Crystal Structure, Spectroscopy, DFT, and Thermal Studies of 3-Cyano-2(1*H*)-Pyridones as Potential Anticancer Agents

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SUPPORTING INFORMATION

1. Copies of FT–IR spectra for compounds 4a–c

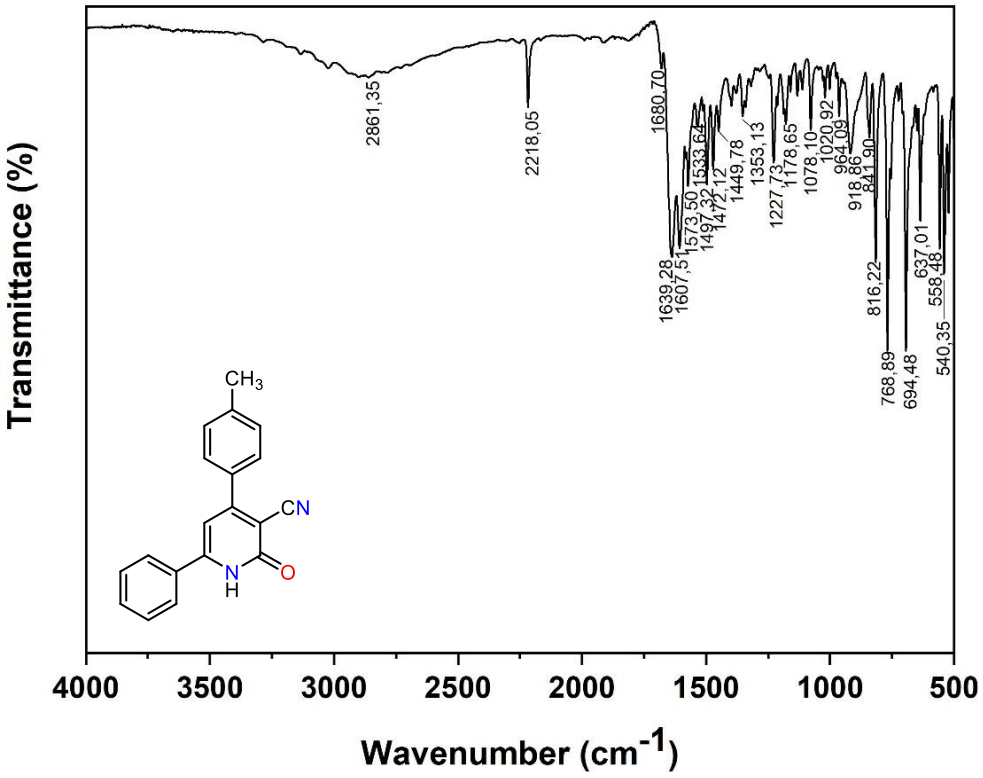


Figure S1. FT–IR spectrum for compound **4a**.

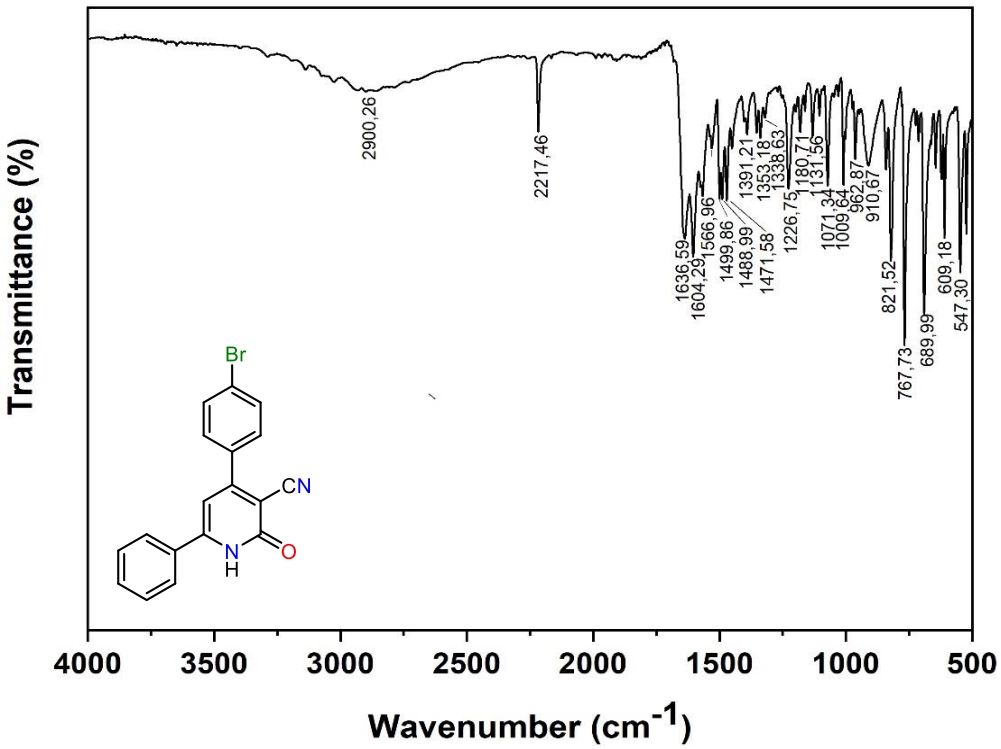


Figure S2. FT–IR spectrum for compound **4b**.

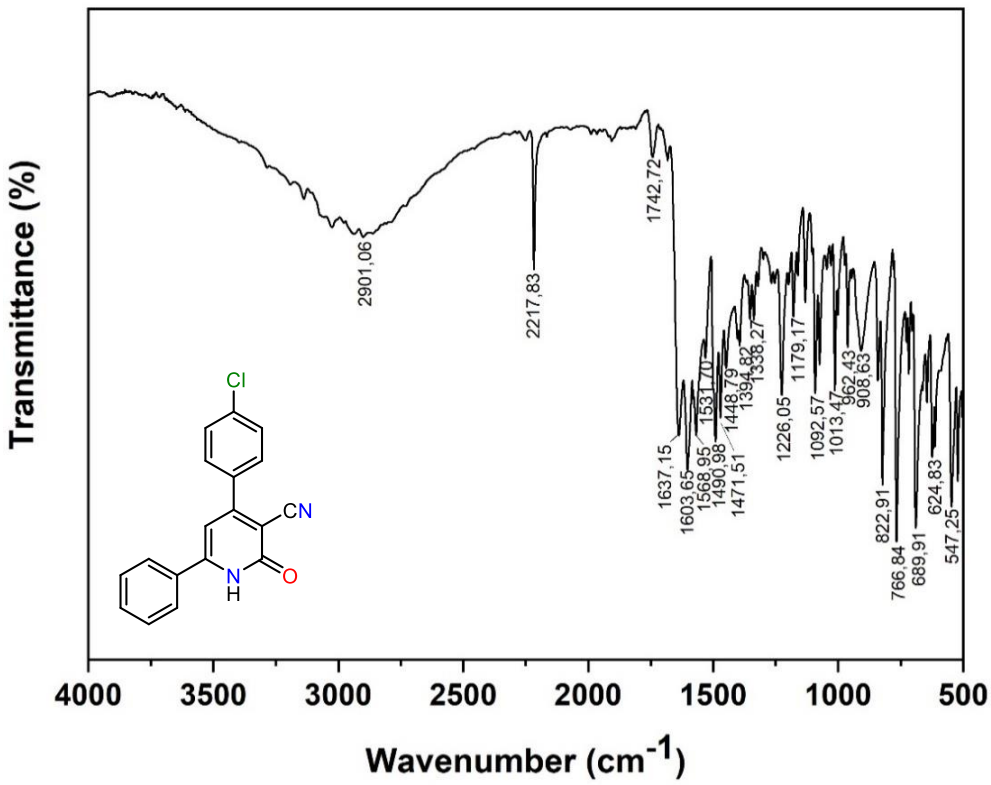


Figure S3. FT–IR spectrum for compound **4c**.

2. Copies of HRMS spectra for compounds 4a–c

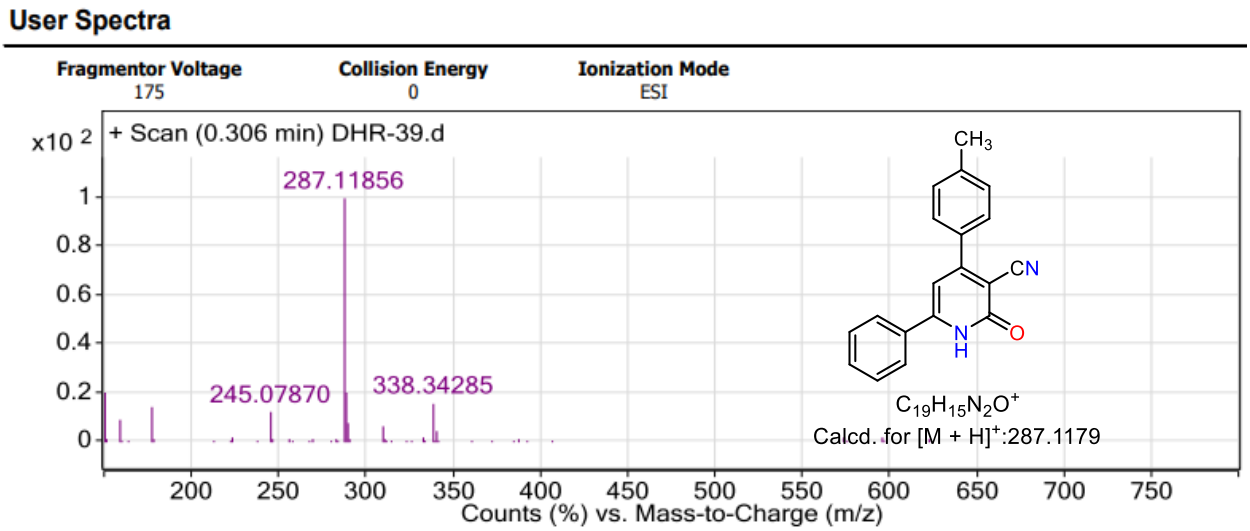


Figure S4. HRMS spectrum for compound **4a**.

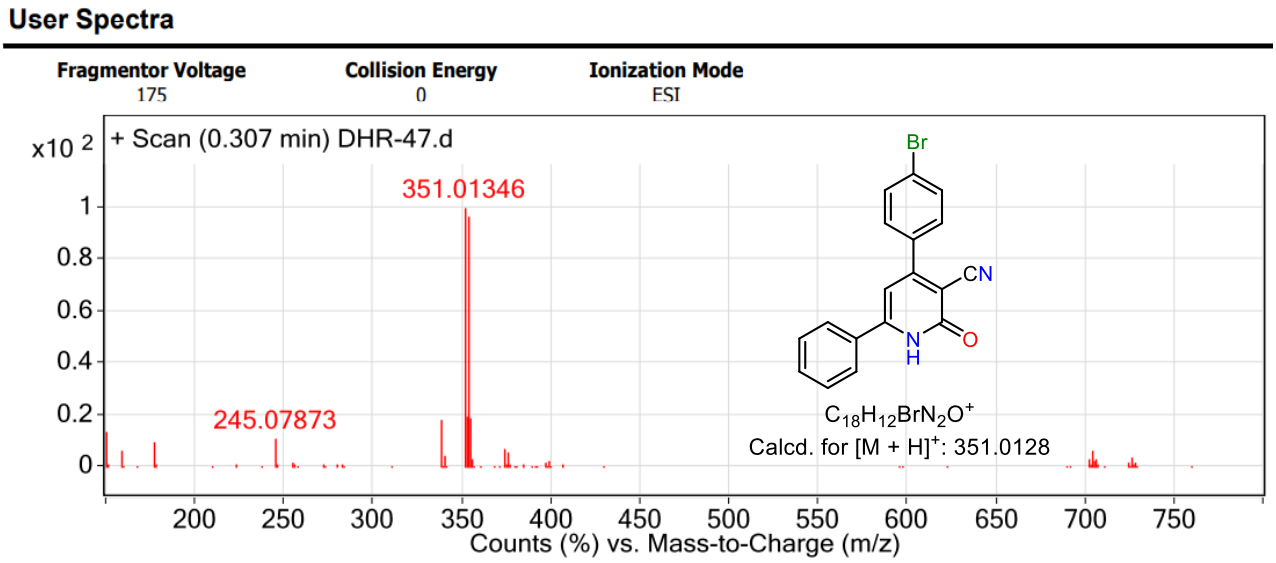


Figure S5. HRMS spectrum for compound **4b**.

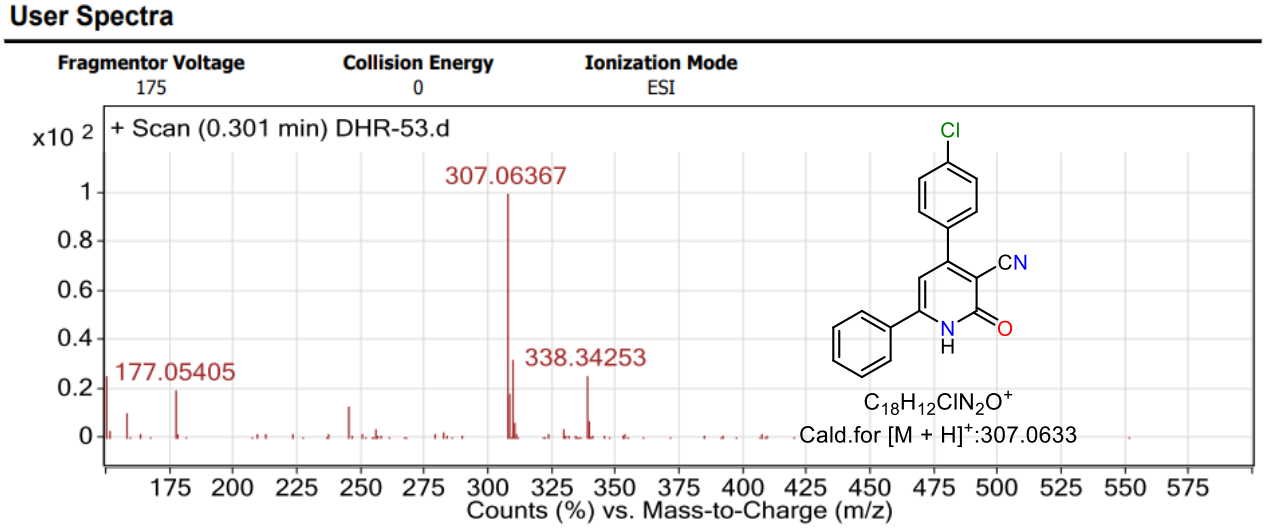


Figure S6. HRMS spectrum for compound **4c**.

3. Copies of NMR spectra for compounds 4a–c

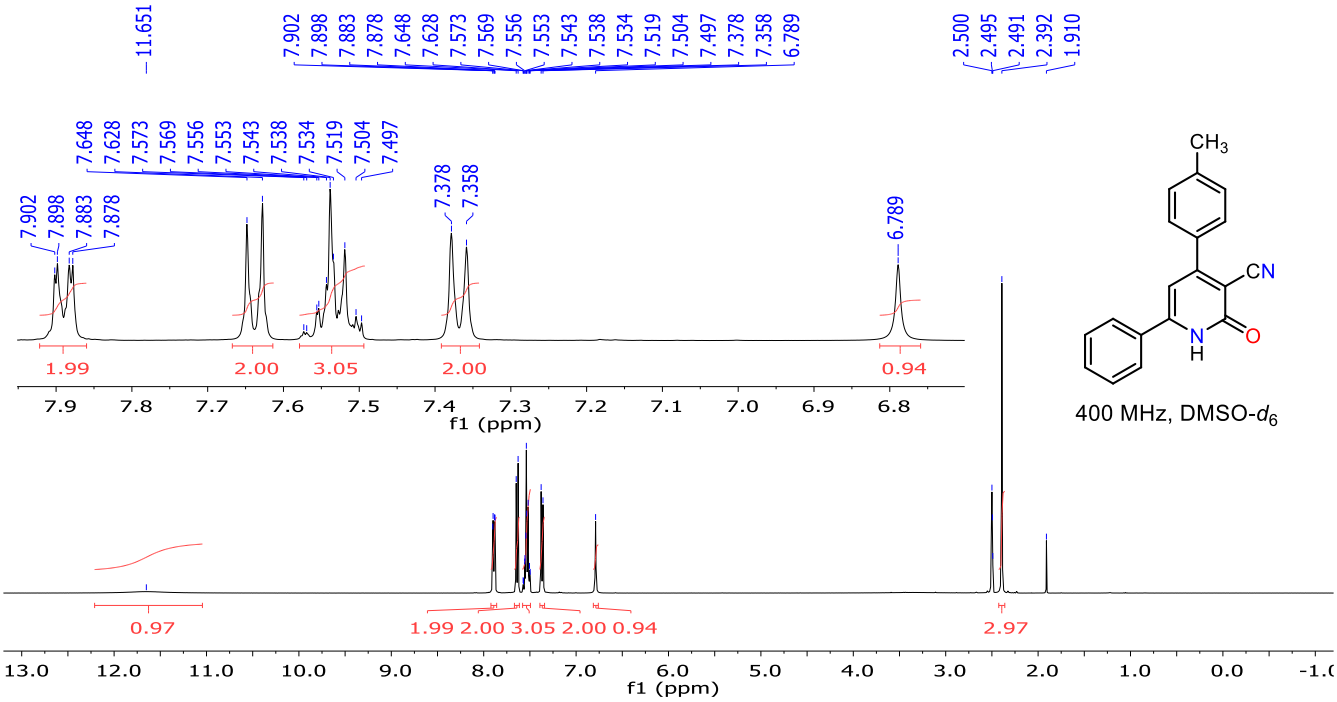


Figure S7. ^{1}H NMR spectrum for compound **4a**.

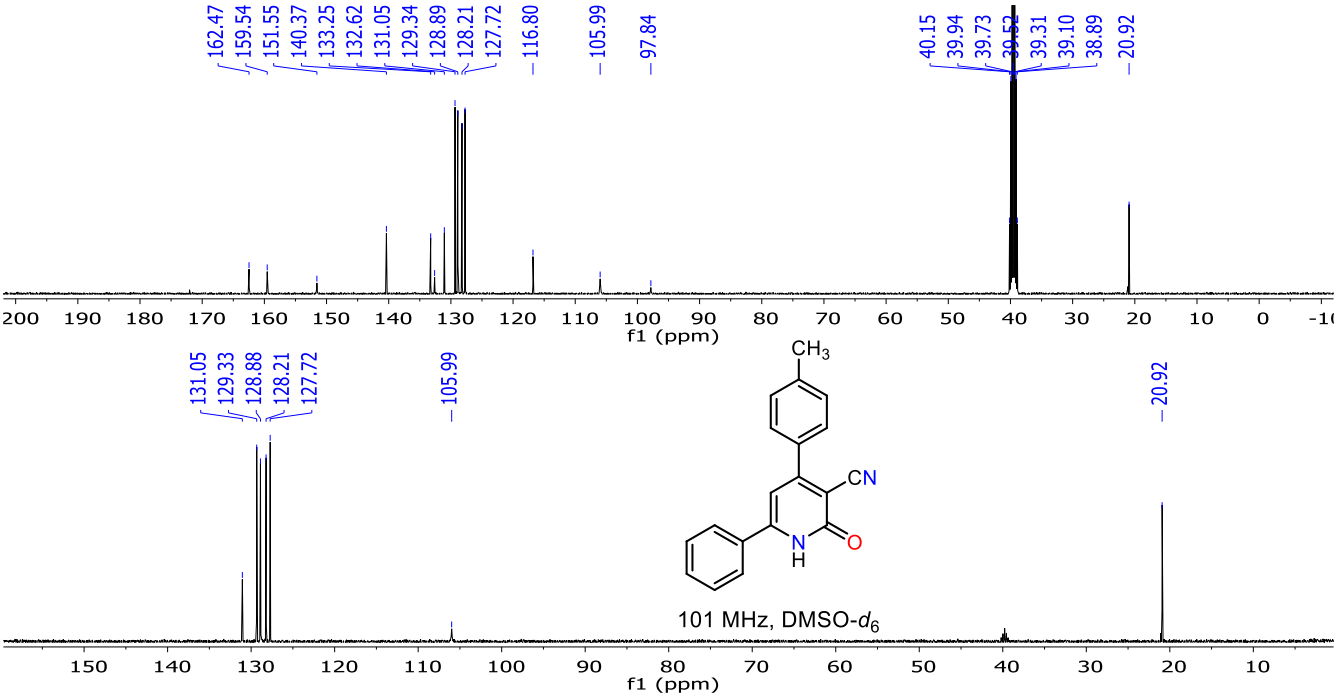


Figure S8. ^{13}C{^{1}H} NMR and DEPT-135 spectra for compound **4a**.

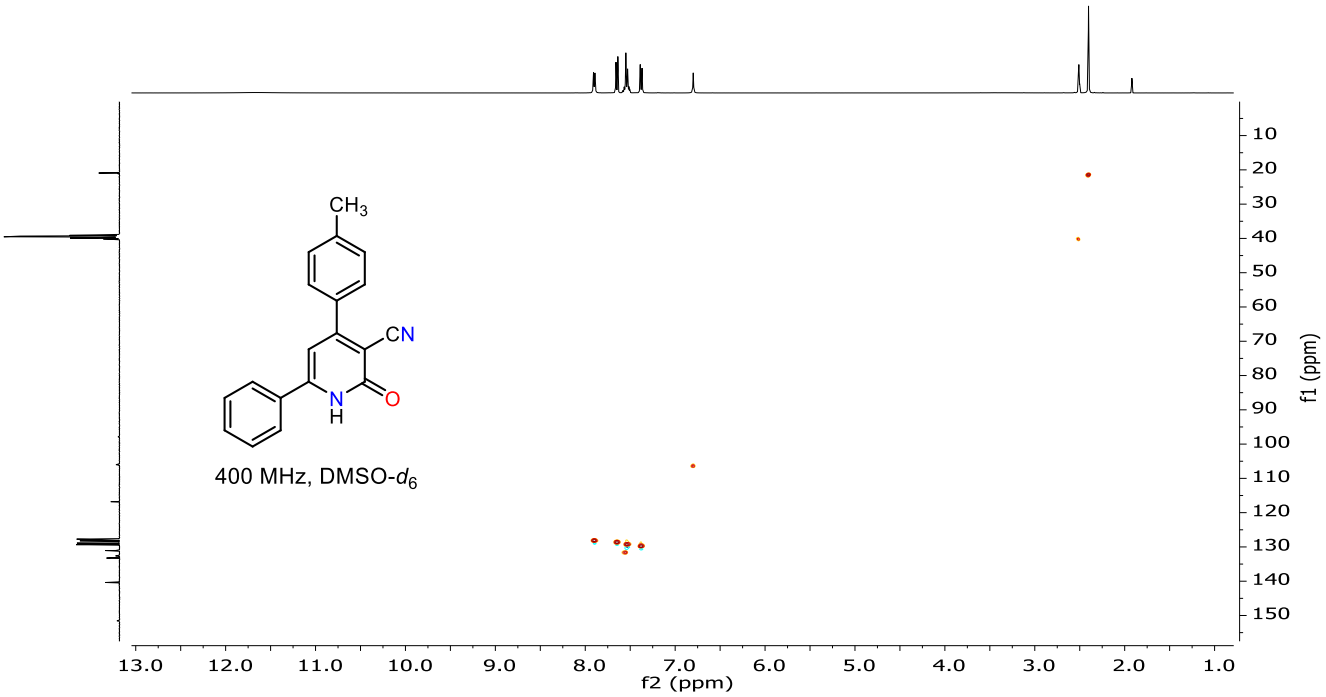


Figure S9. HSQC spectrum for compound **4a**.

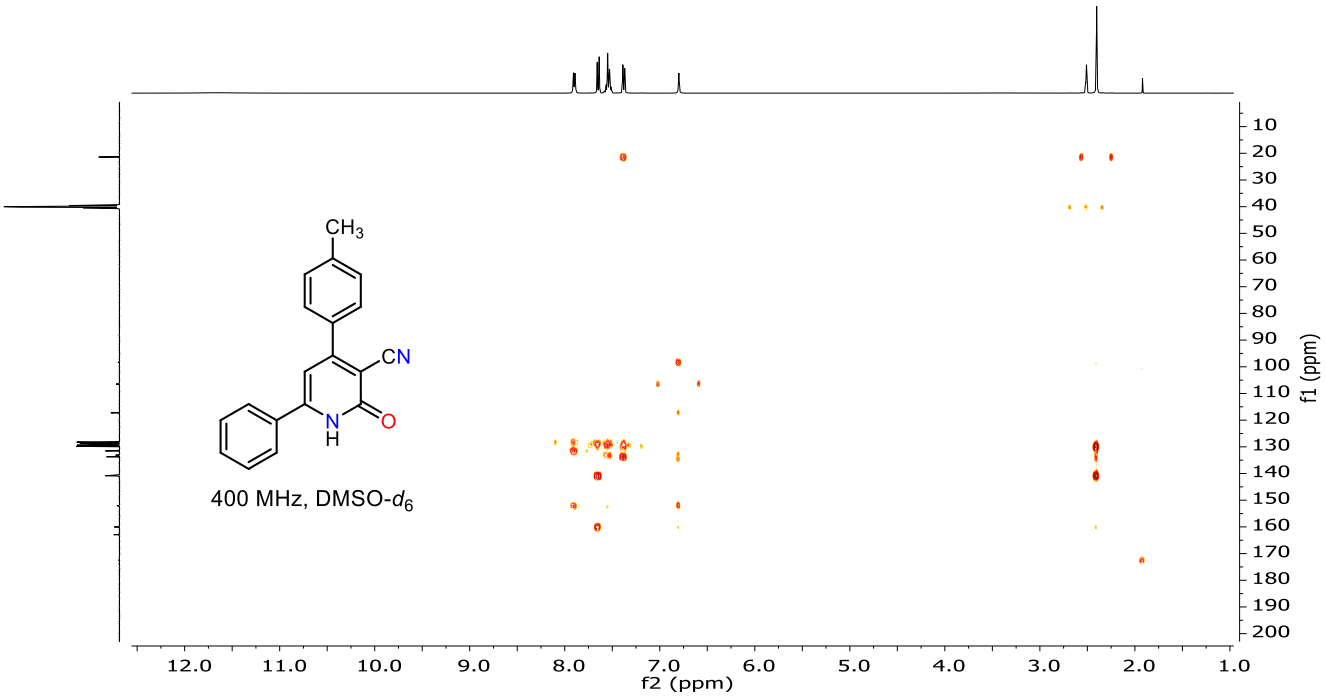


Figure S10. HMBC spectrum for compound **4a**.

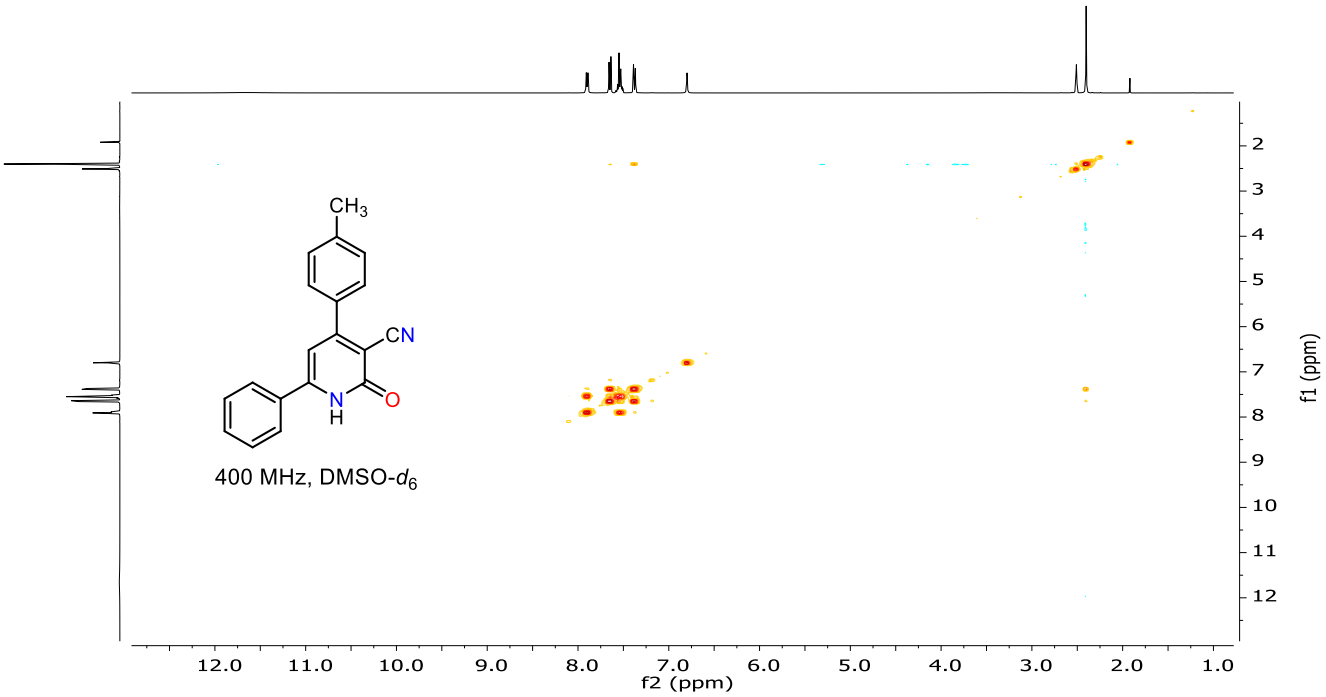


Figure S11. COSY spectrum for compound **4a**.

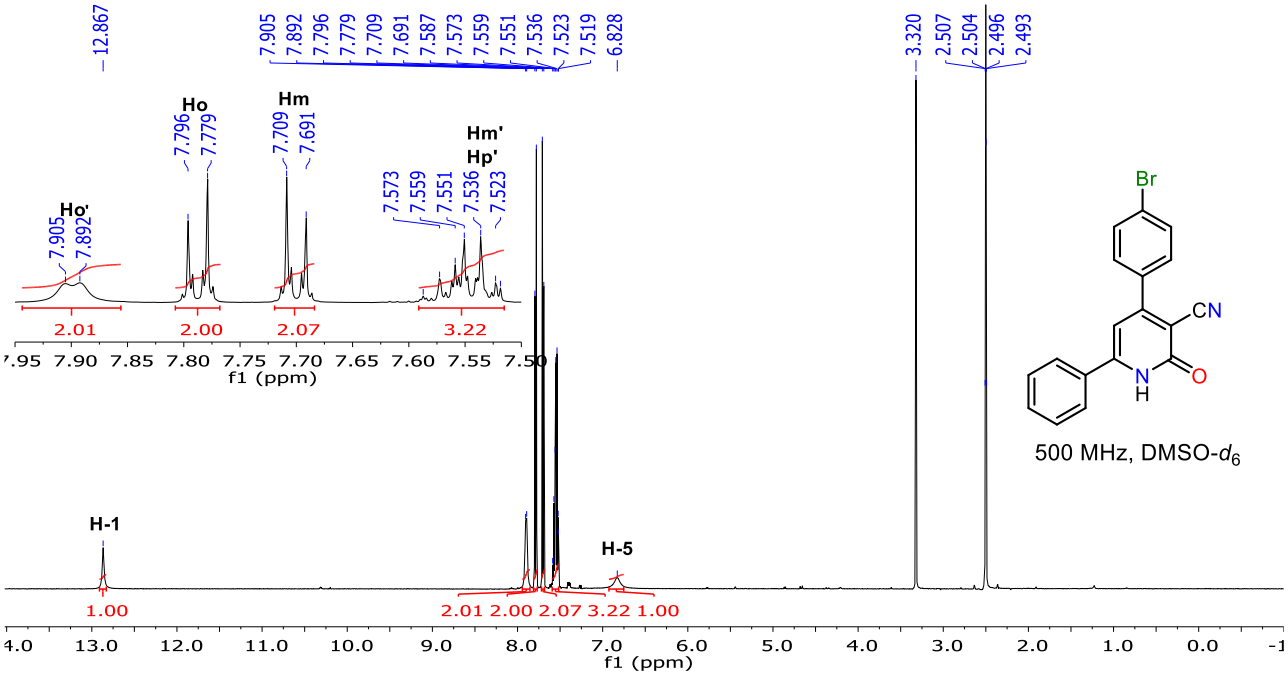


Figure S12. ^{1}H NMR spectrum for compound **4b**.

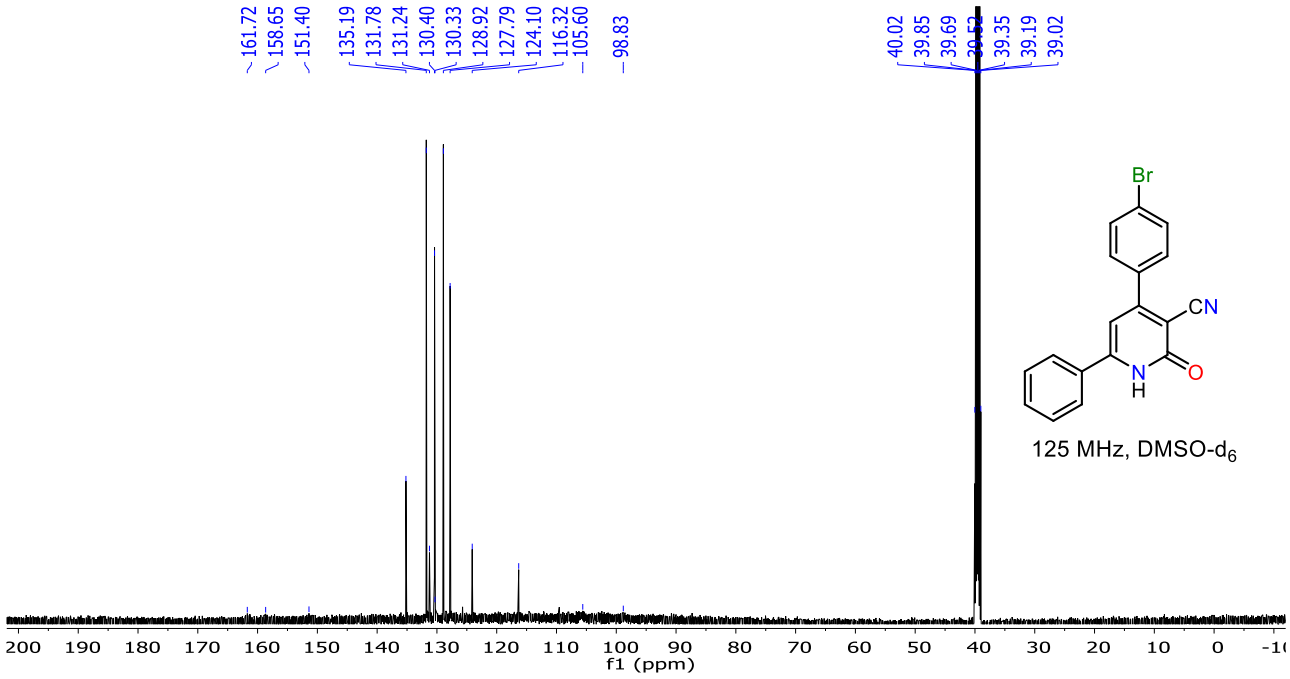


Figure S13. $^{13}C\{^{1}H\}$ NMR spectrum for compound **4b**.

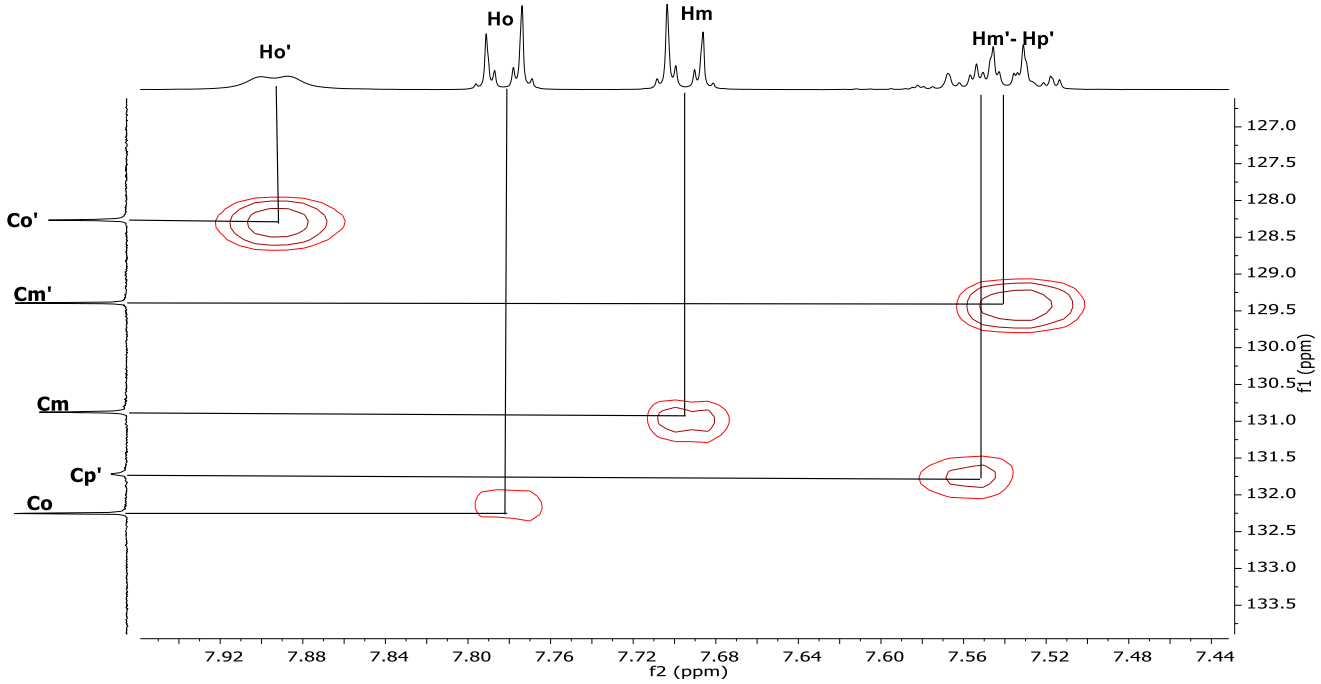


Figure S14. HSQC spectrum for compound **4b**.

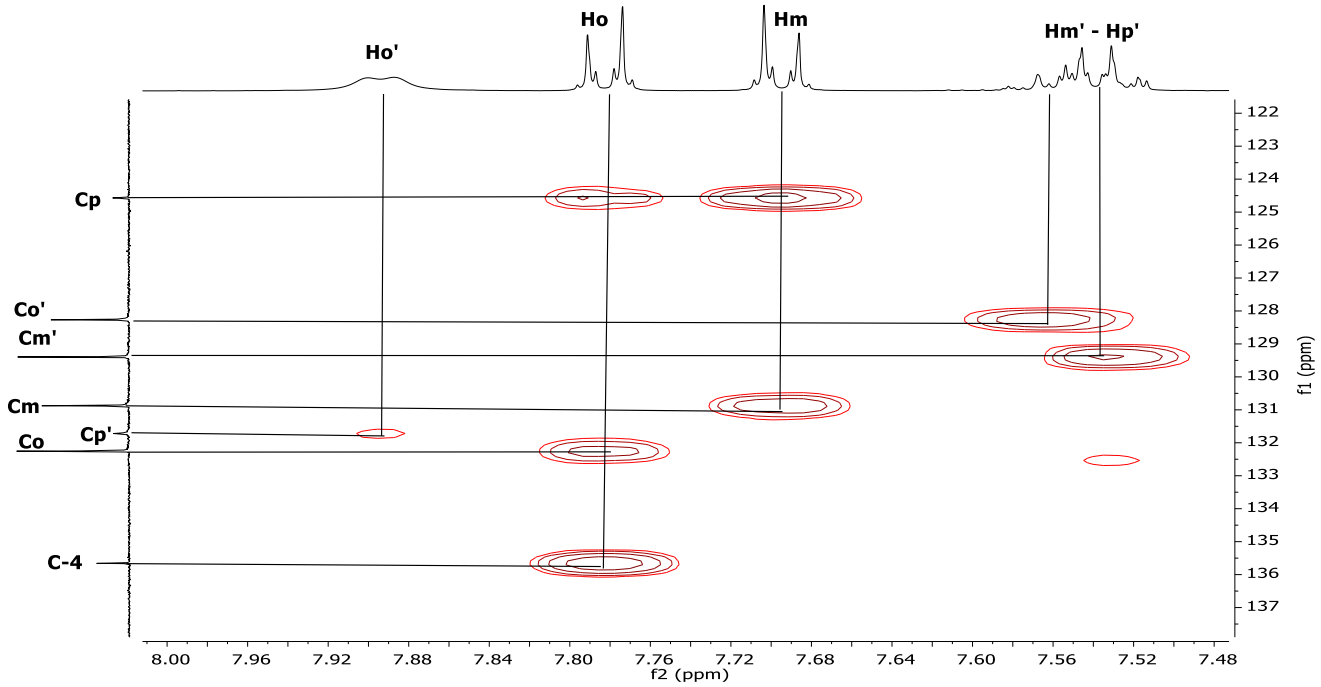


Figure S15. HMBC spectrum for compound **4b**.

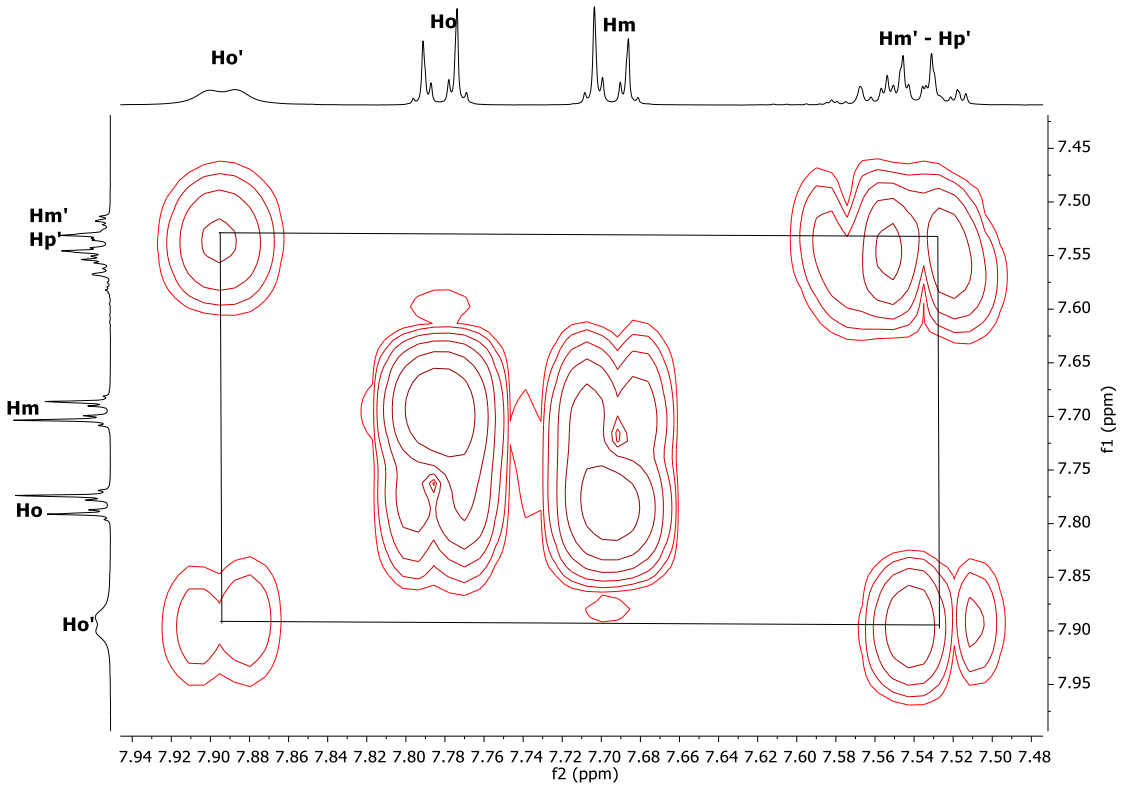


Figure S16. COSY spectrum for compound **4b**.

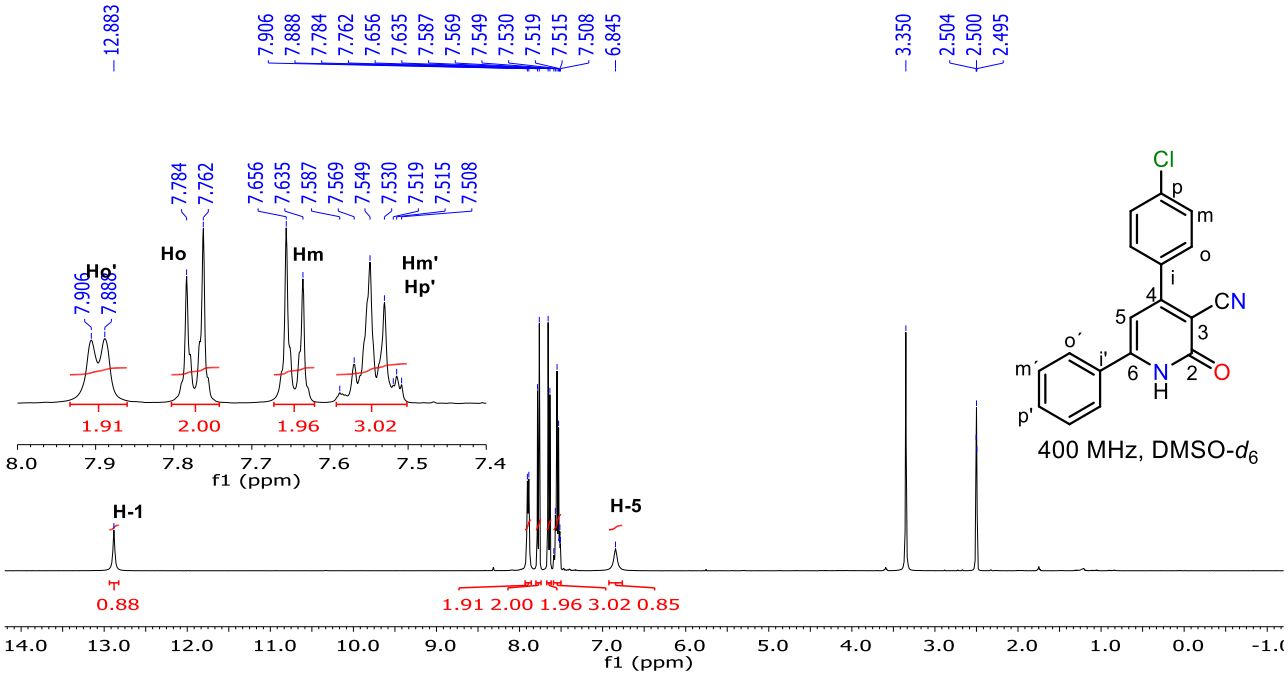


Figure S17. ^{1}H NMR spectrum for compound **4c**.

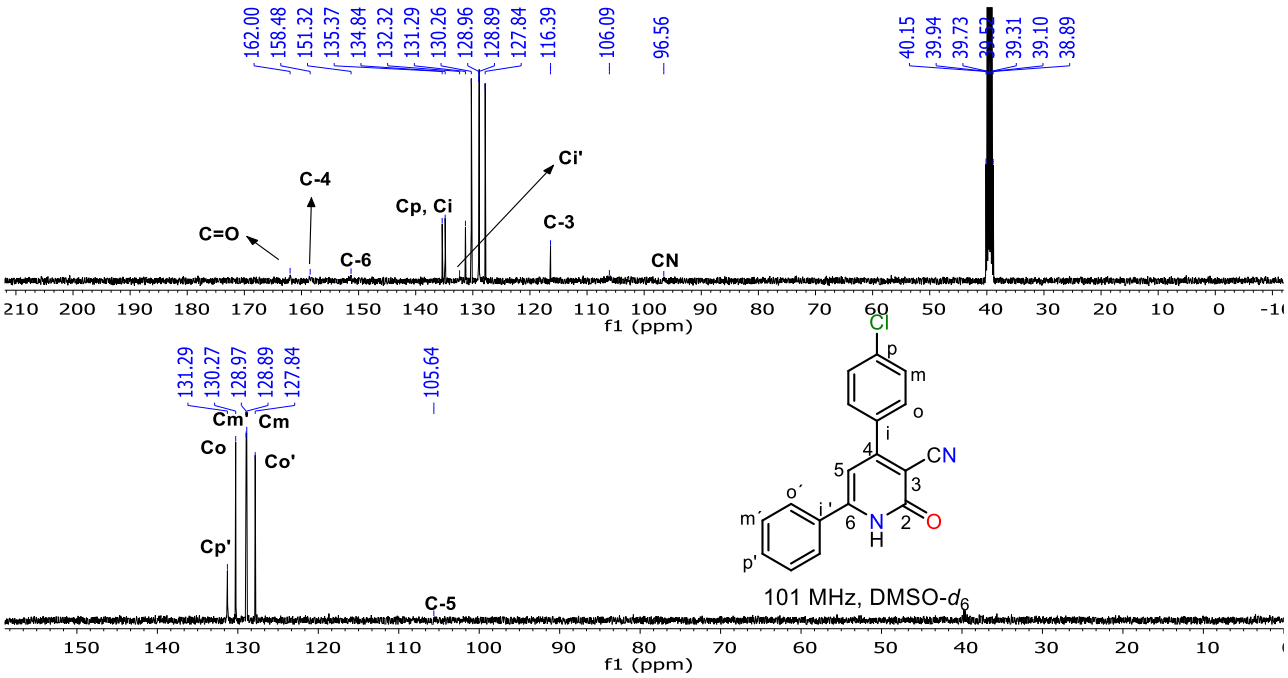


Figure S18. ^{13}C{^{1}H} NMR and DEPT-135 spectra for compound **4c**.

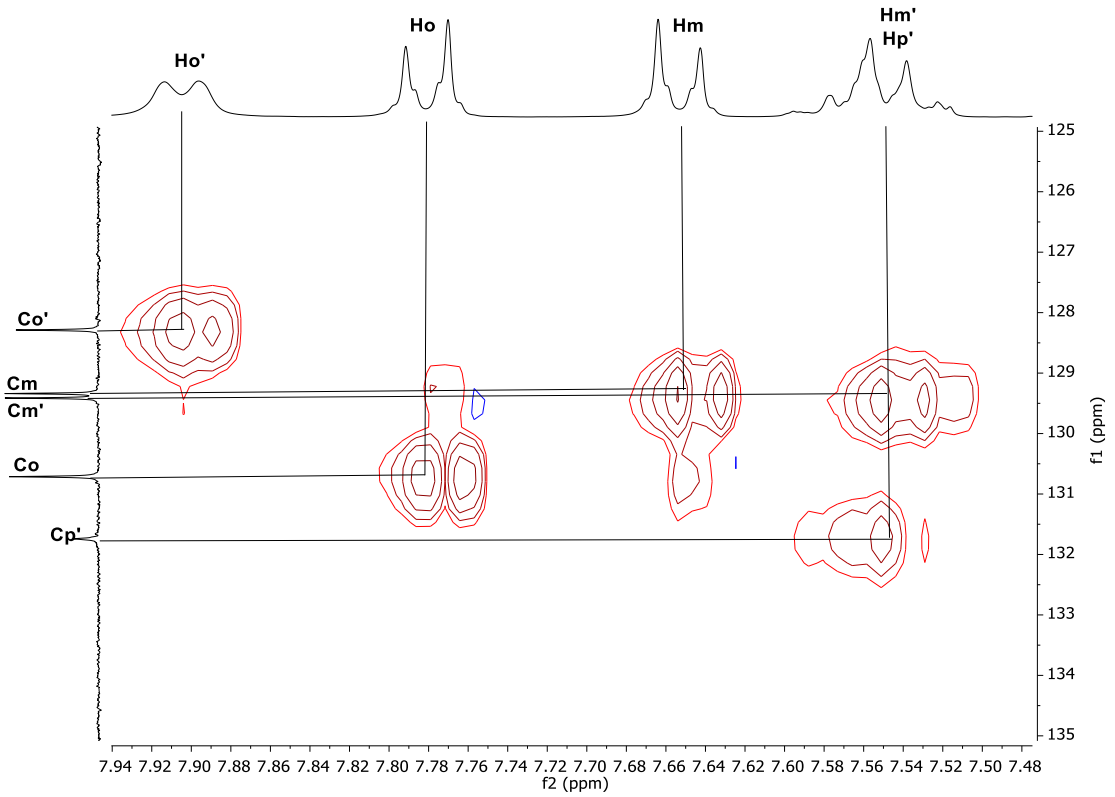


Figure S19. HSQC spectrum for compound **4c**.

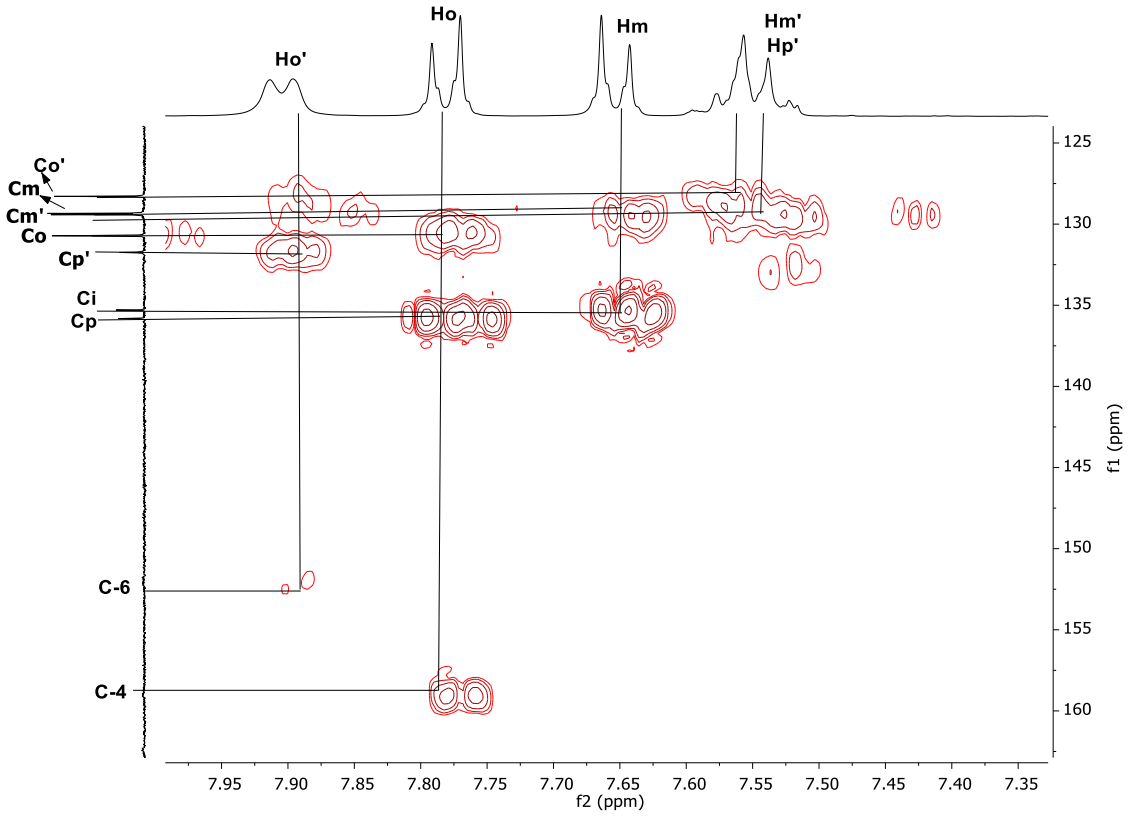


Figure S20. HMBC spectrum for compound **4c**.

Table S1. Assignments of ^{1}H and $^{13}C\{^{1}H\}$ NMR signals along with HMBC correlations for compound **4c**.

Number	δ_H (Multiplicity *J* in Hz)	δ_C (ppm)	HMBC (^{1}H–^{13}C)
2	--	162.0	--
3	--	116.4	--
4	--	158.5	H*o* (^{3}J)
5	6.84 (s)	105.6	--
6	--	151.3	H*o'* (^{3}J)
CN	--	96.6	--
i	--	134.8	H*m* (^{3}J)
o	7.77 (d, *J* = 8.8)	130.3	--
m	7.64 (d, *J* = 8.4)	128.9	--
p	--	135.4	H*o* (^{3}J)
***i*'**	--	132.3	--
***o*'**	7.90 (d, *J* = 7.2)	127.8	H*m'* (^{2}J) H*p'* (^{3}J)
***m*'**	7.51–7.59 (m)	129.0	H*p'* (^{2}J)
***p*'**	7.51–7.59 (m)	131.3	H*o'* (^{3}J)
NH	12.88 (s)	--	--

4. Mean growth, GI%, and lethality values for compounds 4a–c

Table S2. Mean growth, %GI, and lethality values displayed by the tested compound **4a** against 60 NCI human cancer cell lines at 10 μM.

Developmental Therapeutics Program
One Dose Mean Graph

NSC: D-837648 / 1 | **Conc:** 1.00E-5 Molar | **Test Date:** May 09, 2022
Experiment ID: 2205OS14 | **Report Date:** Jul 24, 2022

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	76.68
HL-60(TB)	86.85
K-562	74.41
MOLT-4	91.27
RPMI-8226	76.66
SR	73.28
Non-Small Cell Lung Cancer	
A549/ATCC	77.28
EKVX	82.84
HOP-62	85.32
HOP-92	45.65
NCI-H226	86.82
NCI-H23	96.40
NCI-H322M	91.15
NCI-H460	90.80
NCI-H522	74.95
Colon Cancer	
COLO 205	123.85
HCC-2998	114.36
HCT-116	94.27
HCT-15	71.04
HT29	113.65
KM12	91.17
SW-620	97.77
CNS Cancer	
SF-268	92.86
SF-295	90.39
SF-539	81.95
SNB-19	84.30
SNB-75	99.37
U251	90.77
Melanoma	
LOX IMVI	83.05
MALME-3M	105.82
M14	111.00
MDA-MB-435	106.71
SK-MEL-2	95.47
SK-MEL-28	108.63
SK-MEL-5	90.01
UACC-257	101.48
UACC-62	84.63
Ovarian Cancer	
IGROV1	91.85
OVCAR-3	98.41
OVCAR-4	94.09
OVCAR-5	108.58
OVCAR-8	93.49
NCI/ADR-RES	82.32
SK-OV-3	107.12
Renal Cancer	
786-0	88.44
A498	84.79
ACHN	79.12
CAKI-1	81.88
RXF 393	100.88
SN12C	86.49
TK-10	95.09
UO-31	73.22
Prostate Cancer	
PC-3	83.71
DU-145	97.25
Breast Cancer	
MCF7	75.06
MDA-MB-231/ATCC	83.76
HS 578T	84.56
BT-549	88.51
T-47D	73.46
MDA-MB-468	89.37
Mean	89.74
Delta	44.09
Range	78.20

Mean Growth Percent - Growth Percent

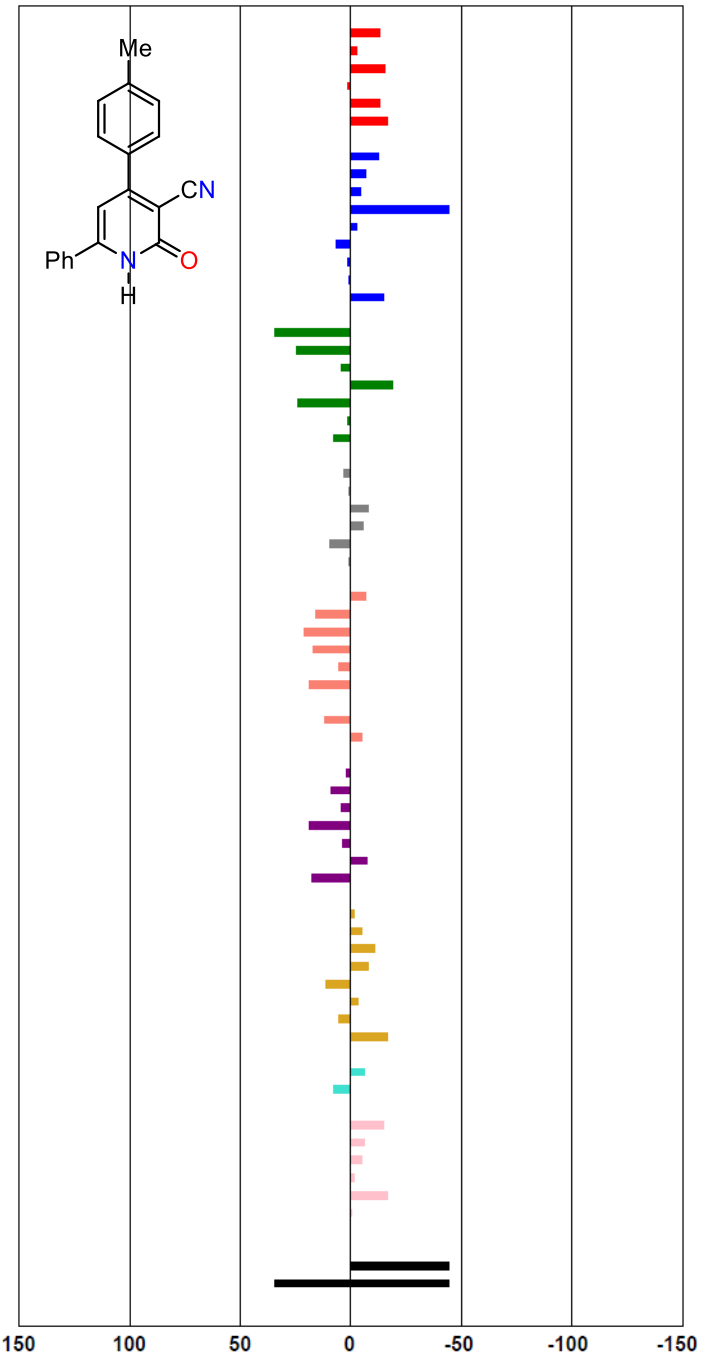


Table S3. Mean growth, %GI, and lethality values displayed by the tested compound **4b** against 60 NCI human cancer cell lines at 10 μM.

Developmental Therapeutics Program

One Dose Mean Graph

NSC: D-837640 / 1	Conc: 1.00E-5 Molar	Test Date: May 09, 2022
Experiment ID: 2205OS14		Report Date: Jul 24, 2022

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	86.02
HL-60(TB)	83.35
K-562	79.43
MOLT-4	77.66
RPMI-8226	76.67
SR	78.14
Non-Small Cell Lung Cancer	
A549/ATCC	85.64
EKVX	81.62
HOP-62	91.74
HOP-92	76.58
NCI-H226	99.21
NCI-H23	89.21
NCI-H322M	105.46
NCI-H460	92.67
NCI-H522	78.78
Colon Cancer	
COLO 205	124.07
HCC-2998	101.86
HCT-116	86.76
HCT-15	81.48
HT29	121.62
KM12	95.42
SW-620	98.52
CNS Cancer	
SF-268	102.15
SF-295	91.53
SF-539	85.35
SNB-19	94.02
SNB-75	95.56
U251	78.87
Melanoma	
LOX IMVI	87.82
MALME-3M	105.04
M14	113.72
MDA-MB-435	110.27
SK-MEL-2	84.82
SK-MEL-28	108.34
SK-MEL-5	92.28
UACC-257	95.97
UACC-62	93.39
Ovarian Cancer	
IGROV1	99.42
OVCAR-3	114.38
OVCAR-4	95.96
OVCAR-5	109.12
OVCAR-8	90.70
NCI/ADR-RES	92.75
SK-OV-3	112.90
Renal Cancer	
786-0	87.25
A498	107.91
ACHN	85.11
CAKI-1	90.85
RXF 393	110.86
SN12C	92.76
TK-10	115.54
UO-31	84.12
Prostate Cancer	
PC-3	94.66
DU-145	93.87
Breast Cancer	
MCF7	75.28
MDA-MB-231/ATCC	83.09
HS 578T	95.05
BT-549	81.46
T-47D	94.01
MDA-MB-468	94.07
Mean	93.87
Delta	18.59
Range	48.79

Mean Growth Percent - Growth Percent

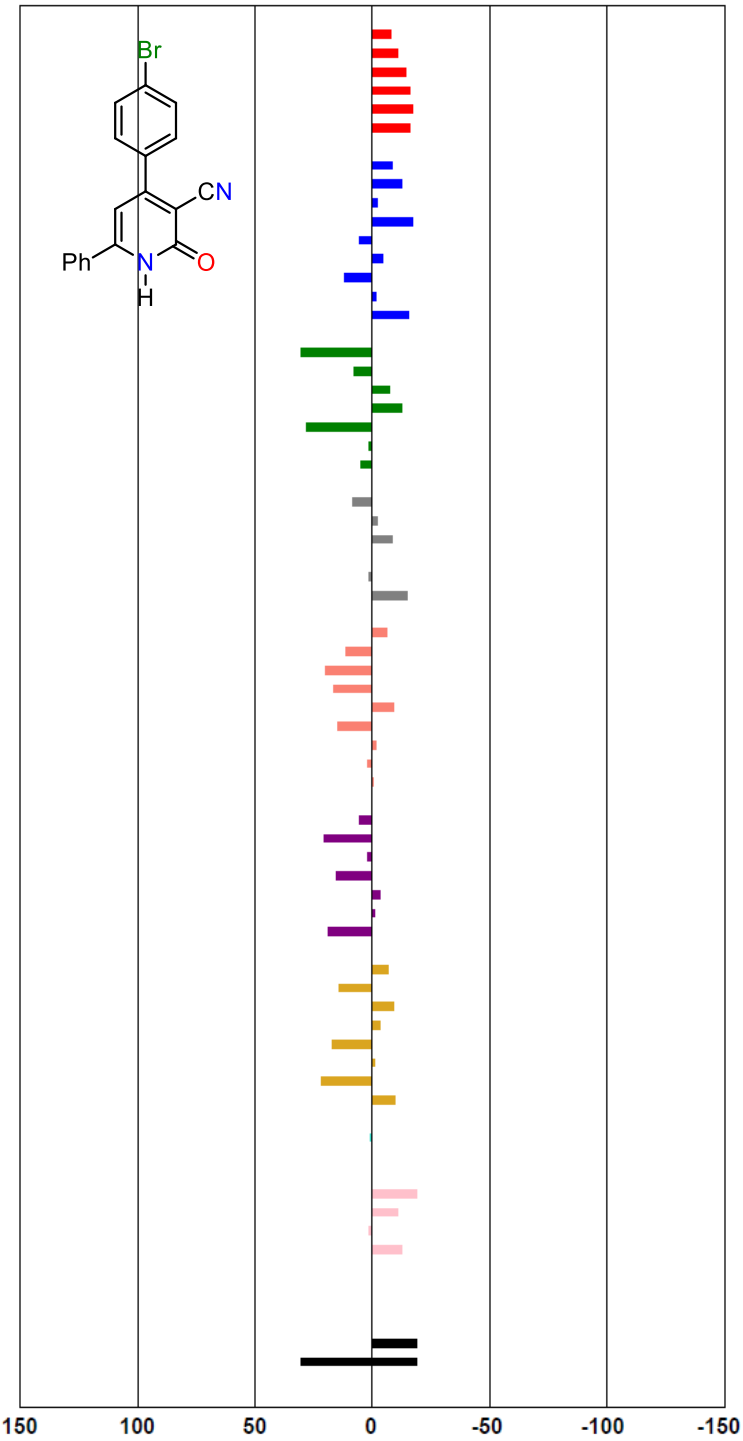


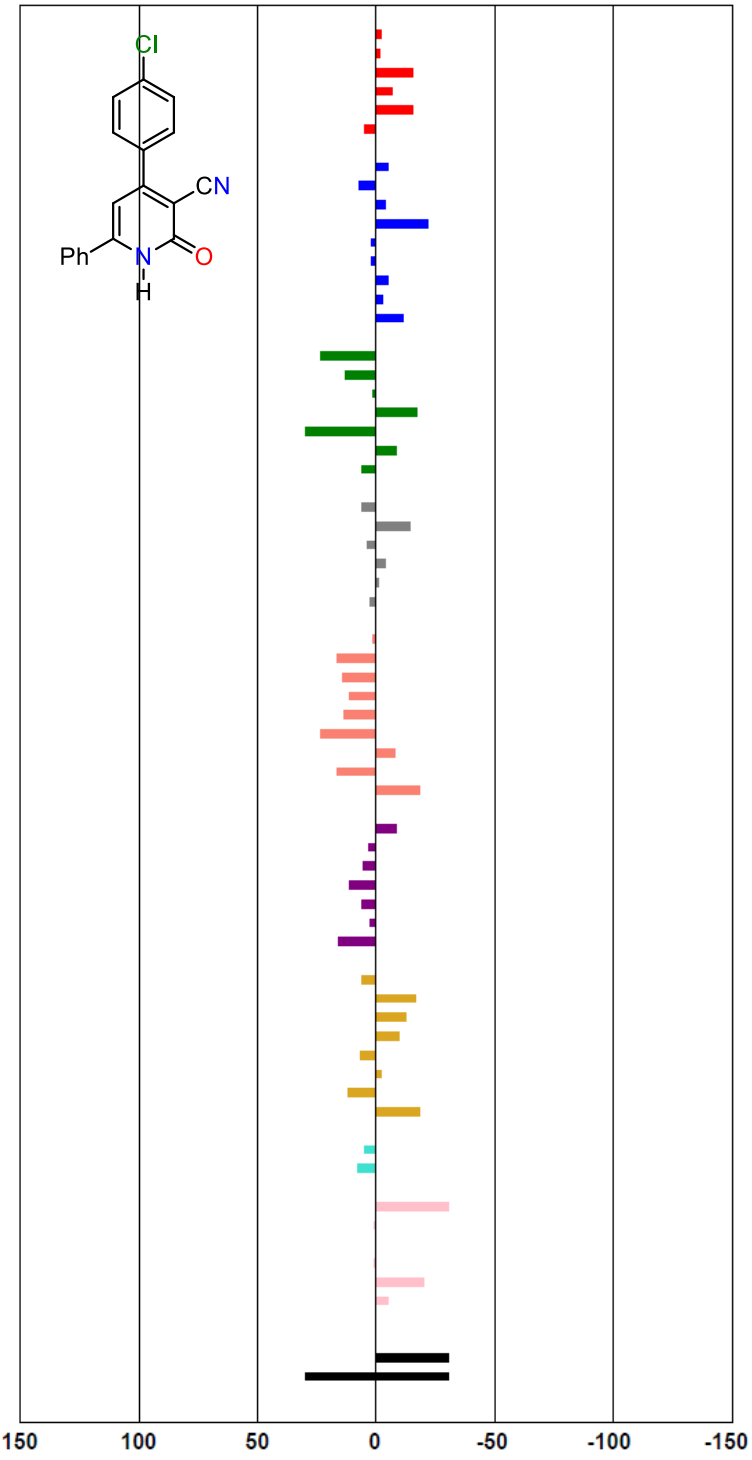
Table S4. Mean growth, %GI, and lethality values displayed by the tested compound **4c** against 60 NCI human cancer cell lines at 10 μM.

Developmental Therapeutics Program

One Dose Mean Graph

NSC: D-829750 / 1	**Conc:** 1.00E-5 Molar	**Test Date:** Apr 19, 2021
Experiment ID: 2104OS18		**Report Date:** May 18, 2021

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	88.04
HL-60(TB)	88.46
K-562	74.49
MOLT-4	83.36
RPMI-8226	74.78
SR	94.79
Non-Small Cell Lung Cancer	
A549/ATCC	85.25
EKVX	97.13
HOP-62	86.24
HOP-92	68.21
NCI-H226	92.06
NCI-H23	91.85
NCI-H322M	84.77
NCI-H460	87.23
NCI-H522	78.71
Colon Cancer	
COLO 205	113.17
HCC-2998	103.18
HCT-116	91.67
HCT-15	72.79
HT29	119.71
KM12	81.79
SW-620	95.87
CNS Cancer	
SF-268	95.81
SF-295	75.97
SF-539	93.90
SNB-19	86.35
SNB-75	89.32
U251	92.33
Melanoma	
LOX IMVI	91.35
MALME-3M	106.30
M14	104.01
MDA-MB-435	101.43
SK-MEL-2	103.72
SK-MEL-28	113.23
SK-MEL-5	82.41
UACC-257	106.53
UACC-62	71.82
Ovarian Cancer	
IGROV1	81.55
OVCAR-3	93.05
OVCAR-4	95.50
OVCAR-5	100.93
OVCAR-8	96.09
NCI/ADR-RES	92.81
SK-OV-3	105.74
Renal Cancer	
786-0	95.73
A498	73.52
ACHN	77.29
CAKI-1	80.66
RXF 393	96.51
SN12C	88.19
TK-10	101.85
UO-31	71.77
Prostate Cancer	
PC-3	95.11
DU-145	97.97
Breast Cancer	
MCF7	59.75
MDA-MB-231/ATCC	90.56
HS 578T	90.50
BT-549	90.54
T-47D	70.14
MDA-MB-468	85.11
Mean	89.98
Delta	30.23
Range	59.96



5. Crystallographic data of compounds 4a–c

Table S5. X-ray crystallographic data and structural refinement for compounds **4a–c**.

Crystal Data	**Compound 4a**	**Compound 4b**	**Compound 4c**
Chemical Formula	$C_{19}H_{14}N_2O$	$C_{18}H_{11}BrN_2O$	$C_{18}H_{11}ClN_2O$
M_r	286.32	351.19	306.74
Solvent for Crystallization	MeOH/DMF (1:5, v/v)	MeOH/DMF (1:5, v/v)	MeOH/DMF (1:5, v/v)
Crystalline system, space group	Triclinic, *P-1*	Monoclinic, $P2_1/c$	Triclinic, *P-1*
a, *b*, *c* (Å)	14.9621 (17), 17.7063 (18), 18.5333 (12)	18.7005 (14), 14.5206 (12), 34.471 (2)	14.4943 (9), 17.8480 (9), 18.7119 (8)
α, β, γ (°)	75.538 (8), 89.907 (8), 73.826 (10)	90, 104.606 (8), 90	106.539 (4), 90.018 (5), 105.413 (5)
Volume, (Å^3)	4553.9 (8)	9057.7 (12)	4458.3 (4)
ρ, g cm^{-3}	1.253	1.545	1.371
Z	12	24	12
Temperature, (°C)	25(2)	25(2)	25(2)
Radiation type	Cu K_α	Cu K_α	Cu K_α
μ (mm^{-1})	0.62	3.73	2.29
Theta range for data collection	3.462°<2θ< 76.626°	3.903°<2θ< 72.127°	3.545°<2θ< 76.873°
Index range	-18≤h≤18, -22≤k≤23, -23≤l≤14	-23≤h≤22, -17≤k≤16, -40≤l≤42	-11≤h≤18, -22≤k≤19, -23≤l≤23
Data collection			
Diffractometer	SuperNova, Dual, Cu at zero, Atlas	SuperNova, Dual, Cu at zero, Atlas	SuperNova, Dual, Cu at zero, Atlas
Absorption correction	Multi-Scan (CrysAlis PRO 1.171.38.43)	Multi-Scan (CrysAlis PRO 1.171.38.43)	Multi-Scan (CrysAlis PRO 1.171.38.43)
Tmin, Tmax	0.400, 1.000	0.112, 1.000	0.816, 1.000
No. of measured, independent and observed reflections [I>2σ(I)]	36258, 18327, 8287	39338, 17698, 8570	35213, 17976, 13270
R_{int}	0.048	0.091	0.037
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.631	0.617	0.632
Refinement			
R[F^2 > 2σ(F^2)], wR(F^2), S	0.087, 0.311, 1.00	0.104, 0.375, 1.06	0.076, 0.237, 1.02
No. of reflections	18327	17698	17976

Refined parameters	1195	1217	1226
No. of restraints	12	21	76
H-atoms treatment	H-atom parameters constrained	H-atom parameters constrained	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.40, −0.32	1.01, −1.00	0.80, −0.43