**Table S2.** Substituting the gatekeeper residue of PKG with a large glutamine residue results in a loss of potency of class 1, pyrimidine-linked compounds. Data shown are from a single experiment other than where the standard deviation from the mean of two independent experiments is indicated in parentheses after the mean EC50.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Compound** | **Structure** | **Enzyme inhibition IC50 (µM)** | **Selectivity** | **Parasite inhibition EC50 (µM)** | **Ratio** |
| **CDPK1** | **PKG** | **PKG T618Q** | **PKG T618Q/****PKG** | **3D7** | **3D7** **PKG T618Q** | **3D7PKG T618Q/****3D7** |
| 7 (Cpd D) |  | 0.013 | 0.484 | 15.51 | 32 | 0.427 (0.045) | 0.477 (0.180) | 1 |
| 20 (Cpd E) |  | 0.008 | 0.012 | 15.33 | 1325 | 0.210 | 0.386 | 2 |
| 22 |  | 0.074 | >1 | 37.53 | <38 | 0.215 | 0.303 | 1 |
| 28 |  | 0.012 | 0.003 | 31.69 | 12100 | 0.059 | 0.640 | 11 |
| 36 (Cpd A) |  | 0.008 | 0.002 | 10.96 | 5641 | 0.034 (0.006) | 0.901 (0.483) | 27 |
| 38 |  | 0.008 | 0.004 | 43.52 | 12187 | 0.073 | 0.859 | 12 |
| 39 (Cpd B) |  | 0.009 | 0.002 | 25.54 | 16520 | 0.034 | 0.982 | 29 |
| 41 (Cpd C) |  | 0.011 | 0.013 | 12.70 | 957 | 0.042 (0.018) | 0.923 (0.226) | 22 |
| 42 |  | 0.081 | nd | nd | — | 0.836 | 1.231 | 1 |
| 43 |  | 0.088 | nd | nd | — | 0.079 | 0.093 | 1 |
| 44 |  | 0.065 | nd | nd | — | 0.236 | 0.477 | 2 |
| 1 |  | 0.010 | 0.109 | 6.236 | 57 |  |  |  |
| 2 |  | 0.026 | 0.069 | 12.810 | 186 |  |  |  |
| 8 |  | 0.017 | 0.237 | 64.64 | 272 |  |  |  |
| 9 |  | 0.034 | 0.048 | 16.84 | 349 |  |  |  |
| 11 |  | 0.015 | 0.256 | 256.30 | 1000 |  |  |  |
| 13 |  | 0.014 | 0.162 | 3.68 | 23 |  |  |  |
| 15 |  | 0.020 | 0.249 | 51.27 | 206 |  |  |  |
| 16 |  | 0.011 | 0.088 | 10.61 | 121 |  |  |  |
| 17 |  | 0.009 | 0.118 | 12.06 | 102 |  |  |  |
| 18 |  | 0.016 | 0.404 | 15.67 | 39 |  |  |  |
| 21 |  | 0.010 | 0.087 | 3.77 | 44 |  |  |  |
| 23 |  | 0.014 | 0.160 | 4.76 | 30 |  |  |  |
| 24 |  | 0.011 | 0.062 | 1.25 | 20 |  |  |  |
| 25 |  | 0.013 | 0.054 | 9.93 | 182 |  |  |  |
| 26 |  | 0.009 | 0.020 | 3.28 | 161 |  |  |  |
| 27 |  | 0.017 | 0.101 | 10.01 | 99 |  |  |  |
| 29 |  | 0.018 | 0.093 | 0.88 | 10 |  |
| 31 |  | 0.093 | 0.287 | 5.95 | 21 |  |
| 32 |  | 0.010 | 0.007 | 6.16 | 931 |  |  |  |
| 33 |  | 0.013 | 0.005 | 10.04 | 2071 |  |  |  |
| 35 |  | 0.017 | 0.050 | 528.20 | 10653 |  |  |  |
| 37 |  | 0.016 | 0.044 | 2.10 | 48 |  |  |  |
| 40 |  | 0.014 | 0.034 | 4.04 | 120 |  |  |  |