**Table S1.** **Mouse plasma protein binding profile of MU380 and SCH900776.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Compound** | % bound | Mean fu | SD |
| MU380 | 87.1 | 0.129 | 0.00679 |
| SCH900776 | 66.0 | 0.340 | 0.00885 |

**Table S2.** **IC50 determination of main P450 cytochrome isoforms in human liver microsomes.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Compound** | CYP2C9  IC50 (μmol/L) | CYP2C19  IC50 (μmol/L) | CYP3A4  IC50 (μmol/L) | CYP2D6  IC50 (μmol/L) | CYP1A  IC50 (μmol/L) |
| MU380 | > 25 | > 25 | > 25 | 13.9 | > 25 |
| SCH900776 | > 25 | > 25 | > 25 | 19.4 | > 25 |

**Table S3. A)** **Evaluation of MU380 and SCH900776 disappearance with time in the presence of human liver microsomes. B) Human microsomal stability intrinsic clearance data for MU380 and SCH900776.**

**A**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Compound** | **Compound Remaining (% of 0 min)** | | | | | |
| 0 min | 5 min | 15 min | 30 min | 45 min | Control |
| MU380 | 100.0 | 93.4 | 85.4 | 82.9 | 76.4 | 91.7 |
| SCH900776 | 100.0 | 99.1 | 86.3 | 87.4 | 88.6 | 99.4 |

**B**

|  |  |  |  |
| --- | --- | --- | --- |
| **Compound** | **CLint (µL/min/mg protein)** | **SE CLint** | **t1/2 (min)** |
| MU380 | 10.09 | 1.76 | 127 |
| SCH900776 | 5.69 | 3.03 | 244 |

**Table S4. Statistical analysis of dose response curves for cell lines indicated in the Figure 3A.**

**MU380 SCH900776**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **A2780** | EC50 | 95% LB | 95% UB | P-value | HU conc\* |  | EC50 | 95% LB | 95% UB | P-value | HU conc\* |
|  |  |  |  |  |  |  |  |  |  |  |  |
| HU (mmol/L) | 0.237 | 0.197 | 0.286 |  | **0.237** |  | 0.237 | 0.197 | 0.286 |  | **0.237** |
| CHK1i (4 μmol/L) + HU | 0.118 | 0.102 | 0.138 | <0.0001 | **0.134** |  | 0.148 | 0.128 | 0.172 | <0.0001 | **0.163** |
| CHK1i (2 μmol/L) + HU | 0.163 | 0.142 | 0.187 | <0.0001 | 0.169 |  | 0.196 | 0.163 | 0.236 | 0.052 | 0.204 |
| CHK1i (1 μmol/L) + HU | 0.159 | 0.144 | 0.177 | <0.0001 | 0.160 |  | 0.174 | 0.147 | 0.205 | 0.000 | 0.180 |
| CHK1i (0.5 μmol/L) + HU | 0.155 | 0.134 | 0.178 | <0.0001 | 0.191 |  | 0.192 | 0.162 | 0.228 | 0.014 | 0.240 |
| CHK1i (0.25 μmol/L) + HU | 0.194 | 0.160 | 0.235 | 0.031 | 0.216 |  | 0.195 | 0.158 | 0.240 | 0.050 | 0.239 |
| CHK1i (0.125 μmol/L) + HU | 0.202 | 0.168 | 0.242 | 0.067 | 0.220 |  | 0.250 | 0.213 | 0.293 | 0.523 | 0.274 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **A2780cis** | EC50 | 95% LB | 95% UB | P-value | HU conc\* |  | EC50 | 95% LB | 95% UB | P-value | HU conc\* |
|  |  |  |  |  |  |  |  |  |  |  |  |
| HU (mmol/L) | 0.138 | 0.083 | 0.229 |  | **0.138** |  | 0.138 | 0.083 | 0.229 |  | **0.138** |
| CHK1i (4 μmol/L) + HU | 0.058 | 0.025 | 0.138 | <0.0001 | 0.071 |  | 0.067 | 0.035 | 0.129 | <0.0001 | 0.081 |
| CHK1i (2 μmol/L) + HU | 0.055 | 0.017 | 0.175 | <0.0001 | 0.067 |  | 0.063 | 0.032 | 0.127 | <0.0001 | 0.077 |
| CHK1i (1 μmol/L) + HU | 0.049 | 0.005 | 0.469 | <0.0001 | **0.060** |  | 0.060 | 0.024 | 0.148 | <0.0001 | **0.074** |
| CHK1i (0.5 μmol/L) + HU | 0.067 | 0.029 | 0.155 | <0.0001 | 0.083 |  | 0.094 | 0.069 | 0.128 | <0.0001 | 0.113 |
| CHK1i (0.25 μmol/L) + HU | 0.080 | 0.046 | 0.141 | 0.000 | 0.095 |  | 0.109 | 0.077 | 0.153 | 0.072 | 0.138 |
| CHK1i (0.125 μmol/L) + HU | 0.084 | 0.042 | 0.168 | 0.008 | 0.110 |  | 0.115 | 0.076 | 0.173 | 0.280 | 0.155 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **A549** | EC50 | 95% LB | 95% UB | P-value | HU conc\* |  | EC50 | 95% LB | 95% UB | P-value | HU conc\* |
|  |  |  |  |  |  |  |  |  |  |  |  |
| HU (mmol/L) | 0.498 | 0.435 | 0.570 |  | **0.498** |  | 0.498 | 0.435 | 0.570 |  | **0.498** |
| CHK1i (4 μmol/L) + HU | 0.211 | 0.150 | 0.297 | <0.0001 | 0.255 |  | 0.248 | 0.217 | 0.285 | <0.0001 | **0.297** |
| CHK1i (2 μmol/L) + HU | 0.233 | 0.190 | 0.287 | <0.0001 | **0.251** |  | 0.273 | 0.246 | 0.303 | <0.0001 | 0.308 |
| CHK1i (1 μmol/L) + HU | 0.258 | 0.231 | 0.287 | <0.0001 | 0.257 |  | 0.291 | 0.259 | 0.328 | <0.0001 | 0.322 |
| CHK1i (0.5 μmol/L) + HU | 0.307 | 0.276 | 0.341 | <0.0001 | 0.361 |  | 0.337 | 0.302 | 0.375 | <0.0001 | 0.427 |
| CHK1i (0.25 μmol/L) + HU | 0.376 | 0.331 | 0.427 | 0.000 | 0.420 |  | 0.456 | 0.394 | 0.527 | 0.226 | 0.539 |
| CHK1i (0.125 μmol/L) + HU | 0.367 | 0.336 | 0.400 | <0.0001 | 0.391 |  | 0.456 | 0.401 | 0.519 | 0.172 | 0.557 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **BPH-1** | EC50 | 95% LB | 95% UB | P-value | HU conc\* |  | EC50 | 95% LB | 95% UB | P-value | HU conc\* |
|  |  |  |  |  |  |  |  |  |  |  |  |
| HU (mmol/L) | 0.716 | 0.454 | 1.129 |  | **0.716** |  | 0.716 | 0.454 | 1.129 |  | **0.716** |
| CHK1i (4 μmol/L) + HU | 0.435 | 0.405 | 0.468 | <0.0001 | 0.422 |  | 0.528 | 0.473 | 0.590 | <0.0001 | 0.480 |
| CHK1i (2 μmol/L) + HU | 0.333 | 0.299 | 0.370 | <0.0001 | **0.328** |  | 0.447 | 0.391 | 0.511 | <0.0001 | **0.423** |
| CHK1i (1 μmol/L) + HU | 0.417 | 0.376 | 0.462 | <0.0001 | 0.388 |  | 0.524 | 0.450 | 0.611 | <0.0001 | 0.483 |
| CHK1i (0.5 μmol/L) + HU | 0.574 | 0.511 | 0.644 | <0.0001 | 0.568 |  | 0.609 | 0.540 | 0.687 | 0.005 | 0.664 |
| CHK1i (0.25 μmol/L) + HU | 0.439 | 0.334 | 0.576 | <0.0001 | 0.536 |  | 0.621 | 0.531 | 0.726 | 0.054 | 0.776 |
| CHK1i (0.125 μmol/L) + HU | 0.580 | 0.488 | 0.689 | 0.011 | 0.591 |  | 0.686 | 0.553 | 0.849 | 0.672 | 0.845 |

LB (UB) = lower (upper) bound of a 95% confidence interval for EC50, P-value = comparison of the best-fit model for HU+CHK1i with the model with constraining the EC50 to equal the EC50 of the model for HU alone \* concentration of HU in combination HU+CHK1i with the same effect (EC50) as HU alone

**Table S4 cont. MU380 SCH900776**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **BPH-1 CAFTD04** | IC50 | 95% LB | 95% UB | P-value | HU conc\* |  | IC50 | 95% LB | 95% UB | P-value | HU conc\* |
|  |  |  |  |  |  |  |  |  |  |  |  |
| HU (mmol/L) | 0.206 | 0.025 | 1.687 |  | **0.206** |  | 0.206 | 0.025 | 1.687 |  | **0.206** |
| CHK1i (4 μmol/L) + HU | 0.165 | 0.083 | 0.327 | 0.163 | 0.167 |  | 0.205 | 0.150 | 0.280 | 0.954 | **0.208** |
| CHK1i (2 μmol/L) + HU | 0.171 | 0.084 | 0.345 | 0.238 | 0.172 |  | 0.229 | 0.185 | 0.283 | 0.258 | 0.219 |
| CHK1i (1 μmol/L) + HU | 0.172 | 0.092 | 0.319 | 0.460 | **0.149** |  | 0.359 | 0.315 | 0.410 | <0.0001 | 0.265 |
| CHK1i (0.5 μmol/L) + HU | 0.341 | 0.246 | 0.474 | 0.000 | 0.275 |  | 0.355 | 0.273 | 0.462 | <0.0001 | 0.362 |
| CHK1i (0.25 μmol/L) + HU | 0.298 | 0.249 | 0.356 | <0.0001 | 0.280 |  | 0.326 | 0.229 | 0.465 | <0.0001 | 0.343 |
| CHK1i (0.125 μmol/L) + HU | 0.444 | 0.347 | 0.567 | <0.0001 | 0.344 |  | 0.431 | 0.331 | 0.561 | <0.0001 | 0.440 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **CAKI-2** | IC50 | 95% LB | 95% UB | P-value | HU conc\* |  | IC50 | 95% LB | 95% UB | P-value | HU conc\* |
|  |  |  |  |  |  |  |  |  |  |  |  |
| HU (mmol/L) | 1.959 | 1.248 | 3.075 |  | **1.959** |  | 1.959 | 1.248 | 3.075 |  | **1.959** |
| CHK1i (4 μmol/L) + HU | 0.228 | 0.132 | 0.395 | 0.000 | 0.333 |  | 0.380 | 0.292 | 0.495 | 0.000 | 0.710 |
| CHK1i (2 μmol/L) + HU | 0.312 | 0.251 | 0.388 | 0.000 | 0.377 |  | 0.419 | 0.331 | 0.531 | 0.000 | **0.606** |
| CHK1i (1 μmol/L) + HU | 0.276 | 0.181 | 0.421 | 0.000 | **0.274** |  | 0.425 | 0.285 | 0.634 | 0.000 | 0.515 |
| CHK1i (0.5 μmol/L) + HU | 0.462 | 0.376 | 0.568 | 0.000 | 0.734 |  | 0.553 | 0.382 | 0.802 | 0.000 | 1.594 |
| CHK1i (0.25 μmol/L) + HU | 0.642 | 0.506 | 0.814 | 0.000 | 1.061 |  | 0.967 | 0.766 | 1.222 | <0.0001 | 1.899 |
| CHK1i (0.125 μmol/L) + HU | 0.995 | 0.771 | 1.286 | <0.0001 | 1.312 |  | 1.081 | 0.837 | 1.397 | <0.0001 | 1.505 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **DU145** | IC50 | 95% LB | 95% UB | P-value | HU conc\* |  | IC50 | 95% LB | 95% UB | P-value | HU conc\* |
|  |  |  |  |  |  |  |  |  |  |  |  |
| HU (mmol/L) | 0.637 | 0.557 | 0.728 |  | **0.637** |  | 0.637 | 0.557 | 0.728 |  | **0.637** |
| CHK1i (4 μmol/L) + HU | 0.082 | 0.005 | 1.463 | <0.0001 | **0.123** |  | 0.130 | 0.046 | 0.367 | <0.0001 | **0.188** |
| CHK1i (2 μmol/L) + HU | 0.138 | 0.052 | 0.364 | <0.0001 | 0.150 |  | 0.177 | 0.100 | 0.315 | <0.0001 | 0.246 |
| CHK1i (1 μmol/L) + HU | 0.102 | 0.037 | 0.287 | <0.0001 | 0.164 |  | 0.266 | 0.215 | 0.329 | <0.0001 | 0.297 |
| CHK1i (0.5 μmol/L) + HU | 0.221 | 0.139 | 0.352 | <0.0001 | 0.336 |  | 0.288 | 0.206 | 0.404 | <0.0001 | 0.449 |
| CHK1i (0.25 μmol/L) + HU | 0.293 | 0.215 | 0.398 | <0.0001 | 0.372 |  | 0.377 | 0.320 | 0.443 | <0.0001 | 0.504 |
| CHK1i (0.125 μmol/L) + HU | 0.429 | 0.361 | 0.510 | <0.0001 | 0.486 |  | 0.455 | 0.387 | 0.534 | <0.0001 | 0.542 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **H441** | IC50 | 95% LB | 95% UB | P-value | HU conc\* |  | IC50 | 95% LB | 95% UB | P-value | HU conc\* |
|  |  |  |  |  |  |  |  |  |  |  |  |
| HU (mmol/L) | 0.085 | 0 | 270078 |  | **0.085** |  | 0.085 | 0.000 | 270078 |  | **0.085** |
| CHK1i (4 μmol/L) + HU | 0.174 | 0.050 | 0.614 | <0.0001 | 0.246 |  | 0.175 | 0.038 | 0.813 | <0.0001 | 0.292 |
| CHK1i (2 μmol/L) + HU | 0.167 | 0.015 | 1.888 | 0.114 | 0.187 |  | 0.173 | 0.003 | 8.796 | 0.000 | 0.283 |
| CHK1i (1 μmol/L) + HU | 0.194 | 0.011 | 3.376 | 0.193 | **0.167** |  | 0.142 | 0.000 | 365.600 | 0.136 | **0.188** |
| CHK1i (0.5 μmol/L) + HU | 0.324 | 0.060 | 1.741 | <0.0001 | 0.501 |  | 0.483 | 0.122 | 1.917 | <0.0001 | 0.740 |
| CHK1i (0.25 μmol/L) + HU | 0.295 | 0.046 | 1.899 | <0.0001 | 0.485 |  | 0.321 | 0.005 | 19.010 | 0.000 | 0.560 |
| CHK1i (0.125 μmol/L) + HU | 0.176 | 0.001 | 21.000 | 0.000 | 0.245 |  | 0.203 | 0.000 | 877.700 | 0.208 | 0.300 |

LB (UB) = lower (upper) bound of a 95% confidence interval for EC50

P-value = comparison of the best-fit model for HU+CHK1i with the model with constraining the EC50 to equal the EC50 of the model for HU alone

\* concentration of HU in combination HU+CHK1i with the same effect (EC50) as HU alone

**Table S4 cont. MU380 SCH900776**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **HCT-116 p53 -/-** | EC50 | 95% LB | 95% UB | P-value | HU conc\* |  | EC50 | 95% LB | 95% UB | P-value | HU conc\* |
|  |  |  |  |  |  |  |  |  |  |  |  |
| HU (mmol/L) | 1.348 | 0.998 | 1.822 |  | **1.348** |  | 1.348 | 0.998 | 1.822 |  | **1.348** |
| CHK1i (4 μmol/L) + HU | 0.552 | 0.500 | 0.610 | <0.0001 | **0.620** |  | 0.693 | 0.615 | 0.782 | <0.0001 | **0.873** |
| CHK1i (2 μmol/L) + HU | 0.585 | 0.497 | 0.688 | <0.0001 | 0.690 |  | 0.658 | 0.466 | 0.929 | <0.0001 | 1.001 |
| CHK1i (1 μmol/L) + HU | 0.757 | 0.587 | 0.975 | 0.000 | 0.860 |  | 0.972 | 0.764 | 1.237 | 0.017 | 1.106 |
| CHK1i (0.5 μmol/L) + HU | 0.839 | 0.735 | 0.957 | <0.0001 | 1.102 |  | 0.965 | 0.779 | 1.195 | 0.004 | 1.424 |
| CHK1i (0.25 μmol/L) + HU | 0.953 | 0.659 | 1.378 | 0.065 | 1.469 |  | 1.169 | 0.768 | 1.779 | 0.502 | 1.812 |
| CHK1i (0.125 μmol/L) + HU | 1.341 | 0.950 | 1.892 | 0.975 | 1.664 |  | 1.324 | 0.877 | 1.997 | 0.929 | 2.007 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **HCT-116 p53 +/+** | EC50 | 95% LB | 95% UB | P-value | HU conc\* |  | EC50 | 95% LB | 95% UB | P-value | HU conc\* |
|  |  |  |  |  |  |  |  |  |  |  |  |
| HU (mmol/L) | 1.577 | 1.337 | 1.860 |  | **1.577** |  | 1.577 | 1.337 | 1.860 |  | **1.577** |
| CHK1i (4 μmol/L) + HU | 0.404 | 0.258 | 0.634 | 0.000 | **0.498** |  | 0.662 | 0.538 | 0.814 | <0.0001 | **0.783** |
| CHK1i (2 μmol/L) + HU | 0.571 | 0.466 | 0.700 | <0.0001 | 0.644 |  | 0.730 | 0.596 | 0.894 | <0.0001 | 0.902 |
| CHK1i (1 μmol/L) + HU | 0.575 | 0.517 | 0.639 | <0.0001 | 0.681 |  | 0.673 | 0.607 | 0.747 | <0.0001 | 0.812 |
| CHK1i (0.5 μmol/L) + HU | 0.809 | 0.675 | 0.969 | <0.0001 | 1.000 |  | 0.737 | 0.666 | 0.816 | <0.0001 | 0.951 |
| CHK1i (0.25 μmol/L) + HU | 0.953 | 0.804 | 1.131 | <0.0001 | 1.233 |  | 0.959 | 0.835 | 1.101 | <0.0001 | 1.361 |
| CHK1i (0.125 μmol/L) + HU | 0.935 | 0.800 | 1.092 | <0.0001 | 1.208 |  | 0.944 | 0.829 | 1.076 | <0.0001 | 1.357 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **HCT-116 PTEN -/-** |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
| HU (mmol/L) | 1.656 | 1.401 | 1.957 |  | **1.656** |  | 1.656 | 1.401 | 1.957 |  | **1.656** |
| CHK1i (4 μmol/L) + HU | 0.636 | 0.573 | 0.707 | <0.0001 | 0.719 |  | 0.775 | 0.696 | 0.863 | <0.0001 | **0.959** |
| CHK1i (2 μmol/L) + HU | 0.650 | 0.587 | 0.721 | <0.0001 | **0.702** |  | 0.853 | 0.777 | 0.935 | <0.0001 | 1.055 |
| CHK1i (1 μmol/L) + HU | 0.714 | 0.651 | 0.783 | <0.0001 | 0.736 |  | 0.841 | 0.763 | 0.927 | <0.0001 | 0.979 |
| CHK1i (0.5 μmol/L) + HU | 1.043 | 0.926 | 1.174 | <0.0001 | 1.315 |  | 1.198 | 1.052 | 1.364 | <0.0001 | 1.633 |
| CHK1i (0.25 μmol/L) + HU | 1.260 | 1.122 | 1.414 | <0.0001 | 1.585 |  | 1.328 | 1.196 | 1.475 | 0.000 | 1.851 |
| CHK1i (0.125 μmol/L) + HU | 1.220 | 1.110 | 1.340 | <0.0001 | 1.503 |  | 1.184 | 1.031 | 1.361 | <0.0001 | 1.762 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **HCT-116 PTEN+/+** | EC50 | 95% LB | 95% UB | P-value | HU conc\* |  | EC50 | 95% LB | 95% UB | P-value | HU conc\* |
|  |  |  |  |  |  |  |  |  |  |  |  |
| HU (mmol/L) | 2.491 | 1.950 | 3.183 |  | **2.491** |  | 2.491 | 1.950 | 3.183 |  | **2.491** |
| CHK1i (4 μmol/L) + HU | 0.640 | 0.555 | 0.739 | 0.000 | **0.749** |  | 0.862 | 0.690 | 1.077 | <0.0001 | **1.158** |
| CHK1i (2 μmol/L) + HU | 0.857 | 0.614 | 1.197 | 0.000 | 1.153 |  | 1.010 | 0.789 | 1.293 | <0.0001 | 1.384 |
| CHK1i (1 μmol/L) + HU | 0.905 | 0.575 | 1.425 | 0.004 | 0.960 |  | 1.112 | 0.896 | 1.379 | <0.0001 | 1.185 |
| CHK1i (0.5 μmol/L) + HU | 1.244 | 0.959 | 1.613 | 0.000 | 1.788 |  | 0.964 | 0.799 | 1.162 | <0.0001 | 1.459 |
| CHK1i (0.25 μmol/L) + HU | 1.492 | 0.997 | 2.233 | 0.034 | 2.206 |  | 1.395 | 1.055 | 1.844 | 0.001 | 2.008 |
| CHK1i (0.125 μmol/L) + HU | 1.776 | 1.391 | 2.269 | 0.020 | 1.954 |  | 2.128 | 1.619 | 2.796 | 0.281 | 2.394 |

LB (UB) = lower (upper) bound of a 95% confidence interval for EC50

P-value = comparison of the best-fit model for HU+CHK1i with the model with constraining the EC50 to equal the EC50 of the model for HU alone

\* concentration of HU in combination HU+CHK1i with the same effect (EC50) as HU alone

**Table S4 cont. MU380 SCH900776**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **HT29** | EC50 | 95% LB | 95% UB | P-value | HU conc\* |  | EC50 | 95% LB | 95% UB | P-value | HU conc\* |
|  |  |  |  |  |  |  |  |  |  |  |  |
| HU (mmol/L) | 2.560 | 2.027 | 3.232 |  | **2.560** |  | 2.560 | 2.027 | 3.232 |  | **2.560** |
| CHK1i (4 μmol/L) + HU | 0.183 | 0.096 | 0.349 | <0.0001 | **0.290** |  | 0.426 | 0.350 | 0.519 | <0.0001 | **0.637** |
| CHK1i (2 μmol/L) + HU | 0.341 | 0.248 | 0.471 | <0.0001 | 0.404 |  | 0.646 | 0.581 | 0.717 | <0.0001 | 0.801 |
| CHK1i (1 μmol/L) + HU | 0.502 | 0.379 | 0.665 | <0.0001 | 0.491 |  | 0.795 | 0.684 | 0.924 | <0.0001 | 0.867 |
| CHK1i (0.5 μmol/L) + HU | 0.650 | 0.553 | 0.764 | <0.0001 | 1.009 |  | 1.078 | 0.838 | 1.386 | <0.0001 | 2.359 |
| CHK1i (0.25 μmol/L) + HU | 1.054 | 0.924 | 1.204 | <0.0001 | 1.371 |  | 1.594 | 1.158 | 2.194 | 0.014 | 3.196 |
| CHK1i (0.125 μmol/L) + HU | 1.281 | 1.048 | 1.566 | <0.0001 | 1.749 |  | 1.116 | 0.654 | 1.905 | 0.034 | 5.178 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **MCF10A** | EC50 | 95% LB | 95% UB | P-value | HU conc\* |  | EC50 | 95% LB | 95% UB | P-value | HU conc\* |
|  |  |  |  |  |  |  |  |  |  |  |  |
| HU (mmol/L) | 0.657 | 0.509 | 0.849 |  | **0.657** |  | 0.657 | 0.509 | 0.849 |  | **0.657** |
| CHK1i (4 μmol/L) + HU | 0.458 | 0.376 | 0.558 | 0.000 | **0.480** |  | 0.513 | 0.408 | 0.644 | 0.019 | **0.499** |
| CHK1i (2 μmol/L) + HU | 0.502 | 0.424 | 0.594 | 0.010 | 0.503 |  | 0.528 | 0.442 | 0.630 | 0.063 | 0.516 |
| CHK1i (1 μmol/L) + HU | 0.536 | 0.466 | 0.617 | 0.015 | 0.489 |  | 0.527 | 0.446 | 0.623 | 0.005 | 0.510 |
| CHK1i (0.5 μmol/L) + HU | 0.641 | 0.523 | 0.785 | 0.794 | 0.627 |  | 0.705 | 0.556 | 0.895 | 0.572 | 0.867 |
| CHK1i (0.25 μmol/L) + HU | 0.833 | 0.725 | 0.958 | 0.003 | 0.799 |  | 0.982 | 0.836 | 1.153 | <0.0001 | 0.986 |
| CHK1i (0.125 μmol/L) + HU | 0.874 | 0.768 | 0.996 | 0.000 | 0.858 |  | 0.970 | 0.865 | 1.088 | <0.0001 | 0.996 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **MDA-MB-231** | EC50 | 95% LB | 95% UB | P-value | HU conc\* |  | EC50 | 95% LB | 95% UB | P-value | HU conc\* |
|  |  |  |  |  |  |  |  |  |  |  |  |
| HU (mmol/L) | 0.879 | 0.548 | 1.409 |  | **0.879** |  | 0.879 | 0.548 | 1.409 |  | **0.879** |
| CHK1i (4 μmol/L) + HU | 0.209 | 0.153 | 0.286 | 0.000 | **0.317** |  | 0.295 | 0.211 | 0.413 | 0.000 | 0.565 |
| CHK1i (2 μmol/L) + HU | 0.283 | 0.222 | 0.362 | 0.000 | 0.404 |  | 0.245 | 0.152 | 0.396 | 0.000 | 0.607 |
| CHK1i (1 μmol/L) + HU | 0.316 | 0.235 | 0.424 | 0.000 | 0.387 |  | 0.322 | 0.255 | 0.406 | <0.0001 | **0.500** |
| CHK1i (0.5 μmol/L) + HU | 0.287 | 0.198 | 0.415 | 0.000 | 0.786 |  | 0.261 | 0.172 | 0.395 | 0.000 | 0.893 |
| CHK1i (0.25 μmol/L) + HU | 0.478 | 0.325 | 0.705 | 0.009 | 1.227 |  | 0.346 | 0.186 | 0.643 | 0.009 | 1.329 |
| CHK1i (0.125 μmol/L) + HU | 0.413 | 0.299 | 0.571 | 0.000 | 0.870 |  | 0.483 | 0.361 | 0.646 | 0.001 | 1.155 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **MDCK** | EC50 | 95% LB | 95% UB | P-value | HU conc\* |  | EC50 | 95% LB | 95% UB | P-value | HU conc\* |
|  |  |  |  |  |  |  |  |  |  |  |  |
| HU (mmol/L) | 1.212 | 0.744 | 1.975 |  | **1.212** |  | 1.212 | 0.744 | 1.975 |  | **1.212** |
| CHK1i (4 μmol/L) + HU | 1.146 | 1.034 | 1.270 | 0.274 | 1.170 |  | 1.488 | 1.332 | 1.662 | 0.000 | **1.467** |
| CHK1i (2 μmol/L) + HU | 1.171 | 1.013 | 1.354 | 0.631 | **1.140** |  | 1.511 | 1.317 | 1.734 | 0.001 | 1.486 |
| CHK1i (1 μmol/L) + HU | 1.218 | 1.023 | 1.450 | 0.958 | 1.185 |  | 1.526 | 1.311 | 1.777 | 0.003 | 1.517 |
| CHK1i (0.5 μmol/L) + HU | 1.477 | 1.340 | 1.629 | 0.000 | 1.501 |  | 1.551 | 1.390 | 1.731 | <0.0001 | 1.598 |
| CHK1i (0.25 μmol/L) + HU | 1.478 | 1.308 | 1.671 | 0.002 | 1.523 |  | 1.524 | 1.359 | 1.710 | 0.000 | 1.596 |
| CHK1i (0.125 μmol/L) + HU | 1.535 | 1.334 | 1.767 | 0.001 | 1.587 |  | 1.693 | 1.313 | 2.183 | 0.000 | 1.754 |

LB (UB) = lower (upper) bound of a 95% confidence interval for EC50

P-value = comparison of the best-fit model for HU+CHK1i with the model with constraining the EC50 to equal the EC50 of the model for HU alone

\* concentration of HU in combination HU+CHK1i with the same effect (EC50) as HU alone

**Table S4 cont. MU380 SCH900776**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **MiaPaCa2** | EC50 | 95% LB | 95% UB | P-value | HU conc\* |  | EC50 | 95% LB | 95% UB | P-value | HU conc\* |
|  |  |  |  |  |  |  |  |  |  |  |  |
| HU (mmol/L) | 1.657 | 1.260 | 2.180 |  | **1.657** |  | 1.657 | 1.260 | 2.180 |  | **1.657** |
| CHK1i (4 μmol/L) + HU | 0.361 | 0.299 | 0.437 | 0.000 | 0.412 |  | 0.379 | 0.283 | 0.507 | 0.000 | 0.504 |
| CHK1i (2 μmol/L) + HU | 0.347 | 0.307 | 0.393 | 0.000 | 0.380 |  | 0.364 | 0.315 | 0.421 | 0.000 | **0.416** |
| CHK1i (1 μmol/L) + HU | 0.323 | 0.267 | 0.390 | 0.000 | **0.329** |  | 0.419 | 0.369 | 0.476 | 0.000 | 0.447 |
| CHK1i (0.5 μmol/L) + HU | 0.386 | 0.326 | 0.457 | 0.000 | 0.465 |  | 0.634 | 0.488 | 0.824 | <0.0001 | 0.879 |
| CHK1i (0.25 μmol/L) + HU | 0.511 | 0.371 | 0.702 | 0.000 | 0.744 |  | 0.948 | 0.782 | 1.149 | <0.0001 | 1.108 |
| CHK1i (0.125 μmol/L) + HU | 0.829 | 0.594 | 1.156 | 0.001 | 0.981 |  | 1.159 | 0.900 | 1.493 | 0.009 | 1.347 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **PANC-1** | EC50 | 95% LB | 95% UB | P-value | HU conc\* |  | EC50 | 95% LB | 95% UB | P-value | HU conc\* |
|  |  |  |  |  |  |  |  |  |  |  |  |
| HU (mmol/L) | 5.471 | 0.341 | 87.680 |  | **5.470** |  | 5.471 | 0.341 | 87.680 |  | **5.470** |
| CHK1i (4 μmol/L) + HU | 0.704 | 0.096 | 5.177 | <0.0001 | **1.668** |  | 2.595 | 0.030 | 223.600 | 0.038 | **3.130** |
| CHK1i (2 μmol/L) + HU | 1.393 | 0.483 | 4.015 | 0.015 | 1.770 |  | 4.025 | 0.889 | 18.220 | 0.340 | 3.675 |
| CHK1i (1 μmol/L) + HU | 0.983 | 0.251 | 3.856 | 0.007 | 2.131 |  | 1.749 | 0.180 | 17.000 | 0.015 | 3.640 |
| CHK1i (0.5 μmol/L) + HU | 2.739 | 1.053 | 7.123 | 0.003 | 3.044 |  | 2.538 | 0.799 | 8.060 | 0.013 | 3.359 |
| CHK1i (0.25 μmol/L) + HU | 4.194 | 1.399 | 12.580 | 0.493 | 4.452 |  | 4.017 | 1.244 | 12.970 | 0.459 | 3.822 |
| CHK1i (0.125 μmol/L) + HU | 2.072 | 0.715 | 6.002 | 0.003 | 3.828 |  | 1.962 | 0.049 | 78.910 | 0.010 | 3.295 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **PC3** | EC50 | 95% LB | 95% UB | P-value | HU conc\* |  | EC50 | 95% LB | 95% UB | P-value | HU conc\* |
|  |  |  |  |  |  |  |  |  |  |  |  |
| HU (mmol/L) | 0.170 | 0.127 | 0.229 |  | **0.170** |  | 0.170 | 0.127 | 0.229 |  | **0.170** |
| CHK1i (4 μmol/L) + HU | 0.063 | 0.011 | 0.354 | 0.002 | **0.082** |  | 0.124 | 0.070 | 0.220 | 0.153 | **0.112** |
| CHK1i (2 μmol/L) + HU | 0.117 | 0.084 | 0.164 | 0.015 | 0.090 |  | 0.129 | 0.087 | 0.191 | 0.116 | 0.113 |
| CHK1i (1 μmol/L) + HU | 0.117 | 0.086 | 0.159 | 0.008 | 0.108 |  | 0.148 | 0.109 | 0.202 | 0.355 | 0.143 |
| CHK1i (0.5 μmol/L) + HU | 0.148 | 0.090 | 0.245 | 0.542 | 0.159 |  | 0.148 | 0.084 | 0.263 | 0.592 | 0.177 |
| CHK1i (0.25 μmol/L) + HU | 0.181 | 0.123 | 0.267 | 0.755 | 0.176 |  | 0.173 | 0.082 | 0.364 | 0.971 | 0.194 |
| CHK1i (0.125 μmol/L) + HU | 0.180 | 0.130 | 0.251 | 0.737 | 0.164 |  | 0.218 | 0.153 | 0.310 | 0.220 | 0.168 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **Sk-Br-3** | EC50 | 95% LB | 95% UB | P-value | HU conc\* |  | EC50 | 95% LB | 95% UB | P-value | HU conc\* |
|  |  |  |  |  |  |  |  |  |  |  |  |
| HU (mmol/L) | 1.121 | 0.446 | 2.818 |  | **1.121** |  | 1.121 | 0.446 | 2.818 |  | **1.121** |
| CHK1i (4 μmol/L) + HU | 0.422 | 0.315 | 0.564 | 0.000 | **0.791** |  | 0.730 | 0.584 | 0.914 | 0.001 | 0.985 |
| CHK1i (2 μmol/L) + HU | 0.496 | 0.345 | 0.714 | 0.001 | 0.830 |  | 0.592 | 0.385 | 0.910 | 0.025 | **0.841** |
| CHK1i (1 μmol/L) + HU | 0.315 | 0.015 | 6.406 | 0.000 | 0.992 |  | 2.608 | 0.026 | 263.800 | 0.428 | 0.847 |
| CHK1i (0.5 μmol/L) + HU | 0.582 | 0.463 | 0.733 | <0.0001 | 0.965 |  | 0.618 | 0.379 | 1.009 | 0.073 | 1.185 |
| CHK1i (0.25 μmol/L) + HU | 0.642 | 0.401 | 1.027 | 0.078 | 1.219 |  | 0.981 | 0.509 | 1.889 | 0.716 | 2.256 |
| CHK1i (0.125 μmol/L) + HU | 2.661 | 0.264 | 26.800 | 0.110 | 1.447 |  | 2.191 | 1.375 | 3.493 | 0.008 | 2.876 |

LB (UB) = lower (upper) bound of a 95% confidence interval for EC50

P-value = comparison of the best-fit model for HU+CHK1i with the model with constraining the EC50 to equal the EC50 of the model for HU alone

\* concentration of HU in combination HU+CHK1i with the same effect (EC50) as HU alone

**Table S4 cont. MU380 SCH900776**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **SKOV-3** | EC50 | 95% LB | 95% UB | P-value | HU conc\* |  | EC50 | 95% LB | 95% UB | P-value | HU conc\* |
|  |  |  |  |  |  |  |  |  |  |  |  |
| HU (mmol/L) | 1.223 | 0.8743 | 1.711 |  | **1.223** |  | 1.223 | 0.8743 | 1.711 |  | **1.223** |
| CHK1i (4 μmol/L) + HU | 0.200 | 0.1331 | 0.2991 | 0.000 | 0.474 |  | 0.312 | 0.2507 | 0.3884 | 0.000 | 0.566 |
| CHK1i (2 μmol/L) + HU | 0.324 | 0.2586 | 0.4058 | 0.000 | 0.485 |  | 0.280 | 0.2122 | 0.3696 | 0.000 | 0.536 |
| CHK1i (1 μmol/L) + HU | 0.328 | 0.2858 | 0.3771 | 0.000 | **0.381** |  | 0.381 | 0.2955 | 0.4923 | 0.000 | **0.397** |
| CHK1i (0.5 μmol/L) + HU | 0.347 | 0.2105 | 0.5720 | 0.000 | 0.771 |  | 0.404 | 0.2629 | 0.6202 | 0.000 | 0.902 |
| CHK1i (0.25 μmol/L) + HU | 0.483 | 0.3430 | 0.6811 | 0.001 | 0.752 |  | 0.595 | 0.3755 | 0.9421 | 0.024 | 1.135 |
| CHK1i (0.125 μmol/L) + HU | 0.470 | 0.3294 | 0.6697 | 0.001 | 0.677 |  | 0.616 | 0.4476 | 0.8489 | 0.003 | 1.059 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **SW480** | EC50 | 95% LB | 95% UB | P-value | HU conc\* |  | EC50 | 95% LB | 95% UB | P-value | HU conc\* |
|  |  |  |  |  |  |  |  |  |  |  |  |
| HU (mmol/L) | 1.251 | 0.831 | 1.885 |  | **1.251** |  | 1.251 | 0.831 | 1.885 |  | **1.251** |
| CHK1i (4 μmol/L) + HU | 0.287 | 0.240 | 0.342 | 0.000 | **0.324** |  | 0.428 | 0.338 | 0.543 | <0.0001 | **0.476** |
| CHK1i (2 μmol/L) + HU | 0.312 | 0.203 | 0.480 | <0.0001 | 0.345 |  | 0.508 | 0.370 | 0.698 | <0.0001 | 0.575 |
| CHK1i (1 μmol/L) + HU | 0.453 | 0.377 | 0.546 | <0.0001 | 0.450 |  | 0.637 | 0.491 | 0.827 | <0.0001 | 0.720 |
| CHK1i (0.5 μmol/L) + HU | 0.544 | 0.432 | 0.684 | <0.0001 | 0.712 |  | 0.633 | 0.497 | 0.805 | <0.0001 | 1.186 |
| CHK1i (0.25 μmol/L) + HU | 0.799 | 0.614 | 1.039 | 0.001 | 1.133 |  | 1.208 | 0.890 | 1.639 | 0.818 | 2.366 |
| CHK1i (0.125 μmol/L) + HU | 0.752 | 0.483 | 1.171 | 0.012 | 1.165 |  | 0.773 | 0.475 | 1.257 | 0.035 | 1.707 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **SW620** | EC50 | 95% LB | 95% UB | P-value | HU conc\* |  | EC50 | 95% LB | 95% UB | P-value | HU conc\* |
|  |  |  |  |  |  |  |  |  |  |  |  |
| HU (mmol/L) | 1.286 | 0.9763 | 1.693 |  | **1.286** |  | 1.286 | 0.9763 | 1.693 |  | **1.286** |
| CHK1i (4 μmol/L) + HU | 0.124 | 0.05786 | 0.2634 | <0.0001 | **0.185** |  | 0.227 | 0.1846 | 0.2779 | <0.0001 | **0.313** |
| CHK1i (2 μmol/L) + HU | 0.172 | 0.1014 | 0.2910 | <0.0001 | 0.205 |  | 0.317 | 0.2787 | 0.3604 | <0.0001 | 0.361 |
| CHK1i (1 μmol/L) + HU | 0.226 | 0.1727 | 0.2951 | <0.0001 | 0.260 |  | 0.356 | 0.3079 | 0.4107 | <0.0001 | 0.397 |
| CHK1i (0.5 μmol/L) + HU | 0.424 | 0.3655 | 0.4925 | <0.0001 | 0.583 |  | 0.535 | 0.4491 | 0.6375 | <0.0001 | 1.057 |
| CHK1i (0.25 μmol/L) + HU | 0.860 | 0.6176 | 1.196 | 0.017 | 1.250 |  | 0.893 | 0.6955 | 1.146 | 0.005 | 1.633 |
| CHK1i (0.125 μmol/L) + HU | 0.681 | 0.5288 | 0.8761 | <0.0001 | 0.832 |  | 0.775 | 0.6012 | 0.9997 | <0.0001 | 1.311 |

LB (UB) = lower (upper) bound of a 95% confidence interval for EC50

P-value = comparison of the best-fit model for HU+CHK1i with the model with constraining the EC50 to equal the EC50 of the model for HU alone

\* concentration of HU in combination HU+CHK1i with the same effect (EC50) as HU alone

**Table S5. Statistical analysis of dose response curves for cell lines indicated in the Figure 3B.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **A2780** | EC50 | 95% LB | 95% UB | P-value | GEM conc\* |
|  |  |  |  |  |  |
| GEM (nmol/L) | 7.584 | 6.450 | 8.917 |  | **7.584** |
| MU380 (4 μmol/L) + GEM | 3.147 | 2.695 | 3.675 | <0.0001 | **3.106** |
| SCH900776 (4 μmol/L) + GEM | 4.710 | 4.162 | 5.331 | <0.0001 | **4.749** |
|  |  |  |  |  |  |
| **CAKI-2** | EC50 | 95% LB | 95% UB | P-value | GEM conc\* |
|  |  |  |  |  |  |
| GEM (nmol/L) | 109.100 | 95.270 | 125.000 |  | **109.144** |
| MU380 (4 μmol/L) + GEM | 11.640 | 10.080 | 13.430 | <0.0001 | **8.832** |
| SCH900776 (4 μmol/L) + GEM | 22.080 | 19.420 | 25.090 | <0.0001 | **23.368** |
|  |  |  |  |  |  |
| **DU145** | EC50 | 95% LB | 95% UB | P-value | GEM conc\* |
|  |  |  |  |  |  |
| GEM (nmol/L) | 37.070 | 32.91 | 41.76 |  | **37.068** |
| MU380 (4 μmol/L) + GEM | 8.200 | 7.499 | 8.966 | <0.0001 | **8.193** |
| SCH900776 (4 μmol/L) + GEM | 13.290 | 12.55 | 14.08 | <0.0001 | **13.537** |
|  |  |  |  |  |  |
|  | EC50 | 95% LB | 95% UB | P-value | GEM conc\* |
| **H441** |  |  |  |  |  |
|  |  |  |  |  |  |
| GEM (nmol/L) | 16.550 | 13.700 | 19.990 |  | **16.558** |
| MU380 (4 μmol/L) + GEM | 5.979 | 4.652 | 7.686 | <0.0001 | **5.946** |
| SCH900776 (4 μmol/L) + GEM | 7.365 | 5.758 | 9.422 | <0.0001 | **8.591** |
|  |  |  |  |  |  |
| **MCF10A** | EC50 | 95% LB | 95% UB | P-value | GEM conc\* |
|  |  |  |  |  |  |
| GEM (nmol/L) | 4.041 | 3.823 | 4.270 |  | **4.040** |
| MU380 (4 μmol/L) + GEM | 2.409 | 2.266 | 2.560 | <0.0001 | **2.391** |
| SCH900776 (4 μmol/L) + GEM | 3.319 | 3.023 | 3.643 | <0.0001 | **3.232** |

LB (UB) = lower (upper) bound of a 95% confidence interval for EC50

P-value = comparison of the best-fit model for GEM+CHK1i with the model with constraining the EC50 to equal the EC50 of the model for HU alone

\* concentration of GEM in combination GEM+CHK1i with the same effect (EC50) as GEM alone

**Table S5 cont.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **MiaPaCa2** | EC50 | 95% LB | 95% UB | P-value | GEM conc\* |
|  |  |  |  |  |  |
| GEM (nmol/L) | 65.760 | 54.950 | 78.700 |  | **65.766** |
| MU380 (4 μmol/L) + GEM | 15.110 | 13.310 | 17.140 | <0.0001 | **13.806** |
| SCH900776 (4 μmol/L) + GEM | 22.780 | 19.670 | 26.380 | <0.0001 | **21.558** |
|  |  |  |  |  |  |
| **PC3** | EC50 | 95% LB | 95% UB | P-value | GEM conc\* |
|  |  |  |  |  |  |
| GEM (nmol/L) | 4.726 | 4.241 | 5.267 |  | **4.726** |
| MU380 (4 μmol/L) + GEM | 2.081 | 1.953 | 2.217 | <0.0001 | **1.866** |
| SCH900776 (4 μmol/L) + GEM | 3.462 | 3.064 | 3.912 | <0.0001 | **3.281** |
|  |  |  |  |  |  |
| **SW620** | EC50 | 95% LB | 95% UB | P-value | GEM conc\* |
|  |  |  |  |  |  |
| GEM (nmol/L) | 62.690 | 53.210 | 73.860 |  | **62.661** |
| MU380 (4 μmol/L) + GEM | 20.840 | 18.610 | 23.340 | <0.0001 | **21.654** |
| SCH900776 (4 μmol/L) + GEM | 31.200 | 27.030 | 36.020 | <0.0001 | **33.186** |

LB (UB) = lower (upper) bound of a 95% confidence interval for EC50

P-value = comparison of the best-fit model for GEM+CHK1i with the model with constraining the EC50 to equal the EC50 of the model for HU alone

\* concentration of GEM in combination GEM+CHK1i with the same effect (EC50) as GEM alone

**Table S6. Distribution properties of SCH900776 and MU380 obtained using Caco-2 permeability drug assay. See Supplementary Material and Methods for details.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Papp (A - B) (cm•s-1 x 106) | Papp (B - A) (cm•s-1 x 106) | Efflux ratio |
|  |  |  |  |
| SCH900776 | 24.3 ± 18.7 | 8.5 ± 3.9 | 1.2 |
| MU380 | 8.5 ± 3.9 | 15.8 ± 6.3 | 2.1 |

**Table S7. Pharmacokinetics of SCH900776 and MU380.** Raw data and statistical analysis are shown (A, B). Concentration of the tested compounds and the metabolite MU379 were measured in blood plasma of 5 animals for each time point. n.d. ~ not detected, limit of detection 0.044 µmol/L, traces ~the observed values are between the limit of detection (0.044 µmol/L) and limit of quantification (0.155 µmol/L).C, Estimation of the area under the concentration versus time curve from zero to the last time point (AUC 0-tlast), total area under the concentration versus time curve from zero to infinity (AUC 0-Inf), area under the first moment curve for zero to infinity (AUMC 0-Inf), mean residence time (MRT), non-compartmental half-life (HL), total clearance (CL) and volume of distribution at steady state (Vss).

**A B**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Time** | | **concentration (μmol/L)** | |  | | | **Time** | | **concentration (μmol/L)** | |
|  |  | |  | |  |  | |  | |  |
|  | **SCH900776** | | **MU379** | |  |  | | **MU380** | | **MU379** |
|  |  | |  | |  |  | |  | |  |
| 30 min | 8.96 ± 0.16 | | traces | |  | 30 min | | 2.94 ± 0.06 | | nd |
|  | 6.97 ± 0.36 | | nd | |  |  | | 3.86 ± 0.21 | | nd |
|  | 3.93 ± 0.05 | | traces | |  |  | | 1.94 ± 0.14 | | nd |
|  | 6.40 ± 0.32 | | traces | |  |  | | 2.24 ± 0.04 | | nd |
|  | 3.31 ± 0.13 | | traces | |  |  | | 8.01 ± 0.13 | | nd |
|  |  | |  | |  |  | |  | |  |
| 1 hr | 5.48 ± 0.37 | | 0.3 ± 0.03 | |  | 1 hr | | 3.96 ± 0.04 | | nd |
|  | 3.63 ± 0.11 | | traces | |  |  | | 4.48 ± 0.02 | | nd |
|  | 6.84 ± 0.49 | | 0.34 ± 0.06 | |  |  | | 3.39 ± 0.04 | | nd |
|  | 3.03 ± 0.22 | | traces | |  |  | | 3.61 ± 0.08 | | nd |
|  | 4.21 ± 0.30 | | 0.3 ± 0.01 | |  |  | | 3.78 ± 0.14 | | nd |
|  |  | |  | |  |  | |  | |  |
| 2 hrs | 2.32 ± 0.21 | | nd | |  | 2 hrs | | 4.27 ± 0.04 | | nd |
|  | 2.15 ± 0.15 | | 0.53 ± 0.2 | |  |  | | 3.58 ± 0.11 | | nd |
|  | 2.02 ± 0.13 | | traces | |  |  | | 2.03 ± 0.08 | | nd |
|  | 0.92 ± 0.08q | | nd | |  |  | | 4.54 ± 0.12 | | nd |
|  | 2.67 ± 0.13 | | traces | |  |  | | 3.69 ± 0.02 | | nd |
|  |  | |  | |  |  | |  | |  |
| 4 hrs | 0.35 ± 0.01 | | nd | |  | 4 hrs | | 3.05 ± 0.07 | | nd |
|  | 0.46 ± 0.01 | | nd | |  |  | | 2.74 ± 0.06 | | nd |
|  | 0.20 ± 0.01 | | nd | |  |  | | 3.57 ± 0.07 | | nd |
|  | 0.39 ± 0.03 | | nd | |  |  | | 2.65 ± 0.07 | | nd |
|  | 0.47 ± 0.02 | | nd | |  |  | | 2.89 ± 0.09 | | nd |
|  |  | |  | |  |  | |  | |  |
| **Table S7 cont.**  8 hrs | 0.20 ± 0.01 | | nd | |  | 8 hrs | | 1.79 ± 0.06 | | nd |
|  | nd | | nd | |  |  | | 1.30 ± 0.07 | | nd |
|  | 0.20 ± 0.01 | | nd | |  |  | | 1.05 ± 0.03 | | nd |
|  | 0.20 ± 0.01 | | nd | |  |  | | 0.91 ± 0.07 | | nd |
|  | 0.20 ± 0.01 | | nd | |  |  | | 1.61 ± 0.07 | | nd |
|  |  | |  | |  |  | |  | |  |
| 16 hrs | nd | | nd | |  | 16 hrs | | 0.37 ± 0.02 | | nd |
|  | nd | | nd | |  |  | | 0.32 ± 0.02 | | nd |
|  | nd | | nd | |  |  | | 0.31 ± 0.02 | | nd |
|  | nd | | nd | |  |  | | 0.45 ± 0.02 | | nd |
|  | nd | | nd | |  |  | | 0.46 ± 0.03 | | nd |
|  |  | |  | |  |  | |  | |  |
| 24 hrs | nd | | nd | |  | 24 hrs | | nd | | nd |
|  | nd | | nd | |  |  | | nd | | nd |
|  | nd | | nd | |  |  | | nd | | nd |
|  | nd | | nd | |  |  | | nd | | nd |
|  | nd | | nd | |  |  | | nd | | nd |

**C**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **SCH900776** | | | **MU380** | | | **p-value** | | |
|  | Estimate | SE | 95% CI | | Estimate | SE | | 95% CI |  |
| AUC to tlast | 10.359 | 0.741 | 8.907; 11.811 | | 28.951 | 1.296 | | 26.410; 31.491 | <0.001 |
| AUC to infinity | 10.359 | 0.753 | 8.883; 11.835 | | 31.285 | 1.304 | | 28.729; 33.841 | <0.001 |
| AUMC to infinity | 24.773 | 1.273 | 22.278; 27.268 | | 199.728 | 11.822 | | 176.558; 222.898 | <0.001 |
| Mean residence time | 2.391 | 0.094 | 2.208;  2.575 | | 6.384 | 0.270 | | 5.856;  6.913 | <0.001 |
| Non-compartmental half-life | 1.658 | 0.065 | 1.530;  1.785 | | 4.425 | 0.187 | | 4.059;  4.792 | <0.001 |
| Clearance | 0.010 | 0.001 | 0.008;  0.011 | | 0.003 | 0.000 | | 0.003;  0.003 | 0.033 |
| Volume of distribution at steady state | 0.023 | 0.003 | 0.018;  0.028 | | 0.020 | 0.001 | | 0.018;  0.023 | 0.340 |

**Table S8. Residual kinase activities for SCH900776, MU380, and MU378 (1 μmol/L) measured in a panel of 207 human kinases (Eurofins KinaseProfiler service).**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Kinases** | **SCH900776 (1 µmol/L)** | **MU378 (1 µmol/L)** | **MU380 (1 µmol/L)** | **MU379 (1 µmol/L)** |
| Abl(h) | 98 | 110 | 131 | 94 |
| ACK1(h) | 66 | 93 | 71 | 69 |
| ALK(h) | 86 | 97 | 91 | 76 |
| ALK4(h) | 108 | 89 | 119 | 92 |
| Arg(h) | 100 | 98 | 99 | 126 |
| AMPKα1(h) | 51 | 70 | 22 | 27 |
| AMPKα2(h) | 67 | 85 | 29 | 16 |
| ARK5(h) | 52 | 75 | 65 | 15 |
| ASK1(h) | 96 | 88 | 117 | 96 |
| Aurora-A(h) | 90 | 108 | 102 | 84 |
| Aurora-B(h) | 139 | 155 | 104 | 55 |
| Aurora-C(h) | 78 | 87 | 65 | 42 |
| Axl(h) | 82 | 109 | 99 | 54 |
| Blk(h) | 86 | 99 | 85 | 41 |
| Bmx(h) | 71 | 94 | 63 | 80 |
| BRK(h) | 80 | 19 | 98 | 73 |
| BrSK1(h) | 78 | 99 | 81 | 45 |
| BrSK2(h) | 71 | 100 | 63 | 36 |
| BTK(h) | 103 | 123 | 118 | 90 |
| B-Raf(h) | 91 | 94 | 84 | 85 |
| CaMKI(h) | 60 | 75 | 47 | 52 |
| CaMKIIβ(h) | 27 | 49 | 12 | 55 |
| CaMKIIγ(h) | 4 | 18 | 2 | 15 |
| CaMKIδ(h) | 30 | 80 | 23 | 19 |
| CaMKIIδ(h) | 3 | 10 | 2 | 12 |
| CaMKIV(h) | 92 | 112 | 100 | 57 |
| CDK1/cyclinB(h) | 80 | 102 | 93 | 18 |
| CDK2/cyclinA(h) | 70 | 96 | 91 | 15 |
| CDK2/cyclinE(h) | 81 | 105 | 112 | 13 |
| CDK3/cyclinE(h) | 77 | 99 | 94 | 14 |
| CDK5/p25(h) | 68 | 90 | 82 | 1 |
| CDK5/p35(h) | 65 | 103 | 93 | 1 |
| **Table S8. Cont** |  |  |  |  |
| **Kinases** | **SCH900776 (1 µmol/L)** | **MU378 (1 µmol/L)** | **MU380 (1 µmol/L)** | **MU379 (1 µmol/L)** |
| CDK6/cyclinD3(h) | 77 | 79 | 83 | 93 |
| CDK7/cyclinH/MAT1(h) | 89 | 97 | 100 | 49 |
| CDK9/cyclin T1(h) | 86 | 105 | 70 | 31 |
| CHK1(h) | 0 | 1 | -1 | 3 |
| CHK2(h) | 65 | 83 | 81 | 11 |
| CK1γ1(h) | 78 | 93 | 113 | 56 |
| CK1γ2(h) | 105 | 111 | 124 | 54 |
| CK1γ3(h) | 90 | 101 | 99 | 67 |
| CK1δ(h) | 78 | 52 | 82 | 62 |
| CK2(h) | 53 | 117 | 43 | 59 |
| CK2α2(h) | 64 | 91 | 26 | 45 |
| CLK1(h) | 64 | 80 | 98 | 8 |
| CLK2(h) | 63 | 57 | 74 | 20 |
| CLK3(h) | 97 | 102 | 121 | 89 |
| CLK4(h) | 45 | 75 | 57 | 8 |
| cKit(h) | 81 | 98 | 100 | 90 |
| CSK(h) | 78 | 100 | 109 | 106 |
| c-RAF(h) | 84 | 98 | 83 | 77 |
| cSRC(h) | 88 | 86 | 90 | 68 |
| DAPK1(h) | 90 | 80 | 106 | 111 |
| DAPK2(h) | 97 | 106 | 106 | 88 |
| DCAMKL2(h) | 82 | 99 | 82 | 65 |
| DDR2(h) | 94 | 99 | 96 | 94 |
| DMPK(h) | 95 | 106 | 101 | 103 |
| DRAK1(h) | 98 | 104 | 80 | 21 |
| DYRK2(h) | 83 | 107 | 117 | 93 |
| eEF-2K(h) | 102 | 96 | 108 | 86 |
| EGFR(h) | 94 | 97 | 110 | 102 |
| FAK(h) | 88 | 101 | 110 | 63 |
| Fer(h) | 109 | 105 | 110 | 100 |
| Fes(h) | 89 | 107 | 101 | 98 |
| FGFR1(h) | 75 | 97 | 106 | 17 |
| **Table S8. Cont** |  |  |  |  |
| **Kinases** | **SCH900776 (1 µmol/L)** | **MU378 (1 µmol/L)** | **MU380 (1 µmol/L)** | **MU379 (1 µmol/L)** |
| FGFR2(h) | 87 | 98 | 112 | 56 |
| FGFR3(h) | 87 | 95 | 114 | 39 |
| FGFR4(h) | 83 | 102 | 114 | 98 |
| Fgr(h) | 82 | 97 | 84 | 36 |
| Flt1(h) | 68 | 92 | 91 | 17 |
| Flt3(h) | 80 | 93 | 96 | 2 |
| Flt4(h) | 70 | 77 | 93 | 16 |
| Fms(h) | 72 | 91 | 76 | 76 |
| Fyn(h) | 83 | 86 | 82 | 27 |
| GCK(h) | 76 | 100 | 88 | 33 |
| GRK5(h) | 99 | 92 | 108 | 91 |
| GRK6(h) | 97 | 106 | 108 | 92 |
| GRK7(h) | 92 | 93 | 113 | 98 |
| GSK3α(h) | 90 | 111 | 96 | 105 |
| GSK3β(h) | 99 | 95 | 99 | 91 |
| Haspin(h) | 19 | 79 | 8 | 7 |
| Hck(h) | 88 | 84 | 90 | 51 |
| Hck(h) activated | 84 | 89 | 86 | 33 |
| HIPK1(h) | 97 | 108 | 104 | 104 |
| HIPK2(h) | 91 | 99 | 87 | 94 |
| HIPK3(h) | 97 | 103 | 109 | 88 |
| IGF-1R(h) | 94 | 115 | 98 | 117 |
| IGF-1R(h), activated | 87 | 93 | 102 | 113 |
| IKKα(h) | 82 | 101 | 81 | 32 |
| IKKβ(h) | 80 | 93 | 97 | 72 |
| IKKε(h) | 95 | 103 | 101 | 95 |
| IR(h) | 92 | 91 | 107 | 114 |
| IRR(h) | 87 | 91 | 106 | 95 |
| IRAK1(h) | 98 | 97 | 110 | 88 |
| IRAK4(h) | 77 | 62 | 80 | 75 |
| Itk(h) | 86 | 90 | 113 | 85 |
| JAK1(h) | 98 | 106 | 92 | 98 |
| **Table S8. Cont** |  |  |  |  |
| **Kinases** | **SCH900776 (1 µmol/L)** | **MU378 (1 µmol/L)** | **MU380 (1 µmol/L)** | **MU379 (1 µmol/L)** |
| JAK2(h) | 93 | 99 | 109 | 114 |
| JAK3(h) | 90 | 91 | 94 | 83 |
| JNK1α1(h) | 94 | 101 | 104 | 96 |
| JNK2α2(h) | 106 | 86 | 118 | 97 |
| JNK3(h) | 95 | 92 | 101 | 109 |
| KDR(h) | 76 | 97 | 98 | 53 |
| Lck(h) | 66 | 102 | 57 | 11 |
| LIMK1(h) | 85 | 92 | 97 | 83 |
| LKB1(h) | 81 | 61 | 104 | 95 |
| LOK(h) | 46 | 33 | 28 | 31 |
| Lyn(h) | 77 | 94 | 76 | 19 |
| LRRK2(h) | 34 | 49 | 55 | 21 |
| MAPK1(h) | 97 | 88 | 101 | 63 |
| MAPK2(h) | 79 | 98 | 98 | 78 |
| MEK1(h) | 63 | 88 | 43 | 57 |
| MARK1(h) | 72 | 84 | 52 | 53 |
| MELK(h) | 39 | 62 | 10 | 3 |
| Mer(h) | 54 | 75 | 51 | 4 |
| Met(h) | 100 | 101 | 106 | 113 |
| MINK(h) | 89 | 71 | 105 | 90 |
| MLCK(h) | 88 | 97 | 61 | 89 |
| MLK1(h) | 78 | 100 | 74 | 52 |
| Mnk2(h) | 88 | 102 | 94 | 65 |
| MRCKα(h) | 91 | 88 | 97 | 97 |
| MRCKβ(h) | 96 | 86 | 102 | 95 |
| MSK1(h) | 83 | 91 | 82 | 74 |
| MSK2(h) | 85 | 90 | 89 | 33 |
| MSSK1(h) | 98 | 90 | 108 | 80 |
| MST1(h) | 81 | 106 | 96 | 64 |
| MST2(h) | 86 | 99 | 99 | 89 |
| MST3(h) | 74 | 102 | 101 | 124 |
| mTOR(h) | 99 | 95 | 110 | 52 |
| **Table S8. Cont** |  |  |  |  |
| **Kinases** | **SCH900776 (1 µmol/L)** | **MU378 (1 µmol/L)** | **MU380 (1 µmol/L)** | **MU379 (1 µmol/L)** |
| mTOR/FKBP12(h) | 86 | 86 | 106 | 51 |
| MuSK(h) | 72 | 98 | 114 | 71 |
| NEK2(h) | 95 | 96 | 112 | 91 |
| NEK3(h) | 92 | 101 | 110 | 92 |
| NEK6(h) | 102 | 110 | 111 | 96 |
| NEK7(h) | 98 | 110 | 106 | 98 |
| NEK11(h) | 81 | 97 | 104 | 94 |
| NLK(h) | 57 | 67 | 34 | 60 |
| p70S6K(h) | 84 | 85 | 89 | 63 |
| PAK1(h) | 96 | 104 | 104 | 96 |
| PAR-1Bα(h) | 85 | 82 | 53 | 57 |
| PASK(h) | 45 | 78 | 36 | 25 |
| PEK(h) | 93 | 83 | 109 | 95 |
| PDGFRα(h) | 82 | 92 | 86 | 95 |
| PDGFRβ(h) | 75 | 87 | 111 | 82 |
| PDK1(h) | 62 | 104 | 73 | 35 |
| PhKγ2(h) | 96 | 94 | 102 | 83 |
| Pim-1(h) | 14 | 68 | 9 | 2 |
| Pim-2(h) | 14 | 93 | 9 | -1 |
| Pim-3(h) | 7 | 54 | -1 | 1 |
| PKA(h) | 95 | 92 | 105 | 102 |
| PKBα(h) | 93 | 104 | 112 | 89 |
| PKBβ(h) | 98 | 104 | 109 | 84 |
| PKBγ(h) | 84 | 94 | 104 | 91 |
| PKCα(h) | 100 | 102 | 109 | 100 |
| PKD2(h) | 82 | 82 | 94 | 18 |
| PKG1α(h) | 87 | 89 | 104 | 86 |
| PKG1β(h) | 95 | 101 | 106 | 95 |
| Plk1(h) | 91 | 86 | 101 | 100 |
| Plk3(h) | 105 | 106 | 106 | 95 |
| PRAK(h) | 89 | 94 | 113 | 95 |
| PRK2(h) | 69 | 79 | 72 | 70 |
| **Table S8. Cont** |  |  |  |  |
| **Kinases** | **SCH900776 (1 µmol/L)** | **MU378 (1 µmol/L)** | **MU380 (1 µmol/L)** | **MU379 (1 µmol/L)** |
| PrKX(h) | 100 | 92 | 107 | 96 |
| PTK5(h) | 83 | 94 | 81 | 78 |
| Pyk2(h) | 63 | 80 | 24 | 29 |
| Ret(h) | 60 | 80 | 45 | 27 |
| RIPK2(h) | 67 | 86 | 89 | 70 |
| ROCK-I(h) | 89 | 89 | 93 | 92 |
| ROCK-II(h) | 77 | 88 | 89 | 79 |
| Ron(h) | 80 | 92 | 98 | 109 |
| Ros(h) | 108 | 115 | 114 | 110 |
| Rse(h) | 94 | 101 | 105 | 96 |
| Rsk1(h) | 47 | 42 | 32 | 25 |
| Rsk2(h) | 26 | 19 | 15 | 9 |
| Rsk3(h) | 17 | 9 | 10 | 10 |
| Rsk4(h) | 28 | 21 | 14 | 14 |
| SGK(h) | 92 | 103 | 92 | 65 |
| SGK2(h) | 82 | 94 | 82 | 72 |
| SGK3(h) | 94 | 103 | 104 | 97 |
| SIK(h) | 24 | 79 | 13 | 11 |
| Snk(h) | 91 | 103 | 113 | 102 |
| SRPK1(h) | 104 | 104 | 99 | 114 |
| SRPK2(h) | 97 | 97 | 108 | 101 |
| STK33(h) | 85 | 86 | 92 | 64 |
| Syk(h) | 90 | 106 | 98 | 90 |
| TAK1(h) | 91 | 95 | 103 | 88 |
| TBK1(h) | 83 | 92 | 96 | 97 |
| TGFBR1(h) | 99 | 100 | 91 | 100 |
| Tie2 (h) | 93 | 100 | 114 | 99 |
| TLK2(h) | 15 | 30 | 12 | 4 |
| TrkA(h) | 61 | 89 | 53 | 41 |
| TrkB(h) | 103 | 111 | 58 | 11 |
| TrkC(h) | 100 | 115 | 64 | 68 |
| TSSK1(h) | 67 | 84 | 55 | 53 |
| **Table S8. Cont** |  |  |  |  |
| **Kinases** | **SCH900776 (1 µmol/L)** | **MU378 (1 µmol/L)** | **MU380 (1 µmol/L)** | **MU379 (1 µmol/L)** |
| TSSK2(h) | 86 | 98 | 102 | 89 |
| Txk(h) | 62 | 84 | 70 | 96 |
| TYK2(h) | 89 | 92 | 99 | 73 |
| ULK2(h) | 78 | 85 | 71 | 39 |
| ULK3(h) | 87 | 101 | 79 | 18 |
| Wee1(h) | 94 | 84 | 108 | 93 |
| WNK2(h) | 86 | 87 | 99 | 97 |
| WNK3(h) | 82 | 96 | 100 | 98 |
| VRK2(h) | 98 | 105 | 102 | 89 |
| Yes(h) | 65 | 73 | 35 | 19 |
| ZAP-70(h) | 97 | 109 | 104 | 133 |
| ZIPK(h) | 79 | 91 | 96 | 83 |
| PIP4K2a(h) | 96 | 95 | 93 | 103 |
| PIP5K1a(h) | 102 | 97 | 96 | 96 |
| PIP5K1g(h) | 91 | 87 | 90 | 87 |

**Table S9. The median survival time.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **vehicle** | **GEM** | **MU380** | **SCH900776** | **GEM + MU380** | **GEM + SCH900776** |
| median survival (days) | 23 | 41 | 23 | 26 | 49 | 37 |

**Table S10. Log-rank (Mantel-Cox) test, used to assess the statistical differences in survival curves among the groups; \* (P<0.05), \*\* (p<0.01).**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **P value** | **vehicle** | **GEM** | **MU380** | **SCH900776** | **GEM + MU380** |
| GEM | 0.0209\* |  |  |  |  |
| MU380 | 0.64444 | 0.0307\* |  |  |  |
| SCH900776 | 0.3908 | 0.0973 | 0.1542 |  |  |
| GEM + MU380 | 0.0021\*\* | 0.0060\*\* | 0.0017\*\* | 0.0034\*\* |  |
| GEM + SCH900776 | 0.0115\* | 0.5687 | 0.0015\*\* | 0.0261\* | 0.6342 |

**Table S11.** **Available data for mutational status of the cell lines included in the screen were extracted from Cancer Cell Line Encyclopedia (CCLE) database. Mutational status have been re-categorized (see supplementary methods) from Sonkin et al (41).**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| gene symbol |  | | H441 | | PC-3 | | A2780 | | MDA-MB-231 | | A549 | | SW480 | | HCT 116 | | SK-OV-3 | | SK-Br-3 | | Caki-2 | | DU 145 | | SW620 | | HT-29 |
|  | | lung c. | | prost.c. | | ovar.c. | | br.c. | | lung c. | | col.c. | | col.c. | | ovar.c. | | br.c. | | kid.c. | | prost.c. | | col.c. | | col.c. |
|  |  | |  | |  | |  | |  | |  | |  | |  | |  | |  | |  | |  | |  | |  |
| APC |  | | WT | | 0 | | WT | | WT | | WT | | M/D | | WT | | WT | | 0 | | 0 | | WT | | M/D | | 0-M/D |
| ARID1A | | | WT | | WT | | 0-M/D | | WT | | 0 | | 0 | | 0 | | 0-M/D | | 0 | | 0 | | 0 | | WT | | WT |
| ATM |  | | 0 | | WT | | 0 | | WT | | 0 | | 0 | | 0 | | 0 | | WT | | 0 | | 0 | | 0 | | WT |
| ATR |  | | WT | | 0 | | WT | | 0 | | 0 | | 0 | | WT | | WT | | 0 | | WT | | WT | | WT | | WT |
| BMPR1A | | | 0 | | 0 | | 0 | | WT | | WT | | 0 | | WT | | 0 | | 0 | | WT | | WT | | 0 | | WT |
| BRCA1 | | | 0 | | 0 | | WT | | 0 | | WT | | 0 | | WT | | WT | | 0-M/D | | WT | | 0 | | 0 | | WT |
| BRCA2 | | | 0 | | WT | | WT | | 0 | | 0 | | 0 | | 0-M/D | | WT | | WT | | 0 | | 0 | | 0 | | 0 |
| BRIP1 |  | | WT | | WT | | WT | | 0 | | WT | | 0 | | WT | | WT | | 0-M/D | | WT | | 0 | | 0 | | WT |
| CDC73 | | | WT | | 0 | | WT | | WT | | WT | | 0 | | WT | | WT | | WT | | WT | | WT | | WT | | WT |
| CDH1 |  | | WT | | 0 | | WT | | 0 | | WT | | 0 | | 0-M/D | | WT | | M/D | | WT | | 0 | | 0 | | WT |
| CDKN1A | | | WT | | WT | | WT | | WT | | 0 | | 0 | | WT | | WT | | 0 | | WT | | WT | | E | | WT |
| CDKN1B | | | 0 | | 0 | | WT | | 0 | | 0 | | 0 | | WT | | 0-M/D | | 0 | | WT | | 0 | | 0 | | WT |
| CDKN2A | | | 0-M/D | | 0 | | WT | | M/D | | M/D | | 0 | | 0 | | M/D | | 0 | | M/D | | 0-M/D | | 0 | | WT |
| CDKN2B | | | 0-M/D | | 0 | | WT | | M/D | | M/D | | 0 | | 0 | | M/D | | 0 | | M/D | | 0 | | 0 | | WT |
| CHEK1 | | | 0 | | WT | | WT | | WT | | 0 | | 0 | | WT | | WT | | WT | | 0-M/D | | WT | | 0 | | WT |
| CHEK2 | | | WT | | 0 | | WT | | 0 | | 0 | | 0 | | 0 | | 0 | | 0 | | WT | | 0 | | 0 | | WT |
| CREBBP | | | 0 | | 0 | | WT | | 0 | | WT | | 0 | | WT | | WT | | WT | | WT | | 0 | | 0 | | WT |
| CYLD |  | | WT | | 0 | | WT | | 0 | | WT | | 0 | | WT | | WT | | WT | | 0 | | WT | | WT | | WT |
| DLC1 |  | | 0-M/D | | 0-M/D | | WT | | 0 | | WT | | 0-M/D | | 0 | | WT | | 0 | | 0 | | 0 | | 0 | | 0-M/D |
| FANCA | | | WT | | 0 | | WT | | 0 | | WT | | 0 | | WT | | WT | | 0-M/D | | WT | | WT | | WT | | WT |
| FANCB | | | 0-M/D | | 0 | | WT | | WT | | 0 | | 0 | | 0-M/D | | WT | | WT | | 0 | | 0-M/D | | 0 | | 0 |
| FANCC | | | 0 | | 0 | | WT | | WT | | 0 | | WT | | WT | | WT | | WT | | 0 | | WT | | 0 | | WT |
| FANCD2 | | | 0 | | WT | | WT | | WT | | WT | | 0 | | 0 | | WT | | 0 | | 0 | | 0 | | WT | | 0 |
| FANCE | | | WT | | WT | | WT | | WT | | 0 | | 0 | | 0 | | 0 | | 0 | | WT | | WT | | WT | | WT |
| FANCF | | | 0 | | WT | | 0 | | WT | | WT | | 0 | | WT | | WT | | WT | | 0 | | 0 | | 0 | | 0 |
| **Table S11 cont.**  gene symbol | |  | H441 | | PC-3 | | A2780 | | MDA-MB-231 | | A549 | | SW480 | | HCT 116 | | SK-OV-3 | | SK-Br-3 | | Caki-2 | | DU 145 | | SW620 | | HT-29 |
|  | lung c. | | prost.c. | | ovar.c. | | br.c. | | lung c. | | col.c. | | col.c. | | ovar.c. | | br.c. | | kid.c. | | prost.c. | | col.c. | | col.c. |
|  | |  |  | |  | |  | |  | |  | |  | |  | |  | |  | |  | |  | |  | |  |
| FANCG | | | WT | | 0 | | WT | | WT | | 0 | | WT | | WT | | 0 | | 0 | | 0 | | WT | | 0 | | WT |
| FANCI |  | | 0 | | 0 | | WT | | 0 | | WT | | 0 | | WT | | WT | | WT | | WT | | WT | | 0 | | WT |
| FANCL | | | WT | | 0 | | WT | | WT | | WT | | WT | | WT | | 0 | | WT | | WT | | WT | | WT | | WT |
| FANCM | | | WT | | WT | | WT | | WT | | WT | | 0 | | WT | | 0 | | WT | | 0 | | WT | | 0 | | 0-M/D |
| FBXW7 | | | 0 | | 0 | | WT | | WT | | 0 | | 0 | | WT | | 0 | | 0 | | 0 | | 0-M/D | | 0 | | WT |
| FH |  | | WT | | WT | | WT | | WT | | 0 | | 0 | | WT | | WT | | WT | | WT | | WT | | WT | | WT |
| FHIT |  | | 0 | | WT | | 0 | | 0 | | 0 | | 0 | | 0 | | 0 | | 0 | | 0 | | 0 | | 0 | | M/D |
| FLCN |  | | WT | | 0 | | WT | | 0 | | WT | | 0 | | WT | | 0-M/D | | 0 | | 0 | | 0-M/D | | 0 | | 0 |
| HIPK2 |  | | WT | | WT | | E | | WT | | WT | | 0 | | 0 | | 0-M/D | | E | | WT | | WT | | WT | | 0 |
| KDM6A | | | 0-M/D | | 0 | | WT | | WT | | 0 | | 0 | | 0-M/D | | WT | | WT | | 0 | | 0-M/D | | 0 | | WT |
| LATS1 | | | 0 | | 0 | | 0-M/D | | 0 | | 0 | | 0 | | 0-M/D | | WT | | WT | | WT | | 0 | | WT | | 0 |
| LATS2 | | | 0 | | WT | | WT | | 0 | | 0 | | 0 | | WT | | WT | | WT | | 0 | | 0 | | 0 | | 0 |
| MEN1 |  | | WT | | WT | | WT | | WT | | WT | | 0 | | WT | | WT | | WT | | 0 | | WT | | 0 | | 0 |
| MLH1 |  | | 0 | | WT | | WT | | WT | | WT | | 0 | | M/D | | M/D | | WT | | 0 | | 0 | | WT | | 0 |
| MSH2 |  | | WT | | 0 | | WT | | WT | | 0 | | WT | | WT | | WT | | WT | | WT | | 0 | | WT | | WT |
| MSH6 |  | | WT | | WT | | WT | | WT | | WT | | 0 | | WT | | WT | | WT | | 0 | | 0 | | 0 | | WT |
| NBN |  | | 0 | | 0 | | WT | | 0 | | WT | | 0 | | WT | | 0 | | 0 | | 0 | | WT | | 0 | | WT |
| NF1 |  | | WT | | 0 | | WT | | 0 | | 0 | | 0 | | 0-M/D | | 0 | | 0-M/D | | WT | | 0 | | 0 | | WT |
| NF2 |  | | WT | | 0 | | WT | | M/D | | 0 | | 0 | | WT | | WT | | 0 | | WT | | 0 | | 0 | | WT |
| PALB2 | | | 0-M/D | | 0 | | WT | | 0 | | 0 | | 0 | | WT | | WT | | WT | | WT | | 0 | | WT | | WT |
| PRKAR1A | | | WT | | WT | | WT | | 0 | | WT | | 0 | | WT | | WT | | WT | | WT | | 0 | | 0 | | WT |
| PTCH1 | | | WT | | 0 | | WT | | WT | | 0 | | WT | | WT | | WT | | WT | | 0 | | WT | | 0 | | WT |
| PTEN |  | | 0 | | E-M/D | | 0 | | WT | | WT | | 0 | | WT | | 0-M/D | | 0 | | WT | | WT | | 0 | | WT |
| RAD50 | | | 0-M/D | | 0 | | WT | | WT | | WT | | 0 | | 0-M/D | | WT | | 0-M/D | | WT | | 0 | | 0 | | WT |
| RAD51 | | | 0 | | WT | | WT | | 0 | | 0 | | 0 | | WT | | WT | | WT | | WT | | WT | | 0 | | WT |
| **Table S11 cont.**  Gene symbol | |  | H441 | | PC-3 | | A2780 | | MDA-MB-231 | | A549 | | SW480 | | HCT 116 | | SK-OV-3 | | SK-Br-3 | | Caki-2 | | DU 145 | | SW620 | | HT-29 |
|  | lung c. | | prost.c. | | ovar.c. | | br.c. | | lung c. | | col.c. | | col.c. | | ovar.c. | | br.c. | | kid.c. | | prost.c. | | col.c. | | col.c. |
|  | |  |  | |  | |  | |  | |  | |  | |  | |  | |  | |  | |  | |  | |  |
| RB1 | |  | 0 | | WT | | WT | | 0 | | 0 | | 0 | | 0 | | WT | | WT | | 0 | | M/D | | 0 | | 0 |
| RUNX1 | | | WT | | WT | | WT | | WT | | 0 | | WT | | WT | | WT | | WT | | WT | | WT | | WT | | 0 |
| SDHB |  | | WT | | WT | | WT | | WT | | 0 | | 0 | | WT | | WT | | 0 | | 0 | | 0 | | WT | | WT |
| SDHD |  | | 0 | | WT | | WT | | WT | | 0 | | 0 | | WT | | WT | | WT | | 0 | | WT | | 0 | | 0 |
| SMAD2 | | | 0 | | 0 | | WT | | 0 | | 0 | | 0-M/D | | WT | | WT | | 0 | | 0 | | 0 | | 0-M/D | | 0 |
| SMAD4 | | | 0 | | 0 | | WT | | 0 | | 0 | | 0-M/D | | WT | | WT | | 0-M/D | | 0 | | 0 | | 0-M/D | | M/D |
| SMARCB1 | | | WT | | 0 | | WT | | 0 | | 0 | | 0 | | WT | | WT | | 0 | | WT | | 0 | | 0 | | 0 |
| STK11 | | | 0 | | 0 | | WT | | WT | | 0-M/D | | 0 | | WT | | WT | | 0 | | 0 | | 0 | | 0 | | 0 |
| STK3 |  | | WT | | 0-M/D | | WT | | 0 | | WT | | 0 | | WT | | WT | | WT | | 0 | | WT | | 0 | | WT |
| SUFU |  | | 0 | | 0 | | 0 | | WT | | 0 | | 0 | | WT | | 0-M/D | | 0-M/D | | WT | | 0 | | 0 | | WT |
| TGFBR2 | | | 0 | | WT | | WT | | WT | | WT | | 0 | | 0-M/D | | 0-M/D | | WT | | 0 | | 0 | | WT | | 0 |
| TNFAIP3 | | | 0 | | 0 | | 0-M/D | | 0 | | 0 | | 0 | | WT | | WT | | WT | | WT | | 0 | | WT | | 0 |
| TP53 |  | | M/D | | E-M/D | | WT | | M/D | | WT | | M/D | | WT | | E-M/D | | M/D | | 0 | | 0 | | M/D | | M/D |
| TP53BP1 | | | 0 | | WT | | 0 | | 0 | | 0 | | 0 | | 0 | | 0 | | WT | | 0 | | 0 | | 0 | | 0 |
| TSC1 |  | | 0 | | 0 | | WT | | WT | | 0 | | WT | | WT | | WT | | WT | | 0 | | WT | | 0 | | WT |
| TSC2 |  | | 0 | | 0 | | WT | | 0 | | WT | | 0 | | WT | | WT | | WT | | WT | | 0 | | 0 | | WT |
| VHL |  | | 0 | | WT | | WT | | WT | | WT | | 0 | | 0 | | WT | | 0 | | M/D | | 0 | | WT | | 0 |
| WRN |  | | 0-M/D | | 0 | | WT | | 0 | | WT | | 0 | | 0 | | WT | | 0 | | 0 | | WT | | 0 | | 0-M/D |
| WT1 |  | | 0 | WT | | WT | | WT | | WT | | 0 | | WT | | WT | | WT | | 0 | | 0 | | 0 | | 0 | |

**Mutational status**

wild - type

no category

mutation / deletion - no loss of mRNA expression

homozygous mutation / deletion

loss of mRNA expression - no mutation / deletion

loss of mRNA expression / heterozygous mutation or deletion

**Cell lines**

br. c. breast carcinoma

col. c. colon carcinoma

ovar c. ovarial carcinoma

lung c. lung carcinoma

panc. c. pancreatic carcinoma

prost c. prostate carcinoma

kid. c. kidney carcinoma