

**Table S3** IC<sub>50</sub> values of **126–165** against cancer and normal cell lines, at different incubation time, mechanism of action, target and cell cycle arrest.

Complex number	Cell line/IC <sub>50</sub> ( $\mu$ M) <sup>1,2</sup>						Mechanism of action	Cell Cycle arrest	Target	Ref.						
<b>3.4. Polynuclear half-sandwich Ir(III) complexes</b>																
<b>3.4.1. N or P-ligands</b>																
126a <sup>*</sup>	A2780	101.9	A2780cisR	> 200	HEK-293T <sup>(N)</sup>	118.8			n.d	281						
126b <sup>*</sup>		97.0		45.5		148.5										
127a	WHCO1	111.5 ± 4.2						n.d	DNA	282						
127b		48.3 ± 8.8														
<b>3.4.2. C<sup>N</sup> ligands</b>																
128a	A2780	29.7 ± 0.1	A2780cisR	28.1 ± 2.0	HEK-293T <sup>(N)</sup>	n.d			n.d	283						
128b <sup>T</sup>		13.7 ± 0.1		3.0 ± 0.2		5.0 ± 1.2										
128c <sup>T</sup>		20.1 ± 13.6		19.0 ± 8.5		72.4 ± 91.1										
<b>3.4.3. N<sup>N</sup> and N<sup>O</sup> ligands</b>																
129a	MCF-7 (Crystal violet); 3.5			HT-29 (Crystal violet); 1.8			DNA (mono-intercalation)		DNA	285						
129b	n.d															
129c	MCF-7	3.1	HT-29	3.8	DNA (bis-intercalation)											
129d		0.109		n.d												
130a	MCF-7 (Crystal violet)	0.61	HT-29 (Crystal violet)	3.7	DNA (mono-intercalation)				DNA	123						
130b		7.9		12.7												
130c		0.49		2.5	DNA (mono-intercalation)											
130d		3.8		4.2												
130e		2.2		5.1	DNA (bis-intercalation)											
130f		3.8		4.4												
131a	B16F10; 10.75 ± 1.3			PC3; 13.26 ± 1.6						287						
	THP1; 18.93 ± 2.5			SKOV-3; 15.12 ± 1.7												
131b	B16F10; 40.32 ± 2.4			PC3; 34.14 ± 2.1												

	THP1; n.d		SKOV-3; n.d										
131c	B16F10; n.d		PC3; 43.81 ± 2.6										
	THP1; n.d		SKOV-3; n.d										
132a	n.d			Apoptosis			n.d		288				
132b													
132c													
133a	HeLa (WST-1)	32.72 ± 2.19	U87 (WST-1)	23.94 ± 1.91	WI 30 (WST-1)	589.57 ± 31.78	DNA interaction	Cytoplasm	289				
133b		39.99 ± 1.29		57.56 ± 2.32		89.04 ± 8.78							
134a <sup>T</sup>	HT-29; 52.17 ± 4.78		HCT-116p53-/; 46.88 ± 2.15					n.d	290				
	HCT-116p53+/+; 41.08 ± 17.74		ARPE-19 <sup>(N)</sup> ; 60.65 ± 4.78										
134b <sup>T</sup>	HT-29; 18.03 ± 3.26		HCT-116p53-/; 18.43 ± 0.24										
	HCT-116p53 <sup>+/+</sup> ; 19.26 ± 0.81		ARPE-19 <sup>(N)</sup> ; 38.82 ± 13.68										
134c <sup>*</sup>	HT-29; 53.51 ± 2.79		HCT-116p53-/; 58.00 ± 5.56										
	HCT-116p53 <sup>+/+</sup> ; 57.84 ± 2.89		ARPE-19 <sup>(N)</sup> ; >100										
134d <sup>*</sup>	HT-29; 37.32 ± 2.54		HCT-116p53-/; 57.19 ± 0.50										
	HCT-116p53 <sup>+/+</sup> ; 52.63 ± 4.96		ARPE-19 <sup>(N)</sup> ; >100										
135a	A2780; 34.2 ± 0.6	MCF-7; > 50		HT-29; > 50		ROS/RNS/Apoptosis	G <sub>2</sub> /M	Mitochondria	291				
	A2780R; > 50	HOS; > 50		PANC-1; > 50									
135b	A2780; 3.1 ± 0.1	MCF-7; 6.0 ± 0.2		HT-29; 25.7 ± 1.4									
	A2780R; 3.8 ± 0.4	HOS; 6.8 ± 1.9		PANC-1; 7.4 ± 1.2									
136a	MCF-7; > 25	HepG2; > 25		A375; > 25		NADH	n.d		292				
	A549; > 25	DU-145; > 25											
136b	MCF-7; > 25	HepG2; 12.6		A375; > 25									
	A549; 16.5	DU-145; > 25											
136c	MCF-7; > 25	HepG2; > 25		A375; > 25									
	A549; > 25	DU-145; > 25											
137	n.d												
138a	A2780	40 ± 2	A2780cisR	60 ± 6	HEK-293T <sup>(N)</sup>	n.d		n.d	294				
138b <sup>T</sup>		2.6 ± 0.5		8.9 ± 1.2		10.2 ± 0.5							
138c <sup>T</sup>		0.75 ± 0.01		3.5 ± 0.3		28.6 ± 1.3							
138d		66 ± 5.2		33.8 ± 3.8		n.d							
138e		40 ± 3		48 ± 4		n.d							
138f		55.1 ± 0.2		49.0 ± 1.6		n.d							
139a		11.58 ± 4.35		41.45 ± 3.28		84.40 ± 1.16		n.d	295				

<b>139b</b>	A2780 (WST-1)	30.79 ± 1.16	A2780cisR (WST-1)	50.49 ± 3.08	KMST-6 (WST-1)	85.04 ± 3.64						
<b>139c</b>		141.88 ± 1.19		80.20 ± 1.71		100.54 ± 5.01						
<b>139d</b>		107.00 ± 3.95		109.91 ± 5.92		116.20 ± 4.35						
<b>140a</b>	WHCO1	> 300					n.d			296		
<b>140b</b>		58.0 ± 19.3					n.d			297		
<b>140c</b>		59.6 ± 23.7										
<b>140d</b>		49.5 ± 19.0										
<b>140e</b>		> 270										
<b>141a</b>		200.8 ± 9.9					n.d			296		
<b>141b</b>		13.0 ± 9.0					n.d			297		
<b>141c</b>		6.2 ± 4.5										
<b>141d</b>		9.6 ± 4.6										
<b>141e</b>		49.5 ± 16.7										

### 3.4.4. O<sup>+</sup>O ligands

<b>142a</b> <sup>T</sup>	A2780	0.07 ± 0.01	A2780cisR	0.25 ± 0.05	HEK-293T <sup>(N)</sup>	0.09 ± 0.02		n.d		298	
<b>142b</b> <sup>T</sup>		0.13 ± 0.02		0.31 ± 0.04		0.11 ± 0.02					
<b>142c</b> <sup>T</sup>		0.17 ± 0.01		0.29 ± 0.03		0.10 ± 0.02					
<b>143a</b> <sup>T</sup>	DU-145; 16.0 ± 0.4	HeLa; 4.16 ± 0.3					n.d	n.d		299	
		A549; 3.18 ± 0.2				HEK-293T <sup>(N)</sup> ; 31.2 ± 0.5					
<b>143b</b> <sup>T</sup>	DU-145; 2.53 ± 0.2	HeLa; 1.04 ± 0.3						Sub-G <sub>1</sub>	DNA		
		A549; 0.84 ± 0.1				HEK-293T <sup>(N)</sup> ; 40.3 ± 0.4					
<b>143c</b> <sup>T</sup>	DU-145; 0.72 ± 0.2	HeLa; 0.59 ± 0.2									
		A549; 0.67 ± 0.4				HEK-293T <sup>(N)</sup> ; 70.8 ± 0.4					
<b>144</b> <sup>T</sup>	MCF-7; 1.0 ± 0.2	A549; 0.7 ± 0.2	CRL-2120 <sup>(N)</sup> ; 1.2 ± 0.2					n.d		300	
	B16F10; 0.8 ± 0.3	CRL-2115 <sup>(N)</sup> ; 1.2 ± 0.3									
<b>145</b> <sup>T</sup>	MCF-7; 0.7 ± 0.2	A549; 0.7 ± 0.4	CRL-2120 <sup>(N)</sup> ; 1.1 ± 0.4		ROS (irradiation with UV)/DNA Cleavage/MMP/Apoptosis	sub-G <sub>1</sub>	Mitochondria				
	B16F10; 0.7 ± 0.4	CRL-2115 <sup>(N)</sup> ; 1.1 ± 0.4									
<b>146a</b>	A549 (WST-1); 59.88 ± 2.69	HeLa (WST-1); 42.39 ± 3.34	WI-38 (WST-1); 11.67 ± 0.11		ROS	sub-G <sub>1</sub>	DNA			301	
	MCF-7 (WST-1); 3.79 ± 0.12	U87 (WST-1); 61.45 ± 3.64									
<b>146b</b>	A549 (WST-1); 3.30 ± 0.14	HeLa (WST-1); 2.22 ± 0.07	WI-38 (WST-1); 2.10 ± 0.17								

	MCF-7 (WST-1); 1.82 ± 0.06	U87 (WST-1); 0.54 ± 0.07												
146c	HeLa (WST-1)	> 500	U87 (WST-1)	> 400	WI-38 (WST-1)	93.79 ± 8.45		n.d	302					
146d		2.13 ± 0.16		2.83 ± 0.13		2.80 ± 0.13								
147a		> 4000		> 900		> 900								
147b		11.65 ± 0.81		8.28 ± 0.09		7.01 ± 0.21								
148a	HT-29 (24h)	1.0 ± 0.1	HT-29 (48h);	0.8 ± 0.1			n.d		303					
148b		0.8 ± 0.1		0.6 ± 0.1		ROS								
149 * (A)	MCF-7; 86 ± 4		A549; 82 ± 4					n.d	304					
	B16; 71 ± 4		NIH 3T3 (N); 116 ± 5											
150a T	A549; 4.0 ± 0.4		Hela; 4.0 ± 0.6					n.d	305					
	MCF-7; 3.0 ± 0.4		NIH 3T3 (N); 5.0 ± 1.4											
150b T	A549; 3.0 ± 0.4		Hela; 2.0 ± 0.3		MMP/Apoptosis	Sub-G <sub>1</sub>	Mitochondria\\ds-DNA intercalation		305					
	MCF-7; 1.3 ± 0.3		NIH 3T3 (N); 1.0 ± 0.8											
150c T	A549; 5.0 ± 0.8		Hela; 4.0 ± 0.6			n.d			306					
	MCF-7; 4.0 ± 0.7		NIH 3T3 (N); 4.0 ± 0.6											
151a	n.d								306					
151b														
151c														
151d	HCT-116 (SRB); 0.38 ± 0.04		SiHa (SRB); 0.75 ± 0.1		S phase				306					
	NCI-H460 (SRB); 0.21 ± 0.05		SW480 (SRB); 0.88 ± 0.09											
• Chalcogen														
152a *	BE; 23.13 ± 3.83		MIA-Pa-Ca2; > 100			n.d		307						
	HT-29; > 100		ARPE-19 (N); > 100											
152b T	BE; 36.29 ± 8.68		MIA-Pa-Ca2; 17.12 ± 4.58											
	HT-29; 49.55 ± 2.97		ARPE-19 (N); 59.71 ± 1.75											
153a T	A549	7.44 ± 1.05	HeLa	6.43 ± 1.02	BEAS-2B (N)	13.01 ± 0.33		n.d	308					
153b T		12.56 ± 0.05		10.46 ± 0.50		24.60 ± 0.23								
153c T		4.98 ± 0.15		5.43 ± 0.49		9.98 ± 0.45								
153d T		3.79 ± 1.15		6.43 ± 0.01		11.50 ± 0.31	2B	G <sub>1</sub>	Lysosome					
154a *		0.442 ± 6	B16F10; 0.319 ± 5			MCF-7; 0.582 ± 6								
	CRL-2115 (N); 1.024 ± 5		CRL-2120 (N); 1.136 ± 4				ROS/Apoptosis	G <sub>2</sub>	DNA					
154b *	A549; 0.472 ± 5		B16F10; 0.358 ± 6			MCF-7; 0.597 ± 7								
								n.d						

	CRL-2115 (N); 1.037 ± 7	CRL-2120 (N); 1.232 ± 6						
154c *	A549; 0.456 ± 4	B16F10; 0.341 ± 5		MCF-7; 0.587 ± 4				
	CRL-2115 (N); 1.025 ± 8	CRL-2120 (N); 1.187 ± 8						
154d *	A549; 0.453 ± 5	B16F10; 0.354 ± 7		MCF-7; 0.568 ± 6				
	CRL-2115 (N); 1.028 ± 7	CRL-2120 (N); 1.254 ± 7						
154e *	A549; 0.446 ± 6	B16F10; 0.346 ± 5		MCF-7; 0.552 ± 5				310
	CRL-2115 (N); 1.017 ± 8	CRL-2120 (N); 1.215 ± 6						
155a T	A2780	0.09 ± 0.01	A2780cisR	0.06 ± 0.01	HEK-293T (N)	0.08 ± 0.01		
155b T		0.11 ± 0.02		0.06 ± 0.01		0.09 ± 0.02		
155c T		0.43 ± 0.01		0.66 ± 0.05		1.24 ± 0.06		
156a T	A2780	0.07 ± 0.01	HEK-293T (N)	0.03 ± 0.01				311
156b T		0.04 ± 0.01		0.03 ± 0.01				
156c T		0.06 ± 0.01		0.03 ± 0.01				
156d T		0.05 ± 0.01		0.08 ± 0.01				
156e T		0.03 ± 0.01		0.07 ± 0.01				
<b>• Ferrocene</b>								
157a	A549	50.09 ± 0.12	HeLa	75.56 ± 1.20	BEAS-2B (N)	82.51 ± 1.33		143
157b *		59.88 ± 0.08		77.90 ± 1.03		> 100		
157c T		27.58 ± 0.23		19.89 ± 1.09		73.11 ± 1.17		
157d *		41.28 ± 0.10		22.47 ± 0.63		> 100		
157e T		6.03 ± 0.05		9.50 ± 0.56		33.85 ± 0.35	2B	G <sub>1</sub> /G <sub>0</sub>
157f T		8.52 ± 0.18		9.86 ± 0.96		47.85 ± 0.19	2B	
158a T	A549	8.44 ± 0.59	A549/DDP	14.57 ± 0.98	BEAS-2B (N)	27.16 ± 0.96	1B	G <sub>1</sub> /G <sub>0</sub>
158b T		12.19 ± 0.92		12.48 ± 1.05		31.50 ± 0.61		n.d
159a T		30.34 ± 4.88	HeLa	21.42 ± 0.81		33.48 ± 0.41	1B	Lysosome
159b T		19.90 ± 0.66		13.90 ± 0.79		23.66 ± 0.72		
159c T		6.70 ± 0.40		7.42 ± 0.41		8.06 ± 0.03		
159d T		4.81 ± 0.27		5.51 ± 0.10		7.32 ± 0.42		
160	DI; > 110					Apoptosis	n.d	DNA
161a T		46.4 ± 2.5		59.0 ± 0.6		35.9 ± 3.4		n.d
								315
								316

<b>161b</b> <sup>T</sup>	A2780	11.7 ± 0.3	A2780cisR	7.6 ± 1.3	HEK-293T <sup>(N)</sup>	13.6 ± 2.0				
<b>161c</b> <sup>T</sup>		39.6 ± 3.0		36.7 ± 0.2		31.1 ± 0.3				
<b>162a</b> <sup>T</sup>	A549	33.1 ± 1.6	HeLa	13.1 ± 0.6	BEAS-2B <sup>(N)</sup>	12.5 ± 1.6		n.d		75
<b>162b</b> <sup>T</sup>		18.1 ± 1.2		12.5 ± 0.5		12.3 ± 0.9				
<b>162c</b> <sup>T</sup>		8.9 ± 1.7		10.5 ± 0.5		10.3 ± 2.3	<b>2A</b>	<b>G<sub>0</sub>/G<sub>1</sub></b>	Mitochondria	

• Heteronuclear

<b>163a</b> *	Caco-2	11 ± 1.0	HeLa	23.4 ± 0.9	HEK-293T <sup>(N)</sup>	> 200	MMP/Apoptosis	G <sub>2</sub> /M	Mitochondria & DNA	318	
<b>163b</b> *		23 ± 2.1		> 100		> 200		n.d			
<b>163c</b> *		8 ± 0.8		70.5 ± 0.8		> 200					
<b>163d</b> *		2.2 ± 0.4		14.2 ± 1.2		> 200	MMP/Apoptosis	G <sub>2</sub> /M	Mitochondria & DNA		
<b>164a</b> *	24h	A549; 35.5 ± 5.6 × 10 <sup>-3</sup>	MCF-7; 35.3 ± 6.5	DU-145; 12.8 ± 2.7 × 10 <sup>-7</sup>		Apoptosis	S phase	Nuclei	319		
		WM2664; 5.2 ± 4.1 × 10 <sup>-3</sup>		HEK-293T <sup>(N)</sup> ; 786.8 ± 11.2							
<b>164a</b> *	72h	A549; 42.4 ± 7.3 × 10 <sup>-5</sup>	MCF-7; > 1000	DU-145; 125.7 ± 3.4							
		WM2664; 137.1 ± 2.2		HEK-293T <sup>(N)</sup> ; 886.8 ± 12.7							
<b>164b</b> *	24h	A549; 11.2 ± 7.8 × 10 <sup>-3</sup>	MCF-7; 30.0 ± 0.7	DU-145; 10.8 ± 1.9 × 10 <sup>-4</sup>							
		WM2664; 9.9 ± 3.8 × 10 <sup>-3</sup>		HEK-293T <sup>(N)</sup> ; 756.8 ± 5.7							
<b>164b</b> *	72h	A549; 36.6 ± 2.8 × 10 <sup>-3</sup>	MCF-7; > 1000	DU-145; 122.7 ± 5.4							
		WM2664; 155.1 ± 3.2		HEK-293T <sup>(N)</sup> ; 856.8 ± 15.9							
<b>164c</b> *	24h	A549; 31.6 ± 7.6 × 10 <sup>-3</sup>	MCF-7; 24.2 ± 7.2	DU-145; 14.2 ± 2.4 × 10 <sup>-3</sup>			S phase				
		WM2664; 10.1 ± 2.2 × 10 <sup>3</sup>		HEK-293T <sup>(N)</sup> ; 775.8 ± 15.7							
<b>164c</b> *	72h	A549; 36.0 ± 2.2 × 10 <sup>-2</sup>	MCF-7; > 1000	DU-145; 126.2 ± 4.4							
		WM2664; 229.3 ± 25.9		HEK-293T <sup>(N)</sup> ; 822.8 ± 12.3							
<b>164d</b> *	24h	A549; 18.1 ± 1.3 × 10 <sup>-3</sup>	MCF-7; 10.5 ± 0.8	DU-145; 10.1 ± 2.9 × 10 <sup>-3</sup>							
		WM2664; 6.2 ± 2.4 × 10 <sup>-3</sup>		HEK-293T <sup>(N)</sup> ; 676.8 ± 9.2							
<b>164d</b> *	72h	A549; 0.6 ± 2.9 × 10 <sup>-4</sup>	MCF-7; > 1000	DU-145; 53.6 ± 0.40			S phase				
		WM2664; 212.2 ± 10.5		HEK-293T <sup>(N)</sup> ; 776.8 ± 15.3							
<b>165</b>		MDA-MB-468; 24.12 ± 1.1				<b>2A</b>	G <sub>2</sub> /M	Mitochondria	320		

<sup>1</sup> IC<sub>50</sub> is defined as the concentration of drug required to inhibit cell growth by 50% compared to the control. Each value represents the mean ± standard deviation from two or three independent experiments.

<sup>2</sup> Cell viability was determined by the MTT assay, other than this is mentioned.

<sup>T</sup>: The complex was examined against normal cell line; \*: The complex was safe to the tested normal cell with IC<sub>50</sub> > 100 µM;. <sup>N</sup>: Normal cell line; n.d: not determined.

Mechanism of action according to Fig. 3 (within the main text): **1A** pathway: NADH/ROS/MMP/Apoptosis. **1B** pathway: NADH/ROS/LMP/Apoptosis. **1AB** pathway: NADH/ROS/MMP/LMP/Apoptosis. **2A** pathway: ROS/MMP/Apoptosis.

**Full names and Abbreviations of Cell lines:** 16HBE, human bronchial epithelial cell lines; 518A2, human melanoma cell line; 5637, human bladder cancer cells; 8505C, human thyroid carcinoma; ARPE-19, human retinal epithelial cells; A253, human submandibular gland carcinoma; A2780, human ovarian carcinoma cell lines; A2780R/A2780cisR; Cisplatin resistant human ovarian; A427, human lung carcinoma cells; A549, Human lung carcinoma cell line; A549R, cisplatin resistant human lung carcinoma cell line; BEAS-2B, human non-tumorigenic lung epithelial cell line; BEL-7402, human hepatoma cell line; BHK21, normal healthy kidney cells; Caco-2, human colon carcinoma cell lines; Capan2, pancreatic adenocarcinoma cell line; CH1/PA-1, ovarian teratocarcinoma cell lines; CHO, normal Chinese hamster ovarian cells; CHO-K1, Chinese Hamster Ovary-K1 Cells; CNS cancer, Central nervous system cancer; Colo-829, human, umbilical metastasis, melanoma; CRL-2115, human skin fibroblast adherent; CT26, mouse colon carcinoma; DL, Dalton's ascites lymphoma; DLD-1, human colorectal adenocarcinoma cells; DU-145, human prostatic carcinoma; EA.hy926, human umbilical vein endothelial cell line; HaCaT, human keratinocyte cell line; HCT-116, colon cancer cell line; HCT-116 p53-/, colon cancer cell line depleted p53; HEK-293T, human embryonic kidney cell lines; HeLa, cervical cancer cell line; HepG2, human liver cancer cell line; HFF-1, human skin cell lines; HL-60, human leukaemia; HT29, human colorectal adenocarcinoma cells; KMST-6, human skin fibroblast cell line; LCLC-103H, human lung carcinoma cells; LoVo, colorectal adenoma; LO2, human normal liver; MCF-7, human breast cancer cell line; MCF-10, human breast cancer cell lines; MDA-MD-435S, human breast cancer cell lines; MDB-MA-231, human breast cancer cell line; MES-OV, ovarian cancer cells; MIA PaCa-2, pancreatic carcinoma cell lines; MRC-5, human fetal lung fibroblast cells; OVCAR-3, ovarian adenocarcinoma cell line; Panc-1, pancreatic ductular adenocarcinoma cell line; PC3, human prostatic carcinoma; PNT2, normal prostate cell line; Saos, osteosarcoma cell line; SiHa, cervical cancer cell line; SISO, human uterine cervical adenocarcinoma cells; SKOV-3, human ovarian cancer cell line; SW620, human colon cell lines; U87, human glioblastoma cell lines; WHCO1, esophageal cancer cell line; WI-38, human fetal lung fibroblast cells.