BA-12 Inhibits Angiogenesis via Glutathione Metabolism Activation

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1. The chemical information of BA-12 by UPLC-MS.

The chromatographic analysis of BA-12 was performed on an Agilent 1290 series UHPLC system coupled to 6550 Q-TOF/MS mass spectrometer. The analysis was conducted on a ZORBAX RRHD 300 SB-C18 column (2.1×100 mm, 1.8 μm). For the ESI+ analysis, the mobile phases used were solvent A (Acetonitrile spiked with 0.1% formic acid), solvent B (Water spiked with 0.1% formic acid), with gradient elution as follows: 25% A at 0 – 15 min, 25% – 60% A at 15 – 20 min, 60 % – 95% A at 20–25 min, 95% A at 25–30 min. The flow rate was kept at 0.3 mL/min. The column and autosampler were maintained at 30°C and 4°C, respectively. The injection volume of reference compounds and samples was 1 μL. The eluent was introduced to the mass spectrometer directly. The mass range was set from m/z 360 to 700. The optimal conditions of analysis were as follows: the capillary voltage was 4 kV; desolvation gas flow was 11.0 L/min, the source temperature was set at 125°C, the desolvation gas temperature was 225°C. Calibrations were automatically conducted from m/z 360 to 700 with a solution of sodium formate. The chemical information and a base peak chromatogram are shown as Supplementary Figure S1.

![Figure S1](image)

Figure S1 | The chemical information and a base peak chromatogram of the UPLC-MS analysis of BA-12 in the ESI+ mode.
2. Desorption electrospray ionization mass spectrometry (DESI-MS) imaging of BA-12 in qCAM samples.

Waters Synapt G2SI HDMS q-TOF coupled with Desi (Desorption electrospray ionization, Desi) (Waters, MA, USA) was used for quality control by detecting BA-12 in the quail chick chorioallantoic membrane (qCAM) sections. The mass range was set from m/z 100 to 1000. The results are shown as Supplementary Figure S2 and Table S1.

Figure S2 | Imaging mass spectrometry of qCAM samples of control (A) and BA-12 (80 μg) (B) group.
### Table S1 | The mass data of imaging mass spectrometry

| Control group | BA-12 (80 μg) group |
|---------------|---------------------|
| Positive mode | Negative mode       |
| M/z           | Max Intensity       | M/z     | Max Intensity       |
| 610.4056      | 2446                | 170.9206| 5362                | 610.4164 | 126790 | 170.9229 | 6308 |
| 611.4067      | 1365                | 265.2677| 5974                | 536.3755 | 72889  | 172.9213 | 4385 |
| 536.3663      | 2100                | 172.9186| 4533                | 611.4172 | 61040  | 265.2709 | 2832 |
| 185.2081      | 1984                | 168.9228| 3623                | 445.302  | 89520  | 134.9414 | 2517 |
| 612.4049      | 1143                | 134.9395| 3320                | 612.4158 | 48146  | 168.925  | 3130 |
| 309.2641      | 2198                | 255.3494| 2995                | 684.4568 | 32270  | 132.943  | 1961 |
| 173.1677      | 2930                | 132.9413| 3375                | 537.3765 | 33126  | 255.3527 | 4231 |
| 684.4451      | 943                 | 174.9171| 2457                | 185.2115 | 34471  | 253.3362 | 1153 |
| 537.3674      | 1157                | 293.308 | 2600                | 149.106  | 62063  | 169.9235 | 1048 |
| 445.2939      | 2727                | 253.3334| 1369                | 446.3031 | 49586  | 293.3117 | 989  |
| 182.2825      | 890                 | 311.3034| 1275                | 215.2115 | 23675  | 325.3274 | 1794 |
| 163.1245      | 2861                | 136.9377| 1294                | 429.2658 | 29774  | 136.9396 | 889  |
| 538.3649      | 669                 | 171.9196| 1051                | 309.2699 | 15547  | 171.9222 | 768  |
| 171.1875      | 1098                | 283.3897| 1141                | 686.4564 | 15737  | 167.9252 | 874  |
| 149.1036      | 2149                | 167.923 | 1147                | 613.4158 | 16327  | 283.3932 | 1053 |
| 613.4053      | 419                 | 339.3436| 971                 | 538.3744 | 23675  | 325.3274 | 1794 |
| 249.2243      | 892                 | 227.3088| 1065                | 173.1706 | 16688  | 309.3119 | 849  |
| 352.3009      | 4579                | 309.3079| 749                 | 467.2908 | 16631  | 227.3118 | 1568 |
| 686.4445      | 355                 | 241.3293| 875                 | 182.286  | 9884   | 334.1297 | 69   |
| 301.2719      | 870                 | 391.2506| 444                 | 341.1668 | 57748  | 216.206  | 81   |
| 353.3042      | 1439                | 389.2505| 424                 | 113.1276 | 26447  | 391.2572 | 322  |
| 265.2243      | 495                 | 266.2713| 1197                | 249.2286 | 22326  | 389.257  | 353  |
| 241.2167      | 755                 | 297.2833| 686                 | 225.1569 | 78818  | 241.3323 | 682  |
| 412.4858      | 260                 | 176.9157| 599                 | 615.3806 | 10993  | 176.9178 | 470  |
| 281.2969      | 502                 | 256.3535| 818                 | 463.3437 | 12057  | 297.287  | 376  |
| 473.5074      | 596                 | 173.9185| 592                 | 217.2126 | 7700   | 173.9207 | 485  |
| 467.2827      | 981                 | 269.3698| 448                 | 301.277  | 10870  | 266.2744 | 441  |
| 446.2949      | 1129                | 417.285 | 267                 | 281.1803 | 24013  | 208.3948 | 64   |
| 557.3017      | 228                 | 194.9462| 625                 | 227.2369 | 12571  | 162.9274 | 425  |
| 631.3409      | 378                 | 353.3483| 429                 | 150.118  | 19053  | 256.3561 | 751  |
| 462.3256      | 1074                | 393.2511| 281                 | 412.493  | 7228   | 417.2912 | 225  |
| 615.3696      | 468                 | 419.2862| 277                 | 430.2666 | 16350  | 419.2932 | 213  |
| 113.1259      | 1027                | 279.3573| 470                 | 687.4561 | 6979   | 269.3726 | 439  |
| 413.4311      | 473                 | 162.925 | 586                 | 539.3749 | 8339   | 393.2578 | 297  |
| 447.4679      | 317                 | 337.3477| 384                 | 213.1183 | 56594  | 205.6349 | 89   |
| 250.2321      | 408                 | 312.307 | 326                 | 265.2281 | 7725   | 233.2671 | 493  |
|     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 325.2438 | 223 | 294.3116 | 541 | 250.2361 | 11985 | 279.3607 | 367 |
| 389.4087 | 563 | 196.9442 | 660 | 355.2238 | 25414 | 234.45 | 72 |
| 413.4878 | 245 | 210.3095 | 65 | 614.4144 | 7317 | 465.4925 | 329 |
| 429.2578 | 958 | 254.3369 | 491 | 171.1905 | 9682 | 353.3527 | 460 |
| 539.3674 | 370 | 326.3269 | 348 | 464.3327 | 12233 | 164.9258 | 363 |
| 365.2893 | 169 | 465.4859 | 364 | 631.3516 | 3195 | 327.9077 | 76 |
| 130.232 | 407 | 321.3485 | 394 | 541.3354 | 7902 | 190.95 | 175 |
| 447.2931 | 775 | 415.28 | 259 | 758.4973 | 5839 | 326.1312 | 86 |
| 740.5228 | 111 | 233.2636 | 407 | 281.302 | 12419 | 267.3569 | 298 |
| 614.4041 | 235 | 324.2624 | 75 | 170.147 | 225.6266 | 86 |
| 213.2486 | 376 | 164.9237 | 493 | 413.4378 | 4489 | 225.6266 | 86 |
| 687.4443 | 224 | 223.134 | 394 | 431.2641 | 13535 | 337.3519 | 329 |
| 541.3251 | 395 | 267.3534 | 415 | 365.2863 | 2028 | 215.5975 | 85 |
| 170.1441 | 646 | 282.3772 | 331 | 227.1531 | 51593 | 197.9077 | 283 |
| 758.4844 | 267 | 272.9509 | 459 | 241.2206 | 4850 | 312.3108 | 286 |
| 310.2687 | 428 | 267.2668 | 417 | 161.147 | 247.33 | 83 |
| 338.4841 | 232 | 343.3551 | 115 | 141.1706 | 18005 | 223.1365 | 472 |
| 285.2571 | 352 | 171.2266 | 510 | 299.2242 | 13945 | 207.7618 | 141 |
| 522.7936 | 214 | 387.2424 | 222 | 557.3115 | 2481 | 326.3308 | 444 |
| 331.3489 | 345 | 197.9046 | 401 | 223.1735 | 12004 | 300.1463 | 67 |
| 483.2608 | 322 | 666.2973 | 307 | 271.1787 | 46753 | 302.2287 | 87 |
| 312.4971 | 219 | 206.9985 | 69 | 448.3016 | 7720 | 282.3808 | 446 |
| 632.3418 | 174 | 284.3936 | 346 | 325.249 | 8244 | 294.3151 | 311 |
| 505.5239 | 183 | 198.9431 | 623 | 215.1142 | 42753 | 321.3525 | 298 |
| 261.2491 | 257 | 421.2879 | 277 | 353.3098 | 3532 | 197.588 | 69 |
| 393.4561 | 226 | 188.9505 | 405 | 415.2093 | 27414 | 415.2848 | 215 |
| 279.216 | 341 | 195.907 | 309 | 616.3778 | 6876 | 210.8195 | 90 |
| 633.3401 | 167 | 160.9259 | 355 | 468.2921 | 6706 | 224.5121 | 84 |
| 741.5244 | 174 | 109.5707 | 76 | 483.2699 | 3683 | 666.3071 | 884 |
| 281.1786 | 350 | 397.3877 | 310 | 759.4984 | 4632 | 232.3251 | 92 |
| 429.4104 | 178 | 307.1353 | 219 | 285.1981 | 36197 | 254.34 | 393 |
| 558.3024 | 149 | 305.1381 | 230 | 279.2208 | 11330 | 304.3123 | 61 |
| 616.3668 | 273 | 187.0079 | 295 | 283.1671 | 18185 | 218.0213 | 85 |
| 336.2652 | 1155 | 377.235 | 194 | 207.1323 | 10818 | 318.1434 | 81 |
| 102.1893 | 306 | 220.6196 | 66 | 338.4904 | 1589 | 250.2623 | 255 |
| 239.2714 | 475 | 363.2143 | 232 | 327.2284 | 11885 | 320.2245 | 83 |
| 759.4851 | 160 | 340.3472 | 255 | 429.4202 | 5041 | 217.2436 | 92 |
| 171.2363 | 230 | 381.3889 | 188 | 689.424 | 3915 | 244.1237 | 81 |
| 284.4569 | 177 | 123.9721 | 314 | 413.4942 | 3524 | 194.9489 | 492 |
| 161.1445 | 270 | 189.0053 | 344 | 519.3432 | 4776 | 227.9016 | 105 |
| 689.4097 | 131 | 223.9037 | 195 | 312.5024 | 3648 | 160.9281 | 337 |
| 186.2123 | 281 | 220.2519 | 579 | 371.2437 | 8524 | 209.3216 | 89 |
| 273.2895 | 244 | 390.2526 | 172 | 327.1109 | 19947 | 195.0259 | 329 |
| 179.1568 | 209 | 205.6616 | 55 | 359.1725 | 7987 | 337.4595 | 134 |
|     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 475.5014 | 151 | 260.0682 | 73 | 164.1334 | 8711 | 624.6671 | 63 |
| 309.3382 | 293 | 222.5853 | 68 | 251.1645 | 9369 | 196.9462 | 433 |
| 559.3007 | 134 | 250.26 | 298 | 473.5136 | 4367 | 231.8253 | 79 |
| 468.2835 | 502 | 200.9053 | 70 | 273.1761 | 19148 | 227.1251 | 95 |
| 463.3265 | 781 | 392.2542 | 267 | 369.2951 | 4670 | 421.2955 | 186 |
| 304.4314 | 1741 | 1288.1565 | 42 | 760.4969 | 3206 | 215.9992 | 102 |
| 369.2833 | 186 | 403.2722 | 144 | 239.2752 | 7818 | 220.5539 | 96 |
| 658.7547 | 132 | 245.2575 | 68 | 327.3969 | 5832 | 420.2969 | 123 |
| 327.2188 | 194 | 316.3174 | 86 | 343.1608 | 18820 | 199.9053 | 184 |
| 663.6987 | 203 | 361.2165 | 167 | 173.2567 | 9033 | 220.2541 | 909 |
| 150.1141 | 1073 | 279.0954 | 254 | 261.2503 | 2715 | 387.248 | 179 |
| 385.4476 | 471 | 309.1346 | 213 | 632.3525 | 2233 | 245.2638 | 79 |
| 742.5231 | 83 | 183.638 | 80 | 679.7484 | 4268 | 267.2699 | 273 |
| 760.4835 | 167 | 1158.1803 | 69 | 229.153 | 32335 | 340.3514 | 290 |
| 561.5956 | 389 | 170.9733 | 353 | 342.1678 | 18388 | 269.8024 | 82 |
| 474.5081 | 182 | 327.3225 | 190 | 257.1572 | 2715 | 228.673 | 85 |
| 158.1801 | 227 | 260.9917 | 567 | 393.4634 | 2207 | 204.6894 | 82 |
3. Vessel area and vessel number analysis for qCAM samples.

Figure S3 | Vessel area and vessel number analysis for qCAM samples. Con, control group treated with PBS; Dis, dissolvent group treated with dissolvent contained 0.5 % DMSO; Pos, positive control group treated with dovitinib (40 μg); BA-12 1-3, groups treated with BA-12 at doses of 20, 40, 80 μg, respectively. ANOVA with the post hoc test was used to calculate the significance of the differences, *, ** and *** represents \( p < 0.05 \), \( p < 0.01 \), and \( p < 0.001 \) compared with the dissolvent group, respectively. All experiments were performed 3 times, and the results are expressed as the mean ± S.D.
4. Analysis for wound scratch and tube formation assay.

Figure S4 | Analysis for wound scratch and tube formation assay by HUVEC. Con, control group treated with PBS; Dis, dissolvent group treated with dissolvent contained 0.5 % DMSO; Pos, positive control group treated with dovitinib (2.5 μM); BA-12 groups treated with BA-12 at doses of 2.5 μM. ANOVA with the post hoc test was used to calculate the significance of the differences, *, ** and *** represents $p < 0.05$, $p < 0.01$, and $p < 0.001$ compared with the dissolvent group, respectively. All experiments were performed 3 times, and the results are expressed as the mean ± S.D.
5. The total ion chromatograms (TIC) of intracellular fingerprint.

Figure S5 | The total ion chromatograms (TIC) of intracellular fingerprint (First: Control group; Second: BA-12 group).

6. The parameters of PCA and OPLS-DA model.

| Model         | Component | R2X  | R2Y  | Q2Y  | R2-intercept | Q2-intercept |
|---------------|-----------|------|------|------|--------------|--------------|
| PCA (M1)      | 2         | 0.465| —    | -0.204| —            | —            |
| PLS-DA (M2)   | 1+1+0     | 0.400| 0.993| 0.873| 0.043        | 0.5          |
Figure S6 | Hotelling’s T2 (A) and score plot (B) of OPLS-DA(M2).
7. The score plots of PCA analysis contained QC samples.

![Scores Plot]

Figure S7 | The score plots of PCA analysis contained QC samples.

8. UPLC-QTOF-MS based metabolomics analysis.

Waters Synapt G2SI HDMS q-TOF coupled with UPLC (Waters, MA, USA) is also used as the main analytical instrument for this part of the experiment.
Figure S8 | The total ion chromatograms (TIC) of intracellular fingerprint (First: Control group; Second: BA-12 group). (A) The total ion chromatograms (TIC) of intracellular fingerprint (First: Control group; Second: BA-12 group). (B) Intracellular chromatograms extracted from TIC for GSH (308.1000) in (First: Control group; Second: BA-12 group).

| Table S3 | The parameters of PCA and OPLS-DA model |
|---------|------------------------------------------|
| Model   | Component | R2X  | R2Y  | Q2Y  | R2-intercept | Q2-intercept |
| PCA (M1) | 2         | 0.611 | —    | 0.167 | —            | —             |
| PLS-DA (M2) | 1+1+0  | 0.954 | 0.999 | 0.992 | 0.001        | 0.5           |
9. Macroscopical observation of Caenorhabditis elegans 240 h after PBS or dissolvent or dovitinib or BA-12 treatment in the experiment.

![Images of micrographs showing control (Con), dissolvent (Dis), dovitinib (Dov), and BA-12 groups (BA-12-1 to BA-12-3).]

Figure S9 | Macroscopical observation of Caenorhabditis elegans 240 h after PBS or dissolvent or dovitinib or BA-12 treatment in the experiment as indicated. Con, control group treated with PBS; Dis, dissolvent group treated with dissolvent contained 0.5 % DMSO; Pos, positive control group treated with dovitinib (40 μg); BA-12 1-3, groups treated with BA-12 at doses of 20, 40, 80 μg, respectively.

10. The compliance of the grouping of gels/blots cropped from different parts of the same gel, or from different gels, fields.

![Images of blots for VEGFR2 and GAPDH at different molecular weights.]

Figure S10 | The compliance of the grouping of gels/blots cropped from different parts of the same gel, or from different gels, fields. The compliance of the grouping of gels/blots for VEGFR2 and GAPDH 36 h after dissolvent or dovitinib or BA-12 treatment.
11. The effect of BA-12 on REDOX balance.

**Figure S11 | Effect of BA-12 on REDOX balance.** (A-F) Shown are the t-AOC, γGCS, GSH-Px, MAO, MDA, and SOD levels in quail samples, respectively. t-AOC, total antioxidant capacity; γGCS, γ-glutamylcysteine synthetase; GSH-Px, glutathione peroxidase; MAO, monoamine oxidase; MDA, malondialdehyde; SOD, superoxide dismutase. (G-I) Shown are the t-AOC, SOD, ROS levels in cell samples, respectively. ANOVA with the post hoc test was used to calculate the significance of the differences, *, ** and *** represents $p < 0.05$, $p < 0.01$, and $p < 0.001$ compared with the dissolvent group, respectively. All experiments were performed 3 times, and the results are expressed as the mean ± S.D.

12. Prediction pathways regulated by BA-12.

| Table S4 | Prediction pathways regulated by BA-12 |
|---------|--------------------------------------|
| No.     | Term                               | Count | %     | P-Value   |
| 1       | Metabolic pathways                  | 42    | 21.4% | 9.00E-03  |
| 2       | Pathways in cancer                  | 33    | 16.8% | 3.70E-10  |
| 3       | PI3K-Akt signaling pathway          | 23    | 11.7% | 1.70E-05  |
| 4       | Proteoglycans in cancer             | 20    | 10.2% | 1.90E-07  |
| 5       | Ras signaling pathway               | 18    | 9.2%  | 2.10E-05  |
| Rank | Pathway                                | q-value | p-value   |
|------|----------------------------------------|---------|-----------|
| 1    | Hepatitis B                            | 8.7     | 2.40E-07  |
| 2    | Osteoclast differentiation             | 8.2     | 3.60E-07  |
| 3    | Estrogen signaling pathway             | 7.7     | 6.20E-08  |
| 4    | FoxO signaling pathway                 | 7.7     | 2.70E-06  |
| 5    | Rap1 signaling pathway                 | 7.7     | 4.00E-04  |
| 6    | Biosynthesis of antibiotics            | 7.7     | 4.40E-04  |
| 7    | Prolactin signaling pathway            | 7.1     | 7.50E-09  |
| 8    | Insulin resistance                     | 7.1     | 1.30E-06  |
| 9    | Hepatitis C                            | 7.1     | 1.30E-05  |
| 10   | Insulin signaling pathway              | 7.1     | 2.00E-05  |
| 11   | Tuberculosis                           | 7.1     | 2.60E-04  |
| 12   | Chemokine signaling pathway            | 7.1     | 4.20E-04  |
| 13   | Focal adhesion                         | 7.1     | 1.10E-03  |
| 14   | Non-small cell lung cancer             | 6.6     | 4.40E-09  |
| 15   | Pancreatic cancer                      | 6.6     | 2.60E-08  |
| 16   | PPAR signaling pathway                 | 6.6     | 3.80E-08  |
| 17   | Prostate cancer                        | 6.6     | 8.50E-07  |
| 18   | TNF signaling pathway                  | 6.6     | 6.90E-06  |
| 19   | Thyroid hormone signaling pathway      | 6.6     | 1.50E-05  |
| 20   | Influenza A                            | 6.6     | 7.80E-04  |
| 21   | cAMP signaling pathway                 | 6.6     | 2.40E-03  |
| 22   | MAPK signaling pathway                 | 6.6     | 1.60E-02  |
| 23   | HTLV-I infection                       | 6.6     | 1.60E-02  |
| 24   | Chronic myeloid leukemia               | 6.1     | 7.70E-07  |
| 25   | ErbB signaling pathway                 | 6.1     | 5.30E-06  |
| 26   | Progesterone-mediated oocyte maturation| 6.1     | 5.30E-06  |
| 27   | T cell receptor signaling pathway      | 6.1     | 2.00E-05  |
| 28   | Choline metabolism in cancer           | 6.1     | 2.20E-05  |
| 29   | Chagas disease (American trypanosomiasis)| 6.1     | 3.00E-05  |
| 30   | Neurotrophin signaling pathway         | 6.1     | 1.10E-04  |
| 31   | Viral carcinogenesis                    | 6.1     | 8.80E-03  |
| 32   | Colorectal cancer                      | 5.6     | 1.50E-06  |
| 33   | Glioma                                 | 5.6     | 2.30E-06  |
| 34   | Fc epsilon RI signaling pathway        | 5.6     | 3.60E-06  |
| 35   | Toll-like receptor signaling pathway   | 5.6     | 1.80E-04  |
| 36   | Toxoplasmosis                          | 5.6     | 2.50E-04  |
| 37   | Epstein-Barr virus infection           | 5.6     | 5.70E-04  |
| 38   | Natural killer cell mediated cytotoxicity| 5.6     | 5.70E-04  |
| 39   | Signaling pathways regulating pluripotency of stem cells | 5.6 | 1.60E-03 |
| 40   | Non-alcoholic fatty liver disease (NAFLD) | 5.6 | 2.90E-03 |
| 41   | Transcriptional misregulation in cancer| 5.6 | 5.90E-03 |
| 42   | Endometrial cancer                     | 5.1     | 2.80E-06  |
| 43   | Central carbon metabolism in cancer    | 5.1     | 1.60E-05  |
| 44   | Adipocytokine signaling pathway        | 5.1     | 3.40E-05  |
|   | Pathway                                                                 | Rank | P-value |   |
|---|------------------------------------------------------------------------|------|---------|---|
| 50| Melanoma                                                               | 10   | 3.80E-05|   |
| 51| HIF-1 signaling pathway                                                | 10   | 4.00E-04|   |
| 52| Sphingolipid signaling pathway                                         | 10   | 2.00E-03|   |
| 53| Measles                                                                | 10   | 4.00E-03|   |
| 54| Jak-STAT signaling pathway                                             | 10   | 7.00E-03|   |
| 55| Acute myeloid leukemia                                                 | 9    | 4.30E-05|   |
| 56| Renal cell carcinoma                                                   | 9    | 1.40E-04|   |
| 57| Epithelial cell signaling in Helicobacter pylori infection             | 9    | 1.60E-04|   |
| 58| Complement and coagulation cascades                                    | 9    | 2.00E-04|   |
| 59| Fc gamma R-mediated phagocytosis                                       | 9    | 7.60E-04|   |
| 60| Small cell lung cancer                                                 | 9    | 8.20E-04|   |
| 61| GnRH signaling pathway                                                 | 9    | 1.30E-03|   |
| 62| Carbon metabolism                                                      | 9    | 5.00E-03|   |
| 63| Bladder cancer                                                         | 8    | 4.00E-05|   |
| 64| VEGF signaling pathway                                                 | 8    | 5.30E-04|   |
| 65| B cell receptor signaling pathway                                       | 8    | 1.10E-03|   |
| 66| Adherens junction                                                      | 8    | 1.30E-03|   |
| 67| Chemical carcinogenesis                                                | 8    | 2.70E-03|   |
| 68| AMPK signaling pathway                                                 | 8    | 2.60E-02|   |
| 69| Platelet activation                                                    | 8    | 3.30E-02|   |
| 70| Apoptosis                                                              | 7    | 3.20E-03|   |
| 71| Metabolism of xenobiotics by cytochrome P450                           | 7    | 7.70E-03|   |
| 72| Pertussis                                                              | 7    | 8.20E-03|   |
| 73| Inflammatory mediator regulation of TRP channels                       | 7    | 2.80E-02|   |
| 74| Serotonergic synapse                                                   | 7    | 4.70E-02|   |
| 75| Cholinergic synapse                                                    | 7    | 4.70E-02|   |
| 76| Renin-angiotensin system                                               | 6    | 1.60E-04|   |
| 77| Type II diabetes mellitus                                              | 6    | 5.10E-03|   |
| 78| Arginine and proline metabolism                                        | 6    | 6.10E-03|   |
| 79| Regulation of lipolysis in adipocytes                                  | 6    | 9.90E-03|   |
| 80| NOD-like receptor signaling pathway                                    | 6    | 9.90E-03|   |
| 81| mTOR signaling pathway                                                 | 6    | 1.10E-02|   |
| 82| Arachidonic acid metabolism                                            | 6    | 1.40E-02|   |
| 83| Glycolysis / Gluconeogenesis                                            | 6    | 2.00E-02|   |
| 84| Drug metabolism - cytochrome P450                                       | 6    | 2.20E-02|   |
| 85| Thyroid cancer                                                         | 5    | 4.40E-03|   |
| 86| Aldosterone-regulated sodium reabsorption                              | 5    | 1.30E-02|   |
| 87| Steroid hormone biosynthesis                                           | 5    | 4.70E-02|   |
| 88| Dorso-ventral axis formation                                           | 4    | 2.50E-02|   |
| 89| Fructose and mannose metabolism                                        | 4    | 3.90E-02|   |
| 90| Tyrosine metabolism                                                    | 4    | 4.80E-02|   |