

Supplementary data for Molecular Pharmacology

Mechanism of the anti-proliferative activity of some naphthalene diimide G-quadruplex ligands

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name	nucleotide type	sequence	cation	T _m [°C]
F21T	G4-DNA	5'-FAM-GGG TTA GGG TTA GGG TTA GGG-TAMRA-3'	K ⁺	58
<i>c-kit1</i>	G4-DNA	5'-FAM-AGA GGG AGG GCG CTG GGA GGA GGG GCT-TAMRA-3'	K ⁺	52
<i>c-kit2</i>	G4-DNA	5'-FAM-CCC GGG CGG GCG CGA GGG AGG GGA GG-TAMRA-3'	K ⁺	55
<i>bcl-2</i>	G4-RNA	5'-FAM-GGG GGC CGU GGG GUG GGA GCU GGG G-TAMRA-3'	Na ⁺	68
<i>hif-1α</i>	G4-DNA	5'-FAM-GGG GAG GGG AGA GGG GGC GGG-TAMRA	K ⁺	78
T-loop	duplex-DNA	5'-FAM-TAT AGC TATA TTT TTT TATA GCT ATA-TAMRA-3'	K ⁺	54

Table S1: Nucleotide sequences used for FRET experiments.

<i>Correlation</i>	<i>Seed</i>	<i>target</i>	<i>mechanism of action</i>	<i>Common cell lines</i>	<i>Seed stand. Dev.</i>	<i>Target stand. Dev.</i>
0.82	BMSG-SH-3 NSC 753939	NSC S342443 phyllanthoside	Inhibition of protein synthesis (Chan et al., 2004).	47	0.48	0.628
0.79	BMSG-SH-3 NSC 753939	NSC S707020 oxa-spermine homologue	affects polyamine metabolism; derivatives interact with DNA (Kuska et al., 2002).	58	0.503	0.293
0.759	BMSG-SH-3 NSC 753939	NSC S764111 olivomycin	Binds to GC-rich stretches in DNA minor groove and alters transcription and replication (Cheglakov et al., 2010).	47	0.511	0.783
0.753	BMSG-SH-3 NSC 753939	NSC S353076 ellipticinium derivative	DNA intercalating agent (Larne et al., 1987). Derivatives stabilise G-quadruplex DNA (Brooks et al., 2011).	47	0.48	0.517
0.751	BMSG-SH-3 NSC 753939	NSC S259969 deoxybouvardin	Inhibits protein synthesis, decreases expression of cell cycle protein cyclin D (Wakita et al., 2001).	47	0.48	0.457
0.745	BMSG-SH-3 NSC 753939	NSC S682066 A phosphonium-porphyrin	Photochemical DNA cleavage (Saito et al., 1994). Analogs are G-quadruplex ligands (Izbicka et al., 1999).	59	0.499	0.53
0.74	BMSG-SH-3 NSC 753939	NSC S259968 bouvardin	Inhibits protein synthesis (Zalacain et al., 1982).	47	0.48	0.683
0.733	BMSG-SH-3 NSC 753939	NSC S667645	n. a.	59	0.499	0.57

			substituted acridine			
0.729	BMSG-SH-3	NSC S715654	DNA binding agent (Spsychala et al.,	56	0.51	0.371
	NSC 753939		2008; Spsychala et al., 2009).			
0.719	BMSG-SH-3	NSC S58514	binds to GC rich DNA, inhibits RNA	47	0.48	0.413
	NSC 753939		synthesis (NCI drug dictionary)			
		chromomycin				
0.704	BMSG-SH-3	NSC 80467	n. a.	46	0.473	0.716
	NSC 753939					
0.701	BMSG-SH-3	NSC S337766	DNA intercalation, DNA single-strand	47	0.48	0.622
	NSC 753939		breaks, DNA-protein crosslinking,			
		bisantrene	inhibition of DNA replication (Elliott et			
		hydrochloride	al., 1989; NCI online drug			
			dictionary).			
0.7	BMSG-SH-3	NSC S35441	DNA intercalator (Wakelin & Waring,	59	0.501	0.513
	NSC 753939		1974).			
		a phenanthridinium				
		derivative				
0.7	BMSG-SH-3	NSC S666489	Inhibitor of histone methyltransferase	59	0.499	0.522
	NSC 753939		Pr-Set7 (Kodama et al., 2011).			
		Phosphonium aryl	Analogs localise in mitochondria and			
		compound	decrease oxygen consumption			
			(Millard et al., 2010).			
0.697	BMSG-SH-3	NSC S38270	Binds to GC-rich stretches in DNA	59	0.499	0.45
	NSC 753939		minor groove and alters transcription			
		olivomycin	and replication (Cheglakov et al.,			
			2010).			
0.693	BMSG-SH-3	NSC S49842	Mitotic block (Jordan et al., 1992).	47	0.535	0.766
	NSC 753939					
		vinblastine sulfate				
0.693	BMSG-SH-3	NSC S682345	antiinflammatory C5a antagonist	59	0.499	0.265

	NSC 753939	Aurantimycin	(Assem et al., 2008).			
0.692	BMSG-SH-3 NSC 753939	NSC S219241 a phosphonium aryl compound	Analogs localise in mitochondria and decrease oxygen consumption (Millard et al., 2010).	58	0.503	0.484
0.691	BMSG-SH-3 NSC 753939	NSC S352671 a phenanthridine	analogs are DNA intercalators (Wakelin & Waring, 1974; De Stefano et al., 2009), and G- quadruplex ligands (Bai, 2008; Maiti & Kumar, 2010; Yang et al., 2010).	56	0.51	0.572
0.688	BMSG-SH-3 NSC 753939	NSC S673349 anthraquinone derivative	analogs are DNA intercalators (NSC724629)	57	0.494	0.351
0.684	BMSG-SH-3 NSC 753939	NSC S324646 malformin a	Inhibitor of protein synthesis (Dawes, 1994).	53	0.506	0.454
0.676	BMSG-SH-3 NSC 753939	NSC S713157 13,14,15- isocrambescidin 800	blocks Ca ²⁺ channel (Berlinck et al., 1993).	54	0.514	0.205
0.672	BMSG-SH-3 NSC 753939	NSC S246012 Benzophenanthridiniu m	analogs are DNA intercalators (Wakelin & Waring, 1974; De Stefano et al., 2009), and G- quadruplex ligands (Bai, 2008; Maiti & Kumar, 2010; Yang et al., 2010).	55	0.513	0.593
0.669	BMSG-SH-3 NSC 753939	NSC S674091	Topoisomerase-targeted anticancer drug, DNA binder (Spicer et al., 2002).	59	0.499	0.339
0.661	BMSG-SH-3 NSC 753939	NSC S339570	Analogs localise in mitochondria and decrease oxygen consumption	51	0.518	0.334

		A phosphonium aryl derivative	(Millard et al., 2010).			
0.66	BMSG-SH-3 NSC 753939	NSC S289922 A phosphonium aryl derivative	Analogs localise in mitochondria and decrease oxygen consumption (Millard et al., 2010).	59	0.499	0.668
0.659	BMSG-SH-3 NSC 753939	NSC S685703 didemnin analog	Analog inhibits protein synthesis (Ahuja et al., 2000).	59	0.499	0.314
0.654	BMSG-SH-3 NSC 753939	NSC S634791	DNA binder (Dimmock et al., 1992).	60	0.497	0.49
0.654	BMSG-SH-3 NSC 753939	NSC S724629	a topoisomerase I inhibitor and DNA intercalator (Dezhenkova et al., 2008).	57	0.506	0.472
0.654	BMSG-SH-3 NSC 753939	NSC S644614 a triarylethene	n. a.	50	0.501	0.393
0.652	BMSG-SH-3 NSC 753939	NSC S632624 ellipticinium derivative	Derivatives stabilise G-quadruplex DNA (Brooks et al., 2011).	47	0.479	0.389
0.651	BMSG-SH-3 NSC 753939	NSC S368672 quassinoid	inhibits translation of hif-1 α and c-myc through eIF4E phosphorylation pathway (Jin et al., 2008; Mata-Greenwood et al., 2002).	47	0.48	0.275
0.648	BMSG-SH-3 NSC 753939	NSC S176878 A phosphonium aryl derivative	Analogs localise in mitochondria and decrease oxygen consumption (Millard et al., 2010).	47	0.48	0.419
0.648	BMSG-SH-3 NSC 753939	NSC S179220 azothiazolium	n. a.	59	0.496	0.544

		derivative				
0.647	BMSG-SH-3 NSC 753939	NSC S747162 mitotempol	mitochondria-targeted antioxidant, decreases reactive oxygen species and muscle differentiation (Lee et al., 2011)	60	0.497	0.346
0.646	BMSG-SH-3 NSC 753939	NSC S714616	nucleic acid binding (Kang et al., 2004; Spsychala, 2008; Spsychala, 2009).	57	0.507	0.207
0.641	BMSG-SH-3 NSC 753939	NSC S710608	DNA binding (Spsychala, 2008; Spsychala, 2009).	59	0.499	0.303
0.638	BMSG-SH-3 NSC 753939	NSC S665806 didemnin analog	Analog inhibits protein synthesis (Ahuja et al., 2000).	58	0.5	0.538
0.638	BMSG-SH-3 NSC 753939	NSC S226510	n. a.	47	0.483	0.192
0.637	BMSG-SH-3 NSC 753939	NSC S694330 didemnin analog	Analog inhibits protein synthesis (Ahuja et al., 2000).	58	0.502	0.177
0.637	BMSG-SH-3 NSC 753939	NSC S711659 azaharman analog; aza-ellipticine derivative	Derivatives stabilise G-quadruplex DNA (Brooks et al., 2011).	57	0.505	0.326
0.91	BMSG-SH-4 NSC 753938	NSC:S753940 Naphthalene diimide BMSG-SH-5	Analog of the seed, G-quadruplex ligand (Cuenca et al., 2008).	60	0.389	0.285
0.584	BMSG-SH-4 NSC 753938	NSC:S625331 aza-ellipticine	DNA affinity (Nguyen et al., 1987). Derivatives stabilise G-quadruplex DNA (Brooks et al., 2011).	46	0.382	0.336

		derivative				
0.577	BMSG-SH-4 NSC 753938	NSC:S721046	n. a.	50	0.401	0.247
0.541	BMSG-SH-4 NSC 753938	NSC:S656125	n. a.	49	0.375	0.213
0.531	BMSG-SH-4 NSC 753938	NSC:S155694	Derivatives stabilise G-quadruplex DNA (Brooks et al., 2011). ellipticinium derivative	47	0.386	0.571
0.525	BMSG-SH-4 NSC 753938	NSC:S656575	n. a. Maleopimaric acid amide	47	0.379	0.197
0.519	BMSG-SH-4 NSC 753938	NSC:S268239	Adriamycin derivative (an anthracycline)	49	0.368	0.298
0.516	BMSG-SH-4 NSC 753938	NSC:S298223	CC-1065	46	0.39	0.64
0.506	BMSG-SH-4 NSC 753938	NSC:S671450	n. a.	54	0.36	0.168
0.505	BMSG-SH-4 NSC 753938	NSC:S32938	antimalarial, a cresol derivative	56	0.376	0.138
0.91	BMSG-SH-5 NSC 753940	NSC:S753938	Naphthalene diimide BMSG-SH-4	60	0.285	0.389

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0.593	BMSG-SH-5 NSC 753940	NSC:S625331 aza-ellipticine derivative	DNA affinity (Nguyen et al., 1987). Derivatives stabilise G-quadruplex DNA (Brooks et al., 2011).	46	0.263	0.336
0.584	BMSG-SH-5 NSC 753940	NSC:S58514 Chromomycin A3	binds to GC rich DNA, inhibits RNA synthesis (http://www.cancer.gov/drugdictionary?cdrid=39184)	47	0.275	0.413
0.577	BMSG-SH-5 NSC 753940	NSC:S753939 Naphthalene diimide BMSG-SH-3	Analog of the seed, G-quadruplex ligand (Hampel et al., 2010).	60	0.285	0.497
0.572	BMSG-SH-5 NSC 753940	NSC:S155694 ellipticinium derivative	Derivatives stabilise G-quadruplex DNA (Brooks et al., 2011).	47	0.275	0.571
0.567	BMSG-SH-5 NSC 753940	NSC:S325319 didemnin B	inhibits protein synthesis via binding to complexes between ribosomes and the elongation factor EF-1 α , which prevents binding to elongation factor EF-2 (Ahuja et al., 2000).	55	0.287	0.346
0.547	BMSG-SH-5 NSC 753940	NSC:S705956 didesmethylrocaglamide	Inhibitor of translation initiation, causes G2/M block (Cencic et al., 2009).	57	0.284	0.121
0.537	BMSG-SH-5 NSC 753940	NSC:S254681 12-iminodaunorubicin (an anthracyclin)	Analogs are G-quadruplex ligands (Manet et al., 2010; Clark et al., 2003). Inhibition of transcription by interacting with DNA in gene promoter regions (Banerjee & Mukhopadhyay, 2008; Sriram et al., 1991; Mansilla & Portugal, 2008).	50	0.284	0.818

0.535	BMSG-SH-5 NSC 753940	NSC:S265450 nogalomycin c (an anthracyclin)	Analogues are G-quadruplex ligands (Manet et al., 2010; Clark et al., 2003). Inhibition of transcription by interacting with DNA in gene promoter regions (Banerjee & Mukhopadhyay, 2008; Sriram et al., 1991; Mansilla & Portugal, 2008).	47	0.275	0.43
0.53	BMSG-SH-5 NSC 753940	NSC:S259968 bouvardin	Inhibits protein synthesis (Zalacain et al., 1982).	51	0.281	0.563
0.526	BMSG-SH-5 NSC 753940	NSC:S259969 deoxybouvardin	Inhibits protein synthesis, decreases expression of cell cycle protein cyclin D (Wakita et al., 2001).	47	0.275	0.457
0.523	BMSG-SH-5 NSC 753940	NSC:S342443 Phyllantoside, S3'-desacetyl-	Analogues inhibit protein synthesis (Chan et al., 2004).	47	0.275	0.628
0.521	BMSG-SH-5 NSC 753940	NSC:S368672 quassinoid	inhibits translation of <i>hif-1α</i> and <i>c-myc</i> through eIF4E phosphorylation pathway (Jin et al., 2008; Mata-Greenwood et al., 2002).	47	0.275	0.275
0.52	BMSG-SH-5 NSC 753940	NSC:S351710 2-methylelliciniumiodide	Derivatives stabilise G-quadruplex DNA (Brooks et al., 2011).	47	0.275	0.62
0.517	BMSG-SH-5 NSC 753940	NSC:S131547 tubulosine	disrupts mitosis (Farjaudon et al., 1988).	59	0.286	0.458
0.516	BMSG-SH-5 NSC 753940	NSC:S672658	n. a.	54	0.283	0.236

		a peptide				
0.51	BMSG-SH-5 NSC 753940	NSC:S83193 C.I. basic blue 1	n. a.	60	0.285	0.193
0.508	BMSG-SH-5 NSC 753940	NSC:S671035	n. a.	58	0.274	0.141
0.502	BMSG-SH-5 NSC 753940	NSC:S670163 an aryl phosphonium compound	Analogs localise in mitochondria and decrease oxygen consumption (Millard et al., 2010).	55	0.28	0.478

Table S2: COMPARE study of compounds BMSG-SH-3 – 5 against NCI compound library. References for the mechanisms of action of correlated compounds are listed in the supplementary material section.

<i>Correlatio n</i>	<i>Seed</i>	<i>target vector</i>	<i>function of vector</i>	<i>Common cell lines</i>	<i>Seed stand. Dev.</i>	<i>Target stand. Dev.</i>
0.627	BMSG-SH-3 NSC 753939	Moltd: GC15718, Genecard: HNRPLL	Encodes for RNA-binding protein which regulates alternative splicing for multiple target mRNAs (Yamamoto et al., 2009).	59	0.499	0.221
0.581	BMSG-SH-3 NSC 753939	Moltd: GC17547, Genecard: ACYP1	Encodes for Acylphosphatase-1 enzyme, which may be involved in alternative splicing and cell cycle regulation (Degl'innocenti et al., 2004; Stone et al., 2010).	59	0.499	0.189
0.564	BMSG-SH-3 NSC 753939	Moltd: GC60277, Genecard: C9orf173	chromosome 9 open reading frame, encoding for hypothetical protein LOC441476, function unknown (Ota et al., 2004).	59	0.499	88.127
0.491	BMSG-SH-3 NSC 753939	Moltd: GC67014,	Encodes for RNA-binding protein which regulates alternative splicing	59	0.499	165.655

		Genecard: HNRPLL	for multiple target mRNAs (Yamamoto et al., 2009).			
0.478	BMSG-SH-3 NSC 753939	MoltId: GC91516, Genecard: SNX31	Sorting nexin 31, involved in protein transport and sorting, membrane trafficking, and alternative splicing (Ghaj et al., 2011).	59	0.499	22.043
0.471	BMSG-SH-3 NSC 753939	MoltId: GC66400, Genecard: FAM124A	unknown (Ota et al., 2004).	59	0.499	108.146
0.522	BMSG-SH-4 NSC 753938	MoltId: GC160652, Genecard: OSCP1	Organic solute carrier partner 1, a transporter which may be involved in drug clearance in placenta (Kobayashi et al., 2005).	59	0.391	29,463
0.494	BMSG-SH-4 NSC 753938	MoltId: GC182826, Genecard: SQSTM1	Sequestosome 1. Involved in polyubiquitination, trafficking, inclusions, and adapter protein binding to ubiquitin. May regulate signaling cascades (e. g. apoptosis, K ⁺ channel regulation) (Young & Keiko, 2009).	59	0.391	368.75
0.494	BMSG-SH-4 NSC 753938	MoltId: GC84738, Genecard: TP53/13	Tumour protein 53 inducible protein 13, may act as tumour suppressor (reference)	59	0.391	199.379
0.486	BMSG-SH-4 NSC 753938	MoltId: GC188357, Genecard: THAP10	Encodes for proteins containing domains similar to DNA binding zinc finger domains; regulates cytokine expression (Champagne et al., 2010 ; Clouaire et al., 2005).	59	0.391	26.648
0.484	BMSG-SH-4 NSC 753938	MoltId: GC169527, Genecard: SQSTM1	Sequestosome 1. Involved in polyubiquitination, trafficking,	59	0.391	68.33

			inclusions, and adapter protein binding to ubiquitin. May regulate signaling cascades (e. g. apoptosis, K ⁺ channel regulation) (Young & Keiko, 2009).			
0.483	BMSG-SH-4 NSC 753938	MolId: GC96959, Genecard: SQSTM1	Sequestosome 1. Involved in polyubiquitination, trafficking, inclusions, and adapter protein binding to ubiquitin. May regulate signaling cascades (e. g. apoptosis, K ⁺ channel regulation) (Young & Keiko, 2009).	59	0.391	476.204
0.48	BMSG-SH-5 NSC 753940	MolId: GC152314, Genecard: ASB1	Encodes for ankyrin repeat and SOCs box protein 1 (suppressor of cytokine signaling) (Kohroki et al., 2005).	59	0.286	31.644
0.471	BMSG-SH-5 NSC 753940	MolId: GC93247, Genecard: IDS	Encodes for Iduronate-2 sulfatase, which is required for lysosomal degradation of heparan and dermatan sulfate, and is related to the Hunter syndrome (Froissart et al., 1995).	59	0.286	92.605
0.469	BMSG-SH-5 NSC 753940	MolId: GC187706, Genecard: ZHHC4	Encodes for zinc finger protein 374, a palmitoyltransferase (Ota et al., 2004).	59	0.286	89.778
0.467	BMSG-SH-5 NSC 753940	MolId: GC36321, Genecard: NFIC	Encodes for protein binding to palindromic sequences in promoters and activates transcription and replication (Santoro et al., 1988).	59	0.286	53.55

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0.464	BMSG-SH-5	MolId: GC47494,	Encodes for a subunit of V-ATPase,	59	0.286	41.437
	NSC 753940	Genecard: ATP6V1B1	which acidifies intercellular compartments (Paunescu et al., 2007).			
0.457	BMSG-SH-5	MolId: GC60277,	chromosome 9 open reading frame,	59	0.286	88.127
	NSC 753940	Genecard: C9orf173	encoding for hypothetical protein LOC441476, function unknown (Ota et al., 2004).			

Table S3: COMPARE study of compounds BMSG-SH-3 – 5 against **Brown/Botstein/Weinstein** microarray dataset. References for the functions of vectors are listed in the supplementary material section.

Uptake study on MCF7 cells

Dimensions: x: 146.11 μm , Y: 146.11 μm

Objective: Plan-Apochromat 63x/1.4 Oil DIC M27

Pixel dwell: 1.60 μs

Average: line 4

Master gain: Ch1 : 775; ChD : 319

Digital gain: 1.00

Digital offset: Ch1 : -0.10; ChD : 0.08

Pinhole: 106 μm

Filter: LP 560

Beam Splitters: MBS : HFT 488/543; DBS1: Mirror; DBS2: Plate.

Laser: 543 nm : 100 %.

Manual corrections: Brightness 45 %; Contrast 55 %.

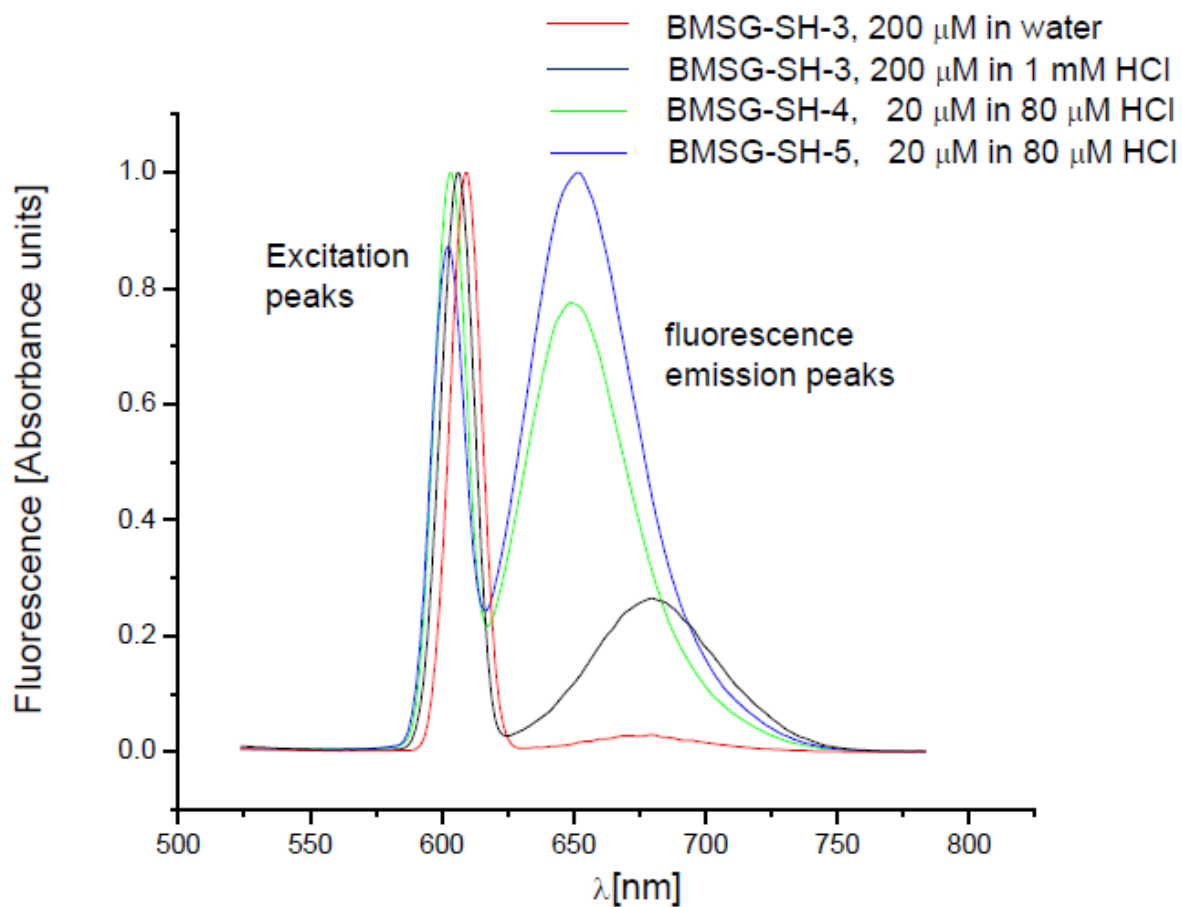
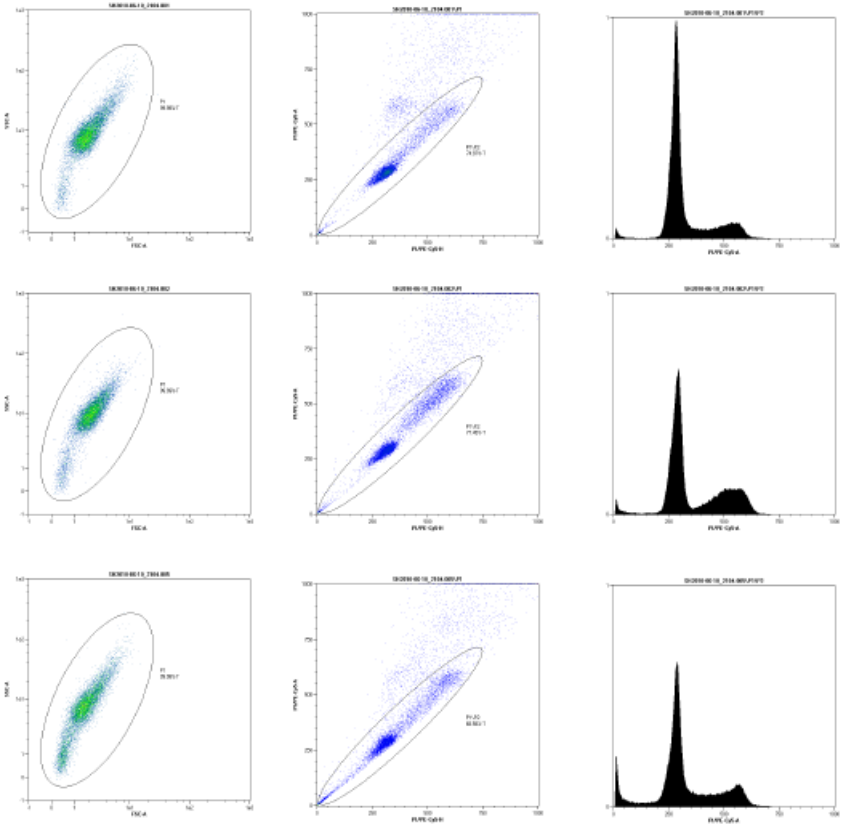


Figure S1: Fluorescence properties of compounds BMSG-SH-3 – 5 at 600 nm excitation. BMSG-SH-3 displays significantly lower fluorescence than the other derivatives, and it increases upon protonation. 4 equivalents of HCl were added to BMSG-SH-4 – 5 to form the soluble chloride salt.



A549 cells

untreated

Etoposide, 14 h, 30 μ M

BMSG-SH-3, 14 h, 1 μ M

FigureS2: Evaluation of cell cycle analysis of A549 cells. 10000 events each.

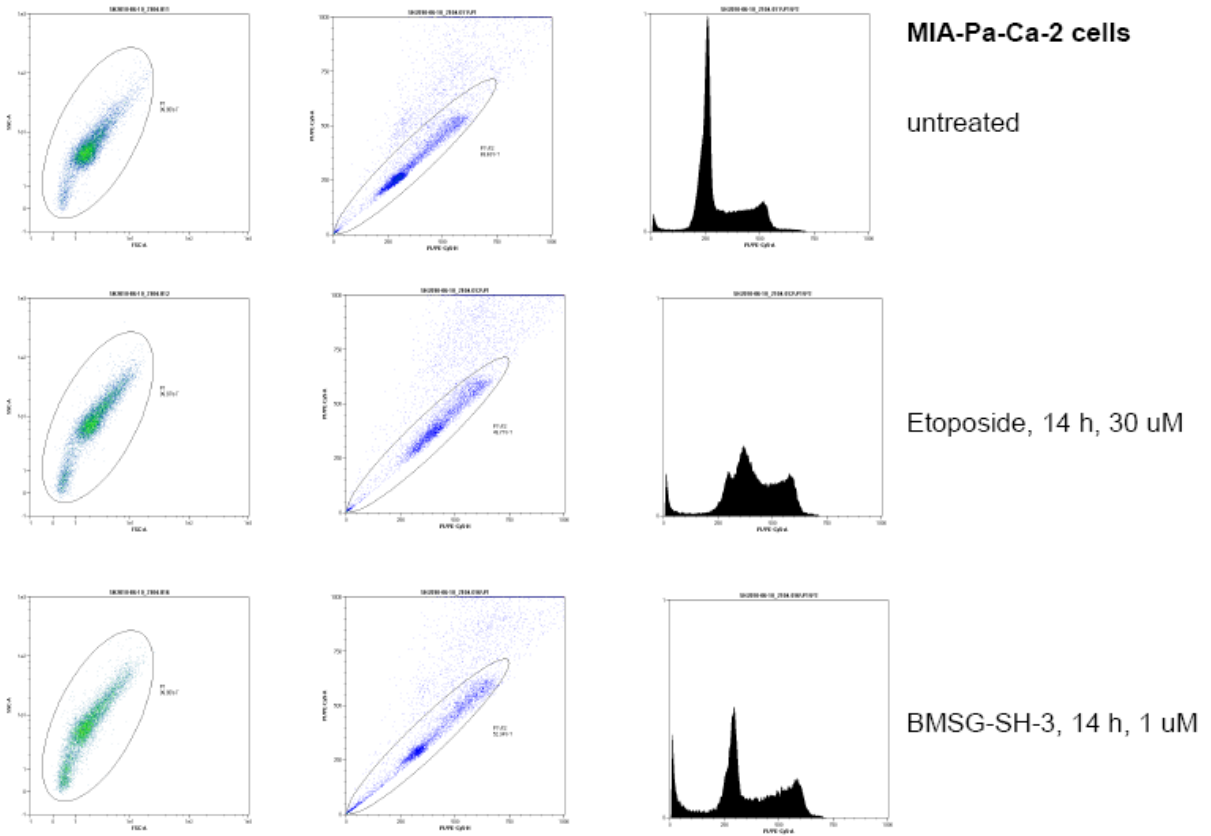
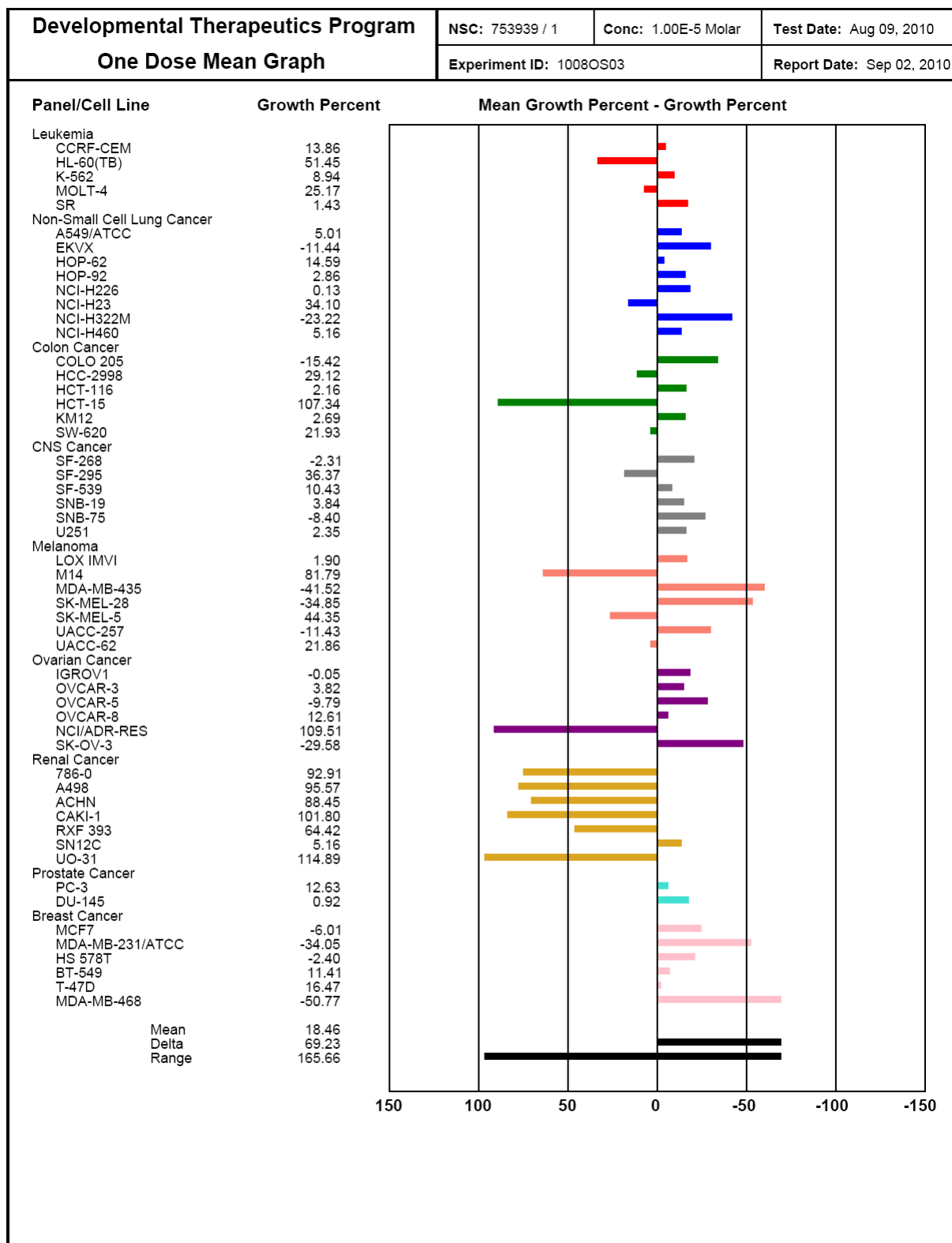


Figure S3: Evaluation of cell cycle analysis of MIA-Pa-Ca-2 cells. 10000 events each.



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Figure S4: NCI 60 cell line panel screen of BMSG-SH-3

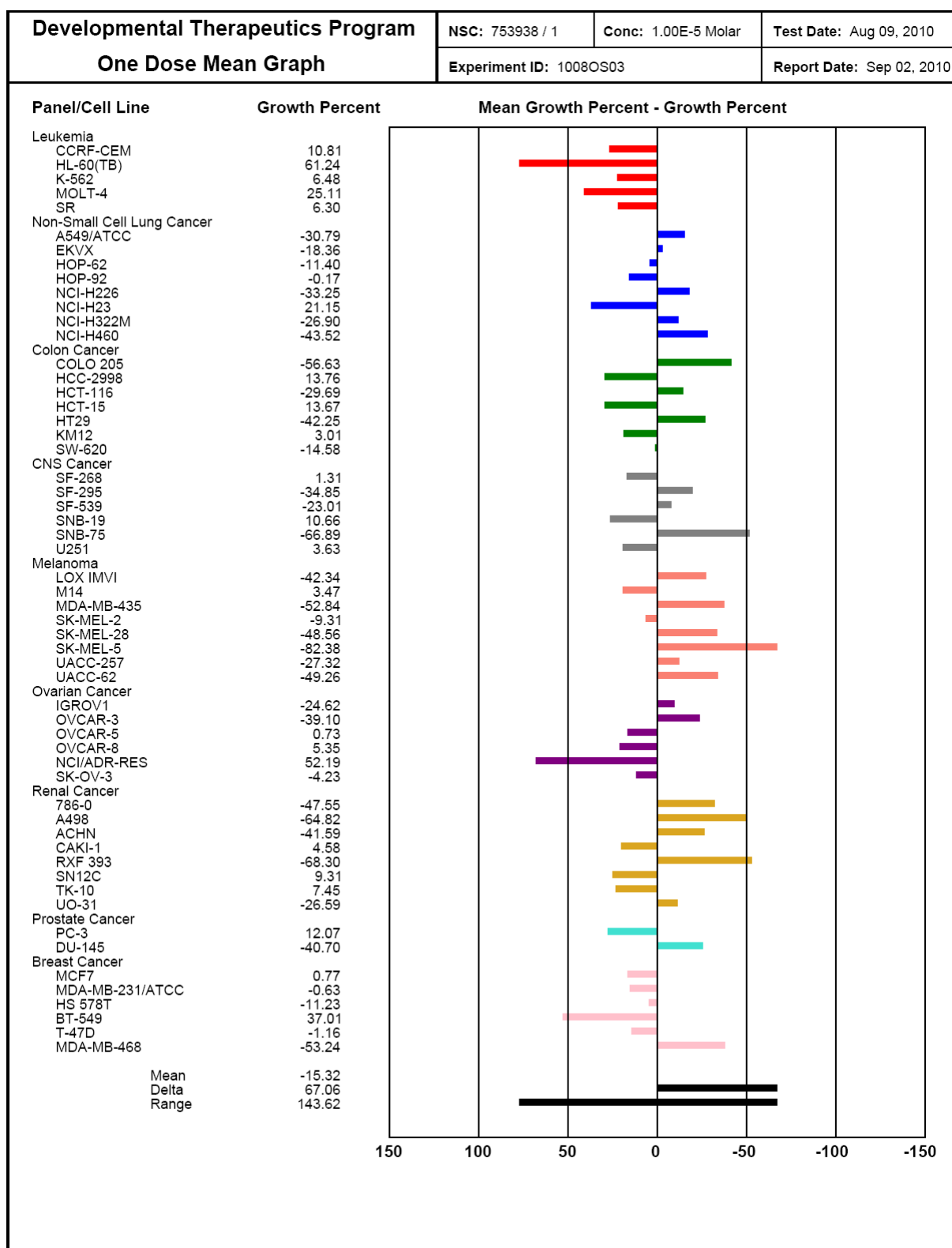


Figure S5: NCI 60 cell line panel screen of BMSG-SH-4

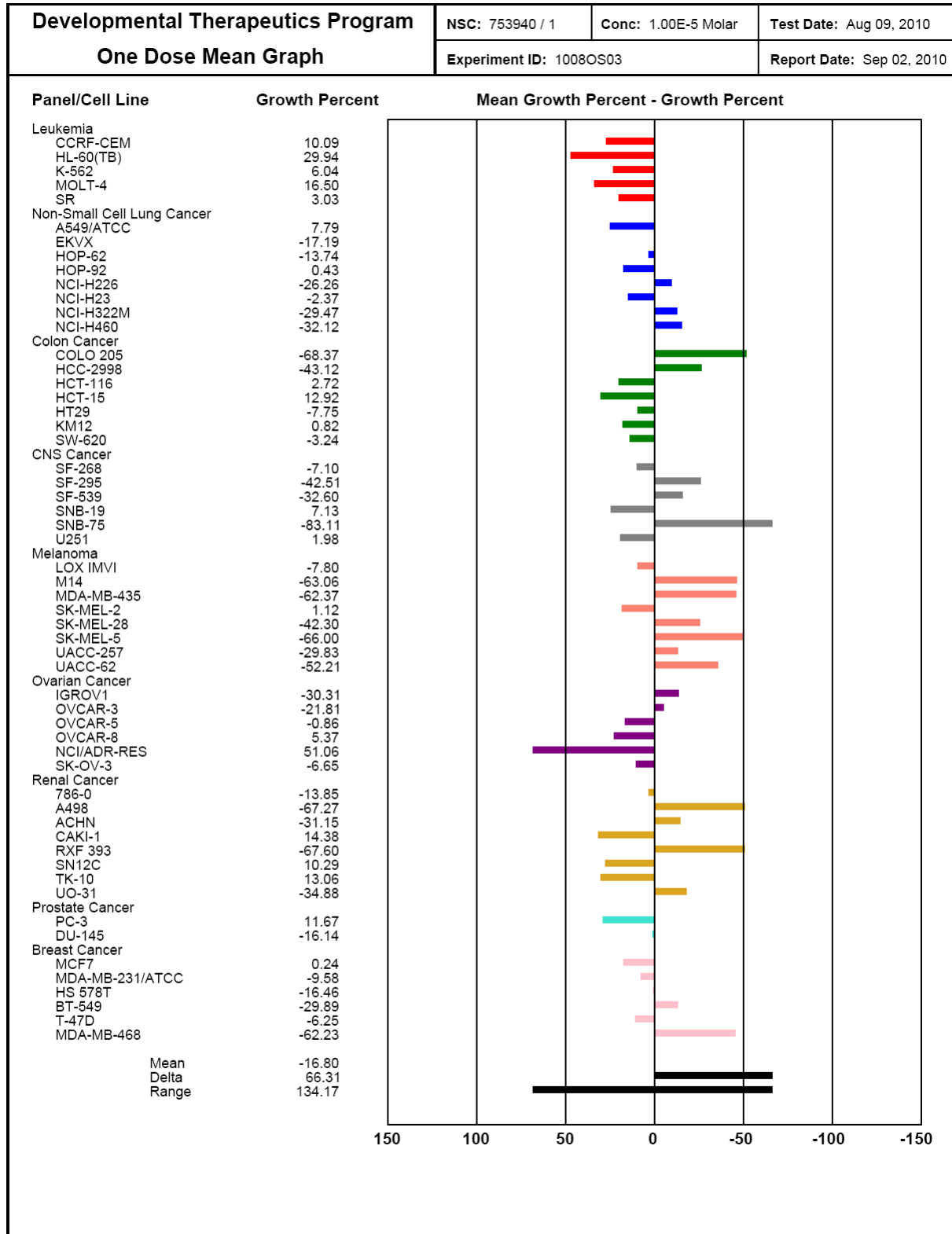


Figure S6: NCI 60 cell line panel screen of BMSG-SH-5

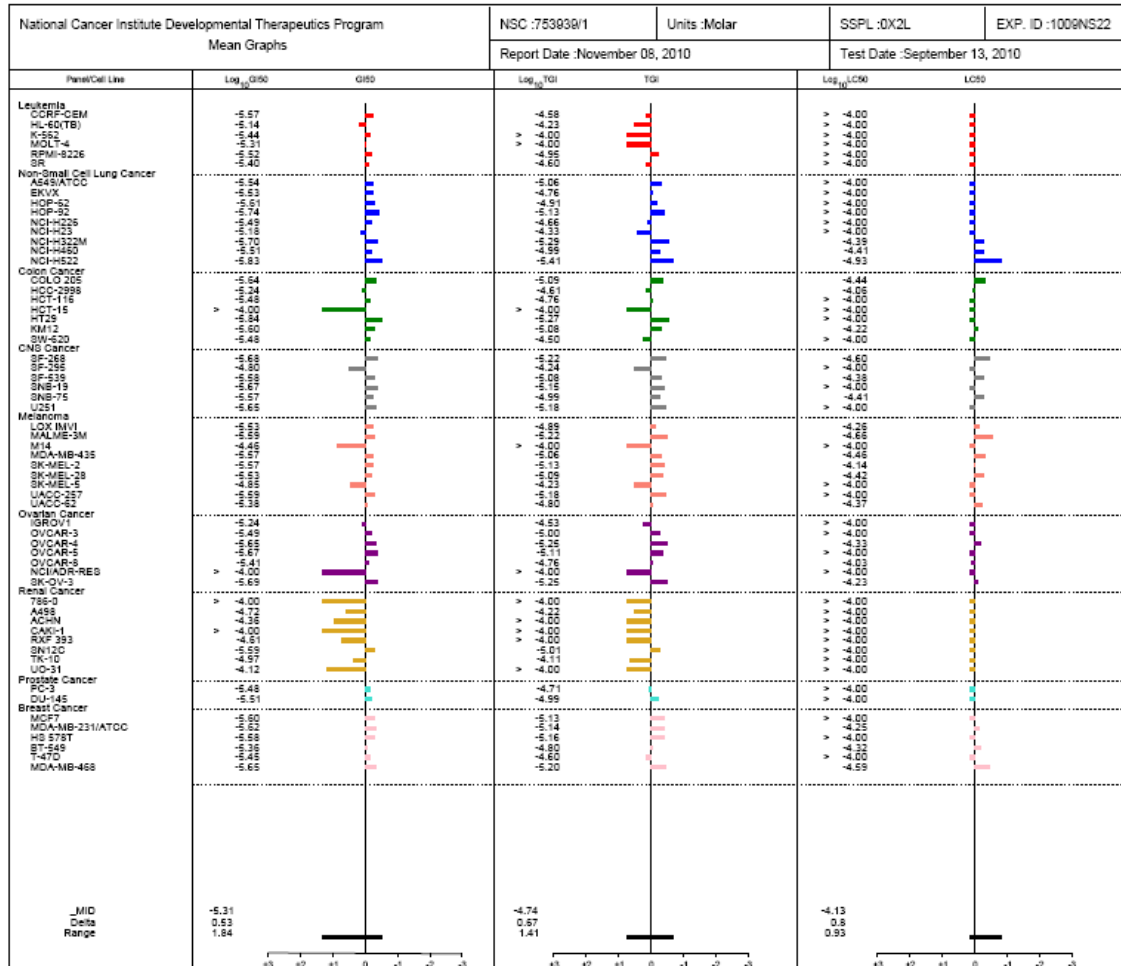


Figure S7: NCI 60 cell line panel screen of BMSG-SH-3, five dose range.

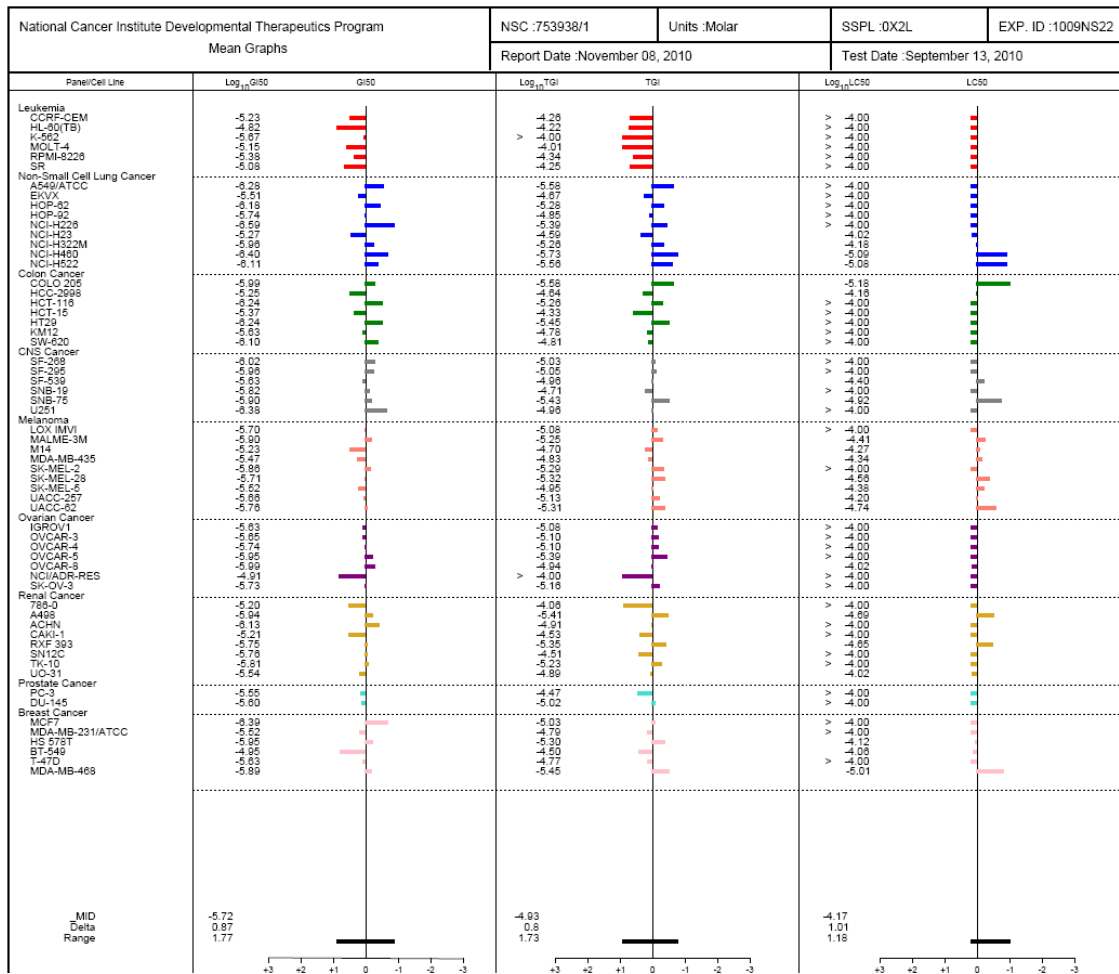


Figure S8: NCI 60 cell line panel screen of BMSG-SH-4, five dose range.

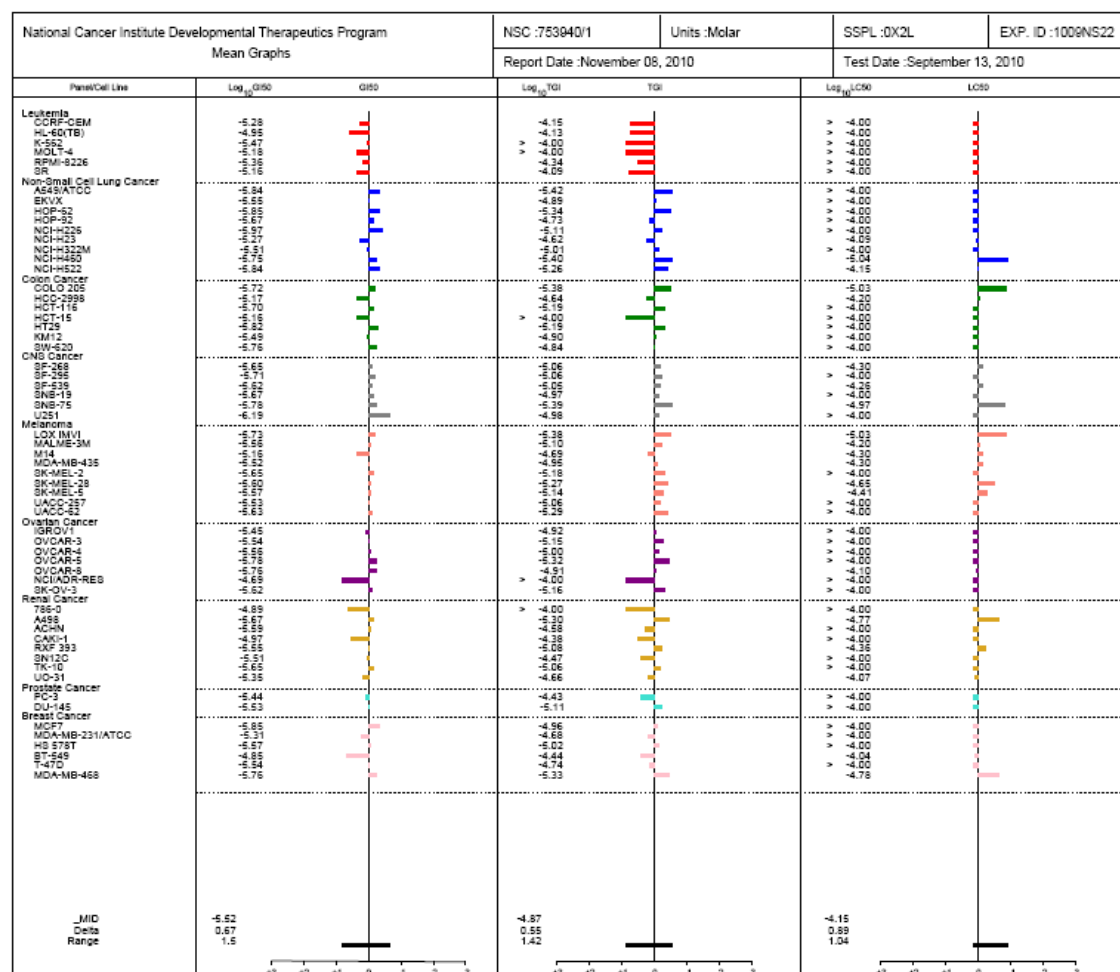


Figure S9: NCI 60 cell line panel screen of BMSG-SH-5, five dose range.

References for Tables S2 and S3

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