

**Supplementary Figure 1.** Dose-response matrices and Bliss drug synergy landscapes for the 50 drug pairs. The total number of drug combinations is 70 due to replicates.

**Supplementary Figure 2.** Histograms of the Bliss drug synergy scores, where the dasatinib-sorafenib combination is highlighted as a red bar.

**Supplementary Figure 3.** Interpretation of the network connectivity for the MDA-MB-231 drug combination network. (A) The predicted sensitivities for drug pairs that include BI 2536 (BI 2536 drug group) versus the others. (B) The predicted sensitivities for drug pairs that break the network (Group 1) versus the others (Group 2).

**Supplementary Figure 4.** %inhibition and %toxicity for *AURKB* siRNAs, *ZAK* siRNAs and their combinations. (A) Qiagen siRNAs and CellTiter-Glo readouts. (B) Ambion siRNAs and CellTiter-Glo readouts. (C) Ambion siRNAs and CellTox Green readouts. (D) The western blot gel images.

**Supplementary Figure 5.** %inhibition and %toxicity for *AURKB* sgRNAs, *ZAK* sgRNAs and sgRNA combinations in CRISPR/Cas9 screen.

**Supplementary Figure 6.** % inhibition and % toxicity for the Aurora B kinase inhibitors + *ZAK* siRNAs combination experiments for MDA-MB-361 and MDA-MB-436 cells.

**Supplementary Figure 7.** The RPKM values for the genes in the MDA-MB-231 specific signaling network, in relation to the distribution of all 675 cell lines reported in Klijn et al.<sup>24</sup>.

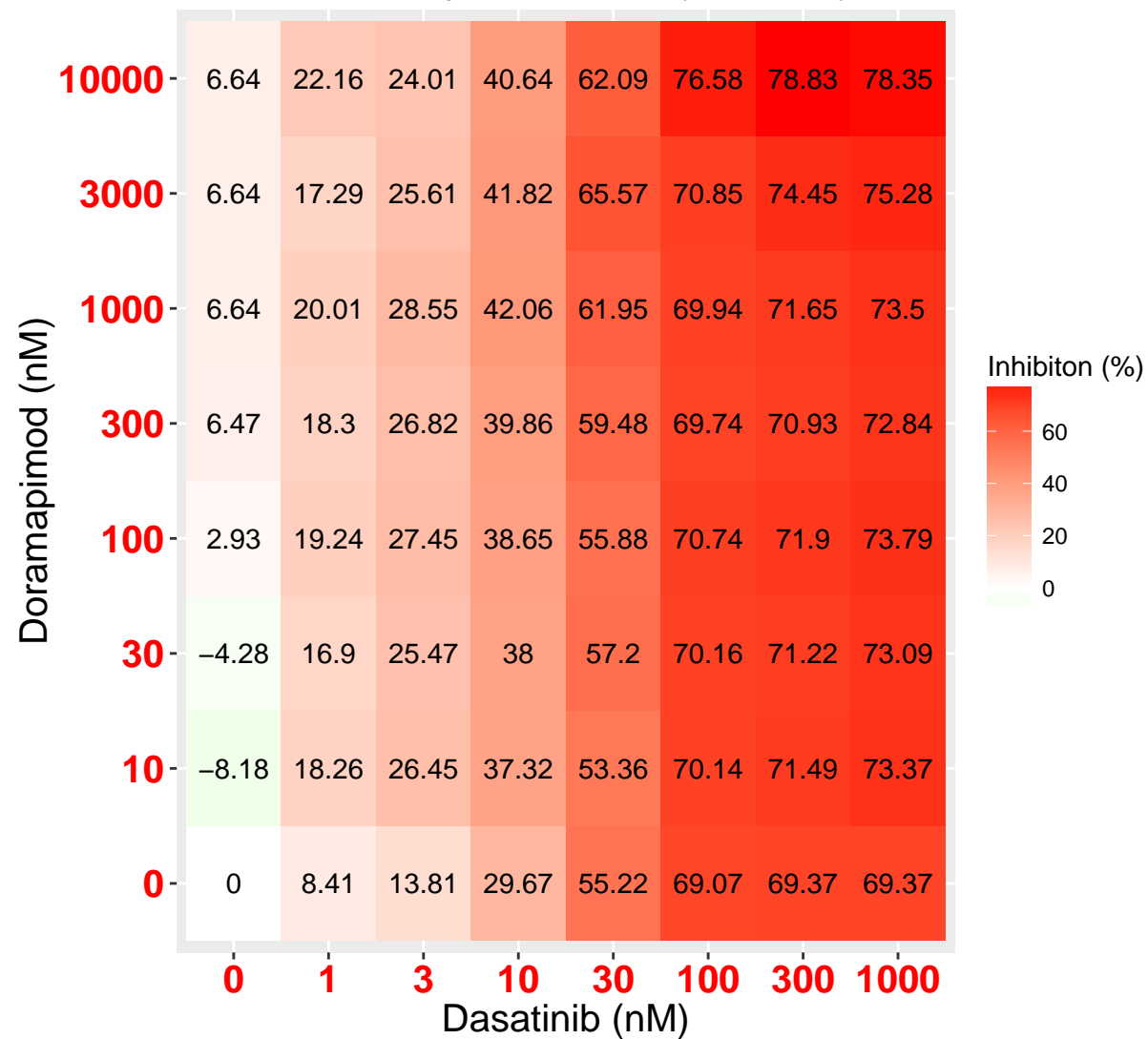
**Supplementary Figure 8.** The *ZAK* and *AURKB* gene expression levels in TNBC versus non-TNBC cell lines from the Klijn et al. study<sup>24</sup>.

**Supplementary Figure 9.** The Kaplan-Meier plot for the overall survival of TNBC patients with up-regulated *AURKB* expression (Z-score >2), down-regulated *CSF1R* (Z-score <0) and TP53 mutation (median months survival = 114, n = 17), as compared to the other TNBC patients (median

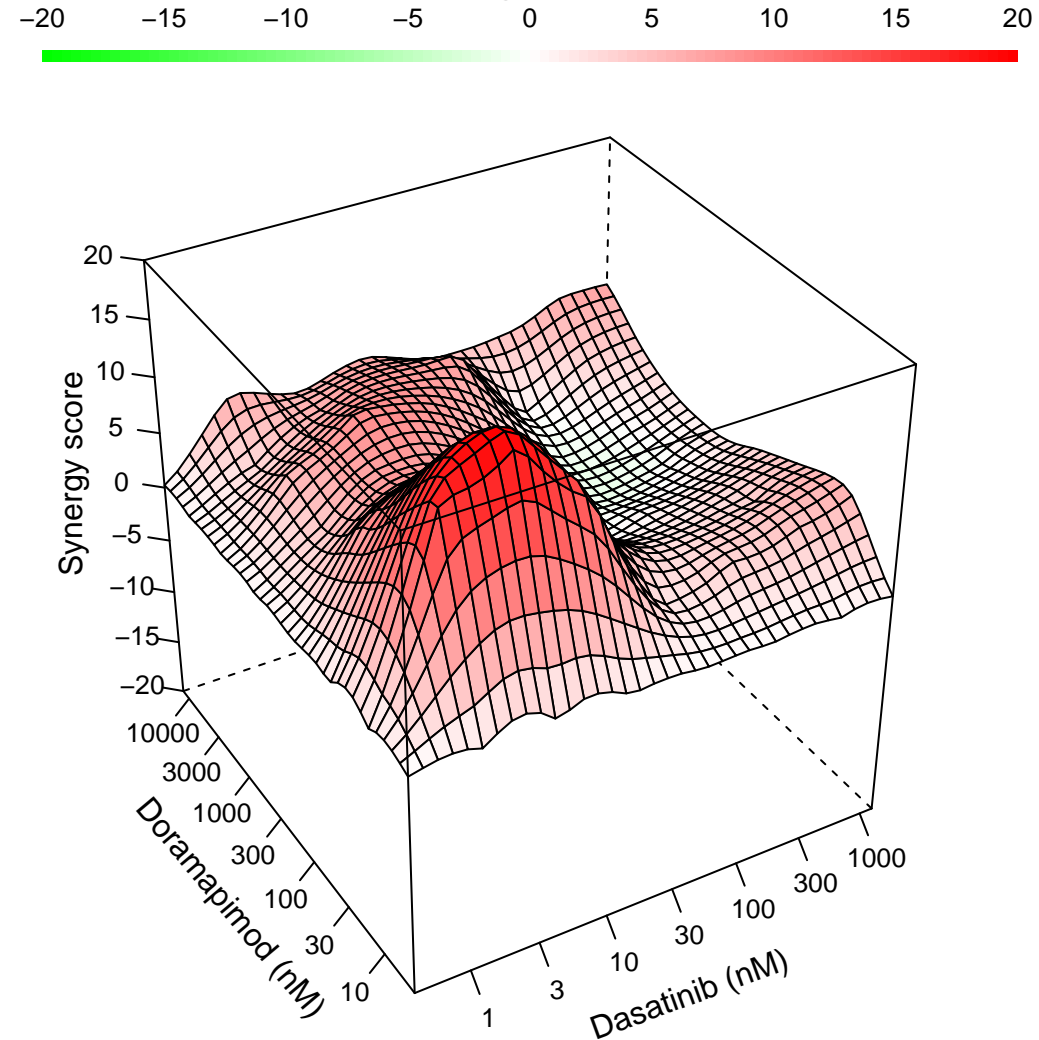
months survival not reached, n = 100). P-value = 0.68 by Fleming-Harrington test with weights p = 1 and q = 1.

**Supplementary Figure 10.** The Kaplan-Meier plot for the overall survival of TNBC patients with up-regulated MAP2K3 or MAPK11 (median months survival = 37.8, n = 20, Gene expression Z-score > 2) as compared to the other TNBC patients (median months survival = 114.1, n = 96).

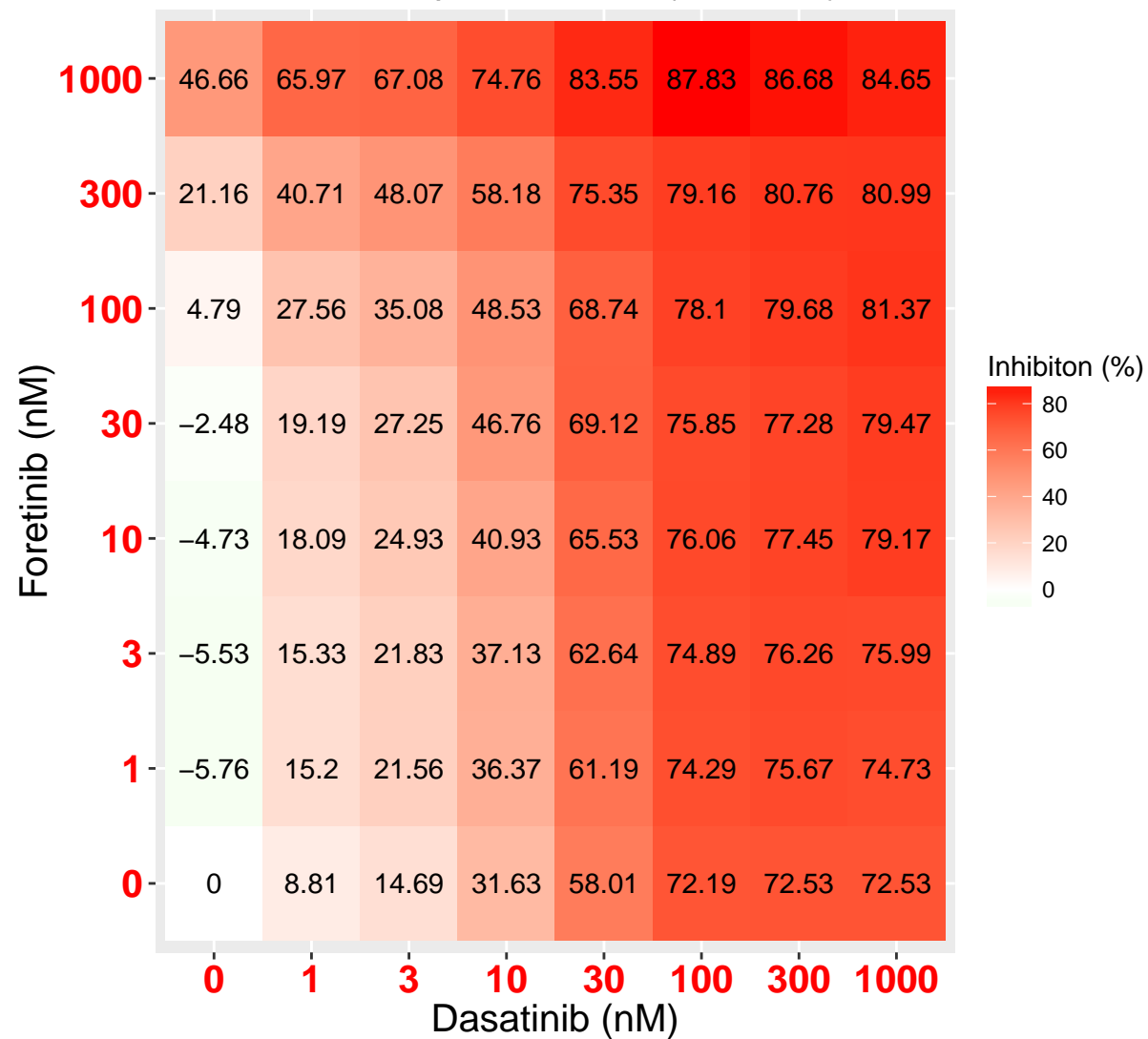
Dose-response matrix (inhibition)



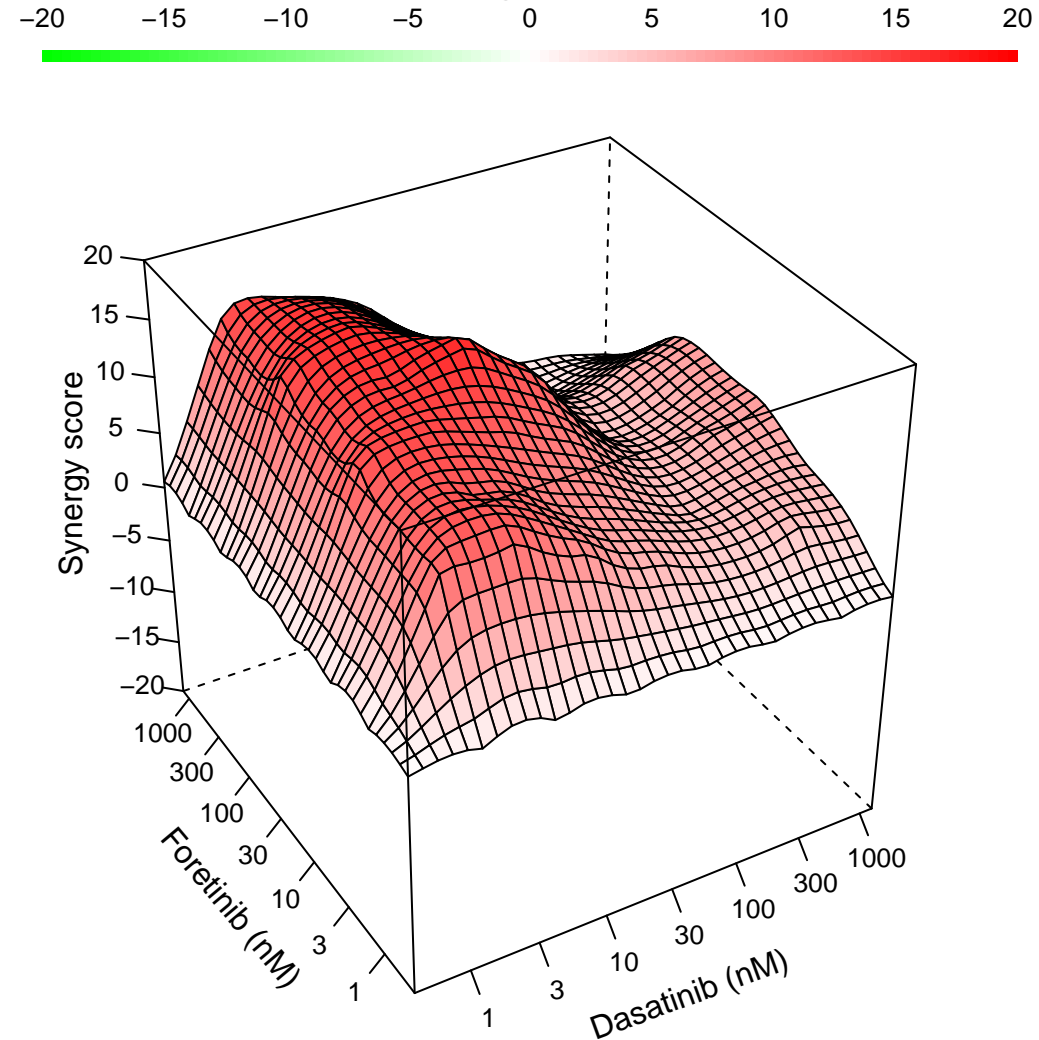
Bliss synergy score: 4.815



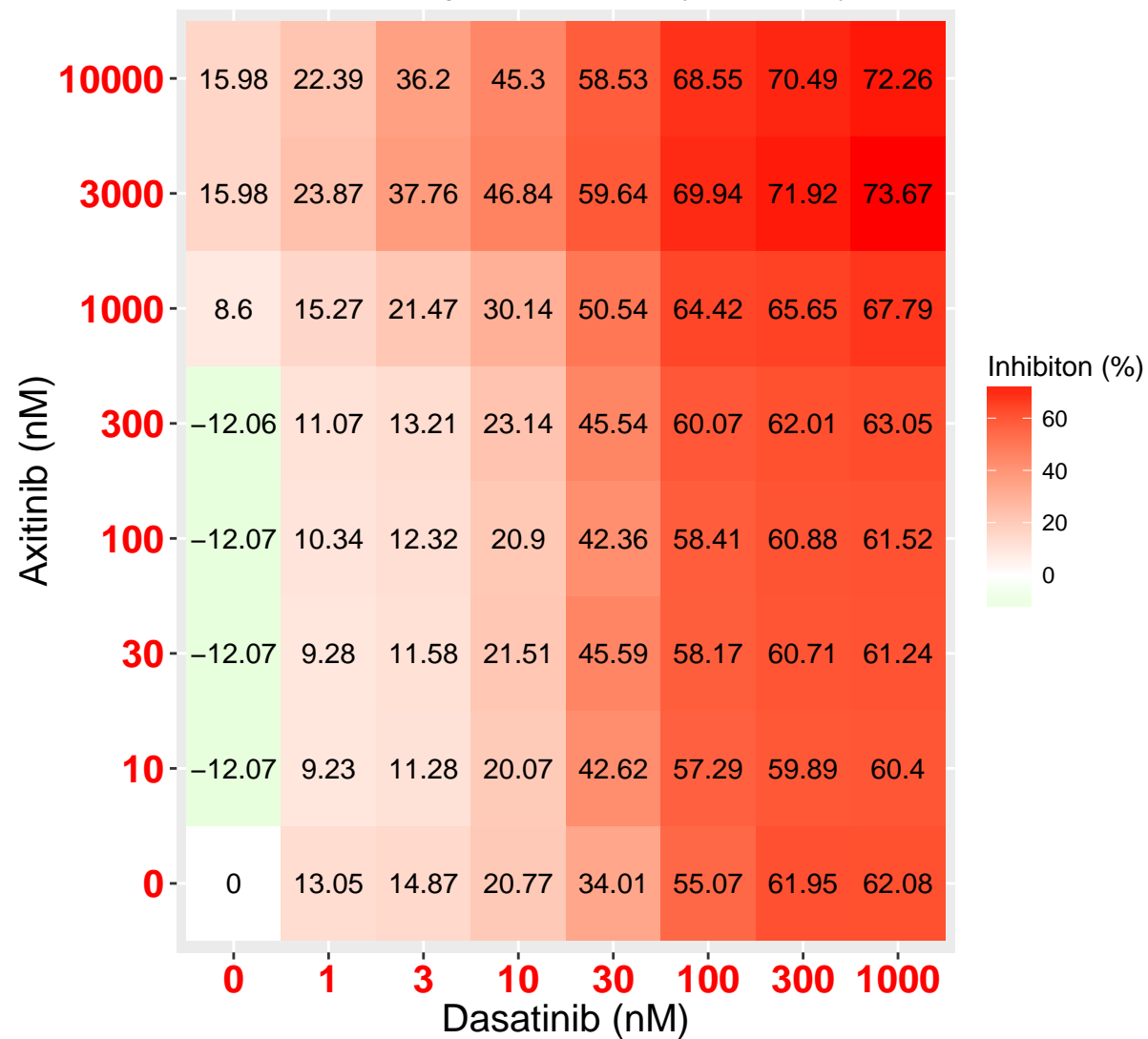
Dose-response matrix (inhibition)



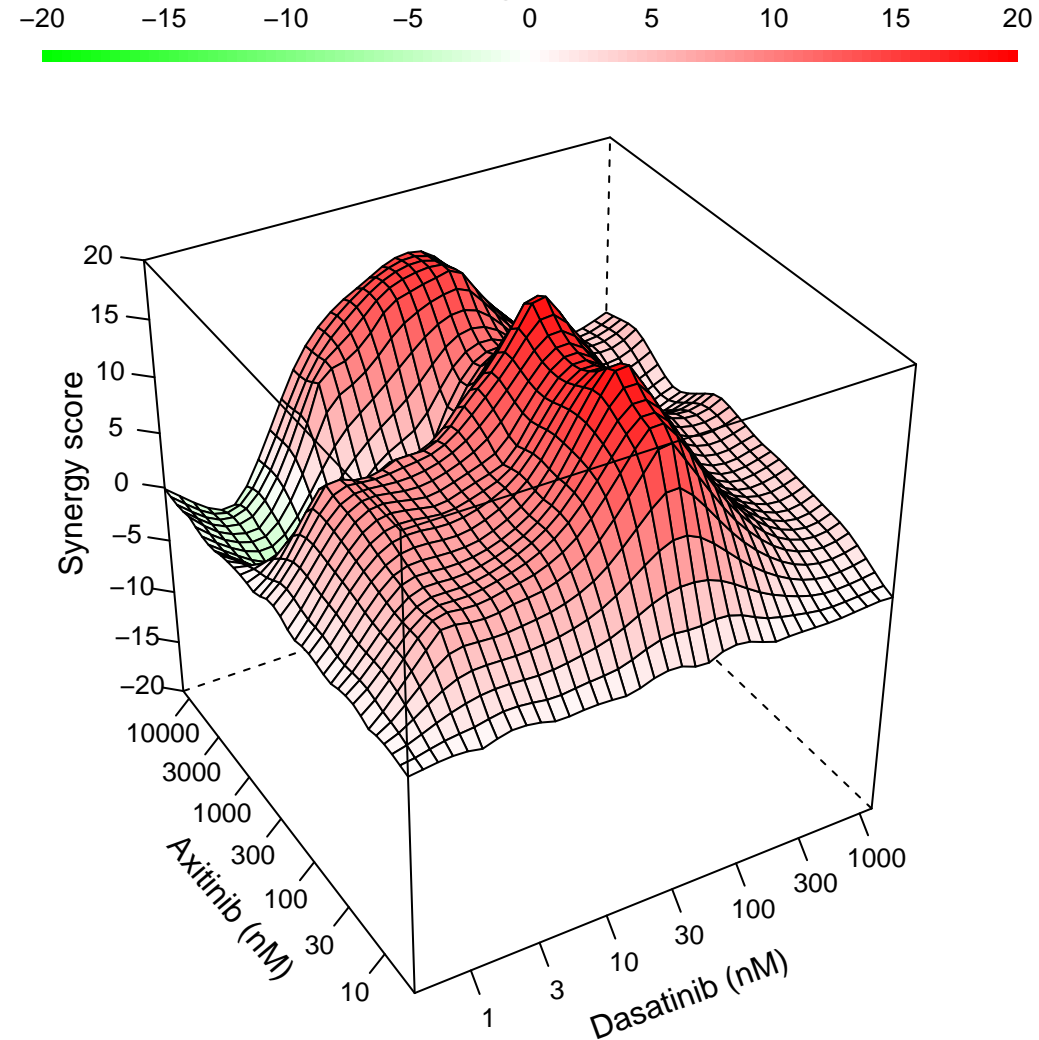
Bliss synergy score: 7.782



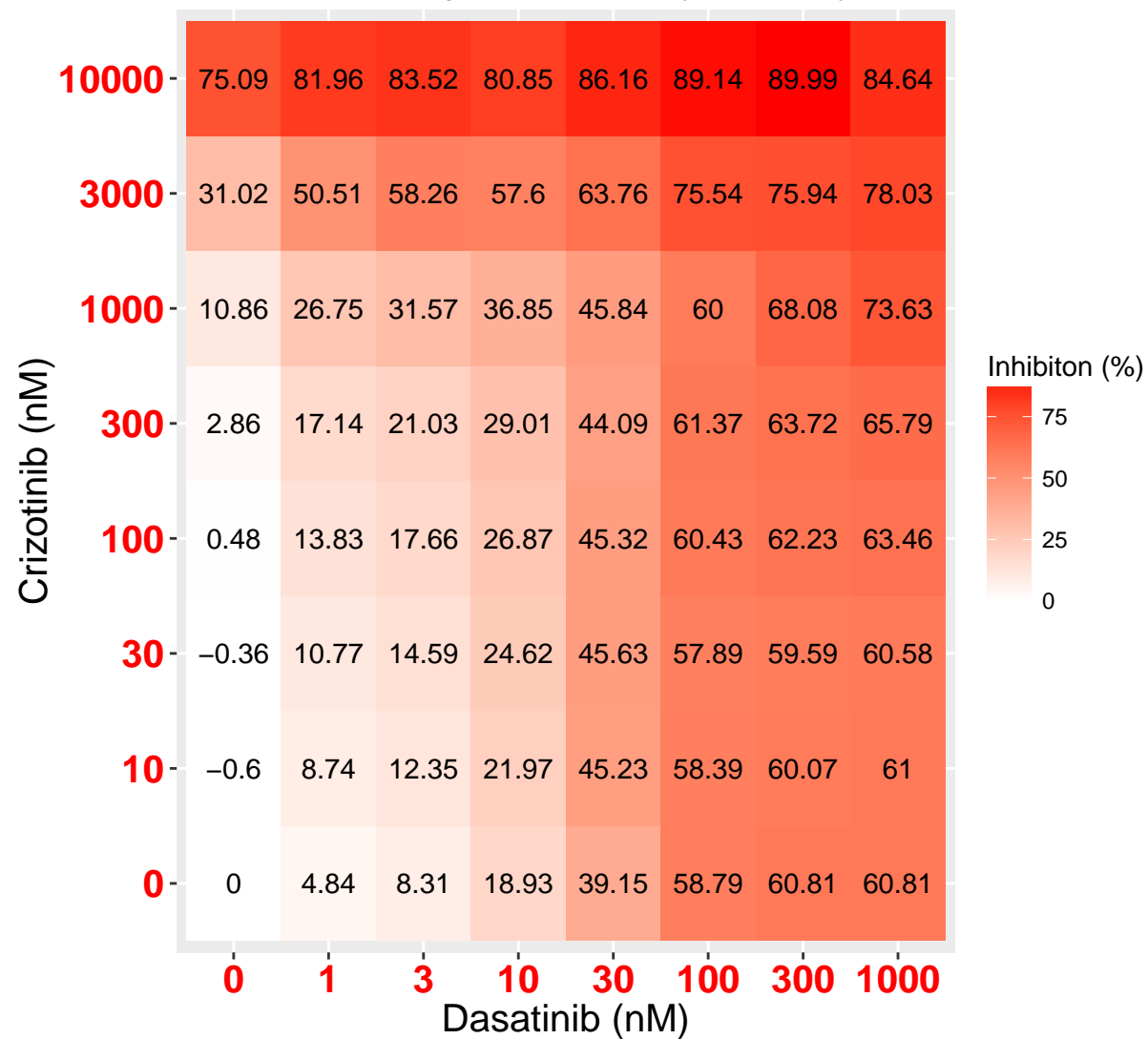
Dose-response matrix (inhibition)



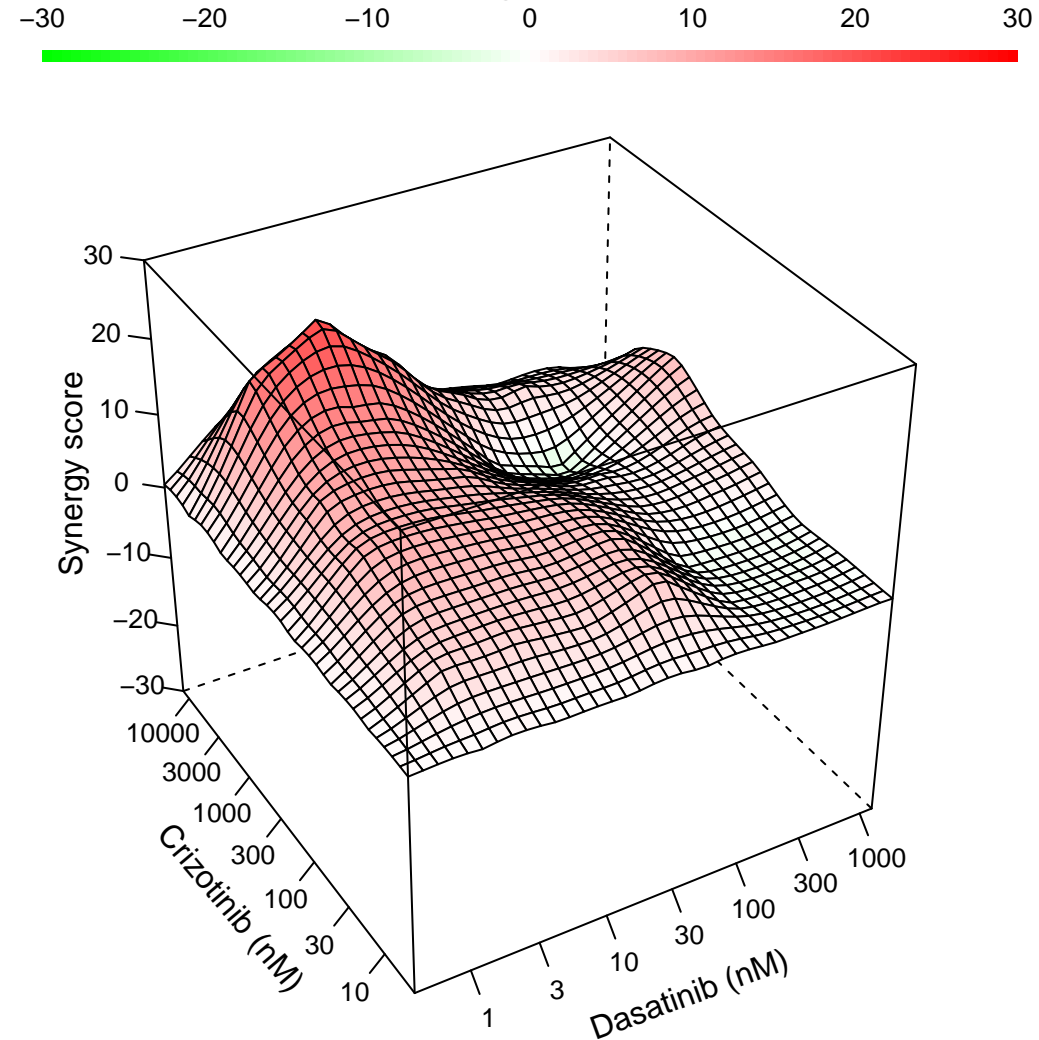
Bliss synergy score: 6.398



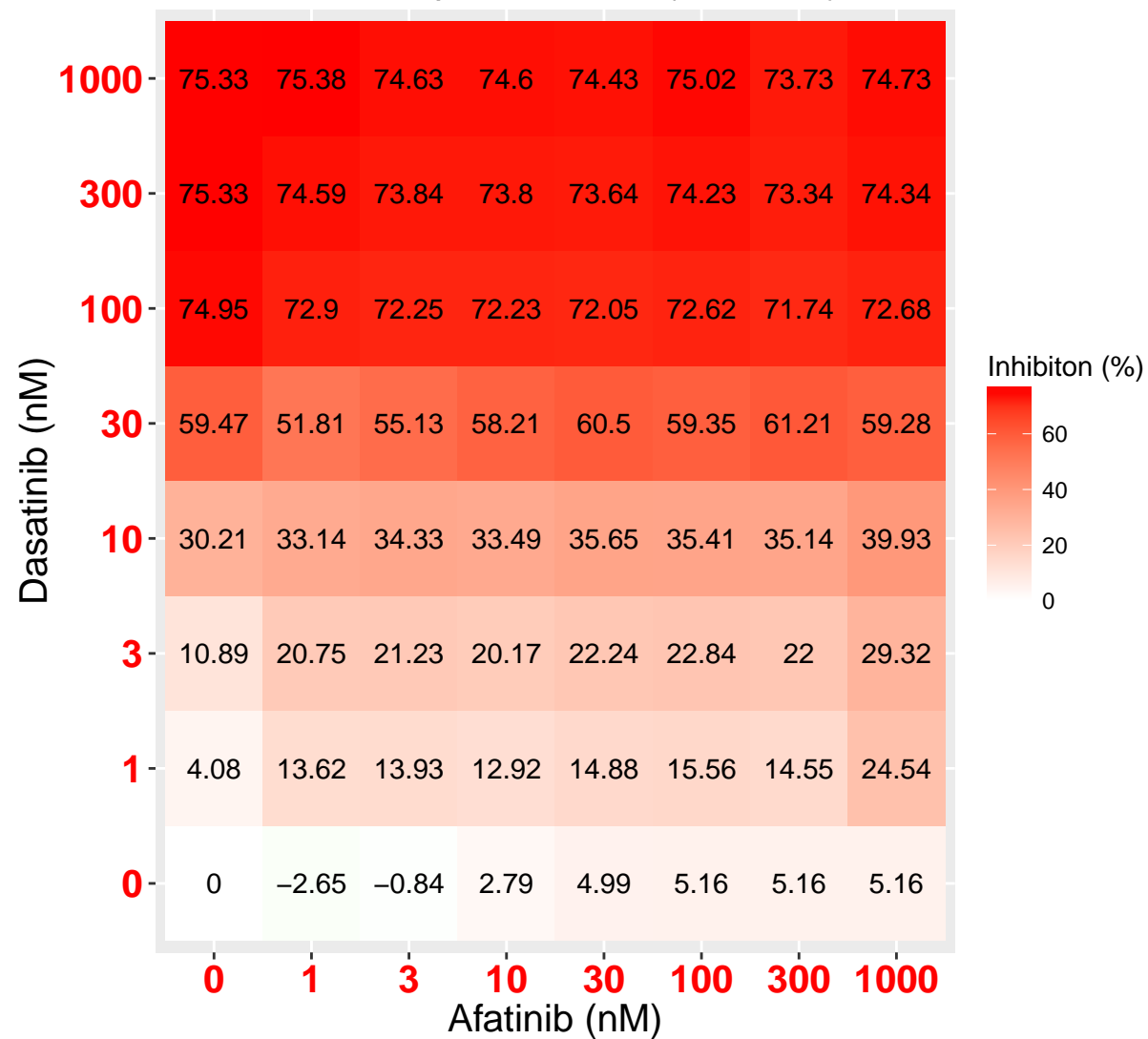
Dose-response matrix (inhibition)



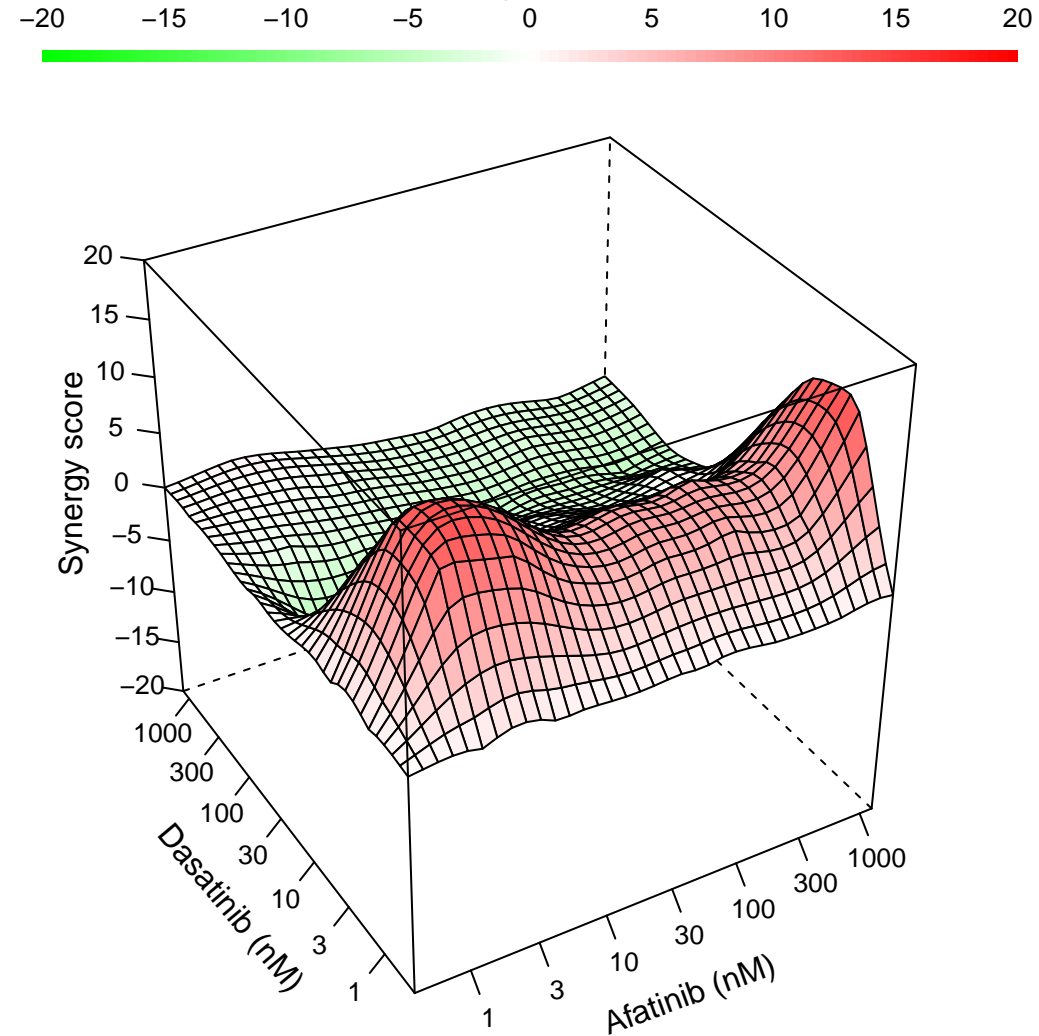
Bliss synergy score: 4.543



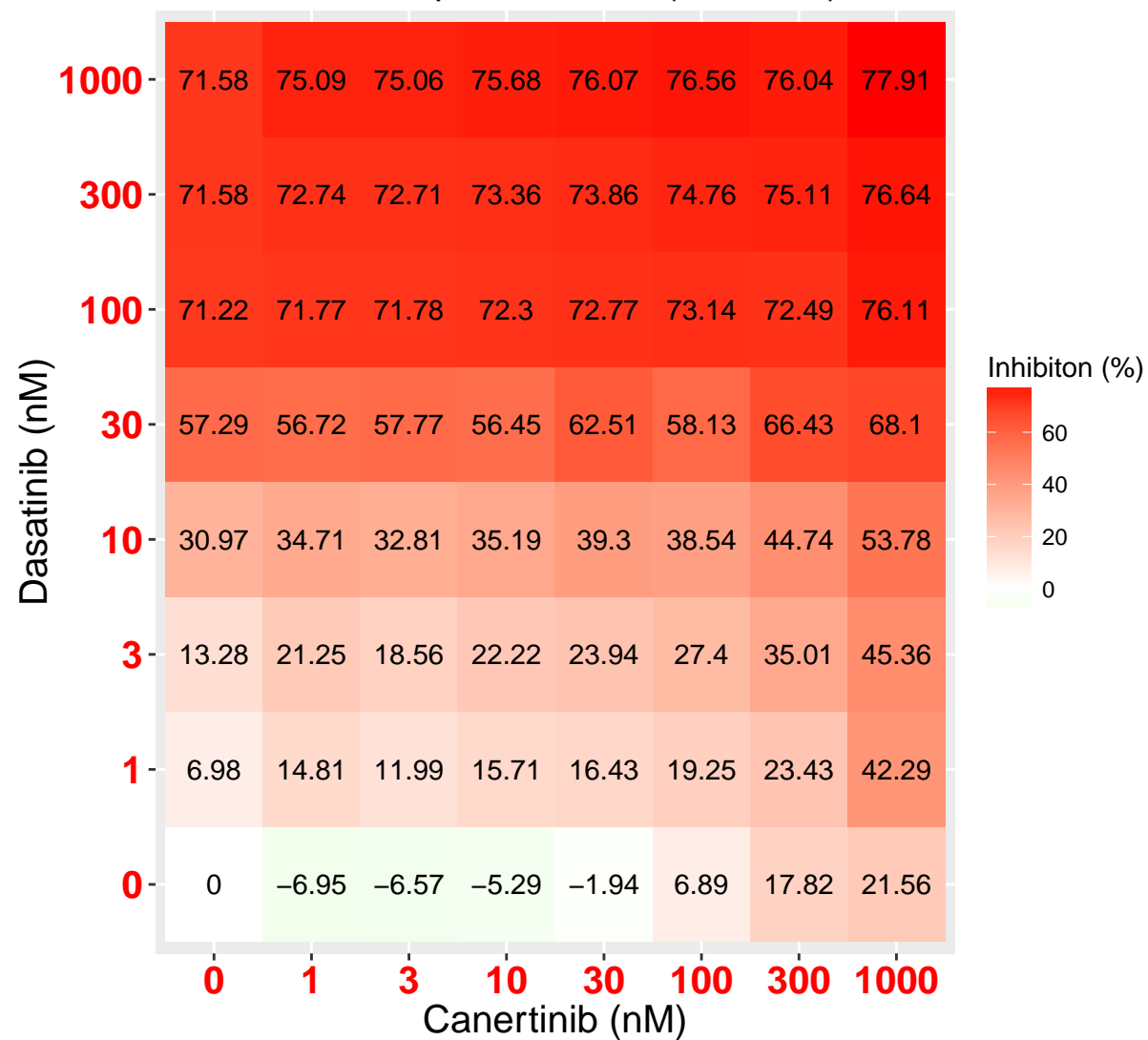
Dose-response matrix (inhibition)



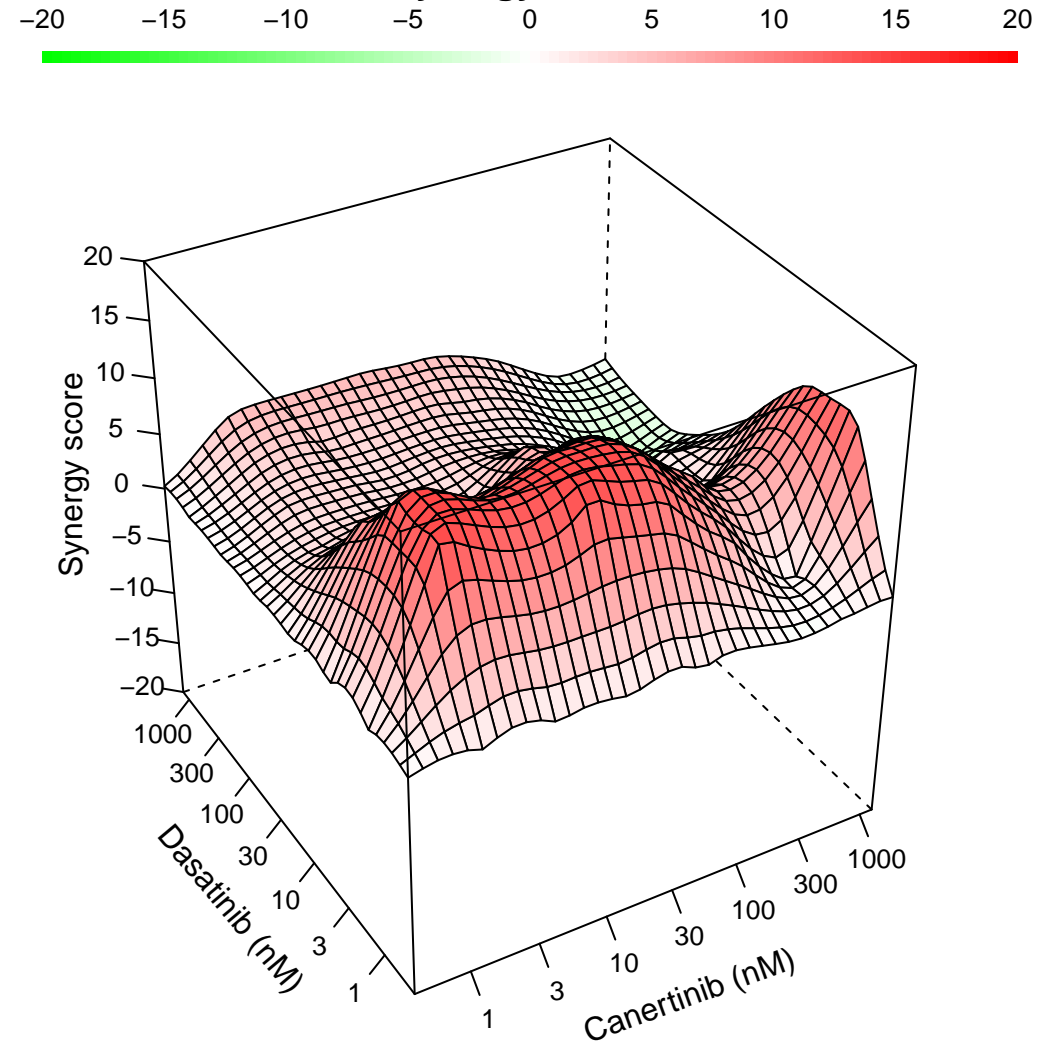
Bliss synergy score: 1.467



Dose-response matrix (inhibition)

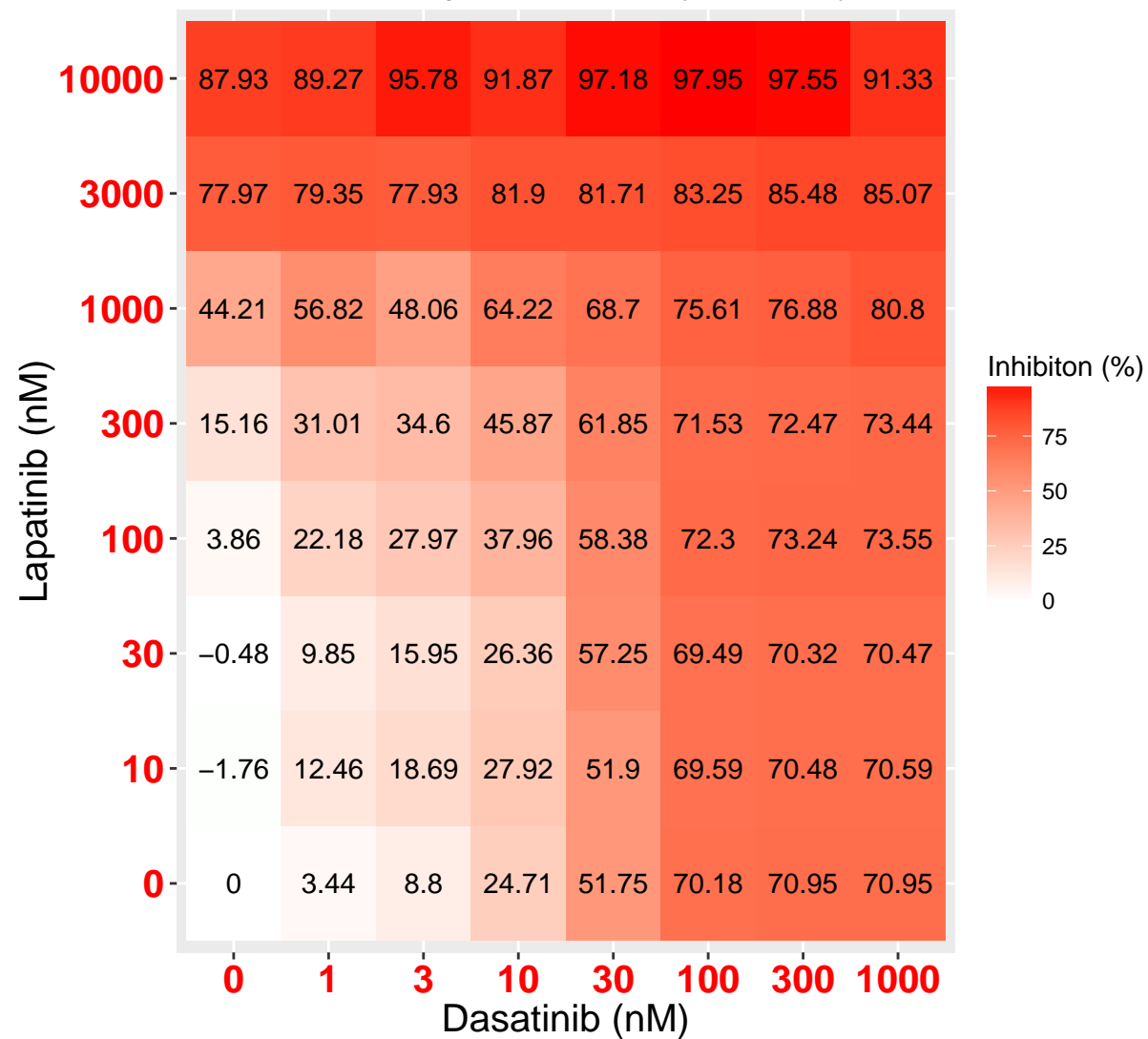


Bliss synergy score: 4.455

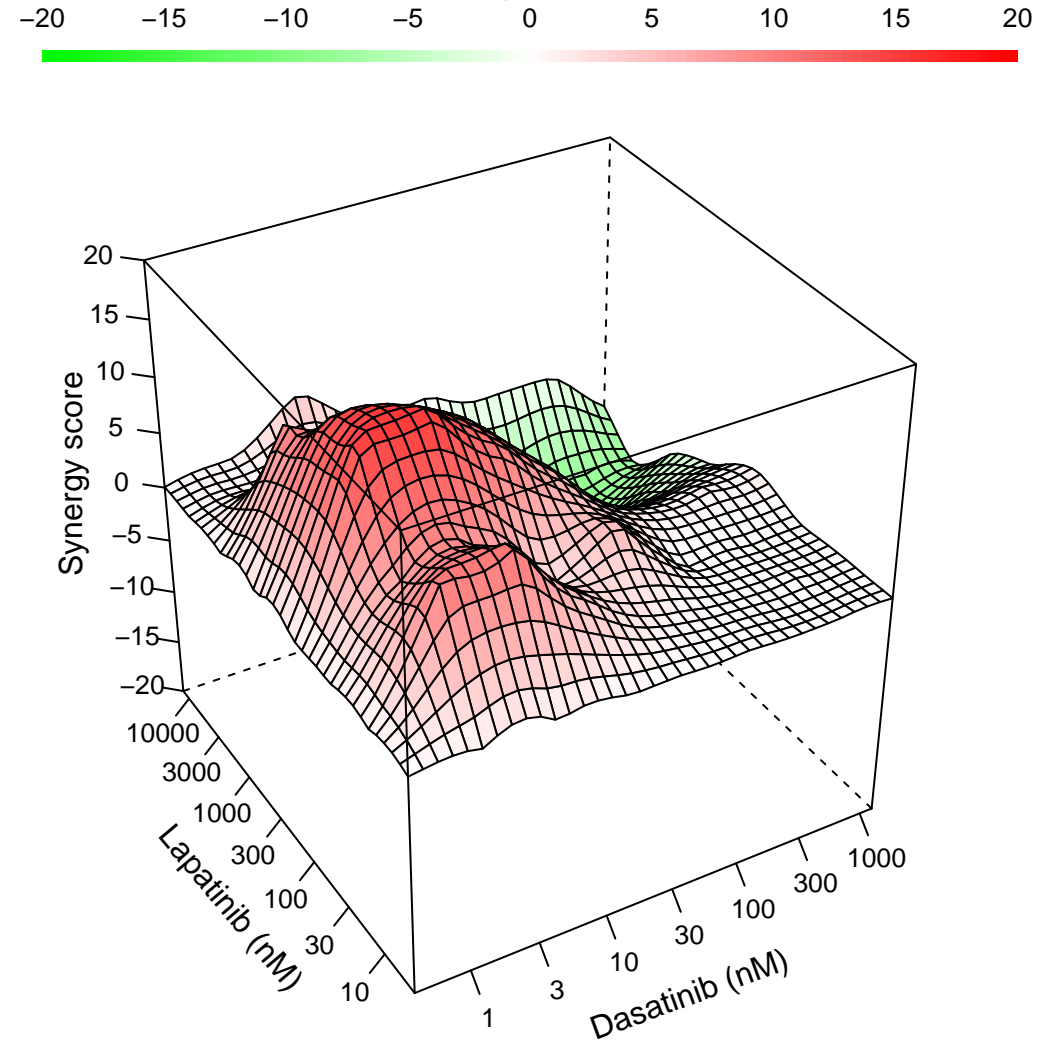




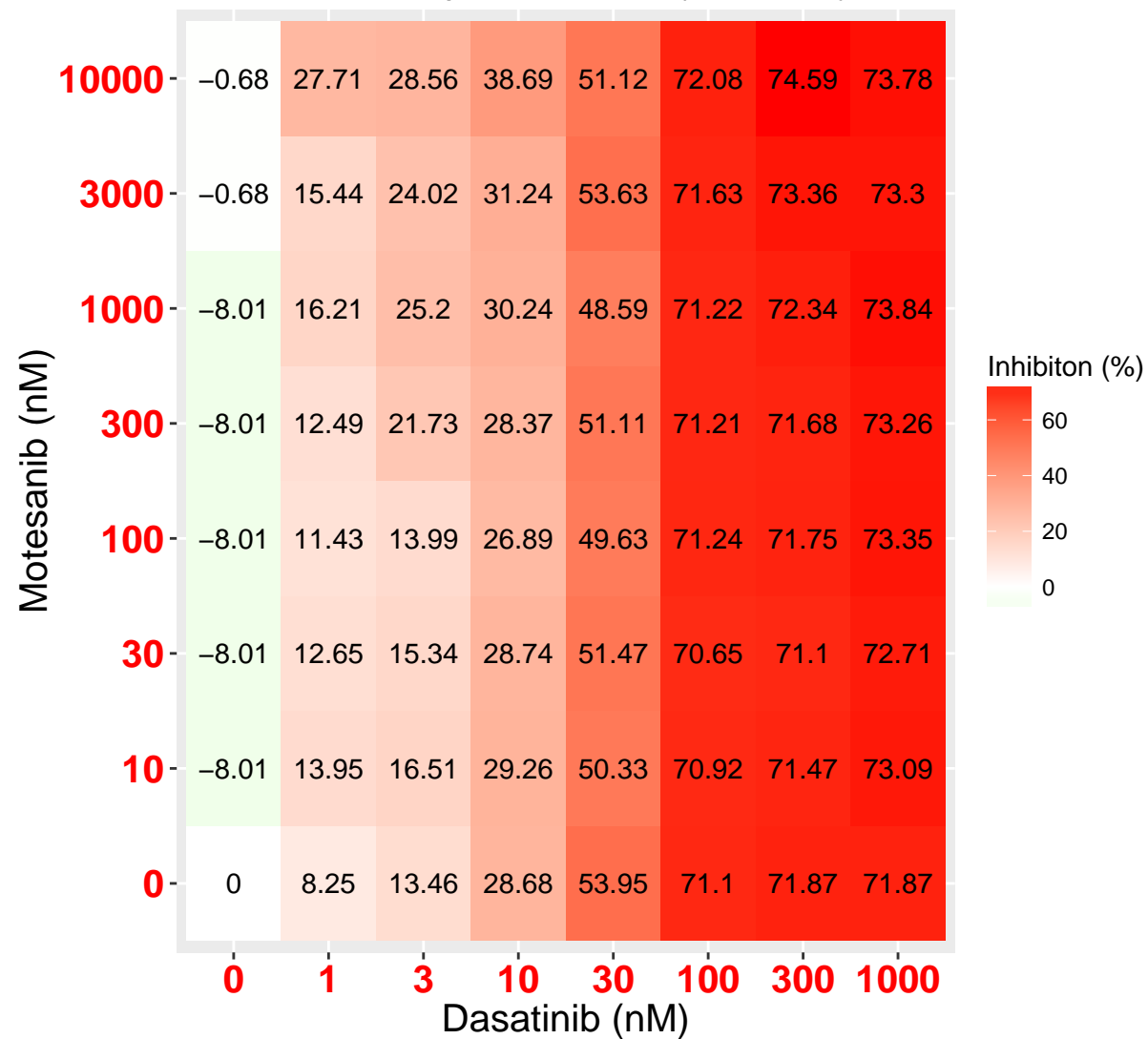
Dose-response matrix (inhibition)



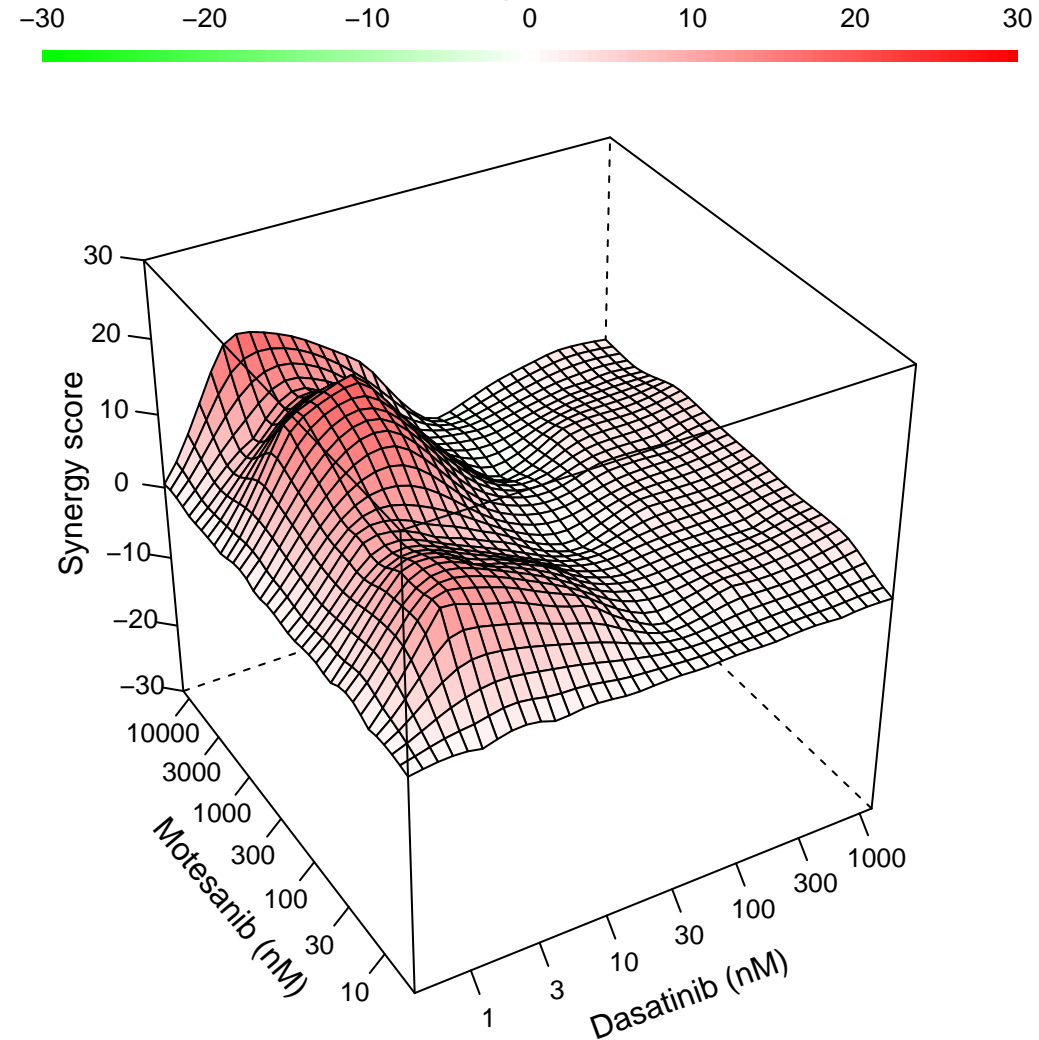
Bliss synergy score: 1.936



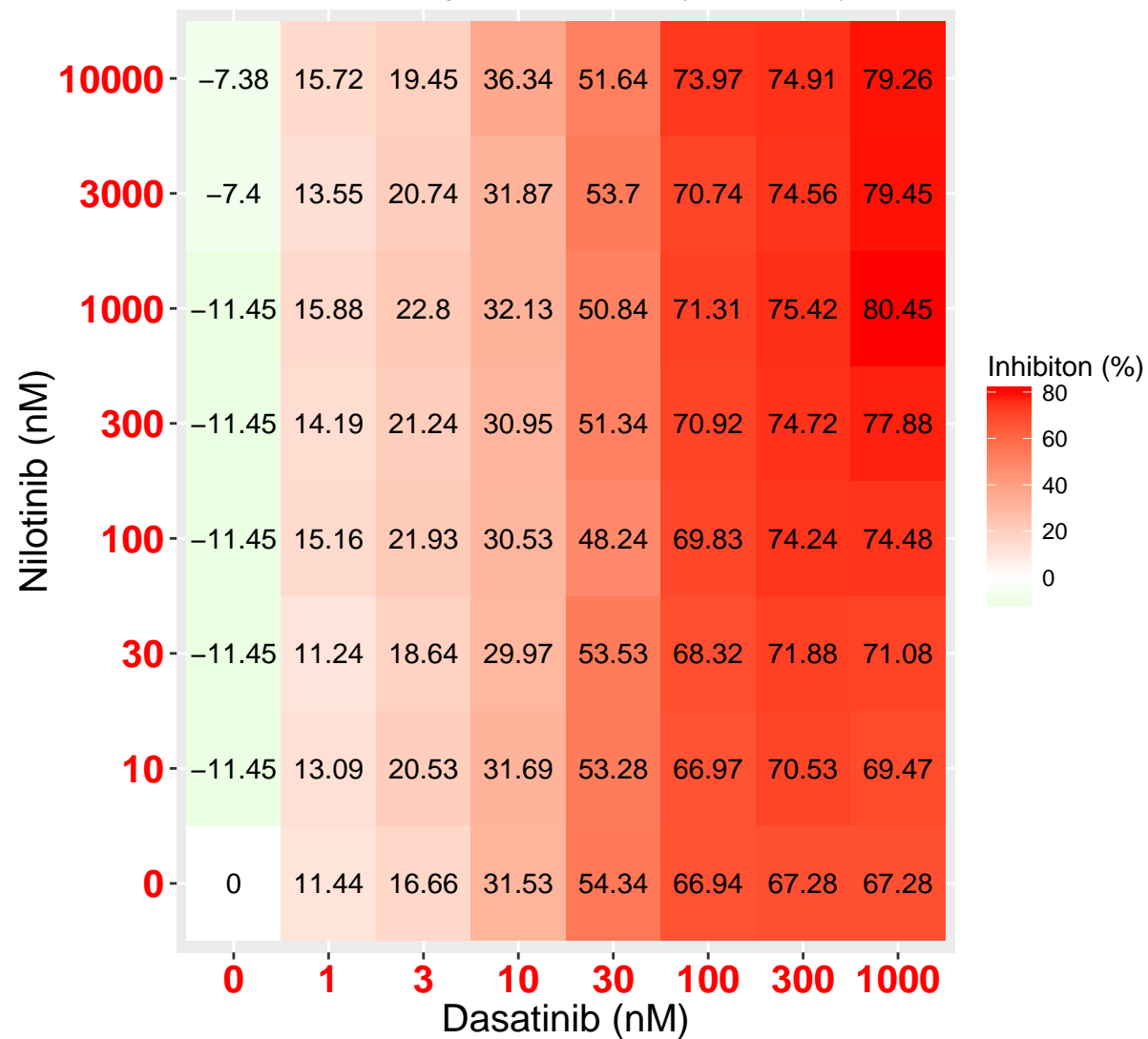
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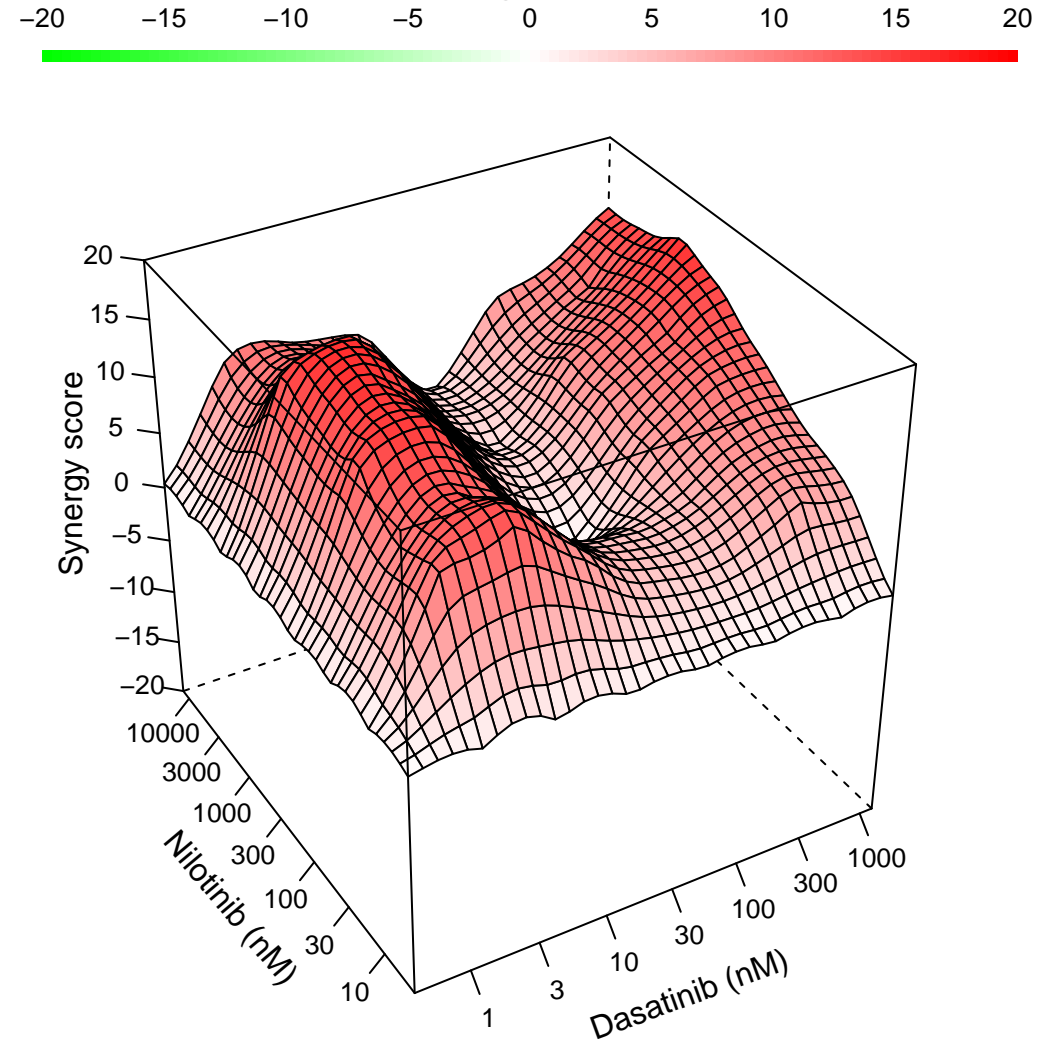
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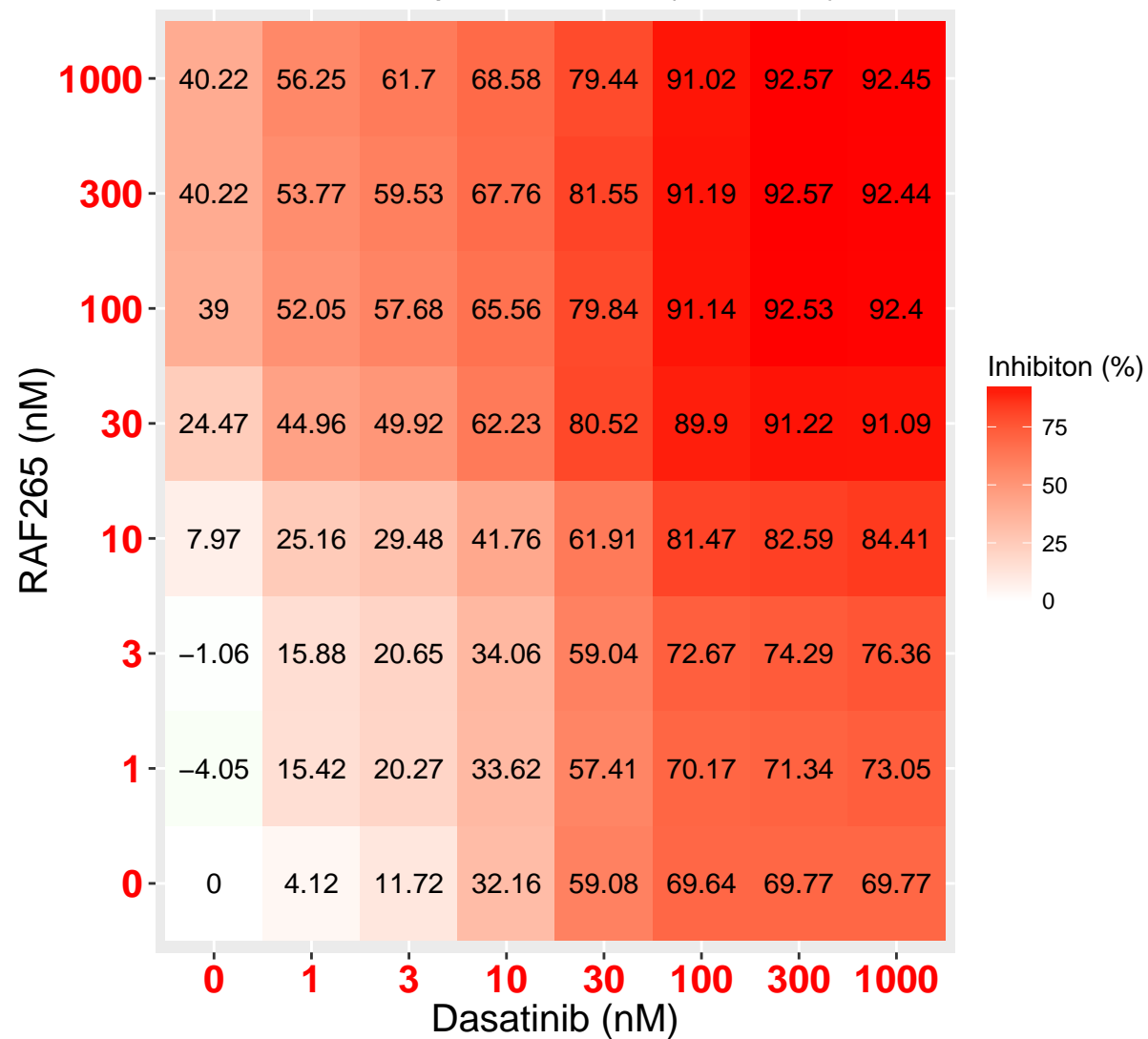
Dose-response matrix (inhibition)



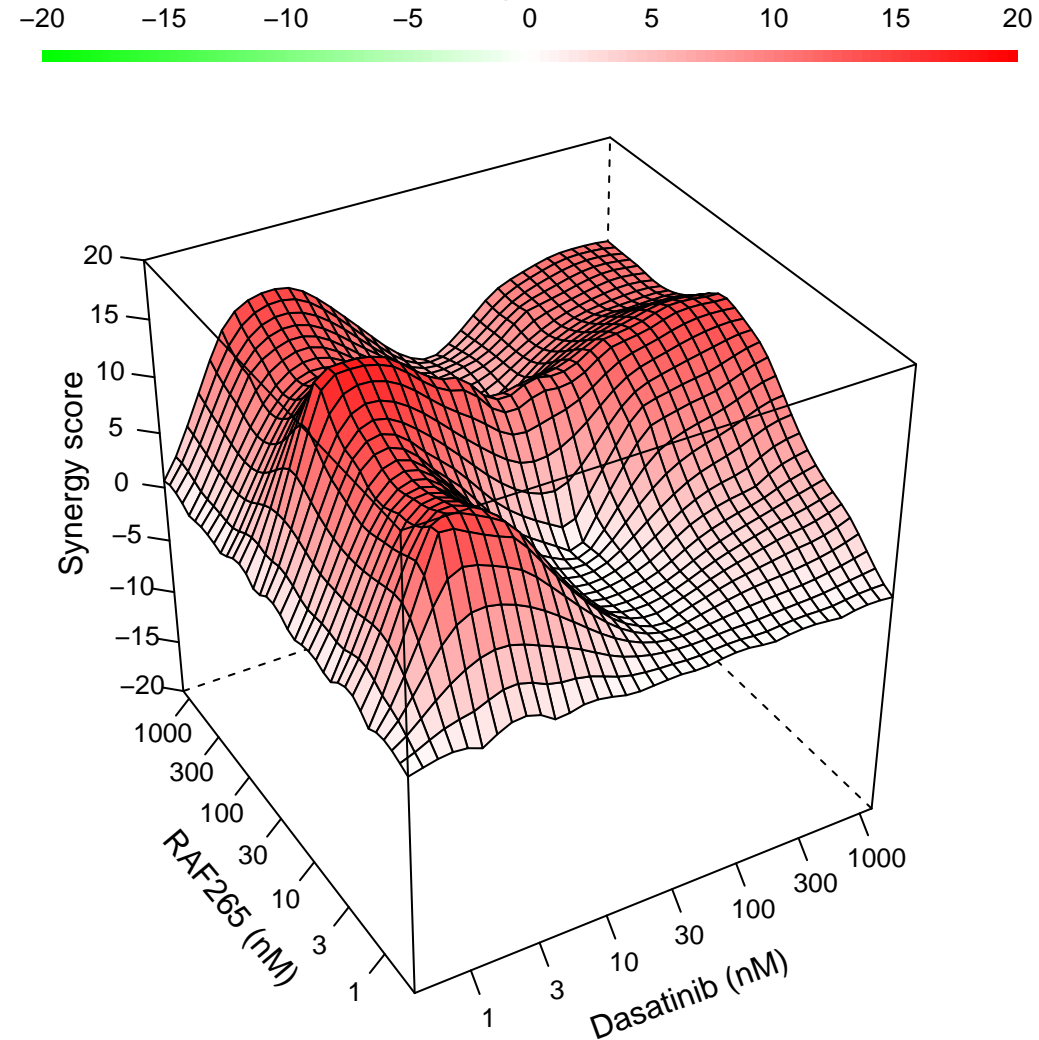
Bliss synergy score: 7.512



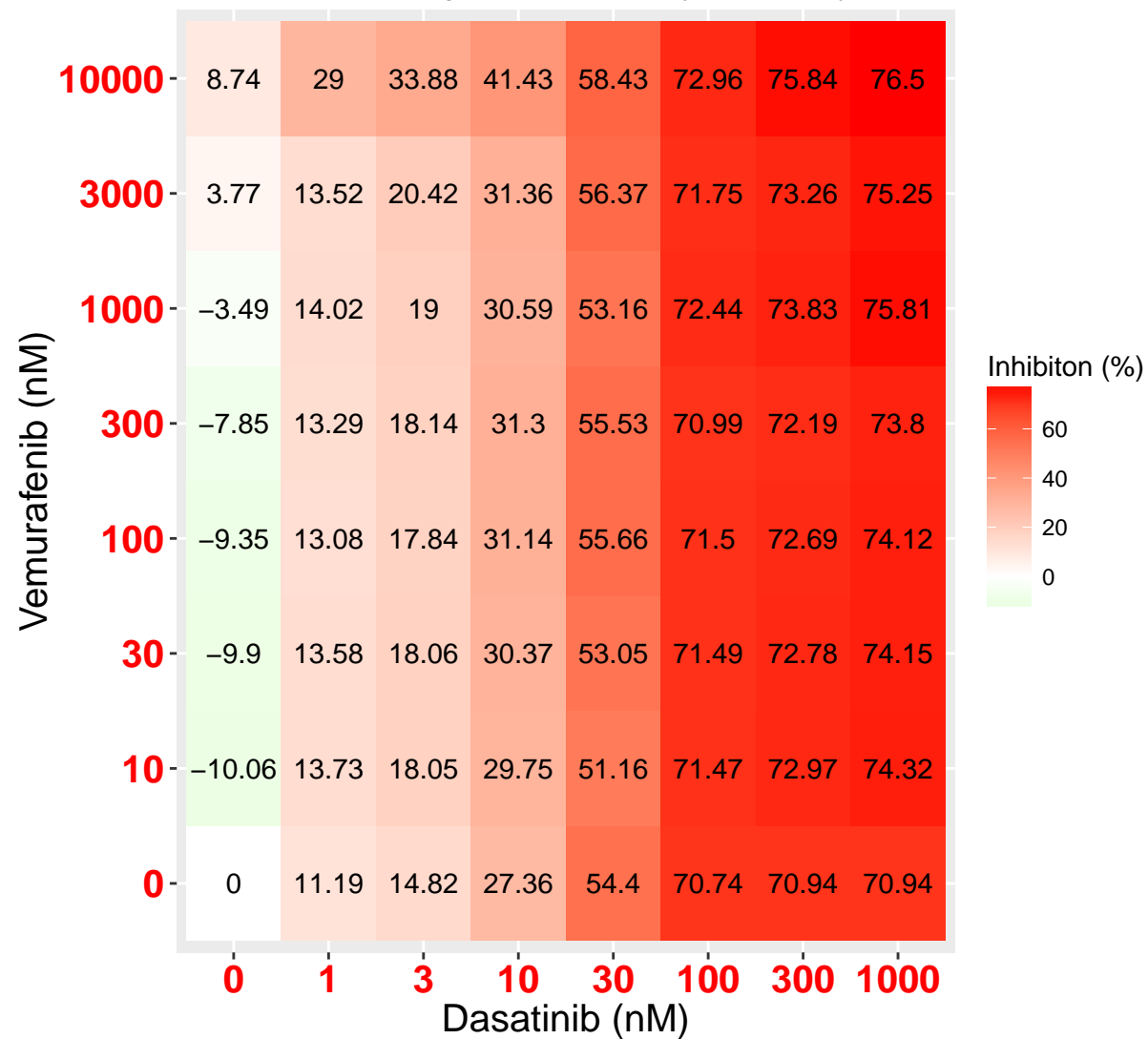
Dose-response matrix (inhibition)



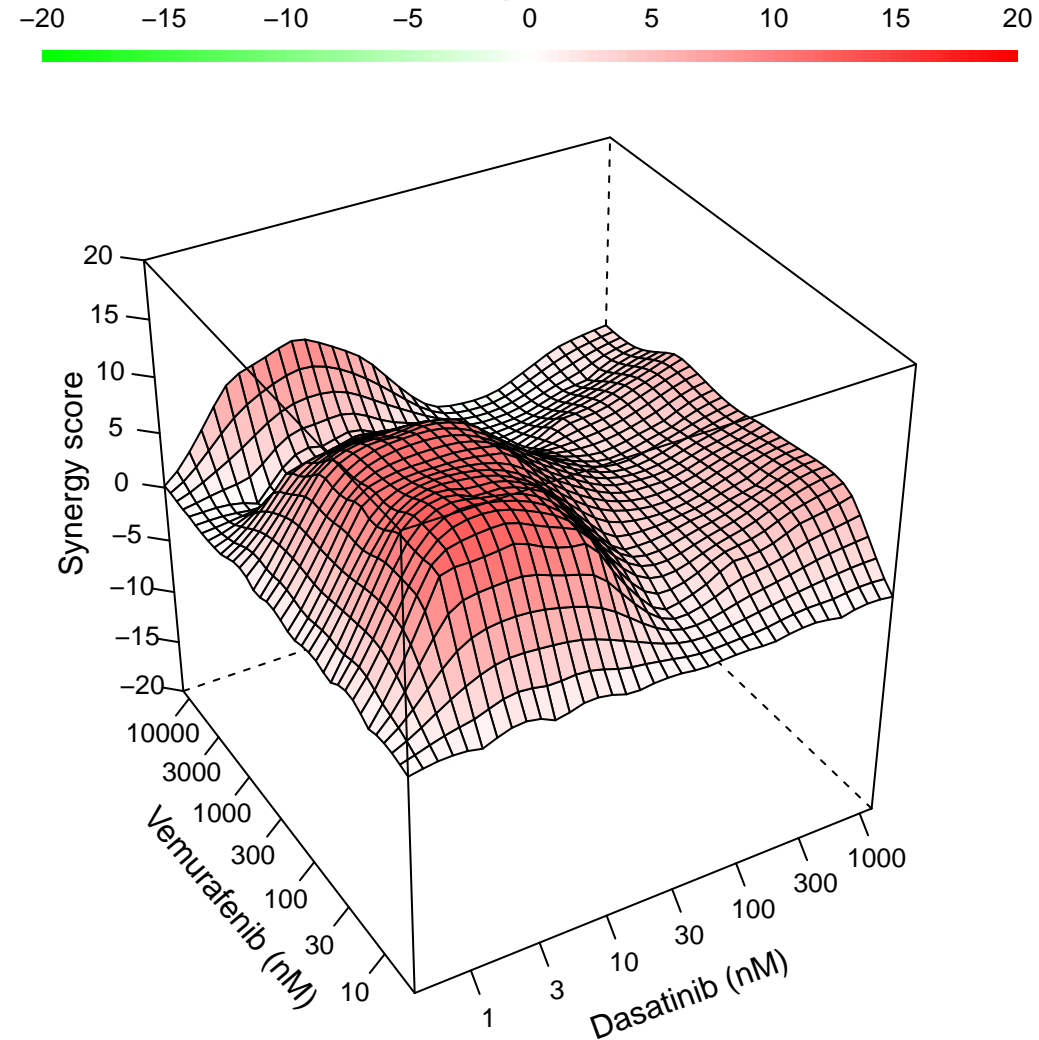
Bliss synergy score: 7.675



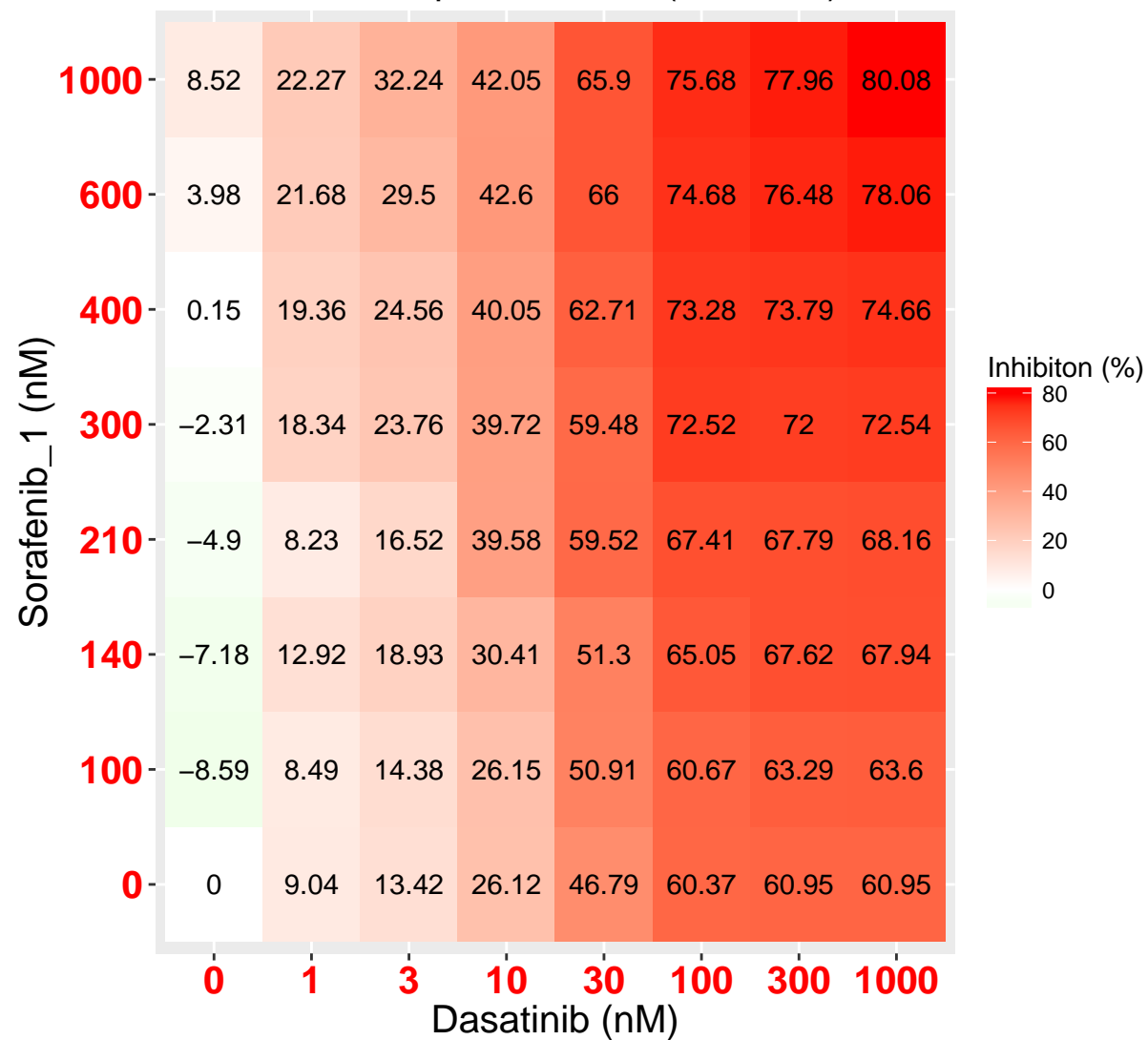
Dose-response matrix (inhibition)



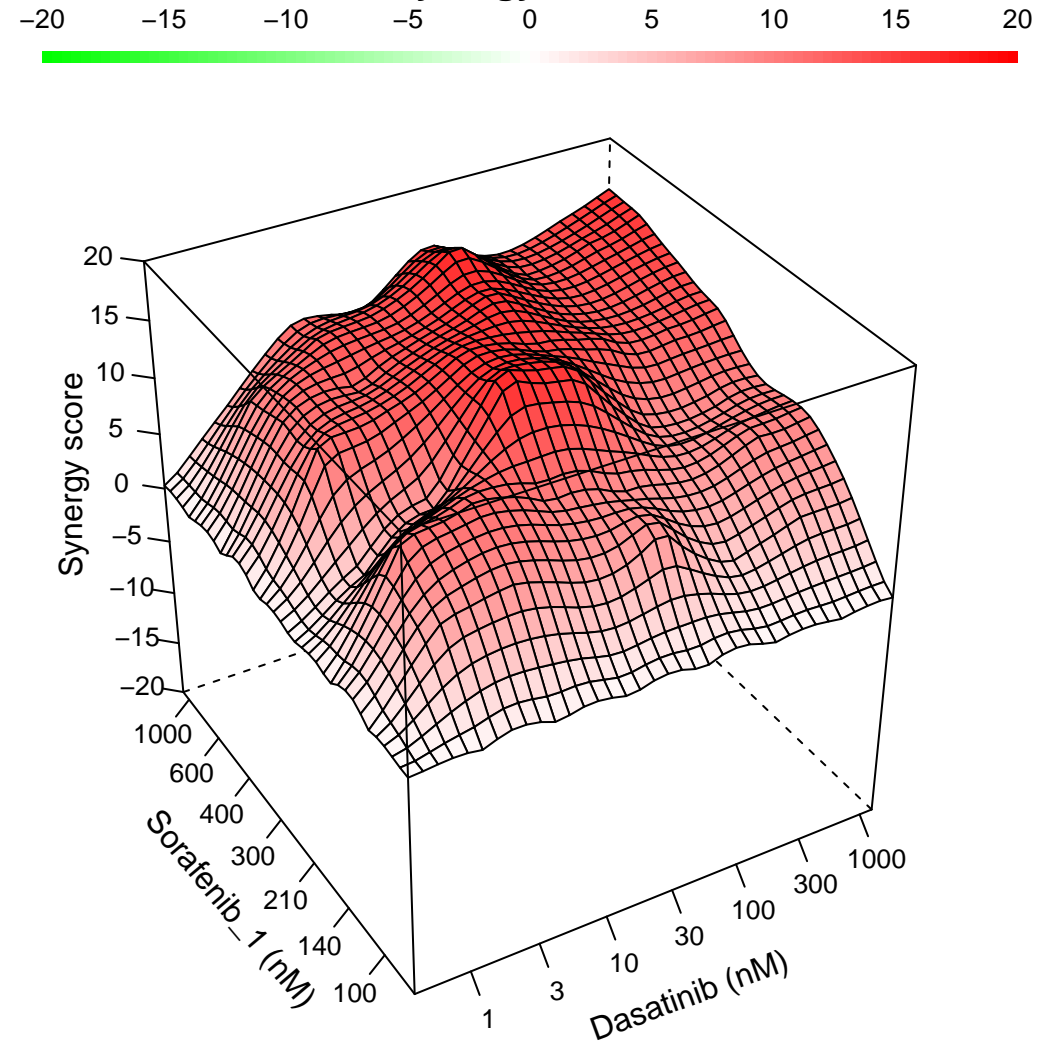
Bliss synergy score: 4.801



Dose-response matrix (inhibition)

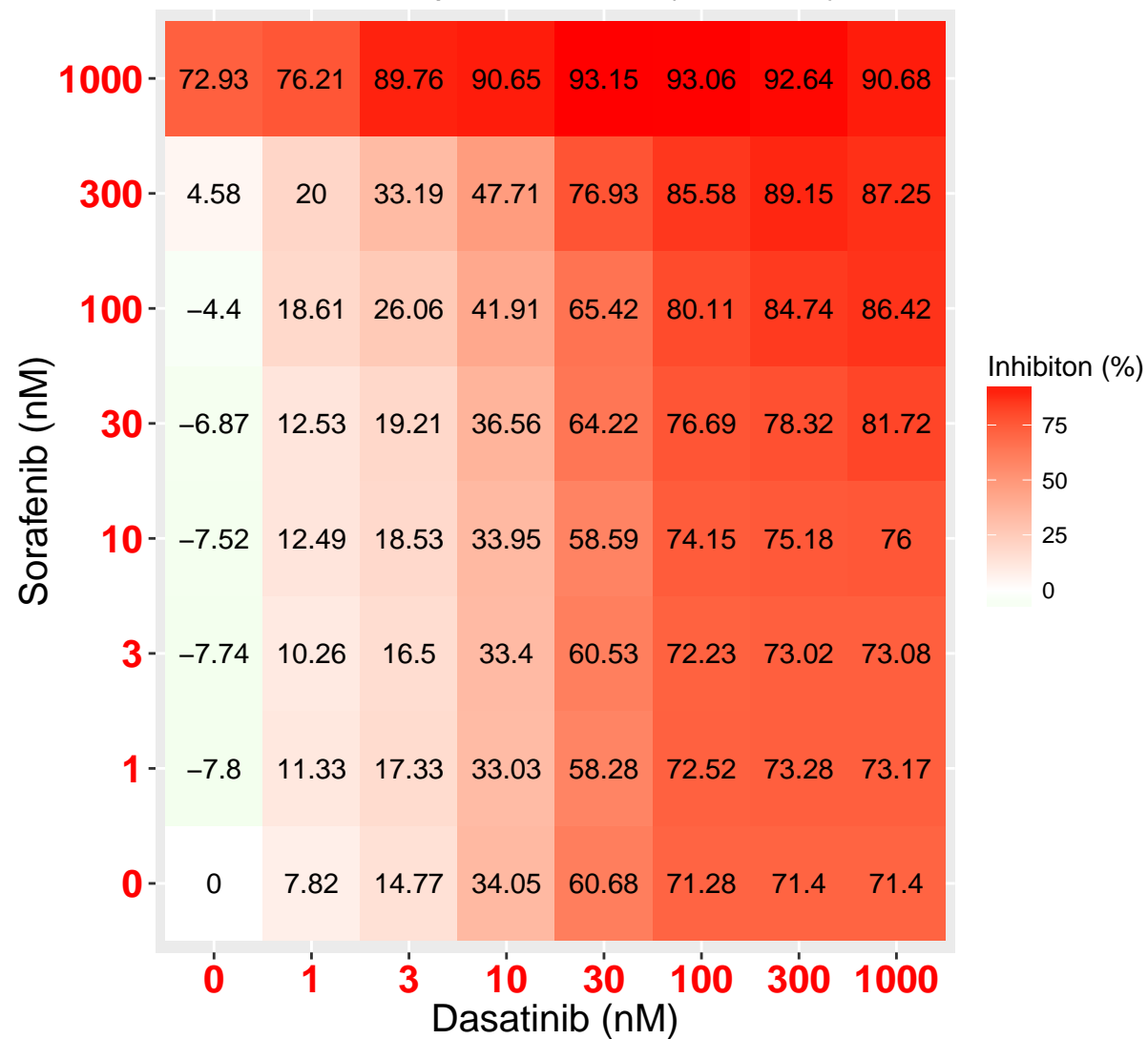


Bliss synergy score: 9.438

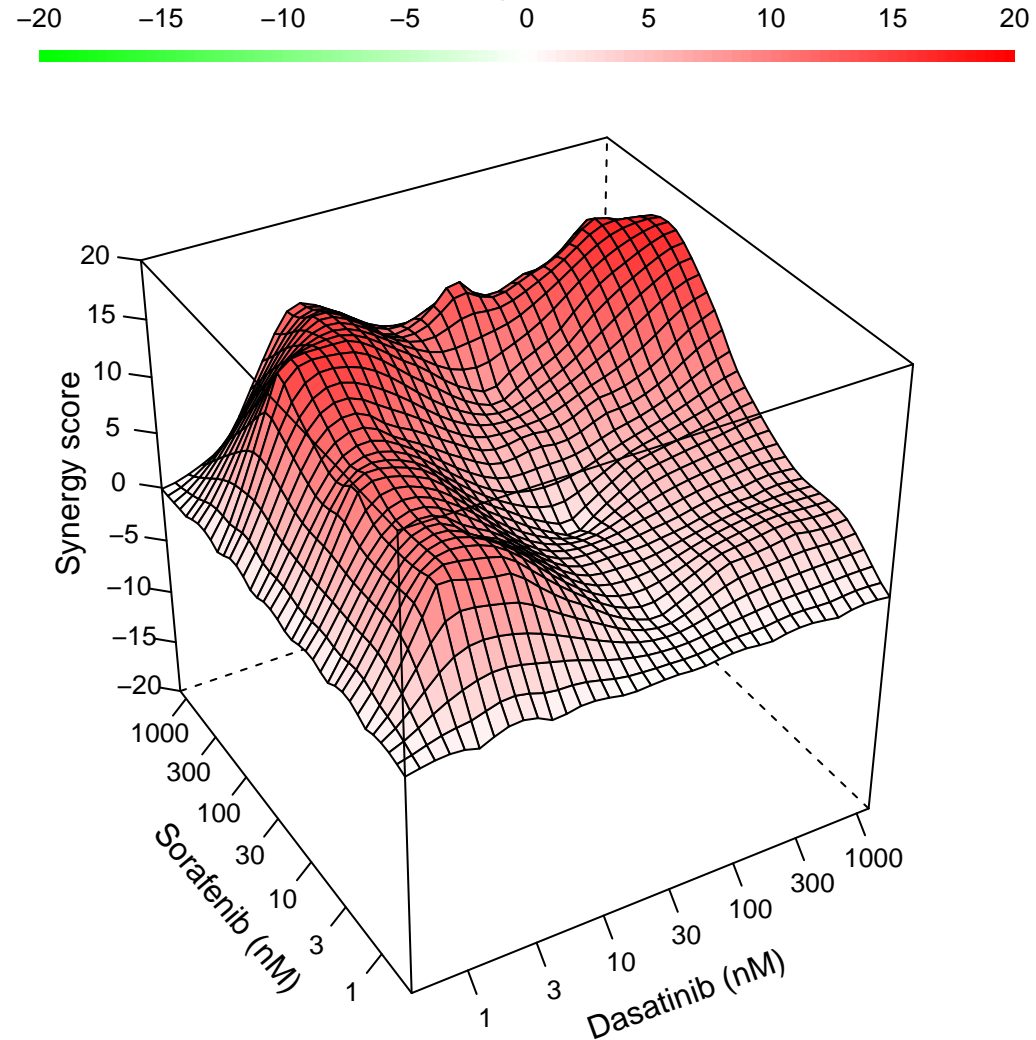




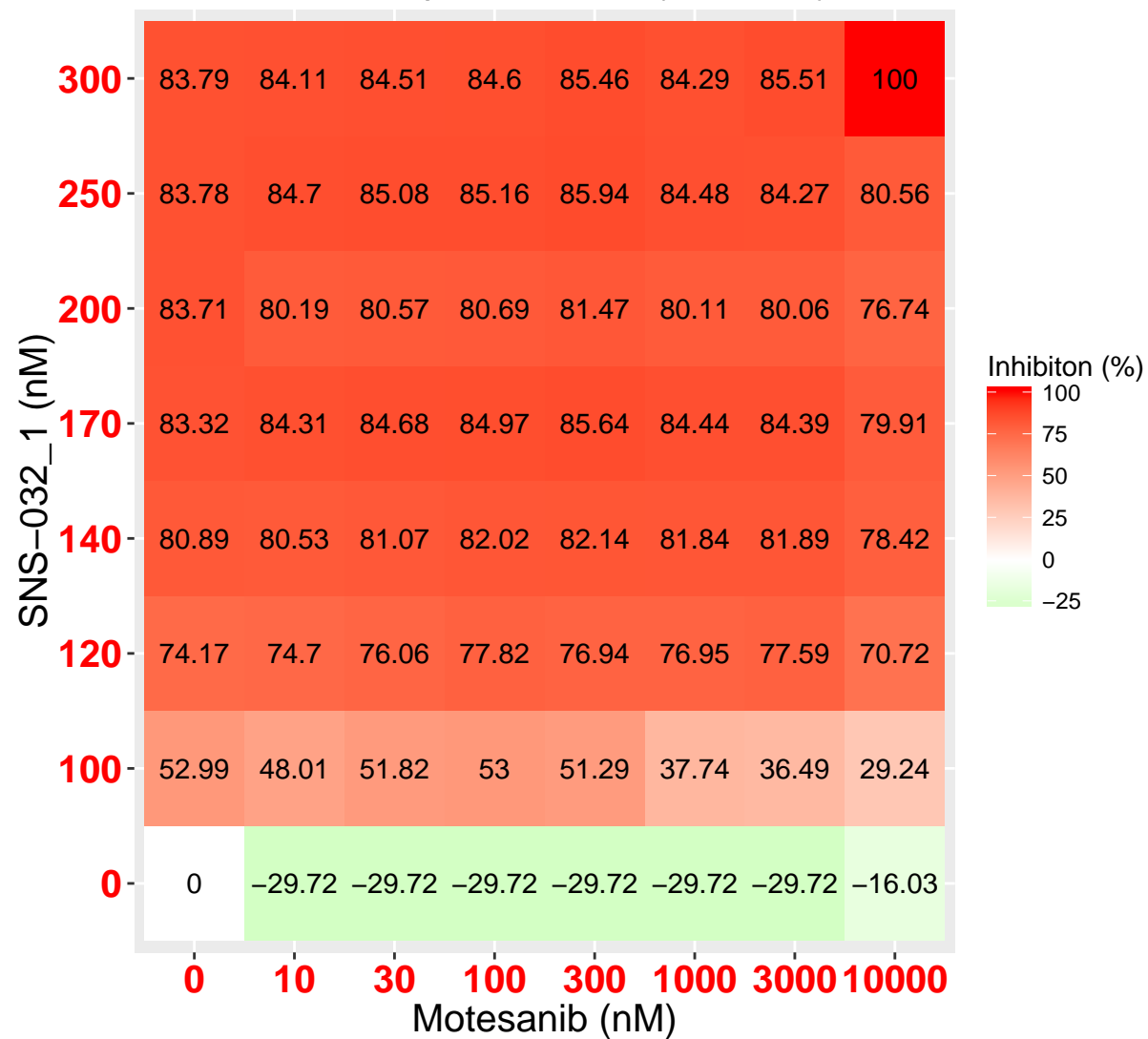
Dose-response matrix (inhibition)



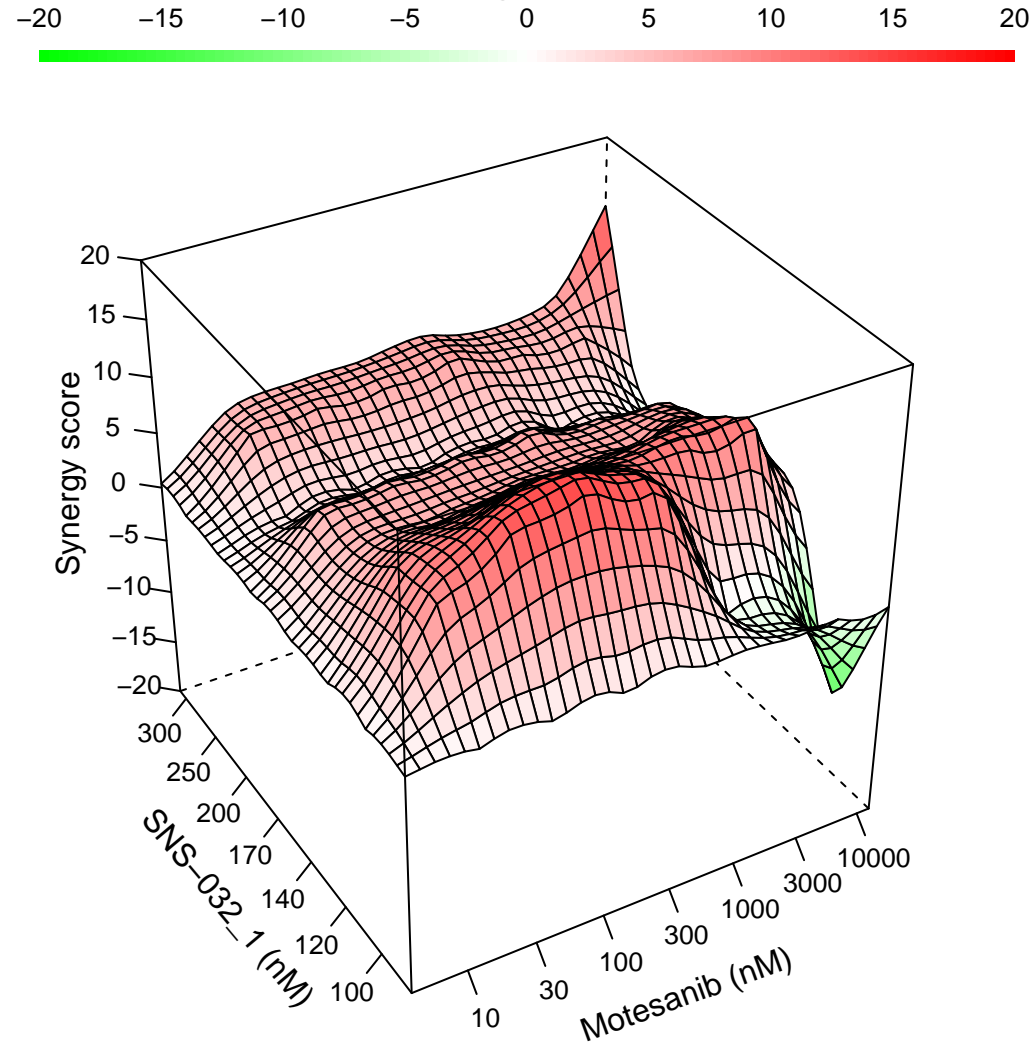
Bliss synergy score: 6.955



Dose-response matrix (inhibition)

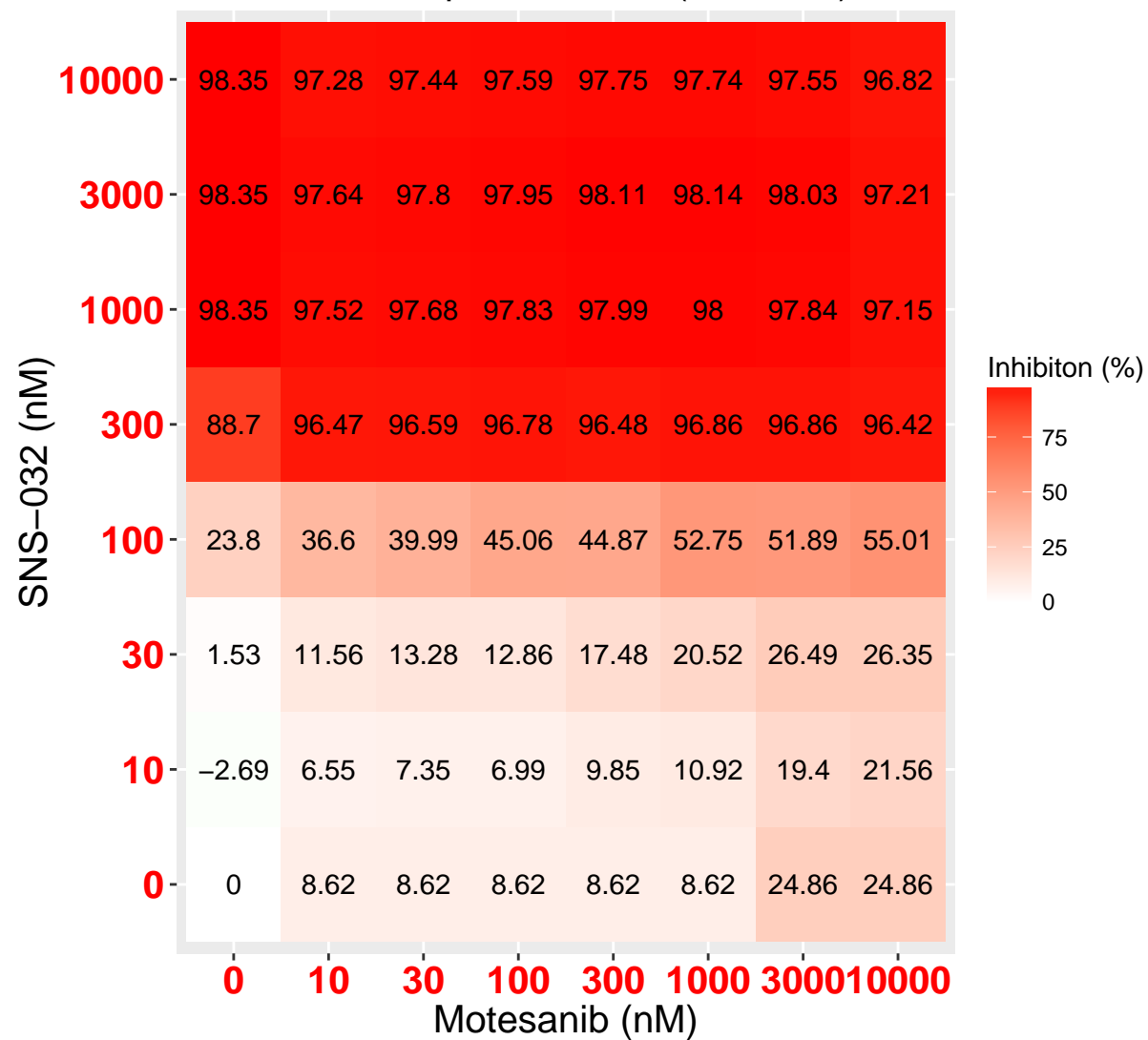


Bliss synergy score: 4.884

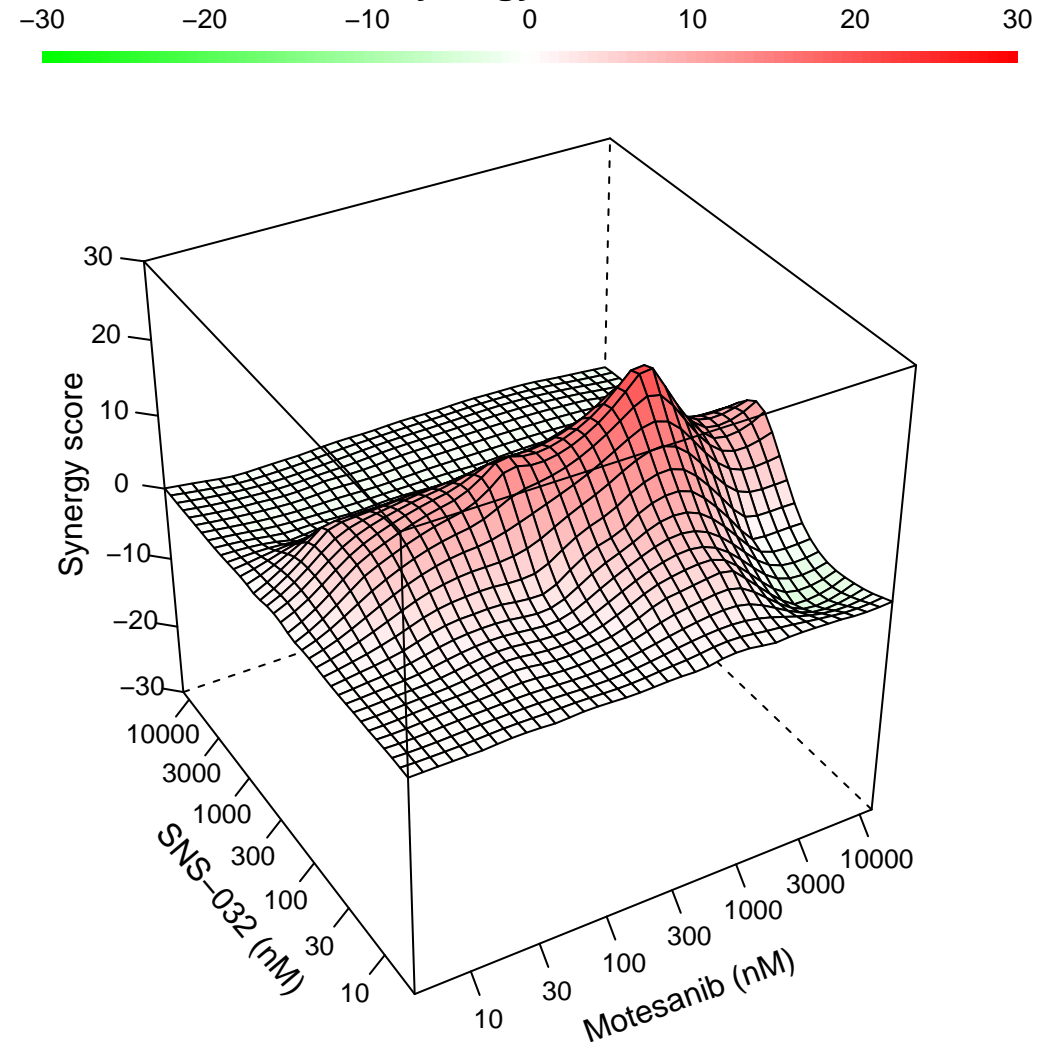




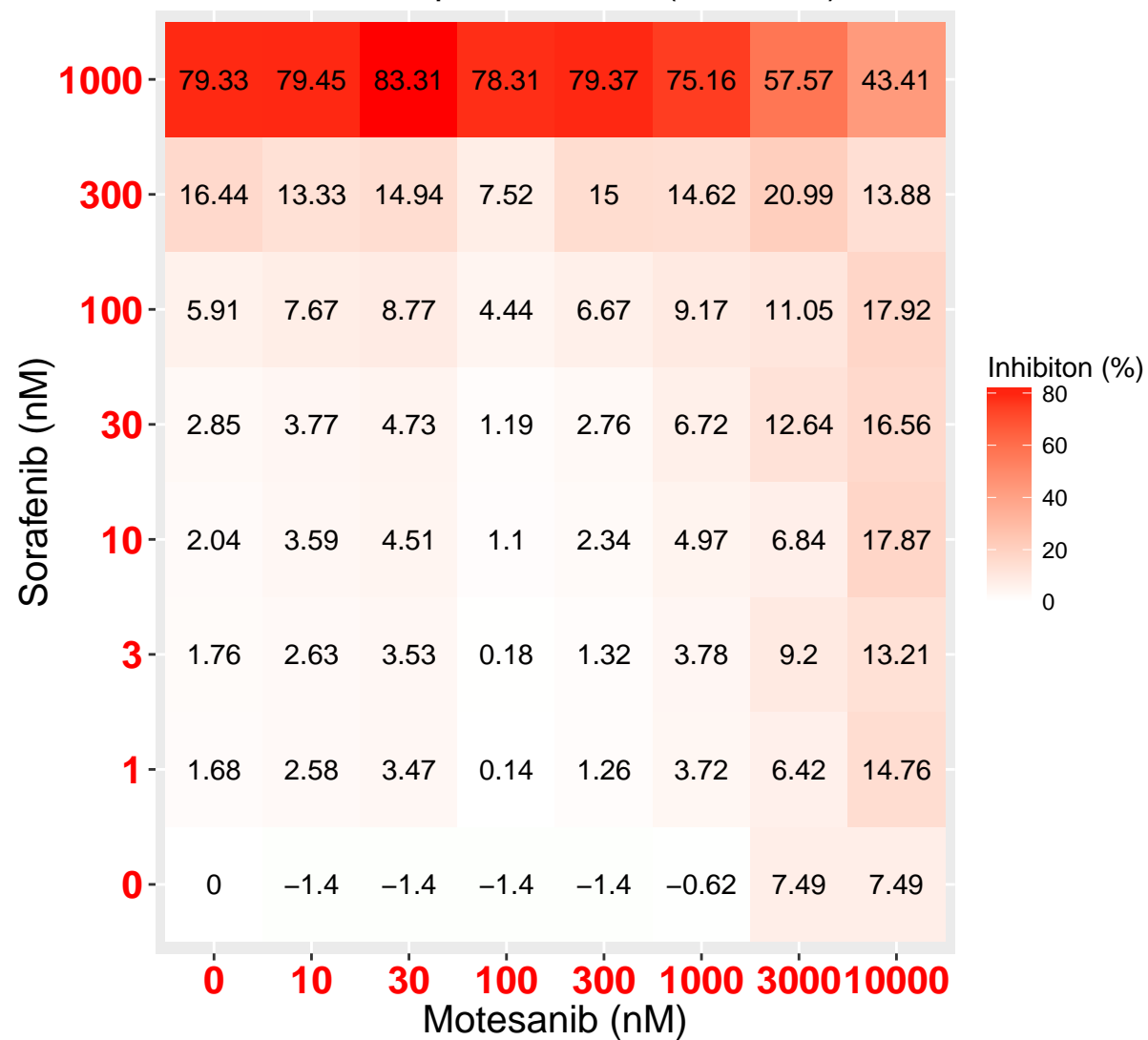
Dose-response matrix (inhibition)



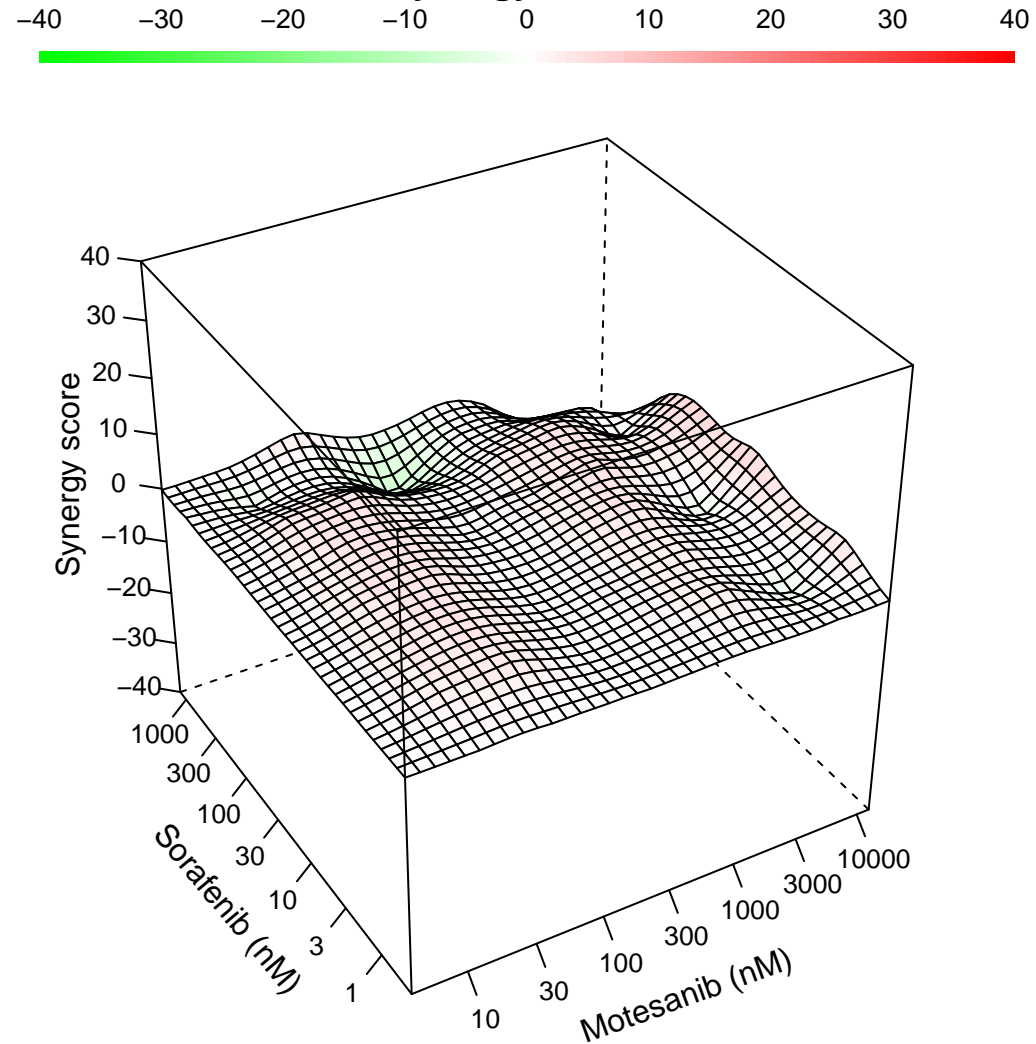
Bliss synergy score: 2.966



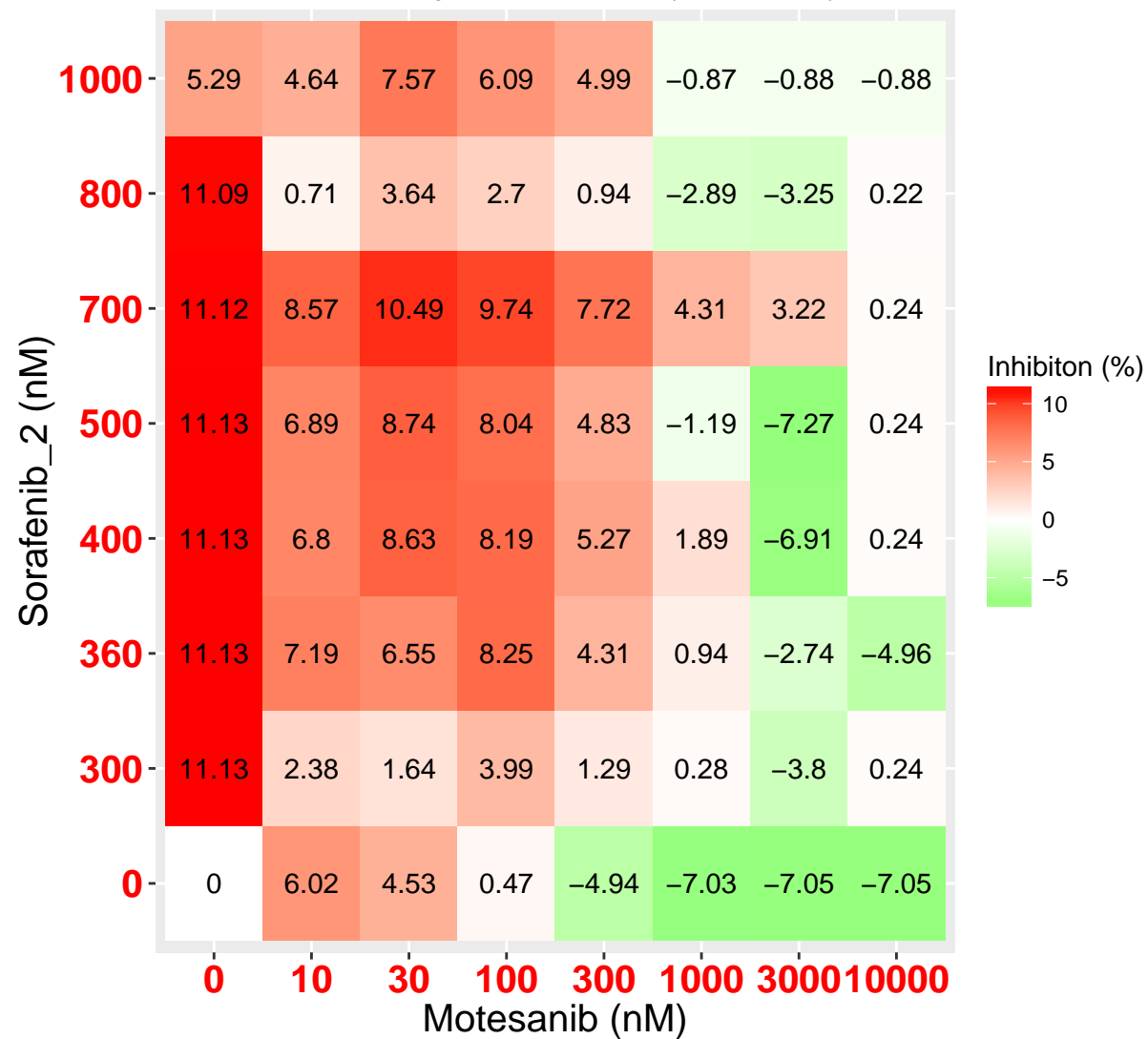
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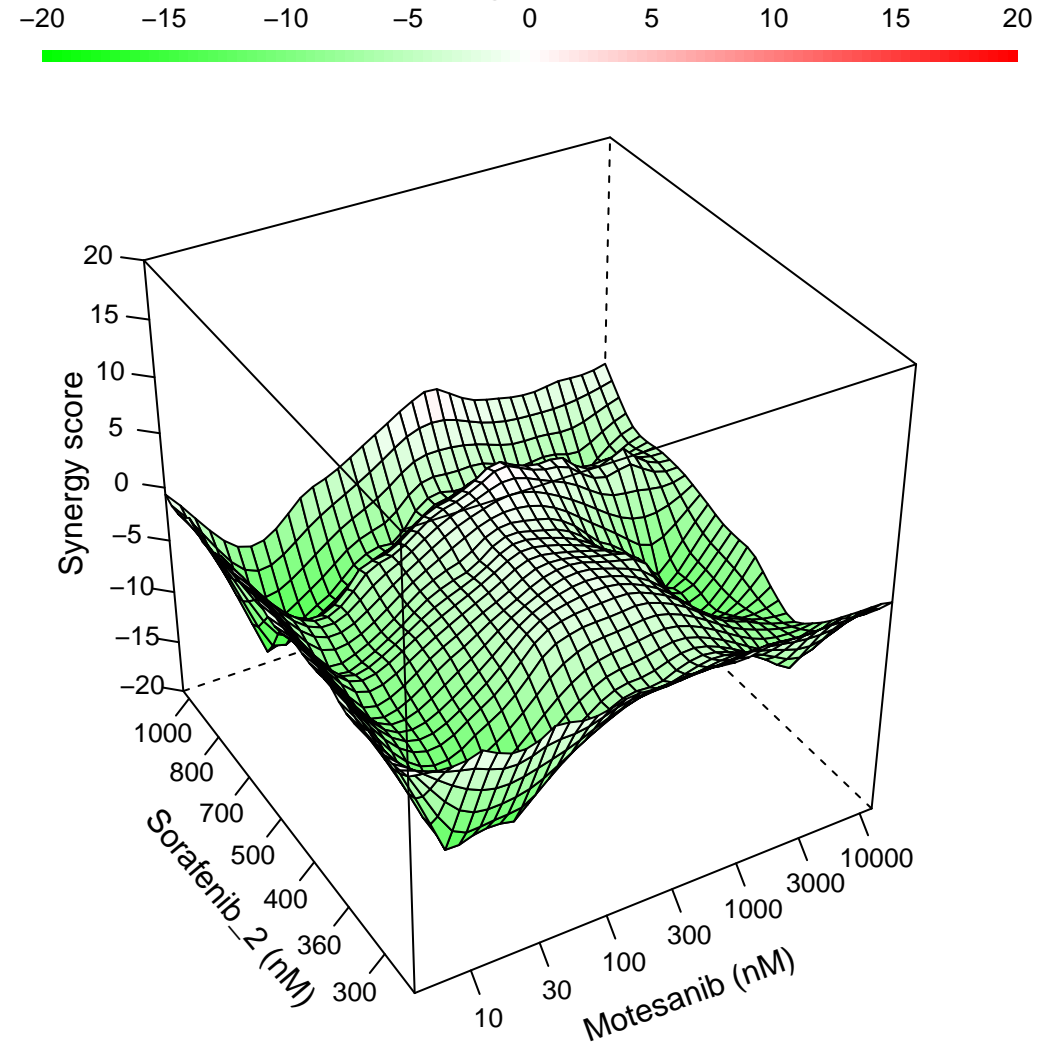
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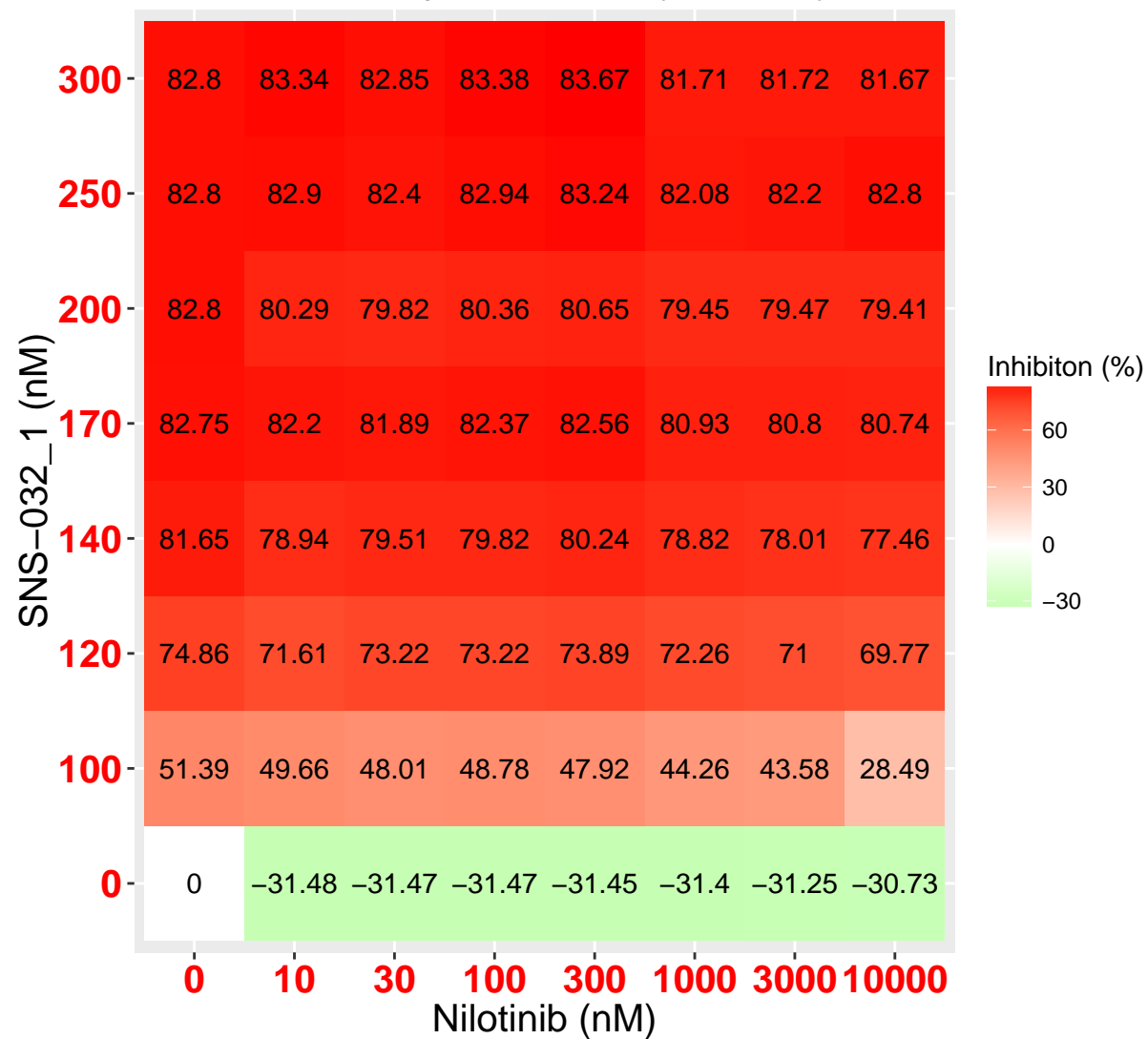
Dose-response matrix (inhibition)



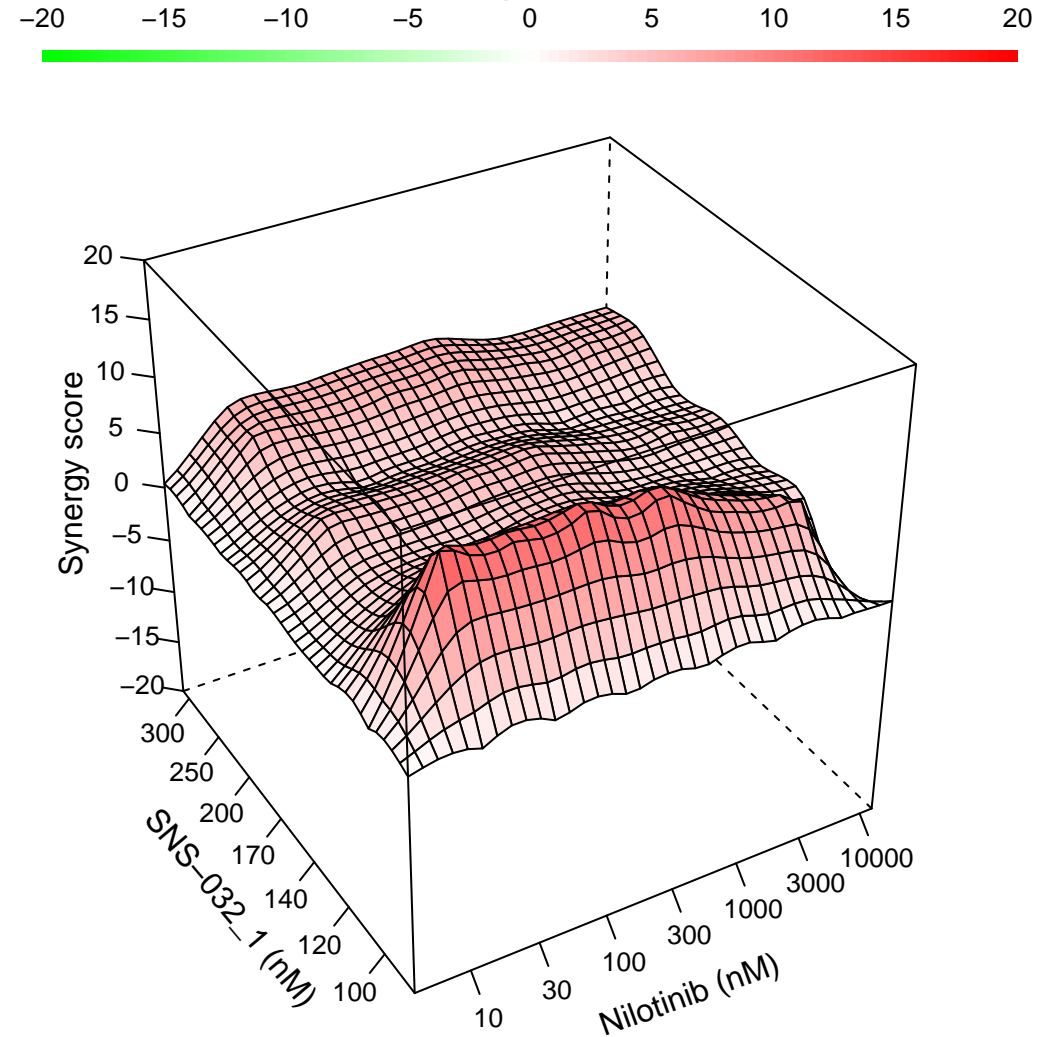
Bliss synergy score: -5.134



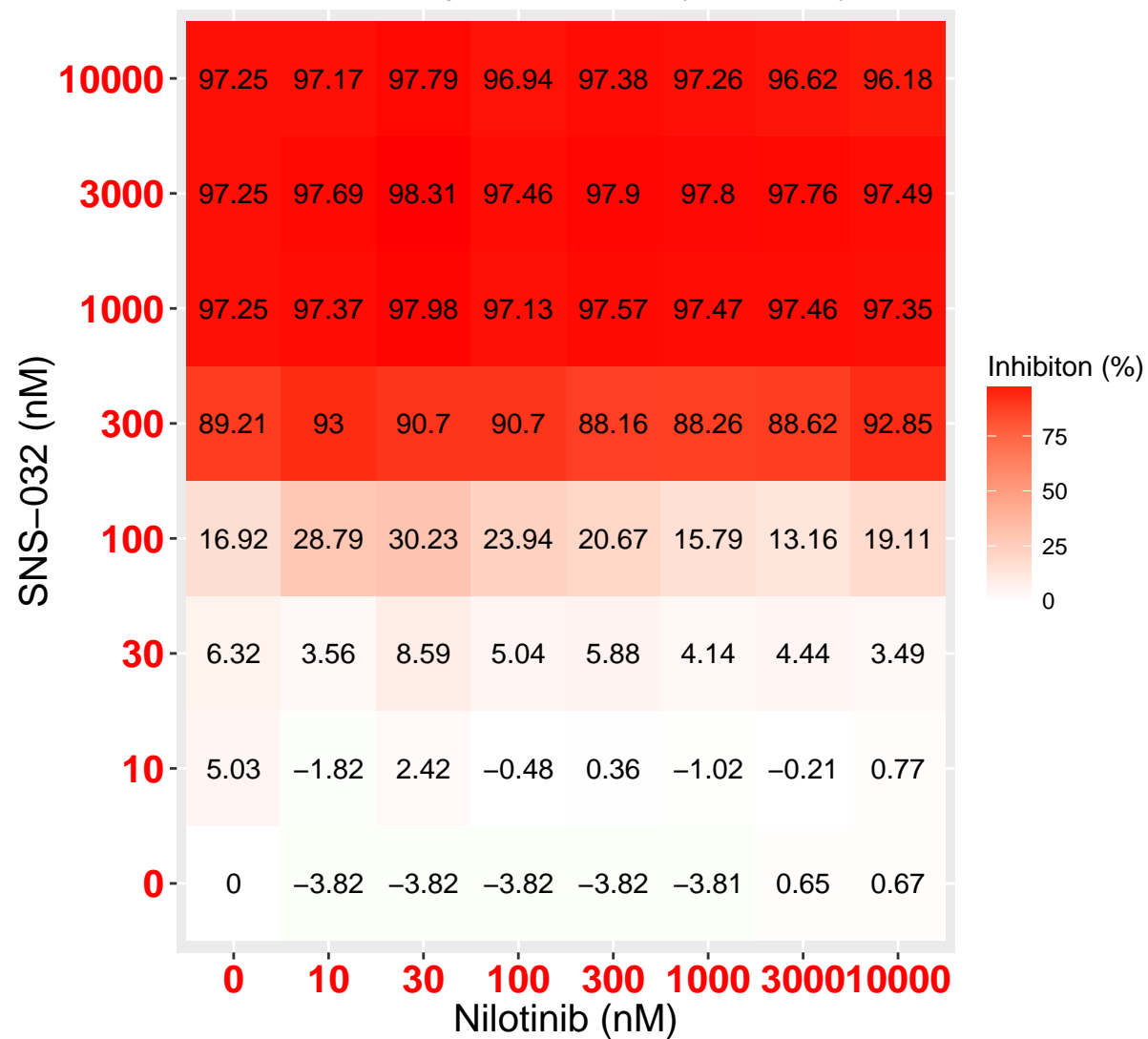
Dose-response matrix (inhibition)



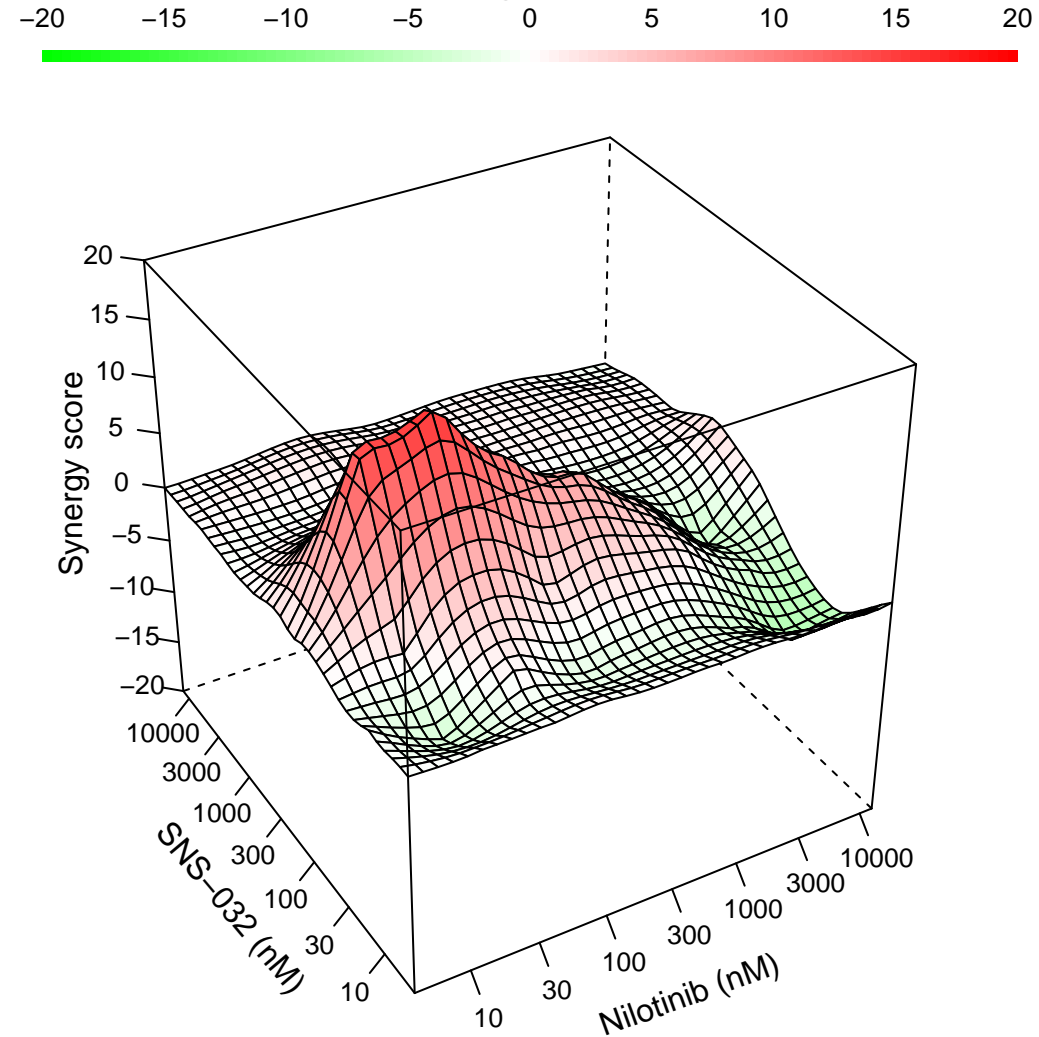
Bliss synergy score: 4.355



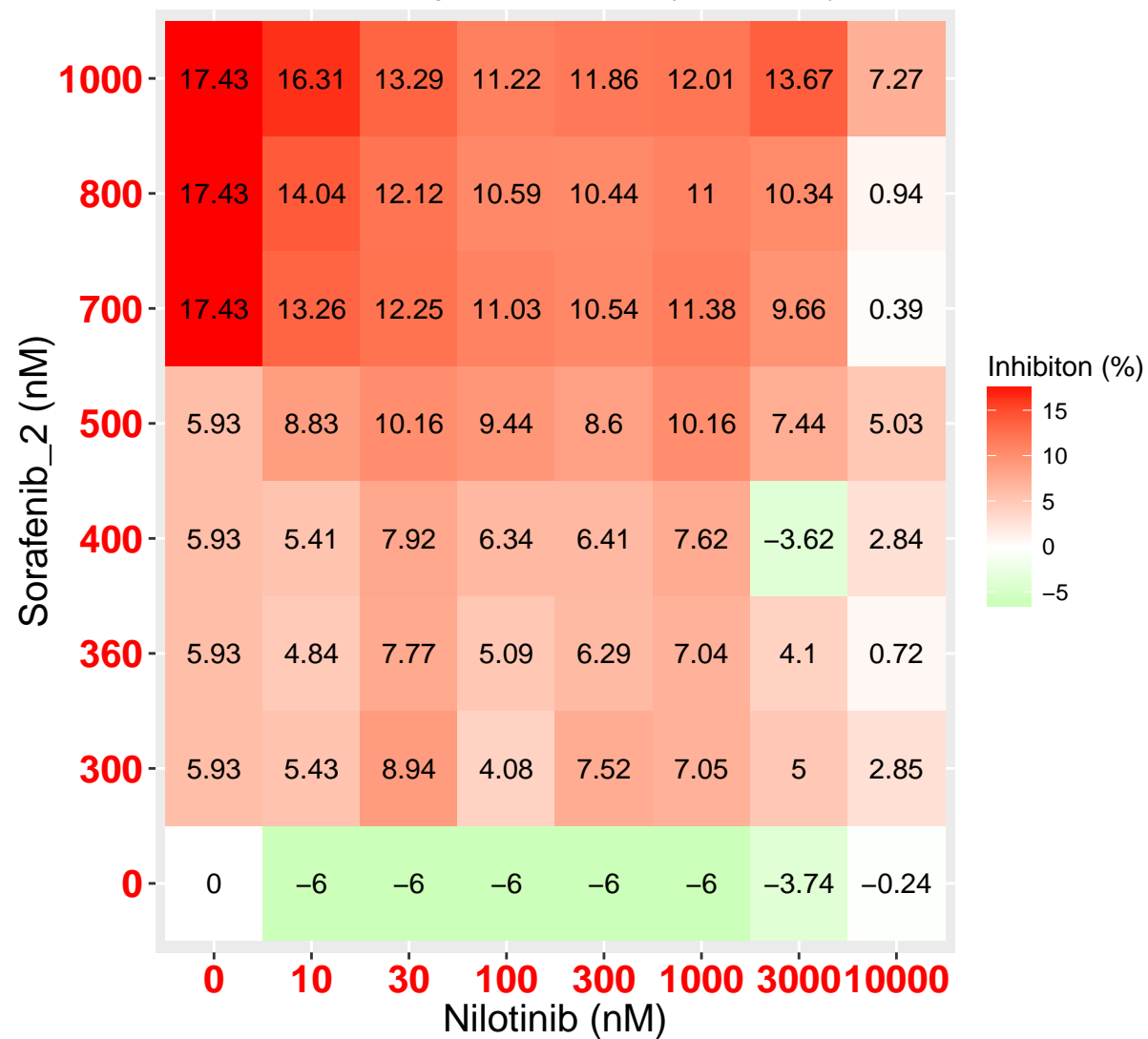
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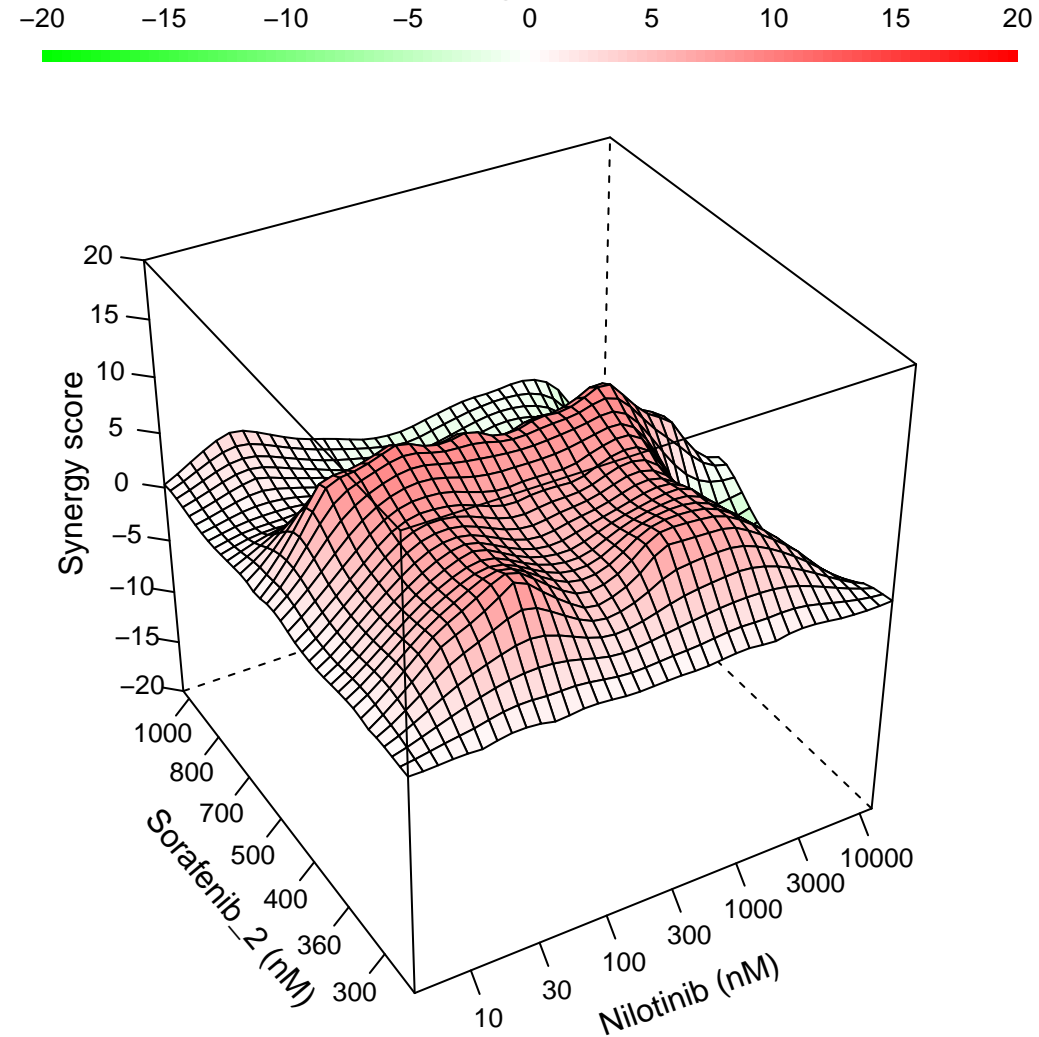
Bliss synergy score: 1.107



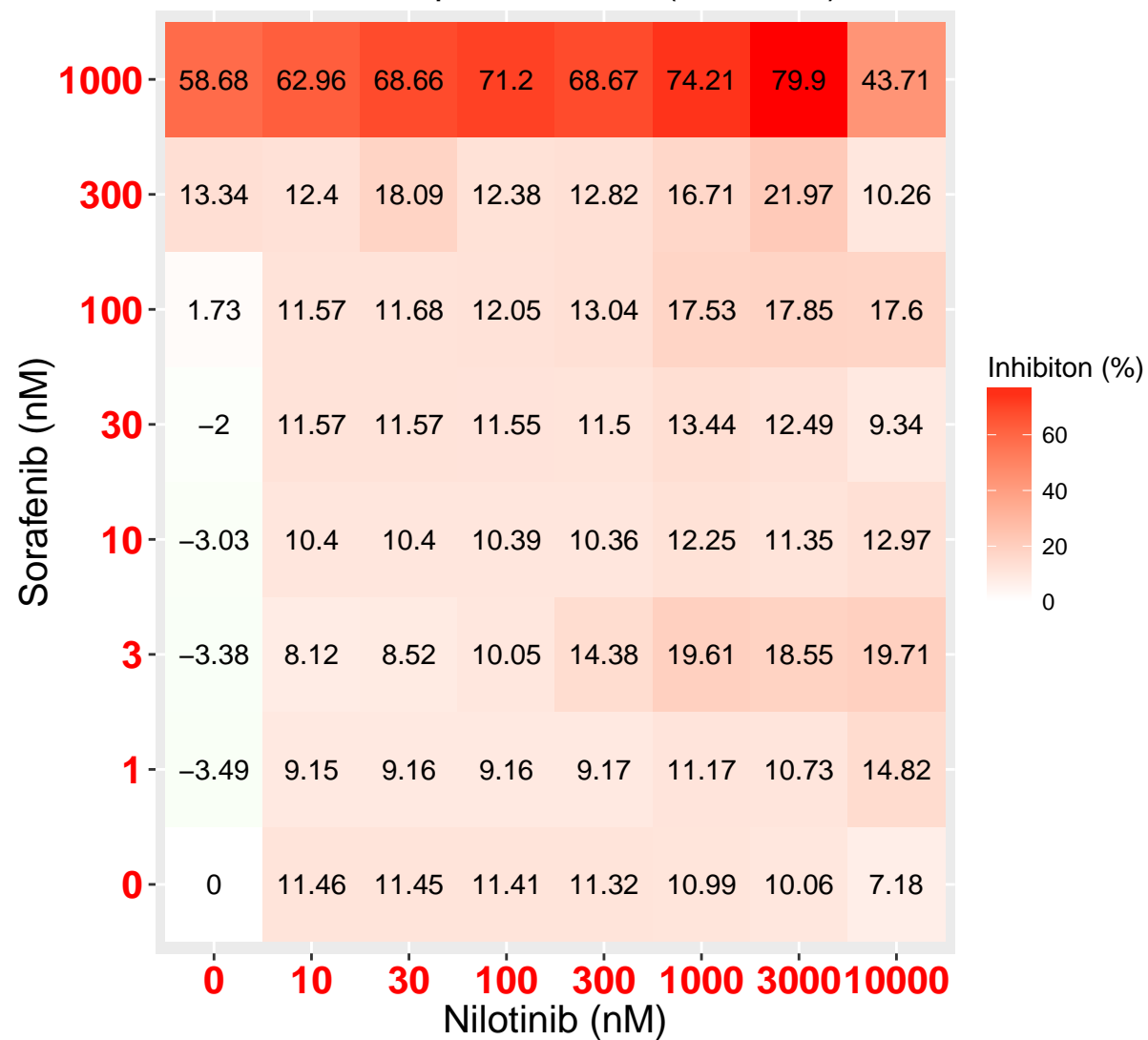
Dose-response matrix (inhibition)



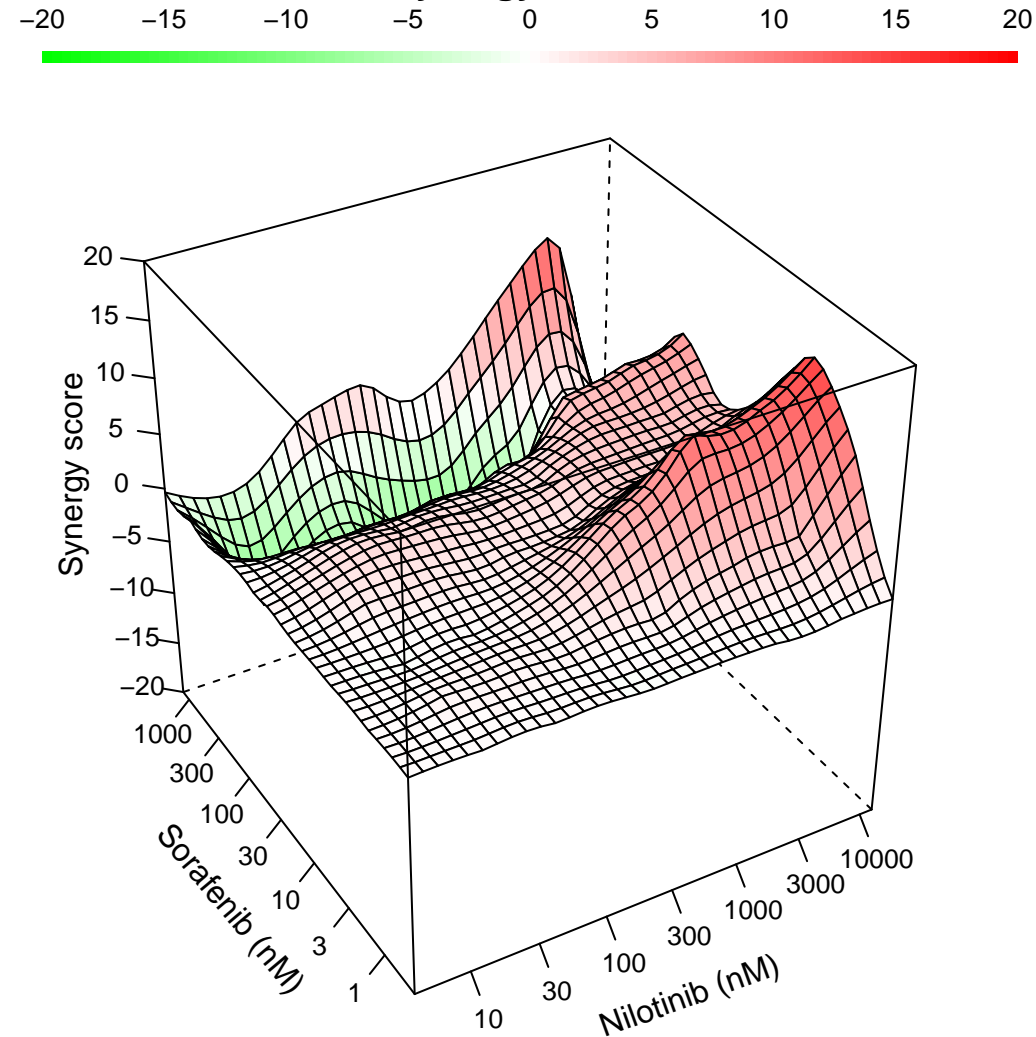
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Dose-response matrix (inhibition)

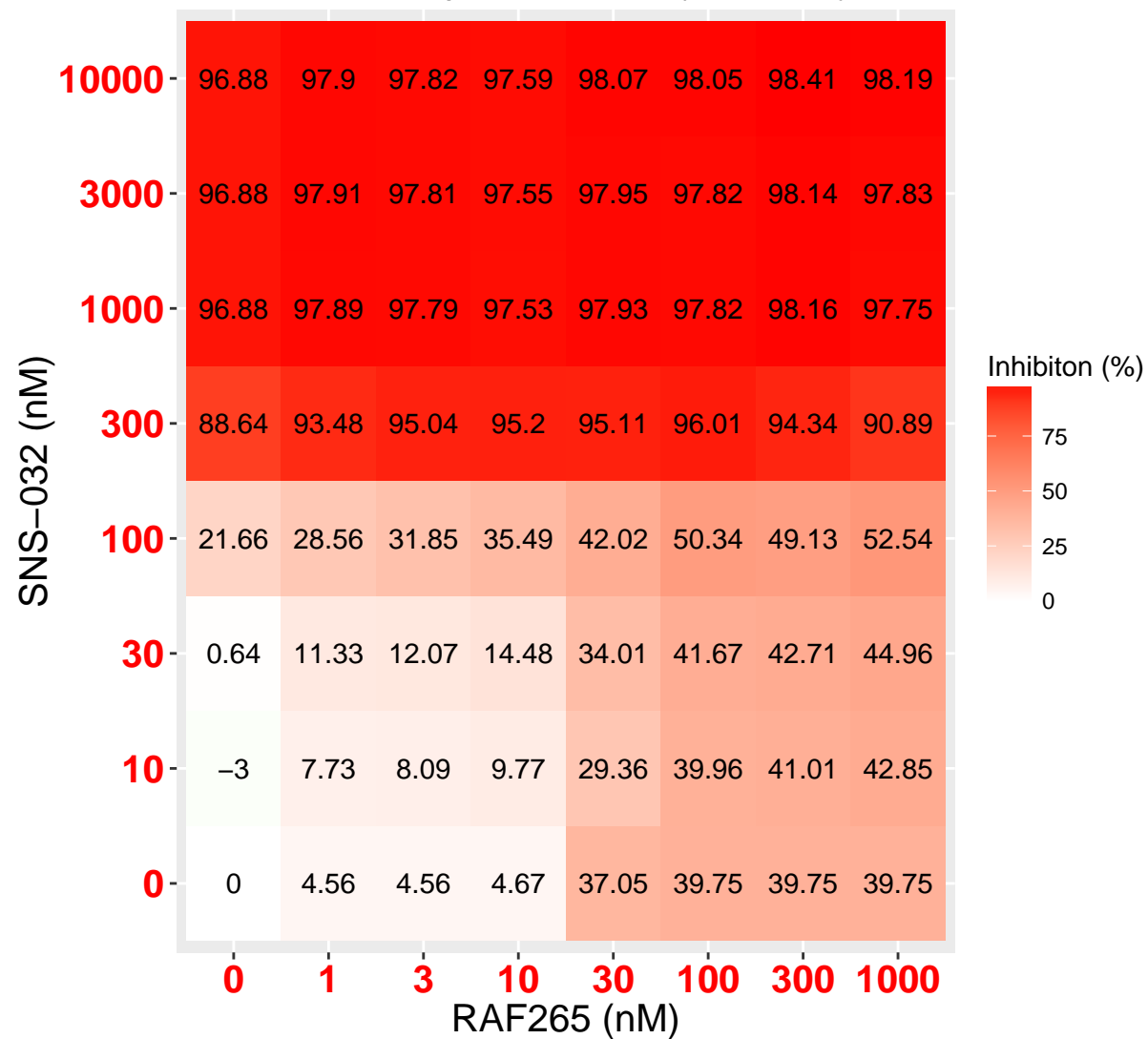


Bliss synergy score: 1.508

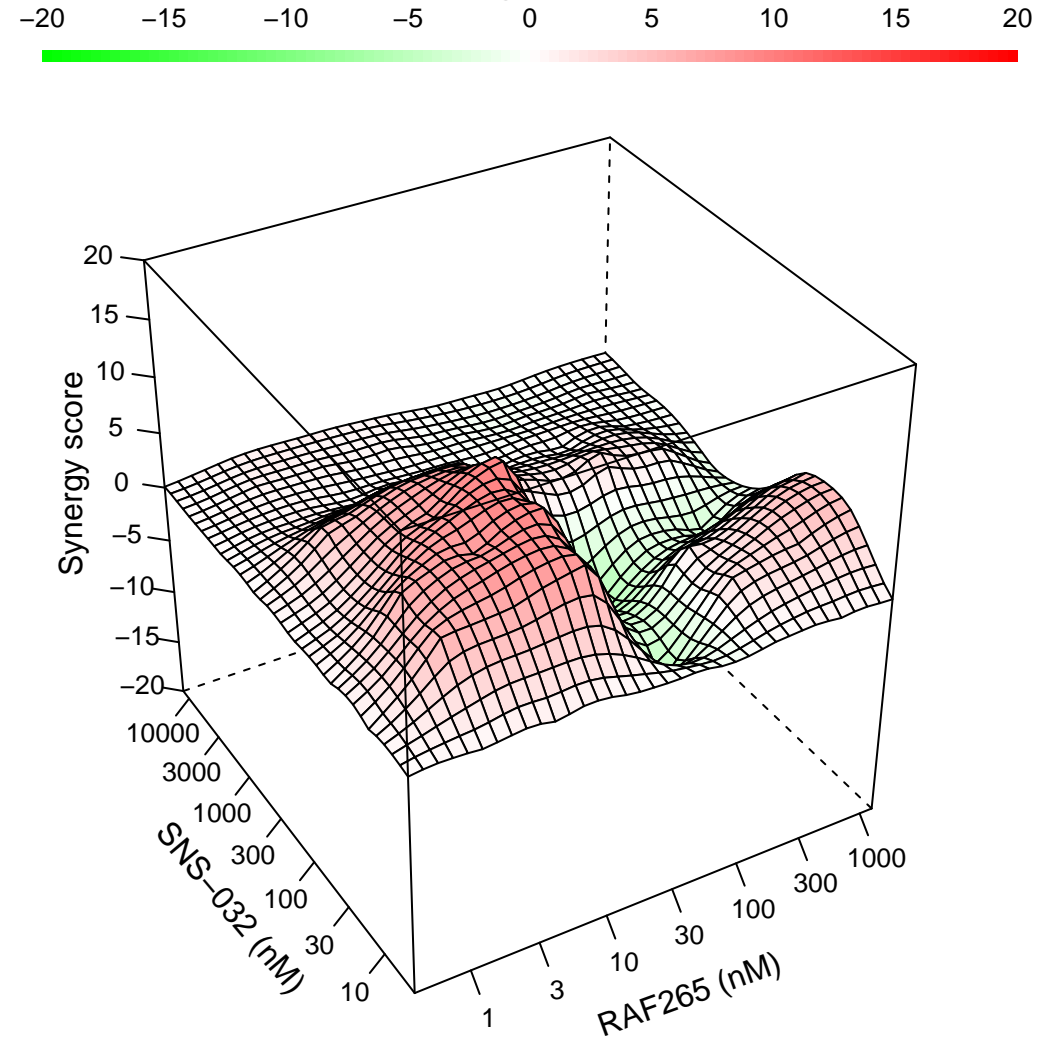




Dose-response matrix (inhibition)

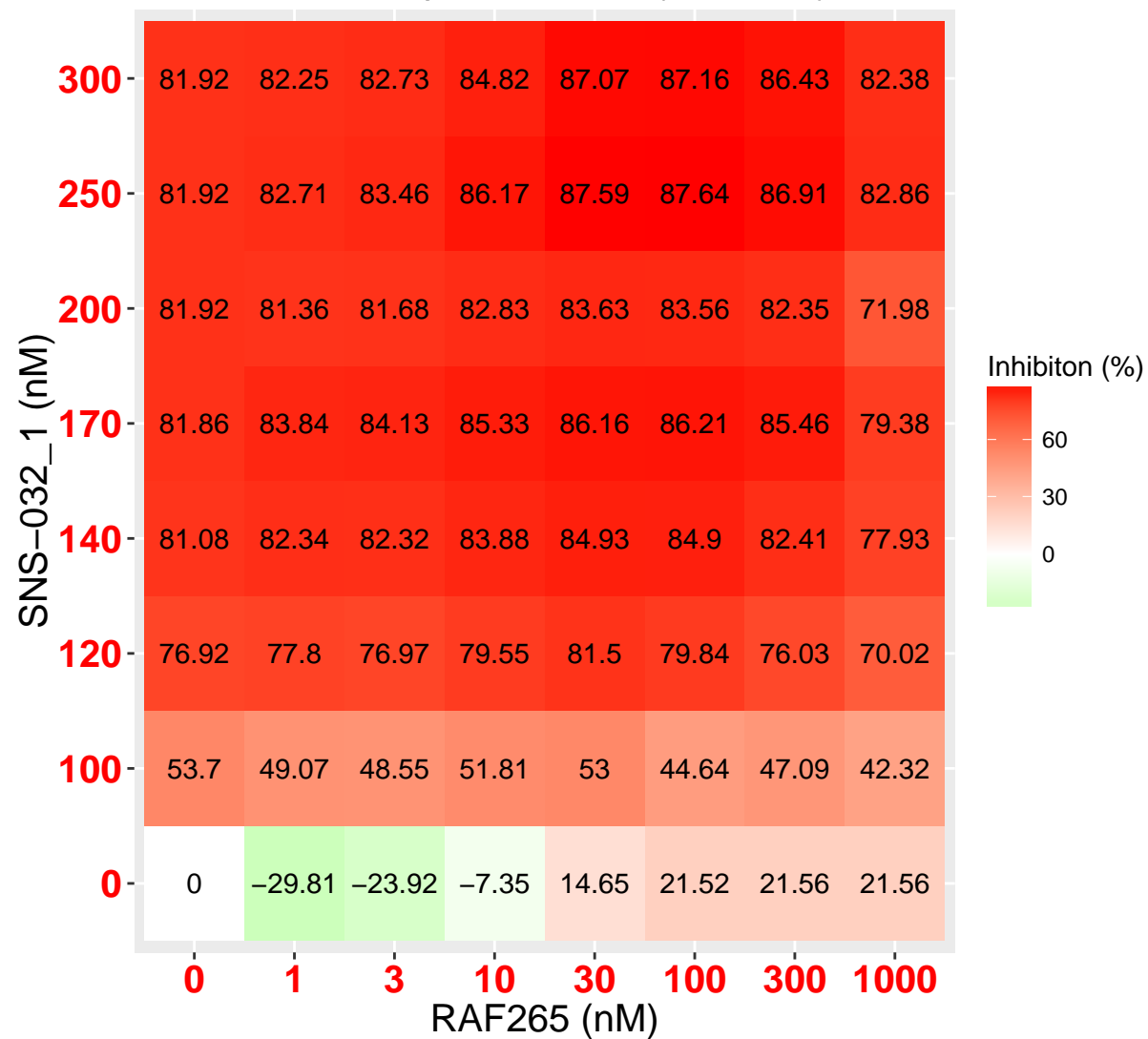


Bliss synergy score: 1.603

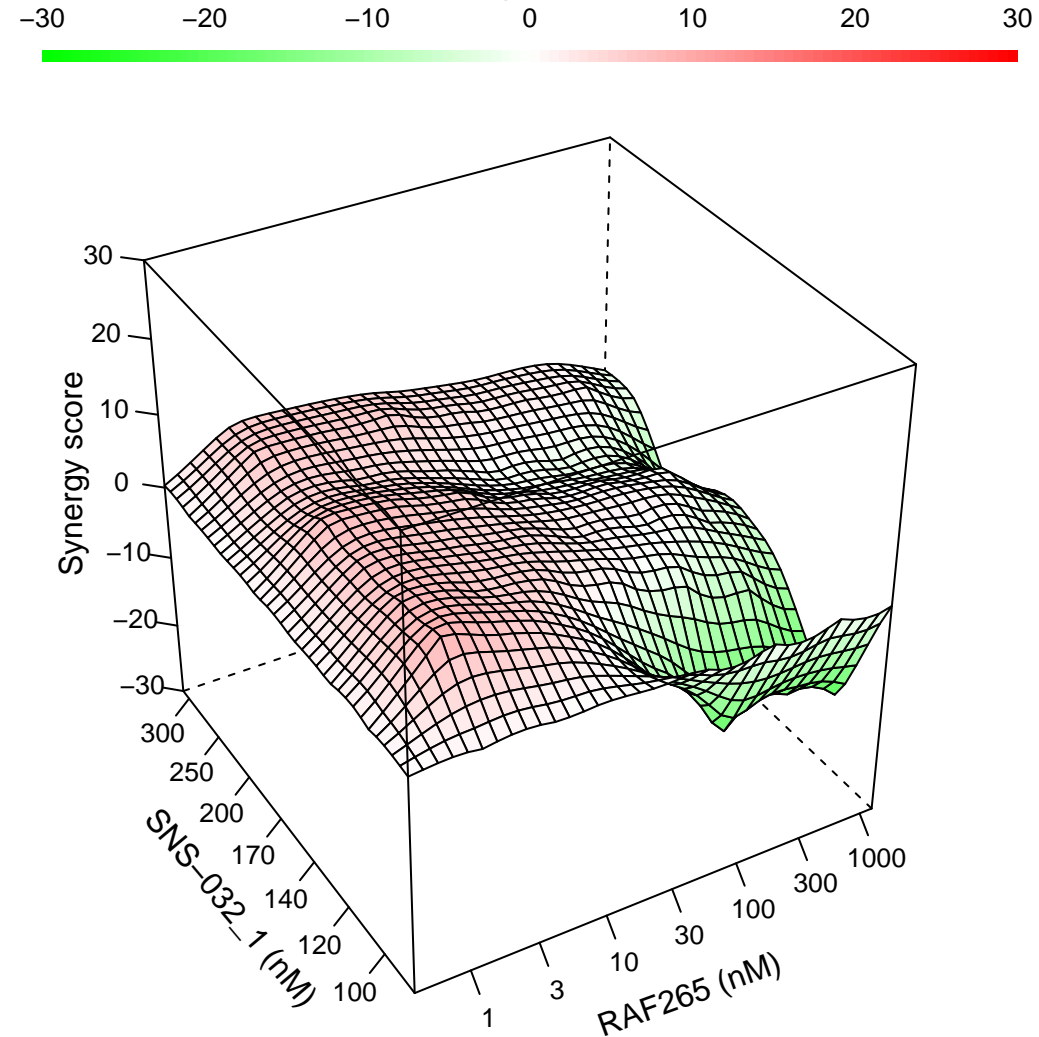




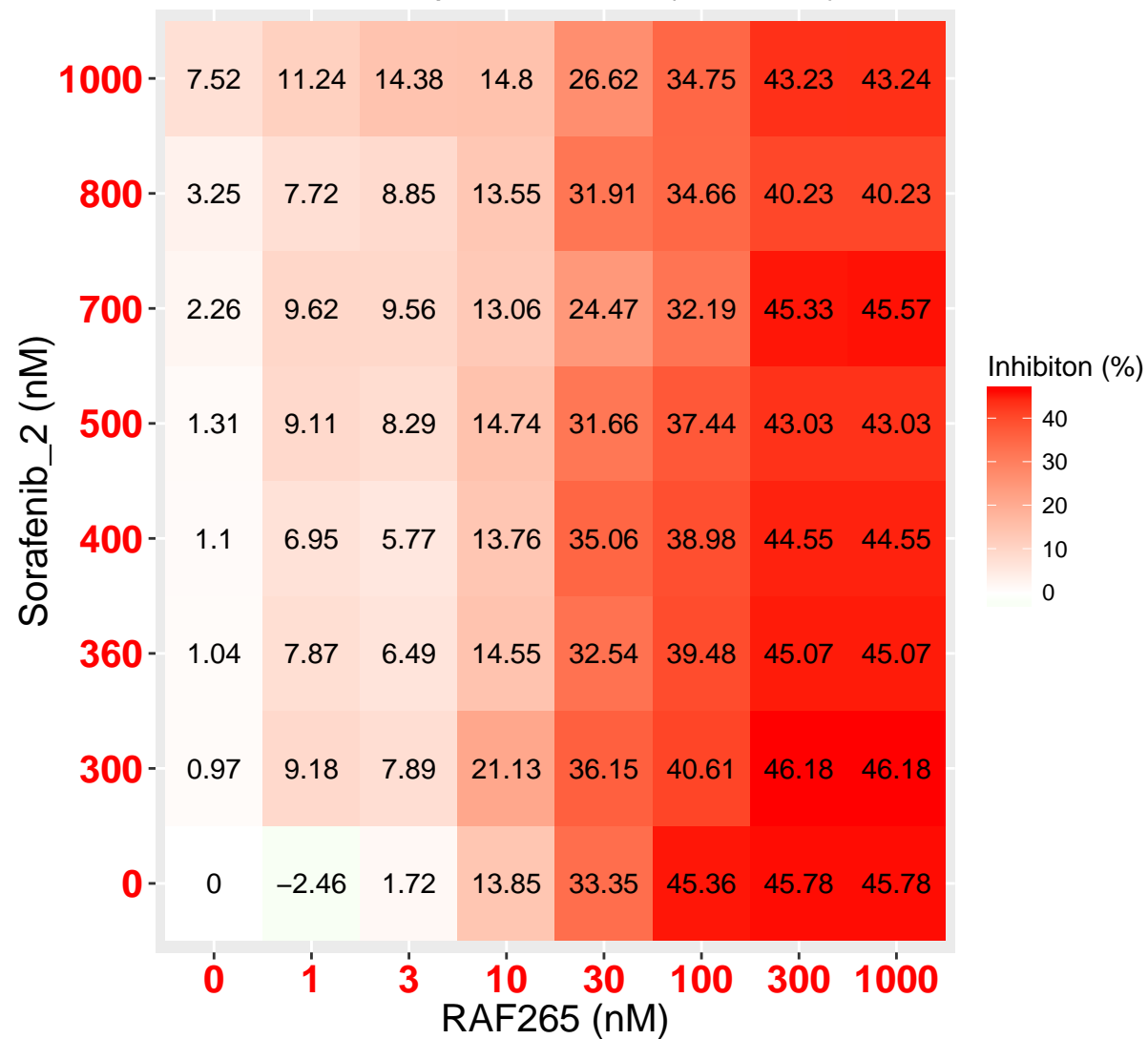
Dose-response matrix (inhibition)



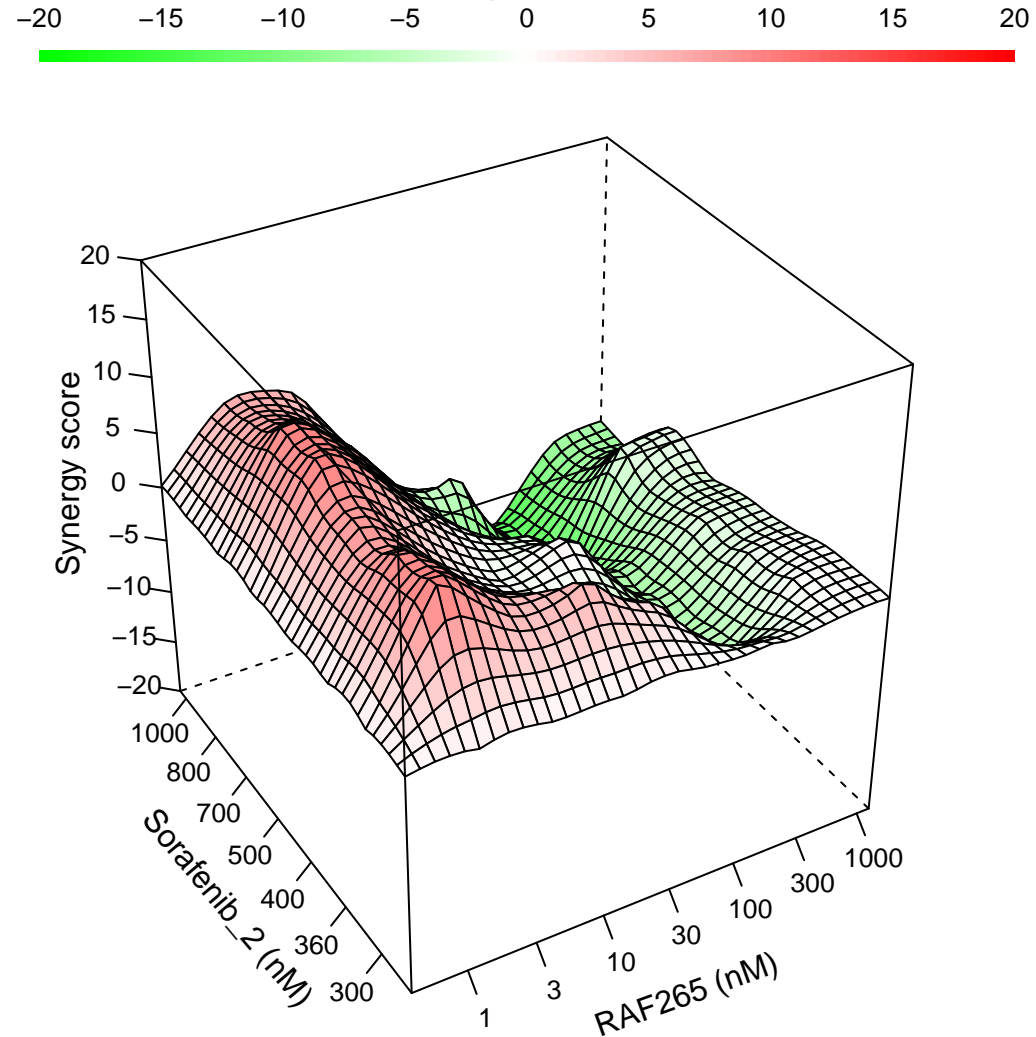
Bliss synergy score: 0.512



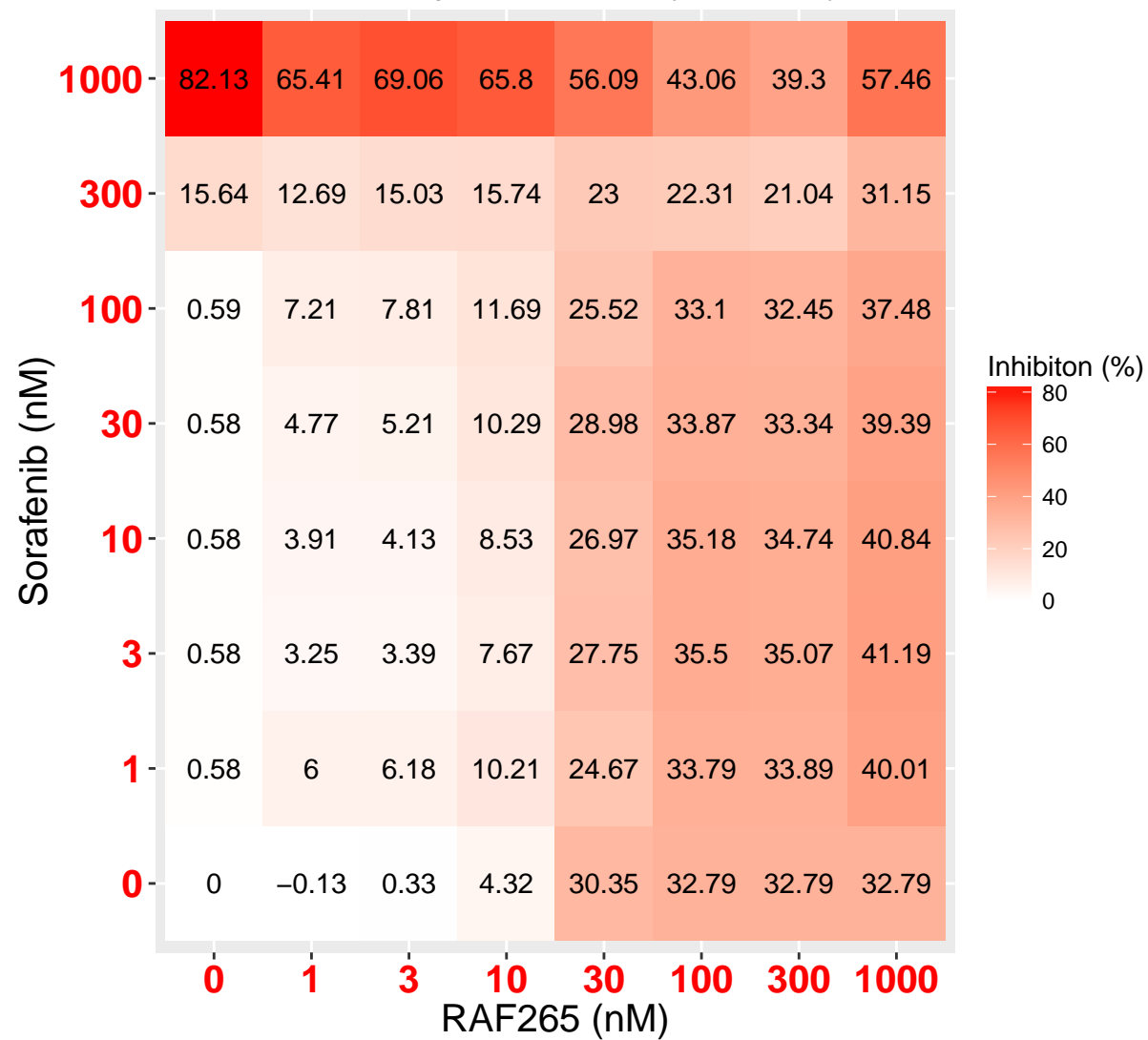
Dose-response matrix (inhibition)



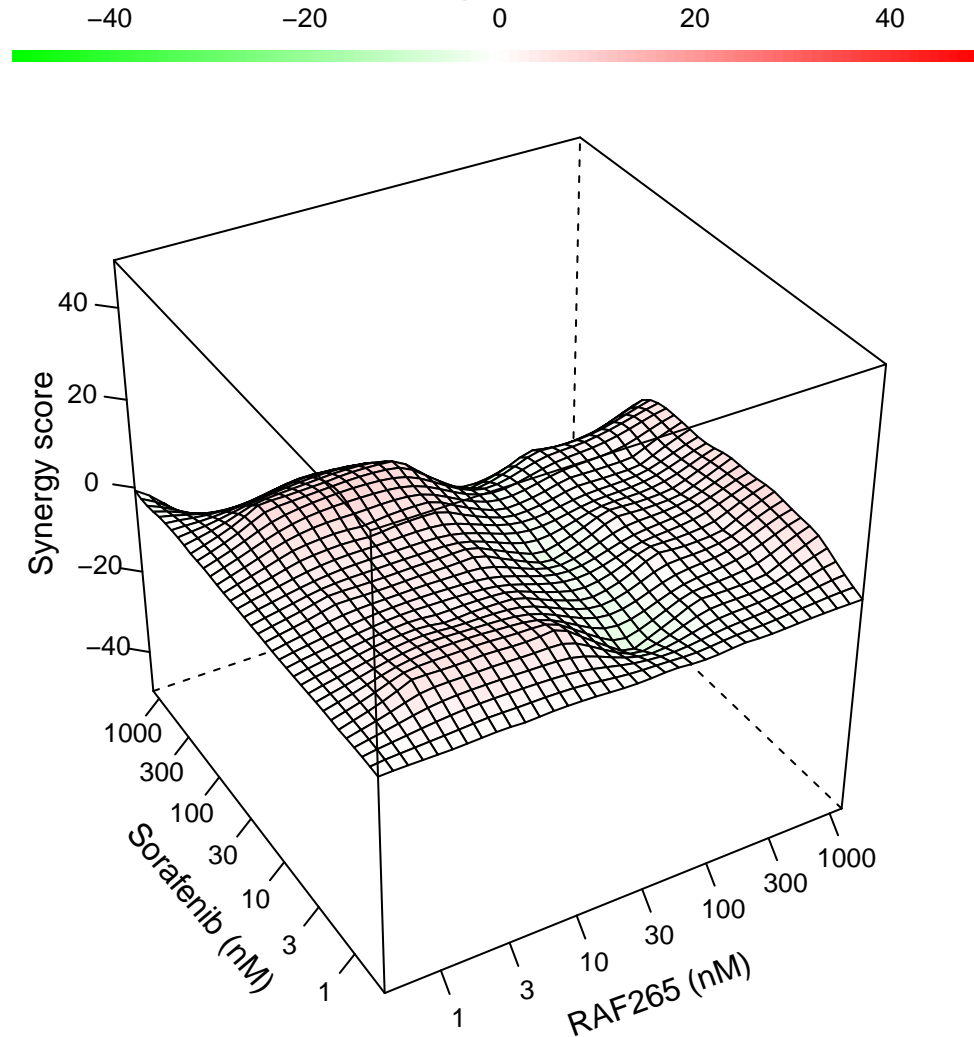
Bliss synergy score: -0.622



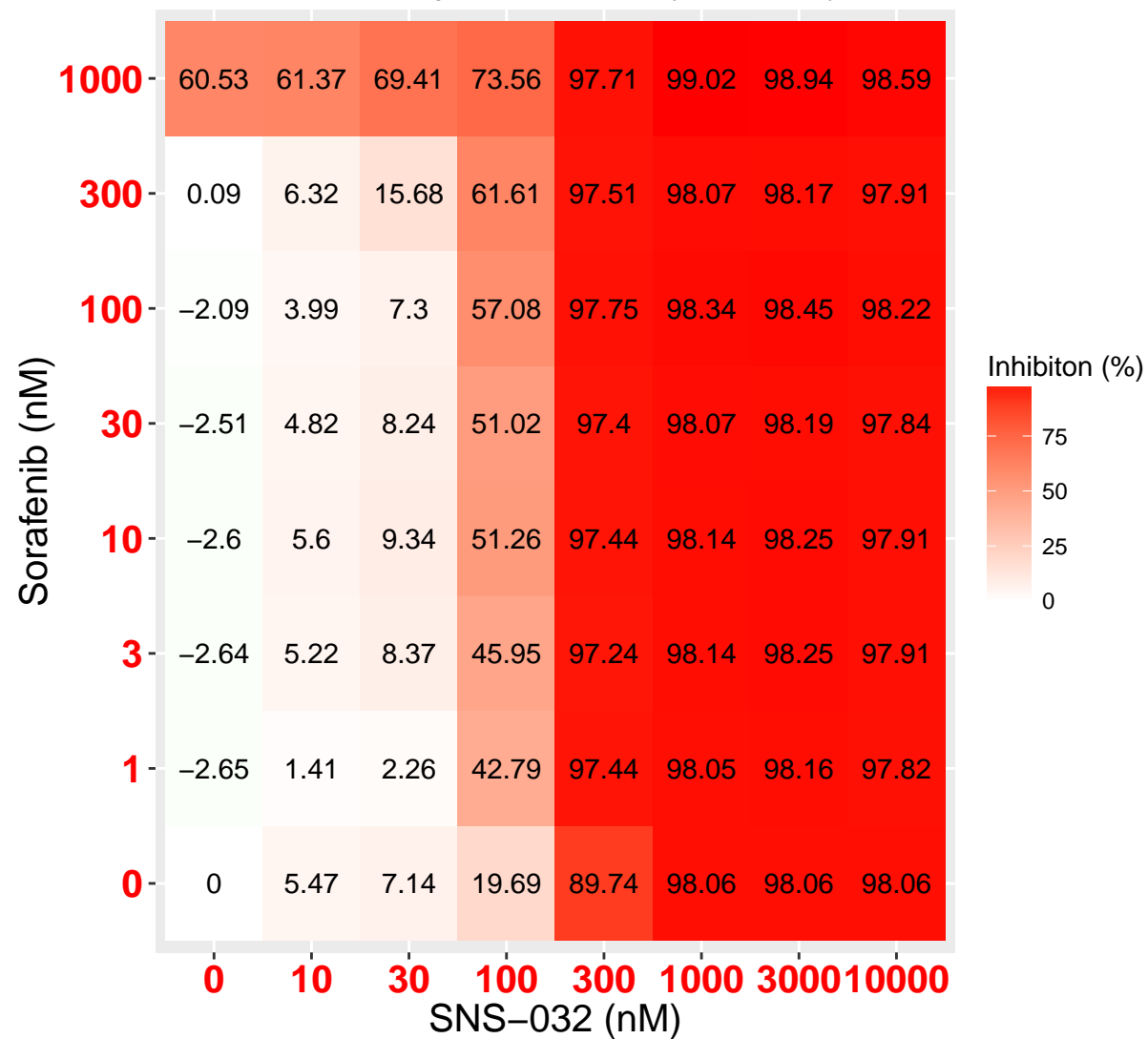
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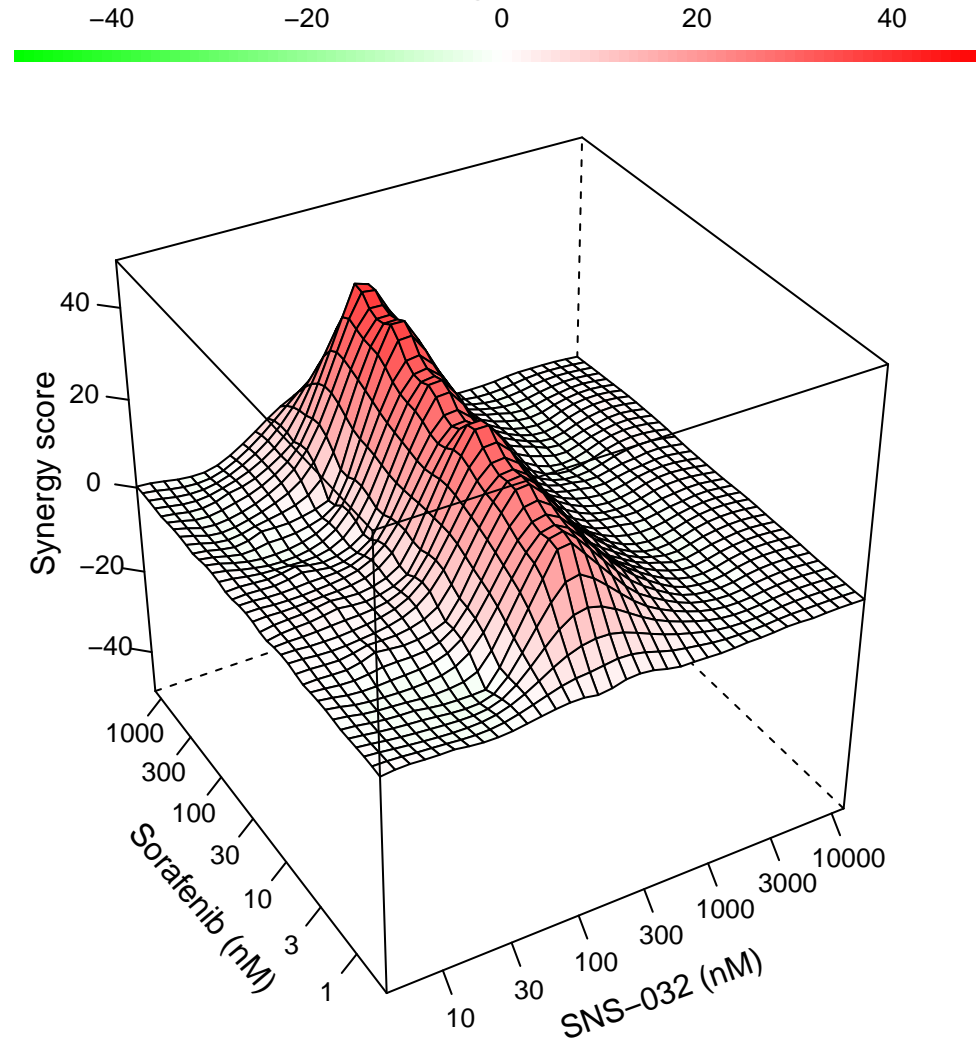
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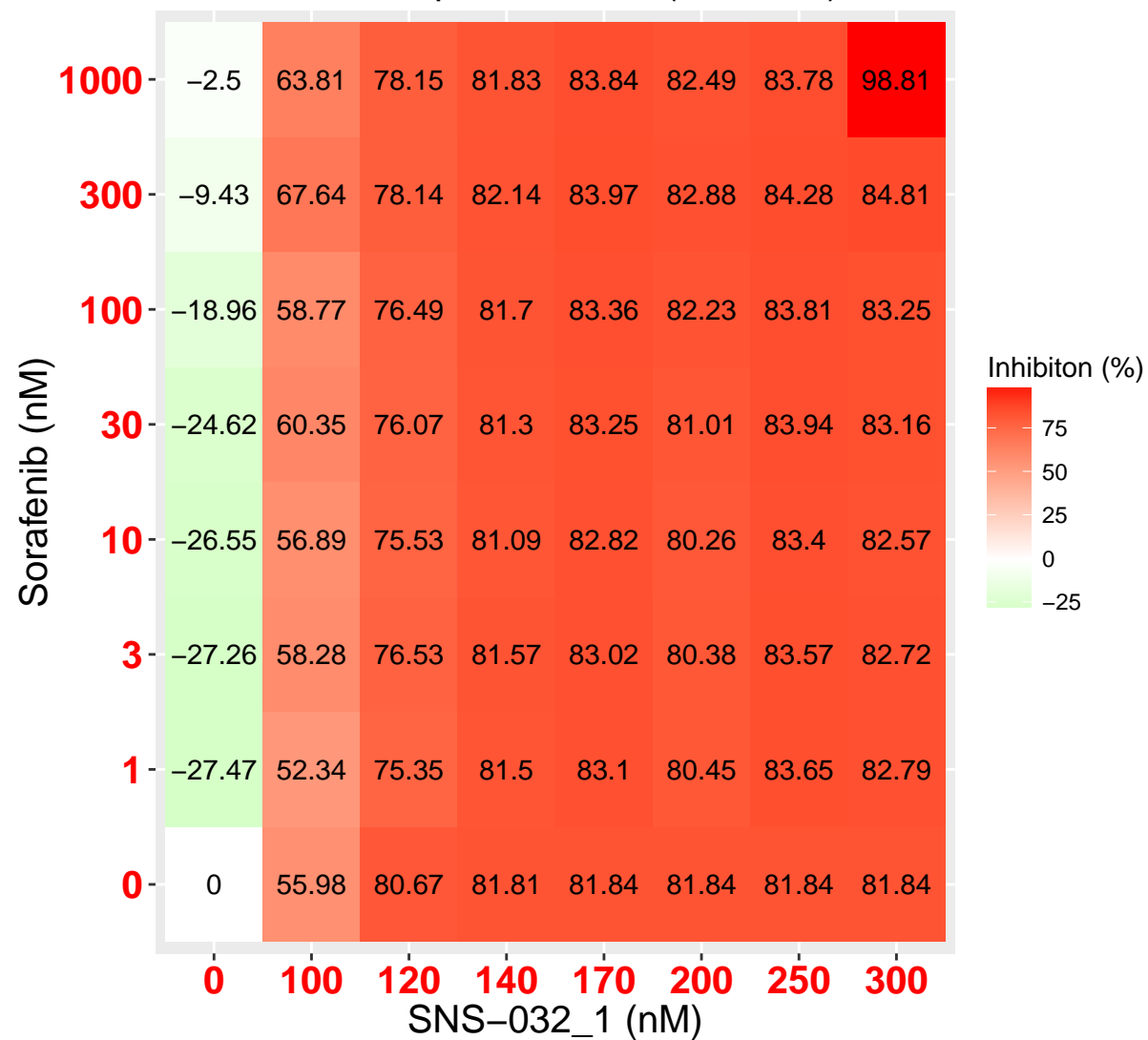
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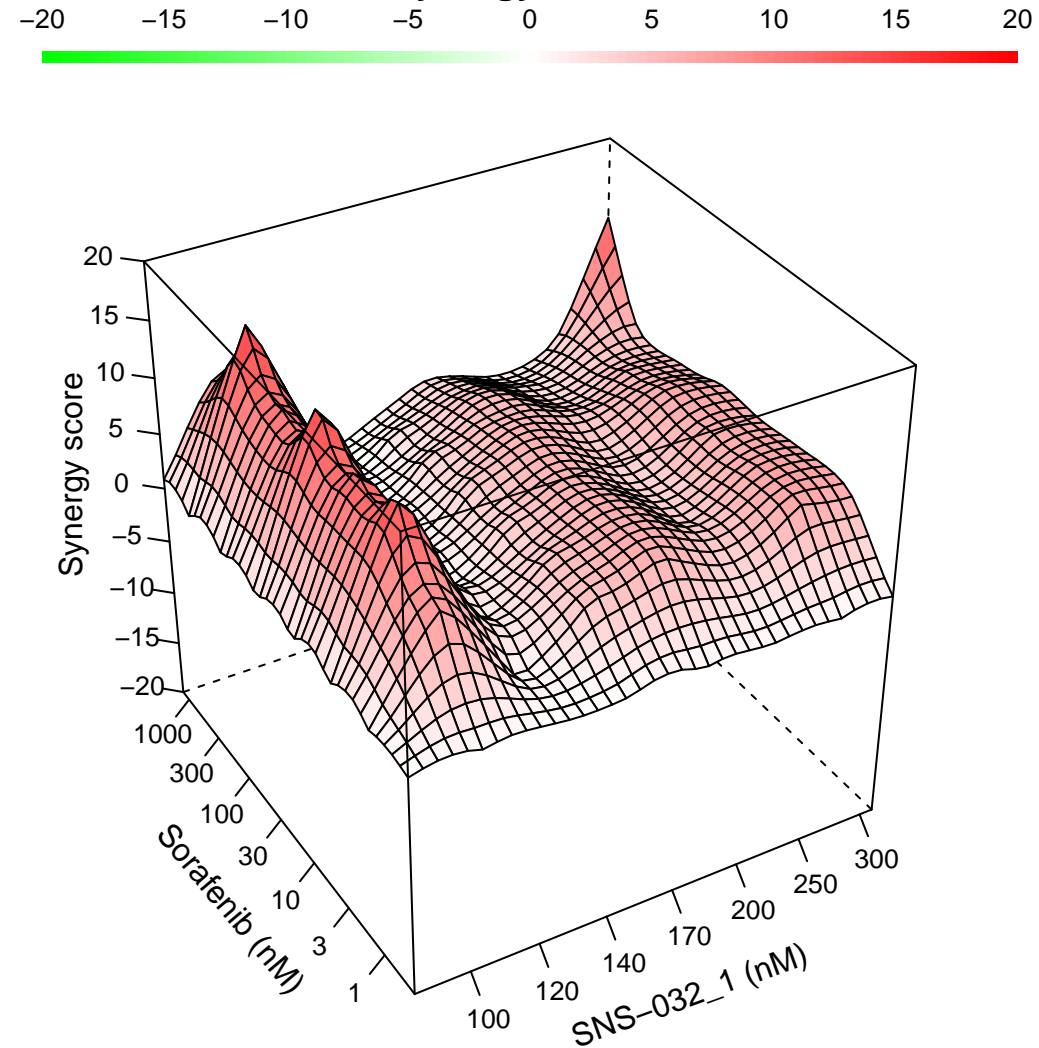
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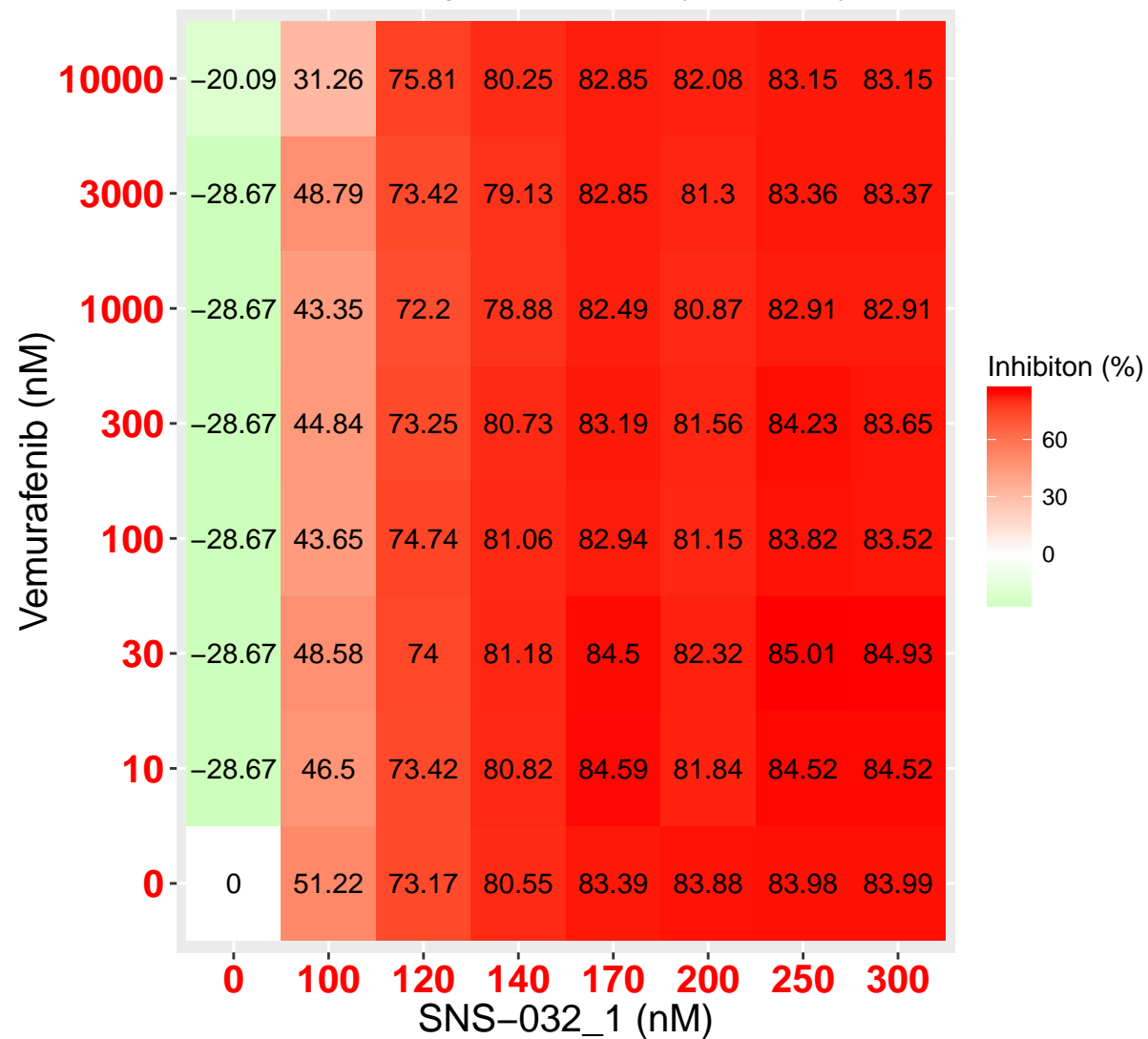
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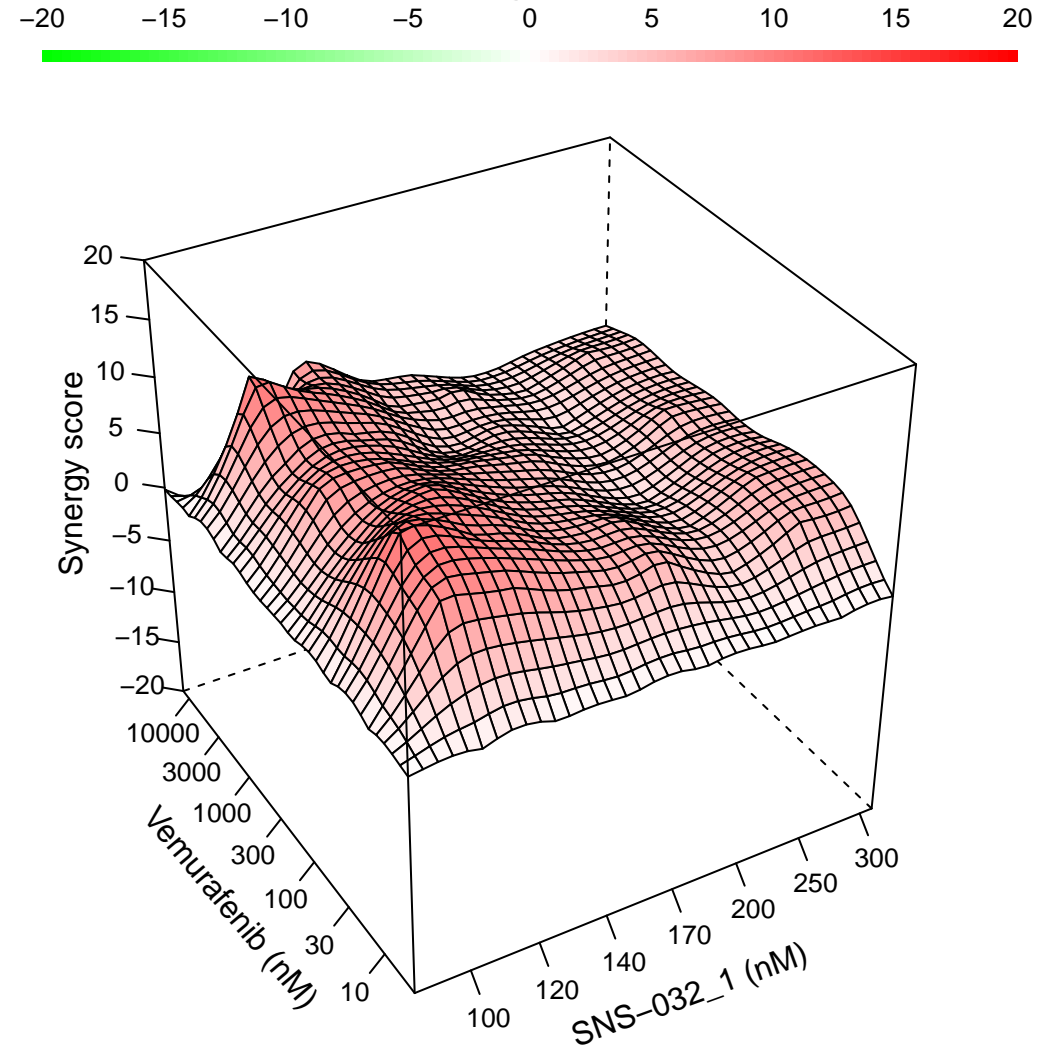
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Dose-response matrix (inhibition)

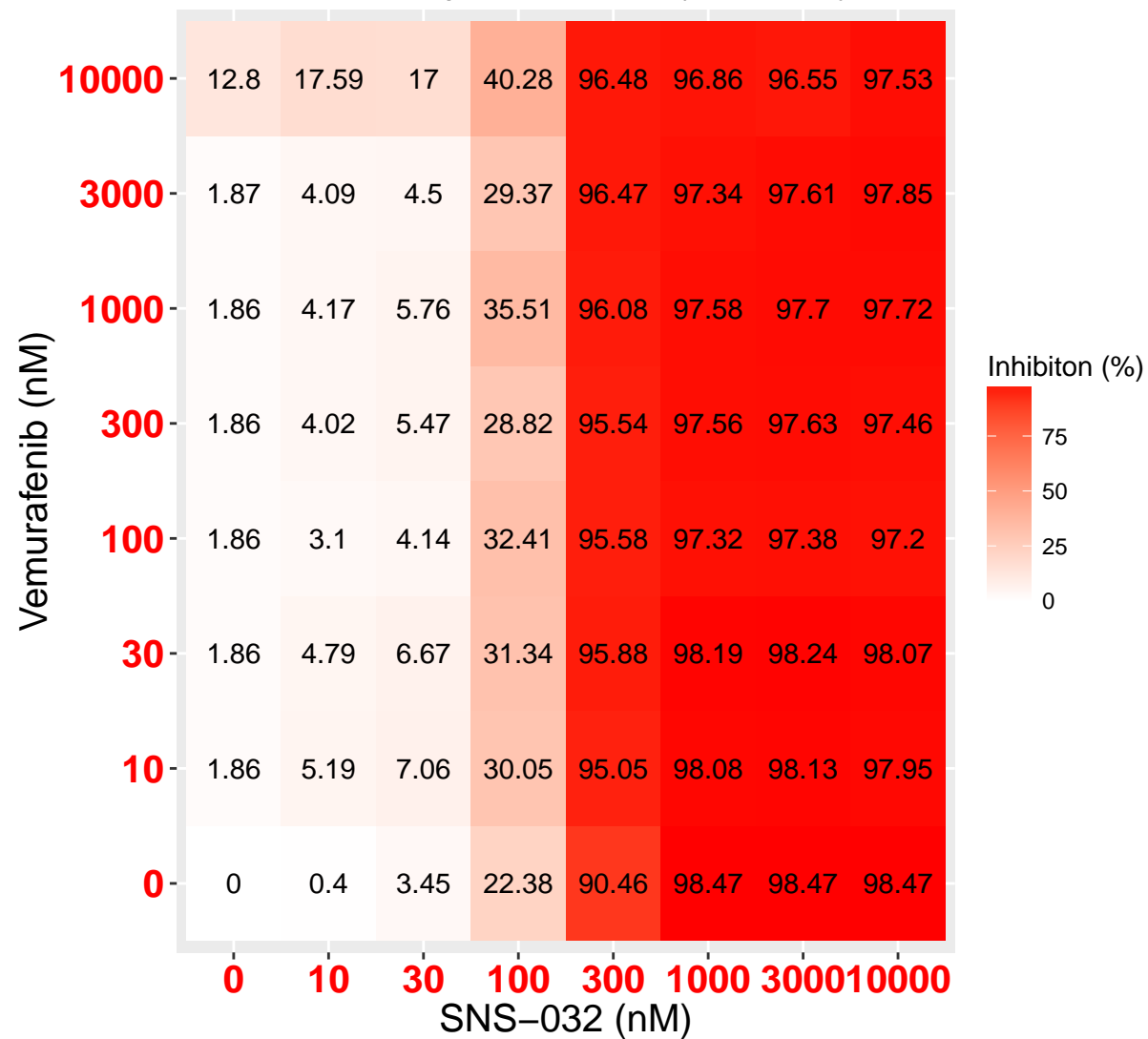


Bliss synergy score: 4.49

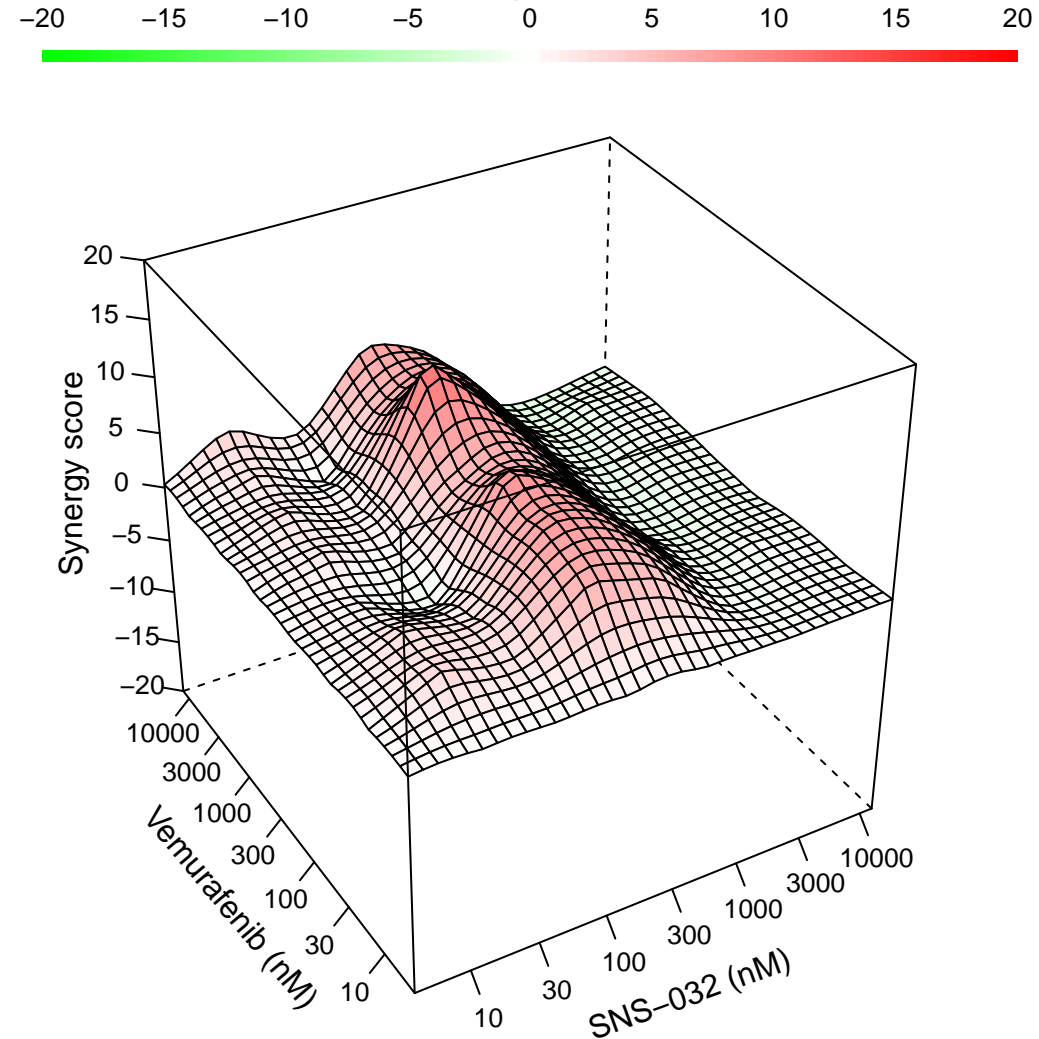




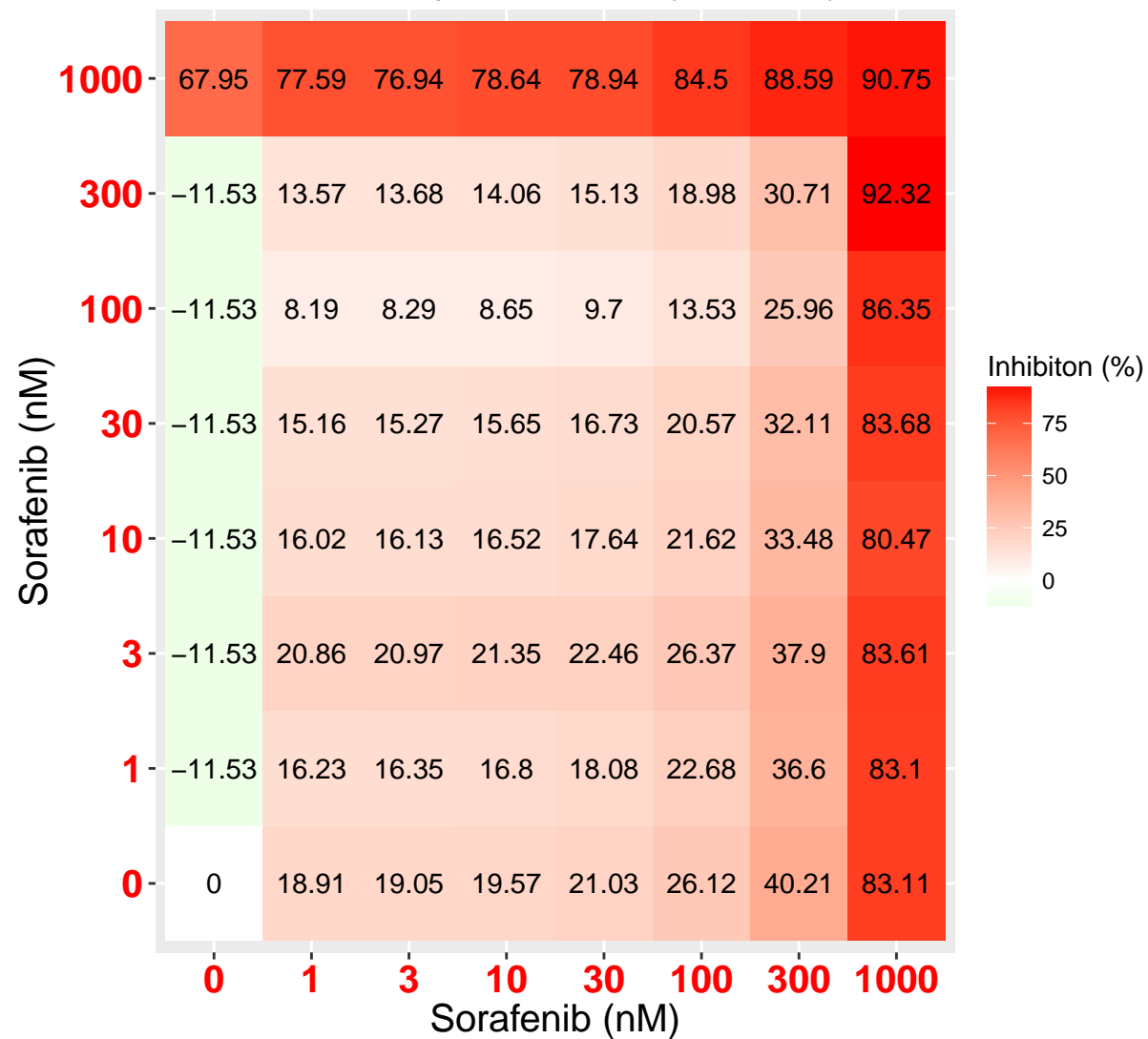
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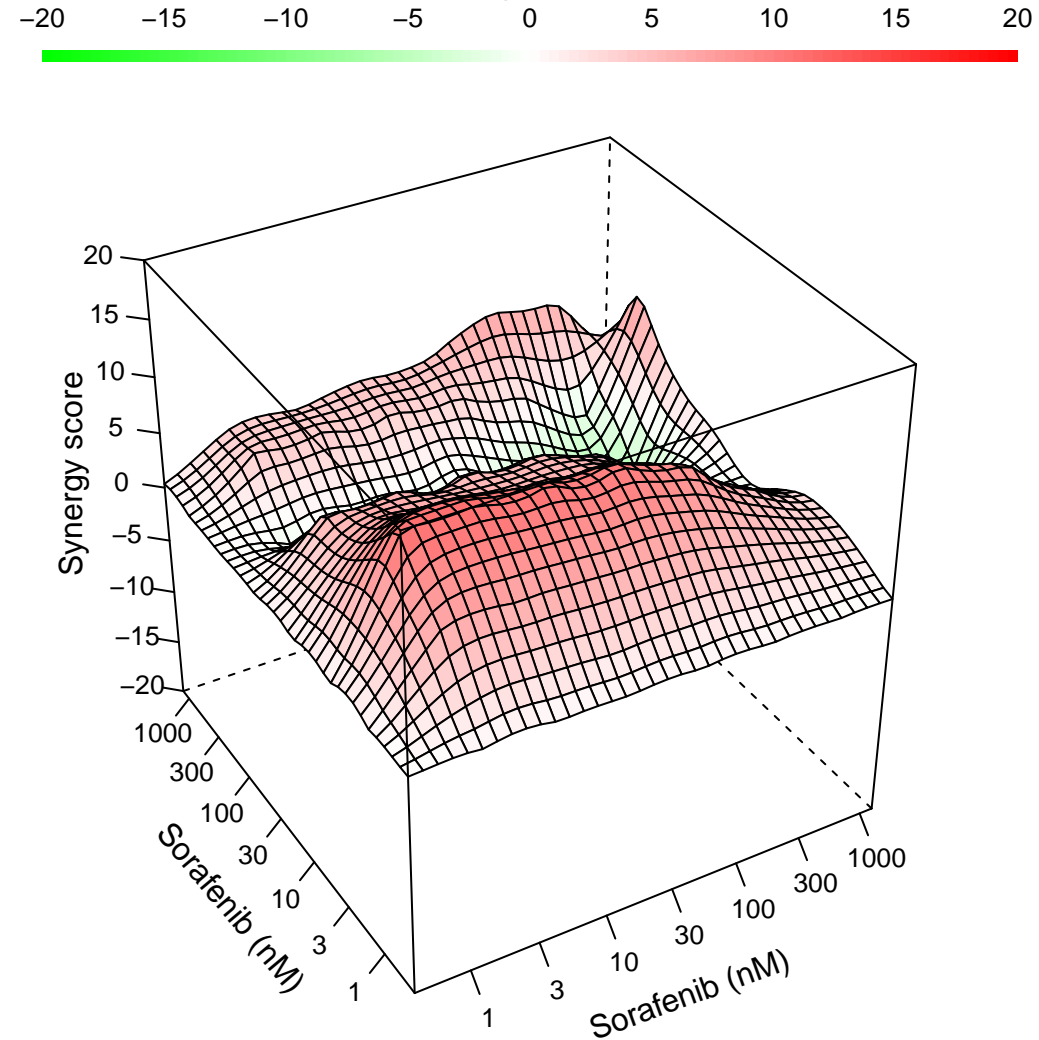
Bliss synergy score: 1.73



Dose-response matrix (inhibition)

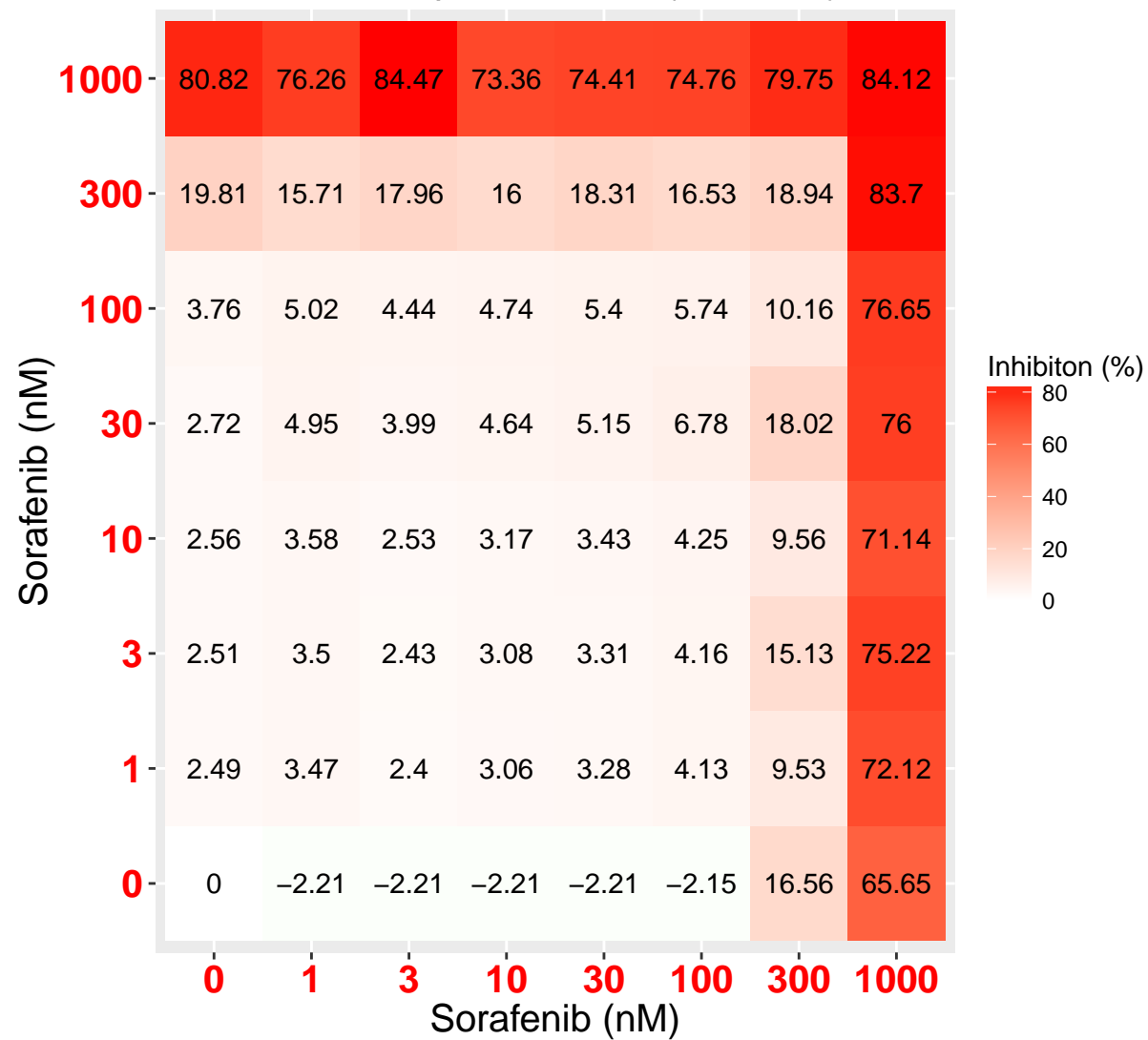


Bliss synergy score: 3.355

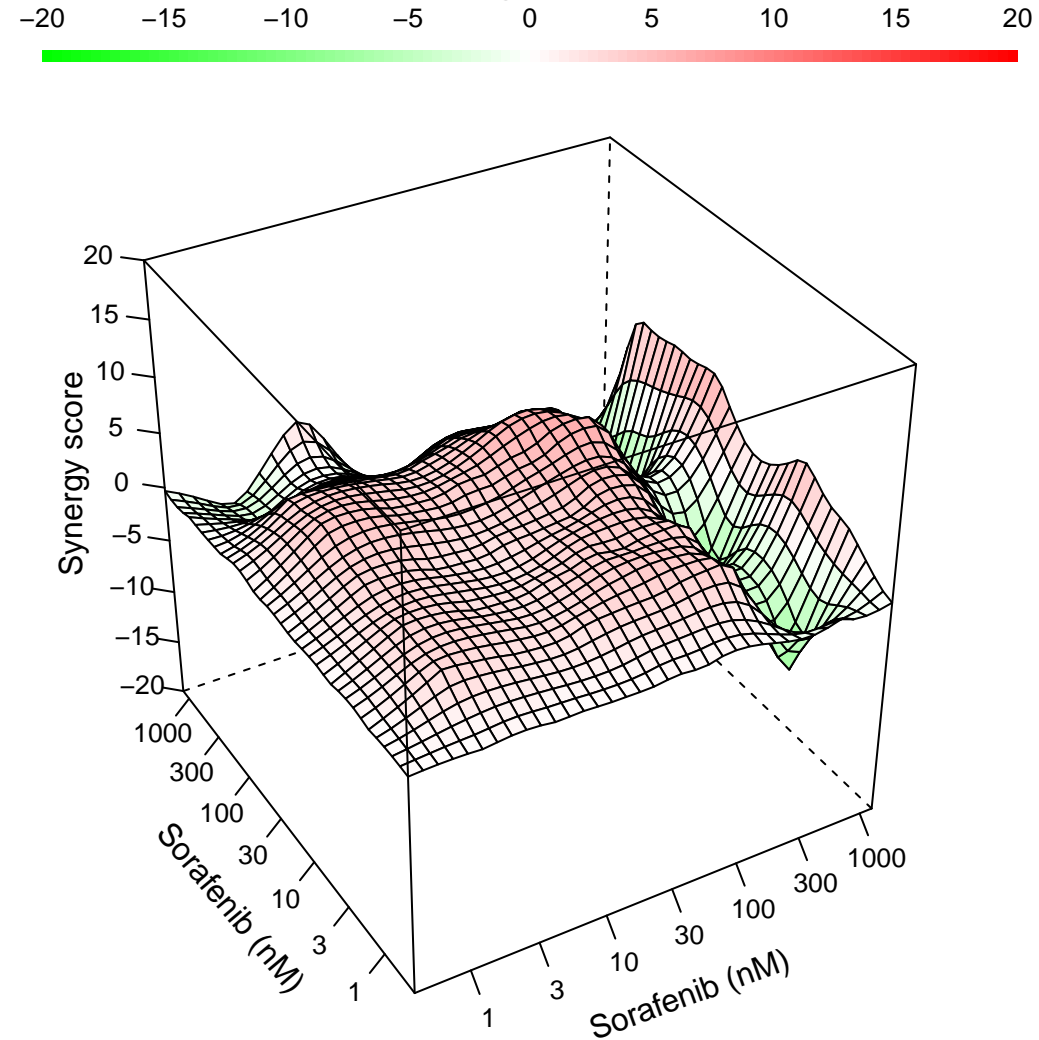




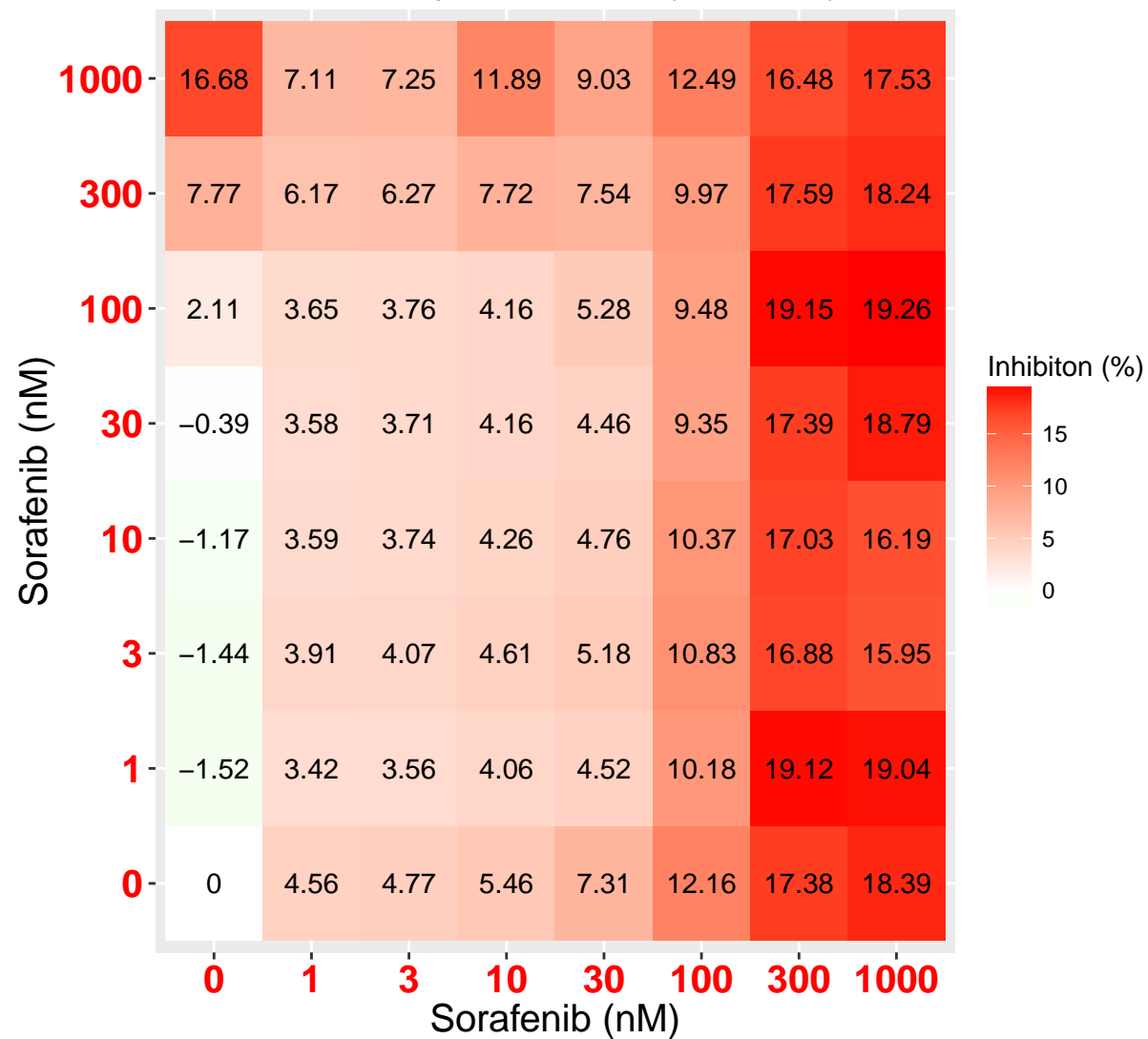
Dose-response matrix (inhibition)



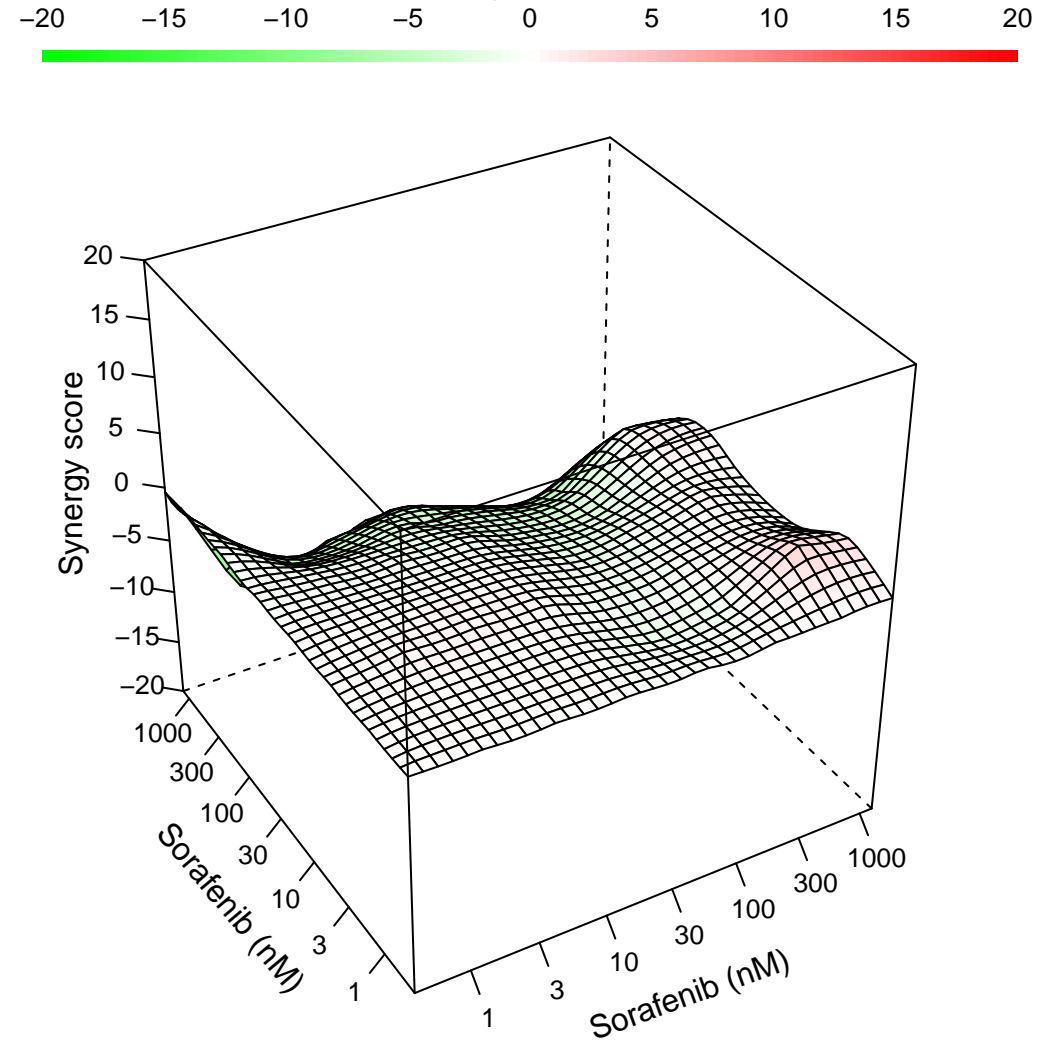
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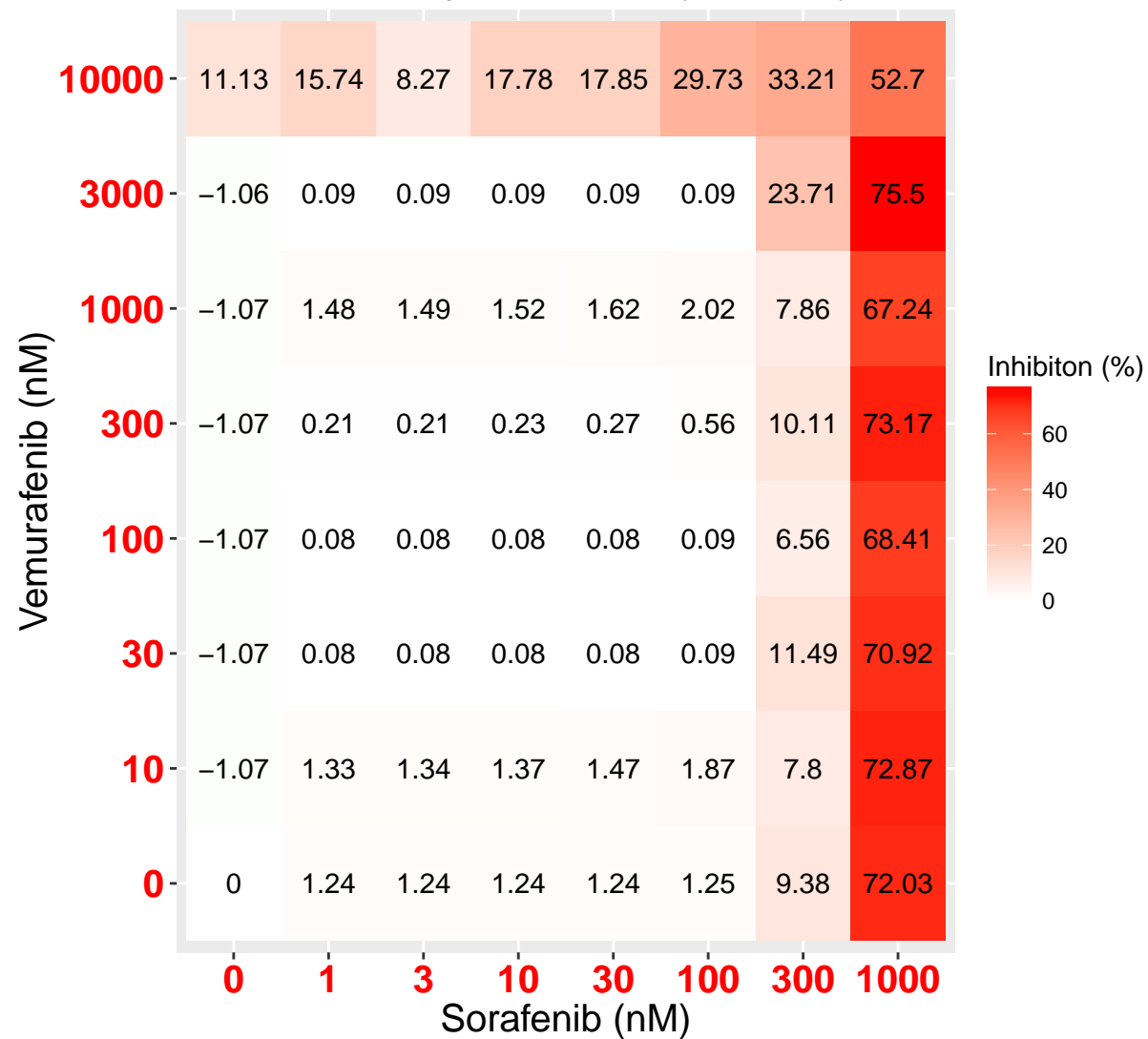
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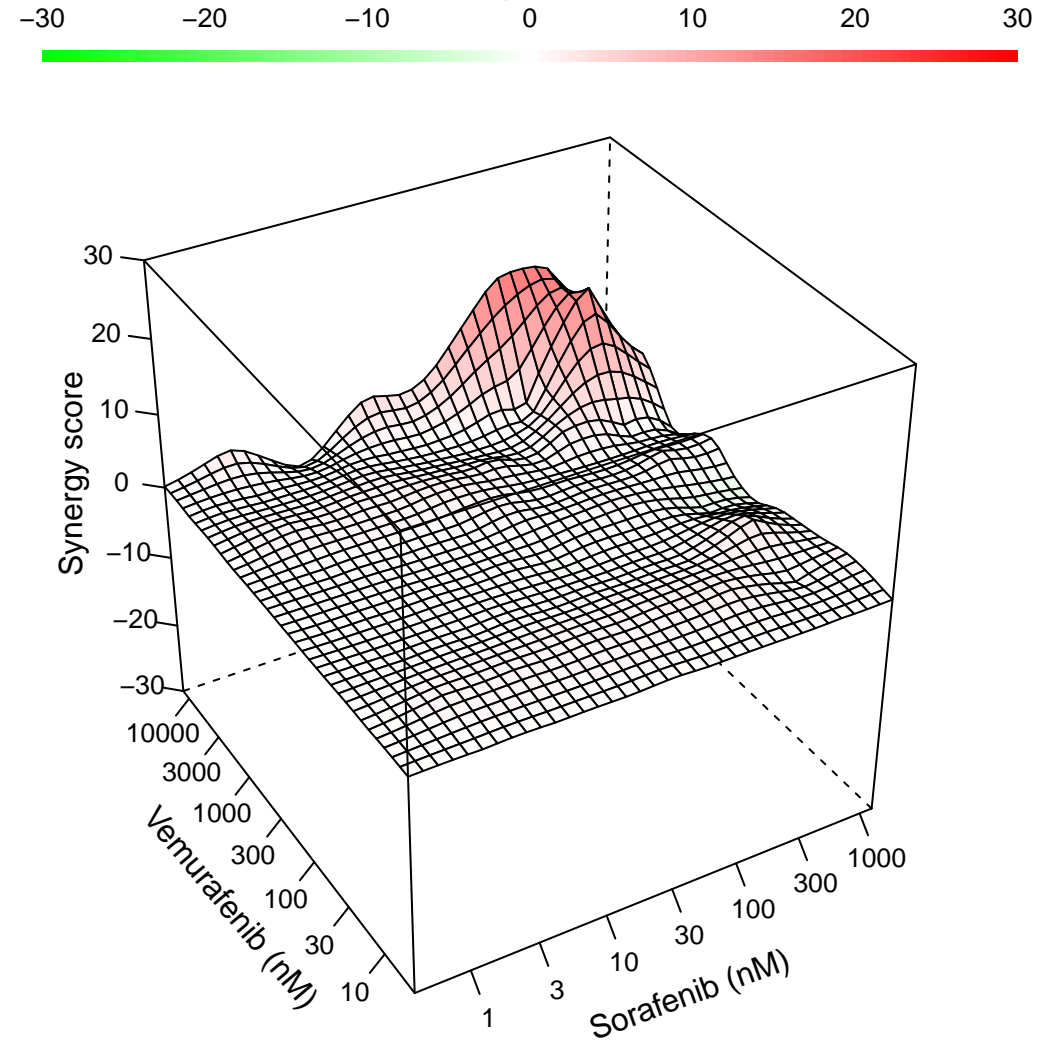
Bliss synergy score: -2.214



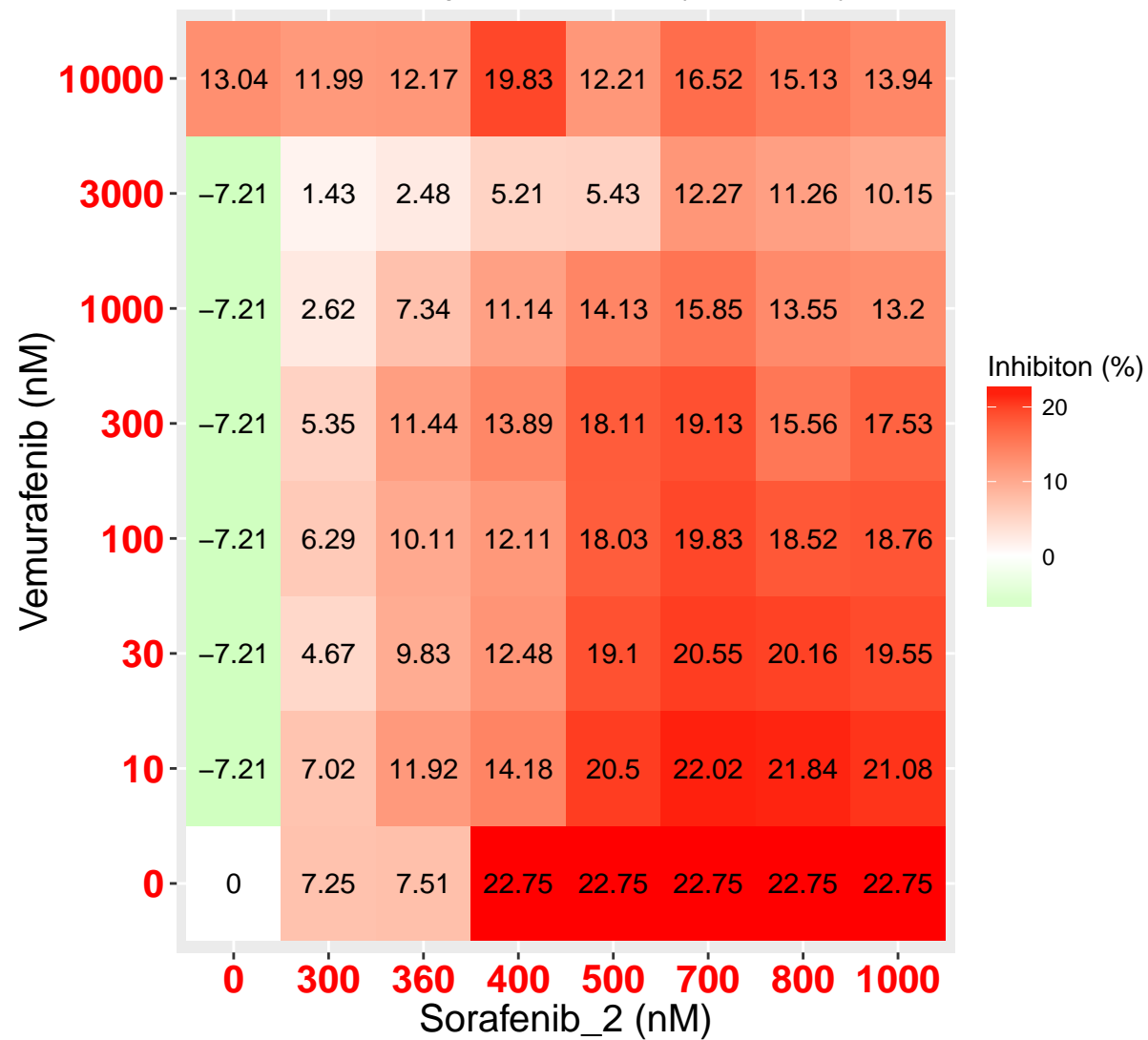
Dose-response matrix (inhibition)



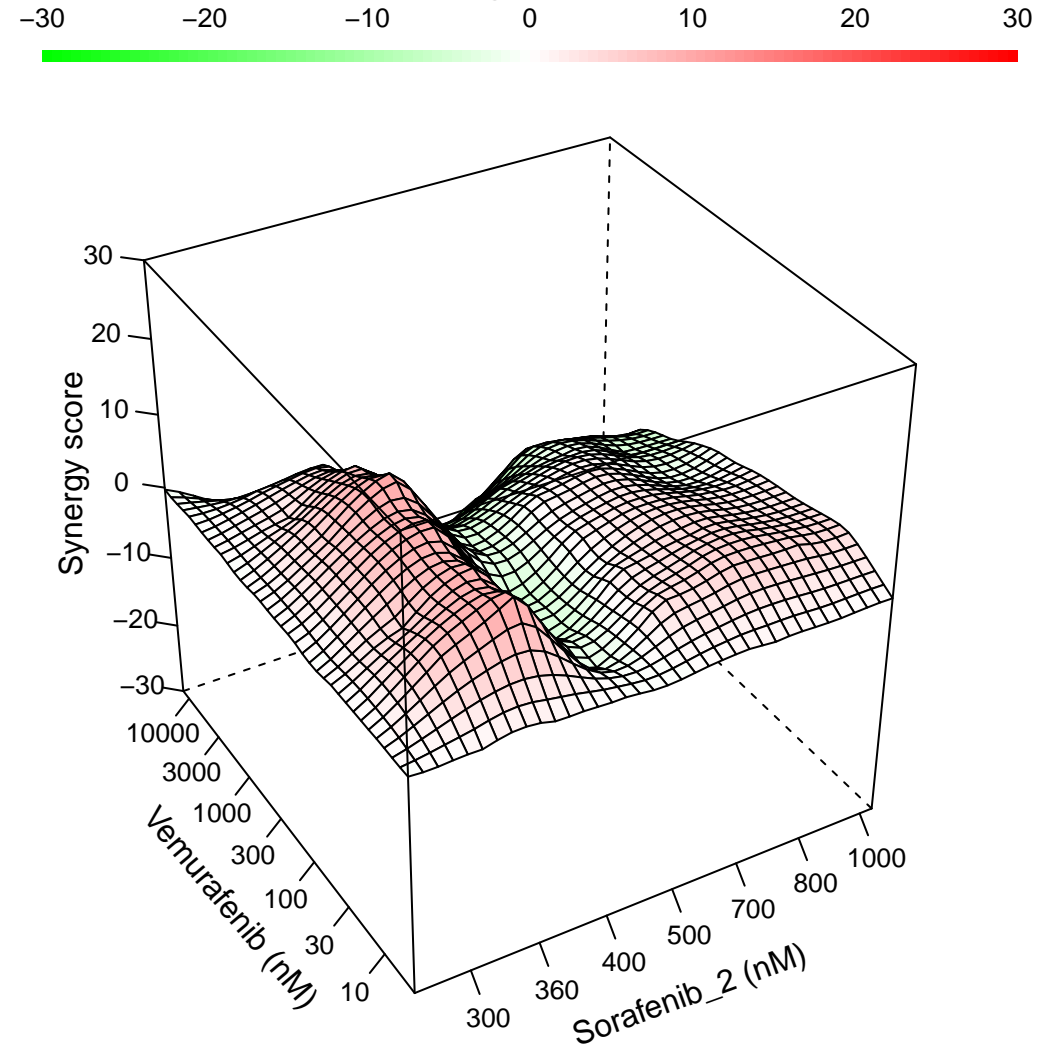
Bliss synergy score: 0.899



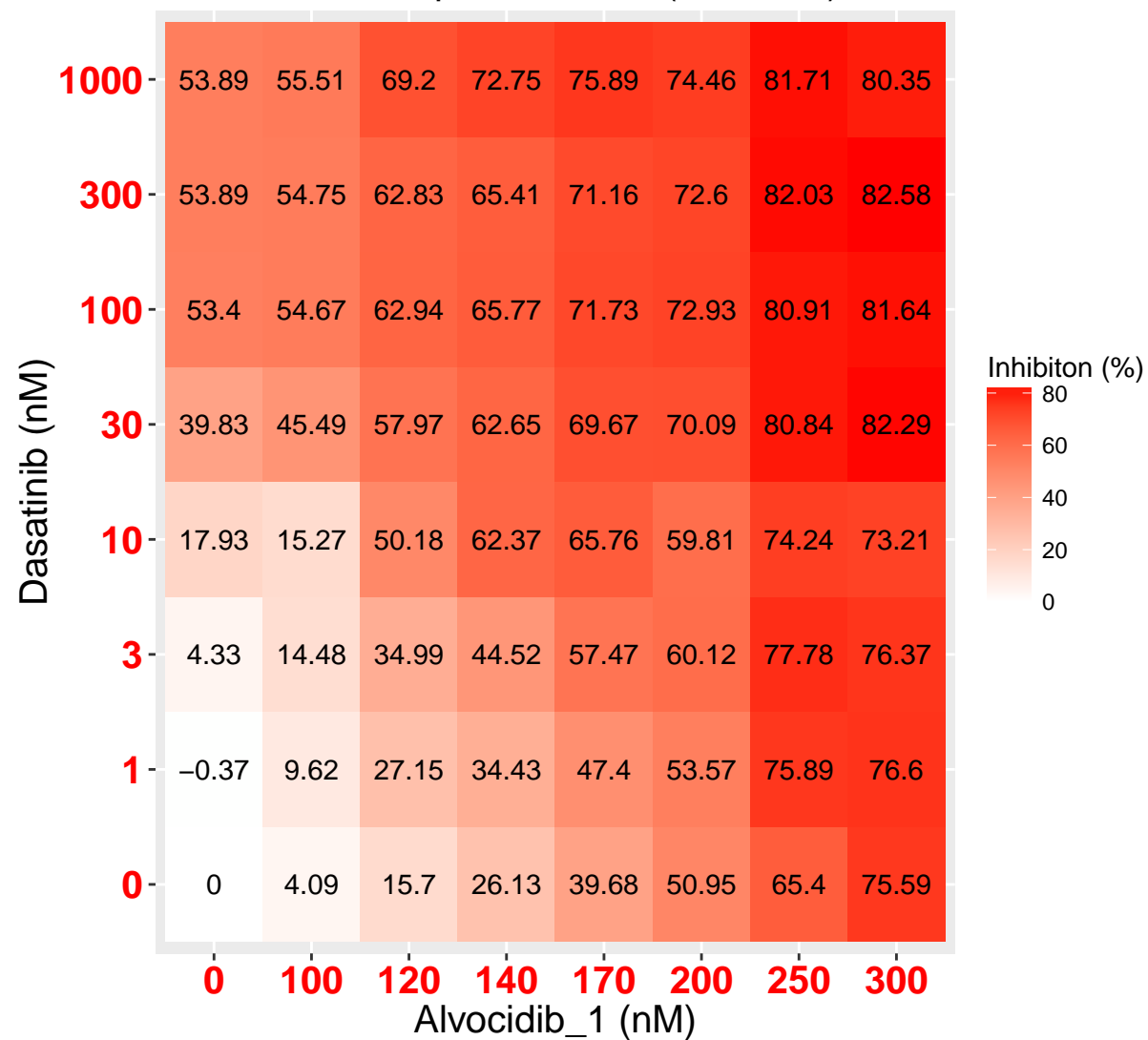
Dose-response matrix (inhibition)



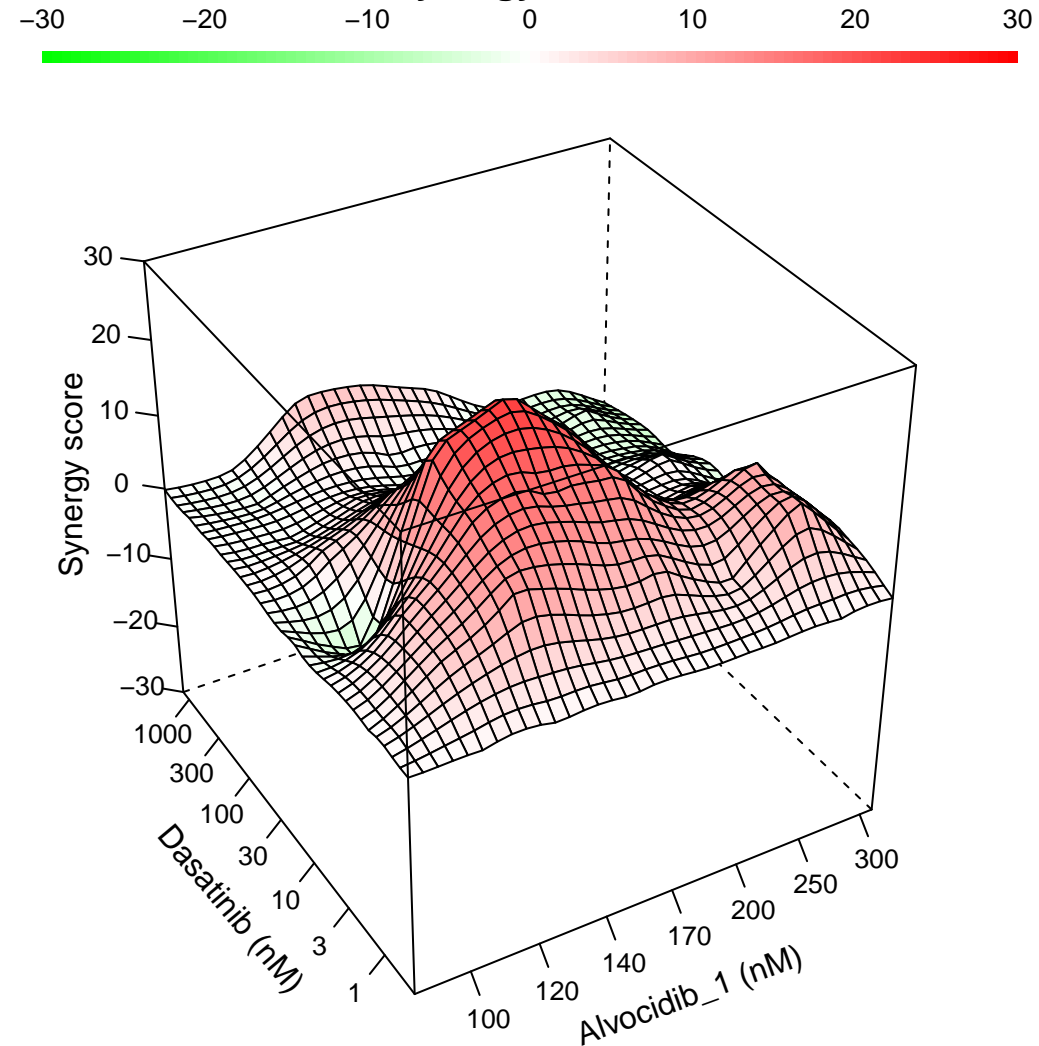
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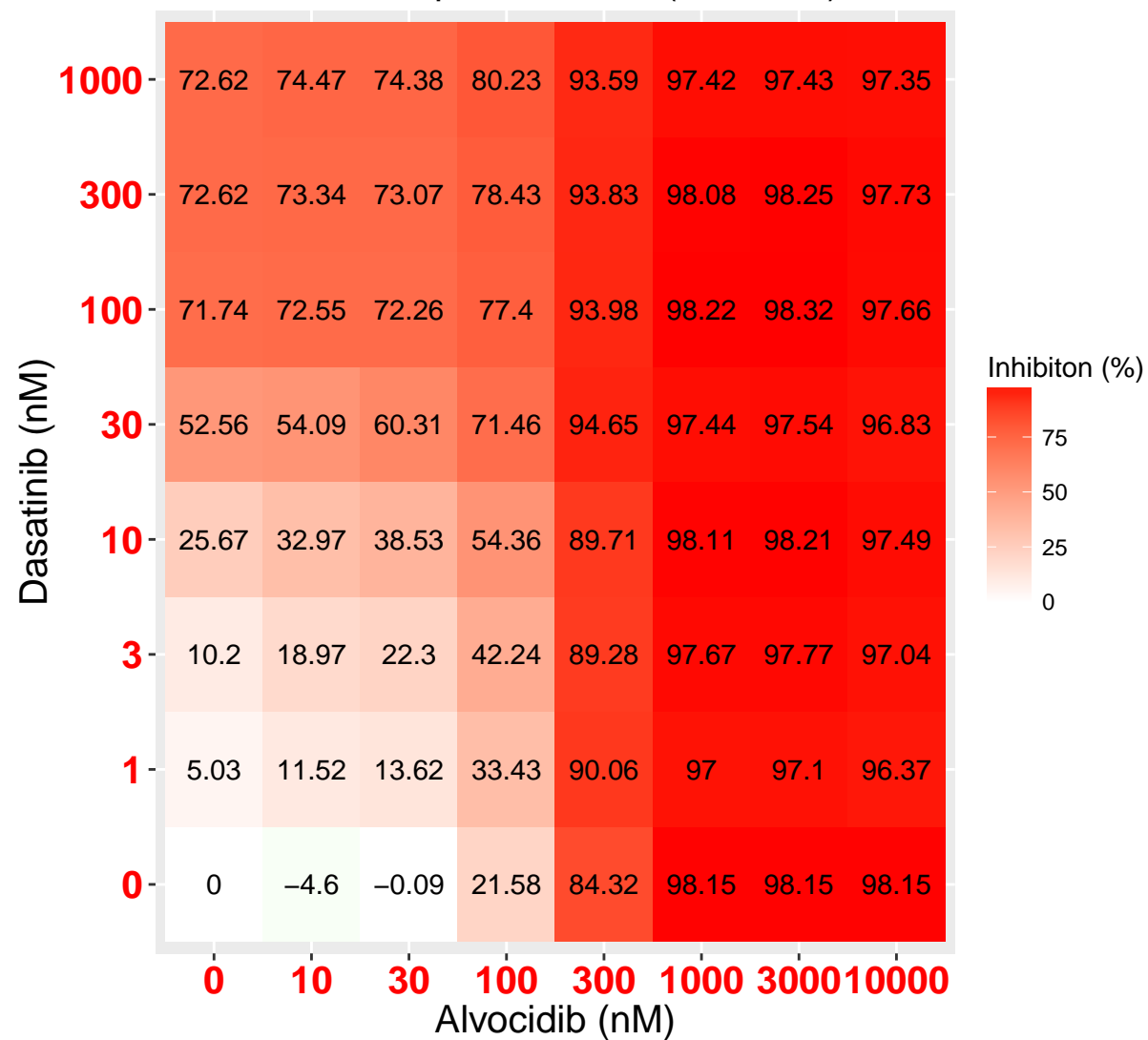
Dose-response matrix (inhibition)



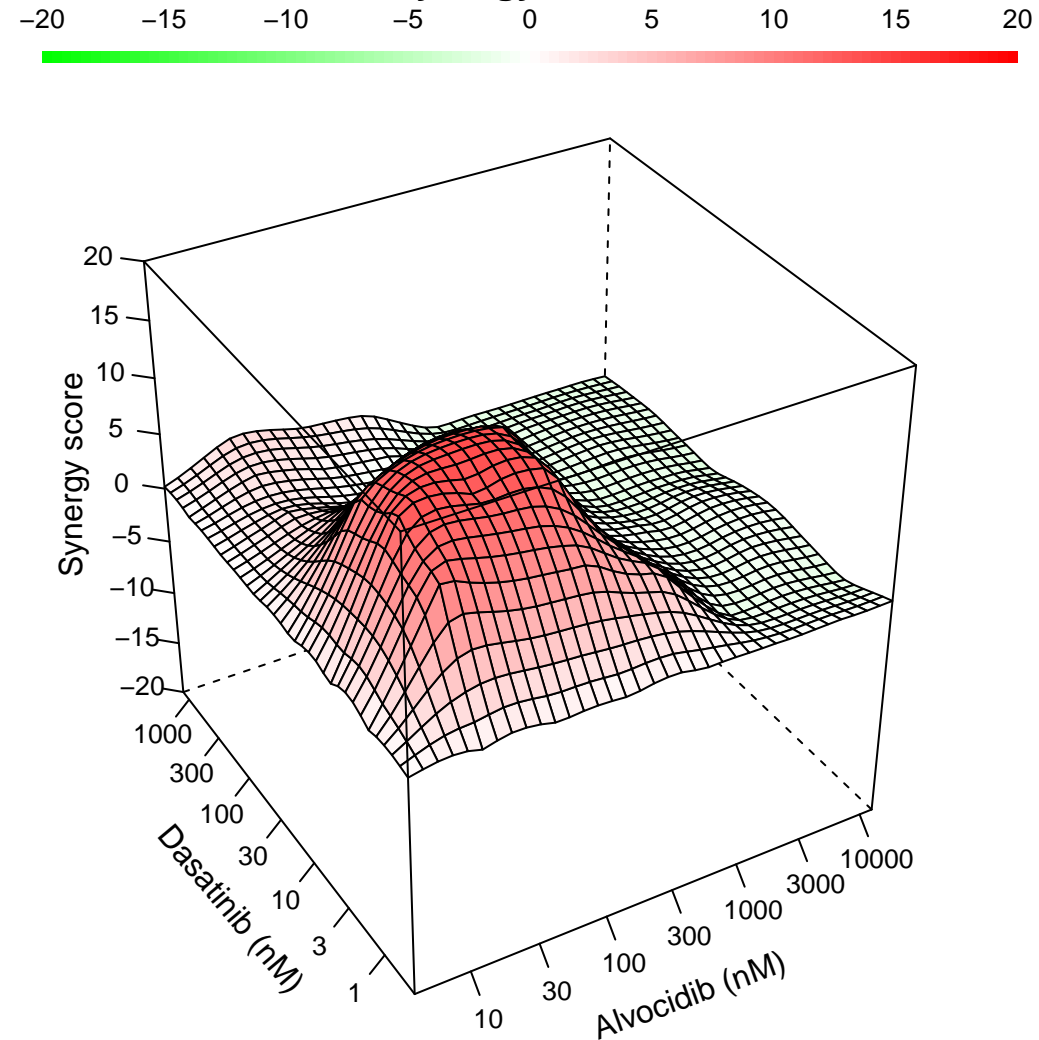
Bliss synergy score: 3.635



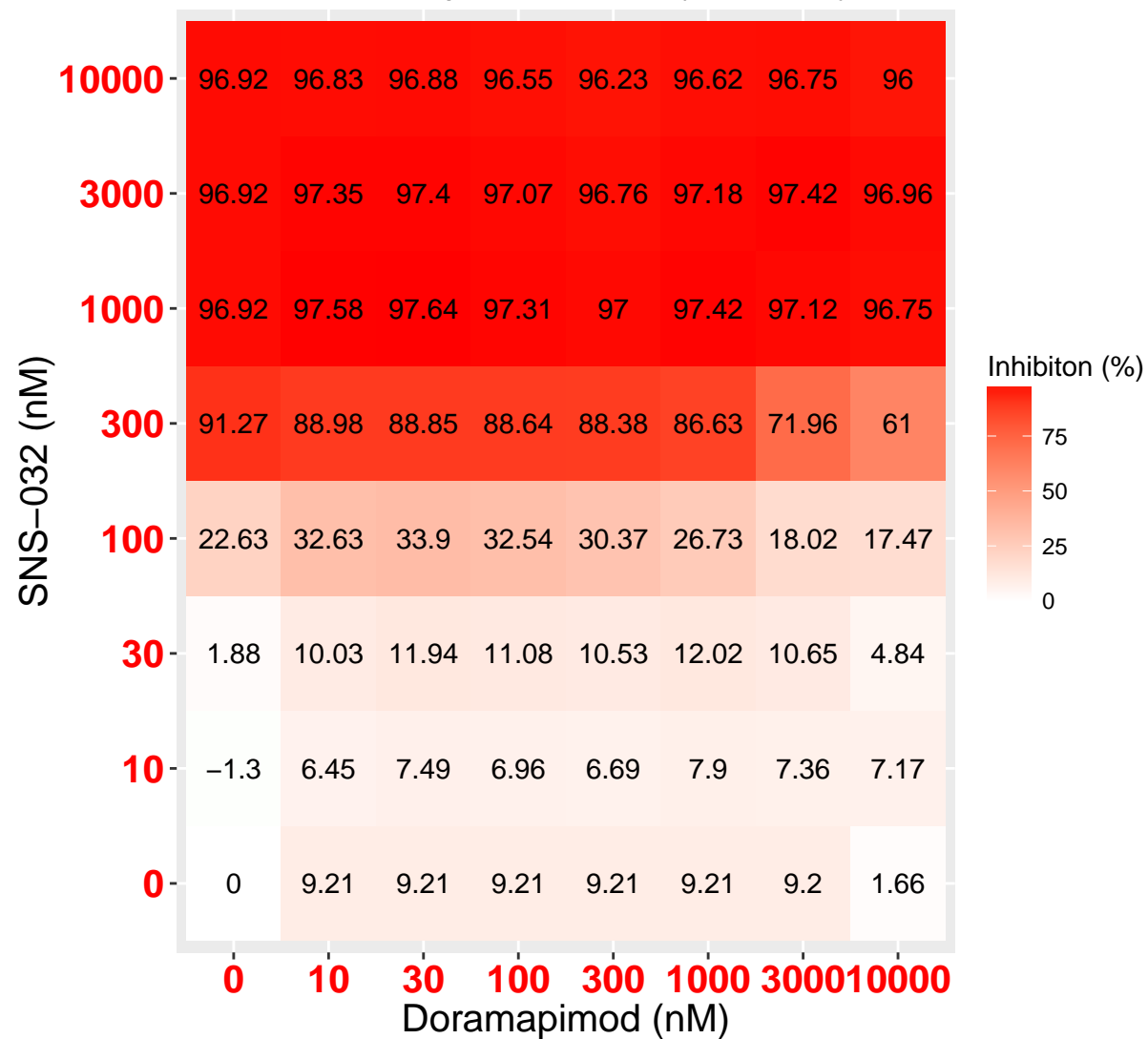
Dose-response matrix (inhibition)



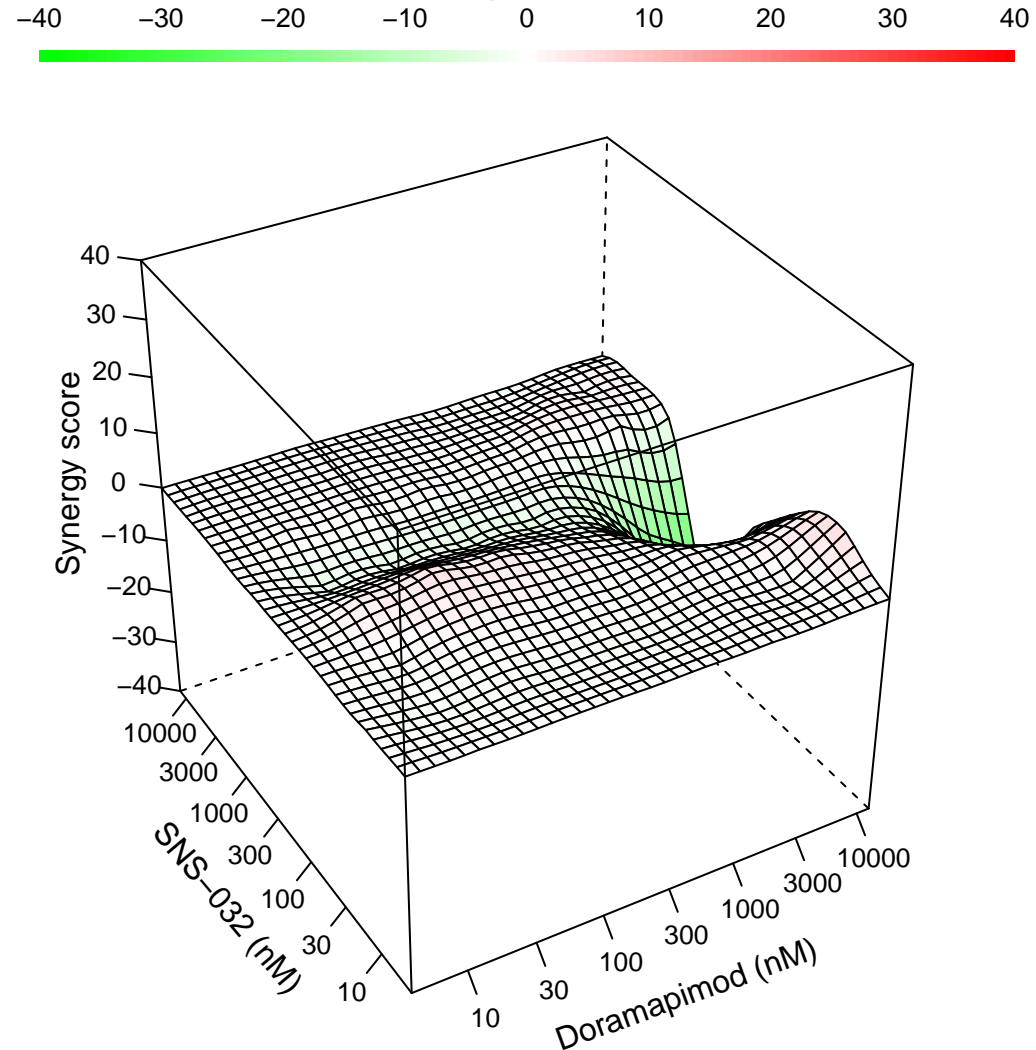
Bliss synergy score: 2.313



Dose-response matrix (inhibition)

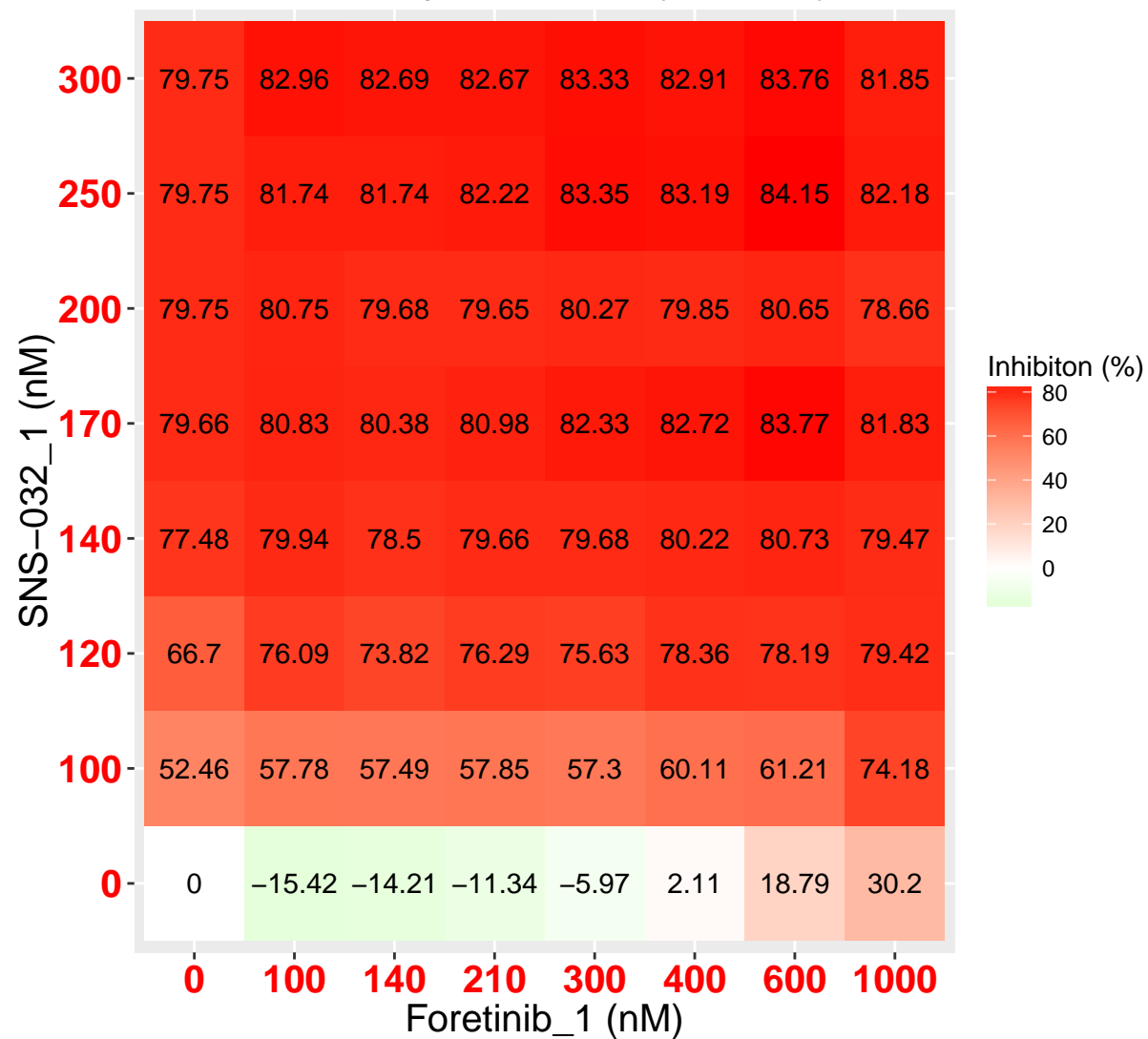


Bliss synergy score: -1.295

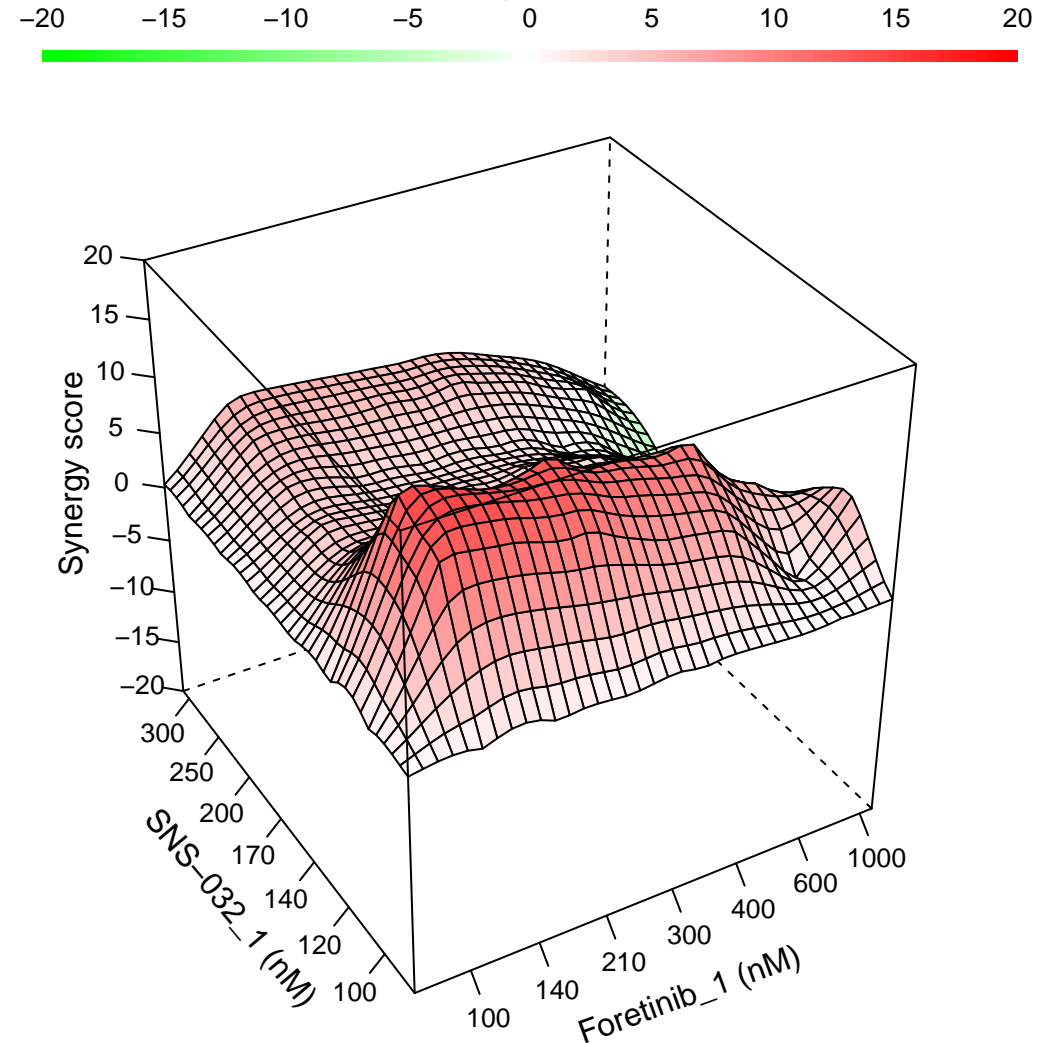




Dose-response matrix (inhibition)

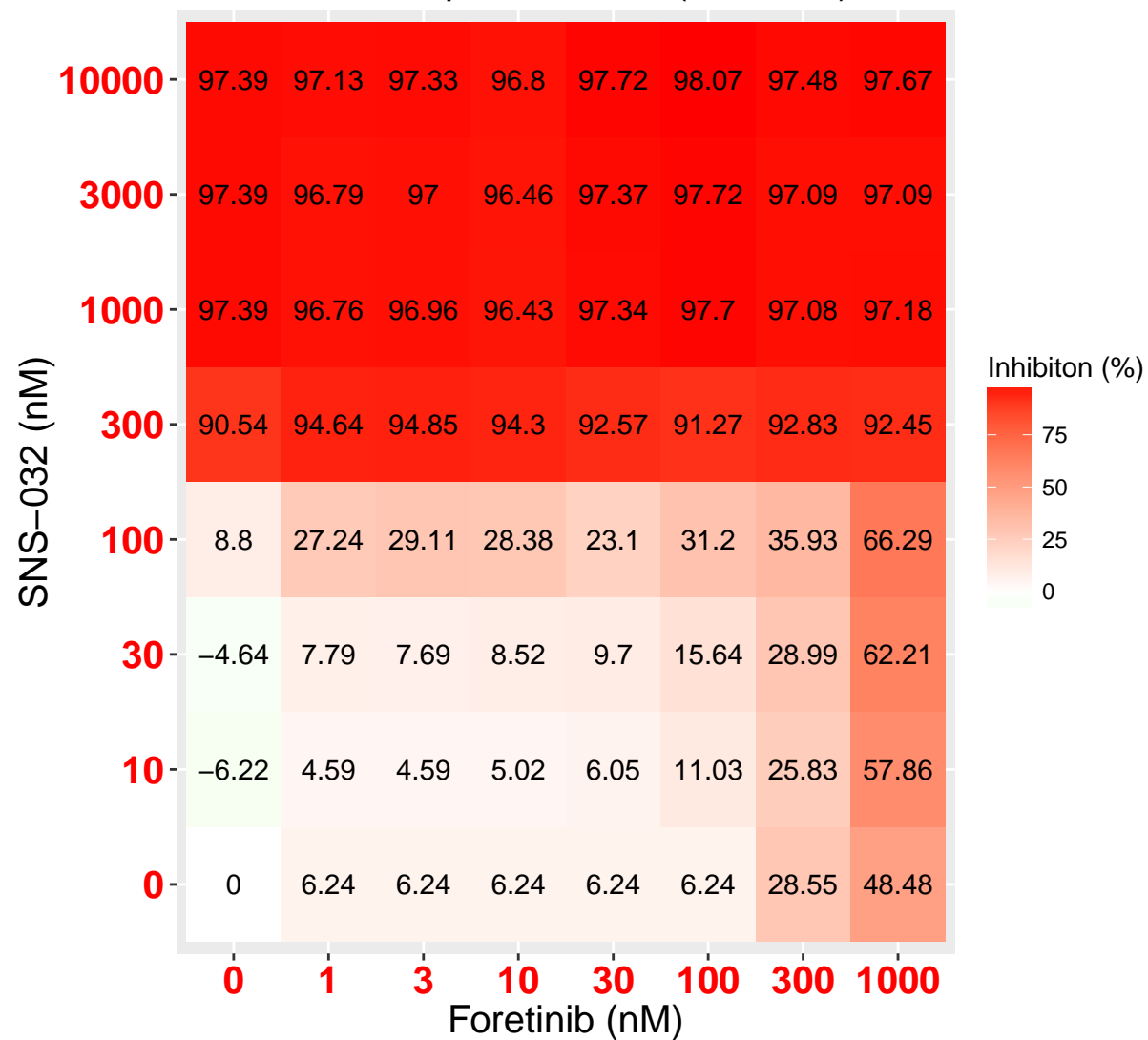


Bliss synergy score: 3.913

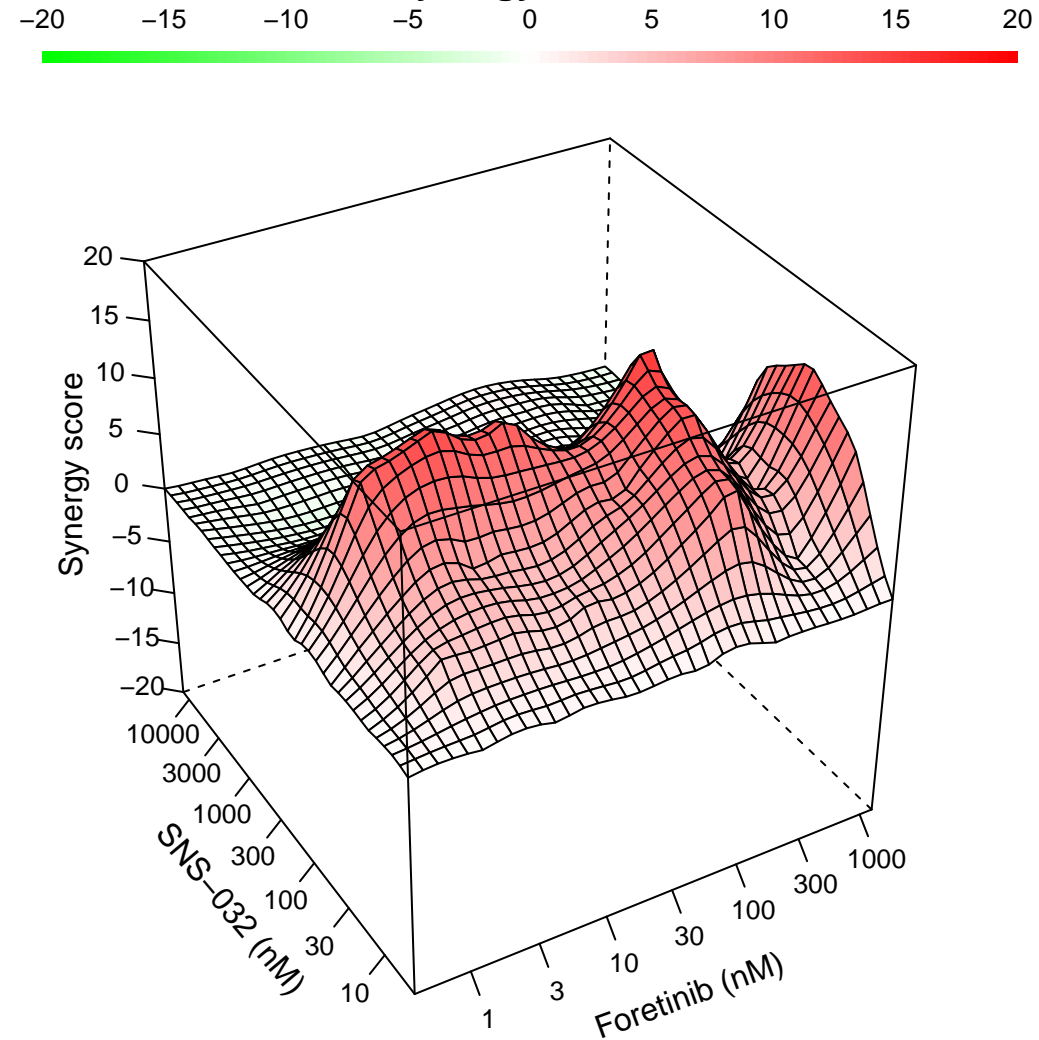




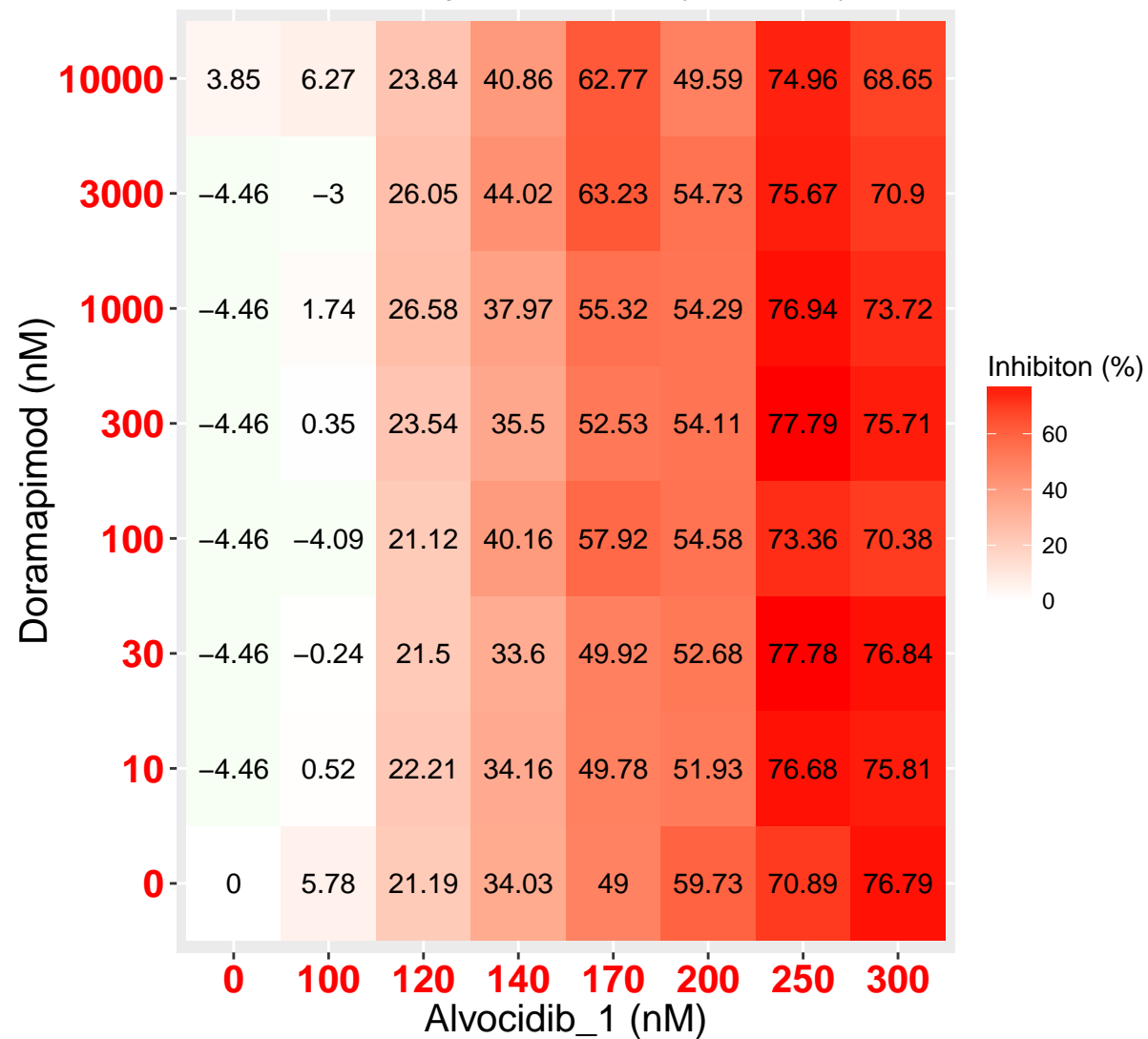
Dose-response matrix (inhibition)



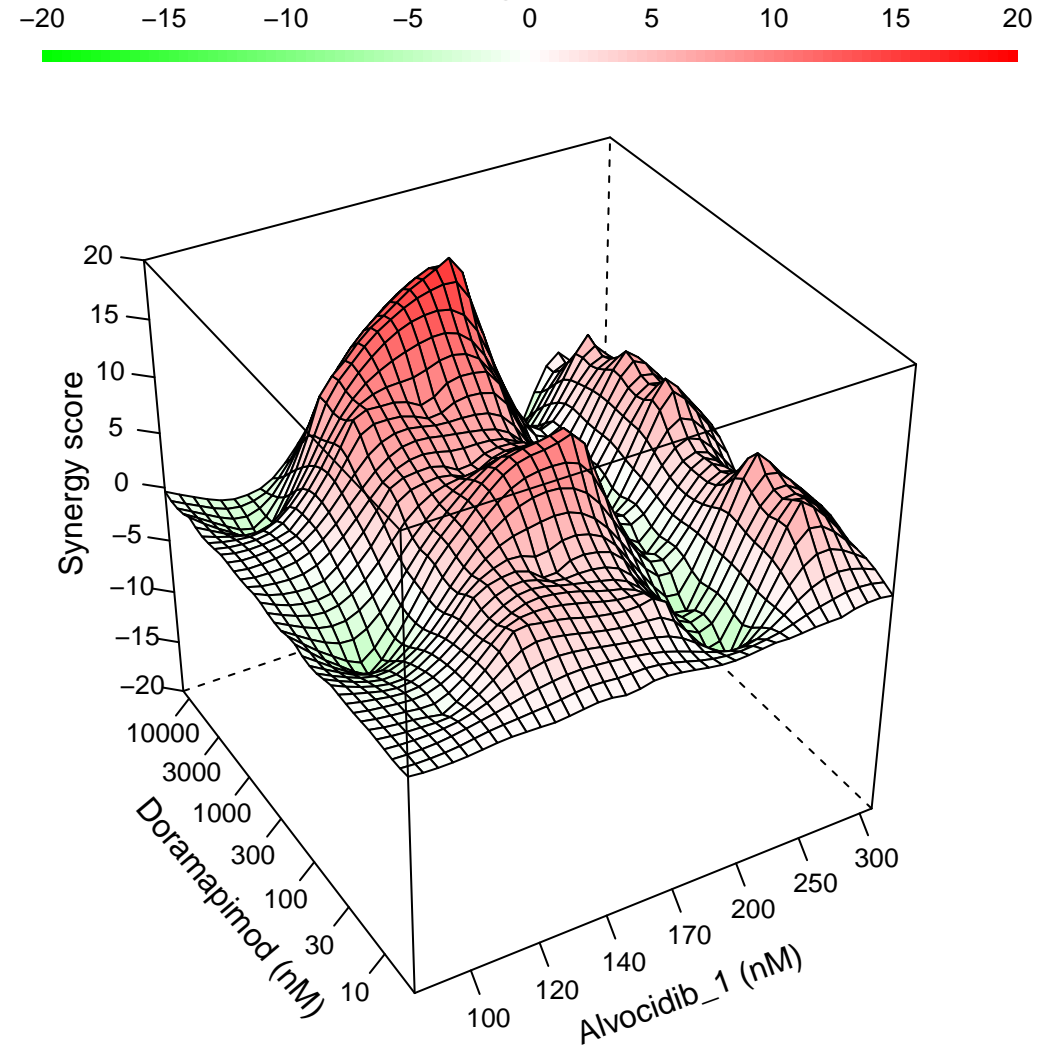
Bliss synergy score: 3.347



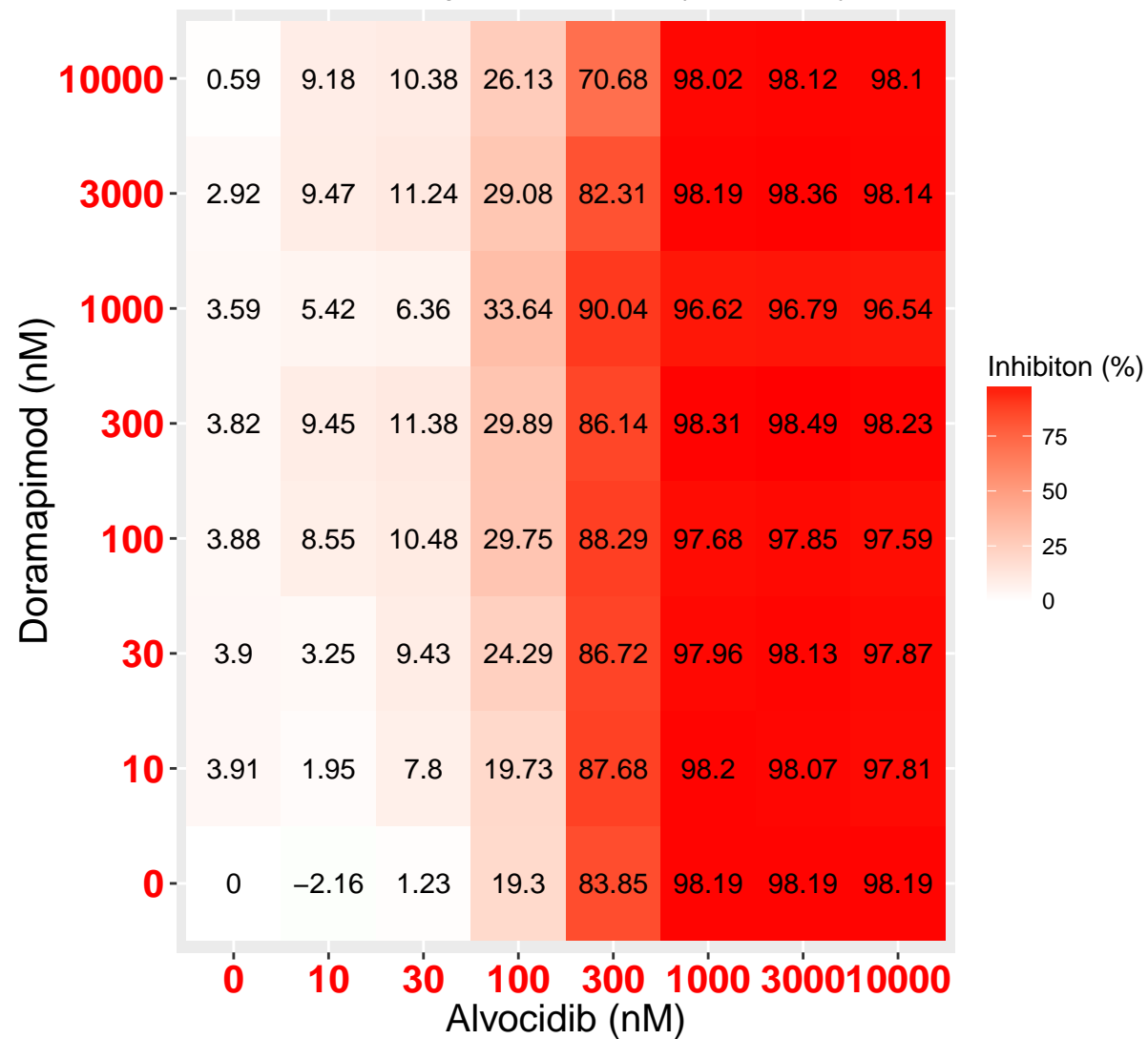
Dose-response matrix (inhibition)



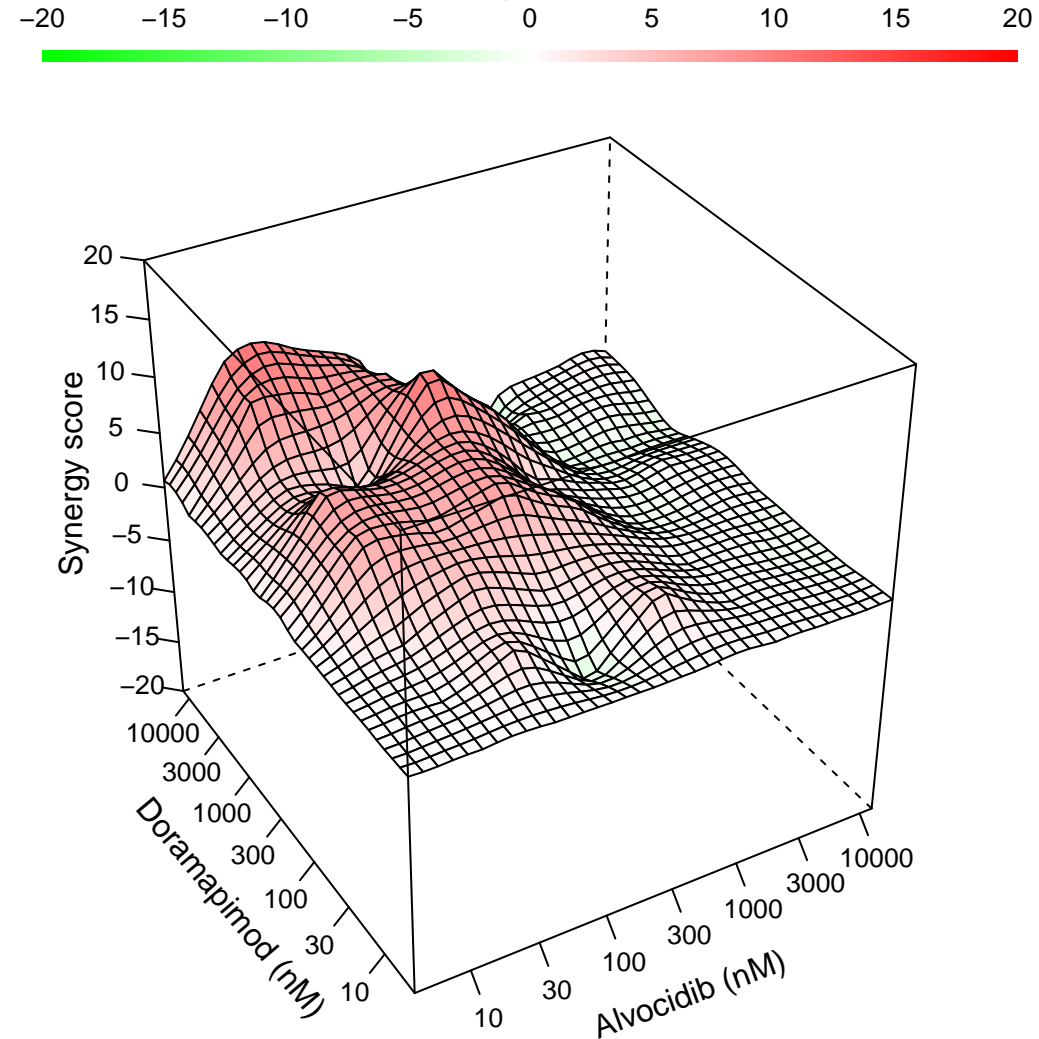
Bliss synergy score: 2.401



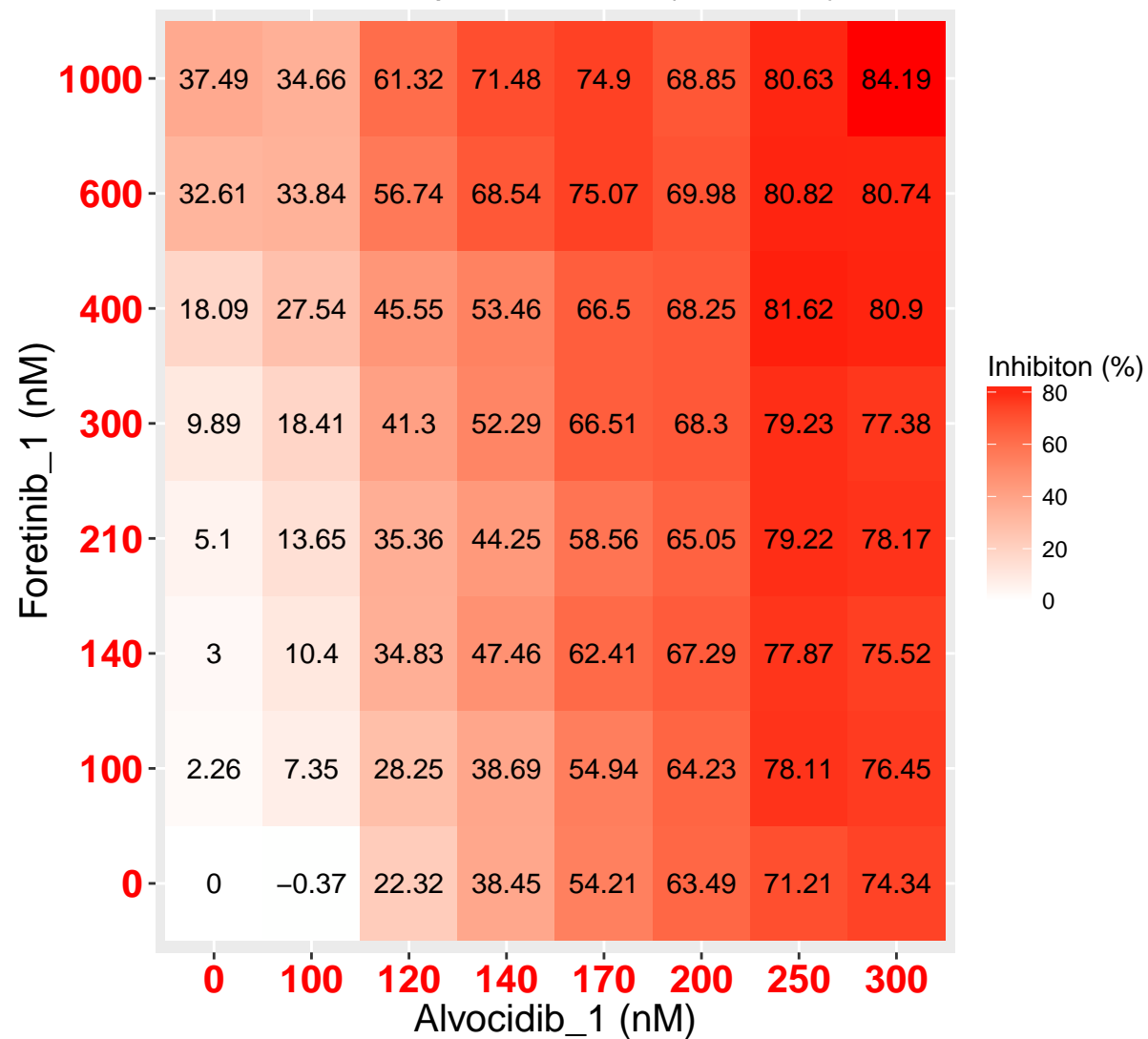
Dose-response matrix (inhibition)



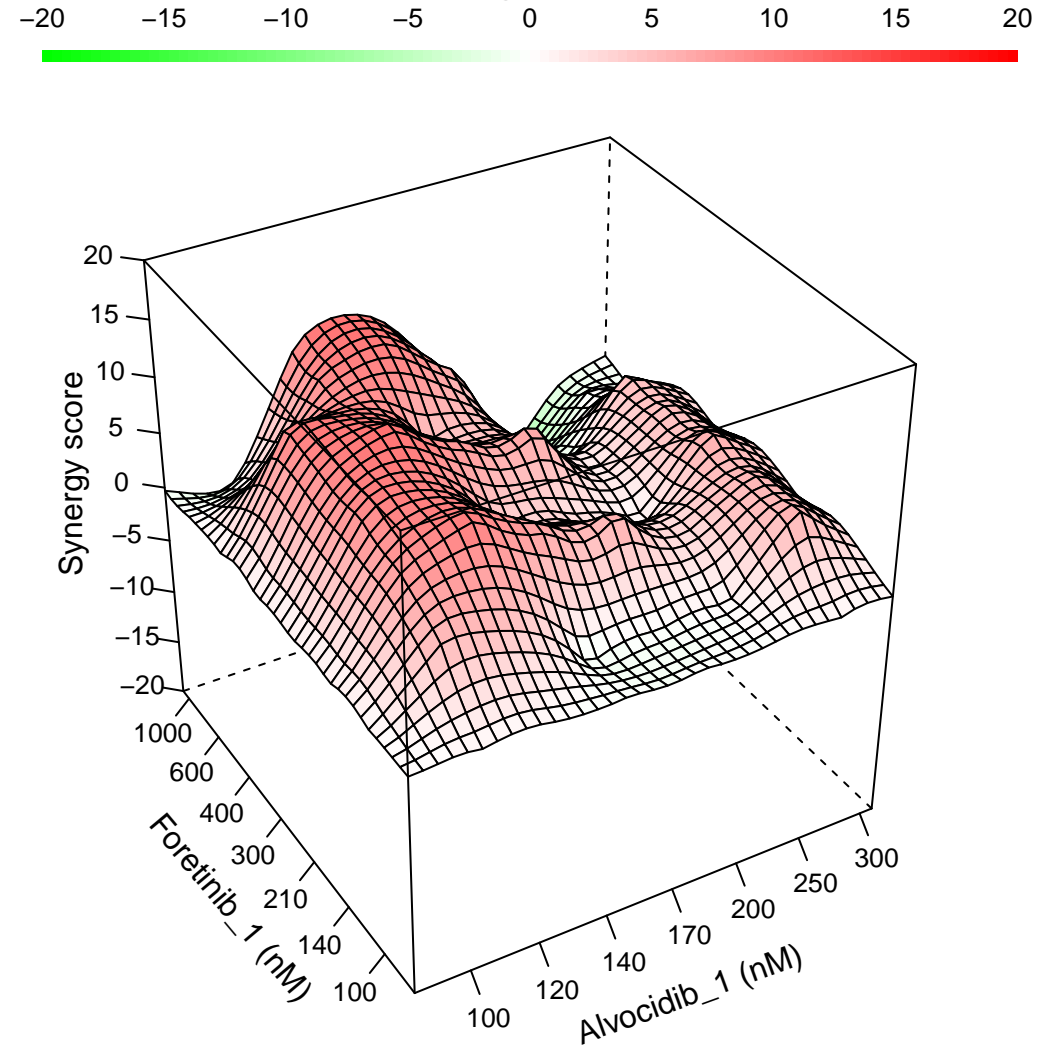
Bliss synergy score: 2.112



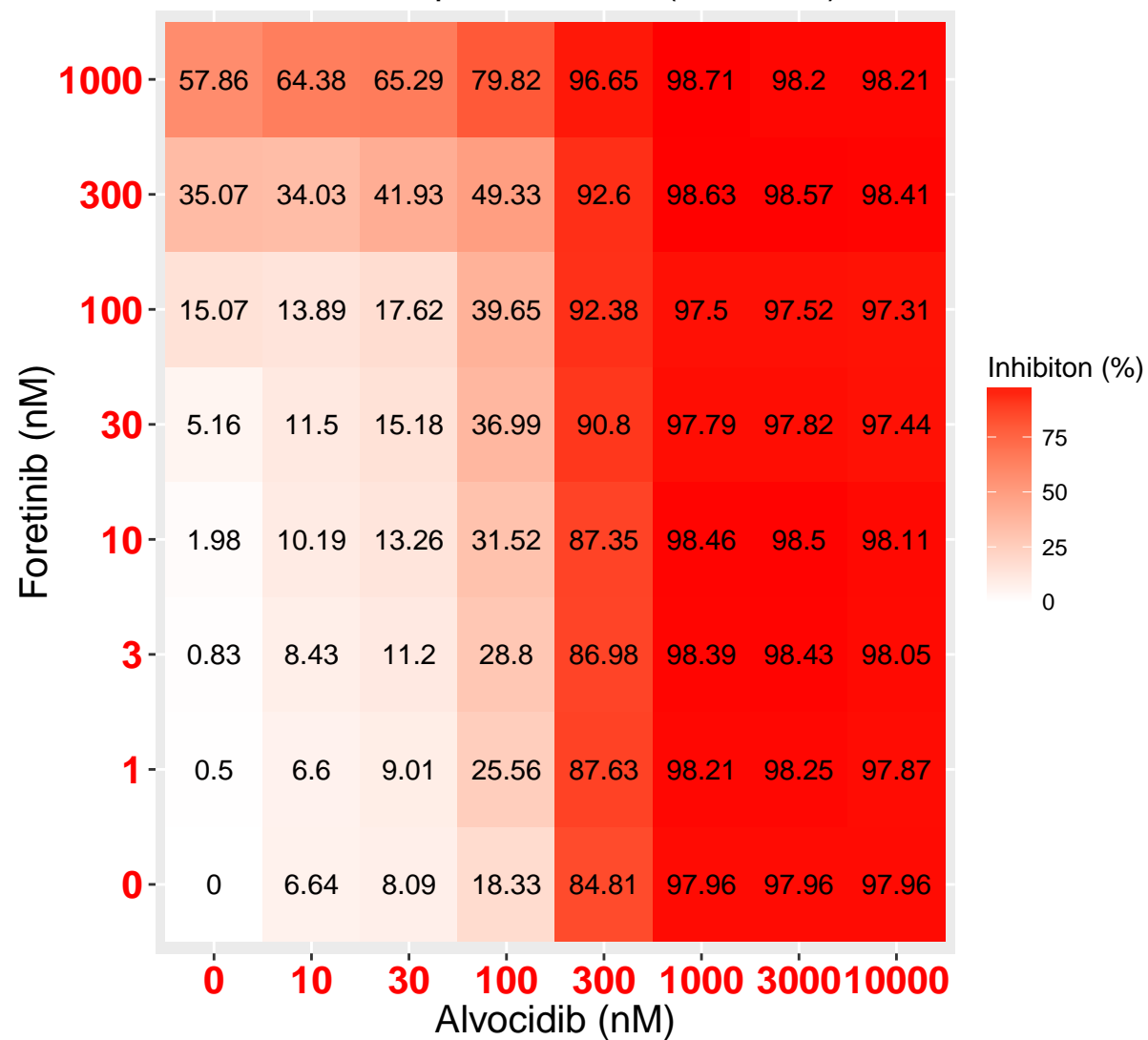
Dose-response matrix (inhibition)



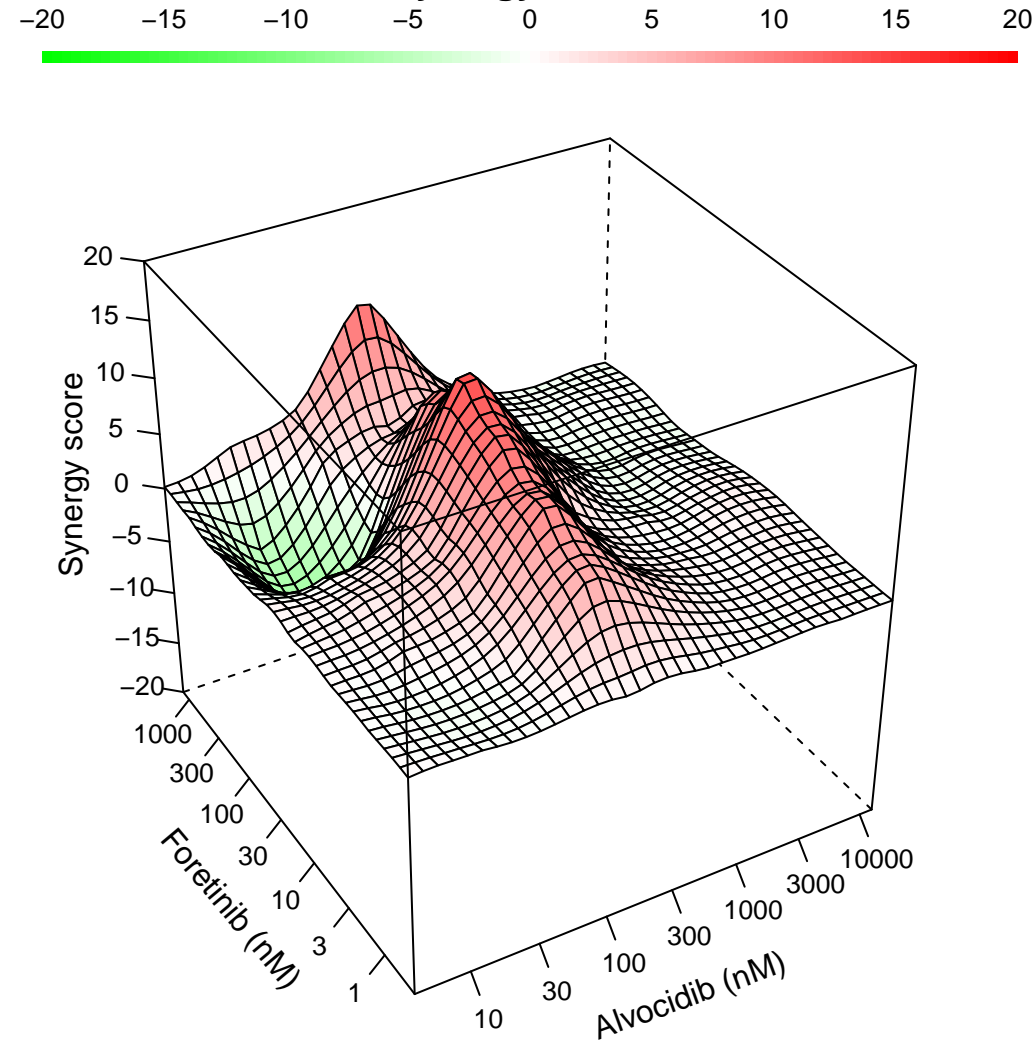
Bliss synergy score: 3.782



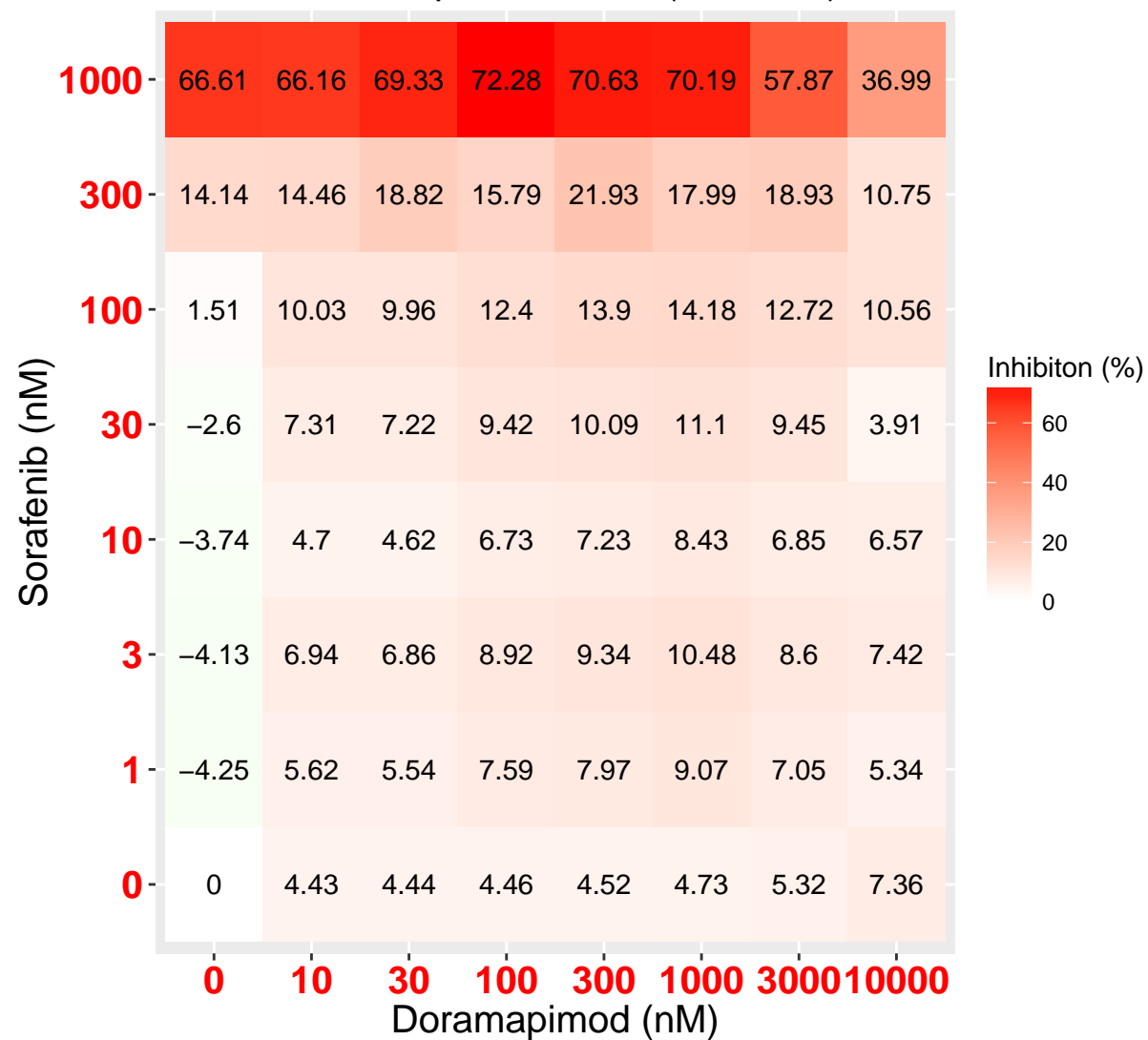
Dose-response matrix (inhibition)



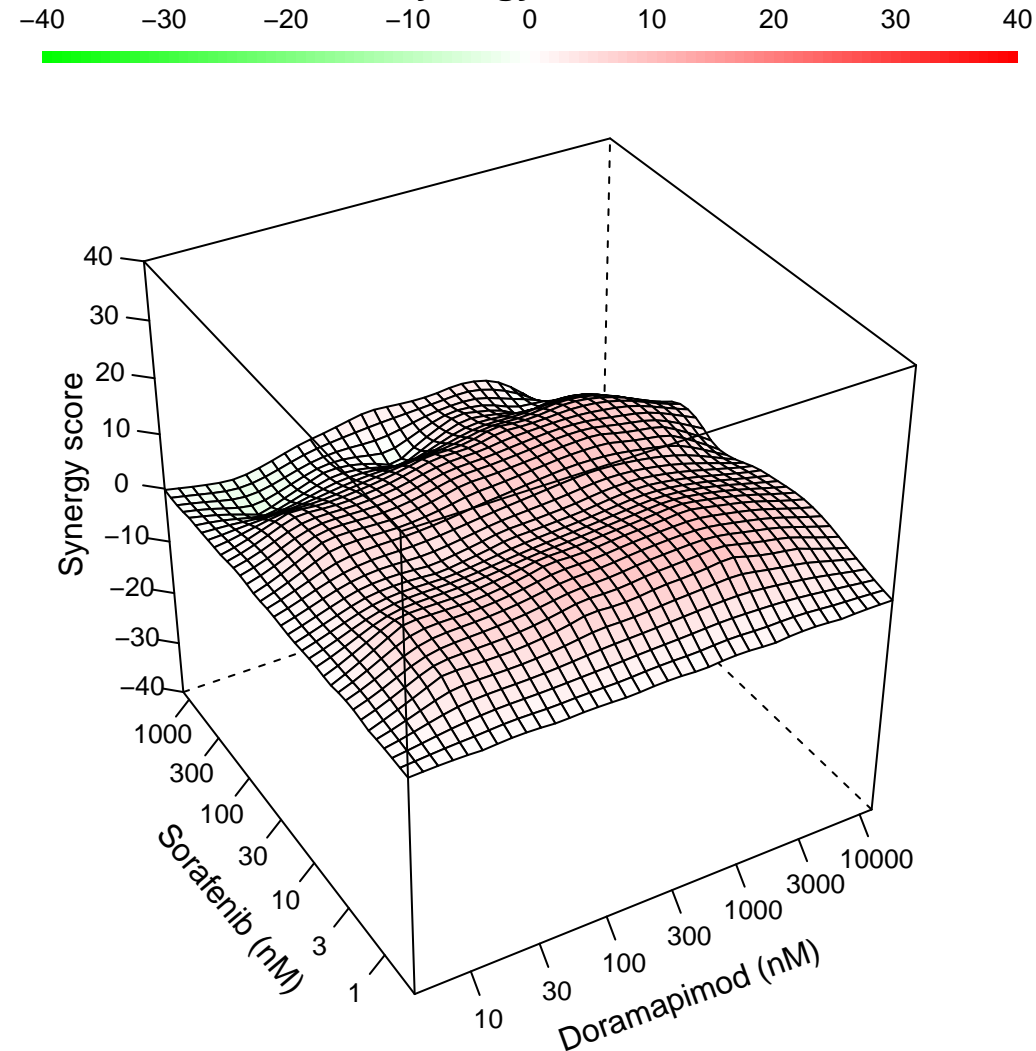
Bliss synergy score: 1.691



Dose-response matrix (inhibition)

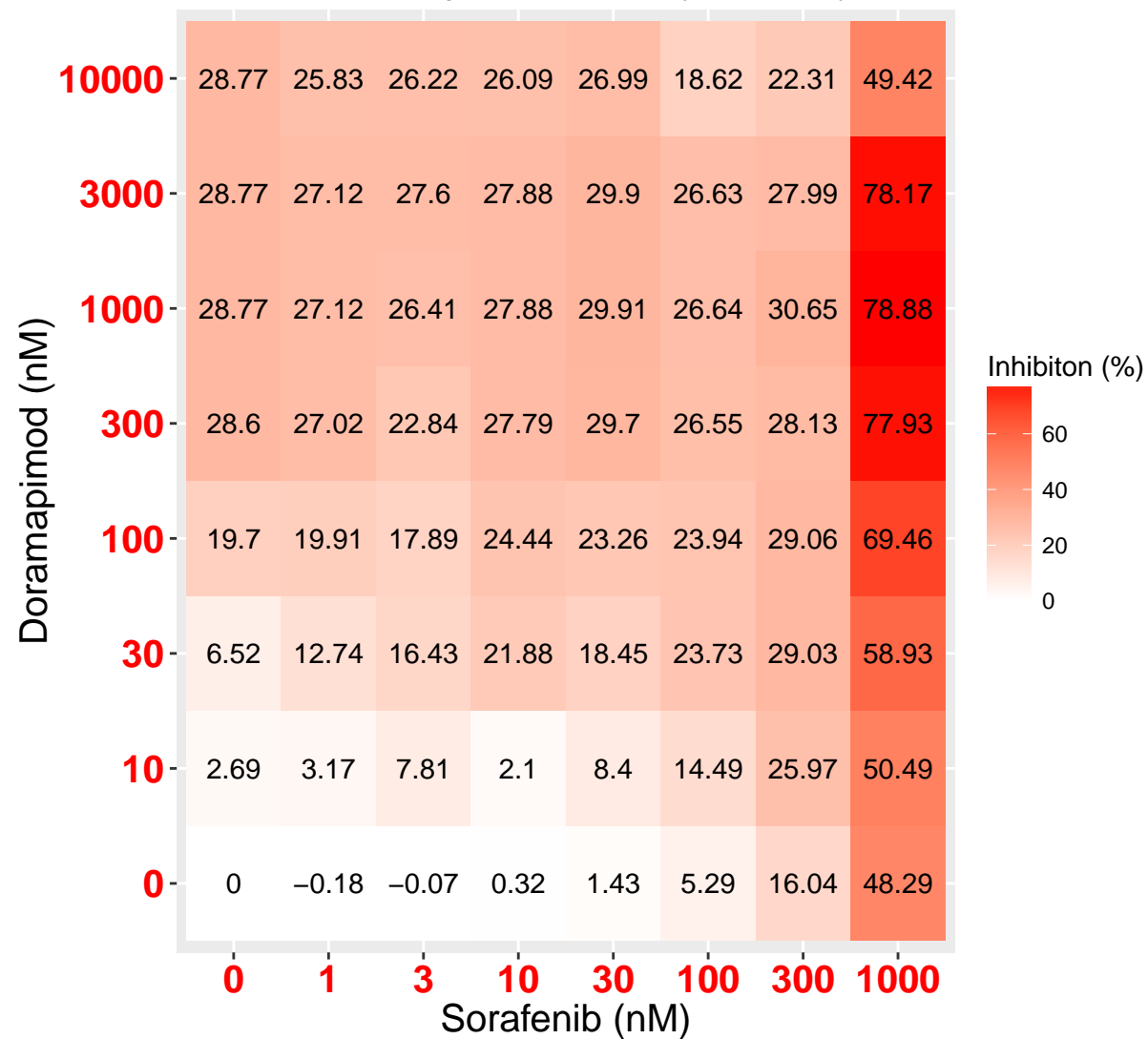


Bliss synergy score: 3.797

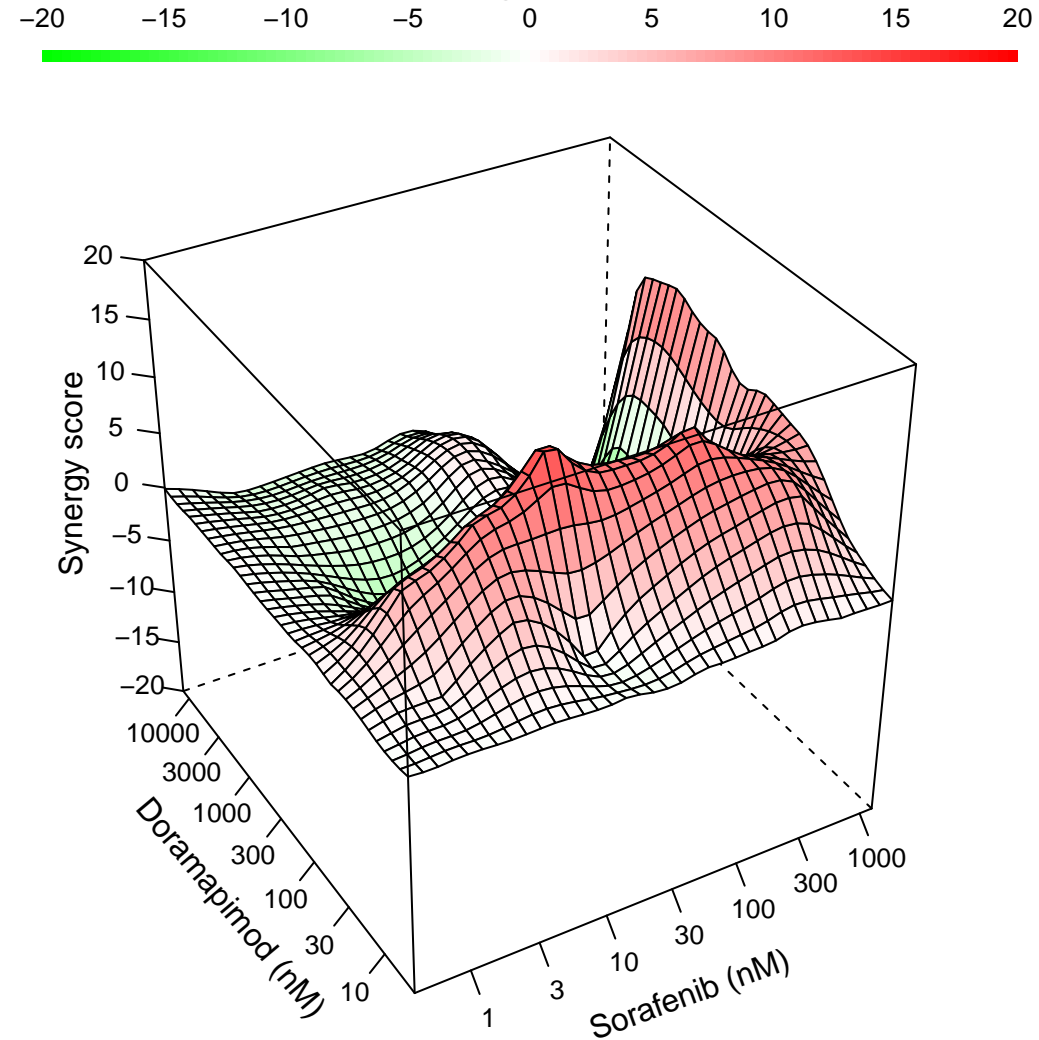




Dose-response matrix (inhibition)

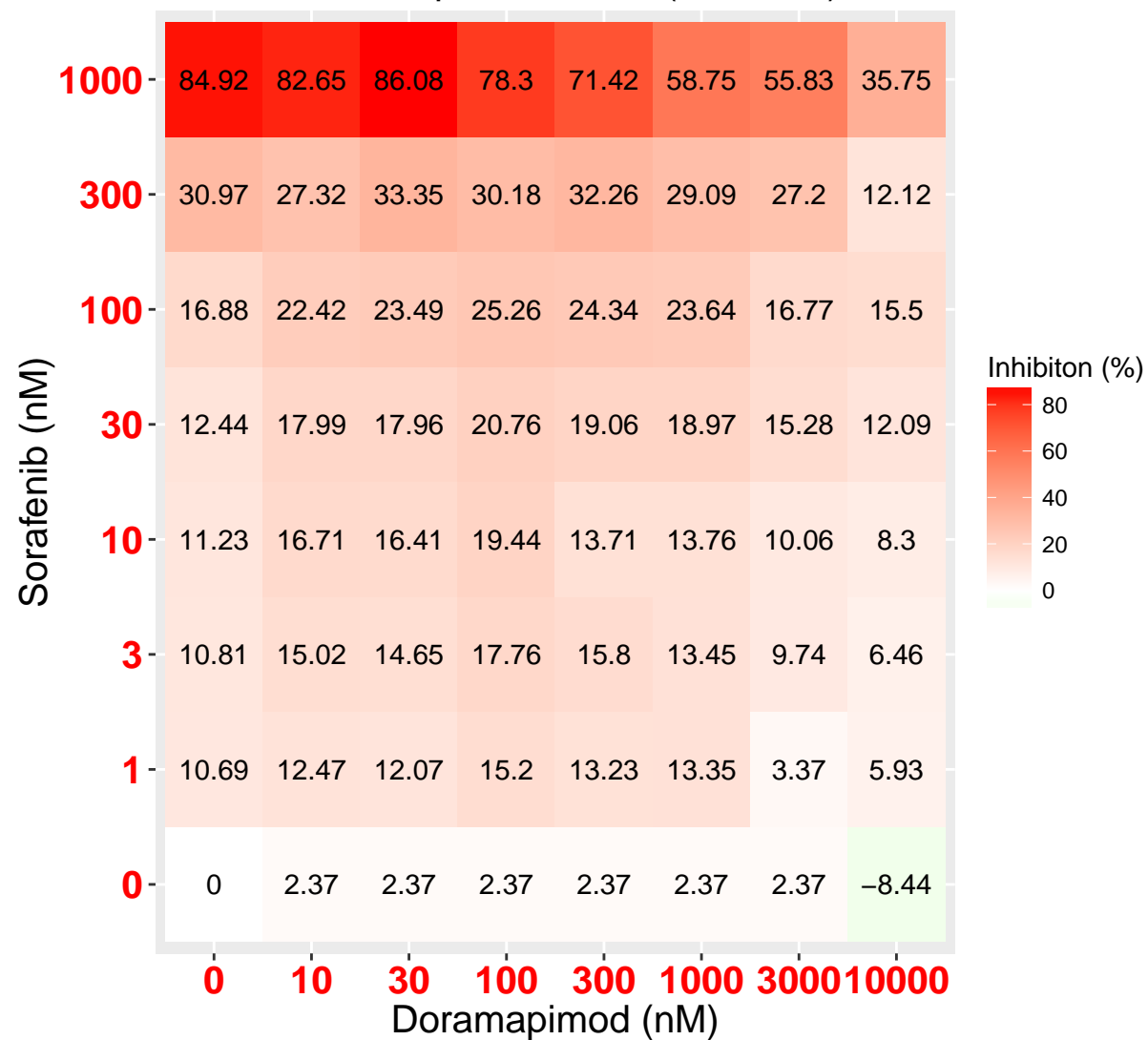


Bliss synergy score: 0.562

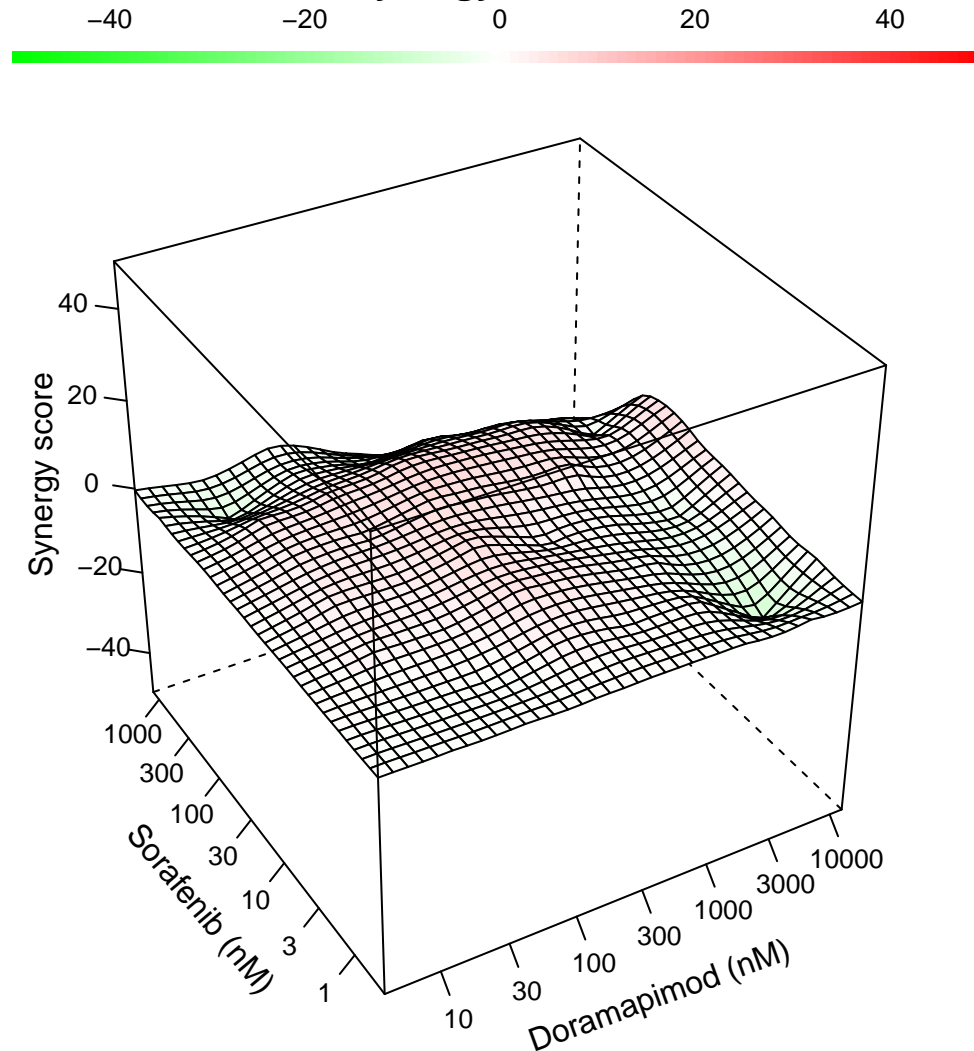




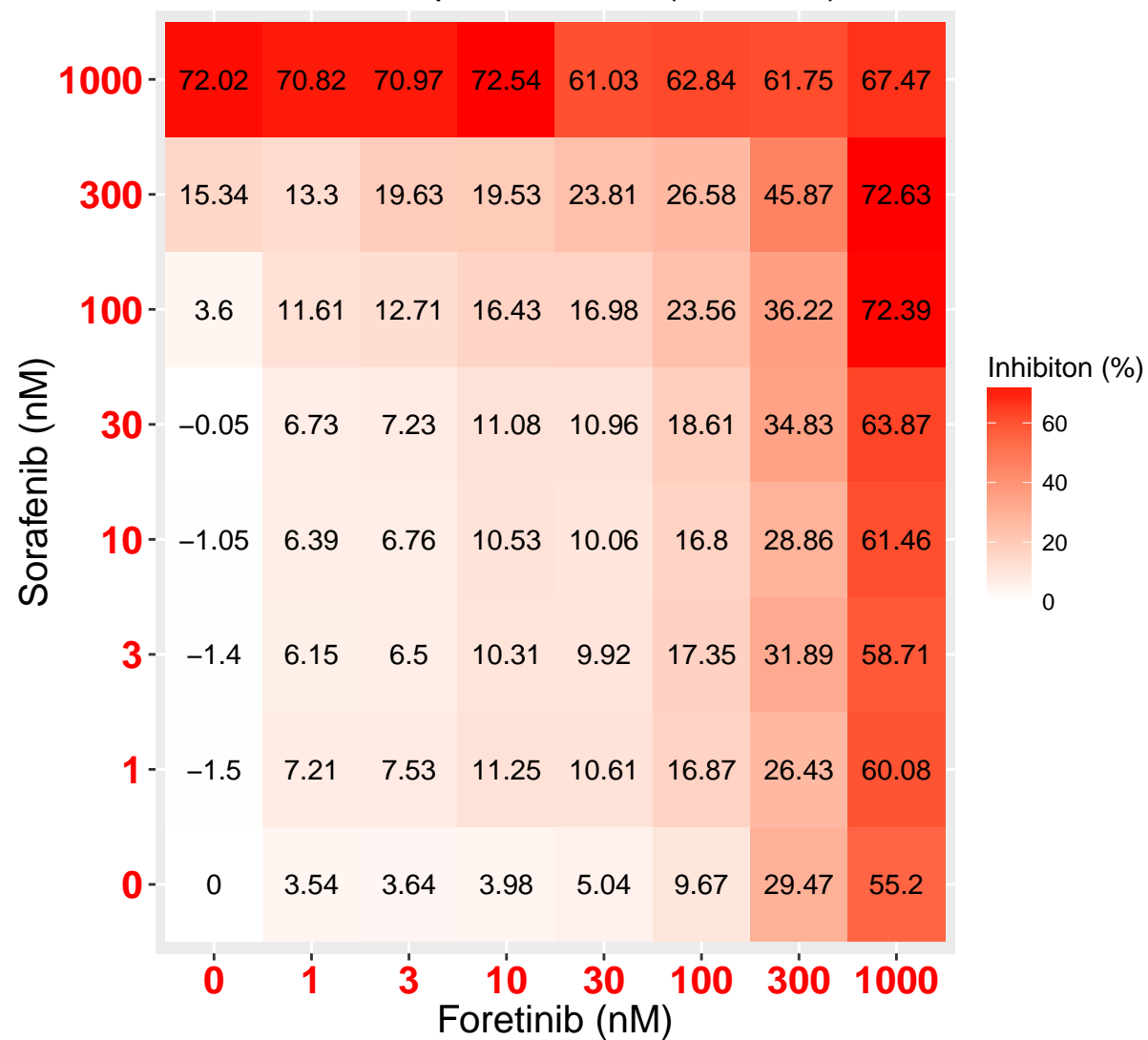
Dose-response matrix (inhibition)



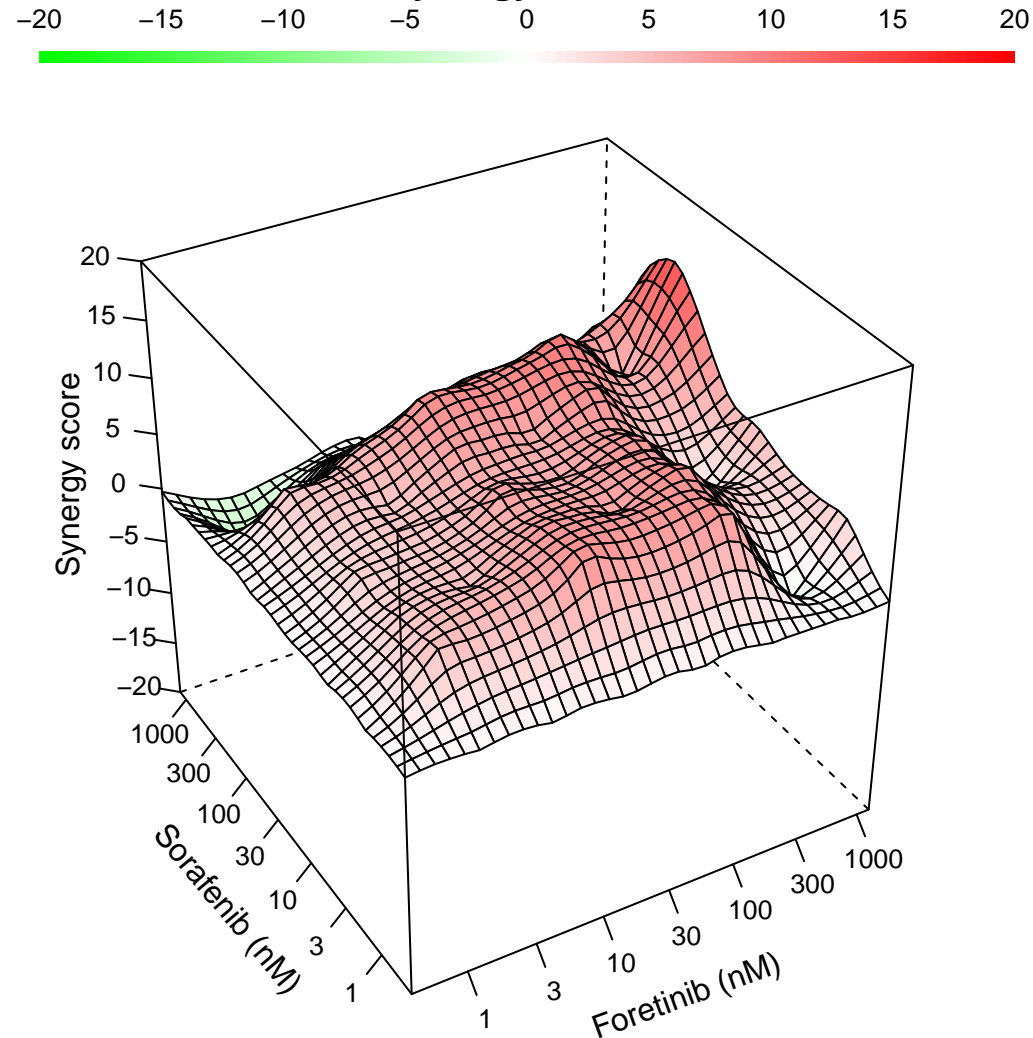
Bliss synergy score: -0.471



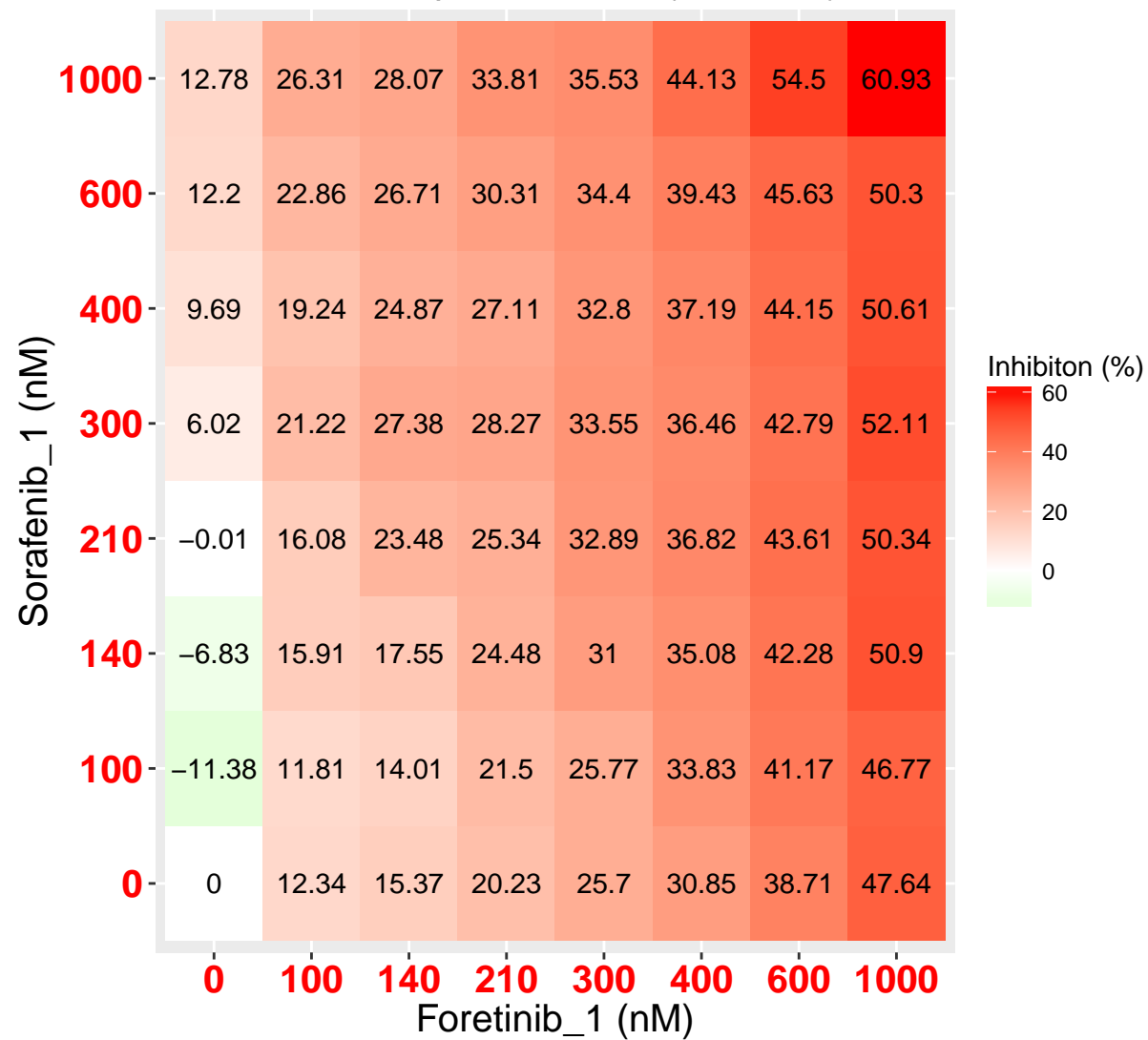
Dose-response matrix (inhibition)



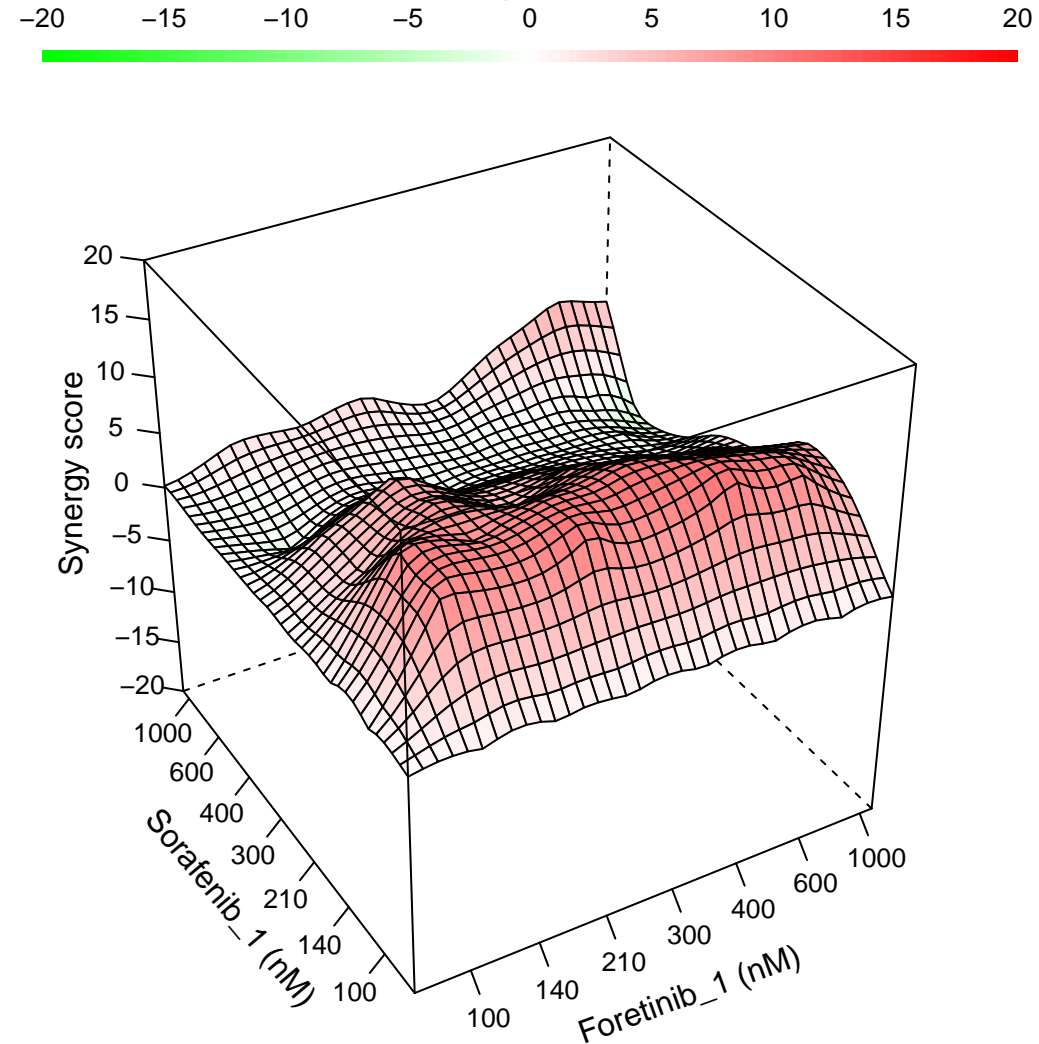
Bliss synergy score: 3.694



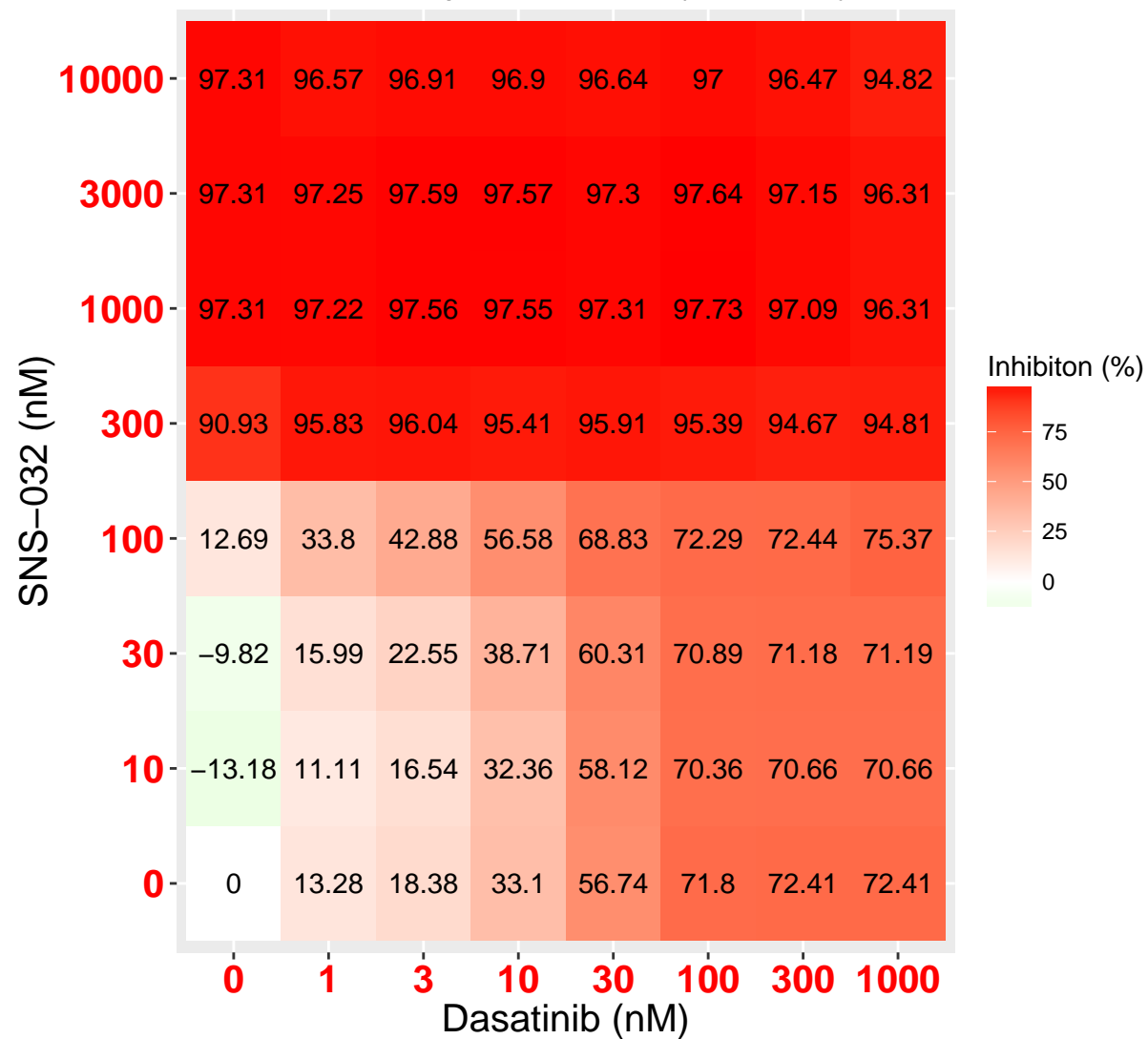
Dose-response matrix (inhibition)



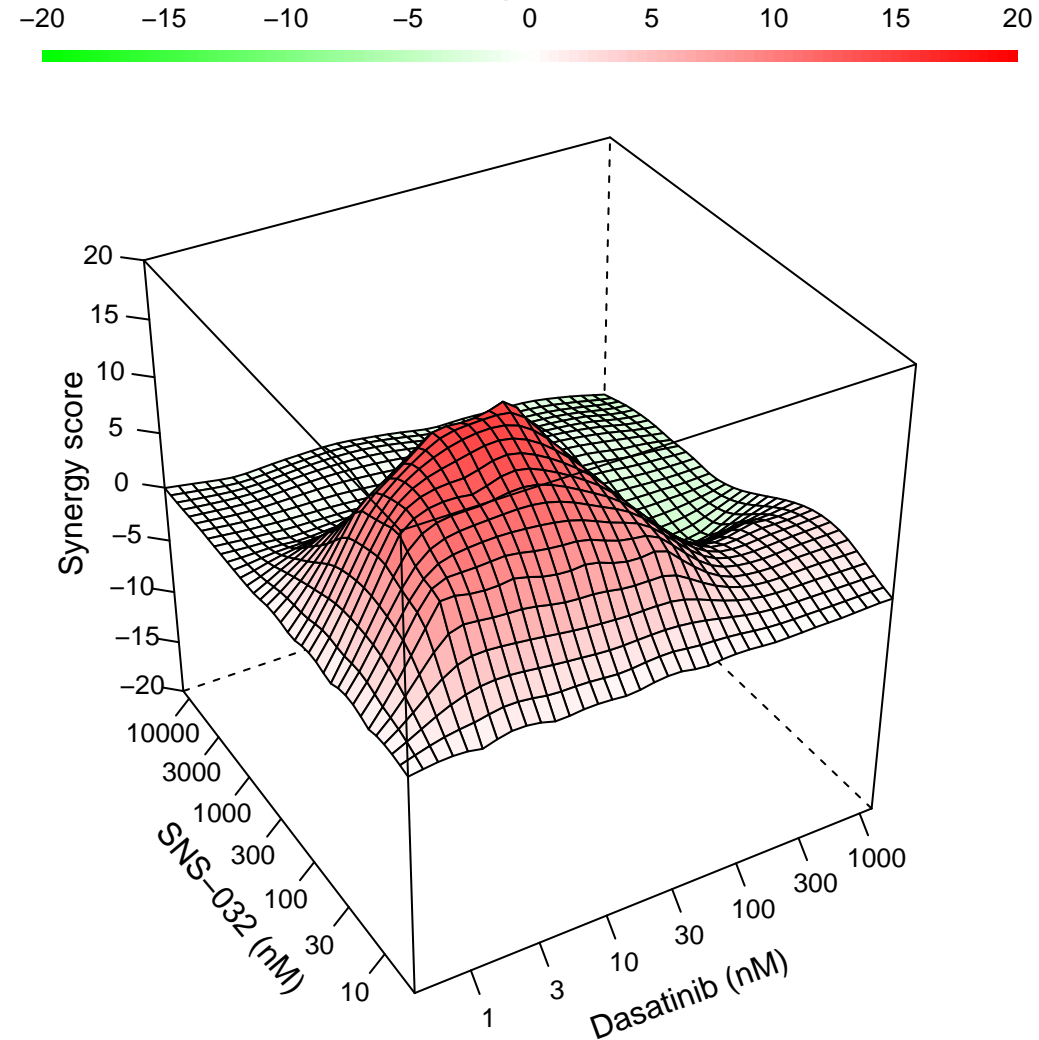
Bliss synergy score: 3.684



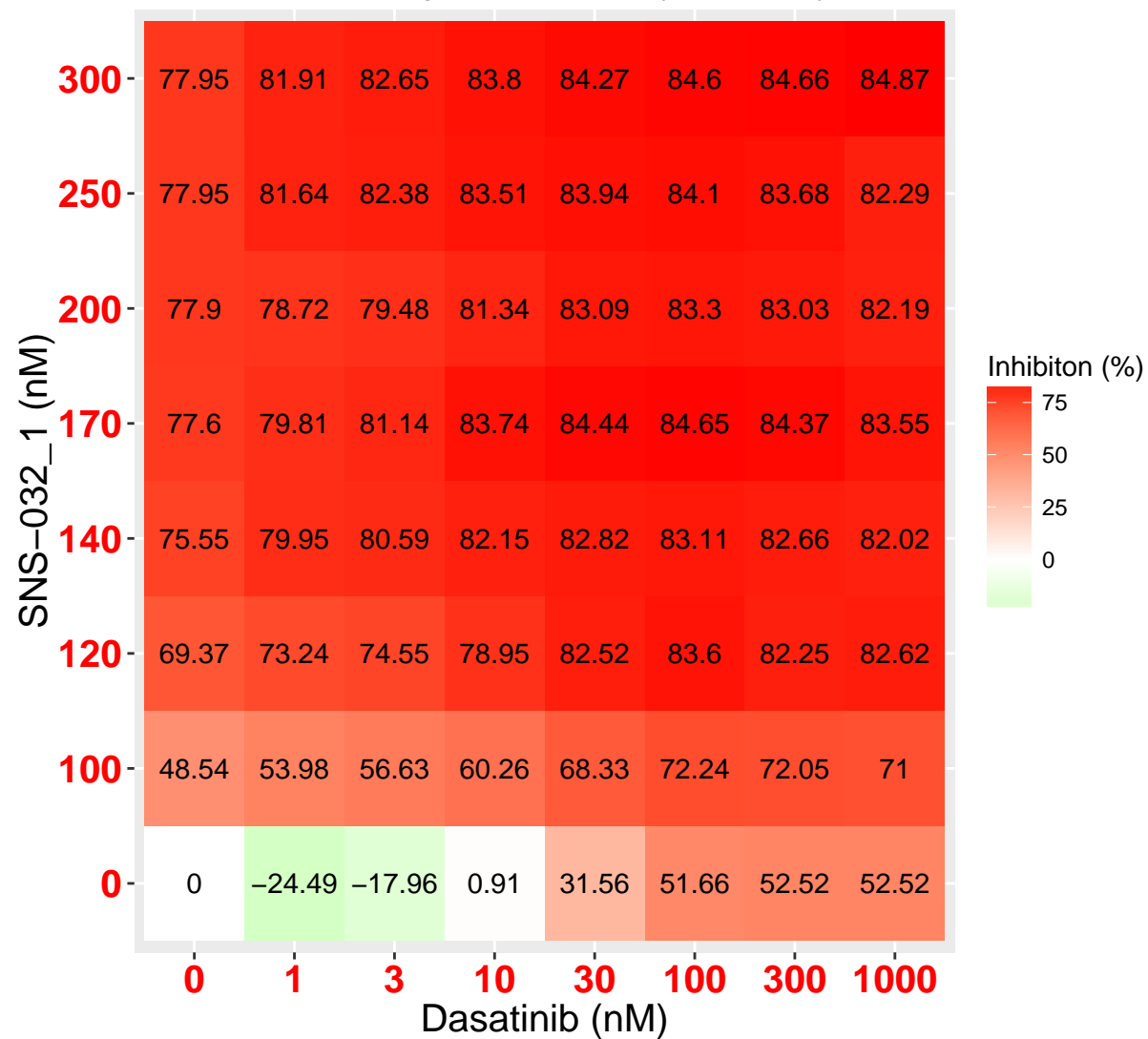
Dose-response matrix (inhibition)



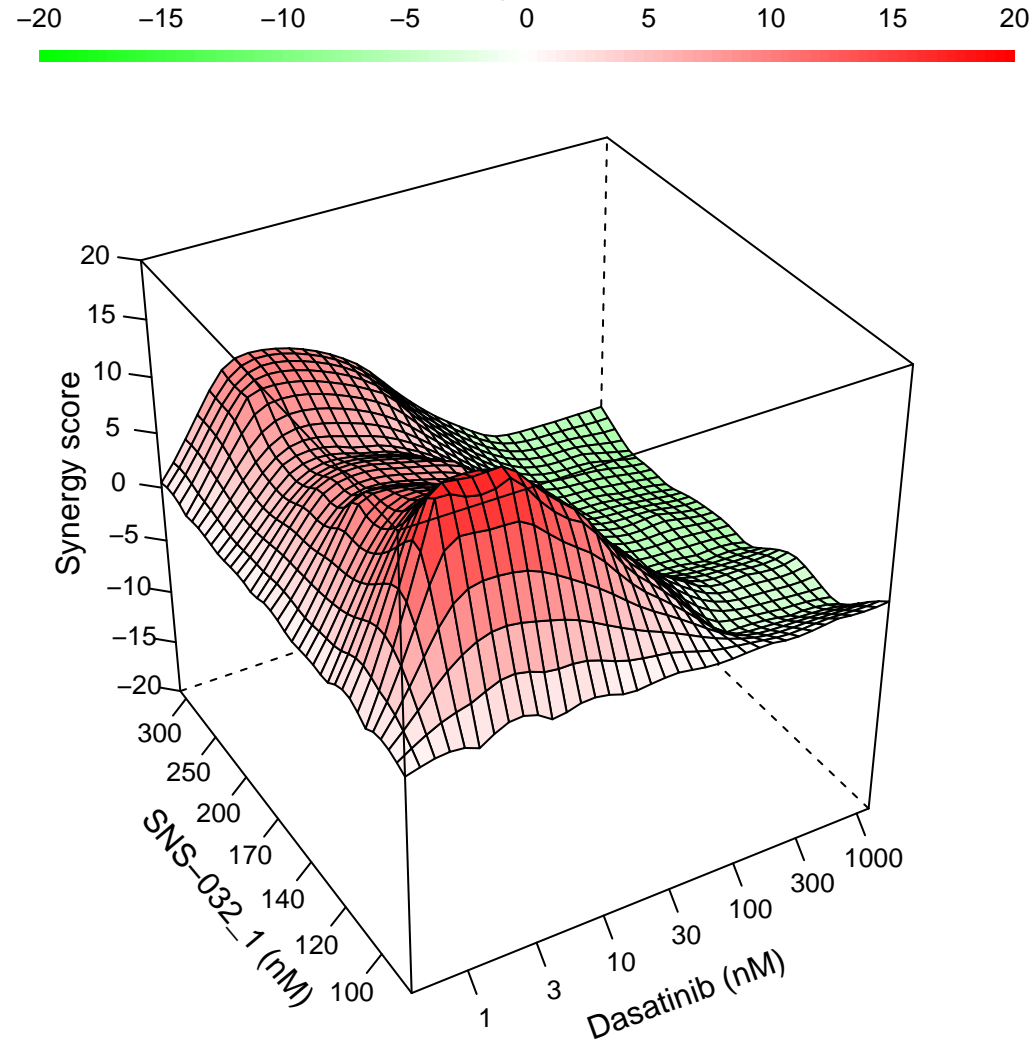
Bliss synergy score: 2.128



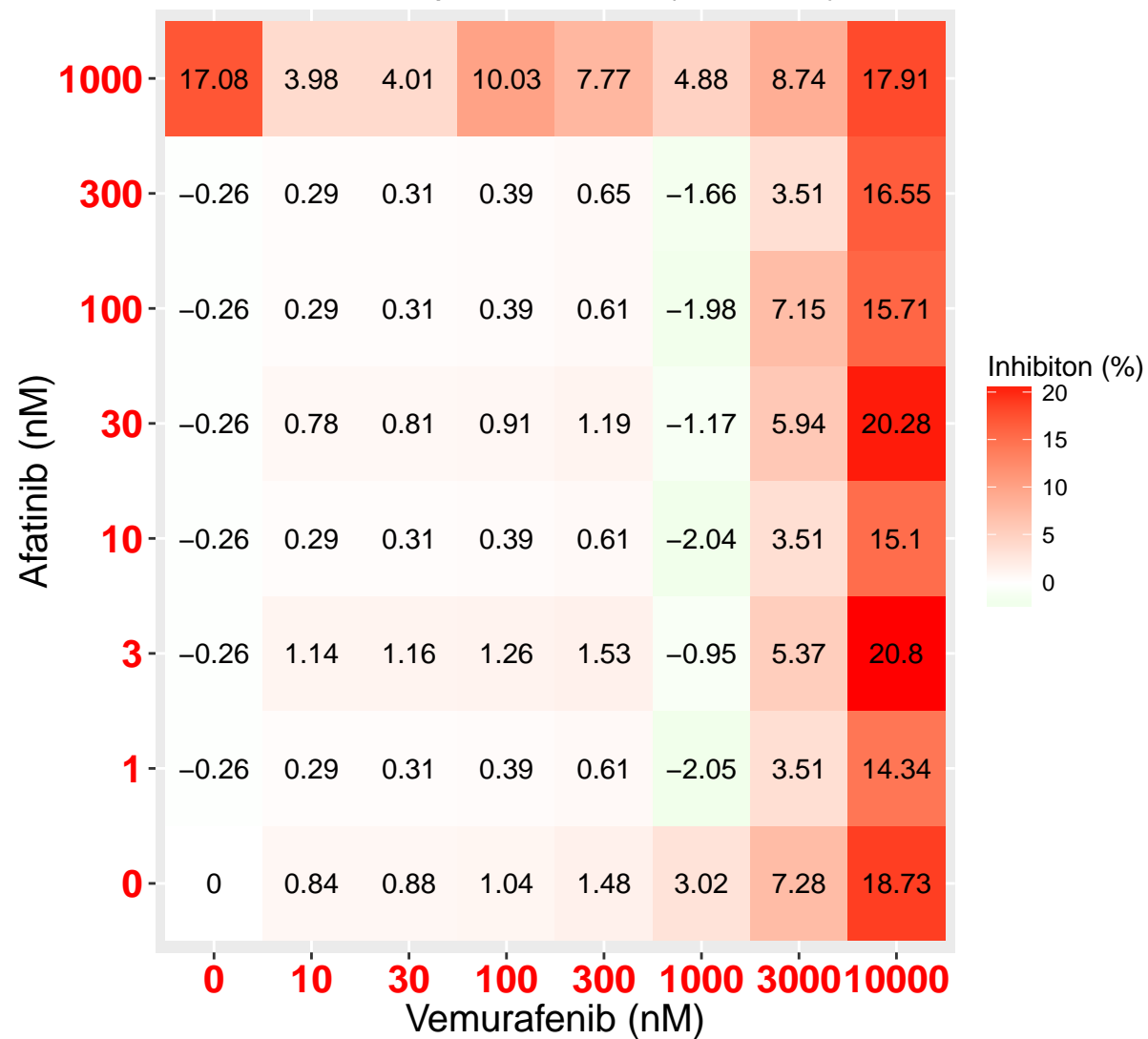
Dose-response matrix (inhibition)



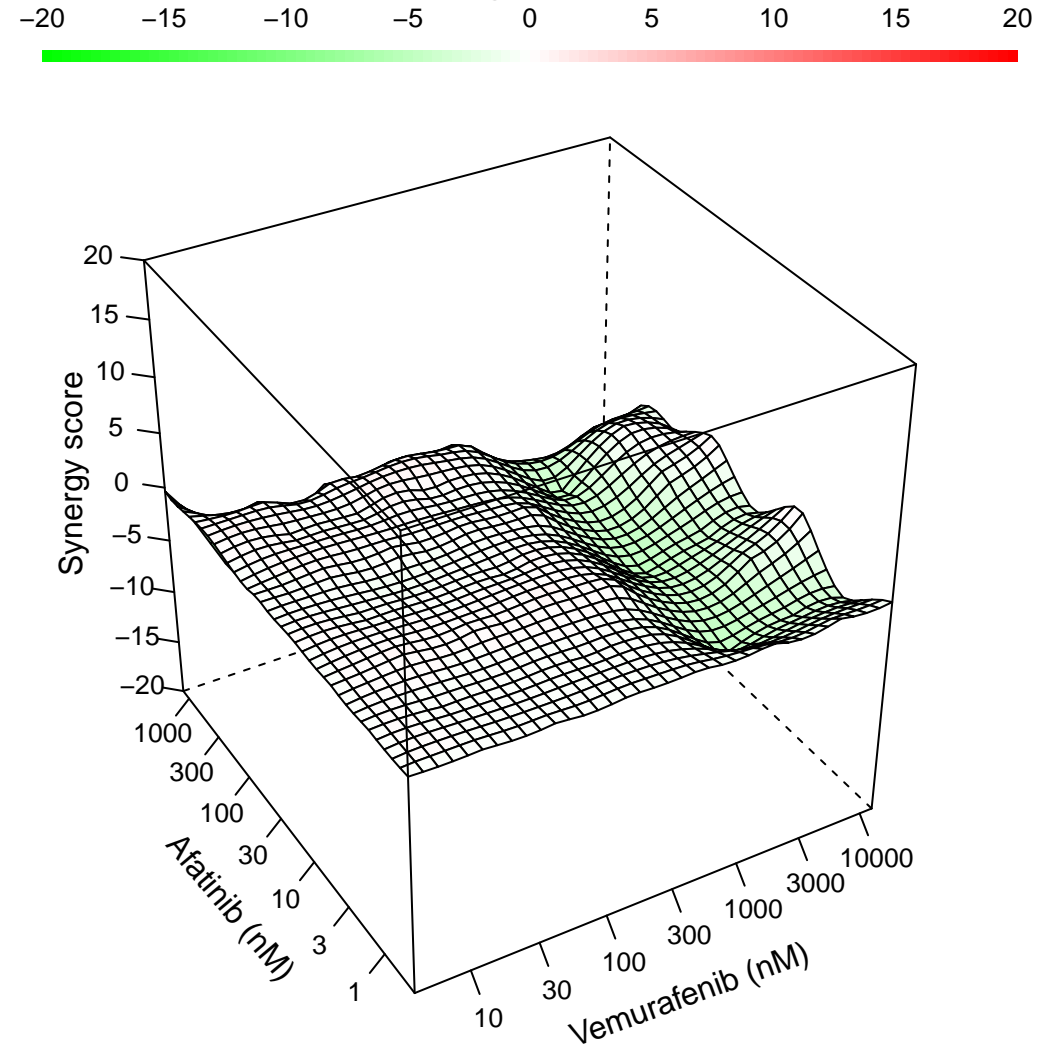
Bliss synergy score: 2.054



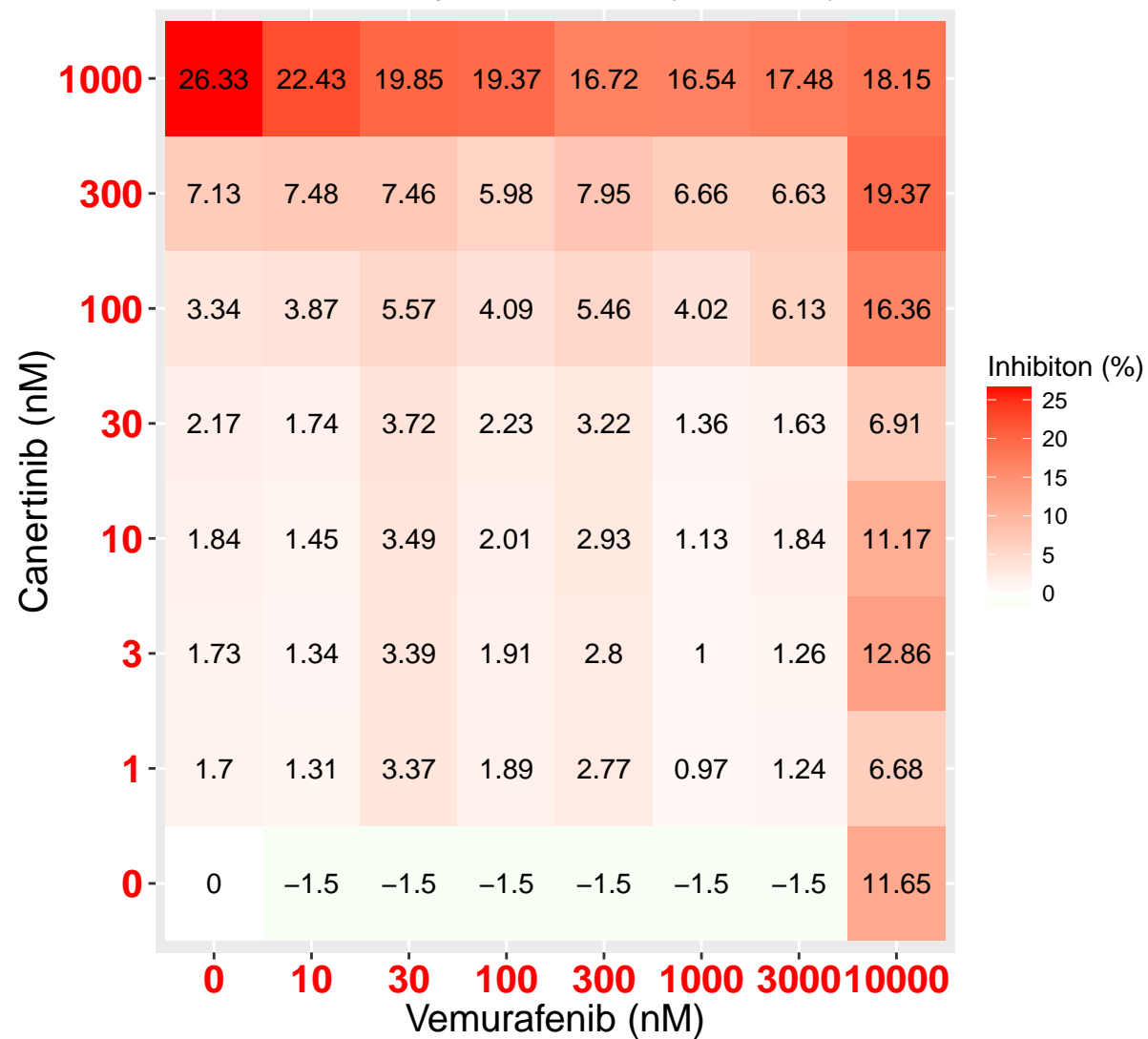
Dose-response matrix (inhibition)



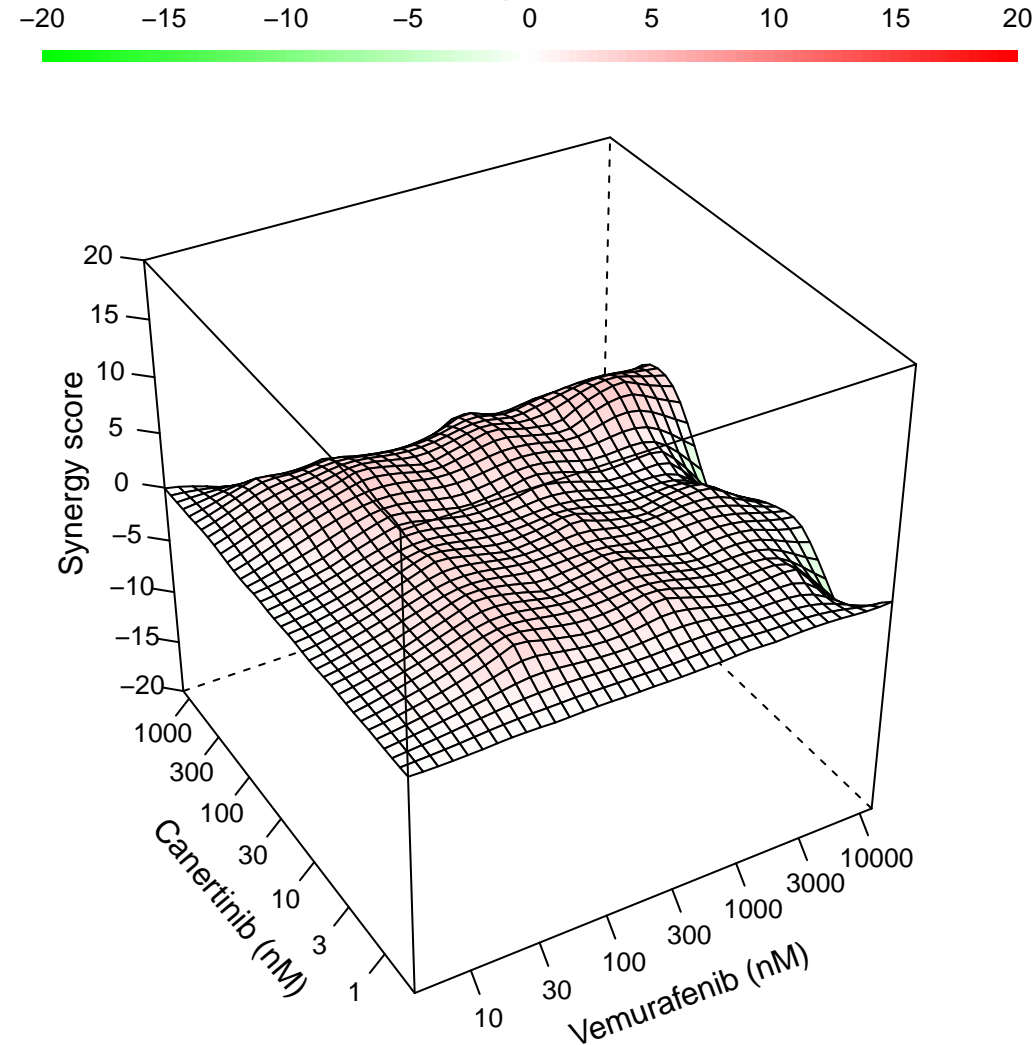
Bliss synergy score: -1.823



Dose-response matrix (inhibition)

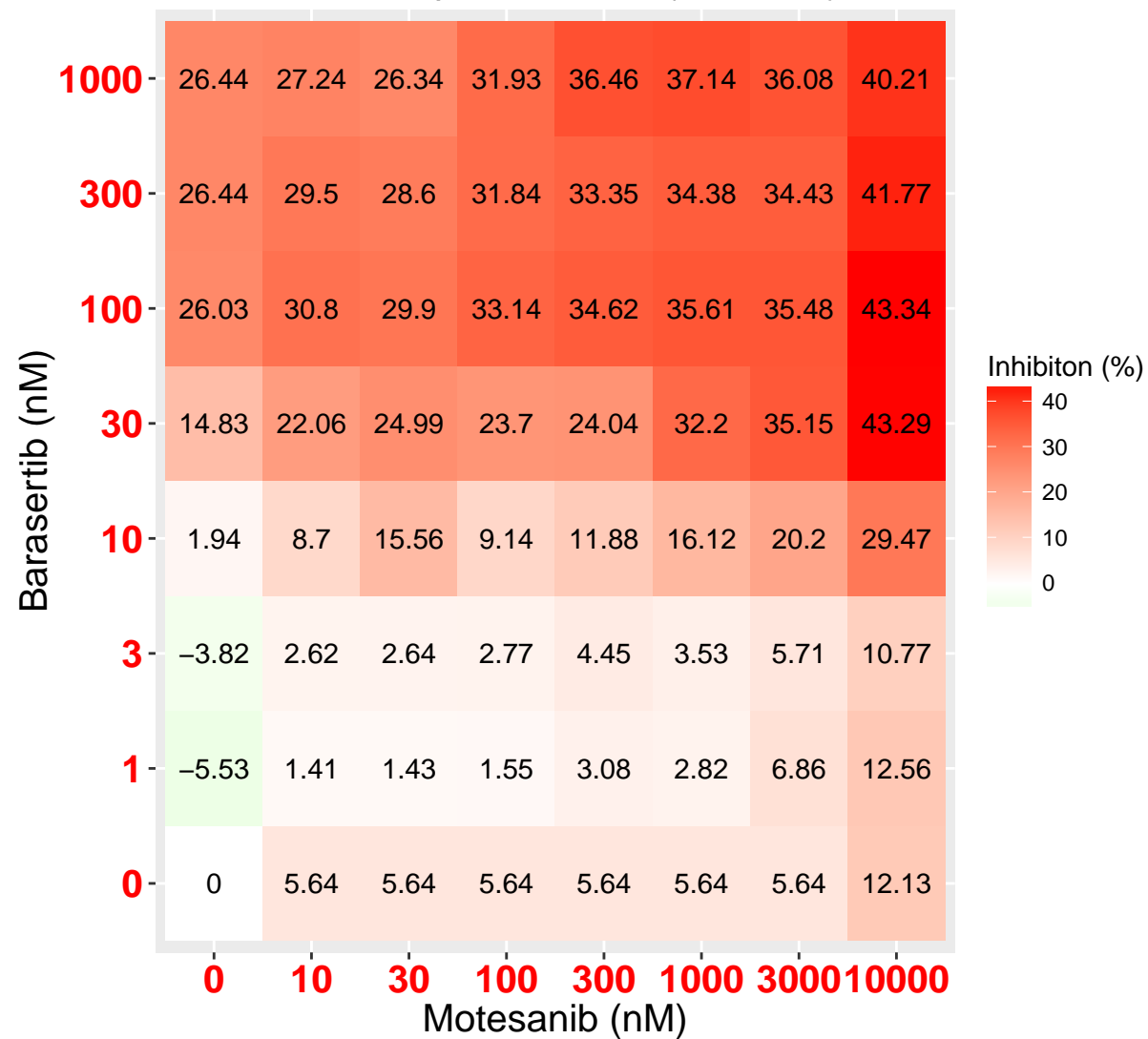


Bliss synergy score: 0.737

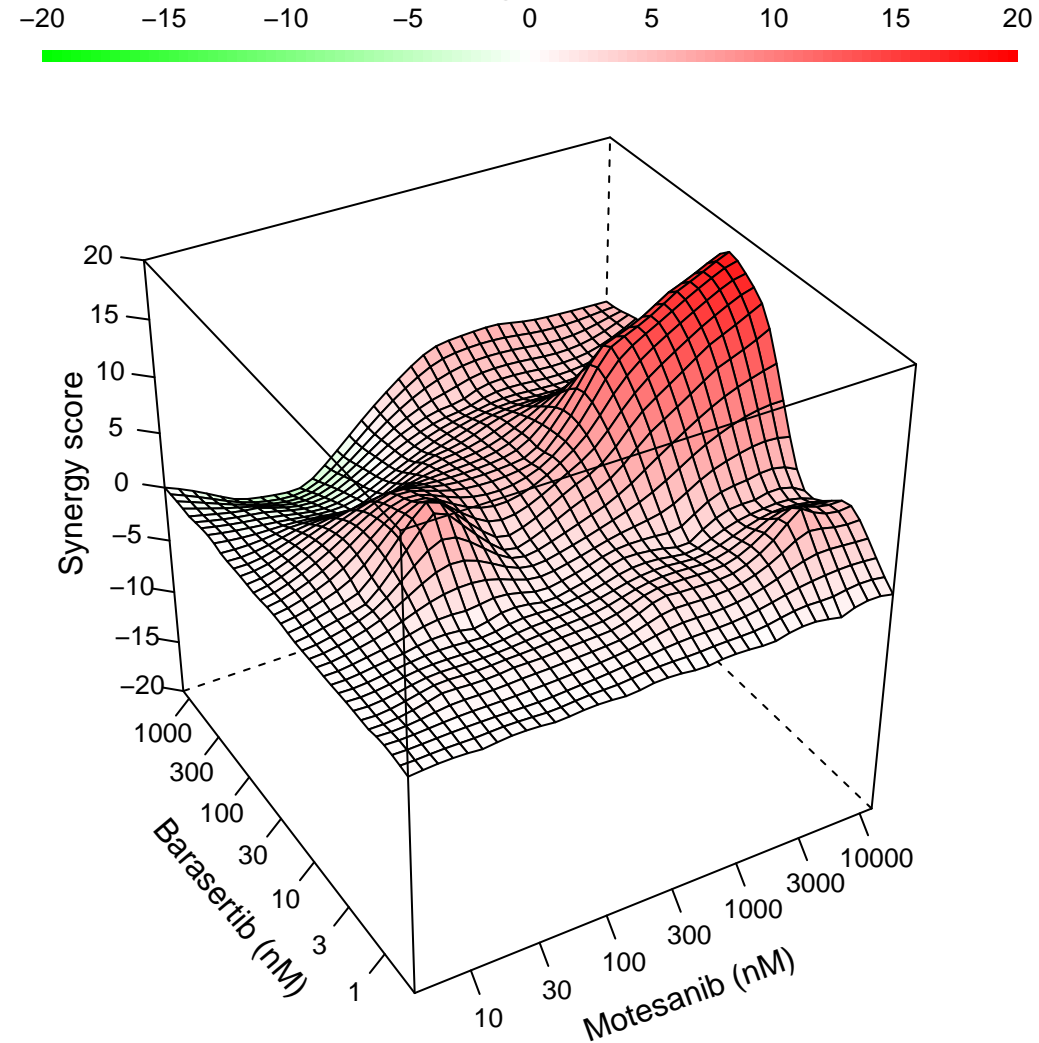




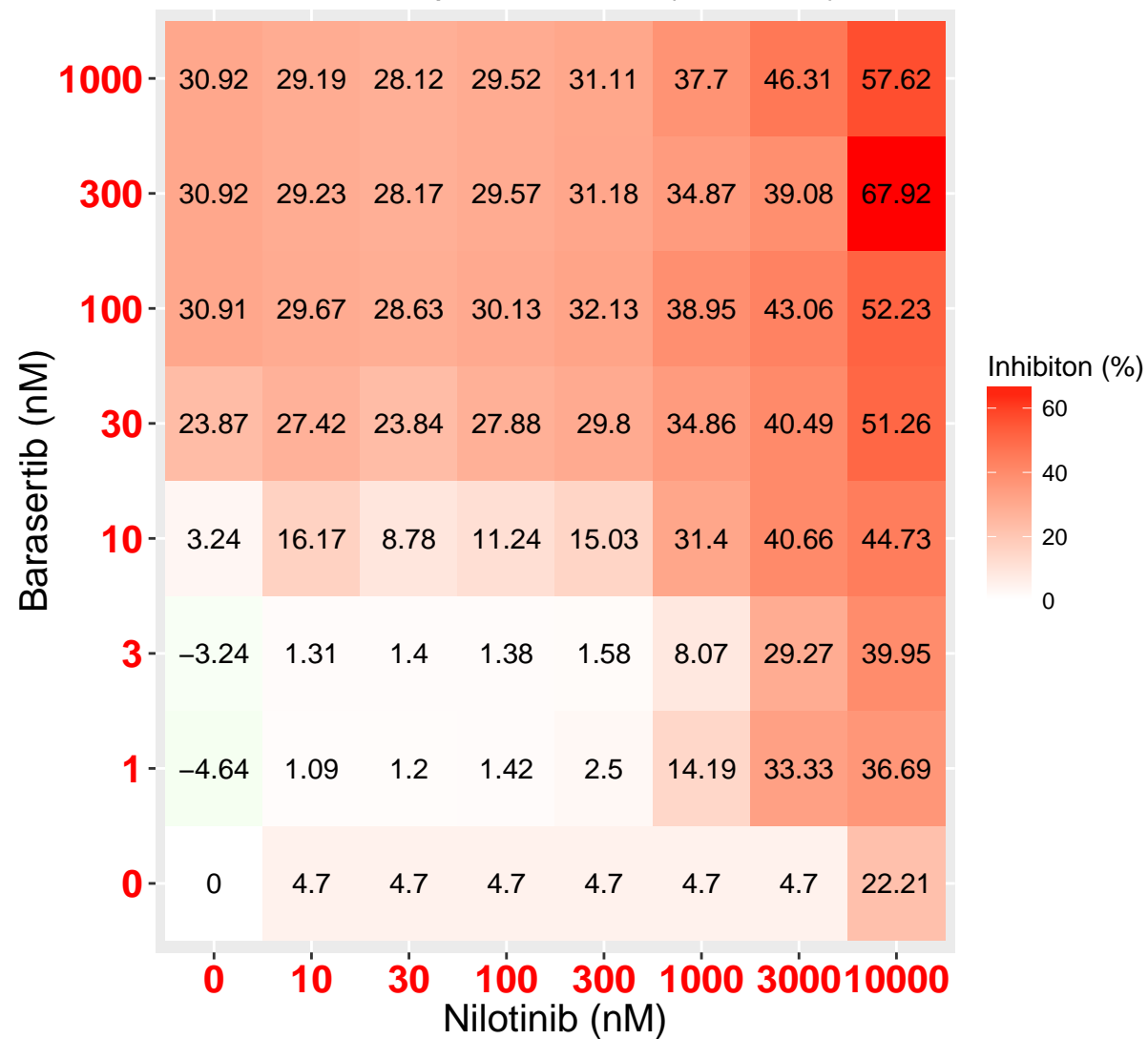
Dose-response matrix (inhibition)



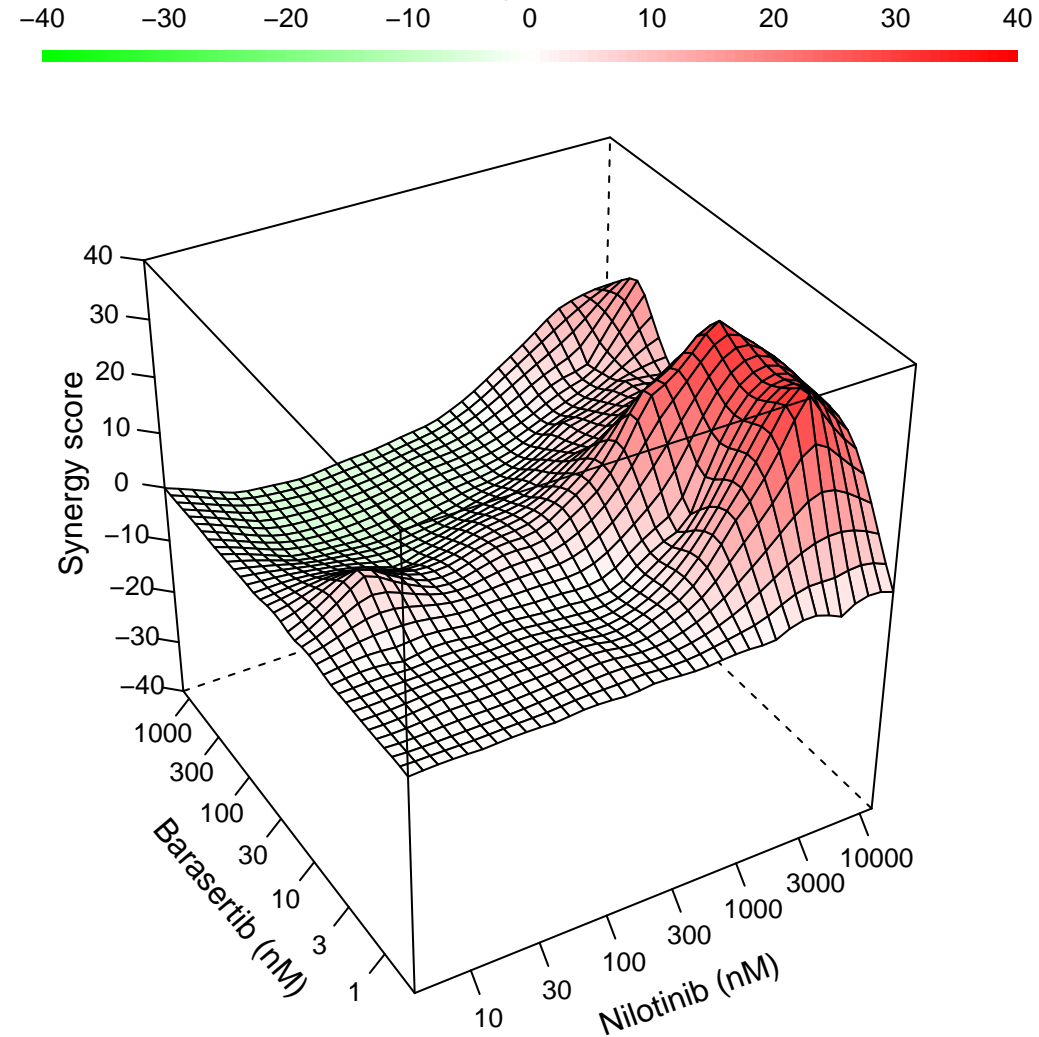
Bliss synergy score: 3.412



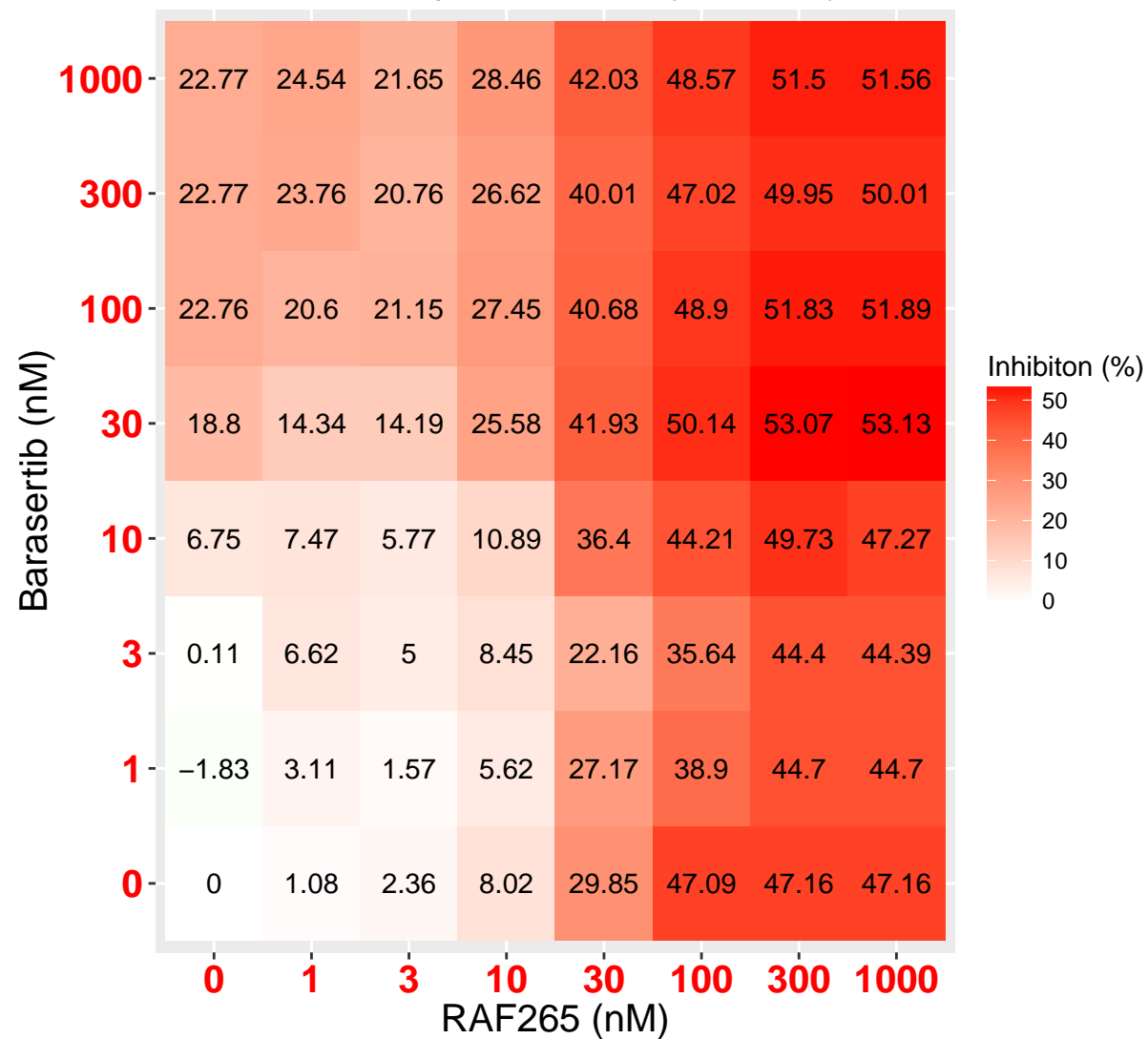
Dose-response matrix (inhibition)



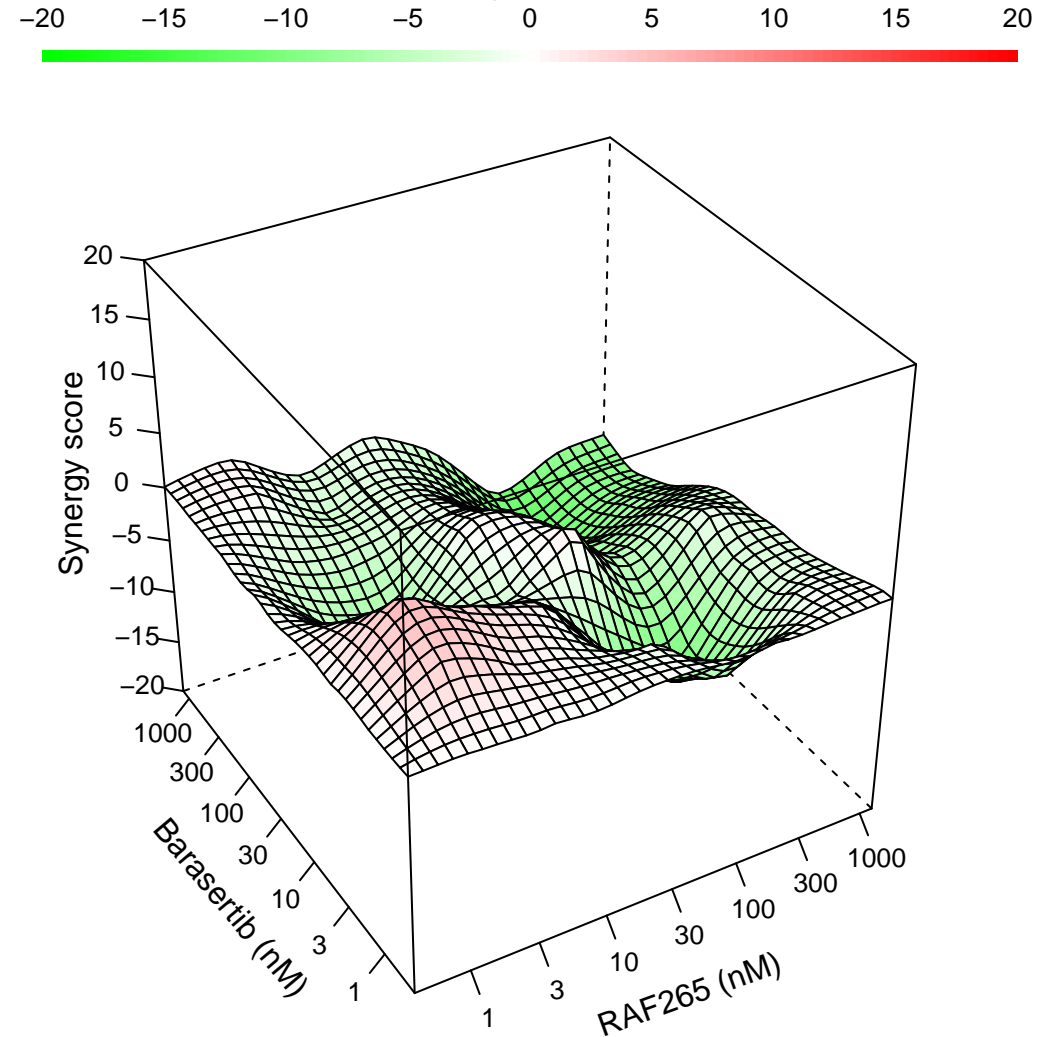
Bliss synergy score: 4.402



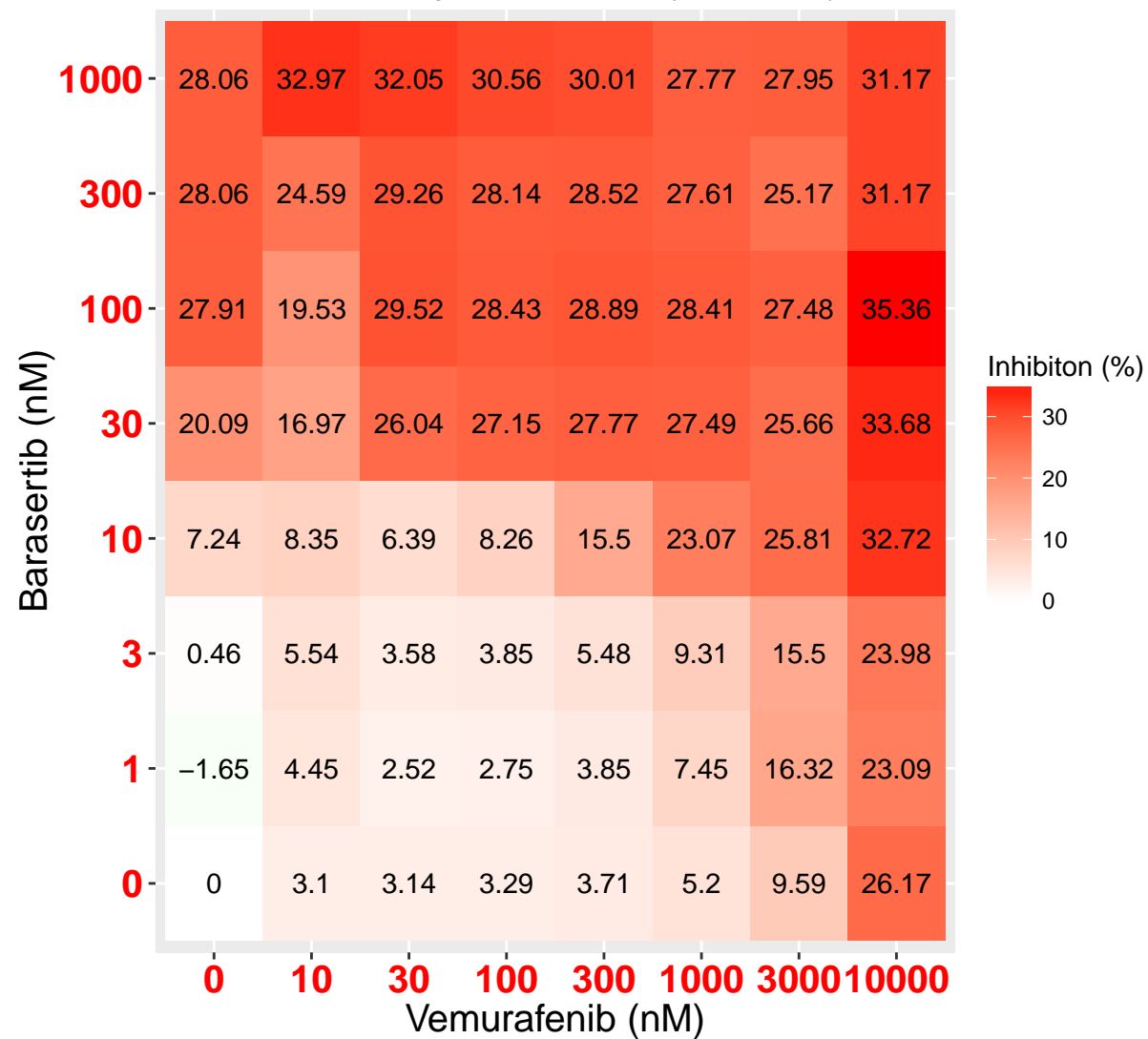
Dose-response matrix (inhibition)



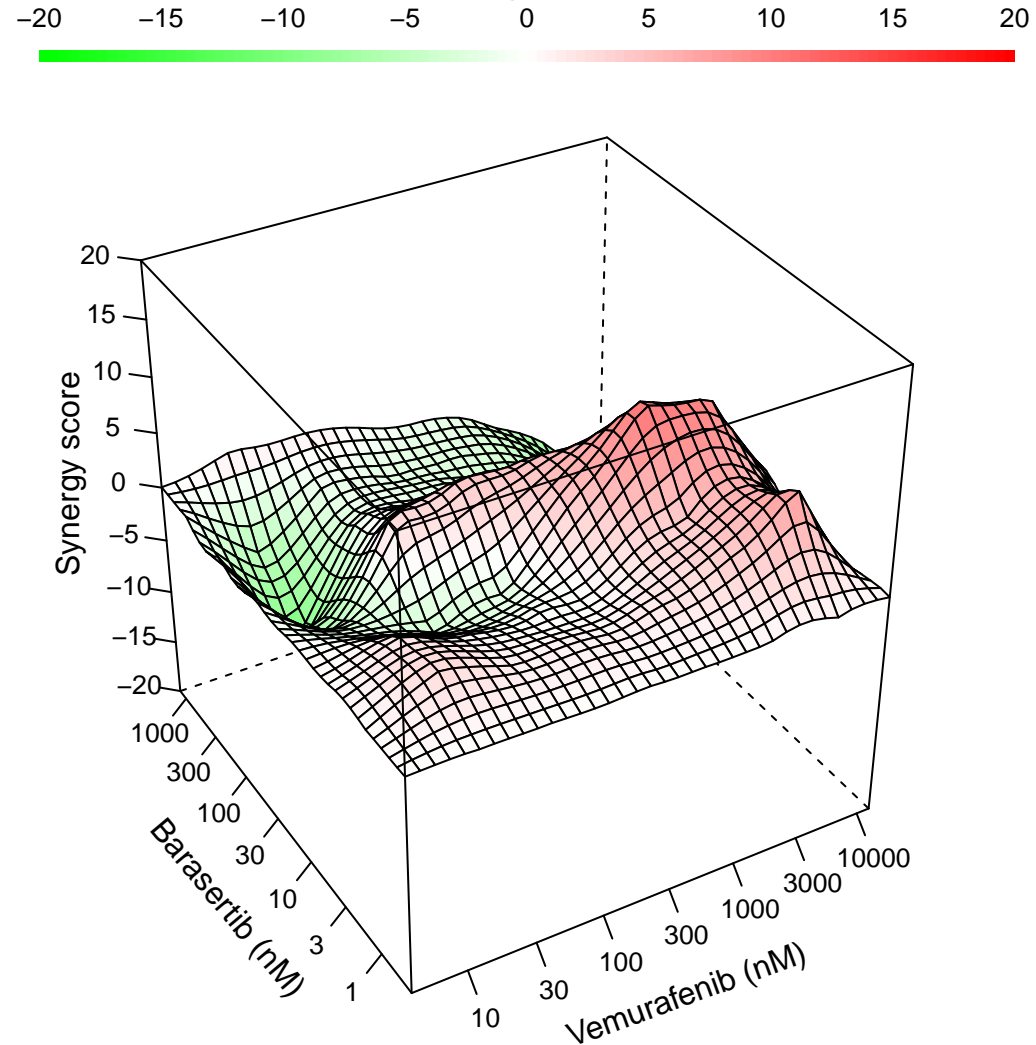
Bliss synergy score: -3.021



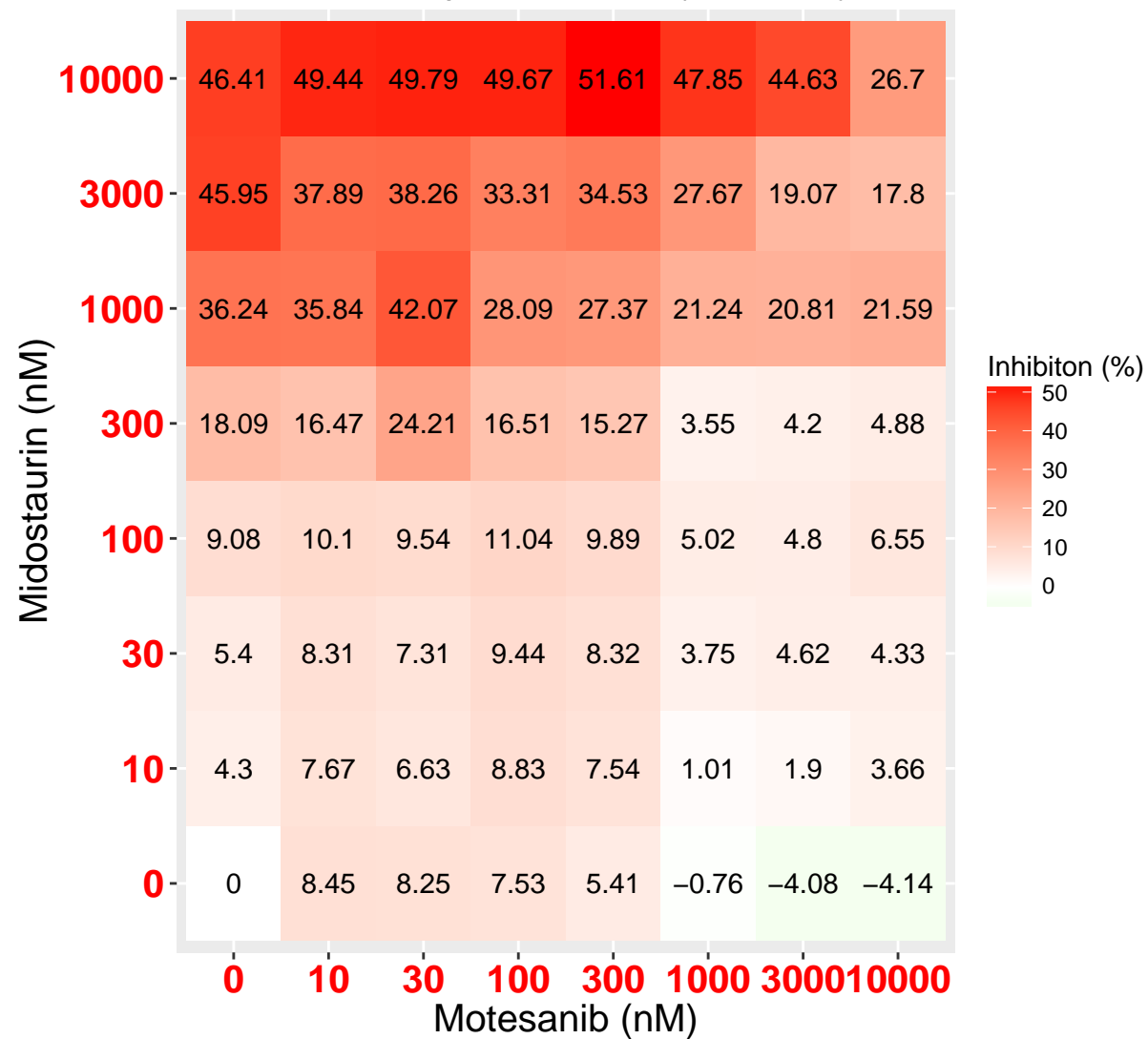
Dose-response matrix (inhibition)



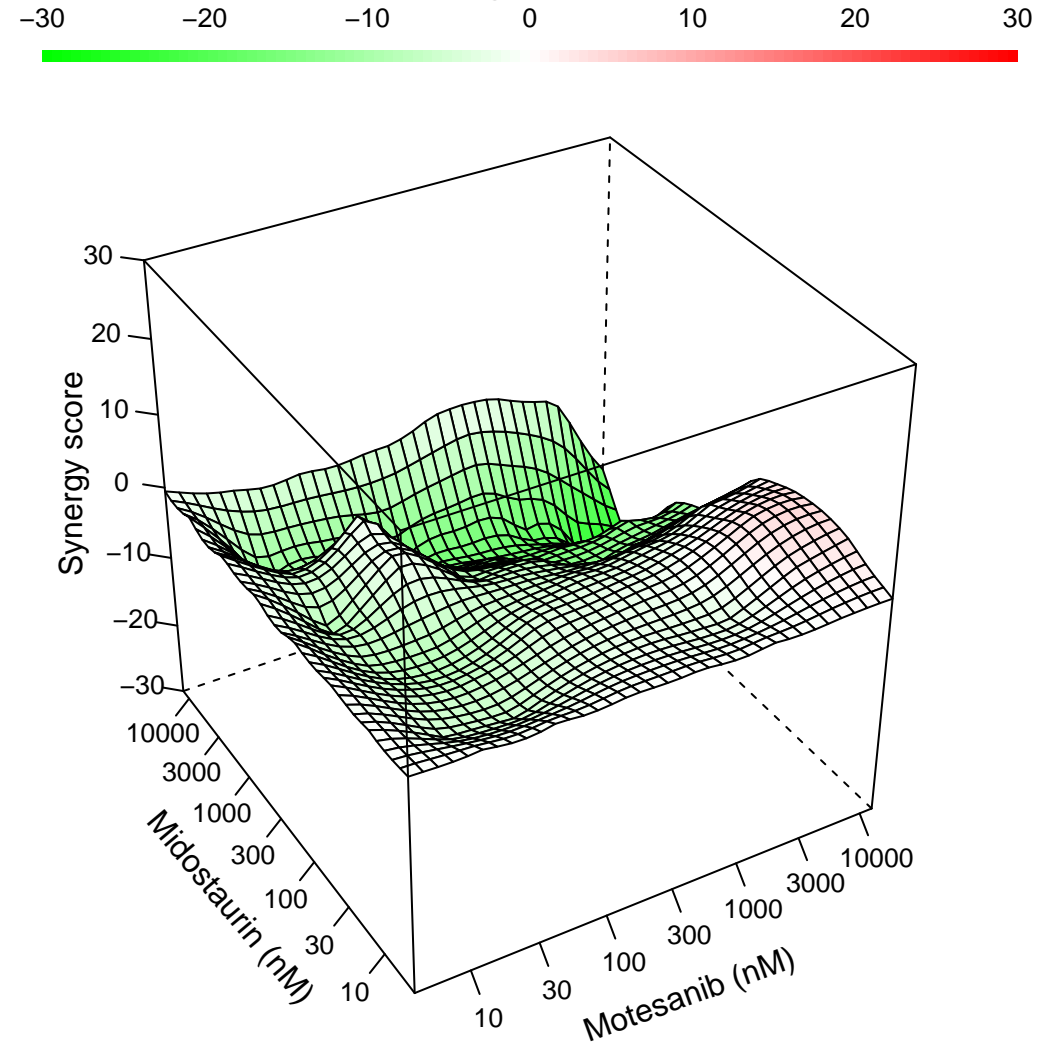
Bliss synergy score: -0.4



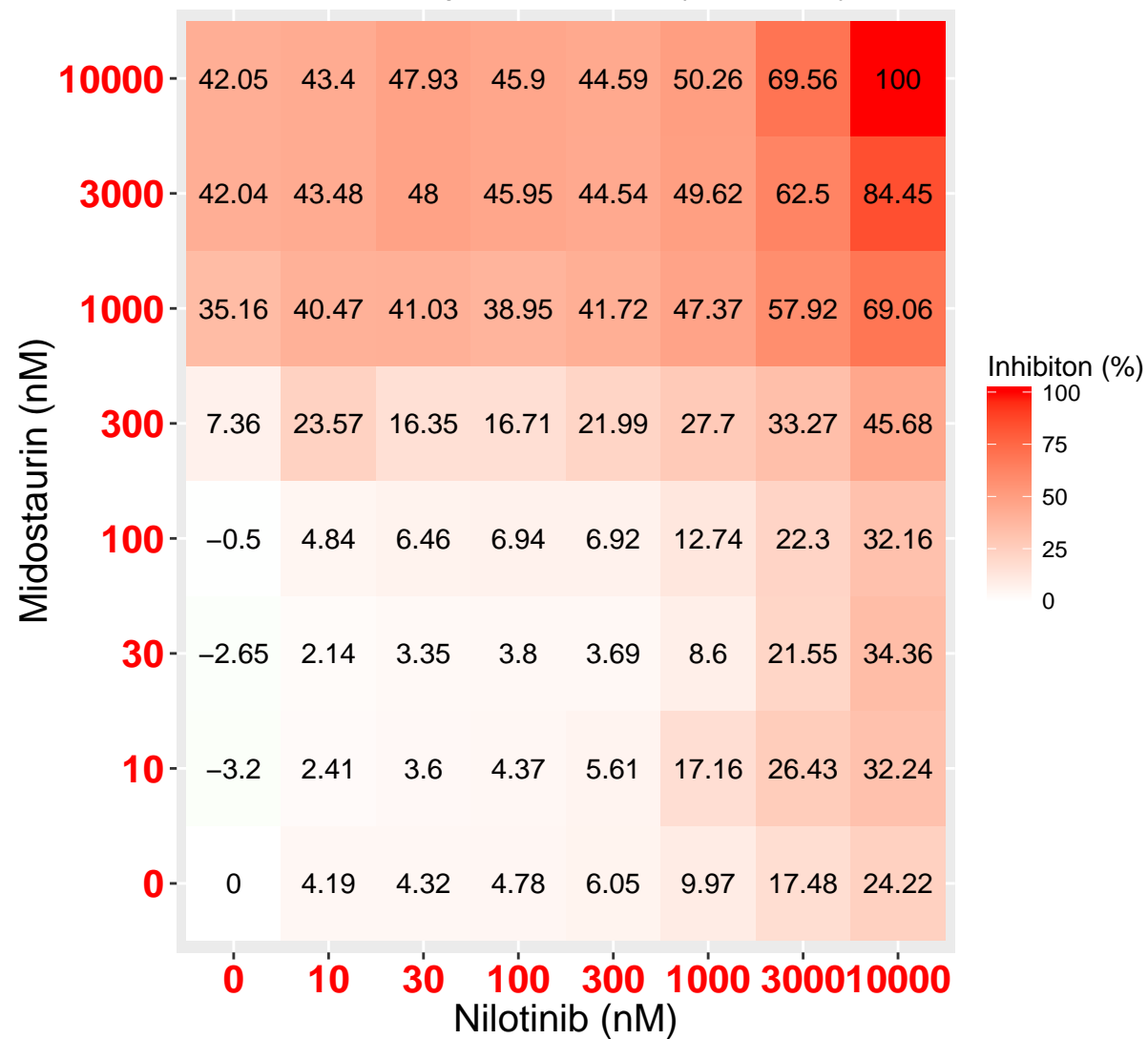
Dose-response matrix (inhibition)



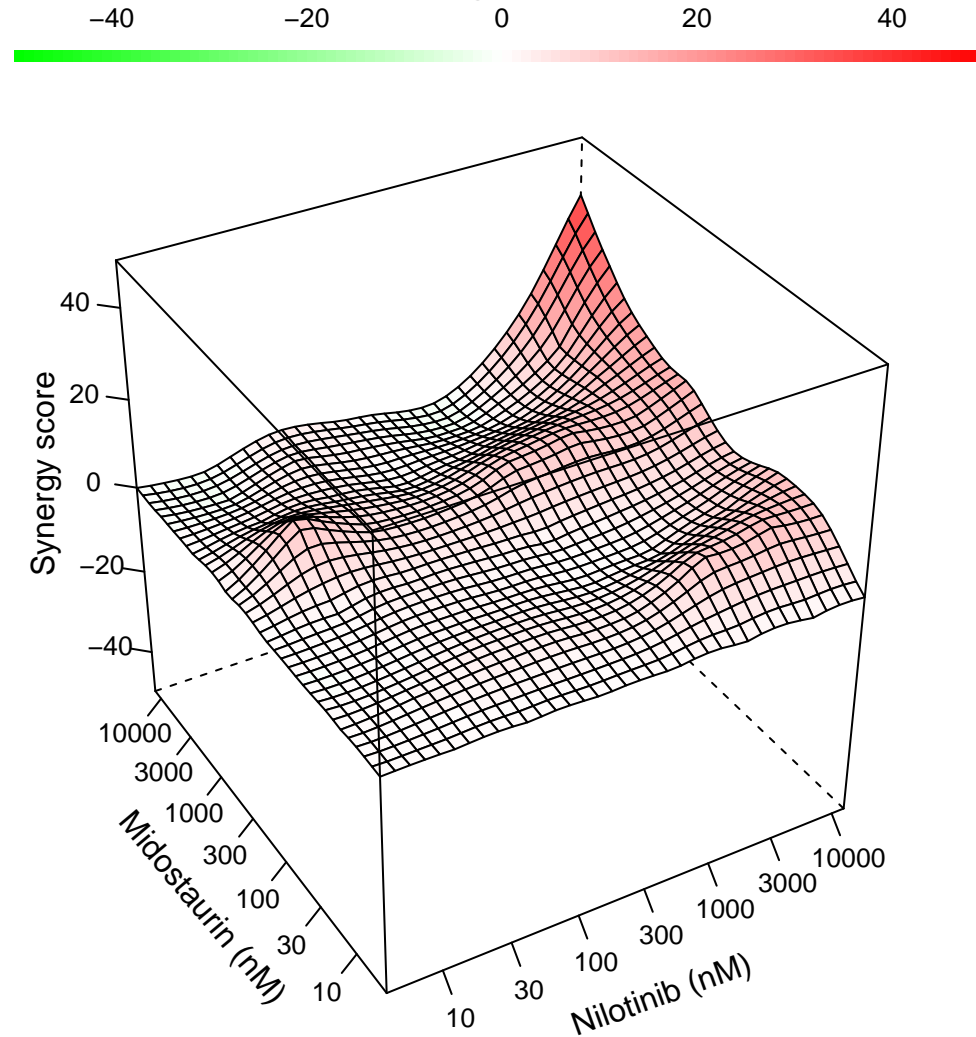
Bliss synergy score: -5.933



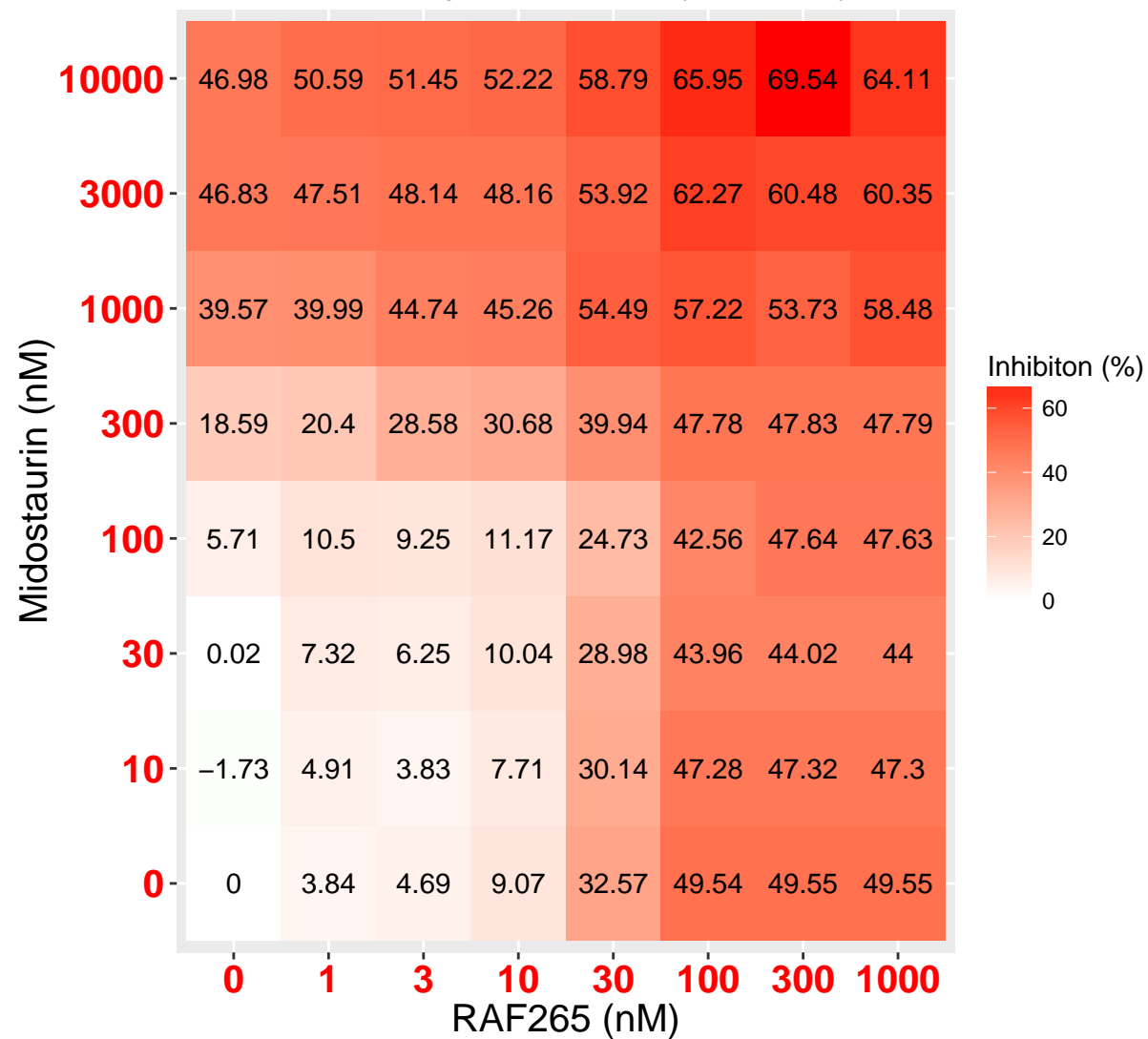
Dose-response matrix (inhibition)



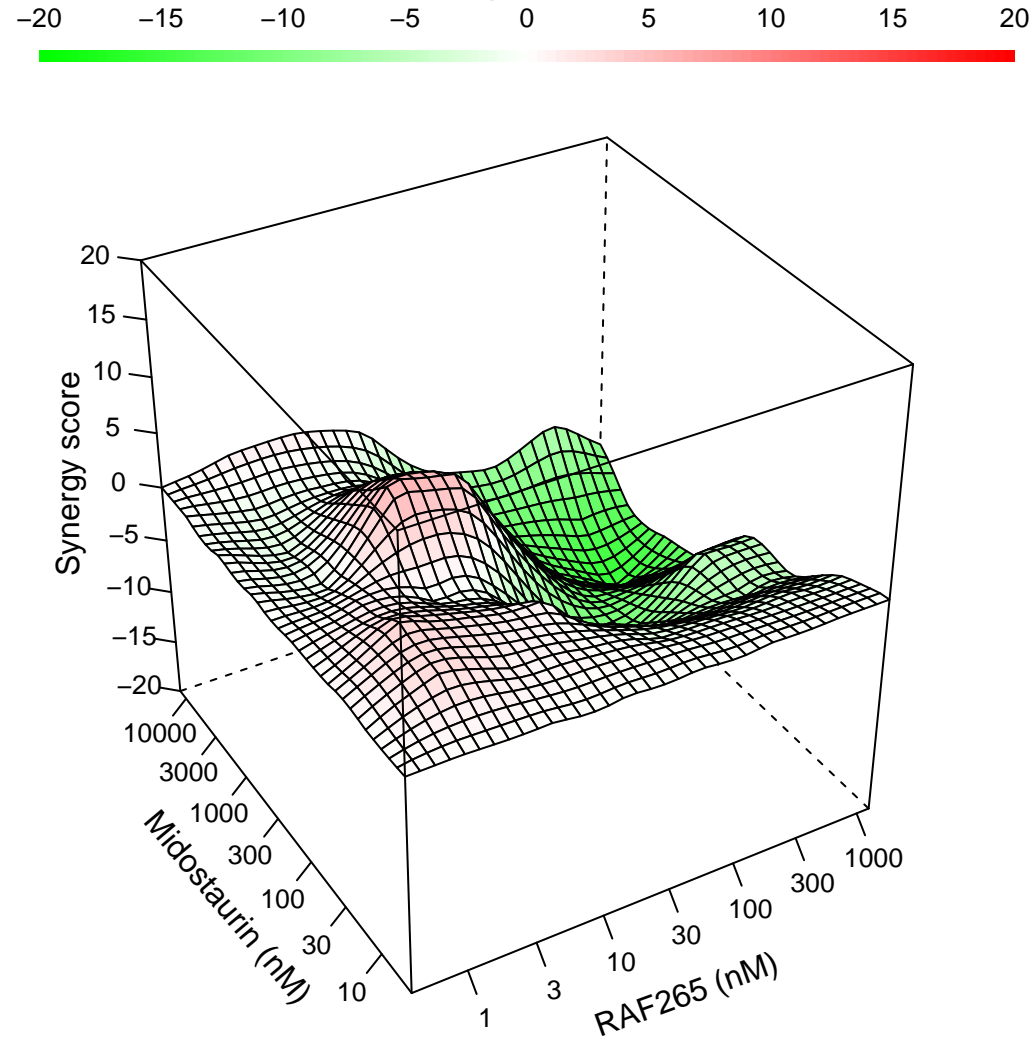
Bliss synergy score: 4.475



Dose-response matrix (inhibition)

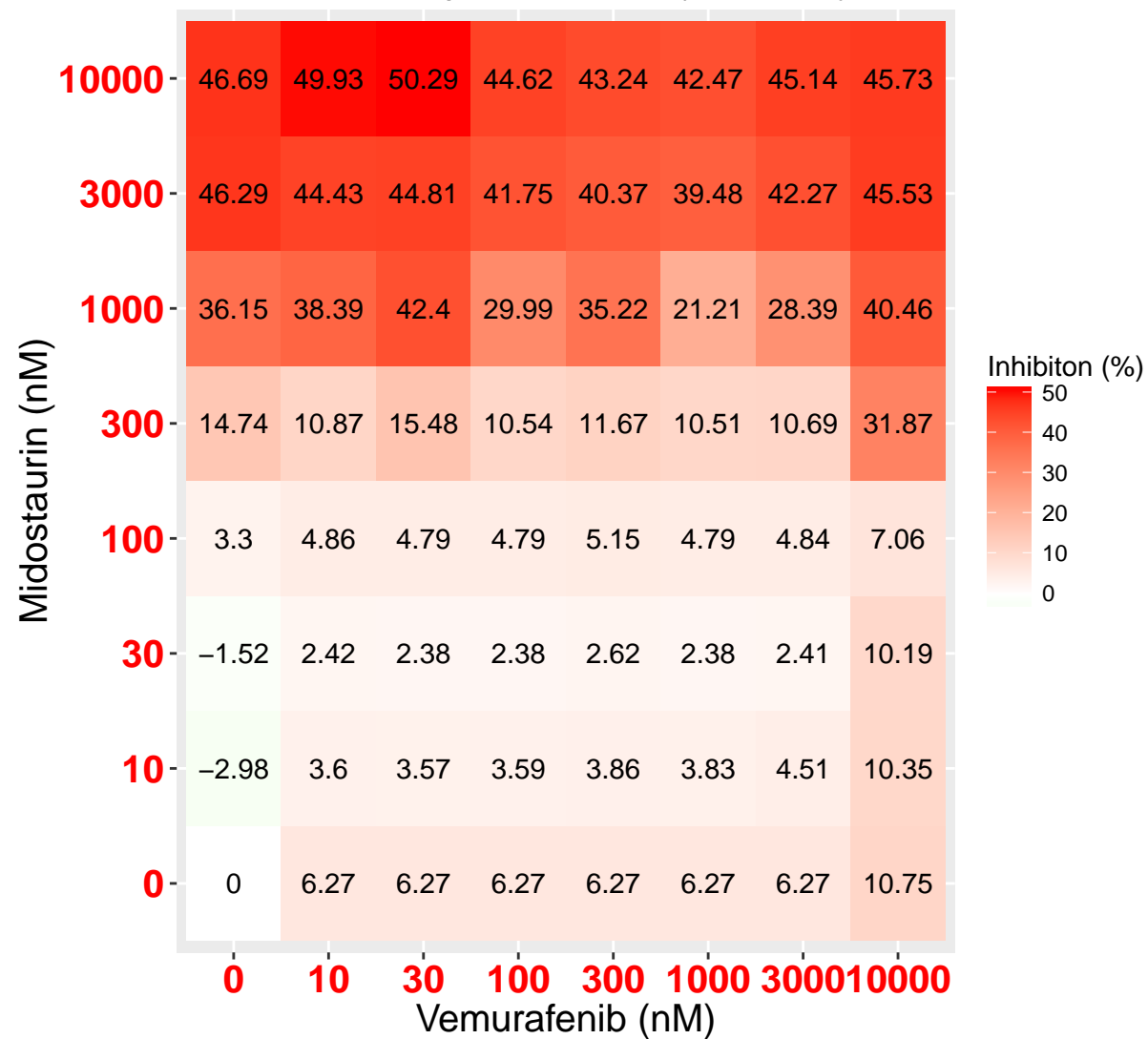


Bliss synergy score: -3.267

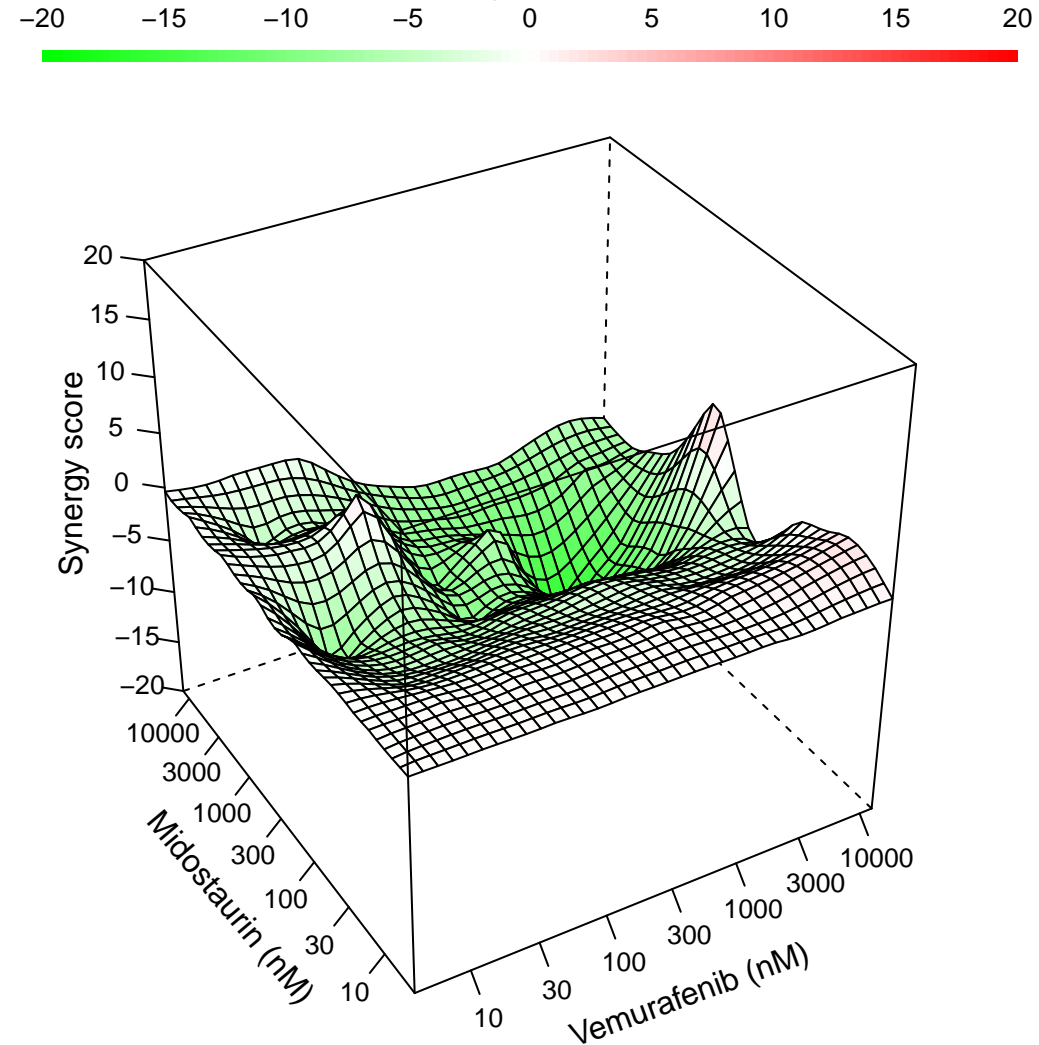




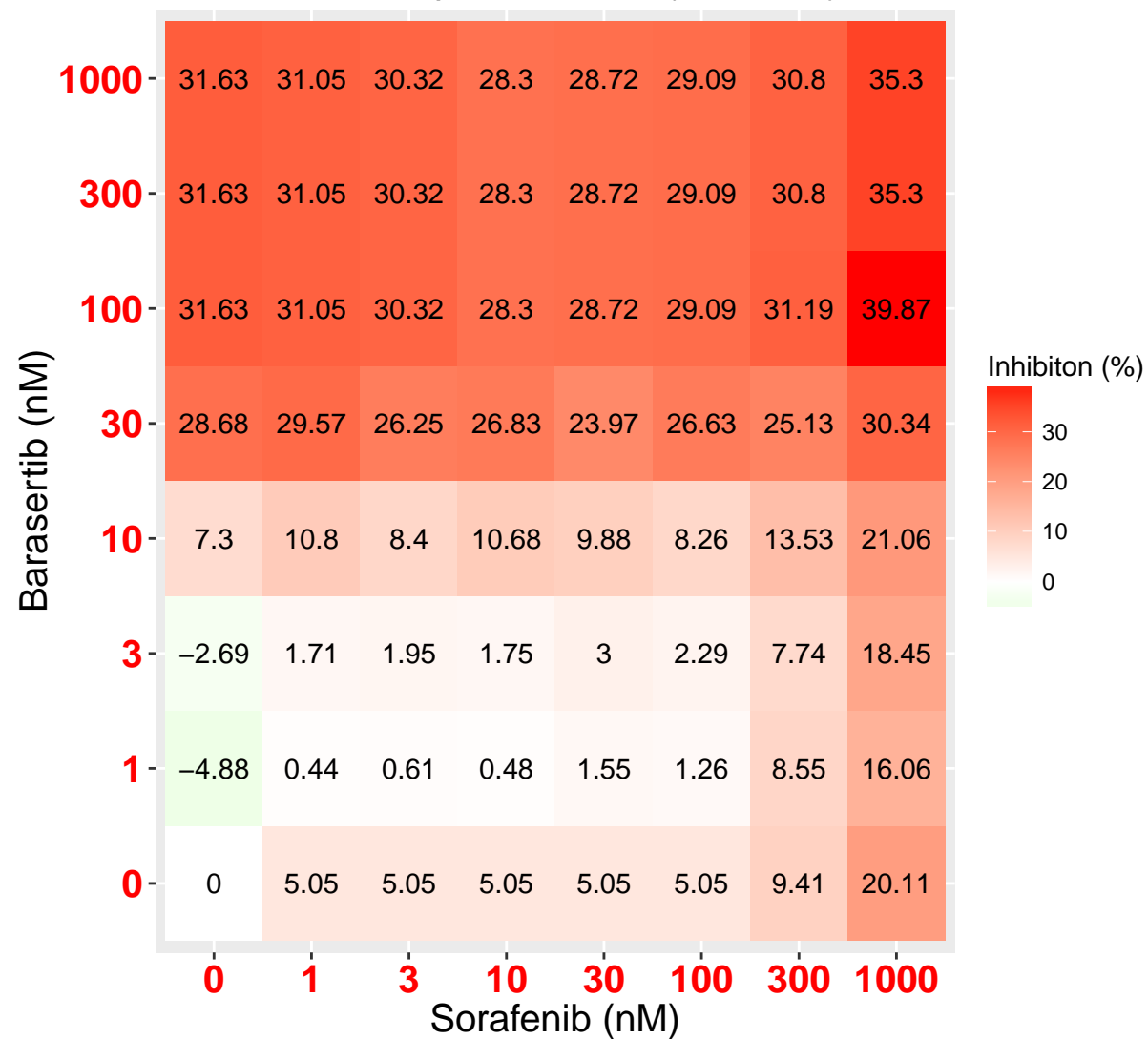
Dose-response matrix (inhibition)



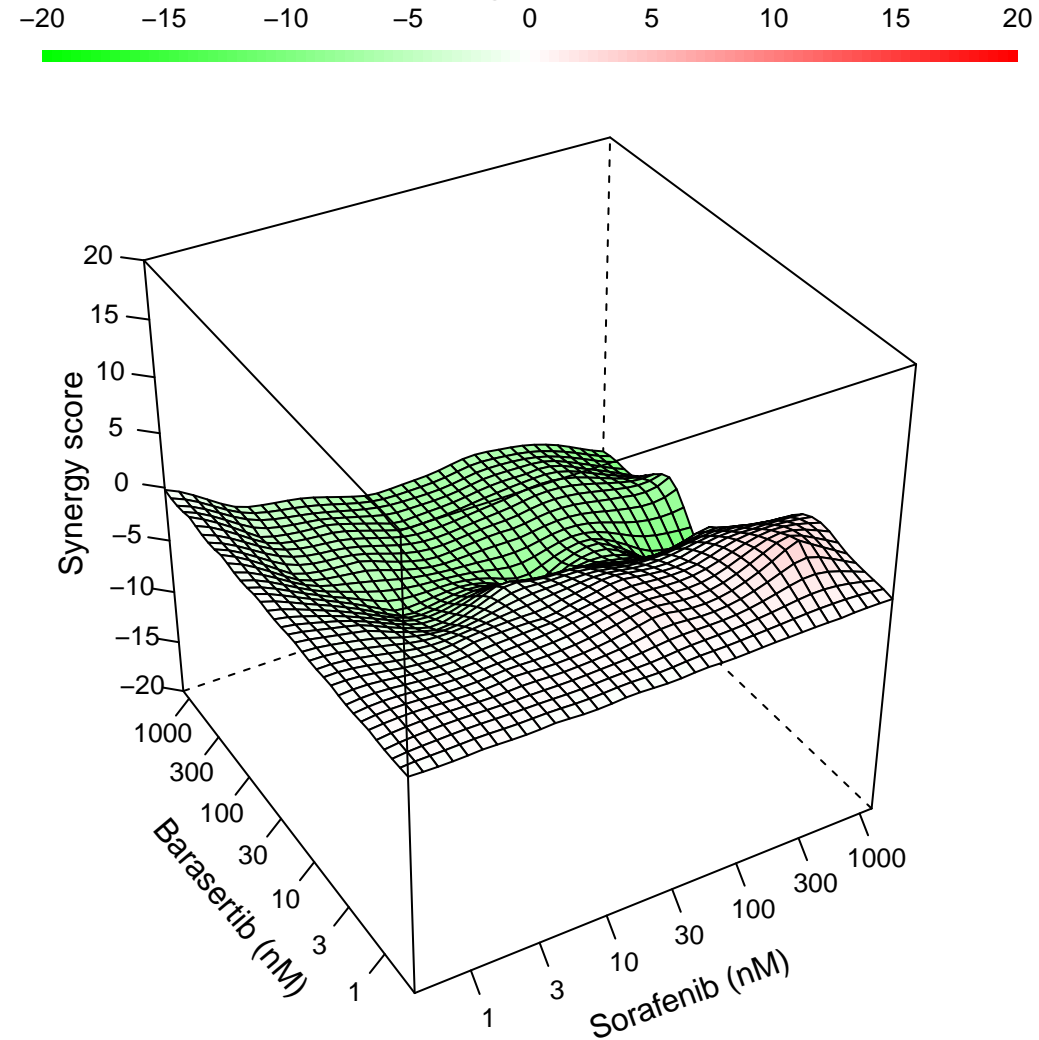
Bliss synergy score: -4.012



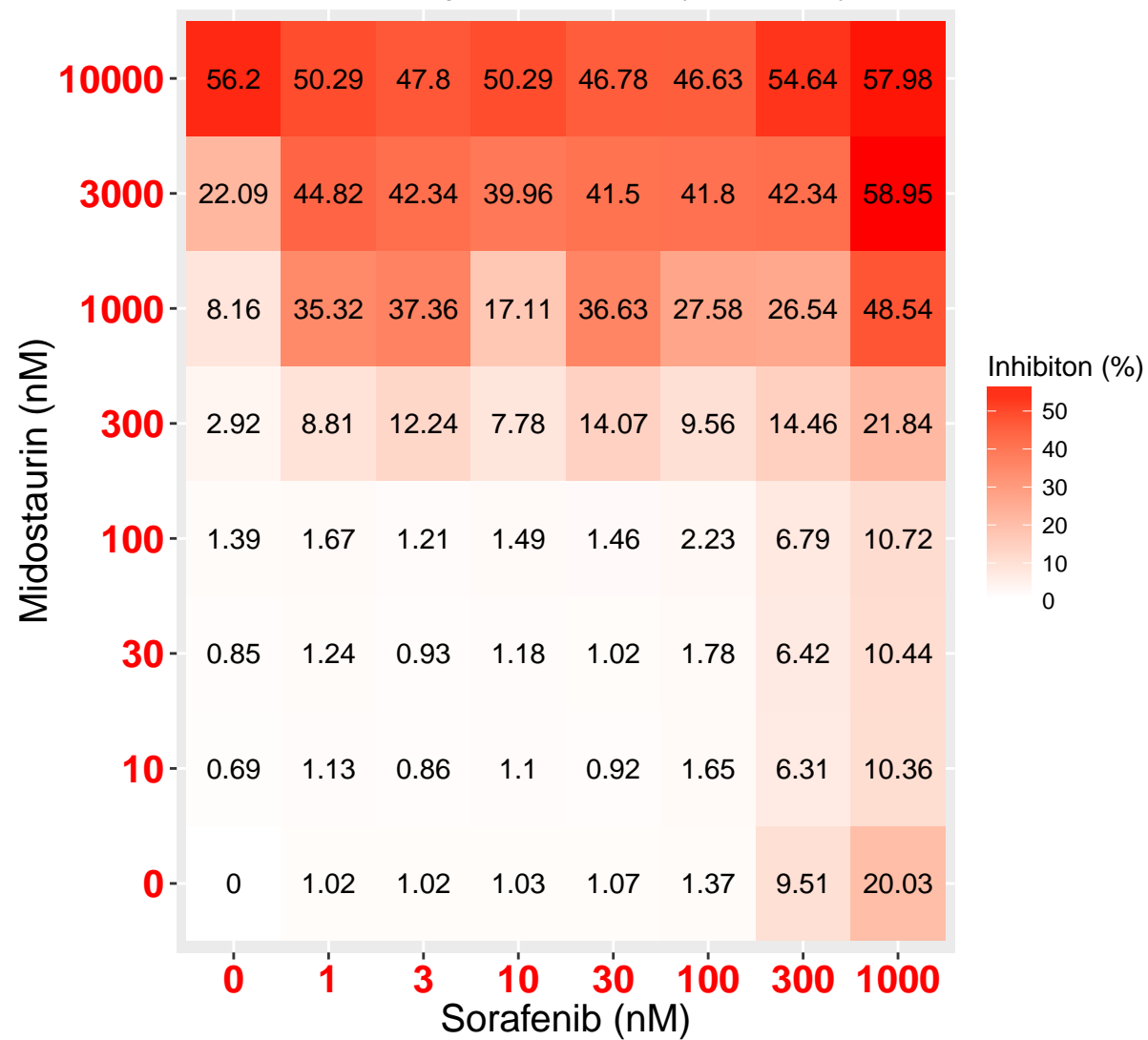
Dose-response matrix (inhibition)



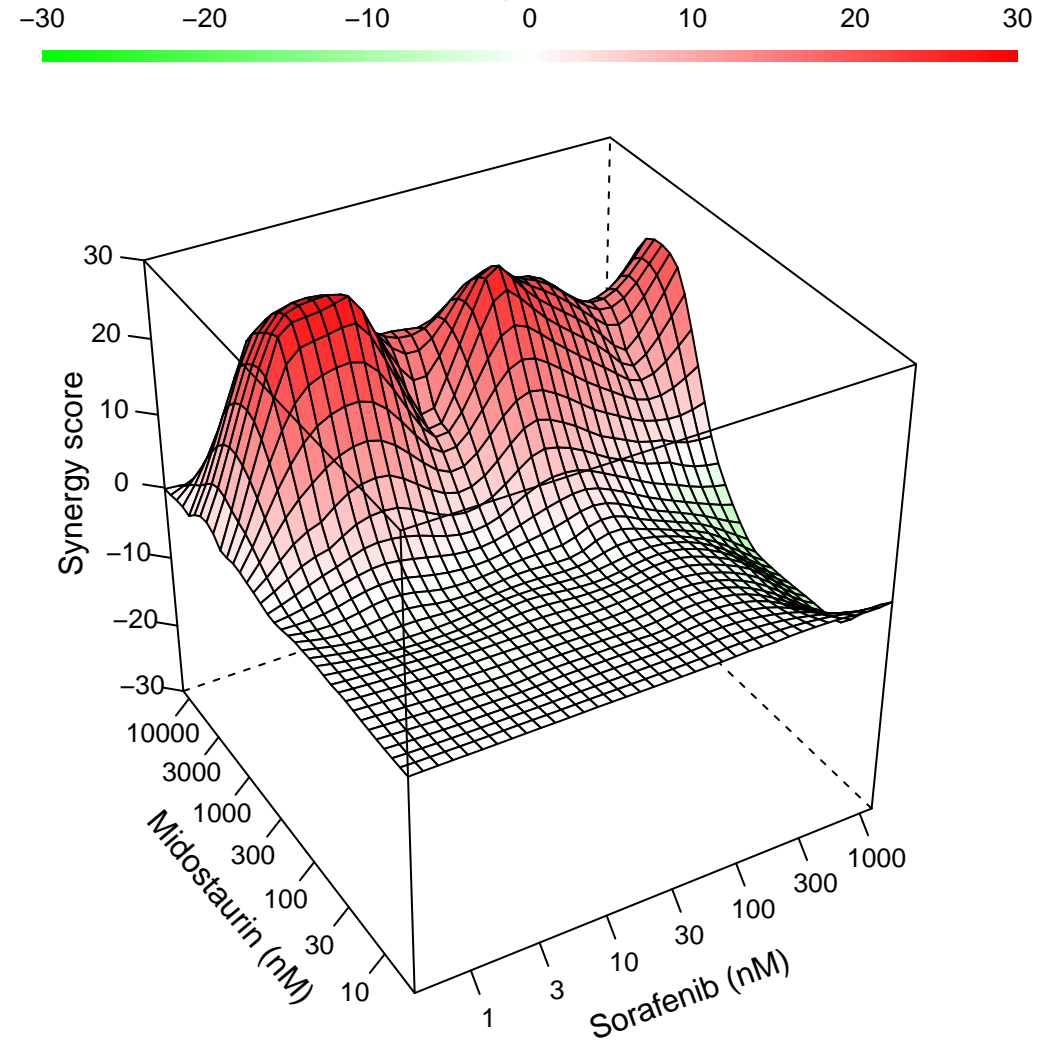
Bliss synergy score: -3.152



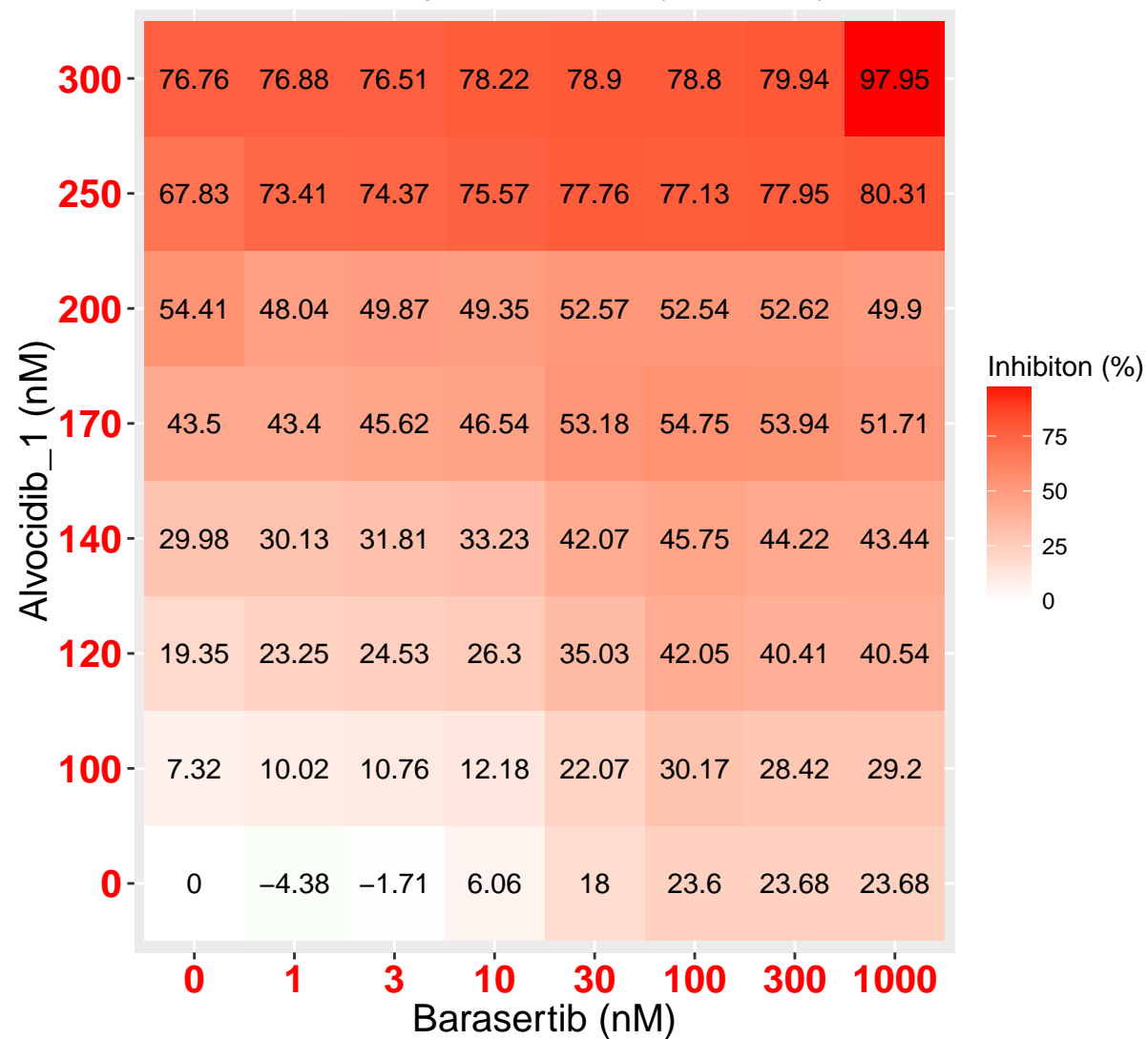
Dose-response matrix (inhibition)



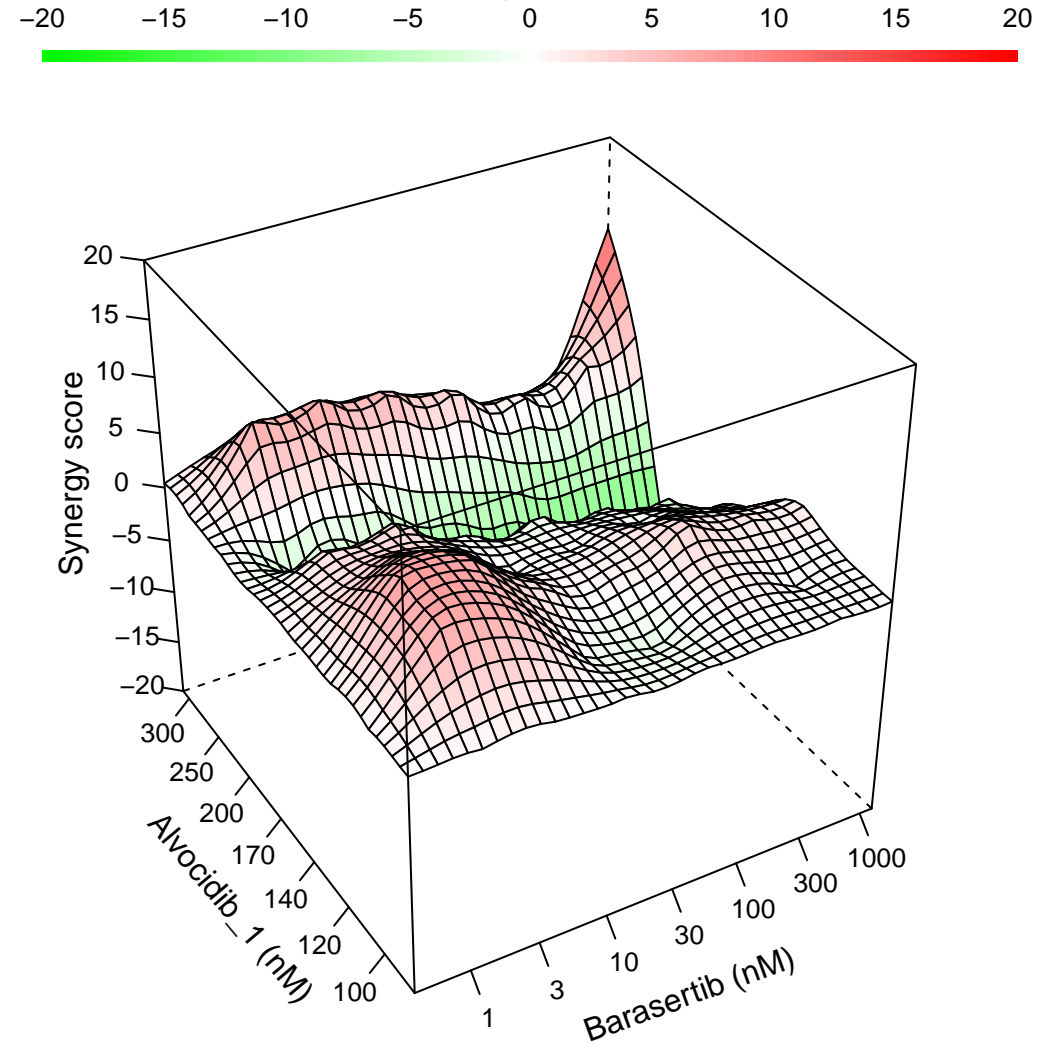
Bliss synergy score: 4.459



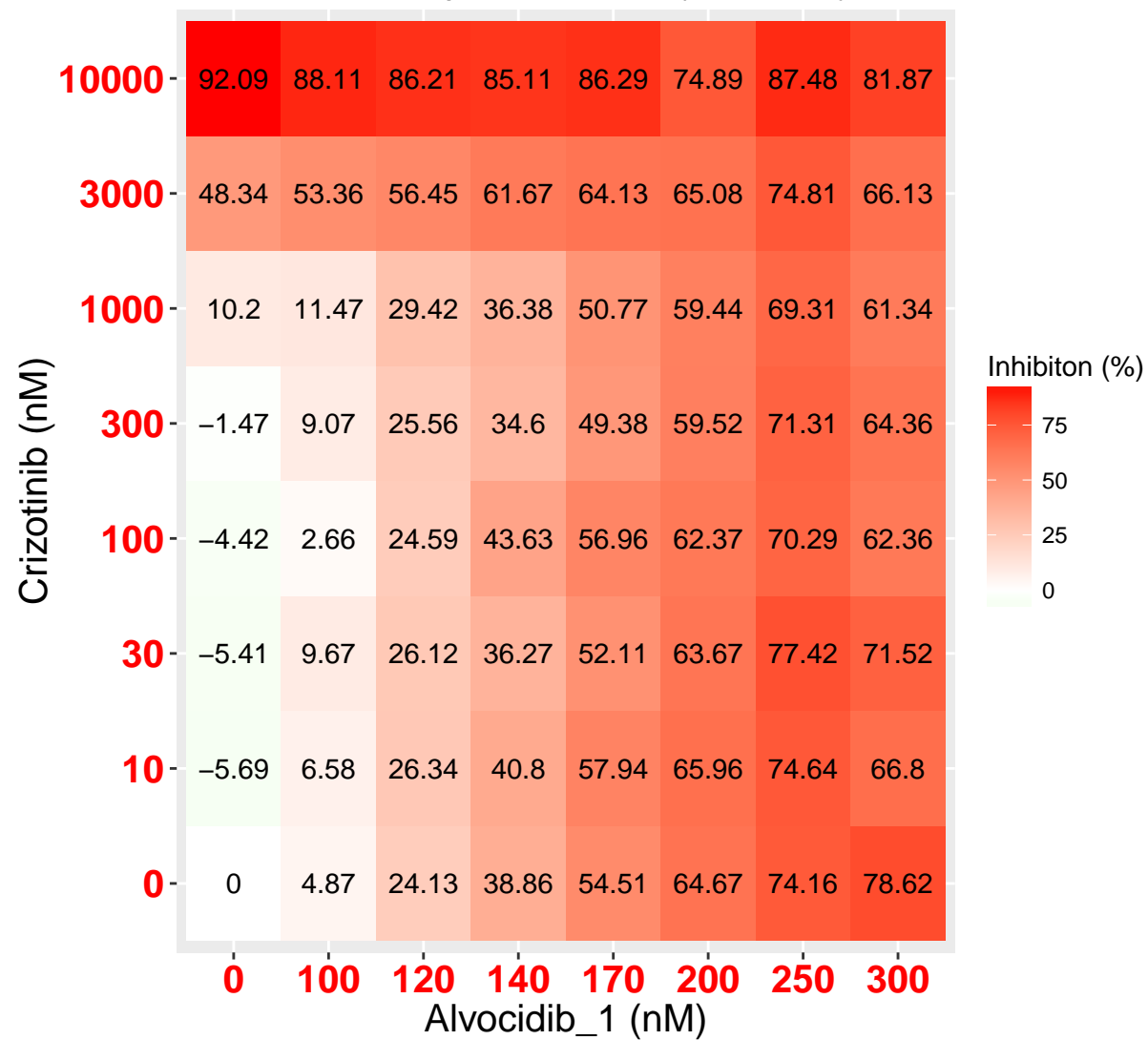
Dose-response matrix (inhibition)



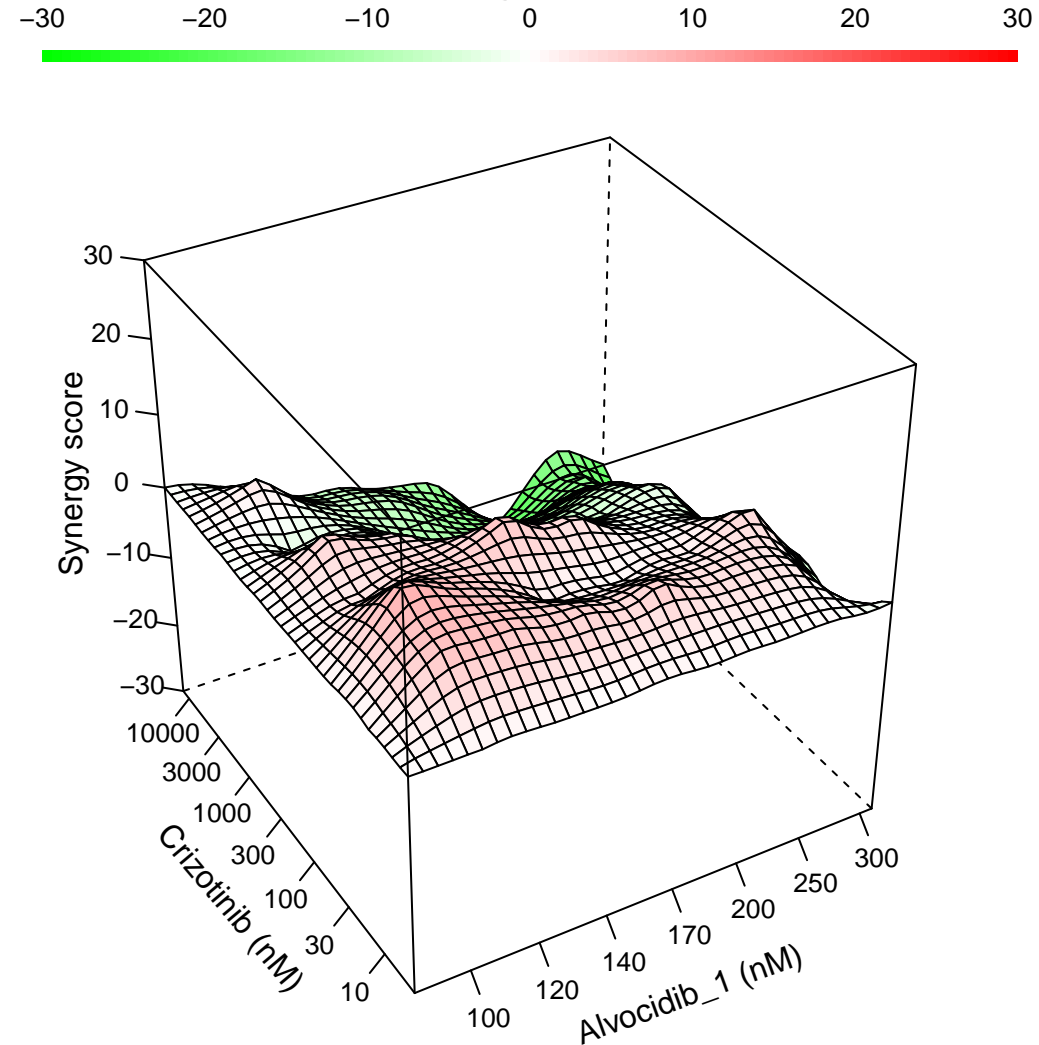
Bliss synergy score: 0.055



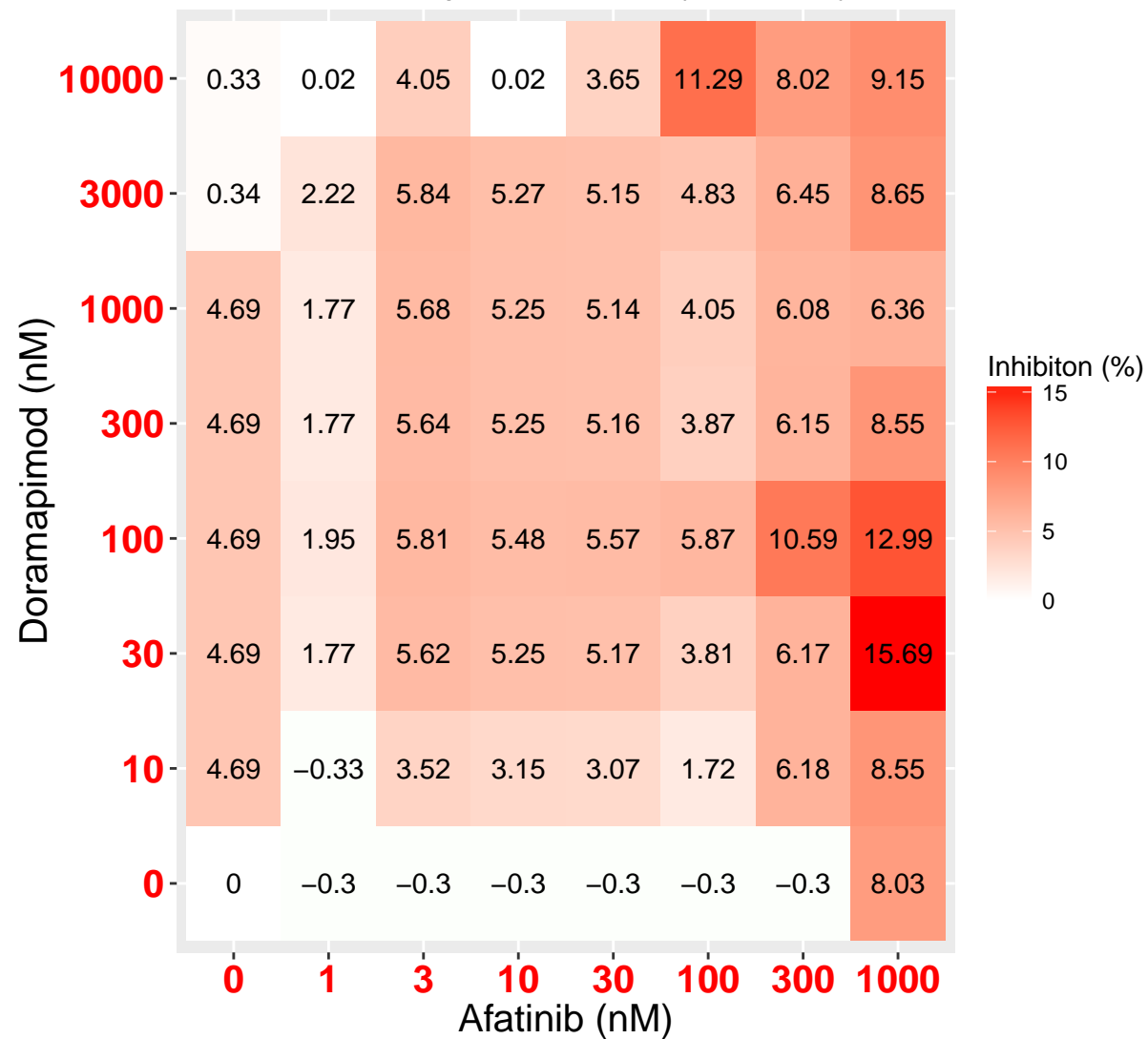
Dose-response matrix (inhibition)



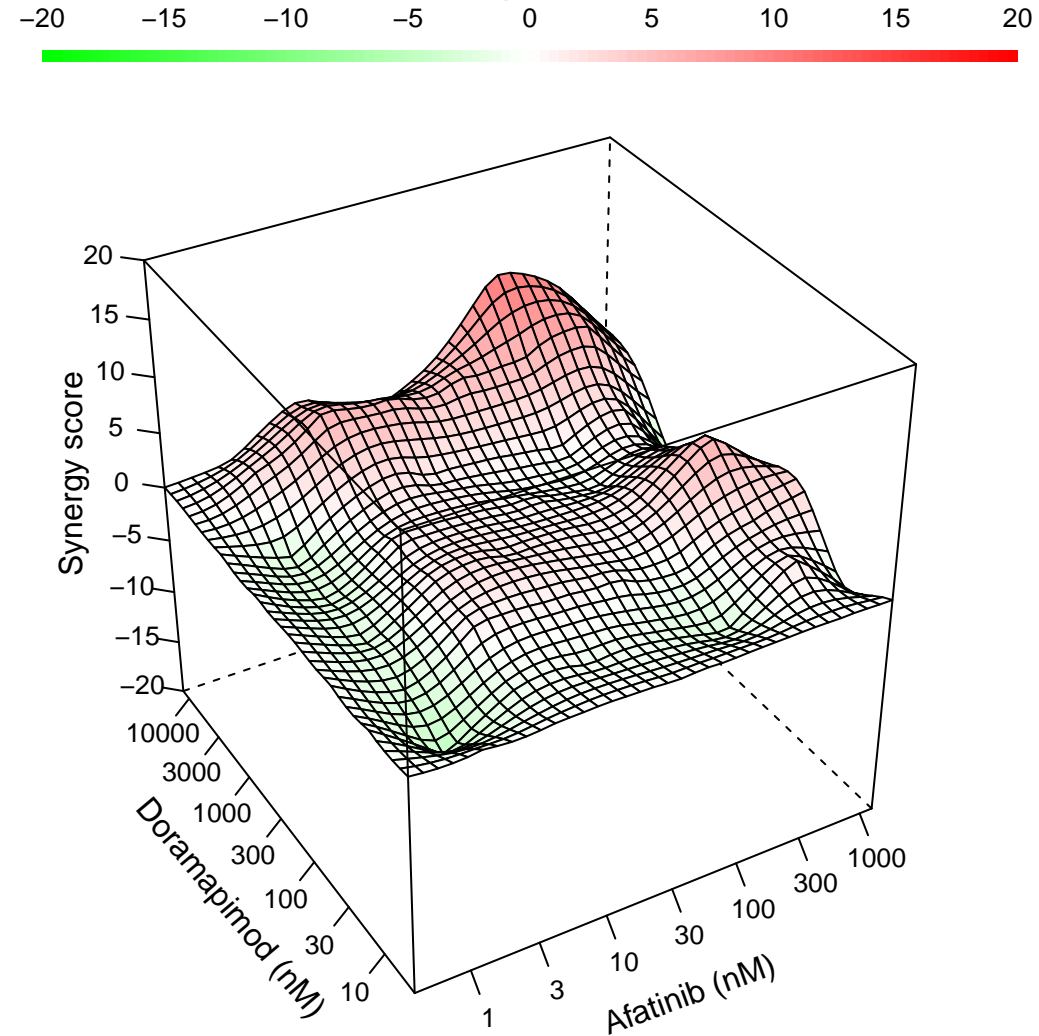
Bliss synergy score: -2.22



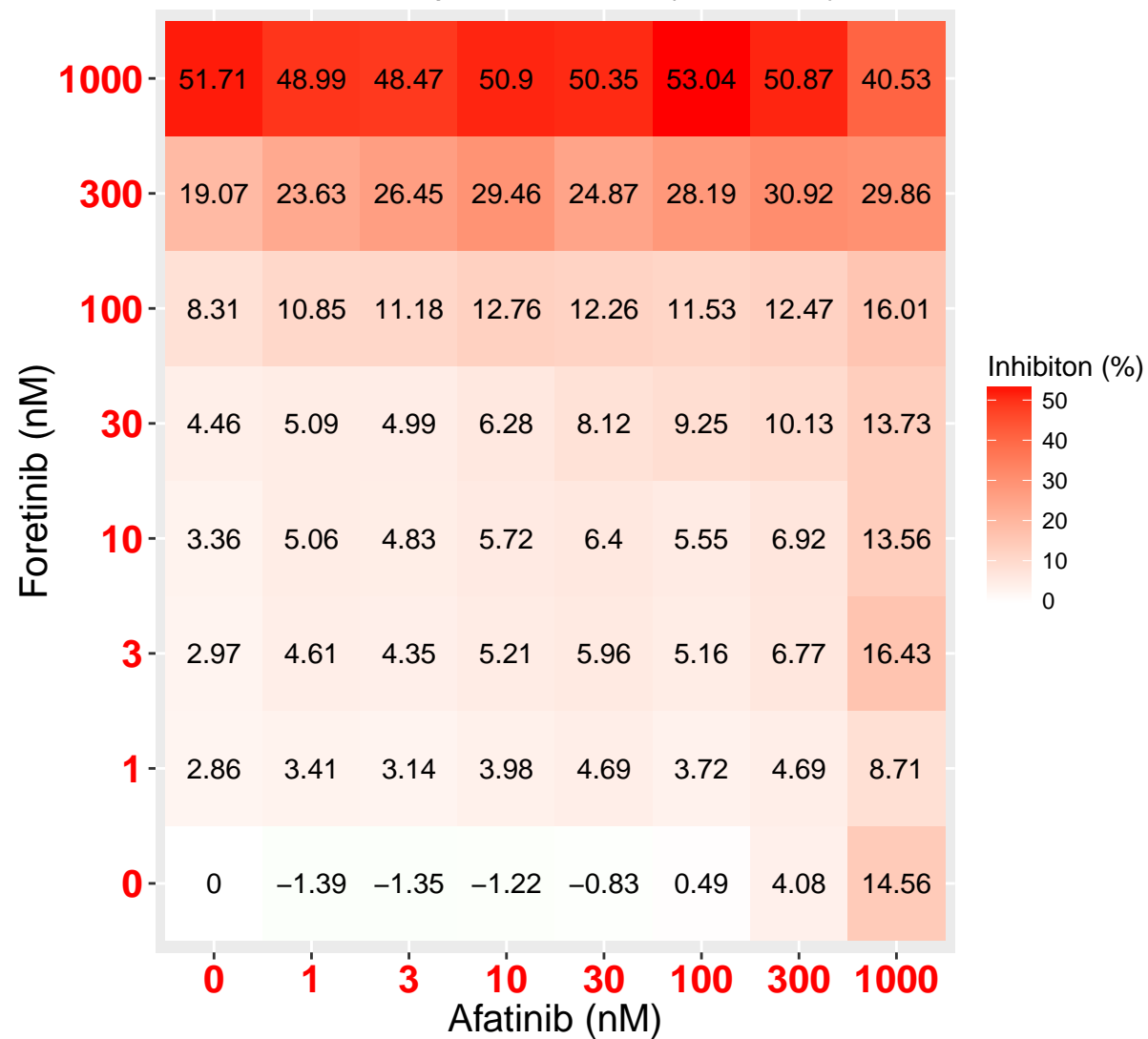
Dose-response matrix (inhibition)



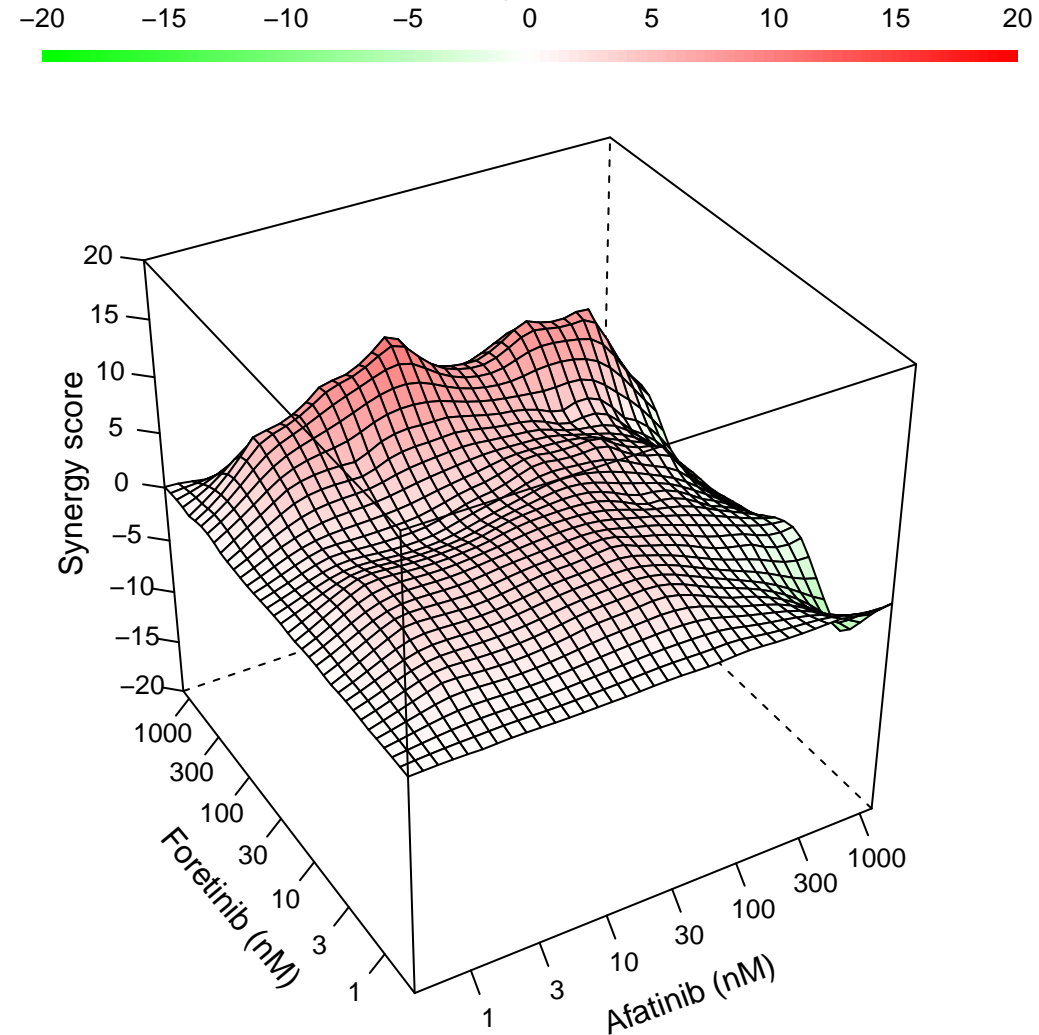
Bliss synergy score: 0.874



Dose-response matrix (inhibition)

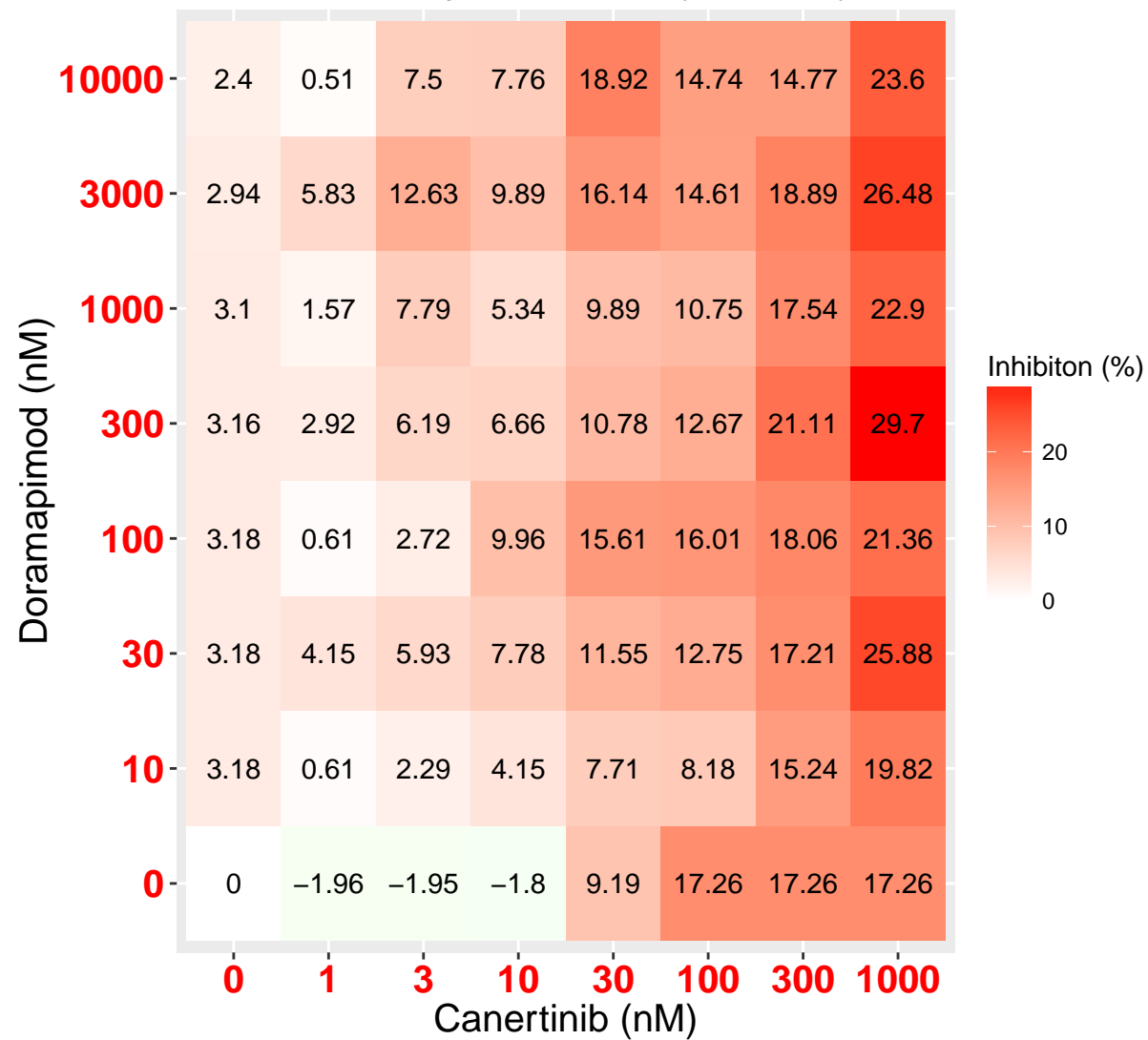


Bliss synergy score: 2.111

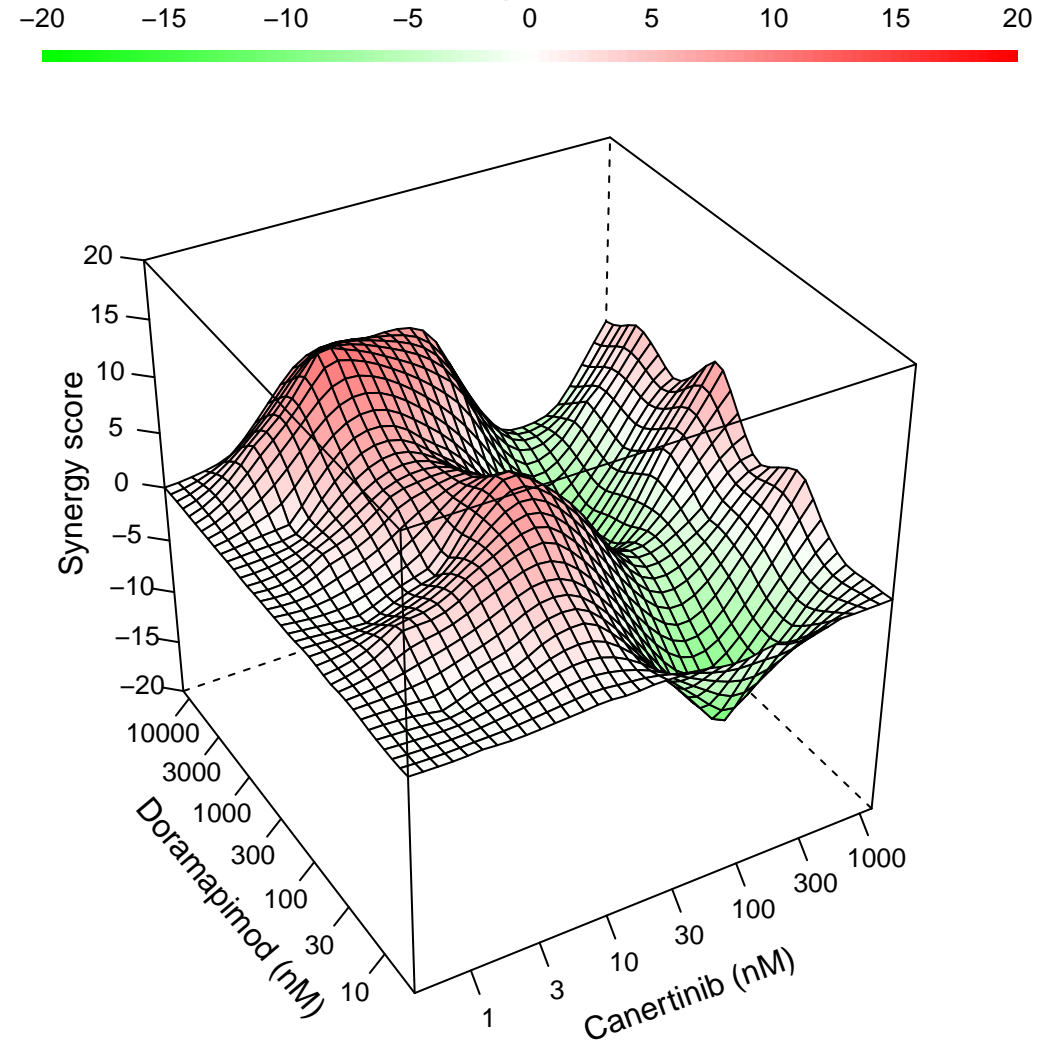




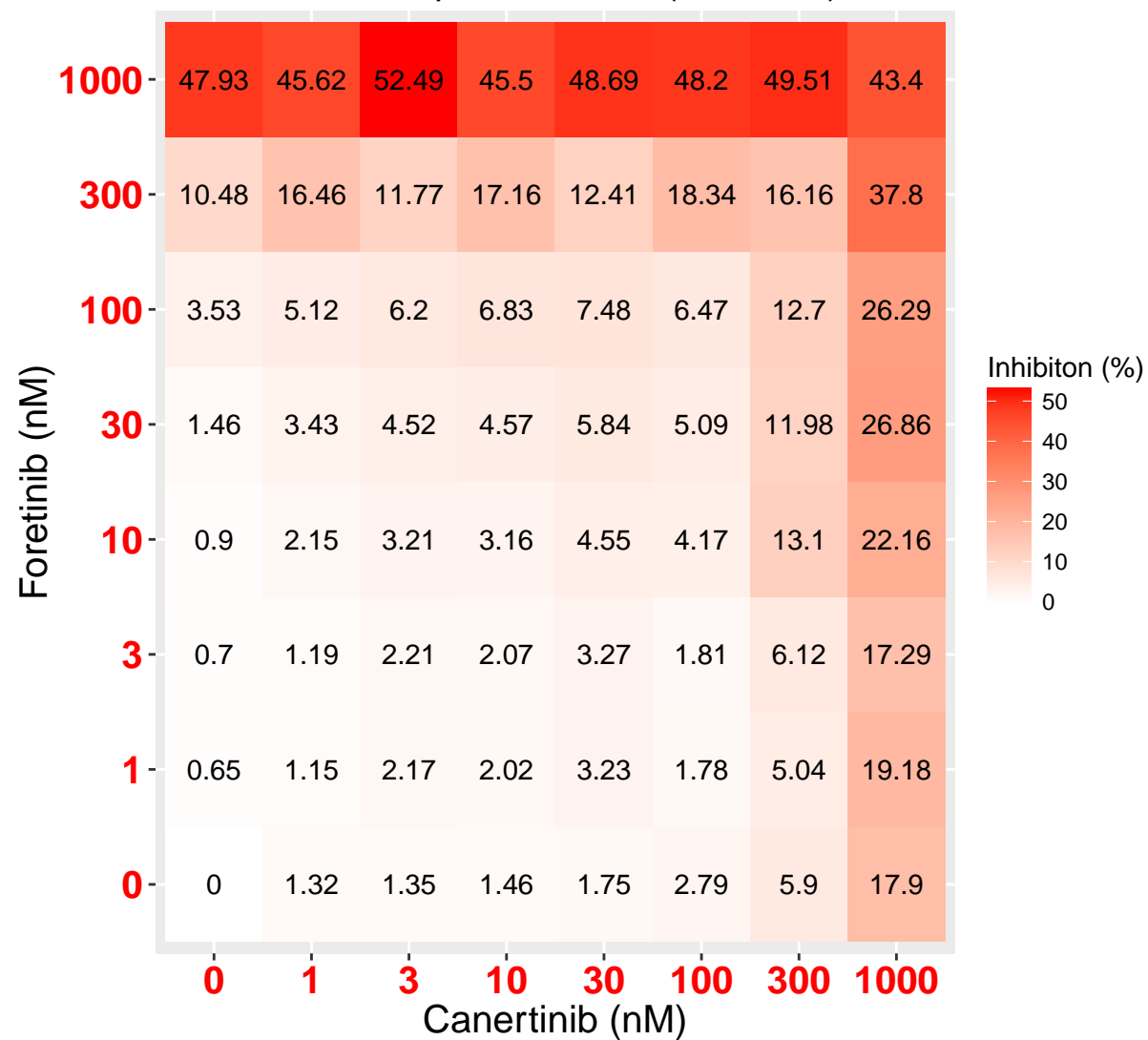
Dose-response matrix (inhibition)



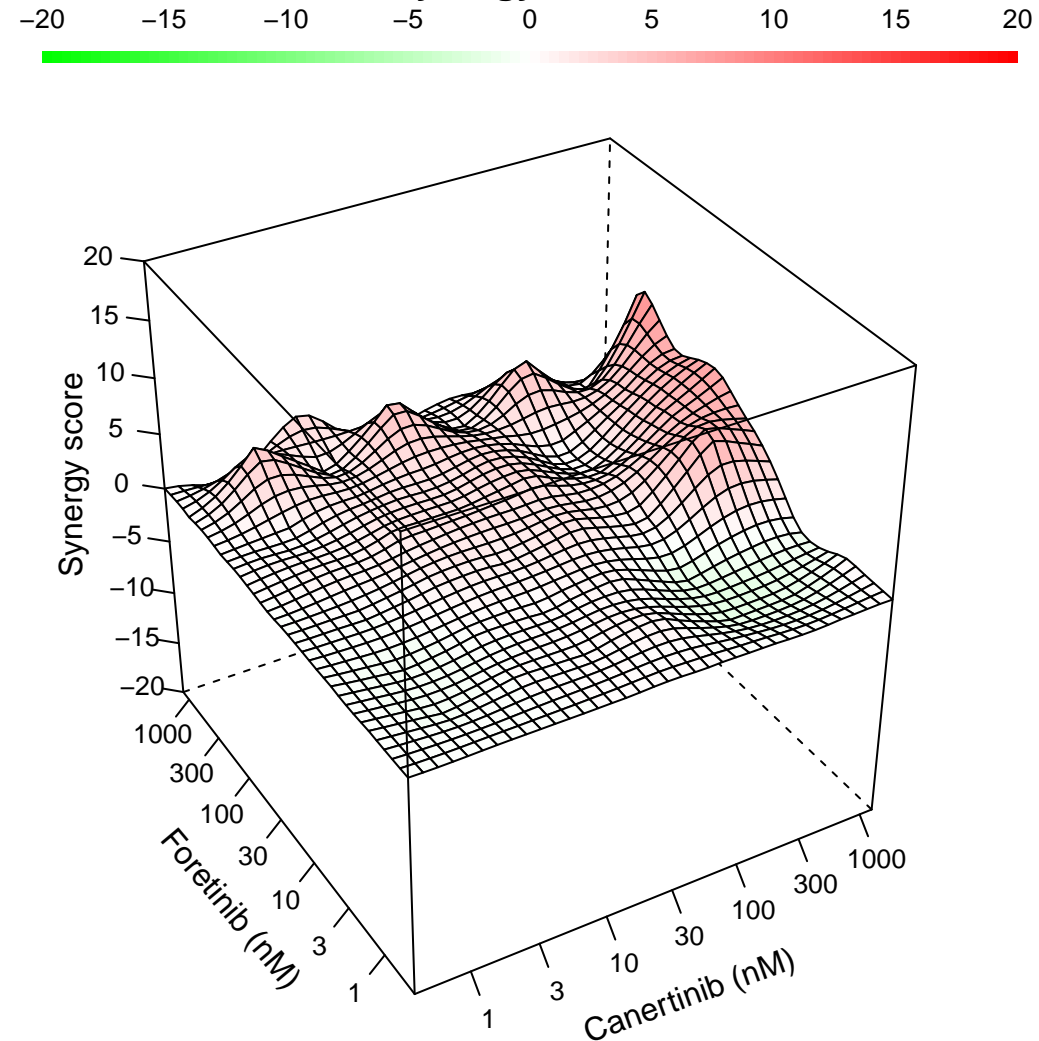
Bliss synergy score: 0.805



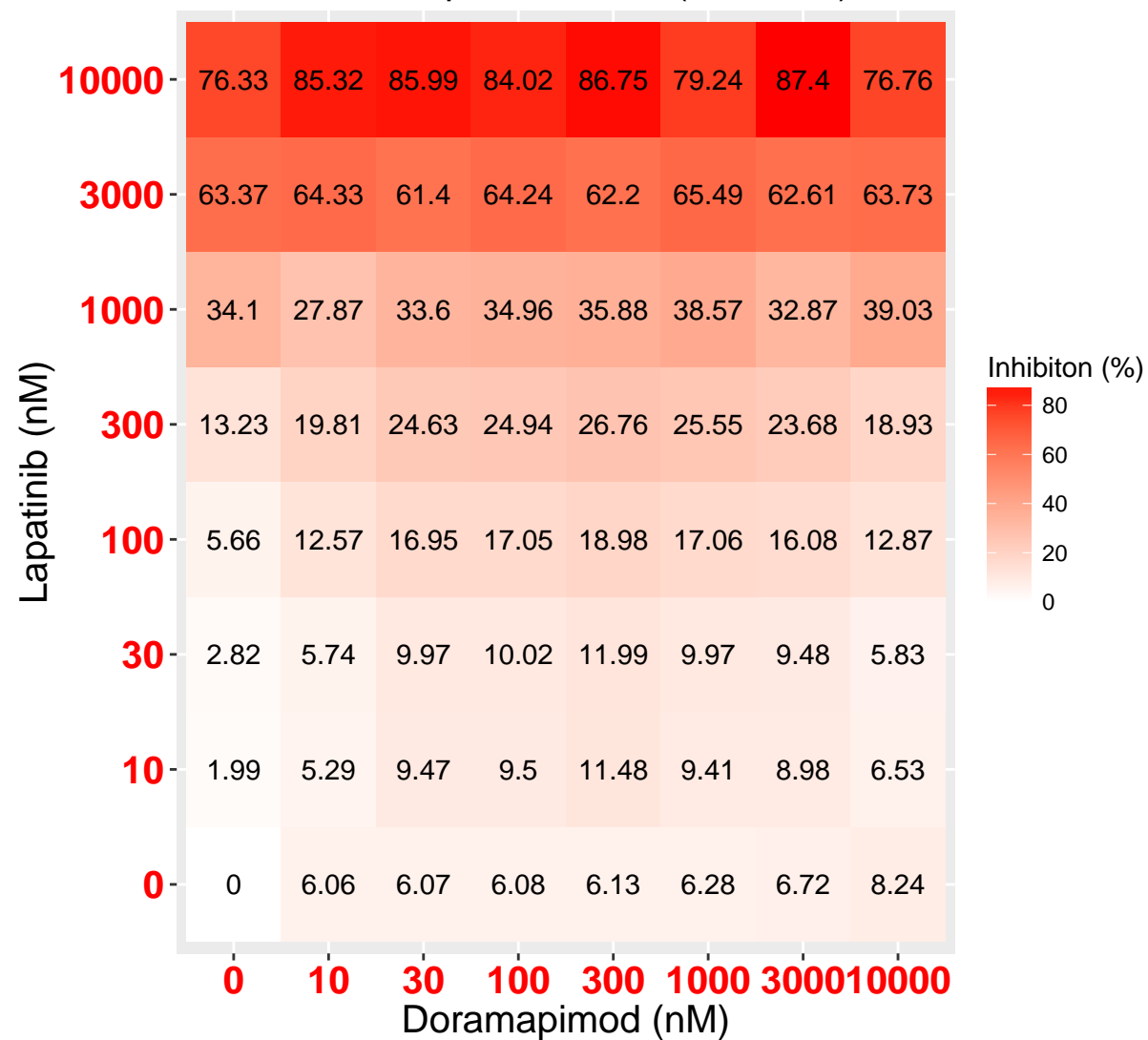
Dose-response matrix (inhibition)



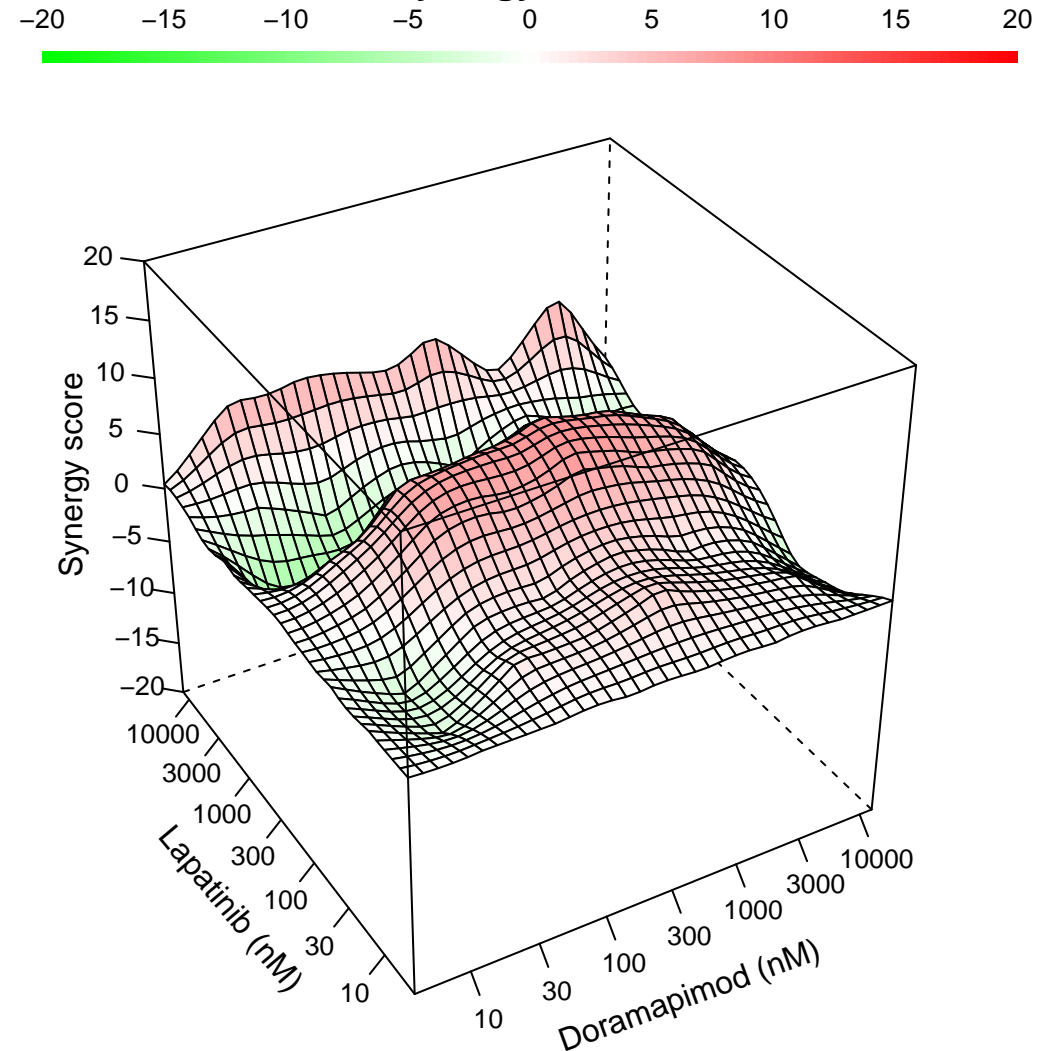
Bliss synergy score: 1.048



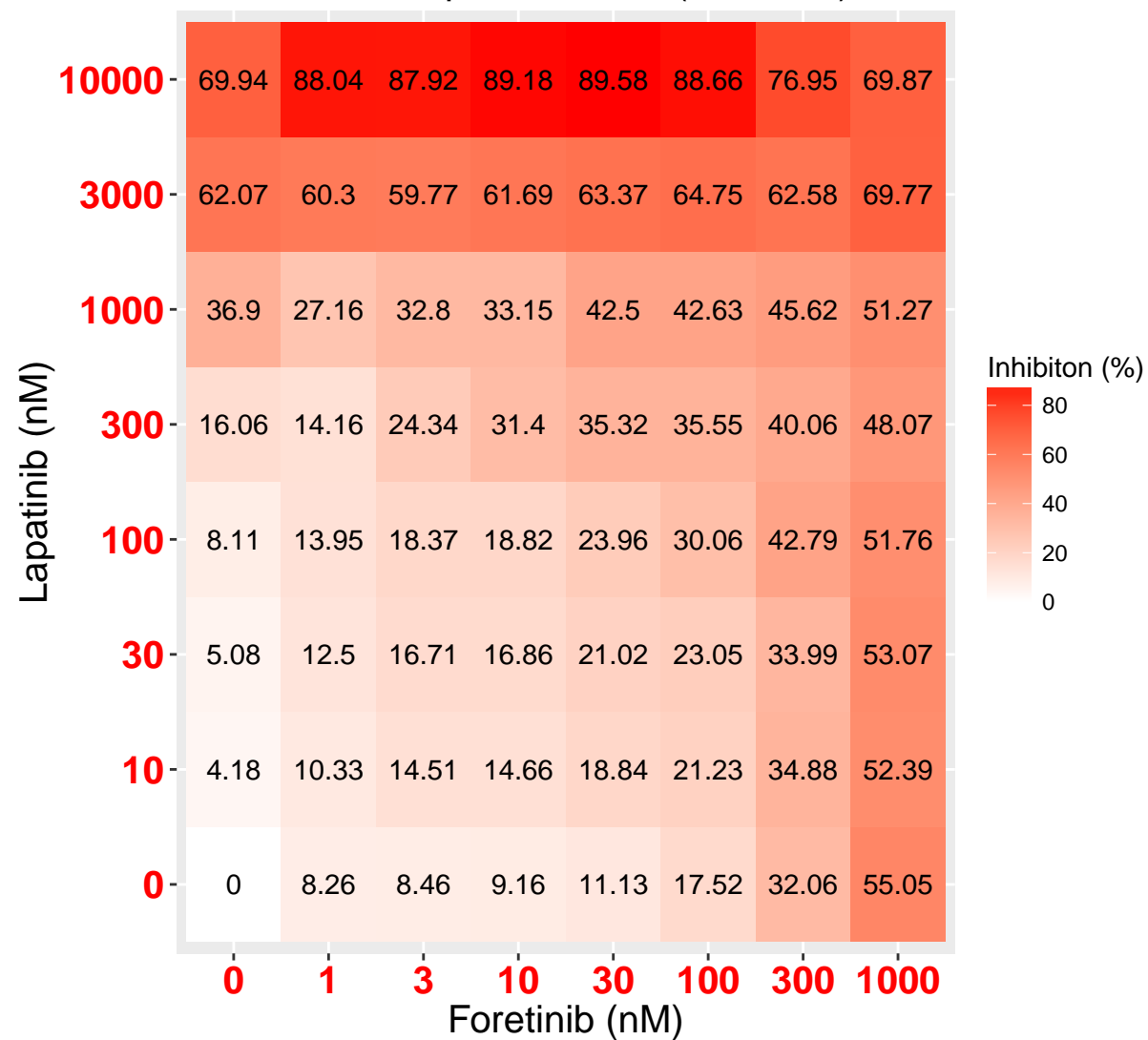
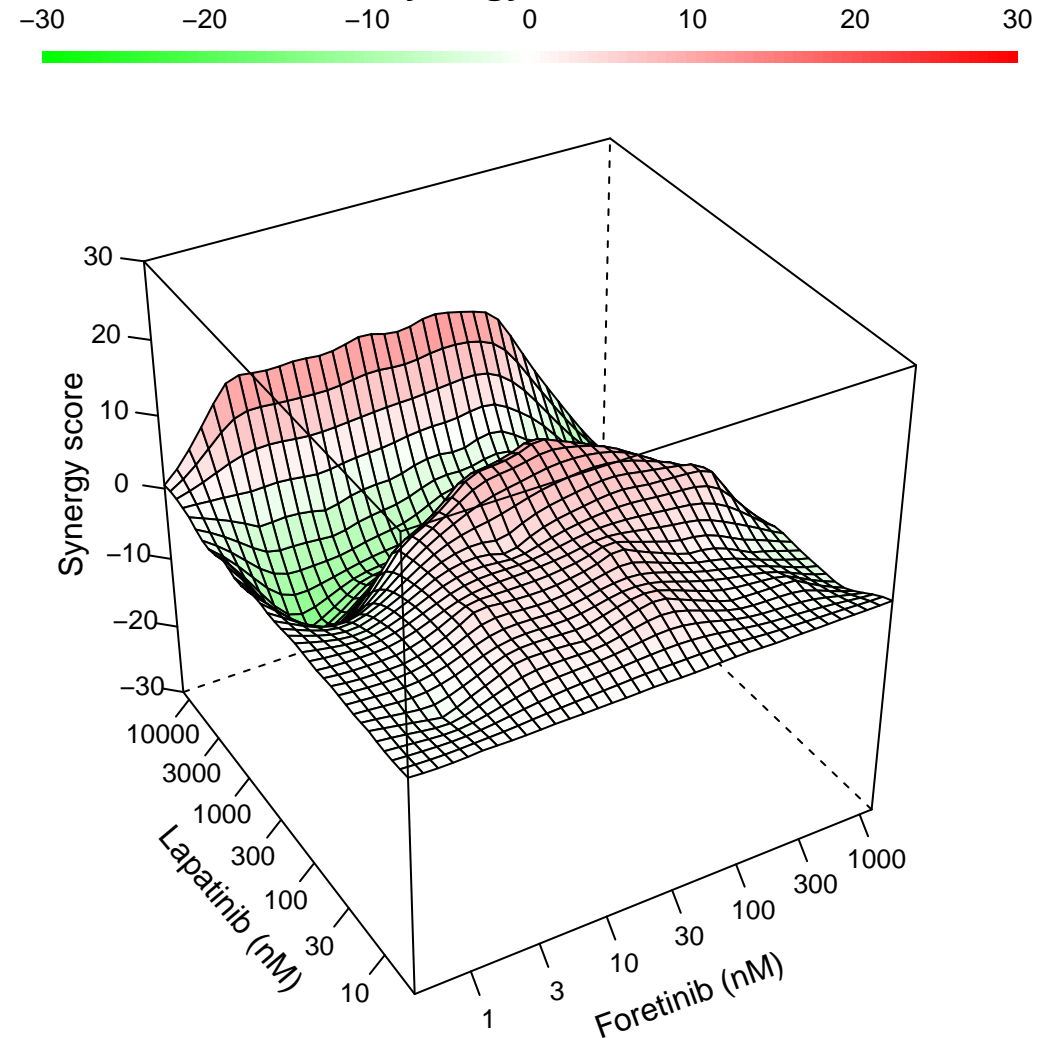
Dose-response matrix (inhibition)



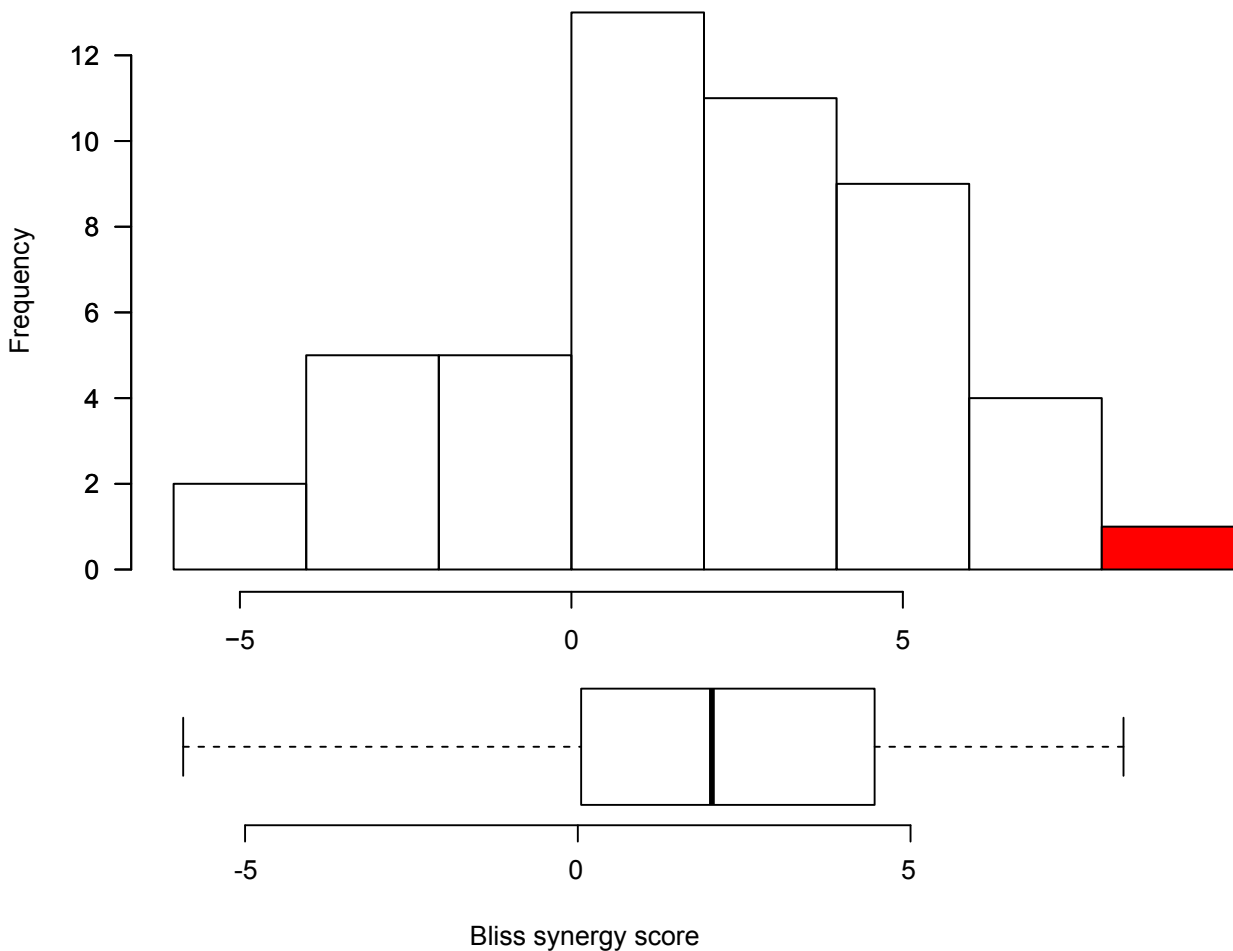
Bliss synergy score: 0.959



Dose-response matrix (inhibition)

Bliss synergy score: **-0.685**

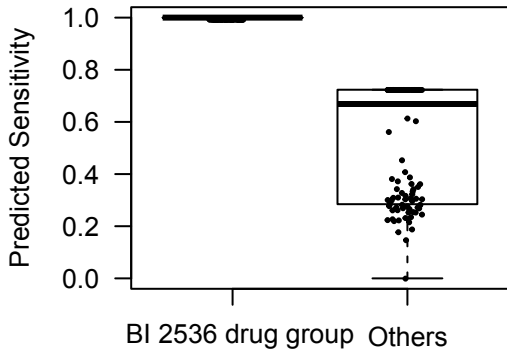
Supplementary Figure 2



# Supplementary Figure 3

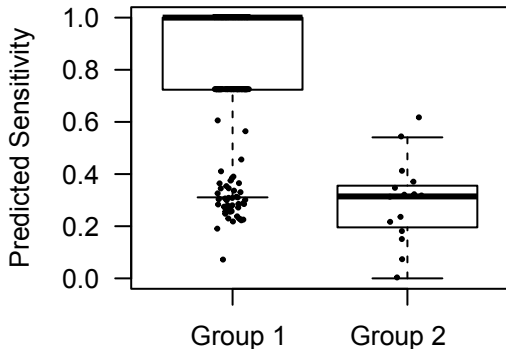
A

$p < 0.0001$

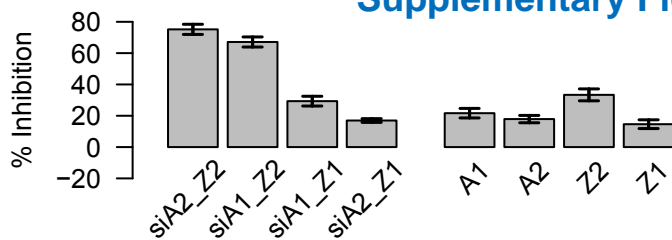


B

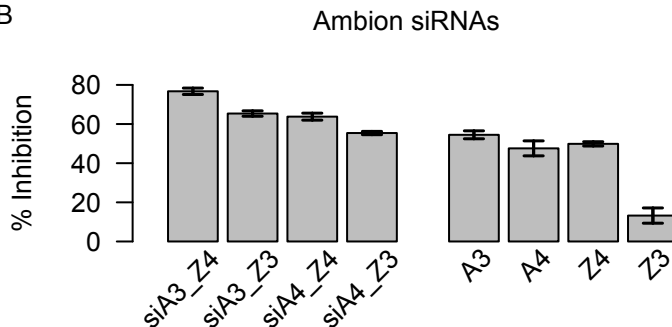
$p < 0.0001$



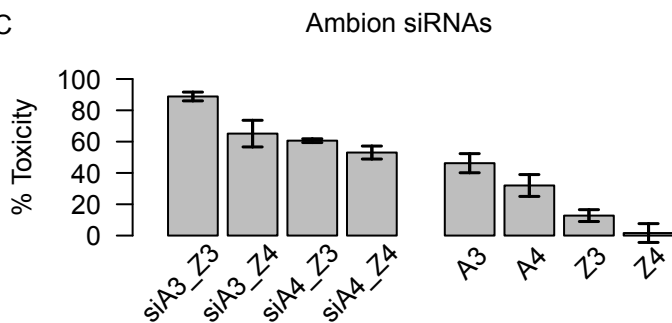
A



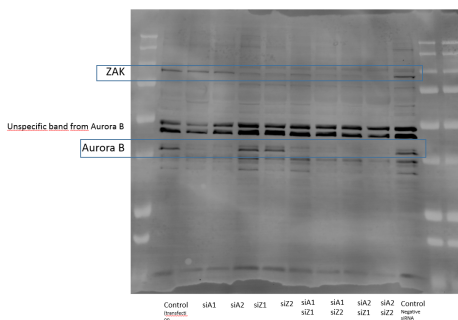
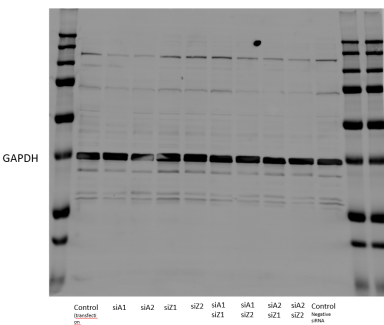
B



C

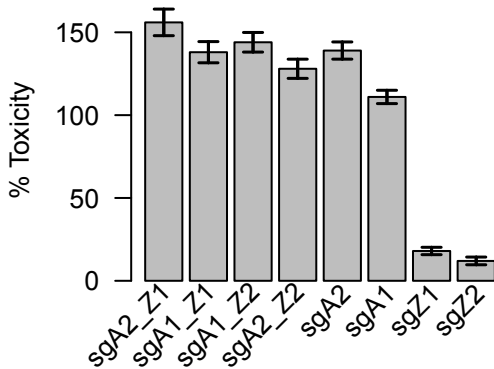
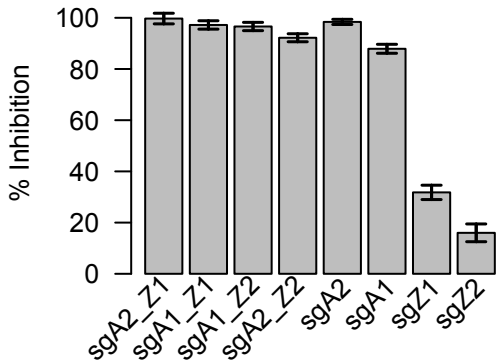


D



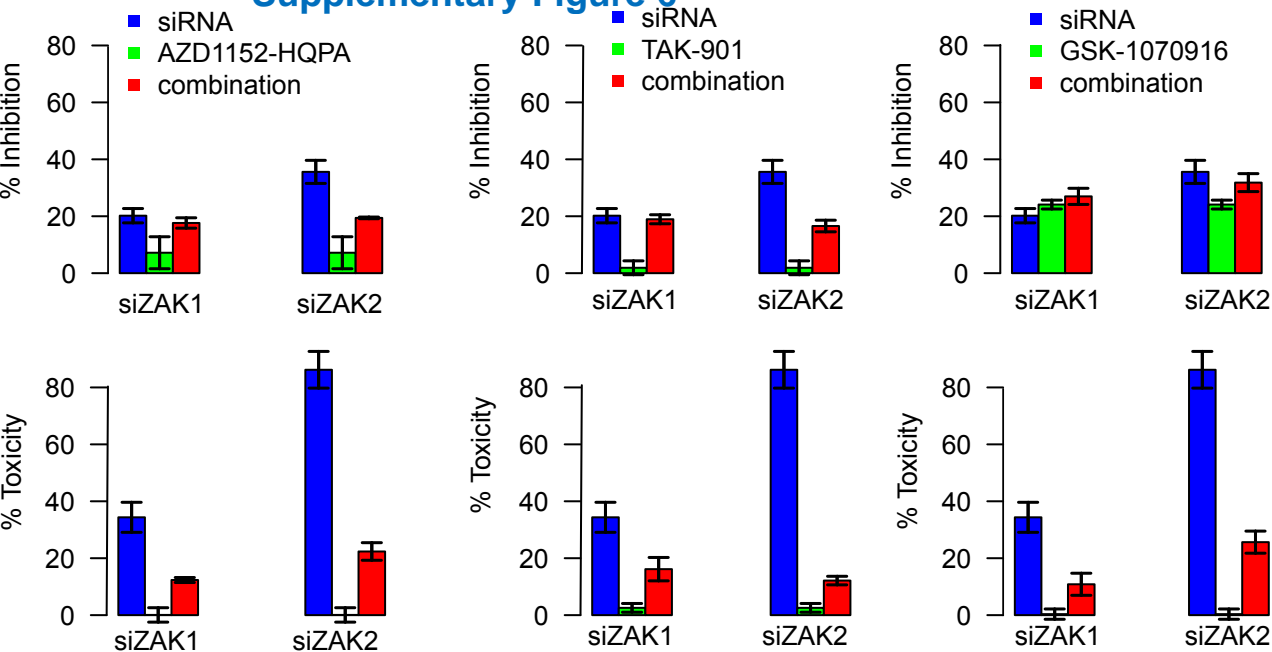


## Supplementary Figure 5

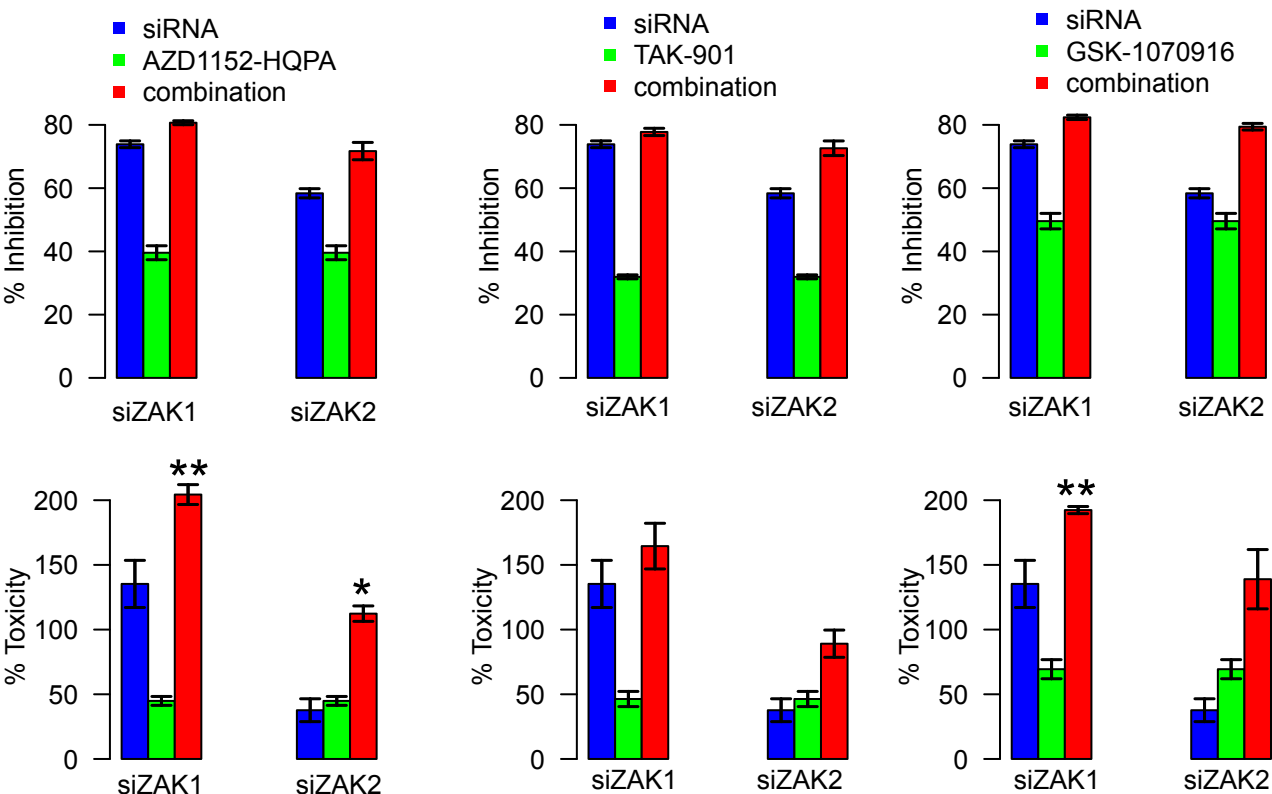


A MDA-MB-361

## Supplementary Figure 6

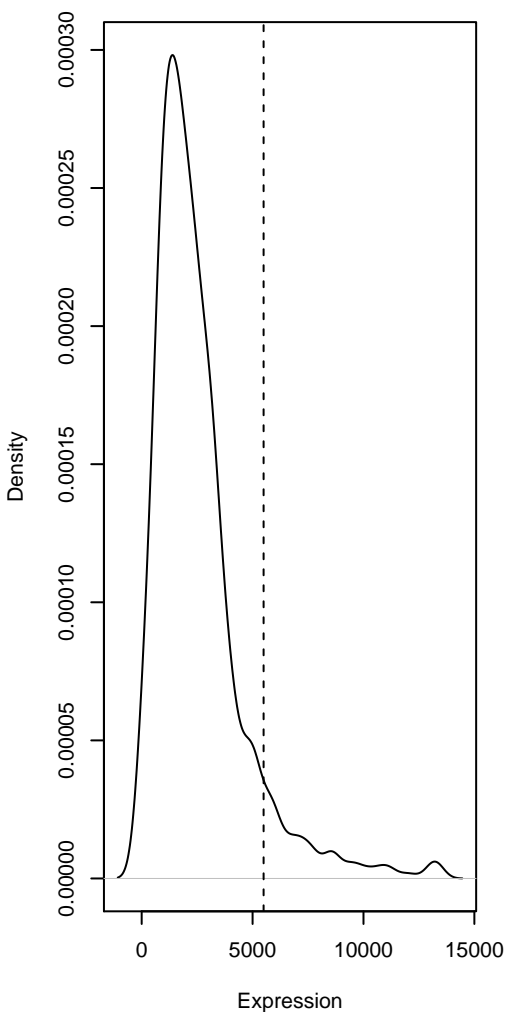


B MDA-MB-436

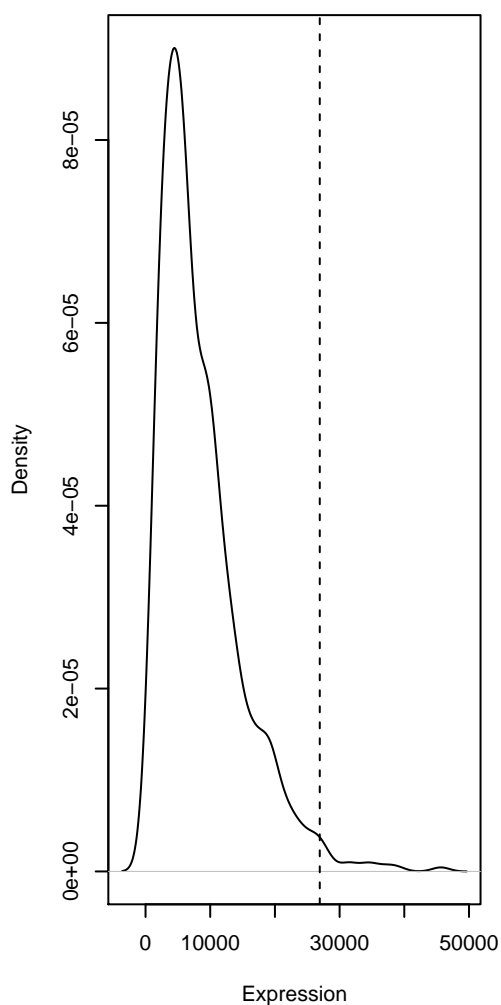


# Supplementary Figure 7

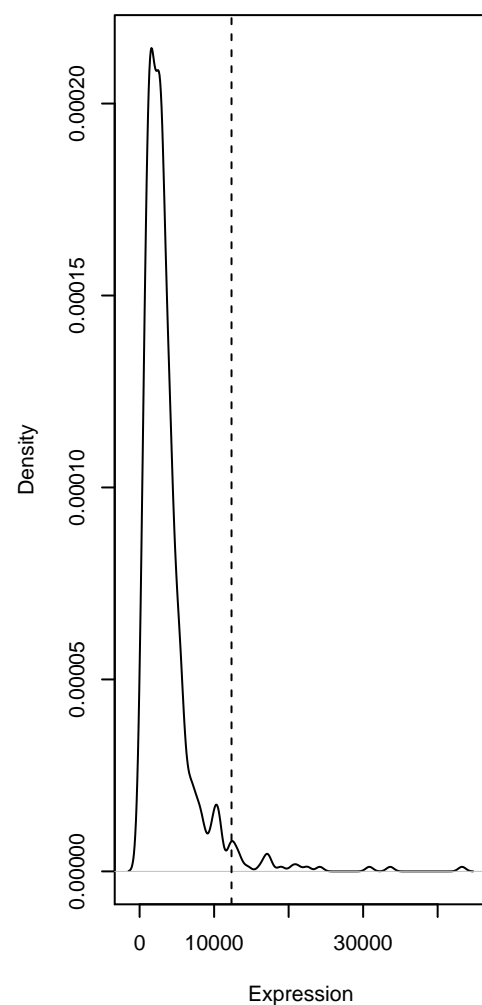
**PTEN, D= 1.16, t-test p-val< 0.01**



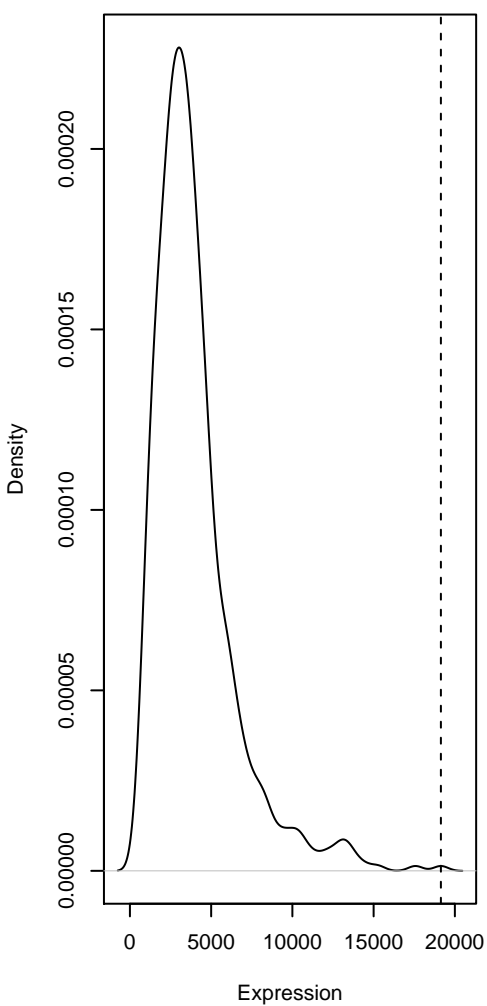
**PKN1, D= 2.16, t-test p-val< 0.01**



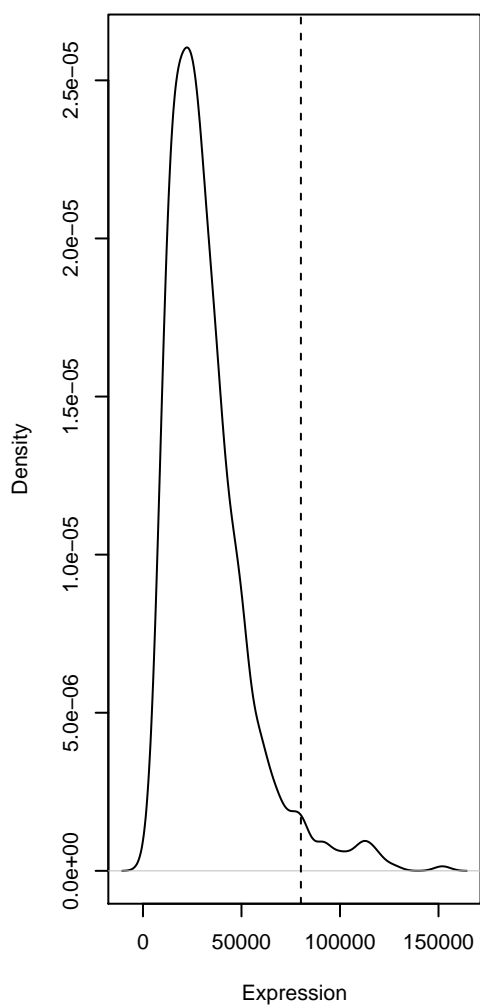
**TGFBR1, D= 2.4, t-test p-val< 0.01**



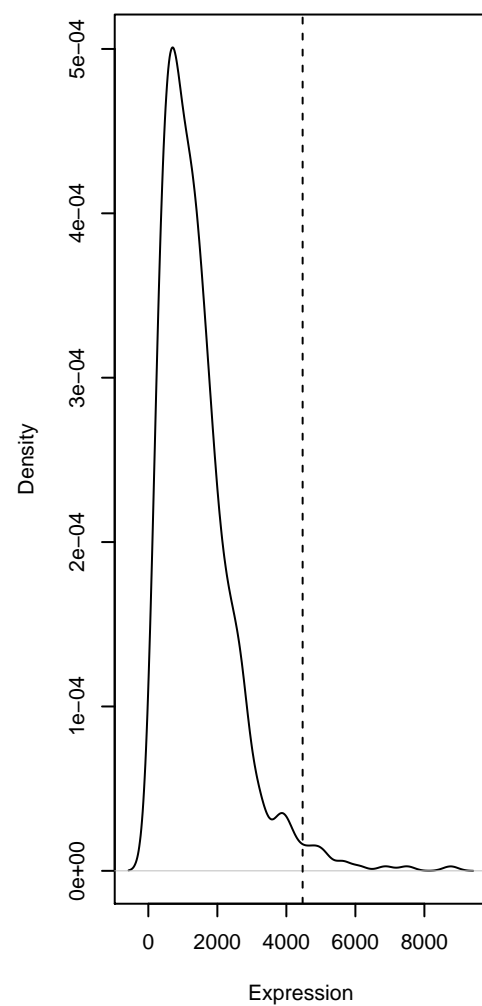
**MAPK14, D= 3.83, t-test p-val< 0.01**



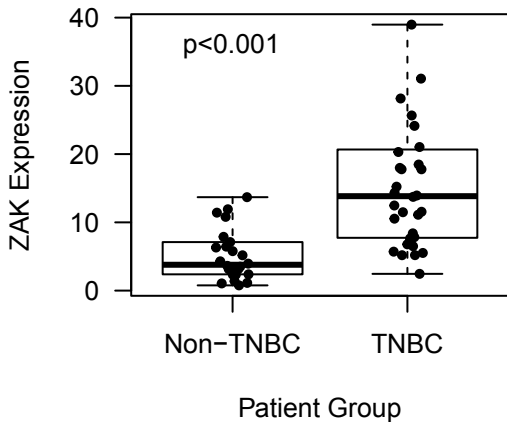
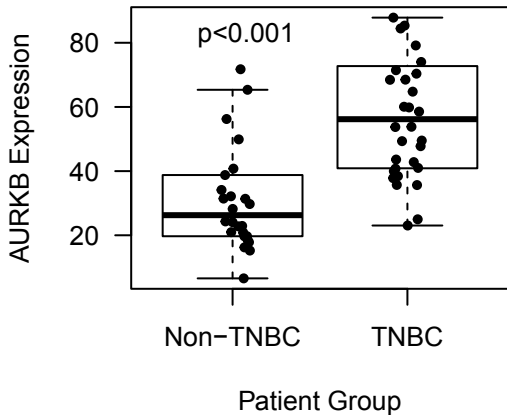
**YWHAZ, D= 1.45, t-test p-val< 0.01**



**BAD, D= 2.13, t-test p-val< 0.01**



## Supplementary Figure 8



# Supplementary Figure 9

Overall survival

