Mathematical models of metabolism from bacterial systems biology have proven their utility across multiple fields, for example metabolic engineering, growth phenotype simulation, and biological discovery. The usefulness of the models stems from their ability to compute a link between genotype and phenotype, but their ability to accurately simulate gene-gene interactions has not been investigated extensively. Here we assess how accurately a metabolic model for Escherichia coli computes one particular type of gene-gene interaction, synthetic lethality, and find that the accuracy rate is between 25% and 43%. The most common failure modes were incorrect computation of single gene essentiality and biological information that was missing from the model. Moreover, we performed virtual and biological screening against several synthetic lethal pairs to explore whether two-compound formulations could be found that inhibit the growth of Gram-negative bacteria. One set of molecules was identified that, depending on the concentrations, inhibits E. coli and S. enterica serovar Typhimurium in an additive or antagonistic manner. These findings pinpoint specific ways in which to improve the predictive ability of metabolic models, and highlight one potential application of systems biology to drug discovery and translational medicine.