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THE EFFECT OF A METAL ATOM ON THE PHOTOCHEMICAL AND PHOTOBIOLOGICAL PROPERTIES OF PORPHYRAZINE AS AN AGENT FOR PDT

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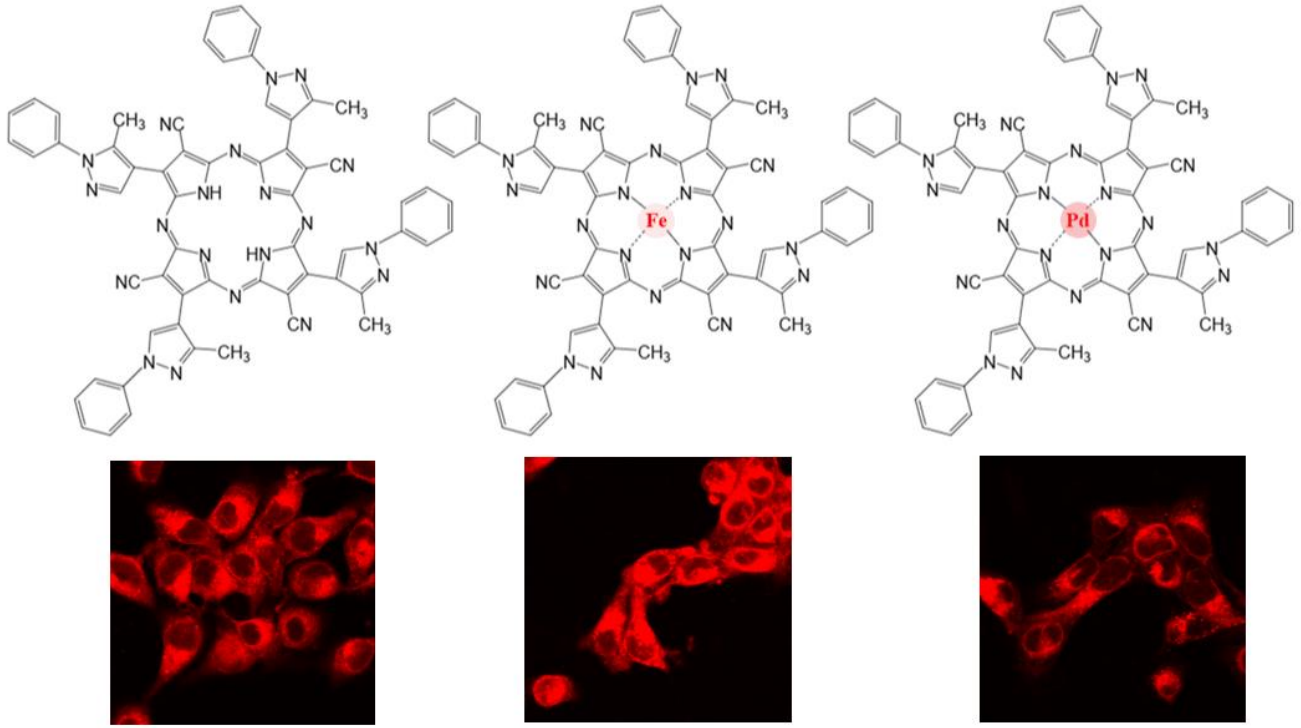

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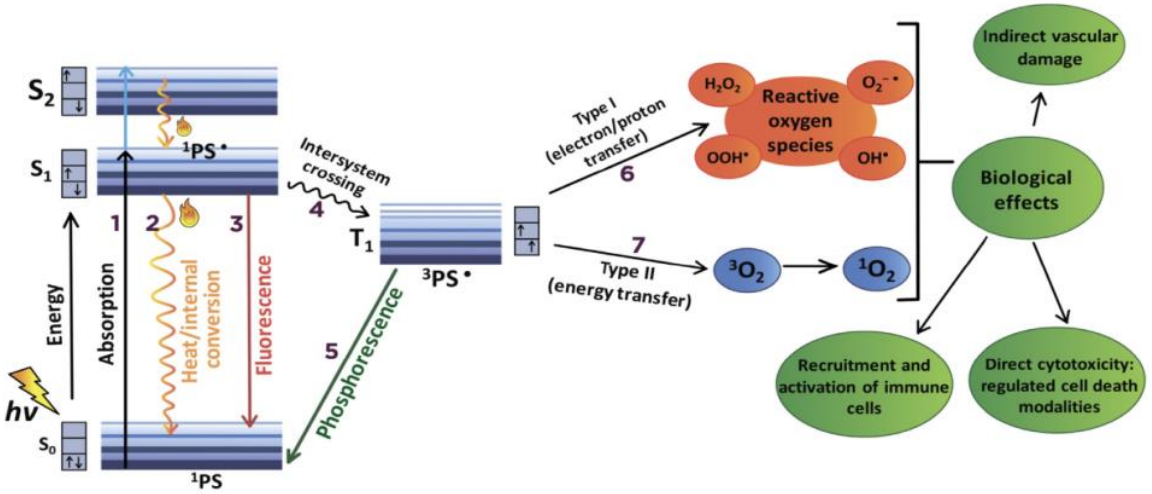
Abstract:

Modification of the known structures of photosensitizers (PS) in purpose to improve their properties is an important direction in the creation of new agents for photodynamic therapy (PDT). Among the approaches, the inclusion of different metals in the structure of the PS molecule can be distinguished. In this research, we investigated the photophysichemic and photobiological properties of tetrakis(3-methyl-1-phenyl-pyrazole-4-yl)-tetracyanoporphyrazine (hereinafter **Pz**) and its metal complexes containing ferrum and palladium cations in the center of the macrocycle.

Keywords: PDT; porphyrazine; metal complex

Background & Motivation

Photodynamic therapy (PDT) is based on the production of the cytotoxic reactive oxygen species (ROS) under light excitation of a sensitizing drug (photosensitizer, PS) in the presence of molecular oxygen



Alzeibak R. et al. J Immunother Cancer, 2021

The main areas of research in the field of PDT:

- ✓ Increased selectivity (+carriers)
- ✓ Increasing the depth of penetration into tissues (infrared dyes, interstitial PDT)
- ✓ Increased effectiveness (hypoxia relief, combination therapy)
- ✓ **New molecules** (+modification of known)

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What is the structural formula of the studied tetracyanotetra(aryl)porphyrazine dyes?

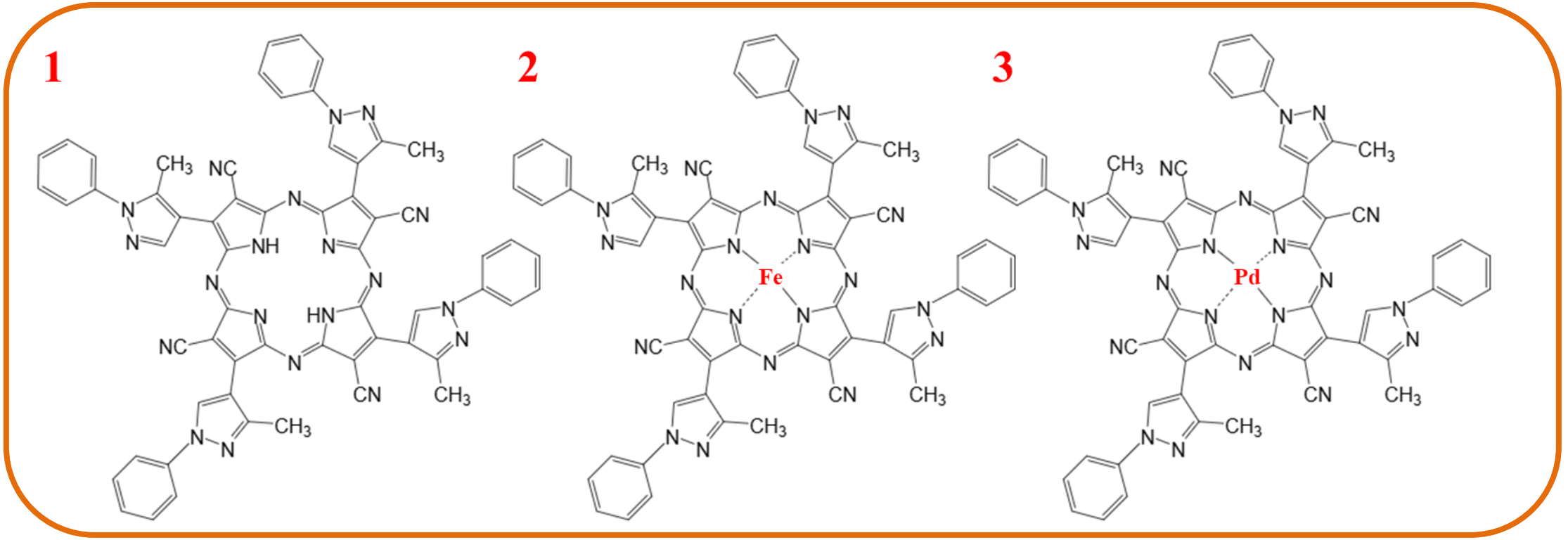

Figure 1. Structural formulas of the studied compounds: **Pz**(1), **FePz** (2), **PdPz** (3).

Impact of the metal atom on the spectral properties of Pz:

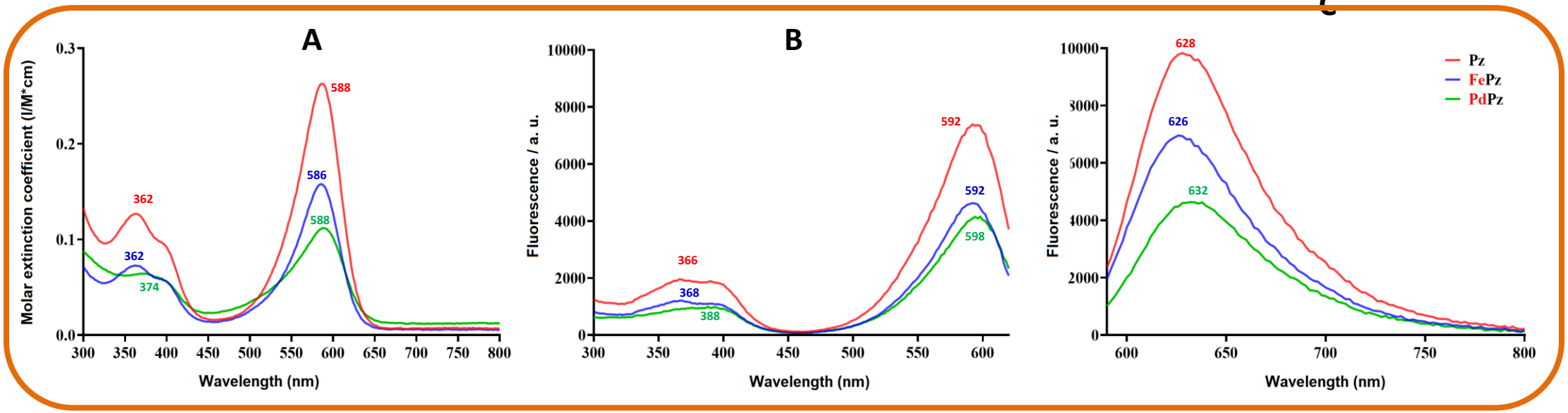

Figure 2. Absorption (**A**) fluorescence emission (**B**) and fluorescence excitation (**C**) spectra of novel porphyrazine derivatives (DMSO, 5 µM).
The fluorescence was excited at λ_{ex} = 570 nm, λ_{em} = 640 nm

The introduction of metal atoms led to a decrease in optical density and fluorescence intensity. PdPz having a more pronounced effect compared with FePz.

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Impact of the metal atom on the rate of accumulation and intensity of the fluorescence signal in cells of Pz:

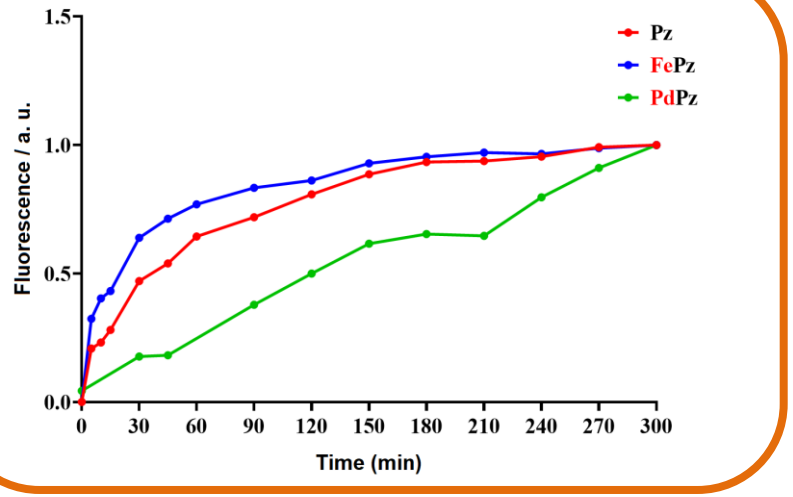

Figure 3. Dynamics of accumulation of **Pz**, **FePz**, **PdPz** by human epidermoid carcinoma cells A431, λ_{ex} = 550 nm, λ_{em} = 650 nm

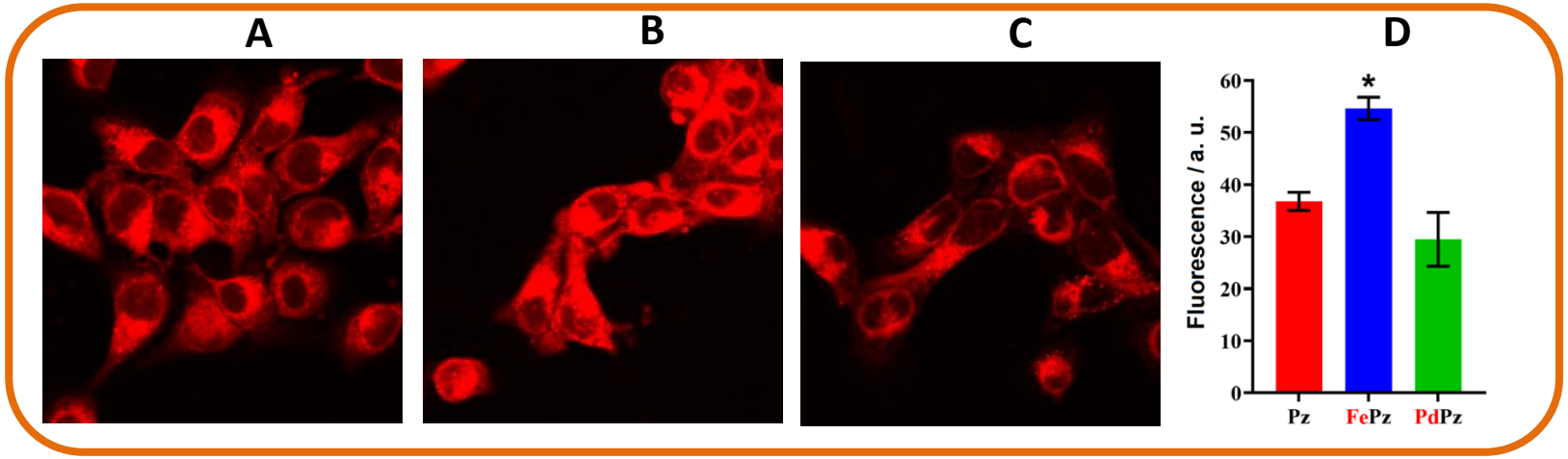

Figure 4. Fluorescent images of human epidermoid carcinoma cells A431 after incubation in DMEM medium with 5 µm **Pz** (A), **FePz** (B), **PdPz** (C), incubation time 3 hours, λ_{ex} = 594 nm, λ_{em} = 610-735, image size 135x135 µm, fluorescence intensity diagram of these compounds (D)

The introduction of an iron atom contributed to a slight increase in the rate of accumulation of the compound in cells, while palladium led to a significant decrease in it. The intensity of the FePz fluorescent signal is higher, which may be an advantage for diagnostic purposes, but the PdPz has demonstrated a decrease in the signal.

Pz and it's metall complexes are efficient photosensitizers against cancer cells

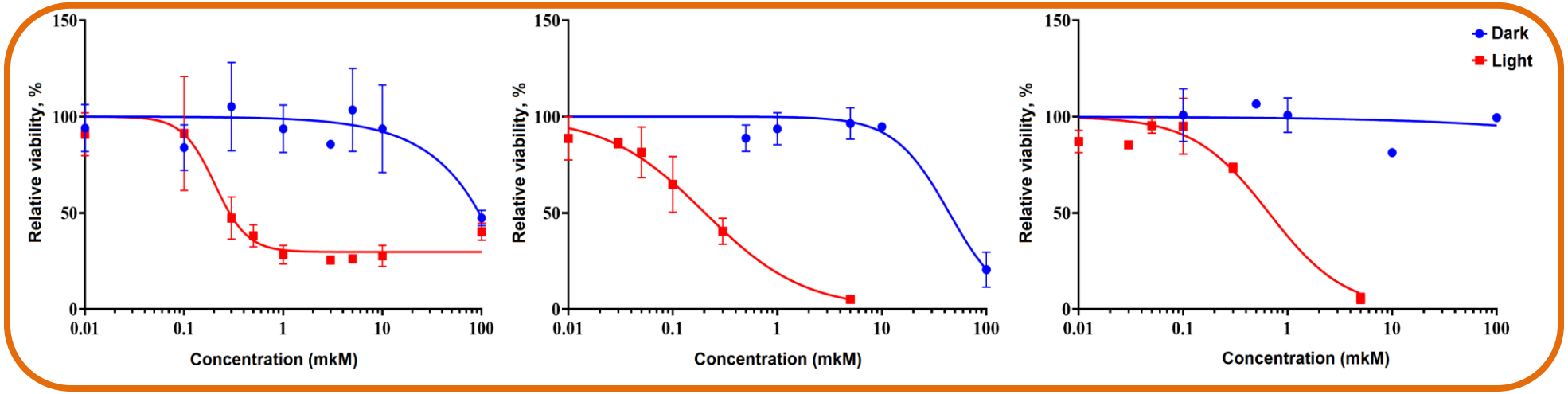

Figure 5. Dark and light toxicity of **Pz**(A), **FePz**(B), **PdPz** (C) against human epidermoid carcinoma cells A431, to induce a photodynamic response, the cells were irradiated with light at a dose of 20 J/cm^2 (655-675 nm, 20 MW/cm^2)

Compound	Dark IC_{50}, mkM	Light IC_{50}, mkM	Photodynamic index
Pz	≥ 100	0,2	≥ 500
FePz	44,17	0,2	220,85
PdPz	≥ 100	0,66	≥ 151,52

For all these compounds, pronounced cytotoxicity was demonstrated in light conditions and moderate in the dark. Pz is characterized by the highest value of the photodynamic index.

The type of cell death?

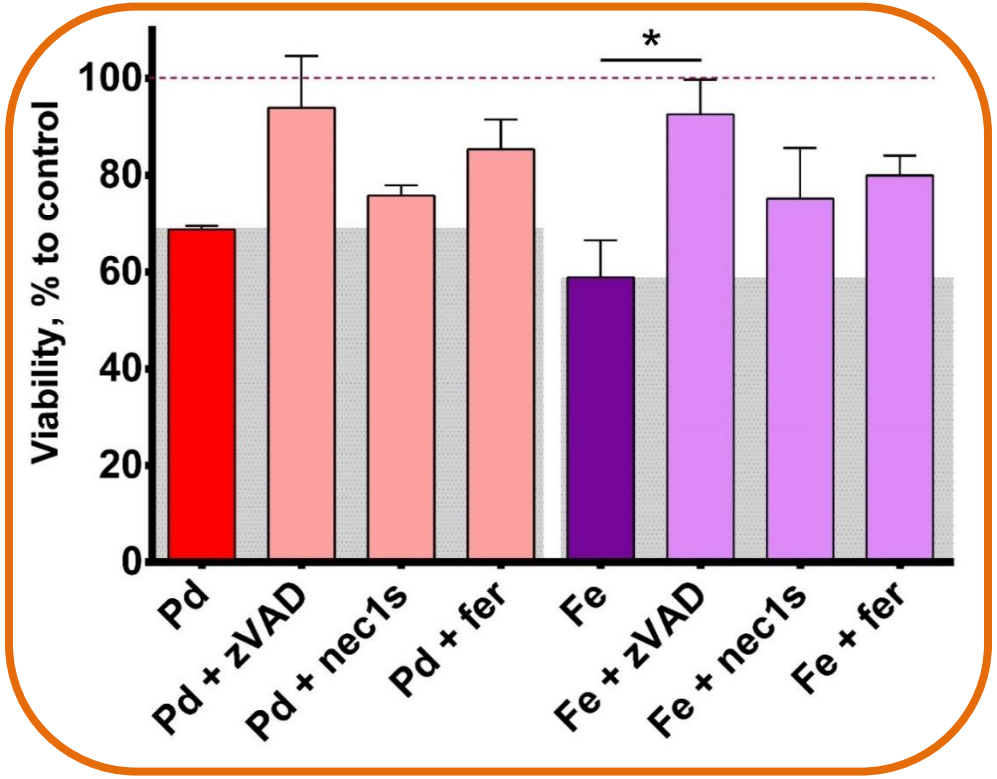

Figure 6. Viability of A431 cells in the presence of cell death inhibitors in the dark and under irradiation at a dose of 20 J/cm^2 .
Pd – incubation with **PdPz**; **Pd+zVAD** – **PdPz** + pancaspase inhibitor zVAD-fmk; **Pd+nec1s** –**PdPz** + necrostatin-1s; **Pd+fer** – **PdPz** + ferrostatin-1; **Fe** – incubation with **FePz**;
Fe+zVAD – **FePz** + pancaspase inhibitor zVAD-fmk; **Fe+nec1s** – **FePz** + necrostatin-1s; **Fe+fer - FePz** + ferrostatin-1.
The value of cell viability in the control without the addition of PS and inhibitors is assumed to be 100% (indicated by a dotted line).
The error bars are represented by the standard deviation (n≥3) * – a statistically significant difference between the indicated processing options is the Welch-adjusted t-test with a significance level of p <0.05

FePz and PzPz are able to direct cell death along the immunogenic pathway. both metal complexes can cause apoptosis, at the same time, a significant contribution of ferroptosis is shown, and with the action of FePz, the involvement of necroptosis is also shown.

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Conclusions

- The introduction of metal atoms led to a decrease in optical density and fluorescence intensity, with palladium having a more pronounced effect compared with iron.
- The introduction of an iron atom contributed to a slight increase in the rate of accumulation of the compound in cells, while palladium led to a significant decrease in it. The intensity of the FePz fluorescent signal is higher, which may be an advantage for diagnostic purposes, but the introduction of palladium leads to a decrease in the signal.
- For all these compounds, pronounced cytotoxicity was demonstrated in light conditions and moderate in the dark. **Pz** is characterized by the highest value of the photodynamic index.
- **FePz** and **PzPz** are able to direct cell death along the immunogenic pathway.

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Ministry of Science and Higher Education of Russian Federation

We are open for collaboration:

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