The 7th International Electronic Conference on Medicinal Chemistry (ECMC 2021)

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Biological effects of copper, silver and gold camphorimine complexes in ovarian cancer cells

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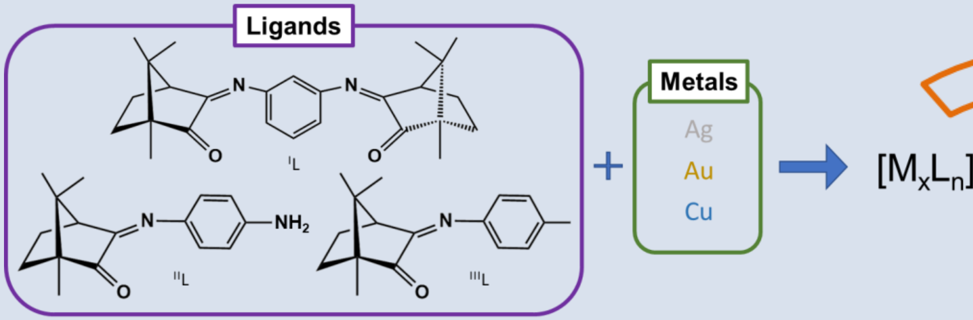
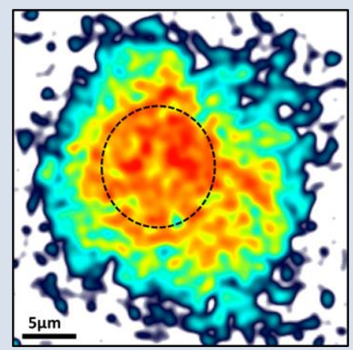
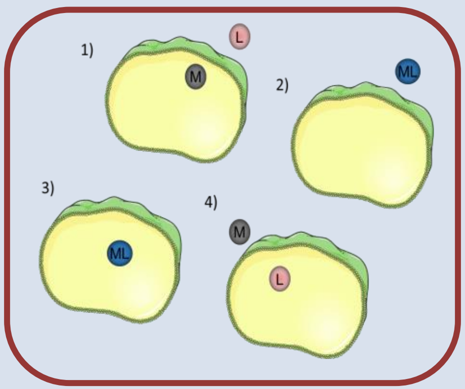
Biological effects of copper, silver and gold camphorimine complexes in ovarian cancer cells



	IC50 (µM)			
	A2780	OVCAR 3	V79	HDF
$[CuCl_2{}^{III}L] \cdot H_2O \cdot HCl$	147 ± 37	115 ± 25	>200	>200
$[(Ag^{III}L)_2(\mu\text{-}O)] \cdot 2H_2O$	0.66 ± 0.28	0.63 ± 0.23	3.0 ± 0.9	28 ± 8.5
$K_2[\{Au(CN)_2\}_2{}^{III}L_3] \cdot {}^1/{}_2H_2O$	0.077 ± 0.01	0.08 ± 0.03	0.48 ± 0.06	0.46 ± 0.17





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Surgical excision combined with chemotherapy with cisplatin derivatives is the main treatment of ovarian cancer. Although it is effective as first-line regime, 75% of the patients can experience recurrence, becoming vulnerable to develop resistance to chemotherapy.

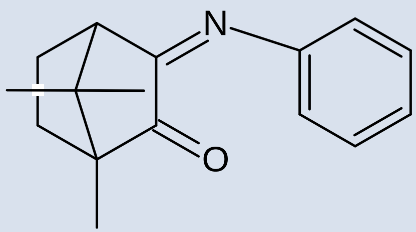
The unique biological properties of camphorimine complexes based on metal sources such as CuCl, CuCl2, Ag(NO3), Ag(OAc) and KAu(CN)2 anticipate their potential use as alternative to cisplatin based therapies.

Some of us (MFNN Carvalho et al.) have been exploring the biological activity of silver camphorimine complexes against ovarian cancer cells (A2780/A2780cisR). The results obtained revealed higher activity than cisplatin in cancer cells and low toxicity in non-tumoral cells HEK 293.

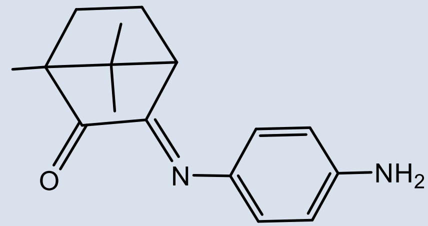
Encouraged by such results, we investigated biological effects of different metals on the properties of camphorimine complexes in order to evaluate their potential therapeutic value. Herein we studied the cytotoxic activity of these complexes, their cellular distribution, uptake and mechanism of action in OVCAR3 ovarian cancer cells. Due to the high spatial resolution in the micrometer range and high sensitivity for metal detection, nuclear microscopy techniques were used to image the metal distribution and evaluate the metal uptake in a whole cell. Data obtained indicate that the low cellular uptake of copper by OVCAR3 cells can explain the lower cytotoxicity of these complexes. Only [(CuCl)2(OC10H14NC6H4NH2)] caused a slight copper accumulation in the nuclear region. Results highlight the importance of characterizing the cellular uptake and distribution in cells to have clues on the cellular targets and understand complexes binding ability in cells.

Keywords: Anticancer activity; Camphor derivatives; Cancer ovarian cell lines; Copper, silver and gold camphorimine complexes.

Introduction



L1



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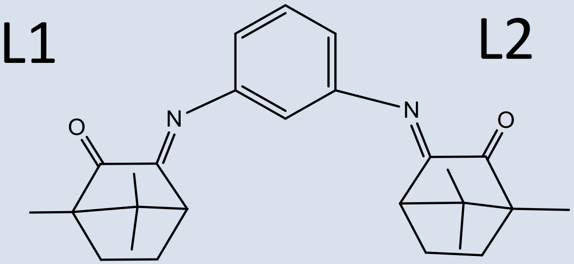


L3

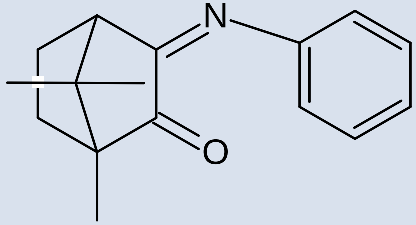
- Cytotoxic Activity
- Stability in Physiological Medium
- Cellular Uptake (Microprobe)
- PIXE Analysis

ID	Complex	Ligand
JP318	$[CuCl_2L_2]$	L1
JP228B	$[\{AgL\}_2(\mu\text{-}O)]$	
40/SL	$[Ag(NO_3)L]$	
JP301	$K[Au(CN)_2L_3]$	

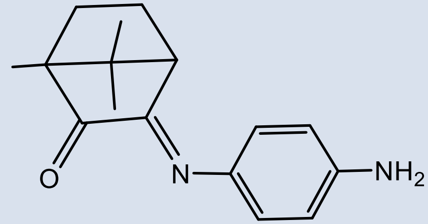
ID	Complex	Ligand
CS 35	$[\{CuCl\}_2L]$	L2
JP246B	$[Ag(OH)L]CH_3COOH$	
JP115	$K[Au(CN)_2L]\cdot H_20$	

ID	Complex	Ligand
TF392	$[(CuCl)_3L]$	L3
14IB	$[CuCl_2L]\cdot 2H_2O$	

Introduction



L1



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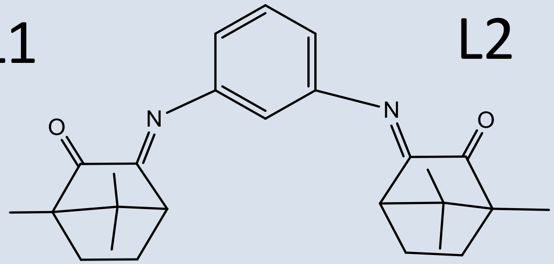

L3

Interaction with DNA

ROS Production

Membrane Lipid Peroxidation

Superoxide Production

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ID	Complex	Ligand
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Cytotoxic Activity Studies

Copper complexes are the less active compounds

$$*SI = selectivity\ index = \frac{IC50(HDF)}{IC50(OVCAR3)}$$

Clinical potential: SI > 10

Gold complexes are the most active compounds

	IC50 (µM)				
Copper complexes	A2780	OVCAR3	V79	HDF	**SI***
CS35	45 ± 11	72 ± 9.1	34.5 ± 9.7	>200	2.7
14/B	49 ± 14	38 ± 8.5	>200	>200	5.3
TF392	43 ± 9.1	38 ± 7.7	45 ± 10	50 ± 27	1.3
JP318	147 ± 37	115 ± 25	>200	>200	1.7
Silver complexes					
40/SL	2.24 ± 0.57	1.43 ± 0.31	>200	>200	139.9
JP228B	0.66 ± 0.28	0.63 ± 0.23	3.0 ± 0.9	28 ± 8.5	44.4
JP246B	10.4 ± 2.9	8.4 ± 3.3	34 ± 15	>200	23.8
Gold complexes					
JP301	0.077 ± 0.01	0.08 ± 0.03	0.48 ± 0.06	0.46 ± 0.17	5.8
JP115	0.04 ± 0.02	0.07 ± 0.01	1.44 ± 0.30	0.58 ± 0.11	8.3

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Cytotoxic Activity Studies

Ligand	OVCAR3 IC50 (μM)
L1	>200
L2	>200

Metal Precursors	OVCAR3 IC50 (μM)
$AgNO_3$	2.66 ± 1.0
$Ag(CH_3COO)_2$	3.38 ± 2.0
$KAu(CN)_2$	4.97 ± 0.2
CuCl	>200
$CuCl_2$	>200

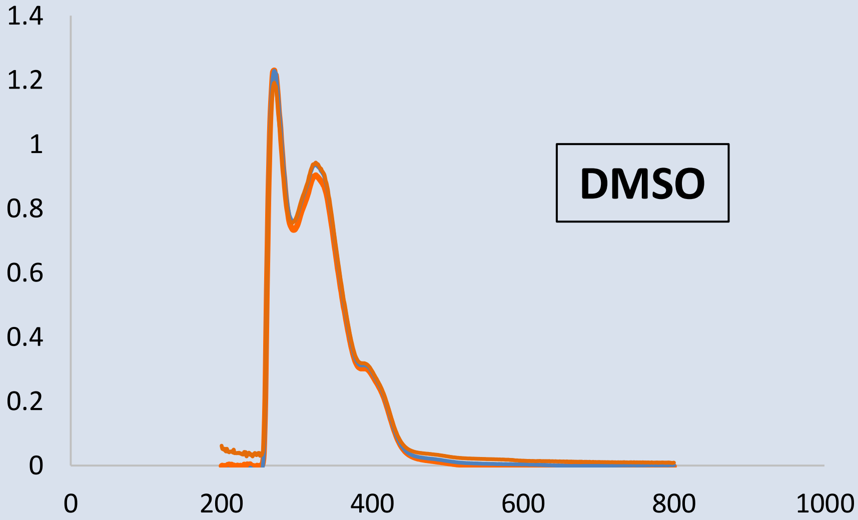
Inactive Ligands

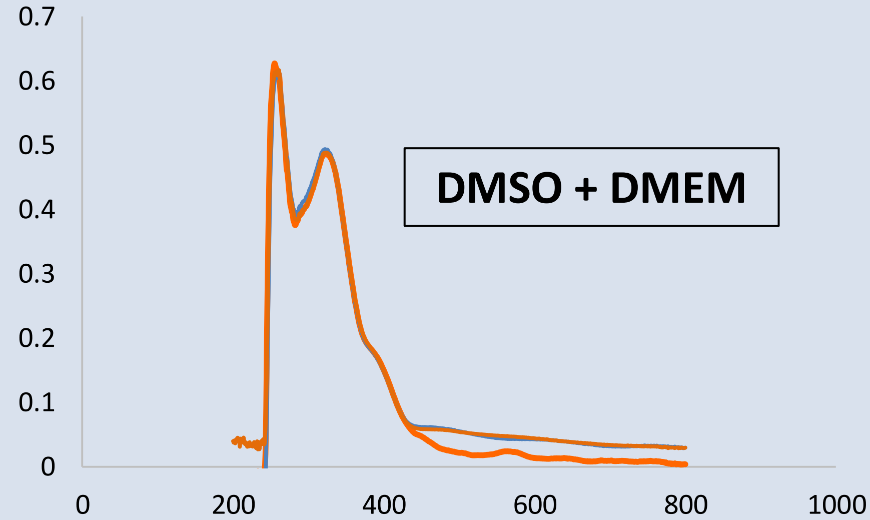
Inactive Copper Precursors

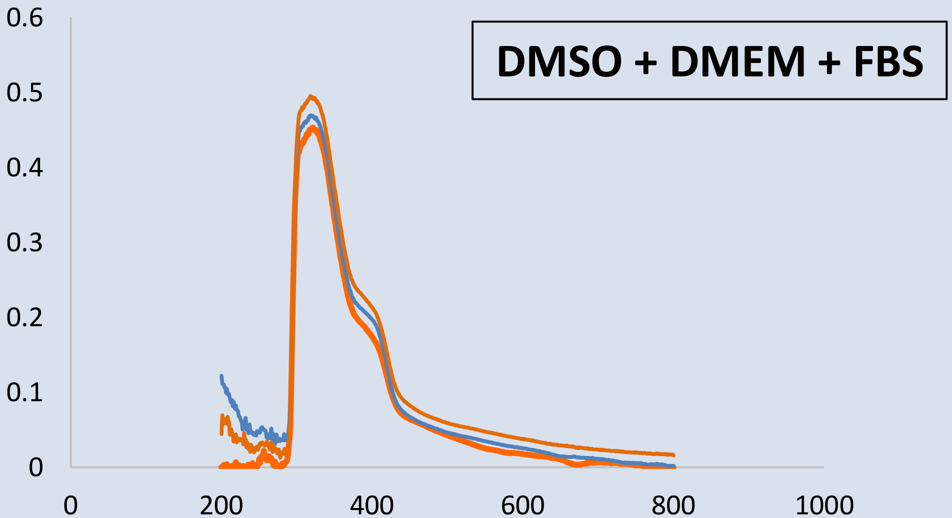
Active Silver and Gold Precursors

Stability Studies

40SL







Vertical Axis:
Absorbance (Abs)

Horizontal Axis:
Wavelength (nm)

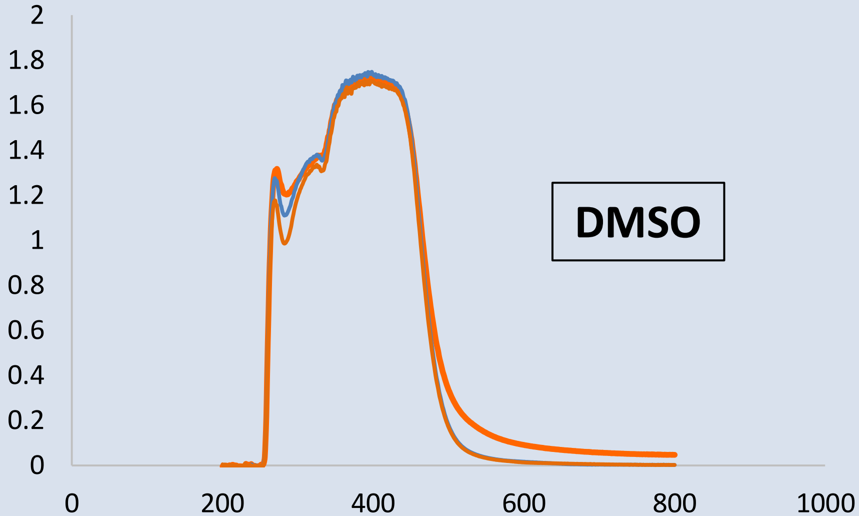
T = 0h

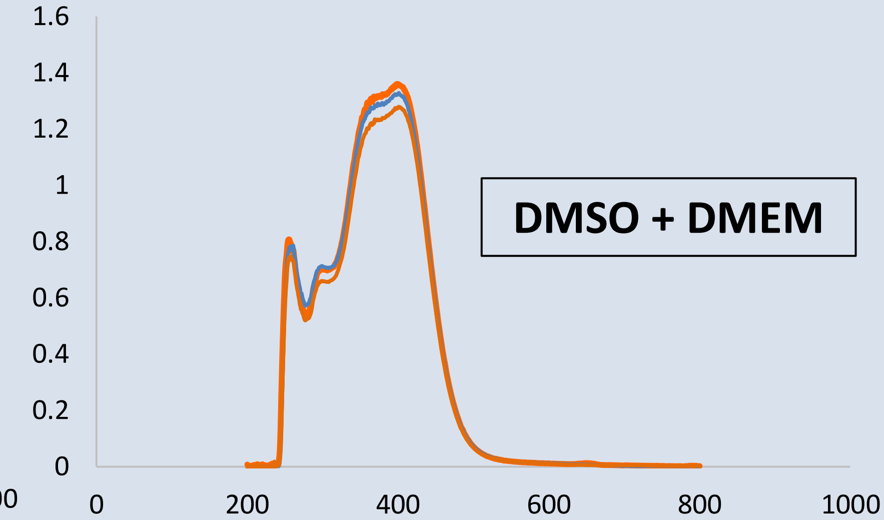
T = 24h

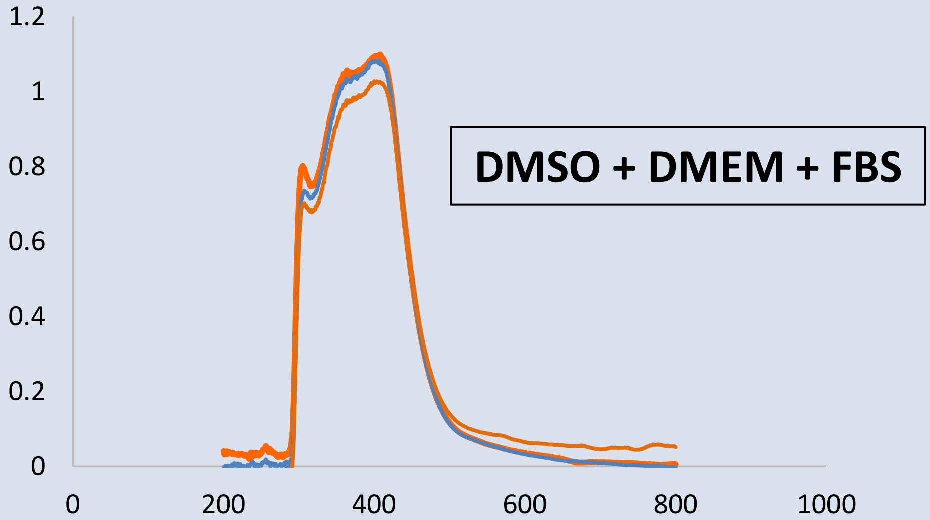
T = 48 h

Stability Studies

JP115





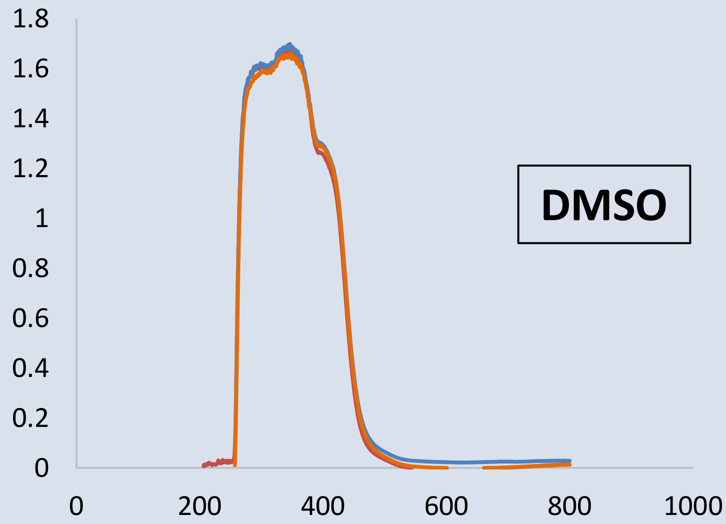


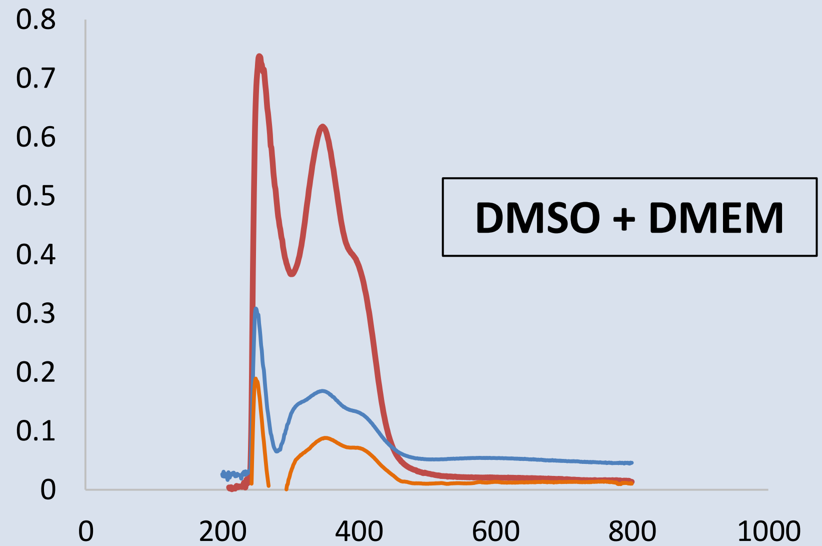
Vertical Axis:
Absorbance (Abs)

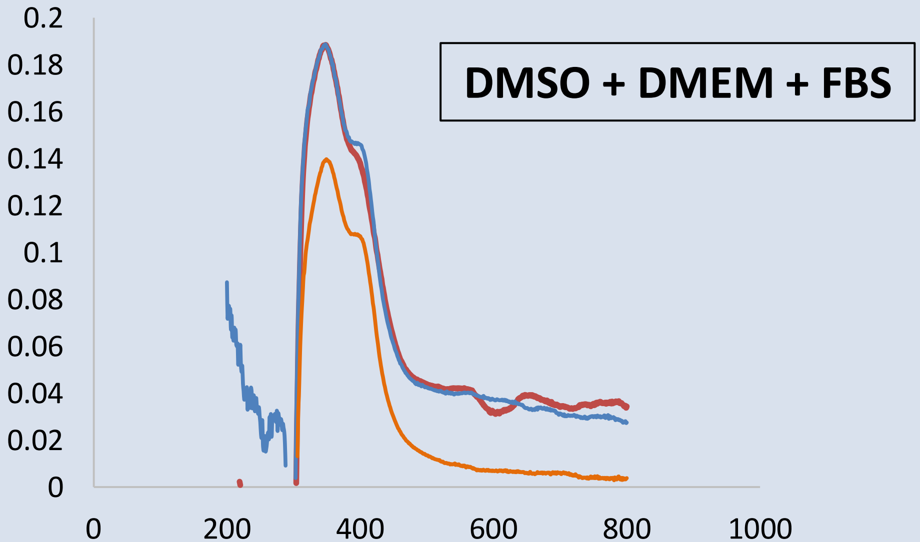
Horizontal Axis:
Wavelength (nm)

T = 0h
T = 24h
T = 48 h

Stability Studies







Vertical Axis:
Absorbance (Abs)

Horizontal Axis:
Wavelength (nm)

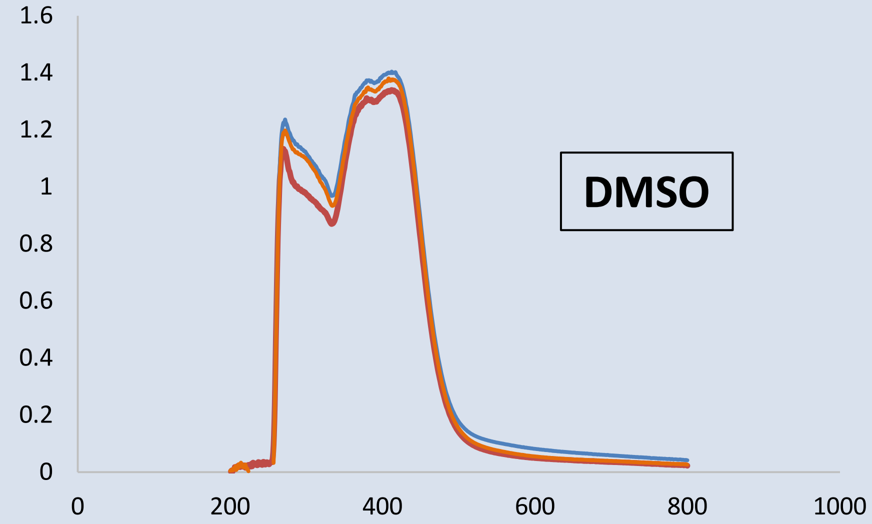
T = 0h

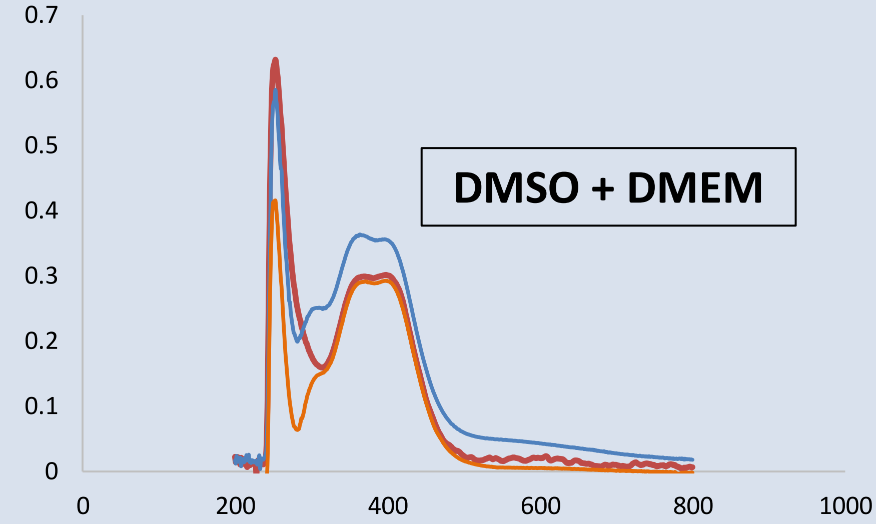
T = 24h

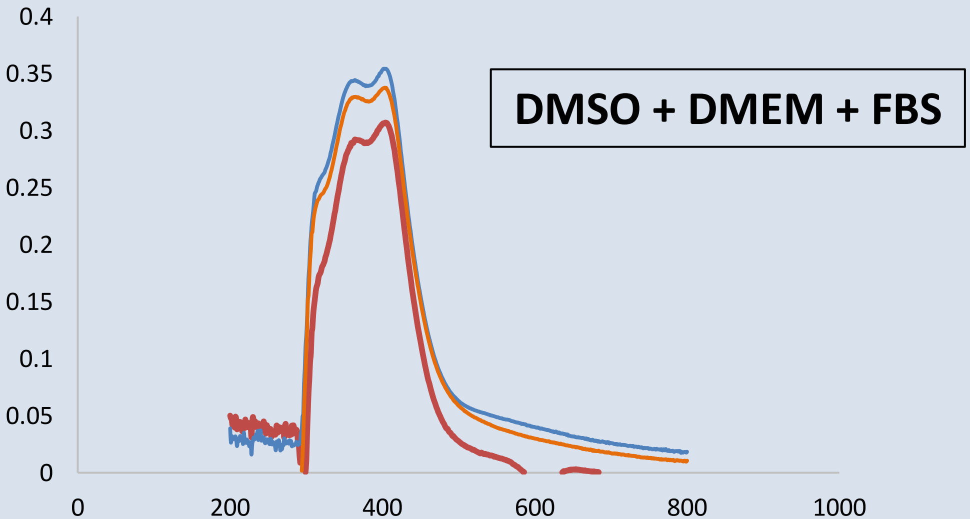
T = 48 h

Stability Studies

CS35







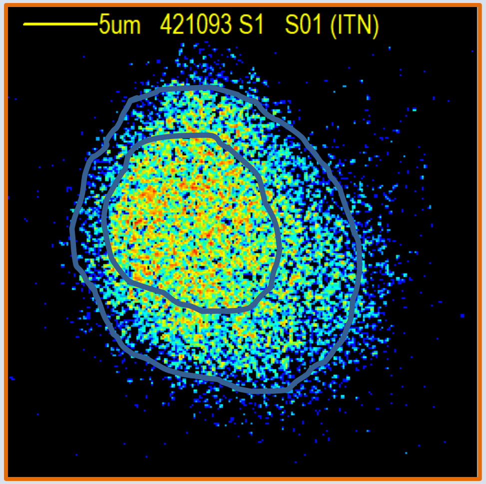
Vertical Axis:
Absorbance (Abs)

Horizontal Axis:
Wavelength (nm)

T = 0h
T = 24h
T = 48 h

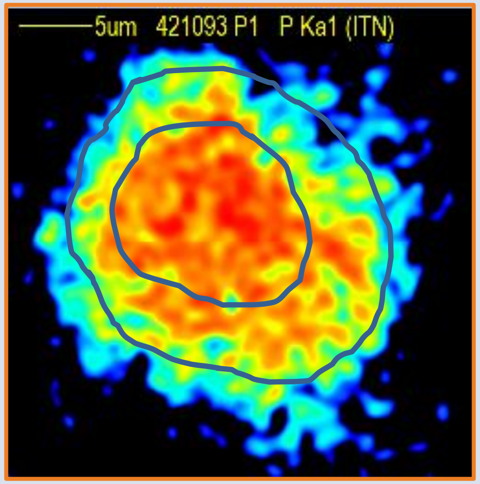
Microprobe Uptake Studies

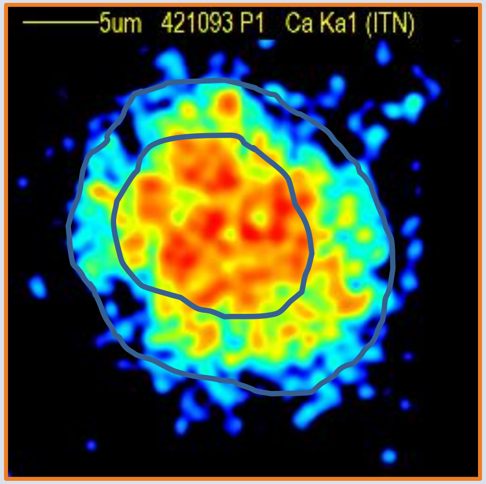
OVCAR3 with CS35

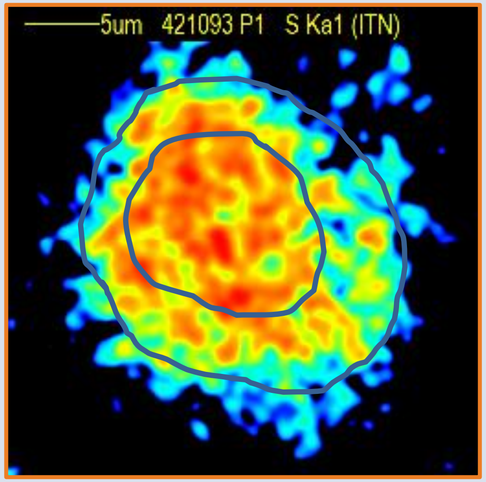


STIM IMAGE (S01)

- Transmitted Protons
- Density Variations Map



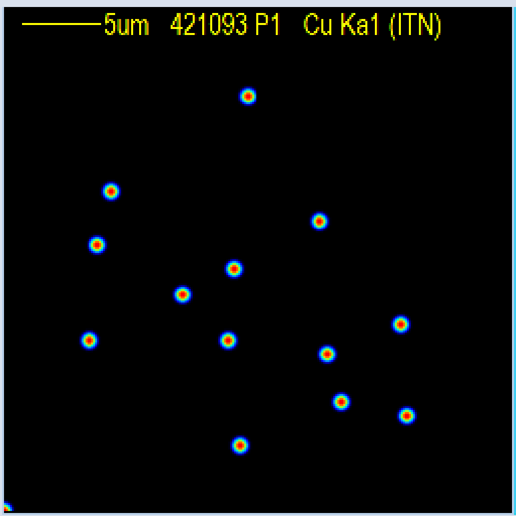


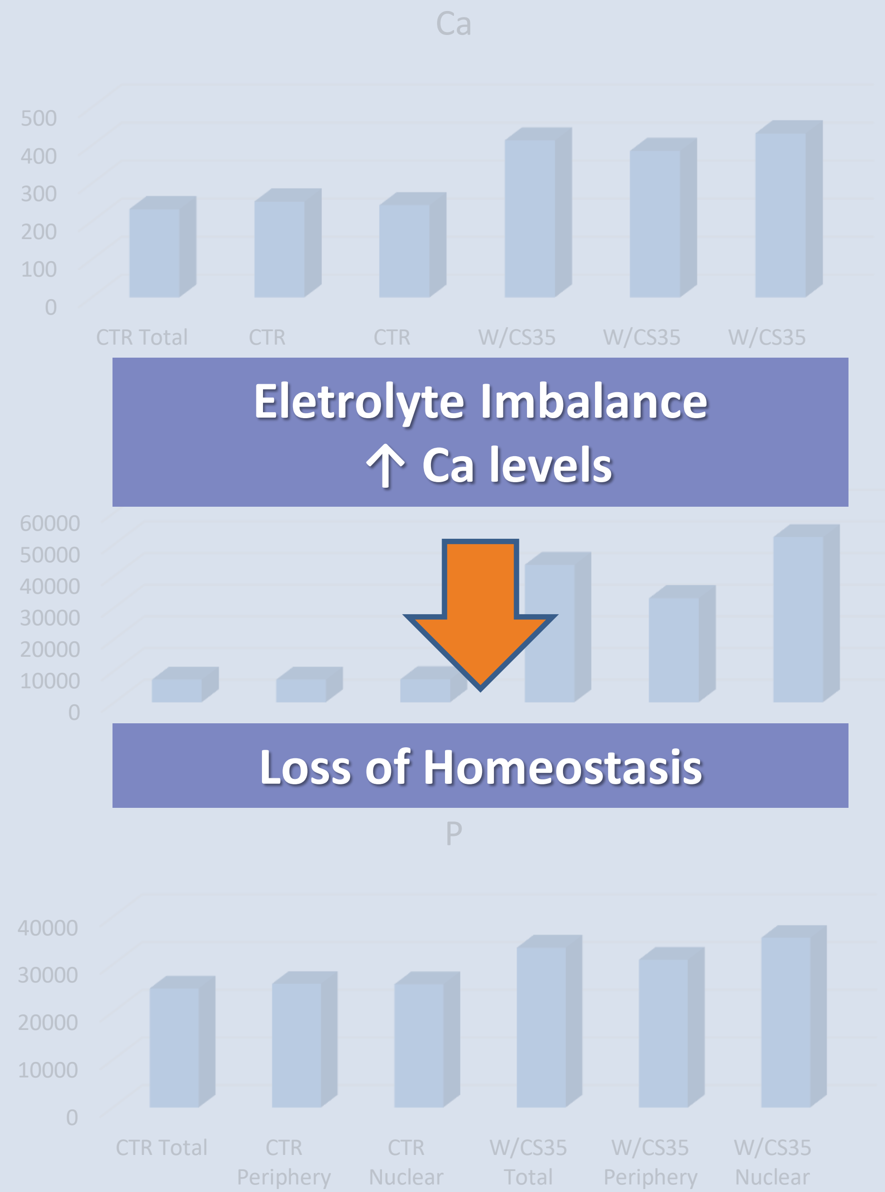


PIXE IMAGE (P, Ca, S)

- X-Ray Radiation
- Elemental Distribution

Microprobe Uptake Studies





Eletrolyte Imbalance
↑ Ca levels

Loss of Homeostasis

PIXE Analysis

Sample	K	SD(%)	Ca	SD(%)	Fe	SD(%)	Cu	SD(%)	Zn	SD(%)
CS35 (72µM)	536.74	0.20	49.61	18.68	13.20	2.96	3.39	8.32	10.87	15.99
JP115 (22µM)	902.26	0.43	49.89	25.25	8.61	2.56	0.90	11.43	6.85	19.22
JP246B (37µM)	835.71	0.77	17.68	18.58	7.19	3.30	0.28	1.68	7.43	14.77
Control	544.09	1.60	42.42	5.75	18.45	0.74	0.74	28.35	8.21	14.69

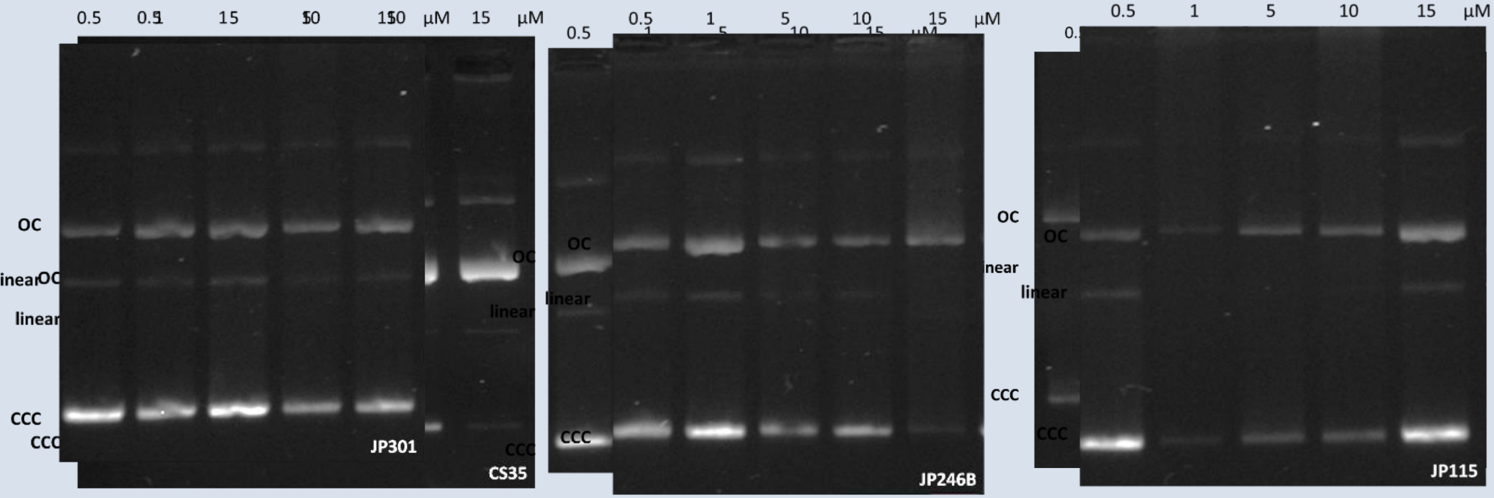
PIXE Analysis

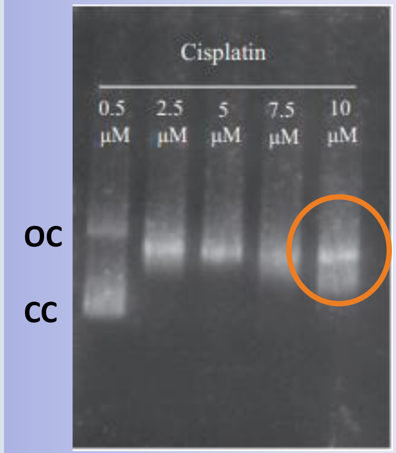
Sample	K	SD(%)	Ca	SD(%)	Fe	SD(%)	Cu	SD(%)	Zn	SD(%)
CS35 (72µM)	536.74	0.20	49.61	18.68	13.20	2.96	3.39	8.32	10.87	15.99
JP115 (22µM)	902.26	0.43	49.89	25.25	8.61	2.56	0.90	11.43	6.85	19.22
JP246B (37µM)	835.71	0.77	17.68	18.58	7.19	3.30	0.28	1.68	7.43	14.77
Control	544.09	1.60	42.42	5.75	18.45	0.74	0.74	28.35	8.21	14.69

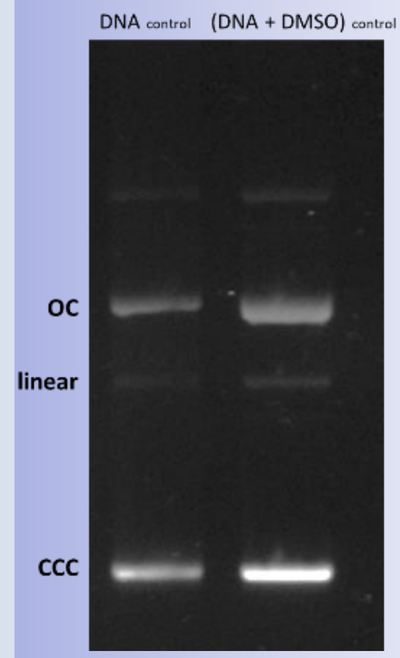
Sample	Cu	SD(%)
CS35 (72µM)	3.39	8.32
JP115 (22µM)	0.90	11.43
JP246B (37µM)	0.28	1.68
Control	0.74	28.35

Indicates the vestigial presence of Copper in OVCAR3 cells treated with CS35

Complexes-DNA interaction



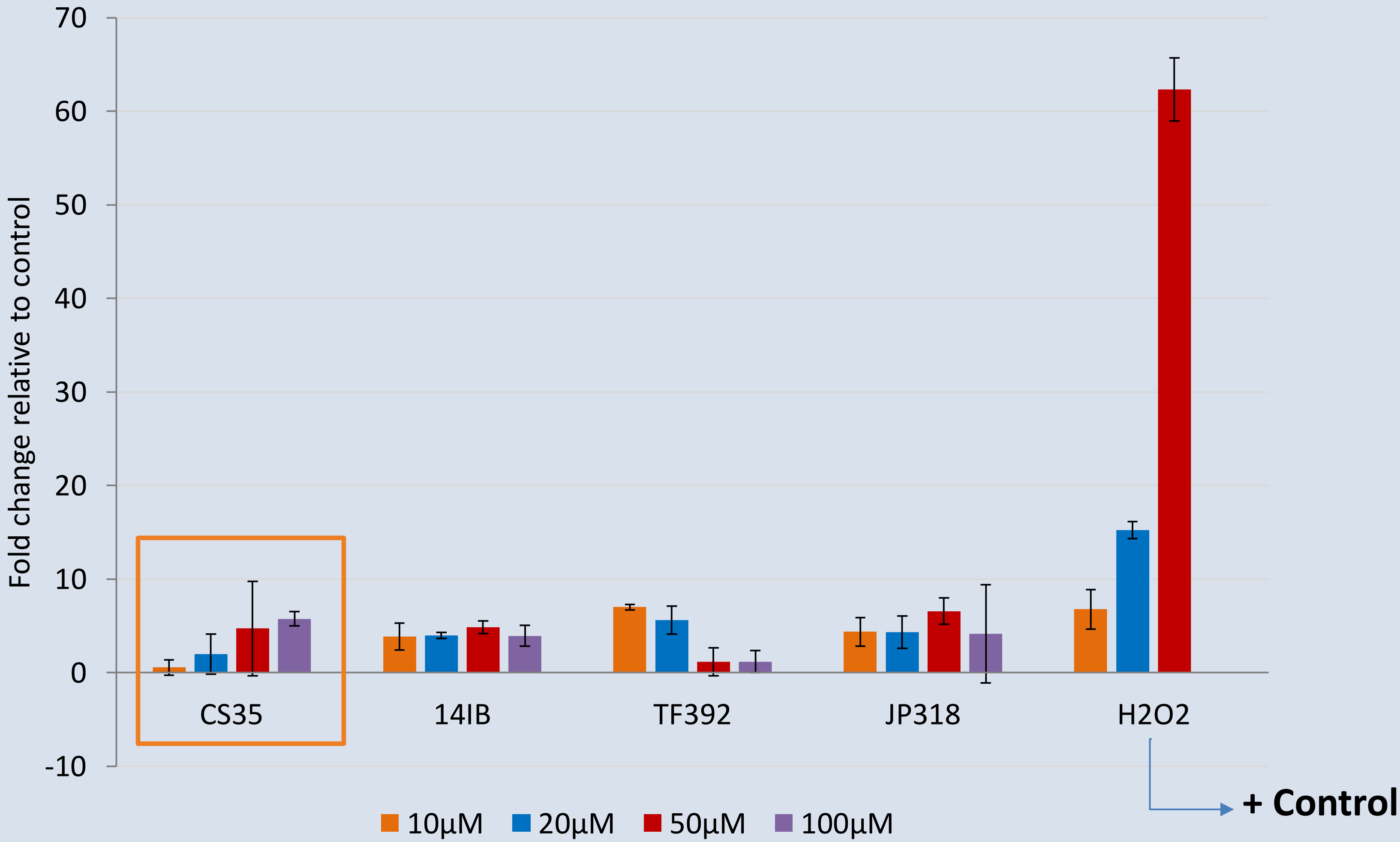




Any of the complexes interact with the DNA molecule

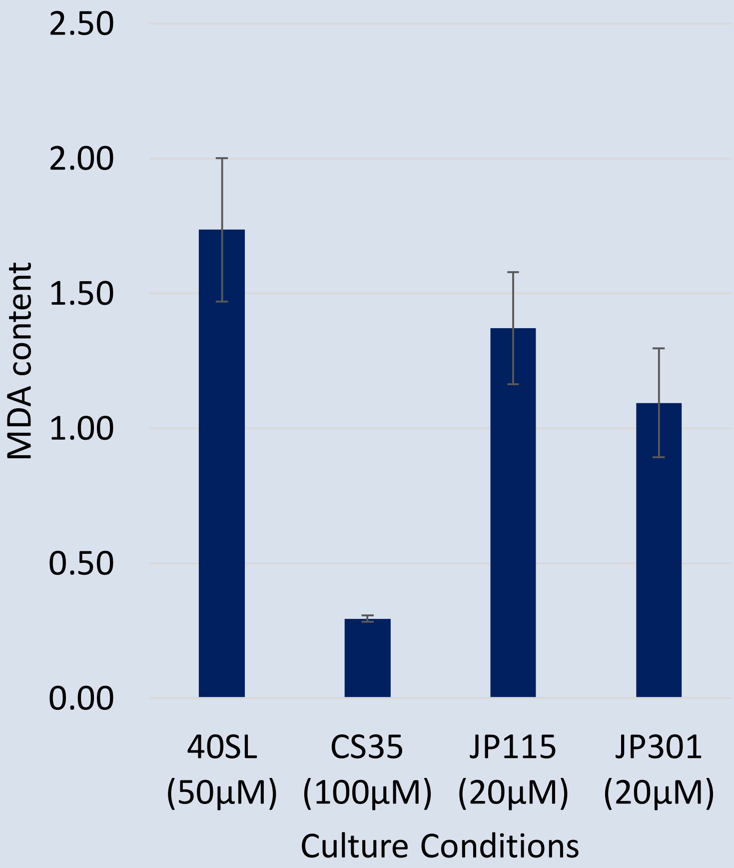
Different mechanism of action from Cisplatin's.

Production of ROS



Production of ROS

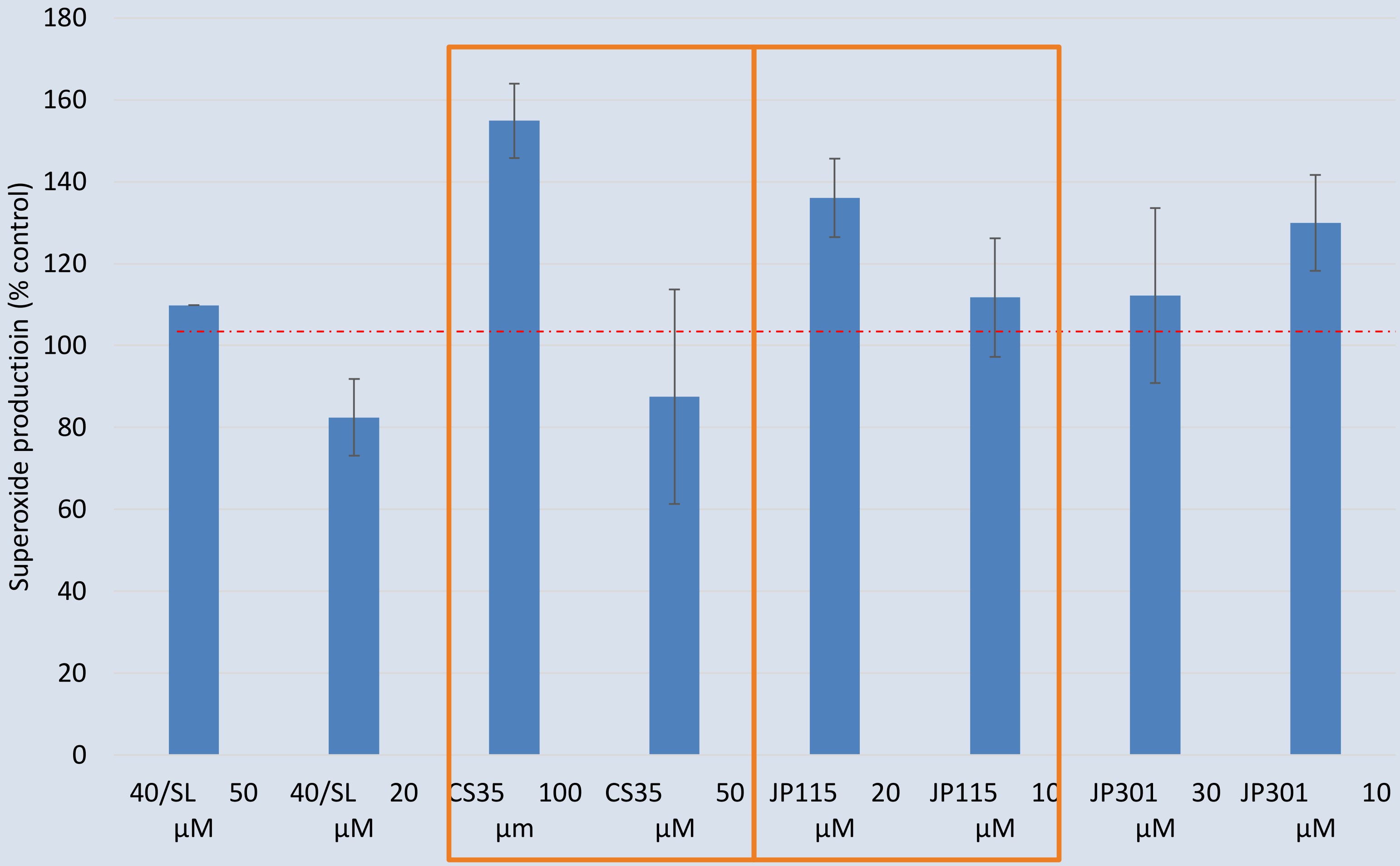
Membrane lipid peroxidation



Most effective complexes in producing reactive oxygen species (ROS)

Higher Lipid Peroxidation

Superoxide Production



Conclusions

Copper complexes ↓ Cytotototoxic
than Gold and Silver complexes w/= ligands

Low stability in physiological medium ► ↓ Ability to enter the cell
↓ Cytotoxic Activity

Mechanism of Action without Linking to DNA

CS35, JP301, JP115:
Dose Dependent ROS Production ↔ Membrane Lipid Peroxidation

CS35, JP115:
Dose Dependent Superoxide Production

40 SL
High Selectivity

Acknowledgments

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