

Supplementary Information

Systematic polypharmacology and drug repurposing via an integrated L1000-based Connectivity Map database mining

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Supplementary Information includes:

Supplementary Figures S1-S3

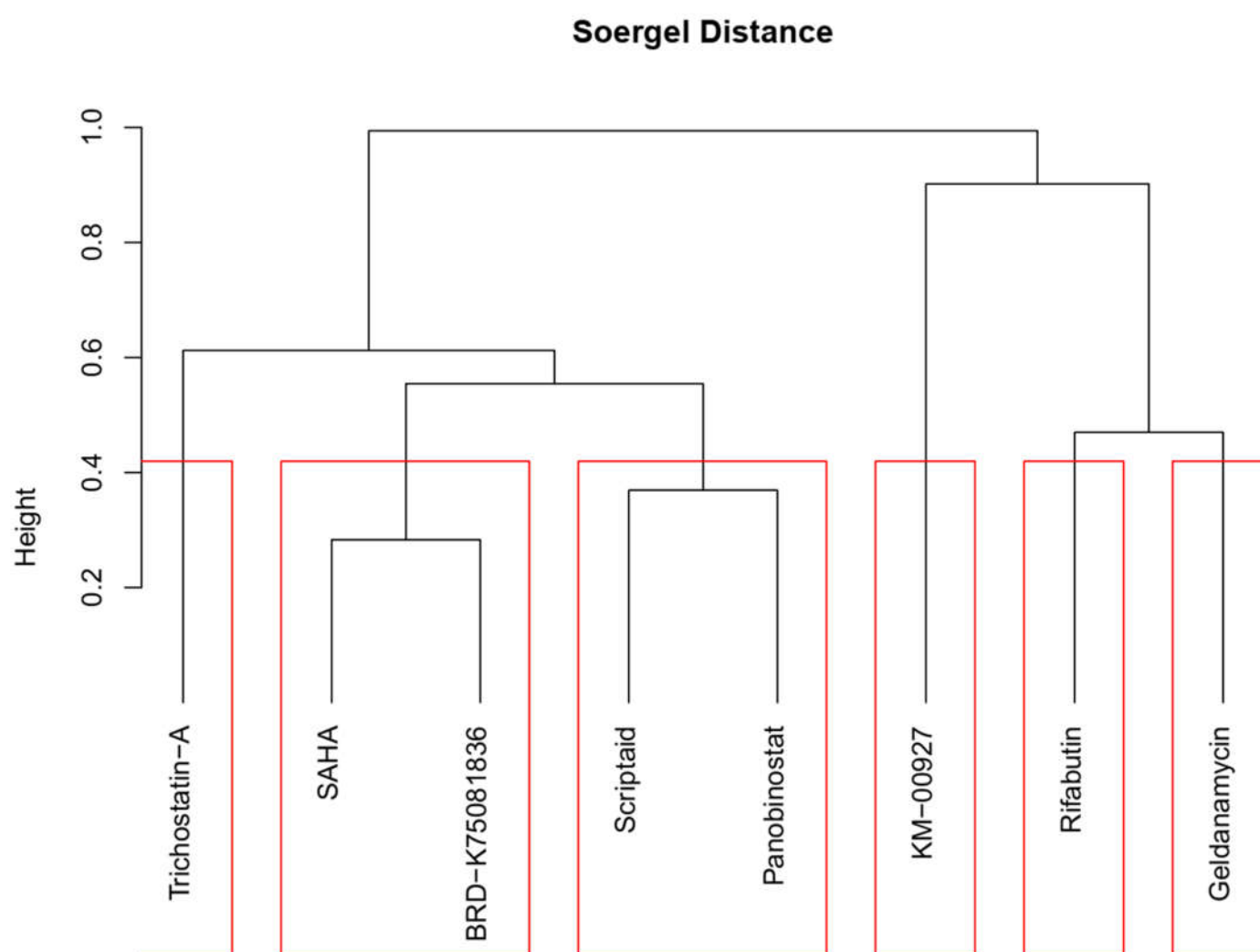
Supplementary Tables S1 and S2

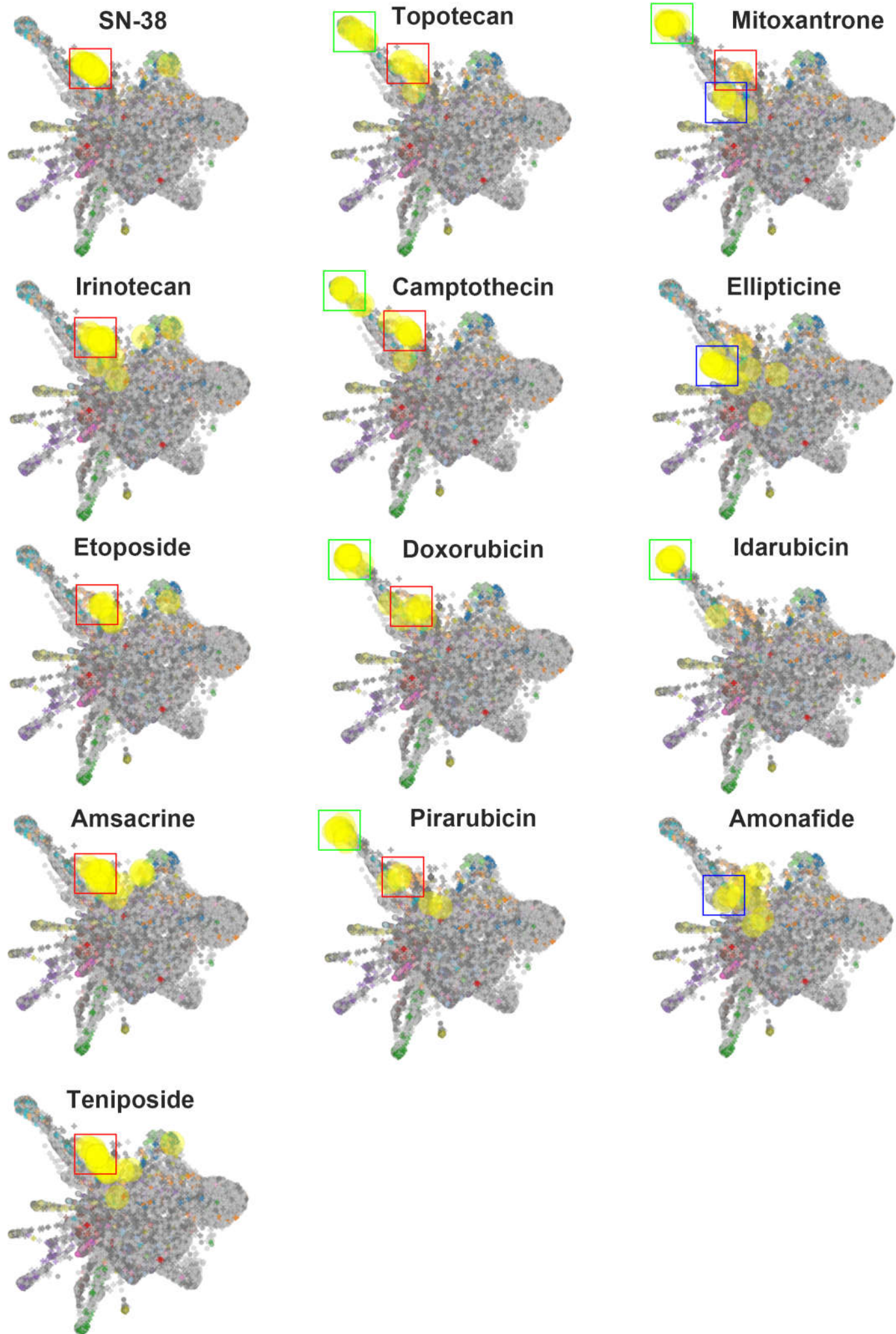
Legends to Supplementary Figures

Figure S1. Chemical structure similarity analysis. A SDF files containing the simplified molecular-input line-entry system (SMILES) of drugs was uploaded to the ChemBioServer for the hierarchical clustering of compounds. The parameters were set as follows: distance = Soergel (Tanimoto coefficient); clustering linkage = Ward; and clustering threshold = 0.4. The compounds in red grids indicated that they were classified in the same clusters with clustering threshold less than 0.4.

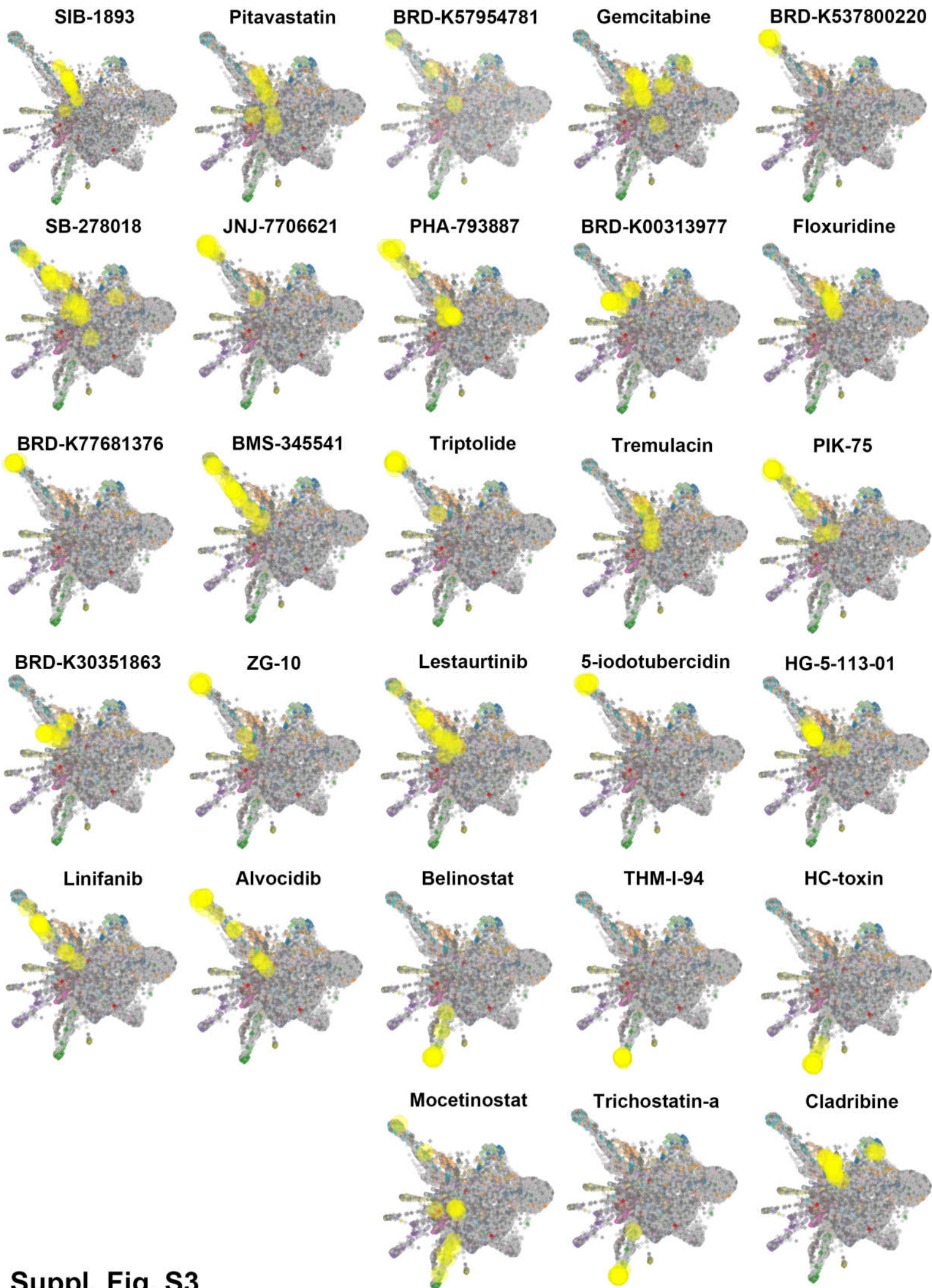
Figure S2. L1000FWD visualization of the drug gene signatures for topoisomerase inhibitors. Drugs sharing similar MOA were clustered together. The red, green, and blue boxes indicated the major clusters of topoisomerase inhibitors.

Figure S3. L1000FWD visualization of the drug gene signatures for the predicted topoisomerase inhibitors. Drugs sharing similar MOA were clustered together.





Suppl. Fig. S2



Suppl. Fig. S3

Table S1. Differentially expressed genes (DEGs) from HDAC inhibitor-treated cancer cells. DEGs from all datasets were prepared by GEO2R web tool. The cut-off criteria were set at adjusted p value < 0.01 and llogFCI > 2.

GSE22061_HCT116-SAHA			GSE22061_HCT116-FK228			GSE60125_MDA-MB-231-SAHA		
ID	logFC	Gene.symbol	ID	logFC	Gene.symbol	ID	logFC	Gene.symbol
214079_at	4.87	DHRS2	206463_s_at	5.09	DHRS2	215704_at	5.88	FLG
206463_s_at	4.84	DHRS2	209197_at	4.92	SYT11	1555673_at	5.23	KRTAP2-3
202149_at	4.01	NEDD9	214079_at	4.89	DHRS2	227803_at	4.55	ENPP5
213139_at	3.65	SNAI2	202149_at	4.18	NEDD9	227140_at	4.31	INHBA
44783_s_at	3.52	HEY1	209198_s_at	4.03	SYT11	214079_at	3.99	DHRS2
203787_at	3.32	SSBP2	227812_at	4.02	TNFRSF19	233504_at	3.96	C9orf84
227354_at	3.3	PAG1	221541_at	3.99	CRISPLD2	203980_at	3.92	FABP4
227812_at	3.3	TNFRSF19	213139_at	3.98	SNAI2	210511_s_at	3.86	INHBA
228715_at	3.3	ZCCHC12	222449_at	3.96	PMEPA1	213931_at	3.85	ID2B
209392_at	3.28	ENPP2	210095_s_at	3.91	IGFBP3	228865_at	3.79	C1orf116
225626_at	3.25	PAG1	209392_at	3.87	ENPP2	206785_s_at	3.74	KLRC2
232165_at	3.18	EPPK1	44783_s_at	3.82	HEY1	206569_at	3.72	IL24
217028_at	3.16	CXCR4	209101_at	3.74	CTGF	201744_s_at	3.71	LUM
208092_s_at	3.16	FAM49A	224225_s_at	3.67	ETV7	204515_at	3.6	HSD3B1
225622_at	3.11	PAG1	203787_at	3.65	SSBP2	209459_s_at	3.56	ABAT
232164_s_at	3.08	EPPK1	208436_s_at	3.65	IRF7	1559336_at	3.54	LOC101928505
218559_s_at	3.08	MAFB	232165_at	3.64	EPPK1	217979_at	3.54	TSPAN13
210095_s_at	3.04	IGFBP3	1570445_a_at	3.56	LOC643201	228221_at	3.52	SLC44A3
205003_at	2.92	DOCK4	217028_at	3.54	CXCR4	207102_at	3.37	AKR1D1
226811_at	2.92	FAM46C	226811_at	3.53	FAM46C	266_s_at	3.37	CD24
201109_s_at	2.91	THBS1	225626_at	3.51	PAG1	1552365_at	3.29	SCIN
209683_at	2.88	FAM49A	228846_at	3.48	MXD1	215785_s_at	3.25	CYFIP2
221541_at	2.87	CRISPLD2	206465_at	3.48	ACSBG1	219874_at	3.24	SLC12A8
209101_at	2.87	CTGF	206619_at	3.45	DKK4	219702_at	3.22	PLAC1
218087_s_at	2.86	SORBS1	218559_s_at	3.45	MAFB	231930_at	3.21	ELMOD1
218839_at	2.84	HEY1	227354_at	3.44	PAG1	216379_x_at	3.2	CD24
222449_at	2.82	PMEPA1	232164_s_at	3.42	EPPK1	208650_s_at	3.19	CD24
209197_at	2.8	SYT11	209189_at	3.39	FOS	243610_at	3.17	C9orf135
226281_at	2.78	DNER	225622_at	3.37	PAG1	206145_at	3.17	RHAG
223484_at	2.77	C15orf48	228228_at	3.37	DACT3	209771_x_at	3.14	CD24
208156_x_at	2.76	EPPK1	226275_at	3.34	MXD1	235230_at	3.14	PLCXD2
228846_at	2.75	MXD1	214414_x_at	3.31	HBA2	204035_at	3.12	SCG2
214414_x_at	2.69	HBA2	1569144_a_at	3.31	CYSRT1	203498_at	3.09	RCAN2
225283_at	2.68	ARRDC4	218839_at	3.21	HEY1	220921_at	3.09	SPANXB1
206100_at	2.68	CPM	212843_at	3.20	NCAM1	242162_at	3.08	DAW1
209189_at	2.68	FOS	209683_at	3.19	FAM49A	210145_at	3.08	PLA2G4A
222513_s_at	2.66	SORBS1	228715_at	3.18	ZCCHC12	241703_at	3.08	RUNDC3B
238532_at	2.61	DPF3	209568_s_at	3.12	RGL1	215321_at	3.07	RUNDC3B
204646_at	2.61	DPYD	210829_s_at	3.12	SSBP2	207733_x_at	3.06	PSG9
224559_at	2.6	MALAT1	218087_s_at	3.09	SORBS1	205352_at	3.06	SERPINI1
212843_at	2.6	NCAM1	208926_at	3.07	NEU1	1557636_a_at	3.05	C7orf57
208926_at	2.59	NEU1	223913_s_at	3.06	MIR7-3HG	205569_at	3.02	LAMP3
210829_s_at	2.58	SSBP2	208156_x_at	3.04	EPPK1	213050_at	3.01	COBL
209839_at	2.56	DNM3	208092_s_at	3.04	FAM49A	219476_at	3	C1orf116
225540_at	2.51	MAP2	227394_at	3.03	NCAM1	209594_x_at	3	PSG9
209459_s_at	2.5	ABAT	205493_s_at	3.02	DPYSL4	229242_at	3	TNFSF15
226275_at	2.49	MXD1	222513_s_at	2.97	SORBS1	209738_x_at	2.96	PSG6
209160_at	2.47	AKR1C3	205372_at	2.95	PLAG1	230147_at	2.94	F2RL2
213256_at	2.47	MARCH3	201109_s_at	2.93	THBS1	223821_s_at	2.94	SUSD4
201110_s_at	2.46	THBS1	222450_at	2.91	PMEPA1	231504_at	2.93	CCDC148
224225_s_at	2.45	ETV7	201627_s_at	2.91	INSIG1	209392_at	2.9	ENPP2
235334_at	2.45	ST6GALNAC3	209201_x_at	2.90	CXCR4	238778_at	2.88	MPP7
227394_at	2.44	NCAM1	238532_at	2.86	DPF3	206907_at	2.88	TNFSF9
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229518_at	2.43	FAM46B	209083_at	2.83	CORO1A	236984_at	2.85	C4orf26
231166_at	2.43	GPR155	226487_at	2.81	FAM222A	203108_at	2.81	GPRC5A
210971_s_at	2.41	ARNTL	205807_s_at	2.77	TUFT1	227399_at	2.81	VGLL3
228570_at	2.41	BTBD11	229518_at	2.77	FAM46B	204830_x_at	2.8	PSG5

227209_at	2.41	CNTN1	220505_at	2.75	C9orf53	206204_at	2.78	GRB14
228228_at	2.4	DACT3	211919_s_at	2.74	CXCR4	211741_x_at	2.77	PSG3
226487_at	2.36	FAM222A	231166_at	2.72	GPR155	203399_x_at	2.76	PSG3
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209568_s_at	2.34	RGL1	209459_s_at	2.70	ABAT	206561_s_at	2.73	AKR1B10
235683_at	2.34	SESN3	226281_at	2.67	DNER	220922_s_at	2.72	SPANXA2
211919_s_at	2.31	CXCR4	209460_at	2.67	ABAT	235228_at	2.71	CCDC85A
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238692_at	2.19	BTBD11	234989_at	2.48	NEAT1	205239_at	2.56	AREG
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205259_at	2.16	NR3C2	234513_at	2.47	ELOVL3	202800_at	2.52	SLC1A3
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205586_x_at	2.15	VGf	210240_s_at	2.46	CDKN2D	227919_at	2.51	UCA1
243087_at	2.14	WDR63	223217_s_at	2.45	NFKBIZ	208134_x_at	2.5	PSG2
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223218_s_at	2.13	NFKBIZ	230104_s_at	2.43	TPPP	220327_at	2.5	VGLL3
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209083_at	2.08	CORO1A	1554178_a_at	2.38	FAM126B	219263_at	2.43	RNF128
222456_s_at	2.08	LIMA1	223484_at	2.35	C15orf48	231166_at	2.42	GPR155
210657_s_at	2.08	SEP4	201110_s_at	2.35	THBS1	222549_at	2.41	CLDN1
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221563_at	2.06	DUSP10	235683_at	2.34	SESN3	238451_at	2.39	MPP7
201626_at	2.05	INSIG1	230900_at	2.34	CCDC110	228523_at	2.39	NANOS1
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235124_at	-2.02	EIF3J-AS1	227868_at	2.26	LOC154761	207148_x_at	2.27	MYOZ2
221935_s_at	-2.02	EOGT	226913_s_at	2.26	SOX8	203413_at	2.27	NELL2
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228280_at	-2.03	ZC3HAV1L	223218_s_at	2.25	NFKBIZ	206029_at	2.26	ANKRD1
220617_s_at	-2.03	ZNF532	1563053_at	2.25	LOC729083	225283_at	2.25	ARRDC4
225181_at	-2.04	ARID1B	204446_s_at	2.24	ALOX5	227209_at	2.25	CNTN1
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201331_s_at	-2.04	STAT6	202508_s_at	2.23	SNAP25	204614_at	2.23	SERPINB2
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224895_at	-2.06	YAP1	212774_at	2.20	ZBTB18	220334_at	2.22	RGS17
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235005_at	-2.07	DIS3L	229669_at	2.19	LOC100507263	227909_at	2.21	LINC00087
231899_at	-2.07	ZC3H12C	210971_s_at	2.19	ARNTL	1556499_s_at	2.2	COL1A1
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1558292_s_at	-2.08	PIGW	239835_at	2.19	KBTBD8	228101_at	2.18	APBA1
1557014_a_at	-2.09	FAM201A	220047_at	2.17	SIRT4	228695_at	2.18	C8orf46
204780_s_at	-2.09	FAS	205858_at	2.17	NGFR	203913_s_at	2.18	HPGD
218826_at	-2.09	SLC35F2	238682_at	2.17	CCDC96	202149_at	2.18	NEDD9
239579_at	-2.1	EPHX4	209305_s_at	2.17	GADD45B	208607_s_at	2.18	SAA2
232271_at	-2.1	HNF4G	243610_at	2.15	C9orf135	36553_at	2.17	ASMTL
244467_at	-2.1	LOC100510485	213348_at	2.15	CDKN1C	205749_at	2.17	CYP1A1
227174_at	-2.1	WDR72	210657_s_at	2.14	SEP4	1559213_at	2.17	LINC01419
225681_at	-2.11	CTHRC1	221903_s_at	2.13	CYLD	1558678_s_at	2.17	MALAT1
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206020_at	-2.11	SOCS6	213295_at	2.12	CYLD	1557523_at	2.16	ATP6AP1L
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229221_at	-2.13	CD44	209160_at	2.11	AKR1C3	213711_at	2.16	KRT81
223895_s_at	-2.13	EPN3	210785_s_at	2.11	THEMIS2	224392_s_at	2.16	OPN3
222664_at	-2.13	KCTD15	222456_s_at	2.10	LIMA1	214247_s_at	2.15	DKK3
221816_s_at	-2.13	PHF11	216060_s_at	2.10	DAAM1	234513_at	2.15	ELOVL3
209679_s_at	-2.13	SMAGP	228645_at	2.10	SNHG9	236289_at	2.15	LOC100506563
225417_at	-2.14	EPC1	205637_s_at	2.10	SH3GL3	236302_at	2.15	PPM1E
226267_at	-2.16	JDP2	221563_at	2.10	DUSP10	203407_at	2.14	PPL
228752_at	-2.17	CRACR2A	200666_s_at	2.09	DNAJB1	201109_s_at	2.14	THBS1
223794_at	-2.18	ARMC4	205352_at	2.08	SERPINI1	53991_at	2.13	DENND2A
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238043_at	-2.19	ARID1B	201150_s_at	2.07	TIMP3	1552477_a_at	2.11	IRF6
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1569322_at	-2.19	LINC00857	230951_at	2.06	EPB41L5	231292_at	2.1	EID3
219924_s_at	-2.19	ZMYM6	213300_at	2.06	ATG2A	239533_at	2.1	GPR155
202136_at	-2.19	ZMYND11	226039_at	2.05	MGAT4A	226258_at	2.09	AMN1
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202417_at	-2.2	KEAP1	209458_x_at	2.05	HBA2	1562921_at	2.08	EP300-AS1
219342_at	-2.21	CASD1	1556129_at	2.05	LOC642533	207980_s_at	2.07	CITED2
202318_s_at	-2.21	SENPA6	223129_x_at	2.04	MYLIP	229656_s_at	2.07	EML6
207992_s_at	-2.22	AMPA3	209604_s_at	2.04	GATA3	235944_at	2.07	HMCN1
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226129_at	-2.23	FAM83H	220331_at	2.02	CYP46A1	202150_s_at	2.06	NEDD9
219545_at	-2.23	KCTD14	204458_at	2.02	PLA2G15	210195_s_at	2.06	PSG1
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1552575_a_at	-2.25	C6orf141	225597_at	2.01	SLC45A4	210538_s_at	2.04	BIRC3
213912_at	-2.25	TBC1D30	228062_at	2.01	NAP1L5	230900_at	2.04	CCDC110
223694_at	-2.25	TRIM7	203855_at	2.01	WDR47	236639_at	2.04	LOC100507596
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226252_at	-2.26	ZBTB20	215321_at	2.00	RUNDC3B	203477_at	2.03	COL15A1
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217523_at	-2.28	CD44	225868_at	-2.06	TRIM47	244407_at	2.02	CYP39A1
227542_at	-2.28	SOCS6	209290_s_at	-2.06	NFIB	236656_s_at	2.02	LOC100288911
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226250_at	-2.28	ZBTB20	203453_at	-2.07	SCNN1A	235004_at	2.02	RBM24
226817_at	-2.29	DSC2	223474_at	-2.07	IRF2BPL	206518_s_at	2.02	RGS9
221081_s_at	-2.3	DENND2D	223642_at	-2.07	ZIC2	219487_at	2.01	BBS10

218898_at	-2.3	FAM57A	215022_x_at	-2.07	ZNF33B	226657_at	2.01	NATD1
225996_at	-2.3	LONRF2	212553_at	-2.07	RPRD2	240187_at	2.01	PPP1R3C
231876_at	-2.3	TRIM56	227919_at	-2.08	UCA1	235874_at	2	PRSS35
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1552946_at	-2.37	ZNF114	203567_s_at	-2.09	TRIM38	220643_s_at	-2.06	FAIM
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203453_at	-2.38	SCNN1A	223974_at	-2.10	DLGAP1-AS2	242931_at	-2.08	LONRF3
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230748_at	-2.38	SLC16A6	226252_at	-2.10	ZBTB20	238576_at	-2.09	MOCOS
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229667_s_at	-3.03	HOXB8	227174_at	-2.23	WDR72
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			1557137_at	-2.28	TMEM17
			235124_at	-2.28	EIF3J-AS1
			226895_at	-2.29	NFIC
			212762_s_at	-2.29	TCF7L2
			212606_at	-2.29	WDFY3
			207029_at	-2.30	KITLG
			209921_at	-2.31	SLC7A11
			202241_at	-2.31	TRIB1
			229221_at	-2.32	CD44
			206032_at	-2.32	DSC3
			223895_s_at	-2.32	EPN3
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			223761_at	-2.33	FGF19
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			210845_s_at	-2.35	PLAUR
			224765_at	-2.35	MSL1
			212096_s_at	-2.35	MTUS1
			202863_at	-2.36	SP100
			218284_at	-2.36	SMAD3
			204750_s_at	-2.36	DSC2
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			209124_at	-2.37	MYD88
			227055_at	-2.37	METTL7B
			55081_at	-2.38	MICALL1
			213342_at	-2.38	YAP1
			220030_at	-2.38	STYK1
			202319_at	-2.38	SENK1
			234969_s_at	-2.38	EPC1
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			226129_at	-2.39	FAM83H

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225961_at	-2.44	KLHL42
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1558292_s_at	-2.45	PIGW
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227474_at	-2.47	PAX8-AS1
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219543_at	-2.51	PBLD
225021_at	-2.52	ZNF532
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223541_at	-2.52	HAS3
228899_at	-2.52	LOC100132884
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226817_at	-2.54	DSC2
224022_x_at	-2.54	WNT16
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230748_at	-2.54	SLC16A6
215719_x_at	-2.55	FAS
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228304_at	-2.56	RBM43
227578_at	-2.56	TMPO-AS1
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213844_at	-2.61	HOXA5
206600_s_at	-2.61	SLC16A5
236207_at	-2.62	SSFA2
201324_at	-2.63	EMP1
224894_at	-2.63	YAP1
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203964_at	-2.67	NMI
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213698_at	-2.91	ZMYM6
1552546_a_at	-2.92	LETM2
217523_at	-2.92	CD44
228999_at	-2.94	CHD2
226284_at	-2.94	ZBTB2
213912_at	-2.94	TBC1D30
217999_s_at	-2.95	PHLDA1
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207360_s_at	-2.97	NTSR1
218963_s_at	-2.97	KRT23
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		232202_at	-4.18	FAM83B		
		227792_at	-4.43	ITPRIPL2		
		225645_at	-4.74	EHF		
		202599_s_at	-4.82	NRIP1		
		206504_at	-4.86	CYP24A1		
		239468_at	-5.04	MKX		
		228640_at	-5.65	PCDH7		
		208025_s_at	-5.96	HMGA2		
		203708_at	-6.74	PDE4B		

Table S2 The interaction profile of TOP2B and drugs by iGEMDOCK analysis

Drug	Total fitness energy	VDW	Hbond	Elect
Etoposide	-116.23	-89.14	-27.09	0
Mitomycin C	-92.88	-61.62	-31.61	0

Note: Fitness (kcal/mol) is the total energy of a predicted pose in the binding site and it is calculated by the following equation: $\text{Fitness} = \text{vdW} + \text{Hbond} + \text{Elect}$. The terms, vdW, Hbond, and Elect, indicate van der Waal energy, hydrogen bonding energy, and Elect term is electro statistic energy, respectively