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New synthesis chemotherapeutic agents and melatonin as coadjutant: Antitumoral potential

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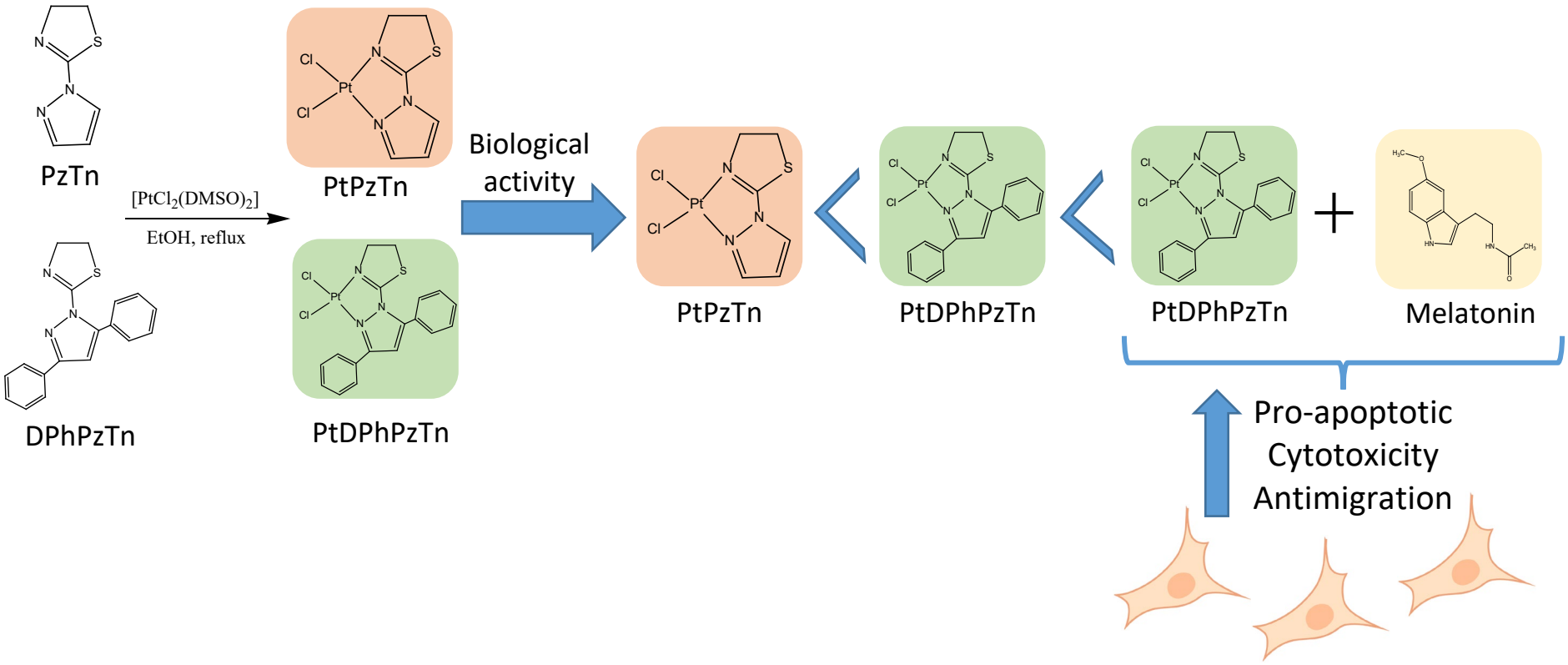
New synthesis chemotherapeutic agents and melatonin as coadjutant: Antitumoral potential

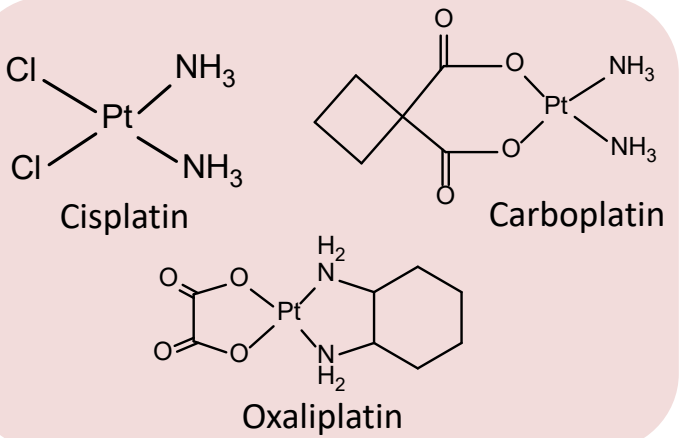
Graphical Abstract

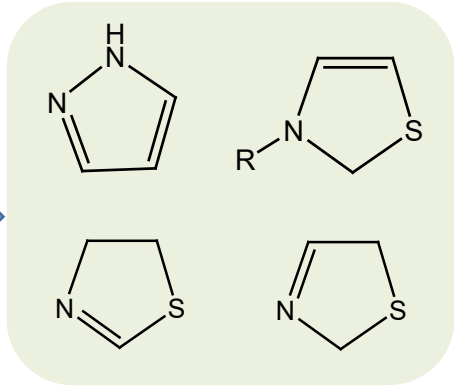


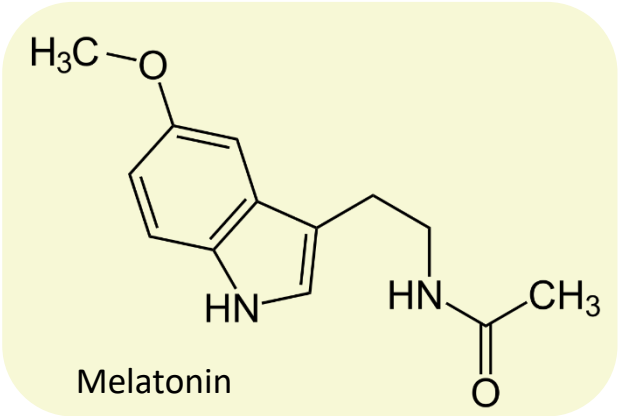
Abstract:
One of the most widely used strategies for drug development is the coordination of bioactive ligands to transition metals, which could improve biological activity. Herein, we have reported the synthesis and characterization of two Pt(II) complexes with thiazoline rings (PtPzTn and PtDPhPzTn) and checked whether the presence of aromatics groups in the ligand could influence the biological activity of the complexes. Likewise, we have analysed their potential anticarcinogenic ability in the absence or presence of melatonin, a renowned antioxidant molecule with antitumoral actions, in several tumour cell lines. Our findings indicated that PtDPhPzTn was far more effective in terms of cytotoxicity than both PtPzTn and cisplatin (reference drug), especially in triple breast negative (TNBC) MDA-MB-231 cells (IC_{50} = 10.4 µM). Besides, its pro-apoptotic effect in TNBC cells was markedly higher than that observed in non-tumour breast epithelial MCF10A cells (~60% vs. ~30% apoptosis induction, respectively). Moreover, PtDPhPzTn significantly reduced the ability of MDA-MB-231 cells to migrate. Most importantly, co-stimulation with PtDPhPzTn and melatonin considerably enhanced the population of apoptotic cells and noticeably increased the anti-migratory actions of the complex. Therefore, our results suggest that aromatic groups improved the cytotoxicity of the compound and provide evidence that PtDPhPzTn and melatonin could be potentially applied to TBNC treatment as powerful synergistic agents.

Keywords: Apoptosis, Cancer, Cytotoxicity, Melatonin, Pt(II) complexes

Introduction



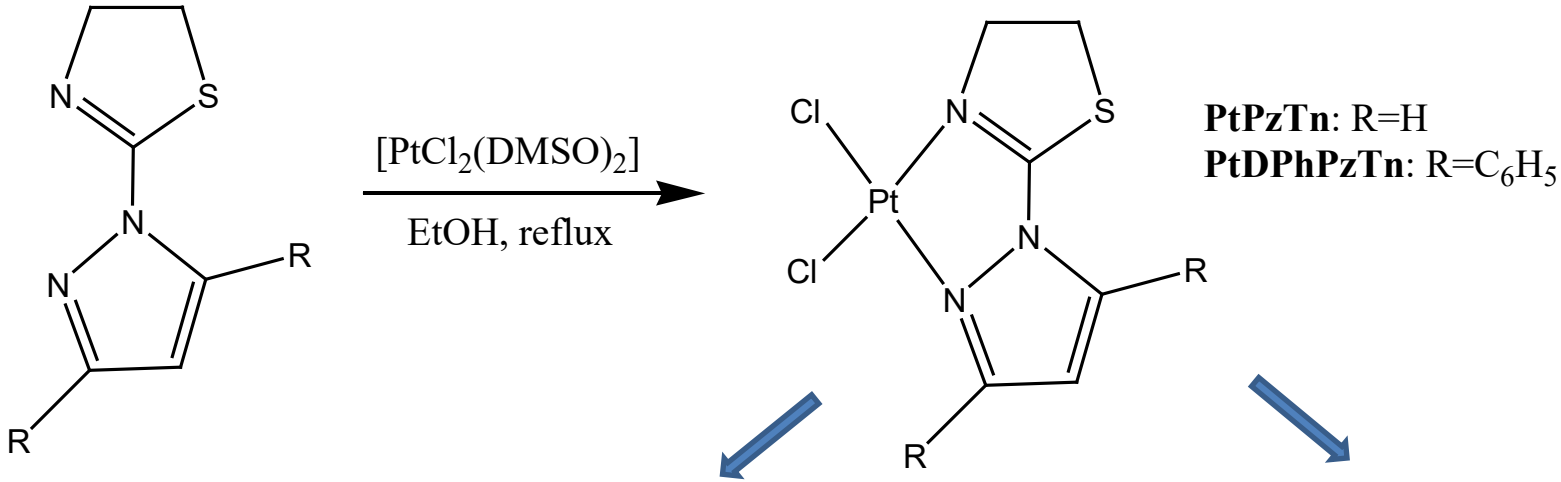




Antitumoral effects

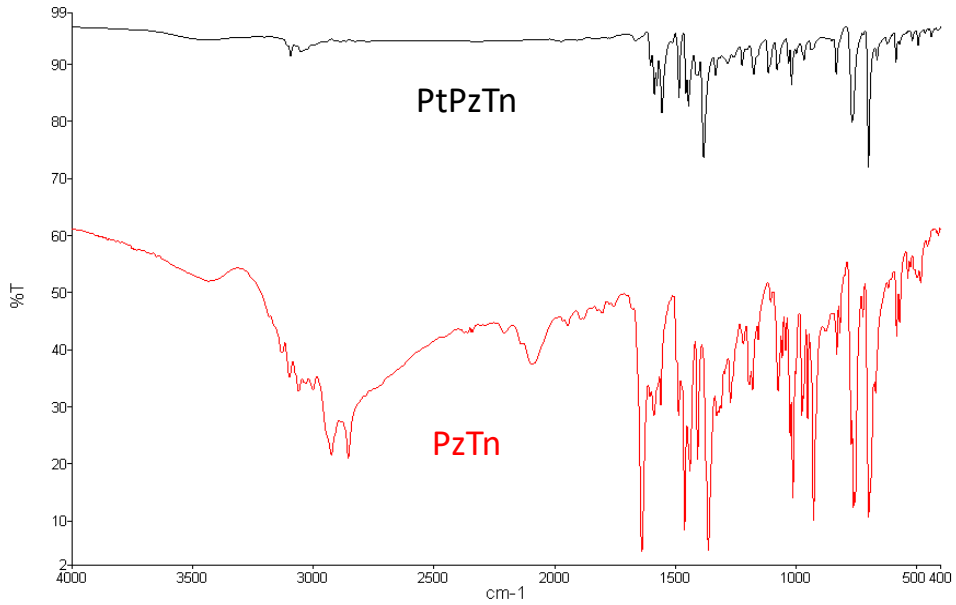
Results and discussion

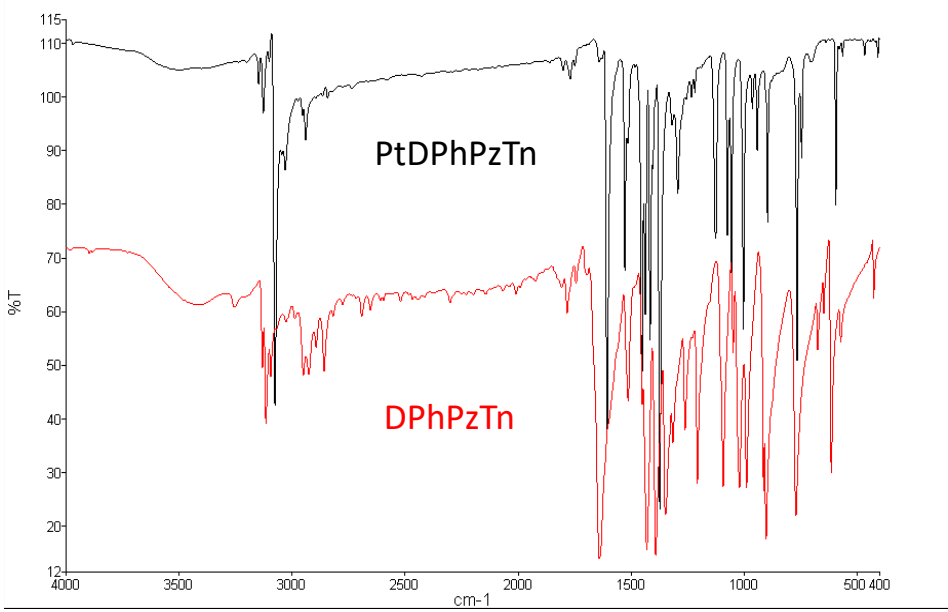
Synthesis:



Results and discussion

IR spectroscopy:



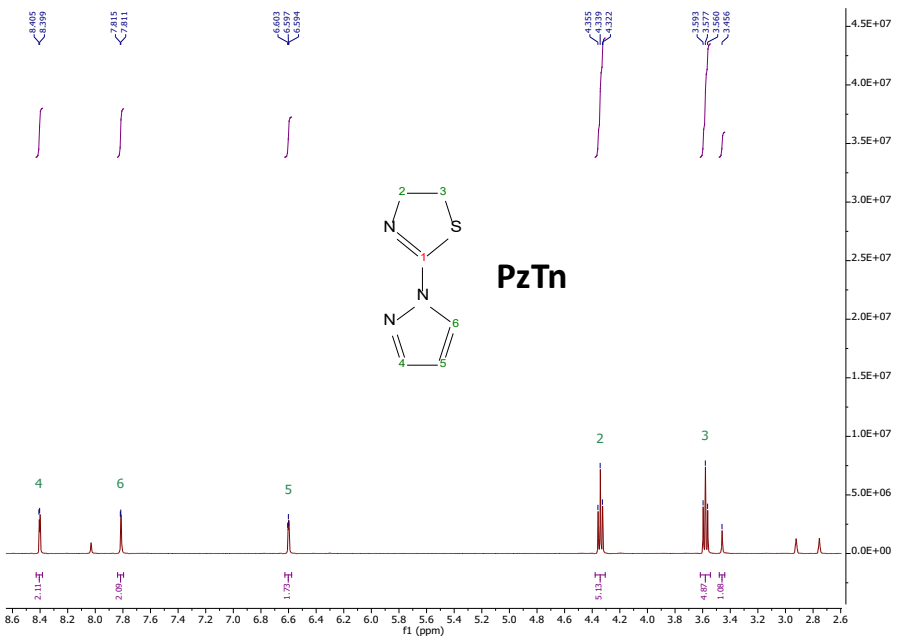


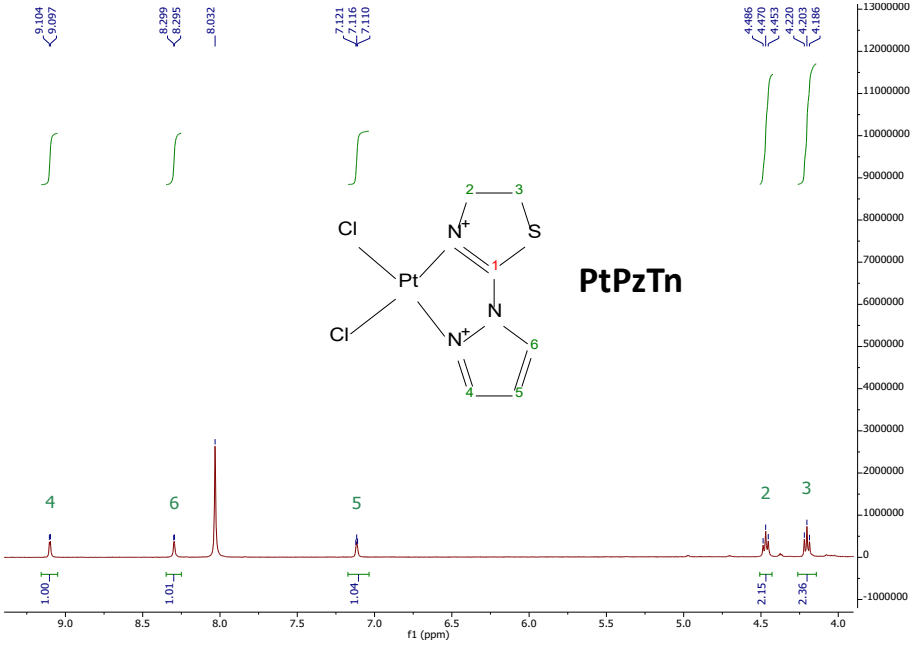
	PzTn	PtPzTn
$W_1[\nu(C=N)]$	1641	1596
Pyrazole ring vibrations	1514	1518
	1382	1413
	1350	1359
	991	1004

	DPhPzTn	PtDPhPzTn
$W_1[\nu(C=N)]$	1639	1587
Pyrazole ring vibrations	1560	1555
	1408	1412
	1319	1319
	1000	998

Results and discussion

^{1}H NMR spectroscopy:

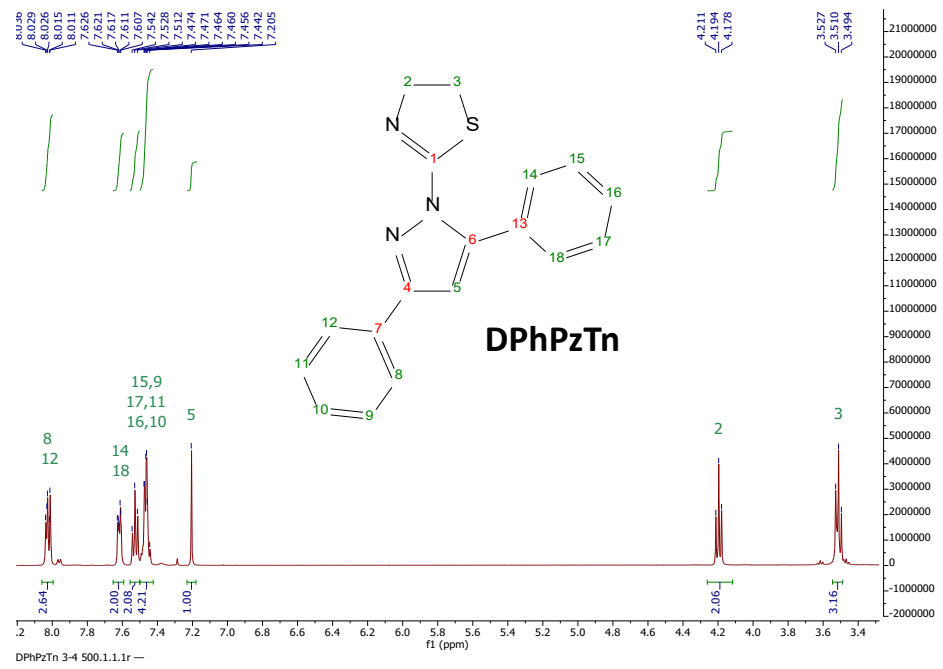


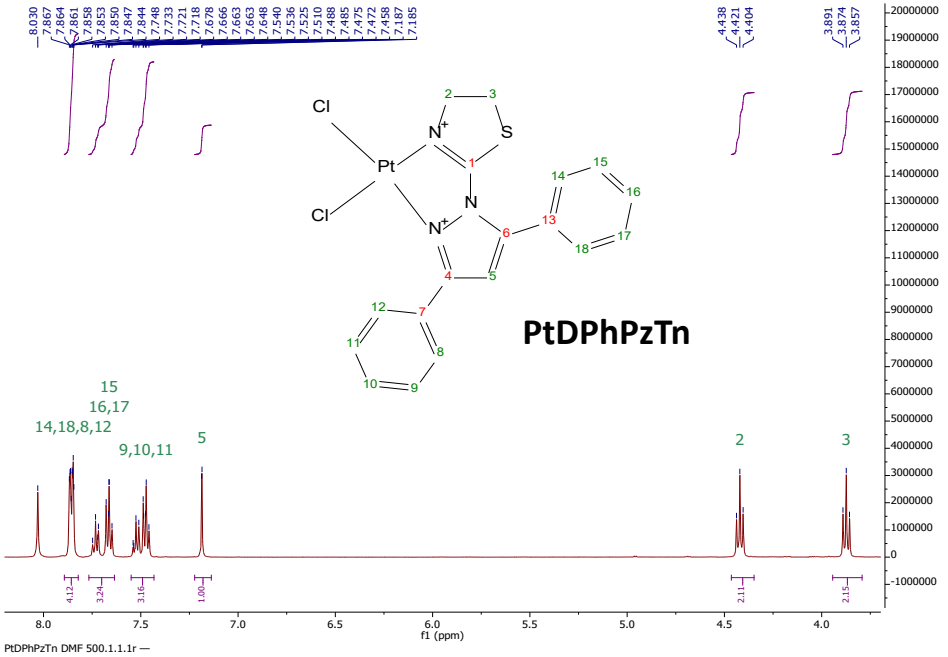


Compound	N-CH$_2$	S-CH$_2$	H(4)	H(5)	H(6)
PzTn	4.34	3.58	8.40	6.60	7.81
PtPzTn	4.47	4.20	9.08	7.11	8.29

Results and discussion

^{1}H NMR spectroscopy:

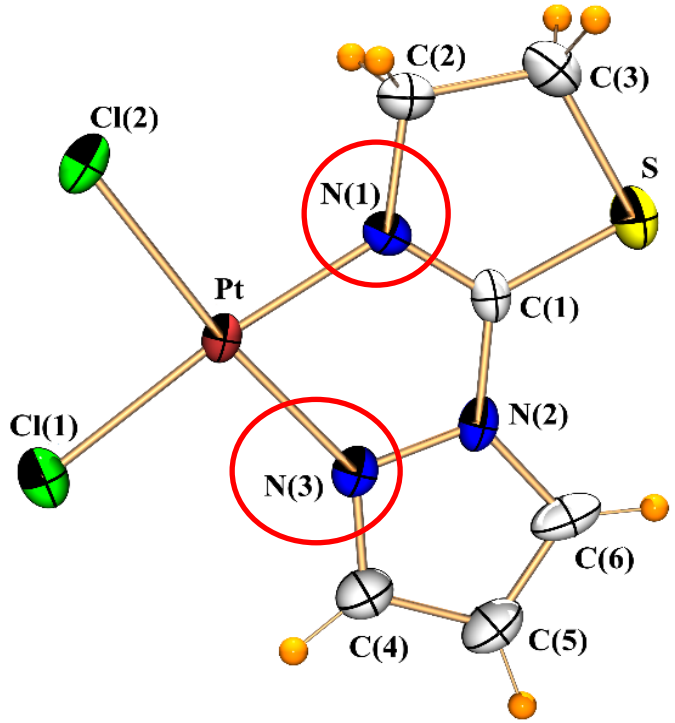




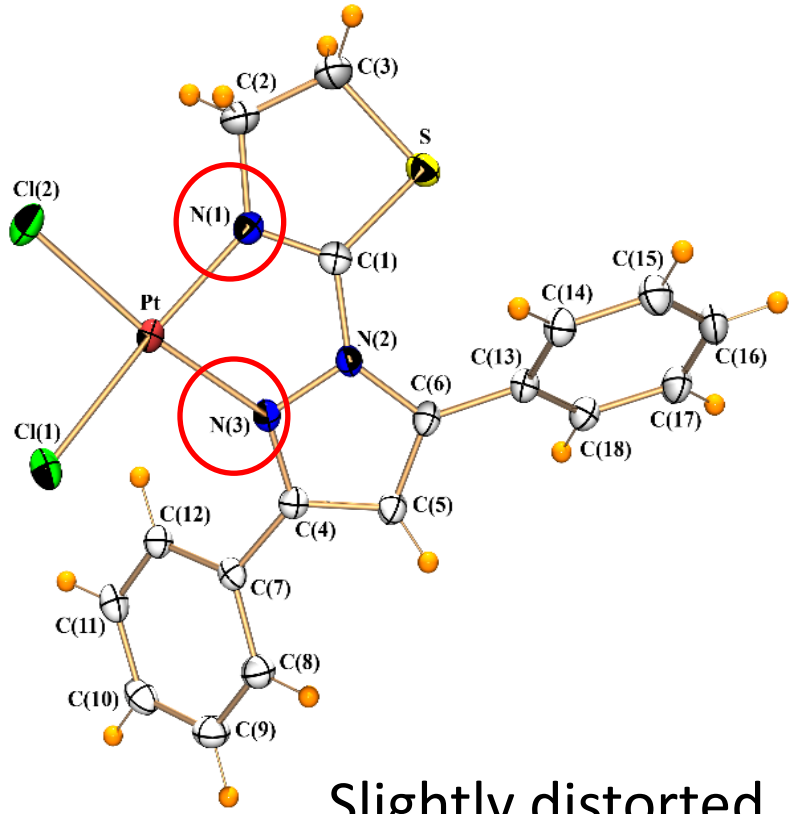
Compound	N-CH_2	S-CH_2	H(5)	H(8-18)
DPhPzTn	4.19	3.51	7.20	7.46-8.08
PtDPhPzTn	4.42	3.87	7.19	7.49-7.86

Results and discussion

Single cristal X-ray analysis:



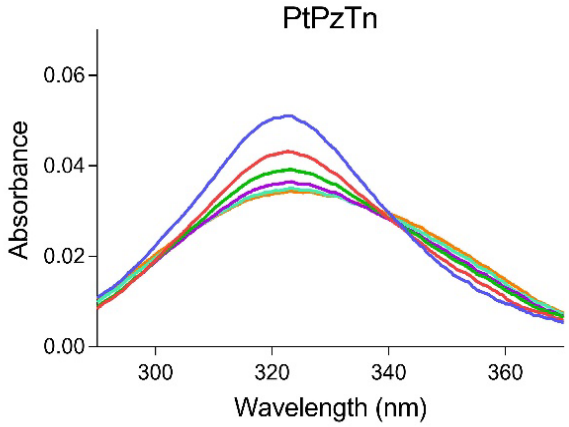
Square planar

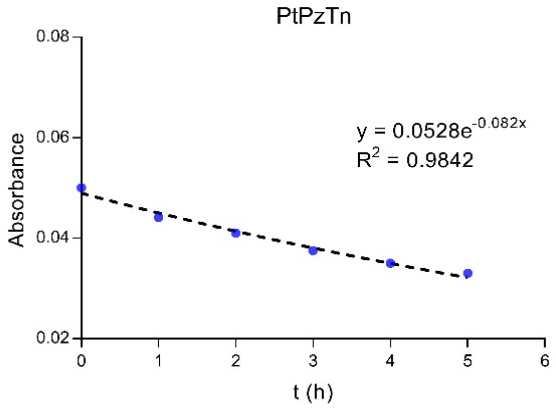


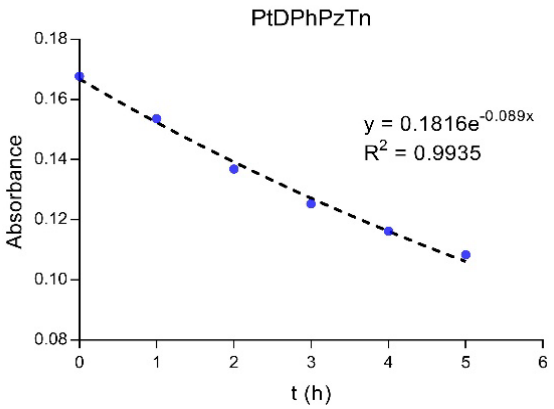
Slightly distorted square planar

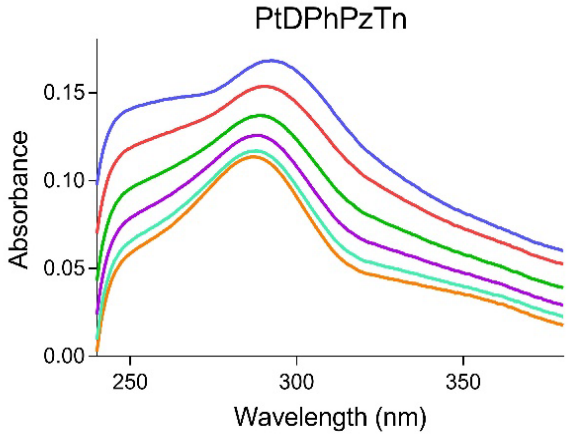
Results and discussion

Hydrolysis studies:









	10^{-5} k_1 (s^{-1})	$t_{1/2}$ (h)
PtPzTn	2.28	8.45
PtDPhPzTn	2.47	7.79

Results and discussion

Viability:

Cytotoxicity (IC_{50} ± SD, μM) of the different Pt(II) complexes towards selected tumour and non-tumour cell lines after 24 h of treatment

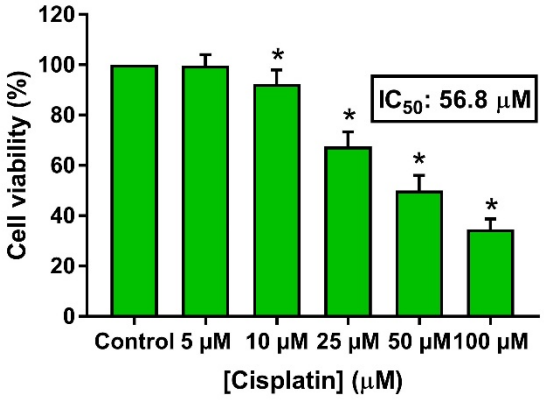
	CisPt	PtPzTn	PtDPhPzTn
HeLa	16.08 ± 1.01	140.20 ± 24.31	12.15 ± 0.89
HL-60	11.32 ± 1.04	15.02 ± 1.41	6.05 ± 0.47
U-937	7.89 ± 0.54	6.48 ± 0.81	3.23 ± 0.34
MDA-MB-231	56.83 ± 2.41	33.51 ± 3.83	10.47 ± 1.02
MCF10-A	50.34 ± 5.16	46.14 ± 5.93	10.29 ± 0.74

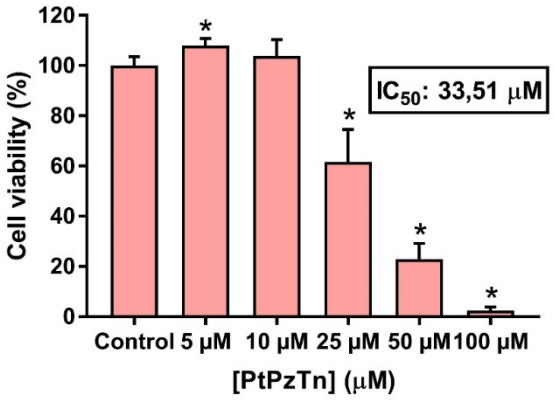
HeLa: epithelial cervix carcinoma cells
HL-60: human promyelocytic leukemia cells
U-937: human histiocytic lymphoma cells
MDA-MB-231: triple negative breast cancer cells
MCF10-A: human breast epithelial cells

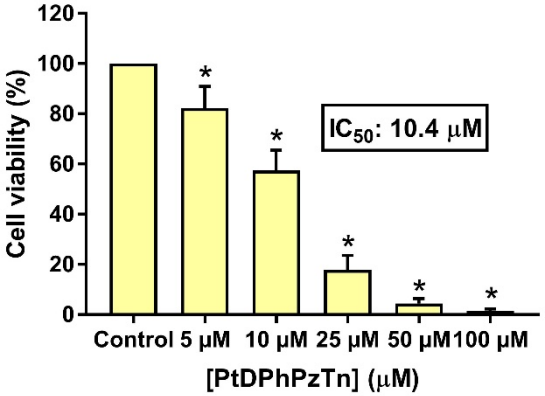
Results and discussion

In vitro cytotoxicity assay:

Dose-response curve of the thiazoline-containing Pt(II) complexes and cisplatin on cell viability of **MDA-MB-231** cells after 24h of treatment





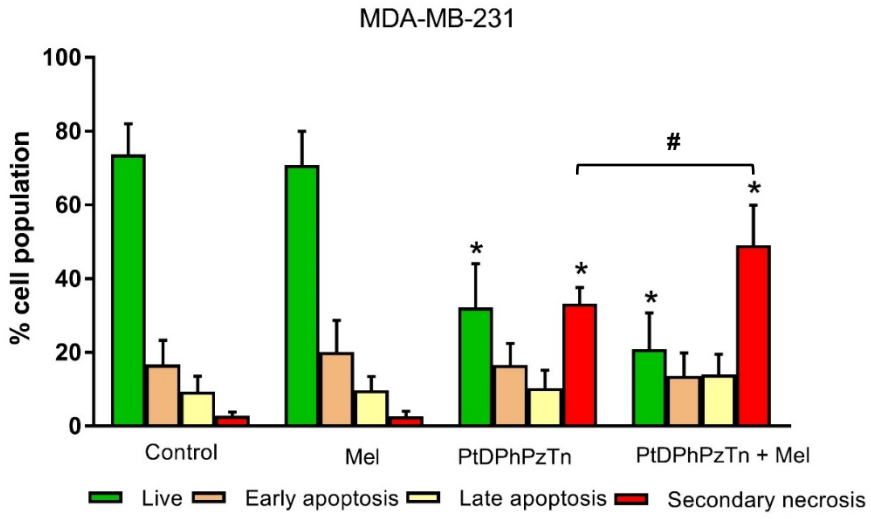


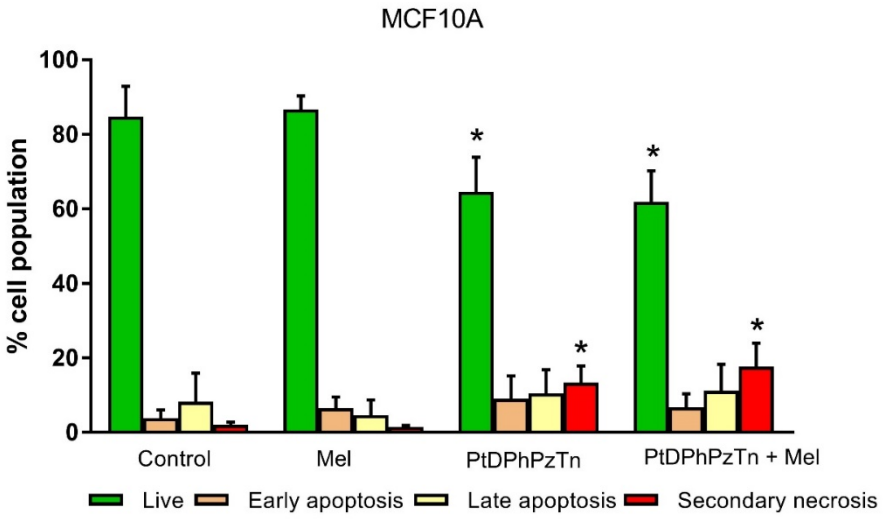
Values are presented as means ± SD of 5 separate experiments and expressed as percentage of control values (DMF-treated samples).
*P < 0.05 compared to control values.

Results and discussion

Determination of apoptosis:

Combinatory treatment of melatonin and PtDPhPzTn differentially affect apoptosis of **MDA-MB-231** and **MCF10A** cells





Values represent means ± S.D. of 5 independent experiments. *P < 0.05 compared to control values. #P < 0.05.

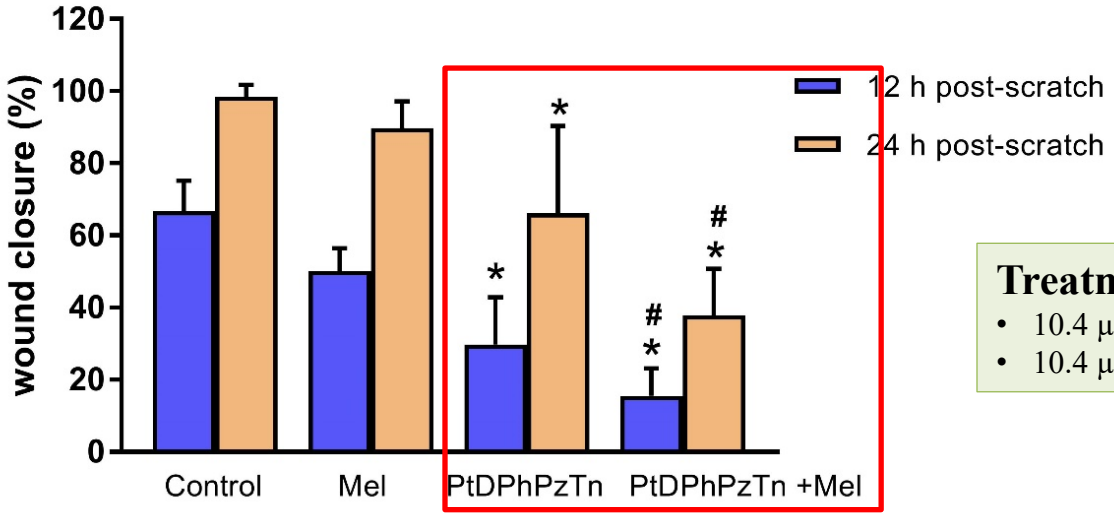
Treatments (24 h):

- 10.4 μM PtDPhPzTn
- 10.4 μM PtDPhPzTn + 1 mM melatonin

Results and discussion

Wound-healing assay:

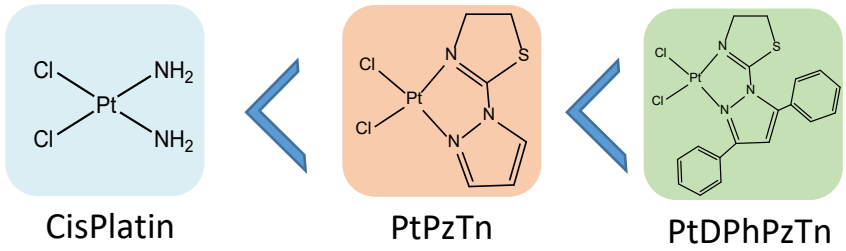
Effect of combinatory treatment of melatonin and PtDPhPzTn on migration properties of **MDA-MB-231** cells



Treatments (24 h):
- 10.4 µM PtDPhPzTn
- 10.4 µM PtDPhPzTn + 1 mM melatonin

Histogram bars show percentage of wound closure after 12 and 24 h after scratch, where 100% represents a fully closed wound.
Values represent means ± S.D. of 5 independent experiments. *P < 0.05 compared to control values. #P < 0.05 compared to PtDPhPzTn values.

Conclusions



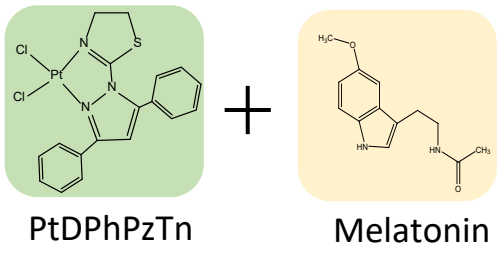
Aromatic groups improved cytotoxicity

~60% apoptosis induction in TNBC

VS

~30% apoptosis induction in MCF10A

Pro-apoptotic effect in TNBC cells was markedly higher than that observed in non-tumour breast epithelial MCF10A cells



Pro-apoptotic
Cytotoxicity
Antimigration

PtDPhPzTn and melatonin could be potentially applied to TBNC treatment as powerful **synergistic agents**

Acknowledgments

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