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Supplementary Materials for

Evaluating biological activity of compounds by transcription factor activity profiling

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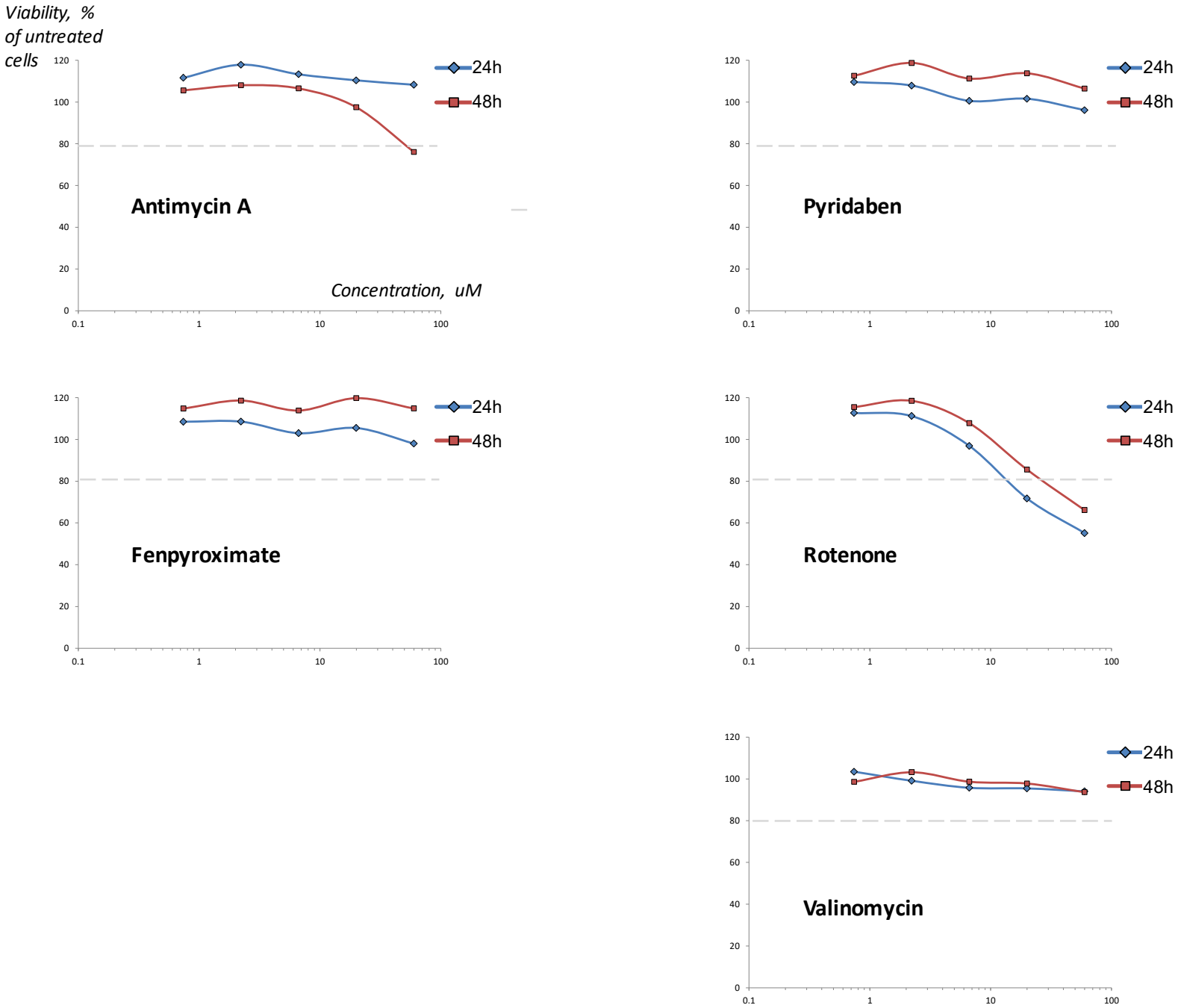
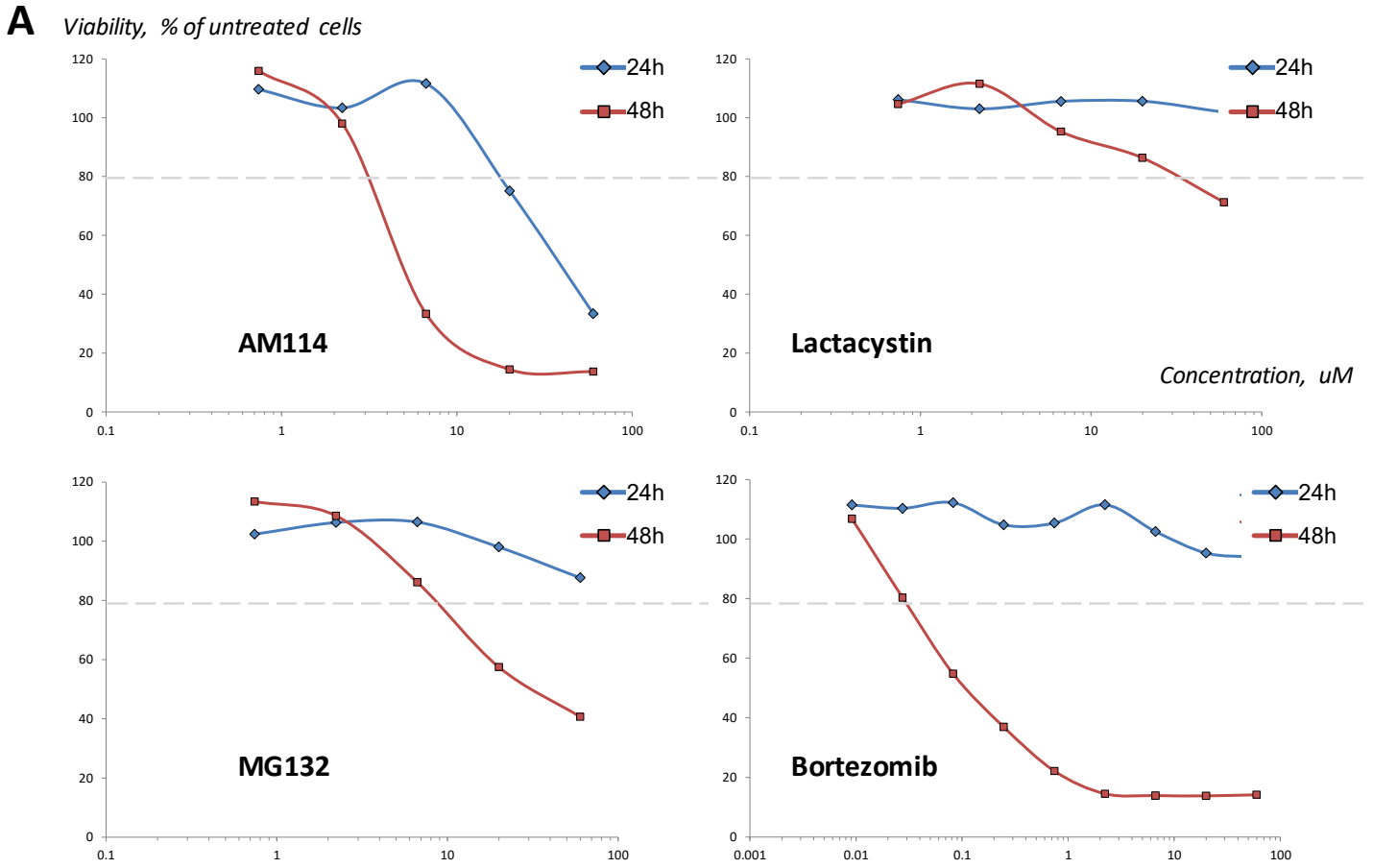


Fig. S1. The effect of mETC inhibitors on the viability of assay cells (HepG2). After a 24-h incubation with indicated compounds, cells were incubated for another 24 h in a compound-free medium. The viability at the 24 h and 48 h endpoints was assessed by XTT assay. Control cells were incubated with corresponding dilutions of the vehicle (DMSO). Cell viability was calculated as the percent of viable cells in compound-treated vs. vehicle-treated cells. Each point is an average of duplicate measurements. The viability threshold was set at 80%.



RTU #	Name
1	TGFRE
2	HNF6
3	TCF
4	Ebox
5	PPAR
6	NF1
7	GR
8	AP-1
9	ISRE
10	MTF-1
11	STAT3
12	TAL
13	NF-κB
14	FoxA2
15	CMV
16	Xbp1
17	CREB
18	AhR
19	EGR
20	NRF2
21	TA
22	ER
23	Oct
24	LXR
25	HSF-1
26	SREBP
27	p53
28	BMPRE
29	Pax6
30	HIF-1α
31	VDR
32	ROR
33	Ets
34	GLI-1
35	NRF1
36	GATA
37	E2F
38	C/EBP
39	Myb
40	PBREM
41	FXR
42	AP-2
43	RAR
44	FoxO
45	SOX
46	Sp1
47	Myc

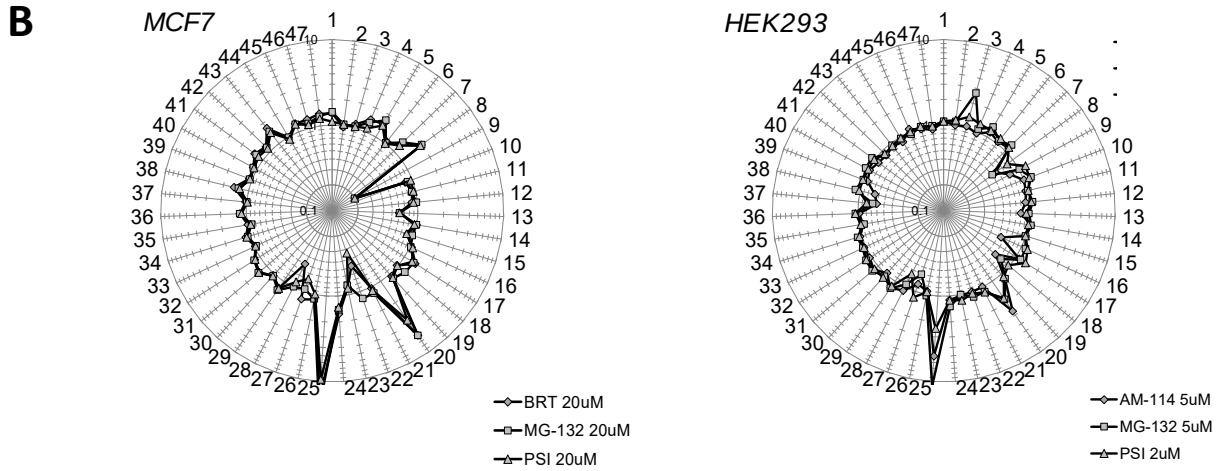
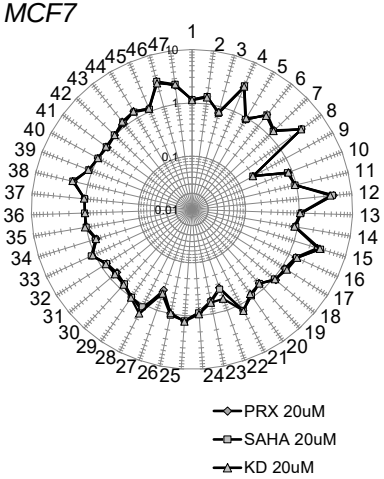


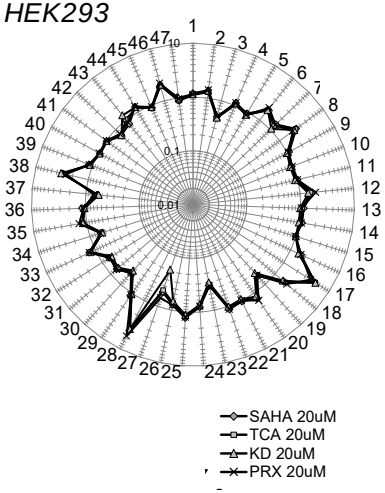
Fig. S2. The effect of UPP inhibitors on the viability of assay cells and the common TFAP signatures for UPP inhibitors in HEK293 and MCF-7 cells. A. The effect of UPP inhibitors on the viability of assay cells. The viability of HepG2 cells was assessed as described by fig. S1 legend. **B**. The common TFAP signatures for UPP inhibitors in different cell types. The signatures in HEK293 and MCF-7 cells for the indicated UPP inhibitors were obtained using the protocol for HepG2 cells.

A

MCF7



HEK293



RTU #	Name
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12	TAL
13	NF-κB
14	FoxA2
15	CMV
16	Xbp1
17	CREB
18	AhR
19	EGR
20	NRF2
21	TA
22	ER
23	Oct
24	LXR
25	HSF-1
26	SREBP
27	p53
28	BMPRE
29	Pax6
30	HIF-1α
31	VDR
32	ROR
33	Ets
34	GLI-1
35	NRF1
36	GATA
37	E2F
38	C/EBP
39	Myb
40	PBREM
41	FXR
42	AP-2
43	RAR
44	FoxO
45	SOX
46	Sp1
47	Myc

B

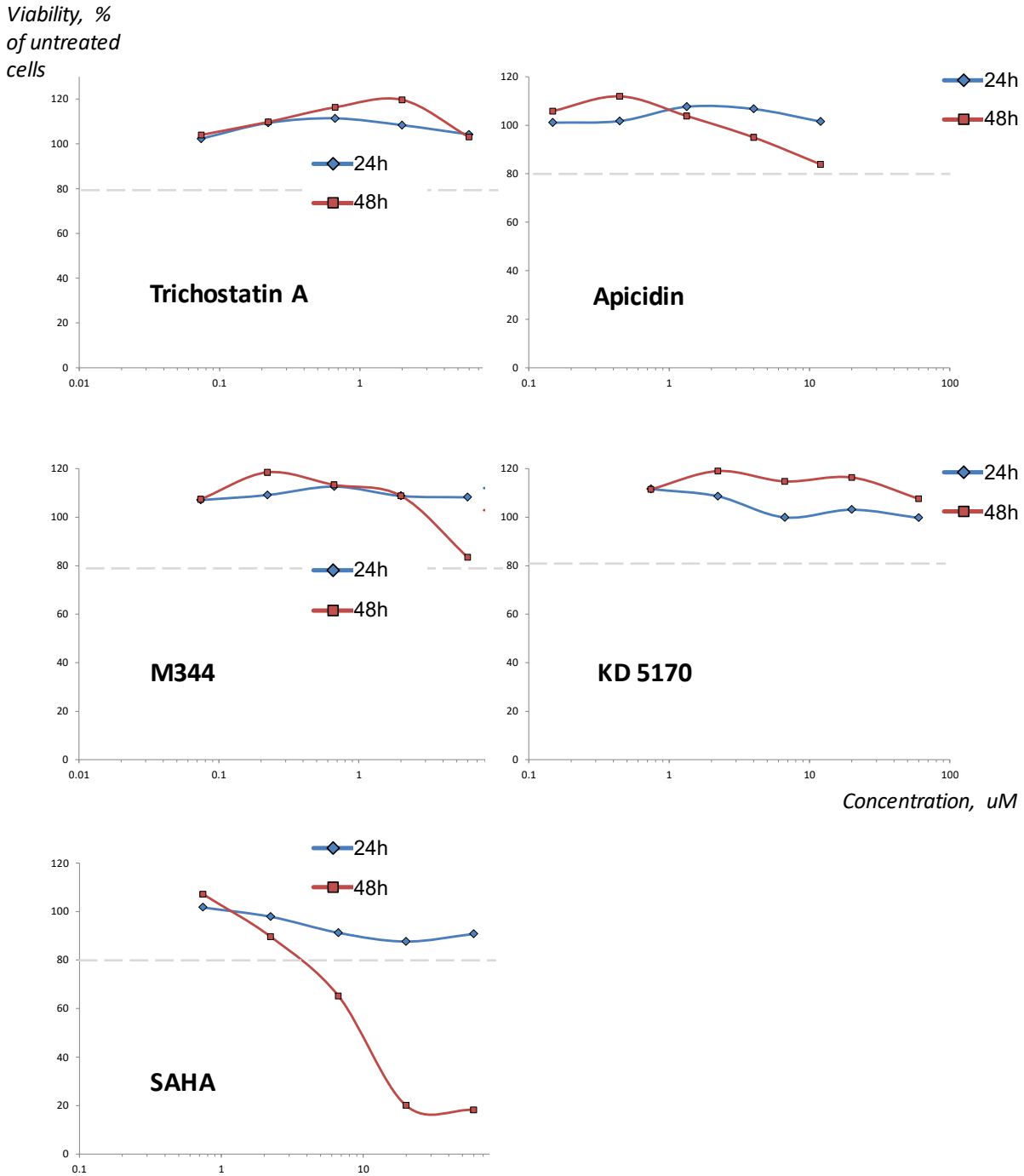

Fig. S3. The common TFAP signatures for HDAC inhibitors in HEK293 and MCF-7 cells and the effect of HDAC inhibitors on the viability of assay cells. A. The common TFAP signatures for HDAC inhibitors in different cell types. The signatures for SAHA, Trichostatin A (TCA), Pyroxamide (PRX), and KD5170 (KD) were obtained in HEK293 and MCF-7 cells using the protocol for HepG2 cells. **B**. The effect of HDAC inhibitors on the viability of assay cells. The viability of HepG2 cells was assessed as described by fig. S1 legend.

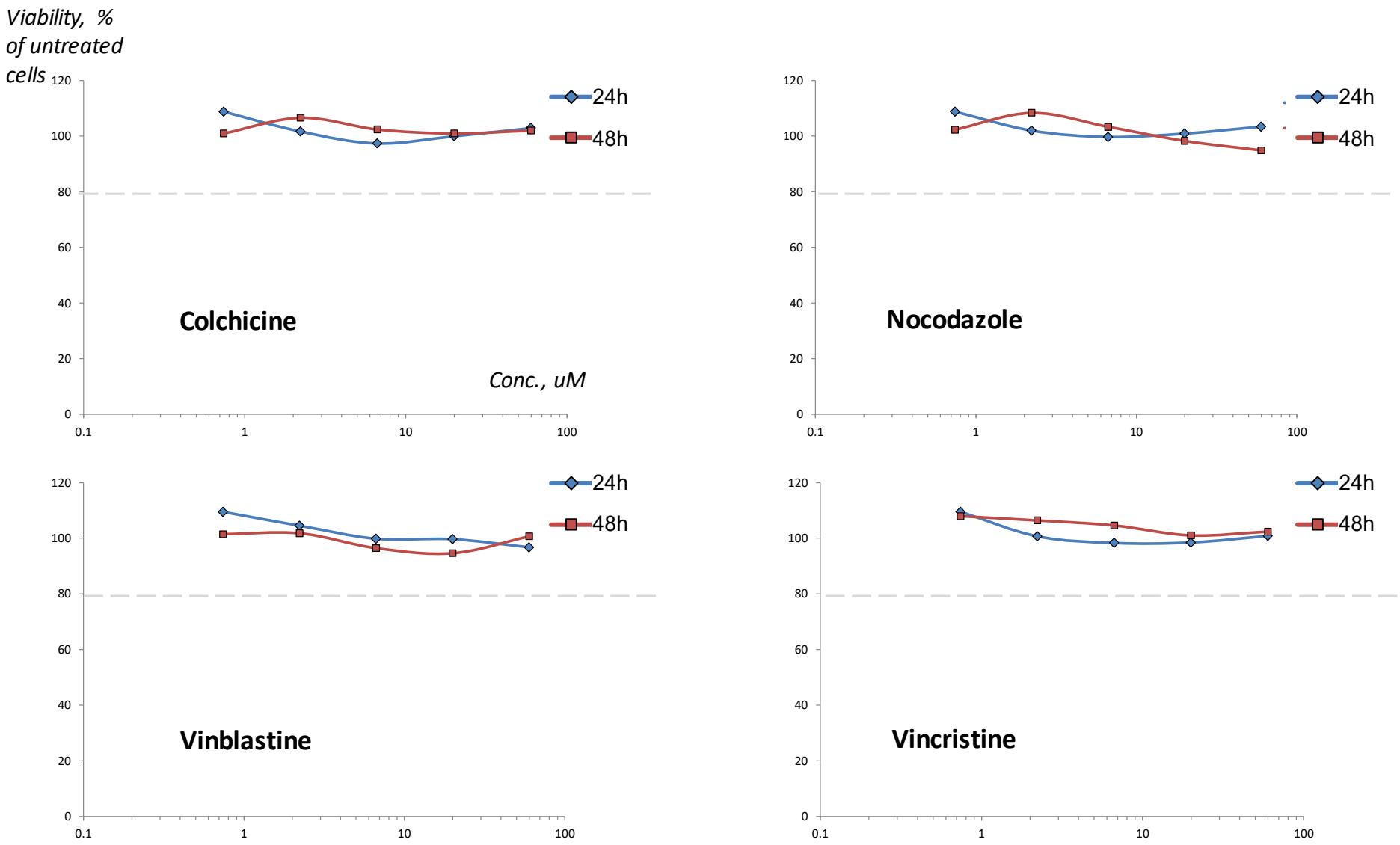

Fig. S4. The effect of MTDs on the viability of assay cells. The viability of HepG2 cells was assessed as described by fig. S1 legend.

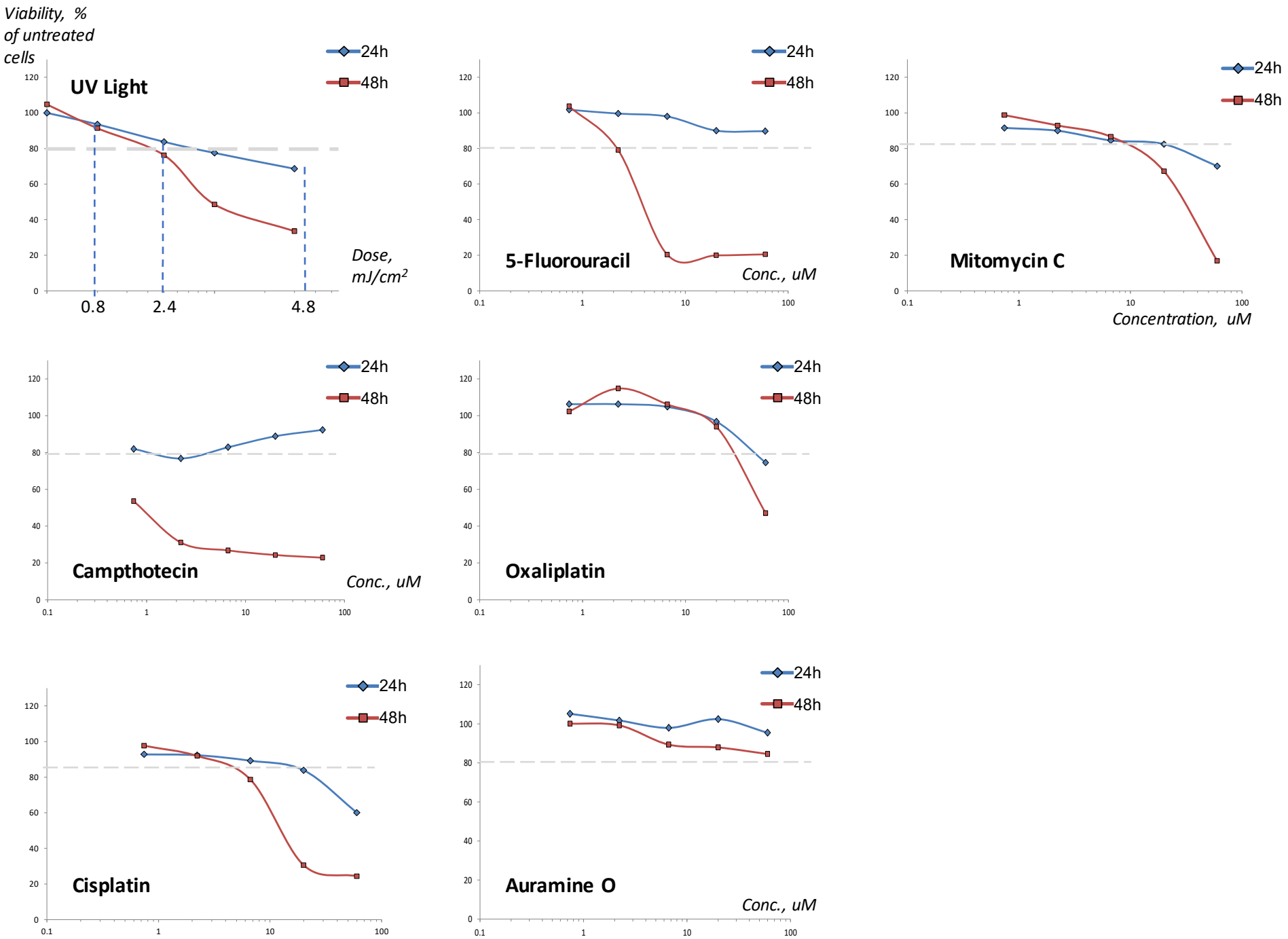

Fig. S5. The effect of microtubule DNA-damaging agents on the viability of assay cells. The viability of HepG2 cells was assessed as described by fig. S1 legend.

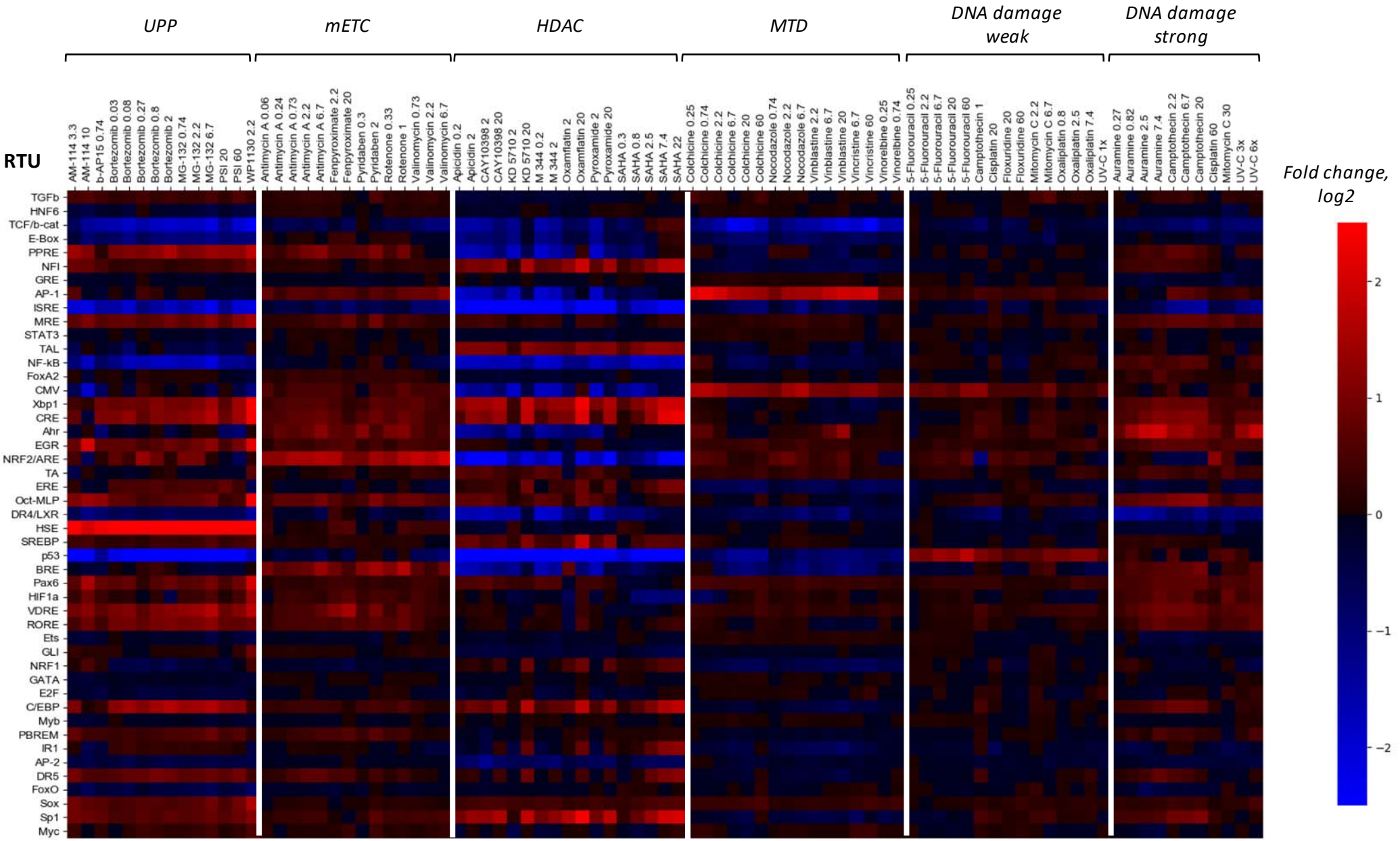

Fig. S6. An alternative presentation of TF responses to perturbagens as a heatmap. The aggregate heatmap shows representative TFAPs for perturbagens of different classes (shown as radial graphs by Figs. 2-4 of the main text.

A

Retrieved MMP-negative chemicals with r>0.800 that are known as mitochondria perturbagens

- Nitrofurazone (ref. *41*);
- Fenitrothion(*42*);
- Diethyl maleate(*43*);
- Phorate(*44*);
- Fenazaquin (*45*);
- Dichlorvos(*46*);
- Cisplatin(*47*);
- Tacrine(*48*);
- Malathion (*49*);
- Clomipramine(*50*);
- Azinphos-methyl (*51*);
- Nilutamide (*52*);
- 2-Chloroacetophenone (chlorophenacyl) (*53*);
- 2-hydroxyethyl acrylate (*54*);
- Dibutyl phthalate (*55*);
- Eugenol (*56*);
- Thiophanate-methyl (*57*, *58*);
- Mancozeb (*59*);
- Dodecyl trimethylammonium (*60*);
- Azoxystrobin (*26*, *61*);
- Fenoxycarb (*62*);
- Kresoxim-methyl (*27*);
- Alachlor (*63*);
- Prochloraz (*64*);
- Dicyclohexylcarbodiimide(*65*).

B

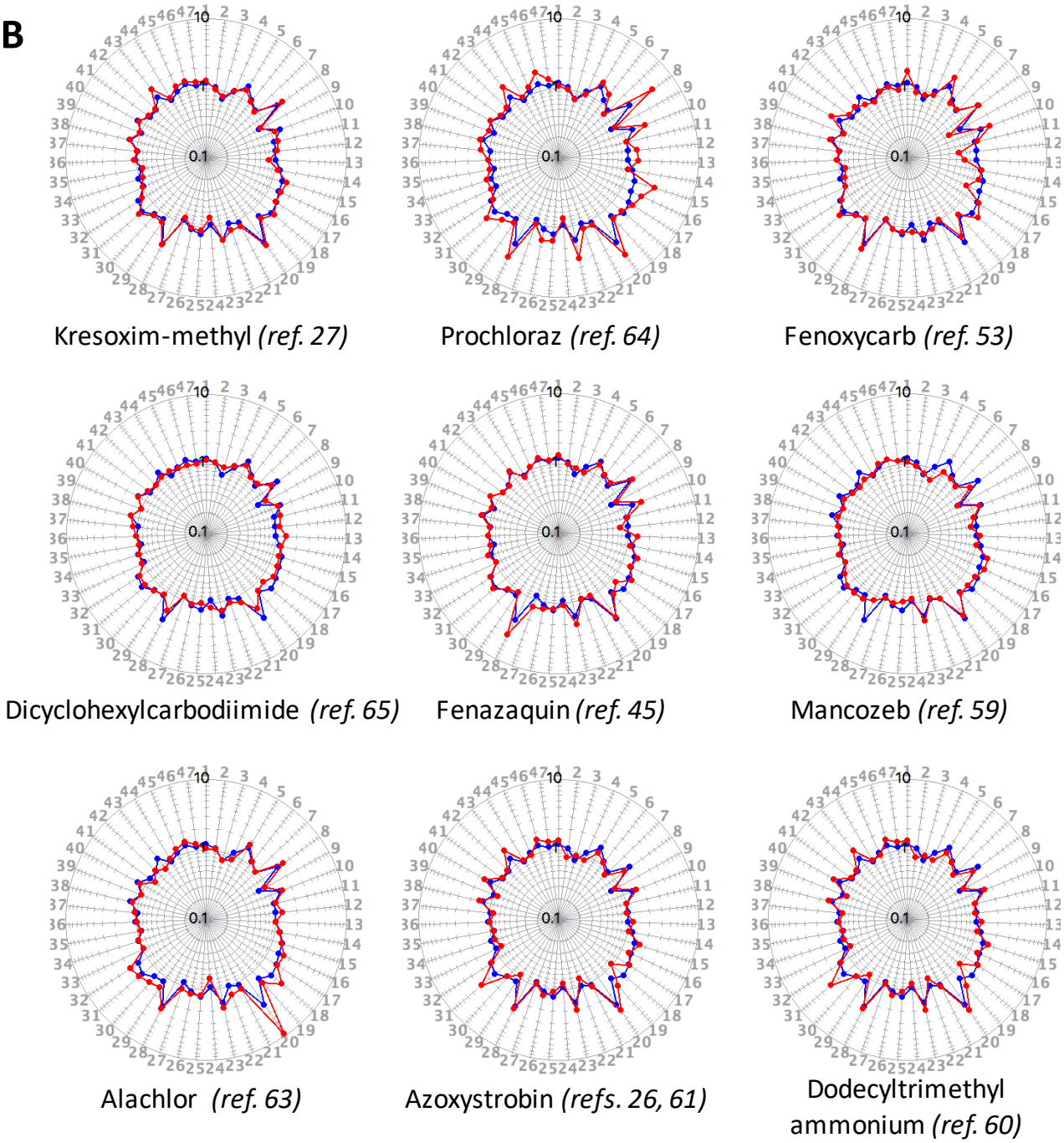

Fig. S7. The list of known mitochondria disruptors with a high (*r* > 0.800) TFAP similarity to the mETC TFAP that were scored negative by the MMP assay. A. The list of known mitochondria disruptors with a high (r>0.800) TFAP similarity to the mETC TFAP that were scored negative by the MMP assay. The literature references characterizing the chemicals' effects at mitochondria in mammalian cells. **B**. Representative examples of TFAPs for known mitochondria disruptors. An overlay with the invariant mETC TFAP.

Table S1. ToxCast chemicals with a high ($r \geq 0.800$) similarity to the invariant mETC TFAP. The dataset of TFAPs for 2,793 ToxCast chemicals was queried using the invariant mETC TFAP. The query retrieved 199 chemicals with the TFAP similarity $r \geq 0.800$ (Fig. 5). The TFAPs for many chemicals were retrieved more than once at multiple concentrations. The redundant signatures are not listed here. The HitCall column indicates the matches with the data by the MMP assay (1-yes; 0-no). The asterisks mark the false-negatives of the MMP assay (known from the literature mitochondria disruptors). For the references, see fig. S7.

#	Chemical	Conc. [uM]	Pearson correlation with the mETC TFAP, *r*	CASRN	MMP assay hitCall
1	Bisphenol A glycidyl methacrylate	22.2	0.939	1565-94-2	1
2	Triclosan	22.2	0.936	3380-34-5	1
3	Swep	200.0	0.927	1918-18-9	1
4	Rotenone	2.0	0.917	83-79-4	1
5	Pyridaben	2.0	0.916	96489-71-3	1
6	Fluorosalan	7.4	0.913	4776-06-1	1
7	Prochloraz	20.0	0.912	67747-09-5	0*
8	Fenitrothion	100.0	0.912	122-14-5	0*
9	Ioxynil	200.0	0.909	1689-83-4	1
10	Dinoseb	66.7	0.908	88-85-7	1
11	Dazomet	100.0	0.907	533-74-4	0
12	Anilazine	100.0	0.906	101-05-3	0
13	Alachlor	20uM	0.906	15972-60-8	0*
14	Ipconazole	22.2	0.906	125225-28-7	1
15	Hydroxyflutamide	200.0	0.904	52806-53-8	1
16	Fenamidone	100.0	0.902	161326-34-7	1
17	Mifepristone	66.7	0.902	84371-65-3	1
18	Fipronil	20uM	0.902	120068-37-3	1
19	Besonprodil	200.0	0.902	253450-09-8	0
20	Triclocarban	66.7	0.901	101-20-2	1
21	Triethyltin bromide	7.4	0.901	2767-54-6	1
22	1-Octen-3-ol	200.0	0.900	3391-86-4	0
23	Norflurazon	33.0	0.898	27314-13-2	0
24	Dinocap	7.4	0.897	39300-45-3	1
25	Flutamide	66.7	0.896	13311-84-7	1
26	N-Isopropyl-N'-phenyl-p-phenylenediamine	22.2	0.896	101-72-4	0
27	Azoxystrobin	66.7	0.894	131860-33-8	0*
28	Methenamine	2.5	0.893	100-97-0	0
29	Z-Tetrachlorvinphos	66.7	0.892	22248-79-9	1
30	Diethyl maleate	200.0	0.892	141-05-9	0*
31	Bifenazate	100.0	0.891	149877-41-8	1
32	Trifloxystrobin	20.0	0.891	141517-21-7	1
33	Metconazole	66.7	0.890	125116-23-6	1
34	Nilutamide	200.0	0.889	63612-50-0	0*
35	Indoxacarb	10.9	0.887	173584-44-6	1
36	Kresoxim-methyl	22.2	0.886	143390-89-0	0*
37	Picoxystrobin	22.2	0.885	117428-22-5	1
38	Celecoxib	20.0	0.883	169590-42-5	1
39	Fenoxycarb	20.0	0.882	72490-01-8	0*
40	Methyl trans-styryl ketone	66.7	0.882	1896-62-4	0
41	1,1-Dimethoxy-3,7-dimethylocta-2,6-diene	200.0	0.881	7549-37-3	0
42	Parathion	100.0	0.880	56-38-2	1
43	Troglitazone	22.0	0.879	97322-87-7	1
44	4,4'-(4-Methylpentane-2,2-diyl)diphenol	22.2	0.879	6807-17-6	1
45	Profenofos	13.2	0.877	41198-08-7	1
46	Methyl red	7.4	0.876	493-52-7	0
47	Trichlorfon	100.0	0.875	52-68-6	0
48	2-tert-Butyl-4-methoxyphenol	200.0	0.875	121-00-6	1
49	Butralin	48.1	0.874	33629-47-9	0
50	Oxyfluorfen	100.0	0.872	42874-03-3	1
51	2,6-Di-tert-butyl-4-nitrophenol	22.2	0.871	728-40-5	1
52	4-Ethenylphenyl acetate	200.0	0.870	2628-16-2	0
53	Etridiazole	100.0	0.870	2593-15-9	0
54	1-Chloro-3,3-dimethyl-butan-2-one	66.7	0.870	13547-70-1	0
55	Flusilazole	33.0	0.868	85509-19-9	1
56	Rhodamine 6G	2.5	0.868	989-38-8	1
57	Dodecyltrimethylammonium chloride	7.4	0.867	112-00-5	0*
58	Methyl isothiocyanate	100.0	0.867	556-61-6	0
59	Mancozeb	22.0	0.867	8018-01-7	0*
60	Thiophanate-methyl	100.0	0.865	23564-05-8	0*
61	Bisphenol AF	22.2	0.865	1478-61-1	1
62	Cyproterone acetate	66.7	0.862	427-51-0	1
63	Oxadiazon	20.0	0.862	19666-30-9	1
64	Bisphenol B	66.7	0.861	77-40-7	1
65	Eugenol	200.0	0.861	97-53-0	0*
66	Chlorethoxyfos	100.0	0.860	54593-83-8	1
67	1-(4-Methoxyphenyl)-1-pentene-3-one	66.7	0.857	104-27-8	0
68	Nitrofurazone	200.0	0.856	59-87-0	0*
69	S-Metolachlor	200.0	0.856	87392-12-9	0
70	Propyzamide	100.0	0.856	23950-58-5	0
71	Propargite	4.8	0.856	2312-35-8	1
72	Clorophene	22.0	0.855	120-32-1	1
73	4-Propylphenol	66.7	0.852	645-56-7	1
74	Dimethomorph	33.0	0.851	110488-70-5	0
75	2-Cyanoethyl prop-2-enoate	66.7	0.850	106-71-8	0
76	Flufenacet	100.0	0.850	142459-58-3	0
77	Phorate	200.0	0.849	298-02-2	0*
78	TNP-470	200.0	0.848	129298-91-5	0
79	7-Diethylamino-4-methylcoumarin	200.0	0.848	91-44-1	1
80	Bisphenol A	100.0	0.848	80-05-7	1
81	Tetramethrin	33.0	0.847	7696-12-0	1
82	Fluoxastrobin	3.9	0.847	361377-29-9	1
83	Diprop-2-en-1-yl (2Z)-but-2-enedioate	22.2	0.846	999-21-3	0
84	Hexythiazox	33.0	0.846	78587-05-0	1
85	Silwet L77	7.4	0.845	27306-78-1	1
86	2-Chloro-4-phenylphenol	66.7	0.845	92-04-6	1
87	Chlorfenapyr	2.5	0.844	122453-73-0	1
88	2,5-Di-tert-butylbenzene-1,4-diol	66.7	0.843	88-58-4	1
89	2-Chloro-N-phenylacetamide	22.2	0.843	587-65-5	0
90	Binapacryl	22.2	0.842	485-31-4	1
91	2-Hydroxyethyl acrylate	200.0	0.842	818-61-1	0*
92	Nelivaptan	66.0	0.840	439687-69-1	0
93	3,4,5,6-Tetrachloro-2-pyridinecarbonitrile	2.5	0.840	17824-83-8	1
94	Prallethrin	33.0	0.840	23031-36-9	1
95	Dodecyltrimethylammonium bromide	22.2	0.839	1119-94-4	1
96	Phosalone	100.0	0.839	2310-17-0	1
97	Bis(2-ethylhexyl) phosphate	66.7	0.838	298-07-7	1
98	Thiazopyr	20uM	0.838	117718-60-2	0
99	Dibutyl phthalate	100.0	0.838	84-74-2	0*
100	Benzalkonium chloride	7.4	0.837	8001-54-5	1

Table S1. (continued)

#	Chemical	Conc. [uM]	Pearson correlation with the mETC TFAP, *r*	CASRN	MMP assay hitCall
101	Famoxadone	6.2	0.837	131807-57-3	1
102	Hexachlorophene	7.4	0.837	70-30-4	1
103	3,7-Dimethyl-2,6-octadienal	200.0	0.836	5392-40-5	0
104	Dicyclohexyl phthalate	7.4	0.836	84-61-7	1
105	Linuron	100.0	0.836	330-55-2	1
106	Tolazamide	2.5	0.836	1156-19-0	0
107	Resmethrin	20.0	0.835	10453-86-8	1
108	Bisphenol F	200.0	0.835	620-92-8	1
109	4-Hexylresorcinol	66.7	0.835	136-77-6	1
110	Tetradonium bromide	22.2	0.835	1119-97-7	0
111	Metolachlor	100.0	0.835	51218-45-2	0
112	2,2',2''-[Methanetriyltris(benzene-4,1-diyloxymethanediyl)]trioxirane	7.4	0.834	66072-38-6	0
113	Flutolanil	100.0	0.834	66332-96-5	1
114	Triadimenol	17.2	0.834	55219-65-3	0
115	Novaluron	100.0	0.833	116714-46-6	0
116	Allethrin	22.0	0.833	584-79-2	1
117	Tiratricol	200.0	0.833	51-24-1	0
118	2-Chloroacetophenone	22.2	0.832	532-27-4	0*
119	Difenoconazole	6.3	0.832	119446-68-3	1
120	Dichlorvos	100.0	0.832	62-73-7	0*
121	Bendiocarb	100.0	0.831	22781-23-3	0
122	Ketoconazole	20.0	0.831	65277-42-1	1
123	Cetylpyridinium bromide	7.4	0.831	140-72-7	1
124	3-(Chloromethyl)pyridine hydrochloride	200.0	0.827	6959-48-4	0
125	2,2'-Methylenebis(ethyl-6-tert-butylphenol)	22.2	0.827	88-24-4	1
126	Chlorpyrifos oxon	100.0	0.827	5598-15-2	1
127	Cyazofamid	23.8	0.827	120116-88-3	1
128	Oxycarboxin	22.2	0.827	5259-88-1	0
129	Fenoxaprop-P-ethyl	200.0	0.827	71283-80-2	0
130	Spiroxamine	33.0	0.826	118134-30-8	0
131	Benoxacor	200.0	0.825	98730-04-2	0
132	Tributyltin methacrylate	0.8	0.824	2155-70-6	1
133	Dihexylamine	200.0	0.824	143-16-8	0
134	Ethofumesate	100.0	0.824	26225-79-6	0
135	Dimethyl maleate	200.0	0.824	624-48-6	0
136	Cisplatin	60.0	0.824	15663-27-1	0*
137	Azinphos-methyl	100.0	0.823	86-50-0	0*
138	4-Aminoazobenzene	7.4	0.823	60-09-3	0
139	Octrizole	200.0	0.823	3147-75-9	1
140	Dicyclohexylcarbodiimide	2.5	0.823	538-75-0	0*
141	4-Biphenylamine hydrochloride	7.4	0.822	2113-61-3	0
142	Phenazopyridine hydrochloride	200.0	0.822	136-40-3	1
143	Pyraclostrobin	4.0	0.821	175013-18-0	1
144	Elzasonan	7.4	0.821	361343-19-3	0
145	4-Nonylphenol	22.2	0.821	104-40-5	1
146	Methyl geranate	200.0	0.820	NOCAS_47129	0
147	Propanil	100.0	0.820	709-98-8	1
148	1-Dodecyl-2-pyrrolidinone	22.2	0.820	2687-96-9	0
149	Malathion	100.0	0.819	121-75-5	0*
150	Bithionol	7.4	0.819	97-18-7	1
151	Pyriproxyfen	33.0	0.819	95737-68-1	0
152	Cyprodinil	33.0	0.818	121552-61-2	0
153	Diphenylamine	100.0	0.818	122-39-4	1
154	Anise oil	200.0	0.817	8007-70-3	0
155	Daminozide	100.0	0.817	1596-84-5	0
156	2,4,6-Tribromophenol	66.7	0.817	118-79-6	1
157	2,5-Bis(2-methylbutan-2-yl)benzene-1,4-diol	7.4	0.816	79-74-3	1
158	Spiromesifen	200.0	0.816	283594-90-1	1
159	Kaempferol	60.0	0.816	520-18-3	1
160	Methyl 2-octynoate	200.0	0.815	111-12-6	0
161	Etoxazole	10.6	0.815	153233-91-1	1
162	2-(2-Ethoxyethoxy)ethyl prop-2-enoate	200.0	0.815	7328-17-8	0
163	Loratadine	20.0	0.814	79794-75-5	1
164	2,4-Hexadienyl isobutyrate	200.0	0.812	16491-24-0	0
165	Diethylstilbestrol	22.2	0.812	56-53-1	1
166	Triadimefon	100.0	0.812	43121-43-3	0
167	Bromoxynil	100.0	0.811	1689-84-5	1
168	Tributyltin chloride	0.3	0.811	1461-22-9	1
169	Rhodamine B	200.0	0.810	81-88-9	0
170	Triphenyl phosphate	66.7	0.810	115-86-6	1
171	Lovastatin	66.7	0.810	75330-75-5	1
172	4,4'-Dichlorodiphenyl sulfone	200.0	0.810	80-07-9	1
173	Bis[4-(glycidyloxy)phenyl]methane	22.2	0.810	2095-03-6	0
174	N,N-Dimethyl-4-nitrosoaniline	7.4	0.810	138-89-6	0
175	Mepronil	200.0	0.810	55814-41-0	1
176	Tacrine	60.0	0.810	321-64-2	0*
177	Didecyldimethylammonium chloride	2.5	0.809	7173-51-5	1
178	Formetanate hydrochloride	100.0	0.809	23422-53-9	0
179	Pentachlorophenol	66.7	0.808	87-86-5	1
180	Nitrofurantoin	180.0	0.808	67-20-9	1
181	Metsulfuron-methyl	100.0	0.808	74223-64-6	0
182	Eugenyl phenylacetate	200.0	0.807	10402-33-2	0
183	Sodium 2-phenylphenate tetrahydrate	66.7	0.807	6152-33-6	1
184	Tris(2,3-dibromopropyl) phosphate	22.2	0.806	126-72-7	1
185	Fenazaquin	0.2	0.806	120928-09-8	0*
186	Clomipramine hydrochloride	22.2	0.806	17321-77-6	0*
187	Pyrimethanil	100.0	0.806	53112-28-0	0
188	Piperonyl butoxide	100.0	0.805	51-03-6	0
189	1-Chloro-2-(chloromethyl)-3-fluorobenzene	22.2	0.804	55117-15-2	0
190	3-Hydroxyfluorene	66.7	0.804	6344-67-8	1
191	2-Methoxy-4-methylphenol	200.0	0.803	93-51-6	0
192	Forchlorfenuron	100.0	0.802	68157-60-8	1
193	2-(Chloromethyl)pyridine hydrochloride	200.0	0.801	6959-47-3	0
194	Benfluralin	100.0	0.801	1861-40-1	0
195	Desmedipham	200.0	0.801	13684-56-5	1
196	Benzyldimethyldodecylammonium chloride	7.4	0.801	139-07-1	1
197	Flumioxazin	100.0	0.800	103361-09-7	0
198	3,3'-Diaminobenzidine	200.0	0.800	91-95-2	1
199	8-Hydroxyquinoline	200.0	0.800	148-24-3	0