Supplementary materials and methods

Random walk in the heterogeneous network

1. Determination of initial probability $p_0$
In the initial probability $p_0$, probability 1 was assigned to the seed nodes, and probability 0 was assigned to other vertices, forming the drug network $h_0$ and the protein network $v_0$. Given that we added disease nodes, the initial probability of disease network $u_0$ is a zero vector containing no seed nodes. Hence, the initial probability of the heterogeneous network can be represented as:

$$p_0 = \begin{bmatrix} a u_0 \\ b v_0 \\ c h_0 \end{bmatrix}$$

2. Construction of transition matrix $M$
In the transition matrix $M$, $M_{\text{disease-disease}}$, $M_{\text{protein-protein}}$ and $M_{\text{drug-drug}}$ are inter-transition matrices representing the probability of the transition from one disease/protein/drug to another disease/protein/drug node. $M_{\text{disease-protein}}$ is the transition matrix from the disease network to the protein network, whereas $M_{\text{protein-disease}}$ is the transition matrix from the protein network to the disease network. Similarly, $M_{\text{protein-drug}}$ is the transition matrix from the protein network to the drug network, whereas $M_{\text{drug-protein}}$ is the transition matrix from the drug network to the protein network.

The transition probability from vertex disease $i$ to protein $j$ was defined as:

$$M_{\text{disease-protein}}(i,j) = \frac{b S_1(i,j)}{\sum_j S_1(i,j)}$$

The transition probability from vertex protein $i$ to disease $j$ was defined as:

$$M_{\text{protein-disease}}(i,j) = \frac{a S_2(j,i)}{\sum_i S_2(j,i)}$$

The transition probability from vertex drug $i$ to protein $j$ was defined as:

$$M_{\text{drug-protein}}(i,j) = \frac{b S_3(i,j)}{\sum_j S_3(i,j)}$$

The transition probability from vertex protein $i$ to drug $j$ was defined as:

$$M_{\text{protein-drug}}(i,j) = \frac{c S_4(j,i)}{\sum_j S_4(j,i)}$$

The transition probability from vertex drug $i$ to disease $j$ was defined as:

$$M_{\text{drug-disease}}(i,j) = \begin{cases} \frac{a S_5(i,j)}{\sum_j S_5(i,j)} & \text{if } \sum_j S_5(i,j) \neq 0 \\ 0 & \text{otherwise} \end{cases}$$

The transition probability from vertex disease $i$ to drug $j$ was defined as:

$$M_{\text{disease-drug}}(i,j) = \begin{cases} \frac{c S_6(j,i)}{\sum_i S_6(j,i)} & \text{if } \sum_i S_6(j,i) \neq 0 \\ 0 & \text{otherwise} \end{cases}$$

Then the random walk can be implemented on the heterogeneous network based on the transition matrix $M$.

The parameter optimization process

Random walk differs from many other machine learning algorithms in that it does not have a loss function during the iteration. Consequently, it can measure only the final accuracy by cross validation after computing and ranking. Thus, normal
parameter optimization cannot be directly implemented. In this research, we selected as many different parameter combinations as possible within our computing power and used AUC values to measure which parameters combination were optimal.

Here, the weight of drug network $a$ was preferentially given a higher proportion (more than 0.5), according to previous studies\textsuperscript{1,2}. The random walk model implemented for drug repurposing has demonstrated to be robust to the selection of $r$; therefore, only 3 values between 0 and 1 (0.3, 0.5, and 0.7) were chosen to test whether the robustness still functions in our model. The results showed that our model was robust to the selection of $r$ (AUC value difference $\leq 0.01$). Therefore, we chose $r = 0.7$ because it had the best performance in both previous studies and our research.

### Enrichment analysis for differentially expressed proteins

The log$_2$-transformed value of each reporter ion intensity (corrected) was obtained. The SVA package was applied to remove batch effects (Supplementary Figure S7). Then the data were imported into Perseus v1.6.1.3 for statistical analysis. The processed intensities were normalized, and two-tailed $t$-tests were performed as described previously\textsuperscript{3}. Proteins meeting significance criteria were subjected to analysis with the Database for Annotation, Visualization and Integrated Discovery (DAVID 6.8) tools with the total human genome information as the background. On the basis of fold change, the proteins with significant differences were classified into 2 data sets: the upregulated data set (fold change $>1.2$) and downregulated data set (fold change $<0.83$). Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis was used to investigate the molecular mechanisms. The adjusted $P$ value (Benjamini–Hochberg correction) cutoff was 0.05.

### Network analysis

Cytoscape (version 3.6.1) software based on the STRING database (version 10.5) was used to analyze protein–protein interactions and the downregulated proteins\textsuperscript{4,5}. Interactions with

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**Figure S1** Metformin was chosen as a positive control for the selected drugs in breast cancer cell lines, a prostate cancer cell line, and a gastric cancer cell line. (A)–(D) Compared with DMSO, metformin had dose-dependent antiproliferative effects on breast cancer cell lines, a prostate cancer cell line, and a gastric cancer cell line. Data are presented as the mean ± SEM ($n = 3$). Statistical significance was calculated with the Kruskal–Wallis test and Dunn’s test (multiple comparisons among treatment groups and controls). One asterisk indicates $P < 0.05$, 2 asterisks indicate $P < 0.01$, and 3 asterisks indicate $P < 0.001$. NS represents no statistical significance.
an interaction score $\geq 0.7$ and active interaction sources from experiments and databases were exported from STRING for Cytoscape analysis.

**Analysis of drug-compound similarity in mechanism**

Connectivity Map (CMAP) of the Broad Institute Drug Repurposing Hub (https://clue.io), data version 1.1.2 and software version 1.1.33, was used for further analysis of compound similarity on the basis of gene-expression profiling. CMAP reveals connections among small molecules by measuring the similarity of transcriptional responses to perturbation in different human cell lines. We extracted the items in “Compound” for nifedipine and nortriptyline. The score threshold was set at 99.

**Figure S2** The model predicted low-ranking drugs (chlorpropamide, tolazoline, tiaprofenic acid, and decamethonium) showed no significant inhibitory effects on the respective cancer cell lines, even at a high concentration of 100 $\mu$M. The MCF-7 and MDA231-LM2-4175 human breast cancer cell lines were selected for studying breast cancer; the LNCaP and DU145 human prostate cancer cell lines were selected for studying prostate cancer; and the MGC-803 cell line was selected for studying gastric cancer. The model predicted low-ranking drugs (chlorpropamide, tolazoline, tiaprofenic acid, and decamethonium) showed no significant inhibitory effects on the respective cancer cell lines, even at a high concentration of 100 $\mu$M. Data are presented as the mean ± SEM ($n = 3$). Statistical significance was calculated with the Kruskal-Wallis test and Dunn’s test (multiple comparisons among treatment groups and controls). One asterisk indicates $P < 0.05$, 2 asterisks indicate $P < 0.01$, and 3 asterisks indicate $P < 0.001$. NS represents no statistical significance.
Figure S3  Pearson correlation analysis was performed to evaluate the data quality. Pearson correlation of protein intensities in response to DMSO (A), nifedipine (B), nortriptyline (C), and metformin (D) treatment between 2 biological replicates.

Figure S4  The average body weight changes in mice treated with vehicle (saline solution), or a single dose of 5-FU (50 mg/kg), nortriptyline (30 mg/kg), or nifedipine (50 mg/kg) intraperitoneally (n = 8 per group). Data are presented as the mean ± SEM.
Figure S5  The PAD database interface. The prediction results of the full model were uploaded to the PAD database, which enabled ranking of queries for 1,419 drugs and 4,096 diseases.

Figure S6  Possible mechanisms of nortriptyline. The cytotoxicity of nortriptyline might be due to its effects on cell cycle progression. Nortriptyline downregulates the expression of Rb, thus potentially affecting the Rb/E2F complex and consequently inhibiting the expression of E2F target genes. In addition, nortriptyline significantly downregulates CDK1. In summary, cell cycle arrest might contribute to the nortriptyline-induced cytotoxicity.

Figure S7  The SVA package was applied to remove batch effects. (A) Distribution of log₂ (intensity) of 4 groups (DMSO, nifedipine, nortriptyline, and metformin) before removal of batch effects. (B) Distribution of log₂ (intensity) of 4 groups (DMSO, nifedipine, nortriptyline, and metformin) after removal of batch effects.
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| DB00808    | D006973        |
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Table S1 Continued

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Table S1 Continued
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| DB00437     | C538228        | DB00313     | D020191        |
| DB01586     | D008105        | DB00909     | D020191        |
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| DB01175     | D001008        | DB00448     | D005764        |
| DB00829     | D001008        | DB00501     | D005764        |
| DB01268     | D002292        | DB01241     | D015228        |
| DB00398     | D002292        | DB00159     | D015228        |
| DB00515     | D002294        | DB00627     | D015228        |
| DB00997     | D002294        | DB00091     | D015352        |
| DB00795     | D013167        | DB00437     | C538235        |
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| DB00959     | D009471        | DB00860     | D014607        |
| DB00860     | D009471        | DB00443     | D014607        |
| DB00993     | D009471        | DB00091     | D014607        |
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| DB00627     | D011928        | DB00641     | D006949        |
| DB00443     | D011928        | DB01095     | D006949        |
| DB01049     | D011928        | DB01098     | D006949        |
| DB03904     | C564491        | DB00973     | D006949        |
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| DB01144     | D020514        | DB01599     | D006949        |
| DB00761     | D020514        | DB00515     | D002289        |
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| DB00819     | D020513        | DB00773     | D002289        |
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| DB00175    | D006937        |
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| DB01033     | D054218         |
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| DB00125     | C56375          |
| DB00181     | C536833         |
| DB00140     | C536833         |
| DB00583     | C536833         |
| DB00811     | D007835         |
| DB00155     | C562687         |
| DB00136     | C562688         |
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| DB00882     | D011085         |
| DB00331     | D011085         |
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| DB01129     | D016481         |
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| DB01033    | C536512        | DB01242    | D009771        |
| DB00666    | C562787        | DB00502    | D009771        |
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| DB00675    | D000172        | DB00741    | C564577        |
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| DB00666    | D004715        | DB00970    | D012512        |
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| DB00537    | D008554        | DB00440    | D006105        |
| DB01165    | D008554        | DB01167    | D006105        |
| DB00544    | D005706        | DB00936    | D010916        |
| DB00997    | D005706        | DB00982    | D010916        |
| DB00441    | D005706        | DB00459    | D010916        |
| DB00502    | D005879        | DB02300    | D010916        |
| DB01100    | D005879        | DB00563    | D010916        |
| DB00158    | D001139        | DB00091    | D010916        |
| DB00415    | D008088        | DB00993    | D010916        |
| DB01015    | D008088        | DB00740    | D000690        |
| DB00798    | D008088        | DB00906    | D000690        |
| DB01393    | D006950        | DB00136    | D006962        |
| DB00175    | D006950        | DB01012    | D006962        |
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| Drug         | Rank | Disease MeSH ID | Disease name                          | Z score | Verified information                  | Purpose       | Article validation | Article name                                                                 | Journal                                      |
|--------------|------|----------------|---------------------------------------|---------|---------------------------------------|---------------|--------------------|-------------------------------------------------------------------------------|----------------------------------------------|
| Sirolimus    | 1    | D008106        | Liver cirrhosis, experimental         | 36.105  | NA                                    |               | Yes                | Low-dose oral rapamycin treatment reduces fibrogenesis, improves liver function, and prolongs survival in rats with established liver cirrhosis | Journal of Hepatology                       |
|              | 2    | C562729        | Esophageal squamous cell carcinoma     | 33.532  | NA                                    |               | Yes                | An activated mTOR/p70S6K signaling pathway in esophageal squamous cell carcinoma cell lines and inhibition of the pathway by rapamycin and siRNA against mTOR | Cancer Letters                               |
|              | 3    | D001254        | Astrocytoma                           | 16.6658 | DrugBank, ClinicalTrials              | Treatment     |                    |                                                                               |                                              |
|              | 4    | D008654        | Mesothelioma                          | 6.6156  | NA                                    |               | Yes                | Combined treatment with cisplatin and sirolimus to enhance cell death in human mesothelioma | The Journal of Thoracic and Cardiovascular Surgery |
|              | 5    | D006528        | Carcinoma, hepatocellular             | 4.5865  | DrugBank, ClinicalTrials              | Treatment     |                    |                                                                               |                                              |
|              | 6    | D012559        | Schizophrenia                         | 4.5449  | NA                                    |               |                    |                                                                               |                                              |
|              | 7    | D006973        | Hypertension                          | 4.5395  | DrugBank, ClinicalTrials              | Treatment     |                    |                                                                               |                                              |
|              | 8    | D002292        | Carcinoma, renal cell                 | 4.4973  | DrugBank, ClinicalTrials              | Treatment     |                    |                                                                               |                                              |
|              | 9    | D010051        | Ovarian neoplasms                     | 4.4841  | ClinicalTrials                        | Treatment     |                    |                                                                               |                                              |
|              | 10   | D000230        | Adenocarcinoma                        | 4.4709  | ClinicalTrials                        | Treatment     |                    |                                                                               |                                              |
|              | 11   | D054218        | Precursor T-cell lymphoblastic leukemia-lymphoma | 4.4539 | ClinicalTrials                        | Treatment     |                    |                                                                               |                                              |
|              | 12   | D020522        | Lymphoma, mantle-cell                 | 4.45    | DrugBank, ClinicalTrials              | Treatment     |                    |                                                                               |                                              |
| Drug    | Rank | Disease MeSH ID | Disease name                              | Z score | Verified information | Purpose | Article validation | Article name                                                                 | Journal                                      |
|---------|------|-----------------|-------------------------------------------|---------|----------------------|---------|-------------------|-------------------------------------------------------------------------------|----------------------------------------------|
|         | 13   | D017379         | Hypertrophy, left ventricular              | 4.443   | NA                   |         | Yes               | Effect of sirolimus on left ventricular hypertrophy in kidney transplant recipients: a 1-year nonrandomized controlled trial | American Journal of Kidney Diseases          |
|         | 14   | D002583         | Uterine cervical neoplasms                | 4.4427  | NA                   |         |                   |                                                                               |                                              |
|         | 15   | D054220         | Malformations of cortical development      | 4.4297  | NA                   |         |                   |                                                                               |                                              |
|         | 16   | D020258         | Neurotoxicity syndromes                   | 4.4249  | NA                   |         |                   |                                                                               |                                              |
|         | 17   | D018288         | Carcinoma, small cell                     | 4.4208  | NA                   |         |                   |                                                                               |                                              |
|         | 18   | C537067         | Focal cortical dysplasia of Taylor         | 4.4181  | NA                   |         |                   |                                                                               |                                              |
|         | 19   | D011471         | Prostatic neoplasms                       | 2.4137  | ClinicalTrials       | Treatment |                   | Rapamycin protects against myocardial ischemia–reperfusion injury through JAK2–STAT3 signaling pathway | Journal of Molecular and Cellular Cardiology |
|         | 20   | D017202         | Myocardial ischemia                       | 2.2391  | NA                   |         | Yes               | The antidiabetic drug metformin inhibits gastric cancer cell proliferation in vitro and in vivo | Molecular Cancer Therapeutics                |
| Metformin | 1    | D013274         | Stomach neoplasms                         | 44.1332 | NA                   |         | Yes               |                                                                               |                                              |
|         | 2    | D018450         | Disease progression                       | 44.0338 | ClinicalTrials       | Treatment|                   |                                                                               |                                              |
|         | 3    | D011085         | Polycystic ovary syndrome                  | 10.8756 | KEGG, DrugBank, ClinicalTrials | Treatment|                   |                                                                               |                                              |
|         | 4    | D003924         | Diabetes mellitus, type 2                  | 10.8566 | KEGG, DrugBank, ClinicalTrials | Treatment|                   |                                                                               |                                              |
|         | 5    | D008106         | Liver cirrhosis, experimental              | 0.1559  | NA                   |         |                   |                                                                               |                                              |
|         | 6    | D001943         | Breast neoplasms                          | 0.1404  | DrugBank, ClinicalTrials | Prevention|                   |                                                                               |                                              |
| Drug  | Rank | Disease MeSH ID | Disease name                                      | Z score | Verified information          | Purpose             | Article validation | Article name | Journal                  |
|-------|------|-----------------|---------------------------------------------------|---------|-------------------------------|---------------------|--------------------|--------------|--------------------------|
|       | 7    | D011471         | Prostatic neoplasms                               | 0.1212  | DrugBank, ClinicalTrials      | Treatment           |                    |              |                          |
|       | 8    | D009765         | Obesity                                           | 0.1122  | DrugBank, ClinicalTrials      | Treatment           |                    |              |                          |
|       | 9    | D006528         | Carcinoma, hepatocellular                         | 0.0784  | DrugBank, ClinicalTrials      | Treatment           |                    |              |                          |
|       | 10   | D007333         | Insulin resistance                                | 0.0585  | DrugBank, ClinicalTrials      | Treatment           |                    |              |                          |
|       | 11   | D002289         | Carcinoma, non-small-cell lung                    | 0.0532  | DrugBank, ClinicalTrials      | Treatment           |                    |              |                          |
|       | 12   | D015464         | Leukemia, myelogenous, chronic, BCR-ABL positive  | 0.041   | NA                            |                     |                    |              |                          |
|       | 13   | D004715         | Endometriosis                                     | 0.0409  | NA                            | Yes                 | Metformin is a potent inhibitor of endometrial cancer cell proliferation—implications for a novel treatment strategy |            | Gynecologic Oncology |
|       | 14   | D003528         | Carcinoma, adenoid cystic                         | 0.0346  | NA                            |                     |                    |              |                          |
|       | 15   | D018149         | Glucose intolerance                               | 0.0338  | DrugBank, ClinicalTrials      | Basic Science       |                    |              |                          |
|       | 16   | D002545         | Brain ischemia                                    | 0.0297  | NA                            |                     |                    |              |                          |
|       | 17   | D008224         | Lymphoma, follicular                              | 0.027   | NA                            | Yes                 | Therapeutic metformin/AMPK activation blocked lymphoma cell growth via inhibition of mTOR pathway and induction of autophagy |            | Cell Death & Disease |
|       | 18   | D010051         | Ovarian neoplasms                                 | 0.0265  | ClinicalTrials                | Treatment           |                    |              |                          |
|       | 19   | C563663         | Immunodeficiency due to defect in MAPBP-interacting protein | 0.0262 | NA                            |                     |                    |              |                          |
|       | 20   | C565485         | Glycogen storage disease 0, liver                 | 0.0258  | NA                            |                     |                    |              |                          |
| Drug          | Rank | Disease MeSH ID | Disease name                      | Z score  | Verified information                      | Purpose       | Article validation | Article name | Journal                      |
|--------------|------|----------------|-----------------------------------|----------|------------------------------------------|---------------|-------------------|--------------|-----------------------------|
| Itraconazole | 1    | D002177        | Candidiasis                       | 190.011  | KEGG, DrugBank, ClinicalTrials          | Treatment     |                   |              |                             |
|              | 2    | D006105        | Granulomatous disease, chronic    | 189.774  | KEGG, ClinicalTrials                   | Treatment     |                   |              |                             |
|              | 3    | D008106        | Liver cirrhosis, experimental     | 5.87     | NA                                       |               |                   |              |                             |
|              | 4    | D011471        | Prostatic neoplasms              | 3.3631   | DrugBank, ClinicalTrials                | Treatment     |                   |              |                             |
|              | 5    | D006528        | Carcinoma, hepatocellular         | 1.908    | NA                                       |               |                   |              |                             |
|              | 6    | D008175        | Lung neoplasms                   | 1.2561   | ClinicalTrials                          | Treatment     |                   |              |                             |
|              | 7    | D009765        | Obesity                          | 1.2313   | NA                                       |               |                   |              |                             |
|              | 8    | D001943        | Breast neoplasms                 | 1.2022   | DrugBank, ClinicalTrials                | Treatment     |                   |              |                             |
|              | 9    | D013274        | Stomach neoplasms                | 1.1423   | NA                                       |               |                   |              |                             |
|              | 10   | D008114        | Liver neoplasms, experimental     | 1.0895   | NA                                       |               |                   |              |                             |
|              | 11   | D000544        | Alzheimer disease                 | 0.8671   | DrugBank, ClinicalTrials                | Treatment     |                   |              |                             |
|              | 12   | D002779        | Cholestasis                       | 0.8584   | NA                                       |               |                   |              |                             |
|              | 13   | D004715        | Endometriosis                    | 0.8474   | NA                                       |               |                   |              |                             |
|              | 14   | D056486        | Chemical and drug induced liver injury | 0.7955 | NA                                       |               |                   |              |                             |
|              | 15   | D010381        | Pelger-Huet anomaly               | 0.7805   | NA                                       |               |                   |              |                             |
|              | 16   | D008325        | Mammary neoplasms, experimental   | 0.7786   | NA                                       |               |                   |              |                             |

**Table S2 Continued**

Itraconazole induces apoptosis and cell cycle arrest via inhibiting Hedgehog signaling in gastric cancer cells

Itraconazole inhibits AKT/mTOR signaling and proliferation in endometrial cancer cells
| Drug      | Rank | Disease MeSH ID | Disease name                              | Z score | Verified information  | Purpose       | Article validation | Article name | Journal                                           |
|----------|------|-----------------|-------------------------------------------|---------|-----------------------|---------------|-------------------|--------------|---------------------------------------------------|
|          |      |                 | Q fever                                   | 0.7616  | NA                    |               |                   |             |                                                   |
|          |      |                 | Colorectal neoplasms                      | 0.7442  | NA                    |               |                   |             |                                                   |
|          |      |                 | Kidney failure, chronic                   | 0.7379  | NA                    |               |                   |             |                                                   |
|          |      |                 | Polycystic ovary syndrome                 | 0.7279  | DrugBank, ClinicalTrials | Basic Science |                   |             |                                                   |
|          |      |                 | Hypotension                               | 8.0016  | DrugBank              | NA            |                   |             |                                                   |
|          |      |                 | Schizophrenia                             | 6.845   | DrugBank, ClinicalTrials | Treatment    |                   |             |                                                   |
|          |      |                 | Obsessive-compulsive disorder             | 6.266   | KEGG, DrugBank, ClinicalTrials | Treatment    |                   |             |                                                   |
|          |      |                 | Cardiomegaly                              | 4.7158  | NA                    |               |                   |             |                                                   |
|          |      |                 | Amphetamine-related disorders             | 4.3576  | NA                    |               |                   |             |                                                   |
|          |      |                 | Hyperkinesis                              | 3.7844  | ClinicalTrials        | Treatment     |                   |             |                                                   |
|          |      |                 | Fibrosis                                  | 3.6146  | NA                    | Yes           | Effects of clozapine, chlorpromazine and risperidone treatment on the liver fibrosis markers | Journal of Radioimmunology |                                                   |
|          |      |                 | Seizures                                  | 3.5542  | DrugBank              | NA            |                   |             |                                                   |
|          |      |                 | Cocaine-related disorders                 | 3.0679  | DrugBank, ClinicalTrials | Treatment    |                   |             |                                                   |
|          |      |                 | Pain                                      | 2.9074  | DrugBank              | NA            |                   |             |                                                   |
|          |      |                 | Substance withdrawal syndrome             | 2.8833  | NA                    |               |                   |             |                                                   |
|          |      |                 | Diabetes mellitus, experimental           | 2.5751  | NA                    |               |                   |             |                                                   |
|          |      |                 | Liver cirrhosis                           | 2.5446  | NA                    |               |                   |             |                                                   |
| Drug Rank | Disease MeSH ID | Disease name                | Z score  | Verified information | Purpose | Article validation | Article name                                                                 | Journal                           |
|-----------|-----------------|-----------------------------|----------|----------------------|---------|-------------------|-------------------------------------------------------------------------------|-----------------------------------|
| 14        | D006333         | Heart failure               | 2.542    | NA                   |         |                   |                                                                              |                                   |
| 15        | D013981         | Tic disorders               | 2.5198   | NA                   | Yes     |                   | Risperidone treatment of children and adolescents with chronic tic disorders: a preliminary report | Child & Adolescent Psychiatry      |
| 16        | D020257         | Ventricular remodeling      | 2.5156   | NA                   |         |                   |                                                                              |                                   |
| 17        | D009765         | Obesity                     | 2.0929   | DrugBank             |         | Screening         |                                                                              |                                   |
| 18        | D008569         | Memory disorders            | 1.9297   | NA                   |         |                   |                                                                              |                                   |
| 19        | D008607         | Intellectual disability     | 1.9045   | ClinicalTrials       |         | Treatment         |                                                                              |                                   |
| 20        | D008171         | Lung diseases               | 1.8888   | NA                   |         |                   |                                                                              |                                   |

Note: The verified information column indicates the information source (KEGG, DrugBank clinical indication, or ClinicalTrials).
| Drug       | Rank | Disease MeSH ID | Disease name                                         | Z score | Verified information | Purpose                  | Article name                                                                 | Journal                                                      |
|------------|------|-----------------|------------------------------------------------------|---------|----------------------|--------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------|
| Sirolimus  | 2121 | D006105         | Granulomatous disease, chronic                       | -0.0563 | NA                   | Yes                      | Sirolimus as an alternative treatment in patients with granulomatous-lymphocytic lung disease and humoral immunodeficiency with impaired regulatory T cells | Respiratory Medicine Case Reports                             |
|            | 2164 | C538258         | ATR-X syndrome                                       | -0.0563 | NA                   |                          |                                                                             |                                                              |
|            | 682  | C537533         | Seckel syndrome 1                                    | -0.0529 | NA                   |                          |                                                                             |                                                              |
|            | 2372 | C566869         | Night blindness, congenital stationary, autosomal dominant 2 | -0.0565 | NA                   |                          |                                                                             |                                                              |
|            | 1148 | C567656         | Cerebellar ataxia, mental retardation, and disequilibrium syndrome 2 | -0.0548 | NA                   |                          |                                                                             |                                                              |
|            | 2303 | C567275         | Craniodiaphyseal dysplasia, autosomal dominant        | -0.0564 | NA                   |                          |                                                                             |                                                              |
|            | 226  | D008569         | Memory disorders                                     | -0.0419 | NA                   | Yes                      | Rapamycin-sensitive late-LTP is enhanced in the hippocampus of IL-6 transgenic mice | Neuroscience                                                  |
|            | 341  | D013163         | Splenomegaly                                         | -0.048  | NA                   | Yes                      | Rapamycin reverses splenomegaly and inhibits tumor development in a transgenic model of Epstein-Barr virus-related Burkitt's lymphoma | Molecular Cancer Therapeutics                                 |
|            | 3101 | D056660         | Hereditary autoinflammatory diseases                 | -0.057  | NA                   |                          |                                                                             |                                                              |
|            | 3313 | D041781         | Jaundice, obstructive                                | -0.0572 | NA                   |                          |                                                                             |                                                              |
|            | 1621 | D014648         | Varicose veins                                       | -0.0557 | NA                   |                          |                                                                             |                                                              |
|            | 2515 | C562626         | Ehlers-Danlos syndrome, type VIII                    | -0.0566 | NA                   |                          |                                                                             |                                                              |
|            | 777  | C536623         | Scalp ear nipple syndrome                            | -0.0534 | NA                   |                          |                                                                             |                                                              |
| Drug   | Rank | Disease MeSH ID | Disease name                                      | Z score | Verified | Purpose                                      | Article name                                                                 | Journal                        |
|--------|------|-----------------|---------------------------------------------------|---------|----------|----------------------------------------------|-------------------------------------------------------------------------------|--------------------------------|
| 3135   | C564485 | Glycogen storage disease, type IXD               | −0.0571                                          | NA      | Yes      | Preclinical development of new therapy for glycogen storage diseases | Preclinical development of new therapy for glycogen storage diseases | Current Gene Therapy |
| 2710   | D010013 | Osteogenesis imperfecta                          | −0.0568                                          | NA      | Yes      | Rapamycin promotes osteogenesis under inflammatory conditions | Rapamycin promotes osteogenesis under inflammatory conditions | Molecular Medicine Reports |
| 86     | C538231 | Adenocarcinoma of lung                           | −0.0113                                          | DrugBank | NA      | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Biological & Pharmaceutical Bulletin |
| 3590   | D012178 | Retinopathy of prematurity                       | −0.0574                                          | NA      | Yes      | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Biological & Pharmaceutical Bulletin |
| 3105   | D002549 | Diffuse cerebral sclerosis of Schilder           | −0.057                                          | NA      | NA       | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Biological & Pharmaceutical Bulletin |
| 1518   | C567482 | Hypospadias 1, X-linked                          | −0.0555                                          | NA      | NA       | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Biological & Pharmaceutical Bulletin |
| 3939   | D018382 | Thyroid hormone resistance syndrome              | −0.0578                                          | NA      | NA       | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Biological & Pharmaceutical Bulletin |
|        |       | Metformin                                       |                                                  |         |          | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Biological & Pharmaceutical Bulletin |
| 1158   | C536739 | Wolcott-Rallison syndrome                        | −0.0276                                          | NA      | NA       | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Biological & Pharmaceutical Bulletin |
| 3867   | D010201 | Panniculitis, nodular nonsuppurative             | −0.029                                           | NA      | NA       | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Biological & Pharmaceutical Bulletin |
| 958    | D008067 | Lipoma                                          | −0.0274                                          | NA      | NA       | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Biological & Pharmaceutical Bulletin |
| 3370   | D009471 | Neuromyelitis optica                            | −0.0288                                          | NA      | NA       | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Biological & Pharmaceutical Bulletin |
| 2359   | D006869 | Hydronephrosis                                  | −0.0285                                          | NA      | NA       | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Biological & Pharmaceutical Bulletin |
| 350    | D012220 | Rhinitis                                        | −0.0253                                          | NA      | NA       | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Biological & Pharmaceutical Bulletin |
| 3561   | D009212 | Myoglobinuria                                   | −0.0289                                          | NA      | NA       | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Biological & Pharmaceutical Bulletin |
| 2720   | D009056 | Mouth abnormalities                             | −0.0286                                          | NA      | NA       | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Biological & Pharmaceutical Bulletin |
| 1155   | C563614 | Long QT syndrome 2                             | −0.0276                                          | NA      | NA       | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Biological & Pharmaceutical Bulletin |
| 110    | D003866 | Depressive disorder                            | −0.0139                                          | NA      | NA       | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Biological & Pharmaceutical Bulletin |
| 1151   | D046351 | Protoporphyria, erythropoietic                   | −0.0276                                          | NA      | NA       | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Anti-angiogenic effects of mammalian target of rapamycin inhibitors in a mouse model of oxygen-induced retinopathy | Biological & Pharmaceutical Bulletin |
| Drug     | Rank | Disease MeSH ID | Disease name                                      | Z score | Verified information | Purpose | Article validation | Article name                                                                 | Journal                                      |
|----------|------|----------------|--------------------------------------------------|---------|----------------------|---------|-------------------|--------------------------------------------------------------------------------|----------------------------------------------|
|          | 251  | D012516        | Osteosarcoma                                     | −0.0235 | NA                   | Yes     |                   | Inhibition of LCMR1 and ATG12 by demethylation-activated miR-570-3p is involved in the anti-metastasis effects of metformin on human osteosarcoma | Cell Death & Disease                         |
|          | 1273 | D016553        | Purpura, thrombocytopenic, idiopathic            | −0.0277 | NA                   |         |                   |                                                                                 |                                              |
|          | 183  | D010580        | Peutz-Jeghers syndrome                           | −0.0214 | NA                   |         |                   |                                                                                 |                                              |
|          | 4044 | C536601        | Amaurosis congenita of Leber, type 2             | −0.0291 | NA                   |         |                   |                                                                                 |                                              |
|          | 3109 | C563676        | Retinitis pigmentosa 33                          | −0.0288 | NA                   | Yes     |                   | Rescue of mutant rhodopsin traffic by metformin-induced AMPK activation accelerates photoreceptor degeneration | Human Molecular Genetics                     |
|          | 3171 | C565188        | Spinocerebellar ataxia, autosomal recessive 8    | −0.0288 | NA                   |         |                   |                                                                                 |                                              |
|          | 2798 | C566882        | Surfactant metabolism dysfunction, pulmonary, 1  | −0.0287 | NA                   |         |                   |                                                                                 |                                              |
|          | 2746 | D008336        | Mandibular diseases                              | −0.0286 | NA                   |         |                   |                                                                                 |                                              |
|          | 2690 | C567709        | Muscular dystrophy, congenital, due to integrin alpha-7 deficiency | −0.0286 | NA                   | Yes     |                   | Effects of single and combined metformin and L-citrulline supplementation on L-arginine-related pathways in Becker muscular dystrophy patients: possible biochemical and clinical implications | Amino Acids                                   |
| Itraconazole | 2105 | C576976        | Hypothyroidism, congenital, nongoitrous, 1       | −0.1167 | NA                   |         |                   |                                                                                 |                                              |
|          | 647  | D011686        | Purine-pyrimidine metabolism, inborn errors      | −0.1011 | NA                   |         |                   |                                                                                 |                                              |
|          | 4089 | C536602        | Amaurosis congenita of Leber, type 5             | −0.1223 | NA                   |         |                   |                                                                                 |                                              |
| Drug  | Rank | Disease MeSH ID | Disease name                                                                 | Z score | Verified information | Purpose | Article validation | Article name | Journal |
|-------|------|----------------|------------------------------------------------------------------------------|---------|----------------------|---------|-------------------|-------------|---------|
| 2657  | C566169 | −0.1178 | Cardiomyopathy, familial hypertrophic, 4                                   | NA      | Article validation   |         |                   |             |         |
| 1252  | C565822 | −0.114  | Congenital cataracts, facial dysmorphism, and neuropathy                    | NA      | Article validation   |         |                   |             |         |
| 2157  | C535420 | −0.1168 | Charcot-Marie-Tooth disease, type 4b1                                       | NA      | Article validation   |         |                   |             |         |
| 609   | D016736 | −0.0993 | Antiphospholipid syndrome                                                    | NA      | Article validation   |         |                   |             |         |
| 3037  | C538157 | −0.1196 | Blau syndrome                                                               | NA      | Article validation   |         |                   |             |         |
| 2386  | C567680 | −0.1173 | Waardenburg syndrome, type 4b                                               | NA      | Article validation   |         |                   |             |         |
| 1619  | C536025 | −0.1155 | Marshall syndrome                                                           | NA      | Article validation   |         |                   |             |         |
| 3961  | D000033 | −0.1216 | Abortion, threatened                                                        | NA      | Article validation   |         |                   |             |         |
| 4037  | D019595 | −0.1219 | Severe dengue                                                               | NA      | Article validation   |         |                   |             |         |
| 2169  | C563408 | −0.1168 | Epidermolysis bullosa simplex, autosomal recessive                           | NA      | Article validation   |         |                   |             |         |
| 2726  | C537194 | −0.1181 | Lethal congenital contracture syndrome 1                                   | NA      | Article validation   |         |                   |             |         |
| 2293  | C567514 | −0.1171 | Long QT syndrome 10                                                         | NA      | Article validation   |         |                   |             |         |
| 1569  | C567195 | −0.1154 | Exocrine pancreatic insufficiency, dyserthrythropoietic anemia, and calvarial hyperostosis | NA | Article validation   |         |                   |             |         |
| 2504  | C538247 | −0.1175 | Amish lethal microcephaly                                                   | NA      | Article validation   |         |                   |             |         |
| 2989  | D052919 | −0.1193 | Refsum disease, infantile                                                   | NA      | Article validation   |         |                   |             |         |
| 3243  | D000402 | −0.1202 | Airway obstruction                                                          | NA      | Article validation   |         |                   |             |         |
| 3333  | C563669 | −0.1204 | Deafness, autosomal recessive 68                                            | NA      | Article validation   |         |                   |             |         |
| Drug         | Rank | Disease MeSH ID | Disease name                                         | Z score | Verified information | Purpose                  | Article validation | Article name                                      | Journal                                |
|--------------|------|-----------------|------------------------------------------------------|---------|----------------------|--------------------------|--------------------|--------------------------------------------------|----------------------------------------|
| **Risperidone** | 3020 | C536271         | Ichthyosis prematurity syndrome                      | −0.031  | NA                   | NA                       |                    | Evaluation of risperidone in the neonatal 6-hydroxydopamine model of Lesch-Nyhan syndrome | Pharmacology Biochemistry & Behavior   |
|              | 3355 | C562440         | Hypophosphatasi, childhood                           | −0.0311 | NA                   | NA                       |                    |                                                   |                                        |
|              | 2962 | C535684         | Ring dermoid of cornea                               | −0.031  | NA                   | NA                       |                    |                                                   |                                        |
|              | 3723 | D009402         | Nephrosis, lipoid                                    | −0.0312 | NA                   | NA                       |                    |                                                   |                                        |
|              | 1553 | D008580         | Meningism                                            | −0.0302 | NA                   | NA                       |                    |                                                   |                                        |
|              | 3116 | C564520         | Retinitis pigmentosa 3                               | −0.031  | NA                   | NA                       |                    |                                                   |                                        |
|              | 419  | D003092         | Colitis                                              | −0.0278 | NA                   | NA                       |                    |                                                   |                                        |
|              | 1128 | C562735         | Osseous heteroplasia, progressive                    | −0.0298 | NA                   | NA                       |                    |                                                   |                                        |
|              | 1135 | C563181         | Histiocytoma, angiomatoid fibrous                    | −0.0298 | NA                   | NA                       |                    |                                                   |                                        |
|              | 2111 | D058489         | 46, XX disorders of sex development                  | −0.0306 | NA                   | NA                       |                    |                                                   |                                        |
|              | 2005 | C537989         | Charcot-Marie-Tooth disease, type 2b                 | −0.0305 | NA                   | NA                       |                    |                                                   |                                        |
|              | 1091 | C535736         | Encephalocraniocutaneous lipomatosis                 | −0.0297 | NA                   | NA                       |                    |                                                   |                                        |
|              | 1121 | C564593         | Gaze palsy, familial horizontal, with progressive scoliosis | −0.0298 | NA                   | NA                       |                    |                                                   |                                        |
|              | 1062 | D007926         | Lesch-Nyhan syndrome                                 | −0.0297 | NA                   | Yes                      |                    | Evaluation of risperidone in the neonatal 6-hydroxydopamine model of Lesch-Nyhan syndrome | Pharmacology Biochemistry & Behavior   |
|              | 2418 | C566910         | Renal tubular acidosis, distal, with hemolytic anemia | −0.0307 | NA                   | NA                       |                    |                                                   |                                        |
|              | 1011 | D011225         | Pre-eclampsia                                        | −0.0296 | NA                   | NA                       |                    |                                                   |                                        |
| Drug | Rank | Disease MeSH ID | Disease name                                                                 | Z score | Verified information | Purpose | Article validation | Article name | Journal |
|------|------|-----------------|------------------------------------------------------------------------------|---------|----------------------|---------|---------------------|--------------|---------|
| 1822 | 1822 | C562710         | Diabetes mellitus, insulin-resistant, with acanthosis nigricans              | −0.0304 | NA                   | NA      |                     |              |         |
| 1398 | 1398 | C564093         | Myopathy, X-linked, with excessive autophagy                               | −0.0301 | NA                   | NA      |                     |              |         |
| 3019 | 3019 | C564714         | Spondyloepimetaphyseal dysplasia, X-linked                                  | −0.031  | NA                   | NA      |                     |              |         |
| 626  | 626  | D014376         | Tuberculosis                                                                | −0.0291 | NA                   | NA      |                     |              |         |

Note: The verified information column indicates the information source (KEGG, DrugBank clinical indication, or ClinicalTrials).
| Drug       | Compound | Activity                                                                 | Article name                                                                 | Journal                                      |
|------------|----------|--------------------------------------------------------------------------|-------------------------------------------------------------------------------|----------------------------------------------|
| Nifedipine | Rilmenidine | Suppression of proliferation and promotion of apoptosis via the mitochondrial pathway in human leukemic K562 cells | Rilmenidine suppresses proliferation and promotes apoptosis via the mitochondrial pathway in human leukemic K562 cells | European Journal of Pharmaceutical Sciences |
| Nomilin    |          | Anti-tumor and immunomodulatory effects *in vivo*                          | Nomilin inhibits metastasis *via* induction of apoptosis and regulates the activation of transcription factors and the cytokine profile in B16F-10 cells | Integrative Cancer Therapies                 |
|            |          |                                                                          | Nomilin inhibits tumor-specific angiogenesis *via* downregulating VEGF, NO and proinflammatory cytokine profile and also *by* inhibiting the activation of MMP-2 and MMP-9 | European Journal of Pharmacology             |
|            |          |                                                                          | Limonoids and their anti-proliferative and anti-aromatase properties in human breast cancer cells | Food & Function                              |
|            |          |                                                                          | Inhibition of tumor progression by naturally occurring terpenoids            | Pharmaceutical Biology                        |
| AICA-ribonucleotide | Induction of apoptosis and programmed necrosis in prostate cancer cells | AICAR induces AMPK-independent programmed necrosis in prostate cancer cells | Activation of AMP-kinase by AICAR induces apoptosis of DU-145 prostate cancer cells *through* generation of reactive oxygen species and activation of c-Jun N-terminal kinase | Biochemical and Biophysical Research Communications |
|            |          |                                                                          | AMP-activated protein kinase activators can inhibit the growth of prostate cancer cells *by* multiple mechanisms | International Journal of Oncology           |
| CGP-57380  |          | Suppression of eIF4E phosphorylation by Mnk inhibitors sensitization of CRPC cells to mTOR and AR inhibitors | The Androgen Receptor is a negative regulator of eIF4E Phosphorylation at S209: Implications for the use of mTOR inhibitors in advanced prostate cancer | Oncogene                                      |
| TPCA-1     |          | Direct dual inhibition of STAT3 and NF-κB and regression of mutant EGFR-associated human non-small cell lung cancers | TPCA-1 is a direct dual inhibitor of STAT3 and NF-κB and regress mutant EGFR-associated human non-small cell lung cancers | Molecular Cancer Therapeutics                 |
| Benzopyrene |          | Induction of cell death, DNA strand breaks, and cell cycle arrest in the DU145 human prostate carcinoma cell line | Induction of cell death, DNA strand breaks, and cell cycle arrest in DU145 human prostate carcinoma cell line by benzo[a]pyrene | International Journal of Environmental Research and Public Health |
| Drug        | Compound | Activity                                                                 | Article name                                                                                                                                                                                                 | Journal                                           |
|------------|----------|--------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|
| Indirubin  |          | Inhibition of prostate tumor growth through inhibiting tumor angiogenesis | Indirubin inhibits tumor growth by antitumor angiogenesis via blocking VEGFR2-mediated JAK/STAT3 signaling in endothelial cell                                                                                   | International Journal of Cancer                  |
| Nortriptyline | Sertraline | Induction of \([Ca(2+)][i]\) rise in human PC3 prostate cancer cells       | The mechanism of sertraline-induced \([Ca(2+)][i]\) rise in human PC3 prostate cancer cells                                                                                                                                 | Basic & Clinical Pharmacology & Toxicology         |
| Tetrindole |          |                                                                           |                                                                                                                                                                                                             |                                                   |
| RS-17053   |          |                                                                           |                                                                                                                                                                                                             |                                                   |
| Tetrindole |          |                                                                           |                                                                                                                                                                                                             |                                                   |
| Triflupromazine | Terfenadine | Induction of anti-proliferative and apoptotic activities in human hormone-refractory prostate cancer through histamine receptor-independent Mcl-1 cleavage and Bak up-regulation | Terfenadine induces anti-proliferative and apoptotic activities in human hormone-refractory prostate cancer through histamine receptor-independent Mcl-1 cleavage and Bak up-regulation | Naunyn-Schmiedeberg's Archives of Pharmacology     |
| T-98475    |          |                                                                           |                                                                                                                                                                                                             |                                                   |
| Ispinesib  |          | Inhibition of the mitotic kinesin spindle protein, thus leading to cell cycle arrest and cell death with activity in a wide spectrum of tumor cell lines and xenografts and preliminary clinical activity in early phase I and II | Increased therapeutic potential of an experimental anti-mitotic inhibitor SB715992 by genistein in PC-3 human prostate cancer cell line Promising novel cytotoxic agents and combinations in metastatic prostate cancer | BMC Cancer The Cancer Journal                    |
| Mibefradil |          | Induction of cell apoptosis in leukemia and glioblastoma cell lines       | T-type calcium channel antagonists, mibefradil and NNC-SS-0396 inhibit cell proliferation and induce cell apoptosis in leukemia cell lines Inhibition of T-type calcium channels disrupts Akt signaling and promotes apoptosis in glioblastoma cells | Journal of Experimental & Clinical Cancer Research Biochemical Pharmacology |
References

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