PSB 2018 paper: Chemical reaction vector embeddings: towards predicting drug metabolism in the human gut microbiome

Authors: Emily K Mallory, Ambika Acharya, Stefano E Rensi, Peter J Turnbaugh, Roselie A Bright, Russ B Altman

Supplemental Tables

Table S1. Compound clusters enrichment for ChEBI Tuples.

| Cluster ID | ChEBI Tuple                  | P-value        |
|------------|------------------------------|----------------|
| 0          | 50047,35352,33285            | 1.574980e-20   |
| 0          | 24532,33832,72695            | 4.379438e-09   |
| 0          | 38166,24532,33285            | 5.124347e-08   |
| 0          | 38166,24532,33832            | 5.124347e-08   |
| 0          | 58945,25696,25699            | 5.843030e-16   |
| 0          | 38101,24532,33285            | 4.192895e-11   |
| 0          | 38101,35352,33285            | 4.192895e-11   |
| 0          | 38101,24532,33832            | 4.192895e-11   |
| 0          | 26873,24913,18059            | 3.157415e-07   |
| 0          | 37622,35352,33285            | 4.910856e-51   |
| 0          | 23449,16670,50047            | 1.685818e-13   |
| 0          | 25676,16670,50047            | 7.499575e-08   |
| 0          | 38106,24532,33832            | 6.399037e-14   |
| 0          | 38106,24532,33285            | 6.399037e-14   |
| 0          | 33261,36962,33285            | 7.664353e-08   |
| 0          | 22315,35352,33285            | 1.405468e-07   |
| 0          | 57248,46895,18059            | 1.079136e-07   |
| 0          | 57248,86478,33285            | 1.079136e-07   |
|   | 46895,16670,50047 | 7.917720e-07 |
|---|------------------|--------------|
|   | 24531,24532,33285 | 2.173519e-24 |
| 0 | 24531,24532,33832 | 2.173519e-24 |
|   | 23643,16670,50047 | 2.737413e-20 |
| 1 | 35681,30879,33822 | 5.101805e-13 |
|   | 26873,24913,18059 | 1.436774e-10 |
| 1 | 51958,33832,72695 | 6.226872e-18 |
| 1 | 25872,51958,33832 | 3.256168e-09 |
|   | 36615,26873,24913 | 3.365423e-09 |
| 1 | 35350,35341,18059 | 7.641364e-12 |
| 1 | 35341,51958,33832 | 8.704472e-14 |
| 1 | 36834,35350,33822 | 3.365423e-09 |
| 2 | 35681,30879,33822 | 4.312257e-38 |
| 2 | 36586,36587,72695 | 6.288919e-07 |
| 2 | 17087,36586,36587 | 1.916202e-18 |
| 2 | 33659,33832,72695 | 3.420148e-11 |
| 2 | 24532,33832,72695 | 2.532204e-09 |
| 2 | 58945,25696,25699 | 8.202568e-10 |
| 2 | 38101,24532,33285 | 1.244699e-07 |
| 2 | 38101,35352,33285 | 1.244699e-07 |
| 2 | 38101,24532,33832 | 1.244699e-07 |
| 2 | 26873,24913,18059 | 4.072683e-35 |
| 2 | 23849,26873,24913 | 4.166277e-13 |
| 2 | 51958,33832,72695 | 1.626478e-102 |
| 2 | 25872,51958,33832 | 1.052389e-22 |
| 2 | 36615,26873,24913 | 8.449820e-22 |
| 2 | 35350,35341,18059 | 1.374603e-56 |
| 2 | 131565,35341,18059 | 4.783441e-07 |
|   | 61313,35341,18059 | 5.083554e-08 |
|---|------------------|---------------|
| 2 | 35341,51958,33832 | 5.693601e-09 |
| 2 | 35789,35341,18059 | 8.076114e-44 |
| 2 | 36853,35350,33822 | 1.149670e-12 |
| 2 | 35788,35341,18059 | 2.018245e-11 |
| 2 | 36834,35350,33822 | 2.263046e-35 |
| 2 | 26124,35350,33822 | 3.093937e-11 |
| 2 | 50403,35341,18059 | 3.711454e-07 |
| 2 | 36838,35350,33822 | 2.610949e-09 |
| 2 | 47909,51689,78840 | 5.924852e-11 |
| 2 | 50402,35341,18059 | 6.196415e-16 |
| 2 | 50401,35341,18059 | 1.267852e-08 |
| 2 | 26658,26873,24913 | 9.137742e-08 |
| 2 | 36078,35341,18059 | 3.441900e-10 |
| 2 | 36863,35350,33822 | 5.656564e-12 |
| 2 | 36840,35350,33822 | 3.711454e-07 |
| 3 | 35681,30879,33822 | 2.257035e-34 |
| 3 | 33659,33832,72695 | 2.095370e-07 |
| 3 | 26873,24913,18059 | 1.116629e-13 |
| 3 | 51958,33832,72695 | 8.568307e-52 |
| 3 | 35350,35341,18059 | 7.111654e-51 |
| 3 | 35341,51958,33832 | 1.254327e-57 |
| 3 | 35789,35341,18059 | 1.259454e-11 |
| 3 | 36834,35350,33822 | 1.660856e-44 |
| 3 | 36845,35350,33822 | 7.041971e-07 |
| 3 | 36844,35350,33822 | 2.366786e-15 |
| 3 | 50401,35341,18059 | 5.193956e-14 |
| 4 | 29067,25696,25699 | 1.198195e-07 |
4  26004,33659,33832  3.277561e-07
4  58945,25696,25699  8.191365e-12
4  27136,26191,33822  2.371420e-07
4  22707,33853,33822  1.097523e-09
4  35281,27369,51151  2.598978e-07
4  26195,33853,33822  3.194037e-07
4  24043,47916,72544  6.684044e-26
4  62732,33659,33832  5.929831e-10
4  35218,47916,72544  5.348636e-13
4  27116,24698,33822  9.133565e-15
4  36087,51702,78840  4.366908e-07
4  38684,24698,33822  2.386137e-10
5  36586,36587,72695  6.335407e-10
5  58945,25696,25699  5.073633e-57
5  33833,33659,33832  5.041600e-11
5  33833,24532,33832  5.041600e-11
5  33833,24532,33285  5.041600e-11
5  25703,25710,33285  1.049242e-07
5  21731,35352,33285  7.168391e-12
6  29067,25696,25699  2.055741e-19
6  2580,28868,18059  5.348717e-27
6  33659,33832,72695  4.706240e-09
6  24532,33832,72695  1.698280e-07
6  58945,25696,25699  3.328165e-08
6  57560,28868,18059  1.882527e-18
6  59835,28868,18059  3.084316e-24
6  26347,23899,61697  1.782505e-07
6  64012,28868,18059  2.977651e-14
|   |      |      |      |      |
|---|------|------|------|------|
| 6 | 59326,28868,18059 | 1.292704e-12 |
| 6 | 27208,35366,18059 | 2.414056e-08 |
| 6 | 15904,35366,18059 | 8.391956e-07 |
| 6 | 47778,35741,18059 | 3.503927e-26 |
| 6 | 18035,76578,18059 | 7.345235e-11 |
| 7 | 50047,35352,33285 | 2.002491e-14 |
| 7 | 33659,33832,72695 | 2.335887e-12 |
| 7 | 24532,33832,72695 | 6.732397e-10 |
| 7 | 38166,24532,33285 | 2.484634e-08 |
| 7 | 38166,24532,33832 | 2.484634e-08 |
| 7 | 58945,25696,25699 | 5.401928e-12 |
| 7 | 33575,36586,36587 | 2.809111e-20 |
| 7 | 35238,27369,51151 | 7.363599e-76 |
| 7 | 27369,51151,72695 | 7.003713e-71 |
| 7 | 33709,33575,64709 | 1.083120e-35 |
| 7 | 83820,33709,50047 | 1.412270e-32 |
| 7 | 33704,33709,50047 | 2.221480e-29 |
| 7 | 83821,35352,33285 | 1.862293e-11 |
| 7 | 37022,35352,33285 | 5.078595e-20 |
| 7 | 33576,33575,64709 | 1.447607e-08 |
| 7 | 26834,33709,50047 | 6.191083e-09 |
| 8 | 33659,33832,72695 | 3.622950e-07 |
| 8 | 24532,33832,72695 | 2.476028e-07 |
| 8 | 58945,25696,25699 | 3.826977e-19 |
| 8 | 59635,25696,25699 | 1.516039e-08 |
| 9 | 29067,25696,25699 | 1.060391e-11 |
| 9 | 58945,25696,25699 | 6.264018e-09 |
| 9 | 38101,24532,33285 | 6.350123e-07 |
|   | X1   | X2   | X3   | Y   |
|---|------|------|------|-----|
| 9 | 38101,35352,33285 | 6.35012e-07 |
| 9 | 38101,24532,33832 | 6.35012e-07 |
| 10 | 33659,33832,72695 | 1.10975e-10 |
| 10 | 24532,33832,72695 | 1.25344e-09 |
| 10 | 58945,25696,25699 | 2.03657e-08 |
| 10 | 35186,24632,33245 | 1.98511e-175 |
| 10 | 35193,35186,24913 | 3.44579e-28 |
| 10 | 35186,24913,18059 | 1.98511e-175 |
| 10 | 33598,33832,72695 | 6.90599e-13 |
| 10 | 26873,24913,18059 | 1.70943e-12 |
| 10 | 35190,35186,24913 | 4.71444e-34 |
| 10 | 33642,33641,78840 | 1.13062e-12 |
| 10 | 33641,24632,33245 | 1.40980e-16 |
| 10 | 33642,33654,33653 | 1.13062e-12 |
| 10 | 33654,33598,33832 | 5.32193e-16 |
| 10 | 35294,33598,33832 | 9.42261e-15 |
| 10 | 35189,35186,24913 | 1.32012e-75 |
| 10 | 36783,53183,24913 | 6.00055e-09 |
| 10 | 53183,24913,18059 | 1.16897e-10 |
| 10 | 48121,33641,78840 | 3.70101e-09 |
| 10 | 35191,35186,24913 | 2.03551e-09 |
| 10 | 33663,24632,33245 | 2.58037e-10 |
| 10 | 33663,33598,33832 | 2.58037e-10 |
| 10 | 35170,35186,24913 | 2.88078e-23 |
| 11 | 35186,24632,33245 | 1.04310e-29 |
| 11 | 35186,24913,18059 | 1.04310e-29 |
| 11 | 35294,33598,33832 | 3.01222e-07 |
| 11 | 35189,35186,24913 | 3.16946e-19 |
|   | X1, X2, X3   | Value         |
|---|-------------|---------------|
| 12| 33853,33659,33832 | 4.851063e-13 |
| 12| 33659,33832,72695 | 2.895727e-08 |
| 12| 33836,33659,33832 | 1.459193e-09 |
| 12| 33836,33598,33832 | 1.459193e-09 |
| 12| 33598,33832,72695 | 1.075680e-09 |
| 13| 33853,33659,33832 | 1.621861e-73 |
| 13| 33659,33832,72695 | 3.545541e-46 |
| 13| 58945,25696,25699 | 5.618294e-12 |
| 13| 33836,33659,33832 | 8.589879e-36 |
| 13| 33836,33598,33832 | 8.589879e-36 |
| 13| 33598,33832,72695 | 3.043942e-36 |
| 13| 35618,33659,33832 | 1.511223e-07 |
| 13| 33854,33659,33832 | 1.994915e-07 |
| 13| 33854,30879,33822 | 1.994915e-07 |
| 13| 24681,33853,33822 | 8.282263e-07 |
| 13| 64459,33659,33832 | 1.994915e-07 |
| 13| 33570,33853,33822 | 5.028487e-25 |
| 13| 36683,36684,33285 | 2.008618e-11 |
| 13| 35294,33598,33832 | 3.757449e-08 |
| 13| 38856,33853,33822 | 5.754220e-12 |
| 13| 38856,36684,33285 | 5.754220e-12 |
| 14| 36963,36962,33285 | 1.302504e-33 |
| 14| 33659,33832,72695 | 2.859987e-08 |
| 14| 58945,25696,25699 | 5.345989e-10 |
| 15| 33659,33832,72695 | 1.070101e-08 |
| 16| 29067,25696,25699 | 4.829739e-08 |
| 16| 50047,35352,33285 | 3.604188e-15 |
| 16| 24532,33832,72695 | 4.860826e-29 |
|    | 38166,24532,33285 | 4.115036e-28 |
|----|-----------------|---------------|
| 16 | 38166,24532,33832 | 4.115036e-28  |
| 16 | 38101,24532,33285 | 6.133930e-29  |
| 16 | 38101,35352,33285 | 6.133930e-29  |
| 16 | 38101,24532,33832 | 6.133930e-29  |
| 16 | 22315,35352,33285 | 8.10188e-96   |
| 16 | 36963,36962,33285 | 1.355938e-09  |
| 17 | 29067,25696,25699 | 7.438098e-18  |
| 17 | 17087,36586,36587 | 4.046818e-08  |
| 17 | 33659,33832,72695 | 9.624095e-17  |
| 17 | 38104,24532,33285 | 2.412600e-08  |
| 17 | 38104,24532,33832 | 2.412600e-08  |
| 17 | 24532,33832,72695 | 9.790684e-19  |
| 17 | 38166,24532,33285 | 1.226471e-10  |
| 17 | 38166,24532,33832 | 1.226471e-10  |
| 17 | 58945,25696,25699 | 3.546739e-169 |
| 17 | 38101,24532,33285 | 8.557902e-11  |
| 17 | 38101,35352,33285 | 8.557902e-11  |
| 17 | 38101,24532,33832 | 8.557902e-11  |
| 17 | 26873,24913,18059 | 8.508090e-08  |
| 17 | 51958,33832,72695 | 3.816378e-08  |
| 17 | 33261,36962,33285 | 3.297693e-20  |
| 17 | 51277,36586,36587 | 4.867099e-58   |
| 18 | 36586,36587,72695 | 2.239276e-08  |
| 18 | 33853,33659,33832 | 1.276167e-22  |
| 18 | 17087,36586,36587 | 3.144608e-18  |
| 18 | 33659,33832,72695 | 8.290524e-09  |
|   |   |   |   |
|---|---|---|---|
| 18 | 24532,33832,72695 | 5.331330e-10 |   |
| 18 | 38166,24532,33285 | 2.906497e-07 |   |
| 18 | 38166,24532,33832 | 2.906497e-07 |   |
| 18 | 58945,25696,25699 | 2.437432e-10 |   |
| 18 | 33836,33659,33832 | 1.523577e-14 |   |
| 18 | 33836,33598,33832 | 1.523577e-14 |   |
| 18 | 33598,33832,72695 | 2.291990e-13 |   |
| 18 | 38101,24532,33285 | 7.489620e-07 |   |
| 18 | 38101,35352,33285 | 7.489620e-07 |   |
| 18 | 38101,24532,33832 | 7.489620e-07 |   |
| 18 | 23086,51689,78840 | 8.842854e-12 |   |
| 18 | 35294,33598,33832 | 2.643978e-08 |   |
| 18 | 26195,33853,33822 | 5.245567e-11 |   |
| 18 | 37485,33853,33822 | 8.987046e-10 |   |
| 19 | 37622,35352,33285 | 3.823728e-32 |   |
| 19 | 17761,26739,18059 | 1.153172e-29 |   |
| 19 | 26739,35352,33285 | 5.076085e-20 |   |
| 19 | 59062,46895,18059 | 2.160729e-07 |   |
| 19 | 83876,25697,25699 | 9.814494e-11 |   |
| 19 | 82829,26739,18059 | 5.412499e-07 |   |
| 20 | 33659,33832,72695 | 6.782468e-29 |   |
| 20 | 24532,33832,72695 | 1.111782e-42 |   |
| 20 | 38166,24532,33285 | 1.428895e-25 |   |
| 20 | 38166,24532,33832 | 1.428895e-25 |   |
| 20 | 58945,25696,25699 | 1.067500e-12 |   |
| 20 | 33833,33659,33832 | 3.021020e-40 |   |
| 20 | 33833,24532,33832 | 3.021020e-40 |   |
| 20 | 38101,24532,33285 | 3.771093e-68 |   |
|   | 38101,35352,33285 | 3.771093e-68 |
|---|------------------|--------------|
|   | 38101,24532,33832 | 3.771093e-68 |
|   | 33833,24532,33285 | 3.021020e-40 |
|   | 51959,51958,33832 | 2.052891e-09 |
|   | 26513,33659,33832 | 3.650960e-30 |
|   | 35571,35552,33245 | 1.639016e-25 |
|   | 35571,35573,33245 | 1.639016e-25 |
| 21 | 58945,25696,25699 | 4.821968e-21 |
| 23 | 24532,33832,72695 | 8.206730e-08 |
| 23 | 38166,24532,33285 | 1.820990e-10 |
| 23 | 38166,24532,33832 | 1.820990e-10 |
| 23 | 58945,25696,25699 | 4.601937e-15 |
| 23 | 33836,33659,33832 | 1.529422e-20 |
| 23 | 33836,33598,33832 | 1.529422e-20 |
| 23 | 33598,33832,72695 | 6.499463e-19 |
| 23 | 17478,36586,36587 | 3.017528e-07 |
| 23 | 38101,24532,33285 | 5.517554e-08 |
| 23 | 38101,35352,33285 | 5.517554e-08 |
| 23 | 38101,24532,33832 | 5.517554e-08 |
| 23 | 36683,36684,33285 | 1.387261e-26 |
| 23 | 24472,36684,33285 | 2.266980e-35 |
| 23 | 33663,24632,33245 | 1.372360e-15 |
| 23 | 33663,33598,33832 | 1.372360e-15 |
| 23 | 33658,33659,33832 | 1.266279e-18 |
| 23 | 23142,134179,72695 | 2.979609e-09 |
| 23 | 23424,35352,33285 | 8.689206e-11 |
| 23 | 36016,134179,72695 | 2.018417e-08 |
| 24 | 36586,36587,72695 | 3.883349e-07 |
|   |       |       |                   |         |
|---|-------|-------|------------------|---------|
| 24| 33659,33832,72695 | 38101,24532,33285 | 38101,35352,33285 | 38101,24532,33832 |
| 24| 24532,33832,72695 | 38101,24532,33285 | 38101,35352,33285 | 38101,24532,33832 |
| 25| 27369,51151,72695 | 27369,51151,72695 | 27369,51151,72695 | 27369,51151,72695 |
| 25| 24532,33832,72695 | 38101,24532,33285 | 38101,35352,33285 | 38101,24532,33832 |
| 25| 25703,25710,33285 | 25703,25710,33285 | 25703,25710,33285 | 25703,25710,33285 |
| 25| 24402,26739,18059 | 24402,26739,18059 | 24402,26739,18059 | 24402,26739,18059 |
| 26| 24397,16247,18059 | 24397,16247,18059 | 24397,16247,18059 | 24397,16247,18059 |
| 26| 36586,36587,72695 | 36586,36587,72695 | 36586,36587,72695 | 36586,36587,72695 |
| 26| 58945,25696,25699 | 58945,25696,25699 | 58945,25696,25699 | 58945,25696,25699 |
| 26  | 25703,25710,33285 | 1.676628e-20 |
| 27  | 15734,30879,33822 | 6.735557e-60 |
| 27  | 59835,28868,18059 | 1.268297e-10 |
| 27  | 2571,30879,33822 | 3.075575e-18 |
| 27  | 26244,30879,33822 | 4.756598e-20 |
| 27  | 26199,26244,24913 | 3.212285e-14 |
| 27  | 26244,24913,18059 | 4.756598e-20 |
| 27  | 17135,24026,18059 | 8.525820e-32 |
| 27  | 24026,30879,33822 | 2.441272e-40 |
| 28  | 36586,36587,72695 | 3.148644e-13 |
| 28  | 33659,33832,72695 | 2.240067e-07 |
| 28  | 38104,24532,33285 | 1.001265e-10 |
| 28  | 38104,24532,33832 | 1.001265e-10 |
| 28  | 24532,33832,72695 | 1.213889e-09 |
| 28  | 38166,24532,33285 | 4.445475e-17 |
| 28  | 38166,24532,33832 | 4.445475e-17 |
| 28  | 58945,25696,25699 | 6.036914e-46 |
| 28  | 33833,33659,33832 | 2.622259e-33 |
| 28  | 33833,24532,33832 | 2.622259e-33 |
| 28  | 38101,24532,33285 | 1.196226e-17 |
| 28  | 38101,35352,33285 | 1.196226e-17 |
| 28  | 38101,24532,33832 | 1.196226e-17 |
| 28  | 33833,24532,33285 | 2.622259e-33 |
| 28  | 25703,25710,33285 | 2.546411e-10 |
| 28  | 25693,24532,33285 | 5.828750e-17 |
| 28  | 25693,24532,33832 | 5.828750e-17 |
| 28  | 21731,35352,33285 | 8.277359e-65 |
| 29  | 64678,25697,25699 | 2.017311e-14 |
|   | A   | B               | C               |
|---|-----|-----------------|-----------------|
| 29| 64290,25697,25699 | 1.562626e-08    |                 |
| 30| 36963,36962,33285 | 5.316451e-34    |                 |
| 30| 29067,25696,25699 | 5.116595e-12    |                 |
| 30| 36586,36587,72695 | 5.816456e-11    |                 |
| 30| 33853,33659,33832 | 1.795584e-12    |                 |
| 30| 17087,36586,36587 | 5.922645e-28    |                 |
| 30| 33659,33832,72695 | 4.769060e-38    |                 |
| 30| 26004,33659,33832 | 2.963013e-113   |                 |
| 30| 38757,50753,72544 | 1.180762e-26    |                 |
| 30| 38104,24532,33285 | 5.302857e-97    |                 |
| 30| 38104,24532,33832 | 5.302857e-97    |                 |
| 30| 24532,33832,72695 | 2.808782e-58    |                 |
| 30| 38166,24532,33285 | 1.916262e-92    |                 |
| 30| 38166,24532,33832 | 1.916262e-92    |                 |
| 30| 55465,38755,33822 | 1.168168e-20    |                 |
| 30| 58945,25696,25699 | 4.724815e-15    |                 |
| 30| 38672,47916,72544 | 1.766644e-35    |                 |
| 30| 35618,33659,33832 | 6.058199e-12    |                 |
| 30| 38101,24532,33285 | 4.151507e-10    |                 |
| 30| 38101,35352,33285 | 4.151507e-10    |                 |
| 30| 38101,24532,33832 | 4.151507e-10    |                 |
| 30| 26873,24913,18059 | 6.840432e-07    |                 |
| 30| 16366,47916,72544 | 5.560430e-07    |                 |
| 30| 16366,25697,25699 | 5.560430e-07    |                 |
| 30| 60038,25696,25699 | 1.126015e-20    |                 |
| 30| 26195,33853,33822 | 4.076859e-13    |                 |
| 30| 58588,25696,25699 | 3.019604e-09    |                 |
| 30| 38686,24698,33822 | 2.270615e-12    |                 |
|   | 24043,47916,72544 | 5.665251e-30 |
|---|-----------------|----------------|
| 30 | 72572,50753,72544 | 6.690806e-21 |
| 30 | 72739,33853,33822 | 3.732296e-11 |
| 30 | 38739,24697,33822 | 3.019604e-09 |
| 30 | 27116,24698,33822 | 4.412023e-09 |
| 30 | 28802,24698,33822 | 2.045357e-08 |
| 31 | 26873,24913,18059 | 1.340217e-33 |
| 31 | 25409,26873,24913 | 2.336588e-10 |
| 31 | 26935,26873,24913 | 1.287744e-24 |
| 32 | 26873,24913,18059 | 1.696895e-16 |
| 32 | 25409,26873,24913 | 8.907116e-09 |
| 32 | 26658,26873,24913 | 7.383128e-07 |
| 34 | 26873,24913,18059 | 6.812548e-34 |
| 34 | 25409,26873,24913 | 4.800100e-10 |
| 34 | 26935,26873,24913 | 1.076695e-18 |
| 35 | 50047,35352,33285 | 3.387492e-13 |
| 35 | 36586,36587,72695 | 4.189028e-07 |
| 35 | 33659,33832,72695 | 2.221490e-42 |
| 35 | 24532,33832,72695 | 1.816506e-75 |
| 35 | 38166,24532,33285 | 7.261056e-33 |
| 35 | 38166,24532,33832 | 7.261056e-33 |
| 35 | 58945,25696,25699 | 1.183808e-09 |
| 35 | 33833,33659,33832 | 5.305900e-69 |
| 35 | 33833,24532,33832 | 5.305900e-69 |
| 35 | 38101,24532,33285 | 6.659145e-108 |
| 35 | 38101,35352,33285 | 6.659145e-108 |
| 35 | 38101,24532,33832 | 6.659145e-108 |
| 35 | 33833,24532,33285 | 5.305900e-69 |
|   |   |   |   |   |
|---|---|---|---|---|
| 35 | 25693,24532,33285 | 3.803250e-42 |
| 35 | 25693,24532,33832 | 3.803250e-42 |
| 35 | 33860,33659,33832 | 1.354381e-13 |
| 35 | 38338,33860,50047 | 1.431768e-18 |
| 35 | 23666,88061,50047 | 1.942225e-12 |
| 35 | 67142,33832,72695 | 2.604228e-16 |
| 36 | 33659,33832,72695 | 3.666467e-08 |
| 36 | 33836,33659,33832 | 3.272438e-16 |
| 36 | 33836,33598,33832 | 3.272438e-16 |
| 36 | 33598,33832,72695 | 4.580677e-14 |
| 36 | 22562,33860,50047 | 1.486494e-07 |
| 36 | 25562,33853,33822 | 1.242657e-07 |
| 37 | 58945,25696,25699 | 7.769977e-10 |
| 37 | 23451,26191,33822 | 1.851109e-15 |
| 38 | 29067,25696,25699 | 1.234790e-10 |
| 38 | 33659,33832,72695 | 5.361864e-15 |
| 38 | 24532,33832,72695 | 2.194009e-09 |
| 38 | 58945,25696,25699 | 1.720355e-08 |
| 38 | 35238,27369,51151 | 3.729289e-16 |
| 38 | 27369,51151,72695 | 5.136585e-29 |
| 38 | 37622,35352,33285 | 3.358436e-14 |
| 38 | 25676,16670,50047 | 2.922021e-12 |
| 38 | 37022,35352,33285 | 7.949283e-10 |
| 38 | 60466,27369,51151 | 5.253413e-24 |
| 38 | 60334,25696,25699 | 4.078102e-16 |
| 38 | 51569,33575,64709 | 3.296073e-07 |
| 39 | 33308,36586,36587 | 1.452043e-11 |
| 39 | 36586,36587,72695 | 2.601425e-09 |
|   |   |   |   |
|---|---|---|---|
| 39 | 38104,24532,33285 | 1.407992e-10 |   |
| 39 | 38104,24532,33832 | 1.407992e-10 |   |
| 39 | 24250,33575,64709 | 1.789743e-09 |   |
| 39 | 26873,24913,18059 | 3.728607e-18 |   |
| 39 | 23849,26873,24913 | 8.221019e-08 |   |
| 39 | 51958,33832,72695 | 3.207033e-09 |   |
| 39 | 35341,51958,33832 | 5.950502e-10 |   |
| 39 | 26658,26873,24913 | 3.58361e-10  |   |
| 39 | 61655,35341,18059 | 1.376364e-09 |   |
| 40 | 36963,36962,33285 | 3.437424e-07  |   |
| 40 | 33308,36586,36587 | 1.644084e-12  |   |
| 40 | 36586,36587,72695 | 1.789090e-08  |   |
| 40 | 33659,33832,72695 | 2.706304e-07  |   |
| 40 | 38104,24532,33285 | 2.086486e-12  |   |
| 40 | 38104,24532,33832 | 2.086486e-12  |   |
| 40 | 58945,25696,25699 | 2.624660e-09  |   |
| 40 | 131927,36586,36587 | 3.663556e-07  |   |
| 40 | 38101,24532,33285 | 4.314570e-07  |   |
| 40 | 38101,35352,33832 | 4.314570e-07  |   |
| 40 | 38101,24532,33832 | 4.314570e-07  |   |
| 40 | 33575,36586,36587 | 6.625023e-08  |   |
| 40 | 24250,33575,64709 | 1.960634e-15  |   |
| 40 | 26873,24913,18059 | 4.917754e-31  |   |
| 40 | 35692,33575,64709 | 8.079061e-07  |   |
| 40 | 23849,26873,24913 | 9.416960e-21  |   |
| 40 | 51958,33832,72695 | 1.787650e-14  |   |
| 40 | 36615,26873,24913 | 2.777547e-14  |   |
| 40 | 35341,51958,33832 | 5.097197e-12  |   |
|   |   |   |   |
|---|---|---|---|
| 40 | 36845,35350,33822 | 3.250833e-11 |   |
| 40 | 26893,51958,33832 | 2.688442e-16 |   |
| 40 | 61655,35341,18059 | 8.581649e-21 |   |
| 40 | 61777,26873,24913 | 9.008188e-19 |   |
Table S2. Reaction clusters enrichment for enzyme name unigrams, for example "reductase".

Per cluster, 1.6 enzyme unigrams were enriched on average. At the unigram level, several clusters captured a majority of the reactions for a specific unigram. For example, Cluster 6 contained all seventeen reactions in the sulfotransferase group. In addition, Cluster 12 contained all reactions in the deiodinase group and 76 out of 79 reactions in the desaturase group.

Cluster 7 is enriched for hydroxylase, monooxygenase, oxidase, methylhydroxylase, which are all oxygen related, suggesting the clustering algorithm detected similar transformations for different (but related) enzymes.

| Cluster ID | Enzyme Name Unigram   | P-value   | EC Number | EC Name |
|------------|------------------------|-----------|-----------|---------|
| 0          | decarboxylase          | 1.45E-20  |           |         |
| 1          | methyltransferase      | 5.64E-55  |           |         |
| 2          | monooxygenase          | 1.96E-15  |           |         |
| 2          | hydroxylase            | 4.02E-17  | 1.14      | Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. The oxygen incorporated need not be derived from O(2). |
| 3          | dehydrogenase          | 4.05E-15  |           |         |
| 4          | dioxygenase            | 1.47E-25  |           |         |
| 5          | acyltransferase        | 4.15E-13  |           |         |
| 5          | malonyltransferase     | 5.57E-12  |           |         |
| 6          | sulfotransferase       | 1.56E-28  |           |         |
| 6          | kinase                 | 2.44E-38  |           |         |
| 7          | monooxygenase          | 7.59E-11  | 1.13      | Oxidoreductases. Acting on single donors with incorporation of molecular oxygen (oxygenases). The oxygen incorporated need not be derived from O(2). |
| No. | Enzyme Name            | EC Number | VGA No. | Description                                                                 |
|-----|------------------------|-----------|---------|-----------------------------------------------------------------------------|
| 7   | monooxygenase          | 7.59E-11  | 1.14    | Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. The oxygen incorporated need not be derived from O(2). |
| 7   | hydroxylase            | 8.66E-10  | 1.14    | Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. The oxygen incorporated need not be derived from O(2). |
| 7   | oxidase                | 5.84E-09  | 1       | Oxidoreductases.                                                               |
| 7   | methylhydroxylase      | 1.94E-07  | 1.17.99 | Oxidoreductases. Acting on CH or CH(2) groups with other, unknown, acceptors |
| 8   | synthetase             | 1.04E-08  |         |                                                                             |
| 8   | ligase                 | 3.36E-07  |         |                                                                             |
| 8   | hydroxycinnamoyltransferase | 3.63E-11 |         |                                                                             |
| 9   | hydroxylase            | 2.06E-07  | 1.14    | Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. The oxygen incorporated need not be derived from O(2). |
| 9   | lipoxygenase           | 4.30E-11  | 1.13.11 | Oxidoreductases. Acting on single donors with incorporation of molecular oxygen (oxygenases). The oxygen incorporated need not be derived from O(2). With incorporation of two atoms of oxygen. |
| 10  | tyrosinase             | 2.01E-07  |         |                                                                             |
| 10  | dioxygenase            | 2.87E-15  |         |                                                                             |
| 11  | phosphorylase          | 1.79E-20  |         |                                                                             |
| 12  | methyltransferase      | 6.17E-14  | 2.1.1   | Transferases. Transferring one-carbon groups. Methyltransferases.              |
| 12  | methyltransferase      | 6.17E-14  | 2.5.1   | Transferases. Transferring alkyl or aryl groups, other than methyl groups      |
| 12  | deiodinase             | 1.42E-08  |         |                                                                             |
| 12  | desaturase             | 3.31E-28  |         |                                                                             |
|   | Enzyme Name                  |   | Enzyme Name                  |   |
|---|------------------------------|---|------------------------------|---|
| 13 | glucosyltransferase          | 6.02E-08 | 2.4.1 Hexosyltransferases  |
| 13 | glucosyltransferase          | 6.02E-08 | 5.4.99 Isomerases. Intramolecular transferases (mutases) transferring other groups  |
| 13 | glucuronosyltransferase      | 1.50E-06 |  |
| 14 | deacetylase                  | 1.14E-07 | 3.1.1 Hydrolases. Acting on ester bonds. Carboxylic ester hydrolases  |
| 14 | deacetylase                  | 1.14E-07 | 3.5.1 Hydrolases. Acting on carbon-nitrogen bonds, other than peptide bonds. In linear amides.  |
| 15 | cycloisomerase               | 1.79E-15 |  |
| 15 | hydrolase                    | 7.74E-13 |  |
| 16 | synthetase                   | 1.73E-07 |  |
| 17 | hydroxylase                  | 1.78E-15 |  |
| 19 | ligase                       | 9.98E-07 |  |
| 19 | cytidylyltransferase         | 5.69E-10 | 2.7.7 Transferases. Transferring phosphorus-containing groups. Nucleotidylyltransferases.  |
| 19 | adenylase                    | 1.02E-08 | 2.7.7 Transferases. Transferring phosphorus-containing groups. Nucleotidylyltransferases.  |
| 20 | glucosyltransferase          | 2.66E-67 |  |
| 21 | synthase                     | 6.04E-14 |  |
| 22 | primeverosidase              | 1.02E-08 |  |
| 23 | phosphatase                  | 2.90E-33 |  |
| 24 | lyase                        | 4.83E-15 |  |
| 25 | dehydrogenase                | 3.87E-14 |  |
| 26 | dioxygenase                  | 4.09E-37 |  |
| 27 | glucosidase | 1.91E-07 | 3.2.1 | Hydrolases. Glycosylases. Glycosidases, i.e. enzymes hydrolyzing O- and S-glycosyl compounds. |
| 27 | oxidase | 1.64E-10 | 1.1.1 | Oxidoreductases. Acting on the CH-OH group of donors. With NAD(+) or NADP(+) as acceptor. |
| 27 | oxidase | 1.64E-10 | 1.1.3 | Oxidoreductases. Acting on the CH-OH group of donors. With oxygen as acceptor |
| 27 | oxidase | 1.64E-10 | 1.1.99 | Oxidoreductases. Acting on the CH-OH group of donors. With other, unknown, acceptors |
| 27 | oxidase | 1.64E-10 | 1.2.3 | Oxidoreductases. Acting on the aldehyde or oxo group of donors. With oxygen as acceptor |
| 27 | oxidase | 1.64E-10 | 1.3.3 | Oxidoreductases. Acting on the CH-CH group of donors. With oxygen as acceptor |
| 27 | oxidase | 1.64E-10 | 1.4.3 | Oxidoreductases. Acting on the CH-NH(2) group of donors. With oxygen as acceptor. |
| 27 | oxidase | 1.64E-10 | 1.5.3 | Oxidoreductases. Acting on the CH-NH group of donors. With oxygen as acceptor |
| 27 | oxidase | 1.64E-10 | 1.6.3 | Oxidoreductases. Acting on NADH or NADPH. With oxygen as acceptor |
| 27 | oxidase | 1.64E-10 | 1.7.3 | Oxidoreductases. Acting on other nitrogenous compounds as donors. With oxygen as acceptor |
| 27 | oxidase | 1.64E-10 | 1.8.3 | Oxidoreductases. Acting on a sulfur group of donors. With oxygen as acceptor |
| 27 | oxidase | 1.64E-10 | 1.10.3 | Oxidoreductases. Acting on diphenols and related substances as donors. With oxygen as acceptor |
| 27 | oxidase | 1.64E-10 | 1.11.1 | Oxidoreductases. Acting on a peroxide as acceptor. Peroxidases |
| 27 | oxidase | 1.64E-10 | 1.13.11 | Oxidoreductases. Acting on single donors with incorporation of molecular oxygen (oxygenases). The oxygen incorporated need not be derived from O(2). With incorporation of two atoms of oxygen. |
| 27 | oxidase | 1.64E-10 | 1.13.12 | Oxidoreductases. Acting on single donors with incorporation of molecular oxygen (oxygenases). With incorporation of one atom of oxygen |
| 27 | oxidase | 1.64E-10 | 1.14.13 | Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. The oxygen incorporated need not be derived from O(2). With NADH or NADPH as one donor, and incorporation of one atom of oxygen. |
| 27 | oxidase | 1.64E-10 | 1.14.19 | Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. The oxygen incorporated need not be derived from O(2). With oxidation of a pair of donors resulting in the reduction of molecular oxygen to two molecules of water. |
| 27 | oxidase | 1.64E-10 | 1.14.21 | Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. With NADH or NADPH as one donor, and the other dehydrogenated |
| 27 | oxidase | 1.64E-10 | 1.21.3 | Oxidoreductases. Acting on x-H and y-H to form an x-y bond. With oxygen as acceptor. |
| 28 | glucosyltransferase | 3.37E-10 | | |
| 28 | glycosyltransferase | 9.87E-33 | | |
| 29 | dehydrogenase | 1.75E-15 | | |
| 29 | oxidase | 1.79E-06 | 1.1.1 | Oxidoreductases. Acting on the CH-OH group of donors. With NAD(+) or NADP(+) as acceptor. |
| 29 | oxidase | 1.79E-06 | 1.1.3 | Oxidoreductases. Acting on the CH-OH group of donors. With oxygen as acceptor |
| 29 | oxidase | 1.79E-06 | 1.1.99 | Oxidoreductases. Acting on the CH-OH group of donors. With other, unknown, acceptors |
| 29 | oxidase | 1.79E-06 | 1.2.3 | Oxidoreductases. Acting on the aldehyde or oxo group of donors. With oxygen as acceptor |
| Enzyme  | EC Number | Enzyme Classification | Function Description |
|---------|-----------|------------------------|----------------------|
| oxidase | 1.79E-06  | 1.3.3                  | Oxidoreductases. Acting on the CH-CH group of donors. With oxygen as acceptor |
| oxidase | 1.79E-06  | 1.4.3                  | Oxidoreductases. Acting on the CH-NH(2) group of donors. With oxygen as acceptor |
| oxidase | 1.79E-06  | 1.5.3                  | Oxidoreductases. Acting on the CH-NH group of donors. With oxygen as acceptor |
| oxidase | 1.79E-06  | 1.6.3                  | Oxidoreductases. Acting on NADH or NADPH. With oxygen as acceptor |
| oxidase | 1.79E-06  | 1.7.3                  | Oxidoreductases. Acting on other nitrogenous compounds as donors. With oxygen as acceptor |
| oxidase | 1.79E-06  | 1.8.3                  | Oxidoreductases. Acting on a sulfur group of donors. With oxygen as acceptor |
| oxidase | 1.79E-06  | 1.10.3                 | Oxidoreductases. Acting on diphenols and related substances as donors. With oxygen as acceptor |
| oxidase | 1.79E-06  | 1.11.1                 | Oxidoreductases. Acting on a peroxide as acceptor. Peroxidases |
| oxidase | 1.79E-06  | 1.13.11                | Oxidoreductases. Acting on single donors with incorporation of molecular oxygen (oxygenases). The oxygen incorporated need not be derived from O(2). With incorporation of two atoms of oxygen. |
| oxidase | 1.79E-06  | 1.13.12                | Oxidoreductases. Acting on single donors with incorporation of molecular oxygen (oxygenases). With incorporation of one atom of oxygen |
| oxidase | 1.79E-06  | 1.14.13                | Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. The oxygen incorporated need not be derived from O(2). With NADH or NADPH as one donor, and incorporation of one atom of oxygen. |
| Page | Enzyme          | EC Number | Description                                                                                                                                 |
|------|----------------|-----------|---------------------------------------------------------------------------------------------------------------------------------------------|
| 29   | oxidase        | 1.79E-06  | 1.14.19 Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. The oxygen incorporated need not be derived from O(2). With oxidation of a pair of donors resulting in the reduction of molecular oxygen to two molecules of water. |
| 29   | oxidase        | 1.79E-06  | 1.14.21 Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. With NADH or NADPH as one donor, and the other dehydrogenated |
| 29   | oxidase        | 1.79E-06  | 1.21.3 Oxidoreductases. Acting on x-H and y-H to form an x-y bond. With oxygen as acceptor.                                                  |
| 30   | dehydrogenase  | 8.89E-10  |                                                                                                                                             |
| 31   | homoaconitase  | 2.61E-08  |                                                                                                                                             |
Table S3. Reaction clusters enrichment for enzyme name bigrams, for example "methylglyoxal reductase".

We see that many enriched enzyme bigrams are more specific versions of their unigram counterpart. For example, cluster 7 is enriched for hydroxylase at the unigram level and then a specific type of hydroxylase, omega;hydroxylase, at the bigram level.

Generally, similar enzymes are enriched in the same cluster and the bigrams give more specificity on the enzyme functionality. However, there are clusters that are enriched for an enzyme unigram but not a more specific bigram and vice versa. For example, Cluster 0 is enriched for salicylate;hydroxylase at the bigram level but not enriched for hydroxylase. In this case, Cluster 0 contained all five reactions catalyzed by enzymes with “salicylate hydroxylase” in their names but did not contain the other 167 reactions in the hydroxylase group.

| Cluster ID | Enzyme Name Bigram | P-value  | EC Number | EC Name |
|------------|---------------------|----------|-----------|---------|
| 0          | acid;decarboxylase   | 9.49E-12 | 4.1.1     | Lyases. Carbon-carbon lyases. Carboxy-lyases. |
| 0          | pyruvate;decarboxylase | 6.32E-11 | 4.1.1     | Lyases. Carbon-carbon lyases. Carboxy-lyases. |
| 0          | salicylate;hydroxylase | 3.27E-09 | 4.1.1     | Lyases. Carbon-carbon lyases. Carboxy-lyases. |
| 1          | flavonoid;methyltransferase | 4.05E-11 | 2.1.1     | Transferases. Transferring one-carbon groups. Methyltransferases. |
| 1          | flavonol;methyltransferase | 2.18E-08 | 2.1.1     | Transferases. Transferring one-carbon groups. Methyltransferases. |
| 1          | carboxyl;methyltransferase | 7.29E-08 | 2.1.1     | Transferases. Transferring one-carbon groups. Methyltransferases. |
| 2          | phenol;monooxygenase  | 1.95E-07 | 1.14.13   | Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. The oxygen incorporated need not be derived from O(2). With NADH or NADPH as one donor, and incorporation of one atom of oxygen. |
| 2          | phenol;monooxygenase  | 1.95E-07 | 1.14.14   | Oxidoreductases. Acting on paired donors, with reduced flavin or flavoprotein as one donor, and incorporation of one atom of oxygen into the other donor |
| 2          | phenol;monooxygenase  | 1.95E-07 | 1.14.18   | Oxidoreductases. Acting on paired donors, with another compound as one donor, and incorporation of one atom of oxygen into the other donor |
| 3          | isopropylmalate;dehydrogenase | 5.09E-10 | 1.1.1     | Oxidoreductases. Acting on the CH-OH group of donors. With NAD(+) or NADP(+) as acceptor. |
| 3          | monooxygenase;monooxygenase | 1.82E-07 |           |         |
|   | Enzyme Name                        | EC Number | Function                                                                 |
|---|-----------------------------------|------------|---------------------------------------------------------------------------|
| 3 | steroid:reductase                 | 5.51E-08   | Oxidoreductases. Acting on the CH-OH group of donors. With NAD(+) or NADP(+) as acceptor. |
| 3 | steroid:reductase                 | 5.51E-08   | Oxidoreductases. Acting on the CH-CH group of donors                       |
| 3 | steroid:reductase                 | 5.51E-08   | Oxidoreductases. Acting on the CH-NH(2) group of donors                    |
| 4 | chlorocatechol:dioxygenase        | 1.83E-22   | Oxidoreductases. Acting on single donors with incorporation of molecular oxygen (oxygenases). The oxygen incorporated need not be derived from O(2). With incorporation of two atoms of oxygen. |
| 5 | glucoside:acyltransferase         | 4.74E-18   | Transferases. Acyltransferases. Transferring groups other than amino-acyl groups. |
| 5 | glucoside:malonyltransferase      | 5.57E-12   | Transferases. Acyltransferases. Transferring groups other than amino-acyl groups. |
| 6 | sulfotransferase                  | 5.16E-12   | Transferases. Transferring sulfur-containing groups. Sulfo transferases.    |
| 6 | hydroxymethylpyrimidine:kinase    | 3.77E-07   | Transferases. Transferring sulfur-containing groups. Phosphotransferases with an alcohol group as acceptor. |
| 6 | desulfoglucosinolate:sulfotransferase | 1.21E-13 | Transferases. Transferring sulfur-containing groups. Sulfo transferases. |
| 6 | deoxynucleoside:kinase            | 9.12E-09   | Transferases. Transferring phosphorus-containing groups. Phosphotransferases with an alcohol group as acceptor. |
| 7 | omega:hydroxylase                 | 2.32E-10   | Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. The oxygen incorporated need not be derived from O(2). With NADH or NADPH as one donor, and incorporation of one atom of oxygen. |
| 7 | omega:hydroxylase                 | 2.32E-10   | Oxidoreductases. Acting on paired donors, with a reduced iron-sulfur protein as one donor, and incorporation of one atom of oxygen into the other donor |
| 7 | xylene:monooxygenase              | 3.93E-07   | None                                                                      |
| 8 | tyramine:hydroxycinnamoyltransferase | 6.37E-08 | Transferases. Acyltransferases. Transferring groups other than amino-acyl groups. |
| 8 | amido:synthetase                  | 2.15E-13   | None                                                                      |
| 8 | serotonin:hydroxycinnamoyltransferase | 6.37E-08 | Transferases. Acyltransferases. Transferring groups other than amino-acyl groups. |
| 9 | methylthioalkylmalate:synthase    | 3.82E-09   | Transferases. Acyltransferases. Acyl groups converted into alkyl groups on transfer. |
| 10| tyrosinase                        | 2.01E-07   | Oxidoreductases. Acting on paired donors, with another compound as one donor, and incorporation of one atom of oxygen into the other donor |
|   | Enzyme Name                        | E. coli    | K.   | Description                                                                                                                                                                                                 |
|---|-----------------------------------|------------|-----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 10| protocatechuate;dioxygenase       | 1.05E-13   | 1.13.11 | Oxidoreductases. Acting on single donors with incorporation of molecular oxygen (dioxygenases). The oxygen incorporated need not be derived from O(2). With incorporation of two atoms of oxygen.                      |
| 11| nucleoside;phosphorylase          | 4.16E-14   | 2.4.2 | Transferases. Glycosyltransferases. Pentosyltransferases.                                                                                                                                                   |
| 12| glucoside;glucosyltransferase    | 3.82E-13   | 2.4.1 | Hexosyltransferases                                                                                                                                                                                        |
| 12| iodothyronine;deiodinase          | 9.61E-08   | none |                                                                                                                                                                                                       |
| 12| omega;desaturase                  | 1.42E-18   | 1.14.19 | Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. The oxygen incorporated need not be derived from O(2). With oxidation of a pair of donors resulting in the reduction of molecular oxygen to two molecules of water. |
| 13| UDP;glucuronosyltransferase       | 1.03E-07   | 2.4.1 | Hexosyltransferases                                                                                                                                                                                        |
| 15| chloromuconate;cycloisomerase     | 9.48E-17   | 5.5.1 | Isomerases. Intramolecular lyases. Intramolecular lyases.                                                                                                                                                   |
| 15| dienelactone;hydrolase            | 8.61E-18   | 3.1.1 | Hydrolases. Acting on ester bonds. Carboxylic ester hydrolases                                                                                                                                             |
| 17| beta;hydroxylase                  | 1.95E-10   | 1.14 | Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. The oxygen incorporated need not be derived from O(2).                                                         |
| 19| AMP;ligase                        | 1.02E-08   | 6.1.1 | Ligases forming aminoacyl-tRNA and related compounds                                                                                                                                                       |
| 19| AMP;ligase                        | 1.02E-08   | 6.2.1 | Acid–thiol ligases                                                                                                                                                                                         |
| 19| AMP;ligase                        | 1.02E-08   | 6.3  | Ligases. Forming carbon-nitrogen bonds.                                                                                                                                                                    |
| 19| AMP;ligase                        | 1.02E-08   | 6.5.1 | Ligases that form phosphoric-ester bonds                                                                                                                                                                   |
| 20| flavonol;glucosyltransferase      | 2.64E-25   | 2.4.1 | Hexosyltransferases                                                                                                                                                                                         |
| 20| beta;glucosyltransferase          | 3.22E-15   | 2.4.1 | Hexosyltransferases                                                                                                                                                                                         |
| 20| flavonoid;glucosyltransferase     | 2.20E-09   | none |                                                                                                                                                                                                       |
| 22| beta;primeverosidase              | 1.02E-08   | 3.2.1 | Hydrolases. Glycosylases. Glycosidases, i.e. enzymes hydrolyzing O- and S-glycosyl compounds.                                                                                                               |
| 23| phosphate;phosphatase             | 7.63E-25   | 3.1.7 | Hydrolases. Acting on ester bonds. Diphosphoric monoester hydrolases                                                                                                                                     |
| 23| phosphate;phosphatase             | 7.63E-25   | 3.6.1 | Hydrolase. Acting on acid anhydrides. In phosphorous-containing anhydrides                                                                                                                                |
| 23| alkaline;phosphatase              | 1.47E-10   | 3.1.3 | Hydrolases. Acting on ester bonds. Phosphoric monoester hydrolases                                                                                                                                         |
| 24| alkylthiohydroximate;lyase        | 4.31E-15   | none |                                                                                                                                                                                                       |
| 24| monooxygenase;monooxygenase       | 2.67E-10   | none |                                                                                                                                                                                                       |
|   | Enzyme                   | EC Number | Description                                                                                     |
|---|--------------------------|------------|-------------------------------------------------------------------------------------------------|
| 25| alcohol;dehydrogenase    | 1.32E-21   | Oxidoreductases. Acting on the CH-OH group of donors. With NAD(+) or NADP(+) as acceptor.       |
| 25| glutathione;dehydrogenase| 1.97E-09   | Oxidoreductases. Acting on the CH-OH group of donors. With NAD(+) or NADP(+) as acceptor.       |
| 25| glutathione;dehydrogenase| 1.97E-09   | Oxidoreductase. Acting on a sulfur group of donors with a quinone or similar compound as acceptor|
| 26| nitroarene;dioxygenase   | 4.87E-10   | Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. The oxygen incorporated need not be derived from O(2). With NADH or NADPH as one donor, and incorporation of two atoms of oxygen into one donor. |
| 26| chlorobenzene;dioxygenase| 2.21E-25   | Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. The oxygen incorporated need not be derived from O(2). With NADH or NADPH as one donor, and incorporation of two atoms of oxygen into one donor. |
| 26| naphthalene;dioxygenase  | 3.68E-08   | Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. The oxygen incorporated need not be derived from O(2). With NADH or NADPH as one donor, and incorporation of two atoms of oxygen into one donor. |
| 26| naphthalene;dioxygenase  | 3.68E-08   | Oxidoreductases. Acting on single donors with incorporation of molecular oxygen (oxygenses). The oxygen incorporated need not be derived from O(2). With incorporation of two atoms of oxygen. |
| 26| naphthalene;dioxygenase  | 3.68E-08   | Oxidoreductases. Acting on iron-sulfur proteins as donors with NAD(+) or NADP(+) as acceptor.   |
| 27| alcohol;dehydrogenase    | 3.13E-09   | Oxidoreductases. Acting on the CH-OH group of donors. With NAD(+) or NADP(+) as acceptor.       |
| 28| cytokinin;glycosyltransferase | 7.21E-14 | none                                                                                           |
| 28| UDP;glycosyltransferase   | 5.50E-22   | Hexosyltransferases                                                                            |
| 28| glycoside;glycosyltransferase | 9.63E-11 | 2.4.1 Hexosyltransferases                                                                       |
| 28| acid;glycosyltransferase  | 4.47E-15   | Hexosyltransferases                                                                            |
| 28| dinitrotoluene;glycosyltransferase | 3.51E-12 | none                                                                                           |
| 29| aldehyde;dehydrogenase   | 1.26E-19   | Oxidoreductases. Acting on the aldehyde or o xo group of donors. With NAD(+) or NADP(+) as acceptor. |
|   | enzyme                     | score  | class  | subclass | description                                                                 |
|---|----------------------------|--------|--------|----------|----------------------------------------------------------------------------|
| 29| benzaldehyde; dehydrogenase | 1.12E-08 | 1.2.1  |          | Oxidoreductases. Acting on the aldehyde or oxo group of donors. With NAD(+) or NADP(+) as acceptor. |
| 30| dihydrodiol; dehydrogenase  | 3.11E-19 | 1.3.1  |          | Oxidoreductases. Acting on the CH-CH group of donors. With NAD(+) or NADP(+) as acceptor. |
| 31| methanogen; homoaconitase  | 2.61E-08 | 4.2.1  |          | Lyases. Carbon-oxygen lyases. Hydro-lyases. |
Table S4. Reaction clusters enrichment for MetaCyc GO numbers.

| Cluster ID | GO Accession   | GO Term                                                                 | P-value    |
|------------|----------------|-------------------------------------------------------------------------|------------|
| 1          | GO:0008171     | O-methyltransferase activity                                             | 7.02E-08   |
| 2          | GO:0004497     | monooxygenase activity                                                  | 7.22E-08   |
| 3          | GO:0003854     | 3-beta-hydroxy-delta5-steroid dehydrogenase activity                    | 5.09E-10   |
| 3          | GO:0051287     | NAD binding                                                            | 1.92E-08   |
| 3          | GO:0016616     | oxidoreductase activity, acting on the CH-OH group of donors, NAD or NADP as acceptor | 7.18E-09   |
| 3          | GO:0000253     | 3-keto sterol reductase activity                                        | 5.51E-08   |
| 3          | GO:0047012     | sterol-4-alpha-carboxylate 3-dehydrogenase (decarboxylating) activity   | 6.55E-11   |
| 3          | GO:0004303     | estradiol 17-beta-dehydrogenase activity                                | 5.51E-08   |
| 3          | GO:0003862     | 3-isopropylmalate dehydrogenase activity                                | 3.21E-07   |
| 6          | GO:0005524     | ATP binding                                                            | 3.75E-21   |
| 6          | GO:0008146     | sulotransferase activity                                                | 7.25E-22   |
| 6          | GO:0080068     | 5-methylthiopentyl-desulfoglucosinolate sulotransferase activity        | 2.18E-10   |
| 6          | GO:0080067     | 4-methylthiobutyl-desulfoglucosinolate sulotransferase activity         | 2.18E-10   |
| 6          | GO:0080071     | indol-3-yl-methyl-desulfoglucosinolate sulotransferase activity         | 2.18E-10   |
| 6          | GO:0047894     | flavonol 3-sulotransferase activity                                     | 9.12E-09   |
| 6          | GO:0019136     | deoxynucleoside kinase activity                                         | 9.12E-09   |
| 6          | GO:0016301     | kinase activity                                                         | 3.20E-20   |
| 6          | GO:0080069     | 7-methylthioheptyl-desulfoglucosinolate sulotransferase activity        | 2.18E-10   |
| 6          | GO:0080066     | 3-methylthiopropyl-desulfoglucosinolate sulotransferase activity        | 2.18E-10   |
| 6          | GO:0047364     | desulfoglucosinolate sulotransferase activity                           | 1.21E-13   |
| 6          | GO:0004062     | aryl sulotransferase activity                                           | 9.12E-09   |
| 6          | GO:0016773     | phosphotransferase activity, alcohol group as acceptor                  | 5.86E-09   |
| 6          | GO:0004797     | thymidine kinase activity                                               | 3.77E-07   |
| 6          | GO:0080070     | 8-methylthiooctyl-desulfoglucosinolate sulotransferase activity         | 2.18E-10   |
| GO:0020037 | heme binding | 8.28E-11 |
| GO:0019825 | oxygen binding | 5.62E-07 |
| GO:0005506 | iron ion binding | 2.90E-16 |
| GO:0000254 | C-4 methylsterol oxidase activity | 4.82E-07 |
| GO:0018685 | alkane 1-monooxygenase activity | 9.60E-09 |
| GO:0019825 | indole-3-acetic acid amido synthetase activity | 2.15E-13 |
| GO:0003852 | 2-isopropylmalate synthase activity | 3.82E-09 |
| GO:0000254 | 2-(2'-methylthio)ethylmalate synthase activity | 3.82E-09 |
| GO:0001972 | retinoic acid binding | 5.09E-07 |
| GO:0052722 | fatty acid in-chain hydroxylase activity | 8.96E-10 |
| GO:0008194 | UDP-glycosyltransferase activity | 6.40E-07 |
| GO:0008194 | flavonol 3-O-glycosyltransferase activity | 1.22E-07 |
| GO:0102360 | daphnetin 3-O-glycosyltransferase activity | 1.22E-07 |
| GO:0102425 | myricetin 3-O-glycosyltransferase activity | 1.22E-07 |
| GO:0009899 | ent-kaurene synthase activity | 9.55E-08 |
| GO:0016791 | phosphatase activity | 4.03E-07 |
| GO:0000287 | magnesium ion binding | 6.78E-07 |
| GO:0008934 | inositol monophosphate 1-phosphatase activity | 8.16E-08 |
| GO:0080043 | transaminase activity | 4.18E-13 |
| GO:0030170 | pyridoxal phosphate binding | 8.58E-11 |
| GO:0016846 | carbon-sulfur lyase activity | 4.31E-15 |
| GO:0080108 | S-alkythiohydroximate lyase activity | 4.31E-15 |
| GO:0103100 | UDP-glucose | 4.50E-16 |
| GO:0008194 | UDP-glycosyltransferase activity | 1.30E-46 |
| GO:0080043 | quercetin 3-O-glycosyltransferase activity | 2.79E-46 |
| GO:0047807 | cytokinin 7-beta-glycosyltransferase activity | 5.27E-20 |
| GO:0080062 | cytokinin 9-beta-glycosyltransferase activity | 5.27E-20 |
| GO:0103101 | UDP-glucose:7-methylthioheptylhydroximate S-glycosyltransferase activity | 4.50E-16 |
| GO:0080044 | quercetin 7-O-glucosyltransferase activity | 2.79E-46 |
| GO:0052638 | indole-3-butyrate beta-glucosyltransferase activity | 3.51E-12 |
| GO:0103103 | UDP-glucose | 4.50E-16 |
| GO:0016757 | transferase activity, transferring glycosyl groups | 2.44E-45 |
| GO:0047251 | thiohydroximate beta-D-glucosyltransferase activity | 4.50E-16 |
| GO:0035251 | UDP-glucosyltransferase activity | 4.47E-15 |
| GO:0016758 | transferase activity, transferring hexosyl groups | 5.08E-17 |
| GO:0102659 | UDP-glucose | 4.50E-16 |
| GO:0050403 | trans-zeatin O-beta-D-glucosyltransferase activity | 7.21E-14 |
| GO:0050502 | cis-zeatin O-beta-D-glucosyltransferase activity | 7.21E-14 |
| GO:0103099 | UDP-glucose:5-methylthiopentylhydroximate S-glucosyltransferase activity | 4.50E-16 |
| GO:0103102 | UDP-glucose:8-methylthiooctylhydroximate S-glucosyltransferase activity | 4.50E-16 |
| GO:0004030 | aldehyde dehydrogenase [NAD(P)+] activity | 1.05E-15 |
| GO:0004029 | aldehyde dehydrogenase (NAD) activity | 1.26E-19 |
| GO:0046577 | long-chain-alcohol oxidase activity | 9.73E-17 |
| GO:0000254 | C-4 methylsterol oxidase activity | 5.91E-07 |
## Table S5. Reaction clusters enrichment for MetaCyc EC numbers.

| Cluster ID | EC number | EC name                                                                 | P-value     |
|------------|-----------|-------------------------------------------------------------------------|-------------|
| 0          | 4.1.1     | Lyases. Carbon-carbon lyases. Carboxy-lyases.                          | 4.04E-31    |
| 0          | 4.1       | Lyases. Carbon-carbon lyases.                                           | 4.80E-32    |
| 1          | 2.1.1     | Transferases. Transferring one-carbon groups. Methyltransferases.        | 1.00E-90    |
| 1          | 2.1       | Transferases. Transferring one-carbon groups.                           | 4.98E-90    |
| 1          | 1.14.13   | Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. The oxygen incorporated need not be derived from O(2). With NADH or NADPH as one donor, and incorporation of one atom of oxygen. | 1.94E-07    |
| 1          | 1.14      | Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. The oxygen incorporated need not be derived from O(2). | 1.06E-13    |
| 2          | 1.14.13   | Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. The oxygen incorporated need not be derived from O(2). With NADH or NADPH as one donor, and incorporation of one atom of oxygen. | 1.50E-38    |
| 2          | 1.14      | Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. The oxygen incorporated need not be derived from O(2). | 2.53E-44    |
| 3          | 1.1       | Oxidoreductases. Acting on the CH-OH group of donors.                    | 1.13E-42    |
| 3          | 1.1.1     | Oxidoreductases. Acting on the CH-OH group of donors. With NAD(+) or NADP(+) as acceptor. | 3.12E-36    |
| 4          | 1.13      | Oxidoreductases. Acting on single donors with incorporation of molecular oxygen (oxygenases). The oxygen incorporated need not be derived from O(2). | 2.19E-19    |
| 4          | 1.13.11   | Oxidoreductases. Acting on single donors with incorporation of molecular oxygen (oxygenases). The oxygen incorporated need not be derived from O(2). With incorporation of two atoms of oxygen. | 8.41E-21    |
| 5          | 2.1.1     | Transferases. Transferring one-carbon groups. Methyltransferases.        | 1.25E-10    |
| 5          | 2.1       | Transferases. Transferring one-carbon groups.                           | 5.11E-11    |
| 5          | 1.1       | Oxidoreductases. Acting on the CH-OH group of donors.                    | 4.52E-19    |
| Code | Enzyme Class | Description | E-value |
|------|--------------|-------------|---------|
| 1.4  | Oxidoreductases. Acting on the CH-NH(2) group of donors. | | 4.94E-09 |
| 2.3.1| Transferases. Acyltransferases. Transferring groups other than amino-acyl groups. | | 8.35E-32 |
| 2.3  | Transferases. Acyltransferases. | | 8.47E-28 |
| 1.1.1| Oxidoreductases. Acting on the CH-OH group of donors. With NAD(+) or NADP(+) as acceptor. | | 2.27E-14 |
| 1.4.3| Oxidoreductases. Acting on the CH-NH(2) group of donors. With oxygen as acceptor. | | 9.31E-10 |
| 2.7  | Transferases. Transferring phosphorus-containing groups. | | 4.79E-55 |
| 2.8.2| Transferases. Transferring sulfur-containing groups. Sulfotransferases. | | 5.97E-28 |
| 2.7.1| Transferases. Transferring phosphorus-containing groups. Phosphotransferases with an alcohol group as acceptor. | | 4.83E-57 |
| 1.14 | Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. The oxygen incorporated need not be derived from O(2). | | 4.69E-09 |
| 2.8  | Transferases. Transferring sulfur-containing groups. | | 3.52E-23 |
| 1.14.13| Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. The oxygen incorporated need not be derived from O(2). With NADH or NADPH as one donor, and incorporation of one atom of oxygen. | | 1.79E-16 |
| 1.14 | Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. The oxygen incorporated need not be derived from O(2). | | 6.02E-15 |
| 2.3.1| Transferases. Acyltransferases. Transferring groups other than amino-acyl groups. | | 5.60E-10 |
| 2.3  | Transferases. Acyltransferases. | | 6.28E-11 |
| 6.3  | Ligases. Forming carbon-nitrogen bonds. | | 7.16E-21 |
| 1.14.13| Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. The oxygen incorporated need not be derived from O(2). With NADH or NADPH as one donor, and incorporation of one atom of oxygen. | | 4.13E-15 |
| 1.14 | Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. The oxygen incorporated need not be derived from O(2). | | 2.98E-16 |
| 2.3.3| Transferases. Acyltransferases. Acyl groups converted into alkyl groups on transfer. | | 3.60E-15 |
| 1.13 | Oxidoreductases. Acting on single donors with incorporation of molecular oxygen (oxygenases). The oxygen incorporated need not be derived from O(2). | | 2.37E-24 |
Oxidoreductases. Acting on single donors with incorporation of molecular oxygen (oxygenases). The oxygen incorporated need not be derived from O(2). With incorporation of two atoms of oxygen.

Transferases. Glycosyltransferases.

Transferases. Glycosyltransferases. Pentosyltransferases.

Transferases. Transferring phosphorus-containing groups. Transferases for other substituted phosphate groups.

Transferases. Transferring one-carbon groups. Methyltransferases.

Transferases. Transferring one-carbon groups.

Oxidoreductases. Acting on the CH-CH group of donors.

Oxidoreductases. Acting on the CH-OH group of donors.

Oxidoreductases. Acting on the CH-OH group of donors. With NAD(+) or NADP(+) as acceptor.

Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. The oxygen incorporated need not be derived from O(2). With oxidation of a pair of donors resulting in the reduction of molecular oxygen to two molecules of water.

Oxidoreductases. Acting on single donors with incorporation of molecular oxygen (oxygenases). The oxygen incorporated need not be derived from O(2).

Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. The oxygen incorporated need not be derived from O(2). With NADH or NADPH as one donor, and incorporation of two atoms of oxygen into one donor.

Transferases. Glycosyltransferases. Hexosyltransferases.

Transferases. Glycosyltransferases.

Hydrolases. Acting on carbon-nitrogen bonds, other than peptide bonds.

Hydrolases. Acting on carbon-nitrogen bonds, other than peptide bonds. In linear amides.
|   |   |   |   |   |   |
|---|---|---|---|---|---|
| 15 | 3.5 | Hydrolases. Acting on carbon-nitrogen bonds, other than peptide bonds. | 2.62E-11 |
| 15 | 3.1.1 | Hydrolases. Acting on ester bonds. Carboxylic ester hydrolases. | 3.46E-12 |
| 15 | 5.5.1 | Isomerases. Intramolecular lyases. Intramolecular lyases. | 3.53E-12 |
| 15 | 3.5.2 | Hydrolases. Acting on carbon-nitrogen bonds, other than peptide bonds. In cyclic amides. | 1.56E-22 |
| 15 | 5.5 | Isomerases. Intramolecular lyases. | 3.53E-12 |
| 17 | 1.14 | Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. The oxygen incorporated need not be derived from O(2). | 9.59E-13 |
| 19 | 2.7 | Transferases. Transferring phosphorus-containing groups. | 1.78E-23 |
| 19 | 2.7.7 | Transferases. Transferring phosphorus-containing groups. Nucleotidytransferases. | 8.79E-43 |
| 20 | 2.4.1 | Transferases. Glycosyltransferases. Hexosyltransferases. | 2.28E-84 |
| 20 | 2.4 | Transferases. Glycosyltransferases. | 2.84E-80 |
| 21 | 4.2 | Lyases. Carbon-oxygen lyases. | 1.05E-13 |
| 21 | 4.2.3 | Lyases. Carbon-oxygen lyases. Acting on phosphates. | 3.78E-24 |
| 22 | 3.2.1 | Hydrolases. Glycosylases. Glycosidases, i.e. enzymes hydrolyzing O- and S-glycosyl compounds. | 9.40E-19 |
| 22 | 3.2 | Hydrolases. Glycosylases. | 2.28E-28 |
| 22 | 3.2.2 | Hydrolases. Glycosylases. Hydrolyzing N-glycosyl compounds. | 1.78E-10 |
| 23 | 3.1 | Hydrolases. Acting on ester bonds. | 5.14E-41 |
| 23 | 3.1.3 | Hydrolases. Acting on ester bonds. Phosphoric monoester hydrolases. | 2.11E-50 |
| 25 | 1.1 | Oxidoreductases. Acting on the CH-OH group of donors. | 8.49E-25 |
| 25 | 1.1.1 | Oxidoreductases. Acting on the CH-OH group of donors. With NAD(+) or NADP(+) as acceptor. | 2.36E-21 |
| 26 | 1.14 | Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. The oxygen incorporated need not be derived from O(2). | 5.93E-22 |
| 26 | 1.14.12 | Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. The oxygen incorporated need not be derived from O(2). With NADH or NADPH as one donor, and incorporation of two atoms of oxygen into one donor. | 6.33E-64 |
| 27 | 3.2.1 | Hydrolases. Glycosylases. Glycosidases, i.e. enzymes hydrolyzing O- and S-glycosyl compounds. | 7.42E-13 |
| 27 | 3.2 | Hydrolases. Glycosylases. | 1.28E-11 |
| 28 | 2.4.1 | Transferases. Glycosyltransferases. Hexosyltransferases. | 4.92E-39 |
|   |   |   |   |
|---|---|---|---|
| 28 | 2.4 | Transferases. Glycosyltransferases. | 1.26E-38 |
| 29 | 1.2.1 | Oxidoreductases. Acting on the aldehyde or oxo group of donors. With NAD(+) or NADP(+) as acceptor. | 2.32E-47 |
| 29 | 1.2 | Oxidoreductases. Acting on the aldehyde or oxo group of donors. | 1.70E-50 |
| 30 | 1.3 | Oxidoreductases. Acting on the CH-CH group of donors. | 7.53E-18 |
| 30 | 1.3.1 | Oxidoreductases. Acting on the CH-CH group of donors. With NAD(+) or NADP(+) as acceptor. | 2.87E-16 |
| 31 | 4.2 | Lyases. Carbon-oxygen lyases. | 4.21E-10 |
| 31 | 4.2.1 | Lyases. Carbon-oxygen lyases. Hydro-lyases. | 5.59E-11 |
| 31 | 3.7 | Hydrolases. Acting on carbon-carbon bonds. | 1.28E-08 |
| 31 | 3.7.1 | Hydrolases. Acting on carbon-carbon bonds. In ketonic substances. | 1.28E-08 |
Table S6. Matrix of reaction cluster ID versus EC number and name. Cluster numbers are grouped by EC high level class (e.g., oxidoreductases) and grouped within each class by a black box.

| Cluster ID | EC number from S2, S3, or S5 | EC name |
|------------|-------------------------------|---------|
| 7          | 1                             | Oxidoreductases. Acting on the CH-OH group of donors. |
| 3 25       | 5                             | Oxidoreductases. Acting on the CH-OH group of donors. With NAD(+) or NADP(+) as acceptor. |
| 3 25       | 12                            | Oxidoreductases. Acting on the CH-OH group of donors. With oxygen as acceptor. |
| 29         | 1.1                           | Oxidoreductases. Acting on the aldehyde or oxo group of donors. |
| 29         | 1.1.1                         | Oxidoreductases. Acting on the aldehyde or oxo group of donors. With NAD(+) or NADP(+) as acceptor. |
| 29         | 1.1.3                         | Oxidoreductases. Acting on the aldehyde or oxo group of donors. With oxygen as acceptor. |
| 29         | 1.1.99                        | Oxidoreductases. Acting on the aldehyde or oxo group of donors. With other, unknown, acceptors. |
| 30         | 1.2                           | Oxidoreductases. Acting on the aldehyde or oxo group of donors. |
| 30         | 1.2.1                         | Oxidoreductases. Acting on the aldehyde or oxo group of donors. With NAD(+) or NADP(+) as acceptor. |
| 30         | 1.2.3                         | Oxidoreductases. Acting on the aldehyde or oxo group of donors. With oxygen as acceptor. |
| 30         | 1.2.99                        | Oxidoreductases. Acting on the aldehyde or oxo group of donors. With other, unknown, acceptors. |
| 30         | 1.3                           | Oxidoreductases. Acting on the CH-NH group of donors. |
| 30         | 1.3.1                         | Oxidoreductases. Acting on the CH-NH group of donors. With NAD(+) or NADP(+) as acceptor. |
| 30         | 1.3.3                         | Oxidoreductases. Acting on the CH-NH group of donors. With oxygen as acceptor. |
| 5          | 1.4                           | Oxidoreductases. Acting on the CH-NH(2) group of donors. |
| 5          | 1.4.3                         | Oxidoreductases. Acting on the CH-NH(2) group of donors. With oxygen as acceptor. |
| 5          | 1.5.3                         | Oxidoreductases. Acting on the CH-NH group of donors. With oxygen as acceptor. |
| 5          | 1.6.3                         | Oxidoreductases. Acting on NADH or NADPH. With oxygen as acceptor. |
| 1.7.3 | Oxidoreductases. Acting on other nitrogenous compounds as donors. With oxygen as acceptor |
| 1.8.3 | Oxidoreductases. Acting on a sulfur group of donors. With oxygen as acceptor |
| 1.8.5 | Oxidoreductase. Acting on a sulfur group of donors with a quinone or similar compound as acceptor |
| 1.10.3 | Oxidoreductases. Acting on a peroxide as acceptor. Peroxidases |
| 1.11.1 | Oxidoreductases. Acting on single donors with incorporation of molecular oxygen (oxygenases). The oxygen incorporated need not be derived from O(2). |
| 1.13 | Oxidoreductases. Acting on single donors with incorporation of molecular oxygen (oxygenases). With incorporation of two atoms of oxygen. |
| 1.13.11 | Oxidoreductases. Acting on single donors with incorporation of molecular oxygen (oxygenases). With incorporation of one atom of oxygen |
| 1.13.12 | Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. The oxygen incorporated need not be derived from O(2). |
| 1.14 | Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. The oxygen incorporated need not be derived from O(2). With NADH or NADPH as one donor, and incorporation of two atoms of oxygen into one donor. |
| 1.14.12 | Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. The oxygen incorporated need not be derived from O(2). With NADH or NADPH as one donor, and incorporation of one atom of oxygen. |
| 1.14.13 | Oxidoreductases. Acting on paired donors, with reduced flavin or flavoprotein as one donor, and incorporation of one atom of oxygen into the other donor |
| 12 | 1.14.15 | Oxidoreductases. Acting on paired donors, with a reduced iron-sulfur protein as one donor, and incorporation of one atom of oxygen into the other donor. |
|----|----------|----------------------------------------------------------------------------------------------------------------------------------|
| 12 | 1.14.18 | Oxidoreductases. Acting on paired donors, with another compound as one donor, and incorporation of one atom of oxygen into the other donor. |
| 12 | 1.14.19 | Oxidoreductases. Acting on paired donors, with incorporation or reduction of molecular oxygen. The oxygen incorporated need not be derived from O(2). With oxidation of a pair of donors resulting in the reduction of molecular oxygen to two molecules of water. |
| 12 | 1.14.21 | Oxidoreductases. Acting on CH or CH(2) groups with other, unknown, acceptors. |
| 26 | 1.17.99 | Oxidoreductases. Acting on iron-sulfur proteins as donors with NAD(+)/NADP(+) as acceptor. |
| 26 | 1.18.1 | Oxidoreductases. Acting on x-H and y-H to form an x-y bond. With oxygen as acceptor. |
| 26 | 1.21.3 | Transferases. Transferring one-carbon groups. Methyltransferases. |
| 12 | 2.1 | Transferases. Transferring one-carbon groups. |
| 5  | 2.1.1 | Methyltransferases. |
| 8  | 2.3 | Transferases. Acyltransferases. Transferases. Acyltransferases. Transferring groups other than aminoacyl groups. Transferases. Acyltransferases. Acyl groups converted into alkyl groups on transfer. |
| 8  | 2.3.1 | Transferases. Acyltransferases. Transferases. Acyltransferases. |
| 20 | 2.4 | Transferases. Glycosyltransferases. Hexosyltransferases. Transferases. Glycosyltransferases. Pentosyltransferases. |
| 13 | 2.4.1 | Transferases. |
| 13 | 2.4.2 | Transferases. Transferases. Transferring alkyl or aryl groups, other than methyl groups. |
| Page | Section | Description |
|------|---------|-------------|
| 6    | 2.7     | Transferases. Transferring phosphorus-containing groups. Transferases. Transferring phosphorus-containing groups. Phosphotransferases with an alcohol group as acceptor. Transferases. Transferring phosphorus-containing groups. Nucleotidyltransferases. Transferases. Transferring phosphorus-containing groups. Transferases for other substituted phosphate groups. |
| 19   | 2.7.1   | Transferases. Transferring phosphorus-containing groups. |
| 19   | 2.7.7   | Transferases. Transferring phosphorus-containing groups. |
| 11   | 2.7.8   | Transferases. Transferring sulfur-containing groups. |
| 6    | 2.8     | Transferases. Transferring sulfur-containing groups. Sulfotransferases. |
| 6    | 2.8.2   | Transferases. Transferring sulfur-containing groups. |
| 23   | 3.1     | Hydrolases. Acting on ester bonds. Hydrolases. Acting on ester bonds. Carboxylic ester hydrolases Hydrolases. Acting on ester bonds. Phosphoric monoester hydrolases. Hydrolases. Acting on ester bonds. Diphosphoric monoester hydrolases |
| 23   | 3.1.1   | Hydrolases. Acting on ester bonds. Carboxylic ester hydrolases |
| 23   | 3.1.3   | Hydrolases. Acting on ester bonds. Phosphoric monoester hydrolases. |
| 23   | 3.1.7   | Hydrolases. Acting on ester bonds. Diphosphoric monoester hydrolases |
| 27   | 3.2     | Hydrolases. Glycosylases. Hydrolases. Glycosylases. Glycosidases, i.e. enzymes hydrolyzing D- and S-glycosyl compounds. Hydrolases. Glycosylases. Hydrolyzing N-glycosyl compounds. |
| 27   | 3.2.1   | Hydrolases. Glycosylases. Glycosidases, i.e. enzymes hydrolyzing D- and S-glycosyl compounds. |
| 27   | 3.2.2   | Hydrolases. Glycosylases. Hydrolyzing N-glycosyl compounds. |
| 14   | 3.5     | Hydrolases. Acting on carbon-nitrogen bonds, other than peptide bonds. Hydrolases. Acting on carbon-nitrogen bonds, other than peptide bonds. In linear amides. Hydrolases. Acting on carbon-nitrogen bonds, other than peptide bonds. In cyclic amides. |
| 14   | 3.5.1   | Hydrolases. Acting on carbon-nitrogen bonds, other than peptide bonds. In linear amides. |
| 15   | 3.5.2   | Hydrolases. Acting on carbon-nitrogen bonds, other than peptide bonds. In cyclic amides. |
| 12   | 3.6     | Hydrolases. Acting on acid anhydrides. Hydrolase. Acting on acid anhydrides. In phosphorus-containing anhydrides |
| 31   | 3.7     | Hydrolases. Acting on carbon-carbon bonds. |
| 31 | 0 | 0 | 4.1 | Lyases. Carbon-carbon lyases. |
|----|----|----|-----|--------------------------------|
| 31 | 21 | 4.1.1 | Lyases. Carbon-carbon lyases. Carboxy-lyases. |
| 31 | 21 | 4.2 | Lyases. Carbon-oxygen lyases. |
| 31 | 21 | 4.2.1 | Lyases. Carbon-oxygen lyases. Hydro-lyases. |
| 31 | 21 | 4.2.3 | Lyases. Carbon-oxygen lyases. Acting on phosphates. |
| 31 | 21 | 5.4.99 | Isomerases. Intramolecular transferases (mutases) transferring other groups |
| 31 | 21 | 5.5 | Isomerases. Intramolecular lyases. |
| 31 | 21 | 5.5.1 | Isomerases. Intramolecular lyases. Intramolecular lyases. |
| 31 | 21 | 6.1.1 | Ligases forming aminoacyl-tRNA and related compounds |
| 31 | 21 | 6.2.1 | Acid–thiol ligases |
| 31 | 21 | 6.3 | Ligases. Forming carbon-nitrogen bonds. |
| 31 | 21 | 6.5.1 | Ligases that form phosphoric-ester bonds |

Hydrolases. Acting on carbon-carbon bonds. In ketonic substances.
Table S7. For 23 drug metabolism reactions, up to 10 calculated nearest neighbor bacterial reactions. At times, another drug metabolism reaction was closer than many bacterial reactions.

| DM ID | Drug                      | Metabolite       | Reaction Rank | MetaCyc Reaction ID | Reaction Common Name              | Reaction Substrate Common Name       | Reaction Product Common Name         | E. coli? | DM Reference PubMed ID |
|-------|---------------------------|------------------|---------------|---------------------|-----------------------------------|--------------------------------------|--------------------------------------|---------|------------------------|
| DM23  | Diclofenac glucuronide    | diclofenac       | 1             | RXN-17095           | 6-deoxy-6-sulfo-D-glucono-1,5-lactone | 6-deoxy-6-sulfo-D-glucurate          |                                      |         | 22328575               |
| DM23  | Diclofenac glucuronide    | diclofenac       | 2             | RXN-9030            | (2S)-2-amino-4-deoxy-chorismate   | (5S,6S)-6-amino-5-hydroxycyclohexa-1,3-diene-1-carboxylate |                                      |         | 22328575               |
| DM23  | Diclofenac glucuronide    | diclofenac       | 3             | 1.2.3.13-RXN       | 4-hydroxyphenylpyruvate           | 4-hydroxyphenylacetate               |                                      |         | 22328575               |
| DM23  | Diclofenac glucuronide    | diclofenac       | 4             | RXN-3945            | isatinate                         | anthranilate                        |                                      |         | 22328575               |
| DM23  | Diclofenac glucuronide    | diclofenac       | 5             | RXN-13530           | formyl hopane synthase            | ribosyl hopane                      | formyl hopane                       |         | 22328575               |
| DM23  | Diclofenac glucuronide    | diclofenac       | 6             | RXNDQC-2            | (indol-3-yl)pyruvate              | indole-3-acetate                    |                                      |         | 22328575               |
| DM23  | Diclofenac glucuronide    | diclofenac       | 7             | RXN-4541            | cis/zeatin riboside               | cis/zeatin                          |                                      |         | 22328575               |
| DM23  | Diclofenac glucuronide    | diclofenac       | 8             | RXN-17047           | 3-acetyldeoxynivalenol            | deoxynivalenol                      |                                      |         | 22328575               |
| DM23  | Diclofenac glucuronide    | diclofenac       | 9             | 4.1.1.51-RXN       | 3-hydroxy-2-methylpyridine-4,5-dicarboxylate | 3-hydroxy-2-methylpyridine-5-carboxylate |                                      |         | 22328575               |
| DM23  | Diclofenac glucuronide    | diclofenac       | 10            | RXN-15750           | fumiquinazoline C                 | fumiquinazoline D                   |                                      |         | 22328575               |
| Reaction | Compound 1 | Compound 2 | Product 1 | Product 2 | Product 3 | R1 | R2 | R3 |
|----------|------------|------------|-----------|-----------|-----------|-----|-----|-----|
| DM22     | Methotrexate | 4-amino-4-deoxy-N10-methylpterinoic acid | 1 | RXN-17061 | isopenicillin N | 6-aminopenicillanate | 5014749 |
| DM22     | Methotrexate | 4-amino-4-deoxy-N10-methylpterinoic acid | 2 | RXN-11665 | indole-3-acetonitrile-\&gamma;-glutamylcysteine conjugate | indole-3-acetonitrile-cysteine conjugate | 5014749 |
| DM22     | Methotrexate | 4-amino-4-deoxy-N10-methylpterinoic acid | 3 | RXN-11428 | phenylacetohydroximoyl-glutathione | phenylacetohydroximoyl-cysteinylglycine | 5014749 |
| DM22     | Methotrexate | 4-amino-4-deoxy-N10-methylpterinoic acid | 4 | RXN-11429 | indole-3-acetoxyhydroximoyl-glutathione | indole-3-acetoxyhydroximoyl-cysteinylglycine | 5014749 |
| DM22     | Methotrexate | 4-amino-4-deoxy-N10-methylpterinoic acid | 5 | RXN-7922 | (2S)-dihydrotricetin (+)-dihydromyricetin | 5014749 |
| DM22     | Methotrexate | 4-amino-4-deoxy-N10-methylpterinoic acid | 6 | RXN-7687 | (2S)-eriodictyol | luteolin | 5014749 |
| DM22     | Methotrexate | 4-amino-4-deoxy-N10-methylpterinoic acid | 7 | RXN-15260 | 6-pyruvoyl tetrahydropterin | 7,8-dihydropterin | 5014749 |
| DM22     | Methotrexate | 4-amino-4-deoxy-N10-methylpterinoic acid | 8 | RXN-9480 | (1'<i>S</i>')-averantin | norsolorinate | 5014749 |
| DM22     | Methotrexate | 4-amino-4-deoxy-N10-methylpterinoic acid | 9 | RXN-14429 | &gamma;-L-glutamyl-S-(hercyn-2-yl)-L-cysteine S-oxide | S-(hercyn-2-yl)-L-cysteine S-oxide | 5014749 |
| DM22     | Methotrexate | 4-amino-4-deoxy-N10-methylpterinoic acid | 10 | RXN-17689 | (1R,6R)-1,2,5,5a,6,7-hexahydrophenezine-1,6-dicarboxylate | (1R,10aS)-1,4,10a-tetrahydrophene-1-carboxylate | 5014749 |
| DM21     | Metronidazole | N-(2-hydroxyethyl)-oxamic acid | 1 | RXN-7587 | 4-imidazolone-5-propanoate | formyl-L-isoglutamine | 430360 |
| DM21     | Metronidazole | N-(2-hydroxyethyl)-oxamic acid | 2 | RXN-15348 | hydrogen sulfide | <i>S</i>/<<i>S</i>>-sulfanylglutathione | Yes | 430360 |
| DM21     | Metronidazole | N-(2-hydroxyethyl)-oxamic acid | 3 | RXN-12867 | hydrogen selenide | glutathioselenol | 430360 |
| No. | Substance 1 | Substance 2 | Substitution | Reaction | Reaction Code | Products 1 | Products 2 | Result | Code |
|-----|-------------|-------------|--------------|----------|---------------|------------|------------|--------|------|
| DM21 | Metronidazole | N-(2-hydroxyethyl)-oxamic acid | N | RXN-12864 | Painter reaction | selenite | selenodiglutathione | Yes | 430360 |
| DM21 | Metronidazole | N-(2-hydroxyethyl)-oxamic acid | 4-amino-2,6-dinitrotoluene | RXN-9751 | 4-amino-2,6-dinitrotoluene | 4-amino-2,6-dinitrotoluene glucoside | 430360 |
| DM21 | Metronidazole | N-(2-hydroxyethyl)-oxamic acid | 2-amino-4,6-dinitrotoluene | RXN-9745 | 2-amino-4,6-dinitrotoluene | 2-amino-4,6-dinitrotoluene glucoside | 430360 |
| DM21 | Metronidazole | N-(2-hydroxyethyl)-oxamic acid | 2-hydroxy-L-tryptophan | RXN-7021 | DIBOA | DIBOA-<i>N</i>-glucosyltransferase | 430360 |
| DM21 | Metronidazole | N-(2-hydroxyethyl)-oxamic acid | phenylacetonitrile oxide | RXN-11420 | phenylacetohydroximoyl-L-glutathione | 430360 |
| DM21 | Metronidazole | N-(2-hydroxyethyl)-oxamic acid | 6-hydroxy-L-tryptophan | RXN-16527 | 6-hydroxy-L-tryptophan | 6-hydroxy-L-tryptophan | 430360 |
| DM21 | Metronidazole | N-(2-hydroxyethyl)-oxamic acid | 5-methylthiopentanal | RXN-11423 | 5-methylthiopentanal | 5-methylthiopentanal | 430360 |
| DM20 | Levodopa | m-tyramine | L-dopa | RXN66-221 | L-dopa | dopamine | 5350345 |
| DM20 | Levodopa | m-tyramine | L-thyroxine | RXN-10612 | L-thyroxine | 3-iodothyronamine | 5350345 |
| DM20 | Levodopa | m-tyramine | 5-hydroxy-L-tryptophan | RXN3DJ-170 | 5-hydroxy-L-tryptophan | serotonin | 5350345 |
| DM20 | Levodopa | m-tyramine | 3,5,3'-triiodo-L-thyronine | RXN-10613 | 3,5,3'-triiodo-L-thyronine | thyronamine | 5350345 |
| DM20 | Levodopa | m-tyramine | 3-sulfinoalanine | SULFINOALA NINE- | 3-sulfinoalanine | hypotaurine | 5350345 |
|   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|
| DM20 | Levodopa | m-tyramine | 6 | 1.97.1.2-RXN | pyrogallol | phloroglucinol |
| DM20 | Levodopa | m-tyramine | 7 | 4.1.1.75-RXN | 5-guanidino-2-oxo-pentanoate | 4-guanidinobutyraldehyde |
| DM20 | Levodopa | m-tyramine | 8 | RXN-7859 | cannabichromenate | cannabichromene |
| DM20 | Levodopa | m-tyramine | 9 | RXN-15062 | 5-<i>trans</i>-O/-&beta;-mycaminosyltylactone | 20-hydroxy-5-<i>trans</i>-mycaminosyltylactone |
| DM20 | Levodopa | m-tyramine | 10 | RXN-7857 | &Delta;<sup>9</sup>-&Delta;<sup>9</sup>-tetrahydrocannabinol | &Delta;<sup>9</sup>-&Delta;<sup>9</sup>-tetrahydrocannabinol |
| DM12 | Prontosil | sulphanilamide | 1 | MCHMBARK-RXN | 5,10-methenyltetrahydrosarcinapterin | 5-formyltetrahydrosarcinapterin |
| DM12 | Prontosil | sulphanilamide | 2 | 3.5.4.27-RXN | 5,10-methenyltetrahydromethanopterin | 5-formyltetrahydromethanopterin |
| DM12 | Prontosil | sulphanilamide | 3 | RXN-11548 | caffeine | 1,3,7-trimethylurate |
| DM12 | Prontosil | sulphanilamide | 4 | RXN-7204 | D-<i>myo</i>-inositol (3,4,6)-trisphosphate | D-<i>myo</i>-inositol (3,4,5,6)-tetrakisphosphate |
| DM12 | Prontosil | sulphanilamide | 5 | 2.7.1.151-RXN | D-<i>myo</i>-inositol (1,4,5)-trisphosphate | D-<i>myo</i>-inositol (1,4,5,6)-tetrakisphosphate |
| DM12 | Prontosil | sulphanilamide | 6 | RXN-15928 | cytosyl-<i>&beta;</i>-D-glucuronate | cytosyl-4'-dehydro-<i>&beta;</i>-D-glucuronate |
| DM12 | Prontosil | sulphanilamide | 7 | RXN-15048 | dTDP-6-deoxy-<i>&alpha;</i>-D-allose | dTDP-4-dehydro-6-deoxy-<i>&alpha;</i>-D-gulose |
| DM12 | Prontosil sulphanilamide | 8 | DTDPEHYR HAMREDUC T-RXN | dTDP-&beta;-L-rhamnose | dTDP-4-dehydro-&beta;-L-rhamnose | Yes | 5173017 |
|---------------------------------------------------------------|-----------------|---------------|--------------------------|----------------------------|--------------------------------|-------|--|------------------|
| DM12 | Prontosil sulphanilamide | 9 | RXN-8955 | GDP-&beta;-L-colitose | GDP-4-dehydro-3,6-dideoxy-&alpha;-D-mannose | 5173017 |
| DM12 | Prontosil sulphanilamide | 10 | RXN-16841 | dTDP-D-ravidosamine | dTDP-4-acetyl-D-ravidosamine | 5173017 |
| DM13 | Risperidone 9-OH-RIS | 1 | RXN-8693 | lupanine | 13-hydroxylupanine | 7512019 |
| DM13 | Risperidone 9-OH-RIS | 2 | RXN-11535 | 3-dehydro-6-deoxoteasterone | 3-dehydro-6-hydroxyteasterone | 7512019 |
| DM13 | Risperidone 9-OH-RIS | 3 | 1.14.13.76-RXN | taxa-4(20),11-dien-5-&alpha;:yl acetate | 10&beta;:-hydroxytaxa-4(20),11-dien-5&alpha;:yl acetate | 7512019 |
| DM13 | Risperidone 9-OH-RIS | 4 | RXN-15065 | phospholipase A2 | 1,2-dipalmitoylphosphatidylcholine | 1,16:0-2-lysophosphatidylcholine | 7512019 |
| DM13 | Risperidone 9-OH-RIS | 5 | RXN-11207 | deguelin | tephrosin | 7512019 |
| DM13 | Risperidone 9-OH-RIS | 6 | RXN66-163 | cotinine | 5'-hydroxyacetate | 7512019 |
| DM13 | Risperidone 9-OH-RIS | 7 | RXN66-163 | cotinine | 5'-hydroxycotinine | 7512019 |
| DM13 | Risperidone 9-OH-RIS | 8 | RXN-15067 | phospholipase A2 | 18:1-2-18:1-lysophosphatidylcholine | 18:1-2-lysophosphatidylcholine | 7512019 |
| DM13 | Risperidone 9-OH-RIS | 9 | RXN66-163 | cotinine | 5'-hydroxycotinine | 7512019 |
| DM10 | Nitrazepam 7-aminonitrazepam | 1 | DM2 | paspalicine | paspalaline | 7512019 |
| DM10 | Nitrazepam 7-aminonitrazepam | 2 | RXN-8833 | 1-chloro-4-nitrobenzene | 1-chloro-4-nitrosobenzene | 9310649 |
| DM10 | Nitrazepam 7-aminonitrazepam | 3 | DM1 | paspalicine | paspalaline | 9310649 |
| DM10 | Nitrazepam 7-aminonitrazepam | 4 | DM7 | paspalicine | paspalaline | 9310649 |
| DM10 | Nitrazepam 7-aminonitrazepam | 5 | DM5 | paspalicine | paspalaline | 9310649 |
| DM10  | Nitrazepam  | 7-aminonitrazepam | 6 | RXN-12130 | nitrous oxide | N<sub>2</sub> | 9310649 |
|-------|-------------|-------------------|---|----------|--------------|-------------|----------|
| DM10  | Nitrazepam  | 7-aminonitrazepam | 7 | RXN-8847 | 2-nitrobenzoate | 2-hydroxylaminobenzoate | 9310649 |
| DM10  | Nitrazepam  | 7-aminonitrazepam | 8 | R364-RXN | 4-nitrobenzoate | 4-hydroxylaminobenzoate | 9310649 |
| DM10  | Nitrazepam  | 7-aminonitrazepam | 9 | RXNQT-4360 | 4-methoxy-3-indolylmethyl glucosinolate aglycone | 4-methoxy-3-indolylmethylisothiocyanate | 9310649 |
| DM11  | Potassium oxonate | 5-azauracil (5-AZU) | 1 | RXN-13867 | 3-amino-4-hydroxybenzaldehyde synthase | 3-amino-4-hydroxybenzoate | 3-amino-4-hydroxybenzaldehyde | 10997934 |
| DM11  | Potassium oxonate | 5-azauracil (5-AZU) | 2 | RXN-12093 | 7-carboxy-7-deazaguanine | preQ<sub>0</sub> | Yes | 10997934 |
| DM11  | Potassium oxonate | 5-azauracil (5-AZU) | 3 | RXN-10930 | holyrine B | 3'-<i>O</i>-demethyl-4'-<i>N</i>-demethyl-staurosporine | 10997934 |
| DM11  | Potassium oxonate | 5-azauracil (5-AZU) | 4 | RXN-15683 | 3-benzyl-3,6-bis(cysteinyl)-6-(hydroxymethyl)-diketopiperazine | 3-benzyl-3,6-dithio-6-(hydroxymethyl)-diketopiperazine | 10997934 |
| DM11  | Potassium oxonate | 5-azauracil (5-AZU) | 5 | RXN-14294 | 3-hexaprenyl-4-amino-5-methoxybenzoate decarboxylase | 3-hexaprenyl-4-amino-5-methoxybenzoate | 2-hexaprenyl-6-methoxyaminobenzene | 10997934 |
| DM11  | Potassium oxonate | 5-azauracil (5-AZU) | 6 | RXN-7858 | cannabidiolate | cannabidiol | 10997934 |
| DM11 | Potassium oxonate | S-azauracil (S-AZU) | 7 | 4.1.1.74-RXN | (indol-3-yl)pyruvate | indole acetaldehyde | 10997934 |
|------|-------------------|---------------------|---|---------------|---------------------|---------------------|------------------|
| DM11 | Potassium oxonate | S-azauracil (S-AZU) | 8 | RXN-3284      | 2,4',7-trihydroxyisoflavone | daidzein          | 10997934 |
| DM11 | Potassium oxonate | S-azauracil (S-AZU) | 9 | RXN-7859      | cannabichromenate | cannabichromene    | 10997934 |
| DM11 | Potassium oxonate | S-azauracil (S-AZU) | 10| RXN-7656      | 2,6,7,4'-tetrahydroxyisoflavone | 6,7,4'-trihydroxyisoflavone | 10997934 |
| DM16 | Sorivudine        | E-5-(2-bromovinyl)uracil | 1 | NICONUCAD ENYLÝTRAN-RXN | &beta;-nicotinate D-ribonucleotide | nicotinate adenine dinucleotide | Yes | 8274153 |
| DM16 | Sorivudine        | E-5-(2-bromovinyl)uracil | 2 | RXN-4541      | <i>cis</i>-zeatin riboside | <i>cis</i>-zeatin | 8274153 |
| DM16 | Sorivudine        | E-5-(2-bromovinyl)uracil | 3 | RXN-8683      | (-)-lariciresinol | (-)-pinoresinol    | 8274153 |
| DM16 | Sorivudine        | E-5-(2-bromovinyl)uracil | 4 | RAUCAFFRIC ÝNE-BETA-GLUCOSIDAS E-RXN | raucaffricine | vomilenine | 8274153 |
| DM16 | Sorivudine        | E-5-(2-bromovinyl)uracil | 5 | RXN-14313      | cyclo-L-tyrosyl-L-tyrosyl | mycocyclosin | 8274153 |
| DM16 | Sorivudine        | E-5-(2-bromovinyl)uracil | 6 | UROGENIIIS YN-RXN | preuroporphyrinogen | uroporphyrinogen-III | 8274153 |
| DM16 | Sorivudine        | E-5-(2-bromovinyl)uracil | 7 | RXN-15506      | 6-methoxypodophyllumodioxygenase 7-glucosidase | 6-methoxypodophyllotoxin 7-glucoside | 6-methoxypodophyllotoxin | 8274153 |
| DM16 | Sorivudine | E-5-(2-bromovinyl)uracil | 8 | RXN-15507 | podophyllotoxin 7-glucoside glucosidase | podophyllotoxin 7-glucoside | podophyllotoxin | 8274153 |
|-------|------------|--------------------------|----|------------|----------------------------------------|--------------------------|----------------|--------|
| DM16 | Sorivudine | E-5-(2-bromovinyl)uracil | 9 | RXN-8719  | 1,2,3,4,6-pentagalloylglucose           | tellimagrandin II       |                |        |
| DM16 | Sorivudine | E-5-(2-bromovinyl)uracil | 10| RXN-17153 | 3-[[2-aminophenyl]amino]-2-oxopropanoate| 3,4-dihydroquinoxaline-2-carboxylate |                |        |
| DM17 | Sulfinpyrazone | Sulfinpyrazone sulfide | 1 | RXN-17166 | triostin A                          | echinomycin              |                | 3630204 |
| DM17 | Sulfinpyrazone | Sulfinpyrazone sulfide | 2 | RXN-9314  | (4S)-reticuline                      | (S)-corytuberine         |                | 3630204 |
| DM17 | Sulfinpyrazone | Sulfinpyrazone sulfide | 3 | RXN-12865 | selenodiglutathione                  | glutathioselenol         |                | 3630204 |
| DM17 | Sulfinpyrazone | Sulfinpyrazone sulfide | 4 | RXN3O-227 | ergosta-5,7,24(28)-trien-3&beta;ol  | ergosta-5,7,22,24(28)-tetraen-3&beta;ol |                | 3630204 |
| DM17 | Sulfinpyrazone | Sulfinpyrazone sulfide | 5 | RXN-16128 | cytochrome P450 dependent oxidoreductase | roquefortine D          | roquefortine C |        |
| DM17 | Sulfinpyrazone | Sulfinpyrazone sulfide | 6 | RXN-13884 | ergosta-5,7-dienol                   | ergosterol               |                | 3630204 |
| DM17 | Sulfinpyrazone | Sulfinpyrazone sulfide | 7 | 2.7.7.51-RXN | adenosine 5'-phosphosulfate | adenosine 5'-phosphoramidate |                | 3630204 |
| DM17 | Sulfinpyrazone | Sulfinpyrazone sulfide | 8 | PHOSPHO-DETHIO-RXN | diethylthiophosphate | diethylphosphate |                | 3630204 |
| DM17 | Sulfinpyrazone | Sulfinpyrazone sulfide | 9 | DM1       | <i>trans</i>-zeatin riboside triphosphate | <i>trans</i>-zeatin riboside diphosphate |                | 3630204 |
| DM14 | SN-38G | SN-38 | 1  | RXN-16479 | 13-dihydrocarminomycin | carminomycin | 21051639 |
|------|--------|-------|----|-----------|------------------------|-------------|----------|
| DM14 | SN-38G | SN-38 | 2  | RXN-13632 | spinosyn 3'-<i>O</i>-<i>O</i>-methylrhamnosyl tetracyclic spinosyn pseudoaglycone | 2',3'-<i>O</i>-methyl-rhamnosyl tetracyclic spinosyn pseudoaglycone | 21051639 |
| DM14 | SN-38G | SN-38 | 3  | RXN-14830 | dihydrodaunorubicin | daunorubicin | 21051639 |
| DM14 | SN-38G | SN-38 | 4  | RXN-16183 | cytoglobosin D oxidase | cytoglobosin D | 21051639 |
| DM14 | SN-38G | SN-38 | 5  | RXN-12924 | erythromycin D | erythromycin B | 21051639 |
| DM14 | SN-38G | SN-38 | 6  | RXN-13843 | 6-hydroxy 3,7,4'-trimethylquercetagetin 6-methyltransferase | 3,7,4'-tetramethylquercetagetin | 21051639 |
| DM14 | SN-38G | SN-38 | 7  | RXN-13841 | 2'-hydroxy 3,7,4'-methylquercetin 3'-methyltransferase | 2'-hydroxy 3,7,4'-tetramethylquercetin | 21051639 |
| DM14 | SN-38G | SN-38 | 8  | RXN-13855 | 3,5,7-trimethylquercetagetin 4'-methyltransferase | 3,6,7,4'-tetramethylquercetin | 21051639 |
| DM14 | SN-38G | SN-38 | 9  | RXN-13923 | 3,7,3'-trimethylmyricetin | 3,7,3'-trimethylmyricetin | 21051639 |
| DM14 | SN-38G | SN-38 | 10 | RXN-13849 | 2'-hydroxy 3,6,7,4'-tetramethylquercetin | 2'-hydroxy 3,6,7,3',4'-pentamethylquercetagetin | 21051639 |
|------|--------|-------|----|-----------|------------------------------------------|-----------------------------------------------|--------|
| DM15 | Sodium picosulfate | 4,4'-dihydroxydiphenyl-(2 pyridyl)-methane | 1 | RXN-624 | 2'-hydroxybiphenyl-2-sulfinate | 2-hydroxybiphenyl | 1507649 |
| DM15 | Sodium picosulfate | 4,4'-dihydroxydiphenyl-(2 pyridyl)-methane | 2 | CHOLINE-SULFATASE-RXN | choline sulfate | choline | 1507649 |
| DM15 | Sodium picosulfate | 4,4'-dihydroxydiphenyl-(2 pyridyl)-methane | 3 | RXN-12027 | benzylglucosinolate aglycone | benzylisothiocyanate | 1507649 |
| DM15 | Sodium picosulfate | 4,4'-dihydroxydiphenyl-(2 pyridyl)-methane | 4 | RXNQT-4360 | 4-methoxy-3-indolylmethyl glucosinolate aglycone | 4-methoxy-3-indolylmethylisothiocyanate | 1507649 |
| DM15 | Sodium picosulfate | 4,4'-dihydroxydiphenyl-(2 pyridyl)-methane | 5 | RXNQT-4350 | indolylmethyl glucosinolate aglycone | indolylmethylisothiocyanate | 1507649 |
| DM15 | Sodium picosulfate | 4,4'-dihydroxydiphenyl-(2 pyridyl)-methane | 6 | TSDOSALCAL-RXN | 4-toluenesulfonate | 4-methylcatechol | 1507649 |
| DM15   | Sodium picosulfate | 4,4'-dihydroxydiphenyl-(2 pyridyl)-methane | 7  | 4- SULFOBENZOATE-34-DIOXYGENASE-RXN | 4-sulfobenzoate | protocatechuate | 1507649 |
|--------|--------------------|---------------------------------------------|----|-------------------------------------|----------------|----------------|---------|
| DM15   | Sodium picosulfate | 4,4'-dihydroxydiphenyl-(2 pyridyl)-methane | 8  | BSDOSALCAL-RXN                      | benzenesulfonate | catechol        | 1507649 |
| DM15   | Sodium picosulfate | 4,4'-dihydroxydiphenyl-(2 pyridyl)-methane | 9  | RXN-12026                            | benzylglucosinolate aglycone | benzyl thiocyanate | 1507649 |
| DM15   | Sodium picosulfate | 4,4'-dihydroxydiphenyl-(2 pyridyl)-methane | 10 | HISTIDPHOS-RXN                       | L-histidinol-phosphate | histidinol      | Yes     | 1507649 |
| DM18   | Zonisamide         | 2-Sulfamoylacetylphenol                     | 1  | RXN-14995                            | 5-phospho-α-D-ribose 1,2-cyclic phosphate | D-ribofuranose 2,5-bisphosphate | 9231340 |
| DM18   | Zonisamide         | 2-Sulfamoylacetylphenol                     | 2  | RXN0-6710                            | phosphoribosyl 1,2-cyclic phosphodiesterase | 5-phospho-α-D-ribose 1,2-cyclic phosphate | &alpha;D-ribose 1,5-bisphosphate | Yes | 9231340 |
| DM18   | Zonisamide         | 2-Sulfamoylacetylphenol                     | 3  | RXN-8936                             | (-)-medicarp | (-)-vestitol | 9231340 |
| DM18   | Zonisamide         | 2-Sulfamoylacetylphenol                     | 4  | RXN-16255                            | medicarp reductase | (-)-medicarp | 7,2'-dihydroxy-4'-methoxyisoflavan | 9231340 |
| DM18   | Zonisamide         | 2-Sulfamoylacetylphenol                     | 5  | RXN-15836                            | &alpha; cyclopiazonate | 2-oxocyclopiazonate | 9231340 |
| DM18   | Zonisamide         | 2-Sulfamoylacetylphenol                     | 6  | 1.14.13.56-RXN                      | dihydrosanguinarine | 10-hydroxydihydrosanguinarine | 9231340 |
| DM18 | Zonisamide | 2-Sulfamoylacetylphenol | 7 | RXN-13817 | sesamin hydroxylase | (+)-sesamin | (+)-sesaminol | 9231340 |
| DM18 | Zonisamide | 2-Sulfamoylacetylphenol | 8 | RXN-16110 |  | notoamide E | notoamide C | 9231340 |
| DM18 | Zonisamide | 2-Sulfamoylacetylphenol | 9 | RXN-12356 | 7,8-dihydronopterin 2',3'-cyclic phosphate phosphodiesterase | 7,8-dihydronopterin 2',3'-cyclic phosphate | 7,8-dihydronopterin 3'-phosphate | 9231340 |
| DM18 | Zonisamide | 2-Sulfamoylacetylphenol | 10 | RXN-6561 | 2-oxosuccinamate | 2-hydroxysuccinamate | 9231340 |
| DM19 | Levodopa | m-hydroxyphenylacetic acid | 1 | RXN-10610 | L-thyroxine | tetraiodothyroacetate | 5350345 |
| DM19 | Levodopa | m-hydroxyphenylacetic acid | 2 | RXN-10611 | 3,5,3'-triiodo-L-thyronine | 3,3',5'-triiodothyroacetate | 5350345 |
| DM19 | Levodopa | m-hydroxyphenylacetic acid | 3 | RXN-10871 | 3'-<i>O</i>-methyldopa | 3-methoxy-4-hydroxyphenylpyruvate | 5350345 |
| DM19 | Levodopa | m-hydroxyphenylacetic acid | 4 | 2.6.1.49-RXN | L-dopa | 3,4-dihydroxyphenylpyruvate | 5350345 |
| DM19 | Levodopa | m-hydroxyphenylacetic acid | 5 | 1.97.1.2-RXN | pyrogallol | phloroglucinol | 5350345 |
| DM19 | Levodopa | m-hydroxyphenylacetic acid | 6 | RXN-9759 | S-methyl-L-methionine | 3-dimethylsulfiniopropionaldehyde | 5350345 |
|   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|
| DM19 Levodopa m-hydroxyphenylacetic acid 7 PREPHENATE E-TRANSAMINE-RXN L-arogenate prephenate 5350345 |
| DM19 Levodopa m-hydroxyphenylacetic acid 8 RXN-12010 1-amino-2-phosphorylethylphosphate 1-oxo-2-phosphorylethylphosphate 5350345 |
| DM19 Levodopa m-hydroxyphenylacetic acid 9 RXN-14730 2-amino-2-deoxy-D-gluconate 6-phosphate 2-dehydro-3-deoxy-D-gluconate 6-phosphate 5350345 |
| DM19 Levodopa m-hydroxyphenylacetic acid 10 RXN-12732 dimethylselenopropionate-amine 3-dimethylselenopropionoic acid 5350345 |
| DM1 BILR 355 BILR 402 1 DM7 22393121 |
| DM1 BILR 355 BILR 402 2 DMS 22393121 |
| DM1 BILR 355 BILR 402 3 RXN-16233 2-[hydroperoxy-(4-glucosyl-hydroxyphenyl)methyl]-6-hydroxy-1-benzofuran-3-one 6-hydroxy-2-[4-glucosyl-hydroxyphenyl]methyl]-1-benzofuran-3-one 22393121 |
| DM1 BILR 355 BILR 402 4 RXN-16871 (5E)-3-imino-4-sulfanyl-5-(sulfanylmethylidene)pyrroloidin-2-one dithioholothin 22393121 |
| DM1 BILR 355 BILR 402 5 RXN 3.5.4.27-5,10-methenyltetrahydromethanopterin 5-formyltetrahydromethanopterin 22393121 |
| DM1 BILR 355 BILR 402 6 MCHMBARK-RXN 5,10-methenyltetrahydrodrosarcinaptein 5-formyltetrahydrodrosarcinapterin 22393121 |
| DM1 BILR 355 BILR 402 7 RXN-17166 triostin A echinomycin 22393121 |
| DM1  | BILR 355 | RXN-16575 | previridicatuxin | viridicatuxin | 22393121 |
|------|----------|------------|------------------|--------------|----------|
| DM1  | BILR 355 | RXN-8880  | &gamma;-solanine | &beta;-solanine | 22393121 |
| DM1  | BILR 355 | RXN-9314  | (<i>5</i>&lt;i&gt;)reticuline | (S)-corytuberine | 22393121 |
| DM2  | Clonazepam | 7-aminoclonazepam | 1 | DM10 | 6506755 |
| DM2  | Clonazepam | 7-aminoclonazepam | 2 | RXN-8833 | 1-chloro-4-nitrobenzene | 1-chloro-4-nitrosobenzene | 6506755 |
| DM2  | Clonazepam | 7-aminoclonazepam | 3 | DM1  | 6506755 |
| DM2  | Clonazepam | 7-aminoclonazepam | 4 | DM7  | 6506755 |
| DM2  | Clonazepam | 7-aminoclonazepam | 5 | DM5  | 6506755 |
| DM2  | Clonazepam | 7-aminoclonazepam | 6 | RXN-12130 | nitrous oxide | N&lt;sub&gt;2&lt;/sub&gt; | 6506755 |
| DM2  | Clonazepam | 7-aminoclonazepam | 7 | RXN-8847 | 2-nitrobenzoate | 2-hydroxylaminobenzoate | 6506755 |
| DM2  | Clonazepam | 7-aminoclonazepam | 8 | R364-RXN | 4-nitrobenzoate | 4-hydroxylaminobenzoate | 6506755 |
| DM2  | Clonazepam | 7-aminoclonazepam | 9 | RXN-8828 | 4-nitrotoluene | 4-hydroxylaminotoluene | 6506755 |
| DM2  | Clonazepam | 7-aminoclonazepam | 10 | RXN-8815 | nitrobenzene | hydroxylaminobenzene | 6506755 |
| DM3  | Digoxin   | dihydrodigoxin | 1 | RXN-13384 | premithramycin B lactone | mithramycin DK | 7266632 |
| DM3  | Digoxin   | dihydrodigoxin | 2 | RXN-9794 | 7&alpha;12&alpha;-dihydroxycholest-4-en-3-one | 7&alpha;12&alpha;-dihydroxy-5&beta;-cholestan-3-one | 7266632 |
| DM3  | Digoxin   | dihydrodigoxin | 3 | RXN-9840 | 7&alpha;-hydroxycholest-4-en-3-one | 7&alpha;-hydroxy-5&beta;-cholestan-3-one | 7266632 |
| DM3  | Digoxin   | dihydrodigoxin | 4 | RXN-17033 | isotrichotriol | trichotriol | 7266632 |
| DM3  | Digoxin   | dihydrodigoxin | 5 | RXN-16092 | andilesin B | andilesin C | 7266632 |
| DM3  | Digoxin   | dihydrodigoxin | 6 | RXN-15641 | 7,8-dihydroberberine | (R)-canadine | 7266632 |
| DM3 | Digoxin | dihydridigoxin | 7 | RXN-12943 | dTDP-2,6-dideoxy-D-glycero-hex-2-enos-4-uloose | dTDP-3,4-didehydro-2,6-dideoxy-&alpha;-D-glucose | 7266632 |
|-----|---------|----------------|---|-----------|-----------------------------------------------|-----------------------------------------------|---------|
| DM3 | Digoxin | dihydridigoxin | 8 | RXN-9891 | 2,5-dichloromaleylacetate | 5-chloromaleylacetate | 7266632 |
| DM3 | Digoxin | dihydridigoxin | 9 | RXN-15960 | 20,21-diprenylerpendole I oxidase | lolitriol | 7266632 |
| DM3 | Digoxin | dihydridigoxin | 10 | RXN-13382 | premithramycin B | premithramycin B lactone | 7266632 |
| DM4 | Eltrombopag | SB-611855 | 1 | RXN-8846 | 2-hydroxylaminobenzoate | 3-hydroxyanthranilate | 21646438 |
| DM4 | Eltrombopag | SB-611855 | 2 | RXN-15187 | 2-formylaminobenzaldehyde | O-aminobenzaldehyde | 21646438 |
| DM4 | Eltrombopag | SB-611855 | 3 | 1.5.1.11-RXN | D-octopine | L-arginine | 21646438 |
| DM4 | Eltrombopag | SB-611855 | 4 | RXN-7933 | \(<i>N</i>-acetyl-L-citrulline | L-citrulline | 21646438 |
| DM4 | Eltrombopag | SB-611855 | 5 | RXN-11066 | melatonin | 5-methoxytryptamine | 21646438 |
| DM4 | Eltrombopag | SB-611855 | 6 | RXN-16871 | (SE)-3-imino-4-sulfanyl-5-(sulfamethylylidene)pyrrolidin-2-one | dithioholothin | 21646438 |
| DM4 | Eltrombopag | SB-611855 | 7 | ARYLFORMAMIDASE-RXN | \(<i>N</i>-formylkynurenine | L-kynurenine | 21646438 |
| DM4 | Eltrombopag | SB-611855 | 8 | RXN-22 | canavaninosuccinate | L-canavanine | 21646438 |
|   |   |   |   |   |
|---|---|---|---|---|
| DM4 | Eltrombopag | SB-611855 | 9 | 1.14.11.26-RXN | deacetoxycephalosporin C | deacetylcephalosporin-C | 21646438 |
| DM4 | Eltrombopag | SB-611855 | 10 | RXN-16305 | O-[3-nitro-5-(oxidonitroso)-4-oxocyclohex-2-en-1-ylidenenitroso]oxida nidolate | 2,4,6-trinitrophenol | 21646438 |
| DM5 | Indicine N-oxide | Indicine | 1 | DM7 |   |   | 476682 |
| DM5 | Indicine N-oxide | Indicine | 2 | DM1 |   |   | 476682 |
| DM5 | Indicine N-oxide | Indicine | 3 | RXN-16233 | 2-[hydroperoxy-(4-glicosyl-hydroxyphenyl)meth yl]-6-hydroxy-1-benzofuran-3-one | 6-hydroxy-2-[(4-glicosyl- hydroxyphenyl)methyl]-1-benzofuran-3-one | 476682 |
| DM5 | Indicine N-oxide | Indicine | 4 | RXN-16871 | (5E)-3-imino-4-sulfanyl-5-(sulfanyl methylidene)pyrroldin-2-one | dithioholothin | 476682 |
| DM5 | Indicine N-oxide | Indicine | 5 | RXN-16208 | gliotoxin | dithiogliotoxin | 476682 |
| DM5 | Indicine N-oxide | Indicine | 6 | 3.5.4.27-RXN | 5,10-methenyltetrahydro methanopterin | 5-formyl-tetrahydrothromappert in | 476682 |
| DM5 | Indicine N-oxide | Indicine | 7 | MCHMBARK-RXN | 5,10-methenyl-tetrahydroaracinapte rin | 5-formyl-tetrahydroaracinapte rin | 476682 |
| DM5 | Indicine N-oxide | Indicine | 8 | RXN-12865 | selenodiglutathione | glutathioselenol | 476682 |
| DM5  | Indicine N-oxide | Indicine   | 9 | RXN-17166 | triostin A | echinomycin | 476682 |
|------|------------------|------------|---|-----------|------------|-------------|--------|
| DM5  | Indicine N-oxide | Indicine   | 10| RXN-8880  | &gamma;-,solanine | &beta;-,solanine | 476682 |
| DM6  | Levamisole       | Levametabol I | 1 | RXN-16141 | roquefortine C | N1-hydroxy-roquefortine C | 1949905 |
| DM6  | Levamisole       | Levametabol I | 2 | RXN-16144 | glandicoline A | glandicoline B | 1949905 |
| DM6  | Levamisole       | Levametabol I | 3 | RXN-16589 | deoxynortryptoquialane | tryptoquialanone | 1949905 |
| DM6  | Levamisole       | Levametabol I | 4 | 1.14.13.73-RXN | tabersonine | 16-hydroxytabersonine | 1949905 |
| DM6  | Levamisole       | Levametabol I | 5 | RXN-10971 | phytate | 1D-<i>myo</i>-inositol 3-diphosphate | 1949905 |
| DM6  | Levamisole       | Levametabol I | 6 | RXN-1405  | tryptamine | <i>N</i>-hydroxyl-tryptamine | 1949905 |
| DM6  | Levamisole       | Levametabol I | 7 | RXN-15079 | CMP-5'-3'-aminopropylphosphate | CMP-5'-<i>N</i>-hydroxy-3-aminopropylphosphonate | 1949905 |
| DM6  | Levamisole       | Levametabol I | 8 | RXN-12451 | (+)-pinoresinol | (-)-lariciresinol | 1949905 |
| DM6  | Levamisole       | Levametabol I | 9 | 1.14.13.101-RXN | senecionine | senecionine N-oxide | 1949905 |
| DM6  | Levamisole       | Levametabol I | 10| RXN0-6710 | phosphoribosyl 1,2-cyclic phosphodiesterase | 5-phospho-<i>&alpha;</i>-D-ribose 1,2-cyclic phosphate | 1949905 |
| DM7  | Loperamide N-oxide | loperamide | 1 | DM1 | 7628301 |
| DM7  | Loperamide N-oxide | loperamide | 2 | DM5 | 7628301 |
|     | Name                  | Chemical Name                | Value | Description                                                                 | Value | Description                       | Value | Description                       | Value | Description                       | Value | Description                       | Value | Description                       | Value | Description                       |
|-----|-----------------------|-----------------------------|-------|-----------------------------------------------------------------------------|-------|-----------------------------------|-------|-----------------------------------|-------|-----------------------------------|-------|-----------------------------------|-------|-----------------------------------|-------|-----------------------------------|
| DM7 | Loperamide N-oxide    | loperamide                  | 3     | RXN-16233 2-[hydroperoxy-(4-glucosyl-hydroxyphenyl)methyl]-6-hydroxy-1-benzofuran-3-one | 6-hydroxy-2-[[4-glucosyl-hydroxyphenyl)methyl]-1-benzofuran-3-one | 7628301 |
| DM7 | Loperamide N-oxide    | loperamide                  | 4     | RXN-16871 (5E)-3-imino-4-sulfanyl-5-(sulfanyl methylidene) pyrrolidin-2-one | dithioholothin | 7628301 |
| DM7 | Loperamide N-oxide    | loperamide                  | 5     | RXN-MCHMBARK-RXN 5,10-methenyl-tetrahydroxosarcinapte-rin | 5-formyl-tetrahydroxosarcinapterin | 7628301 |
| DM7 | Loperamide N-oxide    | loperamide                  | 6     | RXN-3.5.4.27-RXN 5,10-methenyl tetrahydroxosarcinapte-rin | 5-formyl-tetrahydroxosarcinapterin | 7628301 |
| DM7 | Loperamide N-oxide    | loperamide                  | 7     | RXN-17166 triostin A echinomycin | 7628301 |
| DM7 | Loperamide N-oxide    | loperamide                  | 8     | RXN-16208 gliotoxin dithiolgliotoxin | 7628301 |
| DM7 | Loperamide N-oxide    | loperamide                  | 9     | RXN-12865 selenodiglutathione glutathioselenol | 7628301 |
| DM7 | Loperamide N-oxide    | loperamide                  | 10    | RXN-8982 coniceine reductase &gamma;-coniceine coniline | 7628301 |
| DM8 | Lovastatin             | lovastatin acid             | 1     | RXN-886 gibberellin A<sub>44</sub> (closed lactone form) | gibberellin A<sub>98</sub> | 24947972 |
| DM8 | Lovastatin             | lovastatin acid             | 2     | RXN1F-166 gibberellin A<sub>4</sub> | gibberellin A<sub>1</sub> | 24947972 |
| DM8 | Lovastatin             | lovastatin acid             | 3     | RXN-15308 2-nonaprenylphenol 2-[[<i>all-trans</i>]nonaprenyl]benzene-1,4-diol | 24947972 |
| DM8 | Lovastatin | lovastatin acid | 4 | RXN-17053 | 3,4,15-triacetylnivalenol 3-esterase | 3,4,15-triacetylnivalenol | 4,15-diacetylnivalenol | 24947972 |
|-----|------------|----------------|----|----------|------------------------------------|--------------------------|---------------------|----------|
| DM8 | Lovastatin | lovastatin acid | 5 | RXN-17350 | (-)-4'-demethyl-deoxypodophyllotoxin | (-)-4'-demethyl-epipodophyllotoxin | 24947972 |
| DM8 | Lovastatin | lovastatin acid | 6 | RXN-6561 | 2-oxosuccinaminate | 2-hydroxysuccinaminate | 24947972 |
| DM8 | Lovastatin | lovastatin acid | 7 | RXN-14655 | gardenin B | nevadensin | 24947972 |
| DM8 | Lovastatin | lovastatin acid | 8 | RXN-9829 | vitamin D<sub>3</sub> | calcidiol | 24947972 |
| DM8 | Lovastatin | lovastatin acid | 9 | CHOLESTER OL-7-ALPHA-MONOXYGENASE-RXN | cholesterol | 7α,α-hydroxycholesterol | 24947972 |
| DM8 | Lovastatin | lovastatin acid | 10 | RXN-17253 | epoxypheophorbide | red chlorophyll catabolite | 24947972 |
| DM9 | Neoprontosil | sulphanilamide | 1 | DM12 | | | 5173017 |
| DM9 | Neoprontosil | sulphanilamide | 2 | RXN-14546 | decarbamoylnovobiocin | novobiocin | 5173017 |
| DM9 | Neoprontosil | sulphanilamide | 3 | RXN-15641 | 7,8-dihydroberberine | (R)-canadine | 5173017 |
| DM9 | Neoprontosil | sulphanilamide | 4 | RXN-17053 | IMPCYCLOHYDROLASE-RXN | IMP | 5173017 |
| DM9 | Neoprontosil | sulphanilamide | 5 | RXN-15641 | 1.14.18.2-RXN | CMP-<i>N</i>-acetyl-β-neuraminate | 5173017 |
| DM9 | Neoprontosil | sulphanilamide | 6 | RXN-17169 | thiocoraline dithiol | thiocoraline | 5173017 |
| DM9 | Neoprontosil | sulphanilamide | 7 | RXN-9445 | 3'-keto-3'-deoxyATP | 3'-amino-3'-deoxyATP | 5173017 |
|   | Neoprontosil | sulphamamide | 8 | RXN-11073 | <i>N</i><sup>1</sup>-acetyl-<i>N</i><sup>2</sup>-formyl-5-methoxykynuramine | <i>N</i>-acetyl-5-methoxykynurenine | 5173017 |
|---|-------------|--------------|---|-----------|-----------------------------------------------------------------|-------------------------------------------------|---------|
|   | Neoprontosil | sulphamamide | 9 | RXN-8827 | 2-hydroxy-5-nitro-6-oxohepta-2,4-dienoate | 2-hydroxy-5-nitropenta-2,4-dienoate | 5173017 |
|   | Neoprontosil | sulphamamide | 10| RXN0-5227 | L-alanyl-γ-D-glutamyl-<i>meso</i>-2,6-diaminopimeloyl-D-alanine | L-alanyl-γ-D-glutamyl-<i>meso</i>-diaminopimelate | Yes | 5173017 |
Table S8. Structural formulas of the drug metabolism reactions and selected bacterial reactions from Table S7. Structural formulas for drug reactions are from PubChem\textsuperscript{1}. Each drug reaction is followed by the two nearest neighbors found in MetaCyc for bacteria, and their structural formulas from MetaCyc\textsuperscript{2}.

| Reaction code | Reaction substrate | Reaction product |
|---------------|--------------------|------------------|
| DM23         | ![Diclofenac glucuronide](image1) | ![diclofenac](image2) |
| RXN-1795     | 6-deoxy-6-sulfo-D-glucono-1,5-lactone + H$_2$O    | 6-deoxy-6-sulfo-D-gluconate + H$^+$ |
| RXN-9030     | (25)-2-amino-4-deoxy-chorismate + H$_2$O | (5S,6S)-6-amino-5-hydroxycyclohexa-1,3-diene-1-carboxylate + pyruvate |
| Reaction code | Reaction substrate | Reaction product |
|---------------|--------------------|------------------|
| DM22          | (2S)-2-amino-4-deoxy-chorismate | (5S,6S)-6-amino-5-hydroxycyclohexa-1,3-diene-1-carboxylate |
|               | ![DM22 Reaction](image1) | ![DM22 Product](image2) |
| RXN-17961     | Methotrexate       | 4-amino-4-deoxy-N10-methylpteroic acid |
|               | ![RXN-17961 Reaction](image3) | ![RXN-17961 Product](image4) |
|               | isopenicillin N    | 6-aminopenicillanate |
|               | ![isopenicillin N](image5) | ![6-aminopenicillanate](image6) |
| Reaction code | Reaction substrate | Reaction product |
|---------------|--------------------|------------------|
| RXN-11665    | ![Image](image1.png) | ![Image](image2.png) |
|              | 2-(glycylcystein-5-yl)-2-(1H-indol-3-yl)-acetonitrile | 2-(cystein-5-yl)-2-(1H-indol-3-yl)-acetonitrile |
|              | indole-3-acetonitrile-gamma-glutamylcysteine conjugate | indole-3-acetonitrile-cysteine conjugate |
| DM21         | ![Image](image3.png) | ![Image](image4.png) |
|              | Metronidazole      | N-(2-hydroxyethyl)-oxamic acid |
| RXN-7587     | ![Image](image5.png) | ![Image](image6.png) |
|              | 4-imidazolone-5-propanoate | formyl-L-isoglutamine |
|              | 4-imidazolone-5-propanoate | formyl-L-isoglutamine |
| Reaction code | Reaction substrate | Reaction product |
|---------------|--------------------|------------------|
| RXN-15348    | [Diagram of hydrogen sulfide and glutathione disulfide] | [Diagram of S-sulfanylglutathione and glutathione] |
| DM20         | hydrogen sulfide   | S-sulfanylglutathione |
|              | Levodopa           | m-tyramine        |
| RXN66-221    | [Diagram of L-dopa and H⁺] | [Diagram of dopamine and CO₂] |
| Reaction code | Reaction substrate | Reaction product |
|---------------|--------------------|------------------|
| RXN-10512     | L-dopa             | dopamine         |
|               | ![L-dopa structure](image1.png) | ![dopamine structure](image2.png) |
| DM12          | L-thyroxine        | 3-iodothyronamine|
|               | ![L-thyroxine structure](image3.png) | ![3-iodothyronamine structure](image4.png) |
|               | Prontosil          | sulphanilamide   |
|               | ![Prontosil structure](image5.png) | ![sulphanilamide structure](image6.png) |
| Reaction code | Reaction substrate | Reaction product |
|---------------|--------------------|------------------|
| MCHMBARK-RXN | 5,10-methenyl-tetrahydrosarcinapterin | 5-formyl-tetrahydrosarcinapterin |

5,10-methenyl-tetrahydrosarcinapterin $+ \text{H}_2\text{O} \rightarrow 5$-formyl-tetrahydrosarcinapterin
| Reaction code | Reaction substrate | Reaction product |
|---------------|--------------------|------------------|
| 3.5.4.27-RXN | ![5,10-methenyltetrahydromethanopterin](image) + H₂O | ![5-formyl-tetrahydroscarcinapterin](image) + H⁺ |
| DM13         | ![5,10-methenyltetrahydromethanopterin](image) | ![5-formyl-tetrahydromethanopterin](image) |
|              | Risperidone        | 9-OH-RIS         |
| Reaction code | Reaction substrate | Reaction product |
|---------------|-------------------|-----------------|
| RXN-893 | ![lupanine](image) | ![13-hydroxylupanine](image) |
| | lupanine | 13-hydroxylupanine |
| RXN-11535 | ![3-dehydro-6-deoxoteasterone](image) | ![3-dehydro-6-hydroxyteasterone](image) |
| | 3-dehydro-6-deoxoteasterone | 3-dehydro-6-hydroxyteasterone |
| DM10 | ![image](image) | ![image](image) |
| Reaction code | Reaction substrate | Reaction product |
|---------------|--------------------|-----------------|
| RXN-8833     | Nitrazepam         | 7-aminonitrazepam |
|              | ![Nitrazepam](image1) + NADPH + H+ + H+ | ![7-aminonitrazepam](image2) + NADP+ + H2O |
|              | 1-chloro-4-nitrobenzene | 1-chloro-4-hydroxylaminobenzene |
| RXN-1213     | 1-chloro-4-nitrobenzene | 1-chloro-4-nitrosobenzene |
|              | 2 a reduced c-type cytochrome + nitrous oxide + 2 H | 2 an oxidized c-type cytochrome + N2 + H2O |
|              | nitrous oxide | N2 |
| DM11         | Potassium oxonate | 5-azauracil (5-AZU) |
| Reaction code | Reaction substrate | Reaction product |
|---------------|--------------------|------------------|
| RXN:13867     | ![3-amino-4-hydroxybenzoate](image) + ATP + NAD(P)H + H+ | ![3-amino-4-hydroxybenzaldehyde](image) + ATP + NAD(P)H + diphosphate |

**Reaction substrate:**
- 3-amino-4-hydroxybenzoate
- ATP
- NAD(P)H
- H+

**Reaction product:**
- 3-amino-4-hydroxybenzaldehyde
- ATP
- NAD(P)H
- diphosphate
| Reaction code | Reaction substrate | Reaction product |
|---------------|--------------------|------------------|
| RXN-12093    | ![7-carboxy-7-deazaguanine](image1) + ![ATP](image2) | ![preQ0](image3) + ![H+](image4) + ![H2O](image5) |
|  | ![7-carboxy-7-deazaguanine](image1) | ![preQ0](image3) |
| DM16         | ![Sorivudine](image6) | ![E-5-(2-bromovinyl)uracil](image7) |

**Explanation:**

- **RXN-12093:**
  - Reaction substrate: 7-carboxy-7-deazaguanine + ATP
  - Reaction product: preQ0 + H+ + H2O

- **DM16:**
  - Sorivudine
  - E-5-(2-bromovinyl)uracil
| Reaction code          | Reaction substrate                                                                 | Reaction product                                                                                            |
|------------------------|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|
| NICONUCADENYLYL-RXN   | ![Reaction substrate](image1)                                                   | ![Reaction product](image2)                                                                                     |
|                        | beta-nicotinate D-ribonucleotide + ATP                                             | nicotinate adenine dinucleotide + diphosphate                                                                |
| RXN-4541               | ![Reaction substrate](image3)                                                   | ![Reaction product](image4)                                                                                     |
|                        | cis-zeatin riboside                                                              | cis-zeatin                                                                                                   |
| Reaction code | Reaction substrate | Reaction product |
|---------------|--------------------|------------------|
| DM17          | ![Sulfinpyrazone](image1) | ![Sulfinpyrazone sulfide](image2) |

Sulfinpyrazone

Sulfinpyrazone sulfide
| Reaction code | Reaction substrate | Reaction product |
|---------------|--------------------|------------------|
| RXN-17166    | ![Triostin A](image1.png) + ![S-Adenosyl-L-Methionine](image2.png) | ![Echinomycin](image3.png) + ![S-Adenosyl-L-Homocysteine](image4.png) + H^+ |
| Reaction code | Reaction substrate | Reaction product |
|---------------|--------------------|------------------|
| RXN-9314      | triostin A         | echinomycin      |

\[
\text{Reaction substrate: } \text{triostin A} + \text{oxygen} \rightarrow \text{echinomycin} + 2\text{H}_2\text{O} + \text{an oxidized [NADPH-hemoprotein reductase]}
\]

\[
\text{Reaction product: } \text{echinomycin} + 2\text{H}_2\text{O} + \text{an oxidized [NADPH-hemoprotein reductase]}
\]

\[
\text{(S)-reticuline} + \text{oxygen} \rightarrow \text{(S)-corytuberine} + 2\text{H}_2\text{O} + \text{a reduced [NADPH-hemoprotein reductase]}
\]
| Reaction code | Reaction substrate | Reaction product |
|---------------|--------------------|------------------|
| DM14          | ![Reaction substrate](image1) | ![Reaction product](image2) |
| SN-38G        | ![Reaction substrate](image3) | ![Reaction product](image4) |
| RXN-16479     | ![Reaction substrate](image5) | ![Reaction product](image6) |
| Reaction code | Reaction substrate | Reaction product |
|---------------|--------------------|------------------|
| RXN-13632     | 13-dihydrocarminomycin | carminomycin     |

**Reaction**

- **RXN-13632**

**Reaction substrate**
- 2',O-methyl-rhamnosyl tetracyclic spinosyn pseudoaglycone
- S-adenosyl-L-methionine

**Reaction product**
- 2',3',O-methyl-rhamnosyl tetracyclic spinosyn pseudoaglycone
- S-adenosyl-L-homocysteine

\[ + H^+ \]
| Reactio n code | Reaction substrate | Reaction product |
|---------------|--------------------|------------------|
| DM15          | Sodium picosulfate | 4,4'-dihydroxydiphenyl-(2 pyridyl)-methane |
| RXN-624       | 2'-hydroxybiphenyl-2-sulfinate | 2'-hydroxybiphenyl |
| CHOLINE-SULFATASE-RXN | choline sulfate | sulfate + choline + H^+ |
| Reaction code | Reaction substrate                  | Reaction product                  |
|--------------|------------------------------------|-----------------------------------|
| DM18         | choline sulfate                     | choline                           |
| Zonisamide   | 2-Sulfamoylacetylphenol             |                                   |
| RXN-14995    | 5-phospho-α-D-ribose 1,2-cyclic phosphate | D-ribofuranose 2,5-bisphosphate   |
| RXN0-6710    | 5-phospho-α-D-ribose 1,2-cyclic phosphate | α-D-ribose 1,5-bisphosphate      |
| Reaction code | Reaction substrate                                      | Reaction product                                      |
|---------------|--------------------------------------------------------|-------------------------------------------------------|
| DM19          | 5-phospho-alpha-D-ribose 1,2-cyclic phosphate           | alpha-D-ribose 1,5-bisphosphate                       |
|               | ![Chemical Structure](attachment)                      | ![Chemical Structure](attachment)                    |
|               | Levodopa                                               | m-hydroxyphenylacetic acid                            |
|               | ![Chemical Structure](attachment)                      | ![Chemical Structure](attachment)                    |
| RXN-10610     | ![Chemical Structure](attachment)                      | ![Chemical Structure](attachment)                    |
|               | L-thyroxine                                            | tetraiodothyroacetate                                 |
|               | ![Chemical Structure](attachment)                      | ![Chemical Structure](attachment)                    |
| Reaction code | Reaction substrate | Reaction product |
|---------------|--------------------|------------------|
| RXN-10611     | ![3,5,3’-triiodo-L-thyronine](image) | ![3,3’,5-triiodothyroacetate](image) |
|               | 3,5,3’-triiodo-L-thyronine | 3,3’,5-triiodothyroacetate |
| DMI           | ![BILR 355](image) | ![BILR 402](image) |
|               | BILR 355            | BILR 402          |
| Reaction code | Reaction substrate | Reaction product |
|---------------|-------------------|------------------|
| RXN-16233     | ![Reaction substrate](image1) \[2-[\text{hydroperoxy-(4-glucosyl-hydroxyphenyl)methyl}]\-6-hydroxy-1-benzofuran-3-one\] | ![Reaction product](image2) \[6-hydroxy-2-[[4-glucosyl-hydroxyphenyl]methyl]-1-benzofuran-3-one\] |
| RXN-16871     | ![Reaction substrate](image3) \[(5E)-3-imino-4-sulfanyl-5-(sulfanylmethylene)pyrrolidin-2-one\] | ![Reaction product](image4) \[(5E)-3-imino-4-sulfanyl-5-(sulfanylmethylene)pyrrolidin-2-one\] |
| Reaction code | Reaction substrate | Reaction product |
|---------------|--------------------|------------------|
| DM2           | ![Clonazepam](Image) | ![7-aminoclonazepam](Image) |
|               | Clonazepam         | 7-aminoclonazepam|
| Rxn-8833      | ![1-chloro-4-nitrobenzene](Image) + NADPH + H⁺ + H⁺ | ![1-chloro-4-hydroxylaminobenzene](Image) + NAD⁺ + H₂O |
|               | 1-chloro-4-nitrobenzene | 1-chloro-4-nitrosobenzene |
| Rxn-1213      | 2 a reduced c-type cytochrome + nitrous oxide + 2 H⁺ | 2 an oxidized c-type cytochrome + N₂ + H₂O |
|               | nitrous oxide      | N₂               |
| Reaction code | Reaction substrate | Reaction product |
|---------------|-------------------|------------------|
| DM3          | ![Substrate](image1) | ![Product](image2) |
| Digoxin     | ![Substrate](image3) | ![Product](image4) |
| RXN-13384   | ![Substrate](image5) | ![Product](image6) |
|             | premithramycin B lactone | mithramycin DK |
|             | ![Reaction](image7)     | ![Reaction](image8) |
|             | ![H2O](image9)          | ![CO2](image10)  |
| Reaction code | Reaction substrate | Reaction product |
|---------------|--------------------|------------------|
| RXN-9794      | premithramycin B lactone | mithramycin DK |
|               | ![Reaction 1](image1.png) + NADPH + H⁺ | ![Reaction 2](image2.png) + NADP⁺ |
| DM4           | 7α,12α-dihydroxycholest-4-en-3-one | 7α,12α-dihydroxy-5β-cholestan-3-one |
|               | ![Structure 1](image3.png) | ![Structure 2](image4.png) |
|               | Eltrombopag | SB-611855 |
| Reaction code | Reaction substrate | Reaction product |
|---------------|--------------------|------------------|
| RXN-8846     | 2-hydroxylaminobenzoate | 3-hydroxyanthranilate |
|               | 2-hydroxylaminobenzoate | 3-hydroxyanthranilate |
| RXN-15187    | 2-formylaminobenzaldehyde | O-aminobenzaldehyde |
|               | 2-formylaminobenzaldehyde | O-aminobenzaldehyde |
| DM5           | Indicine N-oxide | Indicine |

**Notes:**
- **RXN-8846**: Reaction substrate: 2-hydroxylaminobenzoate, Reaction product: 3-hydroxyanthranilate
- **RXN-15187**: Reaction substrate: 2-formylaminobenzaldehyde, Reaction product: O-aminobenzaldehyde
- **DM5**: Reaction substrate: Indicine N-oxide, Reaction product: Indicine
| Reacti\n| Reaction substrate | Reaction product |
|---|---|---|
| RXN-16233 | 2-[hydroperoxy-(4-glucosyl-hydroxyphenyl)methyl]-6-hydroxy-1-benzofuran-3-one | 6-hydroxy-2-[[4-glucosyl-hydroxyphenyl)methyl]-1-benzofuran-3-one |
| | [hydroperoxy-(4-glucosyl-hydroxyphenyl)methyl]-6-hydroxy-1-benzofuran-3-one | | |
| | a reduced electron acceptor | + an oxidized electron acceptor + H₂O |
| RXN-16871 | (5E)-3-imino-4-sulfanyl-5-(sulfanylmethylidene)pyrrolidin-2-one | dithioholothin |
| | (5E)-3-imino-4-sulfanyl-5-(sulfanylmethylidene)pyrrolidin-2-one | |
| Reaction code | Reaction substrate | Reaction product |
|---------------|--------------------|------------------|
| DM6          | ![Reaction substrate](image1) | ![Reaction product](image2) |
| Levamisole   | ![Substrate](image3) | ![Product](image4) |

**DM6**

**Levamisole**

**Levametabol I**

**RXN-1641**

**roquefortine C**

**roquefortine C**

+ NAD(P)H + H⁺ + oxygen

+ NAD(P)⁺

= **N1-hydroxy-roquefortine C**

= **H₂O**
| Reaction code | Reaction substrate | Reaction product |
|---------------|--------------------|------------------|
| RXN-16144     | ![glandicoline A](image1) + NAD(P)H + H⁺ + oxygen → ![glandicoline B](image2) | ![glandicoline B](image2) + NAD(P)⁺ + H₂O → ![glandicoline A](image1) |
|               | glandicoline A     | glandicoline B   |
| DM7           | ![Loperamide N-oxide](image3) | ![loperamide](image4) |
|               | Loperamide N-oxide | loperamide       |
| Reaction code | Reaction substrate | Reaction product |
|---------------|--------------------|------------------|
| RXN-16233    | ![Image](#)       | ![Image](#)     |
| 2-[hydroperoxy-(4-glucosyl-hydroxyphenyl)methyl]-6-hydroxy-1-benzofuran-3-one | a reduced electron acceptor | ![Image](#) + H₂O + an oxidized electron acceptor |
|               | ![Image](#)       | ![Image](#)     |
| RXN-16871    | ![Image](#)       | ![Image](#)     |
| (5E)-3-imino-4-sulfanyl-5-(sulfanylmethylidene)pyrrolidin-2-one | ![Image](#)       | dithioholothin |
|               | ![Image](#)       | ![Image](#)     |
| Reaction code | Reaction substrate | Reaction product |
|---------------|--------------------|------------------|
| **DM8**       | ![Lovastatin](image) | ![Lovastatin acid](image) |
| **RXN-886**  | ![Gibberellin A44](image) | ![Gibberellin A98](image) |
|               | **gibberellin A44 (closed lactone form)** | **gibberellin A98** |
|               | + ![2-oxoglutarate](image) + **2 H** + **oxygen** | + ![succinate](image) + ![CO2](image) |
| Reaction code | Reaction substrate | Reaction product |
|---------------|--------------------|------------------|
| RXN1F-166     | ![gibberellin A₄](image) + NADPH + oxygen + H⁺ | ![gibberellin A₁](image) + NADP⁺ + H₂O |
| DM9           | ![gibberellin A₄](image) | ![gibberellin A₁](image) |
|               | Neoprontosil       | sulphaniamide    |
| Reaction code | Reaction substrate | Reaction product |
|---------------|--------------------|------------------|
| RXN-14546    | ![decarbamoylnovobiocin](image1) + ![carbamoyl phosphate](image2) | ![novobiocin](image3) + ![phosphate](image4) |

- **decarbamoylnovobiocin**
- **carbamoyl phosphate**
- **novobiocin**
- **phosphate**

| RXN-15641    | ![7,8-dihydroberberine](image5) + ![NADPH + H⁺](image6) | ![7,8-(R)-canadine](image7) + ![NADP⁺](image8) |

- **7,8-dihydroberberine**
- **(R)-canadine**
Table S9. Mean pairwise Tanimoto similarity for molecule clusters. Average similarity calculated over all unique pairs of molecule MACCS keys in a given cluster.

| Cluster | Mean   | Std Dev  |
|---------|--------|----------|
| 0       | 0.514936742 | 0.099999732 |
| 1       | 0.74995862  | 0.107787985 |
| 2       | 0.72611274  | 0.103071569 |
| 3       | 0.737282815 | 0.107167814 |
| 4       | 0.828734752 | 0.085936172 |
| 5       | 0.788959902 | 0.099480222 |
| 6       | 0.586124613 | 0.126909153 |
| 7       | 0.429317499 | 0.117147568 |
| 8       | 0.478037365 | 0.142873839 |
| 9       | 0.482843026 | 0.122480929 |
| 10      | 0.643864351 | 0.133824457 |
| 11      | 0.652284696 | 0.124792357 |
| 12      | 0.452173711 | 0.122813934 |
| 13      | 0.465279598 | 0.123727337 |
| 14      | 0.753385276 | 0.105873983 |
| 15      | 0.755311755 | 0.118692767 |
| 16      | 0.48290433  | 0.125188295 |
| 17      | 0.948635072 | 0.041521352 |
| 18      | 0.605085112 | 0.107824501 |
| 19      | 0.553011732 | 0.145484771 |
| 20      | 0.390650776 | 0.127600312 |
| 21      | 0.857105827 | 0.118561958 |
| 22      | 0.956005432 | 0.027358026 |
| 23      | 0.113554343 | 0.135154803 |
| 24      | 0.783984521 | 0.117187773 |
|  |  |  |  |
|---|---|---|---|
| 25 | 0.838980289 | 0.101223704 |
| 26 | 0.672051503 | 0.127756537 |
| 27 | 0.527247995 | 0.183851608 |
| 28 | 0.761860026 | 0.097303999 |
| 29 | 0.674835072 | 0.111054671 |
| 30 | 0.656880406 | 0.120603219 |
| 31 | 0.505779673 | 0.1491663 |
| 32 | 0.496911753 | 0.149126531 |
| 33 | 0.518492119 | 0.14520645 |
| 34 | 0.505648193 | 0.139376824 |
| 35 | 0.462252474 | 0.127395571 |
| 36 | 0.450184954 | 0.149972792 |
| 37 | 0.603942447 | 0.124288908 |
| 38 | 0.484151781 | 0.126335664 |
| 39 | 0.637659531 | 0.102646643 |
| 40 | 0.636553134 | 0.112359839 |

¹ National Center for Biotechnology Information. The PubChem Project. [https://pubchem.ncbi.nlm.nih.gov/](https://pubchem.ncbi.nlm.nih.gov/). National Library of Medicine, National Institutes of Health, Department of Health and Human Services, USA. (2017).

² SRI International. MetaCyc Metabolic Pathway Database. [https://metacyc.org/](https://metacyc.org/). Menlo Park, CA, USA. (2016).