Supporting Information

Overcoming the imatinib-resistant BCR-ABL mutants with new ureidobenzothiazole chemotypes endowed with potent and broad-spectrum anticancer activity

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[1] These authors contributed equally to this work.

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Contents **Pages**

1. Experimental section

1.1. General

All reactions and manipulations were conducted utilizing standard Schlenk techniques. All solvents and reagents were obtained from commercial suppliers and were used without further purification. The reaction progress was monitored on TLC plate (Merck, silica gel 60 F_{254}). Flash column chromatography was carried out using silica gel (Merck, 230–400 mesh) and the eluent solvents are indicated as a mixed solvent with either given percentage or volume-to-volume ratios. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer, using the proper deuterated solvents, as noted. Chemical shifts (δ) are given in parts per million (ppm) upfield from tetramethylsilane (TMS) as internal standard. s, d, t, and m refer to singlet, doublet, triplet and multiplet, respectively, and coupling constants (*J*) are reported in hertz (Hz). High resolution mass spectra (HRMS) were recorded on JMS 700 (Jeol, Japan) mass spectrometer, with magnetic sector-electric sector double focusing mass analyzer, and FAB+ ion mode. The purity of all final compounds was found to be > 95%, as determined by ^{1}H NMR. 3-(Trifluoromethyl)aniline and 3,5-bis(trifluoromethyl)aniline were commercially available, while the cyclic amine bearing anilines were synthesized adopting the reported procedure \.

1.2. 6-(2-Methoxyphenyl)benzo[d]thiazol-2-amine (**1**)
A solution of 2-methoxyphenyl boronic acid (199 mg, 1.31 mmol) in dimethoxyethane:H_2O (3:1, v/v, 3 mL) was added to a stirred solution of 6-bromo-2-aminothiazol (200 mg, 0.873 mmol), $NaHCO_3$ (220 mg, 2.619 mmol), and $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (143 mg, 0.20 mmol) in dimethoxyethane:H_2O (3:1, v/v, 1 mL). The reaction mixture was stirred at room temperature for 85 min at 80–85 ºC. After the reaction completion, the solvent was evaporated under vacuum, and the residue was filtered by celite pad. The filtrate was evaporated and the resulting residue was purified by column chromatography using (33–50% ethyl acetate in hexane) to afford the title compound as a brown solid; 194 mg (86.6%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 1.4 Hz, 1H), 7.58 (d, *J* = 8.3 Hz, 1H), 7.48 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.35–7.30 (m, 2H), 7.04 (td, *J* = 7.5, 0.84 Hz, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 5.42 (br. s, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 156.4, 146.7, 133.8, 130.9, 129.9, 129.2, 128.8, 128.3, 122.2, 120.9, 117.4, 111.3, 55.6.

*1.3. General procedure for synthesis of compounds **2a–f***
A solution of compound **1** (200 mg, 0.78 mmol) and 1,1'-carbonyldiimidazole (253 mg, 1.56 mmol) in anhydrous dimethylformamide (2 mL) was stirred at room temperature for 15 h. Then, the appropriate aniline (1.56 mmol) was added and the reaction mixture was heated to 100 ºC for 2.5 h. After cooling to room temperature, the reaction was quenched with water (20 mL). The aqueous layer was extracted with ethyl acetate (3×30 mL), and the organic layers were combined, washed with water and brine, dried over anhydrous Na_2SO_4, and filtered. The solvent was evaporated under vacuum, and the resultant residue was purified by flash column chromatography using the proper eluent to afford the target compounds in pure form.

1.3.1. 1-(6-(2-Methoxyphenyl)benzo[d]thiazol-2-yl)-3-(4-(4-methylpiperazin-1-yl)phenyl)urea (**2a**)
Column chromatography was performed using 5% methanol in DCM. White solid (28.1% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.36–7.31 (m, 4H), 7.05–6.99 (m, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 3.82 (s, 3H), 3.17 (t, *J* = 5.0 Hz, 4H), 2.61 (t, *J* = 4.6 Hz, 4H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 156.5, 152.8, 148.3, 147.8, 134.1, 131.0, 130.9, 130.0, 129.8, 128.7, 128.1, 122.2, 122.1,121.0, 119.3, 116.8, 111.3, 55.6, 55.0, 49.3, 46.0; HRMS (FAB) m/z calcd for $C_{26}H_{28}N_5O_2S$ $[M+H]^+$: 474.1963, found: 474.1960.

1.3.2. 1-(4-(4-Ethylpiperazin-1-yl)phenyl)-3-(6-(2-methoxyphenyl)benzo[d]thiazol-2-yl)urea (**2b**)
Column chromatography was performed using 3–7% methanol in dichloromethane (DCM). White solid (23.1% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.77 (br. s, 1H), 7.87 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.32–7.26 (m, 4H), 7.04–6.97 (m, 2H), 6.83 (d, *J* = 7.6 Hz, 2H), 3.81 (s, 3H), 3.14 (s, 4H), 2.59 (s, 4H), 2.48 (q, *J* = 6.9 Hz, 2H), 1.13 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 156.5, 152.8, 148.4, 147.7, 134.1, 131.1, 130.0, 129.8, 128.7, 128.1, 122.1, 122.0, 121.9, 121.0, 119.2, 116.7, 111.3, 55.6, 52.8, 52.4, 49.5, 12.0; HRMS (FAB) m/z calcd for $C_{27}H_{30}N_5O_2S$ $[M+H]^+$: 488.2120, found: 488.2117.

1.3.3. 1-(6-(2-Methoxyphenyl)benzo[d]thiazol-2-yl)-3-(4-morpholinophenyl)urea (**2c**)
Column chromatography was performed using 3–7% methanol in DCM. White solid (23% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.85 (br. s, 1H), 8.96 (s, 1H), 7.98 (s, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.39–7.34 (m, 4H), 7.14 (d, *J* = 8.4 Hz, 1H), 7.05 (t, *J* = 7.2 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 3.79 (s, 3H), 3.36 (s, 4H), 3.09 (s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.4, 156.6, 152.6, 147.8, 133.4, 131.6, 131.1, 130.6, 130.1, 129.2, 128.0, 122.4, 121.3, 120.8, 119.1, 116.5, 116.4, 112.2, 60.8, 59.0, 56.0.

1.3.4. 1-(6-(2-Methoxyphenyl)benzo[d]thiazol-2-yl)-3-(3-(trifluoromethyl)phenyl)urea (**2d**)

Column chromatography was performed using ethyl acetate-hexane (1:3, v/v). White solid (43% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.27 (br. s, 1H), 9.59 (s, 1H), 8.09 (s, 1H), 7.99 (s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.58 (t, J = 8.0 Hz, 1H), 7.52 (dd, J = 8.4, 1.2 Hz, 1H), 7.41 (d, J = 7.6 Hz, 1H), 7.36 (s, 1H), 7.34 (s, 1H), 7.13 (d, J = 8.4 Hz, 1H), 7.05 (t, J = 7.4 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.6, 140.2, 133.7, 132.5, 131.0, 130.5, 130.3, 130.0, 129.9, 129.2, 128.2, 126.0, 123.3, 123.0, 122.6, 121.3, 119.6, 119.5, 115.3, 115.3, 112.2, 56.0; HRMS (FAB) m/z calcd for $C_{22}H_{17}F_3N_3O_2S$ $[M+H]^+$: 444.0993, found: 444.0992.

1.3.5. 1-(3,5-Bis(trifluoromethyl)phenyl)-3-(6-(2-methoxyphenyl)benzo[d]thiazol-2-yl)urea (**2e**)
Column chromatography was performed using 1% methanol in DCM. White solid (76% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89 (br. s, 1H), 9.96 (s, 1H), 8.31 (s, 2H), 7.96 (s, 1H), 7.71 (s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.52 (dd, J = 8.4, 1.2 Hz, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.0 Hz, 1H), 7.05 (t, J = 7.4 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.6, 141.9, 133.8, 131.7, 131.4, 131.1, 131.0, 130.7, 129.9, 129.3, 128.4, 125.1, 122.8, 122.4, 121.3, 119.0, 115.6, 112.2, 56.0; HRMS (FAB) m/z calcd for $C_{23}H_{16}F_6N_3O_2S$ $[M+H]^+$: 512.0867, found: 512.0866.

1.3.6. 1-(6-(2-Methoxyphenyl)benzo[d]thiazol-2-yl)-3-(4-(morpholinomethyl)-3-(trifluoromethyl)phenyl)urea (**2f**)
Column chromatography was performed using ethyl acetate-hexane (1:1, v/v). Yellow solid (18.4% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 1.6 Hz, 1H), 7.91 (br. s, 1H), 7.84–7.73 (m, 3H), 7.63 (dd, J = 8.4, 1.6 Hz, 1H), 7.40–7.36 (m, 2H), 7.09 (d, J = 7.2 Hz, 1H), 7.04 (d, J = 8.8 Hz, 1H), 3.87 (s, 3H), 3.76 (t, J = 4.4 Hz, 4H), 3.66 (s, 2H), 2.52 (t, J = 4.4 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 156.5, 152.8, 148.4, 147.8, 134.3, 134.1, 131.0, 131.0, 130.1, 129.7, 128.8, 128.7, 128.2, 128.1, 122.3, 122.1, 121.0, 119.3, 116.8, 111.3, 55.6, 55.0, 49.3, 46.0; HRMS (FAB) m/z calcd for $C_{27}H_{26}F_3N_4O_3S$ $[M+H]^+$: 543.1677, found: 543.1681.

1.4. In vitro biological evaluations

1.4.1. In vitro kinase screening

Reaction Biology Corporation (RBC) Kinase HotSpot^{SM} service was employed for biochemical kinase evaluation of the target compounds following the reported assay protocol [5].

1.4.2. In vitro cell based assays

1.4.2.1. Preliminary MTT evaluation of antiproliferative activity

The antiproliferative activity of the target benzothiazoles was assessed against human leukemia K562 cancer cell as well as L132 normal cell line, using the MTT assay adopting the reported assay protocols [6].

1.4.2.2. Anti-cancer screening at NCI

The anticancer screening of certain selected target compounds over a full panel of 60-human cancer cell lines was conducted at the National Cancer Institute (NCI), Bethesda, Maryland, USA using Sulforhodamine B (SRB) assay adopting the standard protocol [7].

1.5. In silico studies

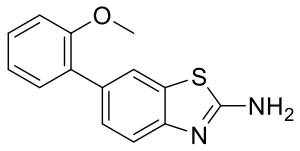
1.5.1. Molecular docking

The docking models of compound **2b** were constructed utilizing the X-ray crystal structure of BCR-ABL^{WT} (PDB: 2GQG) [8] or BCR-ABL^{T315I} (PDB: 2Z60) [9], in its DFG-in conformation using Discovery Studio 2022 (DS). The protein structure of BCR-ABL^{WT} and BCR-ABL^{T315I} were prepared for docking by employing protocol "prepare protein", and ligands were prepared through protonation at pH 7.4 and energy minimization. The binding site was defined based on the ligand interactions with BCR-ABL kinase domain. The ligands were docked into the defined binding sites using the CDOCKER algorithm, and the ligand pose with the best score was selected for analysis of the binding mode.

1.5.2. Bioavailiability Predicition

The bioavailability prediction of compound **2b** was assessed at http://www.swissadme.ch/index.php (accessed on 10 December 2022).

2) ^{1}H NMR and ^{13}C NMR spectra



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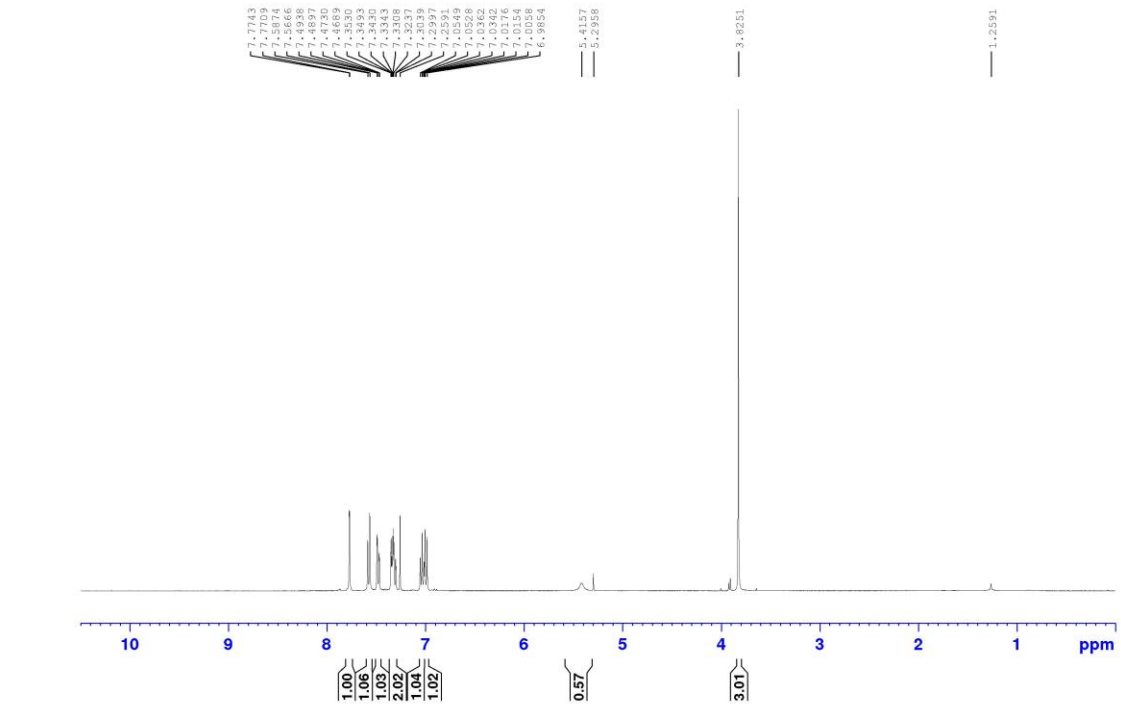

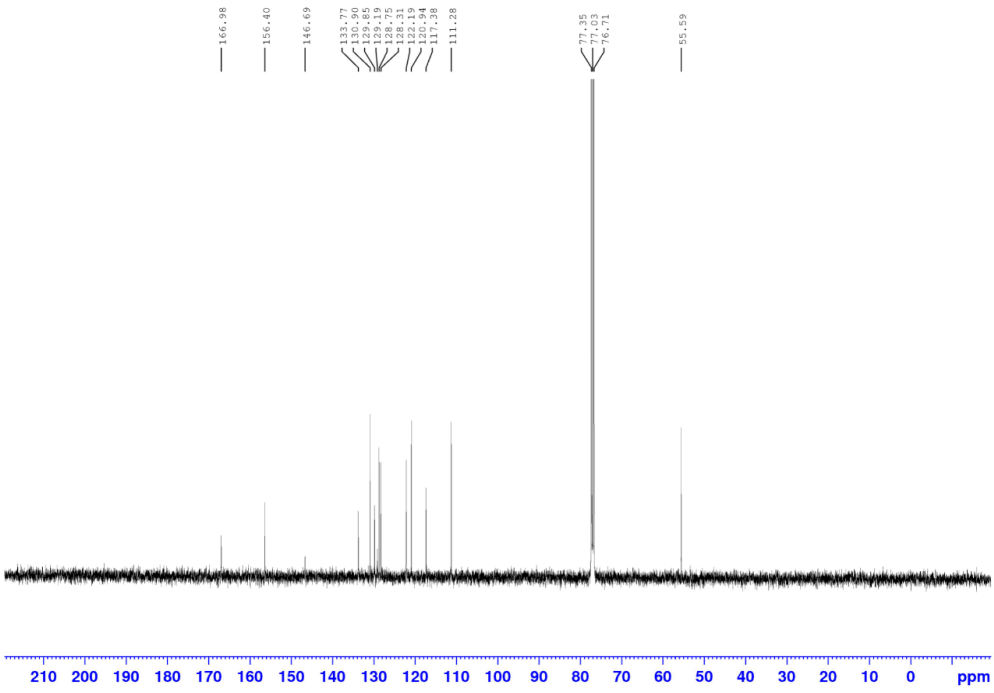

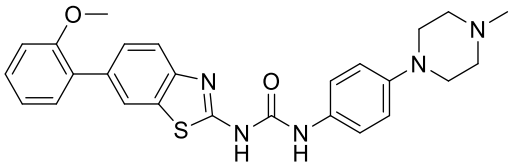
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2a


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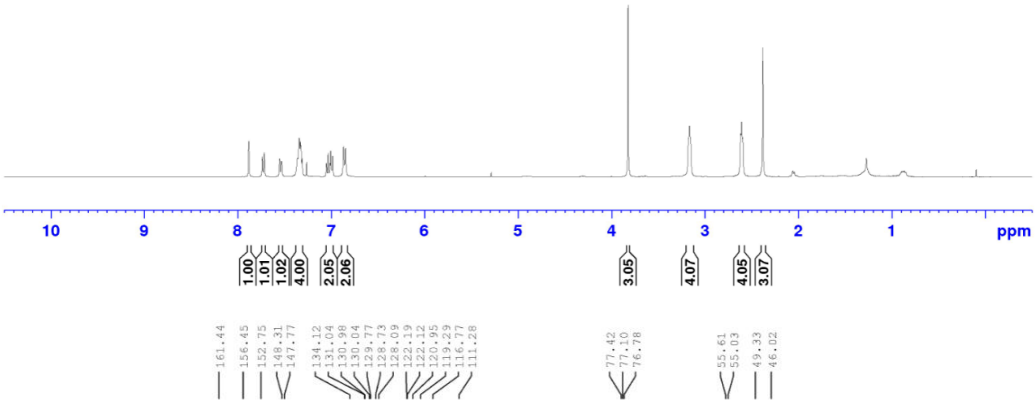
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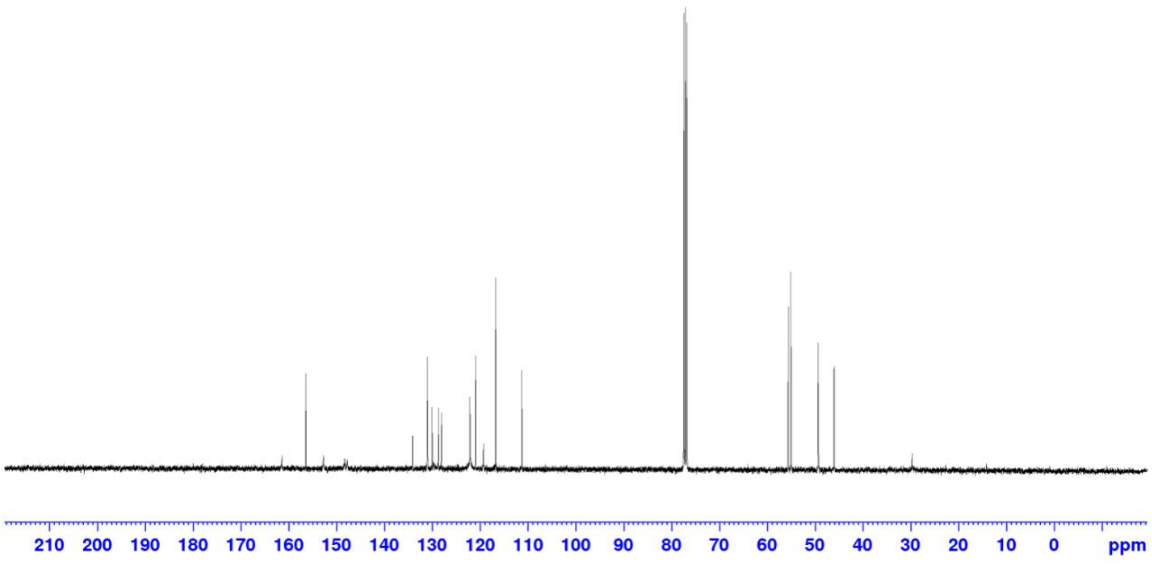
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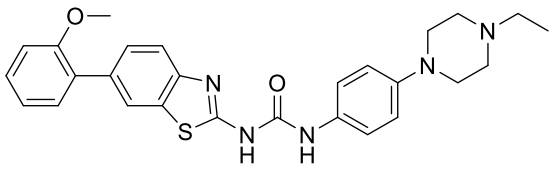
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2b


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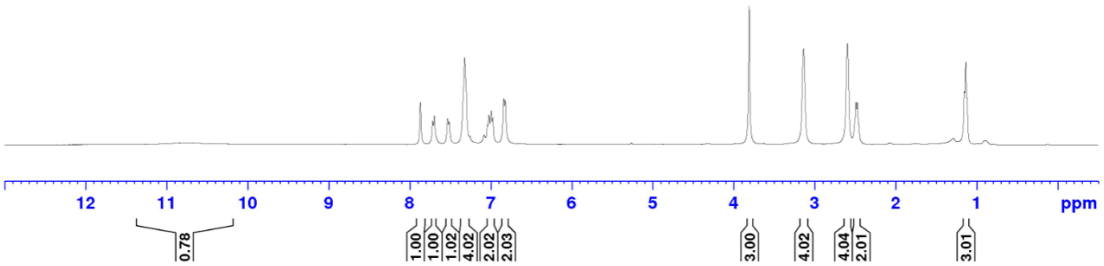
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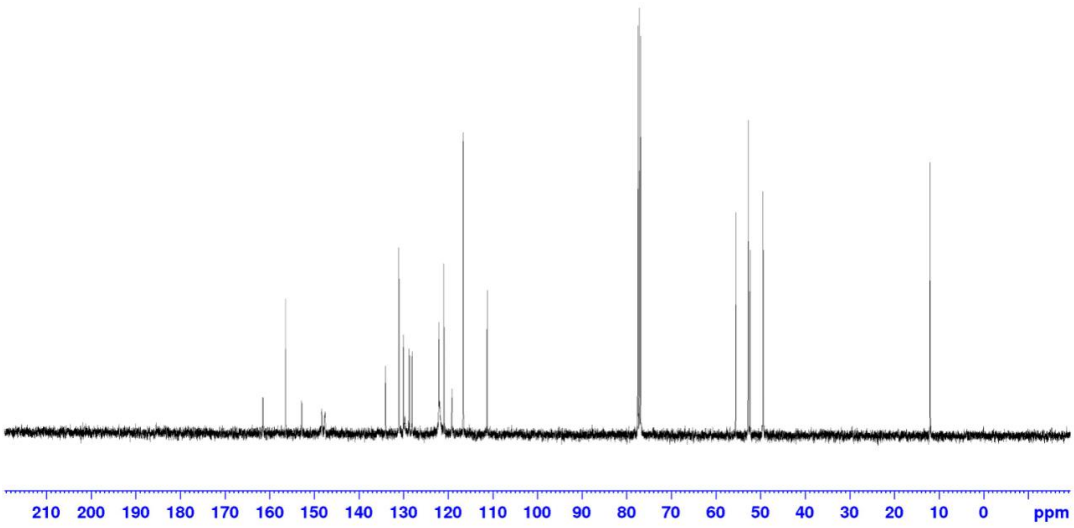
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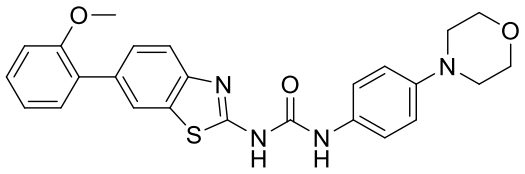

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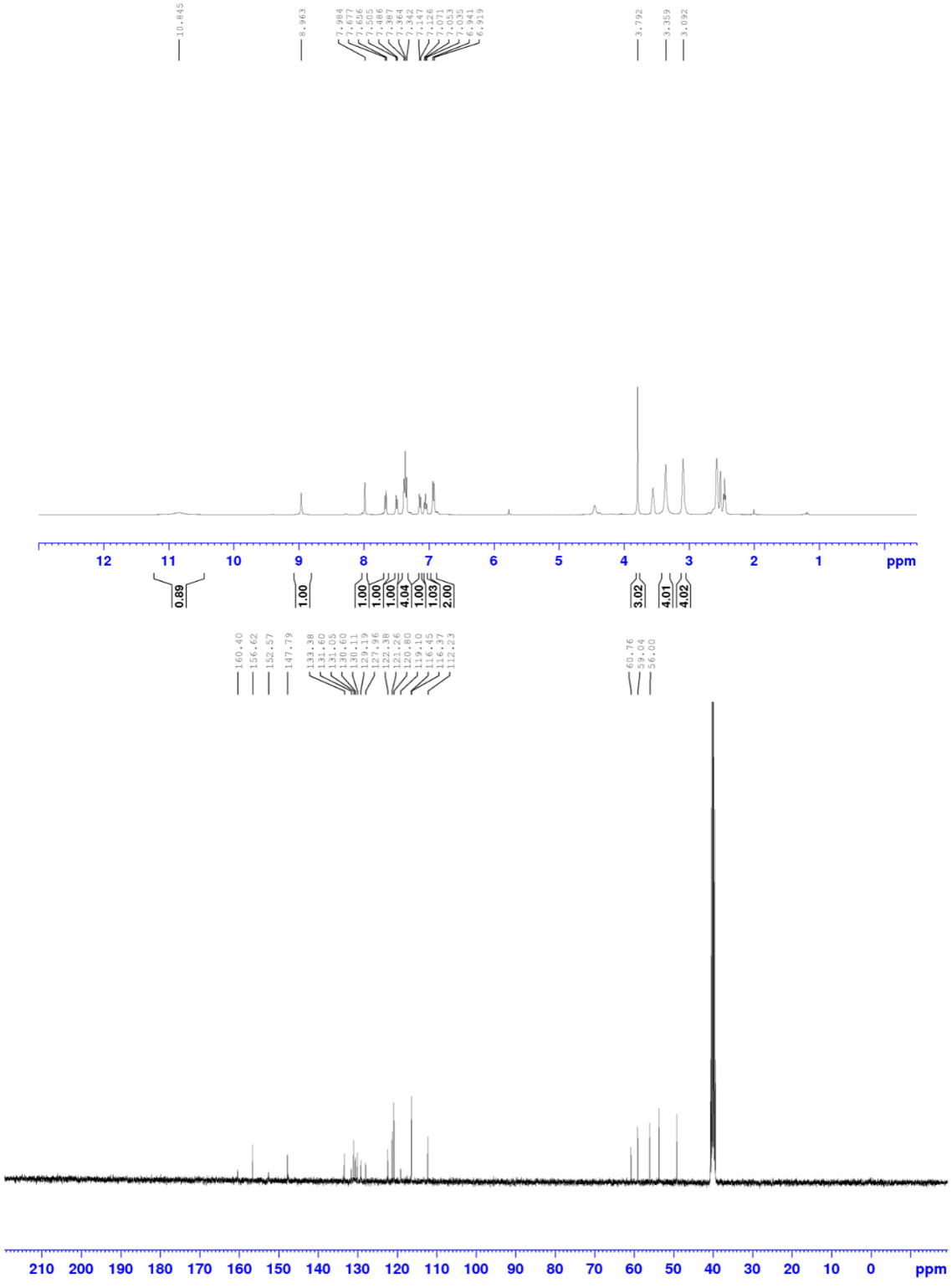

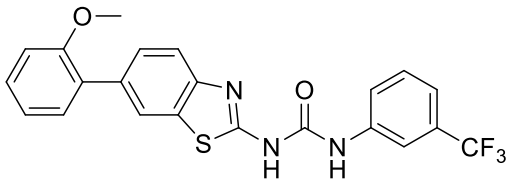
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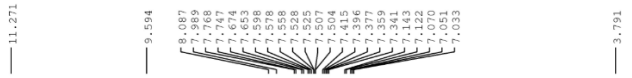
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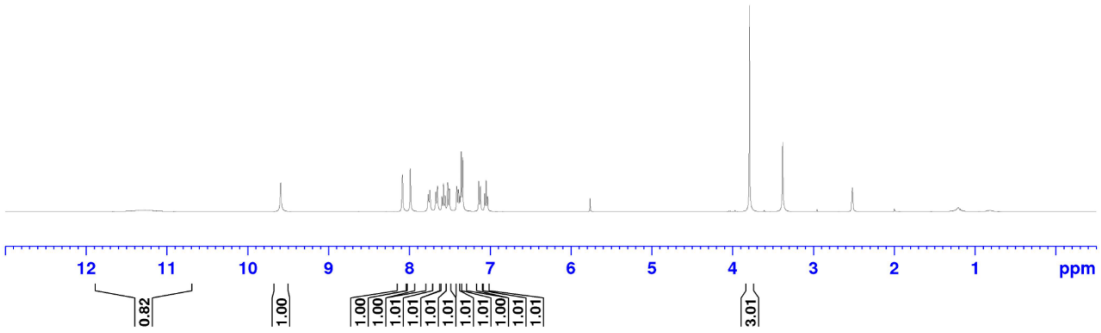
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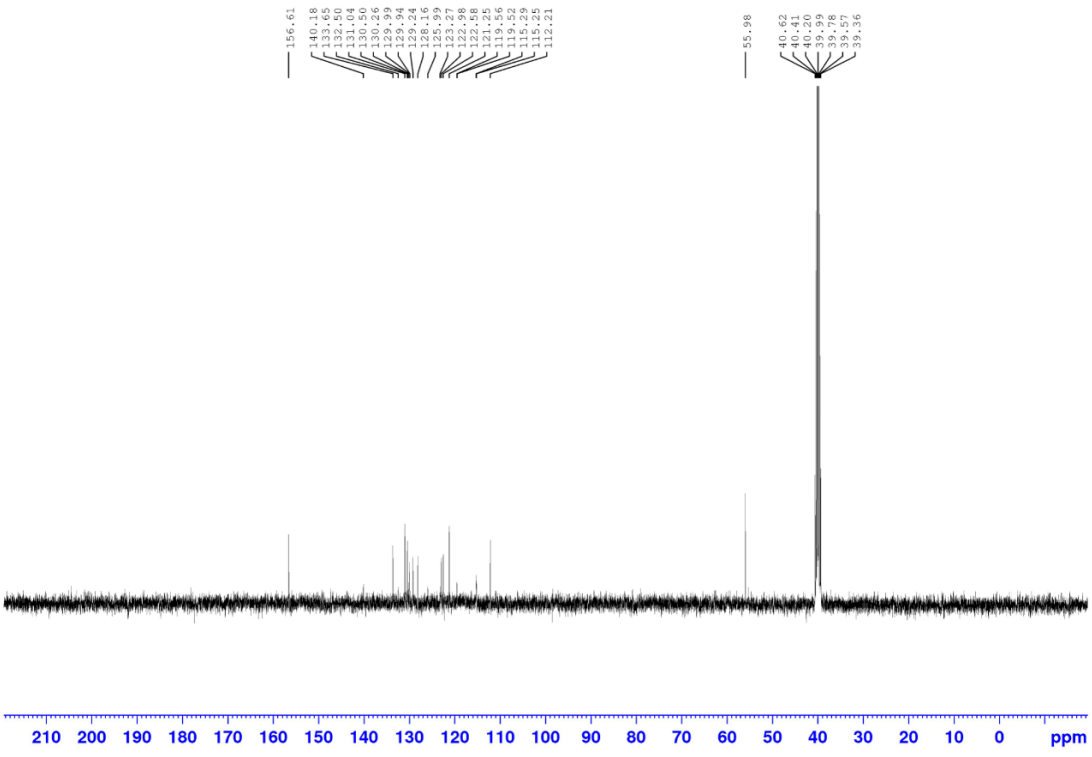
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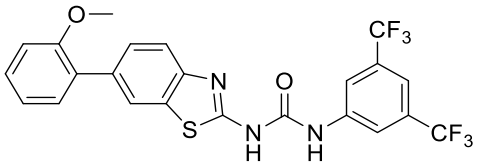
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2e


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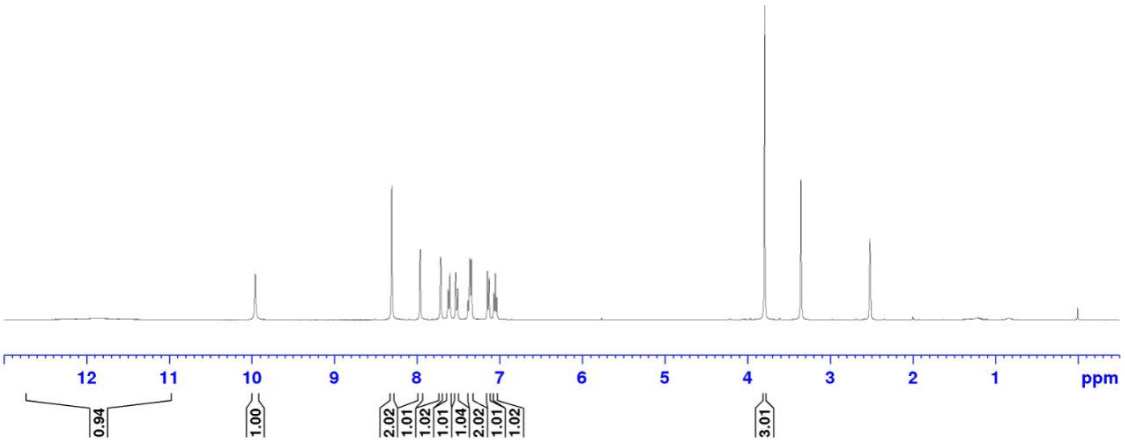
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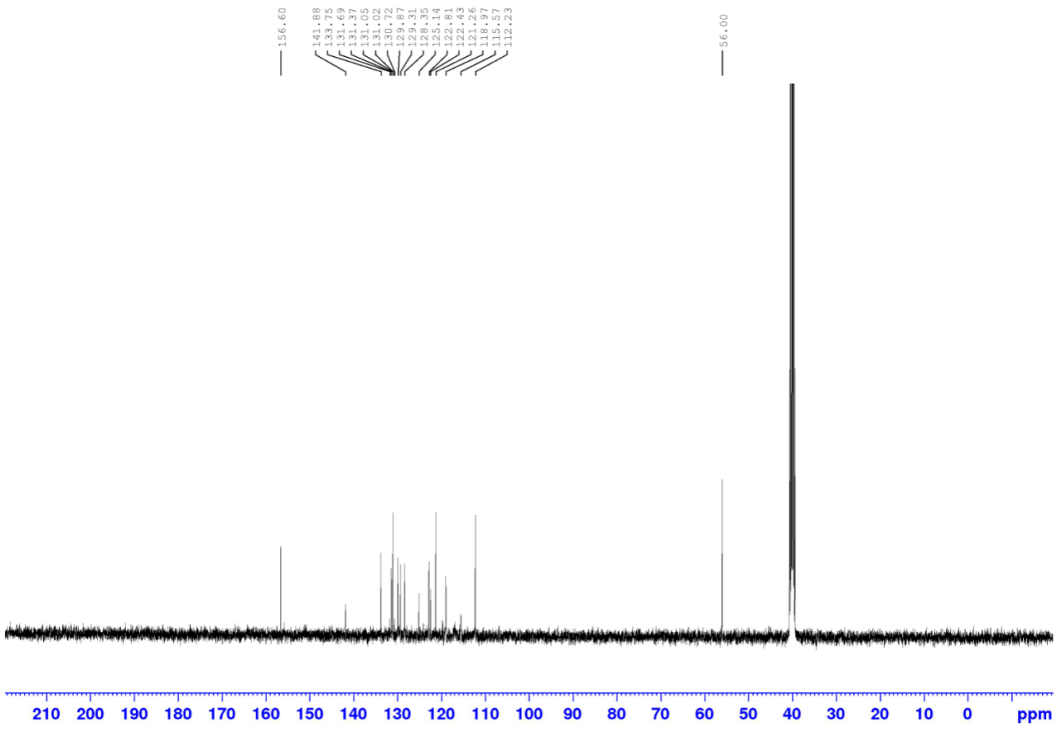
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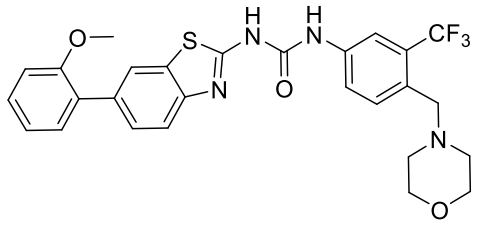

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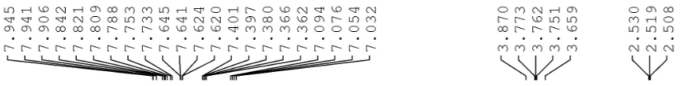
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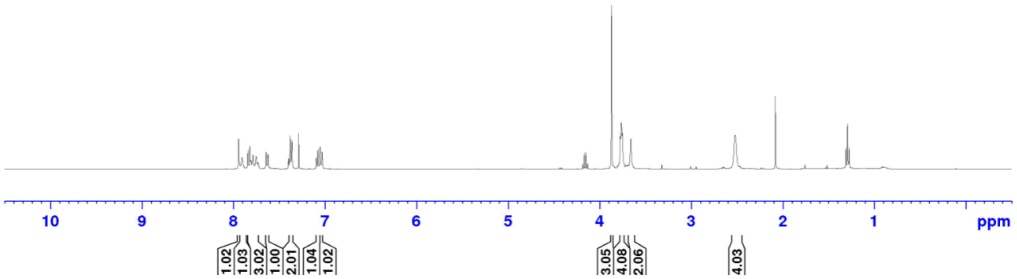
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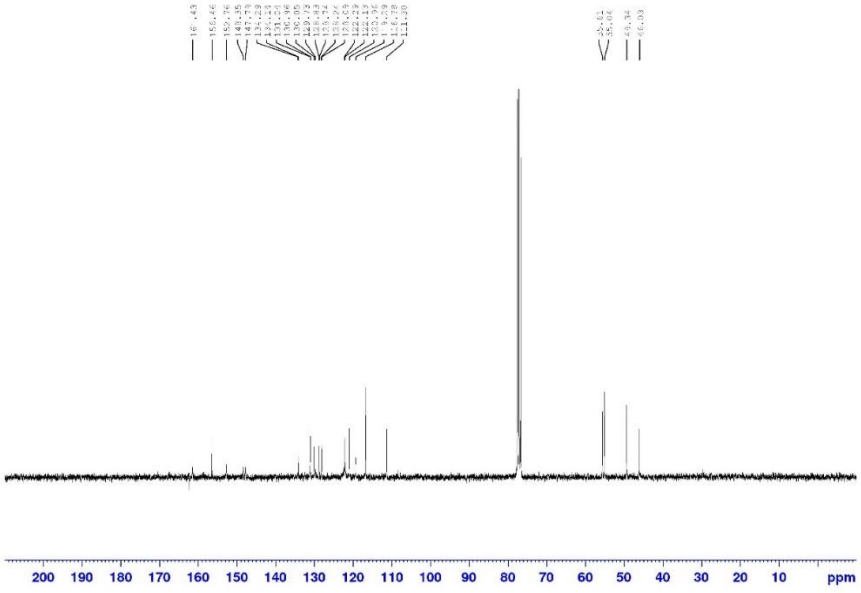
4.03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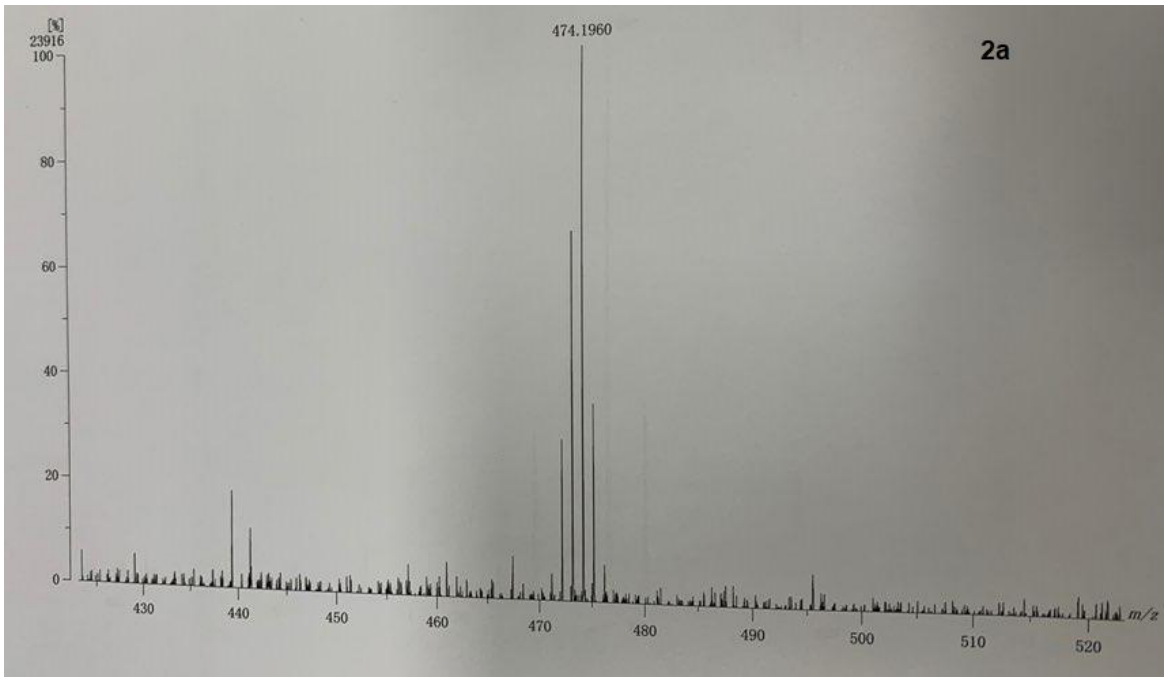
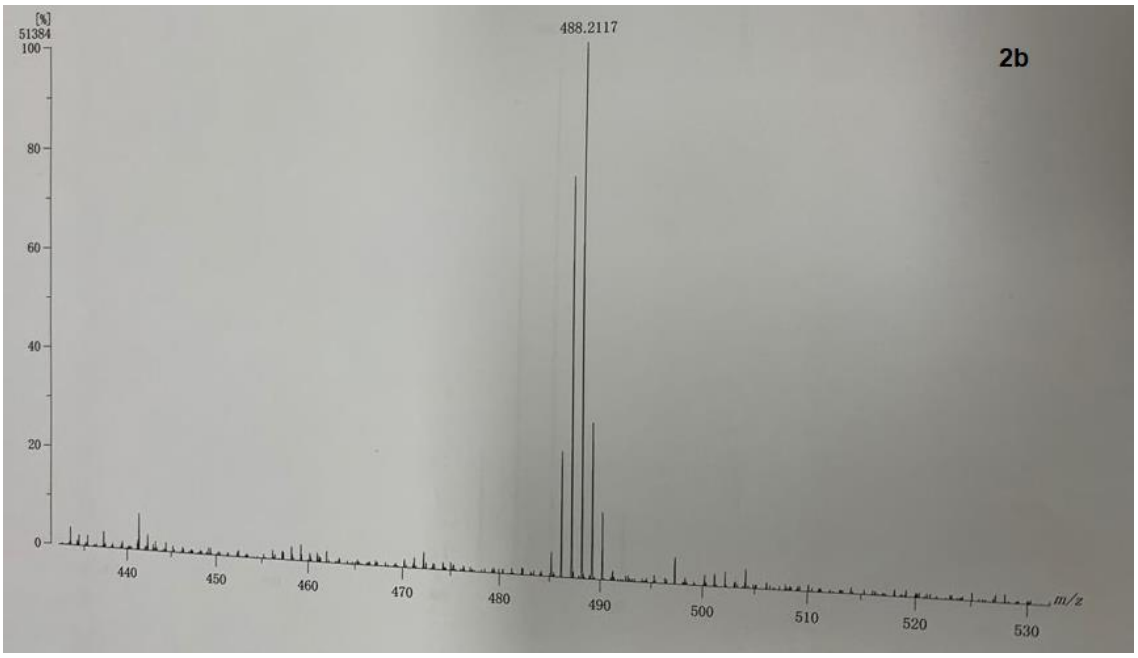
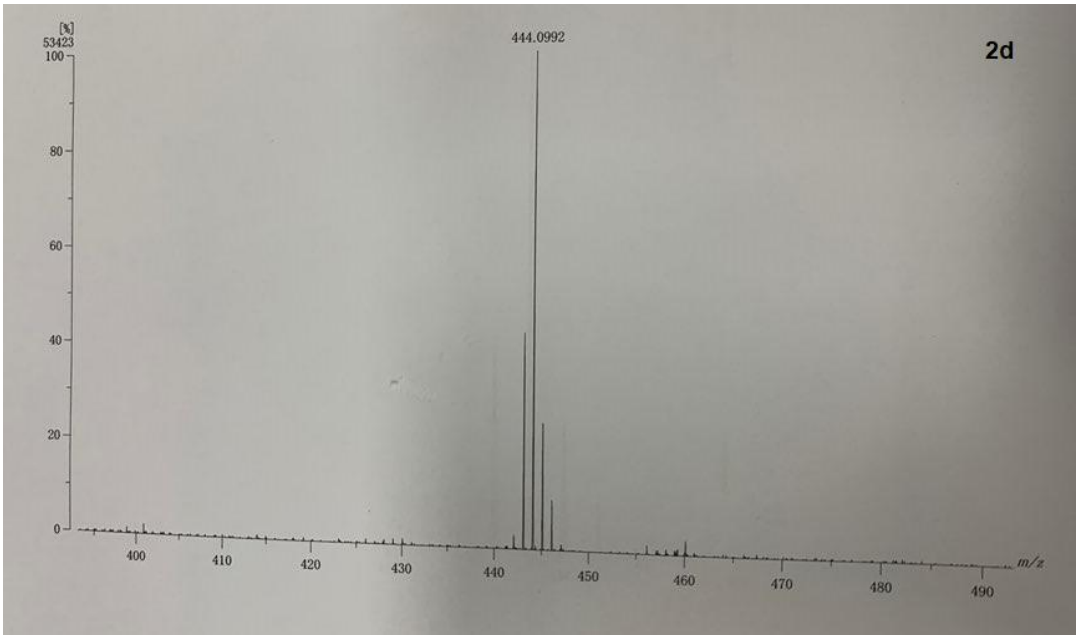
3) HRMS charts



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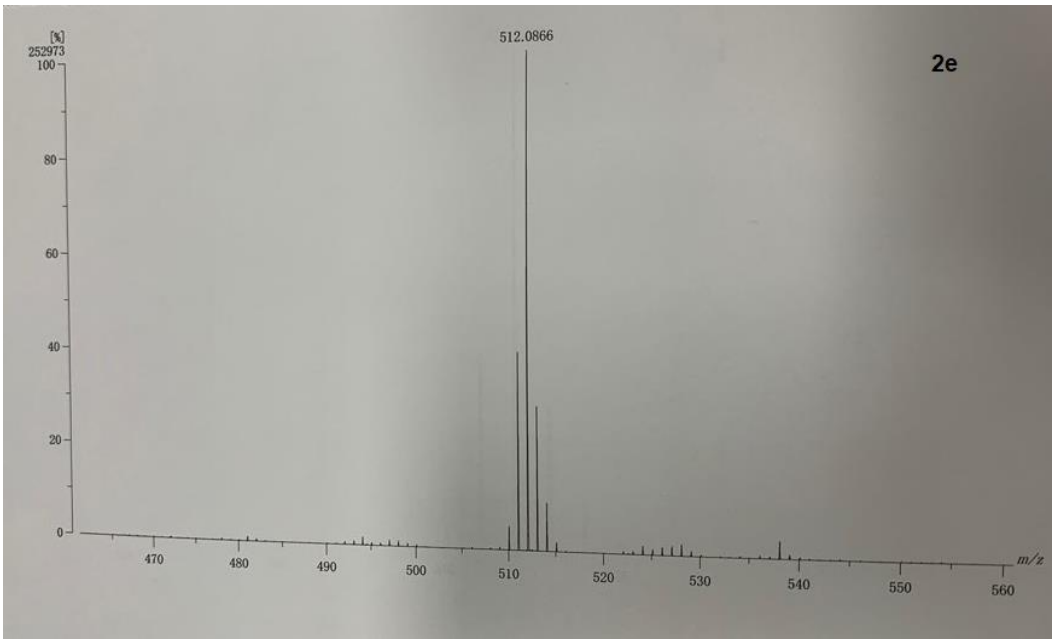
m/z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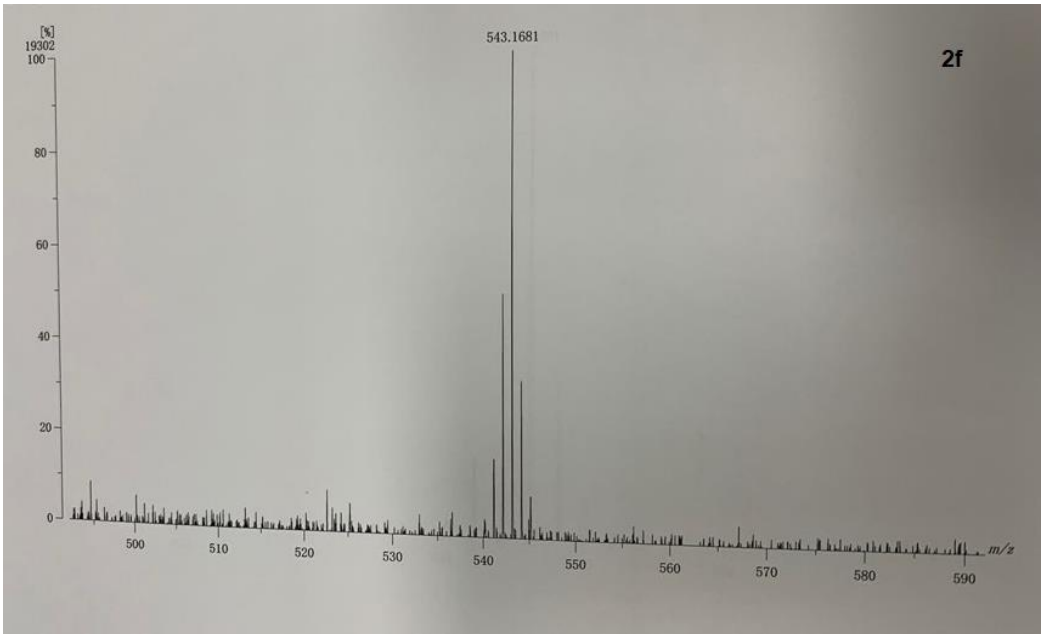
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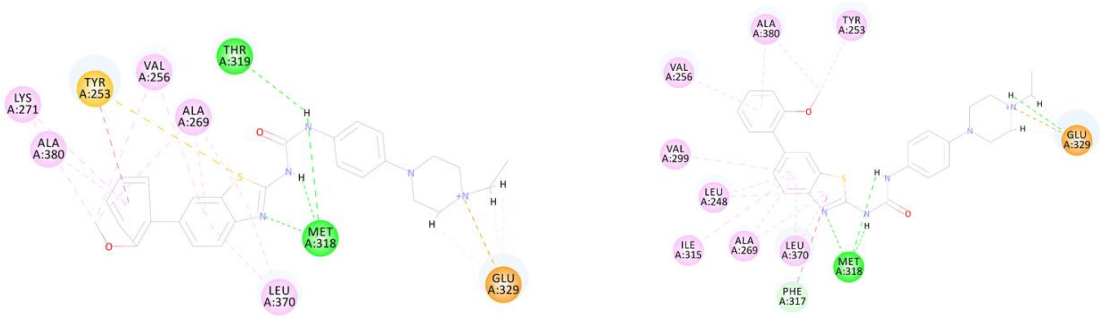
4) 2D binding mode & bioavailability radar of 2b



2b/ BCR-ABL^{WT} **2b/** BCR-ABL^{T315I}

Figure S1. 2D binding mode of compound **2b** with BCR-ABL^{WT} and BCR-ABL^{T315I}. Various interactions are depicted by different color legends. The inhibitor is shown by line, interacting residues by colored sphere, and interactions by dash lines.

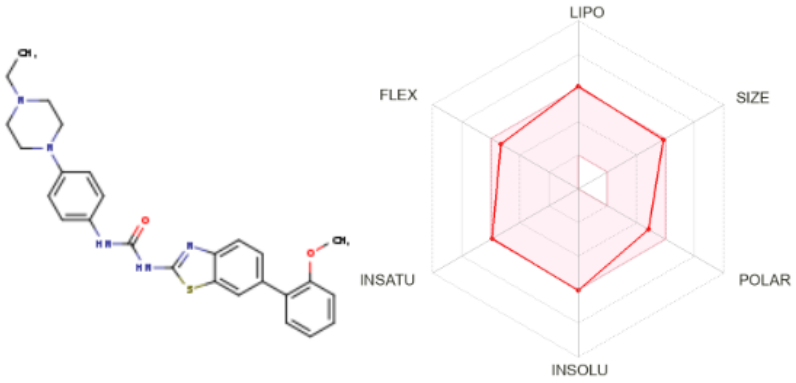
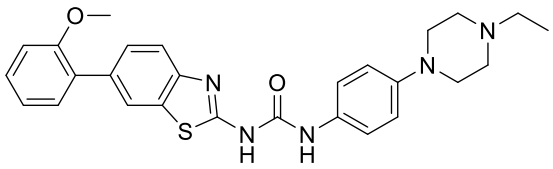


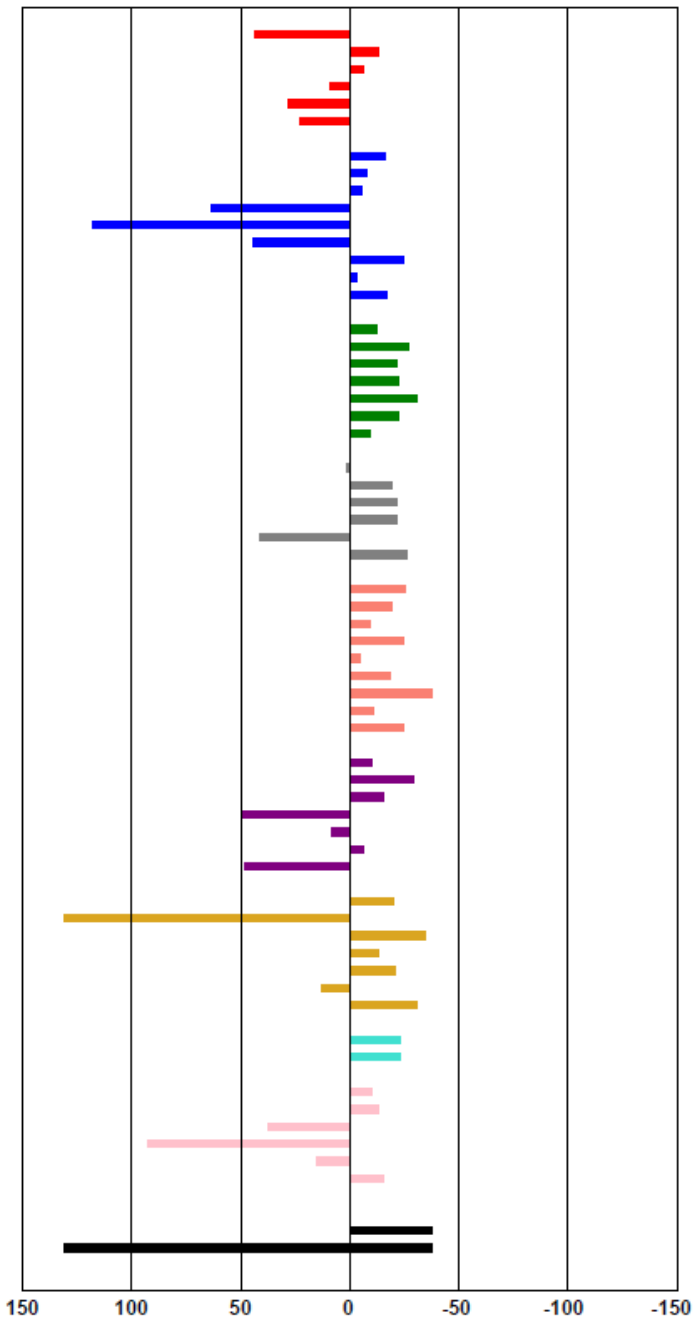
Figure S2. The bioavailability radar of **2b**.

5) NCI data

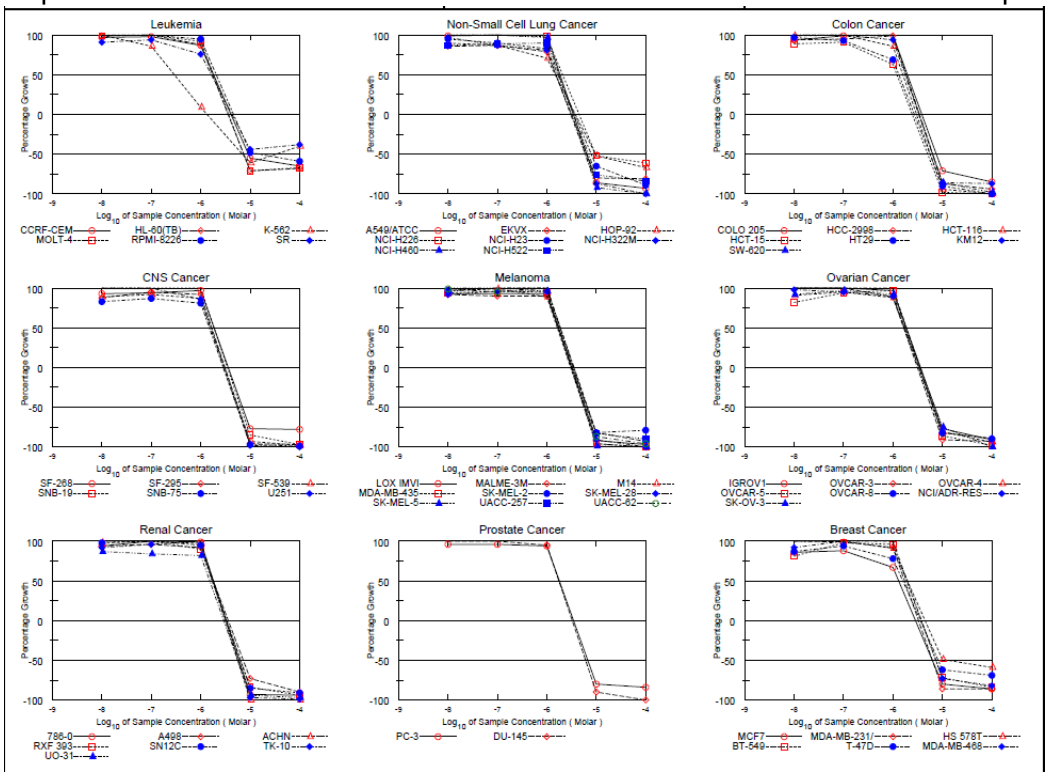


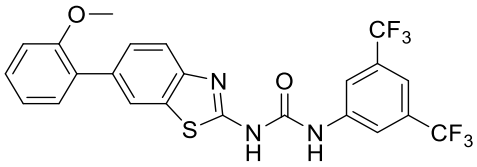
2b

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	-17.32
HL-60(TB)	-74.14
K-562	-67.39
MOLT-4	-51.72
RPMI-8226	-32.99
SR	-37.99
Non-Small Cell Lung Cancer	
A549/ATCC	-77.13
EKVX	-68.43
HOP-62	-66.15
HOP-92	2.16
NCI-H226	56.60
NCI-H23	-16.82
NCI-H322M	-85.96
NCI-H460	-64.36
NCI-H522	-78.09
Colon Cancer	
COLO 205	-73.18
HCC-2998	-88.13
HCT-116	-82.33
HCT-15	-83.17
HT29	-92.03
KM12	-83.47
SW-620	-69.98
CNS Cancer	
SF-268	-59.43
SF-295	-79.95
SF-539	-82.57
SNB-19	-82.82
SNB-75	-19.81
U251	-86.98
Melanoma	
LOX IMVI	-86.40
MALME-3M	-80.30
M14	-70.13
MDA-MB-435	-85.49
SK-MEL-2	-65.48
SK-MEL-28	-79.30
SK-MEL-5	-98.79
UACC-257	-71.94
UACC-62	-85.26
Ovarian Cancer	
IGROV1	-71.35
OVCAR-3	-90.46
OVCAR-4	-76.12
OVCAR-5	-11.52
OVCAR-8	-52.55
NCI/ADR-RES	-67.32
SK-OV-3	-12.52
Renal Cancer	
786-0	-80.66
A498	70.17
ACHN	-95.48
RXF 393	-74.15
SN12C	-82.09
TK-10	-48.01
UO-31	-91.59
Prostate Cancer	
PC-3	-83.78
DU-145	-84.44
Breast Cancer	
MCF7	-70.76
MDA-MB-231/ATCC	-73.96
HS 578T	-23.18
BT-549	31.65
T-47D	-45.42
MDA-MB-468	-76.67
Mean	-60.96
Delta	37.83
Range	168.96



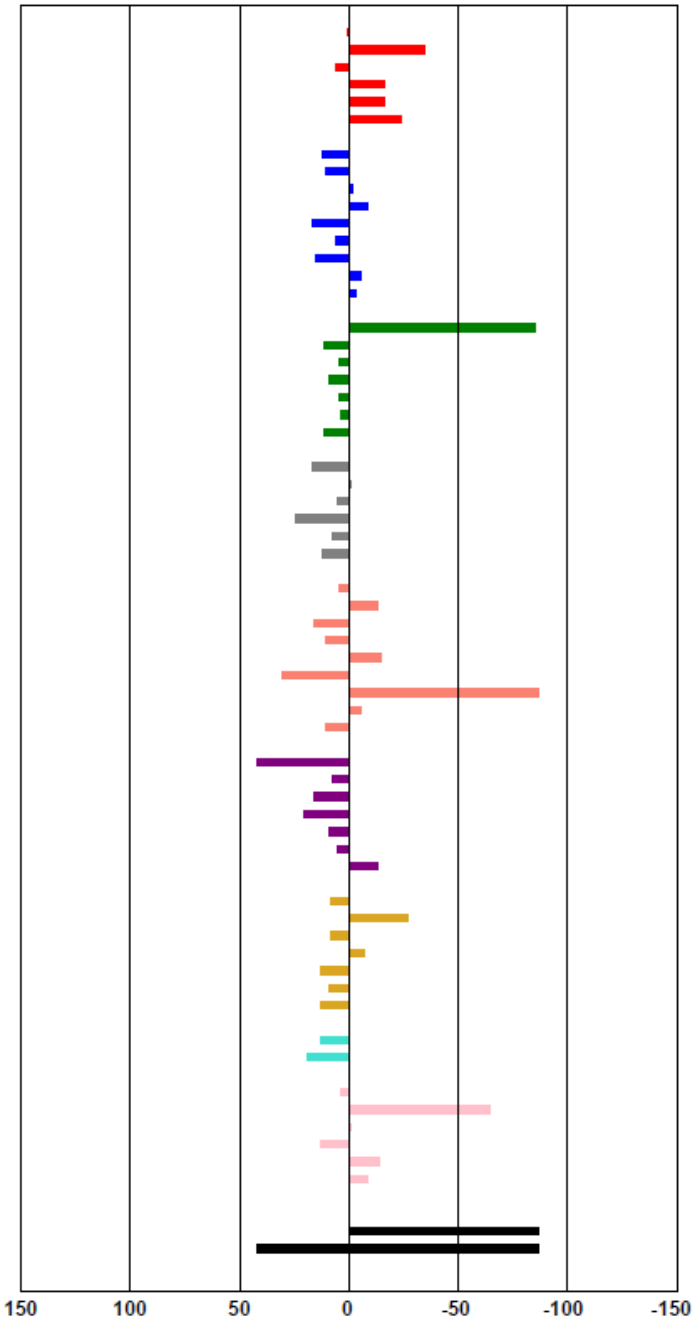
Panel/Cell Line	Time Zero	Mean Optical Densities Ctrl	-8.0	-7.0	-6.0	-5.0	-4.0	Percent Growth -8.0	-7.0	-6.0	-5.0	-4.0	GI50	TGI	LC50
Leukemia															
CCRF-CEM	0.623	2.866	2.809	2.829	2.564	0.282	0.220	97	98	87	-55	-65	1.81E-6	4.09E-6	9.25E-6
HL-60(TB)	0.842	2.792	2.774	2.804	2.553	0.246	0.269	99	101	88	-71	-68	1.73E-6	3.58E-6	7.39E-6
K-562	0.226	2.152	2.181	1.885	0.397	0.088	0.137	101	86	9	-61	-40	2.93E-7	1.34E-6	
MOLT-4	0.803	2.963	2.942	3.017	2.783	0.235	0.268	99	103	92	-71	-67	1.80E-6	3.67E-6	7.45E-6
RPMI-8226	0.767	2.614	2.709	2.712	2.517	0.397	0.318	105	105	95	-48	-59	2.06E-6	4.60E-6	1.48E-5
SR	0.367	1.200	1.123	1.150	1.001	0.206	0.227	91	94	76	-44	-38	1.65E-6	4.31E-6	> 1.00E-4
Non-Small Cell Lung Cancer															
A549/ATCC	0.524	2.482	2.454	2.560	2.628	0.073	0.036	99	104	107	-86	-93	1.98E-6	3.59E-6	6.51E-6
EKVX	0.747	2.375	2.146	2.157	2.028	0.147	0.139	86	87	79	-80	-81	1.51E-6	3.12E-6	6.44E-6
HOP-92	1.233	1.968	1.893	1.873	1.752	0.586	0.406	90	87	71	-52	-67	1.47E-6	3.75E-6	9.55E-6
NCI-H226	1.055	2.311	2.314	2.328	2.283	0.512	0.415	100	101	98	-52	-61	2.09E-6	4.52E-6	9.77E-6
NCI-H23	0.661	2.162	2.091	2.004	1.909	0.233	0.076	95	90	83	-65	-89	1.67E-6	3.65E-6	7.94E-6
NCI-H322M	1.063	2.402	2.367	2.234	2.149	0.133	-0.020	97	87	81	-87	-100	1.53E-6	3.03E-6	5.99E-6
NCI-H460	0.337	3.047	3.123	3.194	2.965	0.028	-0.006	103	105	97	-92	-100	1.77E-6	3.27E-6	6.01E-6
NCI-H522	1.256	2.983	2.765	2.786	2.812	0.308	0.196	87	89	90	-76	-84	1.75E-6	3.50E-6	7.01E-6
Colon Cancer															
COLO 205	0.670	2.527	2.411	2.504	2.539	0.192	0.104	94	99	101	-71	-85	1.97E-6	3.85E-6	7.51E-6
HCC-2998	0.631	2.454	2.350	2.366	2.430	0.080	0.036	94	95	99	-87	-94	1.83E-6	3.39E-6	6.30E-6
HCT-116	0.243	2.129	2.110	2.193	1.862	0.016	-0.022	99	103	86	-94	-100	1.58E-6	3.01E-6	5.71E-6
HCT-15	0.225	1.765	1.603	1.628	1.195	0.006	-0.043	89	91	63	-98	-100	1.20E-6	2.47E-6	5.06E-6
HT29	0.362	2.517	2.453	2.369	1.842	0.035	0.002	97	93	69	-90	-100	1.31E-6	2.70E-6	5.57E-6
KM12	0.508	2.744	2.797	2.812	2.604	0.073	0.067	102	103	94	-86	-87	1.75E-6	3.33E-6	6.33E-6
SW-620	0.331	2.097	2.089	2.223	2.189	0.046	0.008	100	107	105	-86	-98	1.94E-6	3.55E-6	6.48E-6
CNS Cancer															
SF-268	0.709	2.297	2.189	2.198	2.256	0.166	0.156	93	94	97	-77	-78	1.87E-6	3.63E-6	7.03E-6
SF-295	0.631	2.340	2.133	2.247	2.207	0.027	0.020	88	95	92	-96	-97	1.68E-6	3.09E-6	5.71E-6
SF-539	0.873	2.525	2.346	2.386	2.306	0.059	0.017	89	92	87	-93	-98	1.60E-6	3.03E-6	5.75E-6
SNB-19	0.758	2.517	2.535	2.624	2.691	0.111	0.022	101	106	110	-85	-97	2.03E-6	3.65E-6	6.59E-6
SNB-75	0.792	1.768	1.604	1.640	1.582	0.027	0.009	83	87	81	-97	-99	1.49E-6	2.86E-6	5.48E-6
U251	0.534	2.305	2.311	2.372	2.061	0.013	-0.030	100	104	86	-98	-100	1.57E-6	2.94E-6	5.51E-6
Melanoma															
LOX IMVI	0.364	2.746	2.579	2.588	2.568	0.029	0.012	93	93	93	-92	-97	1.70E-6	3.17E-6	5.92E-6
MALME-3M	0.701	1.183	1.146	1.136	1.136	0.128	0.050	92	90	90	-82	-93	1.71E-6	3.34E-6	6.54E-6
M14	0.514	1.903	1.867	1.891	1.748	0.023	-0.006	97	99	89	-96	-100	1.62E-6	3.03E-6	5.66E-6
MDA-MB-435	0.454	2.584	2.464	2.491	2.470	0.018	-0.018	94	96	95	-96	-100	1.71E-6	3.14E-6	5.74E-6
SK-MEL-2	1.090	2.445	2.410	2.484	2.491	0.195	0.232	97	103	103	-82	-79	1.94E-6	3.61E-6	6.71E-6
SK-MEL-28	0.836	2.202	2.090	2.153	2.141	0.077	-0.001	92	96	96	-91	-100	1.76E-6	3.26E-6	6.04E-6
SK-MEL-5	0.816	3.329	3.238	3.339	3.235	0.012	-0.027	96	100	96	-99	-100	1.73E-6	3.12E-6	5.63E-6
UACC-257	1.087	2.269	2.266	2.393	2.433	0.188	0.109	100	110	114	-83	-90	2.11E-6	3.79E-6	6.81E-6
UACC-62	0.929	2.892	2.879	2.802	2.912	0.122	0.034	99	95	101	-87	-96	1.87E-6	3.45E-6	6.36E-6
Ovarian Cancer															
IGROV1	0.481	1.995	2.007	2.074	1.953	0.110	0.043	101	105	97	-77	-91	1.87E-6	3.61E-6	6.99E-6
OVCAR-3	0.459	1.788	1.837	1.854	1.637	0.040	0.033	104	105	89	-91	-93	1.64E-6	3.11E-6	5.90E-6
OVCAR-4	0.710	1.555	1.481	1.516	1.455	0.133	0.044	91	95	88	-81	-94	1.68E-6	3.31E-6	6.53E-6
OVCAR-5	0.789	1.857	1.664	1.793	1.820	0.108	0.017	82	94	97	-86	-98	1.80E-6	3.37E-6	6.33E-6
OVCAR-8	0.593	2.439	2.483	2.635	2.558	0.105	0.061	102	111	106	-82	-90	1.99E-6	3.66E-6	6.74E-6
NCI/ADR-RES	0.529	2.011	1.985	1.933	1.867	0.098	0.058	98	95	90	-82	-89	1.72E-6	3.35E-6	6.55E-6
SK-OV-3	1.180	2.536	2.431	2.492	2.433	0.290	-0.007	92	97	92	-75	-100	1.79E-6	3.55E-6	7.05E-6
Renal Cancer															
786-0	0.745	2.694	2.581	2.728	2.681	0.050	0.042	94	102	99	-93	-94	1.80E-6	3.28E-6	5.96E-6
A498	1.461	2.128	2.090	2.098	2.074	0.397	0.153	94	96	92	-73	-90	1.80E-6	3.61E-6	7.27E-6
ACHN	0.385	1.586	1.563	1.642	1.554	-0.008	-0.031	98	105	97	-100	-100	1.74E-6	3.11E-6	5.58E-6
RXF 393	0.888	1.518	1.544	1.561	1.456	0.145	0.049	104	107	90	-84	-94	1.70E-6	3.30E-6	6.40E-6
SN12C	0.554	2.316	2.273	2.336	2.221	0.084	0.051	98	101	95	-85	-91	1.77E-6	3.37E-6	6.40E-6
TK-10	0.939	1.899	1.825	1.856	2.103	0.032	0.010	92	96	121	-97	-99	2.12E-6	3.60E-6	6.11E-6
UO-31	0.610	1.813	1.653	1.625	1.593	0.038	0.020	87	84	82	-94	-97	1.52E-6	2.92E-6	5.63E-6
Prostate Cancer															
PC-3	0.671	2.722	2.638	2.637	2.598	0.136	0.111	96	96	94	-80	-84	1.79E-6	3.47E-6	6.74E-6
DU-145	0.393	1.779	1.811	1.812	1.705	0.040	-0.001	102	102	95	-90	-100	1.74E-6	3.26E-6	6.08E-6
Breast Cancer															
MCF7	0.440	2.461	2.172	2.210	1.794	0.088	0.063	86	88	67	-80	-86	1.31E-6	2.86E-6	6.25E-6
MDA-MB-231/ATCC	0.663	2.145	2.152	2.137	2.021	0.094	0.096	100	99	92	-86	-86	1.72E-6	3.28E-6	6.28E-6
HS 578T	1.019	1.956	2.017	1.977	1.868	0.519	0.420	107	102	91	-49	-59	1.95E-6	4.45E-6	1.25E-5
BT-549	1.227	2.206	2.022	2.186	2.171	0.343	0.196	81	98	96	-72	-84	1.88E-6	3.73E-6	7.39E-6
T-47D	0.976	2.089	1.949	2.018	1.842	0.373	0.304	87	94	78	-62	-69	1.58E-6	3.61E-6	8.23E-6
MDA-MB-468	0.982	1.980	1.904	2.043	2.101	0.266	0.174	92	106	112	-73	-82	2.17E-6	4.03E-6	7.51E-6



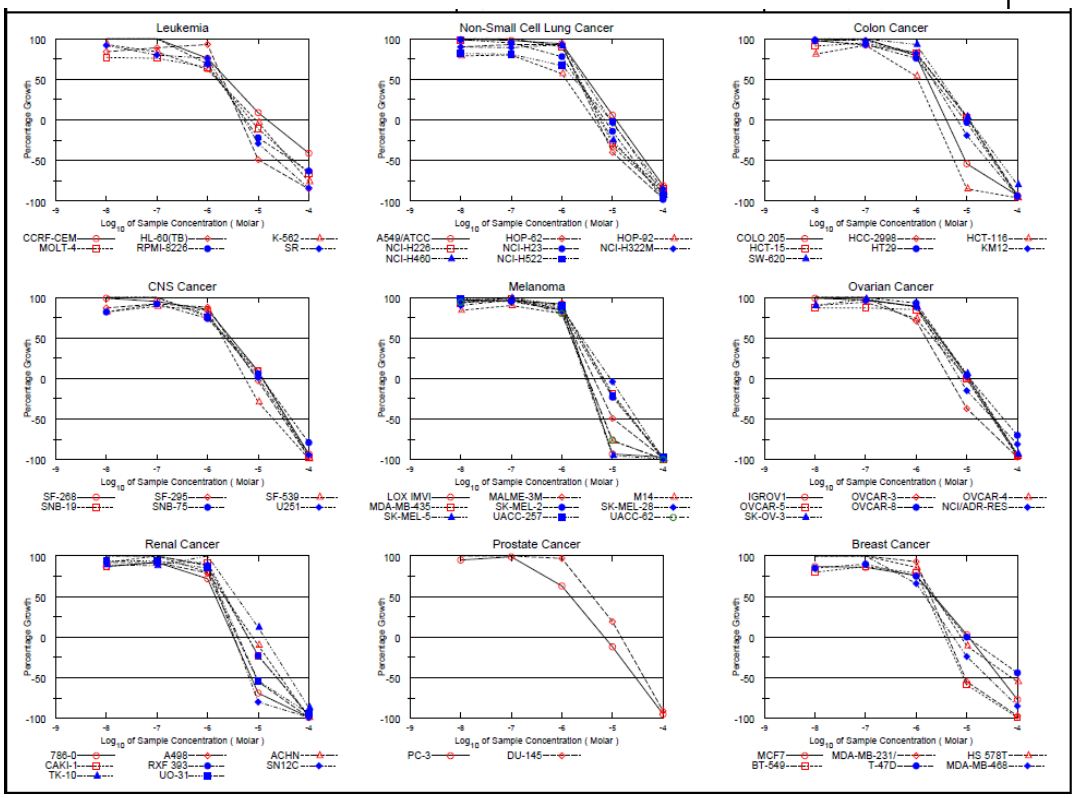


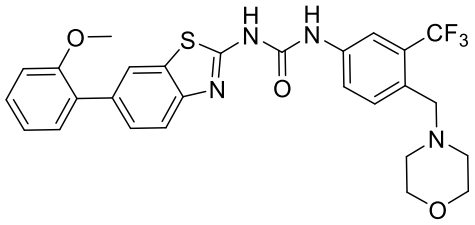
2e

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	0.89
HL-60(TB)	-34.47
K-562	5.97
MOLT-4	-15.65
RPMI-8226	-15.91
SR	-23.77
Non-Small Cell Lung Cancer	
A549/ATCC	12.73
EKVX	10.67
HOP-62	-1.58
HOP-92	-8.46
NCI-H226	16.93
NCI-H23	6.38
NCI-H322M	15.32
NCI-H460	-4.90
NCI-H522	-2.89
Colon Cancer	
COLO 205	-84.84
HCC-2998	11.83
HCT-116	4.85
HCT-15	9.74
HT29	4.76
KM12	3.63
SW-620	11.88
CNS Cancer	
SF-268	16.82
SF-295	-0.29
SF-539	5.20
SNB-19	25.06
SNB-75	8.11
U251	12.49
Melanoma	
LOX IMVI	5.02
MALME-3M	-13.04
M14	16.03
MDA-MB-435	10.94
SK-MEL-2	-14.06
SK-MEL-28	31.11
SK-MEL-5	-86.07
UACC-257	-5.57
UACC-62	10.85
Ovarian Cancer	
IGROV1	42.38
OVCAR-3	8.00
OVCAR-4	16.54
OVCAR-5	20.50
OVCAR-8	9.40
NCI/ADR-RES	5.44
SK-OV-3	-13.23
Renal Cancer	
786-0	8.85
A498	-26.71
ACHN	8.64
RXF 393	-6.71
SN12C	13.03
TK-10	9.11
UO-31	13.14
Prostate Cancer	
PC-3	13.52
DU-145	19.48
Breast Cancer	
MCF7	4.10
MDA-MB-231/ATCC	-64.24
HS 578T	-0.70
BT-549	13.18
T-47D	-13.55
MDA-MB-468	-8.23
Mean	.30
Delta	86.37
Range	128.45



		Log10 Concentration													
	Time	Mean Optical Densities						Percent Growth							
Panel/Cell Line	Zero	Ctrl	-8.0	-7.0	-6.0	-5.0	-4.0	-8.0	-7.0	-6.0	-5.0	-4.0	GI50	TGI	LC50
Leukemia															
CCRF-CEM	0.434	1.384	1.500	1.548	1.154	0.518	0.255	112	117	76	9	-41	2.43E-6	1.50E-5	> 1.00E-4
HL-60(TB)	0.750	1.867	1.687	1.749	1.790	0.384	0.112	84	89	93	-49	-85	2.01E-6	4.53E-6	1.08E-5
K-562	0.269	1.586	1.495	1.380	1.089	0.261	0.065	93	84	62	-3	-76	1.54E-6	8.95E-6	4.39E-5
MOLT-4	0.735	2.182	1.850	1.837	1.678	0.657	0.250	77	76	65	-11	-66	1.59E-6	7.24E-6	5.13E-5
RPMI-8226	0.587	2.118	2.189	2.289	1.647	0.459	0.220	105	111	69	-22	-63	1.63E-6	5.76E-6	4.93E-5
SR	0.441	1.333	1.266	1.158	1.118	0.311	0.071	92	80	76	-29	-84	1.76E-6	5.25E-6	2.38E-5
Non-Small Cell Lung Cancer															
A549/ATCC	0.361	1.574	1.583	1.554	1.506	0.437	0.070	101	98	94	6	-81	3.19E-6	1.18E-5	4.43E-5
HOP-62	0.745	2.019	1.897	1.924	1.931	0.445	0.020	90	93	93	-40	-97	2.10E-6	4.99E-6	1.48E-5
HOP-92	1.114	1.611	1.506	1.512	1.396	0.750	0.123	79	80	57	-33	-89	1.19E-6	4.31E-6	2.03E-5
NCI-H226	0.841	1.812	1.788	1.838	1.714	0.594	0.127	98	103	90	-29	-85	2.16E-6	5.67E-6	2.35E-5
NCI-H23	0.511	1.811	1.795	1.743	1.524	0.441	0.013	99	95	78	-14	-98	2.02E-6	7.09E-6	2.71E-5
NCI-H322M	0.874	2.013	1.895	1.888	1.937	0.838	0.133	90	89	93	-4	-85	2.78E-6	9.06E-6	3.70E-5
NCI-H460	0.221	2.147	2.227	2.333	1.971	0.167	0.016	104	110	91	-25	-93	2.26E-6	6.12E-6	2.35E-5
NCI-H522	0.892	2.064	1.858	1.841	1.676	0.874	0.068	82	81	67	-2	-92	1.76E-6	9.35E-6	3.39E-5
Colon Cancer															
COLO 205	0.508	1.825	1.786	1.825	1.551	0.232	0.034	97	100	79	-54	-93	1.65E-6	3.92E-6	9.28E-6
HCC-2998	0.694	2.320	2.287	2.188	2.051	0.767	0.047	98	92	83	4	-93	2.65E-6	1.11E-5	3.61E-5
HCT-116	0.195	1.417	1.188	1.313	0.854	0.030	0.008	81	92	54	-85	-96	1.07E-6	2.45E-6	5.61E-6
HCT-15	0.192	1.373	1.263	1.309	1.166	0.223	0.010	91	95	82	3	-95	2.55E-6	1.06E-5	3.46E-5
HT29	0.230	1.350	1.332	1.275	1.084	0.224	0.014	98	93	76	-3	-94	2.15E-6	9.21E-6	3.30E-5
KM12	0.508	2.595	2.579	2.549	2.217	0.410	0.032	99	98	82	-19	-94	2.07E-6	6.45E-6	2.59E-5
SW-620	0.265	1.762	1.779	1.817	1.657	0.327	0.053	101	104	93	4	-80	3.04E-6	1.12E-5	4.40E-5
CNS Cancer															
SF-268	0.537	1.918	1.909	1.854	1.704	0.660	0.040	99	95	85	9	-93	2.86E-6	1.22E-5	3.81E-5
SF-295	0.604	2.296	2.074	2.166	2.100	0.588	0.019	87	92	88	-3	-97	2.64E-6	9.33E-6	3.18E-5
SF-539	1.012	2.615	2.324	2.446	2.357	0.714	0.010	82	89	84	-29	-99	1.99E-6	5.50E-6	1.97E-5
SNB-19	0.445	1.798	1.795	1.818	1.470	0.570	0.013	100	101	76	9	-97	2.44E-6	1.22E-5	3.61E-5
SNB-75	0.886	1.716	1.563	1.647	1.499	0.938	0.182	82	92	74	6	-79	2.25E-6	1.18E-5	4.53E-5
U251	0.334	1.474	1.533	1.576	1.223	0.348	0.020	105	109	78	1	-94	2.31E-6	1.03E-5	3.44E-5
Melanoma															
LOX IMVI	0.333	2.312	2.255	2.242	2.147	0.023	0.009	97	96	92	-93	-97	1.68E-6	3.13E-6	5.84E-6
MALME-3M	0.572	1.196	1.156	1.171	1.097	0.292	0.009	94	96	84	-49	-98	1.81E-6	4.29E-6	1.05E-5
M14	0.420	1.512	1.338	1.408	1.289	0.097	0.006	84	90	80	-77	-99	1.54E-6	3.22E-6	6.73E-6
MDA-MB-435	0.592	2.405	2.282	2.381	2.184	0.484	0.001	93	99	88	-18	-100	2.27E-6	6.73E-6	2.45E-5
SK-MEL-2	1.031	2.081	2.030	2.023	1.917	0.792	0.024	95	95	84	-23	-98	2.09E-6	6.09E-6	2.29E-5
SK-MEL-28	0.753	2.248	2.091	2.201	2.036	0.726	0.005	90	97	86	-4	-99	2.51E-6	9.10E-6	3.05E-5
SK-MEL-5	0.632	2.939	2.848	2.917	2.601	0.033	0.009	96	99	85	-95	-99	1.57E-6	2.98E-6	5.64E-6
UACC-257	1.062	1.992	1.973	2.015	1.901	0.844	0.034	98	102	90	-21	-97	2.31E-6	6.52E-6	2.43E-5
UACC-62	0.631	2.445	2.333	2.455	2.091	0.149	-0.005	94	101	80	-76	-100	1.56E-6	3.26E-6	6.78E-6
Ovarian Cancer															
IGROV1	0.375	1.737	1.719	1.691	1.586	0.412	0.024	99	97	89	3	-94	2.83E-6	1.07E-5	3.52E-5
OVCAR-3	0.417	1.450	1.478	1.471	1.155	0.264	0.015	103	102	71	-37	-97	1.58E-6	4.58E-6	1.67E-5
OVCAR-4	0.826	1.664	1.576	1.613	1.448	0.825	0.034	90	94	74	0	-96	2.12E-6	9.96E-6	3.32E-5
OVCAR-5	0.581	1.340	1.245	1.242	1.226	0.574	0.023	87	87	85	-1	-96	2.54E-6	9.66E-6	3.27E-5
OVCAR-8	0.581	2.200	2.228	2.213	2.092	0.642	0.176	102	101	93	4	-70	3.04E-6	1.12E-5	5.38E-5
NCI/ADR-RES	0.487	1.677	1.683	1.636	1.546	0.415	0.093	100	96	89	-15	-81	2.37E-6	7.19E-6	3.40E-5
SK-OV-3	0.894	1.865	1.764	1.849	1.754	0.949	0.067	90	98	88	6	-93	2.92E-6	1.14E-5	3.69E-5
Renal Cancer															
786-0	0.403	1.704	1.537	1.602	1.343	0.126	0.005	87	92	72	-69	-99	1.44E-6	3.25E-6	7.36E-6
A498	1.422	2.138	2.082	2.081	1.987	0.645	0.014	92	92	79	-55	-99	1.64E-6	3.90E-6	9.23E-6
ACHN	0.379	1.616	1.521	1.612	1.364	0.341	0.006	92	100	80	-10	-99	2.14E-6	7.71E-6	2.82E-5
CAKI-1	0.767	2.725	2.463	2.561	2.574	0.594	0.031	87	92	92	-23	-96	2.33E-6	6.35E-6	2.36E-5
RXF 393	0.685	1.324	1.379	1.393	1.248	0.526	0.022	109	111	88	-23	-97	2.19E-6	6.18E-6	2.31E-5
SN12C	0.391	1.688	1.695	1.704	1.544	0.079	0.002	101	101	89	-80	-99	1.70E-6	3.36E-6	6.65E-6
TK-10	0.865	1.691	1.602	1.595	1.762	0.962	0.117	89	88	109	12	-87	4.03E-6	1.32E-5	4.25E-5
UO-31	0.608	2.046	1.960	1.956	1.833	0.277	0.035	94	94	85	-54	-94	1.79E-6	4.07E-6	9.29E-6
Prostate Cancer															
PC-3	0.440	1.367	1.323	1.361	1.023	0.388	0.023	95	99	63	-12	-95	1.49E-6	6.93E-6	2.88E-5
DU-145	0.338	1.482	1.536	1.542	1.444	0.558	0.030	105	105	97	19	-91	4.00E-6	1.49E-5	4.24E-5
Breast Cancer															
MCF7	0.346	2.183	1.937	1.934	1.746	0.401	0.081	87	86	76	3	-77	2.28E-6	1.09E-5	4.62E-5
MDA-MB-231/ATCC	0.547	1.431	1.428	1.460	1.367	0.246	0.019	100	103	93	-55	-97	1.95E-6	4.24E-6	9.23E-6
HS 578T	0.815	1.585	1.617	1.619	1.478	0.724	0.370	104	104	86	-11	-55	2.35E-6	7.67E-6	7.83E-5
BT-549	1.139	1.947	1.789	1.840	1.777	0.463	0.007	80	87	79	-59	-99	1.62E-6	3.72E-6	8.55E-6
T-47D	0.703	1.578	1.451	1.490	1.361	0.701	0.396	85	90	75	0	-44	2.16E-6	9.89E-6	> 1.00E-4
MDA-MB-468	0.640	1.326	1.337	1.353	1.095	0.487	0.095	102	104	66	-24	-85	1.52E-6	5.43E-6	2.67E-5





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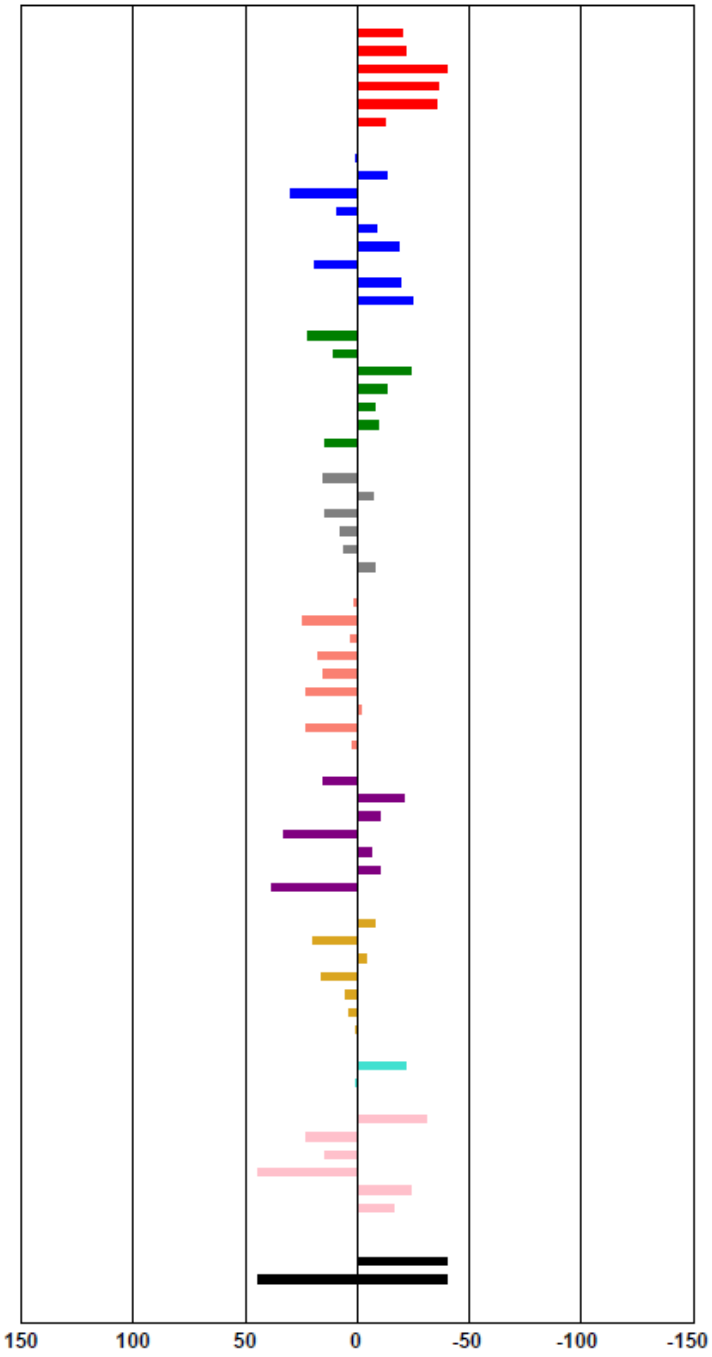
Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	36.25
HL-60(TB)	34.35
K-562	16.28
MOLT-4	20.12
RPMI-8226	21.02
SR	43.86
Non-Small Cell Lung Cancer	
A549/ATCC	56.73
EKVX	43.08
HOP-62	85.54
HOP-92	64.91
NCI-H226	47.72
NCI-H23	37.39
NCI-H322M	74.81
NCI-H460	36.68
NCI-H522	31.16
Colon Cancer	
COLO 205	78.60
HCC-2998	66.86
HCT-116	32.14
HCT-15	42.93
HT29	48.73
KM12	46.83
SW-620	70.33
CNS Cancer	
SF-268	71.62
SF-295	49.07
SF-539	70.30
SNB-19	63.40
SNB-75	62.53
U251	48.57
Melanoma	
LOX IMVI	57.27
MALME-3M	80.24
M14	58.96
MDA-MB-435	73.41
SK-MEL-2	71.59
SK-MEL-28	79.06
SK-MEL-5	54.29
UACC-257	78.71
UACC-62	58.65
Ovarian Cancer	
IGROV1	71.54
OVCAR-3	35.25
OVCAR-4	46.05
OVCAR-5	89.14
OVCAR-8	49.98
NCI/ADR-RES	46.06
SK-OV-3	94.11
Renal Cancer	
786-0	48.29
A498	76.21
ACHN	52.13
RXF 393	72.36
SN12C	61.42
TK-10	60.13
UO-31	56.97
Prostate Cancer	
PC-3	34.90
DU-145	56.86
Breast Cancer	
MCF7	25.52
MDA-MB-231/ATCC	79.35
HS 578T	70.89
BT-549	100.35
T-47D	32.01
MDA-MB-468	39.93
Mean	56.16
Delta	39.88
Range	84.07

Mean Growth Percent - Growth Percent



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