

## Electronic Supplementary Information

Transcriptomic analysis of thermotolerant yeast *Kluyveromyces marxianus* in multiple  
inhibitors tolerance

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**Table S1 Summary of mapping results from RNA-seq of *K. marxianus***

Sample	Clean reads	Clean base (bp)	> Q20 (%)	> Q30 (%)	GC (%)	Uniquely Mapping reads	Mapping rate (%)
I	13,622,794	2.44E+09	97.68	92.79	44.57	12,490,287	91.69
C	17,697,296	1.89E+09	97.31	91.87	46.27	16,279,803	91.99

Note: I and C represent samples of yeast grown on medium with or without multiple fermentation inhibitors in YPD under aerobic condition. Q20, Q30 refer to the proportion of base calls with Phred scores >20 or 30 in the total bases.

**Table S2 Summary of differentially expressed genes involved in GO enrichments in multiple inhibitors treated condition.**

ID	Description	DEGs in study	Background	Ratio in background	Number up	Number down
GO:0006096	glycolytic process	16	26	0.62	2	14
GO:0032787	monocarboxylic acid metabolic process	40	90	0.44	13	27
GO:0006090	pyruvate metabolic process	22	42	0.52	6	16
GO:0006094	gluconeogenesis	17	31	0.55	3	14
GO:0006091	generation of precursor metabolites and energy	27	71	0.38	11	16
GO:0055114	oxidation-reduction process	69	304	0.23	33	36
GO:0016491	oxidoreductase activity	65	286	0.23	36	29
GO:0043436	oxoacid metabolic process	77	394	0.20	26	51
GO:0006082	organic acid metabolic process	77	395	0.19	26	51
GO:0019319	hexose biosynthetic process	17	32	0.53	3	14
GO:0046364	monosaccharide biosynthetic process	17	32	0.53	3	14
GO:0044281	small molecule metabolic process	115	689	0.17	42	73
GO:0019752	carboxylic acid metabolic process	77	393	0.20	26	51
GO:0044763	single-organism cellular process	184	1329	0.14	89	95
GO:0044710	single-organism metabolic process	171	1138	0.15	80	91
GO:0006099	tricarboxylic acid cycle	16	29	0.55	16	0
GO:0044699	single-organism process	220	1602	0.14	113	107
GO:0044711	single-organism biosynthetic process	64	344	0.19	12	52
GO:0006006	glucose metabolic process	18	43	0.42	3	15
GO:0003824	catalytic activity	212	1754	0.12	112	100
GO:1901564	organonitrogen compound metabolic process	98	641	0.15	34	64
GO:0016051	carbohydrate biosynthetic process	18	47	0.38	3	15
GO:0044724	single-organism carbohydrate catabolic process	17	43	0.40	2	15
GO:0016614	oxidoreductase activity, acting on CH-OH group of donors	18	51	0.35	9	9

GO:0016052	carbohydrate catabolic process	17	47	0.36	2	15
GO:0019318	hexose metabolic process	19	58	0.33	4	15
GO:0016616	oxidoreductase activity, acting on the CH-OH group of donors, NAD or NADP as acceptor	17	48	0.35	8	9
GO:0005996	monosaccharide metabolic process	19	60	0.32	4	15
GO:0008152	metabolic process	243	2176	0.11	126	117
GO:0044262	cellular carbohydrate metabolic process	17	50	0.34	7	10
GO:0055085	transmembrane transport	49	269	0.18	35	14
GO:0048037	cofactor binding	31	138	0.22	16	15
GO:0009987	cellular process	230	2047	0.11	118	112
GO:1990204	oxidoreductase complex	10	20	0.50	10	0
GO:0051186	cofactor metabolic process	27	118	0.23	7	20
GO:0015976	carbon utilization	8	13	0.62	4	4
GO:0046487	glyoxylate metabolic process	8	13	0.62	6	2
GO:0005975	carbohydrate metabolic process	35	178	0.20	14	21
GO:1901576	organic substance biosynthetic process	84	599	0.14	18	66
GO:0044712	single-organism catabolic process	39	214	0.18	11	28
GO:0009058	biosynthetic process	86	626	0.14	19	67
GO:0006732	coenzyme metabolic process	22	93	0.24	5	17
GO:0044723	single-organism carbohydrate metabolic process	27	128	0.21	9	18
GO:0003674	molecular_function	291	2817	0.10	166	125
GO:0044237	cellular metabolic process	181	1595	0.11	82	99
GO:1901566	organonitrogen compound biosynthetic process	39	223	0.17	8	31
GO:0051287	NAD binding	9	21	0.43	4	5
GO:0006081	cellular aldehyde metabolic process	9	21	0.43	6	3
GO:1901070	guanosine-containing compound biosynthetic process	4	4	1.00	1	3
GO:0008150	biological_process	314	3115	0.10	180	134
GO:0044283	small molecule biosynthetic process	33	185	0.18	5	28

GO:0050662	coenzyme binding	20	91	0.22	10	10
GO:0071704	organic substance metabolic process	186	1677	0.11	81	105
GO:0006740	NADPH regeneration	8	19	0.42	1	7
GO:0006007	glucose catabolic process	8	19	0.42	1	7
GO:0019320	hexose catabolic process	8	19	0.42	1	7
GO:0006098	pentose-phosphate shunt	8	19	0.42	1	7
GO:0006753	nucleoside phosphate metabolic process	37	222	0.17	14	23
GO:0005985	sucrose metabolic process	7	15	0.47	3	4
GO:0005982	starch metabolic process	7	15	0.47	3	4
GO:0043169	cation binding	73	543	0.13	41	32
GO:0043167	ion binding	132	1127	0.12	73	59
GO:0009117	nucleotide metabolic process	36	218	0.17	13	23
GO:0046872	metal ion binding	72	539	0.13	40	32
GO:0006000	fructose metabolic process	7	16	0.44	2	5
GO:0006013	mannose metabolic process	7	16	0.44	2	5
GO:0006739	NADP metabolic process	8	21	0.38	1	7
GO:0046365	monosaccharide catabolic process	8	21	0.38	1	7
GO:0009152	purine ribonucleotide biosynthetic process	10	32	0.31	3	7
GO:0006164	purine nucleotide biosynthetic process	10	32	0.31	3	7
GO:0046496	nicotinamide nucleotide metabolic process	9	27	0.33	2	7
GO:0005984	disaccharide metabolic process	7	17	0.41	3	4
GO:0009063	cellular amino acid catabolic process	8	22	0.36	3	5
GO:0009260	ribonucleotide biosynthetic process	11	40	0.28	3	8
GO:0046912	transferase activity, transferring acyl groups, acyl groups converted into alkyl on transfer	5	9	0.56	2	3
GO:0006790	sulfur compound metabolic process	15	67	0.22	3	12
GO:0009168	purine ribonucleoside monophosphate biosynthetic process	9	29	0.31	2	7
GO:0009127	purine nucleoside monophosphate biosynthetic process	9	29	0.31	2	7

GO:0000287	magnesium ion binding	11	41	0.27	3	8
GO:0046390	ribose phosphate biosynthetic process	11	41	0.27	3	8
GO:0046037	GMP metabolic process	3	3	1.00	0	3
GO:0004365	glyceraldehyde-3-phosphate dehydrogenase (NAD+) (phosphorylating) activity	3	3	1.00	1	2
GO:0006177	GMP biosynthetic process	3	3	1.00	0	3
GO:0046395	carboxylic acid catabolic process	8	24	0.33	3	5
GO:0016054	organic acid catabolic process	8	24	0.33	3	5
GO:0072522	purine-containing compound biosynthetic process	10	36	0.28	3	7
GO:0006144	purine nucleobase metabolic process	16	77	0.21	4	12
GO:0006733	oxidoreduction coenzyme metabolic process	10	37	0.27	2	8
GO:0019362	pyridine nucleotide metabolic process	9	31	0.29	2	7
GO:0055086	nucleobase-containing small molecule metabolic process	41	281	0.15	16	25
GO:0006073	cellular glucan metabolic process	7	20	0.35	3	4
GO:1901606	alpha-amino acid catabolic process	7	20	0.35	3	4
GO:0009311	oligosaccharide metabolic process	7	20	0.35	3	4
GO:0044042	glucan metabolic process	7	20	0.35	3	4
GO:0072524	pyridine-containing compound metabolic process	10	38	0.26	2	8
GO:0005829	cytosol	8	26	0.31	4	4
GO:0009167	purine ribonucleoside monophosphate metabolic process	21	117	0.18	10	11
GO:0009126	purine nucleoside monophosphate metabolic process	21	117	0.18	10	11
GO:0008483	transaminase activity	7	21	0.33	3	4
GO:0044264	cellular polysaccharide metabolic process	7	21	0.33	3	4
GO:0005976	polysaccharide metabolic process	7	21	0.33	3	4

GO:0016769	transferase activity, transferring nitrogenous groups	7	21	0.33	3	4
GO:0044765	single-organism transport	53	394	0.13	37	16
GO:0045275	respiratory chain complex III	4	7	0.57	3	0
GO:0006553	lysine metabolic process	6	16	0.38	2	4
GO:0072330	monocarboxylic acid biosynthetic process	8	27	0.30	1	7
GO:0051188	cofactor biosynthetic process	14	67	0.21	5	9
GO:0046394	carboxylic acid biosynthetic process	25	151	0.17	4	21
GO:0016053	organic acid biosynthetic process	25	151	0.17	4	21
GO:0009156	ribonucleoside monophosphate biosynthetic process	10	40	0.25	2	8
GO:0044238	primary metabolic process ribonucleoside	171	1604	0.11	79	92
GO:0009161	monophosphate metabolic process	22	128	0.17	10	12
GO:0006520	cellular amino acid metabolic process	45	325	0.14	14	31
GO:0009123	nucleoside monophosphate metabolic process	22	130	0.17	10	12
GO:0004022	alcohol dehydrogenase (NAD) activity	3	4	0.75	2	1
GO:1901659	glycosyl compound biosynthetic process	9	35	0.26	3	6
GO:0009081	branched-chain amino acid metabolic process	7	23	0.30	0	7
GO:0044282	small molecule catabolic process	8	29	0.28	3	5
GO:0070013	intracellular organelle lumen	8	29	0.28	8	0
GO:0043233	organelle lumen	8	29	0.28	8	0
GO:0019637	organophosphate metabolic process	41	294	0.14	15	26
GO:0009124	nucleoside monophosphate biosynthetic process	10	42	0.24	2	8
GO:0009066	aspartate family amino acid metabolic process	15	77	0.19	3	12
GO:0006119	oxidative phosphorylation	6	18	0.33	5	1
GO:0016209	antioxidant activity	6	18	0.33	4	2

GO:0051539	4 iron, 4 sulfur cluster binding	5	13	0.38	3	2
GO:0016021	integral component of membrane	60	479	0.13	41	19
GO:0044425	membrane part	74	617	0.12	51	23
GO:0006793	phosphorus metabolic process	61	487	0.13	24	37
GO:0009112	nucleobase metabolic process	17	93	0.18	4	13
GO:0046129	purine ribonucleoside biosynthetic process	7	25	0.28	3	4
GO:0042451	purine nucleoside biosynthetic process	7	25	0.28	3	4
GO:0031974	membrane-enclosed lumen	9	38	0.24	9	0
GO:1901362	organic cyclic compound biosynthetic process	34	240	0.14	9	25
GO:0034614	cellular response to reactive oxygen species	4	9	0.44	2	2
GO:0022857	transmembrane transporter activity	28	188	0.15	19	9
GO:0020037	heme binding	8	32	0.25	1	7
GO:0046906	tetrapyrrole binding	8	32	0.25	1	7
GO:0009163	nucleoside biosynthetic process	8	32	0.25	3	5
GO:0042455	ribonucleoside biosynthetic process	8	32	0.25	3	5
GO:0009056	catabolic process	42	315	0.13	13	29
GO:0043604	amide biosynthetic process	7	26	0.27	1	6
GO:0005215	transporter activity	33	232	0.14	23	10
GO:0042723	thiamine-containing compound metabolic process	3	5	0.60	0	3
GO:1990351	transporter complex	3	5	0.60	3	0
GO:0030976	thiamine pyrophosphate binding	3	5	0.60	2	1
GO:0006772	thiamine metabolic process	3	5	0.60	0	3
GO:0070469	respiratory chain	3	5	0.60	3	0
GO:1902495	transmembrane transporter complex	3	5	0.60	3	0
GO:0044249	cellular biosynthetic process	69	573	0.12	15	54
GO:0016836	hydro-lyase activity	6	20	0.30	4	2
GO:0006796	phosphate-containing compound metabolic process	59	479	0.12	23	36



GO:1901605	alpha-amino acid metabolic process	39	289	0.13	11	28
GO:0006066	alcohol metabolic process	7	27	0.26	0	7
GO:0009108	coenzyme biosynthetic process	11	55	0.20	3	8
GO:0004449	isocitrate dehydrogenase (NAD+) activity	2	2	1.00	2	0
GO:0003872	6-phosphofructokinase activity	2	2	1.00	0	2
GO:0006002	fructose 6-phosphate metabolic process	2	2	1.00	0	2
GO:0016801	hydrolase activity, acting on ether bonds	2	2	1.00	0	2
GO:0016805	dipeptidase activity	2	2	1.00	0	2
GO:0070283	radical SAM enzyme activity	2	2	1.00	1	1
GO:1903289	regulation of ATP catabolic process	2	2	1.00	2	0
GO:0004410	homocitrate synthase activity	2	2	1.00	0	2
GO:0043171	peptide catabolic process	2	2	1.00	0	2
GO:0006510	ATP-dependent proteolysis	2	2	1.00	2	0
GO:0004176	ATP-dependent peptidase activity	2	2	1.00	2	0
GO:0004347	glucose-6-phosphate isomerase activity	2	2	1.00	0	2
GO:0032781	positive regulation of ATPase activity	2	2	1.00	2	0
GO:0003938	IMP dehydrogenase activity	2	2	1.00	0	2
GO:0001671	ATPase activator activity	2	2	1.00	2	0
GO:0043462	regulation of ATPase activity	2	2	1.00	2	0
GO:0005945	6-phosphofructokinase complex	2	2	1.00	0	2
GO:0006633	fatty acid biosynthetic process	6	21	0.29	1	5
GO:0016765	transferase activity, transferring alkyl or aryl (other than methyl) groups	6	21	0.29	1	5
GO:0044445	cytosolic part	6	21	0.29	0	6
GO:1901615	organic hydroxy compound metabolic process	8	34	0.24	0	8
GO:0009110	vitamin biosynthetic process	9	41	0.22	1	8
GO:0042364	water-soluble vitamin	9	41	0.22	1	8

	biosynthetic process					
GO:0030170	pyridoxal phosphate binding	9	41	0.22	4	5
GO:0072593	reactive oxygen species metabolic process	4	10	0.40	2	2
GO:0008299	isoprenoid biosynthetic process	4	10	0.40	0	4
GO:0000302	response to reactive oxygen species	4	10	0.40	2	2
GO:1901701	cellular response to oxygen- containing compound	4	10	0.40	2	2
GO:0006720	isoprenoid metabolic process	4	10	0.40	0	4
GO:0016684	oxidoreductase activity, acting on peroxide as acceptor	4	10	0.40	2	2
GO:0019751	polyol metabolic process	4	10	0.40	0	4
GO:0044271	cellular nitrogen compound biosynthetic process	32	230	0.14	9	23
GO:0006631	fatty acid metabolic process	7	28	0.25	1	6
GO:0051536	iron-sulfur cluster binding	7	28	0.25	5	2
GO:0051540	metal cluster binding	7	28	0.25	5	2
GO:0006766	vitamin metabolic process	12	61	0.20	2	10
GO:0006767	water-soluble vitamin metabolic process	12	61	0.20	2	10
GO:0022891	substrate-specific transmembrane transporter activity	24	159	0.15	15	9
GO:0042221	response to chemical	8	35	0.23	5	3
GO:1901575	organic substance catabolic process	38	287	0.13	11	27
GO:0050661	NADP binding	6	22	0.27	1	5
GO:0016903	oxidoreductase activity, acting on the aldehyde or oxo group of donors	6	22	0.27	3	3
GO:0006163	purine nucleotide metabolic process	24	163	0.15	11	13
GO:0072521	purine-containing compound metabolic process	31	225	0.14	14	17
GO:0019878	lysine biosynthetic process via aminoadipic acid	3	6	0.50	0	3
GO:0045239	tricarboxylic acid cycle enzyme complex	3	6	0.50	3	0
GO:0051087	chaperone binding	3	6	0.50	3	0
GO:1901681	sulfur compound binding	3	6	0.50	2	1

GO:1901700	response to oxygen-containing compound	4	11	0.36	2	2
GO:0009085	lysine biosynthetic process	4	11	0.36	0	4
GO:0010035	response to inorganic substance	4	11	0.36	2	2
GO:0006694	steroid biosynthetic process	5	17	0.29	0	5
GO:0016620	oxidoreductase activity, acting on the aldehyde or oxo group of donors, NAD or NADP as acceptor	5	17	0.29	2	3
GO:0006807	nitrogen compound metabolic process	115	1071	0.11	47	68
GO:0016835	carbon-oxygen lyase activity	6	24	0.25	4	2
GO:0005759	mitochondrial matrix	6	24	0.25	6	0
GO:0009165	nucleotide biosynthetic process	11	58	0.19	3	8
GO:0034599	cellular response to oxidative stress	5	18	0.28	3	2
GO:0008202	steroid metabolic process	5	18	0.28	0	5
GO:1901293	nucleoside phosphate biosynthetic process	11	60	0.18	3	8
GO:0031072	heat shock protein binding	3	7	0.43	3	0
GO:0044272	sulfur compound biosynthetic process	8	39	0.21	2	6
GO:0009259	ribonucleotide metabolic process	24	170	0.14	11	13
GO:0008643	carbohydrate transport	6	25	0.24	4	2
GO:0005739	mitochondrion	16	101	0.16	11	5
GO:0019693	ribose phosphate metabolic process	24	172	0.14	11	13
GO:0016829	lyase activity	11	62	0.18	7	4
GO:0072528	pyrimidine-containing compound biosynthetic process	5	19	0.26	1	4
GO:0006551	leucine metabolic process	5	19	0.26	0	5
GO:0016310	phosphorylation	27	200	0.14	13	14
GO:0009266	response to temperature stimulus	2	3	0.67	2	0
GO:0016635	oxidoreductase activity, acting on the CH-CH group of donors, quinone or related compound as acceptor	2	3	0.67	1	1
GO:0060590	ATPase regulator activity	2	3	0.67	2	0
GO:0004888	transmembrane signaling	2	3	0.67	2	0

	receptor activity					
GO:0003984	acetolactate synthase activity	2	3	0.67	0	2
GO:0045252	oxoglutarate dehydrogenase complex	2	3	0.67	2	0
GO:0004096	catalase activity	2	3	0.67	0	2
GO:0003994	aconitate hydratase activity	2	3	0.67	2	0
GO:0045281	succinate dehydrogenase complex	2	3	0.67	2	0
GO:0045240	dihydrolipoyl dehydrogenase complex	2	3	0.67	2	0
GO:0042744	hydrogen peroxide catabolic process	2	3	0.67	0	2
GO:0009408	response to heat	2	3	0.67	2	0
GO:0009083	branched-chain amino acid catabolic process	2	3	0.67	0	2
GO:0000104	succinate dehydrogenase activity	2	3	0.67	2	0
GO:0008612	peptidyl-lysine modification to peptidyl-hypusine	2	3	0.67	0	2
GO:0005750	mitochondrial respiratory chain complex III	2	3	0.67	2	0
GO:0004488	methylenetetrahydrofolate dehydrogenase (NADP+) activity	2	3	0.67	0	2
GO:0006097	glyoxylate cycle	2	3	0.67	2	0
GO:0006552	leucine catabolic process	2	3	0.67	0	2
GO:0005948	acetolactate synthase complex	2	3	0.67	0	2
GO:0016860	intramolecular oxidoreductase activity	4	13	0.31	1	3
GO:0042398	cellular modified amino acid biosynthetic process	7	33	0.21	1	6
GO:0070887	cellular response to chemical stimulus	6	26	0.23	4	2
GO:0009150	purine ribonucleotide metabolic process	23	162	0.14	11	12
GO:0005506	iron ion binding	7	34	0.21	2	5
GO:0009082	branched-chain amino acid biosynthetic process	5	20	0.25	0	5
GO:0008204	ergosterol metabolic process	3	8	0.38	0	3
GO:0004659	prenyltransferase activity	3	8	0.38	0	3
GO:0051537	2 iron, 2 sulfur cluster binding	3	8	0.38	2	1

GO:0016776	phosphotransferase activity, phosphate group as acceptor	3	8	0.38	1	2
GO:0016128	phytosteroid metabolic process	3	8	0.38	0	3
GO:0016129	phytosteroid biosynthetic process	3	8	0.38	0	3
GO:0019842	vitamin binding	3	8	0.38	2	1
GO:0006696	ergosterol biosynthetic process	3	8	0.38	0	3
GO:0006189	'de novo' IMP biosynthetic process	3	8	0.38	0	3
GO:0006541	glutamine metabolic process	3	8	0.38	0	3
GO:0044107	cellular alcohol metabolic process	3	8	0.38	0	3
GO:0044108	cellular alcohol biosynthetic process	3	8	0.38	0	3
GO:0019643	reductive tricarboxylic acid cycle	4	14	0.29	4	0
GO:0015977	carbon fixation	4	14	0.29	4	0
GO:0018130	heterocycle biosynthetic process	29	223	0.13	9	20
GO:0022892	substrate-specific transporter activity	24	177	0.14	15	9
GO:0008238	exopeptidase activity	6	28	0.21	2	4
GO:0051082	unfolded protein binding	6	28	0.21	6	0
GO:1901617	organic hydroxy compound biosynthetic process	5	21	0.24	0	5
GO:0006549	isoleucine metabolic process	5	21	0.24	0	5
GO:1901137	carbohydrate derivative biosynthetic process	12	74	0.16	3	9
GO:0006457	protein folding	9	49	0.18	8	1
GO:0046165	alcohol biosynthetic process	4	15	0.27	0	4
GO:0004497	monooxygenase activity	4	15	0.27	0	4
GO:0008652	cellular amino acid biosynthetic process	18	126	0.14	3	15
GO:0046040	IMP metabolic process	3	9	0.33	0	3
GO:0006730	one-carbon metabolic process	3	9	0.33	1	2
GO:0006188	IMP biosynthetic process	3	9	0.33	0	3
GO:0016861	intramolecular oxidoreductase activity, interconverting aldoses and ketoses	3	9	0.33	0	3
GO:0006575	cellular modified amino acid	9	50	0.18	1	8

	metabolic process					
GO:0030554	adenyl nucleotide binding	53	462	0.11	30	23
GO:0016830	carbon-carbon lyase activity	5	22	0.23	3	2
GO:0036094	small molecule binding	78	718	0.11	39	39
GO:0006020	inositol metabolic process	2	4	0.50	0	2
	thiamine-containing					
GO:0042724	compound biosynthetic process	2	4	0.50	0	2
GO:0004448	isocitrate dehydrogenase activity	2	4	0.50	2	0
GO:0043446	cellular alkane metabolic process	2	4	0.50	0	2
GO:0006108	malate metabolic process	2	4	0.50	2	0
GO:0016615	malate dehydrogenase activity	2	4	0.50	2	0
GO:0009228	thiamine biosynthetic process	2	4	0.50	0	2
GO:0015947	methane metabolic process	2	4	0.50	0	2
GO:0004784	superoxide dismutase activity	2	4	0.50	2	0
GO:0042743	hydrogen peroxide metabolic process	2	4	0.50	0	2
	oxidoreductase activity,					
GO:0016721	acting on superoxide radicals as acceptor	2	4	0.50	2	0
GO:0008144	drug binding	2	4	0.50	0	2
GO:0018065	protein-cofactor linkage	2	4	0.50	2	0
GO:0016114	terpenoid biosynthetic process	2	4	0.50	0	2
	misfolded or incompletely synthesized protein catabolic process					
GO:0006515	synthesized protein catabolic process	2	4	0.50	2	0
GO:0006721	terpenoid metabolic process	2	4	0.50	0	2
GO:0008121	ubiquinol-cytochrome-c reductase activity	2	4	0.50	2	0
	oxidoreductase activity,					
GO:0016681	acting on diphenols and related substances as donors, cytochrome as acceptor	2	4	0.50	2	0
	oxidoreductase activity,					
GO:0016679	acting on diphenols and related substances as donors	2	4	0.50	2	0
GO:0009071	serine family amino acid catabolic process	2	4	0.50	0	2

GO:0070301	cellular response to hydrogen peroxide	2	4	0.50	0	2
GO:0006546	glycine catabolic process	2	4	0.50	0	2
GO:0006563	L-serine metabolic process	6	30	0.20	1	5
GO:0043603	cellular amide metabolic process	9	52	0.17	1	8
GO:0005737	cytoplasm	33	266	0.12	8	25
GO:0015940	pantothenate biosynthetic process	4	16	0.25	1	3
GO:0015939	pantothenate metabolic process	4	16	0.25	1	3
GO:0016740	transferase activity	67	607	0.11	30	37
GO:0006950	response to stress	22	164	0.13	19	3

Note: Ratio in background represents the ratio of DEGs in the specific GO categories (background genes). Number up or down represent the number of DEG up- or down-regulated in response to the multiple inhibitors stress.

**Table S3 Summary of differentially expressed genes involved in KEGG pathways in multiple inhibitors treated condition.**

ID	Term	DEGs	Background genes	DEGs/background genes
ko01220	Degradation of aromatic compounds	4	6	0.667
ko00830	Retinol metabolism	3	5	0.600
ko00983	Drug metabolism - other enzymes	4	7	0.571
ko00010	Glycolysis / Gluconeogenesis	25	44	0.568
ko00680	Methane metabolism	11	20	0.550
ko00710	Carbon fixation in photosynthetic organisms	9	17	0.529
ko00020	Citrate cycle (TCA cycle)	14	28	0.500
ko00630	Glyoxylate and dicarboxylate metabolism	10	20	0.500
ko00130	Ubiquinone and other terpenoid-quinone biosynthesis	5	10	0.500
ko00625	Chloroalkane and chloroalkene degradation	4	8	0.500
ko00626	Naphthalene degradation	3	6	0.500
ko00300	Lysine biosynthesis	6	13	0.462
ko01200	Carbon metabolism	42	92	0.457
ko01210	2-Oxocarboxylic acid metabolism	15	35	0.429
ko00730	Thiamine metabolism	3	7	0.429
ko04626	Plant-pathogen interaction	2	5	0.400
ko04612	Antigen processing and presentation	2	5	0.400
ko04621	NOD-like receptor signaling pathway	2	5	0.400
ko00950	Isoquinoline alkaloid biosynthesis	2	5	0.400
ko00521	Streptomycin biosynthesis	2	5	0.400
ko00030	Pentose phosphate pathway	9	23	0.391
ko00500	Starch and sucrose metabolism	12	31	0.387
ko00052	Galactose metabolism	5	13	0.385
ko00380	Tryptophan metabolism	6	16	0.375
ko00750	Vitamin B6 metabolism	3	8	0.375
ko00280	Valine, leucine and isoleucine degradation	4	11	0.364
ko00650	Butanoate metabolism	4	11	0.364
ko05230	Central carbon metabolism in cancer	5	14	0.357
ko00051	Fructose and mannose metabolism	6	17	0.353
ko00910	Nitrogen metabolism	2	6	0.333
ko00260	Glycine, serine and threonine metabolism	10	32	0.313
ko00670	One carbon pool by folate	5	16	0.313
ko00290	Valine, leucine and isoleucine biosynthesis	4	13	0.308
ko00980	Metabolism of xenobiotics by cytochrome P450	3	10	0.300
ko00982	Drug metabolism - cytochrome P450	3	10	0.300
ko01230	Biosynthesis of amino acids	33	112	0.295
ko00071	Fatty acid degradation	5	17	0.294
ko00350	Tyrosine metabolism	5	17	0.294
ko00780	Biotin metabolism	2	7	0.286



ko00620	Pyruvate metabolism	11	39	0.282
ko04152	AMPK signaling pathway	7	25	0.280
ko04066	HIF-1 signaling pathway	5	18	0.278
ko00040	Pentose and glucuronate interconversions	3	11	0.273
ko04260	Cardiac muscle contraction	5	20	0.250
ko04068	FoxO signaling pathway	4	16	0.250
ko00770	Pantothenate and CoA biosynthesis	4	16	0.250
ko00627	Aminobenzoate degradation	3	12	0.250
ko00190	Oxidative phosphorylation	14	58	0.241
ko00900	Terpenoid backbone biosynthesis	4	17	0.235
ko00740	Riboflavin metabolism	3	13	0.231
ko00360	Phenylalanine metabolism	3	13	0.231
ko00960	Tropane, piperidine and pyridine alkaloid biosynthesis	2	9	0.222
ko03320	PPAR signaling pathway	2	9	0.222
ko00250	Alanine, aspartate and glutamate metabolism	5	24	0.208
ko02020	Two-component system	3	15	0.200
ko00410	beta-Alanine metabolism	3	15	0.200
ko00100	Steroid biosynthesis	3	15	0.200
ko04727	GABAergic synapse	2	10	0.200
ko00903	Limonene and pinene degradation	1	5	0.200
ko00860	Porphyrin and chlorophyll metabolism	3	16	0.188
ko00310	Lysine degradation	3	16	0.188
ko00720	Carbon fixation pathways in prokaryotes	2	11	0.182
ko04915	Estrogen signaling pathway	2	11	0.182
ko04146	Peroxisome	7	39	0.179
ko04910	Insulin signaling pathway	4	23	0.174
ko00561	Glycerolipid metabolism	4	23	0.174
ko00270	Cysteine and methionine metabolism	6	36	0.167
ko04622	RIG-I-like receptor signaling pathway	1	6	0.167
ko00520	Amino sugar and nucleotide sugar metabolism	4	25	0.160
ko00230	Purine metabolism	13	87	0.149
ko03010	Ribosome	11	76	0.145
ko00480	Glutathione metabolism	3	21	0.143
ko00061	Fatty acid biosynthesis	1	7	0.143
ko04920	Adipocytokine signaling pathway	1	7	0.143
ko00460	Cyanoamino acid metabolism	1	7	0.143
ko00330	Arginine and proline metabolism	5	36	0.139
ko03430	Mismatch repair	3	22	0.136
ko00640	Propanoate metabolism	2	16	0.125
ko00600	Sphingolipid metabolism	2	16	0.125
ko04122	Sulfur relay system	1	8	0.125
ko04918	Thyroid hormone synthesis	1	8	0.125
ko04140	Regulation of autophagy	2	17	0.118
ko04142	Lysosome	2	17	0.118

ko04071	Sphingolipid signaling pathway	2	17	0.118
ko00790	Folate biosynthesis	1	9	0.111
ko03450	Non-homologous end-joining	1	9	0.111
ko00450	Selenocompound metabolism	1	9	0.111
ko04151	PI3K-Akt signaling pathway	2	20	0.100
ko01212	Fatty acid metabolism	2	21	0.095
ko04020	Calcium signaling pathway	1	11	0.091
ko01040	Biosynthesis of unsaturated fatty acids	1	12	0.083
ko00514	Other types of O-glycan biosynthesis	1	12	0.083
ko04022	cGMP-PKG signaling pathway	1	12	0.083
ko04966	Collecting duct acid secretion	1	12	0.083
ko00340	Histidine metabolism	1	12	0.083
ko03018	RNA degradation	4	49	0.082
ko04141	Protein processing in endoplasmic reticulum	6	76	0.079
ko00920	Sulfur metabolism	1	13	0.077
ko04666	Fc gamma R-mediated phagocytosis	1	13	0.077
ko00562	Inositol phosphate metabolism	1	13	0.077
ko04144	Endocytosis	3	40	0.075
ko04113	Meiosis - yeast	7	99	0.071
ko03040	Spliceosome	4	63	0.063
ko00760	Nicotinate and nicotinamide metabolism	1	16	0.063
ko03022	Basal transcription factors	2	32	0.063
ko00564	Glycerophospholipid metabolism	2	33	0.061
ko03440	Homologous recombination	1	18	0.056
ko03460	Fanconi anemia pathway	1	18	0.056
ko04810	Regulation of actin cytoskeleton	1	18	0.056
ko03060	Protein export	1	18	0.056
ko04010	MAPK signaling pathway	1	18	0.056
ko00400	Phenylalanine, tyrosine and tryptophan biosynthesis	1	19	0.053
ko04921	Oxytocin signaling pathway	1	19	0.053
ko04914	Progesterone-mediated oocyte maturation	1	19	0.053
ko04721	Synaptic vesicle cycle	1	22	0.045
ko00240	Pyrimidine metabolism	3	68	0.044
ko00513	Various types of N-glycan biosynthesis	1	32	0.031
ko04145	Phagosome	1	32	0.031
ko03420	Nucleotide excision repair	1	36	0.028
ko04111	Cell cycle - yeast	3	110	0.027
ko04011	MAPK signaling pathway - yeast	1	37	0.027
ko00970	Aminoacyl-tRNA biosynthesis	1	38	0.026
ko03013	RNA transport	1	79	0.013

Note: The ratio of DEGs/background genes indicates the effects of the DEGs in the specific KEGG pathway (background genes).

**Table S4 Primers used in this study.**

ID	Gene	NR_Description	Primer	Sequence (5'→3')
KMAR_10772		uncharacterized abhydrolase domain-containing protein YGR015C	Forward	CCCTTGTGAAATCTTGCGTAAAGTTG
			Reverse	AATGTAGCATACCGTCGCATAGTTG
KMAR_80057	<i>RPB1</i>	DNA-directed RNA polymerase II subunit RPB1	Forward	CCGTGGTAACACTCCATTCTCAAG
			Reverse	GAGCAGAGGTAGCGTTGTAAGTTG
KMAR_50053	<i>IRC8</i>	uncharacterized protein IRC8	Forward	GCAACAGAAACTCACCACAAAG
			Reverse	TCCCTTCCCGCACCGAAAC
KMAR_10795	<i>NQO2</i>	ribosyldihyronicotinamide dehydrogenase	Forward	GCACCCAGAATTAAGTGATCCAGAAG
			Reverse	ACATTCAAACCCGAGTAACCGAAAG
KMAR_80139		carbonic anhydrase	Forward	TGAAGGTGAACAAAGTCGTCATCTG
			Reverse	TCGTCGAGGTCCTGGAGGTAG
KMAR_50521	<i>SDH4</i>	succinate dehydrogenase	Forward	CCACTCTCGCTTCCGTCCTATTG
			Reverse	CCCATGATACCACCTTCCTTTGTTTC
KMAR_10054	<i>HBN1</i>	putative nitroreductase HBN1	Forward	GGCTTCTGTTACCGATGCTGTTG
			Reverse	TGGATTGGTCTGCGAAGGATGG
KMAR_20313	<i>MCH5</i>	riboflavin transporter MCH5	Forward	ACACTCTTAACCTTCGTCAT
			Reverse	GGCACCAGATATAGGAACT
KMAR_70277	<i>CTR1</i>	copper transport protein CTR1	Forward	CCGTCTCTAATCACATTCCG
			Reverse	CCATCGTCATCTTCATAGGA
KMAR_40093	<i>ARN2</i>	siderophore iron transporter ARN2	Forward	TTCAGAAGCGGTAAGGATT
			Reverse	CGAGGTGATGGATTGGAT
KMAR_10790	<i>SIT1</i>	major facilitator superfamily	Forward	CTATCTGGACCTCTGAACTT
			Reverse	AATAGAACTGACACCAACAC
KMAR_30337	<i>PDR12</i>	ATP-dependent permease PDR12	Forward	CTGCCTACTTCGTGCTTA
			Reverse	CACAGAACAACAACATACCA
KMAR_80266	<i>ITR2</i>	myo-inositol transporter 2	Forward	CTTCTGCTACTTGTGTTATCC
			Reverse	TCTCTTCTGGCTAGTTGTT
KMAR_20248	<i>JEN2</i>	putative sialic acid transporter	Forward	GTGCTTCCTCTACGATTGA
			Reverse	CAGGTCTAGAAATGGTAATGA
KMAR_60075	<i>JEN1</i>	carboxylic acid transporter protein homolog	Forward	AAGAAGGATTACGCTAAGGT
			Reverse	GAGATGGATAGACTGGAGAC
KMAR_50130	<i>FNX1</i>	multidrug resistance protein fnx1	Forward	CGGTCTAATGGCAATAGGA
			Reverse	AGCGAGAAGAGTAACAGTAA
KMAR_70043	<i>ACT1</i>	Actin	Forward	TTGGCTGGTAGAGACATCACTGAC
			Reverse	AGCAGATGATTGAGAAGCGGTTTG



