**Supplementary Table 1** The upstream regulator drugs and natural products with opposite molecular signatures identified using iPathwayGuide sorted based on Z score.

| Chemical Name               | cDE_n | cDE  | cAll  | pv_comb_n_fdr | pv_n_fdr | pv_zscore_fdr | zscore   |
|-----------------------------|-------|------|-------|---------------|----------|---------------|----------|
| Doxorubicin                 | 63    | 79   | 4588  | 0.000769      | 1        | 0.000407      | -4.71986 |
| potassium chromate(VI)      | 43    | 51   | 2029  | 9.37E-06      | 0.137023 | 0.000407      | -4.71495 |
| Methylprednisolone          | 21    | 21   | 48    | 9.65E-14      | 7.41E-24 | 0.000446      | -4.58258 |
| Antirheumatic Agents        | 35    | 40   | 2332  | 0.001029      | 1        | 0.000446      | -4.52904 |
| (+)-JQ1 compound            | 52    | 63   | 1954  | 2.07E-08      | 0.0002   | 0.000446      | -4.52027 |
| Prednisolone                | 18    | 18   | 63    | 2.23E-13      | 1.18E-16 | 0.001225      | -4.24264 |
| dichrotophos                | 34    | 41   | 2782  | 0.005795      | 1        | 0.001225      | -4.21669 |
| Azathioprine                | 23    | 24   | 418   | 1.47E-09      | 3.72E-06 | 0.001225      | -4.2      |
| Gold Sodium Thiomalate      | 20    | 21   | 47    | 2.26E-13      | 1.31E-22 | 0.001423      | -4.14614 |
| jinfukang                   | 45    | 59   | 2710  | 0.002421      | 0.672866 | 0.002113      | -4.03586 |
| Urethane                    | 33    | 42   | 2850  | 0.037143      | 1        | 0.007165      | -3.70328 |
| perfluorooctane sulfonic acid| 16    | 18   | 482   | 0.000733      | 0.073249 | 0.025713      | -3.29983 |
| tofacitinib                 | 10    | 10   | 17    | 5.84E-12      | 1.01E-12 | 0.0371        | -3.16228 |
| Diclofenac                  | 15    | 15   | 55    | 5.84E-12      | 2.06E-13 | 0.0371        | -3.15296 |
| Methotrexate                | 28    | 33   | 896   | 0.000138      | 0.004062 | 0.07071       | -2.91999 |


| Disease       | Drug or Natural Product | Number of associated targets | Therapeutic Area     | All targets                                                                 |
|---------------|-------------------------|------------------------------|----------------------|----------------------------------------------------------------------------|
| COVID-19      | Prednisolone            | 40                           | infectious disease   | DPP4 JAK1 NR3C1 JAK2 AR PTGS1 CHRNA4 IL6 PDE10A SLC5A2 FLT3 MAPK14 TYK2 OPRM1 KIT PPARG KDR ABL1 NR3C2 ESR2 CNR1 ADORA3 MPEG1 PGR ADAM17 CD38 MTOR MPO EGFR SLC6A3 MAPK1 ALK NOS2 SLC5A1 BRD4 MAPK3 ADK LCK RORA SHBG |
| COVID-19      | Withaferin-A            | 36                           | infectious disease   | NR3C1 PTGS2 AR HMGCR PTGS1 GSK3B F10 PDE4D GSK3A IMPDH1 PDE3A PDE3B PDE10A MAPK14 JAK3 NR3C2 IKBKB ADORA2A PGR REN PARP1 ERBB2 CCR1 MAPK1 ALK HDAC3 PRKCB BRAF IL6ST CXCR3 MAPK8 IARS1 BRD4 BCL2L1 MAPK3 MDM2 |