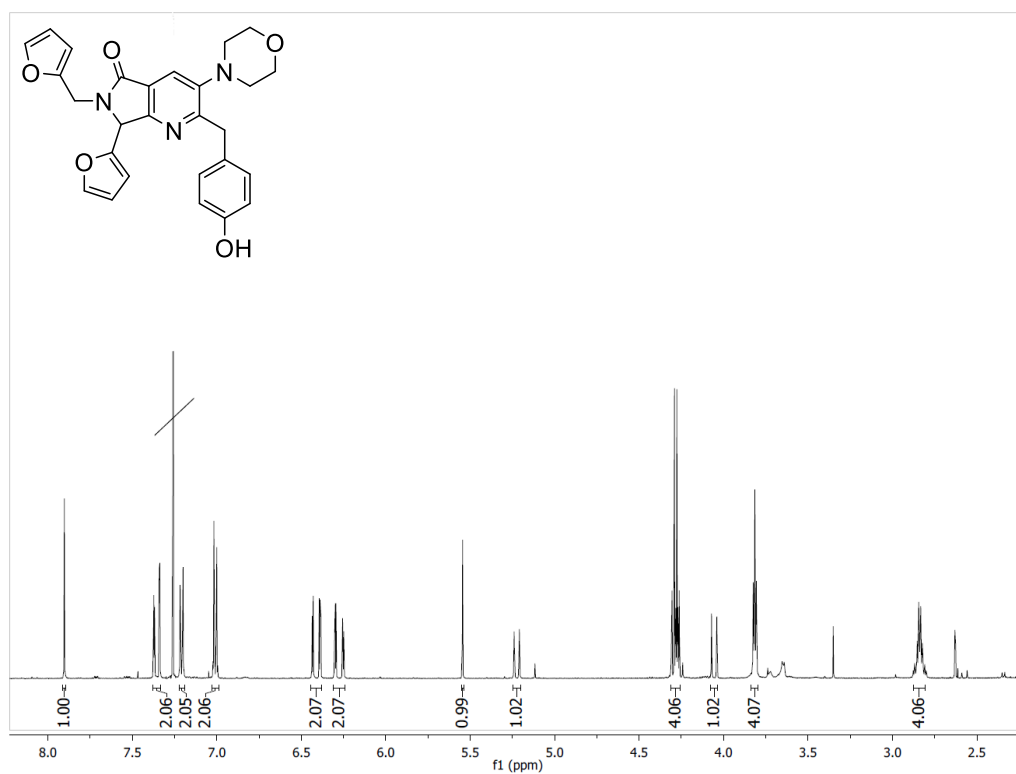


Figure S16. ¹H NMR spectrum of the compound **1e**

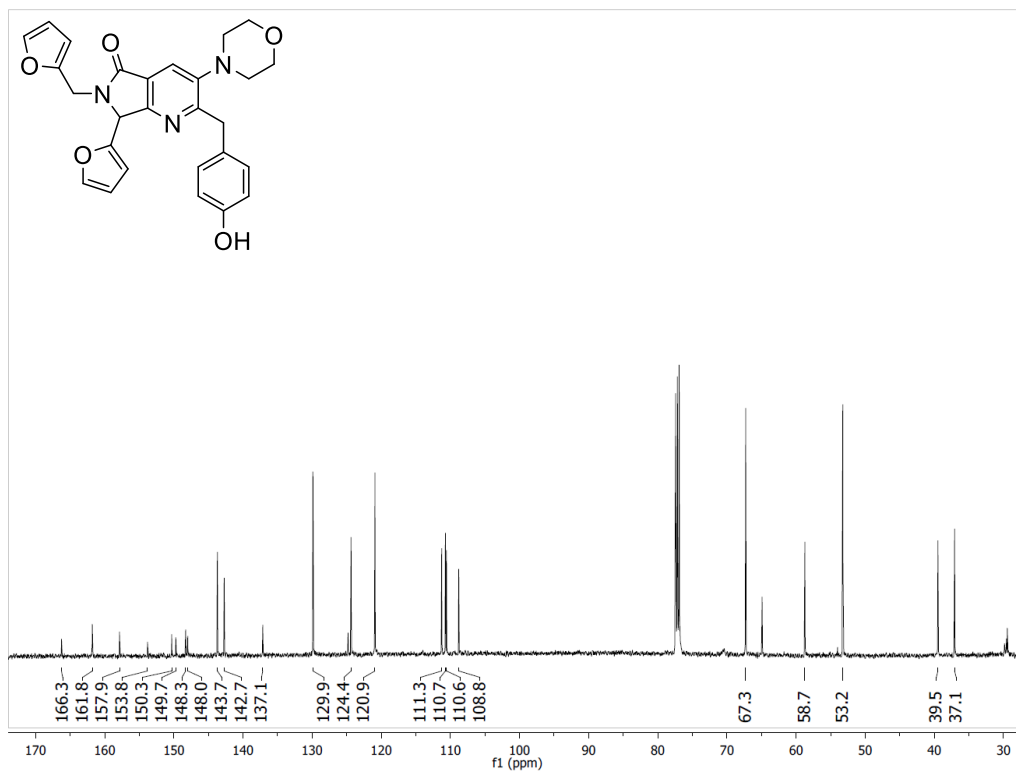
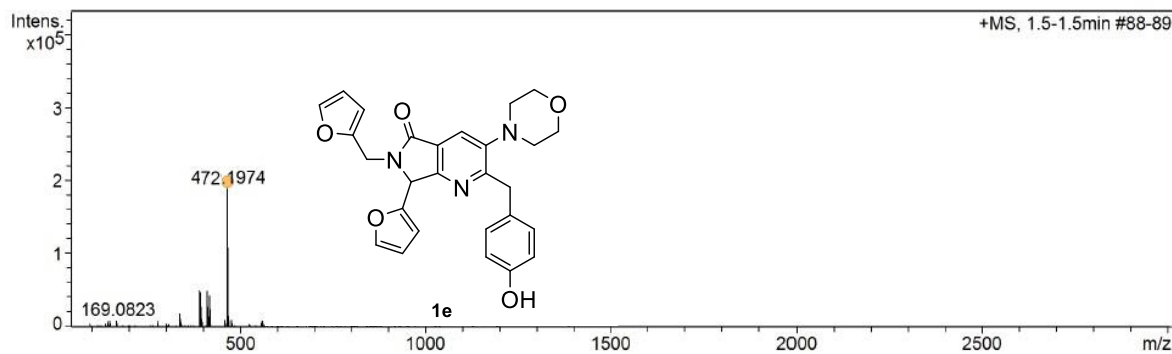


Figure S17. ^{13}C NMR spectrum of the compound **1e**



Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.3 Bar
Focus	Active			Set Dry Heater	180 °C
Scan Begin	50 m/z	Set Capillary	4500 V	Set Dry Gas	4.0 l/min
Scan End	3000 m/z	Set End Plate Offset	-500 V	Set Divert Valve	Waste

Meas. m/z	#	Ion Formula	Sum Formula	m/z	err [ppm]	mSigma	# Sigma
472.1974	1	C ₂₇ H ₂₆ N ₃ O ₅	C ₂₇ H ₂₅ N ₃ O ₅	472.1978	0.8	191.4	1

Figure S18. HRMS spectrum of the compound **1e**

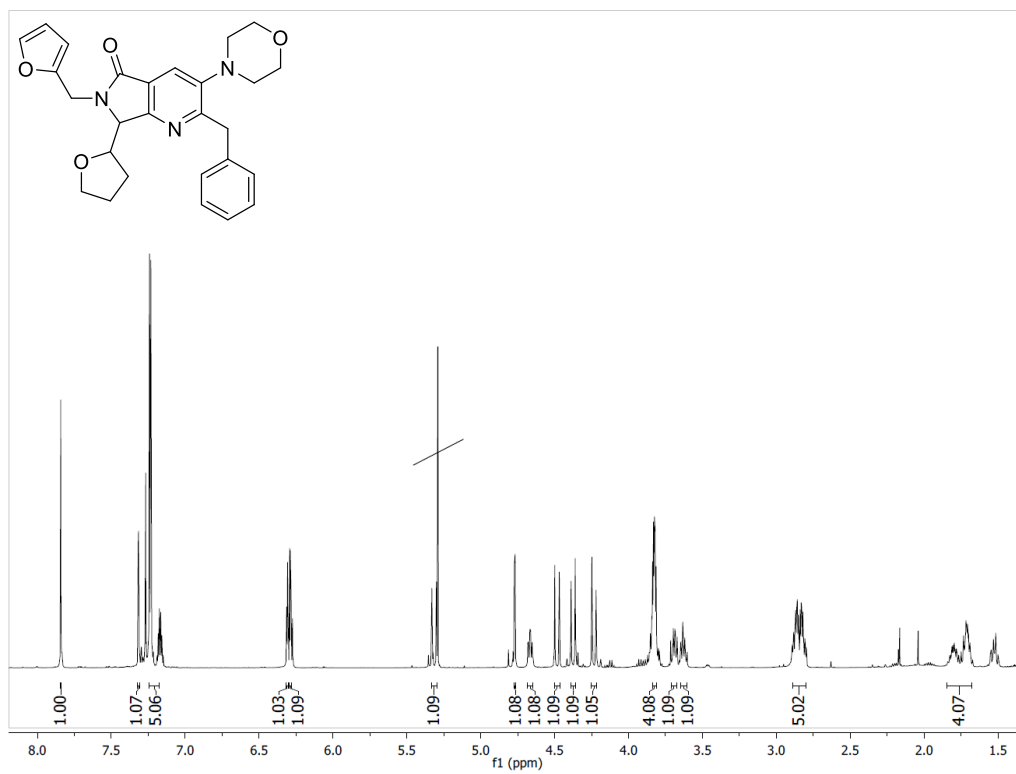


Figure S19. ¹H NMR spectrum of the compound **1f**

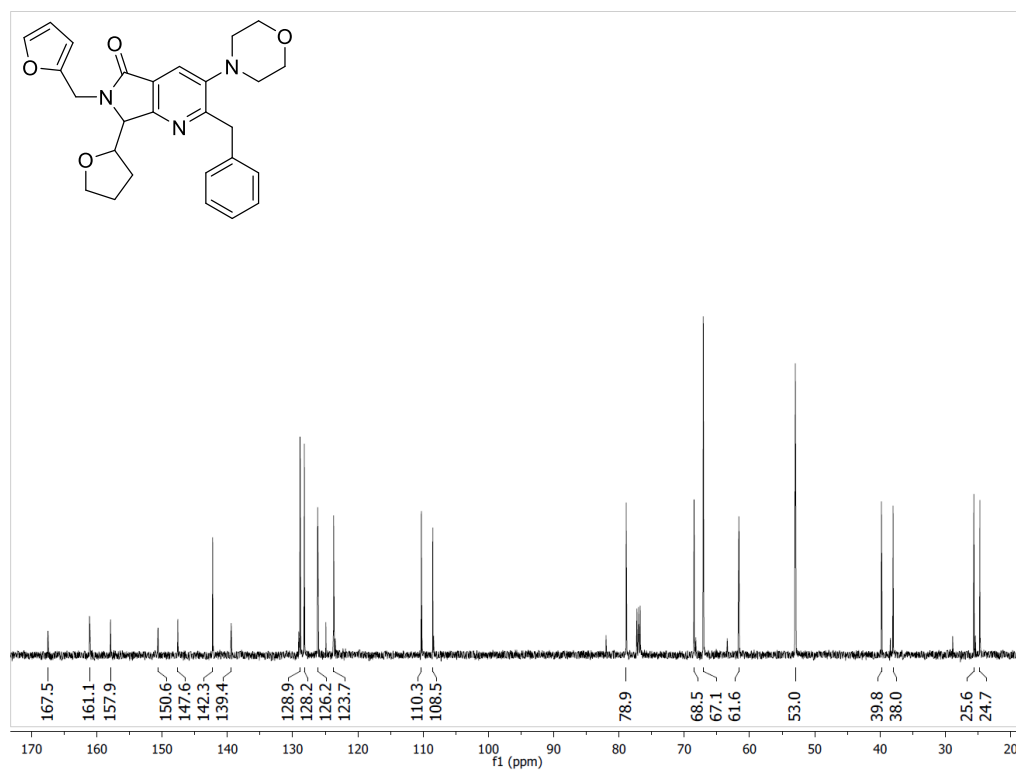
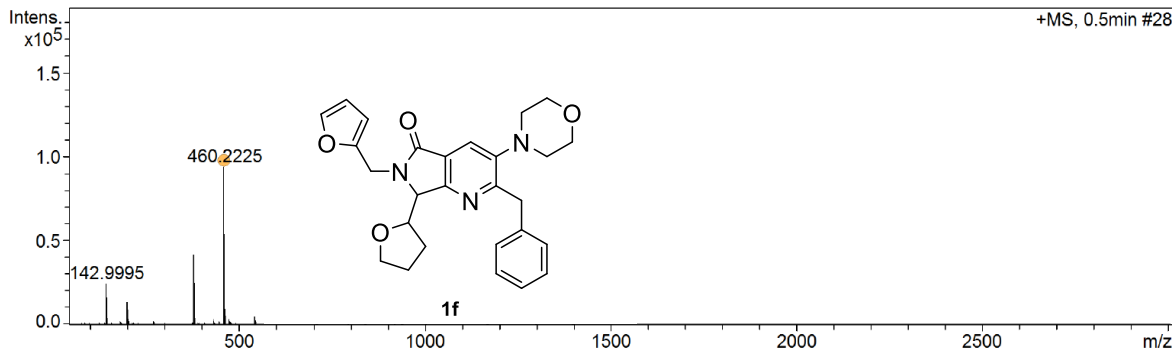


Figure S20. ¹³C NMR spectrum of the compound **1f**



Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.3 Bar
Focus	Active			Set Dry Heater	180 °C
Scan Begin	50 m/z	Set Capillary	4500 V	Set Dry Gas	4.0 l/min
Scan End	3000 m/z	Set End Plate Offset	-500 V	Set Divert Valve	Waste

Meas. m/z	#	Ion Formula	Sum Formula	m/z	err [ppm]	mSigma	# Sigma
460.2225	1	C27H30N3O4	C27 H29 N3 O4	460.2231	-1.3	86.4	1

Figure S21. HRMS spectrum of the compound **1f**

2. Docking

Cartesian coordinates of bioactive conformations

1e in SARS-CoV-2-M^{Pro}

C	-11.50970	11.74480	70.23320
C	-11.66100	10.48970	70.80910
C	-12.62350	10.24370	71.73020
N	-13.48440	11.21310	72.12880
C	-13.40530	12.46900	71.59410
C	-12.40680	12.76760	70.62390
C	-10.92280	9.26630	70.63980
C	-12.59660	8.81830	72.18240
H	-10.58390	16.95490	70.66620
C	-14.38720	13.51240	72.05680
N	-12.33220	14.09750	70.06310
H	-10.72740	11.91810	69.50640
O	-9.92440	9.16530	69.94260
N	-11.42800	8.19380	71.47010
C	-13.94860	8.18880	71.90470
H	-12.38910	8.80130	73.27480
C	-11.73620	6.99350	70.66320
H	-11.40260	7.12310	69.60790
H	-12.83110	6.80490	70.66520
C	-11.10480	5.77560	71.27700
C	-14.28160	6.96410	72.29340
O	-14.96670	8.86560	71.25270
H	-13.65770	6.25550	72.82850
C	-15.64040	6.78520	71.86010
H	-16.27000	5.91130	71.98880

C	-15.97570	7.92010	71.26630
H	-10.57940	3.62420	73.57280
C	-10.21510	5.01110	70.65600
O	-11.41230	5.35370	72.55860
C	-9.88280	3.97770	71.59840
H	-11.72170	15.47620	67.00870
H	-12.99490	15.98610	68.15870
C	-10.60860	4.23390	72.67610
H	-15.17140	13.02040	72.67240
H	-14.89900	13.96560	71.18020
H	-14.67070	16.22470	71.76220
C	-13.69580	14.60950	72.82460
C	-12.77340	14.29260	73.83500
C	-12.14500	15.30780	74.56130
C	-12.42050	16.65210	74.28690
C	-13.33550	16.97240	73.26530
C	-13.96390	15.95750	72.53800
H	-12.54840	13.25830	74.06510
H	-11.44150	15.04840	75.34240
O	-11.78350	17.62410	75.02900
H	-13.56520	18.00490	73.03430
C	-12.04300	14.06910	68.61960
C	-11.36250	14.94010	70.77960
C	-11.34940	16.33780	70.15050
H	-10.33760	14.50950	70.72630
H	-11.65810	15.02830	71.84820
C	-11.99340	15.50550	68.08480
H	-12.84410	13.51260	68.08520
H	-11.06770	13.57550	68.41300
H	-12.33340	16.83940	70.29610
O	-11.01820	16.26430	68.77580
H	-9.82290	5.14560	69.65300
H	-9.18630	3.15650	71.46720
H	-16.95280	8.09860	70.83030
H	-12.45710	18.09160	75.58690

1d in SARS-CoV-2 Nsp3

C	33.09850	-36.25790	9.38940
C	33.98870	-36.46670	8.34380
C	34.34190	-35.46580	7.50270
N	33.85030	-34.21050	7.65070
C	32.97530	-33.92770	8.66290
C	32.57380	-34.95480	9.56440
C	34.67960	-37.64700	7.89550
C	35.30040	-35.94660	6.45930
H	28.29560	-34.93400	11.16190
C	32.44070	-32.52510	8.78310
N	31.64500	-34.64750	10.62820

H	32.82430	-37.07670	10.04100
O	34.53070	-38.75410	8.39040
N	35.51290	-37.39860	6.73840
C	35.40280	-35.95820	3.83030
H	34.69660	-35.75210	1.83880
C	36.92780	-37.67750	7.04980
H	37.02930	-38.18530	8.03780
H	37.49650	-36.72300	7.10080
C	37.55340	-38.49300	5.95350
C	34.49250	-35.69910	2.90300
H	39.09360	-37.12820	5.28920
H	32.71000	-35.21340	5.50890
O	33.25060	-35.35310	3.41000
C	33.47910	-35.42370	4.77240
H	36.43530	-36.24760	3.66490
H	37.90990	-41.05210	4.08310
C	38.57530	-38.07880	5.21520
O	37.10160	-39.76020	5.62940
C	38.84790	-39.16050	4.30850
H	31.29230	-35.43340	13.92400
H	31.06000	-33.81430	13.19710
C	37.96140	-40.10000	4.60060
H	31.35190	-32.57380	9.00300
H	32.55260	-31.99290	7.81340
H	34.03470	-30.31360	8.46030
C	33.17750	-31.74590	9.84210
C	33.09600	-32.13250	11.19110
C	33.76750	-31.40130	12.17560
C	34.52980	-30.28510	11.82120
C	34.62580	-29.90080	10.48130
C	33.95650	-30.62930	9.49330
H	32.50710	-32.99470	11.47880
H	33.69610	-31.69960	13.21350
H	35.04750	-29.71890	12.58470
H	35.21630	-29.03610	10.20800
C	32.03510	-35.28240	11.89810
C	30.26310	-34.99680	10.26520
C	29.32990	-34.62700	11.42390
H	30.16440	-36.08520	10.05440
H	29.95660	-34.42800	9.35990
C	31.02080	-34.90650	12.98510
H	33.04230	-34.92430	12.20520
H	32.06470	-36.39060	11.80310
H	29.31980	-33.52370	11.57850
O	29.71380	-35.30000	12.60900
C	34.72140	-35.77140	5.08200
H	39.61490	-39.20960	3.54290
H	36.23690	-35.34840	6.54510

3. Cell viability

Table. Cell viability at 100 μ M in Vero-E6 cells

Compound	Cell viability (%)
1a	73.64
1b	36.17
1c	76.21
1d	42.64
1e	65.46
1f	82.64