ESI 1 – Supplementary text file to Results and Discussions. The global analysis of the genome-wide transcriptome data is discussed in the text focusing on the effect of nutritional conditions on determining the transcriptional and metabolic response of the deletion mutants and the deletion- and nutrition-specific changes observed at the transcriptional level to reveal how yeast adjusts to cope with the loss of its drug resistance genes.

ESI 2 – Processed and log-normalized gene expression data for *qdr3Δ/qdr3Δ*, *hoΔ/hoΔ,* and *pdr3Δ/pdr3Δ* diploid deletants grown under ammonium or glucose limitation. The processed and log2-normalized expression data, the relative expression changes with respect to the reference mutant (*hoΔ/hoΔ,*), the list of genes with a significant change in their expression levels, the list of transcription factors among the genes with a significant change in their expression levels and the Gene Ontology enrichment of up- or down-regulated genes in the absence of either *QDR3* or *PDR3* are provided in separate tabs.

ESI 3 – Reporter transcription factor analysis for *qdr3Δ/qdr3Δ* and *pdr3Δ/pdr3Δ* deletants under ammonium or glucose limitation. The z-score calculations for *qdr3Δ/qdr3Δ* and *pdr3Δ/pdr3Δ*, the list of genes with a significant change in their expression levels, the perturbation responsive sub-networks for *qdr3Δ/qdr3Δ* and *pdr3Δ/pdr3Δ,* and the Gene Ontology enrichment categories for the perturbation-responsive sub-networks for *qdr3Δ/qdr3Δ* and *pdr3Δ/pdr3Δ* are provided in separate tabs.

ESI 4 – Endo- and Exo-metabolome data for *qdr3Δ/qdr3Δ, hoΔ/hoΔ,* and *pdr3Δ/pdr3Δ* under ammonium or glucose limitation. The control peak-normalized area ratios are provided for the chemical compounds identified with the highest probability for both the exometabolome and endometabolome.

ESI 5 – *In silico* flux distributions for *qdr3Δ/qdr3Δ, hoΔ/hoΔ,* and *pdr3Δ/pdr3Δ* deletants under ammonium or glucose limitation. Glucose and ammonium uptake, the biomass, and glycerol secretion were used as constraints in determining the optimal solution space. Ethanol production and secretion were optimized in ammonium-limited cultures, whereas oxygen uptake was optimized in glucose-limited cultures.

ESI 6 – Phenotype screens carried out for the mutants; *qdr3Δ/qdr3Δ, hoΔ/hoΔ,* and *pdr3Δ/pdr3Δ* and drug screens carried out for *hoΔ/hoΔ* and *gpd1Δ/gpd1Δ*. The growth phenotype of *qdr3Δ/qdr3Δ, hoΔ/hoΔ,* and *pdr3Δ/pdr3Δ* were recorded in the presence of strong/weak acids and bases, the salts of these acids and bases, as well as sorbitol and glycerol as osmotic stress inducers. The screens were also carried out in the presence of cobalt, selenium, excess iron, copper, zinc or magnesium or in the absence of these metal ions using glucose of glycerol as the sole carbon source.

The *hoΔ/ho,* and *gpd1Δ/gpd1Δ* mutants were screened in the presence of bleomycin, barban, cisplatin or quinidine under glucose or ammonium limitation in synthetic defined medium.