

Supplementary material for manuscript:
**DIANA: Drug combination prediction using underlying pathways and
interaction networks**

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Supplementary Text S1: Calculation of the log of Odds Ratio of the function

The logarithm of the odds ratio quantifies the strength of the association of one property with the presence or absence of another property. In this case, it quantifies the enrichment of a function in a certain group of genes. The larger it is, the more enriched the function is.

To calculate it, we define the following parameters:

q = num. genes associated with the function of interest in the profile

k = num. genes in the profile

m = num. genes with the function of interest in the network

t = num. genes in the network

We calculate the log of odds ratio using the same formula as the GOEAST toolkit (<http://omicslab.genetics.ac.cn/GOEAST/>):

$$\log \text{ of odds ratio} = \log_2 \left(\frac{(q/k)}{(m/t)} \right)$$

Supplementary Text S2: Definition of the Spearman's rank correlation coefficient

The Spearman's rank correlation coefficient measures the strength of two ranked variables. There are two types of calculation depending on if we have tied ranks or not. Tied ranks are when two cases have the same value and are ranked the same position. However, as our scores are floats, it does not make a significant difference and we use the calculation without taking into account tied ranks. It is calculated as follows:

$$\rho = 1 - \frac{6 \sum d_i^2}{n(n^2 - 1)}$$

Where d is the difference between ranks, and n is the number of scores. We end up obtaining a value from 1 to -1. The values close to 1 are directly correlated, while the values close to -1 are inversely correlated. The values close to 0 are not correlated.

Here we show an example of calculation if we have two vectors with the scores of the profiles:

Vector drug 1

[1.00, 0.95, 0.92, 0.88]

Vector drug 2

[1.00, 0.88, 0.95, 0.91]

V1 (score)	V2 (score)	V1 (rank)	V2 (rank)	d	d ²
1	1	1	1	0	0
0.95	0.88	2	4	2	4
0.92	0.95	3	2	1	1
0.88	0.91	4	3	1	1

$$\rho = 1 - \frac{6 \cdot (0 + 4 + 1 + 1)}{4(4^2 - 1)} = 0.6$$

We calculate the Spearman's rank correlation coefficient using the function `scipy.stats.stats.spearmanr` from the Python package SciPy.

Supplementary Text S3: Definition of the normalized dot product

The normalized dot product is calculated by dividing every element in the vector by the norm of the vector, which corresponds to the length of the vector.

Therefore, if we calculate the dot product as follows:

$$\text{Dot product} = A \cdot B = \sum_{i=1}^n A_i B_i = A_1 B_1 + A_2 B_2 + \dots + A_n B_n$$

We calculate the dot product as follows:

$$\text{Dot product}_{\text{norm}} = \frac{A}{\|A\|} \cdot \frac{B}{\|B\|} = \frac{A}{\sqrt{A \cdot A}} \cdot \frac{B}{\sqrt{B \cdot B}}$$

We end up obtaining a value which ranges from 0 to 1.

Here we show an example of calculation of the dot product and the normalized dot product if we have two vectors with the scores of the profiles:

Vector drug 1

```
{ "DRD2_HUMAN": 1.00,  
  "DRD3_HUMAN": 0.95,  
  "NMDE2_HUMAN": 0.92,  
  "RADI_HUMAN": 0.88 }
```

[1.00, 0.95, 0.92,
0.88]

Vector drug 2

```
{ "DRD2_HUMAN": 1.00,  
  "DRD3_HUMAN": 0.88,  
  "NMDE2_HUMAN": 0.95,  
  "RADI_HUMAN": 0.91 }
```

[1.00, 0.88, 0.95,
0.91]

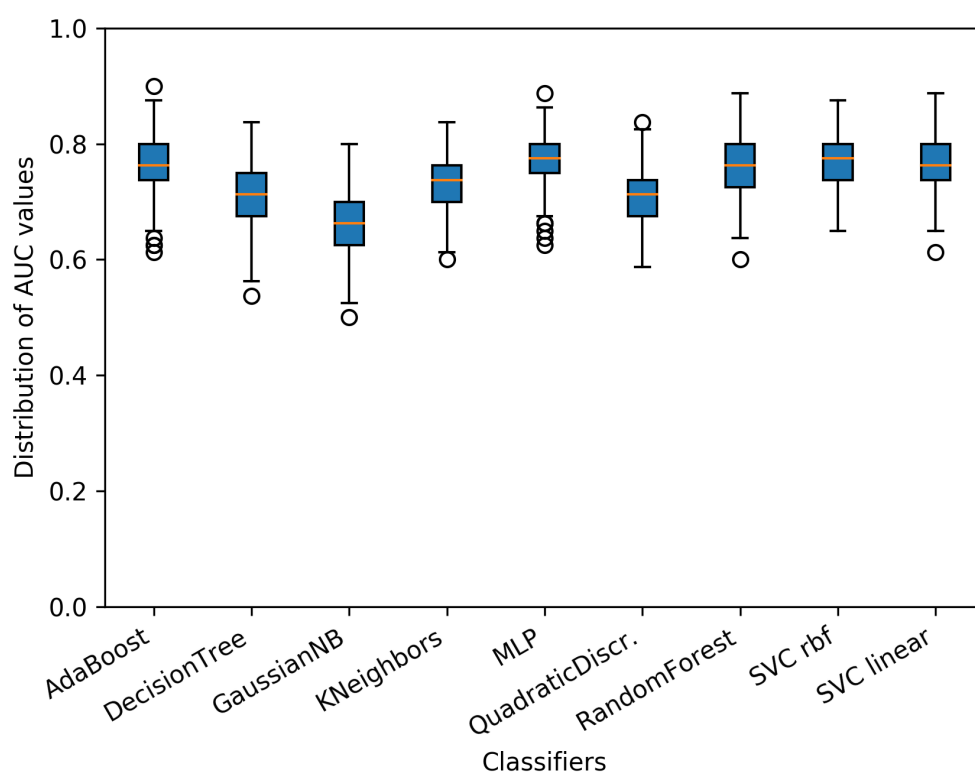
$$\begin{aligned}\text{Dot product} &= V_1 \cdot V_2 \\ &= 1.00 \cdot 1.00 + 0.95 \\ &\quad \cdot 0.88 + 0.92 \cdot 0.95 \\ &\quad + 0.88 \cdot 0.91 = \mathbf{3.51}\end{aligned}$$

$$\begin{aligned}\text{Dot product}_{\text{norm}} &= \frac{V_1}{\|V_1\|} \cdot \frac{V_2}{\|V_2\|} = \frac{V_1}{1.88} \cdot \frac{V_2}{1.87} \\ &= 0.53 \cdot 0.53 + 0.50 \cdot 0.47 \\ &\quad + 0.48 \cdot 0.50 + 0.46 \cdot 0.48 \\ &= \mathbf{0.98}\end{aligned}$$

Supplementary Figure S1: Comparison of the predictive capacity of the classifiers

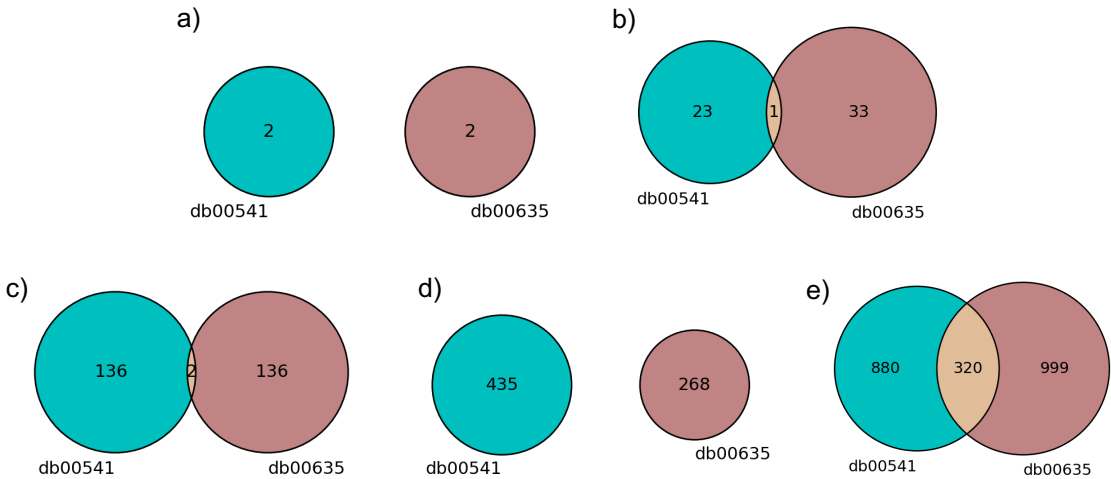
Distribution of the Area Under the Curve (AUC) values for 10 different machine learning classifiers: (1) AdaBoost, (2) Decision trees, (3) Gaussian Naïve Bayes, (4) Nearest neighbors, (5) Multi-layer Perceptron (MLP) neural network model, (6) Quadratic discriminant analysis, (7) Random forest, (8) Super Vector Machine with radial basis function (rbf) kernel, (9) Super Vector Machine with linear kernel.

The AUCs values were obtained from 25 repetitions of a 10-fold cross-validation using the same positive data but different negative data.



Supplementary Figure S2: Overlap between profiles of Vincristine and Prednisone

(a) Overlap between targets; (b) overlap between target-functional profiles; (c) overlap between node profiles; (d) overlap between edge profiles; (e) overlap between PPI-functional profiles.



Supplementary Table S1: Correlation between top thresholds in PPI profiles

Correlation between the information of different top % thresholds.

Top % A	Top % B	Type of profile	Scoring function	Correlation
20	50	edge	Dot product	0.99
10	20	edge	Dot product	0.99
10	20	node	Dot product	0.98
5	10	node	Dot product	0.98
10	20	edge	Spearman	0.97
10	20	node	Spearman	0.97
5	10	edge	Dot product	0.97
5	10	edge	Spearman	0.97
10	20	node	Jaccard	0.97
5	10	node	Jaccard	0.97
20	50	node	Dot product	0.97
10	50	edge	Dot product	0.97
20	50	node	Spearman	0.96
10	20	function	Spearman	0.96
20	50	edge	Spearman	0.96
5	10	node	Spearman	0.96
5	10	function	Jaccard	0.96
5	10	function	Spearman	0.96
10	20	function	Jaccard	0.96
5	10	edge	Jaccard	0.96
10	20	edge	Jaccard	0.95
10	20	function	Dot product	0.95
5	10	function	Dot product	0.95
20	50	function	Jaccard	0.95
20	50	function	Dot product	0.95
20	50	function	Spearman	0.94
10	50	function	Spearman	0.94
20	50	node	Jaccard	0.93
5	20	edge	Dot product	0.93
10	50	function	Jaccard	0.93
10	50	function	Dot product	0.93
5	20	node	Dot product	0.92
10	50	node	Jaccard	0.91
5	20	edge	Spearman	0.91
10	50	node	Dot product	0.91
10	50	edge	Spearman	0.90

5	20	node	Jaccard	0.90
5	50	edge	Dot product	0.90
1	5	node	Dot product	0.89
10	50	node	Spearman	0.89
5	20	node	Spearman	0.89
20	50	edge	Jaccard	0.88
5	20	function	Spearman	0.88
5	50	function	Spearman	0.88
5	20	function	Jaccard	0.87
5	20	edge	Jaccard	0.86
5	50	function	Jaccard	0.86
5	50	node	Jaccard	0.85
5	20	function	Dot product	0.85
5	50	function	Dot product	0.84
5	50	edge	Spearman	0.83
5	50	node	Dot product	0.81
1	10	node	Dot product	0.81
10	50	edge	Jaccard	0.78
1	5	node	Jaccard	0.78
5	50	node	Spearman	0.77
1	5	function	Spearman	0.77
1	5	function	Jaccard	0.76
1	5	function	Dot product	0.74
1	5	edge	Jaccard	0.73
1	20	node	Dot product	0.72
1	10	function	Spearman	0.72
1	10	function	Jaccard	0.71
1	10	node	Jaccard	0.71
1	10	function	Dot product	0.68
1	5	node	Spearman	0.68
5	50	edge	Jaccard	0.68
1	20	function	Spearman	0.68
1	20	function	Jaccard	0.68
1	10	edge	Jaccard	0.66
1	5	edge	Dot product	0.65
1	20	node	Jaccard	0.64
1	20	function	Dot product	0.64
1	5	edge	Spearman	0.64
1	50	function	Spearman	0.62
1	50	function	Jaccard	0.62
1	50	function	Dot product	0.58
1	50	node	Dot product	0.58

1	10	edge	Spearman	0.57
1	10	node	Spearman	0.56
1	20	edge	Jaccard	0.55
1	10	edge	Dot product	0.55
1	50	node	Jaccard	0.54
1	20	edge	Spearman	0.53
1	20	edge	Dot product	0.49
1	50	edge	Spearman	0.49
1	20	node	Spearman	0.48
1	50	edge	Dot product	0.45
1	50	node	Spearman	0.39
1	50	edge	Jaccard	0.37

Supplementary Table S2: Mann-Whitney comparison of the distributions of AUC for Golden Standard 1

For each comparison, we show the resulting Mann-Whitney-U statistic and p-value. The Mann-Whitney test has been calculated with using the `scipy.stats.mannwhitneyu` function of the SciPy Python package. The comparisons with p-value under 0.05 are colored in green, while the rest is colored in red.

	All	Target	PPI	Structure	ATC	Side Effec.	Random
All		0.0, 6.89e-10	0.0, 6.95e-10	0.0, 6.69e-10	188.5, 8.16e-03	0.0, 6.93e-10	0.0, 6.93e-10
Target	0.0, 6.89e-10		69.5, 1.22e-06	22.5, 9.13e-09	0.0, 6.66e-10	0.0, 6.83e-10	35.0, 3.69e-08
PPI	0.0, 6.95e-10	69.5, 1.22e-06		0.0, 6.65e-10	0.0, 6.71e-10	36.5, 4.37e-08	5.0, 1.25e-09
Structure	0.0, 6.69e-10	22.5, 9.13e-09	0.0, 6.65e-10		0.0, 6.46e-10	0.0, 6.63e-10	269.0, 2.01e-01
ATC	188.5, 8.16e-03	0.0, 6.66e-10	0.0, 6.71e-10	0.0, 6.46e-10		0.0, 6.69e-10	0.0, 6.70e-10
Side Effec.	0.0, 6.93e-10	0.0, 6.83e-10	36.5, 4.37e-08	0.0, 6.63e-10	0.0, 6.69e-10		0.0, 6.87e-10
Random	0.0, 6.93e-10	35.0, 3.69e-08	5.0, 1.25e-09	269.0, 2.01e-01	0.0, 6.70e-10	0.0, 6.87e-10	

Supplementary Table S3: Mann-Whitney comparison of the distributions of AUC depending on the number of targets available

For each comparison, we show the resulting Mann-Whitney-U statistic and p-value. The Mann-Whitney test has been calculated with using the `scipy.stats.mannwhitneyu` function of the SciPy Python package. The comparisons with p-value under 0.05 are colored in green, while the rest is colored in red.

		Target	PPI	Structure	ATC	Side effec.	Random
1 target	Target		312.0, 4.78e-11	880.0, 5.27e-03	0.0, 3.15e-18	425.0, 6.25e-09	1166.5, 2.83e-01
	PPI	312.0, 4.78e-11		533.5, 3.74e-07	19.5, 1.02e-17	1133.5, 2.12e-01	553.0, 7.58e-07
	Structure	880.0, 5.27e-03	533.5, 3.74e-07		0.0, 3.06e-18	674.5, 3.51e-05	1077.5, 1.17e-01
	ATC	0.0, 3.15e-18	19.5, 1.02e-17	0.0, 3.06e-18		1.0, 3.40e-18	15.0, 7.88e-18
	Side effec.	425.0, 6.25e-09	1133.5, 2.12e-01	674.5, 3.51e-05	1.0, 3.40e-18		650.5, 1.77e-05
	Random	1166.5, 2.83e-01	553.0, 7.58e-07	1077.5, 1.17e-01	15.0, 7.88e-18	650.5, 1.77e-05	
2 targets	Target		258.0, 3.65e-12	478.5, 4.76e-08	0.0, 3.18e-18	223.0, 6.51e-13	1129.5, 2.03e-01
	PPI	258.0, 3.65e-12		859.5, 3.49e-03	131.5, 6.07e-15	1109.0, 1.66e-01	313.5, 5.15e-11
	Structure	478.5, 4.76e-08	859.5, 3.49e-03		30.0, 1.94e-17	687.5, 5.09e-05	495.5, 9.30e-08
	ATC	0.0, 3.18e-18	131.5, 6.07e-15	30.0, 1.94e-17		118.0, 2.88e-15	16.0, 8.64e-18
	Side effec.	223.0, 6.51e-13	1109.0, 1.66e-01	687.5, 5.09e-05	118.0, 2.88e-15		295.0, 2.20e-11
	Random	1129.5, 2.03e-01	313.5, 5.15e-11	495.5, 9.30e-08	16.0, 8.64e-18	295.0, 2.20e-11	
3≤x≤6 targets	Target		536.0, 3.65e-07	989.0, 3.44e-02	21.0, 8.39e-18	182.5, 7.33e-14	822.5, 1.49e-03
	PPI	536.0, 3.65e-07		666.5, 2.59e-05	260.5, 3.29e-12	932.5, 1.38e-02	813.0, 1.22e-03
	Structure	989.0, 3.44e-02	666.5, 2.59e-05		20.0, 7.63e-18	254.5, 2.52e-12	1045.0, 7.72e-02
	ATC	21.0, 8.39e-18	260.5, 3.29e-12	20.0, 7.63e-18		439.5, 8.56e-09	59.5, 8.06e-17
	Side effec.	182.5, 7.33e-14	932.5, 1.38e-02	254.5, 2.52e-12	439.5, 8.56e-09		428.0, 5.81e-09
	Random	822.5, 1.49e-03	813.0, 1.22e-03	1045.0, 7.72e-02	59.5, 8.06e-17	428.0, 5.81e-09	
≥7 targets	Target		1210.0, 3.92e-01	404.0, 2.18e-09	330.0, 8.87e-11	222.5, 5.67e-13	508.5, 1.38e-07
	PPI	1210.0, 3.92e-01		573.0, 1.42e-06	542.0, 5.01e-07	421.0, 5.21e-09	617.5, 6.20e-06
	Structure	404.0, 2.18e-09	573.0, 1.42e-06		74.5, 2.46e-16	35.0, 2.53e-17	1223.5, 4.29e-01
	ATC	330.0, 8.87e-11	542.0, 5.01e-07	74.5, 2.46e-16		1090.5, 1.36e-01	150.5, 1.62e-14
	Side effec.	222.5, 5.67e-13	421.0, 5.21e-09	35.0, 2.53e-17	1090.5, 1.36e-01		98.0, 9.25e-16
	Random	508.5, 1.38e-07	617.5, 6.20e-06	1223.5, 4.29e-01	150.5, 1.62e-14	98.0, 9.25e-16	

Supplementary Table S4: Mann-Whitney comparison of the distributions of AUC depending on the similarity between the targets of the drug combinations.

For each comparison, we show the resulting Mann-Whitney-U statistic and p-value. The Mann-Whitney test has been calculated with using the `scipy.stats.mannwhitneyu` function of the SciPy Python package. The comparisons with p-value under 0.05 are colored in green, while the rest is colored in red.

		Target	PPI	Structure	ATC	Side effec.	Random
Different targets in different pathways	Target		230.5, 1.04e-12	1111.0, 1.70e-01	0.0, 3.39e-18	378.0, 9.03e-10	524.0, 2.79e-07
	PPI	230.5, 1.04e-12		309.0, 4.29e-11	14.0, 7.88e-18	806.0, 1.10e-03	68.5, 1.90e-16
	Structure	1111.0, 1.70e-01	309.0, 4.29e-11		0.0, 3.40e-18	536.5, 4.22e-07	494.5, 9.49e-08
	ATC	0.0, 3.39e-18	14.0, 7.88e-18	0.0, 3.40e-18		5.5, 4.67e-18	0.0, 3.42e-18
	Side effec.	378.0, 9.03e-10	806.0, 1.10e-03	536.5, 4.22e-07	5.5, 4.67e-18		117.0, 2.80e-15
	Random	524.0, 2.79e-07	68.5, 1.90e-16	494.5, 9.49e-08	0.0, 3.42e-18	117.0, 2.80e-15	
Different targets in similar pathways	Target		53.5, 8.17e-17	744.0, 2.45e-04	0.0, 3.46e-18	29.5, 2.02e-17	222.0, 6.91e-13
	PPI	53.5, 8.17e-17		6.5, 5.14e-18	0.0, 3.45e-18	932.5, 1.44e-02	0.0, 3.49e-18
	Structure	744.0, 2.45e-04	6.5, 5.14e-18		0.0, 3.44e-18	2.0, 3.92e-18	399.5, 2.28e-09
	ATC	0.0, 3.46e-18	0.0, 3.45e-18	0.0, 3.44e-18		0.0, 3.45e-18	0.0, 3.45e-18
	Side effec.	29.5, 2.02e-17	932.5, 1.44e-02	2.0, 3.92e-18	0.0, 3.45e-18		0.0, 3.48e-18
	Random	222.0, 6.91e-13	0.0, 3.49e-18	399.5, 2.28e-09	0.0, 3.45e-18	0.0, 3.48e-18	
Similar targets	Target		483.5, 1.78e-08	0.5, 8.94e-19	5.5, 1.19e-18	0.0, 8.92e-19	0.0, 8.94e-19
	PPI	483.5, 1.78e-08		38.0, 2.39e-17	113.5, 1.66e-15	0.0, 2.63e-18	0.0, 2.63e-18
	Structure	0.5, 8.94e-19	38.0, 2.39e-17		739.5, 1.99e-04	518.0, 2.10e-07	8.5, 5.21e-18
	ATC	5.5, 1.19e-18	113.5, 1.66e-15	739.5, 1.99e-04		199.0, 1.94e-13	1.0, 3.28e-18
	Side effec.	0.0, 8.92e-19	0.0, 2.63e-18	518.0, 2.10e-07	199.0, 1.94e-13		39.5, 3.33e-17
	Random	0.0, 8.94e-19	0.0, 2.63e-18	8.5, 5.21e-18	1.0, 3.28e-18	39.5, 3.33e-17	

Supplementary Table S5: List of me-too pairs of drugs

We have considered that two drugs are me-too drugs when they have a structure similarity score equal or greater than 0.7. We show the names of the drugs in the me-too drug pair and the structural similarity score.

DrugBank ID A	Drug A	DrugBank ID B	Drug B	Similarity score
DB00445	Epirubicin	DB00997	Doxorubicin	1.00
DB00755	Tretinoin	DB00982	Isotretinoin	1.00
DB00215	Citalopram	DB01175	Escitalopram	1.00
DB00443	Betamethasone	DB01234	Dexamethasone	1.00
DB01274	Arformoterol	DB00983	Formoterol	1.00
DB00367	Levonorgestrel	DB00717	Norethisterone	0.99
DB00694	Daunorubicin	DB00997	Doxorubicin	0.99
DB00445	Epirubicin	DB00694	Daunorubicin	0.99
DB01211	Clarithromycin	DB00199	Erythromycin	0.99
DB00541	Vincristine	DB00570	Vinblastine	0.99
DB00959	Methylprednisolone	DB00860	Prednisolone	0.99
DB01177	Idarubicin	DB00694	Daunorubicin	0.99
DB00877	Sirolimus	DB01590	Everolimus	0.99
DB00327	Hydromorphone	DB00956	Hydrocodone	0.99
DB00295	Morphine	DB00318	Codeine	0.99
DB00850	Perphenazine	DB00433	Prochlorperazine	0.98
DB00445	Epirubicin	DB01177	Idarubicin	0.98
DB01177	Idarubicin	DB00997	Doxorubicin	0.98
DB01183	Naloxone	DB00704	Naltrexone	0.98
DB00608	Chloroquine	DB01611	Hydroxychloroquine	0.97
DB00497	Oxycodone	DB01183	Naloxone	0.97
DB00178	Ramipril	DB00519	Trandolapril	0.97
DB00497	Oxycodone	DB00704	Naltrexone	0.97
DB00324	Fluorometholone	DB01234	Dexamethasone	0.96
DB00324	Fluorometholone	DB00443	Betamethasone	0.96
DB00864	Tacrolimus	DB00337	Pimecrolimus	0.96
DB00297	Bupivacaine	DB00961	Mepivacaine	0.96
DB00443	Betamethasone	DB00620	Triamcinolone	0.95
DB00620	Triamcinolone	DB01234	Dexamethasone	0.95
DB01073	Fludarabine	DB00640	Adenosine	0.95
DB00531	Cyclophosphamide	DB01181	Ifosfamide	0.94
DB00641	Simvastatin	DB00227	Lovastatin	0.94
DB00367	Levonorgestrel	DB00294	Etonogestrel	0.94
DB00294	Etonogestrel	DB00717	Norethisterone	0.93

DB00304	Desogestrel	DB00294	Etonogestrel	0.93
DB00324	Fluorometholone	DB00620	Triamcinolone	0.93
DB00175	Pravastatin	DB00227	Lovastatin	0.92
DB08910	Pomalidomide	DB00480	Lenalidomide	0.92
DB00443	Betamethasone	DB00687	Fludrocortisone	0.91
DB00687	Fludrocortisone	DB01234	Dexamethasone	0.91
DB00497	Oxycodone	DB00956	Hydrocodone	0.91
DB00277	Theophylline	DB00201	Caffeine	0.91
DB08910	Pomalidomide	DB01041	Thalidomide	0.91
DB00864	Tacrolimus	DB01590	Everolimus	0.91
DB00320	Dihydroergotamine	DB00696	Ergotamine	0.91
DB00448	Lansoprazole	DB01129	Rabeprazole	0.90
DB00195	Betaxolol	DB00264	Metoprolol	0.90
DB00860	Prednisolone	DB00635	Prednisone	0.90
DB00588	Fluticasone propionate	DB08906	Fluticasone furoate	0.90
DB00860	Prednisolone	DB00741	Hydrocortisone	0.90
DB01577	Methamphetamine	DB00182	Amphetamine	0.90
DB00852	Pseudoephedrine	DB00397	Phenylpropanolamine	0.90
DB00381	Amlodipine	DB01023	Felodipine	0.90
DB00327	Hydromorphone	DB00497	Oxycodone	0.90
DB01024	Mycophenolic acid	DB00688	Mycophenolate mofetil	0.90
DB01151	Desipramine	DB01242	Clomipramine	0.90
DB00864	Tacrolimus	DB00877	Sirolimus	0.90
DB00959	Methylprednisolone	DB00635	Prednisone	0.90
DB01043	Memantine	DB00915	Amantadine	0.90
DB06710	Methyltestosterone	DB00717	Norethisterone	0.90
DB00367	Levonorgestrel	DB06710	Methyltestosterone	0.89
DB00959	Methylprednisolone	DB00741	Hydrocortisone	0.89
DB00327	Hydromorphone	DB01183	Naloxone	0.89
DB00455	Loratadine	DB00967	Desloratadine	0.89
DB00324	Fluorometholone	DB00687	Fludrocortisone	0.89
DB00153	Ergocalciferol	DB02300	Calcipotriol	0.89
DB00327	Hydromorphone	DB00704	Naltrexone	0.89
DB00928	Azacitidine	DB01262	Decitabine	0.89
DB00232	Methyclothiazide	DB01324	Polythiazide	0.89
DB00956	Hydrocodone	DB01183	Naloxone	0.89
DB00436	Bendroflumethiazide	DB00774	Hydroflumethiazide	0.89
DB00956	Hydrocodone	DB00704	Naltrexone	0.88
DB00790	Perindopril	DB00519	Trandolapril	0.88
DB00687	Fludrocortisone	DB00620	Triamcinolone	0.88
DB00929	Misoprostol	DB00770	Alprostadil	0.88
DB00337	Pimecrolimus	DB01590	Everolimus	0.88

DB00537	Ciprofloxacin	DB00978	Lomefloxacin	0.88
DB01075	Diphenhydramine	DB01173	Orphenadrine	0.88
DB00318	Codeine	DB00956	Hydrocodone	0.88
DB01064	Isoprenaline	DB00368	Norepinephrine	0.88
DB00199	Erythromycin	DB00207	Azithromycin	0.88
DB00327	Hydromorphone	DB00295	Morphine	0.87
DB00393	Nimodipine	DB00528	Lercanidipine	0.87
DB00367	Levonorgestrel	DB00304	Desogestrel	0.87
DB00641	Simvastatin	DB00175	Pravastatin	0.87
DB00846	Flurandrenolide	DB00591	Fluocinolone Acetonide	0.87
DB00337	Pimecrolimus	DB00877	Sirolimus	0.87
DB00304	Desogestrel	DB00717	Norethisterone	0.87
DB01211	Clarithromycin	DB00207	Azithromycin	0.87
DB02300	Calcipotriol	DB00910	Paricalcitol	0.87
DB00327	Hydromorphone	DB00318	Codeine	0.86
DB00295	Morphine	DB00956	Hydrocodone	0.86
DB01129	Rabeprazole	DB00338	Omeprazole	0.86
DB00153	Ergocalciferol	DB00910	Paricalcitol	0.86
DB01041	Thalidomide	DB00480	Lenalidomide	0.86
DB00371	Meprobamate	DB00395	Carisoprodol	0.86
DB09085	Tetracaine	DB00721	Procaine	0.86
DB00191	Phentermine	DB00182	Amphetamine	0.86
DB00790	Perindopril	DB00178	Ramipril	0.85
DB06710	Methyltestosterone	DB00396	Progesterone	0.85
DB06710	Methyltestosterone	DB00294	Etonogestrel	0.85
DB00415	Ampicillin	DB00417	Phenoxymethylpenicillin	0.85
DB00846	Flurandrenolide	DB01222	Budesonide	0.85
DB00335	Atenolol	DB00264	Metoprolol	0.85
DB00394	Beclomethasone dipropionate	DB00764	Mometasone	0.84
DB00860	Prednisolone	DB01234	Dexamethasone	0.84
DB00860	Prednisolone	DB00443	Betamethasone	0.84
DB01013	Clobetasol propionate	DB01234	Dexamethasone	0.84
DB00443	Betamethasone	DB01013	Clobetasol propionate	0.84
DB00324	Fluorometholone	DB01013	Clobetasol propionate	0.84
DB00687	Fludrocortisone	DB00741	Hydrocortisone	0.84
DB06710	Methyltestosterone	DB00741	Hydrocortisone	0.84
DB00959	Methylprednisolone	DB00443	Betamethasone	0.84
DB00959	Methylprednisolone	DB01234	Dexamethasone	0.84
DB00448	Lansoprazole	DB00338	Omeprazole	0.84
DB00591	Fluocinolone Acetonide	DB01222	Budesonide	0.83
DB00999	Hydrochlorothiazide	DB00880	Chlorothiazide	0.83
DB00393	Nimodipine	DB01115	Nifedipine	0.83

DB00635	Prednisone	DB00741	Hydrocortisone	0.83
DB00318	Codeine	DB00497	Oxycodone	0.83
DB00959	Methylprednisolone	DB00324	Fluorometholone	0.83
DB00537	Ciprofloxacin	DB01137	Levofloxacin	0.82
DB00612	Bisoprolol	DB00264	Metoprolol	0.82
DB00999	Hydrochlorothiazide	DB00232	Methyclothiazide	0.82
DB00295	Morphine	DB01183	Naloxone	0.82
DB00588	Fluticasone propionate	DB01013	Clobetasol propionate	0.82
DB00860	Prednisolone	DB00324	Fluorometholone	0.82
DB00295	Morphine	DB00497	Oxycodone	0.82
DB01013	Clobetasol propionate	DB00620	Triamcinolone	0.82
DB00860	Prednisolone	DB00764	Mometasone	0.81
DB00318	Codeine	DB01183	Naloxone	0.81
DB00388	Phenylephrine	DB00368	Norepinephrine	0.81
DB00860	Prednisolone	DB00620	Triamcinolone	0.81
DB00295	Morphine	DB00704	Naltrexone	0.81
DB00388	Phenylephrine	DB01064	Isoprenaline	0.81
DB00959	Methylprednisolone	DB00764	Mometasone	0.81
DB00871	Terbutaline	DB01064	Isoprenaline	0.81
DB00318	Codeine	DB00704	Naltrexone	0.81
DB00281	Lidocaine	DB00961	Mepivacaine	0.81
DB00959	Methylprednisolone	DB00620	Triamcinolone	0.81
DB00620	Triamcinolone	DB00591	Fluocinolone Acetonide	0.81
DB05294	Vandetanib	DB00317	Gefitinib	0.80
DB01069	Promethazine	DB00433	Prochlorperazine	0.80
DB00640	Adenosine	DB00631	Clofarabine	0.80
DB00603	Medroxyprogesterone acetate	DB00741	Hydrocortisone	0.80
DB01013	Clobetasol propionate	DB00591	Fluocinolone Acetonide	0.79
DB00277	Theophylline	DB01223	Aminophylline	0.79
DB00297	Bupivacaine	DB00281	Lidocaine	0.79
DB01069	Promethazine	DB00850	Perphenazine	0.79
DB00388	Phenylephrine	DB00871	Terbutaline	0.79
DB00335	Atenolol	DB00195	Betaxolol	0.79
DB06710	Methyltestosterone	DB00304	Desogestrel	0.79
DB01073	Fludarabine	DB00631	Clofarabine	0.79
DB00630	Alendronic acid	DB00710	Ibandronate	0.79
DB00285	Venlafaxine	DB00193	Tramadol	0.78
DB00394	Beclomethasone dipropionate	DB01013	Clobetasol propionate	0.78
DB01577	Methamphetamine	DB00191	Phentermine	0.78
DB00741	Hydrocortisone	DB00396	Progesterone	0.78
DB00635	Prednisone	DB01234	Dexamethasone	0.78
DB00443	Betamethasone	DB00635	Prednisone	0.78

DB00393	Nimodipine	DB01023	Felodipine	0.78
DB00860	Prednisolone	DB00687	Fludrocortisone	0.78
DB01001	Salbutamol	DB00938	Salmeterol	0.78
DB00798	Gentamicin	DB00994	Neomycin	0.78
DB00798	Gentamicin	DB00452	Framycetin	0.78
DB00213	Pantoprazole	DB00338	Omeprazole	0.78
DB00959	Methylprednisolone	DB00687	Fludrocortisone	0.77
DB01013	Clobetasol propionate	DB00687	Fludrocortisone	0.77
DB00612	Bisoprolol	DB00195	Betaxolol	0.77
DB01167	Itraconazole	DB01026	Ketoconazole	0.77
DB00397	Phenylpropanolamine	DB00182	Amphetamine	0.77
DB00852	Pseudoephedrine	DB01577	Methamphetamine	0.77
DB00999	Hydrochlorothiazide	DB01324	Polythiazide	0.77
DB00591	Fluocinolone Acetonide	DB01234	Dexamethasone	0.77
DB00443	Betamethasone	DB00591	Fluocinolone Acetonide	0.77
DB01137	Levofloxacin	DB00978	Lomefloxacin	0.77
DB06710	Methyltestosterone	DB00603	Medroxyprogesterone acetate	0.77
DB00381	Amlodipine	DB00393	Nimodipine	0.77
DB00367	Levonorgestrel	DB00741	Hydrocortisone	0.77
DB00530	Erlotinib	DB00317	Gefitinib	0.77
DB00528	Lercanidipine	DB01115	Nifedipine	0.76
DB00717	Norethisterone	DB00741	Hydrocortisone	0.76
DB00741	Hydrocortisone	DB01234	Dexamethasone	0.76
DB00443	Betamethasone	DB00741	Hydrocortisone	0.76
DB00717	Norethisterone	DB00396	Progesterone	0.76
DB00394	Beclomethasone dipropionate	DB01222	Budesonide	0.76
DB00860	Prednisolone	DB01222	Budesonide	0.76
DB00367	Levonorgestrel	DB00396	Progesterone	0.76
DB00588	Fluticasone propionate	DB00591	Fluocinolone Acetonide	0.76
DB00959	Methylprednisolone	DB01222	Budesonide	0.76
DB00603	Medroxyprogesterone acetate	DB00421	Spironolactone	0.76
DB00635	Prednisone	DB00764	Mometasone	0.76
DB00324	Fluorometholone	DB00635	Prednisone	0.76
DB00860	Prednisolone	DB06710	Methyltestosterone	0.76
DB00750	Prilocaine	DB00961	Mepivacaine	0.76
DB00960	Pindolol	DB01136	Carvedilol	0.76
DB00871	Terbutaline	DB01001	Salbutamol	0.75
DB00381	Amlodipine	DB01115	Nifedipine	0.75
DB00294	Etonogestrel	DB00741	Hydrocortisone	0.75
DB00324	Fluorometholone	DB00591	Fluocinolone Acetonide	0.75
DB00201	Caffeine	DB01223	Aminophylline	0.75
DB00281	Lidocaine	DB00750	Prilocaine	0.75

DB00388	Phenylephrine	DB00852	Pseudoephedrine	0.75
DB00603	Medroxyprogesterone acetate	DB00635	Prednisone	0.75
DB00635	Prednisone	DB00620	Triamcinolone	0.75
DB05294	Vandetanib	DB00530	Erlotinib	0.75
DB01064	Isoprenaline	DB00841	Dobutamine	0.75
DB00275	Olmesartan	DB00678	Losartan	0.75
DB00938	Salmeterol	DB00598	Labetalol	0.75
DB00999	Hydrochlorothiazide	DB00774	Hydroflumethiazide	0.75
DB08906	Fluticasone furoate	DB01013	Clobetasol propionate	0.75
DB00959	Methylprednisolone	DB06710	Methyltestosterone	0.75
DB00327	Hydromorphone	DB00514	Dextromethorphan	0.75
DB01045	Rifampicin	DB00615	Rifabutin	0.75
DB01023	Felodipine	DB01115	Nifedipine	0.75
DB00612	Bisoprolol	DB00335	Atenolol	0.74
DB00959	Methylprednisolone	DB00603	Medroxyprogesterone acetate	0.74
DB06710	Methyltestosterone	DB00635	Prednisone	0.74
DB00588	Fluticasone propionate	DB00443	Betamethasone	0.74
DB00588	Fluticasone propionate	DB01234	Dexamethasone	0.74
DB00860	Prednisolone	DB00603	Medroxyprogesterone acetate	0.74
DB01064	Isoprenaline	DB01001	Salbutamol	0.74
DB00443	Betamethasone	DB00764	Mometasone	0.74
DB00764	Mometasone	DB01234	Dexamethasone	0.74
DB01129	Rabeprazole	DB00213	Pantoprazole	0.74
DB00588	Fluticasone propionate	DB00324	Fluorometholone	0.74
DB00324	Fluorometholone	DB00764	Mometasone	0.74
DB00324	Fluorometholone	DB00741	Hydrocortisone	0.74
DB00448	Lansoprazole	DB00213	Pantoprazole	0.74
DB00317	Gefitinib	DB08916	Afatinib	0.74
DB00514	Dextromethorphan	DB00956	Hydrocodone	0.74
DB06710	Methyltestosterone	DB00910	Paricalcitol	0.74
DB00741	Hydrocortisone	DB00764	Mometasone	0.74
DB00960	Pindolol	DB00571	Propranolol	0.74
DB00294	Etonogestrel	DB00396	Progesterone	0.74
DB00741	Hydrocortisone	DB00620	Triamcinolone	0.74
DB08822	Azilsartan medoxomil	DB00796	Candesartan cilexetil	0.73
DB08822	Azilsartan medoxomil	DB13919	Candesartan	0.73
DB00394	Beclomethasone dipropionate	DB00860	Prednisolone	0.73
DB01013	Clobetasol propionate	DB01222	Budesonide	0.73
DB00635	Prednisone	DB00687	Fludrocortisone	0.73
DB06335	Saxagliptin	DB04876	Vildagliptin	0.73
DB00620	Triamcinolone	DB01222	Budesonide	0.73
DB00334	Olanzapine	DB00363	Clozapine	0.73

DB00959	Methylprednisolone	DB00394	Beclomethasone dipropionate	0.73
DB01001	Salbutamol	DB00598	Labetalol	0.73
DB00394	Beclomethasone dipropionate	DB00603	Medroxyprogesterone acetate	0.73
DB00588	Fluticasone propionate	DB00620	Triamcinolone	0.73
DB00603	Medroxyprogesterone acetate	DB01013	Clobetasol propionate	0.73
DB01068	Clonazepam	DB00829	Diazepam	0.73
DB00432	Trifluridine	DB00495	Zidovudine	0.72
DB00297	Bupivacaine	DB00750	Prilocaine	0.72
DB08906	Fluticasone furoate	DB00591	Fluocinolone Acetonide	0.72
DB00603	Medroxyprogesterone acetate	DB01222	Budesonide	0.72
DB00620	Triamcinolone	DB00764	Mometasone	0.72
DB01067	Glipizide	DB01016	Glyburide	0.72
DB00687	Fludrocortisone	DB00591	Fluocinolone Acetonide	0.72
DB00603	Medroxyprogesterone acetate	DB00396	Progesterone	0.72
DB00397	Phenylpropanolamine	DB01577	Methamphetamine	0.72
DB00381	Amlodipine	DB00528	Lercanidipine	0.72
DB00564	Carbamazepine	DB00776	Oxcarbazepine	0.72
DB01023	Felodipine	DB00528	Lercanidipine	0.72
DB01013	Clobetasol propionate	DB00764	Mometasone	0.71
DB01088	Iloprost	DB00770	Alprostadil	0.71
DB00635	Prednisone	DB01222	Budesonide	0.71
DB00304	Desogestrel	DB00910	Paricalcitol	0.71
DB00603	Medroxyprogesterone acetate	DB00846	Flurandrenolide	0.71
DB00232	Methyclothiazide	DB00880	Chlorothiazide	0.71
DB01119	Diazoxide	DB00880	Chlorothiazide	0.71
DB00860	Prednisolone	DB01013	Clobetasol propionate	0.71
DB00436	Bendroflumethiazide	DB01324	Polythiazide	0.71
DB06825	Triptorelin	DB02638	Terlipressin	0.71
DB00603	Medroxyprogesterone acetate	DB00717	Norethisterone	0.71
DB00603	Medroxyprogesterone acetate	DB00687	Fludrocortisone	0.70
DB00367	Levonorgestrel	DB00603	Medroxyprogesterone acetate	0.70
DB00388	Phenylephrine	DB00397	Phenylpropanolamine	0.70
DB00295	Morphine	DB00514	Dextromethorphan	0.70
DB00687	Fludrocortisone	DB00846	Flurandrenolide	0.70
DB00959	Methylprednisolone	DB01013	Clobetasol propionate	0.70
DB00436	Bendroflumethiazide	DB00232	Methyclothiazide	0.70
DB06710	Methyltestosterone	DB00687	Fludrocortisone	0.70
DB06710	Methyltestosterone	DB00153	Ergocalciferol	0.70
DB00571	Propranolol	DB00264	Metoprolol	0.70
DB00603	Medroxyprogesterone acetate	DB00294	Etonogestrel	0.70
DB00860	Prednisolone	DB00396	Progesterone	0.70