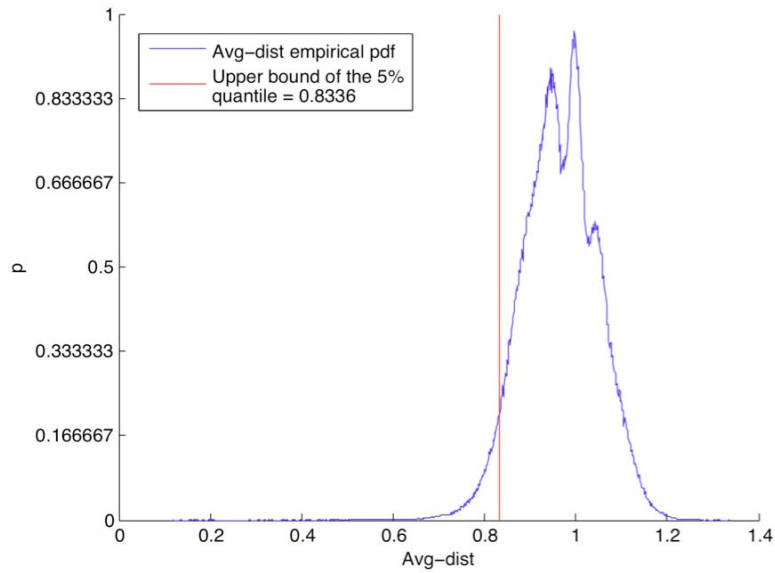
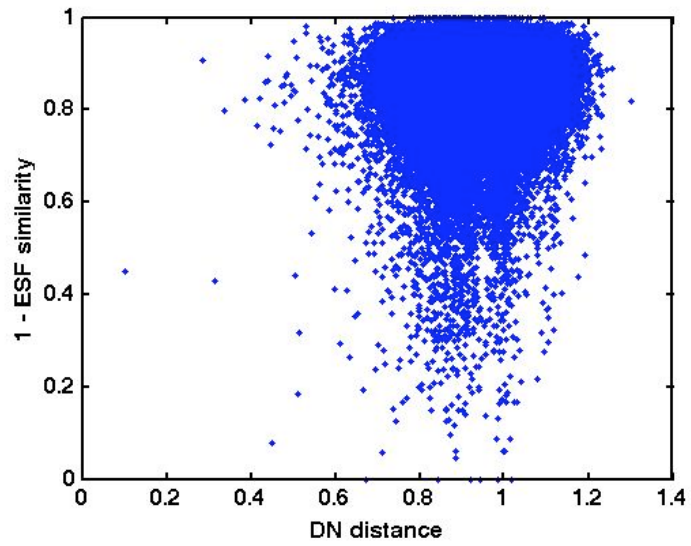


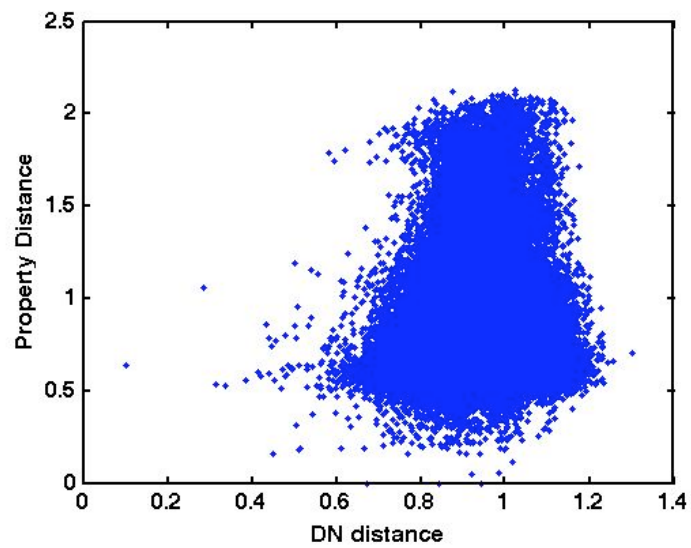
**SI Online: Figure 1** – Empirical probability distribution function of the Maximum-Distance (blue line) and the upper bound of its 5% quantile (red line)



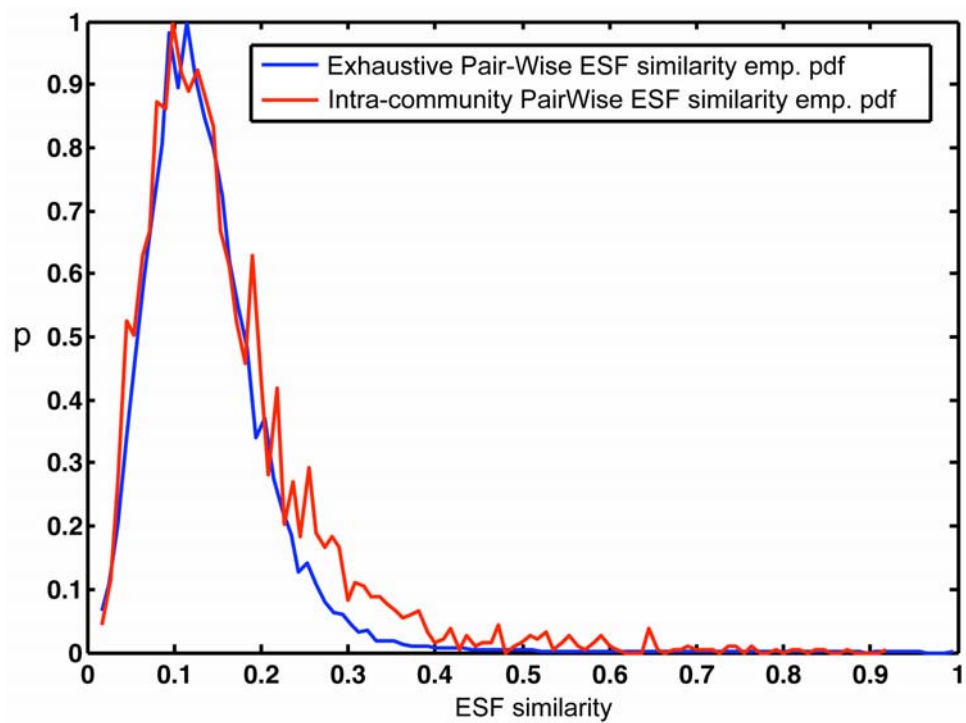
**SI Online: Figure 2** – Empirical probability distribution function of the Average-Distance (blue line) and the upper bound of its 5% quantile (red line)



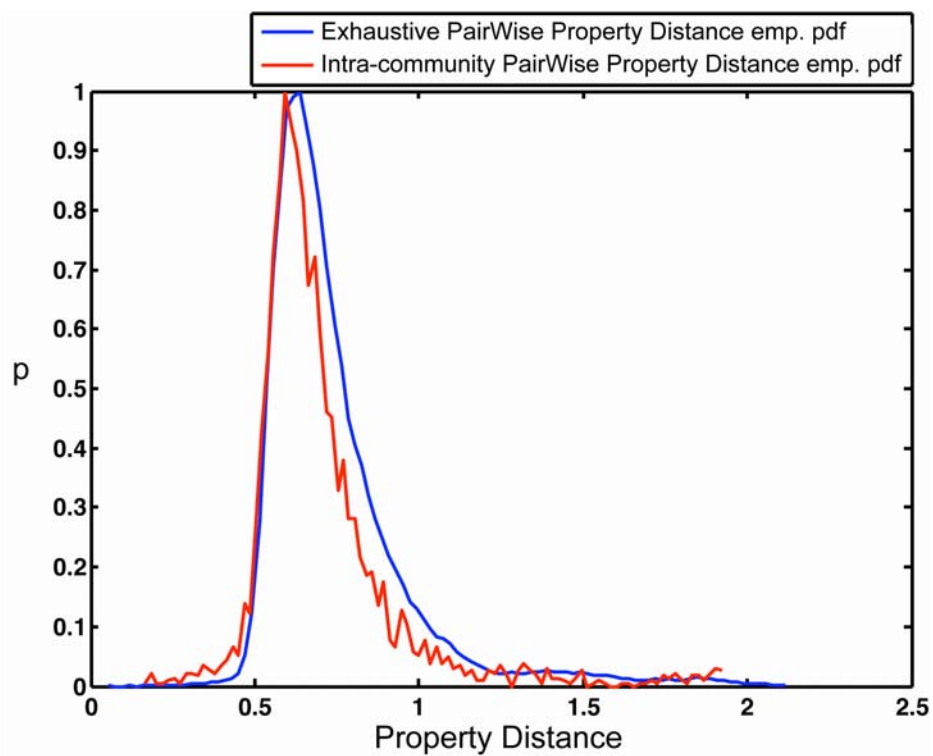
SI Online: Figure 3 – Drug distance versus electro-topological states similarity



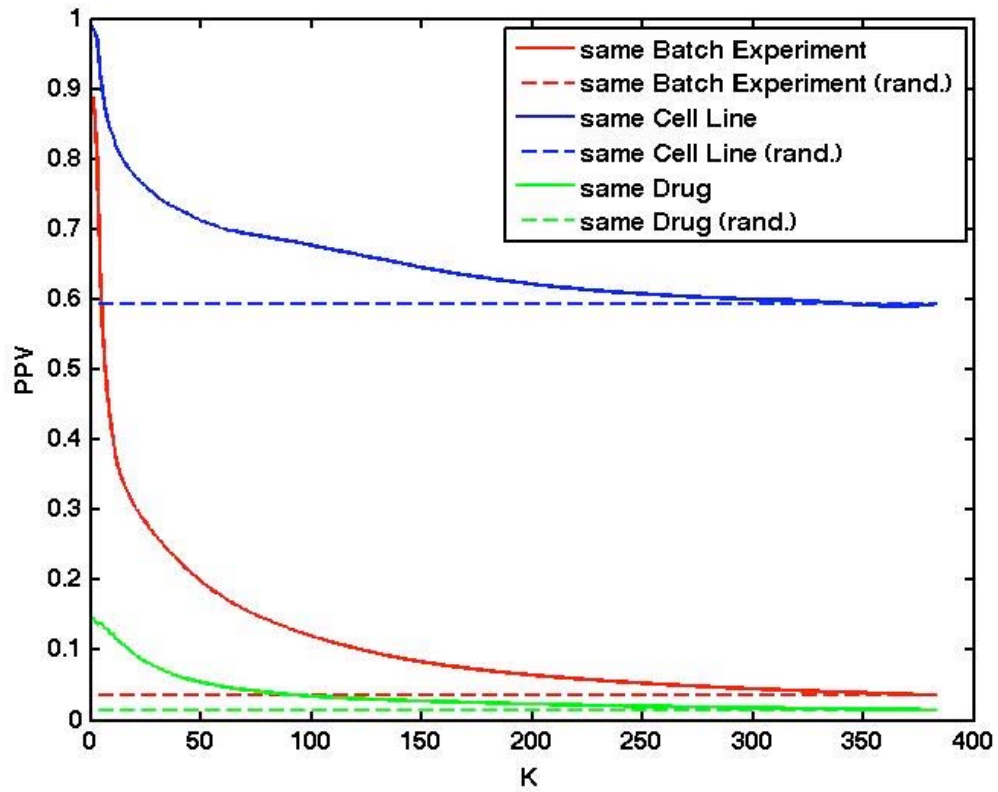
SI Online: Figure 4 – Drug distance versus Extended FingerPrints Property Distance



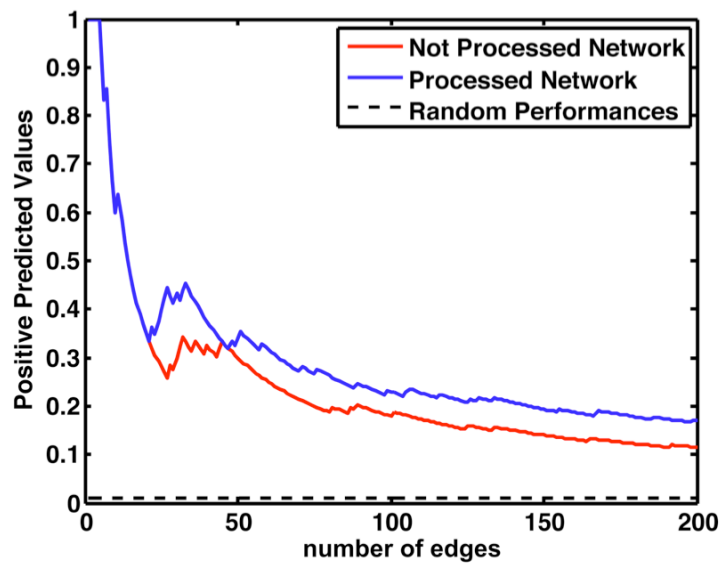
**SI Online: Figure 5** – Empirical probability distribution function of the pair-wise electro-topological states similarity computed between all the possible pairs of drugs (blue line) and between pairs of drugs belonging to the same community (red line)



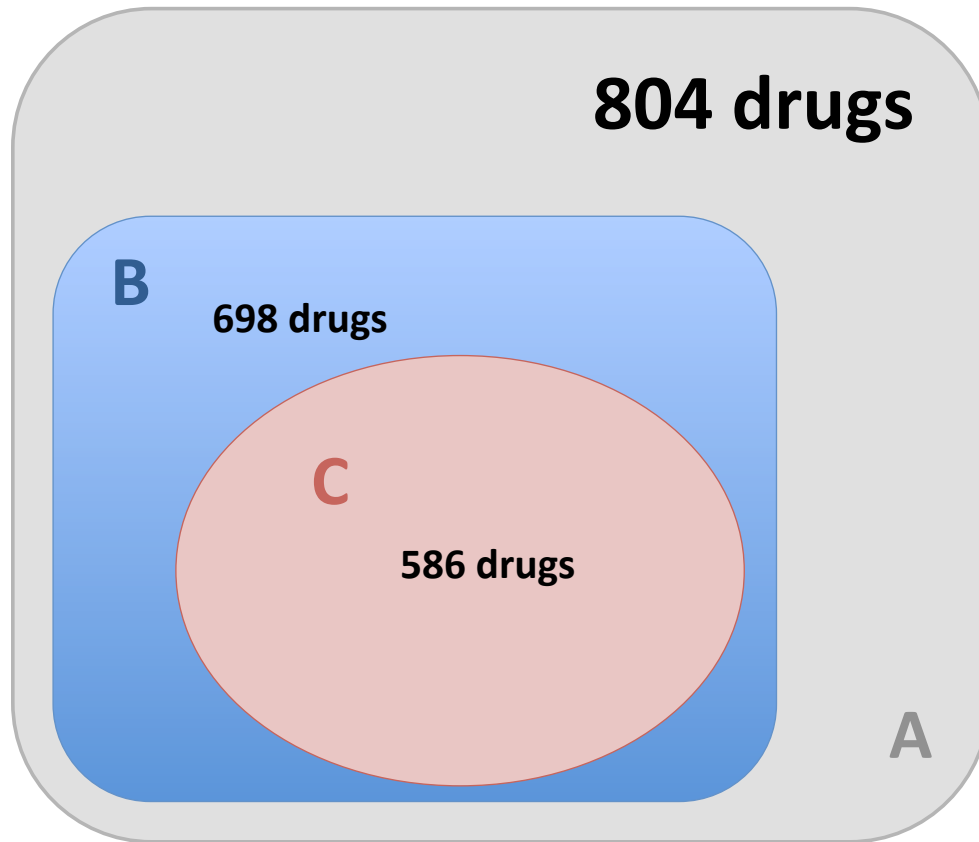
**SI Online: Figure 6** – Empirical probability distribution function of the pair-wise Extended FingerPrints Property Distance computed between all the possible pairs of drugs (blue line) and between pairs of drugs belonging to the same community (red line)



SI Online: Figure 7 - Distance computed between pairs of individual gene expression profile (performances)



SI Online: Figure 8 - Impact of the community identification on the performances



Drugs with a known effect  
(at least one ATC-code or a known target gene)

Drugs sharing ATC-code or target gene with other drugs  
(grouped in sets of distinct MoAs)

Drugs in MoA sets enriched for a give community

<b>Tested Drug</b>	<b>True Positives [HSP90 Inhibitors]</b>
Tanespimycin NVP-AUY922 NMS-E973	<i>Geldanamycin Rifabutin Tanespimycin Alvespimycin Monorden</i>
<b>Tested Drug</b>	<b>True Positives [Topol Inhibitors]</b>
NMS-SN-38	<i>Irinotecan Camptothecin Luteolin Kaempferol Suranin-Sodium Vidarabine Proscillaridin Apigenin Cinoxacin Skiammianine</i>
<b>Tested Drug</b>	<b>True Positives [Topol Inhibitors]</b>
NMS-Doxorubicin	<i>Daunorubicin Podophyllotoxin Mitoxantrone Genistein Ellipticine Oxilinc-Acid Etoposide Doxorubicin Nalidic-Acid Ofloxacin Enoxacin Novobiocin Ciprofoxacin Apigenin</i>
<b>Tested Drug</b>	<b>True Positives [CDK2 Inhibitors]</b>
PHA-848125 PHA-690509 NMS-Flavopiridol PHA-793887	<i>Alsterpaullone Staurosporine GW-8510 H-7 Apigenin Harmine Harmol Luteolin Chrysin Fisetin Sanguinarine Thyropostin-AG825</i>

**SI Online: Table 1** - Drug sets containing the prediction that are assumed to be correct (according to DrugBank and ChemBank)

	N=1	N=2	N=3	N=5	N=10	N=15
cMap Classic Query System	56%	88%	88%	88%	88%	88%
drugON Average-Distance	89%	100%	100%	100%	100%	100%
drugON Max-Distance	77%	100%	100%	100%	100%	100%

**SI Online: Table 2** - Percentage of tested compounds with at least one correct neighbor among the first n

**cMap Classic Query System Performances**

Compound	Cell Line	PPV when keeping the first n neighbors							
		n=1	n=2	n=3	n=5	n=10	n=15	n=20	n=50
PHA-848125	U251	0,00	0,50	0,33	0,40	0,30	0,20	0,20	0,10
NMS-Flavopiridol	A2780	1,00	0,50	0,33	0,60	0,60	0,40	0,35	0,14
PHA-848125	A2780	0,00	0,00	0,00	0,40	0,20	0,13	0,10	0,08
PHA-690509	A2780	0,00	0,50	0,67	0,60	0,30	0,20	0,15	0,12
PHA-793887	A2780	1,00	0,50	0,67	0,60	0,40	0,33	0,25	0,12
PHA-793887	MCF7	1,00	0,50	0,33	0,60	0,30	0,20	0,15	0,12
NMS-Tanespimicyn	MCF7	1,00	1,00	1,00	0,80	0,40	0,40	0,30	0,12
NMS-E973	MCF7	1,00	1,00	1,00	0,80	0,50	0,40	0,30	0,12
NVP-AUY922	MCF7	0,00	0,50	0,67	0,60	0,40	0,27	0,20	0,08
NMS-SN38	MCF7	1,00	0,50	0,33	0,20	0,20	0,13	0,10	0,08
NMS-Doxorubicin	MCF7	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,04
Average Value:		0,54	0,5	0,42	0,50	0,32	0,24	0,19	0,10

**cMap Classic Query System (Best Profile per Drug) Performances**

Compound	Cell Line	PPV when keeping the first n neighbors							
		n=1	n=2	n=3	n=5	n=10	n=15	n=20	n=50
PHA-848125	U251	0,00	0,50	0,33	0,40	0,30	0,20	0,20	0,10
NMS-Flavopiridol	A2780	1,00	0,50	0,33	0,60	0,60	0,40	0,35	0,14
PHA-690509	A2780	0,00	0,50	0,67	0,60	0,30	0,20	0,15	0,12
PHA-793887	A2780	1,00	0,50	0,67	0,60	0,40	0,33	0,25	0,12
NMS-Tanespimicyn	MCF7	1,00	1,00	1,00	0,80	0,40	0,40	0,30	0,12
NMS-E973	MCF7	1,00	1,00	1,00	0,80	0,50	0,40	0,30	0,12
NVP-AUY922	MCF7	0,00	0,50	0,67	0,60	0,40	0,27	0,20	0,08
NMS-SN38	MCF7	1,00	0,50	0,33	0,20	0,20	0,13	0,10	0,08
NMS-Doxorubicin	MCF7	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,04
Average Value:		0,56	0,56	0,56	0,51	0,34	0,26	0,21	0,10

**DN Avg-Distance-Performances**

Compound	Cell Line	PPV when keeping the first n neighbors							
		n=1	n=2	n=3	n=5	n=10	n=15	n=20	n=50
PHA-848125	A2780, MCF7	1,00	1,00	0,67	0,40	0,40	0,33	0,25	0,25
NMS-Flavopiridol	A2780	1,00	1,00	1,00	0,60	0,50	0,40	0,40	0,20
PHA-690509	A2780	1,00	1,00	0,67	0,60	0,40	0,40	0,35	0,18
PHA-793887	A2780, MCF7	1,00	1,00	0,67	0,60	0,40	0,40	0,38	0,12
NMS-Tanespimicyn	MCF7	1,00	1,00	1,00	0,80	0,40	0,27	0,20	0,08
NMS-E973	MCF7	1,00	1,00	1,00	0,80	0,40	0,27	0,20	0,08
NVP-AUY922	MCF7	1,00	1,00	0,67	0,40	0,20	0,13	0,10	0,04
NMS-SN38	MCF7	1,00	1,00	0,67	0,40	0,40	0,27	0,20	0,08
NMS-Doxorubicin	MCF7	0,00	0,50	0,67	0,40	0,20	0,13	0,10	0,04
Average Value:		0,89	0,94	0,78	0,56	0,37	0,29	0,24	0,12

**DN Max-Distance Performances**

Compound	Cell Line	PPV when keeping the first n neighbors							
		n=1	n=2	n=3	n=5	n=10	n=15	n=20	n=50
PHA-848125	A2780, MCF7	0,00	0,50	0,67	0,60	0,40	0,30	0,30	0,12
NMS-Flavopiridol	A2780	1,00	1,00	1,00	0,60	0,40	0,40	0,40	0,20
PHA-690509	A2780	1,00	0,50	0,67	0,60	0,40	0,47	0,35	0,18
PHA-793887	A2780, MCF7	0,00	0,50	0,67	0,60	0,40	0,40	0,25	0,16
NMS-Tanespimicyn	MCF7	1,00	1,00	1,00	0,80	0,50	0,33	0,25	0,10
NMS-E973	MCF7	1,00	1,00	1,00	0,80	0,40	0,33	0,25	0,10
NVP-AUY922	MCF7	1,00	1,00	1,00	0,80	0,40	0,27	0,20	0,08
NMS-SN38	MCF7	1,00	1,00	1,00	0,60	0,40	0,27	0,20	0,08
NMS-Doxorubicin	MCF7	1,00	0,50	0,33	0,40	0,40	0,33	0,25	0,12
Average Value:		0,77	0,77	0,81	0,64	0,41	0,34	0,27	0,13

**SI Online: Table 3 - ROC analysis results**

cMap Classic Query System			DN Max-Distance		DN Avg-Distance	
#Connections = 68, PPV = 3%, First true positive in 29th position			#Connections = 26, PPV = 20%, First true positive in 1st position		#Connections = 5, PPV = 40%, First true positive in 2nd position	
Enrichment	p	Compound	Distance	Compound	Distance	Compound
0.761	0	resveratrol	0.558695	daunorubicin	0.781786	mycophenolic_acid
0.598	0	thioridazine	0.649479	GW-8510	0.793205	etoposide
0.572	0	trichostatin_A	0.653592	hycanthone	0.794405	daunorubicin
0.977	0.00004	camptothecin	0.655487	ellipticine	0.810744	hycanthone
0.927	0.00004	trifluridine	0.668852	irinotecan	0.823146	MG-262
0.574	0.00004	trifluoperazine	0.690000	camptothecin		
0.572	0.00006	15-delta_prostaglandin_J2	0.692053	etoposide		
0.266	0.00006	LY-294002	0.692631	mycophenolic_acid		
0.959	0.0001	mycophenolic_acid	0.699557	phenoxybenzamine		
0.959	0.0001	proscillaridin	0.717513	doxorubicin		
0.885	0.00018	digitoxigenin	0.725793	0175029-0000		
0.476	0.00026	fluphenazine	0.733602	mepacrine		
0.879	0.0003	bufexamac	0.743107	5151277		
0.866	0.00044	thiostrepton	0.743799	apigenin		
0.864	0.00046	phenoxybenzamine	0.752078	5109870		
0.918	0.00114	irinotecan	0.757930	vorinostat		
0.712	0.00159	cloperastine	0.759761	scriptaid		
0.813	0.00235	digoxin	0.762566	alsterpauillone		
0.503	0.00239	vorinostat	0.764030	resveratrol		
0.789	0.00394	norcyclobenzaprine	0.772420	cytochalasin_B		
0.869	0.00413	scriptaid	0.782356	piperlongumine		
0.716	0.00433	antimycin_A	0.785811	tyrphostin_AG-825		
0.775	0.00487	hycanthone	0.789552	HC_toxin		
0.771	0.00525	monobenzene	0.793393	trifluridine		
0.759	0.00635	withaferin_A	0.799587	MG-262		
0.623	0.00886	helveticoside	0.805748	ciclopirox		
0.737	0.00939	pinacidil				
0.927	0.01012	quinostatin				
0.732	0.01017	daunorubicin				
0.927	0.01022	MS-275				
0.82	0.01166	0297417-0002B				
0.718	0.01307	alimemazine				
0.596	0.01412	quercetin				
0.709	0.01476	pimozide				
0.701	0.01643	zalcitabine				
0.795	0.01747	cefotetan				
0.637	0.01788	cinchocaine				
0.688	0.01975	etoposide				
0.687	0.02007	methyl dopate				
0.686	0.02085	zuclopenthixol				
0.68	0.02246	strophanthidin				
0.776	0.02269	fenoterol				

TopoII inhibitors  
 TopoI inhibitors  
 Cdk2 inhibitors

SI Online: Table 4 - ROC analysis results, NSM-Doxorubicin case



	Treated Cell Lines	PPV						Area Under the Curve	
		n=1	n=2	n=3	n=5	n=10	n=50		n=100
1	SF539	0.00	0.50	0.33	0.20	0.10	0.20	0.12	46.81
2	A2780	0.00	0.50	0.33	0.20	0.40	0.12	0.07	48.73
3	U251	0.00	0.50	0.33	0.40	0.40	0.24	0.12	54.27
4	MCF7	0.00	0.50	0.67	0.60	0.40	0.22	0.11	55.70
5	MCF7 SF539	0.00	0.50	0.67	0.40	0.40	0.24	0.12	55.03
6	A2780 MCF7 U251	1.00	0.50	0.33	0.40	0.50	0.22	0.12	57.06
7	A2780 MCF7 U251 SF539	1.00	0.50	0.33	0.40	0.40	0.24	0.12	56.58

SI Online: Table 5 - Impact of the rank merging on the performances

Compound	Inhibition at IC50 ( $\mu\text{M}$ ) concentration
Doxorubicin	Inactive (5% of inhibition at 10 $\mu\text{M}$ )
SN-08	Inactive (9% of inhibition at 10 $\mu\text{M}$ )
PHA-00848125	0.045
PHA-00793887	0.008

SI Online: Table 6 - Biochemical inhibition of CDKs

<b>Comm. Id.</b>	<b>MoA Enrichment type</b>	<b># of drugs with chemical descriptor / # drugs</b>	<b>Average ESF similarity</b>
63	Literature Evidence/ATC-codes/Direct Target Gene	2/11	0.5500
77	Literature Evidence/ATC-codes/Direct Target Gene	3/4	0.3922
43	Literature Evidence/ATC-codes	5/9	0.2726
82	ATC-codes	5/10	0.2350
100	Literature Evidence/ATC-codes	42/76	0.2186
73	Literature Evidence/ATC-codes	5/9	0.1894
65	Literature Evidence/ATC-codes	2/3	0.1857
25	ATC-codes	5/10	0.1853
22	Literature Evidence/ATC-codes	4/12	0.1754
104	Literature Evidence/ATC-codes	5/17	0.1747
88	Literature Evidence/ATC-codes	5/6	0.1717
34	Literature Evidence/ATC-codes/Direct Target Gene	10/18	0.1708
14	Literature Evidence/ATC-codes/Direct Target Gene	8/15	0.1697
13	Literature Evidence/ATC-codes	15/25	0.1686
67	ATC-codes	4/10	0.1645
62	Literature Evidence/ATC-codes/Direct Target Gene	11/30	0.1611
93	Literature Evidence/ATC-codes	5/6	0.1544
58	ATC-codes	6/18	0.1518
53	Literature Evidence	2/6	0.1463
42	Literature Evidence/ATC-codes	10/15	0.1451
50	Literature Evidence/ATC-codes	2/7	0.1449
89	Literature Evidence/ATC-codes/Direct Target Gene	13/33	0.1448
74	ATC-codes	9/14	0.1433
29	ATC-codes/Direct Target Gene	12/21	0.1430
46	ATC-codes	2/7	0.1429
60	Literature Evidence	11/17	0.1414
90	Literature Evidence/ATC-codes	38/79	0.1323
75	Literature Evidence/ATC-codes/Direct Target Gene	3/4	0.1318
61	ATC-codes	7/20	0.1318
32	Literature Evidence/ATC-codes	13/39	0.1317
6	ATC-codes	8/19	0.1314
81	Literature Evidence	2/5	0.1277
52	Literature Evidence/ATC-codes/Direct Target Gene	14/30	0.1273
16	Literature Evidence/ATC-codes	9/16	0.1243
69	Literature Evidence/ATC-codes	4/10	0.1232
28	Literature Evidence	2/5	0.1220
5	ATC-codes	15/24	0.1193
96	Literature Evidence/ATC-codes	2/5	0.1190
102	ATC-codes	7/16	0.1175
7	ATC-codes	14/25	0.1175
40	Literature Evidence/ATC-codes	13/35	0.1158
99	Literature Evidence/ATC-codes	10/14	0.1143
106	ATC-codes	3/9	0.1126
26	Literature Evidence/ATC-codes	5/6	0.1106
76	ATC-codes	4/5	0.1084
3	Literature Evidence	9/19	0.1062
49	Literature Evidence/ATC-codes	6/12	0.0968
97	ATC-codes	6/9	0.0944
36	ATC-codes	3/6	0.0886
48	Literature Evidence/ATC-codes	2/9	0.0805
91	Literature Evidence	2/5	0.0741
39	Literature Evidence	2/5	0.0577

**SI Online: Table 7** – Eletrical/Topological states average similarity for drugs in communities enriched for a given MoA